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(54) 【発明の名称】 ストレプトコッカス・ピオゲネス抗原

(57) 【要約】 (修正有)

【課題】 ストレプトコッカス・ピオゲネス (*Streptococcus pyogenes*) によって引き起こされる細菌感染の予防および治療のためのストレプトコッカス・ピオゲネス抗原の提供。

【解決手段】 ストレプトコッカス・ピオゲネスからの高度免疫血清に反応性の抗原またはその断片をコードする単離核酸分子。該高度免疫血清に反応性の抗原またはその断片、そのような抗原の単離方法、およびその特定の使用。

【選択図】 なし

【特許請求の範囲】

【請求項 1】

(a) 配列番号1、4-8、10-18、20、22、24-32、34-35、38-40、43-46、49-51、53-54、57-61、63、65-71、73、75-77、81-82、88、91-94および96-150から選ばれる核酸分子に対して少なくとも70%の配列同一性を有する核酸分子、

(b) (a) の核酸分子に相補的な核酸分子、

(c) (a) または (b) の核酸分子の少なくとも15の連続塩基を含む核酸分子、

(d) (a)、(b) または (c) の核酸分子にストリンジェントなハイブリダイゼーション条件下でアニールする核酸分子、

(e) 遺伝子コードの縮重を別として、(a)、(b)、(c) または (d) に定める核酸分子にハイブリダイズする核酸分子

よりなる群から選ばれた核酸配列を含む、高度免疫血清反応性の抗原またはその断片をコードする単離核酸分子。

【請求項 2】

配列の同一性が少なくとも80%、好ましくは少なくとも95%、とりわけ100%である、請求項1に記載の単離核酸分子。

【請求項 3】

(a) 配列番号64から選ばれる核酸分子に対して少なくとも96%の配列同一性を有する核酸分子、

(b) (a) の核酸分子に相補的な核酸分子、

(c) (a) または (b) の核酸分子の少なくとも15の連続塩基を含む核酸分子、

(d) (a)、(b) または (c) の核酸分子にストリンジェントなハイブリダイゼーション条件下でアニールする核酸分子、

(e) 遺伝子コードの縮重を別として、(a)、(b)、(c) または (d) に定める核酸分子にハイブリダイズする核酸分子

よりなる群から選ばれた核酸配列を含む、高度免疫血清反応性の抗原またはその断片をコードする単離核酸分子。

【請求項 4】

(a) 配列番号3、36、47-48、55、62、72、80、84、95から選ばれる核酸分子、

(b) (a) の核酸分子に相補的な核酸分子、

(c) 遺伝子コードの縮重を別として、(a)、(b)、(c) または (d) に定める核酸分子にハイブリダイズする核酸分子

よりなる群から選ばれた核酸配列を含む単離核酸分子。

【請求項 5】

該核酸がDNAである、請求項1、2、3または4に記載の核酸分子。

【請求項 6】

該核酸がRNAである、請求項1、2、3、4または5に記載の核酸分子。

【請求項 7】

該核酸分子がゲノムDNA、とりわけストレプトコッカス・ピオゲネスのゲノムDNAから単離される、請求項1ないし5のいずれかに記載の単離核酸分子。

【請求項 8】

請求項1ないし7のいずれかに記載の核酸分子を含むベクター。

【請求項 9】

請求項1ないし7のいずれかに記載の核酸分子によってコードされる高度免疫グロブリン血清反応性の抗原またはその断片の組換え発現用に適合される、請求項8に記載のベクター。

【請求項 10】

請求項8または9に記載のベクターを含む宿主細胞。

【請求項 11】

請求項1、2、5、6または7のいずれかに記載の核酸分子によってコードされるアミ

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ノ酸配列を含む高度免疫血清に反応性の抗原およびその断片であって、該アミノ酸配列が、配列番号151、154-158、160-168、170、172、174-182、184-185、188-190、193-196、199-201、203-204、207-211、213、215-221、223、225-227、231-232、238、241-244および246-300よりなる群から選ばれることを特徴とする高度免疫血清に反応性の抗原およびその断片。

【請求項 1 2】

請求項 3、5、6 または 7 のいずれかに記載の核酸分子によってコードされるアミノ酸配列を含む高度免疫血清に反応性の抗原およびその断片であって、該アミノ酸配列が、配列番号214よりなる群から選ばれることを特徴とする高度免疫血清に反応性の抗原およびその断片。

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【請求項 1 3】

請求項 4、5、6 または 7 のいずれかに記載の核酸分子によってコードされるアミノ酸配列を含む高度免疫血清に反応性の抗原およびその断片であって、該アミノ酸配列が、配列番号153、186、197-198、205、212、222、230、234、245よりなる群から選ばれることを特徴とする高度免疫血清に反応性の抗原およびその断片。

【請求項 1 4】

表 2 の縦列「予測される免疫原性アミノ酸」および「同定された免疫原性領域の位置」のアミノ酸配列を含むペプチド；表 2 の血清反応性エピトープ、とりわけアミノ酸：

配列番号151の4-44、57-65、67-98、101-107、109-125、131-144、146-159、168-173、181-186、191-200、206-213、229-245、261-269、288-301、304-317、323-328、350-361、374-384、388-407、416-425および1-114；配列番号152の5-17、49-64、77-82、87-98、118-125、127-140、142-150、153-159、191-207、212-218、226-270、274-287、297-306、325-331、340-347、352-369、377-382、390-395および29-226；配列番号153の4-16、20-26、32-74、76-87、93-108、116-141、148-162、165-180、206-219、221-228、230-236、239-245、257-268、313-328、330-335、353-359、367-375、394-403、414-434、437-444、446-453、456-464、478-487、526-535、541-552、568-575、577-584、589-598、610-618、624-643、653-665、667-681、697-718、730-748、755-761、773-794、806-821、823-831、837-845、862-877、879-889、896-919、924-930、935-940、947-955、959-964、969-986、991-1002、1012-1036、1047-1056、1067-1073、1079-1085、1088-1111、1130-1135、1148-1164、1166-1173、1185-1192、1244-1254および919-929；配列番号154の5-44、62-74、78-83、99-105、107-113、124-134、161-174、176-194、203-211、216-237、241-247、253-266、272-299、323-349、353-360および145-305；配列番号155の15-39、52-61、72-81、92-97および71-81；配列番号156の13-19、21-31、40-108、115-122、125-140、158-180、187-203、210-223、235-245および173-186；配列番号157の5-12、19-27、29-39、59-67、71-78、80-88、92-104、107-124、129-142、158-168、185-191、218-226、230-243、256-267、272-277、283-291、307-325、331-344、346-352および316-331；配列番号158の6-28、43-53、60-76、93-103および21-99；配列番号159の10-30、120-126、145-151、159-169、174-182、191-196、201-206、214-220、222-232、254-272、292-307、313-323、332-353、361-369、389-396、401-415、428-439、465-481、510-517、560-568および9-26；配列番号160の5-29、39-45、107-128および1-112；配列番号161の4-38、42-50、54-60、65-71、91-102および21-56；配列番号162の4-13、19-25、41-51、54-62、68-75、79-89、109-122、130-136、172-189、192-198、217-224、262-268、270-276、281-298、315-324、333-342、353-370、376-391および23-39；配列番号163の6-41、49-58、62-103、117-124、147-166、173-194、204-211、221-229、255-261、269-284、288-310、319-325、348-380、383-389、402-410、424-443、467-479、496-517、535-553、555-565、574-581、583-591および474-489；配列番号164の8-35、52-57、66-73、81-88、108-114、125-131、160-167、174-180、230-235、237-249、254-262、278-285、308-314、321-326、344-353、358-372、376-383、393-411、439-446、453-464、471-480、485-492、502-508、523-529、533-556、558-563、567-584、589-597、605-619、625-645、647-666、671-678、690-714、721-728、741-763、766-773、777-787、792-802、809-823、849-864および37-241、409-534、

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582-604, 743-804; 配列番号165の4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416および202-337; 配列番号166の4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407および1-48; 配列番号167の18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297および203-217; 配列番号168の20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521および261-273; 配列番号169の6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641および1-414, 443-614, 997-1392; 配列番号170の14-42, 70-75, 90-100, 158-181および1-164; 配列番号171の4-21, 30-36, 54-82, 89-97, 105-118, 138-147および126-207; 配列番号172の4-21, 31-66, 96-104, 106-113, 131-142および180-204; 配列番号173の5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386および11-197, 204-219, 258-372; 配列番号174の4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322および195-289; 配列番号175の4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329および12-130; 配列番号176の10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707および434-444; 配列番号177の6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430および360-375; 配列番号178の4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251および254-260; 配列番号179の12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400および369-382; 配列番号180の11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487および270-312; 配列番号181の5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604および486-598; 配列番号182の4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374および378-396; 配列番号183の5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184および75-235; 配列番号184の6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310および30-51; 配列番号185の17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260

-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647および208-219; 配列番号186の4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039および396-533, 1342-1502, 1672-1920; 配列番号187の4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905および1-113, 210-232, 250-423, 536-564; 配列番号188の4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201および617-635; 配列番号189の7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244および190-203; 配列番号190の4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574および385-398; 配列番号191の5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003および12-190, 276-283, 666-806; 配列番号192の4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664および30-80, 89-105, 111-151; 配列番号193の7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259および195-203; 配列番号194の5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426および32-50; 配列番号195の8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174および75-90; 配列番号196の4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233および69-88; 配列番号197の4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802および96-230, 361-491, 572-585; 配列番号198の4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289および102-210; 配列番号199の13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313および240-248; 配列番号200の5-26, 34-48, 57-77,

84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260および182-198; 配列番号201の10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504および41-56; 配列番号202の5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333および202-217; 配列番号203の6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283および1-127; 配列番号204の4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718および297-458; 配列番号205の5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213および24-135; 配列番号206の4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721および176-330; 配列番号207の31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472および46-62, 296-341; 配列番号208の23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716および667-684; 配列番号209の20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869および258-416; 配列番号210の7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300および278-295; 配列番号211の4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191および183-195; 配列番号212の12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241および63-238; 配列番号213の4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308および1-141; 配列番号214の11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379および231-368; 配列番号215の9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342および247-260; 配列番号216の7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279および64-72; 配列番号217の4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897および222-362, 756-896; 配列番号218の11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255および153-170; 配列番号219の4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212および56-73; 配列番号220の4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334および298-312; 配列番号221の7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254および141-157; 配列番号222の23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-50

3, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663および433-440, 572-593; 配列番号223の4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267および17-319, 417-563; 配列番号224の6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500および46-187; 配列番号225の4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992および21-244, 381-499, 818-959; 配列番号226の19-29, 65-75, 90-109, 111-137, 155-165, 169-175および118-136; 配列番号227の15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465および147-155; 配列番号228の11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161および74-438; 配列番号229の4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413および156-420; 配列番号230の4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343および79-348; 配列番号231の12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168および53-70; 配列番号232の4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522および183-341; 配列番号233の4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822および92-231, 618-757; 配列番号234の11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372および41-170; 配列番号235の6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174および20-487, 757-1153; 配列番号236の10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305および26-74, 91-100, 105-303; 配列番号237の9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480および10-223, 231-251, 264-297, 312-336; 配列番号238の5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537および22-344; 配列番号239

の5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395および1-151;

配列番号240の6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756および91-263; 配列番号241の4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775および261-272; 配列番号242の4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701および541-551; 配列番号243の6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252および84-254; 配列番号244の13-30, 71-120, 125-137, 139-145, 184-199および61-78; 配列番号245の9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855および568-580; 配列番号246の11-21, 29-38および5-17; 配列番号247の2-9; 配列番号248の4-10, 16-28および7-18, 26-34; 配列番号249の10-16および1-15; 配列番号250の4-11; 配列番号251の4-40, 42-51および37-53; 配列番号252の4-21および22-29; 配列番号253の2-11; 配列番号254の9-17, 32-44および1-22; 配列番号255の19-25, 27-32および15-34; 配列番号256の4-12, 15-22および11-33; 配列番号257の10-17, 24-30, 39-46, 51-70および51-61; 配列番号258の6-19; 配列番号259の6-11, 21-27, 31-54および11-29; 配列番号260の4-10, 13-45および11-35; 配列番号261の4-14, 23-32および11-35; 配列番号262の14-39, 45-51および15-29; 配列番号263の4-11, 14-28および4-17; 配列番号264の4-16および2-16; 配列番号265の4-10, 12-19, 39-50および6-22; 配列番号266の2-13; 配列番号267の4-11, 22-65および3-19; 配列番号268の17-23, 30-35, 39-46, 57-62および30-49; 配列番号269の4-19および14-22; 配列番号270の2-9; 配列番号271の7-18, 30-43および4-12; 配列番号272の4-30, 39-47および5-22; 配列番号273の6-15および14-29; 配列番号274の4-34および23-35; 配列番号275の4-36, 44-57, 65-72および14-27; 配列番号276の4-18および11-20; 配列番号277の5-19; 配列番号278の18-36および6-20; 配列番号279の4-10, 19-34, 41-84, 96-104および50-63; 配列番号280の4-9, 19-27および8-21; 配列番号281の4-16, 18-28および22-30; 配列番号282の4-15および21-35; 配列番号283の4-17および3-13; 配列番号284の4-12および4-18; 配列番号285の4-24, 31-36および29-45; 配列番号286の12-22, 34-49および21-32; 配列番号287の4-17および22-32; 配列番号288の4-16, 25-42および7-28; 配列番号289の4-10および7-20; 配列番号290の4-11, 16-36, 39-54および28-44; 配列番号291の5-20, 29-54および14-29; 配列番号292の24-33および10-22; 配列番号293の10-51, 54-61および43-64; 配列番号294の7-1および2-17; 配列番号295の11-20および6-20; 配列番号296の4-30, 34-41および19-28; 配列番号297の11-21; 配列番号298の4-16, 21-26および9-38; 配列番号299の4-12, 15-27, 30-42, 66-72および10-24; 配列番号300の8-17および11-20; および配列番号246の2-19; 配列番号247

の1-12; 配列番号248の21-38; 配列番号254の2-22; 配列番号255の15-33; 配列番号256の11-32; 配列番号259の11-28; 配列番号260の10-27; 配列番号261の9-26; 配列番号263の4-16; 配列番号266の1-18; 配列番号273の12-29; 配列番号276の6-23; 配列番号277の1-21; 配列番号279の47-64; 配列番号285の28-45; 配列番号287の18-35; 配列番号291の14-31; 配列番号292の7-24; 配列番号299の8-25; 配列番号300の1-20; 配列番号151の18-33; 配列番号151の62-72; 配列番号152の118-131; 配列番号154の195-220; 配列番号154の215-240; 配列番号154の255-280, 配列番号155の72-81; 配列番号156の174-186; 配列番号157の317-331; 配列番号158の35-59; 配列番号158の54-84; 配列番号158の79-104; 配列番号159の33-58; 配列番号159の81-101; 配列番号159の136-150; 配列番号159の173-186; 配列番号159の231-251; 配列番号161の22-48; 配列番号162の24-39; 配列番号163の475-489; 配列番号164の38-56; 配列番号164の583-604; 配列番号165の202-223; 配列番号165の222-247; 配列番号165の242-267; 配列番号165の262-287; 配列番号165の282-307; 配列番号165の302-327; 配列番号166の25-48; 配列番号167の204-217; 配列番号168の259-276; 配列番号169の121-139; 配列番号169の260-267; 配列番号169の215-240; 配列番号170の115-140; 配列番号172の182-204; 配列番号173の144-153; 配列番号173の205-219; 配列番号174の196-206; 配列番号174の240-249; 配列番号174の272-287; 配列番号174の199-223; 配列番号174の218-237; 配列番号175の226-249; 配列番号175の287-306; 配列番号176の430-449; 配列番号177の361-375; 配列番号178の241-260; 配列番号181の483-502; 配列番号182の379-396; 配列番号184の31-51; 配列番号186の1436-1460; 配列番号186の1455-1474; 配列番号186の1469-1487; 配列番号187の215-229; 配列番号187の534-561; 配列番号187の59-84; 配列番号187の79-104; 配列番号188の618-635; 配列番号189の191-203; 配列番号190の386-398; 配列番号191の65-83; 配列番号192の90-105; 配列番号192の112-136; 配列番号193の290-209; 配列番号194の33-50; 配列番号195の76-90; 配列番号196の70-88; 配列番号197の418-442; 配列番号197の574-585; 配列番号198の87-104; 配列番号198の124-148; 配列番号198の141-152; 配列番号199の241-248; 配列番号200の183-198; 配列番号201の40-57; 配列番号202の202-217; 配列番号203の50-74; 配列番号203の69-93; 配列番号203の88-112; 配列番号203の107-127; 配列番号205の74-92; 配列番号206の207-232; 配列番号206の227-252; 配列番号206の247-272; 配列番号207の47-60; 配列番号207の297-305; 配列番号207の312-337; 配列番号208の667-384; 配列番号210の279-295; 配列番号211の179-198; 配列番号213の27-51; 配列番号213の46-70; 配列番号213の65-89; 配列番号213の84-108; 配列番号213の112-141; 配列番号215の248-260; 配列番号216の59-78; 配列番号218の154-170; 配列番号219の57-73; 配列番号220の297-314; 配列番号221の142-157; 配列番号222の428-447; 配列番号222の573-593; 配列番号223の523-544; 配列番号223の46-70; 配列番号223の65-89; 配列番号223の84-108; 配列番号223の122-151; 配列番号224の123-142; 配列番号225の903-921; 配列番号226の119-136; 配列番号227の142-161; 配列番号228の258-277; 配列番号228の272-300; 配列番号228の295-322; 配列番号229の311-343; 配列番号229の278-304; 配列番号230の131-150; 配列番号230の195-218; 配列番号231の53-70; 配列番号232の184-208; 配列番号232の222-246; 配列番号232の241-265; 配列番号232の260-284; 配列番号232の279-303; 配列番号232の317-341; 配列番号233の678-696; 配列番号235の88-114; 配列番号235の464-481; 配列番号236の153-172; 配列番号236の137-155, 166-184; 配列番号236の215-228; 配列番号237の37-51; 配列番号237の53-75; 配列番号237の232-251; 配列番号237の318-336; 配列番号238の305-315; 配列番号238の131-156; 配列番号241の258-275; 配列番号243の107-137; 配列番号243の138-162; 配列番号243の157-181; 配列番号243の195-227; 配列番号244の62-7; 配列番号245の567-584を含むペプチドよりなる群から選ばれた高度免疫血清反応性の抗原の断片。

【請求項15】

請求項1～7のいずれかに記載の核酸分子を発現させることを含む、請求項11～14のいずれかに記載のストレプトコッカス・ピオゲネスの高度免疫血清反応性の抗原またはその断片の製造方法。

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【請求項 16】

請求項 8 または 9 に記載のベクターで適当な宿主細胞を形質転換またはトランスフェクションすることを含む、請求項 11～14 のいずれかに記載のストレプトコッカス・ピオゲネスの高度免疫血清反応性の抗原またはその断片を発現する細胞の製造方法。

【請求項 17】

請求項 11～14 のいずれかの高度免疫血清反応性の抗原またはその断片または請求項 1～7 のいずれかに記載の核酸分子を含む医薬組成物、とりわけワクチン。

【請求項 18】

さらに、ポリカチオン性ポリマー、とりわけポリカチオン性ペプチド、免疫促進デオキシヌクレオチド (ODN)、少なくとも 2 つの L y s L e u L y s モチーフを含むペプチド、神経刺激性の化合物、とりわけヒト成長ホルモン、ミョウバン、フロイントの完全または不完全アジュバントまたはこれらの組合せよりなる群から好ましくは選ばれる免疫促進物質をさらに含む、請求項 17 に記載の医薬組成物、とりわけワクチン。

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【請求項 19】

医薬製剤の製造のための、とりわけストレプトコッカス・ピオゲネス感染に対するワクチンの製造のための、請求項 1～7 のいずれかに記載の核酸分子または請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の使用。

【請求項 20】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の少なくとも選択された部分に結合する抗体、または少なくとも有効なその部分。

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【請求項 21】

モノクローナル抗体である、請求項 20 に記載の抗体。

【請求項 22】

抗体の有効な部分が F a b フラグメントを含む、請求項 20 または 21 に記載の抗体。

【請求項 23】

キメラ抗体である、請求項 20～22 のいずれかに記載の抗体。

【請求項 24】

ヒト化抗体である、請求項 20～23 のいずれかに記載の抗体。

【請求項 25】

請求項 20～24 のいずれかに記載の抗体を産生するハイブリドーマ細胞株。

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【請求項 26】

以下の工程：

- ・請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片を非ヒト動物に投与することにより該動物において免疫応答を開始させ、
- ・該動物から抗体含有体液を取り出し、ついで
- ・該抗体含有体液をさらなる精製工程に供することにより該抗体を製造することを特徴とする、請求項 20 に記載の抗体の製造方法。

【請求項 27】

以下の工程：

- ・請求項 12～15 のいずれかに記載の高度免疫血清反応性の抗原またはその断片を非ヒト動物に投与することにより該動物において免疫応答を開始させ、
 - ・該動物から脾臓または脾細胞を取り出し、
 - ・該脾臓または脾細胞のハイブリドーマ細胞を産生させ、
 - ・該高度免疫血清反応性の抗原またはその断片に特異的なハイブリドーマ細胞を選択およびクローニングし、
 - ・該クローニングしたハイブリドーマ細胞の培養により抗体を産生させ、および任意にさらなる精製工程を行う
- ことを特徴とする、請求項 20 に記載の抗体の製造方法。

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【請求項 28】

ストレプトコッカス・ピオゲネス感染の治療用医薬の製造のための、請求項 20～24

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のいずれかに記載の抗体の使用。

【請求項 29】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片に結合するアンタゴニスト。

【請求項 30】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片に結合しうるアンタゴニストの同定方法であって、以下の工程：

(a) 請求項 11～14 のいずれかに記載の単離したまたは固定化した高度免疫血清反応性の抗原またはその断片を候補アンタゴニストと、該候補アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合に応答して検出可能なシグナルを提供することのできる成分の存在下、該候補アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合を可能にする条件下で接触させ、ついで

(b) 該アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合に応答して生成されるシグナルの存在または不在を検出することを含む方法。

【請求項 31】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片のその相互作用パートナーへの相互作用活性を低減または抑制しうるアンタゴニストの同定方法であって、以下の工程：

(a) 請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその高度免疫血清断片を用意し、

(b) 該高度免疫血清反応性の抗原またはその断片に対する相互作用パートナー、とりわけ請求項 20～24 のいずれかに記載の抗体を用意し、

(c) 該高度免疫血清反応性の抗原またはその断片を該相互作用パートナーと相互作用させて相互作用複合体を生成させ、

(d) 候補アンタゴニストを用意し、

(e) 該候補アンタゴニストと該相互作用複合体との間で競合反応を起こさせ、

(f) 該候補アンタゴニストが該高度免疫血清反応性の抗原またはその断片と該相互作用パートナーとの相互作用活性を低減または抑制するか否かを決定する

ことを含む方法。

【請求項 32】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の相互作用パートナーの単離および／または精製および／または同定のための、請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の使用。

【請求項 33】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の発現に関連する疾患をインビトロで診断する方法であって、請求項 1～7 のいずれかに記載の高度免疫血清反応性の抗原および断片をコードする核酸配列の存在または請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の存在を検出することを含む方法。

【請求項 34】

細菌感染、とりわけストレプトコッカス・ピオゲネス感染をインビトロで診断する方法であって、請求項 1～7 のいずれかに記載の該高度免疫血清反応性の抗原および断片をコードする核酸配列の存在または請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の存在を検出することを含む方法。

【請求項 35】

請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片へのペプチド結合を生成するための、請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の使用であって、該ペプチドがアンチカリンであることを特徴とする使用。

【請求項 36】

機能性の核酸を製造するための、請求項 11～14 のいずれかに記載の高度免疫血清反応性の抗原またはその断片の使用であって、該機能性核酸がアプタマーおよびシュピーゲルマーよりなる群から選ばれることを特徴とする使用。

【請求項 37】

機能性のリボ核酸分子を製造するための、請求項 11～14 のいずれかに記載の核酸の使用であって、該機能性のリボ核酸が、リボザイム、アンチセンス核酸および siRNA よりなる群から選ばれることを特徴とする使用。

【発明の詳細な説明】

【技術分野】

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【0001】

本発明は、単離された核酸分子に関し、該核酸分子はストレプトコッカス・ピオゲネス (*Streptococcus pyogenes*) の抗原をコードし、該抗原はストレプトコッカス・ピオゲネスによって引き起こされる細菌感染の予防および治療のための医薬の調製に使用するのに適している。

【背景技術】

【0002】

ストレプトコッカス・ピオゲネスはまた A 群連鎖球菌 (GAS) とも呼ばれるが、重要なグラム陽性細胞外細菌性病原体であって、一般にヒトに感染する。GAS は喉または皮膚にコロニーを形成し、幾つかの化膿性の感染症および非化膿性の続発症の原因である。GAS は主として子供の疾患であり、ヒトで細菌性咽頭炎、猩紅熱、インペチゴおよび敗血症を含む種々の感染症を引き起こす。何十年にもわたる疫学的研究は、ある種の血清型がそれぞれ喉または皮膚感染と関連している別個の喉および皮膚株という概念に導いた {Cunningham, M., 2000}。GAS は、最近、米国で再燃している連鎖球菌中毒性ショック症候群に関連する壊死性筋膜炎の原因であり {Cone, L. ら、1987; Stevens, D., 1992}、皮膚および軟組織に侵入して組織または四肢の破壊に導く「肉食性 (flesh eating) 細菌」として記載されている。

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【0003】

感染に引き続き、急性リウマチ熱、急性糸球体腎炎および反応性関節炎などの幾つかの連鎖球菌感染後の続発症がヒトで起こる。急性リウマチ熱およびリウマチ性心疾患は最も重篤な自己免疫続発症の一つであり、世界中で子供の障害および死亡に導いている。ストレプトコッカス・ピオゲネスはまた、猩紅熱や壊死性筋膜炎などの幾つかの急性疾患をも引き起こすことがあり、ツレット症候群、チックおよび運動および注意障害と関連付けられている。

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【0004】

A 群連鎖球菌は咽喉炎および咽頭炎の最も一般的な細菌病因であり、一般の医療実践、季節依存においてすべての診療所受診の少なくとも 16% を占めている {Hope-Simpson, R., 1981}。それは、年齢が 5～15 歳の就学年齢の子供が主として罹患する {Cunningham, M., 2000}。すべての年齢が、混雑した状況、たとえば学校において該生物の拡散の影響を被る。GAS は正常な微生物叢とは考えられていないが、A 群連鎖球菌の咽頭保菌は臨床的な徴候なしで起こりうる。

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【0005】

A 群連鎖球菌は、その炭水化物に基づく血清型の Lancefield 分類法により区別することができ、または塩酸とともに細菌を沸騰させて抽出することのできる表面タンパク質に基づいて M タンパク質に分類される。これにより 80 を超える血清型が導かれ、これら血清型はまた分子的アプローチによっても分類できる (emm 遺伝子)。ストレプトコッカス・ピオゲネスのある種の M タンパク質血清型は主として咽頭炎およびリウマチ熱と関連しており、一方、他のものは主として膿皮症および糸球体腎炎を引き起こすと思われる {Cunningham, M., 2000}。

【0006】

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咽頭炎および場合により中毒性ショックを引き起こすのに関与していると思われるのは、C群およびG群連鎖球菌であり、これらは咽喉培養後に区別されなければならない {Hope-Simpson, R., 1981; Bisno, A.ら、1987}。

【0007】

現在のところ、連鎖球菌感染は抗生物質療法によってのみ治療できる。しかしながら、抗生物質で治療したものの25～30%は疾患の再発を示し、および／または粘膜分泌液中に該生物を含んでいる。現在のところ、連鎖球菌感染を回避するのに利用できる予防的な治療（ワクチン）は存在しない。

【0008】

それゆえ、連鎖球菌感染を予防または改善するのに有効な治療の必要性が依然として存在する。ワクチンは連鎖球菌による感染を予防できるのみならず、宿主組織のコロニー形成をより特異的に予防または改善し、それによって咽頭炎や他の化膿性感染症の発症率を低下させることができる。リウマチ熱、急性糸球体腎炎、敗血症、中毒性ショックおよび壊死性筋膜炎などの非化膿性続発症の排除は、急性感染症の発症率および該生物の保菌の低下の直接の結果である。他の連鎖球菌に対して交差免疫を示すことのできるワクチンはまた、他のすべてのβ溶血性連鎖球菌種、すなわちA群、B群、C群およびG群によって引き起こされる感染症を予防または改善するのに有用であろう。

【0009】

ワクチンは種々の抗原のあらゆるものを含んでいてよい。抗原の例は、全死菌または弱毒化生物、これら生物／組織のサブ画分、タンパク質、またはその最も単純な形態であるペプチドである。抗原はまた、グリコシル化されたタンパク質またはペプチドの形態で免疫系によって認識されることができ、多糖または脂質であるかまたは含んでいることができる。短いペプチドを用いることができる、なぜなら、たとえば細胞障害性T細胞（CTL）は主要組織複合体（MHC）と結合した通常8～11アミノ酸長の短いペプチドの形態の抗原を認識するからである。B細胞は4～5アミノ酸の短い線状エピトープを三次元構造（コンホメーションエピトープ）と同様に認識することができる。持続された抗原特異的な免疫応答を得るには、アジュバントが免疫系に必要なすべての細胞が関与する免疫カスケードを誘発する必要がある。主として、アジュバントは、いわゆる抗原提示細胞（APC）に作用するが、その作用様式には制限されない。これら細胞はまず抗原と出会い、ついでプロセッシングを受けたまたは修飾されていない抗原が免疫エフェクター細胞へ提示される。中間の細胞種もまた関与する。適切な特異性を有するエフェクター細胞のみが増殖性の（productive）免疫応答において活性化される。アジュバントはまた抗原および同時に注入した他の因子を局所的に保持する。さらに、アジュバントは他の免疫細胞に対しては化学誘引物質として作用し、または免疫系に対して局所的小および／または全身的に刺激剤として作用する。

【0010】

A群連鎖球菌ワクチンを開発するアプローチは、主としてストレプトコッカス・ピオゲネスの細胞表面Mタンパク質に集中してきた {Bessen, D.ら、1988; Bronze, M.ら、1988}。ストレプトコッカス・ピオゲネスには80を超えるM血清型が存在し、新たな血清型が発見され続けていることから {Fischetti, V., 1989}、限られた数の血清型特異的なMタンパク質またはMタンパク質由来ペプチドの接種は他のすべてのM血清型に対する防御において有効でありそうにないであろう。さらに、Mタンパク質はヒト心臓組織と免疫学的に交差反応するアミノ酸配列を含んでいることが示されており、このことが心臓の弁の障害がリウマチ熱と関連することを説明すると考えられている {Fenderson, P.ら、1989}。

【0011】

ワクチン開発のために考慮されている他のタンパク質、たとえば、発赤毒素、ストレプトコッカス・ピオゲネスの体外毒素Aおよびストレプトコッカス・パラサンギスの体外毒素Bなどが存在する {Lee, P. K., 1989}。これら毒素に対する免疫は連鎖球菌の中毒性ショックの致命的な徴候を予防する可能性があるが、A群連鎖球菌のコロニー形成を防ぐ

ことはできない。

【0012】

上記に記載したタンパク質の潜在的なワクチンのための抗原として並びに幾つかのさらなる候補としての使用 {Ji, Y.ら、1997; Guzman, C.ら、1999} は、主として同定の容易さや利用できる機会に基づく選択の結果である。ストレプトコッカス・ピオゲネスの効果的で関連性のある抗原を同定することの必要性が存在する。

【0013】

本発明者らは、特定の病原体、とりわけスタフィロコッカス・アウレウス (*Staphylococcus aureus*) およびスタフィロコッカス・エピデルミディス (*Staphylococcus epidermidis*) からの高度免疫血清反応性抗原の同定、単離および製造方法を開発した (WO 02/059 148)。しかしながら、生物学的な特性、病原的機能および遺伝的背景の差異を考慮すると、ストレプトコッカス・ピオゲネスはスタフィロコッカス株とは区別される。重要なことに、ストレプトコッカス・ピオゲネスからの抗原の同定のための血清の選択はスタフィロコッカス・アウレウスのスクリーニングに適用されるものとは異なる。この目的のために3つの主要なタイプのヒト血清が回収された。第一に、好ましくは家庭に小さな子供のいる年齢が<45歳未満の健康な成人を、ストレプトコッカス・ピオゲネスの鼻咽頭での保菌について試験した。若い子供の相当の割合がストレプトコッカス・ピオゲネスの保菌者であり、その家族の成員の暴露源であると考えられた。相関的なデータに基づき、ストレプトコッカス・ピオゲネスの保菌者でない暴露個体 (家庭において高い保菌率を有する子供) に防御 (コロニー形成中和) 抗体が存在しそうである。関連性のある血清源について選択できるように、抗ストレプトコッカス・ピオゲネス Ig G および Ig A 抗体レベルを測定する一連の ELISA を細菌溶解液および培養上澄み液タンパク質で行った。高力価で非保菌者からの血清をゲノムベースの抗原同定に含めた。このヒト血清の選択アプローチは、保菌または非保菌状態が抗体レベルとは関係しないスタフィロコッカス・アウレウスに対して使用したアプローチとは基本的に非常に異なるものである。

【0014】

第二に、咽頭炎を罹患した患者からの血清試料を特徴付け、同じ仕方で選択した。連鎖球菌感染後の続発症 (急性のリウマチ熱や糸球体腎炎など) を罹患した個体から得た血清試料の第三の群は、主として確認の目的で使用した。この後者の群は、これらの患者において高レベルの抗体を誘発するエピトープを排除するのに助かる、というのは連鎖球菌感染後の疾患は GAS によって誘発される抗体と関係があり、心筋などのヒト組織に対して反応性であるか、または腎臓の糸球体に有害な免疫複合体を形成するのに関与しているからである。2つの細菌種、ストレプトコッカス・ピオゲネスおよびスタフィロコッカス・アウレウスのゲノムは、それ自体幾つかの重要な違いを示す。ストレプトコッカス・ピオゲネスのゲノムは約 1.85 Mb を含み、一方、スタフィロコッカス・アウレウスは 2.85 Mb を有する。これらは、それぞれ 38.5% および 33% の平均 GC 含量を有し、コードされた遺伝子の約 30~45% がこれら2つの病原体で一致していない。さらに、これら2つの細菌種は、増殖のために異なる増殖条件および培地を必要とする。ストレプトコッカス・ピオゲネスが厳格にヒトの病原体であるのに対して、スタフィロコッカス・アウレウスは一定の範囲の温血動物でも感染することを見出すことができる。これら2つの病原体によって蒙り得る最も重要な疾患の列举を以下に示す。スタフィロコッカス・アウレウスは主として院内日和見感染を引き起こす：インペチゴ、毛包炎、膿瘍、せつ、感染裂傷、心内膜炎、髄膜炎、化膿性関節炎、肺炎、骨髓炎、熱傷様皮膚症候群 (SSS)、中毒性ショック症候群。ストレプトコッカス・ピオゲネスは主として共同体獲得感染症 (community acquired infections) を引き起こす：連鎖球菌咽喉炎 (発熱、浸出性扁桃炎、咽頭炎)、連鎖球菌皮膚感染症、猩紅熱、産褥熱、敗血症、丹毒、肛門周辺蜂巣炎、乳様突起炎、中耳炎、肺炎、腹膜炎、創傷感染症、急性糸球体腎炎、急性リウマチ熱、中毒性ショック様症候群、壊死性筋膜炎。

【発明の概要】

【発明が解決しようとする課題】

【0015】

本発明の課題は、ストレプトコッカス・ピオゲネス感染に対するワクチンなどの医薬の開発のための手段を提供することであった。さらに詳細には、課題は、該医薬の製造に使用できるストレプトコッカス・ピオゲネスからの核酸分子または高度免疫血清反応性の抗原の有効で関連性があり、かつ包括的なセットを提供することであった。

【課題を解決するための手段】

【0016】

それゆえ、本発明は、

(a) 配列番号1、4-8、10-18、20、22、24-32、34-35、38-40、43-46、49-51、53-54、57-61、63、65-71、73、75-77、81-82、88、91-94および96-150から選ばれる核酸分子に対して少なくとも70%の配列同一性を有する核酸分子、 10

(b) (a)の核酸分子に相補的な核酸分子、

(c) (a)または(b)の核酸分子の少なくとも15の連続塩基を含む核酸分子、

(d) (a)、(b)または(c)の核酸分子にストリンジェントなハイブリダイゼーション条件下でアニールする核酸分子、

(e) 遺伝子コードの縮重を別として、(a)、(b)、(c)または(d)に定める核酸分子にハイブリダイズする核酸分子

よりなる群から選ばれた核酸配列を含む、高度免疫血清反応性の抗原またはその断片をコードする単離核酸分子を提供する。

【0017】

本発明の好ましい態様によれば、配列の同一性は少なくとも80%、好ましくは少なくとも95%、とりわけ100%である。 20

【0018】

さらに、本発明は、

(a) 配列番号64から選ばれる核酸分子に対して少なくとも96%の配列同一性を有する核酸分子、

(b) (a)の核酸分子に相補的な核酸分子、

(c) (a)または(b)の核酸分子の少なくとも15の連続塩基を含む核酸分子、

(d) (a)、(b)または(c)の核酸分子にストリンジェントなハイブリダイゼーション条件下でアニールする核酸分子、 30

(e) 遺伝子コードの縮重を別として、(a)、(b)、(c)または(d)に定める核酸分子にハイブリダイズする核酸分子

よりなる群から選ばれた核酸配列を含む、高度免疫血清反応性の抗原またはその断片をコードする単離核酸分子を提供する。

【0019】

他の側面において、本発明は、

(a) 配列番号3、36、47-48、55、62、72、80、84、95から選ばれる核酸分子、

(b) (a)の核酸分子に相補的な核酸分子、

(c) 遺伝子コードの縮重を別として、(a)、(b)、(c)または(d)に定める核酸分子にハイブリダイズする核酸分子 40

よりなる群から選ばれた核酸配列を含む単離核酸分子を提供する。

【0020】

好ましくは核酸分子はDNAまたはRNAである。

【0021】

本発明の好ましい態様によれば、核酸分子はゲノムDNA、とりわけストレプトコッカス・ピオゲネスのゲノムDNAから単離される。

【0022】

本発明に従い、本発明のいずれにもよる核酸分子を含むベクターが提供される。

【0023】

好ましい態様において、ベクターは本発明による核酸分子によってコードされる高度免 50

疫グロブリン血清反応性の抗原またはその断片の組換え発現用に適合される。

【0024】

本発明はまた、本発明によるベクターを含む宿主細胞をも提供する。

【0025】

さらなる側面に従い、本発明は、本発明による核酸分子によってコードされるアミノ酸配列を含む高度免疫血清反応性の抗原を提供する。

【0026】

好ましい態様において、アミノ酸配列（ポリペプチド）は、配列番号151、154-158、160-168、170、172、174-182、184-185、188-190、193-196、199-201、203-204、207-211、213、215-221、223、225-227、231-232、238、241-244および246-300よりなる群から選ばれる。 10

【0027】

他の好ましい態様において、アミノ酸配列（ポリペプチド）は、配列番号214よりなる群から選ばれる。

【0028】

さらに好ましい態様において、アミノ酸配列（ポリペプチド）は、配列番号153、186、197-198、205、212、222、230、234、245よりなる群から選ばれる。

【0029】

さらなる側面に従い、本発明は、表1の縦列「予測される免疫原性アミノ酸」および「同定された免疫原性領域の位置」のアミノ酸配列を含むペプチド；表2の血清反応性エピトープ、とりわけアミノ酸： 20

配列番号151の4-44、57-65、67-98、101-107、109-125、131-144、146-159、168-173、181-186、191-200、206-213、229-245、261-269、288-301、304-317、323-328、350-361、374-384、388-407、416-425および1-114；配列番号152の5-17、49-64、77-82、87-98、118-125、127-140、142-150、153-159、191-207、212-218、226-270、274-287、297-306、325-331、340-347、352-369、377-382、390-395および29-226；配列番号153の4-16、20-26、32-74、76-87、93-108、116-141、148-162、165-180、206-219、221-228、230-236、239-245、257-268、313-328、330-335、353-359、367-375、394-403、414-434、437-444、446-453、456-464、478-487、526-535、541-552、568-575、577-584、589-598、610-618、624-643、653-665、667-681、697-718、730-748、755-761、773-794、806-821、823-831、837-845、862-877、879-889、896-919、924-930、935-940、947-955、959-964、969-986、991-1002、1012-1036、1047-1056、1067-1073、1079-1085、1088-1111、1130-1135、1148-1164、1166-1173、1185-1192、1244-1254および919-929；配列番号154の5-44、62-74、78-83、99-105、107-113、124-134、161-174、176-194、203-211、216-237、241-247、253-266、272-299、323-349、353-360および145-305；配列番号155の15-39、52-61、72-81、92-97および71-81；配列番号156の13-19、21-31、40-108、115-122、125-140、158-180、187-203、210-223、235-245および173-186；配列番号157の5-12、19-27、29-39、59-67、71-78、80-88、92-104、107-124、129-142、158-168、185-191、218-226、230-243、256-267、272-277、283-291、307-325、331-344、346-352および316-331；配列番号158の6-28、43-53、60-76、93-103および21-99；配列番号159の10-30、120-126、145-151、159-169、174-182、191-196、201-206、214-220、222-232、254-272、292-307、313-323、332-353、361-369、389-396、401-415、428-439、465-481、510-517、560-568および9-26；配列番号160の5-29、39-45、107-128および1-112；配列番号161の4-38、42-50、54-60、65-71、91-102および21-56；配列番号162の4-13、19-25、41-51、54-62、68-75、79-89、109-122、130-136、172-189、192-198、217-224、262-268、270-276、281-298、315-324、333-342、353-370、376-391および23-39；配列番号163の6-41、49-58、62-103、117-124、147-166、173-194、204-211、221-229、255-261、269-284、288-310、319-325、348-380、383-389、402-410、424-443、467-479、496-517、535-553、555-565、574-581、583-591および474-489；配列番号164の8-35、52-57、66-73、81-88、108-114、125-131、160-167、174-180、230-235、237-249、254-262、278-285、308-314、321-326、344-353、358-37 30 40 50

2, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864および37-241, 409-534, 582-604, 743-804; 配列番号165の4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416および202-337; 配列番号166の4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407および1-48; 配列番号167の18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297および203-217; 配列番号168の20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521および261-273; 配列番号169の6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641および1-414, 443-614, 997-1392; 配列番号170の14-42, 70-75, 90-100, 158-181および1-164; 配列番号171の4-21, 30-36, 54-82, 89-97, 105-118, 138-147および126-207; 配列番号172の4-21, 31-66, 96-104, 106-113, 131-142および180-204; 配列番号173の5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386および11-197, 204-219, 258-372; 配列番号174の4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322および195-289; 配列番号175の4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329および12-130; 配列番号176の10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707および434-444; 配列番号177の6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430および360-375; 配列番号178の4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251および254-260; 配列番号179の12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400および369-382; 配列番号180の11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487および270-312; 配列番号181の5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604および486-598; 配列番号182の4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374および378-396; 配列番号183の5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184および75-235; 配列番号184の6-23, 47-53, 57-63, 75-82,

97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310および30-51; 配列番号185の17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647および208-219; 配列番号186の4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039および396-533, 1342-1502, 1672-1920; 配列番号187の4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905および1-113, 210-232, 250-423, 536-564; 配列番号188の4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201および617-635; 配列番号189の7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244および190-203; 配列番号190の4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574および385-398; 配列番号191の5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003および12-190, 276-283, 666-806; 配列番号192の4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664および30-80, 89-105, 111-151; 配列番号193の7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259および195-203; 配列番号194の5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426および32-50; 配列番号195の8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174および75-90; 配列番号196の4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233および69-88; 配列番号197の4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802および96-230, 361-491, 572-585; 配列番号198の4-12, 21-36, 48-55, 74-82, 121-1

27, 195-203, 207-228, 247-262, 269-278, 280-289および102-210; 配列番号199の13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313および240-248; 配列番号200の5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260および182-198; 配列番号201の10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504および41-56; 配列番号202の5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333および202-217; 配列番号203の6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283および1-127; 配列番号204の4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718および297-458; 配列番号205の5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213および24-135; 配列番号206の4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721および176-330; 配列番号207の31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472および46-62, 296-341; 配列番号208の23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716および667-684; 配列番号209の20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869および258-416; 配列番号210の7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300および278-295; 配列番号211の4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191および183-195; 配列番号212の12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241および63-238; 配列番号213の4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308および1-141; 配列番号214の11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379および231-368; 配列番号215の9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342および247-260; 配列番号216の7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279および64-72; 配列番号217の4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897および222-362, 756-896; 配列番号218の11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255および153-170; 配列番号219の4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212および56-73; 配列番号220の4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334および298-312; 配列番号221の7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219

-238, 247-254および141-157; 配列番号222の23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663および433-440, 572-593; 配列番号223の4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267および17-319, 417-563; 配列番号224の6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500および46-187; 配列番号225の4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992および21-244, 381-499, 818-959; 配列番号226の19-29, 65-75, 90-109, 111-137, 155-165, 169-175および118-136; 配列番号227の15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465および147-155; 配列番号228の11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161および74-438; 配列番号229の4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413および156-420; 配列番号230の4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343および79-348; 配列番号231の12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168および53-70; 配列番号232の4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522および183-341; 配列番号233の4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822および92-231, 618-757; 配列番号234の11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372および41-170; 配列番号235の6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174および20-487, 757-1153; 配列番号236の10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305および26-74, 91-100, 105-303; 配列番号237の9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480および10-223

, 231-251, 264-297, 312-336; 配列番号238の5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537および22-344; 配列番号239の5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395および1-151;

配列番号240の6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756および91-263; 配列番号241の4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775および261-272; 配列番号242の4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701および541-551; 配列番号243の6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252および84-254; 配列番号244の13-30, 71-120, 125-137, 139-145, 184-199および61-78; 配列番号245の9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855および568-580; 配列番号246の11-21, 29-38および5-17; 配列番号247の2-9; 配列番号248の4-10, 16-28および7-18, 26-34; 配列番号249の10-16および1-15; 配列番号250の4-11; 配列番号251の4-40, 42-51および37-53; 配列番号252の4-21および22-29; 配列番号253の2-11; 配列番号254の9-17, 32-44および1-22; 配列番号255の19-25, 27-32および15-34; 配列番号256の4-12, 15-22および11-33; 配列番号257の10-17, 24-30, 39-46, 51-70および51-61; 配列番号258の6-19; 配列番号259の6-11, 21-27, 31-54および11-29; 配列番号260の4-10, 13-45および11-35; 配列番号261の4-14, 23-32および11-35; 配列番号262の14-39, 45-51および15-29; 配列番号263の4-11, 14-28および4-17; 配列番号264の4-16および2-16; 配列番号265の4-10, 12-19, 39-50および6-22; 配列番号266の2-13; 配列番号267の4-11, 22-65および3-19; 配列番号268の17-23, 30-35, 39-46, 57-62および30-49; 配列番号269の4-19および14-22; 配列番号270の2-9; 配列番号271の7-18, 30-43および4-12; 配列番号272の4-30, 39-47および5-22; 配列番号273の6-15および14-29; 配列番号274の4-34および23-35; 配列番号275の4-36, 44-57, 65-72および14-27; 配列番号276の4-18および11-20; 配列番号277の5-19; 配列番号278の18-36および6-20; 配列番号279の4-10, 19-34, 41-84, 96-104および50-63; 配列番号280の4-9, 19-27および8-21; 配列番号281の4-16, 18-28および22-30; 配列番号282の4-15および21-35; 配列番号283の4-17および3-13; 配列番号284の4-12および4-18; 配列番号285の4-24, 31-36および29-45; 配列番号286の12-22, 34-49および21-32; 配列番号287の4-17および22-32; 配列番号288の4-16, 25-42および7-28; 配列番号289の4-10および7-20; 配列番号290の4-11, 16-36, 39-54および28-44; 配列番号291の5-20, 29-54および14-29; 配列番号292の24-33および10-22; 配列番号293の10-51, 54-61および43-64; 配列番号294の7-1および2-17;

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配列番号295の11-20および6-20; 配列番号296の4-30, 34-41および19-28; 配列番号297の11-21; 配列番号298の4-16, 21-26および9-38; 配列番号299の4-12, 15-27, 30-42, 66-72および10-24; 配列番号300の8-17および11-20; および配列番号246の2-19; 配列番号247の1-12; 配列番号248の21-38; 配列番号254の2-22; 配列番号255の15-33; 配列番号256の11-32; 配列番号259の11-28; 配列番号260の10-27; 配列番号261の9-26; 配列番号263の4-16; 配列番号266の1-18; 配列番号273の12-29; 配列番号276の6-23; 配列番号277の1-21; 配列番号279の47-64; 配列番号285の28-45; 配列番号287の18-35; 配列番号291の14-31; 配列番号292の7-24; 配列番号299の8-25; 配列番号300の1-20; 配列番号151の18-33; 配列番号151の62-72; 配列番号152の118-131; 配列番号154の195-220; 配列番号154の215-240; 配列番号154の255-280, 配列番号155の72-81; 配列番号156の174-186; 配列番号157の317-331; 配列番号158の35-59; 配列番号158の54-84; 配列番号158の79-104; 配列番号159の33-58; 配列番号159の81-101; 配列番号159の136-150; 配列番号159の173-186; 配列番号159の231-251; 配列番号161の22-48; 配列番号162の24-39; 配列番号163の475-489; 配列番号164の38-56; 配列番号164の583-604; 配列番号165の202-223; 配列番号165の222-247; 配列番号165の242-267; 配列番号165の262-287; 配列番号165の282-307; 配列番号165の302-327; 配列番号166の25-48; 配列番号167の204-217; 配列番号168の259-276; 配列番号169の121-139; 配列番号169の260-267; 配列番号169の215-240; 配列番号170の115-140; 配列番号172の182-204; 配列番号173の144-153; 配列番号173の205-219; 配列番号174の196-206; 配列番号174の240-249; 配列番号174の272-287; 配列番号174の199-223; 配列番号174の218-237; 配列番号175の226-249; 配列番号175の287-306; 配列番号176の430-449; 配列番号177の361-375; 配列番号178の241-260; 配列番号181の483-502; 配列番号182の379-396; 配列番号184の31-51; 配列番号186の1436-1460; 配列番号186の1455-1474; 配列番号186の1469-1487; 配列番号187の215-229; 配列番号187の534-561; 配列番号187の59-84; 配列番号187の79-104; 配列番号188の618-635; 配列番号189の191-203; 配列番号190の386-398; 配列番号191の65-83; 配列番号192の90-105; 配列番号192の112-136; 配列番号193の290-209; 配列番号194の33-50; 配列番号195の76-90; 配列番号196の70-88; 配列番号197の418-442; 配列番号197の574-585; 配列番号198の87-104; 配列番号198の124-148; 配列番号198の141-152; 配列番号199の241-248; 配列番号200の183-198; 配列番号201の40-57; 配列番号202の202-217; 配列番号203の50-74; 配列番号203の69-93; 配列番号203の88-112; 配列番号203の107-127; 配列番号205の74-92; 配列番号206の207-232; 配列番号206の227-252; 配列番号206の247-272; 配列番号207の47-60; 配列番号207の297-305; 配列番号207の312-337; 配列番号208の667-384; 配列番号210の279-295; 配列番号211の179-198; 配列番号213の27-51; 配列番号213の46-70; 配列番号213の65-89; 配列番号213の84-108; 配列番号213の112-141; 配列番号215の248-260; 配列番号216の59-78; 配列番号218の154-170; 配列番号219の57-73; 配列番号220の297-314; 配列番号221の142-157; 配列番号222の428-447; 配列番号222の573-593; 配列番号223の523-544; 配列番号223の46-70; 配列番号223の65-89; 配列番号223の84-108; 配列番号223の122-151; 配列番号224の123-142; 配列番号225の903-921; 配列番号226の119-136; 配列番号227の142-161; 配列番号228の258-277; 配列番号228の272-300; 配列番号228の295-322; 配列番号229の311-343; 配列番号229の278-304; 配列番号230の131-150; 配列番号230の195-218; 配列番号231の53-70; 配列番号232の184-208; 配列番号232の222-246; 配列番号232の241-265; 配列番号232の260-284; 配列番号232の279-303; 配列番号232の317-341; 配列番号233の678-696; 配列番号235の88-114; 配列番号235の464-481; 配列番号236の153-172; 配列番号236の137-155, 166-184; 配列番号236の215-228; 配列番号237の37-51; 配列番号237の53-75; 配列番号237の232-251; 配列番号237の318-336; 配列番号238の305-315; 配列番号238の131-156; 配列番号241の258-275; 配列番号243の107-137; 配列番号243の138-162; 配列番号243の157-181; 配列番号243の195-227; 配列番号244の62-78; 配列番号245の567-584を含むペプチドよりなる群から選ばれた高度免疫血清反応性の抗原の断片を提供する。

【0030】

本発明はまた、本発明による1またはそれ以上の核酸分子を適当な発現系で発現させることを含む、本発明によるストレプトコッカス・ピオゲネスの高度免疫血清反応性の抗原またはその断片の製造方法をも提供する。

【0031】

さらに、本発明はまた、本発明によるベクターで適当な宿主細胞を形質転換またはトランスフェクションすることを含む、本発明によるストレプトコッカス・ピオゲネスの高度免疫血清反応性の抗原またはその断片を発現する細胞の製造方法を提供する。

【0032】

本発明に従い、本発明で定義される高度免疫血清反応性の抗原またはその断片または本発明で定義される核酸分子を含む医薬組成物、とりわけワクチンが提供される。

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【0033】

好ましい態様において、医薬組成物はさらに、ポリカチオン性ポリマー、とりわけポリカチオン性ペプチド、免疫促進デオキシヌクレオチド(ODN)、少なくとも2つのLysLeuLysモチーフを含むペプチド、とりわけKLKL5KLK、神経刺激性の化合物、とりわけヒト成長ホルモン、ミョウバン、フロイントの完全または不完全アジュバントまたはこれらの組合せよりなる群から好ましくは選ばれる免疫促進物質をさらに含む。

【0034】

さらに好ましい態様において、免疫促進物質は、ポリカチオン性ポリマーと免疫促進デオキシヌクレオチドとの組合せか、または少なくとも2つのLysLeuLysモチーフを含むペプチドと免疫促進デオキシヌクレオチドとの組合せである。

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【0035】

さらに一層好ましい態様において、ポリカチオン性ポリマーはポリカチオン性ペプチド、とりわけポリアルギニンである。

【0036】

本発明によれば、医薬製剤の製造のための、とりわけストレプトコッカス・ピオゲネス感染に対するワクチンの製造のための、本発明による核酸分子または本発明による高度免疫血清反応性の抗原またはその断片の使用が提供される。

【0037】

また、本発明による高度免疫血清反応性の抗原またはその断片の少なくとも選択された部分に結合する抗体、または少なくとも有効なその部分が本発明により提供される。

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【0038】

好ましい態様において、抗体はモノクローナル抗体である。

【0039】

他の好ましい態様において、抗体の有効な部分はFabフラグメントを含む。

【0040】

さらに好ましい態様において、抗体はキメラ抗体である。

【0041】

さらに好ましい態様において、抗体はヒト化抗体である。

【0042】

本発明はまた、本発明による抗体を産生するハイブリドーマ細胞株をも提供する。

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【0043】

さらに、本発明は、以下の工程を特徴とする本発明による抗体の製造方法を提供する：
・本発明により定められる高度免疫血清反応性の抗原またはその断片を非ヒト動物に投与することにより該動物において免疫応答を開始させ、
・該動物から抗体含有体液を取り出し、ついで
・該抗体含有体液をさらなる精製工程に供することにより該抗体を製造する。

【0044】

従って、本発明は、以下の工程を特徴とする本発明による抗体の製造方法を提供する：
・本発明により定められる高度免疫血清反応性の抗原またはその断片を非ヒト動物に投与することにより該動物において免疫応答を開始させ、

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- ・該動物から脾臓または脾細胞を取り出し、
- ・該脾臓または脾細胞のハイブリドーマ細胞を産生させ、
- ・該高度免疫血清反応性の抗原またはその断片に特異的なハイブリドーマ細胞を選択およびクローニングし、
- ・該クローニングしたハイブリドーマ細胞の培養により抗体を産生させ、および任意にさらなる精製工程を行う。

【0045】

上記方法に従って提供されまたは製造される抗体は、ストレプトコッカス・ピオゲネス感染の治療のための医薬の調製に用いることができる。

【0046】

他の側面によれば、本発明は、本発明による高度免疫血清反応性の抗原またはその断片に結合するアンタゴニストを提供する。

【0047】

そのような本発明による高度免疫血清反応性の抗原またはその断片に結合しうるアンタゴニストは、以下の工程を含む方法により同定することができる：

(a) 本発明による単離したまたは固定化した高度免疫血清反応性の抗原またはその断片を候補アンタゴニストと、該候補アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合に応答して検出可能なシグナルを提供することのできる成分の存在下、該候補アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合を可能にする条件下で接触させ、ついで

(b) 該アンタゴニストの該高度免疫血清反応性の抗原またはその断片への結合に応答して生成されるシグナルの存在または不在を検出する。

【0048】

本発明による高度免疫血清反応性の抗原またはその断片のその相互作用パートナーへの相互作用活性を低減または抑制しうるアンタゴニストは、以下の工程を含む方法により同定することができる：

- (a) 本発明による高度免疫血清反応性の抗原またはその高度免疫血清断片を用意し、
- (b) 該高度免疫血清反応性の抗原またはその断片に対する相互作用パートナー、とりわけ本発明による抗体を用意し、
- (c) 該高度免疫血清反応性の抗原またはその断片を該相互作用パートナーと相互作用させて相互作用複合体を生成させ、
- (d) 候補アンタゴニストを用意し、
- (e) 該候補アンタゴニストと該相互作用複合体との間で競合反応を起こさせ、
- (f) 該候補アンタゴニストが該高度免疫血清反応性の抗原またはその断片と該相互作用パートナーとの相互作用活性を低減または抑制するか否かを決定する。

【0049】

本発明による高度免疫血清反応性の抗原またはその断片は、該本発明による高度免疫血清反応性の抗原またはその断片の相互作用パートナーの単離および／または精製および／または同定に用いることができる。

【0050】

本発明はまた、本発明による高度免疫血清反応性の抗原またはその断片の発現に関連する疾患をインビトロで診断する方法であって、本発明による該高度免疫血清反応性の抗原および断片をコードする核酸配列の存在または本発明による高度免疫血清反応性の抗原またはその断片の存在を検出することを含む方法をも提供する。

【0051】

本発明はまた、細菌感染、とりわけストレプトコッカス・ピオゲネス感染をインビトロで診断する方法であって、本発明による該高度免疫血清反応性の抗原および断片をコードする核酸配列の存在または本発明による高度免疫血清反応性の抗原またはその断片の存在を検出することを含む方法をも提供する。

【0052】

さらに、本発明は、本発明による高度免疫血清反応性の抗原またはその断片へのペプチド結合を生成するための該高度免疫血清反応性の抗原またはその断片の使用を提供し、その際、該ペプチドはアンチカリン (anticaline) である。

【0053】

本発明はまた、機能性の核酸を製造するための本発明による高度免疫血清反応性の抗原またはその断片の使用を提供し、その際、該機能性核酸はアプタマーおよびシュピーゲルマー (spiegelmers) よりなる群から選ばれる。

【0054】

本発明による核酸分子はまた、機能性のリボ核酸分子の製造に使用することができ、その際、該機能性のリボ核酸は、リボザイム、アンチセンス核酸および siRNA よりなる群から選ばれる。

【0055】

本発明は有利にも、複数のヒト血漿プールおよびストレプトコッカス・ピオゲネスのゲノムに由来する表面発現ライブラリーからの抗体調製物を用いてストレプトコッカス・ピオゲネスから同定した、単離した核酸分子およびそれによってコードされる高度免疫血清反応性の抗原およびその断片の有効に関連性があり、かつ包括的なセットを提供する。それゆえ、本発明は、ストレプトコッカス・ピオゲネス感染に対して有効な抗体の調製およびストレプトコッカス・ピオゲネス感染に対して有効な化合物の同定の手順に有用なストレプトコッカス・ピオゲネス抗原、ワクチン、診断薬および製品という広く切望された必要性を達成するものである。

【0056】

有効なワクチンは、すべての株で発現され、ストレプトコッカス・ピオゲネスの細胞表面成分に対する高親和性で豊富な抗体を誘発することのできるタンパク質またはポリペプチドから構成されていなければならない。抗体は、オプソニン作用のために IgG1 および／または IgG3、および付着の中和および毒性作用のためにいずれの IgG サブタイプおよび IgA でなければならない。化学的に定められたワクチンは全細胞ワクチン (弱毒化または死菌) に比べて明らかに優れているに違いない、なぜならヒト組織と交差反応したりオプソニン作用を抑制するストレプトコッカス・ピオゲネスの成分 {Whitnack, E. ら、1985} は排除することができ、防御抗体および／または防御免疫応答を誘発する個体タンパク質を選択することができるからである。

【0057】

本発明で用いたアプローチは、A 群連鎖球菌タンパク質またはペプチドとヒト血清中に存在する抗体との相互作用に基づいている。ヒト免疫系によってストレプトコッカス・ピオゲネスに対して産生されヒト血清中に存在する抗体は、抗原タンパク質のインビボ発現およびその免疫原性を示している。さらに、前もって選択した血清のプールを用いて細菌表面ディスプレイ発現ライブラリーによって同定される抗原タンパク質は、第二または第三のスクリーニングにおいて個々の選択したまたは生成した血清によりプロセッシングを受ける。それゆえ、本発明は、医薬組成物として、とりわけストレプトコッカス・ピオゲネスによる感染を予防するワクチンとしての有効に関連性があり、かつ包括的な A 群連鎖球菌抗原のセットを提供する。

【0058】

本発明による包括的な抗原のセットを同定するための抗原同定プログラムでは、少なくとも 2 つの異なる細菌表面発現ライブラリーを幾つかの血清プールまたは血漿画分または他のプールした抗体含有体液 (抗体プール) を用いてスクリーニングする。抗体プールは、ストレプトコッカス・ピオゲネスの抗原性化合物について試験した血清回収物、たとえば全細胞抽出物および培養上澄みタンパク質に由来する。好ましくは、2 つの別個の血清回収物を使用する：1. 非常に安定な抗体レパートリー：非保菌者で以前の遭遇を克服したかまたは急性の疾患または徴候を示すことのないストレプトコッカス・ピオゲネスの現在の保菌者である正常な成人、臨床的に健康な人々、2. 病原微生物の存在によって急性に誘発された抗体：種々の徴候の急性疾患 (たとえば、ストレプトコッカス・ピオゲネス

咽頭炎、創傷感染および菌血症）を罹患した患者。血清は、高度免疫性であるとされ、それゆえ本発明に適用されるスクリーニング法において関連性があるとされるために、複数のA群連鎖球菌特異的抗原と反応することができなければならない。ヒト免疫系によって連鎖球菌に対して産生されヒト血清中に存在する抗体は、抗原タンパク質のインビボ発現およびその免疫原性を示すものである。

【0059】

本発明に用いる発現ライブラリーは、すべての可能な抗原、たとえばストレプトコッカス・ピオゲネスのすべての表面タンパク質に由来する抗原の発現を可能にするものでなければならない。細菌表面ディスプレイライブラリーは、細菌宿主膜 {Georgiou, G., 1997; Etz, H.ら、2001} で幾つかの選択した外膜タンパク質 (LamB、BtuB、FhuA) 上のA群連鎖球菌の発現されたペプチド配列の (全) セットを提示する細菌宿主の組換えライブラリーにより表されるであろう。組換え発現ライブラリーを用いる利点の一つは、同定した高度免疫血清反応性の抗原がさらなる組換えDNA法やクローニング工程を必要とすることなく該高度免疫血清反応性の抗原を発現するスクリーニングおよび選択したクローンのコード配列の発現によって即時に産生できることである。

【0060】

本発明により記載したプログラムによって同定した抗原の包括的なセットは、1またはそれ以上のスクリーニングによりさらに分析される。それゆえ、免疫性であるとして同定した選択したペプチドに対して生成させた個体抗体調製物または抗体を用いる。好ましい態様によれば、2回目のスクリーニングのための個体抗体調製物は、A群連鎖球菌の急性感染を罹患した患者、とりわけ一定の最小レベルを超える抗体力価、たとえば試験したヒト (患者または健康な個体) 血清の80百分順位よりも高い、好ましくは90百分順位よりも高い、とりわけ95百分順位よりも高い抗体力価を示す患者から得る。そのような高力価の個体抗体調製物を2回目のスクリーニングに用いることにより、ストレプトコッカス・ピオゲネスからの高度免疫血清反応性の抗原およびその断片の非常に選択的な同定が可能となる。

【0061】

高処理量のスクリーニング手順の後、組換えタンパク質としてまたは原核生物発現系で発現することのできない場合にインビトロで翻訳した生成物として発現された選択した抗原タンパク質、または同定した抗原ペプチド (合成により製造) を、大きな血清コレクション (>100非感染、>50患者血清) を用いて免疫原性の評価のための一連のELISAおよびウエスタンブロッティングアッセイによる2回目のスクリーニングで試験する。

【0062】

個体抗体調製物 (選択した血清であってもよい) は、最初のスクリーニングからすべての期待のもてる候補からの高度免疫血清反応性の抗原の選択的な同定を可能にすることが重要である。それゆえ、好ましくは少なくとも10の個体抗体調製物 (すなわち、選択した病原体感染を罹患した少なくとも10人の異なる個体からの抗体調製物 (たとえば、血清)) をこれらの抗原を2回目のスクリーニングで同定するのに用いるべきである。もちろん、10未満の個体調製物を用いることも可能であるが、少ない数の個体抗体調製物では工程の選択性は最適ではない。一方、所定の高度免疫血清反応性の抗原 (または抗原性のその断片) が少なくとも10の個体抗体調製物、好ましくは少なくとも30、とりわけ少なくとも50の個体抗体調製物により認識されるなら、高度免疫血清反応性の抗原はまた適切な同定に充分選択的である。高度免疫血清反応性の抗原は、もちろん、できるだけ多くの個体調製物で試験することができる (たとえば、100を超える、あるいは1,000を超える)。

【0063】

それゆえ、本発明の方法による高度免疫血清反応性の抗体調製物の関連する部分は、好ましくは少なくとも10、さらに好ましくは少なくとも30、とりわけ少なくとも50の個体抗体調製物でなければならない。あるいは (または組み合わせて)、高度免疫血清反

応性の抗原はまた2回目のスクリーニングに用いたすべての個体抗体調製物の少なくとも20%、好ましくは少なくとも30%、とりわけ少なくとも40%で同定されてよい。

【0064】

本発明の好ましい態様によれば、2回目のスクリーニングのための個体抗体調製物を調製する（または抗体調製物として用いる）血清は、ストレプトコッカス・ピオゲネス（たとえば、溶解液、細胞壁成分および組換えタンパク質などのこの病原体の調製物）に対するその力価により選択される。好ましくは、病原体の全体（全溶解液または全菌体）を抗原としてELISAに用いる場合には、4,000Uを超える、とりわけ6,000Uを超える全IgA力価、および／または10,000Uを超える、とりわけ12,000U（U＝単位、所定の希釈で読みとったOD_{405nm}から計算）を超えるIgG力価であるものは選択される。

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【0065】

連鎖球菌に対してヒト免疫系によって産生されヒト血清中に存在する抗体は、抗原タンパク質のインビボ発現およびその免疫原性を示すものである。抗体による線状エピトープの認識は、4～5アミノ酸の短い配列に基づくことができる。もちろん、これらの短いペプチドが所定の抗体をインビボで誘発しうることを必ずしも意味するものではない。この理由から、定められたペプチド、ポリペプチドおよびタンパク質は、それが選択されたタンパク質に対する抗体をインビボで誘発する能力について動物（主としてマウス）でさらに試験される。

【0066】

好ましい抗原は細胞表面に位置するかまたは分泌され、それゆえ細胞外で接近できるものである。細胞壁タンパク質に対する抗体は2つの目的を果たす：すなわち、接着の抑制および食作用の促進。分泌タンパク質に対する抗体は、毒素またはビルレント成分としての該タンパク質の機能の中和において有益である。細菌が分泌タンパク質を介して相互に情報伝達することも知られている。これらタンパク質に対する中和抗体は、連鎖球菌種間または連鎖球菌種内での増殖促進クロストーク（cross-talk）を妨害するであろう。バイオインフォーマティクス分析（シグナル配列、細胞壁局在シグナル、膜貫通ドメイン）は、細胞表面の局在または分泌を評価するうえで有用であることがわかっている。実験アプローチとしては、対応ペプチドおよびタンパク質を用いたヒト血清からの抗体の単離、および細菌表面ディスプレイスクリーニングにより選択した（ポリ）ペプチドに対する免疫血清のマウスでの生成が挙げられる。ついで、これら血清を以下のアッセイにおいて試薬として3回目のスクリーニングに用いる：異なる条件下で増殖させたA群連鎖球菌の細胞表面染色（FACS、顕微鏡）、中和能（毒素、接着）の決定、およびオプソニン作用および食作用の促進（インビトロ食作用アッセイ）。

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【0067】

この目的のため、細菌の大腸菌クローンを直接マウスに注射し、免疫血清を採取し、機能的なオプソニン性抗体または中和抗体について関連するインビトロアッセイで試験する。別法として、ペプチドまたはタンパク質を基質として用いて特異的な抗体をヒトまたはマウス血清から精製することができる。

【0068】

ストレプトコッカス・ピオゲネスに対する宿主防禦は、主として生得の免疫機構に依存している。ワクチン接種によりオプソニン性および中和型の高親和性抗体を誘発させることは、生得の免疫系が細菌および毒素を排除するのを助ける。このことは、本発明による方法をA群連鎖球菌抗原タンパク質の同定のための最適の手段にしている。

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【0069】

皮膚および粘膜は連鎖球菌の侵入に対する優れた障壁である。しかしながら、一旦皮膚または粘膜が破られると、非獲得細胞性防禦の最初のラインが補体および食細胞、とりわけ多形核白血球（PMN）を介した協同作用を開始する。これら細胞は侵入する細菌を排除するうえでの基礎とみなすことができる。連鎖球菌は主として細胞外性の病原体であり、主要な抗連鎖球菌獲得応答は免疫系の体液部門から生じ、3つの主要な機構により媒体

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される：すなわち、オプソニン作用の促進、毒素の中和、および接着の抑制。オプソニン作用は、それが有効な食作用に必要であるゆえに特に重要であると考えられている。有効なオプソニン作用のためには、IgG分子のFcフラグメントまたは活性化C3bに対するレセプターを介してPMNによって認識されるように微生物の表面は抗体および補体因子で覆われなければならない。オプソニン作用の後、連鎖球菌は食作用を受け、殺菌される。細菌の細胞表面上の特異的な抗原に結合した抗体は、PMNに付着するためのおよび食作用を促進するためのリガンドとして働く。アドヒージョンおよび他の細胞表面タンパク質に結合した正に同じ抗体は、接着を中和し、コロニー形成を防ぐことが予期される。それゆえ、本発明により提供されるような抗原の選択は、動物モデルまたはヒトにおける感染に対する防禦に導くであろうものを同定するのに極めて適している。

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【0070】

本明細書で使用する本発明による抗原同定法によれば、以下に記載するように、本発明は驚くべきことに、とりわけストレプトコッカス・ピオゲネスの包括的な新規な核酸および新規な高度免疫血清反応性の抗原およびその断片のセットを提供することができる。一つの側面によれば、本発明はとりわけ、配列番号1-150に示す配列である高度免疫血清反応性の抗原をコードするヌクレオチド配列に関し、高度免疫血清反応性の抗原を表す対応のコードされたアミノ酸配列は配列番号151-300に示してある。

【0071】

本発明の好ましい態様によれば、配列番号1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94および96-150に示すヌクレオチド配列に対してその全長にわたって70%の同一性を示す核酸分子が提供される。最も極めて好ましいのは、配列番号1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94および96-150に示す核酸分子に対してその全長にわたって少なくとも80%または少なくとも85%同一である領域を含む核酸である。この点、同分子に対してその全長にわたって少なくとも90%, 91%, 92%, 93%, 94%, 95%または96%同一である核酸分子が特に好ましい。さらに、少なくとも97%同一であるものが非常に好ましく、少なくとも98%および少なくとも99%同一であるものが特に非常に好ましく、少なくとも99%または99.5%同一であるものがさらに好ましく、100%同一性がとりわけ好ましい。さらに、この側面で好ましい態様は、配列番号1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94および96-150に示す核酸によってコードされる成熟ポリペプチドと実質的に同じ生物学的機能または活性を保持している高度免疫血清反応性の抗原またはその断片（ポリペプチド）をコードする核酸である。

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【0072】

同一性とは、当該技術分野で知られ本明細書で使用するように、配列同士を比較することによって決定される、2またはそれ以上のポリペプチド配列間または2またはそれ以上のポリヌクレオチド配列間の関係である。当該技術分野において、同一性はまた、場合に依りてポリペプチドまたはポリヌクレオチド配列の鎖のマッチングによって決定される、そのような配列間での配列の関連性の度合いをも意味する。同一性は容易に計算することができる。2つのポリヌクレオチドまたは2つのポリペプチド配列間の同一性を測定する多くの方法が存在するが、この語は当業者にはよく知られている（たとえば、Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987）。同一性を決定する好ましい方法は、試験する配列間で最大のマッチングが得られるようにデザインされている。同一性を決定する方法はコンピュータープログラムにコーディングされている。2つの配列間の同一性を決定する好ましいコンピュータープログラム法としては、これらに限られるものではないが、GCGプログラムパッケージ {Devereux, J.ら、1984}、BLASTP、BLASTNおよびFASTA {Altschul, S.ら、1990} が挙げられる。

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【0073】

本発明の他の側面によれば、配列番号64に示す核酸配列に対して少なくとも96%の同一性を示す核酸分子が提供される。

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【0074】

本発明のさらなる側面によれば、配列番号3, 36, 47-48, 55, 62, 72, 80, 84, 95に示す核酸配列と同一の核酸分子が提供される。

【0075】

本発明による核酸分子はまた、第二の選択肢として、上記第一の選択肢として記載した核酸に少なくとも本質的に相補的な核酸分子であってもよい。本明細書において相補的とは、ある核酸鎖が第二の核酸鎖とワトソン-クリック型塩基対形成により塩基対を形成することを意味する。本明細書において本質的に相補的とは、塩基対が各鎖の塩基の全部では起こらず、あるパーセントの塩基が塩基対を形成しないかまたは間違った塩基対形成をするものを意味する。正しく塩基対形成するパーセントは、好ましくは少なくとも70%、さらに好ましくは80%、さらに一層好ましくは90%であり、最も好ましくは90%よりも高いいずれかのパーセントである。70%マッチング塩基のパーセントはホモロジーとして考えられ、この程度のマッチング塩基対を有するハイブリダイゼーションはストリンジェントであると考えられることに注意すべきである。この種のストリンジェントなハイブリダイゼーションのためのハイブリダイゼーション条件は、Current Protocols in Molecular Biology (John Wiley and Sons, Inc., 1987) から採用することができる。さらに詳細には、ハイブリダイゼーション条件は以下のとおりであってよい：

- ・ハイブリダイゼーションを、たとえば5xSSPE、5xデンハルト試薬、0.1%SDS、100g/mLの開裂DNA中、68℃で行う
- ・0.2xSSC、0.1%SDS中、42℃で中くらいのストリンジェンシーの洗浄を行う
- ・0.1xSSC、0.1%SDS中、68℃で高ストリンジェンシーの洗浄を行う

【0076】

GC含量が50%のゲノムDNAは約96℃の T_M を有する。1%のミスマッチのためには、 T_M を約1℃下げる。

【0077】

さらに、本明細書に記載するさらなるハイブリダイゼーション条件のいずれも原則として適用することができる。

【0078】

もちろん、本発明によって同定されるポリペプチド分子と同じポリペプチド分子をコードするすべての核酸配列分子が所期のコード配列の開示によって包含される、というのは遺伝コードの縮重は、そのような縮重核酸分子の数が大きい場合であっても所期のポリペプチド分子をコードするすべての可能な核酸分子を明白に決定するのに直接適用されるからである。このことはまた、所期のポリペプチドの断片がワクチン接種に関連して、たとえば能動または受動免疫として使用するのに適したポリペプチドをコードする限りにおいて、かかる断片にも当てはまる。

【0079】

本発明による核酸分子はまた、第三の選択肢として、上記で概説した本発明による核酸分子の第一および第二の選択肢による核酸分子の少なくとも15塩基の連なりを含む核酸であってもよい。好ましくは、これら塩基は塩基の隣接した連なりを形成する。しかしながら、該連なりが幾つかの塩基によって分断された2またはそれ以上の部分からなることも本発明の範囲に包含される。

【0080】

本発明による核酸分子はまた、第四の選択肢として、上記で概説した第一、第二、および第三の選択肢による本発明の核酸のいずれかとストリンジェントなハイブリダイゼーション条件下でアニールする核酸分子であってもよい。ストリンジェントなハイブリダイゼーション条件は典型的には本明細書に記載するものである。

【0081】

最後に、本発明による核酸分子はまた、第五の選択肢として、遺伝子コードの縮重を別として上記で概説した第一、第二、第三、および第四の選択肢による本発明のいずれかの核酸分子による核酸分子のいずれかとハイブリダイズする核酸分子であってもよい。この

種の核酸分子は、本発明による核酸分子が本発明による高度免疫血清反応性の抗原またはその断片をコードしているのが好ましいという事実と関連している。この種の核酸分子は、本発明による核酸分子の検出、それゆえストレプトコッカス・ピオゲネスなどの各微生物およびこの種の微生物が関係する疾患または疾患状態の診断に特に有用である。好ましくは、ハイブリダイゼーションは上記第四の選択肢と関連して記載したストリンジェントな条件下で起こるまたは行う。

【0082】

本明細書において用いる核酸分子は、一般にあらゆるリボ核酸分子またはデオキシリボ核酸分子をいい、修飾していないRNAまたはDNAまたは修飾したRNAまたはDNAであってよい。それゆえ、たとえば、本明細書において用いる核酸分子は、とりわけ、一本鎖および二本鎖DNA、一本鎖および二本鎖RNAの混合物であるDNA、および一本鎖および二本鎖領域の混合物であるRNA、DNAとRNAを含むハイブリッド分子（一本鎖または、より典型的には二本鎖、または三本鎖、または一本鎖領域と二本鎖領域の混合物であってよい）をいう。さらに、本明細書で用いる核酸分子は、RNAまたはDNAまたはRNAとDNAの両者を含む三本鎖の領域をいう。そのような領域の鎖は、同じ分子からまたは異なる分子からのものであってよい。これら領域は、これら分子の1またはそれ以上のすべてを含んでいてよいが、より典型的にはこれら分子の幾つかの一定の領域のみを含んでいる。三重らせん領域の分子の一つは、しばしばオリゴヌクレオチドである。本明細書において用いる核酸分子なる語は、1またはそれ以上の修飾塩基を含む上記DNAまたはRNAを包含する。それゆえ、安定性やその他の理由により修飾した骨格を有するDNAまたはRNAは、本明細書において用いるに際して「核酸分子」とよばれる。さらに、イノシンなどの異常な塩基、またはトリチル化塩基などの修飾塩基（2つの例のみを挙げる）を含むDNAまたはRNAは、本明細書において用いるに際して「核酸分子」とよばれる。DNAおよびRNAには当業者に知られた多くの有用な目的にかなう極めて多数の修飾を施しうることが評価されるであろう。本明細書において用いる核酸分子なる語は、そのような化学的、酵素的または代謝的に修飾した形態の核酸分子、並びにウイルスおよび細胞（とりわけ、単純な細胞および複合した細胞を含む）のDNAおよびRNA特性の化学的形態を包含する。核酸なる語はまた、しばしばオリゴヌクレオチドと称される短い核酸分子をも包含する。「ポリヌクレオチド」および「核酸」または「核酸分子」は、本明細書ではしばしば同義で用いられる。

【0083】

本発明で提供される核酸分子はまた、ストレプトコッカス・ピオゲネスのコード領域の配列表に示す核酸分子の配列よりも長いものおよび短いものである多数の独特の断片をも包含し、これらは標準クローニング法により生成することができる。独特であるためには、断片は他の既知の核酸配列と区別するに十分なサイズでなければならず、選択したストレプトコッカス・ピオゲネスの断片をGenBankなどのコンピューターデータベース中のヌクレオチド配列と比較することにより容易に決定できる。

【0084】

さらに、修飾は、本発明により包含される核酸分子およびポリペプチドに対して行うことができる。たとえば、核酸によってコードされるポリペプチドに影響を及ぼさないヌクレオチド置換を行うことができ、それゆえ高度免疫血清反応性の抗原またはその断片をコードする核酸分子はいずれも本発明により包含される。

【0085】

さらに、本発明によって提供される高度免疫血清反応性の抗原またはその断片をコードする核酸分子はいずれも、標準クローニング法などの標準法を用い、ストレプトコッカス・ピオゲネスの調節配列であるか異種の調節配列であるかを問わず所望の調節配列、異種のリーダー配列、異種のマーカー配列または異種のコード配列に機能的に連結させて融合タンパク質を生成することができる。

【0086】

本発明の核酸分子は、mRNAまたはcRNAなどのRNAの形態、またはたとえばク

ローニングにより得られまたは化学合成法によりまたはそれらの組合せにより製造された cDNA およびゲノム DNA を含む DNA の形態であってよい。DNA は三本鎖、二本鎖または一本鎖であってよい。一本鎖 DNA は、コード鎖（センス鎖としても知られる）であってもよいし、または非コード鎖（アンチセンス鎖ともよばれる）であってもよい。

【0087】

本発明はさらに、配列表に示す削減した (deducted) ストレプトコッカス・ピオゲネスのアミノ酸配列を有する高度免疫血清反応性の抗原およびその断片の断片、アナログおよび誘導体をコードする上記核酸分子の変異体に関する。核酸分子の変異体は、天然に存在する対立遺伝子変異体などの天然に存在する変異体であってもよいし、または天然に存在することが知られていない変異体であってもよい。そのような核酸分子の天然に存在しない変異体は、核酸分子、細胞または生物体に適用するものを含む突然変異誘発法により作成することができる。

【0088】

この観点での変異体には、上記核酸分子とヌクレオチドの置換、欠失または付加によって異なっている変異体がある。置換、欠失または付加には 1 またはそれ以上のヌクレオチドが関与してよい。変異体はコード領域または非コード領域またはその両者で変化させることができる。コード領域での変化は、保存的なまたは非保存的なアミノ酸の置換、欠失または付加を生成する。好ましいのは、配列表に示すストレプトコッカス・ピオゲネスの配列であって、そのうちの幾つか、5～10、1～3、2、1 または 0 のアミノ酸が置換、欠失または付加された（またはこれらの組み合わせ）ものを有する、変異体、アナログ、誘導体または断片、または断片の変異体、アナログまたは誘導体をコードする核酸分子である。特に好ましいのは、配列表に示すストレプトコッカス・ピオゲネスポリペプチドの特性および活性を変化させないサイレントな置換、付加および欠失である。この観点から特に好ましいのはまた、保存された置換である。

【0089】

本発明によるペプチドおよび断片はまた、好ましくは所期のエпитープの 1 または 2 のアミノ酸がたとえば {Tourdot, S. ら、2000} に記載の規則に従って修飾または置換された修飾エпитープ並びにそのような修飾エпитープをコードする核酸配列をも包含する。

【0090】

エпитープの T 細胞活性化能を改善、保存または少なくとも有意に妨害しないアミノ酸交換によって本発明のエピトープから得られるエピトープもまた本発明によるエピトープに包含されることは明らかである。それゆえ、本発明のエピトープはまた、ストレプトコッカス・ピオゲネス由来の当初の配列を含んでいないが同じかまたは好ましくは改善された T 細胞応答を誘起するエピトープをも包含する。これらエピトープは「ヘテロクリティック (heteroclitic)」とよばれる；これらエピトープは MHC / HLA 分子に対して同様または好ましくは一層大きな親和性を有する必要がある、当初のエピトープに向けられた T 細胞レセプター (TCR) を同様または好ましくは一層強く刺激する能力を有する必要がある。

【0091】

ヘテロクリティックエピトープは合理的なデザインによって、すなわち、たとえば {Rammensee, H. ら、1999} によって記載されているように MHC / HLA への結合への個々の残基の寄与を考慮に入れ、これを TCR と相互作用する可能性のある残基を系統的に交換し、得られた配列を当初にエピトープに向けられた T 細胞を用いて試験することと組み合わせることによって、得ることができる。そのようなデザインは当業者であれば過度の実験を要することなく行うことができる。

【0092】

他の可能性は、当初のエピトープに向けられた T 細胞を用いたペプチドライブラリーのスクリーニングを含む。好ましい方法は合成ペプチドライブラリーのポジショナルスクリーニングである。そのようなアプローチは、たとえば {Hemmer, B. ら、1999} およびその中で引用された文献に詳細に記載されている。

【0093】

本発明に由来するアミノ酸配列によって示されるエピトープまたはヘテロクリティックエピトープに代わるものとして、これらエピトープをミミックする物質、たとえば「ペプチデミメチカ (peptidemimetica)」または「レトロインベルソペプチド (retro-inverso-peptides)」を応用できる。

【0094】

改善されたエピトープのデザインの他の側面は、T細胞を刺激する能力を増大させる物質でこれらエピトープを調合 (formulation) または修飾することである。これらにはTヘルパー細胞エピトープ、脂質またはリポソームまたはW001/78767に記載されているような好ましい修飾が含まれる。

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【0095】

エピトープのT細胞刺激能を増大させる他の方法は、免疫促進物質、たとえばインターロイキン-2、-7、-12、-18、クラスIおよびIIインターフェロン (IFN)、とりわけIFN-ガンマ、GM-CSF、TNF-アルファ、flt3-リガンドなどのサイトカインまたはケモカインとともに調合することである。

【0096】

本発明の核酸分子アッセイに関して本明細書でさらに検討するように、たとえば、本発明の上記核酸分子は、本発明のポリペプチドをコードする完全長のcDNAおよびゲノムクローンを単離するため、および本発明の核酸分子と高い配列類似性を有する他の遺伝子のcDNAおよびゲノムクローンを単離するため、RNA、cDNAおよびゲノムDNAのハイブリダイゼーションプローブとして用いることができる。そのようなプローブは、一般に少なくとも15塩基を含むであろう。好ましくは、そのようなプローブは、少なくとも20、少なくとも25または少なくとも30塩基を有し、少なくとも50塩基を有していてもよい。特に好ましいプローブは、少なくとも30塩基を有し、50塩基またはそれ以下、たとえば30、35、40、45、または50塩基を有するであろう。

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【0097】

たとえば、本発明の核酸分子のコード領域は、既知のDNA配列を用いてオリゴヌクレオチドプローブを合成し、関連するライブラリーをスクリーニングすることによって単離することができる。つぎに、本発明の遺伝子の配列に相補的な配列を有する標識オリゴヌクレオチドを用いてcDNA、ゲノムDNAまたはmRNAのライブラリーをスクリーニングし、ライブラリーのどの成員にプローブがハイブリダイズしたかを決定する。

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【0098】

本発明の核酸分子およびポリペプチドは、とりわけ核酸分子アッセイと関連してさらに検討するように、疾患、とりわけヒト疾患の治療剤および診断剤の開発のための試薬および材料として用いることができる。

【0099】

オリゴヌクレオチドである本発明の核酸分子は、本明細書で同定したストレプトコッカス・ピオゲネスの遺伝子が全体としてまたは一部として血液などの感染組織に存在および／または転写されているか否かを決定するため、本明細書に記載した方法、好ましくはPCRに用いることができる。そのような配列はまた、病原体が達成した感染の段階および感染のタイプの診断においても有用性を有するであろう。この目的や他の目的のため、本明細書に記載する本発明による核酸の少なくとも一つを含むアレイを用いることができる。

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【0100】

本発明による核酸分子は、核酸分子およびこれら核酸分子を含む生物または試料の検出に用いることができる。好ましくは、そのような検出は診断のため、さらに好ましくはストレプトコッカス・ピオゲネスの存在または存在量と関係または関連する疾患の診断のためである。

【0101】

ストレプトコッカス・ピオゲネスに感染した真核生物 (本明細書では「個体」ともいう

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）、とりわけ哺乳動物、および特にヒトは、様々な方法によりDNAレベルで検出することができる。ストレプトコッカス・ピオゲネスを他の生物から識別するのに好ましい候補を得ることができる。

【0102】

本発明は、配列表に示す核酸分子の配列を有する核酸分子の上昇した発現レベルを個体から単離または得た試料から決定することを含む、ストレプトコッカス・ピオゲネス感染から生じる疾患の診断方法を提供する。核酸分子の発現は、核酸分子の定量のために当該技術分野でよく知られた方法のいずれか、たとえば、PCR、RT-PCR、Rnase保護、ノーザンブロッティング、本明細書に記載する他のハイブリダイゼーション法およびアレイを用いて測定することができる。

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【0103】

本明細書において単離とは、その天然の状態から「ヒトの手により」分離したことを意味する；すなわち、それが天然に存在するなら、それが当初の環境から変えられているかまたは除去されている、またはその両者であることを意味する。たとえば、この語を本明細書において用いるに際して、生きた生物中にその天然の状態にて天然に存在する天然の核酸分子またはポリペプチドは「単離」されていないが、その天然の状態の共存する物質から分離された同核酸分子またはポリペプチドは「単離」されている。単離の一部としてまたは単離後、そのような核酸分子は他の核酸分子、たとえばDNAと組み合わせ、たとえば突然変異誘発のため、融合タンパク質を生成するため、および宿主中で増殖または発現するために用いることができる。単離した核酸分子は、単独またはベクターなどの他の核酸分子と組み合わせ宿主細胞、培養液または全生物体に導入することができる。宿主細胞、培養液または全生物体に導入されたら、そのようなDNAは、この語を本明細書において用いるに際して、なお単離されているといえる、なぜならこれらDNAはそれらが天然に存在する形態または環境にないからである。同様に、核酸分子およびポリペプチドは組成物、たとえば培地調合物、核酸分子またはポリペプチドをたとえば細胞中に導入するための溶液、たとえば化学反応または酵素反応のための組成物または溶液に存在することができる、これら組成物は天然には存在しない組成物であり、その中で核酸分子またはポリペプチドはこの語が本明細書で用いられる意味の範囲において単離されているといえる。

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【0104】

本発明による核酸は化学的に合成することができる。あるいは、本発明による核酸は当業者に知られた方法によりストレプトコッカス・ピオゲネスから単離することができる。

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【0105】

本発明の他の側面によれば、新規な高度免疫血清に反応性の抗原およびその断片の包括的なセットが本明細書に記載の抗原同定法を用いることにより提供される。本発明の好ましい態様では、本明細書に記載の核酸分子のいずれかによってコードされるアミノ酸配列を含む高度免疫血清に反応性の抗原およびその断片が提供される。本発明の他の好ましい態様では、配列番号151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244および246-300に示すポリペプチド配列よりなる群から選ばれたアミノ酸配列を含む高度免疫血清に反応性の抗原の新規なセットおよびその断片が提供される。本発明のさらに好ましい態様では、配列番号214に示すポリペプチド配列よりなる群から選ばれたアミノ酸配列を含む高度免疫血清に反応性の抗原およびその断片が提供される。本発明のさらになお好ましい態様では、配列番号153, 186, 197-198, 205, 212, 222, 230, 234, 245に示すポリペプチド配列よりなる群から選ばれたアミノ酸配列を含む高度免疫血清に反応性の抗原およびその断片が提供される。

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【0106】

本発明で提供される高度免疫血清に反応性の抗原およびその断片は、配列番号に示すいずれかのポリペプチド、並びに配列番号に示すポリペプチドと少なくとも70%の同一性、好ましくは配列番号に示すポリペプチドに対して少なくとも80%または85%の同一性、さら

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に好ましくは配列番号に示すポリペプチドに対して少なくとも90%の類似性（さらに好ましくは少なくとも90%の同一性）、およびさらに一層好ましくは配列番号に示すポリペプチドに対して少なくとも95%、96%、97%、98%、99%または99.5%の類似性（さらに一層好ましくは少なくとも95%、96%、97%、98%、99%または99.5%の同一性）を有するポリペプチドを含み、そのようなポリペプチドの部分、一般に少なくとも4アミノ酸、さらに好ましくは少なくとも8アミノ酸、さらに一層好ましくは少なくとも30アミノ酸、さらに一層好ましくは少なくとも50アミノ酸、たとえば4、8、10、20、30、35、40、45または50アミノ酸を含むポリペプチドの部分も含む。

【0107】

本発明はまた、これら高度免疫血清に反応性の抗原およびその断片の断片、アナログ、および誘導体にも関する。そのアミノ酸配列が配列番号に示すものである抗原に言及する場合の「断片」、「誘導体」および「アナログ」なる語は、そのような高度免疫血清に反応性の抗原およびその断片と本質的に同じ生物学的機能または活性を保持しているポリペプチドを意味する。

【0108】

高度免疫血清に反応性の抗原およびその断片の断片、誘導体またはアナログは、（1）1またはそれ以上のアミノ酸残基が保存的または非保存的アミノ酸残基（好ましくは保存的アミノ酸残基）で置換されており、そのような置換されたアミノ酸残基が遺伝子コードによってコードされているものであるかまたはコードされていないものであるもの、または（2）1またはそれ以上のアミノ酸残基が置換基を含むもの、または（3）成熟した高度免疫血清に反応性の抗原またはその断片が他の化合物、たとえば、高度免疫血清に反応性の抗原およびその断片の半減期を増大させる化合物（たとえば、ポリエチレングリコール）に融合しているもの、または（4）付加的なアミノ酸、たとえば、リーダーまたは分泌配列または成熟した高度免疫血清に反応性の抗原またはその断片の精製に用いられる配列またはプロタンパク質配列が成熟した高度免疫血清に反応性の抗原またはその断片に融合しているものであってよい。そのような断片、誘導体およびアナログは、本明細書の教示から当業者の範囲内であると思われる。

【0109】

本発明はまた、異なるストレプトコッカス・ピオゲネス単離物の抗原に関する。そのようなホモログは本明細書に開示した核酸配列およびアミノ酸配列に基づいて容易に単離することができる。今日、80を超えるMタンパク質血清型が区別されており、そのタイプ分けはemm遺伝子の5'末端の可変領域に基づいている（たとえば、Vitaliら、2002を参照）。それゆえ、抗原の存在はすべてのM血清型について決定することができる。さらに、sic遺伝子について記載されているように（Hoeら、2001）、種々のM血清型における特定の抗原の変動性（variability）を決定することもできる。種々のM血清型がそれが引き起こす疾患の種類に及ぼす影響は最近の論評でまとめられている（Cunningham、2000）。とりわけ、2つのグループの血清型を区別することができる：

（1）咽頭炎および猩紅熱を引き起こすもの（たとえば、M血清型1、3、5、6、14、18、19、24）

（2）膿皮症および連鎖球菌皮膚感染症を引き起こすもの（たとえば、M血清型2、49、57、59、60、61）。

このことは、ワクチンとしてまたは一般に特定の疾患をターゲティングする医薬として使用するうえでの抗原の関連性を同定する基礎となりうる。

【0110】

たとえば、CDCのホームページ（<http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm>）からの情報は、種々のM血清型の関係を示す系統樹を与えている。さらに関連する文献は、Vitaliら、Journal of Clinical Microbiology 40:679-681. (2002)（分子的emmタイプ分け法）、Enrightら、Infection and Immunity 69:2416-2427 (2001)（別の分子的タイプ分け法（MLST））、Hoeら、The Journal of Infectious Diseases 183:633-639. (2001)（多くの異なる血清型における一つの抗原（sic）の変化の例）およびCunningham

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, CLINICAL MICROBIOLOGY REVIEWS 13:470-511 (2000) (GAS病因論に関する概説) である。
。上記アドレスにはすべてのemm型が完全に列挙されており、ダウンロードが可能である。

【0111】

系統樹はWisconsin Package Version 10.1、Genetics Computer Group (GCG)、Madison programs Pileup、Distances、およびGrowtreeを逐次使用することにより構築した。基本的に、シグナル配列の22残基と83のさらなるN末端残基とを用いてアラインメント（データベースからの選択配列を含む）に使用した。選択した配列は、新たなemm名称103-124（以下の表に記載）並びにそれらの最も近接した「古典的な」Mタンパク質マッチを含む。この分析はC末端が任意に切り取られている点で限界があるが、これは該系統樹がオパシティーファクター（opacity factor）陽性株のM配列のクラスターをオパシティーファクター株陰性のM配列から分離している点で典型的な結果である。

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【0112】

emm型/以前の名称-GenBankアクセス番号-単離された国-最も近接したN末端Mタンパク質配列マッチ（%同一性）：

emm103/st2034 U74320 PNG, Bra, Egy, Mal, Nep, NZ, US M87 (66%)

emm104/st2034 AF056300 PNG, Egy, Mal, Nep, NZ, US M66 (72%)

emm105/st4529 AF060227 Mal, Nep, NZ, US M5 (45%)

emm106/st4532 AF077666 Mal, Egy, Iran, Nep M27G (71%)

emm107/st4264 AF163686 Mal, NZ M25 (52%)

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emm108/st4547 AF052426 Mal, Bra, Egy, Ira, NZ M70 (84%)

emm109/st3018 AF077667 Mal, Egy, NZ M28 (74%)

emm110/st4935 U92492 Ind, Bul, NZ, Rus, US M13 (60%)

emm111/st4973 AF128960 Ind, Bra, Nep, US M80 (40%)

emm112/stCmuk16 AF091806 Thi, Bra, Rus, US M27L/77 (59%)

emm113/st2267 AF078068 NZ, Thai, Chi M13 (50%)

emm114/st2967 U50338 US, Can, Gam, NZ, PNG M73 (80%)

emm115/st2980 AF028712 US, Bra, Rus M36 (64%)

emm116/st2370 AF156180 US, Nep, NZ M52 (60%)

emm117/st436 AF058801 US M13 (59%)

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emm118/st448 AF058802 US, Bra, Egy, Nep, NZ M49 (79%)

emm119/st3365 AF083874 US, Br, Nep M52 (59%)

emm120/st1135 AF296181 Egy M56 (78%)

emm121/st1161 AF296182 Egy M64 (64%)

emm122/st1432 AF222860 Egy, Rus, Nep M18 (40%)

emm123/st6949AF213451Arg, US, NZM80 (68%)

st1160/emm124AF149048 and AF018178 Egy, Mal, NZM2 (82%)

【0113】

略語：Arg, アルゼンチン；Bra, ブラジル；Bul, ブルガリア；Can, カナダ；Chi, チリ；Egy, エジプト；Gam, ガンビア；Ind, インド；Ira, イラン；Mal, マレーシア；Nep, ネパール；NZ, ニュージーランド；PNG, パプアニューギニア；Thi, タイ；Rus, ロシア；US, 米国、%：血清学的に特徴付けたLancefield型からの予測された50の成熟N末端残基への最も近接した成熟Mタンパク質配列のマッチング。

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【0114】

emm型および配列型：

多くの場合、emm配列参照株はRebecca Lancefield博士のM型コレクションから直接得られたものである。そのような株はRCLと称する。

【0115】

「emm」で始まる配列は、この型によって示される単離物がCDC連鎖球菌研究所以外に幾つかの関連研究所によって分析されたことを示している。「新たな」各emm型であるemm94

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～emm124は、重篤な疾患の発現から回収した複数の独立した単離物によって表され、国際的なGAS関連研究所に入手可能なすべてのタイプ分け血清ストックでタイプ分けすることのできないMタンパク質であり、正常ヒト血液中で増殖させることによってインビトロで食作用阻止特性を示す。「st」（sequence type）で始まるemm配列は、関連研究所のすべてによって完全に確認されてはいない。

【0116】

GAS遺伝学：

血清オパシティーファクター陽性（SOF+）株に対する抗血清が株特異的な仕方でOF活性を示すことは長い間知られてきた。それゆえ、少なくとも60の別個のsof（血清オパシティーファクター（serum opacity factor））遺伝子を表すsof遺伝子の500-2700塩基可変領域をGASオパシティーファクター陽性株（および興味深いことに、OF陰性emm12単離物とemm/M型12とに共通して見出されるホモログ）から分析した。sof遺伝子配列は、emm型内では通常よく保存されているものの、異なるGAS株の間では顕著に変異していることがわかった。それゆえ、重要な株としては、emm1, emm100, emm101, emm102, emm103, emm104, emm105, emm106, emm107, emm108, emm109, emm11, emm110, emm111, emm112, emm113, emm114, emm115, emm116, emm117, emm118, emm119, emm12, emm120, emm121, emm122, emm123, emm124, emm13L, emm14, emm15, emm17, emm18, emm19, emm2, emm22, emm23, emm24, emm25, emm26, emm27G, emm28, emm29, emm3, emm30, emm31, emm32, emm33, emm34, emm36, emm37, emm38, emm39, emm4, emm40, emm41, emm42, emm43, emm44, emm46, emm47, emm48, emm49, emm5, emm50, emm51, emm52, emm53, emm54, emm55, emm56, emm57, emm58, emm59, emm6, emm60, emm61, emm62, emm63, emm64, emm65, emm66, emm67, emm68, emm69, emm70, emm71, emm72, emm73, emm74, emm75, emm76, emm77, emm78, emm79, emm8, emm80, emm81, emm82, emm83, emm84, emm85, emm86, emm87, emm88, emm89, emm9, emm90, emm91, emm92, emm93, emm94, emm95, emm96, emm97, emm98, emm99, st1389, st1731, st1759, st1815, st1967, st1969, st1rp31, st1l014, st2037, st204, st211, st213, st2147, st1207, st245, st2460, st2461, st2463, st2904, st2911, st2917, st2926, st2940, st369, st3757, st3765, st3850, st5282, st6735, st7700, st809, st833, st854, st980584, stck249, stck401, std432, std631, std633, stIL103, stIL62, stns292, stns554, sts104, stc1400, stc1741, stc36, stc3852, stc5344, stc5345, stc57, stc6979, stc74a, stc839, stg10, stg11, stg1389, stg166b, stg1750, stg2078, stg3390, stg4222, stg4545, stg480, stg4831, stg485, stg4974, stg5063, stg6, stg62647, stg643, stg652, stg653, stg663, stg840, stg93464, stg97, stL1376, stL1929およびstL2764が挙げられる。

【0117】

この観点から本発明の特に好ましい態様は、配列表に示す高度免疫血清に反応性の抗原、その変異体、アナログ、誘導体および断片、および該断片の変異体、アナログおよび誘導体である。さらに、そのような高度免疫血清に反応性の抗原、その変異体、アナログ、誘導体および断片、および該断片の変異体、アナログおよび誘導体を含む融合ポリペプチドもまた本発明に包含される。そのような融合ポリペプチドおよびタンパク質並びにそれらをコードする核酸分子は、融合タンパク質をコードする組換えポリ核酸を産生および発現するための標準組換え法を含む標準法を用いて容易に製造することができる。

【0118】

好ましい変異体は、保存的なアミノ酸置換によって参照とは異なっているものである。そのような置換は、ポリペプチド中の所定のアミノ酸を同様の特性の他のアミノ酸で置換するものである。保存的置換として典型的なのは、脂肪族アミノ酸Ala, Val, LeuおよびIle相互間での置換、ヒドロキシル残基SerおよびThrの交換、酸性残基AspおよびGluの交換、アミド残基AsnおよびGlnの交換、塩基性残基LysおよびArgの交換および芳香族残基PheおよびTyr間での置換である。

【0119】

この観点から特に好ましいのは、配列表に示すポリペプチドのアミノ酸配列において、

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幾つか、若干、5～10、1～5、1～3、2、1または0のアミノ酸残基の置換、欠失または付加またはそれらの組合せを有する、変異体、アナログ、誘導体および断片、および該断片の変異体、アナログおよび誘導体である。これらの中で特に好ましいのは、本発明のポリペプチドの特性および活性を変えることのないサイレントな置換、付加および欠失である。この観点から同様に好ましいのは保存的な置換である。最も好ましいのは置換されていない配列表に示すアミノ酸配列を有するポリペプチドである。特に適したアミノ酸置換は、本願による配列表に開示した配列のホモログに含まれるものである。それゆえ、本明細書に開示する抗原またはエピトープの適当な配列誘導体としては、ストレプトコッカス・ピオゲネスの1またはそれ以上の株または血清型に存在する1またはそれ以上の変異体が挙げられる（好ましくは、そのようなホモログ変異に基づく1、2、3、4、5、6、7、8、9、または10のアミノ酸変化）。そのような抗原は、天然に存在する配列または新たに作製した人工的な配列である配列を含んでいてよい。これらの好ましい抗原変異体は、そのような天然に存在する配列変異体に基づいており、たとえば、本発明によるポリペプチドの抗原性領域の「マスター配列」を形成する。そのようなホモログ変異体または交換の適当な例は実施例中の表5に示してある。たとえば、1またはそれ以上の変異を導入することにより所定のストレプトコッカス・ピオゲネス配列を修正して、この所定の（天然に存在する）抗原またはエピトープ配列の人工的な（すなわち、天然に存在しない）変異体を作製することができる。

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【0120】

本発明による高度免疫血清に反応性の抗原およびその断片は、好ましくは単離された形態で提供され、好ましくは均質にまで精製される。

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【0121】

本発明の好ましい態様はまた、配列表に示すアミノ酸配列を有するポリペプチドの断片を含むポリペプチド、および配列表に示すポリペプチドの変異体および誘導体の断片である。

【0122】

この観点から、断片は、上記高度免疫血清に反応性の抗原およびその断片、およびその変異体または誘導体、アナログ、断片のアミノ酸配列の全体ではなく一部と完全に同じであるアミノ酸配列を有するポリペプチドである。そのような断片は、「自立した構造（free-standing）」、すなわち他のアミノ酸またはポリペプチドの一部でもなく融合してもしないか、または一層大きなポリペプチド内部に含まれてその一部または領域を形成してもよい。また、本発明のこの側面において好ましいのは、本発明のポリペプチドの構造的または機能的な寄与を特徴とする断片、すなわち、本発明のポリペプチドのアルファヘリックスおよびアルファヘリックス形成領域、ベーターシートおよびベーターシート形成領域、ターンおよびターン形成領域、コイルおよびコイル形成領域、可撓性領域、表面形成領域、基質結合領域、および高抗原性指標領域を含む断片、およびそのような断片の組合せである。好ましい領域は、本発明の高度免疫血清に反応性の抗原およびその断片の活性を媒体する領域である。この観点から最も好ましいのは、本発明の高度免疫血清に反応性の抗原およびその断片の化学的、生物学的または他の活性を有する断片であり、類似の活性または改善された活性を有するかまたは所望でない活性の低減されたものを含む。特に好ましいのは、ストレプトコッカス・ピオゲネスの生存に必須の機能またはヒトにおいて疾患を引き起こす能力を付与する、レセプターまたは酵素のドメインを含む断片である。さらに好ましいポリペプチド断片は、動物、とりわけヒトにおける抗原性または免疫原性の決定基を含むものである。

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【0123】

抗原性の断片は、それ自体で抗原性であるか、またはハプテンとして提供したときに抗原性にするのできる同定された抗原の断片として定義される。それゆえ、1または（一層長い断片の場合は）幾つかのアミノ酸の交換のみを示す抗原または抗原性断片もまた本発明で実施することができるが、アミノ酸の交換を有するそのような断片の抗原としての能力がかかる交換によってひどく損なわれていないこと、すなわち該抗原によってワク

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チン接種された個体において適当な免疫応答を誘起するのに適しており、個体血清からの個体抗体調製物によって同定されることを条件とする。

【0124】

高度免疫血清に反応性の抗原のそのような断片の好ましい例は、表1の縦列「予測される免疫原性アミノ酸」および「同定された免疫原性領域の位置」のアミノ酸配列；表2の血清反応性エピトープ、とりわけアミノ酸：配列番号151の4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425および1-114；配列番号152の5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395および29-226；配列番号153の4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254および919-929；配列番号154の5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360および145-305；配列番号155の15-39, 52-61, 72-81, 92-97および71-81；配列番号156の13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245および173-186；配列番号157の5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352および316-331；配列番号158の6-28, 43-53, 60-76, 93-103および21-99；配列番号159の10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568および9-26；配列番号160の5-29, 39-45, 107-128および1-112；配列番号161の4-38, 42-50, 54-60, 65-71, 91-102および21-56；配列番号162の4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391および23-39；配列番号163の6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591および474-489；配列番号164の8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864および37-241, 409-534, 582-604, 743-804；配列番号165の4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416および202-337；配列番号166の4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407および1-48；配列番号167の18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297および203-217；配列番号168の20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521および261-273；配列番号169の6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543,

561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641および1-414, 443-614, 997-1392; 配列番号170の14-42, 70-75, 90-100, 158-181および1-164; 配列番号171の4-21, 30-36, 54-82, 89-97, 105-118, 138-147および126-207; 配列番号172の4-21, 31-66, 96-104, 106-113, 131-142および180-204; 配列番号173の5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386および11-197, 204-219, 258-372; 配列番号174の4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322および195-289; 配列番号175の4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329および12-130; 配列番号176の10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707および434-444; 配列番号177の6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430および360-375; 配列番号178の4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251および254-260; 配列番号179の12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400および369-382; 配列番号180の11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487および270-312; 配列番号181の5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604および486-598; 配列番号182の4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374および378-396; 配列番号183の5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184および75-235; 配列番号184の6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310および30-51; 配列番号185の17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647および208-219; 配列番号186の4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039および396-533, 1342-1502, 1672-1920; 配列番号187の4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-1

37, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905および1-113, 210-232, 250-423, 536-564;

配列番号188の4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201および617-635; 配列番号189の7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244および190-203; 配列番号190の4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574および385-398; 配列番号191の5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003および12-190, 276-283, 666-806; 配列番号192の4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664および30-80, 89-105, 111-151; 配列番号193の7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259および195-203; 配列番号194の5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426および32-50; 配列番号195の8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174および75-90; 配列番号196の4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233および69-88; 配列番号197の4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802および96-230, 361-491, 572-585; 配列番号198の4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289および102-210; 配列番号199の13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313および240-248; 配列番号200の5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260および182-198; 配列番号201の10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504および41-56; 配列番号202の5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333および202-217; 配列番号203の6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283および1-127; 配列番号204の4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718および297-458; 配列番号205の5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213および24-135; 配列番号206の4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147,

150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721および176-330; 配列番号207の31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472および46-62, 296-341; 配列番号208の23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716および667-684; 配列番号209の20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869および258-416; 配列番号210の7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300および278-295; 配列番号211の4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191および183-195; 配列番号212の12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241および63-238; 配列番号213の4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308および1-141; 配列番号214の11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379および231-368; 配列番号215の9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342および247-260; 配列番号216の7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279および64-72; 配列番号217の4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897および222-362, 756-896; 配列番号218の11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255および153-170; 配列番号219の4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212および56-73; 配列番号220の4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334および298-312; 配列番号221の7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254および141-157; 配列番号222の23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663および433-440, 572-593; 配列番号223の4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267および17-319, 417-563; 配列番号224の6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500および46-187; 配列番号225の4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534

-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992および21-244, 381-499, 818-959; 配列番号226の19-29, 65-75, 90-109, 111-137, 155-165, 169-175および118-136; 配列番号227の15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465および147-155; 配列番号228の11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161および74-438; 配列番号229の4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413および156-420; 配列番号230の4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343および79-348; 配列番号231の12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168および53-70; 配列番号232の4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522および183-341; 配列番号233の4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822および92-231, 618-757; 配列番号234の11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372および41-170; 配列番号235の6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174および20-487, 757-1153; 配列番号236の10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305および26-74, 91-100, 105-303; 配列番号237の9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480および10-223, 231-251, 264-297, 312-336; 配列番号238の5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537および22-344; 配列番号239の5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395および1-151; 配列番号240の6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756および91-263;

10

20

30

40

50

配列番号241の4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775および261-272; 配列番号242の4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701および541-551; 配列番号243の6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252および84-254; 配列番号244の13-30, 71-120, 125-137, 139-145, 184-199および61-78; 10
配列番号245の9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855および568-580; 配列番号246の11-21, 29-38および5-17; 配列番号247の2-9; 配列番号248の4-10, 16-28および7-18, 26-34; 配列番号249の10-16および1-15; 配列番号250の4-11; 配列番号251の4-40, 42-51および37-53; 配列番号252の4-21および22-29; 配列番号253の2-11; 配列番号254の9-17, 32-44および1-22; 配列番号255の19-25, 27-32および15-34; 配列番号256の4-12, 15-22および11-33; 配列番号257の10-17, 24-30, 39-46, 51-70および51-61; 配列番号258の6-19; 配列番号259の6-11, 21-27, 31-54および11-29; 配列番号260の4-10, 13-45および11-35; 配列番号261の4-14, 23-32および11-35; 配列番号262の14-39, 45-51および15-29; 配列番号263の4-11, 14-28および4-17; 配列番号264の4-16および2-16; 配列番号265の4-10, 12-19, 39-50および6-22; 配列番号266の2-13; 配列番号267の4-11, 22-65および3-19; 配列番号268の17-23, 30-35, 39-46, 57-62および30-49; 配列番号269の4-19および14-22; 配列番号270の2-9; 配列番号271の7-18, 30-43および4-12; 配列番号272の4-30, 39-47および5-22; 配列番号273の6-15および14-29; 配列番号274の4-34および23-35; 配列番号275の4-36, 44-57, 65-72および14-27; 配列番号276の4-18および11-20; 配列番号277の5-19; 配列番号278の18-36および6-20; 配列番号279の4-10, 19-34, 41-84, 96-104および50-63; 配列番号280の4-9, 19-27および8-21; 配列番号281の4-16, 18-28および22-30; 配列番号282の4-15および21-35; 配列番号283の4-17および3-13; 配列番号284の4-12および4-18; 30
配列番号285の4-24, 31-36および29-45; 配列番号286の12-22, 34-49および21-32; 配列番号287の4-17および22-32; 配列番号288の4-16, 25-42および7-28; 配列番号289の4-10および7-20; 配列番号290の4-11, 16-36, 39-54および28-44; 配列番号291の5-20, 29-54および14-29; 配列番号292の24-33および10-22; 配列番号293の10-51, 54-61および43-64; 配列番号294の7-1および2-17; 配列番号295の11-20および6-20; 配列番号296の4-30, 34-41および19-28; 配列番号297の11-21; 配列番号298の4-16, 21-26および9-38; 配列番号299の4-12, 15-27, 30-42, 66-72および10-24; 配列番号300の8-17および11-20; および配列番号246の2-19; 配列番号247の1-12; 配列番号248の21-38; 配列番号254の2-22; 配列番号255の15-33; 配列番号256の11-32; 配列番号259の11-28; 配列番号260の10-27; 配列番号261の9-26; 配列番号263の4-16; 配列番号266の1-18; 配列番号273の12-29; 配列番号276の6-23; 配列番号277の1-21; 配列番号279の47-64; 配列番号285の28-45; 配列番号287の18-35; 配列番号291の14-31; 配列番号292の7-24; 配列番号299の8-25; 配列番号300の1-20; 配列番号151の18-33; 配列番号151の62-72; 配列番号152の118-131; 配列番号154の195-220; 配列番号154の215-240; 配列番号154の255-280, 配列番号155の72-81; 配列番号156の174-186; 配列番号157の317-331; 配列番号158の35-59; 配列番号158の54-84; 配列番号158の79-104; 配列番号159の33-58; 配列番号159の81-101; 配列番号159の136-150; 配列番号159の173-186; 配列番号159の231-251; 配列番号161の22-48; 配列番号162の24-39; 配列番号163の475-489; 配列番号164の38-56; 配列番号164の583-604; 配列番号165の202-223; 配列番号165の222-247; 配列番号165の242-267; 配列番号165の262-287; 配列番号165の282-307; 配列番号165の302-327; 配列番号166の25-48; 配列番号167の2 40 50

04-217; 配列番号168の259-276; 配列番号169の121-139; 配列番号169の260-267; 配列番号169の215-240; 配列番号170の115-140; 配列番号172の182-204; 配列番号173の144-153; 配列番号173の205-219; 配列番号174の196-206; 配列番号174の240-249; 配列番号174の272-287; 配列番号174の199-223; 配列番号174の218-237; 配列番号175の226-249; 配列番号175の287-306; 配列番号176の430-449; 配列番号177の361-375; 配列番号178の241-260; 配列番号181の483-502; 配列番号182の379-396; 配列番号184の31-51; 配列番号186の1436-1460; 配列番号186の1455-1474; 配列番号186の1469-1487; 配列番号187の215-229; 配列番号187の534-561; 配列番号187の59-84; 配列番号187の79-104; 配列番号188の618-635; 配列番号189の191-203; 配列番号190の386-398; 配列番号191の65-83; 配列番号192の90-105; 配列番号192の112-136; 配列番号193の290-209; 配列番号194の33-50; 配列番号195の76-90; 配列番号196の70-88; 配列番号197の418-442; 配列番号197の574-585; 配列番号198の87-104; 配列番号198の124-148; 配列番号198の141-152; 配列番号199の241-248; 配列番号200の183-198; 配列番号201の40-57; 配列番号202の202-217; 配列番号203の50-74; 配列番号203の69-93; 配列番号203の88-112; 配列番号203の107-127; 配列番号205の74-92; 配列番号206の207-232; 配列番号206の227-252; 配列番号206の247-272; 配列番号207の47-60; 配列番号207の297-305; 配列番号207の312-337; 配列番号208の667-384; 配列番号210の279-295; 配列番号211の179-198; 配列番号213の27-51; 配列番号213の46-70; 配列番号213の65-89; 配列番号213の84-108; 配列番号213の112-141; 配列番号215の248-260; 配列番号216の59-78; 配列番号218の154-170; 配列番号219の57-73; 配列番号220の297-314; 配列番号221の142-157; 配列番号222の428-447; 配列番号222の573-593; 配列番号223の523-544; 配列番号223の46-70; 配列番号223の65-89; 配列番号223の84-108; 配列番号223の122-151; 配列番号224の123-142; 配列番号225の903-921; 配列番号226の119-136; 配列番号227の142-161; 配列番号228の258-277; 配列番号228の272-300; 配列番号228の295-322; 配列番号229の311-343; 配列番号229の278-304; 配列番号230の131-150; 配列番号230の195-218; 配列番号231の53-70; 配列番号232の184-208; 配列番号232の222-246; 配列番号232の241-265; 配列番号232の260-284; 配列番号232の279-303; 配列番号232の317-341; 配列番号233の678-696; 配列番号235の88-114; 配列番号235の464-481; 配列番号236の153-172; 配列番号236の137-155, 166-184; 配列番号236の215-228; 配列番号237の37-51; 配列番号237の53-75; 配列番号237の232-251; 配列番号237の318-336; 配列番号238の305-315; 配列番号238の131-156; 配列番号241の258-275; 配列番号243の107-137; 配列番号243の138-162; 配列番号243の157-181; 配列番号243の195-227; 配列番号244の62-78; 配列番号245の567-584を含むペプチド、および該配列の少なくとも6、好ましくは8を超える、とりわけ10を超えるアミノ酸を含む断片よりなる群から選ばれる。これら断片はすべて、個々に、およびそれぞれ独立に、本発明の好ましく選択された側面を形成する。

【0125】

特定の抗原のすべての線状の高度免疫血清に反応性の断片は、少なくとも10アミノ酸の長さの1アミノ酸ずつ重複する一連のペプチドによるタンパク質抗原の全体の配列の分析によって同定することができる。その後、非線状エピトープは、発現された完全長タンパク質またはそのドメインポリペプチドを用いた高度免疫血清によるタンパク質抗原の分析により同定することができる。天然のタンパク質とは独立に3D構造を形成するのにタンパク質の個々のドメインで十分であるとの仮定のもと、組換えまたは合成により製造した個々のドメインポリペプチドの高度免疫血清による分析は、マルチドメインタンパク質の個々のドメイン内でのコンホメーションエピトープの同定を可能にする。ドメインが線状エピトープとともにコンホメーションエピトープを有する抗原の場合は、線状エピトープに対応するペプチドを用いた競合実験を用いてコンホメーションエピトープの存在を確認することができる。

【0126】

本発明はまた、とりわけ、上記断片をコードする核酸分子、該断片をコードする核酸分子にハイブリダイズする核酸分子、とりわけストリンジェントな条件下でハイブリダイズ

する核酸分子、および該断片をコードする核酸分子を増幅するためのPCRプライマーなどの核酸分子にも関することが評価されるであろう。これらの観点から、好ましい核酸分子は、上記で検討した好ましい断片に対応する核酸分子である。

【0127】

本発明はまた、核酸分子または本発明の核酸分子を含むベクター、本発明のベクターで遺伝子操作した宿主細胞、および組換え法による高度免疫血清に反応性の抗原およびその断片の製造にも関する。

【0128】

極めて様々な発現ベクターを用いて本発明による高度免疫血清に反応性の抗原またはその抗原を発現させることができる。一般に、核酸を保持、増殖または発現して宿主中でポリペプチドを発現するのに適したいずれのベクターをもこの観点での発現に用いることができる。本発明のこの側面によれば、ベクターは、たとえば、プラスミドベクター、一本鎖または二本鎖ファージベクター、一本鎖または二本鎖RNAまたはDNAウイルスベクターであってよい。本明細書に開示した出発プラスミドは、市販のもの、公的に利用できるもののいずれであってもよく、または利用できるプラスミドからよく知られた刊行物公知の方法の通常的应用によって構築することができる。ある側面において好ましいベクターは、本発明の核酸および高度免疫血清に反応性の抗原またはその断片の発現のためのものである。宿主細胞中の核酸構築物は、組換え配列によってコードされる遺伝子産物を製造するために常法により用いることができる。別法として、本発明の高度免疫血清に反応性の抗原およびその断片は、通常のパепチド合成機によって合成により製造することができる。成熟タンパク質は、適当なプロモーターの制御下、哺乳動物細胞、酵母、細菌、または他の細胞で発現することができる。本発明のDNA構築物に由来するRNAを用い、細胞不含の翻訳系を用いてそのようなタンパク質を製造することもできる。

【0129】

宿主細胞は、本発明の核酸分子を導入し、該核酸分子を発現させるべく遺伝子操作することができる。適当な宿主の代表例としては、連鎖球菌、ブドウ球菌、大腸菌、*Streptomyces* および *Bacillus subtilis* 細胞などの細菌細胞；酵母細胞および *Aspergillus* 細胞などの真菌細胞；*Drosophila* S2 および *Spodoptera* Sf9 細胞などの昆虫細胞；CHO, COS, HeLa, C127, 3T3, BHK, 293 および Bowes メラノーマ細胞などの動物細胞；および植物細胞が挙げられる。

【0130】

本発明はまた、本発明によって提供される核酸分子によってコードされる高度免疫血清に反応性の抗原またはその断片を宿主細胞から発現させることを含む、ストレプトコッカス・ピオゲネス高度免疫血清に反応性の抗原およびその断片の製造方法をも提供する。本発明はさらに、ストレプトコッカス・ピオゲネス高度免疫血清に反応性の抗原またはその断片を発現する細胞の製造方法であって、適当な宿主細胞を本発明によるベクターで形質転換またはトランスフェクションして、形質転換またはトランスフェクションした細胞に該ベクターに含まれる核酸分子によってコードされるポリペプチドを発現させることを含む方法を提供する。

【0131】

本発明のポリペプチドは融合タンパク質などの修飾した形態で発現させることができ、分泌シグナルのみならず付加的な異種の機能的領域を含んでよい。それゆえ、たとえば、付加的なアミノ酸、とりわけ荷電アミノ酸の領域を該ポリペプチドのN末端またはC末端に付加して、精製の際またはその後の取り扱いまたは貯蔵の際の宿主細胞の安定性および抵抗性を改善することができる。また、精製を容易にするために領域を該ポリペプチドに付加することができる。そのような領域は該ポリペプチドの最終的な調製の前に除去することができる。とりわけ分泌または排出させるため、安定性を改善するため、または精製を容易にするためにポリペプチドにペプチド残基を付加することは、当該技術分野でよく知られた常法である。好ましい融合タンパク質は、ポリペプチドを可溶化または精製するのに有用な免疫グロブリンからの異種領域を含む。たとえば、EP-A-0 464 533（対応

カナダ2045869)は、免疫グロブリン分子の定常領域の種々の部分を他のタンパク質またはその部分とともに含む融合タンパク質を開示している。医薬の発見においては、たとえば、アンタゴニストを同定する高処理量スクリーニングアッセイの目的でタンパク質を抗体のFc部分に融合させている。たとえば、{Bennett, D.ら、1995} および {Johanson, K.ら、1995} を参照。

【0132】

ストレプトコッカス・ピオゲネス高度免疫血清に反応性の抗原またはその断片は、硫酸アンモニウムまたはエタノール沈殿、酸抽出、陰イオンまたは陽イオン交換クロマトグラフィー、ホスホセルロースクロマトグラフィー、疎水性相互作用クロマトグラフィー、ヒドロキシルアパタイトクロマトグラフィーおよびレクチンクロマトグラフィーを含む、よく知られた方法により組換え細胞培養液から回収および精製することができる。

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【0133】

本発明による高度免疫血清に反応性の抗原およびその断片は、化学的合成により、並びに生物学的手段により製造することができる。後者は、本発明による核酸を含むベクターによる宿主細胞のトランスフェクションまたは形質転換、および当業者によく知られた条件下でのトランスフェクションしたまたは形質転換した宿主細胞の培養を含む。この製造法はまた、製造すべきポリペプチドを精製または単離するための精製工程をも含んでいてよい。好ましい態様において、ベクターは本発明によるベクターである。

【0134】

本発明による高度免疫血清に反応性の抗原およびその断片は、生物または生物由来のポリペプチドを含む試料中での該生物の検出に用いることができる。好ましくは、そのような検出は、診断のため、さらに好ましくは疾患の診断のため、最も好ましくはグラム陽性菌、とりわけ連鎖球菌、ブドウ球菌およびlactococciよりなる群から選ばれた細菌の存在または存在量と関連する疾患の診断のためである。さらに好ましくは、微生物は、ストレプトコッカス・アガラクチエ (*Streptococcus agalactiae*)、ストレプトコッカス・ニューモニエ (*Streptococcus pneumoniae*) およびストレプトコッカス・ミュータンス (*Streptococcus mutans*) よりなる群から選ばれ、とりわけ微生物はストレプトコッカス・ピオゲネスである。

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【0135】

本発明はまた、正常レベルおよび異常レベルの決定を含む、細胞および組織中の本発明の高度免疫血清に反応性の抗原およびその断片のレベルを検出するための定量および診断アッセイなどの診断アッセイにも関する。それゆえ、たとえば、正常な対照組織試料と比較してポリペプチドの過剰発現を検出するための本発明による診断アッセイは、たとえば、感染の存在を検出するため、および感染生物を同定するために用いることができる。宿主由来の試料中のポリペプチドのレベルを決定するのに用いることのできるアッセイ法は、当業者にはよく知られている。そのようなアッセイ法としては、ラジオイムノアッセイ、競合結合アッセイ、ウエスタンブロット分析およびELISAアッセイが挙げられる。これらのうち、ELISAはしばしば好まれる。ELISAアッセイでは、まずポリペプチドに特異的な抗体、好ましくはモノクローナル抗体を調製することを含む。さらに、該モノクローナル抗体に結合するレポーター抗体を一般に調製する。レポーター抗体は、放射能試薬、蛍光試薬または酵素試薬、たとえば西洋ワサビペルオキシダーゼ酵素などの検出可能な試薬に結合している。

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【0136】

本発明による高度免疫血清に反応性の抗原およびその断片はまた、アレイの目的のため、またはアレイと関連して用いることもできる。さらに詳細には、本発明による高度免疫血清に反応性の抗原およびその断片の少なくとも一つを支持体に固定化する。該支持体は典型的に様々な高度免疫血清に反応性の抗原およびその断片を含み、それにより本発明による高度免疫血清に反応性の抗原およびその断片の一つまたは幾つかおよび／または異なる高度免疫血清に反応性の抗原およびその断片を用いることによって、多様性を生み出すことができる。そのようなアレイ並びに一般にアレイを特徴付ける性質は、該支持体また

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はその表面上の別個のまたは前もって定めた領域または位置に別個のポリペプチドが固定化されるという事実である。この理由から、あるアレイの別個の位置または領域でのいかなる活性も特定のポリペプチドと相関付けることができる。支持体上に固定化される異なる高度免疫血清に反応性の抗原およびその断片の数は、わずか10から数1000の異なる高度免疫血清に反応性の抗原およびその断片までにわたる。 cm^2 当たりの高度免疫血清に反応性の抗原およびその断片の密度は、好ましい態様において、 cm^2 当たりわずか10ペプチド／ポリペプチドから cm^2 当たり少なくとも400の異なるペプチド／ポリペプチド、さらに詳しくは cm^2 当たり少なくとも1000の異なる高度免疫血清に反応性の抗原およびその断片である。

【0137】

そのようなアレイの製造は当業者には知られており、たとえば、米国特許第5,744,309号に記載されている。アレイは好ましくは少なくとも第一表面 (first surface) を有する平面で多孔性または非多孔性固体支持体を含む。本明細書に開示する高度免疫血清に反応性の抗原およびその断片は該表面に固定化される。好ましい支持体材料は、とりわけガラスまたはセルロースである。このアレイが本明細書に記載した診断応用のいずれにも用いられることもまた本発明の範囲内である。本発明による高度免疫血清に反応性の抗原およびその断片とは別に、本発明による核酸分子もまた本明細書に記載のアレイの生成に用いることができる。このことは、抗体、好ましくはとりわけ本明細書に記載のモノクローナル抗体からなるアレイにも当てはまる。

【0138】

さらなる側面において、本発明は、本発明による高度免疫血清に反応性の抗原およびその断片、その誘導体または断片のいずれかに向けられた抗体に関する。本発明は、たとえば、モノクローナル抗体およびポリクローナル抗体、キメラ抗体、一本鎖、およびヒト化抗体、並びに Fab フラグメント、または Fab 発現ライブラリーの産物を含む。抗体がキメラ抗体であること、すなわち、異なる部分が異なる種に由来するかまたは少なくとも各配列が異なる種から取られたものであることは本発明の範囲内である。

【0139】

本発明の配列に対応する高度免疫血清に反応性の抗原およびその断片に対して産生される抗体は、動物に高度免疫血清に反応性の抗原およびその断片を直接注射することによって、または動物、好ましくは非ヒトに高度免疫血清に反応性の抗原およびその断片を投与することによって得ることができる。そのようにして得た抗体は、ついで高度免疫血清に反応性の抗原およびその断片自体に結合するであろう。このようにして、高度免疫血清に反応性の抗原およびその断片の断片しかコードしない配列であっても全体の高度免疫血清に反応性の抗原およびその断片に結合する抗体を得るのに用いることができる。そのような抗体は、ついで高度免疫血清に反応性の抗原およびその断片を発現する組織から該高度免疫血清に反応性の抗原およびその断片を単離するのに用いることができる。

【0140】

モノクローナル抗体を製造するには、連続的な細胞株培養によって産生される抗体を提供する当該技術分野で知られた方法を用いることができる (最初に {Kohler, G. ら1975} に記載)。

【0141】

一本鎖抗体の産生のために記載された方法 (米国特許第4,946,778号) を、本発明による免疫原性の高度免疫血清に反応性の抗原およびその断片に対する一本鎖抗体を産生させるべく適合させることができる。また、トランスジェニックマウス、または他の哺乳動物などの他の生物を、本発明による免疫原性の高度免疫血清に反応性の抗原およびその断片に対するヒト化抗体を発現するのに用いることができる。

【0142】

別法として、ファージディスプレイ法またはリボソームディスプレイを利用して、各標的抗原を有することについてスクリーニングしたヒトからのリンパ球の PCR 増幅した V 遺伝子のレパートリーか、または抗原刺激を受けていないライブラリーのいずれかから、

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高度免疫血清に反応性の抗原およびその断片に対する結合活性により抗体遺伝子を選択することができる。{McCafferty, J.ら、1990} ; {Marks, J.ら、1992}。これら抗体の親和性はまた、チェインシャフリングにより改善することができる {Clackson, T.ら、1991}。

【0143】

2つの抗原結合ドメインが存在する場合は、各ドメインは異なるエピトープに対して向けられてよく、「二重特異性」抗体と呼ばれる。

【0144】

上記抗体は、本発明の高度免疫血清に反応性の抗原およびその断片を発現するクローンを単離または同定するため、または該高度免疫血清に反応性の抗原およびその断片を精製するため、アフィニティークロマトグラフィーによる単離および／または精製のために固相支持体に該抗体を付着させることによって用いることができる。

【0145】

それゆえ、とりわけ本発明の高度免疫血清に反応性の抗原およびその断片に対する抗体は、感染症、特に細菌感染症、とりわけストレプトコッカス・ピオゲネスによる感染症を抑制および／または治療するのに用いることができる。

【0146】

高度免疫血清に反応性の抗原およびその断片は、抗原として、エピトープとして、または免疫学的に等価な誘導体をも包含し、これは本発明の特別の側面を形成する。本明細書において用いる「抗原として等価な誘導体」は、高度免疫血清に反応性の抗原およびその断片またはある種の抗体によって特異的に認識されるその等価物を包含し、該抗体は本発明によるタンパク質または高度免疫血清に反応性の抗原およびその断片に対して産生されたときに病原体と哺乳動物宿主との間の相互作用を妨害する。本明細書において用いる「免疫学的に等価な誘導体」は、適当な製剤中で用いたときに脊椎動物において抗体を産生するペプチドまたはその等価物を包含し、該抗体は病原体と哺乳動物宿主との間の相互作用を妨害するように作用する。

【0147】

高度免疫血清に反応性の抗原およびその断片、たとえば抗原としてまたは免疫学的に等価な誘導体またはその融合タンパク質は、マウスまたは他の動物、たとえばラットやニワトリを免疫すべく抗原として用いることができる。融合タンパク質は、高度免疫血清に反応性の抗原およびその断片に安定性を付与することができる。抗原は、たとえばコンジュゲートにより免疫原性の担体タンパク質、たとえばウシ血清アルブミン (BSA) またはキーホールリンペットヘモシアニン (KLH) と結合させることができる。あるいは、タンパク質または高度免疫血清に反応性の抗原およびその断片の複数のコピーを含む抗原性ペプチド、または抗原としてまたは免疫学的に等価な高度免疫血清に反応性の抗原およびその断片は、担体の使用をなくすべく免疫原性を改善して十分に抗原性にすることができる。

【0148】

抗体またはその誘導体は、個体における免疫原性を少なくするために修飾するのが好ましい。たとえば、個体がヒトである場合、抗体は「ヒト化」するのが最も好ましく、その際、たとえば {Jones, P.ら、1986} または {Tempest, P.ら、1991} に記載されているように、ハイブリドーマ由来抗体の相補性決定領域はヒトモノクローナル抗体中に移植される。

【0149】

遺伝子免疫 (genetic immunization) における本発明のポリヌクレオチドの使用は、適当な送達法、たとえば筋肉中へのプラスミドDNAの直接注入、特定のタンパク質担体と複合体を形成したDNAの送達、リン酸カルシウムによるDNAの共沈、種々の形態のリポソーム中へのDNAの封じ込め、パーティクルガン (particle bombardment) {Tang, D.ら、1992}、{Eisenbraun, M.ら、1993} およびクローニングしたレトロウイルスを用いたインビボ感染 {Seeger, C.ら、1984} を用いるのが好ましいであろう。

【0150】

さらなる側面において、本発明は、本発明による高度免疫血清に反応性の抗原およびその断片のいずれかに結合したペプチド、およびそのようなペプチドの製造方法に関し、その際、該方法は本発明による高度免疫血清に反応性の抗原およびその断片の使用を特徴とし、基本的な工程は当業者に知られたものである。

【0151】

そのようなペプチドは、技術の状態に従った方法、たとえばファージディスプレイまたはリボソームディスプレイを用いて生成することができる。ファージディスプレイの場合、基本的にペプチドのライブラリーはファージの形態で生成され、この種のライブラリーを標的分子、本発明の場合は本発明による高度免疫血清に反応性の抗原およびその断片と接触させる。標的分子に結合したペプチドは、その後、好ましくは標的分子との複合体として各反応から除去する。結合特性がある程度まで特別に実現させた実験的な設定、たとえば塩濃度などに依存することは当業者には知られている。標的分子に結合したペプチドをより高い親和性またはより大きな力でライブラリーの非結合成員から分離した後、および任意に標的分子を標的分子とペプチドとの複合体から除去した後、各ペプチドを引き続き特徴付けることができる。特徴付けに先立ち、任意に増幅工程を、たとえばペプチドコードファージの増幅によって行う。特徴付けは、好ましくは標的結合ペプチドのシーケンシングを含む。基本的にペプチドはその長さに制限されるものではないが、約8～20アミノ酸の長さのペプチドが各方法から得られるのが好ましい。ライブラリーのサイズは約 $10^2 \sim 10^{18}$ 、好ましくは $10^8 \sim 10^{15}$ の異なるペプチドであるが、これに限られるものではない。

【0152】

高度免疫血清に反応性の抗原およびその断片の特別の形態は、いわゆる「アンチカリン (anticalines)」と呼ばれるものであり、このものはドイツ特許出願DE 197 42 706に記載されている。

【0153】

さらなる側面において、本発明は、本発明による高度免疫血清に反応性の抗原およびその断片のいずれかと相互作用する機能性の核酸、およびそのような機能性の核酸の製造方法に関し、その際、該方法は本発明による高度免疫血清に反応性の抗原およびその断片の使用を特徴とし、基本的な工程は当業者に知られたものである。機能性の核酸は好ましくはアプタマーまたはシュピーゲルマー (spiegelmers) である。

【0154】

アプタマーは、一本鎖または二本鎖のいずれかであり、標的分子と特異的に相互作用するD-核酸である。アプタマーの製造または選択は、たとえばヨーロッパ特許EP 0 533 838に記載されている。基本的に以下の工程を行う。まず、核酸の混合物、すなわち潜在的なアプタマーを用意し、その際、各核酸は典型的に幾つかの、好ましくは少なくとも8のその後にランダム化されるヌクレオチドのセグメントを含む。この混合物を引き続き標的分子と接触させると、核酸分子は候補混合物と比べて標的に対するより増大した親和性やより大きな力に基づいて標的分子に結合する。結合した核酸分子は、その後に混合物の残りから分離する。任意に、かくして得られた核酸を、たとえば複製連鎖反応を用いて増幅させる。これらの工程を数回繰り返して最終的に標的に特異的に結合した核酸の比率の増大した混合物を得、ついで該混合物から最終的な結合核酸を任意に選択する。これらの特異的に結合する核酸はアプタマーと呼ばれる。アプタマーの生成または同定の方法のいずれの段階においても、個々の核酸の混合物の試料を取り出してその配列を標準法を用いて決定できることは明らかである。たとえば定められた化学基を導入することによりアプタマーを安定化することは本発明の範囲内であり、このことはアプタマーを生成する当業者には知られているものである。そのような修飾は、たとえば、ヌクレオチドの糖残基の2'位へのアミノ基の導入であってよい。アプタマーは現在、治療剤として用いられている。しかしながら、かくして選択または生成したアプタマーを標的の確認のためおよび／または医薬、好ましくは小分子に基づく医薬の開発のためのリード化合物として用いること

も本発明の範囲内である。このことは実際には競合アッセイにより行われ、その際、標的分子とアプタマーとの間の特異的な相互作用は候補医薬によって抑制され、それゆえ標的とアプタマーとの複合体からアプタマーを置換すると各医薬候補は標的とアプタマーとの間の相互作用の特異的な抑制を可能とし、もしも相互作用が特異的であれば該候補医薬は少なくとも原理的に標的を阻止し、それゆえそのような標的を含む各系において標的の生物学的な利用または活性を低減させるであろうことが推定される。かくして得られた小分子は、ついでさらなる誘導体化および修飾に供してその物理特性、化学特性、生物学的特性および／または医薬的特性、たとえば毒性、特異性、生分解性およびバイオアベイラビリティを最適にすることができる。

【0155】

シュピーゲルマーおよびその生成または製造は同様の原理に基づいている。シュピーゲルマーの製造は、国際特許出願WO 98/08856に記載されている。シュピーゲルマーはL-核酸であり、これはアプタマーがD-ヌクレオチドであるのに対してL-ヌクレオチドから構成されることを意味する。シュピーゲルマーは、生物学的系において非常に高い安定性を有し、アプタマーに匹敵してそれが向けられた標的分子と特異的に相互作用するという事実によって特徴付けられる。シュピーゲルマーを生成するプロセスでは、D-核酸の不均質集団を生成し、この集団を標的分子の光学的对掌体、本発明の場合では、たとえば、本発明による高度免疫血清に反応性の抗原およびその断片の天然に存在するL-エナンシオマーのD-エナンシオマーと接触させる。引き続き、標的分子の光学的对掌体と相互作用しないD-核酸を分離する。しかしながら、標的分子の光学的对掌体と相互作用するD-アミノ酸を分離し、任意に決定および／またはシークエンシングし、その後D-核酸から得られた核酸配列情報に基づいて対応するL-核酸を合成する。これらの標的分子の光学的对掌体と相互作用する上記D-核酸と配列に関して同一であるL-核酸は、標的分子の光学的对掌体よりも天然に存在する標的分子と特異的に相互作用するであろう。アプタマーを生成する方法と同様、種々の工程を数回繰り返し、それゆえ標的分子の光学的对掌体と特異的に相互作用する核酸を富ませることも可能である。

【0156】

さらなる側面において、本発明は、本発明による核酸分子のいずれかと相互作用する機能性の核酸、およびそのような機能性の核酸の製造方法に関し、その際、該方法は本発明による核酸分子およびそのそれぞれの配列の使用を特徴とし、基本的な工程は当業者に知られたものである。機能性の核酸は好ましくはリボザイム、アンチセンスオリゴヌクレオチドおよびsiRNAである。

【0157】

リボザイムは触媒的に活性な核酸であり、好ましくはRNAからなり、基本的に2つの残基を含む。第一の残基は触媒活性を示し、一方、第二の残基は標的核酸、本発明の場合には本発明による高度免疫血清に反応性の抗原およびその断片をコードする核酸との特異的な相互作用を担う。標的核酸とリボザイムの第二の残基とが、典型的にこれらハイブリダイズする2つの鎖上の本質的に相補的な連なりのハイブリダイゼーションおよびワトソン-クリック塩基対形成によって相互作用すると、触媒的に活性な残基は活性となるが、このことはリボザイムの触媒活性がホスホジエステラーゼ活性である場合に標的核酸を分子内または分子間で触媒することを意味する。その後、標的核酸がさらに分解されるが、このことは最終的に標的核酸並びに該標的核酸に由来するタンパク質の分解という結果となる。リボザイム、その使用およびデザイン原理は当業者に知られており、たとえば、{Doherty, E.ら、2001} および {Lewin, A.ら、2001} に記載されている。

【0158】

医薬の製造のためおよび診断剤としてのアンチセンスオリゴヌクレオチドの活性およびデザインは、それぞれ同様の作用様式に基づいている。基本的に、アンチセンスオリゴヌクレオチドは塩基相補性に基づいて標的RNA、好ましくはmRNAとハイブリダイズしてリボヌクレアーゼHを活性化する。リボヌクレアーゼHは、ホスホジエステル結合DNAおよびホスホロチオエート結合DNAの両者によって活性化される。しかしながら、ホ

スホジエステル結合DNAは、ホスホロチオエート結合DNAを例外として細胞のヌクレアーゼによって速やかに分解される。これらの耐性で天然には存在しないDNA誘導体は、RNAとハイブリダイズしてもリボヌクレアーゼHを抑制しない。換言すればアンチセンスポリヌクレオチドはDNA-RNAハイブリッド複合体としてのみ効果がある。この種のアンチセンスオリゴヌクレオチドの例は、とりわけ米国特許第5,849,902号および同第5,989,912号に記載されている。換言すれば、標的核酸、本発明の場合は本発明による高度免疫血清に反応性の抗原およびその断片の核酸分子の核酸配列に基づき、各核酸配列から原則として導かれる標的タンパク質から、または核酸配列、とりわけmRNAをそのまま知ることによることのいずれによっても、適当なアンチセンスオリゴヌクレオチドを塩基相補性の原理に基づいてデザインすることができる。

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【0159】

最も好ましいのはホスホロチオエートDNAの短い連なり（3～9塩基）を有するアンチセンスオリゴヌクレオチドである。細菌のリボヌクレアーゼHの活性化には最小3DNA塩基が必要であり、哺乳動物のリボヌクレアーゼHの活性化には最小5塩基が必要である。これらキメラオリゴヌクレオチドでは、リボヌクレアーゼHの基質を形成する中央領域が存在し、該中央領域は、リボヌクレアーゼHの基質を形成しない修飾ヌクレオチドからなるハイブリダイズする「アーム」によってフランキングされている。キメラオリゴヌクレオチドのハイブリダイズするアームは、2'-O-メチルまたは2'-フルオロなどで修飾されていてよい。別のアプローチでは該アーム中にメチルホスホネート結合またはホスホルアミデート結合を用いた。本発明の実施に有用なアンチセンスオリゴヌクレオチドのさらなる態様は、P-メトキシオリゴヌクレオチド、部分的P-メトキシオリゴデオキシリボヌクレオチドまたはP-メトキシオリゴヌクレオチドである。

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【0160】

本発明と特に関連し有用なものは、上記2つの米国特許においてより詳細に記載されたアンチセンスオリゴヌクレオチドである。これらオリゴヌクレオチドは、天然に存在する5'→3'結合ヌクレオチドを含んでいない。その代わり、これらオリゴヌクレオチドは2つのタイプのヌクレオチドを有する：リボヌクレアーゼHを活性化する2'-デオキシホスホロチオエート、および同活性化しない2'-修飾ヌクレオチド。2'-修飾ヌクレオチド間の結合は、スホジエステル、ホスホロチオエートまたはP-エトキシスホジエステルであってよい。リボヌクレアーゼHの活性化は隣接するリボヌクレアーゼH活性化領域によって達成され、該領域は細菌のリボヌクレアーゼHを活性化するための3～5の2'-デオキシホスホロチオエートヌクレオチド、および真核生物、とりわけ哺乳動物のリボヌクレアーゼHを活性化するための5～10の2'-デオキシホスホロチオエートヌクレオチドを含む。分解からの保護は、5'および3'末端塩基を高度にヌクレアーゼ耐性とすることにより、および任意に3'末端ブロック基を導入することにより、達成される。

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【0161】

さらに詳細には、アンチセンスオリゴヌクレオチドは、5'末端および3'末端；および2'-修飾スホジエステルヌクレオチドおよび2'-修飾P-アルキルオキシホストリエステルヌクレオチドよりなる群から独立に選ばれた11～59の5'→3'結合ヌクレオチドを含み、その際、5'末端ヌクレオチドは3～10の隣接したホスホロチオエート結合デオキシリボヌクレオチドのリボヌクレアーゼH活性化領域に結合しており、該オリゴヌクレオチドの3'末端は、逆デオキシリボヌクレオチド、1～3のホスホロチオエート2'-修飾リボヌクレオチドの隣接する連なり、ビオチン基およびP-アルキルオキシホストリエステルヌクレオチドよりなる群から選ばれる。

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【0162】

また、上記で特定したように5'末端ヌクレオチドではなく3'末端ヌクレオチドがリボヌクレアーゼH活性化領域に結合しているアンチセンスオリゴヌクレオチドを用いることもできる。また、5'末端は該オリゴヌクレオチドの3'末端以外の特定の基から選ばれる。

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【0163】

本発明による核酸並びに高度免疫血清に反応性の抗原およびその断片は、医薬組成物、とりわけワクチンとして、またはその製造のために用いることができる。そのような好ましい医薬組成物、好ましくはワクチンは、ストレプトコッカス・ピオゲネスによって引き起こされる、ストレプトコッカス・ピオゲネスに関連する、またはストレプトコッカス・ピオゲネスに付随する疾患の予防または治療のためのものである。本発明の他の側面において、本発明は、個体、とりわけ哺乳動物において免疫応答を誘起する方法に関し、該方法は、該個体に、該個体を感染、とりわけ連鎖球菌感染、最も詳細にはストレプトコッカス・ピオゲネス感染から防御する抗体を生成するのに適した本発明の高度免疫血清に反応性の抗原およびその断片、またはその断片または変異体を接種することを含む。

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【0164】

本発明のさらに他の側面は、個体において免疫応答を誘起する方法に関し、該方法は、免疫応答を誘起して抗体またはサイトカイン産生T細胞もしくは細胞障害性T細胞のいずれかの細胞媒体T細胞応答を生成して該個体を疾患（該疾患が個体においてすでに確立されているか否かは問わない）から防禦するため、遺伝子療法または他の仕方により、高度免疫血清に反応性の抗原およびその断片、またはその断片または変異体を発現させるために高度免疫血清に反応性の抗原およびその断片、またはその断片または変異体を機能的にコードする核酸をインビボで送達することを含む。遺伝子を投与する一つの方法は、粒子上のコーティングとしてまたは他の仕方では遺伝子を所望の細胞中に促進することによる。

【0165】

本発明のさらなる側面は、免疫組成物に関し、該組成物は免疫応答を誘起できる宿主中に導入したときにそのような宿主中で免疫応答を誘起させ、本発明の高度免疫血清に反応性の抗原およびその断片の抗原をコードし発現する組換えDNAを含む。免疫応答は治療または予防のために用いることができ、抗体免疫またはCTLやCD4+T細胞によって生成するものなどの細胞性免疫の形態を取ってよい。

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【0166】

本発明の高度免疫血清に反応性の抗原およびその断片またはその断片は、それ自体は抗体を産生しないが第一のタンパク質を安定化することができ、免疫原性で防禦性の特性を有する融合タンパク質を生成する補助タンパク質（co-protein）に融合させることができる。この融合した組換えタンパク質は、さらに抗原性の補助タンパク質、たとえばグルタチオン-S-トランスフェラーゼ（GST）またはベーターガラクトシダーゼ、タンパク質を可溶化しその産生および精製を容易にする比較的大きな補助タンパク質を含んでいるのが好ましい。さらに、補助タンパク質は免疫系の一般化した刺激を付与するという意味でアジュバントとして作用してもよい。補助タンパク質は第一のタンパク質のアミノ末端またはカルボキシ末端のいずれかに結合させることができる。

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【0167】

また、本明細書に記載の核酸分子またはその特定の断片をストレプトコッカス・ピオゲネス感染の動物モデルにおけるそのような遺伝子免疫実験に用いる方法も本発明によって提供される。そのような断片は、予防的または治療的な免疫応答を引き起こしうるタンパク質エピトープを同定するのに特に有用であろう。このアプローチは、哺乳動物、特にヒトにおけるストレプトコッカス・ピオゲネス感染の予防剤または治療剤を開発するための、感染に首尾よく抵抗または排除した動物の必要な器官からの特別の価値を有するモノクローナル抗体のその後の調製を可能としうる。

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【0168】

高度免疫血清に反応性の抗原およびその断片は、たとえば障害組織への細菌の付着を阻止することによって細菌の侵入に対して防禦する特異的抗体を産生させるべく宿主のワクチン接種のための抗原として用いることができる。組織障害の例としては、たとえば、機械的障害、化学的障害または熱的障害によってまたは内在デバイスの移植によって引き起こされた皮膚または結合組織の創傷、または粘膜性の膜、たとえば口、乳房、尿道または膣の創傷が挙げられる。

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【0169】

本発明はまた、適当な担体とともに免疫原性の組換えタンパク質を含むワクチン製剤を含む。タンパク質は胃内部では分解されてしまうので、たとえば、皮下、筋肉内、静脈内、または皮内投与を含む非経口により投与するのが好ましい。非経口投与に適した製剤としては、抗酸化剤、緩衝液、静菌剤および製剤を個体の体液、好ましくは血液と等張にする溶質を含む水性または非水性の滅菌注射液；および懸濁化剤または粘稠化剤を含む水性または非水性の懸濁液が挙げられる。製剤は、単位投与または多回投与容器、たとえば密封したアンプルおよびバイアル中で提供されてよく、使用直前に滅菌液体担体を添加するだけでよい凍結乾燥条件下で貯蔵してよい。ワクチン製剤はまた、製剤の免疫原性を高めるためのアジュバント系、たとえば水中油系や当該技術分野で知られた他の系を含んでいてよい。投与量はワクチンの比活性に依存し、常法の実験により容易に決定することができるであろう。

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【0170】

他の側面によれば、本発明は、ストレプトコッカス・ピオゲネスについて本発明において提供されるもののような高度免疫血清に反応性の抗原またはその断片を含む医薬組成物に関する。そのような医薬組成物は、ストレプトコッカス・ピオゲネスに対する1またはそれ以上の高度免疫血清に反応性の抗原またはその断片を含む。場合により、そのようなストレプトコッカス・ピオゲネスの高度免疫血清に反応性の抗原またはその断片はまた、複合医薬組成物における他の病原体に対する抗原と組み合わせることができる。好ましくは、該医薬組成物は、ストレプトコッカス・ピオゲネスおよび／または該ワクチンにその抗原が含まれる他の病原体によって引き起こされる感染症を予防または治療するためのワクチンである。

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【0171】

さらなる側面によれば、本発明は、ストレプトコッカス・ピオゲネスについて上記で同定したような高度免疫血清に反応性の抗原またはその断片をコードする核酸分子を含む医薬組成物に関する。そのような医薬組成物は、ストレプトコッカス・ピオゲネスに対する高度免疫血清に反応性の抗原またはその断片をコードする1またはそれ以上の核酸を含む。場合により、そのようなストレプトコッカス・ピオゲネスの高度免疫血清に反応性の抗原またはその断片をコードする核酸分子はまた、複合医薬組成物における他の病原体に対する抗原をコードする核酸分子と組み合わせることができる。好ましくは、該医薬組成物は、ストレプトコッカス・ピオゲネスおよび／または該ワクチンにその抗原が含まれる他の病原体によって引き起こされる感染症を予防または治療するためのワクチンである。

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【0172】

医薬組成物は、適当な補助物質、たとえば緩衝物質、安定化剤またはさらなる活性成分、とりわけ医薬組成物および／またはワクチンの製造と関連して知られている成分を含んでいてよい。

【0173】

本発明による高度免疫血清に反応性の抗原、その断片またはそのコード核酸分子のために好ましい担体／賦形剤は、所定の高度免疫血清に反応性の抗原、その断片またはそのコード核酸分子に対する免疫応答をさらに刺激する免疫促進化合物である。好ましくは本発明による医薬組成物中の免疫促進化合物は、ポリカチオン性物質、とりわけポリカチオン性ペプチド、免疫促進性核酸分子、好ましくは免疫促進性デオキシヌクレオチド、ミョウバン、フロイントの完全アジュバント、フロイントの不完全アジュバント、神経刺激性の化合物、とりわけヒト成長ホルモン、またはそれらの組合せよりなる群から選ばれる。

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【0174】

医薬組成物、とりわけワクチンが、本発明による高度免疫血清に反応性の抗原、その断片および／またはそのコード核酸分子とは別に生物学的にまたは製剤学的に活性な他の化合物を含むことも本発明の範囲内である。好ましくは、ワクチン組成物は少なくとも1のポリカチオン性ペプチドを含む。本発明に従って用いるポリカチオン性化合物は、WO 97/30721による特徴的な作用を示すあらゆるポリカチオン性化合物であってよい。

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好ましいポリカチオン性化合物は、塩基性ポリペプチド、有機ポリカチオン、塩基性ポリアミノ酸またはその混合物から選ばれる。これらポリアミノ酸は、少なくとも4アミノ酸残基の鎖長を有していなければならない(WO 97/30721)。特に好ましいのは、ポリリシン、ポリアルギニン、および8を超える、とりわけ20を超えるアミノ酸残基の範囲に20%を超える、とりわけ50%を超える塩基性アミノ酸を含むポリペプチドまたはその混合物のようなペプチド結合を含む物質である。他の好ましいポリカチオンおよびその医薬組成物は、WO 97/30721(たとえば、ポリエチレンジイミン)およびWO 99/38528に記載されている。好ましくは、これらポリペプチドは20~500アミノ酸残基、とりわけ30~200残基を含む。

【0175】

これらポリカチオン性化合物は化学的にまたは組換えにより製造してよく、あるいは天然の採取源に由来してもよい。

【0176】

カチオン性(ポリ)ペプチドはまた、{Ganz, T., 1999}に概説された特性を有する抗菌性のものであってもよい。これら(ポリ)ペプチドは、原核生物または動物または植物起源のものであってもよく、化学的にまたは組換えにより製造されてよい(WO 02/13857)。ペプチドはまたデフェンシンのクラスに属していてもよい(WO 02/13857)。そのようなペプチドの配列は、たとえば、以下のインターネットアドレスのもと、抗菌配列データベース(Antimicrobial Sequences Database)で見出すことができる。
<http://www.bbcm.univ.trieste.it/~tossi/pag2.html>

【0177】

そのような宿主防禦ペプチドまたはデフェンシン(defensives)もまた、本発明によるポリカチオン性ポリマーの好ましい形態である。一般に、好ましくはAPC(樹状細胞を含む)によって媒介される獲得免疫系を最終生成物として活性化(またはダウンレギュレーション)することを可能にする化合物はポリカチオン性ポリマーとして用いる。

【0178】

本発明においてポリカチオン性物質として使用するのに特に好ましいのは、カテリシジン(cathelicidin)由来の抗菌ペプチドまたはその誘導体(国際特許出願WO 02/13857、参照のため本明細書中に引用する)、とりわけ哺乳動物、好ましくはヒト、ウシまたはマウスのカテリシジンに由来する抗菌ペプチドである。

【0179】

天然の採取源に由来するポリカチオン性化合物としては、HIV-REVまたはHIV-TAT(由来のカチオン性ペプチド、アンテナペディア(antennapedia)ペプチド、キトサンまたはキトサンの他の誘導体)または生化学的な製造または組換え製造によりこれらペプチドまたはタンパク質に由来する他のペプチドが挙げられる。他の好ましいポリカチオン性化合物は、カテリン(cathelin)またはカテリンの関連物質またはカテリンに由来する物質である。たとえば、マウスカテリンはアミノ酸配列: $\text{NH}_2\text{-RLAGLLRKGGKIGELKKIGOKIKNFFQKLVPQP E-COOH}$ を有するペプチドである。カテリンの関連物質またはカテリンに由来する物質はカテリン配列の全部または一部を含み、少なくとも15~20アミノ酸残基を有する。誘導体化は、20の標準アミノ酸以外のアミノ酸による天然アミノ酸の置換または修飾を含む。さらに、さらなるカチオン性残基がそのようなカテリン分子中に導入されてよい。これらカテリン分子は、抗原と組み合わせるのが好ましい。これらカテリン分子は驚くべきことに、さらなるアジュバントを加えなくとも抗原に対するアジュバントとして有効なことがわかった。それゆえ、そのようなカテリン分子は、さらなる免疫活性化物質を用いまたは用いることなく、ワクチン製剤において有効なアジュバントとして用いることが可能である。

【0180】

本発明に従って用いることのできる他の好ましいポリカチオン性物質は、3~7の疎水性アミノ酸のリンカーによって隔てられた少なくとも2つのKLKモチーフを含む合成ペプチドである(WO 02/32451、参照のため本明細書中に引用する)。

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【0181】

本発明の医薬組成物は、さらに免疫促進性の核酸を含んでいてよい。免疫促進性の核酸は、たとえば、中性または人工的なCpG含有核酸、非脊椎動物由来の核酸の短い連なり、またはある種の塩基の文脈において非メチル化シトシン-グアニンジヌクレオチド(CpG)を含む短いオリゴヌクレオチドの形態であってよい(たとえば、WO 96/02555に記載)。あるいは、たとえばWO 01/93903に記載されているようなイノシンおよびシチジンに基づく核酸、またはデオキシイノシンおよび/またはデオキシウリジンを含むデオキシ核酸(WO 01/93905およびPCT/EP 02/05448; 参照のため本明細書中に引用する)を、本発明のために免疫促進性の核酸として用いるのが好ましい。好ましくは、異なる免疫促進性の核酸の混合物を本発明に従って用いることができる。

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【0182】

上記ポリカチオン性化合物のいずれかを上記免疫促進性の核酸のいずれかと組み合わせることもまた本発明の範囲内である。好ましくは、そのような組合せは、WO 01/93905、WO 02/32451、WO 01/54720、WO 01/93903、WO 02/13857およびPCT/EP 02/05448およびオーストリア特許出願A 1924/2001(参照のため本明細書中に引用する)の記載によるものである。

【0183】

さらにまたは他の態様として、そのようなワクチン組成物は、本発明による高度免疫血清に反応性の抗原およびその断片、およびそのコード核酸分子とは別に神経刺激性の化合物を含んでいてよい。好ましくは、神経刺激性の化合物は、たとえばWO 01/24822に記載されているように、ヒト成長ホルモンである。また、神経刺激性の化合物を上記ポリカチオン性化合物および/または上記免疫促進性の核酸のいずれかと組み合わせるのが好ましい。

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【0184】

さらなる側面において、本発明は医薬組成物に関する。そのような医薬組成物は、たとえば本明細書に記載のワクチンである。医薬組成物はまた、以下の化合物またはその組合せを含む医薬組成物である: 本発明による核酸分子、本発明による高度免疫血清に反応性の抗原およびその断片、本発明によるベクター、本発明による細胞、本発明による抗体、本発明による機能性の核酸、および本発明によるアンチカリンなどの結合性ペプチド、本明細書に記載の方法によりスクリーニングしたアゴニストおよびアンタゴニスト。これに関連して、これら化合物のいずれも、細胞、組織または生体に使用する非滅菌または滅菌担体、たとえば主体に投与するのに適した医薬担体と組み合わせ用いることができる。そのような組成物は、たとえば、培地添加物または治療学的有効量の本発明の高度免疫血清に反応性の抗原およびその断片および医薬担体または賦形剤を含む。そのような担体としては、これらに限られるものではないが、食塩水、緩衝食塩水、デキストロース、水、グリセリン、エタノールおよびそれらの組合せが挙げられる。製剤は投与方法に適合していなければならない。

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【0185】

医薬組成物は、たとえば、局所、経口、肛門、経膈、静脈内、腹腔内、筋肉内、皮下、鼻内または皮内経路による投与を含む、有効で都合のよい仕方で投与してよい。

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【0186】

療法においてまたは予防として、活性剤は注射組成物として、たとえば滅菌水性分散液、好ましくは等張液として個体に投与することができる。

【0187】

あるいは、組成物は、たとえば、軟膏剤、クリーム剤、ローション剤、眼軟膏剤、点眼剤、点耳剤、口腔洗浄剤、含浸させた包帯剤および縫糸およびエアゾル剤の形態の局所投与用に製剤化でき、たとえば、保存剤、薬剤の浸透を助ける溶媒、および軟膏剤およびクリーム剤における皮膚軟化剤を含む適当な通常の添加剤を含んでいてよい。そのような局所製剤はまた、適合性の通常の担体、たとえば、クリーム剤または軟膏剤のベース、およ

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びローション剤のためのエタノールまたはオレイルアルコールをも含んでいてよい。そのような担体は、製剤の約 1 重量%～約 98 重量%を構成してよい；さらに通常には、そのような担体は、製剤の約 80 重量%を構成するであろう。

【0188】

上記療法に加え、本発明の組成物は一般に創傷組織において暴露されたマトリックスタンパク質への細菌の接着を予防するための創傷治療剤として、および抗生物質予防法の代替としてまたは抗生物質予防法とともに歯科治療において予防的使用のために用いることができる。

【0189】

ワクチン組成物は都合よくは注射剤の形態である。通常のアジュバントを免疫応答を促進するために用いることができる。ワクチン接種に適した単位投与量は $0.05 \sim 5 \mu\text{g} / \text{kg}$ の抗原であり、そのような投与量は 1～3 回、1～3 週間の間隔で投与するのが好ましい。

【0190】

指定した投与量の範囲で、本発明の化合物による有害な毒性作用が観察されてはならず、そのような毒性作用は本発明の化合物を適当な個体に投与することを排除するであろう。

【0191】

さらなる態様において、本発明は、本発明の上記組成物の 1 またはそれ以上の成分を充填した 1 またはそれ以上の容器を含む診断および医薬パックおよびキットに関する。成分は、有用な量、剤形、製剤または配合剤中に配合してよい。そのような容器には、ヒトへの投与のための医薬製品または生物学的製品の製造、使用または販売を規制する政府当局の許認可を反映して、該当局によって規定された形態の注意書きが添付されていてよい。

【0192】

本発明に関して、たとえば医薬組成物またはワクチンの使用などの本明細書に開示した疾患に関連した使用は、とりわけ連鎖球菌、さらに好ましくはストレプトコッカス・ピオゲネスによって引き起こされた、関連したまたは付随する疾患または疾患状態である。この点に関連して、ストレプトコッカス・ピオゲネスは本明細書に開示したものを含む幾つかの株を含むことに注意すべきである。本発明により予防および／または治療すべき細菌感染に関連する、引き起こされたまたは付随する疾患は、ヒトでの細菌性咽頭炎、猩紅熱、インペチゴ、リウマチ熱、壊死性筋膜炎および敗血症を含む。

【0193】

なおさらなる態様において、本発明は、本発明による高度免疫血清に反応性の抗原または核酸のいずれかをを用いたスクリーニング法に関する。そのようなスクリーニング法は当業者には知られており、アゴニストまたはアンタゴニストをスクリーニングすべくデザインすることができる。好ましくは、本発明では本発明による高度免疫血清に反応性の抗原およびその断片の相互作用パートナーへの結合を抑制または妨害するアンタゴニストをスクリーニングする。そのような相互作用パートナーは、天然に存在する相互作用パートナーであっても天然に存在しない相互作用パートナーであってもよい。

【0194】

本発明はまた、化合物をスクリーニングして、本発明の高度免疫血清に反応性の抗原およびその断片または核酸の機能、たとえば結合分子との相互作用を促進（アゴニスト）または阻害（アンタゴニスト）するものを同定する方法をも提供する。スクリーニング法は高処理量を含んでいてよい。

【0195】

たとえば、アゴニストまたはアンタゴニストをスクリーニングするため、本発明による核酸分子の相互作用パートナーおよび核酸は、それぞれ、合成反応混合物、細胞の構成成分、たとえば細胞膜、細胞のエンベロープまたは細胞壁、またはそれらの調製物であってよく、本発明の高度免疫血清に反応性の抗原およびその断片に結合する分子を発現する細胞から調製することができる。この調製物をアゴニストまたはアンタゴニストである候補

分子の不在下または存在下、標識した高度免疫血清に反応性の抗原およびその断片とともにインキュベートする。候補分子が結合分子に結合する能力は、標識リガンドの結合の低減に反映される。無償で (gratuitously)、すなわち高度免疫血清に反応性の抗原およびその断片の機能的な作用を誘発することなく結合する分子は、良好なアンタゴニストである可能性が高い。よく結合し、高度免疫血清に反応性の抗原およびその断片と同じかまたは密接に関連した機能的な作用を誘発する分子は良好なアゴニストである。

【0196】

潜在的なアゴニストおよびアンタゴニストの機能的な作用の測定は、たとえば、候補分子と細胞または適当な細胞調製物との相互作用の後にリポーター系の活性を決定し、ついで該作用を本発明の高度免疫血清に反応性の抗原およびその断片または高度免疫血清に反応性の抗原およびその断片と同じ作用を生じさせる分子の作用と比較することによって行う。この観点から有用なリポーター系としては、これらに限られるものではないが、生成物に変換された比色標識基質、高度免疫血清に反応性の抗原およびその断片の機能的活性の変化に応答するリポーター遺伝子、および当該技術分野で知られた結合アッセイが挙げられる。

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【0197】

アンタゴニストのアッセイの他の例は、本発明の高度免疫血清に反応性の抗原およびその断片および潜在的なアンタゴニストを膜結合した結合分子、組換え結合分子、天然の基質またはリガンド、または基質またはリガンドのミメチックと、適当な競合抑制アッセイの条件下で混合する競合アッセイである。高度免疫血清に反応性の抗原およびその断片は、結合分子または生成物に変換された分子に結合した高度免疫血清に反応性の抗原およびその断片の分子数を正確に決定して潜在的なアンタゴニストの有効性を評価できるように、放射能または比色化合物などによって標識することができる。

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【0198】

潜在的なアンタゴニストとしては、本発明の高度免疫血清に反応性の抗原およびその断片に結合し、それによってその活性を抑制または消滅させる小さな有機分子、ペプチド、ポリペプチドおよび抗体が挙げられる。潜在的なアンタゴニストはまた、高度免疫血清に反応性の抗原およびその断片の機能的な活性を誘起することなく結合分子上の同じ部位に結合する小さな有機分子、ペプチド、ポリペプチド、たとえば密接に関連したタンパク質または抗体であってもよい。

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【0199】

潜在的なアンタゴニストは、高度免疫血清に反応性の抗原およびその断片の結合部位に結合してその場所を占め、それによって細胞の結合分子への結合を妨害して正常な生物学的活性を妨害する小分子を含む。小分子の例としては、これらに限られるものではないが、小さな有機分子、ペプチドまたはペプチド様分子が挙げられる。他の潜在的なアンタゴニストとしてはアンチセンス分子が挙げられる。

【0200】

他の潜在的なアンタゴニストとしては、アンチセンス分子が挙げられる（これら分子の記載については、{Okano, H.ら、1991}；OLIGODEOXYNUCLEOTIDES AS ANTISENSE INHIBITORS OF GENE EXPRESSION；CRC Press, Boca Ration, FL (1988)を参照）。

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【0201】

好ましい潜在的なアンタゴニストは、本発明の高度免疫血清に反応性の抗原およびその断片の誘導体を含む。

【0202】

本明細書において本発明による高度免疫血清に反応性の抗原およびその断片の活性とは、それがその相互作用パートナーのいずれかに結合する能力またはその相互作用パートナーのいずれかに結合するそのような能力の程度である。

【0203】

特別の態様において、本発明は、感染の続発症の原因である病原体と哺乳動物宿主との間の最初の身体的な相互作用を妨害するための本発明の高度免疫血清に反応性の抗原およ

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びその断片、核酸またはインヒビターの使用を提供する。とりわけ本発明の分子は、(i) 留置デバイス上の哺乳動物細胞外マトリックスタンパク質への、または創傷中の細胞外マトリックスタンパク質へのストレプトコッカス・ピオゲネスの接着の防止；(ii) たとえば哺乳動物チロシンキナーゼのリン酸化によるタンパク質を媒体した哺乳動物細胞侵入を阻止して組織損傷を媒体する哺乳動物細胞外マトリックスタンパク質と細菌タンパク質との細菌接着を阻止すること；(iv) 留置デバイスの移植または他の外科的手段以外によって開始される感染における病因の正常な進行の阻止に用いることができる。

【0204】

本明細書で提供される配列をコードする各DNAは、抗菌化合物の発見および開発に用いることができる。コードされたタンパク質は発現されると抗菌医薬のスクリーニングのための標的として用いることができる。さらに、コードされたタンパク質のアミノ末端領域または各mRNAのシャインダルガーノ配列または他の翻訳を容易にする配列をコードするDNA配列は、目的とするコード配列の発現を制御するためのアンチセンス配列を構築するのに用いることができる。

【0205】

アンタゴニストおよびアゴニストは、たとえば、連鎖球菌、とりわけストレプトコッカス・ピオゲネスの感染から生じる疾患、たとえば敗血症を抑制するのに用いることができる。

【0206】

さらなる側面において、本発明はアフィニティデバイスに関し、そのようなアフィニティデバイスは、少なくとも支持体材料および該支持体材料に結合した本発明による高度免疫血清に反応性の抗原およびその断片のいずれかを含む。標的細胞または標的分子または相互作用パートナーに対する本発明による高度免疫血清に反応性の抗原およびその断片の特異性のゆえ、高度免疫血清に反応性の抗原およびその断片は、結合条件が満たされることを条件として、該支持体材料に適用したいかなる種類の試料からも相互作用パートナーを選択的に除去することを可能にする。試料としては、これらに限られるものではないが、発酵ブロス、細胞破砕物、細胞調製物、組織調製物、器官調製物、血液、尿、リンパ液、分泌液などの生物学的または医学的試料が挙げられる。

【0207】

高度免疫血清に反応性の抗原およびその断片は、マトリックスに共有結合または非共有結合により結合させることができる。適当な支持体材料は当業者に知られており、セルロース、ケイ素、ガラス、アルミニウム、常磁性ビーズ、デンプンおよびデキストランよりなる群から選択することができる。

【0208】

本発明を以下の図面、実施例および配列表によりさらに説明するが、これらから本発明のさらなる特徴、態様および利点を見出すことができる。本発明の実施例は本発明を説明することのみを目的としたものであって本発明を限定することを目的とするものではないことが理解されなければならない。

【0209】

表1は、ゲノムストレプトコッカス・ピオゲネスライブラリーおよびヒト血清を用いて行ったすべてのスクリーニングの要約を示す。

【0210】

表2は、ヒト血清を用いたエピトープ血清学を示す。

【0211】

表3は、50のストレプトコッカス・ピオゲネス株で同定した抗原の遺伝子分布分析の要約を示す。

【0212】

表4は、免疫実験に使用した抗原性タンパク質に関する情報を要約したものである。

【0213】

表5は、ストレプトコッカス・ピオゲネスの6つの異なる株での抗原性タンパク質の変

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動性を示す。

【0214】

本明細書において言及する図面について以下に一層詳細に説明する。

【0215】

図1は、ELISAにより測定したストレプトコッカス・ピオゲネスについてのヒト血清の特徴付けを示す。

【0216】

図2は、ストレプトコッカス・ピオゲネスSF370/M1の小断片ゲノムライブラリーLSPy-70の断片サイズ分布を示す。576のランダムに選択したクローンをシーケンシングした後、配列を刈り込んでベクター残基を除去し、種々のゲノム断片サイズを有するクローンの数をプロットした。(B)は、ストレプトコッカス・ピオゲネスの染色体でのLSPy-70のランダムにシーケンシングしたクローンの同じセットの分布の模式図である。青色の円は、+/+方向で注釈したORFにマッチングした配列を示す。赤色の四角は、+/+方向で非コード染色体配列に完全にマッチングしたクローンを表す。緑色の菱形は、相補的またはキメラ配列を有するすべてのクローンの位置を示す。塩基対での数値による距離を位置付けのために各円形ゲノムにわたって示してある。ライブラリー内の種々のクローンセットの分割を図の下の方に数字およびパーセントで示してある。

【0217】

図3Aは、ビオチン化ヒトIgGを用いたMACS選択を示す。pMAL9.1中のLSPy-70ライブラリーを、第一の選択では10μgのビオチン化ヒト血清(P4-IgG)を、第二の選択では1μgを用いてスクリーニングした。負の対照として、スクリーニング用ライブラリー細胞に血清を加えなかった。第一および第二の溶出後に選択した細胞の数を各選択について示してある。図3Bは、MACSによる選択に使用したヒト血清(P4-IgG)を1:3,000の希釈で用いたウエスタンブロット分析により分析した細菌表面ディスプレイによって単離した特定のクローン(1~52)の反応性を示す。負荷対照として、同じブロットを1:5,000の希釈でのプラットホームタンパク質LamBに対する抗体を用いても分析した。LB、外来ペプチド挿入を有しないLamBを発現するクローンからの抽出物。

【0218】

図4Aは、遺伝子分布研究のために分析したストレプトコッカス・ピオゲネスのemm型を示す。図4Bは、各オリゴヌクレオチドを用いた遺伝子Spy0269の遺伝子分布のためのPCR分析を示す。PCR断片の予測されたサイズは1,000bpである。1~50、Aのもとに列挙したストレプトコッカス・ピオゲネス株；N、ゲノムDNAを添加せず；P、ストレプトコッカス・ピオゲネスSF310からのゲノムDNA（これはライブラリー構築のための鋳型とした）。

【0219】

図5：フローサイトメトリーによるA群連鎖球菌の細胞表面上の特異的抗体結合の検出。図5Aでは、免疫前のマウス血清およびストレプトコッカス・ピオゲネス溶解液に対して産生させたポリクローナル血清をストレプトコッカス・ピオゲネスSF370/M1とともにインキュベートし、フローサイトメトリーにより分析した。対照は、ストレプトコッカス・ピオゲネス菌体の表面への二次抗体の非特異的結合のレベルを示す。図5Bおよび5Cのヒストグラムは、それぞれ2つのプラットホームタンパク質LamBおよびFhuAに対する対照血清と比較した抗Spy0012(B)抗体または抗Spy1315および抗Spy1798(C)抗体の特異的結合による蛍光の増大を示す。

【0220】

図6：NMRIマウスを組換えタンパク質の3の連続投与量(50μg/投与)で2週間間隔にて0日目、14日目および28日目に免疫した。負の対照として、マウスをアジュバントの存在下、PBSで免疫した。M1タンパク質(Spy2018)は攻撃実験の正の対照とした。細菌の攻撃は 5×10^7 のストレプトコッカス・ピオゲネスAP1細胞

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の静脈内投与にて行い、マウスの生存をそれぞれ（A）18日間、（B）21日間および（C）19日間、毎日観察した。

【0221】

表1：細菌表面ディスプレイによって同定した免疫原性タンパク質

A、IC3-IgGを用いたlamBでのLSPy-70ライブラリー（1588）、B、IC3-IgAを用いたlamBでのLSPy-70ライブラリー（1539）、C、IC6-IgGを用いたlamBでのLSPy-70ライブラリー（1173）、D、P4-IgGを用いたlamBでのLSPy-70ライブラリー（1138）、E、P4-IgAを用いたlamBでのLSPy-70ライブラリー（981）、F、IC3-IgGを用いたbtuBでのLSPy-150ライブラリー（991）、G、IC6-IgGを用いたbtuBでのLSPy-150ライブラリー（1036）、H、P4-IgGを用いたbtuBでのLSPy-150ライブラリー（681）、I、IC3-IgGを用いたfhuAでのLSPy-400ライブラリー（559）、K、IC6-IgGを用いたfhuAでのLSPy-400ライブラリー（543）、L、P4-IgGを用いたfhuAでのLSPy-400ライブラリー（20）、*、5アミノ酸よりも長い抗原性配列の予測はプログラムANTIGENIC {Kolaskar, A.ら、1990}を用いて行った。

【0222】

表2：ヒト血清を用いたエピトープ血清学

個々のヒト血清との選択したエピトープを表す個々の合成ペプチドの免疫反応性を示す。反応性の程度をパターン／グレイコードしてある（pattern/grey coded）；白：-（<50U）、グレイ：+（50～119U）、斜線：++（120～199U）、斜線で交差：+++（200～1000U）および垂直に交差：++++（>1000U）。ELISA単位（U）は、OD_{545nm}での読み取りおよびバックグラウンドに対する補正後の希釈から計算した。スコア、すべての反応性の合計（すべての+の数の加算）；P1～P10血清は急性咽頭炎を罹患する患者からのものであり、N1～N10血清は健康な成人からのものである。PおよびNは内部対照として用いる。

ペプチド名：SPO0012、ORF S_{py}0012と注釈；SPA0450、S_{py}0450の別の読み枠での潜在的な新規ORF；SPC0406、S_{py}0406の相補鎖での潜在的な新規ORF；SPN0001、非コード領域での潜在的な新規ORF。

【0223】

表3：ストレプトコッカス・ピオゲネス株における遺伝子分布

図4Aに示す50のストレプトコッカス・ピオゲネス株を、関連抗原をコードする遺伝子に特異的なオリゴヌクレオチドを用いたPCRにより試験した。一つの選択したPCR断片のPCR断片を正しいDNA断片の増幅を確認するためにシーケンシングした。*、ストレプトコッカス・ピオゲネスSF370（M1）と比較した株M89でのアミノ酸置換の数。#、M89中に遺伝子が存在しなかったためにシーケンシングに用いた別の株。

【0224】

表4：NMR I マウスにおける免疫実験に用いた組換えタンパク質

組換え抗原を用いた免疫および病原性ストレプトコッカス・ピオゲネスAP1による攻撃は、実験手順の記載に従って行った。A、動物における免疫実験に使用した組換えタンパク質に含まれる各抗原のアミノ酸は、完全長タンパク質との関連で示してある。B、生存パーセントを防禦として表してあり、括弧内には負の対照（PBS免疫）の防禦のパーセント、ついで正の対照（S_{py}2018）の防禦のパーセントを記載してある。C、観察の終了時点ではすべてのマウスが死亡したがマウスが良好な生存を示したという事実によりS_{py}0269を選択した。このことは、14.6日目（S_{py}0269）、11.6日目（PBS）および19.3日目（S_{py}2018）に測定した平均生存時間によって反映されている。

【0225】

表5：ストレプトコッカス・ピオゲネスからの抗原性タンパク質の配列の変異

抗原性タンパク質を、実験手順で列挙した6つの異なるストレプトコッカス・ピオゲネス株でのアミノ酸交換について分析した。残基の番号は完全長タンパク質中でのアミノ酸の位置を示す。S p y 1 6 6 6 の場合は、ストレプトコッカス・ニューモニエ T I G R (S P 0 3 3 4) 中の同種遺伝子との比較による変化を列挙してある、なぜなら該遺伝子はストレプトコッカス・ピオゲネスとストレプトコッカス・ニューモニエとの間で高度に保存されているからである。A、ストレプトコッカス・ピオゲネス S F 3 7 0 からのタンパク質中のアミノ酸残基。B、ストレプトコッカス・ピオゲネス S F 3 7 0 と異なる場合に、他の5つのストレプトコッカス・ピオゲネス株からの分析した遺伝子のいずれか一つに存在するアミノ酸残基。C、触媒活性に關与する S p y 0 4 1 6 の残基。これら残基の変化は酵素を不活性にすることが予想され、それゆえアラニン、セリン、トレオニンまたはグリシンと実験的に交換して酵素的に不活性な組換えタンパク質を生成した。

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【図面の簡単な説明】

【0 2 2 6】

【図1】図1は、ストレプトコッカス・ピオゲネス特異的なヒト血清の特徴付けを示す。

【0 2 2 7】

【図2】図2は、ストレプトコッカス・ピオゲネス S F 3 7 0 / M 1 からの小断片ゲノムライブラリー L S P y - 7 0 の特徴付けを示す。

【0 2 2 8】

【図3】図3は、ビオチン化ヒト I g G を用いた M A C S による細菌細胞の選択を示す。

【0 2 2 9】

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【図4】図4は、同定した抗原を用いた遺伝子分布研究の一例を示す。

【0 2 3 0】

【図5】図5は、フローサイトメトリーによる細胞表面染色を示す。

【0 2 3 1】

【図6】図6は、同定した組換えストレプトコッカス・ピオゲネス抗原の防禦値を示す。

【0 2 3 2】

実施例

実施例1：ヒト血清からの抗体の調製

ヒト免疫系によって産生されヒト血清中に存在するA群連鎖球菌に対する抗体は、抗原性タンパク質のインビボでの発現およびその免疫原性を示している。これら分子は本明細書に記載のアプローチにおいて個体の抗原を同定するうえで必須であるが、該アプローチは特異的な抗連鎖球菌抗体と対応のストレプトコッカス・ピオゲネスペプチドまたはタンパク質との相互作用に基づくものである。関連する抗体レパートリーへのアクセスを得るため、ヒト血清を以下から回収した：

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I. 咽頭炎、創傷感染および菌血症などの急性ストレプトコッカス・ピオゲネス感染症を罹患する患者（ストレプトコッカス・ピオゲネスは医学的な微生物試験により病因であることが示された）

II. 未感染の健康な成人、なぜならA群連鎖球菌感染は一般的であり、以前の連鎖球菌との遭遇による自然免疫の結果として抗体が存在するからである。

【0 2 3 3】

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一連の E L I S A およびイムノブロットティングアッセイにより血清を抗ストレプトコッカス・ピオゲネス抗体について特徴付けた。幾つかの連鎖球菌抗原は、測定した力価が交差反応性抗体の合計の結果ではないことを示すのに用いた。この目的のため、2つの異なる抗原調製物を用いた：T H B (Todd-Hewitt Broth) 増殖培地で一夜培養した（定常期）ストレプトコッカス・ピオゲネス S F 3 7 0 / M 1 から調製した全細胞抽出液または培養上澄み液のタンパク質。I g G および I g A の両抗体レベルを決定した。これら2つの抗原調製物に対する全抗体力価に基づくイムノブロットティングによりさらに分析するために血清を選択した。

【0 2 3 4】

応答が線状である所定の希釈で力価を比較した（図1）。複数の連鎖球菌成分に対する

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反応性に基づいて血清をランク付け、最高のランクのものをイムノブロットィングによりさらに分析するために選択した。この広範な抗体特徴付けアプローチは、抗連鎖球菌高度免疫血清の明確な同定に導いた。

【0235】

最近、IgGのみならずIgA血清抗体もPMNのFcRIIIレセプターによって認識されることができ、オプソニン作用を促進することが報告された {Phillips-Quagliata, J.ら、2000; Shibuya, A.ら、2000}。IgA抗体の主たる役割は主として粘膜表面での中和である。血清IgAレベルは、二量体分泌IgAの質、量および特異性を反映している。この理由から、血清回収物を抗連鎖球菌IgGについてのみならずIgAレベルについても分析した。ELISAアッセイでは高度に特異的な二次試薬を用いてIgGやIgAなどの高親和性タイプから抗体を検出したが、IgMは省いた。IgM抗体の産生は一次獲得体液応答の際に生じ、低親和性の抗体という結果となるのに対し、IgGおよびIgA抗体はすでに親和性成熟を経ており、疾患に対抗または予防するうえで一層価値がある。

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【0236】

実験手順

ペプチド合成

SyroII合成機 (Multisynthtech、ヴィッテン、ドイツ) を用いたRinkアミド樹脂 (PepChem、チュービンゲン、ドイツ) 上での標準Fmoc化学を用い、ペプチドを小スケール (4mg樹脂; 平行して288まで) で合成した。配列をアセンブリーした後、ペプチドをFmoc-イプシロン-アミノヘキサ酸 (リンカーとして) およびビオチン (Sigma、セントルイス、ミズーリ; 通常のアミノ酸と同様に活性化) を用いて伸長した。ペプチドを93% TFA、5% トリエチルシラン、および2% 水を用いて樹脂から1時間かけて開裂した。ペプチドを真空乾燥し、アセトニトリル/水 (1:1) から3回凍結乾燥した。正しい質量の存在はReflex III MALDI-TOF (Bruker、ブレーメン、ドイツ) での質量分析により確認した。これらペプチドをさらに精製することなく用いた。

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【0237】

酵素結合抗体免疫吸着アッセイ (ELISA)

血清の特徴付けのため:

ELISAプレート (Maxisorb, Millipore) を、コーティング緩衝液 (0.1 M炭酸ナトリウム、pH 9.2) 中に希釈した5~10 μg/mlの全タンパク質でコーティングした。血清の3つの希釈液 (2,000×、10,000×、50,000×) をPBS-BSA中で調製した。

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【0238】

ペプチド血清学のため:

ビオチン標識ペプチドを、製造業者の指示に従ってストレプトアビジンELISAプレート (EXICON) に10 μg/mlの濃度にてコーティングした。

【0239】

高度に特異的な西洋ワサビペルオキシダーゼ (HRP) コンジュゲート抗ヒトIgGまたは抗ヒトIgA二次抗体 (Southern Biotech) を製造業者の推奨に従って用いた (希釈: 1,000×)。自動ELISA読み取り機 (TECAN SUNRISE) でのOD_{405nm}読み取りに基づいて基質 (ABTS) の着色生成物への変換を測定することにより、抗原-抗体複合体を定量した。手動でのコーティングの後、内蔵読み取り機 (GENIOS, TECAN) を備えたペプチドプレートを処理し、Gemini 160 ELISAロボット (TECAN) により分析した。

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【0240】

イムノブロットィング

全細菌溶解液および培養上澄み液試料をインビトロ増殖したストレプトコッカス・ピオゲネスSF370/M1から調製した。BioRad Mini-Protean 3 Cell電気泳動系を用いたSDS-PAGEにより10~25 μgの全タンパク質/レーンを分離し、タンパク質を

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ニトロセルロース膜 (ECL, Amersham Pharmacia) に移した。5 % 乳中で一夜ブロッキングした後、2,000 × 希釈の抗血清を加え、HRPO 標識抗マウス IgG を検出に用いた。

【0241】

細菌抗原抽出物の調製

全細菌溶解液：細菌を凍結－解凍サイクルを繰り返すことにより溶解した：凍結するまで（1分）ドライアイス／エタノール混合物上でインキュベート、ついで37℃で解凍（5分）：3回繰り返す。この次に超音波処理および遠心分離（3,500 rpm、15分、4℃）による上澄み液の回収を行った。

【0242】

培養上澄み液：細菌を除去した後、一夜増殖した細菌培養液の上澄み液を氷冷エタノール（100%）で沈殿させた：1部の上澄み液／3部のエタノールを－20℃で一夜インキュベートした。沈殿を遠心分離（2,600 g、15分間）により回収し、乾燥させた。乾燥したペレットをELISAについてはPBS中、またはSDS－PAGEおよびイムノブロッティングについては尿素およびSDS－試料緩衝液中に溶解した。試料のタンパク質濃度をBradfordアッセイにより決定した。

【0243】

ゲノムスクリーニングのための抗体の精製

患者グループおよび非感染グループの両者から5つの血清を、スクリーニング手順に使用した血清プールに対する全体の抗連鎖球菌力価に基づいて選択した。大腸菌タンパク質に対する抗体は、熱不活化した血清を全菌体大腸菌細胞（DH5アルファ、pHIE11で形質転換、細菌表面ディスプレイに使用したのと同じ条件下で増殖）とともにインキュベートすることにより除去した。プールし枯渇させた血清からのIgGの高度に富んだ調製物を、プロテインGアフィニティークロマトグラフィーにより、製造業者の指示（UltraLink Immobilized Protein G, Pierce）に従って得た。IgA抗体もまた、ストレプトアビジン－アガロース（GIBCO BRL）上に固定化したビオチン標識抗ヒトIgA（Southern Biotech）を用いたアフィニティークロマトグラフィーにより精製した。枯渇および精製の効率を、SDS－PAGE、ウエスタンブロッティング、ELISAおよびタンパク質濃度測定によりチェックした。

【0244】

実施例2：ストレプトコッカス・ピオゲネスの高度にランダムなフレーム選択した小断片のゲノムDNAライブラリー

実験手順

連鎖球菌ゲノムDNAの調製

50 ml のTodd-Hewittブロス培地に凍結スタブ（stab）からのストレプトコッカス・ピオゲネスSF370／M細菌を接種し、通気および振盪しながら37℃で18時間増殖させた。ついで、培養液を回収し、1,600 × gで15分間遠心分離にかけ、上澄み液を除去した。細菌ペレットをPBSで3回洗浄し、0.5 ml のリゾチーム溶液（100 mg／ml）に注意深く再浮遊させた。0.1 ml の10 mg／mlの熱処理リボヌクレアーゼAおよび20 UのリボヌクレアーゼT1を加え、注意深く混合し、溶液を37℃で1時間インキュベートした。0.2 ml の20 % SDS溶液および0.1 ml のプロテイナーゼK（10 mg／ml）を加えた後、試験管を55℃で一夜インキュベートした。ついで、1／3容量の飽和NaClを加え、溶液を4℃で20分間インキュベートした。抽出物をマイクロ遠心（13,000 rpm）でペレット化し、上澄み液を新たな試験管に移した。この溶液をPhOH／CHCl₃／IAA（25：24：1）およびCHCl₃／IAA（24：1）で抽出した。0.6 × 容量のイソプロパノールを加えてDNAを室温で沈殿させ、滅菌パストールピペットを用いて溶液から巻き取り、80 % 氷冷エタノールを入れた試験管に移した。沈殿を10－12,000 × gで遠心分離してDNAを回収し、ついで空気乾燥し、ddH₂Oに溶解した。

【0245】

小さなゲノムDNA断片の調製

ゲノムDNA断片を機械的に切断して、カップーホーン (cup-horn) ソニケーター (BB 5カップホーンを備えたBandelin Sonoplus UV 2200ソニケーター、100%出力で10秒パルス) を用いて150~300bpのサイズの断片、または穏やかなデオキシリボヌクレアーゼI (Novagen) 処理により50~70bpのサイズの断片とした。超音波処理は、DNAを150~300bpのサイズ範囲の断片に破壊したときに極めて密集した断片サイズ分布が生成することが観察された。しかしながら、超音波誘発による流体力学的剪断力へのDNAの十分な暴露にもかかわらず、その後の断片サイズの低減を効率的かつ再現可能に達成することはできなかった。それゆえ、50~70bpのサイズの断片をNovagenのショットガン開裂キットを用いた穏やかなデオキシリボヌクレアーゼI処理により得た。このキットにより提供されるデオキシリボヌクレアーゼIの1:20希釈を調製し、MnCl₂の存在下、60μl容量、20℃にて5分間消化を行って該酵素による二本鎖開裂を確実にした。反応を2μlの0.5M EDTAで停止させ、断片化効率を2%TAEアガロースゲル上で評価した。この処理の結果、ゲノムDNAはほぼ50~70bp断片に完全に断片化された。ついで、各100μMのdNTPの存在下、T4DNAポリメラーゼを用いて断片を平滑末端として末端の効率的な平滑化 (flushing) を確実にした。断片はライゲーション反応に直ちに用いるか、またはその後の使用のために-20℃で凍結した。

【0246】

ベクターの説明

ベクターpMAL4.31は、ベクターラクタマーゼ (bla) 遺伝子をカナマイシン耐性遺伝子と交換してpASK-IBA骨格 {Skerra, A.ら、1994} 上に構築した。さらに、bla遺伝子をマルチプルクローニングサイトにクローニングした。成熟ベクターラクタマーゼをコードする配列の前にompAのリーダーペプチド配列を置いて細胞質膜を経た効率的な分泌を可能とした。さらに、成熟ベクターラクタマーゼの最初の12のアミノ酸をコードする配列 (スパーサー配列) がompAリーダーペプチド配列に続いており、リーダーペプチダーゼ開裂部位の直後の配列の融合が回避されたが、これはたとえば、この領域の正に荷電したアミノ酸のクラスターが細胞質膜を経た移動を低減ないし不能にさせるからである {Kajava, A.ら、2000}。SmaI制限部位はライブラリーの挿入のためである。上流のFseI部位および下流のNotI部位は選択した断片の回収に用いられ、SmaI部位にフランキングしている。これら3つの制限部位は、bla遺伝子が-1リーディングフレームで転写されNotI部位の15bp後ろで停止する結果となるような仕方で12アミノ酸のスパーサー配列をコードする配列の後ろに挿入される。+1bp挿入によってbla ORFは回復され、ベクターラクタマーゼタンパク質は産生され、その結果、アンピシリン耐性も獲得されるようになる。

【0247】

ベクターpMAL9.1は、lamB遺伝子をpEH1 {Hashemzadeh-Bonehi, L.ら、1998} のマルチプルクローニングサイトにクローニングすることによって構築した。引き続き、制限部位FseI、SmaIおよびNotIを含む配列をlamB中、アミノ酸154の後ろに挿入した。この挿入物のリーディングフレームは、FseIおよびNotIでの消化によりプラスミドpMAL4.31から切り出したフレーム選択したDNA断片の移動がlamBおよび各挿入の連続したフレームを生成するような仕方で構築した。

【0248】

ベクターpMAL10.1は、btuB遺伝子をpEH1のマルチプルクローニングサイトにクローニングすることによって構築した。引き続き、制限部位FseI、XbaIおよびNotIを含む配列をbtuB中、アミノ酸236の後ろに挿入した。この挿入物のリーディングフレームは、FseIおよびNotIでの消化によりプラスミドpMAL4.31から切り出したフレーム選択したDNA断片の移動がbtuBおよび各挿入の連続したフレームを生成するような仕方で構築した。

【0249】

ベクター p H I E 1 1 は、f l u A 遺伝子を p E H 1 のマルチプルクローニングサイトにクローニングすることによって構築した。引き続き、制限部位 F s e I、X b a I および N o t I を含む配列を f l u A 中、アミノ酸 4 0 5 の後ろに挿入した。この挿入物のリーディングフレームは、F s e I および N o t I での消化によりプラスミド p M A L 4 . 3 1 から切り出したフレーム選択した DNA 断片の移動が f l u A および各挿入の連続したフレームを生成するような仕方で構築した。

【0250】

クローニングおよびフレーム選択のためのライブラリーの評価

ストレプトコッカス・ピオゲネスのゲノム DNA 断片をベクター p M A L 4 . 3 1 の S m a I 部位にライゲートした。組換え DNA を D H 1 0 B エレクトロコンピテント大腸菌細胞 (G I B C O B R L) にエレクトロポレーションし、形質転換体をカナマイシン (50 μ g/ml) およびアンピシリン (50 μ g/ml) を添加した LB アガーにプレーティングした。プレートを 37°C で一夜インキュベートし、大スケールの DNA 抽出のためにコロニーを選択した。代表的なプレートを貯蔵し、コロニー PCR 分析および大スケールシーケンシング用のコロニーのために残しておいた。単純な PCR アッセイを用いて最初におおまかな断片サイズの分布並びに挿入効率を決定した。シーケンシングのデータから正確な断片サイズを評価し、挿入部位での連結の完全さ並びにフレーム選択の正確さ (3n+1 則) を評価した。

【0251】

クローニングおよび細菌表面ディスプレイライブラリーの評価

ゲノム DNA 断片をストレプトコッカス・ピオゲネスライブラリーを含む p M A L 4 . 3 1 ベクターから制限酵素 F s e I および N o t I を用いて切り出した。ついで、断片の全集団を、F s e I および N o t I で消化しておいたプラスミド p M A L 9 . 1 (L a m B)、p M A L 1 0 . 1 (B t u B) または p H I E 1 1 (F l u A) に移した。8 b p の G C リッチ配列を認識するこれら 2 つの制限酵素を用い、p M A L 4 . 3 1 ベクターで選択したリーディングフレームが各プラットホームベクターで維持される。ついで、このプラスミドライブラリーをエレクトロポレーションにより大腸菌 D H 5 α 細胞に形質転換した。細胞を 50 μ g/ml のカナマイシンを添加した大きな LB アガープレートにプレーティングし、37°C で一夜、単一コロニーが明確に視認できる密度に増殖させた。ついで、細胞をこれらプレートの表面から掻き落とし、新たな LB 培地で洗浄し、ライブラリースクリーニングのために -80°C でアリコートに貯蔵した。

【0252】

結果

フレーム選択のためのライブラリー

p M A L 4 . 3 1 ベクターでそれぞれ約 70 b p、150 b p および 300 b p のサイズの 3 つのライブラリー (L S P y 70、L S P y 150 および L S P y 300) を生成した。各ライブラリーについて、約 1 μ g の p M A L 4 . 3 1 プラスミド DNA および 50 ng のストレプトコッカス・ピオゲネスの断片化ゲノム DNA のライゲーションおよび引き続き形質転換により、フレーム選択後に $4 \times 10^5 \sim 2 \times 10^6$ クローンが得られた。ライブラリーのランダムさを評価するため、約 600 のランダムに選択した L S P y 70 のクローンをシーケンシングした。バイオインフォーマティクス分析は、これらクローンのうちごくわずかのみが 1 回を超えて存在することを示した。さらに、クローンの 90% が 16~61 b p のサイズ範囲に含まれ、平均サイズは 34 b p であることが示された (図 2)。すべての配列が 3n+1 則に従い、すべてのクローンが正しくフレーム選択されていることが示された。

【0253】

細菌表面ディスプレイライブラリー

大腸菌の表面でのペプチドの提示には、フレーム選択ベクター p M A L 4 . 3 1 からの L P S y ライブラリーからの挿入物をディスプレイプラスミド p M A L 9 . 1 (L a m B)、p M A L 1 0 . 1 (B t u B) または p H I E 1 1 (F l u A) に移す必要があった

。ゲノムDNA断片をFse IおよびNot I制限酵素により切り出し、5 ngの挿入物を0.1 µgのプラスミドDNAとライゲートし、引き続きDH5α細胞を形質転換すると2～5×10⁶ クローンが得られた。これらクローンをLBプレートから掻き落とし、さらに増幅させることなく凍結させた。

【0254】

実施例3：細菌表面ディスプレイゲノムライブラリーおよびヒト血清を用いたストレプトコッカス・ピオゲネスからの高度に免疫原性のペプチド配列の同定

実験手順

MACSスクリーニング

所定のライブラリーからの約2.5×10⁸の細胞を、50 µg/mlのカナマイシンを添加した5 mlのLB培地で増殖させた。発現の誘発は1 mM IPTGを30分間添加することにより行った。細胞を新たなLB培地で2回洗浄し、約2×10⁷の細胞を100 µlのLB培地に再浮遊させ、エッペンドルフ管に移した。

【0255】

10 µgの血清から精製したビオチン化ヒトIgGを細胞に加え、懸濁液を穏やかに振盪しながら4℃で一夜インキュベートした。900 µlのLB培地を加え、懸濁液を混合し、引き続き6,000 rpm、4℃にて10分間遠心分離にかけた(IgAスクリーニングのためには10 µgの精製IgAを用いたが、これらはビオチン化した抗ヒトIgG二次抗体を捕捉した)。細胞を1 mlのLBで1回洗浄し、100 µlのLB培地に再浮遊させた。10 µlのストレプトアビジン結合MACSマイクロビーズ(Miltenyi Biotch、ドイツ)を加え、インキュベーションを4℃にて20分間続けた。その後、900 µlのLB培地を加え、MACSマイクロビーズ細胞浮遊液を磁石に固定した平衡化MSカラム(Miltenyi Biotch、ドイツ)に負荷した。(MSカラムは1 mlの70% EtOHで1回、2 mlのLB培地で2回洗浄することにより平衡化した。)

【0256】

ついで、カラムを3 mlのLB培地で3回洗浄した。磁石を除去した後、細胞を2 mlのLB培地で洗浄して溶出した。3 mlのLB培地でカラムを洗浄後、2 mlの溶出液を同じカラムに2回目の負荷をし、洗浄および溶出のプロセスを繰り返した。この負荷、洗浄および溶出のプロセスを3回繰り返して2 mlの最終溶出液を得た。

【0257】

2回目のスクリーニングは以下のようにして行った。最終溶出液からの細胞を遠心分離により回収し、50 µg/mlのカナマイシンを添加した1 mlのLB培地に再浮遊させた。培養液を37℃で90分間インキュベートし、ついで1 mM IPTGで39分間誘導した。細胞を引き続き回収し、1 mlのLB培地で1回洗浄し、10 µlのLB培地に浮遊させた。容量が減ったので、1 µgのヒトビオチン化IgGを加え、懸濁液を穏やかに振盪しながら4℃で一夜インキュベートした。その後の工程は1回目の選択のものと全く同じであった。2回の選択後に選択された細胞を50 µgのカナマイシンを添加したLB培地にプレーティングし、37℃で一夜増殖させた。

【0258】

シーケンシングおよびウエスタンブロット分析による選択クローンの評価

選択クローンを50 µgのカナマイシンを添加した3 mlのLB培地中、37℃にて一夜培養し、標準法を用いてプラスミドDNAを調製した。シーケンシングはMWG(ドイツ)にて、またはTIGR(米国)と協同で行った。

【0259】

ウエスタンブロット分析のため、10～20 µgの全細胞タンパク質を10% SDS-PAGEにより分離し、ハイボンドC膜(Amersham Pharmacia Biotech、英国)にブロッティングした。LamB、BtuBまたはFluA融合タンパク質を、一次抗体として約1:5,000に希釈したヒト血清および二次抗体として1:5,000に希釈したHRP結合抗ヒトIgGまたはIgA抗体を用いて検出した。検出はECL検出キット(Amersham Pharmacia Biotech、英国)を用いて行った。別法として、一次抗体としてのウサギ抗

F l u Aまたはマウス抗 L a m B抗体をH R Pに結合したそれぞれの二次抗体と組み合わせて融合タンパク質の検出に用いた。

【0260】

結果

ビオチン化 I gを用いたマグネチックアクチベータッドセルソーティング (M A C S) による細菌表面ディスプレイライブラリーのスクリーニング

p M A L 9 . 1 中のライブラリー L S P y 7 0、p M A L 1 0 . 1 中のライブラリー L S P y 1 5 0 および p H I E 1 1 中のライブラリー L S P y 3 0 0 を、患者血清または健康な個体からの血清からのビオチン化ヒト I g G および I g A のプールを用いてスクリーニングした (実施例 1 : ヒト血清からの抗体の調製を参照)。選択手順は実験手順の記載に従って行った。図 3 A は、L S P y - 7 0 ライブラリーおよび P 4 - I g G を用いたスクリーニングの代表例を示す。M A C S スクリーニングからの 1 回目の選択後のコロニーカウントから明らかなように、最終的に回収された細胞の合計数は 3×10^7 細胞から約 5×10^4 細胞に劇的に減少したのに対し、抗体を添加しなかった選択は約 3×10^3 細胞への減少を示した (図 3 A)。2 回目の選択後でも、同様の数の細胞が P 4 - I g G で回収されたのに対し、ヒト血清からの I g G を添加しなかった場合には 10 未満の細胞しか回収されず、この選択がストレプトコッカス・ピオゲネステ異的な抗体に依存していることを明らかに示していた。スクリーニングの性能を評価するため、約 50 の選択クローンをランダムに取り、同じプールした血清を用いたウエスタンブロット分析に供した (図 3 B)。この分析により、選択クローンの 70 % が関連血清中に存在する抗体との反応性を示したのに対し、ストレプトコッカス・ピオゲネステ異的な挿入物を含まず L a m B を発現する対照株は同血清と反応しないことが明らかとなった。一般に、反応性の割合は 35 ~ 75 % の範囲にあることが観察された。コロニー P C R 分析は、すべての選択クローンが予期したサイズの範囲の挿入物を含むことを示した。

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【0261】

一層多数のランダムに取り出したクローン (スクリーニング当たり 600 ~ 1200) のその後のシーケンシングは、スクリーニングに用いたヒト血清によって特異的に認識される遺伝子および対応ペプチドまたはタンパク質配列の同定に導いた。特定のクローンが選択される頻度は、選択に用いられ該クローンによって表されるエピトープを認識する血清中に存在する特異的な抗体の存在量および / または親和性を少なくとも部分的に反映している。この点で、幾つかの O R F に由来するクローン (たとえば、S p y 0 4 3 3、S p y 2 0 2 5) が 80 回を超えて取り出され、その高度に免疫原性の特性が示されたことは驚くべきことである。表 1 は 15 の行ったすべてのスクリーニングで得られたデータを要約したものである。表 1 に示すクローンはすべて、単一クローンからの全細胞抽出物を用いたウエスタンブロット分析により各スクリーニングに使用したヒト血清のプールとの所定の反応性を示すことが確認されている。表 1 から明らかなように、プラットホームタンパク質によってタンパク質の様々なサイズの断片が表面に提示されるので、同定された O R F の別個の領域が免疫原性として同定されている。

【0262】

さらに、細菌表面ディスプレイスクリーニングによって同定された遺伝子の殆どが、ストレプトコッカス・ピオゲネスの表面に結合しているかおよび / または分泌されるタンパク質をコードしていることを認識することは有意義なことである。

【0263】

実施例 4 : 個体ヒト血清との高度に免疫原性のペプチド配列の反応性の評価

約 100 人の患者および 60 人の健康な成人の血清が分析に含まれていた。選択クローンのバイオインフォマティクス分析後、対応ペプチドをデザインし、合成した。28 を超えるアミノ酸残基のエピトープの場合は重複ペプチドを製造した。すべてのペプチドを N 末端ビオチンタグを付して合成し、ストレプトアビジンコーティング E L I S A プレート上でコーティング試薬として用いた。

【0264】

分析は2工程で行った。第一に、ペプチドを個体血清との反応性に基づいて選択したが、この個体血清は細菌表面ディスプレイのIgGおよびIgAスクリーニング試薬の調製に使用した血清プール(5つの個体血清)に含まれていたものであった。陽性の反応を示さないペプチドは、さらなる詳細な研究に含めなかった。第二に、急性の咽頭炎または連鎖球菌感染後疾患を罹患する患者または健康な成人および子供からの一層多数の前もって選択していない個体血清を、スクリーニング血清に対して特異的で高度の反応性を示したペプチドに対して試験した。抗体レベルをELISAにより測定し、陽性血清の数および反応性の程度に基づいて各ペプチドについて計算したスコアにより比較した。ゲノムスクリーニングからのストレプトコッカス・ピオゲネスエピトープを表す174のペプチドと抗原同定に使用した20のヒト血清(5つの血清の4つの異なるプールを表す)との血清反応性の例を表2に示す。ペプチドは高度に広く反応性のものから弱く陽性のものまでであった。最も反応性のものの中には既知の抗原もあり、その中のあるものはまた鼻咽頭保菌の動物攻撃モデルでも防禦的である(たとえば、C5aペプチダーゼおよびMタンパク質)。

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【0265】

実施例5：ストレプトコッカス・ピオゲネスから同定した高度に免疫原性のタンパク質を用いた遺伝子分布研究

PCRによるA群連鎖球菌抗原の遺伝子分布

理想的なワクチンは、当該ワクチンが向けられた標的生物のすべてまたは大部分の株に存在する抗原であろう。同定したストレプトコッカス・ピオゲネスの抗原をコードする遺伝子がストレプトコッカス・ピオゲネス株に普遍的に存在するものであるか否かを確立するため、目的遺伝子に対して特異的なプライマーを用いて一連の独立のストレプトコッカス・ピオゲネス単離物に対してPCRを行った。図4Aに示すように、患者に最も頻繁に存在するemm型をカバーするストレプトコッカス・ピオゲネス単離物を得た。プライマーとしてのオリゴヌクレオチドは、もしも可能なら同定したすべての免疫原性エピトープをカバーする約1,000bpの生成物をするよう同定したすべてのORFについてデザインした。すべてのストレプトコッカス・ピオゲネス株のゲノムDNAは、実施例2の記載と同様にして調製した。PCRは、Taqポリメラーゼ(1U)、200nMのdNTP、10ピコモルの各オリゴヌクレオチドおよびキットを製造業者(Invitrogen、オランダ)の指示に従って25μlの反応容量にて行った。標準として、条件を個々のプライマーペアに適合させる必要のない限り、30サイクル(1×:5分、95℃、30×:30秒、95℃、30秒、56℃、30秒、72℃、1×4分、72℃)を行った。

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【0266】

結果

免疫原性のタンパク質をコードする同定されたすべての遺伝子を、ストレプトコッカス・ピオゲネスの50の異なる株での存在についてPCRにより試験した(図4A)。一例として、図4Bは、示した50のすべての株とのSpy0269のPCR反応性を示す。明らかに見てとれるように、この遺伝子は分析したすべての株に存在している。株No. 8(M89)からのPCR断片をシーケンシングしたところ、ストレプトコッカス・ピオゲネスM1株SF310と比較して917bpのうち2bpのみが異なり、その結果、これら2つの単離物は1アミノ酸の差異しかないことが示された。

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【0267】

分析した合計96の遺伝子のうち、70の遺伝子は試験したすべての株に存在し、一方、22の遺伝子は試験した50の株のうち10を超える株に存在していた(表3)。幾つかの遺伝子(Spy0433、Spy0681)はサイズに変異を示し、すべての株単離物には存在しなかった。幾つかの遺伝子はサイズに変異を示したが、他の点では試験したすべての株で保存されていた(たとえば、Spy1371)。一つの株からの生成したPCR断片のシーケンシングおよびその後のM1株との比較は正しいDNA断片の増幅を確認し、表3に示すようにある程度の配列分散を明らかにした。重要なことには、同定した抗原の多くは配列およびサイズにおいてすべての株でよく保存されており、それゆえA

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群連鎖球菌による感染を防御するための新規なワクチン候補である。

【0268】

実施例6：大腸菌の表面に提示されたストレプトコッカス・ピオゲネスからの高度に免疫原性のタンパク質／ペプチドで免疫したマウスから得られた免疫血清の特徴付け
マウスからの免疫血清の生成

ストレプトコッカス・ピオゲネスペプチドに融合したプラットホームタンパク質をコードするプラスミドを有する大腸菌クローンを、 $50 \mu\text{g}/\text{ml}$ のカナマイシンを添加したLB培地中、 37°C で増殖させた。一夜培養液を1：10に希釈し、 OD_{600} が0.5となるまで増殖させ、 0.2 mM IPTGで2時間誘発した。ペレット化した細菌菌体をPBS緩衝液に浮遊させ、氷上での超音波処理により破碎し、粗製の細胞抽出物を得た。 OD_{600} 測定により、 5×10^7 細胞に対応するアリコートにNMR1マウスに静脈内注射し、ついで2週間後にブースター投与した。第二の注射の1週間後に血清を採取した。エピトープ特異的な抗体レベルをペプチドELISAにより測定した。

【0269】

抗原のインビトロ発現

インビトロで増殖したストレプトコッカス・ピオゲネスSF370/M1による抗原の発現をイムノブロットングにより試験した。異なる増殖培地および培養条件を試験して全溶解液および細菌培養上澄み液中の膠原の存在を検出した。予測した分子量および電気泳動移動度に対応する特異的なバンドが検出されたときに発現が確認されたとした。

【0270】

細胞表面染色

フローサイトメトリー分析を以下のようにして行った。細菌を、イムノブロット分析により示される抗原の発現という結果となる培養条件下で増殖させた。細胞をハンクスの平衡塩類溶液(HBSS)で2回洗浄し、 $100 \mu\text{l}$ のHBSS、 0.5% BSAで細胞密度を約 1×10^6 CFUに調節した。 $50 \sim 100$ 倍に希釈した抗血清とともに 4°C で30～60分間インキュベートした後、未結合の抗体を過剰のHBSS、 0.5% BSA中での遠心分離により洗浄して除いた。フルオレセイン(FITC)で標識したヤギ抗マウス二次抗体(F(ab')_2 フラグメント特異的)を細胞とともに 4°C で30～60分間インキュベートした。細胞を洗浄後、抗体を 2% パラホルムアルデヒドで固定した。結合抗体をBecton Dickinson FACScanフローサイトメーターを用いて検出し、データをコンピュータープログラムCELLQuestでさらに分析した。対照血清には、マウスの免疫前血清、およびストレプトコッカス・ピオゲネスのゲノム挿入物を有しない遺伝子lamBまたはfluAをコードするプラスミドで形質転換しIPTG誘発した大腸菌から調製した溶解液で調製したマウスポリクローナル血清が含まれていた。

【0271】

オプソニン食作用(Opsonophagocytosis) アッセイ

エピトープ特異的な免疫血清を、それがオプソニン食作用を誘発する活性についてFACSベースのアッセイで試験した。血清を熱不活化し、ついで抗大腸菌抗体を全菌体大腸菌($\times 3$)とともにインキュベートすることにより除いた。 10^7 のAlexa 488標識したストレプトコッカス・ピオゲネス細胞を補体源として2～10%免疫血清および2%ハムスター血清の存在下で前オプソニン処理し、ついで 10^6 の食細胞(RAW246.7またはP388.D1マウス単球細胞株)に加えた。細胞混合物を 37°C で30分間インキュベートした。時間、IgG濃度および細菌の補体依存性の取り込みを、フルオレセンスアクチベテッドセルソーターで測定した食細胞の平均蛍光強度の増大として記録した。

【0272】

殺菌アッセイ

マウスマクロファージ細胞(RAW246.7またはP388.D1)および細菌をインキュベートし、60分後の生きた細菌の消失をコロニーカウンティングにより決定した。簡単に説明すると、細菌をハンクスの平衡塩類溶液(HBSS)で2回洗浄し、 $50 \mu\text{l}$ のHBSSで細胞密度を約 1×10^5 CFUに調節した。細菌をマウス血清(25%まで

）およびモルモット補体（5%まで）とともに100 μ lの合計容量にて4℃で60分間インキュベートした。前オプソニン処理した細菌をマクロファージ（マウス細胞株RAW 246.7またはP388.D1；100 μ l当たり 2×10^6 細胞）と1：20の比で混合し、500 rpmの回転シェーカー上、37℃でインキュベートした。各試料のアリコート滅菌水で希釈し、室温で5分間インキュベートしてマクロファージを溶解させた。ついで、系列希釈をTodd-Hewitt Brothアガープレートにプレーティングした。プレートを37℃で一晩インキュベートし、コロニーをCountermatフラッシュコロニーカウンター（IUL Instruments）でカウントした。対照血清には、マウスの免疫前血清、およびストレプトコッカス・ピオゲネスのゲノム挿入物を有しない遺伝子lamBまたはfluAをコードするプラスミドで形質転換しIPTG誘発した大腸菌から調製した溶解液で調製したマウスポリクローナル血清が含まれていた。

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【0273】

結果

インビトロ発現および細胞表面染色

抗原性タンパク質の発現を、ストレプトコッカス・ピオゲネスペプチドに融合したプラットホームタンパク質をコードするプラスミドを有する大腸菌クローンに対して産生させた血清を用いることによりストレプトコッカス・ピオゲネスSF370/M1でインビトロで分析した。この分析は、ポリペプチドの表面発現をFACS分析により評価するためにタンパク質がそもそも発現されるのか否かを決定する第一段階の工程であった。インビトロ条件下ではすべてのタンパク質が発現されるわけではないことは予想されたが、いくつかのタンパク質はウエスタンブロット分析により全細胞溶解液中で検出された（たとえば、Spy0012、Spy0112、Spy0416、Spy0437、Spy0872、Spy1032、Spy1315、Spy1798；データは示していない）。いくつかの抗原性タンパク質についての細胞表面接近可能性（accessibility）は、引き続きフローサイトメトリーに基づくアッセイにより示された。連鎖球菌を、免疫前血清、またはストレプトコッカス・ピオゲネス溶解液またはストレプトコッカス・ピオゲネスペプチドに融合したプラットホームタンパク質をコードするプラスミドを有する大腸菌クローンに対して産生させたポリクローナルマウス血清とともにインキュベートし、ついで蛍光標識した二次抗体で検出した。図5Aに示すように、ストレプトコッカス・ピオゲネス溶解液に対して産生した抗血清はストレプトコッカス・ピオゲネスSF370/M1細胞集団の蛍光にシフトを引き起こす。抗原Spy0012（図5B）、Spy1315およびSpy1798（図5C）のペプチドに対して産生したポリクローナル血清についてもストレプトコッカス・ピオゲネスSF370/M1細胞の同様の細胞表面染色が観察されたが、2つのピークの検出によって示されるように細菌の垂集団が染色されただけであった。この現象は、細菌の増殖の際の遺伝子産物の差別的な発現または他の表面分子によって引き起こされた抗体結合の部分的な抑制の結果である。

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【0274】

これら実験は、これらタンパク質がそのシグナルペプチド配列のゆえに輸送されるというバイオインフォマティクスによる予測を確認し、さらにこれらタンパク質がストレプトコッカス・ピオゲネスSF370/M1の細胞表面に定着する（anchored）ことを示した。これら実験はまた、これらタンパク質がヒト抗体による認識に利用でき、これらタンパク質をA群連鎖球菌疾患に対するワクチンの開発のための価値ある候補とすることを確

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【0275】

実施例7：組換え抗原で免疫したときのA群連鎖球菌感染に対する防御的免疫応答

実験手順

抗原性タンパク質をコードする遺伝子のクローニング

目的とする遺伝子またはDNA断片を、遺伝子特異的なプライマーを用いたPCR増幅によりストレプトコッカス・ピオゲネスSF370のゲノムDNAから増幅した。遺伝子特異的な配列に加え、プライマーは各5'末端に増幅PCR産物のディレクショナルクロ

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ーニングを助ける制限部位からなる付加的塩基を含んでいた。プライマーの遺伝子特異的な配列は長さが15～24塩基の範囲であった。得られたPCR産物を適当な制限酵素で消化し、適当に消化したpET28b(+)ベクター(NOVAGEN)にクローニングした。組換えプラスミドの構築を確認した後、発現宿主としての大腸菌BL21 STAR^R細胞(INVITROGEN)を形質転換した。これら細胞を、pET28bプラスミドによってコードされる目的遺伝子を効率的に発現すべく最適化する。

【0276】

大腸菌での抗原の発現

組換えプラスミドを有する大腸菌BL21 STAR^R細胞を、50 µg/mlのカナマイシンを添加したLB培地中、37℃で対数期まで増殖させた。OD_{600nm}が0.8に達したら、培養液を1mM IPTGとともに37℃で3時間インキュベートした。細胞を遠心分離により回収し、凍結-解凍法の組合せにより溶解し、ついでNOVAGENからのBug-buster^R試薬を用いて細胞を破碎した。溶解液を遠心分離により可溶(上澄み液)画分および不溶(ペレット)画分に分離した。

【0277】

大腸菌からの組換えタンパク質の精製

組換えタンパク質の局在に依存して、異なる精製戦略に従った。可溶画分中の該タンパク質は、細胞破碎後の細胞溶解液の上澄み液をNi-アガロースビーズ(Ni-NTA-Agarose^R, QIAGEN)に結合させることにより精製した。発現タンパク質のC末端、N末端または両末端のペンタヒスチジン(HIS)の存在により、該タンパク質はNi-アガロースに結合し、一方、他の混入タンパク質は緩衝液で洗浄することによりカラムから洗浄除去される。組換えタンパク質は適当な緩衝液中に100mMイミダゾールを含む溶液によって溶出させた。溶出液を濃縮し、Bradfordによりタンパク質濃度についてアッセイし、SDS-PAGEおよびウエスタンブロットにより分析した。不溶性画分中のタンパク質は、8M尿素を含む適当な緩衝液中にペレットを可溶化することにより精製した。この精製は、上記可溶性タンパク質について記載したのと同じ材料および手順を用いた変性条件下(8M尿素を含む緩衝液中)で行った。溶出液を濃縮および透析してすべての尿素を逐次的または段階的な仕方で除去した。最終タンパク質を濃縮し、SDS-PAGEにより分析し、Bradford法により測定した。予測された分子量および電気泳動移動度に対応する特異的なバンドが検出されたときに発現が確認されたとした。変性剤である尿素の除去による透析の際に沈殿したタンパク質については、不溶性の封入体を数回洗浄し、マウスの免疫に直接用いた。

【0278】

組換えタンパク質によるNMR I マウスの免疫およびストレプトコッカス・ピオゲネス A P 1 による攻撃

組換えタンパク質の免疫原性を、NMR I マウスおよび感染因子としてストレプトコッカス・ピオゲネス株A P 1を用いた実験動物モデルでアッセイした。7～8週齢の10匹の雌NMR I マウスを50 µg/投与の組換えタンパク質で2週間毎に合計3投与にて免疫した。最初の投与はフロイントの完全アジュバントをアジュバントとし、一方、残りの2回の投与はフロイントの不完全アジュバントをアジュバントとした。免疫の終了時に採血して抗体価をチェックし、その後、致死量のストレプトコッカス・ピオゲネス(5×10⁷病原性菌体)で静脈内(i.v.)攻撃した。攻撃後18～21日間、マウスの生存をスコアリングした。

【0279】

結果

組換えタンパク質の発現および精製

組換えタンパク質発現のために選択した31のタンパク質のうち29のタンパク質が精製に十分なレベルで大腸菌中で産生させることができた。幾つかのタンパク質は可溶性のタンパク質として発現されたが(表4参照)、幾つかのタンパク質は透析の際に不溶性であるか(たとえば、Spy416B、Spy0872)または沈殿することがわかった。

この透析は S p y 0 0 3 1、S p y 0 2 9 2、S p y 7 2 0 などの不溶性のタンパク質の可溶化後に変性剤の尿素を除去するために行ったものである。これらの場合、洗浄した封入体を直接マウスに注射して免疫した。一般に、アフィニティー精製は少なくとも 8 5 % の純度の組換えタンパク質調製物を生成した。

【0280】

N M R I マウスで組換えタンパク質を免疫後の免疫応答

表 4 は、マウスで試験し、実験動物である程度の防禦を示した抗原を列挙したものである。動物における菌血症モデルでも試験したが記載の実験においていかなるレベルの防禦をも示さなかった組換えタンパク質は当該表に列挙していないが、S p y 0 0 1 2、S p y 1 0 6 3 および S p y 1 4 9 4 などのタンパク質は含めてある。病原性細菌は血中に直接注射しているので、記載の菌血症モデルは侵入性疾患に対するワクチン候補の防禦価を評価するものである。そのような A 群連鎖球菌感染に対して防禦しうる抗体を誘起する組換えタンパク質は、A 群連鎖球菌疾患に対するワクチンを開発するための価値ある候補であると考えられる。以前にストレプトコッカス・ピオゲネス攻撃に対して防禦を提供することが示された正の対照である S p y 2 0 1 8 (M1 タンパク質) と比較して、1 8 日または 2 1 日後に攻撃実験の終点 (表 4) を評価したときに幾つかの抗原は同程度の性能を示した (S p y 0 4 1 6、S p y 1 6 0 7 または S p y 0 2 9 2)。他のタンパク質は部分的な防禦効果しか示さなかったが (S p y 0 7 2 0、S p y 0 8 7 2)、他の抗原と組み合わせたときに非常に有効であることがわかる (図 6)。

【0281】

驚くべきことに、この抗原スクリーニングは、2 つの大きなタンパク質、S p y 0 4 1 6 および S p y 1 9 7 2 の最初の半分に優先的に免疫原性エピトープを同定した。それゆえ、防禦領域もまた該タンパク質の N 末端部に含まれることが推論された。S p y 0 4 1 6 の場合は抗原の両部を組換えタンパク質として産生し (S p y 0 4 1 6 A および S p y 0 4 1 6 B; 表 4 参照)、動物実験で試験した。これら実験は、タンパク質 S p y 0 4 1 6 の最初の半分 (表 4; S p y 0 4 1 6 A) のみが動物モデルにおいて防禦を提供し、一方、タンパク質の第二の半分 (S p y 0 4 1 6 B) は全く防禦効果を有しないことを示し、該タンパク質内の一層小さな領域をワクチン候補として明らかに説明した。抗原 S p y 1 9 7 2 については、完全長タンパク質の最初の半분을組換えタンパク質として産生し、動物モデルで試験した。

【0282】

実施例 8 : 種々の血清型のストレプトコッカス・ピオゲネス株での抗原性タンパク質をコードする遺伝子の変動性

実験手順

P C R 断片のシークエンシングおよびバイオインフォーマティクス分析

ストレプトコッカス・ピオゲネス株の P C R 分析は実施例 5 に記載してある。P C R 断片のシークエンシングは遺伝子の変動性の評価を提供し、その結果の要約を表 3 に列挙してある。5 つのストレプトコッカス・ピオゲネス株 (S F 3 7 0 : M 1 ; M G A S 8 2 3 2 : M 1 8 ; S S I - 1 : M 3 ; M G A S 3 1 5 : M 3 ; M a n f r e d o : M 5) からのゲノム配列を入手できたことにより、抗原の変動性のさらなる評価が可能となった。すべての配列を、ストレプトコッカス・ピオゲネス S F 3 7 0 からの各抗原配列およびストレプトコッカス・ピオゲネス S F 3 7 0 からの抗原性タンパク質のものとは異なると同定されたアミノ酸残基を用いてアラインメントした。抗原性タンパク質の幾つかには挿入配列または欠失配列が検出されたが、この分析には含まれていない。

【0283】

結果

表 5 は、4 つのストレプトコッカス・ピオゲネス株 (M G A S 8 2 3 2 : M 1 8 ; S S I - 1 : M 3 ; M G A S 3 1 5 : M 3 ; M a n f r e d o : M 5) または増幅 P C R 断片のシークエンシングに用いた株 (表 3 参照) の一つにおいて示された抗原の変わりうると同定されたすべての位置を示す。バイオインフォーマティクス分析は、抗原性タンパク質

の幾つかのものは血清型 M 1、M 3、M 5、M 1 8 および M 8 9 の 6 つの株のいずれにおいても単一のアミノ酸交換もなしに非常によく保存されていることを示している。この群に属するタンパク質としては S p y 0 1 0 3 および S p y 1 5 3 6 が挙げられるが、他の抗原性タンパク質における交換は、サイズ自体の差異から予期されるように小さなタンパク質よりも大きなタンパク質の方が多かった。種々の株を分析したが、単一の残基が他の株において 1 を超える他のアミノ酸に交換されることは殆ど観察されなかった。血清型、臨床所見または地理的位置が様々な一層多数の株における各遺伝子の配列のさらなる分析は、列挙したアミノ酸残基におけるまたはさらなる残基における可能な変化を確かに同定することであろう。

【 0 2 8 4 】

10

6 つの遺伝子配列のアラインメントにより分析した抗原性タンパク質のうち 1 つのみがサイズにおいて相当の程度の変動を示した (S p y 1 3 5 7 : S F 3 7 0 2 1 7 アミノ酸 ; M G A S 8 2 3 2 2 4 5 アミノ酸 ; S S I - 1 3 2 9 アミノ酸 ; M G A S 3 1 5 3 2 9 アミノ酸 ; M a n f r e d o 2 7 9 アミノ酸) 。それゆえ、評価した抗原は配列においてもサイズにおいても非常によく保存されており、ワクチン開発のための有望な候補を提供することが明らかである。

【 0 2 8 5 】

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10

【0286】

表1：細菌表面ディスプレイによって同定した免疫原性タンパク質

20

【表 1】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
Spy0012	推定タンパク質	4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425	A:12, I:5, N:2	1-114	1, 151
Spy0019	推定分泌タンパク質 (細胞分裂および抗生 物質耐性)	5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395	F:2, I:16, K:24, N:29, P:12	29-226	2, 152
Spy0025	推定ホスホリボシルホ ルミルグリシンアミジ ンシンターゼII	4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254	D:3	919-929	3, 153
Spy0031	推定コリン結合タンパ ク質	5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360	I:3, K:3, N:3	145-305	4, 154
Spy0103	推定コンピテンスタン パク質	15-39, 52-61, 72-81, 92-97	A:8	71-81	5, 155
Spy0112	推定ピロリンカルボキ シレートレダクターゼ	13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245	B:4	173-186	6, 156
Spy0115	推定グルタリル-アミ ノペプチダーゼ	5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352	A:3, C:26	316-331	7, 157
Spy0166	推定タンパク質	6-28, 43-53, 60-76, 93-103	I:22, K:7, N:17, O:31, P:5	21-99	8, 158
Spy0167	ストレプトリシンO	10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568	A:118, B:14, C:18, D:37, F:141, G:79, H:92, I:97, K:123, L:5, M:21, N:225,	9-264	9, 159

【表 2】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
			O:230, P:265		
Spy0168	推定タンパク質	5-29, 39-45, 107-128	K:4, N:7	1-112	10, 160
Spy0171	推定タンパク質	4-38, 42-50, 54-60, 65-71, 91-102	H:2	21-56	11, 161
Spy0183	推定グリシンペタイン /プロリンABC 輸送体	4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391	C:6	23-39	12, 162
Spy0230	推定ABC 輸送体 (ATP-結合タンパク質)	6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591	C:46	474-489	13, 163
Spy0269	推定表面排除タンパク 質	8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864	A:2, B:12, D:3, F:11, H:5, N:6	37-241 409-534 582-604 743-804	14, 164
Spy0287	保存された 推定タン パク質	4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416	K:1	202-337	15, 165
Spy0292	ペニシリン結合タンパ ク質(D-アラニル-D-ア ラニンcar	4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407	F:2	1-48	16, 166
Spy0295	オリゴペプチドパーミ ターゼ	18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297	A:3	203-217	17, 167
Spy0348	推定アミノデオキシコ リスミ酸リアーゼ	20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521	D:5, E:3, M:3, P:3	261-273	18, 168
Spy0416	推定細胞エンベロープ セリンプロテイナーゼ	6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172,	A:3, B:4, C:30,	1-414	19, 169

【表 3】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641	D:13, F:138, G:120, H:101, I:9, K:14, M:2, N: 15, O:8, P:19	443-614 997-1392	
Spy0430	推定タンパク質	14-42, 70-75, 90-100, 158-181	B:7, I:10, P:18	1-164	20, 170
Spy0433	推定タンパク質	4-21, 30-36, 54-82, 89-97, 105-118, 138-147	A:138, B:8, C:67, D:11, E:13, F:35, G:10, H:5, M:8	126-207	21, 171
Spy0437	推定タンパク質	4-21, 31-66, 96-104, 106-113, 131-142	A:29, B:10, C:21, D:24, E:15	180-204	22, 172
Spy0469	推定42 kDaタンパク質	5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386	B:5, F:77, I:8, K:15, M:3, N:17, O:20	11-197 204-219 258-372	23, 173
Spy0488	推定タンパク質	4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322	A:17, B:11, C:23, D:12, E:4, G:4, H:7	195-289	24, 174
Spy0515	推定糖トランスフェラーゼ	4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329	B:5, L:3	12-130	25, 175
Spy0580	保存された推定タンパク質	10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707	C:5	434-444	26, 176
Spy0621	保存された推定タンパク質	6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149,	C:3	360-375	27, 177

【表 4】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430			
Spy0630	推定FIS依存性N-ア セチル-ガラクトサミ ン-IIIC	4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251	C:2	254-260	28, 178
Spy0681	推定タンパク質,ファ ージ結合	12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400	A:8	369-382	29, 179
Spy0683	推定小カプシドタンパ ク質, ファージ結合	11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487	B:11, D:4	270-312	30, 180
Spy0702	推定タンパク質	5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604	L:2	486-598	31, 181
Spy0710	保存された推定タンパ ク質, ファージ結合	4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374	B:10	378-396	32, 182
Spy0711	発熱性外毒素C前駆体, ファージ結合(speC)	5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184	K:2	75-235	33, 183
Spy0720	保存された推定タンパ ク質	6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310	D:2	30-51	34, 184
Spy0727	推定DNAジャイレ ース,サブユニットB	17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647	M:26	208-219	35, 185
Spy0737	推定細胞外マトリッ クス結合タンパク質	4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963,	B:5, E:3, K:11	396-533 1342-1502 1672-1920	36, 186

【表 5】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039			
Spy0747	細胞外ヌクレアーゼ	4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905	A:72, B:17, H:6, O:3	1-113 210-232 250-423 536-564	37, 187
Spy0777	推定ATP-依存性エキ ソヌクレアーゼ, サブ ユニットA	4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201	C:4, E:2	617-635	38, 188
Spy0789	推定ABC-輸送体(パー ミターゼ タンパク質)	7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244	A:3	190-203	39, 189
Spy0839	推定グリセロホスホジ エステル ホスホジエ ステル	4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574	A:7, D:2	385-398	40, 190
Spy0843	細胞表面タンパク質	5-36, 66-72, 120-127, 146-152, 159-168, 172-184,	A:11, B:3, C:5,	12-190	41, 191

【表 6】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003	D:4, F:50, H:19, G:49, I:112, K:102, L:10, M:3, N:213, O:188, P:310	276-283 666-806	
Spy0872	推定分泌 5'-ヌクレオ チダーゼ	4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664	A:6, D:2, F:5, H:14, I:9, K:10, L:1, N:16, O:12	30-80 89-105 111-151	42, 192
Spy0895	ヒスチジン プロテイン キナーゼ	7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259	C:11	195-203	43, 193
Spy0972	推定ターミナーゼ, 大 サブユニット-ファージ	5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426	B:2	32-50	44, 194
Spy0981	推定タンパク質-ファ ージ結合	8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174	A:7, B:2	75-90	45, 195
Spy1008	連鎖球菌外毒素H 前 駆体(speH)	4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233	C:11	69-88	46, 196
Spy1032	細胞外ヒアルロン酸リ アーゼ	4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802	B:3, K:3, M:5	96-230 361-491 572-585	47, 197
Spy1054	推定コラーゲン様タン パク質(SclC)	4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289	A:71, B:13, C:233, D:41, E:163, F:200, G:442, H:129, N:3	102-210	48, 198
Spy1063	推定ペリプラズム鉄- 結合タンパク質	13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313	A:4	240-248	49, 199
Spy1162	推定リボヌクレアーゼ III	5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260	B:3, C:5	182-198	50, 200

【表 7】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
Spy1206	推定ABC 輸送体	10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504	A:2	41-56	51, 201
Spy1228	推定リボタンパク質	5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333	M:33	202-217	52, 202
Spy1245	推定リン酸ABC 輸送 体	6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283	L:3, K:3	1-127	53, 203
Spy1315	推定タンパク質	4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718	B:4	297-458	54, 204
Spy1357	G タンパク質RAB(G タンパク質結合アルフ ァ2M-結合p	5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213	G:27, H:8, K:2, N:4	24-135	55, 205
Spy1361	推定インターナリン A前駆体	4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721	F:21, G:26, H:6, K:4, N:5	176-330	56, 206
Spy1371	推定NADP-依存性グリ セルアルデヒド-3- リン酸 デヒドロゲナ ーゼ	31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472	D:14, H:3	46-62 296-341	57, 207
Spy1375	推定リボヌクレオチド レダクターゼアルファ -c	23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716	A:2	667-684	58, 208
Spy1389	推定アラニル-tRNAシ ンテターゼ	20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566,	B:2, P:3	258-416	59, 209

【表 8】

ストレプト コッカス・ ピオグネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869			
Spy1390	推定プロテアーゼ成熟 タンパク質	7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300	A:3, B:2, D:3	278-295	60, 210
Spy1422	推定組換えタンパク質	4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191	C:2	183-195	61, 211
Spy1436	推定デオキシリボヌク レアーゼ	12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241	K:1	63-238	62, 212
Spy1494	推定タンパク質	4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308	G:3, I:5, K:6, M:5, N:10, O:6, P:4	1-141	63, 213
Spy1523	細胞分裂タンパク質	11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379	I:2	231-368	64, 214
Spy1536	保存された推定タンパ ク質	9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342	A:19, C:3	247-260	65, 215
Spy1564	保存された推定タンパ ク質	7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279	C:4	64-72	66, 216
Spy1604	保存された推定タンパ ク質	4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897	B:2, K:2	222-362 756-896	67, 217
Spy1607	保存された推定タンパ ク質	11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255	D:5	153-170	68, 218
Spy1615	推定lateコンピテンス タンパク質	4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212	C:4	56-73	69, 219
Spy1666	保存された推定タンパ ク質	4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334	D:2	298-312	70, 220
Spy1727	保存された推定タンパ ク質	7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238,	B:5	141-157	71, 221

【表 9】

ストレプト コッカス・ ピオグネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		247-254			
Spy1785	推定ATP依存性DNA ヘリカーゼ	23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663	D:3	433-440 572-593	72, 222
Spy1798	推定タンパク質	4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267	A:12, I:12, K:7, N:17, O:13, P:8	17-319 417-563	73, 223
Spy1801	免疫原性分泌タンパク 質前駆体ホモログ	6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500	H:2, I:8, K:6, N:11	46-187	74, 224
Spy1813	推定タンパク質	4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992	I:16, K:12, N:6	21-244 381-499 818-959	75, 225
Spy1821	推定翻訳伸長因子 EF-P	19-29, 65-75, 90-109, 111-137, 155-165, 169-175	C:6	118-136	76, 226
Spy1916	推定ホスホペーター-D- ガラクトシダーゼ	15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465	C:8	147-155	77, 227
Spy1972	ブルラナーゼ	11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359,	A:6, I:2, K:5, N:9	74-438	78, 228

【表 10】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161			
Spy1979	ストレプトキナーゼ A 前駆体	4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413	I:6, M:3, N:10	156-420	79, 229
Spy1983	コラーゲン様表面タン パク質(ScID)	4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343	A:81, B:24, F:19, G:41, I:2, K:2	79-348	80, 230
Spy1991	アントラニン酸シンタ ーゼ成分II	12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168	D:2	53-70	81, 231
Spy2000	表面リボタンパク質	4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522	B:3, N:2	183-341	82, 232
Spy2006	推定タンパク質	4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822	A:15, B:9, C:5, D:3, F:18, G:25, H:5, M:10, N:5	92-231 618-757	83, 233
Spy2009	推定タンパク質	11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372	B:2, I:7, K:7, P:2	41-170	84, 234
Spy2010	C5Aペプチダーゼ前駆 体	6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914,	A:47, B:10, D:3, F:48, G:20, H:4, I:6, K:13, M:5, N:10, P:6	20-487 757-1153	85, 235

【表 1 1】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174			
Spy2016	補体のインヒビター (Sic)	10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305	A:11, B:38, C:16, F:56, G:27, H:13, K:5, N:2, O:3, P:14	26-74 91-100 105-303	86, 236
Spy2018	M1-タンパク質	9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480	A:316, B:26, C:107, D:12, E:49, F:88, G:118, H:6, I:7, K:2, M:48, N:43	10-223 231-251 264-297 312-336	87, 237
Spy2025	免疫原性分泌タンパク 質前駆体	5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537	F:7, G:16, H:7, K:63, L:2, N:18, O:42	22-344	88, 238
Spy2039	発熱性 外毒素B	5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395	I:15, K:3, N:12	1-151	89, 239
Spy2043	マイトジェン 因子 MF1(speF)	6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756	K:1	91-263	90, 240
Spy2059	ペニシリン結合タンパ ク質2a	4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305,	D:2, E:2	261-272	91, 241

【表 1 2】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
		311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775			
Spy2110	推定通気性リボスクレ オシド-三リン酸レダ クターゼ	4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701	E:7	541-551	92, 242
Spy2127	推定タンパク質	6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252	E:6, P:2	84-254	93, 243
Spy2191	推定タンパク質	13-30, 71-120, 125-137, 139-145, 184-199	C:20, E:3, M:5	61-78	94, 244
Spy2211	膜貫通タンパク質	9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855	A :3	568-580	95, 245
ARF0450	ホモロジーなし	11-21, 29-38	A:11	5-17	96, 246
ARF0569	ホモロジーなし	なし	A:2	2-9	97, 247
ARF0694	ホモロジーなし	4-10, 16-28	B:7, D:3, M:3	7-18 26-34	98, 248
ARF0700	ホモロジーなし	10-16	M:11	1-15	99, 249
ARF1007	ホモロジーなし	なし	B:2	4-11	100, 250
ARF1145	ホモロジーなし	4-40, 42-51	C:9	37-53	101, 251
ARF1208	ホモロジーなし	4-21	C:1	22-29	102, 252
ARF1262	ホモロジーなし	なし	D:2	2-11	103, 253
ARF1294	SA0131と39% (67 aa の最初の28 aa)	9-17, 32-44	D:2	1-22	104, 254
ARF1316	ホモロジーなし	19-25, 27-32	E:19	15-34	105, 255
ARF1352	SA1142と38% (358の aa 265-295)	4-12, 15-22	D:4	11-33	106, 256
ARF1481	ホモロジーなし	10-17, 24-30, 39-46, 51-70	C:2	51-61	107, 257
ARF1557	ホモロジーなし	なし	C:2	6-19	108, 258

【表 1 3】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
ARF1629	SP0069と36% (211 aa のaa 139-169)	6-11, 21-27, 31-54	A:4, B:6	11-29	109, 259
ARF1654	ホモロジーなし	4-10, 13-45	A:2	11-35	110, 260
ARF2027	ホモロジーなし	4-14, 23-32	D:2	11-35	111, 261
ARF2093	推定伸長 因子TS	14-39, 45-51	C:3	15-29	112, 262
ARF2207	SP1006と38% (67 aa の aa 7-37)	4-11, 14-28	A:117	4-17	113, 263
CRF0038	ホモロジーなし	4-16	C:6	2-16	114, 264
CRF0122	ホモロジーなし	4-10, 12-19, 39-50	C:2	6-22	115, 265
CRF0406	ホモロジーなし	なし	D:5, E:11	2-13	116, 266
CRF0416	ホモロジーなし	4-11, 22-65	C:42	3-19	117, 267
CRF0507	ホモロジーなし	17-23, 30-35, 39-46, 57-62	B:3, C:4	30-49	118, 268
CRF0549	ホモロジーなし	4-19	C:6	14-22	119, 269
CRF0569	ホモロジーなし	なし	N:35	2-9	120, 270
CRF0628	P.aeruginosaと34% (41のうちの14)、保存 された 推定タンパク 質	7-18, 30-43	A:3	4-12	121, 271
CRF0727	S.pneumoniaeと40% (40のうちの16)、転写 調節因子 (70 aa, SP0584)	4-30, 39-47	N:6	5-22	122, 272
CRF0742	SA0422と33% (42 aa タンパク質のaa 11-37, 280 aaタンパク質とし て列挙)	6-15	D:7, E:12	14-29	123, 273
CRF0784	ホモロジーなし	4-34	N:9	23-35	124, 274
CRF0854	ホモロジーなし	4-36, 44-57, 65-72	N:14	14-27	125, 275
CRF0875	ホモロジーなし	4-18	A:4, D:1	11-20	126, 276
CRF0907	リソソーム輸送調節因 子に対してホモロジー LYST[ホモ・サビエン ス]	なし	A:39	5-19	127, 277
CRF0979	ホモロジーなし	18-36	D:21	6-20	128, 278
CRF1068	ホモロジーなし	4-10, 19-34, 41-84, 96-104	C:1, D:3	50-63	129, 279
CRF1152	ホモロジーなし	4-9, 19-27	C:15	8-21	130, 280
CRF1203	ホモロジーなし	4-16, 18-28	N:3	22-30	131, 281
CRF1225	ホモロジーなし	4-15	C:8	21-35	132, 282
CRF1236	ホモロジーなし	4-17	N:3	3-13	133, 283
CRF1362	ホモロジーなし	4-12	C:6	4-18	134, 284
CRF1524	ホモロジーなし	4-24, 31-36	D:3	29-45	135, 285
CRF1525	ホモロジーなし	12-22, 34-49	C:2	21-32	136, 286

【表 1 4】

ストレプト コッカス・ ピオゲネス 抗原性タン パク質	推定機能 (ホモロジー による)	予測される免疫原性アミノ酸**	ORFおよびス クリーニング当 たりで選択した クローンの番号	同定された免 疫原性領域の 位置(アミノ 酸)	配列番号 (DNA、タン パク質)
CRF1527	ホモロジーなし	4-17	D:4, E:1	22-32	137, 287
CRF1588	ホモロジーなし	4-16, 25-42	C:2	7-28	138, 288
CRF1649	ホモロジーなし	4-10	C:3	7-20	139, 289
CRF1749	ホモロジーなし	4-11, 16-36, 39-54	C:15	28-44	140, 290
CRF1903	ホモロジーなし	5-20, 29-54	A:14	14-29	141, 291
CRF1964	ホモロジーなし	24-33	A:8	10-22	142, 292
CRF2055	ホモロジーなし	10-51, 54-61	B:1, F:12, H:14	43-64	143, 293
CRF2091	ホモロジーなし	7-13	C:2	2-17	144, 294
CRF2096	ホモロジーなし	11-20	C:4	6-20	145, 295
CRF2104	ホモロジーなし	4-30, 34-41	C:2	19-28	146, 296
CRF2116	ホモロジーなし	n.d.		11-21	147, 297
CRF2153	ホモロジーなし	4-16, 21-26	F:2	9-38	148, 298
NRF0001	オリゴABC 輸送体に おけるARF(TIGRによ る注釈なし), SA0643 と33% (469aaタンパク 質のaa107-162)	4-12, 15-27, 30-42, 66-72	A:7, B:1	10-24	149, 299
NRF0003	ホモロジーなし	8-17	A:23	11-20	150, 300

【 0 3 0 0 】

表 2

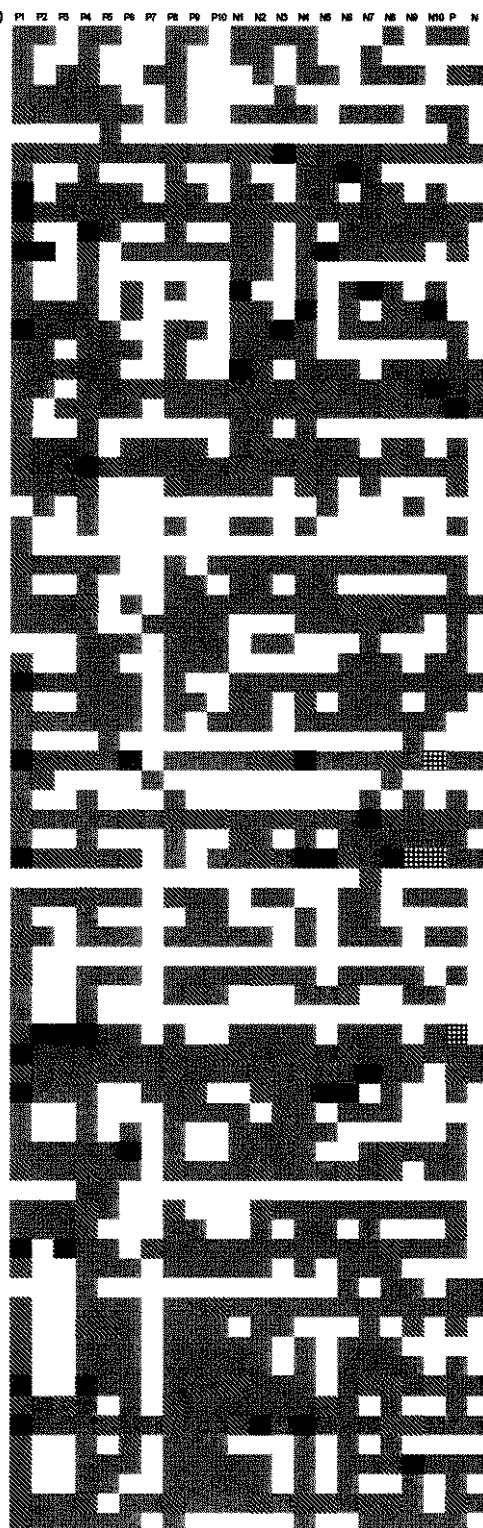
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ペブテド	ペブテド取組
SFA0450.1	SELETRNDZSLSSASAC
SFA0456.1	SRFKNP66.1
SFA0494.2	KTSQIUTPKRQMRRTM
SFA1294.1	MLAKRTKSLTILSOPTKE
SFA1316.1	GRERIDFVACYSPNGICSP
SFA1352.1	QVSHQECPLVLANJYANYSKJCI
SFA1629.1	RDMDQZKGTGKNDPFW
SFA1654.1	MIQINTVLSILFPLTFO
SFA2027.1	PELWKLBSAARRKSLDIC
SFA2207.1	VKQVWSTLKWDR
SFA2408.1	QAFIDJHNNFTVWYSGYL
SFA2742.1	KYSHKSHRINTFRRGG
SFA3575.1	WHLQJLKSQVQMTFFEL
SFA3607.1	ILLUETHEHJHNNRKAOLD
SFA3688.1	FRHILDSVASINNOVRS
SFA3824.1	ILNRGANTISQKVIRW
SFA3827.1	TLRRTFTTINFEDNFW
SFA3903.1	KELVJQVFNKIMAFINPE
SFA3984.1	FIJLQSGKGRPKPTWSE
SFND001.1	TOQLFKPKSLNNLLJHL
SFND003.1	SGQDGLNVLHLSRSPILFS
SFND012.1	PVJSTKELFSNNW
SFND012.2	AYOSULITFLA
SFND013.1	DIALNSKSIJSDV
SFND031.1	DESGTHTFPTRLVKGZTSLISPOLA
SFND031.2	DEPLAYIYAGSGVYVKKVITAGGT
SFND031.4	PINERAGSVQVNTKRSIKVSGVIT
SFND033.1	KPLSLQJLAD
SFND012.1	ZALAKAGVNGIP
SFND015.1	YIHSHQYLVIMDFD
SFND063.1	NDNMSJGQALDLYQAVQVITARNML
SFND063.2	IAEMSLJLQVTFPYLZNSLIANNRL
SFND063.3	MTALKVJLREZAMAHYKLGEFAHQ
SFND067.1	SRQNTASTETTTTNDQFPESSLE
SFND067.2	RHGFLESHRERKSGEKRGK
SFND067.3	FRGSGVQADKTVIE
SFND067.4	TYPAQLQJNKGPT
SFND067.5	NLNMWHNLSGNTLEARTQ
SFND071.1	TRHQVYHVSUTLETRDQNGTVCFG
SFND083.1	MVTKGNKSEI FNKNG
SFND230.1	MSLKPJGTVISDDO
SFND299.1	DRASGETFASNTIDSLSPK
SFND299.2	TLQJSDISLNVQVRLNLSQPT
SFND297.1	EVLQAGSGZKRSALQVIRGSPVTV
SFND287.2	PSVTTYISFRGKLEKDNIDNALVM
SFND287.3	WALWANGNVLADTLEOLIGQSGSA
SFND287.4	GQSGADPLVAFSSSGVDFGIDFV
SFND287.5	GUDTVYHVSQVGHVILQGVILQ
SFND287.6	GVLEKRTLVFNGLHGLKAGLDA
SFND292.1	YSVTARNAVIVLESGVNVYERKA
SFND295.1	SOGLTQPMYKIAV
SFND348.1	EGGTAEPTKSGKLLTIP
SFND415.1	PDNDHIDWVTKGAWNG
SFND418.2	DGSHND
SFND418.4	EDPDELWNEFTAEAEKPAIKRGKI
SFND430.1	QHQRPULTEFAELSGSGSGQSGRQ
SFND437.1	KPWHLKSEKIQDMMFKGLG
SFND493.1	DVPTTFPSA
SFND493.2	KTDISEAPTISANRPV
SFND493.1	INERGRQATIT
SFND482.2	TGGLPECKEY
SFND483.3	NILKIDKESGRFEFF
SFND483.4	KERQATITYGQSDTIDPLPAMVNL
SFND483.5	ALWIKSGVKEPTEDQVSG
SFND515.1	GXYDGMGTDAFFFTSREETES
SFND515.2	GETALFELVSGVASKRWG
SFND550.1	JARLQGLDPAELAKVDKPSI
SFND521.1	LENRTQVLEMMCKG
SFND630.1	NRPQVQVNTVGGQJQXWI
SFND702.1	ALVRKQDTHVAFVHFSNRIP
SFND710.1	NYLGIQGLKQDGRNISLV
SFND720.1	LSGQGLKKEITAGNPDYKRL
SFND737.1	ULAEAAKTRALLIEKNTLTDQKR
SFND737.2	TDQKHEQLJQVDTYKAGI
SFND737.3	EYANGENTPAKQADQV
SFND747.1	VNDOSKSIYVHIDH
SFND747.2	HLKPEKTVILQKLSKLASYNNENB

配列番号	タンパク質中の位置 (aa)
246	2-19
247	1-12
248	21-38
254	2-22
255	15-33
256	11-32
259	11-28
260	10-27
261	9-26
263	4-16
266	1-18
273	12-29
276	6-23
277	1-21
279	47-64
285	28-45
287	18-35
291	14-31
292	7-24
299	8-25
300	1-20
151	18-33
151	62-72
152	118-131
154	196-220
154	215-240
154	255-280
155	72-81
156	174-186
157	317-331
158	35-59
158	54-84
158	79-104
159	33-58
159	81-101
159	136-150
159	173-186
159	231-251
161	22-48
162	24-39
163	475-489
164	38-56
164	583-604
165	202-223
165	222-247
165	242-267
165	262-287
165	282-307
165	302-327
166	25-48
167	204-217
168	259-276
169	121-139
169	260-267
169	215-240
170	115-140
172	182-204
173	144-153
173	205-219
174	196-206
174	240-249
174	272-287
174	199-223
174	218-237
175	226-249
175	287-306
176	430-449
177	361-375
178	241-260
181	483-502
182	379-396
184	31-51
186	1436-1460
186	1455-1474
186	1469-1487
187	215-229
187	534-561



スコア	+	++	+++	++++
13	13			
7	7			
15	11	2		
7	7			
17	15	1		
2	2			
35	10	11	1	
10	7		1	
15	11	2	1	
35	10	11	1	
16	11	1	1	
31	10	4	3	
5	5			
15	7	1	2	
19	7	3	2	
23	13	2	2	
13	9	2		
23	10	5	1	
32	11	9	1	
28	12	7	1	
5	5			
24	10	7		
31	12	8	1	
17	9	4		
4	4			
7	7			
1	1			
19	17	1		
9	9			
24	16	4		
16	14	1		
10	10			
16	10	1		
21	18		1	
17	11	3		
15	16	1		
3	3			
36	11	6	3	1
5	3	1		
5	6			
34	11	10	1	
13	11	1		
40	8	6	4	2
2	2			
18	14	2		
7	7			
17	15	1		
1	1			
16	14	1		
12	8	2		
2	2			
26	11	1	3	1
33	12	9	1	
31	12	8	1	
24	9	2	3	
12	10	1		
11	9	1		
19	14	1	1	
25	13	6		
2	2			
19	13	3		
12	8	2		
25	15	2	2	
14	12	1		
6	6			
21	17	2		
17	7	5		
14	12	1		
16	14	1		
26	10	6	2	
20	12	4		
33	14	5	3	
11	7	2		
21	14	2	1	
12	10	1		
29	11	9		
14	12	1		

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表3：ストレプトコッカス・ピオゲネス株における遺伝子分布

【表 17】

ORF	一般的な名称	遺伝子分布 (50の存在)	アミノ酸置換(株 M89における)	ホモロジー (SP/EC)	配列番号 (DNA、タンパク質)
Spy0012	推定タンパク質	50	3/302	SP0010 - 40%/なし	1, 151
Spy0019	推定分泌タンパク質(細胞分裂および抗生物質耐性)	50	0/300	SP2216 - 44-49%/なし	2, 152
Spy0025	推定ホスホリボシルホルミルグリシンアミジンシンターゼ II	38	0/303	SP0045 - 85%/24%	3, 153
Spy0031	推定コリン結合タンパク質	50	0/297	SP2201 - 42% (cbpD)/なし	4, 154
Spy0103	推定コンピテンス タンパク質	50	0/81	SP2051 - 41%/なし	5, 155
Spy0112	推定ピロリンカルボキシレートレダクターゼ	50	3/235	SP0933 - 32%/34%	6, 156
Spy0115	推定グルタリル-アミノペプチダーゼ	50	6/306	SP1865 - 76%/30%	7, 157
Spy0166	推定タンパク質	50	n.d.	なし/なし	8, 158
Spy0167	ストレプトリシンO	50	7/300	SP1923 - 40% (Pneumolysin)/なし	9, 159
Spy0168	推定タンパク質	8	19/126	なし/なし	10, 160
Spy0171	推定タンパク質	18	8/95	なし/なし	11, 161
Spy0183	推定グリシンペタイン/プロリンABC輸送体	50	0/297	SP0151 - 39%/48%	12, 162
Spy0230	推定ABC 輸送体(ATP-結合タンパク質)	50	1/299	SP2073 - 64%/32%	13, 163
Spy0269	推定表面排除タンパク質	50	1/303	なし/なし	14, 164
Spy0287	保存された 推定タンパク質	50	1/307	SP0868 - 71%/19%	15, 165
Spy0292	ペニシリン結合タンパク質 (D-アラニル-D-アラニンcar)	50	1/359	SP0872 - 47%/27%	16, 166
Spy0295	オリゴペプチドパーミターゼ	50	2/269	SP1889 - 69%/24%	17, 167
Spy0348	推定アミノデオキシコリスミ酸リアーゼ	50	1/307	SP1518 - 47%/25%	18, 168
Spy0416	推定細胞エンベロープセリンプロテイナーゼ	50	4/314	SP0641 - 22%/なし	19, 169
Spy0430	推定タンパク質	13	0/165#	なし/なし	20, 170
Spy0433	推定タンパク質	21 (27/49) ¹	2/174#	なし/なし	21, 171
Spy0437	推定タンパク質	19 (34/49) ¹	0/106#	なし/なし	22, 172
Spy0469	推定42kDaタンパク質	50	6/313	SP2063 - 44% (LysM タンパク質)/なし	23, 173
Spy0488	推定タンパク質	50	9/178	なし/なし	24, 174
Spy0515	推定糖トランスフェラーゼ	50	n.d.	SP1075 - 26%/なし	25, 175
Spy0580	保存された推定タンパク質	50	0/297	SP0908 - 72%/43%	26, 176
Spy0621	保存された推定タンパク質	50	n.d.	SP1290 - 72%/なし	27, 177
Spy0630	推定PTS依存性N-アセチル-ガラクトサミン-IIIC	50	n.d.	SP0324 - 79%/30%	28, 178
Spy0681	推定タンパク質, ファージ結合	27	2/303#	なし/なし	29, 179
Spy0683	推定小カプシドタンパク質, ファージ結合	25	1/233	なし/なし	30, 180
Spy0702	推定タンパク質	22	n.d.	なし/なし	31, 181

【表 18】

Spy0710	保存された推定タンパク質, ファージ結合	32	51/286#	なし/36% 313aa のうちの122	32, 182
Spy0711	発熱性毒素C前駆体,ファージ 結合(speC)	17	1/225	なし/なし	33, 183
Spy0720	保存された推定タンパク質	50	2/270	SP1298 - 60% (DHH 1 タンパ ク質)/なし	34, 184
Spy0727	推定DNAジャイレース, サブ ユニットB	n.d.	n.d.	SP0806 - 80%/46%	35, 185
Spy0737	推定細胞外マトリックス結合 タンパク質	29 (48/49) ¹	0/466#	なし/27% 421aa のうちの340	36, 186
Spy0747	細胞外ヌクレアーゼ	50	0/179	なし/なし	37, 187
Spy0777	推定ATP-依存性エキソヌク レアーゼ, サブユニットA	50	2/306	SP1152 - 48%/22%	38, 188
Spy0789	推定ABC-輸送体(パーミアー ゼタンパク質)	50	1/231	なし/なし	39, 189
Spy0839	推定グリセロホスホジエステ ルホスホジエステル	50	1/301	SP0994 - 24%/31% 358aa のう ちの121	40, 190
Spy0843	細胞表面タンパク質	50	3/312	なし/なし	41, 191
Spy0872	推定分泌5'-ヌクレオチダーゼ	50	2/309	なし/27% 647aa のうちの274	42, 192
Spy0895	ヒスチジンプロテインキナー ゼ	50	0/244	なし/なし	43, 193
Spy0972	推定ターミナーゼ,大サブユ ニット-ファージ	28	1/314#	なし/なし	44, 194
Spy0981	推定タンパク質-ファージ結 合	23	n.d.	なし/なし	45, 195
Spy1008	連鎖球菌毒素H前駆体 (speH)	15 (14/49) ¹	1/223#	なし/なし	46, 196
Spy1032	細胞外ヒアルロン酸リアーゼ	50 (175 of 175, Hynes 2000)	3/311	SP0314 - 51%/なし	47, 197
Spy1054	推定コラーゲン様タンパク質 (ScIC)	26, (45/49) ¹ (50のう ちの50, しかし様々 な数のリピート; Lukomski, 2001)	n.d.	なし/なし	48, 198
Spy1063	推定ペリプラズム鉄結合タン パク質	49/50 (49/49) ¹	2/292#	SP0243 - 52%, 鉄 ABC 輸送体 /26% 348aa のうちの161	49, 199
Spy1162	推定リボヌクレアーゼHII	50	3/240	SP1156 - 67%/46%	50, 200
Spy1206	推定ABC輸送体	50	1/302	SP0770 - 81%/30%	51, 201
Spy1228	推定リボタンパク質	49	n.d.	SP0845-57%/なし	52, 202
Spy1245	推定ABC輸送体	50	n.d.	SP1400-64%/なし	53, 203
Spy1315	推定タンパク質	50	4/305	SP1241 - 64%/32%	54, 204
Spy1357	Gタンパク質RAB(Gタンパ ク質結合アルファ2M-結合タ ンパク質)	49; 12の株のうちの 11 (Rasmussen, 1999)	9/226; 28 aa の挿入	なし/なし	55, 205
Spy1361	推定インターナリンA前駆体	50	7/295	SP1004 - 26% 1039のうちの 283/なし	56, 206
Spy1371	推定NADP依存性グリセルアル デヒド-3-リン酸デヒドロゲ ナーゼ	50	2/308	SP1119 - 71%/34%	57, 207
Spy1375	推定リボヌクレオチドレダク ターゼアルファc	50	4/304	SP1179 - 85%/49%	58, 208
Spy1389	推定アラニル-tRNAシンテタ ーゼ	50	0/309	SP1383 - 74%/40%	59, 209
Spy1390	推定プロテアーゼ成熟タンパ ク質	50	0/232	SP0981 - 42%/なし	60, 210
Spy1422	推定組換えタンパク質	n.d.	n.d.	SP1672 - 88%/64%	61, 211
Spy1436	推定デオキシリボヌクレアー ゼ	25	0/243#	SP1964 - 29% 274aa のうちの 181/なし	62, 212
Spy1494	推定タンパク質	50	13/282	なし/なし	63, 213

【表 19】

Spy1523	細胞分裂タンパク質	49	2/329	SP0690 - 27%/なし	64, 214
Spy1536	保存された推定タンパク質	50	9/280	SP1967 - 57%/なし	65, 215
Spy1564	保存された推定タンパク質	39	n.d.	なし/なし	66, 216
Spy1604	保存された推定タンパク質	50	1/233	SP2143 - 47%/28%	67, 217
Spy1607	保存された推定タンパク質	50	0/241	SP1902 - 55%/なし	68, 218
Spy1615	推定lateコンピテンシタンパク質	50	2/204	SP2207 - 41%/なし	69, 219
Spy1666	保存された推定タンパク質	50	2/305	SP0334 (yIIc) - 78%/40%	70, 220
Spy1727	保存された推定タンパク質	50	0/237	SP0549 - 53%/なし	71, 221
Spy1785	推定ATP依存性DNAヘリカーゼ	50	1/306	SP1697 - 71%/37%	72, 222
Spy1798	推定タンパク質	50	2/128	なし/なし	73, 223
Spy1801	免疫原性分泌タンパク質前駆体ホモログ	50	6/313; 6 aa の挿入	SP2216 - 33% 392aa のうちの119/なし	74, 224
Spy1813	推定タンパク質	46	47/433; 9 aa の挿入, 1 aa の欠失	なし/なし	75, 225
Spy1821	推定翻訳伸長因子EF-P	n.d.	n.d.	SP0435 - 94%/45%	76, 226
Spy1916	推定ホスホペプター-D-ガラクトシダーゼ	n.d.	n.d.	SP1184 - 91%/83%	77, 227
Spy1972	ブルナーゼ	50	1/233	SP0268 - 53%, SP1118 - 29%/25% 657aa のうちの352	78, 228
Spy1979	ストレプトキナーゼA前駆体	50	20.1% 309#と同一	なし/なし	79, 229
Spy1983	コラーゲン様表面タンパク質 (ScID)	50, (50のうちの50, しかしLukomski, 2000によりサイズの変動	n.d.	なし/なし	80, 230
Spy1991	アントラニン酸シンターゼ成分II	50	1/170	SP1816 - 58%/47%	81, 231
Spy2000	表面リボタンパク質	50	0/307	なし/27% 524aa のうちの389	82, 232
Spy2006	推定タンパク質	50	0/234	SP1003 - 36%, SP1174 - 37%, SP1004 - 33%, SP1175 - 48%/なし	83, 233
Spy2009	推定タンパク質	39 (38/49) ¹	58/344; 36 aa の挿入, 4 aa の欠失	なし/なし	84, 234
Spy2010	C5Aペプチダーゼ前駆体	n.d.	n.d.	SP0641 - 23% 2140aa のうちの783/なし	85, 235
Spy2016	補体のインヒビター (Sic)	47; 主としてM1株 (Reid 2001)	11/269#	なし/なし	86, 236
Spy2018	M1-タンパク質	n.d.	n.d.	なし/なし	87, 237
Spy2025	免疫原性分泌タンパク質前駆体	50	3/296	SP2216 - 31% 392aa のうちの138/なし	88, 238
Spy2039	発熱性外毒素B	n.d.	n.d.	なし/なし	89, 239
Spy2043	マイトジェン因子MF1(speF)	50	0/247	なし/なし	90, 240
Spy2059	ペニシリン結合タンパク質2a	50	0/293	SP2010 - 55% (pbp2A)/30% 844aa のうちの539	91, 241
Spy2110	推定通気性リボヌクレオシド-三リン酸レダクターゼ	50	0/311	SP0202 - 80% (nrdD)/50%	92, 242
Spy2127	推定タンパク質	1	n.d.	なし/なし	93, 243
Spy2191	推定タンパク質	50	1/175	なし/なし	94, 244
Spy2211	膜貫通タンパク質	50	2/281	SP2231 - 43%/なし	95, 245
ARF0450	推定タンパク質	50	5/191	なし/なし	96, 246

【表 20】

ARF0569	推定タンパク質	n.d.	n.d.	なし/なし	97, 247
ARF0694	推定タンパク質	23	1/122#	なし/なし	98, 248
ARF0700	推定タンパク質	n.d.	n.d.	なし/なし	99, 249
ARF1007	推定タンパク質	n.d.	n.d.	なし/なし	100, 250
ARF1145	推定タンパク質	n.d.	n.d.	なし/なし	101, 251
ARF1208	推定タンパク質	n.d.	n.d.	なし/なし	102, 252
ARF1262	推定タンパク質	n.d.	n.d.	なし/なし	103, 253
ARF1294	推定タンパク質	50	1/186	SA0131と39%(67 aa タンパク質の最初の28 aa)	104, 254
ARF1316	推定タンパク質	n.d.	n.d.	なし/なし	105, 255
ARF1352	推定タンパク質	n.d.	n.d.	SA1142と38%(358 タンパク質のaa 265-295)	106, 256
ARF1481	推定タンパク質	n.d.	n.d.	なし/なし	107, 257
ARF1557	推定タンパク質	n.d.	n.d.	なし/なし	108, 258
ARF1629	推定タンパク質	n.d.	n.d.	SP0069と36%(211 aa タンパク質のaa 139-169)	109, 259
ARF1654	推定タンパク質	n.d.	n.d.	なし/なし	110, 260
ARF2027	推定タンパク質	n.d.	n.d.	なし/なし	111, 261
ARF2093	推定タンパク質	n.d.	n.d.	なし/なし	112, 262
ARF2207	推定タンパク質	50	n.d.	SP1006と38%(67 aa タンパク質のaa 7-37)	113, 263
CRF0038	推定タンパク質	n.d.	n.d.	なし/なし	114, 264
CRF0122	推定タンパク質	n.d.	n.d.	なし/なし	115, 265
CRF0406	推定タンパク質	n.d.	n.d.	なし/なし	116, 266
CRF0416	推定タンパク質	n.d.	n.d.	なし/なし	117, 267
CRF0507	推定タンパク質	n.d.	n.d.	なし/なし	118, 268
CRF0549	推定タンパク質	n.d.	n.d.	なし/なし	119, 269
CRF0569	推定タンパク質	n.d.	n.d.	なし/なし	120, 270
CRF0628	推定タンパク質	n.d.	n.d.	なし/なし	121, 271
CRF0727	推定タンパク質	n.d.	n.d.	SP0584と40%(70aa タンパク質のaa21-60)	122, 272
CRF0742	推定タンパク質	n.d.	n.d.	SA0422と33%(42 aa タンパク質のaa 11-37, 280 aa タンパク質として列挙)	123, 273
CRF0784	推定タンパク質	n.d.	n.d.	なし/なし	124, 274
CRF0854	推定タンパク質	n.d.	n.d.	なし/なし	125, 275
CRF0875	推定タンパク質	n.d.	n.d.	なし/なし	126, 276
CRF0907	推定タンパク質	n.d.	n.d.	リソソーム輸送調節因子 LYSTに対してホモロジー [ホモ・サビエンス]	127, 277
CRF0979	推定タンパク質	n.d.	n.d.	なし/なし	128, 278
CRF1068	推定タンパク質	50	0/148	なし/なし	129, 279
CRF1152	推定タンパク質	n.d.	n.d.	なし/なし	130, 280
CRF1203	推定タンパク質	n.d.	n.d.	なし/なし	131, 281
CRF1225	推定タンパク質	n.d.	n.d.	なし/なし	132, 282
CRF1236	推定タンパク質	n.d.	n.d.	なし/なし	133, 283

【表 2 1】

CRF1362	推定タンパク質	n.d.	n.d.	なし/なし	134, 284
CRF1524	推定タンパク質	n.d.	n.d.	なし/なし	135, 285
CRF1525	推定タンパク質	n.d.	n.d.	なし/なし	136, 286
CRF1527	推定タンパク質	n.d.	n.d.	なし/なし	137, 287
CRF1588	推定タンパク質	n.d.	n.d.	なし/なし	138, 288
CRF1649	推定タンパク質	n.d.	n.d.	なし/なし	139, 289
CRF1749	推定タンパク質	n.d.	n.d.	なし/なし	140, 290
CRF1903	推定タンパク質	50	0/140	なし/なし	141, 291
CRF1964	推定タンパク質	n.d.	n.d.	なし/なし	142, 292
CRF2055	推定タンパク質	n.d.	n.d.	なし/なし	143, 293
CRF2091	推定タンパク質	n.d.	n.d.	なし/なし	144, 294
CRF2096	推定タンパク質	n.d.	n.d.	なし/なし	145, 295
CRF2104	推定タンパク質	n.d.	n.d.	なし/なし	146, 296
CRF2116	推定タンパク質	n.d.	n.d.	なし/なし	147, 297
CRF2153	推定タンパク質	n.d.	n.d.	なし/なし	148, 298
NRF0001	推定タンパク質	50	0/130	オリゴABC 輸送体のうちの のARF (TIGRによる注釈な し), SA0643と33% (469 aa タ ンパク質のaa 107-162)	149, 299
NRF0003	推定タンパク質	n.d.	n.d.	なし/なし	150, 300

【0307】

表 4 : NMR I マウスにおける免疫実験に用いた組換えタンパク質

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【表 2 2】

ORF	長さ(アミノ酸)	アミノ酸 ^A		溶解性	防禦 ^B	クローニングした断片の全サイズ(Kbp)
		から	まで			
Spy0031	374	39	374	不溶性	20 % (10 %, 40 %)	1.008
Spy0103	108	2	108		50% (10%, 80%)	0.321
Spy 0269	873	36	873	可溶性	40% (40%, 70%) ^C	2.511
<i>Spy 0292</i>	<i>410</i>	22	410	<i>不溶性</i>	70% (10%, 80%)	1.164
<i>Spy0416A</i>	<i>1647</i>	33	867	<i>可溶性</i>	50 % (10 %, 40 %)	2.502
Spy0416B	1647	736	1617	可溶化	0 % (0%, 40 %)	2.646
<i>Spy0720</i>	<i>313</i>	2	313	<i>不溶性</i>	60% (10%, 80%)	0.939
<i>Spy0872</i>	<i>670</i>	27	640	可溶化	60% (10%, 80%)	1.839
Spy1245	288	49	288	可溶性	20 % (10 %, 40 %)	0.717
Spy1357	217	33	186	可溶性	40 % (30%, 90 %)	0.459
Spy1361	792	22	792	可溶性	60 % (30%, 90 %)	2.31
<i>Spy1390</i>	<i>351</i>	21	351		60% (10%, 80%)	0.99
Spy1536	345	31	345		20 % (0%, 40 %)	0.942
Spy1607	258	2	258		40 % (10 %, 40 %)	0.771
Spy1666	337	22	337	可溶性	50 % (30%, 90 %)	0.945
Spy1972	1165	45	500		40 % (30%, 90 %)	1.365
Spy2000	542	24	542	可溶性	20 % (30%, 90 %)	1.554
Spy2025	541	27	541		40 % (40%, 70%)	1.542
Spy2191	204	36	204		50% (10%, 80%)	0.504

【0308】

表 5：ストレプトコッカス・ピオゲネスの株における抗原の変動性

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【表 2 3】

抗原の名称	配列 番号	抗原中の残 基 ^A	残基番号	アミノ酸の 変動 ^B
Spy0031	154	G	126	D
		A	192	S
		V	233	I
		D	328	N
		I	338	T
Spy0103	155	なし		
Spy0269	164	H	97	N
		A	150	V
		A	168	V
		H	482	R
		N	485	K
		Q	577	E
		A	610	V
		L	636	M
		E	640	K
		P	752	S
		I	764	V
		D	765	E
		K	873	R
Spy0292	166	A	214	D
		Y	309	S
		T	317	N
		V	318	C
		K	319	Q
Spy0416	169	V	1	M
		F	25	M
		L	26	M
		V	27	M
		S	38	T
		M	40	T
		A	49	T
		S	68	P
		L	76	P
		S	85	P
		D	87	G
		S	104	P
		S	110	P
		D	151 ^C	A, S, T, G
		S	164	P
		E	215	G
		H	279 ^C	A, S, T, G
		T	395	I
		D	452	N
		N	478	K
		G	484	D
		A	547	V

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【表 2 4】

		S	617 ^c	A, S, T, G
		D	723	A
		H	749	R
		R	770	K
		P	787	S
		D	804	A
		T	874	M
		N	913	S
		H	991	Y
		N	1080	S
		V	1238	A
		D	1313	G
		V	1349	M
		A	1393	V
		N	1479	K
		I	1487	M
		D	1516	G
		N	1555	D
		T	1560	A
		S	1599	F
		S	1605	T
		T	1617	A
Spy0720	184	A	61	T
		I	63	M
		K	99	Q
		K	109	Q
		N	295	S
Spy0872	192	K	178	N
		P	181	S
		V	253	I
		A	393	V
		T	600	I
		V	605	I
Spy1063	199	N	168	S
		A	169	S
		D	170	E
		A	173	E
		M	175	V
		V	180	L
		N	181	S
		E	192	D
		Q	195	E
		K	228	D
		H	243	K
		P	245	K
		N	246	A
		T	248	K
		L	252	Q
		M	257	I
		R	260	S
		Q	277	R
		D	284	E

【表 2 5】

		A	287	P
		E	289	D
		T	290	E
		A	292	I
		A	299	G
		K	303	R
		V	309	L
		A	310	N
		Q	314	R
		R	316	H
		Q	317	E
		R	318	A
		K	321	R
		A	322	G
Spy1245	203	L	72	M
		A	97	P
		Q	213	K
Spy1357	205	C	9	Y
		G	48	R
		I	87	L
		S	91	A
		T	102	A
		L	105	V
		A	111	S
		N	117	T
		E	139	S, A
		Q	142	K
		S	143	A
		N	145	T
		W	151	L
		A	155	D
		T	156	N
		P	157	A
		I	158	T, A
		A	159	S
		L	160	D
		D	161	A
		V	162	L
		K	163	E
		K	164	A
		T	165	L
		K	166	A
		T	168	Q
		K	169	T
		P	170	S, D
		V	171	A
		K	173	Q
		K	174	S
		G	187	S
		A	197	T
		V	207	A
Spy1361	206	R	129	Q
		P	141	S

【表 2 6】

		L	197	P
		A	201	V
		D	230	A
		S	231	N
		D	235	N
		P	262	L
		T	272	N
		Q	274	H
		T	302	A
		T	308	I
		A	346	V
		V	354	F
		P	389	L
		M	391	K
		I	427	L
		P	431	L
		P	503	S
		D	645	N
		S	696	P
		K	738	N
Spy1390	210	T	757	A
		N	3	Q
		S	4	M
		A	9	T
		S	10	G
		S	16	T
		M	18	V
		A	19	T
		A	21	S
		T	26	S
		N	27	H
		D	28	N
		V	32	L
		I	33	V
		S	41	T
		V	54	L
		S	55	A
		N	61	S
		A	70	T
		G	73	A
		D	74	N
		K	78	D
		H	86	K
		K	87	Q
		E	90	D
		A	94	T
		S	97	K
		A	98	T
		A	99	V
		S	104	G
		F	110	Y
		R	112	K
		S	116	L

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【表 2 7】

	S	117	T
	A	127	Q
	K	130	N
	L	132	I
	T	133	S
	T	134	K
	Q	135	K
	E	136	D
	K	138	R
	K	139	Q
	E	142	D
	S	143	A
	A	149	T
	V	150	A
	M	152	I
	I	153	M
	T	154	Q
	L	155	F
	D	156	E
	N	157	K
	E	158	D
	T	160	D
	S	163	A
	V	164	A
	T	176	A
	T	184	I
	T	185	A
	P	186	A
	E	187	D
	V	190	T
	K	193	T
	A	198	E
	T	199	I
	N	200	T
	V	201	L
	T	203	A
	D	204	E
	K	207	R
	S	211	G
	N	213	K
	G	216	N
	I	217	R
	D	219	E
	V	220	I
	S	222	T
	V	223	A
	T	227	A
	S	228	T
	Y	229	S
	Q	230	K
	K	231	R
	K	232	T
	F	233	Y

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【表 28】

		Y	234	H
		V	236	I
		E	243	T
		S	246	A
		Q	249	K
		E	250	A
		E	252	A
		A	257	D
		I	260	V
		A	261	T
		E	262	G
		S	264	L
		M	267	P
		N	268	D
		N	276	K
		Y	297	F
		N	299	K
		L	300	P
		G	301	N
		T	304	Q
		K	305	P
		A	307	Q
		S	308	K
Spy1536	215	なし		
Spy1607	218	E	21	D
		A	91	P
		H	194	R
		D	204	G, N
Spy1666	220	K	90	Q
		K	302	T
		S. pneumoniae TIGR4		
		V	37	I
		I	42	V
		S	56	A
		A	60	E
		G	67	S
		E	69	K
		C	74	A
		K	80	N
		V	87	K
		T	88	R
		K	90	A, Q
		S	91	P
		D	94	E
		Q	97	M
		K	109	Q
		R	111	C
		T	113	R
		A	114	E
		L	115	A
		D	118	Q
		L	124	C
		E	136	Q

【表 2 9】

		Q	145	K
		D	154	N
		R	155	Q
		Q	156	D
		S	157	A
		L	158	S
		T	167	N
		P	169	D
		F	170	Y
		N	171	H
		K	175	R
		A	198	E
		I	199	V
		L	211	I
		A	214	L
		A	215	V
		D	252	Q
		E	255	D
		L	256	M
		D	287	E
		L	294	F
		E	297	D
		M	299	L
		F	303	M
		H	315	A
		S	316	E
		T	319	E
		K	322	N
		A	324	S
		A	332	V
		K	333	R
		R	336	H
Spy1972	228	V	32	M
		L	70	F
		M	98	I
		K	182	R
		F	224	S
		D	226	E
		H	245	P
		P	300	L
		R	363	K
		K	365	T
		T	369	A
		A	376	T
		R	443	K
		V	445	L
		A	460	T
		V	467	I
		D	510	V
		A	496	T
		T	611	K
		T	718	A
		G	831	S

【表 3 0】

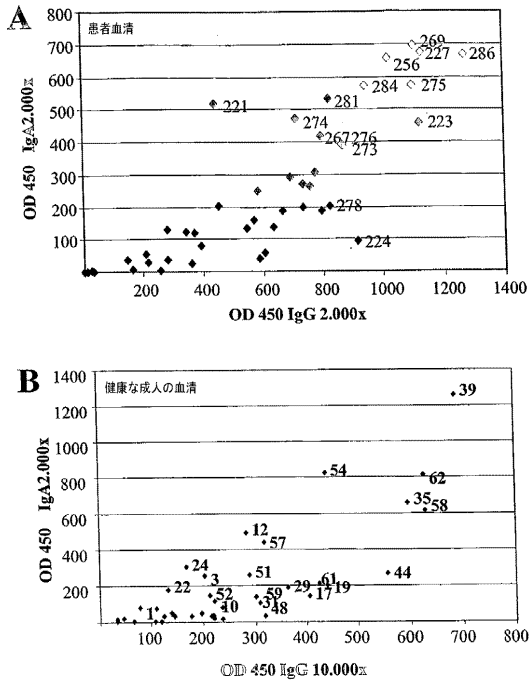
		A	913	V
		Q	930	K
		V	1053	A
		E	1079	D
		N	1094	D
		T	1102	I
		D	1103	G
		I	1149	V
Spy2000	232	K	27	N
		S	101	L
		V	151	I
		D	250	S
		P	335	S
		A	338	P
		V	519	I
Spy2025	238	S	33	N
		D	46	A
		D	49	A
		P	54	A
		T	78	N
		D	107	N
		K	109	N
		D	112	N
		P	119	S
		Q	147	P
		T	160	I
		D	170	E
		I	183	N
		I	194	A
		G	297	E
		S	528	R
Spy2191	244	A	70	V
		V	93	A

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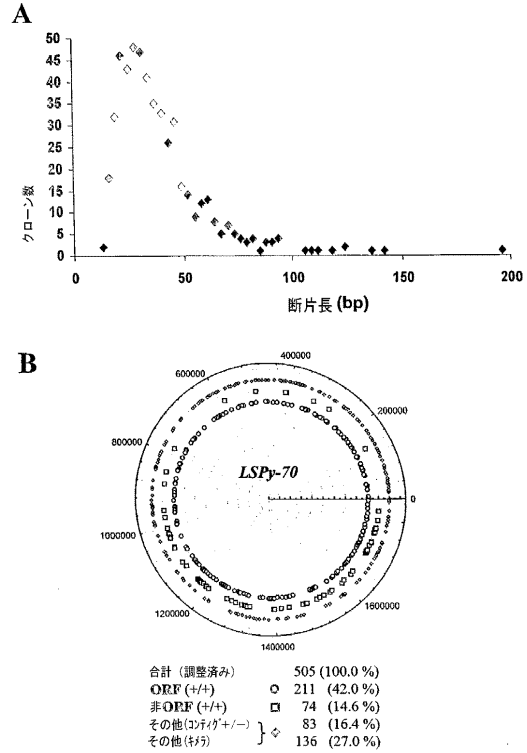
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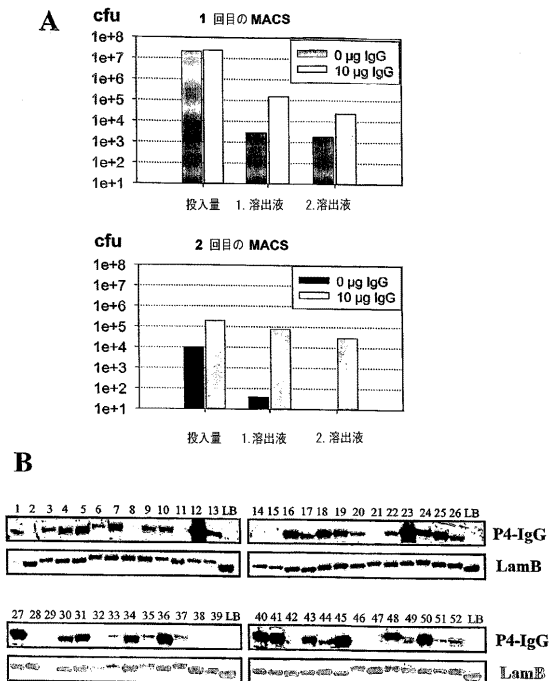
【図 1】



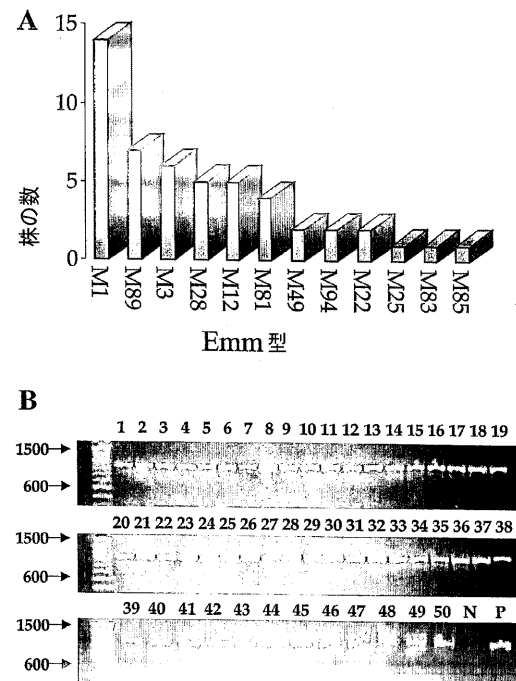
【図 2】



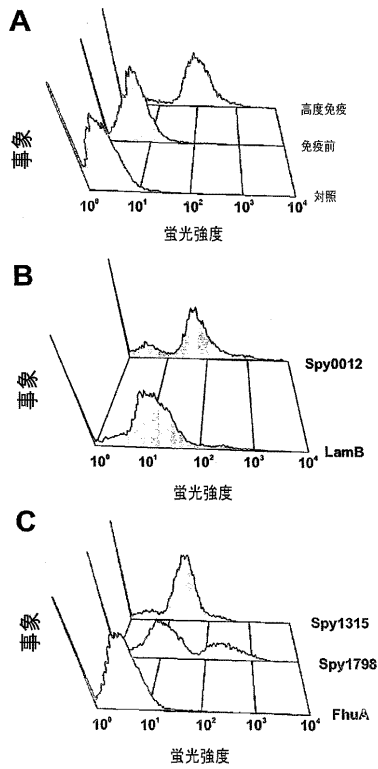
【図 3】



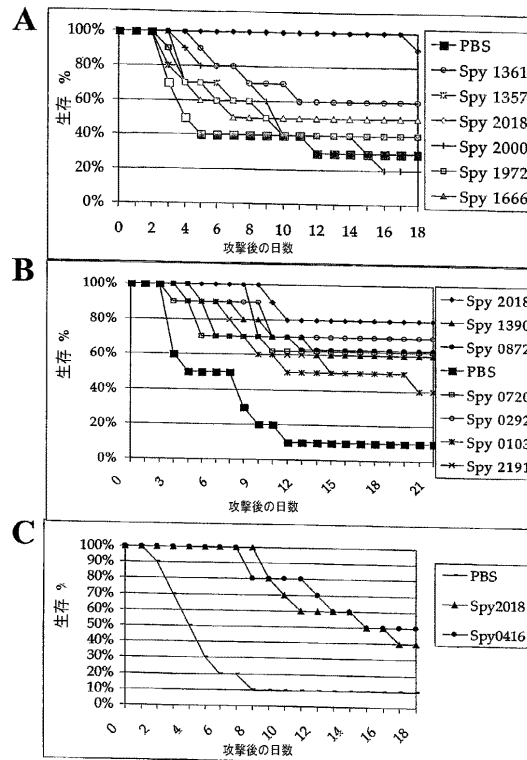
【図 4】



【図 5】



【図 6】



【配列表】

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 QR62 QS25 QS34 QX02
 4B064 CA10 CA20 CE12 DA01 DA15
 4B065 AA01X AA49X AA49Y AA57X AA87X AA90X AA90Y AB01 AB04 AC14
 BA02 CA24 CA25 CA44 CA45 CA46
 4C084 AA13 NA14 ZB351
 4C085 AA03 AA14 AA16 BA14 BB41 CC07 DD62 EE01 EE06 FF01
 FF03 FF11 FF13 FF20
 4H045 AA11 AA20 AA30 BA10 BA40 CA11 DA76 DA86 EA29 EA31
 EA52 FA20 FA72 FA74 GA26

【外国語明細書】

【0001】

- 1 -

Streptococcus pyogenes Antigens

The present invention relates to isolated nucleic acid molecules, which encode antigens for *Streptococcus pyogenes*, which are suitable for use in preparation of pharmaceutical medicaments for the prevention and treatment of bacterial infections caused by *Streptococcus pyogenes*.

Streptococcus pyogenes, also called group A streptococci (GAS), is an important gram-positive extracellular bacterial pathogen and commonly infects humans. GAS colonize the throat or skin and are responsible for a number of suppurative infections and non-suppurative sequelae. It is primarily a disease of children and causes a variety of infections including bacterial pharyngitis, scarlet fever, impetigo and sepsis in humans. Decades of epidemiological studies have led to the concept of distinct throat and skin strains, where certain serotypes are often associated with throat or skin infections, respectively [Cunningham, M., 2000]. GAS have been discovered responsible for streptococcal toxic shock syndrome associated necrotizing fasciitis which is recently resurgent in the USA [Cone, L. et al., 1987; Stevens, D., 1992] and has been described as the "flesh eating" bacterium which invades skin and soft tissues leading to tissue or limb destruction.

Several post-streptococcal sequelae may occur in humans subsequent to infection, such as acute rheumatic fever, acute glomerulonephritis and reactive arthritis. Acute rheumatic fever and rheumatic heart disease are of these the most serious autoimmune sequelae and have led to disability and death of children worldwide. *S. pyogenes* can also causes severe acute diseases such as scarlet fever and necrotizing fasciitis and has been associated with Tourette's syndrome, tics and movement and attention disorders.

Group A streptococci are the most common bacterial cause of sore throat and pharyngitis and account for at least 16% of all office calls in a general medical practice, season dependent [Hope-Simpson, R., 1981]. It primarily affects children in school-age between 5 to 15 years of age [Cunningham, M., 2000]. All ages are susceptible to spread of the organism under crowded conditions, for example in schools. GAS are not considered normal flora though, but pharyngeal carriage of group A streptococci can occur without clinical symptoms.

Group A streptococci can be distinguished by the Lancefield classification scheme of serologic typing based on their carbohydrate or classified into M protein serotypes based on a surface protein that can be extracted by boiling bacteria with hydrochloric acid. This has led to the identification of more than 80 serotypes, which can also be typed by a molecular approach (emm genes). Certain M protein serotypes of *S. pyogenes* are mainly associated with pharyngitis and rheumatic fever, while others mainly seem to cause pyoderma and acute glomerulonephritis [Cunningham, M., 2000].

Also implicated in causing pharyngitis and occasionally toxic shock are group C and G streptococci, which must be distinguished after throat culture [Hope-Simpson, R., 1981; Bisno, A. et al., 1987].

Currently, streptococcal infections can only be treated by antibiotic therapy. However, 25-30% of those treated with antibiotics show recurrent disease and/or shed the organism in mucosal secretions. There is at present no preventive treatment (vaccine) available to avoid streptococcal infections.

Thus, there remains a need for an effective treatment to prevent or ameliorate streptococcal infections. A vaccine could not only prevent infections by streptococci, but more specifically prevent or ameliorate colonization of host tissues, thereby reducing the incidence of pharyngitis and other suppurative infections. Elimination of non-suppurative sequelae such as rheumatic fever, acute glomerulonephritis, sepsis, toxic shock and necrotizing fasciitis would be a direct consequence of reducing the incidence of acute infection and carriage of the organism. Vaccines capable of showing cross-protection against other streptococci would also be useful to prevent or ameliorate infections caused by all other beta-hemolytic streptococcal species, namely groups A, B, C and G.

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- 2 -

A vaccine can contain a whole variety of different antigens. Examples of antigens are whole-killed or attenuated organisms, subfractions of these organisms/tissues, proteins, or, in their most simple form, peptides. Antigens can also be recognized by the immune system in form of glycosylated proteins or peptides and may also be or contain polysaccharides or lipids. Short peptides can be used since for example cytotoxic T-cells (CTL) recognize antigens in form of short usually 8-11 amino acids long peptides in conjunction with major histocompatibility complex (MHC). B-cells can recognize linear epitopes as short as 4-5 amino acids, as well as three-dimensional structures (conformational epitopes). In order to obtain sustained, antigen-specific immune responses, adjuvants need to trigger immune cascades that involve all cells of the immune system necessary. Primarily, adjuvants are acting, but are not restricted in their mode of action, on so-called antigen presenting cells (APCs). These cells usually first encounter the antigen(s) followed by presentation of processed or unmodified antigen to immune effector cells. Intermediate cell types may also be involved. Only effector cells with the appropriate specificity are activated in a productive immune response. The adjuvant may also locally retain antigens and co-injected other factors. In addition the adjuvant may act as a chemoattractant for other immune cells or may act locally and/or systemically as a stimulating agent for the immune system.

Approaches to develop a group A streptococcal vaccine have focused mainly on the cell surface M protein of *S. pyogenes* [Bessen, D. et al., 1988; Bronze, M. et al., 1988]. Since more than 80 different M serotypes of *S. pyogenes* exist and new serotypes continually arise [Fischetti, V., 1989], inoculation with a limited number of serotype-specific M protein or M protein derived peptides will not likely be effective in protecting against all other M serotypes. Furthermore, it has been shown that the M protein contains an amino acid sequence, which is immunologically cross-reactive with human heart tissue, which is thought to account for heart valve damage associated with rheumatic fever [Fenderson, P. et al., 1989].

There are other proteins under consideration for vaccine development, such as the erythrogenic toxins, streptococcal pyrogenic exotoxin A and streptococcal pyrogenic exotoxin B [Lee, P. K., 1989]. Immunity to these toxins could possibly prevent the deadly symptoms of streptococcal toxic shock, but it may not prevent colonization by group A streptococci.

The use of the above described proteins as antigens for a potential vaccine as well as a number of additional candidates [Ji, Y. et al., 1997; Guzman, C. et al., 1999] resulted mainly from a selection based on easiness of identification or chance of availability. There is a demand to identify efficient and relevant antigens for *S. pyogenes*.

The present inventors have developed a method for identification, isolation and production of hyperimmune serum reactive antigens from a specific pathogen, especially from *Staphylococcus aureus* and *Staphylococcus epidermidis* (WO 02/059148). However, given the differences in biological property, pathogenic function and genetic background, *Streptococcus pyogenes* is distinctive from *Staphylococcus* strains. Importantly, the selection of sera for the identification of antigens from *S. pyogenes* is different from that applied to the *S. aureus* screens. Three major types of human sera were collected for that purpose. First, healthy adults below <45 years of age preferably with small children in the household were tested for nasopharyngeal carriage of *S. pyogenes*. A large percentage of young children are carriers of *S. pyogenes*, and they are considered a source for exposure for their family members. Based on correlative data, protective (colonization neutralizing) antibodies are likely to be present in exposed individuals (children with high carriage rate in the household) who are not carriers of *S. pyogenes*. To be able to select for relevant serum sources, a series of ELISAs measuring anti-*S. pyogenes* IgG and IgA antibody levels were performed with bacterial lysates and culture supernatant proteins. Sera from high titer non-carriers were included in the genomic based antigen identification. This approach for selection of human sera is basically very different from that used for *S. aureus*, where carriage or noncarriage state cannot be associated with antibody levels.

- 3 -

Second, serum samples from patients with pharyngitis were characterized and selected in the same way. The third group of serum samples obtained from individuals with post-streptococcal sequelae - such as acute rheumatic fever and glomerulonephritis - were used mainly for validation purposes. This latter group helps in the exclusion of epitopes, which induce high levels of antibodies in these patients, since post-streptococcal disease is associated with antibodies induced by GAS and reactive against human tissues, such as heart muscle, or involved in harmful immune complex formation in the kidney glomeruli. The genomes of the two bacterial species *S. pyogenes* and *S. aureus* by itself show a number of important differences. The genome of *S. pyogenes* contains app. 1.85 Mb, while *S. aureus* harbours 2.85 Mb. They have an average GC content of 38.5 and 33%, respectively and approximately 30 to 45% of the encoded genes are not shared between the two pathogens. In addition, the two bacterial species require different growth conditions and media for propagation. While *S. pyogenes* is a strictly human pathogen, *S. aureus* can also be found infecting a range of warm-blooded animals. A list of the most important diseases, which can be inflicted by the two pathogens is presented below. *S. aureus* causes mainly nosocomial, opportunistic infections: impetigo, folliculitis, abscesses, boils, infected lacerations, endocarditis, meningitis, septic arthritis, pneumonia, osteomyelitis, scalded skin syndrome (SSS), toxic shock syndrome. *S. pyogenes* causes mainly community acquired infections: streptococcal sore throat (fever, exudative tonsillitis, pharyngitis), streptococcal skin infections, scarlet fever, puerperal fever, septicemia, erysipelas, perianal cellulitis, mastoiditis, otitis media, pneumonia, peritonitis, wound infections, acute glomerulonephritis, acute rheumatic fever; toxic shock-like syndrome, necrotizing fasciitis.

The problem underlying the present invention was to provide means for the development of medicaments such as vaccines against *S. pyogenes* infection. More particularly, the problem was to provide an efficient, relevant and comprehensive set of nucleic acid molecules or hyperimmune serum reactive antigens from *S. pyogenes* that can be used for the manufacture of said medicaments.

Therefore, the present invention provides an isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence which is selected from the group consisting of:

- a) a nucleic acid molecule having at least 70% sequence identity to a nucleic acid molecule selected from Seq ID No 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.
- b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
- c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
- d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b), or c)
- e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid molecule defined in a), b), c) or d).

According to a preferred embodiment of the present invention the sequence identity is at least 80%, preferably at least 95%, especially 100%.

Furthermore, the present invention provides an isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence selected from the group consisting of

- a) a nucleic acid molecule having at least 96% sequence identity to a nucleic acid molecule selected from Seq ID No 64,
- b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
- c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
- d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b) or c),

【 0 0 0 4 】

- 4 -

- e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

According to another aspect, the present invention provides an isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of

- a) a nucleic acid molecule selected from Seq ID No 3, 36, 47-48, 55, 62, 72, 80, 84, 95.
- b) a nucleic acid molecule which is complementary to the nucleic acid of a),
- c) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).

Preferably, the nucleic acid molecule is DNA or RNA.

According to a preferred embodiment of the present invention, the nucleic acid molecule is isolated from a genomic DNA, especially from a *S. pyogenes* genomic DNA.

According to the present invention a vector comprising a nucleic acid molecule according to any of the present invention is provided.

In a preferred embodiment the vector is adapted for recombinant expression of the hyperimmune serum reactive antigens or fragments thereof encoded by the nucleic acid molecule according to the present invention.

The present invention also provides a host cell comprising the vector according to the present invention.

According to another aspect the present invention further provides a hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to the present invention.

In a preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of Seq ID No 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300.

In another preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of Seq ID No 214

In a further preferred embodiment the amino acid sequence (polypeptide) is selected from the group consisting of Seq ID No 153, 186, 197-198, 205, 212, 222, 230, 234, 245.

According to a further aspect the present invention provides fragments of hyperimmune serum-reactive antigens selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa" and "location of identified immunogenic region" of Table 1; the serum reactive epitopes of Table 2, especially peptides comprising amino acids 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of Seq ID No 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of Seq ID No 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of Seq ID No 153; 5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360 and 145-305 of Seq ID No 154; 15-39,

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52-61, 72-81, 92-97 and 71-81 of Seq ID No 155; 13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245 and 173-186 of Seq ID No 156; 5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352 and 316-331 of Seq ID No 157; 6-28, 43-53, 60-76, 93-103 and 21-99 of Seq ID No 158; 10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568 and 9-264 of Seq ID No 159; 5-29, 39-45, 107-128 and 1-112 of Seq ID No 160; 4-38, 42-50, 54-60, 65-71, 91-102 and 21-56 of Seq ID No 161; 4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391 and 23-39 of Seq ID No 162; 6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591 and 474-489 of Seq ID No 163; 8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864 and 37-241, 409-534, 582-604, 743-804 of Seq ID No 164; 4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416 and 202-337 of Seq ID No 165; 4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407 and 1-48 of Seq ID No 166; 18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297 and 203-217 of Seq ID No 167; 20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521 and 261-273 of Seq ID No 168; 6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641 and 1-414, 443-614, 997-1392 of Seq ID No 169; 14-42, 70-75, 90-100, 158-181 and 1-164 of Seq ID No 170; 4-21, 30-36, 54-82, 89-97, 105-118, 138-147 and 126-207 of Seq ID No 171; 4-21, 31-66, 96-104, 106-113, 131-142 and 180-204 of Seq ID No 172; 5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386 and 11-197, 204-219, 258-372 of Seq ID No 173; 4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322 and 195-289 of Seq ID No 174; 4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329 and 12-130 of Seq ID No 175; 10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707 and 434-444 of Seq ID No 176; 6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430 and 360-375 of Seq ID No 177; 4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203-237, 245-251 and 254-260 of Seq ID No 178; 12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400 and 369-382 of Seq ID No 179; 11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487 and 270-312 of Seq ID No 180; 5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604 and 486-598 of Seq ID No 181; 4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374 and 378-396 of Seq ID No 182; 5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184 and 75-235 of Seq ID No 183; 6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310 and 30-51 of Seq ID No 184; 17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340,

- 6 -

353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647 and 208-219 of Seq ID No 185; 4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039 and 396-533, 1342-1502, 1672-1920 of Seq ID No 186; 4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905 and 1-113, 210-232, 250-423, 536-564 of Seq ID No 187; 4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201 and 617-635 of Seq ID No 188; 7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244 and 190-203 of Seq ID No 189; 4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574 and 385-398 of Seq ID No 190; 5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003 and 12-190, 276-283, 666-806 of Seq ID No 191; 4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664 and 30-80, 89-105, 111-151 of Seq ID No 192; 7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259 and 195-203 of Seq ID No 193; 5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426 and 32-50 of Seq ID No 194; 8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174 and 75-90 of Seq ID No 195; 4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233 and 69-88 of Seq ID No 196; 4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802 and 96-230, 361-491, 572-585 of Seq ID No 197; 4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289 and 102-210 of Seq ID No 198; 13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313 and 240-248 of Seq ID No 199; 5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260 and 182-198 of Seq ID No 200; 10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504 and 41-56 of Seq ID No 201; 5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333 and 202-217 of Seq ID No 202; 6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283 and 1-127 of Seq ID No 203; 4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718 and 297-458 of Seq ID No 204; 5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213 and 24-135 of Seq ID No 205; 4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721 and 176-330 of Seq ID No 206; 31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472 and 46-62, 296-341 of Seq ID No 207; 23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-

265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716 and 667-684 of Seq ID No 208; 20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869 and 258-416 of Seq ID No 209; 7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300 and 278-295 of Seq ID No 210; 4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191 and 183-195 of Seq ID No 211; 12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241 and 63-238 of Seq ID No 212; 4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308 and 1-141 of Seq ID No 213; 11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379 and 231-368 of Seq ID No 214; 9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342 and 247-260 of Seq ID No 215; 7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279 and 64-72 of Seq ID No 216; 4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897 and 222-362, 756-896 of Seq ID No 217; 11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255 and 153-170 of Seq ID No 218; 4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212 and 56-73 of Seq ID No 219; 4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334 and 298-312 of Seq ID No 220; 7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254 and 141-157 of Seq ID No 221; 23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663 and 433-440, 572-593 of Seq ID No 222; 4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267 and 17-319, 417-563 of Seq ID No 223; 6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500 and 46-187 of Seq ID No 224; 4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992 and 21-244, 381-499, 818-959 of Seq ID No 225; 19-29, 65-75, 90-109, 111-137, 155-165, 169-175 and 118-136 of Seq ID No 226; 15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465 and 147-155 of Seq ID No 227; 11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161 and 74-438 of Seq ID No 228; 4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413 and 156-420 of Seq ID No 229; 4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343 and 79-348 of Seq ID No 230; 12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168 and 53-70 of Seq ID No 231; 4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522 and 183-341 of Seq ID No 232; 4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822 and 92-231, 618-757 of Seq ID No 233; 11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372 and 41-170 of Seq ID No 234; 6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-

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- 8 -

238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174 and 20-487, 757-1153 of Seq ID No 235; 10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305 and 26-74, 91-100, 105-303 of Seq ID No 236; 9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480 and 10-223, 231-251, 264-297, 312-336 of Seq ID No 237; 5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537 and 22-344 of Seq ID No 238; 5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395 and 1-151 of Seq ID No 239; 6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756 and 91-263 of Seq ID No 240; 4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775 and 261-272 of Seq ID No 241; 4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701 and 541-551 of Seq ID No 242; 6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252 and 84-254 of Seq ID No 243; 13-30, 71-120, 125-137, 139-145, 184-199 and 61-78 of Seq ID No 244; 9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855 and 568-580 of Seq ID No 245; 11-21, 29-38 and 5-17 of Seq ID No 246; 2-9 of Seq ID No 247; 4-10, 16-28 and 7-18, 26-34 of Seq ID No 248; 10-16 and 1-15 of Seq ID No 249; 4-11 of Seq ID No 250; 4-40, 42-51 and 37-53 of Seq ID No 251; 4-21 and 22-29 of Seq ID No 252; 2-11 Seq ID No 253; 9-17, 32-44 and 1-22 of Seq ID No 254; 19-25, 27-32 and 15-34 of Seq ID No 255; 4-12, 15-22 and 11-33 of Seq ID No 256; 10-17, 24-30, 39-46, 51-70 and 51-61 of Seq ID No 257; 6-19 of Seq ID No 258; 6-11, 21-27, 31-54 and 11-29 of Seq ID No 259; 4-10, 13-45 and 11-35 of Seq ID No 260; 4-14, 23-32 and 11-35 of Seq ID No 261; 14-39, 45-51 and 15-29 of Seq ID No 262; 4-11, 14-28 and 4-17 of Seq ID No 263; 4-16 and 2-16 of Seq ID No 264; 4-10, 12-19, 39-50 and 6-22 of Seq ID No 265; 2-13 of Seq ID No 266; 4-11, 22-65 and 3-19 of Seq ID No 267; 17-23, 30-35, 39-46, 57-62 and 30-49 of Seq ID No 268; 4-19 and 14-22 of Seq ID No 269; 2-9 of Seq ID No 270; 7-18, 30-43 and 4-12 of Seq ID No 271; 4-30, 39-47 and 5-22 of Seq ID No 272; 6-15 and 14-29 of Seq ID No 273; 4-34 and 23-35 of Seq ID No 274; 4-36, 44-57, 65-72 and 14-27 of Seq ID No 275; 4-18 and 11-20 of Seq ID No 276; 5-19 of Seq ID No 277; 18-36 and 6-20 of Seq ID No 278; 4-10, 19-34, 41-84, 96-104 and 50-63 of Seq ID No 279; 4-9, 19-27 and 8-21 of Seq ID No 280; 4-16, 18-28 and 22-30 of Seq ID No 281; 4-15 and 21-35 of Seq ID No 282; 4-17 and 3-13 of Seq ID No 283; 4-12 and 4-18 of Seq ID No 284; 4-24, 31-36 and 29-45 of Seq ID No 285; 12-22, 34-49 and 21-32 of Seq ID No 286; 4-17 and 22-32 of Seq ID No 287; 4-16, 25-42 and 7-28 of Seq ID No 288; 4-10 and 7-20 of Seq ID No 289; 4-11, 16-36, 39-54 and 28-44 of Seq ID No 290; 5-20, 29-54 and 14-29 of Seq ID No 291; 24-33 and 10-22 of Seq ID No 292; 10-51, 54-61 and 43-64 of Seq ID No 293; 7-13 and 2-17 of Seq ID No 294; 11-20 and 6-20 of Seq ID No 295; 4-30, 34-41 and 19-28 of Seq ID No 296; 11-21 of Seq ID No 297; 4-16, 21-26 and 9-38 of Seq ID No 298; 4-12, 15-27, 30-42, 66-72 and 10-24 of Seq ID No 299; 8-17 and 11-20 of Seq ID No 300; and 2-19 of Seq ID No 246; 1-12 of Seq ID No 247; 21-38 of Seq ID No 248; 2-22 of Seq ID No 254; 15-33 of Seq ID No 255; 11-32 of Seq ID No 256; 11-28 of Seq ID No 259; 10-27 of Seq ID No 260; 9-26 of Seq ID No 261; 4-16 of Seq ID No 263; 1-18 of Seq ID No 266; 12-29 of Seq ID No 273; 6-23 of Seq ID No 276; 1-21 of Seq ID No 277; 47-64 of Seq ID No 279; 28-45 of Seq ID No 285; 18-35 of Seq ID No 287; 14-31 of Seq ID No 291; 7-24 of Seq

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ID No 292; 8-25 of Seq ID No 299; 1-20 of Seq ID No 300; 18-33 of Seq ID No 151; 62-72 of Seq ID No 151; 118-131 of Seq ID No 152; 195-220 of Seq ID No 154; 215-240 of Seq ID No 154; 255-280 of Seq ID No 154; 72-81 of Seq ID No 155; 174-186 of Seq ID No 156; 317-331 of Seq ID No 157; 35-59 of Seq ID No 158; 54-84 of Seq ID No 158; 79-104 of Seq ID No 158; 33-58 of Seq ID No 159; 81-101 of Seq ID No 159; 136-150 of Seq ID No 159; 173-186 of Seq ID No 159; 231-251 of Seq ID No 159; 22-48 of Seq ID No 161; 24-39 of Seq ID No 162; 475-489 of Seq ID No 163; 38-56 of Seq ID No 164; 583-604 of Seq ID No 164; 202-223 of Seq ID No 165; 222-247 of Seq ID No 165; 242-267 of Seq ID No 165; 262-287 of Seq ID No 165; 282-307 of Seq ID No 165; 302-327 of Seq ID No 165; 25-48 of Seq ID No 166; 204-217 of Seq ID No 167; 259-276 of Seq ID No 168; 121-139 of Seq ID No 169; 260-267 of Seq ID No 169; 215-240 of Seq ID No 169; 115-140 of Seq ID No 170; 182-204 of Seq ID No 172; 144-153 of Seq ID No 173; 205-219 of Seq ID No 173; 196-206 of Seq ID No 174; 240-249 of Seq ID No 174; 272-287 of Seq ID No 174; 199-223 of Seq ID No 174; 218-237 of Seq ID No 174; 226-249 of Seq ID No 175; 287-306 of Seq ID No 175; 430-449 of Seq ID No 176; 361-375 of Seq ID No 177; 241-260 of Seq ID No 178; 483-502 of Seq ID No 181; 379-396 of Seq ID No 182; 31-51 of Seq ID No 184; 1436-1460 of Seq ID No 186; 1455-1474 of Seq ID No 186; 1469-1487 of Seq ID No 186; 215-229 of Seq ID No 187; 534-561 of Seq ID No 187; 59-84 of Seq ID No 187; 79-104 of Seq ID No 187; 618-635 of Seq ID No 188; 191-203 of Seq ID No 189; 386-398 of Seq ID No 190; 65-83 of Seq ID No 191; 90-105 of Seq ID No 192; 112-136 of Seq ID No 192; 290-209 of Seq ID No 193; 33-50 of Seq ID No 194; 76-90 of Seq ID No 195; 70-88 of Seq ID No 196; 418-442 of Seq ID No 197; 574-585 of Seq ID No 197; 87-104 of Seq ID No 198; 124-148 of Seq ID No 198; 141-152 of Seq ID No 198; 241-248 of Seq ID No 199; 183-198 of Seq ID No 200; 40-57 of Seq ID No 201; 202-217 of Seq ID No 202; 50-74 of Seq ID No 203; 69-93 of Seq ID No 203; 88-112 of Seq ID No 203; 107-127 of Seq ID No 203; 74-92 of Seq ID No 205; 207-232 of Seq ID No 206; 227-252 of Seq ID No 206; 247-272 of Seq ID No 206; 47-60 of Seq ID No 207; 297-305 of Seq ID No 207; 312-337 of Seq ID No 207; 667-384 of Seq ID No 208; 279-295 of Seq ID No 210; 179-198 of Seq ID No 211; 27-51 of Seq ID No 213; 46-70 of Seq ID No 213; 65-89 of Seq ID No 213; 84-108 of Seq ID No 213; 112-141 of Seq ID No 213; 248-260 of Seq ID No 215; 59-78 of Seq ID No 216; 154-170 of Seq ID No 218; 57-73 of Seq ID No 219; 297-314 of Seq ID No 220; 142-157 of Seq ID No 221; 428-447 of Seq ID No 222; 573-593 of Seq ID No 222; 523-544 of Seq ID No 223; 46-70 of Seq ID No 223; 65-89 of Seq ID No 223; 84-108 of Seq ID No 223; 122-151 of Seq ID No 223; 123-142 of Seq ID No 224; 903-921 of Seq ID No 225; 119-136 of Seq ID No 226; 142-161 of Seq ID No 227; 258-277 of Seq ID No 228; 272-300 of Seq ID No 228; 295-322 of Seq ID No 228; 311-343 of Seq ID No 229; 278-304 of Seq ID No 229; 131-150 of Seq ID No 230; 195-218 of Seq ID No 230; 53-70 of Seq ID No 231; 184-208 of Seq ID No 232; 222-246 of Seq ID No 232; 241-265 of Seq ID No 232; 260-284 of Seq ID No 232; 279-303 of Seq ID No 232; 317-341 of Seq ID No 232; 678-696 of Seq ID No 233; 88-114 of Seq ID No 235; 464-481 of Seq ID No 235; 153-172 of Seq ID No 236; 137-155, 166-184 of Seq ID No 236; 215-228 of Seq ID No 236; 37-51 of Seq ID No 237; 53-75 of Seq ID No 237; 232-251 of Seq ID No 237; 318-336 of Seq ID No 237; 305-315 of Seq ID No 238; 131-156 of Seq ID No 238; 258-275 of Seq ID No 241; 107-137 of Seq ID No 243; 138-162 of Seq ID No 243; 157-181 of Seq ID No 243; 195-227 of Seq ID No 243; 62-78 of Seq ID No 244; 567-584 of Seq ID No 245.

The present invention also provides a process for producing a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to the present invention comprising expressing one or more of the nucleic acid molecules according to the present invention in a suitable expression system.

Moreover, the present invention provides a process for producing a cell, which expresses a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to the present invention comprising transforming or transfecting a suitable host cell with the vector according to the present invention.

According to the present invention a pharmaceutical composition, especially a vaccine, comprising a hyperimmune serum-reactive antigen or a fragment thereof as defined in the present invention or a nucleic acid molecule as defined in the present invention is provided.

- 10 -

In a preferred embodiment the pharmaceutical composition further comprises an immunostimulatory substance, preferably selected from the group comprising polycationic polymers, especially polycationic peptides, immunostimulatory deoxynucleotides (ODNs), peptides containing at least two LysLeuLys motifs, especially KLKLSKLK, neuroactive compounds, especially human growth hormone, alum, Freund's complete or incomplete adjuvants or combinations thereof.

In a more preferred embodiment the immunostimulatory substance is a combination of either a polycationic polymer and immunostimulatory deoxynucleotides or of a peptide containing at least two LysLeuLys motifs and immunostimulatory deoxynucleotides.

In a still more preferred embodiment the polycationic polymer is a polycationic peptide, especially polyarginine.

According to the present invention the use of a nucleic acid molecule according to the present invention or a hyperimmune serum-reactive antigen or fragment thereof according to the present invention for the manufacture of a pharmaceutical preparation, especially for the manufacture of a vaccine against *S. pyogenes* infection, is provided.

Also an antibody, or at least an effective part thereof, which binds at least to a selective part of the hyperimmune serum-reactive antigen or a fragment thereof according to the present invention is provided herewith.

In a preferred embodiment the antibody is a monoclonal antibody.

In another preferred embodiment the effective part of the antibody comprises Fab fragments.

In a further preferred embodiment the antibody is a chimeric antibody.

In a still preferred embodiment the antibody is a humanized antibody.

The present invention also provides a hybridoma cell line, which produces an antibody according to the present invention.

Moreover, the present invention provides a method for producing an antibody according to the present invention, characterized by the following steps:

- initiating an immune response in a non-human animal by administering an hyperimmune serum-reactive antigen or a fragment thereof, as defined in the invention, to said animal,
- removing an antibody containing body fluid from said animal, and
- producing the antibody by subjecting said antibody containing body fluid to further purification steps.

Accordingly, the present invention also provides a method for producing an antibody according to the present invention, characterized by the following steps:

- initiating an immune response in a non-human animal by administering an hyperimmune serum-reactive antigen or a fragment thereof, as defined in the present invention, to said animal,
- removing the spleen or spleen cells from said animal,
- producing hybridoma cells of said spleen or spleen cells,
- selecting and cloning hybridoma cells specific for said hyperimmune serum-reactive antigens or a fragment thereof,
- producing the antibody by cultivation of said cloned hybridoma cells and optionally further purification steps.

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The antibodies provided or produced according to the above methods may be used for the preparation of a medicament for treating or preventing *S. pyogenes* infections.

According to another aspect the present invention provides an antagonist which binds to a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention.

Such an antagonist capable of binding to a hyperimmune serum-reactive antigen or fragment thereof according to the present invention may be identified by a method comprising the following steps:

- a) contacting an isolated or immobilized hyperimmune serum-reactive antigen or a fragment thereof according to the present invention with a candidate antagonist under conditions to permit binding of said candidate antagonist to said hyperimmune serum-reactive antigen or fragment, in the presence of a component capable of providing a detectable signal in response to the binding of the candidate antagonist to said hyperimmune serum reactive antigen or fragment thereof; and
- b) detecting the presence or absence of a signal generated in response to the binding of the antagonist to the hyperimmune serum reactive antigen or the fragment thereof.

An antagonist capable of reducing or inhibiting the interaction activity of a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention to its interaction partner may be identified by a method comprising the following steps:

- a) providing a hyperimmune serum reactive antigen or a hyperimmune fragment thereof according to the present invention,
- b) providing an interaction partner to said hyperimmune serum reactive antigen or a fragment thereof, especially an antibody according to the present invention,
- c) allowing interaction of said hyperimmune serum reactive antigen or fragment thereof to said interaction partner to form an interaction complex,
- d) providing a candidate antagonist,
- e) allowing a competition reaction to occur between the candidate antagonist and the interaction complex,
- f) determining whether the candidate antagonist inhibits or reduces the interaction activities of the hyperimmune serum reactive antigen or the fragment thereof with the interaction partner.

The hyperimmune serum reactive antigens or fragments thereof according to the present invention may be used for the isolation and/or purification and/or identification of an interaction partner of said hyperimmune serum reactive antigen or fragment thereof.

The present invention also provides a process for *in vitro* diagnosing a disease related to expression of a hyperimmune serum-reactive antigen or a fragment thereof according to the present invention comprising determining the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to the present invention or the presence of the hyperimmune serum reactive antigen or fragment thereof according to the present invention.

The present invention also provides a process for *in vitro* diagnosis of a bacterial infection, especially a *S. pyogenes* infection, comprising analyzing for the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to the present invention or the presence of the hyperimmune serum reactive antigen or fragment thereof according to the present invention.

Moreover, the present invention provides the use of a hyperimmune serum reactive antigen or fragment thereof according to the present invention for the generation of a peptide binding to said hyperimmune serum reactive antigen or fragment thereof, wherein the peptide is an anticaline.

The present invention also provides the use of a hyperimmune serum-reactive antigen or fragment

thereof according to the present invention for the manufacture of a functional nucleic acid, wherein the functional nucleic acid is selected from the group comprising aptamers and spiegelmers.

The nucleic acid molecule according to the present invention may also be used for the manufacture of a functional ribonucleic acid, wherein the functional ribonucleic acid is selected from the group comprising ribozymes, antisense nucleic acids and siRNA.

The present invention advantageously provides an efficient, relevant and comprehensive set of isolated nucleic acid molecules and their encoded hyperimmune serum reactive antigens and fragments thereof identified from *S. pyogenes* using an antibody preparation from multiple human plasma pools and surface expression libraries derived from the genome of *S. pyogenes*. Thus, the present invention fulfils a widely felt demand for *S. pyogenes* antigens, vaccines, diagnostics and products useful in procedures for preparing antibodies and for identifying compounds effective against *S. pyogenes* infection.

An effective vaccine should be composed of proteins or polypeptides, which are expressed by all strains and are able to induce high affinity, abundant antibodies against cell surface components of *S. pyogenes*. The antibodies should be IgG1 and/or IgG3 for opsonization, and any IgG subtype and IgA for neutralisation of adherence and toxin action. A chemically defined vaccine must be definitely superior compared to a whole cell vaccine (attenuated or killed), since components of *S. pyogenes*, which cross-react with human tissues or inhibit opsonization [Whitnack, E. et al., 1985] can be eliminated, and the individual proteins inducing protective antibodies and/or a protective immune response can be selected.

The approach, which has been employed for the present invention, is based on the interaction of group A streptococcal proteins or peptides with the antibodies present in human sera. The antibodies produced against *S. pyogenes* by the human immune system and present in human sera are indicative of the *in vivo* expression of the antigenic proteins and their immunogenicity. In addition, the antigenic proteins as identified by the bacterial surface display expression libraries using pools of pre-selected sera, are processed in a second and third round of screening by individual selected or generated sera. Thus the present invention supplies an efficient, relevant, comprehensive set of group A streptococcal antigens as a pharmaceutical composition, especially a vaccine preventing infection by *S. pyogenes*.

In the antigen identification program for identifying a comprehensive set of antigens according to the present invention, at least two different bacterial surface expression libraries are screened with several serum pools or plasma fractions or other pooled antibody containing body fluids (antibody pools). The antibody pools are derived from a serum collection, which has been tested against antigenic compounds of *S. pyogenes*, such as whole cell extracts and culture supernatant proteins. Preferably, 2 distinct serum collections are used: 1. With very stable antibody repertoire: normal adults, clinically healthy people, who are non-carriers and overcame previous encounters or currently carriers of *S. pyogenes* without acute disease and symptoms, 2. With antibodies induced acutely by the presence of the pathogenic organism: patients with acute disease with different manifestations (e.g. *S. pyogenes* pharyngitis, wound infection and bacteraemia). Sera have to react with multiple group A streptococci-specific antigens in order to be considered hyperimmune and therefore relevant in the screening method applied for the present invention. The antibodies produced against streptococci by the human immune system and present in human sera are indicative of the *in vivo* expression of the antigenic proteins and their immunogenicity.

The expression libraries as used in the present invention should allow expression of all potential antigens, e.g. derived from all surface proteins of *S. pyogenes*. Bacterial surface display libraries will be represented by a recombinant library of a bacterial host displaying a (total) set of expressed peptide sequences of group A streptococci on a number of selected outer membrane proteins (LamB, BtuB, FhuA) at the bacterial host membrane [Georgiou, G., 1997; Etz, H. et al., 2001]. One of the advantages of using recombinant expression libraries is that the identified hyperimmune serum-reactive antigens may be instantly produced by expression of the coding sequences of the screened and selected clones expressing

- 13 -

the hyperimmune serum-reactive antigens without further recombinant DNA technology or cloning steps necessary.

The comprehensive set of antigens identified by the described program according to the present invention is analysed further by one or more additional rounds of screening. Therefore individual antibody preparations or antibodies generated against selected peptides which were identified as immunogenic are used. According to a preferred embodiment the individual antibody preparations for the second round of screening are derived from patients who have suffered from an acute infection with group A streptococci, especially from patients who show an antibody titer above a certain minimum level, for example an antibody titer being higher than 80 percentile, preferably higher than 90 percentile, especially higher than 95 percentile of the human (patient or healthy individual) sera tested. Using such high titer individual antibody preparations in the second screening round allows a very selective identification of the hyperimmune serum-reactive antigens and fragments thereof from *S. pyogenes*.

Following the high throughput screening procedure, the selected antigenic proteins, expressed as recombinant proteins or in vitro translated products, in case it can not be expressed in prokaryotic expression systems, or the identified antigenic peptides (produced synthetically) are tested in a second screening by a series of ELISA and Western blotting assays for the assessment of their immunogenicity with a large human serum collection (> 100 uninfected, > 50 patients sera).

It is important that the individual antibody preparations (which may also be the selected serum) allow a selective identification of the hyperimmune serum-reactive antigens from all the promising candidates from the first round. Therefore, preferably at least 10 individual antibody preparations (i.e. antibody preparations (e.g. sera) from at least 10 different individuals having suffered from an infection to the chosen pathogen) should be used in identifying these antigens in the second screening round. Of course, it is possible to use also less than 10 individual preparations, however, selectivity of the step may not be optimal with a low number of individual antibody preparations. On the other hand, if a given hyperimmune serum-reactive antigen (or an antigenic fragment thereof) is recognized by at least 10 individual antibody preparations, preferably at least 30, especially at least 50 individual antibody preparations, identification of the hyperimmune serum-reactive antigen is also selective enough for a proper identification. Hyperimmune serum-reactivity may of course be tested with as many individual preparations as possible (e.g. with more than 100 or even with more than 1,000).

Therefore, the relevant portion of the hyperimmune serum-reactive antibody preparations according to the method of the present invention should preferably be at least 10, more preferred at least 30, especially at least 50 individual antibody preparations. Alternatively (or in combination) hyperimmune serum-reactive antigens may preferably be also identified with at least 20%, preferably at least 30%, especially at least 40% of all individual antibody preparations used in the second screening round.

According to a preferred embodiment of the present invention, the sera from which the individual antibody preparations for the second round of screening are prepared (or which are used as antibody preparations), are selected by their titer against *S. pyogenes* (e.g. against a preparation of this pathogen, such as a lysate, cell wall components and recombinant proteins). Preferably, some are selected with a total IgA titer above 4,000 U, especially above 6,000 U, and/or an IgG titer above 10,000 U, especially above 12,000 U (U = units, calculated from the OD_{405nm} reading at a given dilution) when the whole organism (total lysate or whole cells) is used as antigen in the ELISA.

The antibodies produced against streptococci by the human immune system and present in human sera are indicative of the in vivo expression of the antigenic proteins and their immunogenicity. The recognition of linear epitopes by antibodies can be based on sequences as short as 4-5 amino acids. Of course it does not necessarily mean that these short peptides are capable of inducing the given antibody in vivo. For that reason the defined epitopes, polypeptides and proteins are further to be tested in

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- 14 -

animals (mainly in mice) for their capacity to induce antibodies against the selected proteins in vivo.

The preferred antigens are located on the cell surface or secreted, and are therefore accessible extracellularly. Antibodies against cell wall proteins are expected to serve two purposes: to inhibit adhesion and to promote phagocytosis. Antibodies against secreted proteins are beneficial in neutralisation of their function as toxin or virulence component. It is also known that bacteria communicate with each other through secreted proteins. Neutralizing antibodies against these proteins will interrupt growth-promoting cross-talk between or within streptococcal species. Bioinformatic analyses (signal sequences, cell wall localisation signals, transmembrane domains) proved to be very useful in assessing cell surface localisation or secretion. The experimental approach includes the isolation of antibodies with the corresponding epitopes and proteins from human serum, and the generation of immune sera in mice against (poly)peptides selected by the bacterial surface display screens. These sera are then used in a third round of screening as reagents in the following assays: cell surface staining of group A streptococci grown under different conditions (FACS, microscopy), determination of neutralizing capacity (toxin, adherence), and promotion of opsonization and phagocytosis (in vitro phagocytosis assay).

For that purpose, bacterial *E. coli* clones are directly injected into mice and immune sera taken and tested in the relevant in vitro assay for functional opsonic or neutralizing antibodies. Alternatively, specific antibodies may be purified from human or mouse sera using peptides or proteins as substrate.

Host defence against *S. pyogenes* relies mainly on innate immunological mechanisms. Inducing high affinity antibodies of the opsonic and neutralizing type by vaccination helps the innate immune system to eliminate bacteria and toxins. This makes the method according to the present invention an optimal tool for the identification of group A streptococcal antigenic proteins.

The skin and mucous membranes are formidable barriers against invasion by streptococci. However, once the skin or the mucous membranes are breached the first line of non-adaptive cellular defence begins its co-ordinate action through complement and phagocytes, especially the polymorphonuclear leukocytes (PMNs). These cells can be regarded as the cornerstones in eliminating invading bacteria. As group A streptococci are primarily extracellular pathogens, the major anti-streptococcal adaptive response comes from the humoral arm of the immune system, and is mediated through three major mechanisms: promotion of opsonization, toxin neutralisation, and inhibition of adherence. It is believed that opsonization is especially important, because of its requirement for an effective phagocytosis. For efficient opsonization the microbial surface has to be coated with antibodies and complement factors for recognition by PMNs through receptors to the Fc fragment of the IgG molecule or to activated C3b. After opsonization, streptococci are phagocytosed and killed. Antibodies bound to specific antigens on the cell surface of bacteria serve as ligands for the attachment to PMNs and to promote phagocytosis. The very same antibodies bound to the adhesins and other cell surface proteins are expected to neutralize adhesion and prevent colonization. The selection of antigens as provided by the present invention is thus well suited to identify those that will lead to protection against infection in an animal model or in humans.

According to the antigen identification method used herein, the present invention can surprisingly provide a set of comprehensive novel nucleic acids and novel hyperimmune serum reactive antigens and fragments thereof of *S. pyogenes*, among other things, as described below. According to one aspect, the invention particularly relates to the nucleotide sequences encoding hyperimmune serum reactive antigens which sequences are set forth in the Sequence listing Seq ID No: 1-150 and the corresponding encoded amino acid sequences representing hyperimmune serum reactive antigens are set forth in the Sequence Listing Seq ID No 151-300.

In a preferred embodiment of the present invention, a nucleic acid molecule is provided which exhibit 70% identity over their entire length to a nucleotide sequence set forth with Seq ID No 1, 4-8, 10-18, 20,

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- 15 -

22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150. Most highly preferred are nucleic acids that comprise a region that is at least 80% or at least 85% identical over their entire length to a nucleic acid molecule set forth with Seq ID No 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150. In this regard, nucleic acid molecules at least 90%, 91%, 92%, 93%, 94%, 95%, or 96% identical over their entire length to the same are particularly preferred. Furthermore, those with at least 97% are highly preferred, those with at least 98% and at least 99% are particularly highly preferred, with at least 99% or 99.5% being the more preferred, with 100% identity being especially preferred. Moreover, preferred embodiments in this respect are nucleic acids which encode hyperimmune serum reactive antigens or fragments thereof (polypeptides) which retain substantially the same biological function or activity as the mature polypeptide encoded by said nucleic acids set forth in the Seq ID No 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.

Identity, as known in the art and used herein, is the relationship between two or more polypeptide sequences or two or more polynucleotide sequences, as determined by comparing the sequences. In the art, identity also means the degree of sequence relatedness between polypeptide or polynucleotide sequences, as the case may be, as determined by the match between strings of such sequences. Identity can be readily calculated. While there exist a number of methods to measure identity between two polynucleotide or two polypeptide sequences, the term is well known to skilled artisans (e.g. *Sequence Analysis in Molecular Biology*, von Heinje, G., Academic Press, 1987). Preferred methods to determine identity are designed to give the largest match between the sequences tested. Methods to determine identity are codified in computer programs. Preferred computer program methods to determine identity between two sequences include, but are not limited to, GCG program package [Devereux, J. et al., 1984], BLASTP, BLASTN, and FASTA [Altschul, S. et al., 1990].

According to another aspect of the invention, nucleic acid molecules are provided which exhibit at least 96% identity to the nucleic acid sequence set forth with Seq ID No 64.

According to a further aspect of the present invention, nucleic acid molecules are provided which are identical to the nucleic acid sequences set forth with Seq ID No 3, 36, 47-48, 55, 62, 72, 80, 84, 95.

The nucleic acid molecules according to the present invention can as a second alternative also be a nucleic acid molecule which is at least essentially complementary to the nucleic acid described as the first alternative above. As used herein complementary means that a nucleic acid strand is base pairing via Watson-Crick base pairing with a second nucleic acid strand. Essentially complementary as used herein means that the base pairing is not occurring for all of the bases of the respective strands but leaves a certain number or percentage of the bases unpaired or wrongly paired. The percentage of correctly pairing bases is preferably at least 70 %, more preferably 80 %, even more preferably 90 % and most preferably any percentage higher than 90 %. It is to be noted that a percentage of 70 % matching bases is considered as homology and the hybridization having this extent of matching base pairs is considered as stringent. Hybridization conditions for this kind of stringent hybridization may be taken from Current Protocols in Molecular Biology (John Wiley and Sons, Inc., 1987). More particularly, the hybridization conditions can be as follows:

- Hybridization performed e.g. in 5 x SSPE, 5 x Denhardt's reagent, 0.1% SDS, 100 g/mL sheared DNA at 68°C
- Moderate stringency wash in 0.2xSSC, 0.1% SDS at 42°C
- High stringency wash in 0.1xSSC, 0.1% SDS at 68°C

Genomic DNA with a GC content of 50% has an approximate T_m of 96°C. For 1% mismatch, the T_m is reduced by approximately 1°C.

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- 16 -

In addition, any of the further hybridization conditions described herein are in principle applicable as well.

Of course, all nucleic acid sequence molecules which encode for the same polypeptide molecule as those identified by the present invention are encompassed by any disclosure of a given coding sequence, since the degeneracy of the genetic code is directly applicable to unambiguously determine all possible nucleic acid molecules which encode a given polypeptide molecule, even if the number of such degenerated nucleic acid molecules may be high. This is also applicable for fragments of a given polypeptide, as long as the fragments encode for a polypeptide being suitable to be used in a vaccination connection, e.g. as an active or passive vaccine.

The nucleic acid molecule according to the present invention can as a third alternative also be a nucleic acid which comprises a stretch of at least 15 bases of the nucleic acid molecule according to the first and second alternative of the nucleic acid molecules according to the present invention as outlined above. Preferably, the bases form a contiguous stretch of bases. However, it is also within the scope of the present invention that the stretch consists of two or more moieties which are separated by a number of bases.

The nucleic acid molecule according to the present invention can as a fourth alternative also be a nucleic acid molecule which anneals under stringent hybridisation conditions to any of the nucleic acids of the present invention according to the above outlined first, second, and third alternative. Stringent hybridisation conditions are typically those described herein.

Finally, the nucleic acid molecule according to the present invention can as a fifth alternative also be a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to any of the nucleic acid molecules according to any nucleic acid molecule of the present invention according to the first, second, third, and fourth alternative as outlined above. This kind of nucleic acid molecule refers to the fact that preferably the nucleic acids according to the present invention code for the hyperimmune serum reactive antigens or fragments thereof according to the present invention. This kind of nucleic acid molecule is particularly useful in the detection of a nucleic acid molecule according to the present invention and thus the diagnosis of the respective microorganisms such as *S. pyogenes* and any disease or diseased condition where this kind of microorganisms is involved. Preferably, the hybridisation would occur or be preformed under stringent conditions as described in connection with the fourth alternative described above.

Nucleic acid molecule as used herein generally refers to any ribonucleic acid molecule or deoxyribonucleic acid molecule, which may be unmodified RNA or DNA or modified RNA or DNA. Thus, for instance, nucleic acid molecule as used herein refers to, among other, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded RNA, and RNA that is a mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded, or triple-stranded, or a mixture of single- and double-stranded regions. In addition, nucleic acid molecule as used herein refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The strands in such regions may be from the same molecule or from different molecules. The regions may include all of one or more of the molecules, but more typically involve only a region of some of the molecules. One of the molecules of a triple-helical region often is an oligonucleotide. As used herein, the term nucleic acid molecule includes DNAs or RNAs as described above that contain one or more modified bases. Thus, DNAs or RNAs with backbones modified for stability or for other reasons are "nucleic acid molecule" as that term is intended herein. Moreover, DNAs or RNAs comprising unusual bases, such as inosine, or modified bases, such as tritylated bases, to name just two examples, are nucleic acid molecule as the term is used herein. It will be appreciated that a great variety of modifications have been made to DNA and RNA that serve many useful purposes known to those of skill in the art. The term nucleic acid molecule as it is employed herein

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- 17 -

embraces such chemically, enzymatically or metabolically modified forms of nucleic acid molecule, as well as the chemical forms of DNA and RNA characteristic of viruses and cells, including simple and complex cells, *inter alia*. The term nucleic acid molecule also embraces short nucleic acid molecules often referred to as oligonucleotide(s). "Polynucleotide" and "nucleic acid" or "nucleic acid molecule" are often used interchangeably herein.

Nucleic acid molecules provided in the present invention also encompass numerous unique fragments, both longer and shorter than the nucleic acid molecule sequences set forth in the sequencing listing of the *S. pyogenes* coding regions, which can be generated by standard cloning methods. To be unique, a fragment must be of sufficient size to distinguish it from other known nucleic acid sequences, most readily determined by comparing any selected *S. pyogenes* fragment to the nucleotide sequences in computer databases such as GenBank.

Additionally, modifications can be made to the nucleic acid molecules and polypeptides that are encompassed by the present invention. For example, nucleotide substitutions can be made which do not affect the polypeptide encoded by the nucleic acid, and thus any nucleic acid molecule which encodes a hyperimmune serum reactive antigen or fragments thereof is encompassed by the present invention.

Furthermore, any of the nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof provided by the present invention can be functionally linked, using standard techniques such as standard cloning techniques, to any desired regulatory sequences, whether a *S. pyogenes* regulatory sequence or a heterologous regulatory sequence, heterologous leader sequence, heterologous marker sequence or a heterologous coding sequence to create a fusion protein.

Nucleic acid molecules of the present invention may be in the form of RNA, such as mRNA or cRNA, or in the form of DNA, including, for instance, cDNA and genomic DNA obtained by cloning or produced by chemical synthetic techniques or by a combination thereof. The DNA may be triple-stranded, double-stranded or single-stranded. Single-stranded DNA may be the coding strand, also known as the sense strand, or it may be the non-coding strand, also referred to as the anti-sense strand.

The present invention further relates to variants of the herein above described nucleic acid molecules which encode fragments, analogs and derivatives of the hyperimmune serum reactive antigens and fragments thereof having a deduced *S. pyogenes* amino acid sequence set forth in the Sequence Listing. A variant of the nucleic acid molecule may be a naturally occurring variant such as a naturally occurring allelic variant, or it may be a variant that is not known to occur naturally. Such non-naturally occurring variants of the nucleic acid molecule may be made by mutagenesis techniques, including those applied to nucleic acid molecules, cells or organisms.

Among variants in this regard are variants that differ from the aforementioned nucleic acid molecules by nucleotide substitutions, deletions or additions. The substitutions, deletions or additions may involve one or more nucleotides. The variants may be altered in coding or non-coding regions or both. Alterations in the coding regions may produce conservative or non-conservative amino acid substitutions, deletions or additions. Preferred are nucleic acid molecules encoding a variant, analog, derivative or fragment, or a variant, analogue or derivative of a fragment, which have a *S. pyogenes* sequence as set forth in the Sequence Listing, in which several, a few, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid(s) is substituted, deleted or added, in any combination. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the *S. pyogenes* polypeptides set forth in the Sequence Listing. Also especially preferred in this regard are conservative substitutions.

The peptides and fragments according to the present invention also include modified epitopes wherein preferably one or two of the amino acids of a given epitope are modified or replaced according to the

- 18 -

rules disclosed in e.g. [Tourdot, S. et al., 2000], as well as the nucleic acid sequences encoding such modified epitopes.

It is clear that also epitopes derived from the present epitopes by amino acid exchanges improving, conserving or at least not significantly impeding the T cell activating capability of the epitopes are covered by the epitopes according to the present invention. Therefore the present epitopes also cover epitopes, which do not contain the original sequence as derived from *S. pyogenes*, but trigger the same or preferably an improved T cell response. These epitopes are referred to as "heteroclitic"; they need to have a similar or preferably greater affinity to MHC/HLA molecules, and the need the ability to stimulate the T cell receptors (TCR) directed to the original epitope in a similar or preferably stronger manner.

Heteroclitic epitopes can be obtained by rational design i.e. taking into account the contribution of individual residues to binding to MHC/HLA as for instance described by [Rammensee, H. et al., 1999], combined with a systematic exchange of residues potentially interacting with the TCR and testing the resulting sequences with T cells directed against the original epitope. Such a design is possible for a skilled man in the art without much experimentation.

Another possibility includes the screening of peptide libraries with T cells directed against the original epitope. A preferred way is the positional scanning of synthetic peptide libraries. Such approaches have been described in detail for instance by [Hemmer, B. et al., 1999] and the references given therein.

As an alternative to epitopes represented by the present derived amino acid sequences or heteroclitic epitopes, also substances mimicking these epitopes e.g. "peptidomimetics" or "retro-inverso-peptides" can be applied.

Another aspect of the design of improved epitopes is their formulation or modification with substances increasing their capacity to stimulate T cells. These include T helper cell epitopes, lipids or liposomes or preferred modifications as described in WO 01/78767.

Another way to increase the T cell stimulating capacity of epitopes is their formulation with immune stimulating substances for instance cytokines or chemokines like interleukin-2, -7, -12, -18, class I and II interferons (IFN), especially IFN-gamma, GM-CSF, TNF-alpha, flt3-ligand and others.

As discussed additionally herein regarding nucleic acid molecule assays of the invention, for instance, nucleic acid molecules of the invention as discussed above, may be used as a hybridization probe for RNA, cDNA and genomic DNA to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes that have a high sequence similarity to the nucleic acid molecules of the present invention. Such probes generally will comprise at least 15 bases. Preferably, such probes will have at least 20, at least 25 or at least 30 bases, and may have at least 50 bases. Particularly preferred probes will have at least 30 bases, and will have 50 bases or less, such as 30, 35, 40, 45, or 50 bases.

For example, the coding region of a nucleic acid molecule of the present invention may be isolated by screening a relevant library using the known DNA sequence to synthesize an oligonucleotide probe. A labeled oligonucleotide having a sequence complementary to that of a gene of the present invention is then used to screen a library of cDNA, genomic DNA or mRNA to determine to which members of the library the probe hybridizes.

The nucleic acid molecules and polypeptides of the present invention may be employed as reagents and materials for development of treatments of and diagnostics for disease, particularly human disease, as further discussed herein relating to nucleic acid molecule assays, *inter alia*.

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The nucleic acid molecules of the present invention that are oligonucleotides can be used in the processes herein as described, but preferably for PCR, to determine whether or not the *S. pyogenes* genes identified herein in whole or in part are present and/or transcribed in infected tissue such as blood. It is recognized that such sequences will also have utility in diagnosis of the stage of infection and type of infection the pathogen has attained. For this and other purposes the arrays comprising at least one of the nucleic acids according to the present invention as described herein, may be used.

The nucleic acid molecules according to the present invention may be used for the detection of nucleic acid molecules and organisms or samples containing these nucleic acids. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease related or linked to the present or abundance of *S. pyogenes*.

Eukaryotes (herein also "individual(s)"), particularly mammals, and especially humans, infected with *S. pyogenes* may be detected at the DNA level by a variety of techniques. Preferred candidates for distinguishing a *S. pyogenes* from other organisms can be obtained.

The invention provides a process for diagnosing disease, arising from infection with *S. pyogenes*, comprising determining from a sample isolated or derived from an individual an increased level of expression of a nucleic acid molecule having the sequence of a nucleic acid molecule set forth in the Sequence Listing. Expression of nucleic acid molecules can be measured using any one of the methods well known in the art for the quantitation of nucleic acid molecules, such as, for example, PCR, RT-PCR, Rnase protection, Northern blotting, other hybridisation methods and the arrays described herein.

Isolated as used herein means separated "by the hand of man" from its natural state; i.e., that, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a naturally occurring nucleic acid molecule or a polypeptide naturally present in a living organism in its natural state is not "isolated," but the same nucleic acid molecule or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. As part of or following isolation, such nucleic acid molecules can be joined to other nucleic acid molecules, such as DNAs, for mutagenesis, to form fusion proteins, and for propagation or expression in a host, for instance. The isolated nucleic acid molecules, alone or joined to other nucleic acid molecules such as vectors, can be introduced into host cells, in culture or in whole organisms. Introduced into host cells in culture or in whole organisms, such DNAs still would be isolated, as the term is used herein, because they would not be in their naturally occurring form or environment. Similarly, the nucleic acid molecules and polypeptides may occur in a composition, such as a media formulations, solutions for introduction of nucleic acid molecules or polypeptides, for example, into cells, compositions or solutions for chemical or enzymatic reactions, for instance, which are not naturally occurring compositions, and, therein remain isolated nucleic acid molecules or polypeptides within the meaning of that term as it is employed herein.

The nucleic acids according to the present invention may be chemically synthesized. Alternatively, the nucleic acids can be isolated from *S. pyogenes* by methods known to the one skilled in the art.

According to another aspect of the present invention, a comprehensive set of novel hyperimmune serum reactive antigens and fragments thereof are provided by using the herein described antigen identification method. In a preferred embodiment of the invention, a hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by any one of the nucleic acids molecules herein described and fragments thereof are provided. In another preferred embodiment of the invention a novel set of hyperimmune serum-reactive antigens which comprises amino acid sequences selected from a group consisting of the polypeptide sequences as represented in Seq ID No 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300 and fragments thereof are provided. In a further preferred embodiment of the invention hyperimmune serum-reactive antigens which comprise amino acid sequences selected from a group

- 20 -

consisting of the polypeptide sequences as represented in Seq ID No214 and fragments thereof are provided. In a still preferred embodiment of the invention hyperimmune serum-reactive antigens which comprise amino acid sequences selected from a group consisting of the polypeptide sequences as represented in Seq ID No 153, 186, 197-198, 205, 212, 222, 230, 234, 245. and fragments thereof are provided.

The hyperimmune serum reactive antigens and fragments thereof as provided in the invention include any polypeptide set forth in the Sequence Listing as well as polypeptides which have at least 70% identity to a polypeptide set forth in the Sequence Listing, preferably at least 80% or 85% identity to a polypeptide set forth in the Sequence Listing, and more preferably at least 90% similarity (more preferably at least 90% identity) to a polypeptide set forth in the Sequence Listing and still more preferably at least 95%, 96%, 97%, 98%, 99% or 99.5% similarity (still more preferably at least 95%, 96%, 97%, 98%, 99%, or 99.5% identity) to a polypeptide set forth in the Sequence Listing and also include portions of such polypeptides with such portion of the polypeptide generally containing at least 4 amino acids and more preferably at least 8, still more preferably at least 30, still more preferably at least 50 amino acids, such as 4, 8, 10, 20, 30, 35, 40, 45 or 50 amino acids.

The invention also relates to fragments, analogs, and derivatives of these hyperimmune serum reactive antigens and fragments thereof. The terms "fragment", "derivative" and "analog" when referring to an antigen whose amino acid sequence is set forth in the Sequence Listing, means a polypeptide which retains essentially the same biological function or activity as such hyperimmune serum reactive antigen and fragment thereof.

The fragment, derivative or analog of a hyperimmune serum reactive antigen and fragment thereof may be 1) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or 2) one in which one or more of the amino acid residues includes a substituent group, or 3) one in which the mature hyperimmune serum reactive antigen or fragment thereof is fused with another compound, such as a compound to increase the half-life of the hyperimmune serum reactive antigen and fragment thereof (for example, polyethylene glycol), or 4) one in which the additional amino acids are fused to the mature hyperimmune serum reactive antigen or fragment thereof, such as a leader or secretory sequence or a sequence which is employed for purification of the mature hyperimmune serum reactive antigen or fragment thereof or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The present invention also relates to antigens of different *S. pyogenes* isolates. Such homologues may easily be isolated based on the nucleic acid and amino acid sequences disclosed herein. There are more than 80 M protein serotypes distinguished to date and the typing is based on the variable region at the 5' end of the emm gene (see e.g. Vitali et al. 2002). The presence of any antigen can accordingly be determined for every M serotype. In addition it is possible to determine the variability of a particular antigen in the various M serotypes as described for the sic gene (Hoe et al., 2001). The influence of the various M serotypes on the kind of disease it causes is summarized in a recent review (Cunningham, 2000). In particular, two groups of serotypes can be distinguished:

- 1) Those causing Pharyngitis and Scarlet fever (e.g. M types 1, 3, 5, 6, 14, 18, 19, 24)
- 2) Those causing Pyoderma and Streptococcal skin infections (e.g. M types 2, 49, 57, 59, 60, 61)

This can serve as the basis to identify the relevance of an antigen for the use as a vaccine or in general as a drug targeting a specific disease.

The information e.g. from the homepage of the CDC (<http://www.cdc.gov/ncidod/biotech/strep/emmtypes.htm>) gives a dendrogram showing the relatedness of various M serotypes. Further relevant references are Vitali et al., Journal of Clinical Microbiology

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- 21 -

40:679-681. (2002) (molecular emm typing method), Enright et al., *Infection and Immunity* 69:2416-2427. (2001) (alternative molecular typing method (MLST)) , Hoe et al., *The Journal of Infectious Diseases* 183:633-639. (2001)(example for the variation of one antigen (sic) in many different serotypes) and Cunningham, *CLINICAL MICROBIOLOGY REVIEWS* 13:470-511. (2000)(review on GAS pathogenesis). All emm types are completely listed and may be downloaded from the above mentioned address.

The dendrogram was constructed by sequential use of the Wisconsin Package Version 10.1, Genetics Computer Group (GCG), Madison programs Pileup, Distances, and Growtree. Basically, 22 residues of signal sequence plus 83 additional N terminal residues were used for the alignments which include selected sequences from the database. The selected sequences include new emm designations 103-124 (described in table below) as well as their closest "classical" M protein matches. Although this analysis is limited in that the C terminal ends are truncated arbitrarily, this is a typical result in that the dendrogram separates clusters of opacity factor positive strain M sequences from opacity factor strain negative M sequences.

emm type/previous designation - GenBank accession number - Countries where isolated - Closest N-terminal M protein sequence match (% identity):

emm103/st2034 U74320 PNG, Bra, Egy, Mal,Nep, NZ, US M87 (66%)
 emm104/st2034 AF056300 PNG, Egy, Mal,Nep, NZ, US M66 (72%)
 emm105/st4529 AF060227 Mal, Nep, NZ, US M5 (45%)
 emm106/st4532 AF077666 Mal, Egy, Iran,Nep M27G (71%)
 emm107/st4264 AF163686 Mal, NZ M25 (52%)
 emm108/st4547 AF052426 Mal, Bra, Egy, Ira, NZ M70 (84%) emm109/st3018 AF077667 Mal, Egy, NZ M28(74%)
 emm110/st4935 U92492 Ind, Bul, NZ, Rus, US M13 (60%)
 emm111/st4973 AF128960 Ind, Bra, Nep, US M80 (40%)
 emm112/stCmuk16 AF091806 Thi, Bra, Rus, US M27L/77 (59%) emm113/st2267 AF078068 NZ, Thai, Chi M13 (50%)
 emm114/st2967 U50338 US, Can, Gam, NZ, PNG M73 (80%)
 emm115/st2980 AF028712 US, Bra, Rus M36 (64%)
 emm116/st2370 AF156180 US, Nep, NZ M52 (60%)
 emm117/st436 AF058801 US M13 (59%)
 emm118/st448 AF058802 US, Bra, Egy, Nep, NZ M49 (79%)
 emm119/st3365 AF083874 US, Br, Nep M52 (59%)
 emm120/st1135 AF296181 Egy M56 (78%)
 emm121/st1161 AF296182 Egy M64 (64%)
 emm122/st1432 AF222860 Egy, Rus, Nep M18 (40%)
 emm123/st6949AF213451Arg, US, NZM80 (68%)
 st1160/emm124AF149048 and AF018178Egy, Mal, NZM2 (82%)

Abbreviations: Arg, Argentina; Bra, Brazil; Bul, Bulgaria; Can, Canada; Chi, Chile; Egy, Egypt; Gam, Gambia; Ind, India; Ira, Iran; Mal, Malaysia; Nep, Nepal; NZ, New Zealand; PNG, Papua New Guinea; Thi, Thailand; Rus, Russia; US, United States. %: Closest mature M protein sequence match to predicted 50 mature N terminal residues from serologically characterized Lancefield type.

emm types and sequence types:

In many cases the emm sequence reference strains came directly from the M type collection of Dr. Rebecca Lancefield. Such strains are designated RCL.

The sequences starting with "emm" indicate that isolates represented by this type have been analyzed by several reference laboratories besides the CDC streptococcal laboratories. Each of the "new" emm types

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emm94 through emm124 are represented by multiple independent isolates recovered from serious disease manifestations, are M protein nontypeable with all typing sera stocks available to international GAS reference laboratories, and demonstrate antiphagocytic properties in vitro by multiplying in normal human blood. Strains with emm sequences starting with "st" (sequence type) have not yet been completely validated by all of the reference laboratories.

GAS Genetics:

It has long been known that antiserum against serum opacity factor positive (SOF+) strains inhibits OF activity in a strain-specific manner. Therefore, 500-2700 base variable regions of the sof (serum opacity factor) gene representing at least 60 distinct sof genes were analysed from GAS opacity factor positive strains (and interestingly, a homolog commonly found in OF negative emm12 isolates and emm/M type 12 reference strain). It was found that sof gene sequences are also remarkably variable among the different GAS strains, although usually well conserved within an emm type. Important strains include therefore emm1, emm100, emm101, emm102, emm103, emm104, emm105, emm106, emm107, emm108, emm109, emm11, emm110, emm111, emm112, emm113, emm114, emm115, emm116, emm117, emm118, emm119, emm12, emm120, emm121, emm122, emm123, emm124, emm13L, emm14, emm15, emm17, emm18, emm19, emm2, emm22, emm23, emm24, emm25, emm26, emm27G, emm28, emm29, emm3, emm30, emm31, emm32, emm33, emm34, emm36, emm37, emm38, emm39, emm4, emm40, emm41, emm42, emm43, emm44, emm46, emm47, emm48, emm49, emm5, emm50, emm51, emm52, emm53, emm54, emm55, emm56, emm57, emm58, emm59, emm6, emm60, emm61, emm62, emm63, emm64, emm65, emm66, emm67, emm68, emm69, emm70, emm71, emm72, emm73, emm74, emm75, emm76, emm77, emm78, emm79, emm8, emm80, emm81, emm82, emm83, emm84, emm85, emm86, emm87, emm88, emm89, emm9, emm90, emm91, emm92, emm93, emm94, emm95, emm96, emm97, emm98, emm99, st1389, st1731, st1759, st1815, st1967, st1969, st1rp31, st11014, st2037, st204, st211, st213, st2147, st1207, st245, st2460, st2461, st2463, st2904, st2911, st2917, st2926, st2940, st369, st3757, st3765, st3850, st5282, st6735, st7700, st809, st833, st854, st980584, stck249, stck401, std432, std631, std633, stIL103, stIL62, stns292, stns554, sts104, stc1400, stc1741, stc36, stc3852, stc5344, stc5345, stc57, stc6979, stc74a, stc839, stg10, stg11, stg1389, stg166b, stg1750, stg2078, stg3390, stg4222, stg4545, stg480, stg4831, stg485, stg4974, stg5063, stg6, stg62647, stg643, stg652, stg653, stg663, stg840, stg93464, stg97, stL1376, stL1929 and stL2764.

Among the particularly preferred embodiments of the invention in this regard are the hyperimmune serum reactive antigens set forth in the Sequence Listing, variants, analogs, derivatives and fragments thereof, and variants, analogs and derivatives of fragments. Additionally, fusion polypeptides comprising such hyperimmune serum reactive antigens, variants, analogs, derivatives and fragments thereof, and variants, analogs and derivatives of the fragments are also encompassed by the present invention. Such fusion polypeptides and proteins, as well as nucleic acid molecules encoding them, can readily be made using standard techniques, including standard recombinant techniques for producing and expression a recombinant polynucleic acid encoding a fusion protein.

Among preferred variants are those that vary from a reference by conservative amino acid substitutions. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe and Tyr.

Further particularly preferred in this regard are variants, analogs, derivatives and fragments, and variants, analogs and derivatives of the fragments, having the amino acid sequence of any polypeptide set forth in the Sequence Listing, in which several, a few, 5 to 10, 1 to 5, 1 to 3, 2, 1 or no amino acid residues are substituted, deleted or added, in any combination. Especially preferred among these are silent substitutions, additions and deletions, which do not alter the properties and activities of the

- 23 -

polypeptide of the present invention. Also especially preferred in this regard are conservative substitutions. Most highly preferred are polypeptides having an amino acid sequence set forth in the Sequence Listing without substitutions. Specifically suitable amino acid substitutions are those which are contained in homologues for the sequences disclosed in the Sequence Listing according to the present application. A suitable sequence derivative of an antigen or epitope as disclosed herein therefore includes one or more variations being present in one or more strains or serotypes of *S. pyogenes* (preferably 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 amino acid exchanges which are based on such homolog variations). Such antigens comprise sequences which may be naturally occurring sequences or newly created artificial sequences. These preferred antigen variants are based on such naturally occurring sequence variations, e.g. forming a "master sequence" for the antigenic regions of the polypeptides according to the present invention. Suitable examples for such homolog variations or exchanges are given in table 5 in the example section. For example, a given *S. pyogenes* sequence may be amended by including such one or more variations thereby creating an artificial (i.e. non-naturally occurring) variant of this given (naturally occurring) antigen or epitope sequence.

The hyperimmune serum reactive antigens and fragments thereof of the present invention are preferably provided in an isolated form, and preferably are purified to homogeneity.

Also among preferred embodiments of the present invention are polypeptides comprising fragments of the polypeptides having the amino acid sequence set forth in the Sequence Listing, and fragments of variants and derivatives of the polypeptides set forth in the Sequence Listing.

In this regard a fragment is a polypeptide having an amino acid sequence that entirely is the same as part but not all of the amino acid sequence of the afore mentioned hyperimmune serum reactive antigen and fragment thereof, and variants or derivative, analogs, fragments thereof. Such fragments may be "free-standing", i.e., not part of or fused to other amino acids or polypeptides, or they may be comprised within a larger polypeptide of which they form a part or region. Also preferred in this aspect of the invention are fragments characterised by structural or functional attributes of the polypeptide of the present invention, i.e. fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta-amphipathic regions, flexible regions, surface-forming regions, substrate binding regions, and high antigenic index regions of the polypeptide of the present invention, and combinations of such fragments. Preferred regions are those that mediate activities of the hyperimmune serum reactive antigens and fragments thereof of the present invention. Most highly preferred in this regard are fragments that have a chemical, biological or other activity of the hyperimmune serum reactive antigen and fragments thereof of the present invention, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Particularly preferred are fragments comprising receptors or domains of enzymes that confer a function essential for viability of *S. pyogenes* or the ability to cause disease in humans. Further preferred polypeptide fragments are those that comprise or contain antigenic or immunogenic determinants in an animal, especially in a human.

An antigenic fragment is defined as a fragment of the identified antigen which is for itself antigenic or may be made antigenic when provided as a hapten. Therefore, also antigens or antigenic fragments showing one or (for longer fragments) only a few amino acid exchanges are enabled with the present invention, provided that the antigenic capacities of such fragments with amino acid exchanges are not severely deteriorated on the exchange(s), i.e., suited for eliciting an appropriate immune response in an individual vaccinated with this antigen and identified by individual antibody preparations from individual sera.

Preferred examples of such fragments of a hyperimmune serum-reactive antigen are selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa",

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and "Location of identified immunogenic region" of Table 1; the serum reactive epitopes of Table 2, especially peptides comprising amino acid 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of Seq ID No 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of Seq ID No 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of Seq ID No 153; 5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360 and 145-305 of Seq ID No 154; 15-39, 52-61, 72-81, 92-97 and 71-81 of Seq ID No 155; 13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245 and 173-186 of Seq ID No 156; 5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352 and 316-331 of Seq ID No 157; 6-28, 43-53, 60-76, 93-103 and 21-99 of Seq ID No 158; 10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568 and 9-264 of Seq ID No 159; 5-29, 39-45, 107-128 and 1-112 of Seq ID No 160; 4-38, 42-50, 54-60, 65-71, 91-102 and 21-56 of Seq ID No 161; 4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391 and 23-39 of Seq ID No 162; 6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591 and 474-489 of Seq ID No 163; 8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864 and 37-241, 409-534, 582-604, 743-804 of Seq ID No 164; 4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416 and 202-337 of Seq ID No 165; 4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407 and 1-48 of Seq ID No 166; 18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297 and 203-217 of Seq ID No 167; 20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521 and 261-273 of Seq ID No 168; 6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1268, 1278-1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467-1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641 and 1-414, 443-614, 997-1392 of Seq ID No 169; 14-42, 70-75, 90-100, 158-181 and 1-164 of Seq ID No 170; 4-21, 30-36, 54-82, 89-97, 105-118, 138-147 and 126-207 of Seq ID No 171; 4-21, 31-66, 96-104, 106-113, 131-142 and 180-204 of Seq ID No 172; 5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279-284, 287-297, 313-319, 327-336, 343-363, 380-386 and 11-197, 204-219, 258-372 of Seq ID No 173; 4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150-158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322 and 195-289 of Seq ID No 174; 4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106-135, 161-174, 177-192, 200-209, 216-223, 249-298, 304-312, 315-329 and 12-130 of Seq ID No 175; 10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266-272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466-483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671-692, 694-707 and 434-444 of Seq ID No 176; 6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261-269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430 and 360-375 of Seq ID No 177; 4-26, 28-48, 54-62, 88-121, 147-

- 25 -

162, 164-201, 203-237, 245-251 and 254-260 of Seq ID No 178; 12-21, 26-32, 66-72, 87-93; 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293-318, 346-354, 360-371, 391-400 and 369-382 of Seq ID No 179; 11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225-232, 238-249, 258-266, 271-280, 284-291, 295-300, 329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487 and 270-312 of Seq ID No 180; 5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604 and 486-598 of Seq ID No 181; 4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374 and 378-396 of Seq ID No 182; 5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184 and 75-235 of Seq ID No 183; 6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310 and 30-51 of Seq ID No 184; 17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647 and 208-219 of Seq ID No 185; 4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039 and 396-533, 1342-1502, 1672-1920 of Seq ID No 186; 4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482-491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726-736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905 and 1-113, 210-232, 250-423, 536-564 of Seq ID No 187; 4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293-301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571-582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766-772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957-969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090-1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201 and 617-635 of Seq ID No 188; 7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244 and 190-203 of Seq ID No 189; 4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210-243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442-454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574 and 385-398 of Seq ID No 190; 5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325-332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734-763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003 and 12-190, 276-283, 666-806 of Seq ID No 191; 4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301-311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510-518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664 and 30-80, 89-105, 111-151 of Seq ID No 192; 7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259 and 195-203 of Seq ID No 193; 5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134, 147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426 and 32-50 of Seq ID No 194; 8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174 and 75-90 of Seq ID No 195; 4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233 and 69-88 of Seq ID No 196; 4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802 and 96-230, 361-491, 572-585 of Seq ID No 197; 4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289 and 102-210 of Seq ID No 198; 13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313 and 240-248 of Seq ID No 199; 5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260 and 182-198 of Seq ID No 200; 10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504 and 41-56 of Seq ID No

201; 5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333 and 202-217 of Seq ID No 202; 6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283 and 1-127 of Seq ID No 203; 4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718 and 297-458 of Seq ID No 204; 5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213 and 24-135 of Seq ID No 205; 4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721 and 176-330 of Seq ID No 206; 31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472 and 46-62, 296-341 of Seq ID No 207; 23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716 and 667-684 of Seq ID No 208; 20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869 and 258-416 of Seq ID No 209; 7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300 and 278-295 of Seq ID No 210; 4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191 and 183-195 of Seq ID No 211; 12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241 and 63-238 of Seq ID No 212; 4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308 and 1-141 of Seq ID No 213; 11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379 and 231-368 of Seq ID No 214; 9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342 and 247-260 of Seq ID No 215; 7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279 and 64-72 of Seq ID No 216; 4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897 and 222-362, 756-896 of Seq ID No 217; 11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255 and 153-170 of Seq ID No 218; 4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212 and 56-73 of Seq ID No 219; 4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334 and 298-312 of Seq ID No 220; 7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254 and 141-157 of Seq ID No 221; 23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663 and 433-440, 572-593 of Seq ID No 222; 4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267 and 17-319, 417-563 of Seq ID No 223; 6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500 and 46-187 of Seq ID No 224; 4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992 and 21-244, 381-499, 818-959 of Seq ID No 225; 19-29, 65-75, 90-109, 111-137, 155-165, 169-175 and 118-136 of Seq ID No 226; 15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465 and 147-155 of Seq ID No 227; 11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-

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- 27 -

962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161 and 74-438 of Seq ID No 228; 4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413 and 156-420 of Seq ID No 229; 4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343 and 79-348 of Seq ID No 230; 12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168 and 53-70 of Seq ID No 231; 4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522 and 183-341 of Seq ID No 232; 4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822 and 92-231, 618-757 of Seq ID No 233; 11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372 and 41-170 of Seq ID No 234; 6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174 and 20-487, 757-1153 of Seq ID No 235; 10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305 and 26-74, 91-100, 105-303 of Seq ID No 236; 9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480 and 10-223, 231-251, 264-297, 312-336 of Seq ID No 237; 5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537 and 22-344 of Seq ID No 238; 5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395 and 1-151 of Seq ID No 239; 6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756 and 91-263 of Seq ID No 240; 4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775 and 261-272 of Seq ID No 241; 4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701 and 541-551 of Seq ID No 242; 6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252 and 84-254 of Seq ID No 243; 13-30, 71-120, 125-137, 139-145, 184-199 and 61-78 of Seq ID No 244; 9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855 and 568-580 of Seq ID No 245; 11-21, 29-38 and 5-17 of Seq ID No 246; 2-9 of Seq ID No 247; 4-10, 16-28 and 7-18, 26-34 of Seq ID No 248; 10-16 and 1-15 of Seq ID No 249; 4-11 of Seq ID No 250; 4-40, 42-51 and 37-53 of Seq ID No 251; 4-21 and 22-29 of Seq ID No 252; 2-11 Seq ID No 253; 9-17, 32-44 and 1-22 of Seq ID No 254; 19-25, 27-32 and 15-34 of Seq ID No 255; 4-12, 15-22 and 11-33 of Seq ID No 256; 10-17, 24-30, 39-46, 51-70 and 51-61 of Seq ID No 257; 6-19 of Seq ID No 258; 6-11, 21-27, 31-54 and 11-29 of Seq ID No 259; 4-10, 13-45 and 11-35 of Seq ID No 260; 4-14, 23-32 and 11-35 of Seq ID No 261; 14-39, 45-51 and 15-29 of Seq ID No 262; 4-11, 14-28 and 4-17 of Seq ID No 263; 4-16 and 2-16 of Seq ID No 264; 4-10, 12-19, 39-50 and 6-22 of Seq ID No 265; 2-13 of Seq ID No 266; 4-11, 22-65 and 3-19 of Seq ID No 267; 17-23, 30-35, 39-46, 57-62 and 30-49 of Seq ID No 268; 4-19 and 14-22 of Seq ID No 269; 2-9 of Seq ID No 270; 7-18, 30-43 and 4-12 of Seq ID No 271; 4-30, 39-47 and 5-22 of Seq ID No 272; 6-15 and 14-29 of Seq ID No 273; 4-34 and 23-35 of Seq ID No 274; 4-36, 44-57, 65-72 and 14-27 of Seq ID No 275; 4-18 and 11-20 of Seq ID No 276; 5-19 of Seq ID No 277; 18-36 and 6-20 of Seq ID No 278; 4-10, 19-34, 41-84, 96-104 and 50-63 of Seq ID No 279; 4-

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- 28 -

9, 19-27 and 8-21 of Seq ID No 280; 4-16, 18-28 and 22-30 of Seq ID No 281; 4-15 and 21-35 of Seq ID No 282; 4-17 and 3-13 of Seq ID No 283; 4-12 and 4-18 of Seq ID No 284; 4-24, 31-36 and 29-45 of Seq ID No 285; 12-22, 34-49 and 21-32 of Seq ID No 286; 4-17 and 22-32 of Seq ID No 287; 4-16, 25-42 and 7-28 of Seq ID No 288; 4-10 and 7-20 of Seq ID No 289; 4-11, 16-36, 39-54 and 28-44 of Seq ID No 290; 5-20, 29-54 and 14-29 of Seq ID No 291; 24-33 and 10-22 of Seq ID No 292; 10-51, 54-61 and 43-64 of Seq ID No 293; 7-13 and 2-17 of Seq ID No 294; 11-20 and 6-20 of Seq ID No 295; 4-30, 34-41 and 19-28 of Seq ID No 296; 11-21 of Seq ID No 297; 4-16, 21-26 and 9-38 of Seq ID No 298; 4-12, 15-27, 30-42, 66-72 and 10-24 of Seq ID No 299; 8-17 and 11-20 of Seq ID No 300; and 2-19 of Seq ID No 246; 1-12 of Seq ID No 247; 21-38 of Seq ID No 248; 2-22 of Seq ID No 254; 15-33 of Seq ID No 255; 11-32 of Seq ID No 256; 11-28 of Seq ID No 259; 10-27 of Seq ID No 260; 9-26 of Seq ID No 261; 4-16 of Seq ID No 263; 1-18 of Seq ID No 266; 12-29 of Seq ID No 273; 6-23 of Seq ID No 276; 1-21 of Seq ID No 277; 47-64 of Seq ID No 279; 28-45 of Seq ID No 285; 18-35 of Seq ID No 287; 14-31 of Seq ID No 291; 7-24 of Seq ID No 292; 8-25 of Seq ID No 299; 1-20 of Seq ID No 300; 18-33 of Seq ID No 151; 62-72 of Seq ID No 151; 118-131 of Seq ID No 152; 195-220 of Seq ID No 154; 215-240 of Seq ID No 154; 255-280 of Seq ID No 154; 72-81 of Seq ID No 155; 174-186 of Seq ID No 156; 317-331 of Seq ID No 157; 35-59 of Seq ID No 158; 54-84 of Seq ID No 158; 79-104 of Seq ID No 158; 33-58 of Seq ID No 159; 81-101 of Seq ID No 159; 136-150 of Seq ID No 159; 173-186 of Seq ID No 159; 231-251 of Seq ID No 159; 22-48 of Seq ID No 161; 24-39 of Seq ID No 162; 475-489 of Seq ID No 163; 38-56 of Seq ID No 164; 583-604 of Seq ID No 164; 202-223 of Seq ID No 165; 222-247 of Seq ID No 165; 242-267 of Seq ID No 165; 262-287 of Seq ID No 165; 282-307 of Seq ID No 165; 302-327 of Seq ID No 165; 25-48 of Seq ID No 166; 204-217 of Seq ID No 167; 259-276 of Seq ID No 168; 121-139 of Seq ID No 169; 260-267 of Seq ID No 169; 215-240 of Seq ID No 169; 115-140 of Seq ID No 170; 182-204 of Seq ID No 172; 144-153 of Seq ID No 173; 205-219 of Seq ID No 173; 196-206 of Seq ID No 174; 240-249 of Seq ID No 174; 272-287 of Seq ID No 174; 199-223 of Seq ID No 174; 218-237 of Seq ID No 174; 226-249 of Seq ID No 175; 287-306 of Seq ID No 175; 430-449 of Seq ID No 176; 361-375 of Seq ID No 177; 241-260 of Seq ID No 178; 483-502 of Seq ID No 181; 379-396 of Seq ID No 182; 31-51 of Seq ID No 184; 1436-1460 of Seq ID No 186; 1455-1474 of Seq ID No 186; 1469-1487 of Seq ID No 186; 215-229 of Seq ID No 187; 534-561 of Seq ID No 187; 59-84 of Seq ID No 187; 79-104 of Seq ID No 187; 618-635 of Seq ID No 188; 191-203 of Seq ID No 189; 386-398 of Seq ID No 190; 65-83 of Seq ID No 191; 90-105 of Seq ID No 192; 112-136 of Seq ID No 192; 290-209 of Seq ID No 193; 33-50 of Seq ID No 194; 76-90 of Seq ID No 195; 70-88 of Seq ID No 196; 418-442 of Seq ID No 197; 574-585 of Seq ID No 197; 87-104 of Seq ID No 198; 124-148 of Seq ID No 198; 141-152 of Seq ID No 198; 241-248 of Seq ID No 199; 183-198 of Seq ID No 200; 40-57 of Seq ID No 201; 202-217 of Seq ID No 202; 50-74 of Seq ID No 203; 69-93 of Seq ID No 203; 88-112 of Seq ID No 203; 107-127 of Seq ID No 203; 74-92 of Seq ID No 205; 207-232 of Seq ID No 206; 227-252 of Seq ID No 206; 247-272 of Seq ID No 206; 47-60 of Seq ID No 207; 297-305 of Seq ID No 207; 312-337 of Seq ID No 207; 667-384 of Seq ID No 208; 279-295 of Seq ID No 210; 179-198 of Seq ID No 211; 27-51 of Seq ID No 213; 46-70 of Seq ID No 213; 65-89 of Seq ID No 213; 84-108 of Seq ID No 213; 112-141 of Seq ID No 213; 248-260 of Seq ID No 215; 59-78 of Seq ID No 216; 154-170 of Seq ID No 218; 57-73 of Seq ID No 219; 297-314 of Seq ID No 220; 142-157 of Seq ID No 221; 428-447 of Seq ID No 222; 573-593 of Seq ID No 222; 523-544 of Seq ID No 223; 46-70 of Seq ID No 223; 65-89 of Seq ID No 223; 84-108 of Seq ID No 223; 122-151 of Seq ID No 223; 123-142 of Seq ID No 224; 903-921 of Seq ID No 225; 119-136 of Seq ID No 226; 142-161 of Seq ID No 227; 258-277 of Seq ID No 228; 272-300 of Seq ID No 228; 295-322 of Seq ID No 228; 311-343 of Seq ID No 229; 278-304 of Seq ID No 229; 131-150 of Seq ID No 230; 195-218 of Seq ID No 230; 53-70 of Seq ID No 231; 184-208 of Seq ID No 232; 222-246 of Seq ID No 232; 241-265 of Seq ID No 232; 260-284 of Seq ID No 232; 279-303 of Seq ID No 232; 317-341 of Seq ID No 232; 678-696 of Seq ID No 233; 88-114 of Seq ID No 235; 464-481 of Seq ID No 235; 153-172 of Seq ID No 236; 137-155, 166-184 of Seq ID No 236; 215-228 of Seq ID No 236; 37-51 of Seq ID No 237; 53-75 of Seq ID No 237; 232-251 of Seq ID No 237; 318-336 of Seq ID No 237; 305-315 of Seq ID No 238; 131-156 of Seq ID No 238; 258-275 of Seq ID No 241; 107-137 of Seq ID No 243; 138-162 of Seq ID No 243; 157-181 of Seq ID No 243; 195-227 of Seq ID No 243; 62-78 of Seq ID No 244; 567-584 of Seq ID No 245, and fragments comprising at least 6, preferably more than 8, especially more than 10 aa of said sequences. All these fragments individually and each independently form a preferred selected aspect of the present invention.

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All linear hyperimmune serum reactive fragments of a particular antigen may be identified by analysing the entire sequence of the protein antigen by a set of peptides overlapping by 1 amino acid with a length of at least 10 amino acids. Subsequently, non-linear epitopes can be identified by analysis of the protein antigen with hyperimmune sera using the expressed full-length protein or domain polypeptides thereof. Assuming that a distinct domain of a protein is sufficient to form the 3D structure independent from the native protein, the analysis of the respective recombinant or synthetically produced domain polypeptide with hyperimmune serum would allow the identification of conformational epitopes within the individual domains of multi-domain proteins. For those antigens where a domain possesses linear as well as conformational epitopes, competition experiments with peptides corresponding to the linear epitopes may be used to confirm the presence of conformational epitopes.

It will be appreciated that the invention also relates to, among others, nucleic acid molecules encoding the aforementioned fragments, nucleic acid molecules that hybridise to nucleic acid molecules encoding the fragments, particularly those that hybridise under stringent conditions, and nucleic acid molecules, such as PCR primers, for amplifying nucleic acid molecules that encode the fragments. In these regards, preferred nucleic acid molecules are those that correspond to the preferred fragments, as discussed above.

The present invention also relates to vectors which comprise a nucleic acid molecule or nucleic acid molecules of the present invention, host cells which are genetically engineered with vectors of the invention and the production of hyperimmune serum reactive antigens and fragments thereof by recombinant techniques.

A great variety of expression vectors can be used to express a hyperimmune serum reactive antigen or fragment thereof according to the present invention. Generally, any vector suitable to maintain, propagate or express nucleic acids to express a polypeptide in a host may be used for expression in this regard. In accordance with this aspect of the invention the vector may be, for example, a plasmid vector, a single or double-stranded phage vector, a single or double-stranded RNA or DNA viral vector. Starting plasmids disclosed herein are either commercially available, publicly available, or can be constructed from available plasmids by routine application of well-known, published procedures. Preferred among vectors, in certain respects, are those for expression of nucleic acid molecules and hyperimmune serum reactive antigens or fragments thereof of the present invention. Nucleic acid constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the hyperimmune serum reactive antigens and fragments thereof of the invention can be synthetically produced by conventional peptide synthesizers. Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA construct of the present invention.

Host cells can be genetically engineered to incorporate nucleic acid molecules and express nucleic acid molecules of the present invention. Representative examples of appropriate hosts include bacterial cells, such as streptococci, staphylococci, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, 293 and Bowes melanoma cells; and plant cells.

The invention also provides a process for producing a *S. pyogenes* hyperimmune serum reactive antigen and a fragment thereof comprising expressing from the host cell a hyperimmune serum reactive antigen or fragment thereof encoded by the nucleic acid molecules provided by the present invention. The invention further provides a process for producing a cell, which expresses a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof comprising transforming or transfecting a suitable host cell with the vector according to the present invention such that the transformed or transfected cell expresses

the polypeptide encoded by the nucleic acid contained in the vector.

The polypeptide may be expressed in a modified form, such as a fusion protein, and may include not only secretion signals but also additional heterologous functional regions. Thus, for instance, a region of additional amino acids, particularly charged amino acids, may be added to the N- or C-terminus of the polypeptide to improve stability and persistence in the host cell, during purification or during subsequent handling and storage. Also, regions may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to polypeptides to engender secretion or excretion, to improve stability or to facilitate purification, among others, are familiar and routine techniques in the art. A preferred fusion protein comprises a heterologous region from immunoglobulin that is useful to solubilize or purify polypeptides. For example, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another protein or part thereof. In drug discovery, for example, proteins have been fused with antibody Fc portions for the purpose of high-throughout screening assays to identify antagonists. See for example, (Bennett, D. et al., 1995) and (Johanson, K. et al., 1995).

The *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, hydroxylapatite chromatography and lectin chromatography.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention can be produced by chemical synthesis as well as by biotechnological means. The latter comprise the transfection or transformation of a host cell with a vector containing a nucleic acid according to the present invention and the cultivation of the transfected or transformed host cell under conditions which are known to the ones skilled in the art. The production method may also comprise a purification step in order to purify or isolate the polypeptide to be manufactured. In a preferred embodiment the vector is a vector according to the present invention.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention may be used for the detection of the organism or organisms in a sample containing these organisms or polypeptides derived thereof. Preferably such detection is for diagnosis, more preferable for the diagnosis of a disease, most preferably for the diagnosis of a diseases related or linked to the presence or abundance of Gram-positive bacteria, especially bacteria selected from the group comprising streptococci, staphylococci and lactococci. More preferably, the microorganisms are selected from the group comprising *Streptococcus agalactiae*, *Streptococcus pneumoniae* and *Streptococcus mutans*, especially the microorganism is *Streptococcus pyogenes*.

The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of the hyperimmune serum reactive antigens and fragments thereof of the present invention in cells and tissues, including determination of normal and abnormal levels. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of the polypeptide compared to normal control tissue samples may be used to detect the presence of an infection, for example, and to identify the infecting organism. Assay techniques that can be used to determine levels of a polypeptide, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Among these, ELISAs frequently are preferred. An ELISA assay initially comprises preparing an antibody specific to the polypeptide, preferably a monoclonal antibody. In addition, a reporter antibody generally is prepared which binds to the monoclonal antibody. The reporter antibody is attached to a

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- 31 -

detectable reagent such as radioactive, fluorescent or enzymatic reagent, such as horseradish peroxidase enzyme.

The hyperimmune serum reactive antigens and fragments thereof according to the present invention may also be used for the purpose of or in connection with an array. More particularly, at least one of the hyperimmune serum reactive antigens and fragments thereof according to the present invention may be immobilized on a support. Said support typically comprises a variety of hyperimmune serum reactive antigens and fragments thereof whereby the variety may be created by using one or several of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and/or hyperimmune serum reactive antigens and fragments thereof being different. The characterizing feature of such array as well as of any array in general is the fact that at a distinct or predefined region or position on said support or a surface thereof, a distinct polypeptide is immobilized. Because of this any activity at a distinct position or region of an array can be correlated with a specific polypeptide. The number of different hyperimmune serum reactive antigens and fragments thereof immobilized on a support may range from as little as 10 to several 1000 different hyperimmune serum reactive antigens and fragments thereof. The density of hyperimmune serum reactive antigens and fragments thereof per cm^2 is in a preferred embodiment as little as 10 peptides/polypeptides per cm^2 to at least 400 different peptides/polypeptides per cm^2 and more particularly at least 1000 different hyperimmune serum reactive antigens and fragments thereof per cm^2 .

The manufacture of such arrays is known to the one skilled in the art and, for example, described in US patent 5,744,309. The array preferably comprises a planar, porous or non-porous solid support having at least a first surface. The hyperimmune serum reactive antigens and fragments thereof as disclosed herein, are immobilized on said surface. Preferred support materials are, among others, glass or cellulose. It is also within the present invention that the array is used for any of the diagnostic applications described herein. Apart from the hyperimmune serum reactive antigens and fragments thereof according to the present invention also the nucleic acid molecules according to the present invention may be used for the generation of an array as described above. This applies as well to an array made of antibodies, preferably monoclonal antibodies as, among others, described herein.

In a further aspect the present invention relates to an antibody directed to any of the hyperimmune serum reactive antigens and fragments thereof, derivatives or fragments thereof according to the present invention. The present invention includes, for example, monoclonal and polyclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of a Fab expression library. It is within the present invention that the antibody may be chimeric, i. e. that different parts thereof stem from different species or at least the respective sequences are taken from different species.

Antibodies generated against the hyperimmune serum reactive antigens and fragments thereof corresponding to a sequence of the present invention can be obtained by direct injection of the hyperimmune serum reactive antigens and fragments thereof into an animal or by administering the hyperimmune serum reactive antigens and fragments thereof to an animal, preferably a non-human. The antibody so obtained will then bind the hyperimmune serum reactive antigens and fragments thereof itself. In this manner, even a sequence encoding only a fragment of a hyperimmune serum reactive antigen and fragments thereof can be used to generate antibodies binding the whole native hyperimmune serum reactive antigen and fragments thereof. Such antibodies can then be used to isolate the hyperimmune serum reactive antigens and fragments thereof from tissue expressing those hyperimmune serum reactive antigens and fragments thereof.

For preparation of monoclonal antibodies, any technique known in the art which provides antibodies produced by continuous cell line cultures can be used. (as described originally in [Kohler, G. et al., 1975]).

Techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778) can be

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- 32 -

adapted to produce single chain antibodies to immunogenic hyperimmune serum reactive antigens and fragments thereof according to this invention. Also, transgenic mice, or other organisms such as other mammals, may be used to express humanized antibodies to immunogenic hyperimmune serum reactive antigens and fragments thereof according to this invention.

Alternatively, phage display technology or ribosomal display could be utilized to select antibody genes with binding activities towards the hyperimmune serum reactive antigens and fragments thereof either from repertoires of PCR amplified v-genes of lymphocytes from humans screened for possessing respective target antigens or from naïve libraries (McCafferty, J. et al., 1990); (Marks, J. et al., 1992). The affinity of these antibodies can also be improved by chain shuffling (Clackson, T. et al., 1991).

If two antigen binding domains are present, each domain may be directed against a different epitope – termed ‘bispecific’ antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the hyperimmune serum reactive antigens and fragments thereof or purify the hyperimmune serum reactive antigens and fragments thereof of the present invention by attachment of the antibody to a solid support for isolation and/or purification by affinity chromatography.

Thus, among others, antibodies against the hyperimmune serum reactive antigens and fragments thereof of the present invention may be employed to inhibit and/or treat infections, particularly bacterial infections and especially infections arising from *S. pyogenes*.

Hyperimmune serum reactive antigens and fragments thereof include antigenically, epitopically or immunologically equivalent derivatives which form a particular aspect of this invention. The term “antigenically equivalent derivative” as used herein encompasses a hyperimmune serum reactive antigen and fragments thereof or its equivalent which will be specifically recognized by certain antibodies which, when raised to the protein or hyperimmune serum reactive antigen and fragments thereof according to the present invention, interfere with the interaction between pathogen and mammalian host. The term “immunologically equivalent derivative” as used herein encompasses a peptide or its equivalent which when used in a suitable formulation to raise antibodies in a vertebrate, the antibodies act to interfere with the interaction between pathogen and mammalian host.

The hyperimmune serum reactive antigens and fragments thereof, such as an antigenically or immunologically equivalent derivative or a fusion protein thereof can be used as an antigen to immunize a mouse or other animal such as a rat or chicken. The fusion protein may provide stability to the hyperimmune serum reactive antigens and fragments thereof. The antigen may be associated, for example by conjugation, with an immunogenic carrier protein, for example bovine serum albumin (BSA) or keyhole limpet haemocyanin (KLH). Alternatively, an antigenic peptide comprising multiple copies of the protein or hyperimmune serum reactive antigen and fragments thereof, or an antigenically or immunologically equivalent hyperimmune serum reactive antigen and fragments thereof, may be sufficiently antigenic to improve immunogenicity so as to obviate the use of a carrier.

Preferably the antibody or derivative thereof is modified to make it less immunogenic in the individual. For example, if the individual is human the antibody may most preferably be “humanized”, wherein the complementarity determining region(s) of the hybridoma-derived antibody has been transplanted into a human monoclonal antibody, for example as described in (Jones, P. et al., 1986) or (Tempest, P. et al., 1991).

The use of a polynucleotide of the invention in genetic immunization will preferably employ a suitable delivery method such as direct injection of plasmid DNA into muscle, delivery of DNA complexed with specific protein carriers, coprecipitation of DNA with calcium phosphate, encapsulation of DNA in

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- 33 -

various forms of liposomes, particle bombardment [Tang, D. et al., 1992], [Eisenbraun, M. et al., 1993] and *in vivo* infection using cloned retroviral vectors [Seeger, C. et al., 1984].

In a further aspect the present invention relates to a peptide binding to any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention, and a method for the manufacture of such peptides whereby the method is characterized by the use of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and the basic steps are known to the one skilled in the art.

Such peptides may be generated by using methods according to the state of the art such as phage display or ribosome display. In case of phage display, basically a library of peptides is generated, in form of phages, and this kind of library is contacted with the target molecule, in the present case a hyperimmune serum reactive antigen and fragments thereof according to the present invention. Those peptides binding to the target molecule are subsequently removed, preferably as a complex with the target molecule, from the respective reaction. It is known to the one skilled in the art that the binding characteristics, at least to a certain extent, depend on the particularly realized experimental set-up such as the salt concentration and the like. After separating those peptides binding to the target molecule with a higher affinity or a bigger force, from the non-binding members of the library, and optionally also after removal of the target molecule from the complex of target molecule and peptide, the respective peptide(s) may subsequently be characterised. Prior to the characterisation optionally an amplification step is realized such as, e. g. by propagating the peptide coding phages. The characterisation preferably comprises the sequencing of the target binding peptides. Basically, the peptides are not limited in their lengths, however, preferably peptides having a lengths from about 8 to 20 amino acids are preferably obtained in the respective methods. The size of the libraries may be about 10^2 to 10^{18} , preferably 10^8 to 10^{15} different peptides, however, is not limited thereto.

A particular form of target binding hyperimmune serum reactive antigens and fragments thereof are the so-called "anticalines" which are, among others, described in German patent application DE 197 42 706.

In a further aspect the present invention relates to functional nucleic acids interacting with any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention, and a method for the manufacture of such functional nucleic acids whereby the method is characterized by the use of the hyperimmune serum reactive antigens and fragments thereof according to the present invention and the basic steps are known to the one skilled in the art. The functional nucleic acids are preferably aptamers and spiegelmers.

Aptamers are D-nucleic acids which are either single stranded or double stranded and which specifically interact with a target molecule. The manufacture or selection of aptamers is, e. g., described in European patent EP 0 533 838. Basically the following steps are realized. First, a mixture of nucleic acids, i. e. potential aptamers, is provided whereby each nucleic acid typically comprises a segment of several, preferably at least eight subsequent randomised nucleotides. This mixture is subsequently contacted with the target molecule whereby the nucleic acid(s) bind to the target molecule, such as based on an increased affinity towards the target or with a bigger force thereto, compared to the candidate mixture. The binding nucleic acid(s) are/is subsequently separated from the remainder of the mixture. Optionally, the thus obtained nucleic acid(s) is amplified using, e.g. polymerase chain reaction. These steps may be repeated several times giving at the end a mixture having an increased ratio of nucleic acids specifically binding to the target from which the final binding nucleic acid is then optionally selected. These specifically binding nucleic acid(s) are referred to aptamers. It is obvious that at any stage of the method for the generation or identification of the aptamers samples of the mixture of individual nucleic acids may be taken to determine the sequence thereof using standard techniques. It is within the present invention that the aptamers may be stabilized such as, e. g., by introducing defined chemical groups which are known to the one skilled in the art of generating aptamers. Such modification may for example reside in the

introduction of an amino group at the 2'-position of the sugar moiety of the nucleotides. Aptamers are currently used as therapeutical agents. However, it is also within the present invention that the thus selected or generated aptamers may be used for target validation and/or as lead substance for the development of medicaments, preferably of medicaments based on small molecules. This is actually done by a competition assay whereby the specific interaction between the target molecule and the aptamer is inhibited by a candidate drug whereby upon replacement of the aptamer from the complex of target and aptamer it may be assumed that the respective drug candidate allows a specific inhibition of the interaction between target and aptamer, and if the interaction is specific, said candidate drug will, at least in principle, be suitable to block the target and thus decrease its biological availability or activity in a respective system comprising such target. The thus obtained small molecule may then be subject to further derivatisation and modification to optimise its physical, chemical, biological and/or medical characteristics such as toxicity, specificity, biodegradability and bioavailability.

Spiegelmers and their generation or manufacture is based on a similar principle. The manufacture of Spiegelmers is described in international patent application WO 98/08856. Spiegelmers are L-nucleic acids, which means that they are composed of L-nucleotides rather than D-nucleotides as aptamers are. Spiegelmers are characterized by the fact that they have a very high stability in biological system and, comparable to aptamers, specifically interact with the target molecule against which they are directed. In the process of generating Spiegelmers, a heterogenous population of D-nucleic acids is created and this population is contacted with the optical antipode of the target molecule, in the present case for example with the D-enantiomer of the naturally occurring L-enantiomer of the hyperimmune serum reactive antigens and fragments thereof according to the present invention. Subsequently, those D-nucleic acids are separated which do not interact with the optical antipode of the target molecule. But those D-nucleic acids interacting with the optical antipode of the target molecule are separated, optionally determined and/or sequenced and subsequently the corresponding L-nucleic acids are synthesized based on the nucleic acid sequence information obtained from the D-nucleic acids. These L-nucleic acids which are identical in terms of sequence with the aforementioned D-nucleic acids interacting with the optical antipode of the target molecule, will specifically interact with the naturally occurring target molecule rather than with the optical antipode thereof. Similar to the method for the generation of aptamers it is also possible to repeat the various steps several times and thus to enrich those nucleic acids specifically interacting with the optical antipode of the target molecule.

In a further aspect the present invention relates to functional nucleic acids interacting with any of the nucleic acid molecules according to the present invention, and a method for the manufacture of such functional nucleic acids whereby the method is characterized by the use of the nucleic acid molecules and their respective sequences according to the present invention and the basic steps are known to the one skilled in the art. The functional nucleic acids are preferably ribozymes, antisense oligonucleotides and siRNA.

Ribozymes are catalytically active nucleic acids which preferably consist of RNA which basically comprises two moieties. The first moiety shows a catalytic activity whereas the second moiety is responsible for the specific interaction with the target nucleic acid, in the present case the nucleic acid coding for the hyperimmune serum reactive antigens and fragments thereof according to the present invention. Upon interaction between the target nucleic acid and the second moiety of the ribozyme, typically by hybridisation and Watson-Crick base pairing of essentially complementary stretches of bases on the two hybridising strands, the catalytically active moiety may become active which means that it catalyses, either intramolecularly or intermolecularly, the target nucleic acid in case the catalytic activity of the ribozyme is a phosphodiesterase activity. Subsequently, there may be a further degradation of the target nucleic acid which in the end results in the degradation of the target nucleic acid as well as the protein derived from the said target nucleic acid. Ribozymes, their use and design principles are known to the one skilled in the art, and, for example described in {Doherty, E. et al., 2001} and {Lewin, A. et al., 2001}.

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The activity and design of antisense oligonucleotides for the manufacture of a medicament and as a diagnostic agent, respectively, is based on a similar mode of action. Basically, antisense oligonucleotides hybridise based on base complementarity, with a target RNA, preferably with a mRNA, thereby activate RNase H. RNase H is activated by both phosphodiester and phosphorothioate-coupled DNA. Phosphodiester-coupled DNA, however, is rapidly degraded by cellular nucleases with the exception of phosphorothioate-coupled DNA. These resistant, non-naturally occurring DNA derivatives do not inhibit RNase H upon hybridisation with RNA. In other words, antisense polynucleotides are only effective as DNA RNA hybrid complexes. Examples for this kind of antisense oligonucleotides are described, among others, in US-patent US 5,849,902 and US 5,989,912. In other words, based on the nucleic acid sequence of the target molecule which in the present case are the nucleic acid molecules for the hyperimmune serum reactive antigens and fragments thereof according to the present invention, either from the target protein from which a respective nucleic acid sequence may in principle be deduced, or by knowing the nucleic acid sequence as such, particularly the mRNA, suitable antisense oligonucleotides may be designed base on the principle of base complementarity.

Particularly preferred are antisense-oligonucleotides which have a short stretch of phosphorothioate DNA (3 to 9 bases). A minimum of 3 DNA bases is required for activation of bacterial RNase H and a minimum of 5 bases is required for mammalian RNase H activation. In these chimeric oligonucleotides there is a central region that forms a substrate for RNase H that is flanked by hybridising "arms" comprised of modified nucleotides that do not form substrates for RNase H. The hybridising arms of the chimeric oligonucleotides may be modified such as by 2'-O-methyl or 2'-fluoro. Alternative approaches used methylphosphonate or phosphoramidate linkages in said arms. Further embodiments of the antisense oligonucleotide useful in the practice of the present invention are P-methoxyoligonucleotides, partial P-methoxyoligodeoxyribonucleotides or P-methoxyoligonucleotides.

Of particular relevance and usefulness for the present invention are those antisense oligonucleotides as more particularly described in the above two mentioned US patents. These oligonucleotides contain no naturally occurring 5'→3'-linked nucleotides. Rather the oligonucleotides have two types of nucleotides: 2'-deoxyphosphorothioate, which activate RNase H, and 2'-modified nucleotides, which do not. The linkages between the 2'-modified nucleotides can be phosphodiester, phosphorothioate or P-ethoxyphosphodiester. Activation of RNase H is accomplished by a contiguous RNase H-activating region, which contains between 3 and 5 2'-deoxyphosphorothioate nucleotides to activate bacterial RNase H and between 5 and 10 2'-deoxyphosphorothioate nucleotides to activate eucaryotic and, particularly, mammalian RNase H. Protection from degradation is accomplished by making the 5' and 3' terminal bases highly nuclease resistant and, optionally, by placing a 3' terminal blocking group.

More particularly, the antisense oligonucleotide comprises a 5' terminus and a 3' terminus; and from 11 to 59 5'→3'-linked nucleotides independently selected from the group consisting of 2'-modified phosphodiester nucleotides and 2'-modified P-alkyloxyphosphotriester nucleotides; and wherein the 5'-terminal nucleoside is attached to an RNase H-activating region of between three and ten contiguous phosphorothioate-linked deoxyribonucleotides, and wherein the 3'-terminus of said oligonucleotide is selected from the group consisting of an inverted deoxyribonucleotide, a contiguous stretch of one to three phosphorothioate 2'-modified ribonucleotides, a biotin group and a P-alkyloxyphosphotriester nucleotide.

Also an antisense oligonucleotide may be used wherein not the 5' terminal nucleoside is attached to an RNase H-activating region but the 3' terminal nucleoside as specified above. Also, the 5' terminus is selected from the particular group rather than the 3' terminus of said oligonucleotide.

The nucleic acids as well as the hyperimmune serum reactive antigens and fragments thereof according to the present invention may be used as or for the manufacture of pharmaceutical compositions,

- 36 -

especially vaccines. Preferably such pharmaceutical composition, preferably vaccine is for the prevention or treatment of diseases caused by, related to or associated with *S. pyogenes*. In so far another aspect of the invention relates to a method for inducing an immunological response in an individual, particularly a mammal, which comprises inoculating the individual with the hyperimmune serum reactive antigens and fragments thereof of the invention, or a fragment or variant thereof, adequate to produce antibodies to protect said individual from infection, particularly *Streptococcus* infection and most particularly *S. pyogenes* infections.

Yet another aspect of the invention relates to a method of inducing an immunological response in an individual which comprises, through gene therapy or otherwise, delivering a nucleic acid functionally encoding hyperimmune serum reactive antigens and fragments thereof, or a fragment or a variant thereof, for expressing the hyperimmune serum reactive antigens and fragments thereof, or a fragment or a variant thereof *in vivo* in order to induce an immunological response to produce antibodies or a cell mediated T cell response, either cytokine-producing T cells or cytotoxic T cells, to protect said individual from disease, whether that disease is already established within the individual or not. One way of administering the gene is by accelerating it into the desired cells as a coating on particles or otherwise.

A further aspect of the invention relates to an immunological composition which, when introduced into a host capable of having induced within it an immunological response, induces an immunological response in such host, wherein the composition comprises recombinant DNA which codes for and expresses an antigen of the hyperimmune serum reactive antigens and fragments thereof of the present invention. The immunological response may be used therapeutically or prophylactically and may take the form of antibody immunity or cellular immunity such as that arising from CTL or CD4+ T cells.

The hyperimmune serum reactive antigens and fragments thereof of the invention or a fragment thereof may be fused with a co-protein which may not by itself produce antibodies, but is capable of stabilizing the first protein and producing a fused protein which will have immunogenic and protective properties. This fused recombinant protein preferably further comprises an antigenic co-protein, such as Glutathione-S-transferase (GST) or beta-galactosidase, relatively large co-proteins which solubilise the protein and facilitate production and purification thereof. Moreover, the co-protein may act as an adjuvant in the sense of providing a generalized stimulation of the immune system. The co-protein may be attached to either the amino or carboxy terminus of the first protein.

Also, provided by this invention are methods using the described nucleic acid molecule or particular fragments thereof in such genetic immunization experiments in animal models of infection with *S. pyogenes*. Such fragments will be particularly useful for identifying protein epitopes able to provoke a prophylactic or therapeutic immune response. This approach can allow for the subsequent preparation of monoclonal antibodies of particular value from the requisite organ of the animal successfully resisting or clearing infection for the development of prophylactic agents or therapeutic treatments of *S. pyogenes* infection in mammals, particularly humans.

The hyperimmune serum reactive antigens and fragments thereof may be used as an antigen for vaccination of a host to produce specific antibodies which protect against invasion of bacteria, for example by blocking adherence of bacteria to damaged tissue. Examples of tissue damage include wounds in skin or connective tissue caused e.g. by mechanical, chemical or thermal damage or by implantation of indwelling devices, or wounds in the mucous membranes, such as the mouth, mammary glands, urethra or vagina.

The present invention also includes a vaccine formulation which comprises the immunogenic recombinant protein together with a suitable carrier. Since the protein may be broken down in the stomach, it is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, or intradermal. Formulations suitable for parenteral

- 37 -

administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in-water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

According to another aspect, the present invention relates to a pharmaceutical composition comprising such a hyperimmune serum-reactive antigen or a fragment thereof as provided in the present invention for *S. pyogenes*. Such a pharmaceutical composition may comprise one or more hyperimmune serum reactive antigens or fragments thereof against *S. pyogenes*. Optionally, such *S. pyogenes* hyperimmune serum reactive antigens or fragments thereof may also be combined with antigens against other pathogens in a combination pharmaceutical composition. Preferably, said pharmaceutical composition is a vaccine for preventing or treating an infection caused by *S. pyogenes* and/or other pathogens against which the antigens have been included in the vaccine.

According to a further aspect, the present invention relates to a pharmaceutical composition comprising a nucleic acid molecule encoding a hyperimmune serum-reactive antigen or a fragment thereof as identified above for *S. pyogenes*. Such a pharmaceutical composition may comprise one or more nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof against *S. pyogenes*. Optionally, such *S. pyogenes* nucleic acid molecules encoding hyperimmune serum reactive antigens or fragments thereof may also be combined with nucleic acid molecules encoding antigens against other pathogens in a combination pharmaceutical composition. Preferably, said pharmaceutical composition is a vaccine for preventing or treating an infection caused by *S. pyogenes* and/or other pathogens against which the antigens have been included in the vaccine.

The pharmaceutical composition may contain any suitable auxiliary substances, such as buffer substances, stabilisers or further active ingredients, especially ingredients known in connection of pharmaceutical composition and/or vaccine production.

A preferable carrier/or excipient for the hyperimmune serum-reactive antigens, fragments thereof or a coding nucleic acid molecule thereof according to the present invention is an immunostimulatory compound for further stimulating the immune response to the given hyperimmune serum-reactive antigen, fragment thereof or a coding nucleic acid molecule thereof. Preferably the immunostimulatory compound in the pharmaceutical preparation according to the present invention is selected from the group of polycationic substances, especially polycationic peptides, immunostimulatory nucleic acids molecules, preferably immunostimulatory deoxynucleotides, alum, Freund's complete adjuvants, Freund's incomplete adjuvants, neuroactive compounds, especially human growth hormone, or combinations thereof.

It is also within the scope of the present invention that the pharmaceutical composition, especially vaccine, comprises apart from the hyperimmune serum reactive antigens, fragments thereof and/or coding nucleic acid molecules thereof according to the present invention other compounds which are biologically or pharmaceutically active. Preferably, the vaccine composition comprises at least one polycationic peptide. The polycationic compound(s) to be used according to the present invention may be any polycationic compound which shows the characteristic effects according to the WO 97/30721. Preferred polycationic compounds are selected from basic polypeptides, organic polycations, basic polyamino acids or mixtures thereof. These polyamino acids should have a chain length of at least 4 amino acid residues (WO 97/30721). Especially preferred are substances like polylysine, polyarginine and

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- 38 -

polypeptides containing more than 20 %, especially more than 50 % of basic amino acids in a range of more than 8, especially more than 20, amino acid residues or mixtures thereof. Other preferred polycations and their pharmaceutical compositions are described in WO 97/30721 (e.g. polyethyleneimine) and WO 99/38528. Preferably these polypeptides contain between 20 and 500 amino acid residues, especially between 30 and 200 residues.

These polycationic compounds may be produced chemically or recombinantly or may be derived from natural sources.

Cationic (poly)peptides may also be anti-microbial with properties as reviewed in [Ganz, T., 1999]. These (poly)peptides may be of prokaryotic or animal or plant origin or may be produced chemically or recombinantly (WO 02/13857). Peptides may also belong to the class of defensins (WO 02/13857). Sequences of such peptides can be, for example, be found in the Antimicrobial Sequences Database under the following internet address:

<http://www.bbcm.univ.trieste.it/~tossi/pag2.html>

Such host defence peptides or defensives are also a preferred form of the polycationic polymer according to the present invention. Generally, a compound allowing as an end product activation (or down-regulation) of the adaptive immune system, preferably mediated by APCs (including dendritic cells) is used as polycationic polymer.

Especially preferred for use as polycationic substances in the present invention are cathelicidin derived antimicrobial peptides or derivatives thereof (International patent application WO 02/13857, incorporated herein by reference), especially antimicrobial peptides derived from mammal cathelicidin, preferably from human, bovine or mouse.

Polycationic compounds derived from natural sources include HIV-REV or HIV-TAT (derived cationic peptides, antennapedia peptides, chitosan or other derivatives of chitin) or other peptides derived from these peptides or proteins by biochemical or recombinant production. Other preferred polycationic compounds are cathelin or related or derived substances from cathelin. For example, mouse cathelin is a peptide which has the amino acid sequence NH₂-RLAGLLRKGGKIGEKLLKIGOKIKNFFQKLVPQPE-COOH. Related or derived cathelin substances contain the whole or parts of the cathelin sequence with at least 15-20 amino acid residues. Derivations may include the substitution or modification of the natural amino acids by amino acids which are not among the 20 standard amino acids. Moreover, further cationic residues may be introduced into such cathelin molecules. These cathelin molecules are preferred to be combined with the antigen. These cathelin molecules surprisingly have turned out to be also effective as an adjuvant for a antigen without the addition of further adjuvants. It is therefore possible to use such cathelin molecules as efficient adjuvants in vaccine formulations with or without further immunactivating substances.

Another preferred polycationic substance to be used according to the present invention is a synthetic peptide containing at least 2 KLK-motifs separated by a linker of 3 to 7 hydrophobic amino acids (International patent application WO 02/32451, incorporated herein by reference).

The pharmaceutical composition of the present invention may further comprise immunostimulatory nucleic acid(s). Immunostimulatory nucleic acids are e. g. neutral or artificial CpG containing nucleic acid, short stretches of nucleic acid derived from non-vertebrates or in form of short oligonucleotides (ODNs) containing non-methylated cytosine-guanine di-nucleotides (CpG) in a certain base context (e.g. described in WO 96/02555). Alternatively, also nucleic acids based on inosine and cytidine as e.g. described in the WO 01/93903, or deoxynucleic acids containing deoxy-inosine and/or deoxyuridine residues (described in WO 01/93905 and PCT/EP 02/05448, incorporated herein by reference) may

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- 39 -

preferably be used as immunostimulatory nucleic acids for the present invention. Preferably, the mixtures of different immunostimulatory nucleic acids may be used according to the present invention.

It is also within the present invention that any of the aforementioned polycationic compounds is combined with any of the immunostimulatory nucleic acids as aforementioned. Preferably, such combinations are according to the ones as described in WO 01/93905, WO 02/32451, WO 01/54720, WO 01/93903, WO 02/13857 and PCT/EP 02/05448 and the Austrian patent application A 1924/2001, incorporated herein by reference.

In addition or alternatively such vaccine composition may comprise apart from the hyperimmune serum reactive antigens and fragments thereof, and the coding nucleic acid molecules thereof according to the present invention a neuroactive compound. Preferably, the neuroactive compound is human growth factor as, e.g. described in WO 01/24822. Also preferably, the neuroactive compound is combined with any of the polycationic compounds and/or immunostimulatory nucleic acids as afore-mentioned.

In a further aspect the present invention is related to a pharmaceutical composition. Such pharmaceutical composition is, for example, the vaccine described herein. Also a pharmaceutical composition is a pharmaceutical composition which comprises any of the following compounds or combinations thereof: the nucleic acid molecules according to the present invention, the hyperimmune serum reactive antigens and fragments thereof according to the present invention, the vector according to the present invention, the cells according to the present invention, the antibody according to the present invention, the functional nucleic acids according to the present invention and the binding peptides such as the anticalines according to the present invention, any agonists and antagonists screened as described herein. In connection therewith any of these compounds may be employed in combination with a non-sterile or sterile carrier or carriers for use with cells, tissues or organisms, such as a pharmaceutical carrier suitable for administration to a subject. Such compositions comprise, for instance, a media additive or a therapeutically effective amount of a hyperimmune serum reactive antigen and fragments thereof of the invention and a pharmaceutically acceptable carrier or excipient. Such carriers may include, but are not limited to, saline, buffered saline, dextrose, water, glycerol, ethanol and combinations thereof. The formulation should suit the mode of administration.

The pharmaceutical compositions may be administered in any effective, convenient manner including, for instance, administration by topical, oral, anal, vaginal, intravenous, intraperitoneal, intramuscular, subcutaneous, intranasal or intradermal routes among others.

In therapy or as a prophylactic, the active agent may be administered to an individual as an injectable composition, for example as a sterile aqueous dispersion, preferably isotonic.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1 % to about 98 % by weight of the formulation; more usually they will constitute up to about 80 % by weight of the formulation.

In addition to the therapy described above, the compositions of this invention may be used generally as a wound treatment agent to prevent adhesion of bacteria to matrix proteins exposed in wound tissue and for prophylactic use in dental treatment as an alternative to, or in conjunction with, antibiotic prophylaxis.

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A vaccine composition is conveniently in injectable form. Conventional adjuvants may be employed to enhance the immune response. A suitable unit dose for vaccination is 0.05-5 µg/kg of antigen, and such dose is preferably administered 1-3 times and with an interval of 1-3 weeks.

With the indicated dose range, no adverse toxicological effects should be observed with the compounds of the invention which would preclude their administration to suitable individuals.

In a further embodiment the present invention relates to diagnostic and pharmaceutical packs and kits comprising one or more containers filled with one or more of the ingredients of the aforementioned compositions of the invention. The ingredient(s) can be present in a useful amount, dosage, formulation or combination. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, reflecting approval by the agency of the manufacture, use or sale of the product for human administration.

In connection with the present invention any disease related use as disclosed herein such as, e. g. use of the pharmaceutical composition or vaccine, is particularly a disease or diseased condition which is caused by, linked or associated with Streptococci, more preferably, *S. pyogenes*. In connection therewith it is to be noted that *S. pyogenes* comprises several strains including those disclosed herein. A disease related, caused or associated with the bacterial infection to be prevented and/or treated according to the present invention includes besides others bacterial pharyngitis, scarlet fever, impetigo, rheumatic fever, necrotizing fasciitis and sepsis in humans.

In a still further embodiment the present invention is related to a screening method using any of the hyperimmune serum reactive antigens or nucleic acids according to the present invention. Screening methods as such are known to the one skilled in the art and can be designed such that an agonist or an antagonist is screened. Preferably an antagonist is screened which in the present case inhibits or prevents the binding of any hyperimmune serum reactive antigen and fragment thereof according to the present invention to an interaction partner. Such interaction partner can be a naturally occurring interaction partner or a non-naturally occurring interaction partner.

The invention also provides a method of screening compounds to identify those which enhance (agonist) or block (antagonist) the function of hyperimmune serum reactive antigens and fragments thereof or nucleic acid molecules of the present invention, such as its interaction with a binding molecule. The method of screening may involve high-throughput.

For example, to screen for agonists or antagonists, the interaction partner of the nucleic acid molecule and nucleic acid, respectively, according to the present invention, maybe a synthetic reaction mix, a cellular compartment, such as a membrane, cell envelope or cell wall, or a preparation of any thereof, may be prepared from a cell that expresses a molecule that binds to the hyperimmune serum reactive antigens and fragments thereof of the present invention. The preparation is incubated with labelled hyperimmune serum reactive antigens and fragments thereof in the absence or the presence of a candidate molecule which may be an agonist or antagonist. The ability of the candidate molecule to bind the binding molecule is reflected in decreased binding of the labelled ligand. Molecules which bind gratuitously, i. e., without inducing the functional effects of the hyperimmune serum reactive antigens and fragments thereof, are most likely to be good antagonists. Molecules that bind well and elicit functional effects that are the same as or closely related to the hyperimmune serum reactive antigens and fragments thereof are good agonists.

The functional effects of potential agonists and antagonists may be measured, for instance, by determining the activity of a reporter system following interaction of the candidate molecule with a cell or appropriate cell preparation, and comparing the effect with that of the hyperimmune serum reactive

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- 41 -

antigens and fragments thereof of the present invention or molecules that elicit the same effects as the hyperimmune serum reactive antigens and fragments thereof. Reporter systems that may be useful in the regard include but are not limited to colorimetric labelled substrate converted into product, a reporter gene that is responsive to changes in the functional activity of the hyperimmune serum reactive antigens and fragments thereof, and binding assays known in the art.

Another example of an assay for antagonists is a competitive assay that combines the hyperimmune serum reactive antigens and fragments thereof of the present invention and a potential antagonist with membrane-bound binding molecules, recombinant binding molecules, natural substrates or ligands, or substrate or ligand mimetics, under appropriate conditions for a competitive inhibition assay. The hyperimmune serum reactive antigens and fragments thereof can be labelled such as by radioactivity or a colorimetric compound, such that the molecule number of hyperimmune serum reactive antigens and fragments thereof bound to a binding molecule or converted to product can be determined accurately to assess the effectiveness of the potential antagonist.

Potential antagonists include small organic molecules, peptides, polypeptides and antibodies that bind to a hyperimmune serum reactive antigen and fragments thereof of the invention and thereby inhibit or extinguish its activity. Potential antagonists also may be small organic molecules, a peptide, a polypeptide such as a closely related protein or antibody that binds to the same sites on a binding molecule without inducing functional activity of the hyperimmune serum reactive antigens and fragments thereof of the invention.

Potential antagonists include a small molecule which binds to and occupies the binding site of the hyperimmune serum reactive antigens and fragments thereof thereby preventing binding to cellular binding molecules, such that normal biological activity is prevented. Examples of small molecules include but are not limited to small organic molecules, peptides or peptide-like molecules. Other potential antagonists include antisense molecules.

Other potential antagonists include antisense molecules (see {Okano, H. et al., 1991}; OLIGODEOXYNUCLEOTIDES AS ANTISENSE INHIBITORS OF GENE EXPRESSION; CRC Press, Boca Ration, FL (1988), for a description of these molecules).

Preferred potential antagonists include derivatives of the hyperimmune serum reactive antigens and fragments thereof of the invention.

As used herein the activity of a hyperimmune serum reactive antigen and fragment thereof according to the present invention is its capability to bind to any of its interaction partner or the extent of such capability to bind to its or any interaction partner.

In a particular aspect, the invention provides the use of the hyperimmune serum reactive antigens and fragments thereof, nucleic acid molecules or inhibitors of the invention to interfere with the initial physical interaction between a pathogen and mammalian host responsible for sequelae of infection. In particular the molecules of the invention may be used: i) in the prevention of adhesion of *S. pyogenes* to mammalian extracellular matrix proteins on in-dwelling devices or to extracellular matrix proteins in wounds; ii) to block protein mediated mammalian cell invasion by, for example, initiating phosphorylation of mammalian tyrosine kinases. {Rosenshine, I. et al., 1992} to block bacterial adhesion between mammalian extracellular matrix proteins and bacterial proteins which mediate tissue damage; iv) to block the normal progression of pathogenesis in infections initiated other than by the implantation of in-dwelling devices or by other surgical techniques.

Each of the DNA coding sequences provided herein may be used in the discovery and development of

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antibacterial compounds. The encoded protein upon expression can be used as a target for the screening of antibacterial drugs. Additionally, the DNA sequences encoding the amino terminal regions of the encoded protein or Shine-Delgarno or other translation facilitating sequences of the respective mRNA can be used to construct antisense sequences to control the expression of the coding sequence of interest.

The antagonists and agonists may be employed, for instance, to inhibit diseases arising from infection with *Streptococcus*, especially *S. pyogenes*, such as sepsis.

In a still further aspect the present invention is related to an affinity device such affinity device comprises as least a support material and any of the hyperimmune serum reactive antigens and fragments thereof according to the present invention which is attached to the support material. Because of the specificity of the hyperimmune serum reactive antigens and fragments thereof according to the present invention for their target cells or target molecules or their interaction partners, the hyperimmune serum reactive antigens and fragments thereof allow a selective removal of their interaction partner(s) from any kind of sample applied to the support material provided that the conditions for binding are met. The sample may be a biological or medical sample, including but not limited to, fermentation broth, cell debris, cell preparation, tissue preparation, organ preparation, blood, urine, lymph liquid, liquor and the like.

The hyperimmune serum reactive antigens and fragments thereof may be attached to the matrix in a covalent or non-covalent manner. Suitable support material is known to the one skilled in the art and can be selected from the group comprising cellulose, silicon, glass, aluminium, paramagnetic beads, starch and dextrane.

The present invention is further illustrated by the following figures, examples and the sequence listing from which further features, embodiments and advantages may be taken. It is to be understood that the present examples are given by way of illustration only and not by way of limitation of the disclosure.

In connection with the present invention

Figure 1 shows the characterization of *S. pyogenes* specific human sera.

Figure 2 shows the characterization of the small fragment genomic library, LSPy-70, from *Streptococcus pyogenes* SF370/M1.

Figure 3 shows the selection of bacterial cells by MACS using biotinylated human IgGs.

Figure 4 shows an example for the gene distribution study with the identified antigens.

Figure 5 shows cell surface staining by flow cytometry.

Figure 6 shows the protective value of identified recombinant *S. pyogenes* antigens.

Table 1 shows the summary of all screens performed with genomic *S. pyogenes* libraries and human serum.

Table 2 shows the epitope serology with human sera.

Table 3 shows the summary of the gene distribution analysis for the identified antigens in fifty *S. pyogenes* strains.

Table 4 summarizes the information on the antigenic proteins used for the immunization experiments.

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Table 5 shows the variability of antigenic proteins in six different strains of *S. pyogenes*.

The figures to which it might be referred to in the specification are described in the following in more details.

Figure 1 shows the characterization of human sera for *S. pyogenes* as measured by ELISA.

Figure 2 shows the fragment size distribution of the *Streptococcus pyogenes* SF370/M1 small fragment genomic library, LSPy-70. After sequencing 576 randomly selected clones sequences were trimmed to eliminate vector residues and the number of clones with various genomic fragment sizes were plotted. (B) Graphic illustration of the distribution of the same set of randomly sequenced clones of LSPy-70 over the *S. pyogenes* chromosome. Blue circles indicate matching sequences to annotated ORFs in +/+ orientation. Red rectangles represent fully matched clones to non-coding chromosomal sequences in +/+ orientation. Green diamonds positions all clones with complementary or chimeric sequences. Numeric distances in base pairs are indicated over each circular genome for orientation. Partitioning of various clone sets within the library is given in numbers and percentage at the bottom of the figure.

Figure 3A shows the MACS selection with biotinylated human IgGs. The LSPy-70 library in pMAL9.1 was screened with 10 µg biotinylated, human serum (P4-IgG) in the first and with 1 µg in the second selection round. As negative control, no serum was added to the library cells for screening. Number of cells selected after the 1st and 2nd elution are shown for each selection round. Figure 3B shows the reactivity of specific clones (1-52) isolated by bacterial surface display as analysed by Western blot analysis with the human serum (P4-IgG) used for selection by MACS at a dilution of 1:3,000. As a loading control the same blot was also analysed with antibodies directed against the platform protein LamB at a dilution of 1:5,000. LB, Extract from a clone expressing LamB without foreign peptide insert.

Figure 4A shows the emm types of *S. pyogenes* analysed for the gene distribution study. Figure 4B shows the PCR analysis for the gene distribution of genes Spy0269 with the respective oligonucleotides. The predicted size of the PCR fragments is 1,000 bp. 1-50, *S. pyogenes* strains as listed under A; N, no genomic DNA added; P, genomic DNA from *S. pyogenes* SF310, which served as template for library construction.

Figure 5 Detection of specific antibody binding on the cell surface of Group A Streptococcus by flow cytometry. In Figure 5A preimmune mouse sera and polyclonal sera raised against *S. pyogenes* lysate were incubated with *S. pyogenes* strain SF370/M1 and analysed by flow cytometry. Control represents the level of non-specific binding of the secondary antibody to the surface of *S. pyogenes* cells. The histograms in figure 5B and 5C indicate the increased fluorescence due to specific binding of anti-Spy0012 (B) or anti-Spy1315 and anti-Spy1798 (C) antibodies in comparison to the control sera against the two platform proteins LamB and FhuA, respectively.

Figure 6 NMRI mice were immunized with 3 consecutive doses of recombinant protein (50µg/dose) two weeks apart on days 0, 14 and 28. As negative control, mice were immunized with PBS in the presence of adjuvant. The M1 protein (Spy2018) served as positive control for the challenge experiment. The bacterial challenge was performed with 5x10⁷ *S. pyogenes* AP1 cells i.v. and survival of mice was observed daily for A) 18 days, B) 21 days and C) 19 days, respectively.

Table 1: Immunogenic proteins identified by bacterial surface display.

A, LSPy-70 library in lamB with IC3-IgG (1588), B, LSPy-70 library in lamB with IC3-IgA (1539), C, LSPy-70 library in lamB with IC6-IgG (1173), D, LSPy-70 library in lamB with P4-IgG (1138), E, LSPy-70 library in lamB with P4-IgA (981), F, LSPy-150 library in btuB with IC3-IgG (991), G, LSPy-150 library in btuB with IC6-IgG (1036), H, LSPy-150 library in btuB with P4-IgG (681), I, LSPy-400 library in fhuA with IC3-

- 44 -

IgG (559), K, LSPy-400 library in fhuA with IC6-IgG (543), L, LSPy-400 library in fhuA with P4-IgG (20), *, prediction of antigenic sequences longer than 5 amino acids was performed with the program ANTIGENIC [Kolaskar, A. et al., 1990].

Table 2: Epitope serology with human sera.

Immune reactivity of individual synthetic peptides representing selected epitopes with individual human sera is shown. Extent of reactivity is pattern/grey coded; white: - (<50U), grey: + (50-119U), diagonal: ++ (120-199U), diagonally crossed: +++ (200-1000U) and vertically crossed: ++++ (> 1000U). ELISA units (U) are calculated from OD_{545nm} readings and the serum dilution after correction for background. Score, sum of all reactivities (addition of the number of all +); P1 to P10 sera are from patients with acute pharyngitis and N1 to N10 sera are from healthy adults. P and N are used as internal controls.

Peptide names: SPO0012, annotated ORF Spy0012; SPA0450, potential novel ORF in alternative reading-frame of Spy0450; SPC0406, potential novel ORF on complement of Spy0406; SPN0001, potential novel ORF in non-coding region.

Table 3: Gene distribution in *S. pyogenes* strains.

Fifty *S. pyogenes* strains as shown in Figure 4A were tested by PCR with oligonucleotides specific for the genes encoding relevant antigens. The PCR fragment of one selected PCR fragment was sequenced in order to confirm the amplification of the correct DNA fragment. *, number of amino acid substitutions in strain M89 as compared to *S. pyogenes* SF370 (M1). #, alternative strain used for sequencing, because gene was not present in M89.

Table 4: Recombinant proteins used for immunisation experiments in NMRI mice.

Immunization with recombinant antigens and challenge with pathogenic *S. pyogenes* AP1 was performed as described under Experimental procedures. A, The amino acids of the respective antigen contained within the recombinant protein as used for the immunization experiments in animals are given in relation to the full-length protein. B, Percentage of survival is represented as protection and parentheses describes the percentage of protection of the negative control (PBS immunized) followed by the percentage of protection of the positive control (Spy2018). C, Spy0269 was selected due to the fact that the mice showed better survival although at the end of the observation time all mice died. This is reflected by the average survival time as measured in days: 14.6 (Spy0269), 11.6 (PBS) and 19.3 days (Spy2018).

Table 5: Sequence variation of antigenic proteins from *S. pyogenes*.

Antigenic proteins were analysed for amino acid exchanges in six different *S. pyogenes* strains as listed under experimental procedures. The residue number indicates the position of the amino acid in the full-length protein. In case of Spy1666, changes relative to a homologous gene in *Streptococcus pneumoniae* TIGR4 (SP0334) are listed, because the gene is highly conserved in *S. pyogenes* as well as *S. pneumoniae*. A, amino acid residue in protein from *S. pyogenes* SF370. B, amino acid residue(s), which may occur in any one the analysed genes from the other five *S. pyogenes* strains, if different from *S. pyogenes* SF370. C, residues of Spy0416 involved in catalytic activity. Changes in these residues are anticipated to render the enzyme inactive and are therefore exchanged experimentally with alanine, serine, threonine or glycine to produce an enzymatically inactive recombinant protein.

EXAMPLES

Example 1: Preparation of antibodies from human serum

The antibodies produced against group A streptococci by the human immune system and present in human sera are indicative of the in vivo expression of the antigenic proteins and their immunogenicity. These molecules are essential for the identification of individual antigens in the approach as described in the present invention, which is based on the interaction of the specific anti-streptococcal antibodies and

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the corresponding *S. pyogenes* peptides or proteins. To gain access to relevant antibody repertoires, human sera were collected from

I. patients with acute *S. pyogenes* infections, such as pharyngitis, wound infection and bacteraemia. (*S. pyogenes* was shown to be the causative agent by medical microbiological tests),

II. uninfected healthy adults, since group A streptococcal infections are common, and antibodies are present as a consequence of natural immunization from previous encounters with streptococci.

The sera were characterized for anti-*S. pyogenes* antibodies by a series of ELISA and immunoblotting assays. Several streptococcal antigens have been used to show that the titers measured were not a result of the sum of cross-reactive antibodies. For that purpose two different antigen preparation were used: whole cell extract or culture supernatant proteins prepared from *S. pyogenes* SF370/M1 cultured overnight (stationary phase) in THB (Todd-Hewitt Broth) growth medium. Both IgG and IgA antibody levels were determined. Sera were selected for further analysis by immunoblotting based on total antibody titers against the two antigen preparations.

The titers were compared at given dilutions where the response was linear (Figure 1). Sera were ranked based on the reactivity against multiple streptococcal components, and the highest ones were selected for further analysis by immunoblotting. This extensive antibody characterization approach has led to the unambiguous identification of anti-streptococcal hyperimmune sera.

Recently it was reported that not only IgG, but also IgA serum antibodies can be recognized by the FcRIII receptors of PMNs and promote opsonization [Phillips-Quagliata, J. et al., 2000; Shibuya, A. et al., 2000]. The primary role of IgA antibodies is neutralization, mainly at the mucosal surface. The level of serum IgA reflects the quality, quantity and specificity of the dimeric secretory IgA. For that reason the serum collection was not only analyzed for anti-streptococcal IgG, but also for IgA levels. In the ELISA assays highly specific secondary reagents were used to detect antibodies from the high affinity types, such as IgG and IgA, but avoided IgM. Production of IgM antibodies occurs during the primary adaptive humoral response, and results in low affinity antibodies, while IgG and IgA antibodies had already undergone affinity maturation, and are more valuable in fighting or preventing disease

Experimental procedures

Peptide synthesis

Peptides were synthesized in small scale (4 mg resin; up to 288 in parallel) using standard F-moc chemistry on a Rink amide resin (PepChem, Tübingen, Germany) using a SyroII synthesizer (MultisynTech, Witten, Germany). After the sequence was assembled, peptides were elongated with Fmoc-epsilon-aminohexanoic acid (as a linker) and biotin (Sigma, St. Louis, MO; activated like a normal amino acid). Peptides were cleaved off the resin with 93% TFA, 5% triethylsilane, and 2% water for one hour. Peptides were dried under vacuum and freeze dried three times from acetonitrile/water (1:1). The presence of the correct mass was verified by mass spectrometry on a Reflex III MALDI-TOF (Bruker, Bremen Germany). The peptides were used without further purification.

Enzyme linked immune assay (ELISA).

For serum characterization: ELISA plates (Maxisorb, Millipore) were coated with 5-10 µg/ml total protein diluted in coating buffer (0.1M sodium carbonate pH 9.2). Three dilutions of sera (2,000X, 10,000X, 50,000X) were made in PBS-BSA.

For peptide serology: Biotin-labeled peptides were coating on Streptavidin ELISA plates (EXICON) at 10 µg/ml concentration according to the manufacturer's instructions. Sera were tested at two dilutions, 200X and 1,000X.

Highly specific Horse Radish Peroxidase (HRP)-conjugated anti-human IgG or anti-human IgA secondary antibodies (Southern Biotech) were used according to the manufacturers' recommendations (dilution: 1,000x). Antigen-antibody complexes were quantified by measuring the conversion of the substrate (ABTS) to colored product based on OD_{405nm} readings in an automated ELISA reader (TECAN

- 46 -

SUNRISE). Following manual coating, peptide plates were processed and analyzed by the Gemini 160 ELISA robot (TECAN) with a built-in reader (GENIOS, TECAN).

Immunoblotting

Total bacterial lysate and culture supernatant samples were prepared from *in vitro* grown *S. pyogenes* SF370/M1. 10 to 25 µg total protein/lane was separated by SDS-PAGE using the BioRad Mini-Protean 3 Cell electrophoresis system and proteins transferred to nitrocellulose membrane (ECL, Amersham Pharmacia). After overnight blocking in 5% milk, antisera at 2,000x dilution were added, and HRPO labeled anti-mouse IgG was used for detection.

Preparation of bacterial antigen extracts

Total bacterial lysate: Bacteria were lysed by repeated freeze-thaw cycles: incubation on dry ice/ethanol-mixture until frozen (1 min), then thawed at 37°C (5 min): repeated 3 times. This was followed by sonication and collection of supernatant by centrifugation (3,500 rpm, 15 min, 4°C).

Culture supernatant: After removal of bacteria, the supernatant of overnight grown bacterial cultures was precipitated with ice-cold ethanol (100%): 1 part supernatant/3 parts ethanol incubated o/n at -20°C. Precipitates were collected by centrifugation (2,600 g, for 15 min) and dried. Dry pellets were dissolved either in PBS for ELISA, or in urea and SDS-sample buffer for SDS-PAGE and immunoblotting. The protein concentration of samples was determined by Bradford assay.

Purification of antibodies for genomic screening. Five sera from both the patient and the non-infected group were selected based on the overall anti-streptococcal titers for a serum pool used in the screening procedure. Antibodies against *E. coli* proteins were removed by incubating the heat-inactivated sera with whole cell *E. coli* cells (DH5alpha, transformed with pHIE11, grown under the same condition as used for bacterial surface display). Highly enriched preparations of IgGs from the pooled, depleted sera were generated by protein G affinity chromatography, according to the manufacturer's instructions (UltraLink Immobilized Protein G, Pierce). IgA antibodies were purified also by affinity chromatography using biotin-labeled anti-human IgA (Southern Biotech) immobilized on Streptavidin-agarose (GIBCO BRL). The efficiency of depletion and purification was checked by SDS-PAGE, Western blotting, ELISA and protein concentration measurements.

Example 2: Generation of highly random, frame-selected, small-fragment, genomic DNA libraries of *Streptococcus pyogenes*

Experimental procedures

Preparation of streptococcal genomic DNA. 50 ml Todd-Hewitt Broth medium was inoculated with *S. pyogenes* SF370/M1 bacteria from a frozen stab and grown with aeration and shaking for 18 h at 37°C. The culture was then harvested, centrifuged with 1,600x g for 15 min and the supernatant was removed. Bacterial pellets were washed 3 x with PBS and carefully re-suspended in 0.5 ml of Lysozyme solution (100 mg/ml). 0.1 ml of 10 mg/ml heat treated RNase A and 20 U of RNase T1 were added, mixed carefully and the solution was incubated for 1 h at 37°C. Following the addition of 0.2 ml of 20 % SDS solution and 0.1 ml of Proteinase K (10 mg/ml) the tube was incubated overnight at 55 °C. 1/3 volume of saturated NaCl was then added and the solution was incubated for 20 min at 4°C. The extract was pelleted in a microfuge (13,000 rpm) and the supernatant transferred into a new tube. The solution was extracted with PhOH/CHCl₃/IAA (25:24:1) and with CHCl₃/IAA (24:1). DNA was precipitated at room temperature by adding 0.6x volume of Isopropanol, spooled from the solution with a sterile Pasteur pipette and transferred into tubes containing 80% ice-cold ethanol. DNA was recovered by centrifuging the precipitates with 10-12,000x g, then dried on air and dissolved in ddH₂O.

Preparation of small genomic DNA fragments. Genomic DNA fragments were mechanically sheared into fragments ranging in size between 150 and 300 bp using a cup-horn sonicator (Bandelin Sonoplus UV

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- 47 -

2200 sonicator equipped with a BB5 cup horn, 10 sec. pulses at 100 % power output) or into fragments of size between 50 and 70 bp by mild DNase I treatment (Novagen). It was observed that sonication yielded a much tighter fragment size distribution when breaking the DNA into fragments of the 150-300 bp size range. However, despite extensive exposure of the DNA to ultrasonic wave-induced hydromechanical shearing force, subsequent decrease in fragment size could not be efficiently and reproducibly achieved. Therefore, fragments of 50 to 70 bp in size were obtained by mild DNase I treatment using Novagen's shotgun cleavage kit. A 1:20 dilution of DNase I provided with the kit was prepared and the digestion was performed in the presence of MnCl₂ in a 60 µl volume at 20°C for 5 min to ensure double-stranded cleavage by the enzyme. Reactions were stopped with 2 µl of 0.5 M EDTA and the fragmentation efficiency was evaluated on a 2% TAE-agarose gel. This treatment resulted in total fragmentation of genomic DNA into near 50-70 bp fragments. Fragments were then blunt-ended twice using T4 DNA Polymerase in the presence of 100 µM each of dNTPs to ensure efficient flushing of the ends. Fragments were used immediately in ligation reactions or frozen at -20°C for subsequent use.

Description of the vectors. The vector pMAL4.31 was constructed on a pASK-IBA backbone (Skerra, A., 1994) with the beta-lactamase (*bla*) gene exchanged with the Kanamycin resistance gene. In addition *bla* gene was cloned into the multiple cloning site. The sequence encoding mature beta-lactamase is preceded by the leader peptide sequence of *ompA* to allow efficient secretion across the cytoplasmic membrane. Furthermore a sequence encoding the first 12 amino acids (spacer sequence) of mature beta-lactamase follows the *ompA* leader peptide sequence to avoid fusion of sequences immediately after the leader peptidase cleavage site, since e.g. clusters of positive charged amino acids in this region would decrease or abolish translocation across the cytoplasmic membrane (Kajava, A. et al., 2000). A *Sma*I restriction site serves for library insertion. An upstream *Fse*I site and a downstream *Not*I site, which were used for recovery of the selected fragment, flank the *Sma*I site. The three restriction sites are inserted after the sequence encoding the 12 amino acid spacer sequence in such a way that the *bla* gene is transcribed in the -1 reading frame resulting in a stop codon 15 bp after the *Not*I site. A +1 bp insertion restores the *bla* ORF so that beta-lactamase protein is produced with a consequent gain of Ampicillin resistance.

The vector pMAL9.1 was constructed by cloning the *lamB* gene into the multiple cloning site of pEH1 (Hashemzadeh-Bonehi, L. et al., 1998). Subsequently, a sequence was inserted in *lamB* after amino acid 154, containing the restriction sites *Fse*I, *Sma*I and *Not*I. The reading frame for this insertion was constructed in such a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *lamB* and the respective insert.

The vector pMAL10.1 was constructed by cloning the *btuB* gene into the multiple cloning site of pEH1. Subsequently, a sequence was inserted in *btuB* after amino acid 236, containing the restriction sites *Fse*I, *Xba*I and *Not*I. The reading frame for this insertion was chosen in a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *btuB* and the respective insert.

The vector pHIE11 was constructed by cloning the *fhuA* gene into the multiple cloning site of pEH1. Thereafter, a sequence was inserted in *fhuA* after amino acid 405, containing the restriction site *Fse*I, *Xba*I and *Not*I. The reading frame for this insertion was chosen in a way that transfer of frame-selected DNA fragments excised by digestion with *Fse*I and *Not*I from plasmid pMAL4.31 yields a continuous reading frame of *fhuA* and the respective insert.

Cloning and evaluation of the library for frame selection. Genomic *S. pyogenes* DNA fragments were ligated into the *Sma*I site of the vector pMAL4.31. Recombinant DNA was electroporated into DH10B electrocompetent *E. coli* cells (GIBCO BRL) and transformants plated on LB-agar supplemented with Kanamycin (50 µg/ml) and Ampicillin (50 µg/ml). Plates were incubated over night at 37°C and colonies collected for large scale DNA extraction. A representative plate was stored and saved for collecting colonies for colony PCR analysis and large-scale sequencing. A simple colony PCR assay was used to

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initially determine the rough fragment size distribution as well as insertion efficiency. From sequencing data the precise fragment size was evaluated, junction intactness at the insertion site as well as the frame selection accuracy ($3n+1$ rule).

Cloning and evaluation of the library for bacterial surface display. Genomic DNA fragments were excised from the pMAL4.31 vector, containing the *S. pyogenes* library with the restriction enzymes *FseI* and *NotI*. The entire population of fragments was then transferred into plasmids pMAL9.1 (LamB), pMAL10.1 (BtuB) or pHIE11 (FhuA), which have been digested with *FseI* and *NotI*. Using these two restriction enzymes, which recognise an 8 bp GC rich sequence, the reading frame that was selected in the pMAL4.31 vector is maintained in each of the platform vectors. The plasmid library was then transformed into *E. coli* DH5alpha cells by electroporation. Cells were plated onto large LB-agar plates supplemented with 50 µg/ml Kanamycin and grown over night at 37°C at a density yielding clearly visible single colonies. Cells were then scraped off the surface of these plates, washed with fresh LB medium and stored in aliquots for library screening at -80°C.

Results

Libraries for frame selection. Three libraries (LSPy70, LSPy150 and LSPy300) were generated in the pMAL4.31 vector with sizes of approximately 70, 150 and 300 bp, respectively. For each library, ligation and subsequent transformation of approximately 1 µg of pMAL4.31 plasmid DNA and 50 ng of fragmented genomic *S. pyogenes* DNA yielded 4×10^5 to 2×10^6 clones after frame selection. To assess the randomness of the libraries, approximately 600 randomly chosen clones of LSPy70 were sequenced. The bioinformatic analysis showed that of these clones only very few were present more than once. Furthermore, it was shown that 90% of the clones fell in the size range between 16 and 61 bp with an average size of 34 bp (Figure 2). All sequences followed the $3n+1$ rule, showing that all clones were properly frame selected.

Bacterial surface display libraries. The display of peptides on the surface of *E. coli* required the transfer of the inserts from the LSPy libraries from the frame selection vector pMAL4.31 to the display plasmids pMAL9.1 (LamB), pMAL10.1 (BtuB) or pHIE11 (FhuA). Genomic DNA fragments were excised by *FseI* and *NotI* restriction and ligation of 5ng inserts with 0.1µg plasmid DNA and subsequent transformation into DH5alpha cells resulted in $2\text{-}5 \times 10^6$ clones. The clones were scraped off the LB plates and frozen without further amplification.

Example 3: Identification of highly immunogenic peptide sequences from *S. pyogenes* using bacterial surface displayed genomic libraries and human serum

Experimental procedures

MACS screening. Approximately 2.5×10^8 cells from a given library were grown in 5 ml LB-medium supplemented with 50 µg/ml Kanamycin for 2 h at 37°C. Expression was induced by the addition of 1 mM IPTG for 30 min. Cells were washed twice with fresh LB medium and approximately 2×10^7 cells re-suspended in 100 µl LB medium and transferred to an Eppendorf tube.

10 µg of biotinylated, human IgGs from purified from serum was added to the cells and the suspension incubated over night at 4°C with gentle shaking. 900 µl of LB medium was added, the suspension mixed and subsequently centrifuged for 10 min at 6,000 rpm at 4°C (For IgA screens, 10 µg of purified IgAs were used and these captured with biotinylated anti-human-IgG secondary antibodies). Cells were washed once with 1 ml LB and then re-suspended in 100 µl LB medium. 10 µl of MACS microbeads coupled to streptavidin (Miltenyi Biotech, Germany) were added and the incubation continued for 20 min at 4°C. Thereafter 900 µl of LB medium was added and the MACS microbead cell suspension was loaded onto the equilibrated MS column (Miltenyi Biotech, Germany) which was fixed to the magnet. (The MS

columns were equilibrated by washing once with 1 ml 70% EtOH and twice with 2 ml LB medium.)

The column was then washed three times with 3 ml LB medium. After removal of the magnet, cells were eluted by washing with 2 ml LB medium. After washing the column with 3 ml LB medium, the 2 ml eluate was loaded a second time on the same column and the washing and elution process repeated. The loading, washing and elution process was performed a third time, resulting in a final eluate of 2 ml.

A second round of screening was performed as follows. The cells from the final eluate were collected by centrifugation and re-suspended in 1 ml LB medium supplemented with 50 µg/ml Kanamycin. The culture was incubated at 37°C for 90 min and then induced with 1 mM IPTG for 30 min. Cells were subsequently collected, washed once with 1 ml LB medium and suspended in 10 µl LB medium. Since the volume was reduced, 1 µg of human, biotinylated IgGs was added and the suspension incubated overnight at 4°C with gentle shaking. All further steps were exactly the same as in the first selection round. Cells selected after two rounds of selection were plated onto LB-agar plates supplemented with 50 µg/ml Kanamycin and grown overnight at 37°C.

Evaluation of selected clones by sequencing and Western blot analysis. Selected clones were grown overnight at 37°C in 3 ml LB medium supplemented with 50 µg/ml Kanamycin to prepare plasmid DNA using standard procedures. Sequencing was performed at MWG (Germany) or in collaboration with TIGR (U.S.A.).

For Western blot analysis approximately 10 to 20 µg of total cellular protein was separated by 10% SDS-PAGE and blotted onto HybondC membrane (Amersham Pharmacia Biotech, England). The LamB, BtuB or FhuA fusion proteins were detected using human serum as the primary antibody at a dilution of approximately 1:5,000 and anti-human IgG or IgA antibodies coupled to HRP at a dilution of 1:5,000 as secondary antibodies. Detection was performed using the ECL detection kit (Amersham Pharmacia Biotech, England). Alternatively, rabbit anti FhuA or mouse anti LamB antibodies were used as primary antibodies in combination with the respective secondary antibodies coupled to HRP for the detection of the fusion proteins.

Results

Screening of bacterial surface display libraries by magnetic activated cell sorting (MACS) using biotinylated Igs. The libraries LSPy70 in pMAL9.1, LSPy150 in pMAL10.1 and LSPy300 in pHIE11 were screened with pools of biotinylated, human IgGs and IgAs from patient sera or sera from healthy individuals (see Example 1: *Preparation of antibodies from human serum*). The selection procedure was performed as described under Experimental procedures. Figure 3A shows a representative example of a screen with the LSPy-70 library and P4-IgGs. As can be seen from the colony count after the first selection cycle from MACS screening, the total number of cells recovered at the end is drastically reduced from 3×10^7 cells to approximately 5×10^4 cells, whereas the selection without antibodies added showed a reduction to about 2×10^3 cells (Figure 3A). After the second round, a similar number of cells was recovered with P4-IgG, while fewer than 10 cells were recovered when no IgGs from human serum were added, clearly showing that selection was dependent on *S. pyogenes* specific antibodies. To evaluate the performance of the screen, approximately 50 selected clones were picked randomly and subjected to Western blot analysis with the same, pooled serum (Figure 3B). This analysis revealed that 70% of the selected clones showed reactivity with antibodies present in the relevant serum whereas the control strain expressing LamB without a *S. pyogenes* specific insert did not react with the same serum. In general, the rate of reactivity was observed to lie within the range of 35 to 75%. Colony PCR analysis showed that all selected clones contained an insert in the expected size range.

Subsequent sequencing of a larger number of randomly picked clones (600 to 1200 per screen) led to the identification of the gene and the corresponding peptide or protein sequence that was specifically

- 50 -

recognized by the human serum used for screening. The frequency with which a specific clone is selected reflects at least in part the abundance and/or affinity of the specific antibodies in the serum used for selection and recognizing the epitope presented by this clone. In that regard it is striking that clones derived from some ORFs (e.g. Spy0433, Spy2025) were picked more than 80 times, indicating their highly immunogenic property. Table 1 summarizes the data obtained for all 15 performed screens. All clones that are presented in Table 1 have been verified by Western blot analysis using whole cellular extracts from single clones to show the indicated reactivity with the pool of human serum used in the respective screen. As can be seen from Table 1, distinct regions of the identified ORF are identified as immunogenic, since variably sized fragments of the proteins are displayed on the surface by the platform proteins.

It is further worth noticing that most of the genes identified by the bacterial surface display screen encode proteins that are either attached to the surface of *S. pyogenes* and/or are secreted. This is in accordance with the expected role of surface attached or secreted proteins in virulence of *S. pyogenes*.

Example 4: Assessment of the reactivity of highly immunogenic peptide sequences with individual human sera.

Approximately 100 patients and 60 healthy adult sera were included in the analysis. Following the bioinformatic analysis of selected clones, corresponding peptides were designed and synthesized. In case of epitopes with more than 28 amino acid residues, overlapping peptides were made. All peptides were synthesized with a N-terminal biotin-tag and used as coating reagents on Streptavidin-coated ELISA plates.

The analysis was performed in two steps. First, peptides were selected based on their reactivity with the individual sera, which were included in the serum pools (five individual sera) used for preparations of IgG and IgA screening reagents for bacterial surface display. Peptides not displaying a positive reaction were not included in further, more detailed studies. Second, a large number of not pre-selected individual sera from patients with acute pharyngitis or with post-streptococcal diseases or from healthy adults and children were tested against the peptides showing specific and high reactivity with the screening sera. Antibody levels were measured by ELISA and compared by the score calculated for each peptide based on the number of positive sera and the extent of reactivity. An example for serum reactivity of 174 peptides representing *S. pyogenes* epitopes from the genomic screen with 20 human sera (representing 4 different pools of five sera) used for the antigen identification is shown in table 2. The peptides range from highly and widely reactive to weakly positive ones. Among the most reactive ones there are known antigens, some of them are also protective in animal challenge models for nasopharyngeal carriage (eg. C5a peptidase and M protein).

Example 5: Gene distribution studies with highly immunogenic proteins identified from *S. pyogenes*.

Gene distribution of group A streptococcal antigens by PCR. An ideal vaccine antigen would be an antigen that is present in all, or the vast majority of strains of the target organism to which the vaccine is directed. In order to establish whether the genes encoding the identified *Streptococcus pyogenes* antigens occur ubiquitously in *S. pyogenes* strains, PCR was performed on a series of independent *S. pyogenes* isolates with primers specific for the gene of interest. *S. pyogenes* isolates were obtained covering emm types most frequently present in patients as shown in Figure 4A. Oligonucleotide sequences as primers were designed for all identified ORFs yielding products of approximately 1,000 bp, if possible covering all identified immunogenic epitopes. Genomic DNA of all *S. pyogenes* strains was prepared as described under Example 2. PCR was performed in a reaction volume of 25 µl using Taq polymerase (1U), 200 nM dNTPs, 10 pMol of each oligonucleotide and the kit according to the manufacturers instructions (Invitrogen, The Netherlands). As standard, 30 cycles (1x: 5min. 95°C, 30x: 30sec. 95°C, 30sec. 56°C, 30sec. 72°C, 1x 4min. 72°C) were performed, unless conditions had to be adapted for individual primer pairs.

Results

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- 51 -

All identified genes encoding immunogenic proteins were tested by PCR for their presence in 50 different strains of *S. pyogenes* (Figure 4A). As an example, figure 4B shows the PCR reaction for Spy0269 with all indicated 50 strains. As clearly visible, the gene is present in all strains analysed. The PCR fragment from strain no 8 (M89) was sequenced and showed that of 917 bp only 2 bp are different as compared to the *S. pyogenes* M1 strain SF310, resulting in only one amino acid difference between the two isolates.

From a total of 96 genes analysed, 70 were present in all strains tested, while 22 genes were absent in more than 10 of the tested 50 strains (Table 3). Several genes (Spy0433, Spy0681) showed variation in size and were not present in all strain isolates. Some genes showed variation in size, but were otherwise conserved in all tested strains (e.g. Spy1371). Sequencing of the generated PCR fragment from one strain and subsequent comparison to the M1 strain confirmed the amplification of the correct DNA fragment and revealed a degree of sequence divergence as indicated in Table 3. Importantly, many of the identified antigens are well conserved in all strains in sequence and size and are therefore novel vaccine candidates to prevent infections by group A streptococci.

Example 6: Characterization of immune sera obtained from mice immunized with highly immunogenic proteins/peptides from *S. pyogenes* displayed on the surface of *E. coli*.

Generation of immune sera from mice

E. coli clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide, were grown in LB medium supplemented with 50 µg/ml Kanamycin at 37°C. Overnight cultures were diluted 1:10, grown until an OD₆₀₀ of 0.5 and induced with 0.2 mM IPTG for 2 hours. Pelleted bacterial cells were suspended in PBS buffer and disrupted by sonication on ice, generating a crude cell extract. According to the OD₆₀₀ measurement, an aliquot corresponding to 5x10⁷ cells was injected into NMRI mice i.v., followed by a boost after 2 weeks. Serum was taken 1 week after the second injection. Epitope specific antibody levels were measured by peptide ELISA.

In vitro expression of antigens

Expression of antigens by *in vitro* grown *S. pyogenes* SF370/M1 was tested by immunoblotting. Different growth media and culture conditions were tested to detect the presence of antigens in total lysates and bacterial culture supernatants. Expression was considered confirmed when a specific band corresponding to the predicted molecular weight and electrophoretic mobility was detected.

Cell surface staining

Flow cytometric analysis was carried out as follows. Bacteria were grown under culture conditions, which resulted in expression of the antigen as shown by the immunoblot analysis. Cells were washed twice in Hanks Balanced Salt Solution (HBSS) and the cell density was adjusted to approximately 1 X 10⁶ CFU in 100 µl HBSS, 0.5% BSA. After incubation for 30 to 60 min at 4°C with antisera diluted 50 to 100-fold, unbound antibodies were washed away by centrifugation in excess HBSS, 0.5% BSA. Secondary goat anti-mouse antibody (F(ab')₂ fragment specific) labeled with fluorescein (FITC) was incubated with the cells at 4°C for 30 to 60 min. After washing the cells, antibodies were fixed with 2% paraformaldehyde. Bound antibodies were detected using a Becton Dickinson FACScan flow cytometer and data further analyzed with the computer program CELLQuest. Control sera included mouse pre-immune serum and mouse polyclonal serum generated with lysates prepared from IPTG induced *E. coli* cells transformed with plasmids encoding the genes *lamB* or *fluA* without *S. pyogenes* genomic insert.

Opsonophagocytosis assay

Epitope specific immune sera were tested for their activity to induce opsonophagocytosis in a FACS based assay. Sera were heat inactivated and anti-*E. coli* antibodies then removed by incubation with whole cell *E. coli* (3x). 10⁷ Alexa 488 labeled *S. pyogenes* cells were pre-opsonized in the presence of 2-10% immune serum and 2% hamster serum as complement source and then added to 10⁶ phagocytic cells (RAW246.7 or P388.D1 murine monocytic cell lines). The cell mixture was incubated for 30 min at 37°C. Time, IgG concentration and complement dependent uptake of bacteria was registered as an increase in mean fluorescence intensity of the phagocytic cells measured with a fluorescence activated cell sorter.

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- 52 -

Bactericidal (killing) assay

Murine macrophage cells (RAW246.7 or P388.D1) and bacteria were incubated and the loss of viable bacteria after 60 min was determined by colony counting. In brief, bacteria were washed twice in Hanks Balanced Salt Solution (HBSS) and the cell density was adjusted to approximately 1×10^5 CFU in 50 μ l HBSS. Bacteria were incubated with mouse sera (up to 25%) and guinea pig complement (up to 5%) in a total volume of 100 μ l for 60 min at 4°C. Pre-opsonized bacteria were mixed with macrophages (murine cell line RAW246.7 or P388.D1; 2×10^6 cells per 100 μ l) at a 1:20 ratio and were incubated at 37°C on a rotating shaker at 500 rpm. An aliquot of each sample was diluted in sterile water and incubated for 5 min at room temperature to lyse macrophages. Serial dilutions were then plated onto Todd-Hewitt Broth agar plates. The plates were incubated overnight at 37°C, and the colonies were counted with the CounterMat flash colony counter (IUL Instruments). Control sera included mouse pre-immune serum and mouse polyclonal serum generated with lysates prepared from IPTG induced *E. coli* transformed with plasmids harboring the genes *lamB* or *fluA* without *S. pyogenes* genomic insert.

Results

In vitro expression and cell surface staining. The expression of the antigenic proteins was analyzed *in vitro* in *S. pyogenes* SF370/M1 by using sera raised against *E. coli* clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide. This analysis served as a first step to determine whether a protein is expressed at all in order to evaluate surface expression of the polypeptide by FACS analysis. It was anticipated that not all protein would be expressed under *in vitro* conditions, but several proteins were detected by Western blot analysis in total cell lysates (e.g. Spy0012, Spy0112, Spy0416, Spy0437, Spy0872, Spy1032, Spy1315, Spy1798; data not shown). Cell surface accessibility for several antigenic proteins was subsequently demonstrated by an assay based on flow cytometry. Streptococci were incubated with preimmune and polyclonal mouse sera raised against *S. pyogenes* lysate or *E. coli* clones harboring plasmids encoding the platform protein fused to a *S. pyogenes* peptide, follow by detection with fluorescently tagged secondary antibody. As shown in Fig. 5A, antisera raised against *S. pyogenes* lysate cause a shift in fluorescence of the *S. pyogenes* SF370/M1 cell population. Similar cell surface staining of *S. pyogenes* SF370/M1 cells was observed with polyclonal sera raised against peptides of antigen Spy0012 (Fig. 5B), Spy1315 and Spy1798 (Fig. 5C), although only a subpopulation of the bacteria was stained, as indicated by the detection of two peaks. This phenomenon may be a result of differential expression of the gene products during the growth of the bacterium or partial inhibition of antibody binding caused by other surface molecules.

These experiments confirmed the bioinformatic prediction that these proteins are exported due to their signal peptide sequence and in addition showed that they are anchored on the cell surface of *S. pyogenes* SF370/M1. They also confirm that these proteins are available for recognition by human antibodies and make them valuable candidates for the development of a vaccine against Group A Streptococcal disease.

Example 7: Protective immune responses against infection with group A streptococci upon immunization with recombinant antigens.**Experimental procedures***Cloning of genes encoding antigenic proteins*

The gene or DNA fragment of interest was amplified from genomic DNA of *S. pyogenes* SF370 by PCR amplification using gene specific primers. Apart from the gene specific sequence, the primers contained additional bases at the respective 5' end consisting of restriction sites that aided in the directional cloning of the amplified PCR product. The gene specific sequence of the primer ranged between 15-24 bases in length. The PCR products obtained were digested with the appropriate restriction enzymes and cloned into the appropriately digested pET28b(+) vector (NOVAGEN). After confirmation of the construction of the recombinant plasmid, *E. coli* BL21 STAR® cells (INVITROGEN) that served as expression hosts were transformed. These cells are optimized to efficiently express the gene of interest as encoded by the pET28b plasmid.

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Expression of antigens in Escherichia coli

E. coli BL21 STAR® cells harboring the recombinant plasmid were grown into log phase in LB medium supplemented with 50 µg/ml Kanamycin at 37°C. Once an OD_{600nm} of 0.8 was reached, the culture was induced with 1 mM IPTG for 3 hours at 37°C. The cells were harvested by centrifugation, lysed by a combination of the freeze-thaw method followed by disruption of cells with the Bug-buster® reagent from NOVAGEN. The lysate was separated by centrifugation into soluble (supernatant) and insoluble (pellet) fractions.

Purification of recombinant proteins from E. coli

Depending on the localization of the protein, different purification strategies were followed. Proteins in the soluble fraction were purified by binding the supernatant of the cell lysates after cell disruption to Ni-Agarose beads (Ni-NTA-Agarose®, QIAGEN). Due to the presence of the penta-Histidine (HIS) at the C, N or both termini of the expressed protein, the protein binds to Ni-agarose while other contaminating proteins are washed and removed from the column by washing buffer. The proteins were eluted by a solution containing 100 mM imidazole in the appropriate buffer. The eluate was concentrated, assayed by Bradford for protein concentration and analysed by SDS-PAGE and Western blot. Proteins in the insoluble fraction were purified by solubilization of the pellet in an appropriate buffer containing 8 M Urea. The purification was performed under denaturing conditions (in buffer containing 8M Urea) using the same materials and procedure as mentioned above for soluble proteins. The eluate was concentrated and dialyzed to remove all urea in a gradual or stepwise manner. The final protein solution was concentrated, analysed by SDS-PAGE and measured by Bradford method. Expression was considered confirmed when a specific band corresponding to the predicted molecular weight and electrophoretic mobility was detected. For proteins, which precipitated during dialysis due to the removal of the denaturing reagent urea, the insoluble inclusion bodies were washed several times and directly used for immunization of mice.

Immunisation of NMRI mice with recombinant proteins and challenge with S. pyogenes AP1

The immunogenicity of the proteins was assayed in an experimental animal model using NMRI mice and the *S. pyogenes* strain AP1 as infectious agent. Ten female NMRI mice at 7-8 weeks of age were immunized with 50 µg/dose of recombinant protein every 2 weeks for a total of 3 doses. The initial dose was adjuvanted with Complete Freund's adjuvant while the remaining two doses were adjuvanted with Incomplete Freund's adjuvant. At the end of the immunization the mice were bled to check the antibody titer and subsequently intravenously (i.v.) challenged with a lethal dose of *S. pyogenes* AP1 (5x 10⁷ pathogenic bacteria). The mice were scored for 18 to 21 days post challenge for survival.

Results

Expression and purification of recombinant proteins.

Of the 31 proteins selected for recombinant protein expression, 29 proteins could be produced in *E. coli* to a level sufficient for purification. While some of the proteins could be produced as soluble protein (see Table 4), some proteins turned out to be insoluble (e.g. Spy416B, Spy0872) or precipitated upon dialysis, which was intended to remove the denaturing reagent urea after solubilization of insoluble proteins such as Spy0031, Spy0292, Spy720. In these cases the washed inclusion bodies were directly injected into mice for immunization. In general, the affinity purification yielded a recombinant protein preparation of at least 85% purity.

Immune responses after immunization with recombinant proteins in NMRI mice.

Table 4 lists those antigens, which were tested in mice and showed some degree of protection in experimental animals. Recombinant proteins, which were also tested in the bacteremia model in animals, but did show not any level of protection in the described experiments are not listed here, but include proteins such as Spy0012, Spy1063 and Spy1494. The described bacteremia model evaluates the protective value of vaccine candidates against invasive disease as pathogenic bacteria are directly injected into the blood. Recombinant proteins, which induce antibodies capable of protection against such group A streptococcal infection, are considered as valuable candidates for the development of a vaccine against

Group A Streptococcal disease. In comparison to the positive control Spy2018 (M1 protein), which was previously shown to provide protection against *S. pyogenes* challenge, a number of antigens performed to a similar degree when the endpoint of the challenge experiment after 18 or 21 days (Table 4) was assessed (Spy0416, Spy1607 or Spy0292). Other proteins showed only a partial protective effect (Spy0720, Spy0872), but may prove very effective when combined with other antigens (Fig. 6).

Surprisingly, the antigen screen had identified immunogenic epitopes predominantly in the first half of the two larger proteins, Spy0416 and Spy1972. Therefore it was reasoned that the protective region may also be contained in the N terminal part of the protein. In case of Spy0416, both parts of the antigen were produced as recombinant protein (Spy0416A and Spy0416B; see Table 4) and tested in animal experiments. The experiments showed that only the first half of the protein Spy0416 (Table 4; Spy0416A) provided protection in the animal model, while the second half of the protein (Spy0416B) had no protective effect at all, clearly delineating a smaller region within the protein as the vaccine candidate. For antigen Spy1972 only the first half of the full-length protein was produced as recombinant protein and tested in the animal model.

Example 8: Variability of genes encoding antigenic proteins in *S. pyogenes* strains of various serotypes.

Experimental procedures

Sequencing of PCR fragments and bioinformatic analysis.

The PCR analysis of *S. pyogenes* strains is described in Example 5. The sequencing of the PCR fragments provided an estimate of the variability of the gene and the summary of the results are listed in Table 3. The availability of genomic sequences from five *Streptococcus pyogenes* strains (SF370: M1; MGAS8232: M18; SSI-1: M3; MGAS315: M3; Manfredo: M5) allowed a further assessment of the variability of the antigens. All sequences were aligned with the respective antigen sequence from *S. pyogenes* SF370 and those amino acid residues identified which differed from the ones in the antigenic protein from *S. pyogenes* SF370. Inserted or deleted sequences were detected in some of the antigenic proteins, but are not contained in this analysis.

Results

Table 5 shows all positions that were identified to be variable in the indicated antigens in one of the four *S. pyogenes* strains (MGAS8232: M18; SSI-1: M3; MGAS315: M3; Manfredo: M5) or the strain used for sequencing of the amplified PCR fragment (see Table 3). The bioinformatic analysis shows that some of the antigenic proteins are very well conserved without a single amino exchange in any of the six strains of serotypes M1, M3, M5, M18 and M89. Proteins belonging to this group include Spy0103 and Spy1536, while the exchanges in the other antigenic proteins are more numerous in larger proteins than in smaller ones, as expected from the difference in size by itself. Although a variety of strains was analysed, it was almost never observed that a single residue was changed to more than one other amino acid in the other strains. A further analysis of sequences of the respective genes in a larger number of strains of varying serotypes, clinical indication or geographic location would certainly identify possible changes in those amino acid residues listed or in additional residues.

Only one of the antigenic proteins analysed by the alignment of six gene sequences showed a considerable degree of variation in size (Spy1357: SF370 - 217 amino acids; MGAS8232 - 245 aa; SSI-1 - 329 aa; MGAS315 - 329 aa; Manfredo - 279 aa). Thus it is evident, that most of the evaluated antigens are very well conserved in sequence as well as in size and provide promising candidates for vaccine development.

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Table 1: Immunogenic proteins identified by bacterial surface display.

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
Spy0012	Hypothetical protein	4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425	A:12, I:5, N:2	1-114	1, 151
Spy0019	putative secreted protein (cell division and antibiotic tolerance)	5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395	F:2, I:16, K:24, N:29, P:12	29-226	2, 152
Spy0025	putative phosphoribosylformylglycinamide synthase II	4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254	D:3	919-929	3, 153
Spy0031	putative choline binding protein	5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360	I:3, K:3, N:3	145-305	4, 154
Spy0103	putative competence protein	15-39, 52-61, 72-81, 92-97	A:8	71-81	5, 155
Spy0112	putative pyrroline carboxylate reductase	13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245	B:4	173-186	6, 156
Spy0115	putative glutamyl-aminopeptidase	5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352	A:3, C:26	316-331	7, 157
Spy0166	Hypothetical protein	6-28, 43-53, 60-76, 93-103	I:22, K:7, N:17, O:31, P:5	21-99	8, 158
Spy0167	Streptolysin O	10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568	A:118, B:14, C:18, D:37, F:141, G:79, H:92, I:97, K:123, L:5, M:21, N:225, O:230, P:265	9-264	9, 159
Spy0168	Hypothetical protein	5-29, 39-45, 107-128	K:4, N:7	1-112	10, 160

- 57 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
Spy0171	hypothetical protein	4-38, 42-50, 54-60, 65-71, 91-102	H:2	21-56	11, 161
Spy0183	putative glycine betaine/proline ABC transporter	4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391	C:6	23-39	12, 162
Spy0230	putative ABC transporter (ATP- binding protein)	6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591	C:46	474-489	13, 163
Spy0269	putative surface exclusion protein	8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864	A:2, B:12, D:3, F:11, H:5, N:6	37-241 409-534 582-604 743-804	14, 164
Spy0287	conserved hypothetical protein	4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416	K:1	202-337	15, 165
Spy0292	penicillin-binding protein (D-alanyl-D- alanine car	4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407	F:2	1-48	16, 166
Spy0295	oligopeptidase	18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-207, 212-229, 232-253, 273-297	A:3	203-217	17, 167
Spy0348	putative aminodeoxychorismate lyase	20-26, 54-61, 80-88, 94-101, 113-119, 128-136, 138-144, 156-188, 193-201, 209-217, 221-229, 239-244, 251-257, 270-278, 281-290, 308-315, 319-332, 339-352, 370-381, 388-400, 411-417, 426-435, 468-482, 488-497, 499-506, 512-521	D:5, I:3, M:3, P:3	261-273	18, 168
Spy0416	putative cell envelope serine proteinase	6-12, 16-36, 50-56, 86-92, 115-125, 143-152, 163-172, 193-203, 235-244, 280-289, 302-315, 325-348, 370-379, 399-405, 411-417, 419-429, 441-449, 463-472, 482-490, 500-516, 536-543, 561-569, 587-594, 620-636, 647-653, 659-664, 677-685, 687-693, 713-719, 733-740, 746-754, 756-779, 792-799, 808-817, 822-828, 851-865, 902-908, 920-938, 946-952, 969-976, 988-1005, 1018-1027, 1045-1057, 1063-1069, 1071-	A:3, B:4, C:30, D:13, F:138, G:120, H:101, I:9, K:14, M:2, N: 15, O:8, P:19	1-414 443-614 997-1392	19, 169

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- 58 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
		1078, 1090-1099, 1101-1109, 1113-1127, 1130-1137, 1162-1174, 1211-1221, 1234-1242, 1261-1266, 1278- 1284, 1312-1317, 1319-1326, 1345-1353, 1366-1378, 1382-1394, 1396-1413, 1415-1424, 1442-1457, 1467- 1474, 1482-1490, 1492-1530, 1537-1549, 1559-1576, 1611-1616, 1624-1641			
Spy0430	hypothetical protein	14-42, 70-75, 90-100, 158-181	B:7, E:10, P:18	1-164	20, 170
Spy0433	hypothetical protein	4-21, 30-36, 54-82, 89-97, 105-118, 138-147	A:138, B:8, C:67, D:11, E:13, F:35, G:10, H:5, M:8	126-207	21, 171
Spy0437	Hypothetical protein	4-21, 31-66, 96-104, 106-113, 131-142	A:29, B:10, C:21, D:24, E:15	180-204	22, 172
Spy0469	putative 42 kDa protein	5-23, 31-36, 38-55, 65-74, 79-88, 101-129, 131-154, 156-165, 183-194, 225-237, 245-261, 264-271, 279- 284, 287-297, 313-319, 327-336, 343-363, 380-386	B:5, F:77, I:8, K:15, M:3, N:17, O:20	11-197 204-219 258-372	23, 173
Spy0488	hypothetical protein	4-20, 34-41, 71-86, 100-110, 113-124, 133-143, 150- 158, 160-166, 175-182, 191-197, 213-223, 233-239, 259-278, 298-322	A:17, B:11, C:23, D:12, E:4, G:4, H:7	195-289	24, 174
Spy0515	Putative sugar transferase	4-10, 21-35, 44-52, 54-62, 67-73, 87-103, 106- 135, 161-174, 177-192, 200-209, 216-223, 249- 298, 304-312, 315-329	B:5, I:3	12-130	25, 175
Spy0580	conserved hypothetical protein	10-27, 33-38, 48-55, 70-76, 96-107, 119-133, 141-147, 151-165, 183-190, 197-210, 228-236, 245-250, 266- 272, 289-295, 297-306, 308-315, 323-352, 357-371, 381-390, 394-401, 404-415, 417-425, 427-462, 466- 483, 485-496, 502-507, 520-529, 531-541, 553-570, 577-588, 591-596, 600-610, 619-632, 642-665, 671- 692, 694-707	C:5	434-444	26, 176
Spy0621	conserved hypothetical protein	6-14, 16-25, 36-46, 52-70, 83-111, 129-138, 140-149, 153-166, 169-181, 188-206, 212-220, 223-259, 261- 269, 274-282, 286-293, 297-306, 313-319, 329-341, 343-359, 377-390, 409-415, 425-430	C:3	360-375	27, 177
Spy0630	putative PTS dependent N-acetyl- galactosamine-IIc	4-26, 28-48, 54-62, 88-121, 147-162, 164-201, 203- 237, 245-251	C:2	254-260	28, 178
Spy0681	hypothetical protein, phage associated	12-21, 26-32, 66-72, 87-93, 98-112, 125-149, 179-203, 209-226, 233-242, 249-261, 266-271, 273-289, 293- 318, 346-354, 360-371, 391-400	A:8	369-382	29, 179
Spy0683	putative minor capsid protein, phage associated	11-38, 44-65, 70-87, 129-135, 140-163, 171-177, 225- 232, 238-249, 258-266, 271-280, 284-291, 295-300,	B:11, D:4	270-312	30, 180

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<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		329-337, 344-352, 405-412, 416-424, 426-434, 436-455, 462-475, 478-487			
Spy0702	Hypothetical protein	5-17, 34-45, 59-69, 82-88, 117-129, 137-142, 158-165, 180-195, 201-206, 219-226, 241-260, 269-279, 292-305, 312-321, 341-347, 362-381, 396-410, 413-432, 434-445, 447-453, 482-487, 492-499, 507-516, 546-552, 556-565, 587-604	L:2	486-598	31, 181
Spy0710	conserved hypothetical protein, phage associated	4-15, 17-32, 40-47, 67-78, 90-98, 101-107, 111-136, 161-171, 184-198, 208-214, 234-245, 247-254, 272-279, 288-298, 303-310, 315-320, 327-333, 338-349, 364-374	B:10	378-396	32, 182
Spy0711	pyrogenic exotoxin C precursor, phage associated (speC)	5-27, 33-49, 51-57, 74-81, 95-107, 130-137, 148-157, 173-184	K:2	75-235	33, 183
Spy0720	conserved hypothetical protein	6-23, 47-53, 57-63, 75-82, 97-105, 113-122, 124-134, 142-153, 159-164, 169-179, 181-187, 192-208, 215-243, 247-257, 285-290, 303-310	D:2	30-51	34, 184
Spy0727	putative DNA gyrase, subunit B	17-29, 44-52, 59-73, 77-83, 86-92, 97-110, 118-153, 156-166, 173-179, 192-209, 225-231, 234-240, 245-251, 260-268, 274-279, 297-306, 328-340, 353-360, 369-382, 384-397, 414-423, 431-436, 452-465, 492-498, 500-508, 516-552, 554-560, 568-574, 580-586, 609-617, 620-626, 641-647	M:26	208-219	35, 185
Spy0737	putative extracellular matrix binding protein	4-26, 32-45, 58-72, 111-119, 137-143, 146-159, 187-193, 221-231, 235-242, 250-273, 290-304, 311-321, 326-339, 341-347, 354-368, 397-403, 412-419, 426-432, 487-506, 580-592, 619-628, 663-685, 707-716, 743-751, 770-776, 787-792, 850-859, 866-873, 882-888, 922-931, 957-963, 975-981, 983-989, 1000-1008, 1023-1029, 1058-1064, 1089-1099, 1107-1114, 1139-1145, 1147-1156, 1217-1226, 1276-1281, 1329-1335, 1355-1366, 1382-1394, 1410-1416, 1418-1424, 1443-1451, 1461-1469, 1483-1489, 1491-1501, 1515-1522, 1538-1544, 1549-1561, 1587-1593, 1603-1613, 1625-1630, 1636-1641, 1684-1690, 1706-1723, 1765-1771, 1787-1804, 1850-1857, 1863-1894, 1897-1910, 1926-1935, 1937-1943, 1960-1983, 1991-2005, 2008-2014, 2018-2039	B:5, E:3, K:11	396-533 1342-1502 1672-1920	36, 186
Spy0747	extracellular nuclease	4-25, 45-50, 53-65, 79-85, 87-92, 99-109, 126-137, 141-148, 156-183, 190-203, 212-217, 221-228, 235-	A:72, B:17, H:6, O:3	1-113 210-232	37, 187

- 60 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
		242, 247-277, 287-293, 300-319, 321-330, 341-361, 378-389, 394-406, 437-449, 455-461, 472-478, 482- 491, 507-522, 544-554, 576-582, 587-593, 611-621, 626-632, 649-661, 679-685, 696-704, 706-716, 726- 736, 740-751, 759-766, 786-792, 797-802, 810-822, 824-832, 843-852, 863-869, 874-879, 882-905		250-423 536-564	
Spy0777	putative ATP- dependent exonuclease, subunit A	4-16, 33-39, 43-49, 54-85, 107-123, 131-147, 157-169, 177-187, 198-209, 220-230, 238-248, 277-286, 293- 301, 303-315, 319-379, 383-393, 402-414, 426-432, 439-449, 470-478, 483-497, 502-535, 552-566, 571- 582, 596-601, 608-620, 631-643, 651-656, 663-678, 680-699, 705-717, 724-732, 738-748, 756-763, 766- 772, 776-791, 796-810, 819-827, 829-841, 847-861, 866-871, 876-882, 887-894, 909-934, 941-947, 957- 969, 986-994, 998-1028, 1033-1070, 1073-1080, 1090- 1096, 1098-1132, 1134-1159, 1164-1172, 1174-1201	C:4, E:2	617-635	38, 188
Spy0789	putative ABC- transporter (permease protein)	7-25, 30-40, 42-64, 70-77, 85-118, 120-166, 169-199, 202-213, 222-244	A:3	190-203	39, 189
Spy0839	putative glycerophosphodiester phosphodiester	4-11, 15-53, 55-93, 95-113, 120-159, 164-200, 210- 243, 250-258, 261-283, 298-319, 327-340, 356-366, 369-376, 380-386, 394-406, 409-421, 425-435, 442- 454, 461-472, 480-490, 494-505, 507-514, 521-527, 533-544, 566-574	A:7, D:2	385-398	40, 190
Spy0843	cell surface protein	5-36, 66-72, 120-127, 146-152, 159-168, 172-184, 205-210, 221-232, 234-243, 251-275, 295-305, 325- 332, 367-373, 470-479, 482-487, 520-548, 592-600, 605-615, 627-642, 655-662, 664-698, 718-725, 734- 763, 776-784, 798-809, 811-842, 845-852, 867-872, 879-888, 900-928, 933-940, 972-977, 982-1003	A:11, B:3, C:5, D:4, F:50, H:19, G:49, I:112, K:102, L:10, M:3, N:213, O:188, P:310	12-190 276-283 666-806	41, 191
Spy0872	putative secreted 5'- nucleotidase	4-38, 63-68, 100-114, 160-173, 183-192, 195-210, 212-219, 221-238, 240-256, 258-266, 274-290, 301- 311, 313-319, 332-341, 357-363, 395-401, 405-410, 420-426, 435-450, 453-461, 468-475, 491-498, 510- 518, 529-537, 545-552, 585-592, 602-611, 634-639, 650-664	A:6, D:2, F:5, H:14, I:9, K:10, L:1, N:16, O:12	30-80 89-105 111-151	42, 192
Spy0895	histidine protein kinase	7-29, 31-39, 47-54, 63-74, 81-94, 97-117, 122-127, 146-157, 168-192, 195-204, 216-240, 251-259	C:11	195-203	43, 193
Spy0972	putative terminase, large subunit - phage	5-16, 28-34, 46-65, 79-94, 98-105, 107-113, 120-134,	B:2	32-50	44, 194

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<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
		147-158, 163-172, 180-186, 226-233, 237-251, 253-259, 275-285, 287-294, 302-308, 315-321, 334-344, 360-371, 399-412, 420-426			
Spy0981	hypothetical protein - phage associated	8-20, 30-36, 71-79, 90-96, 106-117, 125-138, 141-147, 166-174	A:7, B:2	75-90	45, 195
Spy1008	streptococcal exotoxin H precursor (speH)	4-13, 15-33, 43-52, 63-85, 98-114, 131-139, 146-174, 186-192, 198-206, 227-233	C:11	69-88	46, 196
Spy1032	extracellular hyaluronate lyase	4-22, 29-35, 59-68, 153-170, 213-219, 224-238, 240-246, 263-270, 285-292, 301-321, 327-346, 356-371, 389-405, 411-418, 421-427, 430-437, 450-467, 472-477, 482-487, 513-518, 531-538, 569-576, 606-614, 637-657, 662-667, 673-690, 743-753, 760-767, 770-777, 786-802	B:3, K:3, M:5	96-230 361-491 572-585	47, 197
Spy1054	putative collagen-like protein (SclC)	4-12, 21-36, 48-55, 74-82, 121-127, 195-203, 207-228, 247-262, 269-278, 280-289	A:71, B:13, C:233, D:41, E:163, F:200, G:442, H:129, N:3	102-210	48, 198
Spy1063	putative periplasmic- iron-binding protein	13-20, 23-31, 38-44, 78-107, 110-118, 122-144, 151-164, 176-182, 190-198, 209-216, 219-243, 251-256, 289-304, 306-313	A:4	240-248	49, 199
Spy1162	putative ribonuclease HII	5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260	B:3, C:5	182-198	50, 200
Spy1206	putative ABC transporter	10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504	A:2	41-56	51, 201
Spy1228	Putative lipoprotein	5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333	M:33	202-217	52, 202
Spy1245	putative phosphate ABC transporter	5-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283	E:3, K:3	1-127	53, 203
Spy1315	hypothetical protein	4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718	B:4	297-458	54, 204
Spy1357	protein GRAB (protein G-related	5-43, 92-102, 107-116, 120-130, 137-144, 155-163,	G:27, H:8, K:2,	24-135	55, 205

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
	alpha 2M-binding p	169-174, 193-213	N:4		
SPy1361	putative internalin A precursor	4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253- 260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503- 517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721	F:21, G:26, H:6, K:4, N:5	176-330	56, 206
SPy1371	putative NADP- dependent glyceraldehyde-3- phosphate dehydrogenase	31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199- 205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442- 447, 451-460, 466-472	D:14, H:3	46-62 296-341	57, 207
SPy1375	putative ribonucleotide reductase alpha-c	23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152- 159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436- 442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694- 700, 711-716	A:2	667-684	58, 208
SPy1389	putative alanyl-tRNA synthetase	20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327- 337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652- 672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869	B:2, P:3	258-416	59, 209
SPy1390	putative protease maturation protein	7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202- 211, 217-227, 229-239, 254-262, 271-278, 291-300	A:3, B:2, D:3	278-295	60, 210
SPy1422	putative recombination protein	4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124- 130, 136-144, 156-179, 183-191	C:2	183-195	61, 211
SPy1436	putative deoxyribonuclease	12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241	K:1	63-238	62, 212
SPy1494	hypothetical protein	4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288- 308	G:3, I:5, K:6, M:5, N:10, O:6, P:4	1-141	63, 213
SPy1523	cell division protein	11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223- 235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379	I:2	231-368	64, 214
SPy1536	conserved hypothetical protein	9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165- 186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342	A:19, C:3	247-260	65, 215

- 63 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
Spy1564	conserved hypothetical protein	7-15, 39-45, 58-64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279	C:4	64-72	66, 216
Spy1604	conserved hypothetical protein	4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320- 343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533- 542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831- 836, 859-869, 890-897	B:2, K:2	222-362 756-896	67, 217
Spy1607	conserved hypothetical protein	11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250- 255	D:5	153-170	68, 218
Spy1615	putative late competence protein	4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184- 192, 198-212	C:4	56-73	69, 219
Spy1666	conserved hypothetical protein	4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107- 118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334	D:2	298-312	70, 220
Spy1727	conserved hypothetical protein	7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163- 169, 172-183, 188-200, 206-211, 219-238, 247-254	B:5	141-157	71, 221
Spy1785	putative ATP- dependent DNA helicase	23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210- 224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478- 503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663	D:3	433-440 572-593	72, 222
Spy1798	hypothetical protein	4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164- 169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322- 334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653- 658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895- 903, 928-934, 940-963, 978-986, 1003-1025, 1027- 1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248- 1267	A:12, I:12, K:7, N:17, O:13, P:8	17-319 417-563	73, 223
Spy1801	immunogenic secreted protein precursor homolog	6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-	H:2, I:8, K:6, N:11	46-187	74, 224

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- 64 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
		328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500			
Spy1813	hypothetical protein	4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165- 172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464- 470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771- 777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992	I:16, K:12, N:6	21-244 381-499 818-959	75, 225
Spy1821	putative translation elongation factor EF-P	19-29, 65-75, 90-109, 111-137, 155-165, 169-175	C:6	118-136	76, 226
Spy1916	putative phospho- beta-D-galactosidase	15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281- 287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465	C:8	147-155	77, 227
Spy1972	Pullulanase	11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173- 181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399- 406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647- 654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956- 962, 969-976, 991-999, 1012-1018, 1024-1029, 1035- 1072, 1078-1091, 1142-1161	A:6, I:2, K:5, N:9	74-438	78, 228
Spy1979	streptokinase A precursor	4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295- 305, 315-328, 335-342, 359-365, 389-394, 404-413	I:6, M:3, N:10	156-420	79, 229
Spy1983	collagen-like surface protein (ScID)	4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276- 285, 304-310, 313-318, 322-343	A:81, B:24, F:19, G:41, I:2, K:2	79-348	80, 230
Spy1991	anthranilate synthase component II	12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168	D:2	53-70	81, 231
Spy2000	surface lipoprotein	4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266- 281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514- 522	B:3, N:2	183-341	82, 232
Spy2006	hypothetical protein	4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171- 186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-	A:15, B:9, C:5, D:3, F:18, G:25, H:5, M:10, N:5	92-231 618-757	83, 233

- 65 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
		445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668- 683, 717-723, 765-771, 781-788, 792-806, 812-822			
Spy2009	hypothetical protein	11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332- 338, 341-346, 351-358, 362-372	B:2, I:7, K:7, P:2	41-170	84, 234
Spy2010	C5A peptidase precursor	6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194- 200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442- 448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686- 693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895- 901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154- 1164, 1166-1174	A:47, B:10, D:3, F:48, G:20, H:4, I:6, K:13, M:5, N:10, P:6	20-487 757-1153	85, 235
Spy2016	inhibitor of complement (Sic)	10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305	A:11, B:38, C:16, F:56, G:27, H:13, K:5, N:2, O:3, P:14	26-74 91-100 105-303	86, 236
Spy2018	M1-Protein	9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353- 359, 377-383, 389-406, 420-426, 460-480	A:316, B:26, C:107, D:12, E:49, F:88, G:118, H:6, I:7, K:2, M:48, N:43	10-223 231-251 264-297 312-336	87, 237
Spy2025	immunogenic secreted protein precursor	5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394- 400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537	F:7, G:16, H:7, K:63, L:2, N:18, O:42	22-344	88, 238
Spy2039	pyrogenic exotoxin B	5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263- 271, 285-291, 299-305, 326-346, 368-375, 390-395	I:15, K:3, N:12	1-151	89, 239
Spy2043	mitogenic factor MF1 (speF)	6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153- 159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445- 451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688- 696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-	K:1	91-263	90, 240

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<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
		976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756			
Spy2059	penicillin-binding protein 2a	4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775	D:2, E:2	261-272	91, 241
Spy2110	putative anaerobic ribonucleoside- triphosphate reductase	4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701	E:7	541-551	92, 242
Spy2127	Hypothetical protein	6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252	E:6, P:2	84-254	93, 243
Spy2191	hypothetical protein	13-30, 71-120, 125-137, 139-145, 184-199	C:20, E:3, M:5	61-78	94, 244
Spy2211	transmembrane protein	9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855	A:3	568-580	95, 245
ARF0450	no homology	11-21, 29-38	A:11	5-17	96, 246
ARF0569	no homology	none	A:2	2-9	97, 247
ARF0694	no homology	4-10, 16-28	B:7, D:3, M:3	7-18 26-34	98, 248
ARF0700	No homology	10-16	M:11	1-15	99, 249
ARF1007	No homology	none	B:2	4-11	100, 250
ARF1145	No homology	4-40, 42-51	C:9	37-53	101, 251
ARF1208	no homology	4-21	C:1	22-29	102, 252

- 67 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogenic region (aa)	Seq. ID (DNA, Prot.)
ARF1262	No homology	none	D:2	2-11	103, 253
ARF1294	39% with SA0131 (first 28 aa of 67 aa protein)	9-17, 32-44	D:2	1-22	104, 254
ARF1316	no homology	19-25, 27-32	E:19	15-34	105, 255
ARF1352	38% with SA1142 (aa 265-295 of 358 protein)	4-12, 15-22	D:4	11-33	106, 256
ARF1481	No homology	10-17, 24-30, 39-46, 51-70	C:2	51-61	107, 257
ARF1557	No homology	none	C:2	6-19	108, 258
ARF1629	36% with SP0069 (aa 139-169 of 211 aa protein)	6-11, 21-27, 31-54	A:4, B:6	11-29	109, 259
ARF1654	no homology	4-10, 13-45	A:2	11-35	110, 260
ARF2027	no homology	4-14, 23-32	D:2	11-35	111, 261
ARF2093	putative elongation factor TS	14-39, 45-51	C:3	15-29	112, 262
ARF2207	38% with SP1006 (aa 7-37 of 67 aa protein)	4-11, 14-28	A:117	4-17	113, 263
CRF0038	No homology	4-16	C:6	2-16	114, 264
CRF0122	No homology	4-10, 12-19, 39-50	C:2	6-22	115, 265
CRF0406	no homology	none	D:5, E:11	2-13	116, 266
CRF0416	No homology	4-11, 22-65	C:42	3-19	117, 267
CRF0507	No homology	17-23, 30-35, 39-46, 57-62	B:3, C:4	30-49	118, 268
CRF0549	No homology	4-19	C:6	14-22	119, 269
CRF0569	No homology	none	N:35	2-9	120, 270
CRF0628	34% (14 of 41) with conserved hypothetical protein of <i>P. aeruginosa</i>	7-18, 30-43	A:3	4-12	121, 271
CRF0727	40% (16 of 40) with transcriptional regulator of <i>S.</i> <i>pneumoniae</i> (70 aa, SP0584)	4-30, 39-47	N:6	5-22	122, 272
CRF0742	33% with SA0422 (aa 11-37 of 42 aa protein, listed as 280 aa protein)	6-15	D:7, E:12	14-29	123, 273
CRF0784	No homology	4-34	N:9	23-35	124, 274
CRF0854	No homology	4-36, 44-57, 65-72	N:14	14-27	125, 275
CRF0875	no homology	4-18	A:4, D:1	11-20	126, 276
CRF0907	Homology to lysosomal trafficking regulator LYST [Homo sapiens]	none	A:39	5-19	127, 277

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- 68 -

<i>S. pyogenes</i> antigenic protein	Putative function (by homology)	predicted immunogenic aa**	No. of selected clones per ORF and screen	Location of identified immunogeni c region (aa)	Seq. ID (DNA, Prot.)
CRF0979	no homology	18-36	D:21	5-20	128, 278
CRF1068	no homology	4-10, 19-34, 41-84, 96-104	C:1, D:3	50-63	129, 279
CRF1152	No homology	4-9, 19-27	C:15	8-21	130, 280
CRF1203	No homology	4-16, 18-28	N:3	22-30	131, 281
CRF1225	No homology	4-15	C:8	21-35	132, 282
CRF1236	No homology	4-17	N:3	3-13	133, 283
CRF1362	No homology	4-12	C:6	4-18	134, 284
CRF1524	no homology	4-24, 31-36	D:3	29-45	135, 285
CRF1525	No homology	12-22, 34-49	C:2	21-32	136, 286
CRF1527	no homology	4-17	D:4, E:1	22-32	137, 287
CRF1588	No homology	4-16, 25-42	C:2	7-28	138, 288
CRF1649	No homology	4-10	C:3	7-20	139, 289
CRF1749	No homology	4-11, 16-36, 39-54	C:15	28-44	140, 290
CRF1903	no homology	5-20, 29-54	A:14	14-29	141, 291
CRF1964	no homology	24-33	A:8	10-22	142, 292
CRF2055	no homology	10-51, 54-61	B:1, F:12, H:14	43-64	143, 293
CRF2091	No homology	7-13	C:2	2-17	144, 294
CRF2096	No homology	11-20	C:4	6-20	145, 295
CRF2104	No homology	4-30, 34-41	C:2	19-28	146, 296
CRF2116	No homology	n.d.		11-21	147, 297
CRF2153	no homology	4-16, 21-26	F:2	9-38	148, 298
NRF0001	ARF in Oligo ABC transporter (not annotated by TIGR), 33% with SA0643 (aa 107-162 of 469 aa protein)	4-12, 15-27, 30-42, 66-72	A:7, B:1	10-24	149, 299
NRF0003	no homology	8-17	A:23	11-20	150, 300

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Table 2-1

Peptide	Peptide sequence	Seq. ID	location in protein (aa)	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22	P23	P24	P25	P26	P27	P28	P29	P30	P31	P32	P33	P34	P35	P36	P37	P38	P39	P40	P41	P42	P43	P44	P45	P46	P47	P48	P49	P50	P51	P52	P53	P54	P55	P56	P57	P58	P59	P60	P61	P62	P63	P64	P65	P66	P67	P68	P69	P70	P71	P72	P73	P74	P75	P76	P77	P78	P79	P80	P81	P82	P83	P84	P85	P86	P87	P88	P89	P90	P91	P92	P93	P94	P95	P96	P97	P98	P99	P100	P101	P102	P103	P104	P105	P106	P107	P108	P109	P110	P111	P112	P113	P114	P115	P116	P117	P118	P119	P120	P121	P122	P123	P124	P125	P126	P127	P128	P129	P130	P131	P132	P133	P134	P135	P136	P137	P138	P139	P140	P141	P142	P143	P144	P145	P146	P147	P148	P149	P150	P151	P152	P153	P154	P155	P156	P157	P158	P159	P160	P161	P162	P163	P164	P165	P166	P167	P168	P169	P170	P171	P172	P173	P174	P175	P176	P177	P178	P179	P180	P181	P182	P183	P184	P185	P186	P187	P188	P189	P190	P191	P192	P193	P194	P195	P196	P197	P198	P199	P200	P201	P202	P203	P204	P205	P206	P207	P208	P209	P210	P211	P212	P213	P214	P215	P216	P217	P218	P219	P220	P221	P222	P223	P224	P225	P226	P227	P228	P229	P230	P231	P232	P233	P234	P235	P236	P237	P238	P239	P240	P241	P242	P243	P244	P245	P246	P247	P248	P249	P250	P251	P252	P253	P254	P255	P256	P257	P258	P259	P260	P261	P262	P263	P264	P265	P266	P267	P268	P269	P270	P271	P272	P273	P274	P275	P276	P277	P278	P279	P280	P281	P282	P283	P284	P285	P286	P287	P288	P289	P290	P291	P292	P293	P294	P295	P296	P297	P298	P299	P300	P301	P302	P303	P304	P305	P306	P307	P308	P309	P310	P311	P312	P313	P314	P315	P316	P317	P318	P319	P320	P321	P322	P323	P324	P325	P326	P327	P328	P329	P330	P331	P332	P333	P334	P335	P336	P337	P338	P339	P340	P341	P342	P343	P344	P345	P346	P347	P348	P349	P350	P351	P352	P353	P354	P355	P356	P357	P358	P359	P360	P361	P362	P363	P364	P365	P366	P367	P368	P369	P370	P371	P372	P373	P374	P375	P376	P377	P378	P379	P380	P381	P382	P383	P384	P385	P386	P387	P388	P389	P390	P391	P392	P393	P394	P395	P396	P397	P398	P399	P400	P401	P402	P403	P404	P405	P406	P407	P408	P409	P410	P411	P412	P413	P414	P415	P416	P417	P418	P419	P420	P421	P422	P423	P424	P425	P426	P427	P428	P429	P430	P431	P432	P433	P434	P435	P436	P437	P438	P439	P440	P441	P442	P443	P444	P445	P446	P447	P448	P449	P450	P451	P452	P453	P454	P455	P456	P457	P458	P459	P460	P461	P462	P463	P464	P465	P466	P467	P468	P469	P470	P471	P472	P473	P474	P475	P476	P477	P478	P479	P480	P481	P482	P483	P484	P485	P486	P487	P488	P489	P490	P491	P492	P493	P494	P495	P496	P497	P498	P499	P500	P501	P502	P503	P504	P505	P506	P507	P508	P509	P510	P511	P512	P513	P514	P515	P516	P517	P518	P519	P520	P521	P522	P523	P524	P525	P526	P527	P528	P529	P530	P531	P532	P533	P534	P535	P536	P537	P538	P539	P540	P541	P542	P543	P544	P545	P546	P547	P548	P549	P550	P551	P552	P553	P554	P555	P556	P557	P558	P559	P560	P561	P562	P563	P564	P565	P566	P567	P568	P569	P570	P571	P572	P573	P574	P575	P576	P577	P578	P579	P580	P581	P582	P583	P584	P585	P586	P587	P588	P589	P590	P591	P592	P593	P594	P595	P596	P597	P598	P599	P600	P601	P602	P603	P604	P605	P606	P607	P608	P609	P610	P611	P612	P613	P614	P615	P616	P617	P618	P619	P620	P621	P622	P623	P624	P625	P626	P627	P628	P629	P630	P631	P632	P633	P634	P635	P636	P637	P638	P639	P640	P641	P642	P643	P644	P645	P646	P647	P648	P649	P650	P651	P652	P653	P654	P655	P656	P657	P658	P659	P660	P661	P662	P663	P664	P665	P666	P667	P668	P669	P670	P671	P672	P673	P674	P675	P676	P677	P678	P679	P680	P681	P682	P683	P684	P685	P686	P687	P688	P689	P690	P691	P692	P693	P694	P695	P696	P697	P698	P699	P700	P701	P702	P703	P704	P705	P706	P707	P708	P709	P710	P711	P712	P713	P714	P715	P716	P717	P718	P719	P720	P721	P722	P723	P724	P725	P726	P727	P728	P729	P730	P731	P732	P733	P734	P735	P736	P737	P738	P739	P740	P741	P742	P743	P744	P745	P746	P747	P748	P749	P750	P751	P752	P753	P754	P755	P756	P757	P758	P759	P760	P761	P762	P763	P764	P765	P766	P767	P768	P769	P770	P771	P772	P773	P774	P775	P776	P777	P778	P779	P780	P781	P782	P783	P784	P785	P786	P787	P788	P789	P790	P791	P792	P793	P794	P795	P796	P797	P798	P799	P800	P801	P802	P803	P804	P805	P806	P807	P808	P809	P810	P811	P812	P813	P814	P815	P816	P817	P818	P819	P820	P821	P822	P823	P824	P825	P826	P827	P828	P829	P830	P831	P832	P833	P834	P835	P836	P837	P838	P839	P840	P841	P842	P843	P844	P845	P846	P847	P848	P849	P850	P851	P852	P853	P854	P855	P856	P857	P858	P859	P860	P861	P862	P863	P864	P865	P866	P867	P868	P869	P870	P871	P872	P873	P874	P875	P876	P877	P878	P879	P880	P881	P882	P883	P884	P885	P886	P887	P888	P889	P890	P891	P892	P893	P894	P895	P896	P897	P898	P899	P900	P901	P902	P903	P904	P905	P906	P907	P908	P909	P910	P911	P912	P913	P914	P915	P916	P917	P918	P919	P920	P921	P922	P923	P924	P925	P926	P927	P928	P929	P930	P931	P932	P933	P934	P935	P936	P937	P938	P939	P940	P941	P942	P943	P944	P945	P946	P947	P948	P949	P950	P951	P952	P953	P954	P955	P956	P957	P958	P959	P960	P961	P962	P963	P964	P965	P966	P967	P968	P969	P970	P971	P972	P973	P974	P975	P976	P977	P978	P979	P980	P981	P982	P983	P984	P985	P986	P987	P988	P989	P990	P991	P992	P993	P994	P995	P996	P997	P998	P999	P1000	P1001	P1002	P1003	P1004	P1005	P1006	P1007	P1008	P1009	P1010	P1011	P1012	P1013	P1014	P1015	P1016	P1017	P1018	P1019	P1020	P1021	P1022	P1023	P1024	P1025	P1026	P1027	P1028	P1029	P1030	P1031	P1032	P1033	P1034	P1035	P1036	P1037	P1038	P1039	P1040	P1041	P1042	P1043	P1044	P1045	P1046	P1047	P1048	P1049	P1050	P1051	P1052	P1053	P1054	P1055	P1056	P1057	P1058	P1059	P1060	P1061	P1062	P1063	P1064	P1065	P1066	P1067	P1068	P1069	P1070	P1071	P1072	P1073	P1074	P1075	P1076	P1077	P1078	P1079	P1080	P1081	P1082	P1083	P1084	P1085	P1086	P1087	P1088	P1089	P1090	P1091	P1092	P1093	P1094	P1095	P1096	P1097	P1098	P1099	P1100	P1101	P1102	P1103	P1104	P1105	P1106	P1107	P1108	P1109	P1110	P1111	P1112	P1113	P1114	P1115	P1116	P1117	P1118	P1119	P1120	P1121	P1122	P1123	P1124	P1125	P1126	P1127	P1128	P1129	P1130	P1131	P1132	P1133	P1134	P1135	P1136	P1137	P1138	P1139	P1140	P1141	P1142	P1143	P1144	P1145	P1146	P1147	P1148	P1149	P1150	P1151	P1152	P1153	P1154	P1155	P1156	P1157	P1158	P1159	P1160	P1161	P1162	P1163	P1164	P1165	P1166	P1167	P1168	P1169	P1170	P1171	P1172	P1173	P1174	P1175	P1176	P1177	P1178	P1179	P1180	P1181	P1182	P1183	P1184	P1185	P1186	P1187	P1188	P1189	P1190	P1191	P1192	P1193	P1194	P1195	P1196	P1197	P1198	P1199	P1200	P1201	P1202	P1203	P1204	P1205	P1206	P1207	P1208	P1209	P1210	P1211	P1212	P1213	P1214	P1215	P1216	P1217	P1218	P1219	P1220	P1221	P1222	P1223	P1224	P1225	P1226	P1227	P1228	P1229	P1230	P1231	P1232	P1233	P1234	P1235	P1236	P1237	P1238	P1239	P1240	P1241	P1242	P1243	P1244	P1245	P1246	P1247	P1248	P1249	P1250	P1251	P1252	P1253	P1254	P1255	P1256	P1257	P1258	P1259	P1260	P1261	P1262	P1263	P1264	P1265	P1266	P1267	P1268	P1269	P1270	P1271	P1272	P1273	P1274	P1275	P1276	P1277	P1278	P1279	P1280	P1281	P1282	P1283	P1284	P1285	P1286	P1287	P1288	P1289	P1290	P1291	P1292	P1293	P1294	P1295	P1296	P1297	P1298	P1299	P1300	P1301	P1302	P1303	P1304	P1305	P1306	P1307	P1308	P1309	P1310	P1311	P1312	P1313	P1314	P1315	P1316	P1317	P1318	P1319	P1320	P1321	P1322	P1323	P1324	P1325	P1326	P1327	P1328	P1329	P1330	P1331	P1332	P1333	P1334	P1335	P1336	P1337	P1338	P1339	P1340	P1341	P1342	P1343	P1344	P1345	P1346	P1347	P1348	P1349	P1350	P1351	P1352	P1353	P1354	P1355	P1356	P1357	P1358	P1359	P1360	P1361	P1362	P1363	P1364	P1365	P1366	P1367	P1368	P1369	P1370	P1371	P1372	P1373	P1374	P1375	P1376	P1377	P1378	P1379	P1380	P1381	P1382	P1383	P1384	P1385	P1386	P1387	P1388	P1389	P1390	P1391	P1392	P1393	P1394	P1395	P1396	P1397	P1398	P1399	P1400	P1401	P1402	P1403	P1404	P1405	P1406	P1407	P1408	P1409	P1410	P1411	P1412	P1413	P1414	P1415	P1416	P1417	P1418	P1419	P1420	P1421	P1422	P1423	P1424	P1425	P1426	P1427	P1428	P1429	P1430	P1431	P1432	P1433	P1434	P1435	P1436	P1437	P1438	P1439	P1440	P1441	P1442	P1443	P1444	P1445	P1446	P1447	P1448	P1449	P1450	P1451	P1452	P1453	P1454	P1455	P1456	P1457	P1458	P1459	P1460	P1461	P1462	P1463	P1464	P1465	P1466	P1467	P1468	P1469	P1470	P1471	P1472	P1473	P1474	P14

33	9	4	4	1
24	15	3	1	
30	7	8	1	1
6	5			
12	12			
17	15	1		
17	11	3		
10	7		1	
20	9	4	1	
15	12	1		
3	3			
41	5	3	10	
19	14	1	1	
23	14	3	2	
14	14			
5	5			
1	1			
1	1			
5	3	1		
13	9	2		
4	4			
6	6			
9	7	1		
5	5			
31	11	4	4	
2	2			
25	13	3	2	
25	15	2	2	
17	15	1		
8	8			
7	7			
19	10	3	1	
14	10	2		
27	12	3	3	
19	13	3		
17	15	1		
28	15	5	1	
15	11	2		
37	11	5	4	1
26	14	3	2	
20	14	3		
12	6		2	
21	11	5		
17	12	1	1	
17	13	2		
18	12	3		
12	10	1		
2	2			
20	16	2		
23	11	1	2	1
12	10	1		
34	10	10		1
27	12	6	1	
18	16	1		
15	12		1	
15	9	3		
42	5	14	3	
24	16	4		
22	20	1		
20	16	2		
11	11			
23	17	3		
12	12			
13	11	1		
26	14	6		
23	9	7		
30	11	3	3	1
45	6	7	7	1
51	6	6	7	3
22	8	4	2	
45	5	12	3	2
18	14	2		
21	13	4		
42	8	8	6	
17	11	3		
27	16	4	1	
8	6		1	
10	10			
12	10	1		

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Table 3: Gene distribution in *S. pyogenes* strains.

ORF	Common name	Gene distribution (present of 50)	Amino acid substitutions (in strain M89)	Homology (SP/EC)	Seq. ID (DNA, Prot.)
Spy0012	Hypothetical protein	50	3/302	SP0010 - 40%/None	1, 151
Spy0019	putative secreted protein (cell division and antibiotic tolerance)	50	0/300	SP2216 - 44-49%/None	2, 152
Spy0025	putative phosphoribosylformylglycine midine synthase II	38	0/303	SP0045 - 85%/24%	3, 153
Spy0031	putative choline binding protein	50	0/297	SP2201 - 42% (cbpD)/None	4, 154
Spy0103	putative competence protein	50	0/81	SP2051 - 41%/None	5, 155
Spy0112	putative pyrroline carboxylate reductase	50	3/235	SP0933 - 32%/34%	6, 156
Spy0115	putative glutamyl- aminopeptidase	50	6/306	SP1865 - 76%/30%	7, 157
Spy0166	hypothetical protein	50	n.d.	None/None	8, 158
Spy0167	Streptolysin O	50	7/300	SP1923 - 40% (Pneumolysin)/None	9, 159
Spy0168	hypothetical protein	8	19/126	None/None	10, 160
Spy0171	hypothetical protein	18	8/95	None/None	11, 161
Spy0183	putative glycine betaine/proline ABC transporter	50	0/297	SP0151 - 39%/48%	12, 162
Spy0230	putative ABC transporter (ATP-binding protein)	50	1/299	SP2073 - 64%/32%	13, 163
Spy0269	putative surface exclusion protein	50	1/303	None/None	14, 164
Spy0287	conserved hypothetical protein	50	1/307	SP0868 - 71%/19%	15, 165
Spy0292	penicillin-binding protein (D- alanine-D-alanine car	50	1/359	SP0872 - 47%/27%	16, 166
Spy0295	oligopeptidase	50	2/269	SP1889 - 69%/24%	17, 167
Spy0348	putative aminodeoxychorismate lyase	50	1/307	SP1518 - 47%/25%	18, 168
Spy0416	putative cell envelope serine proteinase	50	4/314	SP0641 - 22%/None	19, 169
Spy0430	hypothetical protein	13	0/165#	None/None	20, 170
Spy0433	hypothetical protein	21 (27/49) ¹	2/174#	None/None	21, 171
Spy0437	Hypothetical protein	19 (34/49) ¹	0/106#	None/None	22, 172
Spy0469	putative 42 kDa protein	50	6/313	SP2063 - 44% (LysM protein)/None	23, 173
Spy0488	hypothetical protein	50	9/178	None/None	24, 174
Spy0515	Putative sugar transferase	50	n.d.	SP1075 - 26%/None	25, 175
Spy0580	conserved hypothetical protein	50	0/297	SP0908 - 72%/43%	26, 176
Spy0621	conserved hypothetical protein	50	n.d.	SP1290 - 72%/None	27, 177
Spy0630	putative PTS dependent N- acetyl-galactosamine-IIIC	50	n.d.	SP0324 - 79%/30%	28, 178

- 72 -

Spy0681	hypothetical protein, phage associated	27	2/303#	None/None	29, 179
Spy0683	putative minor capsid protein, phage associated	25	1/233	None/None	30, 180
Spy0702	Hypothetical protein	22	n.d.	None/None	31, 181
Spy0710	conserved hypothetical protein, phage associated	32	51/286#	None/36% in 122 of 313aa	32, 182
Spy0711	pyrogenic exotoxin C precursor, phage associated (speC)	17	1/225	None/None	33, 183
Spy0720	conserved hypothetical protein	50	2/270	SP1298 - 60% (DHH 1 protein)/None	34, 184
Spy0727	Putative DNA gyrase, subunit B	n.d.	n.d.	SP0806 - 80%/46%	35, 185
Spy0737	putative extracellular matrix binding protein	29 (48/49) ¹	0/466#	None/27% in 340 of 421aa	36, 186
Spy0747	extracellular nuclease	50	0/179	None/None	37, 187
Spy0777	putative ATP-dependent exonuclease, subunit A	50	2/306	SP1152 - 48%/22%	38, 188
Spy0789	putative ABC-transporter (permease protein)	50	1/231	None/None	39, 189
Spy0839	putative glycerophosphodiester phosphodiester	50	1/301	SP0994 - 24%/31% in 121 of 358aa	40, 190
Spy0843	cell surface protein	50	3/312	None/None	41, 191
Spy0872	putative secreted 5'-nucleotidase	50	2/309	None/27% in 274 of 647aa	42, 192
Spy0895	histidine protein kinase	50	0/244	None/None	43, 193
Spy0972	putative terminase, large subunit - phage	28	1/314#	None/None	44, 194
Spy0981	hypothetical protein - phage associated	23	n.d.	None/None	45, 195
Spy1008	streptococcal exotoxin H precursor (speH)	15 (14/49) ¹	1/223#	None/None	46, 196
Spy1032	extracellular hyaluronate lyase	50 (175 of 175, Hynes 2000)	3/311	SP0314 - 51%/None	47, 197
Spy1054	putative collagen-like protein (SciC)	26, (45/49) ¹ (50 of 50, but varying number of repeats; Lukomski, 2001)	n.d.	None/None	48, 198
Spy1063	putative periplasmic-iron-binding protein	49/50 (49/49) ¹	2/292#	SP0243 - 52%, iron ABC transporter/26% in 161 of 348aa	49, 199
Spy1162	putative ribonuclease HII	50	3/240	SP1156 - 67%/46%	50, 200
Spy1206	putative ABC transporter	50	1/302	SP0770 - 81%/30%	51, 201
Spy1228	Putative lipoprotein	49	n.d.	SP0845-57%/None	52, 202
Spy1245	Putative ABC transporter	50	n.d.	SP1400-64%/None	53, 203
Spy1315	hypothetical protein	50	4/305	SP1241 - 64%/32%	54, 204
Spy1357	protein GRAB (protein G-related alpha 2M-binding protein)	49; 11 of 12 strains (Rasmussen, 1999)	9/226; insertion of 28 aa	None/None	55, 205
Spy1361	putative internalin A precursor	50	7/295	SP1004 - 26% in 283 of 1039/None	56, 206
Spy1371	putative NADP-dependent glyceraldehyde-3-phosphate dehydrogenase	50	2/308	SP1119 - 71%/34%	57, 207
Spy1375	putative ribonucleotide reductase alpha-c	50	4/304	SP1179 - 85%/49%	58, 208

- 73 -

Spy1389	putative alanyl-tRNA synthetase	50	0/309	SP1383 - 74%/40%	59, 209
Spy1390	putative protease maturation protein	50	0/232	SP0981 - 42%/None	60, 210
Spy1422	putative recombination protein	n.d.	n.d.	SP1672 - 88%/64%	61, 211
Spy1436	putative deoxyribonuclease	25	0/243#	SP1964 - 29% in 181 of 274aa/None	62, 212
Spy1494	hypothetical protein	50	13/282	None/None	63, 213
Spy1523	cell division protein	49	2/329	SP0690 - 27%/None	64, 214
Spy1536	conserved hypothetical protein	50	9/280	SP1967 - 57%/None	65, 215
Spy1564	conserved hypothetical protein	39	n.d.	None/None	66, 216
Spy1604	conserved hypothetical protein	50	1/233	SP2143 - 47%/28%	67, 217
Spy1607	conserved hypothetical protein	50	0/241	SP1902 - 55%/None	68, 218
Spy1615	putative late competence protein	50	2/204	SP2207 - 41%/None	69, 219
Spy1666	conserved hypothetical protein	50	2/305	SP0334 (yltC) - 78%/40%	70, 220
Spy1727	conserved hypothetical protein	50	0/237	SP0549 - 53%/None	71, 221
Spy1785	putative ATP-dependent DNA helicase	50	1/306	SP1697 - 71%/37%	72, 222
Spy1798	hypothetical protein	50	2/128	None/None	73, 223
Spy1801	immunogenic secreted protein precursor homolog	50	6/313; insertion of 6 aa	SP2216 - 33% in 119 of 392aa/None	74, 224
Spy1813	hypothetical protein	46	47/433; insertion of 9, deletion of 1 aa	None/None	75, 225
Spy1821	putative translation elongation factor EF-P	n.d.	n.d.	SP0435 - 94%/45%	76, 226
Spy1916	putative phospho-beta-D-galactosidase	n.d.	n.d.	SP1184 - 91%/83%	77, 227
Spy1972	Pullulanase	50	1/233	SP0268 - 53%, SP1118 - 29%/25% in 352 of 657aa	78, 228
Spy1979	streptokinase A precursor	50	20.1% identical of 309#	None/None	79, 229
Spy1983	collagen-like surface protein (ScID)	50, (50 of 50, but size variation according to Lukomski, 2000)	n.d.	None/None	80, 230
Spy1991	anthranilate synthase component II	50	1/170	SP1816 - 58%/47%	81, 231
Spy2000	surface lipoprotein	50	0/307	None/27% in 389 of 524aa	82, 232
Spy2006	hypothetical protein	50	0/234	SP1003 - 36%, SP1174 - 37%, SP1004 - 33%, SP1175 - 48%/None	83, 233
Spy2009	hypothetical protein	39 (38/49) ¹	58/344; insertion of 36, deletion of 4 aa	None/None	84, 234
Spy2010	C5A peptidase precursor	n.d.	n.d.	SP0641 - 23% in 783 of 2140aa/None	85, 235
Spy2016	inhibitor of complement (Sic)	47; mainly in M1 strains (Reid 2001)	11/269#	None/None	86, 236
Spy2018	M1-Protein	n.d.	n.d.	None/None	87, 237
Spy2025	immunogenic secreted protein precursor	50	3/296	SP2216 - 31% in 138 of 392aa/None	88, 238
Spy2039	pyrogenic exotoxin B	n.d.	n.d.	None/None	89, 239

【 0 0 7 4 】

Spy2043	mitogenic factor MF1 (speF)	50	0/247	None/None	90, 240
Spy2059	penicillin-binding protein 2a	50	0/293	SP2010 - 55% (pbp2A)/30% in 539 of 844aa	91, 241
Spy2110	putative anaerobic ribonucleoside-triphosphate reductase	50	0/311	SP0202 - 80% (nrdD)/50%	92, 242
Spy2127	Hypothetical protein	1	n.d.	None/None	93, 243
Spy2191	hypothetical protein	50	1/175	None/None	94, 244
Spy2211	transmembrane protein	50	2/281	SP2231 - 43%/None	95, 245
ARF0450	hypothetical protein	50	5/191	None/None	96, 246
ARF0569	hypothetical protein	n.d.	n.d.	None/None	97, 247
ARF0694	hypothetical protein	23	1/122#	None/None	98, 248
ARF0700	hypothetical protein	n.d.	n.d.	None/None	99, 249
ARF1007	hypothetical protein	n.d.	n.d.	None/None	100, 250
ARF1145	hypothetical protein	n.d.	n.d.	None/None	101, 251
ARF1208	hypothetical protein	n.d.	n.d.	None/None	102, 252
ARF1262	hypothetical protein	n.d.	n.d.	None/None	103, 253
ARF1294	hypothetical protein	50	1/186	39% with SA0131 (first 28 aa of 67 aa protein)	104, 254
ARF1316	hypothetical protein	n.d.	n.d.	None/None	105, 255
ARF1352	hypothetical protein	n.d.	n.d.	38% with SA1142 (aa 265-295 of 358 protein)	106, 256
ARF1481	hypothetical protein	n.d.	n.d.	None/None	107, 257
ARF1557	hypothetical protein	n.d.	n.d.	None/None	108, 258
ARF1629	hypothetical protein	n.d.	n.d.	36% with SP0069 (aa 139-169 of 211 aa protein)	109, 259
ARF1654	hypothetical protein	n.d.	n.d.	None/None	110, 260
ARF2027	hypothetical protein	n.d.	n.d.	None/None	111, 261
ARF2093	hypothetical protein	n.d.	n.d.	None/None	112, 262
ARF2207	hypothetical protein	50	n.d.	38% with SP1006 (aa 7-37 of 67 aa protein)	113, 263
CRF0038	hypothetical protein	n.d.	n.d.	None/None	114, 264
CRF0122	hypothetical protein	n.d.	n.d.	None/None	115, 265
CRF0406	hypothetical protein	n.d.	n.d.	None/None	116, 266
CRF0416	hypothetical protein	n.d.	n.d.	None/None	117, 267
CRF0507	hypothetical protein	n.d.	n.d.	None/None	118, 268
CRF0549	hypothetical protein	n.d.	n.d.	None/None	119, 269
CRF0569	hypothetical protein	n.d.	n.d.	None/None	120, 270
CRF0628	hypothetical protein	n.d.	n.d.	None/None	121, 271
CRF0727	hypothetical protein	n.d.	n.d.	40% with SP0584 (aa21-60 of 70aa protein)	122, 272
CRF0742	hypothetical protein	n.d.	n.d.	33% with SA0422 (aa 11-37 of 42 aa protein, listed as 280 aa protein)	123, 273
CRF0784	hypothetical protein	n.d.	n.d.	None/None	124, 274

- 75 -

CRF0854	hypothetical protein	n.d.	n.d.	None/None	125, 275
CRF0875	hypothetical protein	n.d.	n.d.	None/None	126, 276
CRF0907	hypothetical protein	n.d.	n.d.	Homology to lysosomal trafficking regulator LYST [Homo sapiens]	127, 277
CRF0979	hypothetical protein	n.d.	n.d.	None/None	128, 278
CRF1068	hypothetical protein	50	0/148	None/None	129, 279
CRF1152	hypothetical protein	n.d.	n.d.	None/None	130, 280
CRF1203	hypothetical protein	n.d.	n.d.	None/None	131, 281
CRF1225	hypothetical protein	n.d.	n.d.	None/None	132, 282
CRF1236	hypothetical protein	n.d.	n.d.	None/None	133, 283
CRF1362	hypothetical protein	n.d.	n.d.	None/None	134, 284
CRF1524	hypothetical protein	n.d.	n.d.	None/None	135, 285
CRF1525	hypothetical protein	n.d.	n.d.	None/None	136, 286
CRF1527	hypothetical protein	n.d.	n.d.	None/None	137, 287
CRF1588	hypothetical protein	n.d.	n.d.	None/None	138, 288
CRF1649	hypothetical protein	n.d.	n.d.	None/None	139, 289
CRF1749	hypothetical protein	n.d.	n.d.	None/None	140, 290
CRF1903	hypothetical protein	50	0/140	None/None	141, 291
CRF1964	hypothetical protein	n.d.	n.d.	None/None	142, 292
CRF2055	hypothetical protein	n.d.	n.d.	None/None	143, 293
CRF2091	hypothetical protein	n.d.	n.d.	None/None	144, 294
CRF2096	hypothetical protein	n.d.	n.d.	None/None	145, 295
CRF2104	hypothetical protein	n.d.	n.d.	None/None	146, 296
CRF2116	hypothetical protein	n.d.	n.d.	None/None	147, 297
CRF2153	hypothetical protein	n.d.	n.d.	None/None	148, 298
NRF0001	hypothetical protein	50	0/130	ARF in Oligo ABC transporter (not annotated by TIGR), 33% with SA0643 (aa 107-162 of 469 aa protein)	149, 299
NRF0003	hypothetical protein	n.d.	n.d.	None/None	150, 300

【 0 0 7 6 】

Table 4: Recombinant proteins used for immunisation experiments in NMRI mice.

ORF	Length (amino acids)	Amino acids ^A		Solubility	Protection ^B	Total size of the fragment cloned (Kbp)
		From	to			
Spy0031	374	39	374	Insoluble	20 % (10 %, 40 %)	1.008
Spy0103	108	2	108		50% (10%, 80%)	0.321
Spy 0269	873	36	873	Soluble	40% (40%, 70%) ^c	2.511
<i>Spy 0292</i>	<i>410</i>	22	410	<i>Insoluble</i>	70% (10%, 80%)	1.164
<i>Spy0416A</i>	<i>1647</i>	33	867	<i>Soluble</i>	50 % (10 %, 40 %)	2.502
Spy0416B	1647	736	1617	Solubilized	0 % (0%, 40 %)	2.646
<i>Spy0720</i>	313	2	313	<i>Insoluble</i>	60% (10%, 80%)	0.939
<i>Spy0872</i>	<i>670</i>	27	640	Solubilized	60% (10%, 80%)	1.839
Spy1245	288	49	288	Soluble	20 % (10 %, 40 %)	0.717
Spy1357	217	33	186	Soluble	40 % (30%, 90 %)	0.459
Spy1361	792	22	792	Soluble	60 % (30%, 90 %)	2.31
<i>Spy1390</i>	351	21	351		60% (10%, 80%)	0.99
Spy1536	345	31	345		20 % (0%, 40 %)	0.942
Spy1607	258	2	258		40 % (10 %, 40 %)	0.771
Spy1666	337	22	337	Soluble	50 % (30%, 90 %)	0.945
Spy1972	1165	45	500		40 % (30%, 90 %)	1.365
Spy2000	542	24	542	Soluble	20 % (30%, 90 %)	1.554
Spy2025	541	27	541		40 % (40%, 70%)	1.542
Spy2191	204	36	204		50% (10%, 80%)	0.504

【 0 0 7 7 】

Table 5: Variability of antigens in strains of *S. pyogenes*.

Antigen name	Seq ID	Residue in Antigen ^A	Residue number	Amino acid variations ^B
Spy0031	154	G	126	D
		A	192	S
		V	233	I
		D	328	N
		I	338	T
Spy0103	155	none		
Spy0269	164	H	97	N
		A	150	V
		A	168	V
		H	482	R
		N	485	K
		Q	577	E
		A	610	V
		L	636	M
		E	640	K
		P	752	S
		I	764	V
		D	765	E
		K	873	R
Spy0292	166	A	214	D
		Y	309	S
		T	317	N
		V	318	C
		K	319	Q
Spy0416	169	V	1	M
		F	25	M
		L	26	M
		V	27	M
		S	38	T
		M	40	T
		A	49	T
		S	68	P
		L	76	P
		S	85	P
		D	87	G
		S	104	P
		S	110	P
		D	151 ^C	A, S, T, G
		S	164	P
		E	215	G
		H	279 ^C	A, S, T, G
		T	395	I
		D	452	N
		N	478	K
		G	484	D
		A	547	V
		S	617 ^C	A, S, T, G

- 78 -

		D	723	A
		H	749	R
		R	770	K
		P	787	S
		D	804	A
		T	874	M
		N	913	S
		H	991	Y
		N	1080	S
		V	1238	A
		D	1313	G
		V	1349	M
		A	1393	V
		N	1479	K
		I	1487	M
		D	1516	G
		N	1555	D
		T	1560	A
		S	1599	F
		S	1605	T
		T	1617	A
Spy0720	184	A	61	T
		I	63	M
		K	99	Q
		K	109	Q
		N	295	S
Spy0872	192	K	178	N
		P	181	S
		V	253	I
		A	393	V
		T	600	I
		V	605	I
Spy1063	199	N	168	S
		A	169	S
		D	170	E
		A	173	E
		M	175	V
		V	180	L
		N	181	S
		E	192	D
		Q	195	E
		K	228	D
		H	243	K
		P	245	K
		N	246	A
		T	248	K
		L	252	Q
		M	257	I
		R	260	S
		Q	277	R
		D	284	E
		A	287	P
		E	289	D

【 0 0 7 9 】

- 79 -

		T	290	E
		A	292	I
		A	299	G
		K	303	R
		V	309	L
		A	310	N
		Q	314	R
		R	316	H
		Q	317	E
		R	318	A
		K	321	R
		A	322	G
Spy1245	203	L	72	M
		A	97	P
		Q	213	K
Spy1357	205	C	9	Y
		G	48	R
		I	87	L
		S	91	A
		T	102	A
		L	105	V
		A	111	S
		N	117	T
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		Q	142	K
		S	143	A
		N	145	T
		W	151	L
		A	155	D
		T	156	N
		P	157	A
		I	158	T, A
		A	159	S
		L	160	D
		D	161	A
		V	162	L
		K	163	E
		K	164	A
		T	165	L
		K	166	A
		T	168	Q
		K	169	T
		P	170	S, D
		V	171	A
		K	173	Q
		K	174	S
		G	187	S
		A	197	T
		V	207	A
Spy1361	206	R	129	Q
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- 80 -

		D	230	A
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Spy1390	210	N	3	Q
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		S	10	G
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		M	18	V
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		T	26	S
		N	27	H
		D	28	N
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		I	33	V
		S	41	T
		V	54	L
		S	55	A
		N	61	S
		A	70	T
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		S	104	G
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		S	117	T
		A	127	Q

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- 81 -

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- 82 -

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		G	301	N
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- 83 -

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- 84 -

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<213> Streptococcus pyogenes

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<212> DNA

<213> Streptococcus pyogenes

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gatggtagta	tcactgagaa	acaagaaaaa	gcttatcaag	actattatga	caaacataaa	300
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<210> 6

<211> 771

<212> DNA

<213> Streptococcus pyogenes

<400> 6

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<211> 1068

<212> DNA

<213> Streptococcus pyogenes

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<212> DNA

<213> Streptococcus pyogenes

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<210> 9

<211> 1716

<212> DNA

<213> Streptococcus pyogenes

<400> 9

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<211> 429

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 <213> Streptococcus pyogenes

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<210> 12
 <211> 1197
 <212> DNA
 <213> Streptococcus pyogenes

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<210> 13
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【0090】

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<212> DNA

<213> Streptococcus pyogenes

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<211> 1233

<212> DNA

<213> Streptococcus pyogenes

<400> 16

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<211> 927

<212> DNA

<213> Streptococcus pyogenes

<400> 17

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<212> DNA

<213> Streptococcus pyogenes

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<211> 555

<212> DNA

<213> Streptococcus pyogenes

<400> 20

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<211> 633

<212> DNA

<213> Streptococcus pyogenes

<400> 21

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gcacttcaaa aaaaggaaga ggaagagcaa caaaaacagc tagaagaaag catgctaaag 540
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 <211> 615
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 <213> Streptococcus pyogenes

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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 24
 <211> 996
 <212> DNA
 <213> Streptococcus pyogenes

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【0095】

<210> 25
 <211> 999
 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 2133
 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 1302
 <212> DNA
 <213> Streptococcus pyogenes

【0096】

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<210> 28

<211> 783

<212> DNA

<213> Streptococcus pyogenes

<400> 28

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<210> 29

<211> 1212

<212> DNA

<213> Streptococcus pyogenes

<400> 29

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【 0 0 9 7 】

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 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 1887
 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 1203
 <212> DNA
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 <213> Streptococcus pyogenes

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<210> 34
 <211> 942
 <212> DNA
 <213> Streptococcus pyogenes

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<210> 35
 <211> 1953

【 0 0 9 9 】

<212> DNA

<213> Streptococcus pyogenes

<400> 35

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<210> 36

<211> 6138

<212> DNA

<213> Streptococcus pyogenes

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<213> Streptococcus pyogenes

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<213> Streptococcus pyogenes

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<210> 43

<211> 789

<212> DNA

<213> Streptococcus pyogenes

<400> 43

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<210> 44
<211> 1290
<212> DNA
<213> Streptococcus pyogenes

<400> 44
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<210> 45
<211> 534
<212> DNA
<213> Streptococcus pyogenes

<400> 45
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tttgogaagt ggaagtcaga acaagaagcg gagaatcgg aagctaaaaa aatggctaa 180
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tacggtgcta acttggctag taaggcagca caacaaagca ccaaactttt ttag 534

<210> 46
<211> 711
<212> DNA
<213> Streptococcus pyogenes

<400> 46
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cataatctag aatcgtttta taagcatgat tctaacttga ttgaagccga tagtataaaa 180
aattctccag atattgtaac aagccatag ttgaaatata gtgtcaagga taaaaatttg 240
tcagtttttt ttgagaaaga ttggatatca caggaattca aagataaaga agtagatatt 300
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ggaattacat taactaatc agaaaaaaa gaaattaaag ttccgtgtaa cgtgtggggt 420
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gaacaaaaat actctaaagg aactgttaac tttagattta attcaggtaa agatattgtt 600
tttgatttgt attatttttg caatggagac ttttaatagca tgctaaaaat atattccaat 660
aacgagagaa tagactcaac tcaatttcat gtagatgtgt caatcagcta a 711

<210> 47
<211> 2418
<212> DNA
<213> Streptococcus pyogenes

【 0 1 0 6 】

<400> 47

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atcgacaggca acgatgctta tgataaaacc aatcctgaca tggctacttt tcataataaa 300
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<210> 48

<211> 882

<212> DNA

<213> Streptococcus pyogenes

<400> 48

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ttaaatggtg ataaagagag tatacagtct ctctgtagatt atctgactcg aagaggaaaa 180
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<210> 49

<211> 972

<212> DNA

<213> Streptococcus pyogenes

<400> 49

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【 0 1 0 7 】

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aaagctaagt ag 972

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<210> 50
 <211> 792
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 50
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cgacaaaagg ttattcaggc cgagttagca gaagaagaac gattagaagc catgctttct 180
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<210> 51
 <211> 1566
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 51
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acctaa 1566

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[0 1 0 8]

<210> 52
 <211> 1053
 <212> DNA
 <213> Streptococcus pyogenes

<400> 52
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<210> 53
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 <213> Streptococcus pyogenes

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<213> Streptococcus pyogenes

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<211> 2379

<212> DNA

<213> Streptococcus pyogenes

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 <211> 2160
 <212> DNA
 <213> Streptococcus pyogenes

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<211> 2619

<212> DNA

<213> Streptococcus pyogenes

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<210> 60

<211> 1056

<212> DNA

<213> Streptococcus pyogenes

<400> 60

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agcgttagtg atttttcaaa tgaaacaaaa aacacagaag tatcgcaaaa agcgtatgcta 180
aatctggtaa ttagtctgtt ttttgaagct caatatgggt ataaggtttc aaaaaaagaa 240
gttgaagggt cgtatcataa aacagctgaa cagtatggcg cttcattctc tgcgtctttg 300

```

【 0 1 1 2 】

```

gcacaatcaa gcttgacacc tgagactttt aagcgtcaga tccgctcttc aaaattagta 360
gaatatgcgg tttaaagaagc agctaaaaaa gaattgacaa cacaagaata taagaaagca 420
tatgaatctt atactccaac aatggcagtc gaaatgatta ctttagataa tgaagagaca 480
gctaaatcag tcttagagga actaaaaagcc gaaggcgcag actttacagc tattgctaaa 540
gaaaaaacaa caacacctga gaaaaaagtg acctataaat ttgattcagg tgcgacaaat 600
gtaccgactg atgtcgtaaa agcggcttca agtttgaatg aggggtggcat atcagacgtt 660
atctcgggtt tagatccaac ttcttatcaa aagaagtttt acattgttaa ggtgactaaa 720
aaagcagaaa aaaaatcaga ttggcaagaa tataagaaac gtttgaaagc tatcattata 780
gctgaaaaat caaaagatat gaatttccaa aacaaggtta ttgcaaatgc attggataaa 840
gctaattgta aaattaaaga caaagctttt gctaattatt tggcgcaata tgcaaatctt 900
ggtcaaaaaa ctaaaagctgc aagtgaaggt tcaacaacca gcgaatcatc aaaagctgca 960
gaagagaacc catcagaatc agagcaaaac cagacatcat cagctgaaga accaactgag 1020
actgaggctc agacgcaaga gccagctgca caataa 1056

```

<210> 61
 <211> 597
 <212> DNA
 <213> Streptococcus pyogenes

```

<400> 61
gtgctttatc caacacccat tgcaaaagtt attgacagtt actctaaact tccaggaatt 60
ggtatcaaga cggcgacgag attagccttt tatactattg gaattgcaaa tgaagatgtc 120
aatgattttg ctaaaaactt attagcagct aaaagagaac tgacctattg ttcgattttg 180
ggaaacctta ccgatgacga tctttgtcac acacgagtcg tgatcagacg 240
accattctgg tagtagaaga tgctaaagat gtttctgcca tggaaaaaat ccaagagtat 300
catggctatt atcatgtgct tcacggcttg atttcgccta tgaatgggtg ggggccagat 360
gacatcaacc ttaaaagttt aattaccogt ctaattggatg gtaagggtgag cgaagttatc 420
gtagctacca atgccacagc agatgggggaa gcaacgtcca tgtatatctt acgtgtcttg 480
aaaccagccg ggattaaggt aactcgtttg gcaagaggtc tcgcagtagg ttccagatatt 540
gagtattgtg atgaagtaac attattgaga gctattgaga atcgtactga actttaa 597

```

<210> 62
 <211> 807
 <212> DNA
 <213> Streptococcus pyogenes

```

<400> 62
atggatatgt ctaaatcaaa tcgtcgtact tggcaagggt tagttgttat tttaatagct 60
attctcacca cttttaccac aagtactgtt acggcagcca gaaaaattag aaatttcctt 120
gataccacgg aaattttgtt aggaacgaag gcgactgaga caccaggaat cttaccattc 180
actggtagct accaattagt ttggggcgat cttgacaatc tgcaaaaggcc aaccttcgca 240
cacatccagc taaaagatca agatgagcct aatattaaac gaaaaggact taaattcaat 300
cctcctgggt ggcatattta caaattgact gacgctaagt gaaaaacaac ttggttaatg 360
gacctgtggc atttagttgg ttaccaattt agcgggttaa atgacgagcc taaaaacctt 420
gttacaatga caaaatatct taatactggc tttagtgaac aaaatccttt aggaatgctc 480
tattatgaaa atagattaga tagctgttta gctctacacc ctaacttctg gctagactat 540
aaagttactc ctgtttatca taaaaatgag ttagtctctc gccaaagtag tctacagtat 600
gttggaattg atgaaaatgg agatctactt caaattaagt taggtagtga aaaagaaagt 660
gtagacaact ttggagtaac atcagttaca ttagataacg tatctccttt agctgaattg 720
gattacaaaa caggaatgat gctagattca actcaaaacg aagaagatag taatttagaa 780
accgaagagt ttgaagaagc ggcttaa 807

```

<210> 63
 <211> 942
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 63
atgactagta aaaaagcgtg tttatcaagc atcattgtgt tagcaagttt aacgtgtgga 60
aatgatactg ttagtgccaa tcatctctca gcaactggag ataagtttga tgattgctca 120
acacttgttg aaaaagatgt ggccctctaa gatgaacttg agatgttagc atggtctctc 180
tctcaaaaca ctgatgatgc tgacagagac tatgaagatt ttctcgatga tgattctttt 240
atttctcaaa atgaaactga taagatgttt gagaatttaa ctgatgatag gttattaaat 300
gaatttagatg aattagatga agaaaatgaa gaagatgaag aagatacaat tgagccagag 360
caaaaatgtaa taatgcctag tgacgatgag ctatttgatt taactgatgc tgttgagaca 420
ogccttactg ttictagtgc tcccatatta gaggtgtaat tgcgaaacc acatttgagg 480
agcctatcag atacagcact gcggtctggt gaaattagag gacatttaga taacaaactg 540
gacgctttgt ctgtaacagc tacaaagtta gcattaacga tggctcaaaa atttgatttg 600
acaacgcatt tctattctat aggtgaaagc tttagtgaag tattagctgc tcattatgaa 660
gacagaaaaa cagaatcagc ttttctaaag aaaaagagat ttccacttcc tattgctact 720
ccagatgttg ttatagagga gtttaaggcg ctagtctctt ctatttgaag ttcaaaagaa 780
gatgtttcag ttccttatag tcggaagcta ggtatggcag ttgcaaaaag aaaaatagcc 840

```

[0 1 1 3]

ctgccacaaa cgggagagag gtctcttat tatccagttt tacttggttt aatgatatta 900
 ggattaacgc cgattatgat accaaagaag ataaataatt ag 942

<210> 64

<211> 1149

<212> DNA

<213> Streptococcus pyogenes

<400> 64

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cgtaacattg	aatttttaaa	gaaaaagaag	cagcaagctg	aggaagaaaa	aaaactcaaa	120
gagaattat	tgagtataa	aaaagcgag	cagcaagctc	aaaatgcttc	tgaagcgggt	180
gagcttaaaa	ctgatgagaa	aactgatagt	caggaaattg	agtcagaaac	gacgtcaaaa	240
octaaaaaaa	ccaaaaaagt	tagacaaccc	aaggaaaaaa	gcgcgacaca	aatcgctttt	300
caaaaaatcct	tgccctgttct	tttgggggog	ctcttactca	tggcgggtgc	tatttttatg	360
atcaactcctt	atagcaaaaa	gaaagagttt	totgtaagag	gaaacctca	aacgaacctt	420
gacgaattaa	tcaaagctag	caaagtcaaa	gcactctgact	attggttaac	gctgttaact	480
tgccttggtc	agtatgaacg	accgattctt	cgtaactattc	catgggtgaa	atctgtacat	540
ctctcttacc	aattttcctaa	tcactttcta	tttaacgtta	ttgaatttga	aatcatcgct	600
tatgcacaag	ttgaaaacgg	ttttcagcct	atittggaga	atggaaaacg	tgtggacaag	660
gtcagggcat	cagaactacc	gaaatctttc	ttgattctta	atttaaaaga	tgagaaagcg	720
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tcagtgtctc	ttgcaaatcc	caaaacgaca	gcggatttac	taottattga	aatgcatgac	840
ggtaattgtag	ttagagtaac	gcagtcacaa	ctcacattga	aacttcccta	ttatcaaaaa	900
ttgaaaaaaa	acottgaaaa	tgatagtata	gtggatatgg	aagtgggaat	ttatactaca	960
acacaggaga	ttgaaaatca	acctgaagtt	cctcttacgc	ctgaacaaaa	cgagctgat	1020
aaagaaggag	ataagcctgg	tgaacatcag	gaacagacag	acaatgattc	agaaaacgcca	1080
gcaaatcaga	gtagtctca	gcaaacacca	ccatccccag	aaacggctct	ogaacaggcc	1140
catggctag						1149

<210> 65

<211> 1038

<212> DNA

<213> Streptococcus pyogenes

<400> 65

atgaaagac	ttaaaaaat	caaatgggtg	ttagtgggtc	tgctagcttt	aatctctttg	60
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attcggactg	tcttacaagt	caatggcaca	gaagacaaa	gaaaaggagc	ttaccagttt	180
gttgacgtgg	gcattagtcg	tgccagcctc	gctcagctat	tatatgcttg	gctgacaccg	240
tttactgaaa	ttagtacagc	agaagataca	acaggcggat	acagcgatgc	tgatttcctt	300
cgaattaatc	aattttacat	ggaacatca	caaatgcag	ctattttatca	agctttatcc	360
ttagctggaa	aaccagttac	attagattat	aaaggcgtat	atgtttttaga	cgtaaacacac	420
gaatctactt	ttaaaggaac	gctacactta	gcagatactg	taacagggtg	aaatggtaaa	480
cagtttacta	gttcagcaga	acttattgac	tatgtttctc	acctaaaaact	aggggatgaa	540
gttacggttc	agtttacgag	tgataataag	cctaaaaaag	gagttggcgg	tattatcaaa	600
ctgaaaaatg	ggaaaaatgg	gattggcatt	gcottgactg	atcatacaag	tgtcaattca	660
gaagacacag	tgatctttag	tactaaagga	gtaggaggac	ctagtgtctg	tctaattgtt	720
actcttgata	tatatgatca	aataactaaa	gaagatttac	gcaagggccg	tacaattgca	780
ggtacaggaa	ctattggcaa	ggatggcgaa	gtaggagata	ttggtgtgtc	aggtcttaaa	840
gtagtgtcag	cagctgaagc	tgggtcagat	atattttttg	ttccgaataa	tctgtttgat	900
aaggaaatta	aaaaagttaa	tccaatgct	ataagtaatt	acgaagaagc	caaacgggca	960
gccaacgac	taaagaccaa	aatgaagatt	gttcctgtta	cgactgttca	agaggcactg	1020
gtttatcttc	gcaataaa					1038

<210> 66

<211> 849

<212> DNA

<213> Streptococcus pyogenes

<400> 66

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ggtgatccct	taaaatgaaa	catgcctcgt	acagatgcca	aaggatatgg	tgtgatgagt	120
gatgtctcca	ttaaacgtaa	gattcgtaat	cgtttgcaag	atatggggaa	gtctattttt	180
gtgcaagcta	atgagcgtat	tgaagatgat	tttctgtcac	tggaacaaac	cttttcgcaa	240
caattttacag	ctaagacacc	tgacaaagaa	attgaagaaa	aagcaaatgc	attatggttt	300
gatgttctgt	cttttggaca	agtttttact	tatctgaaaa	aatcaattgg	ggtgcgtgga	360
ccagtttcca	tcagtatggc	taagtctctg	gagccaattg	tcatttccag	ccttcaaat	420
acgcgtagta	ccaatgggat	ggaagctaag	aataatagtg	gccgctcttc	tgatacgatg	480
gggacaaaa	atttttaga	ttatggtgtg	tatgtactta	aaggttctat	caatgcttat	540
tttctgtgaa	agaactggtt	ttctcaggaa	gatgctgagg	ctattaaaga	agttttggtt	600
agcttgtttg	aaaatgatgc	gtcgtctgca	cgtccggaag	gctctatgca	agttttgtgaa	660

【 0 1 1 4 】

```

gtcttttgggt ttacgcattc aagcaaattg ggaaatgttt caagtgcgog tgtctttgac 720
ttgttagagt atcatcaatc aatagaagaa aaaagcactt atgacgctta tcagattcat 780
ctaaatcaag aaaaattggc taaatatgaa gcgaaagggt taacgcttga aatcctagaa 840
ggactctag 849

```

<210> 67
 <211> 2706
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 67
atggcaacta aaaaagtaca tattatttca cacagtcact gggatcgoga gtggtacatg 60
gcttacgaac aacaccacat gcgtctgatt aacttaatag atgacctgtt agaagttttt 120
caaacggatc ctgattttca tagttttcat ttggatgggc aaaccattat cctagatgat 180
tattttaaaag taagcccccga acgagaacct gagatttagac aagccattgc ttccgggaaaa 240
ctccgtatcg gacctttcta tatcttacag gacgattttt tgaccagcag tgaatccaat 300
gtgcgcaata tgcgtattgg taaggaagat tgtgacagat gggcgctag tgtgccactt 360
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ggcctacaag ctgctgcctt tggctgtggc attcgtccaa ctggatttaa caatcagggtg 480
gataccagtg aaaaatacag ctccaattc tctgaaatca gttggcaagg ccagataac 540
agtcttattc ttgactctct ottcgccaac tggtagacga atggcaatga gatcccgaca 600
acagaagctg aggcgcgtct tttttgggat aaaaaacttg ctgatgcoga acgcttcgcc 660
tcaaccaagc acctctgat gatgaacggg tgtgatcatc aaccgctaca acttgatgtc 720
accaagcga tcgccttagc caaccaactc tatcctgact acgaatttgt gcattcctgc 780
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ctccaattca ccacacgttt tgataaccaa atgactaatc atcgcttgcg cgtcctattc 2040
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aagcaaaaga caccagocaa acttggcaaa gcggaaattt taactctago ttggaagaaa 2700
caataa 2706

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<210> 68
 <211> 777
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 68
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gaatcccttt atgtaacaga agatactatt gttcggttta tgttgagtaa agataaagtc 120
cttgacaatg atcagcttga agacatgaaa cattttgccc aactgtccta cggcaaaaaat 180
ttagcccttt attttctttc ctttcaacaa cgcagcaaca agcaagttgc tgattacctg 240
cgcaagcatg agattgaaga acacattatt gctgacatca tcaactcaact ccaagaagaa 300
caatggatag acgacaccaa attggctgat acctacattc gccaaaatca gttaaatggt 360
gataaaggtc ccaagctttt aaaaacaaaa ttattacaaa aaggcattgc aagtcatgac 420
attgatccta tcttatctca aactgacttt agccaactcg ctcaaaaagt aagccaaaaa 480
ctctttgaca aatatcaaga aaaatttgcca ccaaaagcct tgaagataa aatcacccaa 540

```

【 0 1 1 5 】

```

gcattactga ccaaaggctt ttcatacgt ctagctaaac atagcctcaa tcaccttaat 600
tttgaccaag ataatacaaga aatagaagat cticttgaca aagaattaga caaacaatat 660
cgtaaaactca gtgcgaaata tgatggttat accttaaagc aaaagctota tcaggctctc 720
taccgaaaaag gctacaacag cgaogacatt aattgcaagt taagaaatta tttatag 777

```

<210> 69
 <211> 666
 <212> DNA
 <213> Streptococcus pyogenes

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<400> 69
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ggaaaaaagt tttgtgogac atgttgtgtca aactcagata taatagcttg tcgagattgt 180
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gctatgaaag catacttcag tcaatataag ttccaaggag actattttatt aagaaaagt 300
tttgcaagtag aacttgccga tgttatcacc aagtactata aaggctatat ccagtcctcg 360
gttctctgtaa gtcccggttg ttttcgagaa agacaattta atcaagttag cgctattctt 420
gaggcagcta atgttagcta cctttctctt ttgaaaagc tagataatac tcaccaatct 480
tcagaacaaa aaaaagagag attattagta gaaaaatctt atcgactact aaaagtatca 540
aacattctctg ataaaaatcct tatagtagat gatatttata ctactggttag tacaattatc 600
gctcttagaa aacaattggc taaagtagca aatagtgaca ttaaaagtgt gtcaattgca 660
cgttaa

```

<210> 70
 <211> 1014
 <212> DNA
 <213> Streptococcus pyogenes

```

<400> 70
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gttatgacaa aagaatttca tcacgtgacc gtactccctc acgaaacagt ggacatgctt 120
gacataaagc ctgatgggat ttatgtttgat cgcacgctag gtggctcagg ccactcagct 180
tatttggtgt ccaaaacttg tgaagaaggg cacctctatt gttttgacca agacaaaaag 240
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gatgttatct tatatgaact tgggtgttcc agcccgaat tggatgaaag agaacgaggg 420
ttttcttata aacaagatgc tccattggat atgcgcagtg atcgctcagtc gctcttaaca 480
gcttacgaag tgggtgaatac ctatocattc aatgatttgg ttaagatttt tticaaatat 540
ggtagaagata aattctccaa gcagatcgct cgaaaaaattg aacaagcaag agctattaag 600
cctattgaga caacaacaga gttagcagaa ttgattaagg cagcaaaagcc agctaagag 660
tgaagaaaaa aaggccaccc tgcataaacag atttttcaag ctattcgcat tgaagtcaat 720
gatgaattgg gagcgccga tgaatctatt caggacgcta tggaaattatt agcccttgat 780
ggctgtatct cagttattac cttccattct ctggaagatc gcctaaccac gcagttgttt 840
aaagaagcta gtacgggtgga tgtgocaaaa gggcttctct taattcctga agatattgaa 900
cctaagtttg aacttggttc acgtaagccg atcttaaccta gtcattcaga gttaacagct 960
aataaaaggg cacactcagc caagctacgt gtggccaaaa aaattcggaa ataa 1014

```

<210> 71
 <211> 792
 <212> DNA
 <213> Streptococcus pyogenes

```

<400> 71
gtgacaacga cggaacaaga acttaccttg actcccttac gtgggaaaag tggcaaaagct 60
tataaaggca cttatccaaa tggggaatgt gtctttataa aattaaatac gaccctatt 120
ctacctgcct tagcaaaaga acagatttgg ccacagttac tttgggocaa acgcatgggc 180
aatgttgata tgatgagtgc ccaagaatgg cttacggcc gtacattgac caaagaagat 240
atgaacagta agcaaatcat tcatattcta ttgcgccttc acaaatctaa aaaattagtc 300
aatcaactgc ttcagctcaa ttataagatt gaaaacccat acgattttatt ggttgatttt 360
gagcaaaatg cacccttgca aattcagcaa aattcatact tacaagctat cgttaaagaa 420
ttaaaacgga gcttaccaga gttcaaatca gaagtagcaa cgattgtgca tggagatatt 480
aaacatagca attgggtgat tactactagt ggtatgattt ttttagtaga ttgggattct 540
gttcgtctaa ctgatcgat gtatgatgtt gcttacotgt tgagccacta tattccacgg 600
tctcgttggt cagaatggct gtcttattat ggctataaaa ataatgacaa ggttatgcaa 660
aaaaattattt ggtatgttca attttctcac ctgacacaaa ttctcaagtg ttttgacaag 720
cgtgacatgg agcatgtgaa tcaggagatt tatgccttca gaaaatttag agaaatattt 780
agaaagaaat aa

```

<210> 72
 <211> 2016

【 0 1 1 6 】

<212> DNA

<213> Streptococcus pyogenes

<400> 72

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tttcagaaat	tagatattta	tacagtagaa	gattttactgc	tttattatcc	gtttcgctat	120
gaagatttta	aatcaaaatc	tgtttttgat	ttagtggtatg	gtgaaaaagc	agtcattaca	180
ggcttagtcg	ttactccagc	taatgtacaa	tattatgggt	ttaaaccgtaa	ccgtttaagt	240
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<211> 3828

<212> DNA

<213> Streptococcus pyogenes

<400> 73

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<211> 1512

<212> DNA

<213> Streptococcus pyogenes

<400> 74

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<211> 2988

<212> DNA

<213> Streptococcus pyogenes

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<400> 75

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<211> 558

<212> DNA

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<400> 76

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<211> 1407

<212> DNA

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<213> Streptococcus pyogenes

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<210> 78

<211> 3498

<212> DNA

<213> Streptococcus pyogenes

<400> 78

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<211> 1323

<212> DNA

<213> Streptococcus pyogenes

<400> 79

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<211> 1047

<212> DNA

<213> Streptococcus pyogenes

<400> 80

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<210> 81

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<212> DNA

<213> Streptococcus pyogenes

<400> 81

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<212> DNA

<213> Streptococcus pyogenes

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<212> DNA

<213> Streptococcus pyogenes

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<211> 1140

<212> DNA

<213> Streptococcus pyogenes

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<211> 927

<212> DNA

<213> Streptococcus pyogenes

<400> 86

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 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 1626
 <212> DNA
 <213> Streptococcus pyogenes

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<210> 89
 <211> 1197
 <212> DNA
 <213> Streptococcus pyogenes

[0 1 2 5]

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<210> 90

<211> 816

<212> DNA

<213> Streptococcus pyogenes

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<210> 91

<211> 2337

<212> DNA

<213> Streptococcus pyogenes

<400> 91

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<211> 2199

<212> DNA

<213> Streptococcus pyogenes

<400> 92

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<210> 93

<211> 768

<212> DNA

<213> Streptococcus pyogenes

<400> 93

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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 97
 <211> 36
 <212> DNA
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<210> 98
 <211> 141
 <212> DNA
 <213> Streptococcus pyogenes

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<211> 33
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<210> 104
 <211> 144
 <212> DNA
 <213> Streptococcus pyogenes

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 <213> Streptococcus pyogenes

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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 108
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 <213> Streptococcus pyogenes

<400> 108
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cttaccttga ctacg 195

<210> 113
<211> 114
<212> DNA
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<210> 114
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<210> 115
<211> 183
<212> DNA
<213> Streptococcus pyogenes

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<210> 116
<211> 54
<212> DNA
<213> Streptococcus pyogenes

<400> 116
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<210> 117
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 <212> DNA
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 tgcaaaaata gctcc 195

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 <211> 90
 <212> DNA
 <213> Streptococcus pyogenes

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 <211> 36
 <212> DNA
 <213> Streptococcus pyogenes

<400> 120
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<210> 121
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 <212> DNA
 <213> Streptococcus pyogenes

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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 124
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gta 243

<210> 126
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<212> DNA
<213> Streptococcus pyogenes

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<210> 127
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<212> DNA
<213> Streptococcus pyogenes

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<210> 128
<211> 117
<212> DNA
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<211> 99
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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 135
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 <212> DNA
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 ataaaagaag tccgg 135

<210> 136
 <211> 171
 <212> DNA
 <213> Streptococcus pyogenes

<400> 136
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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 138
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 <212> DNA
 <213> Streptococcus pyogenes

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<210> 140
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<210> 141
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<400> 141
 aggggaattat ccagatttag tagctctgca atcctgtctaa aaccactagt taaggtcctt 60
 cctaatagga caatggcacc tcctaatact ccagctgctc cacttctctg tattgtctgt 120
 aatcaaatgg ttgtttggca aaaaactttt ttagcaaatg tacttgcaat t 171

<210> 142
 <211> 108
 <212> DNA
 <213> Streptococcus pyogenes

<400> 142
 gagcactttc aaccaaatac ccaaatiggg caaaaatgga aaaaagagcg accaaaacca 60
 acatggtcaa aaagtgatgt ggcgcataaa cagacctatc aatcacca 108

<210> 143
 <211> 192
 <212> DNA
 <213> Streptococcus pyogenes

<400> 143
 aaatcaagggt ctttaaggac ttcttcgac accctgtcca cggttttttc ctctccaact 60
 attttagtat taagccatc acttggttaac atctgctcag gcgctttttg ttgggattcg 120
 ggattggcac accatggaca totcaagggg caacctttta aaaaaacggt tgcogaata 180
 ccaggaccgt ca 192

<210> 144
 <211> 48
 <212> DNA
 <213> Streptococcus pyogenes

<400> 144
 cgaaatgaaa tcaaaccttc ctctcctacg ctttcttcta ccaaaata 48

<210> 145
 <211> 69
 <212> DNA
 <213> Streptococcus pyogenes

【 0 1 3 5 】

<400> 145
 tgctccttag cagcttttac caaatittca aaatcagcca ttgttccaaa atcagggttg 60
 accgccgta 69

<210> 146
 <211> 138
 <212> DNA
 <213> Streptococcus pyogenes

<400> 146
 gaggccatgt cttgccagcg ttgtgtttot tttttagctg actotttttt gatacgatat 60
 gatttggcca agtcctccgt ggtcatagct gccatgattt ttaaaatggc ttggctgtct 120
 tgtggaagga ggtgtggg 138

<210> 147
 <211> 132
 <212> DNA
 <213> Streptococcus pyogenes

<400> 147
 aatttcaaag ctgcaccacc tgggtgtgtt tcaggatttc caaacatcac accaactttt 60
 tcacgcaatt ggttaataaa gatagcgata gtttttgttt tattaataga agctgataat 120
 ttacgcattg cc 132

<210> 148
 <211> 114
 <212> DNA
 <213> Streptococcus pyogenes

<400> 148
 aaagagacct gccactacag ccaccaacat catgtcattt tccaagccaa gttcgatagg 60
 aactttttgc cacatccaga taaaagcgga catcagaact gttccataga tggc 114

<210> 149
 <211> 234
 <212> DNA
 <213> Streptococcus pyogenes

<400> 149
 attacctgt tgaccaagca aacgcagcaa ctgttcagga agcccagttt ttcaaacat 60
 ctgttgaagc atctcttggc aaagagaatg tcattgtcaa tgttcttgaa acagaaacat 120
 caactcacga agcccaaggc ttctatgctg agaccccgaga acaacaagac tacgatatca 180
 ttcatcatg gtggggacca gactatcaag atccacggac ctacottgac atca 234

<210> 150
 <211> 60
 <212> DNA
 <213> Streptococcus pyogenes

<400> 150
 tcgggaagac aggattcgaa cctgcgacac cttggtccca aaccaagtac totaccaagc 60

<210> 151
 <211> 428
 <212> PRT
 <213> Streptococcus pyogenes

<400> 151
 Met Arg Lys Leu Leu Ala Ala Met Leu Met Thr Phe Phe Leu Thr Pro
 1 5 10 15
 Leu Pro Val Ile Ser Thr Glu Lys Lys Leu Ile Phe Ser Lys Asn Ala
 20 25 30
 Val Tyr Gln Leu Lys Gln Asp Val Val Gln Ser Thr Gln Phe Tyr Asn
 35 40 45
 Gln Ile Pro Ser Asn Pro Asn Leu Tyr Gln Glu Thr Cys Ala Tyr Lys
 50 55 60
 Asp Ser Asp Leu Thr Leu Pro Ala Gly Arg Leu Gly Val Asn Gln Pro
 65 70 75 80

【 0 1 3 6 】

Leu Leu Ile Lys Ser Leu Val Leu Asn Lys Glu Ser Leu Pro Val Phe
 85 90 95
 Glu Leu Ala Asp Gly Thr Tyr Val Glu Ala Asn Arg Gln Leu Ile Tyr
 100 105 110
 Asp Asp Ile Val Leu Asn Gln Val Asp Ile Asp Ser Tyr Phe Trp Thr
 115 120 125
 Gln Lys Lys Leu Arg Leu Tyr Ser Ala Pro Tyr Val Leu Gly Thr Gln
 130 135 140
 Thr Ile Pro Ser Ser Phe Leu Phe Ala Gln Lys Val His Ala Thr Gln
 145 150 155 160
 Met Ala Gln Thr Asn His Gly Thr Tyr Tyr Leu Ile Asp Asp Lys Gly
 165 170 175
 Trp Ala Ser Gln Glu Asp Leu Val Gln Phe Asp Asn Arg Met Leu Lys
 180 185 190
 Val Gln Glu Met Leu Leu Gln Lys Tyr Asn Asn Pro Asn Tyr Ser Ile
 195 200 205
 Phe Val Lys Gln Leu Asn Thr Gln Thr Ser Ala Gly Ile Asn Ala Asp
 210 215 220
 Lys Lys Met Tyr Ala Ala Ser Ile Ser Lys Leu Ala Pro Leu Tyr Ile
 225 230 235 240
 Val Gln Lys Gln Leu Gln Lys Lys Lys Leu Ala Glu Asn Lys Thr Leu
 245 250 255
 Thr Tyr Thr Lys Asp Val Asn His Phe Tyr Gly Asp Tyr Asp Pro Leu
 260 265 270
 Gly Ser Gly Lys Ile Ser Lys Ile Ala Asp Asn Lys Asp Tyr Arg Val
 275 280 285
 Glu Asp Leu Leu Lys Ala Val Ala Gln Gln Ser Asp Asn Val Ala Thr
 290 295 300
 Asn Ile Leu Gly Tyr Tyr Leu Cys His Gln Tyr Asp Lys Ala Phe Arg
 305 310 315 320
 Ser Glu Ile Lys Ala Leu Ser Gly Ile Asp Trp Asp Met Glu Gln Arg
 325 330 335
 Leu Leu Thr Ser Arg Ser Ala Ala Asn Met Met Glu Ala Ile Tyr His
 340 345 350
 Gln Lys Gly Gln Ile Ile Ser Tyr Leu Ser Asn Thr Glu Phe Asp Gln
 355 360 365
 Gln Arg Ile Thr Lys Asn Ile Thr Val Pro Val Ala His Lys Ile Gly
 370 375 380
 Asp Ala Tyr Asp Tyr Lys His Asp Val Ala Ile Val Tyr Gly Asn Thr
 385 390 395 400
 Pro Phe Ile Leu Ser Ile Phe Thr Asn Lys Ser Thr Tyr Glu Asp Ile
 405 410 415
 Thr Ala Ile Ala Asp Asp Val Tyr Gly Ile Leu Lys
 420 425

<210> 152

<211> 398

<212> PRT

<213> Streptococcus pyogenes

<400> 152

Met Lys Lys Arg Ile Leu Ser Ala Val Leu Val Ser Gly Val Thr Leu
 1 5 10 15
 Gly Ala Ala Thr Thr Val Gly Ala Glu Asp Leu Ser Thr Lys Ile Ala
 20 25 30
 Lys Gln Asp Ser Ile Ile Ser Asn Leu Thr Thr Glu Gln Lys Ala Ala
 35 40 45
 Gln Asn Gln Val Ser Ala Leu Gln Ala Gln Val Ser Ser Leu Gln Ser
 50 55 60
 Glu Gln Asp Lys Leu Thr Ala Arg Asn Thr Glu Leu Glu Ala Leu Ser
 65 70 75 80
 Lys Arg Phe Glu Gln Glu Ile Lys Ala Leu Thr Ser Gln Ile Val Ala
 85 90 95
 Arg Asn Glu Lys Leu Lys Asn Gln Ala Arg Ser Ala Tyr Lys Asn Asn
 100 105 110
 Glu Thr Ser Gly Tyr Ile Asn Ala Leu Leu Asn Ser Lys Ser Ile Ser
 115 120 125
 Asp Val Val Asn Arg Leu Val Ala Ile Asn Arg Ala Val Ser Ala Asn
 130 135 140
 Ala Lys Leu Leu Glu Gln Gln Lys Ala Asp Lys Val Ser Leu Glu Glu
 145 150 155 160
 Lys Gln Ala Ala Asn Gln Thr Ala Ile Asn Thr Ile Ala Ala Asn Met
 165 170 175
 Ala Met Ala Glu Glu Asn Gln Asn Thr Leu Arg Thr Gln Gln Ala Asn


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      180      185      190
Leu Val Ala Ala Thr Ala Asn Leu Ala Leu Gln Leu Ala Ser Ala Thr
      195      200      205
Glu Asp Lys Ala Asn Leu Val Ala Gln Lys Glu Ala Ala Glu Lys Ala
      210      215      220
Ala Ala Glu Ala Leu Ala Gln Glu Gln Ala Ala Lys Val Lys Ala Gln
      225      230      235      240
Glu Gln Ala Ala Gln Ala Ala Ser Val Glu Ala Ala Lys Ser Ala
      245      250      255
Ile Thr Pro Ala Pro Gln Ala Thr Pro Ala Ala Gln Ser Ser Asn Ala
      260      265      270
Ile Glu Pro Ala Ala Leu Thr Ala Pro Ala Ala Pro Ser Ala Gly Pro
      275      280      285
Gln Thr Ser Tyr Asp Ser Ser Asn Thr Tyr Pro Val Gly Gln Cys Thr
      290      295      300
Trp Gly Ala Lys Ser Leu Ala Pro Trp Ala Gly Asn Asn Trp Gly Asn
      305      310      315      320
Gly Gly Gln Trp Ala Tyr Ser Ala Gln Ala Ala Gly Tyr Arg Thr Gly
      325      330      335
Ser Thr Pro Met Val Gly Ala Ile Ala Val Trp Asn Asp Gly Gly Tyr
      340      345      350
Gly His Val Ala Val Val Val Glu Val Gln Ser Ala Ser Ser Ile Arg
      355      360      365
Val Met Glu Ser Asn Tyr Ser Gly Arg Gln Tyr Ile Ala Asp His Arg
      370      375      380
Gly Trp Phe Asn Pro Thr Gly Val Thr Phe Ile Tyr Pro His
      385      390      395

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<210> 153
 <211> 1257
 <212> PRT
 <213> Streptococcus pyogenes

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<400> 153
Met Ser Ser Tyr Phe Pro Val Ala Pro Leu Ser Asp Leu Val Ser Tyr
1      5      10      15
Met Asn Lys Arg Ile Phe Val Glu Lys Lys Ala Asp Phe Gly Ile Lys
      20      25      30
Ser Ala Ser Leu Val Lys Glu Leu Thr His Asn Leu Gln Leu Thr Ser
      35      40      45
Leu Lys Ala Leu Arg Ile Val Gln Val Tyr Asp Val Phe Asn Leu Ala
      50      55      60
Glu Asp Leu Leu Ala Arg Ala Glu Lys His Ile Phe Ser Glu Gln Val
      65      70      75      80
Thr Asp Cys Leu Leu Thr Glu Thr Glu Ile Thr Ala Glu Leu Asp Lys
      85      90      95
Val Ala Phe Phe Ala Ile Glu Ala Leu Pro Gly Gln Phe Asp Gln Arg
      100      105      110
Ala Ala Ser Ser Gln Glu Ala Leu Leu Leu Phe Gly Ser Asp Ser Gln
      115      120      125
Val Lys Val Asn Thr Ala Gln Leu Tyr Leu Val Asn Lys Asp Ile Thr
      130      135      140
Glu Ala Glu Leu Glu Ala Val Lys Asn Tyr Leu Leu Asn Pro Val Asp
      145      150      155      160
Ser Arg Phe Lys Asp Ile Thr Leu Pro Leu Glu Glu Gln Ala Phe Ser
      165      170      175
Val Ser Asp Lys Thr Ile Pro Asn Leu Asp Phe Phe Glu Thr Tyr Gln
      180      185      190
Ala Asp Asp Phe Ala Thr Tyr Lys Ala Glu Gln Gly Leu Ala Met Glu
      195      200      205
Val Asp Asp Leu Leu Phe Ile Gln Asn Tyr Phe Lys Ser Ile Gly Cys
      210      215      220
Val Pro Thr Glu Thr Glu Leu Lys Val Leu Asp Thr Tyr Trp Ser Asp
      225      230      235      240
His Cys Arg His Thr Thr Phe Glu Thr Glu Leu Lys Asn Ile Asp Phe
      245      250      255
Ser Ala Ser Lys Phe Gln Lys Gln Leu Gln Thr Thr Tyr Asp Lys Tyr
      260      265      270
Ile Ala Met Arg Asp Glu Leu Gly Arg Ser Glu Lys Pro Gln Thr Leu
      275      280      285
Met Asp Met Ala Thr Ile Phe Gly Arg Tyr Glu Arg Ala Asn Gly Arg
      290      295      300
Leu Asp Asp Met Glu Val Ser Asp Glu Ile Asn Ala Cys Ser Val Glu
      305      310      315      320

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【 0 1 3 8 】

Ile Glu Val Asp Val Asp Gly Val Lys Glu Pro Trp Leu Leu Met Phe
 Lys Asn Glu Thr 325 His Asn His Pro Thr 330 Glu Ile Glu Pro Phe Gly Gly
 Ala Ala Thr 340 Cys Ile Gly Gly Ala Ile Arg Asp Pro Leu Ser Gly Arg
 Ser Tyr Val Tyr Gln Ala Met Arg Ile Ser Gly Ala Gly Asp Ile Thr
 Thr Pro Ile Ala Glu Thr Arg Ala Gly Lys Leu Pro Gln Gln Val Ile
 Ser Lys Thr Ala Ala His Gly Tyr Ser Ser Tyr Gly Asn Gln Ile Gly
 Leu Ala Thr Thr Tyr Val Arg Glu Tyr Phe His Pro Gly Phe Val Ala
 Lys Arg Met Glu Leu Gly Ala Val Val Gly Ala Ala Pro Lys Glu Asn
 Val Val Arg Glu Lys Pro Glu Ala Gly Asp Val Val Ile Leu Leu Gly
 Gly Lys Thr Gly Arg Asp Gly Val Gly Gly Ala Thr Gly Ser Ser Lys
 Val Gln Thr Val Glu Ser Val Glu Thr Ala Gly Ala Glu Val Gln Lys
 Gly Asn Ala Ile Glu Glu Arg Lys Ile Gln Arg Leu Phe Arg Asp Gly
 Asn Val Thr Arg Leu Ile Lys Lys Ser Asn Asp Phe Gly Ala Gly Gly
 Val Cys Val Ala Ile Gly Glu Leu Ala Asp Gly Leu Glu Ile Asp Leu
 Asp Lys Val Pro Leu Lys Tyr Gln Gly Leu Asn Gly Thr Glu Ile Ala
 Ile Ser Glu Ser Gln Glu Arg Met Ser Val Val Val Arg Pro Asn Asp
 Val Asp Ala Phe Ile Ala Ala Cys Asn Lys Glu Asn Ile Asp Ala Val
 Val Val Ala Thr Val Thr Glu Lys Pro Asn Leu Val Met Thr Trp Asn
 Gly Glu Ile Ile Val Asp Leu Glu Arg Arg Phe Leu Asp Thr Asn Gly
 Val Arg Val Val Val Asp Ala Lys Val Val Asp Lys Asp Leu Thr Val
 Pro Glu Ala Arg Thr Thr Ser Ala Glu Thr Leu Glu Ala Asp Thr Leu
 Lys Val Leu Ser Asp Leu Asn His Ala Ser Gln Lys Gly Leu Gln Thr
 Ile Phe Asp Ser Ser Val Gly Arg Ser Thr Val Asn His Pro Ile Gly
 Gly Arg Tyr Gln Ile Thr Pro Thr Glu Ser Ser Val Gln Lys Leu Pro
 Val Gln His Gly Val Thr Thr Thr Ala Ser Val Met Ala Gln Gly Tyr
 Asn Pro Tyr Ile Ala Glu Trp Ser Pro Tyr His Gly Ala Ala Tyr Ala
 Val Ile Glu Ala Thr Ala Arg Leu Val Ala Thr Gly Ala Asp Trp Ser
 Arg Ala Arg Phe Ser Tyr Gln Glu Tyr Phe Glu Arg Met Asp Lys Gln
 Ala Glu Arg Phe Gly Gln Pro Val Ser Ala Leu Leu Gly Ser Ile Glu
 Ala Gln Ile Gln Leu Gly Leu Pro Ser Ile Gly Gly Lys Asp Ser Met
 Ser Gly Thr Phe Glu Asp Leu Thr Val Pro Pro Thr Leu Val Ala Phe
 Gly Val Thr Thr Ala Asp Ser Arg Lys Val Leu Ser Pro Glu Phe Lys
 Ala Ala Gly Glu Asn Ile Tyr Tyr Ile Pro Gly Gln Ala Ile Ser Glu
 Asp Ile Asp Phe Asp Leu Ile Lys Asp Asn Phe Ser Gln Phe Glu Ala
 Ile Gln Ala Gln His Lys Ile Thr Ala Ala Ser Ala Ala Lys Tyr Gly
 Gly Val Leu Glu Ser Leu Ala Leu Met Thr Phe Gly Asn Arg Ile Gly
 Ala Ser Val Glu Ile Ala Glu Leu Asp Ser Ser Leu Thr Ala Gln Leu
 Gly Gly Phe Val Phe Thr Ser Ala Glu Glu Ile Ala Asp Ala Val Lys

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      915      920      925
Ile Gly Gln Thr Gln Ala Asp Phe Thr Val Thr Val Asn Gly Asn Asp
  930      935      940
Leu Ala Gly Ala Ser Leu Leu Ala Ala Phe Glu Gly Lys Leu Glu Glu
  945      950      955      960
Val Tyr Pro Thr Glu Phe Glu Gln Thr Asp Val Leu Glu Glu Val Pro
      965      970      975
Ala Val Val Ser Asp Thr Val Ile Lys Ala Lys Glu Thr Ile Glu Lys
      980      985      990
Pro Val Val Tyr Ile Pro Val Phe Pro Gly Thr Asn Ser Glu Tyr Asp
      995      1000      1005
Ser Ala Lys Ala Phe Glu Gln Val Gly Ala Ser Val Asn Leu Val
  1010      1015      1020
Pro Phe Val Thr Leu Asn Glu Val Ala Ile Ala Glu Ser Val Asp
  1025      1030      1035
Thr Met Val Ala Asn Ile Ala Lys Ala Asn Ile Ile Phe Phe Ala
  1040      1045      1050
Gly Gly Phe Ser Ala Ala Asp Glu Pro Asp Gly Ser Ala Lys Phe
  1055      1060      1065
Ile Val Asn Ile Leu Leu Asn Glu Lys Val Arg Ala Ala Ile Asp
  1070      1075      1080
Ser Phe Ile Glu Lys Gly Gly Leu Ile Ile Gly Ile Cys Asn Gly
  1085      1090      1095
Phe Gln Ala Leu Val Lys Ser Gly Leu Leu Pro Tyr Gly Asn Phe
  1100      1105      1110
Glu Glu Ala Gly Glu Thr Ser Pro Thr Leu Phe Tyr Asn Asp Ala
  1115      1120      1125
Asn Gln His Val Ala Lys Met Val Glu Thr Arg Ile Ala Asn Thr
  1130      1135      1140
Asn Ser Pro Trp Leu Ala Gly Val Glu Val Gly Asp Ile His Ala
  1145      1150      1155
Ile Pro Val Ser His Gly Glu Gly Lys Leu Val Val Ser Ala Ser
  1160      1165      1170
Glu Phe Ala Glu Leu Arg Asp Asn Gly Gln Ile Trp Ser Gln Tyr
  1175      1180      1185
Val Asp Phe Asp Gly Gln Pro Ser Met Asp Ser Lys Tyr Asn Pro
  1190      1195      1200
Asn Gly Ser Val Asn Ala Ile Glu Gly Ile Thr Ser Lys Asn Gly
  1205      1210      1215
Gln Ile Ile Gly Lys Met Gly His Ser Glu Arg Trp Glu Asp Gly
  1220      1225      1230
Leu Phe Gln Asn Ile Pro Gly Asn Lys Asp Gln Ile Leu Phe Ala
  1235      1240      1245
Ser Ala Val Lys Tyr Phe Thr Gly Lys
  1250      1255

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<210> 154
 <211> 374
 <212> PRT
 <213> Streptococcus pyogenes

```

<400> 154
Met Lys Lys Phe His Arg Phe Leu Val Ser Gly Val Ile Leu Leu Gly
 1      5      10      15
Phe Asn Gly Leu Val Pro Thr Met Pro Ser Thr Leu Ile Ser Gln Gln
 20      25      30
Glu Asn Leu Val His Ala Ala Val Leu Gly Asp Asn Tyr Pro Ser Lys
 35      40      45
Trp Lys Lys Gly Asn Gly Ile Asp Ser Trp Asn Met Tyr Ile Arg Gln
 50      55      60
Cys Thr Ser Phe Ala Ala Phe Arg Leu Ser Ser Ala Asn Gly Phe Gln
 65      70      75      80
Leu Pro Lys Gly Tyr Gly Asn Ala Cys Thr Trp Gly His Ile Ala Lys
 85      90      95
Asn Gln Gly Tyr Pro Val Asn Lys Thr Pro Ser Ile Gly Ala Ile Ala
 100      105      110
Trp Phe Asp Lys Asn Ala Tyr Gln Ser Asn Ala Ala Tyr Gly His Val
 115      120      125
Ala Trp Val Ala Asp Ile Arg Gly Asp Thr Val Thr Ile Glu Glu Tyr
 130      135      140
Asn Tyr Asn Ala Gly Gln Gly Pro Glu Arg Tyr His Lys Arg Gln Ile
 145      150      155      160
Pro Lys Ser Gln Val Ser Gly Tyr Ile His Phe Lys Asp Leu Ser Ser
 165      170      175

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【 0 1 4 0 】

Gln Thr Ser His Ser Tyr Pro Arg Gln Leu Lys His Ile Ser Gln Ala
 180 185 190
 Ser Phe Asp Pro Ser Gly Thr Tyr His Phe Thr Thr Arg Leu Pro Val
 195 200 205
 Lys Gly Gln Thr Ser Ile Asp Ser Pro Asp Leu Ala Tyr Tyr Glu Ala
 210 215 220
 Gly Gln Ser Val Tyr Tyr Asp Lys Val Val Thr Ala Gly Gly Tyr Thr
 225 230 235 240
 Trp Leu Ser Tyr Leu Ser Phe Ser Gly Asn Arg Arg Tyr Ile Pro Ile
 245 250 255
 Lys Glu Pro Ala Gln Ser Val Val Gln Asn Asp Asn Thr Lys Pro Ser
 260 265 270
 Ile Lys Val Gly Asp Thr Val Thr Phe Pro Gly Val Phe Arg Val Asp
 275 280 285
 Gln Leu Val Asn Asn Leu Ile Val Asn Lys Glu Leu Ala Gly Gly Asp
 290 295 300
 Pro Thr Pro Leu Asn Trp Ile Asp Pro Thr Pro Leu Asp Glu Thr Asp
 305 310 315 320
 Asn Gln Gly Lys Val Leu Gly Asp Gln Ile Leu Arg Val Gly Glu Tyr
 325 330 335
 Phe Ile Val Thr Gly Ser Tyr Lys Val Leu Lys Ile Asp Gln Pro Ser
 340 345 350
 Asn Gly Ile Tyr Val Gln Ile Gly Ser Arg Gly Thr Trp Val Asn Ala
 355 360 365
 Asp Lys Ala Asn Lys Leu
 370

<210> 155
 <211> 108
 <212> PRT
 <213> Streptococcus pyogenes

<400> 155
 Met Ile Asn Gln Trp Asn Asn Leu Arg His Lys Lys Leu Lys Gly Phe
 1 5 10 15
 Thr Leu Leu Glu Met Leu Leu Val Ile Leu Val Ile Ser Val Leu Met
 20 25 30
 Leu Leu Phe Val Pro Asn Leu Ser Lys Gln Lys Asp Arg Val Thr Glu
 35 40 45
 Thr Gly Asn Ala Ala Val Val Lys Leu Val Glu Asn Gln Ala Glu Leu
 50 55 60
 Tyr Glu Leu Ser Gln Gly Ser Lys Pro Ser Leu Ser Gln Leu Lys Ala
 65 70 75 80
 Asp Gly Ser Ile Thr Glu Lys Gln Glu Lys Ala Tyr Gln Asp Tyr Tyr
 85 90 95
 Asp Lys His Lys Asn Glu Lys Ala Arg Leu Ser Asn
 100 105

<210> 156
 <211> 256
 <212> PRT
 <213> Streptococcus pyogenes

<400> 156
 Met Lys Ile Gly Ile Ile Gly Val Gly Lys Met Ala Ser Ala Ile Ile
 1 5 10 15
 Lys Gly Leu Lys Gln Thr Pro His Glu Leu Ile Ile Ser Gly Ser Ser
 20 25 30
 Leu Glu Arg Ser Lys Glu Ile Ala Glu Gln Leu Ala Leu Pro Tyr Ala
 35 40 45
 Met Ser His Gln Asp Leu Ile Asp Gln Val Asp Leu Val Ile Leu Gly
 50 55 60
 Ile Lys Pro Gln Leu Phe Glu Thr Val Leu Lys Pro Leu His Phe Lys
 65 70 75 80
 Gln Pro Ile Ile Ser Met Ala Ala Gly Ile Ser Leu Gln Arg Leu Ala
 85 90 95
 Thr Phe Val Gly Gln Asp Leu Pro Leu Leu Arg Ile Met Pro Asn Met
 100 105 110
 Asn Ala Gln Ile Leu Gln Ser Ser Thr Ala Leu Thr Gly Asn Ala Leu
 115 120 125
 Val Ser Gln Glu Leu Gln Ala Arg Val Arg Asp Leu Thr Asp Ser Phe
 130 135 140
 Gly Ser Thr Phe Asp Ile Ser Glu Lys Asp Phe Asp Thr Phe Thr Ala

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145      150      155      160
Leu Ala Gly Ser Ser Pro Ala Tyr Ile Tyr Leu Phe Ile Glu Ala Leu
      165      170      175
Ala Lys Ala Gly Val Lys Asn Gly Ile Pro Lys Ala Lys Ala Leu Glu
      180      185      190
Ile Val Thr Gln Thr Val Leu Ala Ser Ala Ser Asn Leu Lys Thr Ser
      195      200      205
Ser Gln Ser Pro His Asp Phe Ile Asp Ala Ile Cys Ser Pro Gly Gly
      210      215      220
Thr Thr Ile Ala Gly Leu Met Glu Leu Glu Arg Leu Gly Leu Thr Ala
225      230      235      240
Thr Val Ser Ser Ala Ile Asp Lys Thr Ile Asp Lys Ala Lys Ser Leu
      245      250      255

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<210> 157
 <211> 355
 <212> PRT
 <213> Streptococcus pyogenes

```

<400> 157
Met Thr Asp Leu Phe Ser Lys Ile Lys Glu Val Thr Glu Leu Asp Gly
1      5      10      15
Ile Ala Gly Tyr Glu His Ser Val Arg Asp Tyr Leu Arg Thr Lys Ile
      20      25      30
Thr Pro Leu Val Asp Arg Val Glu Thr Asp Gly Leu Gly Gly Ile Phe
      35      40      45
Gly Ile Arg Asp Ser Lys Ala Glu Lys Ala Pro Arg Ile Leu Val Ala
      50      55      60
Ala His Met Asp Glu Val Gly Phe Met Val Ser Asp Ile Lys Val Asp
65      70      75      80
Gly Thr Leu Arg Val Val Gly Ile Gly Gly Trp Asn Pro Leu Val Val
      85      90      95
Ser Ser Gln Arg Phe Thr Leu Tyr Thr Arg Thr Gly Gln Val Ile Pro
      100      105      110
Leu Ile Ser Gly Ser Val Pro Pro His Phe Leu Arg Gly Ala Asn Gly
      115      120      125
Ser Ala Ser Leu Pro His Ile Glu Asp Ile Val Phe Asp Gly Gly Phe
      130      135      140
Thr Asp Lys Ala Glu Ala Glu Arg Phe Gly Ile Thr Pro Gly Asp Ile
145      150      155      160
Ile Ile Pro Gln Ser Glu Thr Ile Leu Thr Ala Asn Gln Lys Asn Ile
      165      170      175
Ile Ser Lys Ala Trp Asp Asn Arg Tyr Gly Val Leu Met Ile Thr Glu
      180      185      190
Met Leu Glu Ala Leu Lys Gly Gln Asp Leu Asn Asn Thr Leu Ile Ala
      195      200      205
Gly Ala Asn Val Gln Glu Glu Val Gly Leu Arg Gly Ala His Val Ser
      210      215      220
Thr Thr Lys Phe Asp Pro Glu Leu Phe Phe Ala Val Asp Cys Ser Pro
225      230      235      240
Ala Gly Asp Ile Tyr Gly Asn Pro Gly Thr Ile Gly Asp Gly Thr Leu
      245      250      255
Leu Arg Phe Tyr Asp Pro Gly His Val Met Leu Lys Asp Met Arg Asp
      260      265      270
Phe Leu Leu Thr Thr Ala Glu Glu Ala Gly Val Asn Phe Gln Tyr Tyr
      275      280      285
Cys Gly Lys Gly Gly Thr Asp Ala Gly Ala Ala His Leu Gln Asn Gly
      290      295      300
Gly Val Pro Ser Thr Thr Ile Gly Val Cys Ala Arg Tyr Ile His Ser
305      310      315      320
His Gln Thr Leu Tyr Ala Met Asp Asp Phe Val Glu Ala Gln Ala Phe
      325      330      335
Leu Gln Ala Ile Ile Lys Lys Leu Asp Arg Ser Thr Val Asp Leu Ile
      340      345      350
Lys Cys Tyr
      355

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<210> 158
 <211> 118
 <212> PRT
 <213> Streptococcus pyogenes

<400> 158

【 0 1 4 2 】

```

Met Glu Asp Ile Ser Asp Pro Glu Val Ile Leu Glu Tyr Gly Val Tyr
1      5      10      15
Pro Ala Phe Ile Lys Gly Tyr Thr Gln Leu Lys Ala Asn Ile Glu Glu
      20      25      30
Ala Leu Leu Glu Met Ser Asn Ser Gly Gln Ala Leu Asp Ile Tyr Gln
      35      40      45
Ala Val Gln Thr Leu Asn Ala Glu Asn Met Leu Leu Asn Tyr Tyr Glu
      50      55      60
Ser Leu Pro Phe Tyr Leu Asn Arg Gln Ser Ile Leu Ala Asn Met Thr
65      70      75      80
Lys Ala Leu Lys Asp Ala His Ile Arg Glu Ala Met Ala His Tyr Lys
      85      90      95
Leu Gly Glu Phe Ala His Tyr Gln Asp Thr Met Leu Asp Met Val Glu
      100      105      110
Arg Thr Ile Lys Thr Phe
      115

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<210> 159

<211> 571

<212> PRT

<213> Streptococcus pyogenes

<400> 159

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Met Ser Asn Lys Lys Thr Phe Lys Lys Tyr Ser Arg Val Ala Gly Leu
1      5      10      15
Leu Thr Ala Ala Leu Ile Ile Gly Asn Leu Val Thr Ala Asn Ala Glu
      20      25      30
Ser Asn Lys Gln Asn Thr Ala Ser Thr Glu Thr Thr Thr Asn Glu
      35      40      45
Gln Pro Lys Pro Glu Ser Ser Glu Leu Thr Thr Glu Lys Ala Gly Gln
      50      55      60
Lys Thr Asp Asp Met Leu Asn Ser Asn Asp Met Ile Lys Leu Ala Pro
65      70      75      80
Lys Glu Met Pro Leu Glu Ser Ala Glu Lys Glu Glu Lys Lys Ser Glu
      85      90      95
Asp Lys Lys Lys Ser Glu Glu Asp His Thr Glu Glu Ile Asn Asp Lys
      100      105      110
Ile Tyr Ser Leu Asn Tyr Asn Glu Leu Glu Val Leu Ala Lys Asn Gly
      115      120      125
Glu Thr Ile Glu Asn Phe Val Pro Lys Glu Gly Val Lys Lys Ala Asp
      130      135      140
Lys Phe Ile Val Ile Glu Arg Lys Lys Lys Asn Ile Asn Thr Thr Pro
145      150      155      160
Val Asp Ile Ser Ile Ile Asp Ser Val Thr Asp Arg Thr Tyr Pro Ala
      165      170      175
Ala Leu Gln Leu Ala Asn Lys Gly Phe Thr Glu Asn Lys Pro Asp Ala
      180      185      190
Val Val Thr Lys Arg Asn Pro Gln Lys Ile His Ile Asp Leu Pro Gly
      195      200      205
Met Gly Asp Lys Ala Thr Val Glu Val Asn Asp Pro Thr Tyr Ala Asn
      210      215      220
Val Ser Thr Ala Ile Asp Asn Leu Val Asn Gln Trp His Asp Asn Tyr
225      230      235      240
Ser Gly Gly Asn Thr Leu Pro Ala Arg Thr Gln Tyr Thr Glu Ser Met
      245      250      255
Val Tyr Ser Lys Ser Gln Ile Glu Ala Leu Asn Val Asn Ser Lys
      260      265      270
Ile Leu Asp Gly Thr Leu Gly Ile Asp Phe Lys Ser Ile Ser Lys Gly
      275      280      285
Glu Lys Lys Val Met Ile Ala Tyr Lys Gln Ile Phe Tyr Thr Val
      290      295      300
Ser Ala Asn Leu Pro Asn Asn Pro Ala Asp Val Phe Asp Lys Ser Val
305      310      315      320
Thr Phe Lys Glu Leu Gln Arg Lys Gly Val Ser Asn Glu Ala Pro Pro
      325      330      335
Leu Phe Val Ser Asn Val Ala Tyr Gly Arg Thr Val Phe Val Lys Leu
      340      345      350
Glu Thr Ser Ser Lys Ser Asn Asp Val Glu Ala Ala Phe Ser Ala Ala
      355      360      365
Leu Lys Gly Thr Asp Val Lys Thr Asn Gly Lys Tyr Ser Asp Ile Leu
      370      375      380
Glu Asn Ser Ser Phe Thr Ala Val Val Leu Gly Gly Asp Ala Ala Glu
385      390      395      400
His Asn Lys Val Val Thr Lys Asp Phe Asp Val Ile Arg Asn Val Ile

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【 0 1 4 3 】

405 410 415
 Lys Asp Asn Ala Thr Phe Ser Arg Lys Asn Pro Ala Tyr Pro Ile Ser
 420 425 430
 Tyr Thr Ser Val Phe Leu Lys Asn Asn Lys Ile Ala Gly Val Asn Asn
 435 440 445
 Arg Thr Glu Tyr Val Glu Thr Thr Ser Thr Glu Tyr Thr Ser Gly Lys
 450 455 460
 Ile Asn Leu Ser His Gln Gly Ala Tyr Val Ala Gln Tyr Glu Ile Leu
 465 470 475 480
 Trp Asp Glu Ile Asn Tyr Asp Asp Lys Gly Lys Glu Val Ile Thr Lys
 485 490 495
 Arg Arg Trp Asp Asn Asn Trp Tyr Ser Lys Thr Ser Pro Phe Ser Thr
 500 505 510
 Val Ile Pro Leu Gly Ala Asn Ser Arg Asn Ile Arg Ile Met Ala Arg
 515 520 525
 Glu Cys Thr Gly Leu Ala Trp Glu Trp Trp Arg Lys Val Ile Asp Glu
 530 535 540
 Arg Asp Val Lys Leu Ser Lys Glu Ile Asn Val Asn Ile Ser Gly Ser
 545 550 555 560
 Thr Leu Ser Pro Tyr Gly Ser Ile Thr Tyr Lys
 565 570

<210> 160
 <211> 142
 <212> PRT
 <213> Streptococcus pyogenes

<400> 160
 Met Lys Gln Gln Ser Tyr Gln Pro Leu Arg Phe Val Tyr Leu Leu Val
 1 5 10 15
 Ala Leu Phe Ala Ala Leu Leu Leu Ile Ala Arg Pro Val Met Ala Asp
 20 25 30
 Glu Gly Thr Asn Ser Ala Asp Ala Ala Tyr Tyr Lys Gly Gln Ser Ala
 35 40 45
 Gly Lys Lys Ala Gly Lys Lys Ala Gly Lys Glu Ala Thr Trp Thr Asp
 50 55 60
 Leu Thr Pro Thr Val Pro Thr Asn Pro Glu Thr Pro Ser Asp Ile Gly
 65 70 75 80
 Glu Thr Thr Asn Lys Gln Leu Tyr Lys Glu Gly Tyr Lys Asp Gly Tyr
 85 90 95
 Lys Glu Gly Tyr Asn Glu Gly Trp Lys Ser Gln Tyr Pro Val Leu Thr
 100 105 110
 Pro Val Lys Val Ile Trp Asp Leu Ile Ser Tyr Trp Leu Gln Arg Leu
 115 120 125
 Phe Pro Asn Asn Gln Ser Ser Thr Ala Ala Gln Ser Met Ser
 130 135 140

<210> 161
 <211> 108
 <212> PRT
 <213> Streptococcus pyogenes

<400> 161
 Val Lys Asn Lys Leu Phe Leu Val Ala Leu Ala Thr Val Thr Val Leu
 1 5 10 15
 Gly Pro Ser Leu Ala Thr Pro His His Gln Thr Val His Ala Ser Asp
 20 25 30
 Val Thr Leu Thr Glu Thr Cys Asp Lys Asn Gly Thr Val Cys Phe Gly
 35 40 45
 Tyr Glu Asn Val Asp Gly Glu Val Cys Lys Leu Thr Ala Asp Gly Lys
 50 55 60
 Gly Thr Ile Cys Val Gly Tyr Glu Asn Arg Asp Ile Lys Glu Ser Glu
 65 70 75 80
 Thr Ser Ser Thr Lys Asn Asp Cys Ser Asn Trp Phe Trp Cys Phe Leu
 85 90 95
 Asn Tyr Leu Trp Thr Thr Ile Lys Ser Trp Val Ser
 100 105

<210> 162
 <211> 398
 <212> PRT
 <213> Streptococcus pyogenes

【 0 1 4 4 】

<400> 162

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Met Glu Thr Ile Leu Glu Val Lys His Leu Ser Lys Ile Phe Gly Lys
1      5      10      15
Lys Gln Lys Ala Ala Leu Glu Met Val Lys Thr Gly Lys Asn Lys Ser
20      25      30
Glu Ile Phe Lys Lys Thr Gly Ala Thr Val Gly Val Tyr Asp Ala Ser
35      40      45
Phe Glu Val Lys Lys Gly Glu Ile Phe Val Ile Met Gly Leu Ser Gly
50      55      60
Ser Gly Lys Ser Thr Leu Val Arg Met Leu Asn Arg Leu Ile Glu Pro
65      70      75      80
Ser Ala Gly Ser Ile Leu Leu Glu Gly Lys Asp Ile Ser Thr Met Ser
85      90      95
Ala Asp Gln Leu Arg Glu Val Arg Arg His Asp Ile Asn Met Val Phe
100     105     110
Gln Ser Phe Ala Leu Phe Pro His Lys Thr Ile Leu Glu Asn Thr Glu
115     120     125
Phe Gly Leu Glu Leu Arg Gly Val Pro Lys Glu Glu Arg Gln Arg Leu
130     135     140
Ala Glu Lys Ala Leu Asp Asn Ser Gly Leu Leu Asp Phe Lys Asp Gln
145     150     155     160
Tyr Pro Asn Gln Leu Ser Gly Gly Met Gln Gln Arg Val Gly Leu Ala
165     170     175
Arg Ala Leu Ala Asn Ser Pro Lys Ile Leu Leu Met Asp Glu Ala Phe
180     185     190
Ser Ala Leu Asp Pro Leu Ile Arg Arg Glu Met Gln Asp Glu Leu Leu
195     200     205
Asp Leu Gln Asp Ser Met Lys Gln Thr Ile Ile Phe Ile Ser His Asp
210     215     220
Leu Asn Glu Ala Leu Arg Ile Gly Asp Arg Ile Ala Leu Met Lys Asp
225     230     235     240
Gly Gln Ile Met Gln Ile Gly Thr Gly Glu Ile Leu Thr Asn Pro
245     250     255
Ala Asn Asp Phe Val Arg Glu Phe Val Glu Asp Val Asp Arg Ser Lys
260     265     270
Val Leu Thr Ala Gln Asn Ile Met Ile Lys Pro Leu Thr Thr Thr Val
275     280     285
Glu Leu Asp Gly Pro Gln Val Ala Leu Asn Arg Met His Asn Glu Glu
290     295     300
Val Ser Met Leu Met Ala Thr Asn Arg Arg Arg Gln Leu Val Gly Ser
305     310     315     320
Leu Thr Ala Asp Ala Ala Ile Glu Ala Arg Lys Lys Gly Leu Pro Leu
325     330     335
Ser Glu Val Ile Asp Arg Asp Val Arg Thr Val Ser Lys Asp Thr Ile
340     345     350
Ile Thr Asp Ile Leu Pro Leu Ile Tyr Asp Ser Ser Ala Pro Ile Ala
355     360     365
Val Thr Asp Asp Asn Asn Arg Leu Leu Gly Val Ile Ile Arg Gly Arg
370     375     380
Val Ile Glu Ala Leu Ala Asn Ile Ser Asp Glu Asp Leu Asn
385     390     395

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<210> 163

<211> 594

<212> PRT

<213> Streptococcus pyogenes

<400> 163

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Met Lys Thr Ala Arg Phe Phe Trp Phe Tyr Phe Lys Arg Tyr Arg Phe
1      5      10      15
Ser Phe Thr Val Ile Ala Val Ala Val Ile Leu Ala Thr Tyr Leu Gln
20      25      30
Val Lys Ala Pro Val Phe Leu Gly Glu Ser Leu Thr Glu Leu Gly Lys
35      40      45
Ile Gly Gln Ala Tyr Tyr Val Ala Lys Met Ser Gly Gln Thr His Phe
50      55      60
Ser Pro Asp Leu Ser Ala Phe Asn Ala Val Met Phe Lys Leu Leu Met
65      70      75      80
Thr Tyr Phe Phe Thr Val Leu Ala Asn Leu Ile Tyr Ser Phe Leu Leu
85      90      95
Thr Arg Val Val Ser His Ser Thr Asn Arg Met Arg Lys Gly Leu Phe
100     105     110
Gly Lys Leu Glu Arg Leu Thr Val Ala Phe Phe Asp Arg His Lys Asp

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【 0 1 4 5 】

115 120 125
 Gly Glu Ile Leu Ser Arg Phe Thr Ser Asp Leu Asp Asn Ile Gln Asn
 130 135 140
 Ser Leu Asn Gln Ser Leu Ile Gln Val Val Thr Asn Ile Ala Leu Tyr
 145 150 155 160
 Ile Gly Leu Val Trp Met Met Phe Arg Gln Asp Ser Arg Leu Ala Leu
 165 170 175
 Leu Thr Ile Ala Ser Thr Pro Val Ala Leu Ile Phe Leu Val Ile Asn
 180 185 190
 Ile Arg Leu Ala Arg Lys Tyr Thr Asn Ile Gln Gln Gln Glu Val Ser
 195 200 205
 Ala Leu Asn Ala Phe Met Asp Glu Thr Ile Ser Gly Gln Lys Ala Ile
 210 215 220
 Ile Val Gln Gly Val Gln Glu Asp Thr Met Thr Ala Phe Leu Lys His
 225 230 235 240
 Asn Glu Arg Val Arg Gln Ala Thr Phe Lys Arg Arg Leu Phe Ser Gly
 245 250 255
 Gln Leu Phe Pro Val Met Asn Gly Met Ser Leu Ile Asn Thr Ala Ile
 260 265 270
 Val Ile Phe Val Gly Ser Thr Ile Val Leu Ser Asp Lys Ser Met Pro
 275 280 285
 Ala Ala Ala Ala Leu Gly Leu Val Val Thr Phe Val Gln Tyr Ser Gln
 290 295 300
 Gln Tyr Tyr Gln Pro Met Met Gln Ile Ala Ser Ser Trp Gly Glu Leu
 305 310 315 320
 Gln Leu Ala Phe Thr Gly Ala His Arg Ile Gln Glu Met Phe Asp Glu
 325 330 335
 Thr Glu Glu Val Arg Pro Gln Asn Ala Pro Ala Phe Thr Ser Leu Lys
 340 345 350
 Glu Ala Val Ala Ile Asn His Val Asp Phe Gly Tyr Leu Pro Gly Gln
 355 360 365
 Lys Val Leu Ser Asp Val Ser Ile Val Ala Pro Lys Gly Lys Met Ile
 370 375 380
 Ala Val Val Gly Pro Thr Gly Ser Gly Lys Thr Thr Ile Met Asn Leu
 385 390 395 400
 Ile Asn Arg Phe Tyr Asp Val Asp Ala Gly Ser Ile Thr Phe Asp Gly
 405 410 415
 Arg Asp Ile Arg Asp Tyr Asp Leu Asp Ser Leu Arg Gln Lys Val Gly
 420 425 430
 Ile Val Leu Gln Glu Ser Val Leu Phe Ser Gly Thr Ile Thr Asp Asn
 435 440 445
 Ile Arg Phe Gly Asp Gln Thr Ile Ser Gln Asp Met Val Glu Thr Ala
 450 455 460
 Ala Arg Ala Thr His Ile His Asp Phe Ile Met Ser Leu Pro Lys Gly
 465 470 475 480
 Tyr Asn Thr Tyr Val Ser Asp Asp Asn Val Phe Ser Thr Gly Gln
 485 490 495
 Lys Gln Leu Ile Ser Ile Ala Arg Thr Leu Leu Thr Asp Pro Glu Val
 500 505 510
 Leu Ile Leu Asp Glu Ala Thr Ser Asn Val Asp Thr Val Thr Glu Ser
 515 520 525
 Lys Ile Gln Arg Ala Met Glu Ala Ile Val Ala Gly Arg Thr Ser Phe
 530 535 540
 Val Ile Ala His Arg Leu Lys Thr Ile Leu Asn Ala Asp His Ile Ile
 545 550 555 560
 Val Leu Lys Asp Gly Lys Val Ile Glu Gln Gly Asn His His Glu Leu
 565 570 575
 Leu His Gln Lys Gly Phe Tyr Ala Glu Leu Tyr His Asn Gln Phe Val
 580 585 590
 Phe Glu

<210> 164
 <211> 873
 <212> PRT
 <213> Streptococcus pyogenes

<400> 164
 Met Asp Leu Glu Gln Thr Lys Pro Asn Gln Val Lys Gln Lys Ile Ala
 1 5 10 15
 Leu Thr Ser Thr Ile Ala Leu Leu Ser Ala Ser Val Gly Val Ser His
 20 25 30
 Gln Val Lys Ala Asp Asp Arg Ala Ser Gly Glu Thr Lys Ala Ser Asn
 35 40 45

Thr His Asp Asp Ser Leu Pro Lys Pro Glu Thr Ile Gln Glu Ala Lys
 50 55 60
 Ala Thr Ile Asp Ala Val Glu Lys Thr Leu Ser Gln Gln Lys Ala Glu
 65 70 75 80
 Leu Thr Glu Leu Ala Thr Ala Leu Thr Lys Thr Thr Ala Glu Ile Asn
 85 90 95
 His Leu Lys Glu Gln Gln Asp Asn Glu Gln Lys Ala Leu Thr Ser Ala
 100 105 110
 Gln Glu Ile Tyr Thr Asn Thr Leu Ala Ser Ser Glu Glu Thr Leu Leu
 115 120 125
 Ala Gln Gly Ala Glu His Gln Arg Glu Leu Thr Ala Thr Glu Thr Glu
 130 135 140
 Leu His Asn Ala Gln Ala Asp Gln His Ser Lys Glu Thr Ala Leu Ser
 145 150 155 160
 Glu Gln Lys Ala Ser Ile Ser Ala Glu Thr Thr Arg Ala Gln Asp Leu
 165 170 175
 Val Glu Gln Val Lys Thr Ser Glu Gln Asn Ile Ala Lys Leu Asn Ala
 180 185 190
 Met Ile Ser Asn Pro Asp Ala Ile Thr Lys Ala Ala Gln Thr Ala Asn
 195 200 205
 Asp Asn Thr Lys Ala Leu Ser Ser Glu Leu Glu Lys Ala Lys Ala Asp
 210 215 220
 Leu Glu Asn Gln Lys Ala Lys Val Lys Lys Gln Leu Thr Glu Glu Leu
 225 230 235 240
 Ala Ala Gln Lys Ala Ala Leu Ala Glu Lys Glu Ala Glu Leu Ser Arg
 245 250 255
 Leu Lys Ser Ser Ala Pro Ser Thr Gln Asp Ser Ile Val Gly Asn Asn
 260 265 270
 Thr Met Lys Ala Pro Gln Gly Tyr Pro Leu Glu Glu Leu Lys Lys Leu
 275 280 285
 Glu Ala Ser Gly Tyr Ile Gly Ser Ala Ser Tyr Asn Asn Tyr Tyr Lys
 290 295 300
 Glu His Ala Asp Gln Ile Ile Ala Lys Ala Ser Pro Gly Asn Gln Leu
 305 310 315 320
 Asn Gln Tyr Gln Asp Ile Pro Ala Asp Arg Asn Arg Phe Val Asp Pro
 325 330 335
 Asp Asn Leu Thr Pro Glu Val Gln Asn Glu Leu Ala Gln Phe Ala Ala
 340 345 350
 His Met Ile Asn Ser Val Arg Arg Gln Leu Gly Leu Pro Pro Val Thr
 355 360 365
 Val Thr Ala Gly Ser Gln Glu Phe Ala Arg Leu Leu Ser Thr Ser Tyr
 370 375 380
 Lys Lys Thr His Gly Asn Thr Arg Pro Ser Phe Val Tyr Gly Gln Pro
 385 390 395 400
 Gly Val Ser Gly His Tyr Gly Val Gly Pro His Asp Lys Thr Ile Ile
 405 410 415
 Glu Asp Ser Ala Gly Ala Ser Gly Leu Ile Arg Asn Asp Asp Asn Met
 420 425 430
 Tyr Glu Asn Ile Gly Ala Phe Asn Asp Val His Thr Val Asn Gly Ile
 435 440 445
 Lys Arg Gly Ile Tyr Asp Ser Ile Lys Tyr Met Leu Phe Thr Asp His
 450 455 460
 Leu His Gly Asn Thr Tyr Gly His Ala Ile Asn Phe Leu Arg Val Asp
 465 470 475 480
 Lys His Asn Pro Asn Ala Pro Val Tyr Leu Gly Phe Ser Thr Ser Asn
 485 490 495
 Val Gly Ser Leu Asn Glu His Phe Val Met Phe Pro Glu Ser Asn Ile
 500 505 510
 Ala Asn His Gln Arg Phe Asn Lys Thr Pro Ile Lys Ala Val Gly Ser
 515 520 525
 Thr Lys Asp Tyr Ala Gln Arg Val Gly Thr Val Ser Asp Thr Ile Ala
 530 535 540
 Ala Ile Lys Gly Lys Val Ser Ser Leu Glu Asn Arg Leu Ser Ala Ile
 545 550 555 560
 His Gln Glu Ala Asp Ile Met Ala Ala Gln Ala Lys Val Ser Gln Leu
 565 570 575
 Gln Gly Lys Leu Ala Ser Thr Leu Lys Gln Ser Asp Ser Leu Asn Leu
 580 585 590
 Gln Val Arg Gln Leu Asn Asp Thr Lys Gly Ser Leu Arg Thr Glu Leu
 595 600 605
 Leu Ala Ala Lys Ala Lys Gln Ala Gln Leu Glu Ala Thr Arg Asp Gln
 610 615 620
 Ser Leu Ala Lys Leu Ala Ser Leu Lys Ala Ala Leu His Gln Thr Glu
 625 630 635 640
 Ala Leu Ala Glu Gln Ala Ala Ala Arg Val Thr Ala Leu Val Ala Lys

645 650 655
 Lys Ala His Leu Gln Tyr Leu Arg Asp Phe Lys Leu Asn Pro Asn Arg
 660 665 670
 Leu Gln Val Ile Arg Glu Arg Ile Asp Asn Thr Lys Gln Asp Leu Ala
 675 680 685
 Lys Thr Thr Ser Ser Leu Leu Asn Ala Gln Glu Ala Leu Ala Ala Leu
 690 695 700
 Gln Ala Lys Gln Ser Ser Leu Glu Ala Thr Ile Ala Thr Thr Glu His
 705 710 715 720
 Gln Leu Thr Leu Leu Lys Thr Leu Ala Asn Glu Lys Glu Tyr Arg His
 725 730 735
 Leu Asp Glu Asp Ile Ala Thr Val Pro Asp Leu Gln Val Ala Pro Pro
 740 745 750
 Leu Thr Gly Val Lys Pro Leu Ser Tyr Ser Lys Ile Asp Thr Thr Pro
 755 760 765
 Leu Val Gln Glu Met Val Lys Glu Thr Lys Gln Leu Leu Glu Ala Ser
 770 775 780
 Ala Arg Leu Ala Ala Glu Asn Thr Ser Leu Val Ala Glu Ala Leu Val
 785 790 795 800
 Gly Gln Thr Ser Glu Met Val Ala Ser Asn Ala Ile Val Ser Lys Ile
 805 810 815
 Thr Ser Ser Ile Thr Gln Pro Ser Ser Lys Thr Ser Tyr Gly Ser Gly
 820 825 830
 Ser Ser Thr Thr Ser Asn Leu Ile Ser Asp Val Asp Glu Ser Thr Gln
 835 840 845
 Arg Ala Leu Lys Ala Gly Val Val Met Leu Ala Ala Val Gly Leu Thr
 850 855 860
 Gly Phe Arg Phe Arg Lys Glu Ser Lys
 865 870

<210> 165

<211> 420

<212> PRT

<213> Streptococcus pyogenes

<400> 165

Met Thr Lys Glu Lys Leu Val Ala Phe Ser Gln Ala His Ala Glu Pro
 1 5 10 15
 Ala Trp Leu Gln Glu Arg Arg Leu Ala Leu Glu Ala Ile Pro Asn
 20 25 30
 Leu Glu Leu Pro Thr Ile Glu Arg Val Lys Phe His Arg Trp Asn Leu
 35 40 45
 Gly Asp Gly Thr Leu Thr Glu Asn Glu Ser Leu Ala Ser Val Pro Asp
 50 55 60
 Phe Ile Ala Ile Gly Asp Asn Pro Lys Leu Val Gln Val Gly Thr Gln
 65 70 75 80
 Thr Val Leu Glu Gln Leu Pro Met Ala Leu Ile Asp Lys Gly Val Val
 85 90 95
 Phe Ser Asp Phe Tyr Thr Ala Leu Glu Glu Ile Pro Glu Val Ile Glu
 100 105 110
 Ala His Phe Gly Gln Ala Leu Ala Phe Asp Glu Asp Lys Leu Ala Ala
 115 120 125
 Tyr His Thr Ala Tyr Phe Asn Ser Ala Ala Val Leu Tyr Val Pro Asp
 130 135 140
 His Leu Glu Ile Thr Thr Pro Ile Glu Ala Ile Phe Leu Gln Asp Ser
 145 150 155 160
 Asp Ser Asp Val Pro Phe Asn Lys His Val Leu Val Ile Ala Gly Lys
 165 170 175
 Glu Ser Lys Phe Thr Tyr Leu Glu Arg Phe Glu Ser Ile Gly Asn Ala
 180 185 190
 Thr Gln Lys Ile Ser Ala Asn Ile Ser Val Glu Val Ile Ala Gln Ala
 195 200 205
 Gly Ser Gln Ile Lys Phe Ser Ala Ile Asp Arg Leu Gly Pro Ser Val
 210 215 220
 Thr Thr Tyr Ile Ser Arg Arg Gly Arg Leu Glu Lys Asp Ala Asn Ile
 225 230 235 240
 Asp Trp Ala Leu Ala Val Met Asn Glu Gly Asn Val Ile Ala Asp Phe
 245 250 255
 Asp Ser Asp Leu Ile Gly Gln Gly Ser Gln Ala Asp Leu Lys Val Val
 260 265 270
 Ala Ala Ser Ser Gly Arg Gln Val Gln Gly Ile Asp Thr Arg Val Thr
 275 280 285
 Asn Tyr Gly Gln Arg Thr Val Gly His Ile Leu Gln His Gly Val Ile
 290 295 300

【 0 1 4 8 】

Leu Glu Arg Gly Thr Leu Thr Phe Asn Gly Ile Gly His Ile Leu Lys
 305 310 315 320
 Asp Ala Lys Gly Ala Asp Ala Gln Gln Glu Ser Arg Val Leu Met Leu
 325 330 335
 Ser Asp Gln Ala Arg Ala Asp Ala Asn Pro Ile Leu Leu Ile Asp Glu
 340 345 350
 Asn Glu Val Thr Ala Gly His Ala Ala Ser Ile Gly Gln Val Asp Pro
 355 360 365
 Glu Asp Met Tyr Tyr Leu Met Ser Arg Gly Leu Asp Gln Glu Thr Ala
 370 375 380
 Glu Arg Leu Val Ile Arg Gly Phe Leu Gly Ala Val Ile Ala Glu Ile
 385 390 395 400
 Pro Ile Pro Ser Val Arg Gln Glu Ile Ile Lys Val Leu Asp Glu Lys
 405 410 415
 Leu Leu Asn Arg
 420

<210> 166
 <211> 410
 <212> PRT
 <213> Streptococcus pyogenes

<400> 166
 Met Ile Lys Arg Leu Ile Ser Leu Val Val Ile Ala Leu Phe Phe Ala
 1 5 10 15
 Ala Ser Thr Val Ser Gly Glu Glu Tyr Ser Val Thr Ala Lys His Ala
 20 25 30
 Ile Ala Val Asp Leu Glu Ser Gly Lys Val Leu Tyr Glu Lys Asp Ala
 35 40 45
 Lys Glu Val Val Pro Val Ala Ser Val Ser Lys Leu Leu Thr Thr Tyr
 50 55 60
 Leu Val Tyr Lys Glu Val Ser Lys Gly Lys Leu Asn Trp Asp Ser Pro
 65 70 75 80
 Val Thr Ile Ser Asn Tyr Pro Tyr Glu Leu Thr Thr Asn Tyr Thr Ile
 85 90 95
 Ser Asn Val Pro Leu Asp Lys Arg Lys Tyr Thr Val Lys Glu Leu Leu
 100 105 110
 Ser Ala Leu Val Val Asn Asn Ala Asn Ser Pro Ala Ile Ala Leu Ala
 115 120 125
 Glu Lys Ile Gly Gly Thr Glu Pro Lys Phe Val Asp Lys Met Lys Lys
 130 135 140
 Gln Leu Arg Gln Trp Gly Ile Ser Asp Ala Lys Val Val Asn Ser Thr
 145 150 155
 Gly Leu Thr Asn His Phe Leu Gly Ala Asn Thr Tyr Pro Asn Thr Glu
 160 165 170 175
 Pro Asp Asp Glu Asn Cys Phe Cys Ala Thr Asp Leu Ala Ile Ile Ala
 180 185 190
 Arg His Leu Leu Leu Glu Phe Pro Glu Val Leu Lys Leu Ser Ser Lys
 195 200 205
 Ser Ser Thr Ile Phe Ala Gly Gln Thr Ile Tyr Ser Tyr Asn Tyr Met
 210 215 220
 Leu Lys Gly Met Pro Cys Tyr Arg Glu Gly Val Asp Gly Leu Phe Val
 225 230 235 240
 Gly Tyr Ser Lys Lys Ala Gly Ala Ser Phe Val Ala Thr Ser Val Glu
 245 250 255
 Asn Gln Met Arg Val Ile Thr Val Val Leu Asn Ala Asp Gln Ser His
 260 265 270
 Glu Asp Asp Leu Ala Ile Phe Lys Thr Thr Asn Gln Leu Leu Gln Tyr
 275 280 285
 Leu Leu Ile Asn Phe Gln Lys Val Gln Leu Ile Glu Asn Asn Lys Pro
 290 295 300
 Val Lys Thr Leu Tyr Val Leu Asp Ser Pro Glu Lys Thr Val Lys Leu
 305 310 315 320
 Val Ala Gln Asn Ser Leu Phe Phe Ile Lys Pro Ile His Thr Lys Thr
 325 330 335
 Lys Asn Thr Val His Ile Thr Lys Lys Ser Ser Thr Met Ile Ala Pro
 340 345 350
 Leu Ser Lys Gly Gln Val Leu Gly Arg Ala Thr Leu Gln Asp Lys His
 355 360 365
 Leu Ile Gly Gln Gly Tyr Leu Asp Thr Pro Pro Ser Ile Asn Leu Ile
 370 375 380
 Leu Gln Lys Asn Ile Ser Lys Ser Phe Phe Leu Lys Val Trp Trp Asn
 385 390 395 400
 Arg Phe Val Arg Tyr Val Asn Thr Ser Leu

【 0 1 4 9 】

405

410

<210> 167
 <211> 308
 <212> PRT
 <213> Streptococcus pyogenes

<400> 167
 Met Glu Ser Ile Asp Lys Ser Lys Phe Arg Phe Val Glu Arg Asp Ser
 1 5 10 15
 Glu Ala Ser Glu Val Ile Asp Thr Pro Ala Tyr Ser Tyr Trp Lys Ser
 20 25 30
 Val Phe Arg Gln Phe Phe Ser Lys Lys Ser Thr Val Phe Met Leu Val
 35 40 45
 Ile Leu Val Thr Val Leu Met Met Ser Phe Ile Tyr Pro Met Phe Ala
 50 55 60
 Asn Tyr Asp Phe Asn Asp Val Ser Asn Ile Asn Asp Phe Ser Lys Arg
 65 70 75 80
 Tyr Ile Trp Pro Asn Ala Glu Tyr Trp Phe Gly Thr Asp Lys Asn Gly
 85 90 95
 Gln Ser Leu Phe Asp Gly Val Trp Tyr Gly Ala Arg Asn Ser Ile Leu
 100 105 110
 Ile Ser Val Ile Ala Thr Leu Ile Asn Ile Thr Ile Gly Val Val Leu
 115 120 125
 Gly Ala Ile Trp Gly Val Ser Lys Ala Phe Asp Lys Val Met Ile Glu
 130 135 140
 Ile Tyr Asn Ile Ile Ser Asn Ile Pro Ser Met Leu Ile Ile Ile Val
 145 150 155 160
 Leu Thr Tyr Ser Leu Gly Ala Gly Phe Trp Asn Leu Ile Leu Ala Phe
 165 170 175
 Cys Ile Thr Gly Trp Ile Gly Val Ala Tyr Ser Ile Arg Val Gln Ile
 180 185 190
 Leu Arg Tyr Arg Asp Leu Glu Tyr Asn Leu Ala Ser Gln Thr Leu Gly
 195 200 205
 Thr Pro Met Tyr Lys Ile Ala Val Lys Asn Leu Leu Pro Gln Leu Val
 210 215 220
 Ser Val Ile Met Thr Met Leu Ser Gln Met Leu Pro Val Tyr Val Ser
 225 230 235 240
 Ser Glu Ala Phe Leu Ser Phe Phe Gly Ile Gly Leu Pro Thr Thr Thr
 245 250 255
 Pro Ser Leu Gly Arg Phe Ile Ala Asn Tyr Ser Ser Asn Leu Thr Thr
 260 265 270
 Asn Ala Tyr Leu Phe Trp Ile Pro Leu Val Thr Leu Ile Leu Val Ser
 275 280 285
 Leu Pro Leu Tyr Ile Val Gly Gln Asn Leu Ala Asp Ala Ser Asp Pro
 290 295 300
 Arg Ser His Arg
 305

<210> 168
 <211> 524
 <212> PRT
 <213> Streptococcus pyogenes

<400> 168
 Leu Ala Leu Thr Asp Phe Lys Asp Lys Asp Gln Gln Asp Gln Gln Arg
 1 5 10 15
 Ser Phe Lys Glu Gln Ile Leu Ala Glu Leu Glu Lys Ala Asn Gln Ile
 20 25 30
 Arg Lys Glu Lys Glu Glu Glu Leu Phe Gln Lys Glu Leu Glu Ala Lys
 35 40 45
 Glu Ala Ala Arg Arg Thr Ala Gln Leu Tyr Ala Glu Tyr Lys Arg Gln
 50 55 60
 Asp Ala Phe Gln Lys Glu Ser Ile Ala His Asn Asn Lys Thr Ala Lys
 65 70 75 80
 His Phe Gln Ala Ile Lys Gly Ala Val Met Thr Ser Glu Ala Leu Lys
 85 90 95
 Pro Thr Leu Leu Ser Glu Lys Glu Asn Ser Ser Leu Lys Thr Thr Asn
 100 105 110
 Lys Arg Val Val Gln Ala Asn Glu Leu Gln Glu Thr Ala Ser Lys Glu
 115 120 125
 Ser Gln Val Pro Leu Thr Ile Glu Lys Gly His Ser Val Arg Arg Lys
 130 135 140

【 0 1 5 0 】

Leu Ser Lys Arg Gln Gln Thr Glu Arg Ala Ala Lys Lys Ile Ser Thr
 145 150 155 160
 Val Leu Ile Ser Ser Ile Ile Ile Thr Leu Leu Ala Val Thr Leu Ala
 165 170 175
 Gly Ala Gly Tyr Val Tyr Ser Ala Leu Asn Pro Val Asp Lys Asn Ser
 180 185 190
 Asp Ala Phe Val Gln Val Glu Ile Pro Ser Gly Ser Gly Asn Lys Leu
 195 200 205
 Ile Gly Gln Ile Leu Gln Lys Lys Gly Leu Ile Lys Asn Ser Thr Val
 210 215 220
 Phe Ser Phe Tyr Thr Lys Phe Lys Asn Phe Thr Asn Phe Gln Ser Gly
 225 230 235 240
 Tyr Tyr Asn Leu Gln Lys Ser Met Ser Leu Glu Glu Ile Ala Ser Ala
 245 250 255
 Leu Gln Glu Gly Gly Thr Ala Glu Pro Thr Lys Pro Ser Leu Gly Lys
 260 265 270
 Ile Leu Ile Pro Glu Gly Tyr Thr Ile Lys Gln Ile Ala Lys Ala Val
 275 280 285
 Glu His Asn Ser Lys Gly Lys Thr Lys Lys Ala Lys Thr Pro Phe Asn
 290 295 300
 Glu Lys Asp Phe Leu Asp Leu Val Thr Asp Glu Ala Phe Ile Gln Asp
 305 310 315 320
 Met Val Lys Arg Tyr Pro Lys Leu Leu Ala Thr Ile Pro Thr Lys Glu
 325 330 335
 Lys Ala Ile Tyr Arg Leu Glu Gly Tyr Leu Phe Pro Ala Thr Tyr Asn
 340 345 350
 Tyr Tyr Lys Glu Thr Thr Met Arg Glu Leu Val Glu Asp Met Leu Ala
 355 360 365
 Ala Met Asp Ala Thr Leu Val Pro Tyr Tyr Asp Lys Ile Ala Ala Ser
 370 375 380
 Gly Lys Thr Val Asn Glu Val Leu Thr Leu Ala Ser Leu Val Glu Lys
 385 390 395 400
 Glu Gly Ser Thr Asp Asp Arg Arg Gln Ile Ala Ser Val Phe Tyr
 405 410 415
 Asn Arg Leu Asn Ser Gly Met Ala Leu Gln Ser Asn Ile Ala Ile Leu
 420 425 430
 Tyr Ala Met Gly Lys Leu Gly Glu Lys Thr Thr Leu Ala Glu Asp Ala
 435 440 445
 Thr Ile Asp Thr Thr Ile Asn Ser Pro Tyr Asn Ile Tyr Thr Asn Thr
 450 455 460
 Gly Leu Met Pro Gly Pro Val Ala Ser Ser Gly Val Ser Ala Ile Glu
 465 470 475 480
 Ala Thr Leu Asn Pro Ala Ser Thr Asp Tyr Leu Tyr Phe Val Ala Asn
 485 490 495
 Val His Thr Gly Glu Val Tyr Tyr Ala Lys Thr Phe Glu Glu His Ser
 500 505 510
 Ala Asn Val Glu Lys Tyr Val Asn Ser Gln Ile Gln
 515 520

<210> 169

<211> 1647

<212> PRT

<213> Streptococcus pyogenes

<400> 169

Val Glu Lys Lys Gln Arg Phe Ser Leu Arg Lys Tyr Lys Ser Gly Thr
 1 5 10 15
 Phe Ser Val Leu Ile Gly Ser Val Phe Leu Val Met Thr Thr Val
 20 25 30
 Ala Ala Asp Glu Leu Ser Thr Met Ser Glu Pro Thr Ile Thr Asn His
 35 40 45
 Ala Gln Gln Gln Ala Gln His Leu Thr Asn Thr Glu Leu Ser Ser Ala
 50 55 60
 Glu Ser Lys Ser Gln Asp Thr Ser Gln Ile Thr Leu Lys Thr Asn Arg
 65 70 75 80
 Glu Lys Glu Gln Ser Gln Asp Leu Val Ser Glu Pro Thr Thr Thr Glu
 85 90 95
 Leu Ala Asp Thr Asp Ala Ala Ser Met Ala Asn Thr Gly Ser Asp Ala
 100 105 110
 Thr Gln Lys Ser Ala Ser Leu Pro Pro Val Asn Thr Asp Val His Asp
 115 120 125
 Trp Val Lys Thr Lys Gly Ala Trp Asp Lys Gly Tyr Lys Gly Gln Gly
 130 135 140
 Lys Val Val Ala Val Ile Asp Thr Gly Ile Asp Pro Ala His Gln Ser

145	Met	Arg	Ile	Ser	Asp	150	Val	Ser	Thr	Ala	Lys	155	Val	Lys	Ser	Lys	Glu	Asp	160
					165						170						175		
Met	Leu	Ala	Arg	Gln	Lys	Ala	Ala	Gly	Ile	Asn	Tyr	Gly	Ser	Trp	Ile				
			180					185					190						
Asn	Asp	Lys	Val	Val	Phe	Ala	His	Asn	Tyr	Val	Glu	Asn	Ser	Asp	Asn				
		195					200					205							
Ile	Lys	Glu	Asn	Gln	Phe	Glu	Asp	Phe	Asp	Glu	Asp	Trp	Glu	Asn	Phe				
	210					215					220								
Glu	Phe	Asp	Ala	Glu	Ala	Glu	Pro	Lys	Ala	Ile	Lys	Lys	His	Lys	Ile				
	225				230					235					240				
Tyr	Arg	Pro	Gln	Ser	Thr	Gln	Ala	Pro	Lys	Glu	Thr	Val	Ile	Lys	Thr				
			245						250					255					
Glu	Glu	Thr	Asp	Gly	Ser	His	Asp	Ile	Asp	Trp	Thr	Gln	Thr	Asp	Asp				
			260					265					270						
Asp	Thr	Lys	Tyr	Glu	Ser	His	Gly	Met	His	Val	Thr	Gly	Ile	Val	Ala				
		275					280					285							
Gly	Asn	Ser	Lys	Glu	Ala	Ala	Ala	Thr	Gly	Glu	Arg	Phe	Leu	Gly	Ile				
	290					295					300								
Ala	Pro	Glu	Ala	Gln	Val	Met	Phe	Met	Arg	Val	Phe	Ala	Asn	Asp	Ile				
	305				310					315					320				
Met	Gly	Ser	Ala	Glu	Ser	Leu	Phe	Ile	Lys	Ala	Ile	Glu	Asp	Ala	Val				
			325						330					335					
Ala	Leu	Gly	Ala	Asp	Val	Ile	Asn	Leu	Ser	Leu	Gly	Thr	Ala	Asn	Gly				
		340						345					350						
Ala	Gln	Leu	Ser	Gly	Ser	Lys	Pro	Leu	Met	Glu	Ala	Ile	Glu	Lys	Ala				
		355					360					365							
Lys	Lys	Ala	Gly	Val	Ser	Val	Val	Val	Ala	Ala	Gly	Asn	Glu	Arg	Val				
	370					375					380								
Tyr	Gly	Ser	Asp	His	Asp	Asp	Pro	Leu	Ala	Thr	Asn	Pro	Asp	Tyr	Gly				
	385				390					395					400				
Leu	Val	Gly	Ser	Pro	Ser	Thr	Gly	Arg	Thr	Pro	Thr	Ser	Val	Ala	Ala				
			405					410						415					
Ile	Asn	Ser	Lys	Trp	Val	Ile	Gln	Arg	Leu	Met	Thr	Val	Lys	Glu	Leu				
		420						425					430						
Glu	Asn	Arg	Ala	Asp	Leu	Asn	His	Gly	Lys	Ala	Ile	Tyr	Ser	Glu	Ser				
		435					440					445							
Val	Asp	Phe	Lys	Asp	Ile	Lys	Asp	Ser	Leu	Gly	Tyr	Asp	Lys	Ser	His				
	450					455					460								
Gln	Phe	Ala	Tyr	Val	Lys	Glu	Ser	Thr	Asp	Ala	Gly	Tyr	Asn	Ala	Gln				
	465				470					475					480				
Asp	Val	Lys	Gly	Lys	Ile	Ala	Leu	Ile	Glu	Arg	Asp	Pro	Asn	Lys	Thr				
			485						490					495					
Tyr	Asp	Glu	Met	Ile	Ala	Leu	Ala	Lys	Lys	His	Gly	Ala	Leu	Gly	Val				
		500						505					510						
Leu	Ile	Phe	Asn	Asn	Lys	Pro	Gly	Gln	Ser	Asn	Arg	Ser	Met	Arg	Leu				
		515					520					525							
Thr	Ala	Asn	Gly	Met	Gly	Ile	Pro	Ser	Ala	Phe	Ile	Ser	His	Glu	Phe				
		530				535					540								
Gly	Lys	Ala	Met	Ser	Gln	Leu	Asn	Gly	Asn	Gly	Thr	Gly	Ser	Leu	Glu				
			550							555					560				
Phe	Asp	Ser	Val	Val	Ser	Lys	Ala	Pro	Ser	Gln	Lys	Gly	Asn	Glu	Met				
			565						570					575					
Asn	His	Phe	Ser	Asn	Trp	Gly	Leu	Thr	Ser	Asp	Gly	Tyr	Leu	Lys	Pro				
			580					585					590						
Asp	Ile	Thr	Ala	Pro	Gly	Gly	Asp	Ile	Tyr	Ser	Thr	Tyr	Asn	Asp	Asn				
		595					600					605							
His	Tyr	Gly	Ser	Gln	Thr	Gly	Thr	Ser	Met	Ala	Ser	Pro	Gln	Ile	Ala				
		610				615						620							
Gly	Ala	Ser	Leu	Leu	Val	Lys	Gln	Tyr	Leu	Glu	Lys	Thr	Gln	Pro	Asn				
		625			630					635					640				
Leu	Pro	Lys	Glu	Lys	Ile	Ala	Asp	Ile	Val	Lys	Asn	Leu	Leu	Met	Ser				
			645						650					655					
Asn	Ala	Gln	Ile	His	Val	Asn	Pro	Glu	Thr	Lys	Thr	Thr	Thr	Ser	Pro				
		660						665					670						
Arg	Gln	Gln	Gly	Ala	Gly	Leu	Leu	Asn	Ile	Asp	Gly	Ala	Val	Thr	Ser				
		675				680						685							
Gly	Leu	Tyr	Val	Thr	Gly	Lys	Asp	Asn	Tyr	Gly	Ser	Ile	Ser	Leu	Gly				
		690				695					700								
Asn	Ile	Thr	Asp	Thr	Met	Thr	Phe	Asp	Val	Thr	Val	His	Asn	Leu	Ser				
		705			710					715					720				
Asn	Lys	Asp	Lys	Thr	Leu	Arg	Tyr	Asp	Thr	Glu	Leu	Leu	Thr	Asp	His				
			725						730					735					
Val	Asp	Pro	Gln	Lys	Gly	Arg	Phe	Thr	Leu	Thr	Ser	His	Ser	Leu	Lys				
			740					745					750						

Thr Tyr Gln Gly Gly Glu Val Thr Val Pro Ala Asn Gly Lys Val Thr
 755 760 765
 Val Arg Val Thr Met Asp Val Ser Gln Phe Thr Lys Glu Leu Thr Lys
 770 775 780
 Gln Met Pro Asn Gly Tyr Tyr Leu Glu Gly Phe Val Arg Phe Arg Asp
 785 790 795 800
 Ser Gln Asp Asp Gln Leu Asn Arg Val Asn Ile Pro Phe Val Gly Phe
 805 810 815
 Lys Gly Gln Phe Glu Asn Leu Ala Val Ala Glu Glu Ser Ile Tyr Arg
 820 825 830
 Leu Lys Ser Gln Gly Lys Thr Gly Phe Tyr Phe Asp Glu Ser Gly Pro
 835 840 845
 Lys Asp Asp Ile Tyr Val Gly Lys His Phe Thr Gly Leu Val Thr Leu
 850 855 860
 Gly Ser Glu Thr Asn Val Ser Thr Lys Thr Ile Ser Asp Asn Gly Leu
 865 870 875 880
 His Thr Leu Gly Thr Phe Lys Asn Ala Asp Gly Lys Phe Ile Leu Glu
 885 890 895
 Lys Asn Ala Gln Gly Asn Pro Val Leu Ala Ile Ser Pro Asn Gly Asp
 900 905 910
 Asn Asn Gln Asp Phe Ala Ala Phe Lys Gly Val Phe Leu Arg Lys Tyr
 915 920 925
 Gln Gly Leu Lys Ala Ser Val Tyr His Ala Ser Asp Lys Glu His Lys
 930 935 940
 Asn Pro Leu Trp Val Ser Pro Glu Ser Phe Lys Gly Asp Lys Asn Phe
 945 950 955 960
 Asn Ser Asp Ile Arg Phe Ala Lys Ser Thr Thr Leu Leu Gly Thr Ala
 965 970 975
 Phe Ser Gly Lys Ser Leu Thr Gly Ala Glu Leu Pro Asp Gly His Tyr
 980 985 990
 His Tyr Val Val Ser Tyr Tyr Pro Asp Val Val Gly Ala Lys Arg Gln
 995 1000 1005
 Glu Met Thr Phe Asp Met Ile Leu Asp Arg Gln Lys Pro Val Leu
 1010 1015 1020
 Ser Gln Ala Thr Phe Asp Pro Glu Thr Asn Arg Phe Lys Pro Glu
 1025 1030 1035
 Pro Leu Lys Asp Arg Gly Leu Ala Gly Val Arg Lys Asp Ser Val
 1040 1045 1050
 Phe Tyr Leu Glu Arg Lys Asp Asn Lys Pro Tyr Thr Val Thr Ile
 1055 1060 1065
 Asn Asp Ser Tyr Lys Tyr Val Ser Val Glu Asp Asn Lys Thr Phe
 1070 1075 1080
 Val Glu Arg Gln Ala Asp Gly Ser Phe Ile Leu Pro Leu Asp Lys
 1085 1090 1095
 Ala Lys Leu Gly Asp Phe Tyr Tyr Met Val Glu Asp Phe Ala Gly
 1100 1105 1110
 Asn Val Ala Ile Ala Lys Leu Gly Asp His Leu Pro Gln Thr Leu
 1115 1120 1125
 Gly Lys Thr Pro Ile Lys Leu Lys Leu Thr Asp Gly Asn Tyr Gln
 1130 1135 1140
 Thr Lys Glu Thr Leu Lys Asp Asn Leu Glu Met Thr Gln Ser Asp
 1145 1150 1155
 Thr Gly Leu Val Thr Asn Gln Ala Gln Leu Ala Val Val His Arg
 1160 1165 1170
 Asn Gln Pro Gln Ser Gln Leu Thr Lys Met Asn Gln Asp Phe Phe
 1175 1180 1185
 Ile Ser Pro Asn Glu Asp Gly Asn Lys Asp Phe Val Ala Phe Lys
 1190 1195 1200
 Gly Leu Lys Asn Asn Val Tyr Asn Asp Leu Thr Val Asn Val Tyr
 1205 1210 1215
 Ala Lys Asp Asp His Gln Lys Gln Thr Pro Ile Trp Ser Ser Gln
 1220 1225 1230
 Ala Gly Ala Ser Val Ser Ala Ile Glu Ser Thr Ala Trp Tyr Gly
 1235 1240 1245
 Ile Thr Ala Arg Gly Ser Lys Val Met Pro Gly Asp Tyr Gln Tyr
 1250 1255 1260
 Val Val Thr Tyr Arg Asp Glu His Gly Lys Glu His Gln Lys Gln
 1265 1270 1275
 Tyr Thr Ile Ser Val Asn Asp Lys Lys Pro Met Ile Thr Gln Gly
 1280 1285 1290
 Arg Phe Asp Thr Ile Asn Gly Val Asp His Phe Thr Pro Asp Lys
 1295 1300 1305
 Thr Lys Ala Leu Asp Ser Ser Gly Ile Val Arg Glu Glu Val Phe
 1310 1315 1320
 Tyr Leu Ala Lys Lys Asn Gly Arg Lys Phe Asp Val Thr Glu Gly

1325	Lys Asp Gly Ile Thr Val	1330	Ser Asp Asn Lys Val	1335	Tyr Ile Pro Lys
1340	Asn Pro Asp Gly Ser Tyr	1345	Thr Ile Ser Lys Arg	1350	Asp Gly Val Thr
1355	Leu Ser Asp Tyr Tyr Tyr	1360	Leu Val Glu Asp Arg	1365	Ala Gly Asn Val
1370	Ser Phe Ala Thr Leu Arg	1375	Asp Leu Lys Ala Val	1380	Gly Lys Asp Lys
1385	Ala Val Val Asn Phe Gly	1390	Leu Asp Leu Pro Val	1395	Pro Glu Asp Lys
1400	Gln Ile Val Asn Phe Thr	1405	Tyr Leu Val Arg Asp	1410	Ala Asp Gly Lys
1415	Pro Ile Glu Asn Leu Glu	1420	Tyr Tyr Asn Asn Ser	1425	Gly Asn Ser Leu
1430	Ile Leu Pro Tyr Gly Lys	1435	Tyr Thr Val Glu Leu	1440	Leu Thr Tyr Asp
1445	Thr Asn Ala Ala Lys Leu	1450	Glu Ser Asp Lys Ile	1455	Val Ser Phe Thr
1460	Leu Ser Ala Asp Asn Asn	1465	Phe Gln Gln Val Thr	1470	Phe Lys Ile Thr
1475	Met Leu Ala Thr Ser Gln	1480	Ile Thr Ala His Phe	1485	Asp His Leu Leu
1490	Pro Glu Gly Ser Arg Val	1495	Ser Leu Lys Thr Ala	1500	Gln Asp Gln Leu
1505	Ile Pro Leu Glu Gln Ser	1510	Leu Tyr Val Pro Lys	1515	Ala Tyr Gly Lys
1520	Thr Val Gln Glu Gly Thr	1525	Tyr Glu Val Val Val	1530	Ser Leu Pro Lys
1535	Gly Tyr Arg Ile Glu Gly	1540	Asn Thr Lys Val Asn	1545	Thr Leu Pro Asn
1550	Glu Val His Glu Leu Ser	1555	Leu Arg Leu Val Lys	1560	Val Gly Asp Ala
1565	Ser Asp Ser Thr Gly Asp	1570	His Lys Val Met Ser	1575	Lys Asn Asn Ser
1580	Gln Ala Leu Thr Ala Ser	1585	Ala Thr Pro Thr Lys	1590	Ser Thr Thr Ser
1595	Ala Thr Ala Lys Ala Leu	1600	Pro Ser Thr Gly Glu	1605	Lys Met Gly Leu
1610	Lys Leu Arg Ile Val Gly	1615	Leu Val Leu Leu Gly	1620	Leu Thr Cys Val
1625	Phe Ser Arg Lys Lys Ser	1630	Thr Lys Asp	1635	
1640		1645			

<210> 170
 <211> 184
 <212> PRT
 <213> Streptococcus pyogenes

<400> 170
 Met Lys Trp Ser Gly Phe Met Lys Thr Lys Ser Lys Arg Phe Leu Asn
 1 5 10 15
 Leu Ala Thr Leu Cys Leu Ala Leu Leu Gly Thr Thr Leu Leu Met Ala
 20 25 30
 His Pro Val Gln Ala Glu Val Ile Ser Lys Arg Asp Tyr Met Thr Arg
 35 40 45
 Phe Gly Leu Gly Asp Leu Glu Asp Asp Ser Ala Asn Tyr Pro Ser Asn
 50 55 60
 Leu Glu Ala Arg Tyr Lys Gly Tyr Leu Glu Gly Tyr Glu Lys Gly Leu
 65 70 75 80
 Lys Gly Asp Asp Ile Pro Glu Arg Pro Lys Ile Gln Val Pro Glu Asp
 85 90 95
 Val Gln Pro Ser Asp His Gly Asp Tyr Arg Asp Gly Tyr Glu Glu Gly
 100 105 110
 Phe Gly Glu Gly Gln His Lys Arg Asp Pro Leu Glu Thr Glu Ala Glu
 115 120 125
 Asp Asp Ser Gln Gly Gly Arg Gln Glu Gly Arg Gln Gly His Gln Glu
 130 135 140
 Gly Ala Asp Ser Ser Asp Leu Asn Val Glu Glu Ser Asp Gly Leu Ser
 145 150 155 160
 Val Ile Asp Glu Val Val Gly Val Ile Tyr Gln Ala Phe Ser Thr Ile
 165 170 175
 Trp Thr Tyr Leu Ser Gly Leu Phe
 180

【 0 1 5 4 】

<210> 171
 <211> 210
 <212> PRT
 <213> Streptococcus pyogenes

<400> 171
 Met Lys Lys Thr Leu Thr Leu Leu Leu Ala Leu Phe Ala Ile Gly Val
 1 5 10 15
 Thr Ser Ser Val Arg Ala Glu Asp Glu Gln Ser Ser Thr Gln Lys Pro
 20 25 30
 Val Lys Phe Asp Leu Asp Gly Pro Gln Gln Lys Ile Lys Asp Tyr Ser
 35 40 45
 Gly Asn Thr Ile Thr Leu Glu Asp Leu Tyr Val Gly Ser Lys Val Val
 50 55 60
 Lys Ile Tyr Ile Pro Gln Gly Trp Trp Val Tyr Leu Tyr Arg Gln Cys
 65 70 75 80
 Asp His Asn Ser Lys Glu Arg Gly Ile Leu Ala Ser Pro Ile Leu Glu
 85 90 95
 Lys Asn Ile Thr Lys Thr Asp Pro Tyr Arg Gln Tyr Tyr Thr Gly Val
 100 105 110
 Pro Tyr Ile Leu Asn Leu Gly Glu Asp Pro Leu Lys Lys Gly Glu Lys
 115 120 125
 Leu Thr Phe Ser Phe Lys Gly Glu Asp Gly Phe Tyr Val Gly Ser Tyr
 130 135 140
 Ile Tyr Arg Asp Ser Asp Thr Ile Lys Lys Glu Lys Glu Ala Glu Glu
 145 150 155 160
 Ala Leu Gln Lys Lys Glu Glu Glu Lys Gln Gln Lys Gln Leu Glu Glu
 165 170 175
 Ser Met Leu Lys Gln Ile Arg Glu Glu Asp His Lys Pro Trp His Gln
 180 185 190
 Arg Leu Ser Glu Ser Ile Gln Asp Gln Trp Trp Asn Phe Lys Gly Leu
 195 200 205
 Phe Gln
 210

<210> 172
 <211> 204
 <212> PRT
 <213> Streptococcus pyogenes

<400> 172
 Met Lys Lys Thr Leu Thr Leu Leu Leu Ala Leu Phe Ala Ile Gly Val
 1 5 10 15
 Thr Ser Ser Val Arg Ala Glu Asp Glu Gln Asn Lys Phe Ile Leu Asp
 20 25 30
 Gly Leu Gln Glu Lys Val Lys Glu Val Ser Val Ser Asp Phe Ser Val
 35 40 45
 Gly Glu Ser Lys Ile Lys Val Trp Leu Pro Gln Ala Trp Ser Val Lys
 50 55 60
 Ile Ser Arg Glu His Ser Pro Lys Ser Ser Ile Ser Asn Ser Gly Glu
 65 70 75 80
 Gln Lys Pro Leu Ser Asn Ser Ser Glu Asn Lys Glu Gly Gln Phe Ser
 85 90 95
 Lys Arg Leu Pro Tyr Gly Thr Gln His Thr Ile Lys Leu Ser Ser Gln
 100 105 110
 Leu Thr Lys Gly Glu Arg Val Thr Leu Thr Phe Arg Asp Glu Asp Phe
 115 120 125
 Trp Gly Ala Gly Tyr Cys Phe Tyr Arg Asp Ser Leu Ser Ile Lys Glu
 130 135 140
 Asp Lys Gln Tyr Glu Glu Glu Ile Lys Lys Ile Glu Asp Asp Leu Glu
 145 150 155 160
 Arg Gln Asp Leu Glu Asn Asp Ala Leu Glu Met Phe Lys Lys Gln Thr
 165 170 175
 Glu Arg Glu Ala Asn Lys Pro Trp His Gln Arg Leu Ser Glu Asn Ile
 180 185 190
 Gln Asp Gln Trp Trp Asn Phe Lys Gly Leu Phe Gln
 195 200

<210> 173
 <211> 389
 <212> PRT

【 0 1 5 5 】

<213> Streptococcus pyogenes

<400> 173

Met Ile Ile Thr Lys Lys Ser Leu Phe Val Thr Ser Val Ala Leu Ser
 1 5 10 15
 Leu Val Pro Leu Ala Thr Ala Gln Ala Gln Glu Trp Thr Pro Arg Ser
 20 25 30
 Val Thr Glu Ile Lys Ser Glu Leu Val Leu Val Asp Asn Val Phe Thr
 35 40 45
 Tyr Thr Val Lys Tyr Gly Asp Thr Leu Ser Thr Ile Ala Glu Ala Met
 50 55 60
 Gly Ile Asp Val His Val Leu Gly Asp Ile Asn His Ile Ala Asn Ile
 65 70 75 80
 Asp Leu Ile Phe Pro Asp Thr Ile Leu Thr Ala Asn Tyr Asn Gln His
 85 90 95
 Gly Gln Ala Thr Asn Leu Thr Val Gln Ala Pro Ala Ser Ser Pro Ala
 100 105 110
 Ser Val Ser His Val Pro Ser Ser Glu Pro Leu Pro Gln Ala Ser Ala
 115 120 125
 Thr Ser Gln Pro Thr Val Pro Met Ala Pro Pro Ala Thr Pro Ser Asp
 130 135 140
 Val Pro Thr Thr Pro Phe Ala Ser Ala Lys Pro Asp Ser Ser Val Thr
 145 150 155 160
 Ala Ser Ser Glu Leu Thr Ser Ser Thr Asn Asp Val Ser Thr Glu Leu
 165 170 175
 Ser Ser Glu Ser Gln Lys Gln Pro Glu Val Pro Gln Glu Ala Val Pro
 180 185 190
 Thr Pro Lys Ala Ala Glu Thr Thr Glu Val Glu Pro Lys Thr Asp Ile
 195 200 205
 Ser Glu Ala Pro Thr Ser Ala Asn Arg Pro Val Pro Asn Glu Ser Ala
 210 215 220
 Ser Glu Glu Val Ser Ser Ala Ala Pro Ala Gln Ala Pro Ala Glu Lys
 225 230 235 240
 Glu Glu Thr Ser Ala Pro Ala Ala Gln Lys Ala Val Ala Asp Thr Thr
 245 250 255
 Ser Val Ala Thr Ser Asn Gly Leu Ser Tyr Ala Pro Asn His Ala Tyr
 260 265 270
 Asn Pro Met Asn Ala Gly Leu Gln Pro Gln Thr Ala Ala Phe Lys Glu
 275 280 285
 Glu Val Ala Ser Ala Phe Gly Ile Thr Ser Phe Ser Gly Tyr Arg Pro
 290 295 300
 Gly Asp Pro Gly Asp His Gly Lys Gly Leu Ala Ile Asp Phe Met Val
 305 310 315 320
 Pro Glu Asn Ser Ala Leu Gly Asp Gln Val Ala Gln Tyr Ala Ile Asp
 325 330 335
 His Met Ala Glu Arg Gly Ile Ser Tyr Val Ile Trp Lys Gln Arg Phe
 340 345 350
 Tyr Ala Pro Phe Ala Ser Ile Tyr Gly Pro Ala Tyr Thr Trp Asn Pro
 355 360 365
 Met Pro Asp Arg Gly Ser Ile Thr Glu Asn His Tyr Asp His Val His
 370 375 380
 Val Ser Phe Asn Ala
 385

<210> 174

<211> 331

<212> PRT

<213> Streptococcus pyogenes

<400> 174

Leu Arg Gln Ile Gln Ser Ile Arg Leu Ile Asp Val Leu Glu Leu Ala
 1 5 10 15
 Phe Gly Val Gly Tyr Lys Glu Glu Thr Thr Ser Gln Phe Ser Ser Asp
 20 25 30
 Gln Pro Ser Gln Val Val Leu Tyr Arg Gly Glu Ala Asn Thr Val Arg
 35 40 45
 Phe Ala Tyr Thr Asn Gln Met Ser Leu Met Lys Asp Ile Arg Ile Ala
 50 55 60
 Leu Asp Gly Ser Asp Lys Ser Leu Thr Ala Gln Ile Val Pro Gly Met
 65 70 75 80
 Gly His Val Tyr Glu Gly Phe Gln Thr Ser Ala Arg Gly Ile Phe Thr
 85 90 95
 Met Ser Gly Val Pro Glu Ser Thr Val Pro Val Ala Asn Pro Asn Val
 100 105 110

Gln Thr Lys Tyr Ile Arg Tyr Phe Lys Val Ile Asp Asp Met His Asn
 115 120 125
 Thr Met Tyr Lys Gly Thr Val Phe Leu Val Gln Pro Gln Ala Trp Lys
 130 135 140
 Tyr Thr Met Lys Ser Val Asp Gln Leu Pro Val Asp Asp Leu Asn His
 145 150 155 160
 Ile Gly Val Ala Gly Ile Glu Arg Met Thr Thr Leu Ile Lys Asn Ala
 165 170 175
 Gly Ala Leu Leu Thr Thr Gly Gly Ser Gly Ala Phe Pro Asp Asn Ile
 180 185 190
 Lys Val Ser Ile Asn Pro Lys Gly Arg Gln Ala Thr Ile Thr Tyr Gly
 195 200 205
 Asp Gly Ser Thr Asp Ile Ile Pro Pro Ala Val Leu Trp Lys Lys Gly
 210 215 220
 Ser Val Lys Glu Pro Thr Glu Ala Asp Gln Ser Val Gly Thr Pro Thr
 225 230 235 240
 Pro Gly Ile Pro Gly Lys Phe Lys Arg Asp Gln Ser Leu Asn Glu His
 245 250 255
 Glu Ala Met Val Asn Val Glu Pro Leu Ser His Val Val Lys Asp Asn
 260 265 270
 Ile Lys Val Ile Asp Glu Lys Ser Thr Gly Arg Phe Glu Pro Phe Arg
 275 280 285
 Pro Asn Glu Asp Glu Lys Glu Lys Pro Ala Ser Asp Val Lys Val Arg
 290 295 300
 Pro Ala Glu Val Gly Ser Trp Leu Glu Pro Ala Thr Ala Leu Pro Ser
 305 310 315 320
 Val Glu Met Ser Ala Glu Asp Arg Leu Lys Ser
 325 330

<210> 175
 <211> 332
 <212> PRT
 <213> Streptococcus pyogenes

<400> 175
 Met Lys Val Leu Leu Tyr Leu Glu Ala Glu Asn Tyr Leu Arg Lys Ser
 1 5 10 15
 Gly Ile Gly Arg Ala Ile Lys His Gln Ala Lys Ala Leu Ser Leu Val
 20 25 30
 Gly Gln His Phe Thr Thr Asn Pro Arg Glu Thr Tyr Asp Leu Val His
 35 40 45
 Leu Asn Thr Tyr Gly Leu Lys Ser Trp Leu Leu Met Ile Lys Ala Gln
 50 55 60
 Lys Ala Gly Lys Lys Val Ile Met His Gly His Ser Thr Glu Glu Asp
 65 70 75 80
 Phe Arg Asn Ser Phe Ile Phe Ser Asn Leu Leu Ser Pro Trp Phe Lys
 85 90 95
 Lys Tyr Leu Cys His Phe Tyr Asn Lys Ala Asp Ala Ile Ile Thr Pro
 100 105 110
 Thr Leu Tyr Ser Lys Ser Leu Ile Glu Ser Tyr Gly Val Lys Ser Pro
 115 120 125
 Ile Phe Ala Val Ser Asn Gly Ile Asp Leu Glu Gln Tyr Gly Ala Asp
 130 135 140
 Pro Lys Lys Glu Ala Ala Phe Arg Arg Tyr Phe Asp Ile Lys Glu Gly
 145 150 155 160
 Glu Lys Val Val Met Gly Ala Gly Leu Phe Phe Leu Arg Lys Gly Ile
 165 170 175
 Asp Asp Phe Val Lys Val Ala Gln Ala Met Pro Asp Val Arg Phe Ile
 180 185 190
 Trp Phe Gly Glu Thr Asn Lys Trp Val Ile Pro Ala Gln Val Arg Gln
 195 200 205
 Met Val Asn Gly Asn His Pro Lys Asn Leu Ile Phe Pro Gly Tyr Ile
 210 215 220
 Lys Gly Asp Val Tyr Glu Gly Ala Met Thr Gly Ala Asp Ala Phe Phe
 225 230 235 240
 Phe Pro Ser Arg Glu Glu Thr Glu Gly Ile Val Val Leu Glu Ala Leu
 245 250 255
 Ala Ser Arg Gln His Leu Val Leu Arg Asp Ile Pro Val Tyr Tyr Gly
 260 265 270
 Trp Val Asp Gln Ser Ser Ala Glu Leu Ala Thr Asp Ile Pro Gly Phe
 275 280 285
 Ile Glu Ala Leu Lys Lys Val Phe Ser Gly Ala Ser Asn Lys Val Glu
 290 295 300
 Ala Gly Tyr Lys Val Ala Gln Ser Arg Arg Leu Glu Thr Val Gly His

305 310 315 320
 Ala Leu Val Asp Val Tyr Lys Lys Val Met Glu Leu
 325 330

<210> 176
 <211> 710
 <212> PRT
 <213> Streptococcus pyogenes

<400> 176

Met Glu Asn Asn Asn Asn His Asn Ile Ala Glu Ala Leu Ser Val Ser
 1 5 10 15
 Leu His Gln Ile Glu Gln Val Leu Ala Leu Thr Ala Gln Gly Asn Thr
 20 25 30
 Ile Pro Phe Ile Ala Arg Tyr Arg Lys Glu Val Thr Gly Asn Leu Asp
 35 40 45
 Glu Val Val Ile Lys Ser Ile Ile Asp Met Asp Lys Ser Leu Thr Thr
 50 55 60
 Leu Asn Glu Arg Lys Ala Thr Ile Leu Ala Lys Ile Glu Glu Gln Gly
 65 70 75 80
 Lys Leu Thr Asp Gln Leu Arg Thr Ser Ile Glu Ala Thr Glu Lys Leu
 85 90 95
 Ala Asp Leu Glu Glu Leu Tyr Leu Pro Tyr Lys Glu Lys Arg Arg Thr
 100 105 110
 Lys Ala Thr Ile Ala Arg Glu Ala Gly Leu Phe Pro Leu Ala Arg Leu
 115 120 125
 Ile Leu Gln Asn Ala Gln Asn Leu Glu Thr Ala Ala Glu Pro Phe Val
 130 135 140
 Thr Glu Gly Phe Ala Ser Pro Gln Glu Ala Leu Ala Gly Ala Val Asp
 145 150 155 160
 Ile Leu Val Glu Ala Met Ser Glu Asp Ala Lys Leu Arg Ser Trp Thr
 165 170 175
 Tyr Asn Glu Ile Trp Gln Tyr Ser Arg Leu Val Ser Thr Leu Lys Asp
 180 185 190
 Glu Gln Leu Asp Glu Lys Lys Val Phe Gln Ile Tyr Tyr Asp Phe Ser
 195 200 205
 Asp Gln Val Ser Asn Met Gln Gly Tyr Arg Thr Leu Ala Leu Asn Arg
 210 215 220
 Gly Glu Lys Leu Gly Ile Leu Lys Val Ser Phe Glu His Asn Leu Glu
 225 230 235 240
 Lys Met Gln Arg Phe Ser Ser Val Arg Phe Lys Glu Thr Asn Pro Tyr
 245 250 255
 Ile Glu Glu Val Ile Asn Gln Thr Ile Lys Lys Lys Ile Val Pro Ala
 260 265 270
 Met Glu Arg Arg Val Arg Ser Glu Leu Ser Asp Ala Ala Glu Asp Gly
 275 280 285
 Ala Ile His Leu Phe Ser Glu Asn Leu Arg His Leu Leu Val Ser
 290 295 300
 Pro Leu Lys Gly Lys Met Val Leu Gly Phe Asp Pro Ala Phe Arg Thr
 305 310 315 320
 Gly Ala Lys Leu Ala Ile Val Asp Gln Thr Gly Lys Leu Leu Thr Thr
 325 330 335
 Gln Val Ile Tyr Pro Val Ala Pro Ala Ser Gln Thr Lys Ile Gln Ala
 340 345 350
 Ala Lys Glu Thr Leu Thr Gln Leu Ile Glu Thr Tyr Gln Ile Asp Ile
 355 360 365
 Ile Ala Ile Gly Asn Gly Thr Ala Ser Arg Glu Ser Glu Ala Phe Val
 370 375 380
 Ala Asp Val Leu Lys Asp Phe Pro Asn Thr Ser Tyr Val Ile Val Asn
 385 390 395 400
 Glu Ser Gly Ala Ser Val Tyr Ser Ala Ser Glu Leu Ala Arg His Glu
 405 410 415
 Phe Pro Asp Leu Thr Val Glu Lys Arg Ser Ala Ile Ser Ile Ala Arg
 420 425 430
 Arg Leu Gln Asp Pro Leu Ala Glu Leu Val Lys Ile Asp Pro Lys Ser
 435 440 445
 Ile Gly Val Gly Gln Tyr Gln His Asp Val Ser Gln Lys Lys Leu Ser
 450 455 460
 Glu Asn Leu Gly Phe Val Val Asp Thr Val Val Asn Gln Val Gly Val
 465 470 475 480
 Asn Val Asn Thr Ala Ser Pro Ser Leu Leu Ala His Val Ser Gly Leu
 485 490 495
 Asn Lys Thr Ile Ser Glu Asn Ile Val Lys Tyr Arg Glu Glu Asn Gly
 500 505 510

Ala Leu Thr Ser Arg Ala Asp Ile Lys Lys Val Pro Arg Leu Gly Ala
 515 520 525
 Lys Ala Phe Glu Gln Ala Ala Gly Phe Leu Arg Ile Pro Gly Ala Lys
 530 535 540
 Asn Ile Leu Asp Asn Thr Gly Val His Pro Glu Ser Tyr Pro Ala Val
 545 550 555 560
 Lys Glu Leu Phe Lys Val Leu Gly Ile Gln Asp Leu Asp Asp Ala Ala
 565 570 575
 Lys Ala Thr Leu Ala Ala Val Gln Val Pro Gln Met Ala Glu Thr Leu
 580 585 590
 Ala Ile Gly Gln Glu Thr Leu Lys Asp Ile Ile Ala Asp Leu Leu Lys
 595 600 605
 Pro Gly Arg Asp Leu Arg Asp Asp Phe Glu Ala Pro Ile Leu Arg Gln
 610 615 620
 Asp Ile Leu Asp Leu Lys Asp Leu Glu Ile Gly Gln Lys Leu Glu Gly
 625 630 635 640
 Thr Val Arg Asn Val Val Asp Phe Gly Ala Phe Val Asp Ile Gly Val
 645 650 655
 His Glu Asp Gly Leu Ile His Ile Ser Glu Met Ser Lys Thr Phe Val
 660 665 670
 Asn His Pro Ser Gln Val Val Ser Val Gly Asp Leu Val Thr Val Trp
 675 680 685
 Val Ser Lys Ile Asp Leu Asp Arg His Lys Val Asn Leu Ser Leu Leu
 690 695 700
 Pro Pro Arg Asp Thr His
 705 710

<210> 177
 <211> 433
 <212> PRT
 <213> Streptococcus pyogenes

<400> 177
 Met Asn Glu Lys Val Phe Arg Asp Pro Val His Asn Tyr Ile His Ile
 1 5 10 15
 Asp Asn Pro Leu Ile Tyr Asp Leu Ile Asn Thr Lys Glu Phe Gln Arg
 20 25 30
 Leu Arg Arg Ile Lys Gln Val Pro Thr Thr Ala Phe Thr Phe His Gly
 35 40 45
 Ala Glu His Ser Arg Phe Ser His Cys Leu Gly Val Tyr Glu Ile Ala
 50 55 60
 Arg Arg Val Thr Ala Ile Phe Glu Glu Lys Tyr Ala Asp Ile Trp Asn
 65 70 75 80
 Lys Asp Glu Ser Leu Val Thr Met Thr Ala Ala Leu Leu His Asp Ile
 85 90 95
 Gly His Gly Ala Tyr Ser His Thr Phe Glu Val Leu Phe His Thr Asp
 100 105 110
 His Glu Ala Phe Thr Gln Glu Ile Ile Thr Asn Pro Glu Thr Glu Ile
 115 120 125
 Asn Ala Ile Leu Val Arg His Ala Pro Asp Phe Pro Asp Lys Val Ala
 130 135 140
 Ser Val Ile Asn His Thr Tyr Pro Asn Lys Gln Val Val Gln Leu Ile
 145 150 155 160
 Ser Ser Gln Ile Asp Cys Asp Arg Met Asp Tyr Leu Leu Arg Asp Ser
 165 170 175
 Tyr Phe Ser Ala Ala Asn Tyr Gly Gln Phe Asp Leu Met Arg Ile Leu
 180 185 190
 Arg Val Ile Arg Pro Val Glu Asp Gly Ile Val Phe Glu His Ser Gly
 195 200 205
 Met His Ala Val Glu Asp Tyr Ile Val Ser Arg Phe Gln Met Tyr Met
 210 215 220
 Gln Val Tyr Phe His Pro Ala Ser Arg Ala Val Glu Leu Ile Leu Gln
 225 230 235 240
 Asn Leu Leu Lys Arg Ala Gln His Leu Tyr Pro Glu Gln Gln Ala Tyr
 245 250 255
 Phe Gln Lys Thr Ala Pro Gly Leu Ile Pro Phe Phe Glu Lys Lys Ala
 260 265 270
 Asn Leu Ala Asp Tyr Ile Ala Leu Asp Asp Gly Val Met Asn Thr Tyr
 275 280 285
 Phe Gln Val Trp Met Ala Ser Glu Asp His Ile Leu Ser Asp Leu Ala
 290 295 300
 Ser Arg Phe Ile Asn Arg Lys Ile Leu Lys Ser Val Thr Phe Asp Gln
 305 310 315 320
 Asp Ser Gln Gly Glu Leu Glu Arg Leu Arg Gln Leu Val Glu Ser Val

Gly Phe Asp Pro 325 330 335
 Asp Tyr Tyr Thr Gly Ile His Ile Asn Phe Asp Leu
 340 345 350
 Pro Tyr Asp Ile Tyr Arg Pro Glu Leu Glu Asn Pro Arg Thr Gln Ile
 355 360 365
 Glu Met Met Gln Lys Asp Gly Ser Leu Ala Glu Leu Ser Gln Leu Ser
 370 375 380
 Pro Ile Val Lys Ala Leu Thr Gly Thr Thr Tyr Gly Asp Arg Arg Phe
 385 390 395 400
 Tyr Phe Pro Lys Glu Met Leu Glu Leu Asp Asp Leu Phe Ala Pro Ser
 405 410 415
 Lys Glu Thr Phe Met Ser Tyr Ile Ser Asn Gly His Phe His Phe Ser
 420 425 430
 Gln

<210> 178
 <211> 260
 <212> PRT
 <213> Streptococcus pyogenes

<400> 178
 Met Asp Ile Asn Leu Leu Gln Ala Leu Leu Ile Gly Leu Trp Thr Ala
 1 5 10 15
 Phe Cys Phe Ser Gly Met Leu Leu Gly Ile Tyr Thr Asn Arg Cys Ile
 20 25 30
 Ile Leu Ser Phe Gly Val Gly Ile Ile Leu Gly Asp Leu Pro Thr Ala
 35 40 45
 Leu Ser Met Gly Ala Ile Ser Glu Leu Ala Tyr Met Gly Phe Gly Val
 50 55 60
 Gly Ala Gly Gly Thr Val Pro Pro Asn Pro Ile Gly Pro Gly Ile Phe
 65 70 75 80
 Gly Thr Leu Met Ala Ile Thr Ser Ala Gly Lys Val Thr Pro Glu Ala
 85 90 95
 Ala Leu Ala Leu Ser Thr Pro Ile Ala Val Ala Ile Gln Phe Leu Gln
 100 105 110
 Thr Phe Ala Tyr Thr Ala Phe Ala Gly Ala Pro Glu Thr Ala Lys Lys
 115 120 125
 Gln Leu Gln Lys Gly Asn Ile Arg Gly Phe Lys Phe Ala Ala Asn Gly
 130 135 140
 Thr Ile Trp Ala Phe Ala Phe Ile Gly Leu Gly Leu Gly Leu Leu Gly
 145 150 155 160
 Ala Leu Ser Met Asp Thr Leu Leu His Leu Val Asp Tyr Ile Pro Pro
 165 170 175
 Val Leu Leu Asn Gly Leu Thr Val Ala Gly Lys Met Leu Pro Ala Ile
 180 185 190
 Gly Phe Ala Met Ile Leu Ser Val Met Ala Lys Lys Glu Leu Ile Pro
 195 200 205
 Phe Val Leu Ile Gly Tyr Val Cys Ala Ala Tyr Leu Gln Ile Pro Thr
 210 215 220
 Ile Gly Ile Ala Ile Ile Gly Ile Ile Phe Ala Leu Asn Glu Phe Tyr
 225 230 235 240
 Asn Lys Pro Lys Gln Val Asp Ala Thr Thr Val Gln Gly Gly Gln Gln
 245 250 255
 Asp Asp Trp Ile
 260

<210> 179
 <211> 403
 <212> PRT
 <213> Streptococcus pyogenes

<400> 179
 Leu Thr Pro Arg Ser Gly Lys Thr Thr Ala Gly His Phe Arg Tyr Ala
 1 5 10 15
 Arg Tyr Leu Ile Glu Ser Glu Asp Glu Asn His Leu Val Thr Ala Tyr
 20 25 30
 Asn Gln Glu Gln Ala Tyr Arg Leu Phe Ile Asp Gly Asp Gly Thr Gly
 35 40 45
 Leu Met His Ile Phe Asp Gly Asn Cys Glu Ile Lys His Asp Glu Arg
 50 55 60
 Gly Asp His Leu Leu Ile Thr Thr Pro Lys Gly Asn Lys Arg Val Tyr
 65 70 75 80

Tyr Lys Gly Gly Gly Lys Val Asn Ser Val Gly Ala Ile Thr Gly Met
 85 90 95
 Ser Leu Gly Ser Val Val Phe Cys Glu Ile Asn Leu Leu His Met Asp
 100 105 110
 Phe Ile Gln Glu Cys Phe Arg Arg Thr Trp Ala Ala Lys Leu Arg Tyr
 115 120 125
 His Leu Ala Asp Leu Asn Pro Pro Ala Pro Gln His Pro Val Ile Lys
 130 135 140
 Asp Val Phe Asp Val Gln Asn Thr Arg Trp Thr His Trp Thr Met Asp
 145 150 155 160
 Asp Asn Pro Ile Leu Thr Ala Glu Arg Lys Gln Asn Ile Ile Asn Ser
 165 170 175
 Leu Lys Lys Asn Pro Tyr Leu Tyr Lys Arg Asp Val Leu Gly Gln Arg
 180 185 190
 Val Met Pro Gln Gly Val Ile Tyr Gly Leu Phe Asp Thr Lys Asn
 195 200 205
 Val Leu Asp Ala Leu Ile Gly Glu Pro Val Glu Met Tyr Phe Cys Ala
 210 215 220
 Asp Gly Gly Gln Ser Asp Ala Thr Ser Met Ser Cys Asn Ile Val Thr
 225 230 235 240
 Arg Val Arg Asp Asn Gly Arg Ile Ser Phe Arg Leu Asn Arg Val Ala
 245 250 255
 His Tyr Tyr His Ser Gly Ala Asp Thr Gly Gln Val Lys Ala Met Ser
 260 265 270
 Thr Tyr Ala Leu Glu Leu Lys Val Phe Ile Asp Trp Cys Val Lys Lys
 275 280 285
 Tyr Gln Met Arg Tyr Thr Glu Val Phe Val Asp Pro Ala Cys Lys Ser
 290 295 300
 Leu Arg Glu Glu Leu His Lys Leu Gly Val Phe Thr Leu Gly Ala Pro
 305 310 315 320
 Asn Asn Ser Lys Asp Val Ser Ser Lys Ala Lys Gly Ile Glu Val Gly
 325 330 335
 Ile Glu Arg Gly Gln Asn Ile Ile Ser Asp Gly Ala Phe Tyr Leu Val
 340 345 350
 Asn His Ser Glu Glu Glu Tyr Asp His Tyr His Phe Leu Lys Glu Ile
 355 360 365
 Gly Leu Tyr Ser Arg Asp Asp Asn Gly Lys Pro Ile Asp Lys Asp Asn
 370 375 380
 His Ala Met Asp Glu Phe Arg Tyr Ser Val Asn Val Phe Val His Arg
 385 390 395 400
 Tyr Tyr Asn

<210> 180

<211> 497

<212> PRT

<213> Streptococcus pyogenes

<400> 180

Met Lys Lys Lys Pro Ile Lys Leu Asn Asp Glu Gln Leu Leu Leu Glu
 1 5 10 15
 Ala Ser Gln Leu Ser Asp Met Tyr His Gln Leu Thr Leu Asp Leu Phe
 20 25 30
 Asp Gln Val Ile Glu Arg Ile Lys Ala Arg Gly Ser Ala Ser Leu Ala
 35 40 45
 Asp Asn Pro Tyr Leu Trp Gln Ala Asn Lys Leu His Asp Val Gly Leu
 50 55 60
 Leu Asn Ala Asp Asn Ile Lys Leu Ile Ala Lys Tyr Ser Gly Ile Ala
 65 70 75 80
 Glu Ala Gln Leu Arg Tyr Ile Ile Lys Asn Glu Gly Phe Lys Ile Tyr
 85 90 95
 Lys Asn Thr Ser Glu Gln Leu Glu Glu Ala Leu Gly Arg Glu Ser Gly
 100 105 110
 Val Asn Ser Thr Ile Gln Asp Asp Leu Ser Asn Tyr Ala Arg Gln Ala
 115 120 125
 Ile Asp Asp Val His Asn Leu Thr Asn Thr Thr Leu Pro Phe Ser Val
 130 135 140
 Ile Gly Ala Tyr Gln Gly Ile Ile Gln Asp Ala Val Ala Gly Val Val
 145 150 155 160
 Thr Gly Leu Lys Thr Pro Asp Gln Ala Ile Asn Gln Thr Val Ile Lys
 165 170 175
 Trp Phe Lys Lys Gly Phe Tyr Gly Phe Thr Asp Lys Ala Gly Arg Lys
 180 185 190
 Trp Arg Ala Asp Ser Tyr Ala Arg Thr Val Ile Asn Thr Thr Thr Trp

195 200 205
 Arg Val Phe Asn Glu Ala Lys Glu Ala Pro Ala Arg Glu Phe Gly Ile
 210 215 220
 Asp Thr Phe Tyr Tyr Ser Lys Lys Ala Thr Ala Arg Glu Met Cys Ala
 225 230 235 240
 Pro Leu Gln His Gln Ile Val Thr Thr Gly Glu Ala Arg Glu Glu Gly
 245 250 255
 Gly Ile Lys Ile Leu Ala Leu Ser Asp Tyr Gly His Gly Glu Pro Asp
 260 265 270
 Gly Cys Leu Gly Ile Asn Cys Lys His Thr Lys Thr Pro Phe Val Val
 275 280 285
 Gly Val Asn Ser Lys Pro Glu Leu Pro Glu His Leu Lys Asn Ile Thr
 290 295 300
 Pro Ala Gln Ala Lys Ala Asn Ala Asn Ala Gln Ala Lys Gln Arg Ala
 305 310 315 320
 Ile Glu Arg Ser Ile Arg Lys Ser Lys Glu Leu Leu His Val Ala Lys
 325 330 335
 Gln Leu Gly Asp Lys Glu Leu Ile Arg Gln Tyr Gln Ser Asp Val Arg
 340 345 350
 Ser Lys Gln Asp Ala Leu Asn Tyr Leu Ile Asn Asn Asn Ala Phe Leu
 355 360 365
 His Arg Asn Gln Ala Arg Glu Lys Arg Tyr Asn Asn Pro Tyr Thr Lys
 370 375 380
 Thr Gln Ser Glu Val Glu Val Arg Lys Glu Lys Ala Lys Leu Asp Lys
 385 390 395 400
 Arg Arg Asp Val Glu Ser Ala Ile Ile Gly Val Glu Thr Ser Glu Gly
 405 410 415
 Ile Pro Leu Lys Ile Thr Lys His Leu Ala Glu Arg Ala Val Leu Arg
 420 425 430
 Asn Ile Ala Pro Ile Asp Ile Val Asp Ser Ile Lys Glu Pro Leu Lys
 435 440 445
 Ile Ala Pro Ile Lys Tyr Asp Asn Leu Asp Arg Pro Ser Gln Lys Tyr
 450 455 460
 Ile Gly Lys Cys Val Ser Thr Val Ile Asn Pro Ile Asp Gly Asn Ile
 465 470 475 480
 Val Thr Val His Ala Thr Ser Thr Arg Ile Arg Lys Lys Tyr Gly Gly
 485 490 495
 Asn

<210> 181
 <211> 628
 <212> PRT
 <213> Streptococcus pyogenes

<400> 181
 Met Ser Arg Asp Pro Thr Leu Ile Leu Asp Glu Ser Asn Leu Val Ile
 1 5 10 15
 Gly Lys Asp Gly Arg Val His Tyr Thr Phe Thr Thr Glu Asp Asp Asn
 20 25 30
 Pro Lys Val Arg Leu Ala Ser Lys Cys Leu Gly Thr Ala His Phe Asn
 35 40 45
 Gln Leu Met Ile Glu Arg Gly Asp Gln Ala Thr Ser Tyr Val Ala Pro
 50 55 60
 Val Val Val Glu Gly Thr Gly Asn Pro Thr Gly Leu Phe Lys Asp Leu
 65 70 75 80
 Lys Glu Ile Ser Leu Glu Leu Thr Asp Thr Ala Asn Ser Gln Leu Trp
 85 90 95
 Ser Lys Ile Lys Leu Thr Asn Arg Gly Met Leu Gln Glu Tyr Tyr Asp
 100 105 110
 Gly Lys Ile Lys Thr Glu Ile Val Asn Ser Ala Arg Gly Val Ala Thr
 115 120 125
 Arg Ile Ser Glu Asp Thr Asp Lys Lys Leu Ala Leu Ile Asn Asp Thr
 130 135 140
 Ile Asp Gly Ile Arg Arg Glu Tyr Arg Asp Ala Asp Arg Lys Leu Ser
 145 150 155 160
 Ala Ser Tyr Gln Ala Gly Ile Glu Gly Leu Lys Ala Thr Met Ala Asn
 165 170 175
 Asp Lys Ile Gly Leu Gln Ala Glu Ile Lys Ala Ser Ala Gln Gly Leu
 180 185 190
 Ser Gln Lys Tyr Asp Asp Glu Leu Arg Lys Leu Ser Ala Lys Ile Thr
 195 200 205
 Thr Thr Ser Ser Gly Thr Thr Glu Ala Tyr Glu Ser Lys Leu Ala Gly
 210 215 220

Leu Arg Ala Glu Phe Thr Arg Ser Asn Gln Gly Thr Arg Thr Glu Leu
 225 230 235 240
 Glu Ser Gln Ile Ser Gly Leu Arg Ala Val Gln Gln Ser Thr Ala Ser
 245 250 255
 Gln Ile Ser Gln Glu Ile Arg Asp Arg Gly Ala Val Ser Arg Val
 260 265 270
 Gln Gln Ser Leu Glu Ser Tyr Gln Arg Arg Met Gln Asp Ala Glu Glu
 275 280 285
 Asn Tyr Ser Ser Leu Thr His Thr Val Arg Gly Leu Gln Ser Asp Val
 290 295 300
 Gly Ser Pro Thr Gly Lys Ile Gln Ser Arg Leu Thr Gln Leu Ala Gly
 305 310 315 320
 Gln Ile Glu Gln Arg Val Thr Arg Asp Gly Val Met Ser Ile Ile Ser
 325 330 335
 Gly Ala Gly Asp Ser Ile Lys Leu Ala Ile Gln Lys Ala Gly Gly Ile
 340 345 350
 Asn Ala Lys Met Ser Gly Asn Glu Ile Ile Ser Ala Ile Asn Leu Asn
 355 360 365
 Ser Tyr Gly Val Thr Ile Ala Gly Lys His Ile Ala Leu Asp Gly Asn
 370 375 380
 Thr Thr Val Asn Gly Thr Phe Thr Thr Lys Ile Ala Glu Ala Ile Lys
 385 390 395 400
 Ile Arg Ala Asp Gln Ile Ile Ala Gly Thr Ile Asp Ala Ala Arg Ile
 405 410 415
 Arg Val Ile Asn Leu Asn Ala Ser Ser Ile Val Gly Leu Asp Ala Asn
 420 425 430
 Phe Ile Lys Ala Lys Ile Gly Tyr Ala Ile Thr Asp Leu Leu Glu Gly
 435 440 445
 Lys Val Ile Lys Ala Arg Asn Gly Ala Met Leu Ile Asp Leu Asn Thr
 450 455 460
 Ala Lys Met Asp Phe Asn Ser Asp Ala Thr Ile Asn Phe Asn Ser Lys
 465 470 475 480
 Asn Asn Ala Leu Val Arg Lys Asp Gly Thr His Thr Ala Phe Val His
 485 490 495
 Phe Ser Asn Ala Thr Pro Lys Gly Tyr Thr Gly Ser Ala Leu Tyr Ala
 500 505 510
 Ser Ile Gly Ile Thr Ser Ser Gly Asp Gly Val Asn Ser Ala Ser Ser
 515 520 525
 Gly Arg Phe Ala Gly Leu Arg Ser Phe Arg Tyr Ala Thr Gly Tyr Asn
 530 535 540
 His Thr Ala Ala Val Asp Gln Thr Glu Ile Tyr Gly Asp Asn Val Leu
 545 550 555 560
 Val Val Asp Asp Phe Asn Ile Thr Arg Gly Phe Lys Phe Arg Pro Asp
 565 570 575
 Lys Met Gln Lys Met Leu Asp Met Asn Asp Leu Tyr Ala Ala Val Val
 580 585 590
 Ala Leu Gly Arg Cys Trp Gly His Leu Ala Asn Val Gly Trp Asn Thr
 595 600 605
 Ala His Ser Asn Phe Thr Ser Ala Val Asn Arg Glu Leu Asn Asn Tyr
 610 615 620
 Ile Thr Lys Ile
 625

<210> 182

<211> 400

<212> PRT

<213> Streptococcus pyogenes

<400> 182

Met Thr Phe Leu Asp Lys Ile Lys Gln Gly Cys Leu Asp Gly Trp Ala
 1 5 10 15
 Lys Tyr Lys Ile Leu Pro Ser Leu Thr Ala Ala Gln Ala Ile Leu Glu
 20 25 30
 Ser Gly Trp Gly Lys His Ala Pro His Asn Ala Leu Phe Gly Ile Lys
 35 40 45
 Ala Asp Ser Ser Trp Thr Gly Lys Ser Phe Asp Thr Lys Thr Gln Glu
 50 55 60
 Glu Tyr Gln Ala Gly Val Val Thr Asp Ile Val Asp Arg Phe Arg Ala
 65 70 75 80
 Tyr Asp Ser Trp Asp Glu Ser Ile Ala Asp His Gly Gln Phe Leu Val
 85 90 95
 Asp Asn Pro Arg Tyr Glu Ala Val Ile Gly Glu Thr Asp Tyr Lys Lys
 100 105 110
 Ala Cys Tyr Ala Ile Lys Ala Ala Gly Tyr Ala Thr Ala Ser Ser Tyr

[0 1 6 3]

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      115      120      125
Val Glu Leu Leu Ile Gln Leu Ile Glu Glu Asn Asp Leu Gln Ser Trp
      130      135      140
Asp Arg Glu Ala Leu Lys Asn Asn Lys Glu Glu Thr Met Thr Thr Ala
      145      150      155      160
Asn Glu Ile Val Gln Tyr Cys Val Asn Leu Ala Asn Ser Gly Met Gly
      165      170      175
Val Asp Lys Asp Gly Ala His Gly Thr Gln Cys Cys Asp Leu Pro Cys
      180      185      190
Phe Val Ala Lys Asn Trp Phe Gly Val Asp Leu Trp Gly Asn Ala Ile
      195      200      205
Asp Leu Leu Asp Ser Ala Ser Ala Gln Gly Trp Glu Val His Arg Met
      210      215      220
Pro Thr Glu Ala Asn Pro Lys Ala Gly Ala Thr Phe Val Gln Ser Val
      225      230      235      240
Pro Tyr His Gln Phe Gly His Thr Gly Ile Val Ile Glu Asp Ser Asp
      245      250      255
Gly Tyr Thr Met Arg Thr Val Glu Gln Asn Ile Asp Gly Asn Pro Asp
      260      265      270
Ala Leu Tyr Val Gly Ala Pro Ala Arg Phe Asn Thr Arg Asp Phe Thr
      275      280      285
Gly Val Ile Gly Trp Phe Tyr Pro Pro Tyr Gln Gly Asp Thr Val Thr
      290      295      300
Gln Pro Val Ser Thr Glu Pro Gln Thr Ser Asp Thr Ile Val Glu Thr
      305      310      315      320
Ala Lys Thr Gly Thr Phe Thr Leu Asp Val Ala Glu Ile Asn Ile Arg
      325      330      335
Arg Trp Pro Ser Leu Ala Ser Glu Val Val Gly Ile Tyr Lys Gln Gly
      340      345      350
Asp Thr Val Ser Phe Asp Ser Glu Gly Tyr Ala Asn Gly Tyr Tyr Trp
      355      360      365
Ile Ser Tyr Val Gly Gly Ser Gly Met Arg Asn Tyr Leu Gly Ile Gly
      370      375      380
Gln Thr Asp Lys Asp Gly Asn Arg Ile Ser Leu Trp Gly Lys Leu Asn
      385      390      395      400

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<210> 183

<211> 235

<212> PRT

<213> Streptococcus pyogenes

<400> 183

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Met Lys Lys Ile Asn Ile Ile Lys Ile Val Phe Ile Ile Thr Val Ile
1      5      10      15
Leu Ile Ser Thr Ile Ser Pro Ile Ile Lys Ser Asp Ser Lys Lys Asp
      20      25      30
Ile Ser Asn Val Lys Ser Asp Leu Tyr Ala Tyr Thr Ile Thr Pro
      35      40      45
Tyr Asp Tyr Lys Asn Cys Arg Val Asn Phe Ser Thr Thr His Thr Leu
      50      55      60
Asn Ile Asp Thr Gln Lys Tyr Arg Gly Lys Asp Tyr Tyr Ile Ser Ser
      65      70      75      80
Glu Met Ser Tyr Glu Ala Ser Gln Lys Phe Lys Arg Asp Asp His Val
      85      90      95
Asp Val Phe Gly Leu Phe Tyr Ile Leu Asn Ser His Thr Gly Glu Tyr
      100      105      110
Ile Tyr Gly Gly Ile Thr Pro Ala Gln Asn Asn Lys Val Asn His Lys
      115      120      125
Leu Leu Gly Asn Leu Phe Ile Ser Gly Glu Ser Gln Gln Asn Leu Asn
      130      135      140
Asn Lys Ile Ile Leu Glu Lys Asp Ile Val Thr Phe Gln Glu Ile Asp
      145      150      155      160
Phe Lys Ile Arg Lys Tyr Leu Met Asp Asn Tyr Lys Ile Tyr Asp Ala
      165      170      175
Thr Ser Pro Tyr Val Ser Gly Arg Ile Glu Ile Gly Thr Lys Asp Gly
      180      185      190
Lys His Glu Gln Ile Asp Leu Phe Asp Ser Pro Asn Glu Gly Thr Arg
      195      200      205
Ser Asp Ile Phe Ala Lys Tyr Lys Asp Asn Arg Ile Ile Asn Met Lys
      210      215      220
Asn Phe Ser His Phe Asp Ile Tyr Leu Glu Lys
      225      230      235

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【 0 1 6 4 】

<210> 184
 <211> 313
 <212> PRT
 <213> Streptococcus pyogenes

<400> 184
 Met Ile Thr Thr Phe Glu Thr Ile Leu Asp Lys Ile Lys Ala His Gln
 1 5 10 15
 Thr Ile Ile Ile His Arg His Gln Asn Pro Asp Pro Asp Ala Leu Gly
 20 25 30
 Ser Gln Ala Gly Leu Lys Glu Ile Ile Ala Gln Asn Phe Pro Asp Lys
 35 40 45
 Lys Val Leu Met Thr Gly Phe Asp Glu Pro Ser Leu Ala Trp Ile Ser
 50 55 60
 Gln Met Asp Gln Val Thr Asp Lys Asp Tyr Lys Glu Ala Leu Val Ile
 65 70 75 80
 Ile Thr Asp Thr Ala Asn Arg Pro Arg Ile Asp Asp Glu Arg Tyr Thr
 85 90 95
 Leu Gly Lys Cys Leu Ile Lys Ile Asp His His Pro Asn Asp Asp Val
 100 105 110
 Tyr Gly Asp Phe Tyr Tyr Val Asp Thr Ser Ala Ser Ser Ala Ser Glu
 115 120 125
 Ile Ile Ala Asp Phe Ala Phe Ser Gln Asn Leu Thr Leu Ser Asp Lys
 130 135 140
 Ala Ala Lys Leu Leu Tyr Thr Gly Ile Val Gly Asp Thr Gly Arg Phe
 145 150 155 160
 Leu Tyr Ala Ser Thr Thr Ser Lys Thr Leu Ser Ile Ala Ser Gln Leu
 165 170 175
 Arg His Phe Glu Phe Asp Phe Ala Ala Ile Ser Arg Gln Met Asp Ser
 180 185 190
 Phe Pro Leu Lys Ile Ala Lys Leu Gln Ser Tyr Val Phe Glu His Leu
 195 200 205
 Thr Ile Asp Glu Ser Gly Ala Tyr Val Leu Val Ser Gln Glu Thr
 210 215 220
 Leu Lys His Phe Asp Val Thr Leu Ala Glu Ser Ser Ala Ile Val Cys
 225 230 235 240
 Ala Pro Gly Lys Ile Asp Asn Val Gln Ala Trp Ala Ile Phe Val Glu
 245 250 255
 Leu Thr Asp Gly Asn Tyr Arg Val Arg Met Arg Ser Lys Glu Lys Ile
 260 265 270
 Ile Asn Gly Ile Ala Lys Arg His Gly Gly Gly His Pro Leu Ala
 275 280 285
 Ser Gly Ala Asn Ser Ala Asn Leu Glu Glu Asn Gln Ala Ile Phe Arg
 290 295 300
 Glu Leu Ile Ala Val Cys Gln Glu Ile
 305 310

<210> 185
 <211> 650
 <212> PRT
 <213> Streptococcus pyogenes

<400> 185
 Met Ile Glu Glu Asn Lys His Phe Glu Lys Lys Met Gln Glu Tyr Asp
 1 5 10 15
 Ala Ser Gln Ile Gln Val Leu Glu Gly Leu Glu Ala Val Arg Met Arg
 20 25 30
 Pro Gly Met Tyr Ile Gly Ser Thr Ala Lys Glu Gly Leu His His Leu
 35 40 45
 Val Trp Glu Ile Val Asp Asn Ser Ile Asp Glu Ala Leu Ala Gly Phe
 50 55 60
 Ala Ser His Ile Lys Val Phe Ile Glu Ala Asp Asn Ser Ile Thr Val
 65 70 75 80
 Val Asp Asp Gly Arg Gly Ile Pro Val Asp Ile Gln Ala Lys Thr Gly
 85 90 95
 Arg Pro Ala Val Glu Thr Val Phe Thr Val Leu His Ala Gly Gly Lys
 100 105 110
 Phe Gly Gly Gly Gly Tyr Lys Val Ser Gly Gly Leu His Gly Val Gly
 115 120 125
 Ser Ser Val Val Asn Ala Leu Ser Thr Gln Leu Asp Val Arg Val Tyr
 130 135 140
 Lys Asn Gly Gln Ile His Tyr Gln Glu Phe Lys Arg Gly Ala Val Val
 145 150 155 160
 Ala Asp Leu Glu Val Ile Gly Thr Thr Asp Val Thr Gly Thr Thr Val

【 0 1 6 5 】

165 170 175
 His Phe Thr Pro Asp Pro Glu Ile Phe Thr Glu Thr Thr Gln Phe Asp
 180 185 190
 Tyr Ser Val Leu Ala Lys Arg Ile Gln Glu Leu Ala Phe Leu Asn Arg
 195 200 205
 Gly Leu Lys Ile Ser Ile Thr Asp Lys Arg Ser Gly Met Glu Gln Glu
 210 215 220
 Glu His Phe Leu Tyr Glu Gly Gly Ile Gly Ser Tyr Val Glu Phe Leu
 225 230 235 240
 Asn Asp Lys Lys Asp Val Ile Phe Glu Thr Pro Ile Tyr Thr Asp Gly
 245 250 255
 Glu Leu Glu Gly Ile Ala Val Glu Val Ala Met Gln Tyr Thr Thr Ser
 260 265 270
 Tyr Gln Glu Thr Val Met Ser Phe Ala Asn Asn Ile His Thr His Glu
 275 280 285
 Gly Gly Thr His Glu Gln Gly Phe Arg Ala Ala Leu Thr Arg Val Ile
 290 295 300
 Asn Asp Tyr Ala Lys Lys Asn Lys Ile Leu Lys Glu Asn Glu Asp Asn
 305 310 315 320
 Leu Thr Gly Glu Asp Val Arg Glu Gly Leu Thr Ala Val Ile Ser Val
 325 330 335
 Lys His Pro Asn Pro Gln Phe Glu Gly Gln Thr Lys Thr Lys Leu Gly
 340 345 350
 Asn Ser Glu Val Val Lys Ile Thr Asn Arg Leu Phe Ser Glu Ala Phe
 355 360 365
 Gln Arg Phe Leu Leu Glu Asn Pro Gln Val Ala Arg Lys Ile Val Glu
 370 375 380
 Lys Gly Ile Leu Ala Ser Lys Ala Arg Ile Ala Ala Lys Arg Ala Arg
 385 390 395 400
 Glu Val Thr Arg Lys Lys Ser Gly Leu Glu Ile Ser Asn Leu Pro Gly
 405 410 415
 Lys Leu Ala Asp Cys Ser Ser Asn Asp Ala Asn Gln Asn Glu Leu Phe
 420 425 430
 Ile Val Glu Gly Asp Ser Ala Gly Gly Ser Ala Lys Ser Gly Arg Asn
 435 440 445
 Arg Glu Phe Gln Ala Ile Leu Pro Ile Arg Gly Lys Ile Leu Asn Val
 450 455 460
 Glu Lys Ala Thr Met Asp Lys Ile Leu Ala Asn Glu Glu Ile Arg Ser
 465 470 475 480
 Leu Phe Thr Ala Met Gly Thr Gly Phe Gly Ala Asp Phe Asp Val Ser
 485 490 495
 Lys Ala Arg Tyr Gln Lys Leu Val Ile Met Thr Asp Ala Asp Val Asp
 500 505 510
 Gly Ala His Ile Arg Thr Leu Leu Leu Thr Leu Ile Tyr Arg Phe Met
 515 520 525
 Arg Pro Val Leu Glu Ala Gly Tyr Val Tyr Ile Ala Gln Pro Pro Ile
 530 535 540
 Tyr Gly Val Lys Val Gly Ser Glu Ile Lys Glu Tyr Ile Gln Pro Gly
 545 550 555 560
 Ile Asp Gln Glu Asp Gln Leu Lys Thr Ala Leu Glu Lys Tyr Ser Ile
 565 570 575
 Gly Arg Ser Lys Pro Thr Val Gln Arg Tyr Lys Gly Leu Gly Glu Met
 580 585 590
 Asp Asp His Gln Leu Trp Glu Thr Thr Met Asp Pro Glu Asn Arg Leu
 595 600 605
 Met Ala Arg Val Thr Val Asp Asp Ala Ala Glu Ala Asp Lys Val Phe
 610 615 620
 Asp Met Leu Met Gly Asp Arg Val Glu Pro Arg Arg Asp Phe Ile Glu
 625 630 635 640
 Glu Asn Ala Val Tyr Ser Thr Leu Asp Ile
 645 650

<210> 186

<211> 2045

<212> PRT

<213> Streptococcus pyogenes

<400> 186

Met Arg Lys Val Lys Lys Val Phe Val Ser Ser Cys Met Leu Leu Thr
 1 5 10 15
 Val Gly Leu Gly Val Ala Val Pro Thr Gly Phe Ser Gln Ser Asn Gly
 20 25 30
 Val Met Val Val Lys Ala Ala Glu Val Pro Ala Thr Asp Leu Ser Arg
 35 40 45

【 0 1 6 6 】

Gln Ala Ser Asp Ser Glu Arg Val Asp Glu Ser Ser Leu Leu Gln Lys
 50 55 60
 Glu Asn Leu Ser Val Asp Ser Phe Lys Leu Glu Asn Leu Asn Gly Trp
 65 70 75 80
 Glu Ala Glu Asn Asp Thr Ala Gly Asn Leu Gly Lys Phe Lys Asp Pro
 85 90 95
 Asp Ser Ser Gly Tyr Gln Asn Ile Leu Thr Ser Ser Gly Lys Asn Ile
 100 105 110
 Ser Val Ala Val Ala Pro Lys Gly Ser Gly Lys Met Asn Ile Lys Val
 115 120 125
 Thr Lys Arg Ser Asn Phe Gln Gly Gly Tyr Tyr Val Gly Gly Leu Arg
 130 135 140
 Thr Gln Thr Pro Val Leu Lys Leu Asn Asp Val Tyr Arg Tyr Ser Phe
 145 150 155 160
 Thr Thr Lys Lys Leu Ser Gly Asn Ser Ser Glu Phe Lys Thr Arg Val
 165 170 175
 Lys Pro Val Glu Ser Asn Asn Lys Leu Gly Lys Glu Leu Val Ile Arg
 180 185 190
 Val Asp Asn Lys Asn Val Ser Thr Lys His Asp Trp Leu Pro Asp Ile
 195 200 205
 Ser Asp Gly Thr His Thr Val Asp Phe Thr Gly Leu Asp Lys Lys Leu
 210 215 220
 Ser Val Ala Phe Arg Phe Ser Pro Arg Gln Thr Ser Asn Val Val Tyr
 225 230 235 240
 Glu Phe Ser Asn Ile Asn Ile Lys Asn Ile Ser Pro Ala Ser Val Pro
 245 250 255
 Ala Ile Pro Ser Lys Val Leu Glu Gly Thr Ser Val Leu Ser Gly Thr
 260 265 270
 Ala Ile Ser Ser Gly Asp Thr Leu Glu Lys Arg Lys Ser Phe Asp Gly
 275 280 285
 Asp Ile Leu Arg Val Tyr Lys Asp Ser Lys Ile Ile Ala Arg Thr Val
 290 295 300
 Ile Lys Gly Asn Lys Trp Asp Val Lys Leu Ser Lys Pro Leu Ile Ala
 305 310 315 320
 Gly Glu Lys Leu Asp Phe Glu Ile Leu His Pro Arg Ser Gln Asn Val
 325 330 335
 Ser Lys Lys Ile Ser Lys Gln Val Glu Ala Lys Pro Phe Asp Pro Ala
 340 345 350
 Ser Tyr Lys Glu Lys Val Ile Ala Lys Leu Lys Pro Val Tyr Glu Ala
 355 360 365
 Thr Ser Glu Lys Ile Thr Asn Asp Ala Trp Leu Asp Glu Asn Ala Lys
 370 375 380
 Asp Leu Gln Lys Gln Lys Leu Glu Glu Gln Tyr Ile Ser Gly Lys Val
 385 390 395 400
 Ala Ile Ser Glu Ala Gly Thr Lys Gln Glu Ala Ile Asp Ala Ala Tyr
 405 410 415
 Asn Lys Tyr Ser Ser Gln Thr Asp Pro Asp Ser Leu Pro Ser Gln Tyr
 420 425 430
 Lys Gln Gly Asn Lys Glu Asn Glu Gln Glu Lys Gly Arg Gln Asp Leu
 435 440 445
 Ile Gln Thr Arg Asp Leu Thr Leu Lys Ala Ile Gln Glu Asp Lys Trp
 450 455 460
 Leu Thr Glu Gln Glu Lys Thr Ile Gln Lys Glu Glu Ala Leu Lys Ala
 465 470 475 480
 Phe Glu Thr Gly Ile Glu Ser Val Asn Gln Thr Val Ser Leu Glu Gln
 485 490 495
 Leu Lys Gln Arg Leu Ile Val Tyr Lys Ala Ser Glu Lys Asp Ser Glu
 500 505 510
 Lys Lys Glu Tyr Pro Glu Ser Ile Pro Asn Gln His Ile Pro Gly Lys
 515 520 525
 Glu Lys Glu Val Lys Ala Ala Lys Gln Glu Glu Leu Lys Lys Leu His
 530 535 540
 Asp Thr Thr Leu Glu Lys Ile Asn Gln Asp Lys Trp Leu Thr Pro Asp
 545 550 555 560
 Gln Gln Ala Glu Gln Leu Lys Gln Ala Glu Val Thr Phe Lys Lys Gly
 565 570 575
 Gln Glu Ala Ile Lys Ser Ala Gln Thr Leu Thr Gln Leu Glu Thr Asp
 580 585 590
 Leu Ala Asp Tyr Val Ser Glu Asn Glu Gly Lys Gly Asn Ser Ile Pro
 595 600 605
 Asp Lys Tyr Lys Ser Gly Asn Lys Asp Asp Leu Val Asn Lys Ala Glu
 610 615 620
 Val Lys Leu Lys Glu Ala His Glu Ala Thr Lys Gln Ala Ile Glu Lys
 625 630 635 640
 Asp Pro Trp Leu Ser Pro Glu Gln Lys Lys Ala Gln Lys Glu Lys Ala

645 650 655
 Lys Ala Arg Leu Asp Glu Gly Leu Lys Ala Leu Lys Ala Ala Asp Ser
 660 665 670
 Leu Glu Ile Leu Lys Val Thr Glu Glu Ala Phe Val Asp Lys Glu Lys
 675 680 685
 Asn Pro Asp Ser Ile Pro Asn Gln His Lys Ala Gly Thr Ala Asp Gln
 690 695 700
 Ala Arg Lys Gln Ala Leu Asp Ser Leu Asp Lys Glu Val Gln Lys Glu
 705 710 715 720
 Leu Glu Ser Ile Asp Asn Asp Asn Thr Leu Thr Thr Asp Glu Lys Ala
 725 730 735
 Ala Ala Lys Lys Lys Val Asn Asp Ala Tyr Asp Val Ala Lys Gln Thr
 740 745 750
 Ala Met Glu Ala Asn Ser Tyr Glu Asp Leu Thr Thr Ile Lys Asp Glu
 755 760 765
 Phe Leu Ser Asn Leu Pro His Lys Gln Gly Thr Pro Leu Lys Asp Gln
 770 775 780
 Gln Ser Asp Ala Ile Ala Glu Leu Glu Lys Lys Gln Gln Glu Ile Glu
 785 790 795 800
 Lys Ala Ile Glu Gly Asp Lys Thr Leu Pro Arg Asp Glu Lys Glu Lys
 805 810 815
 Gln Ile Ala Asp Ser Lys Glu Arg Leu Lys Ser Asp Thr Gln Lys Val
 820 825 830
 Lys Asp Ala Lys Asn Ala Asp Ala Ile Lys Lys Ala Phe Glu Glu Gly
 835 840 845
 Lys Val Asn Ile Pro Gln Ala His Ile Pro Gly Asp Leu Asn Lys Asp
 850 855 860
 Lys Glu Lys Leu Leu Ala Glu Leu Lys Gln Lys Ala Asp Asp Thr Glu
 865 870 875 880
 Lys Ala Ile Asp Val Asp Lys Thr Leu Thr Glu Asp Glu Lys Lys Glu
 885 890 895
 Gln Lys Val Lys Thr Lys Ala Glu Leu Glu Lys Ala Lys Thr Asp Val
 900 905 910
 Lys Asn Thr Gln Thr Arg Glu Glu Leu Asp Lys Lys Val Pro Glu Leu
 915 920 925
 Lys Lys Ala Ile Glu Asp Thr His Val Lys Gly Asn Leu Glu Gly Val
 930 935 940
 Lys Asn Lys Ala Ile Glu Asp Leu Lys Lys Ala His Thr Glu Thr Val
 945 950 955 960
 Ala Lys Ile Asn Gly Asp Asp Thr Leu Asp Lys Ala Thr Lys Glu Ala
 965 970 975
 Gln Val Lys Glu Ala Asp Lys Ala Leu Ala Ala Gly Lys Asp Ala Ile
 980 985 990
 Thr Lys Ala Asp Asp Ala Asp Lys Val Ser Thr Ala Val Thr Glu His
 995 1000 1005
 Thr Pro Lys Ile Lys Ala Ala His Lys Thr Gly Asp Leu Lys Lys
 1010 1015 1020
 Ala Gln Val Asp Ala Asn Thr Ala Leu Asp Lys Ala Ala Glu Lys
 1025 1030 1035
 Glu Arg Gly Glu Ile Asn Lys Asp Ala Thr Leu Thr Thr Glu Asp
 1040 1045 1050
 Lys Ala Lys Gln Leu Lys Glu Val Glu Thr Ala Leu Thr Lys Ala
 1055 1060 1065
 Lys Asp Asn Val Lys Ala Ala Lys Thr Ala Asp Ala Ile Asn Asp
 1070 1075 1080
 Ala Arg Asp Lys Gly Val Ala Thr Ile Asp Ala Val His Lys Ala
 1085 1090 1095
 Gly Gln Asp Leu Gly Ala Arg Lys Ser Gly Gln Val Ala Lys Leu
 1100 1105 1110
 Glu Glu Ala Ala Lys Ala Thr Lys Asp Lys Ile Ser Ala Asp Pro
 1115 1120 1125
 Thr Leu Thr Ser Lys Glu Lys Glu Glu Gln Ser Lys Ala Val Asp
 1130 1135 1140
 Ala Glu Leu Lys Lys Ala Ile Glu Ala Val Asn Ala Ala Asp Thr
 1145 1150 1155
 Ala Asp Lys Val Asp Asp Ala Leu Gly Glu Gly Val Thr Asp Ile
 1160 1165 1170
 Lys Asn Gln His Lys Ser Gly Asp Ser Ile Asp Ala Arg Arg Glu
 1175 1180 1185
 Ala His Gly Lys Glu Leu Asp Arg Val Ala Gln Glu Thr Lys Gly
 1190 1195 1200
 Ala Ile Glu Lys Asp Pro Thr Leu Thr Thr Glu Lys Ala Lys
 1205 1210 1215
 Gln Val Lys Asp Val Asp Ala Ala Lys Glu Arg Gly Met Ala Lys
 1220 1225 1230

Leu	Asn	Glu	Ala	Lys	Asp	Ala	Asp	Ala	Leu	Asp	Lys	Ala	Tyr	Gly
1235						1240					1245			
Glu	Gly	Val	Thr	Asp	Ile	Lys	Asn	Gln	His	Lys	Ser	Gly	Asp	Pro
1250						1255					1260			
Val	Asp	Ala	Arg	Arg	Gly	Leu	His	Asn	Lys	Ser	Ile	Asp	Glu	Val
1265						1270					1275			
Ala	Gln	Ala	Thr	Lys	Asp	Ala	Ile	Thr	Ala	Asp	Thr	Thr	Leu	Thr
1280						1285					1290			
Glu	Ala	Glu	Lys	Glu	Thr	Gln	Arg	Gly	Asn	Val	Asp	Lys	Glu	Ala
1295						1300					1305			
Thr	Lys	Ala	Lys	Glu	Glu	Leu	Ala	Lys	Ala	Lys	Asp	Ala	Asp	Ala
1310						1315					1320			
Leu	Asp	Lys	Ala	Tyr	Gly	Asp	Gly	Val	Thr	Ser	Ile	Lys	Asn	Gln
1325						1330					1335			
His	Lys	Ser	Gly	Lys	Gly	Leu	Asp	Val	Arg	Lys	Asp	Glu	His	Lys
1340						1345					1350			
Lys	Ala	Leu	Glu	Ala	Val	Ala	Lys	Arg	Val	Thr	Ala	Glu	Ile	Glu
1355						1360					1365			
Ala	Asp	Pro	Thr	Leu	Thr	Pro	Glu	Val	Arg	Glu	Gln	Gln	Lys	Ala
1370						1375					1380			
Glu	Val	Gln	Lys	Glu	Leu	Glu	Leu	Ala	Thr	Asp	Lys	Ile	Ala	Glu
1385						1390					1395			
Ala	Lys	Asp	Ala	Asp	Glu	Ala	Asp	Lys	Ala	Tyr	Gly	Asp	Gly	Val
1400						1405					1410			
Thr	Ala	Ile	Glu	Asn	Ala	His	Val	Ile	Gly	Lys	Gly	Ile	Glu	Ala
1415						1420					1425			
Arg	Lys	Asp	Leu	Ala	Lys	Lys	Asp	Leu	Ala	Glu	Ala	Ala	Ala	Lys
1430						1435					1440			
Thr	Lys	Ala	Leu	Ile	Ile	Glu	Asp	Lys	Thr	Leu	Thr	Asp	Asp	Gln
1445						1450					1455			
Arg	Lys	Glu	Gln	Leu	Leu	Gly	Val	Asp	Thr	Glu	Tyr	Ala	Lys	Gly
1460						1465					1470			
Ile	Glu	Asn	Ile	Asp	Ala	Ala	Lys	Asp	Ala	Ala	Gly	Val	Asp	Lys
1475						1480					1485			
Ala	Tyr	Ser	Asp	Gly	Val	Arg	Asp	Ile	Leu	Ala	Gln	Tyr	Lys	Glu
1490						1495					1500			
Gly	Gln	Asn	Leu	Asn	Asp	Arg	Arg	Asn	Ala	Ala	Lys	Glu	Phe	Leu
1505						1510					1515			
Leu	Lys	Glu	Ala	Asp	Lys	Val	Thr	Lys	Leu	Ile	Asn	Asp	Asp	Pro
1520						1525					1530			
Thr	Leu	Thr	His	Asp	Gln	Lys	Val	Asp	Gln	Ile	Asn	Lys	Val	Glu
1535						1540					1545			
Gln	Ala	Lys	Leu	Asp	Ala	Ile	Lys	Ser	Val	Asp	Asp	Ala	Gln	Thr
1550						1555					1560			
Ala	Asp	Ala	Ile	Asn	Asp	Ala	Leu	Gly	Lys	Gly	Ile	Glu	Asn	Ile
1565						1570					1575			
Asn	Asn	Gln	Tyr	Gln	His	Gly	Asp	Gly	Val	Asp	Val	Arg	Lys	Ala
1580						1585					1590			
Thr	Ala	Lys	Gly	Asp	Leu	Glu	Lys	Glu	Ala	Ala	Lys	Val	Lys	Ala
1595						1600					1605			
Leu	Ile	Ala	Lys	Asp	Pro	Thr	Leu	Thr	Gln	Ala	Asp	Lys	Asp	Lys
1610						1615					1620			
Gln	Thr	Ala	Ala	Val	Asp	Ala	Ala	Lys	Asn	Thr	Ala	Ile	Ala	Ala
1625						1630					1635			
Val	Asp	Lys	Ala	Thr	Thr	Thr	Glu	Gly	Ile	Asn	Gln	Glu	Leu	Gly
1640						1645					1650			
Lys	Gly	Ile	Thr	Ala	Ile	Asn	Lys	Ala	Tyr	Arg	Pro	Gly	Glu	Gly
1655						1660					1665			
Val	Lys	Ala	Arg	Lys	Glu	Ala	Ala	Lys	Ala	Asp	Leu	Glu	Lys	Glu
1670						1675					1680			
Ala	Ala	Lys	Val	Lys	Ala	Leu	Ile	Thr	Asn	Asp	Pro	Thr	Leu	Thr
1685						1690					1695			
Lys	Ala	Asp	Lys	Ala	Lys	Gln	Thr	Glu	Ala	Val	Ala	Lys	Ala	Leu
1700						1705					1710			
Lys	Ala	Ala	Ile	Ala	Ala	Val	Asp	Lys	Ala	Thr	Thr	Ala	Glu	Gly
1715						1720					1725			
Ile	Asn	Gln	Glu	Leu	Gly	Lys	Gly	Ile	Thr	Ala	Ile	Asn	Lys	Ala
1730						1735					1740			
Tyr	Arg	Pro	Gly	Glu	Gly	Val	Lys	Ala	Arg	Lys	Glu	Ala	Ala	Lys
1745						1750					1755			
Ala	Asp	Leu	Glu	Arg	Glu	Ala	Ala	Lys	Val	Arg	Glu	Ala	Ile	Ala
1760						1765					1770			
Asn	Asp	Pro	Thr	Leu	Thr	Lys	Ala	Asp	Lys	Ala	Lys	Gln	Thr	Glu
1775						1780					1785			
Ala	Val	Ala	Lys	Ala	Leu	Lys	Ala	Ala	Ile	Ala	Ala	Val	Asp	Lys

1790	Ala Thr Thr Ala Glu Gly	1795	Ile Asn Gln Glu Leu	1800	Gly Lys Gly Ile
1805	Thr Ala Ile Asn Lys Ala	1810	Tyr Arg Pro Gly Glu	1815	Gly Val Glu Ala
1820	His Lys Glu Ala Ala Lys	1825	Ala Asn Leu Glu Lys	1830	Val Ala Lys Glu
1835	Thr Lys Ala Leu Ile Ser	1840	Gly Asp Arg Tyr Leu	1845	Ser Glu Thr Glu
1850	Lys Ala Val Gln Lys Gln	1855	Ala Val Glu Gln Ala	1860	Leu Ala Lys Ala
1865	Leu Gly Gln Val Glu Ala	1870	Ala Lys Thr Val Glu	1875	Ala Val Lys Leu
1880	Ala Glu Asn Leu Gly Thr	1885	Val Ala Ile Arg Ser	1890	Ala Tyr Val Ala
1895	Gly Leu Ala Lys Asp Thr	1900	Asp Gln Ala Thr Ala	1905	Ala Leu Asn Glu
1910	Ala Lys Gln Ala Ala Ile	1915	Glu Ala Leu Lys Gln	1920	Ala Ala Ala Glu
1925	Thr Leu Ala Lys Ile Thr	1930	Thr Asp Ala Lys Leu	1935	Thr Glu Ala Gln
1940	Lys Ala Glu Gln Ser Glu	1945	Asn Val Ser Leu Ala	1950	Leu Lys Thr Ala
1955	Ile Ala Thr Val Arg Ser	1960	Ala Gln Ser Ile Ala	1965	Ser Val Lys Glu
1970	Ala Lys Asp Lys Gly Ile	1975	Thr Ala Ile Arg Ala	1980	Ala Tyr Val Pro
1985	Asn Lys Ala Val Ala Lys	1990	Ser Ser Ser Ala Asn	1995	His Leu Pro Lys
2000	Ser Gly Asp Ala Asn Ser	2005	Ile Val Leu Val Gly	2010	Leu Gly Val Met
2015	Ser Leu Leu Leu Gly Met	2020	Val Leu Tyr Ser Lys	2025	Lys Lys Glu Ser
2030	Lys Asp	2035		2040	
2045					

<210> 187

<211> 910

<212> PRT

<213> Streptococcus pyogenes

<400> 187

Met	Ile	Asn	Lys	Lys	Cys	Ile	Ile	Pro	Val	Ser	Leu	Leu	Thr	Leu	Ala
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Ile	Thr	Leu	Thr	Ser	Val	Glu	Glu	Val	Thr	Ser	Arg	Gln	Asn	Leu	Thr
		20						25				30			
Tyr	Ala	Asn	Glu	Ile	Val	Thr	Gln	Arg	Pro	Lys	Arg	Glu	Ser	Val	Ile
		35				40					45				
Ser	Asp	Lys	Ser	Asn	Phe	Pro	Val	Ile	Ser	Pro	Tyr	Leu	Ala	Ser	Val
	50				55					60					
Asp	Phe	Gly	Glu	Arg	Lys	Thr	Pro	Leu	Pro	Thr	Pro	Asp	Lys	Gly	Val
65				70					75					80	
Lys	Val	Thr	Thr	Glu	Gln	Ser	Ile	Ala	Gln	Val	Arg	Lys	Gly	Pro	Glu
		85						90					95		
Glu	Arg	Pro	Tyr	Thr	Val	Thr	Gly	Lys	Ile	Thr	Ser	Val	Ile	Asn	Gly
		100					105						110		
Trp	Gly	Gly	Tyr	Gly	Phe	Tyr	Ile	Gln	Asp	Ser	Glu	Gly	Ile	Gly	Leu
	115					120					125				
Tyr	Val	Tyr	Pro	Gln	Lys	Asp	Leu	Gly	Tyr	Ser	Lys	Gly	Asp	Ile	Val
	130				135					140					
Gln	Leu	Thr	Gly	Thr	Leu	Thr	Arg	Phe	Lys	Gly	Asp	Leu	Gln	Leu	Gln
145				150					155					160	
Gln	Val	Thr	Ala	His	Lys	Lys	Leu	Glu	Leu	Ser	Phe	Pro	Thr	Ser	Val
		165						170					175		
Lys	Glu	Ala	Val	Ile	Ser	Glu	Leu	Glu	Thr	Thr	Thr	Pro	Ser	Thr	Leu
	180						185						190		
Val	Lys	Leu	Ser	His	Val	Thr	Val	Gly	Glu	Leu	Ser	Thr	Asp	Gln	Tyr
	195					200					205				
Asn	Asn	Thr	Ser	Phe	Leu	Val	Arg	Asp	Asp	Ser	Gly	Lys	Ser	Ile	Val
210					215					220					
Val	His	Ile	Asp	His	Arg	Thr	Gly	Val	Lys	Gly	Ala	Asp	Val	Val	Thr
225				230					235					240	
Lys	Ile	Ser	Gln	Gly	Asp	Leu	Ile	Asn	Leu	Thr	Ala	Ile	Leu	Ser	Ile
		245						250					255		

【 0 1 7 0 】

Val Asp Gly Gln Leu Gln Leu Arg Pro Phe Ser Leu Glu Gln Leu Glu
 260 265 270
 Val Val Lys Lys Val Thr Ser Ser Asn Ser Asp Ala Ser Ser Arg Asn
 275 280 285
 Ile Val Lys Ile Gly Glu Ile Gln Gly Ala Ser His Thr Ser Pro Leu
 290 295 300
 Leu Lys Lys Ala Val Thr Val Glu Gln Val Val Val Thr Tyr Leu Asp
 305 310 315 320
 Asp Ser Thr His Phe Tyr Val Gln Asp Leu Asn Gly Asp Gly Asp Leu
 325 330 335
 Ala Thr Ser Asp Gly Ile Arg Val Phe Ala Lys Asn Ala Lys Val Gln
 340 345 350
 Val Gly Asp Val Leu Thr Ile Ser Gly Glu Val Glu Glu Phe Phe Gly
 355 360 365
 Arg Gly Tyr Glu Glu Arg Lys Gln Thr Asp Leu Thr Ile Thr Gln Ile
 370 375 380
 Val Ala Lys Ala Val Thr Lys Thr Gly Thr Ala Gln Val Pro Ser Pro
 385 390 395 400
 Leu Val Leu Gly Lys Asp Arg Ile Ala Pro Ala Asn Ile Ile Asp Asn
 405 410 415
 Asp Gly Leu Arg Val Phe Asp Pro Glu Glu Asp Ala Ile Asp Tyr Trp
 420 425 430
 Glu Ser Met Glu Gly Met Leu Val Ala Val Asp Asp Ala Lys Ile Leu
 435 440 445
 Gly Pro Met Lys Asn Lys Glu Ile Tyr Val Leu Pro Gly Ser Ser Thr
 450 455 460
 Arg Pro Leu Asn Asn Ser Gly Gly Val Leu Leu Pro Ala Asn Ser Tyr
 465 470 475 480
 Asn Thr Asp Val Ile Pro Val Leu Phe Lys Lys Gly Lys Gln Ile Ile
 485 490 495
 Lys Ala Gly Asp Ser Tyr Lys Gly Arg Leu Ala Gly Pro Val Ser Tyr
 500 505 510
 Ser Tyr Gly Asn Tyr Lys Val Phe Val Asp Asp Ser Lys Asn Met Pro
 515 520 525
 Ser Leu Met Asp Gly His Leu Lys Pro Glu Lys Thr Asn Leu Gln Lys
 530 535 540
 Asp Leu Ser Lys Leu Ser Ile Ala Ser Tyr Asn Ile Glu Asn Phe Ser
 545 550 555 560
 Ala Asn Pro Ser Ser Thr Lys Asp Glu Lys Val Lys Arg Ile Ala Glu
 565 570 575
 Ser Phe Ile His Asp Leu Asn Ala Pro Asp Ile Ile Gly Leu Ile Glu
 580 585 590
 Val Gln Asp Asn Asn Gly Pro Thr Asp Asp Gly Thr Thr Asp Ala Thr
 595 600 605
 Gln Ser Ala Gln Arg Leu Ile Asp Ala Ile Lys Lys Leu Gly Gly Pro
 610 615 620
 Thr Tyr Arg Tyr Val Asp Ile Ala Pro Glu Asn Asn Val Asp Gly Gly
 625 630 635 640
 Gln Pro Gly Gly Asn Ile Arg Thr Gly Phe Leu Tyr Gln Pro Glu Arg
 645 650 655
 Val Ser Leu Ser Asp Lys Pro Lys Gly Gly Ala Arg Asp Ala Leu Thr
 660 665 670
 Trp Val Asn Gly Glu Leu Asn Leu Ser Val Gly Arg Ile Asp Pro Thr
 675 680 685
 Asn Ala Ala Trp Lys Asp Val Arg Lys Ser Leu Ala Ala Glu Phe Ile
 690 695 700
 Phe Gln Gly Arg Lys Val Val Val Val Ala Asn His Leu Asn Ser Lys
 705 710 715 720
 Arg Gly Asp Asn Ala Leu Tyr Gly Cys Val Gln Pro Val Thr Phe Lys
 725 730 735
 Ser Glu Gln Arg Arg His Val Leu Ala Asn Met Leu Ala Gln Phe Ala
 740 745 750
 Lys Glu Gly Ala Lys His Gln Ala Asn Ile Val Met Leu Gly Asp Phe
 755 760 765
 Asn Asp Phe Glu Phe Thr Lys Thr Ile Gln Leu Ile Glu Glu Gly Asp
 770 775 780
 Met Val Asn Leu Val Ser Arg His Asp Ile Ser Asp Arg Tyr Ser Tyr
 785 790 795 800
 Phe His Gln Gly Asn Asn Gln Thr Leu Asp Asn Ile Leu Val Ser Arg
 805 810 815
 His Leu Leu Asp His Tyr Glu Phe Asp Met Val His Val Asn Ser Pro
 820 825 830
 Phe Met Glu Ala His Gly Arg Ala Ser Asp His Asp Pro Leu Leu Leu
 835 840 845
 Gln Leu Ser Phe Ser Lys Glu Asn Asp Lys Ala Glu Ser Ser Lys Gln

850 855 860
 Ser Val Lys Ala Lys Lys Thr Ser Lys Gly Lys Leu Leu Pro Lys Thr
 865 870 875 880
 Gly Asp Ser Leu Val Tyr Val Ile Thr Leu Leu Gly Thr Ala Ser Leu
 885 890 895
 Leu Val Pro Ile Leu Leu Leu Thr Lys Gly Lys Lys Glu Ser
 900 905 910

<210> 188
 <211> 1210
 <212> PRT
 <213> Streptococcus pyogenes

<400> 188
 Val Ile Ser Phe Ala Pro Phe Leu Ser Pro Glu Ala Ile Lys His Leu
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 Gln Glu Asn Glu Arg Cys Arg Asp Gln Ser Gln Lys Arg Thr Ala Gln
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 35 40 45
 Ser Ala Gly Ser Gly Lys Thr Phe Val Met Val Glu Arg Ile Leu Asp
 50 55 60
 Lys Ile Leu Arg Gly Val Ser Ile Asp Arg Leu Phe Ile Ser Thr Phe
 65 70 75 80
 Thr Val Lys Ala Ala Thr Glu Leu Arg Glu Arg Ile Glu Asn Lys Leu
 85 90 95
 Tyr Ser Gln Ile Ala Gln Thr Thr Asp Phe Gln Met Lys Val Tyr Leu
 100 105 110
 Thr Glu Gln Leu Gln Ser Leu Cys Gln Ala Asp Ile Gly Thr Met Asp
 115 120 125
 Ala Phe Ala Gln Lys Val Val Ser Arg Tyr Gly Tyr Ser Ile Gly Ile
 130 135 140
 Ser Ser Gln Phe Arg Ile Met Gln Asp Lys Ala Glu Gln Asp Val Leu
 145 150 155 160
 Lys Gln Glu Val Phe Ser Lys Leu Phe Asn Glu Phe Met Asn Gln Lys
 165 170 175
 Glu Ala Pro Val Phe Arg Ala Leu Val Lys Asn Phe Ser Gly Asn Cys
 180 185 190
 Lys Asp Thr Ser Ala Phe Arg Glu Leu Val Tyr Thr Cys Tyr Ser Phe
 195 200 205
 Ser Gln Ser Thr Glu Asn Pro Lys Ile Trp Leu Gln Glu Asn Phe Leu
 210 215 220
 Ser Ala Ala Lys Thr Tyr Gln Arg Leu Glu Asp Ile Pro Asp His Asp
 225 230 235 240
 Ile Glu Leu Leu Leu Leu Ala Met Gln Asp Thr Ala Asn Gln Leu Arg
 245 250 255
 Asp Val Thr Asp Met Glu Asp Tyr Gly Gln Leu Thr Lys Ala Gly Ser
 260 265 270
 Arg Ser Ala Lys Tyr Thr Lys His Leu Thr Ile Ile Glu Lys Leu Ser
 275 280 285
 Asp Trp Val Arg Asp Phe Lys Cys Leu Tyr Gly Lys Ala Gly Leu Asp
 290 295 300
 Arg Leu Ile Arg Asp Val Thr Gly Leu Ile Pro Ser Gly Asn Asp Val
 305 310 315 320
 Thr Val Ser Lys Val Lys Tyr Pro Val Phe Lys Thr Leu His Gln Lys
 325 330 335
 Leu Lys Gln Phe Arg His Leu Glu Thr Ile Leu Met Tyr Gln Lys Asp
 340 345 350
 Cys Phe Ser Leu Leu Glu Gln Leu Gln Asp Phe Val Leu Ala Phe Ser
 355 360 365
 Glu Ala Tyr Leu Ala Val Lys Ile Gln Glu Ser Ala Phe Glu Phe Ser
 370 375 380
 Asp Ile Ala His Phe Ala Ile Lys Ile Leu Glu Glu Asn Thr Asp Ile
 385 390 395 400
 Arg Gln Ser Tyr Gln Gln His Tyr His Glu Val Met Val Asp Glu Tyr
 405 410 415
 Gln Asp Asn Asn His Met Gln Glu Arg Leu Leu Thr Leu Leu Ser Asn
 420 425 430
 Gly His Asn Arg Phe Met Val Gly Asp Ile Lys Gln Ser Ile Tyr Arg
 435 440 445
 Phe Arg Gln Ala Asp Pro Gln Ile Phe Asn Gln Lys Phe Arg Asp Tyr
 450 455 460
 Gln Lys Lys Pro Glu Gln Gly Lys Val Ile Leu Leu Lys Glu Asn Phe
 465 470 475 480

【 0 1 7 2 】

Arg Ser Gln Ser Glu Val Leu Asn Val Ser Asn Ala Val Phe Ser His
 485 490 495
 Leu Met Asp Glu Ser Val Gly Asp Val Leu Tyr Asp Glu Gln His Gln
 500 505 510
 Leu Ile Ala Gly Ser His Ala Gln Thr Val Pro Tyr Leu Asp Arg Arg
 515 520 525
 Ala Gln Leu Leu Leu Tyr Asn Ser Asp Lys Asp Asp Gly Asn Ala Pro
 530 535 540
 Ser Asp Ser Glu Gly Ile Ser Phe Ser Glu Val Thr Ile Val Ala Lys
 545 550 555 560
 Glu Ile Ile Lys Leu His Asn Asp Lys Gly Val Pro Phe Glu Asp Ile
 565 570 575
 Thr Leu Leu Val Ser Ser Arg Thr Arg Asn Asp Ile Ile Ser His Thr
 580 585 590
 Phe Asn Gln Tyr Gly Ile Pro Ile Ala Thr Asp Gly Gly Gln Gln Asn
 595 600 605
 Tyr Leu Lys Ser Val Glu Val Met Val Met Leu Asp Thr Leu Arg Thr
 610 615 620
 Ile Asn Asn Pro Arg Asn Asp Tyr Ala Leu Val Ala Leu Leu Arg Ser
 625 630 635 640
 Pro Met Phe Ala Phe Asp Glu Asp Asp Leu Ala Arg Ile Ala Leu Gln
 645 650 655
 Lys Asp Asn Glu Leu Asp Lys Asp Cys Leu Tyr Asp Lys Ile Gln Arg
 660 665 670
 Ala Val Ile Gly Arg Gly Ala His Pro Glu Leu Ile His Asp Thr Leu
 675 680 685
 Leu Gly Lys Leu Asn Val Phe Leu Lys Thr Leu Lys Ser Trp Arg Arg
 690 695 700
 Tyr Ala Lys Leu Gly Ser Leu Tyr Asp Leu Ile Trp Lys Ile Phe Asn
 705 710 715 720
 Asp Arg Phe Tyr Phe Asp Phe Val Ala Ser Gln Ala Lys Ala Glu Gln
 725 730 735
 Ala Gln Ala Asn Leu Tyr Ala Leu Ala Leu Arg Ala Asn Gln Phe Glu
 740 745 750
 Lys Ser Gly Tyr Lys Gly Leu Tyr Arg Phe Ile Lys Met Ile Asp Lys
 755 760 765
 Val Leu Glu Thr Gln Asn Asp Leu Ala Asp Val Glu Val Ala Thr Pro
 770 775 780
 Lys Gln Ala Val Asn Leu Met Thr Ile His Lys Ser Lys Gly Leu Gln
 785 790 795 800
 Phe Pro Tyr Val Phe Ile Leu Asn Cys Asp Lys Arg Phe Ser Met Thr
 805 810 815
 Asp Ile His Lys Ser Phe Ile Leu Asn Arg Gln His Gly Ile Gly Ile
 820 825 830
 Lys Tyr Leu Ala Asp Ile Lys Gly Leu Leu Gly Glu Thr Thr Leu Asn
 835 840 845
 Ser Val Lys Val Ser Met Glu Thr Leu Pro Tyr Gln Leu Asn Lys Gln
 850 855 860
 Glu Leu Arg Leu Ala Thr Leu Ser Glu Glu Met Arg Leu Leu Tyr Val
 865 870 875 880
 Ala Met Thr Arg Ala Glu Lys Lys Val Tyr Phe Ile Gly Lys Ala Ser
 885 890 895
 Lys Ser Lys Ser Gln Glu Ile Thr Asp Pro Lys Lys Leu Gly Lys Leu
 900 905 910
 Leu Pro Leu Ala Leu Arg Glu Gln Leu Leu Thr Phe Gln Asp Trp Leu
 915 920 925
 Leu Ala Ile Ala Asp Ile Phe Ser Thr Glu Asp Leu Tyr Phe Asp Val
 930 935 940
 Arg Phe Ile Glu Asp Ser Asp Leu Thr Gln Glu Ser Val Gly Arg Leu
 945 950 955 960
 Gln Thr Pro Gln Leu Asn Pro Asp Asp Leu Lys Asp Asn Arg Gln
 965 970 975
 Ser Glu Thr Ile Ala Arg Ala Leu Asp Met Leu Glu Ala Val Ser Gln
 980 985 990
 Leu Asn Ala Asn Tyr Glu Ala Ala Ile His Leu Pro Thr Val Arg Thr
 995 1000 1005
 Pro Ser Gln Leu Lys Ala Thr Tyr Glu Pro Leu Leu Glu Pro Ile
 1010 1015 1020
 Gly Val Asp Ile Ile Glu Lys Ser Ser Arg Ser Leu Ser Asp Phe
 1025 1030 1035
 Thr Leu Pro His Phe Ser Lys Lys Ala Lys Val Glu Ala Ser His
 1040 1045 1050
 Ile Gly Ser Ala Leu His Gln Leu Met Gln Val Leu Pro Leu Ser
 1055 1060 1065
 Lys Pro Ile Asn Gln Gln Thr Leu Leu Asp Ala Leu Arg Gly Ile

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1070      1075      1080
Asp Ser Asn Glu Glu Val Lys Thr Ala Leu Asp Leu Lys Lys Ile
1085      1090      1095
Glu Ser Phe Phe Cys Asp Thr Ser Leu Gly Gln Phe Phe Gln Thr
1100      1105      1110
Tyr Gln Lys His Leu Tyr Arg Glu Ala Pro Phe Ala Ile Leu Lys
1115      1120      1125
Leu Asp Pro Ile Ser Gln Glu Glu Tyr Val Leu Arg Gly Ile Ile
1130      1135      1140
Asp Ala Tyr Phe Leu Phe Asp Asp His Ile Val Leu Val Asp Tyr
1145      1150      1155
Lys Thr Asp Lys Tyr Lys Gln Pro Ile Glu Leu Lys Lys Arg Tyr
1160      1165      1170
Gln Gln Gln Leu Glu Leu Tyr Ala Glu Ala Leu Thr Gln Thr Tyr
1175      1180      1185
Lys Leu Pro Val Thr Lys Arg Tyr Leu Val Leu Met Gly Gly Gly
1190      1195      1200
Lys Pro Glu Ile Val Glu Val
1205      1210

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<210> 189
 <211> 253
 <212> PRT
 <213> Streptococcus pyogenes

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Met Val Lys Thr Asp Phe Lys Leu Arg Tyr Gln Gly Ser Ala Ile Gly
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Tyr Leu Trp Ser Ile Leu Lys Pro Leu Met Met Phe Thr Ile Met Tyr
20      25      30
Leu Val Phe Ile Arg Phe Leu Arg Leu Gly Gly Asn Val Pro His Phe
35      40      45
Pro Val Ala Leu Leu Leu Ala Asn Val Ile Trp Ser Phe Phe Ser Glu
50      55      60
Ala Thr Ser Met Gly Met Val Ser Ile Val Ser Arg Gly Asp Leu Leu
65      70      75      80
Arg Lys Leu Asn Phe Ser Lys His Ile Ile Val Phe Ser Ala Val Leu
85      90      95
Gly Ala Leu Ile Asn Phe Leu Ile Asn Leu Val Val Val Leu Ile Phe
100      105      110
Ala Leu Ile Asn Gly Val Thr Ile Ser Gly Tyr Ala Tyr Leu Ser Leu
115      120      125
Phe Leu Phe Ile Glu Leu Val Val Leu Val Leu Gly Ile Ala Leu Leu
130      135      140
Leu Ser Asn Val Phe Val Tyr Tyr Arg Asp Leu Ala Gln Val Trp Glu
145      150      155      160
Val Leu Leu Gln Ala Gly Met Tyr Ala Thr Pro Ile Ile Tyr Pro Ile
165      170      175
Thr Phe Val Leu Asp Ser His Pro Leu Ala Ala Lys Leu Leu Met Leu
180      185      190
Asn Pro Val Ala Gln Met Ile Gln Asp Phe Arg Tyr Leu Leu Ile Asp
195      200      205
Arg Ala Asn Val Thr Ile Trp Gln Met Ser Thr Asn Trp Phe Tyr Ile
210      215      220
Val Ile Pro Tyr Leu Val Pro Phe Val Ile Leu Phe Ile Gly Ile Phe
225      230      235      240
Val Phe Lys Lys Asn Ala Asp Arg Phe Ala Glu Ile Ile
245      250

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<210> 190
 <211> 577
 <212> PRT
 <213> Streptococcus pyogenes

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<400> 190
Met Thr Phe Leu Ser Asp Leu Ile Ser Leu Met Thr Lys Ile Arg Leu
1      5      10      15
Ser Trp Val Ile Lys Ala Gly Ile Phe Gln Leu Leu Phe Val Thr Ile
20      25      30
Ala Asn Ile Val Leu Ser Glu Phe Phe Tyr Phe Ile Leu Asp Val Thr
35      40      45
Gly Gln Tyr His Leu Asp Lys Asp Asn Val Val Thr Phe Leu Lys Asn
50      55      60

```

【 0 1 7 4 】

Pro Ile Ala Leu Ala Leu Leu Gly Ala Tyr Leu Phe Leu Leu Ala Ala
 65 70 75 80
 Phe Ile His Leu Glu Phe Phe Ala Leu Tyr Arg Ile Ile Ala Asp Gln
 85 90 95
 Glu Ile Ser Phe Tyr Leu Phe Arg Lys Gln Phe Ser Tyr Tyr Leu Arg
 100 105 110
 Gly Leu Trp Lys Thr Phe Ser Gly Tyr Gln Leu Leu Leu Phe Leu Leu
 115 120 125
 Tyr Ile Leu Leu Thr Ile Pro Val Leu His Ile Gly Leu Ser Ser Val
 130 135 140
 Ile Thr Gln Lys Leu Tyr Leu Pro Glu Phe Ile Val Gly Glu Leu Ser
 145 150 155 160
 Lys Ile Thr Ser Thr Lys Tyr Leu Leu Tyr Gly Ser Leu Ile Leu Val
 165 170 175
 Phe Tyr Leu Asn Leu Arg Leu Val Tyr Phe Leu Pro Leu Ile Ala Ile
 180 185 190
 Asn His Arg Thr Val Ala Gln Ala Trp Arg Glu Ser Trp Gln Lys Thr
 195 200 205
 Lys Lys Lys His Val Leu Leu Trp Met Lys Leu Phe Ala Ile Asn Gly
 210 215 220
 Leu Thr Ile Val Val Leu Ser Leu Ala Ile Ser Met Ile Leu Ile Phe
 225 230 235 240
 Val Asp Met Phe Asn Pro Lys Gly Asn Asn Ile Ile Val Gln Leu Gly
 245 250 255
 Ala Leu Thr Phe Thr Trp Glu Leu Ile Phe Phe Thr Thr Ile Phe Phe
 260 265 270
 Lys Leu Cys Ser Ala Met Ile Leu Lys Glu Ala Ile Glu Pro Gln Lys
 275 280 285
 Gln Tyr Asp Glu Pro Arg Arg Ser Asn Lys Ala Tyr Val Val Ile Phe
 290 295 300
 Ile Val Val Thr Val Gly Phe Ala Tyr Gln Ser Leu Glu Arg Leu Thr
 305 310 315 320
 Phe Phe Asp Thr Ser His Ser Lys Thr Val Ile Ala His Arg Gly Leu
 325 330 335
 Val Ser Ala Gly Val Glu Asn Ser Leu Glu Ala Leu Glu Gly Ala Lys
 340 345 350
 Lys Ala Gly Ser Asp Tyr Val Glu Leu Asp Leu Ile Leu Thr Lys Asp
 355 360 365
 Asn His Phe Val Val Ser His Asp Asn Arg Leu Lys Arg Leu Ala Gly
 370 375 380
 Val Asn Lys Thr Ile Arg Asn Leu Thr Leu Lys Glu Val Glu His Leu
 385 390 395 400
 Thr Ser His Gln Gly His Phe Ser Gly Arg Phe Val Ser Phe Asp Thr
 405 410 415
 Phe Tyr Gln Lys Ala Lys Lys Leu Asn Met Pro Leu Leu Ile Glu Leu
 420 425 430
 Lys Pro Ile Gly Thr Glu Pro Gly Asn Tyr Val Asp Leu Phe Leu Glu
 435 440 445
 Thr Tyr His Arg Leu Gly Ile Ser Lys Asp Asn Lys Val Met Ser Leu
 450 455 460
 Asp Leu Glu Val Ile Glu Ala Ile Lys Lys Lys Asn Pro Ser Ile Thr
 465 470 475 480
 Thr Gly Tyr Ile Ile Pro Ile Gln Phe Gly Phe Phe Gly Asp Glu Phe
 485 490 495
 Val Asp Phe Tyr Val Ile Glu Asp Phe Ser Tyr Arg Ser Tyr Leu Ser
 500 505 510
 Ser Gln Ala Phe Trp Asn Asn Lys Glu Ile Tyr Val Trp Thr Ile Asn
 515 520 525
 Asp Pro Lys Arg Ile Glu His Tyr Leu Leu Lys Pro Ile Gln Gly Ile
 530 535 540
 Ile Thr Asp Gln Pro Ala Leu Thr Asn Gln Leu Ile Lys Asp Leu Lys
 545 550 555 560
 Gln Asp Asn Ser Tyr Phe Ser Arg Leu Val Arg Ile Ile Ser Ser Leu
 565 570 575
 Tyr

<210> 191

<211> 1008

<212> PRT

<213> Streptococcus pyogenes

<400> 191

Met Lys Lys His Leu Lys Thr Val Ala Leu Thr Leu Thr Thr Val Ser

【 0 1 7 5 】

1	Val	Val	Thr	His	Asn	Gln	Glu	Val	Phe	Ser	Leu	Val	Lys	Glu	Pro	Ile
			20						25					30		
Leu	Lys	Gln	Thr	Gln	Ala	Ser	Ser	Ser	Ile	Ser	Gly	Ala	Asp	Tyr	Ala	
		35					40					45				
Glu	Ser	Ser	Gly	Lys	Ser	Lys	Leu	Lys	Ile	Asn	Glu	Thr	Ser	Gly	Pro	
	50				55				60							
Val	Asp	Asp	Thr	Val	Thr	Asp	Leu	Phe	Ser	Asp	Lys	Arg	Thr	Thr	Pro	
65				70					75						80	
Glu	Lys	Ile	Lys	Asp	Asn	Leu	Ala	Lys	Gly	Pro	Arg	Glu	Gln	Glu	Leu	
			85						90					95		
Lys	Ala	Val	Thr	Glu	Asn	Thr	Glu	Ser	Glu	Lys	Gln	Ile	Thr	Ser	Gly	
		100					105						110			
Ser	Gln	Leu	Glu	Gln	Ser	Lys	Glu	Ser	Leu	Ser	Leu	Asn	Lys	Thr	Val	
	115					120			125							
Pro	Ser	Thr	Ser	Asn	Trp	Glu	Ile	Cys	Asp	Phe	Ile	Thr	Lys	Gly	Asn	
	130					135			140							
Thr	Leu	Val	Gly	Leu	Ser	Lys	Ser	Gly	Val	Glu	Lys	Leu	Ser	Gln	Thr	
145				150					155						160	
Asp	His	Leu	Val	Leu	Pro	Ser	Gln	Ala	Ala	Asp	Gly	Thr	Gln	Leu	Ile	
			165						170					175		
Gln	Val	Ala	Ser	Phe	Ala	Phe	Thr	Pro	Asp	Lys	Lys	Thr	Ala	Ile	Ala	
	180							185					190			
Glu	Tyr	Thr	Ser	Arg	Ala	Gly	Glu	Asn	Gly	Glu	Ile	Ser	Gln	Leu	Asp	
	195					200						205				
Val	Asp	Gly	Lys	Glu	Ile	Ile	Asn	Glu	Gly	Glu	Val	Phe	Asn	Ser	Tyr	
	210				215				220							
Leu	Leu	Lys	Lys	Val	Thr	Ile	Pro	Thr	Gly	Tyr	Lys	His	Ile	Gly	Gln	
225				230					235						240	
Asp	Ala	Phe	Val	Asp	Asn	Lys	Asn	Ile	Ala	Glu	Val	Asn	Leu	Pro	Glu	
			245					250						255		
Ser	Leu	Glu	Thr	Ile	Ser	Asp	Tyr	Ala	Phe	Ala	His	Leu	Ala	Leu	Lys	
	260							265					270			
Gln	Ile	Asp	Leu	Pro	Asp	Asn	Leu	Lys	Ala	Ile	Gly	Glu	Leu	Ala	Phe	
	275						280					285				
Phe	Asp	Asn	Gln	Ile	Thr	Gly	Lys	Leu	Ser	Leu	Pro	Arg	Gln	Leu	Met	
	290					295					300					
Arg	Leu	Ala	Glu	Arg	Ala	Phe	Lys	Ser	Asn	His	Ile	Lys	Thr	Ile	Glu	
305				310					315						320	
Phe	Arg	Gly	Asn	Ser	Leu	Lys	Val	Ile	Gly	Glu	Ala	Ser	Phe	Gln	Asp	
			325					330						335		
Asn	Asp	Leu	Ser	Gln	Leu	Met	Leu	Pro	Asp	Gly	Leu	Glu	Lys	Ile	Glu	
	340							345					350			
Ser	Glu	Ala	Phe	Thr	Gly	Asn	Pro	Gly	Asp	Asp	His	Tyr	Asn	Asn	Arg	
	355						360					365				
Val	Val	Leu	Trp	Thr	Lys	Ser	Gly	Lys	Asn	Pro	Ser	Gly	Leu	Ala	Thr	
	370					375						380				
Glu	Asn	Thr	Tyr	Val	Asn	Pro	Asp	Lys	Ser	Leu	Trp	Gln	Glu	Ser	Pro	
385				390					395						400	
Glu	Ile	Asp	Tyr	Thr	Lys	Trp	Leu	Glu	Glu	Asp	Phe	Thr	Tyr	Gln	Lys	
			405						410					415		
Asn	Ser	Val	Thr	Gly	Phe	Ser	Asn	Lys	Gly	Leu	Gln	Lys	Val	Lys	Arg	
	420							425					430			
Asn	Lys	Asn	Leu	Glu	Ile	Pro	Lys	Gln	His	Asn	Gly	Val	Thr	Ile	Thr	
	435					440						445				
Glu	Ile	Gly	Asp	Asn	Ala	Phe	Arg	Asn	Val	Asp	Phe	Gln	Asn	Lys	Thr	
	450					455					460					
Leu	Arg	Lys	Tyr	Asp	Leu	Glu	Glu	Val	Lys	Leu	Pro	Ser	Thr	Ile	Arg	
465				470					475						480	
Lys	Ile	Gly	Ala	Phe	Ala	Phe	Gln	Ser	Asn	Asn	Leu	Lys	Ser	Phe	Glu	
			485						490					495		
Ala	Ser	Asp	Asp	Leu	Glu	Glu	Ile	Lys	Glu	Gly	Ala	Phe	Met	Asn	Asn	
	500							505					510			
Arg	Ile	Glu	Thr	Leu	Glu	Leu	Lys	Asp	Lys	Leu	Val	Thr	Ile	Gly	Asp	
	515						520					525				
Ala	Ala	Phe	His	Ile	Asn	His	Ile	Tyr	Ala	Ile	Val	Leu	Pro	Glu	Ser	
	530					535						540				
Val	Gln	Glu	Ile	Gly	Arg	Ser	Ala	Phe	Arg	Gln	Asn	Gly	Ala	Asn	Asn	
545				550					555						560	
Leu	Ile	Phe	Met	Gly	Ser	Lys	Val	Lys	Thr	Leu	Gly	Glu	Met	Ala	Phe	
			565						570					575		
Leu	Ser	Asn	Arg	Leu	Glu	His	Leu	Asp	Leu	Ser	Glu	Gln	Lys	Gln	Leu	
		580						585					590			
Thr	Glu	Ile	Pro	Val	Gln	Ala	Phe	Ser	Asp	Asn	Ala	Leu	Lys	Glu	Val	
	595					600						605				

Leu 610 Pro Ala Ser Leu 615 Lys Thr Ile Arg Glu 620 Glu Ala Phe Lys Lys
 Asn 625 His Leu Lys Gln Leu 630 Glu Val Ala Ser Ala 635 Leu Ser His Ile Ala
 Phe 645 Asn Ala Leu Asp Asn Asp Gly 650 Glu Gln Phe Asp Asn Lys
 Val 660 Val Val Lys Thr His His Asn Ser Tyr Ala Leu Ala Asp Gly Glu
 His 675 Phe Ile Val Asp Pro Asp Lys 680 Leu Ser Ser Thr Ile Val Asp Leu
 Glu 690 Lys Ile Leu Lys Leu 695 Ile Glu Gly Leu Asp Tyr Ser Thr Leu Arg
 Gln 705 Thr Thr Gln Thr Gln 710 Phe Arg Asp Met Thr Thr Ala Gly Lys Ala
 Leu 725 Ser Lys Ser Asn Leu Arg Gln Gly Glu Lys Gln Lys Phe Leu
 Gln 740 Glu Ala Gln Phe Phe Leu Gly Arg Val Asp Leu Asp Lys Ala Ile
 Ala 755 Lys Ala Glu Lys Ala Leu Val Thr Lys Lys Ala Thr Lys Asn Gly
 Gln 770 Leu Glu Arg Ser Ile 775 Asn Lys Ala Val Leu Ala Tyr Asn Asn
 Ser 785 Ala Ile Lys Lys Ala 790 Asn Val Lys Arg Leu Glu Lys Glu Leu Asp
 Leu 805 Leu Thr Gly Leu Val Glu Gly Lys Gly Pro Leu Ala Gln Ala Thr
 Met 820 Val Gln Gly Val Tyr Leu Leu Lys Thr Pro Leu Pro Leu Pro Glu
 Tyr 835 Tyr Ile Gly Leu Asn Val Tyr 840 Phe Asp Lys Ser Gly Lys Leu Ile
 Tyr 850 Ala Leu Asp Met Ser Asp Thr Ile Gly Glu Gly Gln Lys Asp Ala
 Tyr 865 Gly Asn Pro Ile Leu 870 Asn Val Asp Glu Asp Asn Glu Gly Tyr His
 Ala 885 Leu Ala Val Ala Thr Leu Ala Asp Tyr Glu Gly Leu Asp Ile Lys
 Thr 900 Ile Leu Asn Ser Lys Leu Ser Gln 905 Leu Thr Ser Ile Arg Gln Val
 Pro 915 Thr Ala Ala Tyr His Arg Ala Gly Ile Phe Gln Ala Ile Gln Asn
 Ala 930 Ala Glu Ala Glu Gln 935 Leu Leu Pro Lys Pro Gly Thr His Ser
 Glu 945 Lys Ser Ser Ser Ser 950 Glu Ser Ala Asn Ser Lys Asp Arg Gly Leu
 Gln 965 Ser Asn Pro Lys Thr Asn Arg Gly Arg His Ser Ala Ile Leu Pro
 Arg 980 Thr Gly Ser Lys Gly Ser Phe Val Tyr Gly Ile Leu Gly Tyr Thr
 Ser 995 Val Ala Leu Leu Ser Leu Ile 1000 Thr Ala Ile Lys Lys Lys Lys Tyr

<210> 192

<211> 670

<212> PRT

<213> Streptococcus pyogenes

<400> 192

Met 1 Lys Lys Tyr 5 Phe Ile Leu Lys Ser 10 Ser Val Leu Ser Ile Leu Thr
 Ser 20 Phe Thr Leu Leu Val Thr Asp 25 Val Gln Ala Asp Gln Val Asp Val
 Gln 35 Phe Leu Gly Val Asn Asp Phe 40 His Gly Ala Leu Asp Asn Thr Gly
 Thr 50 Ala Tyr Thr Pro Ser Gly 55 Lys Ile Pro Asn Ala Gly Thr Ala Ala
 Gln 65 Leu Gly Ala Tyr Met Asp Asp Ala Glu Ile Asp Phe Lys Gln Ala
 Asn 85 Gln Asp Gly Thr Ser Ile Arg Val Gln 90 Ala Gly Asp Met Val Gly
 Ala 100 Ser Pro Ala Asn Ser Ala Leu Leu 105 Gln Asp Glu Pro Thr Val Lys
 Val 115 Phe Asn Lys Met Lys Phe Glu Tyr Gly Thr Leu Gly Asn His Glu
 Phe 120 Asp Glu Gly Leu Asp Glu Phe Asn Arg Ile Met Thr Gly Gln Ala

【 0 1 7 7 】

130 135 140
 Pro Asp Pro Glu Ser Thr Ile Asn Asp Ile Thr Lys Gln Tyr Glu His
 145 150 155 160
 Glu Ala Ser His Gln Thr Ile Val Ile Ala Asn Val Ile Asp Lys Lys
 165 170 175
 Thr Lys Asp Ile Pro Tyr Gly Trp Lys Pro Tyr Ala Ile Lys Asp Ile
 180 185 190
 Ala Ile Asn Asp Lys Ile Val Lys Ile Gly Phe Ile Gly Val Val Thr
 195 200 205
 Thr Glu Ile Pro Asn Leu Val Leu Lys Gln Asn Tyr Glu His Tyr Gln
 210 215 220
 Phe Leu Asp Val Ala Glu Thr Ile Ala Lys Tyr Ala Lys Glu Leu Gln
 225 230 235 240
 Glu Gln His Val His Ala Ile Val Val Leu Ala His Val Pro Ala Thr
 245 250 255
 Ser Lys Asp Gly Val Val Asp His Glu Met Ala Thr Val Met Glu Lys
 260 265 270
 Val Asn Gln Ile Tyr Pro Glu His Ser Ile Asp Ile Ile Phe Ala Gly
 275 280 285
 His Asn His Gln Tyr Thr Asn Gly Thr Ile Gly Lys Thr Arg Ile Val
 290 295 300
 Gln Ala Leu Ser Gln Gly Lys Ala Tyr Ala Asp Val Arg Gly Thr Leu
 305 310 315 320
 Asp Thr Asp Thr Asn Asp Phe Ile Lys Thr Pro Ser Ala Asn Val Val
 325 330 335
 Ala Val Ala Pro Gly Ile Lys Thr Glu Asn Ser Asp Ile Lys Ala Ile
 340 345 350
 Ile Asn His Ala Asn Asp Ile Val Lys Thr Val Thr Glu Arg Lys Ile
 355 360 365
 Gly Thr Ala Thr Asn Ser Ser Thr Ile Ser Lys Thr Glu Asn Ile Asp
 370 375 380
 Lys Glu Ser Pro Val Gly Asn Leu Ala Thr Thr Ala Gln Leu Thr Ile
 385 390 395 400
 Ala Lys Lys Thr Phe Pro Thr Val Asp Phe Ala Met Thr Asn Asn Gly
 405 410 415
 Gly Ile Arg Ser Asp Leu Val Val Lys Asn Asp Arg Thr Ile Thr Trp
 420 425 430
 Gly Ala Ala Gln Ala Val Gln Pro Phe Gly Asn Ile Leu Gln Val Ile
 435 440 445
 Gln Met Thr Gly Gln His Ile Tyr Asp Val Leu Asn Gln Gln Tyr Asp
 450 455 460
 Glu Asn Gln Thr Tyr Phe Leu Gln Met Ser Gly Leu Thr Tyr Thr Tyr
 465 470 475 480
 Thr Asp Asn Asp Pro Lys Asn Ser Asp Thr Pro Phe Lys Ile Val Lys
 485 490 495
 Val Tyr Lys Asp Asn Gly Glu Glu Ile Asn Leu Thr Thr Thr Tyr Thr
 500 505 510
 Val Val Val Asn Asp Phe Leu Tyr Gly Gly Gly Asp Gly Phe Ser Ala
 515 520 525
 Phe Lys Lys Ala Lys Leu Ile Gly Ala Ile Asn Thr Asp Thr Glu Ala
 530 535 540
 Phe Ile Thr Tyr Ile Thr Asn Leu Glu Ala Ser Gly Lys Thr Val Asn
 545 550 555 560
 Ala Thr Ile Lys Gly Val Lys Asn Tyr Val Thr Ser Asn Leu Glu Ser
 565 570 575
 Ser Thr Lys Val Asn Ser Ala Gly Lys His Ser Ile Ile Ser Lys Val
 580 585 590
 Phe Arg Asn Arg Asp Gly Asn Thr Val Ser Ser Glu Val Ile Ser Asp
 595 600 605
 Leu Leu Thr Ser Thr Glu Asn Thr Asn Asn Ser Leu Gly Lys Lys Glu
 610 615 620
 Thr Thr Thr Asn Lys Asn Thr Ile Ser Ser Ser Thr Leu Pro Ile Thr
 625 630 635 640
 Gly Asp Asn Tyr Lys Met Ser Pro Ile Met Thr Ile Leu Ala Leu Ile
 645 650 655
 Ser Leu Gly Gly Leu Asn Ala Phe Ile Lys Lys Arg Lys Ser
 660 665 670

<210> 193

<211> 262

<212> PRT

<213> Streptococcus pyogenes

<400> 193

【 0 1 7 8 】

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Met Thr Asn Asn Gln Thr Leu Asp Ile Leu Leu Asp Val Tyr Ala Tyr
1      5      10      15
Asn His Ala Phe Arg Ile Ala Lys Ala Leu Pro Asn Ile Pro Lys Thr
20      25      30
Ala Leu Tyr Leu Leu Glu Met Leu Lys Glu Arg Arg Glu Leu Asn Leu
35      40      45
Ala Phe Leu Ala Glu His Ala Ala Glu Asn Arg Thr Ile Glu Asp Gln
50      55      60
Tyr His Cys Ser Leu Trp Leu Asn Gln Ser Leu Glu Asp Glu Gln Ile
65      70      75      80
Ala Asn Tyr Ile Leu Asp Leu Glu Val Lys Val Lys Asn Gly Ala Ile
85      90      95
Ile Asp Phe Val Arg Ser Val Ser Pro Ile Leu Tyr Arg Leu Phe Leu
100      105      110
Arg Leu Ile Thr Ser Glu Ile Pro Asn Phe Lys Ala Tyr Ile Phe Asp
115      120      125
Thr Lys Asn Asp Gln Tyr Asp Thr Trp His Phe Gln Ala Met Leu Glu
130      135      140
Ser Asp His Glu Val Phe Lys Ala Tyr Leu Ser Gln Lys Gln Ser Arg
145      150      155      160
Asn Val Thr Thr Lys Ser Leu Ala Asp Met Leu Thr Leu Thr Ser Leu
165      170      175
Pro Gln Glu Ile Lys Asp Leu Val Phe Leu Leu Arg His Phe Glu Lys
180      185      190
Ala Val Arg Asn Pro Leu Ala His Leu Ile Lys Pro Phe Asp Glu Glu
195      200      205
Glu Leu His Arg Thr Thr His Phe Ser Ser Gln Ala Phe Leu Glu Asn
210      215      220
Ile Ile Thr Leu Ala Thr Phe Ser Gly Val Ile Tyr Arg Arg Glu Pro
225      230      235      240
Phe Tyr Phe Asp Asp Met Asn Ala Ile Ile Lys Lys Glu Leu Ser Leu
245      250      255
Trp Arg Gln Ser Ile Val
260

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<210> 194

<211> 429

<212> PRT

<213> Streptococcus pyogenes

<400> 194

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Met Lys Thr Thr Ser Leu Ile Lys Val Asp Leu Pro Ser Thr Ile Gly
1      5      10      15
Ile Gly Tyr Gly Ala Phe Trp Arg Ser Arg Asn Phe Tyr Arg Val Val
20      25      30
Lys Gly Ser Arg Gly Ser Lys Lys Ser Lys Thr Thr Ala Leu Asn Phe
35      40      45
Ile Val Arg Leu Leu Lys Tyr Pro Trp Ala Asn Leu Val Ile Arg
50      55      60
Arg Tyr Ser Asn Thr Asn Lys Gln Ser Thr Tyr Thr Asp Phe Lys Trp
65      70      75      80
Ala Cys Asn Gln Leu Lys Val Thr His Leu Phe Lys Phe Asn Glu Ser
85      90      95
Leu Pro Glu Ile Thr Val Lys Ala Thr Gly Gln Lys Ile Leu Phe Arg
100      105      110
Gly Leu Asp Asp Glu Leu Lys Ile Thr Ser Ile Thr Val Asp Val Gly
115      120      125
Ala Leu Cys Trp Ala Trp Phe Glu Glu Ala Tyr Gln Ile Glu Thr Glu
130      135      140
Asp Lys Phe Ser Thr Val Val Glu Ser Ile Arg Gly Ser Leu Asp Ala
145      150      155      160
Pro Asp Phe Phe Lys Gln Ile Thr Val Thr Phe Asn Pro Trp Ser Glu
165      170      175
Arg His Trp Leu Lys Arg Val Phe Phe Asp Glu Glu Thr Lys Arg Ala
180      185      190
Asp Thr Phe Ser Gly Thr Thr Thr Phe Arg Val Asn Glu Trp Leu Asp
195      200      205
Asp Val Asp Lys Arg Arg Tyr Glu Asp Leu Tyr Lys Thr Asn Pro Arg
210      215      220
Arg Ala Arg Ile Val Cys Asp Gly Glu Trp Gly Val Ala Glu Gly Leu
225      230      235      240
Val Phe Asp Asn Phe Glu Val Val Asp Phe Asp Val Glu Lys Thr Ile
245      250      255
Gln Arg Val Lys Glu Thr Ser Ala Gly Met Asp Phe Gly Phe Thr Gln

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      260      265      270
Asp Pro Thr Thr Leu Ile Cys Val Ala Val Asp Leu Ala Asn Lys Glu
      275      280      285
Leu Trp Leu Tyr Asn Glu His Tyr Gln Lys Ala Met Leu Thr Asp His
      290      295      300
Ile Val Lys Met Ile Arg Asp Lys Asn Leu His Arg Ser Tyr Ile Ala
305      310      315      320
Gly Asp Ser Ala Glu Lys Arg Leu Ile Ala Glu Ile Lys Ser Lys Gly
      325      330      335
Val Ser Gly Ile Val Pro Ser Ile Lys Gly Lys Gly Ser Ile Met Gln
      340      345      350
Gly Ile Gln Phe Met Gln Gly Phe Lys Ile Tyr Ile His Pro Ser Cys
      355      360      365
Glu His Thr Ile Glu Glu Phe Asn Thr Tyr Thr Phe Lys Gln Asp Lys
      370      375      380
Glu Gly Asn Trp Leu Asn Glu Pro Ile Asp Lys Asn Asn His Val Ile
385      390      395      400
Asp Ala Ile Arg Tyr Ala Leu Glu Lys Tyr His Ile Arg Ser Asn Glu
      405      410      415
Ser Asn Gln Phe Glu Val Leu Arg Ala Gly Phe Gly Tyr
      420      425

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<210> 195
 <211> 177
 <212> PRT
 <213> Streptococcus pyogenes

```

<400> 195
Met Ala Glu Glu Thr Gln Thr Val Glu Thr Val Glu Glu Gln Val Val
1      5      10      15
Pro Glu Ala Lys Gln Pro Gln Asp Glu Lys Lys Tyr Thr Asp Ala Asp
      20      25      30
Val Asp Ala Ile Ile Asp Lys Lys Phe Ala Lys Trp Lys Ser Glu Gln
      35      40      45
Glu Ala Glu Lys Ser Glu Ala Lys Lys Met Ala Lys Met Asn Glu Lys
      50      55      60
Glu Lys Ala Asp Tyr Glu Lys Gln Lys Leu Leu Asp Glu Leu Gln Glu
      65      70      75      80
Leu Lys Asn Asp Lys Thr Arg Asn Glu Leu Thr Ala Val Ala Arg Gln
      85      90      95
Met Phe Ala Glu Ser Glu Ile Asn Val Asn Asp Asp Val Leu Gly Leu
      100      105      110
Val Val Thr Leu Asp Ala Glu Gln Thr Lys Ala Asn Val Thr Thr Leu
      115      120      125
Ala Asn Ala Phe Ala Lys Val Ile Ala Asp Asp Arg Lys Ala Leu Val
      130      135      140
Arg Gln Thr Thr Pro Ser Thr Gly Gly Gly Leu Ser Lys Gln Thr Asn
145      150      155      160
Tyr Gly Ala Asn Leu Ala Ser Lys Ala Ala Gln Gln Ser Thr Lys Leu
      165      170      175
Phe

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<210> 196
 <211> 236
 <212> PRT
 <213> Streptococcus pyogenes

```

<400> 196
Met Arg Tyr Asn Cys Arg Tyr Ser His Ile Asp Lys Lys Ile Tyr Ser
1      5      10      15
Met Ile Ile Cys Leu Ser Phe Leu Leu Tyr Ser Asn Val Val Gln Ala
      20      25      30
Asn Ser Tyr Asn Thr Thr Asn Arg His Asn Leu Glu Ser Leu Tyr Lys
      35      40      45
His Asp Ser Asn Leu Ile Glu Ala Asp Ser Ile Lys Asn Ser Pro Asp
      50      55      60
Ile Val Thr Ser His Met Leu Lys Tyr Ser Val Lys Asp Lys Asn Leu
      65      70      75      80
Ser Val Phe Phe Glu Lys Asp Trp Ile Ser Gln Glu Phe Lys Asp Lys
      85      90      95
Glu Val Asp Ile Tyr Ala Leu Ser Ala Gln Glu Val Cys Glu Cys Pro
      100      105      110

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【 0 1 8 0 】

Gly Lys Arg Tyr Glu Ala Phe Gly Gly Ile Thr Leu Thr Asn Ser Glu
 115 120 125
 Lys Lys Glu Ile Lys Val Pro Val Asn Val Trp Asp Lys Ser Lys Gln
 130 135 140
 Gln Pro Pro Met Phe Ile Thr Val Asn Lys Pro Lys Val Thr Ala Gln
 145 150 155 160
 Glu Val Asp Ile Lys Val Arg Lys Leu Leu Ile Lys Lys Tyr Asp Ile
 165 170 175
 Tyr Asn Asn Arg Glu Gln Lys Tyr Ser Lys Gly Thr Val Thr Leu Asp
 180 185 190
 Leu Asn Ser Gly Lys Asp Ile Val Phe Asp Leu Tyr Tyr Phe Gly Asn
 195 200 205
 Gly Asp Phe Asn Ser Met Leu Lys Ile Tyr Ser Asn Asn Glu Arg Ile
 210 215 220
 Asp Ser Thr Gln Phe His Val Asp Val Ser Ile Ser
 225 230 235

<210> 197
 <211> 805
 <212> PRT
 <213> Streptococcus pyogenes

<400> 197
 Val Asn Thr Tyr Phe Cys Thr His His Lys Gln Leu Leu Leu Tyr Ser
 1 5 10 15
 Asn Leu Phe Leu Ser Phe Ala Met Met Gly Gln Gly Thr Ala Ile Tyr
 20 25 30
 Ala Asp Thr Leu Thr Ser Asn Ser Glu Pro Asn Asn Thr Tyr Phe Gln
 35 40 45
 Thr Gln Thr Leu Thr Thr Thr Asp Ser Glu Lys Lys Val Val Gln Pro
 50 55 60
 Gln Gln Lys Asp Tyr Tyr Thr Glu Leu Leu Asp Gln Trp Asn Ser Ile
 65 70 75 80
 Ile Ala Gly Asn Asp Ala Tyr Asp Lys Thr Asn Pro Asp Met Val Thr
 85 90 95
 Phe His Asn Lys Ala Glu Lys Asp Ala Gln Asn Ile Ile Lys Ser Tyr
 100 105 110
 Gln Gly Pro Asp His Glu Asn Arg Thr Tyr Leu Trp Glu His Ala Lys
 115 120 125
 Asp Tyr Ser Ala Ser Ala Asn Ile Thr Lys Thr Tyr Arg Asn Ile Glu
 130 135 140
 Lys Ile Ala Lys Gln Ile Thr Asn Pro Glu Ser Cys Tyr Tyr Gln Asp
 145 150 155 160
 Ser Lys Ala Ile Ala Ile Val Lys Asp Gly Met Ala Phe Met Tyr Glu
 165 170 175
 His Ala Tyr Asn Leu Asp Arg Glu Asn His Gln Thr Thr Gly Lys Glu
 180 185 190
 Asn Lys Glu Asn Trp Trp Val Tyr Glu Ile Gly Thr Pro Arg Ala Ile
 195 200 205
 Asn Asn Thr Leu Ser Leu Met Tyr Pro Tyr Phe Thr Gln Glu Glu Ile
 210 215 220
 Leu Lys Tyr Thr Ala Pro Ile Glu Lys Phe Val Pro Asp Pro Thr Arg
 225 230 235 240
 Phe Arg Val Arg Ala Ala Asn Phe Ser Pro Phe Glu Ala Asn Ser Gly
 245 250 255
 Asn Leu Ile Asp Met Gly Arg Val Lys Leu Ile Ser Gly Ile Leu Arg
 260 265 270
 Lys Asp Asp Leu Glu Ile Ser Asp Thr Ile Lys Ala Ile Glu Lys Val
 275 280 285
 Phe Thr Leu Val Asp Glu Gly Asn Gly Phe Tyr Gln Asp Gly Ser Leu
 290 295 300
 Ile Asp His Val Val Thr Asn Ala Gln Ser Pro Leu Tyr Lys Lys Gly
 305 310 315 320
 Ile Ala Tyr Thr Gly Ala Tyr Gly Asn Val Leu Ile Asp Gly Leu Ser
 325 330 335
 Gln Leu Ile Pro Ile Ile Gln Lys Thr Lys Ser Pro Ile Lys Ala Asp
 340 345 350
 Lys Met Ala Thr Ile Tyr His Trp Ile Asn His Ser Phe Phe Pro Ile
 355 360 365
 Ile Val Arg Gly Glu Met Met Asp Met Thr Arg Gly Arg Ser Ile Ser
 370 375 380
 Arg Phe Asn Ala Gln Ser His Val Ala Gly Ile Glu Ala Leu Arg Ala
 385 390 395 400
 Ile Leu Arg Ile Ala Asp Met Ser Glu Glu Pro His Arg Leu Ala Leu

405 410 415
 Lys Thr Arg Ile Lys Thr Leu Val Thr Gln Gly Asn Ala Phe Tyr Asn
 420 425 430
 Val Tyr Asp Asn Leu Lys Thr Tyr His Asp Ile Lys Leu Met Lys Glu
 435 440 445
 Leu Leu Ser Asp Thr Ser Val Pro Val Gln Lys Leu Asp Ser Tyr Val
 450 455 460
 Ala Ser Phe Asn Ser Met Asp Lys Leu Ala Leu Tyr Asn Asn Lys His
 465 470 475 480
 Asp Phe Ala Phe Gly Leu Ser Met Phe Ser Asn Arg Thr Gln Asn Tyr
 485 490 495
 Glu Ala Met Asn Asn Glu Asn Leu His Gly Trp Phe Thr Ser Asp Gly
 500 505 510
 Met Phe Tyr Leu Tyr Asn Asn Asp Leu Gly His Tyr Ser Glu Asn Tyr
 515 520 525
 Trp Ala Thr Val Asn Pro Tyr Arg Leu Pro Gly Thr Thr Glu Thr Glu
 530 535 540
 Gln Lys Pro Leu Glu Gly Thr Pro Glu Asn Ile Lys Thr Asn Tyr Gln
 545 550 555 560
 Gln Val Gly Met Thr Gly Leu Ser Asp Asp Ala Phe Val Ala Ser Lys
 565 570 575
 Lys Leu Asn Asn Thr Ser Ala Leu Ala Met Thr Phe Thr Asn Trp
 580 585 590
 Asn Lys Ser Leu Thr Leu Asn Lys Gly Trp Phe Ile Leu Gly Asn Lys
 595 600 605
 Ile Ile Phe Val Gly Ser Asn Ile Lys Asn Gln Ser Ser His Lys Ala
 610 615 620
 Tyr Thr Thr Ile Glu Gln Arg Lys Glu Asn Gln Lys Tyr Pro Tyr Cys
 625 630 635 640
 Ser Tyr Val Asn Asn Gln Pro Val Asp Leu Asn Asn Gln Leu Val Asp
 645 650 655
 Phe Thr Asn Thr Lys Ser Ile Phe Leu Glu Ser Asp Asp Pro Ala Gln
 660 665 670
 Asn Ile Gly Tyr Tyr Phe Phe Lys Pro Thr Thr Leu Ser Ile Ser Lys
 675 680 685
 Ala Leu Gln Thr Gly Lys Trp Gln Asn Ile Lys Ala Asp Asp Lys Ser
 690 695 700
 Pro Glu Ala Ile Lys Glu Val Ser Asn Thr Phe Ile Thr Ile Met Gln
 705 710 715 720
 Asn His Thr Gln Asp Gly Asp Arg Tyr Ala Tyr Met Met Leu Pro Asn
 725 730 735
 Met Thr Arg Gln Glu Phe Glu Thr Tyr Ile Ser Lys Leu Asp Ile Asp
 740 745 750
 Leu Leu Glu Asn Asn Asp Lys Leu Ala Ala Val Tyr Asp His Asp Ser
 755 760 765
 Gln Gln Met His Val Ile His Tyr Gly Lys Lys Ala Thr Met Phe Ser
 770 775 780
 Asn His Asn Leu Ser His Gln Gly Phe Tyr Ser Phe Pro His Pro Val
 785 790 795 800
 Arg Gln Asn Gln Gln
 805

<210> 198

<211> 293

<212> PRT

<213> Streptococcus pyogenes

<400> 198

Leu Leu Thr Phe Gly Gly Ala Ser Ala Val Lys Ala Glu Glu Asn Glu
 1 5 10 15
 Lys Val Arg Glu Gln Glu Lys Leu Ile Gln Gln Leu Ser Glu Lys Leu
 20 25 30
 Val Glu Ile Asn Asp Leu Gln Thr Leu Asn Gly Asp Lys Glu Ser Ile
 35 40 45
 Gln Ser Leu Val Asp Tyr Leu Thr Arg Arg Gly Lys Leu Glu Glu Glu
 50 55 60
 Trp Met Glu Tyr Leu Asn Ser Gly Ile Gln Arg Lys Leu Phe Val Gly
 65 70 75 80
 Pro Lys Gly Pro Ala Gly Glu Lys Gly Glu Gln Gly Pro Thr Gly Lys
 85 90 95
 Gln Gly Glu Arg Gly Glu Thr Gly Pro Ala Gly Pro Arg Gly Asp Lys
 100 105 110
 Gly Glu Thr Gly Asp Lys Gly Ala Gln Gly Pro Val Gly Pro Ala Gly
 115 120 125

【 0 1 8 2 】

Lys Asp Gly Gln Asn Gly Lys Asp Gly Leu Pro Gly Lys Asp Gly Lys
 130 135 140
 Asp Gly Gln Asn Gly Lys Asp Gly Leu Pro Gly Lys Asp Gly Lys Asp
 145 150 155 160
 Gly Gln Asp Gly Lys Asp Gly Leu Pro Gly Lys Asp Gly Lys Asp Gly
 165 170 175
 Gln Asn Gly Lys Asp Gly Leu Pro Gly Lys Asp Gly Gln Pro Gly Lys
 180 185 190
 Pro Ala Pro Lys Thr Pro Glu Val Pro Gln Asn Pro Asp Thr Ala Pro
 195 200 205
 His Thr Pro Lys Thr Pro Arg Ile Pro Gly Gln Ser Lys Asp Val Thr
 210 215 220
 Pro Ala Pro Gln Asn Pro Ser Asn Arg Gly Leu Asn Lys Pro Gln Thr
 225 230 235 240
 Gln Gly Gly Asn Gln Leu Ala Lys Thr Pro Ala Ala His Asp Thr His
 245 250 255
 Arg Gln Leu Pro Ala Thr Gly Glu Thr Thr Asn Pro Phe Phe Thr Ala
 260 265 270
 Ala Ala Val Ala Ile Met Thr Thr Ala Gly Val Val Ala Val Ala Lys
 275 280 285
 Arg Gln Glu Asn Asn
 290

<210> 199

<211> 323

<212> PRT

<213> Streptococcus pyogenes

<400> 199

Met Tyr Ile Phe Ser Ser Ser Lys Lys Asp Ser Ala Lys Glu Leu Val
 1 5 10 15
 Ile Leu Thr Pro Asn Ser Gln Thr Ile Leu Thr Gly Thr Ile Pro Ala
 20 25 30
 Phe Glu Glu Lys Tyr Gly Val Lys Val Arg Leu Ile Gln Gly Gly Thr
 35 40 45
 Gly Gln Leu Ile Asp Gln Leu Gly Arg Lys Asp Lys Pro Leu Asn Ala
 50 55 60
 Asp Ile Phe Phe Gly Gly Asn Tyr Thr Gln Phe Glu Ser His Lys Asp
 65 70 75 80
 Leu Phe Glu Ser Tyr Val Ser Pro Gln Val Ser Thr Val Ile Ser Asp
 85 90 95
 Tyr Gln Leu Pro Ser His Arg Ala Thr Pro Tyr Thr Ile Asn Gly Ser
 100 105 110
 Val Leu Ile Val Asn Asn Glu Leu Ala Arg Gly Leu His Ile Thr Ser
 115 120 125
 Tyr Glu Asp Leu Leu Gln Pro Ala Leu Lys Gly Lys Ile Ala Phe Ala
 130 135 140
 Asp Pro Asn Ser Ser Ser Ala Phe Ser Gln Leu Thr Asn Ile Leu
 145 150 155 160
 Leu Ala Lys Gly Gly Tyr Thr Asn Ala Asp Ala Trp Ala Tyr Met Lys
 165 170 175
 Arg Leu Leu Val Asn Met Asn Ser Ile Arg Ala Thr Ser Ser Ser Glu
 180 185 190
 Val Tyr Gln Ser Val Ala Glu Gly Lys Met Ile Val Gly Leu Thr Tyr
 195 200 205
 Glu Asp Pro Cys Ile Asn Leu Gln Lys Ser Gly Ala Asn Val Ser Ile
 210 215 220
 Val Tyr Pro Lys Glu Gly Thr Val Phe Val Pro Ser Ser Val Ala Ile
 225 230 235 240
 Ile Lys His Ala Pro Asn Met Thr Glu Ala Lys Leu Phe Ile Asn Phe
 245 250 255
 Met Leu Ser Arg Asp Val Gln Asn Ala Phe Gly Gln Ser Thr Ser Asn
 260 265 270
 Arg Pro Ile Arg Gln Asp Ala Gln Thr Ser His Asp Met Lys Ala Leu
 275 280 285
 Glu Thr Ile Ala Thr Leu Lys Glu Asp Tyr Ala Tyr Val Thr Lys His
 290 295 300
 Lys Lys Lys Ile Val Ala Thr Tyr Asn Gln Leu Arg Gln Arg Leu Glu
 305 310 315 320
 Lys Ala Lys

<210> 200

【 0 1 8 3 】

<211> 263
 <212> PRT
 <213> Streptococcus pyogenes

<400> 200
 Met Pro Thr Ser Ile Lys Ala Ile Lys Glu Ser Leu Glu Ala Val Thr
 1 5 10 15
 Ser Leu Leu Asp Pro Leu Phe Gln Glu Leu Ala Thr Asp Thr Arg Ser
 20 25 30
 Gly Val Gln Lys Ala Leu Lys Ser Arg Gln Lys Val Ile Gln Ala Glu
 35 40 45
 Leu Ala Glu Glu Glu Arg Leu Glu Ala Met Leu Ser Tyr Glu Lys Ala
 50 55 60
 Leu Tyr Lys Lys Gly Tyr Lys Ala Ile Ala Gly Ile Asp Glu Val Gly
 65 70 75 80
 Arg Gly Pro Leu Ala Gly Pro Val Val Ala Ala Cys Val Ile Leu Pro
 85 90 95
 Lys Tyr Cys Lys Ile Lys Gly Leu Asn Asp Ser Lys Lys Ile Pro Lys
 100 105 110
 Ala Lys His Glu Thr Ile Tyr Gln Ala Val Lys Glu Lys Ala Leu Ala
 115 120 125
 Ile Gly Ile Gly Ile Ile Asp Asn Gln Leu Ile Asp Glu Val Asn Ile
 130 135 140
 Tyr Glu Ala Thr Lys Leu Ala Met Leu Glu Ala Ile Lys Gln Leu Glu
 145 150 155 160
 Gly Gln Leu Thr Gln Pro Asp Tyr Leu Leu Ile Asp Ala Met Thr Leu
 165 170 175
 Asp Ile Ala Ile Ser Gln Gln Ser Ile Leu Lys Gly Asp Ala Asn Ser
 180 185 190
 Leu Ser Ile Ala Ala Ala Ser Ile Val Ala Lys Val Thr Arg Asp Gln
 195 200 205
 Met Met Ala Asn Tyr Asp Arg Ile Phe Pro Gly Tyr Asp Phe Ala Lys
 210 215 220
 Asn Ala Gly Tyr Gly Thr Lys Glu His Leu Gln Gly Leu Lys Ala Tyr
 225 230 235 240
 Gly Ile Thr Pro Ile His Arg Lys Ser Phe Glu Pro Val Lys Ser Met
 245 250 255
 Cys Cys Asp Ser Thr Asn Pro
 260

<210> 201
 <211> 521
 <212> PRT
 <213> Streptococcus pyogenes

<400> 201
 Met Thr Val Lys Glu Thr Met Ser Ile Leu Glu Val Lys Gln Leu
 1 5 10 15
 Ser His Gly Phe Gly Asp Arg Ala Ile Phe Glu Asn Val Ser Phe Arg
 20 25 30
 Leu Leu Lys Gly Glu His Ile Gly Leu Val Gly Ala Asn Gly Glu Gly
 35 40 45
 Lys Ser Thr Phe Met Ser Ile Val Thr Gly His Leu Gln Pro Asp Glu
 50 55 60
 Gly Lys Val Glu Trp Ser Lys Tyr Val Thr Ala Gly Tyr Leu Asp Gln
 65 70 75 80
 His Thr Val Leu Glu Ser Gly Gln Thr Val Arg Asp Val Leu Arg Thr
 85 90 95
 Ala Phe Asp Glu Leu Phe Lys Thr Glu Asn Arg Ile Asn Glu Ile Tyr
 100 105 110
 Ala Ser Met Ala Asp Asp Lys Ala Asp Ile Ala Val Leu Met Glu Glu
 115 120 125
 Val Gly Glu Leu Gln Asp Arg Leu Glu Ser Arg Asp Phe Tyr Thr Leu
 130 135 140
 Asp Ala Lys Ile Asp Glu Val Ala Arg Ala Leu Gly Val Met Asp Phe
 145 150 155 160
 Gly Met Glu Ser Asp Val Thr Ser Leu Ser Gly Gly Gln Arg Thr Lys
 165 170 175
 Val Leu Leu Ala Lys Leu Leu Leu Glu Lys Pro Asp Ile Leu Leu Leu
 180 185 190
 Asp Glu Pro Thr Asn His Leu Asp Ala Glu His Ile Glu Trp Leu Lys
 195 200 205
 Arg Tyr Leu Gln His Tyr Glu Asn Ala Phe Val Leu Ile Ser His Asp
 210 215 220

【 0 1 8 4 】

Ile Ser Phe Leu Asn Asp Val Ile Asn Ile Val Tyr His Val Glu Asn
 225 230 235 240
 Gln Ser Leu Val Arg Tyr Thr Gly Asp Tyr Tyr Gln Phe Gln Ala Val
 245 250 255
 Tyr Glu Met Lys Gln Ser Gln Leu Glu Ala Ala Tyr Glu Arg Gln Gln
 260 265 270
 Lys Glu Ile Ala Asn Leu Gln Asp Phe Val Asn Arg Asn Lys Ala Arg
 275 280 285
 Val Ala Thr Arg Asn Met Ala Met Ser Arg Gln Lys Lys Leu Asp Lys
 290 295 300
 Met Asp Ile Ile Glu Leu Gln Ala Glu Lys Pro Lys Pro Asn Phe Glu
 305 310 315 320
 Phe Lys Gln Ala Arg Thr Pro Ser Arg Phe Ile Phe Gln Thr Lys Asn
 325 330 335
 Leu Val Ile Gly Tyr Asp Tyr Pro Leu Thr Lys Glu Pro Leu Asn Ile
 340 345 350
 Thr Phe Glu Arg Asn Gln Lys Ile Ala Ile Val Gly Ala Asn Gly Ile
 355 360 365
 Gly Lys Ser Thr Leu Leu Lys Ser Leu Leu Gly Val Ile Glu Pro Leu
 370 375 380
 Glu Gly His Ile Val Thr Gly Asp Phe Leu Glu Val Gly Tyr Phe Glu
 385 390 395 400
 Gln Glu Val Thr Gly Val Asn Arg Gln Thr Pro Leu Glu Val Val Trp
 405 410 415
 Asp Ala Phe Pro Ala Leu Asn Gln Ala Glu Val Arg Ala Ala Leu Ala
 420 425 430
 Arg Cys Gly Leu Thr Ser Lys His Ile Glu Ser Gln Ile Gln Val Leu
 435 440 445
 Ser Gly Gly Glu Gln Ala Lys Val Arg Phe Cys Leu Leu Met Asn Arg
 450 455 460
 Glu Asn Asn Val Leu Ile Leu Asp Glu Pro Thr Asn His Leu Asp Ile
 465 470 475 480
 Asp Ala Lys Asn Glu Leu Lys Arg Ala Leu Lys Ala Tyr Lys Gly Ser
 485 490 495
 Ile Leu Met Val Cys His Glu Pro Asp Phe Tyr Asn Gly Trp Val Thr
 500 505 510
 Asp Thr Trp Asp Phe Ser Lys Leu Thr
 515 520

<210> 202
 <211> 350
 <212> PRT
 <213> Streptococcus pyogenes

<400> 202
 Met Asn Lys Lys Phe Ile Gly Leu Gly Leu Ala Ser Val Ala Val Leu
 1 5 10 15
 Ser Leu Ala Ala Cys Gly Asn Arg Gly Ala Ser Lys Gly Gly Ala Ser
 20 25 30
 Gly Lys Thr Asp Leu Lys Val Ala Met Val Thr Asp Thr Gly Gly Val
 35 40 45
 Asp Asp Lys Ser Phe Asn Gln Ser Ala Trp Glu Gly Leu Gln Ser Trp
 50 55 60
 Gly Lys Glu Met Gly Leu Gln Lys Gly Thr Gly Phe Asp Tyr Phe Gln
 65 70 75 80
 Ser Thr Ser Glu Ser Glu Tyr Ala Thr Asn Leu Asp Thr Ala Val Ser
 85 90 95
 Gly Gly Tyr Gln Leu Ile Tyr Gly Ile Gly Phe Ala Leu Lys Asp Ala
 100 105 110
 Ile Ala Lys Ala Ala Gly Asp Asn Glu Gly Val Lys Phe Val Ile Ile
 115 120 125
 Asp Asp Ile Ile Glu Gly Lys Asp Asn Val Ala Ser Val Thr Phe Ala
 130 135 140
 Asp His Glu Ala Ala Tyr Leu Ala Gly Ile Ala Ala Ala Lys Thr Thr
 145 150 155 160
 Lys Thr Lys Thr Val Gly Phe Val Gly Gly Met Glu Gly Thr Val Ile
 165 170 175
 Thr Arg Phe Glu Lys Gly Phe Glu Ala Gly Val Lys Ser Val Asp Asp
 180 185 190
 Thr Ile Gln Val Lys Val Asp Tyr Ala Gly Ser Phe Gly Asp Ala Ala
 195 200 205
 Lys Gly Lys Thr Ile Ala Ala Ala Gln Tyr Ala Ala Gly Ala Asp Val
 210 215 220
 Ile Tyr Gln Ala Ala Gly Gly Thr Gly Ala Gly Val Phe Asn Glu Ala

【 0 1 8 5 】

225 230 235 240
 Lys Ala Ile Asn Glu Lys Arg Ser Glu Ala Asp Lys Val Trp Val Ile
 Gly Val Asp Arg 245 250 255
 Gly Lys Glu Ala Asn Phe Val Leu Ala Ser Ser Ile Lys Glu Val Gly
 260 265 270
 Lys Ala Val Gln Leu Ile Asn Lys Gln Val Ala Asp Lys Lys Phe Pro
 275 280 285
 Gly Gly Lys Thr Thr Val Tyr Gly Leu Lys Asp Gly Gly Val Glu Ile
 290 295 300
 305 310 315 320
 Ala Thr Thr Asn Val Ser Lys Glu Ala Val Lys Ala Ile Lys Glu Ala
 325 330 335
 Lys Ala Lys Ile Lys Ser Gly Asp Ile Lys Val Pro Glu Lys
 340 345 350

<210> 203

<211> 288

<212> PRT

<213> Streptococcus pyogenes

<400> 203

Met Lys Met Lys Lys Lys Phe Phe Leu Leu Ser Leu Leu Ala Leu Ser
 1 5 10 15
 Thr Phe Phe Leu Ser Ala Cys Ser Ser Trp Ile Asp Lys Gly Glu Ser
 20 25 30
 Ile Thr Ala Val Gly Ser Thr Ala Leu Gln Pro Leu Val Glu Ala Val
 35 40 45
 Ala Asp Glu Phe Gly Ser Ser Asn Leu Gly Lys Thr Val Asn Val Gln
 50 55 60
 Gly Gly Gly Ser Gly Thr Gly Leu Ser Gln Val Gln Ser Gly Ala Val
 65 70 75 80
 Gln Ile Gly Asn Ser Asp Val Phe Ala Glu Glu Lys Asp Gly Ile Asp
 85 90 95
 Ala Ser Lys Leu Val Asp His Gln Val Ala Val Ala Gly Leu Ala Val
 100 105 110
 Ile Ala Asn Pro Lys Val Lys Val Ser Asn Leu Ser Ser Gln Gln Leu
 115 120 125
 Gln Lys Ile Phe Ser Gly Glu Tyr Thr Asn Trp Lys Gln Val Gly Gly
 130 135 140
 Glu Asp Leu Ala Ile Ser Val Ile Asn Arg Ala Ala Ser Ser Gly Ser
 145 150 155 160
 Arg Ala Thr Phe Asp Ser Val Ile Met Lys Gly Val Asn Ala Lys Gln
 165 170 175
 Ser Gln Glu Gln Asp Ser Asn Gly Met Val Lys Ser Ile Val Ser Gln
 180 185 190
 Thr Pro Gly Ala Ile Ser Tyr Leu Ser Phe Ala Tyr Val Asp Ser Ser
 195 200 205
 Val Lys Ser Leu Gln Leu Asn Gly Phe Lys Ala Asn Ala Lys Asn Val
 210 215 220
 Ala Thr Asn Asp Trp Pro Ile Trp Ser Tyr Glu His Met Tyr Thr Lys
 225 230 235 240
 Asp Lys Pro Thr Gly Leu Thr Lys Glu Phe Leu Asp Tyr Met Phe Ser
 245 250 255
 Asp Glu Val Gln Asn Ile Val Thr His Met Gly Tyr Ile Ser Ile
 260 265 270
 Asn Asp Met Glu Val Val Lys Ser His Asp Gly Lys Val Thr Lys Arg
 275 280 285

<210> 204

<211> 724

<212> PRT

<213> Streptococcus pyogenes

<400> 204

Met Thr His Lys Ile Lys Val Leu Leu Leu Ala Ile Met Ser Ile Phe
 1 5 10 15
 Leu Thr Cys Asn Ile Ala Ser Ala Glu Thr Ile Ala Ile Val Ser Asp
 20 25 30
 Thr Ala Tyr Ala Pro Phe Glu Phe Lys Asp Ser Asp Gln Ile Tyr Lys
 35 40 45
 Gly Ile Asp Val Asp Ile Ile Asn Glu Val Ala Lys Arg Gln Ser Trp
 50 55 60

【 0 1 8 6 】

Asp Phe Ser Met Ser Phe Pro Gly Phe Asp Ala Ala Val Asn Ala Val
 65 70 75 80
 Gln Ser Gly Gln Ala Ser Ala Leu Met Ala Gly Thr Thr Ile Thr Asn
 85 90 95
 Ala Arg Lys Lys Val Phe His Phe Ser Glu Pro Tyr Tyr Asp Thr Lys
 100 105 110
 Ile Val Ile Ala Thr Arg Lys Ala Asn Ala Ile Lys Lys Tyr Ser Asp
 115 120 125
 Leu Lys Gly Lys Thr Val Gly Val Lys Asn Gly Thr Ala Ala Gln Ala
 130 135 140
 Phe Leu Asn Asn Tyr Lys Lys Lys Tyr Asp Tyr Thr Val Lys Thr Phe
 145 150 155 160
 Asp Thr Gly Asp Leu Met Tyr Asn Ser Leu Ser Ala Gly Ser Ile Ala
 165 170 175
 Ala Val Met Asp Asp Glu Ala Val Ile Gln Tyr Ala Ile Ser Gln Asn
 180 185 190
 Gln Asp Ile Ala Ile Asn Met Lys Gly Glu Pro Ile Gly Ser Phe Gly
 195 200 205
 Phe Ala Val Lys Lys Gly Ser Gly Tyr Asp Tyr Leu Val Asn Asp Phe
 210 215 220
 Asn Thr Ala Leu Lys Ala Met Lys Ala Asp Gly Thr Tyr Gln Ala Ile
 225 230 235 240
 Met Thr Lys Trp Leu Gly Thr Asp Asp Lys Ala Thr Thr Ser Gln Ala
 245 250 255
 Thr Gly Asn Pro Ser Ala Lys Ala Thr Pro Thr Lys Asp Ser Tyr Lys
 260 265 270
 Ile Val Ser Asp Ser Ser Phe Ala Pro Phe Glu Phe Gln Asn Gly Lys
 275 280 285
 Gly Lys Tyr Val Gly Ile Asp Ile Glu Leu Ile Lys Ala Ile Ala Lys
 290 295 300
 Gln Gln Gly Phe Lys Ile Glu Ile Ala Asn Pro Gly Phe Asp Ala Ala
 305 310 315 320
 Leu Asn Ala Val Gln Ser Ser Gln Ala Asp Gly Val Ile Ala Gly Ala
 325 330 335
 Thr Ile Thr Asp Ala Arg Lys Ala Ile Phe Asp Phe Ser Asp Pro Tyr
 340 345 350
 Tyr Thr Ser Asn Ile Ile Leu Ala Val Lys Ala Gly Lys Asn Ile Lys
 355 360 365
 Asn Tyr Glu Asp Leu Asp Arg Lys Thr Val Gly Ala Lys Asn Gly Thr
 370 375 380
 Ser Ser Tyr Ser Trp Leu Lys Glu Asn Ala Pro Lys Tyr Gly Tyr Asn
 385 390 395 400
 Val Lys Ala Phe Asp Asp Gly Ser Ser Met Tyr Asp Ser Leu Asn Ser
 405 410 415
 Gly Ser Val Asp Ala Ile Met Asp Asp Glu Ala Val Leu Lys Tyr Ala
 420 425 430
 Ile Ser Gln Gly Arg Arg Phe Glu Thr Pro Leu Glu Gly Ile Ser Thr
 435 440 445
 Gly Glu Val Gly Phe Ala Val Lys Lys Gly Thr Asn Pro Glu Leu Ile
 450 455 460
 Glu Met Phe Asn Asn Gly Leu Ala Ala Leu Lys Lys Ser Gly Gln Tyr
 465 470 475 480
 Asp Asp Ile Ile Asp Lys Tyr Leu Asp Ser Lys Lys Ala Ala Thr Pro
 485 490 495
 Ser Glu Lys Gly Ala Asp Glu Ser Thr Ile Ser Gly Leu Leu Ser Asn
 500 505 510
 Asn Tyr Lys Gln Leu Leu Ala Gly Leu Gly Thr Thr Leu Ser Leu Thr
 515 520 525
 Leu Ile Ser Phe Ala Ile Ala Ile Ile Ile Gly Ile Ile Phe Gly Met
 530 535 540
 Met Ala Val Ser Pro Thr Lys Ser Leu Arg Leu Ile Ser Thr Val Phe
 545 550 555 560
 Val Asp Val Val Arg Gly Ile Pro Leu Met Ile Val Ala Ala Phe Ile
 565 570 575
 Phe Trp Gly Val Pro Asn Leu Ile Glu Ser Met Thr Gly His Gln Ser
 580 585 590
 Pro Ile Asn Asp Phe Leu Ala Ala Thr Ile Ala Leu Ser Leu Asn Gly
 595 600 605
 Gly Ala Tyr Ile Ala Glu Ile Val Arg Gly Gly Ile Glu Ala Val Pro
 610 615 620
 Ala Gly Gln Met Glu Ala Ser Arg Ser Leu Gly Leu Ser Tyr Gly Thr
 625 630 635 640
 Thr Met Arg Lys Val Ile Leu Pro Gln Ala Val Lys Leu Met Leu Pro
 645 650 655
 Asn Phe Ile Asn Gln Phe Val Ile Ser Leu Lys Asp Thr Thr Ile Val

Ser Ala Ile Gly Leu Val Glu Leu Phe Gln Thr Gly Lys Ile Ile Ile
 660 675 680 685
 Ala Arg Asn Tyr Gln Ser Phe Arg Met Tyr Ala Ile Leu Ala Ile Ile
 690 695 700
 Tyr Leu Ile Met Ile Ile Leu Leu Thr Arg Leu Ala Lys Arg Leu Glu
 705 710 715 720
 Lys Arg Leu Asn

<210> 205
 <211> 217
 <212> PRT
 <213> Streptococcus pyogenes

<400> 205
 Met Gly Lys Glu Ile Lys Val Lys Cys Phe Leu Arg Arg Ser Ala Phe
 1 5 10 15
 Gly Leu Val Ala Val Ser Ala Ser Val Leu Val Gly Ser Thr Val Ser
 20 25 30
 Ala Val Asp Ser Pro Ile Glu Gln Pro Arg Ile Ile Pro Asn Gly Gly
 35 40 45
 Thr Leu Thr Asn Leu Leu Gly Asn Ala Pro Glu Lys Leu Ala Leu Arg
 50 55 60
 Asn Glu Glu Arg Ala Ile Asp Glu Leu Lys Lys Gln Ala Ile Glu Asp
 65 70 75 80
 Lys Glu Ala Thr Thr Ala Ile Glu Ala Ala Ser Ser Asp Ala Leu Glu
 85 90 95
 Ala Leu Ala Asp Gln Thr Asp Ala Leu Gln Ser Glu Glu Ala Ala Val
 100 105 110
 Val Lys Ala Asp Asn Ala Ala Ser Asp Ala Leu Glu Ala Leu Ala Asp
 115 120 125
 Gln Thr Asp Ala Leu Gln Ser Glu Glu Ala Glu Val Val Gln Ser Asp
 130 135 140
 Asn Ala Ala Ser Asp Ala Trp Glu Lys Ala Ala Thr Pro Ile Ala Leu
 145 150 155 160
 Asp Val Lys Lys Thr Lys Asp Thr Lys Pro Val Val Lys Lys Glu Glu
 165 170 175
 Arg Gln Asn Val Asn Thr Leu Pro Thr Thr Gly Glu Glu Ser Asn Pro
 180 185 190
 Phe Phe Thr Ala Ala Ala Leu Ala Ile Met Val Ser Thr Gly Val Leu
 195 200 205
 Val Val Ser Ser Lys Cys Lys Glu Asn
 210 215

<210> 206
 <211> 792
 <212> PRT
 <213> Streptococcus pyogenes

<400> 206
 Met Lys Thr Lys Lys Val Ile Ile Leu Val Gly Leu Leu Leu Ser Ser
 1 5 10 15
 Gln Leu Thr Leu Ile Ala Cys Gln Ser Arg Gly Asn Gly Thr Tyr Pro
 20 25 30
 Ile Lys Thr Lys Gln Ser Arg Lys Gly Met Thr Ser Asn Lys Ile Lys
 35 40 45
 Pro Ile Lys Lys Ser Lys Lys Thr Asn Lys Thr His Lys Gly Val Ala
 50 55 60
 Gly Val Asp Phe Pro Thr Asp Asp Gly Phe Ile Leu Thr Lys Asp Ser
 65 70 75 80
 Lys Ile Leu Ser Lys Thr Asp Gln Gly Ile Val Val Asp His Asp Gly
 85 90 95
 His Ser His Phe Ile Phe Tyr Ala Asp Leu Lys Gly Ser Pro Phe Glu
 100 105 110
 Tyr Leu Ile Pro Lys Gly Ala Ser Leu Ala Lys Pro Ala Val Ala Gln
 115 120 125
 Arg Ala Ala Ser Gln Gly Thr Ser Lys Val Ala Asp Pro His His His
 130 135 140
 Tyr Glu Phe Asn Pro Ala Asp Ile Val Ala Glu Asp Ala Leu Gly Tyr
 145 150 155 160
 Thr Val Arg His Asp Asp His Phe His Tyr Ile Leu Lys Ser Ser Leu
 165 170 175

Ser Gly Gln Thr Gln Ala Gln Ala Lys Gln Val Ala Thr Arg Leu Pro
 180 185 190
 Gln Thr Ser Ser Leu Val Ser Thr Ala Thr Ala Asn Gly Ile Pro Gly
 195 200 205
 Leu His Phe Pro Thr Ser Asp Gly Phe Gln Phe Asn Gly Gln Gly Ile
 210 215 220
 Val Gly Val Thr Lys Asp Ser Ile Leu Val Asp His Asp Gly His Leu
 225 230 235 240
 His Pro Ile Ser Phe Ala Asp Leu Arg Gln Gly Gly Trp Ala His Val
 245 250 255
 Ala Asp Gln Tyr Asp Pro Ala Lys Lys Ala Glu Lys Pro Ala Glu Thr
 260 265 270
 His Gln Thr Pro Glu Leu Ser Glu Arg Glu Lys Glu Tyr Gln Glu Lys
 275 280 285
 Leu Ala Tyr Leu Ala Glu Lys Leu Gly Ile Asp Pro Ser Thr Ile Lys
 290 295 300
 Arg Val Glu Thr Gln Asp Gly Lys Leu Gly Leu Glu Tyr Pro His His
 305 310 315 320
 Asp His Ala His Val Leu Met Leu Ser Asp Ile Glu Ile Gly Lys Asp
 325 330 335
 Ile Pro Asp Pro His Ala Ile Glu His Ala Arg Glu Leu Glu Lys His
 340 345 350
 Lys Val Gly Met Asp Thr Leu Arg Ala Leu Gly Phe Asp Glu Glu Val
 355 360 365
 Ile Leu Asp Ile Val Arg Thr His Asp Ala Pro Thr Pro Phe Pro Ser
 370 375 380
 Asn Glu Lys Asp Pro Asn Met Met Lys Glu Trp Leu Ala Thr Val Ile
 385 390 395 400
 Lys Leu Asp Leu Gly Ser Arg Lys Asp Pro Leu Gln Arg Lys Gly Leu
 405 410 415
 Ser Leu Leu Pro Asn Leu Glu Thr Leu Gly Ile Gly Phe Thr Pro Ile
 420 425 430
 Lys Asp Ile Ser Pro Val Leu Gln Phe Lys Lys Leu Lys Gln Leu Leu
 435 440 445
 Met Thr Lys Thr Gly Val Thr Asp Tyr Arg Phe Leu Asp Asn Met Pro
 450 455 460
 Gln Leu Glu Gly Ile Asp Ile Ser Gln Asn Asn Leu Lys Asp Ile Ser
 465 470 475 480
 Phe Leu Ser Lys Tyr Lys Asn Leu Thr Leu Val Ala Ala Ala Asp Asn
 485 490 495
 Gly Ile Glu Asp Ile Arg Pro Leu Gly Gln Leu Pro Asn Leu Lys Phe
 500 505 510
 Leu Val Leu Ser Asn Asn Lys Ile Ser Asp Leu Ser Pro Leu Ala Ser
 515 520 525
 Leu His Gln Leu Gln Glu Leu His Ile Asp Asn Asn Gln Ile Thr Asp
 530 535 540
 Leu Ser Pro Val Ser His Lys Glu Ser Leu Thr Val Val Asp Leu Ser
 545 550 555 560
 Arg Asn Ala Asp Val Asp Leu Ala Thr Leu Gln Ala Pro Lys Leu Glu
 565 570 575
 Thr Leu Met Val Asn Asp Thr Lys Val Ser His Leu Asp Phe Leu Lys
 580 585 590
 Asn Asn Pro Asn Leu Ser Ser Leu Ser Ile Asn Arg Ala Gln Leu Gln
 595 600 605
 Ser Leu Glu Gly Ile Glu Ala Ser Ser Val Ile Val Arg Val Glu Ala
 610 615 620
 Glu Gly Asn Gln Ile Lys Ser Leu Val Leu Lys Asp Lys Gln Gly Ser
 625 630 635 640
 Leu Thr Phe Leu Asp Val Thr Gly Asn Gln Leu Thr Ser Leu Glu Gly
 645 650 655
 Val Asn Asn Phe Thr Ala Leu Asp Ile Leu Ser Val Ser Lys Asn Gln
 660 665 670
 Leu Thr Asn Val Asn Leu Ser Lys Pro Asn Lys Thr Val Thr Asn Ile
 675 680 685
 Asp Ile Ser His Asn Asn Ile Ser Leu Ala Asp Leu Lys Leu Asn Glu
 690 695 700
 Gln His Ile Pro Glu Ala Ile Ala Lys Asn Phe Pro Ala Val Tyr Glu
 705 710 715 720
 Gly Ser Met Val Gly Asn Gly Thr Ala Glu Glu Lys Ala Ala Met Ala
 725 730 735
 Thr Lys Ala Lys Glu Ser Ala Gln Glu Ala Ser Glu Ser His Asp Tyr
 740 745 750
 Asn His Asn His Thr Tyr Glu Asp Glu Glu Gly His Ala His Glu His
 755 760 765
 Arg Asp Lys Asp Asp His Asp His Glu His Glu Asp Glu Asn Glu Ala

770
Lys Asp Glu Gln Asn His Ala Asp
785 790

780

<210> 207
<211> 475
<212> PRT
<213> Streptococcus pyogenes

<400> 207
Leu Ala Lys Gln Tyr Lys Asn Leu Val Asn Gly Glu Trp Lys Leu Ser
1 5 10 15
Glu Asn Glu Ile Thr Ile Tyr Ala Pro Ala Thr Gly Glu Glu Leu Gly
20 25 30
Ser Val Pro Ala Met Thr Gln Ala Glu Val Asp Ala Val Tyr Ala Ser
35 40 45
Ala Lys Lys Ala Leu Ser Asp Trp Arg Ala Leu Ser Tyr Val Glu Arg
50 55 60
Ala Ala Tyr Leu His Lys Ala Ala Asp Ile Leu Val Arg Asp Ala Glu
65 70 75 80
Lys Ile Gly Ala Ile Leu Ser Lys Glu Val Ala Lys Gly His Lys Ala
85 90 95
Ala Val Ser Glu Val Ile Arg Thr Ala Glu Ile Ile Asn Tyr Ala Ala
100 105 110
Glu Glu Gly Leu Arg Met Glu Gly Glu Val Leu Glu Gly Gly Ser Phe
115 120 125
Glu Ala Ala Ser Lys Lys Lys Ile Ala Ile Val Arg Arg Glu Pro Val
130 135 140
Gly Leu Val Leu Ala Ile Ser Pro Phe Asn Tyr Pro Val Asn Leu Ala
145 150 155 160
Gly Ser Lys Ile Ala Pro Ala Leu Ile Ala Gly Asn Val Val Ala Leu
165 170 175
Lys Pro Pro Thr Gln Gly Ser Ile Ser Gly Leu Leu Leu Ala Glu Ala
180 185 190
Phe Ala Glu Ala Gly Ile Pro Ala Gly Val Phe Asn Thr Ile Thr Gly
195 200 205
Arg Gly Ser Val Ile Gly Asp Tyr Ile Val Glu His Glu Ala Val Ser
210 215 220
Phe Ile Asn Phe Thr Gly Ser Thr Pro Ile Gly Glu Gly Ile Gly Lys
225 230 235 240
Leu Ala Gly Met Arg Pro Ile Met Leu Glu Leu Gly Gly Lys Asp Ser
245 250 255
Ala Ile Val Leu Glu Asp Ala Asp Leu Ala Leu Ala Lys Asn Ile
260 265 270
Val Ala Gly Ala Phe Gly Tyr Ser Gly Gln Arg Cys Thr Ala Val Lys
275 280 285
Arg Val Leu Val Met Asp Lys Val Ala Asp Gln Leu Ala Ala Glu Ile
290 295 300
Lys Thr Leu Val Glu Lys Leu Ser Val Gly Met Pro Glu Asp Asp Ala
305 310 315 320
Asp Ile Thr Pro Leu Ile Asp Thr Ser Ala Ala Asp Phe Val Glu Gly
325 330 335
Leu Ile Lys Asp Ala Thr Asp Lys Gly Ala Thr Ala Leu Thr Ala Phe
340 345 350
Asn Arg Glu Gly Asn Leu Ile Ser Pro Val Leu Phe Asp His Val Thr
355 360 365
Thr Asp Met Arg Leu Ala Trp Glu Glu Pro Phe Gly Pro Val Leu Pro
370 375 380
Ile Ile Arg Val Thr Thr Val Glu Glu Ala Ile Lys Ile Ser Asn Glu
385 390 395 400
Ser Glu Tyr Gly Leu Gln Ala Ser Ile Phe Thr Thr Asn Phe Pro Lys
405 410 415
Ala Phe Gly Ile Ala Glu Gln Leu Glu Val Gly Thr Val His Leu Asn
420 425 430
Asn Lys Thr Gln Arg Gly Thr Asp Asn Phe Pro Phe Leu Gly Ala Lys
435 440 445
Lys Ser Gly Ala Gly Val Gln Gly Val Lys Tyr Ser Ile Glu Ala Met
450 455 460
Thr Thr Val Lys Ser Val Val Phe Asp Ile Gln
465 470 475

<210> 208
<211> 719

【 0 1 9 0 】

<212> PRT

<213> Streptococcus pyogenes

<400> 208

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Met Ser Leu Lys Asp Leu Gly Asp Ile Ser Tyr Phe Arg Leu Asn Asn
1      5      10      15
Glu Ile Asn Arg Pro Val Asn Gly Lys Ile Pro Leu His Lys Asp Lys
20      25      30
Glu Ala Leu Lys Ala Phe Ser Ala Glu Asn Val Leu Pro Asn Thr Met
35      40      45
Ser Phe Thr Ser Ile Thr Glu Lys Ile Glu Tyr Leu Ile Ser Asn Asp
50      55      60
Tyr Ile Glu Ser Ala Phe Ile Gln Lys Tyr Arg Pro Glu Phe Ile Thr
65      70      75      80
Glu Leu Asp Ser Ile Ile Lys Ser Glu Asn Phe Arg Phe Lys Ser Phe
85      90      95
Met Ala Ala Tyr Lys Phe Tyr Gln Gln Tyr Ala Leu Lys Thr Asn Asp
100     105     110
Gly Glu His Tyr Leu Glu Asn Leu Glu Asp Arg Val Leu Phe Asn Ala
115     120     125
Leu Tyr Phe Ala Asp Gly Gln Glu Asp Leu Ala Lys Asp Leu Ala Val
130     135     140
Glu Met Ile Asn Gln Arg Tyr Gln Pro Ala Thr Pro Ser Phe Leu Asn
145     150     155     160
Ala Gly Arg Ser Arg Arg Gly Glu Leu Val Ser Cys Phe Leu Ile Gln
165     170     175
Val Thr Asp Asp Met Asn Ser Ile Gly Arg Ser Ile Asn Ser Ala Leu
180     185     190
Gln Leu Ser Arg Ile Gly Gly Gly Val Gly Ile Thr Leu Ser Asn Leu
195     200     205
Arg Glu Ala Gly Ala Pro Ile Lys Gly Tyr Ala Gly Ala Ala Ser Gly
210     215     220
Val Val Pro Val Met Lys Leu Phe Glu Asp Ser Phe Ser Tyr Ser Asn
225     230     235     240
Gln Leu Gly Gln Arg Gln Gly Ala Gly Val Val Tyr Leu Asn Val Phe
245     250     255
His Pro Asp Ile Ile Ala Phe Leu Ser Thr Lys Lys Glu Asn Ala Asp
260     265     270
Glu Lys Val Arg Val Lys Thr Leu Ser Leu Gly Ile Thr Val Pro Asp
275     280     285
Lys Phe Tyr Glu Leu Ala Arg Lys Asn Glu Asp Met Tyr Leu Phe Ser
290     295     300
Pro Tyr Asn Val Glu Lys Glu Tyr Gly Ile Pro Phe Asn Tyr Leu Asp
305     310     315     320
Ile Thr Asn Met Tyr Asp Glu Leu Val Ala Asn Pro Lys Ile Thr Lys
325     330     335
Thr Lys Ile Lys Ala Arg Asp Leu Glu Thr Glu Ile Ser Lys Leu Gln
340     345     350
Gln Glu Ser Gly Tyr Pro Tyr Ile Ile Asn Ile Asp Thr Ala Asn Lys
355     360     365
Ala Asn Pro Ile Asp Gly Lys Ile Ile Met Ser Asn Leu Cys Ser Glu
370     375     380
Ile Leu Gln Val Gln Thr Pro Ser Leu Ile Asn Asp Ala Gln Glu Phe
385     390     395     400
Val Glu Met Gly Thr Asp Ile Ser Cys Asn Leu Gly Ser Thr Asn Ile
405     410     415
Leu Asn Met Met Thr Ser Pro Asp Phe Gly Arg Ser Ile Lys Thr Met
420     425     430
Thr Arg Ala Leu Thr Phe Val Thr Asp Ser Ser Ser Ile Glu Ala Val
435     440     445
Pro Thr Ile Lys His Gly Asn Ser Gln Ala His Thr Phe Gly Leu Gly
450     455     460
Ala Met Gly Leu His Ser Tyr Leu Ala Gln His His Ile Glu Tyr Gly
465     470     475     480
Ser Pro Glu Ser Ile Glu Phe Thr Asp Ile Tyr Phe Met Leu Leu Asn
485     490     495
Tyr Trp Thr Leu Val Glu Ser Asn Asn Ile Ala Arg Glu Arg Gln Thr
500     505     510
Thr Phe Val Gly Phe Glu Asn Ser Lys Tyr Ala Asn Gly Ser Tyr Phe
515     520     525
Asp Lys Tyr Val Thr Gly His Phe Val Pro Lys Ser Asp Leu Val Lys
530     535     540
Asp Leu Phe Lys Asp His Phe Ile Pro Gln Ala Ser Asp Trp Glu Ala
545     550     555     560
Leu Arg Asp Ala Val Gln Lys Asp Gly Leu Tyr His Gln Asn Arg Leu

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【 0 1 9 1 】

565 570 575
 Ala Val Ala Pro Asn Gly Ser Ile Ser Tyr Ile Asn Asp Cys Ser Ala
 580 585 590
 Ser Ile His Pro Ile Thr Gln Arg Ile Glu Glu Arg Gln Glu Lys Lys
 595 600 605
 Ile Gly Lys Ile Tyr Tyr Pro Ala Asn Gly Leu Ser Thr Asp Thr Ile
 610 615 620
 Pro Tyr Tyr Thr Ser Ala Tyr Asp Met Asp Met Arg Lys Val Ile Asp
 625 630 635 640
 Val Tyr Ala Ala Thr Glu His Val Asp Gln Gly Leu Ser Leu Thr
 645 650 655
 Leu Phe Leu Arg Ser Glu Leu Pro Met Glu Leu Tyr Glu Trp Lys Thr
 660 665 670
 Gln Ser Lys Gln Thr Thr Arg Asp Leu Ser Ile Leu Arg Asn Tyr Ala
 675 680 685
 Phe Asn Lys Gly Ile Lys Ser Ile Tyr Tyr Ile Arg Thr Phe Thr Asp
 690 700
 Asp Gly Glu Glu Val Gly Ala Asn Gln Cys Glu Ser Cys Val Ile
 705 710 715

<210> 209

<211> 872

<212> PRT

<213> Streptococcus pyogenes

<400> 209

Met Lys Glu Leu Ser Ser Ala Gln Ile Arg Gln Met Trp Leu Asp Phe
 1 5 10 15
 Trp Lys Ser Lys Gly His Cys Val Glu Pro Ser Ala Asn Leu Val Pro
 20 25 30
 Val Asn Asp Pro Thr Leu Leu Trp Ile Asn Ser Gly Val Ala Thr Leu
 35 40 45
 Lys Lys Tyr Phe Asp Gly Ser Val Ile Pro Glu Asn Pro Arg Ile Thr
 50 55 60
 Asn Ala Gln Lys Ser Ile Arg Thr Asn Asp Ile Glu Asn Val Gly Lys
 65 70 75 80
 Thr Ala Arg His His Thr Met Phe Glu Met Leu Gly Asn Phe Ser Ile
 85 90 95
 Gly Asp Tyr Phe Arg Asp Glu Ala Ile Glu Trp Gly Phe Glu Leu Leu
 100 105 110
 Thr Ser Pro Asp Trp Phe Asp Phe Pro Lys Asp Lys Leu Tyr Met Thr
 115 120 125
 Tyr Tyr Pro Asp Asp Lys Asp Ser Tyr Asn Arg Trp Ile Ala Cys Gly
 130 135 140
 Val Glu Pro Ser His Leu Val Pro Ile Glu Asp Asn Phe Trp Glu Ile
 145 150 155 160
 Gly Ala Gly Pro Ser Gly Pro Asp Thr Glu Ile Phe Phe Asp Arg Gly
 165 170 175
 Glu Asp Phe Asp Pro Glu Asn Ile Gly Leu Arg Leu Leu Ala Glu Asp
 180 185 190
 Ile Glu Asn Asp Arg Tyr Ile Glu Ile Trp Asn Ile Val Leu Ser Gln
 195 200 205
 Phe Asn Ala Asp Pro Ala Val Pro Arg Ser Glu Tyr Lys Glu Leu Pro
 210 215 220
 Asn Lys Asn Ile Asp Thr Gly Ala Gly Leu Glu Arg Leu Ala Ala Val
 225 230 235 240
 Met Gln Gly Ala Lys Thr Asn Phe Glu Thr Asp Leu Phe Met Pro Ile
 245 250 255
 Ile Arg Glu Val Glu Lys Leu Ser Gly Lys Thr Tyr Asp Pro Asp Gly
 260 265 270
 Asp Asn Met Ser Phe Lys Val Ile Ala Asp His Ile Arg Ala Leu Ser
 275 280 285
 Phe Ala Ile Gly Asp Gly Ala Leu Pro Gly Asn Glu Gly Arg Gly Tyr
 290 295 300
 Val Leu Arg Arg Leu Leu Arg Arg Ala Val Met His Gly Arg Arg Leu
 305 310 315 320
 Gly Ile Asn Glu Thr Phe Leu Tyr Lys Leu Val Pro Thr Val Gly Gln
 325 330 335
 Ile Met Glu Ser Tyr Tyr Pro Glu Val Leu Glu Lys Arg Asp Phe Ile
 340 345 350
 Glu Lys Ile Val Lys Arg Glu Glu Thr Phe Ala Arg Thr Ile Asp
 355 360 365
 Ala Gly Ser Gly His Leu Asp Ser Leu Leu Ala Gln Leu Lys Ala Glu
 370 375 380

【 0 1 9 2 】

Gly Lys Asp Thr Leu Glu Gly Lys Asp Ile Phe Lys Leu Tyr Asp Thr
 385 390 395 400
 Tyr Gly Phe Pro Val Glu Leu Thr Glu Glu Leu Ala Glu Asp Ala Gly
 405 410 415
 Tyr Lys Ile Asp His Glu Gly Phe Lys Ser Ala Met Lys Glu Gln Gln
 420 425 430
 Asp Arg Ala Arg Ala Ala Val Val Lys Gly Gly Ser Met Gly Met Gln
 435 440 445
 Asn Glu Thr Leu Ala Gly Ile Val Glu Glu Ser Arg Phe Glu Tyr Asp
 450 455 460
 Thr Tyr Ser Leu Glu Ser Ser Leu Ser Val Ile Ile Ala Asp Asn Glu
 465 470 475 480
 Arg Thr Glu Ala Val Ser Glu Gly Gln Ala Leu Leu Val Phe Ala Gln
 485 490 495
 Thr Pro Phe Tyr Ala Glu Met Gly Gly Gln Val Ala Asp Thr Gly Arg
 500 505 510
 Ile Lys Asn Asp Lys Gly Asp Thr Val Ala Glu Val Val Asp Val Gln
 515 520 525
 Lys Ala Pro Asn Gly Gln Pro Leu His Thr Val Asn Val Leu Ala Ser
 530 535 540
 Leu Ser Val Gly Thr Asn Tyr Thr Leu Glu Ile Asn Lys Glu Arg Arg
 545 550 555 560
 Leu Ala Val Glu Lys Asn His Thr Ala Thr His Leu Leu His Ala Ala
 565 570 575
 Leu His Asn Val Ile Gly Glu His Ala Thr Gln Ala Gly Ser Leu Asn
 580 585 590
 Glu Glu Glu Phe Leu Arg Phe Asp Phe Thr His Phe Glu Ala Val Ser
 595 600 605
 Asn Glu Glu Leu Arg His Ile Glu Gln Glu Val Asn Glu Gln Ile Trp
 610 615 620
 Asn Ala Leu Thr Ile Thr Thr Thr Glu Thr Asp Val Glu Thr Ala Lys
 625 630 635 640
 Glu Met Gly Ala Met Ala Leu Phe Gly Glu Lys Tyr Gly Lys Val Val
 645 650 655
 Arg Val Val Gln Ile Gly Asn Tyr Ser Val Glu Leu Cys Gly Gly Thr
 660 665 670
 His Leu Asn Asn Ser Ser Glu Ile Gly Leu Phe Lys Ile Val Lys Glu
 675 680 685
 Glu Gly Ile Gly Ser Gly Thr Arg Arg Ile Ile Ala Val Thr Gly Arg
 690 695 700
 Gln Ala Phe Glu Ala Tyr Arg Asn Gln Glu Asp Ala Leu Lys Glu Ile
 705 710 715 720
 Ala Ala Thr Val Lys Ala Pro Gln Leu Lys Asp Ala Ala Ala Lys Val
 725 730 735
 Gln Ala Leu Ser Asp Ser Leu Arg Asp Leu Gln Lys Glu Asn Ala Glu
 740 745 750
 Leu Lys Glu Lys Ala Ala Ala Ala Ala Glu Asp Val Phe Lys Asp
 755 760 765
 Val Gln Glu Ala Lys Gly Val Arg Phe Ile Ala Ser Gln Val Asp Val
 770 775 780
 Ala Asp Ala Gly Ala Leu Arg Thr Phe Ala Asp Asn Trp Lys Gln Lys
 785 790 795 800
 Asp Tyr Ser Asp Val Leu Val Leu Val Ala Ala Ile Gly Glu Lys Val
 805 810 815
 Asn Val Leu Val Ala Ser Lys Thr Lys Asp Val His Ala Gly Asn Met
 820 825 830
 Ile Lys Glu Leu Ala Pro Ile Val Ala Gly Arg Gly Gly Lys Pro
 835 840 845
 Asp Met Ala Met Ala Gly Gly Ser Asp Ala Ser Lys Ile Ala Glu Leu
 850 855 860
 Leu Ala Ala Val Ala Glu Ile Val
 865 870

<210> 210

<211> 351

<212> PRT

<213> Streptococcus pyogenes

<400> 210

Met Lys Asn Ser Asn Lys Leu Ile Ala Ser Val Val Thr Leu Ala Ser
 1 5 10 15
 Val Met Ala Leu Ala Ala Cys Gln Ser Thr Asn Asp Asn Thr Lys Val
 20 25 30
 Ile Ser Met Lys Gly Asp Thr Ile Ser Val Ser Asp Phe Tyr Asn Glu

35 40 45
 Thr Lys Asn Thr Glu Val Ser Gln Lys Ala Met Leu Asn Leu Val Ile
 50 55 60
 Ser Arg Val Phe Glu Ala Gln Tyr Gly Asp Lys Val Ser Lys Lys Glu
 65 70 75 80
 Val Glu Lys Ala Tyr His Lys Thr Ala Glu Gln Tyr Gly Ala Ser Phe
 85 90 95
 Ser Ala Ala Leu Ala Gln Ser Ser Leu Thr Pro Glu Thr Phe Lys Arg
 100 105 110
 Gln Ile Arg Ser Ser Lys Leu Val Glu Tyr Ala Val Lys Glu Ala Ala
 115 120 125
 Lys Lys Glu Leu Thr Thr Gln Glu Tyr Lys Lys Ala Tyr Glu Ser Tyr
 130 135 140
 Thr Pro Thr Met Ala Val Glu Met Ile Thr Leu Asp Asn Glu Glu Thr
 145 150 155 160
 Ala Lys Ser Val Leu Glu Glu Leu Lys Ala Glu Gly Ala Asp Phe Thr
 165 170 175
 Ala Ile Ala Lys Glu Lys Thr Thr Thr Pro Glu Lys Lys Val Thr Tyr
 180 185 190
 Lys Phe Asp Ser Gly Ala Thr Asn Val Pro Thr Asp Val Val Lys Ala
 195 200 205
 Ala Ser Ser Leu Asn Glu Gly Gly Ile Ser Asp Val Ile Ser Val Leu
 210 215 220
 Asp Pro Thr Ser Tyr Gln Lys Lys Phe Tyr Ile Val Lys Val Thr Lys
 225 230 235 240
 Lys Ala Glu Lys Lys Ser Asp Trp Gln Glu Tyr Lys Lys Arg Leu Lys
 245 250 255
 Ala Ile Ile Ile Ala Glu Lys Ser Lys Asp Met Asn Phe Gln Asn Lys
 260 265 270
 Val Ile Ala Asn Ala Leu Asp Lys Ala Asn Val Lys Ile Lys Asp Lys
 275 280 285
 Ala Phe Ala Asn Ile Leu Ala Gln Tyr Ala Asn Leu Gly Gln Lys Thr
 290 295 300
 Lys Ala Ala Ser Glu Ser Ser Thr Thr Ser Glu Ser Ser Lys Ala Ala
 305 310 315 320
 Glu Glu Asn Pro Ser Glu Ser Glu Gln Thr Gln Thr Ser Ser Ala Glu
 325 330 335
 Glu Pro Thr Glu Thr Glu Ala Gln Thr Gln Glu Pro Ala Ala Gln
 340 345 350

<210> 211

<211> 198

<212> PRT

<213> Streptococcus pyogenes

<400> 211

Val Leu Tyr Pro Thr Pro Ile Ala Lys Leu Ile Asp Ser Tyr Ser Lys
 1 5 10 15
 Leu Pro Gly Ile Gly Ile Lys Thr Ala Thr Arg Leu Ala Phe Tyr Thr
 20 25 30
 Ile Gly Met Ser Asn Glu Asp Val Asn Asp Phe Ala Lys Asn Leu Leu
 35 40 45
 Ala Ala Lys Arg Glu Leu Thr Tyr Cys Ser Ile Cys Gly Asn Leu Thr
 50 55 60
 Asp Asp Asp Pro Cys His Ile Cys Thr Asp Thr Ser Arg Asp Gln Thr
 65 70 75 80
 Thr Ile Leu Val Val Glu Asp Ala Lys Asp Val Ser Ala Met Glu Lys
 85 90 95
 Ile Gln Glu Tyr His Gly Tyr Tyr His Val Leu His Gly Leu Ile Ser
 100 105 110
 Pro Met Asn Gly Val Gly Pro Asp Asp Ile Asn Leu Lys Ser Leu Ile
 115 120 125
 Thr Arg Leu Met Asp Gly Lys Val Ser Glu Val Ile Val Ala Thr Asn
 130 135 140
 Ala Thr Ala Asp Gly Glu Ala Thr Ser Met Tyr Ile Ser Arg Val Leu
 145 150 155 160
 Lys Pro Ala Gly Ile Lys Val Thr Arg Leu Ala Arg Gly Leu Ala Val
 165 170 175
 Gly Ser Asp Ile Glu Tyr Ala Asp Glu Val Thr Leu Leu Arg Ala Ile
 180 185 190
 Glu Asn Arg Thr Glu Leu
 195

【 0 1 9 4 】

<210> 212
 <211> 268
 <212> PRT
 <213> Streptococcus pyogenes

<400> 212
 Met Asp Met Ser Lys Ser Asn Arg Arg Thr Trp Gln Gly Leu Val Val
 1 5 10 15
 Ile Leu Ile Ala Ile Leu Thr Thr Phe Thr Thr Ser Thr Val Thr Ala
 20 25 30
 Ala Arg Lys Ile Arg Asn Phe Pro Asp Thr Thr Glu Ile Leu Leu Gly
 35 40 45
 Thr Lys Ala Thr Glu Thr Pro Gly Ile Leu Pro Phe Thr Gly Ser Tyr
 50 55 60
 Gln Leu Val Leu Gly Asp Leu Asp Asn Leu Gln Arg Pro Thr Phe Ala
 65 70 75 80
 His Ile Gln Leu Lys Asp Gln Asp Glu Pro Asn Ile Lys Arg Lys Gly
 85 90 95
 Leu Lys Phe Asn Pro Pro Gly Trp His Asn Tyr Lys Leu Thr Asp Ala
 100 105 110
 Asn Gly Lys Thr Thr Trp Leu Met Asp Arg Gly His Leu Val Gly Tyr
 115 120 125
 Gln Phe Ser Gly Leu Asn Asp Glu Pro Lys Asn Leu Val Thr Met Thr
 130 135 140
 Lys Tyr Leu Asn Thr Gly Phe Ser Asp Lys Asn Pro Leu Gly Met Leu
 145 150 155 160
 Tyr Tyr Glu Asn Arg Leu Asp Ser Trp Leu Ala Leu His Pro Asn Phe
 165 170 175
 Trp Leu Asp Tyr Lys Val Thr Pro Val Tyr His Lys Asn Glu Leu Val
 180 185 190
 Pro Arg Gln Val Val Leu Gln Tyr Val Gly Ile Asp Glu Asn Gly Asp
 195 200 205
 Leu Leu Gln Ile Lys Leu Gly Ser Glu Lys Glu Ser Val Asp Asn Phe
 210 215 220
 Gly Val Thr Ser Val Thr Leu Asp Asn Val Ser Pro Leu Ala Glu Leu
 225 230 235 240
 Asp Tyr Gln Thr Gly Met Met Leu Asp Ser Thr Gln Asn Glu Glu Asp
 245 250 255
 Ser Asn Leu Glu Thr Glu Glu Phe Glu Glu Ala Ala
 260 265

<210> 213
 <211> 313
 <212> PRT
 <213> Streptococcus pyogenes

<400> 213
 Met Thr Ser Lys Lys Ala Cys Leu Ser Ser Ile Ile Val Leu Ala Ser
 1 5 10 15
 Leu Thr Cys Gly Asn Asp Thr Val Ser Ala Asn His Leu Ser Ala Thr
 20 25 30
 Gly Asp Lys Phe Asp Asp Cys Ser Thr Leu Val Glu Lys Asp Val Ala
 35 40 45
 Pro Lys Asp Glu Leu Glu Met Leu Ala Trp Ser Ser Ser Gln Thr Thr
 50 55 60
 Asp Asp Ala Asp Arg Asp Tyr Glu Asp Phe Leu Asp Asp Asp Ser Phe
 65 70 75 80
 Ile Ser Gln Asn Glu Thr Asp Lys Met Phe Glu Asn Leu Thr Asp Asp
 85 90 95
 Arg Leu Leu Asn Glu Leu Asp Glu Leu Asp Glu Glu Asn Glu Glu Asp
 100 105 110
 Glu Glu Asp Thr Ile Glu Pro Glu Gln Asn Val Ile Met Pro Ser Asp
 115 120 125
 Asp Glu Leu Phe Asp Leu Thr Asp Ala Val Glu Thr Arg Leu Thr Val
 130 135 140
 Ser Ser Ala Pro His Leu Glu Ala Glu Leu Pro Lys Pro His Leu Arg
 145 150 155 160
 Ser Leu Ser Asp Thr Ala Leu Arg Ser Gly Glu Ile Arg Gly His Leu
 165 170 175
 Asp Asn Lys Leu Asp Ala Leu Ser Val Thr Ala Thr Lys Leu Ala Leu
 180 185 190
 Thr Met Ala Gln Lys Phe Asp Leu Thr Thr His Val Tyr Ser Ile Gly
 195 200 205
 Glu Ser Phe Ser Glu Val Leu Ala Ala His Tyr Glu Asp Arg Lys Ala

【 0 1 9 5 】

210 215 220
 Glu Ser Ala Phe Ser Lys Lys Lys Arg Phe His Leu Pro Ile Ala Thr
 225 230 235 240
 Pro Asp Val Val Ile Glu Glu Leu Arg Arg Leu Val Ser Ser Ile Gly
 Ser Ser Lys Glu Asp Val Ser Val Pro Tyr Ser Arg Lys Leu Gly Met
 245 250 255
 Ala Val Ala Lys Arg Lys Ile Ala Leu Pro Gln Thr Gly Glu Arg Phe
 260 265 270
 Ser Tyr Tyr Pro Val Leu Leu Gly Leu Met Ile Leu Gly Leu Thr Pro
 275 280 285
 Ile Met Ile Pro Lys Lys Ile Asn Asn 300
 305 310

<210> 214

<211> 382

<212> PRT

<213> Streptococcus pyogenes

<400> 214

Met Ala Lys Asp Lys Glu Lys Gln Ser Asp Asp Lys Leu Val Leu Thr
 1 5 10 15
 Glu Trp Gln Lys Arg Asn Ile Glu Phe Leu Lys Lys Lys Lys Gln Gln
 20 25 30
 Ala Glu Glu Glu Lys Lys Leu Lys Glu Lys Leu Leu Ser Asp Lys Lys
 35 40 45
 Ala Gln Gln Gln Ala Gln Asn Ala Ser Glu Ala Val Glu Leu Lys Thr
 50 55 60
 Asp Glu Lys Thr Asp Ser Gln Glu Ile Glu Ser Glu Thr Thr Ser Lys
 65 70 75 80
 Pro Lys Lys Thr Lys Lys Val Arg Gln Pro Lys Glu Lys Ser Ala Thr
 85 90 95
 Gln Ile Ala Phe Gln Lys Ser Leu Pro Val Leu Leu Gly Ala Leu Leu
 100 105 110
 Leu Met Ala Val Ser Ile Phe Met Ile Thr Pro Tyr Ser Lys Lys Lys
 115 120 125
 Glu Phe Ser Val Arg Gly Asn His Gln Thr Asn Leu Asp Glu Leu Ile
 130 135 140
 Lys Ala Ser Lys Val Lys Ala Ser Asp Tyr Trp Leu Thr Leu Leu Thr
 145 150 155 160
 Ser Pro Gly Gln Tyr Glu Arg Pro Ile Leu Arg Thr Ile Pro Trp Val
 165 170 175
 Lys Ser Val His Leu Ser Tyr Gln Phe Pro Asn His Phe Leu Phe Asn
 180 185 190
 Val Ile Glu Phe Glu Ile Ile Ala Tyr Ala Gln Val Glu Asn Gly Phe
 195 200 205
 Gln Pro Ile Leu Glu Asn Gly Lys Arg Val Asp Lys Val Arg Ala Ser
 210 215 220
 Glu Leu Pro Lys Ser Phe Leu Ile Leu Asn Leu Lys Asp Glu Lys Ala
 225 230 235 240
 Ile Gln Gln Leu Val Lys Gln Leu Thr Thr Leu Pro Lys Lys Leu Val
 245 250 255
 Lys Asn Ile Lys Ser Val Ser Leu Ala Asn Ser Lys Thr Thr Ala Asp
 260 265 270
 Leu Leu Leu Ile Glu Met His Asp Gly Asn Val Val Arg Val Pro Gln
 275 280 285
 Ser Gln Leu Thr Leu Lys Leu Pro Tyr Tyr Gln Lys Leu Lys Lys Asn
 290 295 300
 Leu Glu Asn Asp Ser Ile Val Asp Met Glu Val Gly Ile Tyr Thr Thr
 305 310 315 320
 Thr Gln Glu Ile Glu Asn Gln Pro Glu Val Pro Leu Thr Pro Glu Gln
 325 330 335
 Asn Ala Ala Asp Lys Glu Gly Asp Lys Pro Gly Glu His Gln Glu Gln
 340 345 350
 Thr Asp Asn Asp Ser Glu Thr Pro Ala Asn Gln Ser Ser Pro Gln Gln
 355 360 365
 Thr Pro Pro Ser Pro Glu Thr Val Leu Glu Gln Ala His Gly
 370 375 380

<210> 215

<211> 345

<212> PRT

<213> Streptococcus pyogenes

<400> 215

Met Lys Arg Leu Lys Lys Ile Lys Trp Trp Leu Val Gly Leu Leu Ala
 1 5 10 15
 Leu Ile Ser Leu Leu Ala Leu Phe Phe Pro Leu Pro Tyr Ile
 20 25 30
 Glu Met Pro Gly Gly Ala Tyr Asp Ile Arg Thr Val Leu Gln Val Asn
 35 40 45
 Gly Lys Glu Asp Lys Arg Lys Gly Ala Tyr Gln Phe Val Ala Val Gly
 50 55 60
 Ile Ser Arg Ala Ser Leu Ala Gln Leu Leu Tyr Ala Trp Leu Thr Pro
 65 70 75 80
 Phe Thr Glu Ile Ser Thr Ala Glu Asp Thr Thr Gly Gly Tyr Ser Asp
 85 90 95
 Ala Asp Phe Leu Arg Ile Asn Gln Phe Tyr Met Glu Thr Ser Gln Asn
 100 105 110
 Ala Ala Ile Tyr Gln Ala Leu Ser Leu Ala Gly Lys Pro Val Thr Leu
 115 120 125
 Asp Tyr Lys Gly Val Tyr Val Leu Asp Val Asn Asn Glu Ser Thr Phe
 130 135 140
 Lys Gly Thr Leu His Leu Ala Asp Thr Val Thr Gly Val Asn Gly Lys
 145 150 155 160
 Gln Phe Thr Ser Ser Ala Glu Leu Ile Asp Tyr Val Ser His Leu Lys
 165 170 175
 Leu Gly Asp Glu Val Thr Val Gln Phe Thr Ser Asp Asn Lys Pro Lys
 180 185 190
 Lys Gly Val Gly Arg Ile Ile Lys Leu Lys Asn Gly Lys Asn Gly Ile
 195 200 205
 Gly Ile Ala Leu Thr Asp His Thr Ser Val Asn Ser Glu Asp Thr Val
 210 215 220
 Ile Phe Ser Thr Lys Gly Val Gly Gly Pro Ser Ala Gly Leu Met Phe
 225 230 235 240
 Thr Leu Asp Ile Tyr Asp Gln Ile Thr Lys Glu Asp Leu Arg Lys Gly
 245 250 255
 Arg Thr Ile Ala Gly Thr Gly Thr Ile Gly Lys Asp Gly Glu Val Gly
 260 265 270
 Asp Ile Gly Gly Ala Gly Leu Lys Val Val Ala Ala Glu Ala Gly
 275 280 285
 Ala Asp Ile Phe Phe Val Pro Asn Asn Pro Val Asp Lys Glu Ile Lys
 290 295 300
 Lys Val Asn Pro Asn Ala Ile Ser Asn Tyr Glu Glu Ala Lys Arg Ala
 305 310 315 320
 Ala Lys Arg Leu Lys Thr Lys Met Lys Ile Val Pro Val Thr Thr Val
 325 330 335
 Gln Glu Ala Leu Val Tyr Leu Arg Lys
 340 345

<210> 216

<211> 282

<212> PRT

<213> Streptococcus pyogenes

<400> 216

Met Leu Glu His Lys Ile Asp Phe Met Val Thr Leu Glu Val Lys Glu
 1 5 10 15
 Ala Asn Ala Asn Gly Asp Pro Leu Asn Gly Asn Met Pro Arg Thr Asp
 20 25 30
 Ala Lys Gly Tyr Gly Val Met Ser Asp Val Ser Ile Lys Arg Lys Ile
 35 40 45
 Arg Asn Arg Leu Gln Asp Met Gly Lys Ser Ile Phe Val Gln Ala Asn
 50 55 60
 Glu Arg Ile Glu Asp Asp Phe Arg Ser Leu Glu Lys Arg Phe Ser Gln
 65 70 75 80
 His Phe Thr Ala Lys Thr Pro Asp Lys Glu Ile Glu Glu Lys Ala Asn
 85 90 95
 Ala Leu Trp Phe Asp Val Arg Ala Phe Gly Gln Val Phe Thr Tyr Leu
 100 105 110
 Lys Lys Ser Ile Gly Val Arg Gly Pro Val Ser Ile Ser Met Ala Lys
 115 120 125
 Ser Leu Glu Pro Ile Val Ile Ser Ser Leu Gln Ile Thr Arg Ser Thr
 130 135 140
 Asn Gly Met Glu Ala Lys Asn Asn Ser Gly Arg Ser Ser Asp Thr Met
 145 150 155 160
 Gly Thr Lys His Phe Val Asp Tyr Gly Val Tyr Val Leu Lys Gly Ser

【 0 1 9 7 】

165 170 175
 Ile Asn Ala Tyr Phe Ala Glu Lys Thr Gly Phe Ser Gln Glu Asp Ala
 180 185 190
 Glu Ala Ile Lys Glu Val Leu Val Ser Leu Phe Glu Asn Asp Ala Ser
 195 200 205
 Ser Ala Arg Pro Glu Gly Ser Met Arg Val Cys Glu Val Phe Trp Phe
 210 215 220
 Thr His Ser Ser Lys Leu Gly Asn Val Ser Ser Ala Arg Val Phe Asp
 225 230 235 240
 Leu Leu Glu Tyr His Gln Ser Ile Glu Glu Lys Ser Thr Tyr Asp Ala
 245 250 255
 Tyr Gln Ile His Leu Asn Gln Glu Lys Leu Ala Lys Tyr Glu Ala Lys
 260 265 270
 Gly Leu Thr Leu Glu Ile Leu Glu Gly Leu
 275 280

<210> 217

<211> 901

<212> PRT

<213> Streptococcus pyogenes

<400> 217

Met Ala Thr Lys Lys Val His Ile Ile Ser His Ser His Trp Asp Arg
 1 5 10 15
 Glu Trp Tyr Met Ala Tyr Glu Gln His His Met Arg Leu Ile Asn Leu
 20 25 30
 Ile Asp Asp Leu Leu Glu Val Phe Gln Thr Asp Pro Asp Phe His Ser
 35 40 45
 Phe His Leu Asp Gly Gln Thr Ile Ile Leu Asp Asp Tyr Leu Lys Val
 50 55 60
 Arg Pro Glu Arg Glu Pro Glu Ile Arg Gln Ala Ile Ala Ser Gly Lys
 65 70 75 80
 Leu Arg Ile Gly Pro Phe Tyr Ile Leu Gln Asp Asp Phe Leu Thr Ser
 85 90 95
 Ser Glu Ser Asn Val Arg Asn Met Leu Ile Gly Lys Glu Asp Cys Asp
 100 105 110
 Arg Trp Gly Ala Ser Val Pro Leu Gly Tyr Phe Pro Asp Thr Phe Gly
 115 120 125
 Asn Met Gly Gln Thr Pro Gln Leu Met Leu Lys Ala Gly Leu Gln Ala
 130 135 140
 Ala Ala Phe Gly Arg Gly Ile Arg Pro Thr Gly Phe Asn Asn Gln Val
 145 150 155 160
 Asp Thr Ser Glu Lys Tyr Ser Ser Gln Phe Ser Glu Ile Ser Trp Gln
 165 170 175
 Gly Pro Asp Asn Ser Arg Ile Leu Gly Leu Leu Phe Ala Asn Trp Tyr
 180 185 190
 Ser Asn Gly Asn Glu Ile Pro Thr Thr Glu Ala Glu Ala Arg Leu Phe
 195 200 205
 Trp Asp Lys Lys Leu Ala Asp Ala Glu Arg Phe Ala Ser Thr Lys His
 210 215 220
 Leu Leu Met Met Asn Gly Cys Asp His Gln Pro Val Gln Leu Asp Val
 225 230 235 240
 Thr Lys Ala Ile Ala Leu Ala Asn Gln Leu Tyr Pro Asp Tyr Glu Phe
 245 250 255
 Val His Ser Cys Phe Glu Asp Tyr Leu Ala Asp Leu Ala Asp Asp Leu
 260 265 270
 Pro Glu Asn Leu Ser Thr Val Gln Gly Glu Ile Thr Ser Gln Glu Thr
 275 280 285
 Asp Gly Trp Tyr Thr Leu Ala Asn Thr Ala Ser Ala Arg Ile Tyr Leu
 290 295 300
 Lys Gln Ala Asn Thr Arg Val Ser Arg Gln Leu Glu Asn Ile Thr Glu
 305 310 315 320
 Pro Leu Ala Ala Met Ala Tyr Glu Val Thr Ser Thr Tyr Pro His Asp
 325 330 335
 Gln Leu Arg Tyr Ala Trp Lys Thr Leu Met Gln Asn His Pro His Asp
 340 345 350
 Ser Ile Cys Gly Cys Ser Val Asp Ser Val His Arg Glu Met Met Thr
 355 360 365
 Arg Phe Glu Lys Ala Tyr Glu Val Gly His Tyr Leu Ala Lys Glu Ala
 370 375 380
 Ala Lys Gln Ile Ala Asp Ala Ile Asp Thr Arg Asp Phe Pro Met Asp
 385 390 395 400
 Ser Gln Pro Phe Val Leu Phe Asn Thr Ser Gly His Ser Lys Thr Ser
 405 410 415

【 0 1 9 8 】

Val Ala Glu Leu Ser Leu Thr Trp Lys Lys Tyr His Phe Gly Gln Arg
 420 425 430
 Phe Pro Lys Glu Val Tyr Gln Glu Ala Gln Glu Tyr Leu Ala Arg Leu
 435 440 445
 Ser Gln Ser Phe Gln Ile Ile Asp Thr Ser Gly Gln Val Arg Pro Glu
 450 455 460
 Ala Glu Ile Leu Gly Thr Ser Ile Ala Phe Asp Tyr Asp Leu Pro Lys
 465 470 475 480
 Arg Ser Phe Arg Glu Pro Tyr Phe Ala Ile Lys Val Arg Leu Arg Leu
 485 490 495
 Pro Ile Thr Leu Pro Ala Met Ser Trp Lys Thr Leu Ala Leu Lys Leu
 500 505 510
 Gly Asn Glu Thr Thr Pro Ser Glu Thr Val Ser Leu Tyr Asp Asp Ser
 515 520 525
 Asn Gln Cys Leu Glu Asn Gly Phe Leu Lys Val Met Ile Gln Thr Asp
 530 535 540
 Gly Arg Leu Thr Ile Thr Asp Lys Gln Ser Gly Leu Ile Tyr Gln Asp
 545 550 555 560
 Leu Leu Arg Phe Glu Asp Cys Gly Asp Ile Gly Asn Glu Tyr Ile Ser
 565 570 575
 Arg Gln Pro Asn His Asp Gln Pro Phe Tyr Ala Asp Gln Gly Thr Ile
 580 585 590
 Lys Leu Asn Ile Ile Ser Asn Thr Ala Gln Val Ala Glu Leu Glu Ile
 595 600 605
 Gln Gln Thr Phe Ala Ile Pro Ile Ser Ala Asp Lys Leu Leu Gln Ala
 610 615 620
 Glu Met Glu Ala Val Ile Asp Ile Thr Glu Arg Gln Ala Arg Arg Ser
 625 630 635 640
 Gln Glu Lys Ala Glu Leu Thr Leu Thr Thr Leu Ile Arg Met Glu Lys
 645 650 655
 Asn Asn Pro Arg Leu Gln Phe Thr Thr Arg Phe Asp Asn Gln Met Thr
 660 665 670
 Asn His Arg Leu Arg Val Leu Phe Pro Thr His Leu Lys Thr Asp His
 675 680 685
 His Leu Ala Asp Ser Ile Phe Glu Thr Val Lys Arg Pro Asn His Pro
 690 695 700
 Asp Ala Thr Phe Trp Lys Asn Pro Ser Asn Pro Gln His Gln Glu Cys
 705 710 715 720
 Phe Val Ser Leu Phe Asp Gly Glu Asn Gly Val Thr Ile Gly Asn Tyr
 725 730 735
 Gly Leu Asn Glu Tyr Glu Ile Leu Pro Asp Thr Asn Thr Ile Ala Ile
 740 745 750
 Thr Leu Leu Arg Ser Val Gly Glu Met Gly Asp Trp Gly Tyr Phe Pro
 755 760 765
 Thr Pro Glu Ala Gln Cys Leu Gly Lys His Ser Leu Ser Tyr Ser Phe
 770 775 780
 Glu Ser Ile Thr Lys Gln Thr Gln Phe Ala Ser Tyr Trp Arg Ala Gln
 785 790 795 800
 Glu Gly Gln Val Pro Val Ile Thr Thr Gln Thr Asn Gln His Glu Gly
 805 810 815
 Thr Leu Ala Ala Glu Tyr Ser Tyr Leu Thr Gly Thr Asn Asp Gln Val
 820 825 830
 Ala Leu Thr Ala Phe Lys Arg Arg Leu Ala Asp Asn Ala Leu Ile Thr
 835 840 845
 Arg Ser Tyr Asn Leu Ser Asn Asp Lys Thr Cys Asp Phe Ser Leu Ser
 850 855 860
 Leu Pro Asn Tyr Asn Ala Lys Val Thr Asn Leu Leu Glu Lys Asp Ser
 865 870 875 880
 Lys Gln Ser Thr Pro Ser Gln Leu Gly Lys Ala Glu Ile Leu Thr Leu
 885 890 895
 Ala Trp Lys Lys Gln
 900

<210> 218

<211> 258

<212> PRT

<213> Streptococcus pyogenes

<400> 218

Met Lys Ile Thr Lys Ile Glu Lys Lys Lys Arg Leu Tyr Leu Ile Glu
 1 5 10 15
 Leu Asp Asn Asp Glu Ser Leu Tyr Val Thr Glu Asp Thr Ile Val Arg
 20 25 30
 Phe Met Leu Ser Lys Asp Lys Val Leu Asp Asn Asp Gln Leu Glu Asp

35 40 45
 Met Lys His Phe Ala Gln Leu Ser Tyr Gly Lys Asn Leu Ala Leu Tyr
 50 55 60
 Phe Leu Ser Phe Gln Gln Arg Ser Asn Lys Gln Val Ala Asp Tyr Leu
 65 70 75 80
 Arg Lys His Glu Ile Glu Glu His Ile Ile Ala Asp Ile Ile Thr Gln
 85 90 95
 Leu Gln Glu Glu Gln Trp Ile Asp Asp Thr Lys Leu Ala Asp Thr Tyr
 100 105 110
 Ile Arg Gln Asn Gln Leu Asn Gly Asp Lys Gly Pro Gln Val Leu Lys
 115 120 125
 Gln Lys Leu Leu Gln Lys Gly Ile Ala Ser His Asp Ile Asp Pro Ile
 130 135 140
 Leu Ser Gln Thr Asp Phe Ser Gln Leu Ala Gln Lys Val Ser Gln Lys
 145 150 155 160
 Leu Phe Asp Lys Tyr Gln Glu Lys Leu Pro Pro Lys Ala Leu Lys Asp
 165 170 175
 Lys Ile Thr Gln Ala Leu Leu Thr Lys Gly Phe Ser Tyr Asp Leu Ala
 180 185 190
 Lys His Ser Leu Asn His Leu Asn Phe Asp Gln Asp Asn Gln Glu Ile
 195 200 205
 Glu Asp Leu Leu Asp Lys Glu Leu Asp Lys Gln Tyr Arg Lys Leu Ser
 210 215 220
 Arg Lys Tyr Asp Gly Tyr Thr Leu Lys Gln Lys Leu Tyr Gln Ala Leu
 225 230 235 240
 Tyr Arg Lys Gly Tyr Asn Ser Asp Asp Ile Asn Cys Lys Leu Arg Asn
 245 250 255
 Tyr Leu

<210> 219

<211> 221

<212> PRT

<213> Streptococcus pyogenes

<400> 219

Met Ile Cys Leu Leu Cys Gln Gln Ile Ser Gln Thr Pro Ile Ser Ile
 1 5 10 15
 Thr Glu Ile Ile Phe Leu Arg Arg Ile Ser Ser Pro Ile Cys Gln Gln
 20 25 30
 Cys Gln Lys Ser Phe Gln Lys Ile Gly Lys Ser Val Cys Ala Thr Cys
 35 40 45
 Cys Ala Asn Ser Asp Ile Ile Ala Cys Arg Asp Cys Leu Lys Trp Glu
 50 55 60
 Asn Lys Gly Tyr Asn Val Asn His Arg Ser Leu Tyr Cys Tyr Asn Ala
 65 70 75 80
 Ala Met Lys Ala Tyr Phe Ser Gln Tyr Lys Phe Gln Gly Asp Tyr Leu
 85 90 95
 Leu Arg Lys Val Phe Ala Val Glu Leu Ala Asp Val Ile Thr Lys Tyr
 100 105 110
 Tyr Lys Gly Tyr Ile Pro Val Pro Val Pro Val Ser Pro Gly Cys Phe
 115 120 125
 Arg Glu Arg Gln Phe Asn Gln Val Ser Ala Ile Leu Glu Ala Ala Asn
 130 135 140
 Val Ser Tyr Leu Ser Leu Phe Glu Lys Leu Asp Asn Thr His Gln Ser
 145 150 155 160
 Ser Arg Thr Lys Lys Glu Arg Leu Leu Val Glu Lys Ser Tyr Arg Leu
 165 170 175
 Leu Lys Val Ser Asn Ile Pro Asp Lys Ile Leu Ile Val Asp Asp Ile
 180 185 190
 Tyr Thr Thr Gly Ser Thr Ile Ile Ala Leu Arg Lys Gln Leu Ala Lys
 195 200 205
 Val Ala Asn Ser Asp Ile Lys Ser Leu Ser Ile Ala Arg
 210 215 220

<210> 220

<211> 337

<212> PRT

<213> Streptococcus pyogenes

<400> 220

Met Lys Ser Phe Ser Leu Thr Phe Ser Phe Leu Asn Leu Leu Lys Tyr
 1 5 10 15

【 0 2 0 0 】

Gly Thr Ile Lys Val Met Thr Lys Glu Phe His His Val Thr Val Leu
 20 25 30
 Leu His Glu Thr Val Asp Met Leu Asp Ile Lys Pro Asp Gly Ile Tyr
 35 40 45
 Val Asp Ala Thr Leu Gly Gly Ser Gly His Ser Ala Tyr Leu Leu Ser
 50 55 60
 Lys Leu Gly Glu Glu Gly His Leu Tyr Cys Phe Asp Gln Asp Gln Lys
 65 70 75 80
 Ala Ile Asp Asn Ala Gln Val Thr Leu Lys Ser Tyr Ile Asp Lys Gly
 85 90 95
 Gln Val Thr Phe Ile Lys Asp Asn Phe Arg His Leu Lys Ala Arg Leu
 100 105 110
 Thr Ala Leu Gly Val Asp Glu Ile Asp Gly Ile Leu Tyr Asp Leu Gly
 115 120 125
 Val Ser Ser Pro Gln Leu Asp Glu Arg Glu Arg Gly Phe Ser Tyr Lys
 130 135 140
 Gln Asp Ala Pro Leu Asp Met Arg Met Asp Arg Gln Ser Leu Leu Thr
 145 150 155 160
 Ala Tyr Glu Val Val Asn Thr Tyr Pro Phe Asn Asp Leu Val Lys Ile
 165 170 175
 Phe Phe Lys Tyr Gly Glu Asp Lys Phe Ser Lys Gln Ile Ala Arg Lys
 180 185 190
 Ile Glu Gln Ala Arg Ala Ile Lys Pro Ile Glu Thr Thr Thr Glu Leu
 195 200 205
 Ala Glu Leu Ile Lys Ala Ala Lys Pro Ala Lys Glu Leu Lys Lys Lys
 210 215 220
 Gly His Pro Ala Lys Gln Ile Phe Gln Ala Ile Arg Ile Glu Val Asn
 225 230 235 240
 Asp Glu Leu Gly Ala Asp Glu Ser Ile Gln Asp Ala Met Glu Leu
 245 250 255
 Leu Ala Leu Asp Gly Arg Ile Ser Val Ile Thr Phe His Ser Leu Glu
 260 265 270
 Asp Arg Leu Thr Lys Gln Leu Phe Lys Glu Ala Ser Thr Val Asp Val
 275 280 285
 Pro Lys Gly Leu Pro Leu Ile Pro Glu Asp Met Lys Pro Lys Phe Glu
 290 295 300
 Leu Val Ser Arg Lys Pro Ile Leu Pro Ser His Ser Glu Leu Thr Ala
 305 310 315 320
 Asn Lys Arg Ala His Ser Ala Lys Leu Arg Val Ala Lys Lys Ile Arg
 325 330 335
 Lys

<210> 221

<211> 263

<212> PRT

<213> Streptococcus pyogenes

<400> 221

Val Thr Thr Thr Glu Gln Glu Leu Thr Leu Thr Pro Leu Arg Gly Lys
 1 5 10 15
 Ser Gly Lys Ala Tyr Lys Gly Thr Tyr Pro Asn Gly Glu Cys Val Phe
 20 25 30
 Ile Lys Leu Asn Thr Thr Pro Ile Leu Pro Ala Leu Ala Lys Glu Gln
 35 40 45
 Ile Ala Pro Gln Leu Leu Trp Ala Lys Arg Met Gly Asn Gly Asp Met
 50 55 60
 Met Ser Ala Gln Glu Trp Leu Asn Gly Arg Thr Leu Thr Lys Glu Asp
 65 70 75 80
 Met Asn Ser Lys Gln Ile Ile His Ile Leu Leu Arg Leu His Lys Ser
 85 90 95
 Lys Lys Leu Val Asn Gln Leu Leu Gln Leu Asn Tyr Lys Ile Glu Asn
 100 105 110
 Pro Tyr Asp Leu Leu Val Asp Phe Glu Gln Asn Ala Pro Leu Gln Ile
 115 120 125
 Gln Gln Asn Ser Tyr Leu Gln Ala Ile Val Lys Glu Leu Lys Arg Ser
 130 135 140
 Leu Pro Glu Phe Lys Ser Glu Val Ala Thr Ile Val His Gly Asp Ile
 145 150 155 160
 Lys His Ser Asn Trp Val Ile Thr Thr Ser Gly Met Ile Phe Leu Val
 165 170 175
 Asp Trp Asp Ser Val Arg Leu Thr Asp Arg Met Tyr Asp Val Ala Tyr
 180 185 190
 Leu Leu Ser His Tyr Ile Pro Arg Ser Arg Trp Ser Glu Trp Leu Ser

195 200 205
 Tyr Tyr Gly Tyr Lys Asn Asn Asp Lys Val Met Gln Lys Ile Ile Trp
 210 215 220
 Tyr Gly Gln Phe Ser His Leu Thr Gln Ile Leu Lys Cys Phe Asp Lys
 225 230 235 240
 Arg Asp Met Glu His Val Asn Gln Glu Ile Tyr Ala Leu Arg Lys Phe
 245 250 255
 Arg Glu Ile Phe Arg Lys Lys
 260

<210> 222

<211> 671

<212> PRT

<213> Streptococcus pyogenes

<400> 222

Met Ile Leu Thr Ala Pro Met Ser Asn Leu Lys Gly Phe Gly Pro Lys
 1 5 10 15
 Ser Ala Glu Lys Phe Gln Lys Leu Asp Ile Tyr Thr Val Glu Asp Leu
 20 25 30
 Leu Leu Tyr Tyr Pro Phe Arg Tyr Glu Asp Phe Lys Ser Lys Ser Val
 35 40 45
 Phe Asp Leu Val Asp Gly Glu Lys Ala Val Ile Thr Gly Leu Val Val
 50 55 60
 Thr Pro Ala Asn Val Gln Tyr Tyr Gly Phe Lys Arg Asn Arg Leu Ser
 65 70 75 80
 Phe Lys Leu Arg Gln Gly Glu Ala Val Leu Asn Val Ser Phe Phe Asn
 85 90 95
 Gln Pro Tyr Leu Ala Asp Lys Ile Glu Leu Gly Gln Glu Val Ala Val
 100 105 110
 Phe Gly Lys Trp Asp Ala Thr Lys Ser Ala Ile Thr Gly Met Lys Val
 115 120 125
 Leu Ala Gln Val Glu Asp Asp Met Gln Pro Val Tyr Arg Val Ala Gln
 130 135 140
 Gly Ile Ser Gln Ser Thr Leu Ile Lys Ala Ile Lys Ser Ala Phe Glu
 145 150 155 160
 Ile Asp Ala His Leu Glu Leu Lys Glu Asn Leu Pro Ala Thr Leu Leu
 165 170 175
 Glu Lys Tyr Arg Leu Met Gly Arg Ser Gln Ala Cys Leu Ala Met His
 180 185 190
 Phe Pro Lys Asp Ile Thr Glu Tyr Lys Gln Ala Leu Arg Arg Ile Lys
 195 200 205
 Phe Glu Glu Leu Phe Tyr Phe Gln Met Asn Leu Gln Val Leu Lys Ala
 210 215 220
 Glu Asn Lys Ser Glu Thr Asn Gly Leu Pro Ile Leu Tyr Ser Lys Arg
 225 230 235 240
 Ala Met Glu Thr Lys Ile Ser Ser Leu Pro Phe Ile Leu Thr Asn Ala
 245 250 255
 Gln Lys Arg Ser Leu Asp Asp Ile Leu Ser Asp Met Ser Ser Gly Ala
 260 265 270
 His Met Asn Arg Leu Leu Gln Gly Asp Val Gly Ser Gly Lys Thr Val
 275 280 285
 Ile Ala Gly Leu Ser Met Tyr Ala Ala Tyr Thr Ala Gly Phe Gln Ser
 290 295 300
 Ala Leu Met Val Pro Thr Glu Ile Leu Ala Glu Gln His Tyr Ile Ser
 305 310 315 320
 Leu Gln Glu Leu Phe Pro Asp Leu Ser Ile Ala Ile Leu Thr Ser Gly
 325 330 335
 Met Lys Ala Ala Val Lys Arg Thr Val Leu Ala Ala Ile Ala Asn Gly
 340 345 350
 Ser Val Asp Met Ile Val Gly Thr His Ala Leu Ile Gln Asp Ser Val
 355 360 365
 Gln Tyr His Lys Leu Gly Leu Val Ile Thr Asp Glu Gln His Arg Phe
 370 375 380
 Gly Val Lys Gln Arg Arg Ile Phe Arg Glu Lys Gly Glu Asn Pro Asp
 385 390 395 400
 Val Leu Met Met Thr Ala Thr Pro Ile Pro Arg Thr Leu Ala Ile Thr
 405 410 415
 Ala Phe Gly Glu Met Asp Val Ser Ile Ile Asp Glu Leu Pro Ala Gly
 420 425 430
 Arg Lys Pro Ile Met Thr Arg Trp Val Lys His Glu Gln Leu Gly Thr
 435 440 445
 Val Leu Glu Trp Val Lys Gly Glu Leu Gln Lys Asp Ala Gln Val Tyr
 450 455 460

【 0 2 0 2 】

Val Ile Ser Pro Leu Ile Glu Glu Ser Glu Ala Leu Asp Leu Lys Asn
 465 470 475 480
 Ala Val Ala Leu His Ala Glu Leu Ser Thr Tyr Phe Glu Gly Ile Ala
 485 490 495
 Lys Val Ala Leu Val His Gly Arg Met Lys Asn Asp Glu Lys Asp Ala
 500 505 510
 Ile Met Gln Asp Phe Lys Asp Lys Lys Ser His Ile Leu Val Ser Thr
 515 520 525
 Thr Val Ile Glu Val Gly Val Asn Val Pro Asn Ala Thr Ile Met Ile
 530 535 540
 Ile Met Asp Ala Asp Arg Phe Gly Leu Ser Gln Leu His Gln Leu Arg
 545 550 555 560
 Gly Arg Val Gly Arg Gly Tyr Lys Gln Ser Tyr Ala Val Leu Val Ala
 565 570 575
 Asn Pro Lys Thr Asp Ser Gly Lys Lys Arg Met Thr Ile Met Thr Glu
 580 585 590
 Thr Thr Asp Gly Phe Val Leu Ala Glu Ser Asp Leu Lys Met Arg Gly
 595 600 605
 Ser Gly Glu Ile Phe Gly Thr Arg Gln Ser Gly Ile Pro Glu Phe Gln
 610 615 620
 Val Ala Asp Ile Val Glu Asp Tyr Pro Ile Leu Glu Glu Ala Arg Lys
 625 630 635 640
 Val Ser Ala Ala Ile Val Ser Asp Pro Asn Trp Ile Tyr Glu Lys Gln
 645 650 655
 Trp Gln Leu Val Ala Gln Asn Ile Arg Lys Lys Glu Val Tyr Asp
 660 665 670

<210> 223
 <211> 1275
 <212> PRT
 <213> Streptococcus pyogenes

<400> 223
 Met Lys Lys Ile Ser Lys Cys Ala Phe Val Ala Ile Ser Ala Leu Val
 1 5 10 15
 Leu Ile Gln Ala Thr Gln Thr Val Lys Ser Gln Glu Pro Leu Val Gln
 20 25 30
 Ser Gln Leu Val Thr Thr Val Ala Leu Thr Gln Asp Asn Arg Leu Leu
 35 40 45
 Val Glu Glu Ile Gly Pro Tyr Ala Ser Gln Ser Ala Gly Lys Glu Tyr
 50 55 60
 Tyr Lys His Ile Glu Lys Ile Ile Val Asp Asn Asp Val Tyr Glu Lys
 65 70 75 80
 Ser Leu Glu Gly Glu Arg Thr Phe Asp Ile Asn Tyr Gln Gly Ile Lys
 85 90 95
 Ile Asn Ala Asp Leu Ile Lys Asp Gly Lys His Glu Leu Thr Ile Val
 100 105 110
 Asn Lys Lys Asp Gly Asp Ile Leu Ile Thr Phe Ile Lys Lys Gly Asp
 115 120 125
 Lys Val Thr Phe Ile Ser Ala Gln Lys Leu Gly Thr Thr Asp His Gln
 130 135 140
 Asp Ser Leu Lys Lys Asp Val Leu Ser Asp Lys Thr Val Pro Gln Asn
 145 150 155 160
 Gln Gly Thr Gln Lys Val Val Lys Ser Gly Lys Asn Thr Ala Asn Leu
 165 170 175
 Ser Leu Ile Thr Lys Leu Ser Gln Glu Asp Gly Ala Ile Leu Phe Pro
 180 185 190
 Glu Ile Asp Arg Tyr Ser Asp Asn Lys Gln Ile Lys Ala Leu Thr Gln
 195 200 205
 Gln Ile Thr Lys Val Thr Val Asn Gly Thr Val Tyr Lys Asp Leu Ile
 210 215 220
 Ser Asp Ser Val Lys Asp Thr Asn Gly Trp Val Ser Asn Met Thr Gly
 225 230 235 240
 Leu His Leu Gly Thr Lys Ala Phe Lys Asp Gly Glu Asn Thr Ile Val
 245 250 255
 Ile Ser Ser Lys Gly Phe Glu Asp Val Thr Ile Thr Val Thr Lys Lys
 260 265 270
 Asp Gly Gln Ile His Phe Val Ser Ala Lys Gln Lys Gln His Val Thr
 275 280 285
 Ala Glu Asp Arg Gln Ser Thr Lys Leu Asp Val Thr Thr Leu Glu Lys
 290 295 300
 Ala Ile Lys Glu Ala Asp Ala Ile Ile Ala Lys Glu Ser Asn Lys Asp
 305 310 315 320
 Ala Val Lys Asp Leu Ala Glu Lys Leu Gln Val Ile Lys Asp Ser Tyr

325 330 335
 Lys Glu Ile Lys Asp Ser Lys Leu Leu Ala Asp Thr His Arg Leu Leu
 340 345 350
 Lys Asp Thr Ile Glu Ser Tyr Gln Ala Gly Glu Val Ser Ile Asn Asn
 355 360 365
 Leu Thr Glu Gly Thr Tyr Thr Leu Asn Phe Lys Ala Asn Lys Glu Asn
 370 375 380
 Ser Glu Glu Ser Ser Met Leu Gln Gly Ala Phe Asp Lys Arg Ala Lys
 385 390 395 400
 Leu Val Val Lys Ala Asp Gly Thr Met Glu Ile Ser Met Leu Asn Thr
 405 410 415
 Ala Leu Gly Gln Phe Leu Ile Asp Phe Ser Ile Glu Ser Lys Gly Thr
 420 425 430
 Tyr Pro Ala Ala Val Arg Lys Gln Val Gly Gln Lys Asp Ile Asn Gly
 435 440 445
 Ser Tyr Ile Arg Ser Glu Phe Thr Met Pro Ile Asp Asp Leu Asp Lys
 450 455 460
 Leu His Lys Gly Ala Val Leu Val Ser Ala Met Gly Gly Gln Glu Ser
 465 470 475 480
 Asp Leu Asn His Tyr Asp Lys Tyr Thr Lys Leu Asp Met Thr Phe Ser
 485 490 495
 Lys Thr Val Thr Lys Gly Trp Ser Gly Tyr Gln Val Glu Thr Asp Asp
 500 505 510
 Lys Glu Lys Gly Val Gly Thr Glu Arg Leu Glu Lys Val Leu Val Lys
 515 520 525
 Leu Gly Lys Asp Leu Asp Gly Asp Gly Lys Leu Ser Lys Thr Glu Leu
 530 535 540
 Glu Gln Ile Arg Gly Glu Leu Arg Leu Asp His Tyr Glu Leu Thr Asp
 545 550 555 560
 Ile Ser Leu Leu Lys His Ala Lys Asn Ile Thr Glu Leu His Leu Asp
 565 570 575
 Gly Asn Gln Ile Thr Glu Ile Pro Lys Glu Leu Phe Ser Gln Met Lys
 580 585 590
 Gln Leu Arg Phe Leu Asn Leu Arg Ser Asn His Leu Thr Tyr Leu Asp
 595 600 605
 Lys Asp Thr Phe Lys Ser Asn Ala Gln Leu Arg Glu Leu Tyr Leu Ser
 610 615 620
 Ser Asn Phe Ile His Ser Leu Glu Gly Gly Leu Phe Gln Ser Leu His
 625 630 635 640
 His Leu Glu Gln Leu Asp Leu Ser Lys Asn Arg Ile Gly Arg Leu Cys
 645 650 655
 Asp Asn Pro Phe Glu Gly Leu Ser Arg Leu Thr Ser Leu Gly Phe Ala
 660 665 670
 Glu Asn Ser Leu Glu Glu Ile Pro Glu Lys Ala Leu Glu Pro Leu Thr
 675 680 685
 Ser Leu Asn Phe Ile Asp Leu Ser Gln Asn Asn Leu Ala Leu Leu Pro
 690 695 700
 Lys Thr Ile Glu Lys Leu Arg Ala Leu Ser Thr Ile Val Ala Ser Arg
 705 710 715 720
 Asn His Ile Thr Arg Ile Asp Asn Ile Ser Phe Lys Asn Leu Pro Lys
 725 730 735
 Leu Ser Val Leu Asp Leu Ser Thr Asn Glu Ile Ser Asn Leu Pro Asn
 740 745 750
 Gly Ile Phe Lys Gln Asn Asn Gln Leu Thr Lys Leu Asp Phe Phe Asn
 755 760 765
 Asn Leu Leu Thr Gln Val Glu Glu Ser Val Phe Pro Asp Val Glu Thr
 770 775 780
 Leu Asn Leu Asp Val Lys Phe Asn Gln Ile Lys Ser Val Ser Pro Lys
 785 790 795 800
 Val Arg Ala Leu Ile Gly Gln His Lys Leu Thr Pro Gln Lys His Ile
 805 810 815
 Ala Lys Leu Glu Ala Ser Leu Asp Gly Glu Lys Ile Lys Tyr His Gln
 820 825 830
 Ala Phe Ser Leu Leu Asp Leu Tyr Trp Glu Gln Lys Thr Asn Ser
 835 840 845
 Ala Ile Asp Lys Glu Leu Val Ser Val Glu Glu Tyr Gln Gln Leu Leu
 850 855 860
 Gln Glu Lys Gly Ser Asp Thr Val Ser Leu Leu Asn Asp Met Gln Val
 865 870 875 880
 Asp Trp Ser Ile Val Ile Gln Leu Gln Lys Lys Ala Ser Asn Gly Gln
 885 890 895
 Tyr Val Thr Val Asp Glu Lys Leu Leu Ser Asn Asp Pro Lys Asp Asp
 900 905 910
 Leu Thr Gly Glu Phe Ser Leu Lys Asp Pro Gly Thr Tyr Arg Ile Arg
 915 920 925

Lys Ala Leu Ile Thr Lys Lys Phe Ala Thr Gln Lys Glu His Ile Tyr
 930 935 940
 Leu Thr Ser Asn Asp Ile Leu Val Ala Lys Gly Pro His Ser His Gln
 945 950 955 960
 Lys Asp Leu Val Glu Asn Gly Leu Arg Ala Leu Asn Gln Lys Gln Leu
 965 970 975
 Arg Asp Gly Ile Tyr Tyr Leu Asn Ala Ser Met Leu Lys Thr Asp Leu
 980 985 990
 Ala Ser Glu Ser Met Ser Asn Lys Ala Ile Asn His Arg Val Thr Leu
 995 1000 1005
 Val Val Lys Lys Gly Val Ser Tyr Leu Glu Val Glu Phe Arg Gly
 1010 1015 1020
 Ile Lys Val Gly Lys Met Leu Gly Tyr Leu Gly Glu Leu Ser Tyr
 1025 1030 1035
 Phe Val Asp Gly Tyr Gln Arg Asp Leu Ala Gly Lys Pro Val Gly
 1040 1045 1050
 Arg Thr Lys Lys Ala Glu Val Val Ser Tyr Phe Thr Asp Val Thr
 1055 1060 1065
 Gly Leu Pro Leu Ala Asp Arg Tyr Gly Lys Asn Tyr Pro Lys Val
 1070 1075 1080
 Leu Arg Met Lys Leu Ile Glu Gln Ala Lys Lys Asp Gly Leu Val
 1085 1090 1095
 Pro Leu Gln Val Phe Val Pro Ile Met Asp Ala Ile Ser Lys Gly
 1100 1105 1110
 Ser Gly Leu Gln Thr Val Phe Met Arg Leu Asp Trp Ala Ser Leu
 1115 1120 1125
 Thr Thr Glu Lys Ala Lys Val Val Lys Glu Thr Asn Asn Pro Gln
 1130 1135 1140
 Glu Asn Ser His Leu Thr Ser Thr Asp Gln Leu Lys Gly Pro Gln
 1145 1150 1155
 Asn Arg Gln Gln Glu Lys Thr Pro Thr Ser Pro Pro Ser Ala Ala
 1160 1165 1170
 Thr Gly Ile Ala Asn Leu Thr Asp Leu Leu Ala Lys Lys Ala Thr
 1175 1180 1185
 Gly Gln Ser Thr Gln Glu Thr Ser Lys Thr Asp Asp Thr Asp Lys
 1190 1195 1200
 Ala Glu Lys Leu Lys Gln Leu Val Arg Asp His Gln Thr Ser Ile
 1205 1210 1215
 Glu Gly Lys Thr Ala Lys Asp Thr Lys Thr Lys Lys Ser Asp Lys
 1220 1225 1230
 Lys His Arg Ser Asn Gln Gln Ser Asn Gly Glu Glu Ser Ser Ser
 1235 1240 1245
 Arg Tyr His Leu Ile Ala Gly Leu Ser Ser Phe Met Ile Val Ala
 1250 1255 1260
 Leu Gly Phe Ile Ile Gly Arg Lys Thr Leu Phe Lys
 1265 1270 1275

<210> 224

<211> 503

<212> PRT

<213> Streptococcus pyogenes

<400> 224

Met Asn Lys Asn Lys Leu Leu Arg Val Ala Met Leu Leu Ser Leu Leu
 1 5 10 15
 Ala Pro Thr Ala Glu Ser Met Thr Val Leu Ala Gln Asp Val Met Leu
 20 25 30
 Glu Thr His Lys Ala Thr Thr Asn Glu Thr Ser Asp Ser Ser Lys
 35 40 45
 Glu Glu Asn Asn Lys Asn Ala Ala Pro Thr Thr Ser Asp Lys Thr Asp
 50 55 60
 Gln Gly Pro Leu Asp Ala Ser Ala Glu Thr Asn Ser Asn Ser Leu Val
 65 70 75 80
 Asn Ala Asp Asp Lys Lys Arg Ser Asp Ser Ser Gln Ser Ala Ile Gly
 85 90 95
 Ser Ser Asp Asn Lys Ala Glu Ala Glu Asn Gln Val Asp Asp Lys Ser
 100 105 110
 Thr Asp His Ser Lys Ser Thr Asp His Ser Lys Pro Thr Asp Gln Pro
 115 120 125
 Lys Pro Ser Pro Ser Lys Val Asp Thr Ala Pro Ala Ser Ser Leu Ser
 130 135 140
 Lys Gln Leu Pro Glu Ala Arg Thr Pro Ile Gln Ser Leu Ser Pro Tyr
 145 150 155 160
 Val Ser Asp Leu Asp Leu Ser Glu Ile Asp Ile Pro Ser Val Asn Thr

【 0 2 0 5 】

Tyr Ala Ala Tyr Val Glu His Trp Ser Gly Lys Asn Ala Tyr Thr His
 165 170 175
 180 185 190
 His Leu Leu Ser Arg Arg Tyr Gly Ile Lys Ala Asp Gln Ile Asp Ser
 195 200 205
 Tyr Leu Lys Ser Thr Gly Ile Ala Tyr Asp Ser Thr Arg Ile Asn Gly
 210 215 220
 Glu Lys Leu Leu Gln Trp Glu Lys Lys Ser Gly Leu Asp Val Arg Ala
 225 230 235 240
 Ile Val Ala Ile Ala Met Ser Glu Ser Ser Leu Gly Thr Gln Gly Ile
 245 250 255
 Ala Thr Leu Leu Gly Ala Asn Met Phe Gly Tyr Ala Ala Phe Asp Leu
 260 265 270
 Asp Pro Thr Gln Ala Ser Lys Phe Asn Asp Asp Ser Ala Ile Val Lys
 275 280 285
 Met Thr Gln Asp Thr Ile Ile Lys Asn Lys Asn Ser Asn Phe Ala Leu
 290 295 300
 Gln Asp Leu Lys Ala Ala Lys Phe Ser Arg Gly Gln Leu Asn Phe Ala
 305 310 315 320
 Ser Asp Gly Gly Val Tyr Phe Thr Asp Thr Thr Gly Ser Gly Lys Arg
 325 330 335
 Arg Ala Gln Ile Met Glu Asp Leu Asp Lys Trp Ile Asp Asp His Gly
 340 345 350
 Gly Thr Pro Ala Ile Pro Ala Glu Leu Lys Val Gln Ser Ser Ala Ser
 355 360 365
 Phe Ala Ser Val Pro Ala Gly Tyr Lys Leu Ser Lys Ser Tyr Asp Val
 370 375 380
 Leu Gly Tyr Gln Ala Ser Ser Tyr Ala Trp Gly Gln Cys Thr Trp Tyr
 385 390 395 400
 Val Tyr Asn Arg Ala Lys Glu Leu Gly Tyr Gln Phe Asp Pro Phe Met
 405 410 415
 Gly Asn Gly Gly Asp Trp Lys Tyr Lys Val Gly Tyr Ala Leu Ser Lys
 420 425 430
 Thr Pro Lys Val Gly Tyr Ala Ile Ser Phe Ala Pro Gly Gln Ala Gly
 435 440 445
 Ala Asp Gly Thr Tyr Gly His Val Ser Ile Val Glu Asp Val Arg Lys
 450 455 460
 Asp Gly Ser Ile Leu Ile Ser Glu Ser Asn Cys Ile Gly Leu Gly Lys
 465 470 475 480
 Ile Ser Tyr Arg Thr Phe Thr Ala Gln Gln Ala Glu Gln Leu Thr Tyr
 485 490 495
 Val Ile Gly Lys Ser Lys Asn
 500

<210> 225
 <211> 995
 <212> PRT
 <213> Streptococcus pyogenes

<400> 225
 Met Asp Lys His Leu Leu Val Lys Arg Thr Leu Gly Cys Val Cys Ala
 1 5 10 15
 Ala Thr Leu Met Gly Ala Ala Leu Ala Thr His His Asp Ser Leu Asn
 20 25 30
 Thr Val Lys Ala Glu Glu Lys Thr Val Gln Val Gln Lys Gly Leu Pro
 35 40 45
 Ser Ile Asp Ser Leu His Tyr Leu Ser Glu Asn Ser Lys Lys Glu Phe
 50 55 60
 Lys Glu Glu Leu Ser Lys Ala Gly Gln Glu Ser Gln Lys Val Lys Glu
 65 70 75 80
 Ile Leu Ala Lys Ala Gln Gln Ala Asp Lys Gln Ala Gln Glu Leu Ala
 85 90 95
 Lys Met Lys Ile Pro Glu Lys Ile Pro Met Lys Pro Leu His Gly Ser
 100 105 110
 Leu Tyr Gly Gly Tyr Phe Arg Thr Trp His Asp Lys Thr Ser Asp Pro
 115 120 125
 Thr Glu Lys Asp Lys Val Asn Ser Met Gly Glu Leu Pro Lys Glu Val
 130 135 140
 Asp Leu Ala Phe Ile Phe His Asp Trp Thr Lys Asp Tyr Ser Leu Phe
 145 150 155 160
 Trp Lys Glu Leu Ala Thr Lys His Val Pro Lys Leu Asn Lys Gln Gly
 165 170 175
 Thr Arg Val Ile Arg Thr Ile Pro Trp Arg Phe Leu Ala Gly Gly Asp
 180 185 190

【 0 2 0 6 】

Asn Ser Gly Ile Ala Glu Asp Thr Ser Lys Tyr Pro Asn Thr Pro Glu
 195 200 205
 Gly Asn Lys Ala Leu Ala Lys Ala Ile Val Asp Glu Tyr Val Tyr Lys
 210 215 220
 Tyr Asn Leu Asp Gly Leu Asp Val Asp Val Glu His Asp Ser Ile Pro
 225 230 235 240
 Lys Val Asp Lys Lys Glu Asp Thr Ala Gly Val Glu Arg Ser Ile Gln
 245 250 255
 Val Phe Glu Glu Ile Gly Lys Leu Ile Gly Pro Lys Gly Val Asp Lys
 260 265 270
 Ser Arg Leu Phe Ile Met Asp Ser Thr Tyr Met Ala Asp Lys Asn Pro
 275 280 285
 Leu Ile Glu Arg Gly Ala Pro Tyr Ile Asn Leu Leu Leu Val Gln Val
 290 295 300
 Tyr Gly Ser Gln Gly Glu Lys Gly Gly Trp Glu Pro Val Ser Asn Arg
 305 310 315 320
 Pro Glu Lys Thr Met Glu Glu Arg Trp Gln Gly Tyr Ser Lys Tyr Ile
 325 330 335
 Arg Pro Glu Gln Tyr Met Ile Gly Phe Ser Phe Tyr Glu Glu Asn Ala
 340 345 350
 Gln Glu Gly Asn Leu Trp Tyr Asp Ile Asn Ser Arg Lys Asp Glu Asp
 355 360 365
 Lys Ala Asn Gly Ile Asn Thr Asp Ile Thr Gly Thr Arg Ala Glu Arg
 370 375 380
 Tyr Ala Arg Trp Gln Pro Lys Thr Gly Gly Val Lys Gly Gly Ile Phe
 385 390 395 400
 Ser Tyr Ala Ile Asp Arg Asp Gly Val Ala His Gln Pro Lys Lys Tyr
 405 410 415
 Ala Lys Gln Lys Glu Phe Lys Asp Ala Thr Asp Asn Ile Phe His Ser
 420 425 430
 Asp Tyr Ser Val Ser Lys Ala Leu Lys Thr Val Met Leu Lys Asp Lys
 435 440 445
 Ser Tyr Asp Leu Ile Asp Glu Lys Asp Phe Pro Asp Lys Ala Leu Arg
 450 455 460
 Glu Ala Val Met Ala Gln Val Gly Thr Arg Lys Gly Asp Leu Glu Arg
 465 470 475 480
 Phe Asn Gly Thr Leu Arg Leu Asp Asn Pro Ala Ile Gln Ser Leu Glu
 485 490 495
 Gly Leu Asn Lys Phe Lys Lys Leu Ala Gln Leu Asp Leu Ile Gly Leu
 500 505 510
 Ser Arg Ile Thr Lys Leu Asp Arg Ser Val Leu Pro Ala Asn Met Lys
 515 520 525
 Pro Gly Lys Asp Thr Leu Glu Thr Val Leu Glu Thr Tyr Lys Lys Asp
 530 535 540
 Asn Lys Glu Glu Pro Ala Thr Ile Pro Pro Val Ser Leu Lys Val Ser
 545 550 555 560
 Gly Leu Thr Gly Leu Lys Glu Leu Asp Leu Ser Gly Phe Asp Arg Glu
 565 570 575
 Thr Leu Ala Gly Leu Asp Ala Ala Thr Leu Thr Ser Leu Glu Lys Val
 580 585 590
 Asp Ile Ser Gly Asn Lys Leu Asp Leu Ala Pro Gly Thr Glu Asn Arg
 595 600 605
 Gln Ile Phe Asp Thr Met Leu Ser Thr Ile Ser Asn His Val Gly Ser
 610 615 620
 Asn Glu Gln Thr Val Lys Phe Asp Lys Gln Lys Pro Thr Gly His Tyr
 625 630 635 640
 Pro Asp Thr Tyr Gly Lys Thr Ser Leu Arg Leu Pro Val Ala Asn Glu
 645 650 655
 Lys Val Asp Leu Gln Ser Gln Leu Leu Phe Gly Thr Val Thr Asn Gln
 660 665 670
 Gly Thr Leu Ile Asn Ser Glu Ala Asp Tyr Lys Ala Tyr Gln Asn His
 675 680 685
 Lys Ile Ala Gly Arg Ser Phe Val Asp Ser Asn Tyr His Tyr Asn Asn
 690 695 700
 Phe Lys Val Ser Tyr Glu Asn Tyr Thr Val Lys Val Thr Asp Ser Thr
 705 710 715 720
 Leu Gly Thr Thr Thr Asp Lys Thr Leu Ala Thr Asp Lys Glu Glu Thr
 725 730 735
 Tyr Lys Val Asp Phe Phe Ser Pro Ala Asp Lys Thr Lys Ala Val His
 740 745 750
 Thr Ala Lys Val Ile Val Gly Asp Glu Lys Thr Met Met Val Asn Leu
 755 760 765
 Ala Glu Gly Ala Thr Val Ile Gly Gly Ser Ala Asp Pro Val Asn Ala
 770 775 780
 Arg Lys Val Phe Asp Gly Gln Leu Gly Ser Glu Thr Asp Asn Ile Ser

【 0 2 0 7 】

785 Leu Gly Trp Asp Ser 790 Lys Gln Ser Ile Ile 795 Phe Lys Leu Lys Glu Asp 800
 Gly Leu Ile Lys His 805 Trp Arg Phe Phe 810 Asn Asp Ser Ala Arg Asn Pro 815
 Glu Thr Thr 820 Asn Lys Pro Ile Gln Glu Ala Ser Leu Gln Ile Phe Asn 830
 Ile Lys Asp Tyr Asn Leu Asp Asn Leu Leu Glu Asn Pro Asn Lys Phe 845
 Asp Asp Glu Lys Tyr Trp 855 Thr Val Asp Thr Tyr Ser Ala Gln Gly 860
 Glu Arg Ala Thr Ala Phe Ser Asn Thr Leu Asn Asn Ile Thr Ser Lys 875
 Tyr Trp Arg Val Phe Asp Thr Lys Gly Asp Arg Tyr Ser Ser Pro 890
 Val Val Pro Glu Leu Gln Ile Leu Gly Tyr Pro Leu Pro Asn Ala Asp 905
 Thr Ile Met Lys Thr Val Thr Thr Ala Lys Glu Leu Ser Gln Gln Lys 920
 Asp Lys Phe Ser Gln Lys Met Leu Asp Glu Leu Lys Ile Lys Glu Met 940
 Ala Leu Glu Thr Ser 950 Leu Asn Ser Lys Ile Phe Asp Val Thr Ala Ile 955
 Asn Ala Asn Ala Gly Val Leu Lys Asp Cys Ile Glu Lys Arg Gln Leu 970
 Leu Lys Lys 980 985 990 995

<210> 226
 <211> 185
 <212> PRT
 <213> Streptococcus pyogenes

<400> 226
 Met Ile Glu Ala Ser Lys Leu Lys Ala Gly Met Thr Phe Glu Ala Glu 1
 Gly Lys Leu Ile Arg Val Leu Glu Ala Ser His His Lys Pro Gly Lys 5
 Gly Asn Thr Ile Met Arg Met Lys Leu Arg Asp Val Arg Thr Gly Ser 20
 Thr Phe Asp Thr Thr Tyr Arg Pro Asp Glu Lys Phe Glu Gln Ala Ile 35
 Ile Glu Thr Val Pro Ala Gln Tyr Leu Tyr Lys Met Asp Asp Thr Ala 40
 Tyr Phe Met Asn Thr Asp Thr Tyr Asp Gln Tyr Glu Ile Pro Val Ala 55
 Asn Val Glu Gln Glu Leu Leu Tyr Ile Leu Glu Asn Ser Asp Val Lys 60
 Ile Gln Phe Tyr Gly Ser Glu Val Ile Gly Val Thr Val Pro Thr Thr 75
 Val Glu Leu Thr Val Ala Glu Thr Gln Pro Ser Ile Lys Gly Ala Thr 80
 Val Thr Gly Ser Gly Lys Pro Ala Thr Leu Glu Thr Gly Leu Val Val 85
 Asn Val Pro Asp Phe Ile Glu Ala Gly Gln Lys Leu Ile Ile Asn Thr 90
 Ala Glu Gly Thr Tyr Val Ser Arg Ala 100
 110 120 130 140 150 160 170 180 185

<210> 227
 <211> 468
 <212> PRT
 <213> Streptococcus pyogenes

<400> 227
 Met Thr Lys Thr Leu Pro Lys Asp Phe Ile Phe Gly Gly Ala Thr Ala 1
 Ala Tyr Gln Ala Glu Gly Ala Thr His Thr Asp Gly Lys Gly Pro Val 5
 Ala Trp Asp Lys Tyr Leu Glu Asp Asn Tyr Trp Tyr Thr Ala Glu Pro 20
 Ala Ser Asp Phe Tyr Asn Arg Tyr Pro Val Asp Leu Lys Leu Ser Glu 35
 40 45 50 55 60

Glu Phe Gly Val Asn Gly Ile Arg Ile Ser Ile Ala Trp Ser Arg Ile
 65 70 75 80
 Phe Pro Thr Gly Lys Gly Glu Val Asn Pro Lys Gly Val Glu Tyr Tyr
 85 90 95
 His Asn Leu Phe Ala Glu Cys His Lys Arg His Val Glu Pro Phe Val
 100 105 110
 Thr Leu His His Phe Asp Thr Pro Glu Ala Leu His Ser Asp Gly Asp
 115 120 125
 Phe Leu Asn Arg Glu Asn Ile Glu His Phe Val Asn Tyr Ala Glu Phe
 130 135 140
 Cys Phe Lys Glu Phe Ser Glu Val Asn Tyr Trp Thr Thr Phe Asn Glu
 145 150 155 160
 Ile Gly Pro Ile Gly Asp Gly Gln Tyr Leu Val Gly Lys Phe Pro Pro
 165 170 175
 Gly Ile Gln Tyr Asp Leu Ala Lys Val Phe Gln Ser His His Asn Met
 180 185 190
 Met Val Ser His Ala Arg Ala Val Lys Leu Phe Lys Asp Ser Gly Tyr
 195 200 205
 Ser Gly Glu Ile Gly Val Val His Ala Leu Pro Thr Lys Tyr Pro Phe
 210 215 220
 Asp Ala Asn Asn Pro Asp Asp Val Arg Ala Ala Glu Leu Glu Asp Ile
 225 230 235 240
 Ile His Asn Lys Phe Ile Leu Asp Ala Thr Tyr Leu Gly Lys Tyr Ser
 245 250 255
 Asp Lys Thr Met Glu Gly Val Asn His Ile Leu Glu Val Asn Gly Gly
 260 265 270
 Glu Leu Asp Leu Arg Glu Glu Asp Phe Ala Ala Leu Asp Ala Ala Lys
 275 280 285
 Asp Leu Asn Asp Phe Leu Gly Ile Asn Tyr Tyr Met Ser Asp Trp Met
 290 295 300
 Gln Ala Phe Asp Gly Glu Thr Glu Ile Ile His Asn Gly Lys Gly Glu
 305 310 315 320
 Lys Gly Ser Ser Lys Tyr Gln Ile Lys Gly Val Gly Arg Arg Lys Ala
 325 330 335
 Pro Val Asp Val Pro Lys Thr Asp Trp Asp Trp Ile Ile Phe Pro Gln
 340 345 350
 Gly Leu Tyr Asp Gln Ile Met Arg Val Lys Ala Asp Tyr Pro Asn Tyr
 355 360 365
 Lys Lys Ile Tyr Ile Thr Glu Asn Gly Leu Gly Tyr Lys Asp Glu Phe
 370 375 380
 Val Asp Asn Thr Val Tyr Asp Gly Gly Arg Ile Asp Tyr Val Lys Lys
 385 390 395 400
 His Leu Glu Val Ile Ser Asp Ala Ile Ser Asp Gly Ala Asn Val Lys
 405 410 415
 Gly Tyr Phe Met Trp Ser Leu Met Asp Val Phe Ser Trp Ser Asn Gly
 420 425 430
 Tyr Glu Lys Arg Tyr Gly Leu Phe Tyr Val Asp Phe Glu Thr Gln Glu
 435 440 445
 Arg Tyr Pro Lys Lys Ser Ala Tyr Trp Tyr Lys Lys Val Ala Glu Thr
 450 455 460
 Gln Val Ile Glu
 465

<210> 228

<211> 1165

<212> PRT

<213> Streptococcus pyogenes

<400> 228

Met Lys Lys Lys Val Asn Gln Gly Ser Lys Arg Tyr Gln Tyr Leu Leu
 1 5 10 15
 Lys Lys Trp Gly Ile Gly Phe Val Ile Ala Ala Thr Gly Thr Val Val
 20 25 30
 Leu Gly Cys Thr Pro Ser Ile Leu Thr His Gln Val Ala Ala Lys Thr
 35 40 45
 Ile Val Gly Leu Ala Arg Asp Glu Ala Gln Gln Gly Asp Gly Asn Ala
 50 55 60
 Lys Ser Gly Asp Gly Leu Gln Ser Ser Ser Lys Glu Ala Lys Pro Val
 65 70 75 80
 Leu Asp Ser Ser Ser Ala Asn Pro Ala Ser Ile Ala Glu His His Leu
 85 90 95
 Arg Met His Phe Lys Thr Leu Pro Ala Gly Glu Ser Leu Gly Ser Leu
 100 105 110
 Gly Leu Trp Val Trp Gly Asp Val Asp Gln Pro Ser Lys Asp Trp Pro

【 0 2 0 9 】

115 120 125
 Asn Gly Ala Ile Thr Met Thr Lys Ala Lys Lys Asp Asp Tyr Gly Tyr
 130 135 140
 Tyr Leu Asp Val Pro Leu Ala Ala Lys His Arg Gln Gln Val Ser Tyr
 145 150 155 160
 Leu Ile Asn Asn Lys Ala Gly Glu Asn Leu Ser Lys Asp Gln His Ile
 165 170 175
 Ser Leu Leu Thr Pro Lys Met Asn Glu Val Trp Ile Asp Glu Asn Tyr
 180 185 190
 His Ala His Ala Tyr Arg Pro Leu Lys Lys Gly Tyr Leu Arg Ile Asn
 195 200 205
 Tyr His Asn Gln Ser Gly His Tyr Asp Asn Leu Ala Val Trp Thr Phe
 210 215 220
 Lys Asp Val Lys Thr Pro Thr Thr Asp Trp Pro Asn Gly Leu Asp Leu
 225 230 235 240
 Ser His Lys Gly His Tyr Gly Ala Tyr Val Asp Val Pro Leu Lys Glu
 245 250 255
 Gly Ala Asn Glu Ile Gly Phe Leu Ile Leu Asp Lys Ser Lys Thr Gly
 260 265 270
 Asp Ala Ile Lys Val Gln Pro Lys Asp Tyr Leu Phe Lys Glu Leu Asp
 275 280 285
 Asn His Thr Gln Val Phe Val Lys Asp Thr Asp Pro Lys Val Tyr Asn
 290 295 300
 Asn Pro Tyr Tyr Ile Asp Gln Val Ser Leu Lys Gly Ala Glu Gln Thr
 305 310 315 320
 Thr Pro Asn Glu Ile Lys Ala Ile Phe Thr Thr Leu Asp Gly Leu Asp
 325 330 335
 Glu Asp Ala Val Lys Gln Asn Ile Lys Ile Thr Asp Lys Ala Gly Lys
 340 345 350
 Thr Val Ala Ile Asp Glu Leu Thr Leu Asp Arg Asp Lys Ser Val Met
 355 360 365
 Thr Leu Lys Gly Asp Phe Lys Ala Gln Gly Ala Val Tyr Thr Val Thr
 370 375 380
 Phe Gly Glu Val Ser Gln Val Ala Arg Gln Ser Trp Gln Leu Lys Asp
 385 390 395 400
 Lys Leu Tyr Ala Tyr Asp Gly Glu Leu Gly Ala Thr Leu Ala Lys Asp
 405 410 415
 Gly Ser Val Asp Leu Ala Leu Trp Ser Pro Ser Ala Asp Thr Val Lys
 420 425 430
 Val Val Val Tyr Asp Lys Gln Asp Gln Thr Arg Val Val Gly Gln Ala
 435 440 445
 Asp Leu Thr Lys Ser Asp Lys Gly Val Trp Arg Ala His Leu Thr Ser
 450 455 460
 Asp Ser Val Lys Gly Ile Ser Asp Tyr Thr Gly Tyr Tyr Tyr Leu Tyr
 465 470 475 480
 Glu Ile Thr Arg Gly Gln Glu Lys Val Met Val Leu Asp Pro Tyr Ala
 485 490 495
 Lys Ser Leu Ala Ala Trp Asn Asp Ala Thr Ala Thr Asp Asp Ile Lys
 500 505 510
 Thr Ala Lys Ala Ala Phe Ile Asp Pro Ser Lys Leu Gly Pro Thr Gly
 515 520 525
 Leu Asp Phe Ala Lys Ile Asn Asn Phe Lys Lys Arg Glu Asp Ala Ile
 530 535 540
 Ile Tyr Glu Ala His Val Arg Asp Phe Thr Ser Asp Lys Ala Leu Glu
 545 550 555 560
 Gly Lys Leu Thr His Pro Phe Gly Thr Phe Ser Ala Phe Val Glu Gln
 565 570 575
 Leu Asp Tyr Leu Lys Asp Leu Gly Val Thr His Val Gln Leu Leu Pro
 580 585 590
 Val Leu Ser Tyr Phe Tyr Ala Asn Glu Leu Asp Lys Ser Arg Ser Thr
 595 600 605
 Ala Tyr Thr Ser Ser Asp Asn Asn Tyr Asn Trp Gly Tyr Asp Pro Gln
 610 615 620
 His Tyr Phe Ala Leu Ser Gly Met Tyr Ser Ala Asn Pro Asn Asp Pro
 625 630 635 640
 Ala Leu Arg Ile Ala Glu Leu Lys Asn Leu Val Asn Glu Ile His Lys
 645 650 655
 Arg Gly Met Gly Val Ile Phe Asp Val Val Tyr Asn His Thr Ala Arg
 660 665 670
 Thr Tyr Leu Phe Glu Asp Leu Glu Pro Asn Tyr Tyr His Phe Met Asn
 675 680 685
 Ala Asp Gly Thr Ala Arg Glu Ser Phe Gly Gly Gly Arg Leu Gly Thr
 690 695 700
 Thr His Ala Met Ser Arg Arg Ile Leu Val Asp Ser Ile Thr Tyr Leu
 705 710 715 720

【 0 2 1 0 】

Thr Arg Glu Phe Lys Val Asp Gly Phe Arg Phe Asp Met Met Gly Asp
 725 730 735
 His Asp Ala Ala Ala Ile Glu Gln Ala Phe Lys Ala Ala Lys Ala Ile
 740 745 750
 Asn Pro Asn Thr Ile Met Ile Gly Glu Gly Trp Arg Thr Tyr Gln Gly
 755 760 765
 Asp Glu Gly Lys Lys Glu Ile Ala Ala Asp Gln Asp Trp Met Lys Ala
 770 775 780
 Thr Asn Thr Val Gly Val Phe Ser Asp Asp Ile Arg Asn Thr Leu Lys
 785 790 795 800
 Ser Gly Phe Pro Asn Glu Gly Thr Ala Ala Phe Ile Thr Gly Gly Ala
 805 810 815
 Lys Asn Leu Glu Gly Leu Phe Lys Thr Ile Lys Ala Gln Pro Gly Asn
 820 825 830
 Phe Glu Ala Asp Ala Pro Gly Asp Val Val Gln Tyr Ile Ala Ala His
 835 840 845
 Asp Asn Leu Thr Leu His Asp Val Ile Ala Lys Ser Ile Asn Lys Asp
 850 855 860
 Pro Lys Val Ala Glu Glu Glu Ile His Lys Arg Ile Arg Leu Gly Asn
 865 870 875 880
 Thr Met Ile Leu Thr Ala Gln Gly Thr Ala Phe Ile His Ser Gly Gln
 885 890 895
 Glu Tyr Gly Arg Thr Lys Gln Leu Leu Asn Pro Asp Tyr Lys Thr Lys
 900 905 910
 Ala Ser Asp Asp Lys Val Pro Asn Lys Ala Thr Leu Ile Asp Ala Val
 915 920 925
 Ala Gln Tyr Pro Tyr Phe Ile His Asp Ser Tyr Asp Ser Ser Asp Ala
 930 935 940
 Val Asn His Phe Asp Trp Ala Lys Ala Thr Asp Ser Ile Ala His Pro
 945 950 955 960
 Ile Ser Asn Gln Thr Lys Ala Tyr Thr Gln Gly Leu Ile Ala Leu Arg
 965 970 975
 Arg Ser Thr Asp Ala Phe Thr Lys Ala Thr Lys Ala Glu Val Asp Arg
 980 985 990
 Asp Val Thr Leu Ile Thr Gln Ala Gly Gln Asp Gly Ile Gln Gln Glu
 995 1000 1005
 Asp Leu Ile Met Gly Tyr Gln Thr Val Ala Ser Asn Gly Asp Arg
 1010 1015 1020
 Tyr Ala Val Phe Val Asn Ala Asp Asn Lys Thr Arg Lys Val Val
 1025 1030 1035
 Leu Pro Gln Ala Tyr Arg Tyr Leu Leu Gly Ala Gln Val Leu Val
 1040 1045 1050
 Asp Ala Glu Gln Ala Gly Val Thr Ala Ile Ala Lys Pro Lys Gly
 1055 1060 1065
 Val Gln Phe Thr Lys Glu Gly Leu Thr Ile Glu Gly Leu Thr Ala
 1070 1075 1080
 Leu Val Leu Lys Val Ser Ser Lys Thr Ala Asn Pro Ser Gln Gln
 1085 1090 1095
 Lys Ser Gln Thr Asp Asn His Gln Thr Lys Thr Pro Asp Gly Ser
 1100 1105 1110
 Lys Asp Leu Asp Lys Ser Leu Met Thr Arg Pro Lys Arg Ala Lys
 1115 1120 1125
 Thr Asn Gln Lys Leu Pro Lys Thr Gly Glu Ala Ser Ser Lys Gly
 1130 1135 1140
 Leu Leu Ala Ala Gly Ile Ala Leu Leu Leu Leu Ala Ile Ser Leu
 1145 1150 1155
 Leu Met Lys Arg Gln Lys Asp
 1160 1165

<210> 229

<211> 440

<212> PRT

<213> Streptococcus pyogenes

<400> 229

Met Lys Asn Tyr Leu Ser Ile Gly Val Ile Ala Leu Leu Phe Ala Leu
 1 5 10 15
 Thr Phe Gly Thr Val Lys Ser Val Gln Ala Ile Ala Gly Tyr Gly Trp
 20 25 30
 Leu Pro Asp Arg Pro Pro Ile Asn Asn Ser Gln Leu Val Val Ser Met
 35 40 45
 Ala Gly Ile Val Glu Gly Thr Asp Lys Lys Val Phe Ile Asn Phe Phe
 50 55 60
 Glu Ile Asp Leu Thr Ser Gln Pro Ala His Gly Gly Lys Thr Glu Gln

【 0 2 1 1 】

65 Gly Leu Ser Pro Lys 70 Ser Lys Pro Phe Ala 75 Thr Asp Asn Gly Ala 80 Met
 85 Leu Glu Lys Ala Asp Leu 90 Leu Lys Ala Ile Gln 95 Lys Gln
 100 Leu Ile Ala Asn Val His Ser Asn 105 Asp Gly Tyr Phe Glu 110 Val Ile Asp
 115 Phe Ala Ser Asp Ala Thr Ile 120 Thr Asp Arg Asn Gly 125 Lys Val Tyr Phe
 130 Ala Asp Lys Asp Gly Ser Val Thr 135 Leu Pro Thr Gln Pro Val Gln Glu
 145 Phe Leu Leu Lys Gly His Val Arg Val 150 Arg Pro Tyr Lys Glu 160 Lys Pro
 165 Val Gln Asn Gln Ala Lys Ser Val Asp 170 Val Glu Tyr Thr Val Gln Phe
 180 Thr Pro Leu Asn Pro Asp Asp 185 Phe Arg Pro Gly Leu Lys Asp Thr
 195 Lys Leu Leu Lys Thr Leu Ala 200 Ile Gly Asp Thr Ile Thr Ser Gln Glu
 210 Leu Leu Ala Gln Ala Gln Ser 215 Ile Leu Asn Lys Thr His Pro Gly Tyr
 225 Thr Ile Tyr Glu Arg Asp Ser Ser 230 Ile Val Thr His Asp Asn Asp Ile
 245 Phe Arg Thr Ile Leu Pro Met Asp Gln Glu Phe Thr Tyr His Val Lys
 260 Asn Arg Glu Gln Ala Tyr Glu Ile 265 Asn Pro Lys Thr Gly Ile Lys Glu
 275 Lys Thr Asn Asn Thr Asp Leu Val 280 Ser Glu Lys Tyr Tyr Val Leu Lys
 290 Gln Gly Glu Lys Pro Tyr Asp Pro Phe Asp Arg Ser His Leu Lys Leu
 305 Phe Thr Ile Lys Tyr Val Asp Val Asn Thr 310 Asn Glu Leu Leu Lys Ser
 325 Glu Gln Leu Leu Thr Ala Ser Glu Arg Asn Leu Asp Phe Arg Asp Leu
 340 Tyr Asp Pro Arg Asp Lys Ala Lys 345 Leu Leu Tyr Asn Asn Leu Asp Ala
 355 Phe Asp Ile Met Asp Tyr Thr Leu Thr Gly Lys Val Glu Asp Asn His
 370 Asp Lys Asn Asn Arg Val Val Thr Val Tyr Met Gly Lys Arg Pro Lys
 385 Gly Ala Lys Gly Ser Tyr His Leu Ala Tyr Asp Lys Asp Leu Tyr Thr
 405 Glu Glu Glu Arg Lys Ala Tyr Ser Tyr 410 Leu Arg Asp Thr Gly Thr Pro
 420 Ile Pro Asp Asn Pro Lys Asp Lys 425 430 440

<210> 230

<211> 348

<212> PRT

<213> Streptococcus pyogenes

<400> 230

1 Met Leu Thr Ser Lys His His Asn Leu Asn Lys Leu Val Trp Arg Tyr
 5 Gly Leu Thr Ser Ala Ala Ala Val Leu 10 Leu Ala Phe Gly Gly Gly Ala
 20 Ser Ser Val Lys Ala Glu Val Ser 25 Thr Thr Met Thr Ser Ser Gln
 35 Arg Glu Ser Lys Ile Lys Glu Ile Glu Glu Ser Leu Lys Lys Tyr Pro
 50 Glu Val Ser Asn Glu Lys Phe Trp Glu Arg Lys 60 Trp Tyr Gly Thr Tyr
 65 Phe Lys Glu Glu Asp Phe Gln Lys Glu Leu Lys Asp Phe Thr Glu Lys
 85 Arg Leu Lys Glu Ile Leu Asp Leu Ile Gly Lys Ser Gly Ile Lys Gly
 100 Asp Arg Gly Glu Thr Gly Pro Ala Gly Pro Ala Gly Pro Gln Gly Lys
 115 Thr Gly Glu Arg Gly Ala Gln Gly Pro Lys Gly Asp Arg Gly Glu Gln
 130 Gly Ile Gln Gly Lys Ala Gly Glu Lys Gly Glu Arg Gly Glu Lys Gly
 145 150 155 160

【 0 2 1 2 】

Asp Lys Gly Glu Thr Gly Glu Arg Gly Glu Lys Gly Glu Ala Gly Ile
 165 170 175
 Gln Gly Pro Gln Gly Glu Ala Gly Lys Asp Gly Ala Pro Gly Lys Asp
 180 185 190
 Gly Ala Pro Gly Glu Lys Gly Glu Lys Gly Asp Arg Gly Glu Thr Gly
 195 200 205
 Ala Gln Gly Pro Val Gly Pro Gln Gly Glu Lys Gly Glu Thr Gly Ala
 210 215 220
 Gln Gly Pro Ala Gly Pro Gln Gly Glu Ala Gly Lys Pro Gly Glu Gln
 225 230 235 240
 Gly Pro Ala Gly Pro Gln Gly Glu Ala Gly Gln Pro Gly Glu Lys Ala
 245 250 255
 Pro Glu Lys Ser Pro Glu Gly Glu Ala Gly Gln Pro Gly Glu Lys Ala
 260 265 270
 Pro Glu Lys Ser Lys Glu Val Thr Pro Ala Ala Glu Lys Pro Ala Asp
 275 280 285
 Lys Glu Ala Asn Gln Thr Pro Glu Arg Arg Asn Gly Asn Met Ala Lys
 290 295 300
 Thr Pro Val Ala Asn Asn His Arg Arg Leu Pro Ala Thr Gly Glu Gln
 305 310 315 320
 Ala Asn Pro Phe Phe Thr Ala Ala Ala Val Ala Val Met Thr Thr Ala
 325 330 335
 Gly Val Leu Ala Val Thr Lys Arg Lys Glu Asn Asn
 340 345

<210> 231
 <211> 188
 <212> PRT
 <213> Streptococcus pyogenes

<400> 231
 Met Ile Leu Leu Ile Asp Asn Tyr Asp Ser Phe Thr Tyr Asn Leu Ala
 1 5 10 15
 Gln Tyr Leu Ser Glu Phe Asp Glu Thr Ile Val Leu Tyr Asn Gln Asp
 20 25 30
 Pro Asn Leu Tyr Asp Met Ala Lys Lys Ala Asn Ala Leu Val Leu Ser
 35 40 45
 Pro Gly Pro Gly Trp Pro Lys Glu Ala Asn Gln Met Pro Lys Leu Ile
 50 55 60
 Gln Asp Phe Tyr Gln Thr Lys Pro Ile Leu Gly Val Cys Leu Gly His
 65 70 75 80
 Gln Ala Ile Ala Glu Thr Leu Gly Gly Thr Leu Arg Leu Ala Lys Arg
 85 90 95
 Val Met His Gly Arg Gln Ser Thr Ile Glu Thr Gln Gly Pro Ala Ser
 100 105 110
 Leu Phe Arg Ser Leu Pro Gln Glu Ile Thr Val Met Arg Tyr His Ser
 115 120 125
 Ile Val Val Asp Gln Leu Pro Lys Gly Phe Ser Val Thr Ala Arg Asp
 130 135 140
 Cys Asp Asp Gln Glu Ile Met Ala Phe Glu His His Thr Leu Pro Leu
 145 150 155 160
 Phe Gly Leu Gln Phe His Pro Glu Ser Ile Gly Thr Pro Asp Gly Met
 165 170 175
 Thr Met Ile Ala Asn Phe Ile Ala Ala Ile Pro Arg
 180 185

<210> 232
 <211> 542
 <212> PRT
 <213> Streptococcus pyogenes

<400> 232
 Val Ser Lys Tyr Leu Lys Tyr Phe Ser Ile Ile Thr Leu Phe Leu Thr
 1 5 10 15
 Gly Leu Ile Leu Val Ala Cys Gln Gln Gln Lys Pro Gln Thr Lys Glu
 20 25 30
 Arg Gln Arg Lys Gln Arg Pro Lys Asp Glu Leu Val Val Ser Met Gly
 35 40 45
 Ala Lys Leu Pro His Glu Phe Asp Pro Lys Asp Arg Tyr Gly Val His
 50 55 60
 Asn Glu Gly Asn Ile Thr His Ser Thr Leu Leu Lys Arg Ser Pro Glu
 65 70 75 80
 Leu Asp Ile Lys Gly Glu Leu Ala Lys Thr Tyr His Leu Ser Glu Asp

【 0 2 1 3 】

【 0 2 1 4 】

Tyr Val Thr Ser His Gly Asp His Tyr His Phe Tyr Asn Gly Lys Val
 85 90 95
 Pro Tyr Asp Ala Ile Ile Ser Glu Glu Leu Leu Met Thr Asp Pro Asn
 100 105 110
 Tyr Arg Phe Lys Gln Ser Asp Val Ile Asn Glu Ile Leu Asp Gly Tyr
 115 120 125
 Val Ile Lys Val Asn Gly Asn Tyr Tyr Val Tyr Leu Lys Pro Gly Ser
 130 135 140
 Lys Arg Lys Asn Ile Arg Thr Lys Gln Gln Ile Ala Glu Gln Val Ala
 145 150 155 160
 Lys Gly Thr Lys Glu Ala Lys Glu Lys Gly Leu Ala Gln Val Ala His
 165 170 175
 Leu Ser Lys Glu Glu Val Ala Ala Val Asn Glu Ala Lys Arg Gln Gly
 180 185 190
 Arg Tyr Thr Thr Asp Asp Gly Tyr Ile Phe Ser Pro Thr Asp Ile Ile
 195 200 205
 Asp Asp Leu Gly Asp Ala Tyr Leu Val Pro His Gly Asn His Tyr His
 210 215 220
 Tyr Ile Pro Lys Lys Asp Leu Ser Pro Ser Glu Leu Ala Ala Ala Gln
 225 230 235 240
 Ala Tyr Trp Ser Gln Lys Gln Gly Arg Gly Ala Arg Pro Ser Asp Tyr
 245 250 255
 Arg Pro Thr Pro Ala Pro Ala Pro Gly Arg Arg Lys Ala Pro Ile Pro
 260 265 270
 Asp Val Thr Pro Asn Pro Gly Gln Gly His Gln Pro Asp Asn Gly Gly
 275 280 285
 Tyr His Pro Ala Pro Pro Arg Pro Asn Asp Ala Ser Gln Asn Lys His
 290 295 300
 Gln Arg Asp Glu Phe Lys Gly Lys Thr Phe Lys Glu Leu Leu Asp Gln
 305 310 315 320
 Leu His Arg Leu Asp Leu Lys Tyr Arg His Val Glu Glu Asp Gly Leu
 325 330 335
 Ile Phe Glu Pro Thr Gln Val Ile Lys Ser Asn Ala Phe Gly Tyr Val
 340 345 350
 Val Pro His Gly Asp His Tyr His Ile Ile Pro Arg Ser Gln Leu Ser
 355 360 365
 Pro Leu Glu Met Glu Leu Ala Asp Arg Tyr Leu Ala Gly Gln Thr Glu
 370 375 380
 Asp Asp Asp Ser Gly Ser Asp His Ser Lys Pro Ser Asp Lys Glu Val
 385 390 395 400
 Thr His Thr Phe Leu Gly His Arg Ile Lys Ala Tyr Gly Lys Gly Leu
 405 410 415
 Asp Gly Lys Pro Tyr Asp Thr Ser Asp Ala Tyr Val Phe Ser Lys Glu
 420 425 430
 Ser Ile His Ser Val Asp Lys Ser Gly Val Thr Ala Lys His Gly Asp
 435 440 445
 His Phe His Tyr Ile Gly Phe Gly Glu Leu Glu Gln Tyr Glu Leu Asp
 450 455 460
 Glu Val Ala Asn Trp Val Lys Ala Lys Gly Gln Ala Asp Glu Leu Ala
 465 470 475 480
 Ala Ala Leu Asp Gln Glu Gln Gly Lys Glu Lys Pro Leu Phe Asp Thr
 485 490 495
 Lys Lys Val Ser Arg Lys Val Thr Lys Asp Gly Lys Val Gly Tyr Met
 500 505 510
 Met Pro Lys Asp Gly Lys Asp Tyr Phe Tyr Ala Arg Asp Gln Leu Asp
 515 520 525
 Leu Thr Gln Ile Ala Phe Ala Glu Gln Glu Leu Met Leu Lys Asp Lys
 530 535 540
 Lys His Tyr Arg Tyr Asp Ile Val Asp Thr Gly Ile Glu Pro Arg Leu
 545 550 555 560
 Ala Val Asp Val Ser Ser Leu Pro Met His Ala Gly Asn Ala Thr Tyr
 565 570 575
 Asp Thr Gly Ser Ser Phe Val Ile Pro His Ile Asp His Ile His Val
 580 585 590
 Val Pro Tyr Ser Trp Leu Thr Arg Asp Gln Ile Ala Thr Ile Lys Tyr
 595 600 605
 Val Met Gln His Pro Glu Val Arg Pro Asp Ile Trp Ser Lys Pro Gly
 610 615 620
 His Glu Glu Ser Gly Ser Val Ile Pro Asn Val Thr Pro Leu Asp Lys
 625 630 635 640
 Arg Ala Gly Met Pro Asn Trp Gln Ile Ile His Ser Ala Glu Glu Val
 645 650 655
 Gln Lys Ala Leu Ala Glu Gly Arg Phe Ala Thr Pro Asp Gly Tyr Ile
 660 665 670
 Phe Asp Pro Arg Asp Val Leu Ala Lys Glu Thr Phe Val Trp Lys Asp

675 680 685
 Gly Ser Phe Ser Ile Pro Arg Ala Asp Gly Ser Ser Leu Arg Thr Ile
 690 695 700
 Asn Lys Ser Asp Leu Ser Gln Ala Glu Trp Gln Gln Ala Gln Glu Leu
 705 710 715 720
 Leu Ala Lys Lys Asn Ala Gly Asp Ala Thr Asp Thr Asp Lys Pro Lys
 725 730 735
 Glu Lys Gln Gln Ala Asp Lys Ser Asn Glu Asn Gln Gln Pro Ser Glu
 740 745 750
 Ala Ser Lys Glu Glu Glu Lys Glu Ser Asp Asp Phe Ile Asp Ser Leu
 755 760 765
 Pro Asp Tyr Gly Leu Asp Arg Ala Thr Leu Glu Asp His Ile Asn Gln
 770 775 780
 Leu Ala Gln Lys Ala Asn Ile Asp Pro Lys Tyr Leu Ile Phe Gln Pro
 785 790 795 800
 Glu Gly Val Gln Phe Tyr Asn Lys Asn Gly Glu Leu Val Thr Tyr Asp
 805 810 815
 Ile Lys Thr Leu Gln Gln Ile Asn Pro
 820 825

<210> 234

<211> 379

<212> PRT

<213> Streptococcus pyogenes

<400> 234

Met Arg Arg Ala Glu Asn Asn Lys His Ser Arg Tyr Ser Ile Arg Lys
 1 5 10 15
 Leu Ser Val Gly Val Thr Ser Ile Ala Ile Ala Ser Leu Phe Leu Gly
 20 25 30
 Lys Val Ala Tyr Ala Val Asp Gly Ile Pro Pro Ile Ser Leu Thr Gln
 35 40 45
 Lys Thr Thr Ala Thr Thr Ser Glu Asn Trp His His Ile Asp Lys Asp
 50 55 60
 Gly Leu Ile Pro Leu Gly Ile Ser Leu Glu Ala Ala Lys Glu Glu Phe
 65 70 75 80
 Lys Lys Glu Val Glu Glu Ser Arg Leu Ser Glu Ala Gln Lys Glu Thr
 85 90 95
 Tyr Lys Gln Lys Ile Lys Thr Ala Pro Asp Lys Asp Lys Leu Leu Phe
 100 105 110
 Thr Tyr His Ser Glu Tyr Met Thr Ala Val Lys Asp Leu Pro Ala Ser
 115 120 125
 Thr Glu Ser Thr Thr Gln Pro Val Glu Ala Pro Val Gln Glu Thr Gln
 130 135 140
 Ala Ser Ala Ser Asp Ser Met Val Thr Gly Asp Ser Thr Ser Val Thr
 145 150 155 160
 Thr Asp Ser Pro Glu Thr Pro Ser Ser Glu Ser Pro Val Ala Pro
 165 170 175
 Ala Leu Ser Glu Ala Pro Ala Gln Pro Ala Glu Ser Glu Glu Pro Ser
 180 185 190
 Val Ala Ala Ser Ser Glu Glu Thr Pro Ser Pro Ser Thr Pro Ala Ala
 195 200 205
 Pro Glu Thr Pro Glu Glu Pro Ala Ala Pro Ser Pro Ser Pro Glu Ser
 210 215 220
 Glu Glu Pro Ser Val Ala Ala Pro Ser Glu Glu Thr Pro Ser Pro Glu
 225 230 235 240
 Thr Pro Glu Glu Pro Ala Ala Pro Ser Gln Pro Ala Glu Ser Glu Glu
 245 250 255
 Ser Ser Val Ala Ala Thr Thr Ser Pro Ser Pro Ser Thr Pro Ala Glu
 260 265 270
 Ser Glu Thr Gln Thr Pro Pro Ala Val Thr Lys Asp Ser Asp Lys Pro
 275 280 285
 Ser Ser Ala Ala Glu Lys Pro Ala Ala Ser Ser Leu Val Ser Glu Gln
 290 295 300
 Thr Val Gln Gln Pro Thr Ser Lys Arg Ser Ser Asp Lys Lys Glu Glu
 305 310 315 320
 Gln Glu Gln Ser Tyr Ser Pro Asn Arg Ser Leu Ser Arg Gln Val Arg
 325 330 335
 Ala His Glu Ser Gly Lys Tyr Leu Pro Ser Thr Gly Glu Lys Ala Gln
 340 345 350
 Pro Leu Phe Ile Ala Thr Met Thr Leu Met Ser Leu Phe Gly Ser Leu
 355 360 365
 Leu Val Thr Lys Arg Gln Lys Glu Thr Lys Lys
 370 375

【 0 2 1 6 】

<210> 235
 <211> 1181
 <212> PRT
 <213> Streptococcus pyogenes

<400> 235

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Leu Arg Lys Lys Gln Lys Leu Pro Phe Asp Lys Leu Ala Ile Ala Leu
1      5      10      15
Met Ser Thr Ser Ile Leu Leu Asn Ala Gln Ser Asp Ile Lys Ala Asn
20      25      30
Thr Val Thr Glu Asp Thr Pro Ala Thr Glu Gln Ala Val Glu Thr Pro
35      40      45
Gln Pro Thr Ala Val Ser Glu Glu Ala Pro Ser Ser Lys Glu Thr Lys
50      55      60
Thr Pro Gln Thr Pro Asp Asp Ala Glu Glu Thr Ile Ala Asp Asp Ala
65      70      75      80
Asn Asp Leu Ala Pro Gln Ala Pro Ala Lys Thr Ala Asp Thr Pro Ala
85      90      95
Thr Ser Lys Ala Thr Ile Arg Asp Leu Asn Asp Pro Ser Gln Val Lys
100     105     110
Thr Leu Gln Glu Lys Ala Gly Lys Gly Ala Gly Thr Val Val Ala Val
115     120     125
Ile Asp Ala Gly Phe Asp Lys Asn His Glu Ala Trp Arg Leu Thr Asp
130     135     140
Lys Thr Lys Ala Arg Tyr Gln Ser Lys Glu Asp Leu Glu Lys Ala Lys
145     150     155     160
Lys Glu His Gly Ile Thr Tyr Gly Glu Trp Val Asn Asp Lys Val Ala
165     170     175
Tyr Tyr His Asp Tyr Ser Lys Asp Gly Lys Thr Ala Val Asp Gln Glu
180     185     190
His Gly Thr His Val Ser Gly Ile Leu Ser Gly Asn Ala Pro Ser Glu
195     200     205
Thr Lys Glu Pro Tyr Arg Leu Glu Gly Ala Met Pro Glu Ala Gln Leu
210     215     220
Leu Leu Met Arg Val Glu Ile Val Asn Gly Leu Ala Asp Tyr Ala Arg
225     230     235     240
Asn Tyr Ala Gln Ala Ile Ile Asp Ala Val Asn Leu Gly Ala Lys Val
245     250     255
Ile Asn Met Ser Phe Gly Asn Ala Ala Leu Ala Tyr Ala Asn Leu Pro
260     265     270
Asp Glu Thr Lys Lys Ala Phe Asp Tyr Ala Lys Ser Lys Gly Val Ser
275     280     285
Ile Val Thr Ser Ala Gly Asn Asp Ser Ser Phe Gly Gly Lys Thr Arg
290     295     300
Leu Pro Leu Ala Asp His Pro Asp Tyr Gly Val Val Gly Thr Pro Ala
305     310     315     320
Ala Ala Asp Ser Thr Leu Thr Val Ala Ser Tyr Ser Pro Asp Lys Gln
325     330     335
Leu Thr Glu Thr Ala Thr Val Lys Thr Ala Asp Gln Gln Asp Lys Glu
340     345     350
Met Pro Val Leu Ser Thr Asn Arg Phe Glu Pro Asn Lys Ala Tyr Asp
355     360     365
Tyr Ala Tyr Ala Asn Arg Gly Met Lys Glu Asp Asp Phe Lys Asp Val
370     375     380
Lys Gly Lys Ile Ala Leu Ile Glu Arg Gly Asp Ile Asp Phe Lys Asp
385     390     395     400
Lys Ile Ala Asn Ala Lys Lys Ala Gly Ala Val Gly Val Leu Ile Tyr
405     410     415
Asp Asn Gln Asp Lys Gly Phe Pro Ile Glu Leu Pro Asn Val Asp Gln
420     425     430
Met Pro Ala Ala Phe Ile Ser Arg Lys Asp Gly Leu Leu Leu Lys Glu
435     440     445
Asn Pro Gln Lys Thr Ile Thr Phe Asn Ala Thr Pro Lys Val Leu Pro
450     455     460
Thr Ala Ser Gly Thr Lys Leu Ser Arg Phe Ser Ser Trp Gly Leu Thr
465     470     475     480
Ala Asp Gly Asn Ile Lys Pro Asp Ile Ala Ala Pro Gly Gln Asp Ile
485     490     495
Leu Ser Ser Val Ala Asn Asn Lys Tyr Ala Lys Leu Ser Gly Thr Ser
500     505     510
Met Ser Ala Pro Leu Val Ala Gly Ile Met Gly Leu Leu Gln Lys Gln
515     520     525
Tyr Glu Thr Gln Tyr Pro Asp Met Thr Pro Ser Glu Arg Leu Asp Leu

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【 0 2 1 7 】

530 535 540
 Ala Lys Lys Val Leu Met Ser Ser Ala Thr Ala Leu Tyr Asp Glu Asp
 545 550 555 560
 Glu Lys Ala Tyr Phe Ser Pro Arg Gln Gln Gly Ala Gly Ala Val Asp
 565 570 575
 Ala Lys Lys Ala Ser Ala Ala Thr Met Tyr Val Thr Asp Lys Asp Asn
 580 585 590
 Thr Ser Ser Lys Val His Leu Asn Asn Val Ser Asp Lys Phe Glu Val
 595 600 605
 Thr Val Thr Val His Asn Lys Ser Asp Lys Pro Gln Glu Leu Tyr Tyr
 610 615 620
 Gln Ala Thr Val Gln Thr Asp Lys Val Asp Gly Lys Leu Phe Ala Leu
 625 630 635 640
 Ala Pro Lys Ala Leu Tyr Glu Thr Ser Trp Gln Lys Ile Thr Ile Pro
 645 650 655
 Ala Asn Ser Ser Lys Gln Val Thr Ile Pro Ile Asp Val Ser Gln Phe
 660 665 670
 Ser Lys Asp Leu Leu Ala Pro Met Lys Asn Gly Tyr Phe Leu Glu Gly
 675 680 685
 Phe Val Arg Phe Lys Gln Asp Pro Thr Lys Glu Glu Leu Met Ser Ile
 690 695 700
 Pro Tyr Ile Gly Phe Arg Gly Asp Phe Gly Asn Leu Ser Ala Leu Glu
 705 710 715 720
 Lys Pro Ile Tyr Asp Ser Lys Asp Gly Ser Tyr Tyr His Glu Ala
 725 730 735
 Asn Ser Asp Ala Lys Asp Gln Leu Asp Gly Asp Gly Leu Gln Phe Tyr
 740 745 750
 Ala Leu Lys Asn Asn Phe Thr Ala Leu Thr Thr Glu Ser Asn Pro Trp
 755 760 765
 Thr Ile Ile Lys Ala Val Lys Glu Gly Val Glu Asn Ile Glu Asp Ile
 770 775 780
 Glu Ser Ser Glu Ile Thr Glu Thr Ile Phe Ala Gly Thr Phe Ala Lys
 785 790 795 800
 Gln Asp Asp Asp Ser His Tyr Tyr Ile His Arg His Ala Asn Gly Lys
 805 810 815
 Pro Tyr Ala Ala Ile Ser Pro Asn Gly Asp Gly Asn Arg Asp Tyr Val
 820 825 830
 Gln Phe Gln Gly Thr Phe Leu Arg Asn Ala Lys Asn Leu Val Ala Glu
 835 840 845
 Val Leu Asp Lys Glu Gly Asn Val Val Trp Thr Ser Glu Val Thr Glu
 850 855 860
 Gln Val Val Lys Asn Tyr Asn Asn Asp Leu Ala Ser Thr Leu Gly Ser
 865 870 875 880
 Thr Arg Phe Glu Lys Thr Arg Trp Asp Gly Lys Asp Lys Asp Gly Lys
 885 890 895
 Val Val Ala Asn Gly Thr Tyr Thr Tyr Arg Val Arg Tyr Thr Pro Ile
 900 905 910
 Ser Ser Gly Ala Lys Glu Gln His Thr Asp Phe Asp Val Ile Val Asp
 915 920 925
 Asn Thr Thr Pro Glu Val Ala Thr Ser Ala Thr Phe Ser Thr Glu Asp
 930 935 940
 Arg Arg Leu Thr Leu Ala Ser Lys Pro Lys Thr Ser Gln Pro Val Tyr
 945 950 955 960
 Arg Glu Arg Ile Ala Tyr Thr Tyr Met Asp Glu Asp Leu Pro Thr Thr
 965 970 975
 Glu Tyr Ile Ser Pro Asn Glu Asp Gly Thr Phe Thr Leu Pro Glu Glu
 980 985 990
 Ala Glu Thr Met Glu Gly Ala Thr Val Pro Leu Lys Met Ser Asp Phe
 995 1000 1005
 Thr Tyr Val Val Glu Asp Met Ala Gly Asn Ile Thr Tyr Thr Pro
 1010 1015 1020
 Val Thr Lys Leu Leu Glu Gly His Ser Asn Lys Pro Glu Gln Asp
 1025 1030 1035
 Gly Ser Asp Gln Ala Pro Asp Lys Lys Pro Glu Thr Lys Pro Glu
 1040 1045 1050
 Gln Asp Gly Ser Gly Gln Ala Pro Asp Lys Lys Pro Glu Thr Lys
 1055 1060 1065
 Pro Glu Gln Asp Gly Ser Gly Gln Thr Pro Asp Lys Lys Pro Glu
 1070 1075 1080
 Thr Lys Pro Glu Gln Asp Gly Ser Gly Gln Thr Pro Asp Lys Lys
 1085 1090 1095
 Pro Glu Thr Lys Pro Glu Lys Asp Ser Ser Gly Gln Thr Pro Gly
 1100 1105 1110
 Lys Thr Pro Gln Lys Gly Gln Pro Ser Arg Thr Leu Glu Lys Arg
 1115 1120 1125

Ser Ser Lys Arg Ala Leu Ala Thr Lys Ala Ser Thr Lys Asp Gln
 1130 1135 1140
 Leu Pro Thr Thr Asn Asp Lys Asp Thr Asn Arg Leu His Leu Leu
 1145 1150 1155
 Lys Leu Val Met Thr Thr Phe Phe Leu Gly Leu Val Ala His Ile
 1160 1165 1170
 Phe Lys Thr Lys Arg Thr Glu Asp
 1175 1180

<210> 236
 <211> 308
 <212> PRT
 <213> Streptococcus pyogenes

<400> 236

Met Asn Ile Arg Asn Lys Ile Glu Asn Ser Lys Thr Leu Leu Phe Thr
 1 5 10 15
 Ser Leu Val Ala Val Ala Leu Leu Gly Ala Thr Gln Pro Val Ser Ala
 20 25 30
 Glu Thr Tyr Thr Ser Arg Asn Phe Asp Trp Ser Gly Asp Asp Trp Ser
 35 40 45
 Gly Asp Asp Trp Pro Glu Asp Asp Trp Ser Gly Asp Gly Leu Ser Lys
 50 55 60
 Tyr Asp Arg Ser Gly Val Gly Leu Ser Gln Tyr Gly Trp Ser Lys Tyr
 65 70 75 80
 Gly Trp Ser Ser Asp Lys Glu Glu Trp Pro Glu Asp Trp Pro Glu Asp
 85 90 95
 Asp Trp Ser Ser Asp Lys Lys Asp Glu Thr Glu Asp Lys Thr Arg Pro
 100 105 110
 Pro Tyr Gly Glu Ala Leu Gly Thr Gly Tyr Glu Lys Arg Asp Asp Trp
 115 120 125
 Gly Gly Pro Gly Thr Val Ala Thr Asp Pro Tyr Thr Pro Pro Tyr Gly
 130 135 140
 Gly Ala Leu Gly Thr Gly Tyr Glu Lys Arg Asp Asp Trp Gly Gly Pro
 145 150 155 160
 Gly Thr Val Ala Thr Asp Pro Tyr Thr Pro Tyr Gly Gly Ala Leu
 165 170 175
 Gly Thr Gly Tyr Glu Lys Arg Asp Asp Trp Arg Gly Pro Gly His Ile
 180 185 190
 Pro Lys Pro Glu Asn Glu Gln Ser Pro Asn Pro Leu His Ile Pro Glu
 195 200 205
 Pro Pro Gln Ile Glu Trp Pro Gln Trp Asn Gly Phe Asp Gly Leu Ser
 210 215 220
 Phe Gly Pro Ser Asp Trp Gly Gln Ser Glu Asp Thr Pro Pro Ser Glu
 225 230 235 240
 Pro Arg Val Pro Glu Lys Pro Gln His Thr Pro Gln Lys Asn Pro Gln
 245 250 255
 Glu Ser Asp Phe Asp Arg Gly Phe Ser Ala Gly Leu Lys Ala Lys Asn
 260 265 270
 Ser Gly Arg Gly Ile Asp Phe Glu Gly Phe Gln Tyr Gly Gly Trp Ser
 275 280 285
 Asp Glu Tyr Lys Lys Gly Tyr Met Gln Ala Phe Gly Thr Pro Tyr Thr
 290 295 300
 Pro Ser Ala Thr
 305

<210> 237
 <211> 484
 <212> PRT
 <213> Streptococcus pyogenes

<400> 237

Met Ala Lys Asn Asn Thr Asn Arg His Tyr Ser Leu Arg Lys Leu Lys
 1 5 10 15
 Thr Gly Thr Ala Ser Val Ala Val Ala Leu Thr Val Leu Gly Ala Gly
 20 25 30
 Phe Ala Asn Gln Thr Glu Val Lys Ala Asn Gly Asp Gly Asn Pro Arg
 35 40 45
 Glu Val Ile Glu Asp Leu Ala Ala Asn Asn Pro Ala Ile Gln Asn Ile
 50 55 60
 Arg Leu Arg Tyr Glu Asn Lys Asp Leu Lys Ala Arg Leu Glu Asn Ala
 65 70 75 80
 Met Glu Val Ala Gly Arg Asp Phe Lys Arg Ala Glu Glu Leu Glu Lys

【 0 2 1 9 】

85 90 95
 Ala Lys Gln Ala Leu Glu Asp Gln Arg Lys Asp Leu Glu Thr Lys Leu
 100 105 110
 Lys Glu Leu Gln Gln Asp Tyr Asp Leu Ala Lys Glu Ser Thr Ser Trp
 115 120 125
 Asp Arg Gln Arg Leu Glu Lys Glu Leu Glu Glu Lys Lys Glu Ala Leu
 130 135 140
 Glu Leu Ala Ile Asp Gln Ala Ser Arg Asp Tyr His Arg Ala Thr Ala
 145 150 155 160
 Leu Glu Lys Glu Leu Glu Lys Lys Lys Ala Leu Glu Leu Ala Ile
 165 170 175
 Asp Gln Ala Ser Gln Asp Tyr Asn Arg Ala Asn Val Leu Glu Lys Glu
 180 185 190
 Leu Glu Thr Ile Thr Arg Glu Gln Glu Ile Asn Arg Asn Leu Leu Gly
 195 200 205
 Asn Ala Lys Leu Glu Leu Asp Gln Leu Ser Ser Glu Lys Glu Gln Leu
 210 215 220
 Thr Ile Glu Lys Ala Lys Leu Glu Glu Glu Lys Gln Ile Ser Asp Ala
 225 230 235 240
 Ser Arg Gln Ser Leu Arg Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys
 245 250 255
 Lys Gln Val Glu Lys Asp Leu Ala Asn Leu Thr Ala Glu Leu Asp Lys
 260 265 270
 Val Lys Glu Asp Lys Gln Ile Ser Asp Ala Ser Arg Gln Gly Leu Arg
 275 280 285
 Arg Asp Leu Asp Ala Ser Arg Glu Ala Lys Lys Gln Val Glu Lys Asp
 290 295 300
 Leu Ala Asn Leu Thr Ala Glu Leu Asp Lys Val Lys Glu Glu Lys Gln
 305 310 315 320
 Ile Ser Asp Ala Ser Arg Gln Gly Leu Arg Arg Asp Leu Asp Ala Ser
 325 330 335
 Arg Glu Ala Lys Lys Gln Val Glu Lys Ala Leu Glu Glu Ala Asn Ser
 340 345 350
 Lys Leu Ala Ala Leu Glu Lys Leu Asn Lys Glu Leu Glu Glu Ser Lys
 355 360 365
 Lys Leu Thr Glu Lys Glu Lys Ala Glu Leu Gln Ala Lys Leu Glu Ala
 370 375 380
 Glu Ala Lys Ala Leu Lys Glu Gln Leu Ala Lys Gln Ala Glu Glu Leu
 385 390 395 400
 Ala Lys Leu Arg Ala Gly Lys Ala Ser Asp Ser Gln Thr Pro Asp Thr
 405 410 415
 Lys Pro Gly Asn Lys Ala Val Pro Gly Lys Gly Gln Ala Pro Gln Ala
 420 425 430
 Gly Thr Lys Pro Asn Gln Asn Lys Ala Pro Met Lys Glu Thr Lys Arg
 435 440 445
 Gln Leu Pro Ser Thr Gly Glu Thr Ala Asn Pro Phe Phe Thr Ala Ala
 450 455 460
 Ala Leu Thr Val Met Ala Thr Ala Gly Val Ala Ala Val Val Lys Arg
 465 470 475 480
 Lys Glu Glu Asn

<210> 238

<211> 541

<212> PRT

<213> Streptococcus pyogenes

<400> 238

Met Lys Lys Arg Lys Leu Leu Ala Val Thr Leu Leu Ser Thr Ile Leu
 1 5 10 15
 Leu Asn Ser Ala Val Pro Leu Val Val Ala Asp Thr Ser Leu Arg Asn
 20 25 30
 Ser Thr Ser Ser Thr Asp Gln Pro Thr Thr Ala Asp Thr Asp Thr Asp
 35 40 45
 Asp Glu Ser Glu Thr Pro Lys Lys Asp Lys Lys Ser Lys Glu Thr Ala
 50 55 60
 Ser Gln His Asp Thr Gln Lys Asp His Lys Pro Ser His Thr His Pro
 65 70 75 80
 Thr Pro Pro Ser Asn Asp Thr Lys Gln Thr Asp Gln Ala Ser Ser Glu
 85 90 95
 Ala Thr Asp Lys Pro Asn Lys Asp Lys Asn Asp Thr Lys Gln Pro Asp
 100 105 110
 Ser Ser Asp Gln Ser Thr Pro Ser Pro Lys Asp Gln Ser Ser Gln Lys
 115 120 125

【 0 2 2 0 】

Glu Ser Gln Asn Lys Asp Gly Arg Pro Thr Pro Ser Pro Asp Gln Gln
 130 135 140
 Lys Asp Gln Thr Pro Asp Lys Thr Pro Glu Lys Ser Ala Asp Lys Thr
 145 150 155 160
 Pro Glu Lys Gly Pro Glu Lys Ala Thr Asp Lys Thr Pro Glu Pro Asn
 165 170 175
 Arg Asp Ala Pro Lys Pro Ile Gln Pro Pro Leu Ala Ala Ala Pro Val
 180 185 190
 Phe Ile Pro Trp Arg Glu Ser Asp Lys Asp Leu Ser Lys Leu Lys Pro
 195 200 205
 Ser Ser Arg Ser Ser Ala Ala Tyr Val Arg His Trp Thr Gly Asp Ser
 210 215 220
 Ala Tyr Thr His Asn Leu Ser Arg Arg Tyr Gly Ile Thr Ala Glu
 225 230 235 240
 Gln Leu Asp Gly Phe Leu Asn Ser Leu Gly Ile His Tyr Asp Lys Glu
 245 250 255
 Arg Leu Asn Gly Lys Arg Leu Leu Glu Trp Glu Lys Leu Thr Gly Leu
 260 265 270
 Asp Val Arg Ala Ile Val Ala Ile Ala Met Ala Glu Ser Ser Leu Gly
 275 280 285
 Thr Gln Gly Val Ala Lys Glu Lys Gly Ala Asn Met Phe Gly Tyr Gly
 290 295 300
 Ala Phe Asp Phe Asn Pro Asn Asn Ala Lys Lys Tyr Ser Asp Glu Val
 305 310 315 320
 Ala Ile Arg His Met Val Glu Asp Thr Ile Ile Ala Asn Lys Asn Gln
 325 330 335
 Thr Phe Glu Arg Gln Asp Leu Lys Ala Lys Lys Trp Ser Leu Gly Gln
 340 345 350
 Leu Asp Thr Leu Ile Asp Gly Gly Val Tyr Phe Thr Asp Thr Ser Gly
 355 360 365
 Ser Gly Gln Arg Arg Ala Asp Ile Met Thr Lys Leu Asp Gln Trp Ile
 370 375 380
 Asp Asp His Gly Ser Thr Pro Glu Ile Pro Glu His Leu Lys Ile Thr
 385 390 395 400
 Ser Gly Thr Gln Phe Ser Glu Val Pro Val Gly Tyr Lys Arg Ser Gln
 405 410 415
 Pro Gln Asn Val Leu Thr Tyr Lys Ser Glu Thr Tyr Ser Phe Gly Gln
 420 425 430
 Cys Thr Trp Tyr Ala Tyr Asn Arg Val Lys Glu Leu Gly Tyr Gln Val
 435 440 445
 Asp Arg Tyr Met Gly Asn Gly Gly Asp Trp Gln Arg Lys Pro Gly Phe
 450 455 460
 Val Thr Thr His Lys Pro Lys Val Gly Tyr Val Val Ser Phe Ala Pro
 465 470 475 480
 Gly Gln Ala Gly Ala Asp Ala Thr Tyr Gly His Val Ala Val Val Glu
 485 490 495
 Gln Ile Lys Glu Asp Gly Ser Ile Leu Ile Ser Glu Ser Asn Val Met
 500 505 510
 Gly Leu Gly Thr Ile Ser Tyr Arg Thr Phe Thr Ala Glu Gln Ala Ser
 515 520 525
 Leu Leu Thr Tyr Val Val Gly Asp Lys Leu Pro Arg Pro
 530 535 540

<210> 239

<211> 398

<212> PRT

<213> Streptococcus pyogenes

<400> 239

Met Asn Lys Lys Lys Leu Gly Val Arg Leu Leu Ser Leu Leu Ala Leu
 1 5 10 15
 Gly Gly Phe Val Leu Ala Asn Pro Val Phe Ala Asp Gln Asn Phe Ala
 20 25 30
 Arg Asn Glu Lys Glu Ala Lys Asp Ser Ala Ile Thr Phe Ile Gln Lys
 35 40 45
 Ser Ala Ala Ile Lys Ala Gly Ala Arg Ser Ala Glu Asp Ile Lys Leu
 50 55 60
 Asp Lys Val Asn Leu Gly Gly Glu Leu Ser Gly Ser Asn Met Tyr Val
 65 70 75 80
 Tyr Asn Ile Ser Thr Gly Gly Phe Val Ile Val Ser Gly Asp Lys Arg
 85 90 95
 Ser Pro Glu Ile Leu Gly Tyr Ser Thr Ser Gly Ser Phe Asp Ala Asn
 100 105 110
 Gly Lys Glu Asn Ile Ala Ser Phe Met Glu Ser Tyr Val Glu Gln Ile

【 0 2 2 1 】

115 120 125
 Lys Glu Asn Lys Lys Leu Asp Thr Thr Tyr Ala Gly Thr Ala Glu Ile
 130 135 140
 Lys Gln Pro Val Val Lys Ser Leu Leu Asp Ser Lys Gly Ile His Tyr
 145 150 155 160
 Asn Gln Gly Asn Pro Tyr Asn Leu Leu Thr Pro Val Ile Glu Lys Val
 165 170 175
 Lys Pro Gly Glu Gln Ser Phe Val Gly Gln His Ala Ala Thr Gly Cys
 180 185 190
 Val Ala Thr Ala Thr Ala Gln Ile Met Lys Tyr His Asn Tyr Pro Asn
 195 200 205
 Lys Gly Leu Lys Asp Tyr Thr Tyr Thr Leu Ser Ser Asn Asn Pro Tyr
 210 215 220
 Phe Asn His Pro Lys Asn Leu Phe Ala Ala Ile Ser Thr Arg Gln Tyr
 225 230 235 240
 Asn Trp Asn Asn Ile Leu Pro Thr Tyr Ser Gly Arg Glu Ser Asn Val
 245 250 255
 Gln Lys Met Ala Ile Ser Glu Leu Met Ala Asp Val Gly Ile Ser Val
 260 265 270
 Asp Met Asp Tyr Gly Pro Ser Ser Gly Ser Ala Gly Ser Ser Arg Val
 275 280 285
 Gln Arg Ala Leu Lys Glu Asn Phe Gly Tyr Asn Gln Ser Val His Gln
 290 295 300
 Ile Asn Arg Gly Asp Phe Ser Lys Gln Asp Trp Glu Ala Gln Ile Asp
 305 310 315 320
 Lys Glu Leu Ser Gln Asn Gln Pro Val Tyr Tyr Gln Gly Val Gly Lys
 325 330 335
 Val Gly Gly His Ala Phe Val Ile Asp Gly Ala Asp Gly Arg Asn Phe
 340 345 350
 Tyr His Val Asn Trp Gly Trp Gly Gly Val Ser Asp Gly Phe Phe Arg
 355 360 365
 Leu Asp Ala Leu Asn Pro Ser Ala Leu Gly Thr Gly Gly Gly Ala Gly
 370 375 380
 Gly Phe Asn Gly Tyr Gln Ser Ala Val Val Gly Ile Lys Pro
 385 390 395

<210> 240

<211> 271

<212> PRT

<213> Streptococcus pyogenes

<400> 240

Met Asn Leu Leu Gly Ser Arg Arg Val Phe Ser Lys Lys Cys Arg Leu
 1 5 10 15
 Val Lys Phe Ser Met Val Ala Leu Val Ser Ala Thr Met Ala Val Thr
 20 25 30
 Thr Val Thr Leu Glu Asn Thr Ala Leu Ala Arg Gln Thr Gln Val Ser
 35 40 45
 Asn Asp Val Val Leu Asn Asp Gly Ala Ser Lys Tyr Leu Asn Glu Ala
 50 55 60
 Leu Ala Trp Thr Phe Asn Asp Ser Pro Asn Tyr Tyr Lys Thr Leu Gly
 65 70 75 80
 Thr Ser Gln Ile Thr Pro Ala Leu Phe Pro Lys Ala Gly Asp Ile Leu
 85 90 95
 Tyr Ser Lys Leu Asp Glu Leu Gly Arg Thr Arg Thr Ala Arg Gly Thr
 100 105 110
 Leu Thr Tyr Ala Asn Val Glu Gly Ser Tyr Gly Val Arg Gln Ser Phe
 115 120 125
 Gly Lys Asn Gln Asn Pro Ala Gly Trp Thr Gly Asn Pro Asn His Val
 130 135 140
 Lys Tyr Lys Ile Glu Trp Leu Asn Gly Leu Ser Tyr Val Gly Asp Phe
 145 150 155 160
 Trp Asn Arg Ser His Leu Ile Ala Asp Ser Leu Gly Gly Asp Ala Leu
 165 170 175
 Arg Val Asn Ala Val Thr Gly Thr Arg Thr Gln Asn Val Gly Gly Arg
 180 185 190
 Asp Gln Lys Gly Gly Met Arg Tyr Thr Glu Gln Arg Ala Gln Glu Trp
 195 200 205
 Leu Glu Ala Asn Arg Asp Gly Tyr Leu Tyr Tyr Glu Ala Ala Pro Ile
 210 215 220
 Tyr Asn Ala Asp Glu Leu Ile Pro Arg Ala Val Val Ser Met Gln
 225 230 235 240
 Ser Ser Asp Asn Thr Ile Asn Glu Lys Val Leu Val Tyr Asn Thr Ala
 245 250 255

【 0 2 2 2 】

Asn Gly Tyr Thr Ile Asn Tyr His Asn Gly Thr Pro Thr Gln Lys
 260 265 270

<210> 241
 <211> 778
 <212> PRT
 <213> Streptococcus pyogenes

<400> 241
 Met Arg Phe Leu Glu Leu Leu Gln Lys Lys Phe Phe Pro Lys Ala Tyr
 1 5 10 15
 Gln Glu Lys Gln Phe Leu Met His Gln Lys Thr Arg Leu Thr Pro Gln
 20 25 30
 His Asn Gln Lys Gln Tyr Ser Pro Asn Ala Asn His Leu Asp Ser Ser
 35 40 45
 Ala Thr Lys Asn Ser Glu Gln Asp Pro Ala Thr Ala Leu Gln Arg Ser
 50 55 60
 Arg Ala Tyr Glu Gly Ser Pro Lys Ser Arg Pro Ala Trp Leu Gln Lys
 65 70 75 80
 Leu Glu Ala Val Leu Pro Ser Pro Gln Arg Pro Ile Arg Arg Phe Trp
 85 90 95
 Arg Arg Tyr His Ile Gly Lys Leu Leu Met Ile Leu Ile Gly Thr Leu
 100 105 110
 Val Leu Leu Leu Gly Ser Tyr Leu Phe Tyr Leu Ser Lys Thr Ala Lys
 115 120 125
 Val Ser Asp Leu Gln Asp Ala Leu Lys Ala Thr Thr Val Ile Tyr Asp
 130 135 140
 His Lys Gly Glu Tyr Ala Gly Ser Leu Ser Gly Gln Lys Gly Ser Tyr
 145 150 155 160
 Val Glu Leu Asn Ala Ile Ser Asp Asp Leu Glu Asn Ala Val Ile Ala
 165 170 175
 Thr Glu Asp Arg Thr Phe Tyr Ser Asn Ser Gly Ile Asn Leu Lys Arg
 180 185 190
 Phe Leu Leu Ala Val Val Thr Ala Gly Arg Phe Gly Gly Gly Ser Thr
 195 200 205
 Ile Thr Gln Gln Leu Ala Lys Asn Ala Tyr Leu Ser Gln Asp Gln Thr
 210 215 220
 Ile Lys Arg Lys Ala Arg Glu Phe Phe Leu Ala Leu Glu Leu Thr Lys
 225 230 235 240
 Lys Tyr Ser Lys Lys Asp Ile Leu Thr Met Tyr Leu Asn Asn Ser Tyr
 245 250 255
 Phe Gly Asn Gly Val Trp Gly Val Glu Asp Ala Ser Gln Lys Tyr Phe
 260 265 270
 Gly Thr Thr Ala Ala Asn Leu Thr Leu Asp Glu Ala Ala Thr Leu Ala
 275 280 285
 Gly Met Leu Lys Gly Pro Glu Ile Tyr Asn Pro Tyr His Ser Leu Lys
 290 295 300
 Asn Ala Thr His Arg Arg Asp Thr Val Leu Gly Ala Met Val Asp Ala
 305 310 315 320
 Lys Lys Ile Thr Gln Thr Lys Ala Gln Gln Ala Arg Ala Val Gly Leu
 325 330 335
 Lys Asn Arg Leu Ala Asp Thr Tyr Val Gly Lys Thr Asp Asp Tyr Lys
 340 345 350
 Tyr Pro Ser Tyr Phe Asp Ala Val Ile Ser Glu Ala Ile Ala Thr Tyr
 355 360 365
 Gly Leu Ser Glu Lys Asp Ile Val Asn Asn Gly Tyr Lys Val Tyr Thr
 370 375 380
 Glu Leu Asp Gln Asn Tyr Gln Thr Gly Met Gln Thr Thr Phe Asn Asn
 385 390 395 400
 Asp Glu Leu Phe Pro Val Ser Ala Tyr Asp Gly Ser Ser Ala Gln Ala
 405 410 415
 Ala Ser Val Ala Leu Asp Pro Lys Thr Gly Gly Val Arg Gly Leu Ile
 420 425 430
 Gly Arg Val Asn Ser Ser Glu Asn Pro Thr Phe Arg Ser Phe Asn Tyr
 435 440 445
 Ala Thr Gln Ala Lys Arg Ser Pro Ala Ser Thr Ile Lys Pro Leu Val
 450 455 460
 Val Tyr Ala Pro Ala Val Ala Ser Gly Trp Ser Ile Glu Lys Glu Leu
 465 470 475 480
 Pro Asn Thr Val Gln Asp Phe Asp Gly Tyr Gln Pro His Asn Tyr Gly
 485 490 495
 Asn Tyr Glu Ser Glu Asp Val Pro Met Tyr Gln Ala Leu Ala Asn Ser
 500 505 510
 Tyr Asn Ile Pro Ala Val Ser Thr Leu Asn Asp Ile Gly Ile Asp Lys

【 0 2 2 3 】

515 520 525
 Ala Phe Thr Tyr Gly Lys Thr Phe Gly Leu Asp Met Ser Ser Ala Lys
 530 535 540
 Lys Glu Leu Gly Val Ala Leu Gly Gly Ser Val Thr Thr Asn Pro Leu
 545 550 555
 Glu Met Ala Gln Ala Tyr Ala Ala Phe Ala Asn Asn Gly Val Ile His
 565 570 575
 Pro Ala His Leu Ile Asn Arg Ile Glu Asn Ala Arg Gly Glu Val Leu
 580 585 590
 Lys Thr Phe Thr Asp Lys Ala Lys Arg Val Val Ser Gln Ser Val Ala
 595 600 605
 Asp Lys Met Thr Ala Met Met Leu Gly Thr Phe Ser Asn Gly Thr Ala
 610 615 620
 Val Asn Ala Asn Val Tyr Gly Tyr Thr Leu Ala Gly Lys Thr Gly Thr
 625 630 635
 Thr Glu Thr Asn Phe Asn Pro Asp Leu Ala Gly Asp Gln Trp Val Ile
 645 650 655
 Gly Tyr Thr Pro Asp Val Val Ile Ser Gln Trp Val Gly Phe Asn Gln
 660 665 670
 Thr Asp Glu Asn His Tyr Leu Thr Asp Ser Ser Ala Gly Thr Ala Ser
 675 680 685
 Ala Ile Phe Ser Thr Gln Ala Ser Tyr Ile Leu Pro Tyr Thr Lys Gly
 690 695 700
 Ser Gln Phe His Val Asp Asn Ala Tyr Ala Gln Asn Gly Ile Ser Ala
 705 710 715
 Val Tyr Gly Val Asn Glu Thr Gly Asn Gln Ser Gly Val Asp Thr Gln
 725 730 735
 Ser Ile Ile Asp Gly Leu Arg Lys Ser Ala Gln Glu Ala Ser Gln Ser
 740 745 750
 Leu Ser Lys Ala Val Asp Gln Ser Gly Leu Arg Asp Lys Ala Gln Ser
 755 760 765
 Ile Trp Lys Glu Ile Val Asp Tyr Phe Arg
 770 775

<210> 242

<211> 732

<212> PRT

<213> Streptococcus pyogenes

<400> 242

Met Val Ser Leu Glu Glu Asp Lys Val Thr Val Gln Pro Asp Ile Lys
 1 5 10 15
 Val Ile Lys Arg Asp Gly Arg Leu Val Asn Phe Asp Ser Thr Lys Ile
 20 25 30
 Tyr Ser Ala Leu Leu Lys Ala Ser Met Lys Val Thr Arg Met Ser Pro
 35 40 45
 Leu Val Glu Ala Lys Leu Glu Ala Ile Ser Asp Arg Ile Ile Ala Glu
 50 55 60
 Ile Ile Glu Arg Phe Pro Thr Asn Ile Lys Ile Tyr Glu Ile Gln Asn
 65 70 75 80
 Ile Val Glu His Lys Leu Leu Ala Ala Asn Glu Tyr Ala Ile Ala Lys
 85 90 95
 Glu Tyr Ile Asn Tyr Arg Thr Gln Arg Asp Phe Ala Arg Ser Gln Ala
 100 105 110
 Thr Asp Ile Asn Phe Ser Ile Asp Lys Leu Ile Asn Lys Asp Gln Thr
 115 120 125
 Val Val Asn Glu Asn Ala Asn Lys Asp Ser Asp Val Phe Asn Thr Gln
 130 135 140
 Arg Asp Leu Thr Ala Gly Ile Val Gly Lys Ser Ile Gly Leu Lys Met
 145 150 155 160
 Leu Pro Ser His Val Ala Asn Ala His Gln Lys Gly Asp Ile His Tyr
 165 170 175
 His Asp Leu Asp Tyr Ser Pro Tyr Thr Pro Met Thr Asn Cys Cys Leu
 180 185 190
 Ile Asp Phe Lys Gly Met Leu Ala Asn Gly Phe Lys Ile Gly Asn Ala
 195 200 205
 Glu Val Glu Ser Pro Lys Ser Ile Gln Thr Ala Thr Ala Gln Ile Ser
 210 215 220
 Gln Ile Ile Ala Asn Val Ala Ser Ser Gln Tyr Gly Gly Cys Thr Ala
 225 230 235 240
 Asp Arg Ile Asp Glu Phe Leu Ala Pro Tyr Ala Glu Leu Asn Phe Lys
 245 250 255
 Lys His Met Ala Asp Ala Lys Lys Trp Ile Val Glu Thr Lys Arg Glu
 260 265 270

【 0 2 2 4 】

Ser Tyr Ala Phe Glu Lys Thr Gln Lys Asp Ile Tyr Asp Ala Met Gln
 275 280 285
 Ser Leu Glu Tyr Glu Ile Asn Thr Leu Phe Thr Ser Asn Gly Gln Thr
 290 295 300
 Pro Phe Thr Ser Leu Gly Phe Gly Leu Gly Thr Ser Trp Phe Glu Arg
 305 310 315 320
 Glu Ile Gln Lys Ala Ile Leu Thr Ile Arg Ile Asn Gly Leu Gly Ser
 325 330 335
 Glu His Arg Thr Ala Ile Phe Pro Lys Leu Ile Phe Thr Val Lys Arg
 340 345 350
 Gly Leu Asn Leu Glu Pro Asp Ser Pro Asn Tyr Asp Ile Lys Thr Leu
 355 360 365
 Ala Leu Glu Cys Ala Thr Lys Arg Met Tyr Pro Asp Met Leu Ser Tyr
 370 375 380
 Asp Lys Ile Ile Asp Leu Thr Gly Ser Phe Lys Ser Pro Met Gly Cys
 385 390 395 400
 Arg Ser Phe Leu Gln Gly Trp Lys Asp Glu Asn Gly Gln Asp Val Thr
 405 410 415
 Ser Gly Arg Met Asn Leu Gly Val Val Thr Leu Asn Leu Pro Arg Ile
 420 425 430
 Ala Met Glu Ser Asn Gly Asp Met Asp Lys Phe Trp Glu Leu Phe Asn
 435 440 445
 Glu Arg Met Leu Ile Ser Lys Asp Ala Leu Ile Tyr Arg Val Glu Arg
 450 455 460
 Val Thr Glu Ala Lys Pro Ala Asn Ala Pro Ile Leu Tyr Gln Tyr Gly
 465 470 475 480
 Ala Phe Gly Lys Arg Leu Glu Lys Thr Gly Asn Val Asn Asp Leu Phe
 485 490 495
 Lys Asn Arg Arg Ala Thr Val Ser Leu Gly Tyr Ile Gly Leu Tyr Glu
 500 505 510
 Val Ala Ser Val Phe Tyr Gly Gly Gln Trp Glu Gly Asn Pro Asp Ala
 515 520 525
 Lys Ala Phe Thr Leu Ser Ile Val Lys Ala Met Lys Gln Ala Cys Glu
 530 535 540
 Asp Trp Ser Asp Glu Tyr Gly Tyr His Phe Ser Val Tyr Ser Thr Pro
 545 550 555 560
 Ser Glu Ser Leu Thr Asp Arg Phe Cys Arg Leu Asp Thr Glu Lys Phe
 565 570 575
 Gly Ile Val Thr Asp Ile Thr Asp Lys Glu Tyr Tyr Thr Asn Ser Phe
 580 585 590
 His Tyr Asp Val Arg Lys Ser Pro Thr Pro Phe Glu Lys Leu Asp Phe
 595 600 605
 Glu Lys Asp Tyr Pro Glu Ala Gly Ala Ser Gly Gly Phe Ile His Tyr
 610 615 620
 Cys Glu Tyr Pro Val Leu Gln Gln Asn Pro Lys Ala Leu Glu Ala Val
 625 630 635 640
 Trp Asp Tyr Ala Tyr Asp Arg Val Gly Tyr Leu Gly Thr Asn Thr Pro
 645 650 655
 Ile Asp Lys Cys Tyr Asn Cys Gln Phe Glu Gly Asp Phe Thr Pro Thr
 660 665 670
 Glu Arg Gly Phe Thr Cys Pro Asn Cys Gly Asn Asn Asp Pro Lys Thr
 675 680 685
 Val Asp Val Val Lys Arg Thr Cys Gly Tyr Leu Gly Asn Pro Gln Ala
 690 695 700
 Arg Pro Met Val Asn Gly Arg His Lys Glu Ile Ser Ala Arg Val Lys
 705 710 715 720
 His Met Asn Gly Ser Thr Ile Lys Tyr Pro Gly Leu
 725 730

<210> 243

<211> 255

<212> PRT

<213> Streptococcus pyogenes

<400> 243

Met Arg Arg Asn Tyr Ser Arg Val Ile Asp Glu Leu Arg Thr Asp Tyr
 1 5 10 15
 Gly Leu Asn Leu Val Ala Ile Gly Gln Arg Leu Gly Thr Asp Pro Arg
 20 25 30
 Thr Val Gly Lys Trp Trp Gln Gly Lys His Asn Pro Asn Gln Glu Ser
 35 40 45
 Arg Lys Lys Leu Asn Arg Leu Tyr Arg Glu Val Lys Glu Thr Met Met
 50 55 60
 Thr Gln Val Asn Ile Phe Glu Glu Ala Asn Asp Asn Thr Lys Gln Val

【 0 2 2 5 】


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65      70      75      80
Met Gln Val Ile Thr Thr Asn Phe His Gly Gln Pro Leu Asp Ile
      85      90      95
Tyr Gly Asp Ile Gln Glu Pro Leu Phe Leu Ala Arg Ala Val Ala Glu
      100     105     110
Met Ile Asp Tyr Thr Lys Thr Ser Gln Gly Tyr Tyr Asp Val Gln Ala
      115     120     125
Met Leu Arg Lys Val Asp Glu Asp Glu Lys Leu Lys Gly Met Ala Leu
      130     135     140
Glu Gly Thr Thr Lys Asn Phe Arg Ser Gly Gln Lys Val Trp Phe Leu
      145     150     155     160
Thr Glu His Gly Leu Tyr Glu Val Leu Met Arg Ser Asn Lys Pro Lys
      165     170     175
Ala Lys Glu Phe Arg Lys Ala Val Lys Asn Ile Leu Lys Glu Ile Arg
      180     185     190
Leu Asn Gly Tyr Tyr Met Gln Gly Glu Leu Val Gln Glu Leu Ala Gln
      195     200     205
Pro Ser Thr Gln Lys Leu Pro Gly Ile Ser Asp Leu Thr Tyr Ile Leu
      210     215     220
Asn Lys Leu Ala Asp Leu Val Asp Met Asp Asn Leu Ala Asp Ile Ser
      225     230     235     240
Asn Gly Ile Asp Arg Val Gln Gln Leu Val Lys Leu Ile Ser Leu
      245     250     255

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<210> 244
 <211> 204
 <212> PRT
 <213> Streptococcus pyogenes

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<400> 244
Met Phe Lys Lys Glu Asn Leu Lys Gln Arg Tyr Phe Asn Phe Gly Leu
1      5      10      15
Val Ala Leu Ala Leu Thr Ile Leu Ala Ile Ile Phe Ala Phe Ser Ser
      20      25      30
Lys Asn Ala Asp Thr Lys Ser Tyr Ala Lys Lys Ser Glu Ser Lys Met
      35      40      45
Val Thr Ile Asp Lys Ala Pro Lys Asn Asn His Ala Ile Thr Lys Glu
      50      55      60
Glu Ser Lys Glu Lys Ala Lys Ser Ile Ala Ser Glu Pro Ile Pro Thr
      65      70      75      80
Val Glu Asn Ser Val Ala Pro Thr Val Thr Glu Glu Val Pro Val Val
      85      90      95
Gln Gln Glu Val Thr Gln Thr Val Gln Gln Val Ser Ser Val Ala Tyr
      100     105     110
Asn Pro Asn Asn Val Val Leu Ser Asn Gly Asn Thr Ala Gly Ile Val
      115     120     125
Gly Ser Gln Ala Ala Ala Gln Met Ala Ala Ala Thr Gly Val Pro Gln
      130     135     140
Ser Thr Trp Glu His Ile Ile Ala Arg Glu Ser Asn Gly Asn Pro Asn
      145     150     155     160
Ala Ala Asn Ala Ser Gly Ala Ser Gly Leu Phe Gln Thr Met Pro Gly
      165     170     175
Trp Gly Ser Thr Ala Thr Val Glu Asp Gln Val Asn Ala Ala Leu Lys
      180     185     190
Ala Tyr Ser Ala Gln Gly Leu Ser Ala Trp Gly Tyr
      195     200

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<210> 245
 <211> 858
 <212> PRT
 <213> Streptococcus pyogenes

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<400> 245
Met Lys Asn Asn Asn Lys Trp Ile Ile Ala Gly Leu Ala Ser Phe Leu
1      5      10      15
Phe Pro Leu Ser Ile Ile Phe Ile Ile Leu Leu Ser Met Gly Ile Tyr
      20      25      30
Tyr Asn Ser Asp Lys Thr Ile Leu Ala Ser Asp Ala Phe His Gln Tyr
      35      40      45
Val Ile Phe Ala Gln Asn Phe Arg Asn Ile Met His Gly Ser Asp Ser
      50      55      60
Phe Phe Tyr Thr Phe Thr Ser Gly Leu Gly Ile Asn Phe Tyr Ala Leu
      65      70      75      80

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Met Cys Tyr Tyr Leu Gly Ser Phe Phe Ser Pro Leu Leu Phe Phe Phe
 85 90 95
 Asn Leu Thr Ser Met Pro Asp Ala Ile Tyr Leu Phe Thr Leu Ile Lys
 100 105 110
 Phe Gly Leu Ile Gly Leu Ala Ala Cys Tyr Ser Phe His Arg Leu Tyr
 115 120 125
 Pro Lys Ile Ser Ala Phe Leu Met Ile Ser Ile Ser Val Phe Tyr Ser
 130 135 140
 Leu Met Ser Phe Leu Thr Ser Gln Met Glu Leu Asn Ser Trp Leu Asp
 145 150 155 160
 Val Phe Ile Leu Leu Pro Leu Val Ile Leu Gly Leu Asn Lys Leu Ile
 165 170 175
 Thr Glu Asn Lys Thr Arg Thr Tyr Tyr Ser Ile Ser Leu Leu Phe
 180 185 190
 Ile Gln Asn Tyr Tyr Phe Gly Tyr Met Ile Ala Leu Phe Cys Ile Leu
 195 200 205
 Tyr Ala Leu Val Cys Leu Leu Arg Leu Asn Asp Phe Asn Lys Met Phe
 210 215 220
 Ile Ala Phe Val Arg Phe Thr Ala Val Ser Ile Cys Ala Ala Leu Thr
 225 230 235 240
 Ser Ala Leu Val Ile Leu Pro Thr Tyr Leu Asp Leu Ser Thr Tyr Gly
 245 250 255
 Glu Asn Leu Ser Pro Ile Lys Gln Leu Val Thr Asn Asn Ala Trp Phe
 260 265 270
 Leu Asp Ile Pro Ala Lys Leu Ser Ile Gly Val Tyr Asp Thr Thr Lys
 275 280 285
 Phe Asn Ala Leu Pro Met Ile Tyr Val Gly Leu Phe Pro Leu Met Leu
 290 295 300
 Ser Val Ile Tyr Phe Thr Leu Glu Ser Ile Pro Leu Lys Ile Lys Leu
 305 310 315 320
 Ala Asn Ala Cys Leu Leu Thr Phe Ile Ile Ile Ser Phe Tyr Leu Gln
 325 330 335
 Pro Leu Asp Leu Phe Trp Gln Gly Met His Ser Pro Asn Met Phe Leu
 340 345 350
 His Arg Tyr Ala Trp Ser Phe Ser Ile Val Ile Leu Leu Ala Cys
 355 360 365
 Glu Thr Leu Ser Arg Leu Lys Glu Val Thr Gln Ile Lys Ala Gly Phe
 370 375 380
 Ala Phe Ile Phe Leu Ile Ile Leu Thr Ser Leu Pro Tyr Ser Phe Ser
 385 390 395 400
 Gln Gln Tyr Asn Phe Leu Pro Leu Thr Leu Phe Leu Leu Ser Val Phe
 405 410 415
 Leu Leu Leu Gly Tyr Thr Ile Ser Leu Phe Ser Phe Arg Asn Ser Gln
 420 425 430
 Ile Pro Ser Thr Phe Ile Ser Ala Phe Ile Leu Ile Phe Ser Leu Leu
 435 440 445
 Glu Ser Gly Leu Asn Thr Tyr Tyr Gln Leu Gln Gly Ile Asn Lys Glu
 450 455 460
 Trp Gly Phe Pro Ser Arg Gln Ile Tyr Asn Ser Gln Leu Lys Asp Ile
 465 470 475 480
 Asn Asn Leu Val Asn Ser Val Ser Lys Asn Ser Gln Pro Phe Phe Arg
 485 490 495
 Met Glu Arg Leu Leu Pro Gln Thr Gly Asn Asp Ser Met Lys Phe Asn
 500 505 510
 Tyr Tyr Gly Ile Ser Gln Phe Ser Val Arg Asn Arg Leu Ser Ser
 515 520 525
 Ser Leu Leu Asp Arg Leu Gly Phe Gln Ser Lys Gly Thr Asn Leu Asn
 530 535 540
 Leu Arg Tyr Gln Asn Asn Thr Ile Ile Met Asp Ser Leu Leu Gly Ile
 545 550 555 560
 Lys Tyr Asn Leu Ser Glu Gly Pro Pro Asn Lys Phe Gly Phe Thr Lys
 565 570 575
 Leu Lys Thr Ser Gly Asn Thr Thr Leu Tyr Gln Asn His Tyr Ser Ser
 580 585 590
 Pro Leu Ala Ile Leu Thr Arg Asn Val Tyr Lys Asp Val Asn Leu Asn
 595 600 605
 Val Asn Thr Leu Asp Asn Gln Thr Lys Leu Leu Asn Gln Leu Ser Gly
 610 615 620
 Lys Ser Leu Thr Tyr Phe Asn Leu Gln Pro Ala Gln Leu Ile Ser Gly
 625 630 635 640
 Ala Asn Gln Phe Asn Gly Gln Ile Ser Ala Gln Ala Ser Asp Tyr Gln
 645 650 655
 Asn Ser Val Thr Leu Asn Tyr Gln Ile Asn Ile Pro Lys His Ser Gln
 660 665 670
 Leu Tyr Val Ser Ile Pro Asn Ile Ile Phe Ser Asn Pro Asp Ala Lys

【 0 2 2 7 】

675 680 685
 Glu Met Arg Ile Gln Thr Asp Asn His Asn Phe Ile Tyr Thr Thr Asp
 690 695 700
 Asn Ala Tyr Ser Phe Phe Asp Leu Gly Tyr Phe Ala Asp Ala Lys Val
 705 710 715 720
 Ala Thr Phe Ser Phe Val Phe Pro Lys Asn Lys Gln Ile Ser Phe Lys
 725 730 735
 Glu Pro His Phe Tyr Ser Leu Ser Ile Glu Ser Tyr Leu Glu Ala Met
 740 745 750
 Asn Ser Ile Lys Gln Lys Asn Val His Thr Tyr Ala Lys Ser Asn Thr
 755 760 765
 Val Ile Thr Asp Tyr Asn Ser Lys Thr Lys Gly Ser Leu Ile Phe Thr
 770 775 780
 Leu Pro Tyr Asp Lys Gly Trp Ser Ala Gln Lys Asp Gly Lys Asn Leu
 785 790 795 800
 Pro Val Lys Lys Ala Gln Gly Gly Phe Leu Ser Val Thr Ile Pro Lys
 805 810 815
 Gly Lys Gly Arg Val Ile Leu Thr Phe Ile Pro Asn Gly Phe Lys Leu
 820 825 830
 Gly Leu Ser Leu Ser Cys Val Gly Ile Ile Ala Tyr Met Leu Leu Tyr
 835 840 845
 Lys Tyr Ile Asp Ile Lys Ser Lys Leu Leu
 850 855

<210> 246
 <211> 44
 <212> PRT
 <213> Streptococcus pyogenes

<400> 246
 Phe Ser Arg Phe Leu Pro Thr Arg Arg Asp Tyr Ser Ser Leu Trp Ser
 1 5 10 15
 Ala Ser Cys Arg Asn Glu His Tyr Asn Ser Gln His His His Gly Val
 20 25 30
 Gly Thr Val Ser Ser Lys Gln Asn Pro Arg Pro Leu
 35 40

<210> 247
 <211> 12
 <212> PRT
 <213> Streptococcus pyogenes

<400> 247
 Ser Phe Ile Trp Glu Lys Arg Asn Pro Glu Gly Ser
 1 5 10

<210> 248
 <211> 47
 <212> PRT
 <213> Streptococcus pyogenes

<400> 248
 Lys Gly Glu Glu Lys Thr Glu Val Thr Lys Glu Lys Leu Leu Glu Leu
 1 5 10 15
 Ala Arg Trp Ile Lys Asp Ile Ser Asp Asp Thr Asp Glu Lys Thr Glu
 20 25 30
 Asp Glu Ala Tyr Tyr Asp Gly Asp Gly Thr Glu Glu Thr Thr Val
 35 40 45

<210> 249
 <211> 32
 <212> PRT
 <213> Streptococcus pyogenes

<400> 249
 Leu Tyr Gln Lys Lys Arg Leu Lys Lys Ser Gln Arg Leu Ser Lys Leu
 1 5 10 15
 Met Thr Ser Arg Leu Leu Asn Lys Ala Leu Met Thr Ser Lys Ile Glu
 20 25 30

【 0 2 2 8 】

<210> 250
 <211> 10
 <212> PRT
 <213> Streptococcus pyogenes

<400> 250
 Phe Val Leu Gln Lys Tyr Ser Leu Trp Gln
 1 5 10

<210> 251
 <211> 57
 <212> PRT
 <213> Streptococcus pyogenes

<400> 251
 Pro Ile Ser Met Gln Lys Ala Ile Gln Val Ile Ala Ile Met Val Glu
 1 5 10 15
 Gln Asn Val Trp Ile Leu Ser Lys Arg Leu Leu Leu Asn Val Leu Arg
 20 25 30
 Asn Phe Ser Val Pro His Leu Pro Met Phe Lys Pro Ile Pro Glu Val
 35 40 45
 Lys Pro Met Gln Gln Leu Ile Trp Pro
 50 55

<210> 252
 <211> 35
 <212> PRT
 <213> Streptococcus pyogenes

<400> 252
 Phe Arg Asn Ile Phe Cys Asp Phe Ser Cys Cys Ser Ser Phe Val Ser
 1 5 10 15
 Cys Tyr Gln Lys Leu Lys Arg Lys Gly Tyr Asn Arg Thr Ser Lys Lys
 20 25 30
 Arg Phe Leu
 35

<210> 253
 <211> 11
 <212> PRT
 <213> Streptococcus pyogenes

<400> 253
 Trp Val Thr Gly Cys Lys Trp Trp Phe Phe Cys
 1 5 10

<210> 254
 <211> 48
 <212> PRT
 <213> Streptococcus pyogenes

<400> 254
 Leu Met Leu Lys Ala Lys Lys Thr Asn Ser Lys Leu Val Thr Leu Ser
 1 5 10 15
 Gln Pro Thr Lys Lys Phe Asn Leu Gln Lys Leu Phe Asn Gln Thr Asn
 20 25 30
 Leu Leu Lys Pro Leu Ser Leu Trp Val Leu Leu Gln Thr Thr Leu Ser
 35 40 45

<210> 255
 <211> 35
 <212> PRT
 <213> Streptococcus pyogenes

<400> 255
 Pro Arg Asn Gly Trp Gly Arg Phe Glu Arg Tyr Glu Arg Leu Gly Arg
 1 5 10 15
 Thr Arg His Asp His Val Asn Cys Tyr Ser Arg Asn Gly Ile Cys Ser
 20 25 30
 Pro Ser Ser

【 0 2 2 9 】

35

<210> 256
 <211> 35
 <212> PRT
 <213> Streptococcus pyogenes

<400> 256
 Leu Met Asn Cys Pro Ser Leu His Phe Leu Gln Pro Lys His Lys Glu
 1 5 10 15
 Gln Pro Val Leu Lys Met Leu Lys Asn Tyr Glu Ser Lys Lys Gln Ile
 20 25 30
 Val Phe Lys
 35

<210> 257
 <211> 84
 <212> PRT
 <213> Streptococcus pyogenes

<400> 257
 Lys Thr Thr Lys Cys Asn Tyr Leu Lys Arg Pro Lys Leu Val Glu Ser
 1 5 10 15
 Arg Leu Gln Arg Thr Arg Phe Arg Arg Ile Cys Ser Arg Lys His Gly
 20 25 30
 Arg Tyr Arg Arg Trp Ile Arg Arg Phe Leu Ile Phe Leu Thr Asn Lys
 35 40 45
 Ser Lys Lys Ile Leu Val Lys Arg Arg Val Lys Arg Leu Leu Leu Ser
 50 55 60
 Leu Leu Val Thr Ala Pro Lys Glu Ser Lys Lys Met Glu Leu Ser Gln
 65 70 75 80
 Phe Leu Ile Gly

<210> 258
 <211> 19
 <212> PRT
 <213> Streptococcus pyogenes

<400> 258
 Gly Arg Arg Leu Pro Pro Arg Leu Pro Gln Glu Lys Ser Lys Trp Leu
 1 5 10 15
 Leu Pro Tyr

<210> 259
 <211> 62
 <212> PRT
 <213> Streptococcus pyogenes

<400> 259
 Phe Trp Ser Pro Gly Ser Arg Tyr Phe Val Arg Asp Ala Asn Asp Cys
 1 5 10 15
 Gln Arg Thr Gly Phe Ser Lys Cys Asp Phe Ser Trp Gly Thr Lys Cys
 20 25 30
 Arg Tyr Phe Leu Lys Phe Ala Gly Phe Ser Ser Val Arg Lys Asn Val
 35 40 45
 Ser Ile Val Asn Thr Gly Cys Trp Ser Gly Arg Pro Cys Pro
 50 55 60

<210> 260
 <211> 51
 <212> PRT
 <213> Streptococcus pyogenes

<400> 260
 Cys Val Pro Ser Val Lys Cys Ser Ile Met Ile Gln Ile Asn Thr Pro
 1 5 10 15
 Leu Ser Ile Leu Phe Pro Asn Thr Leu Val Gln Ala Gly Val Ile Phe
 20 25 30

【 0 2 3 0 】

Arg Val Tyr Pro Ile Gly Phe Pro Leu Phe Leu Leu Glu Trp Gln Lys
 35 40 45
 Ser Gln Gln
 50

<210> 261
 <211> 35
 <212> PRT
 <213> Streptococcus pyogenes

<400> 261
 Ser Asp Tyr Phe Arg His His Ala Pro Phe Leu Lys Trp Leu Arg Ser
 1 5 10 15
 Ala Lys Asn Asn Ser Lys Asp Ile Arg Cys Pro Tyr Tyr Tyr Ala Asn
 20 25 30
 Gly Ile Arg
 35

<210> 262
 <211> 65
 <212> PRT
 <213> Streptococcus pyogenes

<400> 262
 Leu Leu Leu Leu Lys Gln Thr Ser Lys Leu Asn Leu Leu Leu Lys Ala
 1 5 10 15
 Asn Gln Lys Arg Ser Gly Thr Lys Ser Ser Gln Val Lys Trp Thr Ala
 20 25 30
 Ser Cys Leu Thr Thr Leu Lys Leu Thr Lys Leu Thr Leu Phe Leu His
 35 40 45
 Lys Phe Thr Ser Trp Thr Thr Ala Lys Leu Leu Lys Leu Thr Leu Thr
 50 55 60
 Gln
 65

<210> 263
 <211> 38
 <212> PRT
 <213> Streptococcus pyogenes

<400> 263
 His Leu Phe Val Lys Asp Val Trp Ser Thr Leu Lys Ile Trp Glu Arg
 1 5 10 15
 Cys Ser Val Cys Tyr Lys Lys Val Val Lys Lys Gln Glu Leu Trp Gln
 20 25 30
 Pro Arg Leu Tyr Gln Lys
 35

<210> 264
 <211> 19
 <212> PRT
 <213> Streptococcus pyogenes

<400> 264
 Leu Tyr Ala Pro Gln Ser Leu Ser Asn Pro Phe Leu Asp Ser Ile Pro
 1 5 10 15
 Cys Asp Gln

<210> 265
 <211> 61
 <212> PRT
 <213> Streptococcus pyogenes

<400> 265
 Asn Arg Arg Asp Phe Leu Asp Asn Val Val Asn Leu Ile Arg Val Thr
 1 5 10 15
 Glu Pro Leu Gly Thr Ser Leu Val Phe Asp Asn Phe Ile Asn Arg Ala
 20 25 30
 Ala His Ile Asn Ile Asn Asn Ile Gly Leu Gly Ile Gly Leu Asn Glu

Ile Ser Cys Thr Phe Gln Pro Phe Cys Val Thr Thr Lys
 35 40 45
 50 55 60

<210> 266
 <211> 18
 <212> PRT
 <213> Streptococcus pyogenes

<400> 266
 Gln Ala Pro Leu Asp Asp His His Asn Lys Pro Thr Tyr Trp Ser Gly
 1 5 10 15
 Tyr Leu

<210> 267
 <211> 75
 <212> PRT
 <213> Streptococcus pyogenes

<400> 267
 Tyr Phe Leu Lys Lys Thr Pro Leu Lys Ala Ala Lys Ser Trp Leu Leu
 1 5 10 15
 Ser Pro Phe Gly Glu Met Ala Lys Thr Gly Phe Pro Trp Ala Phe Phe
 20 25 30
 Ser Lys Ile Asn Leu Pro Ser Ala Phe Leu Lys Val Pro Ser Val Cys
 35 40 45
 Arg Pro Leu Ser Glu Ile Val Leu Val Asp Thr Leu Val Ser Glu Pro
 50 55 60
 Arg Val Thr Ser Pro Val Lys Cys Leu Pro Thr
 65 70 75

<210> 268
 <211> 65
 <212> PRT
 <213> Streptococcus pyogenes

<400> 268
 Ser Lys Asn Lys Arg Asn Thr Asp Thr Gly Cys Asn Asn Gly Lys Gly
 1 5 10 15
 Ser Lys Ser Val Ser His Asn His Ser Lys Asn Asn His Ala Lys His
 20 25 30
 Ile Ser Glu Asn Ala Lys Glu Ala Ala Ile Ser Arg Tyr Asn Leu Pro
 35 40 45
 Asn Glu Arg Ser Asn His Ile Thr Asn Thr Ser Ser Cys Lys Asn Ser
 50 55 60
 Ser
 65

<210> 269
 <211> 30
 <212> PRT
 <213> Streptococcus pyogenes

<400> 269
 Leu Phe Ile His Arg Ser Arg Leu Ile Leu Asp Phe Leu Val Ile Asn
 1 5 10 15
 Phe Ser Leu Phe Val Gln Ile Tyr Asp Asp Phe Leu Asn Gly
 20 25 30

<210> 270
 <211> 12
 <212> PRT
 <213> Streptococcus pyogenes

<400> 270
 Ser Phe Ile Trp Glu Lys Arg Asn Pro Glu Gly Ser
 1 5 10

【 0 2 3 2 】

<210> 271
 <211> 50
 <212> PRT
 <213> Streptococcus pyogenes

<400> 271
 Ile Lys His Leu Thr Gln Ala Lys Gln Arg Met Pro Val Ser Lys Val
 1 5 10 15
 Leu Val Ala Asn Pro Leu Gly Ser Lys Gly Ile Ala Asp Ser Ile Gln
 20 25 30
 Leu Arg Met Lys Pro Leu Ala Val Lys Arg Tyr Arg Ser Ser Leu Ser
 35 40 45
 Thr Arg
 50

<210> 272
 <211> 50
 <212> PRT
 <213> Streptococcus pyogenes

<400> 272
 Pro Pro Pro Pro Asn Leu Pro Pro Ala Cys Lys Thr Val Lys Thr Val
 1 5 10 15
 Ser Thr Ala Gly Arg Pro Val Leu Ala Trp Ile Ser Thr Gly Ile Pro
 20 25 30
 Arg Pro Ser Ser Thr Thr Val Met Glu Leu Ser Ala Ser Ile Lys Thr
 35 40 45
 Leu Ile
 50

<210> 273
 <211> 32
 <212> PRT
 <213> Streptococcus pyogenes

<400> 273
 Glu Asn Glu Phe Asn Gln Tyr Tyr Gln Asp Ala Lys Tyr Lys Ser His
 1 5 10 15
 Lys Glu Arg Leu Thr Ile Asn Thr Phe Lys Arg Gln Gly Tyr Leu Arg
 20 25 30

<210> 274
 <211> 37
 <212> PRT
 <213> Streptococcus pyogenes

<400> 274
 Thr Arg Val Ala Pro Tyr Phe Pro Gln Ala Leu Ala Ile Phe Ser Glu
 1 5 10 15
 Pro Val Thr Leu Ile Ala Ser Phe Lys Ala Phe Pro Ser Ser Ser Ala
 20 25 30
 Ala Ser Thr Ala Val
 35

<210> 275
 <211> 81
 <212> PRT
 <213> Streptococcus pyogenes

<400> 275
 Ser Pro Phe Thr Lys Ser Val Leu Thr Pro Ser Ala Leu Lys Leu Ser
 1 5 10 15
 Ser Ile Lys Arg Pro Val Lys Pro Pro Lys Asn Pro Val Ala Val Leu
 20 25 30
 Ala Met Ser Lys Arg Cys Lys Met Arg Leu Thr Leu Met Pro Leu Pro
 35 40 45
 Pro Ala Asn Leu Ser Ser Leu Ala Met Arg Phe Thr Asp Pro Arg Phe
 50 55 60
 Ile Trp Ser Ile Leu Thr Ile Lys Ser Ile Glu Gly Phe Lys Val Thr
 65 70 75 80
 Val

【 0 2 3 3 】

<210> 276
 <211> 23
 <212> PRT
 <213> Streptococcus pyogenes

<400> 276
 Asp His Asn Ile Tyr Trp His Tyr Gln Leu Lys Leu Ser Gln Val Gln
 1 5 10 15
 Thr Met Thr Phe Pro Pro Leu
 20

<210> 277
 <211> 21
 <212> PRT
 <213> Streptococcus pyogenes

<400> 277
 Pro Asn Leu Leu Asp His Phe Leu Pro Asn Asn Pro His Gln Asn His
 1 5 10 15
 Lys Ala Lys Leu Asp
 20

<210> 278
 <211> 39
 <212> PRT
 <213> Streptococcus pyogenes

<400> 278
 Gln Cys Leu Ile Ile Ile Asn Asn Ile Asn Phe Arg His Asn Lys Asn
 1 5 10 15
 Thr Pro Ser Cys Ile Leu Lys Arg Ala Ser Leu His Asp Ile Ile Phe
 20 25 30
 His Ala Glu Thr Leu Leu Trp
 35

<210> 279
 <211> 137
 <212> PRT
 <213> Streptococcus pyogenes

<400> 279
 Glu Lys Leu Phe Arg Thr Ala Arg Gln Arg Tyr Asn Phe Lys Trp Val
 1 5 10 15
 Ser Lys Lys Gln Ile Met Gly Leu Val Leu Ile Val Phe Leu Lys Ser
 20 25 30
 Arg Asn Arg Asn Ser Glu Ser Lys Leu Phe Phe Tyr His Ile Phe Gly
 35 40 45
 His Ile Asp Leu Ser Asn Ala Ser Ile Asn Asn Asn Gln Val Arg Ser
 50 55 60
 Leu Gln Ser Leu Leu Phe His Pro Thr Val Pro Ser Lys Lys His Phe
 65 70 75 80
 Ser His Thr Gly Ile Ile Ile Trp Ser His His Cys Phe Asn Leu Lys
 85 90 95
 Phe Thr Ile Ile Phe Leu Thr Arg Phe Ala Ile Asn Lys Asn Asn His
 100 105 110
 Ser Arg Asn Trp Thr Cys Pro Leu Asn Val Arg Ile Ile Lys Gly Phe
 115 120 125
 Asn Ala His Arg Leu Val Asn Pro Lys
 130 135

<210> 280
 <211> 30
 <212> PRT
 <213> Streptococcus pyogenes

<400> 280
 Asp Asn Cys Arg Gly Cys Leu Ser Thr Asn Leu Asp Asn Lys Thr His
 1 5 10 15

Ser Phe Thr Ala Arg Phe Val Thr Asn Cys Cys Asn Thr Phe
20 25 30

<210> 281
<211> 33
<212> PRT
<213> Streptococcus pyogenes

<400> 281
Ile Gly Ser Ile Asn Gln Leu Val Ser Phe Ala Leu Val Thr Met Asp
1 5 10 15
Glu Val Lys Thr Leu Phe Lys Thr Leu Ile Thr Pro Thr Phe Glu Glu
20 25 30
Cys

<210> 282
<211> 39
<212> PRT
<213> Streptococcus pyogenes

<400> 282
Tyr Gln Val Cys Gln Leu Pro Glu Gly Val Pro Gln Leu Ile Val Asn
1 5 10 15
Ala Asp Gln Thr Trp Phe Tyr Lys Ala Lys Thr Lys Gln Arg Thr Lys
20 25 30
Lys Gln Trp Arg Ser Asn Gln
35

<210> 283
<211> 20
<212> PRT
<213> Streptococcus pyogenes

<400> 283
Ile Leu Ala Lys Ile Glu Ile Ser Gln Lys Thr Leu Ile Thr Ile Ile
1 5 10 15
Ile Met Arg Ser
20

<210> 284
<211> 46
<212> PRT
<213> Streptococcus pyogenes

<400> 284
Phe Pro Asp Val Asn Asp Lys Val Ile Ala Arg Asp Ser Arg Phe Phe
1 5 10 15
Gly Lys Glu Arg Thr Cys Leu Leu Ser Asn Arg Phe Trp Glu Val Gly
20 25 30
Asp Lys Lys Val Glu Thr Asn Pro Asn Asn Asp Ile Gly Asp
35 40 45

<210> 285
<211> 45
<212> PRT
<213> Streptococcus pyogenes

<400> 285
Lys Phe Asn Val Thr Leu Leu Pro Leu Cys Gln Asn Glu Leu Val Ile
1 5 10 15
Thr Leu Phe Leu Phe Ile Phe Cys His Leu Leu Leu Leu Asn Arg Gly
20 25 30
Ala Asn Ile Ser Ser Gln Lys Val Ile Lys Glu Val Arg
35 40 45

<210> 286
<211> 57
<212> PRT

【 0 2 3 5 】

<213> Streptococcus pyogenes

<400> 286

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Glu Thr Ser Ala Leu Leu Ala Ala Arg Phe Ile Arg Ser Ala Asp Ser
1      5      10      15
Pro Lys Ile Ile Ile Cys Leu Ser Pro Lys Arg Ser Gly Thr Lys Ser
      20      25      30
Ser Asn Ser Leu Pro Arg Ser Arg Pro Pro Ala Ile Lys Ile Lys Arg
      35      40      45
Leu Leu Ser Lys Pro Asp Lys Ala Phe
      50      55

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<210> 287

<211> 36

<212> PRT

<213> Streptococcus pyogenes

<400> 287

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Lys Arg Leu Asp Asp Cys Thr Leu Ile Phe Phe Trp Cys Ile Asn Leu
1      5      10      15
Asn Thr Leu Lys Arg Phe Thr Phe Asp Thr Ile Asn Phe Phe Asp Asp
      20      25      30
Asn Phe Trp Thr
      35

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<210> 288

<211> 45

<212> PRT

<213> Streptococcus pyogenes

<400> 288

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Glu Trp Leu Ser Gln Gln His Ser His Gln Phe Leu His Asp Lys Arg
1      5      10      15
Ser Tyr Leu Asp Thr Ala Phe Asp Lys Gly Lys Cys Thr Phe His Lys
      20      25      30
Lys Pro Val Leu Leu Leu Arg Trp Ser Ser Tyr Leu Gly
      35      40      45

```

<210> 289

<211> 38

<212> PRT

<213> Streptococcus pyogenes

<400> 289

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His Asp His Leu Ser His Gln Gln Ser Leu Lys Gln Leu Gly Asn Leu
1      5      10      15
Gly Leu Asp Ser Lys His Asn His Gln Asn Asp Lys Tyr Tyr Lys Glu
      20      25      30
Ser Ala Ala His Arg Gly
      35

```

<210> 290

<211> 69

<212> PRT

<213> Streptococcus pyogenes

<400> 290

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Val Met Leu Lys Ala Pro Val Lys Leu Ile Phe Lys Thr Arg Ser Lys
1      5      10      15
Ser Ser Ser Val Ile Leu Ser Ile Asn Leu Ser Leu Val Met Pro Ala
      20      25      30
Leu Leu Thr Lys Thr Ser Ile Glu Pro Lys Leu Ser Ile Ala Ser Leu
      35      40      45
Thr Ile Arg Leu Ala Ser Asp Ala Ser Glu Thr Ser Pro Glu Met Val
      50      55      60
Thr Thr Val Thr Pro
      65

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<210> 291

<211> 57

【 0 2 3 6 】

<212> PRT

<213> Streptococcus pyogenes

<400> 291

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Arg Glu Leu Ser Arg Phe Ser Ser Ser Ala Ile Leu Leu Lys Pro Leu
1          5          10          15
Val Lys Val Pro Pro Asn Arg Thr Met Ala Pro Pro Asn Pro Pro Ala
          20          25          30
Ala Pro Leu Pro Gly Ile Val Cys Lys Ser Met Val Val Trp Gln Lys
          35          40          45
Thr Phe Leu Ala Lys Leu Leu Ala Ile
          50          55

```

<210> 292

<211> 36

<212> PRT

<213> Streptococcus pyogenes

<400> 292

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Glu His Phe Gln Pro Asn His Gln Ile Gly Gln Lys Trp Lys Lys Glu
1          5          10          15
Arg Pro Lys Pro Thr Trp Ser Lys Ser Asp Val Ala His Lys Gln Thr
          20          25          30
Tyr Gln Ser Pro
          35

```

<210> 293

<211> 64

<212> PRT

<213> Streptococcus pyogenes

<400> 293

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Lys Ser Arg Ser Leu Arg Thr Ser Ser Ile Thr Ser Ser Thr Val Phe
1          5          10          15
Ser Ser Pro Thr Ile Leu Val Leu Ser Pro Ser Leu Val Asn Ile Cys
          20          25          30
Ser Gly Ala Phe Cys Trp Asp Ser Gly Leu Ala His His Gly His Leu
          35          40          45
Lys Gly Gln Pro Phe Lys Lys Thr Val Val Arg Ile Pro Gly Pro Ser
          50          55          60

```

<210> 294

<211> 16

<212> PRT

<213> Streptococcus pyogenes

<400> 294

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Arg Asn Glu Ile Asn Thr Ser Ser Pro Thr Leu Ser Ser Thr Lys Ile
1          5          10          15

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<210> 295

<211> 23

<212> PRT

<213> Streptococcus pyogenes

<400> 295

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Cys Ser Leu Ala Ala Phe Thr Lys Phe Ser Lys Ser Ala Ile Val Pro
1          5          10          15
Lys Ser Gly Leu Thr Ala Val
          20

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<210> 296

<211> 46

<212> PRT

<213> Streptococcus pyogenes

<400> 296

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Glu Ala Met Ser Cys Gln Arg Cys Cys Ser Phe Leu Ala Asp Ser Ser
1          5          10          15
Leu Ile Arg Tyr Asp Leu Ala Lys Ser Ser Val Val Ile Ala Ala Met

```

Ile Phe Lys 20 Met Ala Trp Leu Ser 25 Cys Gly Arg Arg Cys Gly 30
 35 40 45

<210> 297
 <211> 44
 <212> PRT
 <213> Streptococcus pyogenes

<400> 297
 Asn Phe Lys Ala Arg Pro Pro Gly Val Val Ser Gly Phe Pro Asn Ile
 1 5 10 15
 Thr Pro Thr Phe Ser Arg Asn Trp Leu Ile Lys Ile Ala Ile Val Phe
 20 25 30
 Val Leu Leu Ile Glu Ala Asp Asn Leu Arg Met Ala
 35 40

<210> 298
 <211> 38
 <212> PRT
 <213> Streptococcus pyogenes

<400> 298
 Lys Glu Thr Cys His Tyr Ser His Gln His His Val Ile Phe Gln Ala
 1 5 10 15
 Lys Phe Asp Arg Asn Phe Leu Pro His Pro Asp Lys Ser Gly His Gln
 20 25 30
 Asn Cys Ser Ile Asp Gly
 35

<210> 299
 <211> 78
 <212> PRT
 <213> Streptococcus pyogenes

<400> 299
 Ile Thr Leu Leu Thr Lys Gln Thr Gln Gln Leu Phe Arg Lys Pro Ser
 1 5 10 15
 Leu Ser Asn Asn Leu Leu Lys His Leu Leu Val Lys Arg Met Ser Leu
 20 25 30
 Ser Met Phe Leu Lys Gln Lys His Gln Leu Thr Lys Pro Lys Ala Ser
 35 40 45
 Met Leu Arg Pro Gln Asn Asn Lys Thr Thr Ile Ser Phe His His Gly
 50 55 60
 Gly Asp Gln Thr Ile Lys Ile His Gly Pro Thr Leu Thr Ser
 65 70 75

<210> 300
 <211> 20
 <212> PRT
 <213> Streptococcus pyogenes

<400> 300
 Ser Gly Arg Gln Asp Ser Asn Leu Arg His Leu Gly Pro Lys Pro Ser
 1 5 10 15
 Thr Leu Pro Ser
 20

Claims:

1. An isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence which is selected from the group consisting of:
 - a) a nucleic acid molecule having at least 70% sequence identity to a nucleic acid molecule selected from Seq ID No 1, 4-8, 10-18, 20, 22, 24-32, 34-35, 38-40, 43-46, 49-51, 53-54, 57-61, 63, 65-71, 73, 75-77, 81-82, 88, 91-94 and 96-150.,
 - b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
 - c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
 - d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b), or c)
 - e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid molecule defined in a), b), c) or d).
2. The isolated nucleic acid molecule according to claim 1, wherein the sequence identity is at least 80%, preferably at least 95%, especially 100%.
3. An isolated nucleic acid molecule encoding a hyperimmune serum reactive antigen or a fragment thereof comprising a nucleic acid sequence selected from the group consisting of
 - a) a nucleic acid molecule having at least 96% sequence identity to a nucleic acid molecule selected from Seq ID No 64.
 - b) a nucleic acid molecule which is complementary to the nucleic acid molecule of a),
 - c) a nucleic acid molecule comprising at least 15 sequential bases of the nucleic acid molecule of a) or b)
 - d) a nucleic acid molecule which anneals under stringent hybridisation conditions to the nucleic acid molecule of a), b) or c),
 - e) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).
4. An isolated nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of
 - a) a nucleic acid molecule selected from Seq ID No 3, 36, 47-48, 55, 62, 72, 80, 84, 95,
 - b) a nucleic acid molecule which is complementary to the nucleic acid of a),
 - c) a nucleic acid molecule which, but for the degeneracy of the genetic code, would hybridise to the nucleic acid defined in a), b), c) or d).
5. The nucleic acid molecule according to any one of the claims 1, 2, 3 or 4, wherein the nucleic acid is DNA.
6. The nucleic acid molecule according to any one of the claims 1, 2, 3, 4, or 5 wherein the nucleic acid is RNA.
7. An isolated nucleic acid molecule according to any one of claims 1 to 5, wherein the nucleic acid molecule is isolated from a genomic DNA, especially from a *S. pyogenes* genomic DNA.
8. A vector comprising a nucleic acid molecule according to any one of claims 1 to 7.
9. A vector according to claim 8, wherein the vector is adapted for recombinant expression of the hyperimmune serum reactive antigens or fragment thereof encoded by the nucleic acid molecule according to any one of claims 1 to 7.

10. A host cell comprising the vector according to claim 8 or 9.
11. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 1, 2, 5, 6 or 7 and fragments thereof, wherein the amino acid sequence is selected from the group consisting of Seq ID No 151, 154-158, 160-168, 170, 172, 174-182, 184-185, 188-190, 193-196, 199-201, 203-204, 207-211, 213, 215-221, 223, 225-227, 231-232, 238, 241-244 and 246-300.
12. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 3, 5, 6, or 7 and fragments thereof, wherein the amino acid sequence is selected from the group consisting of Seq ID No 214.
13. A hyperimmune serum-reactive antigen comprising an amino acid sequence being encoded by a nucleic acid molecule according to any one of the claims 4, 5, 6, or 7 and fragments thereof, wherein the amino acid sequence is selected from the group consisting of Seq ID No 153, 186, 197-198, 205, 212, 222, 230, 234, 245.
14. Fragments of hyperimmune serum-reactive antigens selected from the group consisting of peptides comprising amino acid sequences of column "predicted immunogenic aa" and "location of identified immunogenic region" of Table 2; the serum reactive epitopes of Table 2, especially peptides comprising amino acid 4-44, 57-65, 67-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-269, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425 and 1-114 of Seq ID No 151; 5-17, 49-64, 77-82, 87-98, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-395 and 29-226 of Seq ID No 152; 4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-219, 221-228, 230-236, 239-245, 257-268, 313-328, 330-335, 353-359, 367-375, 394-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-748, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1085, 1088-1111, 1130-1135, 1148-1164, 1166-1173, 1185-1192, 1244-1254 and 919-929 of Seq ID No 153; 5-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360 and 145-305 of Seq ID No 154; 15-39, 52-61, 72-81, 92-97 and 71-81 of Seq ID No 155; 13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245 and 173-186 of Seq ID No 156; 5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352 and 316-331 of Seq ID No 157; 6-28, 43-53, 60-76, 93-103 and 21-99 of Seq ID No 158; 10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568 and 9-264 of Seq ID No 159; 5-29, 39-45, 107-128 and 1-112 of Seq ID No 160; 4-38, 42-50, 54-60, 65-71, 91-102 and 21-56 of Seq ID No 161; 4-13, 19-25, 41-51, 54-62, 68-75, 79-89, 109-122, 130-136, 172-189, 192-198, 217-224, 262-268, 270-276, 281-298, 315-324, 333-342, 353-370, 376-391 and 23-39 of Seq ID No 162; 6-41, 49-58, 62-103, 117-124, 147-166, 173-194, 204-211, 221-229, 255-261, 269-284, 288-310, 319-325, 348-380, 383-389, 402-410, 424-443, 467-479, 496-517, 535-553, 555-565, 574-581, 583-591 and 474-489 of Seq ID No 163; 8-35, 52-57, 66-73, 81-88, 108-114, 125-131, 160-167, 174-180, 230-235, 237-249, 254-262, 278-285, 308-314, 321-326, 344-353, 358-372, 376-383, 393-411, 439-446, 453-464, 471-480, 485-492, 502-508, 523-529, 533-556, 558-563, 567-584, 589-597, 605-619, 625-645, 647-666, 671-678, 690-714, 721-728, 741-763, 766-773, 777-787, 792-802, 809-823, 849-864 and 37-241, 409-534, 582-604, 743-804 of Seq ID No 164; 4-17, 24-36, 38-44, 59-67, 72-90, 92-121, 126-149, 151-159, 161-175, 197-215, 217-227, 241-247, 257-264, 266-275, 277-284, 293-307, 315-321, 330-337, 345-350, 357-366, 385-416 and 202-337 of Seq ID No 165; 4-20, 22-46, 49-70, 80-89, 96-103, 105-119, 123-129, 153-160, 181-223, 227-233, 236-243, 248-255, 261-269, 274-279, 283-299, 305-313, 315-332, 339-344, 349-362, 365-373, 380-388, 391-397, 402-407 and 1-48 of Seq ID No 166; 18-37, 41-63, 100-106, 109-151, 153-167, 170-197, 199-

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5-26, 34-48, 57-77, 84-102, 116-132, 139-145, 150-162, 165-173, 176-187, 192-205, 216-221, 234-248, 250-260 and 182-198 of Seq ID No 200; 10-19, 26-44, 53-62, 69-87, 90-96, 121-127, 141-146, 148-158, 175-193, 204-259, 307-313, 334-348, 360-365, 370-401, 411-439, 441-450, 455-462, 467-472, 488-504 and 41-56 of Seq ID No 201; 5-21, 36-42, 96-116, 123-130, 138-144, 146-157, 184-201, 213-228, 252-259, 277-297, 308-313, 318-323, 327-333 and 202-217 of Seq ID No 202; 6-26, 33-51, 72-90, 97-131, 147-154, 164-171, 187-216, 231-236, 260-269, 275-283 and 1-127 of Seq ID No 203; 4-22, 24-38, 44-58, 72-88, 99-108, 110-117, 123-129, 131-137, 142-147, 167-178, 181-190, 206-214, 217-223, 271-282, 290-305, 320-327, 329-336, 343-352, 354-364, 396-402, 425-434, 451-456, 471-477, 485-491, 515-541, 544-583, 595-609, 611-626, 644-656, 660-681, 683-691, 695-718 and 297-458 of Seq ID No 204; 5-43, 92-102, 107-116, 120-130, 137-144, 155-163, 169-174, 193-213 and 24-135 of Seq ID No 205; 4-25, 61-69, 73-85, 88-95, 97-109, 111-130, 135-147, 150-157, 159-179, 182-201, 206-212, 224-248, 253-260, 287-295, 314-331, 338-344, 365-376, 396-405, 413-422, 424-430, 432-449, 478-485, 487-494, 503-517, 522-536, 544-560, 564-578, 585-590, 597-613, 615-623, 629-636, 640-649, 662-671, 713-721 and 176-330 of Seq ID No 206; 31-37, 41-52, 58-79, 82-105, 133-179, 184-193, 199-205, 209-226, 256-277, 281-295, 297-314, 322-328, 331-337, 359-367, 379-395, 403-409, 417-432, 442-447, 451-460, 466-472 and 46-62, 296-341 of Seq ID No 207; 23-29, 56-63, 67-74, 96-108, 122-132, 139-146, 152-159, 167-178, 189-196, 214-231, 247-265, 274-293, 301-309, 326-332, 356-363, 378-395, 406-412, 436-442, 445-451, 465-479, 487-501, 528-555, 567-581, 583-599, 610-617, 622-629, 638-662, 681-686, 694-700, 711-716 and 667-684 of Seq ID No 208; 20-51, 53-59, 109-115, 140-154, 185-191, 201-209, 212-218, 234-243, 253-263, 277-290, 303-313, 327-337, 342-349, 374-382, 394-410, 436-442, 464-477, 486-499, 521-530, 536-550, 560-566, 569-583, 652-672, 680-686, 698-704, 718-746, 758-770, 774-788, 802-827, 835-842, 861-869 and 258-416 of Seq ID No 209; 7-25, 39-45, 59-70, 92-108, 116-127, 161-168, 202-211, 217-227, 229-239, 254-262, 271-278, 291-300 and 278-295 of Seq ID No 210; 4-20, 27-33, 45-51, 53-62, 66-74, 81-88, 98-111, 124-130, 136-144, 156-179, 183-191 and 183-195 of Seq ID No 211; 12-24, 27-33, 43-49, 55-71, 77-85, 122-131, 168-177, 179-203, 209-214, 226-241 and 63-238 of Seq ID No 212; 4-19, 37-50, 120-126, 131-137, 139-162, 177-195, 200-209, 211-218, 233-256, 260-268, 271-283, 288-308 and 1-141 of Seq ID No 213; 11-17, 40-47, 57-63, 96-124, 141-162, 170-207, 223-235, 241-265, 271-277, 281-300, 312-318, 327-333, 373-379 and 231-368 of Seq ID No 214; 9-33, 41-48, 57-79, 97-103, 113-138, 146-157, 165-186, 195-201, 209-215, 223-229, 237-247, 277-286, 290-297, 328-342 and 247-260 of Seq ID No 215; 7-15, 39-45, 58-

64, 79-84, 97-127, 130-141, 163-176, 195-203, 216-225, 235-247, 254-264, 271-279 and 64-72 of Seq ID No 216; 4-12, 26-42, 46-65, 73-80, 82-94, 116-125, 135-146, 167-173, 183-190, 232-271, 274-282, 300-306, 320-343, 351-362, 373-383, 385-391, 402-409, 414-426, 434-455, 460-466, 473-481, 485-503, 519-525, 533-542, 554-565, 599-624, 645-651, 675-693, 717-725, 751-758, 767-785, 792-797, 801-809, 819-825, 831-836, 859-869, 890-897 and 222-362, 756-896 of Seq ID No 217; 11-17, 22-28, 52-69, 73-83, 86-97, 123-148, 150-164, 166-177, 179-186, 188-199, 219-225, 229-243, 250-255 and 153-170 of Seq ID No 218; 4-61, 71-80, 83-90, 92-128, 133-153, 167-182, 184-192, 198-212 and 56-73 of Seq ID No 219; 4-19, 26-37, 45-52, 58-66, 71-77, 84-92, 94-101, 107-118, 120-133, 156-168, 170-179, 208-216, 228-238, 253-273, 280-296, 303-317, 326-334 and 298-312 of Seq ID No 220; 7-13, 27-35, 38-56, 85-108, 113-121, 123-160, 163-169, 172-183, 188-200, 206-211, 219-238, 247-254 and 141-157 of Seq ID No 221; 23-39, 45-73, 86-103, 107-115, 125-132, 137-146, 148-158, 160-168, 172-179, 185-192, 200-207, 210-224, 233-239, 246-255, 285-334, 338-352, 355-379, 383-389, 408-417, 423-429, 446-456, 460-473, 478-503, 522-540, 553-562, 568-577, 596-602, 620-636, 640-649, 655-663 and 433-440, 572-593 of Seq ID No 222; 4-42, 46-58, 64-76, 118-124, 130-137, 148-156, 164-169, 175-182, 187-194, 203-218, 220-227, 241-246, 254-259, 264-270, 275-289, 296-305, 309-314, 322-334, 342-354, 398-405, 419-426, 432-443, 462-475, 522-530, 552-567, 593-607, 618-634, 636-647, 653-658, 662-670, 681-695, 698-707, 709-720, 732-742, 767-792, 794-822, 828-842, 851-866, 881-890, 895-903, 928-934, 940-963, 978-986, 1003-1025, 1027-1043, 1058-1075, 1080-1087, 1095-1109, 1116-1122, 1133-1138, 1168-1174, 1179-1186, 1207-1214, 1248-1267 and 17-319, 417-563 of Seq ID No 223; 6-19, 23-33, 129-138, 140-150, 153-184, 190-198, 206-219, 235-245, 267-275, 284-289, 303-310, 322-328, 354-404, 407-413, 423-446, 453-462, 467-481, 491-500 and 46-187 of Seq ID No 224; 4-34, 39-57, 78-86, 106-116, 141-151, 156-162, 165-172, 213-237, 252-260, 262-268, 272-279, 296-307, 332-338, 397-403, 406-416, 431-446, 448-453, 464-470, 503-515, 519-525, 534-540, 551-563, 578-593, 646-668, 693-699, 703-719, 738-744, 748-759, 771-777, 807-813, 840-847, 870-876, 897-903, 910-925, 967-976, 979-992 and 21-244, 381-499, 818-959 of Seq ID No 225; 19-29, 65-75, 90-109, 111-137, 155-165, 169-175 and 118-136 of Seq ID No 226; 15-20, 30-36, 55-63, 73-79, 90-117, 120-127, 136-149, 166-188, 195-203, 211-223, 242-255, 264-269, 281-287, 325-330, 334-341, 348-366, 395-408, 423-429, 436-444, 452-465 and 147-155 of Seq ID No 227; 11-18, 21-53, 77-83, 91-98, 109-119, 142-163, 173-181, 193-208, 216-227, 238-255, 261-268, 274-286, 290-297, 308-315, 326-332, 352-359, 377-395, 399-406, 418-426, 428-438, 442-448, 458-465, 473-482, 488-499, 514-524, 543-553, 564-600, 623-632, 647-654, 660-669, 672-678, 710-723, 739-749, 787-793, 820-828, 838-860, 889-895, 901-907, 924-939, 956-962, 969-976, 991-999, 1012-1018, 1024-1029, 1035-1072, 1078-1091, 1142-1161 and 74-438 of Seq ID No 228; 4-31, 41-52, 58-63, 65-73, 83-88, 102-117, 123-130, 150-172, 177-195, 207-217, 222-235, 247-253, 295-305, 315-328, 335-342, 359-365, 389-394, 404-413 and 156-420 of Seq ID No 229; 4-42, 56-69, 98-108, 120-125, 210-216, 225-231, 276-285, 304-310, 313-318, 322-343 and 79-348 of Seq ID No 230; 12-21, 24-30, 42-50, 61-67, 69-85, 90-97, 110-143, 155-168 and 53-70 of Seq ID No 231; 4-26, 41-54, 71-78, 88-96, 116-127, 140-149, 151-158, 161-175, 190-196, 201-208, 220-226, 240-247, 266-281, 298-305, 308-318, 321-329, 344-353, 370-378, 384-405, 418-426, 429-442, 457-463, 494-505, 514-522 and 183-341 of Seq ID No 232; 4-27, 69-77, 79-101, 117-123, 126-142, 155-161, 171-186, 200-206, 213-231, 233-244, 258-263, 269-275, 315-331, 337-346, 349-372, 376-381, 401-410, 424-445, 447-455, 463-470, 478-484, 520-536, 546-555, 558-569, 580-597, 603-618, 628-638, 648-660, 668-683, 717-723, 765-771, 781-788, 792-806, 812-822 and 92-231, 618-757 of Seq ID No 233; 11-47, 63-75, 108-117, 119-128, 133-143, 171-185, 190-196, 226-232, 257-264, 278-283, 297-309, 332-338, 341-346, 351-358, 362-372 and 41-170 of Seq ID No 234; 6-26, 50-56, 83-89, 108-114, 123-131, 172-181, 194-200, 221-238, 241-259, 263-271, 284-292, 304-319, 321-335, 353-358, 384-391, 408-417, 424-430, 442-448, 459-466, 487-500, 514-528, 541-556, 572-578, 595-601, 605-613, 620-631, 634-648, 660-679, 686-693, 702-708, 716-725, 730-735, 749-755, 770-777, 805-811, 831-837, 843-851, 854-860, 863-869, 895-901, 904-914, 922-929, 933-938, 947-952, 956-963, 1000-1005, 1008-1014, 1021-1030, 1131-1137, 1154-1164, 1166-1174 and 20-487, 757-1153 of Seq ID No 235; 10-34, 67-78, 131-146, 160-175, 189-194, 201-214, 239-250, 265-271, 296-305 and 26-74, 91-100, 105-303 of Seq ID No 236; 9-15, 19-32, 109-122, 143-150, 171-180, 186-191, 209-217, 223-229, 260-273, 302-315, 340-346, 353-359, 377-383, 389-406, 420-426, 460-480 and 10-223, 231-251, 264-297, 312-336 of Seq ID No 237; 5-28, 76-81, 180-195, 203-209, 211-219, 227-234, 242-252, 271-282, 317-325, 350-356, 358-364, 394-400, 405-413, 417-424, 430-436, 443-449, 462-482, 488-498, 503-509, 525-537 and 22-344 of Seq ID

No 238; 5-28, 42-54, 77-83, 86-93, 98-104, 120-127, 145-159, 166-176, 181-187, 189-197, 213-218, 230-237, 263-271, 285-291, 299-305, 326-346, 368-375, 390-395 and 1-151 of Seq ID No 239; 6-34, 48-55, 58-64, 84-101, 121-127, 143-149, 153-159, 163-170, 173-181, 216-225, 227-240, 248-254, 275-290, 349-364, 375-410, 412-418, 432-438, 445-451, 465-475, 488-496, 505-515, 558-564, 571-579, 585-595, 604-613, 626-643, 652-659, 677-686, 688-696, 702-709, 731-747, 777-795, 820-828, 836-842, 845-856, 863-868, 874-882, 900-909, 926-943, 961-976, 980-986, 992-998, 1022-1034, 1044-1074, 1085-1096, 1101-1112, 1117-1123, 1130-1147, 1181-1187, 1204-1211, 1213-1223, 1226-1239, 1242-1249, 1265-1271, 1273-1293, 1300-1308, 1361-1367, 1378-1384, 1395-1406, 1420-1428, 1439-1446, 1454-1460, 1477-1487, 1509-1520, 1526-1536, 1557-1574, 1585-1596, 1605-1617, 1621-1627, 1631-1637, 1648-1654, 1675-1689, 1692-1698, 1700-1706, 1712-1719, 1743-1756 and 91-263 of Seq ID No 240; 4-16, 75-90, 101-136, 138-144, 158-164, 171-177, 191-201, 214-222, 231-241, 284-290, 297-305, 311-321, 330-339, 352-369, 378-385, 403-412, 414-422, 428-435, 457-473, 503-521, 546-554, 562-568, 571-582, 589-594, 600-608, 626-635, 652-669, 687-702, 706-712, 718-724, 748-760, 770-775 and 261-272 of Seq ID No 241; 4-19, 30-41, 46-57, 62-68, 75-92, 126-132, 149-156, 158-168, 171-184, 187-194, 210-216, 218-238, 245-253, 306-312, 323-329, 340-351, 365-373, 384-391, 399-405, 422-432, 454-465, 471-481, 502-519, 530-541, 550-562, 566-572, 576-582, 593-599, 620-634, 637-643, 645-651, 657-664, 688-701 and 541-551 of Seq ID No 242; 6-11, 17-25, 53-58, 80-86, 91-99, 101-113, 123-131, 162-169, 181-188, 199-231, 245-252 and 84-254 of Seq ID No 243; 13-30, 71-120, 125-137, 139-145, 184-199 and 61-78 of Seq ID No 244; 9-30, 38-53, 63-70, 74-97, 103-150, 158-175, 183-217, 225-253, 260-268, 272-286, 290-341, 352-428, 434-450, 453-460, 469-478, 513-525, 527-534, 554-563, 586-600, 602-610, 624-640, 656-684, 707-729, 735-749, 757-763, 766-772, 779-788, 799-805, 807-815, 819-826, 831-855 and 568-580 of Seq ID No 245; 11-21, 29-38 and 5-17 of Seq ID No 246; 2-9 of Seq ID No 247; 4-10, 16-28 and 7-18, 26-34 of Seq ID No 248; 10-16 and 1-15 of Seq ID No 249; 4-11 of Seq ID No 250; 4-40, 42-51 and 37-53 of Seq ID No 251; 4-21 and 22-29 of Seq ID No 252; 2-11 Seq ID No 253; 9-17, 32-44 and 1-22 of Seq ID No 254; 19-25, 27-32 and 15-34 of Seq ID No 255; 4-12, 15-22 and 11-33 of Seq ID No 256; 10-17, 24-30, 39-46, 51-70 and 51-61 of Seq ID No 257; 6-19 of Seq ID No 258; 6-11, 21-27, 31-54 and 11-29 of Seq ID No 259; 4-10, 13-45 and 11-35 of Seq ID No 260; 4-14, 23-32 and 11-35 of Seq ID No 261; 14-39, 45-51 and 15-29 of Seq ID No 262; 4-11, 14-28 and 4-17 of Seq ID No 263; 4-16 and 2-16 of Seq ID No 264; 4-10, 12-19, 39-50 and 6-22 of Seq ID No 265; 2-13 of Seq ID No 266; 4-11, 22-65 and 3-19 of Seq ID No 267; 17-23, 30-35, 39-46, 57-62 and 30-49 of Seq ID No 268; 4-19 and 14-22 of Seq ID No 269; 2-9 of Seq ID No 270; 7-18, 30-43 and 4-12 of Seq ID No 271; 4-30, 39-47 and 5-22 of Seq ID No 272; 6-15 and 14-29 of Seq ID No 273; 4-34 and 23-35 of Seq ID No 274; 4-36, 44-57, 65-72 and 14-27 of Seq ID No 275; 4-18 and 11-20 of Seq ID No 276; 5-19 of Seq ID No 277; 18-36 and 6-20 of Seq ID No 278; 4-10, 19-34, 41-84, 96-104 and 50-63 of Seq ID No 279; 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1-18 of Seq ID No 266; 12-29 of Seq ID No 273; 6-23 of Seq ID No 276; 1-21 of Seq ID No 277; 47-64 of Seq ID No 279; 28-45 of Seq ID No 285; 18-35 of Seq ID No 287; 14-31 of Seq ID No 291; 7-24 of Seq ID No 292; 8-25 of Seq ID No 299; 1-20 of Seq ID No 300; 18-33 of Seq ID No 151; 62-72 of Seq ID No 151; 118-131 of Seq ID No 152; 195-220 of Seq ID No 154; 215-240 of Seq ID No 154; 255-280 of Seq ID No 154, 72-81 of Seq ID No 155; 174-186 of Seq ID No 156; 317-331 of Seq ID No 157; 35-59 of Seq ID No 158; 54-84 of Seq ID No 158; 79-104 of Seq ID No 158; 33-58 of Seq ID No 159; 81-101 of Seq ID No 159; 136-150 of Seq ID No 159; 173-186 of Seq ID No 159; 231-251 of Seq ID No 159; 22-48 of Seq ID No 161; 24-39 of Seq ID No 162; 475-489 of Seq ID No 163; 38-56 of Seq ID No 164; 583-604

of Seq ID No 164; 202-223 of Seq ID No 165; 222-247 of Seq ID No 165; 242-267 of Seq ID No 165; 262-287 of Seq ID No 165; 282-307 of Seq ID No 165; 302-327 of Seq ID No 165; 25-48 of Seq ID No 166; 204-217 of Seq ID No 167; 259-276 of Seq ID No 168; 121-139 of Seq ID No 169; 260-267 of Seq ID No 169; 215-240 of Seq ID No 169; 115-140 of Seq ID No 170; 182-204 of Seq ID No 172; 144-153 of Seq ID No 173; 205-219 of Seq ID No 173; 196-206 of Seq ID No 174; 240-249 of Seq ID No 174; 272-287 of Seq ID No 174; 199-223 of Seq ID No 174; 218-237 of Seq ID No 174; 226-249 of Seq ID No 175; 287-306 of Seq ID No 175; 430-449 of Seq ID No 176; 361-375 of Seq ID No 177; 241-260 of Seq ID No 178; 483-502 of Seq ID No 181; 379-396 of Seq ID No 182; 31-51 of Seq ID No 184; 1436-1460 of Seq ID No 186; 1455-1474 of Seq ID No 186; 1469-1487 of Seq ID No 186; 215-229 of Seq ID No 187; 534-561 of Seq ID No 187; 59-84 of Seq ID No 187; 79-104 of Seq ID No 187; 618-635 of Seq ID No 188; 191-203 of Seq ID No 189; 386-398 of Seq ID No 190; 65-83 of Seq ID No 191; 90-105 of Seq ID No 192; 112-136 of Seq ID No 192; 290-209 of Seq ID No 193; 33-50 of Seq ID No 194; 76-90 of Seq ID No 195; 70-88 of Seq ID No 196; 418-442 of Seq ID No 197; 574-585 of Seq ID No 197; 87-104 of Seq ID No 198; 124-148 of Seq ID No 198; 141-152 of Seq ID No 198; 241-248 of Seq ID No 199; 183-198 of Seq ID No 200; 40-57 of Seq ID No 201; 202-217 of Seq ID No 202; 50-74 of Seq ID No 203; 69-93 of Seq ID No 203; 88-112 of Seq ID No 203; 107-127 of Seq ID No 203; 74-92 of Seq ID No 205; 207-232 of Seq ID No 206; 227-252 of Seq ID No 206; 247-272 of Seq ID No 206; 47-60 of Seq ID No 207; 297-305 of Seq ID No 207; 312-337 of Seq ID No 207; 667-384 of Seq ID No 208; 279-295 of Seq ID No 210; 179-198 of Seq ID No 211; 27-51 of Seq ID No 213; 46-70 of Seq ID No 213; 65-89 of Seq ID No 213; 84-108 of Seq ID No 213; 112-141 of Seq ID No 213; 248-260 of Seq ID No 215; 59-78 of Seq ID No 216; 154-170 of Seq ID No 218; 57-73 of Seq ID No 219; 297-314 of Seq ID No 220; 142-157 of Seq ID No 221; 428-447 of Seq ID No 222; 573-593 of Seq ID No 222; 523-544 of Seq ID No 223; 46-70 of Seq ID No 223; 65-89 of Seq ID No 223; 84-108 of Seq ID No 223; 122-151 of Seq ID No 223; 123-142 of Seq ID No 224; 903-921 of Seq ID No 225; 119-136 of Seq ID No 226; 142-161 of Seq ID No 227; 258-277 of Seq ID No 228; 272-300 of Seq ID No 228; 295-322 of Seq ID No 228; 311-343 of Seq ID No 229; 278-304 of Seq ID No 229; 131-150 of Seq ID No 230; 195-218 of Seq ID No 230; 53-70 of Seq ID No 231; 184-208 of Seq ID No 232; 222-246 of Seq ID No 232; 241-265 of Seq ID No 232; 260-284 of Seq ID No 232; 279-303 of Seq ID No 232; 317-341 of Seq ID No 232; 678-696 of Seq ID No 233; 88-114 of Seq ID No 235; 464-481 of Seq ID No 235; 153-172 of Seq ID No 236; 137-155, 166-184 of Seq ID No 236; 215-228 of Seq ID No 236; 37-51 of Seq ID No 237; 53-75 of Seq ID No 237; 232-251 of Seq ID No 237; 318-336 of Seq ID No 237; 305-315 of Seq ID No 238; 131-156 of Seq ID No 238; 258-275 of Seq ID No 241; 107-137 of Seq ID No 243; 138-162 of Seq ID No 243; 157-181 of Seq ID No 243; 195-227 of Seq ID No 243; 62-78 of Seq ID No 244; 567-584 of Seq ID No 245.

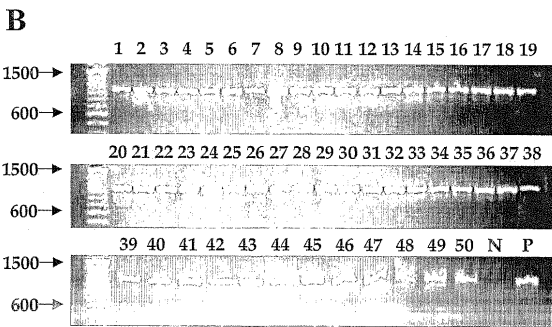
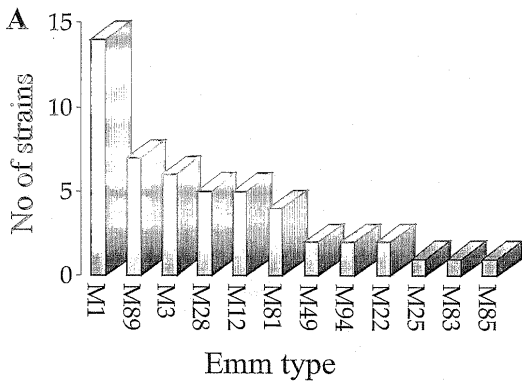
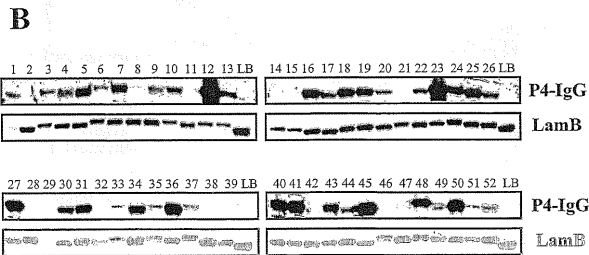
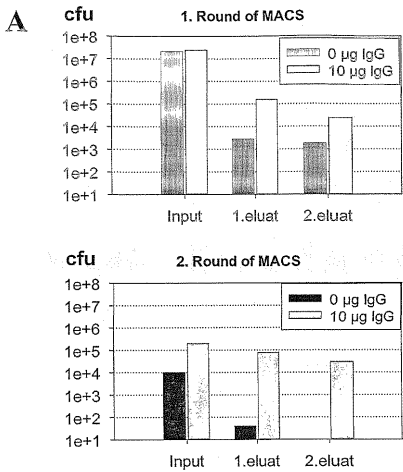
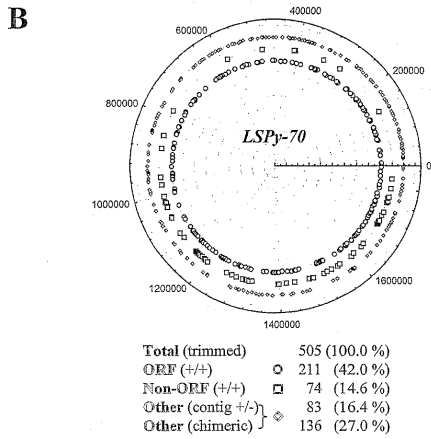
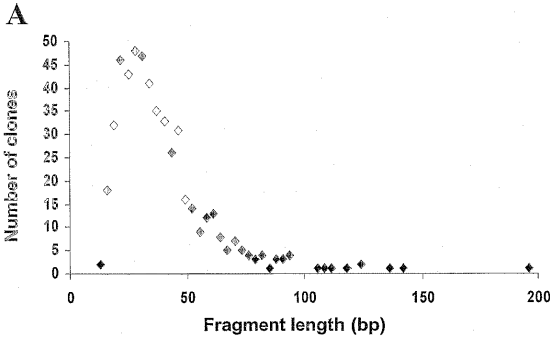
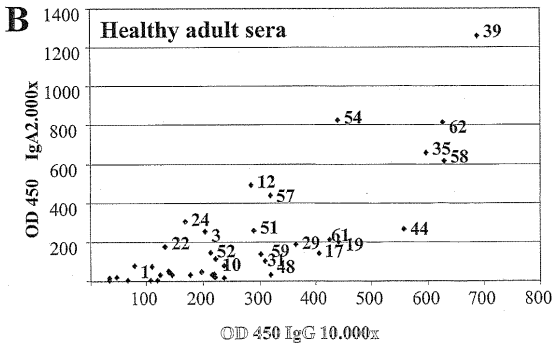
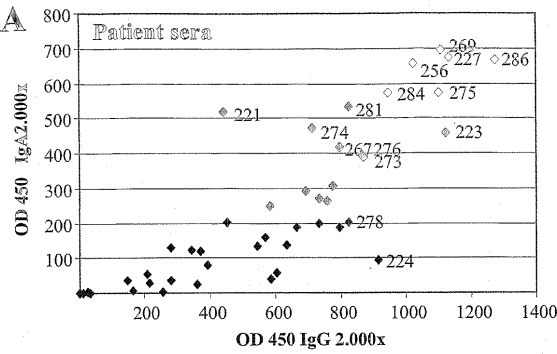
15. A process for producing a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to any one of the claims 11 to 14 comprising expressing the nucleic acid molecule according to any one of claims 1 to 7.
16. A process for producing a cell, which expresses a *S. pyogenes* hyperimmune serum reactive antigen or a fragment thereof according to any one of the claims 11 to 14 comprising transforming or transfecting a suitable host cell with the vector according to claim 8 or claim 9.
17. A pharmaceutical composition, especially a vaccine, comprising a hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of claims 11 to 14 or a nucleic acid molecule according to any one of claims 1 to 7.
18. A pharmaceutical composition, especially a vaccine, according to claim 17, characterized in that it further comprises an immunostimulatory substance, preferably selected from the group comprising polycationic polymers, especially polycationic peptides, immunostimulatory deoxynucleotides (ODNs), peptides containing at least two LysLeuLys motifs, neuroactive compounds, especially human growth hormone, albumin, Freund's complete or incomplete

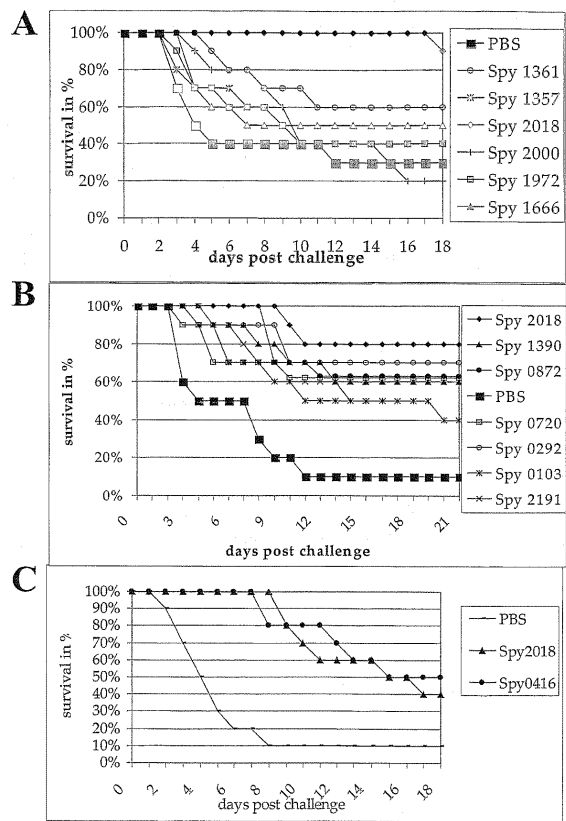
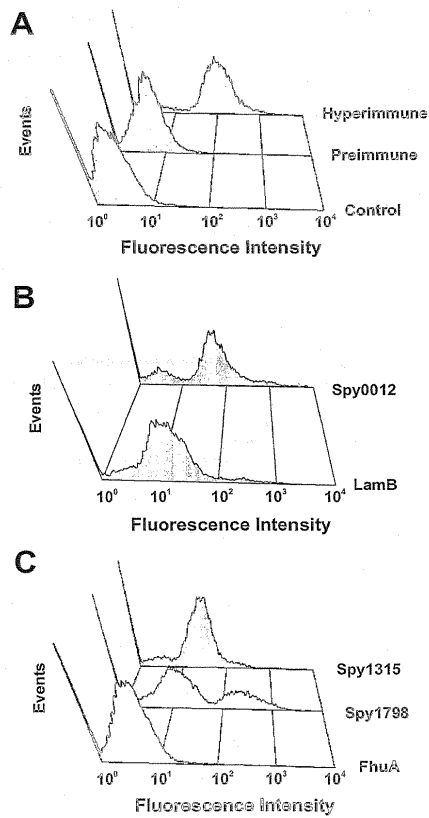
adjuvants or combinations thereof.

19. Use of a nucleic acid molecule according to any one of claims 1 to 7 or a hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 for the manufacture of a pharmaceutical preparation, especially for the manufacture of a vaccine against *S. pyogenes* infection.
20. An antibody, or at least an effective part thereof, which binds at least to a selective part of the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14.
21. An antibody according to claim 20, wherein the antibody is a monoclonal antibody.
22. An antibody according to claim 20 or 21, wherein said effective part comprises Fab fragments.
23. An antibody according to any one of claims 20 to 22, wherein the antibody is a chimeric antibody.
24. An antibody according to any one of claims 20 to 23, wherein the antibody is a humanized antibody.
25. A hybridoma cell line, which produces an antibody according to any one of claims 20 to 24.
26. A method for producing an antibody according to claim 20, characterized by the following steps:
 - initiating an immune response in a non-human animal by administering an hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of the claims 11 to 14, to said animal,
 - removing an antibody containing body fluid from said animal, and
 - producing the antibody by subjecting said antibody containing body fluid to further purification steps.
27. Method for producing an antibody according to claim 21, characterized by the following steps:
 - initiating an immune response in a non-human animal by administering an hyperimmune serum-reactive antigen or a fragment thereof, as defined in any one of the claims 12 to 15, to said animal,
 - removing the spleen or spleen cells from said animal,
 - producing hybridoma cells of said spleen or spleen cells,
 - selecting and cloning hybridoma cells specific for said hyperimmune serum-reactive antigens or a fragment thereof,
 - producing the antibody by cultivation of said cloned hybridoma cells and optionally further purification steps.
28. Use of the antibodies according to any one of claims 20 to 24 for the preparation of a medicament for treating or preventing *S. pyogenes* infections.
29. An antagonist which binds to the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14.
30. A method for identifying an antagonist capable of binding to the hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 comprising:
 - a) contacting an isolated or immobilized hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 with a candidate antagonist under conditions to permit binding of said candidate antagonist to said hyperimmune serum-reactive antigen or

- fragment, in the presence of a component capable of providing a detectable signal in response to the binding of the candidate antagonist to said hyperimmune serum reactive antigen or fragment thereof; and
- b) detecting the presence or absence of a signal generated in response to the binding of the antagonist to the hyperimmune serum reactive antigen or the fragment thereof.
31. A method for identifying an antagonist capable of reducing or inhibiting the interaction activity of a hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 to its interaction partner comprising:
- a) providing a hyperimmune serum reactive antigen or a hyperimmune fragment thereof according to any one of claims 11-14,
 - b) providing an interaction partner to said hyperimmune serum reactive antigen or a fragment thereof, especially an antibody according to any one of the claims 20 to 24,
 - c) allowing interaction of said hyperimmune serum reactive antigen or fragment thereof to said interaction partner to form an interaction complex,
 - d) providing a candidate antagonist,
 - e) allowing a competition reaction to occur between the candidate antagonist and the interaction complex,
 - f) determining whether the candidate antagonist inhibits or reduces the interaction activities of the hyperimmune serum reactive antigen or the fragment thereof with the interaction partner.
32. Use of any of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14 for the isolation and/or purification and/or identification of an interaction partner of said hyperimmune serum reactive antigen or fragment thereof.
33. A process for *in vitro* diagnosing a disease related to expression of the hyperimmune serum-reactive antigen or a fragment thereof according to any one of claims 11 to 14 comprising determining the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to any one of claims 1 to 7 or the presence of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11-14.
34. A process for *in vitro* diagnosis of a bacterial infection, especially a *S. pyogenes* infection, comprising analysing for the presence of a nucleic acid sequence encoding said hyperimmune serum reactive antigen and fragment according to any one of claims 1 to 7 or the presence of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14.
35. Use of the hyperimmune serum reactive antigen or fragment thereof according to any one of claims 11 to 14 for the generation of a peptide binding to said hyperimmune serum reactive antigen or fragment thereof, wherein the peptide is selected from the group comprising anticalines.
36. Use of the hyperimmune serum-reactive antigen or fragment thereof according to any one of claims 11 to 14 for the manufacture of a functional nucleic acid, wherein the functional nucleic acid is selected from the group comprising aptamers and spiegelmers.
37. Use of a nucleic acid molecule according to any one of claims 11 to 14 for the manufacture of a functional ribonucleic acid, wherein the functional ribonucleic acid is selected from the group comprising ribozymes, antisense nucleic acids and siRNA.

Abstract: The present invention discloses isolated nucleic acid molecules encoding a hyperimmune serum reactive antigen or a fragment thereof as well as hyperimmune serum reactive antigens or fragments thereof from *S. pyogenes*, methods for isolating such antigens and specific uses therefor





专利名称(译)	化脓性链球菌抗原		
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发明人	アンドレアス・マインケ エステル・ナデュ ビルギット・ヴィンクラー ディーター・ゲルプマン		
IPC分类号	C12N15/09 C12N1/15 C12N1/19 C12N1/21 C12N5/10 C07K14/305 C12P21/02 C07K16/12 C12P21/08 C12N15/115 C12N15/02 C12Q1/68 C07K1/107 A61P31/04 A61K39/09 A61K39/395 A61K48/00 G01N33/50 G01N33/15 G01N33/53 G01N33/569 A61K39/00 C07K14/315 C12N15/31 C12R1/46 G01N33/68		
CPC分类号	A61K39/00 A61P31/04 A61P37/04 C07K14/315 C07K16/1275 C07K2317/21 A61K39/0208		
FI分类号	C12N15/00.ZNA.A C12N1/15 C12N1/19 C12N1/21 C12N5/00.101 C07K14/305 C12P21/02.C C07K16 /12 C12N5/00.102 C12P21/08 C12N15/00.H C12N15/00.C C12Q1/68.A C07K1/107 A61P31/04 A61K39 /09 A61K39/395.R A61K48/00 G01N33/50.Z G01N33/15.Z G01N33/53.D G01N33/569.F C12N15/00.A C12N15/00.G C12N15/00.AZN.A C12N15/115.Z C12N5/16		
F-TERM分类号	2G045/AA34 2G045/AA35 2G045/DA13 2G045/DA36 2G045/FB02 2G045/FB03 4B024/AA01 4B024 /AA13 4B024/BA31 4B024/BA50 4B024/CA02 4B024/CA11 4B024/DA01 4B024/DA02 4B024/DA05 4B024/DA11 4B024/EA04 4B024/EA10 4B024/GA11 4B024/HA03 4B024/HA17 4B063/QA18 4B063 /QA19 4B063/QQ03 4B063/QQ06 4B063/QQ43 4B063/QQ52 4B063/QQ79 4B063/QR08 4B063/QR42 4B063/QR56 4B063/QR62 4B063/QS25 4B063/QS34 4B063/QX02 4B064/CA10 4B064/CA20 4B064 /CE12 4B064/DA01 4B064/DA15 4B065/AA01X 4B065/AA49X 4B065/AA49Y 4B065/AA57X 4B065 /AA87X 4B065/AA90X 4B065/AA90Y 4B065/AB01 4B065/AB04 4B065/AC14 4B065/BA02 4B065 /CA24 4B065/CA25 4B065/CA44 4B065/CA45 4B065/CA46 4C084/AA13 4C084/NA14 4C084/ZB351 4C085/AA03 4C085/AA14 4C085/AA16 4C085/BA14 4C085/BB41 4C085/CC07 4C085/DD62 4C085 /EE01 4C085/EE06 4C085/FF01 4C085/FF03 4C085/FF11 4C085/FF13 4C085/FF20 4H045/AA11 4H045/AA20 4H045/AA30 4H045/BA10 4H045/BA40 4H045/CA11 4H045/DA76 4H045/DA86 4H045 /EA29 4H045/EA31 4H045/EA52 4H045/FA20 4H045/FA72 4H045/FA74 4H045/GA26		
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摘要(译)

解决的问题：提供化脓性链球菌抗原，用于预防和治疗化脓性链球菌引起的细菌感染。分离的核酸分子，其编码与化脓性链球菌的超免疫血清反应的抗原或其片段。对所述超免疫血清具有反应性的抗原或其片段，分离此类抗原的方法及其特定用途。[选择图]
无

ストレプト コッカス・ ピオグリス 抗原様タン パク質	決定機能（ホモロジ による）	予測される免疫原性アミノ酸**	Q&Fおよびス クリーニング過 たりで選択した クローンの番号	同定された免 疫原性領域の 位置（アミノ 酸）	配列番号 （DNA、タン パク質）
		4-44, 59-65, 69-98, 101-107, 109-125, 131-144, 146-159, 168-173, 181-186, 191-200, 206-213, 229-245, 261-268, 288-301, 304-317, 323-328, 350-361, 374-384, 388-407, 416-425	A-12, E-5, N-2	1-114	1, 151
Spv0012	糖タンパク質	8-17, 49-64, 77-82, 87-96, 118-125, 127-140, 142-150, 153-159, 191-207, 212-218, 226-270, 274-287, 297-306, 325-331, 340-347, 352-369, 377-382, 390-398	F-2, E-16, K-24, N-29, F-12	29-226	2, 152
Spv0019	糖タンパク質 （細胞分裂および抗生 物質耐性）	4-16, 20-26, 32-74, 76-87, 93-108, 116-141, 148-162, 165-180, 206-215, 221-228, 230-236, 239-245, 257-268, 313-326, 330-335, 353-359, 367-375, 384-403, 414-434, 437-444, 446-453, 456-464, 478-487, 526-535, 541-552, 568-575, 577-584, 589-598, 610-618, 624-643, 653-665, 667-681, 697-718, 730-745, 755-761, 773-794, 806-821, 823-831, 837-845, 862-877, 879-889, 896-919, 924-930, 935-940, 947-955, 959-964, 969-986, 991-1002, 1012-1036, 1047-1056, 1067-1073, 1079-1082, 1086-1114, 1130-1135, 1148-1164, 1166-1173, 1180-1192, 1244-1254	D-3	919-929	3, 153
Spv0025	糖タンパク質 （糖タンパク質）	8-44, 62-74, 78-83, 99-105, 107-113, 124-134, 161-174, 176-194, 203-211, 216-237, 241-247, 253-266, 272-299, 323-349, 353-360	E-3, K-3, N-3	145-305	4, 154
Spv0031	糖タンパク質 （糖タンパク質）	15-39, 52-61, 72-81, 92-97	A-8	71-81	5, 155
Spv0103	糖タンパク質	13-19, 21-31, 40-108, 115-122, 125-140, 158-180, 187-203, 210-223, 235-245	B-4	173-186	6, 156
Spv0112	糖タンパク質 （糖タンパク質）	5-12, 19-27, 29-39, 59-67, 71-78, 80-88, 92-104, 107-124, 129-142, 158-168, 185-191, 218-226, 230-243, 256-267, 272-277, 283-291, 307-325, 331-344, 346-352	A-3, C-26	316-331	7, 157
Spv0115	糖タンパク質 （糖タンパク質）	6-28, 43-53, 60-76, 93-103	E-22, K-7, N-17, O-31, F-5	21-99	8, 158
Spv0166	糖タンパク質	10-30, 120-126, 145-151, 159-169, 174-182, 191-196, 201-206, 214-220, 222-232, 254-272, 292-307, 313-323, 332-353, 361-369, 389-396, 401-415, 428-439, 465-481, 510-517, 560-568	A-118, B-14, C-18, D-37, F-141, G-79, H-92, I-97, K-123, L-5, M-21, N-225	9-264	9, 159
Spv0167	糖タンパク質				