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附图 10 页

[54] 发明名称 识别凝血酶阴性的葡萄球菌和金黄色葡萄球菌的表面蛋白的交叉反应性单克隆抗体和多克隆抗体

[57] 摘要

提供了与凝血酶阳性的葡萄球菌细菌，例如溶血葡萄球菌发生交叉反应的多克隆和单克隆抗体，所述的抗体能够识别凝固酶阳性的和凝固酶阴性的葡萄球菌细菌的表面蛋白质。 从基于金黄色葡萄球菌和凝固酶阴性的葡萄球菌之间共有的特性分离的表面蛋白质可以制备抗体，这些重组表面蛋白质可用于制备本发明的抗体。 还提供了利用这些蛋白质和抗体用于治疗或抵抗各种各样的葡萄球菌的感染的疫苗和方法。

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1. 一种分离的抗体，其与葡萄球菌的表面蛋白质结合，所述蛋白质选自于下列组：SEQ ID NOS. 2、4、6、8、10、12、14、16、17、18、19 和 21。

2. 根据权利要求 1 所述的抗体，其中抗体针对所述表面蛋白质的 A 区域。

3. 根据权利要求 1 所述的抗体，其中抗体用于治疗或预防人类或动物的金黄色葡萄球菌感染。

4. 根据权利要求 1 所述的抗体，其中抗体适用于人类或动物的非肠道的，口部的，鼻内的，皮下的，aerosolized 或静脉内的给药。

5. 根据权利要求 1 所述的抗体，其中所述的抗体是单克隆抗体。

6. 根据权利要求 1 所述的抗体，其中所述的抗体是多克隆抗体。

7. 根据权利要求 5 所述的抗体，其中单克隆抗体是一种选自于下列组的类型：鼠的，嵌合的，人性化的，和人的单克隆抗体。

8. 根据权利要求 5 所述的抗体，其中抗体是一种单链单克隆抗体。

9. 根据权利要求 1 所述的抗体，它包括具有类似于一种抗体的结合特异性的抗体片段，所述的抗体结合到具有选自于下列组：SEQ ID NOS. 2、4、6、8、10、12、14、16、17、18、19 和 21 的序列的葡萄球菌的表面蛋白质。

10. 根据权利要求 1 所述的抗体，它针对具有选自于下列组：SEQ ID NOS. 2、4、6、8、10、12、14、16、17、18、19 和 21 的氨基酸序列的蛋白质。

11. 根据权利要求 1 所述的抗体，其中所述的表面蛋白质具有由选自于下列组的核酸序列 SEQ ID NOS. 1、3、5、7、9、11、13、15、20 和编码 Aap 蛋白质的 A 区域或其简并序列的核酸序列编码的一个氨基酸序列的核酸序列。

12. 含有权利要求 1 的抗体的分离的抗血清。

13. 一种诊断试剂盒，包括权利要求 1 的抗体和用于检测该抗体引起的结合的工具。

14. 根据权利要求 13 所述的诊断试剂盒，其中所述的用于检测结合的工具包括连接到所述的抗体的一种可检测标记物。

15. 一种用于诊断金黄色葡萄球菌感染的方法，包括将权利要求 1 的抗体加入到被怀疑感染了金黄色葡萄球菌的样品中，测定抗体是否已经结合到该样品。

16. 一种用于治疗或预防金黄色葡萄球菌感染的药物组合物，包括有效量的权利要求 1 的抗体和药学的可接受的介质，载体或赋形剂。

17. 一种治疗或预防金黄色葡萄球菌感染的方法，包括将有效量的权利要求 1 的抗体给人或动物患者给药。

18. 一种诱导免疫应答的方法，包括以致免疫量的选自于下列组：SEQ ID NOS. 2、4、6、8、10、12、14、16、17、18、19 和 21 的氨基酸序列的分离的蛋白质给人类或动物给药。

19. 根据权利要求 1 所述的分离的抗体，它具有结合到由 SEQID NOS. 1、3、5、7、9、11、13、15、20 的核酸序列和编码 Aap 蛋白质的 A 区域的核酸序列或其简并序列编码的氨基酸序列的能力。

20. 一种来自 DsqA 蛋白质的 A 区域 的分离的活性片段。

21. 根据权利要求 1 所述的分离的抗体，进一步包括生理学上的可接受的抗生素。

22. 一种用于治疗或预防金黄色葡萄球菌感染的疫苗，包括选自于下列组 SEQ ID NOS. 2、4、6、8、10、12、14、16、17、18、19 和 21 的蛋白质序列，和一种药学的可接受的介质，载体或赋形剂，所述的蛋白质的量可有效地激发免疫应答。

识别凝血酶阴性的葡萄球菌和金黄色葡萄球菌的表面蛋白的交叉反应性单克隆抗体和多克隆抗体

相关申请

本申请要求享受2001年6月15日递交的美国临时申请系列号60/298,098的利益。

发明领域

总的来说，本发明涉及来自金黄色葡萄球菌的表面蛋白质及其活性的区域例如它们的A功能域，它具有凝固酶阴性的葡萄球菌例如表皮葡萄球菌和 溶血葡萄球菌上的同源蛋白质，以及识别上述的蛋白质的抗体，具体地说，涉及分离的单克隆和多克隆抗体，它们识别来自金黄色葡萄球菌和凝固酶阴性的葡萄球菌的特定的蛋白质，以及抗金黄色葡萄球菌和凝固酶阴性的葡萄球菌的交叉反应，因此可用于疫苗，以及用于预防或治疗各种各样的由葡萄球菌的细菌引起的感染的方法。

发明背景

对于大多数引起动物和人类的传染病的微生物，在宿主中成功地形成集落是一个必需的过程。微生物的粘附是最后导致疾病的一系列事件的第一个重要步骤。借助细菌表面的特定的adhesins，通过粘附到宿主组织或血清限定的移植入的生物材料，例如导管，人工的关节，血管的移植片，病原微生物在宿主中形成集落。MSCRAMM®s (识别粘附的基质分子的微生物表面成分)

是细胞表面 adhesins 的一个家族，它们识别和特定地结合到宿主的细胞外的基质的不同的组分。一旦细菌成功地粘附并且在宿主组织中形成集落，他们的生理机能被急剧改变并且分泌受损害的成分例如毒素和水解蛋白质的酶。此外，粘连的细菌常常产生生物膜并且很快地变得对大多数的抗生素的杀戮效果更具抗性。

金黄色葡萄球菌产生从皮肤上的损害例如伤口感染，脓疱病，疖到包括肺炎，脓毒性的关节炎，脓毒病，心内膜炎的威胁生命的状况以及生物材料相关的传染病的范围的感染谱。已知金黄色葡萄球菌表达不同的 MSCRAMMs 的全部技能，它们独立地或者协调地促进微生物的粘附到特定的宿主组织组分。另外，葡萄球菌细菌的另一个类型被识别为凝固酶阴性的细菌，包括例如已知同样地表示 MSCRAMMs 的表皮葡萄球菌和溶血葡萄球菌，也对各种各样的细菌的感染和有关的疾病负有责任。关于这一点，通常 MSCRAMMs 由抗体，多克隆和单克隆抗体，对免疫学的攻击提供出色的靶。

然而，由于抗体本性非常特异的，就不同类型的葡萄球菌而言，例如一方面金黄色葡萄球菌(凝固酶阳性)和另一方面表皮葡萄球菌 和溶血葡萄球菌(凝固酶-阴性的)，研制显示不同的类型的细菌之间年的交叉反应性的抗体，仍然是值得注意的问题。这样的交叉的反应的抗体是特别令人想望的，因为他们具有使人类和动物患者致免疫的潜在性和提供抵抗由两种类型的葡萄球菌的细菌，即凝固酶阳性的细菌例如金黄色葡萄球菌和凝固酶阴性的细菌，例如表皮葡萄球菌和溶血葡萄球菌引起的感染潜在性。因此这样的抗体在预防或治疗各种各样的由葡萄球菌的细菌引起的感染中非常地有效。

发明概述

因此，本发明的目的之一提供识别来自凝固酶阳性的细菌例如金黄色葡萄球菌的 MSCRAMM®s 以及来自凝固酶阴性的细菌，例如表皮葡萄球菌和溶血葡萄球菌的 MSCRAMM®s 的单克隆抗体。

本发明的还有一个目的是识别和分离来自葡萄球菌的细菌的 MSCRAMM®s，以及他们的活性的区域例如 A 区域，该区域可用于产生与凝固酶阳性的和凝固酶阴性的葡萄球菌发生交叉反应的单克隆和多克隆抗体。

本发明的另一个目的提供可以识别来自凝固酶阴性的葡萄球菌的表面蛋白质例如 DgsK 蛋白质的 A 区域，同时识别来自金黄色葡萄球菌的表面蛋白质例如 SasA 蛋白质的分离的抗体。

本发明的又一方面是利用本发明的分离的蛋白质，A 区域和抗体生产用于治疗或预防葡萄球菌的感染的疫苗，以及 提供了其中将本发明的疫苗和抗体可用于预防或治疗葡萄球菌的感染的方法。

这些和其他的目的通过本发明实现，所述的发明包括识别和分离一种类型的葡萄球菌的细菌例如凝固酶阴性的或凝固酶阳性的葡萄球菌的表面蛋白质，它导致产生识别两种类型的葡萄球菌的表面蛋白质的交叉的反应性的抗体，并且因此将抗体用于治疗或预防各种各样葡萄球菌的感染的疫苗和方法。本发明还涉及从这些表面蛋白质产生多克隆和单克隆抗体，以及它们用于预防或治疗葡萄球菌的感染。

对本领域内技术人员而言，根据阅读本说明书和/或在此处记载的参考文献，这些具体的实施方案和在公开的发明的精神和范围之内的其他的供替代的选择和改变是显而易见的，所有引用的文献都被并入本文。

附图简述

附图 1 是本发明的 in silico 预测的蛋白质的一级的结构图。

附图 2 显示本发明的开放读框表达的N－末端 His 标记的纯化的重组的蛋白质的考马斯亮蓝染色凝胶。

附图 3A-3C 显示分别用抗-KesK 抗体(附图 3A)，抗-KnkA 抗体（附图 3B）和抗 DsqA 抗体（附图 3C）探测时金黄色葡萄球菌的细胞壁提取物的 Western 印迹。

附图 4A-4B 显示表达金黄色葡萄球菌的 MSCRAMM®称为 KnkA（附图 4A）和 KesK（附图 4B）的乳酸乳球菌的点印迹和 Western 免疫印迹。

附图 5A-5D 代表用康复的人血清体内检测表达本发明重组 LPXTG 蛋白质，包括 RrKn 和 RrKN2(附图 5A)，Kesk1 和 Kesk2A（附图 5B），KnkA（附图 5C）和 DsqA2（附图 5D）的探测情况。

附图 6 显示证实抗金黄色葡萄球菌 SasA 的兔多克隆抗体与从表皮葡萄球菌 HB 细胞表面释放的蛋白质以及来自从表皮葡萄球菌克隆的 DsgK 的重组 A-区域发生交叉反应的 Western 印迹分析结果。

优选的实施方案的详细描述

根据本发明，提供了来自凝固酶阳性的葡萄球菌的细菌例如金黄色葡萄球菌以及凝固酶阴性的葡萄球菌的细菌例如表皮葡萄球菌 和溶血葡萄球菌,的特定的表面蛋白质，包括其活性片段例如这些蛋白质或可以产生识别完整的蛋白质的抗体的其他的表位区域的A区域。根据本发明，基于MSCRAMM®s (识别粘附基质分子的微生物表面成分)的一些共有的特征实施候选肽序列和蛋白质的鉴定和分离，在大多数情况下，这些特征共价地固定到细胞壁肽葡聚糖。这些表面蛋白质具有下列的共有的特征可用于确定和分离本发明的序列，即: (i) Sec-依赖性分泌必需的N-末端信号肽(长度大约 40 个残基), (ii)一个富含脯氨酸和甘氨酸残基或由丝氨酸和门冬氨酸盐二肽重复组成点的跨壁功能域; (iii)蛋白质共价固定到肽葡聚糖中的五个甘氨酸交联桥必需的LPXTG基序，(iv)一个疏水的跨膜功能区，跟随其后的(v)几个带正电荷的残基。

根据本发明，按照以上所述的特性，通过开发金黄色葡萄球菌的完整的基因组，识别了至少八个新的开放读框编码的蛋白质，具有分泌和固定象征MSCRAMMs的基序(即的携带 N-末端信号肽和跟随疏水的功能区之后的 C－末端 LPXTG 基序和一个带正电的尾部)。表1阐明所识别的蛋白质的一览表，包括在金黄色葡萄球菌基因组中的分布，蛋白质的大小和C-末端细胞壁排序序列。

表 1

名称	分布	大小	C-末端
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALL **ARRRSKKEKE**S
DsqA	ENCSJM	-1363-2283aa	**LPDTG**DSIKQNGLLGGVMTLLVGL GLM**KRKKKKDENDQDDSQ**A
KesK	ENCSJM	-909 aa	**LPKTG**ETTSSQSWWGLYALLGMLA LFIP**KFRKESK**
KrkN2	ENCSJM	-278 aa	**LPKTG**LTSVDNFISTVAFATLALLGS LSLLLF**KRKESK**
KrkN	ENCSJM	-661 aa	**LPQTG**EESNKDMTLPLMALIALSSI VAFVLP**RKRKN**
RkaS	ENCSJM	-801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLI ATV**RRRK**AS
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLML LA**RRRKN**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVL MIWLS**RRNKLKNK**A

缩写: eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50。

8 个蛋白质中的 6 个存在于已经被测序的所有六个葡萄球菌的基因组中，剩余的 2 个存在于 5/6 的这些基因组中。

根据本发明，获得上述的蛋白质的氨基酸和编码它的核酸序列，如下所述: Ekes MRSA-SEQ ID NO:1 (DNA 序列); EkeS~MRSA-SEQ ID NO: 2 (蛋白质序列); DsqA(8325)-SEQ ID

NO: 3 (DNA 序列); DsqA(8325)-SEQ ID NO: 4 (蛋白质序列); KesK1(8325)-SEQ ID NO: 5 (DNA 序列); KesK1(8325)-SEQ ID NO: 6 (蛋白质序列); KrkN2(8325)--SEQ ID NO: 7 (DNA 序列); KrkN2(8325)-SEQ ID NO: 8 (蛋白质序列); KrkN (8325)-SEQ ID NO: 9 (DNA 序列); KrkN (8325)-SEQ ID NO: 10 (蛋白质序列); RkaS (COL)-SEQ ID NO: 11 (DNA 序列); RkaS (COL)-SEQ ID NO: 12 (蛋白质序列); RrkN (8325)-SEQID NO: 13 (DNA 序列); RrkN(8325)-SEQ ID NO: 14 (蛋白质序列); KnkA(8325)-SEQ ID NO: 15 (DNA 序列); KnkA (8325)-SEQII7 NO: 16 (蛋白质序列)。

根据本发明，可以从上述的蛋白质或他们的活性区域例如A区域产生分离的抗体以便能够识别上述的蛋白质和/或上述的功能区。这些抗体可以是单克隆的或多克隆的。如果需要多克隆抗体，可以本领域内熟知的许多常规方法的任何一种制备。一种典型的方法是，可以将需要的表面蛋白质或其活性的区域注射到合适的宿主动物，例如，小鼠或兔子，在合适的时间期间之后，可以从该宿主动物分离和回收想要的抗体。对于单克隆抗体，根据本发明，可以许多合适的方法包括例如熟知的 Kohler 和 Milstein, Nature 256: 495-497 (1975)方法，本领域内已知的任何其他方法，例如美国专利 Nos. 6,331,415; 5,981,216; 5,807,715; 和 4,816,567; 欧洲专利申请 519,596; 和 PCT 公开 WO 00/71585 公开的方法制备，所有这些专利文献都通过在此引述而合并于本文。这些方法包括其制备如以本领域内熟知的方式进行嵌合，人性化，或人的单克隆抗体。仍然进一步地，可以从一个单链，例如轻或重链制备，以及还可以从保持完整的抗体的结合特性(例如，特异性和/或亲合力)的抗体的活性的片段制备单克隆抗体。活性的片段是指具有与完全抗体相同的结合特异性的抗体片段，所述完全抗体结合到来自不同的类型的葡萄球菌细菌(即凝固酶阴性的,或凝固酶阳性的)的特定的表面蛋白质或其同系物。本文术语"抗体"包括所

述的片段。另外，也可以利用本发明的单克隆或多克隆抗体制备抗血清，可以本领域内熟知的许多合适方式制备。

如上所述，可以本领域内熟知的许多合适的方式制备本发明的抗分离的表面蛋白质和/或其活性的区域的抗体，例如上述所述的完全建立的 Kohler 和 Milstein 方法，可用于产生单克隆抗体。例如，在这样的一种方法的预备的步骤中使用，可以在长时间的时期用本发明的纯化的重组 MSCRAMM®或其活性的部分长期给小鼠每一周腹膜内注射一次，随后测试从免疫接种的老鼠获得的血液以测定与纯化的蛋白质的反应性。在识别老鼠与该蛋白质的反应性之后，将从小鼠脾脏分离的淋巴细胞与小鼠脊髓细胞融合以产生抗本发明的表面蛋白质的抗体阳性的杂交瘤，然后分离和培养，随后纯化和使之形成同位型。

为了产生本发明的单克隆抗体，优选的是利用本发明的重组制备的 MSCRAMM®'s 来制备，利用本领域内熟知的许多标准方法可以制备这些重组子并且分离。例如，一种这样的方法使用了大肠杆菌表达载体 pQE-30 作为克隆和表达重组蛋白质和肽的表达载体。在一个优选的方法中，利用 PCR，从上面描述的序列扩增识别为 DgsK 或 SasA 的表面蛋白质的 A 区域，再克隆到大肠杆菌表达载体 PQE-30 (Qiagen)，以允许表达一种含有六个组氨酸残基的重组融合蛋白质。 随后将该载体转化到大肠杆菌 ATCC 55151，在 15-升发酵罐中生长到光密度 (OD600) 为 0.7，用 0.2 mM 异丙基-1 β -D 半乳糖苷 (IPTG)诱导 4 小时。利用 AG Technologies 中空纤维组件(孔大小 0.45 um) 收集细胞，将细胞浆在- 80 C 冷冻。利用 2 次穿过 French Press，1100psi，将细胞在 1X PBS (10 mL 缓冲液/1 克的细胞浆)裂解。将裂解的细胞 17,000rpm 旋转 30 分钟以除去细胞碎片。将上清液经过装备了 0.1M $NiCI_2$ 的 5-毫升 Hi 俘获 Cheating (Pharmacia)柱。在上样之

后，用 5 个柱体积的 10mM Tris，pH 8.0，100mM NaCI (缓冲液 A) 洗涤柱子。利用超过 30 个柱体积的 0-100% 梯度的 10mM Tris，pH 8.0，100mM NaCI，200 mM 咪唑 (Buffer B)洗脱蛋白质。SdrGN1N2N3 或 SdrGN2N3 在-13% Buffer B (~26mM 咪唑)被洗脱。监测 280nm 处的吸光率。在 1x PBS 中透析含有 SdrGN1 N2N3 或 SdrGN2N3 的馏分。

接著，然后将各个蛋白质经过一个内毒素除去方案。在该方案中所使用的缓冲液通过一个 5-毫升 Mono-Q 琼脂糖 (Pharmacia)柱而没有内毒素。将蛋白质平衡地分到 4x 15 毫升试管中。各个试管的体积用缓冲液 A 加到 9 毫升。将 1 毫升 的 10% Triton X-114 加入到各个试管中，在 4 ℃旋转保温 1 小时。将试管置于 37℃水浴中以使相位分离。将试管以 2,000rpm 旋转 10 分钟，收集各个试管的上面的含水的相，用去污剂反复提取。将 2 次提取的含水相合并，传递过带有 0. 1M NiCl2 的 5-mL IDA cheating (Sigma) 柱，以除去剩余的洗涤剂。用 9 个柱体积的 Buffer A 洗涤该柱，然后用 3 个柱体积的 Buffer B 洗脱该蛋白质。将洗脱液通过 5-毫升的 Detoxigel (Sigma) 柱，收集流出物，再上样到柱。收集第二次过柱的流出物，在 1x PBS 中透析。分析纯化的产物的浓度，纯度和内毒素水平，然后给小鼠给药。

在该优选的方法，以下面的方式从上面识别的重组蛋白质可以制备本发明的单克隆抗体。在该方法中，将大肠杆菌表达的和纯化的重组 SasA 和 DsgK 蛋白质用于制备一组鼠的单克隆抗体，而将小鼠血清用作为多克隆抗体的来源。简单地说，一组 Balb/C 或 SJL 小鼠接收了一系列皮下的免疫接种 1-10 mg 溶液蛋白质或与下面表 2 描述的佐剂混合的蛋白质。

表 2 免疫接种方案

RIMMS

注射	天数	数量 (微克)	途径	佐剂
#1	0	5	皮下	FCA/RIBI
#2	2	1	皮下	FCA/RIBI
#3	4	1	皮下	FCA/RIBI
#4	7	1	皮下	FCA/RIBI
#5	9	1	皮下	FCA/RIBI

常规注射	天数	数量 (微克)	途径	佐剂
原始	0	5	皮下	FCA
加强#1	14	1	腹膜内	RIBI
加强#2	28	1	腹膜内	RIBI
加强#3	42	1	腹膜内	RIBI

在杀死时(RIMMS)或加强后几天收集(常规的)血清，在 ELISA 测定中测定抗 MSCRAMM®蛋白质或对完整的细胞(表皮葡萄球菌和金黄色葡萄球菌) 的效价。在最后的加强之后 3 天，去除脾脏或淋巴结，挑开成单细胞悬浮液，收集淋巴细胞。然后将淋巴细胞与 P3X63Ag8.653 骨髓瘤细胞系(ATCC &CRL-1580)融合。根据 Current Protocols in Immunology (第 2 章，第 2 单元)中的生产单克隆抗体的方案进行细胞融合，随后涂覆平板和喂养，所述文献都通过在此引述而合并于本文。

然后利用标准的 ELISA 分析方法，从融合产生的任何克隆中筛选特异的抗-SasA 抗体的产生。扩增阳性的克隆，进一步通过流式血细胞计数测试完整的细菌的细胞结合测定中的活性以及 Biacore 分析中 SasA 的结合。在整个 Biacore 分析中，流速保持在 10 毫升/分钟不变。在注射 SasA 或 DgsK 之前，借助于

RAM-Fc 结合，将测试抗体吸附到芯片。在时间 0，将浓度为 30 mg/ml 的 SasA 或 DgsK 注射过芯片 3 分钟，随后解离 2 分钟。对该阶段的分析测定 Mab/SasA 和 DgsK 相互作用的相对关系和解离常数。

接著，对上面提到的抗体与完整细菌的结合情况进行测试。在该测试中，用兔子 IgG (50mg/ml)封闭之后，收集，洗涤细菌的样品金黄色葡萄球菌 Newman，金黄色葡萄球菌 60，金黄色葡萄球菌 397(Sal6)，金黄色葡萄球菌 Wood，金黄色葡萄球菌 8325-4，甲氧苯青霉素抗性的金黄色葡萄球菌 MRSA 16，表皮葡萄球菌 ATCC 35984，表皮葡萄球菌 HB，表皮葡萄球菌 CN-899 和溶血葡萄球菌 ATCC 43253，用浓度为 2 pg/ml 的 Mab 或仅用 PBS(对照)保温。在用抗体保温之后，将用作为检测抗体的山羊-F (ab') 2-抗-小鼠-F (ab') 2-FITC 用于孵育细菌的细胞。在抗体标记之后，用 FACS 管径 流式细胞计数器抽吸细菌的细胞以分析荧光射出 (刺激: 488，发射: 570)。 对于各个细菌的菌株，收集和检测 10,000 个样品。这些资料显示抗金黄色 SasA 的抗体能够识别凝固酶阴性的葡萄球菌的表面的同源的蛋白质。该资料支持 Western 印迹分析，表明抗金黄色葡萄球菌 SasA 的兔子多克隆抗体与从表皮葡萄球菌 HB 细胞表面释放的蛋白质以及来自于从表皮葡萄球菌克隆的 DsgK 的重组 A - 区域发生交叉反应 (参见附图 6 和下表 3)。

表 3 多克隆血清反应性

	Newman	67-0	397 (SAL6)	Wood 46	8325-4	MRSA16	ATCC 3598	HB	CN-899	ATCC 4325
							4			3
常规小鼠血清	-	-	-	-	-	-	-	-	-	
小鼠抗 SasA	+	+	+/-	-	+	+	+	+	+	+

虽然利用重组形式的本发明的表面蛋白质生产抗体是优选的，但是该抗体可以从这些蛋白质天然分离的和纯化形式或其活性区域例如 A 区域制备抗体，以类似于上面所述的方式利用这些蛋白质或活性的区域可以产生单克隆抗体或多克隆抗体以获得这样的抗体。仍然其他的常规的方法，利用重组或天然的纯化蛋白质或其活性区域，可用于产生本发明的抗体，正如本领域内技术人员可以识别的。

正如本领域内技术人员可以认识到的，本发明的抗体也可以配制成可用于人或动物患者给药的合适的药学的组合物，以便治疗或预防葡萄球菌的细菌引起的感染。含有本发明的抗体的药物组合物，或其有效的片段，可以与本领域内常用的合适的药物介质，赋形剂或载体结合配制，包括例如盐水，葡萄糖，水，甘油，乙醇，其他的治疗化合物和其结合使用。本领域内技术人员应该认识到，所使用的特定的介质，赋形剂或载体将依据患者和患者的状况而改变，如本领域内技术人员将会认识到的各种各样的给药方式适用于本发明的组合物。在本申请中公开的以药物组合物给药的合适的方式包括，但不限于，局部的，口部的，肛门的，阴道的，静脉内的，腹膜内的，肌内的，皮下的，鼻内的和真皮内的给药。

对于局部的给药，将组合物配制成软膏，乳膏，凝胶，洗液，滴剂 (例如眼药水和耳朵滴剂)，或溶液(例如漱口剂)。 可以将组合物埋植于伤口或外科的敷料，缝合线和气溶胶。该组合物可以含有常规的添加剂。例如防腐剂，溶剂以促进渗透和润滑药。局部的制剂也可以含有常规的载体例如乳膏或油膏基底，乙醇或油酰醇。另外，通常也可以将抗体组合物，和涉及其他 MSCRAMM® 的组合物，疫苗，方法和应用的其他的信息用于本发明，涉及前面提到的 MSCRAMM®和它们的活性的区域和其抗体，这些其它的 MSCRAMM®公开于例如美国专利 5,175,096; 5,320,951; 5,416,021; 5,440,014; 5,571,514; 5,652,217; 5,707,702; 5,789,549; 5,840,846; 5,980,908; 6,086,895; 6,008,341; 6,177,084; 5,851,794 和 6,288,214; 所有这些专利都通过在此引述而合并于本文。

本发明的抗体组合物也可以与其量可有效地加强致免疫的应答的合适的佐剂一起给药。例如，合适的佐剂可以包括广泛用于人的明矾 (磷酸铝或氢氧化铝),和其他的佐剂例如皂甙和其纯化的组分 Quil A，弗氏完全佐剂，RIBBI 佐剂，和其它用于研究和兽医应用的佐剂，还有其他以化学方法定义的制剂例如 muramyl 二肽，一磷酰脂类 A，磷脂轭合物例如 Goodman-Snitkoff 等人在 J. Immunol. 147: 410-415 (1991) 描述的，该文献通过在此引述而合并于本文，蛋白脂质体内的偶合物的形成胶囊如 Miller 等人，J.Exp.Med.176:1739-1744 (1992)，该文献通过在此引述而合并于本文，脂类载体中蛋白质形成胶囊如 NovasomeTM 脂类载体(Micro Vescular System, Inc., Nashua, NH)也可以使用。

在任何情况下，本发明的识别蛋白质或如上文提出的它们的活性的区域的抗体组合物可用于预防或治疗葡萄球菌的感染的方法，可用于抑制葡萄球菌的细菌与宿主组织和/或细胞的结合。根据本发明，提供了预防或治疗葡萄球菌的感染的方法，包括以

有效量的抗体给本文提出的表面蛋白或其活性的亚区域以便治疗或预防葡萄球菌的感染。另外，这些单克隆抗体可用于损害葡萄球菌的细菌与宿主细胞的结合。

因此，根据本发明，将本发明的抗体以如上所述的任何常规的方法 (例如，局部的，非肠道的，肌内的，等) 给药，因此当将有效量的抗体组合物给人或动物患者给药时，提供了一种治疗或预防人类或动物患者的葡萄球菌的感染的非常地有用的方法。有效量是指足以阻止细菌粘合，抑制葡萄球菌的细菌结合到宿主细胞从而可用于治疗或阻止葡萄球菌的感染的使用水平，例如抗体效价的水平。如本领域内普通技术人员认识到的，有效地治疗或预防葡萄球菌的感染所必需的抗体效价的水平将依据患者的特性和健康状况，和/或预存在的葡萄球菌的感染的严重程度。

除了用于治疗或预防葡萄球菌的感染的方法中，本发明的抗体也可用于葡萄球菌的蛋白质的特定的检测或作为研究工具。本文所述的术语"抗体"包括单克隆，多克隆，嵌合，单链，双特异性，simianize，和人性化的或灵长目化的抗体以及 Fab 片段，例如保持抗体与上面详细说明的表面蛋白质的抗体的结合特异性的那些片段，包括 Fab 免疫球蛋白表达文库的产物。因此，本发明涉及单链的使用例如抗体的可变的重和轻链。这些类型的抗体或抗体片段的制备是本领域内技术人员熟知的。在本发明中，抗表面蛋白质或上面所述的它们的活性的区域的抗体 可以制备，分离和/或纯化，然后用于治疗或免受葡萄球菌的感染。

上面描述的任何抗体可直接用可检测的标签进行标记以识别葡萄球菌细菌和对其定性。免疫测定中使用的标记物通常是本领域内技术人员已知的，并且包括酶，放射性同位素，荧光，发光的和产色的物质，包括有色的颗粒例如胶态的金或胶乳珠子。合适的免疫测定包括酶联免疫吸附(ELISA)。

或者，通过与具有免疫球蛋白亲合力的标记的物质可以间接标记该抗体。该抗体可以与第二物质偶合，用已标记的第三物质进行检测，该第三物质与偶合到抗体的第二物质具有亲和力。例如，可以将抗体结合到生物素，利用标记的抗生物素蛋白 或链生抗生物素蛋白可以检测抗体－生物素偶合物。类似地，可以将该抗体偶合到半肝素，利用标记的抗半肝素抗体检测抗体－半肝素偶合物。这些和其他标记抗体和分析偶合物的其他方法是本领域内技术人员熟知的。

根据本发明，还提供了被设计为治疗或保护其抵抗葡萄球菌感染的主动或被动免疫接种疫苗， 可以利用许多本领域内熟知的常规疫苗制备方法从以上提出的表面蛋白质或活性区域制备这些疫苗。对于典型的疫苗， 将致免疫量的合适的表面蛋白或其活性片段与合适的药物学可接受载体，媒介物或赋形剂结合，合适的是可以以有效地免疫接种人或动物患者的疫苗的量给药。本领域技术人员认识到致免疫量是指能够在人或动物患者中产生免疫应答的蛋白质或活性片段或其亚片段的量。

除了借助于将免疫量的本发明的蛋白质或活性片段导入或给药产生的抗体的活性疫苗以外，也可以将本发明的分离的抗体或活性片段用于研制抗钩环感染的被动免疫接种的疫苗。在这样的情况下，可以将如上所述的抗体组合物，即有效量的抗体和药物学可接受的载体，媒介物或赋形剂以适当方式给药到人或动物患者。

因此，本发明的蛋白质或其活性片段可用作为活性疫苗，本发明的抗体可用作为被动疫苗，可用于提供合适的抗体以治疗或予防葡萄球菌感染。本领域内技术人员将会认识到，可以将一秒包装以适用于许多方式给药，例如非肠道的(即肌内的，透皮的或皮下的)给药或 鼻咽的(即鼻内的)给药。一种这样的方式是将

疫苗通过肌内注射到例如三角肌，但是，给药的特定方式将依赖于待治疗的细菌感染的特性和患者的状况。优选的是将该疫苗与药物学可接受的载体，媒介物或赋形剂结合以有助于给药，通常该载体是有或没有防腐剂的水，或缓冲盐水。该疫苗可以是在给药时重悬浮的冻干形式或溶液形式。

另外，在某些情况下，如必要可以将本发明的抗体进行修饰，以对给药患者的致免疫性降低，例如,如果该患者是人。通过将杂交瘤衍生的抗体的 complimentarity 表位移植到如 Jones 等人，Nature 321:522-525 (1986) 或 Tempest 等人/Biotechnology 9: 266-273 (1991) 描述的人单克隆抗体而将抗体“人性化”或通过将免疫球蛋白可变区中的表面接触的鼠骨架残基改变为模拟同源的人骨架配体如由 Padlan，Molecular Imm. 28: 489-498 (1991) 描述而进行"胶合"，这些文献都通过在此引述而合并于本文。甚至于进一步地，如果需要，本发明的单克隆抗体可以与合适的抗生素结合给药以进一步加强所述组合物抗击细菌感染的能力。

除了治疗人或动物患者以外，本发明的组合物也可以用于停止或予防医学装置或其他生物材料例如移植片的感染。待用抗体，蛋白质和活性片段包被的医学装置或聚合物生物材料包括，但不限于钩环，缝合线，复位心脏瓣膜，心脏的协助装置，硬的和软的接触透镜，眼内的透镜植入片 (前的室或后的室)，其他的植入片例如角膜的镶嵌物，kerato-修补物，血管的斯滕特氏印模，epikeratophalia 装置，绿内障分流术，视网膜的钩环，巩膜的扣子，牙齿的修补物，thyroplastic 装置，laryngoplastic 装置，血管的移植片，软的和硬的组织修补物，包括但不限于，泵，电的装置包括刺激器和记录器，听觉的修复术，起搏器，人工的喉，牙齿的植入片，乳房的植入片，阴茎的植入片， cranio/脸的腱，人工的关节，腱，纽带，menisci，和磁盘，人工的骨骼，人工器

官包括人工胰腺，人工心脏，人工的肢，和心脏瓣膜，斯滕特氏印模，金属丝，导向装置丝，静脉内的和中央的静脉的导管，激光和气球血管成形术装置，血管的和心脏装置(管子，导管，气球)，室的协助，血透析组合物，血氧合器，尿道的/输尿管的/泌尿的装置 (Foley 导管，斯滕特氏印模，管和气球)，导气管导管(气管内的和气管造口术管和胶管管头)，肠内的喂养管(包括 nasogastric，胃内的和空肠的管)，伤口排水管，用于引流体腔的管例如胸膜的，腹膜的，颅侧的和心包的 cavities，血袋，测试管，血收集管，vacutainers，注射器，针，吸移管，吸量管尖端，和血造管。

本领域内技术人员将会明白，本文所用的术语"被包被"或"包被"是指将抗体或活性片段或其衍生的药物组合物应用到装置的表面，优选的是与葡萄球菌细菌感染接触的外表面。该装置的表面不必完全被蛋白质，抗体或活性片段所覆盖。

本发明抗体给药的优选剂量是有效地抑制或治疗葡萄球菌感染的量，易于认识到该量将大大依赖于感染的特性和患者的状况。如上所述，用于本发明的抗体或药物制剂的“有效量”是指无毒但足以产生需要的予防或治疗效果的剂量。正如上文指出的，所需要的抗体或特定试剂的精确量将随患者而变化，取决于患者的种类，年龄，和总的状态，待治疗的状况的严重程度，所使用的特定的载体或赋形剂和给药方式等等。因此，特定抗体组合物的“有效量"将基于特定的环境而变化，普通技术人员利用唯一的常规试验可以测定各种应用情况下合适的有效量。可以将该剂量调节到适应于以该组合物给药的个体，并且随患者的年龄，重量，代谢而变化。该组合物还可以含有稳定剂或药物学可接受的防腐剂，例如硫汞撒 (乙基 (2-mercaptobenzoate-S) 汞钠盐) (Sigma Chemical Company, St. Louis, MO)。

当与合适的标记物或其他合适的可检测的生物分子或化学物质一起使用时，本文描述单克隆抗体可用于体内或体外诊断葡萄球菌感染或检测葡萄球菌细菌的目的。通过这样的抗体的使用也有助于试验室研究。各种类型的标记物和将标记物偶合到本发明的抗体的方法是本领域内技术人员熟知的，例如下面列出的一种方法。

例如，可以将抗体偶合到 (直接或通过螯合剂)放射性标记物例如，但不限于 ^{32}P，^{3}H，^{14}C，^{35}S，^{125}I，或 ^{131}I。通过例如闪烁计数，γ射线分光光度计 放射自显影的方法可以检测标记物。也可以使用生物发光标记物，例如萤火虫荧光素衍生物。采用常规方法生物发光物质可以共价结合到该蛋白质，当酶例如荧光酶催化引起生物发光的与 ATP 的反应以散发光子时，可以检测标记物蛋白质。也可以将荧光团用于标记蛋白质。荧光团的例子包括荧光和衍生物， 藻红蛋白，allo-藻蓝蛋白，藻蓝蛋白，硷性蕊香红，和 德克萨斯红。通常荧光团可以通过荧光检测器进行检测。

通过对如上所述的抗体进行标记和根据本领域内技术人员熟知的方法例如免疫荧光显微镜，利用如 Warren 等人 (Mol. Cell. Biol., 7: 1326-1337，1987)描述的程序，对标记物进行检测可以测定细胞中配体的定位。

如上所述，本发明的单克隆抗体，或活性部分或其片段特别适用于干扰负责感染的葡萄球菌病原体和哺乳动物宿主之间的起始物理相互作用，这种对物理相互作用的干扰可用于治疗患者和 in-dwelling 医学装置予防或降低细菌感染以使它们在使用时更安全。

在本发明的另一个实施例中，提供了一种可用于分离和识别葡萄球菌细菌感染的试剂盒，包括在单个容器中的合适形式，例

如冻干的本发明的抗体，然后通过加入怀疑含有葡萄球菌细菌的含水的样品而变成活性。这样的试剂盒通常包括用于储存合适形式抗体和合适的免疫检测试剂的合适的容器，所述的免疫检测试剂允许识别结合到本发明的表面蛋白质或抗体的复合物。通常，这些试剂盒含有本发明的抗体和识别当来自患者的样品导入到该抗体时识别结合的抗体的工具。例如，合适的免疫检测试剂可以包括合适的可检测的信号或标记物，例如生物素或产生可检测的颜色的酶等，可以连接到抗体或用于其他合适的方式中标记物以便当抗体结合到抗原时提供可检测的结果。

简单地说，识别和结合到本发明的表面蛋白质的本发明的抗体或其活性片段可用于治疗各种各样的人和动物患者的葡萄球菌感染，以及用于医疗或其他 in-dwelling 装置。 根据本发明，由于这些蛋白质的特性，以及它们含有与其他类型的葡萄球菌细菌的蛋白质共有的表位，即来自凝血酶阴性葡萄球菌的蛋白质将产生识别来自金黄色葡萄球菌的同源蛋白的抗体或者相反，本发明的抗体将显示交叉反应性和应该有效地抗击广谱的葡萄球菌感染。因此，本发明提供了用于治疗或抵抗广谱葡萄球菌感染的方法和改善的方法中的组合物。

实施例

提供下面的实施例，举例说明本发明的优选的实施方式的各个方面。本领域内技术人员应该认识到实施例中公开的技术允许代表发明人发现的技术以实施本发明，因此可以认为构成了实施本发明的优选的方式。但是，本领域内技术人员应该认识到，在本发明公开的基础上，可以在公开的特定的实施方式中进行许多改变，仍然可获得类似的结构而不脱离本发明的精神和范围。

实施例 1. 金黄色葡萄球菌的 MSCRAMM's 的分离和测序

已知金黄色葡萄球菌表达一类表面结合的蛋白质，所述的蛋白质通过允许细菌避免宿主防御和通过作为 adhesins 对致病性起重要作用。已知这些蛋白质是 MSCRAMMs (识别粘附的基质的分子的微生物表面成分)，在大多数情况下，可以共价结合到细胞壁肽葡聚糖。它们有几个共同的特征: (i) Sec-依赖性分秘所需要的 N-末端信号肽 (长度约 40 个残基), (ii)富含脯氨酸和甘氨酸残基或由丝氨酸和天冬酰胺二肽重复区组成的跨膜区， (iii) 该蛋白质与肽葡聚糖中的五甘氨酸桥键共价结合需要的 LPXTG 基序，(iv)疏水的跨膜区，以及其后的(v)几个带正电荷的残基。

通过开发金黄色葡萄球菌的整个基因组序列，鉴别 8 个编码具有分秘和锚基基序指示 MSCRAMMs 的蛋白质的新的开放读框(即携带 N-末端的信号肽和 C－末端 LPXTG 基序，随后跟随一个疏水的功能域和一个带正电荷的尾部)。下面的表说明了所识别的蛋白质名录，包括他们在基因组中的分布，他们的蛋白质大小，和挑选 C-末端细胞壁的序列。

名称	分布	大小	C-末端
EkeS	ENCSJM	2189 aa	**LPNTG**SEEMDLPLKELALITGAALL**ARRRSKKEKE**S
DsqA	ENCSJM	-1363-2283aa	**LPDTG**DSIKQNGLLGGVMTLLVGLGLM**KRKKKKDENDQDDSQ**A
KesK	ENCSJM	-909 aa	**LPKTG**ETTSSQSWWGLYALLGMLALFIP**KFRKESK**
KrkN2	ENCSJM	-278 aa	**LPKTG**LTSVDNFISTVAFATLALLGSLSLLLF**KRKESK**

KrkN	ENCSJM	-661 aa	**LPQTG**EESNKDMTLPLMALIALSSI VAFVLP**RKRKN**
RkaS	ENCSJM	-801 aa	**LPKTG**TNQSSSPEAMFVLLAGIGLI ATV**RRRK**AS
RrkN	NCSJM	1629 aa	**LPKTG**LESTQKGLIFSSIIGIAGLML LA**RRRKN**
KnkA	NCSJM	629 aa	**LPKAG**ETIKEHWLPISVIVGAMGVL MIWLS**RRNKLKNKA**

缩写：eMRSA-16; N, 8325; C, COL; S, MSSA; J, N315, M, Mu50。

8 个蛋白质中的 6 个存在于已经被测序的所有六个葡萄球菌的基因组中，剩余的 2 个存在于 5/6 的这些基因组中。

下面是 DNA 和蛋白质序列的名录：

Ekes MRSA (SEQ ID NO : 1)

acaacacagcagagaatagacaaccaggaggaaaacgaaatgaatttgttaaagaaaaataaatatagtattag
aaaatataaagtagggatattctctactttaatcgggacagttttattactttcaaacccaaatggtgcacaagctttaac
tacggatcataatgtgcaaggtggttcaaatcaagcattacctggcaactcacaaaatacaaatgccgatactaatc
gagacatagtaaatgattcgcaaaatactcctaatgcacatgcaacagacaatacatcaacaaatcaagcattgac
taatcatcaaaacgttgatgtggcaaatcaagtcgggcctgctccaatacagcctagcgcgtcgcctgcgcaaaata
ataataattctaatgctaattcaacagcaacagagccagcggcgaatacaaataataatttagcatcaaataacaat
acattaaacgtgcctaataatacagataacaatgattcagcgcgtcatctgactttaaaagaaattcaagaagatgtt
cgtcattcgtctgataagccagagttagttgcgattgctgaagaagcatctaatagaccgaaaaagagaagcagac
gtgctgcgccaacagatcctaatgcaacaccagcagatccaacggctacaccagcagatccaacggcaggaaat
ggtagtgcaccagttgcaattacagcgccatacacgccaacaactgatcccaatgccaataatataggacaaaatg
cacctaacgaagtgctttcatttgatgataacaacattagaccaagtacgaaccgttctgtgcctacagtaactgttgtt
gataatttaccaggctacacactgattaatggtggtaaagtaggggtgtttagtcatgcaatggtaagaacgagcatgt
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aatgatcatggcgattttaatggtatcgagaaaacattaacagtaaatccgaattctgaattaatctttgaatttaatact
atgactactaaaaactatcaaggtatgacaaatttaatcattaaaaatgctgataacgatactgttattggtgaaaaag
tagttgcttatggtccgatttggcgcttattaaaagtacctgaaaatgttagtcatctaaaaattcaatttgtacctaaaaat
gacgcaataacagatgcacgtggtatttatcaattacgagatggatataaatactatgactttgtagactcaatcggtct
tcattctgggtcacatgtctatgttgaaagacgtacaatggagccaacagcaacaaataataaagaatttacagttac
aacgtcattaaagaataatggtaactttggcgcttcattcaatacagatgattttgtatataaaattcaattacctgaaggt

gttgaatatgtaaataattcattgactaaagattttcctagcggtaattcaggtgttgatattaatgatatgaatgtgacgta
tgacgcagcaaatcgaattattacaattaaaagtactggtggaggtacagggaattcgccggcacgactaatgcctg
ataaaatattggatttgaagtataagctacgtgtgaacaatgtgccaacaccaagaacagtaacatttaacgatacat
taacgtataaaacatattcacaagattttattaattcacctgctgaaagtcatactgtaagtacaaatccatatacaattg
atatcatcatgaataaagacgcattgcaagccgaagtcgatagacgaattcaacaagcggattatacatttgcatcat
tagatatttttaatgatcttaaaagacgcgcacaaacaattttagatgaaaaccgtaacaatgtacctttaaacaaaag
agtttctcaagcagatatcgattcattagcaaatcagatgcaacatacgttaattcgcagtgttgacgctgaaaatgcc

gttaatagaaaagttgatgacatggaagatttagttaaccaaaatgatgaactgacagatgaagaaaaacaagca
gcgattcaagtcatcgaggaacataaaaatgaaattattgggaatattggtgaccaaacgactgatgatggcgttact
agaattaaagatcaaggtatacagactttaagtggagacactgcaacaccagttgttaaaccaaatgctaaacaag
ctatacgtgataaagcagcgaaacaaagagaaattatcaatcacacgccagatgctactcaagatgaaattcaag
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tgcaattaatcaagcgacagcaacgaaacgacaacaaataaatagcaatagagaagcaacacaagaagaga
aaaatgcagcattgaatgaattaacgcaagccacgaaccacgcattagaacaaatcaatcaagcgacaaccaat
gatgatgtagatactgccaaaggtgatggtctgaatgccattaatcctattgcgcctgtaactgttgtcaagcaagcag
caagagatgccgtatcacatgatgcacaacagcatatcgcagagatcaatgcaaatcctgatgcgactcaagaag
aaagacaagcagcaatagagaaagtaaatgctgctgtagctgttgcgaatactaatatattaaatgctaataccaat
gctgatgttgagcaagtaaagacaaatgcaattcaaggtatacaagccattgaaccagctacaaaggttaaaaca
gatgctaaaaacgctattgatcaaagtgcggaaacgcaacataatgcgatatttaataataatgatgcgaccttaga
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cgaatcaagaagttgcacaagcaaaagatcagggcacacaaaatatagttgtgattcaaccggcaacacaagtta
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agaaacaaactgctacaggtgtattaacggacttagcaactgcaaaaaaacaagaaattaatcaaaatacaaatg
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acaagcaaatacaaatgcggaagtagaccaagctgcgacagtggcagagaataatatcgatgctgttcaagttga
cgttgtaaaaaaacaagcagcgcgagataaaatcactgctgaagtagcgaagcgtattgaagcggttaaacaaa
cacctaatgcaactgacgaagaaaagcaggctgcagttaatcaaatcaatcaacttaaagatcaagcgtttaatca
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gctgaagtagtaattaaaccaaaggcaattgcagatattgaaaaagctgttaaagaaaagcaacagcaaattgat
aatagtcttgattcaacagataatgagaaagaagttgctttacaagcattagctaaagaaaaagaaaaagcacttg
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ttaatcaagataaagaagcgacagcagaagaaagacaagcggcgttagataaaatcaatgatttagttgctaaag
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DsqA(8325) (SEQ ID NO:3)

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DsqA(8325) (SEQ ID NO:4)

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KesK1(8325) (SEQ ID NO:5)

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KesK1(8325) (SEQ ID NO:6)

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VKIVSSIEYGENIHEDYDYTLMVFAQPITNNPDDYVDEETYNLQKLLAPYHKAKTLE
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GMSSNVDTDKDSNKNKDKVIQLNHIADKNNHTGKAAKLDVVKQNYNNTDKVTDKK
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KrkN2(8325) (SEQ ID NO:7)

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KrkN2(8325) (SEQ ID NO:8)

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AFATLALLGSLSLLLFKRKESK

KrkN(8325) (SEQ ID NO:9)

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KrkN(8325) (SEQ ID NO:10)

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RkaS(COL) (SEQ ID NO:11)

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RkaS(COL) (SEQ ID NO:12)

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RrkN(8325) (SEQ ID NO:13)

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RrkN(8325) (SEQ ID NO:14)

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PVKGDSIVEKEEIPFKKERKFNPDLAPGTEKVTREGQKGEKTITTPTLKNPLTGEIIS
KGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEEVPGKPGIKNPETGD
VVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGTEKVTREGQKGEKTI
TTPTLKNPLTGEIISKGESKEEITKDPINELTEYGPETITPGHRDEFDPKLPTGEKEE
VPGKPGIKNPETGDVVRPPVDSVTKYGPVKGDSIVEKEEIPFEKERKFNPDLAPGT
EKVTREGQKGEKTITTPTLKNPLTGEIISKGESKEEITKDPVNELTEFGGEKIPQGH
KDIFDPNLPTDQTEKVPGKPGIKNPDTGKVIEEPVDDVIKHGPKTGTPETKTVEIPF
ETKREFNPKLQPGEERVKQEGQPGSKTITTPITVNPLTGEKVGEGQPTEEITKQPV
DKIVEFGGEKPKDPKGPENPEKPSRPTHPSGPVNPNNPGLSKDRAKPNGPVHSM
DKNDKVKKSKIAKESVANQEKKRAELPKTGLESTQKGLIFSSIIGIAGLMLLARRRK
N

KnkA(8325) (SEQ ID NO:15)

ggaaggagtatgttgatggctaaatatcgagggaaaccgtttcaattatatgtaaagttatcgtgttcgacaatgatggc
gacaagtatcattttaacgaatatcttgccgtacgatgcccaagctgcatctgaaaaggatactgaaattacaaaaga
gatattatctaagcaagatttattagacaaagttgacaaggcaattcgtcaaattgagcaattaaaacagttatcggctt
catctaaagaacattataaagcacaactaaatgaagcgaaaacagcatcgcaaatagatgaaatcataaaacga
gctaatgagttggatagcaaagacaataaaagttctcacactgaaatgaacggtcaaagtgatatagacagtaaatt
agatcaattgcttaaagatttaaatgaggtttcttcaaatgttgataggggtcaacaaagtggcgaggacgatcttaat
gcaatgaaaaatgatatgtcacaaacggctacaacaaaacatggagaaaaagatgataaaaatgatgaagca
atggtaaataaggcgttagaagacctagaccatttgaatcagcaaatacacaaatcgaaagatgcatcgaaagat
acatcggaagatccagcagtgtctacaacagataataatcatgaagtagctaaaacgccaaataatgatggttctg
gacatgttgtgttaaataaattcctttcaaatgaagagaatcaaagccatagtaatcgactcactgataaattacaagg
aagcgataaaattaatcatgctatgattgaaaaattagctaaaagtaatgcctcaacgcaacattacacatatcataa
actgaatacgttacaatctttagatcaacgtattgcaaatacgcaacttcctaaaaatcaaaaatcagacttaatgagc
gaagtaaataagacgaaagagcgtataaaaagtcaacgaaatattatttggaagaacttgcacgtactgatgata
aaaagtatgctacacaaagcattttagaaagtatatttaataaagacgaggcagttaaaattctaaaagatatacgt
gttgatggtaaaacagatcaacaaattgcagatcaaattactcgtcatattgatcaattatctctgacaacgagtgatg
atttattaacgtcattgattgatcaatcacaagataagtcgctattgatttctcaaattttacaaacgaaattaggaaaag
ctgaagcagataaattggctaaagattggacgaataaaggattatcaaatcgccaaatcgttgaccaattgaagaa
acattttgcatcaactggcgacacgtcttcagatgatatattaaaagcaattttgaataatgccaaagataaaaaaca
agcaattgaaacgattttagcaacacgtatagaaagacaaaaggcaaaattactggcagatttaattactaaaata

gaaacagatcaaaataaaatttttaatttagttaaatcggcattgaatggtaaagcggatgatttattgaatttacaaaa
gagactcaatcaaacgaaaaaagatatagattatattttatcaccaatagtaaatcgtccaagtttactagatcgattg
aataaaaatgggaaaacgacagatttaaataagttagcaaatttaatgaatcaaggatcagatttattagacagtatt
ccagatatacccacaccaaagccagaaaagacgttaacacttggtaaaggtaatggattgttaagtggattattaaa
tgctgatggtaatgtatctttgcctaaagcgggggaaacgataaaagaacattggttgccgatatctgtaattgttggtg
caatgggtgtactaatgatttggttatcacgacgcaataagttgaaaaataaagcataa

KnkA(8325) (SEQ ID NO:16)

GRSMLMAKYRGKPFQLYVKLSCSTMMATSIILTNILPYDAQAASEKDTEITKEILSK
QDLLDKVDKAIRQIEQLKQLSASSKEHYKAQLNEAKTASQIDEIIKRANELDSKDNK
SSHTEMNGQSDIDSKLDQLLKDLNEVSSNVDRGQQSGEDDLNAMKNDMSQTATT
KHGEKDDKNDEAMVNKALEDLDHLNQQIHKSKDASKDTSEDPAVSTTDNNHEVA
KTPNNDGSGHVVLNKFLSNEENQSHSNRLTDKLQGSDKINHAMIEKLAKSNASTQ
HYTYHKLNTLQSLDQRIANTQLPKNQKSDLMSEVNKTKERIKSQRNIILEELARTDD
KKYATQSILESIFNKDEAVKILKDIRVDGKTDQQIADQITRHIDQLSLTTSDDLLTSLID
QSQDKSLLISQILQTKLGKAEADKLAKDWTNKGLSNRQIVDQLKKHFASTGDTSSD
DILKAILNNAKDKKQAIETILATRIERQKAKLLADLITKIETDQNKIFNLVKSALNGKAD
DLLNLQKRLNQTKKDIDYILSPIVNRPSLLDRLNKNGKTTDLNKLANLMNQGSDLLD
SIPDIPTPKPEKTLTLGKGNGLLSGLLNADGNVSLPKAGETIKEHWLPISVIVGAMG
VLMIWLSRRNKLKNKA

一级结构分析:

将生物信息方法（bioinformatic approach）用于一级结构和功能预测 (附图 1)。蛋白质 RrkN 和 DsqA 具有与先前描述的 MSCRAMMs 相似的结构组织。RrkN 的结构类似于分别为金黄色葡萄球菌和表皮葡萄球菌的 Pls/Aap 蛋白质。它在N－末端含有 200 个残基的区域显示与 Pis 和 Aap 有 40% 相同。该蛋白质的 C-末端突出地由 128 个残基重复区域组成，菌株与菌株之间重复区的数量是变化的。这些重复也存在于 Pis 和 Aap。推定的 sar 同源区和 fnbpA 和 fnbpB 正好位于基因组上 RrkN 的上游。

DsqA 的结构的组织相似于蛋白质的 Sdr 家族。它含有典型的 A 区域，其后跟随 TYYFTDVK 基序，该基序类似于在所有 Sdr 蛋白质中存在的保守的 TYTFTVYVD 基序。该基序的功能至今没有被测定。2 个 88 个残基的重复区域居留在该蛋白质的中心，其后跟随类似于在所 Sdr 蛋白质中存在的 SD-重复基序的

C-末端 SX-重复基序。该重复区的大小随菌株变化。在基因组上 DsqA 邻接 secY 和 secA。DsqA 同系物 (> 90% 同一性) 也存在于表皮葡萄球菌。

KnkA 的序列中不含有重复区域。次级的结构预测分析显示该蛋白质主要地由 α - 螺旋。

RkaS 的序列中不含有重复区域。 BLAST 分析显示它类似于 5' 核苷酸酶 UDP-糖水解酶。编码 RkaS 的基因正好地位于 fromoryx 的上游，mec 元件的插入位点。

KesK 在该蛋白质的 N - 末端含有二个 140 个残基的重复区域，有 38%相同。水疗法绘制图分析 (Kyte 和 Doolittle，1982) 显示在该蛋白质的中心点有一个大的亲水的区域(残基 500-560)。

EkeS 在该蛋白质的 N - 末端含有二个 300 个残基的重复区域，有 38%相同。Blast 分析显示该蛋白质的 N-末端(残基 1-1268，携带两种重复)与 FmtB 有 49%等同，所述的 FmtBan 是具有 17 个串联的重复的 LPXTG 蛋白质。FmtB 被推测间接参与甲氧苯青霉素抗性，因为 fmt8 的灭活去除了甲氧苯青霉素抗性。这似乎是由于通过增加细胞壁前体葡萄糖胺 - 1 - 磷酸盐的产生可以减轻对细胞壁组成的影响如甲氧苯青霉素敏感性(Komatsuzawa 等人，2000)。

KrkN 和 KrkN2 在基因组上互相邻接。

表达分析 :

由于与蛋白质数据库之序列没有同源性，不能预知这些蛋白质中每一个的推定的功能，因此以分子的近似值为依据。利用 Qiagen pQE-30 表达系统，四个开放读框的独特的区域可以在大

肠杆菌中表达为重组 his-标记的融合蛋白质。附图 2 表示纯化的 N－末端 his-标记的融合蛋白的考马斯亮蓝染色的 SDS-PAGE 凝胶。将重组蛋白质 RrkN1，DsqA2，KesK1 和 KnkA 用于在兔子中产生抗体。金黄色葡萄球菌细胞壁提取物的 Western 印迹分析显示 KesK，KnkA 和 DsqA 被表达并且细胞壁相关 (附图 3)。菌株 eMRSA-16 代表 aknkA-阴性的菌株，因为它缺乏 knkA 基因。65kDa 的免疫反应谱带与菌株 8325-4 的指数和静止的时期细胞的细胞壁提取物起反应 (附图 3，B)。菌株 eMRSA-16 中没有该谱带暗示它代表了 knkA 的基因产物。

在指数和静止期的培养物中，利用抗-KesK 抗体进行的菌株 8325-4 的细胞壁成分的 Western 免疫印迹识别了 150kDa 免疫反应谱带。表达质粒(pKS80)上全长 KesK 的表达获得的从乳酸乳球菌的细胞壁成分释放的类似大小的免疫反应蛋白质暗示该 150kDa 谱带代表 kesK 基因产物(数据未显示)。需要金黄色葡萄球菌的 kesK 敲出突变体来证实细胞壁释放的 KesK 蛋白质的大小。

利用抗-DsqA 抗体，金黄色葡萄球菌菌株 MSSA 和 eMRSA-16 的细胞壁成分的 Western 免疫印迹结果识别了一个 130kDa 免疫反应谱带。在静止期细胞中表达水平更高。

在乳酸乳球菌中异源表达：

以前已经将金黄色葡萄球菌的的表面蛋白质在乳酸乳球菌(L. lactis)中的异源表达用作为研究蛋白质功能的工具 (Sinha 等人, 2000)。在该研究中，也将该替代系统用于在乳酸乳球菌表面表达各个 in silico-预知的 MSCRAMMs 以查出功能。已经将 KesK 和 KnkA 克隆到乳酸乳球菌，并且通过点印迹显示是在表面表达的 (附图 4)。阴性的对照中没有观察到交叉反应 (pKS80 质粒没有插入物)，显示这是一个特异反应。通过用溶菌酶和

mutanolysin 消化产生了携带 pKS-KnkA 和 pKS-KesK 的 乳酸乳球菌的细胞壁和原生质体成分，并且用于分别利用抗-KnkA 和抗-KesK 的抗体进行的 Western 印迹研究。与在金黄色葡萄球菌中观察到的不同，在乳酸乳球菌细胞壁成分中没有检测到 KnkA，但是发现与原生质体成分相关。KnkA 的固定用基序不同于 一致 LPXTG 序列，其中含有一个丙氨酸残基而不是苏氨酸 (即 LPKAG) (表 1)。最近已经公开了金黄色葡萄球菌含有二个 sortase 基因，srtA 和 srtB (Pallen，2001)。由第二个 sortase 基因加工 LPXTG 基序的变异形式是可能的，乳酸乳球菌中没有该基因。这也可以解释在原生质体成分中观察到的 KnkA 蛋白质大小的轻微的增加，而细胞壁分类拣选信号没有被裂解。

在乳酸乳球菌的细胞壁成分中探测到 KesK ，但是迁移的分子量小于从金黄色葡萄球菌细胞壁释放的 KesK 蛋白质。在乳酸乳球菌表面表达的大多数 MSCRAMMs 被证明在细胞壁提取程序中发生蛋白水解(Louise O'Brien, 个人通讯)。因此，从乳酸乳球菌表面释放 KesK 蛋白质表示截短形式的 KesK 是可能的。已经证明用溶菌酶和 mutanolysin 缩短消化时间以限制蛋白水解的程度。

in silico-预测的 MSCRAMMs 体内表达:

在 ELISA 分析中对来自金黄色葡萄球菌感染痊愈的 33 个患者的康复的人-时期血清进行测试，以检测其识别纯化的 N－末端 his-标记的融合蛋白质的能力。将从儿童和健康的供血者采掘的血清用作为阴性的对照。将阳性的反应其值作为等同于或高于阴性的对照的二倍。附图 5A-5D 阐明在 27-42% 患者中识别了所有的蛋白质，这暗示这些蛋白质在体内表达并且在宿主感染期间是致免疫的。

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实施例 2

从金黄色葡萄球菌和从凝固酶阴性的葡萄球菌分离交叉反应的蛋白质并且进行测序

最近已经证明表皮葡萄球菌含有结构上与金黄色葡萄球菌 MSCRAMM®蛋白质相关的表面蛋白质 (US09/386,962)。从金黄色葡萄球菌中分离一个蛋白质特别有利，因为它与表皮葡萄球菌紧密同源。该蛋白质被称为 DsqA 或 SasA (金黄色葡萄球菌) 和 DgsK (表皮葡萄球菌)。它们的特征是包括一个大约 500 个氨基酸残基的典型的"A"区域，其后跟随约有 40％相同有，各为 88 个残基的二个 B 重复区，和一个独特的 SXSX 二肽重复区，该区域的长度随菌株而变化。金黄色葡萄球菌的 DsqA/SasA 的 A 区域内含有一个 180 残基的区域，该区域与金黄色葡萄球菌蛋白质的 RrkN，Pls 和表皮葡萄球菌 蛋白质 Aap 的 A 区域内的一个相似

的大小的区域有 40％一致性。DsqA/SasA 和 DgsK 蛋白质的 A 区域在氨基酸水平上有 46％的一致性，BB 重复区是 50%一致性。所包括的主动和被动免疫接种策略；疫苗，识别金黄色葡萄球菌和凝固酶阴性的葡萄球菌的蛋白质的多克隆抗体和单克隆抗体是本发明的主题。

与凝固酶阴性的葡萄球菌和金黄色葡萄球菌发生交叉反应的抗体的特异性例子：

凝固酶阴性的葡萄球菌 DgsK A-区域：

氨基酸序列 (SEQID NO：17)

ASETPITSEISSNSETVANQNSTTIKNSQKETVNSTSLESNHSNS
TNKQMSSEVTNTAQSSEKAGISQQSSETSNQSSKLNTYASTDH
VESTTINNDNTAQQDQNKSSNVTSKSTQSNTSSSEKNISSNLTQ
SIETKATDSLATSEARTSTNQISNLTSTSTSNQSSPTSFANLRTFS
RFTVLNTMAAPTTTSTTTTSSLTSNSVWNKDNFNEHMNLSGS
ATYDPKTGIATLTPDAYSQKGAISLNTRLDSNRSFRFIGKVNLG
NRYEGYSPDGVAGGDGIGFAFSPGPLGQIGKEGAAVGIGGLNN
AFGFKLDTYHNTSTPRSDAKAKADPRNVGGGGAFGAFVSTD
RNGMATTEESTAAKLNVQPTDNSFQDFVIDYNGDTKVMTVTY
AGQTFTRNLTDWIKNSGGTTFSLSMTASTGGAKNLQQVQFGT
FEYTESAVAKVRYVDANTGKDIIPPPKTIAGEVDGTVNIDKQL
NNFKNLGYSYVGTDALKAPNYTETSGTPTLKLTNSSQTVIYKF
KDVQ

金黄色葡萄球菌 SasA A-区域 :

氨基酸序列 (SEQ ID NO : 18)

ASDAPLTSELNTQSETVGNQNSTTIEASTSTADSTSVTKNSSSV
QTSNSDTVSSEKSEKVTSTTNSTSNQQEKLTSTSESTSSKNTTS
SSDTKSVASTSSTEQPINTSTNQSTASNNTSQSTTPSSVNLNKTS
TTSTSTAPVKLRTFSRLAMSTFASAATTTAVTANTITVNKDNLK
QYMTTSGNATYDQSTGIVTLTQDAYSQKGAITLGTRIDSNKSF
HFSGKVNLGNKYEGHGNGGDGIGFAFSPGVLGETGLNGAAVG
IGGLSNAFGFKLDTYHNTSKPNSAAKANADPSNVAGGGAFGA
FVTTDSYGVATTYTSSSTADNAAKLNVQPTNNTFQDFDINYNG
DTKVMTVKYAGQTWTRNISDWIAKSGTTNFSLSMTASTGGAT
NLQQVQFGTFEYTESAVTQVRYVDVTTGKDIIPPKTYSGNVDQ
VVTIDNQQSALTAKGYNYTSVDSSYASTYNDTNKTVKMTNA
GQSVTYYFTDW

Aap 蛋白质的完整序列和它的编码 DNA (指示有 A 区域存在)显示如下 :

表皮葡萄球菌 Aap 蛋白质 (加下划线的为 A-区域) (SEQ ID NO : 19)

MGKRRQGPINKKVDFLPNKLNKYSIRKFTVGTASILLGSTLIFGSSSHEAKAAEEKQ
VDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSEPTKA
EEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEEGSNV
KAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEAAQSE
PTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIKANSD
NDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNLNYSS
PFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNATNLTR
YNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGFMFSK
KDGDDFLKNGGILREKGTPSAAGFRIDTGYYNNDPLDKIQKQAGQGYRGYGTFVK

NDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASNQTFT
ATYAGKTWTATLSELGLSPTDSYNFLVTSSQYGNGNSGTYASGVMRADLDGATL
TYTPKAVDGDPIISTKEIPFNKKREFDPNLAPGTEKVVQKGEPGIETTTTPTYVNPN
TGEKVGEGEPTEKITKQPVDEIVHYGGEEIKPGHKDEFDPNAPKGSQTTQPGKPG
VKNPDTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKKREFNPDLKPGEERVKQ
KGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEITEYGGEEIKPGHKDEFD
PNAPKGSQEDVPGKPGVKNPGTGEVVTPPVDDVTKYGPVDGDPITSTEEIPFDKK
REFNPDLKPGEERVKQKGEPGTKTITTPTTKNPLTGEKVGEGEPTEKITKQPVDEI
VHYGGEQIPQGHKDEFDPNAPVDSKTEVPGKPGVKNPDTGEVVTPPVDDVTKYG
PVDGDSITSTEEIPFDKKREFDPNLAPGTEKVVQKGEPGTKTITTPTTKNPLTGEKV
GEGKSTEKVTKQPVDEIVEYGPTKAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGKPA
EPGTPAEPGKPAEPGKPAEPGKPAEPGKPAEPGTPAEPGTPAEPGKPAEPGTPA
EPGKPAEPGTPAEPGKPAESGKPVEPGTPAQSGAPEQPNRSMHSTDNKNQLPD
TGENRQANEGTLVGSLLAIVGSLFIFGRRKKGNEK

表皮葡萄球菌 aap DNA (SEQ ID NO : 20)

atgggcaaac gtagacaagg tcctattaat aaaaaagtgg
attttttacc taacaaatta aacaagtatt ctataagaaa attcactgtt ggtacggcct
caatattact tggttcgaca cttatttttg gaagtagtag ccatgaagcg aaagctgcag
aagaaaaaca agttgatcca attacacaag ctaatcaaaa tgatagtagt gaaagatcac
ttgaaaacac aaatcaacct actgtaaaca atgaagcacc acagatgtct tctacattgc
aagcagaaga aggaagcaat gcagaagcac ctcaatctga gccaacgaag gcagaagaag
gaggcaatgc agaagcagct caatctgagc caacgaaggc agaagaagga ggcaatgcag
aagcacctca atctgagcca acgaaggcag aagaaggagg caatgcagaa gcagctcaat
ctgagccaac gaagacagaa gaaggaagca acgtaaaagc agctcaatct gagccaacga
aggcagaaga aggaagcaat gcagaagcac ctcaatctga gccaacgaag acagaagaag
gaagcaacgc aaaagcagct caatctgagc caacgaaggc agaagaagga ggcaatgcag
aagcagctca atctgagcca acgaagacag aagaaggaag caatgcagaa gcacctcaat
ctgagccaac gaaggcagaa gaaggaggca atgcagaagc acctcaatct gagccaacga
agacagaaga aggaggcaat gcagaagcac cgaatgttcc aactatcaaa gctaattcag

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从 A-区域到表皮葡萄球菌 Aap（氨基酸 55-600） (SEQ ID NO:21)

[55]EKQVDPITQANQNDSSERSLENTNQPTVNNEAPQMSSTLQAEEGSNAEAPQSE PTKAEEGGNAEAAQSEPTKAEEGGNAEAPQSEPTKAEEGGNAEAAQSEPTKTEE GSNVKAAQSEPTKAEEGSNAEAPQSEPTKTEEGSNAKAAQSEPTKAEEGGNAEA AQSEPTKTEEGSNAEAPQSEPTKAEEGGNAEAPQSEPTKTEEGGNAEAPNVPTIK ANSDNDTQTQFSEAPTRNDLARKEDIPAVSKNEELQSSQPNTDSKIEPTTSEPVNL NYSSPFMSLLSMPADSSSNNTKNTIDIPPTTVKGRDNYDFYGRVDIESNPTDLNAT

NLTRYNYGQPPGTTTAGAVQFKNQVSFDKDFDFNIRVANNRQSNTTGADGWGF
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TFVKNDSQGNTSKVGSGTPSTDFLNYADNTTNDLDGKFHGQKLNNVNLKYNASN
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GA^{600}

蛋白质的生产和纯化

利用 P C R，从上面描述的序列扩增识别为 DgsK 或 SasA 的表面蛋白质的 A 区域，再克隆到大肠杆菌表达载体 PQE-30 (Qiagen)，以允许表达一种含有六个组氨酸残基的重组融合蛋白质。 随后将该载体转化到大肠杆菌 ATCC 55151，在 15-升发酵罐中生长到光密度（OD600）为 0.7，用 0.2mM 异丙基-1β-D 半乳糖苷 (IPTG)诱导 4 小时。利用 AG Technologies 中空纤维组件(孔大小 0.45 um) 收集细胞，将细胞浆在- 80 C 冷冻。利用 2 次穿过 French Press，1100psi，将细胞在 1X PBS (10 mL 缓冲液/1 克的细胞浆)裂解。将裂解的细胞 17,000rpm 旋转 30 分钟以除去细胞碎片。将上清液经过装备了 0.1M $NiCI_2$ 的 5-mL Hi 俘获 Cheating (Pharmacia)柱。在上样之后，用 5 个柱体积的 10mM Tris, pH 8.0，100mM NaCI (缓冲液 A) 洗涤柱子。利用超过 30 个柱体积的 0-100% 梯度的 10mM Tris，pH 8.0，100mM NaCI，200 mM 咪唑 (Buffer B)洗脱蛋白质。SdrGN1N2N3 或 SdrGN2N3 在~13% Buffer B (~26mM 咪唑)被洗脱。监测 280nm 处的吸光率。在 1x PBS 中透析含有 SdrGN1 N2N3 或 SdrGN2N3 的馏分。

然后将各个蛋白质经过一个内毒素除去方案。在该方案中所使用的缓冲液通过一个 5-mL Mono-Q 琼脂糖 (Pharmacia)柱而没有内毒素。将蛋白质平衡地分到 4x 15 毫升试管中。各个试管的体积用缓冲液 A 加到 9 毫升。将 1 毫升 的 10% Triton X-114

加入到各个试管中，在 4 ℃旋转保温 1 小时。将试管置于 37℃水浴中以使相位分离。将试管以 2,000rpm 旋转 10 分钟，收集各个试管的上面的含水的相，用去污剂反复提取。将 2 次提取的含水相合并，传递过带有 0. 1M $NiCl_2$ 的 5-毫升 IDA cheating (Sigma) 柱，以除去剩余的洗涤剂。用 9 个柱体积的 Buffer A 洗涤该柱，然后用 3 个柱体积的 Buffer B 洗脱该蛋白质。将洗脱液通过 5-毫升的 Detoxigel (Sigma) 柱，收集流出物，再上样到柱。收集第二次过柱的流出物，在 1x PBS 中透析。分析纯化的产物的浓度，纯度和内毒素水平，然后给小鼠给药。

单克隆抗体的生产

将大肠杆菌表达的和纯化的重组 SasA 和 DsgK 蛋白质用于制备一组鼠的单克隆抗体，而将小鼠血清用作为多克隆抗体的来源。简单地说，一组 Balb/C 或 SJL 小鼠接收了一系列皮下的免疫接种 1-10 mg 溶液蛋白质或与下面表描述的佐剂混合的蛋白质。

免疫接种方案

RIMMS

注射	天数	数量 (微克)	途径	佐剂
#1	0	5	皮下	FCA/RIBI
#2	2	1	皮下	FCA/RIBI
#3	4	1	皮下	FCA/RIBI
#4	7	1	皮下	FCA/RIBI
#5	9	1	皮下	FCA/RIBI

常规注射	天数	数量 (微克)	途径	佐剂
原始	0	5	皮下	FCA
加强#1	14	1	腹膜内	RIBI
加强#2	28	1	腹膜内	RIBI
加强#3	42	1	腹膜内	RIBI

在杀死时(RIMMS)或加强后几天收集(常规的)血清，在 ELISA 测定中测定抗 MSCRAMM®蛋白质或对完整的细胞(表皮葡萄球菌 和金黄色葡萄球菌) 的效价。在最后的加强之后 3 天，去除脾脏或淋巴结，挑开成单细胞悬浮液，收集淋巴细胞。然后将淋巴细胞与 P3X63Ag8.653 骨髓瘤细胞系(ATCC &CRL-1580)融合。根据 Current Protocols in Immunology (第 2 章，第 2 单元) 中的生产单克隆抗体的方案进行细胞融合，随后涂覆平板和喂养。

然后利用标准的 ELISA 分析方法，从融合产生的任何克隆中筛选特异的抗-SasA 抗体的产生。扩增阳性的克隆，进一步通过流式血细胞计数测试完整的细菌的细胞结合测定中的活性以及 Biacore 分析中 SasA 的结合。

Biacore 分析

在整个分析中，流速保持在 10 毫升/分钟不变。在注射 SasA 或 DgsK 之前，借助于 RAM-Fc 结合，将测试抗体吸附到芯片。在时间 0，将浓度为 30 mg/ml 的 SasA 或 DgsK 注射过芯片 3 分钟，随后解离 2 分钟。该阶段的分析测定了 Mab/SasA 或 DgsK 相互作用 的相对关系和分离动力学。

与完整细菌的结合

用兔子 IgG (50mg/ml)封闭之后，收集，洗涤细菌的样品金黄色葡萄球菌 Newman，金黄色葡萄球菌 60，金黄色葡萄球菌 397(Sal6)，金黄色葡萄球菌 Wood，金黄色葡萄球菌 8325-4，甲氧苯青霉素抗性的金黄色葡萄球菌 MRSA 16，表皮葡萄球菌 ATCC 35984，表皮葡萄球菌 HB，表皮葡萄球菌 CN-899 和溶血葡萄球菌 ATCC 43253，用浓度为 2 pg/ml 的 Mab 或仅用 PBS (对照)保温。在用抗体保温之后， 将用作为检测抗体的山羊-F (ab') 2-抗-小鼠-F (ab') 2-FITC 用于孵育细菌的细胞。在抗体标记之后，用 FACS caliber 流式细胞计数器抽吸细菌的细胞以分析荧光射出 (刺激: 488, 发射: 570)。对于各个细菌的菌株，收集和检测 10,000 个样品。这些资料显示抗金黄色 SasA 的抗体能够识别凝固酶阴性的葡萄球菌的表面的同源的蛋白质。该资料支持 Western 印迹分析，表明抗金黄色葡萄球菌 SasA 的兔子多克隆抗体与从表皮葡萄球菌 HB 细胞表面释放的蛋白质以及来自于从表皮葡萄球菌克隆的 DsgK 的重组 A－区域发生交叉反应 (参见附图 6 和下表)。

多克隆血清反应性

	New man	67-0	397 (SAL6)	Wood 46	8325 -4	MRS A16	ATCC 3598 4	HB	CN-899	ATCC 4325 3
常规小鼠血清	－	－	－	－	－	－	－	－	－	
小鼠抗 SasA	+	+	+/－	－	+	+	+	+	+	+

<110> 蒂莫西·J·福斯特等人

<120> 识别凝血酶阴性的葡萄球菌和金黄色葡萄球菌的表面蛋白的交叉反应性单克隆抗体和多克隆抗体

<130> P07263US01/BAS

<140> US 10/172,502
<141> 2002-06-17

<150> US 60/298,098
<151> 2001-06-15

<160> 29

<170> Patent In version 3.1

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Glu Met Phe Lys Ile Met Gly Leu Pro Phe Ile Ser His Ser Leu Val
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Ser Gln Asp Asn Gln Ser Ile Ser Lys Lys Met Thr Gly Tyr Gly Leu
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Asp Gln Gln Ala Phe Ala Ala Ser Asp Ala Pro Leu Thr Ser Glu Leu
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Lys Val Thr Ser Thr Thr Asn Ser Thr Ser Asn Gln Gln Glu Lys Leu
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Thr Ser Thr Ser Glu Ser Thr Ser Ser Lys Asn Thr Thr Ser Ser Ser
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Val Asn Lys Asp Asn Leu Lys Gln Tyr Met Thr Thr Ser Gly Asn Ala
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Thr Tyr Asp Gln Ser Thr Gly Ile Val Thr Leu Thr Gln Asp Ala Tyr
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Ser Gln Lys Gly Ala Ile Thr Leu Gly Thr Arg Ile Asp Ser Asn Lys
305 310 315 320

Ser Phe His Phe Ser Gly Lys Val Asn Leu Gly Asn Lys Tyr Glu Gly
325 330 335

His Gly Asn Gly Gly Asp Gly Ile Gly Phe Ala Phe Ser Pro Gly Val
340 345 350

Leu Gly Glu Thr Gly Leu Asn Gly Ala Ala Val Gly Ile Gly Gly Leu
355 360 365

Ser Asn Ala Phe Gly Phe Lys Leu Asp Thr Tyr His Asn Thr Ser Lys
370 375 380

Pro Asn Ser Ala Ala Lys Ala Asn Ala Asp Pro Ser Asn Val Ala Gly
385 390 395 400

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Thr Thr Tyr Thr Ser Ser Ser Thr Ala Asp Asn Ala Ala Lys Leu Asn
420 425 430

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Gly Asp Thr Lys Val Met Thr Val Lys Tyr Ala Gly Gln Thr Trp Thr
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Arg Asn Ile Ser Asp Trp Ile Ala Lys Ser Gly Thr Thr Asn Phe Ser
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Val Gly Asn Gln Thr Ile Glu Val Gly Lys Thr Met Asn Pro Ile Val
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Leu Thr Thr Thr Asp Asn Gly Thr Gly Thr Val Thr Asn Thr Val Thr
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Gly Leu Pro Ser Gly Leu Ser Tyr Asp Ser Ala Thr Asn Ser Ile Ile
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Asp Thr Thr Ala Pro Thr Val Thr Pro Ile Gly Asp Gln Ser Ser Glu
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Val Tyr Ser Pro Ile Ser Pro Ile Lys Ile Ala Thr Gln Asp Asn Ser
690 695 700

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Phe Asp Ser Thr Asn Asn Thr Ile Ser Gly Thr Pro Thr Asn Ile Gly
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Thr Ser Thr Ile Ser Ile Val Ser Thr Asp Ala Ser Gly Asn Lys Thr
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Thr Thr Thr Phe Lys Tyr Glu Val Thr Arg Asn Ser Met Ser Asp Ser
755 760 765

Val Ser Thr Ser Gly Ser Thr Gln Gln Ser Gln Ser Val Ser Thr Ser
770 775 780

Lys Ala Asp Ser Gln Ser Ala Ser Thr Ser Thr Ser Gly Ser Ile Val
785 790 795 800

Val Ser Thr Ser Ala Ser Thr Ser Lys Ser Thr Ser Val Ser Leu Ser
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Asp Ser Val Ser Ala Ser Lys Ser Leu Ser Thr Ser Glu Ser Asn Ser
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Ser Ser Met Ser Asp Ser Ala Ser Lys Ser Thr Ser Leu Ser Asp Ser
850 855 860

Ile Ser Asn Ser Ser Ser Thr Glu Lys Ser Glu Ser Leu Ser Thr Ser
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Thr Ser Asp Ser Leu Arg Thr Ser Thr Ser Leu Ser Asp Ser Leu Ser
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Asn Ala Ile Ser Thr Ser Thr Ser Leu Ser Glu Ser Ala Ser Thr Ser
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Lys Ser Asp Ser Ile Ser Thr Ser Thr Ser Leu Ser Gly Ser Thr
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Asp Ser Thr Ser Met Ser Ile Ser Met Ser Gln Ser Thr Ser Gly
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Thr Ser Leu Ser Leu Ser Ala Ser Met Asn Gln Ser Gly Val Asp
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Ser Thr Ser Gln Ser Glu Ser Thr Ser Thr Ser Thr Ser Leu Ser
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Asp Ser Thr Ser Ile Ser Lys Ser Thr Ser Gln Ser Gly Ser Val
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Gln Ser Ile Ser Thr Ser Ala Ser Glu Ser Thr Ser Glu Ser Ala
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Ser Thr Ser Gly Ser Met Ser Val Ser Ile Ser Leu Ser Asp Ser
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Ser Glu Ser Val Ser Glu Ser Thr Ser Leu Ser Asp Ser Ile Ser
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Met Ser Asp Ser Thr Ser Thr Ser Asp Ser Asp Ser Leu Ser Gly
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1910 1915 1920

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Asn Ser Thr Ser Thr Ser Leu Ser Thr Ser Asp Ser Met Ser Gly
1940 1945 1950

Ser Val Ser Val Ser Thr Ser Thr Ser Leu Ser Asp Ser Ile Ser
1955 1960 1965

Gly Ser Thr Ser Val Ser Asp Ser Ser Ser Thr Ser Thr Ser Thr
1970 1975 1980

Ser Leu Ser Asp Ser Met Ser Gln Ser Gln Ser Thr Ser Thr Ser
1985 1990 1995

Ala Ser Gly Ser Leu Ser Thr Ser Ile Ser Thr Ser Met Ser Met
2000 2005 2010

Ser Ala Ser Thr Ser Ser Ser Gln Ser Thr Ser Val Ser Thr Ser
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Leu Ser Thr Ser Asp Ser Ile Ser Asp Ser Thr Ser Ile Ser Ile
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Gln His Gln Ala Gln Ala Ala Glu Asn Thr Asn Thr Ser Asp Lys Ile
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Ser Glu Asn Gln Asn Asn Asn Ala Thr Thr Thr Gln Pro Pro Lys Asp
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Thr Asn Gln Thr Gln Pro Ala Thr Gln Pro Ala Asn Thr Ala Lys Asn
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Tyr Pro Ala Ala Asp Glu Ser Leu Lys Asp Ala Ile Lys Asp Pro Ala
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Gln Leu Leu Asp Lys Asn Asn Glu Thr Gln Tyr Tyr His Phe Phe Ser
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Ile Lys Asp Pro Ala Asp Val Tyr Tyr Thr Lys Lys Lys Ala Glu Val
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Glu Leu Asp Ile Asn Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
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Glu Asn Asn Gln Lys Leu Pro Val Arg Leu Val Ser Tyr Ser Pro Val
180 185 190

Pro Glu Asp His Ala Tyr Ile Arg Phe Pro Val Ser Asp Gly Thr Gln
195 200 205

Glu Leu Lys Ile Val Ser Ser Thr Gln Ile Asp Asp Gly Glu Glu Thr
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Asn Tyr Asp Tyr Thr Lys Leu Val Phe Ala Lys Pro Ile Tyr Asn Asp
225 230 235 240

Pro Ser Leu Val Lys Ser Asp Thr Asn Asp Ala Val Val Thr Asn Asp
245 250 255

Gln Ser Ser Ser Val Ala Ser Asn Gln Thr Asn Thr Asn Thr Ser Asn
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Gln Asn Ile Ser Thr Ile Asn Asn Ala Asn Asn Gln Pro Gln Ala Thr
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Gln Ala Ser Ser Gln Pro Ala His Glu Thr Asn Ser Asn Gly Asn Thr
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Tyr Pro Pro Ala Asp Glu Ser Leu Gln Asp Ala Ile Lys Asn Pro Ala
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Gln Met Lys Asn Asp Lys Gly Glu Arg Gln Phe Tyr His Tyr Ala Ser
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Glu Leu Gly Leu Lys Thr Ala Ser Thr Trp Lys Lys Phe Glu Val Tyr
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Glu Gly Asp Lys Lys Leu Pro Val Glu Leu Val Ser Tyr Asp Ser Asp
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Lys Asp Tyr Ala Tyr Ile Arg Phe Pro Val Ser Asn Gly Thr Arg Glu
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Val Lys Ile Val Ser Ser Ile Glu Tyr Gly Glu Asn Ile His Glu Asp
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Tyr Asp Tyr Thr Leu Met Val Phe Ala Gln Pro Ile Thr Asn Asn Pro
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595 600 605

Lys Asp Leu Ile Val Glu Gly Lys Arg Val Thr Thr Val Ser Lys Asp
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Pro Lys Asn Asn Ser Arg Thr Leu Ile Phe Pro Tyr Ile Pro Asp Lys
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Glu Gly Gln Tyr His Val Arg Ile Ile Asn Gln Asp Ile Asn Thr Lys
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Asp Asp Asp Thr Ser Gln Asn Asn Thr Ser Glu Pro Leu Asn Val Gln
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Thr Gly Gln Glu Gly Lys Val Ala Asp Thr Asp Val Ala Glu Asn Ser
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Ser Thr Ala Thr Asn Pro Lys Asp Ala Ser Asp Lys Ala Asp Val Ile
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Glu Pro Glu Ser Asp Val Val Lys Asp Ala Asp Asn Asn Ile Asp Lys
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His Phe Asp Lys Tyr Asp Leu Lys Glu Met Asp Thr Gln Ile Ala Lys
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Ser Ser Asn Val Asp Thr Asp Lys Asp Ser Asn Lys Asn Lys Asp Lys
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Val Ile Gln Leu Asn His Ile Ala Asp Lys Asn Asn His Thr Gly Lys
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Ala Ala Lys Leu Asp Val Val Lys Gln Asn Tyr Asn Asn Thr Asp Lys
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Val Thr Asp Lys Lys Thr Thr Glu His Leu Pro Ser Asp Ile His Lys
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Thr Val Asp Lys Thr Val Lys Thr Lys Glu Lys Ala Gly Thr Pro Ser
850 855 860

Lys Glu Asn Lys Leu Ser Gln Ser Lys Met Leu Pro Lys Thr Gly Glu
865 870 875 880

Thr Thr Ser Ser Gln Ser Trp Trp Gly Leu Tyr Ala Leu Leu Gly Met
885 890 895

Leu Ala Leu Phe Ile Pro Lys Phe Arg Lys Glu Ser Lys
900 905

<210> 7
<211> 1065
<212> DNA
<213> Staphylococcus epidermidis

<400> 7
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tcagctatga aaaagattac aatgggtaca gcatctatca ttttaggttc ccttgtatac 120

ataggcgcag acagccaaca agtcaatgcg gcaacagaag ctacgaacgc aactaataat 180

caaagcacac aagtttctca agcaacatca caaccaatta atttccaagt gcaaaaagat 240

ggctcttcag agaagtcaca catggatgac tatatgcaac accctggtaa agtaattaaa 300

caaaataata aatattattt ccaaaccgtg ttaaacaatg catcattctg gaaagaatac 360

aaatttttaca atgcaaacaa tcaagaatta gcaacaactg ttgttaacga taataaaaaa 420

gcggatacta gaacaatcaa tgttgcagtt gaacctggat ataagagctt aactactaaa 480

gtacatattg tcgtgccaca aattaattac aatcatagat atactacgca tttggaattt 540

gaaaaagcaa ttcctacatt agctgacgca gcaaaaccaa acaatgttaa accggttcaa 600

ccaaaaccag ctcaacctaa aacacctact gagcaaacta aaccagttca acctaaagtt 660

gaaaaagtta aacctactgt aactacaaca agcaaagttg aagacaatca ctctactaaa 720

gttgtaagta ctgacacaac aaaagatcaa actaaaacac aaactgctca tacagttaaa 780

acagcacaaa ctgctcaaga acaaaataaa gttcaaacac ctgttaaaga tgttgcaaca 840

gcgaaatctg aaagcaacaa tcaagctgta agtgataata aatcacaaca aactaacaaa 900

gttacaaaac ataacgaaac gcctaaacaa gcatctaaag ctaaagaatt accaaaaact 960

ggtttaactt cagttgataa ctttattagc acagttgcct tcgcaacact tgccctttta 1020

ggttcattat ctttattact tttcaaaaga aaagaatcta aataa 1065

<210> 8
<211> 354
<212> PRT
<213> Staphylococcus epidermidis

<400> 8

Glu Glu Asn Asn Met Thr Lys His Tyr Leu Asn Ser Lys Tyr Gln Ser
1 5 10 15

Glu Gln Arg Ser Ser Ala Met Lys Lys Ile Thr Met Gly Thr Ala Ser
20 25 30

Ile Ile Leu Gly Ser Leu Val Tyr Ile Gly Ala Asp Ser Gln Gln Val
35 40 45

Asn Ala Ala Thr Glu Ala Thr Asn Ala Thr Asn Asn Gln Ser Thr Gln
50 55 60

Val Ser Gln Ala Thr Ser Gln Pro Ile Asn Phe Gln Val Gln Lys Asp
65 70 75 80

Gly Ser Ser Glu Lys Ser His Met Asp Asp Tyr Met Gln His Pro Gly
85 90 95

Lys Val Ile Lys Gln Asn Asn Lys Tyr Tyr Phe Gln Thr Val Leu Asn
100 105 110

Asn Ala Ser Phe Trp Lys Glu Tyr Lys Phe Tyr Asn Ala Asn Asn Gln
115 120 125

Glu Leu Ala Thr Thr Val Val Asn Asp Asn Lys Lys Ala Asp Thr Arg
130 135 140

Thr Ile Asn Val Ala Val Glu Pro Gly Tyr Lys Ser Leu Thr Thr Lys
145 150 155 160

Val His Ile Val Val Pro Gln Ile Asn Tyr Asn His Arg Tyr Thr Thr
165 170 175

His Leu Glu Phe Glu Lys Ala Ile Pro Thr Leu Ala Asp Ala Ala Lys
180 185 190

Pro Asn Asn Val Lys Pro Val Gln Pro Lys Pro Ala Gln Pro Lys Thr
195 200 205

Pro Thr Glu Gln Thr Lys Pro Val Gln Pro Lys Val Glu Lys Val Lys
210 215 220

Pro Thr Val Thr Thr Thr Ser Lys Val Glu Asp Asn His Ser Thr Lys
225 230 235 240

Val Val Ser Thr Asp Thr Thr Lys Asp Gln Thr Lys Thr Gln Thr Ala
245 250 255

His Thr Val Lys Thr Ala Gln Thr Ala Gln Glu Gln Asn Lys Val Gln
260 265 270

Thr Pro Val Lys Asp Val Ala Thr Ala Lys Ser Glu Ser Asn Asn Gln
275 280 285

Ala Val Ser Asp Asn Lys Ser Gln Gln Thr Asn Lys Val Thr Lys His
290 295 300

Asn Glu Thr Pro Lys Gln Ala Ser Lys Ala Lys Glu Leu Pro Lys Thr
305 310 315 320

Gly Leu Thr Ser Val Asp Asn Phe Ile Ser Thr Val Ala Phe Ala Thr
325 330 335

Leu Ala Leu Leu Gly Ser Leu Ser Leu Leu Leu Phe Lys Arg Lys Glu
340 345 350

Ser Lys

<210> 9
<211> 1965
<212> DNA
<213> Staphylococcus epidermidis

<400> 9
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tattcaatta gaaagtcatc actaggcgtt gcatctgtag caattagtac acttttatta 120

ttaatgtcaa atggcgaagc acaagcagca gctgaagaaa caggtggtac aaatacagaa 180

gcacaaccaa aaactgaagc agttgcaagt ccaacaacaa catctgaaaa agctccagaa 240

actaaaccag tagctaatgc tgtctcagta tctaataaag aagttgaggc ccctacttct 300

gaaacaaaag aagctaaaga agttaaagaa gttaaagccc ctaaggaaac aaaagaagtt 360

aaaccagcag caaaagccac taacaataca tatcctattt tgaatcagga acttagagaa 420

gcgattaaaa accctgcaat aaaagacaaa gatcatagcg caccaaactc tcgtccaatt 480

gattttgaaa tgaaaaagaa agatggaact caacagtttt atcattatgc aagttctgtt 540

aaacctgcta gagttatttt cactgattca aaaccagaaa ttgaattagg attacaatca 600

ggtcaatttt ggagaaaatt tgaagtttat gaaggtgaca aaaagttgcc aattaaatta 660

gtatcatacg atactgttaa agattatgct tacattcgct tctctgtatc aaacggaaca 720

aaagctgtta aaattgttag ttcaacacac ttcaataaca aagaagaaaa atacgattac 780

acattaatgg aattcgcaca accaatttat aacagtgcag ataaattcaa aactgaagaa 840

gattataaag ctgaaaaatt attagcgcca tataaaaaag cgaaaacact agaaagacaa 900

gtttatgaat taaataaaat tcaagataaa cttcctgaaa aattaaaggc tgagtacaag 960

aagaaattag aggatacaaa gaaagcttta gatgagcaag tgaaatcagc tattactgaa 1020

ttccaaaatg tacaaccaac aaatgaaaaa atgactgatt tacaagatac aaaatatgtt 1080

gtttatgaaa gtgttgagaa taacgaatct atgatggata cttttgttaa acaccctatt 1140

aaaacaggta tgcttaacgg caaaaaatat atggtcatgg aaactactaa tgacgattac 1200

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gaagcattta caaaagccaa taccgataaa tctaacaaaa aagaacaaca agataactca 1440

gctaagaagg aagctactcc agctacgcct agcaaaccaa caccatcacc tgttgaaaaa 1500

gaatcacaaa aacaagacag ccaaaaagat gacaataaac aattaccaag tgttgaaaaa 1560

gaaaatgacg catctagtga gtcaggtaaa gacaaaacgc ctgctacaaa accaactaaa 1620

ggtgaagtag aatcaagtag tacaactcca actaaggtag tatctacgac tcaaaatgtt 1680

gcaaaaccaa caactgcttc atcaaaaaca acaaaagatg ttgttcaaac ttcagcaggt 1740

tctagcgaag caaaagatag tgctccatta caaaaagcaa acattaaaaa cacaaatgat 1800

ggacacactc aaagccaaaa caataaaaat acacaagaaa ataaagcaaa atcattacca 1860

caaactggtg aagaatcaaa taaagatatg acattaccat taatggcatt attagcttta 1920

agtagcatcg ttgcattcgt attacctaga aaacgtaaaa actaa 1965

<210> 10
<211> 654
<212> PRT
<213> Staphylococcus epidermidis

<400> 10

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Phe Lys Ser Phe Tyr Ser Ile Arg Lys Ser Ser Leu Gly Val Ala Ser
20 25 30

Val Ala Ile Ser Thr Leu Leu Leu Leu Met Ser Asn Gly Glu Ala Gln
35 40 45

Ala Ala Ala Glu Glu Thr Gly Gly Thr Asn Thr Glu Ala Gln Pro Lys
50 55 60

Thr Glu Ala Val Ala Ser Pro Thr Thr Thr Ser Glu Lys Ala Pro Glu
65 70 75 80

Thr Lys Pro Val Ala Asn Ala Val Ser Val Ser Asn Lys Glu Val Glu
85 90 95

Ala Pro Thr Ser Glu Thr Lys Glu Ala Lys Glu Val Lys Glu Val Lys
100 105 110

Ala Pro Lys Glu Thr Lys Glu Val Lys Pro Ala Ala Lys Ala Thr Asn
115 120 125

Asn Thr Tyr Pro Ile Leu Asn Gln Glu Leu Arg Glu Ala Ile Lys Asn
130 135 140

Pro Ala Ile Lys Asp Lys Asp His Ser Ala Pro Asn Ser Arg Pro Ile
145 150 155 160

Asp Phe Glu Met Lys Lys Lys Asp Gly Thr Gln Gln Phe Tyr His Tyr
165 170 175

Ala Ser Ser Val Lys Pro Ala Arg Val Ile Phe Thr Asp Ser Lys Pro
180 185 190

Glu Ile Glu Leu Gly Leu Gln Ser Gly Gln Phe Trp Arg Lys Phe Glu
195 200 205

Val Tyr Glu Gly Asp Lys Lys Leu Pro Ile Lys Leu Val Ser Tyr Asp
210 215 220

Thr Val Lys Asp Tyr Ala Tyr Ile Arg Phe Ser Val Ser Asn Gly Thr
225 230 235 240

Lys Ala Val Lys Ile Val Ser Ser Thr His Phe Asn Asn Lys Glu Glu
245 250 255

Lys Tyr Asp Tyr Thr Leu Met Glu Phe Ala Gln Pro Ile Tyr Asn Ser
260 265 270

Ala Asp Lys Phe Lys Thr Glu Glu Asp Tyr Lys Ala Glu Lys Leu Leu
275 280 285

Ala Pro Tyr Lys Lys Ala Lys Thr Leu Glu Arg Gln Val Tyr Glu Leu
290 295 300

Asn Lys Ile Gln Asp Lys Leu Pro Glu Lys Leu Lys Ala Glu Tyr Lys
305 310 315 320

Lys Lys Leu Glu Asp Thr Lys Lys Ala Leu Asp Glu Gln Val Lys Ser
325 330 335

Ala Ile Thr Glu Phe Gln Asn Val Gln Pro Thr Asn Glu Lys Met Thr
340 345 350

Asp Leu Gln Asp Thr Lys Tyr Val Val Tyr Glu Ser Val Glu Asn Asn
355 360 365

Glu Ser Met Met Asp Thr Phe Val Lys His Pro Ile Lys Thr Gly Met
370 375 380

Leu Asn Gly Lys Lys Tyr Met Val Met Glu Thr Thr Asn Asp Asp Tyr
385 390 395 400

Trp Lys Asp Phe Met Val Glu Gly Gln Arg Val Arg Thr Ile Ser Lys
405 410 415

Asp Ala Lys Asn Asn Thr Arg Thr Ile Ile Phe Pro Tyr Val Glu Gly
420 425 430

Lys Thr Leu Tyr Asp Ala Ile Val Lys Val His Val Lys Thr Ile Asp
435 440 445

Tyr Asp Gly Gln Tyr His Val Arg Ile Val Asp Lys Glu Ala Phe Thr
450 455 460

Lys Ala Asn Thr Asp Lys Ser Asn Lys Lys Glu Gln Gln Asp Asn Ser
465 470 475 480

Ala Lys Lys Glu Ala Thr Pro Ala Thr Pro Ser Lys Pro Thr Pro Ser
485 490 495

Pro Val Glu Lys Glu Ser Gln Lys Gln Asp Ser Gln Lys Asp Asp Asn
500 505 510

Lys Gln Leu Pro Ser Val Glu Lys Glu Asn Asp Ala Ser Ser Glu Ser
515 520 525

Gly Lys Asp Lys Thr Pro Ala Thr Lys Pro Thr Lys Gly Glu Val Glu
530 535 540

Ser Ser Ser Thr Thr Pro Thr Lys Val Val Ser Thr Thr Gln Asn Val
545 550 555 560

Ala Lys Pro Thr Thr Ala Ser Ser Lys Thr Thr Lys Asp Val Val Gln
565 570 575

Thr Ser Ala Gly Ser Ser Glu Ala Lys Asp Ser Ala Pro Leu Gln Lys
580 585 590

Ala Asn Ile Lys Asn Thr Asn Asp Gly His Thr Gln Ser Gln Asn Asn
595 600 605

Lys Asn Thr Gln Glu Asn Lys Ala Lys Ser Leu Pro Gln Thr Gly Glu
610 615 620

Glu Ser Asn Lys Asp Met Thr Leu Pro Leu Met Ala Leu Leu Ala Leu
625 630 635 640

Ser Ser Ile Val Ala Phe Val Leu Pro Arg Lys Arg Lys Asn
645 650

<210> 11
<211> 2406
<212> DNA
<213> Staphylococcus epidermidis

<400> 11
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ctcgttttgc tttttagtgt aatgggatta tggcaagtct cgaacgcggc tgagcagcat 180

acaccaatga aagcacatgc agtaacaacg atagacaaag caacaacaga taagcaacaa 240

gtaccgccaa caaaggaagc ggctcatcat tctggcaaag aagcggcaac caacgtatca 300

gcatcagcgc agggaacagc tgatgataca aacagcaaag taacatccaa cgcaccatct 360

aacaaaccat ctacagtagt ttcaacaaaa gtaaacgaaa cacgcgacgt agatacacaa 420

caagcctcaa cacaaaaacc aactcacaca gcaacgttca aattatcaaa tgctaaaaca 480

gcatcacttt caccacgaat gtttgctgct aatgcaccac aaacaacaac acataaaata 540

ttacatacaa atgatatcca tggccgacta gccgaagaaa aagggcgtgt catcggtatg 600

gctaaattaa aaacagtaaa agaacaagaa aagcctgatt taatgttaga cgcaggagac 660

gccttccaag gtttaccact ttcaaaccag tctaaaggtg aagaaatggc taaagcaatg 720

aatgcagtag gttatgatgc tatggcagtc ggtaaccatg aatttgactt tggatacgat 780

cagttgaaaa agttagaggg tatgttagac ttcccgatgc taagtactaa cgtttataaa 840

gatggaaaac gcgcgtttaa gccttcaacg attgtaacaa aaaatggtat tcgttatgga 900

attattggtg taacgacacc agaaacaaag acgaaaacaa gacctgaagg cattaaaggc 960

gttgaattta gagatccatt acaaagtgtg acagcggaaa tgatgcgtat ttataaagac 1020

gtagatacat ttgttgttat atcacattta ggaattgatc cttcaacaca agaaacatgg 1080

cgtggtgatt acttagtgaa acaattaagt caaaatccac aattgaagaa acgtattaca 1140

gttattgatg gtcattcaca tacagtactt caaaatggtc aaatttataa caatgatgca 1200

ttggcacaaa caggtacagc acttgcgaat atcggtaaga ttacatttaa ttatcgcaat 1260

ggagaggtat cgaatattaa accgtcattg attaatgtta aagacgttga aaatgtaaca 1320

ccgaacaaag cattagctga acaaattaat caagctgatc aaacatttag agcacaaact 1380

gcagaggtaa ttattccaaa caataccatt gatttcaaag gagaaagaga tgacgttaga 1440

acgcgtgaaa caaatttagg aaacgcgatt gcagatgcta tggaagcgta tggcgttaag 1500

aatttctcta aaaagactga ctttgccgtg acaaatggtg gaggtattcg tgcctctatc 1560

gcaaaaggta aggtgacacg ctatgattta atctcagtat taccatttgg aaatacgatt 1620

gcgcaaattg atgtaaaagg ttcagacgtc tggacggctt tcgaacatag tttaggcgca 1680

ccaacaacac aaaaggacgg taagacagtg ttaacagcga atggcggttt actacatatc 1740

tctgattcaa tccgtgttta ctatgatata aataaaccgt ctggcaaacg aattaatgct 1800

attcaaattt taaataaaga gacaggtaag tttgaaaata ttgatttaaa acgtgtatat 1860

cacgtaacga tgaatgactt cacagcatca ggtggcgacg gatatagtat gttcggtggt 1920

cctagagaag aaggtatttc attagatcaa gtactagcaa gttatttaaa aacagctaac 1980

ttagctaagt atgatacgac agaaccacaa cgtatgttat taggtaaacc agcagtaagt 2040

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gaaggagcta ctgtatcaag caagagtggg aaacaattgg ctagaatgtc agtgcctaaa 2280

ggtagcgcgc atgagaaaca gttaccaaaa actggaacta atcaaagttc aagcccagaa 2340

gcgatgtttg tattattagc aggtataggt ttaatcgcga ctgtacgacg tagaaaagct 2400

agctaa 2406

<210> 12
<211> 801
<212> PRT

<213> Staphylococcus epidermidis

<400> 12

Phe Ile Asn Asn Leu His Lys Ile Asn His Phe Asn Ile Arg Ile Met
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Ile Ile Tyr Trp Cys Met Thr Val Asn Gly Gly Asn Glu Met Lys Ala
20 25 30

Leu Leu Leu Lys Thr Ser Val Trp Leu Val Leu Leu Phe Ser Val Met
35 40 45

Gly Leu Trp Gln Val Ser Asn Ala Ala Glu Gln His Thr Pro Met Lys
50 55 60

Ala His Ala Val Thr Thr Ile Asp Lys Ala Thr Thr Asp Lys Gln Gln
65 70 75 80

Val Pro Pro Thr Lys Glu Ala Ala His His Ser Gly Lys Glu Ala Ala
85 90 95

Thr Asn Val Ser Ala Ser Ala Gln Gly Thr Ala Asp Asp Thr Asn Ser
100 105 110

Lys Val Thr Ser Asn Ala Pro Ser Asn Lys Pro Ser Thr Val Val Ser
115 120 125

Thr Lys Val Asn Glu Thr Arg Asp Val Asp Thr Gln Gln Ala Ser Thr
130 135 140

Gln Lys Pro Thr His Thr Ala Thr Phe Lys Leu Ser Asn Ala Lys Thr
145 150 155 160

Ala Ser Leu Ser Pro Arg Met Phe Ala Ala Asn Ala Pro Gln Thr Thr
165 170 175

Thr His Lys Ile Leu His Thr Asn Asp Ile His Gly Arg Leu Ala Glu
180 185 190

Glu Lys Gly Arg Val Ile Gly Met Ala Lys Leu Lys Thr Val Lys Glu
195 200 205

Gln Glu Lys Pro Asp Leu Met Leu Asp Ala Gly Asp Ala Phe Gln Gly
210 215 220

Leu Pro Leu Ser Asn Gln Ser Lys Gly Glu Glu Met Ala Lys Ala Met
225 230 235 240

Asn Ala Val Gly Tyr Asp Ala Met Ala Val Gly Asn His Glu Phe Asp
245 250 255

Phe Gly Tyr Asp Gln Leu Lys Lys Leu Glu Gly Met Leu Asp Phe Pro
260 265 270

Met Leu Ser Thr Asn Val Tyr Lys Asp Gly Lys Arg Ala Phe Lys Pro
275 280 285

Ser Thr Ile Val Thr Lys Asn Gly Ile Arg Tyr Gly Ile Ile Gly Val
290 295 300

Thr Thr Pro Glu Thr Lys Thr Lys Thr Arg Pro Glu Gly Ile Lys Gly
305 310 315 320

Val Glu Phe Arg Asp Pro Leu Gln Ser Val Thr Ala Glu Met Met Arg
325 330 335

Ile Tyr Lys Asp Val Asp Thr Phe Val Val Ile Ser His Leu Gly Ile
340 345 350

Asp Pro Ser Thr Gln Glu Thr Trp Arg Gly Asp Tyr Leu Val Lys Gln
355 360 365

Leu Ser Gln Asn Pro Gln Leu Lys Lys Arg Ile Thr Val Ile Asp Gly
370 375 380

His Ser His Thr Val Leu Gln Asn Gly Gln Ile Tyr Asn Asn Asp Ala
385 390 395 400

Leu Ala Gln Thr Gly Thr Ala Leu Ala Asn Ile Gly Lys Ile Thr Phe
405 410 415

Asn Tyr Arg Asn Gly Glu Val Ser Asn Ile Lys Pro Ser Leu Ile Asn
420 425 430

Val Lys Asp Val Glu Asn Val Thr Pro Asn Lys Ala Leu Ala Glu Gln
435 440 445

Ile Asn Gln Ala Asp Gln Thr Phe Arg Ala Gln Thr Ala Glu Val Ile
450 455 460

Ile Pro Asn Asn Thr Ile Asp Phe Lys Gly Glu Arg Asp Asp Val Arg
465 470 475 480

Thr Arg Glu Thr Asn Leu Gly Asn Ala Ile Ala Asp Ala Met Glu Ala
485 490 495

Tyr Gly Val Lys Asn Phe Ser Lys Lys Thr Asp Phe Ala Val Thr Asn
500 505 510

Gly Gly Gly Ile Arg Ala Ser Ile Ala Lys Gly Lys Val Thr Arg Tyr
515 520 525

Asp Leu Ile Ser Val Leu Pro Phe Gly Asn Thr Ile Ala Gln Ile Asp
530 535 540

Val Lys Gly Ser Asp Val Trp Thr Ala Phe Glu His Ser Leu Gly Ala
545 550 555 560

Pro Thr Thr Gln Lys Asp Gly Lys Thr Val Leu Thr Ala Asn Gly Gly
565 570 575

Leu Leu His Ile Ser Asp Ser Ile Arg Val Tyr Tyr Asp Ile Asn Lys
580 585 590

Pro Ser Gly Lys Arg Ile Asn Ala Ile Gln Ile Leu Asn Lys Glu Thr
595 600 605

Gly Lys Phe Glu Asn Ile Asp Leu Lys Arg Val Tyr His Val Thr Met
610 615 620

Asn Asp Phe Thr Ala Ser Gly Gly Asp Gly Tyr Ser Met Phe Gly Gly
625 630 635 640

Pro Arg Glu Glu Gly Ile Ser Leu Asp Gln Val Leu Ala Ser Tyr Leu
645 650 655

Lys Thr Ala Asn Leu Ala Lys Tyr Asp Thr Thr Glu Pro Gln Arg Met
660 665 670

Leu Leu Gly Lys Pro Ala Val Ser Glu Gln Pro Ala Lys Gly Gln Gln
675 680 685

Gly Ser Lys Gly Ser Lys Ser Gly Lys Asp Thr Gln Pro Ile Gly Asp
690 695 700

Asp Lys Val Met Asp Pro Ala Lys Lys Pro Ala Pro Gly Lys Val Val
705 710 715 720

Leu Leu Leu Ala His Arg Gly Thr Val Ser Ser Gly Thr Glu Gly Ser
725 730 735

Gly Arg Thr Ile Glu Gly Ala Thr Val Ser Ser Lys Ser Gly Lys Gln
740 745 750

Leu Ala Arg Met Ser Val Pro Lys Gly Ser Ala His Glu Lys Gln Leu
755 760 765

Pro Lys Thr Gly Thr Asn Gln Ser Ser Ser Pro Glu Ala Met Phe Val
770 775 780

Leu Leu Ala Gly Ile Gly Leu Ile Ala Thr Val Arg Arg Arg Lys Ala
785 790 795 800

Ser

<210> 13
<211> 4914
<212> DNA
<213> Staphylococcus epidermidis

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gctgaaaaca atattgagaa tccaactaca ttaaaagata atgtccaatc aaaagaagtg 240

aagattgaag aagtaacaaa caaagacact gcaccacagg gtgtagaagc taaatctgaa 300

gtaacttcaa acaaagacac aatcgaacat gaaccatcag taaaagctga agatatatca 360

aaaaaggagg atacaccaaa agaagtagct gatgttgctg aagttcagcc gaaatcgtca 420

gtcactcata acgcagagac acctaaggtt agaaaagctc gttctgttga tgaaggctct 480

tttgatatta caagagattc taaaaatgta gttgaatcta ccccaattac aattcaaggt 540

aaagaacatt ttgaaggtta cggaagtgtt gatatacaaa aaaaaccaac agatttaggg 600

gtatcagagg taaccaggtt taatgttggt aatgaaagta atggtttgat aggagcttta 660

caattaaaaa ataaaatага ttttagtaag gatttcaatt ttaaagttag agtggcaaat 720

aaccatcaat caaataccac aggtgctgat ggttgggggt tcttatttag taaaggaaat 780

gcagaagaat atttaactaa tggtggaatc cttggggata aaggtctggt aaattcaggc 840

ggatttaaaa ttgatactgg atacatttat acaagttcca tggacaaaac tgaaaagcaa 900

gctggacaag gttatagagg atacggagct tttgtgaaaa atgacagttc tggtaattca 960

caaatggttg gagaaaatat tgataaatca aaaactaatt ttttaaacta tgcggacaat 1020

tcaactaata catcagatgg aaagtttcat gggcaacgtt taaatgatgt catcttaact 1080

tatgttgctt caactggtaa aatgagagca gaatatgctg gtaaaacttg ggagacttca 1140

ataacagatt taggtttatc taaaaatcag gcatataatt tcttaattac atctagtcaa 1200

agatggggcc ttaatcaagg gataaatgca aatggctgga tgagaactga cttgaaaggt 1260

tcagagttta cttttacacc agaagcgcca aaaacaataa cagaattaga aaaaaaagtt 1320

gaagagattc cattcaagaa agaacgtaaa tttaatccgg atttagcacc agggacagaa 1380

aaagtaacaa gagaaggaca aaaaggtgag aagacaataa cgacaccaac actaaaaaat 1440

ccattaactg gagtaattat tagtaaaggt gaaccaaaag aagagattac aaaagatccg 1500

attaatgaat taacagaata cggacctgaa acaatagcgc caggtcatcg agacgaattt 1560

gatccgaagt taccaacagg agagaaagag gaagttccag gtaaaccagg aattaagaat 1620

ccagaaacag gagacgtagt tagaccgccg gtcgatagcg taacaaaata tggacctgta 1680

aaaggagact cgattgtaga aaaagaagag attccattcg agaaagaacg taaatttaat 1740

cctgatttag caccagggac agaaaaagta acaagagaag gacaaaaagg tgagaagaca 1800

ataacgacgc caacactaaa aaatccatta actggagaaa ttattagtaa aggtgaatcg 1860

aaagaagaaa tcacaaaaga tccgattaat gaattaacag aatacggacc agaaacgata 1920

acaccaggtc atcgagacga atttgatccg aagttaccaa caggagagaa agaggaagtt 1980

ccaggtaaac caggaattaa gaatccagaa acaggagatg tagttagacc accggtcgat 2040

agcgtaacaa aatatggacc tgtaaaagga gactcgattg tagaaaaaga agagattcca 2100

ttcgagaaag aacgtaaatt taatcctgat ttagcaccag ggacagaaaa agtaacaaga 2160

gaaggacaaa aaggtgagaa gacaataacg acaccaacac taaaaaatcc attaactgga 2220

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ggaattaaga atccagaaac aggagatgta gttagaccac cggtcgatag cgtaacaaaa 2820

tatggacctg taaaaggaga ctcgattgta gaaaaagaag agattccatt cgagaaagaa 2880

cgtaaattta atcctgattt agcaccaggg acagaaaaag taacaagaga aggacaaaaa 2940

ggtgagaaga caataacgac gccaacacta aaaaatccat taactggaga aattattagt 3000

aaaggtgaat cgaaagaaga aatcacaaaa gatccgatta atgaattaac agaatacgga 3060

ccagaaacga taacaccagg tcatcgagac gaatttgatc cgaagttacc aacaggagag 3120

aaagaggaag ttccaggtaa accaggaatt aagaatccag aaacaggaga cgtagttaga 3180

ccaccggtcg atagcgtaac aaaatatgga cctgtaaaag gagactcgat tgtagaaaaa 3240

gaagaaattc cattcaagaa agaacgtaaa tttaatcctg atttagcacc agggacagaa 3300

aaagtaacaa gagaaggaca aaaaggtgag aagacaataa cgacgccaac actaaaaaat 3360

ccattaactg gagaaattat tagtaaaggt gaatcgaaag aagaaatcac aaaagatccg 3420

attaatgaat taacagaata cggaccagaa acgataacac caggtcatcg agacgaattt 3480

gatccgaagt taccaacagg agagaaagag gaagttccag gtaaaccagg aattaagaat 3540

ccagaaacag gagatgtagt tagaccaccg gtcgatagcg taacaaaata tggacctgta 3600

aaaggagact cgattgtaga aaaagaagaa attccattcg agaaagaacg taaatttaat 3660

cctgatttag caccagggac agaaaaagta acaagagaag gacaaaaagg tgagaagaca 3720

ataacgacgc caacactaaa aaatccatta actggagaaa ttattagtaa aggtgaatcg 3780

aaagaagaaa tcacaaaaga tccgattaat gaattaacag aatacggacc agaaacgata 3840

acaccaggtc atcgagacga atttgatccg aagttaccaa caggagagaa agaggaagtt 3900

ccaggtaaac caggaattaa gaatccagaa acaggagatg tagttagacc accggtcgat 3960

agcgtaacaa aatatggacc tgtaaaagga gactcgattg tagaaaaaga agaaattcca 4020

ttcgagaaag aacgtaaatt taatcctgat ttagcaccag ggacagaaaa agtaacaaga 4080

gaaggacaaa aaggtgagaa gacaataacg acgccaacac taaaaaatcc attaactgga 4140

gaaattatta gtaaaggtga atcgaaagaa gaaatcacaa aagatccagt taatgaatta 4200

acagaattcg gtggcgagaa aataccgcaa ggtcataaag atatctttga tccaaactta 4260

ccaacagatc aaacggaaaa agtaccaggt aaaccaggaa tcaagaatcc agacacagga 4320

aaagtgatcg aagagccagt ggatgatgtg attaaacacg gaccaaaaac gggtacacca 4380

gaaacaaaaa cagtagagat accgtttgaa acaaaacgtg agtttaatcc aaaattacaa 4440

cctggtgaag agcgagtgaa acaagaagga caaccaggaa gtaagacaat cacaacacca 4500

atcacagtga acccattaac aggtgaaaaa gttggcgagg gtcaaccaac agaagagatc 4560

acaaaacaac cagtagataa gattgtagag ttcggtggag agaaaccaaa agatccaaaa 4620

ggacctgaaa acccagagaa gccgagcaga ccaactcatc caagtggccc agtaaatcct 4680

aacaatccag gattatcgaa agacagagca aaaccaaatg gcccagttca ttcaatggat 4740

aaaaatgata aagttaaaaa atctaaaatt gctaaagaat cagtagctaa tcaagagaaa 4800

aaacgagcag aattaccaaa aacaggttta gaaagcacgc aaaaaggttt gatctttagt 4860

agtataattg gaattgctgg attaatgtta ttggctcgta gaagaaagaa ttaa 4914

<210> 14
<211> 1637
<212> PRT
<213> Staphylococcus epidermidis

<400> 14

Ser Gly Lys Tyr Gly Lys Arg Ser Met Gln Met Arg Asp Lys Lys Gly
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Pro Val Asn Lys Arg Val Asp Phe Leu Ser Asn Lys Leu Asn Lys Tyr
20 25 30

Ser Ile Arg Lys Phe Thr Val Gly Thr Ala Ser Ile Leu Ile Gly Ser
35 40 45

Leu Met Tyr Leu Gly Thr Gln Gln Glu Ala Glu Ala Ala Glu Asn Asn
50 55 60

Ile Glu Asn Pro Thr Thr Leu Lys Asp Asn Val Gln Ser Lys Glu Val
65 70 75 80

Lys Ile Glu Glu Val Thr Asn Lys Asp Thr Ala Pro Gln Gly Val Glu
85 90 95

Ala Lys Ser Glu Val Thr Ser Asn Lys Asp Thr Ile Glu His Glu Pro
100 105 110

Ser Val Lys Ala Glu Asp Ile Ser Lys Lys Glu Asp Thr Pro Lys Glu
115 120 125

Val Ala Asp Val Ala Glu Val Gln Pro Lys Ser Ser Val Thr His Asn
130 135 140

Ala Glu Thr Pro Lys Val Arg Lys Ala Arg Ser Val Asp Glu Gly Ser
145 150 155 160

Phe Asp Ile Thr Arg Asp Ser Lys Asn Val Val Glu Ser Thr Pro Ile
165 170 175

Thr Ile Gln Gly Lys Glu His Phe Glu Gly Tyr Gly Ser Val Asp Ile
180 185 190

Gln Lys Lys Pro Thr Asp Leu Gly Val Ser Glu Val Thr Arg Phe Asn
195 200 205

Val Gly Asn Glu Ser Asn Gly Leu Ile Gly Ala Leu Gln Leu Lys Asn
210 215 220

Lys Ile Asp Phe Ser Lys Asp Phe Asn Phe Lys Val Arg Val Ala Asn
225 230 235 240

Asn His Gln Ser Asn Thr Thr Gly Ala Asp Gly Trp Gly Phe Leu Phe
245 250 255

Ser Lys Gly Asn Ala Glu Glu Tyr Leu Thr Asn Gly Gly Ile Leu Gly
260 265 270

Asp Lys Gly Leu Val Asn Ser Gly Gly Phe Lys Ile Asp Thr Gly Tyr
275 280 285

Ile Tyr Thr Ser Ser Met Asp Lys Thr Glu Lys Gln Ala Gly Gln Gly
290 295 300

Tyr Arg Gly Tyr Gly Ala Phe Val Lys Asn Asp Ser Ser Gly Asn Ser
305 310 315 320

Gln Met Val Gly Glu Asn Ile Asp Lys Ser Lys Thr Asn Phe Leu Asn
325 330 335

Tyr Ala Asp Asn Ser Thr Asn Thr Ser Asp Gly Lys Phe His Gly Gln
340 345 350

Arg Leu Asn Asp Val Ile Leu Thr Tyr Val Ala Ser Thr Gly Lys Met
355 360 365

Arg Ala Glu Tyr Ala Gly Lys Thr Trp Glu Thr Ser Ile Thr Asp Leu
370 375 380

Gly Leu Ser Lys Asn Gln Ala Tyr Asn Phe Leu Ile Thr Ser Ser Gln
385 390 395 400

Arg Trp Gly Leu Asn Gln Gly Ile Asn Ala Asn Gly Trp Met Arg Thr
405 410 415

Asp Leu Lys Gly Ser Glu Phe Thr Phe Thr Pro Glu Ala Pro Lys Thr
420 425 430

Ile Thr Glu Leu Glu Lys Lys Val Glu Glu Ile Pro Phe Lys Lys Glu
435 440 445

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
450 455 460

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
465 470 475 480

Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
485 490 495

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
500 505 510

Ala Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
515 520 525

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
530 535 540

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
545 550 555 560

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
565 570 575

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
580 585 590

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
595 600 605

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
610 615 620

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
625 630 635 640

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
645 650 655

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
660 665 670

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
675 680 685

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
690 695 700

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
705 710 715 720

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
725 730 735

Pro Leu Thr Gly Val Ile Ile Ser Lys Gly Glu Pro Lys Glu Glu Ile
740 745 750

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
755 760 765

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
770 775 780

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
785 790 795 800

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
805 810 815

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Lys Lys Glu
820 825 830

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
835 840 845

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
850 855 860

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
865 870 875 880

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr Ile
885 890 895

Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu
900 905 910

Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly
915 920 925

Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val
930 935 940

Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu
945 950 955 960

Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg
965 970 975

Glu Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
980 985 990

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu Ile
995 1000 1005

Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu Thr
1010 1015 1020

Ile Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro Thr
1025 1030 1035

Gly Glu Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn Pro
1040 1045 1050

Glu Thr Gly Asp Val Val Arg Pro Pro Val Asp Ser Val Thr Lys
1055 1060 1065

Tyr Gly Pro Val Lys Gly Asp Ser Ile Val Glu Lys Glu Glu Ile
1070 1075 1080

Pro Phe Lys Lys Glu Arg Lys Phe Asn Pro Asp Leu Ala Pro Gly
1085 1090 1095

Thr Glu Lys Val Thr Arg Glu Gly Gln Lys Gly Glu Lys Thr Ile
1100 1105 1110

Thr Thr Pro Thr Leu Lys Asn Pro Leu Thr Gly Glu Ile Ile Ser
1115 1120 1125

Lys Gly Glu Ser Lys Glu Glu Ile Thr Lys Asp Pro Ile Asn Glu
1130 1135 1140

Leu Thr Glu Tyr Gly Pro Glu Thr Ile Thr Pro Gly His Arg Asp
1145 1150 1155

Glu Phe Asp Pro Lys Leu Pro Thr Gly Glu Lys Glu Glu Val Pro
1160 1165 1170

Gly Lys Pro Gly Ile Lys Asn Pro Glu Thr Gly Asp Val Val Arg
1175 1180 1185

Pro Pro Val Asp Ser Val Thr Lys Tyr Gly Pro Val Lys Gly Asp
1190 1195 1200

Ser Ile Val Glu Lys Glu Glu Ile Pro Phe Glu Lys Glu Arg Lys
1205 1210 1215

Phe Asn Pro Asp Leu Ala Pro Gly Thr Glu Lys Val Thr Arg Glu
1220 1225 1230

Gly Gln Lys Gly Glu Lys Thr Ile Thr Thr Pro Thr Leu Lys Asn
1235 1240 1245

Pro Leu Thr Gly Glu Ile Ile Ser Lys Gly Glu Ser Lys Glu Glu
1250 1255 1260

Ile Thr Lys Asp Pro Ile Asn Glu Leu Thr Glu Tyr Gly Pro Glu
1265 1270 1275

Thr Ile Thr Pro Gly His Arg Asp Glu Phe Asp Pro Lys Leu Pro
1280 1285 1290

Thr Gly Glu Lys Glu Glu Val Pro Gly Lys Pro Gly Ile Lys Asn
1295 1300 1305

Pro Glu Thr Gly Asp Val Val Arg Pro Pro Val Asp Ser Val Thr
1310 1315 1320

Lys Tyr Gly Pro Val Lys Gly Asp Ser Ile Val Glu Lys Glu Glu
1325 1330 1335

Ile Pro Phe Glu Lys Glu Arg Lys Phe Asn Pro Asp Leu Ala Pro
1340 1345 1350

Gly Thr Glu Lys Val Thr Arg Glu Gly Gln Lys Gly Glu Lys Thr
1355 1360 1365

Ile Thr Thr Pro Thr Leu Lys Asn Pro Leu Thr Gly Glu Ile Ile
1370 1375 1380

Ser Lys Gly Glu Ser Lys Glu Glu Ile Thr Lys Asp Pro Val Asn
1385 1390 1395

Glu Leu Thr Glu Phe Gly Gly Glu Lys Ile Pro Gln Gly His Lys
1400 1405 1410

Asp Ile Phe Asp Pro Asn Leu Pro Thr Asp Gln Thr Glu Lys Val
1415 1420 1425

Pro Gly Lys Pro Gly Ile Lys Asn Pro Asp Thr Gly Lys Val Ile
1430 1435 1440

Glu Glu Pro Val Asp Asp Val Ile Lys His Gly Pro Lys Thr Gly
1445 1450 1455

Thr Pro Glu Thr Lys Thr Val Glu Ile Pro Phe Glu Thr Lys Arg
1460 1465 1470

Glu Phe Asn Pro Lys Leu Gln Pro Gly Glu Glu Arg Val Lys Gln
1475 1480 1485

Glu Gly Gln Pro Gly Ser Lys Thr Ile Thr Thr Pro Ile Thr Val
1490 1495 1500

Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Gln Pro Thr Glu
1505 1510 1515

Glu Ile Thr Lys Gln Pro Val Asp Lys Ile Val Glu Phe Gly Gly
1520 1525 1530

Glu Lys Pro Lys Asp Pro Lys Gly Pro Glu Asn Pro Glu Lys Pro
1535 1540 1545

Ser Arg Pro Thr His Pro Ser Gly Pro Val Asn Pro Asn Asn Pro
1550 1555 1560

Gly Leu Ser Lys Asp Arg Ala Lys Pro Asn Gly Pro Val His Ser
1565 1570 1575

Met Asp Lys Asn Asp Lys Val Lys Lys Ser Lys Ile Ala Lys Glu
1580 1585 1590

Ser Val Ala Asn Gln Glu Lys Lys Arg Ala Glu Leu Pro Lys Thr
1595 1600 1605

Gly Leu Glu Ser Thr Gln Lys Gly Leu Ile Phe Ser Ser Ile Ile
1610 1615 1620

Gly Ile Ala Gly Leu Met Leu Leu Ala Arg Arg Arg Lys Asn
1625 1630 1635

<210> 15
<211> 1923
<212> DNA
<213> Staphylococcus epidermidis

<400> 15
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tcgtgttcga caatgatggc gacaagtatc attttaacga atatcttgcc gtacgatgcc 120

caagctgcat ctgaaaagga tactgaaatt acaaaagaga tattatctaa gcaagattta 180

ttagacaaag ttgacaaggc aattcgtcaa attgagcaat taaaacagtt atcggcttca 240

tctaaagaac attataaagc acaactaaat gaagcgaaaa cagcatcgca aatagatgaa 300

atcataaaac gagctaatga gttggatagc aaagacaata aaagttctca cactgaaatg 360

aacggtcaaa gtgatataga cagtaaatta gatcaattgc ttaaagattt aaatgaggtt 420

tcttcaaatg ttgatagggg tcaacaaagt ggcgaggacg atcttaatgc aatgaaaaat 480

gatatgtcac aaacggctac aacaaaacat ggagaaaaag atgataaaaa tgatgaagca 540

atggtaaata aggcgttaga agacctagac catttgaatc agcaaataca caaatcgaaa 600

gatgcatcga aagatacatc ggaagatcca gcagtgtcta caacagataa taatcatgaa 660

gtagctaaaa cgccaaataa tgatggttct ggacatgttg tgttaaataa attcctttca 720

aatgaagaga atcaaagcca tagtaatcga ctcactgata aattacaagg aagcgataaa 780

attaatcatg ctatgattga aaaattagct aaaagtaatg cctcaacgca acattacaca 840

tatcataaac tgaatacgtt acaatcttta gatcaacgta ttgcaaatac gcaacttcct 900

aaaaatcaaa aatcagactt aatgagcgaa gtaaataaga cgaaagagcg tataaaaagt 960

caacgaaata ttattttgga agaacttgca cgtactgatg ataaaaagta tgctacacaa 1020

agcattttag aaagtatatt taataaagac gaggcagtta aaattctaaa agatatacgt 1080

gttgatggta aaacagatca acaaattgca gatcaaatta ctcgtcatat tgatcaatta 1140

tctctgacaa cgagtgatga tttattaacg tcattgattg atcaatcaca agataagtcg 1200

ctattgattt ctcaaatttt acaaacgaaa ttaggaaaag ctgaagcaga taaattggct 1260

aaagattgga cgaataaagg attatcaaat cgccaaatcg ttgaccaatt gaagaaacat 1320

tttgcatcaa ctggcgacac gtcttcagat gatatattaa aagcaatttt gaataatgcc 1380

aaagataaaa aacaagcaat tgaaacgatt ttagcaacac gtatagaaag acaaaaggca 1440

aaattactgg cagatttaat tactaaaata gaaacagatc aaaataaaat ttttaattta 1500

gttaaatcgg cattgaatgg taaagcggat gatttattga atttacaaaa gagactcaat 1560

caaacgaaaa aagatataga ttatatttta tcaccaatag taaatcgtcc aagtttacta 1620

gatcgattga ataaaaatgg gaaaacgaca gatttaaata agttagcaaa tttaatgaat 1680

caaggatcag atttattaga cagtattcca gatataccca caccaaagcc agaaaagacg 1740

ttaacacttg gtaaaggtaa tggattgtta agtggattat taaatgctga tggtaatgta 1800

tctttgccta aagcggggga aacgataaaa gaacattggt tgccgatatc tgtaattgtt 1860

ggtgcaatgg gtgtactaat gatttggtta tcacgacgca ataagttgaa aaataaagca 1920

taa 1923

<210> 16
<211> 640
<212> PRT
<213> Staphylococcus epidermidis

<400> 16

Gly Arg Ser Met Leu Met Ala Lys Tyr Arg Gly Lys Pro Phe Gln Leu
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Tyr Val Lys Leu Ser Cys Ser Thr Met Met Ala Thr Ser Ile Ile Leu
20 25 30

Thr Asn Ile Leu Pro Tyr Asp Ala Gln Ala Ala Ser Glu Lys Asp Thr
35 40 45

Glu Ile Thr Lys Glu Ile Leu Ser Lys Gln Asp Leu Leu Asp Lys Val
50 55 60

Asp Lys Ala Ile Arg Gln Ile Glu Gln Leu Lys Gln Leu Ser Ala Ser
65 70 75 80

Ser Lys Glu His Tyr Lys Ala Gln Leu Asn Glu Ala Lys Thr Ala Ser
85 90 95

Gln Ile Asp Glu Ile Ile Lys Arg Ala Asn Glu Leu Asp Ser Lys Asp
100 105 110

Asn Lys Ser Ser His Thr Glu Met Asn Gly Gln Ser Asp Ile Asp Ser
115 120 125

Lys Leu Asp Gln Leu Leu Lys Asp Leu Asn Glu Val Ser Ser Asn Val
130 135 140

Asp Arg Gly Gln Gln Ser Gly Glu Asp Asp Leu Asn Ala Met Lys Asn
145 150 155 160

Asp Met Ser Gln Thr Ala Thr Thr Lys His Gly Glu Lys Asp Asp Lys
165 170 175

Asn Asp Glu Ala Met Val Asn Lys Ala Leu Glu Asp Leu Asp His Leu
180 185 190

Asn Gln Gln Ile His Lys Ser Lys Asp Ala Ser Lys Asp Thr Ser Glu
195 200 205

Asp Pro Ala Val Ser Thr Thr Asp Asn Asn His Glu Val Ala Lys Thr
210 215 220

Pro Asn Asn Asp Gly Ser Gly His Val Val Leu Asn Lys Phe Leu Ser
225 230 235 240

Asn Glu Glu Asn Gln Ser His Ser Asn Arg Leu Thr Asp Lys Leu Gln
245 250 255

Gly Ser Asp Lys Ile Asn His Ala Met Ile Glu Lys Leu Ala Lys Ser
260 265 270

Asn Ala Ser Thr Gln His Tyr Thr Tyr His Lys Leu Asn Thr Leu Gln
275 280 285

Ser Leu Asp Gln Arg Ile Ala Asn Thr Gln Leu Pro Lys Asn Gln Lys
290 295 300

Ser Asp Leu Met Ser Glu Val Asn Lys Thr Lys Glu Arg Ile Lys Ser
305 310 315 320

Gln Arg Asn Ile Ile Leu Glu Glu Leu Ala Arg Thr Asp Asp Lys Lys
325 330 335

Tyr Ala Thr Gln Ser Ile Leu Glu Ser Ile Phe Asn Lys Asp Glu Ala
340 345 350

Val Lys Ile Leu Lys Asp Ile Arg Val Asp Gly Lys Thr Asp Gln Gln
355 360 365

Ile Ala Asp Gln Ile Thr Arg His Ile Asp Gln Leu Ser Leu Thr Thr
370 375 380

Ser Asp Asp Leu Leu Thr Ser Leu Ile Asp Gln Ser Gln Asp Lys Ser
385 390 395 400

Leu Leu Ile Ser Gln Ile Leu Gln Thr Lys Leu Gly Lys Ala Glu Ala
405 410 415

Asp Lys Leu Ala Lys Asp Trp Thr Asn Lys Gly Leu Ser Asn Arg Gln
420 425 430

Ile Val Asp Gln Leu Lys Lys His Phe Ala Ser Thr Gly Asp Thr Ser
435 440 445

Ser Asp Asp Ile Leu Lys Ala Ile Leu Asn Asn Ala Lys Asp Lys Lys
450 455 460

Gln Ala Ile Glu Thr Ile Leu Ala Thr Arg Ile Glu Arg Gln Lys Ala
465 470 475 480

Lys Leu Leu Ala Asp Leu Ile Thr Lys Ile Glu Thr Asp Gln Asn Lys
485 490 495

Ile Phe Asn Leu Val Lys Ser Ala Leu Asn Gly Lys Ala Asp Asp Leu
500 505 510

Leu Asn Leu Gln Lys Arg Leu Asn Gln Thr Lys Lys Asp Ile Asp Tyr
515 520 525

Ile Leu Ser Pro Ile Val Asn Arg Pro Ser Leu Leu Asp Arg Leu Asn
530 535 540

Lys Asn Gly Lys Thr Thr Asp Leu Asn Lys Leu Ala Asn Leu Met Asn
545 550 555 560

Gln Gly Ser Asp Leu Leu Asp Ser Ile Pro Asp Ile Pro Thr Pro Lys
565 570 575

Pro Glu Lys Thr Leu Thr Leu Gly Lys Gly Asn Gly Leu Leu Ser Gly
580 585 590

Leu Leu Asn Ala Asp Gly Asn Val Ser Leu Pro Lys Ala Gly Glu Thr
595 600 605

Ile Lys Glu His Trp Leu Pro Ile Ser Val Ile Val Gly Ala Met Gly
610 615 620

Val Leu Met Ile Trp Leu Ser Arg Arg Asn Lys Leu Lys Asn Lys Ala
625 630 635 640

<210> 17
<211> 522
<212> PRT
<213> Staphylococcus epidermidis

<400> 17

Ala Ser Glu Thr Pro Ile Thr Ser Glu Ile Ser Ser Asn Ser Glu Thr
1 5 10 15

Val Ala Asn Gln Asn Ser Thr Thr Ile Lys Asn Ser Gln Lys Glu Thr
20 25 30

Val Asn Ser Thr Ser Leu Glu Ser Asn His Ser Asn Ser Thr Asn Lys
35 40 45

Gln Met Ser Ser Glu Val Thr Asn Thr Ala Gln Ser Ser Glu Lys Ala
50 55 60

Gly Ile Ser Gln Gln Ser Ser Glu Thr Ser Asn Gln Ser Ser Lys Leu
65 70 75 80

Asn Thr Tyr Ala Ser Thr Asp His Val Glu Ser Thr Thr Ile Asn Asn
85 90 95

Asp Asn Thr Ala Gln Gln Asp Gln Asn Lys Ser Ser Asn Val Thr Ser
100 105 110

Lys Ser Thr Gln Ser Asn Thr Ser Ser Ser Glu Lys Asn Ile Ser Ser
115 120 125

Asn Leu Thr Gln Ser Ile Glu Thr Lys Ala Thr Asp Ser Leu Ala Thr
130 135 140

Ser Glu Ala Arg Thr Ser Thr Asn Gln Ile Ser Asn Leu Thr Ser Thr
145 150 155 160

Ser Thr Ser Asn Gln Ser Ser Pro Thr Ser Phe Ala Asn Leu Arg Thr
165 170 175

Phe Ser Arg Phe Thr Val Leu Asn Thr Met Ala Ala Pro Thr Thr Thr
180 185 190

Ser Thr Thr Thr Thr Ser Ser Leu Thr Ser Asn Ser Val Val Val Asn
195 200 205

Lys Asp Asn Phe Asn Glu His Met Asn Leu Ser Gly Ser Ala Thr Tyr
210 215 220

Asp Pro Lys Thr Gly Ile Ala Thr Leu Thr Pro Asp Ala Tyr Ser Gln
225 230 235 240

Lys Gly Ala Ile Ser Leu Asn Thr Arg Leu Asp Ser Asn Arg Ser Phe
245 250 255

Arg Phe Ile Gly Lys Val Asn Leu Gly Asn Arg Tyr Glu Gly Tyr Ser
260 265 270

Pro Asp Gly Val Ala Gly Gly Asp Gly Ile Gly Phe Ala Phe Ser Pro
275 280 285

Gly Pro Leu Gly Gln Ile Gly Lys Glu Gly Ala Ala Val Gly Ile Gly
290 295 300

Gly Leu Asn Asn Ala Phe Gly Phe Lys Leu Asp Thr Tyr His Asn Thr
305 310 315 320

Ser Thr Pro Arg Ser Asp Ala Lys Ala Lys Ala Asp Pro Arg Asn Val
325 330 335

Gly Gly Gly Gly Ala Phe Gly Ala Phe Val Ser Thr Asp Arg Asn Gly
340 345 350

Met Ala Thr Thr Glu Glu Ser Thr Ala Ala Lys Leu Asn Val Gln Pro
355 360 365

Thr Asp Asn Ser Phe Gln Asp Phe Val Ile Asp Tyr Asn Gly Asp Thr
370 375 380

Lys Val Met Thr Val Thr Tyr Ala Gly Gln Thr Phe Thr Arg Asn Leu
385 390 395 400

Thr Asp Trp Ile Lys Asn Ser Gly Gly Thr Thr Phe Ser Leu Ser Met
405 410 415

Thr Ala Ser Thr Gly Gly Ala Lys Asn Leu Gln Gln Val Gln Phe Gly
420 425 430

Thr Phe Glu Tyr Thr Glu Ser Ala Val Ala Lys Val Arg Tyr Val Asp
435 440 445

Ala Asn Thr Gly Lys Asp Ile Ile Pro Pro Lys Thr Ile Ala Gly Glu
450 455 460

Val Asp Gly Thr Val Asn Ile Asp Lys Gln Leu Asn Asn Phe Lys Asn
465 470 475 480

Leu Gly Tyr Ser Tyr Val Gly Thr Asp Ala Leu Lys Ala Pro Asn Tyr
485 490 495

Thr Glu Thr Ser Gly Thr Pro Thr Leu Lys Leu Thr Asn Ser Ser Gln
500 505 510

Thr Val Ile Tyr Lys Phe Lys Asp Val Gln
515 520

<210> 18
<211> 485
<212> PRT
<213> Staphylococcus epidermidis

<400> 18

Ala Ser Asp Ala Pro Leu Thr Ser Glu Leu Asn Thr Gln Ser Glu Thr
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Val Gly Asn Gln Asn Ser Thr Thr Ile Glu Ala Ser Thr Ser Thr Ala
20 25 30

Asp Ser Thr Ser Val Thr Lys Asn Ser Ser Ser Val Gln Thr Ser Asn
35 40 45

Ser Asp Thr Val Ser Ser Glu Lys Ser Glu Lys Val Thr Ser Thr Thr
50 55 60

Asn Ser Thr Ser Asn Gln Gln Glu Lys Leu Thr Ser Thr Ser Glu Ser
65 70 75 80

Thr Ser Ser Lys Asn Thr Thr Ser Ser Ser Asp Thr Lys Ser Val Ala
85 90 95

Ser Thr Ser Ser Thr Glu Gln Pro Ile Asn Thr Ser Thr Asn Gln Ser
100 105 110

Thr Ala Ser Asn Asn Thr Ser Gln Ser Thr Thr Pro Ser Ser Val Asn
115 120 125

Leu Asn Lys Thr Ser Thr Thr Ser Thr Ser Thr Ala Pro Val Lys Leu
130 135 140

Arg Thr Phe Ser Arg Leu Ala Met Ser Thr Phe Ala Ser Ala Ala Thr
145 150 155 160

Thr Thr Ala Val Thr Ala Asn Thr Ile Thr Val Asn Lys Asp Asn Leu
165 170 175

Lys Gln Tyr Met Thr Thr Ser Gly Asn Ala Thr Tyr Asp Gln Ser Thr
180 185 190

Gly Ile Val Thr Leu Thr Gln Asp Ala Tyr Ser Gln Lys Gly Ala Ile
195 200 205

Thr Leu Gly Thr Arg Ile Asp Ser Asn Lys Ser Phe His Phe Ser Gly
210 215 220

Lys Val Asn Leu Gly Asn Lys Tyr Glu Gly His Gly Asn Gly Gly Asp
225 230 235 240

Gly Ile Gly Phe Ala Phe Ser Pro Gly Val Leu Gly Glu Thr Gly Leu
245 250 255

Asn Gly Ala Ala Val Gly Ile Gly Gly Leu Ser Asn Ala Phe Gly Phe
260 265 270

Lys Leu Asp Thr Tyr His Asn Thr Ser Lys Pro Asn Ser Ala Ala Lys
275 280 285

Ala Asn Ala Asp Pro Ser Asn Val Ala Gly Gly Gly Ala Phe Gly Ala
290 295 300

Phe Val Thr Thr Asp Ser Tyr Gly Val Ala Thr Thr Tyr Thr Ser Ser
305 310 315 320

Ser Thr Ala Asp Asn Ala Ala Lys Leu Asn Val Gln Pro Thr Asn Asn
325 330 335

Thr Phe Gln Asp Phe Asp Ile Asn Tyr Asn Gly Asp Thr Lys Val Met
340 345 350

Thr Val Lys Tyr Ala Gly Gln Thr Trp Thr Arg Asn Ile Ser Asp Trp
355 360 365

Ile Ala Lys Ser Gly Thr Thr Asn Phe Ser Leu Ser Met Thr Ala Ser
370 375 380

Thr Gly Gly Ala Thr Asn Leu Gln Gln Val Gln Phe Gly Thr Phe Glu
385 390 395 400

Tyr Thr Glu Ser Ala Val Thr Gln Val Arg Tyr Val Asp Val Thr Thr
405 410 415

Gly Lys Asp Ile Ile Pro Pro Lys Thr Tyr Ser Gly Asn Val Asp Gln
420 425 430

Val Val Thr Ile Asp Asn Gln Gln Ser Ala Leu Thr Ala Lys Gly Tyr
435 440 445

Asn Tyr Thr Ser Val Asp Ser Ser Tyr Ala Ser Thr Tyr Asn Asp Thr
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Phe Thr Asp Val Val
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<210> 19
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<213> Staphylococcus epidermidis

<400> 19

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20 25 30

Ala Ser Ile Leu Leu Gly Ser Thr Leu Ile Phe Gly Ser Ser Ser His
35 40 45

Glu Ala Lys Ala Ala Glu Glu Lys Gln Val Asp Pro Ile Thr Gln Ala
50 55 60

Asn Gln Asn Asp Ser Ser Glu Arg Ser Leu Glu Asn Thr Asn Gln Pro
65 70 75 80

Thr Val Asn Asn Glu Ala Pro Gln Met Ser Ser Thr Leu Gln Ala Glu
85 90 95

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
100 105 110

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
115 120 125

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
130 135 140

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
145 150 155 160

Glu Gly Ser Asn Val Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
165 170 175

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
180 185 190

Glu Gly Ser Asn Ala Lys Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu
195 200 205

Glu Gly Gly Asn Ala Glu Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu
210 215 220

Glu Gly Ser Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu
225 230 235 240

Glu Gly Gly Asn Ala Glu Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu
245 250 255

Glu Gly Gly Asn Ala Glu Ala Pro Asn Val Pro Thr Ile Lys Ala Asn
260 265 270

Ser Asp Asn Asp Thr Gln Thr Gln Phe Ser Glu Ala Pro Thr Arg Asn
275 280 285

Asp Leu Ala Arg Lys Glu Asp Ile Pro Ala Val Ser Lys Asn Glu Glu
290 295 300

Leu Gln Ser Ser Gln Pro Asn Thr Asp Ser Lys Ile Glu Pro Thr Thr
305 310 315 320

Ser Glu Pro Val Asn Leu Asn Tyr Ser Ser Pro Phe Met Ser Leu Leu
325 330 335

Ser Met Pro Ala Asp Ser Ser Ser Asn Asn Thr Lys Asn Thr Ile Asp
340 345 350

Ile Pro Pro Thr Thr Val Lys Gly Arg Asp Asn Tyr Asp Phe Tyr Gly
355 360 365

Arg Val Asp Ile Glu Ser Asn Pro Thr Asp Leu Asn Ala Thr Asn Leu
370 375 380

Thr Arg Tyr Asn Tyr Gly Gln Pro Pro Gly Thr Thr Thr Ala Gly Ala
385 390 395 400

Val Gln Phe Lys Asn Gln Val Ser Phe Asp Lys Asp Phe Asp Phe Asn
405 410 415

Ile Arg Val Ala Asn Asn Arg Gln Ser Asn Thr Thr Gly Ala Asp Gly
420 425 430

Trp Gly Phe Met Phe Ser Lys Lys Asp Gly Asp Asp Phe Leu Lys Asn
435 440 445

Gly Gly Ile Leu Arg Glu Lys Gly Thr Pro Ser Ala Ala Gly Phe Arg
450 455 460

Ile Asp Thr Gly Tyr Tyr Asn Asn Asp Pro Leu Asp Lys Ile Gln Lys
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Gln Ala Gly Gln Gly Tyr Arg Gly Tyr Gly Thr Phe Val Lys Asn Asp
485 490 495

Ser Gln Gly Asn Thr Ser Lys Val Gly Ser Gly Thr Pro Ser Thr Asp
500 505 510

Phe Leu Asn Tyr Ala Asp Asn Thr Thr Asn Asp Leu Asp Gly Lys Phe
515 520 525

His Gly Gln Lys Leu Asn Asn Val Asn Leu Lys Tyr Asn Ala Ser Asn
530 535 540

Gln Thr Phe Thr Ala Thr Tyr Ala Gly Lys Thr Trp Thr Ala Thr Leu
545 550 555 560

Ser Glu Leu Gly Leu Ser Pro Thr Asp Ser Tyr Asn Phe Leu Val Thr
565 570 575

Ser Ser Gln Tyr Gly Asn Gly Asn Ser Gly Thr Tyr Ala Ser Gly Val
580 585 590

Met Arg Ala Asp Leu Asp Gly Ala Thr Leu Thr Tyr Thr Pro Lys Ala
595 600 605

Val Asp Gly Asp Pro Ile Ile Ser Thr Lys Glu Ile Pro Phe Asn Lys
610 615 620

Lys Arg Glu Phe Asp Pro Asn Leu Ala Pro Gly Thr Glu Lys Val Val
625 630 635 640

Gln Lys Gly Glu Pro Gly Ile Glu Thr Thr Thr Thr Pro Thr Tyr Val
645 650 655

Asn Pro Asn Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
660 665 670

Ile Thr Lys Gln Pro Val Asp Glu Ile Val His Tyr Gly Gly Glu Glu
675 680 685

Ile Lys Pro Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Lys Gly
690 695 700

Ser Gln Thr Thr Gln Pro Gly Lys Pro Gly Val Lys Asn Pro Asp Thr
705 710 715 720

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
725 730 735

Val Asp Gly Asp Pro Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys
740 745 750

Lys Arg Glu Phe Asn Pro Asp Leu Lys Pro Gly Glu Glu Arg Val Lys
755 760 765

Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr Thr Lys
770 775 780

Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
785 790 795 800

Ile Thr Lys Gln Pro Val Asp Glu Ile Thr Glu Tyr Gly Gly Glu Glu
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Ile Lys Pro Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Lys Gly
820 825 830

Ser Gln Glu Asp Val Pro Gly Lys Pro Gly Val Lys Asn Pro Gly Thr
835 840 845

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
850 855 860

Val Asp Gly Asp Pro Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys
865 870 875 880

Lys Arg Glu Phe Asn Pro Asp Leu Lys Pro Gly Glu Glu Arg Val Lys
885 890 895

Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr Thr Lys
900 905 910

Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Glu Pro Thr Glu Lys
915 920 925

Ile Thr Lys Gln Pro Val Asp Glu Ile Val His Tyr Gly Gly Glu Gln
930 935 940

Ile Pro Gln Gly His Lys Asp Glu Phe Asp Pro Asn Ala Pro Val Asp
945 950 955 960

Ser Lys Thr Glu Val Pro Gly Lys Pro Gly Val Lys Asn Pro Asp Thr
965 970 975

Gly Glu Val Val Thr Pro Pro Val Asp Asp Val Thr Lys Tyr Gly Pro
980 985 990

Val Asp Gly Asp Ser Ile Thr Ser Thr Glu Glu Ile Pro Phe Asp Lys
995 1000 1005

Lys Arg Glu Phe Asp Pro Asn Leu Ala Pro Gly Thr Glu Lys Val
1010 1015 1020

Val Gln Lys Gly Glu Pro Gly Thr Lys Thr Ile Thr Thr Pro Thr
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Thr Lys Asn Pro Leu Thr Gly Glu Lys Val Gly Glu Gly Lys Ser
1040 1045 1050

Thr Glu Lys Val Thr Lys Gln Pro Val Asp Glu Ile Val Glu Tyr
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Gly Pro Thr Lys Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Lys
1070 1075 1080

Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu
1085 1090 1095

Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Lys
1100 1105 1110

Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Lys Pro Ala Glu
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Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Thr
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Pro Ala Glu Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu
1145 1150 1155

Pro Gly Lys Pro Ala Glu Pro Gly Thr Pro Ala Glu Pro Gly Lys
1160 1165 1170

Pro Ala Glu Ser Gly Lys Pro Val Glu Pro Gly Thr Pro Ala Gln
1175 1180 1185

Ser Gly Ala Pro Glu Gln Pro Asn Arg Ser Met His Ser Thr Asp
1190 1195 1200

Asn Lys Asn Gln Leu Pro Asp Thr Gly Glu Asn Arg Gln Ala Asn
1205 1210 1215

Glu Gly Thr Leu Val Gly Ser Leu Leu Ala Ile Val Gly Ser Leu
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Phe Ile Phe Gly Arg Arg Lys Lys Gly Asn Glu Lys
1235 1240 1245

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<213> Staphylococcus epidermidis

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attacacaag ctaatcaaaa tgatagtagt gaaagatcac ttgaaaacac aaatcaacct 240

actgtaaaca atgaagcacc acagatgtct tctacattgc aagcagaaga aggaagcaat 300

gcagaagcac ctcaatctga gccaacgaag gcagaagaag gaggcaatgc agaagcagct 360

caatctgagc caacgaaggc agaagaagga ggcaatgcag aagcacctca atctgagcca 420

acgaaggcag aagaaggagg caatgcagaa gcagctcaat ctgagccaac gaagacagaa 480

gaaggaagca acgtaaaagc agctcaatct gagccaacga aggcagaaga aggaagcaat 540

gcagaagcac ctcaatctga gccaacgaag acagaagaag gaagcaacgc aaaagcagct 600

caatctgagc caacgaaggc agaagaagga ggcaatgcag aagcagctca atctgagcca 660

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gaaggaggca atgcagaagc acctcaatct gagccaacga agacagaaga aggaggcaat 780

gcagaagcac cgaatgttcc aactatcaaa gctaattcag ataatgatac acaaacacaa 840

ttttcagaag cccctacaag aaatgaccta gctagaaaag aagatatccc tgctgtttct 900

aaaaacgagg aattacaatc atcacaacca aacactgaca gtaaaataga acctacaact 960

tcagaacctg tgaatttaaa ttatagttct ccgtttatgt ccttattaag catgcctgct 1020

gatagttcat ccaataacac taaaaataca atagatatac cgccaactac ggttaaaggt 1080

agagataatt acgattttta cggtagagta gatatcgaaa gtaatcctac agatttaaat 1140

gcgacaaatt taacgagata taattatgga cagccacctg gtacaacaac agctggtgca 1200

gttcaattta aaaatcaagt tagttttgat aaagatttcg actttaacat tagagtagca 1260

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gctggtttca gaattgatac aggatattat aataacgatc cattagataa aatacagaaa 1440

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acttctaaag taggatcagg tactccatca acagattttc ttaactacgc agataatact 1560

actaatgatt tagatggtaa attccatggt caaaaattaa ataatgttaa tttgaaatat 1620

aatgcttcaa atcaaacttt tacagctact tatgctggta aaacttggac ggctacgtta 1680

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aaacgtgaat tcaatcctga tttaaaacca ggtgaagagc gcgttaaaca gaaaggtgaa 2700

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accccaccag tggatgatgt gacaaaatat ggtccagttg atggagattc gattacgtca 3000

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gcggaaccag gtaaaccagc ggaaccaggt aaaccagcgg aaccaggtac gccagcagaa 3420

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<211> 546
<212> PRT
<213> Staphylococcus epidermidis

<400> 21

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Glu Arg Ser Leu Glu Asn Thr Asn Gln Pro Thr Val Asn Asn Glu Ala
20 25 30

Pro Gln Met Ser Ser Thr Leu Gln Ala Glu Glu Gly Ser Asn Ala Glu
35 40 45

Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
50 55 60

Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
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Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
85 90 95

Ala Ala Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Ser Asn Val Lys
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Ala Ala Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Ser Asn Ala Glu
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Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Ser Asn Ala Lys
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Ala Pro Gln Ser Glu Pro Thr Lys Ala Glu Glu Gly Gly Asn Ala Glu
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Ala Pro Gln Ser Glu Pro Thr Lys Thr Glu Glu Gly Gly Asn Ala Glu
195 200 205

Ala Pro Asn Val Pro Thr Ile Lys Ala Asn Ser Asp Asn Asp Thr Gln
210 215 220

Thr Gln Phe Ser Glu Ala Pro Thr Arg Asn Asp Leu Ala Arg Lys Glu
225 230 235 240

Asp Ile Pro Ala Val Ser Lys Asn Glu Glu Leu Gln Ser Ser Gln Pro
245 250 255

Asn Thr Asp Ser Lys Ile Glu Pro Thr Thr Ser Glu Pro Val Asn Leu
260 265 270

Asn Tyr Ser Ser Pro Phe Met Ser Leu Leu Ser Met Pro Ala Asp Ser
275 280 285

Ser Ser Asn Asn Thr Lys Asn Thr Ile Asp Ile Pro Pro Thr Thr Val
290 295 300

Lys Gly Arg Asp Asn Tyr Asp Phe Tyr Gly Arg Val Asp Ile Glu Ser
305 310 315 320

Asn Pro Thr Asp Leu Asn Ala Thr Asn Leu Thr Arg Tyr Asn Tyr Gly
325 330 335

Gln Pro Pro Gly Thr Thr Thr Ala Gly Ala Val Gln Phe Lys Asn Gln
340 345 350

Val Ser Phe Asp Lys Asp Phe Asp Phe Asn Ile Arg Val Ala Asn Asn
355 360 365

Arg Gln Ser Asn Thr Thr Gly Ala Asp Gly Trp Gly Phe Met Phe Ser
370 375 380

Lys Lys Asp Gly Asp Asp Phe Leu Lys Asn Gly Gly Ile Leu Arg Glu
385 390 395 400

Lys Gly Thr Pro Ser Ala Ala Gly Phe Arg Ile Asp Thr Gly Tyr Tyr
405 410 415

Asn Asn Asp Pro Leu Asp Lys Ile Gln Lys Gln Ala Gly Gln Gly Tyr
420 425 430

Arg Gly Tyr Gly Thr Phe Val Lys Asn Asp Ser Gln Gly Asn Thr Ser
435 440 445

Lys Val Gly Ser Gly Thr Pro Ser Thr Asp Phe Leu Asn Tyr Ala Asp
450 455 460

Asn Thr Thr Asn Asp Leu Asp Gly Lys Phe His Gly Gln Lys Leu Asn
465 470 475 480

Asn Val Asn Leu Lys Tyr Asn Ala Ser Asn Gln Thr Phe Thr Ala Thr
485 490 495

Tyr Ala Gly Lys Thr Trp Thr Ala Thr Leu Ser Glu Leu Gly Leu Ser
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Gly Ala
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<212> PRT
<213> Staphylococcus aureus

<400> 22

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Ala Leu Ile Thr Gly Ala Ala Leu Leu Ala Arg Arg Arg Ser Lys Lys
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Glu Lys Glu Ser
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<210> 23
<211> 43
<212> PRT
<213> Staphylococcus aureus

<400> 23

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1 5 10 15

Val Met Thr Leu Leu Val Gly Leu Gly Leu Met Lys Arg Lys Lys Lys
20 25 30

Lys Asp Glu Asn Asp Gln Asp Asp Ser Gln Ala
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<210> 24
<211> 35
<212> PRT

<213> Staphylococcus aureus

<400> 24

Leu Pro Lys Thr Gly Glu Thr Thr Ser Ser Gln Ser Trp Trp Gly Leu
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Tyr Ala Leu Leu Gly Met Leu Ala Leu Phe Ile Pro Lys Phe Arg Lys
20 25 30

Glu Ser Lys
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<210> 25
<211> 38
<212> PRT
<213> Staphylococcus aureus

<400> 25

Leu Pro Lys Thr Gly Leu Thr Ser Val Asp Asn Phe Ile Ser Thr Val
1 5 10 15

Ala Phe Ala Thr Leu Ala Leu Leu Gly Ser Leu Ser Leu Leu Leu Phe
20 25 30

Lys Arg Lys Glu Ser Lys
35

<210> 26
<211> 36
<212> PRT
<213> Staphylococcus aureus

<400> 26

Leu Pro Gln Thr Gly Glu Glu Ser Asn Lys Asp Met Thr Leu Pro Leu
1 5 10 15

Met Ala Leu Ile Ala Leu Ser Ser Ile Val Ala Phe Val Leu Pro Arg
20 25 30

Lys Arg Lys Asn
35

<210> 27
<211> 34

<212> PRT
<213> Staphylococcus aureus

<400> 27

Leu Pro Lys Thr Gly Thr Asn Gln Ser Ser Ser Pro Glu Ala Met Phe
1 5 10 15

Val Leu Leu Ala Gly Ile Gly Leu Ile Ala Thr Val Arg Arg Arg Lys
20 25 30

Ala Ser

<210> 28
<211> 33
<212> PRT
<213> Staphylococcus aureus

<400> 28

Leu Pro Lys Thr Gly Leu Glu Ser Thr Gln Lys Gly Leu Ile Phe Ser
1 5 10 15

Ser Ile Ile Gly Ile Ala Gly Leu Met Leu Leu Ala Arg Arg Arg Lys
20 25 30

Asn

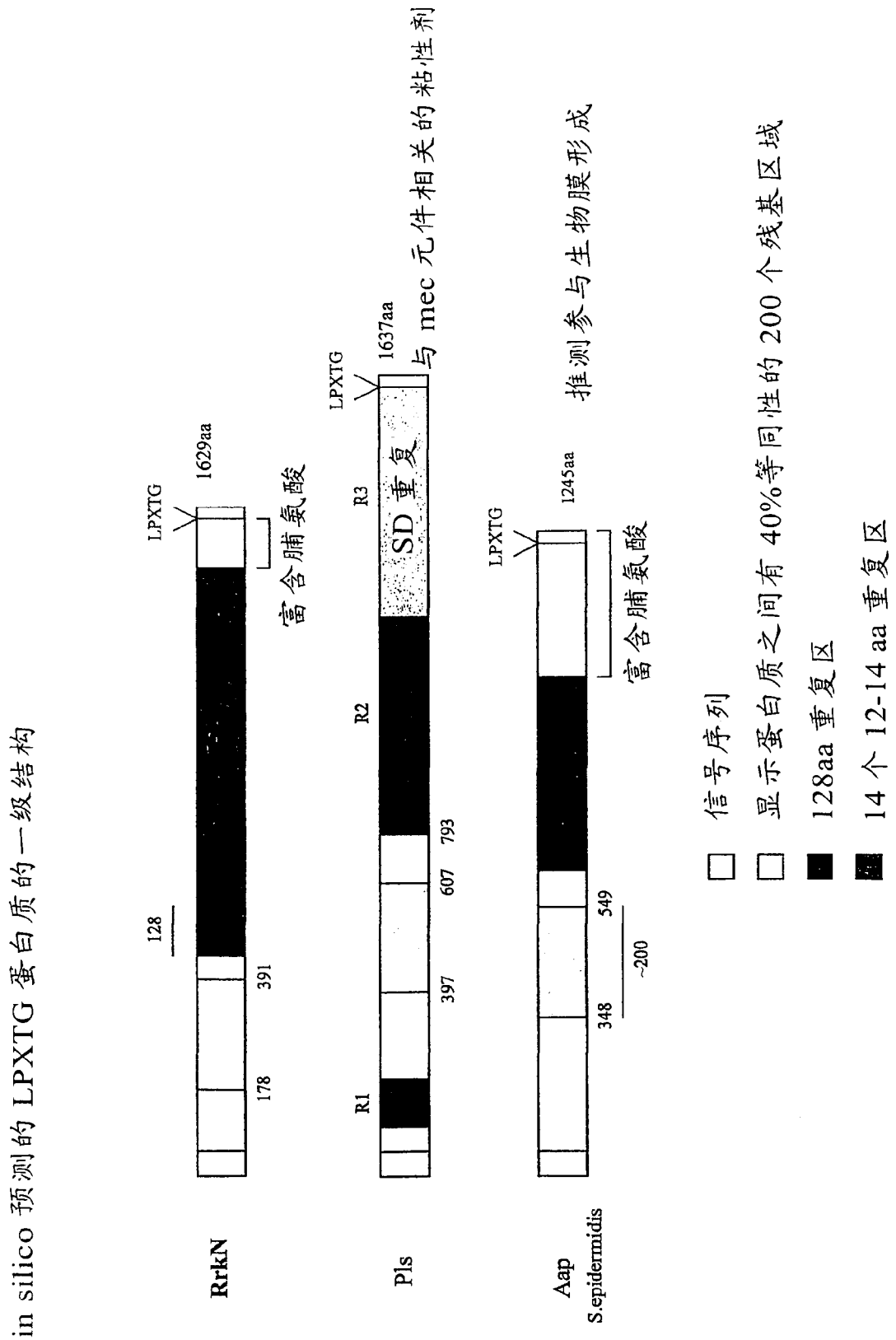
<210> 29
<211> 39
<212> PRT
<213> Staphylococcus aureus

<400> 29

Leu Pro Lys Ala Gly Glu Thr Ile Lys Glu His Trp Leu Pro Ile Ser
1 5 10 15

Val Ile Val Gly Ala Met Gly Val Leu Met Ile Trp Leu Ser Arg Arg
20 25 30

Asn Lys Leu Lys Asn Lys Ala
35


in silico 预测的 LPXTG 蛋白质的一级结构
LPXTG
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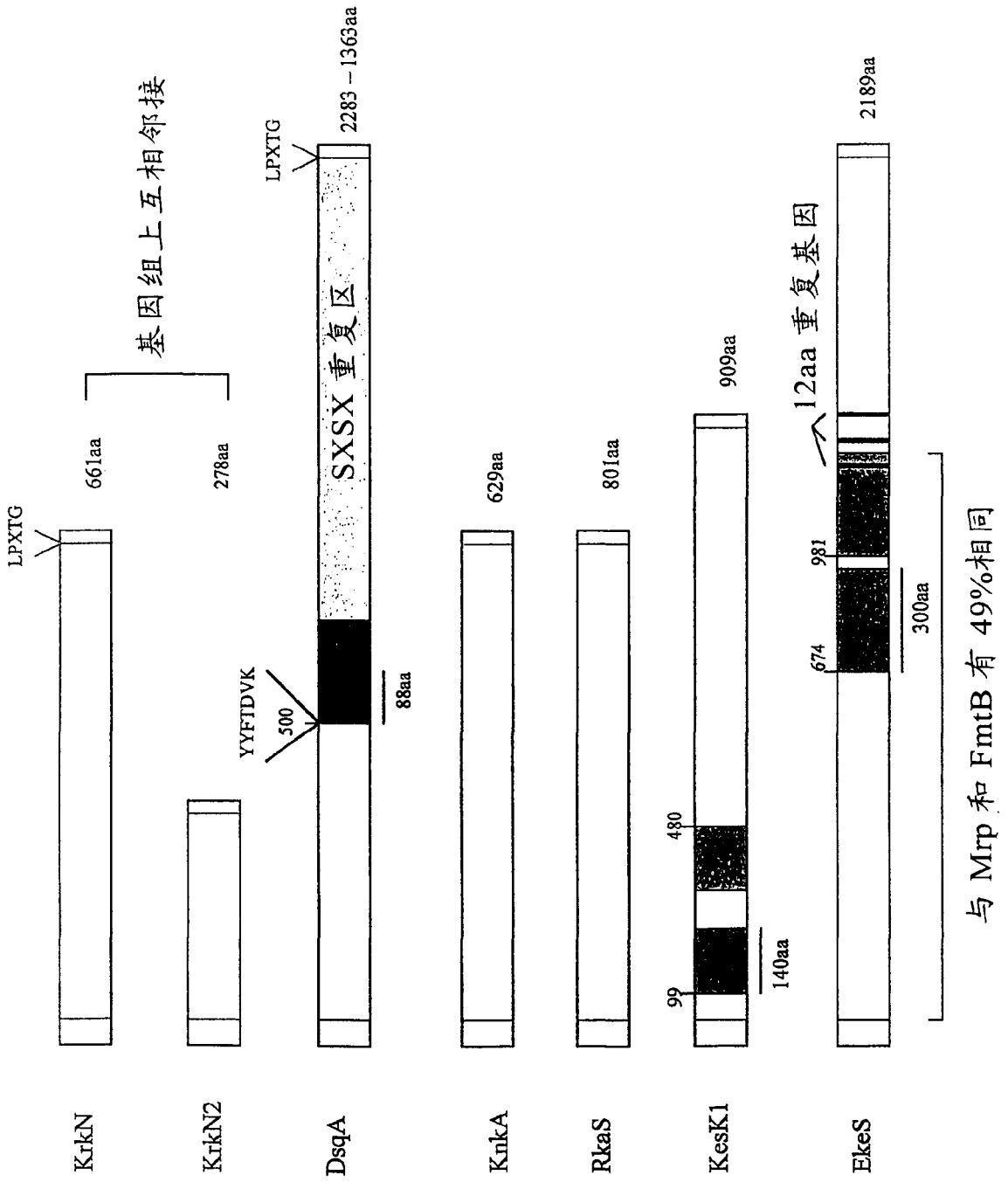
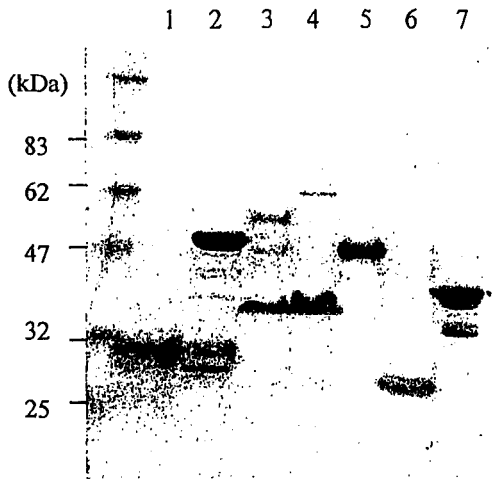
128
178
391
富含脯氨酸
RrkN
LPXTG
1637aa
R3
SD 重复
与 mec 元件相关的粘性剂
R2
R1
397
607
793
Pls
LPXTG
1245aa
推测参与生物膜形成
549
348
~200
富含脯氨酸
Aap
S.epidermidis
信号序列
显示蛋白质之间有 40%等同性的 200 个残基区域
128aa 重复区
14 个 12-14 aa 重复区

图 1



与 Mrp 和 FmtB 有 49%相同

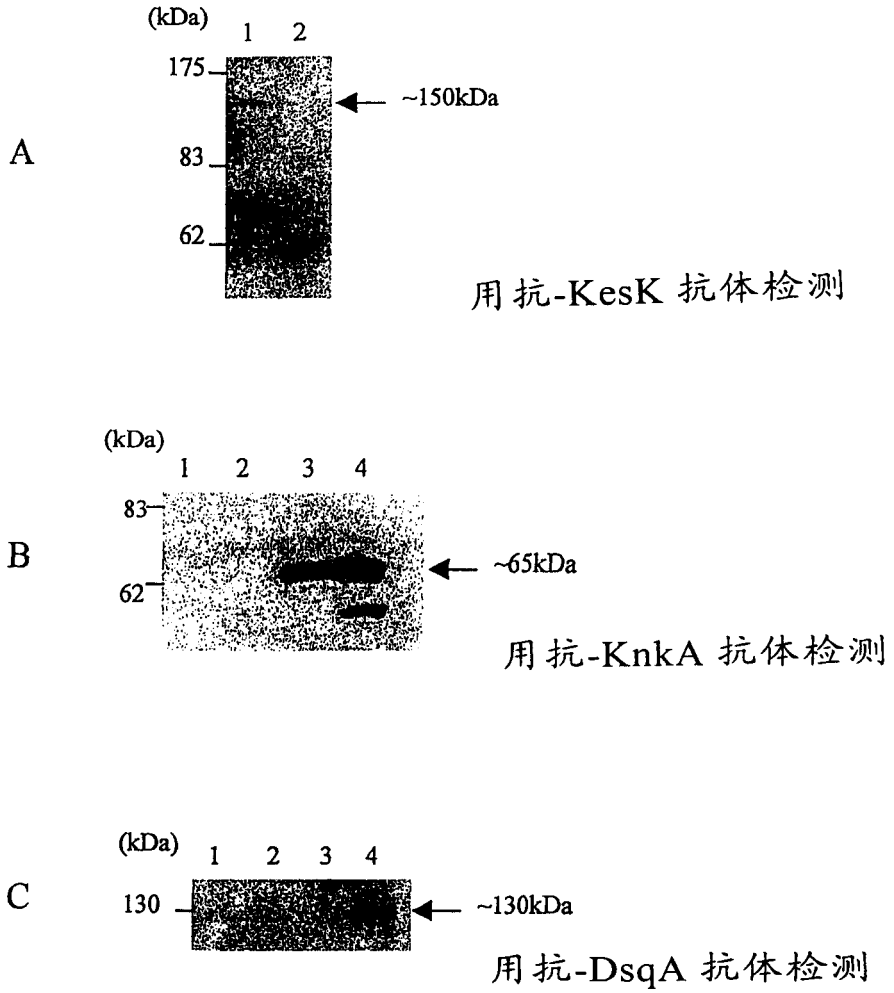
图 1(接上页)



	残基	预测的 MW	表观 MW
• **RrkN 1**	60 - 215	19	29
• **RrkN 2**	60 - 437	45	48
• **DsqA 1**	54 - 279	27	38
• **DsqA 2**	54 - 533	58	62
• **KesK 1**	55 - 335	34	47
• **KnkA**	39 - 210	20	27
• **KesK 2**	329 - 591	31	40

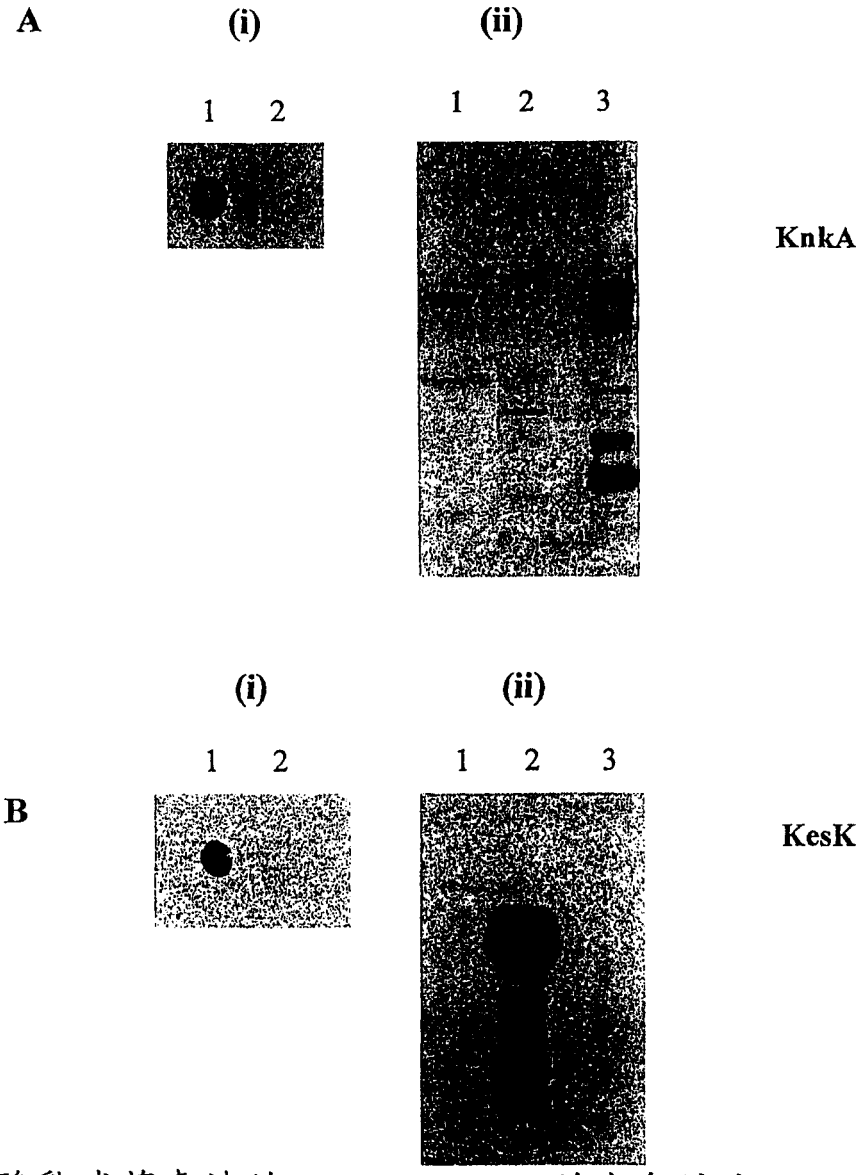
纯化的 N-末端 His-标记的融合蛋白的考马斯亮蓝染色凝胶

图 2



金黄色葡萄球菌细胞壁提取物的 Western 印迹。
将细菌细胞标准化为 $0D_{600}$ 为 50 个单位，并且通过将稳定的原生质体进行络葡萄球菌酶消化分离细胞壁。
A. 泳道 1，8325-4(早期指数期)；泳道 2，8325-4(静止期)。
B. 泳道 1 和 2，eMRSA-16；泳道 3 和 4，8325-4；泳道 1 和 3 代表早期指数期细胞和泳道 2 和 4 代表静止期细胞。
C. 泳道 1 和 2，MSSA；泳道 3 和 4，eMRSA-16；泳道 1 和 3 代表早期指数期细胞和泳道 2 和 4 代表静止期细胞。

图 3



乳酸乳球菌表达的 MSCRAMMs 的点印迹和 Western 免疫印迹分析。将全长 knkA 和 kesK 克隆到乳酸乳球菌表达质粒 pKS80 和电穿孔到感受态乳酸乳球菌 MG1363 细胞。分别利用抗-knkA(A)和抗-kesK(B)抗体进行点印迹分析检测阳性 knkA 和 kesK 表达克隆。将携带 pKS80 的乳酸乳球菌用作为阴性对照。A.(i)泳道，乳酸乳球菌 pKS-knkA；泳道 2，乳酸乳球菌 pKS80。B.(ii)泳道 1，乳酸乳球菌 pKS-kesK；泳道 2，乳酸乳球菌 pKS80。将 Western 印迹分析用于检测 kesK 和 knkA 在金黄色葡萄球菌和乳酸乳球菌中的表达。A(ii) 泳道 1，来自金黄色葡萄球菌 8325-4 指数期的细胞壁提取物，泳道 2，来自携带 pKS80 的乳酸乳球菌的原生质体组分；泳道 3，来自携带 pKS-knkA.B.的乳酸乳球菌的原生质体组分。(ii) 泳道 1，来自指数期金黄色葡萄球菌菌珠 8325-4 的细胞壁提取物；泳道 2，来自携带 pKS- kesK 的乳酸乳球菌的细胞壁提取物；泳道 3，来自携带 pKS80 的乳酸乳球菌的细胞壁提取物。

图 4

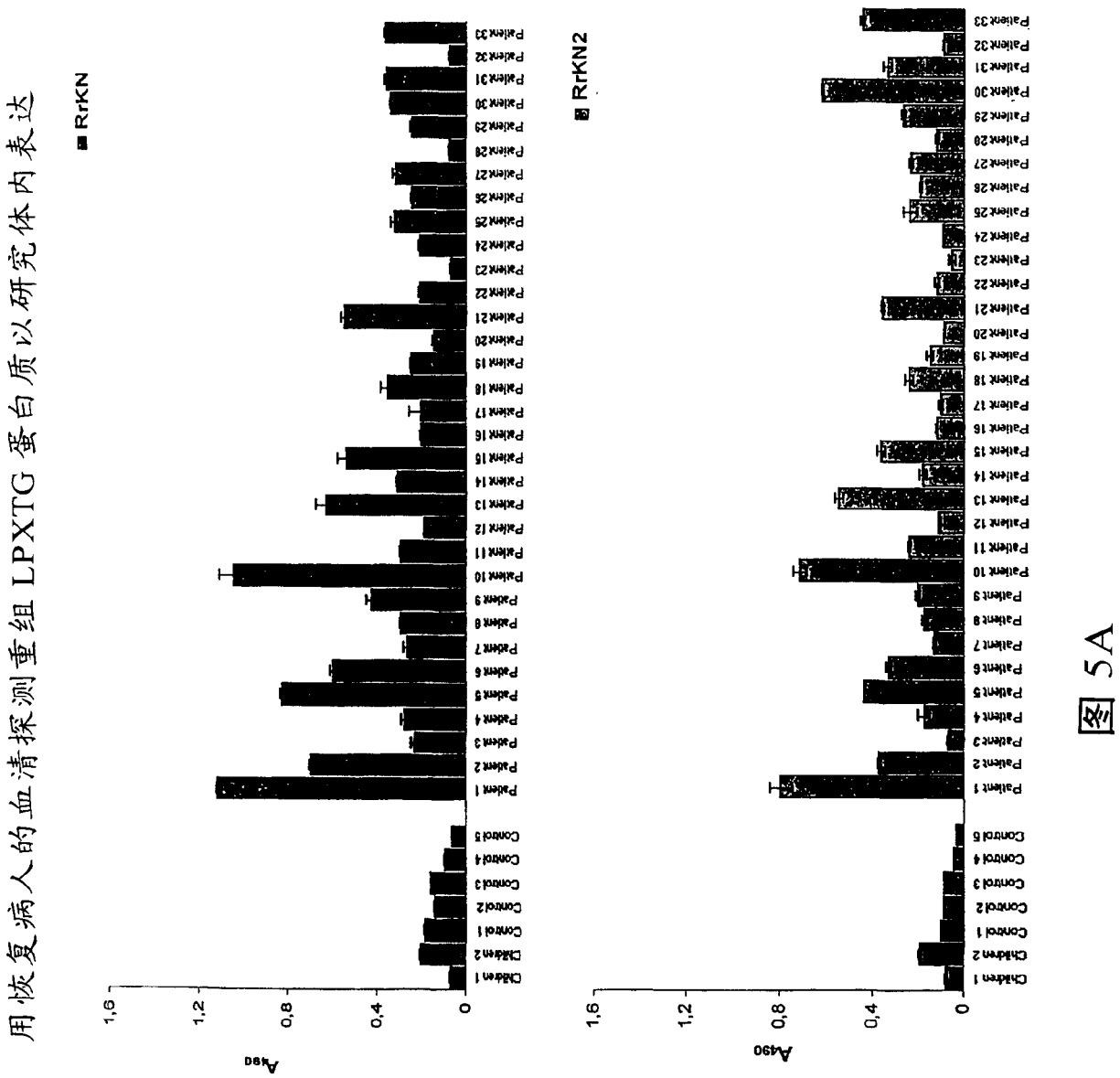
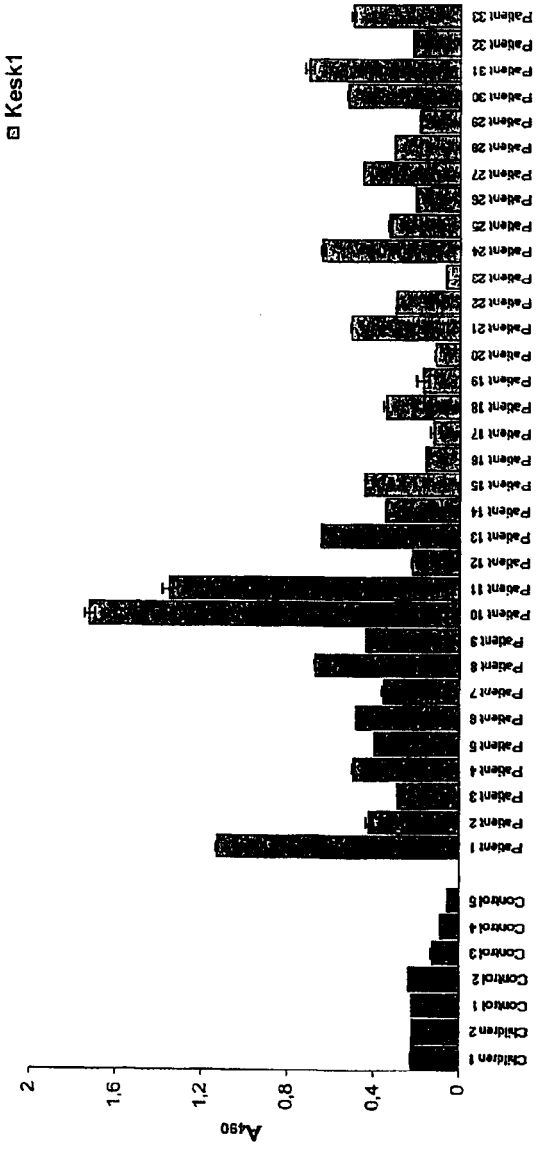
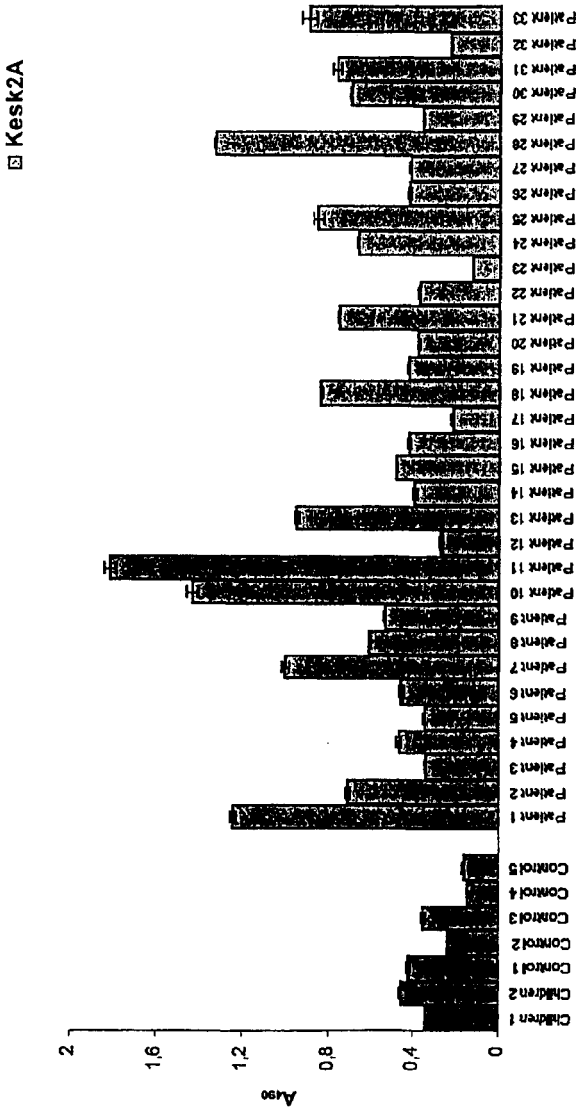

用恢复病人的血清探测重组 LPXTG 蛋白质以研究体内表达
RrKN
RrKN2
A490
1,6
1,2
0,8
0,4
0
Diabetes 1
Diabetes 2
Control 1
Control 2
Control 3
Control 4
Control 5
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 32
Patient 33

图 5A

图 5B


Kesk1
A450
2
1,6
1,2
0,8
0,4
0
Children 1
Children 2
Control 1
Control 2
Control 3
Control 4
Control 5
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 32
Patient 33


Kesk2A
A450
2
1,6
1,2
0,8
0,4
0
Children 1
Children 2
Control 1
Control 2
Control 3
Control 4
Control 5
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 32
Patient 33

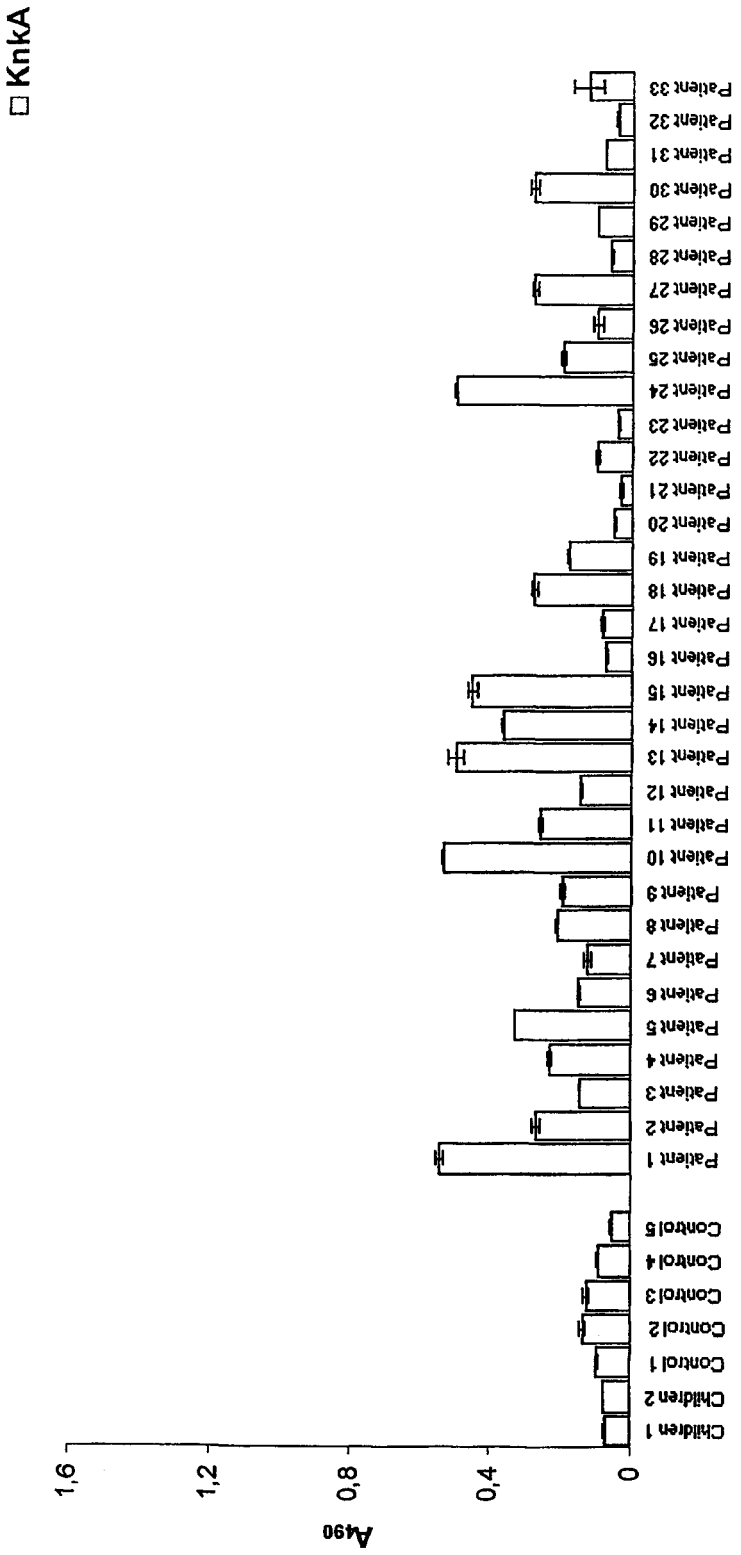

KnkA
A490
0
0,4
0,8
1,2
1,6
Children 1
Children 2
Control 1
Control 2
Control 3
Control 4
Control 5
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 32
Patient 33

图 5C

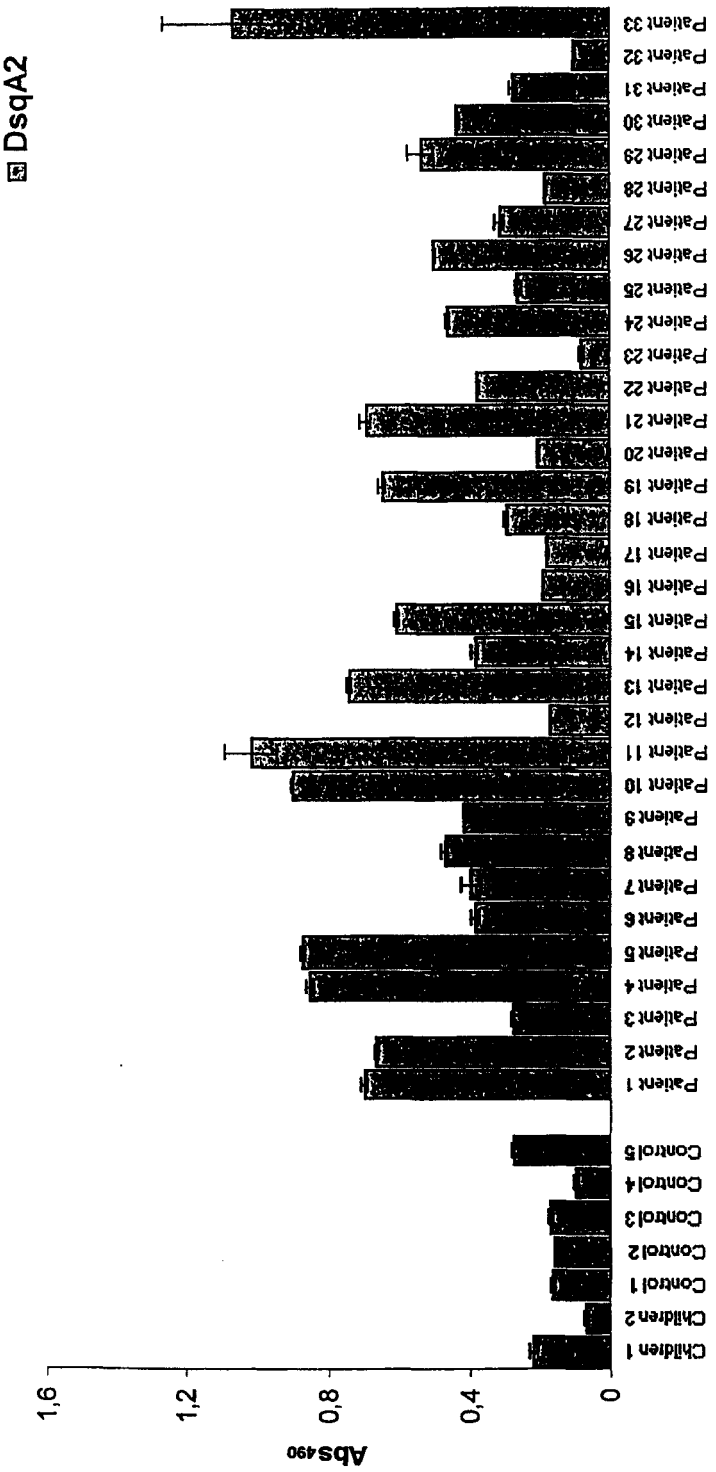
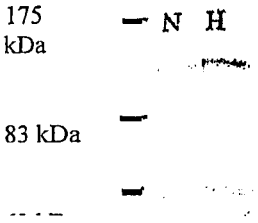
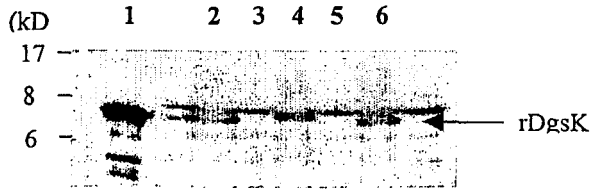

DsqA2
Abs490
0
0,4
0,8
1,2
1,6
Child en 1
Child en 2
Control 1
Control 2
Control 3
Control 4
Control 5
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Patient 8
Patient 9
Patient 10
Patient 11
Patient 12
Patient 13
Patient 14
Patient 15
Patient 16
Patient 17
Patient 18
Patient 19
Patient 20
Patient 21
Patient 22
Patient 23
Patient 24
Patient 25
Patient 26
Patient 27
Patient 28
Patient 29
Patient 30
Patient 31
Patient 32
Patient 33

图 5D



从金黄色葡萄球菌 Newman(N)和表皮葡萄球菌 HB(H)的细胞壁释放的蛋白质的 Western 免疫印迹分析。用免抗-金黄色葡萄球菌 SasA 区域 A 抗体和偶合到辣根过氧化酶的山羊抗-免探测



用大肠杆菌表达的 DgsK 与金黄色葡萄球菌 SasAA-区域抗体交叉反应。泳道 1，FPLC 纯化的 SasAA-区域对照。泳道 2，4 和 6，从大肠杆菌菌株 TOPP-3 的 p^{QE}-30 表达的 DgsKA-区(诱导)；泳道 3，5 和 7，TOPP-3 携带的具有 dgsk 插入物的 p^{QE}-30(未诱导)。

图 6

专利名称(译)	识别凝血酶阴性的葡萄球菌和金黄色葡萄球菌的表面蛋白的交叉反应性单克隆抗体和多克隆抗体		
公开(公告)号	CN1543569A	公开(公告)日	2004-11-03
申请号	CN02816001.0	申请日	2002-06-17
[标]申请(专利权)人(译)	英希比泰克斯公司 都柏林伊丽莎白女皇神学院		
申请(专利权)人(译)	英希比泰克斯公司 都柏林伊丽莎白女皇神学院		
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[标]发明人	蒂莫西J福斯特 菲奥那罗切 约瑟夫M帕蒂 杰夫T哈钦斯 皮特罗斯皮兹利 马克帕伦		
发明人	蒂莫西·J·福斯特 菲奥那·罗切 约瑟夫·M·帕蒂 杰夫·T·哈钦斯 皮特罗·斯皮兹利 马克·帕伦		
IPC分类号	G01N33/53 A61K39/00 A61K39/395 A61K39/40 A61P31/04 C07K14/31 C07K16/12 C12P21/08 G01N33/569 C12N5/06 C12N5/16 C07K16/00		
CPC分类号	C07K16/1271		
优先权	60/298098 2001-06-15 US		
其他公开文献	CN100359327C		
外部链接	Espacenet SIPO		

摘要(译)

提供了与凝血酶阳性的葡萄球菌细菌，例如溶血葡萄球菌发生交叉反应的多克隆和单克隆抗体，所述的抗体能够识别凝固酶阳性的和凝固酶阴性的葡萄球菌细菌的表面蛋白质。从基于金黄色葡萄球菌和凝固酶阴性的葡萄球菌之间共有的特性分离的表面蛋白质可以制备抗体，这些重组表面蛋白质可用于制备本发明的抗体。还提供了利用这些蛋白质和抗体用于治疗或抵抗各种各样的葡萄球菌的感染的疫苗和方法。