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(54)【発明の名称】抗原性ポリペプチド

(57)【要約】
本発明は、病原性微生物によって発現される抗原性ポリペプチドの同定のための方法；このポリペプチドを含むワクチン；このポリペプチドを製造するための組換え方法；およびこのポリペプチドに対する治療用抗体に関する。本発明の別の局面において、本発明は、単離された核酸分子によってコードされるポリペプチドであって、該核酸分子は、以下：（ｉ）配列番号１～１３に示されるＤＮＡ配列；（ｉｉ）上記（ｉ）において同定された配列番号１～１３に示される配列にハイブリダイズし、そして病原性生物体によって発現されるポリペプチドをコードするＤＮＡ配列；（ｉｉｉ）（ｉ）および（ｉｉ）において規定されるＤＮＡ配列に対して遺伝コードの結果として縮重するＤＮＡ配列、からなる群より選択されるＤＮＡ配列を含む、ワクチンとしての使用のためのポリペプチド、に関する。

【特許請求の範囲】
【請求項１】
単離された核酸分子によってコードされるポリペプチドであって、該核酸分子は、以下：
（ｉ）配列番号１～１３に示されるＤＮＡ配列；
（ｉｉ）上記（ｉ）において同定された配列番号１～１３に示される配列にハイブリダイズし、そして病原性生物体によって発現されるポリペプチドをコードするＤＮＡ配列；
（ｉｉｉ）（ｉ）および（ｉｉ）において規定されるＤＮＡ配列に対して遺伝コードの結果として縮重するＤＮＡ配列、
からなる群より選択されるＤＮＡ配列を含む、ワクチンとしての使用のためのポリペプチド。
【請求項２】
配列番号１４～１９からなる群より選択される、請求項１に記載のポリペプチド。
【請求項３】
請求項１または２に記載のポリペプチドを少なくとも１つ含む、ワクチン。
【請求項４】
請求項３に記載のワクチンであって、該ワクチンがさらにキャリアおよび／またはアジュバントを含む、ワクチン。
【請求項５】
病原性微生物に対して動物を免疫する方法であって、該方法は、請求項１もしくは請求項２に記載のポリペプチドの少なくとも１つ、もしくはその一部、または請求項３もしくは請求項４に記載のワクチン、を該動物に投与する工程、を包含する、方法。
【請求項６】
請求項５に記載の方法であって、前記動物がヒトである、方法。
【請求項７】
請求項５または請求項６に記載の方法であって、ここで、前記抗原性ポリペプチドまたはワクチンが、静脈内、筋肉内または皮下のいずれかへの直接注射によって送達される、方法。
【請求項８】
請求項５または請求項６に記載の方法であって、ここで、前記抗原性ポリペプチドまたはワクチンが経口投与される、方法。
【請求項９】
請求項５～８のいずれか１項に記載の方法であって、ここで、前記ワクチンが、細菌Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ｓｐｐ．属に対するものである、方法。
【請求項１０】
請求項９に記載の方法であって、ここで、前記ワクチンが、細菌種Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ａｕｒｅｕｓに対するものである、方法。
【請求項１１】
請求項９に記載の方法であって、ここで、前記ワクチンが、細菌種Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ｅｐｉｄｅｒｍｉｄｉｓに対するものである、方法。
【請求項１２】
抗原性ポリペプチドを同定するための方法であって、該方法は、以下：
（ｉ）病原性生物体の遺伝子または部分的な遺伝子配列をコードする核酸ライブラリーを提供する工程；
（ｉｉ）宿主細胞中に該ライブラリーを形質転換／トランスフェクトする工程；
（ｉｉｉ）該遺伝子／部分的な遺伝子配列によって発現されるポリペプチドと、該病原性生物体に感染されるかまたは感染された動物由来の自己抗血清とを接触させる工程；および
（ｉｖ）該自己抗血清に結合しているポリペプチドまたは部分的なポリペプチドをコードする核酸を精製する工程、
を包含する、方法。

【請求項１３】
請求項１２に記載の方法であって、ここで、前記ライブラリーが、病原性生物体のゲノムＤＮＡを含む、方法。
【請求項１４】
請求項１２または請求項１３に記載の方法であって、ここで、前記病原性生物体が細菌である、方法。
【請求項１５】
請求項１４に記載の方法であって、ここで、前記細菌性生物体が、以下：Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ａｕｒｅｕｓ；Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ｅｐｉｄｅｒｍｉｄｉｓ；Ｅｎｔｅｒｏｃｏｃｃｕｓ ｆａｅｃａｌｉｓ；Ｍｙｃｏｂａｃｔｅｒｉｕｍ ｔｕｂｅｒｃｕｌｓｉｓ；Ｓｔｒｅｐｔｏｃｏｃｃｕｓ ｇｒｏｕｐ Ｂ；Ｓｔｒｅｐｔｏｃｃｃｏｃｕｓ ｐｎｅｕｍｏｎｉａｅ；Ｈｅｌｉｃｏｂａｃｔｅｒ ｐｙｌｏｒｉ；Ｎｅｉｓｓｅｒｉａ ｇｏｎｏｒｒｈｅａ；Ｓｔｒｅｐｔｏｃｏｃｃｕｓ ｇｒｏｕｐ Ａ；Ｂｏｒｒｅｌｉａ ｂｕｒｇｄｏｒｆｅｒｉ；Ｃｏｃｃｉｄｉｏｄｅｓ ｉｍｍｉｔｉｓ；Ｈｉｓｔｏｐｌａｓｍａ ｓａｐｓｕｌａｔｕｍ；Ｎｅｉｓｓｅｒｉａ ｍｅｎｉｎｇｉｔｉｄｉｓ ｔｙｐｅ Ｂ；Ｓｈｉｇｅｌｌａ ｆｌｅｘｎｅｒｉ；Ｅｓｃｈｅｒｉｃｈｉａ ｃｏｌｉ；Ｈａｅｍｏｐｈｉｌｕｓ ｉｎｆｌｕｅｎｚａｅ、
から選択される、方法。
【請求項１６】
請求項１５に記載の方法であって、ここで、前記病原性生物体が、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ａｕｒｅｕｓである、方法。
【請求項１７】
請求項１５に記載の方法であって、前記病原性生物体が、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ｅｐｉｄｅｒｍｉｄｉｓである、方法。
【請求項１８】
請求項１２～１７のいずれか１項に記載の方法であって、ここで、前記核酸ライブラリーが、λライブラリーである、方法。
【請求項１９】
請求項１０～１８のいずれか１項に記載の方法によって同定されるポリペプチド。
【請求項２０】
請求項１または請求項２に記載のポリペプチドの選択的部分と少なくとも結合する、抗体、または少なくともその有効な部分。
【請求項２１】
モノクローナル抗体である、請求項２０に記載の抗体。
【請求項２２】
請求項２０または請求項２１に記載の抗体であって、ここで、前記有効な部分がＦＡｂフラグメントを含む、抗体。
【請求項２３】
キメラ抗体である、請求項２０～２２のいずれか１項に記載の抗体。
【請求項２４】
ヒト化抗体である、請求項２０～２２のいずれか１項に記載の抗体。
【請求項２５】
請求項２０～２４のいずれか１項に記載の抗体であって、該抗体に、マーカー、標識、またはタグが提供される、抗体。
【請求項２６】
請求項２５に記載の抗体であって、ここで、該抗体に、放射活性標識、蛍光標識；エピトープタグからなる群より選択されるマーカーが提供される、抗体。
【請求項２７】
融合ポリペプチドとして産生される、請求項２３～２６のいずれか１項に記載の抗体。
【請求項２８】

請求項２３～２７のいずれか１項に記載の抗体の発現のために適合する、ベクター。
【請求項２９】
請求項２８に記載のベクターを用いて形質転換またはトランスフェクトした細胞。
【請求項３０】
請求項２３～２７のいずれか１項に記載の抗体の産生のための方法であって、該方法は、以下：
（ｉ）請求項２８に記載のベクターを用いて形質転換またはトランスフェクトした細胞を提供し、該細胞に細胞培養条件を提供する工程；
（ｉｉ）該細胞、またはその増殖環境から、該抗体を精製する工程、
を包含する、方法。
【請求項３１】
請求項３０に記載の抗体を産生するハイブリドーマ細胞株。
【請求項３２】
Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ａｕｒｅｕｓ関連敗血症、食中毒または皮膚障害の処置のための医薬品の製造のための、請求項２０～２７のいずれか１項に記載の抗体の使用。
【請求項３３】
Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ｅｐｉｄｅｒｍｉｄｉｓ関連敗血症、腹膜炎または心内膜炎の処置のための医薬品の製造のための、請求項２０～２７のいずれか１項に記載の抗体の使用。
【発明の詳細な説明】
【０００１】
本発明は、病原性微生物によって発現される抗原性ポリペプチドの同定のための方法；このポリペプチドを含むワクチン；このポリペプチドを製造するための組換え方法；およびこのポリペプチドを指向する治療用抗体、に関する。
【０００２】
微生物生物体は、世界中の何百万もの人々を冒す多数の致命的な疾患または消耗性疾患を引き起こす。微生物生物体を制御する現在の方法は、抗微生物剤（抗生物質）および殺菌剤の使用を含む。これらは、これらの薬剤への曝露が抗微生物剤の効果を無効にし得る耐性菌の発生を生じる顕著な選択圧をかけるため、問題となることが示されてきた。例えば、近年、微生物生物体はトリクロサン（家庭および産業環境において用いられる多数の殺菌剤に添加される薬剤）に対して耐性となってきたことが発見されてきた。
【０００３】
まず間違いなくより重大な問題は、多数の顕著な病原性微生物の抗生物質耐性株の進化である。
【０００４】
限定する目的ではなく例示として、５０００万人に至るまでの世界中の人々が薬物耐性結核（ＴＢ）に感染していると推定されている（世界保健機構、１９９８年提供の図）。従来、ＴＢを処置するための抗生物質の使用は、比較的高頻度の耐性を助長した単一薬物（例えば、エチオナミド）の投与に頼っていた。このため、現在、薬物の組合せを用いて、結核を処置している。しかし、結核を処置するために用いられる薬物の少なくとも１つに耐性である株によって引き起こされる場合の死亡率は、処置される場合でさえ、なお５０％に達する。Ｍｙｃｏｂａｃｔｅｒｉｕｍ　ｔｕｂｅｒｃｕｌｏｓｉｓ（ＴＢの原因因子）は、低増殖性細菌であり、かつ死滅させるのに長時間かかる。従って、複合薬物を有効にするために、ＴＢを有する人は少なくとも６ヶ月間、毎日この複合薬物を服用しなければならない。従って、患者は、毎日２個以上の丸剤を頻繁に服用しなければならず、そしてこれは、比較的長期間の処置にわたる厳しく管理された投薬を必要とする。多数の患者は、断続的にのみ投薬を受け、それ故、Ｍ．ｔｕｂｅｒｃｕｌｏｓｉｓ感染を完全に根絶するための、治療の全クールを完了しない。さらに、ＴＢは、ＨＩＶ感染に強く関連し、それ故、ＴＢの馴化は、免疫抑制に強く関連する。
【０００５】

ＴＢに対するワクチン接種は、長年利用可能であった。カルメット－ゲラン杆菌（ＢＣＧ）ワクチン接種は、ＴＢに潜在的に罹患し得る多数の人々をワクチン接種するための安全かつ安価な手段であるので、長期間、世界中で広く用いられてきた。ＢＣＧは、Ｍｙｃｏｂａｃｔｅｒｉｕｍ　ｂｏｖｉｓの生きた弱毒化株由来である。しかし、ＴＢの感染形態に対するワクチン接種の影響は最小であり、それ故、ＢＣＧは、この疾患の全般的制御をほとんど寄与しない。

【０００６】

抗生物質に対する耐性を発生した病原性生物体のさらなる例は、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ａｕｒｅｕｓである。Ｓ．ａｕｒｅｕｓは、正常に健常な人々の約２０～４０％において、通常の生育地が鼻の上皮内壁である細菌であり、そして悪影響を引き起こすことなくたいてい人々の皮膚においても通常見出されている。しかし、特定の環境下で、特に皮膚が損傷を受ける場合、この微生物は、感染を引き起こし得る。これは、患者が外科的処置を受け得、そして／または免疫抑制性薬物を服用し得る病院において特に問題である。これらの患者は、彼らが受けている処置に起因して、Ｓ．ａｕｒｅｕｓに感染に対して非常により無防備である。Ｓ．ａｕｒｅｕｓの耐性株は、近年発生してきた。メチシリン耐性株は、流行しており、そしてこれらの耐性株の多くはまた、いくつかの他の抗生物質に耐性である。現在、Ｓ．ａｕｒｅｕｓに対する有効なワクチン接種手段は存在していない。米国において、Ｓ．ａｕｒｅｕｓ感染は、毎年２００万人の院内感染のうちの１３％の原因となっている。これは、２６０，０００人の人々がＳ．ａｕｒｅｕｓ感染を示し、このうちの６０～８０，０００人が死亡する。

【０００７】

従って、Ｓ．ａｕｒｅｕｓは、敗血症、心内膜炎、関節炎および中毒性ショックを含む、広範囲な生命を脅かす疾患を引き起こし得る主要なヒト病原体である。この可能性は、生物体の変動性、およびビルレンスに関連した成分のその保有量によって決定される。病原性は、多因子性であり、そしてどの成分も特定の感染の原因であることを示さない（Ｐｒｏｊａｎ，Ｓ．Ｊ．＆　Ｎｏｖｉｃｋ，Ｒ．Ｐ．（１９９７）ｉｎ　Ｔｈｅ　Ｓｔａｐｈｙｌｏｃｏｃｃｉ　ｉｎ　Ｈｕｍａｎ　Ｄｉｓｅａｓｅ（Ｃｒｏｓｓｌｅｙ，Ｋ．Ｂ．＆　Ａｒｃｈｅｒ，Ｇ．Ｌ．，ｅｄｓ．）５５～８１頁を参照のこと）。

【０００８】

感染の発症時、そしてそれが進行するにつれて、この生物体の必要性および環境は変化し、そしてこれは、Ｓ．ａｕｒｅｕｓが産生するビルレンス決定因子における対応する変更によって反映される。感染開始時、その病原体が宿主組織に接着することが重要であり、そしてこのようにして豊富なレパートリーの細胞表面関連接着タンパク質が作製される。これらの細胞表面接着タンパク質としては、コラーゲン結合タンパク質、フィブリノーゲン結合タンパク質およびフィブロネクチン結合タンパク質が挙げられる。この病原体はまた、食作用を低下させる因子または抗体を循環させることによって認識されるこれらの細胞の能力を妨害する因子の産生によって宿主の防御を回避する能力を有する。

【０００９】

しばしば、感染の病巣は、膿瘍として発現し、多数の生物体が増加する。Ｓ．ａｕｒｅｕｓは、クオラムセンシング（ｑｕｏｒｕｍ　ｓｅｎｓｉｎｇ）ペプチドの産生によってそれ自体の細胞密度をモニタリングする能力を有する。おそらくこれらの細胞の飢餓の開始によってもたらされる生理学的変化に関連する、このペプチドの蓄積は、ビルレンス決定因子の産生における付着分子から侵襲および組織穿通に関連する成分への転換を誘発する。これらとしては、広範な溶血素、プロテアーゼおよび他の分解酵素が挙げられる。

【００１０】

任意の感染のプロセスの間、Ｓ．ａｕｒｅｕｓによって作製されるビルレンス決定因子は、環境の刺激および生理学的刺激に応じて産生される。これらの刺激は、身体内のニッチに依存し、そして感染進行につれて変化する。インビボでの条件についてはほとんど知られておらず、そしていくつかの成分はこの環境下で単独で産生されるようである。従って、これらは潜在的なワクチン成分であり、これは、先行技術によって発見され得なかった

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【００１１】
最近の医学史において最も重要な開発の１つは、多種多様な病原性生物体由来の予防的防御を提供するワクチンの開発である。多数のワクチンは、個体に注射される不活化病原体または弱毒化病原体によって生成される。免疫された個体は、体液性応答（抗体）および細胞性応答（細胞溶解性Ｔ細胞、ＣＴＬ応答）の両方を引き起こすことによって応答する。例えば、肝炎のワクチンは、ウイルスを不活化する加熱、およびホルムアルデヒドのような架橋剤でこれを処理することによって作製される。ワクチンとして有用な弱毒化病原体の例は、生きた病原体を弱毒化することによって産生されるポリオワクチンによって示される。
【００１２】
しかし、特定の疾患に対するワクチン中の弱毒化生物体の使用は、弱毒化の条件および性質の病理学に関する知識の欠如に起因して問題となる。特定のウイルス剤について、これは、特にレトロウイルスにおけるウイルスが、エラー傾向のある複製サイクル（これは、このウイルスを含む遺伝子中に生存可能な変異を生じる）を有するので、特に問題である。これは、結果として既にワクチンとして用いられてきた抗原性決定因子の代替物を生じ得る。不活化病原体または弱毒化病原体の使用に代わるものとしては、この免疫系が特に感受性である病原体エピトープの同定である。これに関して、感染の間に病原性生物体によって産生される多数の病原性毒素は、特定の病原性生物体から個体を防御するワクチンの開発に特に有用である。
【００１３】
いわゆるサブユニットワクチンの開発（その中の免疫原が特定の病原性生物体によって発現されるタンパク質または複合体のフラグメントまたはサブユニットであるワクチン）は、重要な医薬研究の焦点となってきた。サブユニットワクチンの開発に有用な候補分子を同定する必要性は、少なからず明白である。なぜなら、病原性生物体の制御に対する従来の化学療法アプローチが、つい最近、抗生物質耐性の発生によって窮境に立たされてきたからである。多数の方法は、ワクチンとして用いられ得る潜在的な抗原性ポリペプチドを同定するために開発されてきた。１つのこのような方法が、本明細書中に開示される。
【００１４】
長年の間、腫瘍細胞が多数の腫瘍細胞特異的抗原（この抗原のうちのいくつかは、腫瘍細胞表面に提示されている）を産生することは知られていた。免疫系は、これらの抗原を外来性として認識し、これによって、自己抗原に対する抗体（いわゆる、自己抗体または自己抗血清）の産生を生じる。
【００１５】
１つのこのような技術は、組換え体発現クローニングによる抗原の血清学的同定（略して、ＳＥＲＥＸ）である。
【００１６】
代表的に、この技術は、腫瘍組織からのＲＮＡの抽出に続く単離された総ＲＮＡからのｍＲＮＡの選択的富化に関連する。ｍＲＮＡは、ウイルスの逆転写酵素を用いてｃＤＮＡに逆転写される。従って、合成されたｃＤＮＡは、発現ベクターにサブクローニングされ、そして適切な細菌株に形質転換される。形質転換された細菌は、適切な栄養アガーにプレーティングされ、そして適切な増殖条件下で、サブクローニングされたｃＤＮＡは、細菌細胞中の発現ベクターから発現される。これらの細胞は、ファージベースの発現ベクター（例えば、λファージ）またはファージミドベースのベクターの使用によって自然に溶解され、これらの溶解サイクルを通して、これらの細胞は、細胞溶解を引き起こす。放出されたポリペプチドは、適切な膜支持体（すなわち、ニトロセルロース、ナイロン）に転写され、そして腫瘍組織が本来単離された患者由来の自己抗血清に曝露される。免疫スクリーニング方法論は、患者由来の選択された腫瘍組織において過剰に発現されるかまたは不適切に発現される遺伝子の同定を可能にする。
【００１７】

本発明者らは、感染の間に病原性生物体によって発現される抗原性ポリペプチドを同定するこの技術を開発してきた。感染中に産生される自己抗血清を用いて、ゲノムＤＮＡから作製した発現ライブラリーをスクリーニングして抗原を同定およびクローニングする。

【００１８】

その最も広い局面において、本発明は、病原微生物による感染の間に発現される抗原性ポリペプチドの同定に関する。

【００１９】

本発明の第１の局面に従って、抗原性ポリペプチドを同定する方法が提供され、この方法は、以下：

（ｉ）病原性生物体の遺伝子配列または部分的な遺伝子配列をコードする核酸ライブラリーを提供する工程；

（ｉｉ）宿主細胞中にこのライブラリーを形質転換／トランスフェクトする工程；

（ｉｉｉ）この形質転換／トランスフェクトした遺伝子配列または部分的な遺伝子配列の発現に役立つ条件を提供する工程；

（ｉｖ）この遺伝子配列／部分的な遺伝子配列によって発現されるポリペプチドと、この病原性生物体に感染されるかまたは感染された動物由来の自己抗血清とを接触させる工程；および

（ｖ）この自己抗血清に結合しているポリペプチドまたは部分的なポリペプチドをコードする核酸を精製する工程、を包含する。

【００２０】

本発明の好ましい方法において、このライブラリーは、病原性生物体のゲノムＤＮＡを含む。

【００２１】

理想的には、この病原性生物体は、細菌である。

【００２２】

より好ましくは、なおこの細菌性生物体は、以下から選択される：Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ａｕｒｅｕｓ；Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ｅｐｉｄｅｒｍｉｄｉｓ；Ｅｎｔｅｒｏｃｏｃｃｕｓ ｆａｅｃａｌｉｓ；Ｍｙｃｏｂａｃｔｅｒｉｕｍ ｔｕｂｅｒｃｕｌｓｉｓ；Ｓｔｒｅｐｔｏｃｏｃｃｕｓ ｇｒｏｕｐ Ｂ；Ｓｔｒｅｐｔｏｃｃｏｃｕｓ ｐｎｅｕｍｏｎｉａｅ；Ｈｅｌｉｃｏｂａｃｔｅｒ ｐｙｌｏｒｉ；Ｎｅｉｓｓｅｒｉａ ｇｏｎｏｒｒｈｅａ；Ｓｔｒｅｐｔｏｃｏｃｃｕｓ ｇｒｏｕｐ Ａ；Ｂｏｒｒｅｌｉａ ｂｕｒｇｄｏｒｆｅｒｉ；Ｃｏｃｃｉｄｉｏｄｅｓ ｉｍｍｉｔｉｓ；Ｈｉｓｔｏｐｌａｓｍａ ｓａｐｓｕｌａｔｕｍ；Ｎｅｉｓｓｅｒｉａ ｍｅｎｉｎｇｉｔｉｄｉｓ ｔｙｐｅ Ｂ；Ｓｈｉｇｅｌｌａ ｆｌｅｘｎｅｒｉ；Ｅｓｃｈｅｒｉｃｈｉａ ｃｏｌｉ；Ｈａｅｍｏｐｈｉｌｕｓ ｉｎｆｌｕｅｎｚａｅ。

【００２３】

好ましくは、なおこの病原性生物体は、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ｓｐｐ．属である。理想的には、この生物体は、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ ａｕｒｅｕｓまたはＳｔａｐｈｙｌｏｃｏｃｃｕｓ ｅｐｉｄｅｒｍｉｄｉｓである

本発明のさらに好ましい実施形態において、この核酸ライブラリーは、λライブラリーであり、理想的にはλ発現ライブラリーである。

【００２４】

本発明の第２の局面に従って、以下から選択されるＤＮＡ配列を含む核酸分子が提供される：

（ｉ）配列番号１～１３に示されるＤＮＡ配列；

（ｉｉ）病原性生物体によって発現されるポリペプチドをコードする上記（ｉ）において同定される配列番号１～１３に示される配列にハイブリダイズするＤＮＡ配列；および

（ｉｉｉ）（ｉ）および（ｉｉ）において規定されるＤＮＡ配列に対して遺伝コードの結果として縮重するＤＮＡ配列。

【００２５】

本発明のなおまださらに好ましい実施形態において、この核酸分子は、ゲノムＤＮＡである。

【００２６】

本発明の好ましい実施形態において、ストリンジェントなハイブリダイゼーション条件下で配列番号１～１３に示される配列にアニーリングする単離された核酸分子が提供される。

【００２７】

ストリンジェントなハイブリダイゼーション／洗浄条件は、当該分野において周知である。例えば、核酸は、６０℃にて０．１×ＳＳＣ、０．１％　ＳＤＳ中で洗浄後、安定にハイブリダイズする。核酸の配列が知られている場合、最適なハイブリダイゼーション条件は、算出され得ることが当該分野において周知である。例えば、ハイブリダイゼーション条件は、ハイブリダイゼーションに共される核酸のＧＣ含有量によって決定され得る。Ｓａｍｂｒｏｏｋら（１９８９）Ｍｏｌｅｃｕｌａｒ　Ｃｌｏｎｉｎｇ；Ａ　Ｌａｂｏｒａｔｏｒｙ　Ａｐｐｒｏａｃｈを御参照のこと。特定の相同性のある核酸分子間でハイブリダイゼーションを達成するのに必要とされるストリンジェンシー条件を算出するための一般式は、以下：

T_m＝８１．５℃＋１６．６Ｌｏｇ［Na^+］＋０．４１［Ｇ＋Ｃ（％）］－０．６３（ホルムアミド（％））

である。

【００２８】

本発明の第３の局面に従って、本発明に従う方法によって同定される少なくとも１つのポリペプチドが提供される。

【００２９】

本発明の好ましい実施形態において、このポリペプチドは、本発明の先の任意の局面または実施形態に従う生物体の感染性病原性に関連する。

【００３０】

さらになお好ましくは、このポリペプチドは、配列番号１４～１９の少なくとも１つ、または配列番号１４～１９の一部である。

【００３１】

本発明の第４の局面に従って、核酸分子がこの核酸分子によってコードされるポリペプチドの組換え発現を促進するよう適合するベクターの一部であることを特徴とする核酸分子が提供される。

【００３２】

本発明の好ましい実施形態において、このベクターは原核生物の遺伝子発現のために適合する発現ベクターである。あるいは、この発現ベクターは、真核生物の遺伝子発現のために適合される。

【００３３】

代表的には、この適合は、限定する目的ではなく例示として、細胞特異的発現を媒介する転写制御配列（プロモーター配列）の供給を含む。これらのプロモーター配列は、細胞特異的、誘導性または構成的であり得る。

【００３４】

プロモーターは、当該分野で認識されている用語であり、明瞭さのために、限定する目的ではなく例示としてのみ提供される以下の特徴を含む。エンハンサーエレメントは、遺伝子の転写開始部位に対して５’方向にしばしば見出されるシス作用性核酸配列である（エンハンサーはまた、遺伝子配列に対して３’方向に見出され得るかまたはイントロン配列に位置され得、従って独立した位置である）。エンハンサーは、エンハンサーが連結される遺伝子の転写速度を増加させるよう機能する。エンハンサー活性は、エンハンサーエレメントに特異的に結合することが示されてきたトランス作用性転写因子（ポリペプチド）に応答性である。転写因子の結合／活性（Ｄａｖｉｄ　Ｓ　Ｌａｔｃｈｍａｎによる、Ｅｕｋａｒｙｏｔｉｃ　Ｔｒａｎｓｃｒｉｐｔｉｏｎ　Ｆａｃｔｏｒｓ，Ａｃａｄｅｍｉｃ

Ｐｒｅｓｓ Ｌｔｄ，Ｓａｎ Ｄｉｅｇｏを御参照のこと）は、多数の環境の信号（ｅｎｖｉｒｏｎｍｅｎｔａｌ ｃｕｅ）に応答性であり、これらの信号は、限定する目的ではなく例示として、中間代謝産物（例えば、グルコース、脂質）、環境のエフェクター（例えば、光、熱）を含む。

【００３５】

プロモーターエレメントはまた、いわゆるＴＡＴＡボックスおよび転写開始の部位を選択するよう機能するＲＮＡポリメラーゼ開始選択（ＲＩＳ）配列を含む。これらの配列はまた、とりわけＲＮＡポリメラーゼによる転写開始選択を促進させるよう機能するポリペプチドと結合する。

【００３６】

適合はまた、この選択マーカーおよび自己複製配列の供給を含み、これらは両方とも真核生物細胞または原核生物宿主のいずれかにおけるこのベクターの維持を促進する。自発的に維持されるベクターは、エピソームのベクターと呼ばれる。

【００３７】

ベクターにコードされる遺伝子（ｖｅｃｔｏｒ ｅｎｃｏｄｅｄ ｇｅｎｅ）の発現を促進する適合は、転写終結配列／ポリアデニル化配列の提供を含む。これはまた、二シストロン性発現カセットまたは多重シストロン性発現カセットに配置されるベクターにコードされる遺伝子の発現を最大にするよう機能するリボソーム内部侵入領域（ＩＲＥＳ）の提供を含む。

【００３８】

これらの適合は、当該分野において周知である。一般的に、発現ベクター構築および組換えＤＮＡ技術に関する顕著な量の刊行された文献が存在する。Ｓａｍｂｒｏｏｋら（１９８９）Ｍｏｌｅｃｕｌａｒ Ｃｌｏｎｉｎｇ：Ａ Ｌａｂｏｒａｔｏｒｙ Ｍａｎｕａｌ，Ｃｏｌｄ Ｓｐｒｉｎｇ Ｈａｒｂｏｕｒ Ｌａｂｏｒａｔｏｒｙ，Ｃｏｌｄ Ｓｐｒｉｎｇ Ｈａｒｂｏｕｒ，ＮＹおよびこの文献中の参考文献；Ｍａｒｓｔｏｎ，Ｆ（１９８７）ＤＮＡ Ｃｌｏｎｉｎｇ Ｔｅｃｈｎｉｑｕｅｓ：Ａ Ｐｒａｃｔｉｃａｌ Ａｐｐｒｏａｃｈ 第ＩＩＩ巻 ＩＲＬ Ｐｒｅｓｓ，Ｏｘｆｏｒｄ ＵＫ；ＤＮＡ Ｃｌｏｎｉｎｇ：Ｆ Ｍ Ａｕｓｕｂｅｌら，Ｃｕｒｒｅｎｔ Ｐｒｏｔｏｃｏｌｓ ｉｎ Ｍｏｌｅｃｕｌａｒ Ｂｉｏｌｏｇｙ，Ｊｏｈｎ Ｗｉｌｅｙ ＆ Ｓｏｎｓ，Ｉｎｃ.（１９９４）を御参照のこと。

【００３９】

本発明のなおさらなる局面に従って、本発明の先の任意の局面または実施形態に従うポリペプチドの産生のための方法が提供され、この方法は、以下：

（ｉ）本発明に従うベクターで形質転換／トランスフェクトした細胞を提供する工程；

（ｉｉ）このポリペプチドの製造に役立つ条件下でこの細胞を増殖させる工程；および

（ｉｉｉ）この細胞、またはこの細胞の増殖環境由来のこのポリペプチドを精製する工程、を包含する。

【００４０】

本発明の好ましい方法において、このベクターは、このポリペプチドの精製を促進する分泌シグナルをコードし、それ故、この組換えポリペプチドは、このポリペプチドの精製を促進する分泌シグナルと共に提供される。

【００４１】

本発明の第５の局面に従って、本発明に従うベクターで形質転換またはトランスフェクトした細胞または細胞株が提供される。

【００４２】

本発明の好ましい実施形態において、この細胞は、原核生物細胞である。あるいは、この細胞は、以下から選択される真核生物細胞である：真菌；昆虫；両生類；哺乳動物；植物。

【００４３】

本発明のなおさらなる局面に従って、本発明に従う少なくとも１つのポリペプチドを含む

ワクチンが提供される。
【００４４】
理想的には、このワクチンは、キャリアおよび／またはアジュバントをさらに含む。
【００４５】
用語アジュバントおよび用語キャリアは、以下の様式に解釈される。いくつかのポリペプチド抗原またはペプチド抗原は、Ｂ細胞エピトープを含むがＴ細胞エピトープは含まない。免疫応答は、このポリペプチド／ペプチド中にＴ細胞エピトープを含ませることによってか、または複数のＴ細胞エピトープを含む免疫原性キャリアタンパク質（例えば、キーホールリンペットヘモシアニンもしくは破傷風トキソイド）へのこのポリペプチド／ペプチドの結合体化によって非常に増強され得る。この結合体は、抗原提示細胞によって取り込まれ、プロセスされ、そしてヒト白血球抗原（ＨＬＡの）クラスＩＩ分子によって提示される。これは、キャリアに由来するエピトープに対するＴ細胞の特異性によって、もとの抗原性ポリペプチド／ペプチドに特異的なＢ細胞に対してＴ細胞補助（Ｔ　ｃｅｌｌ　ｈｅｌｐ）が与えられることを可能にする。これは、抗体の産生、分泌およびアイソタイプスイッチの増加を引き起こし得る。
【００４６】
アジュバントは、免疫細胞の活性を調節することによって抗原に対する特異的な免疫応答を増強する物質または手段である。アジュバントの例としては、単なる例として、同時刺激分子に対するアゴニスト性抗体、フロイントアジュバント、ムラミルジペプチド、リポソームが挙げられる。従って、アジュバントは、免疫調節物質である。キャリアは、第２の分子に結合した場合、第２の分子に対する免疫応答を増強する免疫原性分子である。
【００４７】
本発明のなおさらなる局面において、病原性微生物に対して動物を免疫する方法が提供され、この方法は、本発明に従う少なくとも１つのポリペプチドもしくはその一部または本発明に従うワクチンをこの動物に投与する工程を包含する。
【００４８】
本発明の好ましい方法において、この動物はヒトである。
【００４９】
好ましくは、このワクチンまたは抗原性ポリペプチドは、静脈内、筋肉内、皮下のいずれかの直接注射によって送達され得る。さらになお、このワクチンまたは抗原性ポリペプチドは、経口摂取され得る。
【００５０】
好ましくは、このワクチンは、細菌種Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ａｕｒｅｕｓに対するものである。
【００５１】
このワクチンはまた、細菌種Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ｅｐｉｄｅｒｍｉｄｉｓに対するものであり得る。
【００５２】
ワクチンまたは抗原性ポリペプチドが、ヒト以外の動物（限定する目的ではなく例示として、家庭用ペット、家畜、ウマ）において予防する状況または緩和する状況において有効であることもまた、明白である。
【００５３】
本発明のさらなる局面に従って、本発明に従う少なくとも１つのポリペプチドに結合する抗体、または少なくとも有効に結合するその一部が提供される。
【００５４】
本発明の好ましい実施形態において、この抗体は、ポリクローナル抗体またはモノクローナル抗体であり、ここで、この抗体はこのポリペプチドに特異的である。
【００５５】
あるいは、この抗体は、ヒト抗体の不変領域または定常領域と共にこの抗体の可変領域を含むよう組換え方法によって産生されたキメラ抗体である。

【００５６】
本発明のさらなる代替実施形態において、この抗体は、この抗体の相補性決定領域を、ヒト抗体の定常（Ｃ）領域および可変（Ｖ）領域由来のフレームワーク領域の両方と結合させる組換え方法によってヒト化される。
【００５７】
好ましくは、この抗体は、従来の標識またはタグ（例えば、放射活性および／もしくは蛍光および／もしくはエピトープの標識もしくはタグ）を含むマーカーと共に提供される。
【００５８】
好ましくは、このポリペプチドに対するこのヒト化モノクローナル抗体は、原核生物細胞または真核生物細胞のトランスフェクションまたは形質転換に適切に適合する発現ベクターにおいて融合ポリペプチドとして産生される。
【００５９】
抗体（免疫グロブリンとしてもまた公知）は、外来分子（抗原）に対する特異性を有するタンパク質分子である。免疫グロブリン（Ｉｇ）は、二対のポリペプチド鎖、一対の軽（Ｌ）（低分子量）鎖（κまたはλ）、ならびに一対の重（Ｈ）鎖（γ、α、μ、δおよびε）からなる、構造的に関連したタンパク質のクラスである（４つ全てが、ジスルフィド結合によって互いに連結されている）。Ｈ鎖およびＬ鎖は両方とも、抗原の結合に寄与し、かつ１つのＩｇ分子から別のＩｇ分子までにわたり高度に可変性である領域を有する。さらに、Ｈ鎖およびＬ鎖は、非可変領域または定常領域を含む。
【００６０】
Ｌ鎖は、２つのドメインからなる。このカルボキシ末端のドメインは、所定の型のＬ鎖の間で本質的に同一であり、そして「定常」（Ｃ）領域と称される。このアミノ末端のドメインは、Ｌ鎖毎に変化し、この抗体の結合部位に寄与する。この可変性に起因して、これは「可変」（Ｖ）領域と称される。
【００６１】
Ｉｇ分子のＨ鎖は、いくつかのクラス（α、μ、σ、αおよびγ）のものである（これらの中に、サブクラスが存在する）。２つの同一のＨ鎖およびＬ鎖の１つ以上のユニットからなるアセンブルされたＩｇ分子は、それが保有するＨ鎖からその名前が由来する。従って、以下の５つのＩｇアイソタイプが存在する：ＩｇＡ、ＩｇＭ、ＩｇＤ、ＩｇＥおよびＩｇＧ（Ｈ鎖における差異に基づく４つのサブクラス（すなわち、ＩｇＧ１、ＩｇＧ２、ＩｇＧ３およびＩｇＧ４）を有する）。抗体構造およびそれらの種々の機能に関するさらなる詳細は、以下において見出され得る：Ｕｓｉｎｇ Ａｎｔｉｂｏｄｉｅｓ：Ａ ｌａｂｏｒａｔｏｒｙ ｍａｎｕａｌ，Ｃｏｌｄ Ｓｐｒｉｎｇ Ｈａｒｂｏｕｒ Ｌａｂｏｒａｔｏｒｙ Ｐｒｅｓｓ。
【００６２】
キメラ抗体は、マウス抗体またはラット抗体のＶ領域の全てがヒト抗体Ｃ領域と結合される組換え抗体である。ヒト化抗体は、げっ歯類抗体Ｖ領域由来の相補性決定領域とヒト抗体Ｖ領域由来のフレームワーク領域とを融合する組換えハイブリッド抗体である。ヒト抗体由来のＣ領域もまた用いられる。相補性決定領域（ＣＤＲ）は、抗体の重鎖および軽鎖の両方のＮ末端ドメイン内にある領域であり、ここにＶ領域の大部分のバリエーションが制限される。これらの領域は、その抗体分子の表面でループを形成する。これらのループは、抗体と抗原との間の結合表面を提供する。
【００６３】
非ヒト動物由来の抗体は、外来抗体に対する免疫応答および循環からのその抗体の除去を誘発する。キメラ抗体およびヒト化抗体は両方とも、ヒト被験体へ注射した場合、抗原性を低減させる。なぜなら、減少した量のげっ歯類（すなわち、外来）抗体が組換えハイブリッド抗体内に存在する上、ヒト抗体領域は免疫応答を誘発（ｉｌｌｉｃｉｔ）しないからである。これは、より弱い免疫応答および抗体のクリアランスにおける減少を生じる。これは、ヒト疾患の処置において治療用抗体を用いる場合、明らかに望ましい。ヒト化抗体は、より少ない「外来性」抗体の領域を有するよう設計され、従って、キメラ抗体より

もより低い免疫原性であると考えられる。
【００６４】
本発明の別の局面において、本発明に従うヒト化抗体またはキメラ抗体の発現に適合するベクターが提供される。
【００６５】
本発明のなおさらなる局面において、本発明に従うヒト化抗体またはキメラ抗体をコードするベクターで形質転換またはトランスフェクトされた細胞または細胞株が提供される。
【００６６】
本発明のなおさらなる局面において、本発明に従うヒト化抗体またはキメラ抗体の産生のための方法が提供され、この方法は、以下：
（ｉ）本発明に従うヒト化抗体またはキメラ抗体をコードする核酸分子を含むベクターで形質転換またはトランスフェクトした細胞を提供する工程；
（ｉｉ）この抗体の製造に役立つ条件下でこの細胞を増殖させる工程；および
（ｉｉｉ）この細胞、またはその増殖環境からこの抗体を精製する工程、を包含する。
【００６７】
本発明のなおさらなる局面において、本明細書中の前記のようなモノクローナル抗体を産生するハイブリドーマ細胞株が提供される。
【００６８】
本発明のさらなる局面において、本発明に従うハイブリドーマ細胞株を用いて本発明に従うモノクローナル抗体を産生させる方法が提供される。
【００６９】
本発明のさらなる局面において、本発明に従うモノクローナル抗体を産生するハイブリドーマ細胞株を調製する方法が提供され、この方法は、以下の工程：ｉ）免疫応答性哺乳動物を、配列番号１４～１９に示されるアミノ酸配列を有する少なくとも１つのポリペプチドまたはそのフラグメントを含む免疫原を用いて免疫する工程；
ｉｉ）免疫された免疫応答性哺乳動物のリンパ球を骨髄腫細胞と融合してハイブリドーマ細胞を形成する工程；
ｉｉｉ）（ｉ）のアミノ酸配列に対する結合活性について、工程（ｉｉ）のハイブリドーマ細胞によって産生されたモノクローナル抗体をスクリーニングする工程；
ｉｖ）このハイブリドーマ細胞を培養して増殖させ、そして／またはこのモノクローナル抗体を分泌させる工程；および
ｖ）この培養上清からモノクローナル抗体を回収する工程、を包含する。
【００７０】
好ましくは、この免疫応答性哺乳動物は、マウスである。あるいは、この免疫応答性哺乳動物は、ラットである。
【００７１】
ハイブリドーマ細胞を用いたモノクローナル抗体の産生は、当該分野において周知である。モノクローナル抗体を産生するために用いられるこれらの方法は、ＫｏｈｌｅｒおよびＭｉｌｓｔｅｉｎ，Ｎａｔｕｒｅ　２５６，４９５－４９７（１９７５）ならびにまた、ＤｏｎｉｌｌａｒｄおよびＨｏｆｆｍａｎ，“Ｂａｓｉｃ　Ｆａｃｔｓ　ａｂｏｕｔ　Ｈｙｂｒｉｄｏｍａｓ”，Ｃｏｍｐｅｎｄｉｕｍ　ｏｆ　Ｉｍｍｕｎｏｌｏｇｙ　第ＶＩＩ版，Ｓｃｈｗａｒｔｚ，１９８１に開示され、これらは参考として援用される。
【００７２】
本発明のさらなる局面において、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ａｕｒｅｕｓ関連敗血症、食中毒または皮膚障害の処置のための医薬の製造のための、抗体の使用が提供される。
【００７３】
本発明の別の局面において、Ｓｔａｐｈｙｌｏｃｏｃｃｕｓ　ｅｐｉｄｅｒｍｉｄｉｓ関連敗血症、腹膜炎または心内膜炎の処置のための医薬の製造のための、本発明に従う抗体の使用が提供される。

【００７４】
本発明に従う方法によって同定されたポリペプチドは、以下から生じる広範な疾患に対する治療用抗体の産生を容易にすることが明らかである：病原性感染（例えば、敗血症）；結核；細菌関連食中毒；血液感染；腹膜炎；心内膜炎；セプシス；髄膜炎；肺炎；胃潰瘍；淋病；連鎖球菌性咽喉炎（ｓｔｒｅｐ　ｔｈｒｏａｔ）；連鎖球菌関連中毒性ショック；壊死性筋膜炎；膿痂疹；ヒストプラスマ症；ライム病；胃腸炎；赤痢；細菌性赤痢。
【００７５】
既に前で述べたように、微生物は、多種多様な疾患を引き起こす。限定する目的でなく、以下の列挙は、多数の微生物およびこれらが引き起こすいくつかの疾患である。
【００７６】
【表１】

微生物	引き起こされる疾患
Staphylococcus aureus	セプシス、食中毒、敗血症
Staphylococcus epidermidis	腹膜炎、敗血症、心内膜炎、他の病院関連疾患（hospital-associated disease）
Enterococcus faecalis	心内膜炎、膀胱炎、創傷感染
Mycobacterium tuberculosis	結核
Streptococcus group B	セプシス、髄膜炎、肺炎、膀胱感染
Streptococcus pneumoniae	肺炎、髄膜炎
Helicobacter pylori	胃潰瘍
Neisseria gonorrhoea	淋病
Streptococcus group A	連鎖球菌性咽喉炎 、壊死性筋膜炎、膿痂疹、連鎖球菌性中毒性ショック症候群
Borrelia burgdoferi	ライム病
Coccidiodes immitis	肺炎
Histoplasma sapsulatum	ヒストプラスマ症、肺炎
Neisseria meningitidis type B	髄膜炎
Shigella flexneri	胃腸炎、細菌性赤痢、赤痢
Escherichia coli	食中毒、胃腸炎
Haemophilus influenzae	髄膜炎、肺炎、関節炎、蜂巣炎

本発明の実施形態を、ここで、単なる実施例によってならびに以下の材料、方法および配列番号１～１９ならびに表１を参照して記載する。
【００７７】
（材料および方法）
Ｓ．ａｕｒｅｕｓ　８３２５／４のゲノムＤＮＡのλＺＡＰ発現ライブラリーを用いた。これは、全ゲノムＤＮＡの部分的なＳａｕ３Ａ消化由来の２～１０ｋｂのフラグメントを含む。これを、ベクターのＢａｍＨ１部位中にクローニングした。このライブラリーは、このゲノムの１０倍より高いの達成範囲を含む。このライブラリーを直径９ｃｍのペートリー皿上におよそ２０，０００プラーク形成単位の初期スクリーニングを用いたプラークリフト（ｐｌａｑｕｅ　ｌｉｆｔ）によって探索した。用いたプレーティング細胞、それらの処理、プレーティング手順および緩衝液は、製造業者のハンドブック（Ｓｔｒａｔａｇｅｎｅ）に全く記載されるように行った。プレーティング細胞（Ｅｓｃｈｅｒｉｃｈｉａ　ｃｏｌｉ　ＸＬ１－Ｂｌｕｅ　ＭＲＦ’）を、ファージで感染させ、そしてＬＢプレート（１０ｍＭのＭｇＳＯ$_4$を含む）上に、３ｍｌのＬＢトップアガー（１０ｍＭのＭｇＳＯ$_4$を含む）をプレーティングした。次いで、これらのプレートを、４２℃にて４時間、インキュベートした。直径８．５ｃｍのニトロセルロースフィルターディスク（予め１０ｍＭのＩＰＴＧで濡らし、そして風乾した）を、各プレートに配置し、その位置をマー

クした。次いで、このプレートを３７℃でさらに３．５時間インキュベートした。これらのフィルターを回収し、ＴＢＳＴ緩衝液で洗浄し、次いで、６％ｗ／ｖの乾燥脱脂粉乳および３％ｖ／ｖのブタ血清（Ｓｉｇｍａ）を含有するＴＢＳＴ中で４℃にて一晩ブロッキングした。この血清を用いて、フィルター上の任意のプロテインＡクローンをブロックした。次いで、これらのフィルターを、室温にて９０分間、ブロッキング溶液において患者の血清（１／５０００希釈）で処理した。抗血清を、主要なＳ．ａｕｒｅｕｓ感染から回復に向かっている患者から得た。次いで、これらのフィルターを、３回、ＴＢＳＴ中で１０分間洗浄した。用いた二次抗体は、室温にて３０分間、ブロッキング溶液での１／３０，０００希釈のヤギ抗ヒト全ＩｇＧアルカリホスファターゼ結合物（Ｓｉｇｍａ）であった。次いで、これらのフィルターを上記のように洗浄し、標準的な比色手順を用いて発色させた。

【００７８】

交差反応性プラークをアガープレート上に配置し、そして０．０２ｍｌのクロロホルムを含む０．２ｍｌのファージ緩衝液中に芯をくり抜いて入れた（ｃｏｒｅ）。各コアストックの力価を決定し、そしてファージを１プレートあたりおよそ２００プラークでプレーティングした。プラークリフトおよびスクリーニングを上記のように実施して、単一で純粋な交差反応性クローンを得た。

【００７９】

次いで、この純粋なクローンをプレートにスポット（１μｌ）し、直径０．５ｃｍのコンフルエントなプラークを得た。３０の個々のクローンを、各プレートにスポットし得る。プラークリフトを実施し、このフィルターを適切な血清で探索した。この方法において、クローンを他の患者の血清、非感染ドナーの血清および抗プロテインＡ血清とのこれらの交差反応性について試験し得る。

【００８０】

次いで、個々のクローンを切り出して、製造業者のプロトコル（Ｓｔｒａｔａｇｅｎｅ）を用いてＥ．ｃｏｌｉ　ＸＬＯＬＲにファージミドを与えた。プラスミドミニプレップを各々実施し、ゲノムのインサートのサイズを制限マッピングによって決定した。このクローニングしたインサートの正体を、ベクター配列に対するプライマー（これは、このインサートにわたる配列決定を可能にする）を用いてＤＮＡ配列決定によって決定した。誘導された配列の公的ドメインデータベースに対する比較によって、クローニングした遺伝子の性質を決定し得る。

【００８１】

（ハイブリダイゼーション溶液／条件）

代表的に、ハイブリダイゼーション条件は、以下を用いる：４～６×ＳＳＰＥ（２０×ＳＳＰＥは、１ｌに溶解させた１７５．３ｇのＮａＣｌ、８８．２ｇのNaH_2PO_4　H_2Oおよび７．４ｇのＥＤＴＡを含有し、そしてｐＨを７．４に調整した）；５～１０×デンハルト液（５０×デンハルト液は、５ｇのＦｉｃｏｌｌ（タイプ４００，Ｐｈａｒｍａｃｉａ）、５ｇのポリビニルピロリドンおよび（ａｂｄ）５ｇのウシ血清アルブミン；１００μｇ～１．０ｍｇ／ｍｌの超音波処理したサケ／ニシンＤＮＡ；０．１～１．０％のドデシル硫酸ナトリウム；必要に応じて４０～６０％の脱イオン化ホルムアミドを含む）。ハイブリダイゼーション温度は、核酸標的配列のＧＣ含有量に依存して変化させるが、代表的には、４２℃～６５℃である。

【００８２】

【表２】

ヒト血清スクリーニングにおいて同定された *Staphylococcus aureus* クローン
表１

患者血清	クローン	コードされるタンパク質	遺伝子座番号
A	1	γ溶血素Ｂ および Ｃサブユニット	1
A	3	Atl	2
A	4	γ溶血素Ｂ および Ｃサブユニット	1
A	5	γ溶血素Ｂ および Ｃサブユニット	1
A	7	新規推定プロテアーゼ (ORF1新規抗原様)	7
A	8	新規ヌクレアーゼ (YisK)	5
A	9	新規自己溶解素	6
A	10	γ溶血素Ｂ および Ｃサブユニット	1
A	11	Atl	2
A	14	γ溶血素Ｂ および Ｃサブユニット	1
A	15	γ溶血素Ｂ および Ｃサブユニット	1
A	S1	新規推定プロテアーゼ (ORF1新規抗原様)	7
A	S5	新規表面タンパク質	12
A	S17	γ溶血素Ｂ および Ｃサブユニット	1
A	S18	新規推定プロテアーゼ (ORF1新規抗原様)	7
A	S19	新規自己溶解素	6
A	S20	新規表面タンパク質/毒素	13
A	S21	γ溶血素Ｂ および Ｃサブユニット	1
A	S25	γ溶血素Ｂ および Ｃサブユニット	1
A	S29	フィブリノーゲン結合タンパク質)	3
A	S44	新規表面タンパク質	12
A	S45	Atl	2
A	S55	Atl	2
A	S64	Atl	2
A	S66	Atl	2
B	2	新規体外毒素（体外毒素２様）	8
C	1	コアグラーゼ	4
C	2	コアグラーゼ	4
C	3	コアグラーゼ	4
C	4	コアグラーゼ	4
C	5	コアグラーゼ	4
C	6	コアグラーゼ	4
C	7	コアグラーゼ	4
C	8	コアグラーゼ	4
C	9	コアグラーゼ	4
C	10	コアグラーゼ	4

C	11	コアグラーゼ	4
C	13	コアグラーゼ	4
C	14	コアグラーゼ	4
C	15	コアグラーゼ	4
C	19	コアグラーゼ	4
C	20	コアグラーゼ	4
C	25	コアグラーゼ	4
E	6	新規表面タンパク質	9/10
E	7	新規表面タンパク質	9/10
E	11	γ溶血素Ｂ および Ｃサブユニット	1
F	1	新規体外毒素（体外毒素２様）	8
F	2	新規体外毒素（体外毒素２様）	8
F	3	新規体外毒素（体外毒素２様）	8
F	4	新規体外毒素（体外毒素２様）	8
F	5	新規溶血素 (YjfD)	11

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(54) Title: ANTIGENIC POLYPEPTIDES

(57) Abstract: The invention relates to a method for the identification of antigenic polypeptides expressed by pathogenic microbes; vaccines comprising said polypeptides; recombinant methods to manufacture said polypeptides; and therapeutic antibodies directed to said polypeptides.

Antigenic Polypeptides

The invention relates to a method for the identification of antigenic polypeptides expressed by pathogenic microbes; vaccines comprising said polypeptides; recombinant methods to manufacture said polypeptides; and therapeutic antibodies directed to said polypeptides.

Microbial organisms cause a number of fatal or debilitating diseases which affect many millions of people around the world. Currently methods to control microbial organisms include the use of antimicrobial agents (antibiotics) and disinfectants. These have proved to be problematic since exposure to these agents places a significant selection pressure resulting in the creation of resistant microbes which can avoid the effects of the antimicrobial agent(s). For example, recently it has been discovered that microbial organisms have become resistant to triclosan, an agent added to many disinfectants used in households and industrial environments.

An arguably greater problem is the evolution of antibiotic resistant strains of a number of significant pathogenic microbes.

For example, and not by way of limitation, it is estimated that there are up to 50 million people world-wide infected with drug resistant tuberculosis (TB) (Figures from the World Health Organisation, 1998). In the past the use of antibiotics to treat TB relied on the administration of single drugs (eg ethionamide) which promoted a relatively high frequency of resistance. For this reason, combinations of drugs are now used to treat tuberculosis. However the fatality rate in cases caused by strains that are resistant to at least one drug used to treat tuberculosis still approaches 50% even when treatment is given. *Mycobacterium tuberculosis*, the causative agent of TB, is a slow growing bacteria and takes a long time to kill. Therefore, for a drug combination to be effective a person with TB must take the drug combination daily for at least six months. Accordingly, patients frequently have to take two or more pills daily and this requires a regimented dosage over a relatively long period of

treatment. Many patients take the medications only intermittently and therefore do not finish the full course of therapy to completely eradicate the *M. tuberculosis* infection. Moreover, TB is strongly associated with HIV infection and therefore the establishment of TB is strongly correlated with immunosuppression.

Vaccination against TB has been available for many years. The bacillus calmette and guerin (BCG) vaccination has been widely used throughout the world for a long time because it is a safe and inexpensive means to vaccinate large numbers of people who potentially could contract TB. BCG is derived from live, attenuated strains of *Mycobacterium bovis*. However the impact of vaccination on the infectious forms of TB is minimal and BCG has therefore contributed little to the overall control of the disease.

A further example of a pathogenic organism which has developed resistance to antibiotics is *Staphylococcus aureus*. *S.aureus* is a bacterium whose normal habitat is the epithelial lining of the nose in about 20-40% of normal healthy people and is also commonly found on people's skin usually without causing harm. However, in certain circumstances, particularly when skin is damaged, this germ can cause infection. This is a particular problem in hospitals where patients may have surgical procedures and/or be taking immunosuppressive drugs. These patients are much more vulnerable to infection with *S.aureus* because of the treatment they have received. Resistant strains of *S.aureus* have arisen in recent years. Methicillin resistant strains are prevalent and many of these resistant strains are also resistant to several other antibiotics. Currently there is no effective vaccination procedure for *S. aureus*. In the US, *S.aureus* infections are the cause of 13% of the two million hospitalised infections each year. This represents 260,000 people with an infection of *S.aureus*, of which 60-80,000 die.

S. aureus is therefore a major human pathogen capable of causing a wide range of life threatening diseases including septicaemia, endocarditis, arthritis and toxic shock. This ability is determined by the versatility of the organism and its arsenal of

components involved in virulence. Pathogenicity is multifactorial and no one component has shown to be responsible for a particular infection, see Projan, S.J. & Novick, R.P. (1997) in The Staphylococci in Human Disease (Crossley, K.B. & Archer, G.L., eds.) pp.55-81.

At the onset of infection, and as it progresses, the needs and environment of the organism changes and this is mirrored by a corresponding alteration in the virulence determinants which *S. aureus* produces. At the beginning of infection it is important for the pathogen to adhere to host tissues and so a large repertoire of cell surface associated attachment proteins are made. These include collagen-, fibrinogen- and fibronectin-binding proteins. The pathogen also has the ability to evade host defences by the production of factors that reduce phagocytosis or interfere with the ability of the cells to be recognised by circulating antibodies.

Often a focus of infection develops as an abscess and the number of organisms increases. *S. aureus* has the ability to monitor its own cell density by the production of a quorum sensing peptide. Accumulation of the peptide, associated with physiological changes brought about by the beginning of starvation of the cells, elicits a switch in virulence determinant production from adhesins to components involved in invasion and tissue penetration. These include a wide range of hemolysins, proteases and other degradative enzymes.

During the process of any infection the virulence determinants made by *S. aureus* are produced in response to environmental and physiological stimuli. These stimuli will be dependent on the niche within the body and will change as the infection progresses. Little is known of the conditions *in vivo* and it is likely that some components are produced solely in this environment. These are therefore potential vaccine components, which could not be discovered by previous techniques.

One of the most important developments in recent medical history is the development of vaccines which provide prophylactic protection from a wide variety of pathogenic organisms. Many vaccines are produced by inactivated or attenuated pathogens which are injected into an individual. The immunised individual responds by producing both a humoral (antibody) and cellular (cytolytic T cells, CTL's) response. For example, hepatitis vaccines are made by heat inactivating the virus and treating it with a cross linking agent such as formaldehyde. An example of an attenuated pathogen useful as a vaccine is represented by polio vaccines which are produced by attenuating a live pathogen.

However the use of attenuated organisms in vaccines for certain diseases is problematic due to the lack of knowledge regarding the pathology of the condition and the nature of the attenuation. For certain viral agents this is a particular problem since viruses, in particular retroviruses, have an error prone replication cycle which results viable mutations in the genes which comprise the virus. This can result in alterations to antigenic determinants which have previously been used as vaccines. An alternative to the use of inactivated or attenuated pathogens is the identification of pathogen epitopes to which the immune system is particularly sensitive. In this regard many pathogenic toxins produced by pathogenic organisms during an infection are particularly useful in the development of vaccines which protect the individual from a particular pathogenic organism.

The development of so-called subunit vaccines (vaccines in which the immunogen is a fragment or subunit of a protein or complex expressed by a particular pathogenic organism) has been the focus of considerable medical research. The need to identify candidate molecules useful in the development of subunit vaccines is apparent not least because conventional chemotherapeutic approaches to the control of pathogenic organisms has more recently been stymied by the development of antibiotic resistance. A number of methods have been developed to identify potential antigenic polypeptides which can be used as a vaccine. One such method is disclosed herein.

It has been known for many years that tumour cells produce a number of tumour cell specific antigens, some of which are presented at the tumour cell surface. The immune system recognises these antigens as foreign thereby resulting in the production of antibodies to self antigens, so called autoantibodies or autologous antisera.

One such technique is Serological identification of antigens by recombinant Expression Cloning, abbreviated to SEREX.

Typically, the technique involves the extraction of RNA from tumour tissue followed by the selective enrichment of mRNA from the isolated total RNA. The mRNA is reverse transcribed into cDNA using viral reverse transcriptase. The cDNA thus synthesised is subcloned into an expression vector and transformed into an appropriate bacterial strain. The transformed bacteria are plated onto a suitable nutrient agar and under appropriate growth conditions the subcloned cDNA is expressed from the expression vector in the bacterial cell. The cells are lysed naturally by the use of phage based expression vectors, for example λ phage or phagemid based vectors, which through their lytic cycle cause cell lysis. The released polypeptides are transferred to a suitable membrane support (i.e. nitrocellulose, nylon) and exposed to autologous antisera from the patient from which the tumour tissue was originally isolated. The immunoscreening methodology allows the identification of genes that are over expressed or inappropriately expressed in a selected tumour tissue from a patient.

We have exploited this techinque to identify antigenic polypeptides expressed by pathogenic organisms during an infection. Autologous antisera produced during the infection is used to screen an expression library created from genomic DNA to identify and clone antigens.

In its broadest aspect the invention relates to the identification of antigenic polypeptides expressed during an infection by a pathogenic microbe.

According to a first aspect of the invention there is provided a method to identify antigenic polypeptides comprising:

(i) providing a nucleic acid library encoding genes or partial gene sequences of a pathogenic organism;

(ii) transforming/transfecting said library into a host cell;

(iii) providing conditions conducive to the expression of said transformed/transfected genes or partial gene sequences;

(iv) contacting the polypeptides expressed by the genes/partial gene sequences with autologous antisera derived from an animal infected with, or has been infected with, said pathogenic organism; and

(v) purifying the nucleic acid encoding the polypeptide or partial polypeptide binding to said autologous antisera.

In a preferred method of the invention said library comprises genomic DNA of a pathogenic organism.

Ideally said pathogenic organism is bacterial.

More preferably still said bacterial organism is selected from the following: *Staphylococcus aureus; Staphylococcus epidermidis; Enterococcus faecalis; Mycobacterium tuberculsis; Streptococcus group B; Streptococcus pneumoniae; Helicobacter pylori; Neisseria gonorrhea; Streptococcus group A; Borrelia*

burgdorferi; Coccidiodes immitis; Histoplasma capsulatum; Neisseria meningitidis type B; Shigella flexneri; Escherichia coli; Haemophilus influenzae.

Preferably still said pathogenic organism is of the genus *Staphylococcus spp.* Ideally organism is *Staphylococcus aureus* or *Staphylococcus epidermidis.*

In a further preferred embodiment of the invention said nucleic acid library is a lambda library, ideally a lambda expression library.

According to a second aspect of the invention there is provided a nucleic acid molecule comprising a DNA sequence selected from:

(i) the DNA sequence as represented in SEQ ID NO's 1 – 13;

(ii) DNA sequences which hybridise to the sequence presented in the SEQ ID No's 1-13 identified in (i) above which encode a polypeptide expressed by a pathogenic organism and

(iii) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (i) and (ii).

In a yet still further preferred embodiment of the invention said nucleic acid molecule is genomic DNA.

In a preferred embodiment of the invention there is provided an isolated nucleic acid molecule which anneals under stringent hybridisation conditions to the sequences presented in SEQ ID NO's 1- 13.

Stringent hybridisation/washing conditions are well known in the art. For example, nucleic acid hybrids that are stable after washing in 0.1xSSC, 0.1% SDS at 60°C. It

is well known in the art that optimal hybridisation conditions can be calculated if the sequences of the nucleic acid is known. For example, hybridisation conditions can be determined by the GC content of the nucleic acid subject to hybridisation. Please see Sambrook *et al* (1989) Molecular Cloning; A Laboratory Approach. A common formula for calculating the stringency conditions required to achieve hybridisation between nucleic acid molecules of a specified homology is:

$T_m = 81.5^0 C + 16.6 \text{ Log } [Na^+] + 0.41[\% G + C] - 0.63$ (%formamide).

According to a third aspect of the invention there is provided at least one polypeptide identified by the method according to the invention.

In a preferred embodiment of the invention, said polypeptide is associated with infective pathogenicity of an organism according to any previous aspect or embodiment of the invention.

More preferably still said polypeptide is at least one, or part of SEQ ID NO's: 14- 19.

According to a fourth aspect of the invention there is provided a nucleic acid molecule characterised in that said nucleic acid molecule is part of a vector adapted to facilitate recombinant expression of the polypeptide encoded by said nucleic acid molecule.

In a preferred embodiment of the invention said vector is an expression vector adapted for prokaryotic gene expression. Alternatively said expression vector is adapted for eukaryotic gene expression.

Typically said adaptation includes, by example and not by way of limitation, the provision of transcription control sequences (promoter sequences) which mediate cell specific expression. These promoter sequences may be cell specific, inducible or constitutive.

Promoter is an art recognised term and, for the sake of clarity, includes the following features which are provided by example only, and not by way of limitation. Enhancer elements are *cis* acting nucleic acid sequences often found 5' to the transcription initiation site of a gene (enhancers can also be found 3' to a gene sequence or even located in intronic sequences and is therefore position independent). Enhancers function to increase the rate of transcription of the gene to which the enhancer is linked. Enhancer activity is responsive to *trans* acting transcription factors (polypeptides) which have been shown to bind specifically to enhancer elements. The binding/activity of transcription factors (please see Eukaryotic Transcription Factors, by David S Latchman, Academic Press Ltd, San Diego) is responsive to a number of environmental cues which include, by example and not by way of limitation, intermediary metabolites (eg glucose, lipids), environmental effectors (eg light, heat,).

Promoter elements also include so called TATA box and RNA polymerase initiation selection (RIS) sequences which function to select a site of transcription initiation. These sequences also bind polypeptides which function, *inter alia*, to facilitate transcription initiation selection by RNA polymerase.

Adaptations also include the provision of selectable markers and autonomous replication sequences which both facilitate the maintenance of said vector in either the eukaryotic cell or prokaryotic host. Vectors which are maintained autonomously are referred to as episomal vectors.

Adaptations which facilitate the expression of vector encoded genes include the provision of transcription termination/polyadenylation sequences. This also includes the provision of internal ribosome entry sites (IRES) which function to maximise expression of vector encoded genes arranged in bicistronic or multi-cistronic expression cassettes.

These adaptations are well known in the art. There is a significant amount of published literature with respect to expression vector construction and recombinant DNA techniques in general. Please see, Sambrook et al (1989) Molecular Cloning: A Laboratory Manual, Cold Spring Harbour Laboratory, Cold Spring Harbour, NY and references therein; Marston, F (1987) DNA Cloning Techniques: A Practical Approach Vol III IRL Press, Oxford UK; DNA Cloning: F M Ausubel et al, Current Protocols in Molecular Biology, John Wiley & Sons, Inc.(1994).

According to yet a further aspect of the invention there is provided a method for the production of the polypeptides according to any previous aspect or embodiment of the invention comprising:

(i) providing a cell transformed/transfected with a vector according to the invention;

(ii) growing said cell in conditions conducive to the manufacture of said polypeptides; and

(iii) purifying said polypeptide from said cell, or its growth environment.

In a preferred method of the invention said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

According to a fifth aspect of the invention there is provided a cell or cell-line transformed or transfected with the vector according to the invention.

In a preferred embodiment of the invention said cell is a prokaryotic cell. Alternatively said cell is a eukaryotic cell selected from: fungal, insect, amphibian, mammalian; plant.

According to a yet further aspect of the invention there is provided a vaccine comprising at least one polypeptide according to the invention.

Ideally said vaccine further comprises a carrier and/or adjuvant.

The terms adjuvant and carrier are construed in the following manner. Some polypeptide or peptide antigens contain B-cell epitopes but no T cell epitopes. Immune responses can be greatly enhanced by the inclusion of a T cell epitope in the polypeptide/peptide or by the conjugation of the polypeptide/peptide to an immunogenic carrier protein such as key hole limpet haemocyanin or tetanus toxoid which contain multiple T cell epitopes. The conjugate is taken up by antigen presenting cells, processed and presented by human leukocyte antigens (*HLA*'s) class II molecules. This allows T cell help to be given by T cell's specific for carrier derived epitopes to the B cell which is specific for the original antigenic polypeptide/peptide. This can lead to increase in antibody production, secretion and isotype switching.

An adjuvant is a substance or procedure which augments specific immune responses to antigens by modulating the activity of immune cells. Examples of adjuvants include, by example only, agonsitic antibodies to co-stimulatory molecules, Freunds adjuvant, muramyl dipeptides, liposomes. An adjuvant is therefore an immunomodulator. A carrier is an immunogenic molecule which, when bound to a second molecule augments immune responses to the latter.

In yet a further aspect of the invention there is provided a method to immunise an animal against a pathogenic microbe comprising administering to said animal at least one polypeptide, or part thereof, according to the invention or the vaccine according to the invention.

In a preferred method of the invention said animal is human.

Preferably the vaccine, or antigenic polypeptide, can be delivered by direct injection either intravenously, intramuscularly, subcutaneously. Further still, the vaccine or antigenic polypeptide, may be taken orally.

Preferably the vaccine is against the bacterial species *Staphylococcus aureus*.

The vaccine may also be against the bacterial species *Staphylococcus epidermidis*.

It will also be apparent that vaccines or antigenic polypeptides are effective at preventing or alleviating conditions in animals other than humans, for example and not by way of limitation, family pets, livestock, horses.

According to a further aspect of the invention there is provided an antibody, or at least an effective binding part thereof, which binds at least one polypeptide according to the invention.

In a preferred embodiment of the invention said antibody is a polyclonal or monoclonal antibody wherein said antibody is specific to said polypeptide.

Alternatively, said antibody is a chimeric antibody produced by recombinant methods to contain the variable region of said antibody with an invariant or constant region of a human antibody.

In a further alternative embodiment of the invention, said antibody is humanised by recombinant methods to combine the complimentarity determining regions of said antibody with both the constant (C) regions and the framework regions from the variable (V) regions of a human antibody.

Preferably said antibody is provided with a marker including a conventional label or tag, for example a radioactive and/or fluorescent and/or epitope label or tag.

Preferably said humanised monoclonal antibody to said polypeptide is produced as a fusion polypeptide in an expression vector suitably adapted for transfection or transformation of prokaryotic or eukaryotic cells.

Antibodies, also known as immunoglobulins, are protein molecules which have specificity for foreign molecules (antigens). Immunoglobulins (Ig) are a class of structurally related proteins consisting of two pairs of polypeptide chains, one pair of light (L) (low molecular weight) chain (κ or λ), and one pair of heavy (H) chains (γ, α, μ, δ and ε), all four linked together by disulphide bonds. Both H and L chains have regions that contribute to the binding of antigen and that are highly variable from one Ig molecule to another. In addition, H and L chains contain regions that are non-variable or constant.

The L chains consist of two domains. The carboxy-terminal domain is essentially identical among L chains of a given type and is referred to as the "constant" (C) region. The amino terminal domain varies from L chain to L chain and contributes to the binding site of the antibody. Because of its variability, it is referred to as the "variable" (V) region.

The H chains of Ig molecules are of several classes, α, μ, σ, ω, and γ (of which there are several sub-classes). An assembled Ig molecule consisting of one or more units of two identical H and L chains, derives its name from the H chain that it possesses. Thus, there are five Ig isotypes: IgA, IgM, IgD, IgE and IgG (with four sub-classes based on the differences in the H chains, i.e., IgG1, IgG2, IgG3 and IgG4). Further detail regarding antibody structure and their various functions can be found in, Using Antibodies: A laboratory manual, Cold Spring Harbour Laboratory Press.

Chimeric antibodies are recombinant antibodies in which all of the V-regions of a mouse or rat antibody are combined with human antibody C-regions. Humanised antibodies are recombinant hybrid antibodies which fuse the complimentarity determining regions from a rodent antibody V-region with the framework regions from the human antibody V-regions. The C-regions from the human antibody are also used. The complimentarity determining regions (CDRs) are the regions within the N-terminal domain of both the heavy and light chain of the antibody to where the

majority of the variation of the V-region is restricted. These regions form loops at the surface of the antibody molecule. These loops provide the binding surface between the antibody and antigen.

Antibodies from non-human animals provoke an immune response to the foreign antibody and its removal from the circulation. Both chimeric and humanised antibodies have reduced antigenicity when injected to a human subject because there is a reduced amount of rodent (i.e. foreign) antibody within the recombinant hybrid antibody, while the human antibody regions do not illicit an immune response. This results in a weaker immune response and a decrease in the clearance of the antibody. This is clearly desirable when using therapeutic antibodies in the treatment of human diseases. Humanised antibodies are designed to have less "foreign" antibody regions and are therefore thought to be less immunogenic than chimeric antibodies.

In another aspect of the invention there is provided a vector which is adapted for the expression of the humanised or chimeric antibodies according to the invention.

In a yet further aspect of the invention, there is provided a cell or cell line which has been transformed or transfected with the vector encoding the humanised or chimeric antibody according to the invention.

In a yet further aspect of the invention there is provided a method for the production of the humanised or chimeric antibody according to the invention comprising :

(i) providing a cell transformed or transfected with a vector which comprises a nucleic acid molecule encoding the humanised or chimeric antibody according to the invention;

(ii) growing said cell in conditions conducive to the manufacture of said antibody; and

(iii) purifying said antibody from said cell, or its growth environment.

In a yet further aspect of the invention there is provided a hybridoma cell line which produces a monoclonal antibody as hereinbefore described.

In a further aspect of the invention there is provided a method of producing monoclonal antibodies according to the invention using hybridoma cell lines according to the invention.

In a further aspect of the invention there is provided a method for preparing a hybridoma cell-line producing monoclonal antibodies according to the invention comprising the steps of:

i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide having the amino acid sequence as represented in SEQ. ID No 14-19, or fragments thereof;

ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;

iii) screening monoclonal antibodies produced by the hybridoma cells of step (ii) for binding activity to the amino acid sequences of (i);

iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and

v) recovering the monoclonal antibody from the culture supernatant.

Preferably, the said immunocompetent mammal is a mouse. Alternatively, said immunocompetent mammal is a rat.

The production of monoclonal antibodies using hybridoma cells is well-known in the art. The methods used to produce monoclonal antibodies are disclosed by Kohler and Milstein in Nature 256, 495-497 (1975) and also by Donillard and Hoffman, "Basic Facts about Hybridomas" in Compendium of Immunology V.II ed. by Schwartz, 1981, which are incorporated by reference.

In a further aspect of the invention there is provided the use of the antibodies for manufacture of a medicament for the treatment of *Staphylococcus aureus*-associated septicaemia, food-poisoning or skin disorders.

In another aspect of the invention there is provided the use of the antibodies according to the invention for the manufacture of a medicament for the treatment of *Staphylococcus epidermidis*-associated septicaemia, peritonitis or endocarditis.

It will be apparent that the polypeptides identified by the method according to the invention will facilitate the production of therapeutic antibodies to a range of diseases resulting from pathogenic infection, for example, septicaemia; tuberculosis; bacteria-associated food poisoning; blood infections; peritonitis; endocarditis; sepsis; meningitis; pneumonia; stomach ulcers; gonorrhoea; strep throat; streptococcal-associated toxic shock; necrotizing fasciitis; impetigo; histoplasmosis; Lyme disease; gastro-enteritis; dysentery; shigellosis.

As has already been stated earlier, microbial organisms cause a wide variety of diseases. Listed below, and not by way of limitation, are a number of micro-organisms and some of the diseases they cause.

Micro-organism	**Disease(s) caused**
Staphylococcus aureus	Sepsis, food poisoning, septicaemia,
Staphylococcus epidermidis	Peritonitis, septicaemia, endocarditis, other hospital-associated diseases
Enterococcus faecalis	Endocarditis, cystitis, wound infections
Mycobacterium tuberculosis	Tuberculosis
Streptococcus group B	Sepsis, meningitis, pneumonia, bladder infections
Streptococcus pneumoniae	Pneumonia, meningitis
Helicobacter pylori	Stomach ulcers
Neisseria gonorrhoea	Gonorrhoea
Streptococcus group A	Strep throat, necrotizing fasciitis, impetigo, Strep. Toxic shock syndrome
Borrelia burgdoferi	Lyme disease
Coccidiodes immitis	Pneumonia

Histoplasma sapsulatum	Histoplasmosis, pneumonia
Neisseria meningitidis type B	Meningitis
Shigella flexneri	Gastro-enteritis, shigellosis, dysentry
Escherichia coli	Food-poisoning, gastro-enteritis
Haemophilus influenzae	Meningitis, pneumonia, arthritis, cellulitis

An embodiment of the invention will now be described by example only and with reference to the following materials, methods and SEQ ID NO's 1 –19 and Table 1.

Materials and Methods

A λZAP Express library of genomic DNA of *S. aureus* 8325/4 was used. It contains fragments of 2-10kb from a partial *Sau*3A digest of total genomic DNA. This was cloned into the *Bam*H1 site of the vector. The library contains >10x coverage of the genome. The library was probed by plaque lift using an initial screen of approximately 20,000 plaque forming units on a 9cm diameter Petri dish. The plating cells used, their treatment, the plating procedure and buffers were exactly as described in the manufacturers handbook (Stratagene). Plating cells, *Escherichia coli* XL1-Blue MRF', were infected with phage and plated in 3 ml top LB agar containing 10 mM $MgSO_4$ onto LB plates containing 10 mM $MgSO_4$. The plates were then incubated at 42°C for 4 hr. An 8.5cm diameter nitrocellulose filter disc (previously soaked in 10 mM IPTG and air-dried) was placed on each plate and its location marked. The plates were then incubated for a further 3.5 hr at 37°C. The filters were removed and washed in TBST buffer before blocking overnight at 4°C in TBST containing 6% w/v dried skimmed milk and 3% v/v pig serum (Sigma). The serum was used to block any Protein A clones on the filter. The filters are then treated with patient serum (1/5000 dilution) in blocking solution for 90 min at room temperature. Antisera have been obtained from patients convalescing from major *S. aureus* infections. The filters are then washed for 3x10 min in TBST. Secondary antibody used was goat anti-human whole IgG alkaline phosphatase linked (Sigma)

at 1/30,000 dilution in blocking solution at room temperature for 30 min. The filters were then washed as above and developed using a standard colorimetric procedure.

Cross-reactive plaques were located on the agar plates and cored into 0.2ml phage buffer with 0.02 ml chloroform. The titre of each core stock was determined and the phage plated at approximately 200 plaques per plate. A plaque lift and screen was performed as above to give single, pure cross-reactive clones.

The pure clones were then spotted (1µl) onto plates to give a confluent plaque of 0.5cm diameter. 30 individual clones can be spotted on each plate. A plaque lift is performed and the filter probed with an appropriate sera. In this way clones can be tested for their cross-reactivity with other patient sera, non-infected donor sera and anti-Protein A sera.

Individual clones were then excised to give a phagemid in *E. coli* XLOLR using the manufacturers protocol (Stratagene). A plasmid miniprep of each was carried out and the size of the genomic insert determined by restriction mapping. The identity of the cloned insert was determined by DNA sequencing using primers against vector sequence, which allows sequencing across the insert. By comparison of the derived sequence against the public domain databases the nature of the cloned gene(s) can be determined.

Hybridisation Solutions/Conditions

Typically, hybridisation conditions uses 4 – 6 x SSPE (20x SSPE contains 175.3g NaCl, 88.2g NaH_2PO_4 H_2O and 7.4g EDTA dissolved to 1 litre and the pH adjusted to 7.4); 5-10x Denhardts solution (50x Denhardts solution contains 5g Ficoll (type 400, Pharmacia), 5g polyvinylpyrrolidone abd 5g bovine serum albumen; 100µg-1.0mg/ml sonicated salmon/herring DNA; 0.1-1.0% sodium dodecyl sulphate; optionally 40-60% deionised formamide. Hybridisation temperature will vary

depending on the GC content of the nucleic acid target sequence but will typically be between 42^0- 65^0 C.

Staphylococcus aureus clones identified in human sera screen

TABLE 1

Patient Sera	Clone	Encoded proteins	Locus number
A	1	γ hemolysin B and C subunit	1
A	3	Atl	2
A	4	γ hemolysin B and C subunit	1
A	5	γ hemolysin B and C subunit	1
A	7	Novel putative protease (ORF1 novel antigen like)	7
A	8	Novel nuclease (YisK)	5
A	9	Novel autolysin	6
A	10	γ hemolysin B and C subunit	1
A	11	Atl	2
A	14	γ hemolysin B and C subunit	1
A	15	γ hemolysin B and C subunit	1
A	S1	Novel putative protease (ORF1 novel antigen like)	7
A	S5	Novel surface protein	12
A	S17	γ hemolysin B and C subunit	1
A	S18	Novel putative protease (ORF1 novel antigen like)	7
A	S19	Novel autolysin	6
A	S20	Novel surface protein/toxin	13
A	S21	γ hemolysin B and C subunit	1
A	S25	γ hemolysin B and C subunit	1
A	S29	Fibrinogen binding protein)	3
A	S44	Novel surface protein	12
A	S45	Atl	2
A	S55	Atl	2
A	S64	Atl	2
A	S66	Atl	2
B	2	Novel exotoxin (exotoxin 2 like)	8
C	1	Coagulase	4
C	2	Coagulase	4
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C	5	Coagulase	4
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C	11	Coagulase	4
C	13	Coagulase	4
C	14	Coagulase	4
C	15	Coagulase	4
C	19	Coagulase	4
C	20	Coagulase	4
C	25	Coagulase	4
E	6	Novel surface proteins	9/10
E	7	Novel surface proteins	9/10
E	11	γ hemolysin B and C subunit	1
F	1	Novel exotoxin (exotoxin 2 like)	8
F	2	Novel exotoxin (exotoxin 2 like)	8
F	3	Novel exotoxin (exotoxin 2 like)	8
F	4	Novel exotoxin (exotoxin 2 like)	8
F	5	Novel hemolysin (YjfD)	11

CLAIMS

1. An isolated nucleic acid molecule comprising a DNA sequence selected from the group consisting of:

(i) the DNA sequence as represented in SEQ ID NO's 1 – 13;

(ii) DNA sequences which hybridise to the sequence presented in the SEQ ID No's 1-13 identified in (i) above and which encode a polypeptide expressed by a pathogenic organism; and

(iii) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences defined in (i) and (ii).

2. An isolated nucleic acid molecule according to claim 1 which is genomic DNA.

3. An isolated nucleic acid molecule according to claim 1 or 2 which anneals under stringent hybridisation conditions to the sequences presented in SEQ ID NO's 1-13.

4. A vector comprising a nucleic acid molecule according to any of claims 1-3.

5. A vector according to claim 4 wherein the vector is adapted for recombinant expression of the polypeptide encoded by the nucleic acid.

6. A vector according to claim 4 or 5 wherein said vector is an expression vector adapted for prokaryotic gene expression.

7. A vector according to claim 4 or 5 wherein said vector is an expression vector adapted for eukaryotic gene expression.

8. A vector according to any of claims 4 to 7 wherein the adaptation of the vector includes the provision of promoter sequences.

9. A vector according to claim 8 wherein the promoter sequences provide for cell specific, inducible or constitutive expression.

10. A method to identify antigenic polypeptides comprising:

(i) providing a nucleic acid library encoding genes or partial gene sequences of a pathogenic organism;

(ii) transforming/transfecting said library into a host cell;

(iii) contacting the polypeptides expressed by the genes/partial gene sequences with autologous antisera derived from an animal infected with, or has been infected with, said pathogenic organism; and

(iv) purifying the nucleic acid encoding the polypeptide or partial polypeptide binding to said autologous antisera.

11. A method according to claim 10 wherein said library comprises genomic DNA of a pathogenic organism.

12. A method according to claim 10 or claim 11 wherein said pathogenic organism is bacterial.

13. A method according to any of claims 10 to 12 wherein said bacterial organism is selected from the following: *Staphylococcus aureus; Staphylococcus epidermidis; Enterococcus faecalis; Mycobacterium tuberculsis; Streptococcus group B; Streptococcus pneumoniae; Helicobacter pylori;*

Neisseria gonorrhea; Streptococcus group A; Borrelia burgdorferi; Coccidioides immitis; Histoplasma sapsulatum; Neisseria meningitidis type B; Shigella flexneri; Escherichia coli; Haemophilus influenzae

14. A method according to any of claim 13 wherein said pathogenic organism is *Staphylococcus aureus*.

15. A method according to any of claim 13 wherein said pathogenic organism is *Staphylococcus epidermidis*.

16. A method according to any of claims 10 to 15 wherein said nucleic acid library is a lambda library.

17. A polypeptide identified by the method according to any of claims 10 to 16.

18. A polypeptide according to claim 17 which is selected from the group consisting of SEQ ID NO's: 14-19.

19. A method for the production of the polypeptides according to any of claims 17 or 18 comprising:
    (i) providing a cell transformed/transfected with a vector according to any of claims 4 to 9 and with cell culture conditions; and
    (ii) purifying said polypeptide from said cell, or its growth environment.

20. A method according to claim 19 wherein said vector encodes, and thus said recombinant polypeptide is provided with, a secretion signal to facilitate purification of said polypeptide.

21. A cell transformed or transfected with the vector according to any of claims 4 to 9.

22. A cell according to claim 21 which is a prokaryotic cell.

23. A cell according to claim 21 which is a eukaryotic cell selected from the group consisting of: fungal cell, insect cell, amphibian cell; mammalian cell; plant cell.

24. A vaccine comprising at least one polypeptide according to claims 16 or 17.

25. A vaccine according to claim 24 which further comprises a carrier and/or adjuvant.

26. A method to immunise an animal against a pathogenic microbe comprising administering to the animal at least one polypeptide, or part thereof, according to any previous claim or the vaccine of any previous claim.

27. A method according to claim 26 wherein the animal is human.

28. A method according to claim 26 or 27 wherein the vaccine, or antigenic polypeptide, is delivered by direct injection either intravenously, intramuscularly or subcutaneously.

29. A method according to claim 25 or 26 wherein the vaccine or antigenic polypeptide is taken orally.

30. A method according to any of claims 26 to 29 wherein the vaccine is against the bacterial genus *Staphylococcus spp.*

31. A method according to claim 30 wherein the vaccine is against the bacterial species *Staphylococcus aureus.*

32. A method according to claim 30 wherein the vaccine is against the bacterial species *Staphylococcus epidermidis.*

33. An antibody, or at least an effective part thereof, which binds at least with a selective part of the polypeptide according to claim 16 or 17.

34. An antibody according to claim 33 which is a monoclonal antibody.

35. An antibody according to claim 33 or 34 wherein said effective part comprises FAb fragments.

36. An antibody according to any of claims 33 to 35 which is a chimeric antibody.

37. An antibody according to any of claims 33 to 35 which is a humanised antibody.

38. An antibody according to any of claims 33 to 37 wherein said antibody is provided with a marker, label or tag.

39. An antibody according to claim 38 wherein said antibody is provided with a marker selected from a group consisting of: a radioactive label, a fluorescent label; an epitope tag.

40. An antibody according to any of claims 34 to 39 which is produced as a fusion polypeptide.

41. A vector which is adapted for the expression of the antibodies according to any of claims 34-40.

42. A cell which has been transformed or transfected with the vector according to claim 41.

43. A method for the production of the antibody according to any of claims 34 or 40 comprising :
    i) providing a cell transformed or transfected with the vector according to claim 41 and with cell culture conditions; and
    ii) purifying said antibody from said cell, or its growth environment.

44. A hybridoma cell line which produces an antibody according to claim 34.

45. Use of the antibodies according to any of claims 33 to 40 for the manufacture of a medicament for the treatment of *Staphylococcus aureus*-associated septicaemia, food-poisoning or skin disorders.

46. Use of the antibodies according to any of claims 33 to 40 for the manufacture of a medicament for the treatment of *Staphylococcus epidermidis*-associated septicaemia, peritonitis or endocarditis

47. A method for preparing a hybridoma cell-line producing monoclonal antibodies according to claim 34, comprising the steps of:
    i) immunising an immunocompetent mammal with an immunogen comprising at least one polypeptide having the amino acid sequence as set forward in SEQ ID No: 14-19, or fragments thereof;
    ii) fusing lymphocytes of the immunised immunocompetent mammal with myeloma cells to form hybridoma cells;
    iii) screening monoclonal antibodies produced by the hybridoma cells of step (ii) for binding activity to the amino acid sequences of (i);
    iv) culturing the hybridoma cells to proliferate and/or to secrete said monoclonal antibody; and
    v) recovering the monoclonal antibody from the culture supernatant.

48. A method according to claim 47, wherein said immunocompetent mammal is a mouse

49. A method according to claim 47, wherein said immunocompetent mammal is a rat

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gaacgagcaa gaaaagaagt gaattacgct gcaaatacag atgctgttgc tacactttit
420
tctactaaga aaaactttac taaagacaat acagtagatg atgtaatcga actaagtgat
480
aaattatcta atttaaaaaa taaaccagat aaatctaaaa tcacaataca aatagggaaa
540
occactatta atactaagaa agcctttiat gatgataatc gtccaataga atatggggtg
600
cacagtaaag atgaataaaa ttaatgatag ggatttaaca gaattaagta gttactgggt
660
ttatcaacat attgatctaa aaaaagaatt taaagttaat ggaaaaaggt ttaaacaagt
720
agacagttat aatgatgata agaatagtaa tttgaatggt gctgctgata ttaaaatata
780
tgagttatta gatgataaaa gtaaccaaac tggtcaacag acaataattt atcaaggaac
840
atctaatgag gcaattaatc caaataatcc attaaaatca tcgggattig gagatgattg
900
gctccaaact gctaaattaa tgaataatga taatgaaagc acagattatt taaagcaaac
960
agatcaatta tcaaatcaat ataaaataaa gttagaagat gcagatagat tatcaaatag
1020
tgatttttta aaaaaatata gaatggaatc aagtcacttc aaaaacaaaa ccattgtggc
1080

ggatggcggt aatcggaacg gcggtgcagg agcaaaatat caaggagcga aacatccgaa
1140
tgaaaaagtt gttgctactg actcagcaat gattccttat gctgcttggc agaaattgcc
1200
tagacccacgc tttgataata tgattagttt taatagtacc aacgatttat taacatggtt
1260
acaagatcca ttcatcaaag atatgccagg aaaacgcgtt aacattaatg atggtgtgcc
1320
caggttagat actttaatag acagccatgt aggttataaa aggaagttaa atagcaaaga
1380
taacacatac gatactgtac cactaatcaa aataaagtcg gtaaaagata cagaatttaa
1440
aaatggaaaa saaglaaaaa agactattaa cataacatta gatatggatg ggcgaattac
1500
aataaatgtt tggacaggag attcgattgc acgttctgga agaggaactt taattaaact
1560
taatttagaa aatcttgatg cgttgagtaa actgattact ggtgaaacaa gtggtatgtt
1620
agcagaatgc gtaatcttt taaatgaaag ttttaacatc tcagaaaatg aaaataaaaa
1680
ttttgcagat agaaagaaac aattatcaga aggatttaag gataagatta acttatttca
1740
gttagaagaa atggaaagaa ctttaattag taaaataaac tcacttgaag aagttgcaga
1800
tgaaacaata gaaagtatta gtgttgttaa acacttatta cctgattttg cattggatgc
1860
attaaaagaa agaattaatg agttgtttaa aggtataaca tcttttatag aaaaagtgta
1920
tgatagtatt gataatgaaa ttttagaaat tttcaaaaat atagatcacg acttcagaga
1980
tggagtatct gaagaaatga t
2001

<210> 14
<211> 106
<212> PRT
<213> Staphylococcus aureus

<400> 14
Asp Gln Thr Lys Thr Gln Thr Ala His Thr Val Lys Thr Ala Gln Thr
1 5 10 15

Ala Gln Glu Gln Asn Lys Val Gln Thr Pro Val Lys Asp Val Ala Thr
20 25 30

Ala Lys Ser Glu Ser Asn Asn Gln Ala Val Ser Asp Asn Lys Ser Gln
35 40 45

Gln Thr Asn Lys Val Thr Lys His Asn Glu Thr Pro Lys Gln Ala Ser
50 55 60

Lys Ala Lys Glu Leu Pro Lys Thr Gly Leu Thr Ser Val Asp Asn Phe
65 70 75 80

Ile Ser Thr Val Ala Phe Ala Thr Leu Ala Leu Leu Gly Ser Leu Ser
85 90 95

Leu Leu Leu Phe Lys Arg Lys Glu Ser Lys
100 105

<210> 15

<211> 960
<212> PRT
<213> Staphylococcus aureus

<400> 15

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Asp Arg Ile Ile Glu Thr Ala Pro Thr Asp Tyr Leu Ser Trp Gly Val
 1               5                  10                  15

Gly Ala Val Gly Asn Pro Arg Phe Ile Asn Val Glu Ile Val His Thr
            20                  25                  30

His Asp Tyr Ala Ser Phe Ala Arg Ser Met Asn Asn Tyr Ala Asp Tyr
        35                  40                  45

Ala Ala Thr Gln Leu Gln Tyr Tyr Gly Leu Lys Pro Asp Ser Ala Glu
    50                  55                  60

Tyr Asp Gly Asn Gly Thr Val Trp Thr His Tyr Ala Val Ser Lys Tyr
65                  70                  75                  80

Leu Gly Gly Thr Asp His Ala Asp Pro His Gly Tyr Leu Arg Ser His
                85                  90                  95

Asn Tyr Ser Tyr Asp Gln Leu Tyr Asp Leu Ile Asn Glu Lys Tyr Leu
            100                 105                 110

Ile Lys Met Gly Lys Val Ala Pro Trp Gly Thr Gln Ser Thr Thr Thr
        115                 120                 125

Pro Thr Thr Pro Ser Lys Pro Thr Thr Pro Ser Lys Pro Ser Thr Gly
    130                 135                 140

Lys Leu Thr Val Ala Ala Asn Asn Gly Val Ala Gln Ile Lys Pro Thr
145                 150                 155                 160

Asn Ser Gly Leu Tyr Thr Thr Val Tyr Asp Lys Thr Gly Lys Ala Thr
                165                 170                 175

Asn Glu Val Gln Lys Thr Phe Ala Val Ser Lys Thr Ala Thr Leu Gly
            180                 185                 190

Asn Gln Lys Phe Tyr Leu Val Gln Asp Tyr Asn Ser Gly Asn Lys Phe
        195                 200                 205

Gly Trp Val Lys Glu Gly Asp Val Val Tyr Asn Thr Ala Lys Ser Pro
    210                 215                 220

Val Asn Val Asn Gln Ser Tyr Ser Ile Lys Pro Gly Thr Lys Leu Tyr
225                 230                 235                 240

Thr Val Pro Trp Gly Thr Ser Lys Gln Val Ala Gly Ser Val Ser Gly
                245                 250                 255

Ser Gly Asn Gln Thr Phe Lys Ala Ser Lys Gln Gln Gln Ile Asp Lys
            260                 265                 270

Ser Ile Tyr Leu Tyr Gly Ser Val Asn Gly Lys Ser Gly Trp Val Ser
        275                 280                 285

Lys Ala Tyr Leu Val Asp Thr Ala Lys Pro Thr Pro Thr Pro Thr Pro
    290                 295                 300

Lys Pro Ser Thr Pro Thr Thr Asn Asn Lys Leu Thr Val Ser Ser Leu
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305 310 315 320

Asn Gly Val Ala Gln Ile Asn Ala Lys Asn Asn Gly Leu Phe Thr Thr
323 330 335

Val Tyr Asp Lys Thr Gly Lys Pro Thr Lys Glu Val Gln Lys Thr Phe
340 345 350

Ala Val Thr Lys Glu Ala Ser Leu Gly Gly Asn Lys Phe Tyr Leu Val
355 360 365

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

Val Ile Tyr Asn Asn Ala Lys Ser Pro Val Asn Val Met Gln Thr Tyr
385 390 395 400

Thr Val Lys Pro Gly Thr Lys Leu Tyr Ser Val Pro Trp Gly Thr Tyr
405 410 415

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

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

Val Asn Gly Lys Ser Gly Trp Val Ser Lys Ala Tyr Leu Ala Val Pro
450 455 460

Ala Ala Pro Lys Lys Ala Val Ala Gln Pro Lys Thr Ala Val Lys Ala
465 470 475 480

Tyr Thr Val Thr Lys Pro Gln Thr Thr Gln Thr Val Ser Lys Ile Ala
485 490 495

Gln Val Lys Pro Asn Asn Thr Gly Ile Arg Ala Ser Val Tyr Glu Lys
500 505 510

Thr Ala Lys Asn Gly Ala Lys Tyr Ala Asp Arg Thr Phe Tyr Val Thr
515 520 525

Lys Glu Arg Ala His Gly Asn Glu Thr Tyr Val Leu Leu Asn Asn Thr
530 535 540

Ser His Asn Ile Pro Leu Gly Trp Phe Asn Val Lys Asp Leu Asn Val
545 550 555 560

Gln Asn Leu Gly Lys Glu Val Lys Thr Thr Gln Lys Tyr Thr Val Asn
565 570 575

Lys Ser Asn Asn Gly Leu Ser Met Val Pro Trp Gly Thr Lys Asn Gln
580 585 590

Val Ile Leu Thr Gly Asn Asn Ile Ala Gln Gly Thr Phe Asn Ala Thr
595 600 605

Lys Gln Val Ser Val Gly Lys Asp Val Tyr Leu Tyr Gly Thr Ile Asn
610 615 620

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

Val Lys Pro Thr Thr Ser Ala Ala Lys Asp Tyr Asn Tyr Thr Tyr Val

645 650 655

Ile Lys Asn Gly Asn Gly Tyr Tyr Tyr Val Thr Pro Asn Ser Asp Thr
660 665 670

Ala Lys Tyr Ser Leu Lys Ala Phe Asn Glu Gln Pro Phe Ala Val Val
675 680 685

Lys Glu Gln Val Ile Asn Gly Gln Thr Trp Tyr Tyr Gly Lys Leu Ser
690 695 700

Asn Gly Lys Leu Ala Trp Ile Lys Ser Thr Asp Leu Ala Lys Glu Leu
705 710 715 720

Ile Lys Tyr Asn Gln Thr Gly Met Ala Leu Asn Gln Val Ala Gln Ile
725 730 735

Gln Ala Gly Leu Gln Tyr Lys Pro Gln Val Gln Arg Val Pro Gly Lys
740 745 750

Trp Thr Gly Ala Asn Phe Asn Asp Val Lys His Ala Met Asp Thr Lys
755 760 765

Arg Leu Ala Gln Asp Pro Ala Leu Lys Tyr Gln Phe Leu Arg Leu Asp
770 775 780

Gln Pro Gln Asn Ile Ser Ile Asp Lys Ile Asn Gln Phe Leu Lys Gly
785 790 795 800

Lys Gly Val Leu Glu Asn Gln Gly Ala Ala Phe Asn Lys Ala Ala Gln
805 810 815

Met Tyr Gly Ile Asn Glu Val Tyr Leu Ile Ser His Ala Leu Leu Glu
820 825 830

Thr Gly Asn Gly Thr Ser Gln Leu Ala Lys Gly Ala Asp Val Val Asn
835 840 845

Asn Lys Val Val Thr Asn Ser Asn Thr Lys Tyr His Asn Val Phe Gly
850 855 860

Ile Ala Ala Tyr Asp Asn Asp Pro Leu Arg Glu Gly Ile Lys Tyr Ala
865 870 875 880

Lys Gln Ala Gly Trp Asp Thr Val Ser Lys Ala Ile Val Gly Gly Ala
885 890 895

Lys Phe Ile Gly Asn Ser Tyr Val Lys Ala Gly Gln Asn Thr Leu Tyr
900 905 910

Lys Met Arg Trp Asn Pro Ala His Pro Gly Thr His Gln Tyr Ala Thr
915 920 925

Asp Val Asp Trp Ala Asn Ile Asn Ala Lys Ile Ile Lys Gly Tyr Tyr
930 935 940

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

<210> 16
<211> 386
<212> PRT
<213> Staphylococcus aureus

<400> 16

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Asp Gln Tyr Ser Glu Asp Ala Lys Lys Thr Gln Lys Asp Tyr Ala Ser
 1               5                  10                  15

Gln Ser Lys Lys Asp Lys Asn Glu Lys Ser Asn Thr Lys Asn Pro Gln
            20                  25                  30

Leu Pro Thr Gln Asp Glu Leu Lys His Lys Ser Lys Pro Ala Gln Ser
        35                  40                  45

Phe Asn Asn Asp Val Asn Gln Lys Asp Thr Arg Ala Thr Ser Leu Phe
    50                  55                  60

Glu Thr Asp Pro Ser Ile Ser Asn Asn Asp Asp Ser Gly Gln Phe Asn
65                  70                  75                  80

Val Val Asp Ser Lys Asp Thr Arg Gln Phe Val Lys Ser Ile Ala Lys
                85                  90                  95

Asp Ala His Arg Ile Gly Gln Asp Asn Asp Ile Tyr Ala Ser Val Met
            100                 105                 110

Ile Ala Gln Ala Ile Leu Glu Ser Asp Ser Gly Arg Ser Ala Leu Ala
        115                 120                 125

Lys Ser Pro Asn His Asn Leu Phe Gly Ile Lys Gly Ala Phe Glu Gly
    130                 135                 140

Asn Ser Val Pro Phe Asn Thr Leu Glu Ala Asp Gly Asn Gln Leu Tyr
145                 150                 155                 160

Ser Ile Asn Ala Gly Phe Arg Lys Tyr Pro Ser Thr Lys Glu Ser Leu
                165                 170                 175

Lys Asp Tyr Ser Asp Leu Ile Lys Asn Gly Ile Asp Gly Asn Arg Thr
            180                 185                 190

Ile Tyr Lys Pro Thr Trp Lys Ser Glu Ala Asp Ser Tyr Lys Asp Ala
        195                 200                 205

Thr Ser His Leu Ser Lys Thr Tyr Ala Thr Asp Pro Asn Tyr Ala Lys
    210                 215                 220

Lys Leu Asn Ser Ile Ile Lys His Tyr Gln Leu Thr Gln Phe Asp Asp
225                 230                 235                 240

Glu Arg Met Pro Asp Leu Asp Lys Tyr Glu Arg Ser Ile Lys Asp Tyr
                245                 250                 255

Asp Asp Ser Ser Asp Glu Phe Lys Pro Phe Arg Glu Val Ser Asp Ser
            260                 265                 270

Met Pro Tyr Pro His Gly Gln Cys Thr Trp Tyr Val Tyr Asn Arg Met
        275                 280                 285

Lys Gln Phe Gly Thr Ser Ile Ser Gly Asp Leu Gly Asp Ala His Asn
    290                 295                 300
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Trp Asn Asn Arg Ala Gln Tyr Arg Asp Tyr Gln Val Ser His Thr Pro
305                 310                 315                 320

Lys Arg His Ala Ala Val Val Phe Glu Ala Gly Gln Phe Gly Ala Asp
                325                 330                 335

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

Ser Ile Val Ile Ser Glu Ser Asn Val Lys Gly Leu Gly Ile Ile Ser
        355                 360                 365

His Arg Thr Ile Asn Ala Ala Ala Ala Glu Glu Leu Ser Tyr Ile Thr
    370                 375                 380

Gly Lys
385
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<210> 17
<211> 325
<212> PRT
<213> Staphylococcus aureus

<400> 17

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Met Lys Met Asn Lys Leu Val Lys Ser Ser Val Ala Thr Ser Met Ala
  1               5                  10                  15

Leu Leu Leu Leu Ser Gly Thr Ala Asn Ala Glu Gly Lys Ile Thr Pro
            20                  25                  30

Val Ser Val Lys Lys Val Asp Asp Lys Val Thr Leu Tyr Lys Thr Thr
        35                  40                  45

Ala Thr Ala Asp Ser Asp Lys Phe Lys Ile Ser Gln Ile Leu Thr Phe
    50                  55                  60

Asn Phe Ile Lys Asp Lys Ser Tyr Asp Lys Asp Thr Leu Val Leu Lys
65                  70                  75                  80

Ala Thr Gly Asn Ile Asn Ser Gly Phe Val Lys Pro Asn Pro Asn Asp
                85                  90                  95

Tyr Asp Phe Ser Lys Leu Tyr Trp Gly Ala Lys Tyr Asn Val Ser Ile
            100                 105                 110

Ser Ser Gln Ser Asn Asp Ser Val Asn Val Val Asp Tyr Ala Pro Lys
        115                 120                 125

Asn Gln Asn Glu Glu Phe Gln Val Gln Asn Thr Leu Gly Tyr Thr Phe
    130                 135                 140

Gly Gly Asp Ile Ser Ile Ser Asn Gly Leu Ser Gly Gly Leu Asn Gly
145                 150                 155                 160

Asn Thr Ala Phe Ser Glu Thr Ile Asn Tyr Lys Gln Glu Ser Tyr Arg
                165                 170                 175

Thr Thr Leu Ser Arg Asn Thr Asn Tyr Lys Asn Val Gly Trp Gly Val
            180                 185                 190

Glu Ala His Lys Ile Met Asn Asn Gly Trp Gly Pro Tyr Gly Arg Asp
        195                 200                 205
```

Ser Phe His Pro Thr Tyr Gly Asn Glu Leu Phe Leu Ala Gly Arg Gln
210 215 220

Ser Ser Ala Tyr Ala Gly Gln Asn Phe Ile Ala Gln His Gln Met Pro
225 230 235 240

Leu Leu Ser Arg Ser Asn Phe Asn Pro Glu Phe Leu Ser Val Leu Ser
245 250 255

His Arg Gln Asp Gly Ala Lys Lys Ser Lys Ile Thr Val Thr Tyr Gln
260 265 270

Arg Glu Met Asp Leu Tyr Gln Ile Arg Trp Asn Gly Phe Tyr Trp Ala
275 280 285

Gly Ala Asn Tyr Lys Asn Phe Lys Thr Arg Thr Phe Lys Ser Thr Tyr
290 295 300

Glu Ile Asp Trp Glu Asn His Lys Val Lys Leu Leu Asp Thr Lys Glu
305 310 315 320

Thr Glu Asn Asn Lys
325

<210> 18
<211> 157
<212> PRT
<213> Staphylococcus aureus

<400> 18
Ser Phe Asn Tyr Ser Lys Ser Ile Ser Tyr Thr Gln Gln Asn Tyr Val
1 5 10 15

Ser Glu Val Glu Gln Gln Asn Ser Lys Ser Val Leu Trp Gly Val Lys
20 25 30

Ala Asn Ser Phe Ala Thr Glu Ser Gly Gln Lys Ser Ala Phe Asp Ser
35 40 45

Asp Leu Phe Val Gly Tyr Lys Pro His Ser Lys Asp Pro Arg Asp Tyr
50 55 60

Phe Val Pro Asp Ser Glu Leu Pro Pro Leu Val Gln Ser Gly Phe Asn
65 70 75 80

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

Ser Glu Phe Glu Ile Thr Tyr Gly Arg Asn Met Asp Val Thr His Ala
100 105 110

Ile Lys Arg Ser Thr His Tyr Gly Asn Ser Tyr Leu Asp Gly His Arg
115 120 125

Val His Asn Ala Phe Val Asn Arg Asn Tyr Thr Val Lys Tyr Glu Val
130 135 140

Asn Trp Lys Thr His Glu Ile Lys Val Lys Gly Gln Asn
145 150 155

<210> 19
<211> 345
<212> PRT
<213> Staphylococcus aureus

<400> 19
Ile Ile Ala Ile Ile Ile Leu Ile Phe Ile Ser Phe Phe Phe Ser Gly
1 5 10 15

Ser Glu Thr Ala Leu Thr Ala Ala Asn Lys Ala Lys Phe Lys Thr Glu
20 25 30

Ala Asp Lys Gly Asp Lys Lys Ala Lys Gly Ile Val Lys Leu Leu Glu
35 40 45

Lys Pro Ser Glu Phe Ile Thr Thr Ile Leu Ile Gly Asn Asn Val Ala
50 55 60

Asn Ile Leu Leu Pro Thr Leu Val Thr Ile Met Ala Leu Arg Trp Gly
65 70 75 80

Ile Ser Val Gly Ile Ala Ser Ala Val Leu Thr Val Val Ile Ile Leu
85 90 95

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

Ile Thr Arg Leu Val Tyr Pro Ile Ile Asn Ile Cys Val Ile Val Phe
115 120 125

Arg Pro Ile Thr Leu Leu Leu Asn Lys Leu Thr Asp Ser Ile Asn Arg
130 135 140

Ser Leu Ser Lys Gly Gln Pro Gln Glu His Gln Phe Ser Lys Glu Glu
145 150 155 160

Phe Lys Thr Met Leu Ala Ile Ala Gly His Glu Gly Ala Leu Asn Glu
165 170 175

Ile Glu Thr Ser Arg Leu Glu Gly Val Ile Asn Phe Glu Asn Leu Lys
180 185 190

Val Lys Asp Val Asp Thr Thr Pro Arg Ile Asn Val Thr Ala Phe Ala
195 200 205

Ser Asn Ala Thr Tyr Glu Glu Val Tyr Glu Thr Val Met Asn Lys Pro
210 215 220

Tyr Thr Arg Tyr Pro Val Tyr Glu Gly Asp Ile Asp Asn Ile Ile Gly
225 230 235 240

Val Phe His Ser Lys Tyr Leu Leu Ala Trp Ser Asn Lys Lys Glu Asn
245 250 255

Gln Ile Thr Asn Tyr Ser Ala Lys Pro Leu Phe Val Asn Glu His Asn
260 265 270

Lys Ala Glu Trp Val Leu Arg Lys Met Thr Ile Ser Arg Lys His Leu
275 280 285

Ala Ile Val Leu Asp Glu Phe Gly Gly Thr Glu Ala Ile Val Ser His
290 295 300

Glu Asp Leu Ile Glu Glu Leu Leu Gly Met Glu Ile Glu Asp Glu Met
305 310 315 320

Asp Lys Lys Glu Lys Glu Lys Leu Ser Gln Gln Gln Ile Gln Phe Gln
325 330 335

Gln Arg Lys Asn Arg Asn Val Ser Ile
340 345

<210> 20
<211> 133
<212> PRT
<213> Staphylococcus aureus

<400> 20
Met Asn Lys Gln Gln Lys Glu Phe Lys Ser Phe Tyr Ser Ile Arg Lys
1 5 10 15

Ser Ser Leu Gly Val Ala Ser Val Ala Ile Ser Thr Leu Leu Leu Leu
20 25 30

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

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

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

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

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

Pro Ala Ala Lys Ala Thr Asn Asn Thr Tyr Pro Ile Leu Asn Gln Glu
115 120 125

Leu Ile Arg Ser Asp
130

<210> 21
<211> 205
<212> PRT
<213> Staphylococcus aureus

<400> 21
Asp His Gly Ile Val Phe Asn Ala Ser Leu Pro Leu Tyr Lys Asp Ala
1 5 10 15

Ile His Gln Lys Gly Ser Met Arg Ser Asn Asp Asn Gly Asp Asp Met
20 25 30

Ser Met Met Val Gly Thr Val Leu Ser Gly Phe Glu Tyr Arg Ala Gln
35 40 45

Lys Glu Lys Tyr Asp Asn Leu Tyr Lys Phe Phe Lys Glu Asn Glu Lys
50 55 60

Lys Tyr Gln Tyr Thr Gly Phe Thr Lys Glu Ala Ile Asn Lys Thr Gln

65 70 75 80

Asn Val Gly Tyr Lys Asn Glu Tyr Phe Tyr Ile Thr Tyr Ser Ser Arg
85 90 95

Ser Leu Lys Glu Tyr Arg Lys Tyr Tyr Glu Pro Leu Ile Arg Lys Asn
100 105 110

Asp Lys Glu Phe Lys Glu Gly Met Glu Arg Ala Arg Lys Glu Val Asn
115 120 125

Tyr Ala Ala Asn Thr Asp Ala Val Ala Thr Leu Phe Ser Thr Lys Lys
130 135 140

Asn Phe Thr Lys Asp Asn Thr Val Asp Asp Val Ile Glu Leu Ser Asp
145 150 155 160

Lys Leu Tyr Asn Leu Lys Asn Lys Pro Asp Lys Ser Thr Ile Thr Ile
165 170 175

Gln Ile Gly Lys Pro Thr Ile Asn Thr Lys Lys Ala Phe Tyr Asp Asp
180 185 190

Asn Arg Pro Ile Glu Tyr Gly Val His Ser Lys Asp Glu
195 200 205

<210> 22
<211> 510
<212> PRT
<213> Staphylococcus aureus

<400> 22
Asp His Tyr Val Ile Gln Tyr Phe Ser Gly Leu Ile Gly Gly Arg Gly
1 5 10 15

Arg Arg Ala Asn Leu Tyr Gly Leu Phe Asn Lys Ala Ile Glu Phe Glu
20 25 30

Asn Ser Ser Phe Arg Gly Leu Tyr Gln Phe Ile Arg Phe Ile Asp Glu
35 40 45

Leu Ile Glu Arg Gly Lys Asp Phe Gly Glu Glu Asn Val Val Gly Pro
50 55 60

Asn Asp Asn Val Val Arg Met Met Thr Ile His Ser Ser Lys Gly Leu
65 70 75 80

Glu Phe Pro Phe Val Ile Tyr Ser Gly Leu Ser Lys Asp Phe Asn Lys
85 90 95

Arg Asp Leu Lys Gln Pro Val Ile Leu Asn Gln Gln Phe Gly Leu Gly
100 105 110

Met Asp Tyr Phe Asp Val Asp Lys Glu Met Ala Phe Pro Ser Leu Ala
115 120 125

Ser Val Ala Tyr Arg Ala Val Ala Glu Lys Glu Leu Val Ser Glu Glu
130 135 140

Met Arg Leu Val Tyr Val Ala Leu Thr Arg Ala Lys Glu Gln Leu Tyr
145 150 155 160

Leu Ile Gly Arg Val Lys Asn Asp Lys Ser Leu Leu Glu Leu Glu Gln
165 170 175

Leu Ser Ile Ser Gly Glu His Ile Ala Val Asn Glu Arg Leu Thr Ser
180 185 190

Pro Asn Pro Phe His Leu Ile Tyr Ser Ile Leu Ser Lys His Gln Ser
195 200 205

Ala Ser Ile Pro Asp Asp Leu Lys Phe Glu Lys Asp Ile Ala Gln Ile
210 215 220

Glu Asp Ser Ser Arg Pro Asn Val Asn Ile Ser Ile Val Tyr Phe Glu
225 230 235 240

Asp Val Ser Thr Glu Thr Ile Leu Asp Asn Asp Glu Tyr Arg Ser Val
245 250 255

Asn Gln Leu Glu Thr Met Gln Asn Gly Asn Glu Asp Val Lys Ala Gln
260 265 270

Ile Lys His Gln Leu Asp Tyr Arg Tyr Pro Tyr Val Asn Asp Thr Lys
275 280 285

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

Glu Glu Ser Gly Thr Ser Tyr Glu Arg Val Arg Gln Tyr Arg Ile Gly
305 310 315 320

Phe Ser Thr Tyr Glu Arg Pro Lys Phe Leu Ser Glu Gln Gly Lys Arg
325 330 335

Lys Ala Asn Glu Ile Gly Thr Leu Met His Thr Val Met Gln His Leu
340 345 350

Pro Phe Lys Lys Glu Arg Ile Ser Glu Val Glu Leu His Gln Tyr Ile
355 360 365

Asp Gly Leu Ile Asp Lys His Ile Ile Glu Ala Asp Ala Lys Lys Asp
370 375 380

Ile Arg Met Asp Glu Ile Met Thr Phe Ile Asn Ser Glu Leu Tyr Ser
385 390 395 400

Ile Ile Ala Glu Ala Glu Gln Val Tyr Arg Glu Leu Pro Phe Val Val
405 410 415

Asn Gln Ala Leu Val Asp Gln Leu Pro Gln Gly Asp Glu Asp Val Ser
420 425 430

Ile Ile Gln Gly Met Ile Asp Leu Ile Phe Val Lys Asp Gly Val His
435 440 445

Tyr Phe Val Asp Tyr Lys Thr Asp Ala Phe Asn Arg Arg Arg Gly Met
450 455 460

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

Met Lys Tyr Tyr Gln Asn Thr Leu Gln Thr Ile Leu Asn Lys Glu Val
485 490 495

Lys Gly Tyr Leu Tyr Phe Phe Lys Phe Gly Thr Leu Gln Leu
500 505 510

<210> 23
<211> 124
<212> PRT
<213> Staphylococcus aureus

<400> 23
Met Lys Phe Leu Ser Phe Lys Tyr Asn Asp Lys Thr Ser Tyr Gly Val
1 5 10 15

Lys Val Lys Arg Glu Asp Ala Val Trp Asp Leu Thr Gln Val Phe Ala
20 25 30

Asp Phe Ala Glu Gly Asp Phe His Pro Lys Thr Leu Leu Ala Gly Leu
35 40 45

Gln Gln Asn His Thr Leu Asp Phe Gln Glu Gln Val Arg Lys Ala Val
50 55 60

Val Ala Ala Glu Asp Ser Gly Lys Ala Glu Asp Tyr Lys Ile Ser Phe
65 70 75 80

Asn Asp Ile Glu Phe Leu Pro Pro Val Thr Pro Pro Asn Asn Val Ile
85 90 95

Ala Phe Gly Arg Asn Tyr Lys Asp His Ala Asn Glu Leu Asn His Glu
100 105 110

Val Glu Lys Leu Tyr Val Phe Thr Lys Ala Ala Ser
115 120

<210> 24
<211> 180
<212> PRT
<213> Staphylococcus aureus

<400> 24
Ser Gly Thr Gly Phe Ile Val Gly Lys Asn Thr Ile Val Thr Asn Lys
1 5 10 15

His Val Val Ala Gly Met Glu Ile Gly Ala His Ile Ile Ala His Pro
20 25 30

Asn Gly Glu Tyr Asn Asn Gly Gly Phe Tyr Lys Val Lys Lys Ile Val
35 40 45

Arg Tyr Ser Gly Gln Glu Asp Ile Ala Ile Leu His Val Glu Asp Lys
50 55 60

Ala Val His Pro Lys Asn Arg Asn Phe Lys Asp Tyr Thr Gly Ile Leu
65 70 75 80

Lys Ile Ala Ser Glu Ala Lys Glu Asn Glu Arg Ile Ser Ile Val Gly
85 90 95

Tyr Pro Glu Pro Tyr Ile Asn Lys Phe Gln Met Tyr Glu Ser Thr Gly
100 105 110

Lys Val Leu Ser Val Lys Gly Asn Met Ile Ile Thr Asp Ala Phe Val

```
          115                 120                 125

Glu Pro Gly Asn Ser Gly Ser Ala Val Phe Asn Ser Lys Tyr Glu Val
    130                 135                 140

Val Gly Val His Phe Gly Gly Asn Gly Pro Gly Asn Lys Ser Thr Lys
145                 150                 155                 160

Gly Tyr Gly Val Tyr Phe Ser Pro Glu Ile Lys Lys Phe Ile Ala Asp
                165                 170                 175

Asn Thr Asp Lys
            180
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<210> 25
<211> 239
<212> PRT
<213> Staphylococcus aureus

<400> 25

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Met Asn Lys Asn Ile Ile Ile Lys Ser Ile Ala Ala Leu Thr Ile Leu
  1               5                  10                  15

Thr Ser Ile Thr Gly Val Gly Thr Thr Met Val Glu Gly Ile Gln Gln
            20                  25                  30

Thr Ala Lys Ala Glu Asn Thr Val Lys Gln Ile Thr Asn Thr Asn Val
        35                  40                  45

Ala Pro Tyr Ser Gly Val Thr Trp Met Gly Ala Gly Thr Gly Phe Val
    50                  55                  60

Val Gly Asn His Thr Ile Ile Thr Asn Lys His Val Thr Tyr His Met
65                  70                  75                  80

Lys Val Gly Asp Glu Ile Lys Ala His Pro Asn Gly Phe Tyr Asn Asn
                85                  90                  95

Gly Gly Gly Leu Tyr Lys Val Thr Lys Ile Val Asp Tyr Pro Gly Lys
            100                 105                 110

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

Gly Arg Lys Phe Lys Asp Phe Thr Ser Lys Phe Asn Ile Ala Ser Glu
    130                 135                 140

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

Gly Asn Lys Leu Gln Met Tyr Glu Ser Thr Gly Lys Val Leu Ser Val
                165                 170                 175

Asn Gly Asn Ile Val Ser Ser Asp Ala Ile Ile Gln Pro Gly Ser Ser
            180                 185                 190

Gly Ser Pro Ile Leu Asn Ser Lys His Glu Ala Ile Gly Val Ile Tyr
        195                 200                 205

Ala Gly Asn Lys Pro Ser Gly Glu Ser Thr Arg Gly Phe Ala Val Tyr
    210                 215                 220
```

Phe Ser Pro Glu Ile Lys Lys Phe Ile Ala Asp Asn Leu Asp Lys
225 230 235

<210> 26
<211> 470
<212> PRT
<213> Staphylococcus aureus

<400> 26
Met Gly Cys Thr Val Lys Met Asn Lys Ile Asn Asp Arg Asp Leu Thr
1 5 10 15

Glu Leu Ser Ser Tyr Trp Val Tyr Gln Asn Ile Asp Ile Lys Lys Glu
20 25 30

Phe Lys Val Asn Gly Lys Arg Phe Lys Gln Val Asp Ser Tyr Asn Asp
35 40 45

Asp Lys Asn Ser Asn Leu Asn Gly Ala Ala Asp Ile Lys Ile Tyr Glu
50 55 60

Leu Leu Asp Asp Lys Ser Lys Pro Thr Gly Gln Gln Thr Ile Ile Tyr
65 70 75 80

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

Ser Gly Phe Gly Asp Asp Trp Leu Gln Asn Ala Lys Leu Met Asn Asn
100 105 110

Asp Asn Glu Ser Thr Asp Tyr Leu Lys Gln Thr Asp Gln Leu Ser Asn
115 120 125

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

Phe Leu Lys Lys Tyr Arg Met Glu Ser Ser Asn Phe Lys Asn Lys Thr
145 150 155 160

Ile Val Ala Asp Gly Gly Asn Ser Glu Gly Gly Ala Gly Ala Lys Tyr
165 170 175

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

Met Ile Pro Tyr Ala Ala Trp Gln Lys Phe Ala Arg Pro Arg Phe Asp
195 200 205

Asn Met Ile Ser Phe Asn Ser Thr Asn Asp Leu Leu Thr Trp Leu Gln
210 215 220

Asp Pro Phe Ile Lys Asp Met Pro Gly Lys Arg Val Asn Ile Asn Asp
225 230 235 240

Gly Val Pro Arg Leu Asp Thr Leu Ile Asp Ser His Val Gly Tyr Lys
245 250 255

Arg Lys Leu Asn Arg Lys Asp Asn Thr Tyr Asp Thr Val Pro Leu Ile
260 265 270

Lys Ile Lys Ser Val Lys Asp Thr Glu Ile Lys Asn Gly Lys Lys Val
275 280 285

Lys Lys Thr Ile Asn Ile Thr Leu Asp Met Asp Gly Arg Ile Pro Ile
290 295 300

Asn Val Trp Thr Gly Asp Ser Ile Ala Arg Ser Gly Arg Gly Thr Leu
305 310 315 320

Ile Lys Leu Asn Leu Glu Asn Leu Asp Ala Leu Ser Lys Leu Ile Thr
325 330 335

Gly Glu Thr Ser Gly Met Leu Ala Glu Cys Val Ile Phe Leu Asn Glu
340 345 350

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

Lys Gln Leu Ser Glu Gly Phe Lys Asp Lys Ile Asn Leu Phe Gln Leu
370 375 380

Glu Glu Met Glu Arg Thr Leu Ile Ser Lys Ile Asn Ser Leu Glu Glu
385 390 395 400

Val Ala Asp Glu Thr Ile Glu Ser Ile Ser Ala Val Lys His Leu Leu
405 410 415

Pro Asp Phe Ala Leu Asp Ala Leu Lys Glu Arg Ile Asn Glu Leu Phe
420 425 430

Lys Gly Ile Lys Ser Phe Ile Glu Lys Val Tyr Asp Ser Ile Asp Asn
435 440 445

Glu Ile Leu Glu Ile Phe Lys Asn Ile Asp His Asp Phe Arg Asp Gly
450 455 460

Val Ser Glu Glu Met Met
465 470

<210> 27
<211> 306
<212> PRT
<213> Staphylococcus aureus

<400> 27
Met Lys Lys Lys Asp Gly Thr Gln Gln Phe Tyr His Tyr Ala Ser Ser
1 5 10 15

Val Lys Pro Ala Arg Val Ile Phe Thr Asp Ser Lys Pro Glu Ile Glu
20 25 30

Leu Gly Leu Gln Ser Gly Gln Phe Trp Arg Lys Phe Glu Val Tyr Glu
35 40 45

Gly Asp Lys Lys Leu Pro Ile Lys Leu Val Ser Tyr Asp Thr Val Lys
50 55 60

Asp Tyr Ala Tyr Ile Arg Phe Ser Val Ser Asn Gly Thr Lys Ala Val
65 70 75 80

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

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

100 105 110

Phe Lys Thr Glu Glu Asp Tyr Lys Ala Glu Lys Leu Leu Ala Pro Tyr
115 120 125

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

Gln Asp Lys Leu Pro Glu Lys Leu Lys Ala Glu Tyr Lys Lys Lys Leu
145 150 155 160

Glu Asp Thr Lys Lys Ala Leu Asp Glu Gln Val Lys Ser Ala Ile Thr
165 170 175

Glu Phe Gln Asn Val Gln Pro Thr Asn Glu Lys Met Thr Asp Leu Gln
180 185 190

Asp Thr Lys Tyr Val Val Tyr Glu Ser Val Glu Asn Asn Glu Ser Met
195 200 205

Met Asp Thr Phe Val Lys His Pro Ile Lys Thr Gly Met Leu Asn Gly
210 215 220

Lys Lys Tyr Met Val Met Glu Thr Thr Asn Asp Asp Tyr Trp Lys Asp
225 230 235 240

Phe Met Val Glu Gly Gln Arg Val Arg Thr Ile Ser Lys Asp Ala Lys
245 250 255

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

Tyr Asp Ala Ile Val Lys Val His Val Lys Thr Ile Asp Tyr Asp Gly
275 280 285

Gln Tyr His Val Arg Ile Val Asp Lys Glu Ala Phe Thr Lys Ala His
290 295 300

Thr Asp
305

<210> 28
<211> 2659
<212> PRT
<213> Staphylococcus aureus

<400> 28
Asp Gln Thr Thr Ile Ile Asn Ser Leu Thr Phe Thr Glu Thr Val Pro
1 5 10 15

Asn Arg Ser Tyr Ala Arg Ala Ser Ala Asn Glu Ile Thr Ser Lys Thr
20 25 30

Val Ser Asn Val Ser Arg Thr Gly Asn Asn Ala Asn Val Thr Val Thr
35 40 45

Val Thr Tyr Gln Asp Gly Thr Thr Ser Thr Val Thr Val Pro Val Lys
50 55 60

His Val Ile Pro Glu Ile Val Ala His Ser His Tyr Thr Val Glu Gly
65 70 75 80

Gln Asp Phe Pro Ala Gly Asn Gly Ser Ser Ala Ser Asp Tyr Phe Lys
85 90 95

Leu Ser Asn Gly Ser Asp Ile Ala Asp Ala Thr Ile Thr Trp Val Ser
100 105 110

Gly Gln Ala Pro Asn Lys Asp Asn Thr Arg Ile Gly Glu Asp Ile Thr
115 120 125

Val Thr Ala His Ile Leu Ile Asp Gly Glu Thr Thr Pro Ile Thr Lys
130 135 140

Thr Ala Thr Tyr Lys Val Val Arg Thr Val Pro Lys His Val Phe Glu
145 150 155 160

Thr Ala Arg Gly Val Leu Tyr Pro Gly Val Ser Asp Met Tyr Asp Ala
165 170 175

Lys Gln Tyr Val Lys Pro Val Asn Asn Ser Trp Ser Thr Asn Ala Gln
180 185 190

His Met Asn Phe Gln Phe Val Gly Thr Tyr Gly Pro Asn Lys Asp Val
195 200 205

Val Gly Ile Ser Thr Arg Leu Ile Arg Val Thr Tyr Asp Asn Arg Gln
210 215 220

Thr Glu Asp Leu Thr Ile Leu Ser Lys Val Lys Pro Asp Pro Pro Arg
225 230 235 240

Ile Asp Ala Asn Ser Val Thr Tyr Lys Ala Gly Leu Thr Asn Gln Glu
245 250 255

Ile Lys Val Asn Asn Val Leu Asn Asn Ser Ser Val Lys Leu Phe Lys
260 265 270

Ala Asp Asn Thr Pro Leu Asn Val Thr Asn Ile Thr His Gly Ser Gly
275 280 285

Phe Ser Ser Val Val Thr Val Ser Asp Ala Leu Pro Asn Gly Gly Ile
290 295 300

Lys Ala Lys Ser Ser Ile Ser Met Asn Asn Val Thr Tyr Thr Thr Gln
305 310 315 320

Asp Glu His Gly Gln Val Val Thr Val Thr Arg Asn Glu Ser Val Asp
325 330 335

Ser Asn Asp Ser Ala Thr Val Thr Val Thr Pro Gln Leu Gln Ala Thr
340 345 350

Thr Glu Gly Ala Val Phe Ile Lys Gly Gly Asp Gly Phe Asp Phe Gly
355 360 365

His Val Glu Arg Phe Ile Gln Asn Pro Pro His Gly Ala Thr Val Ala
370 375 380

Trp His Asp Ser Pro Asp Thr Trp Lys Asn Thr Val Gly Asn Thr His
385 390 395 400

Lys Thr Ala Val Val Thr Leu Pro Asn Gly Gln Gly Thr Arg Asn Val
405 410 415

Glu Val Pro Val Lys Val Tyr Pro Val Ala Asn Ala Lys Ala Pro Ser
420 425 430

Arg Asp Val Lys Gly Gln Asn Leu Thr Asn Gly Thr Asp Ala Met Asn
435 440 445

Tyr Ile Thr Phe Asp Pro Asn Thr Asn Thr Asn Gly Ile Thr Ala Ala
450 455 460

Trp Ala Asn Arg Gln Gln Pro Asn Asn Gln Gln Ala Gly Val Gln His
465 470 475 480

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

Pro Val Thr Val Asn Val Tyr Gln Phe Glu Phe Pro Gln Thr Thr Tyr
500 505 510

Thr Thr Thr Val Gly Gly Thr Leu Ala Ser Gly Thr Gln Ala Ser Gly
515 520 525

Tyr Ala His Met Gln Asn Ala Thr Gly Leu Pro Thr Asp Gly Phe Thr
530 535 540

Tyr Lys Trp Asn Arg Asp Thr Thr Gly Thr Asn Asp Ala Asn Trp Ser
545 550 555 560

Ala Met Asn Lys Pro Asn Val Ala Lys Val Val Asn Ala Lys Tyr Asp
565 570 575

Val Ile Tyr Asn Gly His Thr Phe Ala Thr Ser Leu Pro Ala Lys Phe
580 585 590

Val Val Lys Asp Val Gln Pro Ala Lys Pro Thr Val Thr Glu Thr Ala
595 600 605

Ala Gly Ala Ile Thr Ile Ala Pro Gly Ala Asn Gln Thr Val Asn Thr
610 615 620

His Ala Gly Asn Val Thr Thr Tyr Ala Asp Lys Leu Val Ile Lys Arg
625 630 635 640

Asn Gly Asn Val Val Thr Thr Phe Thr Arg Arg Asn Asn Thr Ser Pro
645 650 655

Trp Val Lys Glu Ala Ser Ala Ala Thr Val Ala Gly Ile Ala Gly Thr
660 665 670

Asn Asn Gly Ile Thr Val Ala Ala Gly Thr Phe Asn Pro Ala Asp Thr
675 680 685

Ile Gln Val Val Ala Thr Gln Gly Ser Gly Glu Thr Val Ser Asp Glu
690 695 700

Gln Arg Ser Asp Asp Phe Thr Val Val Ala Pro Gln Pro Asn Gln Ala
705 710 715 720

Thr Thr Lys Ile Trp Gln Asn Gly His Ile Asp Ile Thr Pro Asn Asn
725 730 735

Pro Ser Gly His Leu Ile Asn Pro Thr Gln Ala Met Asp Ile Ala Tyr
740 745 750

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Thr Glu Lys Val Gly Asn Gly Ala Glu His Ser Lys Thr Ile Asn Val
        755                 760                 765

Val Arg Gly Gln Asn Asn Gln Trp Thr Ile Ala Asn Lys Pro Asp Tyr
    770                 775                 780

Val Thr Leu Asp Ala Gln Thr Gly Lys Val Thr Phe Asn Ala Asn Thr
785                 790                 795                 800

Ile Lys Pro Asn Ser Ser Ile Thr Ile Thr Pro Lys Ala Gly Thr Gly
                805                 810                 815

His Ser Val Ser Ser Asn Pro Ser Thr Leu Thr Ala Pro Ala Ala His
            820                 825                 830

Thr Val Asn Thr Thr Glu Ile Val Lys Asp Tyr Gly Ser Asn Val Thr
        835                 840                 845

Ala Ala Glu Ile Asn Asn Ala Val Gln Val Ala Asn Lys Arg Thr Ala
    850                 855                 860

Thr Ile Lys Asn Gly Thr Ala Met Pro Thr Asn Leu Ala Gly Gly Ser
865                 870                 875                 880

Thr Thr Thr Ile Pro Val Thr Val Thr Tyr Asn Asp Gly Ser Thr Glu
                885                 890                 895

Glu Val Gln Glu Ser Ile Phe Thr Lys Ala Asp Lys Arg Glu Leu Ile
            900                 905                 910

Thr Ala Lys Asn His Leu Asp Asp Pro Val Ser Thr Glu Gly Lys Lys
        915                 920                 925

Pro Gly Thr Ile Thr Gln Tyr Asn Asn Ala Met His Asn Ala Gln Gln
    930                 935                 940

Gln Ile Asn Thr Ala Lys Thr Glu Ala Gln Gln Val Ile Asn Asn Glu
945                 950                 955                 960

Arg Ala Thr Pro Gln Gln Val Ser Asp Ala Leu Thr Lys Val Arg Ala
                965                 970                 975

Ala Gln Thr Lys Ile Asp Gln Ala Lys Ala Leu Leu Gln Asn Lys Glu
            980                 985                 990

Asp Asn Ser Gln Leu Val Thr Ser Lys Asn Asn Leu Gln Ser Ser Val
        995                1000                1005

Asn Gln Val Pro Ser Thr Ala Gly Met Thr Gln Gln Ser Ile Asp Asn
   1010                1015                1020

Tyr Asn Ala Lys Lys Arg Glu Ala Glu Thr Glu Ile Thr Ala Ala Gln
1025                1030                1035                1040

Arg Val Ile Asp Asn Gly Asp Ala Thr Ala Gln Gln Ile Ser Asp Glu
                1045                1050                1055

Lys His Arg Val Asp Asn Ala Leu Thr Ala Leu Asn Gln Ala Lys His
            1060                1065                1070

Asp Leu Thr Ala Asp Thr His Ala Leu Glu Gln Ala Val Gln Gln Leu
        1075                1080                1085
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Asn Arg Thr Gly Thr Thr Thr Gly Lys Lys Pro Ala Ser Ile Thr Ala
1090 1095 1100

Tyr Asn Asn Ser Ile Arg Ala Leu Gln Ser Asp Leu Thr Ser Ala Lys
1105 1110 1115 1120

Asn Ser Ala Asn Ala Ile Ile Gln Lys Pro Ile Arg Thr Val Glu Glu
1125 1130 1135

Val Gln Ser Ala Leu Thr Asn Val Asn Arg Val Asn Glu Arg Leu Thr
1140 1145 1150

Gln Ala Ile Asn Gln Leu Val Pro Leu Ala Asp Asn Ser Ala Leu Lys
1155 1160 1165

Thr Ala Lys Thr Lys Leu Asp Glu Glu Ile Asn Lys Ser Val Thr Thr
1170 1175 1180

Asp Gly Met Thr Gln Ser Ser Ile Gln Ala Tyr Glu Asn Ala Lys Arg
1185 1190 1195 1200

Ala Gly Gln Thr Glu Ser Thr Asn Ala Gln Asn Val Ile Asn Asn Gly
1205 1210 1215

Asp Ala Thr Asp Gln Gln Ile Ala Ala Glu Lys Thr Lys Val Glu Glu
1220 1225 1230

Lys Tyr Asn Ser Leu Lys Gln Ala Ile Ala Gly Leu Thr Pro Asp Leu
1235 1240 1245

Ala Pro Leu Gln Thr Ala Lys Thr Gln Leu Gln Asn Asp Ile Asp Gln
1250 1255 1260

Pro Thr Ser Thr Thr Gly Met Thr Ser Ala Ser Ile Ala Ala Phe Asn
1265 1270 1275 1280

Glu Lys Leu Ser Ala Ala Arg Thr Lys Ile Gln Glu Ile Asp Arg Val
1285 1290 1295

Leu Ala Ser His Pro Asp Val Ala Thr Ile Arg Gln Asn Val Thr Ala
1300 1305 1310

Ala Asn Ala Ala Lys Ser Ala Leu Asp Gln Ala Arg Asn Gly Leu Thr
1315 1320 1325

Val Asp Lys Ala Pro Leu Glu Asn Ala Lys Asn Gln Leu Gln Tyr Ser
1330 1335 1340

Ile Asp Thr Gln Thr Ser Thr Thr Gly Met Thr Gln Asp Ser Ile Asn
1345 1350 1355 1360

Ala Tyr Asn Ala Lys Leu Thr Ala Ala Arg Asn Lys Ile Gln Gln Ile
1365 1370 1375

Asn Gln Val Leu Ala Gly Ser Pro Thr Val Glu Gln Ile Asn Thr Asn
1380 1385 1390

Thr Ser Thr Ala Asn Gln Ala Lys Ser Asp Leu Asp His Ala Arg Gln
1395 1400 1405

Ala Leu Thr Pro Asp Lys Ala Pro Leu Gln Thr Ala Lys Thr Gln Leu
1410 1415 1420

Glu Gln Ser Ile Asn Gln Pro Thr Asp Thr Thr Gly Met Thr Thr Ala
1425 1430 1435 1440

Ser Leu Asn Ala Tyr Asn Gln Lys Leu Glu Ala Ala Arg Gln Lys Leu
1445 1450 1455

Thr Glu Ile Asn Gln Val Leu Asn Gly Asn Pro Thr Val Gln Asn Ile
1460 1465 1470

Asn Asp Lys Val Thr Glu Ala Asn Gln Ala Lys Asp Gln Leu Asn Thr
1475 1480 1485

Ala Arg Gln Gly Leu Thr Leu Asp Arg Gln Pro Ala Leu Thr Thr Leu
1490 1495 1500

His Gly Ala Ser Asn Leu Asn Gln Ala Gln Gln Asn Asn Phe Thr Gln
1505 1510 1515 1520

Gln Ile Asn Ala Ala Gln Asn His Ala Ala Leu Glu Thr Ile Lys Ser
1525 1530 1535

Asn Ile Thr Ala Leu Asn Thr Ala Met Thr Lys Leu Lys Asp Ser Val
1540 1545 1550

Ala Asp Asn Asn Thr Ile Lys Ser Asp Gln Asn Tyr Thr Asp Ala Thr
1555 1560 1565

Pro Ala Asn Lys Gln Ala Tyr Asp Asn Ala Val Asn Ala Ala Lys Gly
1570 1575 1580

Val Ile Gly Glu Thr Thr Asn Pro Thr Met Asp Val Asn Thr Val Asn
1585 1590 1595 1600

Gln Lys Ala Ala Ser Val Lys Ser Thr Lys Asp Ala Leu Asp Gly Gln
1605 1610 1615

Gln Asn Leu Gln Arg Ala Lys Thr Glu Ala Thr Asn Ala Ile Thr His
1620 1625 1630

Ala Ser Asp Leu Asn Gln Ala Gln Lys Asn Ala Leu Thr Gln Gln Val
1635 1640 1645

Asn Ser Ala Gln Asn Val Gln Ala Val Asn Asp Ile Lys Gln Thr Thr
1650 1655 1660

Gln Ser Leu Asn Thr Ala Met Thr Gly Leu Lys Arg Gly Val Ala Asn
1665 1670 1675 1680

His Asn Gln Val Val Gln Ser Asp Asn Tyr Val Asn Ala Asp Thr Asn
1685 1690 1695

Lys Lys Asn Asp Tyr Asn Asn Ala Tyr Asn His Ala Asn Asp Ile Ile
1700 1705 1710

Asn Gly Asn Ala Gln His Pro Val Ile Thr Pro Ser Asp Val Asn Asn
1715 1720 1725

Ala Leu Ser Asn Val Thr Ser Lys Glu His Ala Leu Asn Gly Glu Ala
1730 1735 1740

Lys Leu Asn Ala Ala Lys Gln Glu Ala Asn Thr Ala Leu Gly His Leu
1745 1750 1755 1760

Asn Asn Leu Asn Asn Ala Gln Arg Gln Asn Leu Gln Ser Glu Ile Asn
1765 1770 1775

Gly Ala His Gln Ile Asp Ala Val Asn Thr Ile Lys Gln Asn Ala Thr
1780 1785 1790

Asn Leu Asn Ser Ala Met Gly Asn Leu Arg Gln Ala Val Ala Asp Lys
1795 1800 1805

Asp Gln Val Lys Arg Thr Glu Asp Tyr Ala Asp Ala Asp Thr Ala Lys
1810 1815 1820

Gln Asn Ala Tyr Asn Ser Ala Val Ser Ser Ala Glu Thr Ile Ile Asn
1825 1830 1835 1840

Gln Thr Thr Asn Pro Thr Met Ser Val Asp Asp Val Asn Arg Ala Thr
1845 1850 1855

Ser Ala Val Thr Ser Asn Lys Asn Ala Leu Asn Gly Tyr Glu Lys Leu
1860 1865 1870

Ala Gln Ser Lys Thr Asp Ala Ala Arg Ala Ile Asp Ala Leu Pro His
1875 1880 1885

Leu Asn Asn Ala Gln Lys Ala Asp Val Lys Ser Lys Ile Asn Ala Ala
1890 1895 1900

Ser Asn Ile Ala Gly Val Asn Thr Val Lys Gln Gln Gly Thr Asp Leu
1905 1910 1915 1920

Asn Thr Ala Met Gly Asn Leu Gln Gly Ala Ile Asn Asp Glu Gln Thr
1925 1930 1935

Thr Leu Asn Ser Gln Asn Tyr Gln Asp Ala Thr Pro Ser Lys Lys Thr
1940 1945 1950

Ala Tyr Thr Asn Ala Val Gln Ala Ala Lys Asp Ile Leu Asn Lys Ser
1955 1960 1965

Asn Gly Gln Asn Lys Thr Lys Asp Gln Val Thr Glu Ala Met Asn Gln
1970 1975 1980

Val Asn Ser Ala Lys Asn Asn Leu Asp Gly Thr Arg Leu Leu Asp Gln
1985 1990 1995 2000

Ala Lys Gln Thr Ala Lys Gln Gln Leu Asn Asn Met Thr His Leu Thr
2005 2010 2015

Thr Ala Gln Lys Thr Asn Leu Thr Asn Gln Ile Asn Ser Gly Thr Thr
2020 2025 2030

Val Ala Gly Val Gln Thr Val Gln Ser Asn Ala Asn Thr Leu Asp Gln
2035 2040 2045

Ala Met Asn Thr Leu Arg Gln Ser Ile Ala Asn Lys Asp Ala Thr Lys
2050 2055 2060

Ala Ser Glu Asp Tyr Val Asp Ala Asn Asn Asp Lys Gln Thr Ala Tyr
2065 2070 2075 2080

Asn Asn Ala Val Ala Ala Ala Glu Thr Ile Ile Asn Ala Asn Ser Asn
2085 2090 2095

Pro Glu Met Asn Pro Ser Thr Ile Thr Gln Lys Ala Glu Gln Val Asn
2100 2105 2110

Ser Ser Lys Thr Ala Leu Asn Gly Asp Glu Asn Leu Ala Ala Ala Lys
2115 2120 2125

Gln Asn Ala Lys Thr Tyr Leu Asn Thr Leu Thr Ser Ile Thr Asp Ala
2130 2135 2140

Gln Lys Asn Asn Leu Ile Ser Gln Ile Thr Ser Ala Thr Arg Val Ser
2145 2150 2155 2160

Gly Val Asp Thr Val Lys Gln Asn Ala Gln His Leu Asp Gln Ala Met
2165 2170 2175

Ala Ser Leu Gln Asn Gly Ile Asn Asn Glu Ser Gln Val Lys Ser Ser
2180 2185 2190

Glu Lys Tyr Arg Asp Ala Asp Thr Asn Lys Gln Gln Glu Tyr Asp Asn
2195 2200 2205

Ala Ile Thr Ala Ala Lys Ala Ile Leu Asn Lys Ser Thr Gly Pro Asn
2210 2215 2220

Thr Ala Gln Asn Ala Val Glu Ala Ala Leu Gln Arg Val Asn Asn Ala
2225 2230 2235 2240

Lys Asp Ala Leu Asn Gly Asp Ala Lys Leu Ile Ala Ala Gln Asn Ala
2245 2250 2255

Ala Lys Gln His Leu Gly Thr Leu Thr His Ile Thr Thr Ala Gln Arg
2260 2265 2270

Asn Asp Leu Thr Asn Gln Ile Ser Gln Ala Thr Asn Leu Ala Gly Val
2275 2280 2285

Glu Ser Val Lys Gln Asn Ala Asn Ser Leu Asp Gly Ala Met Gly Asn
2290 2295 2300

Leu Gln Thr Ala Ile Asn Asp Lys Ser Gly Thr Leu Ala Ser Gln Asn
2305 2310 2315 2320

Phe Leu Asp Ala Asp Glu Gln Lys Arg Asn Ala Tyr Asn Gln Ala Val
2325 2330 2335

Ser Ala Ala Glu Thr Ile Leu Asn Lys Gln Thr Gly Pro Asn Thr Ala
2340 2345 2350

Lys Thr Ala Val Glu Gln Ala Leu Asn Asn Val Asn Asn Ala Lys His
2355 2360 2365

Ala Leu Asn Gly Thr Gln Asn Leu Asn Asn Ala Lys Gln Ala Ala Ile
2370 2375 2380

Thr Ala Ile Asn Gly Ala Ser Asp Leu Asn Gln Lys Gln Lys Asp Ala
2385 2390 2395 2400

Leu Lys Ala Gln Ala Asn Gly Ala Gln Arg Val Ser Asn Ala Gln Asp
2405 2410 2415

Val Gln His Asn Ala Thr Glu Leu Asn Thr Ala Met Gly Thr Leu Lys
2420 2425 2430

His Ala Ile Ala Asp Lys Thr Asn Thr Leu Ala Ser Ser Lys Tyr Val
2435 2440 2445

Asn Ala Asp Ser Thr Lys Gln Asn Ala Tyr Thr Thr Lys Val Thr Asn
2450 2455 2460

Ala Glu His Ile Ile Ser Gly Thr Pro Thr Val Val Thr Thr Pro Ser
2465 2470 2475 2480

Glu Val Thr Ala Ala Ala Asn Gln Val Asn Ser Ala Lys Gln Glu Leu
2485 2490 2495

Asn Gly Asp Glu Arg Leu Arg Glu Ala Lys Gln Asn Ala Asn Thr Ala
2500 2505 2510

Ile Asp Ala Leu Thr Gln Leu Asn Thr Pro Gln Lys Ala Lys Leu Lys
2515 2520 2525

Glu Gln Val Gly Gln Ala Asn Arg Leu Glu Asp Val Gln Thr Val Gln
2530 2535 2540

Thr Asn Gly Gln Ala Leu Asn Asn Ala Met Lys Gly Leu Arg Asp Ser
2545 2550 2555 2560

Ile Ala Asn Glu Thr Thr Val Lys Thr Ser Gln Asn Tyr Thr Asp Ala
2565 2570 2575

Ser Pro Asn Asn Gln Ser Thr Tyr Asn Ser Ala Val Ser Asn Ala Lys
2580 2585 2590

Gly Ile Ile Asn Gln Thr Asn Asn Pro Thr Met Asp Thr Ser Ala Ile
2595 2600 2605

Thr Gln Ala Thr Thr Gln Val Asn Asn Ala Lys Asn Gly Leu Asn Gly
2610 2615 2620

Ala Glu Asn Leu Arg Asn Ala Gln Asn Thr Ala Lys Gln Asn Leu Asn
2625 2630 2635 2640

Thr Leu Ser His Leu Thr Asn Asn Gln Lys Ser Ala Ile Ser Ser Gln
2645 2650 2655

Ile Asp Arg

<210> 29
<211> 496
<212> PRT
<213> Staphylococcus aureus

<400> 29
Met Asn Met Lys Lys Lys Glu Lys His Ala Ile Arg Lys Lys Ser Ile
1 5 10 15

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

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

Ser Ala Ser Asn Glu Ser Lys Ser Asn Asp Ser Ser Ser Val Ser Ala
50 55 60

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

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

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

Val Thr Gly Glu Ala Thr Thr Thr Thr Thr Asn Gln Ala Asn Thr Pro
        115                 120                 125

Ala Thr Thr Gln Ser Ser Asn Thr Asn Ala Glu Glu Leu Val Asn Gln
    130                 135                 140

Thr Ser Asn Glu Thr Thr Phe Asn Asp Thr Asn Thr Val Ser Ser Val
145                 150                 155                 160

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

Asp Thr Ser Thr Glu Ala Thr Pro Ser Asn Asn Glu Ser Ala Pro Gln
            180                 185                 190

Ser Thr Asp Ala Ser Asn Lys Asp Val Val Asn Gln Ala Val Asn Thr
        195                 200                 205

Ser Ala Pro Arg Met Arg Ala Phe Ser Leu Ala Ala Val Ala Ala Asp
    210                 215                 220

Ala Pro Ala Ala Gly Thr Asp Ile Thr Asn Gln Leu Thr Asn Val Thr
225                 230                 235                 240

Val Gly Ile Asp Ser Gly Thr Thr Val Tyr Pro His Gln Ala Gly Tyr
                245                 250                 255

Val Lys Leu Asn Tyr Gly Phe Ser Val Pro Asn Ser Ala Val Lys Gly
            260                 265                 270

Asp Thr Phe Lys Ile Thr Val Pro Lys Glu Leu Asn Leu Asn Gly Val
        275                 280                 285

Thr Ser Thr Ala Lys Val Pro Pro Ile Met Ala Gly Asp Gln Val Leu
    290                 295                 300

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

Asp Tyr Val Asn Thr Lys Asp Asp Val Lys Ala Thr Leu Thr Met Pro
                325                 330                 335

Ala Tyr Ile Asp Pro Glu Asn Val Lys Lys Thr Gly Asn Val Thr Leu
            340                 345                 350

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

Tyr Glu Lys Tyr Gly Lys Phe Tyr Asn Leu Ser Ile Lys Gly Thr Ile
    370                 375                 380

Asp Gln Ile Asp Lys Thr Asn Asn Thr Tyr Arg Gln Thr Ile Tyr Val
385                 390                 395                 400
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Asn Pro Ser Gly Asp Asn Val Ile Ala Pro Val Leu Thr Gly Asn Leu
405 410 415

Lys Pro Asn Thr Asp Ser Asn Ala Leu Ile Asp Gln Gln Asn Thr Ser
420 425 430

Ile Lys Val Tyr Lys Val Asp Asn Ala Ala Asp Leu Ser Glu Ser Tyr
435 440 445

Phe Val Asn Pro Glu Asn Phe Glu Asp Val Thr Asn Ser Val Asn Ile
450 455 460

Thr Phe Pro Asn Pro Asn Gln Tyr Lys Val Glu Phe Asn Thr Pro Asp
465 470 475 480

Asp Gln Ile Thr Thr Pro Tyr Ile Val Val Asn Gly His Ile Asp
485 490 495

<210> 30
<211> 541
<212> PRT
<213> Staphylococcus aureus

<400> 30
Asp Gln Tyr Leu Leu Glu Arg Lys Lys Ser Gln Tyr Glu Asp Tyr Lys
1 5 10 15

Gln Trp Tyr Ala Asn Tyr Lys Lys Glu Asn Pro Arg Thr Asp Leu Lys
20 25 30

Met Ala Asn Phe His Lys Tyr Asn Leu Glu Glu Leu Ser Met Lys Glu
35 40 45

Tyr Asn Glu Leu Gln Asp Ala Leu Lys Arg Ala Leu Asp Asp Phe His
50 55 60

Arg Glu Val Lys Asp Ile Lys Asp Lys Asn Ser Asp Leu Lys Thr Phe
65 70 75 80

Asn Ala Ala Glu Glu Asp Lys Ala Thr Lys Glu Val Tyr Asp Leu Val
85 90 95

Ser Glu Ile Asp Thr Leu Val Val Ser Tyr Tyr Gly Asp Lys Asp Tyr
100 105 110

Gly Glu His Ala Lys Glu Leu Arg Ala Lys Leu Asp Ile Leu Gly
115 120 125

Asp Thr Asp Asn Pro His Lys Ile Thr Asn Glu Arg Ile Lys Lys Glu
130 135 140

Met Ile Asp Asp Leu Asn Ser Ile Ile Asp Asp Phe Phe Met Glu Thr
145 150 155 160

Lys Gln Asn Arg Pro Lys Ser Ile Thr Lys Tyr Asn Pro Thr Thr His
165 170 175

Asn Tyr Lys Thr Asn Ser Asp Asn Lys Pro Asn Phe Asp Lys Leu Val

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                180                 185                 190
Glu Glu Thr Lys Lys Ala Val Lys Glu Ala Asp Asp Ser Trp Lys Lys
        195                 200                 205
Lys Thr Val Lys Lys Tyr Gly Glu Thr Glu Thr Lys Ser Pro Val Val
    210                 215                 220
Lys Glu Glu Lys Lys Val Glu Glu Pro Gln Ala Pro Lys Val Asp Asn
225                 230                 235                 240
Gln Gln Glu Val Lys Thr Thr Ala Gly Lys Ala Glu Glu Thr Thr Gln
                245                 250                 255
Pro Val Ala Gln Pro Leu Val Lys Ile Pro Gln Gly Thr Ile Thr Gly
            260                 265                 270
Glu Ile Val Lys Gly Pro Glu Tyr Pro Thr Met Glu Asn Lys Thr Val
        275                 280                 285
Gln Gly Glu Ile Val Gln Gly Pro Asp Phe Leu Thr Met Glu Gln Ser
    290                 295                 300
Gly Pro Ser Leu Ser Asn Asn Tyr Thr Asn Pro Pro Leu Thr Asn Pro
305                 310                 315                 320
Ile Leu Glu Gly Leu Glu Gly Ser Ser Ser Lys Leu Glu Ile Lys Pro
                325                 330                 335
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Asp Ala Gly Thr Gly Ile Arg Glu Tyr Asn Asp Gly Thr Phe Gly Tyr
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Leu Ala Met Ile Asn Ile Thr Ala Gly Ala Asn Ser Ala Thr Thr Gln
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Ala Ala Asn Thr Arg Gln Glu Arg Thr Pro Lys Leu Glu Lys Ala Pro
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Asn Thr Asn Glu Glu Lys Thr Ser Ala Ser Lys Ile Glu Lys Ile Ser
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Tyr Asp Asn Ile Asp Val Phe Ile Val Leu Glu Asp Asn Lys Tyr Gln
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His Asn Leu Tyr Gly Asn Met Gly Ser Gly Thr Ile Val Ile Lys Met
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Thr Pro Pro Ser Thr Lys Ile Glu Ala Pro Gln Ser Lys Pro Asn Ala
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Thr Thr Pro Pro Ser Thr Lys Val Glu Ala Pro Gln Gln Thr Ala Asn
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Ala Thr Thr Pro Pro Ser Thr Lys Val Thr Thr Pro Pro Ser Thr Asn
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Arg Ala Tyr Tyr Thr Lys Pro Ser Leu Glu Phe Lys Asn Glu Ile Gly
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Ile Ile Leu Lys Lys Trp Thr Thr Ile Arg Phe Met Asn Val Val Pro
145 150 155 160

Asp Tyr Phe Ile Tyr Lys Ile Ala Leu Val Gly Lys Asp Asp Lys Lys
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Thr Lys Glu Gln Ile Ser Leu Lys Glu Leu Asp Phe Lys Leu Arg Lys
                245                 250                 255
Gln Leu Ile Glu Lys Asn Asn Leu Tyr Gly Asn Val Gly Ser Gly Lys
            260                 265                 270
Ile Val Ile Lys Met Lys Asn Gly Gly Lys Tyr Thr Phe Glu Leu His
        275                 280                 285
Lys Lys Leu Gln Glu Asn Arg Met Ala Asp Val Ile Asp Gly Thr Asn
    290                 295                 300
Ile Asp Asn Ile Glu Val Asn Ile Lys
305                 310
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【国際調査報告】

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/02685

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/31 C12N15/63 G01N33/68 C07K14/31 A61K39/085
C07K16/12 C12N5/12 A61K39/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBL, WPI Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ARIFUR RAHMAN ET AL.: "Gamma-Hemolysin genes in the same family with LukF and LukS genes in methicillin resistant Staphylococcus aureus" BIOSCIENCE BIOTECHNOLOGY BIOCHEMISTRY., vol. 57, no. 7, 1993, pages 1234-1236, XP002177747 TOKYO JP the whole document ---	1-9, 18-48
A	WO 99 50418 A (NEUTEC PHARMA PLC) 7 October 1999 (1999-10-07) the whole document -----	1-9, 18-49

☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.

* Special categories of cited documents :
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2001	19. 11. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MONTERO LOPEZ B.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/02685

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-32 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Partially 1-9, 18-49

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially 1-9, 18-49

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:1, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

2. Claims: Partially 1-9, 18-49

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:2, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

3. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:3, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

4. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:4, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

5. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:5, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

6. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:6, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

7. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:7, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

8. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:8, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

9. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

SEQ ID NO:9, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

10. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:10, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

11. Claims: Partially 1-9, 18-48

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:11, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

12. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:12, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

13. Claims: Partially 1-9, 19-46

Staphylococcus aureus antigen encoded by a DNA sequence of SEQ ID NO:13, DNA sequence and variants thereof; vectors and host cells comprising the same and their use for the production of the polypeptide; vaccine comprising the

INTERNATIONAL SEARCH REPORT

International Application No. PCT/GB 01/02685

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

antigen and its use in immunisation; antibodies directed to the antigen and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament; use of the polypeptides for preparing a hybridoma cell-line.

14. Claims: 10-17, and partially 24-46

Method to identify antigenic polypeptides by transfecting a pathogenic organism gene library into a host cell and contacting the expressed polypeptides with autologous antisera from an animal infected with the pathogenic organism; polypeptides so obtained, vaccines comprising the antigenic polypeptides and use in immunisation; antibodies directed to the antigenic polypeptides and vectors and hybridoma cells for their production; use of the antibodies for the manufacture of a medicament.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International Application No
PCT/GB 01/02685

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9950418 A	07-10-1999	AU 3156699 A	18-10-1999
		EP 1068328 A1	17-01-2001
		WO 9950418 A1	07-10-1999

Form PCT/ISA/210 (patent family annex) (July 1992)

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Ｃ０７Ｋ 16/12	Ｃ０７Ｋ 16/12		
Ｃ０７Ｋ 16/46	Ｃ０７Ｋ 16/46		
Ｃ０７Ｋ 19/00	Ｃ０７Ｋ 19/00		
Ｃ１２Ｎ 1/15	Ｃ１２Ｎ 1/15		
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Ｃ１２Ｎ 1/21	Ｃ１２Ｎ 1/21		
Ｃ１２Ｎ 5/10	Ｃ１２Ｐ 21/02	Ｃ	
Ｃ１２Ｐ 21/02	Ｇ０１Ｎ 33/15	Ｚ	
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Ｇ０１Ｎ 33/569	Ｇ０１Ｎ 33/569	Ｂ	
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	Ｃ１２Ｎ 5/00	Ｂ	
	Ｃ１２Ｐ 21/08		

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,UA,UG,US,UZ,VN,YU,ZA,ZW

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(72)発明者 ブラメル, カースティー
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Ｆターム(参考) 2G045 AA34 AA35 AA40 BA11 BB50 DA12 DA13 DA14 DA36 FB02 FB03
4B024 AA01 AA11 BA31 BA41 CA02 DA06 EA03 GA11 HA01 HA14
4B064 AG27 AG31 CA10 CA19 CA20 CC24 DA01 DA13
4B065 AA26X AA53Y AB01 BA02 BA08 CA24 CA25 CA44 CA46
4C085 AA03 AA14 AA16 BA13 BB11 CC07 CC23 CC32 DD06 DD62

DD63 EE06 GG02 GG03 GG04 GG08
4H045 AA10 AA11 AA20 AA30 BA10 BA41 CA11 DA76 DA86 EA20
EA50 FA74

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申请号	JP2002504647	申请日	2001-06-20
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发明人	フォスター, サイモン マックドウェル, フィリップ ブラメル, カースティー クラーク, サイモン		
IPC分类号	G01N33/50 A61K39/00 A61K39/085 A61K39/395 A61P9/00 A61P31/04 C07K14/195 C07K14/31 C07K16/12 C07K16/46 C07K19/00 C12N1/15 C12N1/19 C12N1/21 C12N5/02 C12N5/10 C12N15/02 C12N15/31 C12P21/02 C12P21/08 G01N33/15 G01N33/53 G01N33/569		
CPC分类号	A61K39/00 A61K2039/505 A61P1/00 A61P1/04 A61P11/00 A61P17/00 A61P17/02 C07K14/31 C07K16/12 Y02A50/401 Y02A50/476		
FI分类号	C12N15/00.ZNA.C A61K39/085 A61K39/395.R A61P9/00 A61P31/04 C07K14/195 C07K16/12 C07K16/46 C07K19/00 C12N1/15 C12N1/19 C12N1/21 C12P21/02.C G01N33/15.Z G01N33/50.Z G01N33/53.D G01N33/53.M G01N33/569.B C12N5/00.A C12N5/00.B C12P21/08		
F-TERM分类号	2G045/AA34 2G045/AA35 2G045/AA40 2G045/BA11 2G045/BB50 2G045/DA12 2G045/DA13 2G045/DA14 2G045/DA36 2G045/FB02 2G045/FB03 4B024/AA01 4B024/AA11 4B024/BA31 4B024/BA41 4B024/CA02 4B024/DA06 4B024/EA03 4B024/GA11 4B024/HA01 4B024/HA14 4B064/AG27 4B064/AG31 4B064/CA10 4B064/CA19 4B064/CA20 4B064/CC24 4B064/DA01 4B064/DA13 4B065/AA26X 4B065/AA53Y 4B065/AB01 4B065/BA02 4B065/BA08 4B065/CA24 4B065/CA25 4B065/CA44 4B065/CA46 4C085/AA03 4C085/AA14 4C085/AA16 4C085/BA13 4C085/BB11 4C085/CC07 4C085/CC23 4C085/CC32 4C085/DD06 4C085/DD62 4C085/DD63 4C085/EE06 4C085/GG02 4C085/GG03 4C085/GG04 4C085/GG08 4H045/AA10 4H045/AA11 4H045/AA20 4H045/AA30 4H045/BA10 4H045/BA41 4H045/CA11 4H045/DA76 4H045/DA86 4H045/EA20 4H045/EA50 4H045/FA74		
代理人(译)	夏木森下		
优先权	2000014907 2000-06-20 GB		
外部链接	Espacenet		

摘要(译)

本发明涉及用于鉴定由病原微生物表达的抗原性多肽的方法；包含该多肽的疫苗；用于生产该多肽的重组方法；以及针对该多肽的治疗性抗体。 。 在本发明的另一方面，本发明提供了由分离的核酸分子编码的多肽，其中所述核酸分子是：（i）SEQ ID NO：1-13所示的DNA序列； ii）与上述（i）中鉴定的SEQ ID NOs：1-13中所示的序列杂交的DNA序列，其编码由病原生物表达的多肽;（iii）（i）和（ii） A）由于遗传密码而相对于下面定义的DNA序列简并的DNA序列，并用作疫苗。

微生物	引き起こされる疾患
Staphylococcus aureus	セプシス、食中毒、敗血症
Staphylococcus epidermidis	腹膜炎、敗血症、心内膜炎、他の病院関連疾患 (hospital-associated disease)
Enterococcus faecalis	心内膜炎、膀胱炎、創傷感染
Mycobacterium tuberculosis	結核
Streptococcus group B	セプシス、髄膜炎、肺炎、膀胱感染
Streptococcus pneumoniae	肺炎、髄膜炎
Helicobacter pylori	胃潰瘍
Neisseria gonorrhoea	淋病
Streptococcus group A	連鎖球菌性咽喉炎 、壊死性筋膜炎、膿痂疹、連鎖球菌性中毒性ショック症候群
Borrelia burgdoferi	ライム病
Coccidiodes immitis	肺炎
Histoplasma sapsulatum	ヒストプラスマ症、肺炎
Neisseria meningitidis type B	髄膜炎
Shigella flexneri	胃腸炎、細菌性赤痢、赤痢
Escherichia coli	食中毒、胃腸炎
Haemophilus influenzae	髄膜炎、肺炎、関節炎、蜂巣炎