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(54) 【発明の名称】 抗菌性ワクチン組成物

(57) 【要約】

グラム陰性細菌の病原性遺伝子を同定し、それによってこれらの病原性遺伝子およびその産物を標的とする新規な抗菌剤を同定することが可能となる。また、ワクチンに有用な新規なグラム陰性細菌突然変異体を提供する。

【特許請求の範囲】

【請求項 1】

配列番号：1、3、7、9、21、25、27、29、39、41、51、53、55、57、58、60、68、72、74、76、78、80、82、84、104、108、112、116、118、120、122、124、126、128、および130のいずれか1に記載のヌクレオチド配列またはその種ホモログによって表される遺伝子に突然変異を含み、ここに該突然変異が突然変異遺伝子によってコードされる遺伝子産物の活性の低下を生じるグラム陰性細菌。

【請求項 2】

該突然変異が、突然変異遺伝子によってコードされる遺伝子産物の発現の低下を生じる請求項1に記載のグラム陰性細菌。 10

【請求項 3】

該突然変異が、突然変異遺伝子によってコードされる不活性遺伝子産物の発現を生じる請求項1記載のグラム陰性細菌。

【請求項 4】

該突然変異が該遺伝子の全部または一部分の欠失を生じる請求項1記載のグラム陰性細菌。

【請求項 5】

配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のいずれか1に記載のヌクレオチド配列またはその種ホモログによって表される遺伝子に突然変異を含み、ここに該突然変異が突然変異遺伝子によってコードされる遺伝子産物の活性の低下を生じる弱毒化パスツレラ科細菌。 20

【請求項 6】

該突然変異が、突然変異遺伝子によってコードされる遺伝子産物の発現の低下を生じる請求項5記載のパスツレラ科細菌。 30

【請求項 7】

該突然変異が、突然変異遺伝子によってコードされる不活性遺伝子産物の発現を生じる請求項5記載のパスツレラ科細菌。

【請求項 8】

該突然変異が、該遺伝子の全部または一部分の欠失を生じる請求項5記載のパスツレラ科細菌。

【請求項 9】

パスツレラ（マンハイミア）ヘモリティカ（*Pasteurella (Mannheimia) haemolytica*）、パスツレラ・マルトシーダ（*Pasteurella multocida*）、アクチノバチルス・プレウロニユーモニエ（*Actinobacillus pleuropneumoniae*）およびヘモフィルス・ソムナス（*Haemophilus somnus*）よりなる群から選択される請求項5記載のパスツレラ科細菌。 40

【請求項 10】

該突然変異が、突然変異遺伝子によってコードされる遺伝子産物の発現の低下を生じる請求項9記載のパスツレラ科細菌。

【請求項 11】

該突然変異が、突然変異遺伝子によってコードされる不活性遺伝子産物の発現を生じる請求項9記載のパスツレラ科細菌。

【請求項 12】

該突然変異が、該遺伝子の全部または一部分の欠失を生じる請求項9記載のパスツレラ科 50

細菌。

【請求項 13】

*P. multocida*細菌である請求項9記載の弱毒化パストレラ科細菌。

【請求項 14】

該突然変異が、突然変異遺伝子によってコードされる遺伝子産物の発現の低下を生じる請求項13記載のパストレラ科細菌。

【請求項 15】

該突然変異が、突然変異遺伝子によってコードされる不活性遺伝子産物の発現を生じる請求項13記載のパストレラ科細菌。

【請求項 16】

該突然変異が、該遺伝子の全部または一部分の欠失を生じる請求項13記載のパストレラ科細菌。

【請求項 17】

*A. pleuropneumoniae*細菌である請求項9記載の弱毒化パストレラ科細菌。

【請求項 18】

該突然変異が、突然変異遺伝子によってコードされる遺伝子産物の発現の低下を生じる請求項17記載のパストレラ科細菌。

【請求項 19】

該突然変異が、突然変異遺伝子によってコードされる不活性遺伝子産物の発現を生じる請求項17記載のパストレラ科細菌。

【請求項 20】

該突然変異が、該遺伝子の全部または一部分の欠失を生じる請求項17記載のパストレラ科細菌。

【請求項 21】

請求項1ないし20いずれか1項記載の細菌を含む免疫原性組成物。

【請求項 22】

請求項21記載の免疫原性組成物および医薬上許容し得る担体を含むワクチン組成物。

【請求項 23】

さらに、アジュバントを含む請求項22記載のワクチン組成物。

【請求項 24】

配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のいずれか1に記載のヌクレオチド配列またはその種ホモログによって表される遺伝子に突然変異を導入する工程を含み、ここに該突然変異が突然変異遺伝子によってコードされる遺伝子産物の活性の低下を生じることを特徴とするグラム陰性細菌突然変異体を作成する方法。

【請求項 25】

配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のいずれか1に記載のヌクレオチド配列またはその種ホモログによって表される遺伝子に突然変異を導入する工程を含み、ここに該突然変異が突然変異遺伝子によってコードされる遺伝子産物の活性の低下を生じること

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を特徴とする弱毒化パスツレラ科細菌を作成する方法。

【請求項 26】

配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174に記載のヌクレオチド配列よりなる群から選択されるヌクレオチド配列を含む単離および精製されたパスツレラ科細菌のポリヌクレオチド。 10

【請求項 27】

配列番号：1、3、7、9、21、25、27、29、39、41、51、53、55、57、58、60、68、72、74、76、78、80、82、84、104、108、112、116、118、120、122、124、126、128、および130に記載のヌクレオチド配列よりなる群から選択されるヌクレオチド配列を含む単離および精製されたパスツレラ科細菌のポリヌクレオチド。

【請求項 28】

a) 請求項 27 記載のポリヌクレオチド、
b) (a) のポリヌクレオチドによってコードされるポリペプチドをコードするポリヌクレオチド、および
c) 中程度のストリンジェンシーの条件下で (a) または (b) のポリヌクレオチドの相補体にハイブリダイズするポリヌクレオチド
よりなる群から選択されるパスツレラ科細菌の病原性遺伝子の産物またはその種ホモログをコードする単離および精製されたポリヌクレオチド。 20

【請求項 29】

配列番号：2、4、8、10、12、14、16、18、20、22、24、26、30、32、34、38、40、42、52、54、56、59、61、69、71、73、75、77、79、81、83、85、101、103、105、107、109、111、113、115、117、119、121、123、125、127、129、131、133、135、137、139、141、143、145、147、149、151、153、155、157、159、161、165、167、169、171、173、および175に記載のアミノ酸配列を有するポリペプチドよりなる群から選択されるポリペプチドをコードする精製および単離されたパスツレラ科細菌のポリヌクレオチド。 30

【請求項 30】

DNAである請求項 29 記載のポリヌクレオチド。

【請求項 31】

請求項 30 記載の DNA を含むベクター。

【請求項 32】

DNA が発現制御 DNA 配列に制御可能に連結された発現ベクターである請求項 31 記載のベクター。 40

【請求項 33】

宿主細胞におけるコードされたポリペプチドの発現を許容するように請求項 30 記載の DNA で安定に形質転換またはトランスフェクトされた宿主細胞。

【請求項 34】

栄養培地中で請求項 33 記載の宿主細胞を培養し、ついで該宿主細胞または該栄養培地からコードされたポリペプチドを単離することを含む組換えポリペプチドを作製する方法。

【請求項 35】

請求項 34 記載の方法によって作製した精製されたポリペプチド。

【請求項 36】

配列番号：2、4、8、10、12、14、16、18、20、22、24、26、30、32、34、38、40、42、52、54、56、59、61、69、71、73、75、77、79、81、83、85、101、103、105、107、109、111、113、115、117、119、121、123、125、127、129、131、133、135、137、139、141、143、145、147、149、151、153、155、157、159、161、165、167、169、171、173、および175に記載のアミノ酸配列を有するポリペプチドよりなる群から選択されるポリペプチドを含む精製されたポリペプチド。

【請求項37】

請求項36記載のポリペプチドと特異的に反応性である抗体。

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【請求項38】

モノクローナル抗体である請求項37記載の抗体。

【請求項39】

請求項1、5、9または13記載の細菌の抽出物と請求項38記載のモノクローナル抗体とを接触させ、ついで該モノクローナル抗体の結合の不存在を検出する工程を含む該細菌を同定するための該抗体の使用法。

【請求項40】

配列番号：2、4、8、10、12、14、16、18、20、22、24、26、30、32、34、38、40、42、52、54、56、59、61、69、71、73、75、77、79、81、83、85、101、103、105、107、109、111、113、115、117、119、121、123、125、127、129、131、133、135、137、139、141、143、145、147、149、151、153、155、157、159、161、165、167、169、171、173、および175のいずれか1に記載のアミノ酸配列によって表される遺伝子産物の発現または活性に干渉する能力について潜在的な剤をアッセイし、ついで該遺伝子産物の発現または活性に干渉する剤を同定する工程を含む抗菌剤を同定する方法。

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【請求項41】

a) 配列番号：2、4、8、10、12、14、16、18、20、22、24、26、30、32、34、38、40、42、52、54、56、59、61、69、71、73、75、77、79、81、83、85、101、103、105、107、109、111、113、115、117、119、121、123、125、127、129、131、133、135、137、139、141、143、145、147、149、151、153、155、157、159、161、165、167、169、171、173、および175に記載の遺伝子産物の発現または活性を測定し；

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b) (a) の遺伝子産物と試験化合物とを接触させ；

c) 試験化合物の存在下における遺伝子産物の発現または活性を測定し；ついで

d) 試験化合物の不存在下の発現または活性と比較して試験化合物の存在下では遺伝子産物の発現または活性が低下する場合に、試験化合物を抗菌剤として同定する

工程を含む抗菌剤を同定する方法。

【発明の詳細な説明】

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【技術分野】

【0001】

本願は、1999年9月10日に出願された米国仮特許出願番号60/153,453号および1999年4月9日に出願された米国仮特許出願60/128,689号の優先権を主張して2000年4月6日に出願された米国特許出願番号09/545,199号の一部継続出願である。

【0002】

本発明は、一般的に、パストレラ科細菌の病原性に寄与している遺伝子の同定に関し、それによって、ワクチンに有用な新規な弱毒化突然変異株の生成ならびに病原性遺伝子およびその産物を標的とする新しい抗菌剤の同定が可能となる。

【背景技術】

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【0003】

パスツレラ科細菌には、広範な種々の動物に感染する幾つかの非常に重要な病原菌が包含される。パスツレラ・マルトシーダ (*P. multocida*) に加えて、その科の重要なメンバーには、パスツレラ (マンハイミア) ・ヘモリチカ (*Pasteurella (Mannheimia) haemolytica*)、アクチノバチルス・プレウロニューモニア (*Actinobacillus pleuropneumoniae*) およびヘモフィルス・ソムナス (*Haemophilus somnus*) が含まれる。*P. multocida*は、グラム陰性の非運動性の球桿菌であり、それは多くの野生動物および家畜動物の正常細菌叢で見出され、世界中の多数の動物種において疾患を引き起こすことが知られている [M. Kilian, W. Frederickson および E. L. Biberstein (編), *Haemophilus, Pasteurella, and Actinobacillus*. Academic Press, London における Biberstein, 61-73 (1981)]。感染に続く疾患の発現には、敗血症、気管支肺炎、鼻炎および創傷感染症が含まれる [C. L. Gyles および C. O. Thoen (編), *Pathogenesis of Bacterial Infections in Animals*. Iowa State University Press, Ames における Shewen ら, 216-225 (1993) (出典明示して本明細書の一部とみなす) に概説されている]。 10

【0004】

*P. multocida*による感染は、一般的には、ストレスの期間の侵入に起因するが、エアロゾルまたは接触曝露による伝播も生じ得、あるいはノミおよびマダニ媒介体によっても生じ得る。家禽においては、*P. multocida*感染症は、急性ないし過急性の敗血症を生じ、特に、混雑する、産卵、換羽、または厳しい気候変動に関連したストレス条件下の国内産七面鳥および野生の水鳥において特に流行する。ウシにおいては、感染につづいて同様の出血性敗血症が発現し、高熱および鬱病を含む症状を発現し、一般的には、続いて短期に死亡する。伝播はエアロゾル接触を最も起るようであるが、感染症は顕著な気候変動の期間にも発生し得る。ウサギにおいては、感染症は、再発性化膿性鼻炎に続いて、一般的には、結膜炎、中耳炎、副鼻腔炎、皮下膿瘍および慢性気管支肺炎を生じる。重篤な感染症においては、急性の線維索性気管支肺炎、敗血症または内毒素血症によってウサギの死亡率が上昇する。疾患状態は通常ストレスの期間に発生する。ブタにおいては、普通の *P. multocida* 疾患状態には、萎縮性鼻炎および細菌性肺炎が含まれる。また、同様の肺炎の症状は、イヌ、ネコ、ヤギおよびヒツジにおいても検出される。*P. multocida*は多くの動物の口腔細菌叢において一般的に検出され、したがって、噛み傷および掻き傷における一般的な汚染菌である。 20 30

【0005】

*P. multocida*株は、莢膜血清群および菌体血清型によって通常指定される。5の莢膜血清群 (A、B、D、E および F) および 16の菌体血清型が、特徴的な高温安定性の抗原の発現によって区別されている。大部分の菌株は宿主特異的であって、1または2を超える動物には滅多に感染しない。伝統的な死滅全細胞細菌は通常、血清型特異的な保護しか提供しないので、異なる血清型が存在することは免疫接種に対する問題を示す。しかしながら、1の血清型での自然感染が複数の血清型に対する免疫学的保護に通じ得ること [C. L. Gyles および C. O. Thoen (編), *Pathogenesis of Bacterial Infections in Animals*. Iowa State University Press, Ames における Shewen ら, 216-225 (1993)]、交差保護がイン・ビボ (in vivo) で増殖させた不活化細菌を用いることによって刺激し得る [R. Immler ら, *Am J Vet Res.* 42: 2117-2121 (1981)] が実証されている。1の生きている自然発生突然変異 *P. multocida*株はワクチンとして利用されており、強力な免疫応答を刺激することが示されている [Davis, *Poultry Digest.* 20: 430-434 (1987)、Schlink ら, *Avian Dis.* 31 (1): 13-21 (1987)]。しかしながら、この弱毒化株は、ワクチン受容者がストレスに曝された場合に、病原性状態に戻るまたは死亡を引き起こすことが示されている [Davis, *Poultry Digest.* 20: 430-434 (1987)、Schlink ら, *Avian Dis.* 31 (1): 13-21 (1987)]。 40

【0006】

パスツレラ科のもう1のメンバーである *A. pleuropneumoniae*は、ブタに対して厳密な宿主特異性を示し、高度に伝染性のブタの胸膜肺炎の原因因子である。感染は、通常、集中 50

的な育種状態で発生し、直接様式の伝播によって起ると考えられる。疾患が致死命的で、その結果、ブタ生産産業において重大な経済的損害に通じる場合もある。*A. pleuropneumoniae*感染症は、慢性また急性であり得、感染症は線維素性胸膜炎を伴う出血性の壊死性気管支肺炎によって特徴付けられる。現在までのところ、細菌の病原性は、血清型特異的な莢膜多糖、リポ多糖を含めた構造タンパク質、および表面タンパク質、ならびに細胞外細胞溶解性毒素に起因している。これらの病原性因子が精製され、幾つかの例においてはクローニングされているにもかかわらず、*A. pleuropneumoniae*感染症におけるこれらの病原性因子の正確な役割についてほとんど理解されていない。

【0007】

12の血清型の*A. pleuropneumoniae*が莢膜多糖における抗原性の差異および細胞外毒素の産生に基づいて同定されている。血清型1、2、5、7および9はヨーロッパにおいて優勢であるが、血清型1、5および7は、米国における*A. pleuropneumoniae*感染症に最も関連している。溶血素ファミリーのメンバーであり、RTX毒素と呼ばれる*A. pleuropneumoniae*の少なくとも3の重要な細胞外毒素が存在する。RTX毒素は、イー・コリ (*E. coli*)、プロテウス・ブルガリリサ (*Proteus vulgaris*) およびパスツレラ・ヘモリティカ (*Pasteurella haemolytica*) を含む多くのグラム陰性菌によって産生され、該タンパク質は一般的には構造的および機能的な特徴を共有している。しかしながら、様々な血清型からの毒素は、宿主特異性、標的細胞および生物活性においては異なる。

【0008】

主要な*A. pleuropneumoniae*のRTX毒素には、ApxI、ApxIIおよびApxIIIが含まれる。ApxIおよびApxIIは溶血活性を有しているが、ApxIの方がより強力である。ApxIIIは溶血活性を示さないが、肺胞マクロファージおよび好中球に対して細胞毒性である。大部分の*A. pleuropneumoniae*血清型は、これらの3の毒素のうち2を産生する。例えば、血清型1、5、9および11はApxIおよびApxIIを発現し、血清型2、3、4、6および8はApxIIおよびApxIIIを発現する。しかしながら、血清型10はApxIしか産生せず、血清型7および12はApxIIしか発現しない。ApxIおよびApxIIを共に産生するそれらの*A. pleuropneumoniae*血清型は、最も病原性の細菌株である。

【0009】

Apx毒素は、ランダムに突然変異した野生型細菌を用いて、げっ歯類モデルおよびブタ感染における病原性因子であることが実証されている [Tasconら, *Mol. Microbiol.* 14: 207-216 (1994)]。また、他の*A. pleuropneumoniae*突然変異体も、AopA外膜病原性タンパク質をコードする遺伝子を不活化するために標的化突然変異を用いて生成されている [MullisおよびBuysee, *Gene* 165: 61-66 (1995)]。

【0010】

新生児、離乳後の、生長しているおよび成体の子ヒツジ、子ウシおよびヤギにおける急性肺炎の重篤な大発生に寄与するパスツレラ種である *Mannheimia* [*Pasteurella*] *haemolytica* 内では少なくとも11の血清型 (1、25-9、12-14および16) が実証されている [Ackermannら, *Microbes Infect* 2 (9): 1079-88 (2000)]。輸送、ウイルス感染、過密状態、および他のストレスを発生し得る状態は、動物を *M. haemolytica* 感染症に罹りやすくする [Ackermannら, 前掲]。The leukotoxin (Lkt) of *M. haemolytica* のロイコトキシン (Lkt) は病原性において重要な役割を果たし、ウシ輸送熱の肺病理の特徴に通じる細胞溶解およびアポトーシスならびにウシ肺炎パスツレラ病における肺傷害を引起すると考えられている [Highlanderら, *Infect Immun* 68 (7): 3916-22 (2000)] as well as lung injury in bovine pneumonic pasteurellosis [Jeyaseelan, et al., *Microb Pathog* 30 (2): 59-69 (2001)]。Lktは反芻動物の白血球および血小板にのみ細胞溶解を誘導するユニークな特性を有する孔形成外毒素である [Jeyaseelanら, (2001)、前掲]。多くの細胞型の細胞溶解は、アラキドン酸 (AA) によって仲介され、ホスホリパーゼによるその生成はG-タンパク質共役型受容体によって調節されている [Jeyaseelanら, (2001)、前掲]。細菌の研究では *M. haemolytica* の Lkt が全ベータ2インテグリンの共通のサブユニットであるウシCD18に結合することが示されている [Jeyaseelanら, *Infect Immun*

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68(1): 72-9 (2000)]. また、L F A-1 が L k t 受容体であり、L F A-1 に対する L k t 結合は標的細胞特異的ではなく、ウシ L F A-1 に対する L k t 結合がカルシウム上昇および細胞溶解と関連し、ウシ L F A-1 発現が L k t-1 によって誘導された標的細胞の細胞溶解の程度と関連することも示されている [Jeyaseelanら, Infect Immun 68 (1): 72-9 (2000)].

【0011】

ワクチン組成物を生産する試行において、伝統的な死滅全細菌では血清型特異的な保護しか提供されない [MacInnesおよびSmart、前掲]、しかしながら、強い病原性の血清型を有するものによる自然感染症が複数の血清型に対する強力な保護免疫を刺激し得ることが実証されている [Nielsen, Nord Vet Med. 31: 407-13 (1979)、Nielsen, Nord Vet Med. 36: 221-234 (1984)、Nielsen, Can J Vet Res. 29: 580-582 (1988)、Nielsen, ACTA Vet Scand. 15: 80-89 (1994)]。ApxII毒素の不活性形態を産生する1の明確な生存-弱毒化ワクチン株がブタにおける交差保護を提供する見込みが示されており [Prideauxら, Infection & Immunity 67: 1962-1966 (1999)]、一方、他の不明確な生存-弱毒化突然変異体も見込みが示されている [Inzanaら, Infect Immun., 61: 1682-6, (1993)、International Pig Veterinary SocietyにおけるPaltineanuら, 1992, 214、International Pig Veterinary SocietyにおけるUtreraら, 1992, 213]。

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【発明の開示】

【発明が解決しようとする課題】

【0012】

不明確で自然発生突然変異を有する細菌株を含むワクチン処方に関連する問題により、同種および異種のパスツレラ科の血清型に対して保護免疫を安全に刺激するワクチンに使用するための生存弱毒化細菌株の合理的構築について当該技術分野に要望が存在する。さらに、弱毒化細菌株および細菌の病原性に必要である遺伝子を同定する要望がさらに存在し、それによって抗菌剤を同定する方法の開発が促進される。

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【課題を解決するための手段】

【0013】

一般的には、本発明は弱毒化グラム陰性菌を含むワクチン組成物の生成、ならびにそれを使用するための材料および方法を提供する。1の態様において、本発明のワクチン組成物は、パスツレラ科細菌における弱毒化種を含み、それは、当該技術分野において知られ、出典明示して本明細書の一部とみなすDewhirstら, J. Bacteriol. 174: 2002-2013 (1992) に一部記載されている。該科における種には、限定されるものではないが、*A. actinomycetemcomitans*、*A. capsulatus*、*A. equuli*、*A. lignieresii*、*A. pleuropneumoniae* (*H. pleuropneumoniae*)、*A. seminis*、*A. suis* (*H. suis*)、*A. ureae* (*p. ureae*)、*A. capsulatus*、Bisgaard分類群11、*H. aegyptius*、*H. aphrophilus*、*H. aphrophilus* (*H. parainfluenzae*)、*H. ducreyi*、*H. haemoglobinophilus*、*H. haemolyticus*、*H. influenzae*、*H. paracuniculus*、*H. paragallinarum*、*H. parahaemolyticus*、*H. parainfluenzae*、(*H. paraphrophilus*)、*H. paraphrohaemolyticus*、*H. paraphrophilus*、*H. parassuis*、*H. parasuis* タイプ5、*H. segnis*、*H. somnus*、*Haemophilus* マイナーグループ、*Haemophilus* 分類群C、*P. aerogenes*、*P. anatis*、*P. avium* (*H. avium*)、*P. canis*、*P. dagmatis*、*P. gallinarum*、*P. haemolytica*、*P. trehalosi* (*P. haemolytica* 生物型T)、*P. langaa*、*P. multocida*、*P. pneumotropica*、*P. stomatis*、*P. volantium* (*H. panainflueizae*)、*P. volantium*、*Pasteurella* 種A、*Pasteurella* 種Bおよび*Haemophilus paraphrohaemolyticus*を含む。好ましくは、ワクチン組成物は、弱毒化*Pasteurella haemolytica*、*Actinobacillus pleuropneumoniae*、*Haemophilus somnus*または*Pasteurella multocida*菌を含む。最も好ましい具体例において、本発明のワクチン組成物は、弱毒化*Pasteurella multocida*および*A. plueropneumoniae*菌株を含む。

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【0014】

本発明の1の態様は、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、

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60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170および172のいずれか1によって表わされる遺伝子配列またはその種ホモログ中の機能性突然変異を含むグラム陰性菌を提供し、ここに、該突然変異は、コードされた遺伝子産物（すなわち、遺伝子によってコードされたポリペプチド）の発現および／または生物活性を阻害または廃止し；該機能性突然変異は菌株の病原性の弱毒化を生じる。遺伝子産物の発現および／または生物活性を変調させる（すなわち、増大または低下させる）機能性突然変異には、遺伝子自体の蛋白質コード領域中または、遺伝子発現の制御に寄与もしくは関与する配列中の挿入または欠失が含まれる。欠失突然変異には、特定の遺伝子配列の全部または一部分が欠失したものが含まれる。また、所望により好適なアジュバントおよび／または医薬上許容し得る希釈剤もしくは担体を含んでいてもよい、突然変異し弱毒化されたグラム陰性細菌を含む組成物、好ましくはワクチン組成物も意図する。修飾株をワクチン処方中で有効とするためには、病原菌が重篤な臨床的病徴を発生するのを防ぐのに十分に弱毒化が顕著でなければならないが、宿主における細菌の制限された複製および増殖を許容するよう十分に顕著でないことが必要である。

【0015】

また、本発明は、グラム陰性菌の病原性に必要であるとなる遺伝子産物をコードするポリヌクレオチドも提供する。本発明のポリヌクレオチドには、相補的DNA、相補的もしくはアンチセンスDNAを含むゲノムDNA、および全合成もしくは部分合成DNAのごときDNA；センスおよびアンチセンス鎖を含むRNA；および例えば、Corey, TIBTECH 15:224-229 (1997)に記載のごときペプチド核酸が含まれる。本発明の病原性遺伝子ポリヌクレオチドには、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載のもの、またはその種ホモログ、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174のポリヌクレオチド、またはその種ホモログによってコードされる病原性遺伝子産物をコードするポリヌクレオチド、および中程度ないし高度にストリンジェントな条件下にて、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載されたポリヌクレオチド、またはその種ホモログのいずれか1の非コード鎖（または相補体）にハイブリダイズするポリヌクレオチドが含まれる。したがって、本発明は、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、

60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載されたパスツレラ科からの遺伝子配列、ならびに自然発生する（すなわち、種ホモログ）およびその人工的に誘導された変異型を含む他のグラム陰性菌からの関連する遺伝子配列を包含する。また、本発明は、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、164、166、168、170、172および174に記載されたポリヌクレオチドおよびその種ホモログのいずれか1から推定されるポリペプチドをコードするポリヌクレオチドも包含する。本発明のポリヌクレオチドの配列の知識により、そのポリヌクレオチドの全ての可能な断片の入手が容易となる。したがって、本発明は、本発明のポリヌクレオチドの断片を提供する。

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【0016】

本発明は、本発明のポリヌクレオチドを含む発現構築体をもさらに包含する。また、本発明のポリヌクレオチドで形質変換した、トランスフェクトした、または電気穿孔した宿主細胞も包含する。本発明は、本発明のポリヌクレオチドによってコードされるポリペプチドを生成するための方法を提供し、それは、該ポリヌクレオチドによってコードされる遺伝子産物の発現を許容し、好ましくは促進する条件下にて本発明の宿主細胞を増殖させ、ついで該宿主細胞またはその増殖培地から遺伝子産物を単離する工程を含む。

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【0017】

本発明のポリヌクレオチドの同定により、コード化されたポリペプチドが入手可能となる。本発明のポリペプチドには、同類アミノ酸置換が野生型ポリペプチドに導入されたものを含む、完全長または断片、または切形タンパク質；その変異型；融合またはキメラタンパク質；およびアナログが含まれる。また、本発明のポリペプチドを特異的に認識する抗体も提供し、それにはモノクローナルおよびポリクローナル抗体、単一鎖抗体、キメラ抗体、ヒト化抗体、ヒト抗体および相補性決定領域（CDR）-移植抗体、ならびに本発明のポリペプチドを特異的に認識するCDR配列を含む化合物が含まれる。また、本発明は、本発明の抗体に免疫特異的な抗イディオタイプ抗体も提供する。

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【0018】

本発明のもう1の態様によれば、グラム陰性菌の病原性遺伝子または遺伝子産物の機能を変調する、新規な抗菌剤を同定するための方法を提供する。本発明の方法には、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174のいずれか1に記載されたDNA配列またはその種ホモログによってコード化される病原性遺伝子産物の発現を干渉する能力についての潜在的剤をスクリーニングし、または全体的または部分的に配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135

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、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174のいずれか1に記載されたDNA配列、その種ホモログまたはその相補鎖によってコードされる細菌遺伝子産物の生物機能に干渉する能力につき潜在的剤をスクリーニングし、続いてかかるスクリーニングアッセイにおいてポジティブな結果を供する剤を同定することが含まれる。特に、病原性遺伝子産物の発現に干渉する剤には、病原性遺伝子配列に相補的であるアンチセンスポリヌクレオチドおよびリボザイムが含まれる。本発明は、さらに、オリゴヌクレオチド指令の三重らせん形成の使用を介する本発明の遺伝子産物の転写を変調する方法も包含する。

【0019】

病原性遺伝子産物の機能に干渉する剤には、病原性遺伝子産物の変異型、病原性遺伝子産物の結合パートナーおよびかかる結合パートナーの変異型および（該産物が酵素である場合には）酵素阻害物質を含む。

【0020】

本明細書に記載した方法によって同定された新規な抗菌剤、ならびに細菌の存在を減少させるのに有効な量のかかる新規な抗菌剤の投与を含むグラム陰性菌による感染症に苦しみ対象を治療する方法が提供される。

【0021】

本発明の多数のさらなる態様および利点は、現在準備されたその具体例を記載する以下の発明の詳細な説明を考慮すれば、当業者に明らかとなるであろう。

【0022】

本明細書で用いる「病原性遺伝子」は、機能または産物が宿主動物における細菌感染症の首尾よく確立および／または維持に必要である遺伝子である。したがって、病原性遺伝子および／またはそれによってコードされるタンパク質は、宿主生物における病理に関係するが、増殖には必要ではないかもしれない。

【0023】

本明細書で用いる「シグニチャータグド（signature-tagged）突然変異（STM）」は、一般的には、国際公開WO96/17951（ここに出典明示して本明細書の一部とみなす）に記載された方法であり、例えば、菌血症のげっ歯類モデルにおける病原性に必要な細菌遺伝子を同定する方法を含む。この方法においては、各々がゲノム中にランダムな突然変異を有する菌株をトランスポゾン組込みを用いて作成し；各挿入突然変異は、突然変異体を互いに区別することを可能とする異なるDNAシグニチャータグ（signature-tag）を運搬する。該タグは、20塩基対の不変の「アーム」によって隣接してはさまれた40塩基対の変換中央領域を含み、それは、中央部分がポリメラーゼ鎖反応（PCR）によって増幅されることを可能とする。タグを付した突然変異株はマイクロタイター皿中で組立て、ついで感染試験のための「接種物プール」を形成するために合する。接種後の適当な時点にて、細菌は動物から単離され、プールして「回収プール」を形成する。回収プール中のタグおよび接種プール中のタグは、別々に増幅し、標識し、ついでそれを用いて、接種源中の突然変異体を示す異なるタグの全てで整列したフィルターを調べる。弱毒化病原性を持つ突然変異株は、感染した動物から回収できないものであり、すなわち、回収プールからのタグで調べた場合にはハイブリダイゼーションシグナルを示さないが、接種プールからのタグで調べた場合にはハイブリダイゼーションシグナルを与えるタグを持つ株である。この方法の変形において、化学ルミネセンスのごとき非放射性の検出法を用いることができる。

【0024】

シグニチャータグド突然変異は、多数の挿入突然変異株を、病原性の欠失につき単一の動物において同時にスクリーニングすることを可能とする。突然変異体*P. multocida*株の19のプールのスクリーニングにより、病原性が低下した60を超える株を同定し、その多数は、個々の突然変異体についておよそLD₅₀のその後の決定によって病原性が弱毒化されることが確認された。*A. pleuropneumoniae*突然変異体のスクリーニングにより、

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35の異なる遺伝子中に突然変異を有する100を超える株を同定した。これらのうち、22の遺伝子中の突然変異は顕著に弱毒化された*A. pleuropneumoniae*株を生じた。トランスポゾン挿入によって破壊されたオープン・リーディング・フレームのヌクレオチド配列は、両鎖を配列決定し、コードされるアミノ酸配列を推定することによって決定した。ポリヌクレオチドおよびアミノ酸配列の双方の新規性は、DNAおよびタンパク質のデータ・ベース配列と該配列との比較によって決定した。これらの種における病原性遺伝子の知識は、*P. (Mannheimia) haemolytica*中の種ホモログの同定を可能とした。

【0025】

細菌および、より詳細には、*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*病原性遺伝子の同定は、ワクチンに有用である低下した病原性を示す微生物（すなわち、弱毒化株）のために提供された。かかる微生物には、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174のいずれか1によって表わされる遺伝子を不活化する少なくとも1の機能性突然変異を含むPasteurellaceae突然変異体を含む。当業者ならば、「機能性突然変異」が、本発明の遺伝子のタンパク質コード領域、ならびに病原性遺伝子のRNAの転写を調節する調節領域において生じ得ることを認識するであろう。

【0026】

また、当業者ならば、本発明の弱毒化*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*株が1を超える機能性突然変異を有するものを含むことを認識するであろう。1を超える突然変異は付加的または相乗的な程度の弱毒化を生じ得る。設計によって複数の突然変異を調製できるか、または元来単一の突然変異を導入することを意図した欠失事象から偶然に発生し得る。複数の欠失を持つ弱毒化株の例は、*cya*および*crp*の遺伝子が機能的に欠失した*Salmonella typhimurium*株である。この突然変異体*S. typhimurium*株は、生ワクチンとしての見込みを示している。

【0027】

P. multocida、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*における病原性遺伝子の同定は、他の病原性種における同様の遺伝子に関する情報を提供できる。例えば、*aroA*遺伝子の同定は、*Aeromonas hydrophila*、*Aeromonas salmonicida*、*Salmonella typhimurium*、*Salmonella enteritidis*、*Salmonella dublin*、*Salmonella gallanarum*、*Bordetella pertussis*、*Yersinia enterocolitica*、*Neisseria gonorrhoeae*および*Bacillus anthracis*を含む種々の多数の病原体に保存された遺伝子の同定に導く。これらの種の多くにおいて、*aroA*遺伝子中に突然変異を持つ弱毒化菌株が、ワクチン処方にも有効であることが判明した。*P. multocida*中で同定された病原性遺伝子配列を用いれば、同様または同族の遺伝子を他の生物、特に、*Pasteurella*科ならびに*A. pleuropneumoniae*、*P. (Mannheimia) haemolytica*および*Haemophilus somnus*において同定できる。同様に、*A. pleuropneumoniae*病原性遺伝子の同定は、他の生物中の関連する遺伝子の同定を可能とする。プローブとして*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*遺伝子を用いるサザンハイブリダイゼーションは、他の生物に由来する染色体ライブラリー中のこれらの関連する遺伝子を同定できる。別法として、PCRは、種の境界を超えて遺伝子同定に等しく有効となり得る。また、さらにもう1の別法として、例えば、他の種からの染色体ライブラリーを有する*P. multocida*突然変異体の相補性を用いて、同一または関連する病原活性を有する遺伝子を同定できる。したがって、関連する病原性遺伝子の同定は、なおもう1のワクチン処方として有用となり得る他の生物の弱毒化株の作成に導くことができる。他の種（例えば、*P. (Mannheimia) haemolytica*、*A. pleuropneumoniae*および*H. somnus*）に存在することが実証された*P. multocida*遺伝子の例には、遺伝子*exbB*、*atpG*

、pnp、guaBおよびyjpFが含まれる。

【0028】

S T Mを用いて同定された弱毒化 *P. multocida*株は、病原性遺伝子がオープン・リーディング・フレームまたは調節 D N A 配列のいずれかの中におけるトランスポゾン配列の挿入によって機能性をなくなった挿入突然変異体である。

これらの挿入突然変異体には、いまだ細菌病原性に必要な遺伝子情報のすべてが含まれており、挿入されたトランスポゾンの欠失によって病原性状態におそらく復帰し得る。したがって、ワクチン処方調製することにおいては、弱毒化株から拾い集めた情報を収集し、幾分か、大部分のまたは全ての病原性遺伝子配列が除去された欠失突然変異株を作成し、それによって細菌が病原性状態に復帰する可能性を排除することが望ましい。

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【0029】

S T Mを用いて同定した弱毒化挿入突然変異体のワクチン特性は同一遺伝子中に欠失を有する細菌のものと同一または類似していることが予想される。しかしながら、挿入突然変異が隣接する遺伝子配列に対して“極性”効果を発揮する場合があります、その結果、挿入突然変異体が同一の遺伝子配列中に欠失を有する突然変異株とはことなる特徴を有する場合もある。欠失突然変異体は、当該技術分野でよく知られており、かつ日常的に実施されている多くの技術のいずれかを用いて作製し得る。

【0030】

1の例において、対選択可能な(counterselectable)マーカーを用いる戦略が使用でき、それは多くの細菌中の遺伝子を欠失するために一般的に利用されている。概説については、例えば、Reyratら、*Infection and Immunity* 66: 4011-4017 (1998) (ここに出典明示して本明細書の一部とみなす)を参照されたい。この技術において、二重の選択戦略がしばしば用いられ、ここでは、目的とする欠失の両側に由来するフランキング D N A 配列を用いて、選択可能および対選択可能なマーカーの両方をコードするプラスミドを構築する。選択可能なマーカーを用いて、適当な場所および様式でプラスミドがゲノムに組込まれた細菌について選択する。対選択可能なマーカーは、組込まれたプラスミドを自然に失った非常に低いパーセントの細菌について選択するために用いる。その場合、これらの細菌の画分は、他の外来 D N A が全く存在しない目的の欠失のみを含むであろう。この技術を用いる鍵は、好適な対選択可能なマーカーの入手性である。

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【0031】

もう1の技術において、D N A の部位特異的組換えにcre-lox系を用いる。該系は34塩基対のlox配列からなり、これは細菌creリコンビナーゼ遺伝子によって認識される。lox部位が適当な向きでD N A 中に存在しない場合には、lox部位によって挟まれたD N A がcreリコンビナーゼによって切除され1の残存するLox配列のコピー以外の全ての配列の欠失を生じる。標準的な組換え技術を用いると、*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimi) haemolytica*のゲノム中の目的の標的化遺伝子を欠失し、それとlox部位によって挟まれた選択可能なマーカー(例えば、カナマイシン耐性をコードする遺伝子)とを入替えることが可能である。(*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*中で機能するプロモーターの制御下でcre遺伝子を願する自殺プラスミドの電気穿孔による) creリコンビナーゼの一時的発現は、loxに挟まれたマーカーの有効な除去を生じるにちがいない。このプロセスは、目的の欠失突然変異およびlox配列の1のコピーを含む突然変異体を生じるであろう。選択可能および対選択可能なマーカーの双方をコードし、隣接してはさまれたD N A 配列は、所望の欠失の両側から誘導される。選択可能なマーカーを用いて、該プラスミドが適当な位置および様式でゲノム中に組込まれた細菌を選択する。対選択可能なマーカーを用いて、統合されたプラスミドを自発的に消失される非常に低いパーセンテージの細菌について選択する。ついで、これらの細菌の画分は、他の外来性D N A が存在しない所望の欠失だけを含む。この技術の使用のための鍵は、適当な対選択可能なマーカーの有効性である。

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【0032】

もう1の技術において、cre-lox系をD N A の部位特異的な組換えに用いる。この系は、

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細菌性cre組換え酵素遺伝子によって認識される34塩基対のlox配列よりなる。該lox部位が、適当な配向でDNA中に存在するならば、lox部位によって隣接してはさまれたDNAは、cre組換え酵素によって切り取られ、その結果、残りの1コピーのlox配列を除き全配列を欠失する。標準的組換え技術を用いて、*P. multocida*または*A. pleuropneumoniae*ゲノム中の注目する標的とされた遺伝子を欠失し、それを該lox部位によって隣接してはさまれた選択可能な標識（例えば、カナマイシン耐性につきコードする遺伝子）と置換することが可能である。cre組換え酵素の（*P. multocida*または*A. pleuropneumoniae*において機能するプロモーターの制御下、cre遺伝子を含む自殺プラスミドの電気穿孔による）一過性発現は、loxが隣接してはさむマーカーの効果的な消失を生じさせるであろう。このプロセスの結果、突然変異体は、所望の欠失突然変異および1コピーのlox配列を含む

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【0033】

もう1のアプローチにおいて、*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*のゲノム中の所望の欠失配列とグリーン蛍光タンパク質（GFP）、 β -ガラクトシダーゼまたはルシフェラーゼのごときマーカー遺伝子とを直接的に置換することが可能である。この技術において、所望の欠失を隣接してはさむDNAセグメントをPCRによって調製し、*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*用の自殺（複製しない）ベクターにクローニングする。*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*中で活性なプロモーター、および適当なマーカー遺伝子を含む発現カセットは、フランキング配列の間にクローニングする。該プラスミドは、野生型の*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*に導入する。マーカー遺伝子を取込み、それを発現する（たぶん非常に低頻度）細菌を、単離し、適当な組換え事象（すなわち、野生型遺伝子とマーカー遺伝子との置換）は、単離され、適当な組換え事象（すなわち、野生型遺伝子の標識遺伝子への置換）について調べる。

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【0034】

これらの生物の低下した病原性およびそれらの免疫原性は、対象動物への投与によって確認し得る。本発明の非発病性の微生物については単独で投与できるが、1またはそれを超えるかかる突然変異体微生物は、好適なアジュバントおよび医薬上許容される希釈剤または担体を含むワクチン組成物で好ましくは投与する。担体は本発明の非病原性微生物と適合し得、免疫化する対象に有害でないという意味において「許容される」ものでなければならない。典型的には、該担体は、無菌で発熱物質が存在しない水または塩類溶液であろう。免疫化すべき対象は、病原性形態の*P. multocida*、*A. pleuropneumoniae*、*P. (Mannheimia) haemolytica*または他の病原微生物によって引き起こされる疾患から保護する必要がある対象である。

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【0035】

本発明のワクチンがヒト医学および獣医学の分野で有用であり得ることは、認識されるであろう。したがって、免疫化すべき対象には、ヒトまたは他の動物、例えば、ウシ、ヒツジ、ブタ、ウマ、ヤギおよび家禽（例えば、ニワトリ、シチメンチョウ、アヒルおよびガチョウ）を含む農業動物、イヌおよびネコのような愛玩動物；新種の動物および／または動物園動物；ならびにマウス、ラット、ウサギ、モルモットおよびハムスターを含む実験動物が含まれる。

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【0036】

また、本発明は、*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*の病原性に必要なポリペプチドおよび対応するポリヌクレオチドも提供する。本発明には、天然に存在するおよび天然に存在しないポリヌクレオチドおよびそのポリペプチド産物の双方が含まれる。天然に存在する病原性産物には、異なる遺伝子およびポリペプチド種、ならびに*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*株以外の生物において発現される対応する種ホモログが含まれる。天然に存在しない病原性産物には、共有結合修飾を含むアナログおよび病原性産物のごとき天然に存在する産物

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の変異型が含まれる。好ましい具体例において、本発明は、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載された配列、およびその種ホモログを含む病原性ポリヌクレオチド、ならびに該ポリヌクレオチドによってコードされるアミノ酸配列を有するポリペプチドを提供する。

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【0037】

本発明は、細菌の病原性遺伝子産物をコードする新規な精製され、単離された*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*のポリヌクレオチド（例えば、DNA配列およびRNA転写物、センス鎖および相補的アンチセンス鎖の双方）を提供する。本発明のDNA配列には、ゲノミックおよびcDNA配列ならびに全体または部分的に化学合成したDNA配列が含まれる。本発明のゲノミックDNAには、本発明のポリペプチドについてのタンパク質コード領域が含まれ、同一種の他の菌株において見出され得る変異型が含まれる。本明細書中で用い、また、当該技術分野において理解されている「合成（された）」とは、酵素的とは反対の純粋に化学的なポリヌクレオチドを製造する方法をいう。したがって、「全（体）」合成したDNA配列は全体的に化学的手段によって作製され、「部分（的）」合成したDNAは、得られたDNAの一部分だけを化学的手段によって作製したものを含む。*P. multocida*病原性遺伝子産物をコードする好ましいDNAは、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118および120ならびにその種ホモログに記載されている。病原性遺伝子産物をコードする好ましい*A. pleuropneumoniae*のDNA配列は、配列番号：122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163および164ならびにその種ホモログに記載されている。好ましい*P. (Mannheimia) haemolytica*の病原性遺伝子産物は、配列番号：166、168、170、172および174ならびにその種ホモログに記載されている。当業者であれば、本発明の好ましいDNAが、二本鎖分子、例えば配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174およびその種ホモログに記載の配列を有する分子を、DNAについてのワトソン-クリック塩基対形成ルールに従う配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174の配列から推定し得る配列を有する相補的分子（「非コード鎖」または「相補体」）とともに含むことは容易に認識し得るであろう。また、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、3

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9、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118および120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載されたポリヌクレオチドおよびその種ホモログのいずれか1によってコードされる遺伝子産物をコードするポリヌクレオチドが好ましい。さらに、本発明は、*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*のDNAの種、好ましくは細菌ホモログを含む。

【0038】

本発明によって提供されるポリヌクレオチド配列情報は、サザーンおよび／またはノーザンハイブリダイゼーションおよびポリメラーゼ連鎖反応（PCR）を含むよく知られた技術によって、関連する細菌の病原性分子をコードするポリヌクレオチドの同定および単離を可能とする。関連するポリヌクレオチドの例は、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載されたポリヌクレオチドおよびその種ホモログのいずれか1によってコードされる病原性遺伝子産物に相同的なポリペプチド、ならびに本発明の病原性遺伝子産物の1以上の生物学的および／または物理的特性を共有する構造的に関連するポリペプチドをコードするポリヌクレオチドが含まれる。

【0039】

また、本発明には、中程度ないし高度のストリンジェント条件下で、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118および120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172および174に記載されたポリヌクレオチドおよびその種ホモログのいずれか1の非コード鎖または相補体にハイブリダイズする細菌の遺伝子産物をコードするDNA配列も包含される。遺伝暗号の縮重を除いてそれらにハイブリダイズする病原性ポリペプチドをコードするDNA配列も本発明によって意図される。例示的な高度のストリンジェンシー条件には、65℃ないし75℃の0.2×SSC／0.1%SDSを含む緩衝液中の最終洗浄が含まれ、一方、例示的な中程度のストリンジェンシー条件には、35℃ないし45℃の2×SSC／0.1%SDSを含む緩衝液中の最終洗浄が含まれる。同等のストリンジェンシーの条件を、Ausubelら（編）、*Protocols in Molecular Biology*, John Wiley & Sons (1994)、6.0.3ないし6.4.10頁に記載された温度および緩衝液または塩濃度を変化させることによって達成できることは当該技術分野において理解されている。ハイブリダイゼーション条件における修飾は、プローブの長さおよびグアノシン／シトシン（GC）の塩基対合のパーセンテージに基いて経験的に決定でき、または正確に計算できる。ハイブリダイゼーション条件は、Sambrookら（編）、*Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New York (1989)、9.47ないし9.51頁に記載されているごとく算出し得る。

【0040】

また、病原性遺伝子配列を取込むプラスミドおよびウイルスDNAベクターのごとき自律複製性の組換え発現構築体も提供する。また、病原性ポリペプチドをコードするポリヌク

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レオチドが内因性または外因性の発現制御DNA配列および転写ターミネーターに作動可能に連結された発現構築体も提供する。病原性遺伝子は、鋳型として*P. multocida*ゲノムDNAを用いるPCRによってクローン化し得る。発現ベクターに遺伝子を簡単に挿入するために、PCRプライマーは、PCR増幅した遺伝子が開始コドンATGに先行する5'末端に制限酵素部位を有し、かつ終止コドンTAG、TGAまたはTAAの下流の3'末端に制限酵素部位を有するようにPCRプライマーを選択する。望ましい場合には、遺伝子中のコドンを、GrosjeanおよびFiers, Gene, 18: 199-209 (1982)、ならびにKönigsbergおよびGodson, Proc. Natl. Acad. Sci. (USA), 80:687-691 (1983)によって記載された*E. coli*コドン優先度に従ってアミノ酸を変化することなく変化させる。*E. coli*中で産生された場合、コドン使用の最適化は、遺伝子産物の発現の増加に導き得る。遺伝子産物が*E. coli*または他の細菌のペリプラズム中または細胞培養基へのいずれかで細胞外に産生される場合には、遺伝子はその開始コドンなくしてクローン化し、シグナル配列の背後で発現ベクターに位置する。

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【0041】

本発明のもう1の態様によれば、本発明の病原性ポリペプチドを発現できる様式で本発明のポリヌクレオチド配列で安定してまたは一時的に形質変換した、トランスフェクトしたまたは電気穿孔した原核生物および真核細胞を含む宿主細胞を提供する。本発明の発現系には、細菌、酵母、真菌、ウイルス、無脊椎動物および哺乳動物の細胞系が含まれる。本発明の宿主細胞は、病原性遺伝子産物と特異的に免疫反応する抗体を発生させるための価値ある免疫原である。本発明の宿主細胞は、細胞を好適な培養基で増殖させ、目的のポリペプチド産物を細胞からかまたは細胞を増殖させた培養基から、例えば当該技術分野でよく知られており、日常的に実施されている免疫アフィニティー精製または多くの精製技術のうちのいずれかによって単離する。*E. coli*、*P. multocida*、*Bacillus*および*S. aureus*を含む他の細菌、*Pichia pastoris*および*Saccharomyces cerevisiae*を含む酵母、昆虫細胞またはCHO細胞を含む哺乳動物細胞のごときいずれの好適な宿主細胞も、当該技術分野において知られている好適なベクターを利用して、遺伝子産物の発現のために用いることができる。タンパク質は、細菌細胞の細胞周辺腔へ、または細胞培養基への分泌によって細胞内または細胞外のいずれかで直接的に産生されるか、あるいはペプチドまたはポリペプチドに融合し得る。タンパク質の分泌には、シグナルペプチド（プレ配列としても知られている）を必要とし；原核生物および真核生物からの多数のシグナル配列が組換えタンパク質の分泌のために機能することが知られている。タンパク質分泌プロセスの間に、シグナルペプチドはシグナルペプチターゼによって除去されて成熟タンパク質が得られる。

【0042】

タンパク質精製プロセスを単純化するために、精製タグを遺伝子コード配列の5'または3'末端のいずれかに付加できる。一般的に使用される精製タグには、6のヒスチジン残基のストレッチ（米国特許第5,284,933号および第5,310,663号）、SchmidtおよびSkerra, Protein Engineering, 6: 109-122 (1993)によって記載されているストレプトアビジン-親和性タグ、FLAGペプチド [Hoppら, Biotechnology, 6: 1205-1210 (1988)]、グルタチオンS-トランスフェラーゼ [SmithおよびJohnson, Gene, 67:31-40 (1988)]、およびチオレドキシシン [La Vallieら, Bio/Technology, 11: 187-193(1993)]が含まれる。これらのペプチドまたはポリペプチドを取り除くために、タンパク質分解切断認識部位を融合接合部に挿入できる。一般的に使用されるプロテアーゼは、因子Xa、トロンピンおよびエンテロキナーゼである。

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【0043】

また、本発明は、本発明のポリヌクレオチドによってコードされる精製および単離された*P. multocida*、*A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*病原性ポリペプチドも提供する。配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、

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106、108、110、112、114、116、118および120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、164、166、168、170、172および174に記載されたポリヌクレオチドならびにその種ホモログのいずれか1によってコードされたアミノ酸配列を含むポリペプチドが現在好ましい。本発明は、a) 配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、164、166、168、170、172および174ならびにその種ホモログのいずれか1に記載されたDNA配列；b) 配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、164、166、168、170、172および174のいずれか1によってコードされた*P. multocida*、*A. pleuropneumoniae*または*P. (Mannheimia) haemolytica*のポリペプチドをコードするDNA分子ならびにその種ホモログ；およびc) 中程度のストリンジェンシー条件下にて、(a)または(b)のDNAにハイブリダイズする病原性遺伝子産物をコードするDNA分子よりなる群から選択されるDNAによってコードされる病原性ポリペプチドを包含する。

【0044】

本発明は、本発明の好ましいポリペプチドに対して、少なくとも約99%、少なくとも約95%、少なくとも約90%、少なくとも約85%、少なくとも約80%、少なくとも約75%、少なくとも約70%、少なくとも約65%、少なくとも約60%、少なくとも約55%、および少なくとも約50%の同一性および／または相同性を有するポリペプチドも包含する。本発明の好ましいポリペプチドに関するパーセント(%)アミノ酸配列「同一性」とは、病原性遺伝子産物配列と候補配列の両方を並べて、必要ならギャップを導入して、最大パーセント配列同一性を達成した後の病原性遺伝子産物配列中の残基と同一である候補配列中のアミノ酸残基のパーセンテージとして本明細書中では定義し、配列同一性の部分としていずれの保存的置換も考慮していない。本発明の好ましいポリペプチドに関する%配列「相同性」は、候補配列と病原性遺伝子産物の配列の両方を並べて、必要ならギャップを導入して最大%配列同一性を達成した後の病原性遺伝子産物配列中の残基と同一である候補配列中のアミノ酸残基のパーセンテージとして本明細書中では定義し、配列同一性の一部分としていずれの同類置換も考慮しない。同類置換は、表AおよびBに掲載するように定義し得る。

【0045】

【表1】

表 A
同類置換 I

<u>側鎖の特徴</u>		<u>アミノ酸</u>
脂肪族	非極性	G A P
		I L V
	極性-非荷電	C S T M
		N Q
	極性-荷電	D E
		K R
芳香族		H F W Y
その他		N Q D E

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【0046】

本発明のポリペプチドは、天然の細菌細胞起源から単離するかまたは化学合成し得るが、好ましくは本発明の宿主細胞を含む組換え法によって生成する。本発明の病原性遺伝子産物は、完全長ポリペプチド、生物学的に活性なフラグメント、または特異的な生物学的もしくは免疫学的な活性を保持するそれらの変異型とし得る。変異型には病原性ポリペプチドアナログが含まれ、そこにおいては、(1) 病原性遺伝子産物に特異的な1またはそれを超える生物学的活性または免疫学的特徴を喪失することなく；あるいは(2) 病原性遺伝子産物の特定の生物学的活性の特定の不能性を有しつつ、1またはそれを超える特定の(すなわち、天然にコードされた)アミノ酸が欠失または置換されているか、あるいは1またはそれを超える非特定のアミノ酸が付加されている。意図する欠失変異型には、生物学的活性に必須でないポリペプチドの部分を欠いているフラグメントも含まれ、挿入変異型には野生型ポリペプチドまたはそのフラグメントがもう1のポリペプチドに融合している融合ポリペプチドが含まれる。

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【0047】

変異型病原性ポリペプチドには、本発明のポリペプチドをコードするポリヌクレオチドの改変によって同類置換が導入されているものが含まれる。同類置換は、その関連する物理学的特性に従ってアミノ酸を分類することと当該技術分野では認識されており、(1997年3月13日公開の国際公開W0 97/09433、10頁(9/6/96出願のPCT/GB96/02197)から引用する)表Aに掲載したごとく定義し得る。また、同類アミノ酸は、表Bに掲載するごとくLehninger, [Biochemistry, 第2版; Worth Publishers, Inc. 社 NY: NY (1975), pp71-77]で定義されているごとくグループ分けすることもできる。

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【0048】

【表2】

表 B
同類置換 II

側鎖の特徴	アミノ酸
非極性（疎水性）	
A. 脂肪族：	A L I V P
B. 芳香族：	F W
C. 含硫黄原子：	M
D. 境界：	G
非電荷一極性	
A. ヒドロキシル：	S T Y
B. アミド：	N Q
C. スルフヒドリル：	C
D. 境界：	G
プラスに帯電（塩基性）：	K R H
マイナスに帯電（酸性）：	D E

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【0049】

本発明の変異型病原性産物には、成熟病原性遺伝子産物、すなわちリーダー配列またはシグナル配列が除去され、さらなるアミノ末端残基を有するものが含まれる。ポジション1にさらなるメチオニン残基を有する病原性遺伝子産物は、ポジション2および1にさらなるメチオニンおよびリシン残基を有する病原性産物と同様に意図される。これらの型の変異型は、細菌細胞型における組換えタンパク質産生に特に有用である。本発明の変異型には、他のタンパク質に由来するアミノ末端配列が導入されている遺伝子産物、ならびに天然発生タンパク質には見出されないアミノ末端配列を含む変異型も含まれる。

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【0050】

本発明は、特定の発現系の使用から生じるさらなるアミノ酸残基を有する変異型ポリペプチドをも包含する。例えば、グルタチオン-S-トランスフェラーゼ（GST）との融合タンパク質として目的のポリペプチドを発現する市販のベクターを使用することにより、目的のポリペプチドからGST成分を切断した後にポジション1にさらなるグリシン残基を有する目的のポリペプチドが得られる。他のベクター系を用いる発現から生じる変異型も意図される。

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【0051】

また、本発明によって意図されるのは、抗体（例えば、本発明のポリペプチドを特異的に認識するCDR配列を含む複合物を含む、モノクローナルおよびポリクローナル抗体、一本鎖抗体、キメラ抗体、ヒト化、ヒトおよびCDR-グラフト抗体）ならびに病原性遺伝子産物またはそのフラグメントに特異的な他の結合タンパク質である。「～に特異的な」なる語は、本発明の抗体の可変領域が排他的に病原性ポリペプチドを認識し、かつ、それに結合する（すなわち、ポリペプチドのファミリーに見出される配列の同一性、相同性または類似性にかかわらず、関連する病原性ポリペプチドから単一の病原性ポリペプチドを識別し得る）が、抗体の可変領域の外側の配列、特に分子の定常領域中の配列との相互作用を介して他のタンパク質（例えば、ELISA技術においてはエス・アウレウス（*S. aureus*）プロテインAまたは他の抗体）とも相互作用し得ることを示す。本発明の抗体の結合特異性を測定するスクリーニング・アッセイはよく知られており、当該技術分野で日常的に行われている。かかるアッセイの包括的な議論については、Harlowら（編）、*Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), 第6章を参照されたい。本発明の病原性ポリペプチドのフラグメントを認識し、かつ、それに結合する抗体も意図されるが、但し、当該抗体は、前記に定義したごとく、それからフラグメントが由来する本発明の病原性ポリペプチドに第一にかつ最先に特異

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的である。

【0052】

本発明により提供されるDNAおよびアミノ酸配列情報により、病原性遺伝子およびそれがコードする遺伝子産物の構造および機能の体系的な分析が可能となる。本発明の病原性遺伝子産物をコードするポリヌクレオチドの知見により、本発明の病原性ポリペプチドをコードするポリヌクレオチドを認識し、かつ、それにハイブリダイズするアンチセンス・ポリヌクレオチドも利用可能となる。完全長およびフラグメントのアンチセンス・ポリヌクレオチドが提供される。当業者であれば、本発明のフラグメントのアンチセンス分子に、(i) (他の公知分子をコードするDNAに対する本発明の病原性ポリペプチドをコードするDNAの配列比較によって決定される) 特定のRNAを特異的に認識し、かつ、それにハイブリダイズするもの、ならびに(ii) 病原性タンパク質のファミリーの変異型をコードするRNAを認識し、かつ、それにハイブリダイズするものが含まれることを認識するであろう。タンパク質の病原性ファミリーの他のメンバーをコードするRNAにハイブリダイズするアンチセンス・ポリヌクレオチドは、配列比較を介して同定可能であり、分子のファミリーにつき特徴的または顕著な(signature)配列を同定する。

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【0053】

さらに、本発明は、リボザイムの使用を介して遺伝子発現をモジュレートする方法も意図する。概説については、GibsonおよびShillitoe, Mol. Biotech. 7: 125-137 (1997)を参照されたい。リボザイム技術を利用して、(i) 標的mRNAへの相補的RNAのハイブリダイゼーション、および(ii) 相補鎖に固有のヌクレアーゼ活性を介するハイブリダイズしたmRNAの切断、を介する配列特異的な方法でmRNAの翻訳を阻害し得る。リボザイムは経験的な方法によって同定し得るが、より好ましくは標的mRNA上のアクセス可能な部位に基づいて特異的に設計する[Bramlageら, Trends in Biotech., 16:434-438 (1998)]。標的細胞へのリボザイムのデリバリーは、当該技術分野でよく知られておりかつ日常的に行われている外因的または内因的のいずれかのデリバリー技術を用いて行い得る。外因的デリバリー法には、標的化リボソームまたは直接局所注射の使用が含まれ得る。内因的な方法には、ウイルスベクターおよび非ウイルスプラスミドの使用が含まれる。

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【0054】

リボザイムは、病原性遺伝子産物をコードするポリヌクレオチドにユニークな領域に相補的になるよう設計した場合、病原性遺伝子の発現を特異的にモジュレートし得る。したがって、「特異的にモジュレートする」とは、本発明のリボザイムが単一のポリヌクレオチドのみを認識することを意味することを意図する。同様に、リボザイムは、全てまたは幾つかのファミリーのタンパク質の発現をモジュレートするように設計し得る。この型のリボザイムは、タンパク質のファミリーをコードする全てまたは幾つかのポリヌクレオチド中に保存されたポリヌクレオチド配列を認識するように設計する。

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【0055】

さらに、本発明は、オリゴヌクレオチド指向化三重らせん形成の使用を介して本発明の病原性遺伝子の転写をモジュレートする方法を包含する。概説については、Lavrovskyら, Biochem. Mol. Med., 62:11-22 (1997)を参照されたい。三重らせん形成は、ワトソン・クリック・モデルで定義された主溝で二本鎖DNAにハイブリダイズする配列特異的オリゴヌクレオチドを用いて行う。その後、配列特異的オリゴヌクレオチドのハイブリダイゼーションは、例えば転写因子およびポリメラーゼを含むDNA-結合タンパク質の活性をモジュレートし得る。ハイブリダイゼーション用の好ましい標的配列には、病原性遺伝子産物の発現をモジュレートする転写調節領域が含まれる。三重らせん形成することができるオリゴヌクレオチドは、標的DNA配列の部位-特異的共有的改变にも有用である。共有的改变に有用なオリゴヌクレオチドは、Lavrovskyら, [前掲]に記載されているごとき種々のDNA損傷剤にカップリングする。

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【0056】

P. multocida, *A. pleuropneumoniae*および*P. (Mannheimia) haemolytica*の病原性遺伝子

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の同定は、抗菌剤の同定方法において遺伝子および遺伝子産物を有用としている。かかる方法には、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174ならびにそれらの種ホモログ（すなわち、配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のDNA配列によって表される遺伝子）は病原性遺伝子産物をコードし、あるいは配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のDNA配列が病原性遺伝子産物をコードしている遺伝子に近接しているか、あるいは配列番号：1、3、7、9、11、13、15、17、19、21、23、25、29、31、33、37、39、41、51、53、55、57、58、60、68、70、72、74、76、78、80、82、84、100、102、104、106、108、110、112、114、116、118、および120、122、124、126、128、130、132、134、135、136、138、140、142、144、146、148、150、152、154、156、158、160、162、163、164、166、168、170、172、および174のいずれか1に記載のDNA配列、その種ホモログまたはその相補鎖によって全体または一部分がコードされる細菌遺伝子産物の機能を干渉する能力につき潜在的剤をアッセイし、つづいてかかるアッセイにおいてポジティブである剤を同定することが含まれる。これらのアッセイに有用なポリヌクレオチドおよびポリペプチドには、本明細書中に開示する遺伝子およびコードされるポリペプチドのみならず、野生型の遺伝子およびポリペプチドと実質的に同じ活性を有するその変異型も含まれる。

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【0057】

前記した方法によって作製される病原性遺伝子産物は、高処理量アッセイで用いて阻害因子についてスクリーニングする。スクリーニングすべき潜在的剤の起源は、化学化合物ライブラリー、ストレプトマイセテス（Streptomyces）、他の細菌および菌類の醗酵培地、ならびに植物および他の増殖性植物の細胞抽出物である。公知の酵素活性を有するタンパク質については、活性に基づいてアッセイを確立し、多数の潜在的剤を該活性を阻害する能力についてスクリーニングする。他のタンパク質または核酸と相互作用するタンパク質については、結合アッセイを確立して、かかる相互作用を直接測定し、潜在的剤を結合相互作用を阻害する能力についてスクリーニングする。

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【0058】

当該技術分野で知られている異なるアッセイの使用は、本発明のこの態様に従って意図される。病原性遺伝子産物の機能が公知の遺伝子産物に対する配列類似性によって知られるかまたは予想される場合には、遺伝子産物の機能および／または特性に合わせた酵素的または他のタイプの生物学的および／または生化学的アッセイで潜在的なインヒビターをス

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クリーニングし得る。病原性遺伝子産物が他のタンパク質または核酸と相互作用する公知の遺伝子産物に対する配列類似性によって知られるかまたは予想される場合には、相互作用のインヒビターを結合アッセイで直接スクリーニングし得る。本発明は、病原性遺伝子産物によって結合のインヒビターをスクリーニングおよび同定する多数のアッセイを意図する。1の例において、病原性遺伝子産物を固定化し、結合パートナーとの相互作用を推定インヒビター化合物の存在および不存在下で評価する。もう1の例において、病原性遺伝子産物とその結合パートナーとの間の相互作用は、推定インヒビター化合物の存在および不存在下の両方で、溶液アッセイにおいて評価する。両方のアッセイにおいて、インヒビターは病原性遺伝子産物とその結合パートナーとの間の結合を低下させる化合物として同定する。他のアッセイもこれらの例で意図され、そこでは病原性遺伝子産物結合パートナーはタンパク質である。例えば、ジハイブリッドアッセイの変形が意図され、そこではタンパク質／タンパク質相互作用のインヒビターを、1995年8月3日に公開された国際公開番号W0 95/20652号に記載されているごとき形質転換またはトランスフェクトした宿主細胞におけるポジティブ・シグナルの検出によって同定する。

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【0059】

本発明により意図される候補インヒビターには、潜在的なインヒビターのライブラリーから選択される化合物が含まれる。小分子モジュレーターの同定に用いる多数の異なるライブラリーが存在し、これには(1)化学ライブラリー、(2)天然産物ライブラリー、および(3)ランダムなペプチド、オリゴヌクレオチドまたは有機分子からなるコンビナトリアル・ライブラリーが含まれる。化学ライブラリーは、公知の化合物、あるいは天然物のスクリーニングを介して「ヒット(hits)」または「リード」と同定された化合物の構造アナログからなる。天然産物ライブラリーは、(1)土壌、植物または海洋微生物からのブ罗斯の醗酵および抽出、あるいは(2)植物または海洋生物の抽出、によってスクリーニング用の混合物を生成するために用いる微生物、動物、植物または海洋生物の収集である。天然産物ライブラリーには、ポリペプチド、非ーリボソームペプチドおよびそれらの変異型(非天然発生)が含まれる。概説については、Science, 282:63-68 (1998)を参照されたい。コンビナトリアル・ライブラリーは、混合物として多数のペプチド、オリゴヌクレオチド、または有機化合物よりなる。それは、伝統的な自動化合成法、PCR、クローニングまたは特許合成方法によって調製することが比較的簡単である。特に関心があるのは、ペプチドおよびオリゴヌクレオチドのコンビナトリアル・ライブラリーである。なお他の関心のあるライブラリーには、ペプチド、タンパク質、ペプチド模倣物、マルチ平行合成収集、組換え、およびポリペプチド・ライブラリーが含まれる。それから創製されたコンビナトリアル化学およびライブラリーの概説については、Myers, Curr. Opin. Biotechnol., 8: 701-707 (1997)を参照されたい。本明細書中に記載する種々のライブラリーの使用を介するモジュレーターの同定により、候補「ヒット」(または「リード」)を改変して活性をモジュレートする「ヒット」の能力を最適化し得る。

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【0060】

本発明によって意図されるなお他の候補インヒビターを設計し得、それには可溶性形態の結合パートナー、ならびにキメラタンパク質または融合タンパク質としての結合パートナーが含まれる。本明細書中で用いる結合パートナーは、抗体、抗体フラグメント、ならびに同定した病原性遺伝子の発現産物に対して免疫特異的な抗体ドメインを含む改変化合物を広範囲に包含する。

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【0061】

病原性遺伝子産物に対する結合パートナー(すなわち、リガンド)が知られていない場合には、標的タンパク質への試験結合パートナーの直接結合を測定することを介して標的タンパク質の結合パートナーを同定するアッセイ、ならびにイオンスプレー質量分析／HPLC法または他の物理学的方法もしくは分析方法を用いたアフィニティー限外濾過を介して標的タンパク質の結合パートナーを同定するアッセイが含まれる。また、かかる結合相互作用は、両方とも出典明示して本明細書の一部とみなす、FieldsおよびSong, Nature, 340: 245-246 (1989)、ならびにFieldsおよびSternglanz, Trends in Genetics, 10:286-

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292 (1994)に記載されている酵母ツーハイブリッド系を用いて間接的に評価する。ツーハイブリッド系は、2のタンパク質またはポリペプチド間の相互作用を検出するための遺伝子アッセイである。それを用いて、関心のある公知タンパク質に結合するタンパク質を同定するか、または相互作用に重要なドメインまたは残基を詳細にすることができる。この方法に対する変形が開発されて、DNA-結合タンパク質をコードする遺伝子がクローン化され、タンパク質に結合するペプチドが同定され、薬剤につきスクリーニングされている。ツーハイブリッド系は、レポーター遺伝子の上流活性化配列(UAS)に結合するDNA-結合ドメインのすぐ近接に転写活性ドメインをもってゆく一对の相互作用タンパク質の能力を活用し、一般的に酵母で行う。該アッセイには、(1)第1のタンパク質に融合したDNA-結合ドメイン、および(2)第2のタンパク質に融合した活性ドメイン、をコードするツーハイブリッド遺伝子の構築が必要である。DNA-結合ドメインは第1のハイブリッドタンパク質をレポーター遺伝子のUASに標的化する；しかしながら、大部分のタンパク質は活性化ドメインを欠いているため、このDNA-結合ハイブリッドタンパク質はレポーター遺伝子の転写を活性化することができない。活性化ドメインを含有する第2のハイブリッドタンパク質は、それ自体でレポーター遺伝子の発現を活性化することができない。それはUASに結合しないからである。しかしながら、両方のハイブリッドタンパク質が存在する場合には、第1のタンパク質と第2のタンパク質の非共有的な相互作用が活性化ドメインをUASにつなぎ、レポーター遺伝子の転写を活性化する。病原性遺伝子産物(例えば、第1のタンパク質)がもう1のタンパク質または核酸と相互作用することがすでに知られている場合には、このアッセイを用いて結合相互作用を干渉する剤を検出することができる。異なる試験剤を系に添加しながらレポーター遺伝子の発現をモニターする；インヒビター因子が存在するとレポーター・シグナルの欠失を生じる。

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【0062】

病原性遺伝子産物の機能が知られておらず、かつ、遺伝子産物に結合することが知られているリガンドが存在しない場合には、酵母ツーハイブリッドアッセイを用いて遺伝子産物に結合するタンパク質を同定することもできる。第1のタンパク質(標的タンパク質)に結合するタンパク質を同定するためのアッセイにおいては、各々が異なる第2のタンパク質をコードしている多数のハイブリッド遺伝子をこのアッセイで作製およびスクリーニングする。典型的には、第2のタンパク質は、全cDNAまたはゲノミックDNAが活性化ドメインに連結しているプラスミドのプールによってコードされている。この系は広範な種々のタンパク質に適用可能であり、第2の結合タンパク質の同一性または機能を知ることすら必要でない。該系は非常に感度が高く、他の方法によって明らかにされない相互作用(一時的な相互作用が転写の引き金を引いて、繰返し翻訳することができる安定なmRNAを生成してレポータータンパク質が得られる場合でさえ)を検出することができる。

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【0063】

他のアッセイを用いて標的タンパク質に結合する剤を探索し得る。標的タンパク質への試験リガンドの直接結合を同定するための1のかかるスクリーニング法は、出典明示して本明細書の一部とみなす米国特許第5,585,277号に記載されている。この方法は、タンパク質が一般的にホールドおよびアンホールド状態の混合物として存在し、2の状態の間を連続的に交代しているという原理に基づく。試験リガンドがホールド形態の標的タンパク質に結合する場合(すなわち、試験リガンドが標的タンパク質のリガンドである場合には、リガンドによって結合された標的タンパク質分子はそのホールド状態のまま存在する。したがって、ホールド標的タンパク質は、リガンド不存在下よりも、標的タンパク質に結合する試験リガンドの存在下でより多い程度で存在する。標的タンパク質へのリガンドの結合は、標的タンパク質のホールドおよびアンホールド状態の間を識別するいずれの方法によっても判定し得る。このアッセイを行うために、標的タンパク質の機能が知られている必要はない。試験リガンドとしてこの方法によって実質的にいずれの剤も評価し得、限定されるものではないが、金属、ポリペプチド、タンパク質、脂質、多糖、ポリヌクレオチドおよび小有機分子が含まれる。

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【0064】

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標的タンパク質に対するリガンドを同定するもう1の方法は、出典明示して本明細書の一部とみなす、Wieboldtら, Anal. Chem., 69:1683-1691 (1997)に記載されている。この技術は、標的タンパク質への結合について溶液相中で一時に20-30の剤のコンビナトリアル・ライブラリーをスクリーニングする。標的タンパク質に結合する剤は、遠心限外濾過によって他のライブラリー成分から分離する。つづいて、フィルター上に保持された特異的に選択された分子を標的タンパク質から遊離させ、HPLCおよび空気圧アシスト電子スプレー（イオンスプレー）イオン化質量分析によって分析する。この手法は標的タンパク質に対して最高のアフィニティーを有するライブラリー成分を選択し、特に小分子ライブラリーに有用である。

【0065】

初期スクリーニングによって同定されたインヒビター／バインダーは、P. multocida感染症のイン・ビボ（in vivo）マウス・モデルにおける病原性に対するその効果について評価する。菌血症、心内膜炎、敗血性関節炎、柔組織膿瘍または肺炎のモデルを利用し得る。他の動物の使用を含むモデルも本発明によって理解されている。例えば、ウサギを、変化する量の推定インヒビター／バインダー化合物を投与する前後に野生型P. multocida株で攻撃し得る。推定インヒビター／バインダー化合物の代わりに塩類溶液のみを投与した対照動物は、それによって試験動物の悪化を判定し得る基準を提供する。他の動物モデルには、Animal and Plant Health Inspection Service, USDA, 1994年1月1日 編, 第113章, 69-113.70; PancieraおよびCorstvet, Am. J. Vet. Res. 45: 2532-2537; Amesら, Can. J. Comp. Med. 49: 395-400 (1984);ならびにMukkur, Infection and Immunity 18: 583-585 (1977)に記載されているものが含まれる。細菌の病原性を干渉するインヒビター／バインダーは、感染症の確立を予防し得、あるいは一旦確立した感染症の結果を逆転させ得る。

【0066】

フロイント完全アジュバントおよびフロイント不完全アジュバント、ミコール酸ベースのアジュバント（例えば、トレハロース ジミコレート）、細菌リポ多糖（LPS）、ペプチドグリカン（すなわち、ムレイン、ムコペプチド、またはN-オパカ（N-Opaca）、ムラミルジペプチド[MDP]またはMDPアナログのごとき糖タンパク質）、プロテオグリカン（例えば、クレブシエラ・ニューモニエ（Klebsiella pneumoniae）、連鎖球菌調製物（例えば、OK432）、ビオスチムTM（BiostimTM）（例えば、OLK2）、欧州特許第109 942号、第180 564号および第231 039号の「イスコムス（Iscoms）」、水酸化アルミニウム、サポニン、DEAE-デキストラン、（ミグリオールのごとき）中性油、（落花生油のごとき）植物油、リポソーム、プルロニック^R（Pluronic^R）ポリオール、Ribiアジュバント系（例えば、GB-A-2 189 141号を参照されたい）、またはインターロイキンのごとき油ベースのアジュバントを含む当該技術分野で知られているいずれのアジュバントもワクチン組成物に用い得、特に細胞性免疫を刺激するものを用い得る。アミコラータ（Amicrolata）、アクチノマイセテールス（Actinomycetales）目の細菌属の抽出物よりなるもう1のアジュバントは、米国特許第4,877,612号に記載されている。さらに、特許アジュバント混合物が市販されている。用いるアジュバントは、一部分、レシピエント生物に依存するであろう。投与するアジュバントの量は、動物のタイプおよびサイズに依存するであろう。最適投与量は日常的な方法によって容易に決定し得る。

【0067】

ワクチン組成物は、所望により、医薬的なビヒクル、賦形剤または媒体として作用するワクチン-和合性の医薬上許容し得る（すなわち無菌であって無毒な）液体、半固体または固体の希釈剤を含み得る。当該技術分野で知られているいずれの希釈剤も用い得る。例示的な希釈剤には、限定されるものではないが、モノラウリン酸ポリオキシエチレンソルビタン、ステアリン酸マグネシウム、メチル-およびプロピルヒドロキシベンゾエート、タルク、アルギン酸塩、デンプン、ラクトース、スクロース、デキストロース、ソルビトール、マンニトール、アカシアガム、リン酸カルシウム、鉱油、カカオ脂、およびテオブロマ（theobroma）の油が含まれる。

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【0068】

ワクチン組成物はデリバリーに簡便な形態で包装し得る。組成物はカプセル剤、キャプレンツ剤、サシェ剤、カシェ剤、ゼラチン、紙または他の容器内に入れることができる。レシピエント生物への免疫原性組成物の注入と和合する場合、特に、免疫原性組成物をユニット投与量形でデリバリーする場合、これらのデリバリー形態が好ましい。投与量ユニットは、例えば、錠剤、カプセル剤、坐剤またはカシェ剤に包装し得る。

【0069】

ワクチン組成物は、例えば、経口、舌下、鼻腔、肛門、または腔デリバリーによって、静脈内、皮内、筋肉内、乳房内、腹膜内または皮下注射を含む方法いずれかの慣用的な方法によって免疫感作すべき対象に導入し得る。治療は、単一用量または一定期間にわたる複数用量よりなり得る。

【実施例】

【0070】

本発明は、細菌感染症および／またはそれと関連する病徴を予防または軽減するためのワクチン薬剤を製造するための本発明の弱毒細菌株の使用も包含する。本発明は、細菌感染症および／またはそれと関連する病徴を予防または軽減するための医薬を製造するための本発明のインヒビターの使用も提供する。

【0071】

本発明を以下の実施例によって説明する。実施例1は*P. multocida*突然変異体の構築を記載する。実施例2は*P. multocida*突然変異体のスクリーニングに関する。実施例3は*P. multocida*突然変異体の病原性を判定する方法を扱う。実施例4は*P. multocida*病原性遺伝子のクローニングを記載する。実施例5は*P. multocida*病原性遺伝子に関連する他の種における遺伝子の同定を扱う。実施例6は*A. pleuropneumoniae*突然変異体の構築を記載する。実施例7は弱毒化*A. pleuropneumoniae*突然変異体のスクリーニングを扱う。実施例8は*A. pleuropneumoniae*病原性遺伝子の同定に関する。実施例9は*A. pleuropneumoniae*の突然変異体および野生型細菌の競合的攻撃を記載する。実施例10は同定した*A. pleuropneumoniae*遺伝子の特徴付ける。実施例11は野生型細菌攻撃に対して保護する*A. pleuropneumoniae*突然変異体の効力を扱う。実施例12は*P. (Mannheimia) haemolytica*における種ホモログ病原性遺伝子の同定を記載する。

【0072】

実施例1 タグを付加したトランスポゾン*P. multocida*突然変異体のライブラリーの構築
タグを付加したトランスポゾン突然変異体のライブラリーは、親ベクター pLOF/Km [Herreroら, J. Bacteriol., 172: 6557-67 (1990)]中に構築し、これは*P. multocida*で機能性かつランダムであることが以前に示されている [Leeら, Vet. Microbiol., 50: 143-8(1996)]。プラスミド pLOF/Kmはスーサイド・ベクター pGP704を改変して構築し、それはTacプロモーター制御下のトランスポザーゼ遺伝子ならびにカナマイシン耐性をコードするミニ-Tn10トランスポザブル・エレメントを含んでいた。プラスミド pTEF-1は半ランダム[NK]₃₅配列を含む配列タグを受容するように pLOF/Kmを改変することによって以下に記載するごとく構築した。

【0073】

プラスミド pLOF/Kmをまず改変してマルチプルクローニング領域中のユニークKpnI制限部位を除去し、ついでミニ-Tn10領域中に新たなKpnI部位を導入した。そのプラスミドをKpnIで消化し、生じた突出末端を製造業者が指示するプロトコールに従ってクレノウ・ポリメラーゼで埋めた。本明細書中に記載する制限消化および連結は、製造業者が指示するプロトコールに従って行った (Gibco BRL, Gaithersburg, MD and Boehringer Mannheim, Indianapolis, IN)。平滑末端生成物は自己連結して、pLOF/Km--KpnIと命名したプラスミドを生成し、これを増幅用のイー・コリ (*E. coli*) DH5α: λpir に形質転換した。イー・コリ DH5α: (λpir φ80dlacZ△M15, recA1, endA1, gyrA96, thi-1, hsdR17(r_k⁻, m_k^{sup}E44, relA1, deoR, △(lacZYA-argF)U169を、L

B (Luria-Bertani) 培地中、37℃にて増殖させた。プラスミドはQIAGEN Inc. (Santa Clarita, CA) からのQIAGEN SpinPrepsを用いて調製し、ミニ-Tn10トランスポザブル・エレメント内のユニーク部位を切断するSfiIで消化した。SfiI-KpnI-SfiIアダプターは、オリゴヌクレオチドTEF1 (配列番号: 86) およびTEF3 (配列番号: 87) をアニーリングさせることによって調製し、得られた二本鎖アダプターをSfiI部位に連結させてプラスミドpTEF-1を作製した。オリゴヌクレオチドTEF1およびTEF3 (ならびに本明細書中に記載する全ての他のオリゴヌクレオチド) は、Genosys Biotechnologies (The Woodlands, TX) によって合成した。

【0074】

【化1】

TEF1 5'-AGGCCGGTACCGGCCGCCT 配列番号: 86

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TEF3 5'-CGGCCGGTACCGGCCTAGG 配列番号: 87

【0075】

pTEF-1のKpnI部位へ挿入するためのユニーク配列タグは以下の通り調製した。250μMの各dNTP、1.5mMのMg(OAc)₂、テンプレートDNAとしての100ピコモルの各プライマーTEF14 (配列番号: 88) およびTEF15 (配列番号: 89)、1ngのTEF26 (配列番号: 90) ならびに2.5単位の組換えTthDNAポリメラーゼXLを含む条件下で、GeneAmp XL PCRキット (PE Applied Biosystems, Foster City, CA) を用いてPCRを行って二本鎖DNAタグを作製した。

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【0076】

【化2】

TEF14 5'-CATGGTACCCATTCTAAC 配列番号: 88

TEF15 5'-CTAGGTACCTACAACCTC 配列番号: 89

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TEF26 配列番号: 90

5'-CTAGGTACCTACAACCTCAAGCTT-[NK]₃₅-

AAGCTTGGTTAGAATGGGTACCATG

【0077】

反応条件は、95℃にて1分間の初期インキュベーションにつづく、95℃にて30秒間、45℃にて45秒間、ついで72℃にて15秒間の30サイクルにつづく、72℃にて2分間の最終インキュベーションを含む。PCR産物をKpnIで消化し、製造業者の指示するプロトコールに従ってQIAGEN Nucleotide Removal Kit (QIAGEN, Inc., Chatsworth, GA) を用いて精製した。ユニークタグ配列を、標準的な手法を用いて予めKpnIで消化し、子ウシ腸アルカリホスファターゼ (Boehringer Mannheim) で脱リン酸化した線状pTEF-1のミニ-Tn10エレメントに連結した。得られたプラスミド・ライブラリーをイー・コリDH5α:λpirに形質転換した。ハイブリダイゼーションおよび検出を以下の通り行いつつ、DIGの使用者案内書 (Boehringer-Mannheim) に従ってコロニープロット分析を行った。

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【0078】

ハイブリダイゼーションは、Genius Non-Radioactive User's Guide (Boehringer Mannhe

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im Biochemicals)、DIG-PCR labeling kit (Boehringer Mannheim Biochemicals) 用製品シート、および CSPD (Boehringer Mannheim Biochemicals) 用製品シートに従って本質的に行った。プローブの調製については、Amplitaq PCR 緩衝液 (PE Applied Biosystems)、200 μ M の dNTP、140 ピコモルの各プライマー TEF5 (配列番号: 9) および TEF6 (配列番号: 92)、2 mM の $MgCl_2$ 、2.5 単位の Amplitaq (PE Applied Biosystems) および 1 ng のプラスミド DNA を用いて、100 μ l の一次 PCR 反応を設定した。

【0079】

【化3】

TEF5 5'-TACCTACAACCTCAAGCT 配列番号: 91

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TEF6 5'-TACCCATTCTAACCAAGC 配列番号: 92

【0080】

サイクル条件は、95 $^{\circ}C$ にて2分間の初期インキュベートにつづく、95 $^{\circ}C$ にて30秒間、50 $^{\circ}C$ にて45秒間、72 $^{\circ}C$ にて15秒間の35サイクルにつづく72 $^{\circ}C$ にて3分間の最終インキュベートを含んでいた。増幅産物を2% - 3:1 NuSieve GTG (FMC BioProducts, Rockland, ME, USA): アガロースゲル上の電気泳動を用いて分離し、109 bp を切除して精製した。ゲル抽出は QIAGEN Gel Extraction Kit (QIAGEN) を用いて行った。約15 ng の一次産物を、DIG PCR Kit、50 ピコモルの各プライマー TEF24 および TEF25 および DIG Probe Synthesis Mix と 2 mM の dNTP 保存溶液の1:1混合物を用いる50 μ l の PCR 反応中で標識した。

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【0081】

【化4】

TEF24 5'-TACCTACAACCTCAAGCTT 配列番号: 93

TEF25 5'-TACCCATTCTAACCAAGCTT 配列番号: 94

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【0082】

PCR 条件は、95 $^{\circ}C$ にて4分間の初期インキュベートにつづく、95 $^{\circ}C$ にて30秒間、50 $^{\circ}C$ にて45秒間、72 $^{\circ}C$ にて15秒間の25サイクル、ならびに72 $^{\circ}C$ にて3分間の最終インキュベートを含んでいた。標識したPCR産物を90 μ l の合計反応体積中で HindIII で消化し、2% - 3:1 NuSieve GTG (FMC BioProducts): アガロースゲルを用いるコンスタント・プライマーアームから精製した。標識した可変タグを含有する領域を切除し、全ゲルスライスを10 ml の DIG EasyHyb 中、95 $^{\circ}C$ にて10分間溶解および変性させた。

【0083】

ドットプロットは、Hybond^R - N⁺ 膜 (Amersham-Pharmacia Biotech) を用いて調製した。各タグ用の標的DNAは、ほぼ30 ng のPCR産物を用いて96ウェルプレート中で調製した。等容量の0.1 N NaOH を添加して試料を変性させ、各試料を Schleicher and Schuell (Keene, NH, USA) からの Manifold ITM Dot-Blot Apparatus を用いて最小限の真空中で膜に適用した。各ウェルを150 μ l の中和溶液 (0.5 M トリス / 3 M NaCl、pH 7.5) および150 μ l の 2 $\times$ SSC で洗浄した。膜を Stratallinker (Stratagene, La Jolla, CA, USA) 中で UV-架橋し、20 ml の DIG EasyHyb Buffer 中、42 $^{\circ}C$ にて1時間ハイブリダイズさせた。変性したプローブを添加し、ハイブリダイゼーションを42 $^{\circ}C$ にて一晩行った。膜を0.1% SDS を含有する 2 $\times$ SSC で各洗浄につき5分間2回洗浄

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した。標準Genius Detectionプロトコール (Genius Manual) を用いて進行する前に、2の高ストリンジェンシー洗浄を0.1%のSDSを含有する予め加温した50mlの0.1×SSC緩衝液中、68℃にて15分間行った。

【0084】

安全性、低コスト、使用し易さ、および危険な材料を減少させるために、非一放射性検出系を用いることが望ましい。以前に記載された同様な手法[Meiら, Mol. Microbiol. 26: 399-407 (1997)]を用いる初期実験においては、ネガティブ対照において許容できないバックグラウンド・レベルのハイブリダイゼーションが得られた。バックグラウンドを低下させるために、タグの長さを30bp増加させて合計70とし、増幅プライマーを長くして可変領域を挟む全ての配列を含め、低濃度のdig-dUTPを用い、配列タグ領域を挟む保存配列をゲル精製によって取り出した。最も重要なことは、PCRを用いて、トランスポゾンそれ自体からのバックグラウンド・ハイブリダイゼーションを検出した後にタグを付加したトランスポゾンを含む全プラスミドよりもむしろ、ドット・プロットにおける標的DNAとして[NK]₃₅配列タグを作製した。これらの改変を用いて、バックグラウンドを排除し、化学ルミネセンス／非放射性スクリーニングをより効果的とした。

【0085】

PCR生成配列タグとpTEF-1の連結から生じたほぼ400の異なる形質転換体をコロニープロットによってスクリーニングし、さらなる使用のために96の最も強いハイブリダイズ・コロニーをマイクロタイター・プレートに結合させた。二重のタグの可能性は非常に低い、マスタータグのプレートの半分を他のものに対してプローブして、タグが二重になっていないことを確認した。これらのタグを含むプラスミドを精製して、イー・コリス17-1:λpir(pir, recA, thi, pro, hsd, (r-m+), RP4-2, (Tc::Mu), (Km::Tn7), [TmpR], [SmR])に形質転換し、その形質転換細菌をLB培地中、37℃にて増殖させた。各96のタグを付加したプラスミドpTEF-1を含むイー・コリス17-1:λpir形質転換体を接合交配に用いて、*P. multocida*のトランスポゾン突然変異体を作製した。*P. multocida*株TF5は、ウシ臨床単離株である、UC6731由来の自然発生ナリジキン酸耐性突然変異体である。*P. multocida*株は、プレート上で増殖させる場合には、5%CO₂下、ブレインハート浸出液(BHI)培地(Difco Laboratories, Detroit, MI, USA)上、37℃にて増殖させた。交配は各イー・コリス17-1:λpir/pTEF1:[NK]₃₅クローンおよびTF5株を後期対数増加期まで増殖させることによって設定した。各タグを付加したpTEF-1クローンにつき50μlの培地を200μlのTF5培地と混合し、100mMのIPTGおよび10mMのMgSO₄を含むBHIプレート上に予め置いておいた0.22 μm フィルターに50μlの各交配混合物をスポットした。5%CO₂下、37℃にて一晚インキュベートした後に、各フィルターを3mlのPBSに入れて交配混合物を洗い取り、各25μlをBHIN⁵⁰K¹⁰⁰プレートに平板した。選択的一晩増殖後に、コロニーを200μlのBHIN⁵⁰K⁵⁰へのトゥースピック移植(toothpick transfer)によってマイクロタイター・プレートに合して、マイクロタイター・プレート中の各ウェルが同じ配列タグを有するトランスポゾン突然変異体を常に含むことを確かめた。一晚増殖後に、50μlの75%グリセリンを各ウェルに添加し、プレートを-80℃にて凍結保存した。

【0086】

トランスポゾン突然変異体をマイクロタイター・プレートに移すことによって19のプールを合して、そのウェルに対して適当なタグを有するトランスポゾン突然変異体を各ウェルが含んでいたことを確かめた。他言すれば、これらの突然変異体内のトランスポゾンの位置は異なり得るが、各マイクロタイター・プレート中の特定のウェルは同一配列タグを有するトランスポゾン突然変異体を常に含んでいた。

【0087】

実施例2 弱毒化*P. multocida*突然変異体のげっ歯類スクリーニング

敗血症のげっ歯類モデルを用いて、*Pasteurella multocida*のトランスポゾン突然変異体

の19のプールをスクリーニングした。プールした*P. multocida*トランスポゾン突然変異体の凍結プレートを -80°C 保存から取り出し、各ウェルからの $10\mu\text{l}$ を $50\mu\text{g}/\text{ml}$ のナリジキシン酸 (Sigma) および $50\mu\text{l}/\text{ml}$ のカナマイシン (Sigma) と共に $200\mu\text{l}$ のブレインハート浸出液 (DIFCO) ($\text{BHI N}^{50}\text{K}^{50}$) を含有する新たな96ウェル丸底プレート (Corning Costar, Cambridge, MA, USA) に移すことによって二次培養した。プレートを振盪せずに $5\%\text{CO}_2$ 下、 37°C にて一晩インキュベートした。各ウェルからの $10\mu\text{l}$ をウェル当り $100\mu\text{l}$ のBHIを含有する新たな平底96ウェルプレート (Corning Costar) に移し、ほぼ 150rpm で振盪しつつ 37°C にてインキュベートすることによって一晩プレートを二次培養した。マイクロタイター・プレートリーダーを用いて OD_{540} をモニターした。ほぼ 0.2 ないし 0.25 の OD_{540} で、各プレートをプールして、マイクロタイター・プレートの各ウェルからの $100\mu\text{l}$ を合することによって「投入プール」を形成した。その培養物をBHI中で適当に希釈してほぼ 10^4 、 10^5 、 $10^6\text{CFU}/\text{ml}$ の用量とし、 0.2ml の各希釈物を用いて、腹腔内投与によって雌性 $14-16\text{g}$ のBALB/cマウスに感染させた。感染後2日に、1または2の生存しているマウスを安楽死させて脾臓を採取した。全脾臓を 1.0ml の無菌 0.9% 塩類溶液中でホモジナイズした。 10^{-2} から 10^{-5} のホモジネートの希釈物を調製し、 $\text{BHI N}^{50}\text{K}^{50}$ プレートに平板した。一晩増殖後に、少なくとも $20,000$ コロニーを 10ml のBHIブロス中にプールして「回収プール」を形成し、以前に記載されたプロトコール[F. M. Ausubelら(編), Current Protocols in Molecular Biology, vol. 1. John Wiley and Sons, New York, p.2.4.1-2.4.5.(1997)中のWilson]に従って、 0.5ml の回収プールを $3,500\times\text{g}$ にて遠心し、そのペレットを用いてゲノミックDNAを調製した。

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【0088】

病原性野生型*P. multocida*を用いた初期実験は、生物を脾臓、肺、腎臓および肝臓から回収し得ることを示し、これは感染の真正な敗血症モデルを示している。「投入」および「回収」の両方のプールについてのドット・ブロットを実施例1に記載したのと同様に行い、視覚的検査および半一定量分析の両方によって評価した。ハイブリダイゼーションは、投入および回収プールからの $5\mu\text{g}$ のゲノミックDNAをテンプレートとして用いる以外は、実施例1に記載したのと同様に行った。半一定量分析は、単一クローンにおける顕著な減少が起こったか否かを示している。突然変異体が宿主内で生存することができない場合には、回収シグナルは投入シグナルに比して非常に低く、高い投入／回収比を与えるにちがいない。大部分の突然変異体はイン・ビトロ (in vitro)と同様にイン・ビボ (in vivo)で増殖するであろう。したがって、それらのシグナルの比はほぼ1に等しいにちがいない。回収プールで非常に減少しているとして定量分析によって選抜したクローンを、さらなる実験用に選抜した。疑わしい投入／回収比を有するさらなるクローンは、ドット・ブロットから作成したフィルムを視覚的に評価した後にも選抜した。

【0089】

実施例3 *P. multocida*候補突然変異体についての病原性の決定

脾臓細胞から低い回収率を示した各潜在的な突然変異体を原プールプレートから単離し、個別に攻撃試験に用いて、該トランスポゾン突然変異体により生じた弱毒化を確認し、おおざっぱに評価した。in vivoスクリーンからの個々の候補突然変異体をヒツジ血液寒天プレート上、 $5\%\text{CO}_2$ 中、 37°C にて一晩増殖させた。各突然変異体のおよそ6のコロニーをBHIブロスに接種し、6時間増殖させた。希釈物を調製し、各々5のマウスに、各々 10^2 、 10^3 、 10^4 および 10^5CFU で上記したごとく感染させた。弱毒化を6日後の死亡率をその野生型と比較することによって決定した。生存しているマウスは保護されていたものと推定され、ついで、当該野生型株の LD_{50} のおよそ200倍の濃度の野生型*P. multocida*の用量で攻撃した。ついで、各攻撃した群のマウスについて生存率を決定した。

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【0090】

結果は、120の潜在的トランスポゾン突然変異体のうちの62が弱毒化し、野生型株よ

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りも少なくとも10倍高い概算LD₅₀を有することを示した。該クローンおよびそれらの概算LD₅₀値を表1に掲載する。野生型株での対照実験を各セットの攻撃と並行して行ったが、全ての場合において野生型攻撃群の死亡率は100%であった。

【0091】

LD₅₀値に加えて、表1にはワクチン化および攻撃実験からのデータも掲載している。簡単には、マウス群(n=5ないし10)は、病原性の野生型株のLD₅₀よりもほぼ200倍高い用量で表1に示す個々のP. multocida株を腹膜内注射によりワクチン化した。死亡率の数字を算出した後28日間、動物を観察した。

【0092】

【表3】

表1
P. multocida 病原性遺伝子

ヌクレオチド 配列番号:	代表的単離株	可能性のある 遺伝子の機能	ワクチン化 生存数/合計	攻撃 生存数/合計	LD ₅₀
-	野生型	-	0/10	-	<10
23	PM1B1	guaB	10/10, 10/10, 10/10	9/10, 9/10	4.3 x 10 ⁶
11	PM1D1	dsbB	10/10, 5/10	10/10, 5/5	8.4 x 10 ⁴
3	PM1BD7	atpG	5/5, 10/10	10/10	>3 x 10 ⁵
74	PM1BE11	yhcJ (HI0145)	10/10	5/10	>2 x 10 ⁵
70	PM1BF6	yabK (HI1020)	3/5, 8/10	9/9	>2 x 10 ⁵
19	PM2G8	fhaC	4/5, 9/10	9/9	>4 x 10 ⁵
76	PM3C9	yiaO (HI0146)	3/5		>6 x 10 ⁵
118	PM3G11	UnkO	4/5, 10/10	10/10	>3 x 10 ⁵
31	PM7B4	iroA (UnkB)	0/5		
17	PM4C6	fhaB (fhaB2)	2/5, 10/10, 9/10	10/10, 9/9	>3 x 10 ⁶
9	PM4G10-T9	dnaA	4/5		>5 x 10 ⁵
1	PM4D5-T5	atpB	5/5		>4 x 10 ⁵
53	PM4D5-T1	UnkC2	5/5		>4 x 10 ⁵
15	PM4F2	fhaB (fhaB1)	3/5, 6/10, 10/10	6/6, 10/10	>3 x 10 ⁵
41	PM5F7	mreB	4/5		1 x 10 ³
7	PM5E2	devB	0/5, 3/10	2/3	ND
68	PM6H5-T1	xylA	5/5		>3 x 10 ⁵
78	PM6H8	yigF (HI0719)	5/5, 9/10	9/9	>3 x 10 ⁵
108	PM7D12	pnp	5/5, 9/10	9/9	
51	PM8C1R1-T2	UnkC1	5/5		~6 x 10 ⁵
37	PM8C1-T3	mgIB	5/5		~6 x 10 ⁵
58	PM8C1R1-T6	UnkD1	5/5		~6 x 10 ⁵
45	PM10H7	purF (HI1007)	3/5, 8/10, 8/10	8/8, 8/8	>3 x 10 ⁵
25	PM10H10-T2	HI1501	5/5		>1 x 10 ⁴
72	PM11G8-T2	ygiK	5/5		>2.4 x 10 ³
21	PM11G8-T4	greA	5/5		>2.4 x 10 ³
84	PM12H6	yyam (HI0687)	3/5, 0/10		~2.2 x 10 ³
33	PM15G8-T2	kdtB	5/5		>1.2 x 10 ⁵
116	PM15G8-T1	UnkK	5/5		>1.2 x 10 ⁵
104	PM16G11-T1	hmbR	3/5		>1.9 x 10 ⁵
29	PM16G11-T2	hxuC	3/5		>1.9 x 10 ⁵
35	PM16H8	lgtC	5/5, 10/10	10/10	>2.4 x 10 ⁵
80	PM16H3	yleA (HI0019)	5/5, 10/10		>2.0 x 10 ⁵
49	PM17H6-T1	sopE	4/5		~6 x 10 ⁵
120	PM17H6	UnkP	4/5		~6 x 10 ⁵
5	PM18F5-T8	cap5E	5/5		>2.4 x 10 ⁵
82	PM18F5-T10	yoyB (HI0345)	5/5		>2.4 x 10 ⁵
13	PM19A1	exbB	5/5, 10/10	10/10	>1.2 x 10 ⁵
112	PM19D4	rci	5/5, 8/10	8/8	~1.6 x 10 ⁵
39	PM20A12	mioC (HI0669)	3/5, 8/10	8/8	~2 x 10 ⁴
60	PM20C2	UnkD2	5/5, 10/10	10/10	>8.2 x 10 ⁶

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【0093】

実施例4 *P. multocida*病原性に必要な遺伝子のクローニングおよび同定
弱毒化していることが確認された各トランスポゾン突然変異体を分析して、破壊されたオープン・リーディング・フレームの同一性をさらに決定した。各突然変異体からのDNAを増幅し、精製し、ついでトランスポゾン内を切断せず、該トランスポゾンとハイブリダイズする4~8 kbフラグメントを通常生成することが知られている制限酵素で消化した。該トランスポゾンによりコードされるカナマイシン抵抗性についての選抜を用いて、各トランスポゾン突然変異体につき少なくとも1のフラグメントをクローン化した。

【0094】

複数の制限酵素を用いたサザンハイブリダイゼーションを、クローニングに好適なサイズのフラグメントを同定するためのプローブとしてpLOF/Kmからの標識化1.8 kb *Mlu*Iフラグメントを用いて、各弱毒化突然変異体につき行った。各突然変異体からのミニ-Tn10エレメントおよびフランキングDNAを、内部プライマーTEF32およびTEF40、プライマーウォーキング、およびある場合においてはユニバーサルpUC-19プライマーを用いて決定したpUC19および該フランキング配列にクローン化した。

【0095】

【化5】

TEF-32 GGCAGAGCATTACGCTGAC

配列番号: 95

TEF-40 GTACCGGCCAGGCGGCCACGCGTATTC

配列番号: 96

【0096】

配列決定反応は、PE Applied Biosystems (Foster City, CA) からのBigDyeTM Dye Terminator Chemistry kitを用いて行い、ABI Prism 377 DNA Sequencer上で行った。推定される中断 (interrupted) オープン・リーディング・フレームの二本鎖配列を各クローンにつき得た。Sequencer3.0ソフトウェア (Genecodes, Corp., Ann Arbor, MI) を用いて、配列データを収集して解析した。GCGプログラム [Devereuxら, 1997. Wisconsin Package Version 9.0, 9.0 ed. Genetics Computer Group, Inc., Madison] を用いて、現在入手可能なデータベースにおいて相同な配列を検索した。

【0097】

弱毒化していることが同定されたクローンの37%に、該ミニ-Tn10トランスポザブルエレメントの多重挿入が存在していた。そのフランキング配列を含む各挿入を個別にpGP704中にクローン化し、該野生型株中に交配して、*P. multocida*の新たな突然変異体を作成し、その各々は、複数の起源挿入の1のみを運搬していた。個々の突然変異体を個別に再試験して、弱毒化表現型に寄与している挿入を決定した。該破壊された予想オープン・リーディング・フレームのヌクレオチド配列を両方の鎖を配列決定することによって決定し、ついで予想アミノ酸配列を用いて類似配列について現在入手可能なデータベースを検索した。配列は、知られている遺伝子、知られていない遺伝子および以前に配列決定された仮想オープン・リーディング・フレームに適合するか、または以前同定された配列のいずれにも適合しないかのいずれかであった。以前同定された配列にホモロジーを有する遺伝子については、表1に示すごとく、潜在的な機能を割当てた。

【0098】

実施例5 他の種における関連遺伝子の同定

別の実験において、*Actinobacillus pleuropneumoniae* (APP) を用いてSTMも行った。App株の1は、配列決定した遺伝子 (配列番号: 97) 中に挿入を含有し、*P. multocida*のatpG遺伝子の種ホモログとして同定された。この結果は、以前に知られていなかった*P. multocida*遺伝子に対するホモログが他の細菌種にも存在することを示し、それを突然変異させてワクチン組成物に使用するための他の細菌種の弱毒化株を生成することもできることを示した。他の*P. multocida*遺伝子のホモログが他の細菌種に存在するかどうかを決定するために、プローブとして*A. pleuropneumoniae*のatpG遺伝子を用いて

他の種からのゲノムDNAに対してサザンハイブリダイゼーションを行った。

【0099】

Actinobacillus pleuropneumoniae、*Pasteurella haemolytica* (Ph)、*P. multocida*、および*Haemophilus somnus* (Hs) のゲノムDNAをCTAB法を用いて単離し、EcoRIおよびHindIIIで37℃にて2時間消化した。消化したDNAを、0.7%寒天ゲル上、TAEバッファー中で40Vにて一晩分離した。該ゲルを、順次、0.1M HCl中に30分間、0.5M NaOH/1.5M NaCl中に15分間を各々2回、ついで2.5M NaCl/1M Tris、pH7.5中に2回浸漬した。そのDNAを20×SSCバッファー(3M NaCl/0.3M クエン酸ナトリウム)を用いて、ニトロセルロース膜(Amersham Hybond N⁺)に一晩転写した。該DNAは、自己架橋設定(120ミリジュール)したUV Stratalinkerを用いて該膜に架橋した。該膜を5×SSC/1%ブロッキング溶液/0.1% ラウロイルサルコシナトリウム/0.02% SDS中、50℃にて、ほぼ7時間プレハイブリダイズさせ、ついでPCR生成atgプローブを含有する同溶液中、50℃にて一晩ハイブリダイズさせた。

【0100】

プローブは、GeneAmpPCRシステム2400において、GeneAmpXLPCRキットのプライマーDEL-1389(配列番号:98)およびTEF-46(配列番号:99)を用いて調製した。テンプレートはゲノム*A. pleuropneumoniae* DNAを用いた。

【0101】

【化6】

DEL-1389 TCTCCATTCCCTTGCTGCGGCAGGG

配列番号:98

TEF-46 GGAATTACAGCCGGATCCGGG

配列番号:99

【0102】

PCRは、初期加熱工程を94℃にて5分間、94℃にて30秒間の変性、50℃にて30秒間のアニーリング、および72℃にて3分間の伸長の30サイクル、ついで72℃にて3分間の最終増幅で行った。増幅産物はアガロースゲル上で分離し、QIAquickゲル精製キット(QIAGEN)を用いて精製し、ついでおよびDIG-High Primerキット(Boehringer Mannheim)を用いて標識した。プロットをハイブリダイゼーション溶液から取り出し、2×SSC中で濯ぎ、同バッファー中で各洗浄につき5分間、2回洗浄した。ついで、該プロットを0.5×SSC中、60℃にて各々15分間、2回洗浄した。相同なバンドをDIG Nucleic Acid Detection Kit(Boehringer Mannheim)を用いて視覚化した。

【0103】

EcoRI消化DNAを用いて、*Pasteurella haemolytica*、*Haemophilus somnus*および*A. pleuropneumoniae*において単一のバンドを検出した。*Pasteurella multocida*からはEcoRI消化DNAを用いて2のバンドを検出した。

【0104】

実施例6 タグを付加したトランスポゾン*P. multocida*突然変異体のライブラリーの構築 pLof/Kmを用いるトランスポゾン突然変異誘発は、*A. pleuropneumoniae*において機能的かつランダムであることが以前に報告されている[Tasconら, J. Bacteriol. 175: 5717-22 (1993)]。*A. pleuropneumoniae*のタグを付加したトランスポゾン突然変異体を構築するために、予め選択したタグを付加したプラスミド(pTEF-1:[NK]₃₅)を含む96の各*E. coli* S17-1:αpir形質転換体を接合性交配に用いて、*A. pleuropneumoniae*株AP225、in vivo継代したATCC27088株由来の血清型1の自然発生ナリジキシン酸抵抗性突然変異体を生成した。*A. pleuropneumoniae*株は、10μg/mlのB-ニコチンアミドアデニン=ジヌクレオチド(V¹⁰) (Sigma, St. Louis, Missouri)を含有するブレインハート滲出液(BHI) (Difco Laboratories, Detroit,

MI) 培地上、37℃にて増殖させ、プレート上で増殖させる場合は5% CO₂ 中で増殖させた。E.coli S17-1:λpir (λpir, recA, thi, pro, hsdR (r_k -, m_k +), RP4-2, (Tc^R : : Mu), (Km^R : : Tn7), [Tm p^R], [Sm^R]) をルリアーベルターニ (Luria-Bertani; LB) 培地中、37℃にて繁殖させた。必要な場合には、抗生物質を100 μm/ml アンピシリン (Sigma)、50 μm/ml ナリジキシン酸 (N⁵⁰) (Sigma)、および50 (K⁵⁰) もしくは100 (K¹⁰⁰) μg/ml のカナマイシン (Sigma) で用いた。

【0105】

交配は、各E.coli S17-1:λpir/pTEF1:[NK]₃₅ クローンおよびAP 225株を後期対数増加期まで増殖させることによって設定した。各タグを付加したpTEF-1クローンにつき50 μlのアリコートの培養液を150 μlのAPP255培養液と混合し、ついで100 μM IPTGおよび10 mM MgSO₄ を含有するBHIV¹⁰ プレート上に予め設置した0.22 μm フィルター上に50 μlの各交配混合物をスポットした。5% CO₂ 下、37℃にて一晚インキュベートした後に、各フィルターの交配混合物を2 mlのPBS中に洗い出し、各々の200 μlをBHIV¹⁰ N⁵⁰ K¹⁰⁰ プレートに平板した。選択的に一晚増殖させた後に、200 μl BHIV¹⁰ N⁵⁰ K⁵⁰ に楊枝で移動させることによってコロニーをマイクロタイタープレートに集めて、マイクロタイタープレートの各ウェルが常に同一の配列タグを有するトランスポゾン突然変異体を含むことを確認した。一晚増殖させた後に、50 μlの75% グリセリンを各ウェルに添加し、プレートを-80℃にて凍結保存した。

【0106】

APPは、P. multocidaほどの多くの偏重を該ミニ-Tn10エレメントの多重挿入に対して有していないようである。該突然変異体のうちのほぼ3%しか多重挿入を含んでいないことが決定され、それは以前に報告された4%と一致する[Tasconら, J Bacteriol. 175:5717-22 (1993)]。APPにおける問題は、23S RNA領域への挿入を含有する多数の突然変異体（以下で論ずる）：13のユニーク部位への挿入を有する合計28の突然変異体を同定することからなる。これは、23S RNAが優先挿入部位を含有すること、およびAPPの増殖が宿主内で異なる生存を生じるのに十分なこれらの挿入によって影響を受けることを示しているのかも知れない。APP 23S RNAプローブを用いるサザンブロット解析は、H. influenzae中の5[Fleischmannら, Science 269:496-512 (1995)]およびE.coli中の7の完全オペロン[Blattnerら, Science 277:1453-1474 (1997)]と比較して、APPが3のリボソームオペロンしか含有していない可能性があることを示している。この部位の優先性および増殖速度に対するその影響は「飽和突然変異誘発」に対する明らかな障害となり得る。何故ならば、相当数のクローンがこれらrRNAに挿入を含有し、さらなるユニークな弱毒性突然変異体を得るために大量のスクリーニングが必要であろうからである。

【0107】

実施例7 弱毒化A. pleuropneumoniae突然変異体についてのブタ・スクリーニング
合計ほぼ800の突然変異体を含有するA. pleuropneumoniaeトランスポゾン突然変異体の20のプールを、ブタ気管内感染症モデルを用いてスクリーニングした。各プールを20の別々の動物でスクリーニングした。

【0108】

プールしたA. pleuropneumoniaeトランスポゾン突然変異体の凍結プレートを-80℃の貯蔵庫から取り出し、各ウェルからの20 μlを180 μlのBHIV¹⁰ N⁵⁰ K⁵⁰ を含有する新たな96ウェル丸底プレート (Corning Costar, Cambridge, MA, USA) に移すことによって継代培養した。プレートを振盪することなく5% CO₂ 中、37℃にて一晚インキュベートした。ついで、一晚置いたプレートを、各ウェルからの10 μlをウェルあたり100 μlのBHIV¹⁰ を含有する新たな平底96ウェルプレート (Corning Costar) に移すことによって継代培養し、150 rpmにて振盪しつつ、37℃にてインキュベートした。マイクロタイタープレートリーダーを用いてOD₅₆₂ をモニターし

た。約0.2ないし0.25のOD₅₆₂にて、各プレートプールして、該マイクロタイタープレートの各ウェルからの100 μ lと合することによって、「投入プール(input pool)」を形成した。培養物をBHI中に適当に希釈して、約 2×10^6 CFU/mlとした。各希釈プールにつき、4.0 mlを用いて、気管チューブを用いる気管内投与により10~20 kg SPFブタ(Whiteshire-Hamroc, Albion, IN)に感染させた。感染後約20時間にて、生存している全動物を麻酔し、肺を取り出した。洗浄を行って該肺に150 mlの殺菌PBSを灌流させることによって生存する細菌を回収し、ついで、それを揉んで流体を分散させた。洗浄流体を回収し、このプロセスを2回繰り返した。洗浄流体を450 $\times$ gにて10分間遠心して、大量のデブリを分離した。ついで、上清を2,800 $\times$ gにて遠心して、該細菌をペレット化した。ペレットを5 ml BHIに再懸濁し、 10^{-2} ないし 10^{-5} の範囲の希釈率でBHI V¹⁰ N⁵⁰ K⁵⁰ プレートに平板した。一晩増殖させた後に、少なくとも100,000のコロニーを10 μ lのBHIブロス中にプールして、「回収プール」を形成した。各回収プールの0.7 mlを用いて、CTAB法[Wilson, In Ausubelら, (eds.), Current Protocols in Molecular Biology, vol. 1. John Wiley and Sons, New York, p.2.4.1-2.4.5 (1997)]によりゲノムDNAを調製した。通常の動物からの回収率は、肺洗浄物から 10^8 CFU範囲であった。

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【0109】

先に記載したごとくドットプロットを行い、視覚検査および半定量的分析の両方によって評価した。全てのハイブリダイゼーションおよび検出は記載したごとく行った。簡単には、プローブは、一次PCR増幅につづく目的産物のアガロースゲル精製およびdig-d UTPを取込ませる(incorporating)二次PCR増幅によって調製した。TEF5、TEF6、TEF24、TEF25、TEF48およびTEF62を含むオリゴヌクレオチドは、Genosys Biotechnologies (The Woodlands, TX)により合成した。プライマーTEF69、TEF65およびTEF66もインバースPCRおよび配列決定に用いた。

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【0110】

【化7】

TEF69 GACGTTTCCCGTTGAATATGGCTC

配列番号: 166

TEF65 GCCGGATCCGGGATCATATGACAAGA

配列番号: 167

TEF66 GACAAGATGTGTATCCACCTTAAC

配列番号: 168

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【0111】

ついで、標識したPCR産物をHindIIIで消化して、ユニークタグ領域から一定のプライマーアームを分離した。標識した変化し得るタグを含むリュイ基を切り出し、全体のゲルスライスを溶解し、DIG EasyHyb中で変性した。ドットプロットを調製し、標準CSPD検出プロトコルを用いて検出した。フィルム露光を視覚評価のために行い、ルミネセントカウント・パー・セコンド(LCPS)を各ドットプロット試料につき測定した。各突然変異体に対するLCPS投入/LCPS回収比を用いて、弱毒化しているようである突然変異体を決定した。

投入プール中に存在するが、回収プール中では非常に減少しているとして選択したクローンをさらなる研究のために選択した。疑問のある投入/回収比を有するさらなるクローンも、ドットプロットから作成したフィルムを視覚評価した後に選択した。合計110のコロニーを選択した。

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【0112】

実施例8 A. pleuropneumoniae病原性遺伝子の同定

部分的フランキング配列を、インバースPCRおよび直接産物配列決定により該110の突然変異体の各々について決定した。インバースPCRを用いて、上記した直接配列決定用のフランキングDNA産物を作製した。配列決定反応は、PE Applied Biosystems (Foster City, CA)からのBigDyeTM Terminator Chemistry キットを用いて行い、ABI Prism 377 DNA Sequencer上で行った。Sequencher 3.0ソフトウェア(Genecodes, Corp., Ann

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Arbor, MI) を用いて、配列データをアセンブルして解析した。G C G プログラム [Devereux および Harberli, 1997. Wisconsin Package Version 9.0, 9.0 ed. Genetics Computer Group, Inc., Madison] を用いて、現在入手可能なデータベース中の相同的配列を検索した。

表 2 は、同定した *A. pleuropneumoniae* 遺伝子およびオープン・リーディング・フレームを決定し得る範囲を示す。配列番号は、ヌクレオチド配列および位置する推定されるアミノ酸配列に付される。

【0 1 1 3】

【表 4】

表 2

A. pleuropneumoniae オープンリーディングフレーム

完全オープンリーディングフレーム		開始コドンなしー終止コドン	
atpH	配列番号: 134	dksA	配列番号: 136
aptG	配列番号: 132	dnaK	配列番号: 138
exbB	配列番号: 140	HI0379	配列番号: 144
OmpP5	配列番号: 152	開始コドンなしー終止コドンなし	
OmpP5-2	配列番号: 150	pnp	配列番号: 154
tig	配列番号: 160	apvA-or 1	配列番号: 122
fkpA	配列番号: 142	apvA-or 2	配列番号: 124
hupA	配列番号: 146	apvB	配列番号: 126
rpmF	配列番号: 158	apvD	配列番号: 130
開始コドンー終止コドンなし		RNA または非コード配列	
lpdA	配列番号: 148	tRNA-leu	配列番号: 162
potD	配列番号: 156	tRNA-glu	配列番号: 163
yaeE	配列番号: 164		
apvC	配列番号: 128		

【0 1 1 4】

表 3 (後記、実施例 9) に掲載する推定同一性は、細菌データベースと比較することによって割当てた。1 1 0 の突然変異体は 3 5 群のユニークなトランスポゾン挿入を表した。遺伝子座あたりの異なる突然変異体の個数は変化し、いくつかのコロニーは、常に、同一 O R F の異なる部位内に挿入を含有するクローンに対する O R F 内の単一部位に挿入を含有した。3 の多重挿入が、多重 P C R バンドの産出および多重配列電気泳動図の生成による決定でスクリーンされた該 1 1 0 個のコロニー中に検出された。

【0 1 1 5】

実施例 9 *A. pleuropneumoniae* 突然変異体と野生型 A P P 2 2 5 との競争攻撃

回収した集団中に存在しないかあるいは非常に減少していた前記に同定した各ユニークな弱毒化突然変異体群からの代表的なクローンを、起源プールプレートから単離し、野生型株 (A P 2 2 5) との競争攻撃実験に用いて、トランスポゾン突然変異により生じた相対的弱毒化を確認した。突然変異体および野生型株を B H V I ^{1 0} 中で 0 . 6 - 0 . 9 の O D _{5 9 0} まで増殖させた。ほぼ 5 . 0 × 1 0 ⁶ C F U の野生型および突然変異体株を各々 4 m l の B H I に添加した。合計 4 m l の用量を用いて気管チューブを用いた気管内投与により 1 0 - 2 0 k g の S P F ブタに感染させた。感染後ほぼ 2 0 時間に、全生存動物を麻酔し、肺を取り出した。肺洗浄を記載したごとく行った。プレートカウントを B H I V ^{1 0} N ^{5 0} および B H I V ^{1 0} N ^{5 0} K ^{1 0 0} で行って、両方の投入培養物および肺洗浄試料中の突然変異体に対する野生型の相対数を決定した。競争指数 (Competitive Index; C I) は、[突然変異体 C F U / 野生型 C F U] 投入 / [突然変異体 C F U / 野生型 C F U] 回収として算出した。

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【0116】

35の潜在的トランスポゾン突然変異体のうちで、22が著しく弱毒化し、0.2未満の競争指数(CI)を有していた。STMスクリーニングの結果に基づく弱毒化していないようであったトランスポゾン突然変異体を、ポジティブコントロールとして1のプールから選択した。この突然変異体はほぼ0.6のin vivoのCIを有していた。この突然変異体についてin vitro競争も行い、0.8のCIを得た。その後、該突然変異体は、2のフェニルアラニンtRNAの間に挿入を含むことが決定された。

【0117】

ユニークな弱毒化単一挿入突然変異体の競争指数を表3に掲載する。atpG、pnp、およびexbB App突然変異体についての競争指数は、該突然変異体が野生型株と有効に競争できず、したがって弱毒化していることを示した。 10

【0118】

【表5】

表3
A. pleuropneumoniae 突然変異体の病原性および提唱機能

突然変異体	類似	推定または既知の機能	C.I.
AP20A6	<i>atpH</i>	ATP合成酵素	.009
AP7F10	<i>atpG</i>	ATP合成酵素	.013
AP17C6	<i>lpdA</i>	ジヒドロリポアミド・デヒドロゲナーゼ	.039
AP11E7	<i>exbB</i>	鉄化合物の輸送	.003,.003,.006
AP3H7	<i>potD</i>	スベルミジン/プテレシンの輸送	.308
AP8H6	<i>OmpP5</i>	アドヘシン/OmpAホモログ	.184
AP18H8	<i>OmpP5-2</i>	アドヘシン/OmpAホモログ	.552
AP13E9	<i>tig</i>	ペプチジル-プロリル・イソメラーゼ	.050
AP13C2	<i>fkpA</i>	ペプチジル-プロリル・イソメラーゼ	<.001
AP15C11	<i>pnp</i>	ポリヌクレオチド・ホスホリアーゼ	.032
AP18F12	<i>hupA</i>	ヒストン様タンパク質	.001
AP20F8	<i>dkkA</i>	dnaK 突然変異の用量依存性サプレッサー	.075
AP5G4	<i>dnaK</i>	ヒートショックタンパク質-分子シャペロン	.376
AP17C9	<i>tRNA-leu</i>	タンパク質合成	.059
AP5D6	<i>tRNA-glu</i>	タンパク質合成	.055
AP18B2	<i>rpmF</i>	タンパク質合成	.112
AP10E7	<i>yaeA</i>	未知	.001
AP19A5	H10379	未知	.061
AP10C10	<i>apvA</i>	未知	.157
AP18F5	<i>apvB</i>	未知	.103
AP2A6	<i>apvC</i>	未知	.091
AP2C11	<i>apvD</i>	未知	.014

【0119】

exbB突然変異体が3の異なる動物内で競争して0.003、0.003および0.006のCIが得られたことから、CIの精度は非常に良好のようであった。大きな動物実験における1の競争に基づき弱毒化を割当てするための競争指数の数の使用を、実施例11に 50

後記するごとく7の突然変異体を用いたブタ (n = 8) における予備ワクチン接種の結果に基づいてさらに確かめた。

【0120】

実施例10 弱毒化*A. pleuropneumoniae*病原性遺伝子の特徴付け

同定した*A. pleuropneumoniae*遺伝子は4の広い機能的分類を表す：生合成酵素、細胞内輸送成分、細胞内調節成分および未知物質。

F₀F₁H⁺-ATPase複合体のF₁-γサブユニットをコードするatpG遺伝子は、ATPの産生において、または、ATPを加水分解することによるプロトンの輸送において機能し得る。関連するatpG弱毒化突然変異体は、*P. multocida*においても同定された。F₁δサブユニットをコードするもう1のatp遺伝子、すなわちatpHも同定された。atp突然変異体の表現型には、非適合性酸-感受性表現型 [Foster, J Bacteriol. 173:6896-6902 (1991)]、*Salmonella typhimurium* [Garacia del Portilloら, Infect Immun. 61:4489-4492 (1993)] および*P. multocida* [前掲] における病原性の喪失、および*Haemophilus influenzae* Rdにおける形質転換頻度と反応能調節遺伝子の誘発との両方における低下 [Gwinら, J Bacteriol. 179:7351-20 (1997)] が含まれる。

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【0121】

LpdAは、2の酵素複合体：ピルビン酸デヒドロゲナーゼおよび2-オキソグルタル酸デヒドロゲナーゼのコンポーネントであるジヒドロリポアミド・デヒドロゲナーゼである。病原性に対する関連性は知られていないが、LpdAの産生は*Saomonella typhimurium* においてはヒト由来の殺菌性タンパク質にさらされた場合に誘導され、このことは、この誘導が外膜を修復しようとすることに関与している可能性があることを示唆しているかもしれない [Qiら, Mol Microbiol. 17:523-31 (1993)]。

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【0122】

増殖および生存に必要な欠乏性化合物の輸送はin vivoにおいて極めて重要である。ExbBは、TonB輸送複合体の一部であり [HantkeおよびZimmerman, Microbiology Letters. 49:31-35 (1981)]、少なくとも2の異なる方法でTonBと相互作用する [Karlssonら, Mol Microbiol. 8:389-96 (1993); Karlssonら, Mol Microbiol. 8:379-88 (1993)]。鉄を獲得することは病理に必須である。この研究において、APPおよび*P. multocida*の両方において弱毒化exbB突然変異体を同定した。いくつかのTonB依存性の鉄受容体が他の細菌において同定されている [Biswasら, Mol. Microbiol. 24:169-179 (1997); Braun, FEMS Microbiol Rev. 16:295-307 (1995); Elkinsら, Infect Immun. 66:151-160 (1998); Occhinoら, Mol Microbiol. 29:1493-507 (1998); StojiljkovicおよびSrinivasan, J Bacteriol. 179:805-12 1997)]。A. pleuropneumoniaeは2のトランスフェリン結合タンパク質を産生し、それらは鉄の獲得についてExbB/ExbD/TonB系に依存するようである。PotDは、細胞周辺結合タンパク質であって、それはスペルミジン (ポリアミン) 輸送に必要である [Kashiwagiら, J Biol Chem. 268:19358-63 (1993)]。Pasteurellaceaeファミリーのもう1のメンバーである*Pasteurella haemolytica*は、回復期患者または外膜タンパク質でワクチン化した子ウシにおける主要な免疫原であるpotD (Lpp38) のホモログを含んでいる [PandherおよびMurphy, Vet Microbiol. 51:331-41 (1996)]。P.haemolyticaにおいて、PotDは内外膜の両方に関連するようである。以前の研究が*Streptococcus pneumoniae*のpotD突然変異体が弱毒化していることを示している [Polissiら, Infect. Immun. 66:5620-9 (1998)] にも拘わらず、病原性または保護抗体に対する関係におけるPotDの役割は知られていない。

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【0123】

アドヘンシンまたはトキシンのごとき比較的わずかな「典型的病原性因子」しか、*Haemophilus influenzae*のOMP P5のホモログを除いて、同定されていない。H.influenzaeのOMP P5は主たる外膜タンパク質であり、それはタンパク質のOmpAポリンファミリーのタンパク質と関係がある [Munsonら, M Infect Immun. 61:4017-20 (1993)]。非分類*Haemophilus influenzae*のOMP P5は、繊維状構造として発現されるフィンブリンのサブユニットタンパク質をコードすることが示されており [Sirakovaら, Infect I

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mmun. 62:2002-20 (1994)]、それは病原性ならびにムチンおよび上皮細胞の両方の結合に寄与している [MiyamotoおよびBakaletz, Microb Pathog. 21:343-56 (1996); Reddyら, Infect Immun, 64:1477-9 (1996); Sirakovaら, Infect Immun. 62:2002-20 (1994)]。極めて重要な発見は、OMP P5 ホモログをコードするようである2の異なるORFが同定されたことである。これは、Haemophilus ducreyi由来の2の非常に類似するタンパク質、MOMPおよびOmpA2の場合も同様である。両方ともフィンブリエの産生に機能的に関与しているのか、および、2のかかるORFの存在が重複するまたは相補的な機能を有する分岐複製を表すのかを決定することが残っている。興味深いことに、該2のOMP P5突然変異体は全く異なるCI値を有するようであり、1のみのコピーについての必須性または機能性の差異を示している。OMP P5は長期の感染の間に分子的な変化を受けていることが示されている [Duimら, Infect Immun. 65:1351-1356 (1997)] が、これは点突然変異を受けている単一の遺伝子に限定されているようであり、多重遺伝子の分別発現 (differential expression) に起因する「タイプ・スイッチング」よりもアミノ酸変化を生じる。

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【0124】

タンパク質折畳み酵素は、細胞周辺および細胞外タンパク質を効果的に折畳むための重要な補助物であり、2の遺伝子が同定され、それらの産物はペプチジルプロリルイソメラーゼ活性を有する：fkpAおよびtig (トリガー因子)。FkpAはFK506-結合タンパク質ファミリーのメンバーである細胞周辺タンパク質である [HorneおよびYoung, Arch Microbiol. 163:357-65 (1995); Missiakasら, Mol Microbiol. 21:871-84 (1996)]。FkpAは、Salmonella typhimurium [Horneら, Infect Immun. 65:806-10 (1997)] およびLegionella pneumophilaホモログ、mip [Englebergら, Infect Immun. 57:1263-1270 (1989)] の細胞内生存に寄与することが示されており、病原性およびマクロファージの感染に寄与している [Cianciottoら, J. Infect. Dis. 162:121-6 (1990); Cianciottoら, Infect Immun. 57:1255-1262 (1989)]。Tig、すなわちトリガー因子 [CrookeおよびWickner, Proc. Natl. Acad. Sci. USA. 84:5261-20 (1987); GuthrieおよびWickner, J Bacteriol 172:5555-62 (1990); Hesterkampおよび Bukau., FEBS Lett. 389:32-4 (1996)に概説されている] は典型的なFKBP領域を含有するペプチジルプロリルイソメラーゼであるが [CallebautおよびMornon, FEBS Lett. 374:211-215 (1995)]、FK506によって影響されない [Stollerら, EMBO J. 14:4939-48 (1995)]。Tigは、リボソームおよび発生期ポリペプチド鎖に関連することが示されている [Hesterkampら, Proc Natl. Acad Sci USA 93:4437-41 (1996); Stollerら, EMBO J. 14:4939-48 (1995)]。可能性のある役割には、E.coli中の細胞分裂 [Guthrie, およびWickner, J Bacteriol. 172:5555-62 (1990)]、Streptococcus pyogenesシステインプロテイナーゼの分泌および活性化における役割 [Lyonら, EMBO J. 1:6263-75 (1998)]、およびBacillus subtilis中の飢餓条件下での生存 [Gothelら, Biochemistry 37:13392-9 (1998)]への知られていない影響を含む。

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【0125】

細菌の病理は、宿主内の広く様々な環境条件下で生存するために、多くのメカニズムを用いて、遺伝子発現を配位的に調節する。mRNA安定性における差異は、原核生物中の遺伝子発現を調整し得る [BelascoおよびHiggins, Gene, 72:15-23 (1988)]。例えば、rnr (vacB)がShigella flexneri中のプラスミド運搬毒性遺伝子の発現に要求され [Tobeら, J Bacteriol. 174:6359-67 (1992)]、RnaseRリボヌクレアーゼをコード化する [Chengら, J. Biol. Chem. 273:14077-14080 (1998)]。PNPはmRNAの分解に関わるポリヌクレオチドホスホリラーゼである。致死のpnp/rnr突然変異はなく、機能のありそうな重複を示唆する。したがって、rnrおよびpnpの両方が毒性遺伝子発現に関わる可能性がある。P.mulcosidaのpnp突然変異体は、マウス敗血症モデルにおいて無毒である (実施例2)。他のpnp関連表現型はBacillus subtilisにおける反応能欠乏および低温感受性を含む [WangおよびBechhofer, J Bacteriol. 178:2357-82 (1996)]。

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【0126】

H u p Aは細菌性ヒストン様タンパク質であり、それはH u p Bと組み合わせさせて、E.co
li中にH Uタンパク質を構築する。報告は、h u p Aおよびh u p Bは、いかなる観察可
能な表現型をも示さないことを示しているが [Huismanら, J Bacteriol. 171:3704-12 (1
989); Wadaら, J Mol. Biol. 204:581-91 (1988)]。h u p A-h u p B二重突然変異体
は、低温感受性でありヒートショックに感受性であって、部位特異的D N A組換えの多く
の形態においてブロックされることが示されている [Wadaら, J Mol. Biol. 204:581-91 (1
988); Wadaら, Gene. 76:345-52 (1989)]。一つの限定的データは、以前、h u p Aは毒
性に直接関わることを示した [Turnerら, Infect Immun. 66:2099-106 (1998)]。h u p
A弱毒化のメカニズムが知られないまま残っている。

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【0127】

D n a Kは、よく知られ、高度に保存されたヒートショックタンパク質であり、様々なス
トレスの多い環境変化に対する調節的反応に関わる ([LindquistおよびCraig, Annu Rev
Genet. 22:631-77 (1988)]に論評されている)。D n a Kは、マクロファージに食され
た後に著しく誘発されたストレスタンパク質であり [Yamamotoら, Microbiol Immunol. 3
8:295-300 (1994)]、Brucella suis d n a K突然変異体は、ヒトマクロファージ様細胞
内で繁殖はできなかった [Kohlerら, Mol Microbiol. 20:701-12 (1996)]。対症的に、
もう一つの細胞内病気素因、Listeria monocytogenesは食作用後d n a Kの誘発を示さ
なかった [Hanawaら, Infect Immun. 63:4595-9 (1995)]。Vibrio choleraのdnaK突然変
異体はT o x Rの産生およびin vitroでその調節された毒性因子に影響したが、同様の結
果は、in vivo成長細胞からは得られなかった [Chakarabartiら, Infect Immun. 67:1025
-1033 (1999)]。A.pleuropneumonia d n a K突然変異体のC Iはほとんどの病因性減弱
した突然変異体より高かったが、依然として、陽性対象株のおよそ半分であった。

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【0128】

D k s Aは、E.coliのd n a K突然変異体におけるフィラメンタス (filamentous) およ
び温度感受性成長の用量依存性サプレッサーである [KangおよびCraig, J Bacteriol. 17
2:205-64 (1990)]。現在、D k s Aについて明らかな分子機能はないが、該遺伝子はニ
ワトリおよび孵化したばかりのヒヨコにおけるSalmonella typhimuriumの毒性に重要であ
ることが確認された [Turnerら, Infect Immun. 66:2099-106 (1998)]。その研究におい
て、該D k s A突然変異体はグルコースまたはヒスチジンと一緒にではよく成長しなかつた
が、単に炭素源としてグルタミンまたはグルタミン酸エステルと一緒にだとよく成長したこ
とが記されている。この観察は、該d k s A突然変異体は、グルタミン酸エステルの生合
成において、幾分、力が減じられることを示すのであろう [Turnerら, Infect Immun. 66
:2099-106 (1998)]。

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【0129】

3つの遺伝子がタンパク質合成において役割を有することが確認された：t R N A-l e
u、t R N A-g l u、およびr p m F。タンパク質合成を除いて、t R N Aは、ペプチ
ドグリカン合成 [Stewartら, Nature 230:36-38 (1971)]、ポルフィリン環合成 [Jahnら
, Trends Biochem Sci. 17:215-8 (1992)]、分解のためのタンパク質の標的 [Tobiasら,
Science 254:1374-7 (1991)]、タンパク質への翻訳後アミノ酸付加 [LeibowitzおよびS
offer, B.B.R.C. 36:47-53 (1969)]、および細菌-真核細胞相互作用 [Grayら, J Bacte
riol. 174:1086-98 (1992); Hromokyjら, Mol Microbiol. 6:2113-24 (1992)]において
も、広汎な機能的な役割を有する。より詳しくは、t R N A-l e uは、転写減衰 [Cart
erら, Proc. Natl. Acad. Sci. USA 83:8127-8131 (1986)]、Pseudomonas syringaeによる病変形成 [Rich
およびWillis, J Bacteriol. 179:2247-58 (1997)] およびウロパソゲンE.coliの毒性 [Dorbrindtら,
FEMS Microbiol Lett. 162:135-141 (1998); Ritterら, Mol Microbiol. 17:109-21 (1995)]に
関連する。本発明者らが同定したt R N AがA. pleuropneumoniaeにおけるt R N A-l e uのマイ
ナー種を代表するかどうかは分らない。それにもかかわらず、t R N A-l e uは広汎な機能の
いずれか1を有する可能性がある。R p m Fはリボ染色体タンパク質であり、その遺伝子
もE.coli中の脂肪酸生合成酵素を

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含有するオペロンの部分である。f a b 遺伝子および r p m F の同一のクラスター形成が *Haemophilus influenzae* においても発生するが [Fleischmannら, Science 269:496-512 (1995)]、これは *A. pleuropneumoniae* において事実であるかどうかを示すためのさらなる研究が必要である。該 f a b 遺伝子の発現は、必ずしも、r p m F n o 上流を開始する転写物に依存するとは限らない。それは、r p m F 中に同定された第2のプロモータが存在しているからである [ZhangおよびCronan, Jr., J Bacteriol. 180:3295-303 (1998)]。

【0130】

病因性減弱した突然変異体の最終クラスは、未知の機能を持つ遺伝子、すなわち、以前に同定されていない遺伝子内の突然変異を含む。y a e A および H I O 3 7 9 のホモログは、それぞれ、*Escherichia coli* [Blattnerら, Science 277:1453-1474 (1997)] および *Haemophilus influenzae* [Fleischmannら, Science 269:496-512 (1995)] において、以前同定された。残る未知物は *Actinobacillus pleuropneumoniae* virulence 遺伝子 (a p v) と名付けられている。a p v C 遺伝子は、H I O 8 9 3 に著しい類似性を示すが、脂肪酸反応調節 B m 3 R 1 に類似する転写レプレッサーとしての H I O 8 3 9 の提案された類似性 [Palmer, J Biol Chem. 273:18109-16 (1998)] は疑わしい。a p v D 遺伝子も *E. coli* 由来の未知の機能を持つ推定膜タンパク質 (b 0 8 7 8) に最も類似している [Blattnerら, Science 277:1453-1474 (1997)]。2つの他の未知物、a p v A および a p v B は公開データベースには明らかに適合するものはなかった。

【0131】

実施例 1 1 *A. pleuropneumoniae* 突然変異体の安全性および効能 9つの群 (n=8) の S P F ブタ (4~5週齢、3~10kg) を用いて、生きた弱毒化したワクチン株として7つの *A. pleuropneumoniae* の安全性および効能を決定した。7つの群は、1日目に $10^{1.0}$ C F U の各突然変異体で鼻腔内感染させた。1つの群は、1日目および15日目に市販のワクチン Pleuromune (Bayer) でワクチン化し、1つのナイーブ群 (naive group) はワクチン化しなかった。29日目に、全群は、ブタあたり $1 \sim 5 \times 10^5$ C F U の野生型 A P P 2 2 5 で、鼻腔内免疫性テストした。この研究の42日目に、全ての生存している動物を麻酔し、剖検した。結果を表4に示す。

【0132】

【表6】

表 4

A. pleuropneumoniae 突然変異体の効力

鼻腔内攻撃後の%死亡率

ワクチン

	ワクチン化	攻撃
プレウロムン (Pleuromune)	0	37.5
exbB	0	0
tig	12.5	0
fkpA	12.5	0
HI0385	50.0	0
pnp	0	0
yaeE	0	0
atpG	0	0
なし	N/A	50.0

【0133】

該 *exbB*、*atpG*、*pnp*、および *yaeA* 突然変異体は、 10^{10} CFU の用量を鼻腔内投与したときに死亡を引き起こさなかった。該 *FkpA* および *tig* 突然変異体群は、各々 1 匹の死亡があり、該 *HIO379* 群（最高 2000 年 4 月 6 日、試験した 7 の突然変異体の *CI* は実施例 9 に示す）は 4 匹の死亡があった。このモデルに用いた野生型 *LD50* は、通常、 1×10^7 CFU であり、これらの突然変異体の各々は少なくとも 100 倍弱毒化され、*CI* と弱毒化との間にもっともな相関性があることを示している。

【0134】

実施例 12 *P. (Mannheimia) haemolytica* 種ホモログの同定

P. multocida および *A. pleuropneumoniae* において同定した病原性遺伝子に基づいて、*P. (Mannheimia) haemolytica* における関連する遺伝子、すなわち種ホモログを同定する試みを行った。示したように *P. (Mannheimia) haemolytica* 遺伝子を増幅するために以下の縮重プライマーを用いて PCR を行った。Sigma-Genosys (The Woodlands, TX) によって合成されたプライマー配列は標準的な一次略号を含み、ここで B は (C、G または T) のいずれかを示し、D は (G、A または T) のいずれかを示し、H は (A、C または T) のいずれかを示し、K は (G または T) のいずれかを示し、M は (A または C) のいずれかを示し、N は (A、G、C または T) のいずれかを示し、R は (A または G) のいずれかを示し、S は (G または C) のいずれかを示し、V は (G、A または C) のいずれかを示し、W は (A または T) のいずれかを示し、および Y は (C または T) のいずれかを示す。

【0135】

【化 8】

<i>atpG</i>	TEF146	ATG GCN GGN GCN AAR GAR AT	配列番号: 176
	TEF148	GCN GCY TTC ATN GCN ACC AT	配列番号: 177
<i>guaB</i>	TEF240	GGN TTY ATY CAY AAA AAY ATG	配列番号: 178
	TEF243	TCT TTN GTR ATN GTN ACA TCR TG	配列番号: 179
<i>pnp</i>	TEF141	GCS GGY AAA CCR CGT TGG GAT TGG	配列番号: 180
	TEF142	CRC CTA ARA TRT CTG AAA GCA CCA C	配列番号: 181
<i>purF</i>	TEF244	ATG TGY GGN ATY GTN GGN AT	配列番号: 182
	TEF247	CAT ATC AAT ACC ATA CAC ATT	配列番号: 183
<i>yjgF</i>	TEF162	GGN CCN TAY GTN CAR G	配列番号: 184
	TEF163	NGC NAC YTC NAC RCA	配列番号: 185

【0136】

最初の変性 PCR 産物を増幅するために、 $3.3 \times$ XL バッファー II (PE Applied Biosystems)、 $200 \mu\text{M}$ の dNTP、 25 ピコモルの各適当なプライマー、 0.8 mM の *MgCl₂*、 0.5 U の *rTth* DNA ポリメラーゼ、XL (PE Applied Biosystems) およびほぼ $1 \mu\text{g}$ の TFI DNA を用いて $50 \mu\text{l}$ 反応を設定した。

【0137】

サイクル条件は 94°C にて 1.5 分間につづいて； 94°C にて 15 秒間、 $40-60^\circ\text{C}$ にて 60 秒間、 72°C にて 1.5 分間を 35 サイクル；および 72°C にて 4 分間を最終ホールドとした。各 PCR 産物を QIAGEN Gel Extraction Kit (QIAGEN, Valencia CA) を用いたアガロースゲルからバンド精製した。

【0138】

配列決定反応は、PE Applied Biosystems (Foster City, CA) からの BigDyeTM Dye Terminator Chemistry kit を用いて行い、ABI Prism 377 DNA Sequencer 上で行った。各クローンについてのオープンリーディングフレーム (ORF) 用の二本鎖配列を得た。Sequench

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er 3.0ソフトウェア (Genecodes, Corp., Ann Arbor, MI)を用いて配列データをアセンブルし、解析した。G C Gプログラムを用い、現在利用可能なデータベース中でホモログ配列を検索することによってO R Fの同一性を確認した。

【0139】

Vectorette Kit (Genosys Biotechnologies, The Woodlands, TX)を用いて、各遺伝子のさらなるランキング配列を得た。Vectoretteライブラリーを製造業者の指示するプロトコールに従って調製した。Perkin Elmer Applied Biosystems GeneAmp XL PCR Kitコンポーネントを用いて、以下の反応条件を用いてVectorette P C R産物を作製した。50 μ lの反応は、3.3 $\times$ X Lバッファー I I (PE Applied Biosystems)、200 μ Mのd N T P、25 p m o lの各々の適当なプライマー (以下に示す)、0.8 mMのM g C l₂、0.5 Uのr T t h D N Aポリメラーゼ、X L (PE Applied Biosystems)および1 μ lの適当なvectoretteライブラリーを用いて設定した。 サイクル条件は、94 $^{\circ}$ Cにて1.5分間；につづく94 $^{\circ}$ Cにて20秒間、60 $^{\circ}$ Cにて45秒間、72 $^{\circ}$ Cにて4分間の35サイクル；および72 $^{\circ}$ Cにて7分間の最終保持であった。各ライブラリーの第2のプライマーは製造業者のvectoretteプライマーとした。

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【0140】

【表7】

表 5

遺伝子	Vectoretteライブラリ	プライマー
atpG	BglII, HindIII	TEF217 GAAGCCGCCATACGCTCTTGGG 配列番号: 186
	Clal	TEF218 GTTGCTTCCTTTGCCTGCACTGG 配列番号: 187
guaB	EcoRI	TEF265 GGCTCAGAAACAATACCACTTTCA 配列番号: 188
	HindIII, TaqI	TEF268 GCACCAAAGCAGAATTTGTCC 配列番号: 189
pnf	Clal, HincII	TEF219 GGTGATGATGTCGATGATAGTCCC 配列番号: 190
	TaqI,	TEF220 GGCGTATTAGCCGTGATGCCAACC 配列番号: 191
	BamHI	TEF286 GACCACTTAGGCGATATGGACTT 配列番号: 192
purF	TaqI	TEF271 ACCATCATAAATCGCCTGATTC 配列番号: 193 TEF292 ACCTGCGGCATCTTGTCTCTC 配列番号: 194
	HincII	TEF274 ACGGGTTTATTTTGCCTCTG 配列番号: 195
yjgF	Clal	TEF221 CGCCGGTTTCAGGATTCACGGG 配列番号: 196
	EcoRV	TEF281 CTGAACAACGTGAAAGCCAT 配列番号: 197

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【0141】

VectorettePCR産物を前記したごとくバンド精製し、配列決定した。atpG、guaB、pnf、purFおよびyjgF遺伝子のポリヌクレオチドを各々配列番号: 166、168、170、172および174に記載する。これらの遺伝子によってコードされるポリペプチドを各々配列番号: 167、169、171、173および175に記載する。

【0142】

上記の例示的实施例に記載された本発明の数多くの修飾および変形が当業者にとって生じるものと予測される。したがって、添付した特許請求の範囲に表されるごとき単にそのような限定を本発明におくべきである。

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(54) Title: ANTI-BACTERIAL VACCINE COMPOSITIONS

(57) Abstract: Gram negative bacterial virulence genes are identified, thereby allowing the identification of novel anti-bacterial agents that target these virulence genes and their products, and the provision of novel gram negative bacterial mutants useful in vaccines.

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ANTI-BACTERIAL VACCINE COMPOSITIONS

This application is a continuation-in-part of U.S. Patent Application Serial No: 09/545,199, filed April 6, 2000, which claims benefit of U.S. Provisional Patent Application Serial Nos. 60/153,453, filed September 10, 1999 and 60/128,689, filed April 9, 1999.

FIELD OF THE INVENTION

The present invention relates generally to the identification of genes responsible for virulence of *Pasteurellaceae* bacteria, thereby allowing for production of novel attenuated mutant strains useful in vaccines and identification of new anti-bacterial agents that target the virulence genes and their products.

BACKGROUND OF THE INVENTION

The family *Pasteurellaceae* encompasses several significant pathogens that infect a wide variety of animals. In addition to *P. multocida*, prominent members of the family include *Pasteurella (Mannheimia) haemolytica*, *Actinobacillus pleuropneumoniae* and *Haemophilus somnus*. *P. multocida* is a gram-negative, nonmotile coccobacillus which is found in the normal flora of many wild and domestic animals and is known to cause disease in numerous animal species worldwide [Biberstein, In M. Kilian, W. Frederickson, and E. L. Biberstein (ed.), *Haemophilus, Pasteurella, and Actinobacillus*. Academic Press, London, p. 61-73 (1981)]. The disease manifestations following infection include septicemias, bronchopneumonias, rhinitis, and wound infections [Reviewed in Shewen, *et al.*, In C. L. Gyles and C. O. Thoen (ed.), *Pathogenesis of Bacterial Infections in Animals*. Iowa State University Press, Ames, p. 216-225 (1993), incorporated herein by reference].

Infection by *P. multocida* generally results from invasion during periods of stress, but transmission may also occur by aerosol or contact exposure, or via flea and tick vectors. In fowl, *P. multocida* infection gives rise to acute to peracute septicemia, particularly prevalent in domestic turkeys and wild waterfowl under stress conditions associated with overcrowding, laying, molting, or severe

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climatic change. In cattle, a similar hemorrhagic septicemia follows infection and manifests conditions including high fever and depression, generally followed by quick death. Transmission is most likely through aerosol contact, but infection can also arise during periods of significant climatic change. In rabbits, infection gives rise to recurring purulent rhinitis, generally followed by conjunctivitis, otitis media, sinusitis, subcutaneous abscesses, and chronic bronchopneumonia. In severe infections, rabbit mortality arises from acute fibrinous bronchopneumonia, septicemia, or endotoxemia. Disease states normally arise during periods of stress. In pigs, common *P. multocida* disease states include atrophic rhinitis and bacterial pneumonia. Similar pneumonia conditions are also detected in dogs, cats, goats, and sheep. *P. multocida* is commonly detected in oral flora of many animals and is therefore a common contaminant in bite and scratch wounds.

P. multocida strains are normally designated by capsular serogroup and somatic serotype. Five capsular serogroups (A, B, D, E, and F) and 16 somatic serotypes are distinguished by expression of characteristic heat-stable antigens. Most strains are host specific and rarely infect more than one or two animals. The existence of different serotypes presents a problem for vaccination because traditional killed whole cell bacteria normally provide only serotype-specific protection. However, it has been demonstrated that natural infection with one serotype can lead to immunological protection against multiple serotypes [Shewen, *et al.*, In C. L. Gyles and C. O. Thoen (Ed.), *Pathogenesis of Bacterial Infections in Animals*, Iowa State University Press, Ames, p. 216-225 (1993)] and cross protection can also be stimulated by using inactivated bacteria grown *in vivo* [Rimler, *et al.*, *Am J Vet Res.* 42:2117-2121 (1981)]. One live spontaneous mutant *P. multocida* strain has been utilized as a vaccine and has been shown to stimulate a strong immune response [Davis, *Poultry Digest.* 20:430-434 (1987), Schlink, *et al.*, *Avian Dis.* 31(1):13-21 (1987)]. This attenuated strain, however, has been shown to revert to a virulent state or cause mortality if the vaccine recipient is stressed [Davis, *Poultry Digest.* 20:430-434 (1987), Schlink, *et al.*, *Avian Dis.* 31(1):13-21 (1987)].

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Another member of the *Pasteurella* family, *A. pleuropneumoniae* exhibits strict host specificity for swine and is the causative agent of highly contagious porcine pleuropneumonia. Infection normally arises in intensive breeding conditions, and is believed to occur by a direct mode of transmission. The disease is often fatal and, as a result, leads to severe economic loss in the swine producing industry. *A. pleuropneumoniae* infection may be chronic or acute, and infection is characterized by a hemorrhagic, necrotic bronchopneumonia with accompanying fibrinous pleuritis. To date, bacterial virulence has been attributed to structural proteins, including serotype-specific capsular polysaccharides, lipopolysaccharides, and surface proteins, as well as extracellular cytolytic toxins. Despite purification and, in some instances cloning, of these virulence factors, the exact role of these virulence factors in *A. pleuropneumoniae* infection is poorly understood.

Twelve serotypes of *A. pleuropneumoniae* have been identified based on antigenic differences in capsular polysaccharides and production of extracellular toxins. Serotypes 1, 5, and 7 are most relevant to *A. pleuropneumoniae* infection in the United States, while serotypes 1, 2, 5, 7, and 9 are predominant in Europe. There are at least three significant extracellular toxins of *A. pleuropneumoniae* that are members of the haemolysin family and are referred to as RTX toxins. RTX toxins are produced by many Gram negative bacteria, including *E. coli*, *Proteus vulgaris*, and *Pasteurella haemolytica*, and the proteins generally share structural and functional characteristics. Toxins from the various serotypes differ, however, in host specificity, target cells, and biological activities.

The major *A. pleuropneumoniae* RTX toxins include ApxI, ApxII, and ApxIII. ApxI and ApxII have haemolytic activity, with ApxI being more potent. ApxIII shows no haemolytic activity, but is cytotoxic for alveolar macrophages and neutrophils. Most *A. pleuropneumoniae* serotypes produce two of these three toxins. For example, serotypes 1, 5, 9, and 11 express ApxI and ApxII, and serotypes 2, 3, 4, 6, and 8 express ApxII and ApxIII. Serotype 10, however, produces only ApxI, and serotypes 7 and 12 express only ApxII. Those *A. pleuropneumoniae* serotypes that produce both ApxI and ApxII are the most virulent strains of the bacteria.

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The Apx toxins were demonstrated to be virulence factors in murine models and swine infection using randomly mutated wild type bacteria [Tascon, *et al.*, *Mol. Microbiol.* 14:207-216 (1994)]. Other *A. pleuropneumoniae* mutants have also been generated with targeted mutagenesis to inactivate the gene encoding the AopA outer membrane virulence protein [Mulks and Buysee, *Gene* 163:61-66 (1995)].

At least eleven serotypes (1, 2, 5-9, 12-14 and 16) have been demonstrated within *Mannheimia* [*Pasteurella*] *haemolytica* [Angen, *et al.*, *Vet Microbiol* 65(4):283-90 (1999)], a *Pasteurellaceae* species which is responsible for serious outbreaks of acute pneumonia in neonatal, weaned, growing and adult lambs, calves, and goats [Ackermann, *et al.*, *Microbes Infect* 2(9):1079-88 (2000)]. Transportation, viral infections, overcrowding, and other stressful conditions predispose animals to *M. haemolytica* infection [Ackermann, *et al.*, *supra.*] The leukotoxin (Lkt) of *M. haemolytica* is believed to play a significant role in pathogenesis, causing cell lysis and apoptosis that lead to the lung pathology characteristic of bovine shipping fever [Highlander, *et al.*, *Infect Immun* 68(7):3916-22 (2000)] as well as lung injury in bovine pneumonic pasteurellosis [Jeyaseelan, *et al.*, *Microb Pathog* 30(2):59-69 (2001)]. Lkt is a pore-forming exotoxin that has the unique property of inducing cytolysis only in ruminant leukocytes and platelets [Jeyaseelan, *et al.*, (2001), *supra.*]. Cytolysis of many cell types is mediated by arachidonic acid (AA) and its generation by phospholipases is regulated by G-protein-coupled receptors [Jeyaseelan, *et al.*, (2001) *supra.*] Recent studies indicate that *M. haemolytica* Lkt binds to bovine CD18, the common subunit of all beta2 integrins [Jeyaseelan, *et al.*, *Infect Immun* 68(1):72-9 (2000)]. It has also been shown that LFA-1 is a Lkt receptor, Lkt binding to LFA-1 is not target cell specific, Lkt binding to bovine LFA-1 correlates with calcium elevation and cytolysis, and bovine LFA-1 expression correlates with the magnitude of Lkt-induced target cell cytolysis [Jeyaseelan, *et al.*, *Infect Immun* 68(1):72-9 (2000)].

In attempts to produce vaccine compositions, traditional killed whole cell bacteria have provided only serotype-specific protection [MacInnes and Smart, *supra.*], however, it has been demonstrated that natural infection with a highly virulent

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serotype can stimulate strong protective immunity against multiple serotypes [Nielsen, *Nord Vet Med.* 31:407-13 (1979), Nielsen, *Nord Vet Med.* 36:221-234 (1984), Nielsen, *Can J Vet Res.* 29:580-582 (1988), Nielsen, *ACTA Vet Scand.* 15:80-89 (1994)]. One defined live-attenuated vaccine strain producing an inactive form of the

5 ApxII toxin has shown promise for cross protection in swine [Prideaux, *et al.*, *Infection & Immunity* 67:1962-1966 (1999)], while other undefined live-attenuated mutants have also shown promise [Inzana, *et al.*, *Infect Immun.* 61:1682-6, (1993), Paltineanu, *et al.*, *In International Pig Veterinary Society*, 1992, p. 214, Utrera, *et al.*, *In International Pig Veterinary Society*, 1992, p. 213].

10 Because of the problems associated with vaccine formulations comprising bacterial strains with undefined, spontaneous mutations, there exists a need in the art for rational construction of live attenuated bacterial strains for use in vaccines that will safely stimulate protective immunity against homologous and heterologous *Pasteurellaceae* serotypes. There further exists a need to identify

15 attenuated bacterial strains and genes required for bacterial virulence, thereby facilitating development of methods to identify anti-bacterial agents.

SUMMARY OF THE INVENTION

In general, the present invention provides materials and methods for

20 production and use of vaccine compositions comprising attenuated gram negative bacteria. In one aspect, vaccine compositions of the invention comprise attenuated species in the *Pasteurellaceae* family of bacteria, which is known in the art and described, in part, in Dewhirst, *et al.*, *J. Bacteriol.* 174:2002-2013 (1992), incorporated herein by reference in its entirety. Species in the family include, but are

25 not limited to, *A. actinomycetemcomitans*, *A. capsulatus*, *A. equuli*, *A. lignieresii*, *A. pleuropneumoniae* (*H. pleuropneumoniae*), *A. seminis*, *A. suis* (*H. suis*), *A. ureae* (*p. ureae*), *A. capsulatus*, Bisgaard taxon 11, *H. aegyptius*, *H. aphrophilus*, *H. aphrophilus* (*H. parainfluenzae*), *H. ducreyi*, *H. haemoglobinophilus*, *H. haemolyticus*, *H. influenzae*, *H. paracuniculus*, *H. paragallinarum*, *H. parahaemolyticus*, *H. parainfluenzae*, (*H. paraphrophilus*), *H.*

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paraphrohaemolyticus, *H. paraphrophilus*, *H. parasuis*, *H. parasuis* type 5, *H. segnis*, *H. somnus*, *Haemophilus* minor group, *Haemophilus* taxon C, *P. aerogenes*, *P. anatis*, *P. avium* (*H. avium*), *P. canis*, *P. dagmatis*, *P. gallinarum*, *P. (Mannheimia)* *haemolytica*, *P. trehalosi* (*P. haemolytica* biotype T), *P. langaa*, *P. multocida*, *P.*
5 *pneumotropica*, *P. stomatis*, *P. volantium* (*H. parainfluenzae*), *P. volantium*, *Pasteurella* species A, *Pasteurella* species B, and *Haemophilus* *paraphrohaemolyticus*. Preferably, vaccine compositions comprise attenuated *Pasteurella* (*Mannheimia*) *haemolytica*, *Actinobacillus pleuropneumoniae*, *Haemophilus somnus*, or *Pasteurella multocida* bacteria. In a most preferred
10 embodiment, vaccine compositions of the invention comprise attenuated *Pasteurella multocida* and *A. pleuropneumoniae* bacterial strains.

One aspect of the invention provides gram negative bacterial organisms containing a functional mutation in a gene sequence represented by any one of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51,
15 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, or species homologs thereof, wherein the mutation inhibits or abolishes expression and/or biological activity of an encoded gene product (*i.e.*, the polypeptide
20 encoded by a gene); said functional mutation resulting in attenuated virulence of the bacterial strain. Functional mutations that modulate (*i.e.*, increase or decrease) expression and/or biological activity of a gene product include insertions or deletions in the protein coding region of the gene itself or in sequences responsible for, or involved in, control of gene expression. Deletion mutants include those wherein all or
25 part of a specific gene sequence is deleted. Also contemplated are compositions, and preferably vaccine compositions, comprising mutated and attenuated gram negative bacterial organisms, optionally comprising a suitable adjuvant and/or a pharmaceutically acceptable diluent or carrier. In order for a modified strain to be effective in a vaccine formulation, the attenuation must be significant enough to

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prevent the pathogen from evoking severe clinical symptoms, but also insignificant enough to allow limited replication and growth of the bacteria in the host.

The invention also provides polynucleotides encoding gene products that are required for virulence in gram negative bacteria. Polynucleotides of the invention include DNA, such as complementary DNA, genomic DNA including complementary or anti-sense DNA, and wholly or partially synthesized DNA; RNA, including sense and antisense strands; and peptide nucleic acids as described, for example in Corey, *TIBTECH* 15:224-229 (1997). Virulence gene polynucleotides of the invention include those set forth in SEQ ID NOs:1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, or species homologs thereof, polynucleotides encoding a virulence gene product encoded by a polynucleotide of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, or a species homolog thereof, and polynucleotide that hybridize, under moderately to highly stringent conditions, to the noncoding strand (or complement) of any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, or species homologs thereof. The invention therefore comprehends gene sequences from *Pasteurellaceae* set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, as well as related gene sequences from other

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gram negative bacterial organisms, including naturally occurring (*i.e.*, species homologs) and artificially induced variants thereof. The invention also comprehends polynucleotides which encode polypeptides deduced from any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 164, 166, 168, 170, 172, and 174, and species homologs thereof. Knowledge of the sequence of a polynucleotide of the invention makes readily available every possible fragment of that polynucleotide. The invention therefore provides fragments of a polynucleotide of the invention.

The invention further embraces expression constructs comprising polynucleotides of the invention. Host cells transformed, transfected or electroporated with a polynucleotide of the invention are also contemplated. The invention provides methods to produce a polypeptide encoded by a polynucleotide of the invention comprising the steps of growing a host cell of the invention under conditions that permit, and preferably promote, expression of a gene product encoded by the polynucleotide, and isolating the gene product from the host cell or the medium of its growth.

Identification of polynucleotides of the invention makes available the encoded polypeptides. Polypeptides of the invention include full length and fragment, or truncated, proteins; variants thereof; fusion, or chimeric proteins; and analogs, including those wherein conservative amino acid substitutions have been introduced into wild-type polypeptides. Antibodies that specifically recognize polypeptides of the invention are also provided, and include monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, humanized antibodies, human antibodies, and complementary determining region (CDR)-grafted antibodies, as well as compounds that include CDR sequences which specifically recognize a polypeptide of the invention. The invention also provides anti-idiotypic antibodies immunospecific for antibodies of the invention.

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According to another aspect of the invention, methods are provided for identifying novel anti-bacterial agents that modulate the function of gram negative bacteria virulence genes or gene products. Methods of the invention include screening potential agents for the ability to interfere with expression of virulence gene products encoded by the DNA sequences set forth in any one of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, or species homologs thereof, or screening potential agents for the ability to interfere with biological function of a bacterial gene product encoded in whole or in part by a DNA sequence set forth in any one of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, species homologs thereof, or the complementary strand thereof, followed by identifying agents that provide positive results in such screening assays. In particular, agents that interfere with the expression of virulence gene products include anti-sense polynucleotides and ribozymes that are complementary to the virulence gene sequences. The invention further embraces methods to modulate transcription of gene products of the invention through use of oligonucleotide-directed triplet helix formation.

Agents that interfere with the function of virulence gene products include variants of virulence gene products, binding partners of the virulence gene products and variants of such binding partners, and enzyme inhibitors (where the product is an enzyme).

Novel anti-bacterial agents identified by the methods described herein are provided, as well as methods for treating a subject suffering from infection with gram negative bacteria involving administration of such novel anti-bacterial agents in an amount effective to reduce bacterial presence.

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Numerous additional aspects and advantages of the invention will become apparent to those skilled in the art upon consideration of the following detailed description of the invention which describes presently prepared embodiments thereof.

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DETAILED DESCRIPTION OF THE INVENTION

"Virulence genes," as used herein, are genes whose function or products are required for successful establishment and/or maintenance of bacterial infection in a host animal. Thus, virulence genes and/or the proteins encoded thereby are involved in pathogenesis in the host organism, but may not be necessary for growth.

"Signature-tagged mutagenesis (STM)," as used herein, is a method generally described in International Patent Publication No. WO 96/17951, incorporated herein by reference, and includes, for example, a method for identifying bacterial genes required for virulence in a murine model of bacteremia. In this method, bacterial strains that each have a random mutation in the genome are produced using transposon integration; each insertional mutation carries a different DNA signature tag which allows mutants to be differentiated from each other. The tags comprise 40 bp variable central regions flanked by invariant "arms" of 20 bp which allow the central portions to be co-amplified by polymerase chain reaction (PCR). Tagged mutant strains are assembled in microtiter dishes, then combined to form the "inoculum pool" for infection studies. At an appropriate time after inoculation, bacteria are isolated from the animal and pooled to form the "recovered pool." The tags in the recovered pool and the tags in the inoculum pool are separately amplified, labeled, and then used to probe filters arrayed with all of the different tags representing the mutants in the inoculum. Mutant strains with attenuated virulence are those which cannot be recovered from the infected animal, *i.e.*, strains with tags that give hybridization signals when probed with tags from the inoculum pool but not when probed with tags from the recovered pool. In a variation of this method, non-radioactive detection methods such as chemiluminescence can be used

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Signature-tagged mutagenesis allows a large number of insertional mutant strains to be screened simultaneously in a single animal for loss of virulence. Screening nineteen pools of mutant *P. multocida* strains resulted in the identification of more than 60 strains with reduced virulence, many of which were confirmed to be attenuated in virulence by subsequent determination of an approximate LD₅₀ for the individual mutants. Screening of *A. pleuropneumoniae* mutants resulted in identification of more than 100 strains having mutations in 35 different genes. Of these, mutations in 22 genes results in significantly attenuated *A. pleuropneumoniae* strains. The nucleotide sequence of the open reading frame disrupted by the transposon insertion was determined by sequencing both strands and an encoded amino acid sequence was deduced. Novelty of both the polynucleotide and amino acid sequences was determined by comparison of the sequences with DNA and protein database sequences. Knowledge of the virulence genes in these species permitted identification of species homologs in *P. (Mannheimia) haemolytica*.

The identification of bacterial, and more particularly *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* virulence genes provides for microorganisms exhibiting reduced virulence (*i.e.*, attenuated strains), which are useful in vaccines. Such microorganisms include *Pasteurellaceae* mutants containing at least one functional mutation inactivating a gene represented by any one of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174. The worker of ordinary skill in the art will realize that a "functional mutation" may occur in protein coding regions of a gene of the invention, as well as in regulatory regions that modulate transcription of the virulence gene RNA.

The worker of ordinary skill will also appreciate that attenuated *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* strains of the invention include those bearing more than one functional mutation. More than one mutation may result in additive or synergistic degrees of attenuation. Multiple

mutations can be prepared by design or may fortuitously arise from a deletion event originally intended to introduce a single mutation. An example of an attenuated strain with multiple deletions is a *Salmonella typhimurium* strain wherein the *cya* and *crp* genes are functionally deleted. This mutant *S. typhimurium* strain has shown promise as a live vaccine.

Identification of virulence genes in *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* can provide information regarding similar genes in other pathogenic species. As an example, identification of the *aroA* gene led to identification of conserved genes in a diverse number of pathogens, including *Aeromonas hydrophila*, *Aeromonas salmonicida*, *Salmonella typhimurium*, *Salmonella enteritidis*, *Salmonella dublin*, *Salmonella gallinarum*, *Bordetella pertussis*, *Yersinia enterocolitica*, *Neisseria gonorrhoeae*, and *Bacillus anthracis*. In many of these species, attenuated bacterial strains bearing mutations in the *aroA* gene have proven to be effective in vaccine formulations. Using the virulence genes sequences identified in *P. multocida*, similar or homologous genes can be identified in other organisms, particularly within the *Pasteurella* family, as well as *A. pleuropneumoniae*, *P. (Mannheimia) haemolytica*, and *Haemophilus somnus*. Likewise, identification of *A. pleuropneumoniae* virulence genes can permit identification of related genes in other organisms. Southern hybridization using the *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* genes as probes can identify these related genes in chromosomal libraries derived from other organisms. Alternatively, PCR can be equally effective in gene identification across species boundaries. As still another alternative, complementation of, for example, a *P. multocida* mutant with a chromosomal library from other species can also be used to identify genes having the same or related virulence activity. Identification of related virulence genes can therefore lead to production of an attenuated strain of the other organism which can be useful as still another vaccine formulation. Examples of *P. multocida* genes that have been demonstrated to exist in other species (e.g. *P. (Mannheimia) haemolytica*, *A. pleuropneumoniae* and *H. somnus*) include genes *exxB*, *atpG*, *pnp*, *guaB* and *yjgF*.

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Attenuated *P. multocida* strains identified using STM are insertional mutants wherein a virulence gene has been rendered non-functional through insertion of transposon sequences in either the open reading frame or regulatory DNA sequences. These insertional mutants still contain all of the genetic information
5 required for bacterial virulence and can possibly revert to a pathogenic state by deletion of the inserted transposon. Therefore, in preparing a vaccine formulation, it is desirable to take the information gleaned from the attenuated strain and create a deletion mutant strain wherein some, most, or all of the virulence gene sequence is removed, thereby precluding the possibility that the bacteria will revert to a virulent
10 state.

The vaccine properties of an attenuated insertional mutant identified using STM are expected to be the same or similar to those of a bacteria bearing a deletion in the same gene. However, it is possible that an insertion mutation may exert "polar" effects on adjoining gene sequences, and as a result, the insertion mutant
15 may possess characteristic distinct from a mutant strain with a deletion in the same gene sequence. Deletion mutants can be constructed using any of a number of techniques well known and routinely practiced in the art.

In one example, a strategy using counterselectable markers can be employed which has commonly been utilized to delete genes in many bacteria. For a
20 review, see, for example, Reyat, *et al.*, *Infection and Immunity* 66:4011-4017 (1998), incorporated herein by reference. In this technique, a double selection strategy is often employed wherein a plasmid is constructed encoding both a selectable and counterselectable marker, with flanking DNA sequences derived from both sides of the desired deletion. The selectable marker is used to select for bacteria in which the
25 plasmid has integrated into the genome in the appropriate location and manner. The counterselectable marker is used to select for the very small percentage of bacteria that have spontaneously eliminated the integrated plasmid. A fraction of these bacteria will then contain only the desired deletion with no other foreign DNA present. The key to the use of this technique is the availability of a suitable
30 counterselectable marker.

In another technique, the *cre-lox* system is used for site specific recombination of DNA. The system consists of 34 base pair *lox* sequences that are recognized by the bacterial *cre* recombinase gene. If the *lox* sites are present in the DNA in an appropriate orientation, DNA flanked by the *lox* sites will be excised by the *cre* recombinase, resulting in the deletion of all sequences except for one remaining copy of the *lox* sequence. Using standard recombination techniques, it is possible to delete the targeted gene of interest in the *P. multocida*, *A.*

pleuropneumoniae or *P. (Mannheimia) haemolytica* genome and to replace it with a selectable marker (e.g., a gene coding for kanamycin resistance) that is flanked by the *lox* sites. Transient expression (by electroporation of a suicide plasmid containing the *cre* gene under control of a promoter that functions in *P. multocida*, *A.*

pleuropneumoniae, or *P. (Mannheimia) haemolytica*) of the *cre* recombinase should result in efficient elimination of the *lox* flanked marker. This process would result in a mutant containing the desired deletion mutation and one copy of the *lox* sequences.

In another approach, it is possible to directly replace a desired deleted sequence in the *P. multocida*, *A. pleuropneumoniae* or *P. (Mannheimia) haemolytica* genome with a marker gene, such as green fluorescent protein (GFP), β -galactosidase, or luciferase. In this technique, DNA segments flanking a desired deletion are prepared by PCR and cloned into a suicide (non-replicating) vector for *P. multocida*, *A. pleuropneumoniae*, or *P. (Mannheimia) haemolytica*. An expression cassette, containing a promoter active in *P. multocida*, *A. pleuropneumoniae*, or *P. (Mannheimia) haemolytica* and the appropriate marker gene, is cloned between the flanking sequences. The plasmid is introduced into wild-type *P. multocida*, *A. pleuropneumoniae* or *P. (Mannheimia) haemolytica*. Bacteria that incorporate and express the marker gene (probably at a very low frequency) are isolated and examined for the appropriate recombination event (i.e., replacement of the wild type gene with the marker gene).

The reduced virulence of these organisms and their immunogenicity may be confirmed by administration to a subject animal. While it is possible for an avirulent microorganism of the invention to be administered alone, one or more of

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such mutant microorganisms are preferably administered in a vaccine composition containing suitable adjuvant(s) and pharmaceutically acceptable diluent(s) or carrier(s). The carrier(s) must be "acceptable" in the sense of being compatible with the avirulent microorganism of the invention and not deleterious to the subject to be immunized. Typically, the carriers will be water or saline which will be sterile and pyrogen free. The subject to be immunized is a subject needing protection from a disease caused by a virulent form of *P. multocida*, *A. pleuropneumoniae*, *P. (Mannheimia) haemolytica* or other pathogenic microorganisms.

It will be appreciated that the vaccine of the invention may be useful in the fields of human medicine and veterinary medicine. Thus, the subject to be immunized may be a human or other animal, for example, farm animals including cows, sheep, pigs, horses, goats and poultry (e.g., chickens, turkeys, ducks and geese) companion animals such as dogs and cats; exotic and/or zoo animals; and laboratory animals including mice, rats, rabbits, guinea pigs, and hamsters.

The invention also provides polypeptides and corresponding polynucleotides required for *P. multocida*, *A. pleuropneumoniae* or *P. (Mannheimia) haemolytica* virulence. The invention includes both naturally occurring and non-naturally occurring polynucleotides and polypeptide products thereof. Naturally occurring virulence products include distinct gene and polypeptide species as well as corresponding species homologs expressed in organisms other than *P. multocida*, *A. pleuropneumoniae*, or *P. (Mannheimia) haemolytica* strains. Non-naturally occurring virulence products include variants of the naturally occurring products such as analogs and virulence products which include covalent modifications. In a preferred embodiment, the invention provides virulence polynucleotides comprising the sequences set forth in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 and species homologs thereof, and polypeptides having amino acids sequences encoded by the polynucleotides.

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The present invention provides novel purified and isolated *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* polynucleotides (e.g., DNA sequences and RNA transcripts, both sense and complementary antisense strands) encoding the bacterial virulence gene products. DNA sequences of the invention include genomic and cDNA sequences as well as wholly or partially chemically synthesized DNA sequences. Genomic DNA of the invention comprises the protein coding region for a polypeptide of the invention and includes variants that may be found in other bacterial strains of the same species. "Synthesized," as used herein and is understood in the art, refers to purely chemical, as opposed to enzymatic, methods for producing polynucleotides. "Wholly" synthesized DNA sequences are therefore produced entirely by chemical means, and "partially" synthesized DNAs embrace those wherein only portions of the resulting DNA were produced by chemical means. Preferred DNA sequences encoding *P. multocida* virulence gene products are set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, and 120, and species homologs thereof. Preferred *A. pleuropneumoniae* DNA sequences encoding virulence gene products are set out in SEQ ID NOs: 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, and 164, and species homologs thereof. Preferred *P. (Mannheimia) haemolytica* virulence gene products are set out in SEQ ID NOs: 166, 168, 170, 172 and 174, and species homologs thereof. The worker of skill in the art will readily appreciate that the preferred DNA of the invention comprises a double stranded molecule, for example, molecules having the sequences set forth in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 and species homologs thereof, along with the complementary molecule (the "non-coding strand" or "complement") having a sequence deducible from the sequence of SEQ ID NO: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53,

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55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, according to Watson-Crick base pairing rules for DNA. Also preferred are

5 polynucleotides encoding the gene products encoded by any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166,

10 168, 170, 172, and 174 and species homologs thereof. The invention further embraces species, preferably bacterial, homologs of the *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* DNA.

The polynucleotide sequence information provided by the invention makes possible the identification and isolation of polynucleotides encoding related

15 bacterial virulence molecules by well known techniques including Southern and/or Northern hybridization, and polymerase chain reaction (PCR). Examples of related polynucleotides include polynucleotides encoding polypeptides homologous to a virulence gene product encoded by any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57,

20 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, and species homologs thereof, and structurally related polypeptides sharing one or more biological and/or physical properties of a virulence gene product of the invention.

25 The invention also embraces DNA sequences encoding bacterial gene products which hybridize under moderately to highly stringent conditions to the non-coding strand, or complement, of any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116,

30 118, and 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146,

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148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172 and 174, and species homologs thereof. DNA sequences encoding virulence polypeptides which would hybridize thereto but for the degeneracy of the genetic code are contemplated by the invention. Exemplary high stringency conditions include a final wash in buffer
 5 comprising 0.2X SSC/0.1% SDS, at 65°C to 75°C, while exemplary moderate stringency conditions include a final wash in buffer comprising 2X SSC/0.1% SDS, at 35°C to 45°C. It is understood in the art that conditions of equivalent stringency can be achieved through variation of temperature and buffer, or salt concentration as described in Ausubel, *et al.* (Eds.), Protocols in Molecular Biology, John Wiley &
 10 Sons (1994), pp. 6.0.3 to 6.4.10. Modifications in hybridization conditions can be empirically determined or precisely calculated based on the length and the percentage of guanine/cytosine (GC) base pairing of the probe. The hybridization conditions can be calculated as described in Sambrook, *et al.*, (Eds.), Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press: Cold Spring Harbor, New
 15 York (1989), pp. 9.47 to 9.51.

Autonomously replicating recombinant expression constructions such as plasmid and viral DNA vectors incorporating virulence gene sequences are also provided. Expression constructs wherein virulence polypeptide-encoding polynucleotides are operatively linked to an endogenous or exogenous expression
 20 control DNA sequence and a transcription terminator are also provided. The virulence genes may be cloned by PCR, using *P. multocida* genomic DNA as the template. For ease of inserting the gene into expression vectors, PCR primers are chosen so that the PCR-amplified gene has a restriction enzyme site at the 5' end preceding the initiation codon ATG, and a restriction enzyme site at the 3' end after
 25 the termination codon TAG, TGA or TAA. If desirable, the codons in the gene are changed, without changing the amino acids, according to *E. coli* codon preference described by Grosjean and Fiers, *Gene*, 18:199-209 (1982), and Konigsberg and Godson, *Proc. Natl. Acad. Sci. (USA)*, 80:687-691 (1983). Optimization of codon usage may lead to an increase in the expression of the gene product when produced in
 30 *E. coli*. If the gene product is to be produced extracellularly, either in the periplasm of

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E. coli or other bacteria, or into the cell culture medium, the gene is cloned without its initiation codon and placed into an expression vector behind a signal sequence.

According to another aspect of the invention, host cells are provided, including procaryotic and eukaryotic cells, either stably or transiently transformed,

5 transfected, or electroporated with polynucleotide sequences of the invention in a manner which permits expression of virulence polypeptides of the invention. Expression systems of the invention include bacterial, yeast, fungal, viral, invertebrate, and mammalian cells systems. Host cells of the invention are a valuable source of immunogen for development of antibodies specifically immunoreactive with
10 the virulence gene product. Host cells of the invention are conspicuously useful in methods for large scale production of virulence polypeptides wherein the cells are grown in a suitable culture medium and the desired polypeptide products are isolated from the cells or from the medium in which the cells are grown by, for example, immunoaffinity purification or any of the multitude of purification techniques well
15 known and routinely practiced in the art. Any suitable host cell may be used for expression of the gene product, such as *E. coli*, other bacteria, including *P. multocida*, *Bacillus* and *S. aureus*, yeast, including *Pichia pastoris* and *Saccharomyces cerevisiae*, insect cells, or mammalian cells, including CHO cells, utilizing suitable vectors known in the art. Proteins may be produced directly or fused to a peptide or
20 polypeptide, and either intracellularly or extracellularly by secretion into the periplasmic space of a bacterial cell or into the cell culture medium. Secretion of a protein requires a signal peptide (also known as pre-sequence); a number of signal sequences from prokaryotes and eukaryotes are known to function for the secretion of recombinant proteins. During the protein secretion process, the signal peptide is
25 removed by signal peptidase to yield the mature protein.

To simplify the protein purification process, a purification tag may be added either at the 5' or 3' end of the gene coding sequence. Commonly used purification tags include a stretch of six histidine residues (U.S. Patent Nos. 5,284,933 and 5,310,663), a streptavidin-affinity tag described by Schmidt and Skerra, *Protein*
30 *Engineering*, 6:109-122 (1993), a FLAG peptide [Hopp *et al.*, *Biotechnology*, 6:1205-

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1210 (1988)], glutathione S-transferase [Smith and Johnson, *Gene*, 67:31-40 (1988)], and thioredoxin [LaVallie *et al.*, *Bio/Technology*, 11:187-193 (1993)]. To remove these peptide or polypeptides, a proteolytic cleavage recognition site may be inserted at the fusion junction. Commonly used proteases are factor Xa, thrombin, and enterokinase.

The invention also provides purified and isolated *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* virulence polypeptides encoded by a polynucleotide of the invention. Presently preferred are polypeptides comprising the amino acid sequences encoded by any one of the polynucleotides set out in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 164, 166, 168, 170, 172 and 174, and species homologs thereof. The invention embraces virulence polypeptides encoded by a DNA selected from the group consisting of: a) the DNA sequence set out in any one of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 164, 166, 168, 170, 172, and 174 and species homologs thereof; b) DNA molecules encoding *P. multocida*, *A. pleuropneumoniae* or *P. (Mannheimia) haemolytica* polypeptides encoded by any one of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 164, 166, 168, 170, 172, and 174, and species homologs thereof; and c) a DNA molecule, encoding a virulence gene product, that hybridizes under moderately stringent conditions to the DNA of (a) or (b).

The invention also embraces polypeptides that have at least about 99%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 70%, at least about 65%, at least about 60%, at least

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about 55%, and at least about 50% identity and/or homology to the preferred polypeptides of the invention. Percent amino acid sequence "identity" with respect to the preferred polypeptides of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in the virulence gene product sequence after aligning both sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Percent sequence "homology" with respect to the preferred polypeptides of the invention is defined herein as the percentage of amino acid residues in the candidate sequence that are identical with the residues in one of the virulence polypeptide sequences after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and also considering any conservative substitutions as part of the sequence identity. Conservative substitutions can be defined as set out in Tables A and B.

Table A
Conservative Substitutions I

<u>SIDE CHAIN CHARACTERISTIC</u>	<u>AMINO ACID</u>
Aliphatic	G A P
Non-polar	I L V
Polar - uncharged	C S T M
	N Q
Polar - charged	D E
	K R
Aromatic	H F W Y
Other	N Q D E

Polypeptides of the invention may be isolated from natural bacterial cell sources or may be chemically synthesized, but are preferably produced by recombinant procedures involving host cells of the invention. Virulence gene products of the invention may be full length polypeptides, biologically active fragments, or variants thereof which retain specific biological or immunological activity. Variants may comprise virulence polypeptide analogs wherein one or more

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of the specified (*i.e.*, naturally encoded) amino acids is deleted or replaced or wherein one or more non-specified amino acids are added: (1) without loss of one or more of the biological activities or immunological characteristics specific for the virulence gene product; or (2) with specific disablement of a particular biological activity of the virulence gene product. Deletion variants contemplated also include fragments lacking portions of the polypeptide not essential for biological activity, and insertion variants include fusion polypeptides in which the wild-type polypeptide or fragment thereof have been fused to another polypeptide.

Variant virulence polypeptides include those wherein conservative substitutions have been introduced by modification of polynucleotides encoding polypeptides of the invention. Conservative substitutions are recognized in the art to classify amino acids according to their related physical properties and can be defined as set out in Table A (from WO 97/09433, page 10, published March 13, 1997 (PCT/GB96/02197, filed 9/6/96). Alternatively, conservative amino acids can be grouped as defined in Lehninger, [*Biochemistry*, Second Edition; Worth Publishers, Inc. NY:NY (1975), pp.71-77] as set out in Table B.

Table B
Conservative Substitutions II

SIDE CHAIN	
<u>CHARACTERISTIC</u>	<u>AMINO ACID</u>
Non-polar (hydrophobic)	
A. Aliphatic:	A L I V P
B. Aromatic:	F W
C. Sulfur-containing:	M
D. Borderline:	G
Uncharged-polar	
A. Hydroxyl:	S T Y
B. Amides:	N Q
C. Sulfhydryl:	C
D. Borderline:	G
Positively Charged (Basic):	K R H
Negatively Charged (Acidic):	D E

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Variant virulence products of the invention include mature virulence gene products, *i.e.*, wherein leader or signal sequences are removed, having additional amino terminal residues. Virulence gene products having an additional methionine residue at position -1 are contemplated, as are virulence products having additional methionine and lysine residues at positions -2 and -1. Variants of these types are particularly useful for recombinant protein production in bacterial cell types. Variants of the invention also include gene products wherein amino terminal sequences derived from other proteins have been introduced, as well as variants comprising amino terminal sequences that are not found in naturally occurring proteins.

The invention also embraces variant polypeptides having additional amino acid residues which result from use of specific expression systems. For example, use of commercially available vectors that express a desired polypeptide as a fusion protein with glutathione-S-transferase (GST) provide the desired polypeptide having an additional glycine residue at position -1 following cleavage of the GST component from the desired polypeptide. Variants which result from expression using other vector systems are also contemplated.

Also comprehended by the present invention are antibodies (*e.g.*, monoclonal and polyclonal antibodies, single chain antibodies, chimeric antibodies, humanized, human, and CDR-grafted antibodies, including compounds which include CDR sequences which specifically recognize a polypeptide of the invention) and other binding proteins specific for virulence gene products or fragments thereof. The term "specific for" indicates that the variable regions of the antibodies of the invention recognize and bind a virulence polypeptide exclusively (*i.e.*, are able to distinguish a single virulence polypeptides from related virulence polypeptides despite sequence identity, homology, or similarity found in the family of polypeptides), but may also interact with other proteins (for example, *S. aureus* protein A or other antibodies in ELISA techniques) through interactions with sequences outside the variable region of the antibodies, and in particular, in the constant region of the molecule. Screening assays to determine binding specificity of an antibody of the invention are well known and routinely practiced in the art. For a comprehensive discussion of such assays, see

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Harlow *et al.* (Eds), *Antibodies A Laboratory Manual*; Cold Spring Harbor Laboratory; Cold Spring Harbor, NY (1988), Chapter 6. Antibodies that recognize and bind fragments of the virulence polypeptides of the invention are also contemplated, provided that the antibodies are first and foremost specific for, as
5 defined above, a virulence polypeptide of the invention from which the fragment was derived.

The DNA and amino acid sequence information provided by the present invention also makes possible the systematic analysis of the structure and function of the virulence genes and their encoded gene products. Knowledge of a
10 polynucleotide encoding a virulence gene product of the invention also makes available anti-sense polynucleotides which recognize and hybridize to polynucleotides encoding a virulence polypeptide of the invention. Full length and fragment anti-sense polynucleotides are provided. The worker of ordinary skill will appreciate that fragment anti-sense molecules of the invention include (i) those which
15 specifically recognize and hybridize to a specific RNA (as determined by sequence comparison of DNA encoding a virulence polypeptide of the invention to DNA encoding other known molecules) as well as (ii) those which recognize and hybridize to RNA encoding variants of the family of virulence proteins. Antisense polynucleotides that hybridize to RNA encoding other members of the virulence
20 family of proteins are also identifiable through sequence comparison to identify characteristic, or signature, sequences for the family of molecules.

The invention further contemplates methods to modulate gene expression through use of ribozymes. For a review, see Gibson and Shillito, *Mol. Biotech.* 7:125-137 (1997). Ribozyme technology can be utilized to inhibit translation
25 of mRNA in a sequence specific manner through (i) the hybridization of a complementary RNA to a target mRNA and (ii) cleavage of the hybridized mRNA through nuclease activity inherent to the complementary strand. Ribozymes can be identified by empirical methods but more preferably are specifically designed based on accessible sites on the target mRNA [Bramlage, *et al.*, *Trends in Biotech* 16:434-
30 438 (1998)]. Delivery of ribozymes to target cells can be accomplished using either

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exogenous or endogenous delivery techniques well known and routinely practiced in the art. Exogenous delivery methods can include use of targeting liposomes or direct local injection. Endogenous methods include use of viral vectors and non-viral plasmids.

5 Ribozymes can specifically modulate expression of virulence genes when designed to be complementary to regions unique to a polynucleotide encoding a virulence gene product. "Specifically modulate" therefore is intended to mean that ribozymes of the invention recognizes only a single polynucleotide. Similarly, ribozymes can be designed to modulate expression of all or some of a family of
10 proteins. Ribozymes of this type are designed to recognize polynucleotide sequences conserved in all or some of the polynucleotides which encode the family of proteins.

 The invention further embraces methods to modulate transcription of a virulence gene of the invention through use of oligonucleotide-directed triplet helix formation. For a review, see Lavrovsky, *et al.*, *Biochem. Mol. Med.* 62:11-22 (1997).
15 Triplet helix formation is accomplished using sequence specific oligonucleotides which hybridize to double stranded DNA in the major groove as defined in the Watson-Crick model. Hybridization of a sequence specific oligonucleotide can thereafter modulate activity of DNA-binding proteins, including, for example, transcription factors and polymerases. Preferred target sequences for hybridization
20 include transcriptional regulatory regions that modulate virulence gene product expression. Oligonucleotides which are capable of triplet helix formation are also useful for site-specific covalent modification of target DNA sequences. Oligonucleotides useful for covalent modification are coupled to various DNA damaging agents as described in Lavrovsky, *et al.* [*supra*].

25 The identification of *P. multocida*, *A. pleuropneumoniae* and *P. (Mannheimia) haemolytica* virulence genes renders the genes and gene products useful in methods for identifying anti-bacterial agents. Such methods include assaying potential agents for the ability to interfere with expression of virulence gene products represented by the DNA sequences set forth in any one of SEQ ID NOS: 1,
30 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68,

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70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 and species homologs thereof (*i.e.*, the genes represented by DNA sequences of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 encode the virulence gene product, or the DNA sequences of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 are adjacent the gene encoding the virulence gene product, or are involved in regulation of expression of the virulence gene product), or assaying potential agents for the ability to interfere with the function of a bacterial gene product encoded in whole or in part by a DNA sequence set forth in any one of SEQ ID NOS: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174, species homologs thereof, or the complementary strand thereof, followed by identifying agents that are positive in such assays. Polynucleotides and polypeptides useful in these assays include not only the genes and encoded polypeptides as disclosed herein, but also variants thereof that have substantially the same activity as the wild-type genes and polypeptides.

The virulence gene products produced by the methods described above are used in high throughput assays to screen for inhibitory agents. The sources for potential agents to be screened are chemical compound libraries, fermentation media of *Streptomyces*, other bacteria and fungi, and cell extracts of plants and other vegetations. For proteins with known enzymatic activity, assays are established based

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on the activity, and a large number of potential agents are screened for ability to inhibit the activity. For proteins that interact with another protein or nucleic acid, binding assays are established to measure such interaction directly, and the potential agents are screened for ability to inhibit the binding interaction.

5 The use of different assays known in the art is contemplated according to this aspect of the invention. When the function of the virulence gene product is known or predicted by sequence similarity to a known gene product, potential inhibitors can be screened in enzymatic or other types of biological and/or biochemical assays keyed to the function and/or properties of the gene product. When
10 the virulence gene product is known or predicted by sequence similarity to a known gene product to interact with another protein or nucleic acid, inhibitors of the interaction can be screened directly in binding assays. The invention contemplates a multitude of assays to screen and identify inhibitors of binding by the virulence gene product. In one example, the virulence gene product is immobilized and interaction
15 with a binding partner is assessed in the presence and absence of a putative inhibitor compound. In another example, interaction between the virulence gene product and its binding partner is assessed in a solution assay, both in the presence and absence of a putative inhibitor compound. In both assays, an inhibitor is identified as a compound that decreases binding between the virulence gene product and its binding
20 partner. Other assays are also contemplated in those instances wherein the virulence gene product binding partner is a protein. For example, variations of the di-hybrid assay are contemplated wherein an inhibitor of protein/protein interactions is identified by detection of a positive signal in a transformed or transfected host cell as described in PCT publication number WO 95/20652, published August 3, 1995.

25 Candidate inhibitors contemplated by the invention include compounds selected from libraries of potential inhibitors. There are a number of different libraries used for the identification of small molecule modulators, including: (1) chemical libraries, (2) natural product libraries, and (3) combinatorial libraries comprised of random peptides, oligonucleotides or organic molecules. Chemical
30 libraries consist of structural analogs of known compounds or compounds that are

identified as "hits" or "leads" via natural product screening. Natural product libraries are collections of microorganisms, animals, plants, or marine organisms which are used to create mixtures for screening by: (1) fermentation and extraction of broths from soil, plant or marine microorganisms or (2) extraction of plants or marine organisms. Natural product libraries include polyketides, non-ribosomal peptides, and variants (non-naturally occurring) thereof. For a review, see *Science* 282:63-68 (1998). Combinatorial libraries are composed of large numbers of peptides, oligonucleotides, or organic compounds as a mixture. They are relatively easy to prepare by traditional automated synthesis methods, PCR, cloning, or proprietary synthetic methods. Of particular interest are peptide and oligonucleotide combinatorial libraries. Still other libraries of interest include peptide, protein, peptidomimetic, multiparallel synthetic collection, recombinatorial, and polypeptide libraries. For a review of combinatorial chemistry and libraries created therefrom, see Myers, *Curr. Opin. Biotechnol.* 8:701-707 (1997). Identification of modulators through use of the various libraries described herein permits modification of the candidate "hit" (or "lead") to optimize the capacity of the "hit" to modulate activity.

Still other candidate inhibitors contemplated by the invention can be designed and include soluble forms of binding partners, as well as binding partners as chimeric, or fusion, proteins. Binding partners as used herein broadly encompasses antibodies, antibody fragments, and modified compounds comprising antibody domains that are immunospecific for the expression product of the identified virulence gene.

Other assays may be used when a binding partner (*i.e.*, ligand) for the virulence gene product is not known, including assays that identify binding partners of the target protein through measuring direct binding of test binding partner to the target protein, and assays that identify binding partners of target proteins through affinity ultrafiltration with ion spray mass spectroscopy/HPLC methods or other physical and analytical methods. Alternatively, such binding interactions are evaluated indirectly using the yeast two-hybrid system described in Fields and Song, *Nature*, 340:245-246 (1989), and Fields and Sternglanz, *Trends in Genetics*, 10:286-292 (1994), both of

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which are incorporated herein by reference. The two-hybrid system is a genetic assay for detecting interactions between two proteins or polypeptides. It can be used to identify proteins that bind to a known protein of interest, or to delineate domains or residues critical for an interaction. Variations on this methodology have been developed to clone genes that encode DNA-binding proteins, to identify peptides that bind to a protein, and to screen for drugs. The two-hybrid system exploits the ability of a pair of interacting proteins to bring a transcription activation domain into close proximity with a DNA-binding domain that binds to an upstream activation sequence (UAS) of a reporter gene, and is generally performed in yeast. The assay requires the construction of two hybrid genes encoding (1) a DNA-binding domain that is fused to a first protein and (2) an activation domain fused to a second protein. The DNA-binding domain targets the first hybrid protein to the UAS of the reporter gene; however, because most proteins lack an activation domain, this DNA-binding hybrid protein does not activate transcription of the reporter gene. The second hybrid protein, which contains the activation domain, cannot by itself activate expression of the reporter gene because it does not bind the UAS. However, when both hybrid proteins are present, the noncovalent interaction of the first and second proteins tethers the activation domain to the UAS, activating transcription of the reporter gene. When the virulence gene product (the first protein, for example) is already known to interact with another protein or nucleic acid, this assay can be used to detect agents that interfere with the binding interaction. Expression of the reporter gene is monitored as different test agents are added to the system; the presence of an inhibitory agent results in lack of a reporter signal.

When the function of the virulence gene product is unknown and no ligands are known to bind the gene product, the yeast two-hybrid assay can also be used to identify proteins that bind to the gene product. In an assay to identify proteins that bind to the first protein (the target protein), a large number of hybrid genes each encoding different second proteins are produced and screened in the assay. Typically, the second protein is encoded by a pool of plasmids in which total cDNA or genomic DNA is ligated to the activation domain. This system is applicable to a wide variety

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of proteins, and it is not even necessary to know the identity or function of the second binding protein. The system is highly sensitive and can detect interactions not revealed by other methods; even transient interactions may trigger transcription to produce a stable mRNA that can be repeatedly translated to yield the reporter protein.

5 Other assays may be used to search for agents that bind to the target protein. One such screening method to identify direct binding of test ligands to a target protein is described in U.S. Patent No. 5,585,277, incorporated herein by reference. This method relies on the principle that proteins generally exist as a mixture of folded and unfolded states, and continually alternate between the two
10 states. When a test ligand binds to the folded form of a target protein (i.e., when the test ligand is a ligand of the target protein), the target protein molecule bound by the ligand remains in its folded state. Thus, the folded target protein is present to a greater extent in the presence of a test ligand which binds the target protein, than in the absence of a ligand. Binding of the ligand to the target protein can be determined
15 by any method which distinguishes between the folded and unfolded states of the target protein. The function of the target protein need not be known in order for this assay to be performed. Virtually any agent can be assessed by this method as a test ligand, including, but not limited to, metals, polypeptides, proteins, lipids, polysaccharides, polynucleotides and small organic molecules.

20 Another method for identifying ligands for a target protein is described in Wieboldt *et al.*, *Anal. Chem.*, 69:1683-1691 (1997), incorporated herein by reference. This technique screens combinatorial libraries of 20-30 agents at a time in solution phase for binding to the target protein. Agents that bind to the target protein are separated from other library components by centrifugal ultrafiltration. The
25 specifically selected molecules that are retained on the filter are subsequently liberated from the target protein and analyzed by HPLC and pneumatically assisted electrospray (ion spray) ionization mass spectroscopy. This procedure selects library components with the greatest affinity for the target protein, and is particularly useful for small molecule libraries.

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The inhibitors/binders identified by the initial screens are evaluated for their effect on virulence in *in vivo* mouse models of *P. multocida* infections. Models of bacteremia, endocarditis, septic arthritis, soft tissue abscess, or pneumonia may be utilized. Models involving use of other animals are also comprehended by the invention. For example, rabbits can be challenged with a wild type *P. multocida* strain before or after administration of varying amounts of a putative inhibitor/binder compound. Control animals, administered only saline instead of putative inhibitor/binder compound provide a standard by which deterioration of the test animal can be determined. Other animal models include those described in the Animal and Plant Health Inspection Service, USDA, January 1, 1994 Edition, §§113.69-113.70; Panciera and Corstvet, *Am. J. Vet. Res.* 45:2532-2537; Ames, *et al.*, *Can. J. Comp. Med.* 49:395-400 (1984); and Mukkur, *Infection and Immunity* 18:583-585 (1977). Inhibitors/binders that interfere with bacterial virulence are can prevent the establishment of an infection or reverse the outcome of an infection once it is established.

Any adjuvant known in the art may be used in the vaccine composition, including oil-based adjuvants such as Freund's Complete Adjuvant and Freund's Incomplete Adjuvant, mycolate-based adjuvants (*e.g.*, trehalose dimycolate), bacterial lipopolysaccharide (LPS), peptidoglycans (*i.e.*, mureins, mucopeptides, or glycoproteins such as N-Opaca, muramyl dipeptide [MDP], or MDP analogs), proteoglycans (*e.g.*, extracted from *Klebsiella pneumoniae*), streptococcal preparations (*e.g.*, OK432), Biostim™ (*e.g.*, 01K2), the "Iscoms" of EP 109 942, EP 180 564 and EP 231 039, aluminum hydroxide, saponin, DEAE-dextran, neutral oils (such as miglyol), vegetable oils (such as arachis oil), liposomes, Pluronic® polyols, the Ribi adjuvant system (see, for example GB-A-2 189 141), or interleukins, particularly those that stimulate cell mediated immunity. An alternative adjuvant consisting of extracts of *Amycolata*, a bacterial genus in the order Actinomycetales, has been described in U.S. Patent No. 4,877,612. Additionally, proprietary adjuvant mixtures are commercially available. The adjuvant used will depend, in part, on the

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recipient organism. The amount of adjuvant to administer will depend on the type and size of animal. Optimal dosages may be readily determined by routine methods.

The vaccine compositions optionally may include vaccine-compatible pharmaceutically acceptable (*i.e.*, sterile and non-toxic) liquid, semisolid, or solid diluents that serve as pharmaceutical vehicles, excipients, or media. Any diluent known in the art may be used. Exemplary diluents include, but are not limited to, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, talc, alginates, starches, lactose, sucrose, dextrose, sorbitol, mannitol, gum acacia, calcium phosphate, mineral oil, cocoa butter, and oil of theobroma.

The vaccine compositions can be packaged in forms convenient for delivery. The compositions can be enclosed within a capsule, caplet, sachet, cachet, gelatin, paper, or other container. These delivery forms are preferred when compatible with entry of the immunogenic composition into the recipient organism and, particularly, when the immunogenic composition is being delivered in unit dose form. The dosage units can be packaged, *e.g.*, in tablets, capsules, suppositories or cachets.

The vaccine compositions may be introduced into the subject to be immunized by any conventional method including, *e.g.*, by intravenous, intradermal, intramuscular, intramammary, intraperitoneal, or subcutaneous injection; by oral, sublingual, nasal, anal, or vaginal, delivery. The treatment may consist of a single dose or a plurality of doses over a period of time.

The invention also comprehends use of an attenuated bacterial strain of the invention for manufacture of a vaccine medicament to prevent or alleviate bacterial infection and/or symptoms associated therewith. The invention also provides use of inhibitors of the invention for manufacture of a medicament to prevent or alleviate bacterial infection and/or symptoms associated therewith.

The present invention is illustrated by the following examples. Example 1 describes constructions of *P. multocida* mutants. Example 2 relates to screening for *P. multocida* mutants. Example 3 addresses methods to determine

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virulence of the *P. multocida* mutants. Example 4 describes cloning of *P. multocida* virulence genes. Example 5 addresses identification of genes in other species related to *P. multocida* virulence genes. Example 6 describes construction of *A. pleuropneumoniae* mutants. Example 7 addresses screening for attenuated *A. pleuropneumoniae* mutants. Example 8 relates to identification of *A. pleuropneumoniae* virulence genes. Example 9 describes competition challenge of *A. pleuropneumoniae* mutants and wild type bacteria. Example 10 characterizes *A. pleuropneumoniae* genes identified. Example 11 addresses efficacy of *A. pleuropneumoniae* mutant to protect against wild type bacterial challenge. Example 12 describes identification of species homolog virulence genes in *P. (Mannheimia) haemolytica*.

Example 1

Construction of a Library of Tagged-Transposon *P. multocida* Mutants

A library of tagged-transposon mutants was constructed in parental vector pLOF/Km [Herrero, *et al.*, *J Bacteriol.* 172:6557-67 (1990)] which has previously been demonstrated to be functional and random in *P. multocida* [Lee, *et al.*, *Vet Microbiol.* 50:143-8 (1996)]. Plasmid pLOF/Km was constructed as a modification of suicide vector pGP704 and included a transposase gene under control of the *Tac* promoter as well as the mini-Tn10 transposable element encoding kanamycin resistance. Plasmid pTEF-1 was constructed as described below by modifying pLOF/Km to accept sequence tags which contained a semi-random [NK]₃₅ sequence.

Plasmid pLOF/Km was first modified to eliminate the unique *KpnI* restriction site in the multiple cloning region and then to introduce a new *KpnI* site in the mini-Tn10 region. The plasmid was digested with *KpnI* and the resulting overhanging ends were filled in with Klenow polymerase according to manufacturer's suggested protocol. Restriction digests and ligations described herein were performed according to manufacturer's suggested protocols (Gibco BRL, Gaithersburg, MD and Boehringer Mannheim, Indianapolis, IN). The blunt end product was self-ligated to

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produce a plasmid designated pLOF/Km--*KpnI* which was transformed into *E. coli* DH5 α : λ pir for amplification. *E. coli* DH5 α : (λ pir ϕ 80dlacZ Δ M15, recA1, endA1, gyrA96, thi-1, hsdR17(r_K⁻, m_K⁻, supE44, relA1, deoR, Δ (lacZYA-argF)U169, was propagated at 37°C in Luria-Bertani (LB) medium. Plasmids were prepared using

5 QIAGEN SpinPreps from QIAGEN Inc. (Santa Clarita, CA) and digested with *SfiI* which cuts at a unique site within the mini-Tn10 transposable element. A *SfiI*-*KpnI*-*SfiI* adaptor was prepared by annealing oligonucleotides TEF1 (SEQ ID NO: 86) and TEF3 (SEQ ID NO: 87) and the resulting double-stranded adapter was ligated into the

10 *SfiI* site to create plasmid pTEF-1. Oligonucleotides TEF1 and TEF3 (as well as all other oligonucleotides described herein) were synthesized by Genosys Biotechnologies (The Woodlands, TX).

TEF1 5'-AGGCCGGTACCGCCGCCT SEQ ID NO: 86

15 TEF3 5'-CGGCCGGTACCGCCTAGG SEQ ID NO: 87

Unique sequence tags for insertion into the *KpnI* site of pTEF-1 were prepared as follows. PCR was carried out to generate double stranded DNA tags using a GeneAmp XL PCR Kit (PE Applied Biosystems, Foster City, CA) under

20 conditions including 250 μ M each dNTP, 1.5 mM Mg(OAc)₂, 100 pmol each primer TEF14 (SEQ ID NO: 88) and TEF15 (SEQ ID NO: 89), 1 ng TEF26 (SEQ ID NO: 90) as template DNA and 2.5 units recombinant *Tth* DNA Polymerase XL.

TEF14 5'-CATGGTACCCATTCTAAC SEQ ID NO: 88

25 TEF15 5'-CTAGGTACCTACAACCTC SEQ ID NO: 89

TEF26 SEQ ID NO: 90

30 5'-CTAGGTACCTACAACCTCAAGCTT-[NK]₃₅-
AAGCTTGGTTAGATGGGTACCATG

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Reaction conditions included an initial incubation at 95°C for one minute, followed by thirty cycles of 30 seconds at 95°C, 45 seconds at 45°C, and 15 seconds at 72°C, followed by a final incubation at 72°C for two minutes. The PCR products were digested with *KpnI* and purified using a QIAGEN Nucleotide Removal Kit (QIAGEN, Inc., Chatsworth, GA) according to the manufacturer's suggested protocol. The unique tag sequences were ligated into the mini-Tn10 element of linearized pTEF-1, previously digested with *KpnI* and dephosphorylated with calf intestinal alkaline phosphatase (Boehringer Mannheim) using standard procedures. The resulting plasmid library was transformed into *E.coli* DH5 α : λ pir. Colony blot analysis was performed according to the DIG User's Guide (Boehringer-Mannheim) with hybridization and detection performed as follows.

Hybridizations were essentially performed according to the Genius Non-Radioactive User's Guide (Boehringer Mannheim Biochemicals), the product sheet for the DIG-PCR labeling kit (Boehringer Mannheim Biochemicals), and the product sheet for CSPD (Boehringer Mannheim Biochemicals). For preparation of probes, a 100 μ l primary PCR reaction was set up using Amplitaq PCR buffer (PE Applied Biosystems), 200 μ M dNTPs, 140 pmol each of primers TEF5 (SEQ ID NO: 91) and TEF6 (SEQ ID NO: 92), 2 mM MgCl₂, 2.5 units Amplitaq (PE Applied Biosystems) and 1 ng of plasmid DNA.

20

TEF5	5'-TACCTACAACCTCAAGCT	SEQ ID NO: 91
TEF6	5'-TACCCATTCTAACCAAGC	SEQ ID NO: 92

25 Cycle conditions included an initial incubation at 95°C for two minutes, followed by 35 cycles of 95°C for 30 seconds, 50°C for 45 seconds, 72°C for 15 seconds and a final incubation at 72°C for three minutes. The amplification products were separated using electrophoresis on a 2% - 3:1 NuSieve GTG (FMC BioProducts, Rockland, ME, USA):Agarose gel and the 109 bp product was excised and purified. Gel
30 extractions were carried out using a QIAGEN Gel Extraction kit (QIAGEN).

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Approximately 15 ng of the primary product was labeled in a 50 µl PCR reaction using the DIG PCR Kit, 50 pmol each of primers TEF24 and TEF25, and a 1:1 mix of DIG Probe Synthesis Mix with 2 mM dNTP stock solution.

5 TEF24 5'-TACCTACAACCTCAAGCTT SEQ ID NO: 93

 TEF25 5'-TACCCATTCTAACCAAGCTT SEQ ID NO: 94

10 PCR conditions included an initial incubation at 95°C for four minutes, followed by 25 cycles of 95°C for 30 seconds, 50°C for 45 seconds, 72°C for 15 seconds and a final incubation at 72°C for three minutes. The labeled PCR product was digested with *HindIII* in a total reaction volume of 90 µl and purified from the constant primer arms using a 2% - 3:1 NuSieve GTG (FMC BioProducts):Agarose gel. The region containing the labeled variable tag was excised and the entire gel slice was dissolved and denatured in 10 ml of DIG EasyHyb at 95°C for ten minutes.

15 Dot blots were prepared using a Hybond[®]-N⁺ membrane (Amersham-Pharmacia Biotech). Target DNA for each tag was prepared in 96 well plates using approximately 30 ng of PCR product. An equal volume of 0.1 N NaOH was added to denature the sample and each sample was applied to the membrane with minimal vacuum using a Minifold I[™] Dot-Blot Apparatus from Schleicher and Schuell

20 (Keene, NH, USA). Each well was washed with 150 µl of Neutralization Solution (0.5 M Tris /3 M NaCl, pH 7.5) and 150 µl of 2X SSC. Membranes were UV-crosslinked in a Stratalinker (Stratagene, La Jolla, CA, USA) and prehybridized for one hour in 20 mls DIG EasyHyb Buffer at 42°C. The denatured probe was added and

25 hybridization carried out overnight at 42°C. The membrane was washed two times in 2X SSC containing 0.1% SDS for five minutes each wash. Two high stringency washes were performed in 50 ml of pre-warmed 0.1X SSC buffer containing 0.1% SDS at 68°C for 15 minutes before proceeding with standard Genius Detection protocols (Genius Manual).

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It is desirable to use a non-radioactive detection system for safety, lower cost, ease of use, and reduction of hazardous materials. In initial experiments using similar procedures previously described [Mei, *et al.*, *Mol Microbiol.* 26:399-407 (1997)], unacceptable background levels of hybridization were obtained in negative controls. In order to decrease background, tag length was increased by 30 bp to a total of 70, amplification primers were lengthened to include all sequence flanking the variable region, a lower concentration of dig-dUTP was used, and the conserved sequences flanking the sequence tag region were removed by gel purification. Most significantly, PCR was used to generate [NK]₃ sequence tags as the target DNA in dot blots rather than the entire plasmids containing the tagged transposons after detecting background hybridization from the transposon itself. Using these modifications background was eliminated making chemiluminescent/non-radioactive screening more effective.

Approximately four hundred different transformants resulting from the ligation of pTEF-1 with the PCR generated sequence tags were screened by colony blot and the 96 strongest hybridizing colonies were assembled into microtiter plates for further use. Even though the likelihood of duplicated tags was very low, half of the plate of master tags was probed against the other to confirm that no tags were duplicated. The plasmids containing these tags were purified and transformed into *E.coli* S17-1:λpir (pir, *recA*, *thi*, *pro*, *hsd*, (r-m⁺), RP4-2, (Tc::Mu), (Km::Tn7), [TnpR], [SmR]), and the transformed bacteria propagated at 37°C in Luria-Bertani (LB) medium. Each of the 96 *E.coli* S17-1:λpir transformants containing the tagged plasmid pTEF-1 was used in conjugative matings to generate transposon mutants of *P. multocida*. *P. multocida* strain TF5 is a spontaneous nalidixic acid resistant mutant derived from UC6731, a bovine clinical isolate. *P. multocida* strains were grown on brain heart infusion (BHI) media (Difco Laboratories, Detroit, MI, USA) at 37°C and in 5% CO₂ when grown on plates. Matings were set up by growing each *E.coli* S17-1:λpir /pTEF1:[NK]₃ clone and the TF5 strain to late log phase. Fifty μl of culture for each tagged-pTEF-1 clone was mixed with 200 μl of the TF5 culture and 50 μl of each mating mixture was spotted onto 0.22 TM filters previously placed on BHI plates

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containing 100 mM IPTG and 10 mM MgSO₄. Following overnight incubation at 37°C with 5% CO₂, mating mixtures were washed off of each filter into 3 ml of PBS and 25 µl of each was plated onto BHIN⁵⁰K¹⁰⁰ plates. Following selective overnight growth, colonies were assembled into microtiter plates by toothpick transfer into 200 µl BHIN⁵⁰K⁵⁰ making sure that each well in a microtiter plate always contained a transposon mutant with the same sequence tag. Following overnight growth, 50 µl of 75% glycerol was added to each well and plates were stored frozen at -80°C.

Nineteen pools were assembled by transferring the transposon mutants to microtiter plates making sure that each well contained a transposon mutant with the appropriate tag for that well. In other words, a specific well in each microtiter plate always contained a transposon mutant with the same sequence tag even though the location of the transposon within those mutants may be different.

Example 2

15 Murine Screening for Attenuated *P. multocida* Mutants

Nineteen pools of *Pasteurella multocida* transposon mutants were screened using a murine model of septicemia. Frozen plates of pooled *P. multocida* transposon mutants were removed from -80°C storage and subcultured by transferring 10 µl from each well to a new 96 well round bottom plate (Corning Costar, Cambridge, MA, USA) containing 200 µl of brain heart infusion (DIFCO) with 50 µg/ml nalidixic acid (Sigma) and 50 µg/ml kanamycin (Sigma) (BHIN⁵⁰K⁵⁰). Plates were incubated without shaking overnight at 37°C in 5% CO₂. Overnight plates were subcultured by transferring 10 µl from each well to a new flat bottomed 96-well plate (Corning Costar) containing 100 µl of BHI per well and incubating at 37°C with shaking at approximately 150 rpm. The OD₅₄₀ was monitored using a micro-titer plate reader. At an OD₅₄₀ of approximately 0.2 to 0.25, each plate was pooled to form the "input pool" by combining 100 µl from each of the wells of the micro-titer plate. The culture was diluted appropriately in BHI to doses of approximately 10⁴, 10⁵, 10⁶ CFU/ml and 0.2 ml of each dilution was used to infect female 14-16 g BALB/c mice by intraperitoneal administration. At two days post-infection, one or two surviving mice were euthanized and the spleens harvested. The entire spleen was homogenized

in 1.0 ml sterile 0.9 % saline. Dilutions of the homogenate from 10^{-2} to 10^{-5} were prepared and plated onto BHIN⁶⁰K³⁰ plates. Following overnight growth, at least 20,000 colonies were pooled in 10 mls BHI broth to form the "recovered pool" and 0.5 ml of the recovered pool was centrifuged at 3,500 X g and the pellet used to
5 prepare genomic DNA according to a previously described protocol [Wilson, *In F. M. Ausubel, et al., (ed.), Current Protocols in Molecular Biology*, vol. 1. John Wiley and Sons, New York, p. 2.4.1-2.4.5. (1997)].

Initial experiments with virulent wild-type *P. multocida* indicated that organisms could be recovered from the spleen, lungs, kidneys, and liver indicating a truly septicemic model of infection. Dot blots for both the "input" and "recovered" pools were performed as described in Example 1 and evaluated both by visual
10 inspection and by semi-quantitative analysis. Hybridization was carried out as described in Example 1 except that 5 µg of genomic DNA from input and recovered pools was used as template. Semi-quantitative analysis indicates whether a significant
15 reduction in a single clone has occurred. If a mutant is unable to survive within the host, then the recovered signal should be very low compared to the input signal yielding a high input/recovered ratio. Most mutants will grow as well *in vivo* as *in vitro* and therefore a ratio of their signals should be approximately equal to 1. Clones selected by quantitative analysis as being highly reduced in the recovered pool were
20 selected for further study. Additional clones with questionable input/recovered ratios were also selected after visually evaluating films made from the dot blots.

Example 3 Determination of Virulence for *P. multocida* Candidate Mutants

Each potential mutant which exhibited reduced recovery from splenic
25 tissue was isolated from the original pool plate and used individually in a challenge experiment to verify and roughly estimate the attenuation caused by the transposon mutation. Individual candidate mutants from *in vivo* screens were grown on Sheep Blood Agar plates overnight in 5% CO₂ at 37°C. Approximately six colonies of each
30 mutant were inoculated into BHI broth and allowed to grow for six hours. Dilutions were prepared and five mice each were infected as described above with 10^2 , 10^3 , 10^4

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and 10^5 CFU each. Attenuation was determined by comparing mortality after six days relative to the wild type. Surviving mice were presumed to be protected and then challenged with a dose of wild type *P. multocida* at a concentration approximately 200-fold greater than the LD₅₀ for the wild type strain. Survival rate was then

5 determined for each challenged group of mice.

Results indicated that 62 of 120 potential transposon mutants were attenuated, having an approximate LD₅₀ of at least 10 fold higher than the wild type strain. The clones and their approximate LD₅₀ values are listed in Table 1. A control experiment with the wild type strain was run in parallel with each set of challenges

10 and in all cases mortality in wild type-challenged groups was 100%.

In addition to LD₅₀ values, Table 1 also provides data from vaccination and challenge experiments. Briefly, groups of mice (n = 5 to 10) were vaccinated by intraperitoneal injection with the individual *P. multocida* strains shown in Table 1 at a dose that was approximately 200 times greater than the LD₅₀ of the virulent, wild type

15 strain. Animals were observed for 28 days after which mortality figures were calculated.

Table 1
P. multocida Virulence Genes

Nucleotide SEQ ID NO:	Representative Isolate	Possible Gene Function	Vaccination # survivors/total	Challenge # survivors/total	LD ₅₀
	wild type	-	0/10		<10
23	PM1B1	gusB	10/10, 10/10, 10/10	9/10, 9/10	4.3 x 10 ⁶
11	PM1D1	djbB	10/10, 5/10	10/10, 5/5	8.4 x 10 ⁴
3	PM1BD7	atpC	5/5, 10/10	10/10	>3 x 10 ⁵
74	PM1BE11	yhcJ (H10145)	10/10	2/3	>2 x 10 ⁵
	PM1BF6	yabK (H1020)	3/5, 8/10	9/9	>2 x 10 ⁵
19	PM2G8	flaC	4/5, 9/10	9/9	>4 x 10 ⁵
76	PM3C9	yiaO (H10146)	3/5		>6 x 10 ⁵
118	PM3G11	UnkO	4/5, 10/10	10/10	>3 x 10 ⁵
31	PM7B4	iroA (UnkB)	0/5		
17	PM4C6	flaB (flaB2)	2/5, 10/10, 9/10	10/10, 9/9	>3 x 10 ⁶
9	PM4G10-T9	dnaA	4/5		>5 x 10 ⁵
1	PM4D5-T3	atpB	5/5		>4 x 10 ⁵
53	PM4D5-T1	UnkC2	5/5		>4 x 10 ⁵
15	PM4F2	flaB (flaB1)	3/5, 6/10, 10/10	6/6, 10/10	>3 x 10 ⁵
41	PM5P7	mreB	4/5		1 x 10 ³
7	PM5E2	devB	0/5, 3/10	2/3	ND
48	PM6H5-T1	zylA	5/5		>3 x 10 ⁵
78	PM6H8	ygfE (H10719)	5/5, 9/10	9/9	>3 x 10 ⁵
108	PM7D12	pnp	5/5, 9/10	9/9	
40	31	PM8C1R1-T2	UnkC1	5/5	>6 x 10 ⁵

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Nucleotide SEQ ID NO:	Representative Isolate	Possible Gene Function	Vaccination # survivors/total	Challenge # survivors/total	LD ₅₀
37	PM8C1-T3	mgjB	5/5		~6 x 10 ⁵
58	PM8C1R1-T6	UnkD1	5/5		~6 x 10 ⁵
45	PM10H7	purF (H11707)	3/5, 8/10, 8/10	8/8, 8/8	>3 x 10 ⁵
25	PM10H10-T2	Hli1501	5/5		>1 x 10 ⁴
72	PM11G8-T2	ygiK	5/5		>2.4 x 10 ³
21	PM11G8-T4	greA	5/5		>2.4 x 10 ³
84	PM12H6	yyam (H10687)	3/5, 0/10		~2.2 x 10 ³
33	PM15Q8-T2	kaiB	5/5		>1.2 x 10 ⁵
116	PM15Q8-T1	UnkK	5/5		>1.2 x 10 ⁵
104	PM16G11-T1	hmbR	3/5		>1.9 x 10 ⁵
29	PM16G11-T2	hxcC	3/5		>1.9 x 10 ⁵
35	PM16H8	lgiC	5/5, 10/10	10/10	>2.4 x 10 ⁵
80	PM16H1	yleA (H10019)	5/5, 10/10		>2.0 x 10 ⁵
49	PM17H6-T1	topF	4/5		~6 x 10 ⁵
120	PM17H6	UnkP	4/5		~6 x 10 ⁵
5	PM18F5-T8	cap5E	5/5		>2.4 x 10 ⁵
82	PM18F5-T10	yoyH (H10345)	5/5		>2.4 x 10 ⁵
13	PM19A1	exbB	5/5, 10/10	10/10	>1.2 x 10 ⁵
112	PM19D4	rei	5/5, 8/10	8/8	~1.6 x 10 ⁵
39	PM20A12	mioC (H10669)	3/5, 8/10	8/8	~2 x 10 ⁴
60	PM20C2	UnkD2	5/5, 10/10	10/10	>6.2 x 10 ⁶

Example 4 Cloning and Identification of Genes Required for *P. multocida* Virulence

Each transposon mutant which was verified to be attenuated was analyzed further to determine the identity of the disrupted open reading frame. DNA from each mutant was amplified, purified, and digested with restriction enzymes that were known not to cut within the transposon and generally produced 4-8 kb fragments that hybridized with the transposon. Using selection for kanamycin resistance encoded by the transposon, at least one fragment for each transposon mutant was cloned.

Southern hybridization with multiple restriction enzymes was performed for each attenuated mutant using a labeled 1.8 kb *Mlu*I fragment from pLOF/Km as a probe to identify a suitably sized fragment for cloning. The mini-Tn10 element and flanking DNA from each mutant was cloned into pUC19 and the flanking sequence determined using internal primers TEF32 and TEF40, primer walking and in some cases universal pUC-19 primers.

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TEF-32 GGCAGAGCATTACGCTGAC SEQ ID NO: 95
TEF-40 GTACCGGCCAGGCGGCCACGCGTATTC SEQ ID NO:96

Sequencing reactions were performed using the BigDye™ Dye Terminator Chemistry
5 kit from PE Applied Biosystems (Foster City, CA) and run on an ABI Prism 377
DNA Sequencer. Double stranded sequence for putative interrupted open reading
frames was obtained for each clone. Sequencer 3.0 software (Genecodes, Corp., Ann
Arbor, MI) was used to assemble and analyze sequence data. GCG programs
[Devereux, *et al.*, 1997. Wisconsin Package Version 9.0, 9.0 ed. Genetics Computer
10 Group, Inc., Madison] were used to search for homologous sequences in currently
available databases.

In 37% of the clones that were identified as being attenuated, there
were multiple insertions of the mini-Tn10 transposable element. Each insertion
including its flanking sequence was cloned individually into pGP704 and mated into
15 the wild-type strain to produce new mutants of *P. multocida*, each carrying only one
of the multiple original insertions. Individual mutants were retested individually to
determine the insertion responsible for the attenuated phenotype. The nucleotide
sequence of the disrupted, predicted open reading frame was determined by
sequencing both strands, and the predicted amino acid sequence was used to search
20 currently available databases for similar sequences. Sequences either matched known
genes, unknown genes, and hypothetical open reading frames previously sequenced or
did not match any previously identified sequence. For those genes having homology
to previously identified sequences, potential functions were assigned as set out in
Table 1.

25

Example 5 Identification of Related Genes in Other Species

In separate experiments, STM was also performed using *Actinobacillus*
pleuropneumoniae (App). One of the App strains contained an insertion in a gene that
30 was sequenced (SEQ ID NO: 97) and identified as a species homolog of the *P.*
multocida atpG gene. This result suggested the presence in other bacterial species of

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homologs to previously unknown *P. multocida* genes that can also be mutated to produce attenuated strains of the other bacterial species for use in vaccine compositions. In order to determine if homologs of other *P. multocida* genes exists in other bacterial species, Southern hybridization was performed on genomic DNA from other species using the *A. pleuropneumoniae atpG* gene as a probe.

Actinobacillus pleuropneumoniae, *Pasteurella haemolytica* (Ph), *P. multocida*, and *Haemophilus somnus* (Hs) genomic DNA was isolated using the CTAB method and digested with *EcoRI* and *HindIII* for two hours at 37°C. Digested DNA was separated on a 0.7% agarose gel at 40V in TAE buffer overnight. The gel was immersed sequentially in 0.1 M HCL for 30 minutes, twice in 0.5 M NaOH/1.5 M NaCl for 15 minutes each, and twice in 2.5 M NaCl/1 M Tris, pH 7.5. The DNA was transferred to nitrocellulose membranes (Amersham Hybond N') overnight using 20X SSC buffer (3 M NaCl/0.3 M sodium citrate). The DNA was crosslinked to the membrane using a UV Stratalinker on autocrosslink setting (120 millijoules). The membrane was prehybridized in 5X SSC/ 1% blocking solution/0.1% sodium lauroyl sarcosine/0.02% SDS at 50°C for approximately seven hours and hybridized overnight at 50°C in the same solution containing a PCR generated atpG probe.

The probe was prepared using primers DEL-1389 (SEQ ID NO: 98) and TEF-46 (SEQ ID NO: 99) in a with a GeneAmp XL PCR kit in a GeneAmp PCR System 2400. Template was genomic *A. pleuropneumoniae* DNA.

DEL-1389	TCTCCATTCCCTTGCTGCGGCAGGG	SEQ ID NO: 98
TEF-46	GGAATTACAGCCGGATCCGGG	SEQ ID NO: 99

The PCR was performed with an initial heating step at 94°C for five minutes, 30 cycles of denaturation t 94°C for 30 sec, annealing at 50°C for 30 sec, and elongation at 72°C for three minutes, and a final extension step at 72°C for five minutes. The amplification products were separated on an agarose gel, purified using a QIAquick gel purification kit (QIAGEN), and labeled using a DIG-High Primer kit (Boehringer Mannheim). The blot was removed from the hybridization solution and rinsed in 2X

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SSC and washed two times for five minutes each wash in the same buffer. The blot was then washed two times for 15 minutes each in 0.5X SSC at 60°C. Homologous bands were visualized using a DIG Nucleic Acid Detection Kit (Boehringer Mannheim).

5 Single bands were detected in *Pasteurella haemolytica*, *Haemophilus somnus* and *A. pleuropneumoniae* using *EcoRI* digested DNA. Two bands were detected using *EcoRI* digested DNA from *Pasteurella multocida*.

Example 6

10 Construction of a Library of Tagged-Transposon *P. multocida* Mutants

Transposon mutagenesis using pLOF/Km has previously been reported to be functional and random in *A. pleuropneumoniae* [Tascon, *et al.*, *J Bacteriol.* 175:5717-22 (1993)]. To construct tagged transposon mutants of *A. pleuropneumoniae*, each of 96 *E. coli* S17-1:λpir transformants containing pre-selected tagged plasmids (pTEF-1:[NK]₃₅) was used in conjugative matings to generate transposon mutants of *A. pleuropneumoniae* strain AP225, a serotype 1 spontaneous nalidixic acid resistant mutant derived from an in vivo passaged ATCC 27088 strain. *A. pleuropneumoniae* strains were grown on Brain Heart Infusion (BHI) (Difco Laboratories, Detroit, MI) media with 10 µg/ml B-nicotinamide adenine dinucleotide (V¹⁰), (Sigma, St. Louis, Missouri) at 37°C and in 5% CO₂ when grown on plates. *E. coli* S17-1:λpir (λpir, *recA*, *thi*, *pro*, *hsdR*(r_K⁻,m_K⁺), RP4-2, (Tc^R::Mu), (Km^R::Tn7), [Tnp^R], [Sm^R]) was propagated at 37°C in Luria-Bertani (LB) medium. Antibiotics when necessary were used at 100 µg/ml ampicillin (Sigma), 50 µg/ml nalidixic acid (N⁵⁰)(Sigma), and 50 (K⁵⁰) or 100 (K¹⁰⁰) µg/ml of kanamycin (Sigma).

25 Matings were set up by growing each *E. coli* S17-1:λpir/pTEF1:[NK]₃₅ clone and the AP225 strain to late log phase. A 50 µl aliquot of culture for each tagged-pTEF-1 clone was mixed with 150 µl of the APP225 culture, and then 50 µl of each mating mixture was spotted onto 0.22 µM filters previously placed onto BHIV¹⁰ plates containing 100 µM IPTG and 10 mM MgSO₄. Following overnight incubation at 37°C with 5% CO₂, mating mixtures were washed off of each filter into 2 ml of PBS and 200 µl of each was plated onto BHIV¹⁰N⁵⁰K¹⁰⁰ plates. After selective

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overnight growth, colonies were assembled into microtiter plates by toothpick transfer into 200 μ l BHIV¹⁰N⁵⁰K⁵⁰ making sure that each well in a microtiter plate always contained a transposon mutant with the same sequence tag. Following overnight growth, 50 μ l of 75% glycerol was added to each well and plates were stored frozen at -80°C.

APP does not appear to have as much bias towards multiple insertions of the mini-Tn10 element as did *P. multocida*. Only approximately 3% of the mutants were determined to contain multiple insertions, which is in agreement with the 4% previously reported [Tascon, *et al.*, *J Bacteriol.* 175:5717-22 (1993)]. A problem in APP consisted of identifying numerous mutants (discussed below) containing insertions into 23S RNA regions: 28 total mutants with insertions into 13 unique sites. This may indicate that 23S RNA contains preferential insertion sites and that the growth of APP is affected by these insertions enough to result in differential survival within the host. Southern blot analysis using an APP 23S RNA probe suggests that APP may contain only three ribosomal operons as compared to five in *H. influenzae* [Fleischmann, *et al.*, *Science* 269:496-512 (1995)] and seven complete operons in *E. coli* [Blattner, *et al.*, *Science* 277:1453-1474 (1997)]. This site preference and its effect on growth rate may be a significant barrier to "saturation mutagenesis" since a significant number of clones will contain insertions into these rRNAs and large volume screening will be necessary to obtain additional unique attenuating mutations.

Example 7

Porcine Screening for Attenuated *A. pleuropneumoniae* Mutants

Twenty pools of *A. pleuropneumoniae* transposon mutants, containing a total of approximately 800 mutants, were screened using a porcine intratracheal infection model. Each pool was screened in two separate animals.

Frozen plates of pooled *A. pleuropneumoniae* transposon mutants were removed from -80°C storage and subcultured by transferring 20 μ l from each well to a new 96 well round bottom plate (Corning Costar, Cambridge, MA, USA) containing 180 μ l of BHIV¹⁰N⁵⁰K⁵⁰. Plates were incubated without shaking overnight at 37°C in

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5% CO₂. Overnight plates were then subcultured by transferring 10 µl from each well to a new flat bottomed 96 well plate (Corning Costar) containing 100 µl of BHIV¹⁰ per well and incubating at 37°C with shaking at 150 rpm. The OD₅₆₂ was monitored using a microtiter plate reader. At an OD₅₆₂ of approximately 0.2 to 0.25, each plate was pooled to form the "input pool" by combining 100 µl from each of the wells of the microtiter plate. The culture was diluted appropriately in BHI to approximately 2 X 10⁶ CFU/ml. For each diluted pool, 4.0 ml was used to infect 10-20 kg SPF pigs (Whiteshire-Hamroc, Albion, IN) by intratracheal administration using a tracheal tube. At approximately 20 hours post-infection, all surviving animals were euthanized and the lungs removed. Lavage was performed to recover surviving bacteria by infusing 150 mls of sterile PBS into the lungs, which were then massaged to distribute the fluid. The lavage fluid was recovered, and the process was repeated a second time. The lavage fluid was centrifuged at 450 x g for 10 minutes to separate out large debris. Supernatants were then centrifuged at 2,800 x g to pellet the bacteria. Pellets were resuspended in 5 mls BHI and plated in dilutions ranging from 10⁻² to 10⁻⁵ onto BHIV¹⁰N⁵⁰K⁵⁰ plates. Following overnight growth, at least 100,000 colonies were pooled in 10 mls BHI broth to form the "recovered pools". A 0.7 ml portion of each recovered pool was used to prepare genomic DNA by the CTAB method [Wilson, *In Ausubel, et al.*, (eds.), *Current Protocols in Molecular Biology*, vol. 1. John Wiley and Sons, New York, p. 2.4.1-2.4.5 (1997)].

Recovery from the animals routinely was in the 10⁸ CFU range from lung lavage.

Dot blots were performed and evaluated both by visual inspection and by semi-quantitative analysis as described previously. All hybridizations and detections were performed as described. Briefly, probes were prepared by a primary PCR amplification, followed by agarose gel purification of the desired product and secondary PCR amplification incorporating dig-dUTP. Oligonucleotides including TEF5, TEF6, TEF24, TEF25, TEF48 and TEF62, were synthesized by Genosys Biotechnologies (The Woodlands, TX). Primers TEF69, TEF65, and TEF66 were also used for inverse PCR reactions and sequencing.

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TEF69	GACGTTTCCCGTTGAATATGGCTC	SEQ ID NO: 166
TEF65	GCCGGATCCGGGATCATATGACAAGA	SEQ ID NO: 167
TEF66	GACAAGATGTGTATCCACCTTAAC	SEQ ID NO: 168

5

The labeled PCR product was then digested with *HindIII* to separate the constant primer arms from the unique tag region. The region containing the labeled variable tag was excised and the entire gel slice was then dissolved and denatured in DIG EasyHyb. Dot blots were prepared and detected using the standard CSPD detection protocol. Film exposures were made for visual evaluation, and

10

luminescent counts per second (LCPS) were determined for each dot blot sample. The $LCPS_{input} / LCPS_{recovered}$ ratio for each mutant was used to determine mutants likely to be attenuated.

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Clones selected as being present in the input pool but highly reduced in the recovered pool were selected for further study. Additional clones with questionable input/recovered ratios were also selected after visually evaluating films made from the dot blots. A total of 110 clones were selected.

20

Example 8 **Identification of *A. pleuropneumoniae* Virulence Genes**

A partial flanking sequence was determined for each of the 110 mutants by inverse PCR and direct product sequencing. Inverse PCR was used to generate flanking DNA products for direct sequencing as described above. Sequencing reactions were performed using the BigDye™ Dye Terminator Chemistry kit from PE Applied Biosystems (Foster City, CA) and run on an ABI Prism 377 DNA Sequencer. Sequencher 3.0 software (Genecodes, Corp., Ann Arbor, MI) was used to assemble and analyze sequence data. GCG programs [Devereux and Haeberli, Wisconsin Package Version 9.0, 9.0 ed. Genetics Computer Group, Inc., Madison (1997)] were used to search for homologous sequences in currently available

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30

databases.

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Table 2 shows the *A. pleuropneumoniae* genes identified and extent to which open reading frames were determinable. Sequence identification numbers are provided for nucleotide sequences as well as deduced amino acid sequences where located.

5

Table 2
***A. pleuropneumoniae* Open Reading Frames**

<u>Complete Open Reading Frame</u>		<u>NO Start Codon - Stop Codon</u>	
atpH	SEQ ID NO: 134	dksA	SEQ ID NO: 136
aptG	SEQ ID NO: 132	dnaK	SEQ ID NO: 138
exbB	SEQ ID NO: 140	HI0379	SEQ ID NO: 144
OmpP5	SEQ ID NO: 152		
OmpP5-2	SEQ ID NO: 150	<u>NO Start Codon - NO Stop Codon</u>	
tig	SEQ ID NO: 160	pnp	SEQ ID NO: 154
fkpA	SEQ ID NO: 142	apvA-or 1	SEQ ID NO: 122
hupA	SEQ ID NO: 146	apvA-or 2	SEQ ID NO: 124
rpmF	SEQ ID NO: 158	apvB	SEQ ID NO: 126
		apvD	SEQ ID NO: 130
<u>Start Codon - NO Stop Codon</u>		<u>RNA or Noncoding Sequences</u>	
lpdA	SEQ ID NO: 148	tRNA-leu	SEQ ID NO: 162
potD	SEQ ID NO: 156	tRNA-glu	SEQ ID NO: 163
yaeE	SEQ ID NO: 164		
apvC	SEQ ID NO: 128		

25

The putative identities listed in Table 3 (below, Example 9) were assigned by comparison with bacterial databases. The 110 mutants represented 35 groups of unique transposon insertions. The number of different mutations per loci varied, with some clones always containing an insertion at a single site within an ORF to clones containing insertions within different sites of the same ORF. Three multiple

insertions were detected in the 110 mutants screened as determined by production of multiple PCR bands and generation of multiple sequence electropherograms.

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Example 9
Competition Challenge of *A. pleuropneumoniae*
Mutants with Wild Type APP225

A representative clone from each of the unique attenuated mutant groups identified above that was absent or highly reduced in the recovered population was isolated from the original pool plate and used in a competition challenge experiment with the wild type strain (AP225) to verify the relative attenuation caused by the transposon mutation. Mutant and wild type strains were grown in BHIV¹⁰ to an OD₅₉₀ of 0.6 – 0.9. Approximately 5.0×10^6 CFU each of the wild type and mutant strains were added to 4 mls BHL. The total 4 ml dose was used to infect a 10-20 kg SPF pig by intratracheal administration with a tracheal tube. At approximately 20 hours post-infection, all surviving animals were euthanized and the lungs removed. Lung lavages were performed as described above. Plate counts were carried out on BHIV¹⁰N⁵⁰ and BHIV¹⁰N⁵⁰K¹⁰⁰ to determine the relative numbers of wild type to mutant in both the input cultures and in the lung lavage samples. A Competitive Index (CI) was calculated as the $[\text{mutant CFU} / \text{wild type CFU}]_{\text{input}} / [\text{mutant CFU} / \text{wild type CFU}]_{\text{recovered}}$.

Of the 35 potential transposon mutants, 22 were significantly attenuated, having a competitive index (CI) of less than 0.2. A transposon mutant that did not seem to be attenuated based on the STM screening results was chosen from one of the pools as a positive control. This mutant had a CI in vivo of approximately 0.6. An in vitro competition was also done for this mutant resulting in a CI of 0.8. The mutant was subsequently determined to contain an insertion between 2 phenylalanine tRNA's.

Competitive indices for unique attenuated single-insertion mutants are listed in Table 3. Competitive indices for *atpG*, *pnp*, and *exbB* App mutants indicated that the mutants were unable to compete effectively with the wild type strains and were therefore attenuated.

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Table 3
Virulence and Proposed Function of *A. pleuropneumoniae* Mutants

Mutant	Similarity	Putative or Known Functions	C.I.
AP20A6	<i>atpH</i>	ATP synthase	.009
AP7F10	<i>atpG</i>	ATP synthase	.013
AP17C6	<i>tpdA</i>	dihydroliipoamide dehydrogenase	.039
AP11E7	<i>exbB</i>	transport of iron compounds	.003,.003,.006
AP3H7	<i>potD</i>	Spermidine/putrescine transport	.308
AP8H6	<i>OmpP5</i>	Adhesin / OmpA homolog	.184
AP18H8	<i>OmpP5-2</i>	Adhesin / OmpA homolog	.552
AP13E9	<i>tig</i>	Peptidyl-prolyl isomerase	.050
AP13C2	<i>fkpA</i>	Peptidyl-prolyl isomerase	<.001
AP15C11	<i>pnp</i>	Polynucleotide phosphorylase	.032
AP18F12	<i>hupA</i>	Histone – like protein	.001
AP20F8	<i>dksA</i>	Dosage dependent suppressor of <i>dnaK</i> mutations	.075
AP5G4	<i>dnaK</i>	Heat shock protein – molecular chaperone	.376
AP17C9	<i>tRNA-leu</i>	Protein Synthesis	.059
AP5D6	<i>tRNA-glu</i>	Protein Synthesis	.055
AP18B2	<i>rpmF</i>	Protein Synthesis	.112
AP10E7	<i>ylaeA</i>	Unknown	.001
AP19A5	HI0379	Unknown	.061
AP10C10	<i>apvA</i>	Unknown	.157
AP18F5	<i>apvB</i>	Unknown	.103
AP2A6	<i>apvC</i>	Unknown	.091
AP2C11	<i>apvD</i>	Unknown	.014

Accuracy of the CI appeared to be very good as the *exbB* mutant was competed within three different animals yielding CIs of 0.003, 0.003 and 0.006. The use of a Competitive Index number to assign attenuation based upon one competition in a large animal study was further confirmed based on preliminary vaccination results in pigs with 7 mutants (n=8) described below in Example 11.

Example 10
Characterization of Attenuated *A. pleuropneumoniae* Virulence Genes

The *A. pleuropneumoniae* genes identified represent four broad functional classes: biosynthetic enzymes, cellular transport components, cellular regulation components and unknowns.

The *atpG* gene, encoding the F1- γ subunit of the F₀F₁ H⁺-ATPase complex, can function in production of ATP or in the transport of protons by hydrolyzing ATP. A related *atpG* attenuated mutant was also identified in *P. multocida*. Another *atp* gene, *atpH*, that encodes the F₁ δ subunit was also identified. Phenotypes of *atp* mutants include non-adaptable acid-sensitivity phenotype [Foster, *J Bacteriol.* 173:6896-6902 (1991)], loss of virulence in *Salmonella typhimurium* [Garcia del Portillo, *et al.*, *Infect Immun.* 61:4489-4492 (1993)] and *P. multocida* (above) and a reduction in both transformation frequencies and induction of competence regulatory genes in *Haemophilus influenzae* Rd [Gwinn, *et al.*, *J Bacteriol.* 179:7315-20 (1997)].

LpdA is a dihydrolipoamide dehydrogenase that is a component of two enzymatic complexes: pyruvate dehydrogenase and 2-oxoglutarate dehydrogenase. While the relationship to virulence is unknown, production of LpdA is induced in *Salmonella typhimurium* when exposed to a bactericidal protein from human which may suggest that this induction may be involved in attempts to repair the outer membrane [Qi, *et al.*, *Mol Microbiol.* 17:523-31 (1995)].

Transport of scarce compounds necessary for growth and survival are critical in vivo. ExbB is a part of the TonB transport complex [Hantke, and Zimmerman, *Microbiology Letters.* 49:31-35 (1981)], interacting with TonB in at least two distinct ways [Karlsson, *et al.*, *Mol Microbiol.* 8:389-96 (1993), Karlsson, *et al.*, *Mol Microbiol.* 8:379-88 (1993)]. Iron acquisition is essential for pathogens. In this work, attenuated *exbB* mutants in both APP and *P. multocida* have been identified. Several TonB-dependent iron receptors have been identified in other bacteria [Biswas, *et al.*, *Mol. Microbiol.* 24:169-179 (1997), Braun, *FEMS Microbiol Rev.* 16:295-307 (1995), Elkins, *et al.*, *Infect Immun.* 66:151-160 (1998), Occhino, *et*

al., *Mol Microbiol.* 29:1493-507 (1998), Stojiljkovic and Srinivasan, *J Bacteriol.*
 179:805-12 (1997)]. *A. pleuropneumoniae* produces 2 transferrin-binding proteins,
 which likely depend on the ExbB/ExbD/TonB system, for acquisition of iron. PotD
 is a periplasmic binding protein that is required for spermidine (a polyamine) transport
 5 [Kashiwagi, et al., *J Biol Chem.* 268:19358-63 (1993)]. Another member of the
Pasteurellaceae family, *Pasteurella haemolytica*, contains a homologue of *potD*
 (Lpp38) that is a major immunogen in convalescent or outer membrane protein
 vaccinated calves [Pandher and Murphy, *Vet Microbiol.* 51:331-41 (1996)]. In *P.*
haemolytica, PotD appeared to be associated with both the inner and outer
 10 membranes. The role of PotD in virulence or in relationship to protective antibodies
 is unknown although previous work has shown *potD* mutants of *Streptococcus*
pneumoniae to be attenuated [Polissi, et al., *Infect. Immun.* 66:5620-9 (1998)].
 Relatively few "classical virulence factors," such as adhesins or toxins
 with the exception of homologues to OMP P5 of *Haemophilus influenzae*, were
 15 identified. *H. influenzae* OMP P5 is a major outer membrane protein that is related to
 the OmpA porin family of proteins [Munson, et al., *M Infect Immun.* 61:4017-20
 (1993)]. OMP P5 in nontypeable *Haemophilus influenzae* has been shown to encode
 a fimbrial subunit protein expressed as a filamentous structure [Sirakova, et al., *Infect*
Immun. 62:2002-20 (1994)] that contributes to virulence and binding of both mucin
 20 and epithelial cells [Miyamoto and Bakaletz, *Microb Pathog.* 21:343-56 (1996),
 Reddy, et al., *Infect Immun.* 64:1477-9 (1996), Sirakova, et al., *Infect Immun.*
 62:2002-20 (1994)]. A significant finding was identification of two distinct ORFs
 that appear to encode OMP P5 homologues. This is also the case with two very
 similar proteins, MOMP and OmpA2 from *Haemophilus ducreyi*. It remains to be
 25 determined whether both are functionally involved in the production of fimbriae and
 whether the presence of two such ORFs represents a divergent duplication with
 redundant or complementing functions. Interestingly, the two OMP P5 mutants seem
 to have disparate CI values, suggesting a difference in essentiality or functionality for
 only one copy. OMP P5 has been shown to undergo molecular variation during
 30 chronic infections [Duim, et al., *Infect Immun.* 65:1351-1356 (1997)], however, this

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appears to be restricted to a single gene undergoing point mutations resulting in amino acid changes rather than "type switching" due to differential expression of multiple genes.

Protein folding enzymes are important accessories for the efficient folding of periplasmic and extracellular proteins, and two genes were identified whose products have peptidyl-prolyl isomerase activity: *fkpA* and *tig* (trigger factor). FkpA is a periplasmic protein that is a member of the FK506-binding protein family [Horne and Young, *Arch Microbiol.* 163:357-65 (1995); Missiakas, *et al.*, *Mol Microbiol.* 21:871-84 (1996)]. FkpA has been shown to contribute to intracellular survival of *Salmonella typhimurium* [Horne, *et al.*, *Infect Immun.* 65:806-10 (1997)] and a *Legionella pneumophila* homolog, *mip* [Engleberg, *et al.*, *Infect Immun.* 57:1263-1270 (1989)], is responsible for virulence and infection of macrophages [Cianciotto, *et al.*, *J. Infect. Dis.* 162:121-6 (1990); Cianciotto, *et al.*, *Infect. Immun.* 57:1255-1262 (1989)]. *Tig*, or trigger factor [Crooke and Wickner, *Proc. Natl. Acad. Sci. USA.* 84:5216-20 (1987), Guthrie, and Wickner, *J. Bacteriol.* 172:5555-62 (1990), reviewed in Hesterkamp, and Bukau, *FEBS Lett.* 389:32-4 (1996)], is a peptidyl prolyl isomerase containing a typical FKBP region [Callebaut and Mornon, *FEBS Lett.* 374:211-215 (1995)], but is unaffected by FK506 [Stoller, *et al.*, *EMBO J.* 14:4939-48 (1995)]. *Tig* has been shown to associate with the ribosomes and nascent polypeptide chains [Hesterkamp, *et al.*, *Proc Natl Acad Sci USA* 93:4437-41 (1996), Stoller, *et al.*, *EMBO J.* 14:4939-48 (1995)]. Possible roles include an unknown influence on cell division [Guthrie, and Wickner, *J. Bacteriol.* 172:5555-62 (1990)] in *E. coli*, a role in the secretion and activation of the *Streptococcus pyogenes* cysteine proteinase [Lyon, *et al.*, *EMBO J.* 17:6263-75 (1998)] and survival under starvation conditions in *Bacillus subtilis* [Gothel, *et al.*, *Biochemistry* 37:13392-9 (1998)].

Bacterial pathogens employ many mechanisms to coordinately regulate gene expression in order to survive a wide variety of environmental conditions within the host. Differences in mRNA stability can modulate gene expression in prokaryotes [Belasco and Higgins, *Gene* 72:15-23 (1988)]. For example, *rnr* (*vacB*) is required for expression of plasmid borne virulence genes in *Shigella flexneri* [Tobe, *et al.*, *J*

Bacteriol. 174:6359-67 (1992)] and encodes the RNaseR ribonuclease [Cheng, *et al.*, *J. Biol. Chem.* 273:14077-14080 (1998)]. PNP is a polynucleotide phosphorylase that is involved in the degradation of mRNA. Null *pnp* / *rnr* mutants are lethal, suggesting a probable overlap of function. It therefore is possible that both *rnr* and *pnp* are involved in the regulation of virulence gene expression. A *pnp* mutant of *P. multocida* is avirulent in a mouse septicemic model (Example 2). Other *pnp*-associated phenotypes include competence deficiency and cold sensitivity in *Bacillus subtilis* [Wang and Bechhofer, *J Bacteriol.* 178:2375-82 (1996)].

HupA is a bacterial histone-like protein, which in combination with HupB constitute the HU protein in *E. coli*. Reports have suggested that *hupA* and *hupB* single mutants do not demonstrate any observable phenotype [Huisman, *et al.*, *J Bacteriol.* 171:3704-12 (1989), Wada, *et al.*, *J Mol Biol.* 204:581-91 (1988)], however, *hupA-hupB* double mutants have been shown to be cold sensitive, sensitive to heat shock and blocked in many forms of site-specific DNA recombination [Wada, *et al.*, *J Mol Biol.* 204:581-91 (1988), Wada, *et al.*, *Gene.* 76:345-52 (1989)]. One limited data previously indicated that *hupA* is directly involved in virulence [Turner, *et al.*, *Infect Immun.* 66:2099-106 (1998)]. The mechanism of *hupA* attenuation remains unknown.

DnaK is a well known and highly conserved heat shock protein involved in regulatory responses to various stressful environmental changes [reviewed in Lindquist and Craig, *Annu Rev Genet.* 22:631-77 (1988)]. DnaK is also one of the most significantly induced stress proteins in *Yersinia enterocolitica* after being phagocytosed by macrophages [Yamamoto, *et al.*, *Microbiol Immunol.* 38:295-300 (1994)] and a *Brucella suis dnaK* mutant failed to multiply within human macrophage-like cells [Kohler, *et al.*, *Mol Microbiol.* 20:701-12 (1996)]. In contrast, another intracellular pathogen, *Listeria monocytogenes*, did not show induction of *dnaK* after phagocytosis [Hanawa, *et al.*, *Infect Immun.* 63:4595-9 (1995)]. A *dnaK* mutant of *Vibrio cholera* affected the production of ToxR and its regulated virulence factors in vitro but similar results were not obtained from in vivo grown cells [Chakrabarti, *et al.*, *Infect Immun.* 67:1025-1033 (1999)]. The CI of *A.*

pleuropneumonia dnaK mutant was higher than most of the attenuated mutants although still approximately half of the positive control strain.

DksA is a dosage dependent suppressor of filamentous and temperature-sensitive growth in a *dnaK* mutant of *E. coli* [Kang and Craig, *J Bacteriol.* 172:2055-64 (1990)]. There is currently no defined molecular function for DksA, but the gene has been identified as being critical for the virulence of *Salmonella typhimurium* in chickens and newly hatched chicks [Turner, *et al., Infect Immun.* 66:2099-106 (1998)]. In that work, it was noted that the *dksA* mutant did not grow well with glucose or histidine but did grow well with glutamine or glutamate as the sole carbon source. This observation may indicate that the *dksA* mutant is somehow impaired in the biosynthesis of glutamate [Turner, *et al., Infect Immun.* 66:2099-106 (1998)].

Three genes were identified that have roles in protein synthesis: tRNA-leu, tRNA-glu and *rpmF*. Excluding protein synthesis, tRNA's also have a wide variety of functional roles in peptidoglycan synthesis [Stewart, *et al., Nature* 230:36-38 (1971)], porphyrin ring synthesis [Jahn, *et al., Trends Biochem Sci.* 17:215-8 (1992)], targeting of proteins for degradation [Tobias, *et al., Science* 254:1374-7 (1991)], post-translational addition of amino acids to proteins [Leibowitz and Soffer, *B.B.R.C.* 36:47-53 (1969)] and mediation of bacterial-eukaryotic interactions [Gray, *et al., J Bacteriol.* 174:1086-98 (1992), Hromockyj, *et al., Mol Microbiol.* 6:2113-24 (1992)]. More specifically, tRNA-leu is implicated in transcription attenuation [Carter, *et al., Proc. Natl. Acad. Sci. USA* 83:8127-8131 (1986)], lesion formation by *Pseudomonas syringae* [Rich and Willis, *J Bacteriol.* 179:2247-58 (1997)] and virulence of uropathogenic *E. coli* [Dobrindt, *et al., FEMS Microbiol Lett.* 162:135-141 (1998), Ritter, *et al., Mol Microbiol.* 17:109-21 (1995)]. It is unknown whether the tRNA that we have identified represents a minor species of tRNA-leu in *A. pleuropneumoniae*. Regardless, it is possible that tRNA-leu may have any one of a wide range of functions. RpmF is a ribosomal protein whose gene is also part of an operon containing fatty acid biosynthesis enzymes in *E. coli*. Further work will be required to indicate if this is the case in *A. pleuropneumoniae*, although the same

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clustering of *fab* genes and *rpmF* occurs in *Haemophilus influenzae* [Fleischmann, *et al.*, *Science* 269:496-512 (1995)]. The expression of the *fab* genes is not necessarily dependent on transcripts originating upstream of *rpmF* as there has been a secondary promoter identified within *rpmF* [Zhang and Cronan, Jr., *J Bacteriol.* 180:3295-303 (1998)].

The final class of attenuated mutants includes mutations within genes of unknown function or genes that have not been previously identified. Homologs of *yaeA* and HI0379 have previously been identified in *Escherichia coli* [Blattner, *et al.*, *Science* 277:1453-1474 (1997)] and *Haemophilus influenzae* [Fleischmann, *et al.*, *Science* 269:496-512 (1995)], respectively. The remaining unknowns have been designated *Actinobacillus pleuropneumoniae* virulence genes (*apv*). The *apvC* gene shows significant similarity to HI0893, however, the proposed similarity of HI0893 as a transcriptional repressor similar to the fatty acid response regulator Bm3R1 [Palmer, *J Biol Chem.* 273:18109-16 (1998)] is doubtful. The *apvD* gene is also most similar to a putative membrane protein (b0878) with unknown function from *E. coli* [Blattner, *et al.*, *Science* 277:1453-1474 (1997)]. Two other unknowns, *apvA* and *apvB* had no significant matches in the public databases.

Example 11

Safety and Efficacy of *A. pleuropneumoniae* Mutants

Nine groups (n=8) of SPF pigs (4-5 weeks old, 3-10 kg) were used to determine the safety and efficacy of seven *A. pleuropneumoniae* mutants as live attenuated vaccine strains. Seven groups were infected intranasally with 10^{10} CFU of each mutant on day 1. One group was vaccinated on days 1 and 15 with the commercially available vaccine Pleuromune (Bayer), and one naive group was not vaccinated. On day 29, all groups were challenged intranasally with 1.5×10^5 CFU per pig of wild type APP225. All surviving animals were euthanized and necropsied on day 42 of the study. Results are shown in Table 4.

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Table 4
Efficacy of *A. pleuropneumoniae* Mutants

	<u>Vaccine</u>	<u>% Mortality following intranasal challenge</u>	
		<u>Vaccination</u>	<u>Challenge</u>
5	Pleuromune	0	37.5
	exbB	0	0
	tig	12.5	0
	fkpA	12.5	0
	HI0385	50.0	0
10	pnp	0	0
	yaeE	0	0
	atpG	0	0
	None	N/A	50.0

- 15 The *exbB*, *atpG*, *pnp*, and *yaeA* mutants caused no mortality when administered at a dosage of 10^{10} CFU intranasally. The *fkpA* and *tig* mutant groups had one death each and the HI0379 group (highest CI of the 7 mutants tested shown in Example 9) had four deaths. Wildtype LD₅₀ using this model was generally 1×10^7 CFU, indicating that each of these mutants is at least 100 fold attenuated and that
- 20 there is a reasonable correlation between CI and attenuation.

Example 12
Identification of *P.(Mannheimia) haemolytica* Species Homologs

- 25 Based on the sequences of virulence genes identified in *P. multocida* and *A. pleuropneumoniae*, attempt were made to identify related genes, *i.e.*, species homologs, in *P. (Mannheimia) haemolytica*. PCR was utilized with the degenerate primers shown below to attempt amplification of the *P. (Mannheimia) haemolytica* genes as indicated. Primer sequences, synthesized by Sigma-Genosys (The Woodlands, TX), include standard single letter designations, wherein B indicates

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either (C,G or T), D indicates either (G,A or T), H indicates either (A,C or T), K indicates either (G or T), M indicates either (A or C), N indicates either (A,G,C or T), R indicates either (A or G), S indicates either (G or C), V indicates either (G, A, or C), W indicates either (A or T), and Y indicates either (C or T).

5

atpG	TEF146	ATG GCN GGN GCN AAR GAR AT	SEQ ID NO: 176
	TEF148	GCN GCY TTC ATN GCN ACC AT	SEQ ID NO: 177

10

guaB	TEF240	GGN TTY ATY CAY AAA AAY ATG	SEQ ID NO: 178
	TEF243	TCT TTN GTR ATN GTN ACA TCR TG	SEQ ID NO: 179

pnp	TEF141	GCS GGY AAA CCR CGT TGG GAT TGG	SEQ ID NO: 180
	TEF142	CRC CTA ARA TRT CTG AAA GCA CCA C	SEQ ID NO: 181

15

purF	TEF244	ATG TGY GGN ATY GTN GGN AT	SEQ ID NO: 182
	TEF247	CAT ATC AAT ACC ATA CAC ATT	SEQ ID NO: 183

yjgF	TEF162	GGN CCN TAY GTN CAR G	SEQ ID NO: 184
	TEF163	NGC NAC YTC NAC RCA	SEQ ID NO: 185

20

For amplification of initial degenerate PCR products, a 50 µl reaction was set up using 3.3X XL buffer II (PE Applied Biosystems), 200 µM dNTPs, 25 pmol each of the appropriate primers, 0.8 mM MgCl₂, 0.5 U *r7h* DNA polymerase, XL (PE Applied Biosystems) and approximately 1 µg of TF1 DNA.

25

Cycle conditions were 94°C for 1.5 min; followed by 35 cycles of 94°C for 15 s, 40-60°C for 60 s, 72°C for 1.5 min; and a final hold at 72°C for 5 min. Each PCR product was band purified from an agarose gel using the QIAGEN Gel Extraction Kit (QIAGEN, Valencia CA).

30

Sequencing reactions were performed using the BigDye™ Dye Terminator Chemistry kit from PE Applied Biosystems (Foster City, CA) and run on an ABI Prism 377 DNA Sequencer. Double stranded sequence for the open reading frame (ORF) for each clone was obtained. Sequencher 3.0 software (Genecodes, Corp., Ann Arbor, MI) was used to assemble and analyze sequence data. GCG programs were used to confirm the identity of the ORF by searching for homologous sequences in currently available databases.

35

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The Vectorette Kit (Genosys Biotechnologies, The Woodlands, TX) was used to obtain additional flanking sequence for each of the genes. Vectorette libraries were prepared according to the manufacturer's suggested protocol. Perkin Elmer Applied Biosystems GeneAmp XL PCR Kit components were used to create the

5 Vectorette PCR products with the following reaction conditions. A 50 µl reaction was set up using 3.3X XL buffer II (PE Applied Biosystems), 200 µM dNTPs, 25 pmol each of the appropriate primers (shown below), 0.8 mM MgCl₂, 0.5 U *r7h* DNA polymerase, XL (PE Applied Biosystems) and 1 µl of the appropriate vectorette library. Cycle

10 conditions were 94°C for 1.5 min; followed by 35 cycles of 94°C for 20 s, 60°C for 45s, 72°C for 4 min; and a final hold of 72°C for 7 min. The second primer for each library was the manufacturer's vectorette primer.

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Table 5

Gene	Vectorette library	Primer(s)
5	atpG	TEF217 GAAGCCGCCATACGCTCTTGGG SEQ ID NO: 186
		TEF218 GTTGCTTCCTTTGCCTGCACTGG SEQ ID NO: 187
	guaB	TEF265 GGCTCAGAAACAATACCACTTTCA SEQ ID NO: 188
		TEF268 GCACCAAAGCAGAATTGTCC SEQ ID NO: 189
10	pnp	TEF219 GGTGATGATGTCGATGATAGTCCC SEQ ID NO: 190
		TEF220 GGCGTATTAGCCGTGATGCCAACC SEQ ID NO: 191
	purF	TEF286 GACCACTTAGGCGATATGGACTT SEQ ID NO: 192
		TEF271 ACCATCATAAATCGCCTGATTC SEQ ID NO: 193
15	yigF	TEF292 ACCTGCGGCATCTTGTCTC SEQ ID NO: 194
		TEF274 ACGGGTTTATTTGCCTCTG SEQ ID NO: 195
	yigF	TEF221 CGCCGGTTTCAGGATTCACGGG SEQ ID NO: 196
		TEF281 CTGAACAACGTGAAAGCCAT SEQ ID NO: 197

Vectorette PCR products were band purified and sequenced as described above.

20 Polynucleotide sequences for the atpG, guaB, pnp, purF, and yigF genes are set out in SEQ ID NOs: 166, 168, 170, 172 and 174, respectively. Polypeptides encoded by these genes are set out in SEQ ID NOs: 167, 169, 171, 173, and 175, respectively.

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;

Numerous modifications and variations in the invention as set forth in the above illustrative examples are expected to occur to those skilled in the art. Consequently only such limitations as appear in the appended claims should be placed on the invention.

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WHAT IS CLAIMED IS:

1. A gram-negative bacteria comprising a mutation in a gene represented by a nucleotide sequence set forth in any one of SEQ ID NOs: 1, 3, 7, 9, 21, 25, 27, 29, 39, 41, 51, 53, 55, 57, 58, 60, 68, 72, 74, 76, 78, 80, 82, 84, 104, 108, 112, 116, 118, 120, 122, 124, 126, 128, and 130, or species homologs thereof, said mutation resulting in decreased activity of a gene product encoded by the mutated gene.
2. The gram-negative bacteria of claim 1 wherein said mutation results in decreased expression of a gene product encoded by the mutated gene.
3. The gram-negative bacteria of claim 1 wherein said mutation results in expression of an inactive gene product encoded by the mutated gene.
4. The gram-negative bacteria of claim 1 wherein said mutation results in deletion of all or part of said gene.
5. An attenuated *Pasteurellaceae* bacteria comprising a mutation in a gene represented by a nucleotide sequence set forth in any one of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172 and 174 or a species homolog thereof, said mutation resulting in decreased activity of a gene product encoded by the mutated gene.
6. The *Pasteurellaceae* bacteria of claim 5 wherein said mutation results in decreased expression of a gene product encoded by the mutated gene.
7. The *Pasteurellaceae* bacteria of claim 5 wherein said mutation results in expression of an inactive gene product encoded by the mutated gene.

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8. The *Pasteurellaceae* bacteria of claim 5 wherein said mutation results in deletion of all or part of said gene.

9. The *Pasteurellaceae* bacteria of claim 5 selected from the group consisting of *Pasteurella (Mannheimia) haemolytica*, *Pasteurella multocida*, *Actinobacillus pleuropneumoniae* and *Haemophilus somnus*.

10. The *Pasteurellaceae* bacteria of claim 9 wherein said mutation results in decreased expression of a gene product encoded by the mutated gene.

11. The *Pasteurellaceae* bacteria of claim 9 wherein said mutation results in expression of an inactive gene product encoded by the mutated gene.

12. The *Pasteurellaceae* bacteria of claim 9 wherein said mutation results in deletion of all or part of said gene.

13. The attenuated *Pasteurellaceae* bacteria of claim 9 that is a *P. multocida* bacteria.

14. The *Pasteurellaceae* bacteria of claim 13 wherein said mutation results in decreased expression of a gene product encoded by the mutated gene.

15. The *Pasteurellaceae* bacteria of claim 13 wherein said mutation results in expression of an inactive gene product encoded by the mutated gene.

16. The *Pasteurellaceae* bacteria of claim 13 wherein said mutation results in deletion of all or part of said gene.

17. The attenuated *Pasteurellaceae* bacteria of claim 9 that is a *A. pleuropneumoniae* bacteria.

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18. The *Pasteurellaceae* bacteria of claim 17 wherein said mutation results in decreased expression of a gene product encoded by the mutated gene.

19. The *Pasteurellaceae* bacteria of claim 17 wherein said mutation results in expression of an inactive gene product encoded by the mutated gene.

20. The *Pasteurellaceae* bacteria of claim 17 wherein said mutation results in deletion of all or part of said gene.

21. An immunogenic composition comprising the bacteria according to any one of claims 1 through 20.

22. A vaccine composition comprising the immunogenic composition according to claim 21 and a pharmaceutically acceptable carrier.

23. The vaccine composition according to claim 22 further comprising an adjuvant.

24. A method for producing a gram-negative bacteria mutant comprising the step of introducing a mutation in a gene represented by a nucleotide sequence set forth in any one of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 or a species homolog thereof, said mutation resulting in decreased activity of a gene product encoded by the mutated gene.

25. A method for producing an attenuated *Pasteurellaceae* bacteria comprising the step of introducing a mutation in a gene represented by a nucleotide sequence set forth in any one of SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29,

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31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172, and 174 or a species homolog thereof, said mutation resulting in decreased activity of a gene product encoded by the mutated gene.

26. A purified and isolated *Pasteurellaceae* polynucleotide comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth in SEQ ID NOs: 1, 3, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 29, 31, 33, 37, 39, 41, 51, 53, 55, 57, 58, 60, 68, 70, 72, 74, 76, 78, 80, 82, 84, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 135, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 163, 164, 166, 168, 170, 172 and 174.

27. A purified and isolated *Pasteurellaceae* polynucleotide comprising a nucleotide sequence selected from the group consisting of nucleotide sequences set forth in SEQ ID NOs: 1, 3, 7, 9, 21, 25, 27, 29, 39, 41, 51, 53, 55, 57, 58, 60, 68, 72, 74, 76, 78, 80, 82, 84, 104, 108, 112, 116, 118, 120, 122, 124, 126, 128, and 130.

28. A purified and isolated polynucleotide encoding a *Pasteurellaceae* virulence gene product, or species homolog thereof, selected from the group consisting of:

- a) the polynucleotide according to claim 27,
- b) polynucleotides encoding a polypeptide encoded by the polynucleotide of (a), and
- c) polynucleotides that hybridize to the complement of the polynucleotides of (a) or (b) under moderate stringency conditions.

29. A purified and isolated *Pasteurellaceae* polynucleotide encoding a polypeptide selected from the group consisting of polypeptides having amino acid sequences set forth in SEQ ID NOs: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 32, 34, 38, 40, 42, 52, 54, 56, 59, 61, 69, 71, 73, 75, 77, 79, 81, 83, 85, 101, 103, 105, 107, 109,

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111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 165, 167, 169, 171, 173, and 175.

30. The polynucleotide of claim 29 which is a DNA.

31. A vector comprising the DNA of claim 30.

32. The vector of claim 31 that is an expression vector, wherein the DNA is operatively linked to an expression control DNA sequence.

33. A host cell stably transformed or transfected with the DNA of claim 30 in a manner allowing the expression of the encoded polypeptide in said host cell.

34. A method for producing a recombinant polypeptide comprising culturing the host cell of claim 33 in a nutrient medium and isolating the encoded polypeptide from said host cell or said nutrient medium.

35. A purified polypeptide produced by the method of claim 34.

36. A purified polypeptide comprising a polypeptide selected from the group consisting of polypeptides having amino acid sequences set forth in SEQ ID NOs: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 32, 34, 38, 40, 42, 54, 56, 59, 61, 69, 71, 73, 75, 77, 79, 81, 83, 85, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 165, 167, 169, 171, 173, and 175.

37. An antibody that is specifically reactive with the polypeptide of claim 36.

38. The antibody of claim 33 that is a monoclonal antibody.

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39. A method of using the monoclonal antibody of claim 39 for identifying a bacteria of claim 1, 5, 9, or 13 comprising the step of contacting an extract of bacteria with said monoclonal antibody and detecting the absence of binding of said monoclonal antibody.

40. A method of identifying an anti-bacterial agent comprising the steps of assaying potential agents for the ability to interfere with expression or activity of gene products represented by the amino acid sequences set forth in any one of SEQ ID NOS: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 32, 34, 38, 40, 42, 52, 54, 56, 59, 61, 69, 71, 73, 75, 77, 79, 81, 83, 85, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 165, 167, 169, 171, 173, and 175 and identifying an agent that interferes with expression or activity of said gene products.

41. A method of identifying an anti-bacterial agent comprising the steps of:

- a) measuring expression or activity of a gene product as set out in SEQ ID NOS: 2, 4, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 30, 32, 34, 38, 40, 42, 52, 54, 56, 59, 61, 69, 71, 73, 75, 77, 79, 81, 83, 85, 101, 103, 105, 107, 109, 111, 113, 115, 117, 119, 121, 123, 125, 127, 129, 131, 133, 135, 137, 139, 141, 143, 145, 147, 149, 151, 153, 155, 157, 159, 161, 165, 167, 169, 171, 173, and 175;
- b) contacting the gene product in (a) with a test compound
- c) measuring expression or activity of the gene product in the presence of the test compound; and
- d) identifying the test compound as an antibacterial agent when expression or activity of the gene product is decreased in the presence of the test compound as compared to expression or activity in the presence of the test compound.

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 ttttcataaa tatcaataaa ggattagtt atg gca gca gag ctt aca aca gcg 233
 Met Ala Ala Glu Leu Thr Thr Ala
 1 5
 gga tat att ggg cac cat tta gca ttc ttg aaa aca ggg gat tct ttc 281
 Gly Tyr Ile Gly His His Leu Ala Phe Leu Lys Thr Gly Asp Ser Phe
 10 15 20

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tgg cat gtt cat tta gat acc ctt cta ttt tca att att tca ggt gca 329
Trp His Val His Leu Asp Thr Leu Leu Phe Ser Ile Ile Ser Gly Ala
25 30 35 40

att ttt ctt ttt gtt ttt tca aaa gtt gca aaa aaa gca acg ccg ggt 377
Ile Phe Leu Phe Val Phe Ser Lys Val Ala Lys Lys Ala Thr Pro Gly
45 50 55

gtg cct agc aag atg caa tgt ttt gtt gag ata atg gtt gat tgg att 425
Val Pro Ser Lys Met Gln Cys Phe Val Glu Ile Met Val Asp Trp Ile
60 65 70

gat ggg atc gta aaa gaa aat ttc cat ggt cct cgt cat gct gtt gga 473
Asp Gly Ile Val Lys Glu Asn Phe His Gly Pro Arg His Ala Val Gly
75 80 85

cca tta gca tta act att ttc tgc tgg gta ttc att atg aat gct atc 521
Pro Leu Ala Leu Thr Ile Phe Cys Trp Val Phe Ile Met Asn Ala Ile
90 95 100

gat ttg atc cca gta gat ttc cta cct caa tta gcc cat tta ttt ggt 569
Asp Leu Ile Pro Val Asp Phe Leu Pro Gln Leu Ala His Leu Phe Gly
105 110 115 120

att gaa tac tta aga gct gtt cca aca gca gat atc agt gga aca tta 617
Ile Glu Tyr Leu Arg Ala Val Pro Thr Ala Asp Ile Ser Gly Thr Leu
125 130 135

ggc tta tca att ggt gtc ttc ttc tta att att ttc tat aca atc aaa 665
Gly Leu Ser Ile Gly Val Phe Phe Leu Ile Ile Phe Tyr Thr Ile Lys
140 145 150

tca aaa ggt atg agt ggc ttt gtt aaa gaa tat acg ctt cat cct ttt 713
Ser Lys Gly Met Ser Gly Phe Val Lys Glu Tyr Thr Leu His Pro Phe
155 160 165

aat cat cct ttg tta att ccg gtt aac tta gcg ctt gaa tca gtc aca 761
Asn His Pro Leu Leu Ile Pro Val Asn Leu Ala Leu Glu Ser Val Thr
170 175 180

tta tta gca aaa cct gtt tct ttg gcg ttc cgt ctt ttc ggg aat atg 809
Leu Leu Ala Lys Pro Val Ser Leu Ala Phe Arg Leu Phe Gly Asn Met
185 190 195 200

tat gca ggt gaa ctt atc ttt att ctt att gca gtg atg tac atg gca 857
Tyr Ala Gly Glu Leu Ile Phe Ile Leu Ile Ala Val Met Tyr Met Ala
205 210 215

aat aat ttt gca ctt aat tca atg ggt att ttc atg cat ttg gct tgg 905
Asn Asn Phe Ala Leu Asn Ser Met Gly Ile Phe Met His Leu Ala Trp
220 225 230

gct att ttc cat att ctt gtg att acc tta caa gca ttt att ttt atg 953
Ala Ile Phe His Ile Leu Val Ile Thr Leu Gln Ala Phe Ile Phe Met
235 240 245

atg ctt aca gtg gtt tat ttg agt atg ggt tat aac aaa gca gaa cac 1001
Met Leu Thr Val Val Tyr Leu Ser Met Gly Tyr Asn Lys Ala Glu His
250 255 260

taatttttta taaacaaaaa cagaccttgg gtctaaattt caatcttatg gagaacatta 1061

tggaacactg taattactac aacaatcatt gcattcgnaa ttntctttgc t 1112

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<210> 2
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 <212> PRT
 <213> *Pasteurella multocida*

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 Phe Leu Lys Thr Gly Asp Ser Phe Trp His Val His Leu Asp Thr Leu
 20 25 30
 Leu Phe Ser Ile Ile Ser Gly Ala Ile Phe Leu Phe Val Phe Ser Lys
 35 40 45
 Val Ala Lys Lys Ala Thr Pro Gly Val Pro Ser Lys Met Gln Cys Phe
 50 55 60
 Val Glu Ile Met Val Asp Trp Ile Asp Gly Ile Val Lys Glu Asn Phe
 65 70 75 80
 His Gly Pro Arg His Ala Val Gly Pro Leu Ala Leu Thr Ile Phe Cys
 85 90 95
 Trp Val Phe Ile Met Asn Ala Ile Asp Leu Ile Pro Val Asp Phe Leu
 100 105 110
 Pro Gln Leu Ala His Leu Phe Gly Ile Glu Tyr Leu Arg Ala Val Pro
 115 120 125
 Thr Ala Asp Ile Ser Gly Thr Leu Gly Leu Ser Ile Gly Val Phe Phe
 130 135 140
 Leu Ile Ile Phe Tyr Thr Ile Lys Ser Lys Gly Met Ser Gly Phe Val
 145 150 155 160
 Lys Glu Tyr Thr Leu His Pro Phe Asn His Pro Leu Leu Ile Pro Val
 165 170 175
 Asn Leu Ala Leu Glu Ser Val Thr Leu Leu Ala Lys Pro Val Ser Leu
 180 185 190
 Ala Phe Arg Leu Phe Gly Asn Met Tyr Ala Gly Glu Leu Ile Phe Ile
 195 200 205
 Leu Ile Ala Val Met Tyr Met Ala Asn Asn Phe Ala Leu Asn Ser Met
 210 215 220
 Gly Ile Phe Met His Leu Ala Trp Ala Ile Phe His Ile Leu Val Ile
 225 230 235 240
 Thr Leu Gln Ala Phe Ile Phe Met Met Leu Thr Val Val Tyr Leu Ser
 245 250 255
 Met Gly Tyr Asn Lys Ala Glu His
 260

<210> 3
 <211> 1972
 <212> DNA
 <213> *Pasteurella multocida*

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<222> (364)...(1230)

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acaacaagca ttagtggtat ttgcagtaga gtttggttac ttagaagaag tggacttaga 180
tcgtattggt tcatttgaat cagcaacttt agagtatgct aaccataact atgctgattt 240
tatgcgtgag ttaacccaat ctggcaatta caatgatgaa attaaagagt cattaaaagg 300
cattttggat agcttcaaag caaacagtgc gtgtaagtt aacactttaa atggagagac 360
aaa atg gca ggt gct aaa gag ata aga acc aaa atc gcg agt gta aaa 408
Met Ala Gly Ala Lys Glu Ile Arg Thr Lys Lys Ile Ala Ser Val Lys
1 5 10 15
agt aca caa aaa att act aaa gcg atg gaa atg gtt gct gcc tcg aaa 456
Ser Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Ala Ser Lys
20 25 30
atg cgt aaa acg caa gaa cgc atg tct tct tca cgc cct tat tca gaa 504
Met Arg Lys Thr Gln Glu Arg Met Ser Ser Arg Pro Tyr Ser Glu
35 40 45
aca ata cgt aac gtg att agc cac gtt tcc aaa gca acg att ggt tac 552
Thr Ile Arg Asn Val Ile Ser His Val Ser Lys Ala Thr Ile Gly Tyr
50 55 60
aag cat cca ttt tta gtg gat cgc gaa gta aaa aaa gtg ggc atg att 600
Lys His Pro Phe Leu Val Asp Arg Glu Val Lys Lys Val Gly Met Ile
65 70 75
gtt gtg tcc aca gat cgt ggt ctt tgt ggt ggc tta aac gtg aac ttg 648
Val Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Val Asn Leu
80 85 90 95
ttt aaa act gta tta aat gaa atg aaa gaa tgg aaa gaa aaa gat gtt 696
Phe Lys Thr Val Leu Asn Glu Met Lys Glu Trp Lys Glu Lys Asp Val
100 105 110
tcc gtt caa ttg agt tta atc ggt tct aaa tct atc aac ttt ttc caa 744
Ser Val Gln Leu Ser Leu Ile Gly Ser Lys Ser Ile Asn Phe Phe Gln
115 120 125
tct ttg gga att aaa att tta acc caa gat tca ggt att ggt gat act 792
Ser Leu Gly Ile Lys Ile Leu Thr Gln Asp Ser Gly Ile Gly Asp Thr
130 135 140
ccc tct gtt gag cag tta att ggt tca gtc aat tct atg att gat gct 840
Pro Ser Val Glu Gln Leu Ile Gly Ser Val Asn Ser Met Ile Asp Ala
145 150 155
tat aaa aaa ggg gaa gta gat gtt gtg tat tta gtt tat aac aaa ttt 888
Tyr Lys Lys Gly Glu Val Asp Val Val Tyr Leu Val Tyr Asn Lys Phe
160 165 170 175

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att aac acg atg tcg caa aag cca gta ttg gaa aaa tta att cca tta 936
lle asn thr met ser gln lys pro val leu glu lys leu ile pro leu
180 185 190

cca gaa tta gat aat gat gaa tta ggc gaa aga aaa caa gtt tgg gat 984
pro glu leu asp asn asp glu leu gly glu arg lys gln val trp asp
195 200 205

tat att tac gaa cct gat gcg aaa gta tta tta gat aat tta ttg gtt 1032
tyr ile tyr glu pro asp ala lys val leu leu asp asn leu leu val
210 215 220

cgt tat tta gaa tct cag gtt tat caa gca gca gtt gaa aac ctt gct 1080
arg tyr leu glu ser gln val tyr gln ala ala val glu asn leu ala
225 230 235

tct gag caa gcc gct cga atg gtc gcc atg aaa gca gca aca gat aac 1128
ser glu gln ala ala arg met val ala met lys ala ala thr asp asn
240 245 250 255

gca ggt aac tta att aat gag tta cag tta gtc tat aac aaa gct cgt 1176
ala gly asn leu ile asn glu leu gln leu val tyr asn lys ala arg
260 265 270

caa gca agt att aca aat gaa tta aat gaa att gtt gcc ggt gca gca 1224
gln ala ser ile thr asn glu leu asn glu ile val ala gly ala ala
275 280 285

gca att taacaaatag aggatcggt atggcaactg gaaaaattgt acaaatcacc 1280
ala ile

ggtagcggtta ttgacgttga attccacaa gatgcagttac caaaagtata tgatgcctta 1340

aatgttgaaa caggtttagt acttgaagtt caacaacaat taggtggtgg tgtagttcgc 1400

tgtatcgcaa tgggatcatc tgatggatta aaacgcggtt taagcgtaac aaatacgaat 1460

aaccacaatt ctgttcagtg gggaaacgaaa acattgggtc gtatcatgaa cgtattgggt 1520

gaaccaatcg atgagcaagg tgaatcggt gcagaagaga attggtctat tcaccgtgcg 1580

ccaccaagtt atgaagaaca atctaacagt actgaacttt tagaaacggg aattaaagtt 1640

atcgacttag ttgtccggt tgcgaaaggg ggtaaagtag gtttattcgg tggtagcggt 1700

gtcggtaaaa cgtcaatat gatggaatta atccgtaaca tcgcaattga gcaatcaggt 1760

tactctgtct ttgcgggggt aggtgagcgt acgcgtgaag gtaacgaact ctatcatgag 1820

atgaaagact ctaacgtatt agataaagtg tctcttggtt atggtcaaat gaacgagcca 1880

ccaggtaacc gttacgtgt ggcattaaca ggcittaacta tggcggaata attccgtgat 1940

gaaggtagtg atgtcttatt ctccgttgat aa 1972

<210> 4
<211> 289
<212> PRT
<213> Pasteurella multocida

<400> 4
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      20           25           30
Arg Lys Thr Gln Glu Arg Met Ser Ser Ser Arg Pro Tyr Ser Glu Thr
      35           40           45
Ile Arg Asn Val Ile Ser His Val Ser Lys Ala Thr Ile Gly Tyr Lys
      50           55           60
His Pro Phe Leu Val Asp Arg Glu Val Lys Lys Val Gly Met Ile Val
      65           70           75
Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Val Asn Leu Phe
      85           90           95
Lys Thr Val Leu Asn Glu Met Lys Glu Trp Lys Glu Lys Asp Val Ser
      100          105          110
Val Gln Leu Ser Leu Ile Gly Ser Lys Ser Ile Asn Phe Phe Gln Ser
      115          120          125
Leu Gly Ile Lys Ile Leu Thr Gln Asp Ser Gly Ile Gly Asp Thr Pro
      130          135          140
Ser Val Glu Gln Leu Ile Gly Ser Val Asn Ser Met Ile Asp Ala Tyr
      145          150          155
Lys Lys Gly Glu Val Asp Val Val Tyr Leu Val Tyr Asn Lys Phe Ile
      165          170          175
Asn Thr Met Ser Gln Lys Pro Val Leu Glu Lys Leu Ile Pro Leu Pro
      180          185          190
Glu Leu Asp Asn Asp Glu Leu Gly Glu Arg Lys Gln Val Trp Asp Tyr
      195          200          205
Ile Tyr Glu Pro Asp Ala Lys Val Leu Leu Asp Asn Leu Leu Val Arg
      210          215          220
Tyr Leu Glu Ser Gln Val Tyr Gln Ala Ala Val Glu Asn Leu Ala Ser
      225          230          235
Glu Gln Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Ala
      245          250          255
Gly Asn Leu Ile Asn Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln
      260          265          270
Ala Ser Ile Thr Asn Glu Leu Asn Glu Ile Val Ala Gly Ala Ala Ala
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Ile

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<210> 5
<211> 1357
<212> DNA
<213> Pasteurella multocida
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 <222> (1)...(813)

<220>
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 gag ttt tat ccg tta gag gca gtg aaa acc aat att tta ggt acg gca 96
 Glu Phe Tyr Pro Leu Glu Ala Val Lys Thr Asn Ile Leu Gly Thr Ala
 20 25 30
 aat gtc tta gaa gcc gcc atc caa aac cag ata aaa cgc gtc gtc tgt 144
 Asn Val Leu Glu Ala Ala Ile Gln Asn Gln Ile Lys Arg Val Val Cys
 35 40 45
 ctt agc aca gat aaa gcg gtg tac cca att aat gcg atg ggc att tct 192
 Leu Ser Thr Asp Lys Ala Val Tyr Pro Ile Asn Ala Met Gly Ile Ser
 50 55 60
 aaa gca atg atg gaa aaa gtc atc atc gca aaa tcg cgt aac cta gaa 240
 Lys Ala Met Met Glu Lys Val Ile Ile Ala Lys Ser Arg Asn Leu Glu
 65 70 75 80
 ggc aca cca acg aca atc tgt tgt act cgc tat ggc aat gtc atg gca 288
 Gly Thr Pro Thr Thr Ile Cys Cys Thr Arg Tyr Gly Asn Val Met Ala
 85 90 95
 tcg cgt ggt tcg gtt atc cca tta ttt gtc gat caa ata cgt caa ggc 336
 Ser Arg Gly Ser Val Ile Pro Leu Phe Val Asp Gln Ile Arg Gln Gly
 100 105 110
 aag cct ttt act att act gat cct gag atg aca cgc ttt atg atg aca 384
 Lys Pro Phe Thr Ile Thr Asp Pro Glu Met Thr Arg Phe Met Met Thr
 115 120 125
 ttg gaa gat gct gtg gat tta gtc cta tat gca ttt aaa aat ggt caa 432
 Leu Glu Asp Ala Val Asp Leu Val Leu Tyr Ala Phe Lys Asn Gly Gln
 130 135 140
 aat ggt gat gtt ttt gta caa aaa gcc ccc gca gca acc att ggt acc 480
 Asn Gly Asp Val Phe Val Gln Lys Ala Pro Ala Ala Thr Ile Gly Thr
 145 150 155 160
 ctt gcc aaa gca att acc gaa tta tta tct gtc cca aat cac cct att 528
 Leu Ala Lys Ala Ile Thr Glu Leu Leu Ser Val Pro Asn His Pro Ile
 165 170 175
 tcc att ata ggt acg cgt cat gga gag aaa gca ttc gaa gct tta tta 576
 Ser Ile Ile Gly Thr Arg His Gly Glu Lys Ala Phe Glu Ala Leu Leu
 180 185 190
 agc cgt gaa gaa atg gtt cat gca att aat gaa ggt aat tat tat cgc 624
 Ser Arg Glu Glu Met Val His Ala Ile Asn Glu Gly Asn Tyr Tyr Arg
 195 200 205
 atc cca gcc gat caa cgc agt tta aat tac agt aaa tat gtc gaa aaa 672
 Ile Pro Ala Asp Gln Arg Ser Leu Asn Tyr Ser Lys Tyr Val Glu Lys
 210 215 220

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ggg gaa cca aaa att acc gaa gtc acc gac tac aac tca cat aat act 720
Gly Glu Pro Lys Ile Thr Glu Val Thr Asp Tyr Asn Ser His Asn Thr
225                230                235                240

gag cgt tts act gtc aag gaa atg aag cag tta ctg ctt aaa ctt gaa 768
Glu Arg Leu Thr Val Lys Glu Met Lys Gln Leu Leu Leu Lys Leu Glu
245                250                255

ttc ata cag aaa atg att gag ggt gaa tac atc tca cag gag gta 813
Phe Ile Gln Lys Met Ile Glu Gly Glu Tyr Ile Ser Pro Glu Val
260                265                270

taaaaatgaa agtcttagta actggttcaa atgggtttat tgcgaaaaat ctgattcagt 873
ctttatctga ggaacaagat attgagattt tatgttatca cagtcaatcc tctgagaaaa 933
cgcttattca tcatgtattg agtgcgtgatt ggattattca tcttgcggtt gcgaatcgtc 993
cacctgaaga acaagaattt atgacatcaa atacacaatt gacggaaaaa atttgccgta 1053
ttttacagcg tcatcagaaa aaaacgcctt tgttatattc ctctagcatt caagtagaaa 1113
gtcccaaaat aagtacttat tcgcaaacca aattagaag tgaatatcat gttcatcaat 1173
tacataaaga aaatggtaat cagatttata tctgccgttt agctaagtc tttggcaaat 1233
ggtcacgacc tcaactatac tcggtagtcg ccacattttg ccataactta attcatgatt 1293
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ttga
1357

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<210> 6
<211> 271
<212> PRT
<213> Pasteurella multocida

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1      5      10      15

Glu Phe Tyr Pro Leu Glu Ala Val Lys Thr Asn Ile Leu Gly Thr Ala
20     25     30

Asn Val Leu Glu Ala Ala Ile Gln Asn Gln Ile Lys Arg Val Val Cys
35     40     45

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

Lys Ala Met Met Glu Lys Val Ile Ile Ala Lys Ser Arg Asn Leu Glu
65     70     75     80

Gly Thr Pro Thr Thr Ile Cys Cys Thr Arg Tyr Gly Asn Val Met Ala
85     90     95

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

Lys Pro Phe Thr Ile Thr Asp Pro Glu Met Thr Arg Phe Met Met Thr
115    120    125

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Leu Glu Asp Ala Val Asp Leu Val Leu Tyr Ala Phe Lys Asn Gly Gln
 130              135              140
Asn Gly Asp Val Phe Val Gln Lys Ala Pro Ala Ala Thr Ile Gly Thr
 145              150              155              160
Leu Ala Lys Ala Ile Thr Glu Leu Leu Ser Val Pro Asn His Pro Ile
 165              170              175
Ser Ile Ile Gly Thr Arg His Gly Glu Lys Ala Phe Glu Ala Leu Leu
 180              185              190
Ser Arg Glu Glu Met Val His Ala Ile Asn Glu Gly Asn Tyr Tyr Arg
 195              200              205
Ile Pro Ala Asp Gln Arg Ser Leu Asn Tyr Ser Lys Tyr Val Glu Lys
 210              215              220
Gly Glu Pro Lys Ile Thr Glu Val Thr Asp Tyr Asn Ser His Asn Thr
 225              230              235              240
Glu Arg Leu Thr Val Lys Glu Met Lys Gln Leu Leu Lys Leu Glu
 245              250              255
Phe Ile Gln Lys Met Ile Glu Gly Glu Tyr Ile Ser Pro Glu Val
 260              265              270

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<210> 7
<211> 6132
<212> DNA
<213> Pasteurella multocida

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cgtacttttag caaaagacat gattgatggc ggtaaagtgc attataatgg gcagcgacag 180
aaacccaata aaacggttga aattggtggt gtgatcaaac ttcgtaagg taatgacgaa 240
aaagaagtgg aagtgccttc gctttctacg caacgtcgtg gggcgccaga agcacaattg 300
ttgtatcaag aaacagaaaa aagccttgaa caacgtgcga aaatggcgat tgcacgtaag 360
attaatgcat taacgatgcc gcacccgtat cgtcgccga ataaaaaga gcggcgatgat 420
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cttattaaag aaaggaatat ggggaagctg tgtgcttgc cttaacctga ataaaggctt 540
tttatgacag acaacacaga caatgacaaa ctgtatcgct accttttcca agatcgcgcg 600
gtgcgcggtg aatgggtacg gttaaaccaa acgtttactg atacgttaaa tacacatcaa 660

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 gcgacgttaa aatttgaagg ggatattact gttcaagtac aaggatgatgg accattaaaa 780
 ttagcattag ttaattggcaa tcatcagcag caaattcccg cattagcgcg tttacaagcg 840
 gatgtcagtg atgatatgag tttggcgcaa ttagtcggga aaggggattt agtgattacg 900
 attgcaccga cagaagcgga gcgttaccaa ggctgattg cgttagataa gccaacattt 960
 actgocctgc ttgaagatta ttttgtgcgt tcagaacaat tgcaaaccca gcttattatt 1020
 cgtgctggcg aatttgaagg acaacctgtg gcagccggta tgttgttaca aattatgccg 1080
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 cgtgttgaaa ttttcccttc acagccgacg tcaattttct gtggctgctc acaagaacgt 1260
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 acggatttca ggaaaaaaat gaaaattgaa gcagacaaca attgtattgt aatttttggt 2520
 gcacaggtg atttaactta tcgtaaatg attcctgcac tgtataactt atataaaac 2580

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ggtcgtttga ctgagcattt ctccgtgtta ggtgtggcaa gaacggaatt aagtgatgag 2640
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1 5 10
gag aaa att gca caa gaa ttg tta gcg tat agc tta gaa ggt cgc cct 4118
Glu lys Ile Ala Gln Glu Leu Leu Ala Tyr Ser Leu Glu Gly Arg Pro
15 20 25
gtg cat att tcc tta tcc gga ggc tca acg ccg aaa ttg tta ttt aaa 4166
Val His Ile Ser Leu Ser Gly Gly Ser Thr Pro Lys Leu Leu Phe Lys
30 35 40 45
act tta gct caa gca ccg tat aac acc gag att caa tgg aaa aat ttg 4214
Thr Leu Ala Gln Ala Pro Tyr Asn Thr Glu Ile Gln Trp Lys Asn Leu
50 55 60

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His Phe Trp Trp Gly Asp Asp Arg Met Val Pro Pro Thr Asp Pro Glu
65 70 75

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Ser Asn Tyr Gly Glu Val Gln Lys Leu Leu Phe Asp His Ile Gln Ile
80 85 90

cct gca gaa aat att cac cgc att cgt ggt gaa gcc ccc gtt gag agt 4358
Pro Ala Glu Asn Ile His Arg Ile Arg Gly Glu Ala Pro Val Glu Ser
95 100 105

gaa ctt cac cgt ttt gaa caa gcg cta agt gcg gtc att cct ggg caa 4406
Glu Leu His Arg Phe Glu Gln Ala Leu Ser Ala Val Ile Pro Gly Gln
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gtt ttt gat tgg att att ttg ggc atg gga acg gac ggg cac acg gcc 4454
Val Phe Asp Trp Ile Ile Leu Gly Met Gly Thr Asp Gly His Thr Ala
130 135 140

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Ser Leu Phe Pro His Gln Thr Asp Phe Asp Pro His Phe Ala Val
145 150 155

atc gcg aaa cac cct gaa aca ggg caa att cgt att tca aaa aca gcg 4550
Ile Ala Lys His Pro Glu Thr Gly Gln Ile Arg Ile Ser Lys Thr Ala
160 165 170

aaa ttg att gaa caa gca aag gcg gtg acc tat ttg gtg aca ggt agc 4598
Lys Leu Ile Glu Gln Ala Lys Arg Val Thr Tyr Leu Val Thr Gly Ser
175 180 185

agt aaa gcc gag atc tta aaa gaa att caa act act ccg gca gaa caa 4646
Ser Lys Ala Glu Ile Leu Lys Glu Ile Gln Thr Thr Pro Ala Glu Gln
190 195 200 205

ctg cct tat cct gct gcg aaa atc aaa gcg aag cat ggg gtg acg gaa 4694
Leu Pro Tyr Pro Ala Ala Lys Ile Lys Ala Lys His Gly Val Thr Glu
210 215 220

tgg tat ttg gat aag gat gcg gca aaa tta ctg taatgcgtcg tgagattttt 4747
Trp Tyr Leu Asp Lys Asp Ala Ala Lys Leu Leu
225 230

caacattttt gcaaaagagac ttgaaacaaa atagaccata gcgttcgttt tcaacgagtg 4807

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cagacagcgc tatcaaaaagg gtaaaaagaat gtatcaactc tattttaatc caccaaaatc 4927

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 35 40 45
 Gln Ala Pro Tyr Asn Thr Glu Ile Gln Trp Lys Asn Leu His Phe Trp
 50 55 60
 Trp Gly Asp Asp Arg Met Val Pro Pro Thr Asp Pro Glu Ser Asn Tyr
 65 70 75 80
 Gly Glu Val Gln Lys Leu Leu Phe Asp His Ile Gln Ile Pro Ala Glu
 85 90 95
 Asn Ile His Arg Ile Arg Gly Glu Ala Pro Val Glu Ser Glu Leu His
 100 105 110
 Arg Phe Glu Gln Ala Leu Ser Ala Val Ile Pro Gly Gln Val Phe Asp
 115 120 125
 Trp Ile Ile Leu Gly Met Gly Thr Asp Gly His Thr Ala Ser Leu Phe
 130 135 140
 Pro His Gln Thr Asp Phe Asp Asp Pro His Phe Ala Val Ile Ala Lys

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His Pro Glu Thr Gly Gln Ile Arg Ile Ser Lys Thr Ala Lys Leu Ile
      155          170          175
Glu Gln Ala Lys Arg Val Thr Tyr Leu Val Thr Gly Ser Ser Lys Ala
      180          185          190
Glu Ile Leu Lys Glu Ile Gln Thr Thr Pro Ala Glu Gln Leu Pro Tyr
      195          205
Pro Ala Ala Lys Ile Lys Ala Lys His Gly Val Thr Glu Trp Tyr Leu
      210          215          220
Asp Lys Asp Ala Ala Lys Leu Leu
      225          230

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<210> 9
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gaagctgogc accctgatat cgaattatat accgcacag ttgatagtca cttaaatgaa 180
caaggctata ttattccagg tcttggtgat gccggtgata aaatttttgg cactaaataa 240
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ttaacagctt gaacactata aaatgaaaag ttaattcaga cagagagttg aaacttaaca 360
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          Leu Leu Asn Pro Ser Phe Phe Val Tyr Pro Tyr Ser
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Pro Phe Phe Asp Phe Val Gly Cys Phe Leu Leu Glu Asn Phe Gln Leu
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cct ttg cct att cat caa ctc gat gat gaa acg ctg gat aat ttc tat 1766
Pro Leu Pro Ile His Gln Leu Asp Asp Glu Thr Leu Asp Asn Phe Tyr
          30          35          40
ccc gac aat aat tta ttg ttg ctc aat tcg cta cgc aaa aat ttt act 1814
Pro Asp Asn Asn Leu Leu Leu Leu Asn Ser Leu Arg Lys Asn Phe Thr
          45          50          55          60
tgt cta aca caa caa ttt ttt tat att tgg ggc gag caa agc agt ggt 1862
Cys Leu Thr Gln Gln Phe Phe Tyr Ile Trp Gly Glu Gln Ser Ser Gly
          65          70          75
aaa agt cac ctc tta aaa ggc att act cat cat ttt ttc ctt tta cag 1910
Lys Ser His Leu Leu Lys Gly Ile Thr His His Phe Phe Leu Leu Gln
          80          85          90
cgc ccc gct atc tat gtg ccc tta gaa aaa tcc caa tat ttc tca ccg 1958
Arg Pro Ala Ile Tyr Val Pro Leu Glu Lys Ser Gln Tyr Phe Ser Pro
          95          100          105
gcg gta ctc gaa aac tta gaa caa caa caa ttg gtt tgt tta gat aat 2006
Ala Val Leu Glu Asn Leu Glu Gln Gln Gln Leu Val Cys Leu Asp Asn
          110          115          120
tta cag gca att ata ggc aat act gaa tgg gaa tta gcg att ttt gat 2054
Leu Gln Ala Ile Ile Gly Asn Thr Glu Trp Glu Leu Ala Ile Phe Asp
          125          130          135          140
tta ttt aat cgc ata aaa tct gtt gaa aat aca ctg ctt gtg atc agt 2102
Leu Phe Asn Arg Ile Lys Ser Val Glu Asn Thr Leu Leu Val Ile Ser
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Ala Asn Gln Ser Pro Thr Ala Leu Pro Val Ser Leu Pro Asp Leu Ala
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Ser Arg Leu Arg Trp Gly Glu Ser Tyr Gln Leu Val Pro Leu Asn Asp
175 180 185
caa caa aaa atc cat gta ttg caa aaa aat gca cat caa cgt ggt atc 2246
Gln Gln Lys Ile His Val Leu Gln Lys Asn Ala His Gln Arg Gly Ile
190 195 200
gaa ctc ccc gat gaa gta gct aat ttt ctt ttg aaa cgc tta gag cgc 2294
Glu Leu Pro Asp Glu Val Ala Asn Phe Leu Leu Lys Arg Leu Glu Arg
205 210 215 220
gat atg aaa acg tta ttt gaa gca cta agt aaa tta gat aaa gca tca 2342
Asp Met Lys Thr Leu Phe Glu Ala Leu Ser Lys Leu Asp Lys Ala Ser
225 230 235
tta caa gcc caa cgt aaa tta acg att ccc ttt gta aaa gaa att tta 2390
Leu Gln Ala Gln Arg Lys Leu Thr Ile Pro Phe Val Lys Glu Ile Leu
240 245 250
aag cta taaaaaaga ccacctttt atcaggtgat ctttcttgtc ga 2438
Lys Leu

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<213> Pasteurella multocida

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Phe Val Gly Cys Phe Leu Leu Glu Asn Phe Gln Leu Pro Leu Pro Ile
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His Gln Leu Asp Asp Glu Thr Leu Asp Asn Phe Tyr Pro Asp Asn Asn
35 40 45
Leu Leu Leu Leu Asn Ser Leu Arg Lys Asn Phe Thr Cys Leu Thr Gln
50 55 60
Gln Phe Phe Tyr Ile Trp Gly Glu Gln Ser Ser Gly Lys Ser His Leu
65 70 75 80
Leu Lys Gly Ile Thr His His Phe Phe Leu Leu Gln Arg Pro Ala Ile
85 90 95
Tyr Val Pro Leu Glu Lys Ser Gln Tyr Phe Ser Pro Ala Val Leu Glu
100 105 110
Asn Leu Glu Gln Gln Leu Val Cys Leu Asp Asn Leu Gln Ala Ile
115 120 125
Ile Gly Asn Thr Glu Trp Glu Leu Ala Ile Phe Asp Leu Phe Asn Arg
130 135 140
Ile Lys Ser Val Glu Asn Thr Leu Leu Val Ile Ser Ala Asn Gln Ser
145 150 155 160

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Pro Thr Ala Leu Pro Val Ser Leu Pro Asp Leu Ala Ser Arg Leu Arg
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 Trp Gly Glu Ser Tyr Gln Leu Val Pro Leu Asn Asp Gln Gln Lys Ile
 180 185 190
 His Val Leu Gln Lys Asn Ala His Gln Arg Gly Ile Glu Leu Pro Asp
 195 200 205
 Glu Val Ala Asn Phe Leu Leu Lys Arg Leu Glu Arg Asp Met Lys Thr
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 atggcattgc cttataccat cgtattatcc tgtattggtt tattgactgt ggaatatatt 780
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 1 5 10

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15 20 25

gct ctt tat ttt caa cat ggc atg ggg ctc gcc cct tgt gtc atg tgt 987
Ala Leu Tyr Phe Gln His Gly Met Gly Leu Ala Pro Cys Val Met Cys
30 35 40

att tac gag agg gta gct att ctt ggc att gct ttc tcc ggt tta ttg 1035
Ile Tyr Glu Arg Val Ala Ile Leu Gly Ile Ala Phe Ser Gly Leu Leu
45 50 55 60

ggg tta ctc tac ccg agt tgg atg ctt ttg cgc ctt gtg gcg tta tta 1083
Gly Leu Leu Tyr Pro Ser Ser Met Leu Leu Arg Leu Val Ala Leu Leu
65 70 75

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80 85 90

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Leu Asp Leu Gln Leu Tyr Pro Ala Pro Trp Lys Gln Cys Ser Ala Val
95 100 105

gca gaa ttt ccc gag act tta ccc tta gat cag tgg ttt cct gca ctc 1227
Ala Glu Phe Pro Glu Thr Leu Pro Leu Asp Gln Trp Phe Pro Ala Leu
110 115 120

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Phe Leu Pro Ser Gly Ser Cys Ser Glu Val Thr Trp Gln Phe Leu Gly
125 130 135 140

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Phe Ser Met Val Gln Trp Ile Val Ile Phe Ala Leu Tyr Thr Leu
145 150 155

tta ctt gct ctc att ttc atc agc caa gtc aaa cgt cta aaa ccc aag 1371
Leu Leu Ala Leu Ile Phe Ile Ser Gln Val Lys Arg Leu Lys Pro Lys
160 165 170

cag cgc aga ctc ttt cat taagtcaataa aaaatgggtgc gataaagcac 1419
Gln Arg Arg Leu Phe His
175

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2060

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 <213> Pasteurella multocida

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 Gln His Gly Met Gly Leu Ala Pro Cys Val Met Cys Ile Tyr Glu Arg
 35 40 45
 Val Ala Ile Leu Gly Ile Ala Phe Ser Gly Leu Leu Gly Leu Tyr
 50 55 60
 Pro Ser Ser Met Leu Leu Arg Leu Val Ala Leu Leu Ile Gly Leu Ser
 65 70 75 80
 Ser Ala Ile Lys Gly Leu Met Ile Ser Ile Thr His Leu Asp Leu Gln
 85 90 95
 Leu Tyr Pro Ala Pro Trp Lys Gln Cys Ser Ala Val Ala Glu Phe Pro
 100 105 110
 Glu Thr Leu Pro Leu Asp Gln Trp Phe Pro Ala Leu Phe Leu Pro Ser
 115 120 125
 Gly Ser Cys Ser Glu Val Thr Trp Gln Phe Leu Gly Phe Ser Met Val
 130 135 140
 Gln Trp Ile Val Val Ile Phe Ala Leu Tyr Thr Leu Leu Leu Ala Leu
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 Ile Phe Ile Ser Gln Val Lys Arg Leu Lys Pro Lys Gln Arg Arg Leu
 165 170 175
 Phe His

<210> 13
 <211> 4426
 <212> DNA
 <213> Pasteurella multocida

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35 40 45
Ile His Glu Leu Asp Ile Asp Leu Gln Arg His Leu Thr Ala Ile Ser
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Thr Ile Gly Ser Asn Ala Pro Tyr Val Gly Leu Leu Gly Thr Val Ile

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325 330 335

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595 600 605

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1155 1160 1165

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ser lys ala tyr phe asp phe ala glu gln ala lys lys ala pro
1170 1175 1180 1185

gaa aac aat cga ttt gaa ttg tct gcg aaa gaa att aag tcg agc aaa 4136
glu asn asn arg phe glu leu ser ala lys glu ile lys ser ser lys
1190 1195 1200

caa aaa gac caa tat gat cat gag tct gaa cgg acg act ttt aaa gtt 4184
gln lys asp gln tyr asp his glu ser glu arg thr thr phe lys val
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gga cct gaa gcg gag gct cat tct gcg gtt gcc gat atg gtg agc cat 4232
gly pro glu ala glu ala his ser ala val ala asp met val ser his
1220 1225 1230

tta gtg aaa gaa tat aga gat gca caa aat ggg act aaa caa gac ggt 4280
leu val lys glu tyr arg asp ala gln asn gly thr lys gln asp gly
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aca gta gca tta caa cat gct agt gat gtc tta aat att gtg acg ggg 4328
thr val ala leu gln his ala ser asp val leu asn ile val thr gly
1250 1255 1260 1265

gat tta gcg ggg agt tca gct aaa ttg tct gtt gaa aga aca cat gag 4376
asp leu ala gly ser ser ala lys leu ser val glu arg thr his glu
1270 1275 1280

aca aaa cga acg aca gaa acg ggg gat att gtt act aag att ggt ggc 4424
thr lys arg thr thr glu thr gly asp ile val thr lys ile gly gly
1285 1290 1295

aat gtc aca ctg tca gca cgc agt ggt agt gtg aac ctt aaa aat gta 4472
asn val thr leu ser ala arg ser gly ser val asn leu lys asn val
1300 1305 1310

caa agt gat gaa caa gct aat ttg acc tta aga gca aaa gaa gat gtg 4520
gln ser asp glu gln ala asn leu thr leu arg ala lys glu asp val
1315 1320 1325

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aat gtg ctg tct ggt gaa aaa aca cga gaa acc aca gaa aca gta tca 4568
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aga cag aaa ctt tct cat ggt gtg aac gca ggt tgc agt atg atg agt 4616
Arg Gln Lys Leu Ser His Gly Val Asn Ala Gly Cys Ser Met Met Ser
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ggc gcc tgt act gcc ggt gtt agc aca tca ctt gaa gga aat gaa agc 4664
Gly Ala Cys Thr Ala Gly Val Ser Thr Ser Leu Glu Gly Asn Glu Ser
1365      1370      1375

tat acg tca gaa cgt gaa acg gct caa aat aac agt ttc tta aaa gca 4712
Tyr Thr Ser Glu Arg Glu Thr Ala Gln Asn Asn Ser Phe Leu Lys Ala
1380      1385      1390

cgc aac atg aaa gtt gaa gca ggt cgc gat ttt aat gtt gtc agt tgc 4760
Arg Asn Met Lys Val Glu Ala Gly Arg Asp Phe Asn Val Val Ser Ser
1395      1400      1405

aat att gat gca gat aag ctc gat ctc cac gtt aaa gga aaa acg aat 4808
Asn Ile Asp Ala Asp Lys Leu Asp Leu His Val Lys Gly Lys Thr Asn
1410      1415      1420      1425

gtg gta tcc aaa caa gat acg tta caa aaa gtg acg cat gga gtt gac 4856
Val Val Ser Lys Gln Asp Thr Leu Gln Lys Val Thr His Gly Val Asp
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Tyr Asn Leu Ser Ala Gly Val Ala Leu Ser Ser Ala Thr Ile Ala Thr
1445      1450      1455

cca acc ggt aat gtt ggt ttc ggt tat acc aat gag acc gaa agc aag 4952
Pro Thr Gly Asn Val Gly Phe Gly Tyr Thr Asn Glu Thr Glu Ser Lys
1460      1465      1470

cgg acg gtt aat caa caa gca ggg att aaa gcg aat aaa att aca ggg 5000
Arg Thr Val Asn Gln Gln Ala Gly Ile Lys Ala Asn Lys Ile Thr Gly
1475      1480      1485

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Gln Thr His Asp Leu Asn Leu Glu Gly Gly Tyr Leu Val Ser Asn Asp
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cac gat caa cat gat aaa gat ggt gga aca ttt ggt tta tct gtg ggt 5144
His Asp Gln His Asp Lys Asp Gly Gly Thr Phe Gly Leu Ser Val Gly
1525      1530      1535

atc agt gaa cgt ggt act acc gcc ttt aat gta cga ggt ggg cga gct 5192
Ile Ser Glu Arg Gly Thr Thr Ala Phe Asn Val Arg Gly Gly Arg Ala
1540      1545      1550

gaa cag aaa cac tat aat gca acg cag aaa tcc act ctt tct gcc gtg 5240
Glu Gln Lys His Tyr Asn Ala Thr Gln Lys Ser Thr Leu Ser Gly Val
1555      1560      1565

gat acc tct caa gcg aat gta tca ggt caa gtg aat aca gat tta acc 5288
Asp Thr Ser Gln Ala Asn Val Ser Gly Gln Val Asn Thr Asp Leu Thr
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agt ttt gaa gtg gca gat att gtg gaa tta gga cag aga gcg aaa aac 5384
ser phe glu val ala asp ile val glu leu gly gln arg ala lys asn
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aag ctg tca gca cca aac aat gac acc gat atg gcg tca ggc tcc aca 5432
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tcg cgt gta acg gat gag gcg gat tct gta tcc gtg aaa aat ccg att 5528
ser arg val thr asp glu ala asp ser val ser val lys asn pro ile
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tyr glu ser ala asp ala val val pro thr pro arg ser arg asn val
1670 1675 1680

gac agt acc gat ctt gtg gac aat cca ctg tat gct agt gcc act aca 5624
asp ser thr asp leu val asp asn pro leu tyr ala ser ala thr thr
1685 1690 1695

aaa gca aac atc cat gat tat gaa gaa att cca gcc gtt tat agc aaa 5672
lys ala asn ile his asp tyr glu glu ile pro ala val tyr ser lys
1700 1705 1710

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val gly asp asn asn ala asp leu val arg his lys thr ala thr ser
1715 1720 1725

gat gag cat ctt tat gca gag att aat gaa cca aca tat agc cgt gtt 5768
asp glu his leu tyr ala glu ile asn glu pro thr tyr ser arg val
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gly asp lys asn ala asp met arg arg his asn ala ala gly thr thr
1750 1755 1760

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asp tyr ala asp val val gln ala his thr arg lys ala asp asp pro
1765 1770 1775

cta cca gca tta ccg aat cag ggt aaa gca aga acg gta aac gac ggt 5912
leu pro ala leu pro asn gln gly lys ala arg thr val asn asp gly
1780 1785 1790

tca gag cat att tat act gat att agc gac gtg ggc act caa act aaa 5960
ser glu his ile tyr thr asp ile ser asp val gly thr gln thr lys
1795 1800 1805

gct att gat agt act tat gca aca gta ggc atg ccg aaa gcg aat gcc 6008
ala ile asp ser thr tyr ala thr val gly met pro lys ala asn ala
1810 1815 1820 1825

gtt aac ttg ata ggg caa aat ggc tta ggc agc att tat cac agc cca 6056
val asn leu ile gly gln asn gly leu gly ser ile tyr his ser pro
1830 1835 1840

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 Gly Gly Asp Ala Val Phe Leu Arg Pro Ala Thr Glu Met Lys Cys Ala
 1860 1865 1870

ggt gca cct tta aaa tat acc ttt atc gtg cgt gat tat ttg ctc aga 6200
 Arg Ala Pro Leu Lys Tyr Thr Phe Ile Val Arg Asp Tyr Leu Leu Arg
 1875 1880 1885

cgc cat acc tta gat aaa tca aga tta ttt tat aac gca cat aat aaa 6248
 Arg His Thr Leu Asp Lys Ser Arg Leu Phe Tyr Asn Ala His Asn Lys
 1890 1895 1900 1905

acc tta ttt agc gtg cct atc gtt gat gca aaa gtc aaa atg ctg ttt 6296
 Thr Leu Phe Ser Val Pro Ile Val Asp Ala Lys Val Lys Met Leu Phe
 1910 1915 1920

gct gaa aaa aat atc caa gtc aat tac gat cgt agc ctt aca gcc att 6344
 Ala Glu Lys Asn Ile Gln Val Asn Tyr Asp Arg Ser Leu Thr Ala Ile
 1925 1930 1935

gat ctg agt aaa cgt att gcg acc ttt aat agc cca gaa gga gtt gta 6392
 Asp Leu Ser Lys Arg Ile Ala Thr Phe Asn Ser Pro Glu Gly Val Val
 1940 1945 1950

gaa gtc cct tat gat ttt att aat gtg gta cct cca atg cga gca cct 6440
 Glu Val Pro Tyr Asp Phe Ile Asn Val Val Pro Pro Met Arg Ala Pro
 1955 1960 1965

gat gcc gtt cgt caa tca gca ctc gcg tgg caa gaa gga aaa tgg gct 6488
 Asp Ala Val Arg Gln Ser Ala Leu Ala Trp Gln Glu Gly Lys Trp Ala
 1970 1975 1980 1985

aac gat ggt tgg gtt gaa gta gaa aaa cat acc ttg cgt cac cgt cgt 6536
 Asn Asp Gly Trp Val Glu Val Glu Lys His Thr Leu Arg His Arg Arg
 1990 1995 2000

tat gcc aat gtg ttt gct gtg ggt gat gtg gca ggs gtc cca aaa ggc 6584
 Tyr Ala Asn Val Phe Ala Val Gly Asp Val Ala Gly Val Pro Lys Gly
 2005 2010 2015

aaa acg gct gcc agt gtc aaa tgg caa gtt cct gtt gca gtg gca cat 6632
 Lys Thr Ala Ala Ser Val Lys Trp Gln Val Pro Val Ala Val Ala His
 2020 2025 2030

tta ctc gca gaa tta gag ggc aaa cct tgt gat gaa att tac aac ggt 6680
 Leu Leu Ala Glu Leu Glu Gly Lys Pro Cys Asp Glu Ile Tyr Asn Gly
 2035 2040 2045

tat aca tct tgt cca tta att act caa tta gga aag ggg atg cta gta 6728
 Tyr Thr Ser Cys Pro Leu Ile Thr Gln Leu Gly Lys Gly Met Leu Val
 2050 2055 2060 2065

gaa ttt gat tat aac aac cac tta aca cct tct ttc ccc ggt gta ata 6776
 Glu Phe Asp Tyr Asn Asn His Leu Thr Pro Ser Phe Pro Gly Val Ile
 2070 2075 2080

gcg cca tta gaa gaa ctg tgg gca aca tgg gca att aaa aca tta ggt 6824
 Ala Pro Leu Glu Glu Leu Trp Ala Thr Trp Ala Ile Lys Thr Leu Gly
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tga 6876

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    20      25      30
Glu Arg Ser Val Tyr Asn Ile Gly Asp Ile Tyr Ala Ser Lys Lys Leu
    35      40      45
Thr Val His Thr His Asn Leu Ile Asn Asp Val Arg Leu Ser Gly Asn
    50      55      60
Val Ser Tyr Lys Pro Ile Gly Ser Ser Arg Asp Tyr Asp Ile Ser Arg
    65      70      75      80
Val Ala Val His Gly Trp His Asn Asn Val Tyr Lys Leu Asn Leu Asn
    85      90      95
Leu Gln Glu Gln Asp Lys Thr Asp Ile Lys Val Val Lys Met Gly Ala
    100     105     110
Ile Arg Ser Asp Gly Asp Phe Asp Phe Lys Gly Ile Lys Ala Thr Ser
    115     120     125
Ser Glu Ser Lys Pro Gln Leu Ile Asn His Gly Leu Ile Asn Val Lys
    130     135     140
Gly Thr Phe Asn Ala Glu Ala Asp Gln Val Val Asn Gln Met Lys Ala
    145     150     155     160
Phe Asn Gln Asn Ala Leu Ala Ser Val Phe Lys Asn Pro Ala Lys Ile
    165     170     175
Thr Met Tyr Tyr Gln Pro Leu Thr Arg Tyr Ile Trp Thr Pro Leu Ser
    180     185     190
Gly Asn Ala Ser Arg Glu Phe Asn Asn Leu Glu Ser Phe Leu Asp Ala
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Leu Phe Gly Ser Thr Thr Ile Leu Lys Ser Ser Phe Tyr Ser Thr Glu
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Asn Phe Ser Ala Tyr Gln Leu Leu Ser His Ile Gln His Ser Pro Met
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Tyr Gln Lys Ala Met Ala Gln Val Phe Gly Ala Glu Trp His Ser Lys
    245     250     255
Ser Tyr Asp Glu Met Arg Asn Lys Trp Lys Ser Phe Lys Glu Asn Pro
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Thr Asp Phe Ile Tyr Tyr Pro Ser Glu Lys Ala Lys Ile Leu Ala Gly
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 Lys Leu Glu Gly Lys Leu Thr Thr Leu Gln Asn Gly Glu Tyr Ala Glu
 290 295 300
 Arg Gly Lys Phe Asp Glu Ser Ile Gln Ile Gly Lys His Gln Leu Ser
 305 310 315 320
 Leu Pro Ser Val Glu Leu Lys Ala Glu Phe Ser Asp Lys Glu Arg Leu
 325 330 335
 Glu Glu Asp Gly Val Asp Leu Ser Ser Ile Ala Glu Leu Glu Met
 340 345 350
 Pro Asn Leu Phe Ile Asp Asn Ser Ile Gln Leu Glu Lys Lys Leu
 355 360 365
 Ser Pro Ile Glu Asp Leu Asp Glu Glu Pro Arg Lys Asn Leu Asp Ile
 370 375 380
 Glu Glu Ser His Ser Asn Ser Ser Asp Asp Val Leu Ser Met Asn Asp
 385 390 395 400
 Asp Glu Ser Asp Thr Asp Asp Ser Lys Trp Ser Met Gly Asn Asp Glu
 405 410 415
 Lys Glu Met Pro Asp Asp Lys Leu Gly Ile Ser Arg Asp Asp Arg Gly
 420 425 430
 Asn Lys Pro Pro Arg Thr Asp Pro Thr Val Asp Tyr Leu Asn Pro Asp
 435 440 445
 Glu Phe Phe Glu Asn Gly Tyr Leu Leu Asn Glu Leu Leu Gln Glu Leu
 450 455 460
 Gly Glu Glu Pro Leu Leu Lys Glu Gly Glu Asp His Phe Lys Arg Ser
 465 470 475 480
 Thr Asn Leu Val Arg Leu Gly Glu Arg Asp Arg Gln Asn Arg Glu Lys
 485 490 495
 Arg Glu Lys Glu Gly Tyr Phe Asp Leu Pro Gly Thr Leu Asp Met Lys
 500 505 510
 Leu Gln Glu Leu Phe Glu Lys Arg Lys Gln Lys His Glu Ala Glu Gln
 515 520 525
 Lys Ala Arg Ile Glu Lys Ala Leu Leu Gln Lys Ser Glu Gln Gln Glu
 530 535 540
 Lys Arg Val Glu Glu Arg Lys Gln Glu Glu Lys Arg Gln Ala Gln Asp
 545 550 555 560
 Lys Ile Ala Lys Gln Val Glu Ile Ala Lys Glu Met Gln Arg Val Glu
 565 570 575
 Glu Ile Arg Gln Arg Glu Lys Gln Leu Ala Ile Gln Leu Gln Glu Glu
 580 585 590
 Glu Lys Lys Gln Gln Glu Glu Lys His Leu Ser Glu Glu Lys Lys Gln
 595 600 605

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Ala Glu Gln Lys Gln Lys Ala Glu Glu Lys Val Ala Gln Glu Arg Leu
 610 615 620
 Asp Ile Glu Gln Gln Lys Ala Tyr Glu Glu Met Ala Lys Arg Glu Ala
 625 630 635 640
 Glu Ala Ser Lys Asn Val Leu Leu Lys Ala Ile Asp Glu Glu Arg Pro
 645 650 655
 Lys Val Glu Thr Asp Pro Leu Phe Arg Thr Lys Leu Lys Tyr Ile Asn
 660 665 670
 Gln Asp Asp Tyr Ala Gly Ala Asn Tyr Phe Phe Asn Lys Val Gly Leu
 675 680 685
 Asn Thr Lys Gly His Gln Lys Val Asn Val Leu Gly Asp Asn Tyr Phe
 690 695 700
 Asp His Gln Val Ile Thr Arg Ser Ile Glu Lys Lys Val Asp Asn His
 705 710 715 720
 Leu Asn Gln Lys Tyr Asn Leu Ser Asp Val Glu Leu Val Lys Gln Leu
 725 730 735
 Met Asp Asn Ser Thr Thr Gln Ala Gln Glu Leu Asp Leu Lys Leu Gly
 740 745 750
 Ala Ala Leu Thr Lys Glu Gln Gln Ala Asn Leu Thr Gln Asp Ile Val
 755 760 765
 Trp Tyr Val Lys Thr Lys Val Lys Gly Lys Asp Val Phe Val Pro Lys
 770 775 780
 Val Tyr Phe Ala Ser Glu Thr Leu Val Glu Ala Gln Lys Leu Gln Gly
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 Leu Gly Thr Gly Thr Ile Arg Val Gly Glu Ala Lys Ile Lys Ala Lys
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 820 825 830
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 Thr Arg Leu Val Gly Arg Lys Gly Ile Glu Asn Val Ser Arg Ser Phe
 850 855 860
 Ala Asn Asp Glu Leu Gly Val Thr Ala Gln Arg Ser Glu Ile Lys Thr
 865 870 875 880
 Glu Gly His Leu His Leu Glu Thr Asp Lys Asp Ser Thr Ile Asp Val
 885 890 895
 Gln Ala Ser Asp Ile Lys Ala Lys Thr Ser Phe Val Lys Thr Gly Asp
 900 905 910
 Val Asn Leu Lys Asn Thr Tyr Asn Thr Lys His Ala Tyr Arg Glu Lys
 915 920 925
 Phe Ser Pro Ser Ala Leu Gln Val Ala Glu Leu Asp Val Ala Gly Leu
 930 935 940

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Lys Val Pro Leu Leu Gly Val Ser Ser Pro Ser Ser Tyr Ser Glu His
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 Thr Ser Glu Ala Thr Ser Glu Gly Ser Ile Phe Glu Val Gly His Leu
 965 970 975
 His Leu Ala Val Asp Arg Asp Val Asn Gln Ala Gly Ser Lys Ile Lys
 980 985 990
 Ala Lys Tyr Thr Thr Gly Val Val Lys Gly Asn Phe Asn Thr Glu Ala
 995 1000 1005
 Gly Lys Asn Ile Lys His Val Glu Lys Glu Glu Tyr Ser Ser Gln Leu
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 Tyr Asn Ser Gln Asp Gly Gly Asn Ala Ser Val Gly Val Pro Thr Asn
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 Asp Lys Glu Thr Leu Leu Thr His Thr Asn Ser Glu Leu Gln Val Lys
 1075 1080 1085
 His Gly Lys Leu His Val Leu Gly Tyr Ala Asp Ile Gly Gly Val Asp
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 Gly Thr Val Ala Leu Gln His Ala Ser Asp Val Leu Asn Ile Val Thr
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 Gly Asp Leu Ala Gly Ser Ser Ala Lys Leu Ser Val Glu Arg Thr His
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 1315 1320 1325
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 Ser Tyr Thr Ser Glu Arg Glu Thr Ala Gln Asn Asn Ser Phe Leu Lys
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 Thr Pro Thr Gly Asn Val Gly Phe Gly Tyr Thr Asn Glu Thr Glu Ser
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 Gly Gln Thr His Asp Leu Asn Leu Glu Gly Gly Tyr Leu Val Ser Asn
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Asn Lys Leu Ser Ala Pro Asn Asn Asp Thr Asp Met Ala Ser Gly Ser
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 Thr Leu Arg Ser Arg Ser Thr Thr Glu Glu Ala Asp Val Pro Thr Thr
 1635 1640 1645
 Arg Ser Arg Val Thr Asp Glu Ala Asp Ser Val Ser Val Lys Asn Pro
 1650 1655 1660
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 Val Asp Ser Thr Asp Leu Val Asp Asn Pro Leu Tyr Ala Ser Ala Thr
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 Thr Lys Ala Asn Ile His Asp Tyr Glu Glu Ile Pro Ala Val Tyr Ser
 1700 1705 1710
 Lys Val Gly Asp Asn Asn Ala Asp Leu Val Arg His Lys Thr Ala Thr
 1715 1720 1725
 Ser Asp Glu His Leu Tyr Ala Glu Ile Asn Glu Pro Thr Tyr Ser Arg
 1730 1735 1740
 Val Gly Asp Lys Asn Ala Asp Met Arg Arg His Asn Ala Ala Gly Thr
 1745 1750 1755 1760
 Thr Asp Tyr Ala Asp Val Val Gln Ala His Thr Arg Lys Ala Asp Asp
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 1780 1785 1790
 Gly Ser Glu His Ile Tyr Thr Asp Ile Ser Asp Val Gly Thr Gln Thr
 1795 1800 1805
 Lys Ala Ile Asp Ser Thr Tyr Ala Thr Val Gly Met Pro Lys Ala Asn
 1810 1815 1820
 Ala Val Asn Leu Ile Gly Gln Asn Gly Leu Gly Ser Ile Tyr His Ser
 1825 1830 1835 1840
 Pro Asp Ser Ala Tyr Lys Thr Trp Gln Leu Leu Asp Gln Phe Ala Asn
 1845 1850 1855
 Lys Gly Gly Asp Ala Val Phe Leu Arg Pro Ala Thr Glu Met Lys Cys
 1860 1865 1870
 Ala Gly Ala Pro Leu Lys Tyr Thr Phe Ile Val Arg Asp Tyr Leu Leu
 1875 1880 1885
 Arg Arg His Thr Leu Asp Lys Ser Arg Leu Phe Tyr Asn Ala His Asn
 1890 1895 1900
 Lys Thr Leu Phe Ser Val Pro Ile Val Asp Ala Lys Val Lys Met Leu
 1905 1910 1915 1920
 Phe Ala Glu Lys Asn Ile Gln Val Asn Tyr Asp Arg Ser Leu Thr Ala
 1925 1930 1935
 Ile Asp Leu Ser Lys Arg Ile Ala Thr Phe Asn Ser Pro Glu Gly Val
 1940 1945 1950

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Val Glu Val Pro Tyr Asp Phe Ile Asn Val Val Pro Pro Met Arg Ala
 1955 1960 1965
 Pro Asp Ala Val Arg Gln Ser Ala Leu Ala Trp Gln Glu Gly Lys Trp
 1970 1975 1980
 Ala Asn Asp Gly Trp Val Glu Val Glu Lys His Thr Leu Arg His Arg
 1985 1990 1995 2000
 Arg Tyr Ala Asn Val Phe Ala Val Gly Asp Val Ala Gly Val Pro Lys
 2005 2010 2015
 Gly Lys Thr Ala Ala Ser Val Lys Trp Gln Val Pro Val Ala Val Ala
 2020 2025 2030
 His Leu Leu Ala Glu Leu Glu Gly Lys Pro Cys Asp Glu Ile Tyr Asn
 2035 2040 2045
 Gly Tyr Thr Ser Cys Pro Leu Ile Thr Gln Leu Gly Lys Gly Met Leu
 2050 2055 2060
 Val Glu Phe Asp Tyr Asn Asn His Leu Thr Pro Ser Phe Pro Gly Val
 2065 2070 2075 2080
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 Gly Leu Lys Pro Thr Tyr Leu Gly Met Leu Arg Gly Leu Ala
 2100 2105 2110

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 ttaagtattc acgacattga ccagttgatc gaaatcttaa atactacgaa taaaaaagcc 360
 acagtgaatg tgggtgcaag tgaagaaaaa ggcagctcaa atctaaatat tgaagacaaa 420
 tatgatgttt ttccgcaagt gagtgcgga ttcaataatt caggtgctgg caataatgcc 480
 aatgggcgta atcaagctac attgaatatt gcttggagtg atctattagg cacgaatgat 540
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aattatactt tgtcttacag tcagccctata ggcttttcta cagtagaaat taaagcatcg 660
gaatctacgt atgaaaaaga acttcgcggt ataatatctc attcttctca tgggaaaacc 720
caaaagcttag ctgtcaagct gatgcatgtg ttattgcgta ataaggagag tattttatct 780
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Met Asn Lys Asn Arg Tyr
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aaa ctc att ttt agt caa gtc aaa ggt tgt ctc gtt cct gtg gca gaa 1544
Lys Leu Ile Phe Ser Gln Val Lys Gly Cys Leu Val Pro Val Ala Glu
10 15 20
tgt att aac tca gct att agc aat ggt tca tct gat tca aca tcc aca 1592
Cys Ile Asn Ser Ala Ile Ser Asn Gly Ser Ser Asp Ser Thr Ser Thr
25 30 35
tca gaa caa gtt gaa gag gaa cct ttc ctt cta gaa caa tat tca ctt 1640
Ser Glu Gln Val Glu Glu Glu Pro Phe Leu Leu Glu Gln Tyr Ser Leu
40 45 50
tcc tcc gtg tct tta tta gta aaa agc acg ttc aat cct gtt tcg tat 1688
Ser Ser Val Ser Leu Leu Val Lys Ser Thr Phe Asn Pro Val Ser Tyr
55 60 65 70
gca atg caa ttg act tgg aaa cag ctt tct att tta ttt tta act gtg 1736
Ala Met Gln Leu Thr Trp Lys Gln Leu Ser Ile Leu Phe Leu Thr Val
75 80 85
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Ile Ser Val Pro Val Leu Ala Glu Gly Lys Gly Asp Glu Arg Asn Gln
90 95 100
tta aca gtg att gat aat agc gat cat att aaa tta gat gca tct aat 1832
Leu Thr Val Ile Asp Asn Ser Asp His Ile Lys Leu Asp Ala Ser Asn
105 110 115
ctt gct ggt aat gat aaa aca aaa atc tat caa gca gaa aat aaa gtt 1880
Leu Ala Gly Asn Asp Lys Thr Lys Ile Tyr Gln Ala Glu Asn Lys Val
120 125 130

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ctg gtt att gat att gct aaa cca aat ggg aaa ggg att tca gat aac 1928
Leu Val Ile Asp Ile Ala Lys Pro Asn Gly Lys Gly Ile Ser Asp Asn
135 140 145 150

cgt ttt gaa aaa ttt aat att cca aat agc gcg gtc ttt aat aat aat 1976
Arg Phe Glu Lys Phe Asn Ile Pro Asn Ser Ala Val Phe Asn Asn Asn
155 160 165

ggg act gaa gcg cag gca aga tca aca tta att ggt tac att ccg caa 2024
Gly Thr Glu Ala Gln Ala Arg Ser Thr Leu Ile Gly Tyr Ile Pro Gln
170 175 180

aat caa aat tta agg gga ggg aaa gaa gct gat gtt ata tta aat caa 2072
Asn Gln Asn Leu Arg Gly Gly Lys Glu Ala Asp Val Ile Leu Asn Gln
185 190 195

gtg aca ggt cct caa gaa agt aaa att gtt ggc gcg ctt gaa gta tta 2120
Val Thr Gly Pro Gln Glu Ser Lys Ile Val Gly Ala Leu Glu Val Leu
200 205 210

ggt aaa aaa gct gat atc gtc att gca aac caa aat ggt att acc tta 2168
Gly Lys Lys Ala Asp Ile Val Ile Ala Asn Gln Asn Gly Ile Thr Leu
215 220 225 230

aat ggt gta aga aca ata aat tca gat cgt ttt gtt gcc act acg agt 2216
Asn Gly Val Arg Thr Ile Asn Ser Asp Arg Phe Val Ala Thr Thr Ser
235 240 245

gag ctt ata gat ccg aat cag atg atg tta aag gtt aca aaa gga aat 2264
Glu Leu Ile Asp Pro Asn Gln Met Met Leu Lys Val Thr Lys Gly Asn
250 255 260

gtg atc att gat att gat ggt ttt tcg aca gat gga tta aag tat tta 2312
Val Ile Ile Asp Ile Asp Gly Phe Ser Thr Asp Gly Leu Lys Tyr Leu
265 270 275

gat att att gct aaa aaa att gaa caa aag caa tca att aca tca ggg 2360
Asp Ile Ile Ala Lys Lys Ile Glu Gln Lys Gln Ser Ile Thr Ser Gly
280 285 290

gat aat tca gaa gca aaa aca gat gtc act ctt att gcg ggt tcc agt 2408
Asp Asn Ser Glu Ala Lys Thr Asp Val Thr Leu Ile Ala Gly Ser Ser
295 300 305 310

gaa tat gat tta agc aaa cat gag ctg aaa aaa acg agc ggt gaa aat 2456
Glu Tyr Asp Leu Ser Lys His Glu Leu Lys Lys Thr Ser Gly Glu Asn
315 320 325

gta tct aat gat gtt att gct atc acg gga tct agt aca ggc gca atg 2504
Val Ser Asn Asp Val Ile Ala Ile Thr Gly Ser Ser Thr Gly Ala Met
330 335 340

cat ggt aaa aat att aag ttg att ttg aca gat aaa ggt gca ggc gta 2552
His Gly Lys Asn Ile Lys Leu Ile Val Thr Asp Lys Gly Ala Gly Val
345 350 355

aaa cat gat gga att att ttg tct gaa aat gat att cag att gaa atg 2600
Lys His Asp Gly Ile Ile Leu Ser Glu Asn Asp Ile Gln Ile Glu Met
360 365 370

aat gaa ggt gac tta gaa ctt ggc aat acg att cag caa aca gtc gta 2648
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Lys Lys Asp Arg Asn Ile Arg Ala Lys Lys Lys Ile Glu Val Lys Asn
395 400 405

gct aat cgt gtt ttt gtt ggt agt caa acg aaa tca gat gaa att tgg 2744
Ala Asn Arg Val Phe Val Gly Ser Gln Thr Lys Ser Asp Glu Ile Ser
410 415 420

tta gag gcg aaa caa gtt aaa atc aga aaa aac gca gag att agg agt 2792
Leu Glu Ala Lys Gln Val Lys Ile Arg Lys Asn Ala Glu Ile Arg Ser
425 430 435

acg aca caa gcc aaa atc gta gca aag ggt gcc ctg tct att gag caa 2840
Thr Thr Gln Ala Lys Ile Val Ala Lys Gly Ala Leu Ser Ile Glu Gln
440 445 450

aat gcg aag ctc gtc gct aaa aag ata gat gtg gca aca gaa act cta 2888
Asn Ala Lys Leu Val Ala Lys Lys Ile Asp Val Ala Thr Glu Thr Leu
455 460 465

act aat gct ggg cgt att tat ggt cga gag gtt aag ctt gac act aat 2936
Thr Asn Ala Gly Arg Ile Tyr Gly Arg Glu Val Lys Leu Asp Thr Asn
475 480 485

aat ttg att aat gat aaa gaa att tat gct gaa cgg aaa ttg agt att 2984
Asn Leu Ile Asn Asp Lys Glu Ile Tyr Ala Glu Arg Lys Leu Ser Ile
490 495 500

ttg acg aaa gga aaa gat ctt gaa att att caa gat aga tat ttg tct 3032
Leu Thr Lys Gly Lys Asp Leu Glu Ile Ile Gln Asp Arg Tyr Leu Ser
505 510 515

cca ctg atg cgc gta aaa agt agt gtc cgc ttt tta ggc tct ccg ttt 3080
Pro Leu Met Arg Val Lys Ser Ser Val Arg Phe Leu Gly Ser Pro Phe
520 525 530

ttc tca ata tct ccg tgg atg ctc gca agc ctt agt gca cag ttt aag 3128
Phe Ser Ile Ser Pro Ser Met Leu Ala Ser Leu Ser Ala Gln Phe Lys
535 540 545

cct ggt ttt gtg aat aag gga ctc att gaa agt gcg ggg agt gca gaa 3176
Pro Gly Phe Val Asn Lys Gly Leu Ile Glu Ser Ala Gly Ser Ala Glu
555 560 565

tta act ttt aaa gaa aaa acc agt ttt tta aca gag ggc aat aat ttt 3224
Leu Thr Phe Lys Glu Lys Thr Ser Phe Leu Thr Glu Gly Asn Asn Phe
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<212> PRT

<213> Pasteurella multocida

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 Ser Asp Ser Thr Ser Thr Ser Glu Gln Val Glu Glu Pro Phe Leu
 35 40 45
 Leu Glu Gln Tyr Ser Leu Ser Ser Val Ser Leu Val Lys Ser Thr
 50 55 60
 Phe Asn Pro Val Ser Tyr Ala Met Gln Leu Thr Trp Lys Gln Leu Ser
 65 70 75 80
 Ile Leu Phe Leu Thr Val Ile Ser Val Pro Val Leu Ala Glu Gly Lys
 85 90 95
 Gly Asp Glu Arg Asn Gln Leu Thr Val Ile Asp Asn Ser Asp His Ile
 100 105 110
 Lys Leu Asp Ala Ser Asn Leu Ala Gly Asn Asp Lys Thr Lys Ile Tyr
 115 120 125
 Gln Ala Glu Asn Lys Val Leu Val Ile Asp Ile Ala Lys Pro Asn Gly
 130 135 140
 Lys Gly Ile Ser Asp Asn Arg Phe Glu Lys Phe Asn Ile Pro Asn Ser
 145 150 155 160
 Ala Val Phe Asn Asn Asn Gly Thr Glu Ala Gln Ala Arg Ser Thr Leu
 165 170 175
 Ile Gly Tyr Ile Pro Gln Asn Gln Asn Leu Arg Gly Gly Lys Glu Ala
 180 185 190
 Asp Val Ile Leu Asn Gln Val Thr Gly Pro Gln Glu Ser Lys Ile Val
 195 200 205
 Gly Ala Leu Glu Val Leu Gly Lys Lys Ala Asp Ile Val Ile Ala Asn
 210 215 220
 Gln Asn Gly Ile Thr Leu Asn Gly Val Arg Thr Ile Asn Ser Asp Arg
 225 230 235 240
 Phe Val Ala Thr Thr Ser Glu Leu Ile Asp Pro Asn Gln Met Met Leu
 245 250 255
 Lys Val Thr Lys Gly Asn Val Ile Ile Asp Ile Asp Gly Phe Ser Thr
 260 265 270
 Asp Gly Leu Lys Tyr Leu Asp Ile Ile Ala Lys Lys Ile Glu Gln Lys
 275 280 285
 Gln Ser Ile Thr Ser Gly Asp Asn Ser Glu Ala Lys Thr Asp Val Thr
 290 295 300
 Leu Ile Ala Gly Ser Ser Glu Tyr Asp Leu Ser Lys His Glu Leu Lys
 305 310 315 320
 Lys Thr Ser Gly Glu Asn Val Ser Asn Asp Val Ile Ala Ile Thr Gly
 325 330 335
 Ser Ser Thr Gly Ala Met His Gly Lys Asn Ile Lys Leu Ile Val Thr
 340 345 350

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Asp Lys Gly Ala Gly Val Lys His Asp Gly Ile Ile Leu Ser Glu Asn
355                      360                      365
Asp Ile Gln Ile Glu Met Asn Glu Gly Asp Leu Glu Leu Gly Asn Thr
370                      375                      380
Ile Gln Gln Thr Val Val Lys Lys Asp Arg Asn Ile Arg Ala Lys Lys
385                      390                      395                      400
Lys Ile Glu Val Lys Asn Ala Asn Arg Val Phe Val Gly Ser Gln Thr
405                      410                      415
Lys Ser Asp Glu Ile Ser Leu Glu Ala Lys Gln Val Lys Ile Arg Lys
420                      425                      430
Asn Ala Glu Ile Arg Ser Thr Thr Gln Ala Lys Ile Val Ala Lys Gly
435                      440                      445
Ala Leu Ser Ile Glu Gln Asn Ala Lys Leu Val Ala Lys Lys Ile Asp
450                      455                      460
Val Ala Thr Glu Thr Leu Thr Asn Ala Gly Arg Ile Tyr Gly Arg Glu
465                      470                      475                      480
Val Lys Leu Asp Thr Asn Asn Leu Ile Asn Asp Lys Glu Ile Tyr Ala
485                      490                      495
Glu Arg Lys Leu Ser Ile Leu Thr Lys Gly Lys Asp Leu Glu Ile Ile
500                      505                      510
Gln Asp Arg Tyr Leu Ser Pro Leu Met Arg Val Lys Ser Ser Val Arg
515                      520                      525
Phe Leu Gly Ser Pro Phe Phe Ser Ile Ser Pro Ser Met Leu Ala Ser
530                      535                      540
Leu Ser Ala Gln Phe Lys Pro Gly Phe Val Asn Lys Gly Leu Ile Glu
545                      550                      555                      560
Ser Ala Gly Ser Ala Glu Leu Thr Phe Lys Glu Lys Thr Ser Phe Leu
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His Ala Tyr Gln Asn Gln Pro Leu Ser Thr Lys Val Val Phe Gln Leu
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gtg aaa gat ttg acg gaa gtt tta tac cgt tct ggc tac gtg aca agt 144
Val Lys Asp Leu Thr Gly Arg Thr Val Leu Tyr Arg Ser Gly Tyr Val Thr Ser
      35      40      45
gca att ggt tta aaa aat tca aaa atc agc aat ggc gat ctt gaa ttt 192
Ala Ile Gly Leu Lys Asn Ser Lys Ile Ser Asn Gly Asp Leu Glu Phe
      50      55      60
att gta ctg tgg gga aga act cgc gat ctg ttt gtg aat ggg gag aaa 240
Ile Val Leu Trp Gly Arg Thr Arg Asp Leu Phe Val Asn Gly Glu Lys
      65      70      75      80
cca acc cgt ttt aga gat aaa aca atg tta tca gtc cta ccc aat tta 288
Pro Thr Arg Phe Arg Asp Lys Thr Met Leu Ser Val Leu Pro Asn Leu
      85      90      95
atc gga aat cgc tta agt att cac gac att gac cag ttg atc gaa atc 336
Ile Gly Asn Arg Leu Ser Ile His Asp Ile Asp Gln Leu Ile Glu Ile
      100      105      110
tta aat act acg aat aaa aaa gcc aca gtg aat gtg gtt gca agt gaa 384
Leu Asn Thr Thr Asn Lys Lys Ala Thr Val Asn Val Val Ala Ser Glu
      115      120      125
gaa aaa ggc agc tca aat cta aat att gaa aga caa tat gat gtt ttt 432
Glu Lys Gly Ser Ser Asn Leu Asn Ile Glu Arg Gln Tyr Asp Val Phe
      130      135      140
ccg caa gtg agt gtc gga ttc aat aat tca ggt gct ggc aat aat gcc 480
Pro Gln Val Ser Val Gly Phe Asn Asn Ser Gly Ala Gly Asn Asn Ala
      145      150      155      160
aat ggg cgt aat caa gct aca ttg aat att gct tgg agt gat cta tta 528
Asn Gly Arg Asn Gln Ala Thr Leu Asn Ile Ala Trp Ser Asp Leu Leu
      165      170      175
ggc acg aat gat cgt tgg agt ttc tcg agt agt tac cgt tta tat aaa 576
Gly Thr Asn Asp Arg Trp Ser Phe Ser Ser Ser Tyr Arg Leu Tyr Lys
      180      185      190
aat cat cat gct aac cag caa cgc aat tat act ttg tct tac agt cag 624
Asn His His Ala Asn Gln Gln Arg Asn Tyr Thr Leu Ser Tyr Ser Gln
      195      200      205
cct ata ggc ttt tct aca gta gaa att aaa gca tcg gaa tct acg tat 672
Pro Ile Gly Phe Ser Thr Val Glu Ile Lys Ala Ser Glu Ser Thr Tyr
      210      215      220
gaa aaa gaa ctt cgc ggt ata aat act cat tct tct cat ggg aaa acc 720
Glu Lys Glu Leu Arg Gly Ile Asn Thr His Ser Ser His Gly Lys Thr
      225      230      235      240
caa agc tta gct gtc aag ctg atg cat gtg tta ttg cgt aat aag gag 768
Gln Ser Leu Ala Val Lys Leu Met His Val Leu Leu Arg Asn Lys Glu
      245      250      255
agt att tta tct aca tat acc gag ttc gag ttt aaa aaa cgg att agt 816
Ser Ile Leu Ser Thr Tyr Thr Glu Phe Glu Phe Lys Lys Arg Ile Ser
      260      265      270

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tat ttt tct gat att ttg att ggg aaa tat cac aat aat aaa gtg agc 864
Tyr Phe Ser Asp Ile Leu Ile Gly Lys Tyr His Asn Asn Lys Val Ser
275 280 285

gta ggg tta tct tac atg act aat ttt gct tac ggg aag ctt tac agc 912
Val Gly Leu Ser Tyr Met Thr Asn Phe Ala Tyr Gly Lys Leu Tyr Ser
290 295 300

gac att gct tac gcg aat ggg ttg aga tgg ttt ggg gcg aat tat tca 960
Asp Ile Ala Tyr Ala Asn Gly Leu Arg Trp Phe Gly Ala Asn Tyr Ser
305 310 315

gca tat gat gca aat cgt gaa aaa acc tta aaa tta ttg tca gga agt 1008
Ala Tyr Asp Ala Asn Arg Glu Lys Thr Leu Lys Leu Ser Gly Ser
325 330 335

att aat tgg cag cgt cca ata tcc ctg ttt gaa cgt gcg atg aat tat 1056
Ile Asn Trp Gln Arg Pro Ile Ser Leu Phe Glu Arg Ala Met Asn Tyr
340 345 350

caa tta cgt att ggt gcc caa tat ggt ttt gat agt ttg tat tct gaa 1104
Gln Leu Arg Ile Gly Ala Gln Tyr Gly Phe Asp Ser Leu Tyr Ser Glu
355 360 365

aat caa ttt tca att ggt gat gaa tat aca gta aga gga ttt aaa ggt 1152
Asn Gln Phe Ser Ile Gly Asp Glu Tyr Thr Val Arg Gly Phe Lys Gly
370 375 380

ggt gcg gtt tct ggt gat agt ggt gcg tat tta tca caa aca ctg acg 1200
Gly Ala Val Ser Gly Asp Ser Gly Ala Tyr Leu Ser Gln Thr Leu Thr
385 390 395

gtt cct ttt tat cca caa aaa gca tat tta tct cag gta tcc cct ttt 1248
Val Pro Phe Tyr Pro Gln Lys Ala Tyr Leu Ser Gln Val Ser Pro Phe
405 410 415

att gga ttt gat atg ggt aaa gta cat att aaa tca aag cat aaa aca 1296
Ile Gly Phe Asp Met Gly Lys Val His Ile Lys Ser Lys His Lys Thr
420 425 430

acc act tta gtc ggt ttt gcc cta gcc ttg aaa acg caa ata aag tta 1344
Thr Thr Leu Val Gly Phe Ala Leu Gly Leu Lys Thr Gln Ile Lys Leu
435 440 445

ttt tca tta tca tta acc tat gca caa cca atg aat ggt gtg agt ggt 1392
Phe Ser Leu Ser Leu Thr Tyr Ala Gln Pro Met Asn Gly Val Ser Gly
450 455 460

gtt acg caa cat cgt caa aaa ccg att tat tat ttc tca gga tca ctt 1440
Val Thr Gln His Arg Gln Lys Pro Ile Tyr Tyr Phe Ser Gly Ser Leu
465 470 475 480

tct ttt taatctcttt taagttaaag gattaactta atatgaacaa aaatcggtac 1496
Ser Phe

aaactcattt ttagtcaagt caaagggtgt ctggttcctg tggcagaatg tattaactca 1556

gctattagca atgggttcac tgattcaaca tccacatcag aacaagttga agaggaaact 1616

ttccttctag aacaatatcc actttctctc gtgtctttat tagtaaaaaag cacgttcaat 1676

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3247

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 <212> PRT
 <213> Pasteurella multocida

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 1 5 10 15

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His Ala Tyr Gln Asn Gln Pro Leu Ser Thr Lys Val Val Phe Gln Leu
 20 25 30
 Val Lys Asp Leu Thr Glu Val Leu Tyr Arg Ser Gly Tyr Val Thr Ser
 35 40 45
 Ala Ile Gly Leu Lys Asn Ser Lys Ile Ser Asn Gly Asp Leu Glu Phe
 50 55 60
 Ile Val Leu Trp Gly Arg Thr Arg Asp Leu Phe Val Asn Gly Glu Lys
 65 70 75 80
 Pro Thr Arg Phe Arg Asp Lys Thr Met Leu Ser Val Leu Pro Asn Leu
 85 90 95
 Ile Gly Asn Arg Leu Ser Ile His Asp Ile Asp Gln Leu Ile Glu Ile
 100 105 110
 Leu Asn Thr Thr Asn Lys Lys Ala Thr Val Asn Val Val Ala Ser Glu
 115 120 125
 Glu Lys Gly Ser Ser Asn Leu Asn Ile Glu Arg Gln Tyr Asp Val Phe
 130 135 140
 Pro Gln Val Ser Val Gly Phe Asn Asn Ser Gly Ala Gly Asn Asn Ala
 145 150 155 160
 Asn Gly Arg Asn Gln Ala Thr Leu Asn Ile Ala Trp Ser Asp Leu Leu
 165 170 175
 Gly Thr Asn Asp Arg Trp Ser Phe Ser Ser Ser Tyr Arg Leu Tyr Lys
 180 185 190
 Asn His His Ala Asn Gln Gln Arg Asn Tyr Thr Leu Ser Tyr Ser Gln
 195 200 205
 Pro Ile Gly Phe Ser Thr Val Glu Ile Lys Ala Ser Glu Ser Thr Tyr
 210 215 220
 Glu Lys Glu Leu Arg Gly Ile Asn Thr His Ser Ser His Gly Lys Thr
 225 230 235 240
 Gln Ser Leu Ala Val Lys Leu Met His Val Leu Leu Arg Asn Lys Glu
 245 250 255
 Ser Ile Leu Ser Thr Tyr Thr Glu Phe Glu Phe Lys Lys Arg Ile Ser
 260 265 270
 Tyr Phe Ser Asp Ile Leu Ile Gly Lys Tyr His Asn Asn Lys Val Ser
 275 280 285
 Val Gly Leu Ser Tyr Met Thr Asn Phe Ala Tyr Gly Lys Leu Tyr Ser
 290 295 300
 Asp Ile Ala Tyr Ala Asn Gly Leu Arg Trp Phe Gly Ala Asn Tyr Ser
 305 310 315 320
 Ala Tyr Asp Ala Asn Arg Glu Lys Thr Leu Lys Leu Leu Ser Gly Ser
 325 330 335
 Ile Asn Trp Gln Arg Pro Ile Ser Leu Phe Glu Arg Ala Met Asn Tyr
 340 345 350

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Gln Leu Arg Ile Gly Ala Gln Tyr Gly Phe Asp Ser Leu Tyr Ser Glu
 355 360 365
 Asn Gln Phe Ser Ile Gly Asp Glu Tyr Thr Val Arg Gly Phe Lys Gly
 370 375 380
 Gly Ala Val Ser Gly Asp Ser Gly Ala Tyr Leu Ser Gln Thr Leu Thr
 385 390 395 400
 Val Pro Phe Tyr Pro Gln Lys Ala Tyr Leu Ser Gln Val Ser Pro Phe
 405 410 415
 Ile Gly Phe Asp Met Gly Lys Val His Ile Lys Ser Lys His Lys Thr
 420 425 430
 Thr Thr Leu Val Gly Phe Ala Leu Gly Leu Lys Thr Gln Ile Lys Leu
 435 440 445
 Phe Ser Leu Ser Leu Thr Tyr Ala Gln Pro Met Asn Gly Val Ser Gly
 450 455 460
 Val Thr Gln His Arg Gln Lys Pro Ile Tyr Tyr Phe Ser Gly Ser Leu
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 Ser Phe

<210> 21
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 <213> Pasteurella multocida

<220>
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 <222> (639)...(1022)

<220>
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 gtacgataag atcgccatgc atttcattgt tttttatttt tccattgggt aatagaactgg 180
 tttcaaattg aaattggtca cttagtacga gtttggcggg taaggcgggt agcacttttt 240
 gtgtactggc gggtaacata aagggtactgg cttggtgcgc tacaattttt tcattacgat 300
 ttaagttttt agccacaaaa cctagggtgg tcccttcggg taaatgagcg ttgatttcag 360
 caagatcaat ctcagcataa ctgaaatgac tgacgagtaa actacatata agtatcgctc 420
 gtttgaaaag gcgtaaaagc gtggcagtaa aaaaagaaga tattttatata ataattggct 480
 cgagcagttg ctattttttt attgtcgaac aataatagta ttgaaacct cgagagtaaa 540
 tccctttctc gttaaacact tattttttta ttcaactacg gcattgtttt tacaatgttg 600

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tggttttggt tttatctaaa aaggaagaaa aaacgatt atg aaa cag att cca atg 656
Met Lys Gln Ile Pro Met
1 5
act ata cgt ggt gcg gaa caa tta aga caa gaa ctc gat ttt ttg aaa 704
Thr Ile Arg Gly Ala Glu Gln Leu Arg Gln Glu Leu Asp Phe Leu Lys
10 15 20
aac act cgt cgc cca gaa att att aat gct atc gca gaa gct cgt gaa 752
Asn Thr Arg Arg Pro Glu Ile Ile Asn Ala Ile Ala Glu Ala Arg Glu
25 30 35
cat ggc gat cta aaa gaa aat gca gaa tac cat gct gcg cgt gaa cag 800
His Gly Asp Leu Lys Glu Asn Ala Glu Tyr His Ala Ala Arg Glu Gln
40 45 50
caa gga ttt tgt gaa gga cga atc caa gaa att gaa ggg aaa tta gcg 848
Gln Gly Phe Cys Glu Gly Arg Ile Gln Glu Ile Glu Gly Lys Leu Ala
55 60 65 70
aat agt caa att att gat gtc aca aag atc cca aat aat ggc aaa gtg 896
Asn Ser Gln Ile Ile Asp Val Thr Lys Ile Pro Asn Asn Gly Lys Val
75 80 85
att ttt ggt gcc aca att ttg tta ctg aat att gac acg gaa gaa gaa 944
Ile Phe Gly Ala Thr Ile Leu Leu Leu Asn Ile Asp Thr Glu Glu Glu
90 95 100
gtc tcg tac caa att gta ggc gat gat gaa gcc aat att aaa gca ggg 992
Val Ser Tyr Gln Ile Val Gly Asp Asp Glu Ala Asn Ile Lys Ala Gly
105 110 115
cta att tca gtt aac gcc acg cga ttg aat tagagaaagc taaatggatt 1042
Leu Ile Ser Val Asn Ala Thr Arg Leu Asn
120 125
gcccaagatc ttggcgtcaa acaaacgtta attgacactt ccgtcattaa agcgattacg 1102
caaaatgcct taatggacga acaggcaaga attgagcaac atggcagtac accgaatact 1162
ttcgttga 1170

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<210> 22
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 <212> PRT
 <213> *Pasteurella multocida*

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Glu Leu Asp Phe Leu Lys Asn Thr Arg Arg Pro Glu Ile Ile Asn Ala
20 25 30
Ile Ala Glu Ala Arg Glu His Gly Asp Leu Lys Glu Asn Ala Glu Tyr
35 40 45
His Ala Ala Arg Glu Gln Gln Gly Phe Cys Glu Gly Arg Ile Gln Glu
50 55 60
Ile Glu Gly Lys Leu Ala Asn Ser Gln Ile Ile Asp Val Thr Lys Ile
65 70 75 80

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Pro Asn Asn Gly Lys Val Ile Phe Gly Ala Thr Ile Leu Leu Leu Asn
      85              90              95
Ile Asp Thr Glu Glu Val Ser Tyr Gln Ile Val Gly Asp Asp Glu
      100            105            110
Ala Asn Ile Lys Ala Gly Leu Ile Ser Val Asn Ala Thr Arg Leu Asn
      115            120            125

<210> 23
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<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (980)..(2440)

<220>
<223> guaB

<400> 23
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gcgatcaatt tattccgata aatcgttgtt aatacttcaa tcagctctgc ccaaggttga 180
tcaatttgct gtgtttgttt tgggaaagac aaattaatgc caaagccaat cagagatta 240
tgttgattat tctgacgatt ggcgatttcg accaaaaatcc ctgctaattt gcgcccattg 300
aatagcaaat catttggcca ttttaacca atgttcaaag cacctgcttg ctttagcgtt 360
tcgogattg ccatacccaac tactaaactc aagccttcta aattgacctt ttggtcacat 420
gcccaataca aactcataat cacttgcca gcaaaaggag aaagccattg acgaccacgt 480
cgtccacgtc ccgcagtttg atattctgct aagcaaatag cgcccttttc caaatgtgca 540
atattgtcaa gcaagaattg attggtcgag ttaataatcg gcttaataata aagtgggtaa 600
ggtgctaacy cttgcgtcaa ataagattca ttaagcgac ttaattgagg tatgagacga 660
aaatgttggg cttgctgttc tatttgtatc cctgttgtt tcaatttttc gatattggt 720
aagatatctt gttctgaata acctaaaagt gcagtcaatt ctgctaaga aagtgttga 780
tagctaagca gtaatgcaag tacgttttgc ataaaaatcc ttatttatat aaccaagag 840
aggcaactta ttatagacaa tgattttctc gaaaatcgat aaaaaaatcc attttcaaac 900
agcaacgaaa tctgtataat gcgacggcaa tattttttac ccttttattt ttcatatcaa 960
cctaagagag aatattgca atg tta cga gta ata aaa gaa gca tta acc ttc 1012
      Met Leu Arg Val Ile Lys Glu Ala Leu Thr Phe
      1              5              10
gat gat gtt ttg ctt gtc cca gca cat tct act gtg ctc cca aat acc 1060
Asp Asp Val Leu Leu Val Pro Ala His Ser Thr Val Leu Pro Asn Thr
      15              20              25

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gca gac ctt tcc act caa ctc acc aaa act atc cgc ctc aat atc cca 1108
Ala Asp Leu Ser Thr Gln Leu Thr Lys Thr Ile Arg Leu Asn Ile Pro
30 35 40

atg tta tcc gcc gcc atg gat acc gtg aca gaa act aaa ctg gca atc 1156
Met Leu Ser Ala Ala Met Asp Thr Val Thr Glu Thr Lys Leu Ala Ile
45 50 55

tct ctt gca caa gaa ggt ggc atc ggg ttt att cat aaa aat atg tct 1204
Ser Leu Ala Gln Glu Gly Gly Ile Gly Phe Ile His Lys Asn Met Ser
60 65 70 75

att gag cgt caa gcg gaa cgt gtc cgc aaa gtg aaa aaa ttt gag agc 1252
Ile Glu Arg Gln Ala Glu Arg Val Arg Lys Val Lys Lys Phe Glu Ser
80 85 90

ggg att gta tcc gat cct gtc acc gtt tca cca acc tta tct tta gca 1300
Gly Ile Val Ser Asp Pro Val Thr Val Ser Pro Thr Leu Ser Leu Ala
95 100 105

gaa tta agt gaa tta gtg aag aaa aat ggt ttt gcg agt ttc cct gtt 1348
Glu Leu Ser Glu Leu Val Lys Lys Asn Gly Phe Ala Ser Phe Pro Val
110 115 120

gtt gat gat gaa aaa aat ctt gtc ggt atc att act ggt cgt gat aca 1396
Val Asp Asp Glu Lys Asn Leu Val Gly Ile Ile Thr Gly Arg Asp Thr
125 130 135

cgc ttt gtc acg gat tta aat aaa aca gtg gcg gac ttt atg acc cct 1444
Arg Phe Val Thr Asp Leu Asn Lys Thr Val Ala Asp Phe Met Thr Pro
140 145 150 155

aaa gct cgt ctt gtc acg gtg aaa cgc aat gca agt cgc gat gaa att 1492
Lys Ala Arg Leu Val Thr Val Lys Arg Asn Ala Ser Arg Asp Glu Ile
160 165 170

ttt ggt cta atg cat aca cac cgt gta gaa aaa gtc ctt gtt gtc agc 1540
Phe Gly Leu Met His Thr His Arg Val Glu Lys Val Leu Val Val Ser
175 180 185

gac gat ttc aaa tta aaa ggc atg atc acc tta aaa gac tac caa aaa 1588
Asp Asp Phe Lys Leu Lys Gly Met Ile Thr Leu Lys Asp Tyr Gln Lys
190 195 200

tcc gag caa aaa cca caa gcc tgt aaa gat gaa ttt ggt cgt tta cgt 1636
Ser Glu Gln Lys Pro Gln Ala Cys Lys Asp Glu Phe Gly Arg Leu Arg
205 210 215

gtc ggt gct gca gta gga gca gga cct ggt aat gaa gaa cgt att gat 1684
Val Gly Ala Ala Val Gly Ala Gly Pro Gly Asn Glu Glu Arg Ile Asp
220 225 230 235

gca tta gtg aaa gca ggg gtc gat gtg tta ttg att gac tca tca cac 1732
Ala Leu Val Lys Ala Gly Val Asp Val Leu Leu Ile Asp Ser Ser His
240 245 250

ggg cat tca gaa ggt gtg tta caa cgt gtg cgt gaa act cgt gcg aaa 1780
Gly His Ser Glu Gly Val Leu Gln Arg Val Arg Glu Thr Arg Ala Lys
255 260 265

tac cca gat ttg cca att gtt gca ggt aat gtg gca acc gct gaa ggc 1828
Tyr Pro Asp Leu Pro Ile Val Ala Gly Asn Val Ala Thr Ala Glu Gly
270 275 280

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gca att gcg ttg gct gat gca ggg gca agt gca gtg aaa gtg ggg att 1876
Ala Ile Ala Leu Ala Asp Ala Gly Ala Ser Ala Val Lys Val Gly Ile
285 290 295

ggg cct ggt tca att tgt aca aca cgt att gtc aca ggc gtg ggc gtt 1924
Gly Pro Gly Ser Ile Cys Thr Thr Arg Ile Val Thr Gly Val Gly Val
300 305 310 315

cca caa att aca gcg att gcc gat gcg gca gaa gca cta aaa gat cgg 1972
Pro Gln Ile Thr Ala Ile Ala Asp Ala Ala Glu Ala Leu Lys Asp Arg
320 325 330

ggg att cct gtg att gca gat ggc ggt atc cgt ttc tct ggt gat att 2020
Gly Ile Pro Val Ile Ala Asp Gly Ile Arg Phe Ser Gly Asp Ile
335 340 345

tcg aaa gcc att gcg gcg ggc gcc tct tgt gtt atg gtg ggt tcc atg 2068
Ser Lys Ala Ile Ala Ala Gly Ala Ser Cys Val Met Val Gly Ser Met
350 355 360

ttt gca ggt aca gaa gaa gca cca ggt gaa atc gaa ctt tat caa ggt 2116
Phe Ala Gly Thr Glu Glu Ala Pro Gly Glu Ile Glu Leu Tyr Gln Gly
365 370 375

cgt gcc ttt aaa tct tat cga ggt atg gga tcg tta ggt gcg atg agc 2164
Arg Ala Phe Lys Ser Tyr Arg Gly Met Gly Ser Leu Gly Ala Met Ser
380 385 390 395

aaa ggc tca agc gac cgc tat ttc cag tcc gat aat gca gct gac aaa 2212
Lys Gly Ser Ser Asp Arg Tyr Phe Gln Ser Asp Asn Ala Ala Asp Lys
400 405 410

tta gta cca gaa ggt att gaa gga cgt att cca tat aaa gga ttc tta 2260
Leu Val Pro Glu Gly Ile Glu Gly Arg Ile Pro Tyr Lys Gly Phe Leu
415 420 425

aaa gaa att atc cat caa caa atg ggt gga ttg cgt tct tgt atg ggc 2308
Lys Glu Ile Ile His Gln Gln Met Gly Gly Leu Arg Ser Cys Met Gly
430 435 440

tta acg ggt tgt gca acc att gat gaa ctc cgt acc aaa gcg cag ttt 2356
Leu Thr Gly Cys Ala Thr Ile Asp Glu Leu Arg Thr Lys Ala Gln Phe
445 450 455

gtg cgc att agt ggt gca ggg atc caa gaa agc cat gtg cat gat gtg 2404
Val Arg Ile Ser Gly Ala Gly Ile Gln Glu Ser His Val His Asp Val
460 465 470 475

act atc aca aaa gaa gcc cct aat tat cgt atg ggt taaacattgc 2450
Thr Ile Thr Lys Glu Ala Pro Asn Tyr Arg Met Gly
480 485

ttagggtggg attatcccca cctaagttta ttttaataaa caacgttaat agagaagcct 2510
atttttatgt atggcattaa aattaaaaat gttattaaac tttttctatt aaagttttta 2570
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agaataatc gactgacct gtacttgaat gattttttca aaattggggt aaattatcat 2750
ggatttactc aaatgtatca gacactatca tccaagtatg gttttgatga cgcaacgttt 2810

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tttgaatattc ttgttaagaa agggcctttt tctattcaaa ttggcgtaa aaaacaaact 2870
caaaattatg tgattcttga tgaagcctat actgactata cacaaggttt tgaatttcaa 2930
tctcctgaaa aaatatttat tcttggggg actacttatg aagccttatt tcagcagaca 2990
caatttaaaag aaaaaggaat ctcttatgac ttatcttccc ctattcggat agggcggtta 3050
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cgagacgatt ttgatagggg atacactaaa ttcagcatta gagatacag agactattta 3350
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cataaaatcg gttttaccag tgatgaccgc gctatcgtct ttgataaagc ggaacttgaa 3590
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accagattga ttgcccgcgc tgtaoctgaa attggcgtgt actgcgaact ttgggcattg 4010
gatgtatccg aagccgatat tctgtagttt aatccaactg ggattattct tctggtggt 4070
cctgaaagta ccactgaaga aaacagccca cgagctcccg aatacgtatt caacgccggt 4130
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atctgtggtt gtgaacgtaa ctggacacca gaaaatatca ttgaagatgc cgttgctcgt 4550
cttaagacac aagtgggcga tgatgaagtg attttaggct tatctgggtg cgttaactgc 4610
cgtataggca gcttagaaaa agtgtccgcg ctacagttaa tccccgtaag cgttga 4666

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<210> 24
 <211> 487
 <212> PRT
 <213> *Pasteurella multocida*
 <400> 24
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 Val Pro Ala His Ser Thr Val Leu Pro Asn Thr Ala Asp Leu Ser Thr
 20 25 30
 Gln Leu Thr Lys Thr Ile Arg Leu Asn Ile Pro Met Leu Ser Ala Ala
 35 40 45
 Met Asp Thr Val Thr Glu Thr Lys Leu Ala Ile Ser Leu Ala Gln Glu
 50 55 60
 Gly Gly Ile Gly Phe Ile His Lys Asn Met Ser Ile Glu Arg Gln Ala
 65 70 75 80
 Glu Arg Val Arg Lys Val Lys Lys Phe Glu Ser Gly Ile Val Ser Asp
 85 90 95
 Pro Val Thr Val Ser Pro Thr Leu Ser Leu Ala Glu Leu Ser Glu Leu
 100 105 110
 Val Lys Lys Asn Gly Phe Ala Ser Phe Pro Val Val Asp Asp Glu Lys
 115 120 125
 Asn Leu Val Gly Ile Ile Thr Gly Arg Asp Thr Arg Phe Val Thr Asp
 130 135 140
 Leu Asn Lys Thr Val Ala Asp Phe Met Thr Pro Lys Ala Arg Leu Val
 145 150 155 160
 Thr Val Lys Arg Asn Ala Ser Arg Asp Glu Ile Phe Gly Leu Met His
 165 170 175
 Thr His Arg Val Glu Lys Val Leu Val Val Ser Asp Asp Phe Lys Leu
 180 185 190
 Lys Gly Met Ile Thr Leu Lys Asp Tyr Gln Lys Ser Glu Gln Lys Pro
 195 200 205
 Gln Ala Cys Lys Asp Glu Phe Gly Arg Leu Arg Val Gly Ala Ala Val
 210 215 220
 Gly Ala Gly Pro Gly Asn Glu Glu Arg Ile Asp Ala Leu Val Lys Ala
 225 230 235 240
 Gly Val Asp Val Leu Leu Ile Asp Ser Ser His Gly His Ser Glu Gly
 245 250 255
 Val Leu Gln Arg Val Arg Glu Thr Arg Ala Lys Tyr Pro Asp Leu Pro
 260 265 270
 Ile Val Ala Gly Asn Val Ala Thr Ala Glu Gly Ala Ile Ala Leu Ala
 275 280 285
 Asp Ala Gly Ala Ser Ala Val Lys Val Gly Ile Gly Pro Gly Ser Ile
 290 295 300

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Cys Thr Thr Arg Ile Val Thr Gly Val Gly Val Pro Gln Ile Thr Ala
 305 310 315 320
 Ile Ala Asp Ala Ala Glu Ala Leu Lys Asp Arg Gly Ile Pro Val Ile
 325 330 335
 Ala Asp Gly Gly Ile Arg Phe Ser Gly Asp Ile Ser Lys Ala Ile Ala
 340 345 350
 Ala Gly Ala Ser Cys Val Met Val Gly Ser Met Phe Ala Gly Thr Glu
 355 360 365
 Glu Ala Pro Gly Glu Ile Glu Leu Tyr Gln Gly Arg Ala Phe Lys Ser
 370 375 380
 Tyr Arg Gly Met Gly Ser Leu Gly Ala Met Ser Lys Gly Ser Ser Asp
 385 390 395 400
 Arg Tyr Phe Gln Ser Asp Asn Ala Ala Asp Lys Leu Val Pro Glu Gly
 405 410 415
 Ile Glu Gly Arg Ile Pro Tyr Lys Gly Phe Leu Lys Glu Ile Ile His
 420 425 430
 Gln Gln Met Gly Gly Leu Arg Ser Cys Met Gly Leu Thr Gly Cys Ala
 435 440 445
 Thr Ile Asp Glu Leu Arg Thr Lys Ala Gln Phe Val Arg Ile Ser Gly
 450 455 460
 Ala Gly Ile Gln Glu Ser His Val His Asp Val Thr Ile Thr Lys Glu
 465 470 475 480
 Ala Pro Asn Tyr Arg Met Gly
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<210> 25
 <211> 2364
 <212> DNA
 <213> Pasteurella multocida

<220>
 <221> CDS
 <222> (191)..(1828)

<220>
 <223> H11501

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 aattgacggc gatttagggc gtgatgaatt tgatgacggc gatttataca gtatttggcg 180
 gagataaaaa atg gcg aag aaa aag aaa aaa tta caa caa gcg aaa aaa 229
 Met Ala Lys Lys Lys Lys Lys Leu Gln Gln Ala Lys Lys
 1 5 10
 gta caa gtt ggc tta gat aca caa aca aat gag gcg cgt gtc acg gag 277
 Val Gln Val Gly Leu Asp Thr Gln Thr Asn Glu Ala Arg Val Thr Glu
 15 20 25

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aca gga aga att tct gat cac cca agc aat aaa att acc ccc gca 325
Thr Gly Arg Ile Ile Ser Asp His Pro Ser Asn Lys Ile Thr Pro Ala
30          35          40          45

aag tta aaa ggg att tta gaa gat gct gaa ggt ggt gat att acc gcg 373
Lys Leu Lys Gly Ile Leu Glu Asp Ala Glu Gly Gly Asp Ile Thr Ala
50          55          60

caa cat gag ctt ttc atg gat att gaa gaa cgc gac agt tgc atc ggg 421
Gln His Glu Leu Phe Met Asp Ile Glu Glu Arg Asp Ser Cys Ile Gly
65          70          75

gca aat att caa acc cgt aag cgt gcg att tta acc ctt gac tgg cgc 469
Ala Asn Ile Gln Thr Arg Lys Arg Ala Ile Leu Thr Leu Asp Trp Arg
80          85          90

att gca gag cca cgt aat gcc aca ccg caa gaa gaa aaa ctg caa gtc 517
Ile Ala Glu Pro Arg Asn Ala Thr Pro Gln Glu Glu Lys Leu Gln Val
95          100          105

gaa att gac gag ctt ttc tat caa ttc cca atg cta gaa gat tta atg 565
Glu Ile Asp Glu Leu Phe Tyr Gln Phe Pro Met Leu Glu Asp Leu Met
110          115          120          125

gtg gat atg atg gat gcg gta gga cat ggt ttt tgc gcg tta gaa att 613
Val Asp Met Met Asp Ala Val Gly His Gly Phe Ser Ala Leu Glu Ile
130          135          140

gaa tgg aag caa gct gaa agt aaa tgg att cca gtt aat ttt atc gca 661
Glu Trp Lys Gln Ala Glu Ser Lys Trp Ile Pro Val Asn Phe Ile Ala
145          150          155

cgt ccg cag tgc tgg ttt aaa cta gac aag gat gat aat tta ctg ctt 709
Arg Pro Gln Ser Trp Phe Lys Leu Asp Lys Asp Asp Asn Leu Leu Leu
160          165          170

aaa acg cca gat aat caa gac ggt gag ccg ttg aga caa tat gcc tgg 757
Lys Thr Pro Asp Asn Gln Asp Gly Glu Pro Leu Arg Gln Tyr Gly Trp
175          180          185

gta gtg cat acc cac aaa tca aga aca gta cag ctt gct cgt atg ggt 805
Val Val His Thr His Lys Ser Arg Thr Val Gln Leu Ala Arg Met Gly
190          195          200          205

tta ttt aga acg ctc gca tgg ctt tat atg ttt aaa cac tac tgc gtg 853
Leu Phe Arg Thr Leu Ala Trp Leu Tyr Met Phe Lys His Tyr Ser Val
210          215          220

cat gat ttt gcc gaa ttt cta gag ctt tat ggt atg ccg att cgt att 901
His Asp Phe Ala Glu Phe Leu Glu Leu Tyr Gly Met Pro Ile Arg Ile
225          230          235

ggt aaa tac cca ttt ggg gca acg aat gac gaa aag cgc aca tta ttg 949
Gly Lys Tyr Pro Phe Gly Ala Thr Asn Asp Glu Lys Arg Thr Leu Leu
240          245          250

cgt gca ctt gct caa atc gga cat aac gca gca ggg att atg cca gaa 997
Arg Ala Leu Ala Gln Ile Gly His Asn Ala Ala Gly Ile Met Pro Glu
255          260          265

gga atg aat gtt gag ttg cat aat gtg aca aac act act ggc tgc gct 1045
Gly Met Asn Val Glu Leu His Asn Val Thr Asn Thr Thr Gly Ser Ala
270          275          280          285

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Gly Ser Asn Pro Phe Leu Gln Met Val Asp Trp Cys Glu Lys Ser Ala
290 295 300

gca cgt ttg att cta ggg caa aca tta aca agc ggt gca gat ggt aaa 1141
Ala Arg Leu Ile Leu Gly Gln Thr Leu Thr Ser Gly Ala Asp Gly Lys
305 310 315

act tca act aat gcc ctt gga caa gtg cat aat gaa gtc aga cgt gac 1189
Thr Ser Thr Asn Ala Leu Gly Gln Val His Asn Glu Val Arg Arg Asp
320 325 330

ttg ctt gtg tct gat gct aaa cag att gca caa act att aca caa cag 1237
Leu Leu Val Ser Asp Ala Lys Gln Ile Ala Gln Thr Ile Thr Gln Gln
335 340 345

att att ctg cca tat ctt caa att aac att gat ccg aat att ttg cct 1285
Ile Ile Leu Pro Tyr Leu Gln Ile Asn Ile Asp Pro Asn Ile Leu Pro
350 355 360

tct cgt gtg ccg tat ttc gag ttt gac acg aaa gaa tat gct gat tta 1333
Ser Arg Val Pro Tyr Phe Glu Phe Asp Thr Lys Glu Tyr Ala Asp Leu
370 375 380

agt gtc cta gcg gat gct att cct aag ctt gtg agc gta gga gtg cgc 1381
Ser Val Leu Ala Asp Ala Ile Pro Lys Leu Val Ser Val Gly Val Arg
385 390 395

att cct gaa aat tgg gtg cgt gat aaa gcg gcc att cca gaa ccg cag 1429
Ile Pro Glu Asn Trp Val Arg Asp Lys Ala Gly Ile Pro Glu Pro Gln
400 405 410

gaa aat gaa acg att tta agt gcg gtt caa cat gat ttt aaa aca gat 1477
Glu Asn Glu Thr Ile Leu Ser Ala Val Gln His Asp Phe Lys Thr Asp
415 420 425

tta aac gat gtt gaa aat ccg aaa aaa cag acc gca ctt tct gta caa 1525
Leu Asn Asp Val Glu Asn Pro Lys Lys Gln Thr Ala Leu Ser Val Gln
430 435 440

aat cac gtg aca ggt tgt cag tgt gat gcc tgt cgt ggt gtt gca tta 1573
Asn His Val Thr Gly Cys Gln Cys Asp Gly Cys Arg Gly Val Ala Leu
450 455 460

tct gcg aat aat aac agt tct act gcg cag gcc gtg cta gat ggt gga 1621
Ser Ala Asn Asn Asn Ser Ser Thr Ala Gln Gly Val Leu Asp Gly Gly
465 470 475

ctt gcg caa gca ttt aat gag cct gat ttt aat aaa caa tta aat cca 1669
Leu Ala Gln Ala Phe Asn Glu Pro Asp Phe Asn Lys Gln Leu Asn Pro
480 485 490

atg gta aag aaa gct gtt gcg gta ctc atg gca tgt gac tct tac gat 1717
Met Val Lys Lys Ala Val Ala Val Leu Met Ala Cys Asp Ser Tyr Asp
495 500 505

gag gcg gca gaa aaa ctc gct gaa gca tac cca gaa att tca agt cac 1765
Glu Ala Ala Glu Lys Leu Ala Glu Ala Tyr Pro Glu Ile Ser Ser His
510 515 520

gaa cac gaa cag tat ctc tca aat gcg ctg ttt tta gct gat tta ctt 1813
Glu His Glu Gln Tyr Leu Ser Asn Ala Leu Phe Leu Ala Asp Leu Leu
530 535 540

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gga gga act aat gtc taaacgcgtt agttttctat toggacttga accaacgcaa 1868
 Gly Gly Thr Asn Val
 545
 gccattgagt ttttacataa taaaaaatta cttgcaacga aagtggttaa aaaatcaactg 1928
 catgatagtg ccatcgcaag agctacaaca atcgcgagat tatctagtct tgagatgacg 1988
 aatgatattt ataatcaat ggaagttgcc aaaaagagg gtaagagctt tacacaatgg 2048
 aaaaaagact tggtaagtga gtttgagaaa aaaggctggg tattcgggca tgataaatct 2108
 atcagtcgcg gtatcgacgg aaaactgttg gctgatccga aaacagcgca atattttggt 2168
 acaccgcgtc ggctgaatac aatttatcgt acaaactgac aagccgcata ttctgcggcg 2228
 cgctatcagc gcatgatgga taatattgat catcgccctt attggcaata ttccgctgtc 2288
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 gaccgcgtttt ggtcga 2364

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 <212> PRT
 <213> Pasteurella multocida

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 Gly Leu Asp Thr Gln Thr Asn Glu Ala Arg Val Thr Glu Thr Gly Arg
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 Ile Ile Ser Asp His Pro Ser Asn Lys Ile Thr Pro Ala Lys Leu Lys
 35 40 45
 Gly Ile Leu Glu Asp Ala Glu Gly Gly Asp Ile Thr Ala Gln His Glu
 50 55 60
 Leu Phe Met Asp Ile Glu Glu Arg Asp Ser Cys Ile Gly Ala Asn Ile
 65 70 75 80
 Gln Thr Arg Lys Arg Ala Ile Leu Thr Leu Asp Trp Arg Ile Ala Glu
 85 90 95
 Pro Arg Asn Ala Thr Pro Gln Glu Glu Lys Leu Gln Val Glu Ile Asp
 100 105 110
 Glu Leu Phe Tyr Gln Phe Pro Met Leu Glu Asp Leu Met Val Asp Met
 115 120 125
 Met Asp Ala Val Gly His Gly Phe Ser Ala Leu Glu Ile Glu Trp Lys
 130 135 140
 Gln Ala Glu Ser Lys Trp Ile Pro Val Asn Phe Ile Ala Arg Pro Gln
 145 150 155 160
 Ser Trp Phe Lys Leu Asp Lys Asp Asp Asn Leu Leu Leu Lys Thr Pro
 165 170 175

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Asp Asn Gln Asp Gly Glu Pro Leu Arg Gln Tyr Gly Trp Val Val His
 180 185 190
 Thr His Lys Ser Arg Thr Val Gln Leu Ala Arg Met Gly Leu Phe Arg
 195 200 205
 Thr Leu Ala Trp Leu Tyr Met Phe Lys His Tyr Ser Val His Asp Phe
 210 215 220
 Ala Glu Phe Leu Glu Leu Tyr Gly Met Pro Ile Arg Ile Gly Lys Tyr
 225 230 235 240
 Pro Phe Gly Ala Thr Asn Asp Glu Lys Arg Thr Leu Leu Arg Ala Leu
 245 250 255
 Ala Gln Ile Gly His Asn Ala Ala Gly Ile Met Pro Glu Gly Met Asn
 260 265 270
 Val Glu Leu His Asn Val Thr Asn Thr Thr Gly Ser Ala Gly Ser Asn
 275 280 285
 Pro Phe Leu Gln Met Val Asp Trp Cys Glu Lys Ser Ala Ala Arg Leu
 290 295 300
 Ile Leu Gly Gln Thr Leu Thr Ser Gly Ala Asp Gly Lys Thr Ser Thr
 305 310 315 320
 Asn Ala Leu Gly Gln Val His Asn Glu Val Arg Arg Asp Leu Leu Val
 325 330 335
 Ser Asp Ala Lys Gln Ile Ala Gln Thr Ile Thr Gln Gln Ile Ile Leu
 340 345 350
 Pro Tyr Leu Gln Ile Asn Ile Asp Pro Asn Ile Leu Pro Ser Arg Val
 355 360 365
 Pro Tyr Phe Glu Phe Asp Thr Lys Glu Tyr Ala Asp Leu Ser Val Leu
 370 375 380
 Ala Asp Ala Ile Pro Lys Leu Val Ser Val Gly Val Arg Ile Pro Glu
 385 390 395 400
 Asn Trp Val Arg Asp Lys Ala Gly Ile Pro Glu Pro Gln Glu Asn Glu
 405 410 415
 Thr Ile Leu Ser Ala Val Gln His Asp Phe Lys Thr Asp Leu Asn Asp
 420 425 430
 Val Glu Asn Pro Lys Lys Gln Thr Ala Leu Ser Val Gln Asn His Val
 435 440 445
 Thr Gly Cys Gln Cys Asp Gly Cys Arg Gly Val Ala Leu Ser Ala Asn
 450 455 460
 Asn Asn Ser Ser Thr Ala Gln Gly Val Leu Asp Gly Gly Leu Ala Gln
 465 470 475 480
 Ala Phe Asn Glu Pro Asp Phe Asn Lys Gln Leu Asn Pro Met Val Lys
 485 490 495
 Lys Ala Val Ala Val Leu Met Ala Cys Asp Ser Tyr Asp Glu Ala Ala
 500 505 510

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Glu Lys Leu Ala Glu Ala Tyr Pro Glu Ile Ser Ser His Glu His Glu
  515                      520                      525

Gln Tyr Leu Ser Asn Ala Leu Phe Leu Ala Asp Leu Leu Gly Gly Thr
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Asn Val
  545

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<213> Pasteurella multocida

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<223> Xaa = any or unknown amino acid

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    1              5              10              15

ttt tta gaa gat cgc cgt gaa aag aag ctt acc gaa gaa aaa aca tta 97
Phe Leu Glu Asp Arg Arg Glu Lys Lys Leu Thr Glu Glu Lys Thr Leu
    20              25              30

ggg ctt agt gat gca gtg cgt ttt gct aat gat caa acc cct tat ctc 145
Gly Leu Ser Asp Ala Val Arg Phe Ala Asn Asp Gln Thr Pro Tyr Leu
    35              40              45

cgt tat ggt att gaa tat cga tat aac ggc ttg tct tgg ttg gaa acg 193
Arg Tyr Gly Ile Glu Tyr Arg Tyr Asn Gly Leu Ser Trp Leu Glu Thr
    50              55              60

gta aag ctt ttt ttg gca aag cag aaa atc gaa caa cgt tct gct ctc 241
Val Lys Leu Phe Leu Ala Lys Gln Lys Ile Glu Gln Arg Ser Ala Leu
    65              70              75              80

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caa gag ttt gat att aat aat agg aat aaa ttg gat tcg act atg tcg 289
Gln Glu Phe Asp Ile Asn Asn Arg Asn Lys Leu Asp Ser Thr Met Ser
      85              90              95

ttt gta tat tta caa aga cag aat ata gct cgg gga gaa ttt tca acg 337
Phe Val Tyr Leu Gln Arg Gln Asn Ile Ala Arg Gly Glu Phe Ser Thr
      100              105              110

agt cct tta tat tgg ggg ccg agt cgc cat cgt tta tnt gcg aaa ttc 385
Ser Pro Leu Tyr Trp Gly Pro Ser Arg His Arg Leu Xaa Ala Lys Phe
      115              120              125

gaa ttt cgt gat ang ttt tta gaa aat atg aat aag cnt ttt acg ttt 433
Glu Phe Arg Asp Xaa Phe Leu Glu Asn Met Asn Lys Xaa Phe Thr Phe
      130              135              140

cgg ccg tgg caa atc aat ana ttc aga caa caa ggt cga aat aac tat 481
Arg Pro Trp Gln Ile Asn Xaa Phe Arg Gln Gln Gly Arg Asn Asn Tyr
      145              150              155              160

aca gaa gtg ttt ccc gtt aaa tcc cga gag ttt tct ttt tct ctt atg 529
Thr Glu Val Phe Pro Val Lys Ser Arg Glu Phe Ser Phe Ser Leu Met
      165              170              175

gac gac att aag att ggc gaa ttg cta cat ctc gga ttg ggc ggt cgg 577
Asp Asp Ile Lys Ile Gly Glu Leu Leu His Leu Gly Leu Gly Gly Arg
      180              185              190

tgg gat cac tat aac tat aag cca tta tta aat tct cag cat aat atc 625
Trp Asp His Tyr Asn Tyr Lys Pro Leu Leu Asn Ser Gln His Asn Ile
      195              200              205

aac agg aca cag aga tta cct tat cca aaa aca tca tcc aaa ttt tcg 673
Asn Arg Thr Gln Arg Leu Pro Tyr Pro Lys Thr Ser Ser Lys Phe Ser
      210              215              220

tat caa ttg agt tta gag tat caa tta cat cca tca cat caa att gca 721
Tyr Gln Leu Ser Leu Glu Tyr Gln Leu His Pro Ser His Gln Ile Ala
      225              230              235              240

tac cgt tta agt acc ggt ttt agg gtt ccc cgt gtt gaa gat ctt tat 769
Tyr Arg Leu Ser Thr Gly Phe Arg Val Pro Arg Val Glu Asp Leu Tyr
      245              250              255

ttt gaa gac cga gga aaa agt tct tca caa ttt ctt cct aac ccc gat 817
Phe Glu Asp Arg Gly Lys Ser Ser Ser Gln Phe Leu Pro Asn Pro Asp
      260              265              270

cta caa ccg gaa act gca ctg aat cat gaa ata agt tac cgt ttc caa 865
Leu Gln Pro Glu Thr Ala Leu Asn His Glu Ile Ser Tyr Arg Phe Gln
      275              280              285

aat caa tat gcc cat ttc agc gtc ggg ctt ttc cgt aca cgt tat cat 913
Asn Gln Tyr Ala His Phe Ser Val Gly Leu Phe Arg Thr Arg Tyr His
      290              295              300

aac ttt att caa gaa cgt gag atg acc tgt gat aaa att cca tat gag 961
Asn Phe Ile Gln Glu Arg Glu Met Thr Cys Asp Lys Ile Pro Tyr Glu
      305              310              315              320

tat aat agg act tat gga tat tgc acg cat aat act tat gta atg ttt 1009
Tyr Asn Arg Thr Tyr Gly Tyr Cys Thr His Asn Thr Tyr Val Met Phe
      325              330              335

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gtt aat gaa cct gaa gcc gtg att aaa ggg gtt gaa gta agc ggt gct 1057
Val Asn Glu Pro Glu Ala Val Ile Lys Gly Val Glu Val Ser Gly Ala
      340              345              350

tta aat ggg tgg gca ttc gga ctt tcc gac ggt tta act ttc cgt ctc 1105
Leu Asn Gly Ser Ala Phe Gly Leu Ser Asp Gly Leu Thr Phe Arg Leu
      355              360              365

aaa ggg agc tac agc aaa ggt caa aat cat gac ggc gat ccg tta aaa 1153
Lys Gly Ser Tyr Ser Lys Gly Gln Asn His Asp Gly Asp Pro Leu Lys
      370              375              380

tct att caa cca tgg aca gtg gta acc ggt att gat tac gaa act gaa 1201
Ser Ile Gln Pro Trp Thr Val Val Thr Gly Ile Asp Tyr Glu Thr Glu
      385              390              395

ggg tgg agc gtg agt ttg agc ggg cgt tat agt gcg gct aaa aaa gcc 1249
Gly Trp Ser Val Ser Leu Ser Gly Arg Tyr Ser Ala Ala Lys Lys Ala
      405              410              415

aaa gat gcg ata gaa acg gaa tac aca cat gat aaa aag gtt gtc aaa 1297
Lys Asp Ala Ile Glu Thr Glu Tyr Thr His Asp Lys Lys Val Val Lys
      420              425              430

caa tgg ccg cat tta agt cca tcc tac ttt gtt gtt gat ttt acg ggg 1345
Gln Trp Pro His Leu Ser Pro Ser Tyr Phe Val Val Asp Phe Thr Gly
      435              440              445

caa gtt ga 1353
Gln Val
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<210> 28
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Phe Leu Glu Asp Arg Arg Glu Lys Lys Leu Thr Glu Glu Lys Thr Leu
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 Gly Leu Ser Asp Ala Val Arg Phe Ala Asn Asp Gln Thr Pro Tyr Leu
 35 40 45
 Arg Tyr Gly Ile Glu Tyr Arg Tyr Asn Gly Leu Ser Trp Leu Glu Thr
 50 55 60
 Val Lys Leu Phe Leu Ala Lys Gln Lys Ile Glu Gln Arg Ser Ala Leu
 65 70 75 80
 Gln Glu Phe Asp Ile Asn Asn Arg Asn Lys Leu Asp Ser Thr Met Ser
 85 90 95
 Phe Val Tyr Leu Gln Arg Gln Asn Ile Ala Arg Gly Glu Phe Ser Thr
 100 105 110
 Ser Pro Leu Tyr Trp Gly Pro Ser Arg His Arg Leu Xaa Ala Lys Phe
 115 120 125
 Glu Phe Arg Asp Xaa Phe Leu Glu Asn Met Asn Lys Xaa Phe Thr Phe
 130 135 140
 Arg Pro Trp Gln Ile Asn Xaa Phe Arg Gln Gln Gly Arg Asn Asn Tyr
 145 150 155 160
 Thr Glu Val Phe Pro Val Lys Ser Arg Glu Phe Ser Phe Ser Leu Met
 165 170 175
 Asp Asp Ile Lys Ile Gly Glu Leu Leu His Leu Gly Leu Gly Gly Arg
 180 185 190
 Trp Asp His Tyr Asn Tyr Lys Pro Leu Leu Asn Ser Gln His Asn Ile
 195 200 205
 Asn Arg Thr Gln Arg Leu Pro Tyr Pro Lys Thr Ser Ser Lys Phe Ser
 210 215 220
 Tyr Gln Leu Ser Leu Glu Tyr Gln Leu His Pro Ser His Gln Ile Ala
 225 230 235 240
 Tyr Arg Leu Ser Thr Gly Phe Arg Val Pro Arg Val Glu Asp Leu Tyr
 245 250 255
 Phe Glu Asp Arg Gly Lys Ser Ser Ser Gln Phe Leu Pro Asn Pro Asp
 260 265 270
 Leu Gln Pro Glu Thr Ala Leu Asn His Glu Ile Ser Tyr Arg Phe Gln
 275 280 285
 Asn Gln Tyr Ala His Phe Ser Val Gly Leu Phe Arg Thr Arg Tyr His
 290 295 300
 Asn Phe Ile Gln Glu Arg Glu Met Thr Cys Asp Lys Ile Pro Tyr Glu
 305 310 315 320
 Tyr Asn Arg Thr Tyr Gly Tyr Cys Thr His Asn Thr Tyr Val Met Phe
 325 330 335
 Val Asn Glu Pro Glu Ala Val Ile Lys Gly Val Glu Val Ser Gly Ala
 340 345 350

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Leu Asn Gly Ser Ala Phe Gly Leu Ser Asp Gly Leu Thr Phe Arg Leu
 355 360 365
 Lys Gly Ser Tyr Ser Lys Gly Gln Asn His Asp Gly Asp Pro Leu Lys
 370 375 380
 Ser Ile Gln Pro Trp Thr Val Val Thr Gly Ile Asp Tyr Glu Thr Glu
 385 390 395 400
 Gly Trp Ser Val Ser Leu Ser Gly Arg Tyr Ser Ala Ala Lys Lys Ala
 405 410 415
 Lys Asp Ala Ile Glu Thr Glu Tyr Thr His Asp Lys Lys Val Val Lys
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 Gln Trp Pro His Leu Ser Pro Ser Tyr Phe Val Val Asp Phe Thr Gly
 435 440 445
 Gln Val
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 catggctagc attctagcaa aaattagttg aggaataatag cgggtttggt ttgcttaaaa 180
 aacaacccac ccgtagggc acggctgttt ctttttgaga aattacgctt cttcatcttg 240
 atcttttttc aagatctcat cttcattgag ttttaaaaga cgggcaatcg cattgcggta 300
 ggagatttca aggcttttct gactagtagc aatgacacct tgatcgatta agaaaccgtc 360
 attgacatca taaacccaac catgtaatga gagtttttcc ccatttttcc acgcggattt 420
 aatgattgac gagcgacctt agttataaac ttgcctctgc acgttaattt tcgtcagcat 480
 atcagcccggt ttttcaggcg gtaaatggcc aagtaaatga ctatgcitatt accaaatato 540
 gcgtaagtgg agtaaccagt tattaattaa acctaaatct tgatccgcca ttgcggcttt 600
 aattccacca cagtttgtat gtccacaaat aataatgtgt tcaatattta agacctcaac 660
 ggcatattgc acaacagata aacagtttaa atcgggtgta atgacttgat ttgcaacatt 720
 acgatgcaca aacagctcac ccggtcctaa atttggttaatt tttttctgag gaacacggct 780
 atccgagcaa ccaatccaaa gatagctcgg ggtttgatga tcagccaatt ctttaaagta 840

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agaggagttt tctcttttca tccgtaacgc ccagctataa ttattggcaa aaagttgttc 900
aatttttttc attagagtga ttctataacc gcaaaaataa gggggctagt atagcttaga 960
aatagacagt gggtaaagaa aggcataaaa ttgtatagga taacttggtt ttattgcca 1020
tttatttaga attagaatct ttaataataa aaataattat cattaagggtt aatagtt 1077
atg gat aaa aat tta atg aag gga tgt gta ttc tta tca ata gtc ggt 1125
Met Asp Lys Asn Leu Met Lys Gly Cys Val Phe Leu Ser Ile Val Gly
1 5 10 15
tgc ggt atc caa ata ggg cta gca tca aat cca aat cct cca gat gtg 1173
Cys Gly Ile Gln Ile Gly Leu Ala Ser Asn Pro Asn Pro Pro Asp Val
20 25 30
gat gag tta tta cct att att gtg aat gct gat gaa gat aat aaa tta 1221
Asp Glu Leu Leu Pro Ile Ile Val Asn Ala Asp Glu Asp Asn Lys Leu
35 40 45
cca ggt cgt tct gta tta aaa cag aaa aat atc gat caa caa caa gca 1269
Pro Gly Arg Ser Val Leu Lys Gln Lys Asn Ile Asp Gln Gln Gln Ala
50 55 60
gat aat gcc gct gac tta ata aat att tta cct ggg gta aat atg gcg 1317
Asp Asn Ala Ala Asp Leu Ile Asn Ile Leu Pro Gly Val Asn Met Ala
65 70 75 80
gga gga ttt cgc cct ggt ggt caa aca tta aat att aat gga atg ggt 1365
Gly Gly Phe Arg Pro Gly Gly Gln Thr Leu Asn Ile Asn Gly Met Gly
85 90 95
gat gct gaa gat gtt aga gtt caa cta gac gcc gca aca aaa agt ttc 1413
Asp Ala Glu Asp Val Arg Val Gln Leu Asp Gly Ala Thr Lys Ser Phe
100 105 110
gaa aaa tat caa caa gcc tct att ttt att gaa cct gag tta tta aga 1461
Glu Lys Tyr Gln Gln Gly Ser Ile Phe Ile Glu Pro Glu Leu Leu Arg
115 120 125
aag gtg aca gta gac aaa gga aat tat tct cct caa tat gcc aat ggt 1509
Lys Val Thr Val Asp Lys Gly Asn Tyr Ser Pro Gln Tyr Gly Asn Gly
130 135 140
ggc ttt gct ggt act gta aaa ttt gaa aca aaa gat gca act gat ttt 1557
Gly Phe Ala Gly Thr Val Lys Phe Glu Thr Lys Asp Ala Thr Asp Phe
145 150 155 160
ttg aaa gaa aat cag aaa ata ggt gga tta ttt aaa tat gga aat aat 1605
Leu Lys Glu Asn Gln Lys Ile Gly Gly Leu Phe Lys Tyr Gly Asn Asn
165 170 175
agc aat aat aac caa aaa act tat agt aca gcc cta gtt tta cag aat 1653
Ser Asn Asn Asn Gln Lys Thr Tyr Ser Thr Ala Leu Val Leu Gln Asn
180 185 190
gaa caa aaa aat att gat ttg tta tta ttt ggt tct gta aga aat gca 1701
Glu Gln Lys Asn Ile Asp Leu Leu Leu Phe Gly Ser Val Arg Asn Ala
195 200 205
agc aat tat aca aga cct gat aaa agt aaa att ctt ttt tca aaa aac 1749
Ser Asn Tyr Thr Arg Pro Asp Lys Ser Lys Ile Leu Phe Ser Lys Asn
210 215 220

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aat caa aaa agt gga tta ata aaa gta aat tgg caa att act cct gaa 1797
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 225 230 235 240
 cat tta tta act tta tcc agt gtt tat ggc att cat aaa ggg tgg gaa 1845
 His Leu Leu Thr Leu Ser Ser Val Tyr Gly Ile His Lys Gly Trp Glu
 245 250 255
 cct tgg gca gca aaa aga gat gtg atg tgg aga cca aca gaa aca gaa 1893
 Pro Trp Ala Ala Lys Arg Asp Val Met Ser Arg Pro Thr Glu Thr Glu
 260 265 270
 ata aaa cac tat ggg att gat gtt gcg tgg aaa cgt aaa ctt gtt tat 1941
 Ile Lys His Tyr Gly Ile Asp Val Ala Trp Lys Arg Lys Leu Val Tyr
 275 280 285
 cga gat caa aaa gat gaa agt tat tca ttg aaa tat cgc tat tta cct 1989
 Arg Asp Gln Lys Asp Glu Ser Tyr Ser Leu Lys Tyr Arg Tyr Leu Pro
 290 295 300
 gaa aat aat aag tgg att aat ttg tct gtt cag ctg agt tat agt aaa 2037
 Glu Asn Asn Lys Trp Ile Asn Leu Ser Val Gln Leu Ser Tyr Ser Lys
 305 310 315 320
 aca gag cag aat gat act cgc cat gag aaa gtc act tct tca ttc cta 2085
 Thr Glu Gln Asn Asp Thr Arg His Glu Lys Val Thr Ser Ser Phe Leu
 325 330 335
 ggt aca tta gga aat aaa agt tgg ata act tat tca gat ctt act ttt 2133
 Gly Thr Leu Gly Asn Lys Ser Trp Ile Thr Tyr Ser Asp Leu Thr Phe
 340 345 350
 gat ata agt aac aca agt act cta aat att ggg cgt gct gag cat gaa 2181
 Asp Ile Ser Asn Thr Ser Thr Leu Asn Ile Gly Arg Ala Glu His Glu
 355 360 365
 cta cta ttt ggt tta cag tgg tta aaa aat aaa aga aat acc ctt atg 2229
 Leu Leu Phe Gly Leu Gln Trp Leu Lys Asn Lys Arg Asn Thr Leu Met
 370 375 380
 tat cat aaa ggg gga gtc aag aag gca gac tat aat tat ggc tat ttt 2277
 Tyr His Lys Gly Gly Val Lys Lys Ala Asp Tyr Asn Tyr Gly Tyr Phe
 385 390 395 400
 cag cct tat tat atg oct tct gga cgc cag tat aca caa gca ttt tat 2325
 Gln Pro Tyr Tyr Met Pro Ser Gly Arg Gln Tyr Thr Gln Ala Phe Tyr
 405 410 415
 tta caa gat caa ata aaa tgg cag aat ttc ctc ttt aca gga ggg ata 2373
 Leu Gln Asp Gln Ile Lys Trp Gln Asn Phe Leu Phe Thr Gly Gly Ile
 420 425 430
 aga tat gac cat atc aat aat ata ggg cag aaa aat tta gcg cca cga 2421
 Arg Tyr Asp His Ile Asn Asn Ile Gly Gln Lys Asn Leu Ala Pro Arg
 435 440 445
 tat aat gat atc tct gca gga cat gat tat agc cag aaa aat tat aat 2469
 Tyr Asn Asp Ile Ser Ala Gly His Asp Tyr Ser Gln Lys Asn Tyr Asn
 450 455 460
 ggt tgg tct tat tat tta ggt ctt aag tat gat gta aat cat tat tta 2517
 Gly Trp Ser Tyr Tyr Leu Gly Leu Lys Tyr Asp Val Asn His Tyr Leu
 465 470 475 480

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agt tta ttt acg aat ttt agt aaa act tgg cga gcc cct gtt att gat 2565
Ser Leu Phe Thr Asn Phe Ser Lys Thr Trp Arg Ala Pro Val Ile Asp
485 490 495

gaa cag tat gag aca caa tat agt caa gct tct gta tct gcg act tct 2613
Glu Gln Tyr Glu Thr Gln Tyr Ser Gln Ala Ser Val Ser Ala Thr Ser
500 505 510

tta aat tta gaa aaa gaa atg att aat caa acc aga gtg ggt gga att 2661
Leu Asn Leu Glu Lys Glu Met Ile Asn Gln Thr Arg Val Gly Gly Ile
515 520 525

att act ctc aat cat cta ttt cag gaa aat gat gct ttt caa ttt aga 2709
Ile Thr Leu Asn His Leu Phe Gln Glu Asn Asp Ala Phe Gln Phe Arg
530 535 540

act act tat ttt tac aat cgc gcc aag aat gaa atc ttc aaa acg aga 2757
Thr Thr Tyr Phe Tyr Asn Arg Gly Lys Asn Glu Ile Phe Lys Thr Arg
545 550 555 560

ggg gtt aac cgt tagagttggt tgaatgact gaaaaattag acctatacgt 2809
Gly Val Asn Arg

tactgttaaa ggtggcggta tttctggta agcgggtgca atccgtcacg gtatcactcg 2869

tgcatataac gaatatgatg agagtgttacg ctctgtatta cgcgcagctg gtttcgttac 2929

tcgcgatgca cgtcaagttg aacgtaaaaa agtgggttta cgcgaagcgc gtcgtcgtcc 2989

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 Thr Ser Val Phe Gln Thr Lys Tyr Arg His Phe Ile Asp Leu Ala Tyr
 750 755 760
 tta ggt tca aga aat tta tcy aat tcc gtg gga ggg cag gca caa gca 7095
 Leu Gly Ser Arg Asn Leu Ser Asn Ser Val Gly Gly Gln Ala Gln Ala
 765 770 775
 aga gat ttc caa gtt tat caa aat gtc aat gtc gat aat gcc aaa gtt 7143
 Arg Asp Phe Gln Val Tyr Gln Asn Val Asn Val Asp Asn Ala Lys Val
 780 785 790
 aaa gga ctt gaa att aat gca cgt ttg aat ttg gga tat ttt tgg cat 7191
 Lys Gly Leu Glu Ile Asn Ala Arg Leu Asn Leu Gly Tyr Phe Trp His
 795 800 805
 gtg ttg gat gga ttt aat acg agc tat aaa ttc act tac caa cgt ggt 7239
 Val Leu Asp Gly Phe Asn Thr Ser Tyr Lys Phe Thr Tyr Gln Arg Gly
 815 820 825
 cgt ttg gat gcc gat cgt cca atg aat gcg att cag cct aaa gct tct 7287
 Arg Leu Asp Gly Asp Arg Pro Met Asn Ala Ile Gln Pro Lys Ala Ser
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 gtt ttt ggt ttg ggc tac gat cat aaa gaa aat aaa ttt ggc gct gat 7335
 Val Phe Gly Leu Gly Tyr Asp His Lys Glu Asn Lys Phe Gly Ala Asp
 845 850 855
 tta tat att aca cgt gtg agt gag aaa aaa gcg aaa gac act tat aat 7383
 Leu Tyr Ile Thr Arg Val Ser Glu Lys Lys Ala Lys Asp Thr Tyr Asn
 860 865 870
 atg ttc tat aaa gaa cag gga tat aaa gat agt gct gtt cgt tgg aga 7431
 Met Phe Tyr Lys Glu Gln Gly Tyr Lys Asp Ser Ala Val Arg Trp Arg
 875 880 885 890
 agt gat gac tat acg cta gtt gat gcg gtt ggt tat att aaa ccg att 7479
 Ser Asp Asp Tyr Thr Leu Val Asp Ala Val Gly Tyr Ile Lys Pro Ile
 895 900 905
 aag aat tta acg tta cag ttt ggc gtt tat aat ttg aca gac cgt aaa 7527
 Lys Asn Leu Thr Leu Gln Phe Gly Val Tyr Asn Leu Thr Asp Arg Lys
 910 915 920
 tac ttg aca tgg gaa tct gct cgt tcy att aaa cca ttt ggt aca agt 7575
 Tyr Leu Thr Trp Glu Ser Ala Arg Ser Ile Lys Pro Phe Gly Thr Ser
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 Asn Leu Ile Asn Gln Lys Thr Gly Ala Gly Ile Asn Arg Phe Tyr Ser
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 Pro Gly Arg Asn Phe Lys Leu Ser Ala Glu Ile Thr Phe
 955 960 965
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 35 40 45
 Glu Lys Lys Ile Gly Glu Thr Val Lys Thr Ala Ser Gln Leu Lys Arg
 50 55 60
 Gln Gln Val Gln Asp Ser Arg Asp Leu Val Arg Tyr Glu Thr Gly Val
 65 70 75 80
 Thr Val Val Glu Ala Gly Arg Phe Gly Ser Ser Gly Tyr Ala Ile Arg
 85 90 95
 Gly Val Asp Glu Asn Arg Val Ala Ile Thr Val Asp Gly Leu His Gln
 100 105 110
 Ala Glu Thr Thr Leu Ser Ser Gln Gly Phe Lys Glu Leu Phe Glu Gly Tyr
 115 120 125
 Gly Asn Phe Asn Asn Thr Arg Asn Ser Val Glu Ile Glu Thr Leu Lys
 130 135 140
 Val Ala Lys Ile Ala Lys Gly Ala Asp Ser Val Lys Val Gly Ser Gly
 145 150 155 160
 Ser Leu Gly Gly Ala Val Leu Phe Glu Thr Lys Asp Ala Arg Asp Phe
 165 170 175
 Leu Thr Glu Lys Asp Trp His Ile Gly Tyr Lys Ala Gly Tyr Ser Thr
 180 185 190
 Ala Asp Asn Gln Gly Leu Asn Ala Val Thr Leu Ala Gly Arg Tyr Gln
 195 200 205
 Met Phe Asp Ala Leu Ile Met His Ser Lys Arg His Gly His Glu Leu
 210 215 220
 Glu Asn Tyr Asp Tyr Lys Asn Gly Arg Asp Ile Gln Gly Lys Glu Arg
 225 230 235 240
 Glu Lys Ala Asp Pro Tyr Thr Ile Thr Lys Glu Ser Thr Leu Val Lys
 245 250 255
 Phe Ser Phe Ser Pro Thr Glu Asn His Arg Phe Thr Val Ala Ser Asp
 260 265 270
 Thr Tyr Leu Gln His Ser Arg Gly His Asp Leu Ser Tyr Asn Leu Val
 275 280 285
 Ala Thr Thr His Ile Gln Leu Asp Glu Lys Glu Ser Arg His Ala Asn
 290 295 300

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Asp Leu Thr Lys Arg Lys Asn Val Ser Phe Thr Tyr Glu Asn Tyr Thr
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Val Thr Pro Phe Trp Asp Thr Leu Lys Leu Ser Tyr Ser Gln Gln Arg
325                      330                      335
Ile Thr Thr Arg Ala Arg Thr Glu Asp Tyr Cys Asp Gly Asn Glu Leu
340                      345                      350
Cys Asp Ser Tyr Lys Asn Pro Leu Gly Leu Gln Phe Lys Asp Gly Gln
355                      360                      365
Ile Leu Asp Pro Ala Gly Asn Lys Ile Lys Leu Gln Gly Ser Gly Leu
370                      375                      380
Ser Thr Gln Ile Val Asp Glu Asn Gly Lys Pro Phe Pro Thr Thr Thr
385                      390                      395                      400
Gly Thr Asn Asn Ala Ala Phe Ser Asn Asn Leu Arg Leu Arg Pro Thr
405                      410                      415
Gly Phe Trp Leu Asp Cys Ser Val Phe Asp Cys Asn Lys Pro Phe Thr
420                      425                      430
Val Tyr Asn Ile Ser Asn Gly Thr Tyr Gln Ala Arg Glu Val Leu Leu
435                      440                      445
Ser Glu Glu Ile Thr Val Asp Gly Lys Leu Tyr Lys Thr Ala Lys Glu
450                      455                      460
Glu Gly Gly Leu Pro Asn Tyr Leu Ile Leu Pro Asn Ser Lys Gly Tyr
465                      470                      475                      480
Leu Pro Tyr Asp Tyr Lys Glu Arg Asp Leu Asn Thr Asn Thr Lys Gln
485                      490                      495
Ile Asn Leu Asp Leu Thr Lys Thr Phe Leu Thr Phe Asn Ile Glu Asn
500                      505                      510
Asn Leu Ser Tyr Gly Gly Val Tyr Ser Arg Ile Glu Lys Glu Met Ile
515                      520                      525
Asn Lys Ala Gly Tyr Glu Gly Arg Asn Pro Thr Trp Trp Ala Asp Arg
530                      535                      540
Ile Leu Gly Gln Ser Ser Tyr Cys Gly Tyr Asn Ala Leu Lys Cys Pro
545                      550                      555                      560
Lys His Glu Pro Leu Thr Ser Phe Leu Ile Pro Val Glu Ala Thr Thr
565                      570                      575
Gln Ser Leu Tyr Phe Ala Asn Ile Leu Lys Val His Asn Met Ile Ser
580                      585                      590
Ile Asp Leu Gly Tyr Arg Tyr Asp His Ile Lys Tyr Asn Pro Glu Tyr
595                      600                      605
Thr Pro Gly Val Thr Pro Lys Ile Pro Asp Asp Met Val Lys Gly Leu
610                      615                      620
Phe Ile Pro Met Pro Lys Glu Pro Gln Leu Lys Asp Phe Asp Tyr Asn
625                      630                      635                      640

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Tyr Ala Lys Phe Gly Glu Ala Tyr Lys Lys Trp Lys Glu Tyr Leu Pro
 645 650 655
 Lys Asn Ala Glu Glu Asn Ile Ala Tyr Ile Ala Gln Asp Lys Thr Phe
 660 665 670
 Lys Lys His Ser Tyr Ser Leu Gly Ala Thr Phe Asp Pro Leu Asn Phe
 675 680 685
 Leu Arg Val Gln Val Lys Tyr Ser Lys Gly Phe Arg Ala Pro Thr Ser
 690 695 700
 Asp Glu Leu Tyr Phe Thr Phe Lys His Pro Asp Phe Thr Ile Leu Pro
 705 710 715 720
 Asn Pro Val Leu Lys Pro Glu Glu Ala Lys Asn Gln Glu Ile Ala Leu
 725 730 735
 Thr Val His Asp Asn Trp Gly Phe Val Ser Thr Ser Val Phe Gln Thr
 740 745 750
 Lys Tyr Arg His Phe Ile Asp Leu Ala Tyr Leu Gly Ser Arg Asn Leu
 755 760 765
 Ser Asn Ser Val Gly Gly Gln Ala Gln Ala Arg Asp Phe Gln Val Tyr
 770 775 780
 Gln Asn Val Asn Val Asp Asn Ala Lys Val Lys Gly Leu Glu Ile Asn
 785 790 795 800
 Ala Arg Leu Asn Leu Gly Tyr Phe Trp His Val Leu Asp Gly Phe Asn
 805 810 815
 Thr Ser Tyr Lys Phe Thr Tyr Gln Arg Gly Arg Leu Asp Gly Asp Arg
 820 825 830
 Pro Met Asn Ala Ile Gln Pro Lys Ala Ser Val Phe Gly Leu Gly Tyr
 835 840 845
 Asp His Lys Glu Asn Lys Phe Gly Ala Asp Leu Tyr Ile Thr Arg Val
 850 855 860
 Ser Glu Lys Lys Ala Lys Asp Thr Tyr Asn Met Phe Tyr Lys Glu Gln
 865 870 875 880
 Gly Tyr Lys Asp Ser Ala Val Arg Trp Arg Ser Asp Asp Tyr Thr Leu
 885 890 895
 Val Asp Ala Val Gly Tyr Ile Lys Pro Ile Lys Asn Leu Thr Leu Gln
 900 905 910
 Phe Gly Val Tyr Asn Leu Thr Asp Arg Lys Tyr Leu Thr Trp Glu Ser
 915 920 925
 Ala Arg Ser Ile Lys Pro Phe Gly Thr Ser Asn Leu Ile Asn Gln Lys
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 Thr Gly Ala Gly Ile Asn Arg Phe Tyr Ser Pro Gly Arg Asn Phe Lys
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cgtttaaata accaagaggt ggaag atg aca gaa gaa aat aaa gga aag aga 1132
Met Thr Glu Glu Asn Lys Gly Lys Arg
1 5

tat ttt tta tgg ttc ata ttg ttt atc att tca atc tat tta ttt att 1180
Tyr Phe Leu Trp Phe Ile Leu Phe Ile Leu Ser Ile Tyr Leu Phe Ile
10 15 20 25

acc ata caa gaa aga cga ggt tat tgt ttt gac aaa cgt gca tat att 1228
Thr Ile Gln Glu Arg Arg Gly Tyr Cys Phe Asp Lys Arg Ala Tyr Ile
30 35 40

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cat gag ctt tat act gag caa gag tta att gat cgg ggg att gaa tat 1276
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gtg gta tcc acc atg ccg tca ggt gtt att aaa cca gat ggc aca ata 1324
Val Val Ser Thr Met Pro Ser Gly Val Ile Lys Pro Asp Gly Thr Ile
      60              65              70

aaa gaa gta aag cgt tac acg agt gtc gag gag ttt aaa cag atg aac 1372
Lys Glu Val Lys Arg Tyr Thr Ser Val Glu Glu Phe Lys Gln Met Asn
      75              80              85

cca gct tgt tgt aca tta acc acc ttt att gat gaa gga ggc gat ggc 1420
Pro Ala Cys Cys Thr Leu Thr Thr Phe Ile Asp Glu Gly Gly Asp Gly
      90              95              100

tat cca gat gat gat gga tat ggt tat gtc aga att gaa tat tta aga 1468
Tyr Pro Asp Asp Asp Gly Tyr Gly Tyr Val Arg Ile Glu Tyr Leu Arg
      110              115              120

cat tat gtt gag aat cta aaa cct tat cat aga gtg att tat ctt gaa 1516
His Tyr Val Glu Asn Leu Lys Pro Tyr His Arg Val Ile Tyr Leu Glu
      125              130              135

tat acg ccc tgt gga gag tta agg gaa gag gcg gct ttt tca aaa aat 1564
Tyr Thr Pro Cys Gly Glu Leu Arg Glu Glu Ala Ala Phe Ser Lys Asn
      140              145              150

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 Tyr Cys Phe Asp Lys Arg Ala Tyr Ile His Glu Leu Tyr Thr Glu Gln
 35 40 45
 Glu Leu Ile Asp Arg Gly Ile Glu Tyr Val Val Ser Thr Met Pro Ser
 50 55 60
 Gly Val Ile Lys Pro Asp Gly Thr Ile Lys Glu Val Lys Arg Tyr Thr
 65 70 75 80
 Ser Val Glu Glu Phe Lys Gln Met Asn Pro Ala Cys Cys Thr Leu Thr
 85 90 95
 Thr Phe Ile Asp Glu Gly Gly Asp Gly Tyr Pro Asp Asp Asp Gly Tyr
 100 105 110
 Gly Tyr Val Arg Ile Glu Tyr Leu Arg His Tyr Val Glu Asn Leu Lys
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gcagaactgg cttagcttacc acttttagat aattgtatta ttaaaagaag ctgtatgatt 180
gttattctat cattagtggg taataaatat tctttatttt ttgagagata aaaacaattc 240
atatttcaat agaaaacaga aaataaagat tatcaaaaga attatccgtc cttataaata 300
tgagtctgta ttgtgagatg atat atg aat att tta ttt gtt tct gat gat 351
                               Met Asn Ile Leu Phe Val Ser Asp Asp
                               1           5

ggt tat gct aaa cat ctg gtg gtt gcg att aaa agc att ata aat cat 399
Val Tyr Ala Lys His Leu Val Val Ala Ile Lys Ser Ile Ile Asn His
10           15           20           25

aat gaa aaa ggt att tca ttt tat att ttt gat ttg ggt ata aag gat 447
Asn Glu Lys Gly Ile Ser Phe Tyr Ile Phe Asp Leu Gly Ile Lys Asp
30           35           40

gaa aat aag aga aat att aat gat att gtt tct tct tat gga agt gaa 495
Glu Asn Lys Arg Asn Ile Asn Asp Ile Val Ser Ser Tyr Gly Ser Glu
45           50           55

gtc aac ttt att gct gtg aat gag aaa gaa ttt gag agt ttt cct gtt 543
Val Asn Phe Ile Ala Val Asn Glu Lys Glu Phe Glu Ser Phe Pro Val
60           65           70

caa att agt tat att tct tta gca aca tat gca agg cta aaa gcg gca 591
Gln Ile Ser Tyr Ile Ser Leu Ala Thr Tyr Ala Arg Leu Lys Ala Ala
75           80           85

gag tat ttg ccg gat aat tta aat aaa att att tat tta gat gtt gat 639
Glu Tyr Leu Pro Asp Asn Leu Asn Lys Ile Ile Tyr Leu Asp Val Asp
90           95           100           105

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110 115 120

aat ttt ctt acc gca gcc tgt tat gat tct ttc atc gaa aat gaa aag 735
Asn Phe Leu Thr Ala Ala Cys Tyr Asp Ser Phe Ile Glu Asn Glu Lys
125 130 135

tct gag cat aaa aaa tcg att tca atg tca gat aag gaa tat tat ttt 783
Ser Glu His Lys Lys Ser Ile Ser Met Ser Asp Lys Glu Tyr Tyr Phe
140 145 150

aat gca gga gta atg cta ttt aat tta gat gaa tgg cgg aag atg gat 831
Asn Ala Gly Val Met Leu Phe Asn Leu Asp Glu Trp Arg Lys Met Asp
155 160 165

gta ttc tca aga gct tta gac ctg tta gct atg tat cct aat caa atg 879
Val Phe Ser Arg Ala Leu Asp Leu Leu Ala Met Tyr Pro Asn Gln Met
170 175 180 185

att tat cag gat caa gat ata ttg aat atc ctt ttt agg aat aaa gtc 927
Ile Tyr Gln Asp Gln Asp Ile Leu Asn Ile Leu Phe Arg Asn Lys Val
190 195 200

tgt tat tta gat tgc aga ttt aat ttc atg cca aat caa ctt gaa aga 975
Cys Tyr Leu Asp Cys Arg Phe Asn Phe Met Pro Asn Gln Leu Glu Arg
205 210 215

ata aan caa tac cat aaa gga aaa ntg agc aac tta cat tct tta gaa 1023
Ile Xaa Gln Tyr His Lys Lys Gly Lys Xaa Ser Asn Leu His Ser Leu Glu
220 225 230

aaa aca acg atg cct gtc gtt att tca cat tat tgt ggt cca gaa aaa 1071
Lys Thr Thr Met Pro Val Val Ile Ser His Tyr Cys Gly Pro Glu Lys
235 240 245

gcg tgg cat gcg gat tgt aaa cat ttt aat gta tat ttc tat cag aaa 1119
Ala Trp His Ala Asp Cys Lys His Phe Asn Val Tyr Phe Tyr Gln Lys
250 255 260 265

ata tta gca naa atn tcg aga gcc ncg gat aaa gaa cgc gta tta tct 1167
Ile Leu Ala Xaa Xaa Ser Arg Gly Xaa Asp Lys Glu Arg Val Leu Ser
270 275 280

ata aaa act tat ctc aag gcc ttg att aga agg att aga tat aaa ttc 1215
Ile Lys Thr Tyr Leu Lys Ala Leu Ile Arg Arg Ile Arg Tyr Lys Phe
285 290 295

aaa tat caa gtc tat taactattga atttttgcaa atgagataag agtatagtgc 1270
Lys Tyr Gln Val Tyr
300

tgatttcttc aaagcgaataa ggaggaaata gcttgttcta atttattaca ataaggttg 1330

tattcatctt gattttgaag gaaagagagt gttttttgta taaaagcatt ttctgcacct 1390

aaatttacta atctctcaaaa ttctctctct cgnagaattt ctttcggacc ggtagggcag 1450

tccatggata ttacaggtgt accgcaagcc atgctttcta ggataactgt cggtaacccc 1510

tctttcaag aggtgtgtaa aaatagctta gcatttttta ttaatggata cggattatct 1570

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Tyr Ile Phe Asp Leu Gly Ile Lys Asp Glu Asn Lys Arg Asn Ile Asn
35 40 45
Asp Ile Val Ser Ser Tyr Gly Ser Glu Val Asn Phe Ile Ala Val Asn
50 55 60
Glu Lys Glu Phe Glu Ser Phe Pro Val Gln Ile Ser Tyr Ile Ser Leu
65 70 75 80
Ala Thr Tyr Ala Arg Leu Lys Ala Ala Glu Tyr Leu Pro Asp Asn Leu
85 90 95
Asn Lys Ile Ile Tyr Leu Asp Val Asp Val Leu Val Phe Asn Ser Leu
100 105 110
Glu Met Leu Trp Asn Val Asp Val Asn Asn Phe Leu Thr Ala Ala Cys
115 120 125
Tyr Asp Ser Phe Ile Glu Asn Glu Lys Ser Glu His Lys Lys Ser Ile
130 135 140

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Ser Met Ser Asp Lys Glu Tyr Tyr Phe Asn Ala Gly Val Met Leu Phe
145                      150                      155                      160
Asn Leu Asp Glu Trp Arg Lys Met Asp Val Phe Ser Arg Ala Leu Asp
165                      170                      175
Leu Leu Ala Met Tyr Pro Asn Gln Met Ile Tyr Gln Asp Gln Asp Ile
180                      185                      190
Leu Asn Ile Leu Phe Arg Asn Lys Val Cys Tyr Leu Asp Cys Arg Phe
195                      200                      205
Asn Phe Met Pro Asn Gln Leu Glu Arg Ile Xaa Gln Tyr His Lys Gly
210                      215                      220
Lys Xaa Ser Asn Leu His Ser Leu Glu Lys Thr Thr Met Pro Val Val
225                      230                      235
Ile Ser His Tyr Cys Gly Pro Glu Lys Ala Trp His Ala Asp Cys Lys
245                      250                      255
His Phe Asn Val Tyr Phe Tyr Gln Lys Ile Leu Ala Xaa Xaa Ser Arg
260                      265                      270
Gly Xaa Asp Lys Glu Arg Val Leu Ser Ile Lys Thr Tyr Leu Lys Ala
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<223> n = A or T or G or C

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    1             5             10             15

gga cac cca gat gca gaa gct cgt aca aaa ttc gtc att aaa gaa tta 97
  Gly His Pro Asp Ala Glu Ala Arg Thr Lys Phe Val Ile Lys Glu Leu
    20             25             30

nat aat aaa ggc att caa gat gag caa tta ttc atc gac acg ggg atg 145
  Xaa Asn Lys Gly Ile Gln Asp Glu Gln Leu Phe Ile Asp Thr Gly Met
    35             40             45

tgg gat gcc gct tta gcg aaa gat aaa atg gat gca tgg tta tct agc 193
  Trp Asp Ala Ala Leu Ala Lys Asp Lys Met Asp Ala Trp Leu Ser Ser
    50             55             60

tct aaa gca aat caa att gaa gtg atc atc gct aac aac gat ggt atg 241
  Ser Lys Ala Asn Gln Ile Glu Val Ile Ile Ala Asn Asn Asp Gly Met
    65             70             75

gcg atg ggg gca ttg gaa gcc acg aaa gca cat ggt aaa aaa tta cca 289
  Ala Met Gly Ala Leu Glu Ala Thr Lys Ala His Gly Lys Lys Leu Pro
    85             90             95

atc ttc ngg gta nat gcg tta cca gaa gtc ctc caa tta atc aaa aaa 337
  Ile Phe Xaa Val Xaa Ala Leu Pro Glu Val Leu Gln Leu Ile Lys Lys
    100            105            110

ggt gaa att gca ggt acg gtg tta aat gac ggt gtg aac caa ggt aaa 385
  Gly Glu Ile Ala Gly Thr Val Leu Asn Asp Gly Val Asn Gln Gly Lys
    115            120            125

gcc gtt gtt caa tta agt aat aat ctt gca aaa gga aaa cct gcc act 433
  Ala Val Val Gln Leu Ser Asn Asn Leu Ala Lys Gly Lys Pro Ala Thr
    130            135            140

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145          150          155          160

tgt tgg tgt gga tgc gga taacttaaac gagttcctaa aataataaac 529
Cys Trp Cys Gly Cys Gly
165

tataacaaaa caagamgttg taattctcgg ggaggtatag cctccccctt tttatgtgag 589

gttggatag acaactcaaa ttccaaatca agacagtgaa atactgtca caatgaccaa 649

cgtctgtaaa tcccttcccg gtgttaaagc gttagacaat gcaaacctaa ctgtgcgctc 709

gcattctgtc catgccttaa tgggcgaaaa tggggcgggc aaatcgacct tattaaaatg 769

cttatttggt atttacgta aagatgaagg tgacatcctt ttcttaggca agccagtcga 829

ctttaaacy tcgaagaag ccttagagaa cgggattttc atggtgcacc aagaacttaa 889

cttgggtaaa caatgtactg taatggataa tccctttgnt aggacgttat ccattaaaag 949

caggctttgt cgtacacggc aaaaatgtatc gtgataccaa agcagatttt tgaagaanta 1009

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gtatcgacat tggtcgaaa tatgaaattt atcagctgat tatggagtta gccaaaaaag 1969

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 <213> Pasteurella multocida

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Gly His Pro Asp Ala Glu Ala Arg Thr Lys Phe Val Ile Lys Glu Leu
 20             25             30

Xaa Asn Lys Gly Ile Gln Asp Glu Gln Leu Phe Ile Asp Thr Gly Met
 35             40             45

Trp Asp Ala Ala Leu Ala Lys Asp Lys Met Asp Ala Trp Leu Ser Ser
 50             55             60

Ser Lys Ala Asn Gln Ile Glu Val Ile Ile Ala Asn Asn Asp Gly Met
 65             70             75             80

Ala Met Gly Ala Leu Glu Ala Thr Lys Ala His Gly Lys Lys Leu Pro
 85             90             95

Ile Phe Xaa Val Xaa Ala Leu Pro Glu Val Leu Gln Leu Ile Lys Lys
100             105             110

Gly Glu Ile Ala Gly Thr Val Leu Asn Asp Gly Val Asn Gln Gly Lys
115             120             125

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

Glu Gly Thr Lys Trp Gln Leu Lys Arg Ser Cys Pro Thr Tyr Pro Leu
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Cys Trp Cys Gly Cys Gly
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<210> 39
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<213> Pasteurella multocida

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<220>
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tcaattggaa attgatgaat taaaagaaaa aaataaccaa tctcaacaag caaatgacgc 180
attacgcagt gaaaatgaac aactaaagag tgagcaccac aactggcaag aacgtttacg 240
ctcattatta ggcaaaattg ataacgtata attcacttct tattaaggct tagtttttct 300
aagccttatt ttttaggaga aatta atg aaa aca aaa att tgt att atc act 352
Met Lys Thr Lys Ile Cys Ile Ile Thr
1 5
ggc agt acg ctt ggt ggt gca gaa tat gtt gca gaa cat att gct gaa 400
Gly Ser Thr Leu Gly Gly Ala Glu Tyr Val Ala Glu His Ile Ala Glu
10 15 20 25
ata tta gaa caa caa gat tat cct gta cgt tta gaa cat gga cca aat 448
Ile Leu Glu Gln Gln Asp Tyr Pro Val Arg Leu Glu His Gly Pro Asn
30 35 40
ttt gaa gaa gtg atc gat gaa aaa tgt tgg ctt gtt gtc acc tct acc 496
Phe Glu Glu Val Ile Asp Glu Lys Cys Trp Leu Val Val Thr Ser Thr
45 50 55
cat ggt gca ggt gaa tta ccg gat aat att aaa cct ctg ttt gaa aaa 544
His Gly Ala Gly Glu Leu Pro Asp Asn Ile Lys Pro Leu Phe Glu Lys
60 65 70
tta gca ttt cac cca aaa cag tta gct gac tta cgc ttt gcg gtg atc 592
Leu Ala Phe His Pro Lys Gln Leu Ala Asp Leu Arg Phe Ala Val Ile
75 80 85
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Gly Leu Gly Asn Ser Asp Tyr Asp Thr Phe Cys His Ala Val Asp His
90 95 100 105
gtg gaa caa tta ctg cta agc aaa gat gct tta caa ctg tgt gaa tcg 688
Val Glu Gln Leu Leu Leu Ser Lys Asp Ala Leu Gln Leu Cys Glu Ser
110 115 120
cta aga atg gat atg cta acc att act gat cct gaa cac acg gcc gaa 736
Leu Arg Met Asp Met Leu Thr Ile Thr Asp Pro Glu His Thr Ala Glu
125 130 135
caa tgg ctc cca caa ttt ctc agt caa tta taatatttat tccctataca 786
Gln Trp Leu Pro Gln Phe Leu Ser Gln Leu
140 145
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 <213> Pasteurella multocida

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 20 25 30
 Pro Val Arg Leu Glu His Gly Pro Asn Phe Glu Glu Val Ile Asp Glu
 35 40 45

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Lys Cys Trp Leu Val Val Thr Ser Thr His Gly Ala Gly Glu Leu Pro
 50 55 60
 Asp Asn Ile Lys Pro Leu Phe Glu Lys Leu Ala Phe His Pro Lys Gln
 65 70 75 80
 Leu Ala Asp Leu Arg Phe Ala Val Ile Gly Leu Gly Asn Ser Asp Tyr
 85 90 95
 Asp Thr Phe Cys His Ala Val Asp His Val Glu Gln Leu Leu Leu Ser
 100 105 110
 Lys Asp Ala Leu Gln Leu Cys Glu Ser Leu Arg Met Asp Met Leu Thr
 115 120 125
 Ile Thr Asp Pro Glu His Thr Ala Glu Gln Trp Leu Pro Gln Phe Leu
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 Ser Gln Leu
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<210> 41
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Met Leu Phe Lys Lys Ile Arg Gly Leu Phe
1 5 10
tca aat gat ctg tcc atc gat ctt ggc aca gcg aat acc tta att tat 3280
Ser Asn Asp Leu Ser Ile Asp Leu Gly Thr Ala Asn Thr Leu Ile Tyr
15 20 25
gtc aaa gga caa ggg att gtt tta gat gaa cct tct gtt gtg gcg att 3328
Val Lys Gly Gln Gly Ile Val Leu Asp Glu Pro Ser Val Val Ala Ile
30 35 40
cgc caa gaa cgt tca ggt gca tta aaa agc att gct gcg gtt ggt cgt 3376
Arg Gln Glu Arg Ser Gly Ala Leu Lys Ser Ile Ala Ala Val Gly Arg
45 50 55
gat gcc aaa tta atg tta ggc cgt aca ccg aaa agc att gca gcg att 3424
Asp Ala Lys Leu Met Leu Gly Arg Thr Pro Lys Ser Ile Ala Ala Ile
60 65 70
cgt cct atg aaa gat ggg gtg atc gca gat ttc ttt gtg aca gaa aaa 3472
Arg Pro Met Lys Asp Gly Val Ile Ala Asp Phe Phe Val Thr Glu Lys
75 80 85 90
atg ttg caa tat ttt att aaa caa gtg cac agc agc aat ttt atg cgt 3520
Met Leu Gln Tyr Phe Ile Lys Gln Val His Ser Ser Asn Phe Met Arg
95 100 105
cca agt cca cgt gtc tta gtt tgt gta cct gcg gga gct acg caa gtc 3568
Pro Ser Pro Arg Val Leu Val Cys Val Pro Ala Gly Ala Thr Gln Val
110 115 120
gaa cga cgt gca atc aaa gaa tct gcc att ggt gct ggg gca cgc gag 3616
Glu Arg Arg Ala Ile Lys Glu Ser Ala Ile Gly Ala Gly Ala Arg Glu
125 130 135
gtg tac ttg att gag gaa ccg atg gcg gca gcg att ggt gct aaa tta 3664
Val Tyr Leu Ile Glu Glu Pro Met Ala Ala Ala Ile Gly Ala Lys Leu
140 145 150
cct gtt tcg act gcc aca ggt tcg atg gtg atc gat atc ggt ggt ggt 3712
Pro Val Ser Thr Ala Thr Gly Ser Met Val Ile Asp Ile Gly Gly Gly
155 160 165 170
acg acg gaa gtt gcg gtg att tct tta aat ggc att gtg tat tcc tct 3760
Thr Thr Glu Val Ala Val Ile Ser Leu Asn Gly Ile Val Tyr Ser Ser
175 180 185
tca gtc cgc att ggt ggt gat cgt ttt gat gag gcg att att tct tat 3808

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Ser Val Arg Ile Gly Gly Asp Arg Phe Asp Glu Ala Ile Ile Ser Tyr
      190      195      200
gta cgc aag acg ttc ggt tca att att ggg gaa ccg aca gca gag cgt 3856
Val Arg Lys Thr Phe Gly Ser Ile Ile Gly Glu Pro Thr Ala Glu Arg
      205      210      215
atc aaa caa gag att ggt agt gcg ttt att caa gaa ggc gat gaa gtc 3904
Ile Lys Gln Glu Ile Gly Ser Ala Phe Ile Gln Glu Gly Asp Glu Val
      220      225      230
cgt gaa att gaa gtg cat ggt cat aac tta gca gaa ggt gcg ccg cgt 3952
Arg Glu Ile Glu Val His Gly His Asn Leu Ala Glu Gly Ala Pro Arg
      235      240      245      250
tct ttc aaa ctc acc tca cgt gat gtg tta gaa gct att caa gcc ccg 4000
Ser Phe Lys Leu Thr Ser Arg Asp Val Leu Glu Ala Ile Gln Ala Pro
      255      260      265
tta aat ggc att gtt gcg gca gtg cgc acg gcc ttg gaa gag tgt caa 4048
Leu Asn Gly Ile Val Ala Ala Val Arg Thr Ala Leu Glu Glu Cys Gln
      270      275      280
cca gaa cat gct gcg gat att ttt gaa cgt ggc atg gtc tta act ggt 4096
Pro Glu His Ala Ala Asp Ile Phe Glu Arg Gly Met Val Leu Thr Gly
      285      290      295
ggc ggt gcc ctt att cgt aat att gat gtt tta ctg tca aaa gaa acc 4144
Gly Gly Ala Leu Ile Arg Asn Ile Asp Val Leu Leu Ser Lys Glu Thr
      300      305      310
ggg gtg ccg gtt atc atc gcc gat gat cct tta acc tgt gtt gcc cgt 4192
Gly Val Pro Val Ile Ile Ala Asp Asp Pro Leu Thr Cys Val Ala Arg
      315      320      325      330
ggg ggt gcc gag gca tta gag atg atc gat atg cac ggt ggt gat att 4240
Gly Gly Gly Glu Ala Leu Glu Met Ile Asp Met His Gly Gly Asp Ile
      335      340      345
ttt agt gac gat atc taatatgatt taaaagtgcg gtgatattag accgcacttt 4295
Phe Ser Asp Asp Ile
      350
tacttctctt ttattgctga caaggctagc ctaattcgta tatgaaacct atttttgaa 4355
aagcacctcc tttaggtctt cgettaattc tggcgatttt agcatccatt gcattgattg 4415
tttcggacgg tcaatccaat gcgatgatta aagcacgcag tattatggaa accgcagtag 4475
gcgggctgta ttatcttgcc aatacacgga gaacggtatt ggatgggggt tcagataatt 4535
tgggtgatac caataaattg caaattgaaa accgagtttt gcgtgatcaa ctgcgtgaaa 4595
aaaatgcaga ttattgttg ttagatcaac tcaaatgaga aaatcaacgc ctgcgcttat 4655
tgcttaattc cctctacgt acagatgagt ataaaaaat tgctgaagtt ttaacggcag 4715
aaactgatgt gtatcgtaag caagtcgtga ttaaccaagg acaacgtgac ggtgcttatg 4775
tcgggcagcc gattattgat gaaaaggata ttgttgggca acttatctcc gttggtgaaa 4835
atcagagtcg cgtctctcta ttgacagatg tgaetcatc tattccagta caagtactac 4895

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gtaatgatgt cggtttgatt gctagtggaa caggacggaa tgatgaactg agtttagatc 4955
 atgtgccgcg ttcgggtogat attgtcaaaag gggatttatt agtoacttct ggattagggtg 5015
 ggcggttttt agaaggttat cctgttgcca ttgtggaatc cgtatcacgt gatgggcaaa 5075
 attattttgc tactgtaaca gcaaagccat tagcttcgat tgaacgttta cgctatgttt 5135
 tgcttttatg gccgaagaat gaagagatgc gcaaagtcca gtctatttca cctgca 5191

<210> 42
 <211> 351
 <212> PRT
 <213> Pasteurella multocida

<400> 42
 Met Leu Phe Lys Lys Ile Arg Gly Leu Phe Ser Asn Asp Leu Ser Ile
 1 5 10 15
 Asp Leu Gly Thr Ala Asn Thr Leu Ile Tyr Val Lys Gly Gln Gly Ile
 20 25 30
 Val Leu Asp Glu Pro Ser Val Val Ala Ile Arg Gln Glu Arg Ser Gly
 35 40 45
 Ala Leu Lys Ser Ile Ala Ala Val Gly Arg Asp Ala Lys Leu Met Leu
 50 55 60
 Gly Arg Thr Pro Lys Ser Ile Ala Ala Ile Arg Pro Met Lys Asp Gly
 65 70 75 80
 Val Ile Ala Asp Phe Phe Val Thr Glu Lys Met Leu Gln Tyr Phe Ile
 85 90 95
 Lys Gln Val His Ser Ser Asn Phe Met Arg Pro Ser Pro Arg Val Leu
 100 105 110
 Val Cys Val Pro Ala Gly Ala Thr Gln Val Glu Arg Arg Ala Ile Lys
 115 120 125
 Glu Ser Ala Ile Gly Ala Gly Ala Arg Glu Val Tyr Leu Ile Glu Glu
 130 135 140
 Pro Met Ala Ala Ala Ile Gly Ala Lys Leu Pro Val Ser Thr Ala Thr
 145 150 155 160
 Gly Ser Met Val Ile Asp Ile Gly Gly Thr Thr Glu Val Ala Val
 165 170 175
 Ile Ser Leu Asn Gly Ile Val Tyr Ser Ser Ser Val Arg Ile Gly Gly
 180 185 190
 Asp Arg Phe Asp Glu Ala Ile Ile Ser Tyr Val Arg Lys Thr Phe Gly
 195 200 205
 Ser Ile Ile Gly Glu Pro Thr Ala Glu Arg Ile Lys Gln Glu Ile Gly
 210 215 220
 Ser Ala Phe Ile Gln Glu Gly Asp Glu Val Arg Glu Ile Glu Val His
 225 230 235 240
 Gly His Asn Leu Ala Glu Gly Ala Pro Arg Ser Phe Lys Leu Thr Ser

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                245                250                255
Arg Asp Val Leu Glu Ala Ile Gln Ala Pro Leu Asn Gly Ile Val Ala
      260                265                270
Ala Val Arg Thr Ala Leu Glu Glu Cys Gln Pro Glu His Ala Ala Asp
      275                280                285
Ile Phe Glu Arg Gly Met Val Leu Thr Gly Gly Gly Ala Leu Ile Arg
      290                295                300
Asn Ile Asp Val Leu Leu Ser Lys Glu Thr Gly Val Pro Val Ile Ile
      305                310                315                320
Ala Asp Asp Pro Leu Thr Cys Val Ala Arg Gly Gly Gly Glu Ala Leu
      325                330                335
Glu Met Ile Asp Met His Gly Gly Asp Ile Phe Ser Asp Asp Ile
      340                345                350

<210> 43
<211> 2172
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (1)..(1464)

<220>
<223> pnp

<400> 43
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Thr Arg Val Gly Ile Gly Trp His Leu Asn Pro Asn Thr Ala Leu Ile
      1                5                10                15

gaa aaa gtg aaa gcg att gca gaa gcg cgt tta gcc gaa gca tac cgt 96
Glu Lys Val Lys Ala Ile Ala Glu Ala Arg Leu Gly Glu Ala Tyr Arg
      20                25                30

atc act gaa aac aag cac gtt atg aac aaa att gat gcg att aaa gct 144
Ile Thr Glu Asn Lys His Val Met Asn Lys Ile Asp Ala Ile Lys Ala
      35                40                45

gat gtg att gca caa atc aca gct gaa gta gca gaa gcc gaa gac atc 192
Asp Val Ile Ala Gln Ile Thr Ala Glu Val Ala Glu Gly Glu Asp Ile
      50                55                60

agt gaa ggg aaa att gtc gat att ttc acc gca ctt gaa agc caa atc 240
Ser Glu Gly Lys Ile Val Asp Ile Phe Thr Ala Leu Glu Ser Gln Ile
      65                70                75                80

gta cgt agc cgt atc att gct ggt gaa cca cgt att gat ggt cgt aca 288
Val Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile Asp Gly Arg Thr
      85                90                95

gtg gat act gtt cgt gca tta gat att tgt act ggt gtt tta cca cgt 336
Val Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Gly Val Leu Pro Arg
      100                105                110

aca cac ggt tct gcg att ttc acc cgt ggt gaa aca cag gcg tta gct 384

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Thr His Gly Ser Ala Ile Phe Thr Arg Gly Glu Thr Gln Ala Leu Ala
115                               120                               125

gtc gcg aca tta ggt aca gaa cgt gat gca caa att att gat gaa tta 432
Val Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile Ile Asp Glu Leu
130                               135                               140

aca ggt gag cgt tca gat cac ttc tta ttc cac tac aac ttc ccg cca 480
Thr Gly Glu Arg Ser Asp His Phe Leu Phe His Tyr Asn Phe Pro Pro
145                               150                               155                               160

tat tct gtg ggt gaa acc ggt atg att ggt tca cca aaa cgt cgt gaa 528
Tyr Ser Val Gly Glu Thr Gly Met Ile Gly Ser Pro Lys Arg Arg Glu
165                               170                               175

att ggt cat ggt cgt tta gcg aaa cgc ggt gta gct gca gtg atg cca 576
Ile Gly His Gly Arg Leu Ala Lys Arg Gly Val Ala Ala Val Met Pro
180                               185                               190

aca ctt gcc gag ttc ccg tat gtg gta cgt gtt gtc tct gaa atc aca 624
Thr Leu Ala Glu Phe Pro Tyr Val Val Arg Val Val Ser Glu Ile Thr
195                               200                               205

gaa tca aat ggt tct tct tct atg gca tcg gtt tgt ggt gcg tct tta 672
Glu Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys Gly Ala Ser Leu
210                               215                               220

gca tta atg gat gcg ggt gta cca att aaa gcg gcg gtt gca ggt att 720
Ala Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala Val Ala Gly Ile
225                               230                               235                               240

gca atg gcc tta gtc aaa gaa gac gaa aaa ttt gtg gtg ctt tca gac 768
Ala Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val Val Leu Ser Asp
245                               250                               255

atc tta ggt gat gaa gat cac tta ggt gac atg gac ttc aaa gtc gcg 816
Ile Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp Phe Lys Val Ala
260                               265                               270

ggt aca cgt acg ggt gtg acg gca tta caa atg gat atc aaa atc gaa 864
Gly Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp Ile Lys Ile Glu
275                               280                               285

ggt atc aca gca gaa atc atg caa att gcg tta aac caa gcg aaa agc 912
Gly Ile Thr Ala Glu Ile Met Gln Ile Ala Leu Asn Gln Ala Lys Ser
290                               295                               300

gca cgt tta cac att tta ggt gtg atg gag caa gcg atc cca gcg cca 960
Ala Arg Leu His Ile Leu Gly Val Met Glu Gln Ala Ile Pro Ala Pro
305                               310                               315                               320

cgt gcg gat att tct gat ttt gca ccg cgt att tac act atg aaa att 1008
Arg Ala Asp Ile Ser Asp Phe Ala Pro Arg Ile Tyr Thr Met Lys Ile
325                               330                               335

gat ccg aag aaa atc aaa gat gtg atc ggt aaa ggt ggt gca acc att 1056
Asp Pro Lys Lys Ile Lys Asp Val Ile Gly Lys Gly Gly Ala Thr Ile
340                               345                               350

cgt gcc tta aca gaa gaa aca ggt acc tca att gat atc gat gat gat 1104
Arg Ala Leu Thr Glu Glu Thr Gly Thr Ser Ile Asp Ile Asp Asp Asp
355                               360                               365

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ggg acg gtg aag att gct gcg gtt gat ggc aat tca gca aaa gag gtg 1152
Gly Thr Val Lys Ile Ala Ala Val Asp Gly Asn Ser Ala Lys Glu Val
370 375 380

atg gcg cgt att gaa gat att act gca gaa gtt gaa gcg ggt gca gtg 1200
Met Ala Arg Ile Glu Asp Ile Thr Ala Glu Val Glu Ala Gly Ala Val
385 390 395 400

tat aaa ggt aaa gtt act cgt tta gct gat ttt ggt gcc ttc gtt tct 1248
Tyr Lys Gly Lys Val Thr Arg Leu Ala Asp Phe Gly Ala Phe Val Ser
405 410 415

atc gta ggt aac aaa gaa ggc tta gtg cat att tct caa atc gcg gaa 1296
Ile Val Gly Asn Lys Glu Gly Leu Val His Ile Ser Gln Ile Ala Glu
420 425 430

gag cgt gtt gag aaa gtg agt gat tat ctt gca gtg ggg caa gaa gtg 1344
Glu Arg Val Glu Lys Val Ser Asp Tyr Leu Ala Val Gly Gln Glu Val
435 440 445

act gtt aaa gtg gtt gag att gat cgt caa ggt cgt att cgt tta acc 1392
Thr Val Lys Val Val Glu Ile Asp Arg Gln Gly Arg Ile Arg Leu Thr
450 455 460

atg aaa gaa gtt gca cca aag caa gaa cac gtt gat tct gtt gtc gca 1440
Met Lys Glu Val Val Ala Pro Lys Gln Glu His Val Asp Ser Val Val Ala
465 470 475 480

gac gtt gcc gca gaa gaa aac gca taagcaataa acaccaacgc ccttcgtgat 1494
Asp Val Ala Ala Glu Glu Asn Ala
485

aaagggcggtt ggtgtgcatg ttgataagta caatttgtgc tttaaggcga agcgaaatga 1554
agcaatttca tccgtgggta aagtgcctgc taattttccc attttgggta tgttgtttaa 1614
cagcttggtt taatcatgaa caagtttttc ttccaaaaga gaaattaatg ttagcagagc 1674
aacatcgaa tgatcatctt gagcatgagg tgatggttgc gcaaatagc gaattgttac 1734
ttgttaaagg gttaaaaaaa gaagaacgtg cgattttaca ttttgagcga ggcgtgctgt 1794
acgatagctt aggatgttgg gcattggcgc gttatgattt tgaccaaaaca ttagcgttgt 1854
atccaaagtt ggcagcagcg tttaattatt taggtttata ttatttgta gaggaagatt 1914
acagcgcatc tctagatata tttaattgtt gttttgaact tgatcctcaa tatgagtatg 1974
cattcctaaa tagagggcta aatttttatt acgtcggagc ttatgaatta gctcagcggg 2034
attttttcca atttttcaa gccgataaat cagatccata ccgcacttta tggctttatt 2094
taaatgaatt aaagcataat cctcaggatg cttctasaaa tcttgcctca cgagcaatgg 2154
ggctttctga tgaatatt 2172

<210> 44
<211> 488
<212> PRT
<213> Pasteurella multocida

<400> 44

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Thr Arg Val Gly Ile Gly Trp His Leu Asn Pro Asn Thr Ala Leu Ile
 1           5           10           15
Glu Lys Val Lys Ala Ile Ala Glu Ala Arg Leu Gly Glu Ala Tyr Arg
 20           25           30
Ile Thr Glu Asn Lys His Val Met Asn Lys Ile Asp Ala Ile Lys Ala
 35           40           45
Asp Val Ile Ala Gln Ile Thr Ala Glu Val Ala Glu Gly Glu Asp Ile
 50           55           60
Ser Glu Gly Lys Ile Val Asp Ile Phe Thr Ala Leu Glu Ser Gln Ile
 65           70           75           80
Val Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile Asp Gly Arg Thr
 85           90           95
Val Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Gly Val Leu Pro Arg
100           105           110
Thr His Gly Ser Ala Ile Phe Thr Arg Gly Glu Thr Gln Ala Leu Ala
115           120           125
Val Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile Ile Asp Glu Leu
130           135           140
Thr Gly Glu Arg Ser Asp His Phe Leu Phe His Tyr Asn Phe Pro Pro
145           150           155           160
Tyr Ser Val Gly Glu Thr Gly Met Ile Gly Ser Pro Lys Arg Arg Glu
165           170           175
Ile Gly His Gly Arg Leu Ala Lys Arg Gly Val Ala Ala Val Met Pro
180           185           190
Thr Leu Ala Glu Phe Pro Tyr Val Val Arg Val Val Ser Glu Ile Thr
195           200           205
Glu Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys Gly Ala Ser Leu
210           215           220
Ala Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala Val Ala Gly Ile
225           230           235           240
Ala Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val Val Leu Ser Asp
245           250           255
Ile Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp Phe Lys Val Ala
260           265           270
Gly Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp Ile Lys Ile Glu
275           280           285
Gly Ile Thr Ala Glu Ile Met Gln Ile Ala Leu Asn Gln Ala Lys Ser
290           295           300
Ala Arg Leu His Ile Leu Gly Val Met Glu Gln Ala Ile Pro Ala Pro
305           310           315           320
Arg Ala Asp Ile Ser Asp Phe Ala Pro Arg Ile Tyr Thr Met Lys Ile
325           330           335

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Asp Pro Lys Lys Ile Lys Asp Val Ile Gly Lys Gly Gly Ala Thr Ile
    340                      345                      350
Arg Ala Leu Thr Glu Glu Thr Gly Thr Ser Ile Asp Ile Asp Asp Asp
    355                      360                      365
Gly Thr Val Lys Ile Ala Ala Val Asp Gly Asn Ser Ala Lys Glu Val
    370                      375                      380
Met Ala Arg Ile Glu Asp Ile Thr Ala Glu Val Glu Ala Gly Ala Val
    385                      390                      395                      400
Tyr Lys Gly Lys Val Thr Arg Leu Ala Asp Phe Gly Ala Phe Val Ser
    405                      410                      415
Ile Val Gly Asn Lys Glu Gly Leu Val His Ile Ser Gln Ile Ala Glu
    420                      425                      430
Glu Arg Val Glu Lys Val Ser Asp Tyr Leu Ala Val Gly Gln Glu Val
    435                      440                      445
Thr Val Lys Val Val Glu Ile Asp Arg Gln Gly Arg Ile Arg Leu Thr
    450                      455                      460
Met Lys Glu Val Ala Pro Lys Gln Glu His Val Asp Ser Val Val Ala
    465                      470                      475                      480
Asp Val Ala Ala Glu Glu Asn Ala
    485

<210> 45
<211> 633
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (2)...(631)

<220>
<223> purF

<400> 45
c gat ggg gtt tct gtt tat gct gcc cgt gtt cat atg gga caa cgt tta 49
  Asp Gly Val Ser Val Tyr Ala Ala Arg Val His Met Gly Gln Arg Leu
    1           5           10           15
ggg gaa aaa att gca cgg gaa tgg gcg gat gtg gat gat att gat gtg 97
Gly Glu Lys Ile Ala Arg Glu Trp Ala Asp Val Asp Asp Ile Asp Val
    20           25           30
gtc att cct gtg cct gaa acc tct aac gat att gct tta cgt att gcg 145
Val Ile Pro Val Pro Glu Thr Ser Asn Asp Ile Ala Leu Arg Ile Ala
    35           40           45
cgc gtg tta aat aaa ccg tat cgt caa ggt ttt gtg aaa aat cgc tat 193
Arg Val Leu Asn Lys Pro Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr
    50           55           60
gta gga cgt acg ttt att atg cgg ggg cag gca ttg cga gtc agt tct 241
Val Gly Arg Thr Phe Ile Met Pro Gly Gln Ala Leu Arg Val Ser Ser
    65           70           75           80

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gtt aga cgt aaa ctc aat acc att gct tca gaa ttt aaa gat aag aat 289
Val Arg Arg Lys Leu Asn Thr Ile Ala Ser Glu Phe Lys Asp Lys Asn
85 90 95

gtg tta tta gtt gac gac tcg att gta cgt ggt acc acg tct gaa caa 337
Val Leu Leu Val Asp Asp Ser Ile Val Arg Gly Thr Thr Ser Glu Gln
100 105 110

att gtc gaa atg gcg aga gcg gca ggt gcg aag aaa att tat ttt gcc 385
Ile Val Glu Met Ala Arg Ala Ala Gly Ala Lvs Lys Ile Tyr Phe Ala
115 120 125

tct gct gca cca gaa att cgt tat cca aat gtg tat ggt att gat atg 433
Ser Ala Ala Pro Glu Ile Arg Tyr Pro Asn Val Tyr Gly Ile Asp Met
130 135 140

cca acc aaa aat gaa ttg atc gct tat ggt cgt gat gta gat gaa att 481
Pro Thr Lys Asn Glu Leu Ile Ala Tyr Gly Arg Asp Val Asp Glu Ile
145 150 155

gct aac tta att ggt gtg gat aaa ttg att ttc caa gat ttg gat gcg 529
Ala Asn Leu Ile Gly Val Asp Lys Leu Ile Phe Gln Asp Leu Asp Ala
165 170 175

tta act ggt tct gtg caa caa gaa aat cca agt att caa gac ttt gat 577
Leu Thr Gly Ser Val Gln Gln Glu Asn Pro Ser Ile Gln Asp Phe Asp
180 185 190

tgt tcg gtg ttt aca ggg gtt tat gtg acg ggc gat att aca cct gaa 625
Cys Ser Val Phe Thr Gly Val Tyr Val Thr Gly Asp Ile Thr Pro Glu
195 200 205

tat ctg ga 633
Tyr Leu
210

<210> 46
<211> 210
<212> PRT
<213> Pasteurella multocida

<400> 46
Asp Gly Val Ser Val Tyr Ala Ala Arg Val His Met Gly Gln Arg Leu
1 5 10 15

Gly Glu Lys Ile Ala Arg Glu Trp Ala Asp Val Asp Asp Ile Asp Val
20 25 30

Val Ile Pro Val Pro Glu Thr Ser Asn Asp Ile Ala Leu Arg Ile Ala
35 40 45

Arg Val Leu Asn Lys Pro Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr
50 55 60

Val Gly Arg Thr Phe Ile Met Pro Gly Gln Ala Leu Arg Val Ser Ser
65 70 75 80

Val Arg Arg Lys Leu Asn Thr Ile Ala Ser Glu Phe Lys Asp Lys Asn
85 90 95

Val Leu Leu Val Asp Asp Ser Ile Val Arg Gly Thr Thr Ser Glu Gln
100 105 110

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Ile Val Glu Met Ala Arg Ala Ala Gly Ala Lys Lys Ile Tyr Phe Ala
   115               120               125
Ser Ala Ala Pro Glu Ile Arg Tyr Pro Asn Val Tyr Gly Ile Asp Met
   130               135               140
Pro Thr Lys Asn Glu Leu Ile Ala Tyr Gly Arg Asp Val Asp Glu Ile
   145               150               155
Ala Asn Leu Ile Gly Val Asp Lys Leu Ile Phe Gln Asp Leu Asp Ala
   165               170               175
Leu Thr Gly Ser Val Gln Gln Glu Asn Pro Ser Ile Gln Asp Phe Asp
   180               185               190
Cys Ser Val Phe Thr Gly Val Tyr Val Thr Gly Asp Ile Thr Pro Glu
   195               200               205
Tyr Leu
   210

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<210> 47
<211> 4788
<212> DNA
<213> Pasteurella multocida

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<220>
<221> CDS
<222> (1)...(876)

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<220>
<223> rci

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<220>
<223> Nucleotide at position 3084 is A, T, G, or C.

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<400> 47
gac gag gag aga aaa tta gct gat ttg gca aaa ggt atc gct cca gat   48
Asp Glu Glu Arg Lys Leu Ala Asp Leu Ala Lys Gly Ile Ala Pro Asp
   1               5               10               15
att att ttt aga gat gta ata gaa cgc tat caa aat gaa gtg tct ata   96
Ile Ile Phe Arg Asp Val Ile Glu Arg Tyr Gln Asn Glu Val Ser Ile
   20               25               30
act aaa aaa ggc gcg cga aat gaa att ata aga tta aac cgc ttt tta  144
Thr Lys Lys Gly Ala Arg Asn Glu Ile Ile Arg Leu Asn Arg Phe Leu
   35               40               45
aga tat gat att tct aat ctg tat att cgt gat tta aga aaa gaa gat  192
Arg Tyr Asp Ile Ser Asn Leu Tyr Ile Arg Asp Leu Arg Lys Glu Asp
   50               55               60
ttt gag gag tgg atc aga att cgc cta acc gaa gta tcg gat gct agc  240
Phe Glu Glu Trp Ile Arg Ile Arg Leu Thr Glu Val Ser Asp Ala Ser
   65               70               75
gtt aga cgt gag ctt gtt act ata tcg tca gtg ctg aca aca gca ata  288
Val Arg Arg Glu Leu Val Thr Ile Ser Ser Val Leu Thr Thr Ala Ile
   85               90               95
aat aag tgg gga tat att tca agg cat cca atg act ggt att gaa aaa  336

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Asn Lys Trp Gly Tyr Ile Ser Arg His Pro Met Thr Gly Ile Glu Lys
      100                      105                      110
cca aaa aac tcg gca gaa aga aaa gaa cga tat tca gaa cag gac att 384
Pro Lys Asn Ser Ala Glu Arg Lys Glu Arg Tyr Ser Glu Gln Asp Ile
      115                      120                      125
aaa aca ata tta gaa aca gct aga tat tgt gaa gat aaa cta ccc ata 432
Lys Thr Ile Leu Glu Thr Ala Arg Tyr Cys Glu Asp Lys Leu Pro Ile
      130                      135                      140
aca ctc aaa caa aga gta gca att gca atg tta ttt gct att gaa acc 480
Thr Leu Lys Gln Arg Val Ala Ile Ala Met Leu Phe Ala Ile Glu Thr
      145                      150                      155
gct atg cgt gct ggt gag att gct agt ata aaa tgg gat aat gtt ttt 528
Ala Met Arg Ala Gly Glu Ile Ala Ser Ile Lys Trp Asp Asn Val Phe
      165                      170                      175
ctt gaa aag aga ata gta cat tta cag aca act aaa aac ggg cac tct 576
Leu Glu Lys Arg Ile Val His Leu Pro Thr Thr Lys Asn Gly His Ser
      180                      185                      190
aga gat gtg ccg ctt tcg caa aga gct gtt gcg cta att tta aaa atg 624
Arg Asp Val Pro Leu Ser Gln Arg Ala Val Ala Leu Ile Leu Lys Met
      195                      200                      205
aaa gag gta gaa aat gga gat ctt gtg ttt cag acc acg cct gaa tca 672
Lys Glu Val Glu Asn Gly Asp Leu Val Phe Gln Thr Thr Pro Glu Ser
      210                      215                      220
tta agc acc acg ttt aga gtg tta aag aaa gag tgt gga ctt gaa cat 720
Leu Ser Thr Thr Phe Arg Val Leu Lys Lys Glu Cys Gly Leu Glu His
      225                      230                      235
ctc cat ttt cat gat acg aga agg gaa gcg ttg acg aga tta tct aag 768
Leu His Phe His Asp Thr Arg Arg Glu Ala Leu Thr Arg Leu Ser Lys
      245                      250                      255
aaa gta gat gta atg act cta gcc aaa att agc gga cat aga gat tta 816
Lys Val Asp Val Met Thr Leu Ala Lys Ile Ser Gly His Arg Asp Leu
      260                      265                      270
aga att tta caa aac aca tat tac gca ccg aat atg agt gaa gtg gca 864
Arg Ile Leu Gln Asn Thr Tyr Tyr Ala Pro Asn Met Ser Glu Val Ala
      275                      280                      285
aac ttg ttg gat taattcactc ttcttaaata cgccttttgc cacttgatta 916
Asn Leu Leu Asp
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cagtgcttct ttctgatcaa caaatcttcc gaagttggta ataacaccct gtttcttacc 1336
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gaatcggttg ccagtgtgta acgttaatag ctatgcata aattggacca ttctgattta 3256
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<210> 48
 <211> 292
 <212> PRT
 <213> Pasteurella multocida

<400> 48
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 1 5 10 15

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Ile Ile Phe Arg Asp Val Ile Glu Arg Tyr Gln Asn Glu Val Ser Ile
      20          25          30
Thr Lys Lys Gly Ala Arg Asn Glu Ile Ile Arg Leu Asn Arg Phe Leu
      35          40          45
Arg Tyr Asp Ile Ser Asn Leu Tyr Ile Arg Asp Leu Arg Lys Glu Asp
      50          55          60
Phe Glu Glu Trp Ile Arg Ile Arg Leu Thr Glu Val Ser Asp Ala Ser
      65          70          75          80
Val Arg Arg Glu Leu Val Thr Ile Ser Ser Val Leu Thr Thr Ala Ile
      85          90          95
Asn Lys Trp Gly Tyr Ile Ser Arg His Pro Met Thr Gly Ile Glu Lys
      100         105         110
Pro Lys Asn Ser Ala Glu Arg Lys Glu Arg Tyr Ser Glu Gln Asp Ile
      115         120         125
Lys Thr Ile Leu Glu Thr Ala Arg Tyr Cys Glu Asp Lys Leu Pro Ile
      130         135         140
Thr Leu Lys Gln Arg Val Ala Ile Ala Met Leu Phe Ala Ile Glu Thr
      145         150         155         160
Ala Met Arg Ala Gly Glu Ile Ala Ser Ile Lys Trp Asp Asn Val Phe
      165         170         175
Leu Glu Lys Arg Ile Val His Leu Pro Thr Thr Lys Asn Gly His Ser
      180         185         190
Arg Asp Val Pro Leu Ser Gln Arg Ala Val Ala Leu Ile Leu Lys Met
      195         200         205
Lys Glu Val Glu Asn Gly Asp Leu Val Phe Gln Thr Thr Pro Glu Ser
      210         215         220
Leu Ser Thr Thr Phe Arg Val Leu Lys Lys Glu Cys Gly Leu Glu His
      225         230         235         240
Leu His Phe His Asp Thr Arg Arg Glu Ala Leu Thr Arg Leu Ser Lys
      245         250         255
Lys Val Asp Val Met Thr Leu Ala Lys Ile Ser Gly His Arg Asp Leu
      260         265         270
Arg Ile Leu Gln Asn Thr Tyr Tyr Ala Pro Asn Met Ser Glu Val Ala
      275         280         285
Asn Leu Leu Asp
      290

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<210> 49
<211> 1618
<212> DNA
<213> Pasteurella multocida

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<222> (2)...(1195)

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<220>

<223> sopE

<400> 49

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Gly Asp Leu Cys Leu Lys Ile Ser Thr Trp Cys Gln Ser His Arg Ile
1      5      10     15

aat caa gca att cgc aca att caa agt cta tca acc gca gtc atc ggt 97
Asn Gln Ala Ile Arg Thr Ile Gln Ser Leu Ser Thr Ala Val Ile Gly
20     25     30

att gtc tgt act gca aat gac gca gac aat gaa aca ttc cca ctc aat 145
Ile Val Cys Thr Ala Asn Asp Ala Asp Asn Glu Thr Phe Pro Leu Asn
35     40     45

gaa ccc gtt ctc atc aca aac gtg gca gcg gca att ggc aag gct gga 193
Glu Pro Val Leu Ile Thr Asn Val Ala Ala Ala Ile Gly Lys Ala Gly
50     55     60

aaa caa ggc acg ctt tca cgt gcg ctt gac ggg att tct gat gta gtc 241
Lys Gln Gly Thr Leu Ser Arg Ala Leu Asp Gly Ile Ser Asp Val Val
65     70     75     80

aat tgc aaa gtg att gtt gtg cga gtg caa gaa agt gcg caa gaa gac 289
Asn Cys Lys Val Ile Val Val Arg Val Gln Glu Ser Ala Gln Glu Asp
85     90     95

gaa gaa aca aaa gca agt gaa atg aac acg gca att att ggc aca atc 337
Glu Glu Thr Lys Ala Ser Glu Met Asn Thr Ala Ile Ile Gly Thr Ile
100    105    110

aca gaa gaa ggg cag tac aca ggc ttg aag gcg tta ttg att gcg aaa 385
Thr Glu Glu Gly Gln Tyr Thr Gly Leu Lys Ala Leu Leu Ile Ala Lys
115    120    125

aac aaa ttc ggt atc aaa cca cgt att tta tgt gtg cca aaa ttc gac 433
Asn Lys Phe Gly Ile Lys Pro Arg Ile Leu Cys Val Pro Lys Phe Asp
130    135    140

aca aaa gaa gtc gcc aca gag ctt gca agt atc gcc gcc aaa ctc aac 481
Thr Lys Glu Val Ala Thr Glu Leu Ala Ser Ile Ala Ala Lys Leu Asn
145    150    155    160

gca ttt gct tac att tca tgt caa ggg tgt aaa acg aaa gaa caa gcg 529
Ala Phe Ala Tyr Ile Ser Cys Gln Gly Cys Lys Thr Lys Glu Gln Ala
165    170    175

gtg caa tat aaa cgc aac ttc tca caa cgt gaa gtc atg ctg atc atg 577
Val Gln Tyr Lys Arg Asn Phe Ser Gln Arg Glu Val Met Leu Ile Met
180    185    190

ggc gat ttt ctg tca ttt aat gtc aac aca tca aaa gtt gag att gac 625
Gly Asp Phe Leu Ser Phe Asn Val Asn Thr Ser Lys Val Glu Ile Asp
195    200    205

tat gcc gtc act cgt gcg gcg gca atg cgt gca tat ctt gat aaa gaa 673
Tyr Ala Val Thr Arg Ala Ala Ala Met Arg Ala Tyr Leu Asp Lys Glu
210    215    220

cag ggc tgg cat acg tct att tca aat aaa ggc att aat ggc gtg agc 721
Gln Gly Trp His Thr Ser Ile Ser Asn Lys Gly Ile Asn Gly Val Ser
225    230    235    240

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ggg gtc aca caa cca ctc tat ttt gac att aac gac agc tcg act gat 769
Gly Val Thr Gln Pro Leu Tyr Phe Asp Ile Asn Asp Ser Ser Thr Asp
245 250 255

gtg aac tat ctc aat gaa caa ggc atc acg tgt tgc gtg aat cat aat 817
Val Asn Tyr Leu Asn Glu Gln Gly Ile Thr Cys Cys Val Asn His Asn
260 265 270

ggc ttt cgt ttt tgg ggc tta cgc acg act gca gaa gat cca tta ttc 865
Gly Phe Arg Phe Trp Gly Leu Arg Thr Thr Ala Glu Asp Pro Leu Phe
275 280 285

aag ttt gaa gtg tac acc cgc act gca caa atc tta aaa gat acg att 913
Lys Phe Glu Val Tyr Thr Arg Thr Ala Gln Ile Leu Lys Asp Thr Ile
290 295 300

gca ggg ggc ttt gat tgg gca gtg gat aaa gat att tct gtc acg cta 961
Ala Gly Ala Phe Asp Trp Ala Val Asp Lys Asp Ile Ser Val Thr Leu
305 310 315 320

gtg aaa gat att att gaa gca atc aat gcg aag tgg cgt gat tac acc 1009
Val Lys Asp Ile Ile Glu Ala Ile Asn Ala Lys Trp Arg Asp Tyr Thr
325 330 335

aca aaa ggc tac tta att ggc ggt aaa ggc tgg ctt aat aaa gag ctt 1057
Thr Lys Gly Tyr Leu Ile Gly Gly Lys Ala Trp Leu Asn Lys Glu Leu
340 345 350

aac agt gca acg aat tta aaa gat gcg aag ttg atc tct tat gat 1105
Asn Ser Ala Thr Asn Leu Lys Asp Ala Lys Leu Leu Ile Ser Tyr Asp
355 360 365

tat cac cca gta cca ccg ctc gaa cag cta ggc ttt aat cag tac att 1153
Tyr His Pro Val Pro Pro Leu Glu Gln Leu Gly Phe Asn Gln Tyr Ile
370 375 380

tct gat gaa tac ctt gtt gat ttt tca aat cgt tta gca tcg 1195
Ser Asp Glu Tyr Leu Val Asp Phe Ser Asn Arg Leu Ala Ser
385 390 395

taaggggtag aaaatggctt taccacgcaa acctaaattg atgaatttaa tcatcgacgg 1255

taacaaatat ctggcggaag tcacggaagt gactcaacca aaattagcaa tgaataatga 1315

agaatttcgc gcgggcggtg tgattgggtc ggtggatgtc aatctcgggc ttgaaaagct 1375

cgaagcggaa tttaaagccg gtggctacat ggtcgaatta attaaaaaat tcggcggggtc 1435

aatcaacggc attccattgc gttttcttgg ctcatatcag cgtgatgaca cagaagaagt 1495

cacatctgtt gagcttgtag tgcaaggctg atttactgaa attgacagcg gaaacagcaa 1555

agtggcgcat gacactgaac aaacattcaa agtgccttta acgtattaca aaatcattgt 1615

tga 1618

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<210> 50
<211> 398
<212> PRT
<213> Pasteurella multocida
<400> 50

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Gly Asp Leu Cys Leu Lys Ile Ser Thr Trp Cys Gln Ser His Arg Ile
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 Asn Gln Ala Ile Arg Thr Ile Gln Ser Leu Ser Thr Ala Val Ile Gly
 20 25 30
 Ile Val Cys Thr Ala Asn Asp Ala Asp Asn Glu Thr Phe Pro Leu Asn
 35 40 45
 Glu Pro Val Leu Ile Thr Asn Val Ala Ala Ala Ile Gly Lys Ala Gly
 50 55 60
 Lys Gln Gly Thr Leu Ser Arg Ala Leu Asp Gly Ile Ser Asp Val Val
 65 70 75 80
 Asn Cys Lys Val Ile Val Val Arg Val Gln Glu Ser Ala Gln Glu Asp
 85 90 95
 Glu Glu Thr Lys Ala Ser Glu Met Asn Thr Ala Ile Ile Gly Thr Ile
 100 105 110
 Thr Glu Glu Gly Gln Tyr Thr Gly Leu Lys Ala Leu Leu Ile Ala Lys
 115 120 125
 Asn Lys Phe Gly Ile Lys Pro Arg Ile Leu Cys Val Pro Lys Phe Asp
 130 135 140
 Thr Lys Glu Val Ala Thr Glu Leu Ala Ser Ile Ala Ala Lys Leu Asn
 145 150 155 160
 Ala Phe Ala Tyr Ile Ser Cys Gln Gly Cys Lys Thr Lys Glu Gln Ala
 165 170 175
 Val Gln Tyr Lys Arg Asn Phe Ser Gln Arg Glu Val Met Leu Ile Met
 180 185 190
 Gly Asp Phe Leu Ser Phe Asn Val Asn Thr Ser Lys Val Glu Ile Asp
 195 200 205
 Tyr Ala Val Thr Arg Ala Ala Met Arg Ala Tyr Leu Asp Lys Glu
 210 215 220
 Gln Gly Trp His Thr Ser Ile Ser Asn Lys Gly Ile Asn Gly Val Ser
 225 230 235 240
 Gly Val Thr Gln Pro Leu Tyr Phe Asp Ile Asn Asp Ser Ser Thr Asp
 245 250 255
 Val Asn Tyr Leu Asn Glu Gln Gly Ile Thr Cys Cys Val Asn His Asn
 260 265 270
 Gly Phe Arg Phe Thr Gly Leu Arg Thr Thr Ala Glu Asp Pro Leu Phe
 275 280 285
 Lys Phe Glu Val Tyr Thr Arg Thr Ala Gln Ile Leu Lys Asp Thr Ile
 290 295 300
 Ala Gly Ala Phe Asp Trp Ala Val Asp Lys Asp Ile Ser Val Thr Leu
 305 310 315 320
 Val Lys Asp Ile Ile Glu Ala Ile Asn Ala Lys Trp Arg Asp Tyr Thr
 325 330 335

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Thr Lys Gly Tyr Leu Ile Gly Gly Lys Ala Trp Leu Asn Lys Glu Leu
 340 345 350
 Asn Ser Ala Thr Asn Leu Lys Asp Ala Lys Leu Leu Ile Ser Tyr Asp
 355 360 365
 Tyr His Pro Val Pro Pro Leu Glu Gln Leu Gly Phe Asn Gln Tyr Ile
 370 375 380
 Ser Asp Glu Tyr Leu Val Asp Phe Ser Asn Arg Leu Ala Ser
 385 390 395

<210> 51
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 <212> DNA
 <213> *Pasteurella multocida*

<220>
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 <222> (1)..(351)

<220>
 <223> unknown C1

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 1 5 10 15
 cta att tgt gat gaa gag aag gat tgt gta atg gat aag ttt tat ttc 96
 Leu Ile Cys Asp Glu Glu Lys Asp Cys Val Met Asp Lys Phe Tyr Phe
 20 25 30
 tat ttc ttg gaa aag aaa gag gaa ttt aat ttt caa gat tat tca ttt 144
 Tyr Phe Leu Glu Lys Lys Glu Glu Phe Asn Phe Gln Asp Tyr Ser Phe
 35 40 45
 gaa gaa atg tat ata ttt tca aaa atg gaa cct gtg tat gtt tta tgt 192
 Glu Glu Met Tyr Ile Phe Ser Lys Met Glu Pro Val Tyr Val Leu Cys
 50 55 60
 gat agc tct aat ata cct ttg ttt agg agt aat tgg gaa ttg att atc 240
 Asp Ser Ser Asn Ile Pro Leu Phe Arg Ser Asn Trp Glu Leu Ile Ile
 65 70 75 80
 aat aat ata tat gat gtt gtc tgt tta tct aca aaa gta ttt ttt cta 288
 Asn Asn Ile Tyr Asp Val Val Cys Leu Ser Thr Lys Val Phe Phe Leu
 85 90 95
 gat gat gaa aag tta atg atg gaa tta ttt cct gaa gat aaa gta aga 336
 Asp Asp Glu Lys Leu Met Met Glu Leu Phe Pro Glu Asp Lys Val Arg
 100 105 110
 gtc atc tat aaa aga ta 353
 Val Ile Tyr Lys Arg
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<210> 52
 <211> 117
 <212> PRT
 <213> *Pasteurella multocida*

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<400> 52
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 1 5 10 15
 Leu Ile Cys Asp Glu Glu Lys Asp Cys Val Met Asp Lys Phe Tyr Phe
 20 25 30
 Tyr Phe Leu Glu Lys Lys Glu Glu Phe Asn Phe Gln Asp Tyr Ser Phe
 35 40 45
 Glu Glu Met Tyr Ile Phe Ser Lys Met Glu Pro Val Tyr Val Leu Cys
 50 55 60
 Asp Ser Ser Asn Ile Pro Leu Phe Arg Ser Asn Trp Glu Leu Ile Ile
 65 70 75 80
 Asn Asn Ile Tyr Asp Val Val Cys Leu Ser Thr Lys Val Phe Phe Leu
 85 90 95
 Asp Asp Glu Lys Leu Met Met Glu Leu Phe Pro Glu Asp Lys Val Arg
 100 105 110
 Val Ile Tyr Lys Arg
 115

<210> 53
 <211> 509
 <212> DNA
 <213> *Pasteurella multocida*

<220>
 <221> CDS
 <222> (1)..(507)

<220>
 <223> unknown C2

<400> 53
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 Met Lys Asn Phe Arg Asn Ile Asn Ile Tyr Ser Asp Tyr Gly Lys Val
 1 5 10 15
 gat aag gaa att ata tta gaa ttc gaa aat gaa ttt aat ata aag ctt 96
 Asp Lys Glu Ile Ile Leu Glu Phe Glu Asn Glu Phe Asn Ile Lys Leu
 20 25 30
 cct tct tta tac ata gat tta att acg gcg cat aat gct ccg aag agt 144
 Pro Ser Leu Tyr Ile Asp Leu Ile Thr Ala His Asn Ala Pro Lys Ser
 35 40 45
 gaa gag aat tgc ttt gaa tat tac aat gag cgt aat gag ccc acg ttt 192
 Glu Glu Asn Cys Phe Glu Tyr Tyr Asn Glu Arg Asn Glu Pro Thr Phe
 50 55 60
 tct tcc ttt gga ttt gaa ggg ttt gag aca gag cgg tct agc gcc tct 240
 Ser Ser Phe Gly Phe Glu Gly Phe Glu Thr Glu Arg Ser Ser Ala Ser
 65 70 75 80
 ctt gaa aat ata tat gct cag tat att tat gat gat cca atc tat ggt 288
 Leu Glu Asn Ile Tyr Ala Gln Tyr Ile Tyr Asp Asp Pro Ile Tyr Gly
 85 90 95

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tat gaa cat gtg tat tct ttt ggt agt act ggc gag gga cat ttt atc 336
Tyr Glu His Val Tyr Ser Phe Gly Ser Thr Gly Glu Gly His Phe Ile
      100              105              110

tgt ttt gat tat cgt gat gat cca aaa ggt gat gaa ccc aaa atc tgt 384
Cys Phe Asp Tyr Arg Asp Asp Pro Lys Gly Asp Glu Pro Lys Ile Cys
      115              120              125

atc gtg att cac gat gaa tat gat gaa aaa aca ggg aaa atg cga ctg 432
Ile Val Ile His Asp Glu Tyr Asp Glu Lys Thr Gly Lys Met Arg Leu
      130              135              140

ttt cct ata gca gag aat ttt gaa gcg ttt tta gat agt ttg aaa tca 480
Phe Pro Ile Ala Glu Asn Phe Glu Ala Phe Leu Asp Ser Leu Lys Ser
      145              150              155

ttt gat gaa atg ata gag aag tat tcg ta 509
Phe Asp Glu Met Ile Glu Lys Tyr Ser
      165

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<210> 54
 <211> 169
 <212> PRT
 <213> Pasteurella multocida

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<400> 54
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Asp Lys Glu Ile Ile Leu Glu Phe Glu Asn Glu Phe Asn Ile Lys Leu
  20           25           30

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

Glu Glu Asn Cys Phe Glu Tyr Tyr Asn Glu Arg Asn Glu Pro Thr Phe
  50           55           60

Ser Ser Phe Gly Phe Glu Gly Phe Glu Thr Glu Arg Ser Ser Ala Ser
  65           70           75           80

Leu Glu Asn Ile Tyr Ala Gln Tyr Ile Tyr Asp Asp Pro Ile Tyr Gly
  85           90           95

Tyr Glu His Val Tyr Ser Phe Gly Ser Thr Gly Glu Gly His Phe Ile
  100          105          110

Cys Phe Asp Tyr Arg Asp Asp Pro Lys Gly Asp Glu Pro Lys Ile Cys
  115          120          125

Ile Val Ile His Asp Glu Tyr Asp Glu Lys Thr Gly Lys Met Arg Leu
  130          135          140

Phe Pro Ile Ala Glu Asn Phe Glu Ala Phe Leu Asp Ser Leu Lys Ser
  145          150          155          160

Phe Asp Glu Met Ile Glu Lys Tyr Ser
  165

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<210> 55
 <211> 443

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<212> DNA
<213> Pasteurella multocida

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Leu Lys His Gly Phe Ser Ile Glu Asp Ile Ile Arg Phe Leu Gly Glu
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135                               140                               145
tta cct aca gct aat gag tat gca cgt cgt aaa cct att gtt tgt gaa 3177
Leu Pro Thr Ala Asn Glu Tyr Ala Arg Arg Lys Pro Ile Val Cys Glu
150                               155                               160
gtg caa ggt ggc gtc aat cgt aaa ttt tgg ctt cct gtc agt gaa tcg 3225
Val Gln Gly Gly Val Asn Arg Lys Phe Trp Leu Pro Val Ser Glu Ser
165                               170                               175                               180
tta gtt agt gaa gat aaa ctg aaa aaa gat cga gtt aga ctg gaa tcc 3273
Leu Val Ser Glu Asp Lys Leu Lys Lys Asp Arg Val Arg Leu Glu Ser
185                               190                               195
gat acc agt tat gcg att aaa gaa aaa ggc atc gtg att cct gtg gag 3321
Asp Thr Ser Tyr Ala Ile Lys Glu Lys Gly Ile Val Ile Pro Val Glu
200                               205                               210
cta atg ctt gtt tcg gat tat tct ggt tcg atg aat agt cat tta cag 3369
Leu Met Leu Val Ser Asp Tyr Ser Gly Ser Met Asn Ser His Leu Gln
215                               220                               225
gat aaa aac ggt aga tct cta gga aaa gct aaa att act att tta aga 3417
Asp Lys Asn Gly Arg Ser Leu Gly Lys Ala Lys Ile Thr Ile Leu Arg
230                               235                               240
gaa gtg gtt agt gaa att tcg aaa att tta ttg cca gaa gat gtt agc 3465
Glu Val Val Ser Glu Ile Ser Lys Ile Leu Leu Pro Glu Asp Val Ser
245                               250                               255                               260
gaa ggt gtg agc cct ttc aac cgt att ggc ttt acg act ttt tct ggc 3513
Glu Gly Val Ser Pro Phe Asn Arg Ile Gly Phe Thr Thr Phe Ser Gly
265                               270                               275
ggt gtt aga caa cgg gat gtc act gaa ggc tgt gtg ctt cca tat gaa 3561
Gly Val Arg Gln Arg Asp Val Thr Glu Gly Cys Val Leu Pro Tyr Glu
280                               285                               290
gga aaa ata tca caa act tct cga aaa tta act att cgt tat tgg att 3609
Gly Lys Ile Ser Gln Thr Ser Arg Lys Leu Thr Ile Arg Tyr Trp Ile
295                               300                               305
acg ggt aat aat aca cct tgg aaa ttt aat gct ggg aga tgg gag aga 3657
Thr Gly Asn Asn Thr Pro Trp Lys Phe Asn Ala Gly Arg Trp Glu Arg
310                               315                               320
agt aca gtg tct ttc cag gag cat tat aaa ggc tat tat gac aaa ttc 3705
Ser Thr Val Ser Phe Gln Glu His Tyr Lys Gly Tyr Tyr Asp Lys Phe
325                               330                               335                               340

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cat tct tca act tgt aga ggc tca ggg agc tct aga act tgt caa att 3753
His Ser Ser Thr Cys Arg Gly Ser Gly Ser Ser Arg Thr Cys Gln Ile
345 350 355

gat gca aat cct aag aaa att atg gat tat gca cta aaa att aat gac 3801
Asp Ala Asn Pro Lys Lys Ile Met Asp Tyr Ala Leu Lys Ile Asn Asp
360 365 370

tgg acg aca att aga gaa tta ttt aat act tat ata gat gta agt ggg 3849
Trp Thr Thr Ile Arg Glu Leu Phe Asn Thr Tyr Ile Asp Val Ser Gly
375 380 385

acg att gac caa att tcc cag ttt gat ggt tca aac aga cgt tat gat 3897
Thr Ile Asp Gln Ile Ser Gln Phe Asp Gly Ser Asn Arg Arg Tyr Asp
390 395 400

atg gtg ttt act gat gaa gaa cgg tgt ctt ggc gga aat att ggt aga 3945
Met Val Phe Thr Asp Glu Glu Arg Cys Leu Gly Gly Asn Ile Gly Arg
405 410 415 420

aga aca act cga gct tgg ttt gat caa aaa aat aaa gat att aca aga 3993
Arg Thr Thr Arg Ala Trp Phe Asp Gln Lys Asn Lys Asp Ile Thr Arg
425 430 435

gag ttg aat att gtt cgt cct tct ggt tgg act tct gca tct tgg ggg 4041
Glu Leu Asn Ile Val Arg Pro Ser Gly Trp Thr Ser Ala Ser Ser Gly
440 445 450

ctt ctt gtt gga gct aat atc atg atg gac gag aat aag aat cct gat 4089
Leu Leu Val Gly Ala Asn Ile Met Met Asp Glu Asn Lys Asn Pro Asp
455 460 465

gcg caa cct tgg aaa ctc ggg aca aat att caa cgt gtt atc tta gta 4137
Ala Gln Pro Ser Lys Leu Gly Thr Asn Ile Gln Arg Val Ile Leu Val
470 475 480

tta tct gat ggt gaa gat aac tgg cca act tat agt aca tta acg act 4185
Leu Ser Asp Gly Glu Asp Asn Trp Pro Thr Tyr Ser Thr Leu Thr Thr
485 490 495 500

ctt tta aac aat ggt atg tgt gac aaa att cga gaa caa ttg ggc aag 4233
Leu Leu Asn Asn Gly Met Cys Asp Lys Ile Arg Glu Gln Leu Gly Lys
505 510 515

tta caa gat cca aat tta cga gag tta cca gga aga att gcg ttt gtt 4281
Leu Gln Asp Pro Asn Leu Arg Glu Leu Pro Gly Arg Ile Ala Phe Val
520 525 530

gcg ttt ggc tat agt cca cca gca aac caa gtt gcc gct tgg aaa aaa 4329
Ala Phe Gly Tyr Ser Pro Pro Ala Asn Gln Val Ala Ala Trp Lys Lys
535 540 545

tgt gta ggt gat caa tat tat acg gct tat tgg aaa gaa gag ttg tta 4377
Cys Val Gly Asp Gln Tyr Tyr Thr Ala Tyr Ser Lys Glu Glu Leu Leu
550 555 560

gat agt ttc aaa caa att att gga ttt gaa gaa gag gtg ggg cgt tct 4425
Asp Ser Phe Lys Gln Ile Ile Gly Phe Glu Glu Glu Val Gly Arg Ser
565 570 575 580

tca tct cat aaa ccg aaa ttt taagattgtc caaggataac gctaaaaaat 4476
Ser Ser His Lys Pro Lys Phe
585

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 cgtataaag tagaagcgat ttttcttttg gctgaaaggt ggtgttagcc ttttccggct 4776
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 <213> Pasteurella multocida

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 Ala Phe Pro Leu Leu Val Leu Ile Gly Phe Thr Val Asp Gly Thr Gly
 35 40 45
 Val Val Leu Asp Lys Ala Arg Leu Ala Gln Gly Met Asp Gln Ala Ala

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65          70          75          80
Gly Asp Val Asn Arg Gln Val Val Ser Pro Gln Asp Lys Ala Lys Phe
85          90          95
Gly Gly Asn Glu Phe Met Ala Lys Gln Glu Lys Arg Asn Gln Glu Leu
100         105         110
Ile Gln Gly Ile Ala Lys Leu Tyr Leu Arg Ser Glu Asn Ala Asn Ala
115         120         125
Ser Ser Asp Ala Pro Ile Thr Ile Asp Lys Pro Phe His Tyr Ser Cys
130         135         140
Glu Glu Leu Asp Leu Pro Thr Ala Asn Glu Tyr Ala Arg Arg Lys Pro
145         150         155         160
Ile Val Cys Glu Val Gln Gly Gly Val Asn Arg Lys Phe Trp Leu Pro
165         170         175
Val Ser Glu Ser Leu Val Ser Glu Asp Lys Leu Lys Lys Asp Arg Val
180         185         190
Arg Leu Glu Ser Asp Thr Ser Tyr Ala Ile Lys Glu Lys Gly Ile Val
195         200         205
Ile Pro Val Glu Leu Met Leu Val Ser Asp Tyr Ser Gly Ser Met Asn
210         215         220
Ser His Leu Gln Asp Lys Asn Gly Arg Ser Leu Gly Lys Ala Lys Ile
225         230         235         240
Thr Ile Leu Arg Glu Val Val Ser Glu Ile Ser Lys Ile Leu Leu Pro
245         250         255
Glu Asp Val Ser Glu Gly Val Ser Pro Phe Asn Arg Ile Gly Phe Thr
260         265         270
Thr Phe Ser Gly Gly Val Arg Gln Arg Asp Val Thr Glu Gly Cys Val
275         280         285
Leu Pro Tyr Glu Gly Lys Ile Ser Gln Thr Ser Arg Lys Leu Thr Ile
290         295         300
Arg Tyr Trp Ile Thr Gly Asn Asn Thr Pro Trp Lys Phe Asn Ala Gly
305         310         315         320
Arg Trp Glu Arg Ser Thr Val Ser Phe Gln Glu His Tyr Lys Gly Tyr
325         330         335
Tyr Asp Lys Phe His Ser Ser Thr Cys Arg Gly Ser Gly Ser Ser Arg
340         345         350
Thr Cys Gln Ile Asp Ala Asn Pro Lys Lys Ile Met Asp Tyr Ala Leu
355         360         365
Lys Ile Asn Asp Trp Thr Thr Ile Arg Glu Leu Phe Asn Thr Tyr Ile
370         375         380
Asp Val Ser Gly Thr Ile Asp Gln Ile Ser Gln Phe Asp Gly Ser Asn

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385          390          395          400
Arg Arg Tyr Asp Met Val Phe Thr Asp Glu Glu Arg Cys Leu Gly Gly
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Asn Ile Gly Arg Arg Thr Thr Arg Ala Trp Phe Asp Gln Lys Asn Lys
      420          425          430
Asp Ile Thr Arg Glu Leu Asn Ile Val Arg Pro Ser Gly Trp Thr Ser
      435          440          445
Ala Ser Ser Gly Leu Leu Val Gly Ala Asn Ile Met Met Asp Glu Asn
      450          455          460
Lys Asn Pro Asp Ala Gln Pro Ser Lys Leu Gly Thr Asn Ile Gln Arg
      465          470          475          480
Val Ile Leu Val Leu Ser Asp Gly Glu Asp Asn Trp Pro Thr Tyr Ser
      485          490          495
Thr Leu Thr Thr Leu Leu Asn Asn Gly Met Cys Asp Lys Ile Arg Glu
      500          505          510
Gln Leu Gly Lys Leu Gln Asp Pro Asn Leu Arg Glu Leu Pro Gly Arg
      515          520          525
Ile Ala Phe Val Ala Phe Gly Tyr Ser Pro Pro Ala Asn Gln Val Ala
      530          535          540
Ala Trp Lys Lys Cys Val Gly Asp Gln Tyr Tyr Thr Ala Tyr Ser Lys
      545          550          555          560
Glu Glu Leu Leu Asp Ser Phe Lys Gln Ile Ile Gly Phe Glu Glu Glu
      565          570          575
Val Gly Arg Ser Ser Ser His Lys Pro Lys Phe
      580          585

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<210> 60
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 <212> DNA
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<220>
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 <222> (698)..(1468)

<220>
 <223> unknown D2

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ttattattat caggcctata ttatttatat gcagtaaaaa acgattcaaa ttttgtcata 180
ggtttatcta ttatttttagt ttttattatt gtcattccag ggattttgac aaatgctatt 240
ttgaaagcta aggtgaaaaa aatcatggta gatttaccag gttttattga cttagttgca 300
gtaaatgttc aaacagggat tagtattgat gcggcttttaa aacaagtggc aatcgatttt 360

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aagaactta atccagatct tacctatgtg atgttaagga ttattagaaa atctgaactt 420
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atgtttttgta ctgtttttaca acagagttta aatttttggtt ctccaattta ttctcactta 540
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acattatcag ctaaaatgag tatcccatgt atttttgtta ttatgttccc aataatcatt 660
ttaattctag caccagggtat aatgagggtta ttcccaa atg ttt ttt aaa ttt acc 715
                               Met Phe Phe Lys Phe Thr
                               1       5
aag aaa atc gtt ttt gtt agt tta gct tta tct gtc gtt ggt tgt tct 763
Lys Lys Ile Val Phe Val Ser Leu Ala Leu Ser Val Val Gly Cys Ser
                               10       15       20
acc cat tct cag caa ggc atg aca cag aaa agt atg tca tct gaa aca 811
Thr His Ser Gln Gln Gly Met Thr Gln Lys Ser Met Ser Ser Glu Thr
                               25       30       35
ata acg gca aaa gag act tta tat gaa agt acg caa aat tat tgc gca 859
Ile Thr Ala Lys Glu Thr Leu Tyr Glu Ser Thr Gln Asn Tyr Ser Ala
                               40       45       50
ctc att tca ctg tat cgc gat gtg ttg aaa gcc aaa gaa gat cct tca 907
Leu Ile Ser Leu Tyr Arg Asp Val Leu Lys Ala Lys Glu Asp Pro Ser
                               55       60       65       70
ata cgc tat aaa tta gcg aag aca tac tat cag cga ggt gac agc aaa 955
Ile Arg Tyr Lys Leu Ala Lys Thr Tyr Tyr Gln Arg Gly Asp Ser Lys
                               75       80       85
tct tct tta ctt tat tta acg cca tta ctg aat gat aat acg aag ctt 1003
Ser Ser Leu Leu Tyr Leu Thr Pro Leu Leu Asn Asp Asn Thr Lys Leu
                               90       95       100
gct aca caa gcg aaa ata tta cag ata aaa aat cta att caa tta aat 1051
Ala Thr Gln Ala Lys Ile Leu Gln Ile Lys Asn Leu Ile Gln Leu Asn
                               105       110       115
aat ttc caa gaa gca att tct gtc gca aat gaa ctc tta tta aaa tca 1099
Asn Phe Gln Glu Ala Ile Ser Val Ala Asn Glu Leu Leu Leu Lys Ser
                               120       125       130
cct aat gaa gga gaa gta tat aat tta aga ggt atc gct tat gcg caa 1147
Pro Asn Glu Gly Glu Val Tyr Asn Leu Arg Gly Ile Ala Tyr Ala Gln
                               135       140       145       150
aat ggg aat ttg gtg aat gcc cga aat gat atc aat aaa gca aga gag 1195
Asn Gly Asn Leu Val Asn Ala Arg Asn Asp Ile Asn Lys Ala Arg Glu
                               155       160       165
ttc ttt att aat gat aat gtt gct att aat aat tta gcc atg cta aat 1243
Phe Phe Ile Asn Asp Asn Val Ala Ile Asn Asn Leu Ala Met Leu Asn
                               170       175       180
att att aat ggc gat ttt aat aat gct gtt tct tta ctg ttg cca caa 1291
Ile Ile Asn Gly Asp Phe Asn Asn Ala Val Ser Leu Leu Leu Pro Gln
                               185       190       195
tat tta aat ggc gtt aag aat tct cga ttg att cat aat ctt gtt ttt 1339

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Tyr Leu Asn Gly Val Lys Asn Ser Arg Leu Ile His Asn Leu Val Phe
 200 205 210
 gct tta gtt aaa aat ggt gat ctt gat tat gca aaa gat atc att gtt 1387
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 215 220 225 230
 aaa gag cgt tta aat act tca cca gat gat tta att aat gca ttg aaa 1435
 Lys Glu Arg Leu Asn Thr Ser Pro Asp Asp Leu Ile Asn Ala Leu Lys
 235 240 245
 aaa act aca cat gta tca aaa ggt gta act cgg taacactaag gatttgatat 1488
 Lys Thr Thr His Val Ser Lys Gly Val Thr Arg
 250 255
 gaaaaagttt ctatcaata taaaaggaac ctctcaatt gaatttgctt tgacgatagc 1548
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<211> 257

<212> PRT

<213> Pasteurella multocida

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 35 40 45
 Thr Gln Asn Tyr Ser Ala Leu Ile Ser Leu Tyr Arg Asp Val Leu Lys
 50 55 60
 Ala Lys Glu Asp Pro Ser Ile Arg Tyr Lys Leu Ala Lys Thr Tyr Tyr
 65 70 75 80
 Gln Arg Gly Asp Ser Lys Ser Ser Leu Leu Tyr Leu Thr Pro Leu Leu
 85 90 95
 Asn Asp Asn Thr Lys Leu Ala Thr Gln Ala Lys Ile Leu Gln Ile Lys
 100 105 110
 Asn Leu Ile Gln Leu Asn Asn Phe Gln Glu Ala Ile Ser Val Ala Asn
 115 120 125

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Glu Leu Leu Lys Ser Pro Asn Glu Gly Glu Val Tyr Asn Leu Arg
 130 135 140
 Gly Ile Ala Tyr Ala Gln Asn Gly Asn Leu Val Asn Ala Arg Asn Asp
 145 150 155 160
 Ile Asn Lys Ala Arg Glu Phe Phe Ile Asn Asp Asn Val Ala Ile Asn
 165 170 175
 Asn Leu Ala Met Leu Asn Ile Ile Asn Gly Asp Phe Asn Asn Ala Val
 180 185 190
 Ser Leu Leu Leu Pro Gln Tyr Leu Asn Gly Val Lys Asn Ser Arg Leu
 195 200 205
 Ile His Asn Leu Val Phe Ala Leu Val Lys Asn Gly Asp Leu Asp Tyr
 210 215 220
 Ala Lys Asp Ile Ile Val Lys Glu Arg Leu Asn Thr Ser Pro Asp Asp
 225 230 235 240
 Leu Ile Asn Ala Leu Lys Lys Thr Thr His Val Ser Lys Gly Val Thr
 245 250 255
 Arg

<210> 62
 <211> 1788
 <212> DNA
 <213> Pasteurella multocida

<220>
 <221> CDS
 <222> (1)..(600)

<220>
 <223> unknown K

<400> 62
 gtc aac act ggg cta att cac agt aac ggt aat gcc aag ctc act ttt 48
 Val Asn Thr Gly Leu Ile His Ser Asn Gly Asn Ala Lys Leu Thr Phe
 1 5 10 15
 aaa gat gac acc agt ttt gtg act gaa gga aat aac ttt atc aca gca 96
 Lys Asp Asp Thr Ser Phe Val Thr Glu Gly Asn Asn Phe Ile Thr Ala
 20 25 30
 aaa gac aac tta gaa atc acg gca aaa aat gtt caa att gat caa gcg 144
 Lys Asp Asn Leu Glu Ile Thr Ala Lys Asn Val Gln Ile Asp Gln Ala
 35 40 45
 aaa aat att caa tta aac gcg aat atc acg atc aat acc aag tct ggt 192
 Lys Asn Ile Gln Leu Asn Ala Asn Ile Thr Ile Asn Thr Lys Ser Gly
 50 55 60
 ttt gtg aat tac ggt acc tta gca agt gct caa aat tta acg att aat 240
 Phe Val Asn Tyr Gly Thr Leu Ala Ser Ala Gln Asn Leu Thr Ile Asn
 65 70 75 80
 acc gaa caa ggc agc att tat aac ata ggc ggt atc ttg ggg gcg ggt 288
 Thr Glu Gln Gly Ser Ile Tyr Asn Ile Gly Gly Ile Leu Gly Ala Gly

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      85      90      95
aaa agt ttg aat ctg agc gcg aaa aga gga gaa aac caa gga gga tat 336
Lys Ser Leu Asn Leu Ser Ala Lys Arg Gly Glu Asn Gln Gly Gly Tyr
      100      105      110

ctt att aat caa ggt aag agt cta ctc cat tct gaa ggc gcc atg aac 384
Leu Ile Asn Gln Gly Lys Ser Leu Leu His Ser Glu Gly Ala Met Asn
      115      120      125

ctc aca gcg gat cgc acg gty tac aat tta ggg aat att ttt gct aaa 432
Leu Thr Ala Asp Arg Thr Val Tyr Asn Leu Gly Asn Ile Phe Ala Lys
      130      135      140

ggg gac gcg acg atc aat gca aac gcg tta att aat gat gtt act ctc 480
Gly Asp Ala Thr Ile Asn Ala Asn Ala Leu Ile Asn Asp Val Thr Leu
      145      150      155      160

aca ggt cgt ctt gag tat caa gat ctg aaa aaa gat tat acg cgt tat 528
Thr Gly Arg Leu Glu Tyr Gln Asp Leu Lys Lys Asp Tyr Thr Arg Tyr
      165      170      175

tat cgt atc aat gaa acg gca aaa cat ggt tgg cat aat aac ttc tat 576
Tyr Arg Ile Asn Glu Thr Ala Lys His Gly Trp His Asn Asn Phe Tyr
      180      185      190

gaa tta aac gtc gac aga gtt tct tgatttgtgc atcaattttg taaccacggg 630
Glu Leu Asn Val Asp Arg Val Ser
      195      200

ttaataaaac accagcaatt tcaacgccat tcatggcaga taatgccgct gcgacgatca 690
catcaggacg atccgcggaa gtgacaagta aactccaac gcggaaatgt tccaccatat 750
tggtcaaatt acgtgcacag aaagtgtatg caccgaatgcg acgttcattg atcgcgcttt 810
catgaataat ggcagcacct aaatgtttgg ctaaatcaat ggcacgagtc gcaattaatt 870
ctgcgtccca aggaatacat gccaaagatt taattgggct tttctcaaat aaatgataaa 930
tctcagatac ttgattttgt gtgtgtttga aagaatcaaa aatttctgcc aagtcagggc 990
gagtcagacc agattcatca atcgccgcat taaatttatt gatcacaaca ccaagtaaat 1050
tagggttatt ttgtctgcca aataatgagg ctgcggcttt gatgcgttct ttgagttctg 1110
ccggtgttcc cgtcgccggt gctgcaacaa gaatgatttc cgcatcaagt gcttgagcaa 1170
tttcataggt aatgctattg gcataagaat gcttacgcgt agggattaaa cttccacca 1230
cgacaatttc attgtttttg gcgagttgtt gatgatttcc aacaattttt tctagtacca 1290
catcagattg attttgacg atgagtgtt cagctacact taacataaat ggttcaactg 1350
tttcaatggt ggtactggtg cgaataattg atgttgtgcg atcaatcata tcttcacctg 1410
agttcgcgct agaaattggt ttcataaagc cgactttcgc ccttttttgc tccagtgcac 1470
gtgttaaaac taagctgaca ctggttaagc ctacaccagc actaatcggg ataaggataa 1530
ttgtacgtga cataataaac cctaatttgt tgataattta tacaaaaaga aactgccgat 1590
gaatcggcag ttaattgac tttacgcgat gcaaaggcgc gcggtatctt gtgcaataac 1650

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aagttcttca ttcgttggga tcaccatggc aacaggcgta ttgtctgctg taatcaacccc 1710
 ttcattgacca aagcgagccg ctttgccttt atctgaatcc acctgataac cgaacagttt 1770
 taaatgggtt aaggttga 1788

<210> 63
 <211> 200
 <212> PRT
 <213> Pasteurella multocida

<400> 63
 Val Asn Thr Gly Leu Ile His Ser Asn Gly Asn Ala Lys Leu Thr Phe
 1 5 10 15
 Lys Asp Asp Thr Ser Phe Val Thr Glu Gly Asn Asn Phe Ile Thr Ala
 20 25 30
 Lys Asp Asn Leu Glu Ile Thr Ala Lys Asn Val Gln Ile Asp Gln Ala
 35 40 45
 Lys Asn Ile Gln Leu Asn Ala Asn Ile Thr Ile Asn Thr Lys Ser Gly
 50 55 60
 Phe Val Asn Tyr Gly Thr Leu Ala Ser Ala Gln Asn Leu Thr Ile Asn
 65 70 75 80
 Thr Glu Gln Gly Ser Ile Tyr Asn Ile Gly Gly Ile Leu Gly Ala Gly
 85 90 95
 Lys Ser Leu Asn Leu Ser Ala Lys Arg Gly Glu Asn Gln Gly Gly Tyr
 100 105 110
 Leu Ile Asn Gln Gly Lys Ser Leu Leu His Ser Glu Gly Ala Met Asn
 115 120 125
 Leu Thr Ala Asp Arg Thr Val Tyr Asn Leu Gly Asn Ile Phe Ala Lys
 130 135 140
 Gly Asp Ala Thr Ile Asn Ala Asn Ala Leu Ile Asn Asp Val Thr Leu
 145 150 155 160
 Thr Gly Arg Leu Glu Tyr Gln Asp Leu Lys Lys Asp Tyr Thr Arg Tyr
 165 170 175
 Tyr Arg Ile Asn Glu Thr Ala Lys His Gly Trp His Asn Asn Phe Tyr
 180 185 190
 Glu Leu Asn Val Asp Arg Val Ser
 195 200

<210> 64
 <211> 278
 <212> DNA
 <213> Pasteurella multocida

<220>
 <221> CDS
 <222> (108)..(278)
 <220>

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<400> 66
gtc aac aca tca aaa gtt gag att gac tat gcc gtc act cgt gcg gcg 48
Val Asn Thr Ser Lys Val Glu Ile Asp Tyr Ala Val Thr Arg Ala Ala
      1             5             10             15
gca atg cgt gca tat ctt gat aaa gaa cag gcc tgg cat acg tct att 96

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Ala Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly Trp His Thr Ser Ile
 20 25 30
 tca aat aaa ggc att aat ggc gtg agc ggt gtc aca caa cca ctc tat 144
 Ser Asn Lys Gly Ile Asn Gly Val Ser Gly Val Thr Gln Pro Leu Tyr
 35 40 45
 ttt gac att aac gac agc tcg act gat gtg aac tat ctc aat gaa caa 192
 Phe Asp Ile Asn Asp Ser Ser Thr Asp Val Asn Tyr Leu Asn Glu Gln
 50 55 60
 ggc atc acg tgc tgc gtg aat cat aat ggc ttt cgt ttt tgg ggc tta 240
 Gly Ile Thr Cys Cys Val Asn His Asn Gly Phe Arg Phe Trp Gly Leu
 65 70 75 80
 cgc acg act gca gaa gat cca tta ttc aag ttt gaa gtg tac acc cgc 288
 Arg Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe Glu Val Tyr Thr Arg
 85 90 95
 act gca caa atc tta aaa gat acg att gca ggg gcg ttt gat tgg gca 336
 Thr Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly Ala Phe Asp Trp Ala
 100 105 110
 gtg gat aaa gat att tct gtc acg cta gtg aaa gat att att gaa gca 384
 Val Asp Lys Asp Ile Ser Val Thr Leu Val Lys Asp Ile Ile Glu Ala
 115 120 125
 atc aat gcg aag tgg cgt gat tac acc aca aaa ggc tac tta att ggc 432
 Ile Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys Gly Tyr Leu Ile Gly
 130 135 140
 ggt aaa gcg tgg ctt aat aaa gag ctt aac agt gca acg aat tta aaa 480
 Gly Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser Ala Thr Asn Leu Lys
 145 150 155 160
 gat gcg aag ttg ttg atc tct tat gat tat cac cca gta cca ccg ctc 528
 Asp Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His Pro Val Pro Pro Leu
 165 170 175
 gaa cag cta ggc ttt aat cag tac att tct gat gaa tac ctt gtt gat 576
 Glu Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp Glu Tyr Leu Val Asp
 180 185 190
 ttt tca aat cgt tta gca tcg taaggggtag aaaatggctt taccacgcaa 627
 Phe Ser Asn Arg Leu Ala Ser
 195
 acttaaatg atgaatttaa tcatcgacgg taacaaatat ctccggcgaag tcacggaagt 687
 gactcaacca aaattagcaa tgaatatcga agaatttcgc gcgggcgcta tgattggctc 747
 ggtggatgtc aatctcgggc ttgaaaagct cgaagcggaa tttaaagccg gtggctacat 807
 ggtcgaatta attaaaaaat tcggcgggtc aatcaacggc attccattgc gttttcttgg 867
 ctcatatcag cgtgatgaca cagaagaagt cacatctgtt gagcttctga tgcaaggctc 927
 atttactgaa attgacagcg gaaacagcaa agtggggcgt gacactgaac aaacattcaa 987
 agtgccttta acgtattaca aaatcattgt tga 1020

<210> 67

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<211> 199
 <212> PRT
 <213> *Pasteurella multocida*

<400> 67
 Val Asn Thr Ser Lys Val Glu Ile Asp Tyr Ala Val Thr Arg Ala Ala
 1 5 10 15
 Ala Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly Trp His Thr Ser Ile
 20 25 30
 Ser Asn Lys Gly Ile Asn Gly Val Ser Gly Val Thr Gln Pro Leu Tyr
 35 40 45
 Phe Asp Ile Asn Asp Ser Ser Thr Asp Val Asn Tyr Leu Asn Glu Gln
 50 55 60
 Gly Ile Thr Cys Cys Val Asn His Asn Gly Phe Arg Phe Trp Gly Leu
 65 70 75 80
 Arg Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe Glu Val Tyr Thr Arg
 85 90 95
 Thr Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly Ala Phe Asp Trp Ala
 100 105 110
 Val Asp Lys Asp Ile Ser Val Thr Leu Val Lys Asp Ile Ile Glu Ala
 115 120 125
 Ile Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys Gly Tyr Leu Ile Gly
 130 135 140
 Gly Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser Ala Thr Asn Leu Lys
 145 150 155 160
 Asp Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His Pro Val Pro Pro Leu
 165 170 175
 Glu Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp Glu Tyr Leu Val Asp
 180 185 190
 Phe Ser Asn Arg Leu Ala Ser
 195

<210> 68
 <211> 2584
 <212> DNA
 <213> *Pasteurella multocida*

<220>
 <221> CDS
 <222> (1042)..(2286)

<220>
 <223> xylA

<400> 68
 gtcgaccagc ttagattttg cgacgggggt aatttcttct atcgtttcaa tcattgcgtt 60
 taaccattatt ttatggaatc tctctggacc gatgaccatt gccaatattg aaattcctca 120
 cgcgatggtc tttttggtct ttatttacgt gctgttttagc agtattgtgg catitaaaaa 180

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cggtcgccc ttaattcagc tcaattttgc caatgaacgc ttaaacgcc actaccgtta 240
ttcacttatt cgtctgaag aatatgctga aagcattgct ttttatcgtg gtgaaaaat 300
ggaaaaacgt ctattgacca cacaatttaa tcaggtgatt gataacgttt ggcaagtaat 360
ctaccgcacc ttgaaattat ccggttttaa cttaatcatt acgcagattt cggtggtttt 420
tcgctggtg attcaagtga caggttattt tcgtcgacaa taggtgcata tgagggtgtt 480
agaatagcga tactttctgt tggaaaagta aactctttaa tataaataga aatcgcttga 540
atgattctcg ggcaaaaaat aatgtactca ttgctgatct catactgata atggcggaagt 600
aaatattctt ttacaattat atggttaata tcaggttaata ccgtatagcc atagattcca 660
gttctatttt gttttgctaa ataattgatg agcatttgag gcgcaggtaa atccatatct 720
gcaacagaca ttgaaatcat atccttgccg tatttacgag taattgcaca tttagcacta 780
tgacaatctg atctatcagt aaaaacatca acaaaattat ccgtcataca tgttctccaa 840
tattggattt atataaactt tagaacttga ggtagattgt tggaaattgt aaatctggtt 900
ttctattac gttttttctt ttttgtgata taagccacaa taaccaataa tcttaattgt 960
taagtgaat aacgtaattg atcctcccat tgttttacta aattatgtct ctgaaactta 1020
ttgttcagg agaaatcatt t atg tcc act tac ttc gac aaa att gaa aaa 1071
Met Ser Thr Tyr Phe Asp Lys Ile Glu Lys
1 5 10
gta aat tat gaa ggt gta act tca tct aat ccg ttt gca tat aag cat 1119
Val Asn Tyr Glu Gly Val Thr Ser Ser Asn Pro Phe Ala Tyr Lys His
15 20 25
tat gat gct aat caa gtt att tta ggt aag acg atg gct gaa cac tta 1167
Tyr Asp Ala Asn Gln Val Ile Leu Gly Lys Thr Met Ala Glu His Leu
30 35 40
cgt tta gcc gtc tgt tat tgg cac act ttc tgt tgg aca ggg aat gat 1215
Arg Leu Ala Val Cys Tyr Trp His Thr Phe Cys Trp Thr Gly Asn Asp
45 50 55
atg ttc ggt gtc ggt tct ttc gat cgt tgt tgg cag aag gcg agt gat 1263
Met Phe Gly Val Gly Ser Phe Asp Arg Cys Trp Gln Lys Ala Ser Asp
60 65 70
tca tta gca ggt gca aaa caa aaa gca gat atc gct ttt gaa ttt ttc 1311
Ser Leu Ala Gly Ala Lys Gln Lys Ala Asp Ile Ala Phe Glu Phe Phe
75 80 85 90
agt aaa tta gcc ata cct tat tat tgt ttt cat gat gtt gat gtt gcg 1359
Ser Lys Leu Gly Ile Pro Tyr Tyr Cys Phe His Asp Val Asp Val Ala
95 100 105
cca gaa ggt cat tca ttt aaa gaa tat ttg tgg aac ttt aat aca atg 1407
Pro Glu Gly His Ser Phe Lys Glu Tyr Leu Ser Asn Phe Asn Thr Met
110 115 120
atc gat gtt tta gcg cag aaa caa gaa gaa aca gcc gtc aaa ttg ttg 1455
Ile Asp Val Leu Ala Gln Lys Gln Glu Glu Thr Gly Val Lys Leu Leu
125 130 135

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tgg ggg act gca aat tgt ttt aca cac cct cgt tat atg tct ggt gct 1503
 Trp Gly Thr Ala Asn Cys Phe Thr His Pro Arg Tyr Met Ser Gly Ala
 140 145 150
 gca aca aat cgg aat cca gaa att ttt gct tgg gct gct gca caa gta 1551
 Ala Thr Asn Pro Asn Pro Glu Ile Phe Ala Trp Ala Ala Ala Gln Val
 155 160 165 170
 ttt act gcc atg ggg gca act cag cgt tta ggt ggt gaa aat tat gtt 1599
 Phe Thr Ala Met Gly Ala Thr Gln Arg Leu Gly Gly Glu Asn Tyr Val
 175 180 185
 ttg tgg gga gga cgt gaa gga tat gaa acg tta tta aat acc aat tta 1647
 Leu Trp Gly Gly Arg Glu Gly Tyr Glu Thr Leu Leu Asn Thr Asn Leu
 190 195 200
 aaa cag gag cga gag caa att gga cgt ttc atg caa atg gtg gtt gag 1695
 Lys Gln Glu Arg Glu Gln Ile Gly Arg Phe Met Gln Met Val Val Glu
 205 210 215
 cat aaa tat aaa atc ggt ttt aac ggg act ttg ctg att gaa cca aag 1743
 His Lys Tyr Lys Ile Gly Phe Asn Gly Thr Leu Leu Ile Glu Pro Lys
 220 225 230
 cca caa gag cca acg aaa cat caa tat gac tat gat gtg gcg acc gtt 1791
 Pro Gln Glu Pro Thr Lys His Gln Tyr Asp Tyr Asp Val Ala Thr Val
 235 240 245 250
 tat ggc ttt tta aag cag ttt ggt tta gaa aaa gaa att aaa gtg aat 1839
 Tyr Gly Phe Leu Lys Gln Phe Gly Leu Glu Lys Glu Ile Lys Val Asn
 255 260 265
 att gaa gct aat cac gca aca tta gct gga cac act ttc cag cat gaa 1887
 Ile Glu Ala Asn His Ala Thr Leu Ala Gly His Thr Phe Gln His Glu
 270 275 280
 gtc gcc atg gct aca gcg tta gat att ttt ggt tct att gat gca aat 1935
 Val Ala Met Ala Thr Ala Leu Asp Ile Phe Gly Ser Ile Asp Ala Asn
 285 290 295
 cgt ggt gat cca caa tta ggt tgg gat acc gat caa ttc cct aat agc 1983
 Arg Gly Asp Pro Gln Leu Gly Trp Asp Thr Asp Gln Phe Pro Asn Ser
 300 305 310
 gta gaa gaa aat act ttg gtc ata tat gaa att ctg aaa gca ggg ggc 2031
 Val Glu Glu Asn Thr Leu Val Ile Tyr Glu Ile Leu Lys Ala Gly Gly
 315 320 325 330
 ttt aca acc ggt ggt ttt aat ttt gat gct aaa atc cgt cgg cag agt 2079
 Phe Thr Thr Gly Gly Phe Asn Phe Asp Ala Lys Ile Arg Arg Gln Ser
 335 340 345
 acg gat cct tac gat tta ttt cat gga cat att ggc gcg att gat gta 2127
 Thr Asp Pro Tyr Asp Leu Phe His Gly His Ile Gly Ala Ile Asp Val
 350 355 360
 ctt gcc tta tca cta aaa tgt gcg gcg aaa atg ctt gaa gag caa gct 2175
 Leu Ala Leu Ser Leu Lys Cys Ala Ala Lys Met Leu Glu Glu Gln Ala
 365 370 375
 tta caa aaa gtc gtc aat caa cgt tat gct ggt tgg aca tca tca ctt 2223
 Leu Gln Lys Val Val Asn Gln Arg Tyr Ala Gly Trp Thr Ser Ser Leu
 380 385 390

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ggt caa ctt gtt caa atc cgg tcc tac cac gcg tgt ctg caa tac aga 2271
 Gly Gln Leu Val Gln Ile Arg Ser Tyr His Ala Cys Leu Gln Tyr Arg
 395 400 405 410
 cta aca aaa gtg ctt taaaacgttc cggcttacgc cagacatcta gacgattgaa 2326
 Leu Thr Lys Val Leu
 415
 taatttcaat attgtctccg cagtaattc aaaggctttg tgtatgtgcg aatgatattc 2386
 acaacaaagt tctgcaaaat cttgaattgc gtgaggtaat ttaaagcgt gacataagcg 2446
 tcttgctcgc atgacaccag ctttttcatg tccataatga tgtggcaata tttcttttgg 2506
 tgttaaggct tttctaaat catgacaaat tgcagcaaaa cgtaccgcac ttttgtcaat 2566
 gtccgtgttt tctgtcga 2584

<210> 69
 <211> 415
 <212> PRT
 <213> Pasteurella multocida

<400> 69
 Met Ser Thr Tyr Phe Asp Lys Ile Glu Lys Val Asn Tyr Glu Gly Val
 1 5 10 15
 Thr Ser Ser Asn Pro Phe Ala Tyr Lys His Tyr Asp Ala Asn Gln Val
 20 25 30
 Ile Leu Gly Lys Thr Met Ala Glu His Leu Arg Leu Ala Val Cys Tyr
 35 40 45
 Trp His Thr Phe Cys Trp Thr Gly Asn Asp Met Phe Gly Val Gly Ser
 50 55 60
 Phe Asp Arg Cys Trp Gln Lys Ala Ser Asp Ser Leu Ala Gly Ala Lys
 65 70 75 80
 Gln Lys Ala Asp Ile Ala Phe Glu Phe Phe Ser Lys Leu Gly Ile Pro
 85 90 95
 Tyr Tyr Cys Phe His Asp Val Asp Val Ala Pro Glu Gly His Ser Phe
 100 105 110
 Lys Glu Tyr Leu Ser Asn Phe Asn Thr Met Ile Asp Val Leu Ala Gln
 115 120 125
 Lys Gln Glu Glu Thr Gly Val Lys Leu Leu Trp Gly Thr Ala Asn Cys
 130 135 140
 Phe Thr His Pro Arg Tyr Met Ser Gly Ala Ala Thr Asn Pro Asn Pro
 145 150 155 160
 Glu Ile Phe Ala Trp Ala Ala Ala Gln Val Phe Thr Ala Met Gly Ala
 165 170 175
 Thr Gln Arg Leu Gly Gly Glu Asn Tyr Val Leu Trp Gly Gly Arg Glu
 180 185 190
 Gly Tyr Glu Thr Leu Leu Asn Thr Asn Leu Lys Gln Glu Arg Glu Gln
 195 200 205

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Ile Gly Arg Phe Met Gln Met Val Val Glu His Lys Tyr Lys Ile Gly
210                215                220
Phe Asn Gly Thr Leu Leu Ile Glu Pro Lys Pro Gln Glu Pro Thr Lys
225                230                235                240
His Gln Tyr Asp Tyr Asp Val Ala Thr Val Tyr Gly Phe Leu Lys Gln
245                250                255
Phe Gly Leu Glu Lys Glu Ile Lys Val Asn Ile Glu Ala Asn His Ala
260                265                270
Thr Leu Ala Gly His Thr Phe Gln His Glu Val Ala Met Ala Thr Ala
275                280                285
Leu Asp Ile Phe Gly Ser Ile Asp Ala Asn Arg Gly Asp Pro Gln Leu
290                295                300
Gly Trp Asp Thr Asp Gln Phe Pro Asn Ser Val Glu Glu Asn Thr Leu
305                310                315                320
Val Ile Tyr Glu Ile Leu Lys Ala Gly Gly Phe Thr Thr Gly Gly Phe
325                330                335
Asn Phe Asp Ala Lys Ile Arg Arg Gln Ser Thr Asp Pro Tyr Asp Leu
340                345                350
Phe His Gly His Ile Gly Ala Ile Asp Val Leu Ala Leu Ser Leu Lys
355                360                365
Cys Ala Ala Lys Met Leu Glu Glu Gln Ala Leu Gln Lys Val Val Asn
370                375                380
Gln Arg Tyr Ala Gly Trp Thr Ser Ser Leu Gly Gln Leu Val Gln Ile
385                390                395                400
Arg Ser Tyr His Ala Cys Leu Gln Tyr Arg Leu Thr Lys Val Leu
405                410                415

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<210> 70
<211> 3501
<212> DNA
<213> Pasteurella multocida

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<220>
<221> CDS
<222> (298)..(1905)

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<220>
<223> yabk

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<400> 70
gaattcgaagg aagggggcgt attacaaatt gaaacggctg cacgtgtagc acaacatgat 60
aatgcctgtg cggatcattt ccttgccttt ttacttcate cagaagcaca agggcattta 120
gtcaagaata atgtgatgtt accggtgatt aataccaata ttgaaccgca ctttgatgcc 180
cttagagcca cccaatgaa cgcgaaagtg ctcgatacct caaaagtga tgccgaacaa 240
gtcaaaaaat ggattgctgt ttggcaaacg accctaacc aataattgtt tgtcttg 297

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atg ttt aag cga ttt cgt gca ttc aca tac cgt ccc gcc agt tat ctt 345
Met Phe Lys Arg Phe Arg Ala Phe Thr Tyr Arg Pro Ala Ser Tyr Leu
1 5 10 15

ggc ggg atg ttg gtg att gtt ttt ctg agc gct ttt tat gcg ttc gcc 393
Gly Gly Met Leu Val Ile Val Phe Leu Ser Ala Phe Tyr Ala Phe Ala
20 25 30

tta ggg gcg gtt ttt tcg ctc cct ttt gcg cgc agt tgg aca gcg ttg 441
Leu Gly Ala Val Phe Ser Leu Pro Phe Ala Arg Ser Trp Thr Ala Leu
35 40 45

ttg agt gat cag tat tta caa cao gtg atc atc ttt agc ttt tgg caa 489
Leu Ser Asp Gln Tyr Leu Gln His Val Ile Ile Phe Ser Phe Trp Gln
50 55 60

gcc ttt ctg tcg gcg gta ctt gcg gtc ctc ttt ggt gcc att gta gca 537
Ala Phe Leu Ser Ala Val Leu Ala Val Leu Phe Gly Gly Ile Val Ala
65 70 75 80

cga gcc ttt ttt tat caa ccg ttt gtg ggc aag aaa ctg atc ctc aaa 585
Arg Ala Phe Phe Tyr Gln Pro Phe Val Gly Lys Lys Leu Ile Leu Lys
85 90 95

tta ttt tca ctg act ttt gtg tta cct gcc tta gtg gcg att ttt ggt 633
Leu Phe Ser Leu Thr Phe Val Leu Pro Ala Leu Val Ala Ile Phe Gly
100 105 110

tta tta ggc gtg tat ggc gct tct ggc tgg tta gcg atg tta agc cag 681
Leu Leu Gly Val Tyr Gly Ala Ser Gly Trp Leu Ala Met Leu Ser Gln
115 120 125

ttt ttc gct tgg gat tgg act cct aat att tac ggc tta aca ggt att 729
Phe Phe Ala Trp Asp Trp Thr Pro Asn Ile Tyr Gly Leu Thr Gly Ile
130 135 140

tta ctg gcg cat ctt ttt ttt aat gtc cca tta gct tgt cgc ctg ttt 777
Leu Leu Ala His Leu Phe Phe Asn Val Pro Leu Ala Cys Arg Leu Phe
145 150 155 160

tta caa ggt ttg caa gca att ccg gtg caa caa cgt cag ctc gcg gca 825
Leu Gln Gly Leu Gln Ala Ile Pro Val Gln Gln Arg Gln Leu Ala Ala
165 170 175

caa ctc aat tta cgt ggt tgg cat ttt ata cgt ctg att gag tgg ccc 873
Gln Leu Asn Leu Arg Gly Trp His Phe Ile Arg Leu Ile Gln Trp Pro
180 185 190

tat tta cgc cag caa ttg tta cct gca ttt act ttg att ttc atg ctg 921
Tyr Leu Arg Gln Gln Leu Leu Pro Ala Phe Thr Leu Ile Phe Met Leu
195 200 205

tgt ttt acc agt ttt gcg att gtg ctc act tta ggt gcc gga ccg aaa 969
Cys Phe Thr Ser Phe Ala Ile Val Leu Thr Leu Gly Gly Gly Pro Lys
210 215 220

tat acc acg ttg gaa gtg gct atc tat caa gcg att tta ttt gag ttt 1017
Tyr Thr Thr Leu Glu Val Ala Ile Tyr Gln Ala Ile Leu Phe Gln Phe
225 230 235 240

gat gta ccg aaa gcc gcc tta ttt gcg tta tta caa ttt gtt ttt tgt 1065
Asp Val Pro Lys Ala Gly Leu Phe Ala Leu Leu Gln Phe Val Phe Cys
245 250 255

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ttt ctg tta ttc acg ctg agt agc ttt ttt tct cca gcc ccc gcc acg 1113
Phe Leu Leu Phe Thr Leu Ser Ser Phe Phe Ser Pro Ala Pro Ala Thr
260 265 270

aca tta cac agt caa cct act tgg ttt gcg ccc caa tgg tat tgg gtt 1161
Thr Leu His Ser Gln Pro Thr Trp Phe Ala Pro Gln Ser Tyr Trp Val
275 280 285

aaa tta tgg caa cgt atg atc att gtg tgt gcg aca gta ttt atc tta 1209
Lys Leu Trp Gln Arg Met Ile Ile Val Cys Ala Thr Val Phe Ile Leu
290 295 300

tta cgg cta ctc aat acg cta gtt tct gct ttg ctt tgg tct cag ttt 1257
Leu Pro Leu Leu Asn Thr Leu Val Ser Ala Leu Leu Ser Ser Gln Phe
305 310 315

ttt acc ttg tgg tta caa cct caa tta tgg aaa gca tta ggt tac tgg 1305
Phe Thr Leu Trp Leu Gln Pro Gln Leu Trp Lys Ala Leu Gly Tyr Ser
325 330 335

ctc acc atc gcc ccc act tct gca ttg ctc gct tta gta ctg tct ttt 1353
Leu Thr Ile Ala Pro Thr Ser Ala Leu Leu Ala Leu Val Leu Ser Phe
340 345 350

gcc tta tta ttg ctt gcc aga gaa tta cat tgg cga cat tat cgc agc 1401
Ala Leu Leu Leu Leu Ala Arg Glu Leu His Trp Arg His Tyr Arg Ser
355 360 365

tta tcc cat gtg att tta aat atc ggt gcg acc att tta gcc att cca 1449
Leu Ser His Val Ile Leu Asn Ile Gly Ala Thr Ile Leu Ala Ile Pro
370 375 380

acg tta gtg tta gct att ggt tta ttc att tta tta cgt gag atc gat 1497
Thr Leu Val Leu Ala Ile Gly Leu Phe Ile Leu Leu Arg Glu Ile Asp
385 390 395 400

ttt tct cca tac cat ctt ttt ggg gtt gtg gta tgc tgt aac gcg tta 1545
Phe Ser Pro Tyr His Leu Phe Gly Val Val Cys Cys Asn Ala Leu
405 410 415

gct gct atg cct ttt gtg ttg cgt att ttg gct tta cgg atg cat aac 1593
Ala Ala Met Pro Phe Val Leu Arg Ile Leu Ala Leu Pro Met His Asn
420 425 430

aat atg att tat tat gaa aaa tta tgc caa tca ctt aac ctg cgt ggt 1641
Asn Met Ile Tyr Tyr Glu Lys Leu Cys Gln Ser Leu Asn Leu Arg Gly
435 440 445

tgg caa cgt ttt cga ttg att gaa tgg cac aag ctt cgt gcg cca atg 1689
Trp Gln Arg Phe Arg Leu Ile Glu Trp His Lys Leu Arg Ala Pro Met
450 455 460

aaa tac gcc ttt gca ctg gct tgt gcg tta tca tta ggc gat ttc acc 1737
Lys Tyr Ala Phe Ala Leu Ala Cys Ala Leu Ser Leu Gly Asp Phe Thr
465 470 475 480

gca atc gcg tta ttt ggt cag gct gac ttc aca tgg tta cgg cat ttg 1785
Ala Ile Ala Leu Phe Gly Gln Ala Asp Phe Thr Ser Leu Pro His Leu
485 490 495

ttg tat caa caa ttg ggg cat tat cgt agt cag gaa gcg gca gta aca 1833
Leu Tyr Gln Gln Leu Gly His Tyr Arg Ser Gln Glu Ala Ala Val Thr
500 505 510

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gcg ttg att tta ttg gtt ttt tgg ttg agt gtt ttt atg att att gaa 1881
Ala Phe Ile Leu Leu Val Phe Cys Leu Ser Val Phe Met Ile Ile Glu
515 520 525
cga cat cag gaa cgg cgt gat gat taatttaaac ggtgttcagt ttctctataa 1935
Arg His Gln Glu Pro Arg Asp Asp
530 535
tacctttact tttagctgg atttgcagat tctgtctcaa caaaaagtgg ctattattgg 1995
cgccagtggc gcagggaaga gtaccttatt aaatttgatt ggggttttg cattgccaca 2055
gcaaggggaa atttggttga atggtgaaaa tcatagccaa actcaacctt atgaacgtcc 2115
ggatctctatt ttgtttcaag aaaacaacct gtttacgcat ttgactgtgg cagagaatat 2175
ggcattaggg ctgaaaccaa gccataaact gaccgcactt gaacaacaac gcgtacaaca 2235
agtgccaagt gcagtgggtt tgcagggttt tcttaataca ttaccacccc agttatcggg 2295
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cattttgaag gataatttta acgaaaaaca gaccgcactt taggcggcctt attaataga 2595
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acccgacctt agaattattg tctgtgtgta aaattgaagc cctgtttgag accccttttt 2715
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aattatccac tttaatgtcg attaaaaacg ggggatgtcc agaggattgt ggctactgtc 2835
cgcagtcagc acgttatcat actggagtag aaaagcagca attactcgat gtggaagaaa 2895
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catggcgtgg accgaaaacc aaagacattg aaaaagtta cgcacatcatt aaagcgggtg 3015
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atttaaaaga agcgggtttg gattattata accataatct cgatacagcc ccagaacct 3135
acggtaattg gattggtacc cgtcaattg atgacgtat taatacgtta ggtaaaagtc 3195
gtaaagctgg cttaaaagtg tgctgtggcg ggattattgg catgaatgaa acccgtaaag 3255
aaagagcagg attaatgtct agcttageta atttagaccc gcaacccgaa tcggtgcga 3315
ttaatcaatt agtgaaagtg gaaggtaacc ctttagccga tgcggcagaa ttagactgga 3375
cagaatttgt gcgcactatt gcggtggcgc gtattaccat gccgaaaagc tatgtacgtt 3435
tatcagcagg gcgtcaaggc atgtcggaa gaaatgcaagc catgtgcttt atggctggcg 3495
cgaatt 3501

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<210> 71
 <211> 536
 <212> PRT
 <213> *Pasteurella multocida*

<400> 71
 Met Phe Lys Arg Phe Arg Ala Phe Thr Tyr Arg Pro Ala Ser Tyr Leu
 1 5 10 15
 Gly Gly Met Leu Val Ile Val Phe Leu Ser Ala Phe Tyr Ala Phe Ala
 20 25 30
 Leu Gly Ala Val Phe Ser Leu Pro Phe Ala Arg Ser Trp Thr Ala Leu
 35 40 45
 Leu Ser Asp Gln Tyr Leu Gln His Val Ile Ile Phe Ser Phe Trp Gln
 50 55 60
 Ala Phe Leu Ser Ala Val Leu Ala Val Leu Phe Gly Gly Ile Val Ala
 65 70 75 80
 Arg Ala Phe Phe Tyr Gln Pro Phe Val Gly Lys Lys Leu Ile Leu Lys
 85 90 95
 Leu Phe Ser Leu Thr Phe Val Leu Pro Ala Leu Val Ala Ile Phe Gly
 100 105 110
 Leu Leu Gly Val Tyr Gly Ala Ser Gly Trp Leu Ala Met Leu Ser Gln
 115 120 125
 Phe Phe Ala Trp Asp Trp Thr Pro Asn Ile Tyr Gly Leu Thr Gly Ile
 130 135 140
 Leu Leu Ala His Leu Phe Phe Asn Val Pro Leu Ala Cys Arg Leu Phe
 145 150 155 160
 Leu Gln Gly Leu Gln Ala Ile Pro Val Gln Gln Arg Gln Leu Ala Ala
 165 170 175
 Gln Leu Asn Leu Arg Gly Trp His Phe Ile Arg Leu Ile Glu Trp Pro
 180 185 190
 Tyr Leu Arg Gln Gln Leu Leu Pro Ala Phe Thr Leu Ile Phe Met Leu
 195 200 205
 Cys Phe Thr Ser Phe Ala Ile Val Leu Thr Leu Gly Gly Gly Pro Lys
 210 215 220
 Tyr Thr Thr Leu Glu Val Ala Ile Tyr Gln Ala Ile Leu Phe Glu Phe
 225 230 235 240
 Asp Val Pro Lys Ala Gly Leu Phe Ala Leu Leu Gln Phe Val Phe Cys
 245 250 255
 Phe Leu Leu Phe Thr Leu Ser Ser Phe Phe Ser Pro Ala Pro Ala Thr
 260 265 270
 Thr Leu His Ser Gln Pro Thr Trp Phe Ala Pro Gln Ser Tyr Trp Val
 275 280 285
 Lys Leu Trp Gln Arg Met Ile Ile Val Cys Ala Thr Val Phe Ile Leu
 290 295 300

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Leu Pro Leu Leu Asn Thr Leu Val Ser Ala Leu Leu Ser Ser Gln Phe
305              310              315              320
Phe Thr Leu Trp Leu Gln Pro Gln Leu Trp Lys Ala Leu Gly Tyr Ser
              325              330              335
Leu Thr Ile Ala Pro Thr Ser Ala Leu Leu Ala Leu Val Leu Ser Phe
340              345              350
Ala Leu Leu Leu Leu Ala Arg Glu Leu His Trp Arg His Tyr Arg Ser
355              360              365
Leu Ser His Val Ile Leu Asn Ile Gly Ala Thr Ile Leu Ala Ile Pro
370              375              380
Thr Leu Val Leu Ala Ile Gly Leu Phe Ile Leu Leu Arg Glu Ile Asp
385              390              395
Phe Ser Pro Tyr His Leu Phe Gly Val Val Val Cys Cys Asn Ala Leu
405              410              415
Ala Ala Met Pro Phe Val Leu Arg Ile Leu Ala Leu Pro Met His Asn
420              425              430
Asn Met Ile Tyr Tyr Glu Lys Leu Cys Gln Ser Leu Asn Leu Arg Gly
435              440              445
Trp Gln Arg Phe Arg Leu Ile Glu Trp His Lys Leu Arg Ala Pro Met
450              455              460
Lys Tyr Ala Phe Ala Leu Ala Cys Ala Leu Ser Leu Gly Asp Phe Thr
465              470              475
Ala Ile Ala Leu Phe Gly Gln Ala Asp Phe Thr Ser Leu Pro His Leu
485              490              495
Leu Tyr Gln Gln Leu Gly His Tyr Arg Ser Gln Glu Ala Ala Val Thr
500              505              510
Ala Phe Ile Leu Leu Val Phe Cys Leu Ser Val Phe Met Ile Ile Glu
515              520              525
Arg His Gln Glu Pro Arg Asp Asp
530              535

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<210> 72
<211> 3182
<212> DNA
<213> Pasteurella multocida

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<220>
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<222> (1544)..(2809)

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<220>
<223> ygiK

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<220>
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<222> 452
<223> N = A or T or G or C

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tgcaggagaa aaagtttatg aaatccaaaa agaattggact gacaatttg aaaaagcttc 180
caatgggaga ataagtatag agttattacc tctcgactca gtcttaaat ctagtacat 240
gctttctggt gttegaata aaattattga tggagcgggt gcaacagcgg caatgtatgc 300
aggcactgac cctggattcg gattaattgg tgatactatt tctgcttgg accatgacga 360
agatatttta aatttttact ataattggagg tggttttgaa gttgttgata atattttcca 420
acaatatggt gccaaactca ttggtgtatc anttacggga gcagaatcat taccatcgaa 480
agtaaaaaa gctaactctg aagattttta aggtataaaa attcgggctc cctctggctc 540
tatccaaaaa ttgtttgcaa gattaggagc cgtctctgtt ggtcttctg gttegaatat 600
ctatactagt ttagaaaaag gtattattga tgcctccgat ttctcaacgt ttgcaataa 660
tcaagcacia ggagtccatg atattgcaa atatccaatc tatccgggaa ttctattctc 720
accagccgtt catatgatta tgaatcataa aacttggagt agcttaactc catcgatca 780
agcattctta attgcttact ttaaagggat ggctctcgat actctgactc gtctcatta 840
tgaagataaa ctacatata aagaagcact tgagaaggga gtacaaccag ttctttggaa 900
tcaacagaa attacaaaag ttctgttctat cgctaaagaa atttggcaag agatagctca 960
acaatctgaa ataggtaac aagtattatc aagtattaat gaaattccta gaatctcaag 1020
gaatgctgca ataactgtca agatggataa gacgatctcg tcttatccat taaggagtaa 1080
aacatgctta ttctaaaaa ttattatttg ctctgtaata agctagatca aatattcatt 1140
aaagtagggt attacgtttc ttatattttt ctattagttg ttatcattgg ttttcaggag 1200
ttgttctcg gtatttattc tctagcccaa cactttgggt tcatgaagta acaacatttt 1260
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ccatgacatt tattagacaa aaattaccta ataagatcaa atggttacta gaactcttag 1380
ttgaaatact tatttttatt ttctttattt tgcttagtta cggagcatac ttatcagcta 1440
gagaagcatt atttactcca tcaggaaaat tcaaaatgca aacttctgga agtgtattag 1500
acatgccatt tccagcaatt gaaaaaagtt tcttttttat ttc atg cct cat cat 1555
Met Pro His His
1

tgt tgt tct ttc agt act aca tat att ceg tca cat cta tac aaa ata 1603
Cys Cys Ser Phe Ser Thr Thr Tyr Ile Pro Ser His Leu Tyr Lys Ile
5 10 15 20

tca gga gga att atc atg ata agt gca ttt ggg ata ggt att gga act 1651
Ser Gly Gly Ile Ile Met Ile Ser Ala Phe Gly Ile Gly Ile Gly Thr
25 30 35

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ctt att atc ttt tta atg atg att tcc ctt tta ttt att gga atg cca 1699
 Leu Ile Ile Phe Leu Met Met Ile Ser Leu Leu Phe Ile Gly Met Pro
 40 45 50

tta ggt ttt ctc act ggg tta atc gct tta gtt att tca tat ctt tgg 1747
 Leu Gly Phe Phe Leu Thr Gly Leu Ile Ala Leu Val Ile Ser Tyr Leu Trp
 55 60 65

ttt gat act acc gca ata atg caa atg ata gct tca cgt gtc act gat 1795
 Phe Asp Thr Thr Ala Ile Met Gln Met Ile Ala Ser Arg Val Thr Asp
 70 75 80

ttc aca tca tct tac act ttt gta gct gtg cct atg ttt gtt ctt atg 1843
 Phe Thr Ser Ser Tyr Thr Phe Val Ala Val Pro Met Phe Val Leu Met
 85 90 95 100

gca aca tta ctt gat aag act gga att gct aga gat ctc tac aac gca 1891
 Ala Thr Leu Leu Asp Lys Thr Gly Ile Ala Arg Asp Leu Tyr Asn Ala
 105 110 115

atg cga gtc att ggc ggt cga tta cga ggt gga att gca att caa tcg 1939
 Met Arg Val Ile Gly Gly Arg Leu Arg Gly Gly Ile Ala Ile Gln Ser
 120 125 130

atg ttt gtt gca gtt cta ctt gct acg atg tca ggt att atc ggt gga 1987
 Met Phe Val Ala Val Leu Leu Ala Thr Met Ser Gly Ile Ile Gly Gly
 135 140 145

gaa act gtt tta tta ggc atg ttg gca tta cca caa atg tta cgc tta 2035
 Glu Thr Val Leu Leu Gly Met Leu Ala Leu Pro Gln Met Leu Arg Leu
 150 155 160

ggc tat aat aaa aac tta gct ata gga act gtt gta gca gga gga gca 2083
 Gly Tyr Asn Lys Asn Leu Ala Ile Gly Thr Val Val Ala Gly Gly Ala
 165 170 175 180

ttg ggt aca atg gtt cct cca agt atc gtg ttg att att tac gga atg 2131
 Leu Gly Thr Met Val Pro Pro Ser Ile Val Leu Ile Ile Tyr Gly Met
 185 190 195

acc gca aat gtt tct att gga gaa cta ttt ctt gca gca att cca gcc 2179
 Thr Ala Asn Val Ser Ile Gly Glu Leu Phe Leu Ala Ala Ile Pro Ala
 200 205 210

tcc tta cta ctt tct aca ttc tat att tta tat att cta gta ctt tgc 2227
 Ser Leu Leu Leu Ser Thr Phe Tyr Ile Leu Tyr Ile Leu Val Leu Cys
 215 220 225

tac ttc aaa cct agc tat ggc cct gca atg cct agc tca gaa aat cat 2275
 Tyr Phe Lys Pro Ser Tyr Gly Pro Ala Met Pro Ser Ser Glu Asn His
 230 235 240

aca tta acg aaa gaa gat att aaa aaa att att cat gat att gca att 2323
 Thr Leu Thr Lys Glu Asp Ile Lys Lys Ile Ile His Asp Ile Ala Ile
 245 250 255 260

cca gta gct atc gcc aca tgg att tta gga agt att tat ggc ggg ata 2371
 Pro Val Ala Ile Ala Thr Trp Ile Leu Gly Ser Ile Tyr Gly Gly Ile
 265 270 275

gca tca atc act gaa tct gcc tgt gtt ggt gta gtt ggg gta ata tta 2419
 Ala Ser Ile Thr Glu Ser Ala Cys Val Gly Val Val Gly Val Ile Leu
 280 285 290

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gca gca ttc tat cga aaa gaa tta aat ttc aaa ata gta caa gaa tca 2467
Ala Ala Phe Tyr Arg Lys Glu Leu Asn Phe Lys Ile Val Gln Glu Ser
295 300 305

cta aaa cat aca atc aat act gtt ggt atg ata atc tgg gtc ggc att 2515
Leu Lys His Thr Ile Asn Thr Val Gly Met Ile Ile Trp Val Gly Ile
310 315 320

ggc gca aca atg att ata ggt att tat aat cta atg ggt ggc gac cga 2563
Gly Ala Thr Met Ile Ile Gly Ile Tyr Asn Leu Met Gly Gly Asp Arg
325 330 335 340

ttt ata gct aac tta ttc gct agc tta gat gcc tct cca att tat act 2611
Phe Ile Ala Asn Leu Phe Ala Ser Leu Asp Ala Ser Pro Ile Tyr Thr
345 350 355

atc att att atg atg gtt att tta tta ata ctt ggt atg ttc tta gat 2659
Ile Ile Ile Met Met Val Ile Leu Leu Ile Leu Gly Met Phe Leu Asp
360 365 370

tgg att ggt gtt gcc atg ttg act ttc ctc aag aca agt aaa gcg aca 2707
Trp Ile Gly Val Ala Met Leu Thr Phe Leu Lys Thr Ser Lys Ala Thr
375 380 385

atc aat ttg tgt ttt gac ata gtc agg tac agt att tgg cgt ggt ccc 2755
Ile Asn Leu Cys Phe Asp Ile Val Arg Tyr Ser Ile Trp Arg Gly Pro
390 395 400

tcc ttc cac agt acc aat gtt cat cgt ggt acc ttt gtc ggc cgc ggt 2803
Ser Phe His Ser Thr Asn Val His Arg Gly Thr Phe Val Gly Arg Gly
405 410 415 420

act ttt tagtaaatct tgcgcgatac gaataaacgc attgatggca ttgctccgt 2859
Thr Phe

tttgtggatc gactgcgcga tgagcagatt tgccaaaaaa ttcaattaca tacttcccaa 2919

tcccttttct ttctgttaacg ttccacttta gattgccccag aagccgatct gtctgaatgg 2979

gaacaagtgt tataccaaga agcgaatcca acaggtgaag tggatgatcg tatggtgggt 3039

aaatacactg aattacggga tgcctacaaa tcggttaatg aagccttgaa acacgcaggc 3099

ttaaaaaacc gtcttagcgt gcaaatcaaa tatattgatt cacaagatgt ggaaacccaa 3159

ggcacagaag tgtagaagg cgt 3182

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<212> PRT
<213> Pasteurella multocida

<400> 73
Met Pro His His Cys Ser Phe Ser Thr Thr Tyr Ile Pro Ser His
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Leu Tyr Lys Ile Ser Gly Gly Ile Ile Met Ile Ser Ala Phe Gly Ile
20 25 30

Gly Ile Gly Thr Leu Ile Ile Phe Leu Met Met Ile Ser Leu Leu Phe
35 40 45

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Ile Gly Met Pro Leu Gly Phe Leu Thr Gly Leu Ile Ala Leu Val Ile
  50          55          60
Ser Tyr Leu Trp Phe Asp Thr Thr Ala Ile Met Gln Met Ile Ala Ser
  65          70          75          80
Arg Val Thr Asp Phe Thr Ser Ser Tyr Thr Phe Val Ala Val Pro Met
  85          90          95
Phe Val Leu Met Ala Thr Leu Leu Asp Lys Thr Gly Ile Ala Arg Asp
 100          105          110
Leu Tyr Asn Ala Met Arg Val Ile Gly Gly Arg Leu Arg Gly Gly Ile
 115          120          125
Ala Ile Gln Ser Met Phe Val Ala Val Leu Leu Ala Thr Met Ser Gly
 130          135          140
Ile Ile Gly Gly Glu Thr Val Leu Leu Gly Met Leu Ala Leu Pro Gln
 145          150          155          160
Met Leu Arg Leu Gly Tyr Asn Lys Asn Leu Ala Ile Gly Thr Val Val
 165          170          175
Ala Gly Gly Ala Leu Gly Thr Met Val Pro Pro Ser Ile Val Leu Ile
 180          185          190
Ile Tyr Gly Met Thr Ala Asn Val Ser Ile Gly Glu Leu Phe Leu Ala
 195          200          205
Ala Ile Pro Ala Ser Leu Leu Leu Ser Thr Phe Tyr Ile Leu Tyr Ile
 210          215          220
Leu Val Leu Cys Tyr Phe Lys Pro Ser Tyr Gly Pro Ala Met Pro Ser
 225          230          235          240
Ser Glu Asn His Thr Leu Thr Lys Glu Asp Ile Lys Lys Ile Ile His
 245          250          255
Asp Ile Ala Ile Pro Val Ala Ile Ala Thr Trp Ile Leu Gly Ser Ile
 260          265          270
Tyr Gly Gly Ile Ala Ser Ile Thr Glu Ser Ala Cys Val Gly Val Val
 275          280          285
Gly Val Ile Leu Ala Ala Phe Tyr Arg Lys Glu Leu Asn Phe Lys Ile
 290          295          300
Val Gln Glu Ser Leu Lys His Thr Ile Asn Thr Val Gly Met Ile Ile
 305          310          315          320
Trp Val Gly Ile Gly Ala Thr Met Ile Ile Gly Ile Tyr Asn Leu Met
 325          330          335
Gly Gly Asp Arg Phe Ile Ala Asn Leu Phe Ala Ser Leu Asp Ala Ser
 340          345          350
Pro Ile Tyr Thr Ile Ile Ile Met Met Val Ile Leu Leu Ile Leu Gly
 355          360          365
Met Phe Leu Asp Trp Ile Gly Val Ala Met Leu Thr Phe Leu Lys Thr
 370          375          380

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Ser Lys Ala Thr Ile Asn Leu Cys Phe Asp Ile Val Arg Tyr Ser Ile
385 390 395 400

Trp Arg Gly Pro Ser Phe His Ser Thr Asn Val His Arg Gly Thr Phe
405 410 415

Val Gly Arg Gly Thr Phe
420

<110> 74

<211> 2787

<212> DNA

<213> Pasteurella multocida

<220>

<221> CDS

<222> (463)...(936)

<220>

<223> yhcJ

<400> 74

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ggcgttgcaa tctgttggcg ttgtctatt ttgcgctctg ttacaatagc cgaggcaatt 180

tttgttccac caatatctaa tgctaaacag cgcataggct ctctctctgt gatgacttat 240

tttgccgatt tgacggcctc ggcaaaaccag cttaagatat gttcagaggc agtcagcgca 300

gatcctacgg tgacagagta agcaaccaatc tcaattgcgg ttttcgcca ttctgggggtg 360

ttatagcgcc ctctgccat cactcggcag ccagcagcat tcaaatcttt gactaactga 420

taatccggtt cagctggaat ttaccccca gtataaccag ac atg gtg cta cca 474

Met Val Leu Pro

1

ata att tct acc cct aag ttg tgg caa tac atc cct tct tca aaa tta 522

ile ile Ser Thr Pro Lys Leu Trp Gln Tyr ile Pro Ser Ser Lys Leu 20

5 10 15

gaa caa tcc gcc atg gct aaa caa cct aat tct ttg att cgt tta ata 570

Glu Gln Ser Ala Met Ala Lys Gln Pro Asn Ser Leu ile Arg Leu ile 35

25 30

atg gct tca cgt gta gtt gga cgg acg cga tcc gta cca tca aaa gca 618

Met Ala Ser Arg Val Val Gly Arg Thr Arg Ser Val Pro Ser Lys Ala 50

40 45

ata ata tcc gcg cct gct gcg gct aac tct tca atg tct tgt aaa aat 666

ile ile Ser Ala Pro Ala Ala Ala Asn Ser Ser Met Ser Cys Lys Asn 65

55 60

ggg cta ata cga acg gga ctg tca ggt aaa tcc cgt tta acg ata cca 714

Gly Leu ile Arg Thr Gly Leu Ser Gly Lys Ser Arg Leu Thr ile Pro 80

70 75

ata atc ggt aca ttg acg acg tta cgc gtg gct ttt aaa ttt tcc atc 762

ile ile Gly Thr Leu Thr Thr Leu Arg Val Ala Phe Lys Phe Ser ile

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      85              90              95              100
cct tca ata cgt aac ccg gca gca coa ccg ata acg gat gct tgc gcc 810
Pro Ser Ile Arg Asn Pro Ala Ala Pro Pro Ile Thr Asp Ala Cys Ala
              105              110              115

atg gcg gca aca att tct ggc gag tcc att ggc cca tta tct acg ggc 858
Met Ala Ala Thr Ile Ser Gly Glu Ser Ile Gly Pro Leu Ser Thr Gly
              120              125              130

tgg caa gat gcg att aag cca tat tta att tgt tct aaa act tgc gga 906
Trp Gln Asp Ala Ile Lys Pro Tyr Leu Ile Cys Ser Lys Thr Cys Gly
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tgt gat agt ttt gac ata tta act cca gtc taaatttattc aaaagaagat 956
Cys Asp Ser Phe Asp Ile Leu Thr Pro Val
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 <212> PRT
 <213> Pasteurella multocida

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 Ser Ser Lys Leu Glu Gln Ser Ala Met Ala Lys Gln Pro Asn Ser Leu
 20 25 30
 Ile Arg Leu Ile Met Ala Ser Arg Val Val Gly Arg Thr Arg Ser Val
 35 40 45
 Pro Ser Lys Ala Ile Ile Ser Ala Pro Ala Ala Ala Asn Ser Ser Met
 50 55 60
 Ser Cys Lys Asn Gly Leu Ile Arg Thr Gly Leu Ser Gly Lys Ser Arg
 65 70 75 80
 Leu Thr Ile Pro Ile Ile Gly Thr Leu Thr Thr Leu Arg Val Ala Phe
 85 90 95
 Lys Phe Ser Ile Pro Ser Ile Arg Asn Pro Ala Ala Pro Pro Ile Thr
 100 105 110
 Asp Ala Cys Ala Met Ala Ala Thr Ile Ser Gly Glu Ser Ile Gly Pro
 115 120 125
 Leu Ser Thr Gly Trp Gln Asp Ala Ile Lys Pro Tyr Leu Ile Cys Ser
 130 135 140
 Lys Thr Cys Gly Cys Asp Ser Phe Asp Ile Leu Thr Pro Val
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<210> 76
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caacgtaacc aatagaggag aactcata atg aaa ttt aaa aaa cta cta ctt 1972
Met Lys Phe Lys Lys Leu Leu Leu
1 5
gca tct tta tgt tta ggt gtt tca gct tct gta ttt gca gca gat tac 2020
Ala Ser Leu Cys Leu Gly Val Ser Ala Ser Val Phe Ala Ala Asp Tyr
10 15 20
gat ctt aaa ttc ggt atg gtt gcg ggt cca agc tca aac gaa tat aaa 2068
Asp Leu Lys Phe Gly Met Val Ala Gly Pro Ser Ser Asn Glu Tyr Lys
25 30 35 40
gca gta gaa ttc ttt gcg aaa gaa gtg aaa gaa aaa tcc aat ggc aaa 2116
Ala Val Glu Phe Phe Ala Lys Glu Val Lys Glu Lys Ser Asn Gly Lys
45 50 55
att gat gtg gct att ttc cct agc tca cag tta ggt gat gac cgt gtg 2164
Ile Asp Val Ala Ile Phe Pro Ser Ser Gln Leu Gly Asp Asp Arg Val
60 65 70
atg att aaa caa tta aaa gac ggt gca tta gac ttt acg tta ggt gaa 2212
Met Ile Lys Gln Leu Lys Asp Gly Ala Leu Asp Phe Thr Leu Gly Glu
75 80 85
tca gca cgt ttc caa att tac ttc cca gaa gca gaa gta ttt gcg ttg 2260
Ser Ala Arg Phe Gln Ile Tyr Phe Pro Glu Ala Glu Val Phe Ala Leu
90 95 100
cct tat atg att cct aat ttt gaa acc tct aaa aaa gcg ttg ctc gac 2308
Pro Tyr Met Ile Pro Asn Phe Glu Thr Ser Lys Lys Ala Leu Leu Asp
105 110 115 120
aca aaa ttt ggt caa ggt tta ttg aaa aaa att gat aaa gag tta aac 2356
Thr Lys Phe Gly Gln Gly Leu Leu Lys Lys Ile Asp Lys Glu Leu Asn
125 130 135
gta caa gtg tta tct gtg gcg tat aac ggt aca cgt caa aca act tct 2404
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140 145 150
aac cgt gca atc aac agc att gaa gac atg aaa ggg tta aaa tta cgt 2452
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155 160 165
gta cct aac gcg gca acc aac ctt gct tat gca aaa tac gtg ggt gca 2500
Val Pro Asn Ala Ala Thr Asn Leu Ala Tyr Ala Lys Tyr Val Gly Ala
170 175 180
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Ala Pro Thr Pro Met Ala Phe Ser Glu Val Tyr Leu Ala Leu Gln Thr
185 190 195 200
aac tct gtg gat ggt caa gaa aac cca tta ccg aca atc caa gca caa 2596
Asn Ser Val Asp Gly Gln Glu Asn Pro Leu Pro Thr Ile Gln Ala Gln
205 210 215
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220 225 230

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gaa gat tta caa aaa gtg gtt aaa gat gca gca gcg aaa gcc gct gaa 2740
Glu Asp Leu Gln Lys Val Val Lys Asp Ala Ala Ala Lys Ala Ala Glu
      250              255              260

tat cac act aaa ctc ttc gtt gac ggt gag aac agc tta gtt gaa tt 2787
Tyr His Thr Lys Leu Phe Val Asp Gly Glu Asn Ser Leu Val Glu
      265              270              275

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<213> Pasteurella multocida

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Gly Pro Ser Ser Asn Glu Tyr Lys Ala Val Glu Phe Phe Ala Lys Glu
      35              40              45

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

Ser Gln Leu Gly Asp Asp Arg Val Met Ile Lys Gln Leu Lys Asp Gly
      65              70              75              80

Ala Leu Asp Phe Thr Leu Gly Glu Ser Ala Arg Phe Gln Ile Tyr Phe
      85              90              95

Pro Glu Ala Glu Val Phe Ala Leu Pro Tyr Met Ile Pro Asn Phe Glu
      100             105             110

Thr Ser Lys Lys Ala Leu Leu Asp Thr Lys Phe Gly Gln Gly Leu Leu
      115             120             125

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

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

Asp Met Lys Gly Leu Lys Leu Arg Val Pro Asn Ala Ala Thr Asn Leu
      165             170             175

Ala Tyr Ala Lys Tyr Val Gly Ala Ala Pro Thr Pro Met Ala Phe Ser
      180             185             190

Glu Val Tyr Leu Ala Leu Gln Thr Asn Ser Val Asp Gly Gln Glu Asn
      195             200             205

Pro Leu Pro Thr Ile Gln Ala Gln Lys Phe Tyr Glu Val Gln Lys Tyr
      210             215             220

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

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Asn Asp Thr Leu Ala Asp Leu Pro Glu Asp Leu Gln Lys Val Val Lys
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Asp Ala Ala Ala Lys Ala Ala Glu Tyr His Thr Lys Leu Phe Val Asp
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Gly Glu Asn Ser Leu Val Glu
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<222> (908)..(1294)

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      Met Thr Lys Val Ile His Thr Asp Asn Ala Pro Ala Ala Ile
      1              5              10

ggg cct tat gta caa gcg gta gat tta ggt aat atg ctg tta acc tct 997
Gly Pro Tyr Val Gln Ala Val Asp Leu Gly Asn Met Leu Leu Thr Ser
      15              20              25              30

ggg caa att cca gtg aat cca aaa acc ggt gaa gtg cca gcg gat atc 1045
Gly Gln Ile Pro Val Asn Pro Lys Thr Gly Glu Val Pro Ala Asp Ile

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Val Ala Gln Ala Arg Gln Ser Leu Glu Asn Val Lys Ala Ile Val Glu
      50          55          60
caa gcg gga tta caa gtc gca aat atc gtg aaa acc acg gtg ttt gtg 1141
Gln Ala Gly Leu Gln Val Ala Asn Ile Val Lys Thr Thr Val Phe Val
      65          70          75
aaa gat tta aat gac ttt gca g g gtc aat gcg gag tat gaa cgt ttc 1189
Lys Asp Leu Asn Asp Phe Ala Ala Val Asn Ala Glu Tyr Glu Arg Phe
      80          85          90
ttt aaa gag aac aat cac cct agc ttc cct gct cgt tca tgt gtg gaa 1237
Phe Lys Glu Asn Asn His Pro Ser Phe Pro Ala Arg Ser Cys Val Glu
      95          100          105          110
gtg gca cgt ttg ccg aaa gat gtg ggg att gaa atc gag gca atc gct 1285
Val Ala Arg Leu Pro Lys Asp Val Gly Ile Glu Ile Glu Ala Ile Ala
      115          120          125

gta aaa gcc taatgaatag cttagcattta tcttagtcgt agcaaaacaa 1334
Val Lys Ala

tctcttttca ctgtctctct tcaaaagcaag ttgataagtg atttttattg ggcgttrttc 1394

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35 40 45
Gln Ala Arg Gln Ser Leu Glu Asn Val Lys Ala Ile Val Glu Gln Ala
50 55 60
Gly Leu Gln Val Ala Asn Ile Val Lys Thr Thr Val Phe Val Lys Asp
65 70 75 80
Leu Asn Asp Phe Ala Ala Val Asn Ala Glu Tyr Glu Arg Phe Phe Lys
85 90 95
Glu Asn Asn His Pro Ser Phe Pro Ala Arg Ser Cys Val Glu Val Ala
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Arg Leu Pro Lys Asp Val Gly Ile Glu Ile Glu Ala Ile Ala Val Lys
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Met Thr Gln Lys
1

tta cat att aaa acg tgg ggt tgt cag atg aat gaa tat gat tca tct 522
Leu His Ile Lys Thr Trp Gly Cys Gln Met Asn Glu Tyr Asp Ser Ser
5 10 15 20

aaa atg gca gat ctg tta aac agt act cac ggc tta gag tta aca gaa 570
Lys Met Ala Asp Leu Leu Asn Ser Thr His Gly Leu Glu Leu Thr Glu
25 30 35

att ccg gaa gaa gcg gat gtg tta ttg tta aac act tgc tca att cgt 618
Ile Pro Glu Glu Ala Asp Val Leu Leu Leu Asn Thr Cys Ser Ile Arg
40 45 50

gaa aaa gca caa gaa aaa gtt ttc cat caa tta gga cgt tgg aaa gaa 666
Glu Lys Ala Gln Glu Lys Val Phe His Gln Leu Gly Arg Trp Lys Glu
55 60 65

tta aag aaa cat aag ccg gga ctg gtt atc ggt gtt ggg ggc tgt gtt 714
Leu Lys Lys His Lys Pro Gly Leu Val Ile Gly Val Gly Gly Cys Val
70 75 80

gcc tca caa gaa gga gaa cac att cgt act cgt gct cct tat gtc gat 762
Ala Ser Gln Glu Gly Glu His Ile Arg Thr Arg Ala Pro Tyr Val Asp
85 90 95 100

att att ttt gga cca caa acc tta cat cgt tta cct gaa atg atc aat 810
Ile Ile Phe Gly Pro Gln Thr Leu His Arg Leu Pro Glu Met Ile Asn
105 110 115

cag atc aga ggt ggt aaa agc tca gta gtc gat gtc agt ttt cca gaa 858
Gln Ile Arg Gly Gly Lys Ser Ser Val Val Asp Val Ser Phe Pro Glu
120 125 130

att gaa aaa ttc gac cgt tta cca gaa ccg cgt gca gaa ggt cca act 906
Ile Glu Lys Phe Asp Arg Leu Pro Glu Pro Arg Ala Glu Gly Pro Thr
135 140 145

gct ttc gta tcc att atg gaa ggc tgt aat aaa tat tgc tca ttc tgt 954
Ala Phe Val Ser Ile Met Glu Gly Cys Asn Lys Tyr Cys Ser Phe Cys
150 155 160

gtc gtg cct tat acg cgt ggt gaa gaa gtc agt cgt cca gtg gat gat 1002
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165 170 175

gta tta ttt gaa att gca cag ttg gca gag caa ggc gtg cgt gaa gtg 1050
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185 190 195

aat tta tta gga caa aac gtg aac gct tat cgt ggt gca act cat gat 1098
Asn Leu Leu Gly Gln Asn Val Asn Ala Tyr Arg Gly Ala Thr His Asp
200 205 210

gac ggt att tgt act ttt gcg gaa ttg tta cgt tta gta gcc gct att 1146
Asp Gly Ile Cys Thr Phe Ala Glu Leu Leu Arg Leu Val Ala Ala Ile
215 220 225

gat ggt att gac cgt tta cgt ttt acc acc agt cac cca att gag ttc 1194

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Val Glu Gly Pro Ser Lys Lys Asp Leu Met Glu Leu Thr Gly Arg Thr
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Lys Gln Ser Leu Ala Arg Glu Gly Val Ala Leu Arg Pro Pro Phe Ala
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Leu Glu Asn Glu Lys Ala Phe Ser Ala Ala Cys Ile Arg Cys Gly Gln
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Cys Val Gln Ala Cys Pro His Glu Met Leu His Leu Ala Ser Leu Ile
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 tagtcccaaa tattgctcaa caggctttct caacgcaaga tcttgataat gacgtgctac 4726
 caccgcccat tgatccgtga gtgcccatgc cacagttaga ccaagctgtt ttatgtcttg 4786
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 <211> 250
 <212> PRT
 <213> Pasteurella multocida

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 20 25 30
 Leu Gln Gln Lys Gln Ser Leu Ala Arg Glu Gly Val Ala Leu Arg Pro
 35 40 45
 Pro Phe Ala Leu Glu Asn Glu Lys Ala Phe Ser Ala Ala Cys Ile Arg
 50 55 60
 Cys Gly Gln Cys Val Gln Ala Cys Pro His Glu Met Leu His Leu Ala
 65 70 75 80
 Ser Leu Ile Ser Pro Met Glu Ala Gly Thr Pro Tyr Phe Ile Ala Arg
 85 90 95
 Asp Lys Pro Cys Glu Met Cys Val Asp Ile Pro Cys Ala Lys Ala Cys
 100 105 110
 Pro Thr Gly Ala Leu Asp Asn Gln Ala Thr Glu Ile Asp Asp Ala Arg
 115 120 125
 Met Gly Leu Ala Val Leu Leu Asp His Glu Thr Cys Leu Asn Trp Gln
 130 135 140
 Gly Leu Arg Cys Asp Val Cys Tyr Arg Val Cys Pro Leu Ile Asn Lys
 145 150 155 160
 Ala Ile Thr Leu Val Met His Arg Asn Glu Arg Thr Gly Lys His Ala
 165 170 175

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Val Phe Ile Pro Thr Val His Ser Glu Ala Cys Thr Gly Cys Gly Lys
 180 185 190
 Cys Glu Glu Ala Cys Val Leu Glu Glu Ala Ala Ile Lys Val Leu Pro
 195 200 205
 Met Ala Leu Ala Lys Gly Met Leu Gly Lys His Tyr Arg Leu Gly Trp
 210 215 220
 Glu Glu Lys Glu Lys Ala Gly His Ser Leu Ala Pro Glu Gly Ile Ile
 225 230 235 240
 Ser Leu Pro Thr Arg Leu Pro Glu Ser Leu
 245 250

<210> 84
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 <213> Pasteurella multocida

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<220>
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<400> 84
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 gaaaatgctt tacgcgaata tgggtgttat ctaggcacag cttttcaatt agtcgatgat 180
 atttttagatt atagtgcaga tgcaaaagca ctccggcaaaa atattggtga tgatttagcg 240
 gaaggtaaac caacattacc gttattacac gccatgcac acggcaatcc agcacaagca 300
 aaattgattc gcgaagcgat tgagcaagg ggttaagcgtg atattttaga ggaatgaactg 360
 acaattatga cagaacataa atccctcgac tatgcgatga tgcgcgctaa acaagaagca 420
 caaaaagccg ttgatgcgat tgcattattg cctgaaaatg aatataaaca agcgttaatt 480
 tcattagctt acctatcogt cgatcgcgct tattaaccac ttaataaggc gagacatgtt 540
 agcgttaacga ccgcctaaag tgcggtcatt tatttagtaa ttttaaacac gacaatgaca 600
 gaacaaaaca tccttacgaa aaaaacacgc aaaggcaaa atcctcagcg gcccttttga 660
 cgcgaaaaat tatccctacc aaatgggcat aacaaattgt tattgcattc ttgttgtgcg 720
 ccttgctcgg gagaagtaat ggaggcaatt catgcttcag gtattgaatt tactatttac 780
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 tttgaccgtg ccaaaggcat ggaagatgag ccagagcgtg gtattcgttg cactatgtgc 960
 ttgatatgc gttttgaaa agccgcagaa tatgcacaca acaatggttt ccccgatttt 1020

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actagctgct taggtatttc acgttggaaa gacatgaacc aaatcaacgg ttgtggacac 1080
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ggctcacaaac gtatgattga aatcagtaag cgtgaacgtt ttaccagca agaattattgc 1200
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cagttaagcg ccttagggaa gcaaaagtgc gtggtgatga ccgatgatga tggcaatgcg 2340
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Met Thr Lys Leu Ser Ile Gln Arg Asp Asn Leu Ile Cys
1 5 10
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Leu Ser Tyr Val Ala Leu Met Gly Phe Gly Phe Pro Ile Met Arg Tyr
15 20 25
atg agt att cat ttt gat aca tta aat aat aac gct gtt cgc ttt ctc 2545
Met Ser Ile His Phe Asp Thr Leu Asn Asn Asn Ala Val Arg Phe Leu
30 35 40 45
tca ggg ggc agc gtt ttt att tta gcc tgt ttt ttt tat tat cgc gct 2593
Ser Gly Gly Ser Val Phe Ile Leu Ala Cys Phe Phe Tyr Tyr Arg Ala
50 55 60
gag tta aca tct tcg ggg gct ggc gtc cag tcc gtt gcg atg ttg ccg 2641

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Glu Leu Thr Ser Ser Gly Ala Gly Val Gln Ser Val Ala Met Leu Pro
 65 70 75
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 Ser Ser Ser Leu Gly Phe Leu Ile Leu Lys Thr Val Pro Ser Phe Ser
 80 85 90
 tac gtt aca atc tca aca ctt aat cgc gtt tgaccttcg atttttgata 2739
 Tyr Val Thr Ile Ser Thr Leu Asn Arg Val
 95 100
 gtcaaaagact actgagtaac gctttagtc gctgaatcg actgttacat aagccgatat 2799
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 <211> 103
 <212> PRT
 <213> Pasteurella multocida

 <400> 85
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 His Phe Asp Thr Leu Asn Asn Asn Ala Val Arg Phe Leu Ser Gly Gly
 35 40 45
 Ser Val Phe Ile Leu Ala Cys Phe Phe Tyr Tyr Arg Ala Glu Leu Thr
 50 55 60
 Ser Ser Gly Ala Gly Val Gln Ser Val Ala Met Leu Pro Ser Ser Ser
 65 70 75 80
 Leu Gly Phe Leu Ile Leu Lys Thr Val Pro Ser Phe Ser Tyr Val Thr
 85 90 95
 Ile Ser Thr Leu Asn Arg Val

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100

<210> 86
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PRIMER

<400> 86
aggccgggtac cggccgcct

19

<210> 87
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PRIMER

<400> 87
cggccgggtac cggcctagg

19

<210> 88
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 88
catggtaccc attctaac

18

<210> 89
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 89
ctaggtaacct acaacctc

18

<210> 90
<211> 119
<212> DNA
<213> Artificial Sequence

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insert

<220>

173

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<223> N = A or T or G or C

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<223> N = A or T or G or C

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<221> misc_feature
<222> 93
<223> N = A or T or G or C

<400> 90
ctaggtacct acaacctcaa gettnknknk nknknknknk nknknknknk nknknknknk 60
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<210> 91
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

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<400> 91
tacctacaac ctcaagct 18

<210> 92
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 92
taccattct aaccaagc 18

<210> 93
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 93
tacctacaac ctcaagctt 19

<210> 94
<211> 20
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 94
taccattct aaccaagctt 20

<210> 95
<211> 19
<212> DNA
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<220>
<223> Description of Artificial Sequence: primer

<400> 95
ggcagagcat tacgtgac 19

<210> 96
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 96
gtaccggcca ggcggccacg cgtattc 27

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<210> 97
<211> 531
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>

<223> atpG

<400> 97

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agttaatgaa atgattaatg cgttccgaaa cggagaagtg gatcggttt acgtcgctta 180
caaccgtttt gaaaatacga tgtcacaata acctgttacc gcacagttac ttccgttacc 240
taaaatagat gacgatgaat tagatacgaagggttcattg gattatattt atgaaccgaa 300
tcacaaagtt ttattggata gtttacttgt tcgttattta gaaactcagg tataccaagc 360
agttgtagat aacctagctt ctgaacaagc cgctcgaatg gtacgatga aagccgcaac 420
agataatgcg ggtacattaa tcgatgaatt acaattagt tataacaag ctgcgaagc 480
aagcattaca aatgaattaa acgaattgt tgcgggtgcc gcagcaattt a 531

<210> 98

<211> 25

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

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<211> 20

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: primer

<400> 99

ggattacagc cggatccggg 20

<210> 100

<211> 1034

<212> DNA

<213> Pasteurella multocida

<220>

<223> cap5E

<220>

<221> CDS

<222> (1)...(1032)

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ggt aat gct gta ctc aaa cgt ttc tta gaa aca gat att cga gaa att 96
Gly Asn Ala Val Leu Lys Arg Phe Leu Glu Thr Asp Ile Arg Glu Ile
20 25 30

cgt gtt ttt tcg cgt gat gag aag aaa caa gat gac atg cgg aaa aaa 144
Arg Val Phe Ser Arg Asp Glu Lys Lys Gln Asp Asp Met Arg Lys Lys
35 40 45

tat aat gat gca aaa tta aaa ttt tat att ggc gat gtt cgt gac tac 192
Tyr Asn Asp Ala Lys Leu Lys Phe Tyr Ile Gly Asp Val Arg Asp Tyr
50 55 60

gat agt att tta aat gcc tcg cga ggt gtt gac tat att tat cat gct 240
Asp Ser Ile Leu Asn Ala Ser Arg Gly Val Asp Tyr Ile Tyr His Ala
65 70 75 80

gcc gca tta aag caa gtg cct tca tgc gag ttt tat ccg tta gag gca 288
Ala Ala Leu Lys Gln Val Pro Ser Cys Glu Phe Tyr Pro Leu Glu Ala
85 90 95

gtg aaa acc aat att tta ggt acg gca aat gtc tta gaa gcc gcc atc 336
Val Lys Thr Asn Ile Leu Gly Thr Ala Asn Val Leu Glu Ala Ala Ile
100 105 110

caa aac cag ata aaa cgc gtc gtc tgt ctt agc aca gat aaa gcg gtg 384
Gln Asn Gln Ile Lys Arg Val Val Cys Leu Ser Thr Asp Lys Ala Val
115 120 125

tac cca att aat gcg atg gcc att tct aaa gca atg atg gaa aaa gtc 432
Tyr Pro Ile Asn Ala Met Gly Ile Ser Lys Ala Met Met Glu Lys Val
130 135 140

atc atc goa aaa tcg cgt aac cta gaa gcc aca cca acg aca atc tgt 480
Ile Ile Ala Lys Ser Arg Asn Leu Glu Gly Thr Pro Thr Thr Ile Cys
145 150 155 160

tgt act cgc tat gcc aat gtc atg gca tcg cgt ggt tcg gtt atc cca 528
Cys Thr Arg Tyr Gly Asn Val Met Ala Ser Arg Gly Ser Val Ile Pro
165 170 175

tta ttt gtc gat caa ata cgt caa gcc aag cct ttt act att act gat 576
Leu Phe Val Asp Gln Ile Arg Gln Gly Lys Pro Phe Thr Ile Thr Asp
180 185 190

cct gag atg aca cgc ttt atg atg aca ttg gaa gat gct gtg gat tta 624
Pro Glu Met Thr Arg Phe Met Met Thr Leu Glu Asp Ala Val Asp Leu
195 200 205

gtc cta tat gca ttt aaa aat ggt caa aat ggt gat gtt ttt gta caa 672
Val Leu Tyr Ala Phe Lys Asn Gly Gln Asn Gly Asp Val Phe Val Gln
210 215 220

aaa gcc ccc gca gca acc att ggt acc ctt gcc aaa gca att acc gaa 720
Lys Ala Pro Ala Ala Thr Ile Gly Thr Leu Ala Lys Ala Ile Thr Glu
225 230 235 240

tta tta tct gtc cca aat cac cct att tcc att ata ggt acg cgt cat 768
Leu Leu Ser Val Pro Asn His Pro Ile Ser Ile Ile Gly Thr Arg His

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      245      250      255
gga gag aaa gca ttc gaa gct tta tta agc cgt gaa gaa atg gtt cat 816
Gly Glu Lys Ala Phe Glu Ala Leu Leu Ser Arg Glu Glu Met Val His
      260      265      270
gca att aat gaa ggt aat tat tat cgc atc cca gcc gat caa cgc agt 864
Ala Ile Asn Glu Gly Asn Tyr Tyr Arg Ile Pro Ala Asp Gln Arg Ser
      275      280      285
tta aat tac agt aaa tat gtc gaa aaa ggg gaa cca aaa att acc gaa 912
Leu Asn Tyr Ser Lys Tyr Val Glu Lys Gly Glu Pro Lys Ile Thr Glu
      290      295      300
gtc acc gac tac aac tca cat aat act gag cgt ttg act gtc aag gaa 960
Val Thr Asp Tyr Asn Ser His Asn Thr Glu Arg Leu Thr Val Lys Glu
      305      310      315
atg aag cag tta ctg ctt aaa ctt gaa ttc ata cag aaa atg att gag 1008
Met Lys Gln Leu Leu Leu Lys Leu Glu Phe Ile Gln Lys Met Ile Glu
      320      325      330      335
ggc gaa tac atc tca ccg gag gta ta 1034
Gly Glu Tyr Ile Ser Pro Glu Val
      340

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<210> 101
 <211> 344
 <212> PRT
 <213> Pasteurella multocida

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  20          25          30
Arg Val Phe Ser Arg Asp Glu Lys Lys Gln Asp Asp Met Arg Lys Lys
  35          40          45
Tyr Asn Asp Ala Lys Leu Lys Phe Tyr Ile Gly Asp Val Arg Asp Tyr
  50          55          60
Asp Ser Ile Leu Asn Ala Ser Arg Gly Val Asp Tyr Ile Tyr His Ala
  65          70          75          80
Ala Ala Leu Lys Gln Val Pro Ser Cys Glu Phe Tyr Pro Leu Glu Ala
  85          90          95
Val Lys Thr Asn Ile Leu Gly Thr Ala Asn Val Leu Glu Ala Ala Ile
 100          105          110
Gln Asn Gln Ile Lys Arg Val Val Cys Leu Ser Thr Asp Lys Ala Val
 115          120          125
Tyr Pro Ile Asn Ala Met Gly Ile Ser Lys Ala Met Met Glu Lys Val
 130          135          140
Ile Ile Ala Lys Ser Arg Asn Leu Glu Gly Thr Pro Thr Thr Ile Cys
 145          150          155          160

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Cys Thr Arg Tyr Gly Asn Val Met Ala Ser Arg Gly Ser Val Ile Pro
 165 170 175
 Leu Phe Val Asp Gln Ile Arg Gln Gly Lys Pro Phe Thr Ile Thr Asp
 180 185 190
 Pro Glu Met Thr Arg Phe Met Met Thr Leu Glu Asp Ala Val Asp Leu
 195 200 205
 Val Leu Tyr Ala Phe Lys Asn Gly Gln Asn Gly Asp Val Phe Val Gln
 210 215 220
 Lys Ala Pro Ala Ala Thr Ile Gly Thr Leu Ala Lys Ala Ile Thr Glu
 225 230 235 240
 Leu Leu Ser Val Pro Asn His Pro Ile Ser Ile Ile Gly Thr Arg His
 245 250 255
 Gly Glu Lys Ala Phe Glu Ala Leu Leu Ser Arg Glu Glu Met Val His
 260 265 270
 Ala Ile Asn Glu Gly Asn Tyr Tyr Arg Ile Pro Ala Asp Gln Arg Ser
 275 280 285
 Leu Asn Tyr Ser Lys Tyr Val Glu Lys Gly Glu Pro Lys Ile Thr Glu
 290 295 300
 Val Thr Asp Tyr Asn Ser His Asn Thr Glu Arg Leu Thr Val Lys Glu
 305 310 315 320
 Met Lys Gln Leu Leu Lys Leu Glu Phe Ile Gln Lys Met Ile Glu
 325 330 335
 Gly Glu Tyr Ile Ser Pro Glu Val
 340

<210> 102
 <211> 4931
 <212> DNA
 <213> Pasteurella multocida

<220>
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 <222> (1)..(4929)

<220>
 <221> misc_feature
 <222> 1632
 <223> Xaa = any or unknown amino acid

<400> 102
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 1 5 10 15
 ctc gtt cct gtg gca gaa tgt att aac tca gct att agc aat ggt tca 96
 Leu Val Pro Val Ala Glu Cys Ile Asn Ser Ala Ile Ser Asn Gly Ser

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      20      25      30
tct gat tca aca tcc aca tca gaa caa gtt gaa gag gaa cct ttc ctt 144
Ser Asp Ser Thr Ser Thr Ser Glu Gln Val Glu Glu Glu Pro Phe Leu
      35      40      45
cta gaa caa tat tca ctt tcc tcc gtg tct tta tta gta aaa agc acg 192
Leu Glu Gln Tyr Ser Leu Ser Ser Val Ser Leu Leu Val Lys Ser Thr
      50      55      60
ttc aat cct gtt tcg tat gca atg caa ttg act tgg aaa cag ctt tct 240
Phe Asn Pro Val Ser Tyr Ala Met Gln Leu Thr Trp Lys Gln Leu Ser
      65      70      75      80
att tta ttt tta act gtg att tct gtt cct gtt ttg gct gag gga aaa 288
Ile Leu Phe Leu Thr Val Ile Ser Val Pro Val Leu Ala Glu Gly Lys
      85      90      95
ggg gat gaa aga aat caa tta aca gtg att gat aat agc gat cat att 336
Gly Asp Glu Arg Asn Gln Leu Thr Val Ile Asp Asn Ser Asp His Ile
      100      105      110
aaa tta gat gca tct aat ctt gct ggt aat gat aaa aca aaa atc tat 384
Lys Leu Asp Ala Ser Asn Leu Ala Gly Asn Asp Lys Thr Lys Ile Tyr
      115      120      125
caa gca gaa aat aaa gtt ctg gtt att gat att gct aaa cca aat ggg 432
Gln Ala Glu Asn Lys Val Leu Val Ile Asp Ile Ala Lys Pro Asn Gly
      130      135      140
aaa ggg att tca gat aac cgt ttt gaa aaa ttt aat att cca aat agc 480
Lys Gly Ile Ser Asp Asn Arg Phe Glu Lys Phe Asn Ile Pro Asn Ser
      145      150      155
gcg gtg ttt aat aat aat ggg act gaa gcg cag gca aga tca aca tta 528
Ala Val Phe Asn Asn Asn Gly Thr Glu Ala Gln Ala Arg Ser Thr Leu
      165      170      175
att ggt tac att ccg caa aat caa aat tta agg gga ggg aaa gaa gct 576
Ile Gly Tyr Ile Pro Gln Asn Gln Asn Leu Arg Gly Gly Lys Glu Ala
      180      185      190
gat gtt ata tta aat caa gtg aca ggt cct caa gaa agt aaa att gtt 624
Asp Val Ile Leu Asn Gln Val Thr Gly Pro Gln Glu Ser Lys Ile Val
      195      200      205
ggc gcg ctt gaa gta tta ggt aaa aaa gct gat atc gtc att gca aac 672
Gly Ala Leu Glu Val Leu Gly Lys Lys Ala Asp Ile Val Ile Ala Asn
      210      215      220
caa aat ggt att acc tta aat ggt gta aga aca ata aat tca gat cgt 720
Gln Asn Gly Ile Thr Leu Asn Gly Val Arg Thr Ile Asn Ser Asp Arg
      225      230      235      240
ttt gtt gcc act acg agt gag ctt ata gat ccg aat cag atg atg tta 768
Phe Val Ala Thr Thr Ser Glu Leu Ile Asp Pro Asn Gln Met Met Leu
      245      250      255
aag gtt aca aaa gga aat gtg atc att gat att gat ggt ttt tcg aca 816
Lys Val Thr Lys Gly Asn Val Ile Ile Asp Ile Asp Gly Phe Ser Thr
      260      265      270
gat gga tta aag tat tta gat att att gct aaa aaa att gaa caa aag 864

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Asp Gly Leu Lys Tyr Leu Asp Ile Ile Ala Lys Lys Ile Glu Gln Lys
275                280                285
caa tca att aca tca ggg gat aat tca gaa gca aaa aca gat gtc act 912
Gln Ser Ile Thr Ser Gly Asp Asn Ser Glu Ala Lys Thr Asp Val Thr
290                295                300
ctt att gcg ggt tcc agt gaa tat gat tta agc aaa cat gag ctg aaa 960
Leu Ile Ala Gly Ser Ser Glu Tyr Asp Leu Ser Lys His Glu Leu Lys
305                310                315
aaa acg agc ggt gaa aat gta tct aat gat gtt att gct atc acg gga 1008
Lys Thr Ser Gly Glu Asn Val Ser Asn Asp Val Ile Ala Ile Thr Gly
325                330                335
tct agt aca ggc gca atg cat ggt aaa aat att aag ttg att gtg aca 1056
Ser Ser Thr Gly Ala Met His Gly Lys Asn Ile Lys Leu Ile Val Thr
340                345                350
gat aaa ggt gca ggc gta aaa cat gat gga att att ttg tct gaa aat 1104
Asp Lys Gly Ala Gly Val Lys His Asp Gly Ile Ile Leu Ser Glu Asn
355                360                365
gat att cag att gaa atg aat gaa ggt gac tta gaa ctt ggc aat acg 1152
Asp Ile Gln Ile Glu Met Asn Glu Gly Asp Leu Glu Leu Gly Asn Thr
370                375                380
att cag caa aca gtg gta aaa aaa gac cga aat att cga gcc aag aaa 1200
Ile Gln Gln Thr Val Val Lys Lys Asp Arg Asn Ile Arg Ala Lys Lys
385                390                395                400
aaa att gaa gtg aaa aac gct aat cgt gtt ttt gtt ggt agt caa acg 1248
Lys Ile Glu Val Lys Asn Ala Asn Arg Val Phe Val Gly Ser Gln Thr
405                410                415
aaa tca gat gaa att tcg tta gag gcg aaa caa gtt aaa atc aga aaa 1296
Lys Ser Asp Glu Ile Ser Leu Glu Ala Lys Gln Val Lys Ile Arg Lys
420                425                430
aac gca gag att agg agt acy aca caa gcc aaa atc gta gca aag ggt 1344
Asn Ala Glu Ile Arg Ser Thr Thr Gln Ala Lys Ile Val Ala Lys Gly
435                440                445
gcc ctg tct att gag caa aat gcg aag ctc gtc gct aaa aag ata gat 1392
Ala Leu Ser Ile Glu Gln Asn Ala Lys Leu Val Ala Lys Lys Ile Asp
450                455                460
gtg gca aca gaa act cta act aat gct ggg cgt att tat ggt cga gag 1440
Val Ala Thr Glu Thr Leu Thr Asn Ala Gly Arg Ile Tyr Gly Arg Glu
465                470                475                480
gtt aag ctt gac act aat aat ttg att aat gat aaa gaa att tat gct 1488
Val Lys Leu Asp Thr Asn Asn Leu Ile Asn Asp Lys Glu Ile Tyr Ala
485                490                495
gaa cgg aaa ttg agt att ttg acg aaa gga aaa gat ctt gaa att att 1536
Glu Arg Lys Leu Ser Ile Leu Thr Lys Gly Lys Asp Leu Glu Ile Ile
500                505                510
caa gat aga tat ttg tct cca ctg atg cgc gta aaa agt agt gtc cgc 1584
Gln Asp Arg Tyr Leu Ser Pro Leu Met Arg Val Lys Ser Ser Val Arg
515                520                525

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ttt tta ggc tct cgg ttt ttc tca ata tct cgg tog atg ctc gca agc 1632
Phe Leu Gly Ser Pro Phe Phe Ser Ile Ser Pro Ser Met Leu Ala Ser
530 535 540

ctt agt gca cag ttt aag cct ggt ttt gtg aat aag gga ctc att gaa 1680
Leu Ser Ala Gln Phe Lys Pro Gly Phe Val Asn Lys Gly Leu Ile Glu
545 550 555 560

agt gcg ggg agt gca gaa tta act ttt aaa gaa aaa acc agt ttt tta 1728
Ser Ala Gly Ser Ala Glu Leu Thr Phe Lys Glu Lys Thr Ser Phe Leu
565 570 575

aca gag ggc aat aat ttt att aga gct aaa gat gcg tta act att aac 1776
Thr Glu Gly Asn Asn Phe Ile Arg Ala Lys Asp Ala Leu Thr Ile Asn
580 585 590

gcc caa aat att gaa att gat aaa aat caa gat att caa ttg ggt gct 1824
Ala Gln Asn Ile Glu Ile Asp Lys Asn Gln Asp Ile Gln Leu Gly Ala
595 600 605

aat ata acg ttg aat gtg gaa gaa aac ttt gtt aat cgt gca gga aca 1872
Asn Ile Thr Leu Asn Val Glu Glu Asn Phe Val Asn Arg Ala Gly Thr
610 615 620

ctg gca act ggt aaa aca ctg aca att aat acc gaa agt ggc agt att 1920
Leu Ala Thr Gly Lys Thr Leu Thr Ile Asn Thr Glu Ser Gly Ser Ile
625 630 635 640

tac aat ctt ggt ggg aca tta ggt gct gga aaa tca tta aaa ctg act 1968
Tyr Asn Leu Gly Gly Thr Leu Gly Ala Gly Lys Ser Leu Lys Leu Thr
645 650 655

gct aaa tca acg gaa gaa ggt atg gga aat att gtt aac caa gaa aac 2016
Ala Lys Ser Thr Glu Glu Gly Met Gly Asn Ile Val Asn Gln Glu Asn
660 665 670

ggt tta ttc cat aca ctc ggt aat atg atg tta gaa gca gag cgt tct 2064
Gly Leu Phe His Thr Leu Gly Asn Met Met Leu Glu Ala Glu Arg Ser
675 680 685

gtt tat aat att ggc gat att tat gcg agt aaa aaa tta aca gtt cat 2112
Val Tyr Asn Ile Gly Asp Ile Tyr Ala Ser Lys Lys Leu Thr Val His
690 695 700

act cat aat ttg att aat gat gtg cgt tta tct ggc aat gtg agt tat 2160
Thr His Asn Leu Ile Asn Asp Val Arg Leu Ser Gly Asn Val Ser Tyr
705 710 715 720

aag cct atc ggt tca agt cgt gat tat gat atc agt cgt gtt gcg gta 2208
Lys Pro Ile Gly Ser Ser Arg Asp Tyr Asp Ile Ser Arg Val Ala Val
725 730 735

cat ggt tgg cac aat aat gtt tat aag ctc aac tta aat ctg caa gaa 2256
His Gly Trp His Asn Asn Val Tyr Lys Leu Asn Leu Asn Leu Gln Glu
740 745 750

caa gat aaa acc gat att aaa gtt gtg aaa atg ggg gct atc cgt tct 2304
Gln Asp Lys Thr Asp Ile Lys Val Val Lys Met Gly Ala Ile Arg Ser
755 760 765

gat ggt gat ttt gac ttt aag gga ata aag gcg aca tca tca gaa tca 2352
Asp Gly Asp Phe Asp Phe Lys Gly Ile Lys Ala Thr Ser Ser Glu Ser
770 775 780

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aaa ccg cag tta att aat cat gga tta att aat gtc aaa gga aca ttt 2400
Lys Pro Gln Leu Ile Asn His Gly Leu Ile Asn Val Lys Gly Thr Phe
785          790          795          800

aat gcg gaa gct gat caa gtg gtg aac caa atg aaa gcg ttt aac caa 2448
Asn Ala Glu Ala Asp Gln Val Val Asn Gln Met Lys Ala Phe Asn Gln
805          810          815

aat gca tta gca agc gtg ttt aag aat cca gcg aaa atc acg atg tac 2496
Asn Ala Leu Ala Ser Val Phe Lys Asn Pro Ala Lys Ile Thr Met Tyr
820          825          830

tat caa cca ctt act cgt tat att tgg aca cca tta tcg ggt aat gca 2544
Tyr Gln Pro Leu Thr Arg Tyr Ile Trp Thr Pro Leu Ser Gly Asn Ala
835          840          845

tcg cgt gaa ttt aac aat tta gag tct ttc ctc gat gcc ttg ttt ggc 2592
Ser Arg Glu Phe Asn Asn Leu Glu Ser Phe Leu Asp Ala Leu Phe Gly
850          855          860

tca aca aca atc tta aaa tca agt ttc tat agt acg gaa aat ttt agt 2640
Ser Thr Thr Ile Leu Lys Ser Ser Phe Tyr Ser Thr Glu Asn Phe Ser
865          870          875          880

gct tat cag ctt cta tct cat att cag cat tca cca atg tac caa aaa 2688
Ala Tyr Gln Leu Leu Ser His Ile Gln His Ser Pro Met Tyr Gln Lys
885          890          895

gcg atg gca caa gtg ttt ggt gca gag tgg cat agt aaa tcc tat gat 2736
Ala Met Ala Gln Val Phe Gly Ala Glu Trp His Ser Lys Ser Tyr Asp
900          905          910

gag atg cga aac aaa tgg aaa agc ttt aaa gaa aat cca aca gat ttc 2784
Glu Met Arg Asn Lys Trp Lys Ser Phe Lys Glu Asn Pro Thr Asp Phe
915          920          925

att tat tac cca tca gaa aaa gca aaa atc cta gcg gga aaa cta gaa 2832
Ile Tyr Tyr Pro Ser Glu Lys Ala Lys Ile Leu Ala Gly Lys Leu Glu
930          935          940

ggt aag ctt aca acg cta caa aat ggt gaa tat gcc gaa cgt ggt aag 2880
Gly Lys Leu Thr Thr Leu Gln Asn Gly Glu Tyr Ala Glu Arg Gly Lys
945          950          955          960

ttt gat gag agt atc caa att ggt aaa cac caa tta tcg cta cca tca 2928
Phe Asp Glu Ser Ile Gln Ile Gly Lys His Gln Leu Ser Leu Pro Ser
965          970          975

gta gag ctt aaa gcg gag ttt agt gat aaa gaa cgt ttg gaa gag gac 2976
Val Glu Leu Lys Ala Glu Phe Ser Asp Lys Glu Arg Leu Glu Glu Asp
980          985          990

ggg gta gat tta tcc tcg atc gcc gaa ctc tta gaa atg cca aac tta 3024
Gly Val Asp Leu Ser Ser Ile Ala Glu Leu Leu Glu Met Pro Asn Leu
995          1000          1005

ttt att gat aat agt atc caa tta gaa aag aaa aag ttg tct cct att 3072
Phe Ile Asp Asn Ser Ile Gln Leu Glu Lys Lys Lys Leu Ser Pro Ile
1010          1015          1020

gag gat cta gat gaa gaa cca cgt aaa aat ctg gat ata gaa gaa agc 3120
Glu Asp Leu Asp Glu Glu Pro Arg Lys Asn Leu Asp Ile Glu Glu Ser
1025          1030          1035          1040

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cat tct aat tca tcg gat gac gtg ctt agc atg aat gat gat gag tct 3168
His Ser Asn Ser Ser Asp Asp Val Leu Ser Met Asn Asp Asp Glu Ser
1045 1050 1055

gat aca gac gat agc aag tgg agt atg ggc aat gat gag aaa gag atg 3216
Asp Thr Asp Asp Ser Lys Trp Ser Met Gly Asn Asp Glu Lys Glu Met
1060 1065 1070

ccc gat gat aag ctg ggt ata agt cgt gat gat cgt gga aat aaa cca 3264
Pro Asp Asp Lys Leu Gly Ile Ser Arg Asp Asp Arg Gly Asn Lys Pro
1075 1080 1085

cct cgt act gat cct aca gtt gat tat ctt aac cct gat gaa ttc ttt 3312
Pro Arg Thr Asp Pro Thr Val Asp Tyr Leu Asn Pro Asp Glu Phe Phe
1090 1095 1100

gaa aat ggt tat ctc ttg aat gag cta cta cag gag ctt gga gaa gag 3360
Glu Asn Gly Tyr Leu Leu Asn Glu Leu Leu Gln Glu Leu Gly Glu Glu
1105 1110 1115 1120

cgg tta cta aaa gaa ggg gaa gat cat ttt aaa cgt tct acc aat cta 3408
Pro Leu Leu Lys Glu Gly Glu Asp His Phe Lys Arg Ser Thr Asn Leu
1125 1130 1135

gtc cgt cta ggc gag aga gat agg caa aat aga gaa aag aga gaa aaa 3456
Val Arg Leu Gly Glu Arg Asp Arg Gln Asn Arg Glu Lys Arg Glu Lys
1140 1145 1150

gag ggg tat ttt gat ctg cct ggt aca tta gat atg aaa ctg cag gag 3504
Glu Gly Tyr Phe Asp Leu Pro Gly Thr Leu Asp Met Lys Leu Gln Glu
1155 1160 1165

tta ttc gaa aaa aga aaa caa aaa cac gaa gca gaa cag aaa gca aga 3552
Leu Phe Glu Lys Arg Lys Gln Lys His Glu Ala Glu Gln Lys Ala Arg
1170 1175 1180

ata gaa aaa gca ctt cta caa aaa tca gaa caa caa gaa aaa cgt gtt 3600
Ile Glu Lys Ala Leu Leu Gln Lys Ser Glu Gln Gln Glu Lys Arg Val
1185 1190 1195 1200

gaa gaa cgt aag caa gag gaa aaa cgt caa gcg caa gat aaa att gct 3648
Glu Glu Arg Lys Gln Glu Glu Lys Arg Gln Ala Gln Asp Lys Ile Ala
1205 1210 1215

aag caa gta gaa att gca aaa gaa atg caa cgg gta gaa gaa att cgc 3696
Lys Gln Val Glu Ile Ala Lys Glu Met Gln Arg Val Glu Glu Ile Arg
1220 1225 1230

cag aga gaa aaa caa ctt gcg atc caa ctg caa gaa gaa gag aag aaa 3744
Gln Arg Glu Lys Gln Leu Ala Ile Gln Leu Gln Glu Glu Lys Lys
1235 1240 1245

caa caa gaa gaa aaa cat tta tcc gag gag aaa aaa caa gct gaa cag 3792
Gln Gln Glu Glu Lys His Leu Ser Glu Glu Lys Lys Gln Ala Glu Gln
1250 1255 1260

aaa caa aaa gct gag gag aaa gtt gca caa gaa aga tta gac att gaa 3840
Lys Gln Lys Ala Glu Glu Lys Val Ala Gln Glu Arg Leu Asp Ile Glu
1265 1270 1275 1280

caa cag aaa gcg tat gaa gaa atg gcg aag cga gag gca gag gca tca 3888
Gln Gln Lys Ala Tyr Glu Glu Met Ala Lys Arg Glu Ala Glu Ala Ser
1285 1290 1295

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aaa aat gtt tta ttg aaa gcg att gat gaa gaa cgt cca aaa gtg gaa 3936
Lys Asn Val Leu Leu Lys Ala Ile Asp Glu Glu Arg Pro Lys Val Glu
1300 1305 1310

act gat cca ctt ttc cgt aca aaa ttg aaa tat atc aat caa gat gac 3984
Thr Asp Pro Leu Phe Arg Thr Lys Leu Lys Tyr Ile Asn Gln Asp Asp
1315 1320 1325

tat gct ggt gca aat tat ttc ttc aat aaa gtt ggt tta aat aca aaa 4032
Tyr Ala Gly Ala Asn Tyr Phe Phe Asn Lys Val Gly Leu Asn Thr Lys
1330 1335 1340

ggt cat caa aaa gta aat gtg tta ggg gat aac tat ttt gat cat caa 4080
Gly His Gln Lys Val Asn Val Leu Gly Asp Asn Tyr Phe Asp His Gln
1345 1350 1355 1360

gtg att act cgc tcg att gag aaa aaa gta gat aac cac ctt aac caa 4128
Val Ile Thr Arg Ser Ile Glu Lys Lys Val Asp Asn His Leu Asn Gln
1365 1370 1375

aaa tac aat ctc agc gat gtg gaa tta gtt aaa cag ctg atg gac aat 4176
Lys Tyr Asn Leu Ser Asp Val Glu Leu Val Lys Gln Leu Met Asp Asn
1380 1385 1390

tcc aca aca caa gcg cag gag ttg gat ttg aaa cta ggt gcg gca tta 4224
Ser Thr Thr Gln Ala Gln Glu Leu Asp Leu Lys Leu Gly Ala Ala Leu
1395 1400 1405

act aaa gaa caa caa gct aac ttg acc caa gat atc gtt tgg tat gtc 4272
Thr Lys Glu Gln Gln Ala Asn Leu Thr Gln Asp Ile Val Trp Tyr Val
1410 1415 1420

aaa acg aag gta aag ggc aaa gat gtg ttt gtt cca aag gtt tat ttc 4320
Lys Thr Lys Val Lys Gly Lys Asp Val Phe Val Pro Lys Val Tyr Phe
1425 1430 1435 1440

gct tct gaa acg ctc gta gaa gcc caa aaa tta caa ggt tta ggc act 4368
Ala Ser Glu Thr Leu Val Glu Ala Gln Lys Leu Gln Gly Leu Gly Thr
1445 1450 1455

ggg act atc aga gtt ggt gaa gct aag att aaa gcc aaa gat gtg gtg 4416
Gly Thr Ile Arg Val Gly Glu Ala Lys Ile Lys Ala Lys Asp Val Val
1460 1465 1470

aat acc ggg aca tta gct ggg aga aaa ctc aat gtt gaa gcg agt aat 4464
Asn Thr Gly Thr Leu Ala Gly Arg Lys Leu Asn Val Glu Ala Ser Asn
1475 1480 1485

aaa atc aaa aat caa ggg agt atc tta agt act caa gaa aca cgt tta 4512
Lys Ile Lys Asn Gln Gly Ser Ile Leu Ser Thr Gln Glu Thr Arg Leu
1490 1495 1500

gtc ggg cgt aaa ggt att gaa aac gta tct cgt tca ttt gca aat gat 4560
Val Gly Arg Lys Gly Ile Glu Asn Val Ser Arg Ser Phe Ala Asn Asp
1505 1510 1515 1520

gaa tta gga gtc act gca caa cgc tca gaa atc aaa acg gaa ggt cat 4608
Glu Leu Gly Val Thr Ala Gln Arg Ser Glu Ile Lys Thr Glu Gly His
1525 1530 1535

tta cat ctt gaa aca gat aag gat tca act att gat gta caa gca tcg 4656
Leu His Leu Glu Thr Asp Lys Asp Ser Thr Ile Asp Val Gln Ala Ser
1540 1545 1550

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gat att aaa gca aaa aca agc ttt gtg aag act ggt gat gtg aat ctc 4704
Asp Ile Lys Ala Lys Thr Ser Phe Val Lys Thr Gly Asp Val Asn Leu
1555 1560 1565

aaa aat aca tac aat act aaa cat gcc tac cgt gag aaa ttc tog ccg 4752
Lys Asn Thr Tyr Asn Thr Lys His Ala Tyr Arg Glu Lys Phe Ser Pro
1570 1575 1580

agt gca cta caa gtt gca gaa ctt gat gtg gca ggg ctt aaa gtc cca 4800
Ser Ala Leu Gln Val Ala Glu Leu Asp Val Ala Gly Leu Lys Val Pro
1585 1590 1595

ctt tta ggc gtg tcc gtc tcc atc cag ttt att cag agc ata cta gtg 4848
Leu Leu Gly Val Ser Val Ser Ile Gln Phe Ile Gln Ser Ile Leu Val
1605 1610 1615

agg caa ctt caa gag gga tca atc ttc gaa gta ggg cac tta cat ntt 4896
Arg Gln Leu Gln Glu Gly Ser Ile Phe Glu Val Gly His Leu His Xaa
1620 1625 1630

gag gta gac aga aga tgt gaa cca agc ggg gag ta 4931
Ala Val Asp Arg Arg Cys Glu Pro Ser Gly Glu
1635 1640

<210> 103
<211> 1643
<212> PRT
<213> Pasteurella multocida

<220>
<221> misc_feature
<222> 1632
<223> Xaa = any or unknown amino acid

<400> 103
Met Asn Lys Asn Arg Tyr Lys Leu Ile Phe Ser Gln Val Lys Gly Cys
1 5 10 15

Leu Val Pro Val Ala Glu Cys Ile Asn Ser Ala Ile Ser Asn Gly Ser
20 25 30

Ser Asp Ser Thr Ser Thr Ser Glu Gln Val Glu Glu Glu Pro Phe Leu
35 40 45

Leu Glu Gln Tyr Ser Leu Ser Ser Val Ser Leu Leu Val Lys Ser Thr
50 55 60

Phe Asn Pro Val Ser Tyr Ala Met Gln Leu Thr Trp Lys Gln Leu Ser
65 70 75 80

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

Gly Asp Glu Arg Asn Gln Leu Thr Val Ile Asp Asn Ser Asp His Ile
100 105 110

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

Gln Ala Glu Asn Lys Val Leu Val Ile Asp Ile Ala Lys Pro Asn Gly
130 135 140

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Lys Gly Ile Ser Asp Asn Arg Phe Glu Lys Phe Asn Ile Pro Asn Ser
 145 150 155 160
 Ala Val Phe Asn Asn Asn Gly Thr Glu Ala Gln Ala Arg Ser Thr Leu
 165 170 175
 Ile Gly Tyr Ile Pro Gln Asn Gln Asn Leu Arg Gly Gly Lys Glu Ala
 180 185 190
 Asp Val Ile Leu Asn Gln Val Thr Gly Pro Gln Glu Ser Lys Ile Val
 195 200 205
 Gly Ala Leu Glu Val Leu Gly Lys Lys Ala Asp Ile Val Ile Ala Asn
 210 215 220
 Gln Asn Gly Ile Thr Leu Asn Gly Val Arg Thr Ile Asn Ser Asp Arg
 225 230 235 240
 Phe Val Ala Thr Thr Ser Glu Leu Ile Asp Pro Asn Gln Met Met Leu
 245 250 255
 Lys Val Thr Lys Gly Asn Val Ile Ile Asp Ile Asp Gly Phe Ser Thr
 260 265 270
 Asp Gly Leu Lys Tyr Leu Asp Ile Ile Ala Lys Lys Ile Glu Gln Lys
 275 280 285
 Gln Ser Ile Thr Ser Gly Asp Asn Ser Glu Ala Lys Thr Asp Val Thr
 290 295 300
 Leu Ile Ala Gly Ser Ser Glu Tyr Asp Leu Ser Lys His Glu Leu Lys
 305 310 315 320
 Lys Thr Ser Gly Glu Asn Val Ser Asn Asp Val Ile Ala Ile Thr Gly
 325 330 335
 Ser Ser Thr Gly Ala Met His Gly Lys Asn Ile Lys Leu Ile Val Thr
 340 345 350
 Asp Lys Gly Ala Gly Val Lys His Asp Gly Ile Ile Leu Ser Glu Asn
 355 360 365
 Asp Ile Gln Ile Glu Met Asn Glu Gly Asp Leu Glu Leu Gly Asn Thr
 370 375 380
 Ile Gln Gln Thr Val Val Lys Lys Asp Arg Asn Ile Arg Ala Lys Lys
 385 390 395 400
 Lys Ile Glu Val Lys Asn Ala Asn Arg Val Phe Val Gly Ser Gln Thr
 405 410 415
 Lys Ser Asp Glu Ile Ser Leu Glu Ala Lys Gln Val Lys Ile Arg Lys
 420 425 430
 Asn Ala Glu Ile Arg Ser Thr Thr Gln Ala Lys Ile Val Ala Lys Gly
 435 440 445
 Ala Leu Ser Ile Glu Gln Asn Ala Lys Leu Val Ala Lys Lys Ile Asp
 450 455 460
 Val Ala Thr Glu Thr Leu Thr Asn Ala Gly Arg Ile Tyr Gly Arg Glu
 465 470 475 480

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Val Lys Leu Asp Thr Asn Asn Leu Ile Asn Asp Lys Glu Ile Tyr Ala
 485 490 495
 Glu Arg Lys Leu Ser Ile Leu Thr Lys Gly Lys Asp Leu Glu Ile Ile
 500 505 510
 Gln Asp Arg Tyr Leu Ser Pro Leu Met Arg Val Lys Ser Ser Val Arg
 515 520 525
 Phe Leu Gly Ser Pro Phe Phe Ser Ile Ser Pro Ser Met Leu Ala Ser
 530 535 540
 Leu Ser Ala Gln Phe Lys Pro Gly Phe Val Asn Lys Gly Leu Ile Glu
 545 550 555 560
 Ser Ala Gly Ser Ala Glu Leu Thr Phe Lys Glu Lys Thr Ser Phe Leu
 565 570 575
 Thr Glu Gly Asn Asn Phe Ile Arg Ala Lys Asp Ala Leu Thr Ile Asn
 580 585 590
 Ala Gln Asn Ile Glu Ile Asp Lys Asn Gln Asp Ile Gln Leu Gly Ala
 595 600 605
 Asn Ile Thr Leu Asn Val Glu Glu Asn Phe Val Asn Arg Ala Gly Thr
 610 615 620
 Leu Ala Thr Gly Lys Thr Leu Thr Ile Asn Thr Glu Ser Gly Ser Ile
 625 630 635 640
 Tyr Asn Leu Gly Gly Thr Leu Gly Ala Gly Lys Ser Leu Lys Leu Thr
 645 650 655
 Ala Lys Ser Thr Glu Glu Gly Met Gly Asn Ile Val Asn Gln Glu Asn
 660 665 670
 Gly Leu Phe His Thr Leu Gly Asn Met Met Leu Glu Ala Glu Arg Ser
 675 680 685
 Val Tyr Asn Ile Gly Asp Ile Tyr Ala Ser Lys Lys Leu Thr Val His
 690 695 700
 Thr His Asn Leu Ile Asn Asp Val Arg Leu Ser Gly Asn Val Ser Tyr
 705 710 715 720
 Lys Pro Ile Gly Ser Ser Arg Asp Tyr Asp Ile Ser Arg Val Ala Val
 725 730 735
 His Gly Trp His Asn Asn Val Tyr Lys Leu Asn Leu Asn Leu Gln Glu
 740 745 750
 Gln Asp Lys Thr Asp Ile Lys Val Val Lys Met Gly Ala Ile Arg Ser
 755 760 765
 Asp Gly Asp Phe Asp Phe Lys Gly Ile Lys Ala Thr Ser Ser Glu Ser
 770 775 780
 Lys Pro Gln Leu Ile Asn His Gly Leu Ile Asn Val Lys Gly Thr Phe
 785 790 795 800
 Asn Ala Glu Ala Asp Gln Val Val Asn Gln Met Lys Ala Phe Asn Gln
 805 810 815

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Asn Ala Leu Ala Ser Val Phe Lys Asn Pro Ala Lys Ile Thr Met Tyr
 820 825 830
 Tyr Gln Pro Leu Thr Arg Tyr Ile Trp Thr Pro Leu Ser Gly Asn Ala
 835 840 845
 Ser Arg Glu Phe Asn Asn Leu Glu Ser Phe Leu Asp Ala Leu Phe Gly
 850 855 860
 Ser Thr Thr Ile Leu Lys Ser Ser Phe Tyr Ser Thr Glu Asn Phe Ser
 865 870 875 880
 Ala Tyr Gln Leu Leu Ser His Ile Gln His Ser Pro Met Tyr Gln Lys
 885 890 895
 Ala Met Ala Gln Val Phe Gly Ala Glu Trp His Ser Lys Ser Tyr Asp
 900 905 910
 Glu Met Arg Asn Lys Trp Lys Ser Phe Lys Glu Asn Pro Thr Asp Phe
 915 920 925
 Ile Tyr Tyr Pro Ser Glu Lys Ala Lys Ile Leu Ala Gly Lys Leu Glu
 930 935 940
 Gly Lys Leu Thr Thr Leu Gln Asn Gly Glu Tyr Ala Glu Arg Gly Lys
 945 950 955 960
 Phe Asp Glu Ser Ile Gln Ile Gly Lys His Gln Leu Ser Leu Pro Ser
 965 970 975
 Val Glu Leu Lys Ala Glu Phe Ser Asp Lys Glu Arg Leu Glu Glu Asp
 980 985 990
 Gly Val Asp Leu Ser Ser Ile Ala Glu Leu Leu Glu Met Pro Asn Leu
 995 1000 1005
 Phe Ile Asp Asn Ser Ile Gln Leu Glu Lys Lys Lys Leu Ser Pro Ile
 1010 1015 1020
 Glu Asp Leu Asp Glu Glu Pro Arg Lys Asn Leu Asp Ile Glu Glu Ser
 1025 1030 1035 1040
 His Ser Asn Ser Ser Asp Asp Val Leu Ser Met Asn Asp Asp Glu Ser
 1045 1050 1055
 Asp Thr Asp Asp Ser Lys Trp Ser Met Gly Asn Asp Glu Lys Glu Met
 1060 1065 1070
 Pro Asp Asp Lys Leu Gly Ile Ser Arg Asp Asp Arg Gly Asn Lys Pro
 1075 1080 1085
 Pro Arg Thr Asp Pro Thr Val Asp Tyr Leu Asn Pro Asp Glu Phe Phe
 1090 1095 1100
 Glu Asn Gly Tyr Leu Leu Asn Glu Leu Leu Gln Glu Leu Gly Glu Glu
 1105 1110 1115 1120
 Pro Leu Leu Lys Glu Gly Glu Asp His Phe Lys Arg Ser Thr Asn Leu
 1125 1130 1135
 Val Arg Leu Gly Glu Arg Asp Arg Gln Asn Arg Glu Lys Arg Glu Lys
 1140 1145 1150

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Glu Gly Tyr Phe Asp Leu Pro Gly Thr Leu Asp Met Lys Leu Gln Glu
 1155 1160 1165
 Leu Phe Glu Lys Arg Lys Gln Lys His Glu Ala Glu Gln Lys Ala Arg
 1170 1175 1180
 Ile Glu Lys Ala Leu Leu Gln Lys Ser Glu Gln Gln Glu Lys Arg Val
 1185 1190 1195 1200
 Glu Glu Arg Lys Gln Glu Glu Lys Arg Gln Ala Gln Asp Lys Ile Ala
 1205 1210 1215
 Lys Gln Val Glu Ile Ala Lys Glu Met Gln Arg Val Glu Glu Ile Arg
 1220 1225 1230
 Gln Arg Glu Lys Gln Leu Ala Ile Gln Leu Gln Glu Glu Lys Lys
 1235 1240 1245
 Gln Gln Glu Glu Lys His Leu Ser Glu Glu Lys Lys Gln Ala Glu Gln
 1250 1255 1260
 Lys Gln Lys Ala Glu Glu Lys Val Ala Gln Glu Arg Leu Asp Ile Glu
 1265 1270 1275 1280
 Gln Gln Lys Ala Tyr Glu Glu Met Ala Lys Arg Glu Ala Glu Ala Ser
 1285 1290 1295
 Lys Asn Val Leu Leu Lys Ala Ile Asp Glu Glu Arg Pro Lys Val Glu
 1300 1305 1310
 Thr Asp Pro Leu Phe Arg Thr Lys Leu Lys Tyr Ile Asn Gln Asp Asp
 1315 1320 1325
 Tyr Ala Gly Ala Asn Tyr Phe Phe Asn Lys Val Gly Leu Asn Thr Lys
 1330 1335 1340
 Gly His Gln Lys Val Asn Val Leu Gly Asp Asn Tyr Phe Asp His Gln
 1345 1350 1355 1360
 Val Ile Thr Arg Ser Ile Glu Lys Lys Val Asp Asn His Leu Asn Gln
 1365 1370 1375
 Lys Tyr Asn Leu Ser Asp Val Glu Leu Val Lys Gln Leu Met Asp Asn
 1380 1385 1390
 Ser Thr Thr Gln Ala Gln Glu Leu Asp Leu Lys Leu Gly Ala Ala Leu
 1395 1400 1405
 Thr Lys Glu Gln Gln Ala Asn Leu Thr Gln Asp Ile Val Trp Tyr Val
 1410 1415 1420
 Lys Thr Lys Val Lys Gly Lys Asp Val Phe Val Pro Lys Val Tyr Phe
 1425 1430 1435 1440
 Ala Ser Glu Thr Leu Val Glu Ala Gln Lys Leu Gln Gly Leu Gly Thr
 1445 1450 1455
 Gly Thr Ile Arg Val Gly Glu Ala Lys Ile Lys Ala Lys Asp Val Val
 1460 1465 1470
 Asn Thr Gly Thr Leu Ala Gly Arg Lys Leu Asn Val Glu Ala Ser Asn
 1475 1480 1485

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Lys Ile Lys Asn Gln Gly Ser Ile Leu Ser Thr Gln Glu Thr Arg Leu
 1490 1495 1500
 Val Gly Arg Lys Gly Ile Glu Asn Val Ser Arg Ser Phe Ala Asn Asp
 1505 1510 1515 1520
 Glu Leu Gly Val Thr Ala Gln Arg Ser Glu Ile Lys Thr Glu Gly His
 1525 1530 1535
 Leu His Leu Glu Thr Asp Lys Asp Ser Thr Ile Asp Val Gln Ala Ser
 1540 1545 1550
 Asp Ile Lys Ala Lys Thr Ser Phe Val Lys Thr Gly Asp Val Asn Leu
 1555 1560 1565
 Lys Asn Thr Tyr Asn Thr Lys His Ala Tyr Arg Glu Lys Phe Ser Pro
 1570 1575 1580
 Ser Ala Leu Gln Val Ala Glu Leu Asp Val Ala Gly Leu Lys Val Pro
 1585 1590 1595 1600
 Leu Leu Gly Val Ser Val Ser Ile Gln Phe Ile Gln Ser Ile Leu Val
 1605 1610 1615
 Arg Gln Leu Gln Glu Gly Ser Ile Phe Glu Val Gly His Leu His Xaa
 1620 1625 1630
 Ala Val Asp Arg Arg Cys Glu Pro Ser Gly Glu
 1635 1640

<210> 104
 <211> 2009
 <212> DNA
 <213> Pasteurella multocida

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 <223> hmbR

<220>
 <221> CDS
 <222> (1)..(2007)

<400> 104
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 ccg cag gct gaa tcg act ata tct act tcc gca cgt tat tcg act gaa 96
 Pro Gln Ala Glu Ser Thr Ile Ser Thr Ser Ala Arg Tyr Ser Thr Glu
 20 25 30
 cgt cat aat ggt aat att aat att gaa tac gaa aat gtt agt tcg 144
 Arg His Asn Gly Asn Ile Asn Asn Ile Glu Tyr Glu Asn Val Ser Ser
 35 40 45
 ttg aaa gtt caa aaa ggg gca gct tct gta atg tat ggt agc ggt gcg 192
 Leu Lys Val Gln Lys Gly Ala Ala Ser Val Met Tyr Gly Ser Gly Ala
 50 55 60
 tta ggt gga acc gtg gag ttt acc aca aaa gat att gag gac ttt gtc 240
 Leu Gly Gly Thr Val Glu Phe Thr Thr Lys Asp Ile Glu Asp Phe Val
 65 70 75 80

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gaa cct ggt cgc cat ttg ggc ttt ttg tct aaa acc ggc tat act tca 288
 Glu Pro Gly Arg His Leu Gly Phe Leu Ser Lys Thr Gly Tyr Thr Ser
 85 90 95

aaa aac aga gaa tat cgt caa gtc atc gga gtt gga ggg aaa ggg gaa 336
 Lys Asn Arg Glu Tyr Arg Gln Val Ile Gly Val Gly Lys Gly Glu
 100 105 110

cac ttt ttt ggt ttt gta caa tta acc aaa cgt tgg ggg cat gaa aca 384
 His Phe Phe Gly Phe Val Gln Leu Thr Lys Arg Trp Gly His Glu Thr
 115 120 125

atc aac aac ggc aaa ggt aca gac att ctc ggc gaa cat cga ggt aaa 432
 Ile Asn Asn Gly Lys Gly Thr Asp Ile Leu Gly Glu His Arg Gly Lys
 130 135 140

ccc aat cgc ctc aac tac tat act aca tca tgg tta acg aaa gtc ggt 480
 Pro Asn Pro Leu Asn Tyr Thr Thr Ser Trp Leu Thr Lys Val Gly
 145 150 155

tac gat att aat aac act cat cgt ttt aca ctg ttt tta gaa gat cgc 528
 Tyr Asp Ile Asn Asn Thr His Arg Phe Thr Leu Phe Leu Glu Asp Arg
 165 170 175

cgt gaa aag aag ctt acc gaa gaa aaa aca tta ggg ctt agt gat gca 576
 Arg Glu Lys Lys Leu Thr Glu Glu Lys Thr Leu Gly Leu Ser Asp Ala
 180 185 190

gtg cgt ttt gct aat gat caa acc cct tat ctc cgt tat ggt att gaa 624
 Val Arg Phe Ala Asn Asp Gln Thr Pro Tyr Leu Arg Tyr Gly Ile Glu
 195 200 205

tat cga tat aac ggc ttg tct tgg ttg gaa acg gta aag ctt ttt ttg 672
 Tyr Arg Tyr Asn Gly Leu Ser Trp Leu Glu Thr Val Lys Leu Phe Leu
 210 215 220

gca aag cag aaa atc gaa caa cgt tct gct ctc caa gag ttt gat att 720
 Ala Lys Gln Lys Ile Glu Gln Arg Ser Ala Leu Gln Glu Phe Asp Ile
 225 230 235 240

aat aat agg aat aaa ttg gat tgc act atg tgc ttt gta tat tta caa 768
 Asn Asn Arg Asn Lys Leu Asp Ser Thr Met Ser Phe Val Tyr Leu Gln
 245 250 255

aga cag aat ata gct cgg gga gaa ttt tca acg agt cct tta tat tgg 816
 Arg Gln Asn Ile Ala Arg Gly Glu Phe Ser Thr Ser Pro Leu Tyr Trp
 260 265 270

ggg cgg agt cgc cat cgt tta tct gcg aaa ttc gaa ttt cgt gat aag 864
 Gly Pro Ser Arg His Arg Leu Ser Ala Lys Phe Glu Phe Arg Asp Lys
 275 280 285

ttt tta gaa aat atg aat aag cat ttt acg ttt cgg cgg tgg caa atc 912
 Phe Leu Glu Asn Met Asn Lys His Phe Thr Phe Arg Pro Trp Gln Ile
 290 295 300

aat aga ttc aga caa caa ggt cga aat aac tat aca gaa gtg ttt ccc 960
 Asn Arg Phe Arg Gln Gln Gly Arg Asn Asn Tyr Thr Glu Val Phe Pro
 305 310 315 320

gtt aaa tcc cga gag ttt tct ttt tct ctt atg gac gac att aag att 1008
 Val Lys Ser Arg Glu Phe Ser Phe Ser Leu Met Asp Asp Ile Lys Ile
 325 330 335

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ggc gaa ttg cta cat ctc gga ttg ggc ggt cgg tgg gat cac tat aac 1056
Gly Glu Leu Leu His Leu Gly Leu Gly Arg Trp Asp His Tyr Asn
340 345 350

tat aag cca tta tta aat tct cag cat aat atc aac agg aca cag aga 1104
Tyr Lys Pro Leu Leu Asn Ser Gln His Asn Ile Asn Arg Thr Gln Arg
355 360 365

tta cct tat cca aaa aca tca tcc aaa ttt tgg tat caa ttg agt tta 1152
Leu Pro Tyr Pro Lys Thr Ser Ser Lys Phe Ser Tyr Gln Leu Ser Leu
370 375 380

gag tat caa tta cat cca tca cat caa att gca tac cgt tta agt acc 1200
Glu Tyr Gln Leu His Pro Ser His Gln Ile Ala Tyr Arg Leu Ser Thr
385 390 395

ggt ttt agg gtt ccc cgt gtt gaa gat ctt tat ttt gaa gac cga gga 1248
Gly Phe Arg Val Pro Arg Val Glu Asp Leu Tyr Phe Glu Asp Arg Gly
405 410 415

aaa agt tct tca caa ttt ctt cct aac ccc gat cta caa ccg gaa act 1296
Lys Ser Ser Ser Gln Phe Leu Pro Asn Pro Asp Leu Gln Pro Glu Thr
420 425 430

gca ctg aat cat gaa ata agt tac cgt ttc caa aat caa tat gcc cat 1344
Ala Leu Asn His Glu Ile Ser Tyr Arg Phe Gln Asn Gln Tyr Ala His
435 440 445

ttc agc gtc ggg ctt ttc cgt aca cgt tat cat aac ttt att caa gaa 1392
Phe Ser Val Gly Leu Phe Arg Thr Arg Tyr His Asn Phe Ile Gln Glu
450 455 460

cgt gag atg acc tgt gat aaa att cca tat gag tat aat agg act tat 1440
Arg Glu Met Thr Cys Asp Lys Ile Pro Tyr Glu Tyr Asn Arg Thr Tyr
465 470 475

gga tat tgc acg cat aat act tat gta atg ttt gtt aat gaa cct gaa 1488
Gly Tyr Cys Thr His Asn Thr Tyr Val Met Phe Val Asn Glu Pro Glu
485 490 495

gcc gtg att aaa ggg gtt gaa gta agc ggt gct tta aat ggg tgg gca 1536
Ala Val Ile Lys Gly Val Glu Val Ser Gly Ala Leu Asn Gly Ser Ala
500 505 510

ttc gga ctt tcc gac ggt tta act ttc cgt ctc aaa ggg agc tac agc 1584
Phe Gly Leu Ser Asp Gly Leu Thr Phe Arg Leu Lys Gly Ser Tyr Ser
515 520 525

aaa ggt caa aat cat gac ggc gat ccg tta aaa tct att caa cca tgg 1632
Lys Gly Gln Asn His Asp Gly Asp Pro Leu Lys Ser Ile Gln Pro Trp
530 535 540

aca gtg gta acc ggt att gat tac gaa act gaa ggg tgg agc gtg agt 1680
Thr Val Val Thr Gly Ile Asp Tyr Glu Thr Glu Gly Trp Ser Val Ser
545 550 555

ttg agc ggg cgt tat agt gcg gct aaa aaa gcc aaa gat gcg ata gaa 1728
Leu Ser Gly Arg Tyr Ser Ala Ala Lys Lys Ala Lys Asp Ala Ile Glu
565 570 575

acg gaa tac aca cat gat aaa aag gtt gtc aaa caa tgg ccg cat tta 1776
Thr Glu Tyr Thr His Asp Lys Lys Val Val Lys Gln Trp Pro His Leu
580 585 590

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agt cca tcc tac ttt gtt gtt gat ttt acg ggg caa gtt aac ctc agt 1824
Ser Pro Ser Tyr Phe Val Val Asp Phe Thr Gly Gln Val Asn Leu Ser
595 600 605

aaa aat gtc att ttg aat atg ggg gta ttt aac ttg ttc aat cgt gat 1872
Lys Asn Val Ile Leu Asn Met Gly Val Phe Asn Leu Phe Asn Arg Asp
610 615 620

tat atg acg tgg gac agt gca tat aac ttg ttt act agg ggg tat act 1920
Tyr Met Thr Trp Asp Ser Ala Tyr Asn Leu Phe Thr Arg Gly Tyr Thr
625 630 635 640

tcc cgt tct gtc cgt gct aac agc cca ggc att aat cgg ttt acc gca 1968
Ser Arg Ser Val Arg Ala Asn Ser Pro Gly Ile Asn Arg Phe Thr Ala
645 650 655

cca aaa cgt aat ttt gct gcc tcg gtg gaa att cgt ttt ta 2009
Pro Lys Arg Asn Phe Ala Ala Ser Val Glu Ile Arg Phe
660 665

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<210> 105
 <211> 669
 <212> PRT
 <213> Pasteurella multocida

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<400> 105
Ile Arg Gly Val Asp Lys Asp Arg Val Ala Val Ile Val Asp Gly Ile
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Pro Gln Ala Glu Ser Thr Ile Ser Thr Ser Ala Arg Tyr Ser Thr Glu
20 25 30

Arg His Asn Gly Asn Ile Asn Asn Ile Glu Tyr Glu Asn Val Ser Ser
35 40 45

Leu Lys Val Gln Lys Gly Ala Ala Ser Val Met Tyr Gly Ser Gly Ala
50 55 60

Leu Gly Gly Thr Val Glu Phe Thr Thr Lys Asp Ile Glu Asp Phe Val
65 70 75 80

Glu Pro Gly Arg His Leu Gly Phe Leu Ser Lys Thr Gly Tyr Thr Ser
85 90 95

Lys Asn Arg Glu Tyr Arg Gln Val Ile Gly Val Gly Gly Lys Gly Glu
100 105 110

His Phe Phe Gly Phe Val Gln Leu Thr Lys Arg Trp Gly His Glu Thr
115 120 125

Ile Asn Asn Gly Lys Gly Thr Asp Ile Leu Gly Glu His Arg Gly Lys
130 135 140

Pro Asn Pro Leu Asn Tyr Tyr Thr Thr Ser Trp Leu Thr Lys Val Gly
145 150 155 160

Tyr Asp Ile Asn Asn Thr His Arg Phe Thr Leu Phe Leu Glu Asp Arg
165 170 175

Arg Glu Lys Lys Leu Thr Glu Glu Lys Thr Leu Gly Leu Ser Asp Ala
180 185 190

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Val Arg Phe Ala Asn Asp Gln Thr Pro Tyr Leu Arg Tyr Gly Ile Glu
 195 200 205
 Tyr Arg Tyr Asn Gly Leu Ser Trp Leu Glu Thr Val Lys Leu Phe Leu
 210 215 220
 Ala Lys Gln Lys Ile Glu Gln Arg Ser Ala Leu Gln Glu Phe Asp Ile
 225 230 235 240
 Asn Asn Arg Asn Lys Leu Asp Ser Thr Met Ser Phe Val Tyr Leu Gln
 245 250 255
 Arg Gln Asn Ile Ala Arg Gly Glu Phe Ser Thr Ser Pro Leu Tyr Trp
 260 265 270
 Gly Pro Ser Arg His Arg Leu Ser Ala Lys Phe Glu Phe Arg Asp Lys
 275 280 285
 Phe Leu Glu Asn Met Asn Lys His Phe Thr Phe Arg Pro Trp Gln Ile
 290 295 300
 Asn Arg Phe Arg Gln Gln Gly Arg Asn Asn Tyr Thr Glu Val Phe Pro
 305 310 315 320
 Val Lys Ser Arg Glu Phe Ser Phe Ser Leu Met Asp Asp Ile Lys Ile
 325 330 335
 Gly Glu Leu Leu His Leu Gly Leu Gly Gly Arg Trp Asp His Tyr Asn
 340 345 350
 Tyr Lys Pro Leu Leu Asn Ser Gln His Asn Ile Asn Arg Thr Gln Arg
 355 360 365
 Leu Pro Tyr Pro Lys Thr Ser Ser Lys Phe Ser Tyr Gln Leu Ser Leu
 370 375 380
 Glu Tyr Gln Leu His Pro Ser His Gln Ile Ala Tyr Arg Leu Ser Thr
 385 390 395 400
 Gly Phe Arg Val Pro Arg Val Glu Asp Leu Tyr Phe Glu Asp Arg Gly
 405 410 415
 Lys Ser Ser Ser Gln Phe Leu Pro Asn Pro Asp Leu Gln Pro Glu Thr
 420 425 430
 Ala Leu Asn His Glu Ile Ser Tyr Arg Phe Gln Asn Gln Tyr Ala His
 435 440 445
 Phe Ser Val Gly Leu Phe Arg Thr Arg Tyr His Asn Phe Ile Gln Glu
 450 455 460
 Arg Glu Met Thr Cys Asp Lys Ile Pro Tyr Glu Tyr Asn Arg Thr Tyr
 465 470 475 480
 Gly Tyr Cys Thr His Asn Thr Tyr Val Met Phe Val Asn Glu Pro Glu
 485 490 495
 Ala Val Ile Lys Gly Val Glu Val Ser Gly Ala Leu Asn Gly Ser Ala
 500 505 510
 Phe Gly Leu Ser Asp Gly Leu Thr Phe Arg Leu Lys Gly Ser Tyr Ser
 515 520 525

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Lys Gly Gln Asn His Asp Gly Asp Pro Leu Lys Ser Ile Gln Pro Trp
 530 535 540
 Thr Val Val Thr Gly Ile Asp Tyr Glu Thr Glu Gly Trp Ser Val Ser
 545 550 555 560
 Leu Ser Gly Arg Tyr Ser Ala Ala Lys Lys Ala Lys Asp Ala Ile Glu
 565 570 575
 Thr Glu Tyr Thr His Asp Lys Lys Val Val Lys Gln Trp Pro His Leu
 580 585 590
 Ser Pro Ser Tyr Phe Val Val Asp Phe Thr Gly Gln Val Asn Leu Ser
 595 600 605
 Lys Asn Val Ile Leu Asn Met Gly Val Phe Asn Leu Phe Asn Arg Asp
 610 615 620
 Tyr Met Thr Trp Asp Ser Ala Tyr Asn Leu Phe Thr Arg Gly Tyr Thr
 625 630 635 640
 Ser Arg Ser Val Arg Ala Asn Ser Pro Gly Ile Asn Arg Phe Thr Ala
 645 650 655
 Pro Lys Arg Asn Phe Ala Ala Ser Val Glu Ile Arg Phe
 660 665

<210> 106
 <211> 908
 <212> DNA
 <213> Pasteurella multocida

<220>
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<220>
 <221> CDS
 <222> (1)...(906)

<400> 106
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 1 5 10 15
 gtt gcg att aaa agc att ata aat cat aat gaa aaa ggt att tca ttt 96
 Val Ala Ile Lys Ser Ile Ile Asn His Asn Glu Lys Gly Ile Ser Phe
 20 25 30
 tat att ttt gat ttg ggt ata aag gat gaa aat aag aga aat att aat 144
 Tyr Ile Phe Asp Leu Gly Ile Lys Asp Glu Asn Lys Arg Asn Ile Asn
 35 40 45
 gat att gtt tct tct tat gga agt gaa gtc aac ttt att gct gtg aat 192
 Asp Ile Val Ser Ser Tyr Gly Ser Glu Val Asn Phe Ile Ala Val Asn
 50 55 60
 gag aaa gaa ttt gag agt ttt cct gtt caa att agt tat att tct tta 240
 Glu Lys Glu Phe Glu Ser Phe Pro Val Gln Ile Ser Tyr Ile Ser Leu
 65 70 75 80

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gca aca tat gca agg cta aaa gcg gca gag tat ttg ccg gat aat tta 288
Ala Thr Tyr Ala Arg Leu Lys Ala Ala Glu Tyr Leu Pro Asp Asn Leu
      85                      90                      95

aat aaa att att tat tta gat gtt gat gtt ttg gtt ttt aac tca tta 336
Asn Lys Ile Ile Tyr Leu Asp Val Asp Val Leu Val Phe Asn Ser Leu
      100                    105                    110

gaa atg tta tgg aat gtt gat gtt aat aat ttt ctt acc gca gcc tgt 384
Glu Met Leu Trp Asn Val Asp Val Asn Asn Phe Leu Thr Ala Ala Cys
      115                    120                    125

tat gat tct ttc atc gaa aat gaa aag tct gag cat aaa aaa tcg att 432
Tyr Asp Ser Phe Ile Glu Asn Glu Lys Ser Glu His Lys Lys Ser Ile
      130                    135                    140

tca atg tca gat aag gaa tat tat ttt aat gca gga gta atg cta ttt 480
Ser Met Ser Asp Lys Glu Tyr Tyr Phe Asn Ala Gly Val Met Leu Phe
      145                    150                    155                    160

aat tta gat gaa tgg cgg aag atg gat gta ttc tca aga gct tta gac 528
Asn Leu Asp Glu Trp Arg Lys Met Asp Val Phe Ser Arg Ala Leu Asp
      165                    170                    175

ctg tta gct atg tat cct aat caa atg att tat cag gat caa gat ata 576
Leu Leu Ala Met Tyr Pro Asn Gln Met Ile Tyr Gln Asp Gln Asp Ile
      180                    185                    190

ttg aat atc ctt ttt agg aat aaa gtc tgt tat tta gat tgc aga ttt 624
Leu Asn Ile Leu Phe Arg Asn Lys Val Cys Tyr Leu Asp Cys Arg Phe
      195                    200                    205

aat ttc atg cca aat caa ctt gaa aga ata aaa caa tac cat aaa gga 672
Asn Phe Met Pro Asn Gln Leu Glu Arg Ile Lys Gln Tyr His Lys Gly
      210                    215                    220

aaa ttg agc aac tta cat tct tta gaa aaa aca acg atg cct gtc gtt 720
Lys Leu Ser Asn Leu His Ser Leu Glu Lys Thr Thr Met Pro Val Val
      225                    230                    235                    240

att tca cat tat tgt ggt cca gaa aaa gcg tgg cat gcg gat tgt aaa 768
Ile Ser His Tyr Cys Gly Pro Glu Lys Ala Trp His Ala Asp Cys Lys
      245                    250                    255

cat ttt aat gta tat ttc tat cag aaa ata tta gca gaa ata acg aga 816
His Phe Asn Val Tyr Phe Tyr Gln Lys Ile Leu Ala Glu Ile Thr Arg
      260                    265                    270

ggc acg gat aaa gaa cgc gta tta tct ata aaa act tat ctc aag gcc 864
Gly Thr Asp Lys Glu Arg Val Leu Ser Ile Lys Thr Tyr Leu Lys Ala
      275                    280                    285

ttg att aga agg att aga tat aaa ttc aaa tat caa gtc tat ta 908
Leu Ile Arg Arg Ile Arg Tyr Lys Phe Lys Tyr Gln Val Tyr
      290                    295                    300

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<210> 107
 <211> 302
 <212> PRT
 <213> Pasteurella multocida
 <400> 107

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Met Asn Ile Leu Phe Val Ser Asp Asp Val Tyr Ala Lys His Leu Val
 1           5           10           15
Val Ala Ile Lys Ser Ile Ile Asn His Asn Glu Lys Gly Ile Ser Phe
 20           25           30
Tyr Ile Phe Asp Leu Gly Ile Lys Asp Glu Asn Lys Arg Asn Ile Asn
 35           40           45
Asp Ile Val Ser Ser Tyr Gly Ser Glu Val Asn Phe Ile Ala Val Asn
 50           55           60
Glu Lys Glu Phe Glu Ser Phe Pro Val Gln Ile Ser Tyr Ile Ser Leu
 65           70           75           80
Ala Thr Tyr Ala Arg Leu Lys Ala Ala Glu Tyr Leu Pro Asp Asn Leu
 85           90           95
Asn Lys Ile Ile Tyr Leu Asp Val Asp Val Leu Val Phe Asn Ser Leu
100           105           110
Glu Met Leu Trp Asn Val Asp Val Asn Asn Phe Leu Thr Ala Ala Cys
115           120           125
Tyr Asp Ser Phe Ile Glu Asn Glu Lys Ser Glu His Lys Lys Ser Ile
130           135           140
Ser Met Ser Asp Lys Glu Tyr Tyr Phe Asn Ala Gly Val Met Leu Phe
145           150           155           160
Asn Leu Asp Glu Trp Arg Lys Met Asp Val Phe Ser Arg Ala Leu Asp
165           170           175
Leu Leu Ala Met Tyr Pro Asn Gln Met Ile Tyr Gln Asp Gln Asp Ile
180           185           190
Leu Asn Ile Leu Phe Arg Asn Lys Val Cys Tyr Leu Asp Cys Arg Phe
195           200           205
Asn Phe Met Pro Asn Gln Leu Glu Arg Ile Lys Gln Tyr His Lys Gly
210           215           220
Lys Leu Ser Asn Leu His Ser Leu Glu Lys Thr Thr Met Pro Val Val
225           230           235           240
Ile Ser His Tyr Cys Gly Pro Glu Lys Ala Trp His Ala Asp Cys Lys
245           250           255
His Phe Asn Val Tyr Phe Tyr Gln Lys Ile Leu Ala Glu Ile Thr Arg
260           265           270

Gly Thr Asp Lys Glu Arg Val Leu Ser Ile Lys Thr Tyr Leu Lys Ala
275           280           285
Leu Ile Arg Arg Ile Arg Tyr Lys Phe Lys Tyr Gln Val Tyr
290           295           300

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<210> 108
 <211> 2054
 <212> DNA
 <213> Pasteurella multocida

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<221> CDS
<222> (1) .. (2052)
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1 5 10 15
aaa gat gtg aaa gaa ggt caa gac ttc ttc cca tta act gtt aac tat 96
Lys Asp Val Lys Glu Gly Gln Asp Phe Phe Pro Leu Thr Val Asn Tyr
20 25 30
caa gag cgt act tat gct gca ggc cgt att cct ggt ggc ttt ttc aaa 144
Gln Glu Arg Thr Tyr Ala Ala Gly Arg Ile Pro Gly Gly Phe Phe Lys
35 40 45
cgt gaa ggt cgt cct tct gaa ggc gaa act tta att gct cgt tta att 192
Arg Glu Gly Arg Pro Ser Glu Gly Glu Thr Leu Ile Ala Arg Leu Ile
50 55 60
gac cgt cca att cgt cct ctt ttc cca gaa ggt ttt tat aac gaa atc 240
Asp Arg Pro Ile Arg Pro Leu Phe Pro Glu Gly Phe Tyr Asn Glu Ile
65 70 75 80
caa atc gtg gcg aca gtg gtg tct gtt aat ccg caa att tgt cca gat 288
Gln Ile Val Ala Thr Val Val Ser Val Asn Pro Gln Ile Cys Pro Asp
85 90 95
tta gtg gca atg atc ggt gca tct gcg gca ctt tct tta tca ggt gtg 336
Leu Val Ala Met Ile Gly Ala Ser Ala Ala Leu Ser Leu Ser Gly Val
100 105 110
cca ttt aat ggc cct atc ggt gcg gca cgt gtt ggt ttt att gat gat 384
Pro Phe Asn Gly Pro Ile Gly Ala Ala Arg Val Gly Phe Ile Asp Asp
115 120 125
caa ttt gtg tta aac cca acc atg aac gag caa aaa caa agc cgt tta 432
Gln Phe Val Leu Asn Pro Thr Met Asn Glu Gln Lys Gln Ser Arg Leu
130 135 140
gac ttg gtt gtc gcg gga aca gat aaa gcg gtg tta atg gtg gaa tct 480
Asp Leu Val Val Ala Gly Thr Asp Lys Ala Val Leu Met Val Glu Ser
145 150 155 160
gaa gcc gat gta tta acc gaa gaa caa atg tta gct gcg gtg gtg ttt 528
Glu Ala Asp Val Leu Thr Glu Glu Gln Met Leu Ala Ala Val Val Phe
165 170 175
ggt cat cag caa caa caa gtg gtg att gac gcg atc aaa gaa ttt acc 576
Gly His Gln Gln Gln Gln Val Val Ile Asp Ala Ile Lys Glu Phe Thr
180 185 190
gca gaa gcc ggt aaa ccg cgt tgg gat tgg gtg gca cct gaa cca aat 624
Ala Glu Ala Gly Lys Pro Arg Trp Asp Trp Val Ala Pro Glu Pro Asn
195 200 205
acc gcg tta att gaa aaa gtg aaa gcg att gca gaa gcg cgt tta gcc 672
Thr Ala Leu Ile Glu Lys Val Lys Ala Ile Ala Glu Ala Arg Leu Gly
210 215 220

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gaa gca tac cgt atc act gaa aaa caa gca cgt tat gaa caa att gat 720
Glu Ala Tyr Arg Ile Thr Glu Lys Gln Ala Arg Tyr Glu Gln Ile Asp
225          230          235          240

gcg att aaa gct gat gtg att gca caa atc aca gct gaa gta gca gaa 768
Ala Ile Lys Ala Asp Val Ile Ala Gln Ile Thr Ala Glu Val Ala Glu
245          250          255

ggc gaa gac atc agt gaa ggg aaa att gtc gat att ttc acc gca ctt 816
Gly Glu Asp Ile Ser Glu Gly Lys Ile Val Asp Ile Phe Thr Ala Leu
260          265          270

gaa agc caa atc gta cgt agc cgt atc att gct ggt gaa cca cgt att 864
Glu Ser Gln Ile Val Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile
275          280          285

gat ggt cgt aca gtg gat act gtt cgt gca tta gat att tgt act ggt 912
Asp Gly Arg Thr Val Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Gly
290          295          300

gtt tta cca cgt aca cac ggt tct gcg att ttc acc cgt ggt gaa aca 960
Val Leu Pro Arg Thr His Gly Ser Ala Ile Phe Thr Arg Gly Glu Thr
305          310          315          320

cag gcg tta gct gtc gcg aca tta ggt aca gaa cgt gat gca caa att 1008
Gln Ala Leu Ala Val Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile
325          330          335

att gat gaa tta aca ggt gag cgt tca gat cac ttc tta ttc cac tac 1056
Ile Asp Glu Leu Thr Gly Glu Arg Ser Asp His Phe Leu Phe His Tyr
340          345          350

aac ttc ccg cca tat tct gtg ggt gaa acc ggt atg att ggt tca cca 1104
Asn Phe Pro Pro Tyr Ser Val Gly Glu Thr Gly Met Ile Gly Ser Pro
355          360          365

aaa cgt cgt gaa att ggt cat ggt cgt tta gcg aaa cgc ggt gta gct 1152
Lys Arg Arg Glu Ile Gly His Gly Arg Leu Ala Lys Arg Gly Val Ala
370          375          380

gca gtg atg cca aca ctt gcc gag ttc cgc tat gtg gta cgt gtt gtc 1200
Ala Val Met Pro Thr Leu Ala Glu Phe Pro Tyr Val Val Arg Val Val
385          390          395          400

tct gaa atc aca gaa tca aat ggt tct tct tct atg gca tcg gtt tgt 1248
Ser Glu Ile Thr Glu Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys
405          410          415

ggt gcg tct tta gca tta atg gat gcg ggt gta cca att aaa gcg gcg 1296
Gly Ala Ser Leu Ala Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala
420          425          430

gtt gca ggt att gca atg gcc tta gtc aaa gaa gac gaa aaa ttt gtg 1344
Val Ala Gly Ile Ala Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val
435          440          445

gtg ctt tca gac atc tta ggt gat gaa gat cac tta ggt gac atg gac 1392
Val Leu Ser Asp Ile Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp
450          455          460

ttc aaa gtc gcg ggt aca cgt acg ggt gtg acg gca tta caa atg gat 1440
Phe Lys Val Ala Gly Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp
465          470          475          480

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atc aaa atc gaa ggt atc aca gca gaa atc atg caa att gcg tta aac 1488
ile lys ile glu gly ile thr ala glu ile met gln ile ala leu asn
      485      490      495

caa gcg aaa agc gca cgt tta cac att tta ggt gtg atg gag caa gcg 1536
gln ala lys ser ala arg leu his ile leu gly val met glu gln ala
      500      505      510

atc cca gcg cca cgt gcg gat att tct gat ttt gca ccg cgt att tac 1584
ile pro ala pro arg ala asp ile ser asp phe ala pro arg ile tyr
      515      520      525

act atg aaa att gat ccg aag aaa atc aaa gat gtg atc ggt aaa ggt 1632
thr met lys ile asp pro lys lys ile lys asp val ile gly lys gly
      530      535      540

ggt gca acc att cgt gcc tta aca gaa gaa aca ggt acc tca att gat 1680
gly ala thr ile arg ala leu thr glu glu thr gly thr ser ile asp
      545      550      555

atc gat gat gat ggt acg gtg aag att gct gcg gtt gat ggc aat tca 1728
ile asp asp asp gly thr val lys ile ala ala val asp gly asn ser
      565      570      575

gca aaa gag gtg atg gcg cgt att gaa gat att act gca gaa gtt gaa 1776
ala lys glu val met ala arg ile glu asp ile thr ala glu val glu
      580      585      590

gcg ggt gca gtg tat aaa ggt aaa gtt act cgt tta gct gat ttt ggt 1824
ala gly ala val tyr lys gly lys val thr arg leu ala asp phe gly
      595      600      605

gcc ttc gtt tct atc gta ggt aac aaa gaa ggc tta gtg cat att tct 1872
ala phe val ser ile val gly asn lys glu gly leu val his ile ser
      610      615      620

caa atc gcg gaa gag cgt gtt gag aaa gtg agt gat tat ctt gca gtg 1920
gln ile ala glu glu arg val glu lys val ser asp tyr leu ala val
      625      630      635

ggg caa gaa gtg act gtt aaa gtg gtt gag att gat cgt caa ggt cgt 1968
gly gln glu val thr val lys val val glu ile asp arg gln gly arg
      645      650      655

att cgt tta acc atg aaa gaa gtt gca cca aag caa gaa cac gtt gat 2016
ile arg leu thr met lys glu val ala pro lys gln glu his val asp
      660      665      670

tct gtt gtc gca gac gtt gcc gca gaa gaa aac gca ta 2054
ser val val ala asp val ala ala glu glu asn ala
      675      680

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<210> 109
 <211> 684
 <212> PRT
 <213> Pasteurella multocida

<400> 109
 Met Ala Ser Met Asp Asp Thr Thr Val Phe Val Thr Val Val Ala Lys
 1 5 10 15
 Lys Asp Val Lys Glu Gly Gln Asp Phe Phe Pro Leu Thr Val Asn Tyr

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      20      25      30
Gln Glu Arg Thr Tyr Ala Ala Gly Arg Ile Pro Gly Gly Phe Phe Lys
   35           40           45
Arg Glu Gly Arg Pro Ser Glu Gly Glu Thr Leu Ile Ala Arg Leu Ile
   50           55           60
Asp Arg Pro Ile Arg Pro Leu Phe Pro Glu Gly Phe Tyr Asn Glu Ile
   65           70           75           80
Gln Ile Val Ala Thr Val Val Ser Val Asn Pro Gln Ile Cys Pro Asp
   85           90           95
Leu Val Ala Met Ile Gly Ala Ser Ala Ala Leu Ser Leu Ser Gly Val
  100           105           110
Pro Phe Asn Gly Pro Ile Gly Ala Ala Arg Val Gly Phe Ile Asp Asp
  115           120           125
Gln Phe Val Leu Asn Pro Thr Met Asn Glu Gln Lys Gln Ser Arg Leu
  130           135           140
Asp Leu Val Val Ala Gly Thr Asp Lys Ala Val Leu Met Val Glu Ser
  145           150           155           160
Glu Ala Asp Val Leu Thr Glu Glu Gln Met Leu Ala Ala Val Val Phe
  165           170           175
Gly His Gln Gln Gln Gln Val Val Ile Asp Ala Ile Lys Glu Phe Thr
  180           185           190
Ala Glu Ala Gly Lys Pro Arg Trp Asp Trp Val Ala Pro Glu Pro Asn
  195           200           205
Thr Ala Leu Ile Glu Lys Val Lys Ala Ile Ala Glu Ala Arg Leu Gly
  210           215           220
Glu Ala Tyr Arg Ile Thr Glu Lys Gln Ala Arg Tyr Glu Gln Ile Asp
  225           230           235           240
Ala Ile Lys Ala Asp Val Ile Ala Gln Ile Thr Ala Glu Val Ala Glu
  245           250           255
Gly Glu Asp Ile Ser Glu Gly Lys Ile Val Asp Ile Phe Thr Ala Leu
  260           265           270
Glu Ser Gln Ile Val Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile
  275           280           285
Asp Gly Arg Thr Val Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Gly
  290           295           300
Val Leu Pro Arg Thr His Gly Ser Ala Ile Phe Thr Arg Gly Glu Thr
  305           310           315           320
Gln Ala Leu Ala Val Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile
  325           330           335
Ile Asp Glu Leu Thr Gly Glu Arg Ser Asp His Phe Leu Phe His Tyr
  340           345           350
Asn Phe Pro Pro Tyr Ser Val Gly Glu Thr Gly Met Ile Gly Ser Pro

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355 360 365
Lys Arg Arg Glu Ile Gly His Gly Arg Leu Ala Lys Arg Gly Val Ala
370 375 380
Ala Val Met Pro Thr Leu Ala Glu Phe Pro Tyr Val Val Arg Val Val
385 390 395 400
Ser Glu Ile Thr Glu Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys
405 410 415
Gly Ala Ser Leu Ala Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala
420 425 430
Val Ala Gly Ile Ala Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val
435 440 445
Val Leu Ser Asp Ile Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp
450 455 460
Phe Lys Val Ala Gly Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp
465 470 475 480
Ile Lys Ile Glu Gly Ile Thr Ala Glu Ile Met Gln Ile Ala Leu Asn
485 490 495
Gln Ala Lys Ser Ala Arg Leu His Ile Leu Gly Val Met Glu Gln Ala
500 505 510
Ile Pro Ala Pro Arg Ala Asp Ile Ser Asp Phe Ala Pro Arg Ile Tyr
515 520 525
Thr Met Lys Ile Asp Pro Lys Lys Ile Lys Asp Val Ile Gly Lys Gly
530 535 540
Gly Ala Thr Ile Arg Ala Leu Thr Glu Glu Thr Gly Thr Ser Ile Asp
545 550 555 560
Ile Asp Asp Asp Gly Thr Val Lys Ile Ala Ala Val Asp Gly Asn Ser
565 570 575
Ala Lys Glu Val Met Ala Arg Ile Glu Asp Ile Thr Ala Glu Val Glu
580 585 590
Ala Gly Ala Val Tyr Lys Gly Lys Val Thr Arg Leu Ala Asp Phe Gly
595 600 605
Ala Phe Val Ser Ile Val Gly Asn Lys Glu Gly Leu Val His Ile Ser
610 615 620
Gln Ile Ala Glu Glu Arg Val Glu Lys Val Ser Asp Tyr Leu Ala Val
625 630 635 640
Gly Gln Glu Val Thr Val Lys Val Val Glu Ile Asp Arg Gln Gly Arg
645 650 655
Ile Arg Leu Thr Met Lys Glu Val Ala Pro Lys Gln Glu His Val Asp
660 665 670
Ser Val Val Ala Asp Val Ala Ala Glu Glu Asn Ala
675 680

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<210> 110
 <211> 1514
 <212> DNA
 <213> *Pasteurella multocida*

<220>
 <223> purF

<220>
 <221> CDS
 <222> (1)..(1512)

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<400> 110
atg tgt ggt att gtt ggt att gtt agc caa agc ccc gtt aac caa tca 48
Met Cys Gly Ile Val Gly Ile Val Ser Gln Ser Pro Val Asn Gln Ser
1 5 10 15

att tat gat gcg tta acc tta ttg caa cac cgc ggg caa gac gcc gcc 96
Ile Tyr Asp Ala Leu Thr Leu Leu Gln His Arg Gly Gln Asp Ala Ala
20 25 30

ggg att gta acc gta gat gat gaa aac cga ttc cgc ttg cgt aaa gcg 144
Gly Ile Val Thr Val Asp Asp Glu Asn Arg Phe Arg Leu Arg Lys Ala
35 40 45

aac ggg tta gtc agc gat gta ttt gaa caa gtt cat atg tta cgt tta 192
Asn Gly Leu Val Ser Asp Val Phe Glu Gln Val His Met Leu Arg Leu
50 55 60

caa ggc aat gct ggc att gga cat gtt cgt tat cct acg gct ggg agc 240
Gln Gly Asn Ala Gly Ile Gly His Val Arg Tyr Pro Thr Ala Gly Ser
65 70 75 80

tca agt gtc tct gaa gcg caa cct ttt tat gta aat tcg cct tat ggc 288
Ser Ser Val Ser Glu Ala Gln Pro Phe Tyr Val Asn Ser Pro Tyr Gly
85 90 95

tta acc tta gtg cat aat ggt aac ttg acc aat tca agt gaa tta aaa 336
Leu Thr Leu Val His Asn Gly Asn Leu Thr Asn Ser Ser Glu Leu Lys
100 105 110

gaa aag tta ttt cgt ctc gca cgt cgc cat gta aat acc aat tca gat 384
Glu Lys Leu Phe Arg Leu Ala Arg Arg His Val Asn Thr Asn Ser Asp
115 120 125

tct gaa tta tta ctc aat atc tta gcc aat cac ctt gat cac ttc gaa 432
Ser Glu Leu Leu Leu Asn Ile Leu Ala Asn His Leu Asp His Phe Glu
130 135 140

aaa tac caa tta gat ccg caa gat gta ttc agt gct gtc aaa caa acg 480
Lys Tyr Gln Leu Asp Pro Gln Asp Val Phe Ser Ala Val Lys Gln Thr
145 150 155 160

cat cag gat att cgt ggt gct tat gct tgt atc gcc atg att att ggt 528
His Gln Asp Ile Arg Gly Ala Tyr Ala Cys Ile Ala Met Ile Ile Gly
165 170 175

cat ggt atg gtc gcg ttt cgt gat ccg aac ggt atc cgt ccg tta gtg 576
His Gly Met Val Ala Phe Arg Asp Pro Asn Gly Ile Arg Pro Leu Val
180 185 190

tta ggg aaa cgc gag gaa aat ggc aaa aca gag tat atg ttt gcc tcc 624
Leu Gly Lys Arg Glu Glu Asn Gly Lys Thr Glu Tyr Met Phe Ala Ser

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195          200          205
gaa agt atc gca tta gat aca gtg ggt ttt gag ttt gta cga gat gta 672
Glu Ser Ile Ala Leu Asp Thr Val Gly Phe Glu Phe Val Arg Asp Val
210          215          220

caa ccc gcc gaa gcg att tat gtc acg ttt gaa ggg gaa atg tat gct 720
Gln Pro Gly Glu Ala Ile Tyr Val Thr Phe Glu Gly Glu Met Tyr Ala
225          230          235          240

cag caa tgc gca gac aaa cca aca tta aca cct tgt att ttt gaa tac 768
Gln Gln Cys Ala Asp Lys Pro Thr Leu Thr Pro Cys Ile Phe Glu Tyr
245          250          255

gtc tat ttt gca cgt cca gac tct tgc atc gat ggg gtt tct gtt tat 816
Val Tyr Phe Ala Arg Pro Asp Ser Cys Ile Asp Gly Val Ser Val Tyr
260          265          270

gct gcc cgt gtt cat atg gga caa cgt tta ggt gaa aaa att gca cgg 864
Ala Ala Arg Val His Met Gly Gln Arg Leu Gly Glu Lys Ile Ala Arg
275          280          285

gaa tgg gcg gat gtg gat att gat gtg gtc att cct gtg cct gaa 912
Glu Trp Ala Asp Val Asp Asp Ile Asp Val Val Ile Pro Val Pro Glu
290          295          300

acc tct aac gat att gct tta cgt att gcg cgc gtg tta aat aaa ccg 960
Thr Ser Asn Asp Ile Ala Leu Arg Ile Ala Arg Val Leu Asn Lys Pro
305          310          315          320

tat cgt caa ggt ttt gtg aaa aat cgc tat gta gga cgt acg ttt att 1008
Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr Val Gly Arg Thr Phe Ile
325          330          335

atg ccg ggg cag gca ttg cga gtc agt tct gtt aga cgt aaa ctc aat 1056
Met Pro Gly Gln Ala Leu Arg Val Ser Ser Val Arg Arg Lys Leu Asn
340          345          350

acc att gct tca gaa ttt aaa gat aag aat gtg tta tta gtt gac gac 1104
Thr Ile Ala Ser Glu Phe Lys Asp Lys Asn Val Leu Leu Val Asp Asp
355          360          365

tcg att gta cgt ggt acc acg tct gaa caa att gtc gaa atg gcg aga 1152
Ser Ile Val Arg Gly Thr Thr Ser Glu Gln Ile Val Glu Met Ala Arg
370          375          380

gcg gca ggt gcg aag aaa att tat ttt gcc tct gct gca cca gaa att 1200
Ala Ala Gly Ala Lys Lys Ile Tyr Phe Ala Ser Ala Ala Pro Glu Ile
385          390          395          400

cgt tat cca aat gtg tat ggt att gat atg cca acc aaa aat gaa ttg 1248
Arg Tyr Pro Asn Val Tyr Gly Ile Asp Met Pro Thr Lys Asn Glu Leu
405          410          415

atc gct tat ggt cgt gat gta gat gaa att gct aac tta att ggt gtg 1296
Ile Ala Tyr Gly Arg Asp Val Asp Glu Ile Ala Asn Leu Ile Gly Val
420          425          430

gat aaa ttg att ttc caa gat ttg gat gcg tta act ggt tct gtg caa 1344
Asp Lys Leu Ile Phe Gln Asp Leu Asp Ala Leu Thr Gly Ser Val Gln
435          440          445

caa gaa aat cca agt att caa gac ttt gat tgt tgc gtg ttt aca ggg 1392

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Gln Glu Asn Pro Ser Ile Gln Asp Phe Asp Cys Ser Val Phe Thr Gly
 450 455 460
 gtt tat gtg acg ggc gat att aca cct gaa tat ctg gat aat att gca 1440
 Val Tyr Val Thr Gly Asp Ile Thr Pro Glu Tyr Leu Asp Asn Ile Ala
 465 470 475 480
 gaa cag cgt aat gat atc gcc aag aaa aag cgt gaa aaa gat gct acc 1488
 Glu Gln Arg Asn Asp Ile Ala Lys Lys Lys Arg Glu Lys Asp Ala Thr
 485 490 495
 aat ctt gaa atg cac aat gaa aaa ta 1514
 Asn Leu Glu Met His Asn Glu Lys
 500
 <210> 111
 <211> 504
 <212> PRT
 <213> *Pasteurella multocida*
 <400> 111
 Met Cys Gly Ile Val Gly Ile Val Ser Gln Ser Pro Val Asn Gln Ser
 1 5 10 15
 Ile Tyr Asp Ala Leu Thr Leu Leu Gln His Arg Gly Gln Asp Ala Ala
 20 25 30
 Gly Ile Val Thr Val Asp Asp Glu Asn Arg Phe Arg Leu Arg Lys Ala
 35 40 45
 Asn Gly Leu Val Ser Asp Val Phe Glu Gln Val His Met Leu Arg Leu
 50 55 60
 Gln Gly Asn Ala Gly Ile Gly His Val Arg Tyr Pro Thr Ala Gly Ser
 65 70 75 80
 Ser Ser Val Ser Glu Ala Gln Pro Phe Tyr Val Asn Ser Pro Tyr Gly
 85 90 95
 Leu Thr Leu Val His Asn Gly Asn Leu Thr Asn Ser Ser Glu Leu Lys
 100 105 110
 Glu Lys Leu Phe Arg Leu Ala Arg Arg His Val Asn Thr Asn Ser Asp
 115 120 125
 Ser Glu Leu Leu Leu Asn Ile Leu Ala Asn His Leu Asp His Phe Glu
 130 135 140
 Lys Tyr Gln Leu Asp Pro Gln Asp Val Phe Ser Ala Val Lys Gln Thr
 145 150 155 160
 His Gln Asp Ile Arg Gly Ala Tyr Ala Cys Ile Ala Met Ile Ile Gly
 165 170 175
 His Gly Met Val Ala Phe Arg Asp Pro Asn Gly Ile Arg Pro Leu Val
 180 185 190
 Leu Gly Lys Arg Glu Glu Asn Gly Lys Thr Glu Tyr Met Phe Ala Ser
 195 200 205
 Glu Ser Ile Ala Leu Asp Thr Val Gly Phe Glu Phe Val Arg Asp Val
 210 215 220

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Gln Pro Gly Glu Ala Ile Tyr Val Thr Phe Glu Gly Glu Met Tyr Ala
 225 230 235 240
 Gln Gln Cys Ala Asp Lys Pro Thr Leu Thr Pro Cys Ile Phe Glu Tyr
 245 250 255
 Val Tyr Phe Ala Arg Pro Asp Ser Cys Ile Asp Gly Val Ser Val Tyr
 260 265 270
 Ala Ala Arg Val His Met Gly Gln Arg Leu Gly Glu Lys Ile Ala Arg
 275 280 285
 Glu Trp Ala Asp Val Asp Asp Ile Asp Val Val Ile Pro Val Pro Glu
 290 295 300
 Thr Ser Asn Asp Ile Ala Leu Arg Ile Ala Arg Val Leu Asn Lys Pro
 305 310 315
 Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr Val Gly Arg Thr Phe Ile
 325 330 335
 Met Pro Gly Gln Ala Leu Arg Val Ser Val Arg Arg Lys Leu Asn
 340 345 350
 Thr Ile Ala Ser Glu Phe Lys Asp Lys Asn Val Leu Leu Val Asp Asp
 355 360 365
 Ser Ile Val Arg Gly Thr Thr Ser Glu Gln Ile Val Glu Met Ala Arg
 370 375 380
 Ala Ala Gly Ala Lys Lys Ile Tyr Phe Ala Ser Ala Ala Pro Glu Ile
 385 390 395 400
 Arg Tyr Pro Asn Val Tyr Gly Ile Asp Met Pro Thr Lys Asn Glu Leu
 405 410 415
 Ile Ala Tyr Gly Arg Asp Val Asp Glu Ile Ala Asn Leu Ile Gly Val
 420 425 430
 Asp Lys Leu Ile Phe Gln Asp Leu Asp Ala Leu Thr Gly Ser Val Gln
 435 440 445
 Gln Glu Asn Pro Ser Ile Gln Asp Phe Asp Cys Ser Val Phe Thr Gly
 450 455 460
 Val Tyr Val Thr Gly Asp Ile Thr Pro Glu Tyr Leu Asp Asn Ile Ala
 465 470 475 480
 Glu Gln Arg Asn Asp Ile Ala Lys Lys Lys Arg Glu Lys Asp Ala Thr
 485 490 495
 Asn Leu Glu Met His Asn Glu Lys
 500

<210> 112
 <211> 989
 <212> DNA
 <213> Pasteurella multocida

<220>
 <223> rci

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<220>
<221> CDS
<222> (1)..(987)

<400> 112
atg gca aca ata aga aaa cgt ggt aac tca tat cgt gct gag ata agc 48
Met Ala Thr Ile Arg Lys Arg Gly Asn Ser Tyr Arg Ala Glu Ile Ser
1 5 10 15

aaa aac gga gta agg aaa tca gca aca ttt aag act aaa tca gaa gct 96
Lys Asn Gly Val Arg Lys Ser Ala Thr Phe Lys Thr Lys Ser Glu Ala
20 25 30

aat gcg tgg gct gtt gac gag gag aga aaa tta gct gat ttg gca aaa 144
Asn Ala Trp Ala Val Asp Glu Glu Arg Lys Leu Ala Asp Leu Ala Lys
35 40 45

ggt atc gct cca gat att att ttt aga gat gta ata gaa cgc tat caa 192
Gly Ile Ala Pro Asp Ile Ile Phe Arg Asp Val Ile Glu Arg Tyr Gln
50 55 60

aat gaa gtg tct ata act aaa aaa ggc gcg cga aat gaa att ata aga 240
Asn Glu Val Ser Ile Thr Lys Lys Gly Ala Arg Asn Glu Ile Ile Arg
65 70 75 80

tta aac cgc ttt tta aga tat gat att tct aat ctg tat att cgt gat 288
Leu Asn Arg Phe Leu Arg Tyr Asp Ile Ser Asn Leu Tyr Ile Arg Asp
85 90 95

tta aga aaa gaa gat ttt gag gag tgg atc aga att cgc cta acc gaa 336
Leu Arg Lys Glu Asp Phe Glu Glu Trp Ile Arg Ile Arg Leu Thr Glu
100 105 110

gta tcg gat gct agc gtt aga cgt gag ctt gtt act ata tcg tca gtg 384
Val Ser Asp Ala Ser Val Arg Arg Glu Leu Val Thr Ile Ser Ser Val
115 120 125

ctg aca aca gca ata aat aag tgg gga tat att tca agg cat cca atg 432
Leu Thr Thr Ala Ile Asn Lys Trp Gly Tyr Ile Ser Arg His Pro Met
130 135 140

act ggt att gaa aaa cca aaa aac tcg gca gaa aga aaa gaa cga tat 480
Thr Gly Ile Glu Lys Pro Lys Asn Ser Ala Glu Arg Lys Glu Arg Tyr
145 150 155 160

tca gaa cag gac att aaa aca ata tta gaa aca gct aga tat tgt gaa 528
Ser Glu Gln Asp Ile Lys Thr Ile Leu Glu Thr Ala Arg Tyr Cys Glu
165 170 175

gat aaa cta ccc ata aca ctc aaa caa aga gta gca att gca atg tta 576
Asp Lys Leu Pro Ile Thr Leu Lys Gln Arg Val Ala Ile Ala Met Leu
180 185 190

ttt gct att gaa acc gct atg cgt gct ggt gag att gct agt ata aaa 624
Phe Ala Ile Glu Thr Ala Met Arg Ala Gly Glu Ile Ala Ser Ile Lys
195 200 205

tgg gat aat gtt ttt ctt gaa aag aga ata gta cat tta ccg aca act 672
Trp Asp Asn Val Phe Leu Glu Lys Arg Ile Val His Leu Pro Thr Thr
210 215 220

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aaa aac ggg cac tct aga gat gtg ccg ctt tcg caa aga gct gtt gcg 720
Lys Asn Gly His Ser Arg Asp Val Pro Leu Ser Gln Arg Ala Val Ala
225          230          235          240

cta att tta aaa atg aaa gag gta gaa aat gga gat ctt gtg ttt cag 768
Leu Ile Leu Lys Met Lys Glu Val Glu Asn Gly Asp Leu Val Phe Gln
245          250          255

acc acg cct gaa tca tta agc acc acg ttt aga gtg tta aag aaa gag 816
Thr Thr Pro Glu Ser Leu Ser Thr Thr Phe Arg Val Leu Lys Lys Glu
260          265          270

tgt gga ctt gaa cat ctc cat ttt cat gat acg aga agg gaa gcg ttg 864
Cys Gly Leu Glu His Leu His Phe His Asp Thr Arg Arg Glu Ala Leu
275          280          285

acg aga tta tct aag aaa gta gat gta atg act cta gcc aaa att agc 912
Thr Arg Leu Ser Lys Lys Val Asp Val Met Thr Leu Ala Lys Ile Ser
290          295          300

gga cat aga gat tta aga att tta caa aac aca tat tac gca ccg aat 960
Gly His Arg Asp Leu Arg Ile Leu Gln Asn Thr Tyr Ala Pro Asn
305          310          315          320

atg agt gaa gtg gca aac ttg ttg gat ta 989
Met Ser Glu Val Ala Asn Leu Leu Asp
325

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<210> 113
 <211> 329
 <212> PRT
 <213> *Pasteurella multocida*

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<400> 113
Met Ala Thr Ile Arg Lys Arg Gly Asn Ser Tyr Arg Ala Glu Ile Ser
1          5          10          15

Lys Asn Gly Val Arg Lys Ser Ala Thr Phe Lys Thr Lys Ser Glu Ala
20          25          30

Asn Ala Trp Ala Val Asp Glu Glu Arg Lys Leu Ala Asp Leu Ala Lys
35          40          45

Gly Ile Ala Pro Asp Ile Ile Phe Arg Asp Val Ile Glu Arg Tyr Gln
50          55          60

Asn Glu Val Ser Ile Thr Lys Lys Gly Ala Arg Asn Glu Ile Ile Arg
65          70          75          80

Leu Asn Arg Phe Leu Arg Tyr Asp Ile Ser Asn Leu Tyr Ile Arg Asp
85          90          95

Leu Arg Lys Glu Asp Phe Glu Glu Trp Ile Arg Ile Arg Leu Thr Glu
100         105         110

Val Ser Asp Ala Ser Val Arg Arg Glu Leu Val Thr Ile Ser Ser Val
115         120         125

Leu Thr Thr Ala Ile Asn Lys Trp Gly Tyr Ile Ser Arg His Pro Met
130         135         140

Thr Gly Ile Glu Lys Pro Lys Asn Ser Ala Glu Arg Lys Glu Arg Tyr

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145          150          155          160
Ser Glu Gln Asp Ile Lys Thr Ile Leu Glu Thr Ala Arg Tyr Cys Glu
      165          170          175
Asp Lys Leu Pro Ile Thr Leu Lys Gln Arg Val Ala Ile Ala Met Leu
      180          185          190
Phe Ala Ile Glu Thr Ala Met Arg Ala Gly Glu Ile Ala Ser Ile Lys
      195          200          205
Trp Asp Asn Val Phe Leu Glu Lys Arg Ile Val His Leu Pro Thr Thr
      210          215          220
Lys Asn Gly His Ser Arg Asp Val Pro Leu Ser Gln Arg Ala Val Ala
      225          230          235
Leu Ile Leu Lys Met Lys Glu Val Glu Asn Gly Asp Leu Val Phe Gln
      245          250          255
Thr Thr Pro Glu Ser Leu Ser Thr Thr Phe Arg Val Leu Lys Lys Glu
      260          265          270
Cys Gly Leu Glu His Leu His Phe His Asp Thr Arg Arg Glu Ala Leu
      275          280          285
Thr Arg Leu Ser Lys Lys Val Asp Val Met Thr Leu Ala Lys Ile Ser
      290          295          300
Gly His Arg Asp Leu Arg Ile Leu Gln Asn Thr Tyr Tyr Ala Pro Asn
      305          310          315          320
Met Ser Glu Val Ala Asn Leu Leu Asp
      325

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<210> 114
 <211> 1190
 <212> DNA
 <213> *Pasteurella multocida*

<220>
 <223> sopE

<220>
 <221> CDS
 <222> (1)..(1188)

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<400> 114
atg tct gaa gaa tat cta cat ggt gtc aaa gtc aca gaa atc aat caa 48
Met Ser Glu Glu Tyr Leu His Gly Val Lys Val Thr Glu Ile Asn Gln
      1      5      10      15
gca att cgc aca att caa agt cta tca acc gca gtc atc ggt att gtc 96
Ala Ile Arg Thr Ile Gln Ser Leu Ser Thr Ala Val Ile Gly Ile Val
      20      25      30
tgt act gca aat gac gca gac aat gaa aca ttc cca ctc aat gaa ccc 144
Cys Thr Ala Asn Asp Ala Asp Asn Glu Thr Phe Pro Leu Asn Glu Pro
      35      40      45
gtt ctc atc aca aac gtg gca gcg gca att ggc aag gct gga aaa caa 192
Val Leu Ile Thr Asn Val Ala Ala Ala Ile Gly Lys Ala Gly Lys Gln

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      50      55      60
ggc acg ctt tca cgt gcg ctt gac ggg att tct gat gta gtc aat tgc 240
Gly Thr Leu Ser Arg Ala Leu Asp Gly Ile Ser Asp Val Val Asn Cys
65      70      75      80

aaa gtg att gtt gtg cga gtg caa gaa agt gcg caa gaa gac gaa gaa 288
Lys Val Ile Val Val Arg Val Gln Glu Ser Ala Gln Glu Asp Glu Glu
85      90      95

aca aaa gca agt gaa atg aac acg gca att att ggc aca atc aca gaa 336
Thr Lys Ala Ser Glu Met Asn Thr Ala Ile Ile Gly Thr Ile Thr Glu
100     105     110

gaa ggg cag tac aca ggc ttg aag gcg tta ttg att gcg aaa aac aaa 384
Glu Gly Gln Tyr Thr Gly Leu Lys Ala Leu Leu Ile Ala Lys Asn Lys
115     120     125

ttc ggt atc aaa cca cgt att tta tgt gtg cca aaa ttc gac aca aaa 432
Phe Gly Ile Lys Pro Arg Ile Leu Cys Val Pro Lys Phe Asp Thr Lys
130     135     140

gaa gtc gcc aca gag ctt gca agt atc gcc gcc aaa ctc aac gca ttt 480
Glu Val Ala Thr Glu Leu Ala Ser Ile Ala Ala Lys Leu Asn Ala Phe
145     150     155

gct tac att tca tgt caa ggg tgt aaa acg aaa gaa caa gcg gtg caa 528
Ala Tyr Ile Ser Cys Gln Gly Cys Lys Thr Lys Glu Gln Ala Val Gln
165     170     175

tat aaa cgc aac ttc tca caa cgt gaa gtc atg ctg atc atg ggc gat 576
Tyr Lys Arg Asn Phe Ser Gln Arg Glu Val Met Leu Ile Met Gly Asp
180     185     190

ttt ctg tca ttt aat gtc aac aca tca aaa gtt gag att gac tat gcc 624
Phe Leu Ser Phe Asn Val Asn Thr Ser Lys Val Glu Ile Asp Tyr Ala
195     200     205

gtc act cgt gcg gcg gca atg cgt gca tat ctt gat aaa gaa cag gcc 672
Val Thr Arg Ala Ala Ala Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly
210     215     220

tgg cat acg tct att tca aat aaa ggc att aat ggc gtg agc ggt gtc 720
Trp His Thr Ser Ile Ser Asn Lys Gly Ile Asn Gly Val Ser Gly Val
225     230     235     240

aca caa cca ctc tat ttt gac att aac gac agc tcg act gat gtg aac 768
Thr Gln Pro Leu Tyr Phe Asp Ile Asn Asp Ser Ser Thr Asp Val Asn
245     250     255

tat ctc aat gaa caa ggc atc acg tgt tgc gtg aat cat aat ggc ttt 816
Tyr Leu Asn Glu Gln Gly Ile Thr Cys Cys Val Asn His Asn Gly Phe
260     265     270

cgt ttt tgg ggc tta cgc acg act gca gaa gat cca tta ttc aag ttt 864
Arg Phe Trp Gly Leu Arg Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe
275     280     285

gaa gtg tac acc cgc act gca caa atc tta aaa gat acg att gca ggg 912
Glu Val Tyr Thr Arg Thr Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly
290     295     300

gcg ttt gat tgg gca gtg gat aaa gat att tct gtc acg cta gtg aaa 960

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Ala Phe Asp Trp Ala Val Asp Lys Asp Ile Ser Val Thr Leu Val Lys 1008
 305 310 315 320
 gat att att gaa gca atc aat gcg aag tgg cgt gat tac acc aca aaa 1008
 Asp Ile Ile Glu Ala Ile Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys 325 330 335
 ggc tac tta att ggc ggt aaa gcg tgg ctt aat aaa gag ctt aac agt 1056
 Gly Tyr Leu Ile Gly Gly Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser 340 345 350
 gca acg aat tta aaa gat gcg aag ttg ttg atc tct tat gat tat cac 1104
 Ala Thr Asn Leu Lys Asp Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His 355 360 365
 cca gta cca ccg ctc gaa cag cta ggc ttt aat cag tac att tct gat 1152
 Pro Val Pro Pro Leu Glu Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp 370 375 380
 gaa tac ctt gtt gat ttt tca aat cgt tta gca tcg ta 1190
 Glu Tyr Leu Val Asp Phe Ser Asn Arg Leu Ala Ser 385 390 395

 <210> 115
 <211> 396
 <212> PRT
 <213> Pasteurella multocida

 <400> 115
 Met Ser Glu Glu Tyr Leu His Gly Val Lys Val Thr Glu Ile Asn Gln 1 5 10 15
 Ala Ile Arg Thr Ile Gln Ser Leu Ser Thr Ala Val Ile Gly Ile Val 20 25 30
 Cys Thr Ala Asn Asp Ala Asp Asn Glu Thr Phe Pro Leu Asn Glu Pro 35 40 45
 Val Leu Ile Thr Asn Val Ala Ala Ala Ile Gly Lys Ala Gly Lys Gln 50 55 60
 Gly Thr Leu Ser Arg Ala Leu Asp Gly Ile Ser Asp Val Val Asn Cys 65 70 75 80
 Lys Val Ile Val Val Arg Val Gln Glu Ser Ala Gln Glu Asp Glu Glu 85 90 95
 Thr Lys Ala Ser Glu Met Asn Thr Ala Ile Ile Gly Thr Ile Thr Glu 100 105 110
 Glu Gly Gln Tyr Thr Gly Leu Lys Ala Leu Leu Ile Ala Lys Asn Lys 115 120 125
 Phe Gly Ile Lys Pro Arg Ile Leu Cys Val Pro Lys Phe Asp Thr Lys 130 135 140

 Glu Val Ala Thr Glu Leu Ala Ser Ile Ala Ala Lys Leu Asn Ala Phe 145 150 155 160
 Ala Tyr Ile Ser Cys Gln Gly Cys Lys Thr Lys Glu Gln Ala Val Gln 165 170 175

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Tyr Lys Arg Asn Phe Ser Gln Arg Glu Val Met Leu Ile Met Gly Asp
 180 185 190
 Phe Leu Ser Phe Asn Val Asn Thr Ser Lys Val Glu Ile Asp Tyr Ala
 195 200 205
 Val Thr Arg Ala Ala Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly
 210 215 220
 Trp His Thr Ser Ile Ser Asn Lys Gly Ile Asn Gly Val Ser Gly Val
 225 230 235 240
 Thr Gln Pro Leu Tyr Phe Asp Ile Asn Asp Ser Ser Thr Asp Val Asn
 245 250 255
 Tyr Leu Asn Glu Gln Gly Ile Thr Cys Val Asn His Asn Gly Phe
 260 265 270
 Arg Phe Trp Gly Leu Arg Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe
 275 280 285
 Glu Val Tyr Thr Arg Thr Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly
 290 295 300
 Ala Phe Asp Trp Ala Val Asp Lys Asp Ile Ser Val Thr Leu Val Lys
 305 310 315 320
 Asp Ile Ile Glu Ala Ile Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys
 325 330 335
 Gly Tyr Leu Ile Gly Gly Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser
 340 345 350
 Ala Thr Asn Leu Lys Asp Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His
 355 360 365
 Pro Val Pro Pro Leu Glu Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp
 370 375 380
 Glu Tyr Leu Val Asp Phe Ser Asn Arg Leu Ala Ser
 385 390 395

 <210> 116
 <211> 2204
 <212> DNA
 <213> Pasteurella multocida

 <220>
 <223> unkK

 <220>
 <221> CDS
 <222> (1)...(2202)

 <400> 116
 atg aat aaa aat cgc tat aaa ctc att ttt agt aaa act aaa ggc tgt 48
 Met Asn Lys Asn Arg Tyr Lys Leu Ile Phe Ser Lys Thr Lys Gly Cys
 1 5 10 15
 ctt gta cct gtt gct gaa acg att aat tct gca gta gga aat gcc tca 96
 Leu Val Pro Val Ala Glu Thr Ile Asn Ser Ala Val Gly Asn Ala Ser
 20 25 30

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tca aaa gac gtt tct gac acc gag ata agt gct tct caa cca gcg ctc 144
Ser Lys Asp Val Ser Asp Thr Glu Ile Ser Ala Ser Gln Pro Ala Leu
35 40 45

aac tcg ccg ctt tcg acc ctt tct gta tta gtc aaa acc gca ttt aat 192
Asn Ser Pro Leu Ser Thr Leu Ser Val Leu Val Lys Thr Ala Phe Asn
50 55 60

ccg gtt tca aca ttg atg tcg ttg act tgg aaa gaa tac gcc gtt tta 240
Pro Val Ser Thr Leu Met Ser Leu Thr Trp Lys Glu Tyr Ala Val Leu
65 70 75 80

tta tta agt gtg gtg tct ttt cct ctt atg gca caa gcc tct gat aca 288
Leu Leu Ser Val Val Ser Phe Pro Leu Met Ala Gln Ala Ser Asp Thr
85 90 95

gat tca gtg gta caa aga aaa cct gaa tta act gat gtg acg aat agc 336
Asp Ser Val Val Gln Arg Lys Pro Glu Leu Thr Asp Val Thr Asn Ser
100 105 110

aac agc tat cat gtg gaa tta gat aga gag cat cat aaa ggg gag cat 384
Asn Ser Tyr His Val Glu Leu Asp Arg Glu His His Lys Gly Glu His
115 120 125

caa aca aaa atc aaa cat act gag aat aat gtc atc att gtt gat att 432
Gln Thr Lys Ile Lys His Thr Glu Asn Asn Val Ile Ile Val Asp Ile
130 135 140

gca aaa cca aac caa aag ggc att tca gat aac cgt ttt aaa cac ttc 480
Ala Lys Pro Asn Gln Lys Gly Ile Ser Asp Asn Arg Phe Lys His Phe
145 150 155 160

aac atc cca aat ggg gcg gta ttt aac aat agc gcc aag gaa aaa cgc 528
Asn Ile Pro Asn Gly Ala Val Phe Asn Asn Ser Ala Lys Glu Lys Arg
165 170 175

tca cag tta gtg ggg tat ttg cca ggt aac cag aat tta acg gaa ggt 576
Ser Gln Leu Val Gly Tyr Leu Pro Gly Asn Gln Asn Leu Thr Glu Gly
180 185 190

agt gaa gca aaa gcg atc tta aat cag gtg act gga ccg gat gcc agt 624
Ser Glu Ala Lys Ala Ile Leu Asn Gln Val Thr Gly Pro Asp Ala Ser
195 200 205

aaa att gaa ggc gcc ctt gaa att tta ggg caa aaa gcc gat ttg gtg 672
Lys Ile Glu Gly Ala Leu Glu Ile Leu Gly Gln Lys Ala Asp Leu Val
210 215 220

att gcg aac caa aat ggc att gtg ctt aat ggg gta aaa acc att aat 720
Ile Ala Asn Gln Asn Gly Ile Val Leu Asn Gly Val Lys Thr Ile Asn
225 230 235 240

gcc aat cgt ttt gtg gca aca acc agt agt acc att gat cct gag caa 768
Ala Asn Arg Phe Val Ala Thr Thr Ser Ser Thr Ile Asp Pro Glu Gln
245 250 255

atg cag tta aat gtc acg caa ggt aca gtg aca att ggg gtg gat gga 816
Met Gln Leu Asn Val Thr Gln Gly Thr Val Thr Ile Gly Val Asp Gly
260 265 270

ttt gcc aca gat ggc tta cct tat ttg gat atc att gcc aaa aag att 864
Phe Ala Thr Asp Gly Leu Pro Tyr Leu Asp Ile Ile Ala Lys Lys Ile
275 280 285

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gaa caa aaa caa gcg att aca aaa gaa aga aca gga aat tcc gaa acc 912
Glu Gln Lys Gln Ala Ile Thr Lys Glu Arg Thr Gly Asn Ser Glu Thr
290 295 300

gat atc act ttt gtc gca ggt aac agt aaa tat gat tta aag aca cat 960
Asp Ile Thr Phe Val Ala Gly Asn Ser Lys Tyr Asp Leu Lys Thr His
305 310 315 320

caa gtg aca gaa aag cat acc gct gag gca caa ggt gaa att gcg att 1008
Gln Val Thr Glu Lys His Thr Ala Glu Ala Gln Gly Glu Ile Ala Ile
325 330 335

agc ggt gcg agt acc ggt gca atg tac ggt aaa aat atc aaa tta atc 1056
Ser Gly Ala Ser Thr Gly Ala Met Tyr Gly Lys Asn Ile Lys Leu Ile
340 345 350

gta acg gat aaa ggc gct ggg gta aaa cat gat ggc att att tta tct 1104
Val Thr Asp Lys Gly Ala Gly Val Lys His Asp Gly Ile Ile Leu Ser
355 360 365

gag gcg gat att caa att gaa acc cat gag ggc gat gtt gaa tta ggc 1152
Glu Ala Asp Ile Gln Ile Glu Thr His Glu Gly Asp Val Glu Leu Gly
370 375 380

aat aca aaa aat aat cag aat gag aat tat gcc aaa gct cat gcg gaa 1200
Asn Thr Lys Asn Asn Gln Asn Glu Asn Tyr Ala Lys Ala His Ala Glu
385 390 395 400

ggg aat ttt acg gtt aaa ggc ggt aag cac gtt att att ggt aag gaa 1248
Gly Asn Phe Thr Val Lys Gly Gly Lys His Val Ile Ile Gly Lys Glu
405 410 415

gtt aaa gcc aac aaa gcg gtc gat att caa gca caa gaa aca aca gta 1296
Val Lys Ala Asn Lys Ala Val Asp Ile Gln Ala Gln Glu Thr Thr Val
420 425 430

aga caa aat gcg aaa tta act gcc aaa acg agt gcc aaa att aca gca 1344
Arg Gln Asn Ala Lys Leu Thr Ala Lys Thr Ser Ala Lys Ile Thr Ala
435 440 445

agt aag agt gtg aat ctt gaa gat aac gcg aaa ctt att gct aat gag 1392
Ser Lys Ser Val Asn Leu Glu Asp Asn Ala Lys Leu Ile Ala Asn Glu
450 455 460

ctg agc aca aca acc aat aaa tta acc aat aaa ggt agc att tac ggc 1440
Leu Ser Thr Thr Thr Asn Lys Leu Thr Asn Lys Gly Ser Ile Tyr Gly
465 470 475 480

aag aaa gtg acg cta gat gct gat aat tta gtc aat agt aaa gaa atc 1488
Lys Lys Val Thr Leu Asp Ala Asp Asn Leu Val Asn Ser Lys Glu Ile
485 490 495

tat gcg tct agc gaa ctt gat att caa acc aaa ggt cgt gat ctt tta 1536
Tyr Ala Ser Ser Glu Leu Asp Ile Gln Thr Lys Gly Arg Asp Leu Leu
500 505 510

ctt gag gat ggg gtt aat caa cca ctg agt ttc tta aaa ggc gct tca 1584
Leu Glu Asp Gly Val Asn Gln Pro Leu Ser Phe Leu Lys Gly Ala Ser
515 520 525

ttg tta gcg ccg ggg ttt gtc aac act ggg cta att cac agt aac ggt 1632
Leu Leu Ala Pro Gly Phe Val Asn Thr Gly Leu Ile His Ser Asn Gly
530 535 540

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aat gcc aag ctc act ttt aaa gat gac acc agt ttt gtg act gaa gga 1680
Asn Ala Lys Leu Thr Phe Lys Asp Asp Thr Ser Phe Val Thr Glu Gly
545 550 555 560

aat aac ttt atc aca gca aaa gac aac tta gaa atc acg gca aaa aat 1728
Asn Asn Phe Ile Thr Ala Lys Asp Asn Leu Glu Ile Thr Ala Lys Asn
565 570 575

gtt caa att gat caa gcg aaa aat att caa tta aac gcg aat atc acg 1776
Val Gln Ile Asp Gln Ala Lys Asn Ile Gln Leu Asn Ala Asn Ile Thr
580 585 590

atc aat acc aag tct ggt ttt gtg aat tac ggt acc tta gca agt gct 1824
Ile Asn Thr Lys Ser Gly Phe Val Asn Tyr Gly Thr Leu Ala Ser Ala
595 600 605

caa aat tta acg att aat acc gaa caa ggc agc att tat aac ata ggc 1872
Gln Asn Leu Thr Ile Asn Thr Glu Gln Gly Ser Ile Tyr Asn Ile Gly
610 615 620

ggt atc ttg ggg gcg ggt aaa agt ttg aat ctg agc gcg aaa aga gga 1920
Gly Ile Leu Gly Ala Gly Lys Ser Leu Asn Leu Ser Ala Lys Arg Gly
625 630 635 640

gaa aac caa gga gga tat ctt att aat caa ggt aag agt cta ctc cat 1968
Glu Asn Gln Gly Gly Tyr Leu Ile Asn Gln Gly Lys Ser Leu Leu His
645 650 655

tct gaa ggc gcc atg aac ctc aca gcg gat cgc acg gtg tac aat tta 2016
Ser Glu Gly Ala Met Asn Leu Thr Ala Asp Arg Thr Val Tyr Asn Leu
660 665 670

ggg aat att ttt gct aaa ggt gac gcg acg atc aat gca aac gcg tta 2064
Gly Asn Ile Phe Ala Lys Gly Asp Ala Thr Ile Asn Ala Asn Ala Leu
675 680 685

att aat gat gtt act ctc aca ggt cgt ctt gag tat caa gat ctg aaa 2112
Ile Asn Asp Val Thr Leu Thr Gly Arg Leu Glu Tyr Gln Asp Leu Lys
690 695 700

aaa gat tat acg cgt tat tat cgt atc aat gaa acg gca aaa cat ggt 2160
Lys Asp Tyr Thr Arg Tyr Arg Ile Asn Glu Thr Ala Lys His Gly
705 710 715 720

tgg cat aat aac ttc tat gaa tta aac gtc gac aga gtt tct tg 2204
Trp His Asn Asn Phe Tyr Glu Leu Asn Val Asp Arg Val Ser
725 730

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<210> 117
<211> 734
<212> PRT
<213> Pasteurella multocida

<400> 117
Met Asn Lys Asn Arg Tyr Lys Leu Ile Phe Ser Lys Thr Lys Gly Cys
1 5 10 15
Leu Val Pro Val Ala Glu Thr Ile Asn Ser Ala Val Gly Asn Ala Ser
20 25 30
Ser Lys Asp Val Ser Asp Thr Glu Ile Ser Ala Ser Gln Pro Ala Leu
35 40 45

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Asn Ser Pro Leu Ser Thr Leu Ser Val Leu Val Lys Thr Ala Phe Asn
 50          55          60
Pro Val Ser Thr Leu Met Ser Leu Thr Trp Lys Glu Tyr Ala Val Leu
 65          70          75          80
Leu Leu Ser Ser Val Val Ser Phe Pro Leu Met Ala Gln Ala Ser Asp Thr
 85          90          95
Asp Ser Val Val Gln Arg Lys Pro Glu Leu Thr Asp Val Thr Asn Ser
100          105          110
Asn Ser Tyr His Val Glu Leu Asp Arg Glu His His Lys Gly Glu His
115          120          125
Gln Thr Lys Ile Lys His Thr Glu Asn Asn Val Ile Ile Val Asp Ile
130          135          140
Ala Lys Pro Asn Gln Lys Gly Ile Ser Asp Asn Arg Phe Lys His Phe
145          150          155          160
Asn Ile Pro Asn Gly Ala Val Phe Asn Asn Ser Ala Lys Glu Lys Arg
165          170          175
Ser Gln Leu Val Gly Tyr Leu Pro Gly Asn Gln Asn Leu Thr Glu Gly
180          185          190
Ser Glu Ala Lys Ala Ile Leu Asn Gln Val Thr Gly Pro Asp Ala Ser
195          200          205
Lys Ile Glu Gly Ala Leu Glu Ile Leu Gly Gln Lys Ala Asp Leu Val
210          215          220
Ile Ala Asn Gln Asn Gly Ile Val Leu Asn Gly Val Lys Thr Ile Asn
225          230          235          240
Ala Asn Arg Phe Val Ala Thr Thr Ser Ser Thr Ile Asp Pro Glu Gln
245          250          255
Met Gln Leu Asn Val Thr Gln Gly Thr Val Thr Ile Gly Val Asp Gly
260          265          270
Phe Ala Thr Asp Gly Leu Pro Tyr Leu Asp Ile Ile Ala Lys Lys Ile
275          280          285
Glu Gln Lys Gln Ala Ile Thr Lys Glu Arg Thr Gly Asn Ser Glu Thr
290          295          300
Asp Ile Thr Phe Val Ala Gly Asn Ser Lys Tyr Asp Leu Lys Thr His
305          310          315          320
Gln Val Thr Glu Lys His Thr Ala Glu Ala Gln Gly Glu Ile Ala Ile
325          330          335
Ser Gly Ala Ser Thr Gly Ala Met Tyr Gly Lys Asn Ile Lys Leu Ile
340          345          350
Val Thr Asp Lys Gly Ala Gly Val Lys His Asp Gly Ile Ile Leu Ser
355          360          365
Glu Ala Asp Ile Gln Ile Glu Thr His Glu Gly Asp Val Glu Leu Gly
370          375          380

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Asn Thr Lys Asn Asn Gln Asn Glu Asn Tyr Ala Lys Ala His Ala Glu
 385 390 395 400
 Gly Asn Phe Thr Val Lys Gly Gly Lys His Val Ile Ile Gly Lys Glu
 405 410 415
 Val Lys Ala Asn Lys Ala Val Asp Ile Gln Ala Gln Glu Thr Thr Val
 420 425 430
 Arg Gln Asn Ala Lys Leu Thr Ala Lys Thr Ser Ala Lys Ile Thr Ala
 435 440 445
 Ser Lys Ser Val Asn Leu Glu Asp Asn Ala Lys Leu Ile Ala Asn Glu
 450 455 460
 Leu Ser Thr Thr Thr Asn Lys Leu Thr Asn Lys Gly Ser Ile Tyr Gly
 465 470 475 480
 Lys Lys Val Thr Leu Asp Ala Asp Asn Leu Val Asn Ser Lys Glu Ile
 485 490 495
 Tyr Ala Ser Ser Glu Leu Asp Ile Gln Thr Lys Gly Arg Asp Leu Leu
 500 505 510
 Leu Glu Asp Gly Val Asn Gln Pro Leu Ser Phe Leu Lys Gly Ala Ser
 515 520 525
 Leu Leu Ala Pro Gly Phe Val Asn Thr Gly Leu Ile His Ser Asn Gly
 530 535 540
 Asn Ala Lys Leu Thr Phe Lys Asp Asp Thr Ser Phe Val Thr Glu Gly
 545 550 555 560
 Asn Asn Phe Ile Thr Ala Lys Asp Asn Leu Glu Ile Thr Ala Lys Asn
 565 570 575
 Val Gln Ile Asp Gln Ala Lys Asn Ile Gln Leu Asn Ala Asn Ile Thr
 580 585 590
 Ile Asn Thr Lys Ser Gly Phe Val Asn Tyr Gly Thr Leu Ala Ser Ala
 595 600 605
 Gln Asn Leu Thr Ile Asn Thr Glu Gln Gly Ser Ile Tyr Asn Ile Gly
 610 615 620
 Gly Ile Leu Gly Ala Gly Lys Ser Leu Asn Leu Ser Ala Lys Arg Gly
 625 630 635 640
 Glu Asn Gln Gly Gly Tyr Leu Ile Asn Gln Gly Lys Ser Leu Leu His
 645 650 655
 Ser Glu Gly Ala Met Asn Leu Thr Ala Asp Arg Thr Val Tyr Asn Leu
 660 665 670
 Gly Asn Ile Phe Ala Lys Gly Asp Ala Thr Ile Asn Ala Asn Ala Leu
 675 680 685
 Ile Asn Asp Val Thr Leu Thr Gly Arg Leu Glu Tyr Gln Asp Leu Lys
 690 695 700
 Lys Asp Tyr Thr Arg Tyr Tyr Arg Ile Asn Glu Thr Ala Lys His Gly
 705 710 715 720

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Trp His Asn Asn Phe Tyr Glu Leu Asn Val Asp Arg Val Ser
 725 730

<210> 118
 <211> 251
 <212> DNA
 <213> Pasteurella multocida

<220>
 <223> unkO

<220>
 <221> CDS
 <222> (1)..(249)

<400> 118
 atg aaa att act att aca cga aat cat cca gaa gta ttt caa gaa tcc 48
 Met Lys Ile Thr Ile Thr Arg Asn His Pro Glu Val Phe Gln Glu Ser
 1 5 10 15
 gct cgt tta gta gcc gaa aag ttc att aaa gcc caa tgt gta gaa gca 96
 Ala Arg Leu Val Ala Glu Lys Phe Ile Lys Ala Gln Cys Val Glu Ala
 20 25 30
 tta aca ttg gct ttg att gag ggt gtc gag cac ttt gtg ctg gaa ggt 144
 Leu Thr Leu Ala Leu Ile Glu Gly Val Glu His Phe Val Leu Glu Gly
 35 40 45
 gag gag gaa agc aaa agg gga cat agt att aag gtt gta tta aaa gga 192
 Glu Glu Glu Ser Lys Arg Gly His Ser Ile Lys Val Val Leu Lys Gly
 50 55 60
 agt cac gaa gtt att aag tca gag ctg aat aca aat gaa aaa aat cat 240
 Ser His Glu Val Ile Lys Ser Glu Val Asn Thr Asn Glu Lys Asn His
 65 70 75 80
 tgt aat cat ta 251
 Cys Asn His

<210> 119
 <211> 83
 <212> PRT
 <213> Pasteurella multocida

<400> 119
 Met Lys Ile Thr Ile Thr Arg Asn His Pro Glu Val Phe Gln Glu Ser
 1 5 10 15
 Ala Arg Leu Val Ala Glu Lys Phe Ile Lys Ala Gln Cys Val Glu Ala
 20 25 30
 Leu Thr Leu Ala Leu Ile Glu Gly Val Glu His Phe Val Leu Glu Gly
 35 40 45
 Glu Glu Glu Ser Lys Arg Gly His Ser Ile Lys Val Val Leu Lys Gly
 50 55 60
 Ser His Glu Val Ile Lys Ser Glu Val Asn Thr Asn Glu Lys Asn His
 65 70 75 80

221

WO 02/075507

PCT/US02/01971

Cys Asn His

<210> 120
 <211> 548
 <212> DNA
 <213> Pasteurella multocida

<220>
 <223> unkP

<220>
 <221> CDS
 <222> (1)..(546)

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<400> 120
atg cgt gca tat ctt gat aaa gaa cag ggc tgg cat acg tct att tca 48
Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly Trp His Thr Ser Ile Ser
1 5 10 15
aat aaa ggc att aat ggc gtg agc ggt gtc aca caa cca ctc tat ttt 96
Asn Lys Gly Ile Asn Gly Val Ser Gly Val Thr Gln Pro Leu Tyr Phe
20 25 30
gac att aac gac agc tcg act gat gtg aac tat ctc aat gaa caa ggc 144
Asp Ile Asn Asp Ser Ser Thr Asp Val Asn Tyr Leu Asn Glu Gln Gly
35 40 45
atc acg tgt tgc gtg aat cat aat ggc ttt cgt ttt tgg ggc tta cgc 192
Ile Thr Cys Cys Val Asn His Asn Gly Phe Arg Phe Trp Gly Leu Arg
50 55 60
acg act gca gaa gat cca tta ttc aag ttt gaa gtg tac acc cgc act 240
Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe Glu Val Tyr Thr Arg Thr
65 70 75 80
gca caa atc tta aaa gat acg att gca ggc gcg ttt gat tgg gca gtg 288
Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly Ala Phe Asp Trp Ala Val
85 90 95
gat aaa gat att tct gtc acg cta gtg aaa gat att att gaa gca atc 336
Asp Lys Asp Ile Ser Val Thr Leu Val Lys Asp Ile Ile Glu Ala Ile
100 105 110
aat gcg aag tgg cgt gat tac acc aca aaa ggc tac tta att ggc ggt 384
Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys Gly Tyr Leu Ile Gly Gly
115 120 125
aaa gcg tgg ctt aat aaa gag ctt aac agt gca acg aat tta aaa gat 432
Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser Ala Thr Asn Leu Lys Asp
130 135 140
gcg aag ttg ttg atc tct tat gat tat cac cca gta cca ccg ctc gaa 480
Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His Pro Val Pro Pro Leu Glu
145 150 155 160
cag cta ggc ttt aat cag tac att tct gat gaa tac ctt gtt gat ttt 528
Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp Glu Tyr Leu Val Asp Phe
165 170 175
tca aat cgt tta gca tcg ta 548

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Ser Asn Arg Leu Ala Ser
180

<210> 121
<211> 182
<212> PRT
<213> Pasteurella multocida

<400> 121
Met Arg Ala Tyr Leu Asp Lys Glu Gln Gly Trp His Thr Ser Ile Ser
1 5 10 15
Asn Lys Gly Ile Asn Gly Val Ser Gly Val Thr Gln Pro Leu Tyr Phe
20 25 30
Asp Ile Asn Asp Ser Ser Thr Asp Val Asn Tyr Leu Asn Glu Gln Gly
35 40 45
Ile Thr Cys Cys Val Asn His Asn Gly Phe Arg Phe Trp Gly Leu Arg
50 55 60
Thr Thr Ala Glu Asp Pro Leu Phe Lys Phe Glu Val Tyr Thr Arg Thr
65 70 75 80
Ala Gln Ile Leu Lys Asp Thr Ile Ala Gly Ala Phe Asp Trp Ala Val
85 90 95
Asp Lys Asp Ile Ser Val Thr Leu Val Lys Asp Ile Ile Glu Ala Ile
100 105 110
Asn Ala Lys Trp Arg Asp Tyr Thr Thr Lys Gly Tyr Leu Ile Gly Gly
115 120 125
Lys Ala Trp Leu Asn Lys Glu Leu Asn Ser Ala Thr Asn Leu Lys Asp
130 135 140
Ala Lys Leu Leu Ile Ser Tyr Asp Tyr His Pro Val Pro Pro Leu Glu
145 150 155 160
Gln Leu Gly Phe Asn Gln Tyr Ile Ser Asp Glu Tyr Leu Val Asp Phe
165 170 175
Ser Asn Arg Leu Ala Ser
180

<210> 122
<211> 69
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> apvA-or1

<220>
<221> CDS
<222> (1)..(69)

<400> 122
atg ttt tat gtc atg ctt gcc aat agg acg tct ata att tca tca atc 48
Met Phe Tyr Val Met Leu Ala Asn Arg Thr Ser Ile Ile Ser Ser Ile
1 5 10 15

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gat aag ttt aag ata ctt agc
Asp Lys Phe Lys Ile Leu Ser
20

69

<210> 123
<211> 23
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 123
Met Phe Tyr Val Met Leu Ala Asn Arg Thr Ser Ile Ile Ser Ser Ile
1 5 10 15

Asp Lys Phe Lys Ile Leu Ser
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<210> 124
<211> 64
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> apvA-or2

<220>
<221> CDS
<222> (3)...(62)

<400> 124
ag cta agt atc tta aac tta tcg att gat gaa att ata gac gtc cta 47
Leu Ser Ile Leu Asn Leu Ser Ile Asp Glu Ile Ile Asp Val Leu
1 5 10 15

ttg gca agc atg aca ta 64
Leu Ala Ser Met Thr
20

<210> 125
<211> 20
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 125
Leu Ser Ile Leu Asn Leu Ser Ile Asp Glu Ile Ile Asp Val Leu Leu
1 5 10 15

Ala Ser Met Thr
20

<210> 126
<211> 653
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> apvB

<220>
<221> CDS

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<222> (1)...(651)

<400> 126

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tta att agc ttt cct ttt att act ttt gca agt aat gtt aat gga gcc 48
Leu Ile Ser Phe Pro Phe Ile Thr Phe Ala Ser Asn Val Asn Gly Ala
1 5 10 15

gaa att gga ttg gga gga gcc cgt gag agt agt att tac tat tct aaa 96
Glu Ile Gly Leu Gly Gly Ala Arg Glu Ser Ser Ile Tyr Tyr Ser Lys
20 25 30

cat aaa gta gca aca aat ccc ttt tta gca ctt gat ctt tct tta ggt 144
His Lys Val Ala Thr Asn Pro Phe Leu Ala Leu Asp Leu Ser Leu Gly
35 40 45

aat ttt tat atg aga ggg act gca gga att agc gaa ata gga tat gaa 192
Asn Phe Tyr Met Arg Gly Thr Ala Gly Ile Ser Glu Ile Gly Tyr Glu
50 55 60

caa tct ttc act gac aat ttc agc gta tca ctg ttt gtt aac cca ttt 240
Gln Ser Phe Thr Asp Asn Phe Ser Val Ser Leu Phe Val Asn Pro Phe
65 70 75 80

gat ggt ttt tca att aaa gga aaa gac ttg tta cct gga tat caa agt 288
Asp Gly Phe Ser Ile Lys Gly Lys Asp Leu Leu Pro Gly Tyr Gln Ser
85 90 95

att caa act cgc aaa act caa ttt gcc ttt ggt tgg gga tta aat tat 336
Ile Gln Thr Arg Lys Thr Gln Phe Ala Phe Gly Trp Gly Leu Asn Tyr
100 105 110

aat ttg gga ggt tta ttc ggc tta aat gat act ttt ata tcc ttg gaa 384
Asn Leu Gly Gly Leu Phe Gly Leu Asn Asp Thr Phe Ile Ser Leu Glu
115 120 125

gga aaa agc gga aaa cgt ggt gcg agt agt aat gtc agc tta ctt aaa 432
Gly Lys Ser Gly Lys Arg Gly Ala Ser Ser Asn Val Ser Leu Leu Lys
130 135 140

tcg ttt aat atg acg aaa aat tgg aaa gtt tca cca tat att ggc tca 480
Ser Phe Asn Met Thr Lys Asn Trp Lys Val Ser Pro Tyr Ile Gly Ser
145 150 155 160

agt tat tat tca tct aaa tat aca gat tat tac ttt ggt att aaa caa 528
Ser Tyr Tyr Ser Ser Lys Tyr Thr Asp Tyr Tyr Phe Gly Ile Lys Gln
165 170 175

tcc gaa tta ggt aat aaa att aca tcc gta tat aaa cct aaa gca gct 576
Ser Glu Leu Gly Asn Lys Ile Thr Ser Val Tyr Lys Pro Lys Ala Ala
180 185 190

tat gca aca cac ata ggt att aat act gat tat gct ttc acg aac aat 624
Tyr Ala Thr His Ile Gly Ile Asn Thr Asp Tyr Ala Phe Thr Asn Asn
195 200 205

ctt ggc atg ggt tta tct gtc ggt tgg at 653
Leu Gly Met Gly Leu Ser Val Gly Trp
210 215

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<210> 127

<211> 217

<212> PRT

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<213> Actinobacillus pleuropneumoniae

<400> 127

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Leu Ile Ser Phe Pro Phe Ile Thr Phe Ala Ser Asn Val Asn Gly Ala
 1           5           10           15
Glu Ile Gly Leu Gly Gly Ala Arg Glu Ser Ser Ile Tyr Tyr Ser Lys
 20           25           30
His Lys Val Ala Thr Asn Pro Phe Leu Ala Leu Asp Leu Ser Leu Gly
 35           40           45
Asn Phe Tyr Met Arg Gly Thr Ala Gly Ile Ser Glu Ile Gly Tyr Glu
 50           55           60
Gln Ser Phe Thr Asp Asn Phe Ser Val Ser Leu Phe Val Asn Pro Phe
 65           70           75           80
Asp Gly Phe Ser Ile Lys Gly Lys Asp Leu Leu Pro Gly Tyr Gln Ser
 85           90           95
Ile Gln Thr Arg Lys Thr Gln Phe Ala Phe Gly Trp Gly Leu Asn Tyr
100           105           110
Asn Leu Gly Gly Leu Phe Gly Leu Asn Asp Thr Phe Ile Ser Leu Glu
115           120           125
Gly Lys Ser Gly Lys Arg Gly Ala Ser Ser Asn Val Ser Leu Leu Lys
130           135           140
Ser Phe Asn Met Thr Lys Asn Trp Lys Val Ser Pro Tyr Ile Gly Ser
145           150           155           160
Ser Tyr Tyr Ser Ser Lys Tyr Thr Asp Tyr Tyr Phe Gly Ile Lys Gln
165           170           175
Ser Glu Leu Gly Asn Lys Ile Thr Ser Val Tyr Lys Pro Lys Ala Ala
180           185           190
Tyr Ala Thr His Ile Gly Ile Asn Thr Asp Tyr Ala Phe Thr Asn Asn
195           200           205
Leu Gly Met Gly Leu Ser Val Gly Trp
210           215

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<210> 128

<211> 242

<212> DNA

<213> Actinobacillus pleuropneumoniae

<220>

<223> apvC

<220>

<221> CDS

<222> (1)..(240)

<400> 128

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atg tgg cgg atg gga gat ttt atg tct aaa aaa gag agg ctg aat gat 48
Met Trp Arg Met Gly Asp Phe Met Ser Lys Lys Glu Arg Leu Asn Asp
 1           5           10           15

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atg gct cgc cag att tta tca gcg gcg gag ttg ctc att gca aag gaa 96
Met Ala Arg Gln Ile Leu Ser Ala Ala Glu Leu Leu Ile Ala Lys Glu
      20      25      30

ggg ttg caa aat tta tcg atg agg aaa atc gca agt gaa gcc ggt atc 144
Gly Leu Gln Asn Leu Ser Met Arg Lys Ile Ala Ser Glu Ala Gly Ile
      35      40      45

gca aca gcc acg ctt tat ctc tat ttc aaa acg aaa gac gag tta ctg 192
Ala Thr Gly Thr Leu Tyr Leu Tyr Phe Lys Thr Lys Asp Glu Leu Leu
      50      55      60

gat tgt ttg gcg gaa caa tta cat gaa cga tat tat cgt tat ctg aat 240
Asp Cys Leu Ala Glu Gln Leu His Glu Arg Tyr Tyr Arg Tyr Leu Asn
      65      70      75      80

at 242

<210> 129
<211> 80
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 129
Met Trp Arg Met Gly Asp Phe Met Ser Lys Lys Glu Arg Leu Asn Asp
  1      5      10      15
Met Ala Arg Gln Ile Leu Ser Ala Ala Glu Leu Leu Ile Ala Lys Glu
      20      25      30
Gly Leu Gln Asn Leu Ser Met Arg Lys Ile Ala Ser Glu Ala Gly Ile
      35      40      45
Ala Thr Gly Thr Leu Tyr Leu Tyr Phe Lys Thr Lys Asp Glu Leu Leu
      50      55      60
Asp Cys Leu Ala Glu Gln Leu His Glu Arg Tyr Tyr Arg Tyr Leu Asn
      65      70      75      80

<210> 130
<211> 527
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> apvD

<220>
<221> CDS
<222> (1)..(525)

<400> 130
aat att caa aaa aca gtt att gct agc gcc aca ttg caa gcg act gaa 48
Asn Ile Gln Lys Thr Val Ile Ala Ser Gly Thr Leu Gln Ala Thr Glu
  1      5      10      15
caa gta gat att ggt gca caa gta tct ggg cag att aag cat att tta 96
Gln Val Asp Ile Gly Ala Gln Val Ser Gly Gln Ile Lys His Ile Leu
      20      25      30
gta caa gaa gga cag aag gtt aaa aaa ggt gag cta tta gct gta att 144

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val gln glu gly gln lys val lys lys gly glu leu leu ala val ile
    35          40          45
gat cca cgt ctg gct gaa acg gaa tta aaa cta gca aaa gct gag cta 192
asp pro arg leu ala glu thr glu leu lys leu ala lys ala glu leu
    50          55          60
gca aat gct tct gct aat ttg gat aca aaa aaa att aat ctt aag caa 240
ala asn ala ser ala asn leu asp thr lys lys ile asn leu lys gln
    65          70          75          80
ctg caa tca gat tgg gaa cgt cat caa cgt ttg ata cga acc aat gcg 288
leu gln ser asp trp glu arg his gln arg leu ile arg thr asn ala
    85          90          95
aca agc caa aag gaa aca gaa gaa gca aaa agt aga tta aat acg gcc 336
thr ser gln lys glu thr glu glu ala lys ser arg leu asn thr ala
    100          105          110
aaa gca gaa ctt caa att gcg caa aat aat cta gat atc gct aaa atc 384
lys ala glu leu gln ile ala gln asn asn leu asp ile ala lys ile
    115          120          125
aga gtg gaa aaa gct gaa acc gaa cta gga tat aca gaa att cgt tct 432
arg val glu lys ala glu thr glu leu gly tyr thr glu ile arg ser
    130          135          140
cca ctt gat gca aca gta att tca gta ttt gcg caa aat ggt caa act 480
pro leu asp ala thr val ile ser val phe ala gln asn gly gln thr
    145          150          155          160
tta gtc acc acc caa caa gta cca gtg ctg atg aaa tta gct aat at 527
leu val thr thr gln gln val pro val leu met lys leu ala asn
    165          170          175

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<210> 131
 <211> 175
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

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<400> 131
asn ile gln lys thr val ile ala ser gly thr leu gln ala thr glu
    1          5          10          15
gln val asp ile gly ala gln val ser gly gln ile lys his ile leu
    20          25          30
val gln glu gly gln lys val lys lys gly glu leu leu ala val ile
    35          40          45
asp pro arg leu ala glu thr glu leu lys leu ala lys ala glu leu
    50          55          60
ala asn ala ser ala asn leu asp thr lys lys ile asn leu lys gln
    65          70          75          80
leu gln ser asp trp glu arg his gln arg leu ile arg thr asn ala
    85          90          95
thr ser gln lys glu thr glu glu ala lys ser arg leu asn thr ala
    100          105          110

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Lys Ala Glu Leu Gln Ile Ala Gln Asn Asn Leu Asp Ile Ala Lys Ile
 115 120 125
 Arg Val Glu Lys Ala Glu Thr Glu Leu Gly Tyr Thr Glu Ile Arg Ser
 130 135 140
 Pro Leu Asp Ala Thr Val Ile Ser Val Phe Ala Gln Asn Gly Gln Thr
 145 150 155 160
 Leu Val Thr Thr Gln Gln Val Pro Val Leu Met Lys Leu Ala Asn
 165 170 175

<210> 132
 <211> 867
 <212> DNA
 <213> Actinobacillus pleuropneumoniae

<220>
 <223> atpG

<220>
 <221> CDS
 <222> (1)..(864)

<400> 132
 atg gca ggt gcg aaa gag ata aga acc aaa att gca agt gtg aaa aat 48
 Met Ala Gly Ala Lys Glu Ile Arg Thr Lys Ile Ala Ser Val Lys Asn
 1 5 10 15
 act caa aaa atc acc aaa gca atg gaa atg gtt gct acc tct aaa atg 96
 Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Thr Ser Lys Met
 20 25 30
 cgt aaa acg caa gag cgt atg gct gcc agt cgt cct tat tcg gaa aca 144
 Arg Lys Thr Gln Glu Arg Met Ala Ala Ser Arg Pro Tyr Ser Glu Thr
 35 40 45
 atc cgt aag gtg att agc cat att gcg aaa gga agc att ggt tat aag 192
 Ile Arg Lys Val Ile Ser His Ile Ala Lys Gly Ser Ile Gly Tyr Lys
 50 55 60
 cac cgg ttt tta act gaa cgt gat att aaa aaa gta gcc tat ctt gtc 240
 His Pro Phe Leu Thr Glu Arg Asp Ile Lys Lys Val Gly Tyr Leu Val
 65 70 75 80
 gtt tcg acc gat cgc ggt tta tgc ggt gcc ctt aat atc aat tta ttc 288
 Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Ile Asn Leu Phe
 85 90 95
 aaa gcg act ttg aat gaa ttt aaa acg tgg aaa gat aaa gac gtt agt 336
 Lys Ala Thr Leu Asn Glu Phe Lys Thr Trp Lys Asp Lys Val Ser
 100 105 110
 gtt gag ctt ggt tta gta ggg tcg aaa gcc gta agc ttt tac caa aat 384
 Val Glu Leu Gly Leu Val Gly Ser Lys Gly Val Ser Phe Tyr Gln Asn
 115 120 125
 cta gcc tta aac gtg aga tct caa gta acg gga tta gcc gat aat ccg 432
 Leu Gly Leu Asn Val Arg Ser Gln Val Thr Gly Leu Gly Asp Asn Pro
 130 135 140
 gaa atg gaa cgt atc gtg gcc gca gtt aat gaa atg att aat gcg ttc 480

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Glu Met Glu Arg Ile Val Gly Ala Val Asn Glu Met Ile Asn Ala Phe
 145 150 155 160
 cga aac gga gaa gtg gat gcg gtt tac gtc gct tac aac cgt ttt gaa 528
 Arg Asn Gly Glu Val Asp Ala Val Tyr Val Ala Tyr Asn Arg Phe Glu
 165 170 175
 aat acg atg tca caa aaa cct gtt atc gca cag tta ctt ccg tta cct 576
 Asn Thr Met Ser Gln Lys Pro Val Ile Ala Gln Leu Leu Pro Leu Pro
 180 185 190
 aaa cta gat gac gat gaa tta gat acg aaa ggt tca tgg gat tat att 624
 Lys Leu Asp Asp Glu Leu Asp Thr Lys Gly Ser Trp Asp Tyr Ile
 195 200 205
 tat gaa ccg aat cca caa gtt tta ttg gat agt tta ctt gtt cgt tat 672
 Tyr Glu Pro Asn Pro Gln Val Leu Leu Asp Ser Leu Leu Val Arg Tyr
 210 215 220
 tta gaa act cag gta tac caa gca gtt gta gat aac cta gct tct gaa 720
 Leu Glu Thr Gln Val Tyr Gln Ala Val Val Asp Asn Leu Ala Ser Glu
 225 230 235 240
 caa gcc gct cga atg gta gcg atg aaa gcc gca aca gat aat gcg ggt 768
 Gln Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Ala Gly
 245 250 255
 aca tta atc gat gaa tta caa tta gtg tat aac aaa gct cgc caa gca 816
 Thr Leu Ile Asp Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln Ala
 260 265 270
 agc att aca aat gaa tta aac gaa att gtt gcg ggt gcc gca gca att 864
 Ser Ile Thr Asn Glu Leu Asn Glu Ile Val Ala Gly Ala Ala Ile
 275 280 285
 taa 867

 <210> 133
 <211> 288
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

 <400> 133
 Met Ala Gly Ala Lys Glu Ile Arg Thr Lys Ile Ala Ser Val Lys Asn
 1 5 10 15
 Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Thr Ser Lys Met
 20 25 30
 Arg Lys Thr Gln Glu Arg Met Ala Ala Ser Arg Pro Tyr Ser Glu Thr
 35 40 45

 Ile Arg Lys Val Ile Ser His Ile Ala Lys Gly Ser Ile Gly Tyr Lys
 50 55 60
 His Pro Phe Leu Thr Glu Arg Asp Ile Lys Lys Val Gly Tyr Leu Val
 65 70 75 80
 Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Ile Asn Leu Phe
 85 90 95

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Lys Ala Thr Leu Asn Glu Phe Lys Thr Trp Lys Asp Lys Asp Val Ser
 100 105 110
 Val Glu Leu Gly Leu Val Gly Ser Lys Gly Val Ser Phe Tyr Gln Asn
 115 120 125
 Leu Gly Leu Asn Val Arg Ser Gln Val Thr Gly Leu Gly Asp Asn Pro
 130 135 140
 Glu Met Glu Arg Ile Val Gly Ala Val Asn Glu Met Ile Asn Ala Phe
 145 150 155 160
 Arg Asn Gly Glu Val Asp Ala Val Tyr Val Ala Tyr Asn Arg Phe Glu
 165 170 175
 Asn Thr Met Ser Gln Lys Pro Val Ile Ala Gln Leu Leu Pro Leu Pro
 180 185 190
 Lys Leu Asp Asp Asp Glu Leu Asp Thr Lys Gly Ser Trp Asp Tyr Ile
 195 200 205
 Tyr Glu Pro Asn Pro Gln Val Leu Leu Asp Ser Leu Leu Val Arg Tyr
 210 215 220
 Leu Glu Thr Gln Val Tyr Gln Ala Val Val Asp Asn Leu Ala Ser Glu
 225 230 235 240
 Gln Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Ala Gly
 245 250 255
 Thr Leu Ile Asp Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln Ala
 260 265 270
 Ser Ile Thr Asn Glu Leu Asn Glu Ile Val Ala Gly Ala Ala Ile
 275 280 285

<210> 134
 <211> 534
 <212> DNA
 <213> Actinobacillus pleuropneumoniae
 <220>
 <223> atpH
 <220>
 <221> CDS
 <222> (1)..(531)
 <400> 134
 atg tca gaa tta agt aca gta gct cgc ccc tac gct aaa gca gct ttt 48
 Met Ser Glu Leu Ser Thr Val Ala Arg Pro Tyr Ala Lys Ala Ala Phe
 1 5 10 15
 gat ttt gct tta gaa caa ggt cag ttg gac aaa tgg caa gaa atg tta 96
 Asp Phe Ala Leu Glu Gln Gly Gln Leu Asp Lys Trp Gln Glu Met Leu
 20 25 30
 cag ttt tct gca ttc gtt gct gaa aac gaa caa gtg gcg gaa tat att 144
 Gln Phe Ser Ala Phe Val Ala Glu Asn Glu Gln Val Ala Glu Tyr Ile
 35 40 45
 aat tct tcc ctt gca agc ggt cag att tct gaa act ttt atc aaa atc 192

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Asn Ser Ser Leu Ala Ser Gly Gln Ile Ser Glu Thr Phe Ile Lys Ile
50          55          60
tgc ggc gac caa ctt gat caa tat ggg caa aat ttt att cgt gta atg 240
Cys Gly Asp Gln Leu Asp Gln Tyr Gly Gln Asn Phe Ile Arg Val Met
65          70          75          80
gct gaa aat aaa cgt ctg gct gtg ttg cct atg gtt ttt gat act ttc 288
Ala Glu Asn Lys Arg Leu Ala Val Leu Pro Met Val Phe Asp Thr Phe
85          90          95
gta tca tta cga gcg gaa cat gaa gcg gta aaa gat gta aca att gtt 336
Val Ser Leu Arg Ala Glu His Glu Ala Val Lys Asp Val Thr Ile Val
100         105         110
tcg gca aac gaa tta agt caa gca caa gaa gat aaa atc gca aaa gcg 384
Ser Ala Asn Glu Leu Ser Gln Ala Gln Glu Asp Lys Ile Ala Lys Ala
115         120         125
atg gaa aaa cgc tta ggt caa aaa gtt cgt tta acc aac caa atc gat 432
Met Glu Lys Arg Leu Gly Gln Lys Val Arg Leu Thr Asn Gln Ile Asp
130         135         140
aac agc ctg att gca gcg gta att att aaa tac gat gat gtt gtt att 480
Asn Ser Leu Ile Ala Gly Val Ile Ile Lys Tyr Asp Asp Val Val Ile
145         150         155         160
gat ggt agt agc cgc ggt cag tta aat cgc tta gcg tca gcg ttg agc 528
Asp Gly Ser Ser Arg Gly Gln Leu Asn Arg Leu Ala Ser Ala Leu Ser
165         170         175
ttg taa 534
Leu

<210> 135
<211> 177
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 135
Met Ser Glu Leu Ser Thr Val Ala Arg Pro Tyr Ala Lys Ala Ala Phe
1      5      10      15
Asp Phe Ala Leu Glu Gln Gly Gln Leu Asp Lys Trp Gln Glu Met Leu
20     25     30
Gln Phe Ser Ala Phe Val Ala Glu Asn Glu Gln Val Ala Glu Tyr Ile
35     40     45
Asn Ser Ser Leu Ala Ser Gly Gln Ile Ser Glu Thr Phe Ile Lys Ile
50     55     60

Cys Gly Asp Gln Leu Asp Gln Tyr Gly Gln Asn Phe Ile Arg Val Met
65     70     75     80
Ala Glu Asn Lys Arg Leu Ala Val Leu Pro Met Val Phe Asp Thr Phe
85     90     95
Val Ser Leu Arg Ala Glu His Glu Ala Val Lys Asp Val Thr Ile Val
100    105    110

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Ser Ala Asn Glu Leu Ser Gln Ala Gln Glu Asp Lys Ile Ala Lys Ala
 115 120 125
 Met Glu Lys Arg Leu Gly Gln Lys Val Arg Leu Thr Asn Gln Ile Asp
 130 135 140
 Asn Ser Leu Ile Ala Gly Val Ile Ile Lys Tyr Asp Asp Val Val Ile
 145 150 155 160
 Asp Gly Ser Ser Arg Gly Gln Leu Asn Arg Leu Ala Ser Ala Leu Ser
 165 170 175
 Leu

<210> 136
 <211> 321
 <212> DNA
 <213> Actinobacillus pleuropneumoniae

<220>
 <223> dksA

<220>
 <221> CDS
 <222> (1)..(318)

<400> 136
 gca tgg cat gtc caa att atg gac gaa gct gag cgt aca aaa aac caa 48
 Ala Trp His Val Gln Ile Met Asp Glu Ala Glu Arg Thr Lys Asn Gln
 1 5 10 15
 atg cag gaa gaa gtc gct aat ttc gcc gat cct gcg gac cgc gcc act 96
 Met Gln Glu Glu Val Ala Asn Phe Ala Asp Pro Ala Asp Arg Ala Thr
 20 25 30
 cag gaa gaa gaa ttc agt ctt gaa tta aga aac cgt gac cgt gag cgt 144
 Gln Glu Glu Glu Phe Ser Leu Glu Leu Arg Asn Arg Asp Arg Glu Arg
 35 40 45
 aaa ttg ctt aag aag att gag caa acg tta aat agc att gcc gaa gac 192
 Lys Leu Leu Lys Lys Ile Glu Gln Thr Leu Asn Ser Ile Ala Glu Asp
 50 55 60
 gaa tac ggc tat tgc gaa act tgc ggt gtt gaa atc ggt tta cgt cgt 240
 Glu Tyr Gly Tyr Cys Glu Thr Cys Gly Val Glu Ile Gly Leu Arg Arg
 65 70 75 80
 tta gaa gcg cgc ccg acc gcg gat atg tgt atc gat tgc aaa aca ctt 288
 Leu Glu Ala Arg Pro Thr Ala Asp Met Cys Ile Asp Cys Lys Thr Leu
 85 90 95
 gcg gaa atc cgt gaa aag caa atg ggc tta taa 321
 Ala Glu Ile Arg Glu Lys Gln Met Gly Leu
 100 105

<210> 137
 <211> 106
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

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<400> 137
Ala Trp His Val Gln Ile Met Asp Glu Ala Glu Arg Thr Lys Asn Gln
1 5 10 15
Met Gln Glu Glu Val Ala Asn Phe Ala Asp Pro Ala Asp Arg Ala Thr
20 25 30
Gln Glu Glu Glu Phe Ser Leu Glu Leu Arg Asn Arg Asp Arg Glu Arg
35 40 45
Lys Leu Leu Lys Lys Ile Glu Gln Thr Leu Asn Ser Ile Ala Glu Asp
50 55 60
Glu Tyr Gly Tyr Cys Glu Thr Cys Gly Val Glu Ile Gly Leu Arg Arg
65 70 75 80
Leu Glu Ala Arg Pro Thr Ala Asp Met Cys Ile Asp Cys Lys Thr Leu
85 90 95
Ala Glu Ile Arg Glu Lys Gln Met Gly Leu
100 105

<210> 138
<211> 33
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> dnaK

<220>
<221> CDS
<222> (1)..(30)

<400> 138
gct gag ttt gaa gaa gtg aaa gat aat aaa taa 33
Ala Glu Phe Glu Glu Val Lys Asp Asn Lys
1 5 10

<210> 139
<211> 10
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 139
Ala Glu Phe Glu Glu Val Lys Asp Asn Lys
1 5 10

<210> 140
<211> 453
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> exxB

<220>
<221> CDS
<222> (1)..(450)

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<400> 140
atg gaa caa atg ctt gaa ctt tta caa ggt cat gtt gat tat att att 48
Met Glu Gln Met Leu Glu Leu Leu Gln Gly His Val Asp Tyr Ile Ile
1 5 10 15

tta ggc tta tta cta tta atg agt gtt gtg tgg gta tgg aaa att att 96
Leu Gly Leu Leu Leu Leu Met Ser Val Val Leu Val Trp Lys Ile Ile
20 25 30

gaa cgc gta ctt ttc tac aaa caa ttg gat gtg acc aaa tat gac acg 144
Glu Arg Val Leu Phe Tyr Lys Gln Leu Asp Val Thr Lys Tyr Asp Thr
35 40 45

cta caa gat ttg gaa att gat acc act cgc aat tta acc acc att tcc 192
Leu Gln Asp Leu Glu Ile Asp Thr Thr Arg Asn Leu Thr Thr Ile Ser
50 55 60

act atc ggt gcc aac gcc cct tat atc ggt tta tta gga acc gta tta 240
Thr Ile Gly Ala Asn Ala Pro Tyr Ile Gly Leu Leu Gly Thr Val Leu
65 70 75 80

ggg atc tta ctt acc ttc tat cat tta ggg cat tcc ggc ggt gat att 288
Gly Ile Leu Leu Thr Phe Tyr His Leu Gly His Ser Gly Gly Asp Ile
85 90 95

gac gcc gca tcc att atg gtt cac ctt tcg ctt gca tta aaa gca acc 336
Asp Ala Ala Ser Ile Met Val His Leu Ser Leu Ala Leu Lys Ala Thr
100 105 110

gca gcc ggt atc tta gtc gct att ccg gca atg atg ttc tac agc ggt 384
Ala Ala Gly Ile Leu Val Ala Ile Pro Ala Met Met Phe Tyr Ser Gly
115 120 125

ttt aac cgt aaa gtg gat gaa agc aaa ctt aaa tgg caa gcg att caa 432
Phe Asn Arg Lys Val Asp Glu Ser Lys Leu Lys Trp Gln Ala Ile Gln
130 135 140

gct cgt aaa gcc aat caa taa 453
Ala Arg Lys Ala Asn Gln
145 150

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<210> 141
<211> 150
<212> PRT
<213> Actinobacillus pleuropneumoniae

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<400> 141
Met Glu Gln Met Leu Glu Leu Leu Gln Gly His Val Asp Tyr Ile Ile
1 5 10 15

Leu Gly Leu Leu Leu Met Ser Val Val Leu Val Trp Lys Ile Ile
20 25 30

Glu Arg Val Leu Phe Tyr Lys Gln Leu Asp Val Thr Lys Tyr Asp Thr
35 40 45

Leu Gln Asp Leu Glu Ile Asp Thr Thr Arg Asn Leu Thr Thr Ile Ser
50 55 60

Thr Ile Gly Ala Asn Ala Pro Tyr Ile Gly Leu Leu Gly Thr Val Leu
65 70 75 80

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Gly Ile Leu Leu Thr Phe Tyr His Leu Gly His Ser Gly Gly Asp Ile
85 90 95

Asp Ala Ala Ser Ile Met Val His Leu Ser Leu Ala Leu Lys Ala Thr
100 105 110

Ala Ala Gly Ile Leu Val Ala Ile Pro Ala Met Met Phe Tyr Ser Gly
115 120 125

Phe Asn Arg Lys Val Asp Glu Ser Lys Leu Lys Trp Gln Ala Ile Gln
130 135 140

Ala Arg Lys Ala Asn Gln
145 150

<210> 142
<211> 720
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> fkpA

<220>
<221> CDS
<222> (1)..(717)

<400> 142
atg tta aaa aat aaa ctt tct gtt ctt gca atc gta gcc ggt acg ttc 48
Met Leu Lys Asn Lys Leu Ser Val Leu Ala Ile Val Ala Gly Thr Phe
1 5 10 15

ggt tca gct caa act gca ttt gca gcg gat caa aaa ttc att gac gat 96
Val Ser Ala Gln Thr Ala Phe Ala Ala Asp Gln Lys Phe Ile Asp Asp
20 25 30

tca tca tat gca gtc ggc gta ttg atg ggt aaa aat atc gaa ggc gtc 144
Ser Ser Tyr Ala Val Gly Val Leu Met Gly Lys Asn Ile Glu Gly Val
35 40 45

ggt gaa tca caa aaa gaa att ttt tct tat aac caa gat aaa atc ttg 192
Val Glu Ser Gln Lys Glu Ile Phe Ser Tyr Asn Gln Asp Lys Ile Leu
50 55 60

gcg ggt gtc caa gat acc atc aaa aaa acc ggt aaa tta acc gat gaa 240
Ala Gly Val Gln Asp Thr Ile Lys Lys Thr Gly Lys Leu Thr Asp Glu
65 70 75 80

gat cta caa aaa caa tta aaa tcg ctt gat act tat ctt gca agt caa 288
Asp Leu Gln Lys Gln Leu Lys Ser Leu Asp Thr Tyr Leu Ala Ser Gln
85 90 95

gaa agc aaa att gcg gcg gag aaa agc aaa gca acc gta gaa gcc ggt 336
Glu Ser Lys Ile Ala Ala Glu Lys Ser Lys Ala Thr Val Glu Ala Gly
100 105 110

aat aaa ttt cgt acc gac tac gaa aaa caa agc ggc gtg aaa aaa acc 384
Asn Lys Phe Arg Thr Asp Tyr Glu Lys Gln Ser Gly Val Lys Lys Thr
115 120 125

gct tcc ggt tta ctt tat aaa att gaa aaa gcc ggc acg ggc gaa tcg 432

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Ala Ser Gly Leu Leu Tyr Lys Ile Glu Lys Ala Gly Thr Gly Glu Ser
 130 135 140

cct aaa gcg gaa gat acc gtt aaa gtt cac tat aaa ggg aca tta acc 480
 Pro Lys Ala Glu Asp Thr Val Lys Val His Tyr Lys Gly Thr Leu Thr
 145 150 155 160

gat ggt acg gta ttc gat agc tca tac gat cgc ggt gag ccg att gaa 528
 Asp Gly Thr Val Phe Asp Ser Ser Tyr Asp Arg Gly Glu Pro Ile Glu
 165 170 175

ttc caa tta aac caa tta att ccg ggt tgg att gaa gcg att cca atg 576
 Phe Gln Leu Asn Gln Leu Ile Pro Gly Trp Ile Glu Ala Ile Pro Met
 180 185 190

ttg aaa aaa ggc gga aaa atg gaa atc gtc gtt ccg cct gaa ctt ggt 624
 Leu Lys Lys Gly Gly Lys Met Glu Ile Val Val Pro Pro Glu Leu Gly
 195 200 205

tac ggc gaa cgc caa gca ggt aag att ccg gca agt tca acc tta aaa 672
 Tyr Gly Glu Arg Gln Ala Gly Lys Ile Pro Ala Ser Ser Thr Leu Lys
 210 215 220

ttc gag att gaa ttg tta gat ttc aaa gcg gcc gaa gcg aaa aaa taa 720
 Phe Glu Ile Glu Leu Leu Asp Phe Lys Ala Ala Glu Ala Lys Lys
 225 230 235

<210> 143
 <211> 239
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

<400> 143
 Met Leu Lys Asn Lys Leu Ser Val Leu Ala Ile Val Ala Gly Thr Phe
 1 5 10 15

Val Ser Ala Gln Thr Ala Phe Ala Ala Asp Gln Lys Phe Ile Asp Asp
 20 25 30

Ser Ser Tyr Ala Val Gly Val Leu Met Gly Lys Asn Ile Glu Gly Val
 35 40 45

Val Glu Ser Gln Lys Glu Ile Phe Ser Tyr Asn Gln Asp Lys Ile Leu
 50 55 60

Ala Gly Val Gln Asp Thr Ile Lys Lys Thr Gly Lys Leu Thr Asp Glu
 65 70 75 80

Asp Leu Gln Lys Gln Leu Lys Ser Leu Asp Thr Tyr Leu Ala Ser Gln
 85 90 95

Glu Ser Lys Ile Ala Ala Glu Lys Ser Lys Ala Thr Val Glu Ala Gly
 100 105 110

Asn Lys Phe Arg Thr Asp Tyr Glu Lys Gln Ser Gly Val Lys Lys Thr
 115 120 125

Ala Ser Gly Leu Leu Tyr Lys Ile Glu Lys Ala Gly Thr Gly Glu Ser
 130 135 140

Pro Lys Ala Glu Asp Thr Val Lys Val His Tyr Lys Gly Thr Leu Thr
 145 150 155 160

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Asp Gly Thr Val Phe Asp Ser Ser Tyr Asp Arg Gly Glu Pro Ile Glu
      165              170              175
Phe Gln Leu Asn Gln Leu Ile Pro Gly Trp Ile Glu Ala Ile Pro Met
      180              185              190
Leu Lys Lys Gly Gly Lys Met Glu Ile Val Val Pro Pro Glu Leu Gly
      195              200              205
Tyr Gly Glu Arg Gln Ala Gly Lys Ile Pro Ala Ser Ser Thr Leu Lys
      210              215              220
Phe Glu Ile Glu Leu Leu Asp Phe Lys Ala Ala Glu Ala Lys Lys
      225              230              235

<210> 144
<211> 290
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> HI0379

<220>
<221> CDS
<222> (3)..(287)

<400> 144
tg cat agc gtg aga ggt cgg ggc ggc ggt tat caa ctc ggt aag caa 47
  His Ser Val Arg Gly Pro Gly Gly Tyr Gln Leu Gly Lys Gln
    1              5              10              15
cct gaa gag att agt gtg ggg atg att att gcg gcg gtg aat gaa aat 95
  Pro Glu Glu Ile Ser Val Gly Met Ile Ile Ala Ala Val Asn Glu Asn
    20              25              30
ctc gac gta acc aaa tgt aaa ggt agc ggc aac tgt agc aaa aac tct 143
  Leu Asp Val Thr Lys Cys Lys Gly Ser Gly Asn Cys Ser Lys Asn Ser
    35              40              45
cag tgc tta acc cat cat tta tgg gaa cgt tta gaa gaa caa atc ggt 191
  Gln Cys Leu Thr His His Leu Trp Glu Arg Leu Glu Glu Gln Ile Gly
    50              55              60
gtg ttt tta aat acg att act tta gcg gaa ctt gtt gaa gaa cat tcg 239
  Val Phe Leu Asn Thr Ile Thr Leu Ala Glu Leu Val Glu Glu His Ser
    65              70              75
gat cac gat tgt gaa aaa gaa cat tgc cac gat cat tca cac aaa cat 287
  Asp His Asp Cys Glu Lys Glu His Cys His Asp His Ser His Lys His
    80              85              90              95
taa
      290

<210> 145
<211> 95
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 145
His Ser Val Arg Gly Pro Gly Gly Tyr Gln Leu Gly Lys Gln Pro

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      1           5           10           15
Glu Glu Ile Ser Val Gly Met Ile Ile Ala Ala Val Asn Glu Asn Leu
      20           25           30
Asp Val Thr Lys Cys Lys Gly Ser Gly Asn Cys Ser Lys Asn Ser Gln
      35           40           45
Cys Leu Thr His His Leu Trp Glu Arg Leu Glu Glu Gln Ile Gly Val
      50           55           60
Phe Leu Asn Thr Ile Thr Leu Ala Glu Leu Val Glu Glu His Ser Asp
      65           70           75           80
His Asp Cys Glu Lys Glu His Cys His Asp His Ser His Lys His
      85           90           95

<210> 146
<211> 273
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> hupA

<220>
<221> CDS
<222> (1)..(270)

<400> 146
atg aac aaa act gag tta atc gat gca atc gca gct ggt gca gag tta 48
Met Asn Lys Thr Glu Leu Ile Asp Ala Ile Ala Ala Gly Ala Glu Leu
      1           5           10           15
agc aag aaa gac gcg aaa gcg gca tta gaa gcg act tta aat gcg atc 96
Ser Lys Lys Asp Ala Lys Ala Ala Leu Glu Ala Thr Leu Asn Ala Ile
      20           25           30
tct gaa agc cta aaa aat ggc gac acc gtt cag tta atc ggc ttc ggt 144
Ser Glu Ser Leu Lys Asn Gly Asp Thr Val Gln Leu Ile Gly Phe Gly
      35           40           45
act ttt aaa gta aac gag cgt aat gca cgt acg ggt cgt aac ccg cgt 192
Thr Phe Lys Val Asn Glu Arg Asn Ala Arg Thr Gly Arg Asn Pro Arg
      50           55           60
acc ggc gaa gaa atc aaa atc gca gca tct aaa gtg ccg gcg ttt gtt 240
Thr Gly Glu Glu Ile Lys Ile Ala Ala Ser Lys Val Pro Ala Phe Val
      65           70           75           80
gca ggt aaa gca tta aaa gat tta gta aaa taa 273
Ala Gly Lys Ala Leu Lys Asp Leu Val Lys
      85           90

<210> 147
<211> 90
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 147
Met Asn Lys Thr Glu Leu Ile Asp Ala Ile Ala Ala Gly Ala Glu Leu

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      1           5           10           15
Ser Lys Lys Asp Ala Lys Ala Ala Leu Glu Ala Thr Leu Asn Ala Ile
      20           25           30
Ser Glu Ser Leu Lys Asn Gly Asp Thr Val Gln Leu Ile Gly Phe Gly
      35           40           45
Thr Phe Lys Val Asn Glu Arg Asn Ala Arg Thr Gly Arg Asn Pro Arg
      50           55           60
Thr Gly Glu Glu Ile Lys Ile Ala Ala Ser Lys Val Pro Ala Phe Val
      65           70           75           80
Ala Gly Lys Ala Leu Lys Asp Leu Val Lys
      85           90

<210> 148
<211> 551
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> lpda

<220>
<221> CDS
<222> (1)...(549)

<400> 148
atg agc aaa gaa atc aaa acg caa gtc gtg gta ctt ggt gcg ggt cct 48
Met Ser Lys Glu Ile Lys Thr Gln Val Val Val Leu Gly Ala Gly Pro
      1           5           10           15
gcc ggt tat tca gcg gca ttc cgt tgt gcc gac tta ggc tta gaa aca 96
Ala Gly Tyr Ser Ala Ala Phe Arg Cys Ala Asp Leu Gly Leu Glu Thr
      20           25           30
gta att gtc gaa cgt tat tca act ttg gcc ggt gta tgc tta aac gta 144
Val Ile Val Glu Arg Tyr Ser Thr Leu Gly Gly Val Cys Leu Asn Val
      35           40           45
ggt tgt att ccg tct aaa gca tta tta cac gtt gca aaa gtt atc gaa 192
Gly Cys Ile Pro Ser Lys Ala Leu Leu His Val Ala Lys Val Ile Glu
      50           55           60
gaa gca aaa cac gca gag aaa aac ggt att act ttc ggt gag ccc aac 240
Glu Ala Lys His Ala Glu Lys Asn Gly Ile Thr Phe Gly Glu Pro Asn
      65           70           75           80
att gat tta gat aaa gtg cgt gcg ggt aaa gaa gcg gtt gtt tct aaa 288
Ile Asp Leu Asp Lys Val Arg Ala Gly Lys Glu Ala Val Val Ser Lys
      85           90           95

tta acc gcc ggt tta gcg ggt atg gct aaa gca cgt aaa gta aca gta 336
Leu Thr Gly Gly Leu Ala Gly Met Ala Lys Ala Arg Lys Val Thr Val
      100           105           110
gtg gaa ggt tta gcg gcg ttt acc gat ccg aat act tta gta gct cgt 384
Val Glu Gly Leu Ala Ala Phe Thr Asp Pro Asn Thr Leu Val Ala Arg
      115           120           125

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240

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gac cgt gac ggt aat ccg aca acg att aaa ttt gat tat gca att att 432
Asp Arg Asp Gly Asn Pro Thr Thr Ile Lys Phe Asp Tyr Ala Ile Ile
130 135 140

gca gcc ggt tct cgt ccg att cag ctt ccg ttc att cca cac gaa gat 480
Ala Ala Gly Ser Arg Pro Ile Gln Leu Pro Phe Ile Pro His Glu Asp
145 150 155 160

ccg cgt gtg tgg gat tct acg gat gca ctt aaa tta aaa gaa gta ccc 528
Pro Arg Val Trp Asp Ser Thr Asp Ala Leu Lys Leu Lys Glu Val Pro
165 170 175

gaa aaa att act cat tat ggg cc 551
Glu Lys Ile Thr His Tyr Gly
180

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<210> 149
 <211> 183
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

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<400> 149
Met Ser Lys Glu Ile Lys Thr Gln Val Val Val Leu Gly Ala Gly Pro
1 5 10 15

Ala Gly Tyr Ser Ala Ala Phe Arg Cys Ala Asp Leu Gly Leu Glu Thr
20 25 30

Val Ile Val Glu Arg Tyr Ser Thr Leu Gly Gly Val Cys Leu Asn Val
35 40 45

Gly Cys Ile Pro Ser Lys Ala Leu Leu His Val Ala Lys Val Ile Glu
50 55 60

Glu Ala Lys His Ala Glu Lys Asn Gly Ile Thr Phe Gly Glu Pro Asn
65 70 75 80

Ile Asp Leu Asp Lys Val Arg Ala Gly Lys Glu Ala Val Val Ser Lys
85 90 95

Leu Thr Gly Gly Leu Ala Gly Met Ala Lys Ala Arg Lys Val Thr Val
100 105 110

Val Glu Gly Leu Ala Ala Phe Thr Asp Pro Asn Thr Leu Val Ala Arg
115 120 125

Asp Arg Asp Gly Asn Pro Thr Thr Ile Lys Phe Asp Tyr Ala Ile Ile
130 135 140

Ala Ala Gly Ser Arg Pro Ile Gln Leu Pro Phe Ile Pro His Glu Asp
145 150 155 160

Pro Arg Val Trp Asp Ser Thr Asp Ala Leu Lys Leu Lys Glu Val Pro
165 170 175

Glu Lys Ile Thr His Tyr Gly
180

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<210> 150
 <211> 1095
 <212> DNA

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<213> Actinobacillus pleuropneumoniae

<220>

<223> Omp5-2

<220>

<221> CDS

<222> (1)..(1092)

<400> 150

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atg aaa aaa tca tta gtt gct tta aca gta tta tgg gct gca gcg gta 48
Met Lys Lys Ser Leu Val Ala Leu Thr Val Leu Ser Ala Ala Ala Val
1 5 10 15

gct caa gca gcg cca caa caa aat act ttc tac gca ggt gcg aaa gca 96
Ala Gln Ala Ala Pro Gln Gln Asn Thr Phe Tyr Ala Gly Ala Lys Ala
20 25 30

ggg tgg gcg tca ttc cat gat ggt atc gaa caa tta gat tca gct aaa 144
Gly Trp Ala Ser Phe His Asp Gly Ile Glu Gln Leu Asp Ser Ala Lys
35 40 45

aac aca gat cgc ggt aca aaa tac ggt atc aac cgt aat tca gta act 192
Asn Thr Asp Arg Gly Thr Lys Tyr Gly Ile Asn Arg Asn Ser Val Thr
50 55 60

tac ggc gta ttc ggc ggt tac caa att tta aac caa gac aaa tta ggt 240
Tyr Gly Val Phe Gly Gly Tyr Gln Ile Leu Asn Gln Asp Lys Leu Gly
65 70 75 80

tta gcg gct gaa tta ggt tat gac tat ttc ggt cgt gtg cgc ggt tct 288
Leu Ala Ala Glu Leu Gly Tyr Asp Tyr Phe Gly Arg Val Arg Gly Ser
85 90 95

gaa aaa cca aac ggt aaa gcg gac aag aaa act ttc cgt cac gct gca 336
Glu Lys Pro Asn Gly Lys Ala Asp Lys Lys Thr Phe Arg His Ala Ala
100 105 110

cac ggt gcg aca atc gca tta aaa cct agc tac gaa gta tta cct gac 384
His Gly Ala Thr Ile Ala Leu Lys Pro Ser Tyr Glu Val Leu Pro Asp
115 120 125

tta gac gtt tac ggt aaa gta ggt atc gca tta gta aac aat aca tat 432
Leu Asp Val Tyr Gly Lys Val Gly Ile Ala Leu Val Asn Asn Thr Tyr
130 135 140

aaa aca ttc aat gca gca caa gag aaa gtg aaa act cgt cgt ttc caa 480
Lys Thr Phe Asn Ala Ala Gln Glu Lys Val Lys Thr Arg Arg Phe Gln
145 150 155 160

agt tct tta att tta ggt gcg ggt gtt gag tac gca att ctt cct gaa 528
Ser Ser Leu Ile Leu Gly Ala Gly Val Glu Tyr Ala Ile Leu Pro Glu
165 170 175

tta gcg gca cgt gtt gaa tac caa tgg tta aac aac gca ggt aaa gca 576
Leu Ala Ala Arg Val Glu Tyr Gln Trp Leu Asn Asn Ala Gly Lys Ala
180 185 190

agc tac tct act tta aat cgt atg ggt gca act gac tac cgt tgg gat 624
Ser Tyr Ser Thr Leu Asn Arg Met Gly Ala Thr Asp Tyr Arg Ser Asp
195 200 205

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atc agt tcc gta tct gca ggt tta agc tac cgt ttc ggt caa ggt gcg 672
Ile Ser Ser Val Ser Ala Gly Leu Ser Tyr Arg Phe Gly Gln Gly Ala
210 215 220

gca ccg gtt gca gct ccg gca gtt gaa act aaa aac ttc gca ttc agc 720
Ala Pro Val Ala Ala Pro Ala Val Glu Thr Lys Asn Phe Ala Phe Ser
225 230 235 240

tct gac gta tta ttc gca ttc ggt aaa tca aac tta aaa ccg gct gcg 768
Ser Asp Val Leu Phe Ala Phe Gly Lys Ser Asn Leu Lys Pro Ala Ala
245 250 255

gca aca gca tta gat gca atg caa acc gaa atc aat aac gca ggt tta 816
Ala Thr Ala Leu Asp Ala Met Gln Thr Glu Ile Asn Asn Ala Gly Leu
260 265 270

tca aat gct gcg atc caa gta aac ggt tac acg gac cgt atc ggt aaa 864
Ser Asn Ala Ala Ile Gln Val Asn Gly Tyr Thr Asp Arg Ile Gly Lys
275 280 285

gaa gct tca aac tta aaa ctt tca caa cgt cgt gcg gaa aca gta gct 912
Glu Ala Ser Asn Leu Lys Leu Ser Gln Arg Arg Ala Glu Thr Val Ala
290 295 300

aac tac atc gtt tct aaa ggt gct ccg gca gct aac gta act gca gta 960
Asn Tyr Ile Val Ser Lys Gly Ala Pro Ala Ala Asn Val Thr Ala Val
305 310 315 320

ggt tac ggt gaa gca aac cct gta acc ggc gca aca tgt gac aaa gtt 1008
Gly Tyr Gly Glu Ala Asn Pro Val Thr Gly Ala Thr Cys Asp Lys Val
325 330 335

aaa ggt cgt aaa gca tta atc gct tgc tta gca ccg gat cgt cgt gtt 1056
Lys Gly Arg Lys Ala Leu Ile Ala Cys Leu Ala Pro Asp Arg Arg Val
340 345 350

gaa gtt caa gtt caa ggt act aaa gaa gta act atg taa 1095
Glu Val Gln Val Gln Gly Thr Lys Glu Val Thr Met
355 360

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<210> 151
 <211> 364
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

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<400> 151
Met Lys Lys Ser Leu Val Ala Leu Thr Val Leu Ser Ala Ala Ala Val
1 5 10 15

Ala Gln Ala Ala Pro Gln Gln Asn Thr Phe Tyr Ala Gly Ala Lys Ala
20 25 30

Gly Trp Ala Ser Phe His Asp Gly Ile Glu Gln Leu Asp Ser Ala Lys
35 40 45

Asn Thr Asp Arg Gly Thr Lys Tyr Gly Ile Asn Arg Asn Ser Val Thr
50 55 60

Tyr Gly Val Phe Gly Gly Tyr Gln Ile Leu Asn Gln Asp Lys Leu Gly
65 70 75 80

Leu Ala Ala Glu Leu Gly Tyr Asp Tyr Phe Gly Arg Val Arg Gly Ser

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      85              90              95
Glu Lys Pro Asn Gly Lys Ala Asp Lys Lys Thr Phe Arg His Ala Ala
      100              105              110
His Gly Ala Thr Ile Ala Leu Lys Pro Ser Tyr Glu Val Leu Pro Asp
      115              120              125
Leu Asp Val Tyr Gly Lys Val Gly Ile Ala Leu Val Asn Asn Thr Tyr
      130              135              140
Lys Thr Phe Asn Ala Ala Gln Glu Lys Val Lys Thr Arg Arg Phe Gln
      145              150              155              160
Ser Ser Leu Ile Leu Gly Ala Gly Val Glu Tyr Ala Ile Leu Pro Glu
      165              170              175
Leu Ala Ala Arg Val Glu Tyr Gln Trp Leu Asn Asn Ala Gly Lys Ala
      180              185              190
Ser Tyr Ser Thr Leu Asn Arg Met Gly Ala Thr Asp Tyr Arg Ser Asp
      195              200              205
Ile Ser Ser Val Ser Ala Gly Leu Ser Tyr Arg Phe Gly Gln Gly Ala
      210              215              220
Ala Pro Val Ala Ala Pro Ala Val Glu Thr Lys Asn Phe Ala Phe Ser
      225              230              235              240
Ser Asp Val Leu Phe Ala Phe Gly Lys Ser Asn Leu Lys Pro Ala Ala
      245              250              255
Ala Thr Ala Leu Asp Ala Met Gln Thr Glu Ile Asn Asn Ala Gly Leu
      260              265              270
Ser Asn Ala Ala Ile Gln Val Asn Gly Tyr Thr Asp Arg Ile Gly Lys
      275              280              285
Glu Ala Ser Asn Leu Lys Leu Ser Gln Arg Arg Ala Glu Thr Val Ala
      290              295              300
Asn Tyr Ile Val Ser Lys Gly Ala Pro Ala Ala Asn Val Thr Ala Val
      305              310              315              320
Gly Tyr Gly Glu Ala Asn Pro Val Thr Gly Ala Thr Cys Asp Lys Val
      325              330              335
Lys Gly Arg Lys Ala Leu Ile Ala Cys Leu Ala Pro Asp Arg Val
      340              345              350
Glu Val Gln Val Gln Gly Thr Lys Glu Val Thr Met
      355              360

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<210> 152
<211> 1110
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> Omp5

<220>

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<221> CDS

<222> (1)...(1107)

<400> 152

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atg aaa aaa tca tta gtt gct tta gca gta tta tgg gct gca gca gta 48
Met Lys Lys Ser Leu Val Ala Leu Ala Val Leu Ser Ala Ala Ala Val
1 5 10 15

gct caa gca gct cca caa caa aat act ttc tac gca ggt gcg aaa gtt 96
Ala Gln Ala Ala Pro Gln Gln Asn Thr Phe Tyr Ala Gly Ala Lys Val
20 25 30

ggt caa tca tca ttt cac cac ggt gtt aac caa tta aaa tct ggt cac 144
Gly Gln Ser Ser Phe His His Gly Val Asn Gln Leu Lys Ser Gly His
35 40 45

gat gat cgt tat aat gat aaa aca cgt aag tat ggt atc aac cgt aac 192
Asp Asp Arg Tyr Asn Asp Lys Thr Arg Lys Tyr Gly Ile Asn Arg Asn
50 55 60

tct gta act tac ggt gta ttc ggc ggt tac caa atc tta aac caa aat 240
Ser Val Thr Tyr Gly Val Phe Gly Gly Tyr Gln Ile Leu Asn Gln Asn
65 70 75

aac ttc ggt tta gca gct gaa tta ggc tat gac tac tac ggt cgc gta 288
Asn Phe Gly Leu Ala Ala Glu Leu Gly Tyr Asp Tyr Tyr Gly Arg Val
85 90 95

cgt ggt aac gta gat gaa ttc cgt aca gtt aaa cac tct gct cac ggt 336
Arg Gly Asn Val Asp Glu Phe Arg Thr Val Lys His Ser Ala His Gly
100 105 110

tta aac tta gcg tta aaa cca agc tac gaa gta tta cct gac tta gac 384
Leu Asn Leu Ala Leu Lys Pro Ser Tyr Glu Val Leu Pro Asp Leu Asp
115 120 125

gtt tac ggt aaa gta ggt att gcg gtt gtt cgt aat gac tat aaa aaa 432
Val Tyr Gly Lys Val Gly Ile Ala Val Val Arg Asn Asp Tyr Lys Lys
130 135 140

tat ggt gcg gaa aac act aac gaa tca aca aca aaa ttc cac aaa tta 480
Tyr Gly Ala Glu Asn Thr Asn Glu Ser Thr Thr Lys Phe His Lys Leu
145 150 155

aaa gca tca act att tta ggt gca ggt gtt gag tac gca att ctt cct 528
Lys Ala Ser Thr Ile Leu Gly Ala Gly Val Glu Tyr Ala Ile Leu Pro
165 170 175

gaa tta gcg gca cgt gtt gaa tac caa tac tta aac aaa gcg ggt aac 576
Glu Leu Ala Ala Arg Val Glu Tyr Gln Tyr Leu Asn Lys Ala Gly Asn
180 185 190

tta aat aaa gca tta gtt cgt tca ggc aca caa gat gtg gac ttc caa 624
Leu Asn Lys Ala Leu Val Arg Ser Gly Thr Gln Asp Val Asp Phe Gln
195 200 205

tat gct cct gat atc cac tct gta aca gca ggt tta tca tac cgt ttc 672
Tyr Ala Pro Asp Ile His Ser Val Thr Ala Gly Leu Ser Tyr Arg Phe
210 215 220

ggt caa ggc gct gta gca cca gtt gtt gag cca gaa gtt gta act aaa 720
Gly Gln Gly Ala Val Ala Pro Val Val Glu Pro Glu Val Val Thr Lys
225 230 235 240

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245

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aac ttc gca ttc agc tca gac gtt tta ttt gat ttc ggt aaa tca agc 768
Asn Phe Ala Phe Ser Ser Asp Val Leu Phe Asp Phe Gly Lys Ser Ser
      245                250                255

tta aaa cca gca gca gca aca gct tta gac gca gct aac act gaa atc 816
Leu Lys Pro Ala Ala Ala Thr Ala Leu Asp Ala Ala Asn Thr Glu Ile
      260                265                270

gct aac tta ggt tta gca act cca gct atc caa gtt aac ggt tat aca 864
Ala Asn Leu Gly Leu Ala Thr Pro Ala Ile Gln Val Asn Gly Tyr Thr
      275                280                285

gac cgt atc ggt aaa gaa gct tca aac tta aaa ctt tca caa cgc cgt 912
Asp Arg Ile Gly Lys Glu Ala Ser Asn Leu Lys Leu Ser Gln Arg Arg
      290                295                300

gca gaa act gta gct aac tac tta gtt tct aaa ggt caa aac cct gca 960
Ala Glu Thr Val Ala Asn Tyr Leu Val Ser Lys Gly Gln Asn Pro Ala
      305                310                315

aac gta act gca gta ggt tac ggt gaa gca aac cca gta acc ggc gca 1008
Asn Val Thr Ala Val Gly Tyr Gly Glu Ala Asn Pro Val Thr Gly Ala
      325                330                335

aca tgt gat gca gtt aaa ggt cgt aaa gca tta atc gct tgc tta gca 1056
Thr Cys Asp Ala Val Lys Gly Arg Lys Ala Leu Ile Ala Cys Leu Ala
      340                345                350

ccg gat cgt cgt gtt gaa gtt caa gta caa ggt gct aaa aac gta gct 1104
Pro Asp Arg Arg Val Glu Val Gln Val Gln Gly Ala Lys Asn Val Ala
      355                360                365

atg taa 1110
Met

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<210> 153
 <211> 369
 <212> PRT
 <213> Actinobacillus pleuropneumoniae

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<400> 153
Met Lys Lys Ser Leu Val Ala Leu Ala Val Leu Ser Ala Ala Ala Val
  1           5           10           15

Ala Gln Ala Ala Pro Gln Gln Asn Thr Phe Tyr Ala Gly Ala Lys Val
  20           25           30

Gly Gln Ser Ser Phe His His Gly Val Asn Gln Leu Lys Ser Gly His
  35           40           45

Asp Asp Arg Tyr Asn Asp Lys Thr Arg Lys Tyr Gly Ile Asn Arg Asn
  50           55           60

Ser Val Thr Tyr Gly Val Phe Gly Gly Tyr Gln Ile Leu Asn Gln Asn
  65           70           75           80

Asn Phe Gly Leu Ala Ala Glu Leu Gly Tyr Asp Tyr Tyr Gly Arg Val
  85           90           95

Arg Gly Asn Val Asp Glu Phe Arg Thr Val Lys His Ser Ala His Gly
  100          105          110

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Leu Asn Leu Ala Leu Lys Pro Ser Tyr Glu Val Leu Pro Asp Leu Asp
115 120 125
Val Tyr Gly Lys Val Gly Ile Ala Val Val Arg Asn Asp Tyr Lys Lys
130 135 140
Tyr Gly Ala Glu Asn Thr Asn Glu Ser Thr Thr Lys Phe His Lys Leu
145 150 155 160
Lys Ala Ser Thr Ile Leu Gly Ala Gly Val Glu Tyr Ala Ile Leu Pro
165 170 175
Glu Leu Ala Ala Arg Val Glu Tyr Gln Tyr Leu Asn Lys Ala Gly Asn
180 185 190
Leu Asn Lys Ala Leu Val Arg Ser Gly Thr Gln Asp Val Asp Phe Gln
195 200 205
Tyr Ala Pro Asp Ile His Ser Val Thr Ala Gly Leu Ser Tyr Arg Phe
210 215 220
Gly Gln Gly Ala Val Ala Pro Val Val Glu Pro Glu Val Val Thr Lys
225 230 235 240
Asn Phe Ala Phe Ser Ser Asp Val Leu Phe Asp Phe Gly Lys Ser Ser
245 250 255
Leu Lys Pro Ala Ala Ala Thr Ala Leu Asp Ala Ala Asn Thr Glu Ile
260 265 270
Ala Asn Leu Gly Leu Ala Thr Pro Ala Ile Gln Val Asn Gly Tyr Thr
275 280 285
Asp Arg Ile Gly Lys Glu Ala Ser Asn Leu Lys Leu Ser Gln Arg Arg
290 295 300
Ala Glu Thr Val Ala Asn Tyr Leu Val Ser Lys Gly Gln Asn Pro Ala
305 310 315 320
Asn Val Thr Ala Val Gly Tyr Gly Glu Ala Asn Pro Val Thr Gly Ala
325 330 335
Thr Cys Asp Ala Val Lys Gly Arg Lys Ala Leu Ile Ala Cys Leu Ala
340 345 350
Pro Asp Arg Arg Val Glu Val Gln Val Gln Gly Ala Lys Asn Val Ala
355 360 365

Met

<210> 154
<211> 1076
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> pnp new

<220>
<221> CDS
<222> (1)...(1074)

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<400> 154
aat att aaa gaa ttc gta aaa gaa gcg ggt aaa ccg cgt tgg gat tgg 48
Asn Ile Lys Glu Phe Val Lys Glu Ala Gly Lys Pro Arg Trp Asp Trp
1 5 10 15

ggt gcg ccg gaa ccg aat acc gca tta atc aac caa gtt aaa gcg tta 96
Val Ala Pro Glu Pro Asn Thr Ala Leu Ile Asn Gln Val Lys Ala Leu
20 25 30

gcg gaa gcg cgt atc ggc gat ccg tat cgt att aca gaa aaa caa gcg 144
Ala Glu Ala Arg Ile Gly Asp Ala Tyr Arg Ile Thr Glu Lys Gln Ala
35 40 45

cgt tac gaa caa atc gat gca att aaa gcg gat gtt atc gca caa tta 192
Arg Tyr Glu Gln Ile Asp Ala Ile Lys Ala Asp Val Ile Ala Gln Leu
50 55 60

acc gca caa gac gaa acc gtt tct gaa ggt gcg att att gat att att 240
Thr Ala Gln Asp Glu Thr Val Ser Glu Gly Ala Ile Ile Asp Ile Ile
65 70 75 80

acc gca tta gaa agt tct att gtt cgc ggt cgt att att gcc ggc gaa 288
Thr Ala Leu Glu Ser Ser Ile Val Arg Gly Arg Ile Ile Ala Gly Glu
85 90 95

ccg cgt att gac ggt cgt acg gta gat acg gtt cgt gca tta gac att 336
Pro Arg Ile Asp Gly Arg Thr Val Asp Thr Val Arg Ala Leu Asp Ile
100 105 110

tgc acc ggc gta tta cct cgt acg cac ggt tct gca atc ttt act cgc 384
Cys Thr Gly Val Leu Pro Arg Thr His Gly Ser Ala Ile Phe Thr Arg
115 120 125

ggt gaa aca caa gca tta gcg gtt gca acc tta ggt act gag cgc gat 432
Gly Glu Thr Gln Ala Leu Ala Val Ala Thr Leu Gly Thr Glu Arg Asp
130 135 140

gca caa att gtt gac gaa tta acc ggc gag aaa tca gac cgt ttc tta 480
Ala Gln Ile Val Asp Glu Leu Thr Gly Glu Lys Ser Asp Arg Phe Leu
145 150 155

ttc cac tat aac ttc cct ccg tac tct gtc ggt gaa acc ggt cgt atc 528
Phe His Tyr Asn Phe Pro Pro Tyr Ser Val Gly Glu Thr Gly Arg Ile
165 170 175

ggt tgg ccg aaa cgt cgt gaa atc ggc cac ggt cgt tta gcg aaa cgc 576
Gly Ser Pro Lys Arg Arg Glu Ile Gly His Gly Arg Leu Ala Lys Arg
180 185 190

ggt gta tta gcg gta atg ccg act gct gaa gaa ttc ccg tat gta gtg 624
Gly Val Leu Ala Val Met Pro Thr Ala Glu Glu Phe Pro Tyr Val Val
195 200 205

cgc gta gta tct gaa att acc gaa tca aac ggt tct tct tca atg gct 672
Arg Val Val Ser Glu Ile Thr Glu Ser Asn Gly Ser Ser Ser Met Ala
210 215 220

tcc gta tgc ggc gca tct tta gcg tta atg gac gca ggc gta ccg att 720
Ser Val Cys Gly Ala Ser Leu Ala Leu Met Asp Ala Gly Val Pro Ile
225 230 235 240

aaa gcg gcg gtt gcg ggt atc gca atg ggc tta gtg aaa gaa gaa gaa 768
Lys Ala Ala Val Ala Gly Ile Ala Met Gly Leu Val Lys Glu Glu Glu

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      245      250      255
aaa ttt gtg gtg ctt tca gac atc tta ggt gac gaa gac cat tta ggc 816
Lys Phe Val Val Leu Ser Asp Ile Leu Gly Asp Glu Asp His Leu Gly
      260      265      270
gat atg gac ttc aaa gta gcc ggt acg cgt gaa ggt gta acc gca ctt 864
Asp Met Asp Phe Lys Val Ala Gly Thr Arg Glu Gly Val Thr Ala Leu
      275      280      285
caa atg gat att aaa atc gaa ggt atc acg cct gaa att atg caa atc 912
Gln Met Asp Ile Lys Ile Glu Gly Ile Thr Pro Glu Ile Met Gln Ile
      290      295      300
gca tta aat caa gcg aaa ggt gcg cgt atg cac atc tta agc gtg atg 960
Ala Leu Asn Gln Ala Lys Gly Ala Arg Met His Ile Leu Ser Val Met
      305      310      315
gaa caa gcg att cct gca cct cgt gcc gat att tcc gat ttt gcg cct 1008
Glu Gln Ala Ile Pro Ala Pro Arg Ala Asp Ile Ser Asp Phe Ala Pro
      325      330      335
cgt att cat acg atg aag atc gat cgg aag aaa atc aaa gac gtg atc 1056
Arg Ile His Thr Met Lys Ile Asp Pro Lys Lys Ile Lys Asp Val Ile
      340      345      350
ggg aaa ggc ggt gcg gtt at 1076
Gly Lys Gly Gly Ala Val
      355

<210> 155
<211> 358
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 155
Asn Ile Lys Glu Phe Val Lys Glu Ala Gly Lys Pro Arg Trp Asp Trp
      1      5      10      15
Val Ala Pro Glu Pro Asn Thr Ala Leu Ile Asn Gln Val Lys Ala Leu
      20      25      30
Ala Glu Ala Arg Ile Gly Asp Ala Tyr Arg Ile Thr Glu Lys Gln Ala
      35      40      45
Arg Tyr Glu Gln Ile Asp Ala Ile Lys Ala Asp Val Ile Ala Gln Leu
      50      55      60
Thr Ala Gln Asp Glu Thr Val Ser Glu Gly Ala Ile Ile Asp Ile Ile
      65      70      75      80
Thr Ala Leu Glu Ser Ser Ile Val Arg Gly Arg Ile Ile Ala Gly Glu
      85      90      95
Pro Arg Ile Asp Gly Arg Thr Val Asp Thr Val Arg Ala Leu Asp Ile
      100      105      110
Cys Thr Gly Val Leu Pro Arg Thr His Gly Ser Ala Ile Phe Thr Arg
      115      120      125
Gly Glu Thr Gln Ala Leu Ala Val Ala Thr Leu Gly Thr Glu Arg Asp

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130 135 140
 Ala Gln Ile Val Asp Glu Leu Thr Gly Glu Lys Ser Asp Arg Phe Leu
 145 150 155 160
 Phe His Tyr Asn Phe Pro Pro Tyr Ser Val Gly Glu Thr Gly Arg Ile
 165 170 175
 Gly Ser Pro Lys Arg Arg Glu Ile Gly His Gly Arg Leu Ala Lys Arg
 180 185 190
 Gly Val Leu Ala Val Met Pro Thr Ala Glu Glu Phe Pro Tyr Val Val
 195 200 205
 Arg Val Val Ser Glu Ile Thr Glu Ser Asn Gly Ser Ser Ser Met Ala
 210 215 220
 Ser Val Cys Gly Ala Ser Leu Ala Leu Met Asp Ala Gly Val Pro Ile
 225 230 235 240
 Lys Ala Ala Val Ala Gly Ile Ala Met Gly Leu Val Lys Glu Glu Glu
 245 250 255
 Lys Phe Val Val Leu Ser Asp Ile Leu Gly Asp Glu Asp His Leu Gly
 260 265 270
 Asp Met Asp Phe Lys Val Ala Gly Thr Arg Glu Gly Val Thr Ala Leu
 275 280 285
 Gln Met Asp Ile Lys Ile Glu Gly Ile Thr Pro Glu Ile Met Gln Ile
 290 295 300
 Ala Leu Asn Gln Ala Lys Gly Ala Arg Met His Ile Leu Ser Val Met
 305 310 315 320
 Glu Gln Ala Ile Pro Ala Pro Arg Ala Asp Ile Ser Asp Phe Ala Pro
 325 330 335
 Arg Ile His Thr Met Lys Ile Asp Pro Lys Lys Ile Lys Asp Val Ile
 340 345 350
 Gly Lys Gly Gly Ala Val
 355

<210> 156

<211> 1055

<212> DNA

<213> Actinobacillus pleuropneumoniae

<220>

<223> potD

<220>

<221> CDS

<222> (1)..(1053)

<400> 156

atg aaa aaa tta gcg ggt tta ttt gca gca ggt tta gcg aca gtt gca 48
 Met Lys Lys Leu Ala Gly Leu Phe Ala Ala Gly Leu Ala Thr Val Ala
 1 5 10 15

tta aca gcg tgt aat gaa gaa aag cca aaa gcg gct gaa gca gcg gct 96

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Leu Thr Ala Cys Asn Glu Glu Lys Pro Lys Ala Ala Glu Ala Ala Ala
      20              25              30
caa ccg gca gca gcg gga aca gtt cac ctt tat act tgg act gaa tat 144
Gln Pro Ala Ala Ala Gly Thr Val His Leu Tyr Thr Trp Thr Glu Tyr
      35              40              45
gtg cct gaa ggc ttg tta gat gaa ttt aca aag caa acc ggt atc aaa 192
Val Pro Glu Gly Leu Leu Asp Glu Phe Thr Lys Gln Thr Gly Ile Lys
      50              55              60
gta gag gtt tca agc ctt gaa tct aac gaa acc atg tat gcg aaa tta 240
Val Glu Val Ser Ser Leu Glu Ser Asn Glu Thr Met Tyr Ala Lys Leu
      65              70              75
aaa tta caa ggt aaa gac ggc ggt tac gat gtt atc gca cct tct aac 288
Lys Leu Gln Gly Lys Asp Gly Gly Tyr Asp Val Ile Ala Pro Ser Asn
      85              90              95
tac ttc gtt tca aaa atg gcg aaa gaa ggt atg tta gcg gaa tta gat 336
Tyr Phe Val Ser Lys Met Ala Lys Glu Gly Met Leu Ala Glu Leu Asp
      100             105             110
cac gca aaa ctt cct gta atc aaa gag tta aac caa gat tgg tta aac 384
His Ala Lys Leu Pro Val Ile Lys Glu Leu Asn Gln Asp Trp Leu Asn
      115             120             125
aaa cct tat gac caa ggt aac aaa tac tct tta ccg caa tta tta ggt 432
Lys Pro Tyr Asp Gln Gly Asn Lys Tyr Ser Leu Pro Gln Leu Leu Gly
      130             135             140
gca ccg ggt atc gca ttt aac tca aat gac tat aag ggc gat gcg ttc 480
Ala Pro Gly Ile Ala Phe Asn Ser Asn Asp Tyr Lys Gly Asp Ala Phe
      145             150             155
act tct tgg ggt gat tta tgg aaa cct gag ttt gcg aat aaa gta caa 528
Thr Ser Trp Gly Asp Leu Trp Lys Pro Glu Phe Ala Asn Lys Val Gln
      165             170             175
tta tta gat gac gca cgt gaa gta ttt aac att gcg tta tta aaa tta 576
Leu Leu Asp Asp Ala Arg Glu Val Phe Asn Ile Ala Leu Leu Lys Leu
      180             185             190
ggt aaa aac cct aat aca acc aat ccg gaa gag att aaa gcg gct tac 624
Gly Lys Asn Pro Asn Thr Thr Asn Pro Glu Glu Ile Lys Ala Ala Tyr
      195             200             205
gaa gag tta aga aaa tta cgt cca aac gta ctt tct ttc act tca gac 672
Glu Glu Leu Arg Lys Leu Arg Pro Asn Val Leu Ser Phe Thr Ser Asp
      210             215             220

aac cca gcg aac tca ttt atc gca ggt gaa gta tct gta ggt caa tta 720
Asn Pro Ala Asn Ser Phe Ile Ala Gly Glu Val Ser Val Gly Gln Leu
      225             230             235
tgg aac ggt tct gta cgt att gcg aaa aaa gaa caa gcg ccg gta aac 768
Trp Asn Gly Ser Val Arg Ile Ala Lys Lys Glu Gln Ala Pro Val Asn
      245             250             255
atg gtg ttc cca aaa gaa ggt cct gta ctt tgg gtt gat acg tta gcc 816
Met Val Phe Pro Lys Glu Gly Pro Val Leu Trp Val Asp Thr Leu Ala

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      260      265      270
att ccg gcg aat gcg aaa aac aaa gaa aat gcg cat aag tta atc aac 864
ile pro ala asn ala lys asn lys glu asn ala his lys leu ile asn
      275      280      285
tac tta tta agc gca ccg gtt gcg gaa aaa tta acg tta gaa atc ggt 912
tyr leu leu ser ala pro val ala glu lys leu thr leu glu ile gly
      290      295      300
tat ccg act tca aac gta gaa gcg tta aaa aca tta cca aaa gag att 960
tyr pro thr ser asn val glu ala leu lys thr leu pro lys glu ile
      305      310      315      320
acc gaa gat ccg gca atc tat ccg aca gct gat gtg tta aaa gcg gca 1008
thr glu asp pro ala ile tyr pro thr ala asp val leu lys ala ala
      325      330      335
caa tgg caa gac gat gta ggt aat gca atc gaa ctt tac gaa aaa ta 1055
gin trp gln asp val gly asn ala ile glu leu tyr glu lys
      340      345      350

<210> 157
<211> 351
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 157
Met Lys Lys Leu Ala Gly Leu Phe Ala Ala Gly Leu Ala Thr Val Ala
      1      5      10      15
Leu Thr Ala Cys Asn Glu Glu Lys Pro Lys Ala Ala Glu Ala Ala Ala
      20      25      30
Gln Pro Ala Ala Ala Gly Thr Val His Leu Tyr Thr Trp Thr Glu Tyr
      35      40      45
Val Pro Glu Gly Leu Leu Asp Glu Phe Thr Lys Gln Thr Gly Ile Lys
      50      55      60
Val Glu Val Ser Ser Leu Glu Ser Asn Glu Thr Met Tyr Ala Lys Leu
      65      70      75      80
Lys Leu Gln Gly Lys Asp Gly Gly Tyr Asp Val Ile Ala Pro Ser Asn
      85      90      95
Tyr Phe Val Ser Lys Met Ala Lys Glu Gly Met Leu Ala Glu Leu Asp
      100      105      110
His Ala Lys Leu Pro Val Ile Lys Glu Leu Asn Gln Asp Trp Leu Asn
      115      120      125
Lys Pro Tyr Asp Gln Gly Asn Lys Tyr Ser Leu Pro Gln Leu Leu Gly
      130      135      140
Ala Pro Gly Ile Ala Phe Asn Ser Asn Asp Tyr Lys Gly Asp Ala Phe
      145      150      155      160
Thr Ser Trp Gly Asp Leu Trp Lys Pro Glu Phe Ala Asn Lys Val Gln
      165      170      175
Leu Leu Asp Asp Ala Arg Glu Val Phe Asn Ile Ala Leu Leu Lys Leu

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180          185          190
Gly Lys Asn Pro Asn Thr Thr Asn Pro Glu Glu Ile Lys Ala Ala Tyr
195          200          205
Glu Glu Leu Arg Lys Leu Arg Pro Asn Val Leu Ser Phe Thr Ser Asp
210          215          220
Asn Pro Ala Asn Ser Phe Ile Ala Gly Glu Val Ser Val Gly Gln Leu
225          230          235
Trp Asn Gly Ser Val Arg Ile Ala Lys Lys Glu Gln Ala Pro Val Asn
245          250          255
Met Val Phe Pro Lys Glu Gly Pro Val Leu Trp Val Asp Thr Leu Ala
260          265          270
Ile Pro Ala Asn Ala Lys Asn Lys Glu Asn Ala His Lys Leu Ile Asn
275          280          285
Tyr Leu Leu Ser Ala Pro Val Ala Glu Lys Leu Thr Leu Glu Ile Gly
290          295          300
Tyr Pro Thr Ser Asn Val Glu Ala Leu Lys Thr Leu Pro Lys Glu Ile
305          310          315
Thr Glu Asp Pro Ala Ile Tyr Pro Thr Ala Asp Val Leu Lys Ala Ala
325          330          335
Gln Trp Gln Asp Asp Val Gly Asn Ala Ile Glu Leu Tyr Glu Lys
340          345          350

<210> 158
<211> 525
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> rpmF

<220>
<221> CDS
<222> (1) .. (522)

<400> 158
atg caa aag gta aaa cta ccc ctc acc att gac cca tat aaa gac gct 48
Met Gln Lys Val Lys Leu Pro Leu Thr Ile Asp Pro Tyr Lys Asp Ala
1      5      10      15
cag cgt cga atg gat tac gaa ggc tac atc tca cgt agt ctg ctt aat 96
Gln Arg Arg Met Asp Tyr Glu Gly Tyr Ile Ser Arg Ser Leu Leu Asn
20     25     30
cgt ttg ggt gaa tct gtg agc aat gtg cta agc gat gca caa gtt act 144
Arg Leu Gly Glu Ser Val Ser Asn Val Leu Ser Asp Ala Gln Val Thr
35     40     45
ctc tcg tta tat atc gat cag caa cgc tta acc gtt att aaa ggt acg 192
Leu Ser Leu Tyr Ile Asp Pro Gln Arg Leu Thr Val Ile Lys Gly Thr
50     55     60
gcg aca gtg gaa gtg gaa ttc gat tgc caa cga tgc ggt aac cag ttt 240

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Ala Thr Val Glu Val Glu Phe Asp Cys Gln Arg Cys Gly Asn Pro Phe
65 70 75 80
aca caa acg ctt gac tgt tct ttt tgt ttc agt ccg gtg tcc aat atg 288
Thr Gln Thr Leu Asp Cys Ser Phe Cys Phe Ser Pro Val Ser Asn Met
85 90 95
gat cag gcg gac aat ttg ccc gaa att tat gaa cca atc gaa gta aac 336
Asp Gln Ala Asp Asn Leu Pro Glu Ile Tyr Glu Pro Ile Glu Val Asn
100 105 110
gag ttc ggt gaa gta aat tta cta gat atg atc gaa gat gga ttt atc 384
Glu Phe Gly Glu Val Asn Leu Asp Met Ile Glu Asp Gly Phe Ile
115 120 125
atc gaa ttg cct cta gtc ccg atg cat agt gaa gaa cac tgt gaa gtg 432
Ile Glu Leu Pro Leu Val Pro Met His Ser Glu Glu His Cys Glu Val
130 135 140
tcc gtg agt gaa cag gtg ttt ggc gaa ttg cct gaa gaa ttg gcg aaa 480
Ser Val Ser Glu Gln Val Phe Gly Glu Leu Pro Glu Glu Leu Ala Lys
145 150 155 160
aaa cct aac ccg ttc gct gta tta gct aat tta aag aaa aac tag 525
Lys Pro Asn Pro Phe Ala Val Leu Ala Asn Leu Lys Lys Asn
165 170

<210> 159

<211> 174

<212> PRT

<213> Actinobacillus pleuropneumoniae

<400> 159

Met Gln Lys Val Lys Leu Pro Leu Thr Ile Asp Pro Tyr Lys Asp Ala
1 5 10 15
Gln Arg Arg Met Asp Tyr Glu Gly Tyr Ile Ser Arg Ser Leu Leu Asn
20 25 30
Arg Leu Gly Glu Ser Val Ser Asn Val Leu Ser Asp Ala Gln Val Thr
35 40 45
Leu Ser Leu Tyr Ile Asp Pro Gln Arg Leu Thr Val Ile Lys Gly Thr
50 55 60
Ala Thr Val Glu Val Glu Phe Asp Cys Gln Arg Cys Gly Asn Pro Phe
65 70 75 80
Thr Gln Thr Leu Asp Cys Ser Phe Cys Phe Ser Pro Val Ser Asn Met
85 90 95
Asp Gln Ala Asp Asn Leu Pro Glu Ile Tyr Glu Pro Ile Glu Val Asn
100 105 110
Glu Phe Gly Glu Val Asn Leu Leu Asp Met Ile Glu Asp Gly Phe Ile
115 120 125
Ile Glu Leu Pro Leu Val Pro Met His Ser Glu Glu His Cys Glu Val
130 135 140
Ser Val Ser Glu Gln Val Phe Gly Glu Leu Pro Glu Glu Leu Ala Lys
145 150 155 160

WO 02/075507

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Lys Pro Asn Pro Phe Ala Val Leu Ala Asn Leu Lys Lys Asn
 165 170

<210> 160

<211> 1302

<212> DNA

<213> Actinobacillus pleuropneumoniae

<220>

<223> tig

<220>

<221> CDS

<222> (1)..(1299)

<400> 160

atg tca att tct att gaa act tta gaa ggc tta caa cgc cgc gta act 48
 Met Ser Ile Ser Ile Glu Thr Leu Glu Gly Leu Gln Arg Arg Val Thr
 1 5 10 15

att acc gta gct gct gat aaa atc gaa gcg gct tac aaa gag caa tta 96
 Ile Thr Val Ala Ala Asp Lys Ile Glu Ala Ala Tyr Lys Glu Gln Leu
 20 25 30

aaa ggc tat gcg aaa aac gct cgt gta gac ggt ttc cgt aaa ggt aaa 144
 Lys Gly Tyr Ala Lys Asn Ala Arg Val Asp Gly Phe Arg Lys Gly Lys
 35 40 45

gta ccg cac gca att atc gaa caa cgt ttc ggt tta gcg gct cgc caa 192
 Val Pro His Ala Ile Ile Glu Gln Arg Phe Gly Leu Ala Ala Arg Gln
 50 55 60

gac gta tta tcc gat gaa atg caa cgt gcg ttc ttt gat gcg gta atc 240
 Asp Val Leu Ser Asp Glu Met Gln Arg Ala Phe Phe Asp Ala Val Ile
 65 70 75 80

gct gag aaa att aac ctt gcc ggt cgt cct acc ttc aca cgc aac aac 288
 Ala Glu Lys Ile Asn Leu Ala Gly Arg Pro Thr Phe Thr Pro Asn Asn
 85 90 95

tac caa ccg agt caa gaa ttc agc ttc act gca act ttt gaa gta ttc 336
 Tyr Gln Pro Ser Gln Glu Phe Ser Phe Thr Ala Thr Phe Glu Val Phe
 100 105 110

ccg gaa gtt gaa tta aaa ggc tta gaa aat atc gaa gtt gaa aaa ccg 384
 Pro Glu Val Glu Leu Lys Gly Leu Glu Asn Ile Glu Val Glu Lys Pro
 115 120 125

gtt gta gaa atc aca gaa gct gat tta gac aaa atg atc gat gtg tta 432
 Val Val Glu Ile Thr Glu Ala Asp Leu Asp Lys Met Ile Asp Val Leu
 130 135 140

cgt aaa caa caa gcg act tgg gct gaa tct caa gca gcg gca caa gcg 480
 Arg Lys Gln Gln Ala Thr Trp Ala Glu Ser Gln Ala Ala Ala Gln Ala
 145 150 155 160

gaa gac cgt gtt gta atc gac ttc gta ggt tct gta gac ggt gaa gag 528
 Glu Asp Arg Val Val Ile Asp Phe Val Gly Ser Val Asp Gly Glu Glu
 165 170 175

ttt gaa ggc ggt aaa gcg aca gac ttc act tta gca atg ggt caa agt 576
 Phe Glu Gly Gly Lys Ala Thr Asp Phe Thr Leu Ala Met Gly Gln Ser

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180      185      190
cgt atg atc cct ggt ttt gaa gaa ggt atc gtt ggt cac aaa gcc ggc 624
Arg Met Ile Pro Gly Phe Glu Glu Gly Ile Val Gly His Lys Ala Gly
195      200      205

gaa caa ttc gat atc gat gtt act ttc cct gaa gaa tac cac gct gaa 672
Glu Gln Phe Asp Ile Asp Val Thr Phe Pro Glu Glu Tyr His Ala Glu
210      215      220

aac tta aaa ggt aaa gcg gcg aaa ttc gca att aca ctt aag aaa gta 720
Asn Leu Lys Gly Lys Ala Ala Lys Phe Ala Ile Thr Leu Lys Lys Val
225      230      235      240

gaa aat atc gta tta cct gaa tta acc gaa gaa ttc gtg aaa aaa ttc 768
Glu Asn Ile Val Leu Pro Glu Leu Thr Glu Glu Phe Val Lys Lys Phe
245      250      255

ggt tca gca aaa act gta gaa gat tta cgt gcg gaa att aag aaa aat 816
Gly Ser Ala Lys Thr Val Glu Asp Leu Arg Ala Glu Ile Lys Lys Asn
260      265      270

atg caa cgt gaa ctt aaa aac gca gta acc gca cgc gtt aaa aac caa 864
Met Gln Arg Glu Leu Lys Asn Ala Val Thr Ala Arg Val Lys Asn Gln
275      280      285

gta atc aac ggt tta atc gca caa aat gaa att gaa gtg ccg gct gca 912
Val Ile Asn Gly Leu Ile Ala Gln Asn Glu Ile Glu Val Pro Ala Ala
290      295      300

gcg gta gcg gaa gaa gtg sac gta tta cgt cgt caa gcg gtt caa cgt 960
Ala Val Ala Glu Glu Val Asp Val Leu Arg Arg Gln Ala Val Gln Arg
305      310      315      320

ttc ggt ggt aaa ccg gaa atg gct gca caa tta ccg gcg gaa tta ttc 1008
Phe Gly Gly Lys Pro Glu Met Ala Ala Gln Leu Pro Ala Glu Leu Phe
325      330      335

gaa gcg gat gca aaa cgt cgt gtt caa gta ggt tta tta ctt tca acc 1056
Glu Ala Asp Ala Lys Arg Arg Val Gln Val Gly Leu Leu Ser Thr
340      345      350

gta atc ggt act aac gaa tta aaa gtt gat gaa aaa cgt gtt gaa gaa 1104
Val Ile Gly Thr Asn Glu Leu Lys Val Asp Glu Lys Arg Val Glu Glu
355      360      365

acg att gca gaa atc gct tca gct tac gaa caa ccg gcg gaa gtt gtt 1152
Thr Ile Ala Glu Ile Ala Ser Ala Tyr Glu Gln Pro Ala Glu Val Val
370      375      380

gct cat tat gcg aaa aac cgt caa tta acc gaa aat atc cgt aac gta 1200
Ala His Tyr Ala Lys Asn Arg Gln Leu Thr Glu Asn Ile Arg Asn Val
385      390      395      400

gtg tta gaa gag caa gcg gtt gaa gtt gta ctt gcg aaa gca aaa gta 1248
Val Leu Glu Glu Gln Ala Val Glu Val Val Leu Ala Lys Ala Lys Val
405      410      415

act gaa aaa gcg act tct ttt gat gaa gta atg gct caa caa gct caa 1296
Thr Glu Lys Ala Thr Ser Phe Asp Glu Val Met Ala Gln Gln Ala Gln
420      425      430

ggc taa 1302

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Gly

<210> 161
<211> 433
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 161
Met Ser Ile Ser Ile Glu Thr Leu Glu Gly Leu Gln Arg Arg Val Thr
1 5 10 15
Ile Thr Val Ala Ala Asp Lys Ile Glu Ala Ala Tyr Lys Glu Gln Leu
20 25 30
Lys Gly Tyr Ala Lys Asn Ala Arg Val Asp Gly Phe Arg Lys Gly Lys
35 40 45
Val Pro His Ala Ile Ile Glu Gln Arg Phe Gly Leu Ala Ala Arg Gln
50 55 60
Asp Val Leu Ser Asp Glu Met Gln Arg Ala Phe Phe Asp Ala Val Ile
65 70 75 80
Ala Glu Lys Ile Asn Leu Ala Gly Arg Pro Thr Phe Thr Pro Asn Asn
85 90 95
Tyr Gln Pro Ser Gln Glu Phe Ser Phe Thr Ala Thr Phe Glu Val Phe
100 105 110
Pro Glu Val Glu Leu Lys Gly Leu Glu Asn Ile Glu Val Glu Lys Pro
115 120 125
Val Val Glu Ile Thr Glu Ala Asp Leu Asp Lys Met Ile Asp Val Leu
130 135 140
Arg Lys Gln Gln Ala Thr Trp Ala Glu Ser Gln Ala Ala Ala Gln Ala
145 150 155 160
Glu Asp Arg Val Val Ile Asp Phe Val Gly Ser Val Asp Gly Glu Glu
165 170 175
Phe Glu Gly Gly Lys Ala Thr Asp Phe Thr Leu Ala Met Gly Gln Ser
180 185 190
Arg Met Ile Pro Gly Phe Glu Glu Gly Ile Val Gly His Lys Ala Gly
195 200 205
Glu Gln Phe Asp Ile Asp Val Thr Phe Pro Glu Glu Tyr His Ala Glu
210 215 220
Asn Leu Lys Gly Lys Ala Ala Lys Phe Ala Ile Thr Leu Lys Lys Val
225 230 235 240
Glu Asn Ile Val Leu Pro Glu Leu Thr Glu Glu Phe Val Lys Lys Phe
245 250 255
Gly Ser Ala Lys Thr Val Glu Asp Leu Arg Ala Glu Ile Lys Lys Asn
260 265 270
Met Gln Arg Glu Leu Lys Asn Ala Val Thr Ala Arg Val Lys Asn Gln
275 280 285

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Val Ile Asn Gly Leu Ile Ala Gln Asn Glu Ile Glu Val Pro Ala Ala
 290 295 300
 Ala Val Ala Glu Glu Val Asp Val Leu Arg Arg Gln Ala Val Gln Arg
 305 310 315 320
 Phe Gly Gly Lys Pro Glu Met Ala Ala Gln Leu Pro Ala Glu Leu Phe
 325 330 335
 Glu Ala Asp Ala Lys Arg Arg Val Gln Val Gly Leu Leu Leu Ser Thr
 340 345 350
 Val Ile Gly Thr Asn Glu Leu Lys Val Asp Glu Lys Arg Val Glu Glu
 355 360 365
 Thr Ile Ala Glu Ile Ala Ser Ala Tyr Glu Gln Pro Ala Glu Val Val
 370 375 380
 Ala His Tyr Ala Lys Asn Arg Gln Leu Thr Glu Asn Ile Arg Asn Val
 385 390 395 400
 Val Leu Glu Glu Gln Ala Val Glu Val Val Leu Ala Lys Ala Lys Val
 405 410 415
 Thr Glu Lys Ala Thr Ser Phe Asp Glu Val Met Ala Gln Gln Ala Gln
 420 425 430

Gly

<210> 162
 <211> 316
 <212> DNA
 <213> Actinobacillus pleuropneumoniae

<220>
 <223> tRNA-glu

<400> 162
 aatattgagc tcaaatggca aagcggagag catctttaa tgtgtcccc atcgtctaga 60
 ggcctaggac atcgcccttt caccggcgta accgggggtc gaatccccgt ggggacgcca 120
 tttaaagatg acttttgtg tctgaattgt tctttaaaaa attggaaca agctgaaaac 180
 tgagagattt tcgaaagaaa gtctgagtag taaaagataa gtaattatct tgaatatctt 240
 agctgaacaa aagcagctaa gtgttagtt gaataaagta tcgcgttgaa tgcgttcaaa 300
 taaaattga aaatat 316

<210> 163
 <211> 85
 <212> DNA
 <213> Actinobacillus pleuropneumoniae

<220>
 <223> tRNA-leu

<400> 163
 gctctggtgg tgggaattggt agacacgcta tcttgagggg gtagtgcca taggatgtgc 60

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gagttcgagt ctgcccaga gcacc

85

<210> 164

<211> 623

<212> DNA

<213> Actinobacillus pleuropneumoniae

<220>

<223> yaeE

<220>

<221> CDS

<222> (1) .. (621)

<400> 164

atg caa gaa ctc aca cct caa atg tgg ggc tta gtc ggc act tca acg 48
 Met Gln Glu Leu Thr Pro Gln Met Trp Gly Leu Val Gly Thr Ser Thr
 1 5 10 15

ctt gaa acg ctc tat atg ggc ttt gcg ggc act tta ctt gct gtg gta 96
 Leu Glu Thr Leu Tyr Met Gly Phe Ala Ala Thr Leu Leu Ala Val Val
 20 25 30

gtc ggt ttg ccg atc ggt ttt ctg gca ttt tta acc ggt aaa gga gag 144
 Val Gly Leu Pro Ile Gly Phe Leu Ala Phe Leu Thr Gly Lys Gly Glu
 35 40 45

att tta gag aat ccg cgt tta cat caa gta tta gat gtg att att aat 192
 Ile Leu Glu Asn Pro Arg Leu His Gln Val Leu Asp Val Ile Ile Asn
 50 55 60

atc ggt cgt tcc gta ccg ttt att att ttg tta gtc gtg ttg tta cct 240
 Ile Gly Arg Ser Val Pro Phe Ile Ile Leu Leu Val Val Leu Leu Pro
 65 70 75 80

ttt acg cgt tta ttg gtc ggg aca acg ctc ggt act acg gcg gcg att 288
 Phe Thr Arg Leu Leu Val Gly Thr Thr Leu Gly Thr Thr Ala Ala Ile
 85 90 95

gtg ccg tta agc gtt tgc gca att ccg ttt ttt gcg cgt tta act tca 336
 Val Pro Leu Ser Val Ser Ala Ile Pro Phe Phe Ala Arg Leu Thr Ser
 100 105 110

aat gcg tta tta gaa atc cca gca ggt tta acc gaa gcg gcg aaa tcg 384
 Asn Ala Leu Leu Glu Ile Pro Ala Gly Leu Thr Glu Ala Ala Lys Ser
 115 120 125

atg ggc gca acg aat tgg caa gtg gtc agt aaa ttt tat tta ccg gaa 432
 Met Gly Ala Thr Asn Trp Gln Val Val Ser Lys Phe Tyr Leu Pro Glu
 130 135 140

tca ctg ccg att tta atc aat ggt atc aca tta act tta gtc gct tta 480
 Ser Leu Pro Ile Leu Ile Asn Gly Ile Thr Leu Thr Leu Val Ala Leu
 145 150 155 160

atc ggt tat tgc gca atg gcg ggt gcg gtc ggc ggc ggc ggt ttg ggt 528
 Ile Gly Tyr Ser Ala Met Ala Gly Ala Val Gly Gly Gly Gly Leu Gly
 165 170 175

aac ctt gcc atc agt tac ggt gaa cac cga aat atg gtc tat gta aaa 576
 Asn Leu Ala Ile Ser Tyr Gly Glu His Arg Asn Met Val Tyr Val Lys
 180 185 190

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tgg atc tca aca att att atc gta gcg att gtg atg atc agt caa aa 623
Trp Ile Ser Thr Ile Ile Ile Val Ala Ile Val Met Ile Ser Gln
195 200 205

<210> 165
<211> 207
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 165
Met Gln Glu Leu Thr Pro Gln Met Trp Gly Leu Val Gly Thr Ser Thr
1 5 10 15
Leu Glu Thr Leu Tyr Met Gly Phe Ala Ala Thr Leu Leu Ala Val Val
20 25 30
Val Gly Leu Pro Ile Gly Phe Leu Ala Phe Leu Thr Gly Lys Gly Glu
35 40 45
Ile Leu Glu Asn Pro Arg Leu His Gln Val Leu Asp Val Ile Ile Asn
50 55 60
Ile Gly Arg Ser Val Pro Phe Ile Ile Leu Leu Val Val Leu Leu Pro
65 70 75 80
Phe Thr Arg Leu Leu Val Gly Thr Thr Leu Gly Thr Thr Ala Ala Ile
85 90 95
Val Pro Leu Ser Val Ser Ala Ile Pro Phe Phe Ala Arg Leu Thr Ser
100 105 110
Asn Ala Leu Leu Glu Ile Pro Ala Gly Leu Thr Glu Ala Ala Lys Ser
115 120 125
Met Gly Ala Thr Asn Trp Gln Val Val Ser Lys Phe Tyr Leu Pro Glu
130 135 140
Ser Leu Pro Ile Leu Ile Asn Gly Ile Thr Leu Thr Leu Val Ala Leu
145 150 155 160
Ile Gly Tyr Ser Ala Met Ala Gly Ala Val Gly Gly Gly Gly Leu Gly
165 170 175
Asn Leu Ala Ile Ser Tyr Gly Glu His Arg Asn Met Val Tyr Val Lys
180 185 190
Trp Ile Ser Thr Ile Ile Ile Val Ala Ile Val Met Ile Ser Gln
195 200 205

<210> 166
<211> 866
<212> DNA
<213> Pasteurella (Mannheimia) haemolytica

<220>
<221> CDS
<222> (1)..(864)
<220>
<223> atpG

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<400> 166
atg gca ggt gct aaa gag ata aga acc aaa att gca agt gtt cgt aat 48
Met Ala Gly Ala Lys Glu Ile Arg Thr Lys Ile Ala Ser Val Arg Asn
1 5 10 15

aca caa aaa att acc aaa gcg atg gaa atg gtt gcc gca tca aaa atg 96
Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Ala Ser Lys Met
20 25 30

cgt aaa acc caa gag cgt atg gcg gct tct cgc cct tat gct gaa agt 144
Arg Lys Thr Gln Glu Arg Met Ala Ala Ser Arg Pro Tyr Ala Glu Ser
35 40 45

att cgc aag gca att agc cat att gcc aaa ggt aac att gag tat aaa 192
Ile Arg Lys Ala Ile Ser His Ile Ala Lys Gly Asn Ile Glu Tyr Lys
50 55 60

cac cca ttt ttg acc cca cgt ccg gta aaa aaa gtt gcc tat tta gta 240
His Pro Phe Leu Thr Pro Arg Pro Val Lys Lys Val Gly Tyr Leu Val
65 70 75 80

gtt tca acc gat cgc ggt tta tgt ggt gcc tta aat atc aat tta ttt 288
Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Ile Asn Leu Phe
85 90 95

aaa acc gtt tta cat gaa ttg aaa gaa aaa gat gac caa ggt gtt aag 336
Lys Thr Val Leu His Glu Leu Lys Glu Lys Asp Asp Gln Gly Val Lys
100 105 110

tct cga ctt gct gtg gtg gga aat aaa ggg atc tcc ttt ttt aac cca 384
Ser Arg Leu Ala Val Val Gly Asn Lys Gly Ile Ser Phe Phe Asn Pro
115 120 125

atg ggg cta gag att aaa ggt cat atc aat gga ttg ggt gat aca ccg 432
Met Gly Leu Glu Ile Lys Gly His Ile Asn Gly Leu Gly Asp Thr Pro
130 135 140

gca atg gaa gat tta gtc ggt att gtt aat ggt atg gta aat gcc tac 480
Ala Met Glu Asp Leu Val Gly Ile Val Asn Gly Met Val Asn Ala Tyr
145 150 155 160

cgt gaa ggc gaa att gat gaa gtg tat gtg gta tat aac cgt ttt ata 528
Arg Glu Gly Glu Ile Asp Glu Val Tyr Val Val Tyr Asn Arg Phe Ile
165 170 175

aac acg atg tca caa aaa ccg aca gta caa cag ttg ctt cct ttg cct 576
Asn Thr Met Ser Gln Lys Pro Thr Val Gln Gln Leu Leu Pro Leu Pro
180 185 190

gca ctg gaa aat gac tca tta gag caa act ggt tct tgg gat tat ctc 624
Ala Leu Glu Asn Asp Ser Leu Glu Gln Thr Gly Ser Trp Asp Tyr Leu
195 200 205

tat gaa cca aat cca caa gcg tta tta gac agc tta ctg gtt cgt tat 672
Tyr Glu Pro Asn Pro Gln Ala Leu Leu Asp Ser Leu Leu Val Arg Tyr
210 215 220

tta gaa tct caa gtt tat cag gca gtg gta gat aat ctt gcg tct gaa 720
Leu Glu Ser Gln Val Tyr Gln Ala Val Val Asp Asn Leu Ala Ser Glu
225 230 235 240

cag gct gct cga atg gtg gca atg aaa gca gca acc gat aac gca ggt 768
Gln Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Ala Gly

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      245      250      255
aat ctg att aat gag tta cag tta gtg tat aac aaa gct cgt caa gca 816
Asn Leu Ile Asn Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln Ala
      260      265      270
agt att acg aat gaa tta aat gaa att gtc gcg ggt gcc gca gca att 864
Ser Ile Thr Asn Glu Leu Asn Glu Ile Val Ala Gly Ala Ala Ala Ile
      275      280      285

ta 866

<210> 167
<211> 288
<212> PRT
<213> Pasteurella (Mannheimia) haemolytica

<400> 167
Met Ala Gly Ala Lys Glu Ile Arg Thr Lys Ile Ala Ser Val Arg Asn
  1          5          10          15
Thr Gln Lys Ile Thr Lys Ala Met Glu Met Val Ala Ala Ser Lys Met
  20          25          30
Arg Lys Thr Gln Glu Arg Met Ala Ala Ser Arg Pro Tyr Ala Glu Ser
  35          40          45
Ile Arg Lys Ala Ile Ser His Ile Ala Lys Gly Asn Ile Glu Tyr Lys
  50          55          60
His Pro Phe Leu Thr Pro Arg Pro Val Lys Lys Val Gly Tyr Leu Val
  65          70          75          80
Val Ser Thr Asp Arg Gly Leu Cys Gly Gly Leu Asn Ile Asn Leu Phe
  85          90          95
Lys Thr Val Leu His Glu Leu Lys Glu Lys Asp Asp Gln Gly Val Lys
 100          105          110
Ser Arg Leu Ala Val Val Gly Asn Lys Gly Ile Ser Phe Phe Asn Pro
 115          120          125
Met Gly Leu Glu Ile Lys Gly His Ile Asn Gly Leu Gly Asp Thr Pro
 130          135          140
Ala Met Glu Asp Leu Val Gly Ile Val Asn Gly Met Val Asn Ala Tyr
 145          150          155          160
Arg Glu Gly Glu Ile Asp Glu Val Tyr Val Val Tyr Asn Arg Phe Ile
 165          170          175
Asn Thr Met Ser Gln Lys Pro Thr Val Gln Gln Leu Leu Pro Leu Pro
 180          185          190
Ala Leu Glu Asn Asp Ser Leu Glu Gln Thr Gly Ser Trp Asp Tyr Leu
 195          200          205
Tyr Glu Pro Asn Pro Gln Ala Leu Leu Asp Ser Leu Leu Val Arg Tyr
 210          215          220
Leu Glu Ser Gln Val Tyr Gln Ala Val Val Asp Asn Leu Ala Ser Glu
 225          230          235          240

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Gln Ala Ala Arg Met Val Ala Met Lys Ala Ala Thr Asp Asn Ala Gly
245 250 255

Asn Leu Ile Asn Glu Leu Gln Leu Val Tyr Asn Lys Ala Arg Gln Ala
260 265 270

Ser Ile Thr Asn Glu Leu Asn Glu Ile Val Ala Gly Ala Ala Ala Ile
275 280 285

<210> 168
<211> 1463
<212> DNA
<213> Pasteurella (Mannheimia) haemolytica

<220>
<221> CDS
<222> (1)..(1461)

<220>
<223> guaB

<400> 168
atg cta cga att aaa caa gaa gcc ctc act ttt gat gat gtt ctt ctc 48
Met Leu Arg Ile Lys Gln Glu Ala Leu Thr Phe Asp Asp Val Leu Leu
1 5 10 15

gtc ccg gca cat tct act gtg ctt cct aat act gct gat ctt tct act 96
Val Pro Ala His Ser Thr Val Leu Pro Asn Thr Ala Asp Leu Ser Thr
20 25 30

caa tta act aaa acc att cgt tta aac att ccg atg ctt tct gct gca 144
Gln Leu Thr Lys Thr Ile Arg Leu Asn Ile Pro Met Leu Ser Ala Ala
35 40 45

atg gat acc gtt aca gaa act aag ctt gcg atc tcc ctt gct caa gaa 192
Met Asp Thr Val Thr Glu Thr Lys Leu Ala ile Ser Leu Ala Gln Glu
50 55 60

ggc ggc att ggt ttt atc cat aaa aat atg tcg att gaa cgc cag gca 240
Gly gly Ile Gly Phe Ile His Lys Asn Met Ser Ile Glu Arg Gln Ala
65 70 75 80

gac cgt gtg cgt aaa gtg aaa aaa ttt gaa agt ggt att gtt tct gag 288
Asp Arg Val Arg Lys Val Lys Lys Phe Glu Ser Gly Ile Val Ser Glu
85 90 95

cca gtg acg att tct cct gat atg aca tta gcg gaa ttg gct gaa ttg 336
Pro Val Thr Ile Ser Pro Asp Met Thr Leu Ala Glu Leu Ala Glu Leu
100 105 110

gtg aaa aag aac ggt ttt gca ggc tat ccg gtg att gat gaa aac caa 384
Val Lys Lys Asn Gly Phe Ala Gly Tyr Pro Val Ile Asp Glu Asn Gln
115 120 125

aat tta gtg gga att att acc gga cgt gat acc cga ttt gtc acg gat 432
Asn Leu Val Gly Ile Ile Thr Gly Arg Asp Thr Arg Phe Val Thr Asp
130 135 140

tta agc aaa aca gtg cgt gaa ttt atg aca cca aaa gac cgt tta gtg 480
Leu Ser Lys Thr Val Arg Glu Phe Met Thr Pro Lys Asp Arg Leu Val
145 150 155 160

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acg gta aaa gaa aac gca agc cgt gaa gaa att ttc cac tta atg cac 528
 Thr Val Lys Glu Asn Ala Ser Arg Glu Glu Ile Phe His Leu Met His
 165 170 175
 gaa cac cga gtg gag aaa gtg ctg gta gtg aat aat gaa ttt cag tta 576
 Glu His Arg Val Glu Lys Val Leu Val Val Asn Asn Glu Phe Gln Leu
 180 185 190
 aaa gga atg att acc cta aaa gac tac caa aaa gcg gaa agc aaa ccg 624
 Lys Gly Met Ile Thr Leu Lys Asp Tyr Gln Lys Ala Glu Ser Lys Pro
 195 200 205
 aat gcc tgt aaa gat gag ttt ggg cgt ttg cgt gtg ggg gcg gca gtg 672
 Asn Ala Cys Lys Asp Glu Phe Gly Arg Leu Arg Val Gly Ala Ala Val
 210 215 220
 gga gcc ggt ccg gcc aat gaa gaa cga att gat gct tta gta aaa gcg 720
 Gly Ala Gly Pro Gly Asn Glu Glu Arg Ile Asp Ala Leu Val Lys Ala
 225 230 235
 ggt gtc gat gtg cta tta atc gac tct tcg cac ggg cat tct gaa ggt 768
 Gly Val Asp Val Leu Leu Ile Asp Ser Ser His Gly His Ser Glu Gly
 245 250 255
 gta tta caa cgt gtg cgt gaa acc cgt gca aaa tac cct gat tta ccg 816
 Val Leu Gln Arg Val Arg Glu Thr Arg Ala Lys Tyr Pro Asp Leu Pro
 260 265 270
 att gtt gcc ggt aat att gcc act gca gaa gga gcg att gcg tta gct 864
 Ile Val Ala Gly Asn Ile Ala Thr Ala Glu Gly Ala Ile Ala Leu Ala
 275 280 285
 gat gca gga gcc agt gct gtg aaa gta gga atc gcc ccg ggt tca att 912
 Asp Ala Gly Ala Ser Ala Val Lys Val Gly Ile Gly Pro Gly Ser Ile
 290 295 300
 tgt acc acc aga att gta aca gcc gtt gcc gtg cca caa atc acg gca 960
 Cys Thr Thr Arg Ile Val Thr Gly Val Gly Val Pro Gln Ile Thr Ala
 305 310 315 320
 atc gca gaa gcg gca gct gcg ctt aaa gaa cga gcc att cct gtg att 1008
 Ile Ala Glu Ala Ala Ala Leu Lys Glu Arg Gly Ile Pro Val Ile
 325 330 335
 gct gat ggt gga att cgt tat tca gcc gat att tca aaa gct att gcc 1056
 Ala Asp Gly Gly Ile Arg Tyr Ser Gly Asp Ile Ser Lys Ala Ile Ala
 340 345 350
 gcc ggt gca agt tgc gta atg gtc ggt tcg atg ttt gcc gcc aca gaa 1104
 Ala Gly Ala Ser Cys Val Met Val Gly Ser Met Phe Ala Gly Thr Glu
 355 360 365
 gaa gcc ccg ggt gaa att gag ctt tat caa gcc aga gca ttc aaa tcc 1152
 Glu Ala Pro Gly Glu Ile Glu Leu Tyr Gln Gly Arg Ala Phe Lys Ser
 370 375 380
 tac cgt gga atg gga tca tta ggt gca atg agt aaa gcc tcg tca gat 1200
 Tyr Arg Gly Met Gly Ser Leu Gly Ala Met Ser Lys Gly Ser Ser Asp
 385 390 395 400
 cgc tat ttc caa tct gat aat gcc gcc gac aag ctc gta ccg gaa ggg 1248
 Arg Tyr Phe Gln Ser Asp Asn Ala Ala Asp Lys Leu Val Pro Glu Gly
 405 410 415

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att gaa ggg cgt atc gct tac aaa ggc tac ttg aaa gaa att atc cac 1296
ile glu gly arg ile ala tyr lys gly tyr leu lys glu ile ile his
      420      425      430

caa caa atg ggc ggc tta cgc tcc tgt atg gga tta acc ggc tgt gcc 1344
gln gln met gly gly leu arg ser cys met gly leu thr gly cys ala
      435      440      445

act att gaa gaa ctc cgc acc aaa gca gaa ttt gtc cgc att agt ggt 1392
thr ile glu leu leu arg thr lys ala glu phe val arg ile ser gly
      450      455      460

gct ggt att aaa gaa agc cac gtc cac gat gtg aca att acc aaa gaa 1440
ala gly ile lys glu ser his val his asp val thr ile thr lys glu
      465      470      475      480

gca ccg aac tac cga atg ggt ta 1463
ala pro asn tyr arg met gly
      485

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<210> 169

<211> 487

<212> PRT

<213> Pasteurella (Mannheimia) haemolytica

<400> 169

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Met Leu Arg ile lys gln glu ala leu thr phe asp asp val leu leu
  1           5           10           15

Val Pro Ala his ser thr val leu pro asn thr ala asp leu ser thr
      20           25           30

Gln leu thr lys thr ile arg leu asn ile pro met leu ser ala ala
      35           40           45

Met asp thr val thr glu thr lys leu ala ile ser leu ala gln glu
      50           55           60

Gly gly ile gly phe ile his lys asn met ser ile glu arg gln ala
      65           70           75           80

asp arg val arg lys val lys phe glu ser gly ile val ser glu
      85           90           95

Pro val thr ile ser pro asp met thr leu ala glu leu ala glu leu
      100          105          110

Val lys lys asn gly phe ala gly tyr pro val ile asp glu asn gln
      115          120          125

asn leu val gly ile ile thr gly arg asp thr arg phe val thr asp
      130          135          140

Leu ser lys thr val arg glu phe met thr pro lys asp arg leu val
      145          150          155          160

Thr val lys glu asn ala ser arg glu glu ile phe his leu met his
      165          170          175

glu his arg val glu lys val leu val val asn asn glu phe gln leu
      180          185          190

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Lys Gly Met Ile Thr Leu Lys Asp Tyr Gln Lys Ala Glu Ser Lys Pro
 195 200 205
 Asn Ala Cys Lys Asp Glu Phe Gly Arg Leu Arg Val Gly Ala Ala Val
 210 215 220
 Gly Ala Gly Pro Gly Asn Glu Glu Arg Ile Asp Ala Leu Val Lys Ala
 225 230 235 240
 Gly Val Asp Val Leu Leu Ile Asp Ser Ser His Gly His Ser Glu Gly
 245 250 255
 Val Leu Gln Arg Val Arg Glu Thr Arg Ala Lys Tyr Pro Asp Leu Pro
 260 265 270
 Ile Val Ala Gly Asn Ile Ala Thr Ala Glu Gly Ala Ile Ala Leu Ala
 275 280 285
 Asp Ala Gly Ala Ser Ala Val Lys Val Gly Ile Gly Pro Gly Ser Ile
 290 295 300
 Cys Thr Thr Arg Ile Val Thr Gly Val Gly Val Pro Gln Ile Thr Ala
 305 310 315 320
 Ile Ala Glu Ala Ala Ala Leu Lys Glu Arg Gly Ile Pro Val Ile
 325 330 335
 Ala Asp Gly Gly Ile Arg Tyr Ser Gly Asp Ile Ser Lys Ala Ile Ala
 340 345 350
 Ala Gly Ala Ser Cys Val Met Val Gly Ser Met Phe Ala Gly Thr Glu
 355 360 365
 Glu Ala Pro Gly Glu Ile Glu Leu Tyr Gln Gly Arg Ala Phe Lys Ser
 370 375 380
 Tyr Arg Gly Met Gly Ser Leu Gly Ala Met Ser Lys Gly Ser Ser Asp
 385 390 395 400
 Arg Tyr Phe Gln Ser Asp Asn Ala Ala Asp Lys Leu Val Pro Glu Gly
 405 410 415
 Ile Glu Gly Arg Ile Ala Tyr Lys Gly Tyr Leu Lys Glu Ile Ile His
 420 425 430
 Gln Gln Met Gly Gly Leu Arg Ser Cys Met Gly Leu Thr Gly Cys Ala
 435 440 445
 Thr Ile Glu Glu Leu Arg Thr Lys Ala Glu Phe Val Arg Ile Ser Gly
 450 455 460
 Ala Gly Ile Lys Glu Ser His Val His Asp Val Thr Ile Thr Lys Glu
 465 470 475 480
 Ala Pro Asn Tyr Arg Met Gly
 485

<210> 170

<211> 2150

<212> DNA

<213> Pasteurella (Mannheimia) haemolytica

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<220>
<221> CDS
<222> (1)..(2148)

<220>
<223> pnp

<400> 170
atg act cca att gta aaa cag ttt aaa tac ggt cag cac acc gtg acc 48
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1 5 10 15

tta gaa acc ggt gct atc gca cgc caa gca acg gca gca gta atg gca 96
Leu Glu Thr Gly Ala Ile Ala Arg Gln Ala Thr Ala Ala Val Met Ala
20 25 30

agt atg gac gac aca acc gta ttt gtt acc gta gta gcg aaa aaa gac 144
Ser Met Asp Asp Thr Thr Val Phe Val Thr Val Val Ala Lys Lys Asp
35 40 45

gta aaa gaa ggg caa gat ttc ttc cca tta acc gta gat tat caa gag 192
Val Lys Glu Gly Gln Asp Phe Phe Pro Leu Thr Val Asp Tyr Gln Glu
50 55 60

cgt act tac gca gcc ggt cgt att ccg gcc ggt ttc ttc aaa cgt gaa 240
Arg Thr Tyr Ala Ala Gly Arg Ile Pro Gly Gly Phe Phe Lys Arg Glu
65 70 75 80

gga cgt cct agc gaa ggt gaa acc tta atc gct cgc ttg atc gac cgt 288
Gly Arg Pro Ser Glu Gly Glu Thr Leu Ile Ala Arg Leu Ile Asp Arg
85 90 95

cct gtg cgt cca ctt ttc cca gaa ggt ttc ttt aac gaa att caa gtg 336
Pro Val Arg Pro Leu Phe Pro Glu Gly Phe Phe Asn Glu Ile Gln Val
100 105 110

att gcg acc gta gta tcg gta aac cca caa atc agt cct gat ctg gtt 384
Ile Ala Thr Val Val Ser Val Asn Pro Gln Ile Ser Pro Asp Leu Val
115 120 125

gcg atg atc ggt gca tcg gct gcc ctt tca tta tcc gcc gtg ccg ttt 432
Ala Met Ile Gly Ala Ser Ala Ala Leu Ser Leu Ser Gly Val Pro Phe
130 135 140

aac ggt cca atc ggt gcg gct cgt gtc ggt ttt atc aac gat caa ttc 480
Asn Gly Pro Ile Gly Ala Ala Arg Val Gly Phe Ile Asn Asp Gln Phe
145 150 155 160

gta tta aac cca acc acc agc gag caa aaa atc agc cgc tta gat tta 528
Val Leu Asn Pro Thr Thr Ser Glu Gln Lys Ile Ser Arg Leu Asp Leu
165 170 175

gtg gtt tca ggt aca gac aaa gcc gtg ttg atg gtg gaa tct gaa gcg 576
Val Val Ser Gly Thr Asp Lys Ala Val Leu Met Val Glu Ser Glu Ala
180 185 190

gat atc tta acc gaa gag caa atg tta gcg gcg gtg gtg ttc gcc cac 624
Asp Ile Leu Thr Glu Glu Gln Met Leu Ala Ala Val Val Phe Gly His
195 200 205

gag caa caa cag gtt gta atc gaa aac atc aaa gaa ttt gtt aaa gaa 672
Glu Gln Gln Gln Val Val Ile Glu Asn Ile Lys Glu Phe Val Lys Glu
210 215 220

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gcg ggc aaa cca cgt tgg gat tgg gtt gca cca gag cca aat aca gat 720
Ala Gly Lys Pro Arg Trp Asp Trp Val Ala Pro Glu Pro Asn Thr Asp
225 230 235 240

tta atc aac aaa gta aaa gca tta gca gaa aca cgc ctt ggc gat gct 768
Leu Ile Asn Lys Val Lys Ala Leu Ala Glu Thr Arg Leu Gly Asp Ala
245 250 255

tat cgt atc gta gaa aaa caa gtt cgt tac gag caa atc gat gcg att 816
Tyr Arg Ile Val Glu Lys Gln Val Arg Tyr Glu Gln Ile Asp Ala Ile
260 265 270

aaa gca gag gtg att gca caa ctt acc gca gaa gat gaa act gtt tct 864
Lys Ala Glu Val Ile Ala Gln Leu Thr Ala Glu Asp Glu Thr Val Ser
275 280 285

gaa ggg act atc atc gac atc atc acc gca tta gag agc caa atc gtg 912
Glu Gly Thr Ile Ile Asp Ile Ile Thr Ala Leu Glu Ser Gln Ile Val
290 295 300

cgt agc cgt att att gca ggc gaa cca cgc att gac ggc cgt acg gtg 960
Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile Asp Gly Arg Thr Val
305 310 315 320

gat acc gtg cgt gca ttg gat att tgc acc agt gtg tta cca cgc acc 1008
Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Ser Val Leu Pro Arg Thr
325 330 335

cac ggt tct gct ctt ttc acc cgt ggc gaa acc caa gca tta gca gta 1056
His Gly Ser Ala Leu Phe Thr Arg Gly Glu Thr Gln Ala Leu Ala Val
340 345 350

gca aca ttg ggc aca gag cgt gat gcc caa atc att gac gaa ttg acc 1104
Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile Ile Asp Glu Leu Thr
355 360 365

ggc gaa aaa tct gac cgt ttc tta ttc cac tac aat ttc cct cca tac 1152
Gly Glu Lys Ser Asp Arg Phe Leu Phe His Tyr Asn Phe Pro Pro Tyr
370 375 380

tct gtg ggc gaa acc ggt cgt atc ggc tgc cca aaa cgc cgt gaa atc 1200
Ser Val Gly Glu Thr Gly Arg Ile Gly Ser Pro Lys Arg Arg Glu Ile
385 390 395 400

ggt cac ggt cgt tta gca aaa cgt ggc gta tta gcc gtg atg cca acc 1248
Gly His Gly Arg Leu Ala Lys Arg Gly Val Leu Ala Val Met Pro Thr
405 410 415

gct gaa gag ttc ccg tat gta gtg cgt gtg gtg tct gaa atc act gaa 1296
Ala Glu Glu Phe Pro Tyr Val Val Arg Val Val Ser Glu Ile Thr Glu
420 425 430

tct aac ggt tct tct tca atg gca tct gtg tgt ggt gcg tct ctt gcg 1344
Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys Gly Ala Ser Leu Ala
435 440 445

ttg atg gac gca ggt gtg cca atc aaa gca gcg gtt gcc ggt atc gca 1392
Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala Val Ala Gly Ile Ala
450 455 460

atg ggg ctc gtg aaa gaa gac gag aaa ttc gtg gta ctt tct gac atc 1440
Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val Val Leu Ser Asp Ile
465 470 475 480

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tta ggt gat gaa gac cac tta ggc gat atg gac ttt aaa gta gcg gga 1488
Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp Phe Lys Val Ala Gly
485 490 495

acc cgt acc ggt gtg act gcg ctg caa atg gac atc aaa atc gaa ggg 1536
Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp Ile Lys Ile Glu Gly
500 505 510

atc acc cct gaa att atg cgt att gcc tta aac caa gct aaa ggt gca 1584
Ile Thr Pro Glu Ile Met Arg Ile Ala Leu Asn Gln Ala Lys Gly Ala
515 520 525

aga atg cac att tta ggt gta atg gaa caa gcc att ccg gca cct cgt 1632
Arg Met His Ile Leu Gly Val Met Glu Gln Ala Ile Pro Ala Pro Arg
530 535 540

gca gat att tct gac tat gcc cca cgc att cac aca atg aag atc gat 1680
Ala Asp Ile Ser Asp Tyr Ala Pro Arg Ile His Thr Met Lys Ile Asp
545 550 555

ccg aag aaa atc aaa gat gtg att ggt aaa ggc ggt gca aca att cgt 1728
Pro Lys Lys Ile Lys Asp Val Ile Gly Lys Gly Gly Ala Thr Ile Arg
565 570 575

gct tta acc gaa gag acc aat act tct atc gac att gat gat gac ggt 1776
Ala Leu Thr Glu Glu Thr Asn Thr Ser Ile Asp Ile Asp Asp Asp Gly
580 585 590

acg gtg aaa att gcg gca act gac gcc aat gca gcg aaa gca gta atg 1824
Thr Val Lys Ile Ala Ala Thr Asp Gly Asn Ala Ala Lys Ala Val Met
595 600 605

gct cgt att gaa gag atc gtt gcc gaa gtg gaa gta aac caa atc tac 1872
Ala Arg Ile Glu Glu Ile Val Ala Glu Val Glu Val Asn Gln Ile Tyr
610 615 620

aac ggt aaa gta acc cgt gtg gtg gac ttc ggt gca ttc gtt tcc atc 1920
Asn Gly Lys Val Thr Arg Val Val Asp Phe Gly Ala Phe Val Ser Ile
625 630 635 640

tta ggt ggc aaa gaa ggt tta gtc cac att tca caa atc acc aac gaa 1968
Leu Gly Gly Lys Glu Gly Leu Val His Ile Ser Gln Ile Thr Asn Glu
645 650 655

cgt gtt gag cgt gta gcg gac tac tta acc gtt ggt caa gaa gta caa 2016
Arg Val Glu Arg Val Ala Asp Tyr Leu Thr Val Gly Gln Glu Val Gln
660 665 670

gtg aaa gtg gta gaa att gac cgt caa gga cgc att cgt ctg acg atg 2064
Val Lys Val Val Glu Ile Asp Arg Gln Gly Arg Ile Arg Leu Thr Met
675 680 685

aaa gac atc aat aat acc aac gag gca aat gca gaa gaa act gta gct 2112
Lys Asp Ile Asn Asn Thr Asn Glu Ala Asn Ala Glu Glu Thr Val Ala
690 695 700

gaa aat gtg gta gaa aca gaa caa gaa aat aat ttc ta 2150
Glu Asn Val Val Glu Thr Glu Gln Glu Asn Asn Phe
705 710 715

<210> 171
<211> 716

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<212> PRT

<213> Pasteurella (Mannheimia) haemolytica

<400> 171

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Leu Glu Thr Gly Ala Ile Ala Arg Gln Ala Thr Ala Val Met Ala
      20           25           30

Ser Met Asp Asp Thr Thr Val Phe Val Thr Val Val Ala Lys Lys Asp
      35           40           45

Val Lys Glu Gly Gln Asp Phe Phe Pro Leu Thr Val Asp Tyr Gln Glu
      50           55           60

Arg Thr Tyr Ala Ala Gly Arg Ile Pro Gly Gly Phe Phe Lys Arg Glu
      65           70           75           80

Gly Arg Pro Ser Glu Gly Glu Thr Leu Ile Ala Arg Leu Ile Asp Arg
      85           90           95

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

Ile Ala Thr Val Val Ser Val Asn Pro Gln Ile Ser Pro Asp Leu Val
      115          120          125

Ala Met Ile Gly Ala Ser Ala Ala Leu Ser Leu Ser Gly Val Pro Phe
      130          135          140

Asn Gly Pro Ile Gly Ala Ala Arg Val Gly Phe Ile Asn Asp Gln Phe
      145          150          155          160

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

Val Val Ser Gly Thr Asp Lys Ala Val Leu Met Val Glu Ser Glu Ala
      180          185          190

Asp Ile Leu Thr Glu Glu Gln Met Leu Ala Ala Val Val Phe Gly His
      195          200          205

Glu Gln Gln Gln Val Val Ile Glu Asn Ile Lys Glu Phe Val Lys Glu
      210          215          220

Ala Gly Lys Pro Arg Trp Asp Trp Val Ala Pro Glu Pro Asn Thr Asp
      225          230          235          240

Leu Ile Asn Lys Val Lys Ala Leu Ala Glu Thr Arg Leu Gly Asp Ala
      245          250          255

Tyr Arg Ile Val Glu Lys Gln Val Arg Tyr Glu Gln Ile Asp Ala Ile
      260          265          270

Lys Ala Glu Val Ile Ala Gln Leu Thr Ala Glu Asp Glu Thr Val Ser
      275          280          285

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

Arg Ser Arg Ile Ile Ala Gly Glu Pro Arg Ile Asp Gly Arg Thr Val
      305          310          315          320

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270

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Asp Thr Val Arg Ala Leu Asp Ile Cys Thr Ser Val Leu Pro Arg Thr
 325 330 335
 His Gly Ser Ala Leu Phe Thr Arg Gly Glu Thr Gln Ala Leu Ala Val
 340 345 350
 Ala Thr Leu Gly Thr Glu Arg Asp Ala Gln Ile Ile Asp Glu Leu Thr
 355 360 365
 Gly Glu Lys Ser Asp Arg Phe Leu Phe His Tyr Asn Phe Pro Pro Tyr
 370 375 380
 Ser Val Gly Glu Thr Gly Arg Ile Gly Ser Pro Lys Arg Arg Glu Ile
 385 390 395 400
 Gly His Gly Arg Leu Ala Lys Arg Gly Val Leu Ala Val Met Pro Thr
 405 410 415
 Ala Glu Glu Phe Pro Tyr Val Val Arg Val Val Ser Glu Ile Thr Glu
 420 425 430
 Ser Asn Gly Ser Ser Ser Met Ala Ser Val Cys Gly Ala Ser Leu Ala
 435 440 445
 Leu Met Asp Ala Gly Val Pro Ile Lys Ala Ala Val Ala Gly Ile Ala
 450 455 460
 Met Gly Leu Val Lys Glu Asp Glu Lys Phe Val Val Leu Ser Asp Ile
 465 470 475 480
 Leu Gly Asp Glu Asp His Leu Gly Asp Met Asp Phe Lys Val Ala Gly
 485 490 495
 Thr Arg Thr Gly Val Thr Ala Leu Gln Met Asp Ile Lys Ile Glu Gly
 500 505 510
 Ile Thr Pro Glu Ile Met Arg Ile Ala Leu Asn Gln Ala Lys Gly Ala
 515 520 525
 Arg Met His Ile Leu Gly Val Met Glu Gln Ala Ile Pro Ala Pro Arg
 530 535 540
 Ala Asp Ile Ser Asp Tyr Ala Pro Arg Ile His Thr Met Lys Ile Asp
 545 550 555 560
 Pro Lys Lys Ile Lys Asp Val Ile Gly Lys Gly Gly Ala Thr Ile Arg
 565 570 575
 Ala Leu Thr Glu Glu Thr Asn Thr Ser Ile Asp Ile Asp Asp Asp Gly
 580 585 590
 Thr Val Lys Ile Ala Ala Thr Asp Gly Asn Ala Ala Lys Ala Val Met
 595 600 605
 Ala Arg Ile Glu Glu Ile Val Ala Glu Val Glu Val Asn Gln Ile Tyr
 610 615 620
 Asn Gly Lys Val Thr Arg Val Val Asp Phe Gly Ala Phe Val Ser Ile
 625 630 635 640
 Leu Gly Gly Lys Glu Gly Leu Val His Ile Ser Gln Ile Thr Asn Glu
 645 650 655

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Arg Val Glu Arg Val Ala Asp Tyr Leu Thr Val Gly Gln Glu Val Gln
 660 665 670
 Val Lys Val Val Glu Ile Asp Arg Gln Gly Arg Ile Arg Leu Thr Met
 675 680 685
 Lys Asp Ile Asn Asn Thr Asn Glu Ala Asn Ala Glu Glu Thr Val Ala
 690 695 700
 Glu Asn Val Val Glu Thr Glu Gln Glu Asn Asn Phe
 705 710 715

 <210> 172
 <211> 1517
 <212> DNA
 <213> *Pasteurella (Mannheimia) haemolytica*

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 <222> (1)..(1515)

 <220>
 <223> purF

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 1 5 10 15
 att tat gat ggt tta aca tta ctt caa cac cga gga caa gat gcc gca 96
 Ile Tyr Asp Gly Leu Thr Leu Leu Gln His Arg Gly Gln Asp Ala Ala
 20 25 30
 ggt atc gtc acc ata gac gat gaa aat cgt ttc cgc tta cgc aaa gct 144
 Gly Ile Val Thr Ile Asp Asp Glu Asn Arg Phe Arg Leu Arg Lys Ala
 35 40 45
 aac ggc tta gtc agc gat gtt ttc cag caa gag cat atg gtg aga tta 192
 Asn Gly Leu Val Ser Asp Val Phe Gln Gln Glu His Met Val Arg Leu
 50 55 60
 caa ggc aat gtt gga att ggt cac gtt cgc tac cca aca gca ggt agc 240
 Gln Gly Asn Val Gly Ile Gly His Val Arg Tyr Pro Thr Ala Gly Ser
 65 70 75 80
 tca agt gtg tct gaa gcc cag cca ttt tat gtc aat tca cct ttc ggt 288
 Ser Ser Val Ser Glu Ala Gln Pro Phe Tyr Val Asn Ser Pro Phe Gly
 85 90 95
 att acc tta gtt cac aac ggt aat tta act aat aat gcg gaa ctt aaa 336
 Ile Thr Leu Val His Asn Gly Asn Leu Thr Asn Asn Ala Glu Leu Lys
 100 105 110
 gct cgc tta tac aac gaa gcc cgc cgc cat gtg aac act aat tct gat 384
 Ala Arg Leu Tyr Asn Glu Ala Arg Arg His Val Asn Thr Asn Ser Asp
 115 120 125
 tct gaa tcc ctt ctt aat att ttt gct tac ttt tta gat ctc tat tcc 432
 Ser Glu Ser Leu Leu Asn Ile Phe Ala Tyr Phe Leu Asp Leu Tyr Ser
 130 135 140
 act cag cat tta agc cca gac aat atc ttt gaa acg gtt cgt aaa acc 480

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Thr Gln His Leu Ser Pro Asp Asn Ile Phe Glu Thr Val Arg Lys Thr
145                               150                               155                               160

aat gat agc att cgt ggt gct tat gct tgc att gcg atg att atc gga 528
Asn Asp Ser Ile Arg Gly Ala Tyr Ala Cys Ile Ala Met Ile Ile Gly
165                               170                               175

cac ggt atg gtt gct ttc cgt gac cca ttc ggt att cgc cgg tta gtg 576
His Gly Met Val Ala Phe Arg Asp Pro Phe Gly Ile Arg Pro Leu Val
180                               185                               190

ctg ggt aaa cgt gaa atc gag ggt aaa acc gaa tat atg ttt gct tcg 624
Leu Gly Lys Arg Glu Ile Glu Gly Lys Thr Glu Tyr Met Phe Ala Ser
195                               200                               205

gaa agt gtg gct ctt gat gta gtg ggg ttt gaa ttt gtg cga gat gtg 672
Glu Ser Val Ala Leu Asp Val Val Gly Phe Glu Phe Val Arg Asp Val
210                               215                               220

ctg cgg ggt gaa gcg att tat gtt acc ttt gat ggg caa tta cat tcg 720
Leu Pro Gly Glu Ala Ile Tyr Val Thr Phe Asp Gly Gln Leu His Ser
225                               230                               235

caa att tgt gcc gat aat cca aaa ctg aat cct tgt att ttt gaa tat 768
Gln Ile Cys Ala Asp Asn Pro Lys Leu Asn Pro Cys Ile Phe Glu Tyr
245                               250                               255

gtt tat ttt gcc cgt cct gat tcc gtc att gat ggc gtt tct gta tat 816
Val Tyr Phe Ala Arg Pro Asp Ser Val Ile Asp Gly Val Ser Val Tyr
260                               265                               270

tct gca cga gtg cat atg ggc gaa tta tta ggt gag aaa att aaa cgt 864
Ser Ala Arg Val His Met Gly Glu Leu Leu Gly Glu Lys Ile Lys Arg
275                               280                               285

gaa tgg gga cga att atc gat gat att gat gtg gtg atc cgg att cct 912
Glu Trp Gly Arg Ile Ile Asp Asp Ile Asp Val Val Ile Pro Ile Pro
290                               295                               300

gaa acc tca aat gat att gcg gta cgt att gct aat atg ttg tat aaa 960
Glu Thr Ser Asn Asp Ile Ala Val Arg Ile Ala Asn Met Leu Tyr Lys
305                               310                               315

ccc tat cgt caa ggg ttt gtt aaa aac cgc tat gta gct cga act ttt 1008
Pro Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr Val Ala Arg Thr Phe
325                               330                               335

att atg cgg ggg caa gca cag cgt aaa agc tcg gtt cgc cgt aaa tta 1056
Ile Met Pro Gly Gln Ala Gln Arg Lys Ser Ser Val Arg Arg Lys Leu
340                               345                               350

aat gcg att gcc tct gaa ttt aaa ggc aaa agc gtg tta ctg gtt gat 1104
Asn Ala Ile Ala Ser Glu Phe Lys Gly Lys Ser Val Leu Leu Val Asp
355                               360                               365

gat tct att gta cga ggt aca acg tct gaa caa atc gtg gaa atg gca 1152
Asp Ser Ile Val Arg Gly Thr Thr Ser Glu Gln Ile Val Glu Met Ala
370                               375                               380

cga gca gct ggt gca aaa cgg gtt tat ttt gcc tct gcc gca cgg gaa 1200
Arg Ala Ala Gly Ala Lys Arg Val Tyr Phe Ala Ser Ala Ala Pro Glu
385                               390                               395                               400

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att cgc tac ccg aat gtg tat ggc att gat atg ccg act tgt gaa gaa 1248
ile arg tyr pro asn val tyr gly ile asp met pro thr cys glu glu
      405      410      415

tta gtg gct tat gat cgc tca gtg gaa gag gtt gca cag atg ata ggg 1296
leu val ala tyr asp arg ser val glu glu val ala gln met ile gly
      420      425      430

gtg gat aaa ttg att ttc caa gac ctt gaa gca ctt tat aag tct att 1344
val asp lys leu ile phe gln asp leu glu ala leu tyr lys ser ile
      435      440      445

caa ctg gaa aat ccg act att cat cgc ttt gat gac tct gta ttt aca 1392
gln leu glu asn pro thr ile his arg phe asp asp ser val phe thr
      450      455      460

gga gaa tat att aca ggt gat gta gat aaa tgc tat tta gac agt ata 1440
gly glu tyr ile thr gly asp val asp lys cys tyr leu asp ser ile
      465      470      475

gca aga tct cga aac gat aaa gca aaa gca gag gcg gca aaa caa gcc 1488
ala arg ser arg asn asp lys ala lys ala glu ala ala lys gln ala
      485      490      495

acc aat tta gaa att cat aac gaa aga ta 1517
thr asn leu glu ile his asn glu arg
      500      505

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<210> 173

<211> 505

<212> PRT

<213> Pasteurella (Mannheimia) haemolytica

<400> 173

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Met Cys Gly Ile Val Gly Ile Ile Gly Asn Ser Pro Val Asn Gln Ala
 1      5      10      15

Ile Tyr Asp Gly Leu Thr Leu Leu Gln His Arg Gly Gln Asp Ala Ala
 20      25      30

Gly Ile Val Thr Ile Asp Asp Glu Asn Arg Phe Arg Leu Arg Lys Ala
 35      40      45

Asn Gly Leu Val Ser Asp Val Phe Gln Gln Glu His Met Val Arg Leu
 50      55      60

Gln Gly Asn Val Gly Ile Gly His Val Arg Tyr Pro Thr Ala Gly Ser
 65      70      75      80

Ser Ser Val Ser Glu Ala Gln Pro Phe Tyr Val Asn Ser Pro Phe Gly
 85      90      95

Ile Thr Leu Val His Asn Gly Asn Leu Thr Asn Asn Ala Glu Leu Lys
100      105      110

Ala Arg Leu Tyr Asn Glu Ala Arg Arg His Val Asn Thr Asn Ser Asp
115      120      125

Ser Glu Ser Leu Leu Asn Ile Phe Ala Tyr Phe Leu Asp Leu Tyr Ser
130      135      140

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Thr Gln His Leu Ser Pro Asp Asn Ile Phe Glu Thr Val Arg Lys Thr
 145 150 155 160
 Asn Asp Ser Ile Arg Gly Ala Tyr Ala Cys Ile Ala Met Ile Ile Gly
 165 170 175
 His Gly Met Val Ala Phe Arg Asp Pro Phe Gly Ile Arg Pro Leu Val
 180 185 190
 Leu Gly Lys Arg Glu Ile Glu Gly Lys Thr Glu Tyr Met Phe Ala Ser
 195 200 205
 Glu Ser Val Ala Leu Asp Val Val Gly Phe Glu Phe Val Arg Asp Val
 210 215 220
 Leu Pro Gly Glu Ala Ile Tyr Val Thr Phe Asp Gly Gln Leu His Ser
 225 230 235 240
 Gln Ile Cys Ala Asp Asn Pro Lys Leu Asn Pro Cys Ile Phe Glu Tyr
 245 250 255
 Val Tyr Phe Ala Arg Pro Asp Ser Val Ile Asp Gly Val Ser Val Tyr
 260 265 270
 Ser Ala Arg Val His Met Gly Glu Leu Leu Gly Glu Lys Ile Lys Arg
 275 280 285
 Glu Trp Gly Arg Ile Ile Asp Asp Ile Asp Val Val Ile Pro Ile Pro
 290 295 300
 Glu Thr Ser Asn Asp Ile Ala Val Arg Ile Ala Asn Met Leu Tyr Lys
 305 310 315 320
 Pro Tyr Arg Gln Gly Phe Val Lys Asn Arg Tyr Val Ala Arg Thr Phe
 325 330 335
 Ile Met Pro Gly Gln Ala Gln Arg Lys Ser Ser Val Arg Arg Lys Leu
 340 345 350
 Asn Ala Ile Ala Ser Glu Phe Lys Gly Lys Ser Val Leu Leu Val Asp
 355 360 365
 Asp Ser Ile Val Arg Gly Thr Thr Ser Glu Gln Ile Val Glu Met Ala
 370 375 380
 Arg Ala Ala Gly Ala Lys Arg Val Tyr Phe Ala Ser Ala Ala Pro Glu
 385 390 395 400
 Ile Arg Tyr Pro Asn Val Tyr Gly Ile Asp Met Pro Thr Cys Glu Glu
 405 410 415
 Leu Val Ala Tyr Asp Arg Ser Val Glu Glu Val Ala Gln Met Ile Gly
 420 425 430
 Val Asp Lys Leu Ile Phe Gln Asp Leu Glu Ala Leu Tyr Lys Ser Ile
 435 440 445
 Gln Leu Glu Asn Pro Thr Ile His Arg Phe Asp Asp Ser Val Phe Thr
 450 455 460
 Gly Glu Tyr Ile Thr Gly Asp Val Asp Lys Cys Tyr Leu Asp Ser Ile
 465 470 475 480

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Ala Arg Ser Arg Asn Asp Lys Ala Lys Ala Glu Ala Ala Lys Gln Ala
 485 490 495
 Thr Asn Leu Glu Ile His Asn Glu Arg
 500 505

<210> 174
 <211> 386
 <212> DNA
 <213> Pasteurella (Mannheimia) haemolytica
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 <221> CDS
 <222> (1) .. (384)
 <220>
 <223> yjgF

<400> 174
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 Met Thr Val Ile His Thr Glu Asn Ala Pro Ala Ala Ile Gly Pro Tyr
 1 5 10 15
 gtg caa gca gtt gat tta ggc aat atg gtt tta act tct ggg caa att 96
 Val Gln Ala Val Asp Leu Gly Asn Met Val Leu Thr Ser Gly Gln Ile
 20 25 30
 ccc gtg aat cct gaa acc ggc gaa atc cgc agt gat att gtg caa caa 144
 Pro Val Asn Pro Glu Thr Gly Glu Ile Pro Ser Asp Ile Val Gln Gln
 35 40 45
 acc cgc caa tct ctg aac aac gtg aaa gcc att atc gaa caa gcc ggc 192
 Thr Arg Gln Ser Leu Asn Asn Val Lys Ala Ile Ile Glu Gln Ala Gly
 50 55 60
 tta acc gtt gcc gat att gta aag acc acc gta ttt gtc aaa gat ctt 240
 Leu Thr Val Ala Asp Ile Val Lys Thr Thr Val Phe Val Lys Asp Leu
 65 70 75 80
 aac gac ttc gca aag gta aat gcg gaa tac caa gcc ttc ttc caa gaa 288
 Asn Asp Phe Ala Lys Val Asn Ala Glu Tyr Gln Ala Phe Phe Gln Glu
 85 90 95
 aac gaa cac cct aat ttt cgc gct cgt tct tgc gta gaa gtg gct cgt 336
 Asn Glu His Pro Asn Phe Pro Ala Arg Ser Cys Val Glu Val Ala Arg
 100 105 110
 tta cca aaa gat gtt ggc att gag atc gaa gcg att gca gta cgc cga 384
 Leu Pro Lys Asp Val Gly Ile Glu Ile Glu Ala Ile Ala Val Arg Arg
 115 120 125
 ta 386

<210> 175
 <211> 128
 <212> PRT
 <213> Pasteurella (Mannheimia) haemolytica
 <400> 175
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 1 5 10 15

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(21) International Application Number: PCT/US02/01971

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(25) Filing Language: English

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LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,
SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ,
VN, YU, ZA, ZW.(84) Designated States (regional): ARIPO patent (GH, GM,
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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
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(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NE, SN, TD, TG).(71) Applicant (for all designated States except US): PHAR-
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[US/US]; 2364 Quincy Avenue, Portage, MI 49024 (US).(88) Date of publication of the international search report:
12 September 2003For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.(74) Agent: WILLIAMS, Joseph, A., Jr.; Marshall, Gerstein
& Borun, 6300 Sears Tower, 233 South Wacker Drive,
Chicago, IL 60606 (US).

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(54) Title: ANTI-BACTERIAL VACCINE COMPOSITIONS

(57) Abstract: Gram negative bacterial virulence genes are identified, thereby allowing the identification of anti-bacterial agents that target these virulence genes and their products, and the provision of gram negative bacterial mutants useful in vaccines.

【国際公開パンフレット（コレクトバージョン）】

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
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26 September 2002 (26.09.2002)

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WO 02/075507 A3(51) International Patent Classification: C12N 1/20,
A61K 39/02, 35/74, C12N 15/31, 15/63, C07K 14/285,
16/12, C12Q 1/18, G01N 33/68

(21) International Application Number: PCT/US02/01971

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(25) Filing Language: English

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(30) Priority Data: 09/809,665 15 March 2001 (15.03.2001) US

(71) Applicant (for all designated States except US): PHAR-
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(72) Inventors; and

(75) Inventors/Applicants (for US only): LOWERY, David,
E. [US/US]; 1207 Woodland Drive, Portage, MI 49024
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& Boron, 6300 Sears Tower, 233 South Wacker Drive,
Chicago, IL 60606 (US).(81) Designated States (national): AI, 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, GI,
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MX, MY, NZ, OM, PA, PE, PG, PH, PL, PT, RO, RU, SD, SE,
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KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
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European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent
(BF, BJ, CI, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
NI, SN, TD, TG).Published:
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with amended claims(88) Date of publication of the international search report:
12 September 2003

Date of publication of the amended claims: 11 December 2003

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

WO 02/075507 A3

(54) Title: ANTI-BACTERIAL VACCINE COMPOSITIONS

(57) Abstract: Gram negative bacterial virulence genes are identified, thereby allowing the identification of anti-bacterial agents that target these virulence genes and their products, and the provision of gram negative bacterial mutants useful in vaccines.

【国際調査報告】

INTERNATIONAL SEARCH REPORT		International Application No. PCT/US 02/01971
A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C12N1/20 A61K39/102 A61K35/74 C12N15/31 C12N15/63 C07K14/285 C07K16/12 C12Q1/18 G01N33/68		
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 A61K C07K C12Q G01N		
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)		
EMBL, EPO-Internal, WPI Data, BIOSIS, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL [Online] 10 February 2001 (2001-02-10) MAY B.J. ET AL.: "Pasteurella multocida PM70 section 152 of 204 of the complete genome" Database accession no. AE006064 XP002224305	1-41
X	nucleotides 3352-4146 & DATABASE EMBL [Online] Entry AE006064, 10 February 2001 (2001-02-10) MAY B.J. ET AL.: "Pasteurella multocida PM70 section 31 of 204 of the complete genome"	5-23,25, 28
A	the whole document & BARBARA J. MAY ET AL.: "Complete genomic sequence of Pasteurella multocida, Pm70" PROCEEDINGS OF THE NATIONAL ACADEMY OF -/-	1-41
☒ 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 "Z" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
12 May 2003		16. 05. 2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentplan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tlx. 31 851 epo nl, Fax: (+31-70) 340-3916		Authorized officer Montero Lopez, B

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 02/01971

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SCIENCES OF USA, vol. 98, no. 6, 13 March 2001 (2001-03-13), pages 3460-3465, XP002202785 WASHINGTON US page 3463, right-hand column, paragraph 2 -page 3464, left-hand column, paragraph 1 --- COONEY ET AL: "Three contiguous lipoprotein genes in Pasteurella haemolytica A1 which are homologous to a lipoprotein gene in Haemophilus influenza Type b" INFECTION AND IMMUNITY, AMERICAN SOCIETY OF MICROBIOLOGY, WASHINGTON, DC, US, vol. 61, no. 11, November 1993 (1993-11), pages 4682-4688, XP002148894 ISSN: 0019-9567 abstract page 4683, left-hand column, last paragraph -page 4685, left-hand column, paragraph 1; figures 3,4 page 4686, right-hand column, paragraph 2 ---	5-23,25, 28
A	TROY E. FULLER ET AL.: "Identification of Pasteurella multocida virulence genes in a septicemic mouse model using signature-tagged mutagenesis" MICROBIAL PATHOGENESIS, vol. 29, 2000, pages 25-38, XP002224304 the whole document -----	1-41

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/01971**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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
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.:
1-41 partially
4. ☐ 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.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

International Application No. PCT/US 02/01971

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 219

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

1. Claims: 1-41 partially

Gram-negative bacteria comprising a mutation in a gene of sequence SEQ ID NO:1 resulting in decreased activity of the gene product; immunogenic composition comprising the bacteria; method of producing such mutant bacteria; nucleotide sequence comprising SEQ ID NO:1, vector and host cell comprising the same and use thereof to produce a polypeptide; encoded polypeptide of sequence SEQ ID NO:2; antibody against it; use of the polypeptide of sequence SEQ ID NO:2 for identifying antibacterial agents.

2. Claims: 1-41 partially

Idem as subject 1 for, respectively sequences SEQ ID NO:3 and 4; 7 and 8; 9 and 10; 21 and 22; 25 and 26.

3. Claims: 1-4, 21-23, 27, 28 partially

Gram-negative bacteria comprising a mutation in a gene of sequence SEQ ID NO:27 resulting in decreased activity of the gene product; immunogenic composition comprising the bacteria; nucleotide sequence comprising SEQ ID NO:27.

4. Claims: 1-41 partially

Idem as subject 1 for, respectively, sequences SEQ ID NOs:29 and 30; 39 and 40; 41 and 42; 51 and 52; 53 and 54; 55 and 56.

5. Claims: 1-28 partially

Gram-negative bacteria comprising a mutation in a gene of sequence SEQ ID NO:57 resulting in decreased activity of the gene product; immunogenic composition comprising the bacteria; method of producing such mutant bacteria; nucleotide sequence comprising SEQ ID NO:57.

6. Claims: 1-41 partially

Idem as subject 1 for, respectively sequences SEQ ID NOs:58 and 59; 60 and 61; 68 and 69; 72 and 73; 74 and 75; 76 and 77; 78 and 79; 80 and 81; 82 and 83; 84 and 85; 104 and 105; 108 and 109; 112 and 113; 116 and 117; 118 and 119; 120 and 121; 122 and 123; 124 and 125; 126 and 127; 128 and 129; 130 and 131

page 1 of 2

International Application No. PCT/US 02/01971

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

7. Claims: 5-26, 29-41 partially

Attenuated Pasteurellaceae bacteria comprising a mutation in a gene of sequence SEQ ID NO:11; immunogenic composition containing it; method of producing such mutant bacteria; nucleotide sequence comprising SEQ ID NO:11, vector and host cell comprising the same and use thereof to produce a polypeptide; encoded polypeptide of sequence SEQ ID NO:12; antibody against it; use of the polypeptide of sequence SEQ ID NO:12 for identifying antibacterial agents.

8. Claims: 5-26, 28-41 partially

Idem as subject 36 for, respectively, sequences SEQ ID NOs:13 and 14; 15 and 16; 17 and 18; 19 and 20; 23 and 24; 31 and 32; 33 and 34; 35 and 36; 37 and 38; 70 and 71; 100 and 101; 102 and 103; 106 and 107; 110 and 111; 114 and 115; 132 and 133; 134 and 135; 136 and 137; 138 and 139; 140 and 141; 142 and 143; 144 and 145; 146 and 147; 148 and 149; 150 and 151; 152 and 153; 154 and 155; 156 and 157; 158 and 159; 160 and 161

9. Claims: 5-26 partially

Attenuated Pasteurellaceae bacteria comprising a mutation in, respectively a gene of sequence SEQ ID NO:162 and 163; immunogenic composition containing it; method of producing such mutant bacteria; nucleotide sequence comprising SEQ ID NO:162 or 163.

10. Claims: 5-26, 28-41 partially

Idem as subject 36 for, respectively, sequences SEQ ID NOs:164 and 165; 166 and 167; 168 and 169; 170 and 171; 172 and 173; 174 and 175

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C 1 2 N 5/10	C 1 2 N 1/21	
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C 1 2 Q 1/68	C 1 2 Q 1/68	A
G 0 1 N 33/15	G 0 1 N 33/15	Z
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4B063 QA01 QA05 QA11 QQ05 QQ42 QQ79 QR32 QR74 QR80

4B064 AG30 CA01 CA19 CC24 DA01 DA13

4B065 AA01Y AB01 AC14 BA02 CA24 CA44 CA46

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申请号	JP2002574050	申请日	2002-01-17
[标]申请(专利权)人(译)	法玛西雅厄普约翰美国公司		
申请(专利权)人(译)	法玛西亚和普强公司		
[标]发明人	デイビッドイーローワリー トロイイーフラー マイケルジェイケネディ		
发明人	デイビッドイーローワリー トロイイーフラー マイケル・ジェイ・ケネディ		
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摘要(译)

有可能鉴定革兰氏阴性细菌的毒力基因，从而鉴定出针对这些毒力基因及其产物的新型抗菌剂。还提供了可用于疫苗的新型革兰氏阴性细菌突变体。

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