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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。
【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。
【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。
【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・プレウロニューモニエ（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。
【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

細菌。
【請求項１３】
P. multocida細菌である請求項９記載の弱毒化パスツレラ科細菌。
【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記載のパスツレラ科細菌。
【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記載のパスツレラ科細菌。
【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記載のパスツレラ科細菌。
【請求項１７】
A. pleuropneumoniae細菌である請求項９記載の弱毒化パスツレラ科細菌。
【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記載のパスツレラ科細菌。
【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記載のパスツレラ科細菌。
【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記載のパスツレラ科細菌。
【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

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。
【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。
【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。
【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。
【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。

【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方法。

【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。

【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；

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】

【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、パスツ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】

【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］。

【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、急性の線維素性気管支肺炎、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。

【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も刺激し得る［Rimler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）］。

【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

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. pleuropiieunioniae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 vulgarisa）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［Mulks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こすと考えられている[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

68(1): 72-9 (2000)]。また、ＬＦＡ－１がＬｋｔ受容体であり、ＬＦＡ－１に対するＬｋｔ結合は標的細胞特異的ではなく、ウシＬＦＡ－１に対するＬｋｔ結合がカルシウム上昇および細胞溶解と相関し、ウシＬＦＡ－１発現がＬｋｔ－１によって誘導された標的細胞の細胞溶解の程度と相関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］。

【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。

【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、ならい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. parasuis、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. panainflueizzae) 、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 haemolvtica、Actinobacillus pleuropneumonae、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。

【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、

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。

【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。

【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。

【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

、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む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い確立および／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塩基対の可変中央領域を含み、それは、中央部分がポリメラーゼ鎖反応（ＰＣＲ）によって共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のＬＤ$_{50}$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. pleuropnetmoniae突然変異体のスクリーニングにより、

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 enteritdis、Salmonella dublin、Salmonella gallanerum、Bordella pertussis、Yersinia entericolitica、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ー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】
ＳＴＭ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ＤＮＡ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で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、ワクチン処方を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、幾分かの、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。
【００２９】
ＳＴＭ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、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ＤＮＡ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ＤＮＡ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。
【００３１】
もう１の技術において、ＤＮＡ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ＤＮＡ中に存在しない場合には、lox部位によって挟まれたＤＮＡ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. multosida、A. pleuropneumonieae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刺による）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ＤＮＡ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ＤＮＡ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。
【００３２】
もう１の技術において、cre-lox系をＤＮＡの部位特異的な組換えに用いる。この系は、

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配列を含むであろう。

【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有する発現カセットは、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。

【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。

【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。

【００３６】

また、本発明は、P. multocida、A. pleuropneumonicae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

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。

【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

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

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Konigsberg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。

【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、無脊髄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、トロンビンおよびエンテロキナーゼである。

【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、

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

側鎖の特徴		アミノ酸
脂肪族	非極性	GAP
		ILV
	極性-非荷電	CSTM
		NQ
	極性-荷電	DE
		KR
芳香族		HFWY
その他		NQDE

【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。
【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WO 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。
【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：	ＡＬＩＶＰ
B.芳香族：	ＦＷ
C.含硫黄原子：	Ｍ
D.境界：	Ｇ
非電荷－極性	
A.ヒドロキシル：	ＳＴＹ
B.アミド：	ＮＱ
C.スルフヒドリル：	Ｃ
D.境界：	Ｇ
プラスに帯電（塩基性）：	ＫＲＨ
マイナスに帯電（酸性）：	ＤＥ

【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。
【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。
【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

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。
【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、標的化リポ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。
【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。
【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－特異的共有的改変にも有用である。共有的改変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。
【００５６】
P. multocida、A. pleuropneumoniaeおよびP. (Mannheimia) haemolyticaの病原性遺伝子

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。

【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（Streptomycetes）、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。

【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

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WO 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。

【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ロスの醗酵および抽出、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。天産物ライブラリーには、ポリペプチド、非－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。

【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。

【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-

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対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。

【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。

【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。

【００６４】

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 Sevice, 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、０１Ｋ２）、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（Amycolata）、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、およびテオブローマ（theobroma）の油が含まれる。

【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、キャプレッツ剤、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、または膣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遺伝子を特徴付ける。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トランスポーザブル・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 ｓｕｐＥ４４，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トランスポーザブル・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

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ＴｈＤＮＡ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。

【００７６】

【化２】

TEF14 5′-CATGGTACCCATTCTAAC 配列番号: 88

TEF15 5′-CTAGGTACCTACAACCTC 配列番号: 89

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トにつづく、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トを含む。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）に従ってコロニーブロット分析を行った。

【００７８】

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

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。プローブの調製ついては、Ａｍｐｌｉｔａｑ ＰＣＲ緩衝液（PE Applied Biosystems）、２００μＭ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）、２ｍＭの$MgCl_2$、２.５単位のＡｍｐｌｉｔａｑ（PE Applied Biosystems）および１ｎｇのプラスミドＤＮＡを用いて、１００μｌの一次ＰＣＲ反応を設定した。

【００７９】

【化３】

TEF5　5′-TACCTACAACCTCAAGCT　配列番号: 91

TEF6　5′-TACCCATTCTAACCAAGC　配列番号: 92

【００８０】

サイクル条件は、９５℃にて２分間の初期インキュベートにつづく、９５℃にて３０秒間、５０℃にて４５秒間、７２℃にて１５秒間の３５サイクルにつづく７２℃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、１０９ｂｐ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１５ｎｇ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２ｍＭのｄＮＴＰ保存溶液の１：１混合物を用いる５０μｌのＰＣＲ反応中で標識した。

【００８１】

【化４】

TEF24　5′-TACCTACAACCTCAAGCTT　配列番号: 93

TEF25　5′-TACCCATTCTAACCAAGCTT　配列番号: 94

【００８２】

ＰＣＲ条件は、９５℃にて４分間の初期インキュベートにつづく、９５℃にて３０秒間、５０℃にて４５秒間、７２℃にて１５秒間の２５サイクル、ならびに７２℃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９０μｌ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１０ｍｌのＤＩＧ ＥａｓｙＨｙｂ中、９５℃にて１０分間溶解および変性させた。

【００８３】

ドットブロットは、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３０ｎｇ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０.１Ｎ 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 Ｉ^{TM} Ｄｏｔ－Ｂｌｏｔ Ａｐｐａｒａｔｕｓを用いて最小限の真空で膜に適用した。各ウェルを１５０μｌの中和溶液（０.５Ｍ トリス／３Ｍ ＮａＣｌ、ｐＨ７.５）および１５０μｌの２×ＳＳＣで洗浄した。膜をＳｔｒａｔａｌｉｎｋｅｒ（Stratagene, La Jolla, CA, USA）中でＵＶ－架橋し、２０ｍｌのＤＩＧ ＥａｓｙＨｙｂ Ｂｕｆｆｅｒ中、４２℃にて１時間プレ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℃にて一晩行った。膜を０.１％ＳＤＳを含有する２×ＳＳＣで各洗浄につき５分間２回洗浄

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－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有する全プラスミドよりもむしろ、ドット・ブ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ブ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が、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。これらのタグを含有するプラスミドを精製して、イー・コリＳ１７-１：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を含有するイー・コリＳ１７－１：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シ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％CO_2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Ｓ１７－１：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$MgSO_4$を含有するＢＨＩプレート上に予め置いておいた０．２２ ＴＭ フィルターに５０μｌの各交配混合物をスポットした。５％CO_2下、３７℃にて一晩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$BHIN^{50}K^{100}$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$BHIN^{50}K^{50}$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。一晩増殖後に、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℃保存から取り出し、各ウェルからの１０μｌを５０μｇ／ｍｌのナリジキシン酸（Sigma）および５０μｌ／ｍｌのカナマイシン（Sigma）と共に２００μｌのブレインハート浸出液（DIFCO）（ＢＨＩＮ^{50}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％ＣＯ$_2$下、３７℃にて一晩インキュベートした。各ウェルからの１０μｌをウェル当り１００μｌ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℃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１００μｌ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}ＣＦＵ／ｍｌの用量とし、０.２ｍｌの各希釈物を用いて、腹膜内投与によって雌性１４-１６ｇ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、ＢＨＩＮ^{50}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×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。

【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－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５μｇ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－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％ＣＯ$_2$中、３７℃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^{5}ＣＦＵ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。

【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

りも少なくとも１０倍高い概算ＬＤ$_{50}$を有することを示した。該クローンおよびそれらの概算ＬＤ$_{50}$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】

ＬＤ$_{50}$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ＬＤ$_{50}$よりもほぼ２００倍高い用量で表１に示す個々のP. mutocida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 106
11	PM1D1	dsbB	10/10, 5/10	10/10, 5/5	8.4 x 104
3	PM1BD7	atpG	5/5, 10/10	10/10	>3 x 105
74	PM1BE11	yhcJ (HI0145)	10/10	5/10	>2 x 105
70	PM1BF6	yabK (HI1020)	3/5, 8/10	9/9	>2 x 105
19	PM2G8	fhaC	4/5, 9/10	9/9	>4 x 105
76	PM3C9	yiaO (HI0146)	3/5		>6 x 105
118	PM3G11	UnkO	4/5, 10/10	10/10	>3 x 105
31	PM7B4	iroA (UnkB)	0/5		
17	PM4C6	fhaB (fhaB2)	2/5, 10/10, 9/10	10/10, 9/9	>3 x 106
9	PM4G10-T9	dnaA	4/5		>5 x 105
1	PM4D5-T5	atpB	5/5		>4 x 105
53	PM4D5-T1	UnkC2	5/5		>4 x 105
15	PM4F2	fhaB (fhaB1)	3/5, 6/10, 10/10	6/6, 10/10	>3 x 105
41	PM5F7	mreB	4/5		1 x 103
7	PM5E2	devB	0/5, 3/10	2/3	ND
68	PM6H5-T1	xylA	5/5		>3 x 105
78	PM6H8	yigF (HI0719)	5/5, 9/10	9/9	>3 x 105
108	PM7D12	pnp	5/5, 9/10	9/9	
51	PM8C1R1-T2	UnkC1	5/5		~6 x 105
37	PM8C1-T3	mglB	5/5		~6 x 105
58	PM8C1R1-T6	UnkD1	5/5		~6 x 105
45	PM10H7	purF (HI1207)	3/5, 8/10, 8/10	8/8, 8/8	>3 x 105
25	PM10H10-T2	HI1501	5/5		>1 x 104
72	PM11G8-T2	ygiK	5/5		>2.4 x 103
21	PM11G8-T4	greA	5/5		>2.4 x 103
84	PM12H6	yyam (HI0687)	3/5, 0/10		~2.2 x 103
33	PM15G8-T2	kdtB	5/5		>1.2 x 105
116	PM15G8-T1	UnkK	5/5		>1.2 x 105
104	PM16G11-T1	hmbR	3/5		>1.9 x 105
29	PM16G11-T2	hxuC	3/5		>1.9 x 105
35	PM16H8	lgtC	5/5, 10/10	10/10	>2.4 x 105
80	PM16H3	yleA (HI0019)	5/5, 10/10		> 2.0 x 105
49	PM17H6-T1	sopE	4/5		~6 x 105
120	PM17H6	UnkP	4/5		~6 x 105
5	PM18F5-T8	cap5E	5/5		>2.4 x 105
82	PM18F5-T10	yojB (HI0345)	5/5		>2.4 x 105
13	PM19A1	exbB	5/5, 10/10	10/10	>1.2 x 105
112	PM19D4	rci	5/5, 8/10	8/8	~1.6 x 105
39	PM20A12	mioC (HI0669)	3/5, 8/10	8/8	~2 x 104
60	PM20C2	UnkD2	5/5, 10/10	10/10	>8.2 x 106

【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４～８ｋｂ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１．８ｋｂ　ＭｌｕＩ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BigDye™ 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（interupted）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トランスポー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否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×ＳＣＣ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ンナトリウム／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。

【００１００】

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。

【００１０１】

【化６】

DEL-1389	TCTCCATTCCCTTGCTGCGGCAGGG	配列番号: 98
TEF-46	GGAATTACAGCCGGATCCGGG	配列番号: 99

【００１０２】

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。ブ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、該ブロットを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。

【００１０３】

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。

【００１０４】

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（V^{10}）（Sigma, St. Lous, Missouri）を含有するブレインハート滲出液（ＢＨＩ）（Difco Labratories, 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％ CO_2 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），[Tmp^R]，[Sm^R]）をルリア－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１００μｍ／ｍｌ アンピシリン（Sigma）、５０μｍ／ｍｌ ナリジキシン酸（N^{50}）（Sigma）、および５０（K^{50}）もしくは１００（K^{100}）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ＡＰ２２５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のアリコートの培養液を１５０μｌのＡＰＰ２５５培養液と混合し、ついで１００μＭ ＩＰＴＧおよび１０ｍＭ $MgSO_4$ を含有するＢＨＩＶ^{10}プレート上に予め設置した０.２２μＭ フィルター上に５０μｌの各交配混合物をスポットした。５％ CO_2 下、３７℃にて一晩インキュベートした後に、各フィルターの交配混合物を２ｍｌのＰＢＳ中に洗い出し、各々の２００μｌをＢＨＩＶ^{10}Ｎ^{50}Ｋ^{100}プレートに平板した。選択的に一晩増殖させた後に、２００μｌ ＢＨＩＶ^{10}Ｎ^{50}Ｋ^{50}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。一晩増殖させた後に、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。

【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２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２０μｌを１８０μｌのＢＨＩＶ^{10}Ｎ^{50}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継代培養した。プレートを振盪することなく５％ CO_2 中、３７℃にて一晩インキュベートした。ついで、一晩置いたプレートを、各ウェルからの１０μｌをウェルあたり１００μｌのＢＨＩＶ^{10}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、１５０ｒｐｍ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OD_{562}をモニターし

た。約０.２ないし０.２５のＯＤ$_{562}$にて、各プレートをプールして、該マイクロタイタープレートの各ウェルからの１００μｌ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、４.０ｍｌを用いて、気管チューブを用いる気管内投与により１０～２０ｋｇＳＰＦ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１５０ｍｌの殺菌ＰＢＳを潅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×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×ｇにて遠心して、該細菌をペレット化した。ペレットを５ｍｌ ＢＨＩに再懸濁し、１０$^{-2}$ないし１０$^{-5}$の範囲の希釈率でＢＨＩＶ^{10}Ｎ^{50}Ｋ^{50}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１０μｌ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０.７ｍｌ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。

【０１０９】

先に記載したごとくドットブロットを行い、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－ｄＵＴＰ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。

【０１１０】

【化７】

TEF69	GACGTTTCCCGTTGAATATGGCTC	配列番号: 166
TEF65	GCCGGATCCGGGATCATATGACAAGA	配列番号: 167
TEF66	GACAAGATGTGTATCCACCTTAAC	配列番号: 168

【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。ドットブロットを調製し、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）を各ドットブ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、ドットブ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。

【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BigDye^{TM} 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

Arbor, MI）を用いて、配列データをアセンブルして解析した。ＧＣＧ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。

【０１１３】

【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－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		
OmpP5-2	配列番号: 150	開始コドンなし－終止コドンなし	
tig	配列番号: 160	pnp	配列番号: 154
fkpA	配列番号: 142	apvA-or 1	配列番号: 122
hupA	配列番号: 146	apvA-or 2	配列番号: 124
rpmF	配列番号: 158	apvB	配列番号: 126
		apvD	配列番号: 130
開始コドン－終止コドンなし			
lpdA	配列番号: 148	ＲＮＡまたは非コード配列	
potD	配列番号: 156	tRNA-leu	配列番号: 162
yaeE	配列番号: 164	tRNA-glu	配列番号: 163
apvC	配列番号: 128		

【０１１４】

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。１１０の突然変異体は３５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ＯＲＦの異なる部位内に挿入を含有するクローンに対するＯＲＦ内の単一部位に挿入を含有した。３の多重挿入が、多重ＰＣＲ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１１０個のコロニー中に検出された。

【０１１５】

実施例９　A. pleuropneumoniae突然変異体と野生型ＡＰＰ２２５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（ＡＰ２２５）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ＢＨＶＩ^{10}中で０.６－０.９のＯＤ$_{590}$まで増殖させた。ほぼ５.０×１０^{6}ＣＦＵの野生型および突然変異体株を各々４ｍｌのＢＨＩに添加した。合計４ｍｌ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１０－２０ｋｇのＳＰＦブタに感染させた。感染後ほぼ２０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ＢＨＩＶ^{10}Ｎ^{50}およびＢＨＩＶ^{10}Ｎ^{50}Ｋ^{100}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; ＣＩ）は、[突然変異体ＣＦＵ／野生型ＣＦＵ]投入／[突然変異体ＣＦＵ／野生型ＣＦＵ]回収として算出した。

【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と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合指数は、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。
【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	*atpH*	ATP合成酵素	.009
AP7F10	*atpG*	ATP合成酵素	.013
AP17C6	*lpdA*	ジヒドロリポアミド・デヒドロゲナーゼ	.039
AP11E7	exbB	鉄化合物の輸送	.003,.003,.006
AP3H7	*potD*	スペルミジン／プテレシンの輸送	.308
AP8H6	*OmpP5*	アドヘシン/OmpAホモログ	.184
AP18H8	*OmpP5-2*	アドヘシン/OmpAホモログ	.552
AP13E9	*tig*	ペプチジループロリル・イソメラーゼ	.050
AP13C2	*fkpA*	ペプチジループロリル・イソメラーゼ	<.001
AP15C11	*pnp*	ポリヌクレオチド・ホスホリアーゼ	.032
AP18F12	*hupA*	ヒストン様タンパク質	.001
AP20F8	*dksA*	dnaK突然変異の用量依存性サプレッサー	.075
AP5G4	*dnaK*	ヒートショックタンパク質ー分子シャペロン	.376
AP17C9	*tRNA-leu*	タンパク質合成	.059
AP5D6	*tRNA-glu*	タンパク質合成	.055
AP18B2	*rpmF*	タンパク質合成	.112
AP10E7	*yaeA*	未知	.001
AP19A5	HI0379	未知	.061
AP10C10	*apvA*	未知	.157
AP18F5	*apvB*	未知	.103
AP2A6	*apvC*	未知	.091
AP2C11	*apvD*	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るための競合指数の数の使用を、実施例１１に

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. pleunopneumoniae病原性遺伝子の特徴付け

同定したA. pleunopneumoniae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。

F_0F_1 Ｈ＋ －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。F_1 δ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［Gwinnら, J Bacteriol. 179:7351-20 (1997)］が含まれる。

【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)］。

【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輸送複合体の一部分であり［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Streptococus 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。

【０１２３】

アドヘシ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

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。

【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ー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 Bacterol 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。

【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Shigellaflexneri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 Bacterol. 178:2357-82 (1996)］。

【０１２６】
ＨｕｐＡは細菌性ヒストン様タンパク質であり、それはＨｕｐＢと組み合わさって、E.coli中にＨＵタンパク質を構築する。報告は、ｈｕｐＡおよびｈｕｐＢ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 (1989); Wadaら，Ｊ Mol. Biol. 204:581-91 (1988)］。ｈｕｐＡ－ｈｕｐＢ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ＤＮＡ組換えの多くの形態においてブロックされことが示されている［Wadaら，Ｊ Mol. Biol. 204:581-91 (1988); Wadaら，Gene. 76:345-52 (1989)］。一つの限定的データは、以前、ｈｕｐＡは毒性に直接関わることを示した［Turnerら，Infect Immun. 66:2099-106 (1998)］。ｈｕｐＡ弱毒化のメカニズムが知られないまま残っている。

【０１２７】
ＤｎａＫ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）。ＤｎａＫ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. 38:295-300 (1994)］、Brucella suis ｄｎａＫ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)］。対象的に、もう一つの細胞内病気素因、Listeria monnocytogenesは食作用後ｄｎａＫ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ＴｏｘＲ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 ｄｎａＫ突然変異体のＣＩ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。

【０１２８】
ＤｋｓＡは、E.coliのｄｎａＫ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. 172:205-64 (1990)］。現在、ＤｋｓＡ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ＤｋｓＡ突然変異体はグルコースまたはヒスチジンと一緒ではよく成長しなかったが、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だとよく成長したことが記されている。この観察は、該ｄｋｓＡ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)］。

【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：ｔＲＮＡ－ｌｅｕ、ｔＲＮＡ－ｇｌｕ、およびｒｐｍＦ。タンパク質合成を除いて、ｔＲＮＡ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Soffer, B.B.R.C. 36:47-53 (1969)］、および細菌－真核細胞相互作用［Grayら，Ｊ Bacteriol. 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、ｔＲＮＡ－ｌｅｕは、転写減衰［Carter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ｔＲＮＡがA. pleuropneumoniaeにおけるｔＲＮＡ－ｌｅｕ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、ｔＲＮＡ－ｌｅｕは広汎な機能のいずれか１を有する可能性がある。ＲｐｍＦ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

含有するオペロンの部分である。ｆａｂ遺伝子およびｒｐｍＦ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ｆａｂ遺伝子の発現は、必ずしも、ｒｐｍＦｎｏ上流を開始する転写物に依存するとは限らない。それは、ｒｐｍＦ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。ｙａｅＡおよびＨＩ０３７９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（ａｐｖ）と名付けられている。ａｐｖＣ遺伝子は、ＨＩ０８９３に著しい類似性を示すが、脂肪酸反応調節Ｂｍ３Ｒ１に類似する転写レプレッサーとしてのＨＩ０８３９の提案された類似性［Palmer，J Biol Chem. 273:18109-16 (1998)］は疑わしい。ａｐｖＤ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（ｂ０８７８）に最も類似している［Blattnerら，Science 277:1453-1474 (1997)］。２つの他の未知物、ａｐｖＡおよびａｐｖＢは公開データベースには明らかに適合するのもはなかった。

【０１３１】

実施例１１　A. pleuropneumoniae突然変異体の安全性および効能　９つの群（ｎ＝８）のＳＰＦ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^{10}ＣＦＵ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１～５×１０５ＣＦＵの野生型ＡＰＰ２２５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

ワクチン	鼻腔内攻撃後の%死亡率	
	ワクチン化	攻撃
ﾌﾟﾚｳﾛﾐｭｰﾝ(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ＨＩ０３７９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 Woodkans, 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】

atpG	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
guaB	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
pnp	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
purF	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
yjgF	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×　ＸＬバッファーＩＩ（PE Applied Biosystems）、２００μＭのｄＮＴＰ、２５ピコモルの各適当なプライマー、０．８ｍＭの$MgCl_2$、０．５ＵのｒＴｔｈ　ＤＮＡポリメラーゼ、ＸＬ（PE Applied Biosystems）およびほぼ１μｇのＴＦ１　ＤＮＡを用いて５０μｌ反応を設定した。
【０１３７】
サイクル条件は９４℃にて１．５分間につづいて；９４℃にて１５秒間、４０－６０℃にて６０秒間、７２℃にて１．５分間を３５サイクル；および７２℃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BigDye™ 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ティングフレーム（ＯＲＦ）用の二本鎖配列を得た。Sequench

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。ＧＣＧ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ＯＲＦ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フ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 ＰＣＲ産物を作製した。５０μｌの反応は、３.３×ＸＬバッファーＩＩ(PE Applied Biosystems)、２００μＭのｄＮＴＰ、２５ｐｍｏｌの各々の適当なプライマー (以下に示す)、０.８ｍＭのＭｇＣｌ$_2$、０.５ＵのｒＴｔｈ ＤＮＡポリメラーゼ、ＸＬ(PE Applied Biosystems)および１μｌ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℃にて１.５分間;につづく９４℃にて２０秒間、６０℃にて４５秒間、７２℃にて４分間の３５サイクル;および７２℃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。

【０１４０】

【表７】

表 5

遺伝子	Vectoretteﾗｲﾌﾞﾗﾘｰ	プライマー
atpG	BglII, HindIII	TEF217 GAAGCCGCCATACGCTCTTGGG 配列番号: 186
	ClaI	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
pnp	ClaI, 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 ACCTGCGGCATCTTGTCCTC 配列番号: 194
	HincII	TEF274 ACGGGTTTATTTTGCCTCTG 配列番号: 195
yjgF	ClaI	TEF221 CGCCGGTTTCAGGATTCACGGG 配列番号: 196
	EcorV	TEF281 CTGAACAACGTGAAAGCCAT 配列番号: 197

【０１４１】

VectorettePＣＲ産物を前記したごとくバンド精製し、配列決定した。ａｔｏＧ、ｇｕａＢ、ｐｎｐ、ｐｕｒＦおよびｙｊｐＦ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】

上記の例示的実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.

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

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)].

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 vulgarisa*, 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.

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 165*: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

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 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].

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 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 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 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.*

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. 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 embodiment, vaccine compositions of the invention comprise attenuated *Pasteurella multocida* and *A. plueropneumoniae* 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, 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 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 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

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

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-idiotype antibodies immunospecific for antibodies of the invention.

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.

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.

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

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 LD_{50} 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 gallanerum, Bordella pertussis, Yersinia entericolitica, 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 *exbB, atpG, pnp, guaB* and *yjgF*.

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 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 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 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 review, see, for example, Reyrat, *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 plasmid has integrated into the genome in the appropriate location and manner. The counterselecteable 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 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

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.

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,

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 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, 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 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, 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.

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, 118, and 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. 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 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 & 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 guanosine/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 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 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 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 *E. coli*. If the gene product is to be produced extracellularly, either in the periplasm of

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, 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 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 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 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 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 Engineering, 6*:109-122 (1993), a FLAG peptide [Hopp *et al.*, *Biotechnology, 6*:1205-

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

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

SIDE CHAIN CHARACTERISTIC		AMINO ACID
Aliphatic	Non-polar	G A P 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

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 CHARACTERISTIC	AMINO ACID
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

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

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 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 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 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 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 Shillitoe, *Mol. Biotech.* 7:125-137 (1997). Ribozyme technology can be utilized to inhibit translation 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*:434-438 (1998)]. Delivery of ribozymes to target cells can be accomplished using either

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.

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 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). 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 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*].

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, 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 (*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 *Streptomycetes*, other bacteria and fungi, and cell extracts of plants and other vegetations. For proteins with known enzymatic activity, assays are established based

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.

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 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 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 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.

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 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

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

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.

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 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 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.

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 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.

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 Sevice, 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

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

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 *Kpn*I restriction site in the multiple cloning region and then to introduce a new *Kpn*I site in the mini-Tn10 region. The plasmid was digested with *Kpn*I 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

produce a plasmid designated pLOF/Km--*Kpn*I which was transformed into *E.coli* DH5α:λpir for amplification. *E.coli* DH5α: (λpir φ80dlacZΔM15, 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 QIAGEN SpinPreps from QIAGEN Inc. (Santa Clarita, CA) and digested with *Sfi*I which cuts at a unique site within the mini-Tn10 transposable element. A *Sfi*I-*Kpn*I-*Sfi*I 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 *Sfi*I 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′-AGGCCGGTACCGGCCGCCT SEQ ID NO: 86

TEF3 5′-CGGCCGGTACCGGCCTAGG SEQ ID NO: 87

Unique sequence tags for insertion into the *Kpn*I 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 conditions including 250 μM 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

TEF15 5′-CTAGGTACCTACAACCTC SEQ ID NO: 89

TEF26 SEQ ID NO: 90

5′-CTAGGTACCTACAACCTCAAGCTT-$[NK]_{35}$-

AAGCTTGGTTAGAATGGGTACCATG

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 *Kpn*I 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 *Kpn*I and dephosphorylated with calf intestinal alkaline phosphatase (Boehringer Mannheim) using standard procedures. The resulting plasmid library was transformed into *E.coli* DH5α:λpir. 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 µl primary PCR reaction was set up using Amplitaq PCR buffer (PE Applied Biosystems), 200 µM dNTPs, 140 pmol each of primers TEF5 (SEQ ID NO: 91) and TEF6 (SEQ ID NO: 92), 2 mM $MgCl_2$, 2.5 units Amplitaq (PE Applied Biosystems) and 1 ng of plasmid DNA.

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

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 extractions were carried out using a QIAGEN Gel Extraction kit (QIAGEN).

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.

TEF24	5'-TACCTACAACCTCAAGCTT	SEQ ID NO: 93
TEF25	5'-TACCCATTCTAACCAAGCTT	SEQ ID NO: 94

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 *Hin*dIII 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.

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 (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 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).

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 $[NK]_{35}$ 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), [TmpR], [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% CO_2 when grown on plates. Matings were set up by growing each *E.coli* S17-1:λpir /pTEF1:$[NK]_{35}$ 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

containing 100 mM IPTG and 10 mM $MgSO_4$. Following overnight incubation at 37°C with 5% CO_2, mating mixtures were washed off of each filter into 3 ml of PBS and 25 µl of each was plated onto $BHIN^{50}K^{100}$ plates. Following selective overnight growth, colonies were assembled into microtiter plates by toothpick transfer into 200 µl $BHIN^{50}K^{50}$ 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

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) ($BHIN^{50}K^{50}$). Plates were incubated without shaking overnight at 37°C in 5% CO_2. 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 OD_{540} was monitored using a micro-titer plate reader. At an OD_{540} 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 10^4, 10^5, 10^6 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 $BHIN^{50}K^{50}$ 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 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 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 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 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 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% CO_2 at 37°C. Approximately six colonies of each 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

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 LD_{50} for the wild type strain. Survival rate was then determined for each challenged group of mice.

Results indicated that 62 of 120 potential transposon mutants were attenuated, having an approximate LD_{50} of at least 10 fold higher than the wild type strain. The clones and their approximate LD_{50} values are listed in Table 1. A control experiment with the wild type strain was run in parallel with each set of challenges and in all cases mortality in wild type-challenged groups was 100%.

In addition to LD_{50} 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 LD_{50} of the virulent, wild type 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	PossibleGene Function	Vaccination # survivors/total	Challenge # survivors/total	LD_{50}
–	wild type	-	0/10	-	<10
23	PM1B1	guaB	10/10, 10/10, 10/10	9/10, 9/10	4.3 x 106
11	PM1D1	dsbB	10/10, 5/10	10/10, 5/5	8.4 x 104
3	PM1BD7	atpG	5/5, 10/10	10/10	>3 x 105
74	PM1BE11	yhcJ (HI0145)	10/10	5/10	>2 x 105
70	PM1BF6	yabK (HI1020)	3/5, 8/10	9/9	>2 x 105
19	PM2G8	fhaC	4/5, 9/10	9/9	>4 x 105
76	PM3C9	yiaO (HI0146)	3/5		>6 x 105
118	PM3G11	UnkO	4/5, 10/10	10/10	>3 x 105
31	PM7B4	iroA (UnkB)	0/5		
17	PM4C6	fhaB (fhaB2)	2/5, 10/10, 9/10	10/10, 9/9	>3 x 106
9	PM4G10-T9	dnaA	4/5		>5 x 105
1	PM4D5-T5	atpB	5/5		>4 x 105
53	PM4D5-T1	UnkC2	5/5		>4 x 105
15	PM4F2	fhaB (fhaB1)	3/5, 6/10, 10/10	6/6, 10/10	>3 x 105
41	PM5F7	mreB	4/5		1 x 103
7	PM5E2	devB	0/5, 3/10	2/3	ND
68	PM6H5-T1	xylA	5/5		>3 x 105
78	PM6H8	yigF (HI0719)	5/5, 9/10	9/9	>3 x 105
108	PM7D12	pnp	5/5, 9/10	9/9	
51	PM8C1R1-T2	UnkC1	5/5		~6 x 105

Nucleotide SEQ ID NO:	Representative Isolate	PossibleGene Function	Vaccination # survivors/total	Challenge # survivors/total	LD_{50}
37	PM8C1-T3	mglB	5/5		~8 x 105
58	PM8C1R1-T6	UnkD1	5/5		~6 x 105
45	PM10H7	purF (HI1707)	3/5, 8/10, 8/10	8/8, 8/8	>3 x 105
25	PM10HI0-T2	HI1501	5/5		>1 x 104
72	PM11G8-T2	ygiK	5/5		>2.4 x 103
21	PM11G8-T4	greA	5/5		>2.4 x 103
84	PM12H6	yyam (HI0687)	3/5, 0/10		~2.2 x 103
33	PM15G8-T2	kdtB	5/5		>1.2 x 105
116	PM15G8-T1	UnkK	5/5		>1.2 x 105
104	PM16G11-T1	hmbR	3/5		>1.9 x 105
29	PM16G11-T2	hxuC	3/5		>1.9 x 105
35	PM16H8	lgtC	5/5, 10/10	10/10	>2.4 x 105
80	PM16H3	yleA (HI0019)	5/5, 10/10		> 2.0 x 105
49	PM17H6-T1	sopE	4/5		~6 x 105
120	PM17H6	UnkP	4/5		~6 x 105
5	PM18F5-T8	cap5E	5/5		>2.4 x 105
82	PM18F5-T10	yojH (HI0345)	5/5		>2.4 x 105
13	PM19A1	exbB	5/5, 10/10	10/10	>1.2 x 105
112	PM19D4	rci	5/5, 8/10	8/8	~1.6 x 105
39	PM20A12	mioC (HI0669)	3/5, 8/10	8/8	~2 x 104
60	PM20C2	UnkD2	5/5, 10/10	10/10	>8.2 x 106

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.

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

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 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 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 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 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.

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 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

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 *Eco*RI and *Hin*dIII 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 atgG 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

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).

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

Example 6

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 (V^{10}), (Sigma, St. Louis, Missouri) at 37°C and in 5% CO_2 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), [Tmp^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 (N^{50})(Sigma), and 50 (K^{50}) or 100 (K^{100}) μg/ml of kanamycin (Sigma).

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 $BHIV^{10}$ plates containing 100 μM IPTG and 10 mM $MgSO_4$. Following overnight incubation at 37°C with 5% CO_2, mating mixtures were washed off of each filter into 2 ml of PBS and 200 μl of each was plated onto $BHIV^{10}N^{50}K^{100}$ plates. After selective

overnight growth, colonies were assembled into microtiter plates by toothpick transfer into 200 µl BHIV^{10}N^{50}K^{50} 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.

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 µl from each well to a new 96 well round bottom plate (Corning Costar, Cambridge, MA, USA) containing 180 µl of BHIV^{10}N^{50}K^{50}. Plates were incubated without shaking overnight at 37°C in

5% CO_2. 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 $BHIV^{10}$ per well and incubating at 37°C with shaking at 150 rpm. The OD_{562} was monitored using a microtiter plate reader. At an OD_{562} 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 10^6 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 $BHIV^{10}N^{50}K^{50}$ 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 10^8 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.

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

The labeled PCR product was then digested with *Hin*dIII 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 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.

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.

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 databases.

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.

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

Complete Open Reading Frame		NO Start Codon - Stop Codon	
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	NO Start Codon - NO Stop Codon	
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
Start Codon - NO Stop Codon			
lpdA	SEQ ID NO: 148	RNA or Noncoding Sequences	
potD	SEQ ID NO: 156	tRNA-leu	SEQ ID NO: 162
yaeE	SEQ ID NO: 164	tRNA-glu	SEQ ID NO: 163
apvC	SEQ ID NO: 128		

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.

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 $BHIV^{10}$ to an OD_{590} of 0.6 – 0.9. Approximately 5.0 x 10^6 CFU each of the wild type and mutant strains were added to 4 mls BHI. The total 4 ml dose was used 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 $BHIV^{10}N^{50}$ and $BHIV^{10}N^{50}K^{100}$ 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 [mutant CFU / wild type CFU]$_{input}$ / [mutant CFU / wild type CFU]$_{recovered}$.

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.

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

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

Accuracy of the CI appeared to be very good as the *exbB* mutant was competed within three different animals yielding CI's 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 F_0F_1 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 F_1 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 [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 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 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 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 ORF's 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 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 chronic infections [Duim, *et al., Infect Immun. 65*:1351-1356 (1997)], however, this

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

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 intranaslally with 1-5 x 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.

Table 4
Efficacy of *A. pleuropneumoniae* Mutants

Vaccine	% Mortality following intranasal challenge	
	Vaccination	Challenge
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
None	N/A	50.0

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 LD_{50} using this model was generally 1×10^7 CFU, indicating that each of these mutants is at least 100 fold attenuated and that there is a reasonable correlation between CI and attenuation.

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

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

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).

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
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
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

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 $MgCl_2$, 0.5 U r*Tth* DNA polymerase, XL (PE Applied Biosystems) and approximately 1 µg of TF1 DNA.

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).

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.

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 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 $MgCl_2$, 0.5 U *rTth* DNA polymerase, XL (PE Applied Biosystems) and 1 µl of the appropriate vectorette library. Cycle 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.

Table 5

Gene	Vectorette library	Primer(s)
atpG	BglII, HindIII	TEF217 GAAGCCGCCATACGCTCTTGGG SEQ ID NO: 186
	ClaI	TEF218 GTTGCTTCCTTTGCCTGCACTGG SEQ ID NO: 187
guaB	EcoRI	TEF265 GGCTCAGAAACAATACCACTTTCA SEQ ID NO: 188
	HindIII, TaqI	TEF268 GCACCAAAGCAGAATTTGTCC SEQ ID NO: 189
pnp	ClaI, HincII	TEF219 GGTGATGATGTCGATGATAGTCCC SEQ ID NO: 190
	TaqI,	TEF220 GGCGTATTAGCCGTGATGCCAACC SEQ ID NO: 191
	BamHI	TEF286 GACCACTTAGGCGATATGGACTT SEQ ID NO: 192
purF	TaqI	TEF271 ACCATCATAAATCGCCTGATTC SEQ ID NO: 193 TEF292 ACCTGCGGCATCTTGTCCTC SEQ ID NO: 194
	HincII	TEF274 ACGGGTTTATTTTGCCTCTG SEQ ID NO: 195
yjgF	ClaI	TEF221 CGCCGGTTTCAGGATTCACGGG SEQ ID NO: 196
	EcorV	TEF281 CTGAACAACGTGAAAGCCAT SEQ ID NO: 197

Vectorette PCR products were band purified and sequenced as described above. Polynucleotide sequences for the atpG, guaB, pnp, purF, and yjgF 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.

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.

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.

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.

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,

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,

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, 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.

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

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

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.

SEQUENCE LISTING

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act tta gct caa gca ccg tat aac acc gag att caa tgg aaa aat ttg   4214
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Ser Asn Tyr Gly Glu Val Gln Lys Leu Leu Phe Asp His Ile Gln Ile
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Pro Ala Glu Asn Ile His Arg Ile Arg Gly Glu Ala Pro Val Glu Ser
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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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Val Phe Asp Trp Ile Ile Leu Gly Met Gly Thr Asp Gly His Thr Ala
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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
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Pro	His	Gln	Thr	Asp	Phe	Asp	Asp	Pro	His	Phe	Ala	Val	Ile	Ala	Lys

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165 170 175

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Glu Ile Leu Lys Glu Ile Gln Thr Thr Pro Ala Glu Gln Leu Pro Tyr
195 200 205

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Asp Lys Asp Ala Ala Lys Leu Leu
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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
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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
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Cys Leu Thr Gln Gln Phe Phe Tyr Ile Trp Gly Glu Gln Ser Ser Gly
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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
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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
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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
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Leu Gln Ala Ile Ile Gly Asn Thr Glu Trp Glu Leu Ala Ile Phe Asp
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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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Ser Arg Leu Arg Trp Gly Glu Ser Tyr Gln Leu Val Pro Leu Asn Asp
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Gln Gln Lys Ile His Val Leu Gln Lys Asn Ala His Gln Arg Gly Ile
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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
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tta caa gcc caa cgt aaa tta acg att ccc ttt gta aaa gaa att tta   2390
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His Gln Leu Asp Asp Glu Thr Leu Asp Asn Phe Tyr Pro Asp Asn Asn
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Gln Phe Phe Tyr Ile Trp Gly Glu Gln Ser Ser Gly Lys Ser His Leu
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Tyr Val Pro Leu Glu Lys Ser Gln Tyr Phe Ser Pro Ala Val Leu Glu
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Asn Leu Glu Gln Gln Gln Leu Val Cys Leu Asp Asn Leu Gln Ala Ile
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Ile Gly Asn Thr Glu Trp Glu Leu Ala Ile Phe Asp Leu Phe Asn Arg
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Ile Lys Ser Val Glu Asn Thr Leu Leu Val Ile Ser Ala Asn Gln Ser
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His Val Leu Gln Lys Asn Ala His Gln Arg Gly Ile Glu Leu Pro Asp
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aaagcggcat tagaggctgg cttaattgct caaccacaat atgaattact ggcagtagca 600

attaataccg gtaccaatct tccttctgtt gcaaccccaa atggtcaagc cgcattctta 660

tttttattga cctcatcact ggcaccatta attcgtcttt cttatggtag aatggtttat 720

atggcattgc cttataccat cgtattatcc tgtattggtt tattgactgt ggaatatatt 780

ttgcctggcg caaccaatgt gctcattcaa attggtttat taaaaccaat gtaatgacaa 840

gtaaaaggag gaaac atg cta agc ttt ttt aag aca ctc tca aca aaa cga 891
Met Leu Ser Phe Phe Lys Thr Leu Ser Thr Lys Arg
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agt gca tgg ttt cta ttg ttt agc tca gct tta cta tta gag gct atc   939
Ser Ala Trp Phe Leu Leu Phe Ser Ser Ala Leu Leu Leu Glu Ala Ile
        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 tcg 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

att ggt tta agc agt gca atc aaa ggc tta atg att agc atc acc cat  1131
Ile Gly Leu Ser Ser Ala Ile Lys Gly Leu Met Ile Ser Ile Thr His
            80                  85                  90

tta gat cta caa ctt tac cct gca cct tgg aaa caa tgt tca gcg gtg  1179
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

ttc ctc cct tca ggc tca tgc agt gaa gta aca tgg caa ttt ctc ggc  1275
Phe Leu Pro Ser Gly Ser Cys Ser Glu Val Thr Trp Gln Phe Leu Gly
125                 130                 135                 140

ttt tct atg gtg caa tgg atc gtc gtc att ttt gca ctc tat acc tta  1323
Phe Ser Met Val Gln Trp Ile Val 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 taagtcataa aaaatggtgc gataaagcac         1419
Gln Arg Arg Leu Phe His
        175

cattttcat ttctcgttcg gtatagatta aatttcttgc acgacaaact gcagggaatg 1479

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gctcatcttc tttaatcgta tcaggcattt gcgtaataag ccaatgtaaa tattctgaac 2019
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<213> Pasteurella multocida

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Leu Leu Phe Ser Ser Ala Leu Leu Leu Glu Ala Ile Ala Leu Tyr Phe
20 25 30

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 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
145 150 155 160

Ile Phe Ile Ser Gln Val Lys Arg Leu Lys Pro Lys Gln Arg Arg Leu
165 170 175

Phe His

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

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<222> (2756)..(3211)

<220>
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gaatttctta tttaccccgt ttttggcttt tgctagaatc ttgcaattga aattaattct 2700

caataccgta taatgttcaa cattattttg cgatacaaat taaaggatta ttaaa atg  2758
                                                              Met
                                                               1

cca caa tta ttc caa ttc tta caa caa tat att gat tac att att cta   2806
Pro Gln Leu Phe Gln Phe Leu Gln Gln Tyr Ile Asp Tyr Ile Ile Leu
          5                  10                  15

ggc tta ctt gcc ttc atg agc ttt att atg gtt tgg ctt gtg att gaa   2854
Gly Leu Leu Ala Phe Met Ser Phe Ile Met Val Trp Leu Val Ile Glu
      20                  25                  30

cgc ttt ctt ttc tta agt cgc gtc aac gtg gca tct tat gaa agc ata   2902
Arg Phe Leu Phe Leu Ser Arg Val Asn Val Ala Ser Tyr Glu Ser Ile
  35                  40                  45

cat gaa tta gac att gac tta caa cgc cac ctc aca gct atc tct aca   2950
His Glu Leu Asp Ile Asp Leu Gln Arg His Leu Thr Ala Ile Ser Thr
50                  55                  60                  65

atc ggt tct aat gca cct tat gta ggt ttg ctt ggt acc gtc att ggt   2998
Ile Gly Ser Asn Ala Pro Tyr Val Gly Leu Leu Gly Thr Val Ile Gly
              70                  75                  80

att ctc tta act ttc tat gaa tta ggt cac tcc ggt ggc gat att gat   3046
Ile Leu Leu Thr Phe Tyr Glu Leu Gly His Ser Gly Gly Asp Ile Asp
          85                  90                  95

gcg gcg gcc att atg gtg cac tta tca tta gcc tta aaa gcc aca gca   3094
Ala Ala Ala Ile Met Val His Leu Ser Leu Ala Leu Lys Ala Thr Ala
      100                 105                 110

gta ggt att tta gtc gcc att cct gca atg gtg tgt tac aac ggt tta   3142
Val Gly Ile Leu Val Ala Ile Pro Ala Met Val Cys Tyr Asn Gly Leu
  115                 120                 125

gga cgt aaa gtc gaa gtt aat cgt ttg aaa tgg ttt gcc tta aat gag   3190
Gly Arg Lys Val Glu Val Asn Arg Leu Lys Trp Phe Ala Leu Asn Glu
130                 135                 140                 145

aaa aaa gcc aaa caa caa gca tagggagccg tcatgaaaaa gtttgatgaa      3241
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Lys Lys Ala Lys Gln Gln Ala
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atcaacatta tccctttat tgacatcatg ttggtactat tggctatcgt tctgattaca 3301

gcctctttta tttcacaagg taaaatccaa gtgaatgtac caaaagcaag ttcaacagtt 3361

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cgttccatct taataatgcc ggcgtaatta gtaatgcgcg aatcagcaaa tcttccggct 4261

cagaagaatt agataacgct gcactggtag ctgtcaataa tgcccgtcca attggtccac 4321

tgcctgttgg tatgccaaat gaagtgagcg ttcctgtcag tttcagaatc acaaattaaa 4381

aaagtgcggt aaaatttacc gcacttttt ctctctatta gaatt 4426

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<212> PRT
<213> Pasteurella multocida

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

Glu Arg Phe Leu Phe Leu Ser Arg Val Asn Val Ala Ser Tyr Glu Ser
35 40 45

Ile His Glu Leu Asp Ile Asp Leu Gln Arg His Leu Thr Ala Ile Ser
50 55 60

Thr Ile Gly Ser Asn Ala Pro Tyr Val Gly Leu Leu Gly Thr Val Ile

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 65                  70                  75                  80

Gly Ile Leu Leu Thr Phe Tyr Glu Leu Gly His Ser Gly Gly Asp Ile
                85                  90                  95

Asp Ala Ala Ala Ile Met Val His Leu Ser Leu Ala Leu Lys Ala Thr
            100                 105                 110

Ala Val Gly Ile Leu Val Ala Ile Pro Ala Met Val Cys Tyr Asn Gly
        115                 120                 125

Leu Gly Arg Lys Val Glu Val Asn Arg Leu Lys Trp Phe Ala Leu Asn
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Glu Lys Lys Ala Lys Gln Gln Ala
145                 150
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aactcatcga gcatcaaatg aaactgcaat ttattcatat caggattatc aataccatat 180

ttttgaaaaa gccgtttctg taatgaagga gaaaactcac cgaggcagtt ccataggatg 240

gcaagatcct ggtatcggtc tgcgattccg actcgtccaa catcaataca acctattaat 300

ttcccctcgt caaaaataag gttatcaagt gagaaatcac catgagtgac gactgaatcc 360

ggtgagaatg gcaaaagctt atgcatttct ttccagactt gttcaacagg ccagccatta 420

cgctcgtcat caaaatcact cgcatcaacc aaaccgttat tcattcgtga ttgcgcctga 480

gcgagacgaa atacgcgatc gctgttaaaa ggacaattac aaacaggaat cga atg     536
                                                          Met
                                                            1

caa ccg gcg cag gaa cac tgc cag cgc atc aac aat att gtt aac caa     584
Gln Pro Ala Gln Glu His Cys Gln Arg Ile Asn Asn Ile Val Asn Gln
          5                  10                  15

gaa aac ggt tta ttc cat aca ctc ggt aat atg atg tta gaa gca gag     632
Glu Asn Gly Leu Phe His Thr Leu Gly Asn Met Met Leu Glu Ala Glu
      20                  25                  30

cgt tct gtt tat aat att ggc gat att tat gcg agt aaa aaa tta aca     680
Arg Ser Val Tyr Asn Ile Gly Asp Ile Tyr Ala Ser Lys Lys Leu Thr
  35                  40                  45
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gtt cat act cat aat ttg att aat gat gtg cgt tta tct ggc aat gtg   728
Val His Thr His Asn Leu Ile Asn Asp Val Arg Leu Ser Gly Asn Val
 50                  55                  60                  65

agt tat aag cct atc ggt tca agt cgt gat tat gat atc agt cgt gtt   776
Ser Tyr Lys Pro Ile Gly Ser Ser Arg Asp Tyr Asp Ile Ser Arg Val
                 70                  75                  80

gcg gta cat ggt tgg cac aat aat gtt tat aag ctc aac tta aat ctg   824
Ala Val His Gly Trp His Asn Asn Val Tyr Lys Leu Asn Leu Asn Leu
             85                  90                  95

caa gaa caa gat aaa acc gat att aaa gtt gtg aaa atg ggg gct atc   872
Gln Glu Gln Asp Lys Thr Asp Ile Lys Val Val Lys Met Gly Ala Ile
        100                 105                 110

cgt tct gat ggt gat ttt gac ttt aag gga ata aag gcg aca tca tca   920
Arg Ser Asp Gly Asp Phe Asp Phe Lys Gly Ile Lys Ala Thr Ser Ser
    115                 120                 125

gaa tca aaa ccg cag tta att aat cat gga tta att aat gtc aaa gga   968
Glu Ser Lys Pro Gln Leu Ile Asn His Gly Leu Ile Asn Val Lys Gly
130                 135                 140                 145

aca ttt aat gcg gaa gct gat caa gtg gtg aac caa atg aaa gcg ttt   1016
Thr Phe Asn Ala Glu Ala Asp Gln Val Val Asn Gln Met Lys Ala Phe
                150                 155                 160

aac caa aat gca tta gca agc gtg ttt aag aat cca gcg aaa atc acg   1064
Asn Gln Asn Ala Leu Ala Ser Val Phe Lys Asn Pro Ala Lys Ile Thr
            165                 170                 175

atg tac tat caa cca ctt act cgt tat att tgg aca cca tta tcg ggt   1112
Met Tyr Tyr Gln Pro Leu Thr Arg Tyr Ile Trp Thr Pro Leu Ser Gly
        180                 185                 190

aat gca tcg cgt gaa ttt aac aat tta gag tct ttc ctc gat gcc ttg   1160
Asn Ala Ser Arg Glu Phe Asn Asn Leu Glu Ser Phe Leu Asp Ala Leu
    195                 200                 205

ttt ggc tca aca aca atc tta aaa tca agt ttc tat agt acg gaa aat   1208
Phe Gly Ser Thr Thr Ile Leu Lys Ser Ser Phe Tyr Ser Thr Glu Asn
210                 215                 220                 225

ttt agt gct tat cag ctt cta tct cat att cag cat tca cca atg tac   1256
Phe Ser Ala Tyr Gln Leu Leu Ser His Ile Gln His Ser Pro Met Tyr
                230                 235                 240

caa aaa gcg atg gca caa gtg ttt ggt gca gag tgg cat agt aaa tcc   1304
Gln Lys Ala Met Ala Gln Val Phe Gly Ala Glu Trp His Ser Lys Ser
            245                 250                 255

tat gat gag atg cga aac aaa tgg aaa agc ttt aaa gaa aat cca aca   1352
Tyr Asp Glu Met Arg Asn Lys Trp Lys Ser Phe Lys Glu Asn Pro Thr
        260                 265                 270

gat ttc att tat tac cca tca gaa aaa gca aaa atc cta gcg gga aaa   1400
Asp Phe Ile Tyr Tyr Pro Ser Glu Lys Ala Lys Ile Leu Ala Gly Lys
    275                 280                 285

cta gaa ggt aag ctt aca acg cta caa aat ggt gaa tat gcc gaa cgt   1448
Leu Glu Gly Lys Leu Thr Thr Leu Gln Asn Gly Glu Tyr Ala Glu Arg
290                 295                 300                 305
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ggt aag ttt gat gag agt atc caa att ggt aaa cac caa tta tcg cta   1496
Gly Lys Phe Asp Glu Ser Ile Gln Ile Gly Lys His Gln Leu Ser Leu
                310                 315                 320

cca tca gta gag ctt aaa gcg gag ttt agt gat aaa gaa cgt ttg gaa   1544
Pro Ser Val Glu Leu Lys Ala Glu Phe Ser Asp Lys Glu Arg Leu Glu
            325                 330                 335

gag gac ggg gta gat tta tcc tcg atc gcc gaa ctc tta gaa atg cca   1592
Glu Asp Gly Val Asp Leu Ser Ser Ile Ala Glu Leu Leu Glu Met Pro
        340                 345                 350

aac tta ttt att gat aat agt atc caa tta gaa aag aaa aag ttg tct   1640
Asn Leu Phe Ile Asp Asn Ser Ile Gln Leu Glu Lys Lys Lys Leu Ser
    355                 360                 365

cct att gag gat cta gat gaa gaa cca cgt aaa aat ctg gat ata gaa   1688
Pro Ile Glu Asp Leu Asp Glu Glu Pro Arg Lys Asn Leu Asp Ile Glu
370                 375                 380                 385

gaa agc cat tct aat tca tcg gat gac gtg ctt agc atg aat gat gat   1736
Glu Ser His Ser Asn Ser Ser Asp Asp Val Leu Ser Met Asn Asp Asp
                390                 395                 400

gag tct gat aca gac gat agc aag tgg agt atg ggc aat gat gag aaa   1784
Glu Ser Asp Thr Asp Asp Ser Lys Trp Ser Met Gly Asn Asp Glu Lys
            405                 410                 415

gag atg ccc gat gat aag ctg ggt ata agt cgt gat gat cgt gga aat   1832
Glu Met Pro Asp Asp Lys Leu Gly Ile Ser Arg Asp Asp Arg Gly Asn
        420                 425                 430

aaa cca cct cgt act gat cct aca gtt gat tat ctt aac cct gat gaa   1880
Lys Pro Pro Arg Thr Asp Pro Thr Val Asp Tyr Leu Asn Pro Asp Glu
    435                 440                 445

ttc ttt gaa aat ggt tat ctc ttg aat gag cta cta cag gag ctt gga   1928
Phe Phe Glu Asn Gly Tyr Leu Leu Asn Glu Leu Leu Gln Glu Leu Gly
450                 455                 460                 465

gaa gag ccg tta cta aaa gaa ggg gaa gat cat ttt aaa cgt tct acc   1976
Glu Glu Pro Leu Leu Lys Glu Gly Glu Asp His Phe Lys Arg Ser Thr
                470                 475                 480

aat cta gtc cgt cta ggc gag aga gat agg caa aat aga gaa aag aga   2024
Asn Leu Val Arg Leu Gly Glu Arg Asp Arg Gln Asn Arg Glu Lys Arg
            485                 490                 495

gaa aaa gag ggg tat ttt gat ctg cct ggt aca tta gat atg aaa ctg   2072
Glu Lys Glu Gly Tyr Phe Asp Leu Pro Gly Thr Leu Asp Met Lys Leu
        500                 505                 510

cag gag tta ttc gaa aaa aga aaa caa aaa cac gaa gca gaa cag aaa   2120
Gln Glu Leu Phe Glu Lys Arg Lys Gln Lys His Glu Ala Glu Gln Lys
    515                 520                 525

gca aga ata gaa aaa gca ctt cta caa aaa tca gaa caa caa gaa aaa   2168
Ala Arg Ile Glu Lys Ala Leu Leu Gln Lys Ser Glu Gln Gln Glu Lys
530                 535                 540                 545

cgt gtt gaa gaa cgt aag caa gag gaa aaa cgt caa gcg caa gat aaa   2216
Arg Val Glu Glu Arg Lys Gln Glu Glu Lys Arg Gln Ala Gln Asp Lys
                550                 555                 560
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att gct aag caa gta gaa att gca aaa gaa atg caa cgg gta gaa gaa   2264
Ile Ala Lys Gln Val Glu Ile Ala Lys Glu Met Gln Arg Val Glu Glu
            565                 570                 575

att cgc cag aga gaa aaa caa ctt gcg atc caa ctg caa gaa gaa gag   2312
Ile Arg Gln Arg Glu Lys Gln Leu Ala Ile Gln Leu Gln Glu Glu Glu
        580                 585                 590

aag aaa caa caa gaa gaa aaa cat tta tcc gag gag aaa aaa caa gct   2360
Lys Lys Gln Gln Glu Glu Lys His Leu Ser Glu Glu Lys Lys Gln Ala
    595                 600                 605

gaa cag aaa caa aaa gct gag gag aaa gtt gca caa gaa aga tta gac   2408
Glu Gln Lys Gln Lys Ala Glu Glu Lys Val Ala Gln Glu Arg Leu Asp
610                 615                 620                 625

att gaa caa cag aaa gcg tat gaa gaa atg gcg aag cga gag gca gag   2456
Ile Glu Gln Gln Lys Ala Tyr Glu Glu Met Ala Lys Arg Glu Ala Glu
                630                 635                 640

gca tca aaa aat gtt tta ttg aaa gcg att gat gaa gaa cgt cca aaa   2504
Ala Ser Lys Asn Val Leu Leu Lys Ala Ile Asp Glu Glu Arg Pro Lys
            645                 650                 655

gtg gaa act gat cca ctt ttc cgt aca aaa ttg aaa tat atc aat caa   2552
Val Glu Thr Asp Pro Leu Phe Arg Thr Lys Leu Lys Tyr Ile Asn Gln
        660                 665                 670

gat gac tat gct ggt gca aat tat ttc ttc aat aaa gtt ggt tta aat   2600
Asp Asp Tyr Ala Gly Ala Asn Tyr Phe Phe Asn Lys Val Gly Leu Asn
    675                 680                 685

aca aaa ggt cat caa aaa gta aat gtg tta ggg gat aac tat ttt gat   2648
Thr Lys Gly His Gln Lys Val Asn Val Leu Gly Asp Asn Tyr Phe Asp
690                 695                 700                 705

cat caa gtg att act cgc tcg att gag aaa aaa gta gat aac cac ctt   2696
His Gln Val Ile Thr Arg Ser Ile Glu Lys Lys Val Asp Asn His Leu
                710                 715                 720

aac caa aaa tac aat ctc agc gat gtg gaa tta gtt aaa cag ctg atg   2744
Asn Gln Lys Tyr Asn Leu Ser Asp Val Glu Leu Val Lys Gln Leu Met
            725                 730                 735

gac aat tcc aca aca caa gcg cag gag ttg gat ttg aaa cta ggt gcg   2792
Asp Asn Ser Thr Thr Gln Ala Gln Glu Leu Asp Leu Lys Leu Gly Ala
        740                 745                 750

gca tta act aaa gaa caa caa gct aac ttg acc caa gat atc gtt tgg   2840
Ala Leu Thr Lys Glu Gln Gln Ala Asn Leu Thr Gln Asp Ile Val Trp
    755                 760                 765

tat gtc aaa acg aag gta aag ggc aaa gat gtg ttt gtt cca aag gtt   2888
Tyr Val Lys Thr Lys Val Lys Gly Lys Asp Val Phe Val Pro Lys Val
770                 775                 780                 785

tat ttc gct tct gaa acg ctc gta gaa gcc caa aaa tta caa ggt tta   2936
Tyr Phe Ala Ser Glu Thr Leu Val Glu Ala Gln Lys Leu Gln Gly Leu
                790                 795                 800

ggc act ggg act atc aga gtt ggt gaa gct aag att aaa gcc aaa gat   2984
Gly Thr Gly Thr Ile Arg Val Gly Glu Ala Lys Ile Lys Ala Lys Asp
            805                 810                 815
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gtg gtg aat acc ggg aca tta gct ggg aga aaa ctc aat gtt gaa gcg   3032
Val Val Asn Thr Gly Thr Leu Ala Gly Arg Lys Leu Asn Val Glu Ala
        820                 825                 830

agt aat aaa atc aaa aat caa ggg agt atc tta agt act caa gaa aca   3080
Ser Asn Lys Ile Lys Asn Gln Gly Ser Ile Leu Ser Thr Gln Glu Thr
    835                 840                 845

cgt tta gtc ggg cgt aaa ggt att gaa aac gta tct cgt tca ttt gca   3128
Arg Leu Val Gly Arg Lys Gly Ile Glu Asn Val Ser Arg Ser Phe Ala
850                 855                 860                 865

aat gat gaa tta gga gtc act gca caa cgc tca gaa atc aaa acg gaa   3176
Asn Asp Glu Leu Gly Val Thr Ala Gln Arg Ser Glu Ile Lys Thr Glu
                870                 875                 880

ggt cat tta cat ctt gaa aca gat aag gat tca act att gat gta caa   3224
Gly His Leu His Leu Glu Thr Asp Lys Asp Ser Thr Ile Asp Val Gln
            885                 890                 895

gca tcg gat att aaa gca aaa aca agc ttt gtg aag act ggt gat gtg   3272
Ala Ser Asp Ile Lys Ala Lys Thr Ser Phe Val Lys Thr Gly Asp Val
        900                 905                 910

aat ctc aaa aat aca tac aat act aaa cat gcc tac cgt gag aaa ttc   3320
Asn Leu Lys Asn Thr Tyr Asn Thr Lys His Ala Tyr Arg Glu Lys Phe
    915                 920                 925

tcg ccg agt gca cta caa gtt gca gaa ctt gat gtg gca ggg ctt aaa   3368
Ser Pro Ser Ala Leu Gln Val Ala Glu Leu Asp Val Ala Gly Leu Lys
930                 935                 940                 945

gtc cca ctt tta ggc gtg tcg tct cca tcc agt tat tca gag cat act   3416
Val Pro Leu Leu Gly Val Ser Ser Pro Ser Ser Tyr Ser Glu His Thr
                950                 955                 960

agt gag gca act tca gag gga tca atc ttc gaa gta ggg cac tta cat   3464
Ser Glu Ala Thr Ser Glu Gly Ser Ile Phe Glu Val Gly His Leu His
            965                 970                 975

ctt gcg gta gac aga gat gtg aac caa gcg ggg agt aaa att aag gct   3512
Leu Ala Val Asp Arg Asp Val Asn Gln Ala Gly Ser Lys Ile Lys Ala
        980                 985                 990

aag tat acc act ggt gtt gtg aaa ggg aac ttt aat act gaa gcg ggc   3560
Lys Tyr Thr Thr Gly Val Val Lys Gly Asn Phe Asn Thr Glu Ala Gly
    995                1000                1005

aag aat att aaa cat gtc gaa aaa gaa gaa tat agt tca cag cta ttt   3608
Lys Asn Ile Lys His Val Glu Lys Glu Glu Tyr Ser Ser Gln Leu Phe
1010                1015                1020                1025

gct tca gca cac gcg agt ggt ggt ggc acc tca gtt cgt tat gac tat   3656
Ala Ser Ala His Ala Ser Gly Gly Gly Thr Ser Val Arg Tyr Asp Tyr
                1030                1035                1040

aac agc caa gat ggt ggc aat gcc tct gtt ggt gtt ccg aca aac cat   3704
Asn Ser Gln Asp Gly Gly Asn Ala Ser Val Gly Val Pro Thr Asn His
            1045                1050                1055

act gga gtt ggg gca gag gca gga atg tca ttc acc cat acc aaa gac   3752
Thr Gly Val Gly Ala Glu Ala Gly Met Ser Phe Thr His Thr Lys Asp
        1060                1065                1070
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aaa gaa aca ctg ctc act cac acc aat agt gaa tta caa gtc aaa cat   3800
Lys Glu Thr Leu Leu Thr His Thr Asn Ser Glu Leu Gln Val Lys His
   1075                1080                1085

ggg aaa tta cat gtg ctt ggt tat gcc gat att ggt gga gta gat att   3848
Gly Lys Leu His Val Leu Gly Tyr Ala Asp Ile Gly Gly Val Asp Ile
1090                1095                1100                1105

aat act aaa cta cca gaa gat gca caa agc aaa gca cag aaa gag ata   3896
Asn Thr Lys Leu Pro Glu Asp Ala Gln Ser Lys Ala Gln Lys Glu Ile
                1110                1115                1120

gcg gct agc aag cca gag aag acc gag caa tct gca cag gat gtg gct   3944
Ala Ala Ser Lys Pro Glu Lys Thr Glu Gln Ser Ala Gln Asp Val Ala
            1125                1130                1135

caa gct caa tca aat gcc aat aag gat aag gaa aat aaa gcc cca gaa   3992
Gln Ala Gln Ser Asn Ala Asn Lys Asp Lys Glu Asn Lys Ala Pro Glu
        1140                1145                1150

ata aaa gaa tta tca gag gct gaa atc gcg gat ctc atg tca gaa aaa   4040
Ile Lys Glu Leu Ser Glu Ala Glu Ile Ala Asp Leu Met Ser Glu Lys
   1155                1160                1165

tca aaa gcg tat ttt gat gat ttt gca gag caa gcg aaa aaa gca cct   4088
Ser Lys Ala Tyr Phe Asp 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
            1205                1210                1215

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
   1235                1240                1245

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
Asn Val Leu Ser Gly Glu Lys Thr Arg Glu Thr Thr Glu Thr Val Ser
1330                1335                1340                1345

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
                1350                1355                1360

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 tcg   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
                1430                1435                1440

tat aat ctt tcc gct ggc gtt gca ctt tct agt gca aca att gct acc   4904
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

caa acg cat gac tta aat ctt gag ggg gga tat ctt gtc agc aac gat   5048
Gln Thr His Asp Leu Asn Leu Glu Gly Gly Tyr Leu Val Ser Asn Asp
1490                1495                1500                1505

aag gat aat cag ctg aaa gtt acc ggc gat gtc aca act aaa gcc ctt   5096
Lys Asp Asn Gln Leu Lys Val Thr Gly Asp Val Thr Thr Lys Ala Leu
                1510                1515                1520

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 ggc 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
1570                1575                1580                1585
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aag gca aaa gct gtc aca cgt gat gat act tac gca agt acg caa ttt   5336
Lys Ala Lys Ala Val Thr Arg Asp Asp Thr Tyr Ala Ser Thr Gln Phe
                1590                1595                1600

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
            1605                1610                1615

aag ctg tca gca cca aac aat gac acc gat atg gcg tca ggc tcc aca   5432
Lys Leu Ser Ala Pro Asn Asn Asp Thr Asp Met Ala Ser Gly Ser Thr
        1620                1625                1630

tta cgc tcg cgt tct act aca gaa gaa gca gat gta cca aca aca aga   5480
Leu Arg Ser Arg Ser Thr Thr Glu Glu Ala Asp Val Pro Thr Thr Arg
    1635                1640                1645

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
1650                1655                1660                1665

tat gaa agt gca gat gct gtt gta cca aca cca cgt agt aga aat gtg   5576
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

gtc ggt gat aac aat gct gat ctt gtt cgt cat aaa acg gca act agt   5720
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
1730                1735                1740                1745

ggt gat aaa aat gca gat atg aga cgt cat aac gcg gca ggt aca aca   5816
Gly Asp Lys Asn Ala Asp Met Arg Arg His Asn Ala Ala Gly Thr Thr
                1750                1755                1760

gac tat gcc gat gtc gtg caa gca cat aca aga aag gca gat gat cca   5864
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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gac agt gct tat aaa aca tgg caa ttg ctt gat caa ttt gcc aac aaa   6104
Asp Ser Ala Tyr Lys Thr Trp Gln Leu Leu Asp Gln Phe Ala Asn Lys
          1845                1850                1855

ggc gga gat gcg gtc ttc tta cgc cct gca aca gaa atg aaa tgt gca   6152
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
Gly 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 ggg 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
          2085                2090                2095
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tta aaa ccc act tat tta ggt atg tta cgt gga tta gct taaggagcgt    6873
Leu Lys Pro Thr Tyr Leu Gly Met Leu Arg Gly Leu Ala
       2100                2105                2110

tga                                                              6876
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<210> 16
<211> 2110
<212> PRT
<213> Pasteurella multocida

<400> 16

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Met Gln Pro Ala Gln Glu His Cys Gln Arg Ile Asn Asn Ile Val Asn
  1               5                  10                  15

Gln Glu Asn Gly Leu Phe His Thr Leu Gly Asn Met Met Leu Glu Ala
             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
        195                 200                 205

Leu Phe Gly Ser Thr Thr Ile Leu Lys Ser Ser Phe Tyr Ser Thr Glu
    210                 215                 220

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

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
            260                 265                 270
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Thr Asp Phe Ile Tyr Tyr Pro Ser Glu Lys Ala Lys Ile Leu Ala Gly
        275                 280                 285

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 Leu Glu Met
            340                 345                 350

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

Leu Gly Thr Gly Thr Ile Arg Val Gly Glu Ala Lys Ile Lys Ala Lys
                805                 810                 815

Asp Val Val Asn Thr Gly Thr Leu Ala Gly Arg Lys Leu Asn Val Glu
            820                 825                 830

Ala Ser Asn Lys Ile Lys Asn Gln Gly Ser Ile Leu Ser Thr Gln Glu
        835                 840                 845

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
945                 950                 955                 960

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
    1010                1015                1020

Phe  Ala Ser Ala His Ala  Ser Gly Gly Gly Thr  Ser Val Arg Tyr Asp
1025                1030                1035                1040

Tyr Asn Ser Gln Asp  Gly Gly Asn Ala Ser  Val Gly Val Pro Thr  Asn
                1045                1050                1055

His Thr Gly Val  Gly Ala Glu Ala Gly  Met Ser Phe Thr His  Thr Lys
            1060                1065                1070

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
    1090                1095                1100

Ile  Asn Thr Lys Leu Pro  Glu Asp Ala Gln Ser  Lys Ala Gln Lys Glu
1105                1110                1115                1120

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

Ala Gln Ala Gln  Ser Asn Ala Asn Lys  Asp Lys Glu Asn Lys  Ala Pro
            1140                1145                1150

Glu Ile Lys  Glu Leu Ser Glu Ala  Glu Ile Ala Asp Leu  Met Ser Glu
        1155                1160                1165

Lys Ser  Lys Ala Tyr Phe Asp  Asp Phe Ala Glu Gln  Ala Lys Lys Ala
    1170                1175                1180

Pro  Glu Asn Asn Arg Phe  Glu Leu Ser Ala Lys  Glu Ile Lys Ser Ser
1185                1190                1195                1200

Lys Gln Lys Asp Gln  Tyr Asp His Glu Ser  Glu Arg Thr Thr Phe  Lys
                1205                1210                1215

Val Gly Pro Glu  Ala Glu Ala His Ser  Ala Val Ala Asp Met  Val Ser
            1220                1225                1230

His Leu Val  Lys Glu Tyr Arg Asp  Ala Gln Asn Gly Thr  Lys Gln Asp
        1235                1240                1245

Gly Thr  Val Ala Leu Gln His  Ala Ser Asp Val Leu  Asn Ile Val Thr
    1250                1255                1260

Gly  Asp Leu Ala Gly Ser  Ser Ala Lys Leu Ser  Val Glu Arg Thr His
1265                1270                1275                1280
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Glu Thr Lys Arg Thr  Thr Glu Thr Gly Asp  Ile Val Thr Lys Ile  Gly
                1285                1290                1295

Gly Asn Val Thr  Leu Ser Ala Arg Ser  Gly Ser Val Asn Leu  Lys Asn
            1300                1305                1310

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

Val Asn  Val Leu Ser Gly Glu  Lys Thr Arg Glu Thr  Thr Glu Thr Val
    1330                1335                1340

Ser  Arg Gln Lys Leu Ser  His Gly Val Asn Ala  Gly Cys Ser Met Met
1345                1350                1355                1360

Ser Gly Ala Cys Thr  Ala Gly Val Ser Thr  Ser Leu Glu Gly Asn  Glu
                1365                1370                1375

Ser Tyr Thr Ser  Glu Arg Glu Thr Ala  Gln Asn Asn Ser Phe  Leu Lys
            1380                1385                1390

Ala Arg Asn  Met Lys Val Glu Ala  Gly Arg Asp Phe Asn  Val Val Ser
        1395                1400                1405

Ser Asn  Ile Asp Ala Asp Lys  Leu Asp Leu His Val  Lys Gly Lys Thr
    1410                1415                1420

Asn  Val Val Ser Lys Gln  Asp Thr Leu Gln Lys  Val Thr His Gly Val
1425                1430                1435                1440

Asp Tyr Asn Leu Ser  Ala Gly Val Ala Leu  Ser Ser Ala Thr Ile  Ala
                1445                1450                1455

Thr Pro Thr Gly  Asn Val Gly Phe Gly  Tyr Thr Asn Glu Thr  Glu Ser
            1460                1465                1470

Lys Arg Thr  Val Asn Gln Gln Ala  Gly Ile Lys Ala Asn  Lys Ile Thr
        1475                1480                1485

Gly Gln  Thr His Asp Leu Asn  Leu Glu Gly Gly Tyr  Leu Val Ser Asn
    1490                1495                1500

Asp  Lys Asp Asn Gln Leu  Lys Val Thr Gly Asp  Val Thr Thr Lys Ala
1505                1510                1515                1520

Leu His Asp Gln His  Asp Lys Asp Gly Gly  Thr Phe Gly Leu Ser  Val
                1525                1530                1535

Gly Ile Ser Glu  Arg Gly Thr Thr Ala  Phe Asn Val Arg Gly  Gly Arg
            1540                1545                1550

Ala Glu Gln  Lys His Tyr Asn Ala  Thr Gln Lys Ser Thr  Leu Ser Gly
        1555                1560                1565

Val Asp  Thr Ser Gln Ala Asn  Val Ser Gly Gln Val  Asn Thr Asp Leu
    1570                1575                1580

Thr  Lys Ala Lys Ala Val  Thr Arg Asp Asp Thr  Tyr Ala Ser Thr Gln
1585                1590                1595                1600

Phe Ser Phe Glu Val  Ala Asp Ile Val Glu  Leu Gly Gln Arg Ala  Lys
                1605                1610                1615
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Asn Lys Leu Ser  Ala Pro Asn Asn Asp  Thr Asp Met Ala Ser  Gly Ser
            1620                 1625                 1630

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

Ile  Tyr Glu Ser Ala Asp  Ala Val Val Pro Thr  Pro Arg Ser Arg Asn
1665                 1670                 1675                 1680

Val Asp Ser Thr Asp  Leu Val Asp Asn Pro  Leu Tyr Ala Ser Ala  Thr
                1685                 1690                 1695

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
                1765                 1770                 1775

Pro Leu Pro Ala  Leu Pro Asn Gln Gly  Lys Ala Arg Thr Val  Asn Asp
            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
```

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

Ile Ala Pro Leu Glu Glu Leu Trp Ala Thr Trp Ala Ile Lys Thr Leu
2085 2090 2095

Gly Leu Lys Pro Thr Tyr Leu Gly Met Leu Arg Gly Leu Ala
2100 2105 2110

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aaccagcccc tatcaacaaa agttgttttt caattagtga aagatttgac ggaagtttta 120

taccgttctg gctacgtgac aagtgcaatt ggtttaaaaa attcaaaaat cagcaatggc 180

gatcttgaat ttattgtact gtggggaaga actcgcgatc tgtttgtgaa tggggagaaa 240

ccaacccgtt ttagagataa aacaatgtta tcagtcctac ccaatttaat cggaaatcgc 300

ttaagtattc acgacattga ccagttgatc gaaatcttaa atactacgaa taaaaaagcc 360

acagtgaatg tggttgcaag tgaagaaaaa ggcagctcaa atctaaatat tgaaagacaa 420

tatgatgttt ttccgcaagt gagtgtcgga ttcaataatt caggtgctgg caataatgcc 480

aatgggcgta atcaagctac attgaatatt gcttggagtg atctattagg cacgaatgat 540

cgttggagtt tctcgagtag ttaccgttta tataaaaatc atcatgctaa ccagcaacgc 600

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aattatactt tgtcttacag tcagcctata ggcttttcta cagtagaaat taaagcatcg 660

gaatctacgt atgaaaaaga acttcgcggt ataaatactc attcttctca tgggaaaacc 720

caaagcttag ctgtcaagct gatgcatgtg ttattgcgta ataaggagag tattttatct 780

acatataccg agttcgagtt taaaaaacgg attagttatt tttctgatat tttgattggg 840

aaatatcaca ataataaagt gagcgtaggg ttatcttaca tgactaattt tgcttacggg 900

aagctttaca gcgacattgc ttacgcgaat gggttgagat ggtttggggc gaattattca 960

gcatatgatg caaatcgtga aaaaaccttа aaattattgt caggaagtat taattggcag 1020

cgtccaatat ccctgtttga acgtgcgatg aattatcaat tacgtattgg tgcccaatat 1080

ggttttgata gtttgtattc tgaaaatcaa ttttcaattg gtgatgaata tacagtaaga 1140

ggatttaaag gtggtgcggt ttctggtgat agtggtgcgt atttatcaca aacactgacg 1200

gttccttttt atccacaaaa agcatattta tctcaggtat ccccttttat tggatttgat 1260

atgggtaaag tacatattaa atcaaagcat aaaacaacca ctttagtcgg ttttgcccta 1320

ggcttgaaaa cgcaaataaa gttattttca ttatcattaa cctatgcaca accaatgaat 1380

ggtgtgagtg gtgttacgca acatcgtcaa aaaccgattt attatttctc aggatcactt 1440

tctttttaat ctcttttaag tttaaggatt aacttaat atg aac aaa aat cgt tac 1496
                                        Met Asn Lys Asn Arg Tyr
                                          1               5

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

att tct gtt cct gtt ttg gct gag gga aaa ggg gat gaa aga aat caa   1784
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 gtg 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 gtg 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 gtg gta   2648
Asn Glu Gly Asp Leu Glu Leu Gly Asn Thr Ile Gln Gln Thr Val Val
375                 380                 385                 390
```

```
aaa aaa gac cga aat att cga gcc aag aaa aaa att gaa gtg aaa aac   2696
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 tcg   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                 470

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 tcg 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                 550

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
            570                 575                 580

att aga gct aaa gat gcg tta ac                                   3247
Ile Arg Ala Lys Asp Ala Leu
        585
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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

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

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
            580                 585
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Val Asp Leu Ala Gly Glu Lys Val Ser Leu Asn Phe Gly Asp Ile Ile
  1               5                  10                  15
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```
cat gct tac caa aac cag ccc cta tca aca aaa gtt gtt ttt caa tta   96
His Ala Tyr Gln Asn Gln Pro Leu Ser Thr Lys Val Val Phe Gln Leu
                20                  25                  30

gtg aaa gat ttg acg gaa gtt tta tac cgt tct ggc tac gtg aca agt   144
Val Lys Asp Leu Thr Glu 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                 320

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 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                 400

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 ggc 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 taagtttaag gattaactta atatgaacaa aaatcgttac   1496
Ser Phe

aaactcattt ttagtcaagt caaaggttgt ctcgttcctg tggcagaatg tattaactca 1556

gctattagca atggttcatc tgattcaaca tccacatcag aacaagttga agaggaacct 1616

ttccttctag aacaatattc actttcctcc gtgtctttat tagtaaaaag cacgttcaat 1676

cctgtttcgt atgcaatgca attgacttgg aaacagcttt ctattttatt tttaactgtg 1736
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atttctgttc ctgttttggc tgagggaaaa ggggatgaaa gaaatcaatt aacagtgatt 1796

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ttaacttta aagaaaaaac cagtttttta acagagggca ataattttat tagagctaaa 3236

gatgcgttaa c 3247

<210> 20
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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
465 470 475 480

Ser Phe

<210> 21
<211> 1170
<212> DNA
<213> Pasteurella multocida

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<221> CDS
<222> (639)..(1022)

<220>
<223> greA

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gtacgataag atcgccatgc atttcattgt tttttatttt tccattggtt aatagactgg 180

tttcaaattg aaattggtca cttagtacga gtttggcggt taaggcggtg agcacttttt 240

gtgtactggc gggtaacata aaggtactgg cttggtgcgc tacaattttt tcattacgat 300

ttaagttttt agccacaaaa cctaggctgg tcccttcggg taaatgagcg ttgatttcag 360

caagatcaat ctcagcataa ctgaaatgac tgacgagtaa actacatata agtatcgttc 420

gtttgaaaag gcgtaaaagc gtggcagtaa aaaaagaaga tattttatac ataattggct 480

cgagcagttg ctatttttttt attgtcgaac aataatagta tttgaaccct cgagagtaaa 540

tccttttctc gttaaacact tatttttttta ttcaactacg gcattgtttt tacaatgttg 600

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tggttttgtt 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


<210> 22
<211> 128
<212> PRT
<213> Pasteurella multocida

<400> 22
Met Lys Gln Ile Pro Met Thr Ile Arg Gly Ala Glu Gln Leu Arg Gln
  1               5                  10                  15

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 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
<211> 4666
<212> DNA
<213> Pasteurella multocida

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<222> (980)..(2440)

<220>
<223> guaB

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tcatcaattc ctgcttgttc aaaatgttgt aaacgtgcaa tcaacttttt acctaattct 120

gcgatcaatt tattccgatc aatcgttggt aatacttcaa tcagctctgc ccaaggttga 180

tcaatttgct gtgtttgttt tgggaaagac aaattaatgc caaagccaat cacgagatta 240

tgttgattat tctgacgatt ggcgatttcg accaaaatcc ctgctaattt gcgcccatgt 300

aatagcacat catttggcca ttttaatcca atgttcaaag cacctgcttg ctttagcgtt 360

tctgcgattg ccatacccac tactaaactc aagccttcta aattgacctt ttggtcacat 420

gcccaataca aactcataat cacttgtcca gcaaaaggag aaagccattg acgaccacgt 480

cgtccacgtc ccgcagtttg atattctgct aagcaaatag cgccttttcc caaatgtgca 540

atattgtcaa gcaagaattg attggtcgag ttaataatcg gcttaatata aagtgggtaa 600

ggtgctaacg cttgcgtcaa ataagattca tttaagcgac ttaattgagg tatgagacga 660

aaatgttgga cttgctgttc tatttgtatc ccttgttgtt tcaatttttc gatattgtgt 720

aagatatctt gttctgaata acctaaaagt gcagtcaatt ctgctaaaga aagttgttga 780

tagctagcga gtaatgcaag tacgttttgc ataaaaatcc ttatttatat aaccaaagag 840

aggcaactta ttatagacaa tgattttctc gaaaatcgat aaaaaaatcc attttcaaac 900

agcaacgaaa tctgtataat gcgaccgcaa tatttttttac 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

ggt 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

ggt 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

ggt 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

ggt att cct gtg att gca gat ggc ggt atc cgt ttc tct ggt gat att   2020
Gly Ile Pro Val Ile Ala Asp Gly 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

ttaggtgggg attatcccca cctaagttta ttttaaataa caacgttaat agagaagctt 2510

atttttatgt atggcattaa aattaaaaat gttattaaac tttttctatt aaagttttta 2570

agaaataaat atcgatataa aatcaatatt caacatcatc tcattagtat tgaaggaaaa 2630

tgcggtgagt ttgatttaag ccagctaaac tatgtttatt tggtgaaaga tcctgagata 2690

agaaataatc gactgacact gtacttgaat gatttttca aaattggggt aaattatcat 2750

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gatgtatccg aagccgatat tcgtgagttt aatccaactg ggattattct ttctggtggt 4070
cctgaaagta ccactgaaga aaacagccca cgagctcccg aatacgtatt caacgccggt 4130
gtacccgtat tagggatctg ttatggtatg caaaccatgg cgatgcaact aggtggttta 4190
actgaaactt ctactcaccg agaatttggt tatgcatcag tgaatctaaa agccgcggac 4250
gcgttatttg ctcaattaaa tgatgatgtc gcaagttcac agcccaaatt agacgtttgg 4310
atgagccatg gcgataaagt gacgcgtttg ccagatcatt tccaagtcac cgcaatgacc 4370
tcaacctgtc caatcgcagc tatgtcggat gaacgtcgtc gtttttatgg tgtccaattc 4430
cacccagaag tgactcatac aaaaagcggg cttgaattat taacgaattt tgtggtgaag 4490
atctgtggtt gtgaacgtaa ctggacacca gaaaatatca ttgaagatgc cgttgctcgt 4550
cttaaagcac aagtgggcga tgatgaagtg attttaggct tatctggtgg cgttaactgc 4610
cgtataggca gcttagaaaa agtgtccgcg ctcacgttaa tccccgtaag cgttga 4666

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<212> PRT
<213> Pasteurella multocida

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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

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
                485


<210> 25
<211> 2364
<212> DNA
<213> Pasteurella multocida

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<222> (191)..(1828)

<220>
<223> Hi1501

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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 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 tcg 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 tcg 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 ggc 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 tcg 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 tcg 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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gga agc aac ccg ttt ttg caa atg gtg gac tgg tgt gaa aag tcc gcc   1093
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                 365

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 ggc 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                 445

aat cac gtg aca ggt tgt cag tgt gat ggc 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 ggc 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                 525

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 taaaccgctt agttttctat tcggacttga accaacgcaa   1868
Gly Gly Thr Asn Val
            545

gccattgagt ttttacataa taaaaaatta cttgcaacga aagtgtttaa aaaatcactg 1928

catgatagtg ccatcgcaag agctacaaca atcgcgagat tatctagtct tgagatgacg 1988

aatgatattt ataaatcaat ggaagttgcc aaaaaagagg gtaagagctt tacacaatgg 2048

aaaaaagact tggtaagtga gtttgagaaa aaaggctggg tattcgggca tgataaatct 2108

atcagtcgcg gtatcgacgg aaaactgttg gctgatccga aaacaggcga atattttggt 2168

acaccgcgtc ggctgaatac aatttatcgt acaaacgtgc aagccgcata ttctgcggcg 2228

cgctatcagc gcatgatgga taatattgat catcgcccct attggcaata ttccgctgtc 2288

agcgatgagc gtacacgacc ctctcatctt gcactaaacg gtcgaattta tcgctatgat 2348

gacccgtttt ggtcga                                                  2364


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<213> Pasteurella multocida

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Met Ala Lys Lys Lys Lys Leu Gln Gln Ala Lys Lys Val Gln Val
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Gly Leu Asp Thr Gln Thr Asn Glu Ala Arg Val Thr Glu Thr Gly Arg
            20                  25                  30

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
    530                 535                 540

Asn Val
545


<210> 27
<211> 1353
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<223> Xaa = any or unknown amino acid

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g tca acg aaa gtc ggt tac gat att aat aac act cat cgt ttt aca ctg 49
  Ser Thr Lys Val Gly Tyr Asp Ile Asn Asn Thr His Arg Phe Thr Leu
    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 tcg 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                 400

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
    450
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<210> 28
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<212> PRT
<213> Pasteurella multocida

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<223> Xaa = any or unknown amino acid

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Ser Thr Lys Val Gly Tyr Asp Ile Asn Asn Thr His Arg Phe Thr Leu
  1   5   10   15

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Phe Leu Glu Asp Arg Arg Glu Lys Lys Leu Thr Glu Glu Lys Thr Leu
                 20                  25                  30

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
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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
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ggagatttca aggctttctc gactagtagc aatgacacct tgatcgatta agaaaccgtc 360

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tttatttaga attagaatct ttaataataa aaataattat cattaaggtt 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
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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
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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 ggc 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 ggc 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 ggc 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
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aat caa aaa agt gga tta ata aaa gta aat tgg caa att act cct gaa   1797
Asn Gln Lys Ser Gly Leu Ile Lys Val Asn Trp Gln Ile Thr Pro Glu
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 tcg 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
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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
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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
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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 cct 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
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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
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act act tat ttt tac aat cgc ggc 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

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Asp Glu Leu Leu Pro Ile Ile Val Asn Ala Asp Glu Asp Asn Lys Leu
         35                  40                  45

Pro Gly Arg Ser Val Leu Lys Gln Lys Asn Ile Asp Gln Gln Gln Ala
     50                  55                  60

Asp Asn Ala Ala Asp Leu Ile Asn Ile Leu Pro Gly Val Asn Met Ala
 65                  70                  75                  80

Gly Gly Phe Arg Pro Gly Gly Gln Thr Leu Asn Ile Asn Gly Met Gly
                 85                  90                  95

Asp Ala Glu Asp Val Arg Val Gln Leu Asp Gly Ala Thr Lys Ser Phe
            100                 105                 110

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

Glu Gln Lys Asn Ile Asp Leu Leu Leu Phe Gly Ser Val Arg Asn Ala
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Ser Asn Tyr Thr Arg Pro Asp Lys Ser Lys Ile Leu Phe Ser Lys Asn
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Asn Gln Lys Ser Gly Leu Ile Lys Val Asn Trp Gln Ile Thr Pro Glu
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His Leu Leu Thr Leu Ser Ser Val Tyr Gly Ile His Lys Gly Trp Glu
                245                 250                 255

Pro Trp Ala Ala Lys Arg Asp Val Met Ser Arg Pro Thr Glu Thr Glu
            260                 265                 270

Ile Lys His Tyr Gly Ile Asp Val Ala Trp Lys Arg Lys Leu Val Tyr
        275                 280                 285

Arg Asp Gln Lys Asp Glu Ser Tyr Ser Leu Lys Tyr Arg Tyr Leu Pro
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Glu Asn Asn Lys Trp Ile Asn Leu Ser Val Gln Leu Ser Tyr Ser Lys
305                 310                 315                 320

Thr Glu Gln Asn Asp Thr Arg His Glu Lys Val Thr Ser Ser Phe Leu
                325                 330                 335

Gly Thr Leu Gly Asn Lys Ser Trp Ile Thr Tyr Ser Asp Leu Thr Phe
            340                 345                 350

Asp Ile Ser Asn Thr Ser Thr Leu Asn Ile Gly Arg Ala Glu His Glu
        355                 360                 365

Leu Leu Phe Gly Leu Gln Trp Leu Lys Asn Lys Arg Asn Thr Leu Met
    370                 375                 380

Tyr His Lys Gly Gly Val Lys Lys Ala Asp Tyr Asn Tyr Gly Tyr Phe
385                 390                 395                 400

Gln Pro Tyr Tyr Met Pro Ser Gly Arg Gln Tyr Thr Gln Ala Phe Tyr
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Leu Gln Asp Gln Ile Lys Trp Gln Asn Phe Leu Phe Thr Gly Gly Ile
            420                 425                 430

Arg Tyr Asp His Ile Asn Asn Ile Gly Gln Lys Asn Leu Ala Pro Arg
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Tyr Asn Asp Ile Ser Ala Gly His Asp Tyr Ser Gln Lys Asn Tyr Asn
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Gly Trp Ser Tyr Tyr Leu Gly Leu Lys Tyr Asp Val Asn His Tyr Leu
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Ser Leu Phe Thr Asn Phe Ser Lys Thr Trp Arg Ala Pro Val Ile Asp
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Glu Gln Tyr Glu Thr Gln Tyr Ser Gln Ala Ser Val Ser Ala Thr Ser
            500                 505                 510

Leu Asn Leu Glu Lys Glu Met Ile As.. Gln Thr Arg Val Gly Gly Ile
        515                 520                 525

Ile Thr Leu Asn His Leu Phe Gln Glu Asn Asp Ala Phe Gln Phe Arg
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Thr Thr Tyr Phe Tyr Asn Arg Gly Lys Asn Glu Ile Phe Lys Thr Arg
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tatttacttg aggttaggaa a atg cgt aca aca aca ata aaa ttt tct gca   4791
                        Met Arg Thr Thr Thr Ile Lys Phe Ser Ala
                          1               5                  10

att aca ttg gca tta ttg agt tat tgt ggg acc att ttg gcg gat agt   4839
Ile Thr Leu Ala Leu Leu Ser Tyr Cys Gly Thr Ile Leu Ala Asp Ser
                     15                  20                  25

cat caa gag gcg act gaa ctt gat acg att acc gtt tct tct caa caa   4887
His Gln Glu Ala Thr Glu Leu Asp Thr Ile Thr Val Ser Ser Gln Gln
                 30                  35                  40

gat gag atg aat att aaa gag aaa aaa atc ggt gaa act gtg aaa acg   4935
Asp Glu Met Asn Ile Lys Glu Lys Lys Ile Gly Glu Thr Val Lys Thr
             45                  50                  55

gcg agt caa ttg aaa cgc cag caa gta cag gat agt cgt gat ctt gtg   4983
Ala Ser Gln Leu Lys Arg Gln Gln Val Gln Asp Ser Arg Asp Leu Val
         60                  65                  70

cgc tat gaa acc ggt gtg act gtg gta gaa gct gga cgt ttt ggt tcg   5031
Arg Tyr Glu Thr Gly Val Thr Val Val Glu Ala Gly Arg Phe Gly Ser
 75                  80                  85                  90

agc ggt tat gcc att cgt ggt gtg gat gag aac cga gta gca att aca   5079
Ser Gly Tyr Ala Ile Arg Gly Val Asp Glu Asn Arg Val Ala Ile Thr
                 95                 100                 105

gta gat ggc tta cat caa gca gaa acc ctt tct tct caa ggc ttt aaa   5127
Val Asp Gly Leu His Gln Ala Glu Thr Leu Ser Ser Gln Gly Phe Lys
            110                 115                 120

gaa tta ttc gaa ggt tac ggc aat ttt aac aat acc cga aat agt gtg   5175
Glu Leu Phe Glu Gly Tyr Gly Asn Phe Asn Asn Thr Arg Asn Ser Val
        125                 130                 135

gaa att gag acg ttg aaa gtc gct aaa atc gcg aaa ggt gct gat tct   5223
Glu Ile Glu Thr Leu Lys Val Ala Lys Ile Ala Lys Gly Ala Asp Ser
    140                 145                 150

gta aaa gtg ggt agt ggt tct ttg gga ggc gct gta ctt ttt gaa aca   5271
Val Lys Val Gly Ser Gly Ser Leu Gly Gly Ala Val Leu Phe Glu Thr
155                 160                 165                 170

aaa gat gcc aga gat ttc ctg act gaa aaa gat tgg cat atc ggc tat   5319
Lys Asp Ala Arg Asp Phe Leu Thr Glu Lys Asp Trp His Ile Gly Tyr
                175                 180                 185

aaa gcg ggc tac tca acg gca gat aat cag gga tta aat gca gtg act   5367
Lys Ala Gly Tyr Ser Thr Ala Asp Asn Gln Gly Leu Asn Ala Val Thr
            190                 195                 200

ctt gca ggt cgc tat caa atg ttt gat gca ttg att atg cat tct aag   5415
Leu Ala Gly Arg Tyr Gln Met Phe Asp Ala Leu Ile Met His Ser Lys
        205                 210                 215

cga cat gga cat gaa tta gaa aat tat gac tat aaa aat ggc aga gat   5463
Arg His Gly His Glu Leu Glu Asn Tyr Asp Tyr Lys Asn Gly Arg Asp
    220                 225                 230
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att caa ggg aaa gaa aga gag aaa gcg gat cct tat acg att acg aaa   5511
Ile Gln Gly Lys Glu Arg Glu Lys Ala Asp Pro Tyr Thr Ile Thr Lys
235                 240                 245                 250

gaa agt aca tta gtg aaa ttc tct ttt tcg cca aca gaa aat cat cgt   5559
Glu Ser Thr Leu Val Lys Phe Ser Phe Ser Pro Thr Glu Asn His Arg
                255                 260                 265

ttt aca gtc gct tct gat act tat ctt cag cat tcc cgc gga cat gat   5607
Phe Thr Val Ala Ser Asp Thr Tyr Leu Gln His Ser Arg Gly His Asp
            270                 275                 280

ctt tca tat aat ctt gtt gca aca aca cat att cag tta gat gag aaa   5655
Leu Ser Tyr Asn Leu Val Ala Thr Thr His Ile Gln Leu Asp Glu Lys
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gaa tct cgt cat gca aat gat ttg aca aaa cgt aaa aat gtt tcc ttt   5703
Glu Ser Arg His Ala Asn Asp Leu Thr Lys Arg Lys Asn Val Ser Phe
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act tat gaa aat tat act gtt acg cca ttt tgg gat acg ctc aag tta   5751
Thr Tyr Glu Asn Tyr Thr Val Thr Pro Phe Trp Asp Thr Leu Lys Leu
315                 320                 325                 330

agc tat tca caa caa aga att aca aca aga gca aga aca gaa gat tat   5799
Ser Tyr Ser Gln Gln Arg Ile Thr Thr Arg Ala Arg Thr Glu Asp Tyr
                335                 340                 345

tgt gat gga aat gag tta tgt gat tct tat aaa aat cca tta ggt ctc   5847
Cys Asp Gly Asn Glu Leu Cys Asp Ser Tyr Lys Asn Pro Leu Gly Leu
            350                 355                 360

caa ttt aaa gat ggt cag att ctt gat cct gca ggg aat aaa att aaa   5895
Gln Phe Lys Asp Gly Gln Ile Leu Asp Pro Ala Gly Asn Lys Ile Lys
        365                 370                 375

cta cag ggg tct gga ttg agc act cag att gta gat gaa aat gga aaa   5943
Leu Gln Gly Ser Gly Leu Ser Thr Gln Ile Val Asp Glu Asn Gly Lys
    380                 385                 390

cca ttt cct aca aca aca ggt act aat aat gct gct ttt agt aat aat   5991
Pro Phe Pro Thr Thr Thr Gly Thr Asn Asn Ala Ala Phe Ser Asn Asn
395                 400                 405                 410

tta cga ctc agg cct aca ggt ttt tgg tta gat tgc tcg gtt ttt gac   6039
Leu Arg Leu Arg Pro Thr Gly Phe Trp Leu Asp Cys Ser Val Phe Asp
                415                 420                 425

tgt aat aaa cca ttc act gtt tat aat att agt aat gga aca tat caa   6087
Cys Asn Lys Pro Phe Thr Val Tyr Asn Ile Ser Asn Gly Thr Tyr Gln
            430                 435                 440

gca aga gag gtt cta ctg tct gaa gag ata act gtg gat ggt aaa tta   6135
Ala Arg Glu Val Leu Leu Ser Glu Glu Ile Thr Val Asp Gly Lys Leu
        445                 450                 455

tac aaa aca gct aag gaa gaa gga ggg ctt cca aat tat ttg att tta   6183
Tyr Lys Thr Ala Lys Glu Glu Gly Gly Leu Pro Asn Tyr Leu Ile Leu
    460                 465                 470

cct aat tct aaa ggt tat ctt cct tat gat tat aaa gaa agg gat ctt   6231
Pro Asn Ser Lys Gly Tyr Leu Pro Tyr Asp Tyr Lys Glu Arg Asp Leu
475                 480                 485                 490
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aat acg aat aca aaa caa att aat tta gat tta act aaa aca ttt tta   6279
Asn Thr Asn Thr Lys Gln Ile Asn Leu Asp Leu Thr Lys Thr Phe Leu
                495                 500                 505

act ttc aac atc gaa aat aat ctg tca tat ggt gga gtt tat tct cgg   6327
Thr Phe Asn Ile Glu Asn Asn Leu Ser Tyr Gly Gly Val Tyr Ser Arg
            510                 515                 520

ata gag aaa gaa atg att aat aaa gct ggt tat gag ggg aga aat cct   6375
Ile Glu Lys Glu Met Ile Asn Lys Ala Gly Tyr Glu Gly Arg Asn Pro
        525                 530                 535

act tgg tgg gct gat aga att tta ggg caa agt agt tac tgt ggt tat   6423
Thr Trp Trp Ala Asp Arg Ile Leu Gly Gln Ser Ser Tyr Cys Gly Tyr
    540                 545                 550

aat gca ttg aag tgt ccg aaa cat gag cca tta acg tca ttt tta att   6471
Asn Ala Leu Lys Cys Pro Lys His Glu Pro Leu Thr Ser Phe Leu Ile
555                 560                 565                 570

cca gtt gaa gca acg aca cag tca tta tat ttt gca aat att ctt aag   6519
Pro Val Glu Ala Thr Thr Gln Ser Leu Tyr Phe Ala Asn Ile Leu Lys
                575                 580                 585

gta cat aat atg att agc ata gat tta gga tat cgt tat gat cat att   6567
Val His Asn Met Ile Ser Ile Asp Leu Gly Tyr Arg Tyr Asp His Ile
            590                 595                 600

aaa tat aac cct gaa tac act cca gga gta act cca aaa att cca gat   6615
Lys Tyr Asn Pro Glu Tyr Thr Pro Gly Val Thr Pro Lys Ile Pro Asp
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gat atg gta aaa ggt ttg ttt att cct atg cca aaa gag cca cag cta   6663
Asp Met Val Lys Gly Leu Phe Ile Pro Met Pro Lys Glu Pro Gln Leu
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aag gat ttt gat tat aac tat gct aaa ttt ggt gag gcc tat aaa aaa   6711
Lys Asp Phe Asp Tyr Asn Tyr Ala Lys Phe Gly Glu Ala Tyr Lys Lys
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tgg aaa gaa tat ctg cca aaa aat gcg gaa gaa aat att gct tac att   6759
Trp Lys Glu Tyr Leu Pro Lys Asn Ala Glu Glu Asn Ile Ala Tyr Ile
                655                 660                 665

gct caa gat aag aca ttt aaa aaa cat tct tat tct ctt ggt gca act   6807
Ala Gln Asp Lys Thr Phe Lys Lys His Ser Tyr Ser Leu Gly Ala Thr
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ttc gat cct ctg aat ttt tta cga gta caa gta aaa tat tca aaa ggg   6855
Phe Asp Pro Leu Asn Phe Leu Arg Val Gln Val Lys Tyr Ser Lys Gly
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Phe Arg Ala Pro Thr Ser Asp Glu Leu Tyr Phe Thr Phe Lys His Pro
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gat ttt acg att tta ccg aac ccc gtg ttg aaa cca gag gaa gca aaa   6951
Asp Phe Thr Ile Leu Pro Asn Pro Val Leu Lys Pro Glu Glu Ala Lys
715                 720                 725                 730

aat caa gag att gca tta aca gtg cac gat aat tgg gga ttt gtt agc   6999
Asn Gln Glu Ile Ala Leu Thr Val His Asp Asn Trp Gly Phe Val Ser
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aca agt gtt ttc caa aca aag tat cgt cat ttt att gat tta gcg tat   7047
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 tcg 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
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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                 810

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
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cgt ttg gat ggc 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
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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
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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 tcg 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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aat tta att aat caa aaa aca ggc gca gga att aat cgt ttt tac tca   7623
Asn Leu Ile Asn Gln Lys Thr Gly Ala Gly Ile Asn Arg Phe Tyr Ser
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cca ggt cgt aac ttt aaa ctc agt gcc gaa atc acc ttc taatcctaag    7672
Pro Gly Arg Asn Phe Lys Leu Ser Ala Glu Ile Thr Phe
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Glu Lys Lys Ile Gly Glu Thr Val Lys Thr Ala Ser Gln Leu Lys Arg
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Gln Gln Val Gln Asp Ser Arg Asp Leu Val Arg Tyr Glu Thr Gly Val
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Thr Val Val Glu Ala Gly Arg Phe Gly Ser Ser Gly Tyr Ala Ile Arg
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Gly Val Asp Glu Asn Arg Val Ala Ile Thr Val Asp Gly Leu His Gln
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Ala Glu Thr Leu Ser Ser Gln Gly Phe Lys Glu Leu Phe Glu Gly Tyr
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Gly Asn Phe Asn Asn Thr Arg Asn Ser Val Glu Ile Glu Thr Leu Lys
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Val Ala Lys Ile Ala Lys Gly Ala Asp Ser Val Lys Val Gly Ser Gly
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Ser Leu Gly Gly Ala Val Leu Phe Glu Thr Lys Asp Ala Arg Asp Phe
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Leu Thr Glu Lys Asp Trp His Ile Gly Tyr Lys Ala Gly Tyr Ser Thr
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Ala Asp Asn Gln Gly Leu Asn Ala Val Thr Leu Ala Gly Arg Tyr Gln
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Met Phe Asp Ala Leu Ile Met His Ser Lys Arg His Gly His Glu Leu
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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
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Thr Tyr Leu Gln His Ser Arg Gly His Asp Leu Ser Tyr Asn Leu Val
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Ala Thr Thr His Ile Gln Leu Asp Glu Lys Glu Ser Arg His Ala Asn
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Val Thr Pro Phe Trp Asp Thr Leu Lys Leu Ser Tyr Ser Gln Gln Arg
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Ile Thr Thr Arg Ala Arg Thr Glu Asp Tyr Cys Asp Gly Asn Glu Leu
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Cys Asp Ser Tyr Lys Asn Pro Leu Gly Leu Gln Phe Lys Asp Gly Gln
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Ile Leu Asp Pro Ala Gly Asn Lys Ile Lys Leu Gln Gly Ser Gly Leu
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Ser Thr Gln Ile Val Asp Glu Asn Gly Lys Pro Phe Pro Thr Thr Thr
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Gly Thr Asn Asn Ala Ala Phe Ser Asn Asn Leu Arg Leu Arg Pro Thr
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Gly Phe Trp Leu Asp Cys Ser Val Phe Asp Cys Asn Lys Pro Phe Thr
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Val Tyr Asn Ile Ser Asn Gly Thr Tyr Gln Ala Arg Glu Val Leu Leu
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Ser Glu Glu Ile Thr Val Asp Gly Lys Leu Tyr Lys Thr Ala Lys Glu
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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
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Ile Asn Leu Asp Leu Thr Lys Thr Phe Leu Thr Phe Asn Ile Glu Asn
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Asn Leu Ser Tyr Gly Gly Val Tyr Ser Arg Ile Glu Lys Glu Met Ile
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Ile Leu Gly Gln Ser Ser Tyr Cys Gly Tyr Asn Ala Leu Lys Cys Pro
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Lys His Glu Pro Leu Thr Ser Phe Leu Ile Pro Val Glu Ala Thr Thr
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Gln Ser Leu Tyr Phe Ala Asn Ile Leu Lys Val His Asn Met Ile Ser
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Ile Asp Leu Gly Tyr Arg Tyr Asp His Ile Lys Tyr Asn Pro Glu Tyr
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Phe Ile Pro Met Pro Lys Glu Pro Gln Leu Lys Asp Phe Asp Tyr Asn
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Lys Lys His Ser Tyr Ser Leu Gly Ala Thr Phe Asp Pro Leu Asn Phe
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Leu Arg Val Gln Val Lys Tyr Ser Lys Gly Phe Arg Ala Pro Thr Ser
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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
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Thr Val His Asp Asn Trp Gly Phe Val Ser Thr Ser Val Phe Gln Thr
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Lys Tyr Arg His Phe Ile Asp Leu Ala Tyr Leu Gly Ser Arg Asn Leu
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Pro Met Asn Ala Ile Gln Pro Lys Ala Ser Val Phe Gly Leu Gly Tyr
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Asp His Lys Glu Asn Lys Phe Gly Ala Asp Leu Tyr Ile Thr Arg Val
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Ser Glu Lys Lys Ala Lys Asp Thr Tyr Asn Met Phe Tyr Lys Glu Gln
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Gly Tyr Lys Asp Ser Ala Val Arg Trp Arg Ser Asp Asp Tyr Thr Leu
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Val Asp Ala Val Gly Tyr Ile Lys Pro Ile Lys Asn Leu Thr Leu Gln
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Phe Gly Val Tyr Asn Leu Thr Asp Arg Lys Tyr Leu Thr Trp Glu Ser
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Ala Arg Ser Ile Lys Pro Phe Gly Thr Ser Asn Leu Ile Asn Gln Lys
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gtcagaaaca cgcataaata gggttataaa aagttatcta aaaaatcgtg ggcgtaagtc 660

tagtgtgaat tccgctcttg cacaaggaaa aatccagatt ttgttgttta gtatcgaatt 720

gagatgattt tggacaaaaa aaaagccctt tcaagaaaga cgaaagggcg aaaatatatt 780

tggagtcata ctttttaggg tatgtgtcgg attatacaca caaaaataac aaatgcaaca 840

ttttttttaac aatcatatgt aagcgtattg tgtgagaacg agcgtaaaaa tgaacgcatt 900

ctaaaggatg atttatttag cctattaaaa aaacacatga gatgagagtt tgcgagagcg 960

gtaataaaag tgcggtgggt tttagaaaag ttttgaatag gatcacaaat taaacaaagt 1020

ttgtgaaata ccaagtagta gtttttaagt atatgatgaa tcatatgcta aagtttaaac 1080

ccgttaaata 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 ctt 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
His Glu Leu Tyr Thr Glu Gln Glu Leu Ile Asp Arg Gly Ile Glu Tyr
                45                  50                  55

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                 105

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

taagagtgag gtgaagaaat ggcattacca acagcaacaa taatgaggaa tttatcttta 1624

tctaaaaatc aattcactct gaaagggatg gaatgcgtag attccctatt tcaagcatgc 1684

agtaatatgg atcatgggta ctgaggtgga agatggcaga agaaaataaa ggaaagagat 1744

atttttatg gttcatattg tttatccttt caatctattt atttattacc atacaagaaa 1804

gacgaggtta ttgttttgac aaatgggaat atatccataa cctttatacc gagcaagagt 1864

tgatcgatag aggggttgaa tatgtggtat ccaccatgcc gtcaggtgtt tttgaaccag 1924

atggcacaac aaccgaaata aaacgttatg ctagtgttga ggagtttaaa cagatgaacc 1984

ctgattgttg taaattaaca agatttatta atgaaggaat agatggctat ccagatgatg 2044

atggatatgg ttatataaga attgaatatt taagacatta tgttgggaat tttaaacctg 2104

atcatagagt gctttatctc gaatatacgc cttgtggaga attaagggaa gaggtttctt 2164

tttaaaaaat aaataatagt gaggtgaaga aatggcatta ccaacagcaa cagaaatcac 2224

aaatgcatat ttatataaaa ataaattaac tcctaaagcg gaggaaagag tagattcaat 2284

acaaattctt gaaaaaggag atgaacattt cgaagtaaat tttaattgat caaagtactc 2344

tattgattga aggaaaaaca gtggaattaa tggcaggtat ggcagtttct gcggaaatta 2404

aaacaggtaa acgcagtgta ttagattact tatttagccc attaaaaacc acaaaataat 2464

attaaggaga ataatatgtc gtataataaa tatactgttg ctttgattac gttctcaaca 2524

gggatctgta ttccggcaat atgctacgct ctaaattcgc tgggatacag atcctgtttg 2584

agactatgta gaaaagacta aactttgtgt ggttaactgg gcttcggtaa aattctggaa 2644
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acaaatgggc ttaacccgcg tgatcttatc ccgtgagctt tcgcttgatg aaattgccga 2704

aattcgtcag caagtgccag aaatggaaat tgaagtgttc gtgcatgggg cattatgcat 2764

ggcgtattct ggacgttgtt tattatcagg ctatattaat aaacgtgatc caaatcaagg 2824

cacctgtacc aatgcgtgcc gttgggaata cagtgtaacc gaagccaaag aagatgagat 2884

cggcaacatt gtgaatgtgg gtgaagaaat tccagtgaaa aatgtagcac cgacacttgg 2944

cgaaggcgac accaccagta aagtattttt attagcagaa agtcga 2990

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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
115 120 125

Pro Tyr His Arg Val Ile Tyr Leu Glu Tyr Thr Pro Cys Gly Glu Leu
130 135 140

Arg Glu Glu Ala Ala Phe Ser Lys Asn
145 150

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gcagaactgg ctagcttatc acttttagat aattgtatta ttaaaagaag ctgtatgatt 180

gttattctat cattagtgga 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

gtt 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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gtt ttg gtt ttt aac tca tta gaa atg tta tgg aat gtt gat gtt aat   687
Val Leu Val Phe Asn Ser Leu Glu Met Leu Trp Asn Val Asp Val Asn
                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 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 ggc 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 aaagcgaaaa ggaggaaata gcttgttcta atttattaca ataatggttg 1330

tattcatctt gattttgaag gaaagagagt gttttttgta taaaagcatt ttcgtcacct 1390

aaatttacta atcctccaaa ttctcctcct cgnagaattt ctttcggacc ggtagggcag 1450

tccatggata ttacaggtgt accgcaagcc atgcttttcta ggataactgt cggtaacccc 1510

tctttcaaag aggtgtgtaa aaatagctta gcatttttta ttaatggata cggattatct 1570

ttatttccta aaagaaaaca atcttcttgt agattgagtg attctatttg tttctctaat 1630
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Val Ala Ile Lys Ser Ile Ile Asn His Asn Glu Lys Gly Ile Ser Phe
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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                 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 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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Leu Ile Arg Arg Ile Arg Tyr Lys Phe Lys Tyr Gln Val Tyr
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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   80

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 ngt 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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gaa ggc aca aaa tgg cag tta aaa cga tcg tgt cct acg tat ccc tta   481
Glu Gly Thr Lys Trp Gln Leu Lys Arg Ser Cys Pro Thr Tyr Pro Leu
145                 150                 155                 160

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

tataacaaaa caagamgttg taattctcgg ggaggtatac cctccccctt tttatgtgag 589

gttggatatg acaactcaaa ttccaaatca agacagtgaa atactgctca caatgaccaa 649

cgtctgtaaa tcctttcccg gtgttaaagc gttagacaat gcaaacctaa ctgtgcgctc 709

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ctttaaaacg tcgaaagaag ccttagagaa cgggattttc atggtgcacc aagaacttaa 889

cttggttaaa caatgtactg taatggataa tcctttggnt aggacgttat ccattaaaag 949

caggctttgt cgatcacggc aaaatgtatc gtgataccaa agcagatttt tgaagaanta 1009

gatatcgata tcgatccaaa agaaaaagtg gccaaattgt cagtgtcaca aatgcaaatg 1069

atcgagatcg caaaggcctt ttcatacaat gccaaaatcg taatcatgga cgaaccgact 1129

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cgtggctgtg gcattattta tatttcgcac aaaatggacg aaatcttcaa aatttgtgac 1249

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gtatcgacat tggtgcgaaa tatgaaattt atcagctgat tatggagtta gccaaaaaag 1969

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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
165

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tcaattggaa attgatgaat taaaagaaaa aaataaccaa tctcaacaag caaatgacgc 180

attacgcagt gaaaatgaac aactaaagag tgagcaccaa 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

ggg tta ggt aat tcg gat tat gat acc ttc tgt cac gca gtg gat cat   640
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

atggcatatg taaatcaaat atgccatttt tcatctcgat caagcataat atttaaccaa 846

tcaaatcaat attttctctg tggataacta agatcaaaac tgtataaaag ctgtttttat 906

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

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
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Ser Gln Leu
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                        Met Leu Phe Lys Lys Ile Arg Gly Leu Phe
                          1               5                  10

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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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

ggt 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

ggt ggt ggc 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
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Phe Ser Asp Asp Ile
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Val	Leu	Asp	Glu	Pro	Ser	Val	Val	Ala	Ile	Arg	Gln	Glu	Arg	Ser	Gly
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Ala	Leu	Lys	Ser	Ile	Ala	Ala	Val	Gly	Arg	Asp	Ala	Lys	Leu	Met	Leu
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Gly	Arg	Thr	Pro	Lys	Ser	Ile	Ala	Ala	Ile	Arg	Pro	Met	Lys	Asp	Gly
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Val	Ile	Ala	Asp	Phe	Phe	Val	Thr	Glu	Lys	Met	Leu	Gln	Tyr	Phe	Ile
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Lys	Gln	Val	His	Ser	Ser	Asn	Phe	Met	Arg	Pro	Ser	Pro	Arg	Val	Leu
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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
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Gly	Ser	Met	Val	Ile	Asp	Ile	Gly	Gly	Gly	Thr	Thr	Glu	Val	Ala	Val
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Ile	Ser	Leu	Asn	Gly	Ile	Val	Tyr	Ser	Ser	Ser	Val	Arg	Ile	Gly	Gly
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Asp	Arg	Phe	Asp	Glu	Ala	Ile	Ile	Ser	Tyr	Val	Arg	Lys	Thr	Phe	Gly
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Ser	Ala	Phe	Ile	Gln	Glu	Gly	Asp	Glu	Val	Arg	Glu	Ile	Glu	Val	His
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Gly	His	Asn	Leu	Ala	Glu	Gly	Ala	Pro	Arg	Ser	Phe	Lys	Leu	Thr	Ser

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Arg Asp Val Leu Glu Ala Ile Gln Ala Pro Leu Asn Gly Ile Val Ala
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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

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gaa aaa gtg aaa gcg att gca gaa gcg cgt tta ggc 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 ggc 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
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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 ggc 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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Gly Thr Val Lys Ile Ala Ala Val Asp Gly Asn Ser Ala Lys Glu Val
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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 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

aaagggcgtt ggtgtgcatg ttgataagta caatttgtgc tttaaggcga agcgaaatga 1554

agcaatttca tccgtggtta aagtgcctgc taatttttcc attttgggta tgttgtttaa 1614

cagcttgtgt taatcatgaa caagtttttc tttcaaaaga gaaattaatg ttagcagagc 1674

aacatccgaa tgatcatctt gagcatgagg tgatggttgc gcaaattagc gaattgttac 1734

ttgttaaagg gttaaaaaaa gaagaacgtg cgattttaca ttttgagcga ggcgtgctgt 1794

acgatagctt aggattgtgg gcattggcgc gttatgattt tgaccaaaca ttagcgttgt 1854

atccaaagtt ggcagcagcg tttaattatt taggtttata tttattgtta gaggaagatt 1914

acagcgcatc tctagatatc tttaatgtgt tgtttgaact tgatcctcaa tatgagtatg 1974

cattcctaaa tagagggcta aatttttatt acgtcggacg ttatgaatta gctcagcggg 2034

attttcttca attttatcaa gccgataaat cagatccata ccgcacttta tggctttatt 2094

taaatgaatt aaagcataat cctcaggatg cttctaaaaa tcttgctcaa cgagcaatgg 2154

ggctttctga tgaatatt                                              2172
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<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
```

```
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

ggt 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 ccg 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
```

```
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 Lys 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                 160

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
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<210> 46
<211> 210
<212> PRT
<213> Pasteurella multocida

<400> 46

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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
```

```
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                 160

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


<210> 47
<211> 4788
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (1)..(876)

<220>
<223> rci

<220>
<223> Nucleotide at position 3084 is A, T, G, or C.

<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                  80

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                 160

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 ccg 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                 240

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
    290

catcgccagc cttatatctt ttactttcat tacttccttt ttctaatgaa actggggatg 976

gaaagtcttg gcgggtaata atatgacgag atgtgtaatt gtaagaacga ttaatcatga 1036

tagaaatgtc ttcaatacta agaagaactg gactatcttc tttaagttga gctaaggctc 1096

caaacctcac agagcgtagc acttcatctt gttgtttctt tgttagagaa atattttcca 1156

tttttacctc acttaaataa aaaagccgtc atggacggct taataaagca tttcgctata 1216

cagttctttt gaggtgtacc caatatcgaa cttgatttga ttgttttgtt ttgcgatttc 1276
```

cagtgcttct tttcgatcaa caaatcttcc gaagttggta ataacaccct gtttcttacc 1336
aattagcgga tattgtgtac cgttctcaat agatttaatt tgtttacgca taaacatgtc 1396
atagtgtctc gcgccagtca ctaaatgaag ttcttttgtt gtgtaatctt caagctcgca 1456
cgcagcgcag acgattaatt ctggacgatc tcccattttc ctatctccga gcatttttca 1516
tagcctcaaa ccaagcttgt gcgtctcctt cactgtaaaa taatgaaccg ctttctagca 1576
ttttttctgtg cttatctcta ttagcatcaa aatagaatct aataattgtt gagttacctc 1636
ttttaaagac ctcttgattg tggtgtgctg ttttgattgg agcgggcaaa gtaagcgtta 1696
ctgttgggcg tggttcttcc cacattccga ctatatcaaa tggattttct aaatgcggat 1756
atttgttatg ttcaaaaaaa gaagatccat caatcgtcca agaatttctc tcaaattgtg 1816
tcttgctctt gccaatttga aatacacctt gatataagaa agtgttgaac ggaaagaact 1876
ttgaataatc agcagttaca tatcctttac ttccatttct aagcacaact ggctcaccgg 1936
ttaatgcttt ttctaagtca aatgctttca ttttttactc tccagcttgc tcatcaataa 1996
gctcatcaat ccattctcga atttcagatt ggaaattttc taacgaatta ttttcattaa 2056
aataatctgc ttcttttaac ttactcaccg ctgttttact aaagcattta taaaaaagac 2116
gcttttcttc aaacaaatca tcttttgaga ttgcgcatac ttttcctacg ccctctatac 2176
ttttgtcttg aataaaacta ttaaaaagaa cctcttcttg ctgcttgttt tctactaaaa 2236
tagaaatcgt atattttttt ggatattcca tttttaatcc tttcttttag ataacaaaaa 2296
accgcatttc tgcggttatt ctgtgtattt atttaaaata ttacttatag tttcagcatc 2356
ttctaatgtt aatttagaat agcttgaggt cattttcct ttaacggcaa tcctcaattc 2416
ttccagcttt aagctataca agtagtcttt tttatcttta taaatacgac cgtacaccat 2476
tccggataat ttaccttctt catacccatt agataaattg atctttctat ctcgaccgcg 2536
cactctaatt gttaaatatt ttcttccaat ttttaagact tcagcctcat gttcaatgtt 2596
tgagcgcatg agtgtttcta aaaaatatac ggtatcgcca actttaagat ttttaatcca 2656
atctttattc ataaataccc ttatactttc ggtggcagtg gaagtggttg ccaatgagtt 2716
actgaagata gatggtaagt acgaagagac ataaagaaaa catcatctcg ccacgcgatt 2776
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tcacacatat catctgcgaa ctcatgagct tctactgcac catctaaaca actttgctta 3076
gcttgatnta atgtttcgtg taagttaacg atatgtatgt cattagatac atctactgag 3136
aaaaattttt tttctgtttc tatcatagtt aaattcctta ttctttttatt aatgggcgag 3196

gaatcggttg ccagtgtgta acgttaatag ctagatcata aattggacca ttctgattta 3256

tagctaccca aaaatattca ccatcagcaa tttctcttga tgcaattgcg taatgctcgc 3316

catattcacc ttcacaaaaa gcaatgactg gtgtttcaac ttctggtaac ttgtcatcaa 3376

cactaatcca gttgctatat tcccaatgaa aattaagctt ctcatagcca ttgatgactt 3436

gatctaacgc aggtcttaat tgggtttctc caacaataat atgtgttgtt atcttaatct 3496

ctgggattcc atctattact tcacaccagt ttttttcaat aaagtccaat ctttttttat 3556

ctgctaaaag actttcatat tctgcttttg tgattgttac tgtttctgtc atagttaaat 3616

tcctcatgat aaattccatg tttatttacc ttttttctgg cacaaaaaaa cacgctattg 3676

cgtgctgtct tgattgatat aatcaattaa tctaagccca atccatttca taactggaac 3736

agccatactg tttccaattg ctttgtatcg tggagaatca gggcattcat ctattgattt 3796

gttgcgatat gggattttag tgtaatcgtc tggaaatccc tgtaatcttt cacactcacg 3856

cggcgttagt tttctaacaa ctgattctac tgataaagca acgcaaggaa cattattacc 3916

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ccctcgcacg cttttggact caatgagtat ttgtgcaaca cttcgttttc tagcacttgc 4276

cacaagaaac actcttttac gacgttgggc aactccgaag tattgagcat cgagaactcg 4336

ccagcagatt gttcggattg aatgcacata accagcgttc gtccatcttc tccctgtgtg 4396

ctgcaatggc tcacactctt gaaccagtcc agccagaagg tgtccgaatg cgttgtccga 4456

ggtggatagc acacccggaa cgttttccca cacgagaatg cacggtggtt tgttgtcatt 4516

gaatctaaca tagtcgatcg cttctaaaat tttaattaaa actaacgtga gatttcctcg 4576

ctcatcgtct aaactttgac gattgccagc aactgaaaaa gattgacaag gagtaccacc 4636

aactaaaacg tctggtgccg gaatttcacg atctaatatt ttctgttgca attcagtcat 4696

atcaccaaga ttgggaacgt tagggtaatg gtaagctaat actgcgcttg ggaattgctc 4756

aatttcagaa aaccagagtg gctctgcgaa tt 4788

<210> 48
<211> 292
<212> PRT
<213> Pasteurella multocida

<400> 48
Asp Glu Glu Arg Lys Leu Ala Asp Leu Ala Lys Gly Ile Ala Pro Asp
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


<210> 49
<211> 1618
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (2)..(1195)
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<220>
<223> sopE

<400> 49

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g ggc gat cta tgt ctg aaa ata tct aca tgg tgt caa agt cac aga atc 49
  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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ggt 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 gcg 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 gcg 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 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 acttaaattg atgaatttaa tcatcgacgg 1255

taacaaatat ctcggcgaag tcacggaagt gactcaacca aaattagcaa tgaaaatcga 1315

agaatttcgc gcgggcggta tgattggttc ggtggatgtc aatctcgggc ttgaaaagct 1375

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aatcaacggc attccattgc gttttcttgg ctcatatcag cgtgatgaca cagaagaagt 1495

cacatctgtt gagcttgtga tgcaaggtcg atttactgaa attgacagcg gaaacagcaa 1555

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tga                                                               1618


<210> 50
<211> 398
<212> PRT
<213> Pasteurella multocida

<400> 50
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             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 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 Trp 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


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<212> DNA
<213> Pasteurella multocida

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<222> (1)..(351)

<220>
<223> unknown C1

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Met Thr Leu Phe Asp Glu Cys Lys Leu Ala Leu Arg Asp Asp Phe Asn
  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
        115


<210> 52
<211> 117
<212> PRT
<213> Pasteurella multocida
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<400> 52
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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
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<212> DNA
<213> Pasteurella multocida

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<222> (1)..(507)

<220>
<223> unknown C2

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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                 160

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

<400> 54

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Met Lys Asn Phe Arg Asn Ile Asn Ile Tyr Ser Asp Tyr Gly Lys Val
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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
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Met Ile Lys Tyr Leu Glu Gly Asn Ile Asn Ser Phe Ile Ser Ala Leu
1 5 10 15

ggt aaa aac gaa agt aat aaa gat att tta aaa tta gta gaa ata gtt 96
Gly Lys Asn Glu Ser Asn Lys Asp Ile Leu Lys Leu Val Glu Ile Val
20 25 30

tct tca gat ttt gaa gtg gat gaa cta agt cat aaa gat gaa cac gag 144
Ser Ser Asp Phe Glu Val Asp Glu Leu Ser His Lys Asp Glu His Glu
35 40 45

ata tat tat ttg ttt tat aag agg ggt gtt gaa ttt tgt ttt aaa aga 192
Ile Tyr Tyr Leu Phe Tyr Lys Arg Gly Val Glu Phe Cys Phe Lys Arg
50 55 60

ata gat gaa gag tat gtc tta tat tcg gtt ttc ttt ttc ttg gta gag 240
Ile Asp Glu Glu Tyr Val Leu Tyr Ser Val Phe Phe Phe Leu Val Glu
65 70 75 80

gtt gat aat tat ttt tca tgc cca ttt att cat gaa tta ata tgt gat 288
Val Asp Asn Tyr Phe Ser Cys Pro Phe Ile His Glu Leu Ile Cys Asp
85 90 95

ctt aaa cac gga ttc tca ata gag gat att ata agg ttt tta ggg gag 336
Leu Lys His Gly Phe Ser Ile Glu Asp Ile Ile Arg Phe Leu Gly Glu
100 105 110

cca aat ttt aaa ggt agt ggc tgg gta aga tat tct tat aat gga aga 384
Pro Asn Phe Lys Gly Ser Gly Trp Val Arg Tyr Ser Tyr Asn Gly Arg
115 120 125

aat att cat ttc gaa ttt aat gaa tct aat gaa tta tcc cag att agc 432
Asn Ile His Phe Glu Phe Asn Glu Ser Asn Glu Leu Ser Gln Ile Ser
130 135 140

att ttt att ta 443
Ile Phe Ile
145

<210> 56
<211> 147
<212> PRT
<213> Pasteurella multocida

<400> 56
Met Ile Lys Tyr Leu Glu Gly Asn Ile Asn Ser Phe Ile Ser Ala Leu
1 5 10 15

Gly Lys Asn Glu Ser Asn Lys Asp Ile Leu Lys Leu Val Glu Ile Val
20 25 30

Ser Ser Asp Phe Glu Val Asp Glu Leu Ser His Lys Asp Glu His Glu
35 40 45

Ile Tyr Tyr Leu Phe Tyr Lys Arg Gly Val Glu Phe Cys Phe Lys Arg
50 55 60

Ile Asp Glu Glu Tyr Val Leu Tyr Ser Val Phe Phe Phe Leu Val Glu
65 70 75 80

Val Asp Asn Tyr Phe Ser Cys Pro Phe Ile His Glu Leu Ile Cys Asp
85 90 95

Leu Lys His Gly Phe Ser Ile Glu Asp Ile Ile Arg Phe Leu Gly Glu
100 105 110

Pro Asn Phe Lys Gly Ser Gly Trp Val Arg Tyr Ser Tyr Asn Gly Arg
115 120 125

Asn Ile His Phe Glu Phe Asn Glu Ser Asn Glu Leu Ser Gln Ile Ser
130 135 140

Ile Phe Ile
145

<210> 57
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<212> DNA
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aaaagtgtgg tacaacttaa accagaagag gtggaatggt catcaatcca ttatcttttc 180

tttgctggcg atattcagca agtcgctcat ctcgcgaaag ccgcagaaat gggttgcgtg 240

gtgattgata tgaaagggat ttgtgccagc ttgcaagacg tccctgtggt gataccggga 300

gtaaatcagg aaaaattggt agatttacgt cagcgtaata ttgtgtcctt agccgatcca 360

caagtgacac aacttgcatt agtcatcgcc tcgttgatgt caaatcacga aatcaaagac 420

attgccgtaa cctcgttatt acctgcatct tatactaacg gagaaacggt aggtaaatta 480

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caaatggtga gcgtattatc ggattatgca ttagatcctc aatcttgctt agcgagctgg 720

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Tyr Leu Ile Arg Ser Cys Tyr Asp Ser Val Arg Lys Phe Tyr Glu Asn
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gag cta ggt gtt tat aca gta atg act gca tta cta gca ttt cca tta   2793
Glu Leu Gly Val Tyr Thr Val Met Thr Ala Leu Leu Ala Phe Pro Leu
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Leu Val Leu Ile Gly Phe Thr Val Asp Gly Thr Gly Val Val Leu Asp
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aaa gca cgt tta gct caa gga atg gat caa gct gct tta gct ttg gtt   2889
Lys Ala Arg Leu Ala Gln Gly Met Asp Gln Ala Ala Leu Ala Leu Val
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gct gaa aac aat gac tac cga gaa aat aaa aaa cat ggt gat gtt aat   2937
Ala Glu Asn Asn Asp Tyr Arg Glu Asn Lys Lys His Gly Asp Val Asn
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cgg caa gta gta tcg cct caa gac aaa gca aaa ttt ggt ggt aat gaa   2985
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Phe Met Ala Lys Gln Glu Lys Arg Asn Gln Glu Leu Ile Gln Gly Ile
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gcc aaa ctt tat tta cgt tca gaa aat gcg aat gct tca tct gat gca   3081
Ala Lys Leu Tyr Leu Arg Ser Glu Asn Ala Asn Ala Ser Ser Asp Ala
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cca atc act att gat aaa cct ttt cat tat tca tgt gag gag tta gat   3129
Pro Ile Thr Ile Asp Lys Pro Phe His Tyr Ser Cys Glu Glu Leu Asp
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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 tcg ggg   4041
Glu Leu Asn Ile Val Arg Pro Ser Gly Trp Thr Ser Ala Ser Ser Gly
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Leu Leu Val Gly Ala Asn Ile Met Met Asp Glu Asn Lys Asn Pro Asp
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gcg caa cct tcg 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
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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
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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
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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
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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
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Cys Val Gly Asp Gln Tyr Tyr Thr Ala Tyr Ser Lys Glu Glu Leu Leu
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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
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tca tct cat aaa ccg aaa ttt taagattgtc caaggataac gctaaaaaat      4476
Ser Ser His Lys Pro Lys Phe
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Gly Gly Asn Glu Phe Met Ala Lys Gln Glu Lys Arg Asn Gln Glu Leu
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Ile Gln Gly Ile Ala Lys Leu Tyr Leu Arg Ser Glu Asn Ala Asn Ala
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Ser Ser Asp Ala Pro Ile Thr Ile Asp Lys Pro Phe His Tyr Ser Cys
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Glu Glu Leu Asp Leu Pro Thr Ala Asn Glu Tyr Ala Arg Arg Lys Pro
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Ile Val Cys Glu Val Gln Gly Gly Val Asn Arg Lys Phe Trp Leu Pro
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Val Ser Glu Ser Leu Val Ser Glu Asp Lys Leu Lys Lys Asp Arg Val
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Arg Leu Glu Ser Asp Thr Ser Tyr Ala Ile Lys Glu Lys Gly Ile Val
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Ile Pro Val Glu Leu Met Leu Val Ser Asp Tyr Ser Gly Ser Met Asn
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Ser His Leu Gln Asp Lys Asn Gly Arg Ser Leu Gly Lys Ala Lys Ile
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Tyr Asp Lys Phe His Ser Ser Thr Cys Arg Gly Ser Gly Ser Ser Arg
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acattatcag ctaaaatgag tatcccattg attttgttta ttatgttccc aataatcatt 660

ttaattctag caccaggtat aatgagggta tttccaa 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 tcg 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
Ala Leu Val Lys Asn Gly Asp Leu Asp Tyr Ala Lys Asp Ile Ile Val
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 ctatcaaata taaaaggaac ctcgtcaatt gaatttgctt tgacgatagc 1548

gttctattta tttgttgtga tgtttatttt tgaattttgt cgattagcgg ttgcgacagc 1608

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atcgacaatt ggatatttgg cgttgttaga agataataaa tttgatgtaa aagtccaata 1788

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<211> 257
<212> PRT
<213> Pasteurella multocida

<400> 61

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			20					25				30			
Ser	Met	Ser	Ser	Glu	Thr	Ile	Thr	Ala	Lys	Glu	Thr	Leu	Tyr	Glu	Ser
		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 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
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Arg
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<210> 62
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<212> DNA
<213> Pasteurella multocida

<220>
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<222> (1)..(600)

<220>
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<400> 62

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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 gtg 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

ggt 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 taaccaccgg  630
Glu Leu Asn Val Asp Arg Val Ser
        195                 200

ttaataaaac accagcaatt tcaacgccat tcatggcaga taatgccgct gcgacgatca 690

catcaggacg atccgcggaa gtgacaagta aacttccaac gcggaaatgt tccaccatat 750

tggtcaaatt acgtgcacag aaagtgatgc cacgaatgcg acgttcattg atcgcgcctt 810

catgaataat ggcagcacct aaatgtttgg ctaaatcaat ggcacgagtc gcaattaatt 870

ctgcgctcca aggaatacat gccaagattt taattgggct tttctcaaat aaatgataaa 930

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gagtacgacc agattcatca atcggcgcat taaatttatt gatcacaaca ccaagtaaat 1050

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gaatcggcag ttaattgatc tttacgcgat gcaaaggcgc gcggtatctt gtgcaataac 1650
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aagttcttca ttcgttggga tcaccatggc aacaggcgta ttgtctgctg taatcacccc 1710

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<210> 63
<211> 200
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<213> Pasteurella multocida

<400> 63

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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
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Glu	Leu	Asn	Val	Asp	Arg	Val	Ser								
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<210> 64
<211> 278
<212> DNA
<213> Pasteurella multocida

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<223> unknown O

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Met Lys Ile
1

act att aca cga aat cat cca gaa gta ttt caa gaa tcc gct cgt tta 164
Thr Ile Thr Arg Asn His Pro Glu Val Phe Gln Glu Ser Ala Arg Leu
5 10 15

gta gcc gaa aag ttc att aaa gcc caa tgt gta gaa gca tta aca ttg 212
Val Ala Glu Lys Phe Ile Lys Ala Gln Cys Val Glu Ala Leu Thr Leu
20 25 30 35

gct ttg att gag ggt gtc gag cac ttt gtg ctg gaa ggt gag gag gaa 260
Ala Leu Ile Glu Gly Val Glu His Phe Val Leu Glu Gly Glu Glu Glu
40 45 50

agc aaa agg gga cat agt 278
Ser Lys Arg Gly His Ser
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<210> 65
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Ala Arg Leu Val Ala Glu Lys Phe Ile Lys Ala Gln Cys Val Glu Ala
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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
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<210> 66
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1 5 10 15

gca atg cgt gca tat ctt gat aaa gaa cag ggc 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 tgt 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

acttaaattg atgaatttaa tcatcgacgg taacaaatat ctcggcgaag tcacggaagt 687

gactcaacca aaattagcaa tgaaaatcga agaatttcgc gcgggcggta tgattggttc 747

ggtggatgtc aatctcgggc ttgaaaagct cgaagcggaa tttaaagccg gtggctacat 807

ggtcgaatta attaaaaaat tcggcgggtc aatcaacggc attccattgc gttttcttgg 867

ctcatatcag cgtgatgaca cagaagaagt cacatctgtt gagcttgtga tgcaaggtcg 927

atttactgaa attgacagcg gaaacagcaa agtgggcgat gacactgaac aaacattcaa 987

agtgccttta acgtattaca aaatcattgt tga                              1020
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<210> 67

<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 cgacggggtt aatttcttct atcgtttcaa tcattgcgtt 60

taccattatt ttatggaatc tctctggacc gatgaccatt gccaatattg aaattcctca 120

cgcgatggtc tttttggtct ttatttacgt gctgtttagc agtattgtgg catttaaaat 180

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cggtcgcccg ttaattcagc tcaattttgc caatgaacgc ttaaacgcca actaccgtta 240

ttcacttatc cgtctgaaag aatatgctga aagcattgct ttttatcgtg gtgaaaaaat 300

ggaaaaacgt ctattgacca cacaatttaa tcaggtgatt gataacgttt ggcaagtaat 360

ctaccgcacc ttgaaattat ccggttttaa cttaatcatt acgcagattt cggtggtttt 420

tccgctggtg attcaagtga cacgttattt tcgtcgacaa taggtgcata tgagggtgtt 480

agaatagcga tactttctgt tggaaaagta aactctttaa tataaataga aatcgcttga 540

atgattctcg ggcaaaaaat aatgtactca tttgcgatct catactgata atggcgaagt 600

aaatatcttc ttacaatatt atggtaatta tcaggtaata ccgtatagcc atagattcca 660

gttctatttt gttttgctaa ataattgatg agcatttgag gcgcaggtaa atccatatct 720

gcaacagaca ttgaaatcat atccttgccg tatttacgag taattgccca tttagcacta 780

tgacaatctg atctatcagt aaaaacatca aacaaattat ccgtcataca tgttctccaa 840

tattggattt atataaactt tagaacttga ggtagattgt tggaattgtt aaatctggta 900

tttctattac gttttttctt ttttgtgata taagccacaa taaccaataa tcttaattgt 960

taagtgaaat aacgtaattg atcctcccat tgttttacta aattatgtct ctgaaactta 1020

tttgttcagg 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 ggc 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 tcg 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 ggc 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 ccg 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 ctc 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 cacgtaattc aaaggctttg tgtatgtgcg aatgatattc 2386

acaacaaagt tctgcaaaat cttgaattgc gtgaggtaat ttaaagcgct gacataagcg 2446

tcttgtcggc atgacaccag ctttttcatg tccataatga tgtggcaata tttcttttgg 2506

tgttaaggct tttcctaaat catgacaaat tgcagcaaaa cgtaccgcac ttttgtcact 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

<220>
<221> CDS
<222> (298)..(1905)

<220>
<223> yabk

<400> 70
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aatgcctgtg cggatcattt ccttgccttt ttacttcatc cagaagcaca agggcattta 120

gtcaagaata atgtgatgtt accggtgatt aataccaata ttgaaccgca ctttgatgcc 180

cttagagcca cccaaatgaa cacgaaagtg ctcgatacct caaaagtgaa tgccgaacaa 240

gtcaaaaaat ggattgctgt ttggcaaacg accctaaccc 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 cac 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 ggc 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 Glu 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 ggc 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 Glu Phe
225                 230                 235                 240

gat gta ccg aaa gcc ggc 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 tcg 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 ccg cta ctc aat acg cta gtt tct gct ttg ctt tcg tct cag ttt   1257
Leu Pro Leu Leu Asn Thr Leu Val Ser Ala Leu Leu Ser Ser Gln Phe
305                 310                 315                 320

ttt acc ttg tgg tta caa cct caa tta tgg aaa gca tta ggt tac tcg   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 Val Cys Cys Asn Ala Leu
                405                 410                 415

gct gct atg cct ttt gtg ttg cgt att ttg gct tta ccg 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 tcg tta ccg 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 ttt att tta ttg gtt ttt tgt 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 ccg cgt gat gat taatttaaac ggtgttcagt tttcctataa  1935
Arg His Gln Glu Pro Arg Asp Asp
    530                 535

tacctttact tttgagctgg atttgcagat tcctgctcaa caaaaagttg ctattattgg 1995

cgccagtggc gcagggaaga gtaccttatt aaatttgatt gcgggttttg cattgccaca 2055

gcaaggggaa atttggttga atggtgaaaa tcatagccaa actcaacctt atgaacgtcc 2115

ggtatctatt ttgtttcaag aaaacaactt gtttacgcat ttgactgtgg cagagaatat 2175

ggcattaggg ctgaaaccaa gcctaaaact gaccgcactt gaacaacaac gcgtacaaca 2235

agtggcaagt gcagtgggtt tgcagggttt tcttaatcaa ttacccaccc agttatcggg 2295

tgggcaaaaa cagcgtgtgg cgttggcgcg ttgtttatta cgcgataagc caattttgtt 2355

attggatgaa ccttttctg ccttagatcc cgatttacgg gcagaaatgt tgcatttatt 2415

gttacagttg tgtgatgaaa aaaaattaac actcctgatc gtgacacatc aagtgaacga 2475

attacagcag aaaatggatc gtatgattcg ttttgaacat ggtaggatga gtgagtccac 2535

cattttgaag gataatttta acgaaaaaca gaccgcactt taggcggctt attaattaga 2595

taaggaaaga gaaaaatatg acaacggcaa cggcatttga gattcgtaca cttactcctc 2655

acccgacctt agaatattgg tctgtgtgta aaattgaagc cctgtttgag acccctttt 2715

tagatttggt ttatcgggct gcgcaagtgc accgagaaaa ctttaatcct aaagccattc 2775

aattatccac tttaatgtcg attaaaacgg ggggatgtcc agaggattgt ggctactgtc 2835

cgcagtcagc acgttatcat actggagtag aaaagcagca attactcgat gtggaagaaa 2895

ttgttgaaaa agccaaaatt gccaaagcac gtggtgcagg gcgcttttgt atgggggctg 2955

catggcgtgg accgaaaccg aaagacattg aaaaagttac cgcaatcatt aaagcggtga 3015

aagaactggg cttagaaacc tgtggtacct ttggtttatt gcaagatggg atggcagaag 3075

atttaaaaga agcgggtttg gattattata accataatct cgatacagcc ccagaacact 3135

acggtaatgt gattggtacc cgtcaatttg atgatcgtat taatacgtta ggtaaagtgc 3195

gtaaagctgg cttaaaagtg tgctgtggcg ggattattgg catgaatgaa acccgtaaag 3255

aaagagcagg attaattgct agcttagcta atttagaccc gcaacccgaa tcggtgccga 3315

ttaatcaatt agtgaaagtg gaaggtaccc ctttagccga tgcggcagaa ttagactgga 3375

cagaatttgt gcgcactatt gcggtggcgc gtattaccat gccgaaaagc tatgtacgtt 3435

tatcagcagg gcgtcaaggc atgtcggaag aaatgcaagc 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                 400

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                 480

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


<210> 72
<211> 3182
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (1544)..(2809)

<220>
<223> ygiK

<220>
<221> misc_feature
<222> 452
<223> N = A or T or G or C
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cttcatgtca ctttcagttt cagctgcaga aattaatttg aaatttgaaa gttcgaattt 120

tgcaggagaa aaagtttatg aaatccaaaa agaatggact gacaatattg aaaaagcttc 180

caatgggaga ataagtatag agttattacc tctcgactca gtcttaaaat ctagtgacat 240

gctttctggt gttcgaaata aaattattga tggagcggtt gcaacagcgg caatgtatgc 300

aggcactgac cctggattcg gattaattgg tgatactatt tctgcttgga accatgacga 360

agatatttta aatttttact ataatggagg tggttttgaa gttgttgata atattttcca 420

acaatatggt gccaaactca ttggtgtatc anttacggga gcagaatcat taccatcgaa 480

agtaaaaata gctaatactg aagattttaa aggtataaaa attcgggctc cctctggtcc 540

tatccaaaaa ttgtttgcaa gattaggagc cgctcctgtt ggtcttcctg gttcagaaat 600

ctatactagt ttagaaaaag gtattattga tgctgccgat ttctcaacgt ttgcaaataa 660

tcaagcacaa ggagtccatg atattgcaaa atatccaatc tatccgggaa ttcattcttc 720

accagccgtt catatgatta tgaatcataa aacttggagt agcttaactc catcggatca 780

agcattctta attgcttact ttaaagggat ggctctcgat actctgactc gtgctcatta 840

tgaagataaa ctagcatata aagaagcact tgagaaagga gtacaaccag tttcttggaa 900

tcaacaagaa attacaaaag ttcgttctat cgctaaagaa atttggcaag agatagctca 960

acaatctgaa ataggtaatc aagtattatc aagtattaat gaaattccta gaatctcaag 1020

gaatgctgca ataatcgtca agatggataa gacgatatcg tcttatccat taaggagtaa 1080

aacatgctta tttctaaata tttattatgg ctctgtaata agctagatca aatattcatt 1140

aaagtaggtt attacgtttc ttatattttt ctattagttg ttatcattgg ttttacgagg 1200

ttgttgctcg gtatttattc tctagcccaa cactttgggt tcatgaagta acaacatttt 1260

taataagtct atcattactt tatggtggag tagcttgtta cgccagtaat aaacatattg 1320

ccatgacatt tattagacaa aaattaccta ataagatcaa atggttacta gaactcttag 1380

ttgaaatact tatttttatc ttctttattt tgcttagtta cggagcatac ttatcagcta 1440

gagaagcatt atttactcca tcaggaaaat tcaaaatgca aacttctgga agtgtattag 1500

acatgccatt tccagcaatt gaaaaaagtt tcttctttat ttc atg cct cat cat 1555
Met Pro His His
1

tgt tgt tct ttc agt act aca tat att ccg 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 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 ggg 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 ggg 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 tttgctccgt    2859
Thr Phe

tttgtggatc gactgccgca tgagcagatt tgccaaaaaa ttcaattaca tacttcccaa 2919

tccctttttct ttcgttaacg tttccactta gattgcccag aagccgatct gtctgaatgg 2979

gaacaagtgt tataccaaga agcgaatcca acaggtgaag tggtgatcgg tatggtgggt 3039

aaatacactg aattaccgga tgcctacaaa tcggttaatg aagccttgaa acacgcaggc 3099

ttaaaaaacc gtcttagcgt gcaaatcaaa tatattgatt cacaagatgt ggaaaccaaa 3159

ggcacagaag tgttagaagg cgt                                          3182


<210> 73
<211> 422
<212> PRT
<213> Pasteurella multocida

<400> 73
Met Pro His His Cys Cys Ser Phe Ser Thr Thr Tyr Ile Pro Ser His
  1               5                  10                  15

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


<210> 74
<211> 2787
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (463)..(936)

<220>
<223> yhcJ

<400> 74
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gcatacaaag caagaatgtt ggccagtgtg tcatgcatcg cattggcagc atcagcttgt 120

ggcgttgcaa tctgttggcg ttgttctatt ttgccgtctg ttacaatagc cgaggcaatt 180

tttgttccac caatatctaa tgctaaacag cgcataggct ctccttctgt gatgacttat 240

tttgccgatt tgacggcatc ggcaaaccag cttacgatat gttcgaggcg agtcagcgca 300

gatcctacgg tgacagagta agcaccaatc tcaattgcgg ttttcgccaa ttctggggtg 360

ttatagcgcc cttctgccat cactcggcag ccagcagcat tcaaatcttt gactaactga 420

taatccggtt cagctggaat ttcaccgcca 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
  5                  10                  15                  20

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
                25                  30                  35

atg gct tca cgt gta gtt gga cgg acg cga tcg gta cca tca aaa gca   618
Met Ala Ser Arg Val Val Gly Arg Thr Arg Ser Val Pro Ser Lys Ala
            40                  45                  50

ata ata tcg 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
        55                  60                  65

ggg cta ata cga acg gga ctg tca ggt aaa tcg cgt tta acg ata cca   714
Gly Leu Ile Arg Thr Gly Leu Ser Gly Lys Ser Arg Leu Thr Ile Pro
    70                  75                  80

ata atc ggt aca ttg acg acg tta cgc gtg gct ttt aaa ttt tcg 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 cca 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
        135                 140                 145

tgt gat agt ttt gac ata tta act cca gtc taaatttatc aaaagaagat     956
Cys Asp Ser Phe Asp Ile Leu Thr Pro Val
    150                 155

tgactccaat ttgcataggt taatcttaga attaaaaaat aacaaccaaa ataataaaaa 1016

tttgagatct ttgtcgcata tttattcata gggaatagac agcttaattt tagttatgat 1076

ttgtcaatcc ttgctatttt ttgtgtttgc tggtttgcga tacactgttc taatattgct 1136

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tgagtcagaa tgtcatttaa ctatcgcatg acttgcgccg gtgaatacgt ttcttcctta 1436

caaatatcat tgacgcctaa aaaaagaaaa acagattgtc caagttgttg aatccgttta 1496

ggtttaacga taacatccaa atattgtcgc gtactgacgc cagaaagtcc taaattggcg 1556

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tagtttttc actttagaat gccaaacgtg tgaaatttat ttcatcatca ttttaacgta 1916

atcccaacgt aaccaataga ggagaactca taatgaaatt taaaaaacta ctacttgcat 1976

ctttatgttt aggtgtttca gcttctgtat ttgcagcaga ttacgatctt aaattcggta 2036

tggttgcggg tccaagctca aacgaatata aagcagtaga attctttgcg aaagaagtga 2096

aagaaaaatc caatggcaaa attgatgtgg ctattttccc tagctcacag ttaggtgatg 2156

accgtgtgat gattaaacaa ttaaaagacg gtgcattaga ctttacgtta ggtgaatcag 2216

cacgtttcca aatttacttc ccagaagcag aagtatttgc gttgccttat atgattccta 2276

attttgaaac ctctaaaaaa gcgttgctcg acacaaaatt tggtcaaggt ttattgaaaa 2336
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aaattgataa agagttaaac gtacaagtgt tatctgtggc gtataacggt acacgtcaaa 2396

caacttctaa ccgtgcaatc aacagcattg aagacatgaa agggttaaaa ttacgtgtac 2456

ctaacgcggc aaccaacctt gcttatgcaa aatacgtggg tgcagcgcca acaccaatgg 2516

cattctctga agtttacctt gcgcttcaaa caaactctgt ggatggtcaa gaaaacccat 2576

taccgacaat ccaagcacaa aaattctatg aagtacaaaa atacttagcg ttaactaacc 2636

acatcttaaa tgaccaactt tacttaatca gtaacgatac gttggcagat ttaccagaag 2696

atttacaaaa agtggttaaa gatgcagcag cgaaagccgc tgaatatcac actaaactct 2756

tcgttgacgg tgagaacagc ttagttgaat t 2787

<210> 75
<211> 158
<212> PRT
<213> Pasteurella multocida

<400> 75
Met Val Leu Pro Ile Ile Ser Thr Pro Lys Leu Trp Gln Tyr Ile Pro
1 5 10 15

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
145 150 155

<210> 76
<211> 2787
<212> DNA
<213> Pasteurella multocida

<220>
<221> CDS
<222> (1949)..(2785)

<220>
<223> yiaO

<400> 76
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ggcgttgcaa tctgttggcg ttgttctatt ttgccgtctg ttacaatagc cgaggcaatt 180

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tctaccccta agttgtggca atacatccct tctttcaaaat tagaacaatc cgccatggct 540

aaacaaccta attcttttgat tcgtttaata atggcttcac gtgtagttgg acggacgcga 600

tcggtaccat caaaagcaat aatatcggcg cctgctgcgg ctaactcttc aatgtcttgt 660

aaaaatgggc taatacgaac gggactgtca ggtaaatcgc gtttaacgat accaataatc 720

ggtacattga cgacgttacg cgtggctttt aaattttcga tcccttcaat acgtaacccg 780

gcagcaccac cgataacgga tgcttgcgcc atggcggcaa caatttctgg cgagtccatt 840

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tgcggatgtg atagttttga catattaact ccagtctaaa tttatcaaaa gaagattgac 960

tccaatttgc ataggttaat cttagaatta aaaaataaca accaaaataa taaaaatttg 1020

agatctttgt cgcatattta ttcataggga atagacagct taattttagt tatgatttgt 1080

caatccttgc tatttttttgt gtttgctggt ttgcgataca ctgttctaat attgctttga 1140

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caccgttaga atcacaaaag tatttttgtg tttcaacgta agtcacgtct gacggacaat 1260

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tgaccggtgt ggcttctaat aaaaagtagt gggacgtagg agaaatggtg tgtaggtgag 1380

tcagaatgtc atttaactat cgcatgactt gcgccggtga atacgtttct tccttacaaa 1440

tatcattgac gcctaaaaaa agaaaaacag attgtccaag ttgttgaatc cgtttaggtt 1500

taacgataac atccaaatat tgtcgcgtac tgacgccaga aagtcctaaa ttggcgacgg 1560

tttgtcccgc taattgaggt gtgcctgcta cctgttcgtc ccacatgtca aaaagtgaat 1620

gaccaattaa gctgatattg gcaggtttgg aaaatttcgc cattttgctc tgatagcgtt 1680

gataaatatc ctgatcactt agcatgtgtg gacctctatt ttgaaataaa acgctaagta 1740

ttatataaaa cctgatatgc cggtaaacag taaacttatc ttccgtaggg gtaaatattc 1800

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tttttcactt tagaatgcca aacgtgtgaa atttatttca tcatcatttt aacgtaatcc 1920

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
Val Gln Val Leu Ser Val Ala Tyr Asn Gly Thr Arg Gln Thr Thr Ser
            140                 145                 150

aac cgt gca atc aac agc att gaa gac atg aaa ggg tta aaa tta cgt   2452
Asn Arg Ala Ile Asn Ser Ile Glu Asp Met Lys Gly Leu Lys Leu Arg
        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

gcg cca aca cca atg gca ttc tct gaa gtt tac ctt gcg ctt caa aca   2548
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
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aaa ttc tat gaa gta caa aaa tac tta gcg tta act aac cac atc tta   2644
Lys Phe Tyr Glu Val Gln Lys Tyr Leu Ala Leu Thr Asn His Ile Leu
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aat gac caa ctt tac tta atc agt aac gat acg ttg gca gat tta cca   2692
Asn Asp Gln Leu Tyr Leu Ile Ser Asn Asp Thr Leu Ala Asp Leu Pro
        235                 240                 245

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
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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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aaacgac atg acg aaa gta att cat act gac aat gca cca gcc gcc att   949
       Met Thr Lys Val Ile His Thr Asp Asn Ala Pro Ala Ala Ile
         1               5                  10

ggt 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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                35                  40                  45

gta gca caa gca cgt caa tcg tta gaa aac gtg aaa gcg att gtg gaa   1093
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 cttgcattta tcttagtcgt agcaaaacaa           1334
Val Lys Ala

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20 25 30

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

Arg Leu Pro Lys Asp Val Gly Ile Glu Ile Glu Ala Ile Ala Val Lys
115 120 125

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gaattaggtt gaaactgtgg gagtggggcg tgttcgataa gctggacttg atgtccttgt 240

ttacgtaagc caagcgcaca ggctgcacca accatgccac cgccaaccac gatcatgtct 300

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gtcagtcaca tttttatagg ttaactgaat tttttaaacg at atg acg caa aaa    474
                                              Met Thr Gln Lys
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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 ctc 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 ctc 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
Val Val Pro Tyr Thr Arg Gly Glu Glu Val Ser Arg Pro Val Asp Asp
165                 170                 175                 180

gta tta ttt gaa att gca cag ttg gca gag caa ggc gtg cgt gaa gtg   1050
Val Leu Phe Glu Ile Ala Gln Leu Ala Glu Gln Gly Val Arg Glu Val
                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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Asp Gly Ile Asp Arg Leu Arg Phe Thr Thr Ser His Pro Ile Glu Phe
    230                 235                 240

act gat gac att att gat gtg tac cgt gat acg cca gag ttg gtg agt   1242
Thr Asp Asp Ile Ile Asp Val Tyr Arg Asp Thr Pro Glu Leu Val Ser
245                 250                 255                 260

ttc tta cac tta cct gta caa agt ggt tct gat cgt gtg tta tct atg   1290
Phe Leu His Leu Pro Val Gln Ser Gly Ser Asp Arg Val Leu Ser Met
                265                 270                 275

atg aaa cgc aat cat acg gca tta gaa tat aaa tcg att att cgg aag   1338
Met Lys Arg Asn His Thr Ala Leu Glu Tyr Lys Ser Ile Ile Arg Lys
            280                 285                 290

tta aga gcg gtg cgt cca gag att caa att agc tca gat ttt att gtc   1386
Leu Arg Ala Val Arg Pro Glu Ile Gln Ile Ser Ser Asp Phe Ile Val
        295                 300                 305

ggt ttc ccg ggc gaa aca gca gaa gat ttc gag caa acc atg aat tta   1434
Gly Phe Pro Gly Glu Thr Ala Glu Asp Phe Glu Gln Thr Met Asn Leu
    310                 315                 320

att gca caa gta aat ttt gat atg agt ttc agc ttc att tat tca gca   1482
Ile Ala Gln Val Asn Phe Asp Met Ser Phe Ser Phe Ile Tyr Ser Ala
325                 330                 335                 340

cgt cca ggc acg cca gca gca gat atg cct gat gat gtg aca gaa gaa   1530
Arg Pro Gly Thr Pro Ala Ala Asp Met Pro Asp Asp Val Thr Glu Glu
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gag aag aaa caa cgt tta tat gtg ttg caa caa cgc att aac aat caa   1578
Glu Lys Lys Gln Arg Leu Tyr Val Leu Gln Gln Arg Ile Asn Asn Gln
            360                 365                 370

gcc gcg caa ttt agt cga gca atg tta ggc aca gaa cag cgc gtg tta   1626
Ala Ala Gln Phe Ser Arg Ala Met Leu Gly Thr Glu Gln Arg Val Leu
        375                 380                 385

gtg gaa gga ccc tcg aaa aaa gat tta atg gaa ctc aca ggg cgt aca   1674
Val Glu Gly Pro Ser Lys Lys Asp Leu Met Glu Leu Thr Gly Arg Thr
    390                 395                 400

gaa act aat cgt atc gtc aat ttt gtg ggc acg cct gat atg att ggg   1722
Glu Thr Asn Arg Ile Val Asn Phe Val Gly Thr Pro Asp Met Ile Gly
405                 410                 415                 420

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Lys Phe Val Asp Ile Lys Ile Thr Asp Val Phe Thr Asn Ser Leu Arg
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Gly Glu Val Val Arg Thr Glu Glu Gln Met Gly Leu Arg Val Val Gln
            440                 445                 450

tcg cca caa atg gtg att aat cgt act cgt aaa gaa gat gaa ctc ggc   1866
Ser Pro Gln Met Val Ile Asn Arg Thr Arg Lys Glu Asp Glu Leu Gly
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gtg gga cgt tat cac gcg tagtcgtgct atcccttcaa atatttaacc          1914
Val Gly Arg Tyr His Ala
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Ser	Phe	Pro	Glu	Ile	Glu	Lys	Phe	Asp	Arg	Leu	Pro	Glu	Pro	Arg	Ala
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Cys Ser Phe Cys Val Val Pro Tyr Thr Arg Gly Glu Glu Val Ser Arg
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Pro Val Asp Asp Val Leu Phe Glu Ile Ala Gln Leu Ala Glu Gln Gly
            180                 185                 190

Val Arg Glu Val Asn Leu Leu Gly Gln Asn Val Asn Ala Tyr Arg Gly
        195                 200                 205

Ala Thr His Asp Asp Gly Ile Cys Thr Phe Ala Glu Leu Leu Arg Leu
    210                 215                 220

Val Ala Ala Ile Asp Gly Ile Asp Arg Leu Arg Phe Thr Thr Ser His
225                 230                 235                 240

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

Thr Met Asn Leu Ile Ala Gln Val Asn Phe Asp Met Ser Phe Ser Phe
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Ile Tyr Ser Ala Arg Pro Gly Thr Pro Ala Ala Asp Met Pro Asp Asp
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Val Thr Glu Glu Glu Lys Lys Gln Arg Leu Tyr Val Leu Gln Gln Arg
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Ile Asn Asn Gln Ala Ala Gln Phe Ser Arg Ala Met Leu Gly Thr Glu
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Gln Arg Val Leu Val Glu Gly Pro Ser Lys Lys Asp Leu Met Glu Leu
385                 390                 395                 400

Thr Gly Arg Thr Glu Thr Asn Arg Ile Val Asn Phe Val Gly Thr Pro
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Asp Met Ile Gly Lys Phe Val Asp Ile Lys Ile Thr Asp Val Phe Thr
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Asn Ser Leu Arg Gly Glu Val Val Arg Thr Glu Glu Gln Met Gly Leu
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Thr Val Val Asn Pro Glu Arg Arg Arg Phe Phe Lys Glu Ala Thr Arg
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Lys Gln Ser Leu Ala Arg Glu Gly Val Ala Leu Arg Pro Pro Phe Ala
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ctt gag aat gag aaa gcg ttt tct gct gcg tgc att cgt tgt ggt cag 607
Leu Glu Asn Glu Lys Ala Phe Ser Ala Ala Cys Ile Arg Cys Gly Gln
55 60 65

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Cys Val Gln Ala Cys Pro His Glu Met Leu His Leu Ala Ser Leu Ile
70 75 80

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Ser Pro Met Glu Ala Gly Thr Pro Tyr Phe Ile Ala Arg Asp Lys Pro
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Cys Glu Met Cys Val Asp Ile Pro Cys Ala Lys Ala Cys Pro Thr Gly
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Leu Val Met His Arg Asn Glu Arg Thr Gly Lys His Ala Val Phe Ile
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cca aca gtg cat tcc gaa gcc tgt aca gga tgt ggc aaa tgt gaa gaa   991
Pro Thr Val His Ser Glu Ala Cys Thr Gly Cys Gly Lys Cys Glu Glu
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Ala Cys Val Leu Glu Glu Ala Ala Ile Lys Val Leu Pro Met Ala Leu
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gcg aaa ggc atg tta ggt aaa cat tac cgt tta ggt tgg gaa gag aaa   1087
Ala Lys Gly Met Leu Gly Lys His Tyr Arg Leu Gly Trp Glu Glu Lys
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gaa aaa gcc ggg cat tcc ctt gcg cca gaa ggc att att tct ctc ccg   1135
Glu Lys Ala Gly His Ser Leu Ala Pro Glu Gly Ile Ile Ser Leu Pro
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Thr Arg Leu Pro Glu Ser Leu
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Cys Gly Gln Cys Val Gln Ala Cys Pro His Glu Met Leu His Leu Ala
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Ser Leu Ile Ser Pro Met Glu Ala Gly Thr Pro Tyr Phe Ile Ala Arg
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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
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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
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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
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     15                  20                  25

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Met Ser Ile His Phe Asp Thr Leu Asn Asn Asn Ala Val Arg Phe Leu
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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
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Ser Ser Ser Leu Gly Phe Leu Ile Leu Lys Thr Val Pro Ser Phe Ser
        80                  85                  90

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Tyr Val Thr Ile Ser Thr Leu Asn Arg Val
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gtcagaataa gtactgccgg tatatcgtct taatctaaga ttaagcttgc cacttttgtt 2859

cgataaagcg tcaaacgaaa gcacgacttt accgtccttg acttccacct gatcttcaat 2919

gagcacttga cttagtgcga ccaatcgacc gttggcagtc agtgtcgcaa tgccgtgatc 2979

cgtatcaagc gttacaccgc tatttttcc ccagttttta ttgagctttt cactatgttt 3039

cagtaagttt ctgccaccaa tctgcaactg attaaactta gcttcaagcg tttcactctt 3099

gactgcaagc gactttgttt cattgctaac cgtctgctca agtgctgtga ttttggatgt 3159

taaatctaac ttagttgcat tgacttcatc agtccattct gactttaact cttttctcgc 3219

aagtgacgcc acttcatctt tgctagcttt cgtttctttt aagtcagaaa tgccactagt 3279

attttgcgcc actttagaat cgagcgtttc tagttttgta gagaaagatt tgtctttttc 3339

gctagccgtt ttttgaatta gctgtatttc actttcgctc aatccaactc tagcagttag 3399

actgtctagc ttgtcagcag tagatttatt cacagtcgct tgtgattgct tgtgttgaat 3459

aatatccgcg cttacttccg agatagccac gtcga                            3494


<210> 85
<211> 103
<212> PRT
<213> Pasteurella multocida

<400> 85
Met Thr Lys Leu Ser Ile Gln Arg Asp Asn Leu Ile Cys Leu Ser Tyr
  1               5                  10                  15

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

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
aggccggtac cggccgcct 19

<210> 87
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PRIMER

<400> 87
cggccggtac 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
ctaggtacct acaacctc 18

<210> 90
<211> 119
<212> DNA
<213> Artificial Sequence

<220>
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<223> Description of Artificial Sequence: transposon insert

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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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<223> N = A or T or G or C

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<222> 35
<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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<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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<223> N = A or T or G or C

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<223> N = A or T or G or C

<220>
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<222> 87
<223> N = A or T or G or C

<220>
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<222> 89
<223> N = A or T or G or C

<220>
<221> misc_feature
<222> 91
<223> N = A or T or G or C

<220>
<221> misc_feature
<222> 93
<223> N = A or T or G or C

<400> 90
ctaggtacct acaacctcaa gcttnknknk nknknknknk nknknknknk nknknknknk 60

nknknknknk nknknknknk nknknknknk nknkaagctt ggttagaatg ggtaccatg 119

<210> 91
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 91
tacctacaac ctcaagct 18

<210> 92
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificia_ Sequence: primer

<400> 92
tacccattct 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
tacccattct aaccaagctt 20

<210> 95
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 95
ggcagagcat tacgctgac 19

<210> 96
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 96
gtaccggcca ggcggccacg cgtattc 27

<210> 97
<211> 531
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> atpG

<400> 97
tgttgagctt ggtttagtag ggtcgaaagg cgtaagcttt taccaaaatc taggcttaaa 60

cgtgagatct caagtaacgg gattaggcga taatccggaa atggaacgta tcgtgggcgc 120

agttaatgaa atgattaatg cgttccgaaa cggagaagtg gatgcggttt acgtcgctta 180

caaccgtttt gaaaatacga tgtcacaaaa acctgttatc gcacagttac ttccgttacc 240

taaactagat gacgatgaat tagatacgaa aggttcatgg gattatattt atgaaccgaa 300

tccacaagtt ttattggata gtttacttgt tcgttattta gaaactcagg tataccaagc 360

agttgtagat aacctagctt ctgaacaagc cgctcgaatg gtagcgatga aagccgcaac 420

agataatgcg ggtacattaa tcgatgaatt acaattagtg tataacaaag ctcgccaagc 480

aagcattaca aatgaattaa acgaaattgt tgcgggtgcc gcagcaattt a 531

<210> 98
<211> 25
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: primer

<400> 98
tctccattcc cttgctgcgg caccc 25

<210> 99
<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)

<400> 100

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atg ttt aaa aat aaa aca ctt tta att aca ggt gga acg ggt tct ttt   48
Met Phe Lys Asn Lys Thr Leu Leu Ile Thr Gly Gly Thr Gly Ser Phe
  1               5                  10                  15

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 ggc 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 gca aaa tcg cgt aac cta gaa ggc 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 ggc 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 ggc 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
```

```
                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                 320

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
                325                 330                 335

ggt 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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<400> 101
Met Phe Lys Asn Lys Thr Leu Leu Ile Thr Gly Gly Thr Gly Ser Phe
  1               5                  10                  15

Gly Asn Ala Val Leu Lys Arg Phe Leu Glu Thr Asp Ile Arg Glu Ile
            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
```

```
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 Leu Lys Leu Glu Phe Ile Gln Lys Met Ile Glu
                325                 330                 335

Gly Glu Tyr Ile Ser Pro Glu Val
            340
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<210> 102
<211> 4931
<212> DNA
<213> Pasteurella multocida

<220>
<223> fhaB2

<220>
<221> CDS
<222> (1)..(4929)

<220>
<221> misc_feature
<222> 1632
<223> Xaa = any or unknown amino acid

<400> 102

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atg aac aaa aat cgt tac aaa ctc att ttt agt caa gtc aaa ggt tgt   48
Met Asn Lys Asn Arg Tyr Lys Leu Ile Phe Ser Gln Val Lys Gly Cys
  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
```

```
                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                 160

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                 320

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 acg 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 ccg ttt ttc tca ata tct ccg tcg 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

ccg 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  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 tcg 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                 1600

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

gcg 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
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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  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


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<400> 104
atc cgt ggc gtt gat aaa gat cgt gtc gct gtt att gtt gat gga ata   48
Ile Arg Gly Val Asp Lys Asp Arg Val Ala Val Ile Val Asp Gly Ile
  1               5                  10                  15

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 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 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 ccg ctc aac tac tat act aca tca tgg tta acg aaa gtc ggt   480
Pro Asn Pro Leu Asn Tyr Tyr Thr Thr Ser Trp Leu Thr Lys Val Gly
145                 150                 155                 160

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 tcg act atg tcg 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 ccg 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 ccg 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 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 tcg 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                 400

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                 480

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 tcg 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                 560

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
```

```
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
```

<210> 105
<211> 669
<212> PRT
<213> Pasteurella multocida

<400> 105

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Ile Arg Gly Val Asp Lys Asp Arg Val Ala Val Ile Val Asp Gly Ile
  1               5                  10                  15

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
```

```
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
```

```
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>
<223> lgtC

<220>
<221> CDS
<222> (1)..(906)

<400> 106

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atg aat att tta ttt gtt tct gat gat gtt tat gct aaa cat ctg gtg   48
Met Asn Ile Leu Phe Val Ser Asp Asp Val Tyr Ala Lys His Leu Val
  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
```

```
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
```

<210> 108
<211> 2054
<212> DNA
<213> Pasteurella multocida

<220>
<223> pnp

<220>
<221> CDS
<222> (1)..(2052)

<400> 108

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atg gca agt atg gat gat act act gtg ttt gtc aca gtg gtt gcc aaa   48
Met Ala Ser Met Asp Asp Thr Thr Val Phe Val Thr Val Val Ala Lys
  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 ggc  672
Thr Ala Leu Ile Glu Lys Val Lys Ala Ile Ala Glu Ala Arg Leu Gly
    210                 215                 220
```

```
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 ccg 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 ggc 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
```

```
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                 560

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                 640

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
```

<210> 109
<211> 684
<212> PRT
<213> Pasteurella multocida

<400> 109

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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
```

```
                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
```

```
        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
```

<210> 110
<211> 1514
<212> DNA
<213> Pasteurella multocida

<220>
<223> purF

<220>
<221> CDS
<222> (1)..(1512)

<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

```
        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 ggc 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 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 tcg gtg ttt aca ggg  1392
```

```
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
```

```
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                 320

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 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
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<210> 112
<211> 989
<212> DNA
<213> Pasteurella multocida

<220>
<223> rci

<220>
<221> CDS
<222> (1)..(987)

<400> 112

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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
```

```
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 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
```

```
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                 240

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
```

<210> 114
<211> 1190
<212> DNA
<213> Pasteurella multocida

<220>
<223> sopE

<220>
<221> CDS
<222> (1)..(1188)

<400> 114

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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
```

```
     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                 160

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 ggc   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
```

```
Ala Phe Asp Trp Ala Val Asp Lys Asp Ile Ser Val Thr Leu Val Lys
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
```

```
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 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 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
```

```
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
```

```
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
```

```
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 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
```

<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
```

```
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 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
```

```
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
```

```
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 gtg 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
```

Cys Asn His

<210> 120
<211> 548
<212> DNA
<213> Pasteurella multocida

<220>
<223> unkP

<220>
<221> CDS
<222> (1)..(546)

<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 ggg 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
```

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

```
gat aag ttt aag ata ctt agc                                          69
Asp Lys Phe Lys Ile Leu Ser
            20


<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
            20


<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

<213> Actinobacillus pleuropneumoniae

<400> 127
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

<210> 128
<211> 242
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> apvC

<220>
<221> CDS
<222> (1)..(240)

<400> 128
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

```
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

ggt 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 ggc 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)

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<400> 130
aat att caa aaa aca gtt att gct agc ggc 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
```

```
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


<210> 131
<211> 175
<212> PRT
<213> Actinobacillus pleuropneumoniae

<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
```

```
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 ccg ttt tta act gaa cgt gat att aaa aaa gta ggc 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 ggc 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 Asp Val Ser
            100                 105                 110

gtt gag ctt ggt tta gta ggg tcg aaa ggc 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 ggc tta aac gtg aga tct caa gta acg gga tta ggc 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 ggc gca gtt aat gaa atg att aat gcg ttc   480
```

```
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 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 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
```

```
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 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 tcg 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
```

```
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 ggc 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
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<210> 135
<211> 177
<212> PRT
<213> Actinobacillus pleuropneumoniae

<400> 135

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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
```

```
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
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<210> 136
<211> 321
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> dksA

<220>
<221> CDS
<222> (1)..(318)

<400> 136

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gca tgg cat gtg 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

<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> exbB

<220>
<221> CDS
<222> (1)..(450)

<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 ttg 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

<210> 141
<211> 150
<212> PRT
<213> Actinobacillus pleuropneumoniae

<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 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

```
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

gtt 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

gtt 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
```

```
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
```

```
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

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tg cat agc gtg aga ggt ccg ggc ggc ggt tat caa ctc ggt aag caa    47
   His Ser Val Arg Gly Pro Gly 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 Gly Tyr Gln Leu Gly Lys Gln Pro
```

```
  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

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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
```

```
  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 ggc 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 ggc 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
```

```
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
```

<210> 149
<211> 183
<212> PRT
<213> Actinobacillus pleuropneumoniae

<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
```

<210> 150
<211> 1095
<212> DNA

<213> Actinobacillus pleuropneumoniae

<220>
<223> Omp5-2

<220>
<221> CDS
<222> (1)..(1092)

<400> 150

```
atg aaa aaa tca tta gtt gct tta aca gta tta tcg 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

ggt 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 tcg gat   624
Ser Tyr Ser Thr Leu Asn Arg Met Gly Ala Thr Asp Tyr Arg Ser Asp
        195                 200                 205
```

```
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
```

<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
```

```
                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 Arg Val
            340                 345                 350

Glu Val Gln Val Gln Gly Thr Lys Glu Val Thr Met
        355                 360


<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 tcg 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                  80

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                 160

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
```

```
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                 320

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

<400> 153

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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
```

```
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
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<210> 154
<211> 1076
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> pnp new

<220>
<221> CDS
<222> (1)..(1074)

<400> 154

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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

gtt 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                 160

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 tcg 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
```

```
                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                 320

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 ccg 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

ggt aaa ggc ggt gcg gtt at                                      1076
Gly Lys Gly Gly Ala Val
        355
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<210> 155
<211> 358
<212> PRT
<213> Actinobacillus pleuropneumoniae

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<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
```

```
    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
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<210> 156
<211> 1055
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> potD

<220>
<221> CDS
<222> (1)..(1053)

<400> 156

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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
```

```
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                  80

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                 160

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                 240

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
```

```
            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
Gln Trp Gln Asp 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
```

```
            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                 240

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                 320

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 ccg 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 ccg ttt   240
```

```
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 tcg 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 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

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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
```

```
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 ccg 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
```

```
            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 gac 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 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
```

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 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

```
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
aatattgcgc tcaaatggca aagcggagag catctttaaa tgttgtcccc atcgtctaga 60

ggcctaggac atcgcccttt cacggcggta accggggttc gaatccccgt ggggacgcca 120

tttaaagatg acttttgttg tctgaattgt tctttaaaaa attggaaaca agctgaaaac 180

tgagagattt tcgaaagaaa gtctgagtag taaaagataa gtaattatct tgaaaatctt 240

agctgaacaa aagcagctaa gtgtttagtt gaataaagta tcgcgttgaa tgcgttcaaa 300

taaaatttga aaatat 316

<210> 163
<211> 85
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> tRNA-leu

<400> 163
gctctggtgg tggaattggt agacacgcta tcttgagggg gtagtgtcca taggatgtgc 60

gagttcgagt ctcgcccaga gcacc 85

<210> 164
<211> 623
<212> DNA
<213> Actinobacillus pleuropneumoniae

<220>
<223> yaeE

<220>
<221> CDS
<222> (1)..(621)

<400> 164

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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 gcg 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 tcg 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 tcg 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
```

```
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

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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 ggc 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 ggc 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
```

```
                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

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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
```

```
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
```

```
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 ggc 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                 240

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 ggc 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 ggc gtt ggc 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 ggc att cct gtg att  1008
Ile Ala Glu Ala Ala Ala Ala Leu Lys Glu Arg Gly Ile Pro Val Ile
                325                 330                 335

gct gat ggt gga att cgt tat tca ggc 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 ggc 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 ggc 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 ggc 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
```

```
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 Glu 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
```

<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 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
```

```
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 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
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<210> 170
<211> 2150
<212> DNA
<213> Pasteurella (Mannheimia) haemolytica

<220>
<221> CDS
<222> (1)..(2148)

<220>
<223> pnp

<400> 170

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atg act cca att gta aaa cag ttt aaa tac ggt cag cac acc gtg acc   48
Met Thr Pro Ile Val Lys Gln Phe Lys Tyr Gly Gln His Thr Val Thr
  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 ggc 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 ggc 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 ggc 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 tcg 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                 560

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 ggc 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
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<210> 171
<211> 716

<212> PRT
<213> Pasteurella (Mannheimia) haemolytica

<400> 171
Met Thr Pro Ile Val Lys Gln Phe Lys Tyr Gly Gln His Thr Val Thr
1 5 10 15

Leu Glu Thr Gly Ala Ile Ala Arg Gln Ala Thr Ala 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

```
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
```

```
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

<220>
<221> CDS
<222> (1)..(1515)

<220>
<223> purF

<400> 172
atg tgc ggc att gtc ggt att att ggg aat tcg ccg gtg aat cag gcg   48
Met Cys Gly Ile Val Gly Ile Ile Gly Asn Ser Pro Val Asn Gln Ala
  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 ccg 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 ccg 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                 240

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 ccg 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                 320

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 ccg 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 ccg gaa  1200
Arg Ala Ala Gly Ala Lys Arg Val Tyr Phe Ala Ser Ala Ala Pro Glu
385                 390                 395                 400
```

```
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                 480

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
```

<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
```

```
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
```

```
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

<220>
<221> CDS
<222> (1)..(384)

<220>
<223> yjgF

<400> 174
atg aca gtt atc cac aca gaa aat gca ccg gca gcg att ggg cct tat   48
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 ccg 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 ccg 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
Met Thr Val Ile His Thr Glu Asn Ala Pro Ala Ala Ile Gly Pro Tyr
  1               5                  10                  15
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Val Gln Ala Val Asp Leu Gly Asn Met Val Leu Thr Ser Gly Gln Ile
20 25 30

Pro Val Asn Pro Glu Thr Gly Glu Ile Pro Ser Asp Ile Val Gln Gln
35 40 45

Thr Arg Gln Ser Leu Asn Asn Val Lys Ala Ile Ile Glu Gln Ala Gly
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Leu Thr Val Ala Asp Ile Val Lys Thr Thr Val Phe Val Lys Asp Leu
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Asn Asp Phe Ala Lys Val Asn Ala Glu Tyr Gln Ala Phe Phe Gln Glu
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(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: **PHARMACIA & UPJOHN COMPANY** [US/US]; 301 Henrietta Street, Kalamazoo, MI 49007 (US).

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(74) Agent: **WILLIAMS, Joseph, A., Jr.**; Marshall, Gerstein & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, 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, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 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, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning 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)

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(51) International Patent Classification⁷: C12N 1/20, A61K 39/102, 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

(22) International Filing Date: 17 January 2002 (17.01.2002)

(25) Filing Language: English

(26) Publication Language: English

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(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **LOWERY, David, E.** [US/US]; 1207 Woodland Drive, Portage, MI 49024 (US). **FULLER, Troy, E.** [US/US]; 111 Dreamfield Drive, Battle Creek, MI 49014 (US). **KENNEDY, Michael, J.** [US/US]; 2364 Quincy Avenue, Portage, MI 49024 (US).

(74) Agent: **WILLIAMS, Joseph, A., Jr.**; Marshall, Gerstein & Borun, 6300 Sears Tower, 233 South Wacker Drive, Chicago, IL 60606 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, 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, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), 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, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning 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 nucleotides 3352-4146	1-41
X	& 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" the whole document	5-23,25, 28
A	& BARBARA J. MAY ET AL.: "Complete genomic sequence of Pasteurella multocida, Pm70" PROCEEDINGS OF THE NATIONAL ACADEMY OF -/--	1-41

[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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

Date of the actual completion of the international search	Date of mailing of the international search report
12 May 2003	16. 05. 2003

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/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.
	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 ---	
X	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

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

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/ 210

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

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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Ｃ１２Ｎ 1/19	Ｃ１２Ｎ 1/15		４Ｈ０４５
Ｃ１２Ｎ 1/21	Ｃ１２Ｎ 1/19		
Ｃ１２Ｎ 5/10	Ｃ１２Ｎ 1/21		
Ｃ１２Ｐ 21/02	Ｃ１２Ｐ 21/02	C	
Ｃ１２Ｑ 1/68	Ｃ１２Ｑ 1/68	A	
Ｇ０１Ｎ 33/15	Ｇ０１Ｎ 33/15	Z	
Ｇ０１Ｎ 33/50	Ｇ０１Ｎ 33/50	Z	
Ｇ０１Ｎ 33/53	Ｇ０１Ｎ 33/53	D	
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(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,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

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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
4C085 AA03 BA18 CC07 DD23 DD62 EE01 EE06 FF24
4H045 AA10 AA11 AA20 AA30 BA10 CA11 DA83 EA20 EA50 FA74