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Fortsættes ...



# DESCRIPTION

## Field of the invention

**[0001]** The present invention relates to prevention or treatment of allergic disorders, in particular asthma and food allergy and in particular to compositions useful for the prevention of hypersensitivity to allergens, in particular asthma disorders and/or the desensitization to allergens.

## Background of the Invention

**[0002]** The prevalence of allergic asthma and allergic diseases has reached epidemic proportions in both adult and pediatric, developed and developing populations (Eder et al., 2006, N. Engl. J. Med. 355:2226-2235). The lack of early childhood infections or microbial exposure due to improved sanitation, and the gradual loss of the indigenous microbiota have alternately been proposed to account for this major public health trend (Blaser, 2009, Nat. Rev. Microbiol., 7:887-894). In 2011, 235-300 million people globally have been diagnosed with asthma, and it caused 250,000 deaths.

**[0003]** Asthma is now the most prevalent chronic disease in childhood in developed countries; approximately 300 million people suffer from this disease worldwide. Asthma is caused by a combination of genetic and environmental factors. The Global Initiative of Asthma defines asthma as a chronic inflammatory disorder of the airways. Chronic pulmonary inflammation is associated with airway hyper-responsiveness, which leads to the classical symptoms of asthma: recurrent episodes of wheezing, breathlessness, chest tightness and coughing. The most common clinical phenotype is allergic asthma. In childhood, more than 90 % of patients with severe asthma are allergic; among asthmatic adults, 60 % are sensitized to common aero-allergens (Holgate et al., 2003, Eur. Respir. J. 2003; 22:470-477). In allergic asthma, inflammation and airway obstruction are triggered by allergen exposure in atopic individuals. The pathophysiology underlying the disease is rather complex. The inflammatory processes underlying the development of allergic airway disease have been investigated in humans and also in animal models of the disease. The understanding of the different cell types and mediators involved in asthma development has increased in the last decade. Indeed, findings support an important role of Th2 cells and Th2 cytokines (IL-4, IL-5 and IL-13) in the development of allergen-induced inflammation and airway hyper-responsiveness (AHR).

**[0004]** The state-of-the-art immunomodulatory treatment of acute symptoms of asthma involves inhaled or oral corticosteroids. Asthma patients generally respond to  $\beta$ 2-adrenergic receptor agonists (such as salbutamol) and leukotrienes, which relax smooth muscle cells. In very severe cases, intravenous administration of corticosteroids or immunomodulatory drugs such as neutralizing antibodies to interleukins and hospitalization may be required. Anti-IL-13,

anti-IL-5 and anti-IL-9 monoclonal antibodies are all currently in clinical trials for asthma.

**[0005]** *Helicobacter pylori* is a persistent bacterial pathogen colonizing the gastric mucosa of humans. It is typically acquired in early childhood and, in the absence of antibiotic therapy, may persist for the entire life span of the host. The extraordinary ability of *H. pylori* to resist a vigorous adaptive immune response driven in large part by Th1 and/or Th17-polarized effector T-cells has been attributed to its adaptation to -and manipulation of- the human innate and adaptive immune systems. *H. pylori* has colonized its human host for at least 60.000 years and during this long period of co-evolution has evolved elaborate ways to systemically manipulate adaptive immune responses and to promote its persistence through the preferential induction of regulatory T-cell (Treg) over immunogenic T-cell response through T-effector cell responses. Treg-predominant responses are characteristic of heavily colonized, but asymptomatic carriers.

**[0006]** It has been shown that experimental live *H. pylori* infection, especially when initiated during the neonatal period, protects effectively against allergen-induced asthma that is induced by allergen sensitization and challenge (Arnold et al., 2011, The Journal of Clinical Investigation, 121:3088-3093). Mechanistically, asthma protection is due to the development of (Treg-mediated) immune tolerance to *H. pylori*, which cross-protects against allergen-specific Th2 responses. The protective effects of live *H. pylori* are abrogated by antibiotic eradication therapy clearing the bacteria (Arnold et al., 2011, *supra*). Similarly, the induction of protective Tregs required live bacteria *in vivo* and could not be achieved by dead extract.

**[0007]** Aside from Tregs, dendritic cells (DCs) have emerged as a critical cell type required for immune tolerance. *H. pylori*-experienced DCs are re-programmed to towards a tolerance-promoting phenotype *in vitro* and *in vivo* (Oertli et al., 2013, PNAS, 110(8), 3047-3052). It has been observed that DC re-programming requires two *H. pylori*-secreted proteins (virulence determinants or factors), the vacuolating cytotoxin (VacA) and the  $\gamma$ -glutamyl-transpeptidase (GGT) (Oertli et al., 2013, *supra*) since *H. pylori* mutants that lack one of the two virulence factors (but are otherwise wild type), fail to re-program DCs *in vivo* and *in vitro*, and therefore cannot induce Tregs with suppressive activity in mice (Oertli et al., 2013, *supra*). As a consequence, both *H. pylori* mutant strains are cleared effectively by the mice (Oertli et al., 2013, *supra*). Furthermore, both GGT and VacA have been used or reported to be used to trigger vaccine-induced protective immunity to *H. pylori*, i.e. with the opposite goal (strong T effector rather than Treg responses) of the present aim of the invention (Malfertheiner et al., 2008, Gastroenterology 135(3):787-95).

**[0008]** The use of live *H. pylori* as a therapeutic intervention or preventive measure has been unattractive due to the well-documented carcinogenic potential of chronic infection with this organism since *H. pylori* induces gastric and duodenal ulcers (Marshall et al., 1984, Lancet 1:1311-1315), and is also widely accepted to be the leading cause of gastric adenocarcinoma (Parsonnet et al., 1991, N. Engl. J. Med., 325:1127-1131). Further, it is important to note that those vaccination strategies using *H. pylori* are aiming at inducing an immune response that would protect the subject from *H. pylori* infection and counter-acting the ability of *H. pylori* to

avoid or by-pass the immune system response.

**[0009]** Since all the current treatments of asthma induce more or less severe side effects, alternative treatment strategies are desperately needed. Therefore, there are important needs for new strategies of prevention or asthma development, particularly for children and young people that present a predisposition towards developing hypersensitivity reactions and for treatment of asthma causes and symptoms.

### **Summary of the invention**

**[0010]** The present invention relates to the unexpected finding that oral, intranasal or intraperitoneal (i.e. systemic) administration of a composition comprising *H. pylori* VacA (administered either in the form of a dead cell extract such as prepared by mechanic disruption of logarithmically growing *H. pylori* using a French pressure cell «French press » or in the form of purified or recombinant protein), when administered in regular intervals, is able to induce protection against allergen-induced asthma. Although the presence of this virulence determinant or factor was earlier found to be required for persistence and Treg induction, it was in combination with the virulence determinant GGT and in the context of live bacteria and it could not be anticipated that it would have been alone sufficient for asthma protection. Further, the fact that VacA has successfully been included in preclinical and phase 1 human trials of *H. pylori*-specific vaccination argues that it is immunogenic (at least in combination with a suitable adjuvant) and triggers either T-cell and/or antibody mediated immunity. Since strong immunogenicity and strong immunomodulatory properties, as required for the suppression of allergen-specific immune responses, are usually mutually exclusive and not typically found in the same protein, the tolerogenic properties of compositions according to the invention are particularly surprising. The present invention further relates to the unexpected finding that it is possible to induce a peripheral tolerance avoiding an immune response to *H. pylori* infection through the use of VacA and thereby achieving a rather non-specific form of tolerogenic immunomodulation.

**[0011]** A first aspect of the invention provides a polypeptide of a Vac A protein, selected from SEQ ID NO : 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11 or a sequence having at least 90% identity with a VacA protein selected from SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11 or a formulation thereof for use in the prevention and/or treatment of an allergic disorder, in particular allergen-induced or atopic asthma, wherein said VacA protein is essentially free from an immunogenic component, in particular from other *H. pylori* antigen components. According to an aspect of the invention, a polypeptide of the invention is useful for inducing a tolerization response to an allergen.

**[0012]** Another aspect according to the invention relates to a pharmaceutical tolerogenic formulation comprising a Vac A protein consisting in a sequence selected from SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11 or a sequence having at least 90% identity with a VacA protein selected from SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11 and at least one pharmaceutically

acceptable carrier, diluent or excipient thereof, wherein said VacA protein is essentially free from an immunogenic component, in particular from other *H. pylori* antigen components.

**[0013]** Another aspect of the invention relates to a pharmaceutical formulation of the invention wherein said Vac A protein is combined with at least one co-agent useful in the prevention and/or treatment of an allergic disorder, in particular atopic asthma and/or for inducing a tolerization response to an allergen.

### Description of the figures

#### [0014]

**Figure 1** shows the alleviation of experimentally induced asthma by treatment with a composition according to the invention as described in Example 1, for the group subjected to *H. pylori* extract (-▲-) as compared to positive controls (sensitized mice but no treatment) (-■-) and negative controls (mock-sensitized mice) (-●-). **A, B:** Airway hyper-responsiveness in response (change in % from baseline levels, which are individually determined for every mouse) to increasing doses of metacholine ([C] in mg/ml) and the highest dose of 100 mg/ml, respectively; **C, D:** Total cells and eosinophils contained in 1 ml of BALF; **E-G:** Tissue inflammation and goblet cell metaplasia as scored by two blinded experimenters on H&E and PAS-stained tissue sections; representative micrographs taken at 100x (H&E) and 400x (PAS) original magnification are shown in G. Pooled data from 5 independent studies are shown in A-F; **H, I:** IL-5 and IL-13 secretion by single cell lung preparations restimulated with ovalbumin, as assessed by ELISA as described in Example 1. Pooled data from two studies are shown.

**Figure 2** shows that IL-10 signalling is required for dead cell extract-induced protection against asthma. **A, B:** IL-10 secretion by murine bone-marrow-derived DCs and human monocyte-derived DCs from six healthy volunteers after exposure to the indicated amounts of *H. pylori* dead cell extract ([C]) of the invention as described in Example 2. **A:** one representative experiment of three; **B:** pooled data for all six donors is shown in B. **C-F:** Mice treated as described in Figure 1; the indicated groups received 3 doses of anti-IL-10R antibody during the challenge phase of the protocol as described in Example 2; **C, D:** Total cells and eosinophils contained in 1 ml of BALF; **E, F:** Tissue inflammation and goblet cell metaplasia. In scatter plots, each symbol represents one mouse; horizontal lines indicate the medians.

**Figure 3** shows that VacA is both required and sufficient for protection against allergic airway disease in the model of allergen-induced asthma. Extract from an *H. pylori* mutant lacking the VacA gene ("extr. ΔvacA") was consistently less efficient than wild-type extract ("extr. wt") at protecting allergen-sensitized and -challenged mice against bronchoalveolar and pulmonary inflammation, eosinophilia and goblet cell metaplasia (Fig. 3A-D). To examine whether VacA alone is sufficient to provide protection, oligomeric VacA purified from culture supernatants of *H. pylori*, as described in example 1, was intraperitoneally administered, once weekly from day 7 of age onwards. No adverse effects were observed in any of the mice, despite their young age at the time of the first doses. Strikingly, VacA provided a level of protection against asthma

that was comparable to the protection conferred by extract treatment (Fig. 3A-D). A negative control VacA protein lacking an amino-terminal hydrophobic region of three tandem repeats that have been described as being essential for VacA's cytotoxic activity (*Vinion-Dubiel et al., 1999, supra*), i.e. of SEQ ID NO: 3 (Figure 5) failed to protect against asthma (Fig. 3A-D).

**Figure 4** shows the beneficial effects of various concentrations, delivery routes and dosing regimens of purified VacA in allergic asthma. VacA that was prepared as described above was either administered intraperitoneally or intragastrically at various concentrations and intervals in mice. 5 µg of VacA administered intraperitoneally in weekly intervals from age day 7 onwards until 2 weeks before challenge (as indicated by subscript "a" was as effective as 20 µg of VacA at preventing bronchoalveolar inflammation and eosinophilia (Figure 4 A,B). Intragastrically (perorally, p.o.) administered VacA (again delivered weekly from day 7 until 2 weeks before challenge) also provided significant protection (Figure 4 A,B). Three doses of intraperitoneally delivered VacA (delivered in weeks 1, 2 and 3 of life, denoted by subscript "b" in Figure 4) were insufficient to provide full protection (Figure 4A,B). Blocking IL-10 signaling with two doses of a neutralizing antibody delivered intraperitoneally during ovalbumin challenge abrogated protection (Figure 4 A,B). These data support that, unexpectedly, the administration of VacA alone in purified form is able to induce asthma protection comparable to the whole cell extract and therefore may be administered in purified form to prevent allergic asthma,

**Figure 5** shows examples of amino acid sequences of the Vac A polypeptides described herein. A: s1m1 VacA (Q48245 *H. pylori* strain ATCC 49503/60190) of SEQ ID NO: 1; B: s2m2 VacA of SEQ ID NO: 2; C: negative control mutant ( $\Delta$ 6-27) VacA of SEQ ID NO: 3; D- K: SEQ ID NO 4 to SEQ ID NO: 11.

**Figure 6** shows beneficial effects of *H. pylori* extract and HpVacA based on clinical scoring (A) and on systemic parameters of food allergy (C to F) as described in Example 5. These data support that, unexpectedly, the administration of VacA alone in purified form is able to induce food allergy protection comparable to the whole cell extract and therefore may be administered in purified form to prevent allergic asthma.

### Detailed description

**[0015]** The term "allergic disorder" refers to allergic settings and hypersensitivity to allergens such as allergen-induced or atopic asthma, atopic dermatitis (eczema), atopic rhinitis (hay fever), allergic conjunctivitis, food allergy, occupational allergy, allergic broncho-pulmonal aspergillosis and hypersensitivity pneumonitis.

**[0016]** The term "asthma" refers to a disorder of the airways characterized by airway inflammation, hyper-responsiveness, and obstruction which often causes spasms of the bronchial smooth muscle system, and affects both the upper and lower respiratory tracts. There are several forms of asthma, characterized by varying degrees of severity.

**[0017]** Mild asthma, for example, is defined as brief episodes of wheezing, with or without dyspnea or cough. Moderately severe asthma is defined as wheezing and dyspnea, and can be with or without cough and expectoration, but generally interferes with daily activities and/or sleeping. Severe asthma is characterized by incapacitation due to dyspnea, and the afflicted patient typically is unable to eat or sleep normally, is very anxious, and is often exhausted. A condition known as status asthmaticus is the most severe form of asthma, and generally requires intensive hospital care, and may even prove fatal. The disease may occur as a result of both allergic and non-allergic mechanisms.

**[0018]** The term "allergen induced asthma" or "atopic asthma" refers to asthma resulting from a hypersensitivity to an antigen/allergen. This includes, but is not limited to, all inhalable allergens including pollen from trees, grass, weeds or herbs or other group of allergens such as house dust mite, animal dander, cockroach, fungi and moulds. Furthermore, occupational allergens, such as flour, soy cow, latex and different mites (*Tyrophagus putrescentiae*; *Lepidoglyphus destructor*; *Acarus siro*) are included. Hypersensitivity to allergens, in particular antigen/allergen induced asthma is usually diagnosed on the basis of the pattern of symptoms such as coughing, sneezing, irritation/itching of the nose or eyes, increased lacrimation and running nose, itching of the skin with formation of an eczema as well as nausea, vomiting, abdominal pain and discomfort and diarrhoea in food allergy. Atopic asthma is clinically classified according to the frequency of symptoms, decreased forced expiratory volume in one second (FEV1), or peak expiratory flow rate (Peak Flow), increased Peak Flow variability, airway hyper-responsiveness and increased levels of allergen specific IgE.

**[0019]** The term "food allergy" refers to an abnormal response of the human immune system to harmless foods, caused by the immune system's reaction to some food proteins, usually involving human antibodies produced against specific allergens found in the food. Examples of common food allergens include components of milk, soy, fish and shellfish, tree nuts, peanuts, wheat (gluten), and eggs.

**[0020]** As used herein, the term "polypeptide" is used in its conventional meaning, i.e., as a sequence of amino acids. The polypeptides are not limited to a specific length of the product; thus, peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising tolerogenic fragments.

**[0021]** The term "fragments" refers to polypeptides comprising a portion of peptide sequence corresponding to contiguous amino acids of a polypeptide set forth herein, including all intermediate lengths and variants thereof.

**[0022]** The term "VacA" includes s1m1 VacA (SEQ ID NO: 1, 4-11) and s2m2 VacA (SEQ ID NO: 2). Such as described in Cover et al., 1992, J. Biol. Chem., 267:10570-1057 and Cover et al., 1997, J. Cell. Biol., 138:759-769. According to a particular embodiment, Vac A is s1m1 VacA of SEQ ID NO: 1. According to another embodiment, Vac A is s2m2 VacA of SEQ ID NO: 2. According to another embodiment, Vac A is s1m1 VacA of SEQ ID NO: 9.

**[0023]** The term "variant" applies to both a polynucleotide or a polypeptide. A polypeptide "variant," as the term is used herein, is a peptide or a polypeptide substantially homologous to the referenced peptide sequence, but which has an amino acid sequence different from that of the referenced. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention described herein using any of a number of techniques well known in the art. In many instances, a variant will contain conservative substitutions. Substantially homologous means a variant amino acid sequence which is identical to the referenced peptide sequence except for the deletion, insertion and/or substitution of a few amino acids, e.g. 1, 2, 3, 4, 5, or 6 amino acids. Substantially homologous means a variant amino acid sequence that is at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the referenced amino acid sequence. A variant nucleic acid sequence can be at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98% or at least 99% identical to the referenced nucleic acid sequence. The identity of two amino acid sequences or of two nucleic acid sequences can be determined by visual inspection and/or mathematical calculation, or more easily by comparing sequence information using known computer program used for sequence comparison such as Clustal package version 1.83.

**[0024]** A variant may comprise a sequence having at least one conservatively substituted amino acid. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged (e.g. having similar physiochemical characteristics). Modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics, e.g., with tolerogenic characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, tolerogenic variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence. In making such changes, the hydropathic index, polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the amino acids are considered. The importance of the hydropathic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte, et al, 1982, J. Mol. Biol., 157: 105- 131). Examples of conservative substitutions include substitution of one aliphatic residue for another, such as Ile, Val, Leu, or Ala for one another, or substitutions of one polar residue for another, such as between Lys and Arg; Glu and Asp; or Gln and Asn. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics, are well known (Kyte, et al, 1982, *supra*). For example, a "conservative amino acid substitution" may involve a

substitution of a native amino acid residue with a non-native residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. Exemplary amino acid substitutions are presented in Table 1 below. The term "variant" also includes a peptide or polypeptide substantially homologous to the referenced peptide sequence, but which has an amino acid sequence different from that of the referenced sequence because one or more amino acids have been chemically modified or substituted by amino acids analogs. This term also includes glycosylated polypeptides.

**Table 1**

| Original residues | Examples of substitutions |
|-------------------|---------------------------|
| Ala (A)           | Val, Leu, Ile             |
| Arg (R)           | Lys, Gln, Asn             |
| Asn (N)           | Gln                       |
| Asp (D)           | Glu                       |
| Cys (C)           | Ser, Ala                  |
| Gln (Q)           | Asn                       |
| Glu (E)           | Asp                       |
| Gly (G)           | Pro, Ala                  |
| His (H)           | Asn, Gln, Lys, Arg        |
| Ile (I)           | Leu, Val, Met, Ala, Phe   |
| Leu (L)           | Ile, Val, Met, Ala, Phe   |
| Lys (K)           | Arg, Gln, Asn             |
| Met (M)           | Leu, Ile, Phe             |
| Phe (F)           | Leu, Val, Ile, Ala, Tyr   |
| Pro (P)           | Ala, Gly                  |
| Ser (S)           | Thr, Ala, Cys             |
| Trp (W)           | Phe, Tyr                  |
| Thr (T)           | Ser                       |
| Tyr (Y)           | Trp, Phe, Thr, Ser        |
| Val (V)           | Ile, Met, Leu, Phe, Ala   |

**[0025]** Generally, substitutions for one or more amino acids present in the original polypeptide should be made conservatively. Polypeptides of the invention, polypeptide fragments and variants thereof are capable of inducing tolerance to an antigen/allergen when administered *in vivo*.

**[0026]** By "tolerogenic fragment" is meant a fragment that can induce tolerance to

antigens/allergens described in the present application. In certain embodiments, a tolerogenic fragment can induce tolerance to antigens/allergens at least as well as the full-length VacA polypeptide can and in certain embodiments may be more effective than the full-length VacA polypeptide at inducing tolerance. However, in certain embodiments, a tolerogenic fragment induces tolerance to antigens/allergens but may not induce tolerance as effectively as the full-length VacA polypeptide. Such tolerogenic fragments may still be useful in the present invention particularly where said tolerogenic fragments have other advantageous properties, such as, but not limited to, ease of preparation or purification as compared to the full-length VacA polypeptide. As would be recognized by the skilled person, a variety of known assays can be used to assess induction of tolerance, including measuring delayed-type hypersensitivity (DTH) responses, measuring cytokine productions by ELISA or other methods, T cell proliferation or cytotoxicity assays, B cell proliferation assays, antibody production, and the like. Such assays are known in the art and are described, for example, in Current Protocols in Immunology, Edited by: Coligan et al., 2001 John Wiley & Sons, NY, N.Y.; Ausubel et al., 2001, Current Protocols in Molecular Biology, Greene Publ. Assoc. Inc. & John Wiley & Sons, Inc., NY, N.Y.).

**[0027]** Polypeptides of the invention are prepared using any of a variety of well-known synthetic and/or recombinant techniques, the latter of which are further described below. Polypeptides, portions and other variants generally less than about 150 amino acids can be generated by synthetic means, using techniques well known to those of ordinary skill in the art. In one illustrative example, such polypeptides are synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain (Merrifield, 1963, J. Am. Chem. Soc., 85:2149-2146).

**[0028]** The term "pharmaceutically acceptable" refers to a carrier comprised of a material that is not biologically or otherwise undesirable.

**[0029]** The term "carrier" refers to any components present in a pharmaceutical formulation other than the active agent and thus includes diluents, binders, lubricants, disintegrants, fillers, coloring agents, wetting or emulsifying agents, pH buffering agents, preservatives and the like.

**[0030]** As used herein, "treatment" and "treating" and the like generally mean obtaining a desired pharmacological and physiological effect. The effect may be prophylactic in terms of preventing or partially preventing a disease, symptom or condition thereof and/or may be therapeutic in terms of a partial or complete cure of a disease, condition, symptom or adverse effect attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a mammal, particularly a human, and is not necessarily meant to imply cure or complete abolition of symptoms, but refers to any type of treatment that imparts a benefit to a patient and includes: (a) preventing the disease from occurring in a subject which may be predisposed to the disease but has not yet been diagnosed as having it for example based on familial history, overweight status or age; (b) inhibiting the disease, i.e., arresting its development; or relieving the disease, i.e., causing regression of the disease and/or its

symptoms or conditions such as improvement or remediation of damage.

**[0031]** In particular, prevention and/or treatment of allergic disorders according to the invention comprises normalization or decrease of the antigen/allergen sensitivity of an individual. The term "treatment" refers to any type of treatment or prevention that imparts a benefit to a subject afflicted with or at risk of developing a hypersensitivity immune response to an allergen/allergen of interest, including improvement in the condition of the subject (e.g., in one or more symptoms), delay in the onset of symptoms or slowing the progression of symptoms, etc.. According to a particular aspect, prevention and/or treatment of allergic disorders according to the invention comprises inducing peripheral tolerance to allergens.

**[0032]** According to one aspect, effects of a treatment according to the invention may be observed through one or more the following: prevention or reduction of the airway hyper-responsiveness, prevention or reduction of cell penetration into bronchial tubes (typically through the functional mechanisms for inhibiting production of IL-4, which is a cytokine secreted by Th2 cells and involved in inflammatory mechanisms of allergic reaction) prevention or reduction of pulmonary inflammation, of bronchoalveolar eosinophilia, of goblet cell metaplasia, of mucus production and Th2 cytokine production that are hallmarks of allergen-induced asthma. Treatment success may also be evident by the observation of the generation of IL-10 in regulatory lymphocytes or other cells or in total lungs (BALF, sputum) or serum, which can be assessed by ELISA. The term "subject" as used herein refers to mammals. For example, mammals contemplated by the present invention include human, primates, domesticated animals such as cattle, sheep, pigs, horses, laboratory rodents and the like.

**[0033]** The term "high-risk" subjects or individuals are subjects that are at risk to develop hypersensitivity to allergens/antigens, in particular of developing atopic or allergen-induced asthma. Those include genetic predisposition such as a family history of atopic diseases in close relatives, smoking mother during pregnancy, and smoking environment after birth, viral respiratory infections, such as by respiratory syncytial virus and rhinovirus and occupational exposure to known occupational allergens (e.g. flour). The risk or predisposition of developing hypersensitivity to allergens/antigens, in particular of developing atopic or allergen-induced asthma can be assessed by recording complete history including family history of the patient, skin prick testing, assessment of serum IgE, specific serum IgE levels and measurement of airway hyperreactivity. The term "efficacy" of a treatment or method according to the invention can be measured based on changes in the course of disease or condition in response to a use or a method according to the invention. For example, the efficacy of a treatment or method according to the invention can be measured by measuring the level of tolerance of the subject before and after the treatment, for example as described below.

**[0034]** The term "tolerance" as referred herein is defined as immune unresponsiveness to an antigen/allergen, usually an antigen/allergen implicated in causing disease. Although tolerance may be induced by administering antigens/allergens by different routes, oral tolerance refers to the oral administration of the composition, which results in inducing tolerance to an antigen/allergens when administered *in vivo*. The induction of tolerance can therefore be

monitored by various techniques including: measuring the response to allergen in skin prick test, assessment of allergen specific IgE and assessment of specific T cell responses for the allergen (proliferation and cytokine production).

**[0035]** The term "tolerogenic effective amount" as used herein refers to an amount of at least one polypeptide selected from VacA, a VacA fragment and a VacA variant or a pharmaceutical formulation thereof according to the invention that elicits a detectable tolerogenic response in a subject that is being administered the said subject.

**[0036]** As used herein, the term "antigen" refers to a foreign substance that when introduced into the body triggers an immune system response, resulting in production of an antibody as part of the body's defense against disease

**[0037]** The term "allergen" is meant to designate an antigen capable of eliciting a hypersensitivity immune response (such as described herein) in an individual, such as in an animal, such as in a human. The allergen may be a sensitizing allergen or a cross-reacting allergen.

**[0038]** The term "non-denaturated" refers to the absence of observed denaturation of the protein (e.g. structure). This can be verified by any method well-known in the art such as gel electrophoresis, gel filtration or mass spectrometry.

**[0039]** The polypeptides of the invention and formulations thereof have immunomodulatory properties that can be useful for tolerization strategies such as in allergic disorders and in particular allergic asthma. The polypeptides of the invention and formulations thereof can be useful in particular in tolerization treatments for asthma prevention in high-risk individuals.

**[0040]** *VacA polypeptides of the invention in the form of dead cell extracts or purified peptides* VacA polypeptides of the invention, include substances described in the detailed description and they can be administered in different forms including in a form of a cell extract (dead) containing VacA or in a form of a purified synthetic polypeptide (recombinantly produced or obtained by synthesis).

**[0041]** In one aspect, the present invention provides VacA polypeptides of the invention, in the form of a *H. pylori* bacteria dead cell extract.

**[0042]** In a further aspect, the present invention provides VacA polypeptides of the invention, in the form of a *H. pylori* bacteria cell extract, wherein bacteria cells are non-denaturated killed *H. pylori* bacteria cells.

**[0043]** In a further aspect, the present invention provides VacA polypeptides of the invention, in the form of a *H. pylori* bacteria dead cell extract, wherein the *H. pylori* bacteria strain is *H. pylori* PMSS1 (Arnold et al. 2011, Gastroenterology, 140, 199-209), or any other useful human patient isolate of *H. pylori*, or mutants of said isolates that lack one or more genes due to gene

deletion or insertion mutagenesis or point mutations.

**[0044]** The processes which may be used for preparing *H. pylori* cell extract are known to the skilled person and include the use of physical means that produce non-denaturated killed cell bacteria, i.e. under non-denaturing conditions such as described in Laemmli et al., 1970, Nature, 277, 680-, such as for example use of the so called "French pressure cell press" (Kelemen et al., 1979, J. Cell Sci. 35:431-141).

**[0045]** Alternatively, ultra sonication or other methods such as extended freeze drying, repeated cycles of freezing and thawing, lyophilization, homogenization techniques and other cell disruption techniques using physical forces can be applied, as long as they preserve *H. pylori* proteins in native form such as described in Bhaduri et al., 1983, Appl. Environ. Microbiol., 46 (4): 941-3).

**[0046]** In another further aspect, the present invention provides VacA polypeptides of the invention in the form of a *H. pylori* bacterial cell extract obtainable by a process comprising the steps of:

1. (i) harvesting a culture of living bacteria cells;
2. (ii) submitting the harvested bacteria to several freeze/thaw cycles in water or aqueous solution of a salt;
3. (iii) disrupting the bacterial cells under high pressure, e.g. using a French pressure cell press;
4. (iv) collecting the cell extract.

**[0047]** In another further aspect, the present invention provides VacA polypeptides of the invention in the form of a *H. pylori* bacterial cell extract obtainable by a process as described above comprising a further step of removing the cell debris after or when collecting the cell extract.

**[0048]** In another aspect, the present invention provides VacA polypeptides of the invention, in the form of a purified VacA polypeptide.

**[0049]** In another further aspect, the present invention provides VacA polypeptides of the invention, in the form of a purified recombinant VacA polypeptide.

**[0050]** In another further aspect, the present invention provides VacA polypeptides of the invention, in the form of VacA polypeptide composition essentially pure, i.e. essentially free from other native extract antigen components such as CagA and or NAP (neutrophil activating protein). For example, such essentially pure VacA polypeptide composition can be obtained from mutated *H. pylori* strains that have the other component(s)'s genes knocked out such as where the CagA gene is knocked out.

**[0051]** The preparation of VacA polypeptide, according to the invention recombinantly, can be achieved by various techniques known in the art.

**[0052]** Nucleic acid sequence encoding for said VacA polypeptide, thereof can be inserted in the recombinant expression vector by methods well known to a person skilled in the art such as, for example, those that are described in MOLECULAR CLONING: A LABORATORY MANUAL, Sambrook et al., 4th Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N. Y., 2001.

**[0053]** The introduction of the recombinant vector in a host cell can be carried out according to methods that are well known to a person skilled in the art, such as those described in BASIC METHODS IN MOLECULAR BIOLOGY, Davis et al., 2nd ed, McGraw-Hill Professional Publishing, 1995, and MOLECULAR CLONING: A LABORATORY MANUAL, *supra*, such as transfection by calcium phosphate, transfection by DEAE dextran, transfection, microinjection, transfection by cationic lipids, electroporation, transduction or infection.

**[0054]** The host cell can be, for example, bacterial cells such as *E. coli*, cells of fungi such as yeast cells and cells of Aspergillus, Streptomyces, insect cells, Chinese Hamster Ovary cells (CHO), C127 mouse cell line, BHK cell line of Syrian hamster cells, Human Embryonic Kidney 293 (HEK 293) cells. In a particular embodiment, the host cell is a CHO cell or a HEK 293 cell.

**[0055]** The host cells can be used, for example, to express a polypeptide of the invention. After purification by standard methods, the polypeptide of the invention can be used in a method described hereinafter.

**[0056]** For instance, when expression systems that secrete the recombinant protein are employed, the culture medium may first be concentrated using a commercially available protein concentration filter, for example, an ultrafiltration unit. Following the concentration step, the concentrate can be applied to a purification matrix such as a gel filtration medium. Alternatively, an anion exchange and/or an affinity resin can be employed. The matrices can be acrylamide, agarose, dextran, cellulose or other types commonly employed in protein purification. Alternatively, a cation exchange step can be employed. Some or all of the foregoing purification steps, in various combinations, are well known and can be employed to provide a substantially homogeneous recombinant protein.

**[0057]** Recombinant polypeptides produced in bacterial culture can be isolated by initial disruption of the host cells, centrifugation, extraction from cell pellets if an insoluble polypeptide, or from the supernatant fluid if a soluble polypeptide, followed by one or more concentration, salting-out, ion exchange, affinity purification or size exclusion chromatography steps. Microbial cells can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of other physical or chemical cell lysing agents, including detergents.

**[0058]** In another aspect, VacA polypeptide of the invention can be prepared recombinantly as

a full length protein as described in McClain et al., 2003, J. Biol. Chem., 278:12101-12108, or through the reconstitution of its two domains, p33 and p55, in the presence of detergents as described in Gonzalez-Rivera et al., 2010, Biochemistry 49:5743-5752 and Gangwer et al., 2007, PNAS, 104(41):16293-8.

**[0059]** In another aspect, the present invention provides VacA polypeptides described herein. Polypeptide encompassed by the present invention will typically exhibit at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% or more identity (determined as described below), along its length, to a polypeptide sequences set forth herein.

**[0060]** In another aspect, the VacA polypeptides, can be used associated with a pharmaceutically acceptable salt or a combination of pharmaceutically acceptable salts.

### ***Compositions***

**[0061]** The invention provides VacA polypeptides, pharmaceutical compositions thereof which are useful for treating a subject, in particular a mammalian subject, and most particularly a human patient who is suffering from a hypersensitivity to an allergens/antigen or a risk of developing hypersensitivity to an antigen/allergen, in particular allergen-induced or atopic asthma or food allergy.

**[0062]** According to another aspect, the invention provides VacA polypeptides, pharmaceutical compositions thereof which are useful for controlling hypersensitivity to an antigen/allergen in a subject, in particular inducing a tolerance to said antigen/allergen.

**[0063]** Pharmaceutical compositions of the invention can contain at least one VacA polypeptide according to the invention in any form described herein. According to a particular aspect, the pharmaceutical compositions of the invention are tolerogenic compositions. In a particular aspect, pharmaceutical compositions of the invention are tolerogenic compositions capable of inducing a peripheral tolerance and diminishing the immune response to antigens through immunoregulation. In a particular embodiment, pharmaceutical compositions of the invention comprises at least one VacA polypeptide, variant or fragment thereof which is essentially free from immunogenic component such as immunogenic epitope or allergen.

**[0064]** In another particular aspect, pharmaceutical compositions of the invention are tolerogenic compositions comprising at least one VacA polypeptide, in combination with known allergens such as food allergens such as allergens deriving from milk, peanut, fish or shellfish, wheat (gluten), soy, egg or the like.

**[0065]** In another particular aspect, pharmaceutical compositions of the invention are tolerogenic compositions comprising at least one VacA polypeptide in combination with known allergens such as allergen derived from pollens such as pollens from grasses, trees, and weeds or the like. According to a particular aspect, such tolerogenic compositions have the

ability of inducing allergen-specific immune tolerance and diminishing the immune response through immunoregulation (known as desensitization or hypo-sensitization or immunotherapy).

**[0066]** According to a particular aspect, at least one VacA polypeptide of the invention is administered in combination with known allergens, in particular food allergens. The combination might be achieved by concomitant administration of said at least one VacA polypeptide and of the allergen or administration of said at least one VacA polypeptide and of the allergen within the same single formulation or administration of said at least one VacA polypeptide when covalently linked to some immunogenic component of said allergen.

**[0067]** Compositions of this invention may further comprise one or more pharmaceutically acceptable additional ingredient(s) such as alum, stabilizers, antimicrobial agents, buffers, coloring agents, flavoring agents, adjuvants, and the like.

**[0068]** The compositions according to the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use by injection or continuous infusion. Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. According to a particular embodiment, compositions according to the invention are injectable.

**[0069]** Compositions of this invention may be liquid formulations including, but not limited to, aqueous or oily suspensions, solutions, emulsions, syrups, and elixirs. The compositions may also be formulated as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain additives including, but not limited to, suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. Suspending agents include, but are not limited to, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminum stearate gel, and hydrogenated edible fats. Emulsifying agents include, but are not limited to, lecithin, sorbitan monooleate, and acacia. Preservatives include, but are not limited to, methyl or propyl p-hydroxybenzoate and sorbic acid. Dispersing or wetting agents include but are not limited to poly(ethylene glycol), glycerol, bovine serum albumin, Tween®, Span®.

**[0070]** Further materials as well as formulation processing techniques and the like are set out in Part 5 of *Part 5 of Remington's "The Science and Practice of Pharmacy"*, 22nd Edition, 2012, University of the Sciences in Philadelphia, Lippincott Williams & Wilkins.

**[0071]** Compositions of this invention may also be formulated as a depot preparation, which may be administered by implantation or by intramuscular injection.

**[0072]** Solid compositions of this invention may be in the form of tablets or lozenges formulated in a conventional manner. For example, tablets and capsules for oral administration may contain conventional excipients including, but not limited to, binding agents, fillers, lubricants, disintegrants and wetting agents. Binding agents include, but are not limited to, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch and polyvinylpyrrolidone. Fillers include, but are not limited to, lactose, sugar, microcrystalline cellulose, maizestarch, calcium phosphate, and sorbitol. Lubricants include, but are not limited to, magnesium stearate, stearic acid, talc, polyethylene glycol, and silica. Disintegrants include, but are not limited to, potato starch and sodium starch glycollate. Wetting agents include, but are not limited to, sodium lauryl sulfate. Tablets may be coated according to methods well known in the art.

**[0073]** Compositions of this invention may also be formulated for inhalation, which may be in a form including, but not limited to, a solution, suspension, or emulsion that may be administered as a dry powder or in the form of an aerosol or spray using a propellant. The compounds of this invention can also be administered in sustained release forms or from sustained release drug delivery systems.

**[0074]** In certain embodiments, the therapeutic compound(s) are directly administered as a pressurized aerosol or nebulized formulation to the patient's lungs via inhalation. Such formulations may contain any of a variety of known aerosol propellants useful for endopulmonary and/or intranasal inhalation administration. In addition, water may be present, with or without any of a variety of cosolvents, surfactants, stabilizers (e.g., antioxidants, chelating agents, inert gases and buffers). For compositions to be administered from multiple dose containers, antimicrobial agents are typically added. Such compositions are also generally filtered and sterilized, and may be lyophilized to provide enhanced stability and to improve solubility.

**[0075]** The pharmaceutical composition of the invention may consist of dosage units that can be administered as an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system that dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. One of ordinary skill in the art, without undue experimentation may determine preferred aerosols. According to one aspect, the invention provides an oral pharmaceutical composition. According to one aspect, the invention provides an injectable pharmaceutical composition.

**[0076]** According to one aspect, the invention provides an inhalable pharmaceutical composition.

**[0077]** As described elsewhere herein, in certain embodiments, a prophylactic/therapeutically effective dose of a VacA polypeptide, pharmaceutical composition thereof as used herein is a dose sufficient to induce tolerance to an antigen/allergen measured using any of a variety of methods as described herein. In a further embodiment, a prophylactic/therapeutically effective dose of a VacA polypeptide pharmaceutical composition thereof as used herein is a dose sufficient to induce T cell tolerance to an antigen/allergen as measured using any of a variety of methods as described herein, such as cytokine release assays, intracellular cytokine staining and flow cytometry, and the like. Functional T cell assays, T-cell suppression assays measuring the suppression of proliferation or cytokine secretion by co-cultured effector T-cells may also be used.

### ***Mode of administration***

**[0078]** Polypeptides and compositions of this invention may be administered in any manner including intravenous injection, intraperitoneal injection, subcutaneous injection, oral route, intranasal administration, intrapulmonary instillation or by inhalation. In certain embodiments, a combination of different routes may also be used.

**[0079]** The exact dose of polypeptides and compositions is readily determined by one of skill in the art based on the teachings herein, along with the potency of the specific polypeptide and composition, the age, weight, sex and physiological condition of the subject.

**[0080]** By way of example, in various embodiments the dosage of a tolerizing polypeptide and composition required to achieve (or maintain) tolerance in a subject is low relative to traditional tolerization regimens. For instance, as few as one or a few doses (e.g., fewer than about three, or fewer than about five doses) of agent may be sufficient to induce tolerance. By way of example, a weekly from about 5 to about 500 mg/dose might be used to achieve tolerisation effects.

**[0081]** According to one embodiment, polypeptides and compositions of the invention are administered before or at the beginning of the onset of the allergic symptoms or the exposure to the allergen challenge. For example, polypeptides and compositions of the invention are administered before the subject is subjected to the allergen(s), typically in case of patients at risk of suffering from a seasonal allergic disorder such as pollen allergy or before the patient has already developed allergic symptoms in case of infants at risk of suffering from an allergic disorder (e.g. genetic or environmental risk) such as atopic asthma. Administration during pregnancy (oral, intranasal or via any other route) to pregnant mothers at risk of atopy can be envisioned as well, either alone or in combination with continued treatment of the newborn infant such as described in Pfefferle et al., 2013, J. Allergy Clin. Immunol., 131(6):1453-63.

**[0082]** According to a further embodiment, the polypeptides and compositions of the invention are administered at least two weeks (e.g. from about two to about 12 weeks) before the usual

period of allergen exposure. According to a further embodiment, the polypeptides and compositions of the invention are administered by repeated administrations before and/or until and/or, through-out the allergen exposure, such as for example from about once or twice a week to about once or twice a month. In case of administration to pregnant mothers with the goal to reduce asthma and allergic risk in the newborn, the administration should be initiated early, ideally already in the first trimester (*Pfefferle et al., 2013, supra*).

### **Combination**

**[0083]** According to the invention, a Vac A polypeptide and pharmaceutical formulations thereof can be administered alone or in combination with a co-agent useful in the prevention and/or treatment of hypersensitivity, in particular allergic disorders such as atopic asthma e.g. for example a co-agent selected from a bronchodilator, a co-administered allergen used for hyposensitization with a co-agent useful in the tolerization to an antigen/allergen e.g. for example antibodies or other reagents that interfere with co-stimulation or co-inhibition (e.g. via PD1, CTLA-4, CD28, CD40 and others expressed on lymphocytes and other immune cells).

**[0084]** The invention encompasses the administration of a Vac A polypeptide and pharmaceutical formulations thereof to an individual prior to, simultaneously or sequentially with other therapeutic/prophylactic/immunotherapeutic regimens or co-agents in the prevention or treatment of antigen/allergen hypersensitivity, in particular allergic disorders such as atopic asthma (e.g. combined tolerization regimen), in a therapeutically effective amount. A Vac A polypeptide, the pharmaceutical formulation thereof that is administered simultaneously with said co-agents can be administered in the same or different composition(s) and by the same or different route(s) of administration.

**[0085]** According to another aspect, the Vac A polypeptides according to the invention may be used in an immunotherapy regimen wherein the Vac A polypeptides according to the invention are associated with at least one antigen of a broad range of antigens (allergens). *H. pylori* extract or VacA polypeptides could be mixed and administered with house dust mite allergen, pollen-derived allergens, or any of the above listed food allergens (peanut-, milk-, soy-derived or other) or any other allergens to promote desensitization (hypo-sensitization) in an allergen-specific manner (Khinchi et al., 2004, *Allergy*, 59(1):45-53).

**[0086]** According to one embodiment, is provided a pharmaceutical formulation comprising a Vac A polypeptide combined with at least one co-agent useful in the prevention and/or treatment of hypersensitivity, in particular allergic disorders such as atopic asthma, and at least one pharmaceutically acceptable carrier, diluent or excipient thereof.

**[0087]** The dosage administered, as single or multiple doses, to an individual will vary depending upon a variety of factors, including pharmacokinetic properties, patient conditions and characteristics (sex, age, body weight, health, size), extent of symptoms, concurrent treatments, frequency of treatment and the effect desired.

***Patients***

**[0088]** In an embodiment, patients according to the invention are patients suffering from a disorder selected from an allergic disorder such as allergen-induced or atopic asthma (eczema), atopic dermatitis (hay fever), atopic rhinitis, allergic conjunctivitis, food allergy, occupational allergy, allergic broncho-pulmonal aspergillosis and hypersensitivity pneumonitis.

**[0089]** In another embodiment, patients according to the invention are patients at risk of suffering from an allergic disorder.

**[0090]** In another further embodiment, patients according to the invention are suffering from allergen-induced or atopic asthma.

**[0091]** In another embodiment, patients according to the invention are patients at risk of suffering from a seasonal allergic disorder such as pollen allergy, including food-pollen allergy.

**[0092]** In another further embodiment, patients according to the invention are children or infants, for example infants before the age of about three years.

**[0093]** In another further embodiment, patients according to the invention are pregnant mothers with a high risk of atopy or pregnant mothers of children with a high risk of atopy, which may be treated during pregnancy.

**[0094]** In another further embodiment, patients according to the invention are suffering from an allergic disorder selected from atopic dermatitis, atopic rhinitis and allergic conjunctivitis.

**[0095]** In another further embodiment, patients according to the invention are suffering from food allergy.

***Use according to the invention***

**[0096]** In accordance with one aspect of the present invention, the polypeptides of the invention are useful in a process for tolerizing a subject or inducing a tolerization response in said subject to at least one antigen/allergen by use of a polypeptide or a formulation or a combination as herein. The polypeptide, formulation or combination according to the invention can be administered in an amount and in accordance with a dosage regimen that is effective for inducing tolerance in a subject.

**[0097]** In one embodiment of the invention the allergic disorder is atopic asthma.

**[0098]** In a further embodiment of the invention the polypeptides according to the invention, are useful to subject predisposed or at risk to develop an allergic disorder, in particular atopic asthma, for example based on familial history, overweight status or age.

**[0099]** According to another embodiment, the invention relates to a pharmaceutical formulation comprising a polypeptide selected from a Vac A protein, combined with at least one co-agent useful in the prevention, repression and/or treatment of an allergic disorder, in particular atopic asthma and/or for inducing a tolerization response to an allergen, and at least one pharmaceutically acceptable carrier, diluent or excipient thereof.

**[0100]** In another embodiment, is provided a use or a method according to the invention, wherein a polypeptide or a composition of the invention are to be used in combination with an allergen.

**[0101]** In another embodiment, is provided polypeptide or a composition according to the invention wherein said polypeptide or a composition thereof is to be administered by the oral, intranasal, intrapulmonary, parenteral or systemic route. In another embodiment, is provided polypeptide or a composition according to the invention wherein VacA is s1m1 VacA.

**[0102]** In another embodiment, is provided polypeptide, or a composition according to the invention wherein VacA is s2m2 VacA.

**[0103]** In another embodiment, is provided polypeptide or a composition according to the invention wherein VacA is a Vac A protein comprising an amino acid sequence selected from SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 and 11.

**[0104]** In another embodiment, is provided polypeptide or a composition according to the invention wherein a Vac A protein has an amino acid sequence of SEQ ID NO: 1 or at least 90% identity therewith.

**[0105]** In another embodiment, is provided polypeptide or a composition according to the invention wherein a Vac A protein has an amino acid sequence of SEQ ID NO: 2 or at least 90% identity therewith.

**[0106]** Examples illustrating the invention will be described hereinafter in a more detailed manner and by reference to the embodiments represented in the Figures.

## **EXAMPLES**

**[0107]** The following abbreviations refer respectively to the definitions below:

**BALF** (Broncho-alveolar lavage fluid), **BCA** (Bicinchoninic acid assay), **EDTA** (ethylenediaminetetraacetic acid), **FCS** (Foetal Calf Serum), **GM-CSF** (granulocyte macrophage- colony stimulating factor), **H&E** (Hematoxylin and eosin, **i.p.** (intraperitoneally), **MCTP1** (mast cell

protease PI), **MLN** (mesenteric lymph node), **PAS** (periodic acid Schiff), **PBS** (Phosphate Buffer Sulfate), **RPMI** (Royal Park Memorial Institute (culture medium)).

**Example 1: *H. pylori* dead cell extract in allergen-induced asthma**

**[0108]** To assess whether regular administration of compositions of the invention provided in the form of a *H. pylori* dead cell extract protects against allergen-induced responses such as asthma, the following model was used: mice were administered with weekly doses of intragastrically of whole dead cell extract (prepared as described below) from age day 7 onwards prior to subjecting them to ovalbumin sensitization and challenge with alum-adjuvanted ovalbumin as described below. Control mice that had received ovalbumin but no *H. pylori* dead cell extract developed airway hyper-responsiveness to methacholine (Fig. 1A,B) and bronchoalveolar immune cell infiltration and eosinophilia as measured by staining and quantification of cells harvested by bronchoalveolar lavage (Fig. 1C,D), as well as histologically evident lung inflammation and goblet cell metaplasia as determined by histological assessment and scoring of H&E and PAS-stained paraffin sections (Fig. 1 E-G). The re-stimulation of single cell lung preparations with ovalbumin induced the production of high levels of the Th2 cytokines IL-5 and IL-13 as measured by ELISA and cytometric bead array (following the manufacturer's instructions, R&D Biosystems; BD Biosciences) (Fig. 1H,I). In contrast, mice that had received *H. pylori* dead cell extract were protected against airway hyper-responsiveness (Fig. 1A,B), and exhibited significantly lower levels of bronchoalveolar and pulmonary inflammation, eosinophilia and goblet cell metaplasia (Fig. 1C-G). Th2 cytokine production upon allergen re-stimulation of lung preparations ELISA and cytometric bead array was also reduced (Fig. 1H,I). The failure of dead cell extract-treated mice to develop allergen-induced symptoms of asthma was not due to an impaired primary response to the allergen, as the levels of ovalbumin-specific serum IgE as measured by ELISA were similar in all sensitized mice.

**[0109]** To address the specificity of the observed effects and elucidate key prerequisites of protection, various administration routes and regimens, ages at treatment onset were investigated, as well as extracts from other gastrointestinal pathogens. Interestingly, the systemic (intraperitoneal) administration of *H. pylori* dead cell extract was as efficient as the intragastric route at conferring protection against allergen-induced asthma. Intragastric treatment was less effective when initiated in adult mice as opposed to neonates. Heat inactivated *H. pylori* extract, as well as identical amounts of extracts generated from cultures of *E. coli* or *Salmonella typhimurium*, failed to confer protection against the examined hallmarks of allergic airway disease.

**[0110]** In conclusion, the beneficial effects of dead cell extract treatment are specific to *H. pylori* and require a heat-sensitive component of the bacteria, and are most pronounced if the treatment is initiated in young mice.

***Preparation of H. pylori dead cell extract and purification of GGT and VacA***

**[0111]** *H. pylori* strain PMSS1 (Arnold et al. 2011, supra) secreting s2m2 VacA was cultured in Brucella broth supplemented with 10% FCS, pelleted by centrifugation and washed once with PBS. Bacteria were subjected to three freeze/thaw cycles and disrupted by three passes through a French pressure cell press (Stansted Fluid Power, Cell Pressure Homogenizer) at 30,000 bars. Cell debris were removed by centrifugation and the supernatant filtered through a 2 µm filter leading to the dead cell extracts used in the present examples. Protein concentrations were determined using the BCA Protein Kit (R&D systems).

**[0112]** *H. pylori* VacA was purified from *H. pylori* culture supernatants using previously published procedures (Cover et al., 1992, J. Biol. Chem., 267:10570-1057; Cover et al., 1997, J. Cell. Biol., 138:759-769), with the following slight modifications. *H. pylori* strain ATCC 49503/60190 which was first described in 1990 (Cover et al., 1990, Infect. Immun. 58: 603-610) was cultured in sulfite-free Brucella broth containing either cholesterol or 0.5% charcoal. After centrifugation of the culture, supernatant proteins were precipitated with a 50% saturated solution of ammonium sulfate. The oligomeric form of VacA was isolated by gel filtration chromatography with a Superose 6 HR 16/50 column in PBS containing 0.02% sodium azide and 1 mM EDTA..

### ***Animal experimentation***

**[0113]** C57BL/6 and BL/6.BATF3<sup>-/-</sup> mice (Jackson Labs) were orally infected with *H. pylori* strain PMSS1 as described (Arnold et al., 2011, supra), or received either once-weekly oral or i.p. doses of 200 µg dead cell extract (prepared as described above) of *H. pylori* wild type PMSS1 or the mutant strain, lacking the vac A gene (PMSS1ΔvacA) (described in Oertli et al., 2013, supra), *Salmonella typhimurium*, or *E. coli* or once-weekly i.p. doses of 25 µg s1m1 type VacA (SEQ ID NO: 1) -wild type produced as explained above or the deleted variant Δ6-27 purified from *H. pylori* strain ATCC 49503/0190 of SEQ ID NO: 3 as described in Vinion-Dubiel et al., 1999, J. Biol. Chem., 274:37736-37742.

**[0114]** Mice were sensitized by intraperitoneal injection with alum-adjuvanted ovalbumin (20 µg ovalbumin, Sigma-Aldrich emulsified in 2.25 mg aluminum hydroxide (Alum Imject; Pierce)) at 8 and 10 weeks of age and challenged with 1% aerosolized ovalbumin using an ultrasonic nebulizer (NE-U17; Omron) for 20 min daily on days 31, 32 and 33 post initial sensitization. Unsensitized mice served as negative controls. One group received once-weekly doses of 200 µg *H. pylori* dead extract intragastrically from day 7 of age until the second sensitization.

**[0115]** Airway resistance measurements were performed on anesthetized, intubated and mechanically ventilated mice and airway resistance (as measured using the FinePointe Resistance and Compliance System, Buxco Electronics) was recorded in response to increasing doses of inhaled metacholine.

[0116] *In vivo* blocking of IL-10 signaling as described in Example 2 was achieved by three i.p. injections of 250 µg anti-IL-10R antibody (clone 1B1.3A, BioXCell) during the challenge phase. Lungs were lavaged via the trachea with 1 ml PBS. Broncho-alveolar lavage fluid (BALF) cells were counted using trypan blue dye exclusion. Differential cell counts of macrophages, lymphocytes, neutrophils and eosinophils were performed on cyto-centrifuged preparations stained with the Microscopy Hemacolor ®-Set (Merck). For lung histopathology, lungs were fixed by inflation and immersion in 10% formalin and embedded in paraffin. Tissue sections were stained with H&E and periodic acid-Schiff and examined in blinded fashion on a BX40 Olympus microscope. Peribronchial inflammation was scored on a scale from 0 to 4. PAS-positive goblet cells were quantified per 1 mm of basement membrane.

### **Example 2: Role of cell extracts on IL-10 production**

[0117] *H. pylori* is known to induce the production of IL-10 in various immune cell compartments (Sayi et al., 2011, J. Immunol., 186:878-890) and high gastric levels of IL-10 ensure *H. pylori* persistence and promote *H. pylori*-specific immune tolerance (Arnold et al., 2011, *supra*).

[0118] In order to assess whether DCs produce IL-10 in response to *H. pylori* dead extract, cultured murine bone marrow-derived (BM) DCs were treated with increasing concentrations of dead cell extract prepared as described above. Indeed, BM-DCs produced and secreted large amounts of IL-10, and this was dependent on TLR2 and MyD88 signalling (Fig. 2A). A clear dose-dependent secretion of IL-10 could also be observed in human blood-derived DCs from six independent donors cultured with *H. pylori* dead cell extract (Fig. 2B). To address whether IL-10 is required for asthma protection conferred by dead extract tolerization two doses of IL-10 receptor (IL-10R)-neutralizing antibody were administered during the challenge phase of the protocol to mice that had either received dead cell extract from the neonatal period onwards and it was shown that IL-10 signalling was required for protection against asthma (Fig. 2C-F)

[0119] In summary, *H. pylori* dead cell extracts are able to induce IL-10 production in both murine and human DCs and the beneficial effects of dead cell extract treatment in allergic asthma depend on IL-10 signalling proficiency of the host.

### **Preparation of murine and human DCs and IL-10 ELISA**

[0120] For generation of murine BM-DCs, bone marrow isolated from the hind legs of donor mice (BL/6.TLR2<sup>-/-</sup>, BL/6.TLR4<sup>-/-</sup>, BL/6.MyD88<sup>-/-</sup> mice, all from Jackson Labs) was seeded at 50,000 cells per well in 96 well plates in RPMI/10% FCS and 4 ng/ml GM-CSF and cultured for 5 days. DCs were stimulated with the indicated amounts of *H. pylori* PMSS1 extract prepared as described above for 16h and supernatants were subjected to mIL-10 ELISA (BD

Pharmingen). Human monocyte-derived dendritic cells were generated from peripheral blood mononuclear cells as follows. Venous blood was drawn from 6 healthy volunteers according to protocols approved by the Institutional Review Board of Leiden University Medical Center. Cells were collected after density gradient centrifugation on Ficoll and CD14<sup>+</sup> monocytes were positively isolated by magnetic-activated cell sorting (MACS) using CD14 microbeads (Miltenyi Biotec). Cells were cultured in RPMI-1640 (Invitrogen) supplemented with penicillin (100 U/ml, Astellas Pharma), streptomycin (100 µg/ml, Sigma), pyruvate (1 mM, Sigma), glutamate (2 mM, Sigma), 10% fetal calf serum (FCS), 20 ng/ml human recombinant granulocyte-macrophage colony-stimulating factor (rGM-CSF, Invitrogen/Life Technologies), and 0.86 ng/ml human rIL-4 (R&D Systems) for 6 days. On day 3, the medium and the supplements were refreshed. Monocyte-derived DCs were stimulated with *H. pylori* dead cell extract for 48 hours. Secretion of IL-10 by the DCs in the supernatant was measured by ELISA (Sanquin).

**[0121]** The differential susceptibility to successful tolerization of neonates and adults may be attributable to the general tolerogenic bias of the immature neonatal immune system, with its higher Treg/Teffector cell ratios and Treg-predominant responses to foreign antigens (Arnold et al., 2005, Trends Immunol 26:406-411). Parallel observations have been reported in humans: *H. pylori*-infected children, but not adults, are characterized by Treg-predominant gastric *H. pylori*-specific T-cell responses (Harris et al., 2008, Gastroenterology 134:491-4). Children benefit more from harboring *H. pylori* than adults in terms of their asthma risk (Chen et al., 2007, Arch Intern Med 167:821-827); similarly, early onset asthma in adolescents and young adults is more strongly inversely correlated with *H. pylori* seropositivity than adult-onset asthma (Chen et al, 2008, J. Infect. Dis., 198:553-560). The available epidemiological and experimental data thus suggest that childhood acquisition of *H. pylori*, and the Treg-predominant immune responses associated with early-life acquisition, mediate the reduced risks of asthma and other allergic disease manifestations by suppressing allergen-specific T-cell responses.

**[0122]** The data presented here imply that children at high risk of developing asthma are more likely than adults to benefit from tolerization strategies of the invention.

**Example 3: Role of Vac A polypeptide and truncated variant thereof in purified form from the invention**

**[0123]** In order to support that VacA in the form of a purified polypeptide might contribute alone to asthma protection conferred by extract tolerization, the protective properties of bacterial extracts (prepared as described above) from wild-type bacteria and a VacA<sup>-</sup> deficient isogenic mutants (as described above) were compared. Interestingly, mutant extracts were consistently less efficient than wild-type extract at protecting allergen-sensitized and -challenged mice against bronchoalveolar and pulmonary inflammation, eosinophilia and goblet cell metaplasia (Fig. 3A-D). To examine whether VacA alone is sufficient to provide protection, oligomeric VacA purified from culture supernatants of *H. pylori* as described above was intraperitoneally

administered, once weekly from day 7 of age onwards. No adverse effects were observed in any of the mice, despite their young age at the time of the first doses. Strikingly, VacA provided a level of protection against asthma that was comparable to the protection conferred by extract treatment (Fig. 3A-D).

[0124] A negative control VacA deleted protein lacking an amino-terminal hydrophobic region of three tandem that are described as being essential for VacA's cytotoxic activity (*Vinion-Dubiel et al., 1999, supra*), i.e. of SEQ ID NO: 3 (Figure 5) fails to protect against asthma (Fig. 3A-D).

**Example 4: Role of Vac A polypeptide in purified form from the invention at various concentrations and delivery routes**

[0125] In order to elucidate the minimal effective dose, number of required doses and optimal delivery route, purified VacA prepared as described above was either administered intraperitoneally or intragastrically at various concentrations and intervals in mice as described above. 5 µg of VacA administered intraperitoneally in weekly intervals from age day 7 onwards until 2 weeks before challenge (as indicated by subscript "a" in Figure 4) was as effective as 20 µg of VacA at preventing bronchoalveolar inflammation and eosinophilia (Figure 4 A,B). Intragastrically (perorally, p.o.) administered VacA (again delivered weekly from day 7 until 2 weeks before challenge) also provided significant protection (Figure 4A,B). Three doses of intraperitoneally delivered VacA (delivered in weeks 1, 2 and 3 of life, denoted by subscript "b" in Figure 4) were insufficient to provide full protection (Figure 4A,B). Blocking IL-10 signaling with two doses of a neutralizing antibody delivered intraperitoneally during ovalbumin challenge abrogated protection (Figure 4A,B).

[0126] Those data support that, unexpectedly, the administration of VacA alone in purified form is able to induce asthma protection comparable to the whole cell extract and therefore may be administered in purified form to prevent allergic asthma,

These findings are particularly unexpected as it was believed that only live *H. pylori* extracts would exhibit the ability to induce Tregs and that VacA alone was not expected to be sufficient for asthma protection, since, in particular, mutants lacking the *ggf* gene have been observed of being incapable of colonizing mice persistently and this phenotype has been attributed to DC tolerization by GGT *in vitro* and *in vivo* (*Oertli et al., 2013, supra*).

[0127] Altogether those data show that asthma protection of compositions of the invention, were highly specific and was not conferred by extract from other gram-negative enteropathogens such as *E. coli* or *Salmonella typhimurium*. The treatment was particularly successful when initiated in young mice relative to adult mice. Therefore, VacA and compositions thereof can be exploited for therapeutic purposes as a viable tolerization strategy for asthma prevention and treatment in high-risk individuals.

**Example 5: Role of *H. pylori* dead cell extract and of Vac A polypeptide of the invention**

**in purified form in a preclinical model of food allergy**

**[0128]** In order to assess a protective effect of *H. pylori* whole cell extract or of purified VacA on the development of food allergy, mice were sensitized with two intraperitoneal doses of alum-adjuvanted ovalbumin prior to intragastric injection of ovalbumin as described below. Symptoms of food allergy were measured by clinical scoring and in serum by mast cell protease ELISA and ovalbumin-specific IgE and IgG1 ELISA. Th2 cytokines were quantified in ovalbumin-restimulated MLN or spleen single cell cultures.

**[0129]** Mice were sensitized twice i.p. at 2 weekly intervals with alum-adjuvanted ovalbumin and challenged with intragastrically delivered ovalbumin on three consecutive days starting 2 weeks after the last sensitization. One group of mice received once-weekly doses of 200 µg *H. pylori* strain PMSS1 wild-type extract intragastrically from day 7 of age onwards ("extract p.o."). Another group received once-weekly doses of 20 µg of purified HpVacA from *H. pylori* strain ATCC 49503/60190. All mice were observed for 40 min after the last challenge and scored with respect to scratching, puffiness of the eyes, mouth and nose and other symptoms of anaphylaxis such as described in Sun et al., 2007, J. Immunol., 179:6696-6703. The obtained scores are represented on Figure 6A. Ovalbumin-specific IgE and IgG1, and the mast cell protease MCPT1 were quantified in serum by ELISA and the corresponding levels are represented on Figures 6B to D. Splenocytes were re-stimulated with the above allergen for three days and the production and secretion of the Th2 cytokines IL-5 and IL-13 was measured by ELISA and the corresponding levels are represented on Figures 6E and F). MCPT1 data are normalized to the negative controls. Pooled data from three studies are shown for all groups except for the VacA-treated group.

**[0130]** Altogether, those data obtained in a food allergy model strongly suggest protective effects of *H. pylori* extract as well as VacA protein treatment.

**SEQUENCE LISTING**

**[0131]**

<110> UNIVERSITÄT ZÜRICH LEIDEN UNIVERSITY MEDICAL CENTER

<120> TOLEROGENIC COMPOSITIONS COMPRISING AND USES THEREOF

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<150> EP14153365.3

<151> 2014-01-31

<160> 11

&lt;170&gt; PatentIn version 3.3

&lt;210&gt; 1

&lt;211&gt; 980

&lt;212&gt; PRT

&lt;213&gt; Helicobacter pylori strain ATCC 49503/60190

&lt;400&gt; 1

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Thr | Ala | Val | Gly | Thr | Val | Ser | Gly | Leu | Leu | Gly | Trp | Gly | Leu |
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|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
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| Lys | Gln | Ala | Glu | Glu | Ala | Asn | Lys | Thr | Pro | Asp | Lys | Pro | Asp | Lys | Val |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Arg | Ile | Gln | Ala | Gly | Lys | Gly | Phe | Asn | Glu | Phe | Pro | Asn | Lys | Glu |
|     | 50  |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Asp | Leu | Tyr | Lys | Ser | Leu | Leu | Ser | Ser | Lys | Ile | Asp | Gly | Gly | Trp |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

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| Asp | Trp | Gly | Asn | Ala | Ala | Thr | His | Tyr | Trp | Ile | Lys | Gly | Gly | Gln | Trp |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

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| Asn | Lys | Leu | Glu | Val | Asp | Met | Lys | Asp | Ala | Val | Gly | Thr | Tyr | Lys | Leu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     | 110 |     |     |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gly | Leu | Arg | Asn | Phe | Thr | Gly | Gly | Asp | Leu | Asp | Val | Asn | Met | Gln |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Ala | Thr | Leu | Arg | Leu | Gly | Gln | Phe | Asn | Gly | Asn | Ser | Phe | Thr | Ser |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Lys | Asp | Ser | Ala | Asp | Arg | Thr | Thr | Arg | Val | Asp | Phe | Asn | Ala | Lys |
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| Asn | Ile | Leu | Ile | Asp | Asn | Phe | Leu | Glu | Ile | Asn | Asn | Arg | Val | Gly | Ser |
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| Gly | Ala | Gly | Arg | Lys | Ala | Ser | Ser | Thr | Val | Leu | Thr | Leu | Gln | Ala | Ser |
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|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Gly | Ile | Thr | Ser | Ser | Lys | Asn | Ala | Glu | Ile | Ser | Leu | Tyr | Asp | Gly |
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 435 440 445  
 Gln Val Gly Gly Ala Ala Ile Ala Gly Ser Ser Ala Asn Phe Glu Phe  
 450 455 460  
 Lys Ala Gly Glu Asp Thr Asn Asn Ala Thr Ala Thr Phe Asn Asn Asp  
 465 470 475 480  
 Ile His Leu Gly Lys Ala Val Asn Leu Arg Val Asp Ala His Thr Ala  
 485 490 495  
 Asn Phe Asn Gly Asn Ile Tyr Leu Gly Lys Ser Thr Asn Leu Arg Val  
 500 505 510  
 Asn Gly His Thr Ala His Phe Lys Asn Ile Asp Ala Thr Lys Ser Asp  
 515 520 525  
 Asn Gly Leu Asn Thr Ser Thr Leu Asp Phe Ser Gly Val Thr Asp Lys  
 530 535 540  
 Val Asn Ile Asn Lys Leu Thr Thr Ala Ala Thr Asn Val Asn Ile Lys  
 545 550 555 560  
 Asn Phe Asp Ile Lys Glu Leu Val Val Thr Thr Arg Val Gln Ser Phe  
 565 570 575  
 Gly Gln Tyr Thr Ile Phe Gly Glu Asn Ile Gly Asp Lys Ser Arg Ile  
 580 585 590  
 Gly Val Val Ser Leu Gln Thr Gly Tyr Ser Pro Ala Tyr Ser Gly Gly  
 595 600 605  
 Val Thr Phe Lys Gly Gly Lys Lys Leu Val Ile Asp Glu Ile Tyr His  
 610 615 620  
 Ala Pro Trp Asn Tyr Phe Asp Ala Arg Asn Val Thr Asp Val Glu Ile  
 625 630 635 640  
 Asn Lys Arg Ile Leu Phe Gly Ala Pro Gly Asn Ile Ala Gly Lys Thr  
 645 650 655  
 Gly Leu Met Phe Asn Asn Leu Thr Leu Asn Ser Asn Ala Ser Met Asp  
 660 665 670  
 Tyr Gly Lys Asp Leu Asp Leu Thr Ile Gln Gly His Phe Thr Asn Asn  
 675 680 685  
 Gln Gly Thr Met Asn Leu Phe Val Gln Asp Gly Arg Val Ala Thr Leu  
 690 695 700  
 Asn Ala Gly His Gln Ala Ser Met Ile Phe Asn Asn Leu Val Asp Ser  
 705 710 715 720  
 Thr Thr Gly Phe Tyr Lys Pro Leu Ile Lys Ile Asn Asn Ala Gln Asn

Phe Thr Gly Phe Tyr Lys Phe Leu Ile Lys Ile Asn Asn Ala Gln Asn  
 725 730 735  
 Leu Thr Lys Asn Lys Glu His Val Leu Val Lys Ala Arg Asn Ile Asp  
 740 745 750  
 Tyr Asn Leu Val Gly Val Gln Gly Ala Ser Tyr Asp Asn Ile Ser Ala  
 755 760 765  
 Ser Asn Thr Asn Leu Gln Glu Gln Phe Lys Glu Arg Leu Ala Leu Tyr  
 770 775 780  
 Asn Asn Asn Asn Arg Met Asp Thr Cys Val Val Arg Lys Asp Asn Leu  
 785 790 795 800  
 Asn Asp Ile Lys Ala Cys Gly Met Ala Ile Gly Asn Gln Ser Met Val  
 805 810 815  
 Asn Asn Pro Glu Asn Tyr Lys Tyr Leu Glu Gly Lys Ala Trp Lys Asn  
 820 825 830  
 Thr Gly Ile Asn Lys Thr Ala Asn Asn Thr Thr Ile Ala Val Asn Leu  
 835 840 845  
 Gly Asn Asn Ser Thr Pro Thr Asn Ser Thr Thr Asp Thr Thr Asn Leu  
 850 855 860  
 Pro Thr Asn Thr Thr Asn Asn Ala Arg Phe Ala Ser Tyr Ala Leu Ile  
 865 870 875 880  
 Lys Asn Ala Pro Phe Ala His Ser Ala Thr Pro Asn Leu Val Ala Ile  
 885 890 895  
 Asn Gln His Asp Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala Asn  
 900 905 910  
 Arg Ser Ser Asp Ile Asp Thr Leu Tyr Ala Asn Ser Gly Ala Gln Gly  
 915 920 925  
 Arg Asp Leu Leu Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly Tyr  
 930 935 940  
 Ala Arg Thr Met Ile Asp Ala Thr Ser Ala Asn Glu Ile Thr Gln Gln  
 945 950 955 960  
 Leu Asn Ala Ala Thr Thr Thr Leu Asn Asn Ile Ala Ser Leu Glu His  
 965 970 975  
 Lys Thr Ser Gly Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile Leu  
 980 985 990  
 Asn Ser Arg Leu Val Asn Leu Ser Arg Lys His Thr Asn His Ile Asp  
 995 1000 1005  
 Ser Phe Ala Lys Arg Leu Gln Ala Leu Lys Asp Gln Arg Phe Ala  
 1010 1015 1020  
 Ser Leu Glu Ser Ala Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys

|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
| Ser  | Leu | Glu | Ser | Ala | Ala | Glu  | Val | Leu | Tyr | Gln | Phe  | Ala | Pro | Lys |
| 1025 |     |     |     |     |     | 1030 |     |     |     |     | 1035 |     |     |     |
| Tyr  | Glu | Lys | Pro | Thr | Asn | Val  | Trp | Ala | Asn | Ala | Ile  | Gly | Gly | Thr |
| 1040 |     |     |     |     |     | 1045 |     |     |     |     | 1050 |     |     |     |
| Ser  | Leu | Asn | Asn | Gly | Ser | Asn  | Ala | Ser | Leu | Tyr | Gly  | Thr | Ser | Ala |
| 1055 |     |     |     |     |     | 1060 |     |     |     |     | 1065 |     |     |     |
| Gly  | Val | Asp | Ala | Tyr | Leu | Asn  | Gly | Glu | Val | Glu | Ala  | Ile | Val | Gly |
| 1070 |     |     |     |     |     | 1075 |     |     |     |     | 1080 |     |     |     |
| Gly  | Phe | Gly | Ser | Tyr | Gly | Tyr  | Ser | Ser | Phe | Ser | Asn  | Gln | Ala | Asn |
| 1085 |     |     |     |     |     | 1090 |     |     |     |     | 1095 |     |     |     |
| Ser  | Leu | Asn | Ser | Gly | Ala | Asn  | Asn | Thr | Asn | Phe | Gly  | Val | Tyr | Ser |
| 1100 |     |     |     |     |     | 1105 |     |     |     |     | 1110 |     |     |     |
| Arg  | Ile | Phe | Ala | Asn | Gln | His  | Glu | Phe | Asp | Phe | Glu  | Ala | Gln | Gly |
| 1115 |     |     |     |     |     | 1120 |     |     |     |     | 1125 |     |     |     |
| Ala  | Leu | Gly | Ser | Asp | Gln | Ser  | Ser | Leu | Asn | Phe | Lys  | Ser | Ala | Leu |
| 1130 |     |     |     |     |     | 1135 |     |     |     |     | 1140 |     |     |     |
| Leu  | Gln | Asp | Leu | Asn | Gln | Ser  | Tyr | His | Tyr | Leu | Ala  | Tyr | Ser | Ala |
| 1145 |     |     |     |     |     | 1150 |     |     |     |     | 1155 |     |     |     |
| Thr  | Thr | Arg | Ala | Ser | Tyr | Gly  | Tyr | Asp | Phe | Ala | Phe  | Phe | Arg | Asn |
| 1160 |     |     |     |     |     | 1165 |     |     |     |     | 1170 |     |     |     |
| Ala  | Leu | Val | Leu | Lys | Pro | Ser  | Val | Gly | Val | Ser | Tyr  | Asn | His | Leu |
| 1175 |     |     |     |     |     | 1180 |     |     |     |     | 1185 |     |     |     |
| Gly  | Ser | Thr | Asn | Phe | Lys | Ser  | Asn | Ser | Asn | Gln | Val  | Ala | Leu | Ser |
| 1190 |     |     |     |     |     | 1195 |     |     |     |     | 1200 |     |     |     |
| Asn  | Gly | Ser | Ser | Ser | Gln | His  | Leu | Phe | Asn | Ala | Asn  | Ala | Asn | Val |
| 1205 |     |     |     |     |     | 1210 |     |     |     |     | 1215 |     |     |     |
| Glu  | Ala | Arg | Tyr | Tyr | Tyr | Gly  | Asp | Thr | Ser | Tyr | Phe  | Tyr | Met | Asn |
| 1220 |     |     |     |     |     | 1225 |     |     |     |     | 1230 |     |     |     |
| Ala  | Gly | Val | Leu | Gln | Glu | Phe  | Ala | Arg | Phe | Gly | Ser  | Asn | Asn | Ala |
| 1235 |     |     |     |     |     | 1240 |     |     |     |     | 1245 |     |     |     |
| Val  | Ser | Leu | Asn | Thr | Phe | Lys  | Val | Asn | Ala | Thr | Arg  | Asn | Pro | Leu |
| 1250 |     |     |     |     |     | 1255 |     |     |     |     | 1260 |     |     |     |
| Asn  | Thr | His | Ala | Arg | Val | Met  | Met | Gly | Gly | Glu | Leu  | Gln | Leu | Ala |
| 1265 |     |     |     |     |     | 1270 |     |     |     |     | 1275 |     |     |     |
| Lys  | Glu | Val | Phe | Leu | Asn | Leu  | Gly | Val | Val | Tyr | Leu  | His | Asn | Leu |
| 1280 |     |     |     |     |     | 1285 |     |     |     |     | 1290 |     |     |     |
| Ile  | Ser | Asn | Ala | Ser | His | Phe  | Ala | Ser | Asn | Leu | Gly  | Met | Arg | Tyr |

1295

1300

1305

Ser

&lt;210&gt; 3

&lt;211&gt; 957

&lt;212&gt; PRT

&lt;213&gt; Artificial sequence

&lt;220&gt;

&lt;223&gt; Deletion variant del 6-27 VacA

&lt;400&gt; 3

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Phe | Phe | Thr | Thr | Leu | Gly | Trp | Gly | Leu | Lys | Gln | Ala | Glu | Glu | Ala |
| 1   |     |     |     | 5   |     |     |     |     | 10  |     |     |     |     | 15  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Lys | Thr | Pro | Asp | Lys | Pro | Asp | Lys | Val | Trp | Arg | Ile | Gln | Ala | Gly |
|     |     |     | 20  |     |     |     |     | 25  |     |     |     |     | 30  |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Gly | Phe | Asn | Glu | Phe | Pro | Asn | Lys | Glu | Tyr | Asp | Leu | Tyr | Lys | Ser |
|     |     | 35  |     |     |     |     | 40  |     |     |     |     | 45  |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Ser | Ser | Lys | Ile | Asp | Gly | Gly | Trp | Asp | Trp | Gly | Asn | Ala | Ala |
| 50  |     |     |     |     |     | 55  |     |     |     |     | 60  |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | His | Tyr | Trp | Ile | Lys | Gly | Gly | Gln | Trp | Asn | Lys | Leu | Glu | Val | Asp |
| 65  |     |     |     |     | 70  |     |     |     |     | 75  |     |     |     |     | 80  |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Lys | Asp | Ala | Val | Gly | Thr | Tyr | Lys | Leu | Ser | Gly | Leu | Arg | Asn | Phe |
|     |     |     |     | 85  |     |     |     |     | 90  |     |     |     |     | 95  |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Gly | Gly | Asp | Leu | Asp | Val | Asn | Met | Gln | Lys | Ala | Thr | Leu | Arg | Leu |
|     |     |     | 100 |     |     |     |     | 105 |     |     |     |     |     | 110 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gln | Phe | Asn | Gly | Asn | Ser | Phe | Thr | Ser | Tyr | Lys | Asp | Ser | Ala | Asp |
|     |     | 115 |     |     |     |     | 120 |     |     |     |     | 125 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Thr | Thr | Arg | Val | Asp | Phe | Asn | Ala | Lys | Asn | Ile | Leu | Ile | Asp | Asn |
|     | 130 |     |     |     |     | 135 |     |     |     |     | 140 |     |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Glu | Ile | Asn | Asn | Arg | Val | Gly | Ser | Gly | Ala | Gly | Arg | Lys | Ala |
| 145 |     |     |     |     | 150 |     |     |     |     | 155 |     |     |     |     | 160 |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Thr | Val | Leu | Thr | Leu | Gln | Ala | Ser | Glu | Gly | Ile | Thr | Ser | Ser |
|     |     |     |     | 165 |     |     |     |     | 170 |     |     |     |     | 175 |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asn | Ala | Glu | Ile | Ser | Leu | Tyr | Asp | Gly | Ala | Thr | Leu | Asn | Leu | Ala |
|     |     |     | 180 |     |     |     |     | 185 |     |     |     |     | 190 |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Asn | Ser | Val | Lys | Leu | Asn | Gly | Asn | Val | Trp | Met | Gly | Arg | Leu | Gln |
|     |     | 195 |     |     |     |     | 200 |     |     |     |     | 205 |     |     |     |

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Val | Gly | Ala | Tyr | Leu | Ala | Pro | Ser | Tyr | Ser | Thr | Ile | Asn | Thr | Ser |
|     | 210 |     |     |     |     | 215 |     |     |     |     | 220 |     |     |     |     |

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

| 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Arg | Ser | Ile | Phe | Ser | Gly | Gly | Val | Lys | Phe | Lys | Ser | Gly | Glu | Lys |
| 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |     |
| Leu | Val | Ile | Asp | Glu | Phe | Tyr | Tyr | Ser | Pro | Trp | Asn | Tyr | Phe | Asp | Ala |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Arg | Asn | Ile | Lys | Asn | Val | Glu | Ile | Thr | Arg | Lys | Phe | Ala | Ser | Ser | Thr |
|     |     |     |     | 565 |     |     |     |     | 570 |     |     |     |     | 575 |     |
| Pro | Glu | Asn | Pro | Trp | Gly | Thr | Ser | Lys | Leu | Met | Phe | Asn | Asn | Leu | Thr |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |
| Leu | Gly | Gln | Asn | Ala | Val | Met | Asp | Tyr | Ser | Gln | Phe | Ser | Asn | Leu | Thr |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |
| Ile | Gln | Gly | Asp | Phe | Ile | Asn | Asn | Gln | Gly | Thr | Ile | Asn | Tyr | Leu | Val |
|     | 610 |     |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |
| Arg | Gly | Gly | Lys | Val | Ala | Thr | Leu | Asn | Val | Gly | Asn | Ala | Ala | Ala | Met |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |
| Met | Phe | Asn | Asn | Asp | Ile | Asp | Ser | Ala | Thr | Gly | Phe | Tyr | Lys | Pro | Leu |
|     |     |     |     | 645 |     |     |     |     | 650 |     |     |     |     | 655 |     |
| Ile | Lys | Ile | Asn | Ser | Ala | Gln | Asp | Leu | Ile | Lys | Asn | Thr | Glu | His | Val |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |
| Leu | Leu | Lys | Ala | Lys | Ile | Ile | Gly | Tyr | Gly | Asn | Val | Ser | Thr | Gly | Thr |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |
| Asn | Gly | Ile | Ser | Asn | Val | Asn | Leu | Glu | Glu | Gln | Phe | Lys | Glu | Arg | Leu |
|     | 690 |     |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |
| Ala | Leu | Tyr | Asn | Asn | Asn | Asn | Arg | Met | Asp | Thr | Cys | Val | Val | Arg | Asn |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |
| Thr | Asp | Asp | Ile | Lys | Ala | Cys | Gly | Met | Ala | Ile | Gly | Asn | Gln | Ser | Met |
|     |     |     |     | 725 |     |     |     |     | 730 |     |     |     |     | 735 |     |
| Val | Asn | Asn | Pro | Asp | Asn | Tyr | Lys | Tyr | Leu | Ile | Gly | Lys | Ala | Trp | Lys |
|     |     |     | 740 |     |     |     |     | 745 |     |     |     |     | 750 |     |     |
| Asn | Ile | Gly | Ile | Ser | Lys | Thr | Ala | Asn | Gly | Ser | Lys | Ile | Ser | Val | Tyr |
|     |     | 755 |     |     |     |     | 760 |     |     |     |     | 765 |     |     |     |
| Tyr | Leu | Gly | Asn | Ser | Thr | Pro | Thr | Glu | Asn | Gly | Gly | Asn | Thr | Thr | Asn |
|     | 770 |     |     |     |     | 775 |     |     |     |     | 780 |     |     |     |     |
| Leu | Pro | Thr | Asn | Thr | Thr | Asn | Asn | Ala | Arg | Phe | Ala | Ser | Tyr | Ala | Leu |
| 785 |     |     |     |     | 790 |     |     |     |     | 795 |     |     |     |     | 800 |
| Ile | Lys | Asn | Ala | Pro | Phe | Ala | His | Ser | Ala | Thr | Pro | Asn | Leu | Val | Ala |
|     |     |     | 805 |     |     |     |     |     | 810 |     |     |     |     | 815 |     |
| Ile | Asn | Gln | His | Asp | Phe | Gly | Thr | Ile | Glu | Ser | Val | Phe | Glu | Leu | Ala |
|     |     | 820 |     |     |     |     | 825 |     |     |     |     | 830 |     |     |     |

Asn Arg Ser Lys Asp Ile Asp Thr Leu Tyr Ala Asn Ser Gly Ala Gln  
835 840 845

Gly Arg Asp Leu Leu Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly  
850 855 860

Tyr Ala Arg Thr Met Ile Asp Ala Thr Ser Ala Asn Glu Ile Thr Lys  
865 870 875 880

Gln Leu Asn Thr Ala Thr Thr Thr Leu Asn Asn Ile Ala Ser Leu Glu  
885 890 895

His Lys Thr Ser Ser Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile  
900 905 910

Leu Asn Ser Arg Leu Val Asn Leu Ser Arg Arg His Thr Asn Asn Ile  
915 920 925

Asp Ser Phe Ala Lys Arg Leu Gln Ala Leu Lys Asp Gln Arg Phe Ala  
930 935 940

Ser Leu Glu Ser Ala Ala Glu Val Leu Tyr Gln Phe Ala  
945 950 955

<210> 4

<211> 1293

<212> PRT

<213> Helicobacter pylori strain G27

<400> 4

Met Glu Ile Gln Gln Thr His Arg Lys Met Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Val Leu Ala Gly Ala Leu Ile Ser Ala Ile Pro Gln Glu Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Thr Ala Val Gly Thr Val Ser Gly Leu Leu Ser Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Asn Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

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

Trp Asp Trp Gly Asn Ala Ala Arg His Tyr Trp Val Lys Gly Gly Gln  
115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Lys  
 130 135 140

Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met  
 145 150 155 160

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
 165 170 175

Ser Tyr Lys Asp Ala Ala Asp Arg Thr Thr Arg Val Asn Phe Asn Ala  
 180 185 190

Lys Asn Ile Ser Ile Asp Asn Phe Val Glu Ile Asn Asn Arg Val Gly  
 195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
 210 215 220

Ser Glu Gly Ile Thr Ser Asp Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
 225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Ser Ser Val Lys Leu Met Gly Asn  
 245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
 260 265 270

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

His Leu Thr Val Gly Asp Lys Asn Ala Ala Gln Ala Gly Ile Ile Ala  
 290 295 300

Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly  
 305 310 315 320

Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Asn  
 325 330 335

Asn Thr Pro Ser Gln Ser Gly Thr Lys Asn Asp Lys Asn Glu Ser Ala  
 340 345 350

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

Ile Asn Pro Pro Asn Ser Thr Gln Lys Thr Glu Ile Gln Pro Thr Gln  
 370 375 380

Val Ile Asp Gly Pro Phe Ala Gly Gly Lys Asp Thr Val Val Asn Ile  
 385 390 395 400

Asn Arg Ile Asn Thr Asn Ala Asp Gly Thr Ile Arg Val Gly Gly Phe  
 405 410 415

Lys Ala Ser Leu Thr Thr Asn Ala Ala His Leu His Ile Gly Lys Gly  
 420 425 430

Gly Val Asn Leu Ser Asn Gln Ala Ser Gly Arg Thr Leu Leu Val Glu  
435 440 445

Asn Leu Thr Gly Asn Ile Thr Val Asp Gly Pro Leu Arg Val Asn Asn  
450 455 460

Gln Val Gly Gly Tyr Ala Leu Ala Gly Ser Ser Ala Asn Phe Glu Phe  
465 470 475 480

Lys Ala Gly Val Asp Thr Lys Asn Gly Thr Ala Thr Phe Asn Asn Asp  
485 490 495

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

Asn Phe Lys Gly Ile Asp Thr Gly Asn Gly Gly Phe Asn Thr Leu Asp  
515 520 525

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

Ser Thr Asn Val Ala Val Lys Asn Phe Asn Ile Asn Glu Leu Ile Val

545 550 555 560

Lys Thr Asn Gly Ile Ser Val Gly Glu Tyr Thr His Phe Ser Glu Asp  
565 570 575

Ile Gly Ser Gln Ser Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr  
580 585 590

Arg Ser Ile Phe Ser Gly Gly Val Lys Phe Lys Ser Gly Glu Lys Leu  
595 600 605

Val Ile Asp Glu Phe Tyr Tyr Ser Pro Trp Asn Tyr Phe Asp Ala Arg  
610 615 620

Asn Val Lys Asn Val Glu Ile Thr Arg Lys Phe Ala Ser Ser Thr Pro  
625 630 635 640

Glu Asn Pro Trp Gly Thr Ser Lys Leu Met Phe Asn Asn Leu Thr Leu  
645 650 655

Gly Gln Asn Ala Val Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile  
660 665 670

Gln Gly Asp Phe Ile Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg  
675 680 685

Gly Gly Lys Val Ala Thr Leu Ser Val Gly Asn Ala Ala Ala Met Met  
690 695 700

Phe Asn Asn Asp Ile Asp Ser Ala Thr Gly Phe Tyr Lys Pro Leu Ile  
705 710 715 720

Lvs Ile Asn Ser Ala Gln Asp Leu Ile Lvs Asn Thr Glu His Val Leu

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              725              730              735
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Leu Lys Ala Lys Ile Ile Gly Tyr Gly Asn Val Ser Thr Gly Thr Asn
      740              745              750

Ser Ile Ser Asn Val Asn Leu Glu Glu Gln Phe Lys Glu Arg Leu Ala
      755              760              765

Leu Tyr Asn Asn Asn Asn Arg Met Asp Thr Cys Val Val Arg Asn Thr
      770              775              780

Asp Asp Ile Lys Ala Cys Gly Met Ala Ile Gly Asn Gln Ser Met Val
      785              790              795              800

Asn Asn Pro Asp Asn Tyr Lys Tyr Leu Ile Gly Lys Ala Trp Lys Asn
      805              810              815

Ile Gly Ile Ser Lys Thr Ala Asn Gly Ser Lys Ile Ser Val Tyr Tyr
      820              825              830

Leu Gly Asn Ser Thr Pro Thr Glu Asn Gly Gly Asn Thr Thr Asn Leu
      835              840              845

Pro Thr Asn Thr Thr Asn Asn Ala Arg Ser Ala Asn Tyr Ala Leu Val
      850              855              860

Lys Asn Ala Pro Phe Ala His Ser Ala Thr Pro Asn Leu Val Ala Ile
      865              870              875              880

Asn Gln His Asp Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala Asn
      885              890              895

Arg Ser Lys Asp Ile Asp Thr Leu Tyr Thr His Ser Gly Val Gln Gly
      900              905              910

Arg Asp Leu Leu Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly Tyr
      915              920              925

Ala Arg Gln Met Ile Asp Asn Thr Ser Thr Gly Glu Ile Thr Lys Gln
      930              935              940

Leu Asn Ala Ala Thr Asp Ala Leu Asn Asn Ile Ala Ser Leu Glu His
      945              950              955              960

Lys Thr Ser Gly Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile Leu
      965              970              975

Asn Ser Arg Leu Val Asn Leu Ser Arg Lys His Thr Asn His Ile Asp
      980              985              990

Ser Phe Ala Gln Arg Leu Gln Ala Leu Lys Gly Gln Arg Phe Ala Ser
      995              1000              1005

Leu Glu Ser Ala Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys Tyr
      1010              1015              1020

Glu Lys Pro Thr Asn Val Trp Ala Asn Ala Ile Gly Gly Ala Ser

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| 1025                                                                          | 1030 | 1035 | - |
|-------------------------------------------------------------------------------|------|------|---|
| Leu Asn Asn Gly Gly Asn Ala Ser Leu Tyr Gly Thr Ser Ala Gly<br>1040 1045 1050 |      |      |   |
| Val Asp Ala Tyr Leu Asn Gly Glu Val Glu Ala Ile Val Gly Gly<br>1055 1060 1065 |      |      |   |
| Phe Gly Ser Tyr Gly Tyr Ser Ser Phe Ser Asn Arg Ala Asn Ser<br>1070 1075 1080 |      |      |   |
| Leu Asn Ser Gly Ala Asn Asn Ala Asn Phe Gly Val Tyr Ser Arg<br>1085 1090 1095 |      |      |   |
| Ile Phe Ala Asn Gln His Glu Phe Asp Phe Glu Ala Gln Gly Ala<br>1100 1105 1110 |      |      |   |
| Leu Gly Ser Asp Gln Ser Ser Leu Asn Phe Lys Ser Ala Leu Leu<br>1115 1120 1125 |      |      |   |
| Gln Asp Leu Asn Gln Ser Tyr His Tyr Leu Ala Tyr Ser Ala Ala<br>1130 1135 1140 |      |      |   |
| Thr Arg Ala Ser Tyr Gly Tyr Asp Phe Ala Phe Phe Arg Asn Ala<br>1145 1150 1155 |      |      |   |
| Leu Val Leu Lys Pro Ser Val Gly Val Ser Tyr Asn His Leu Gly<br>1160 1165 1170 |      |      |   |
| Ser Thr Asn Phe Lys Ser Ser Ser Asn Gln Val Ala Leu Lys Asn<br>1175 1180 1185 |      |      |   |
| Gly Ser Ser Ser Gln His Leu Phe Asn Ala Asn Ala Asn Val Glu<br>1190 1195 1200 |      |      |   |
| Ala Arg Tyr Tyr Tyr Gly Asp Thr Ser Tyr Phe Tyr Met Asn Ala<br>1205 1210 1215 |      |      |   |
| Gly Val Leu Gln Glu Phe Ala Arg Phe Gly Ser Asn Asn Ala Ala<br>1220 1225 1230 |      |      |   |
| Ser Leu Asn Thr Phe Lys Val Asn Thr Ala Arg Asn Pro Leu Asn<br>1235 1240 1245 |      |      |   |
| Thr His Ala Arg Val Met Met Gly Gly Glu Leu Gln Leu Ala Lys<br>1250 1255 1260 |      |      |   |
| Glu Val Phe Leu Asn Leu Gly Val Val Tyr Leu His Asn Leu Ile<br>1265 1270 1275 |      |      |   |
| Ser Asn Ile Gly His Phe Ala Ser Asn Leu Gly Met Arg Tyr Ser<br>1280 1285 1290 |      |      |   |

&lt;210&gt; 5

&lt;211&gt; 1287

&lt;212&gt; PRT

&lt;213&gt; Helicobacter pylori strain 60190

&lt;400&gt; 5

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Thr Ala Val Gly Thr Val Ser Gly Leu Leu Gly Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

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

Trp Asp Trp Gly Asn Ala Ala Thr His Tyr Trp Ile Lys Gly Gly Gln  
115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Lys  
130 135 140

Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met  
145 150 155 160

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
165 170 175

Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala  
180 185 190

Lys Asn Ile Leu Ile Asp Asn Phe Leu Glu Ile Asn Asn Arg Val Gly  
195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
210 215 220

Ser Glu Gly Ile Thr Ser Ser Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Asn Ser Val Lys Leu Asn Gly Asn  
245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
260 265 270

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

His Leu Thr Val Gly Asp His Asn Ala Ala Gln Ala Gly Ile Ile Ala  
290 295 300

Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly  
305 310 315 320

Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Asn  
325 330 335

Asn Thr Pro Ser Gln Ser Gly Ala Lys Asn Asp Lys Gln Glu Ser Ser  
340 345 350

Gln Asn Asn Ser Asn Thr Gln Val Ile Asn Pro Pro Asn Ser Thr Gln  
355 360 365

Lys Thr Glu Val Gln Pro Thr Gln Val Ile Asp Gly Pro Phe Ala Gly  
370 375 380

Gly Lys Asp Thr Val Val Asn Ile Asp Arg Ile Asn Thr Lys Ala Asp  
385 390 395 400

Gly Thr Ile Lys Val Gly Gly Phe Lys Ala Ser Leu Thr Thr Asn Ala  
405 410 415

Ala His Leu Asn Ile Gly Lys Gly Gly Val Asn Leu Ser Asn Gln Ala  
420 425 430

Ser Gly Arg Thr Leu Leu Val Glu Asn Leu Thr Gly Asn Ile Thr Val  
435 440 445

Asp Gly Pro Leu Arg Val Asn Asn Gln Val Gly Gly Tyr Ala Leu Ala  
450 455 460

Gly Ser Ser Ala Asn Phe Glu Phe Lys Ala Gly Val Asp Thr Lys Asn

465 470 475 480

Gly Thr Ala Thr Phe Asn Asn Asp Ile Ser Leu Gly Arg Phe Val Asn  
485 490 495

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

Asn Gly Gly Phe Asn Thr Leu Asp Phe Ser Gly Val Thr Asn Lys Val  
515 520 525

Asn Ile Asn Lys Leu Ile Thr Ala Ser Thr Asn Val Ala Val Lys Asn  
530 535 540

Phe Asn Ile Asn Glu Leu Ile Val Lys Thr Asn Gly Val Ser Val Gly  
545 550 555 560

Glu Tyr Thr His Phe Ser Glu Asp Ile Gly Ser Gln Ser Arg Ile Asn  
565 570 575

Thr Val Arg Leu Glu Thr Gly Thr Arg Ser Ile Phe Ser Gly Gly Val  
 580 585 590  
 Lys Phe Lys Ser Gly Glu Lys Leu Val Ile Asp Glu Phe Tyr Tyr Ser  
 595 600 605  
 Pro Trp Asn Tyr Phe Asp Ala Arg Asn Ile Lys Asn Val Glu Ile Thr  
 610 615 620  
 Arg Lys Phe Ala Ser Ser Thr Pro Glu Asn Pro Trp Gly Thr Ser Lys  
 625 630 635 640  
 Leu Met Phe Asn Asn Leu Thr Leu Gly Gln Asn Ala Val Met Asp Tyr  
 645 650 655  
 Ser Gln Phe Ser Asn Leu Thr Ile Gln Gly Asp Phe Ile Asn Asn Gln  
 660 665 670  
 Gly Thr Ile Asn Tyr Leu Val Arg Gly Gly Lys Val Ala Thr Leu Asn  
 675 680 685  
 Val Gly Asn Ala Ala Ala Met Met Phe Asn Asn Asp Ile Asp Ser Ala  
 690 695 700  
 Thr Gly Phe Tyr Lys Pro Leu Ile Lys Ile Asn Ser Ala Gln Asp Leu  
 705 710 715 720  
 Ile Lys Asn Thr Glu His Val Leu Leu Lys Ala Lys Ile Ile Gly Tyr  
 725 730 735  
 Gly Asn Val Ser Thr Gly Thr Asn Gly Ile Ser Asn Val Asn Leu Glu  
 740 745 750  
 Glu Gln Phe Lys Glu Arg Leu Ala Leu Tyr Asn Asn Asn Asn Arg Met  
 755 760 765  
 Asp Thr Cys Val Val Arg Asn Thr Asp Asp Ile Lys Ala Cys Gly Met  
 770 775 780  
 Ala Ile Gly Asn Gln Ser Met Val Asn Asn Pro Asp Asn Tyr Lys Tyr  
 785 790 795 800  
 Leu Ile Gly Lys Ala Trp Lys Asn Ile Gly Ile Ser Lys Thr Ala Asn  
 805 810 815  
 Gly Ser Lys Ile Ser Val Tyr Tyr Leu Gly Asn Ser Thr Pro Thr Glu  
 820 825 830  
 Asn Gly Gly Asn Thr Thr Asn Leu Pro Thr Asn Thr Thr Asn Asn Ala  
 835 840 845  
 Arg Phe Ala Ser Tyr Ala Leu Ile Lys Asn Ala Pro Phe Ala His Ser  
 850 855 860  
 Ala Thr Pro Asn Leu Val Ala Ile Asn Gln His Asp Phe Gly Thr Ile  
 865 870 875 880

Glu Ser Val Phe Glu Leu Ala Asn Arg Ser Lys Asp Ile Asp Thr Leu  
 885 890 895  
 Tyr Ala Asn Ser Gly Ala Gln Gly Arg Asp Leu Leu Gln Thr Leu Leu  
 900 905 910  
 Ile Asp Ser His Asp Ala Gly Tyr Ala Arg Thr Met Ile Asp Ala Thr  
 915 920 925  
 Ser Ala Asn Glu Ile Thr Lys Gln Leu Asn Thr Ala Thr Thr Thr Leu  
 930 935 940  
 Asn Asn Ile Ala Ser Leu Glu His Lys Thr Ser Ser Leu Gln Thr Leu  
 945 950 955 960  
 Ser Leu Ser Asn Ala Met Ile Leu Asn Ser Arg Leu Val Asn Leu Ser  
 965 970 975  
 Arg Arg His Thr Asn Asn Ile Asp Ser Phe Ala Lys Arg Leu Gln Ala  
 980 985 990  
 Leu Lys Asp Gln Arg Phe Ala Ser Leu Glu Ser Ala Ala Glu Val Leu  
 995 1000 1005  
 Tyr Gln Phe Ala Pro Lys Tyr Glu Lys Pro Thr Asn Val Trp Ala  
 1010 1015 1020  
 Asn Ala Ile Gly Gly Ala Ser Leu Asn Asn Gly Gly Asn Ala Ser  
 1025 1030 1035  
 Leu Tyr Gly Thr Ser Ala Gly Val Asp Ala Tyr Leu Asn Gly Gln  
 1040 1045 1050  
 Val Glu Ala Ile Val Gly Gly Phe Gly Ser Tyr Gly Tyr Ser Ser  
 1055 1060 1065  
 Phe Asn Asn Gln Ala Asn Ser Leu Asn Ser Gly Ala Asn Asn Thr  
 1070 1075 1080  
 Asn Phe Gly Val Tyr Ser Arg Ile Phe Ala Asn Gln His Glu Phe  
 1085 1090 1095  
 Asp Phe Glu Ala Gln Gly Ala Leu Gly Ser Asp Gln Ser Ser Leu  
 1100 1105 1110  
 Asn Phe Lys Ser Ala Leu Leu Arg Asp Leu Asn Gln Ser Tyr Asn  
 1115 1120 1125  
 Tyr Leu Ala Tyr Ser Ala Ala Thr Arg Ala Ser Tyr Gly Tyr Asp  
 1130 1135 1140  
 Phe Ala Phe Phe Arg Asn Ala Leu Val Leu Lys Pro Ser Val Gly  
 1145 1150 1155  
 Val Ser Tyr Asn His Leu Gly Ser Thr Asn Phe Lys Ser Asn Ser  
 1160 1165 1170

Thr Asn Lys Val Ala Leu Ser Asn Gly Ser Ser Ser Gln His Leu  
1175 1180 1185

Phe Asn Ala Ser Ala Asn Val Glu Ala Arg Tyr Tyr Tyr Gly Asp  
1190 1195 1200

Thr Ser Tyr Phe Tyr Met Asn Ala Gly Val Leu Gln Glu Phe Ala  
1205 1210 1215

Asn Phe Gly Ser Ser Asn Ala Val Ser Leu Asn Thr Phe Lys Val  
1220 1225 1230

Asn Ala Thr Arg Asn Pro Leu Asn Thr His Ala Arg Val Met Met  
1235 1240 1245

Gly Gly Glu Leu Lys Leu Ala Lys Glu Val Phe Leu Asn Leu Gly  
1250 1255 1260

Val Val Tyr Leu His Asn Leu Ile Ser Asn Ile Gly His Phe Ala  
1265 1270 1275

Ser Asn Leu Gly Met Arg Tyr Ser Phe  
1280 1285

<210> 6

<211> 1290

<212> PRT

<213> Helicobacter pylori strain 26695

<400> 6

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Ala Ala Val Gly Thr Val Ser Gly Leu Leu Gly Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

Glu Tyr Asp Leu Tyr Arg Ser Leu Leu Ser Ser Lys Ile Asp Gly Gly  
100 105 110

Trp Asp Trp Gly Asn Ala Ala Thr His Tyr Trp Val Lys Gly Gly Gln  
115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Asn  
130 135 140

| 130                                                                                | 135 | 140 |
|------------------------------------------------------------------------------------|-----|-----|
| Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met<br>145 150 155 160 |     |     |
| Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr<br>165 170 175     |     |     |
| Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala<br>180 185 190     |     |     |
| Lys Asn Ile Leu Ile Asp Asn Phe Leu Glu Ile Asn Asn Arg Val Gly<br>195 200 205     |     |     |
| Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala<br>210 215 220     |     |     |
| Ser Glu Gly Ile Thr Ser Ser Lys Asn Ala Glu Ile Ser Leu Tyr Asp<br>225 230 235 240 |     |     |
| Gly Ala Thr Leu Asn Leu Ala Ser Asn Ser Val Lys Leu Met Gly Asn<br>245 250 255     |     |     |
| Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser<br>260 265 270     |     |     |
| Tyr Ser Thr Ile Asn Thr Ser Lys Val Thr Gly Glu Val Asn Phe Asn<br>275 280 285     |     |     |
| His Leu Thr Val Gly Asp His Asn Ala Ala Gln Ala Gly Ile Ile Ala<br>290 295 300     |     |     |
| Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly<br>305 310 315 320 |     |     |
| Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Lys<br>325 330 335     |     |     |
| Asp Lys Pro Ser Asn Thr Thr Gln Asn Asn Ala Asn Asn Asn Gln Gln<br>340 345 350     |     |     |
| Asn Ser Ala Gln Asn Asn Ser Asn Thr Gln Val Ile Asn Pro Pro Asn<br>355 360 365     |     |     |
| Ser Ala Gln Lys Thr Glu Ile Gln Pro Thr Gln Val Ile Asp Gly Pro<br>370 375 380     |     |     |
| Phe Ala Gly Gly Lys Asp Thr Val Val Asn Ile Asp Arg Ile Asn Thr<br>385 390 395 400 |     |     |
| Asn Ala Asp Gly Thr Ile Lys Val Gly Gly Tyr Lys Ala Ser Leu Thr<br>405 410 415     |     |     |
| Thr Asn Ala Ala His Leu His Ile Gly Lys Gly Gly Ile Asn Leu Ser<br>420 425 430     |     |     |

Asn Gln Ala Ser Gly Arg Thr Leu Leu Val Glu Asn Leu Thr Gly Asn  
 435 440 445  
 Ile Thr Val Asp Gly Pro Leu Arg Val Asn Asn Gln Val Gly Gly Tyr  
 450 455 460  
 Ala Leu Ala Gly Ser Ser Ala Asn Phe Glu Phe Lys Ala Gly Thr Asp  
 465 470 475 480  
 Thr Lys Asn Gly Thr Ala Thr Phe Asn Asn Asp Ile Ser Leu Gly Arg  
 485 490 495  
 Phe Val Asn Leu Lys Val Asp Ala His Thr Ala Asn Phe Lys Gly Ile  
 500 505 510  
 Asp Thr Gly Asn Gly Gly Phe Asn Thr Leu Asp Phe Ser Gly Val Thr  
 515 520 525  
 Gly Lys Val Asn Ile Asn Lys Leu Ile Thr Ala Ser Thr Asn Val Ala  
 530 535 540  
 Val Lys Asn Phe Asn Ile Asn Glu Leu Val Val Lys Thr Asn Gly Val  
 545 550 555 560  
 Ser Val Gly Glu Tyr Thr His Phe Ser Glu Asp Ile Gly Ser Gln Ser  
 565 570 575  
 Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr Arg Ser Ile Phe Ser  
 580 585 590  
 Gly Gly Val Lys Phe Lys Ser Gly Glu Lys Leu Val Ile Asp Glu Phe  
 595 600 605  
 Tyr Tyr Ser Pro Trp Asn Tyr Phe Asp Ala Arg Asn Ile Lys Asn Val  
 610 615 620  
 Glu Ile Thr Arg Lys Phe Ala Ser Ser Thr Pro Glu Asn Pro Trp Gly  
 625 630 635 640  
 Thr Ser Lys Leu Met Phe Asn Asn Leu Thr Leu Gly Gln Asn Ala Val  
 645 650 655  
 Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile Gln Gly Asp Phe Ile  
 660 665 670  
 Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg Gly Gly Gln Val Ala  
 675 680 685  
 Thr Leu Asn Val Gly Asn Ala Ala Ala Met Phe Phe Ser Asn Asn Val  
 690 695 700  
 Asp Ser Ala Thr Gly Phe Tyr Gln Pro Leu Met Lys Ile Asn Ser Ala  
 705 710 715 720  
 Gln Asp Leu Ile Lys Asn Lys Glu His Val Leu Leu Lys Ala Lys Ile  
 725 730 735

Ile Gly Tyr Gly Asn Val Ser Leu Gly Thr Asn Ser Ile Ser Asn Val  
 740 745 750  
 Asn Leu Ile Glu Gln Phe Lys Glu Arg Leu Ala Leu Tyr Asn Asn Asn  
 755 760 765  
 Asn Arg Met Asp Ile Cys Val Val Arg Asn Thr Asp Asp Ile Lys Ala  
 770 775 780  
 Cys Gly Thr Ala Ile Gly Asn Gln Ser Met Val Asn Asn Pro Asp Asn  
 785 790 795 800  
 Tyr Lys Tyr Leu Ile Gly Lys Ala Trp Lys Asn Ile Gly Ile Ser Lys  
 805 810 815  
 Thr Ala Asn Gly Ser Lys Ile Ser Val Tyr Tyr Leu Gly Asn Ser Thr  
 820 825 830  
 Pro Thr Glu Lys Gly Gly Asn Thr Thr Asn Leu Pro Thr Asn Thr Thr  
 835 840 845  
 Ser Asn Val Arg Ser Ala Asn Asn Ala Leu Ala Gln Asn Ala Pro Phe  
 850 855 860  
 Ala Gln Pro Ser Ala Thr Pro Asn Leu Val Ala Ile Asn Gln His Asp  
 865 870 875 880  
 Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala Asn Arg Ser Lys Asp  
 885 890 895  
 Ile Asp Thr Leu Tyr Ala Asn Ser Gly Ala Gln Gly Arg Asp Leu Leu  
 900 905 910  
 Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly Tyr Ala Arg Gln Met  
 915 920 925  
 Ile Asp Asn Thr Ser Thr Gly Glu Ile Thr Lys Gln Leu Asn Ala Ala  
 930 935 940  
 Thr Thr Thr Leu Asn Asn Ile Ala Ser Leu Glu His Lys Thr Ser Ser  
 945 950 955 960  
 Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile Leu Asn Ser Arg Leu  
 965 970 975  
 Val Asn Leu Ser Arg Arg His Thr Asn Asn Ile Asp Ser Phe Ala Gln  
 980 985 990  
 Arg Leu Gln Ala Leu Lys Asp Gln Lys Phe Ala Ser Leu Glu Ser Ala  
 995 1000 1005  
 Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys Tyr Glu Lys Pro Thr  
 1010 1015 1020  
 Asn Val Trp Ala Asn Ala Ile Gly Gly Thr Ser Leu Asn Asn Gly  
 1025 1030 1035

Gly Asn Ala Ser Leu Tyr Gly Thr Ser Ala Gly Val Asp Ala Tyr  
 1040 1045 1050  
 Leu Asn Gly Glu Val Glu Ala Ile Val Gly Gly Phe Gly Ser Tyr  
 1055 1060 1065  
 Gly Tyr Ser Ser Phe Asn Asn Gln Ala Asn Ser Leu Asn Ser Gly  
 1070 1075 1080  
 Ala Asn Asn Thr Asn Phe Gly Val Tyr Ser Arg Ile Phe Ala Asn  
 1085 1090 1095  
 Gln His Glu Phe Asp Phe Glu Ala Gln Gly Ala Leu Gly Ser Asp  
 1100 1105 1110  
 Gln Ser Ser Leu Asn Phe Lys Ser Ala Leu Leu Arg Asp Leu Asn  
 1115 1120 1125  
 Gln Ser Tyr Asn Tyr Leu Ala Tyr Ser Ala Ala Thr Arg Ala Ser  
 1130 1135 1140  
 Tyr Gly Tyr Asp Phe Ala Phe Phe Arg Asn Ala Leu Val Leu Lys  
 1145 1150 1155  
 Pro Ser Val Gly Val Ser Tyr Asn His Leu Gly Ser Thr Asn Phe  
 1160 1165 1170  
 Lys Ser Asn Ser Asn Gln Val Ala Leu Lys Asn Gly Ser Ser Ser  
 1175 1180 1185  
 Gln His Leu Phe Asn Ala Ser Ala Asn Val Glu Ala Arg Tyr Tyr  
 1190 1195 1200  
 Tyr Gly Asp Thr Ser Tyr Phe Tyr Met Asn Ala Gly Val Leu Gln  
 1205 1210 1215  
 Glu Phe Ala Asn Phe Gly Ser Ser Asn Ala Val Ser Leu Asn Thr  
 1220 1225 1230  
 Phe Lys Val Asn Ala Ala His Asn Pro Leu Ser Thr His Ala Arg  
 1235 1240 1245  
 Val Met Met Gly Gly Glu Leu Lys Leu Ala Lys Glu Val Phe Leu  
 1250 1255 1260  
 Asn Leu Gly Phe Val Tyr Leu His Asn Leu Ile Ser Asn Ile Gly  
 1265 1270 1275  
 His Phe Ala Ser Asn Leu Gly Met Arg Tyr Ser Phe  
 1280 1285 1290

&lt;210&gt; 7

&lt;211&gt; 1288

&lt;212&gt; PRT

&lt;213&gt; Helicobacter pylori strain J99

&lt;400&gt; 7

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
 1 5 10 15

Leu Val Leu Ala Gly Ala Leu Ile Ser Ala Ile Pro Gln Glu Ser His  
 20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
 35 40 45

Ala Thr Gly Thr Ala Val Gly Thr Val Ser Gly Leu Leu Ser Trp Gly  
 50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
 65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
 85 90 95

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

Trp Asp Trp Gly Asn Ala Ala Arg His Tyr Trp Val Lys Gly Gly Gln  
 115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Lys  
 130 135 140

Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met  
 145 150 155 160

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
 165 170 175

Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asn Phe Asn Ala  
 180 185 190

Lys Asn Ile Ser Ile Asp Asn Phe Val Glu Ile Asn Asn Arg Val Gly  
 195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
 210 215 220

Ser Glu Gly Ile Thr Ser Ser Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
 225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Asn Ser Val Lys Leu Asn Gly Asn  
 245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
 260 265 270

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

His Leu Thr Val Gly Asp Gln Asn Ala Ala Gln Ala Gly Ile Ile Ala

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290          295          300

Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly

305          310          315          320

Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Asn
      325          330          335

Ser Thr Thr Ser Gln Ser Gly Thr Lys Asn Asp Lys Lys Glu Ile Ser
      340          345          350

Gln Asn Asn Asn Ser Asn Thr Glu Val Ile Asn Pro Pro Asn Asn Thr
      355          360          365

Gln Lys Thr Glu Thr Glu Pro Thr Gln Val Ile Asp Gly Pro Phe Ala
      370          375          380

Gly Gly Lys Asp Thr Val Val Asn Ile Phe His Leu Asn Thr Lys Ala
385          390          395          400

Asp Gly Thr Ile Lys Val Gly Gly Phe Lys Ala Ser Leu Thr Thr Asn
      405          410          415

Ala Ala His Leu Asn Ile Gly Lys Gly Gly Val Asn Leu Ser Asn Gln
      420          425          430

Ala Ser Gly Arg Thr Leu Leu Val Glu Asn Leu Thr Gly Asn Ile Thr
      435          440          445

Val Asp Gly Pro Leu Arg Val Asn Asn Gln Val Gly Gly Tyr Ala Leu
      450          455          460

Ala Gly Ser Ser Ala Asn Phe Glu Phe Lys Ala Gly Val Asp Thr Lys
465          470          475          480

Asn Gly Thr Ala Thr Phe Asn Asn Asp Ile Ser Leu Gly Arg Phe Val
      485          490          495

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

Gly Asn Gly Gly Phe Asn Thr Leu Asp Phe Ser Gly Val Thr Asp Lys
      515          520          525

Val Asn Ile Asn Lys Leu Ile Thr Ala Ser Thr Asn Val Ala Val Lys
      530          535          540

Asn Phe Asn Ile Asn Glu Leu Ile Val Lys Thr Asn Gly Ile Ser Val
545          550          555          560

Gly Glu Tyr Thr His Phe Ser Glu Asp Ile Gly Ser Gln Ser Arg Ile
      565          570          575

Asn Thr Val Arg Leu Glu Thr Gly Thr Arg Ser Ile Phe Ser Gly Gly
      580          585          590

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Val Lys Phe Lys Ser Gly Glu Lys Leu Val Ile Asn Asp Phe Tyr Tyr  
 595 600 605

Ser Pro Trp Asn Tyr Phe Asp Ala Arg Asn Val Lys Asn Val Glu Ile  
 610 615 620

Thr Arg Lys Phe Ala Ser Ser Thr Pro Glu Asn Pro Trp Gly Thr Ser  
 625 630 635

Lys Leu Met Phe Asn Asn Leu Thr Leu Gly Gln Asn Ala Val Met Asp  
 645 650 655

Tyr Ser Gln Phe Ser Asn Leu Thr Ile Gln Gly Asp Phe Ile Asn Asn  
 660 665 670

Gln Gly Thr Ile Asn Tyr Leu Val Arg Gly Gly Lys Val Ala Thr Leu  
 675 680 685

Asn Val Gly Asn Ala Ala Ala Met Met Phe Asn Asn Asp Ile Asp Ser  
 690 695 700

Ala Thr Gly Phe Tyr Lys Pro Leu Ile Lys Ile Asn Ser Ala Gln Asp  
 705 710 715 720

Leu Ile Lys Asn Thr Glu His Val Leu Leu Lys Ala Lys Ile Ile Gly  
 725 730 735

Tyr Gly Asn Val Ser Thr Gly Thr Asn Gly Ile Ser Asn Val Asn Leu  
 740 745 750

Glu Glu Gln Phe Lys Glu Arg Leu Ala Leu Tyr Asn Asn Asn Asn Arg  
 755 760 765

Met Asp Thr Cys Val Val Arg Asn Thr Asp Asp Ile Lys Ala Cys Gly  
 770 775 780

Met Ala Ile Gly Asn Gln Ser Met Val Asn Asn Pro Asp Asn Tyr Lys  
 785 790 795 800

Tyr Leu Ile Gly Lys Ala Trp Arg Asn Ile Gly Ile Ser Lys Thr Ala  
 805 810 815

Asn Gly Ser Lys Ile Ser Val Tyr Tyr Leu Gly Asn Ser Thr Pro Thr  
 820 825 830

Glu Asn Gly Gly Asn Thr Thr Asn Leu Pro Thr Asn Thr Thr Asn Asn  
 835 840 845

Ala His Ser Ala Asn Tyr Ala Leu Val Lys Asn Ala Pro Phe Ala His  
 850 855 860

Ser Ala Thr Pro Asn Leu Val Ala Ile Asn Gln His Asp Phe Gly Thr  
 865 870 875 880

Ile Glu Ser Val Phe Glu Leu Ala Asn Arg Ser Lys Asp Ile Asp Thr  
 885 890 895

Leu Tyr Thr His Ser Gly Ala Gln Gly Arg Asp Leu Leu Gln Thr Leu  
 900 905 910

Leu Ile Asp Ser His Asp Ala Gly Tyr Ala Arg Gln Met Ile Asp Asn  
 915 920 925

Thr Ser Thr Gly Glu Ile Thr Lys Gln Leu Asn Ala Ala Thr Asp Ala  
 930 935 940

Leu Asn Asn Val Ala Ser Leu Glu His Lys Gln Ser Gly Leu Gln Thr  
 945 950 955 960

Leu Ser Leu Ser Asn Ala Met Ile Leu Asn Ser Arg Leu Val Asn Leu  
 965 970 975

Ser Arg Lys His Thr Asn His Ile Asn Ser Phe Ala Gln Arg Leu Gln  
 980 985 990

Ala Leu Lys Gly Gln Glu Phe Ala Ser Leu Glu Ser Ala Ala Glu Val  
 995 1000 1005

Leu Tyr Gln Phe Ala Pro Lys Tyr Glu Lys Pro Thr Asn Val Trp  
 1010 1015 1020

Ala Asn Ala Ile Gly Gly Ala Ser Leu Asn Ser Gly Ser Asn Ala  
 1025 1030 1035

Ser Leu Tyr Gly Thr Ser Ala Gly Val Asp Ala Phe Leu Asn Gly  
 1040 1045 1050

Asn Val Glu Ala Ile Val Gly Gly Phe Gly Ser Tyr Gly Tyr Ser  
 1055 1060 1065

Ser Phe Ser Asn Gln Ala Asn Ser Leu Asn Ser Gly Ala Asn Asn  
 1070 1075 1080

Ala Asn Phe Gly Val Tyr Ser Arg Phe Phe Ala Asn Gln His Glu  
 1085 1090 1095

Phe Asp Phe Glu Ala Gln Gly Ala Leu Gly Ser Asp Gln Ser Ser  
 1100 1105 1110

Leu Asn Phe Lys Ser Thr Leu Leu Gln Asp Leu Asn Gln Ser Tyr  
 1115 1120 1125

Asn Tyr Leu Ala Tyr Ser Ala Thr Ala Arg Ala Ser Tyr Gly Tyr  
 1130 1135 1140

Asp Phe Ala Phe Phe Arg Asn Ala Leu Val Leu Lys Pro Ser Val  
 1145 1150 1155

Gly Val Ser Tyr Asn His Leu Gly Ser Thr Asn Phe Lys Ser Asn  
 1160 1165 1170

Ser Gln Ser Gln Val Ala Leu Lys Asn Gly Ala Ser Ser Gln His  
 1175 1180 1185

Leu Phe Asn Ala Asn Ala Asn Val Glu Ala Arg Tyr Tyr Tyr Gly  
1190 1195 1200

Asp Thr Ser Tyr Phe Tyr Leu His Ala Gly Val Leu Gln Glu Phe  
1205 1210 1215

Ala His Phe Gly Ser Asn Asp Val Ala Ser Leu Asn Thr Phe Lys  
1220 1225 1230

Ile Asn Ala Ala Arg Ser Pro Leu Ser Thr Tyr Ala Arg Ala Met  
1235 1240 1245

Met Gly Gly Glu Leu Gln Leu Ala Lys Glu Val Phe Leu Asn Leu  
1250 1255 1260

Gly Val Val Tyr Leu His Asn Leu Ile Ser Asn Ala Ser His Phe  
1265 1270 1275

Ala Ser Asn Leu Gly Met Arg Tyr Ser Phe  
1280 1285

<210> 8

<211> 1290

<212> PRT

<213> Helicobacter pylori strain NCTC 11637

<400> 8

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Ala Ala Val Gly Thr Val Ser Gly Leu Leu Ser Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Arg Gly Phe Asn Asn Phe Pro His Lys  
85 90 95

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

Trp Asp Trp Gly Asn Ala Ala Arg His Tyr Trp Val Lys Gly Gly Gln  
115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Lys  
130 135 140

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

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
 165 170 175

Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala  
 180 185 190

Lys Asn Ile Leu Ile Asp Asn Phe Leu Glu Ile Asn Asn Arg Val Gly  
 195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
 210 215 220

Ser Glu Gly Ile Thr Ser Ser Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
 225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Ser Ser Val Lys Leu Met Gly Asn  
 245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
 260 265 270

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

His Leu Thr Val Gly Asp His Asn Ala Ala Gln Ala Gly Ile Ile Ala  
 290 295 300

Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly  
 305 310 315 320

Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Lys  
 325 330 335

Asp Lys Pro Ser Asn Thr Thr Gln Asn Asn Ala Asn Asn Asn Gln Gln  
 340 345 350

Asn Ser Ala Gln Asn Asn Asn Asn Thr Gln Val Ile Asn Pro Pro Asn  
 355 360 365

Ser Ala Gln Lys Thr Glu Ile Gln Pro Thr Gln Val Ile Asn Gly Pro  
 370 375 380

Phe Ala Gly Gly Lys Asp Thr Val Val Asn Ile Asn Arg Ile Asn Thr  
 385 390 395 400

Asn Ala Asp Gly Thr Ile Arg Val Gly Gly Tyr Lys Ala Ser Leu Thr  
 405 410 415

Thr Asn Ala Ala His Leu His Ile Gly Lys Gly Gly Ile Asn Leu Ser  
 420 425 430

Asn Gln Ala Ser Gly Arg Ser Leu Leu Val Glu Asn Leu Thr Gly Asn  
 435 440 445  
 Ile Thr Val Asp Gly Pro Leu Arg Val Asn Asn Gln Val Gly Gly Tyr  
 450 455 460  
 Ala Leu Ala Gly Ser Asn Ala Asn Phe Glu Phe Lys Ala Gly Thr Asp  
 465 470 475 480  
 Thr Lys Asn Gly Thr Ala Thr Phe Asn Asn Asp Ile Ser Leu Gly Arg  
 485 490 495  
 Phe Val Asn Leu Lys Val Asp Ala His Thr Ala Asn Phe Lys Gly Ile  
 500 505 510  
 Asp Thr Gly Asn Gly Gly Phe Asn Thr Leu Asp Phe Ser Gly Val Thr  
 515 520 525  
 Asp Lys Val Asn Ile Asn Lys Leu Ile Thr Ala Ser Thr Asn Val Ala  
 530 535 540  
 Ile Lys Asn Phe Asn Ile Asn Glu Leu Leu Val Lys Thr Asn Gly Val  
 545 550 555 560  
 Ser Val Gly Glu Tyr Thr His Phe Ser Glu Asp Ile Gly Ser Gln Ser  
 565 570 575  
 Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr Arg Ser Ile Phe Ser  
 580 585 590  
 Gly Gly Val Lys Phe Lys Ser Gly Glu Lys Leu Val Ile Asp Glu Phe  
 595 600 605  
 Tyr Tyr Ser Pro Trp Asn Tyr Phe Asp Ala Arg Asn Ile Lys Asn Val  
 610 615 620  
 Glu Ile Thr Arg Lys Phe Ala Ser Ser Thr Pro Glu Asn Pro Trp Gly  
 625 630 635 640  
 Thr Ser Lys Leu Met Phe Asn Asn Leu Thr Leu Gly Gln Asn Ala Val  
 645 650 655  
 Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile Gln Gly Asp Phe Ile  
 660 665 670  
 Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg Gly Gly Lys Val Ala  
 675 680 685  
 Thr Leu Asn Val Gly Asn Ala Ala Ala Met Met Phe Asn Asn Asp Ile  
 690 695 700  
 Asp Ser Ala Thr Gly Phe Tyr Lys Pro Leu Ile Lys Ile Asn Ser Ala  
 705 710 715 720  
 Gln Asp Leu Ile Lys Asn Thr Glu His Val Leu Leu Lys Ala Lys Ile  
 725 730 735  
 Ile Glv Trv Glv Asn Val Ser Thr Glv Thr Asn Glv Ile Ser Asn Val

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740              745              750
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Asn Leu Glu Glu Gln Phe Lys Glu Arg Leu Ala Leu Tyr Asn Asn Asn
755              760              765

Asn Arg Met Asp Thr Cys Val Val Arg Asn Thr Asp Asp Ile Lys Ala
770              775              780

Cys Gly Met Ala Ile Gly Asn Gln Ser Met Val Asn Asn Pro Asp Asn
785              790              795              800

Tyr Lys Tyr Leu Ile Gly Lys Ala Trp Lys Asn Ile Gly Ile Ser Lys
805              810              815

Thr Ala Asn Gly Ser Lys Ile Ser Val Tyr Tyr Leu Gly Asn Ser Thr
820              825              830

Pro Thr Glu Asn Gly Gly Asn Thr Thr Asn Leu Pro Thr Asn Thr Thr
835              840              845

Asn Asn Ala Arg Ser Ala Asn Tyr Ala Leu Val Lys Asn Ala Pro Phe
850              855              860

Ala His Ser Ala Thr Pro Asn Leu Val Ala Ile Asn Gln His Asp Phe
865              870              875              880

Gly Thr Ile Glu Ser Val Phe Glu Leu Ala Asn Arg Ser Lys Asp Ile
885              890              895

Asp Thr Leu Tyr Thr His Ser Gly Ala Lys Gly Arg Asp Leu Leu Gln
900              905              910

Thr Leu Leu Ile Asp Ser His Asp Ala Gly Tyr Ala Arg Gln Met Ile
915              920              925

Asp Asn Thr Ser Thr Gly Glu Ile Thr Lys Gln Leu Asn Ala Ala Thr
930              935              940

Thr Thr Leu Asn Asn Ile Ala Ser Leu Glu His Lys Thr Ser Ser Leu
945              950              955              960

Gln Thr Leu Ser Leu Ser Asn Ala Met Ile Leu Asn Ser Arg Leu Val
965              970              975

Asn Leu Ser Arg Lys His Thr Asn Asn Ile Asp Ser Phe Ala Lys Arg
980              985              990

Leu Gln Ala Leu Lys Asp Gln Arg Phe Ala Ser Leu Glu Ser Ala Ala
995              1000              1005

Glu Val Leu Tyr Gln Phe Ala Pro Lys Tyr Glu Lys Pro Thr Asn
1010              1015              1020

Val Trp Ala Asn Ala Ile Gly Gly Ala Ser Leu Asn Asn Gly Ser
1025              1030              1035

Asn Ala Ser Leu Tyr Gly Thr Ser Ala Gly Val Asp Ala Tyr Leu

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|                 |                             |                             |             |      |
|-----------------|-----------------------------|-----------------------------|-------------|------|
| 1040            |                             | 1045                        |             | 1050 |
| Asn Gly<br>1055 | Gln Val Glu Ala Ile<br>1060 | Val Gly Gly Phe Gly<br>1065 | Ser Tyr Gly |      |
| Tyr Ser<br>1070 | Ser Phe Ser Asn Arg<br>1075 | Ala Asn Ser Leu Asn<br>1080 | Ser Gly Ala |      |
| Asn Asn<br>1085 | Thr Asn Phe Gly Val<br>1090 | Tyr Ser Arg Ile Phe<br>1095 | Ala Asn Gln |      |
| His Glu<br>1100 | Phe Asp Phe Glu Ala<br>1105 | Gln Gly Ala Leu Gly<br>1110 | Ser Asp Gln |      |
| Ser Ser<br>1115 | Leu Asn Phe Lys Ser<br>1120 | Ala Leu Leu Gln Asp<br>1125 | Leu Asn Gln |      |
| Ser Tyr<br>1130 | Asn Tyr Leu Ala Tyr<br>1135 | Ser Ala Ala Thr Arg<br>1140 | Ala Ser Tyr |      |
| Gly Tyr<br>1145 | Asp Phe Ala Phe Phe<br>1150 | Lys Asn Ala Leu Val<br>1155 | Leu Lys Pro |      |
| Ser Val<br>1160 | Gly Val Ser Tyr Asn<br>1165 | His Leu Gly Ser Thr<br>1170 | Asn Phe Lys |      |
| Ser Asn<br>1175 | Ser Thr Asn Lys Val<br>1180 | Ala Leu Ser Asn Gly<br>1185 | Ser Ser Ser |      |
| Gln His<br>1190 | Leu Phe Asn Ala Ser<br>1195 | Ala Asn Val Glu Ala<br>1200 | Arg Tyr Tyr |      |
| Tyr Gly<br>1205 | Asp Thr Ser Tyr Phe<br>1210 | Tyr Met Asn Ala Gly<br>1215 | Val Leu Gln |      |
| Glu Phe         | Ala Asn Phe Gly Ser         | Ser Asn Ala Val Ser         | Leu Asn Thr |      |
| 1220            |                             | 1225                        |             | 1230 |
| Phe Lys<br>1235 | Val Asn Ala Ala Arg<br>1240 | Asn Pro Leu Asn Thr<br>1245 | His Ala Arg |      |
| Val Met<br>1250 | Met Gly Gly Glu Leu<br>1255 | Gln Leu Ala Lys Glu<br>1260 | Val Phe Leu |      |
| Asn Leu<br>1265 | Gly Phe Val Tyr Leu<br>1270 | His Asn Leu Ile Ser<br>1275 | Asn Ile Gly |      |
| His Phe<br>1280 | Ala Ser Asn Leu Gly<br>1285 | Met Arg Tyr Ser Phe<br>1290 |             |      |

&lt;210&gt; 9

&lt;211&gt; 1296

&lt;212&gt; PRT

&lt;213&gt; Helicobacter pylori P12

&lt;400&gt; 9

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Ser Gly Ala Ala Val Gly Thr Val Ser Gly Leu Leu Gly Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

Glu Tyr Asp Leu Tyr Arg Ser Leu Leu Ser Ser Lys Ile Asp Gly Gly  
100 105 110

Trp Asp Trp Gly Asn Ala Ala Thr His Tyr Trp Val Lys Gly Gly Gln  
115 120 125

Trp Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Asn  
130 135 140

Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met

145 150 155 160

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
165 170 175

Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala  
180 185 190

Lys Asn Ile Ser Ile Asp Asn Phe Leu Glu Ile Asn Asn Arg Val Gly  
195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
210 215 220

Ser Glu Gly Ile Thr Ser Ser Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Ser Ser Val Lys Leu Met Gly Asn  
245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
260 265 270

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

275                      280                      285  
 His Leu Thr Val Gly Asp Arg Asn Ala Ala Gln Ala Gly Ile Ile Ala  
 290                      295                      300  
 Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly  
 305                      310                      315                      320  
 Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Asn  
 325                      330                      335  
 Asn Thr Pro Ser Gln Ser Gly Ala Lys Asn Asp Lys Asn Glu Ser Ala  
 340                      345                      350  
 Lys Asn Asp Lys Gln Glu Ser Ser Gln Asn Asn Ser Asn Thr Gln Val  
 355                      360                      365  
 Ile Asn Pro Pro Asn Ser Ala Gln Lys Thr Glu Val Gln Pro Thr Gln  
 370                      375                      380  
 Val Ile Asp Gly Pro Phe Ala Gly Gly Lys Asp Thr Val Val Asn Ile  
 385                      390                      395                      400  
 Asn Arg Ile Asn Thr Asn Ala Asp Gly Thr Ile Arg Val Gly Gly Tyr  
 405                      410                      415  
 Lys Ala Ser Leu Thr Thr Asn Ala Ala His Leu His Ile Gly Lys Gly  
 420                      425                      430  
 Gly Val Asn Leu Ser Asn Gln Ala Ser Gly Arg Thr Leu Leu Val Glu  
 435                      440                      445  
 Asn Leu Thr Gly Asn Ile Thr Val Asp Gly Pro Leu Arg Val Asn Asn  
 450                      455                      460  
 Gln Val Gly Gly Tyr Ala Leu Ala Gly Ser Ser Ala Asn Phe Glu Phe  
 465                      470                      475                      480  
 Lys Ala Gly Thr Asp Thr Lys Asn Gly Thr Ala Thr Phe Asn Asn Asp  
 485                      490                      495  
 Ile Ser Leu Gly Arg Phe Val Asn Leu Lys Val Asp Ala His Thr Ala  
 500                      505                      510  
 Asn Phe Lys Gly Ile Asp Thr Gly Asn Gly Gly Phe Asn Thr Leu Asp  
 515                      520                      525  
 Phe Ser Gly Val Thr Asp Lys Val Asn Ile Asn Lys Leu Ile Thr Ala  
 530                      535                      540  
 Ser Thr Asn Val Ala Ile Lys Asn Phe Asn Ile Asn Glu Leu Leu Val  
 545                      550                      555                      560  
 Lys Thr Asn Gly Val Ser Val Gly Glu Tyr Thr His Phe Ser Glu Asp  
 565                      570                      575  
 Ile Gly Ser Gln Ser Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr  
 580                      585                      590

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          580          585          590
Arg Ser Ile Phe Ser Gly Gly Val Lys Phe Lys Gly Gly Glu Lys Leu
    595                                600                                605

Val Ile Asn Asp Phe Tyr Tyr Ala Pro Trp Asn Tyr Phe Asp Ala Arg
    610                                615                                620

Asn Ile Lys Asn Val Glu Ile Thr Asn Lys Leu Ala Phe Gly Pro Gln
    625                                630                                635                                640

Gly Ser Pro Trp Gly Thr Ser Lys Leu Met Phe Asn Asn Leu Thr Leu
    645                                650                                655

Gly Gln Asn Ala Val Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile
    660                                665                                670

Gln Gly Asp Phe Val Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg
    675                                680                                685

Gly Gly Gln Val Ala Thr Leu Asn Val Gly Asn Ala Ala Ala Met Phe
    690                                695                                700

Phe Asn Asn Asn Val Asp Ser Ala Thr Gly Phe Tyr Gln Pro Leu Met
    705                                710                                715                                720

Lys Ile Asn Ser Ala Gln Asp Leu Ile Lys Asn Lys Glu His Val Leu
    725                                730                                735

Leu Lys Ala Lys Ile Ile Gly Tyr Gly Asn Val Ser Ala Gly Thr Asn
    740                                745                                750

Ser Ile Ser Asn Val Asn Leu Ile Glu Gln Phe Lys Glu Arg Leu Ala
    755                                760                                765

Leu Tyr Glu His Asn Asn Arg Met Asp Ile Cys Val Val Arg Asn Thr
    770                                775                                780

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

Asn Asn Pro Asp Asn Tyr Lys Tyr Leu Ile Gly Lys Ala Trp Lys Asn
    805                                810                                815

Ile Gly Ile Ser Lys Thr Ala Asn Gly Ser Lys Ile Ser Val His Tyr
    820                                825                                830

Leu Gly Asn Ser Thr Pro Thr Glu Asn Ser Gly Asn Thr Thr Asn Leu
    835                                840                                845

Pro Thr Asn Thr Thr Ser Asn Ala Arg Ser Ala Lys Asn Ala Leu Ala
    850                                855                                860

Gln Asn Ala Pro Phe Ala Gln Pro Ser Ala Thr Pro Ser Leu Val Ala
    865                                870                                875                                880

Ile Asn Gln His Asp Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala
    885                                890                                895

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Asn Arg Ser Lys Asp Ile Asp Thr Leu Tyr Thr His Ser Gly Ala Gln  
 900 905 910

Gly Arg Asn Leu Leu Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly  
 915 920 925

Tyr Ala Arg Gln Met Ile Asp Asn Thr Ser Thr Gly Glu Ile Ile Lys  
 930 935 940

Gln Leu Asn Ala Ala Thr Thr Thr Leu Asn Asn Val Ala Ser Leu Glu  
 945 950 955 960

His Lys Gln Ser Gly Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile  
 965 970 975

Leu Asn Ser Arg Leu Val Asn Leu Ser Arg Arg His Thr Asn Asn Ile  
 980 985 990

Asp Ser Phe Ala Gln Arg Leu Gln Ala Leu Lys Asp Gln Lys Phe Ala  
 995 1000 1005

Ser Leu Glu Ser Ala Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys  
 1010 1015 1020

Tyr Glu Lys Pro Thr Asn Val Trp Ala Asn Ala Ile Gly Gly Thr  
 1025 1030 1035

Ser Leu Asn Asn Gly Gly Asn Ala Ser Leu Tyr Gly Thr Ser Ala  
 1040 1045 1050

Gly Val Asp Ala Tyr Leu Asn Gly Glu Val Glu Ala Ile Val Gly  
 1055 1060 1065

Gly Phe Gly Ser Tyr Gly Tyr Ser Ser Phe Ser Asn Gln Ala Asn  
 1070 1075 1080

Ser Leu Asn Ser Gly Ala Asn Asn Thr Asn Phe Gly Val Tyr Ser  
 1085 1090 1095

Arg Leu Phe Ala Asn Gln His Glu Phe Asp Phe Glu Ala Gln Gly  
 1100 1105 1110

Ala Leu Gly Ser Asp Gln Ser Ser Leu Asn Phe Lys Ser Ala Leu  
 1115 1120 1125

Leu Arg Asp Leu Asn Gln Ser Tyr Asn Tyr Leu Ala Tyr Ser Ala  
 1130 1135 1140

Ala Thr Arg Ala Ser Tyr Gly Tyr Asp Phe Ala Phe Phe Arg Asn  
 1145 1150 1155

Ala Leu Val Leu Lys Pro Ser Val Gly Val Ser Tyr Asn His Leu  
 1160 1165 1170

Gly Ser Thr Asn Phe Lys Ser Asn Ser Thr Asn Gln Val Ala Leu  
1175 1180 1185

Lys Asn Gly Ser Ser Ser Gln His Leu Phe Asn Ala Ser Ala Asn  
1190 1195 1200

Val Glu Ala Arg Tyr Tyr Tyr Gly Asp Thr Ser Tyr Phe Tyr Met  
1205 1210 1215

Asn Ala Gly Val Leu Gln Glu Phe Ala Asn Phe Gly Ser Ser Asn  
1220 1225 1230

Ala Val Ser Leu Asn Thr Phe Lys Val Asn Ala Ala Arg Asn Pro  
1235 1240 1245

Leu Asn Thr His Ala Arg Val Met Met Gly Gly Glu Leu Lys Leu  
1250 1255 1260

Ala Lys Glu Val Phe Leu Asn Leu Gly Phe Val Tyr Leu His Asn  
1265 1270 1275

Leu Ile Ser Asn Ile Gly His Phe Ala Ser Asn Leu Gly Met Arg  
1280 1285 1290

Tyr Ser Phe  
1295

<210> 10

<211> 1291

<212> PRT

<213> Helicobacter pylori

<400> 10

Met Glu Ile Gln Gln Thr His Arg Lys Ile Asn Arg Pro Leu Val Ser  
1 5 10 15

Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
20 25 30

Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Ala Ala Val Gly Thr Val Ser Gly Leu Leu Gly Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

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

Trp Asp Trp Gly Asn Ala Ala Arg His Tyr Trp Val Lys Asp Gly Gln  
 115 120 125  
 Trp Asn Lys Leu Glu Val Asp Met Gln Asn Ala Val Gly Thr Tyr Asn  
 130 135 140  
 Leu Ser Gly Leu Ile Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met  
 145 150 155 160  
 Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
 165 170 175  
 Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala  
 180 185 190  
 Lys Asn Ile Leu Ile Asp Asn Phe Leu Glu Ile Asn Asn Arg Val Gly  
 195 200 205  
 Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
 210 215 220  
 Ser Glu Gly Ile Thr Ser Arg Glu Asn Ala Glu Ile Ser Leu Tyr Asp  
 225 230 235 240  
 Gly Ala Thr Leu Asn Leu Ala Ser Asn Ser Val Lys Leu Met Gly Asn  
 245 250 255  
 Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser  
 260 265 270  
 Tyr Ser Thr Ile Asn Thr Ser Lys Val Thr Gly Glu Val Asn Phe Asn  
 275 280 285  
 His Leu Thr Val Gly Asp His Asn Ala Ala Gln Ala Gly Ile Ile Ala  
 290 295 300  
 Ser Asn Lys Thr His Ile Gly Thr Leu Asp Leu Trp Gln Ser Ala Gly  
 305 310 315 320  
 Leu Asn Ile Ile Ala Pro Pro Glu Gly Gly Tyr Lys Asp Lys Pro Asn  
 325 330 335  
 Asp Lys Pro Ser Asn Thr Thr Gln Asn Asn Ala Lys Asn Asp Lys Gln  
 340 345 350  
 Glu Ser Ser Gln Asn Asn Ser Asn Thr Gln Val Ile Asn Pro Pro Asn  
 355 360 365  
 Ser Ala Gln Lys Thr Glu Ile Gln Pro Thr Gln Val Ile Asp Gly Pro  
 370 375 380  
 Phe Ala Gly Gly Lys Asn Thr Val Val Asn Ile Asn Arg Ile Asn Thr  
 385 390 395 400  
 Asn Ala Asp Gly Thr Ile Arg Val Gly Gly Phe Lys Ala Ser Leu Thr  
 405 410 415

Thr Asn Ala Ala His Leu His Ile Gly Lys Gly Gly Ile Asn Leu Ser  
 420 425 430  
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 435 440 445  
 Ile Thr Val Asp Gly Pro Leu Arg Val Asn Asn Gln Val Gly Gly Tyr  
 450 455 460  
 Ala Leu Ala Gly Ser Ser Ala Asn Phe Glu Phe Lys Ala Gly Thr Asp  
 465 470 475 480  
 Thr Lys Asn Gly Thr Ala Thr Phe Asn Asn Asp Ile Ser Leu Gly Arg  
 485 490 495  
 Phe Val Asn Leu Lys Val Asp Ala His Thr Ala Asn Phe Lys Gly Ile  
 500 505 510  
 Asp Thr Gly Asn Gly Gly Phe Asn Thr Leu Asp Phe Ser Gly Val Thr  
 515 520 525  
 Asn Lys Val Asn Ile Asn Lys Leu Ile Thr Ala Ser Thr Asn Val Ala  
 530 535 540  
 Val Lys Asn Phe Asn Ile Asn Glu Leu Val Val Lys Thr Asn Gly Val  
 545 550 555 560  
 Ser Val Gly Glu Tyr Thr His Phe Ser Glu Asp Ile Gly Ser Gln Ser  
 565 570 575  
 Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr Arg Ser Ile Tyr Ser  
 580 585 590  
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 595 600 605  
 Tyr Tyr Ala Pro Trp Asn Tyr Phe Asp Ala Arg Asn Ile Lys Asn Val  
 610 615 620  
 Glu Ile Thr Asn Lys Leu Ala Phe Gly Pro Gln Gly Ser Pro Trp Gly  
 625 630 635 640  
 Thr Ala Lys Leu Met Phe Asn Asn Leu Thr Leu Gly Gln Asn Ala Val  
 645 650 655  
 Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile Gln Gly Asp Phe Val  
 660 665 670  
 Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg Gly Gly Gln Val Ala  
 675 680 685  
 Thr Leu Asn Val Gly Asn Ala Ala Ala Met Phe Phe Ser Asn Asn Val  
 690 695 700  
 Asp Ser Ala Thr Gly Phe Tyr Gln Pro Leu Met Lys Ile Asn Ser Ala  
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Gln Asp Leu Ile Lys Asn Lys Glu His Val Leu Leu Lys Ala Lys Ile  
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 Ile Gly Tyr Gly Asn Val Ser Ala Gly Thr Asp Ser Ile Ala Asn Val  
 740 745 750  
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 Cys Gly Thr Ala Ile Gly Asn Gln Ser Met Val Asn Asn Pro Glu Asn  
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 Thr Ala Asn Gly Ser Lys Ile Ser Val His Tyr Leu Gly Asn Ser Thr  
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 Pro Thr Glu Asn Gly Gly Asn Thr Thr Asn Leu Pro Thr Asn Thr Thr  
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 850 855 860  
 Ala Arg Tyr Ser Ala Thr Pro Asn Leu Val Ala Ile Asn Gln His Asp  
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 Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala Asn Arg Ser Asn Asp  
 885 890 895  
 Ile Asp Thr Leu Tyr Ala Asn Ser Gly Ala Gln Gly Arg Asp Leu Leu  
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 Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly Tyr Ala Arg Thr Met  
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 Ile Asp Ala Thr Ser Ala Asn Glu Ile Thr Lys Gln Leu Asn Thr Ala  
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 Val Asn Leu Ser Arg Arg His Thr Asn His Ile Asp Ser Phe Ala Lys  
 980 985 990  
 Arg Leu Gln Ala Leu Lys Asp Gln Arg Phe Ala Ser Leu Glu Ser Ala  
 995 1000 1005  
 Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys Tyr Glu Lys Pro Thr  
 1010 1015 1020

|      |     |     |     |     |     |      |     |     |     |     |      |     |     |     |
|------|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|------|-----|-----|-----|
| Asn  | Val | Trp | Ala | Asn | Ala | Ile  | Gly | Gly | Thr | Ser | Leu  | Asn | Ser | Gly |
| 1025 |     |     |     |     |     | 1030 |     |     |     |     | 1035 |     |     |     |
| Gly  | Asn | Ala | Ser | Leu | Tyr | Gly  | Thr | Ser | Ala | Gly | Val  | Asp | Ala | Tyr |
| 1040 |     |     |     |     |     | 1045 |     |     |     |     | 1050 |     |     |     |
| Leu  | Asn | Gly | Glu | Val | Glu | Ala  | Ile | Val | Gly | Gly | Phe  | Gly | Ser | Tyr |
| 1055 |     |     |     |     |     | 1060 |     |     |     |     | 1065 |     |     |     |
| Gly  | Tyr | Ser | Ser | Phe | Ser | Asn  | Gln | Ala | Asn | Ser | Leu  | Asn | Ser | Gly |
| 1070 |     |     |     |     |     | 1075 |     |     |     |     | 1080 |     |     |     |
| Ala  | Asn | Asn | Thr | Asn | Phe | Gly  | Val | Tyr | Ser | Arg | Ile  | Phe | Ala | Asn |
| 1085 |     |     |     |     |     | 1090 |     |     |     |     | 1095 |     |     |     |
| Gln  | His | Glu | Phe | Asp | Phe | Glu  | Ala | Gln | Gly | Ala | Leu  | Gly | Ser | Asp |
| 1100 |     |     |     |     |     | 1105 |     |     |     |     | 1110 |     |     |     |
| Gln  | Ser | Ser | Leu | Asn | Phe | Lys  | Ser | Ala | Leu | Leu | Arg  | Asp | Leu | Asn |
| 1115 |     |     |     |     |     | 1120 |     |     |     |     | 1125 |     |     |     |
| Gln  | Ser | Tyr | Asn | Tyr | Leu | Ala  | Tyr | Ser | Ala | Ala | Thr  | Arg | Ala | Ser |
| 1130 |     |     |     |     |     | 1135 |     |     |     |     | 1140 |     |     |     |
| Tyr  | Gly | Tyr | Asp | Phe | Ala | Phe  | Phe | Arg | Asn | Ala | Leu  | Val | Leu | Lys |
| 1145 |     |     |     |     |     | 1150 |     |     |     |     | 1155 |     |     |     |
| Pro  | Ser | Val | Gly | Val | Ser | Tyr  | Asn | His | Leu | Gly | Ser  | Thr | Asn | Phe |
| 1160 |     |     |     |     |     | 1165 |     |     |     |     | 1170 |     |     |     |
| Lys  | Ser | Asn | Ser | Asn | Gln | Lys  | Val | Ala | Leu | Lys | Asn  | Gly | Ala | Ser |
| 1175 |     |     |     |     |     | 1180 |     |     |     |     | 1185 |     |     |     |
| Ser  | Gln | His | Leu | Phe | Asn | Ala  | Ser | Ala | Asn | Val | Glu  | Ala | Arg | Tyr |
| 1190 |     |     |     |     |     | 1195 |     |     |     |     | 1200 |     |     |     |
| Tyr  | Tyr | Gly | Asp | Thr | Ser | Tyr  | Phe | Tyr | Met | Asn | Ala  | Gly | Val | Leu |
| 1205 |     |     |     |     |     | 1210 |     |     |     |     | 1215 |     |     |     |
| Gln  | Glu | Phe | Ala | Asn | Phe | Gly  | Ser | Ser | Asn | Ala | Val  | Ser | Leu | Asn |
| 1220 |     |     |     |     |     | 1225 |     |     |     |     | 1230 |     |     |     |
| Thr  | Phe | Lys | Val | Asn | Ala | Thr  | Arg | Asn | Pro | Leu | Asn  | Thr | His | Ala |
| 1235 |     |     |     |     |     | 1240 |     |     |     |     | 1245 |     |     |     |
| Arg  | Val | Met | Met | Gly | Gly | Glu  | Leu | Lys | Leu | Ala | Lys  | Glu | Val | Phe |
| 1250 |     |     |     |     |     | 1255 |     |     |     |     | 1260 |     |     |     |
| Leu  | Asn | Leu | Gly | Phe | Val | Tyr  | Leu | His | Asn | Leu | Ile  | Ser | Asn | Ile |
| 1265 |     |     |     |     |     | 1270 |     |     |     |     | 1275 |     |     |     |
| Gly  | His | Phe | Ala | Ser | Asn | Leu  | Gly | Met | Arg | Tyr | Ser  | Phe |     |     |
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$\langle 210 \rangle$  11

<211> 1297

<212> PRT

<213> *Helicobacter pylori* NCTC 11638

**<400> 11**

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Leu Ala Leu Val Gly Ala Leu Val Ser Ile Thr Pro Gln Gln Ser His  
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Ala Ala Phe Phe Thr Thr Val Ile Ile Pro Ala Ile Val Gly Gly Ile  
35 40 45

Ala Thr Gly Thr Ala Val Gly Thr Val Ser Gly Leu Leu Ser Trp Gly  
50 55 60

Leu Lys Gln Ala Glu Glu Ala Asn Lys Thr Pro Asp Lys Pro Asp Lys  
65 70 75 80

Val Trp Arg Ile Gln Ala Gly Lys Gly Phe Asn Glu Phe Pro Asn Lys  
85 90 95

Glu Tyr Asp Leu Tyr Arg Ser Leu Leu Ser Ser Lys Ile Asp Gly Gly  
100 105 110

Trp Asp Trp Gly Asn Ala Ala Arg His Tyr Trp Val Lys Gly Gly Gln  
115 120 125

Gln Asn Lys Leu Glu Val Asp Met Lys Asp Ala Val Gly Thr Tyr Thr  
130 135 140

Leu Ser Gly Leu Arg Asn Phe Thr Gly Gly Asp Leu Asp Val Asn Met  
145 150 155 160

Gln Lys Ala Thr Leu Arg Leu Gly Gln Phe Asn Gly Asn Ser Phe Thr  
165 170 175

Ser Tyr Lys Asp Ser Ala Asp Arg Thr Thr Arg Val Asp Phe Asn Ala  
180 185 190

Lys Asn Ile Ser Ile Asp Asn Phe Val Glu Ile Asn Asn Arg Val Gly  
195 200 205

Ser Gly Ala Gly Arg Lys Ala Ser Ser Thr Val Leu Thr Leu Gln Ala  
210 215 220

Ser Glu Gly Ile Thr Ser Asp Lys Asn Ala Glu Ile Ser Leu Tyr Asp  
225 230 235 240

Gly Ala Thr Leu Asn Leu Ala Ser Ser Ser Val Lys Leu Met Gly Asn  
245 250 255

Val Trp Met Gly Arg Leu Gln Tyr Val Gly Ala Tyr Leu Ala Pro Ser

| 260 |     |     |     |     | 265 |     |     |     |     | 270 |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Ser | Thr | Ile | Asn | Thr | Ser | Lys | Val | Thr | Gly | Glu | Val | Asn | Phe | Asn |
|     |     | 275 |     |     |     |     | 280 |     |     |     |     | 285 |     |     |     |
| His | Leu | Thr | Val | Gly | Asp | Lys | Asn | Ala | Ala | Gln | Ala | Gly | Ile | Ile | Ala |
|     | 290 |     |     |     |     | 295 |     |     |     |     | 300 |     |     |     |     |
| Asn | Lys | Lys | Thr | Asn | Ile | Gly | Thr | Leu | Asp | Leu | Trp | Gln | Ser | Ala | Gly |
| 305 |     |     |     |     | 310 |     |     |     |     | 315 |     |     |     |     | 320 |
| Leu | Asn | Ile | Ile | Ala | Pro | Pro | Glu | Gly | Gly | Tyr | Lys | Asp | Lys | Pro | Asn |
|     |     |     |     | 325 |     |     |     |     | 330 |     |     |     |     | 335 |     |
| Asn | Thr | Pro | Ser | Gln | Ser | Gly | Ala | Lys | Asn | Asp | Lys | Asn | Glu | Ser | Ala |
|     |     |     | 340 |     |     |     |     | 345 |     |     |     |     | 350 |     |     |
| Lys | Asn | Asp | Lys | Gln | Glu | Ser | Ser | Gln | Asn | Asn | Ser | Asn | Thr | Gln | Val |
|     |     | 355 |     |     |     |     | 360 |     |     |     |     | 365 |     |     |     |
| Ile | Asn | Pro | Pro | Asn | Ser | Ala | Gln | Lys | Thr | Glu | Val | Gln | Pro | Thr | Gln |
|     | 370 |     |     |     |     | 375 |     |     |     |     | 380 |     |     |     |     |
| Val | Ile | Asp | Gly | Pro | Phe | Ala | Gly | Gly | Lys | Asp | Thr | Val | Val | Asn | Ile |
| 385 |     |     |     |     | 390 |     |     |     |     | 395 |     |     |     |     | 400 |
| Asn | Arg | Ile | Asn | Thr | Asn | Ala | Asp | Gly | Thr | Ile | Arg | Val | Gly | Gly | Phe |
|     |     |     |     | 405 |     |     |     |     | 410 |     |     |     |     | 415 |     |
| Lys | Ala | Ser | Leu | Thr | Thr | Asn | Ala | Ala | His | Leu | His | Ile | Gly | Lys | Gly |
|     |     |     | 420 |     |     |     |     | 425 |     |     |     |     | 430 |     |     |
| Gly | Val | Asn | Leu | Ser | Asn | Gln | Ala | Ser | Gly | Arg | Ser | Leu | Ile | Val | Glu |
|     |     | 435 |     |     |     |     | 440 |     |     |     |     | 445 |     |     |     |
| Asn | Leu | Thr | Gly | Asn | Ile | Thr | Val | Asp | Gly | Pro | Leu | Arg | Val | Asn | Asn |
|     | 450 |     |     |     |     | 455 |     |     |     |     | 460 |     |     |     |     |
| Gln | Val | Gly | Gly | Tyr | Ala | Leu | Ala | Gly | Ser | Ser | Ala | Asn | Phe | Glu | Phe |
| 465 |     |     |     |     | 470 |     |     |     |     | 475 |     |     |     |     | 480 |
| Lys | Ala | Gly | Thr | Asp | Thr | Lys | Asn | Gly | Thr | Ala | Thr | Phe | Asn | Asn | Asp |
|     |     |     |     | 485 |     |     |     |     | 490 |     |     |     |     | 495 |     |
| Ile | Ser | Leu | Gly | Arg | Phe | Val | Asn | Leu | Lys | Val | Asp | Ala | His | Thr | Ala |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |
| Asn | Phe | Lys | Gly | Ile | Asp | Thr | Gly | Asn | Gly | Gly | Phe | Asn | Thr | Leu | Asp |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |
| Phe | Ser | Gly | Val | Thr | Asp | Lys | Val | Asn | Ile | Asn | Lys | Leu | Ile | Thr | Ala |
|     | 530 |     |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |
| Ser | Thr | Asn | Val | Ala | Val | Lys | Asn | Phe | Asn | Ile | Asn | Glu | Leu | Ile | Val |
| 545 |     |     |     |     | 550 |     |     |     |     | 555 |     |     |     |     | 560 |
| Lys | Thr | Asn | Gly | Ile | Ser | Val | Gly | Glu | Tyr | Thr | His | Phe | Ser | Glu | Asp |
|     |     |     | 565 |     |     |     |     |     | 570 |     |     |     |     | 575 |     |

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Ile Gly Ser Gln Ser Arg Ile Asn Thr Val Arg Leu Glu Thr Gly Thr
580                               585                               590

Arg Ser Leu Phe Ser Gly Gly Val Lys Phe Lys Gly Gly Glu Lys Leu
595                               600                               605

Val Ile Asp Glu Phe Tyr Tyr Ser Pro Trp Asn Tyr Phe Asp Ala Arg
610                               615                               620

Asn Ile Lys Asn Val Glu Ile Thr Asn Lys Leu Ala Phe Gly Pro Gln
625                               630                               635                               640

Gly Ser Pro Trp Gly Thr Ser Lys Leu Met Phe Asn Asn Leu Thr Leu
645                               650                               655

Gly Gln Asn Ala Val Met Asp Tyr Ser Gln Phe Ser Asn Leu Thr Ile
660                               665                               670

Gln Gly Asp Phe Ile Asn Asn Gln Gly Thr Ile Asn Tyr Leu Val Arg
675                               680                               685

Gly Gly Lys Val Ala Thr Leu Ser Val Gly Asn Ala Ala Ala Met Met
690                               695                               700

Phe Asn Asn Asp Ile Asp Ser Ala Thr Gly Phe Tyr Lys Pro Leu Ile
705                               710                               715                               720

Lys Ile Asn Ser Ala Gln Asp Leu Ile Lys Asn Thr Glu His Val Leu
725                               730                               735

Leu Lys Ala Lys Ile Ile Gly Tyr Gly Asn Val Ser Thr Gly Thr Asn
740                               745                               750

Gly Ile Ser Asn Val Asn Leu Glu Glu Gln Phe Lys Glu Arg Leu Ala
755                               760                               765

Leu Tyr Asn Asn Asn Asn Arg Met Asp Thr Cys Val Val Arg Asn Thr
770                               775                               780

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

Asn Asn Pro Asp Asn Tyr Lys Tyr Leu Ile Gly Lys Ala Trp Lys Asn
805                               810                               815

Ile Gly Ile Ser Lys Thr Ala Asn Gly Ser Lys Ile Ser Val Tyr Tyr
820                               825                               830

Leu Gly Asn Ser Thr Pro Thr Glu Asn Gly Gly Asn Thr Thr Asn Leu
835                               840                               845

Pro Thr Asn Thr Thr Ser Asn Ala Arg Ser Ala Asn Asn Ala Leu Ala
850                               855                               860

Gln Asn Ala Pro Phe Ala Gln Pro Ser Ala Thr Pro Asn Leu Val Ala
865                               870                               875                               880

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Ile Asn Gln His Asp Phe Gly Thr Ile Glu Ser Val Phe Glu Leu Ala
      885                      890                      895

Asn Arg Ser Lys Asp Ile Asp Thr Leu Tyr Ala Asn Ser Gly Ala Gln
      900                      905                      910

Gly Arg Asp Leu Leu Gln Thr Leu Leu Ile Asp Ser His Asp Ala Gly
      915                      920                      925

Tyr Ala Arg Lys Met Ile Asp Ala Thr Ser Ala Asn Glu Ile Thr Lys
      930                      935                      940

Gln Leu Asn Thr Ala Thr Thr Thr Leu Asn Asn Ile Ala Ser Leu Glu
      945                      950                      955                      960

His Lys Thr Ser Gly Leu Gln Thr Leu Ser Leu Ser Asn Ala Met Ile
      965                      970                      975

Leu Asn Ser Arg Leu Val Asn Leu Ser Arg Arg His Thr Asn His Ile
      980                      985                      990

Asp Ser Phe Ala Lys Arg Leu Gln Ala Leu Lys Asp Gln Lys Phe Ala
      995                      1000                      1005

Ser Leu Glu Ser Ala Ala Glu Val Leu Tyr Gln Phe Ala Pro Lys
      1010                      1015                      1020

Tyr Glu Lys Pro Thr Asn Val Trp Ala Asn Ala Ile Gly Gly Thr
      1025                      1030                      1035

Ser Leu Asn Asn Gly Ser Asn Ala Ser Leu Tyr Gly Thr Ser Ala
      1040                      1045                      1050

Gly Val Asp Ala Tyr Leu Asn Gly Gln Val Glu Ala Ile Val Gly
      1055                      1060                      1065

Gly Phe Gly Ser Tyr Gly Tyr Ser Ser Phe Asn Asn Arg Ala Asn
      1070                      1075                      1080

Ser Leu Asn Ser Gly Ala Asn Asn Thr Asn Phe Gly Val Tyr Ser
      1085                      1090                      1095

Arg Ile Phe Ala Asn Gln His Glu Phe Asp Phe Glu Ala Gln Gly
      1100                      1105                      1110

Ala Leu Gly Ser Asp Gln Ser Ser Leu Asn Phe Lys Ser Ala Leu
      1115                      1120                      1125

Leu Gln Asp Leu Asn Gln Ser Tyr His Tyr Leu Ala Tyr Ser Ala
      1130                      1135                      1140

Ala Thr Arg Ala Ser Tyr Gly Tyr Asp Phe Ala Phe Phe Arg Asn
      1145                      1150                      1155

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Ala Leu Val Leu Lys Pro Ser Val Gly Val Ser Tyr Asn His Leu  
1160 1165 1170

Gly Ser Thr Asn Phe Lys Ser Asn Ser Thr Asn Gln Val Ala Leu  
1175 1180 1185

Lys Asn Gly Ser Ser Ser Gln His Leu Phe Asn Ala Ser Ala Asn  
1190 1195 1200

Val Glu Ala Arg Tyr Tyr Tyr Gly Asp Thr Ser Tyr Phe Tyr Met  
1205 1210 1215

Asn Ala Gly Val Leu Gln Glu Phe Ala His Val Gly Ser Asn Asn  
1220 1225 1230

Ala Ala Ser Leu Asn Thr Phe Lys Val Asn Ala Ala Arg Asn Pro  
1235 1240 1245

Leu Asn Thr His Ala Arg Val Met Met Gly Gly Glu Leu Lys Leu  
1250 1255 1260

Ala Lys Glu Val Phe Leu Asn Leu Gly Val Val Tyr Leu His Asn  
1265 1270 1275

Leu Ile Ser Asn Ile Gly His Phe Ala Ser Asn Leu Gly Met Arg  
1280 1285 1290

Tyr Ser Phe Phe  
1295

# REFERENCES CITED IN THE DESCRIPTION

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## PATENTKRAV

1. Polypeptid bestående af en aminosyresekvens af et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 eller en sekvens med i det mindste 90% identitet med et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11, eller en formulering deraf til anvendelse ved forebyggelse og/eller behandling af en allergisk forstyrrelse, hvor det nævnte VacA protein i det væsentlige er fri for en immunogen komponent, især for andre *H. pylori*-antigenkomponenter.
2. Polypeptid til anvendelse ifølge krav 1, hvor polypeptidet foreligger i form af dødcelleekstrakt af *H. pylori*-bakterier og *H. pylori*-bakteriestammen er ATCC 49503/60190, og hvor det nævnte VacA protein er essentielt fri for en immunogen komponent, især for andre *H. pylori*-antigenkomponenter.
3. Polypeptid til anvendelse ifølge ethvert af kravene 1 til 2, hvor VacA er oprenset fra ekstrakter fra ikke-denaturerede dræbte *H. pylori*-bakterieceller, og hvor det nævnte VacA protein er essentielt fri for en immunogen komponent, især for andre *H. pylori*-antigenkomponenter.
4. Polypeptid til anvendelse ifølge ethvert af kravene 2 til 3, hvor dødcelleekstraktet af *H. pylori*-bakterier kan opnås ved en fremgangsmåde omfattende følgende trin:
  - (i) høstning af en kultur af levende bakterieceller;
  - (ii) underkastning af de høstede bakterier for adskillige fryse/optøningscycluser i vand eller vandig opløsning af et salt;
  - (iii) ødelæggelse af bakteriecellerne under højt tryk;
  - (iv) opsamling af celleekstraktet.
5. Polypeptid til anvendelse ifølge krav 1, hvor VacA er rekombinant VacA.
6. Polypeptid bestående af en sekvens af VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 eller sekvens, som har i det mindste 90% identitet med et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 eller en formulering deraf, til anvendelse ved induktion af en tolereringsreaktion på et allergen.

7. Polypeptid, som består af en sekvens af et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11, eller en sekvens med i det mindste 90% identitet med et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 eller en formulering deraf, til anvendelse i overensstemmelse med ethvert af kravene 1 til 6, hvor polypeptidet skal indgives i en form, som er essentielt fri for enhver immunogen komponent.
8. Polypeptid til anvendelse ifølge ethvert af kravene 1 til 7, hvor den allergiske forstyrrelse er atopisk astma.
9. Polypeptid til anvendelse ifølge ethvert af kravene 1 til 7, hvor den allergiske forstyrrelse er fødevareallergi.
10. Polypeptid til anvendelse ifølge ethvert af kravene 1 til 9, hvor sammensætningen skal indgives oralt, intranasalt, parenteralt, intrapulmonært eller systemisk.
11. Farmaceutisk tolerogen formulering omfattende et VacA protein bestående af en sekvens valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 eller en sekvens med i det mindste 90% identitet med et VacA protein valgt blandt SEQ ID NO: 1, 2, 4, 5, 6, 7, 8, 9, 10 og 11 og i det mindste et farmaceutisk acceptabelt bærerstoff, fortyndingsmiddel eller excipients derfor, hvor det nævnte VacA protein er essentielt fri for en immunogen komponent, især for andre *H. pylori*-antigenkomponenter.
12. Farmaceutisk formulering ifølge krav 11, hvor det nævnte VacA protein er kombineret med i det mindste ét co-agens, som er nyttigt til forebyggelse og/eller behandling af en allergisk forstyrrelse eller en allergisk reaktion eller til inducering af en tolereringsreaktion på et allergen.
13. Sammensætning ifølge krav 12, hvor sammensætningen er en oral farmaceutisk sammensætning eller en injicerbar farmaceutisk sammensætning.
14. Sammensætning ifølge krav 11 eller 13, som yderligere omfatter et allergen, især i det mindste et fødevareallergen.
15. Formulering til anvendelse ifølge krav 1, hvor formuleringen er en farmaceutisk formulering i overensstemmelse med ethvert af kravene 11 til 14.

# DRAWINGS

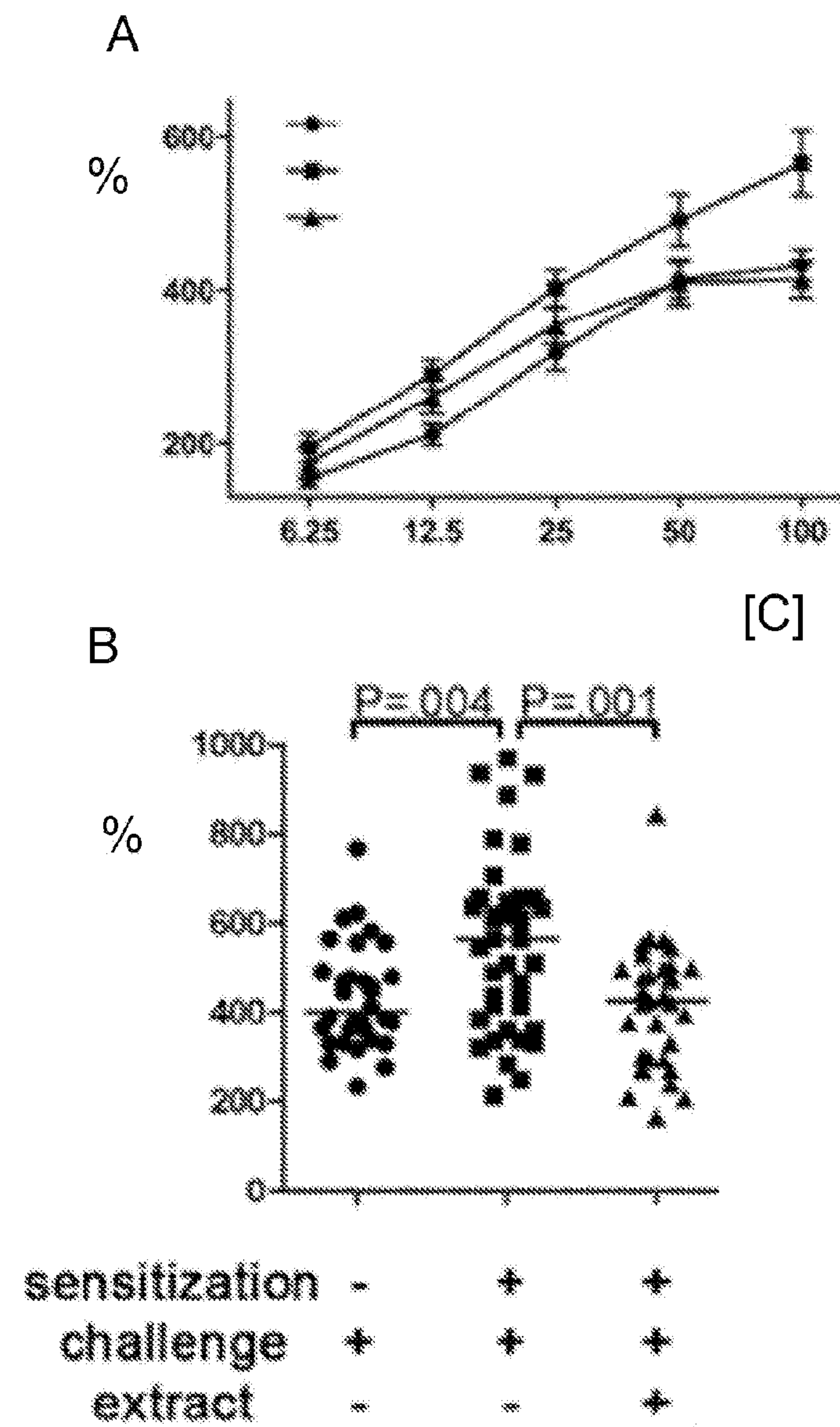


Figure 1

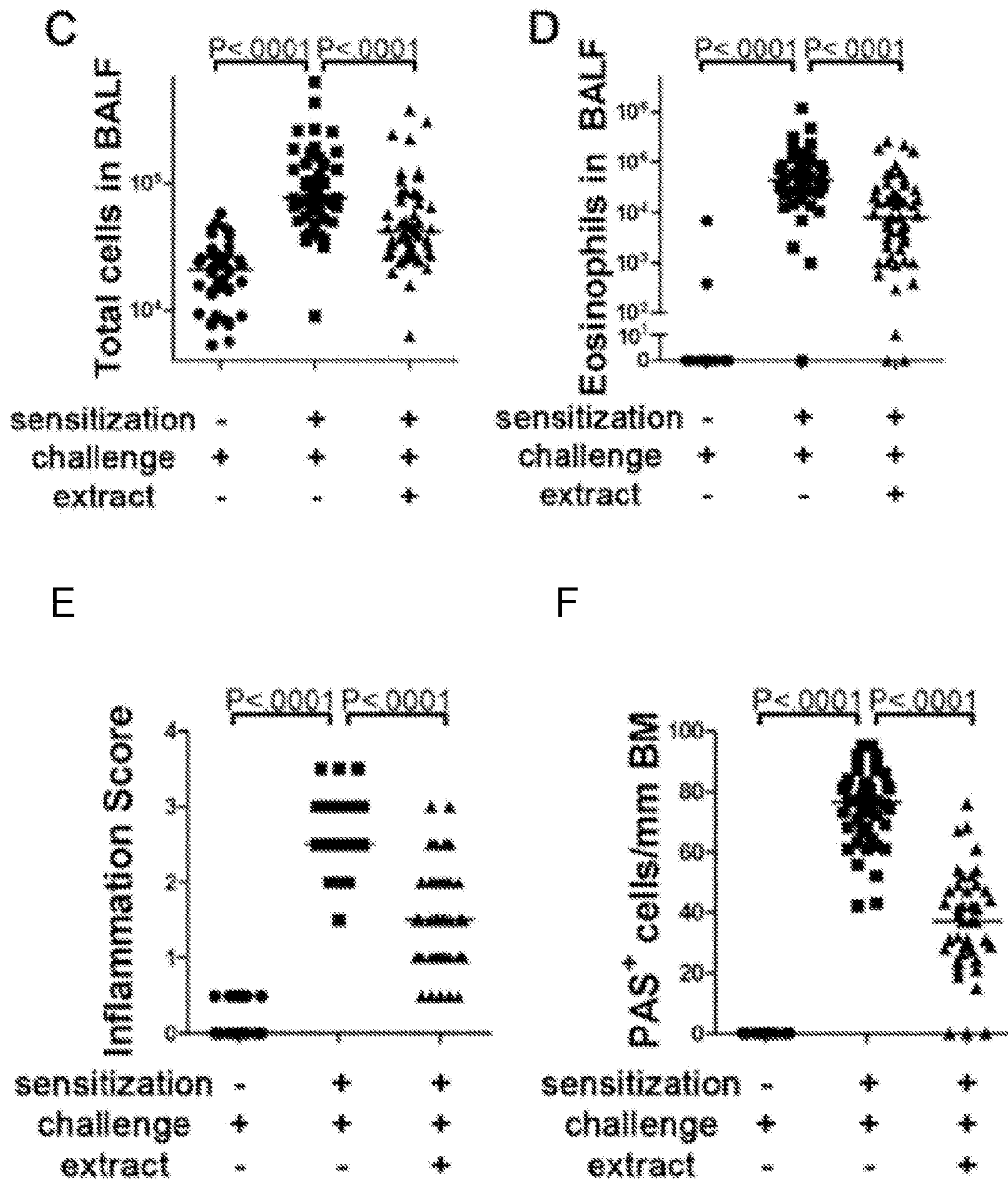


Figure 1 (continued)

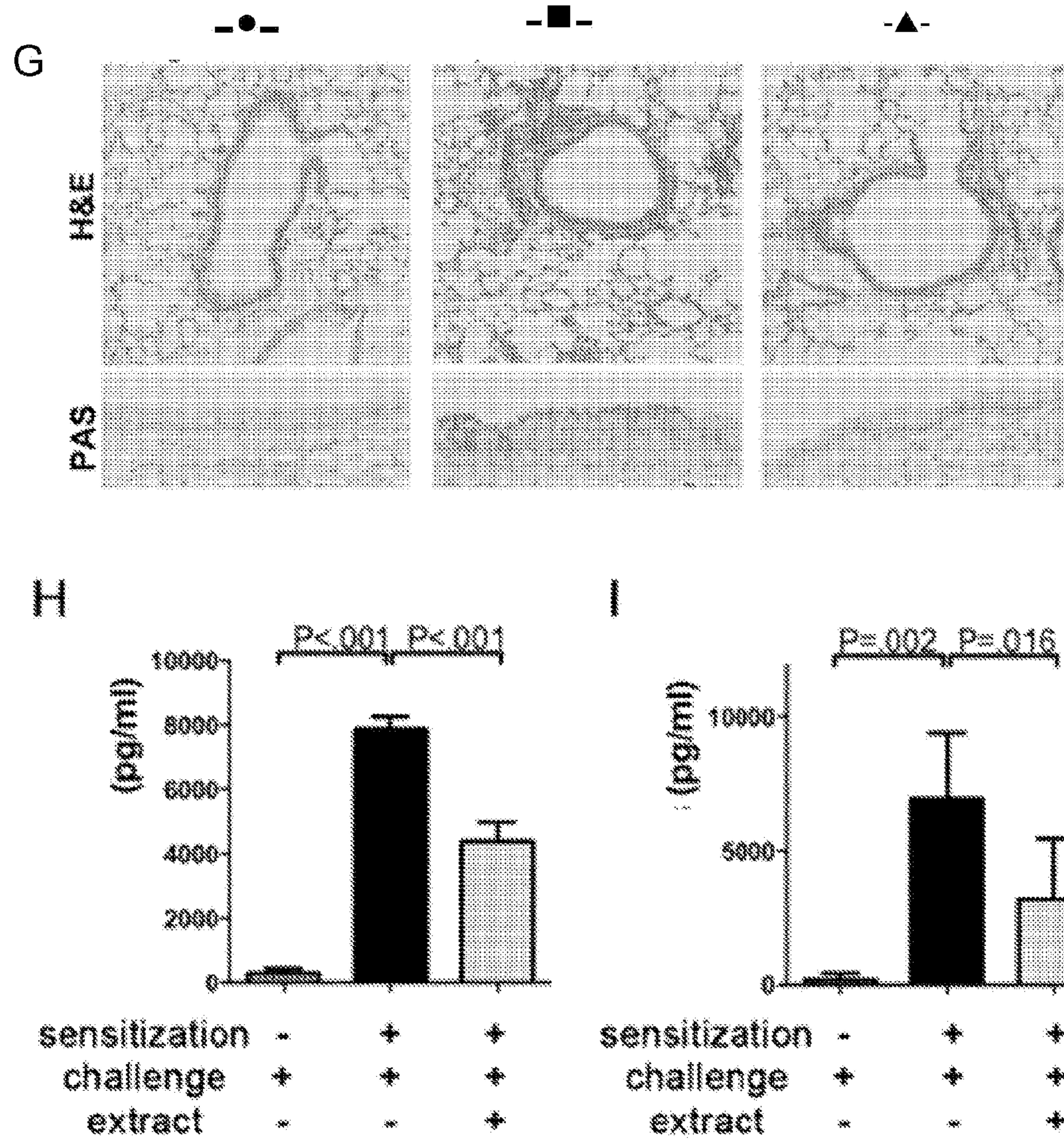


Figure 1 (continued)

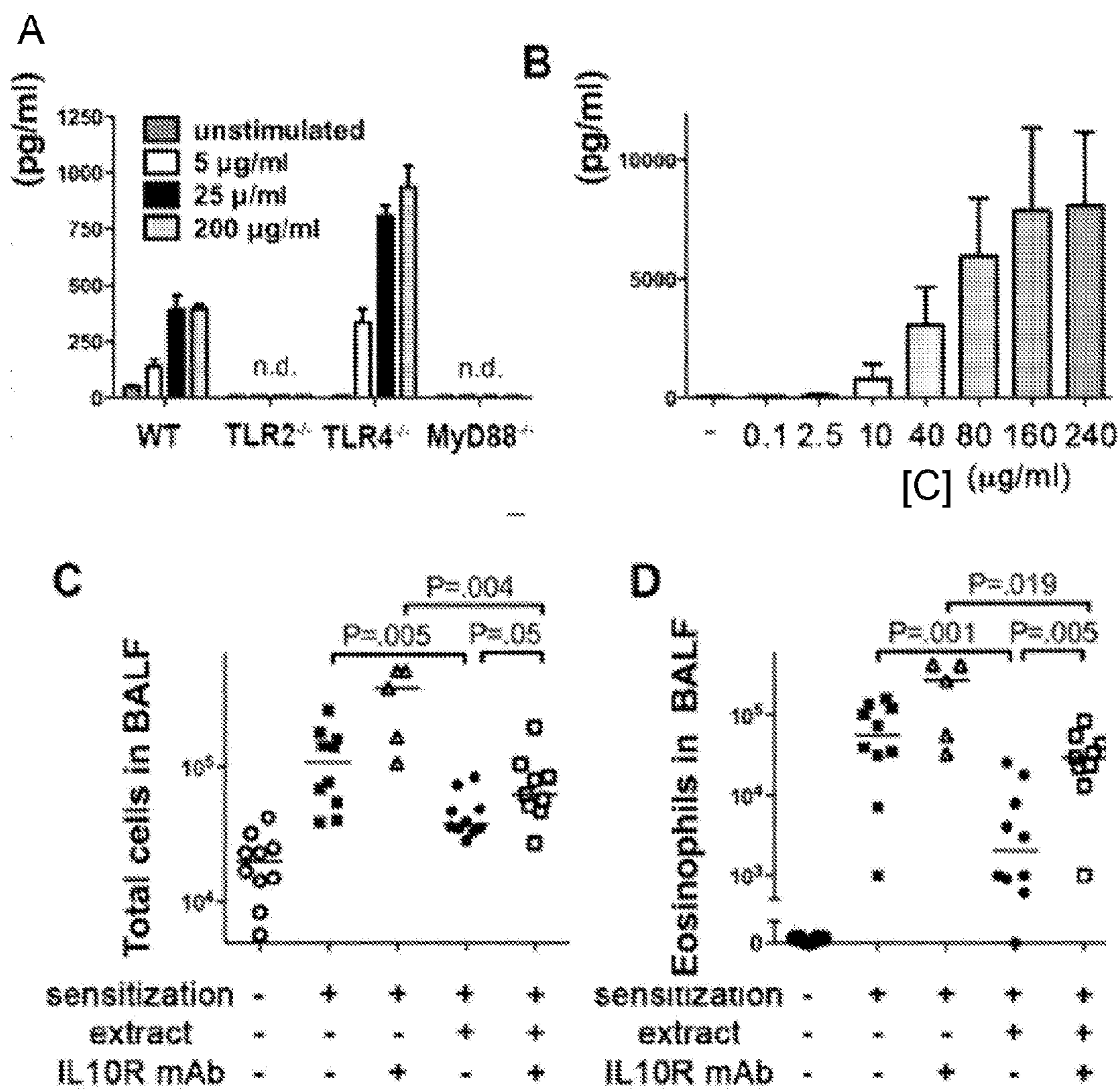


Figure 2

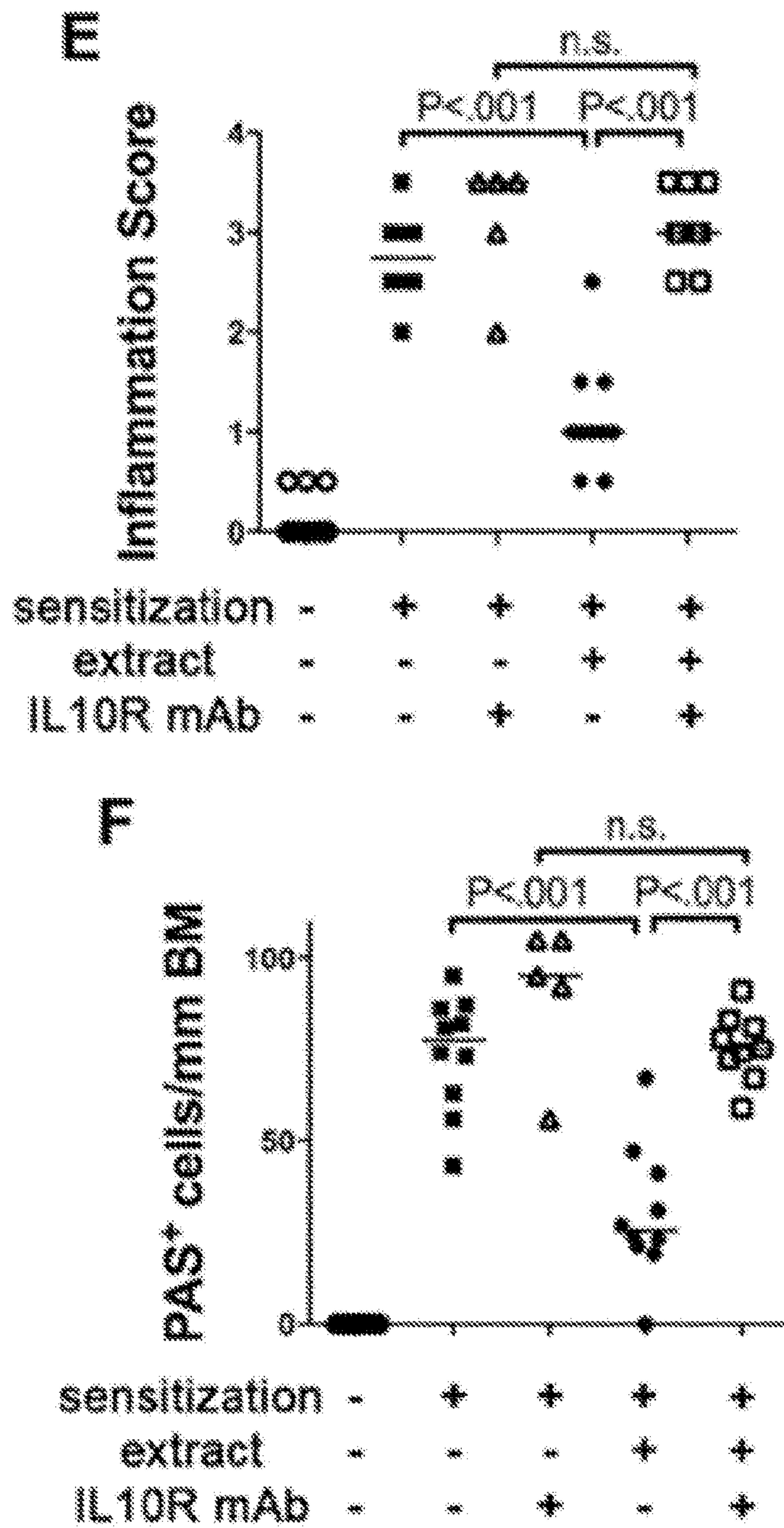
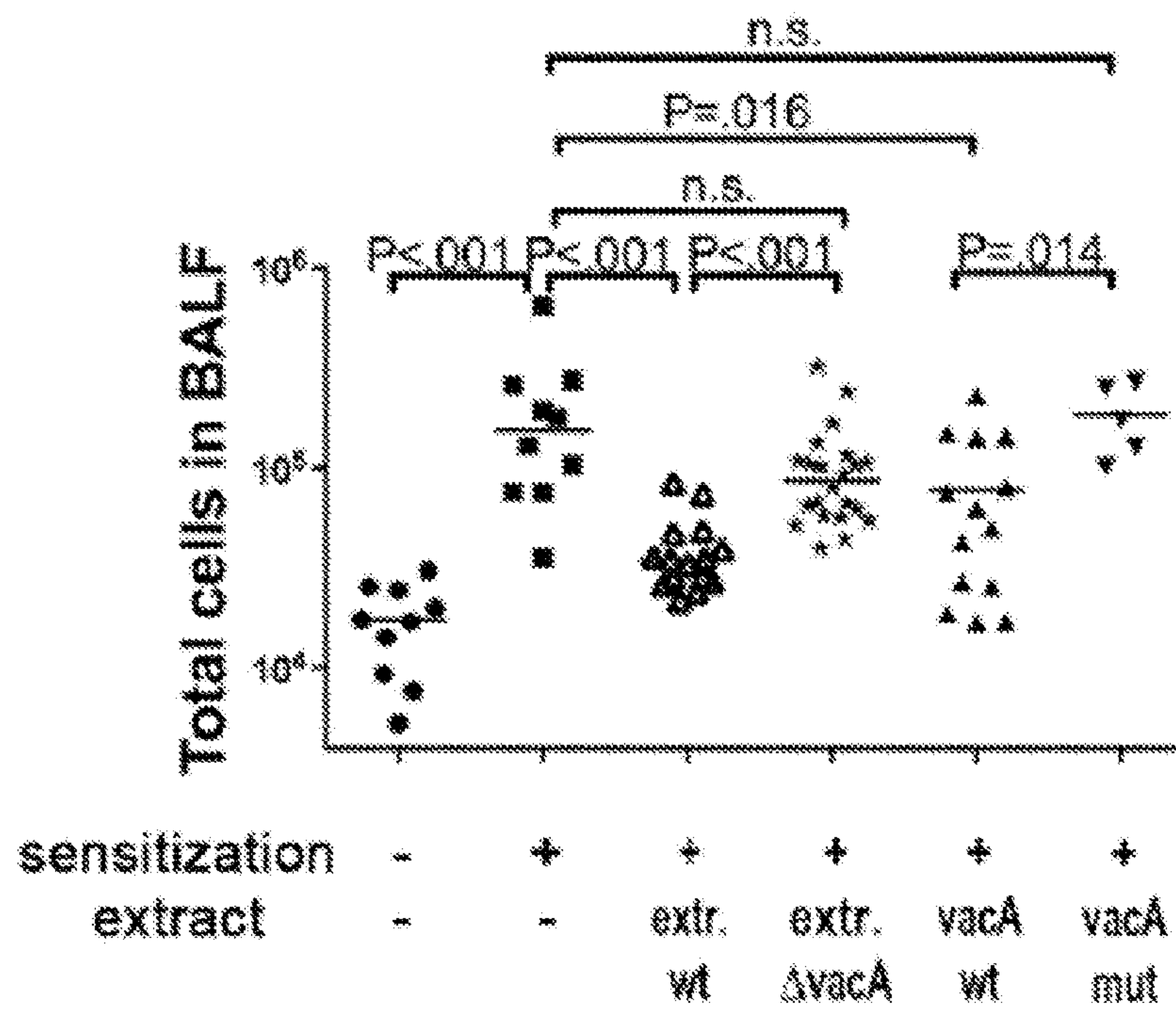


Figure 2 (continued)

A



B

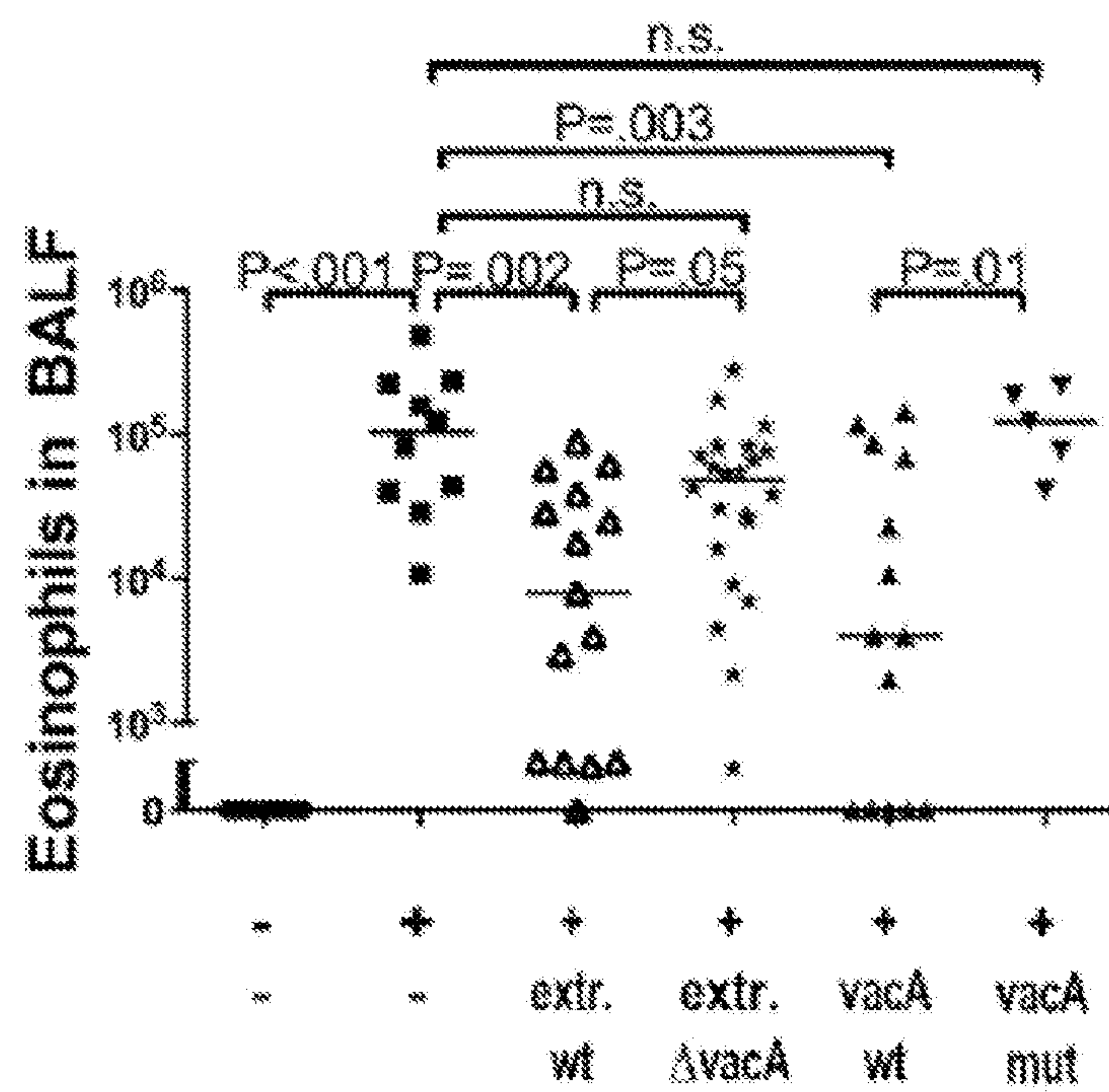
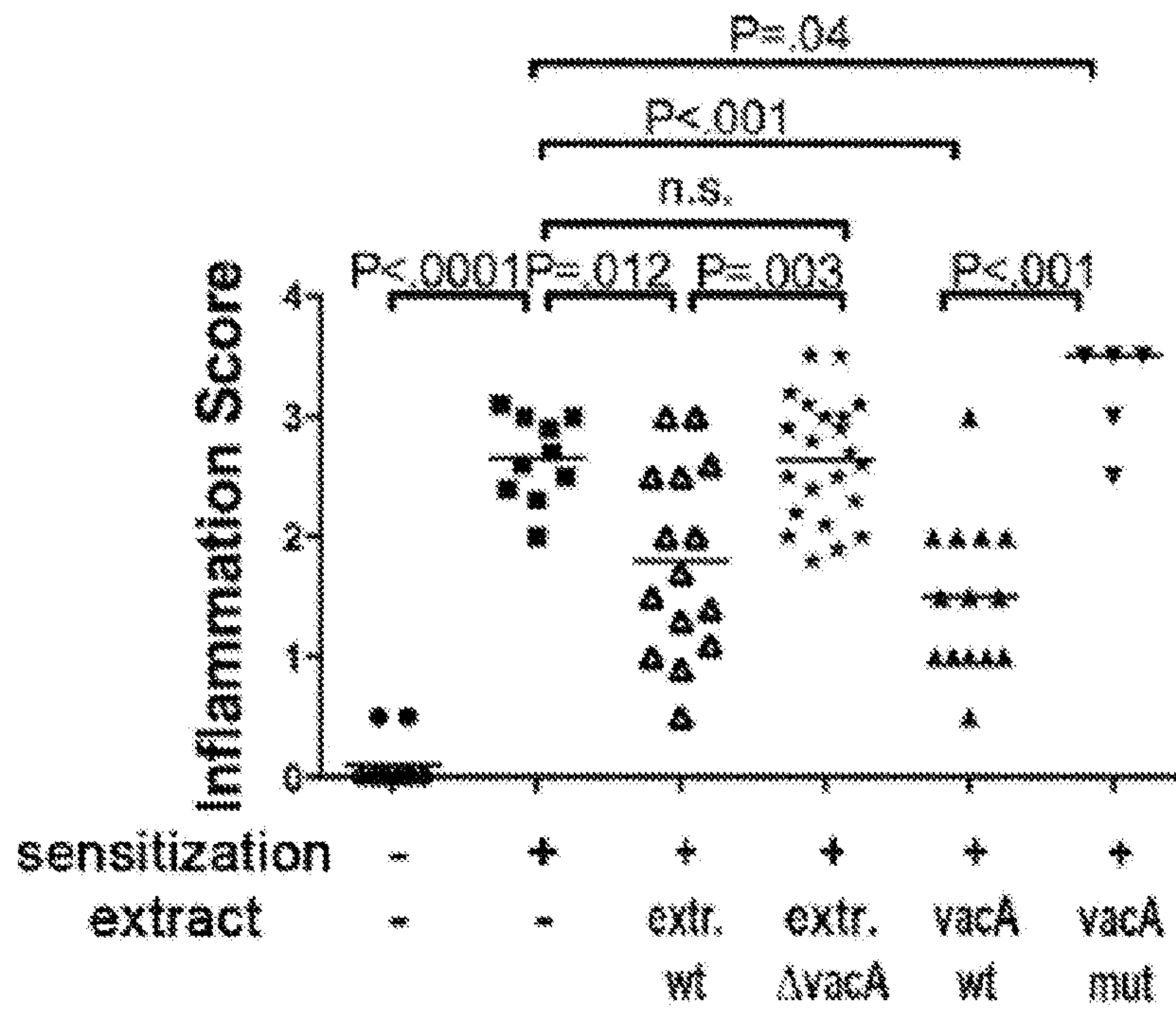


Figure 3

C



D

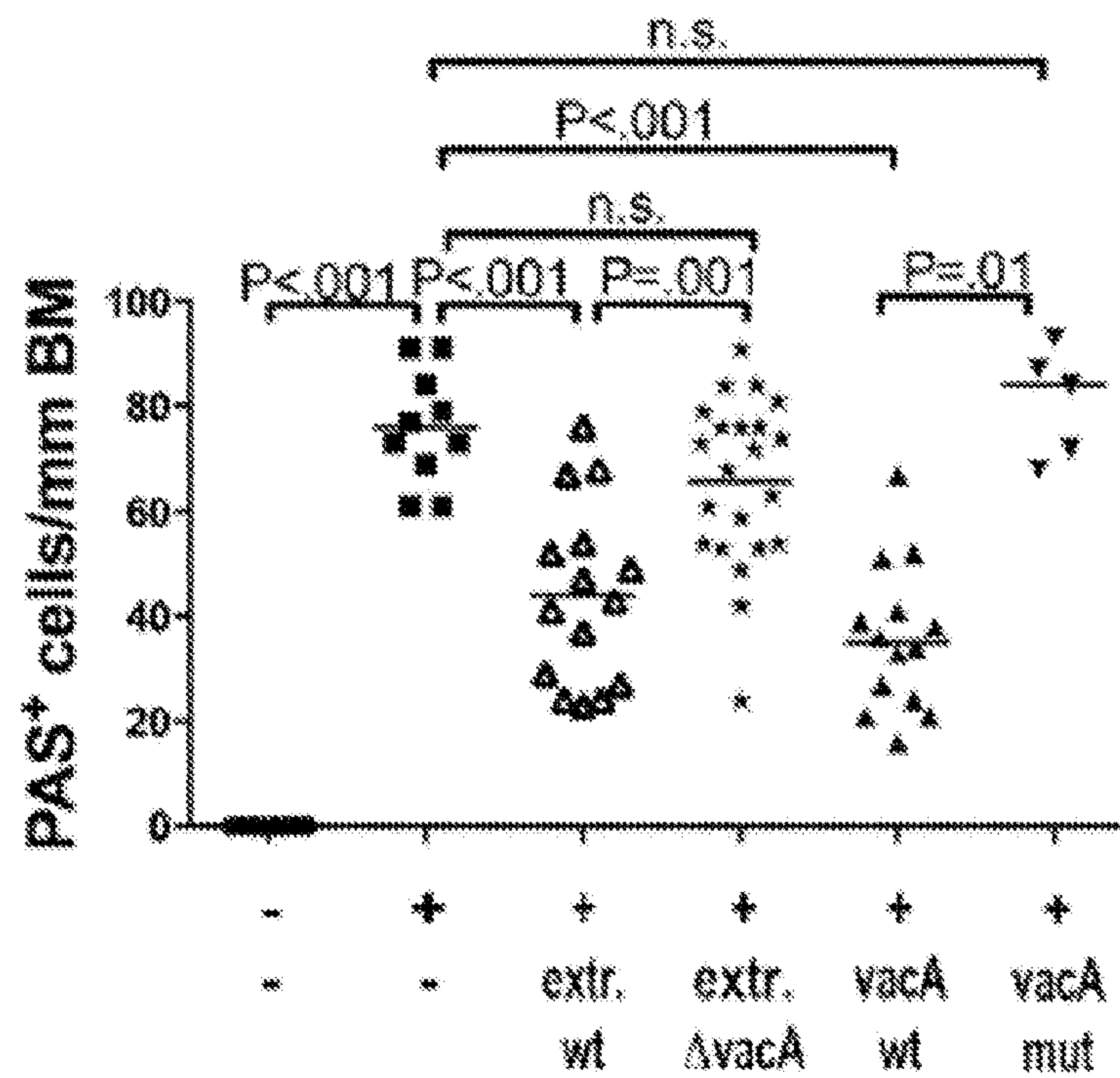


Figure 3 (continued)



A

**Q48245 *H. pylori* strain ATCC 49503/60190 (Cover et. al., 1994) (SEQ ID NO: 1)**

AFFTTVIIPAIVGGIATGTAVGTVSGLLGWGLKQAEAEANKTPDKPDKVWRIQAGKGFNEFPN  
 KEYDLYKSLLSSKIDGGWDWGNAATHYWIKGGQWNKLEVDMKDAVGTYKLSGLRNFTGG  
 DLDVNMQKATLRLGQFNGNSFTSYKDSADRTTRVDFNAKNILIDNFLEINNVRVSGAGRKA  
 SSTVLTQASEGITSSKNAEISLYDGATLNLASNSVKLNGNVMMGRLQYVGAYLAPSYSTIN  
 TSKVTGEVNFNHLTVGDHNAQAQAGIIASNKTHIGTLDLWQSAGLNIIAPPEGGYKDKPNNT  
 SQSGAKNDKQESSQNNSNTQVINPPNSTQKTEVQPTQVIDGPFAGGKDTVVNIDRINTKAD  
 GTIKVGGFKASLTNNAAHLNIGKGGVNLNQASGRTLLVENLTGNITVDGPLRVNNQVGGYA  
 LAGSSANFEFKAGVDTKNGTATFNNDISLGRFVNLKVDHAHTANFKGIDTGNGGFNTLDFSG  
 VTNKVNINKLITASTNVAVKNFNINELIVKTNGVSVGEYTHFSEDIGSQSRINTVRLETGTRSIF  
 SGGVKFKSGEKLVIDEFYSPWNYFDARNIKNVEITRKFASTPENPWGTSKLMFNNLTGQ  
 NAVMDYSQFSNLTIQGDFINNQGTINYLVRRGGKVATLNVGNAAAMMFNNNDIDSATGFYKPLI  
 KINSAQDLIKNTEHVLLKAKIIGYGNVSTGTNGISNVNLEEQFKERLALYNNNNRMDTCVVRN  
 TDDIKACGMAIGNQSMVNNPDNYKYLGKAWKNIGISKTANGSKISVYYLGNSTPTENGNT  
 TNLPTNTTNNARFASYALIKNAPFAHSATPNLVAINQHDFGTIESVFELANRSKDIDTLYANS  
 GAQGRDLLQTLLIDSHDAGYARTMIDATSANEITKQLNTATTTLNNIASLEHKTSSLQTLSLSN  
 AMILNSRLVNLRRHTNNIDSAKRLQALKDQRFASLESAAEVLYQFAP

B

**s2m2 VacA from strain *H. pylori* Tx30a (Atherton et al., 1995, J. Biol. Chem..  
 270 (30), 17771-17777) (SEQ ID NO: 2)**

MEIQQTHRKINRPIISLALVGVLMGTELGANTPNDPIHSESRAFFTTVIIPAIVGGIATGAAVGT  
 VSGLLSWGLKQAEQANKAPDKPDKVWRIQAGRGFDNFPKQYDLYKSLLSSKIDGGWDW  
 GNAARHYWVKDGGQWNKLEVDMQNAVGTYNLSGLINFTGGDLDVNMQKATLRLGQFNGNS  
 FTSFKDGANRTTRVNFDAKNILIDNFVEINNVRVSGAGRKASSTVLTLSSEKITSRENAEISL  
 YDGATLNLVSSSNQSVLDYGVWMGRLQYVGAYLAPSYSTIDTSKVQGEMNFRHLAVGDQ  
 NAAQAGIIANKKTNIGTLDLWQSAGLSIITPPEGGYESKTKDNPQNNPKNDAQKTEIQPTQVI  
 DGPFAGGKDTVVNIFHLNTKADGTLRAGGFKASLTNAAHLHIGEGGVNLNQASGRTLLV  
 ENLTGNITVEGTLRVNNQVGGAAIAGSSANFEFKAGEDTNNATATFNNDIHLGKAVNLRVDA  
 HTANFNNGNIYLKSTNLRVNGHTAHFKNIDATKSDNGLNTSTLDFSGVTDKVNINKLTTAAT  
 NVNIKNFDIKELVVTTRVQSFGQYTIFGENIGDKSRIGVVSLSLQTYGSPAYSGGVTFKGGKKLV  
 IDEIYHAPWNYFDARNVTDVEINKRILFGAPGNIAGKTGLMFNNLTLSNASMDYGKDLDLTI  
 QGHFTNNQGTMNLFVQDGRVATLNAGHQASMIFNNLVDSTTGFKYKPLIKINNAQNLTKNKE  
 HVLVKARNIDYNLVGVQGASYDNISASNTNLQEQFKERLALYNNNNRMDTCVVRKDNLDNI  
 KACGMAIGNQSMVNNPENYKYLEGKAWKNTGINKTANNTTIAVNLGNNSTPTNSTTDTTNL  
 PTNTTNNARFASYALIKNAPFAHSATPNLVAINQHDFGTIESVFELANRSSDIDTLYANSQAQ  
 GRDLLQTLLIDSHDAGYARTMIDATSANEITQQLNAATTTLNNIASLEHKTSGLQTLSLSNAMI  
 LNSRLVNLRSRKHTNHIDSAKRLQALKDQRFASLESAAEVLYQFAPKYEKPTNVWANAIGGT  
 SLNNGSNASLYGTSAGVDAYLNGEVEAIVGGFGSYGYSSFSNQANSLSNGANNTNFGVYS  
 RIFANQHEFDFAAQGALGSDQSSLNFKSALLQDLNQSYHYLAYSATTRASYGYDFAFRNA  
 LVLKPSVGVSYNHLGSTNFKSNSNQVALSNGSSSQHLFNANANVEARYYYGDTSYFYMNA  
 GVLQEFARFGSNNVSLNTFKVNATRNLNTHARVMMGGELQLAKEVFLNLGVVYLHNLS  
 NASHFASNLGMRYSF

Figure 5

**C Negative control mutant ( $\Delta 6-27$ ) VacA (SEQ ID NO: 3)**

AFFTTLGWGLKQAE EANKTPDKPDKVWRIQAGKGFNEFPNKEYDLYKSLLSSKIDGGWD  
 WGNAATHYWIKGGQWNKLEVDMKDAVGTYKLSGLRNFTGGDLVDNMQKATLRLGQFNG  
 NSFTSYKDSADRTTRVDFNAKNILIDNFLEINN RVGSGAGRKASSTVLT LQASEGITSSKNA  
 EISLYDGATLNLASNSVKLNGNVMMGR LQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGD  
 HNAAQAGIIASNKTHIGTLDLWQSAGLNIIAPPEGGYKDKPNNTPSQSGAKNDKQESSQNN  
 SNTQVINPPNSTQKTEVQPTQVIDGPFAGGKDTVVNIDRINTKADGTIKVGGFKASLT TNAA  
 HLNIGKGGVNLSNQASGR TLLVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGVD  
 TKNGTATFNNDISLGRFVN LKVD AHTANFKGIDTGNNGGFNTLDFSGVTNKNVINKLITASTN  
 VAVKNFNINELIVKTNGVSVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVI  
 DEFYSPWNYFDARNIKNVEITRK FASSTPENPWGTSKLMFNNTLGQNAVMDYSQFSNL  
 TIQGD FINNQGTINYLVRGGKVATLNVGNAAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTE  
 HVLLKAKIIGYGNVSTGTNGISNVNLEE QFKERLALYNNNNRMDTCVVRNTDDIKACGMAI  
 GNQSMVNNPDNYKYLI GKAWKNIGISK TANGSKISVYYLGNSTPTENGNTTNLPTNTTNN  
 ARFASYALIKNAPFAHSATPNLVAINQHDFGTIESVFELANRSKDIDTLYANSGAQGRDLLQ  
 TLLIDSHDAGYARTMIDATSANEITKQLNTATTTLN NIASLEHKTSSLQTL SLSNAMILNSRLV  
 NLSRRHTNNIDSFAKRLQALKDQRFASLESAAEVLYQFAP

**D s1m1 VacA from strain H. pylori G27 (Baltrus et al., 2009, J. Bacteriol., 191(1):447-8) (SEQ ID NO: 4)**

MEIQQTHRKMNRPLVSLVLAGALISAIPQESHAAFFTTVIIPAIVGGIATGTAVGTVSGLLSWGL  
 KQAE EANKNPDKPDKVWRIQAGKGFNEFPNKEYDLYKSLLSSKIDGGWDWGNAARHYWVK  
 GGQWNKLEVDMKDAVGTYKLSGLRNFTGGDLVDNMQKATLRLGQFNGNSFTSYKDAADR  
 TTRVNFNAKNISIDNFVEINN RVGSGAGRKASSTVLT LQASEGITS DKN AEISLYDGATLNLAS  
 SSVKLMGNVMMGR LQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDKNAAQAGIIASNKTHI  
 GTLDLWQSAGLNIIAPPEGGYKDKPNNTPSQSGTKNDKNESAKNDKQESSQNN SNTQVINP  
 PNSTQKTEIQPTQVIDGPFAGGKDTVVNINRINTNADGTIRVGGFKASLT TNAAHLHIGKGGV  
 NLSNQASGR TLLVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGVDTKNGTATFN  
 DISLGRFVN LKVD AHTANFKGIDTGNNGGFNTLDFSGVTDKVNINKLITASTNVAVKNFNINELI  
 VKTNGISVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVIDEFYSPWNYFD  
 ARNVKNVEITRK FASSTPENPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGD FINNQGTIN  
 YLVRGGKVATLSVGNAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTEHVLLKAKIIGYGNVS  
 TGTNSISNVNLEE QFKERLALYNNNNRMDTCVVRNTDDIKACGMAIGNQSMVNNPDNYKYLI  
 GKAWKNIGISK TANGSKISVYYLGNSTPTENGNTTNLPTNTTNNARSANYALVKNAPFAHS  
 ATPNLVAINQHDFGTIESVFELANRSKDIDTLYTHSGVQGRDLLQTLLIDSHDAGYARQMIDN  
 TSTGEITKQLNAATDALNNIASLEHKTSG LQTL SLSNAMILNSRLVNL SRKHTNHIDSFAQR LQ  
 ALKGQRFASLESAAEVLYQFAPKYEKPTNVWANAIGGASLNNGGNASLYGTSAGV DAYLNG  
 EVEAIVGGFGSYGYSSFSNRANSLNSGANNANFGVYSRIFANQHEFD FEAQ GALGSDQSSL  
 NFKSALLQDLNQSYHYLAYSAA TRASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSSSN  
 QVALKNGSSSQHLFNANANVEARYYYGDTSYFYMNAGVLQEFARFGSNNAASLNTFKVNT  
 ARNPLNTHARVMMGGELQLAKEVFLNLGVVYLHN LISNIGHFASN LGMRYSF

Figure 5 (continued)

**E s1m1 VacA from strain H. pylori 60190 (Cover et al., 1994, J. Biol. Chem., 269(14):10566-73) (SEQ ID NO: 5)**

MEIQQTTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIPAIVGGIATGTAVGTVSGLLGWGL  
KQAEAEANKTPDKPDKVWRIQAGKGFNEFPNKEYDLYKSLLSSKIDGGWDWGNAATHYWIKG  
GQWNKLEVDMKDAVGTYKLSGLRNFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSADRTT  
RVDFNAKNILIDNFLEINNVRVGSGAGRKASSTVLTQASEGITSSKNAEISLYDGATLNLASNSV  
KLNNGNVWMGRQLQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDHNAQAAGIIASNKTHIGTLD  
LWQSAGLNIIAPPEGGYKDKPNNTPSQSGAKNDKQESSQNNSTQVINPPNSTQKTEVQPT  
QVIDGPFAGGKDTVNIIDRINTKADGTIKVGGFKASLTNAAHLNIGKGGVNLSNQASGRTLLV  
ENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGVDTKNGTATFNNDISLGRFVNLKVDA  
HTANFKGIDTGNNGGFNTLDFSGVTNKVNINKLITASTNVAVKNFNINELIVKTNGVSVGEYTHF  
SEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVIDEFYYPWNYFDARNIKNVEITRKFFAS  
STPENPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGDFINNQGTTINYLVRRGGKVATLNVGN  
AAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTEHVLLKAKIIGYGNVSTGTNGISNVNLEEQFK  
ERLALYNNNNRMDTCVVRNTDDIKACGMAIGNQSMVNNPDNYKYLGKAWKNIGISKTAGS  
KISVYYLGNSTPTENGNTTNLPTNTTNARFASYALIKNAPFAHSATPNLVAINQHDFGTIES  
VFELANRSKDIDTLYANSGAQGRDLLQTLIDSHDAGYARTMIDATSANEITKQLNTATTTLLNNI  
ASLEHKTSSLQTLSSNAMILNSRLVNLSSRRHTNNIDSFARLQALKDQRFASLESAAEVLYQF  
APKYEKPTNVWANAIGGASLNNGGNASLYGTSAGVDAYLNGQVEAIVGGFGSYGYSSFNNQ  
ANSLNSGANNTNFGVYSRIFANQHEFDFAQAGALGSDQSSLNFKSALLRDLNQSYNYLAYS  
ATRASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSNSNTNKVALSNGSSSQHLFNASANVE  
ARYYYGDTSYFYMNAGVLQEFANFGSSNAVSLNTFKVNATRNPLNTHARVMMGGELKLAKE  
VFLNLGVVYLHNLISNIGHFASNLGMRYSF

**s1m1 VacA from strain H. pylori 26695 (Tomb et al., 1997, Nature, 388(6642):539-47) (SEQ ID NO: 6)**

**F** MEIQQTTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIPAIVGGIATGAAVGTVSGLLGWGL  
LKQAEAEANKTPDKPDKVWRIQAGKGFNEFPNKEYDLYRSLSSKIDGGWDWGNAATHYWW  
KGGQWNKLEVDMKDAVGTYNLSGLRNFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSAD  
RTTRVDFNAKNILIDNFLEINNVRVGSGAGRKASSTVLTQASEGITSSKNAEISLYDGATLNL  
SNSVKLMGNVWMGRQLQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDHNAQAAGIIASNKT  
HIGTLDLWQSAGLNIIAPPEGGYKDKPKDKPSNTTQNNANNNNQNSAQNNSTQVINPPNS  
AQKTEIQPTQVIDGPFAGGKDTVNIIDRINTNADGTIKVGGYKASLTNAAHLHIGKGGINLSN  
QASGRTLLVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGTDTKNGTATFNNDISL  
RFVNLKVDAHTANFKGIDTGNNGGFNTLDFSGVTGKVNINKLITASTNVAVKNFNINELVVKT  
GVSVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVIDEFYYPWNYFDARNI  
KNVEITRKFFASSTPENPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGDFINNQGTTINYLV  
GGQVATLNVGNAAAMFFSNNVDSATGFYQPLMKINSAQDLIKNKEHVLLKAKIIGYGNVSLG  
TNSISNVNLTIEQFKERLALYNNNNRMDICVVRNTDDIKACGTAIGNQSMVNNPDNYKYLGK  
WKNIGISKTAGSKISVYYLGNSTPTEKGGNTTNLPTNTTNSNRSANNALAQNAQPSAT  
PNLVAINQHDFGTIESVFELANRSKDIDTLYANSGAQGRDLLQTLIDSHDAGYARQMIDNTS  
TGEITKQLNAATTTLLNNIASLEHKTSSLQTLSSNAMILNSRLVNLSSRRHTNNIDSFARLQAL  
KDQKFASLESAAEVLYQFAPKYEKPTNVWANAIGGTSLNNGGNASLYGTSAGVDAYLNGEV  
EAIVGGFGSYGYSSFNNQANSLNSGANNTNFGVYSRIFANQHEFDFAQAGALGSDQSSLNF  
KSALLRDLNQSYNYLAYSATRASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSNSNQV  
ALKNGSSSQHLFNASANVEARYYYGDTSYFYMNAGVLQEFANFGSSNAVSLNTFKVNAAH  
NPLSTHARVMMGGELKLAKEVFLNLGVVYLHNLISNIGHFASNLGMRYSF

Figure 5 (continued)

**G** s1m1 VacA of strain H. pylori J99 (*Merrell et al., 2003, Infect Immun., 71(11):6510-25*) (SEQ ID NO: 7)

MEIQQTHRKINRPLVSLVLAGALISAIPQESHAAFFTTVIIPAIVGGIATGTAVGTVSGLLSWGL  
KQAEAEANKTPDKPDVWRIQAGKGFNEFPNKEYDLYKSLLSSKIDGGWDWGNAARHYWW  
KGGQWNKLEVDMKDAVGTYKLSGLRNFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSAD  
RTTRVNFNAKNISIDNFVEINNVRVSGAGRKASSTVLTQASEGITSSKNAEISLYDGATLNL  
ASNSVKLNGNVWMGRLQYVGAYLAPSYSTINTSKVQGEVDFNHLTVGDQNAQAQAGIIASNK  
THIGTLDLWQSAGLNIIAPPEGGYKDKPNSTTSQSGTKNDKKEISQNNNSNTEVINPPNNTQ  
KTETEPTQVIDGPFAGGKDTVVNIFHLNLTAKDGTIKVGGFKASLTNAAHLNIGKGGVNLSN  
QASGRITLLVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGVDTKNGTATFNNDISL  
GRFVNLKVDHAHTANFKGIDTGNGGFNTLDFSGVTDKVNINKLITASTNVAVKNFNINELIVKT  
NGISVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVINDFYSPWNYFDAR  
NVKNVEITRKFASTPENPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGDFFINNQGTTINYL  
VRGGKVATLNVGNAAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTEHVLLKAKIIGYGNVST  
GTNGISNVNLEEQFKERLALYNNNNRMDTCVVRNTDDIKACGMAIGNQSMVNNPDNYKYLI  
GKAWRNIGISKTAGSKISVYYLGNSTPTENGNTTNLPTNTTNNNAHSANYALVKNAPFAHS  
ATPNLVAINQHDFGTIESVFELANRSKDIDTLYTHSGAQGRDLLQTLLIDSHDAGYARQMIDN  
TSTGEITKQLNAATDALNNVASLEHKQSGQLTSLSNAMILNSRLVNLNRKHTNHINSFAQRL  
QALKGQEFASLESAAEVLYQFAPKYEKPTNVWANAIGGASLNSGSNASLYGTSAGVDAFLN  
GNVEAIVGGFGSYGYSSFSNQANSLNSGANNANFGVYSRFFANQHEFDFAQAGALGSDQS  
SLNFKSTLLQDLNQSYNYLAYSATARASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSN  
SQSQVALKNGASSQHLLFNANANVEARYYYGDTSYFYHAGVLQEFANFGSNDVASLNTFKI  
NAARSPLSTYARAMMGGELQLAKEVFLNLGVVYLHNLSNASHFASNLGMRYSF

**H** s1m1 VacA from strain NCTC 11637 (*Ito et al., 1998, J. Infect. Dis., 178(5):1391-8*) (SEQ ID NO: 8)

MEIQQTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIPAIVGGIATGAAVGTVSGLLSWG  
LKQAEAEANKTPDKPDVWRIQAGRGFNFPNKEYDLYKSLLSSKIDGGWDWGNAARHYWW  
VKGQWNKLEVDMKDAVGTYKLSGLINFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSA  
DRTRVDFNAKNILIDNFLEINNVRVSGAGRKASSTVLTQASEGITSSKNAEISLYDGATLNL  
LASSSVKLMGNVWMGRLQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDHNAQAQAGIIASN  
KTHIGTLDLWQSAGLNIIAPPEGGYKDKPKDKPSNTTQNNANNNQQNSAQNNNNTQVINPP  
NSAQKTEIQPTQVINGPFAGGKDTVNNINRINTNADGTIRVGGYKASLTNAAHLHIGKGGIN  
LSNQASGRSLLVENLTGNITVDGPLRVNNQVGGYALAGSNANFEFKAGTDTKNGTATFNN  
DISLGRFVNLKVDHAHTANFKGIDTGNGGFNTLDFSGVTDKVNINKLITASTNVAIKNFNINELL  
VKTNGVSVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKSGEKLVIDEFYSPWNYF  
DARNIKNVEITRKFASTPENPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGDFFINNQGTTI  
NYLVRGGKVATLNVGNAAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTEHVLLKAKIIGYGN  
VSTGTNGISNVNLEEQFKERLALYNNNNRMDTCVVRNTDDIKACGMAIGNQSMVNNPDNY  
KYLIGKAWKNIGISKTAGSKISVYYLGNSTPTENGNTTNLPTNTTNNARSANYALVKNAP  
FAHSATPNLVAINQHDFGTIESVFELANRSKDIDTLYTHSGAKGRDLLQTLLIDSHDAGYARQ  
MIDNTSTGEITKQLNAATTTLNIIASLEHKTSSLQTLTSLSNAMILNSRLVNLNRKHTNNIDSFA  
KRLQALKDQRFASLESAAEVLYQFAPKYEKPTNVWANAIGGASLNNGSNASLYGTSAGVD  
AYLNGQVEAIVGGFGSYGYSSFSNRANSLNSGANNTNFGVYSRIFANQHEFDFAQAGALG  
SDQSSLNFKSALLQDLNQSYNYLAYSAAATRASGYDFAFFKNALVLKPSVGVSYNHLGSTN  
FKSNSTNKVALSNGSSSQHLFNANANVEARYYYGDTSYFYMNAGVLQEFANFGSSNAVSL  
NTFKVNAARNPLNTHARVMMGGELQLAKEVFLNLGFVYLHNLSNIGHFASNLGMRYSF

Figure 5 (continued)

**I s1m1 VacA of strain *H. pylori* P12 (Fischer et al., 2010, *Nucleic Acids Res.* 38(18):6089-101) (SEQ ID NO: 9)**

MEIQQTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIIPAIVGGIASGAAVGTVSGLLGWGL  
KQAE EANKTPDKPDKVWRIQAGKGFNEFPNKEYDLYRSLSSKIDGGWDWGNAATHYWWK  
GGQWNKLEVDMKDAVGTYNLSGLRNFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSADRT  
TRVDFNAKNISIDNFLEINN RVGSGAGRKASSTVLT LQASEGITSSKNAEISLYDGATLNLASSS  
VKLMGNVWMGR LQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDRNAAQAGIIASNKTHIGTL  
DLWQSAGLNIIAPPEGGYKDKPNNTPSQSGAKNDKNESAKNDKQESSQNNSTQVINPPNS  
AQKTEVQPTQVIDGPFAGGKDTVVNINRINTNADGTIRVGGYKASLT TNAAHLHIGKGGVNLS  
NQASGR TLLVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGTDTKNGTATFNNDISL  
GRFVN LK VDAHTANFKGIDTGNGGFNTLDFSGVTDKVNINKLITASTNVAIKNFNINELLVKTNG  
VSVGEYTHFSEDIGSQSRINTVRLETGTRSIFSGGVKFKGGEKLVINDFYYPWNYFDARNIKN  
VEITNKLAFGPQGSPWGTSKLMFNNTLGQNAVMDYSQFSNLTIQGDFVNNQGTINYLV RGG  
QVATLNVGNAAAMFFNNVDSATGFYQPLMKINSAQDLIKNKEHVLLKAKIIGYGNVSAGTNSI  
SNVNLIEQFKERLALYEHNNRMDICVVRNTDDIKACGTAIGNQSMVNNPDNYKYLIGKAWKNI  
GISKTANGSKISVHYLGNSTPTENSGNTTNLPTNTTNSARSAKNALAQNAAPFAQPSATPSLVAI  
NQHDFGTIESVFELANRSKDIDTLYTHSGAQGRNLLQTLLIDSHDAGYARQMIDNTSTGEI IKQL  
NAATTTLNNVASLEHKQSGLQTL SLSNAMILNSRLVNL SRRHTNNIDSFAQRLQALKDQKFAS  
LESAAEVLYQFAPKYEKPTNVWANAIGGTS LNNGGNASLYGTSAGV DAYLNGEVEAIVGGFG  
SYGYSSFSNQANSLNSGANNTNFGVYSRLFANQHEFD FEAQ GALGSDQSSLNFKSALLRDL  
NQSYNLAYSAATRASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSNSNTNQVALKNGSSS  
QHLFNASANVEARYYYGDTSYFYMNAGVLQEFANFGSSNAVSLNTFKVNAARNPLNTHARV  
MMGGELKLAKEVFLNLGFVYLHNLISNIGHFASN LGMRYSF

**J s1m1 VacA of strain *H. pylori* (Haas et al., 1994, *Mol. Microbiol.*, 12:307-319) (SEQ ID NO: 10)**

MEIQQTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIIPAIVGGIATGAAVGTVSGLLGWGL  
KQAE EANKTPDKPDKVWRIQAGKGFNEFPNKEYDLYKSLLSSKIDGGWDWGNAARHYWWK  
DGQWNKLEVDMQNAVGTYNLSGLINFTGGDLVDNMQKATLRLGQFNGNSFTSYKDSADRT  
TRVDFNAKNILIDNFLEINN RVGSGAGRKASSTVLT LQASEGITSRENAEISLYDGATLNLASN  
SVKLMGNVWMGR LQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDHNAQAGIIASNKTHIG  
TLDLWQSAGLNIIAPPEGGYKDKPNDKPSNTTQNNAKNDKQESSQNNSTQVINPPNSAQKT  
EIQPTQVIDGPFAGGKNTVVNINRINTNADGTIRVGGFKASLT TNAAHLHIGKGGINLSNQASG  
RSLLENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGTDTKNGTATFNNDISLGRFVN  
LKVDAHTANFKGIDTGNGGFNTLDFSGVTNKVNINKLITASTNVAVKNFNINELVVKTNGVSVG  
EYTHFSEDIGSQSRINTVRLETGTRSIYSGGVKFKGGEKLVINDFYYPWNYFDARNIKNVEIT  
NKLAFGPQGSPWGTA KLMFNNTLGQNAVMDYSQFSNLTIQGDFVNNQGTINYLV RGGQVA  
TLNVGNAAAMFFSNNVDSATGFYQPLMKINSAQDLIKNKEHVLLKAKIIGYGNVSAGTDSIANV  
NLIEQFKERLALYNNNNRMDICVVRNTDDIKACGTAIGNQSMVNNPENYKYLEGKAWKNIGIS  
KTANGSKISVHYLGNSTPTENGGNTTNLPTNTTNKVRFASYALIKNAPFARYSATPNLVAINQ  
HDFGTIESVFELANRSNDIDTLYANSGAQGRDLLQTLLIDSHDAGYARTMIDATSANEITKQLN  
TATTTLNNIASLEHKTSGLQTL SLSNAMILNSRLVNL SRRHTNHIDSFAKRLQALKDQRFASLE  
SAAEVLYQFAPKYEKPTNVWANAIGGTS LNNGGNASLYGTSAGV DAYLNGEVEAIVGGFGSY  
GYSSFSNQANSLNSGANNTNFGVYSRIFANQHEFD FEAQ GALGSDQSSLNFKSALLRDLNQ  
SYNYLAYSAATRASYGYDFAFFRNALVLKPSVGVSYNHLGSTNFKSNSNQKVALKNGASSQ  
HLFNASANVEARYYYGDTSYFYMNAGVLQEFANFGSSNAVSLNTFKVNATRNPLNTHARVM  
MGGELKLAKEVFLNLGFVYLHNLISNIGHFASN LGMRYSF

Figure 5 (continued)

K s1m1 VacA of strain *H. pylori* NCTC 11638 (*Phadnis et al., 1994, Infect. Immun. 62:1557-1565*) (SEQ ID NO: 11)

MEIQQTTHRKINRPLVSLALVGALVSITPQQSHAAFFTTVIIPAIVGGIATGTAVGTVSGLLSWGLK  
 QAEEANKTPDKPDVWRIQAGKGFNEFPNKEYDLYRSLLSSKIDGGWDWGNAARHYWKG  
 GQQNKLEVDMKDAVGTYTSLGLRNFTGGDLVDNMQKATLRLGQFNNGNSFTSYKDSADRTTR  
 VDFNAKNISIDNFVEINNVRVGSGAGRKASSTVLTQASEGITSDKNAEISLYDGATLNLASSS  
 VKLMGNVWMGRQLQYVGAYLAPSYSTINTSKVTGEVNFNHLTVGDKNAAQAGIANKKTNIGTL  
 DLWQSAGLNIIAPPEGGYKDKPNNTPSQSGAKNDKNESAKNDKQESSQNNNSNTQVINPPNS  
 AQKTEVQPTQVIDGPFAGGKDTVVNINRINTNADGTIRVGGFKASLTTNAAHLHIGKGGVNLS  
 NQASGRSLIVENLTGNITVDGPLRVNNQVGGYALAGSSANFEFKAGTDTKNGTATFNNDISLG  
 RFVNLKVDAHTANFKGIDTGNGGFNTLDFSGVTDKVNINKLITASTNVAVKNFNINELIVKTNGI  
 SVGEYTHFSEDIGSQSRINTVRLETGTRSLFSGGVKFKGGEKLVIDEFYYSPWNYFDARNIKN  
 VEITNKLAFGPQGSPWGTSKLMFNNTLGGQNAVMDYSQFSNLTIQGDFINNQGTYNYLVRGGK  
 VATLSVGNAAMMFNNDIDSATGFYKPLIKINSAQDLIKNTEHVLLKAKIIGYGNVSTGTNGISN  
 VNLEEQFKERLALYNNNNRMDTCVVRNTDDIKACGMAIGDQSMVNNPDNYKYLIGKAWKNIG  
 ISKTANGSKISVYYLGNSTPTENGNTTNLPTNTTNSNARSANALAQNAQPSATPNLVAI  
 NQHDFGTIESVFELANRSKDIDTLYANSGAQGRDLLQTLLIDSHDAGYARKMIDATSANEITKQ  
 LNTATTTLNNIASLEHKTSGLQTLSLSNAMILNSRLVNLSRRHTNHIDSFARKLQALKDQKFASL  
 ESAAEVLYQFAPKYEKPTNVWANAIGGTSLNNGSNASLYGTSAGVDAYLNGQVEAIVGGFGS  
 YGYSSFNNRANSLNSGANNTNFGVYSRIFANQHEFDFAQGALGSDQSSLNFKSALLQDLNQ  
 SYHYLAYSAAATRASYGDFAFFRNALVLKPSVGVSYNHLGSTNFKSNSTNQVALKNGSSSQH  
 LFNASANVEARYYYGDTSYFYMNAGVLQEFHVGSNNAASLNTFKVNAARNPLNTHARVMM  
 GGELKLAKEVFLNLGVVYLHNLISNIGHFASNLGMRYSSF

Figure 5 (continued)



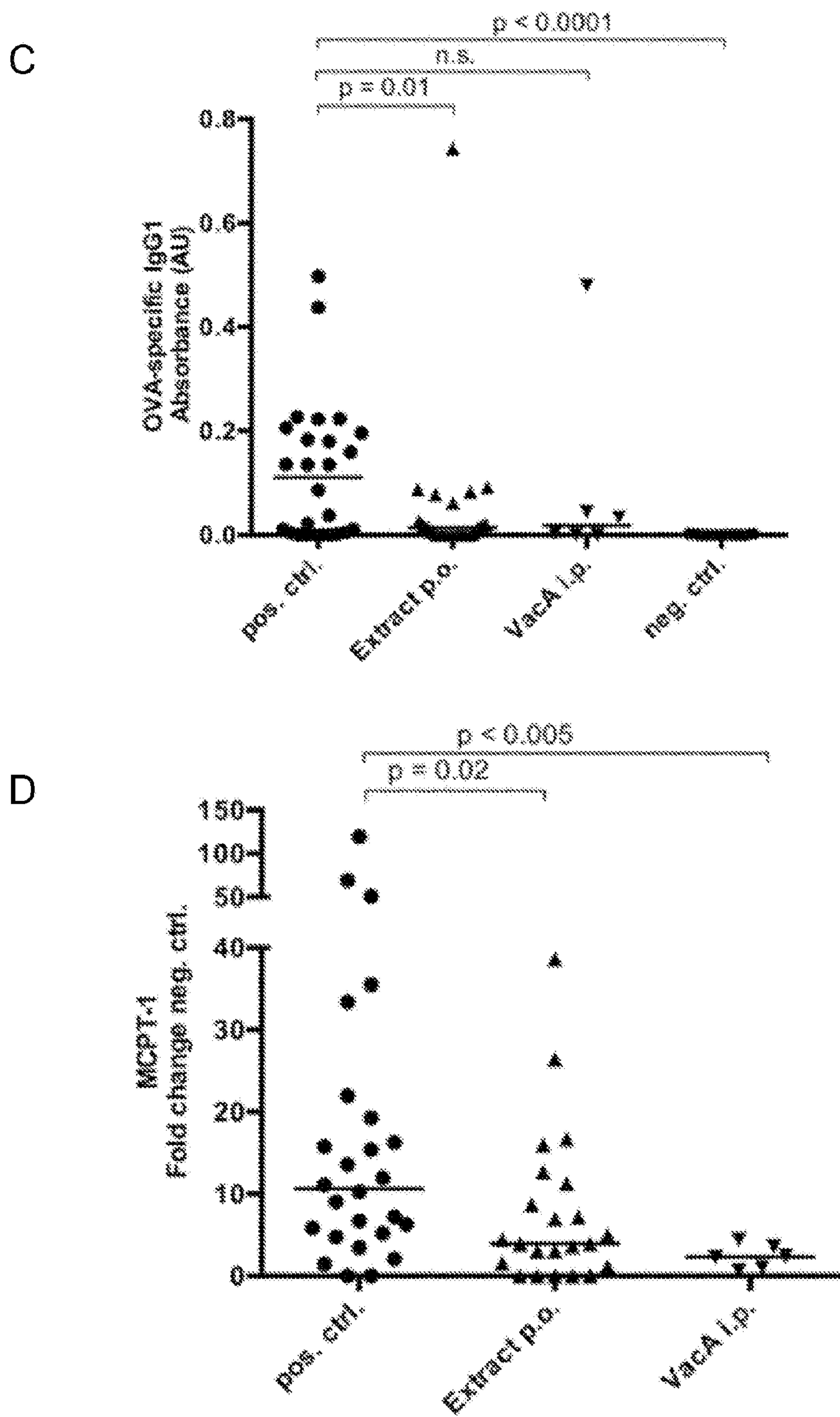
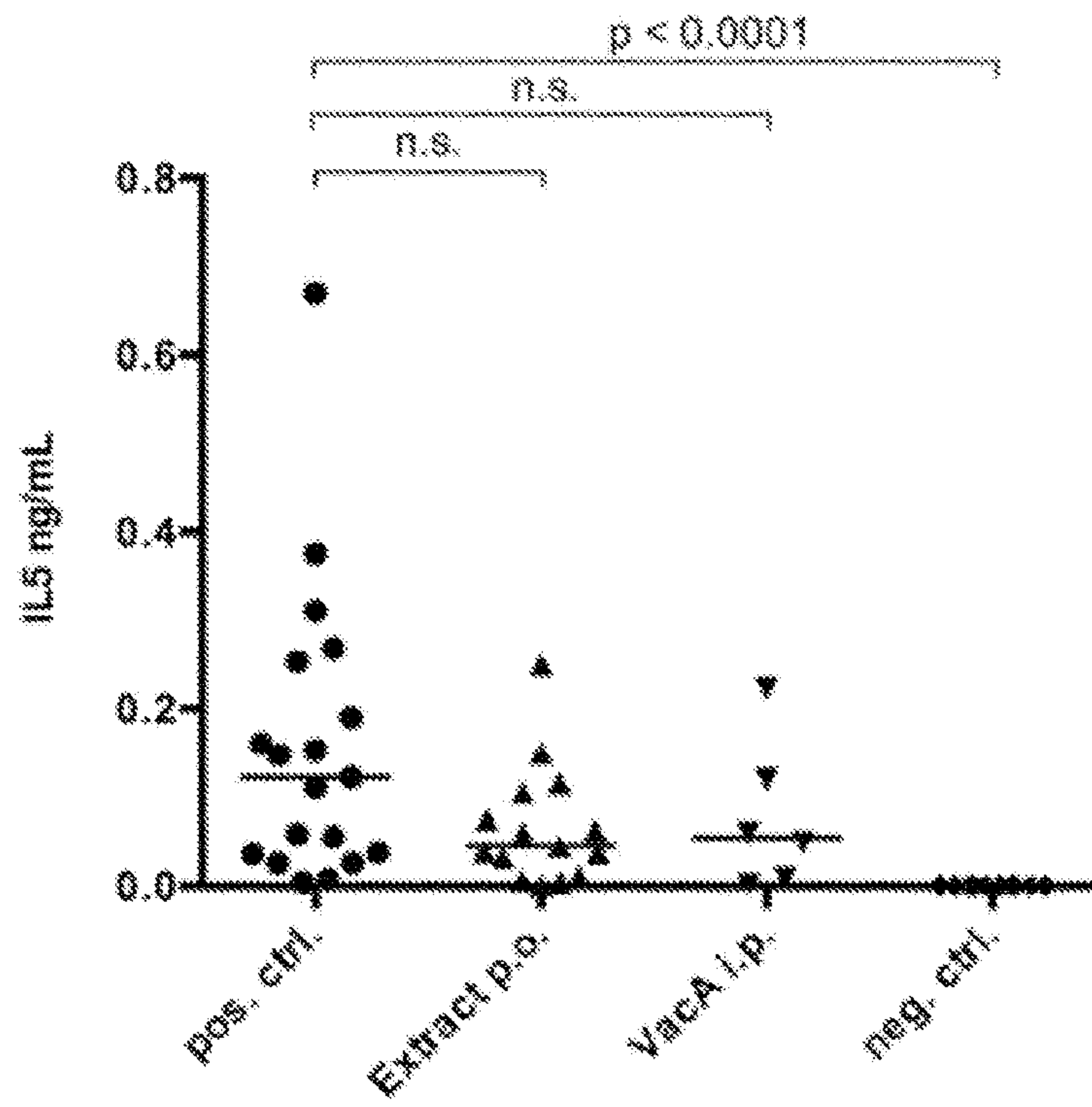


Figure 6 (continued)

E



F

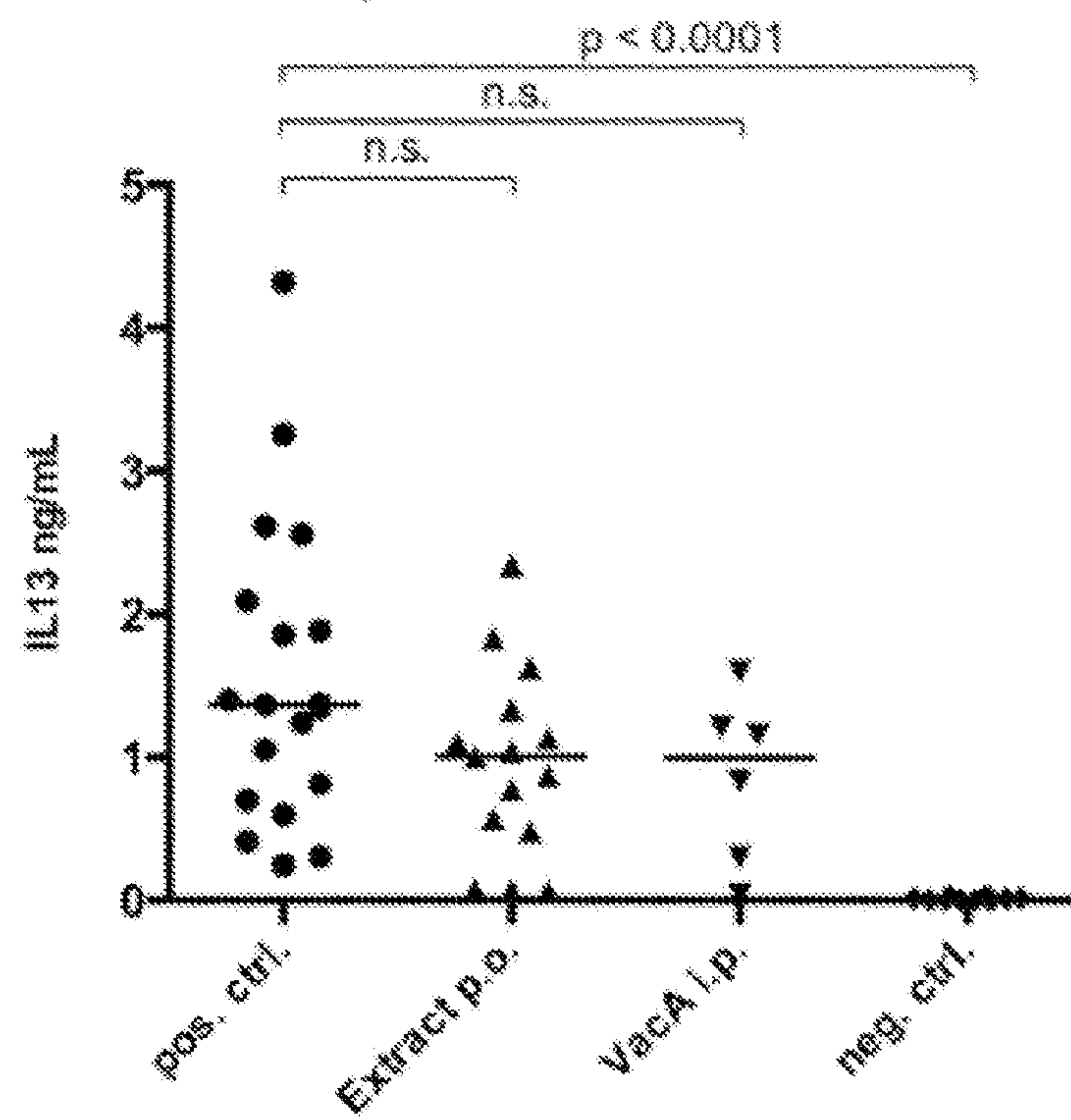


Figure 6 (continued)