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(54) USE OF IMMUNE SUPPRESSIVE DOMAINS AS MEDICAMENTS

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(57) **ABSTRACT**

The present invention concerns uses of immune suppressive domains. In particular, the present invention concerns a use of an immune suppressive domain (ISD) for immune suppression and for reduction of inflammation.

Specification includes a Sequence Listing.

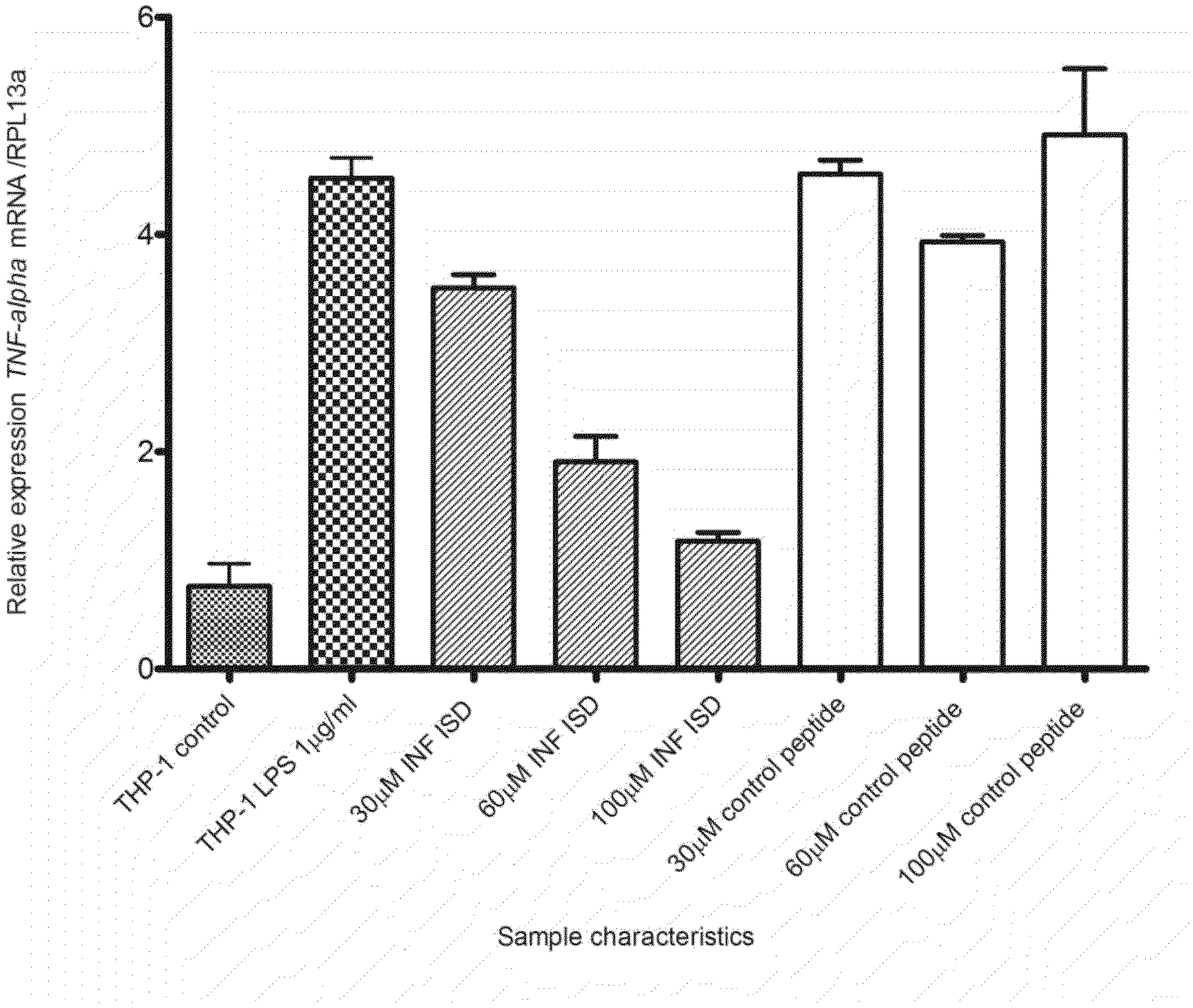

Relative expression TNF-alpha mRNA /RPL13a
0
2
4
6
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 1

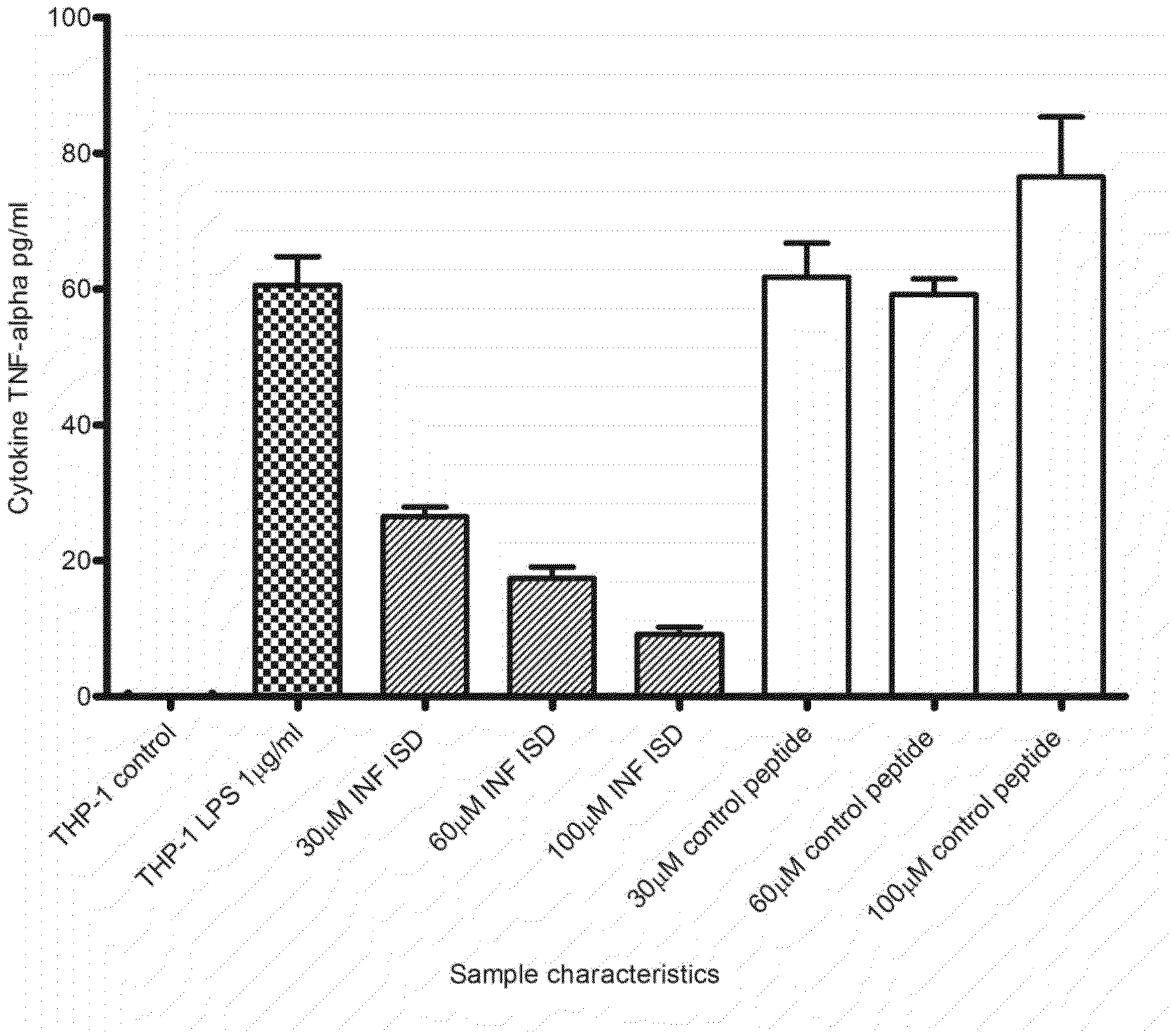

100
80
60
40
20
0
Cytokine TNF-alpha pg/ml
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 2

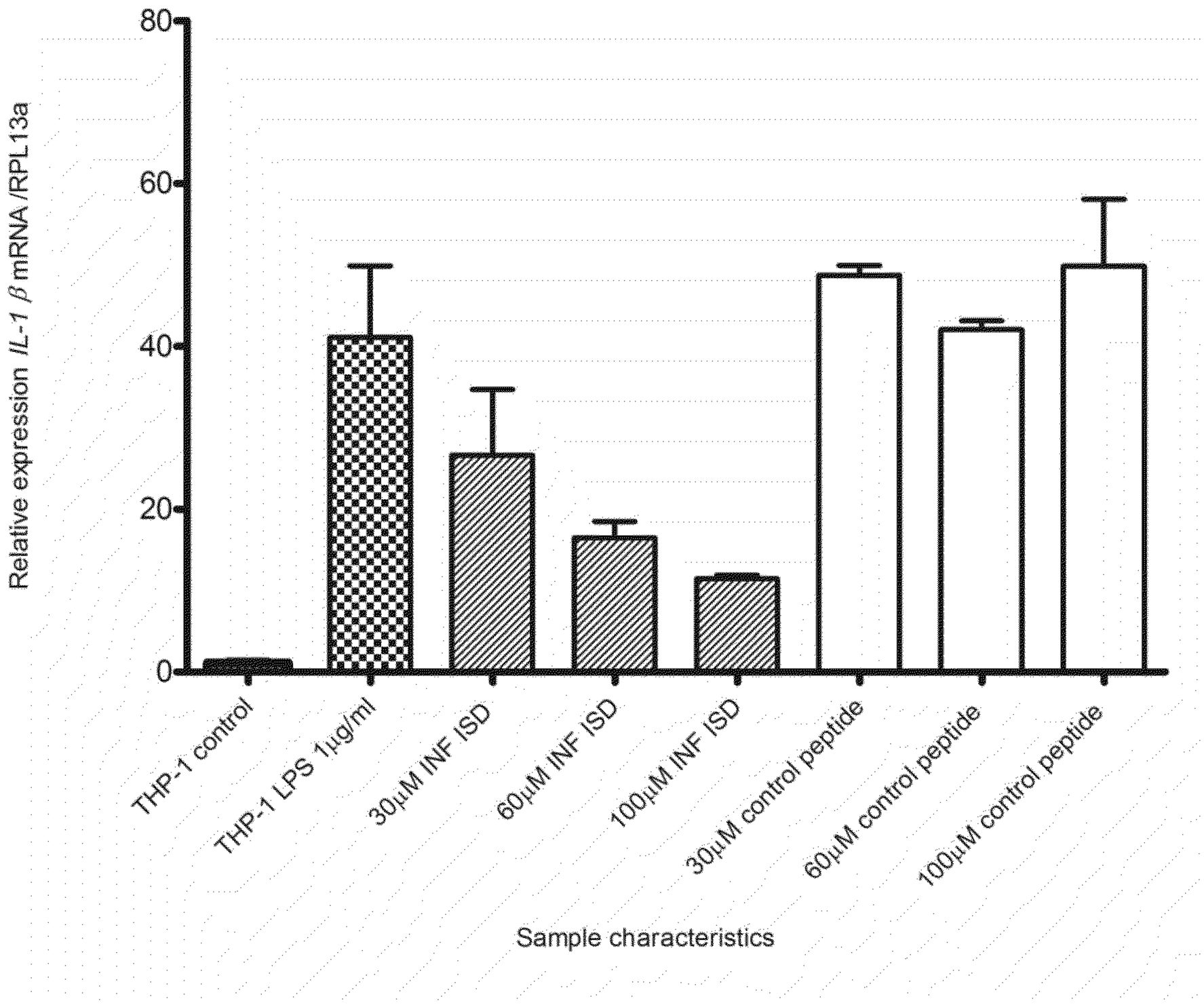

Relative expression IL-1 β mRNA /RPL13a
0
20
40
60
80
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 3

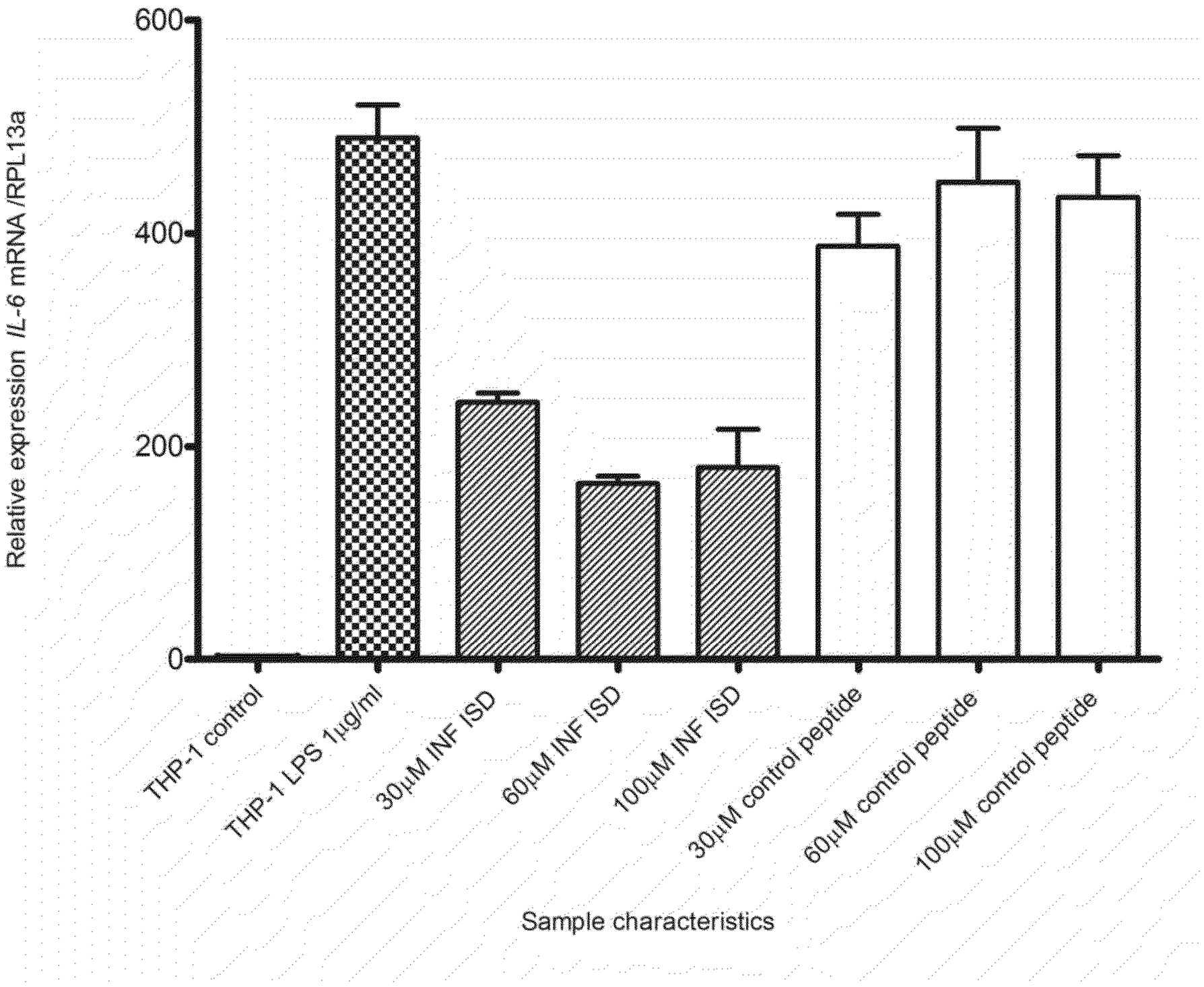

600
400
200
0
Relative expression IL-6 mRNA /RPL13a
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 4

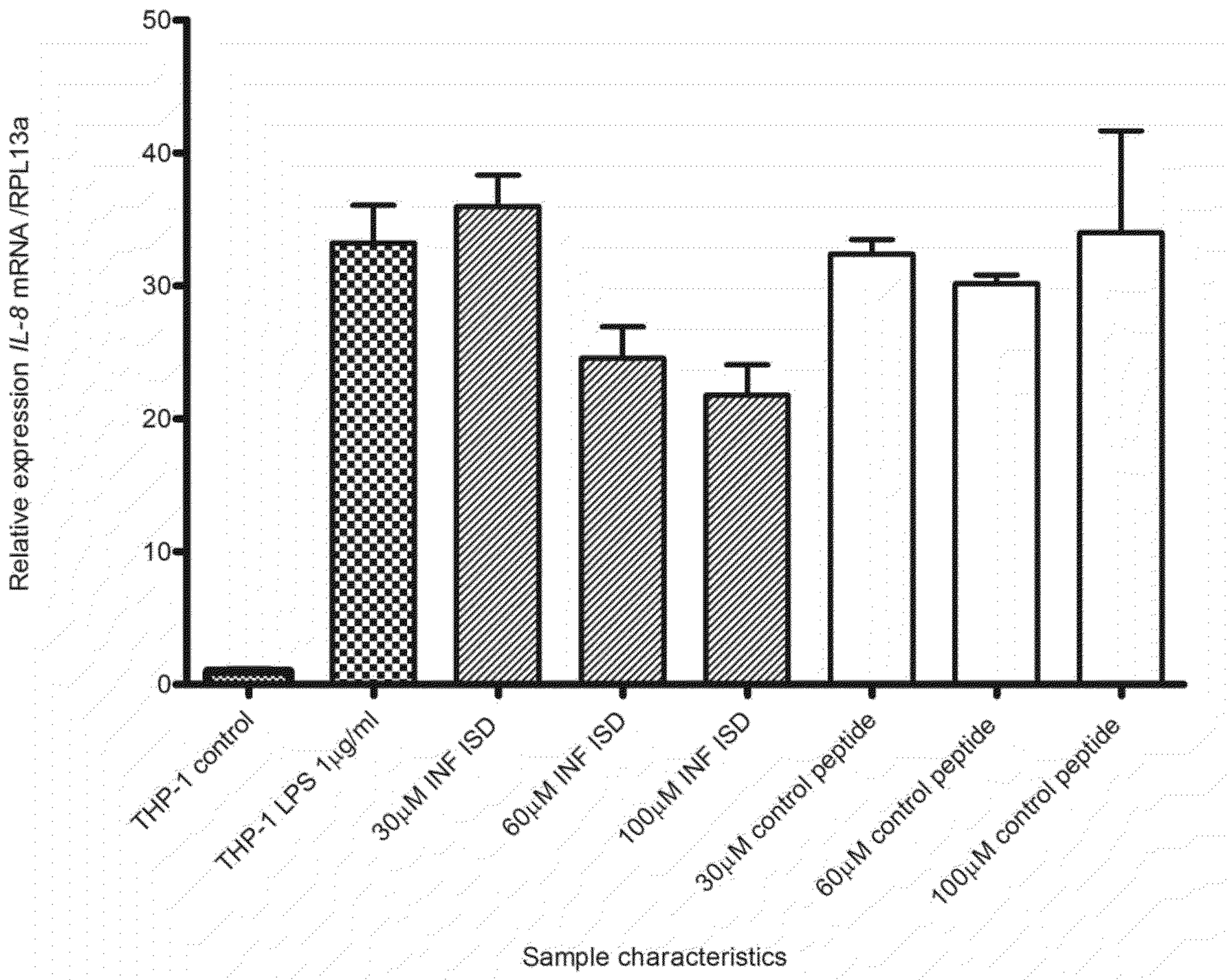

Relative expression IL-8 mRNA /RPL13a
50
40
30
20
10
0
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 5

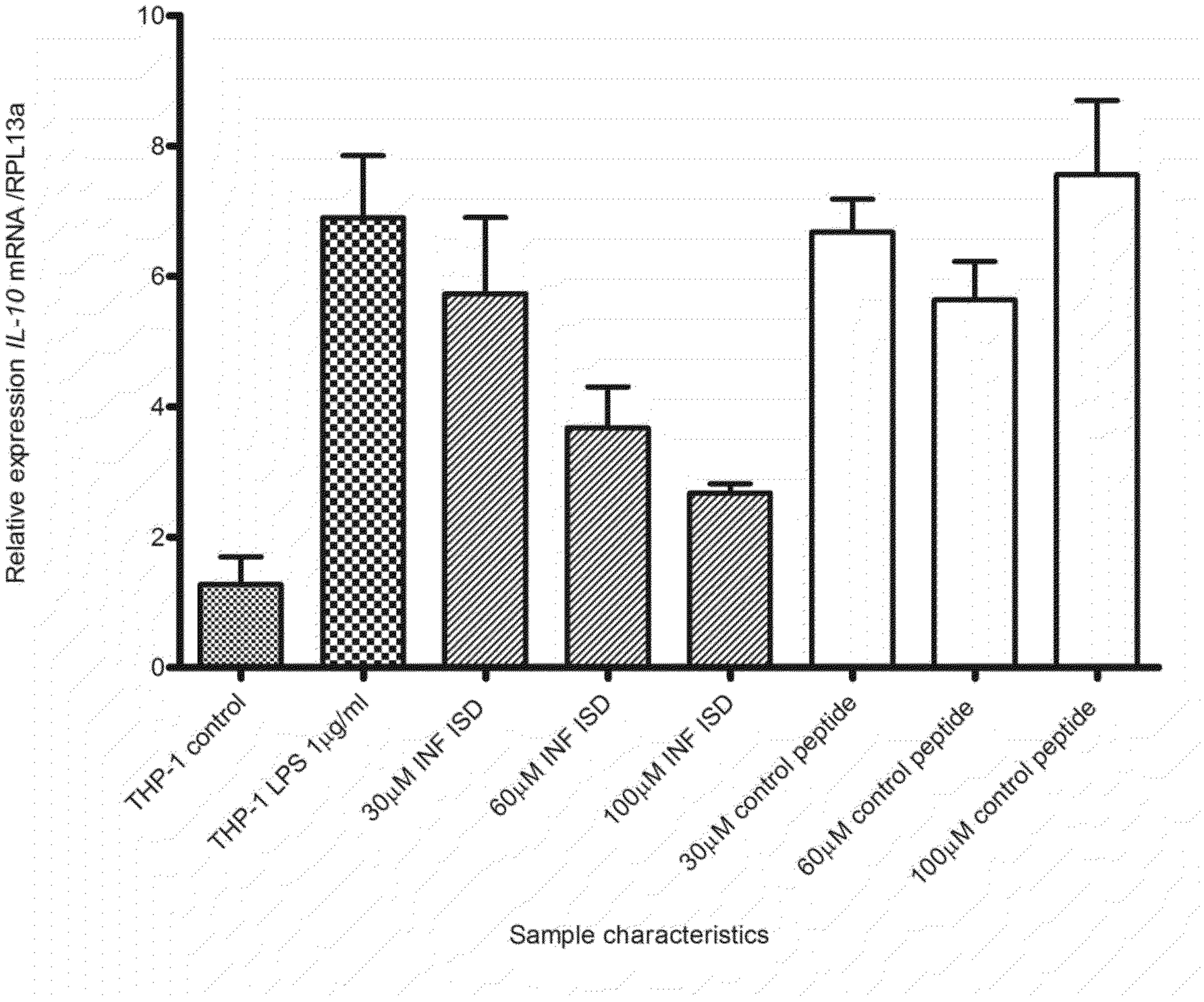

Relative expression IL-10 mRNA /RPL13a
0
2
4
6
8
10
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 6

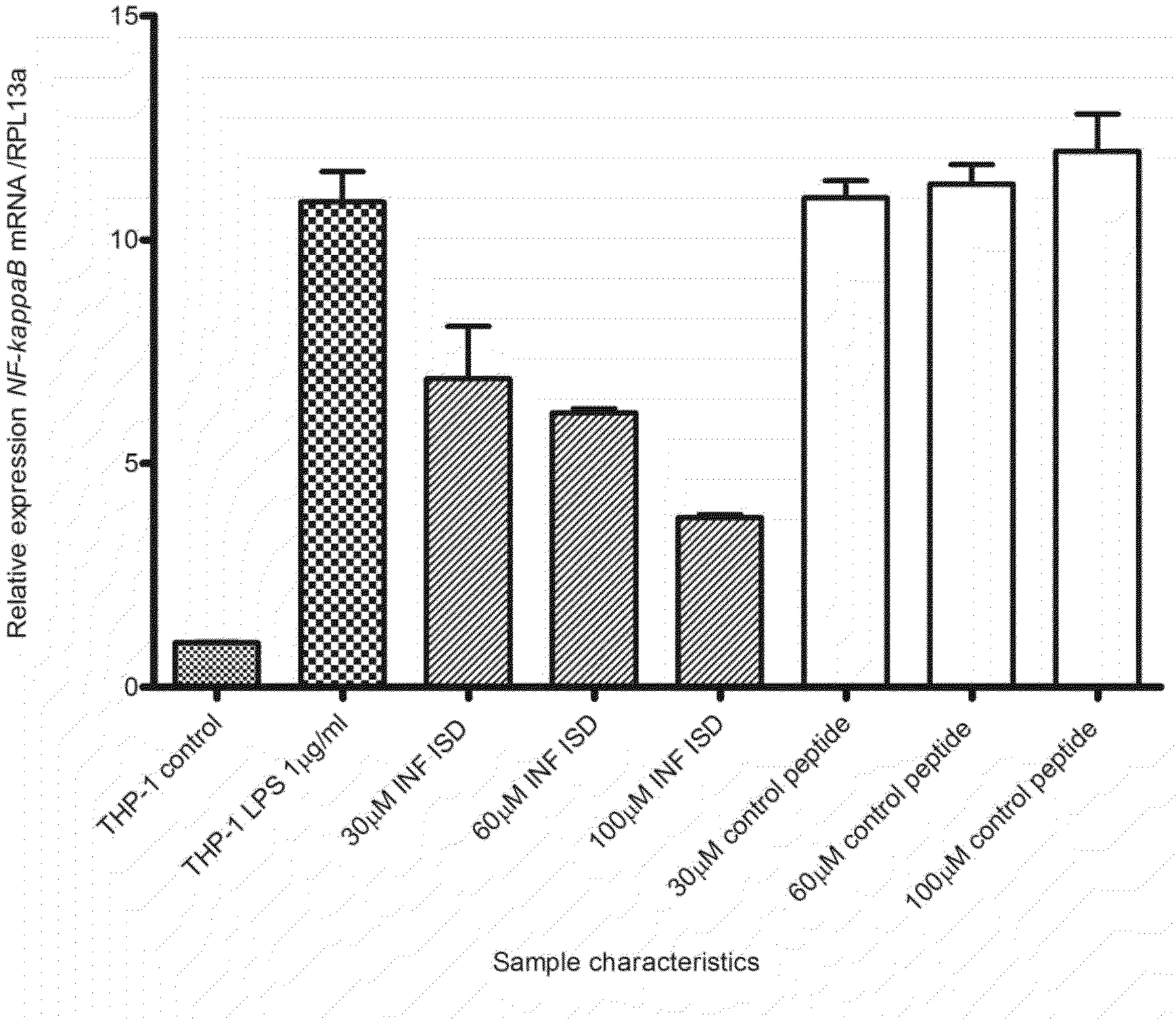

15
10
5
0
Relative expression NF-kappaB mRNA /RPL13a
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 7

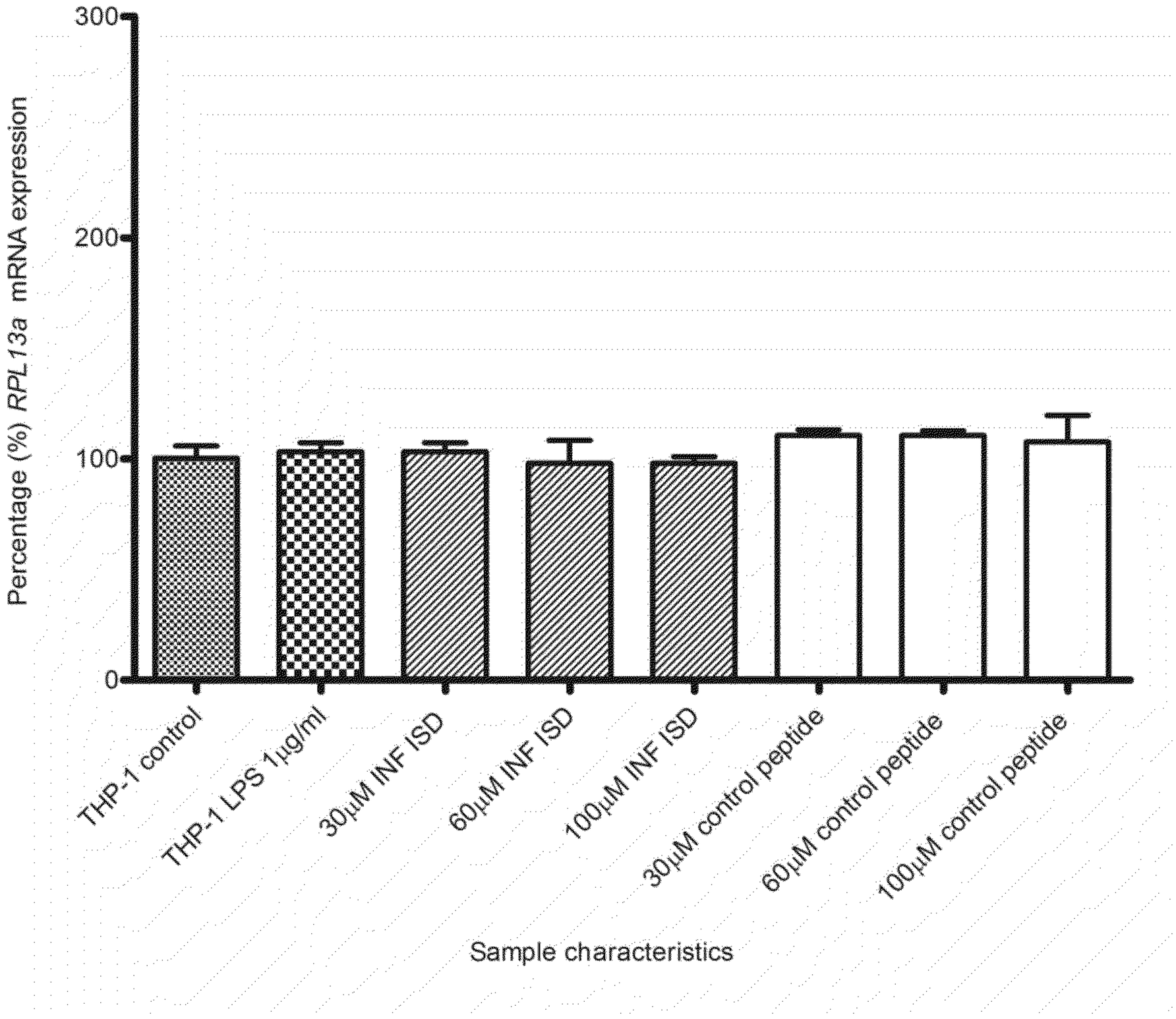
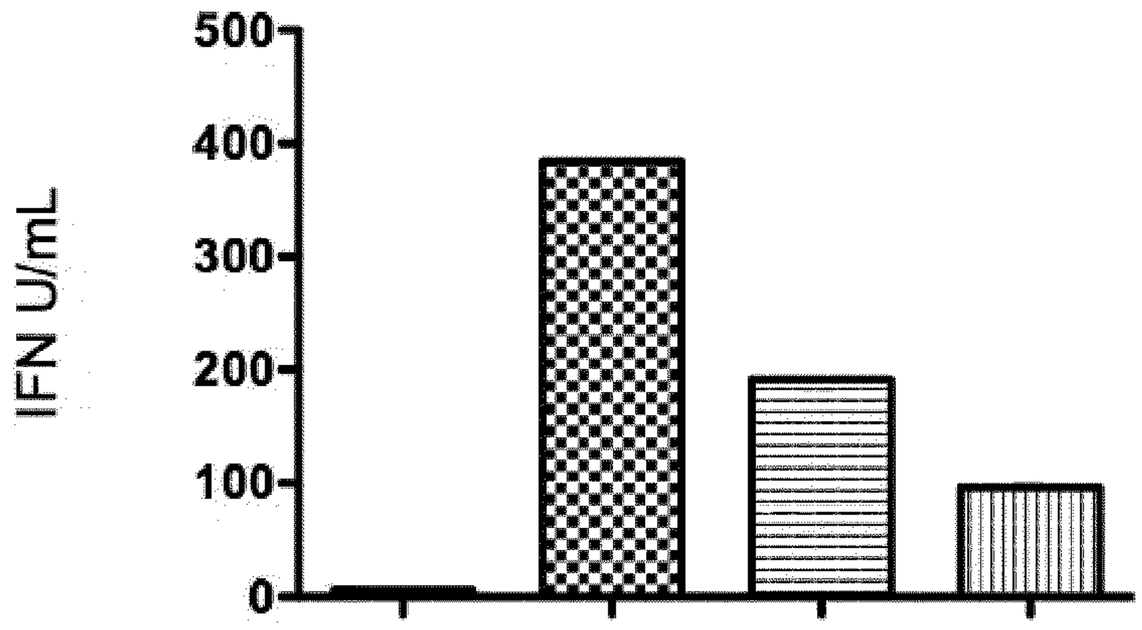

300
200
100
0
Percentage (%) RPL13a mRNA expression
THP-1 control
THP-1 LPS 1μg/ml
30μM INF ISD
60μM INF ISD
100μM INF ISD
30μM control peptide
60μM control peptide
100μM control peptide
Sample characteristics

Fig. 8



LPS	–	+	+	+
DI6			+	
INF F#2				+

Fig. 9

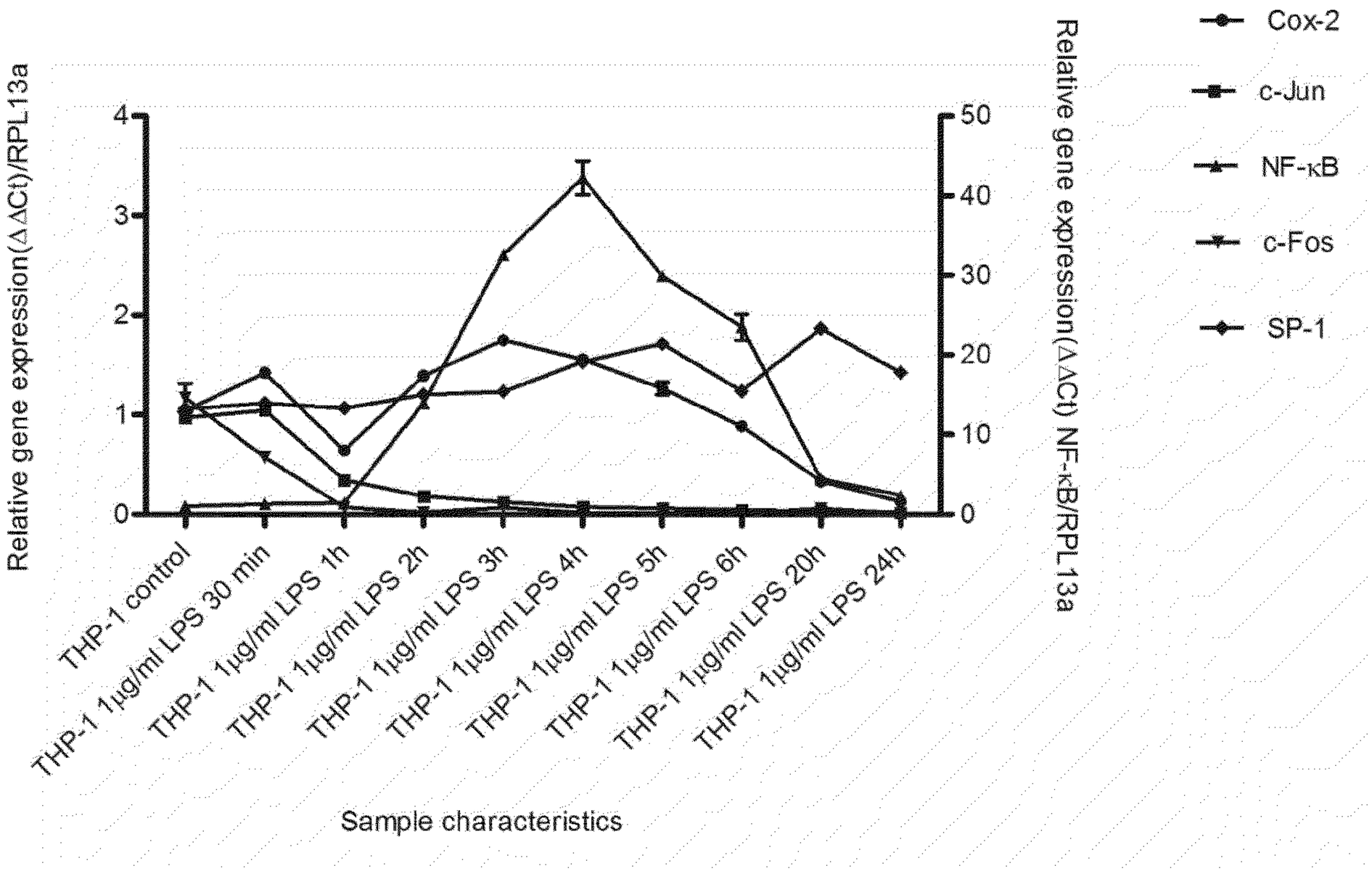


Fig. 10

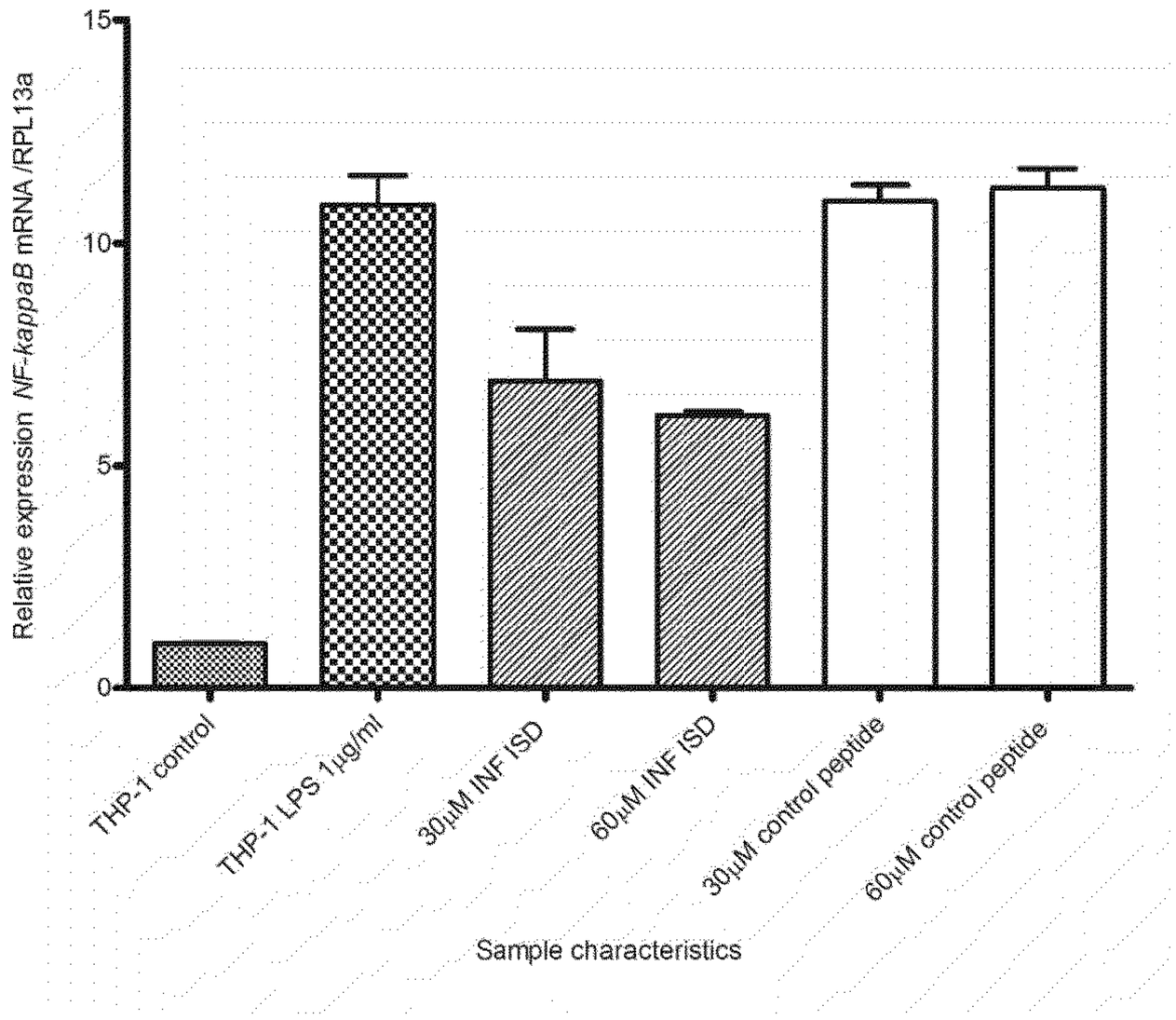

15
10
5
0
Relative expression NF-kappaB mRNA /RPL13a
THP-1 control
THP-1 LPS 1µg/ml
30µM INF ISD
60µM INF ISD
30µM control peptide
60µM control peptide
Sample characteristics

Fig. 11

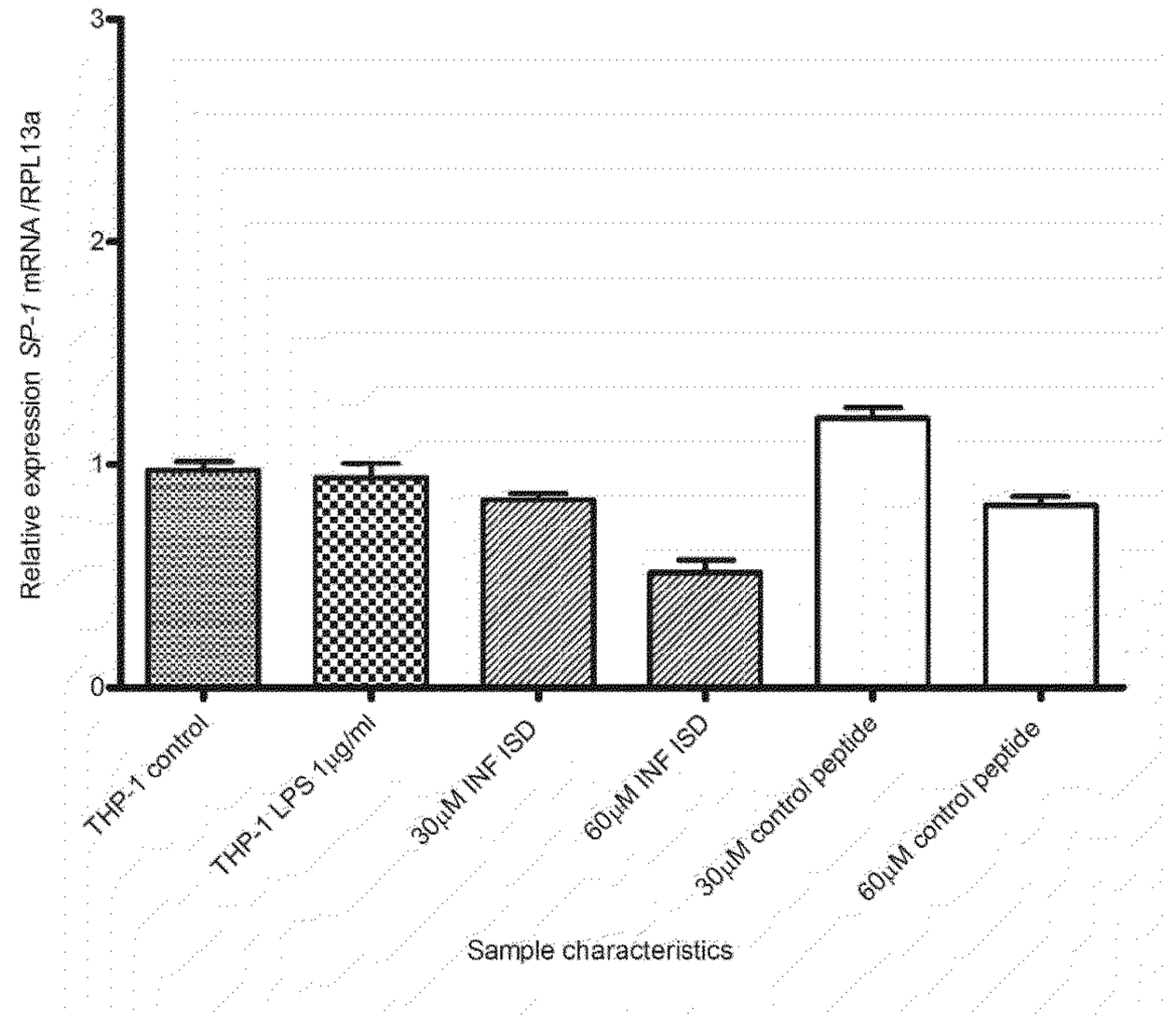

3
2
1
0
Relative expression SP-1 mRNA /RPL13a
THP-1 control
THP-1 LPS 1µg/ml
30µM INF ISD
60µM INF ISD
30µM control peptide
60µM control peptide
Sample characteristics

Fig. 12

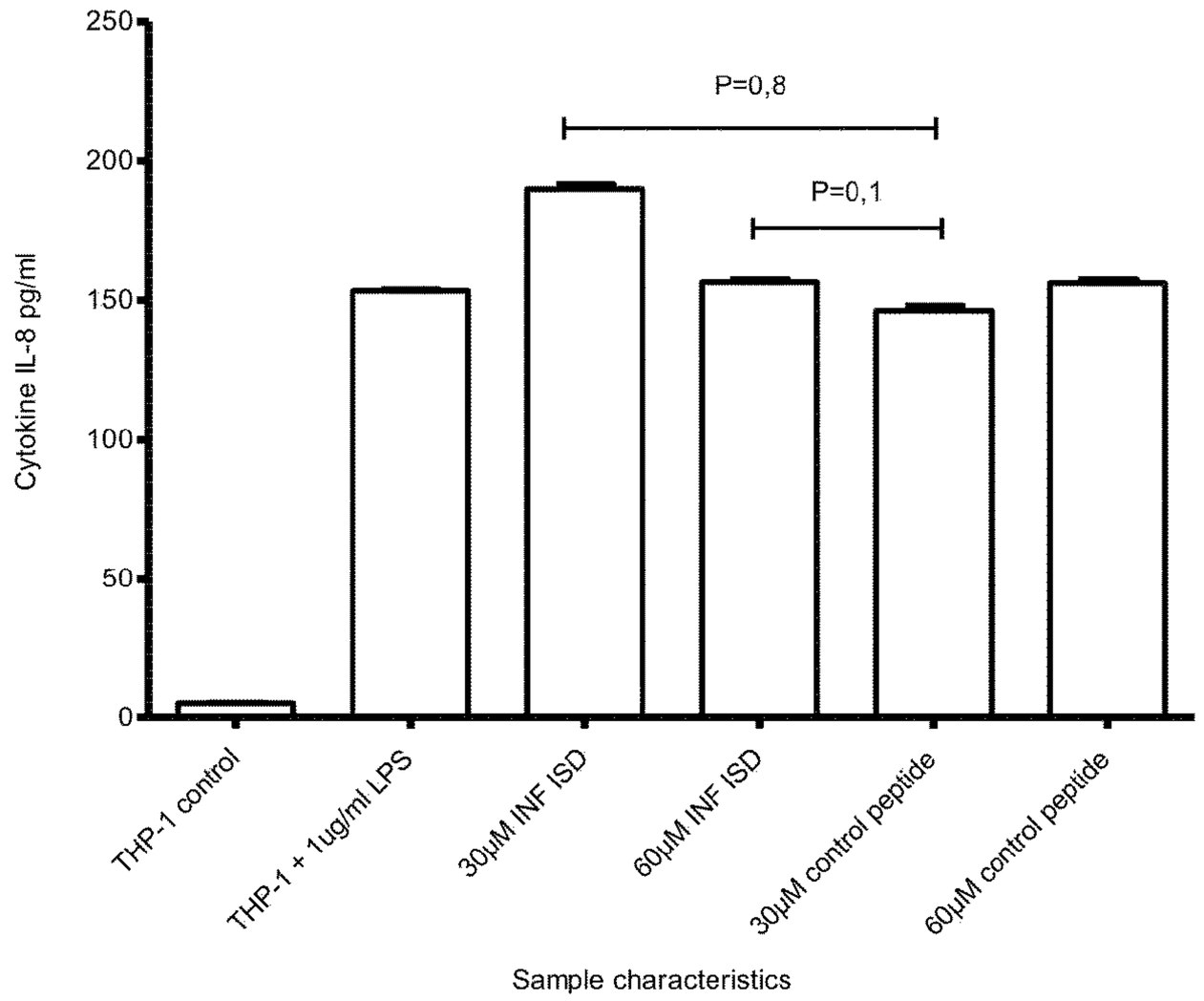

250
200
150
100
50
0
Cytokine IL-8 pg/ml
P=0,8
P=0,1
THP-1 control
THP-1 + 1ug/ml LPS
30µM INF ISD
60µM INF ISD
30µM control peptide
60µM control peptide
Sample characteristics

Fig. 13

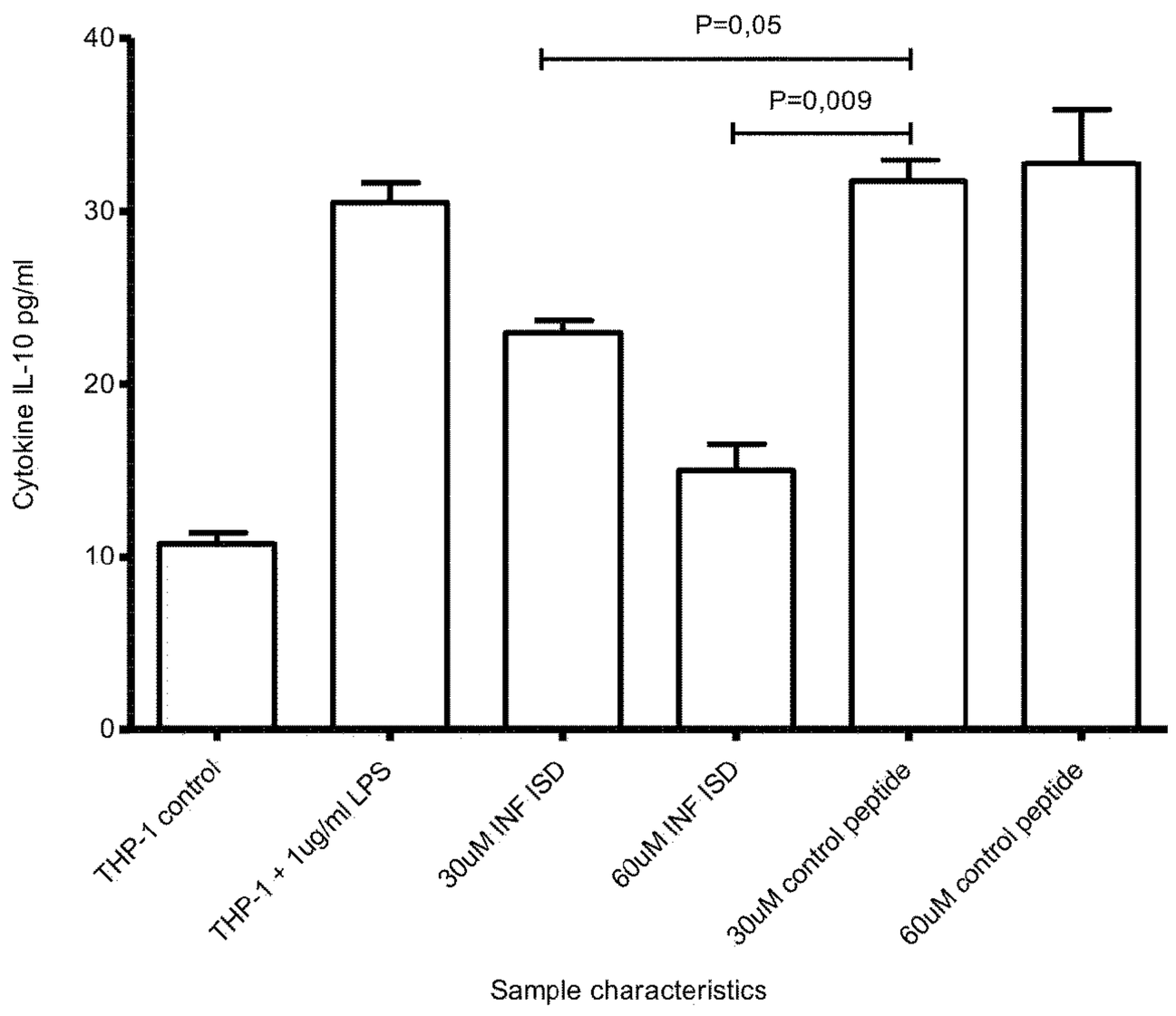

40
30
20
10
0
Cytokine IL-10 pg/ml
P=0,05
P=0,009
THP-1 control
THP-1 + 1ug/ml LPS
30uM INF ISD
60uM INF ISD
30uM control peptide
60uM control peptide
Sample characteristics

Fig. 14

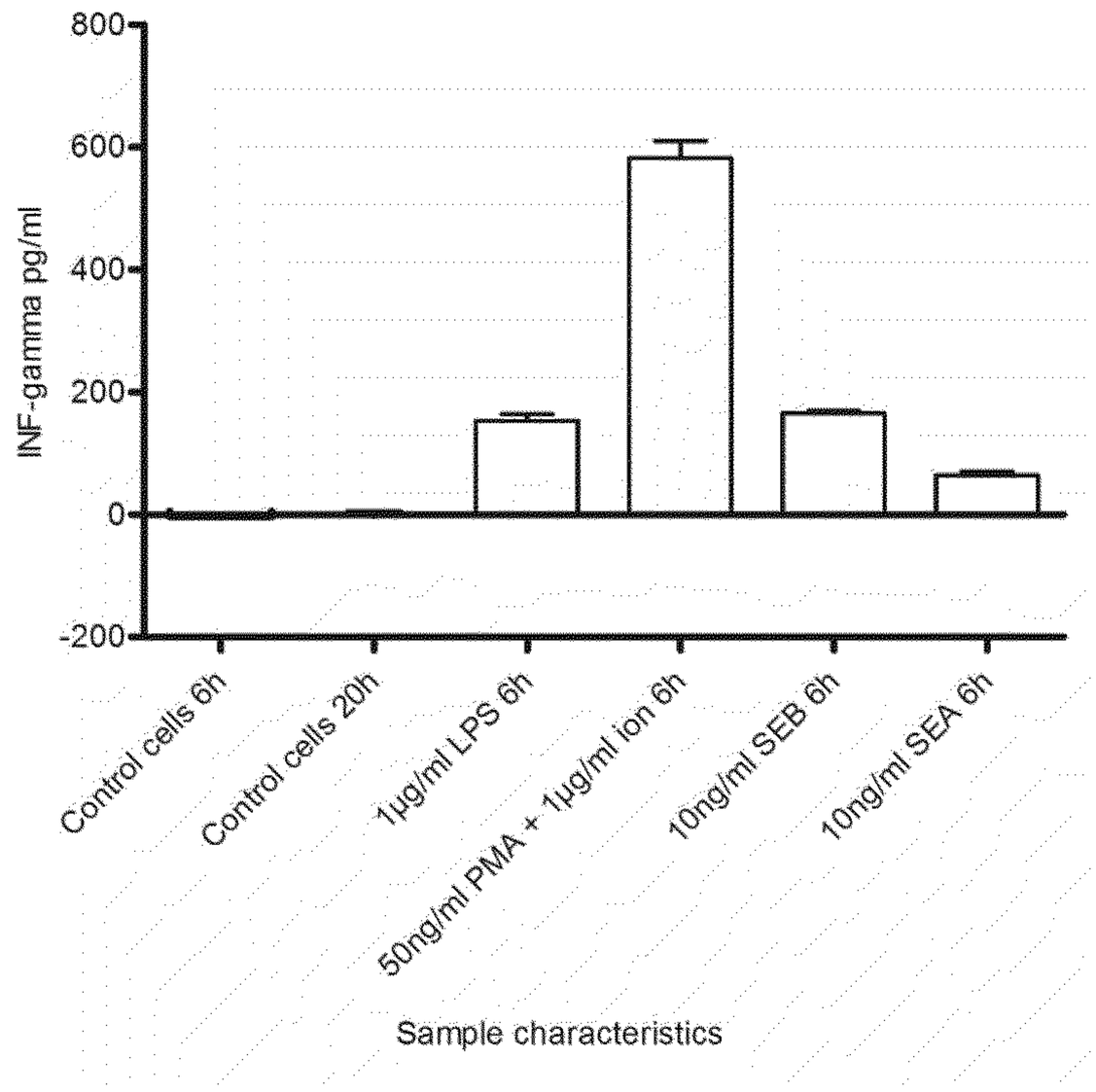

800
600
400
200
0
-200
INF-gamma pg/ml
Control cells 6h
Control cells 20h
1µg/ml LPS 6h
50ng/ml PMA + 1µg/ml ion 6h
10ng/ml SEB 6h
10ng/ml SEA 6h
Sample characteristics

Fig. 15

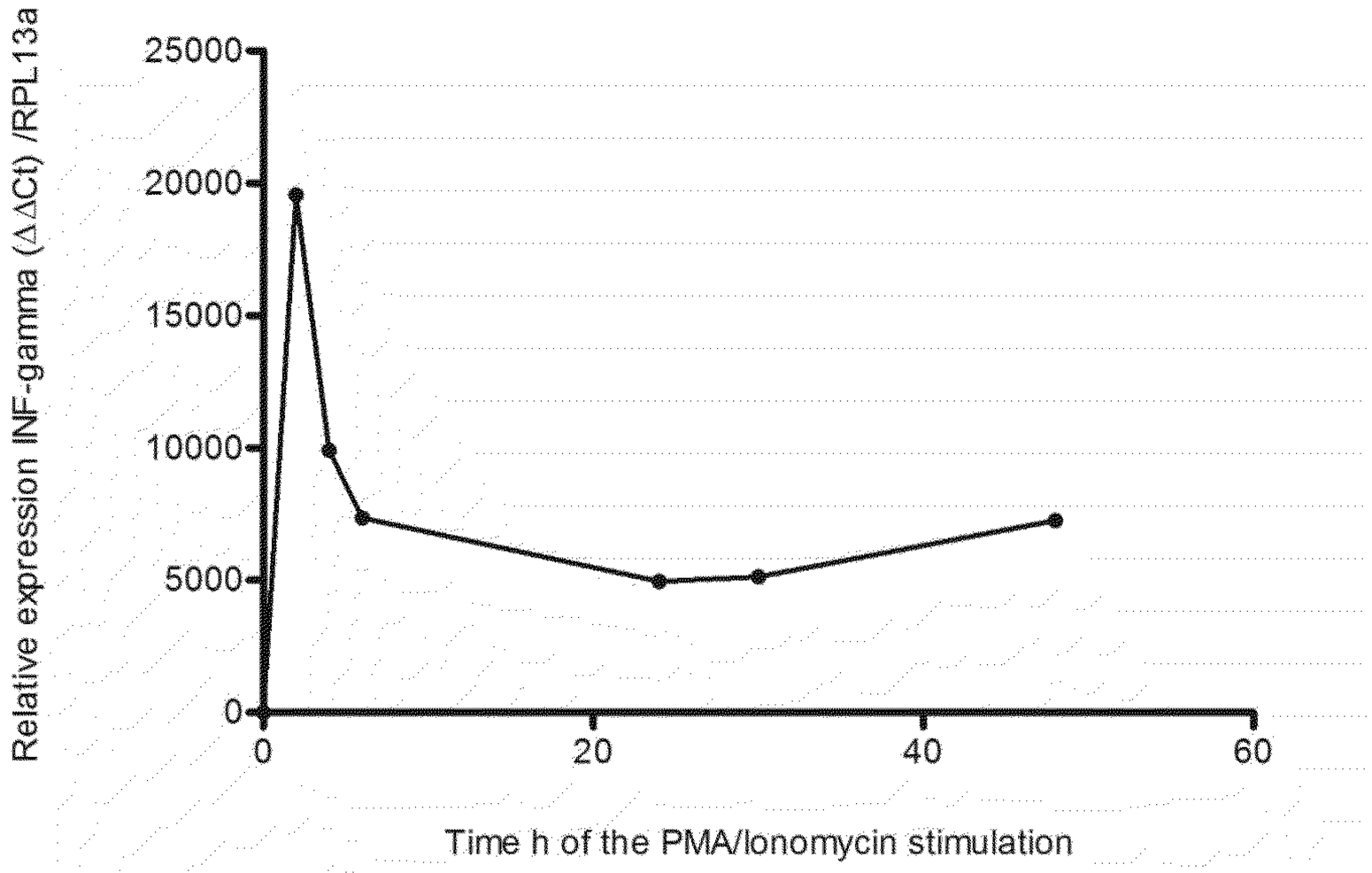

Relative expression INF-gamma (ΔΔCt) /RPL13a
25000
20000
15000
10000
5000
0
0
20
40
60
Time h of the PMA/Ionomycin stimulation

Fig. 16

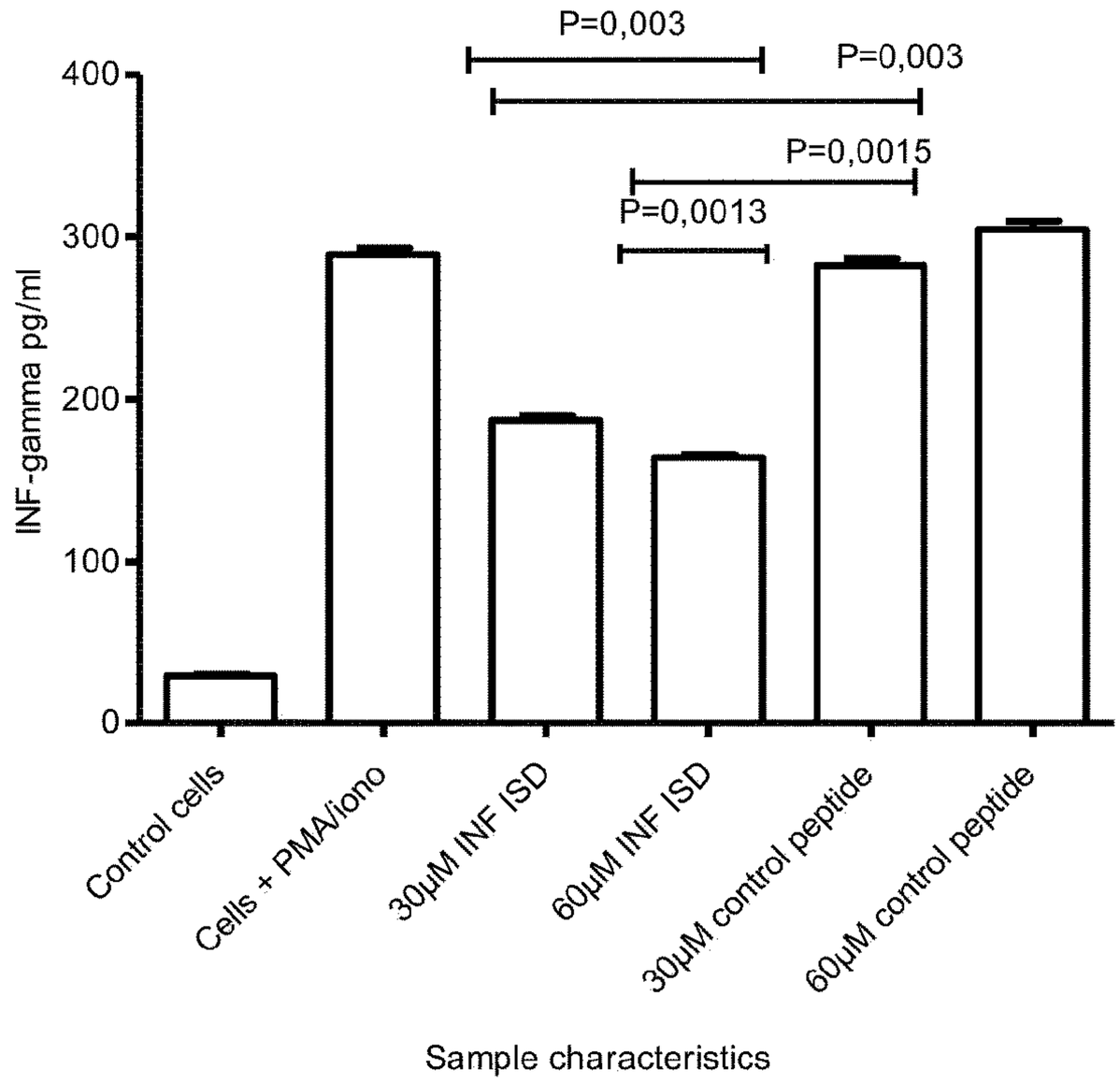

P=0,003
P=0,003
P=0,0015
P=0,0013
400
300
200
100
0
INF-gamma pg/ml
Control cells
Cells + PMA/iono
30µM INF ISD
60µM INF ISD
30µM control peptide
60µM control peptide
Sample characteristics

Fig. 17

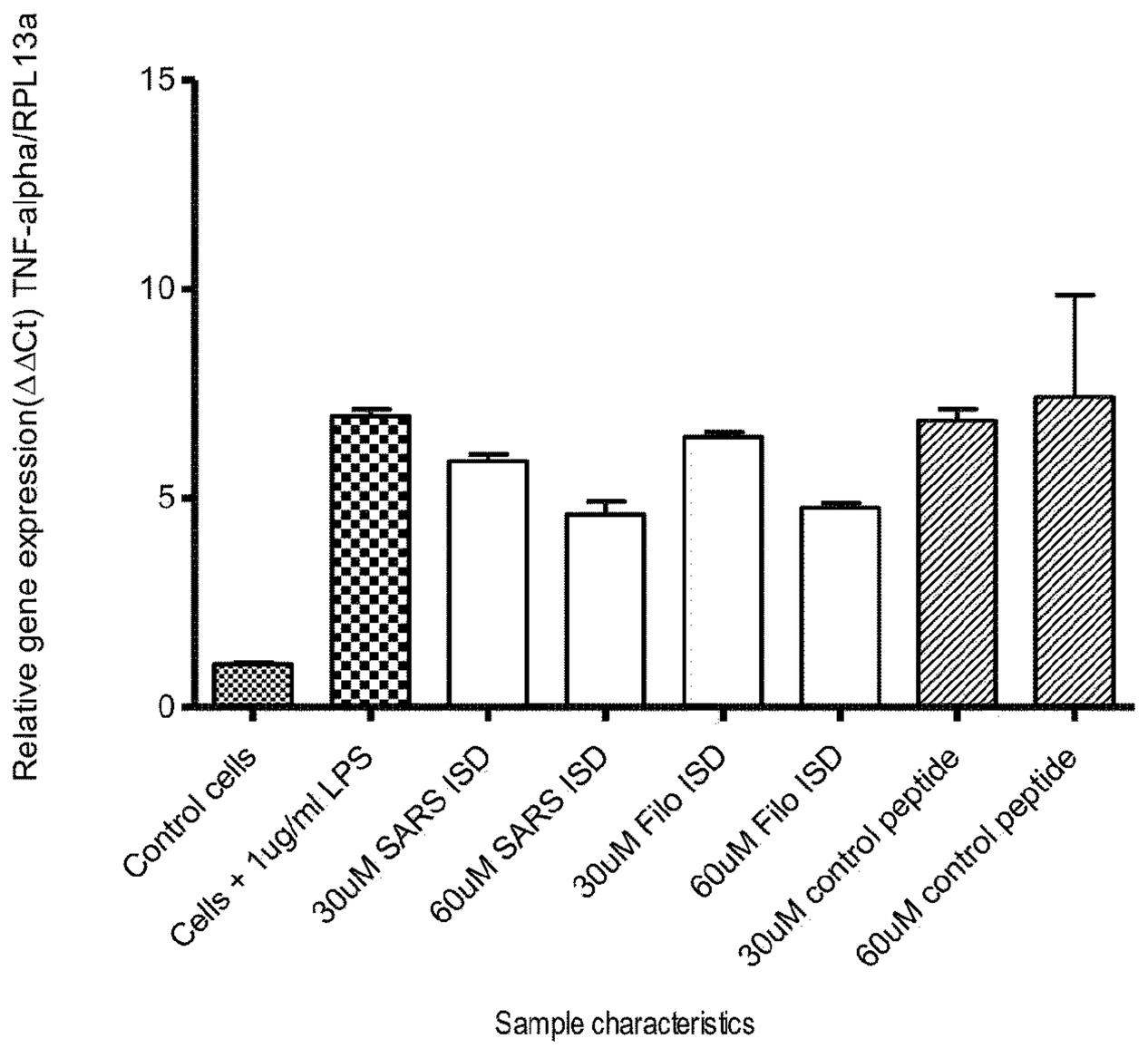

15
10
5
0
Relative gene expression(ΔΔCt) TNF-alpha/RPL13a
Control cells
Cells + 1ug/ml LPS
30uM SARS ISD
60uM SARS ISD
30uM Filo ISD
60uM Filo ISD
30uM control peptide
60uM control peptide
Sample characteristics

Fig. 18

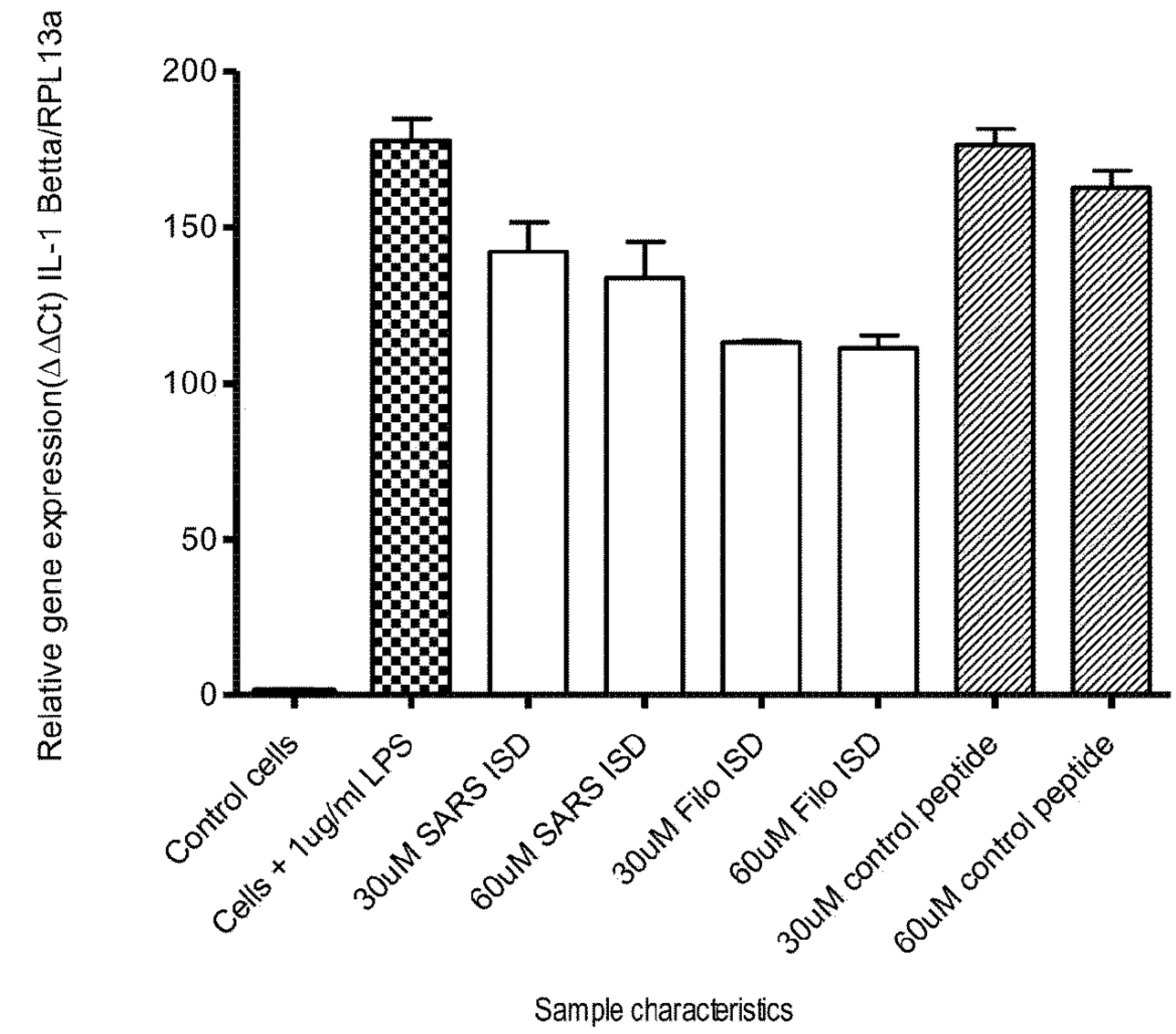

Relative gene expression(ΔΔCt) IL-1 Betta/RPL13a
200
150
100
50
0
Control cells
Cells + 1ug/ml LPS
30uM SARS ISD
60uM SARS ISD
30uM Filo ISD
60uM Filo ISD
30uM control peptide
60uM control peptide
Sample characteristics

Fig. 19

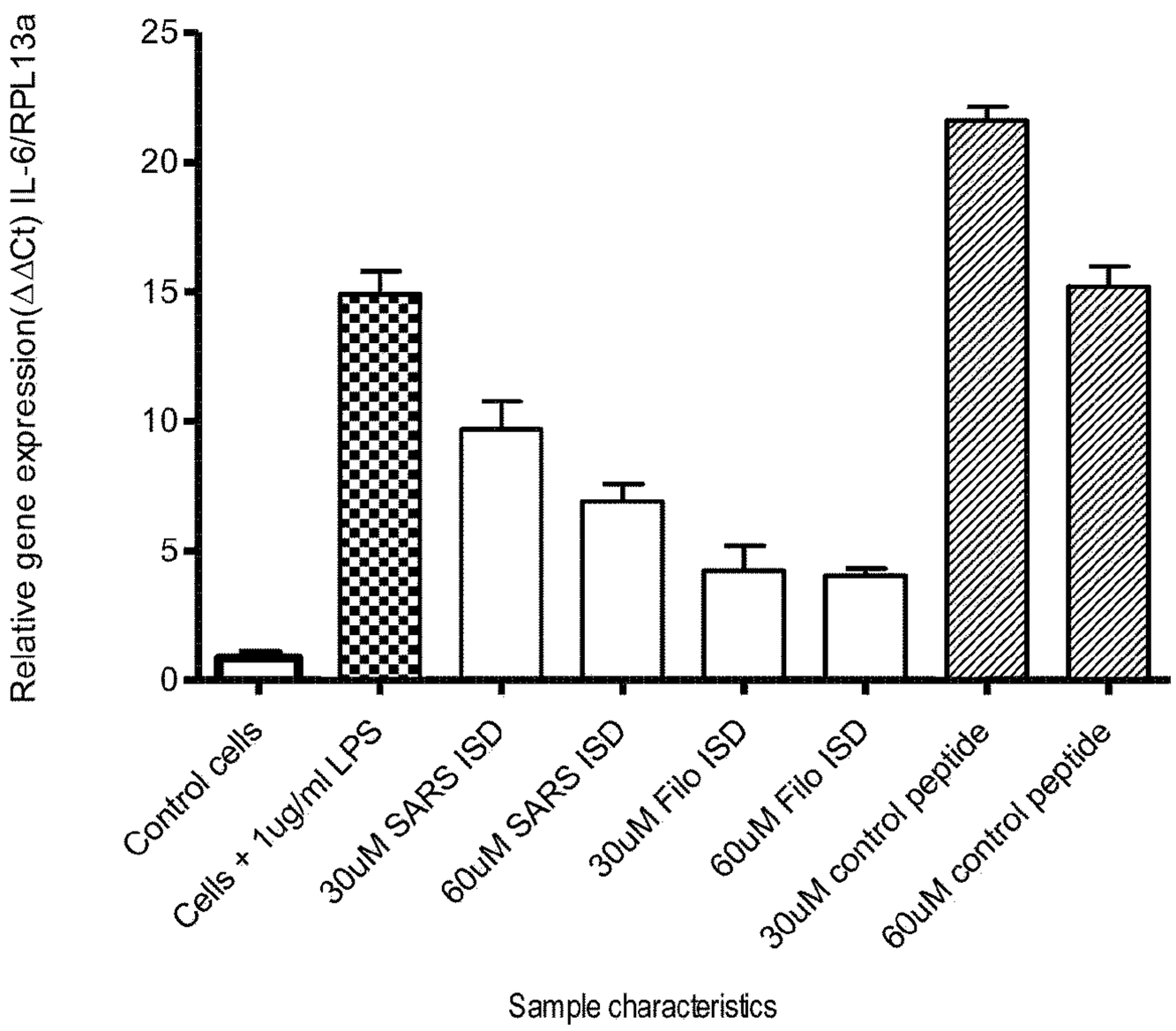

Relative gene expression(ΔΔCt) IL-6/RPL13a
25
20
15
10
5
0
Control cells
Cells + 1ug/ml LPS
30uM SARS ISD
60uM SARS ISD
30uM Filo ISD
60uM Filo ISD
30uM control peptide
60uM control peptide
Sample characteristics

Fig. 20

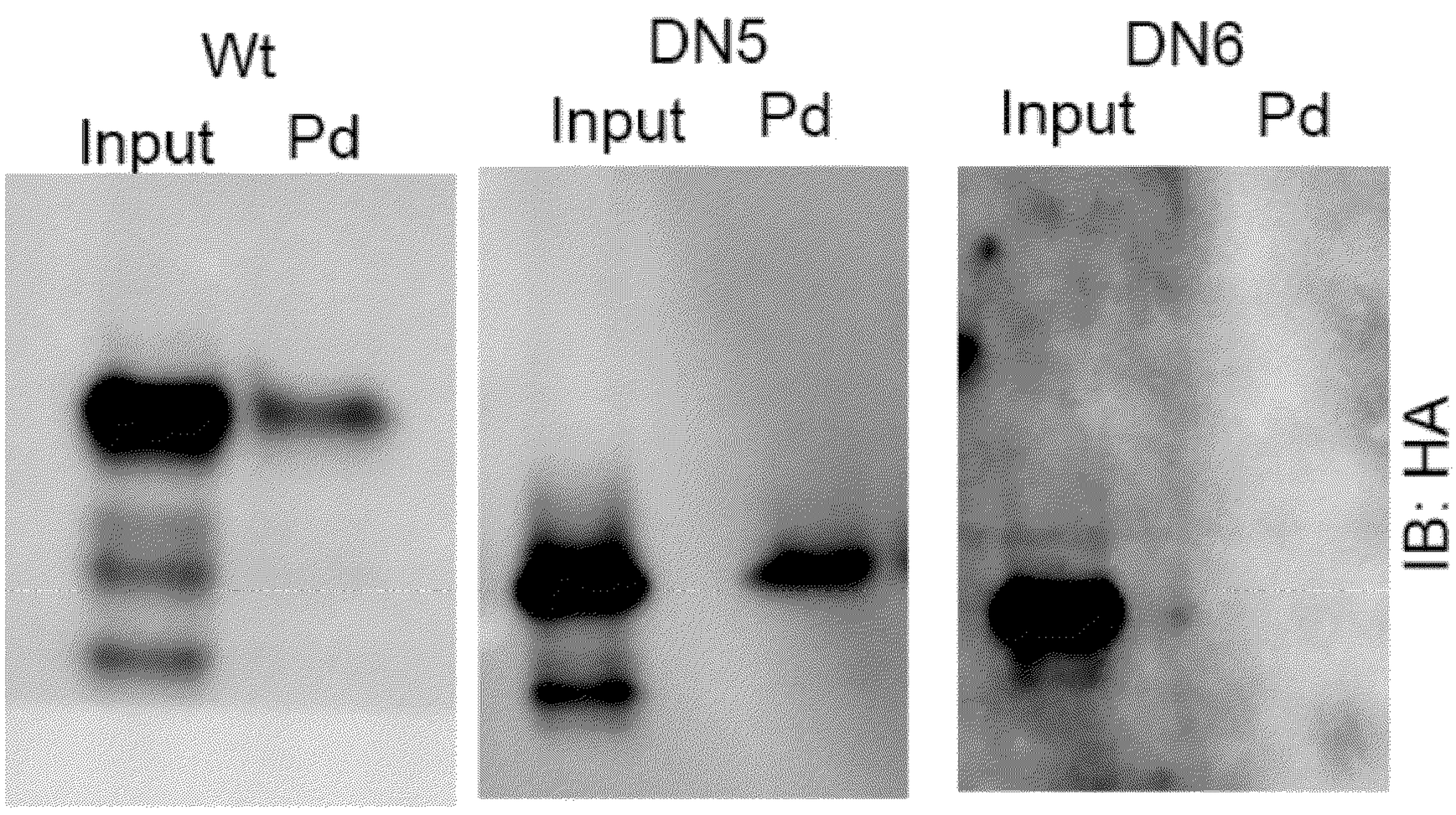


Fig. 21

USE OF IMMUNE SUPPRESSIVE DOMAINS AS MEDICAMENTS

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Appl. No. 14/783,286, filed 8 Oct. 2015, which is the national phase of PCT/DK2014/050091, filed 10 Apr. 2014, and further claims priority to Danish Appl. Nos. PA 2013 70202, filed 10 Apr. 2013, PA 2013 70200, filed 10 Apr. 2013, and PA 2013 70204, filed 11 Apr. 2013. Each of the aforementioned applications is hereby incorporated by reference in its entirety.

TECHNICAL BACKGROUND

[0002] Retroviral infections cause a significant immunosuppression. A small part of the viral glycoprotein induces a significant immunosuppressive effect. This part has been termed the immunosuppressive domain (ISD) and comprise only 17 amino acids. ISD when produced as an isolated 17 amino acid peptide has several effects on the immune response, which among others are: In vitro inhibition of Natural Killer cells, cytotoxic T lymphocytes (CTLs) and inhibition of IL-2 dependent proliferation of T lymphocytes [Cianciolo 1985, Denner 1994, Harrell 1986, Kleinerman 1987]. Furthermore, human endogenous retroviruses can antagonize the immune-dependent elimination of tumor cells injected into immunocompetent mice after transduction of these tumor cells by an envelope-expression vector [Mangeney 1998]. ISD activates intracellular signaling molecules causing inhibition of Th1 cytokines (IL-1a ,IL-2, IL-6 IL-12, INF-α/γ, TNF-α) [Haraguchi 1995, Haraguchi 1995a, Haraguchi 2008, coelcialli 2012]). Finally, a human gene syncytin-2 contains a homologous domain with immunosuppressive activity. This gene is expressed during placental morphogenesis and is believed to be involved in paterno-fetal immune tolerance [Mangeney 2007].

[0003] For sepsis many papers has described the desired effect upon the cytokine profile following treatment. Below are reference for three such papers:

[0004] In one investigation plasma levels of critically ill patients of resistin, active PAI-1, MCP-1, IL-1 alpha, IL-6, IL-8, IL-10, and TNF-alpha were significantly elevated compared to 60 healthy blood donors. Making these cytokines tagets for downregulation by immunosuppressive peptides (BMC Surg. 2010 Sep 9;10:26.Sepsis induced changes of adipokines and cytokines - septic patients compared to morbidly obese patients.Hillenbrand A, Knippschild U, Weiss M, Schrezenmeier H, Henne-Bruns D, Huber-Lang M, Wolf AM. Department of General-, Visceral-, and Transplantation Surgery, University Hospital of Ulm, Steinhoevelstr, Ulm, Germany. Andreas.Hillenbrand@uniklinik-ulm.)

[0005] In a second paper A prospective observational study was used to determine the predictive role of Tumor Necrosis Factor alpha (TNF-α), Interleukin (IL)-1β and IL-6 as three main pro-inflammatory cytokines and Acute Physiology and Chronic Health Evaluation (APACHE II) and Sequential Organ Failure Assessment (SOFA) as two scoring systems in mortality of critically ill patients with severe sepsis. Fifty and five patients with criteria of severe sepsis were included in this study. An exclusion criterion was post Cardiopulmonary Resuscitation (CPR) status. Cytokines (TNF-α, IL-1β and IL-6)were assayed in the first, third and seventh days in blood of patients. RESULTS AND MAJOR CONCLUSION: Among three measured cytokines, sequential levels of TNF-α and IL-6 showed significant differences between survivors and nonsurvivors. IL-6 had a good correlation with outcome and scoring systems during the period of this study. The areas under the receiver operating characteristic (AUROC) curve indicated that APACHE II (0.858, 0.848, 0.861) and IL-6 (0.797, 0.799, 0.899) had discriminative power in prediction of mortality during sequental measured days. Multiple logestic regression analysis identified that evaluation of APACHE II and TNF-α in the first day and APACHE II and IL-6 in the third and seventh days of severe septic patients are independent outcome predictors. Results of this study suggest that IL-6 and APACHE II are useful cytokine and scoring systems respectively in prediction of mortality and clinical evaluation of severe septic patients. (Daru. 2010;18(3):155-62. Identification of enhanced cytokine generation following sepsis. Dream of magic bullet for mortality prediction and therapeutic evaluation. Hamishehkar H, Beigmohammadi MT, Abdollahi M, Ahmadi A, Mahmoodpour A, Mirjalili MR, Abrishami R, Khoshayand MR, Eslami K, Kanani M, Baeeri M, Mojtahedzadeh M. Department of Clinical Pharmacy, aculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran).

[0006] Paper 3: J Immunol. 2010 Oct 1;185(7):4302-10. Epub 2010 Sep 3. The agonists of formyl peptide receptors prevent development of severe sepsis after microbial infection. Kim SD, Kim YK, Lee HY, Kim YS, Jeon SG, Baek SH, Song DK, Ryu SH, Bae YS. Department of Biological Sciences, Sungkyunkwan University, Suwon, South Korea.

Autoimmune Diseases

[0007] Autoimmune diseases arise from an inappropriate immune response of the body against substances and tissues normally present in the body. In other words, the immune system mistakes some part of the body as a pathogen and attacks its own cells. This may be restricted to certain organs (e.g. in autoimmune thyroiditis) or involve a particular tissue in different places (e.g. Goodpasture's disease which may affect the basement membrane in both the lung and the kidney). The treatment of autoimmune diseases is typically with immunosuppression-medication which decreases the immune responseFor autoimmune diseases several papers has described the desired effect upon the cytokine profile following treatment. Below is the abstract and reference for one such

[0008] As described in one paper: The concept of therapeutic vaccination represents a novel strategy of active immunotherapy that can be applied to autoimmune disease. The principle is to design molecules which can trigger an immune response, targeting a cytokine that is pathogenic and over-expressed in a given disease. The mostly available vaccines are an application of vaccination using either the self-protein coupled to a carrier (type I A), or a modified form of the protein engineered to include neo-epitopes (type I B). These approaches have been developed in models of several autoimmune diseases, mainly in TNFα-dependent diseases such as rheumatoid arthritis and Crohn's disease, but also in systemic lupus erythematosus, multiple sclerosis and myasthenia gravis. Clinical trials are in progress in rheumatoid arthritis, Crohn's disease and diabetes. The ben-

efit/risk ratio of anti-cytokine vaccination is currently under study to further develop the vaccination strategies. (Swiss Med Wkly. 2010 Nov 1;140:w13108. doi: 10.4414/smw.2010.13108. Anti-cytokine vaccination in autoimmune diseases. Delavallee L, Duvallet E, Semerano L, Assier E, Boissier MC. University Paris 13, PRES Paris Cité Sorbonne, Bobigny, France. laure.delavallee@upmc.fr).

Asthma

[0009] Asthma is the common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction, and bronchospasm. Symptoms include wheezing, coughing, chest tightness, and shortness of breath. Asthma is clinically classified according to the frequency of symptoms, forced expiratory volume in 1 second (FEV1), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic).

[0010] It is thought to be caused by a combination of genetic and environmental factors. Treatment of acute symptoms is usually with an inhaled short-acting beta-2 agonist (such as salbutamol). Symptoms can be prevented by avoiding triggers, such as allergens and irritants, and by inhaling corticosteroids. Leukotriene antagonists are less effective than corticosteroids and thus less preferred. Its diagnosis is usually made based on the pattern of symptoms and/or response to therapy over time. The prevalence of asthma has increased significantly since the 1970 s. As of 2010, 300 million people were affected worldwide. In 2009 asthma caused 250,000 deaths globally.

[0011] For Asthma several papers has described the desired effect upon the cytokine profile following treatment. Below is the abstract and reference for two such papers:

[0012] The first paper notes that Asthma is a common, disabling inflammatory respiratory disease that has increased in frequency and severity in developed nations. We review studies of murine allergic airway disease (MAAD) and human asthma that evaluate the importance of Th2 cytokines, Th2 response-promoting cytokines, IL-17, and proinflammatory and anti-inflammatory cytokines in MAAD and human asthma. We discuss murine studies that directly stimulate airways with specific cytokines or delete, inactivate, neutralize, or block specific cytokines or their receptors, as well as controversial issues including the roles of IL-5, IL-17, and IL-13Ralpha2 in MAAD and IL-4Ralpha expression by specific cell types. Studies of human asthmatic cytokine gene and protein expression, linkage of cytokine polymorphisms to asthma, cytokine responses to allergen stimulation, and clinical responses to cytokine antagonists are discussed as well. Results of these analyses establish the importance of specific cytokines in MAAD and human asthma and have therapeutic implications. (J Immunol. 2010 Feb 15;184(4):1663-74. Importance of cytokines in murine allergic airway disease and human asthma. Finkelman FD, Hogan SP, Hershey GK, Rothenberg ME, Wills-Karp M. Department of Medicine, Cincinnati Veterans Affairs Medical Center, Cincinnati, OH 45220, USA. finkelman@pol.net).

[0013] The second paper notes that a growing list of cytokines that contribute to the pathogenesis of asthma has been identified. The purpose of this review is to explore the specific cytokines involved in asthma, including their functions, cell sources, and clinical evidence that they participate in asthma. Existing data from clinical trials of cytokine antagonists in asthmatic patients are then reviewed to determine the efficacy and safety of these compounds. RECENT FINDINGS: Cytokine antagonists that have been investigated recently in asthma include monoclonal antibodies directed against interleukin (IL)-5, tumor necrosis factor-alpha (TNF-α), and IL-4/IL-13. Ongoing and future clinical investigations of inhibitors directed at IL-9, IL-13, IL-17, and thymic stromal lymphopoietin may offer potential new agents that will play roles in the treatment of severe asthma. (Curr Opin Pulm Med. 2011 Jan;17(1):29-33. Cytokine inhibition in severe asthma: current knowledge and future directions. Corren J. Research Division, Allergy Medical Clinic, Los Angeles, California 90025, USA. jcorren@ucla.edu).

Arthritis

[0014] Arthritis (from Greek arthro-, joint + -itis, inflammation; plural: arthritides) is a form of joint disorder that involves inflammation of one or more joints.

[0015] There are over 100 different forms of arthritis. The most common form, osteoarthritis (degenerative joint disease), is a result of trauma to the joint, infection of the joint, or age. Other arthritis forms are rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases. Septic arthritis is caused by joint infection.

[0016] The major complaint by individuals who have arthritis is joint pain. Pain is often a constant and may be localized to the joint affected. The pain from arthritis is due to inflammation that occurs around the joint, damage to the joint from disease, daily wear and tear of joint, muscle strains caused by forceful movements against stiff, painful joints and fatigue.

[0017] For Arthritis several papers has described the desired effect upon the cytokine profile following treatment. Below is the abstract and reference for two such papers:

[0018] The first paper sets out to analyze circulating cytokines and regulatory T cells (Treg) in patients with rheumatoid arthritis (RA) of different durations, and their association with functional interleukin 10 (IL-10) and tumor necrosis factor-a (TNF-α) genotypes in patients treated with corticosteroids. METHODS: Serum levels of IL-6, IL-10, IL-17, IL-18, TNF-α, and transforming growth factor-β (TGF-β) were quantified in 196 patients and 61 healthy controls. Percentage of CD4+CD25high cells was determined by flow cytometry and Foxp3 expression by real-time reverse-transcription polymerase chain reaction. Data were related to clinical measurements and presence of the genotype -1082GG IL-10/-308GG TNF-α, previously associated with good response to corticosteroids. RESULTS: Levels of TNF-α, IL-6, and IL-18 were significantly higher in patients compared to controls, while TGF-R and IL-10 were lower. Serum samples of patients at disease onset (n = 32) had increased IL-6 and decreased TGF-β, but there were no differences in other cytokines. These patients also presented a higher percentage of CD4+CD25high cells than those with established disease, although no significant differences were detected in Foxp3. Patients under corticosteroid treatment who were carriers of the good responder genotype had higher levels of TGF-R, Foxp3, and Treg compared to patients with other genotypes, while relatively lower levels of TNF-α and IL-17 were observed. CONCLUSION: Patients at onset of RA present fewer alterations in

cytokine levels and Treg than those with longer disease duration, supporting the role of disease progression in subsequent changes. The antiinflammatory balance observed in high IL-10/low TNF-α patients treated with prednisone supports the use of these genetic polymorphisms as predictors of response to corticosteroid therapy. (J Rheumatol. 2010 Dec; 37(12):2502-10. Epub 2010 Oct 15. Cytokines and regulatory T cells in rheumatoid arthritis and their relationship with response to corticosteroids. de Paz B, Alperi-López M, Ballina-Garcia FJ, Prado C, Gutiérrez C, Suárez A. Department of Functional Biology, Immunology Area, University of Oviedo, Oviedo, Spain.)

[0019] The second paper provides studies of the inflammatory process in the inflamed synovium from rheumatoid arthritis patients have shown an intricate network of molecules involved in its initiation, perpetuation and regulation trial balances the pro- and anti-inflammatory process. This system is self-regulating though the action of anti-inflammatory and pro-inflammatory cytokines cytokine receptor antagonists and naturally occurring antibodies cytokines. Inflammatory synovitis in rheumatoid arthritis (and possibly in other inflammatory arthritidies) appears to be the result of an imbalance in the cytokine network with either an excess production of pro-inflammatory cytokines or from inadequacy of the natural anti-inflammatory mechanisms. Using this knowledge the newer therapeutic approaches to RA and other inflammatory arthritides are being aimed at correcting this imbalance. Monoclonal antibodies to INF-alpha (humanised form of this is called infliximab), soluble TNF-alpha receptors (etanercept) are already in clinical use and adalimumab (humanised TNF-alpha antibody). IL-1Ra is undergoing clinical trials. Other promising therapeutic agents that could regulate the cytokine network are in various stages of laboratory and clinical evaluation. These studies promise to yield therapeutic targets that could dramatically change the way inflammatory diseases would he treated in the future. The now established efficacy of infliximab and etanercept in inflammatory arthritides could be considered just a glimpse of the exciting scenario of the future. (J Assoc Physicians India. 2006 Jun; 54 Suppl:15-8. Cytokine network and its manipulation in rheumatoid arthritis. Malaviya AM. A7R Clinic for Arthritis and Rheumatism, Consultant Rheumatologist Indian Spinal Centre, New Delhi - 110 07.)

Inflammatory Bowel Disease

[0020] In medicine, inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis.

[0021] For Inflammatory bowel disease several papers has described the desired effect upon the cytokine profile following treatment. Below is the abstract and reference for two such papers:

[0022] The first paper discloses that Cytokines play a central role in the modulation of the intestinal immune system. They are produced by lymphocytes (especially T cells of the Th1 and Th2 phenotypes), monocytes, intestinal macrophages, granulocytes, epithelial cells, endothelial cells, and fibroblasts. They have proinflammatory functions [interleukin-1 (IL-1), tumor necrosis factor (TNF), IL-6, IL-8, IL-12] or antiinflammatory functions [interleukin-1 receptor antagonist (IL-1ra), IL-4, IL-10, IL-11, transforming growth factor beta (TGF beta)]. Mucosal and systemic concentrations of many pro- and antiinflammatory cytokines are elevated in inflammatory bowel disease (IBD). An imbalance between proinflammatory and antiinflammatory cytokines was found for the IL-1/IL-1ra ratio in the inflamed mucosa of patients with Crohn's disease, ulcerative colitis, diverticulitis, and infectious colitis. Furthermore, the inhibition of proinflammatory cytokines and the upplementations with antiinflammatory cytokines reduced inflammation in animal models, such as the dextran sulfate colitis (DSS) model, the trinitrobenzene sulfonic acid (TNBS) model, or the genetically engineered model of IL-10 knockout mice. Based on these findings a rationale for cytokine treatment was defined. The first clinical trials using neutralizing monoclonal antibodies against TNF alpha (cA2) or the antiinflammatory cytokine IL-10 have shown promising results. However, many questions must be answered before cytokines can be considered standard therapy for IBD. (World J Surg. 1998 Apr;22(4):382-9. Cytokines in inflammatory bowel disease. Rogler G, Andus T. Department of Internal Medicine I, University of Regensburg, Germany.)

[0023] The second paper discloses that Ulcerative colitis and Crohn's disease are chronic inflammatory disorders of the GI tract. Although the disorders can usually be distinguished on clinical and pathological criteria, there are similarities in natural history and response to therapy. The purpose of this article is to examine the inflammatory infiltrate in both disorders and the cytokine profiles in intestinal mucosa and peripheral blood. For both disorders, the predominant cells in inflamed mucosa are neutrophils and lymphocytes positive for CD4. There are also increases in the number of B cells, macrophages, dendritic cells, plasma cells, eosinophils and perhaps mast cells. Cytokine levels and cytokine expression are also similar for both disorders, with increases in TNF-α and IFN-γ consistent with a Th1 response. As inflammation occurs in a microbial environment, one possibility is that the nature of the inflammatory response is largely independent of initiating factors. One concept that might be useful is that of initiating cells and cytokines and effector cells and cytokines. Persuasive evidence exists for a defect in phagocytic cells in Crohn's disease, perhaps with the expansion of a subset of activated macrophages. There are also possible links to natural killer cells and changes in the regulation of IL-8 and perhaps IL-22. For ulcerative colitis, the cellular events are less clear, but natural killer T cells may be important as initiating cells, and there is some evidence for upregulation of cytokines involved in Th2 responses, including IL-4 and IL-13. For both disorders, proinflammatory cytokines include TNF-α, IL-12, IL-23, and perhaps IL-17 and IFN-γ. Research challenges include the identification, activation and function of subsets of inflammatory cells, as well as new ways to terminate the inflammatory response. (Expert Rev Gastroenterol Hepatol. 2011 Dec;5(6):703-16. Cells, cytokines and inflammatory bowel disease: a clinical perspective. Roberts-Thomson IC, Fon J, Uylaki W, Cummins AG, Barry S. Department of Gastroenterology and Hepatology, The Queen Elizabeth Hospital,Adelaide, South Australia, Australia, ian.roberts-thomson@health.sa.gov.au).

Food Allergy

[0024] A food allergy is an adverse immune response to a food protein. They are distinct from other adverse responses

to food, such as food intolerance, pharmacological reactions, and toxin-mediated reactions.

[0025] The protein in the food is the most common allergic component. These kinds of allergies occur when the body's immune system mistakenly identifies a protein as harmful. Some proteins or fragments of proteins are resistant to digestion and those that are not broken down in the digestive process are tagged by the Immunoglobulin E (IgE). These tags fool the immune system into thinking that the protein is harmful. The immune system, thinking the organism (the individual) is under attack, triggers an allergic reaction. These reactions can range from mild to severe. Allergic responses include dermatitis, gastrointestinal and respiratory distress, including such life-threatening anaphylactic responses as biphasic anaphylaxis and vasodilation; these require immediate emergency intervention. Individuals with protein allergies commonly avoid contact with the problematic protein. Some medications may prevent, minimize or treat protein allergy reactions.

[0026] Treatment consists of either immunotherapy (desensitisation) or avoidance, in which the allergic person avoids all forms of contact with the food to which they are allergic. Areas of research include anti-IgE antibody (omalizumab, or Xolair) and specific oral tolerance induction (SOTI), which have shown some promise for treatment of certain food allergies. People diagnosed with a food allergy may carry an injectable form of epinephrine such as an EpiPen, or wear some form of medical alert jewelry, or develop an emergency action plan, in accordance with their doctor.

[0027] The scope of the problem, particularly for young people, is a significant public health issue.

[0028] Food allergy is thought to develop more easily in patients with the atopic syndrome, a very common combination of diseases: allergic rhinitis and conjunctivitis, eczema and asthma. The syndrome has a strong inherited component; a family history of allergic diseases can be indicative of the atopic syndrome.

Food Intolerance

[0029] Food intolerance or non-allergic food hypersensitivity is a term used widely for varied physiological responses associated with a particular food, or compound found in a range of foods.

[0030] Food intolerance is negative reaction, often delayed, to a food, beverage, food additive, or compound found in foods that produces symptoms in one or more body organs and systems, but it is not a true food allergy. A true food allergy requires the presence of Immunoglobin E (IgE) antibodies against the food, and a food intolerance does not.

[0031] Food intolerances can be classified according to their mechanism. Intolerance can result from the absence of specific chemicals or enzymes needed to digest a food substance, as in hereditary fructose intolerance. It may be a result of an abnormality in the body's ability to absorb nutrients, as occurs in fructose malabsorption. Food intolerance reactions can occur to naturally occurring chemicals in foods, as in salicylate sensitivity. Drugs sourced from plants, such as aspirin, can also cause these kinds of reactions. Finally, it may be the result of non-IgE-mediated immune responses.

[0032] Non-allergic food hypersensitivity is the medical name for food intolerance, loosely referred to as food hypersensitivity, or previously as pseudo-allergic reactions. Non-allergic food hypersensitivity should not be confused with true food allergies

[0033] Food intolerance reactions can include pharmacologic, metabolic, and gastro-intestinal responses to foods or food compounds. Food intolerance does not include either psychological responses or foodborne illness.

Nanoparticle

[0034] In nanotechnology, a particle is defined as a small object that behaves as a whole unit in terms of its transport and properties. Particles are further classified according to size: in terms of diameter, coarse particles cover a range between 10,000 and 2,500 nanometers. Fine particles are sized between 2,500 and 100 nanometers. Ultrafine particles, or nanoparticles are sized between 100 and 1 nanometers. The reason for this double name of the same object is that, during the 1970-80's, when the first thorough fundamental studies were running with "nanoparticles" in the USA (by Granqvist and Buhrman) and Japan, (within an ERATO Project) they were called "ultrafine particles" (UFP). However, during the 1990s before the National Nanotechnology Initiative was launched in the USA, the new name, "nanoparticle" had become fashionable (see, for example the same senior author's paper 20 years later addressing the same issue, lognormal distribution of sizes). Nanoparticles may or may not exhibit size-related properties that differ significantly from those observed in fine particles or bulk materials. Although the size of most molecules would fit into the above outline, individual molecules are usually not referred to as nanoparticles.

[0035] Nanoparticle research is currently an area of intense scientific interest due to a wide variety of potential applications in biomedical, optical and electronic fields.

[0036] For coating and production of nanoparticles several papers has described the desired effect upon the cytokine profile following injection into the patient. Below is the abstract and reference two such papers:

[0037] The first paper discloses novel adjuvants and antigen-delivery systems with immunomodulatory properties that shift the allergenic Th2 response towards a Th1 or regulatory T cell response are desired for allergen-specific immunotherapy. This study demonstrates that 200-nm sized biodegradable poly(gamma-glutamic acid) (gamma-PGA) nanoparticles (NPs) are activators of human monocyte-derived dendritic cells (MoDCs). Gamma-PGA NPs are efficiently internalized by immature MoDCs and strongly stimulate production of chemokines and inflammatory cytokines as well as upregulation of co-stimulatory molecules and immunomodulatory mediators involved in efficient T cell priming. Furthermore, MoDCs from allergic subjects stimulated in vitro with a mixture of gamma-PGA NPs and extract of grass pollen allergen Phleum pratense (Phl p) augment allergen-specific IL-10 production and proliferation of autologous CD4(+) memory T cells. Thus, gamma-PGA NPs are promising as sophisticated adjuvants and allergen-delivery systems in allergen-specific immunotherapy. (Vaccine. 2010 Jul 12;28(31):5075-85. Epub 2010 May 15. Immunomodulatory nanoparticles as adjuvants and allergen-delivery system to human dendritic cells: Implications for specific immunotherapy. Broos S, Lundberg K, Akagi T, Kadowaki K, Akashi M, Greiff L,

Borrebaeck CA, Lindstedt M. Department of Immunotechnology, Lund University, Lund, Sweden.)

[0038] The second paper has the objective to examine what kinds of cytokines are related to lung disorder by well-dispersed nanoparticles. The mass median diameter of nickel oxide in distilled water was 26 nm. Rats intratracheally received 0.2 mg of nickel oxide suspended in distilled water, and were sacrificed from three days to six months. The concentrations of 21 cytokines including inflammation, fibrosis and allergy-related ones were measured in the lung. Infiltration of alveolar macrophages was observed persistently in the nickel oxide-exposed group. Expression of macrophage inflammatory protein-1alpha showed a continued increase in lung tissue and broncho-alveolar lavage fluid (BALF) while interleukin-1alpha (IL-lalpha), IL-1beta in lung tissue and monocyte chemotactic protein-1 in BALF showed transient increases. Taken together, it was suggested that nano-agglomerates of nickel oxide nanoparticles have a persistent inflammatory effect, and the transient increase in cytokine expression and persistent increases in CC chemokine were involved in the persistent pulmonary inflammation. (Nanotoxicology. 2010 Jun;4(2):161-76. Expression of inflammation-related cytokines following intratracheal instillation of nickel oxide nanoparticles. Morimoto Y, Ogami A, Todoroki M, Yamamoto M, Murakami M, Hirohashi M, Oyabu T, Myojo T, Nishi K, Kadoya C, Yamasaki S, Nagatomo H, Fujita K, Endoh S, Uchida K, Yamamoto K, Kobayashi N, Nakanishi J, Tanaka I. Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Kitakyushu, Fukuoka, Japan, yasuom@-med.uoeh-u.ac.jp).

Biomaterials

[0039] A biomaterial is any matter, surface, or construct that interacts with biological systems. The development of biomaterials, as a science, is about fifty years old. The study of biomaterials is called biomaterials science. It has experienced steady and strong growth over its history, with many companies investing large amounts of money into the development of new products. Biomaterials science encompasses elements of medicine, biology, chemistry, tissue engineering and materials science.

[0040] Biomaterials can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches utilizing metallic components or ceramics. They are often used and/or adapted for a medical application, and thus comprises whole or part of a living structure or biomedical device which performs, augments, or replaces a natural function. Such functions may be benign, like being used for a heart valve, or may be bioactive with a more interactive functionality such as hydroxyapatite coated hip implants. Biomaterials are also used every day in dental applications, surgery, and drug delivery. E.G. A construct with impregnated pharmaceutical products can be placed into the body, which permits the prolonged release of a drug over an extended period of time. A biomaterial may also be an autograft, allograft or xenograft used as a transplant material.

[0041] Materials scientists are currently paying more and more attention to the process inorganic crystallization within a largely organic matrix of naturally occurring compounds. This process typically generally occurs at ambient temperature and pressure. Interestingly, the vital organisms through which these crystalline minerals form are capable of consistently producing intricately complex structures. Understanding the processes in which living organisms are capable of regulating the growth of crystalline minerals such as silica could lead to significant scientific advances and novel synthesis techniques for nanoscale composite materials—or nanocomposites.

[0042] Biomaterials are used in: Joint replacements, Bone plates, Bone cement, Artificial ligaments and tendons, Dental implants for tooth fixation, Blood vessel prostheses, Heart valves, Skin repair devices (artificial tissue), Cochlear replacements, Contact lenses, Breast implants

[0043] Biomaterials must be compatible with the body, and there are often issues of biocompatibility which must be resolved before a product can be placed on the market and used in a clinical setting. Because of this, biomaterials are usually subjected to the same requirements as those undergone by new drug therapies.

[0044] For coating and production of biomaterials several papers has described the desired effect upon the cytokine profile following injection into the patient. Below is the abstract and reference three such papers:

[0045] The first paper discloses that some nickel (Ni) allergic patients develop complications following Ni-containing arthroplasty. In the peri-implant tissue of such patients, we had observed lymphocyte dominated inflammation together with IFN-gamma and IL-17 expression. OBJECTIVES: To determine whether Ni stimulation of peripheral blood mononuclear cells (PBMCs) of such patients would lead to a different cytokine pattern as compared to Ni-allergic patients with symptom-free arthroplasty. PATIENTS AND METHODS: Based on history and patch testing in 15 Ni-allergic patients (five without implant, five with symptom-free arthroplasty, five with complicated arthroplasty) and five non-allergic individuals, lymphocyte transformation test (LTT) was performed using PBMC. In parallel in vitro cytokine response to Ni was assessed by real-time reverse anscriptase-polymerase chain reaction (RT-PCR).

[0046] RESULTS: All 15 Ni-allergic individuals showed enhanced LTT reactivity to Ni (mean SI = 8.42 +/- 1.8) compared to the non-allergic control group. Predominant IFN-gamma expression to Ni was found both in the five allergic patients without arthroplasty and also in the five allergic, symptom-free arthroplasty patients. In contrast, in the five Ni-allergic patients with arthroplasty-linked complications a predominant, significant IL-17 expression to Ni was seen but not in patients with symptom-free arthroplasty. CONCLUSIONS: The predominant IL-17 type response to Ni may characterize a subgroup of Ni-allergic patients prone to develop lymphocytic peri-implant hyper-reactivity. (Contact Dermatitis. 2010 Jul;63(l):15-22. Nickel (Ni) allergic patients with complications to Ni containing joint replacement show preferential IL-17 type reactivity to Ni. Summer B, Paul C, Mazoochian F, Rau C, Thomsen M, Banke I, Gollwitzer H, Dietrich KA, Mayer-Wagner S, Ruzicka T, Thomas P. Klinik und Poliklinik für Dermatologie und Allergologie, Ludwig-Maximilians-Universität, München, Germany. Burkhard.Summer@med.uni-muenchen.de).

[0047] The second paper says that cytokines, chemokines, and growth factors were analyzed periodically over eight weeks from the wound exudate fluid surrounding biomaterials implanted subcutaneously within stainless steel mesh cages. TNF-alpha, MCP-1, MIP-1alpha, IL-2, IL-6, IL-

1beta, VEGF, IL-4, and IL-10 were measured from exudate samples collected from cages containing specimens of polyethylene (PE), polyurethane (PU), or organotin polyvinyl chloride (ot-PVC). Empty cages served as negative controls, and lipopolysaccharide (LPS) served as a positive control. Cytokine, chemokine, and growth factor concentrations decreased from the time of implantation to eight weeks post-implantation, and there was an overall increase in cytokine, chemokine, and growth factor production for material-containing cages compared to empty cages. However, cytokine production was only modestly affected by the different surface chemistries of the three implanted polymeric materials. (Biomaterials. 2009 Jan;30(2):160-8. Epub 2008 Oct 11. In vivo cytokine-associated responses to biomaterials. Schutte RJ, Xie L, Klitzman B, Reichert WM. Department of Biomedical Engineering, Duke University, Durham, NC 27708, USA.)

[0048] The third paper sets out to further elucidate the foreign body reaction, investigation of cytokines at biomaterial implant sites was carried out using a multiplex immunoassay and ELISA. Macrophage activation cytokines (IL-1beta, IL-6, and TNFalpha), cytokines important for macrophage fusion (IL-4 and IL-13), antiinflammatory cytokines (IL-10 and TGFbeta), chemokines (GRO/KC, MCP-1), and the T-cell activation cytokine IL-2 were quantified at biomaterial implant sites. Empty cages (controls) or cages containing synthetic biomedical polymer (Elasthane 80A (PEU), silicone rubber (SR), or polyethylene terephthalate (PET)) were implanted subcutaneously in Sprague-Dawley rats for 4, 7, or 14 days, and cytokines in exudate supernatants and macrophage surface adhesion and fusion were quantified. The presence of a polymer implant did not affect the levels of IL-1beta, TGFbeta, and MCP-1 in comparison to the control group. IL-2 was not virtually detected in any of the samples. Although the levels of IL-4, IL-13, IL-10, and GRO/KC were affected by polymer implantation, but not dependent on a specific polymer, IL-6 and TNFalpha were significantly greater in those animals implanted with PEU and SR, materials that do not promote fusion. The results indicate that differential material-dependent cytokine profiles are produced by surface adherent macrophagesand foreign body giant cells in vivo. (J Biomed Mater Res A. 2009 Apr;89(1):152-9. Quantitative in vivo cytokine analysis at synthetic biomaterial implant sites. Rodriguez A, Meyerson H, Anderson JM. Department of Pathology, Case Western Reserve University, Cleveland, Ohio 44106, USA.)

SUMMARY OF THE INVENTION

[0049] The present invention relates to uses of immune suppressive domains. In particular, the present invention concerns a use of an immune suppressive domain (ISD) for immune suppression and for reduction of inflammation. Further, the invention concerns a class of multifunctional drugs for treatment of inflammatory diseases or as coatings for biomaterial or nanoparticles. Additionally, the invention relates to compositions comprising immunosuppressive polypeptides that are derived from enveloped RNA viruses. The present invention also relates to methods for producing said compositions, as well as the usage of said compositions for treatment of inflammatory disorders or protection of nanoparticles, biomaterials and/or medical devices such as cathedra, implants, plaster, etc to prevent or subdue undesired immunological adverse effects from the host.

[0050] According to an aspect, the present invention relates to compositions of immunosuppressive peptides derived from enveloped RNA viruses.

[0051] In another aspect the present invention relates to compositions of immunosuppressive peptides derived from the fusion peptide of enveloped RNA viruses.

[0052] In third aspect the present invention relates to compositions of immunosuppressive peptides derived from the fusion peptide of influenza virus.

[0053] In fourth aspect the present invention relates to a composition comprising one or more of said immunosuppressive peptides, or part thereof.

[0054] In a fifth aspect the present invention relates to a pharmaceutical composition comprising one or more immunosuppressive peptides and further comprising a pharmaceutical acceptable carrier or salt.

[0055] In a sixth aspect the present invention relates to usage of compositions of said immunosuppressive peptides for treatment of inflammatory disorders.

[0056] In a seventh aspect the present invention relates to usage of compositions of said immunosuppressive peptides for usage for protection of nanoparticles or biomaterials from undesirable immunological adverse reactions.

[0057] In a further aspect the present invention relates to a method of producing a composition comprising immunosuppressive peptides, said method comprising the steps of:

[0058] a) providing one or more immunosuppressive peptides

[0059] b) optionally cross-linking the immunosuppressive peptides provided in step a),

[0060] c) optionally providing a carrier

[0061] d) providing a substance

[0062] e) mixing the peptides of step a) or optionally step b) or step c) with the substance of step d.

[0063] f) obtaining the composition of the present invention.

[0064] According to an additional aspect, the invention concerns an immune suppressive domain for use as a medicament.

[0065] According to another aspect, the invention concerns a use of an immune suppressive domain for the manufacture of a medicament for immune suppression.

[0066] According to an additional aspect, the invention concerns a method for the preparation of a pharmaceutical composition comprising the steps of:

[0067] a. Providing one or more immunosuppressive peptides selected from Seqid 1 to Seqid 287, and optionally cross-linking said one or more immunosuppressive peptides;

[0068] b. Optionally providing a carrier;

[0069] c. Providing a substance;

[0070] d. Mixing the provided one or more peptides with any carrier of optional step b. and the substance of step d. to obtain the pharmaceutical composition.

[0071] According to an additional aspect, the invention concerns a pharmaceutical composition obtainable according to the invention.

[0072] According to another aspect, the invention concerns a pharmaceutical composition comprising an immune suppressive domain as an active substance.

[0073] According to an additional aspect, the invention concerns a use of the composition according to the invention, for treatment of a disease by IV injection.

[0074] According to an additional aspect, the invention concerns the use of the composition according to the inven-

tion, to increase the half-life of nanoparticles or biomaterials in vivo in a patient.

[0075] According to an additional aspect, the invention concerns a vaccine comprising an immune suppressive domain selected among Seqid 275 to 287 against PRRS.

[0076] According to another aspect, the invention concerns a vaccine against PRRS comprising a mutated immunosuppressive domain selected among Seqid 275 to Seqid 287, subject to the proviso that the immunosuppressive properties of said domain have been abrogated.

[0077] According to another aspect, the invention concerns a peptide having the sequence of an Immune Suppressive Domain according to the invention.

[0078] According to an aspect, the invention concerns the use of a peptide according to the invention, said use being selected among any of the uses of Immune Suppressive Domains of the invention.

[0079] According to an aspect, the invention concerns a method of treatment of an indication selected among the indications of the present application and the viral infections of Table 1 comprising administration of an effective amount of an entity selected among the Immune Suppressive Domains of the invention, the compositions of the invention, and the peptides of the invention.

BRIEF DESCRIPTION OF DRAWINGS

[0080] INF ISD peptide is identical to INF-F#2 and are dimeric form of the peptide with the sequence [Seq id 287] GLFGAIAGFIENGWEGCGGEKEKEK

[0081] FIG. **1** shows the effect of the INF ISD peptide on TNF-alpha mRNA levels.

[0082] FIG. **2** shows the effect of peptide incubation on secreted TNF-alpha levels in the supernatant of THP-1 cells.

[0083] FIG. **3** shows the effect of the INF ISD peptide on IL-1 beta mRNA levels in THP-1 cells.

[0084] FIG. **4** shows the effect of the INF ISD peptide on IL-6 mRNA levels in THP-1 cells.

[0085] FIG. **5** shows the effect of the INF ISD peptide on IL-8 mRNA levels in THP-1 cells.

[0086] FIG. **6** shows the effect of the INF ISD peptide on IL-10 mRNA levels in THP-1 cells.

[0087] FIG. **7** shows the effect of the INF ISD peptide on NF-kappa B mRNA levels in THP-1 cells.

[0088] FIG. **8** shows the effect of the INF ISD peptide on the house holding gene RPL13a mRNA levels in THP-1 cells.

[0089] FIG. **9** shows that in the presence of INF F#2, cells treated with LPS release significantly lower amounts of cytokines.

[0090] BM DCs were treated with LPS for 16 hours. Cell supernatants were then collected and analyzed for type I IFN using bioassay. Before LPS treatment cells were either pretreated with INF F#2, with the deletion mutant DI6 or not pretreated with any peptide.

[0091] FIG. **10** shows inflammation-related enzyme and transcription factor gene expression kinetics of THP-1 monocytes stimulated with 1 μg/ml LPS. Gene expression was expressed as relative gene expression towards RPL13a-expression and non-stimulated cells at time zero (ΔΔCt). Data shown are means + standard deviation from two independent biological replications.

[0092] FIG. **11** shows effects of INF ISD peptide on expression of NF-kappaB mRNA in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM, 60 μM INF ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the medians ± standard deviation from two independent biological replications.

[0093] FIG. **12** shows effects of INF ISD peptide on expression of SP-1 mRNA in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM, 60 μM INF ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the medians ± standard deviation from two independent biological replications.

[0094] FIG. **13** shows effects of INF ISD peptide on protein secretion of IL-8 in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM or 60 μM INF ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the median ± standard deviation from three independent experiments performed in duplicates.

[0095] FIG. **14** shows effects of INF ISD peptide on protein secretion of IL-10 in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM or 60 μM INF ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the median ± standard deviation from three independent experiments performed in duplicates.

[0096] FIG. **15** shows effect of different stimulus on the secretion of IFN-gamma in PBMCs. PBMCs were incubated either with 1 μg/ml or 50 ng/ml PMA and 1 μg/ml ionomycin or 10 ng/ml SEB for indicated time periods. Data shown are the medians ± standard deviation from three independent technical replicates.

[0097] FIG. **16** shows expression kinetics of IFN gamma expression in response to PMA/ionomycin treatment. Gene expression was expressed as relative gene expression towards RPL13a expression and non-stimulated cells at time zero (ΔΔ Ct). Data shown are the medians ± standard deviation from three independent technical replicates.

[0098] FIG. **17** shows effect of INF ISD on secretion of protein of IFN-gamma in PMA/ionomycin stimulated PBMCs. PBMCs were incubated with either medium alone, 30 μM or 60 μM Flu ISU or 30 μM or 60 μM control peptide, and stimulated with 50 ng/ml PMA and 1 μg/ml ionomycin. Data shown are the medians ± standard deviation from three independent experiments performed in duplicates.

[0099] FIG. **18** shows effects of SARS ([Seq id 285] AEVQIDRLITGRLQSLQTYVCGGEKEKEK) or Filo ISD ([Seq id 286] GAAIGLAWIPYFGPAAECGGEKEKEK) on expression of TNF-alpha mRNA in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM, 60 μM SARS or Filo ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the medians ± standard deviation from two independent biological replications.

[0100] FIG. **19** shows effects of SARS or Filo ISD on expression of IL-1 j3 mRNA in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium alone, 30 μM, 60 μM SARS or Filo ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the medians ± standard deviation from two independent biological replications.

[0101] FIG. **20** shows effects of SARS or Filo ISD on expression of IL-1 β mRNA in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either medium

alone, 30 μM, 60 μM SARS or Filo ISD peptide or 30 μM, 60 μM control peptide, and stimulated with 1 μg/ml LPS. Data shown are the medians ± standard deviation from two independent biological replications.

[0102] FIG. **21** shows interactions between INF ISD peptide (pFlu) and STING depends on distinct STING domains. To investigate further the interaction between STING and INF ISD peptide (pFlu) the C-terminal domian of STING was expressed with a HA-tag in HEK293 cells. STING was either in a wt form or with deletions. Lysates from tansfected cells were used for pulldown using biotinylated INF ISD peptide (pFlu) and streptavidin coated beads. The bead eluate was then immunoblotted using antibodies against HA-tag. As seen in the figure wt STING and the deletion mutant DN5 (162-N) was readily pulled down using INF ISD peptide (pFLu) whereas the deletion mutants DN6 (172-N) was not. These data indicate that amino acids 162-172 are necessary for interactions between pFlu and STING.

DETAILED DISCLOSURE

[0103] According to an embodiment, the present invention concerns compositions of one or more immunosuppressive peptides. Immunosuppressive polypeptides are polypeptides that are capable of suppressing an immune response in animals, including human beings and other animal such as domestic or agricultural (cats, dogs, cows, sheep, horses, pigs, etc.) or test species such as mouse, rats, rabbits and the like.

[0104] In one embodiment of the present invention the immunosuppressive polypeptides are capable of at least 5% inhibition of T-lymphocyte proliferation, at least 10%, at least 20%, such as at least 30%, at least 40%, at least 50%, such as at least 60%, such as at least 70% inhibition of T-lymphocyte proliferation. In particular embodiments the immunosuppressive peptides of the present invention are capable of at least 75% inhibition of T-lymphocyte proliferation, at least 80%, such as at least 85%, at least 90%, such as at least 95%, at least 97%, such as at least 99%, at least 100% inhibition of T-lymphocyte proliferation.

[0105] According to another embodiment of the present invention the immunosuppressive polypeptides are capable of suppressing the immune response in an animal suffering from a general skin inflammation according to the TPA model, an irritant contact dermatitis model, as described herein below. According to the present invention, the immunosuppressive polypeptides of the present invention are capable of reducing the ear thickening in mice challenged with phorbol 12-myristate 13-acetate (TPA), the ear thickening being reduced with at least 5%, such as least 10%, at least, 15%, at least 20%, such as at least 25%, at least 30%, at least 35%, such as at least 40%, at least 45%, such as at least 50%, at least 55%, such as at least 60%, at least 65%, such as at least 70%, at least 75%, such as at least 80%, at least 85% reduction of ear thickening following TPA challenge.

[0106] Hence, the present invention comprise one or more immunosuppressive peptides, such as 2, for example 3, such as 4, such as 5, for example 6, such as 7, such as 8, for example 9, such as 10, such as 11, for example 12, such as 13, such as 14, for example 15, such as 16, such as 17, for example 18, such as 19, such as 20 immunosuppressive peptides.

[0107] The present invention may comprise the same immunosuppressive polypeptide, or the compositions may comprise different immunosuppressive polypeptides. In one embodiment of the present invention, the immunosuppressive polypeptides are monomeric. In another embodiment of the present invention the immunosuppressive polypeptides are dimeric. In another embodiment of the present invention the immunosuppressive polypeptides are trimeric. In yet another embodiment of the present invention the immunosuppressive polypeptides are multimeric. Thus, according to the present invention the immunosuppressive polypeptides may be monomeric, homologous dimeric, heterologous dimeric, homologous trimeric, heterologous trimeric, homologous multimeric and/or heterologous multimeric. In a particular preferred embodiment the immunosuppressive polypeptides of the present invention are homologous dimeric.

[0108] Additionally, the present invention may comprise combinations of di-, tri-and/or multimeric immunosuppressive peptides. In one embodiment the present invention comprises homologues dimeric peptides in combination with other homologous dimeric peptides. In another embodiment the invention comprises homologous dimeric peptides in combination with heterologous dimeric peptides. The following combinations of peptides are also within the scope of this invention: homologous dimeric peptides with homologous trimeric, homologuos dimeric with heterologous trimeric, heterologous dimeric with homologous trimeric, heterologous dimeric with heterologous trimeric, homologous dimeric with homologous multimeric, heterologous dimeric with homologous multimeric, homologous dimeric with heterologous multimeric, heterologous dimeric with heterologous multimeric, homologous trimeric with homologous multimeric, homologous trimeric with heterologous multimeric, heterologous trimeric with homologous multimeric and heterologous trimeric with heterologous multimeric immusuppressive peptides.

[0109] In certain embodiments of the present invention the immunosuppressive polypeptides are homologous dimers, such as homologous dimers formed by two of the peptides SEQ ID NO: 4, and/or two of the peptides with SEQ ID NO: 119, and/or two of the peptides with SEQ ID NO: 120, and/or two of the peptides with SEQ ID NO: 121, and/or two of the peptides with SEQ ID NO: 122, and/or two of the peptides with SEQ ID NO: 123, and/or two of the peptides with SEQ ID NO: 124, and/or two of the peptides with SEQ ID NO: 125, and/or two of the peptides with SEQ ID NO: 126. In one embodiment the monomeric peptides are cross-linked into a dimer by cross-linking the peptides N-terminal to N-terminal or C-terminal to C-terminal. I a preferred embodiment the peptides are cross-linked via a disulfide bond wherein the peptides are cross-linked C-terminal to C-terminal.

[0110] In other certain embodiments of the present invention the immunosuppressive polypeptides are heterologous dimers, such as heterologus dimers formed by two peptides in the following combinations: SEQ ID NO: 4 with SEQ ID NO: 119; and/or SEQ ID NO: 4 with SEQ ID NO: 120, and/or SEQ ID NO: 4 with SEQ ID NO: 121, and/or SEQ ID NO: 4 with SEQ ID NO:122, and/or SEQ ID NO: 4 with SEQ ID NO: 123, and/or SEQ ID NO: 4 with SEQ ID NO: 124, and/or SEQ ID NO: 4 with SEQ ID NO: 125, and/or SEQ ID NO: 4 with SEQ ID NO: 126 and/or with a sequence selected from SEQ ID NO: 119 to 126 with a sequence selected from SEQ ID NO: 119 to 126.

[0111] In one embodiment the monomeric peptides are cross-linked into a dimer by cross-linking the peptides N-terminal to N-terminal or C-terminal to C-terminal. I a preferred embodiment the peptides are cross-linked via a disulfide bond wherein the peptides are cross-linked C-terminal to C-terminal.

[0112] The immunosuppressive polypeptides of the present invention may be of different length. However, it is appreciated that the active component of the immunosuppressive peptides have a maximum length of about 100 amino acids, such as about 90 amino acids, for example about 80 amino acids, such as about 70 amino acids, such as about 60 amino acids, for example about 50 amino acids, such as 40 amino acids, for example about 35 amino acids.

[0113] In particular embodiments the length of the active component of the immunosuppressive peptides is 35 amino acids, or 34, or 33, or 32, or 31, or 30, or 29, or 28, or 27, or 26, or 25, or 24, or 23, or 22, or 21, or 20, or 19, or 18, or 17, or 16, or 15, or 14, or 13, or 12, or11,or10,or9, or 8, or7, or 6, or 5, or 4, or 3 amino acids long. Thus, the immunosuppressive peptides of the present invention have lengths and amino acid sequences corresponding to any of SEQ ID NO:1 to SEQ ID NO:287 as listed herein below. A special feature of the immunosuppressive peptides of the present invention is that they may contain an extra cysteine (Cys or C) residue, either in the N-terminal or C-terminal of the polypeptide. In a particular embodiment the cysteine residue is located in the C-terminal of the peptides. The presence and function of this cysteine residue is primarily so as to crosslink two or more polypeptides together, preferable via disulfide bonds, as described herein below. However, the function of the extra cysteine may be other than that of cross-linking. Thus, the immunosuppressive peptides of the present invention may have amino acid sequences corresponding to any of SEQ ID:1 to SEQ ID:287, and wherein the immunosuppressive peptides further contain an extra cystein (Cys og C) residue at either the N-terminal or C-terminal of the peptide.

[0114] The immusuppressive peptides of the present invention may be a combination of the peptides corresponding to SEQ ID NO:1 to SEQ ID NO:287. Thus also comprise one part of one of the peptides

[0115] Moreover, the present invention also encompasses polypeptides, wherein one or more amino acid residues are modified, wherein said one or more modification(s) are preferably selected from the group consisting of in vivo or in vitro chemical derivatization, such as but not limited to acetylation or carboxylation, glycosylation, such as glycosylation resulting from exposing the polypeptide to enzymes which affect glycosylation, for example mammalian glycosylating or deglycosylating enzymes, phosphorylation, such as modification of amino acid residues which results in phosphorylated amino acid residues, for example phosphotyrosine, phosphoserine and phosphothreonine. The polypeptide according to the invention can comprise one or more amino acids independently selected from the group consisting of naturally occurring L-amino acids, naturally occurring D-amino acids as well as non-naturally occurring, synthetic amino acids. One or more amino acid residues of the polypeptide of the present invention are modified so as to preferably improve the resistance to proteolytic degradation and stability or to optimize solubility properties or to render the polypeptide more suitable as a therapeutic agent. The invention also relates to polypeptides of the invention where blocking groups are introduced in order to protect and/or stabilize the N-and/or C-termini of the polypeptide from undesirable degradation. Such blocking groups may be selected from the group comprising but not limited to branched or non-branched alkyl groups and acyl groups, such as formyl and acetyl groups, as well substituted forms thereof, such as acetamidomethyl. The invention also relates to the following: The polypeptides according to present invention, wherein the one or more blocking groups are selected from N-terminal blocking groups comprising desamino analogs of amino acids, which are either coupled to the N-terminus of the peptide or used in place of the N-terminal amino acid residue. The polypeptide according to present invention, but not limited to wherein the one or more blocking groups are selected from C-terminal blocking groups wherein the carboxyl group of the C-terminus is either incorporated or not, such as esters, ketones, and amides, as well as descarboxylated amino acid analogues. The polypeptide according to present invention, wherein the one or more blocking groups are selected from C-terminal blocking groups comprising ester or ketoneforming alkyl groups, such as lower (C1 to C6) alkyl groups, for example methyl, ethyl and propyl, and amide-forming amino groups, such as primary amines (-NH2), and mono-and dialkylamino groups, such as methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino, and the like. The polypeptide according to present invention, wherein free amino group(s) at the N-terminal end and free carboxyl group(s) at the termini can be removed altogether from the polypeptide to yield desamino and descarboxylated forms thereof without significantly affecting the biological activity of the polypeptide. The increased properties may be achieved for example by chemical protection, i.e. by reacting the proteins and peptides of the present invention with protecting chemical groups, or by the incorporation of non-naturally occurring amino acids, e.g. D-amino acids, with the result of prolonging the half-life of the proteins and peptides of the present invention.

Cross-linking

[0116] The immunosuppressive polypeptides of the present invention are suitably used alone, but is preferably coupled to another material or cross-linked to itself to increase its biological or immunological activity, particularly if the polypeptide is relatively short, or to achieve certain properties on the material being coupled. In a specific aspect of this invention, any or all of the immunosuppressive polypeptides may be cross-linked to increase its activity, to facilitate its delivery in vivo, and/or to render the polypeptides resistant towards hydrolysis and/or proteolysis. The cross-linked polypeptide may be formed in situ by allowing the monomers to oxidize (e.g., for disulfide bonds) or it may be synthesized by using a specific cross-linking agent.

[0117] The cross-linking between the polypeptide chains may occur at either end of the polypeptide, or in the middle of the polypeptide, depending on which end is most appropriate. For example, if the N-terminal or the C-terminal of the polypeptides comprises cysteine residues, these are preferably cross-linked by linking it to another cysteine residue on another homologous or heterologous polypeptide of the present invention, thereby forming a disulfide bond. Preferably the immunosuppressive polypeptides of the present

invention are cross-linked by disulfide bonds at the C-terminal.

[0118] Polypeptide chains may be polymerized by cross-linking agents, either directly or indirectly through multifunctional polymers. Two polypeptides may be cross linked at their C-or N-termini using a multifunctional cross-linking agent. The agent is used to cross-link the terminal amino-or carboxyl groups. Generally, both terminal carboxyl groups or both terminal amino groups are crosslinked to one another, although by selection of the appropriate crosslinking agent the alpha amino group of one polypeptide is crosslinked to the terminal carboxyl group of the other polypeptide. Preferably, the polypeptides are substituted at their C-termini with cysteine. Under conditions well known in the art a disulfide bond can be formed between the terminal cysteines, thereby cross-linking the polypeptide chains.

[0119] Additional cross-linking sites on the polypeptides, include epsilon amino groups found on lysine residues, as well as amino, imino, carboxyl, sulfhydryl and hydroxyl groups located on the side chains of internal residues of the peptides. Cross-linking through externally added cross-linking agents is obtained, e.g., using any of a number of reagents familiar to those skilled in the art, for example, via carbodiimide treatment of the polypeptides. Other non-limiting examples of suitable multifunctional cross-linking agents include 1,1-bis(diazoacetyl)-2-phenylethane; glutaraldehyde; Nhydroxysuccinimide esters such as esters with 4-azidosalicylic acid; homobifunctional imidoesters including disuccinimidyl esters such as 3,3′-dithiobis (succinimidylpropionate) and dimethyl adipimidate dihydrochloride, bifunctional maleimides such as bis-N-maleimidol,8-octane; disuccinimidyl suberate, and bis(sulfosuccinimidyl) suberate.

[0120] Heterobifunctional cross-linking reagents include those with an N-hydroxysuccinimide moiety at one end and a maleimido group on the other end; succinimidyl 4-(Nmaleimidomethyl)cyclohexane-1-carboxylate (SMCC), sulfo-SMCC, mmaleimidobenzoyl-N-hydroxysuccinimide ester (MBS); sulfo-MBS; suceinimidyl 4-(pmaleimidophenyl)butyrate (SMPB); sulfo-SMPB; N-succinimidyl(4-iodoacetyl)aminobenzoate (SlAB); sulfo-SIAB; 1-ethyl-3-(3dimethylaminopropyl)carbodiimide hydrochloride (EDC); and Nhydroxysulfosuccinimide. Cross-linking agents such as methyl-3-[(p-azido-phenyl)dithio) propioimidate yield photoactivatable intermediates which are capable of forming cross-links in the presence of light. If necessary, sensitive residues such as the side chains of the diargininyl group are protected during cross-linking and the protecting groups removed thereafter.

[0121] Polymers capable of multiple cross-linking serve as indirect cross-linking agents. For example, cyanogen bromide activated carbohydrates may be used for cross-linking the peptides herein. Cross-linking to amino groups of the peptides is accomplished by known chemistries based upon eyanuric chloride, carbonyl diimidazole, aldehyde reactive groups (PEG alkoxide plus diethyl acetal of bromoacetaldehyde; PEG plus DMSO and acetic anhydride, or PEG chloride plus the phenoxide of 4-hydroxybenzaldehyde). Also useful are succinimidyl active esters, activated dithiocarbonate PEG, and 2,4,5-trichlorophenylchloroformate-or pnitrophenylchloroformate-activated PEG. Carboxyl groups are derivatized by coupling PEG-amine using carbodiimide.

Administration Forms, Formulations and Dosage Regimes

[0122] Pharmaceutical compositions containing a composition of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practice of Pharmacy 1995, edited by E. W. Martin, Mack Publishing Company, 19th edition, Easton, Pa. The compositions may appear in conventional forms, for example suspensions or topical applications such as a solution, gel, cream, lotion, shake lotion, ointment, foam, shampoo, mask or similar forms. But also patches, gazes and bandages and the like may be used for topical application of the composition of the present invention.

[0123] Whilst it is possible for the compositions or salts of the present invention to be administered as the raw chemical, it is preferred to present them in the form of a pharmaceutical formulation. Accordingly, the present invention further provides a pharmaceutical formulation, for medicinal application, which comprises a composition of the present invention or a pharmaceutically acceptable salt thereof, as herein defined, and a pharmaceutically acceptable carrier therefore.

[0124] The pharmaceutical compositions and dosage forms may comprise the compositions of the invention or its pharmaceutically acceptable salt or a crystal form thereof as the active component. The pharmaceutically acceptable carriers can be either solid, semisolid or liquid. Emulsions may be prepared in solutions in aqueous propylene glycol solutions or may contain emulsifying agents such as lecithin, sorbitan monooleate, or acacia. Aqueous solutions can be prepared by suspending or mixing the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents. Aqueous suspensions can be prepared by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well known suspending agents. Solid form preparations include suspensions and emulsions, and may contain, in addition to the active component, colorants, stabilizers, buffers, artificial and natural dispersants, thickeners, and the like.

[0125] The compositions of the present invention may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, for example solutions in aqueous polyethylene glycol. Examples of oily or nonaqueous carriers, diluents, solvents or vehicles include propylene glycol, polyethylene glycol, vegetable oils (e.g., olive oil), and injectable organic esters (e.g., ethyl oleate), and may contain formulatory agents such as preserving, wetting, emulsifying or suspending, stabilizing or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution for constitution before use with a suitable vehicle, e.g., sterile, pyrogen-free water.

[0126] Oils useful in formulations include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils useful in such formulations include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters.

[0127] Suitable soaps for use in formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides; (b) anionic detergents such as, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c) nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanolamides, and polyoxyethylenepolypropylene copolymers, (d) amphoteric detergents such as, for example, alkyl.beta.-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium salts, and (e) mixtures thereof.

[0128] The formulations typically will contain from about 0.5 to about 25% by weight of the active ingredient in solution. Preservatives and buffers may be used. In order to minimize or eliminate irritation at the site of injection, such compositions may contain one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulations will typically range from about 5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol. The parenteral formulations can be presented in unit-dose or multi-dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, immediately prior to use.

Pharmaceutically Acceptable Salts

[0129] Pharmaceutically acceptable salts of the instant compositions, where they can be prepared, are also intended to be covered by this invention. These salts will be ones which are acceptable in their application to a pharmaceutical use. By that it is meant that the salt will retain the biological activity of the parent composition and the salt will not have untoward or deleterious effects in its application and use in treating diseases.

[0130] Pharmaceutically acceptable salts are prepared in a standard manner. If the parent composition is a base it is treated with an excess of an organic or inorganic acid in a suitable solvent. If the parent composition is an acid, it is treated with an inorganic or organic base in a suitable solvent.

[0131] The compositions of the invention may be administered in the form of an alkali metal or earth alkali metal salt thereof, concurrently, simultaneously, or together with a pharmaceutically acceptable carrier or diluent, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parenteral (including subcutaneous) route, in an effective amount.

[0132] Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

Uses of Compositions Containing Said Immunosuppressive Peptides

[0133] The present invention comprises in one embodiment a pharmaceutical composition and/or compositions for the treatment and/or prevention and/or amelioration of inflammatory disorders. Below is a non-limiting list of the inflammatory disorders that the compositions of the present invention can be used to treat, prevent or ameliorate. The compositions of the present invention may be directed towards the treatment, prevention or amelioration of other inflammatory disorders than the ones listed herein below. The list below may thus be regarded as the inflammatory disorders that in preferred embodiments are target conditions for the compositions of the present invention.

[0134] We anticipate that the immunosuppressive peptides disclosed in this application will be advantageous for treatment of many other types of inflammatory disorders where a reduction of anti-inflammatory responses in the patient is desirable. This is especially valid for diseases/applications where a reduction in the level of cytokines like TNF-α, IL-17, IL-6. Especially for diseases/applications like Arthritis, Asthma, Autoimmune diseases, Sepsis, Inflammatory bowel disease, Coating of biomaterials and nanoparticles where a reduction of one or several of these cytokines has been reported as desirable.

[0135] Below a number of such inflammatory disorders where a decreased immunogenic response is required is described in more detail. The description of relevant diseases should only be considered as examples as many more diseases could be treated these immunosuppressive peptides. Also included is the usage of these immunosuppressive peptides for coating of nanoparticles and biomaterials as a decreased immunogenic response is also desired in these cases to prolong the half-life of these materials, increase biocompatibility or decrease foreign body reactions.

Sepsis

[0136] Sepsis is a potentially deadly medical condition characterized by a whole-body inflammatory state (called a systemic inflammatory response syndrome or SIRS) that is triggered by an infection. The body may develop this inflammatory response by the immune system to microbes in the blood, urine, lungs, skin, or other tissues. A lay term for sepsis is blood poisoning, also used to describe septicaemia. Severe sepsis is the systemic inflammatory response, infection and the presence of organ dysfunction.

[0137] Severe sepsis is usually treated in the intensive care unit with intravenous fluids and antibiotics. If fluid replacement isn't sufficient to maintain blood pressure, specific vasopressor medications can be used. Mechanical ventilation and dialysis may be needed to support the function of the lungs and kidneys, respectively. To guide therapy, a central venous catheter and an arterial catheter may be placed; measurement of other hemodynamic variables (such as cardiac output, mixed venous oxygen saturation, or stroke volume variation) may also be used. Sepsis patients require preventive measures for deep vein thrombosis, stress ulcers and pressure ulcers, unless other conditions prevent this. Some patients might benefit from tight control of blood sugar levels with insulin (targeting stress hyperglycemia). The use of corticosteroids (low dose or otherwise) is contro-

versial. Activated drotrecogin alfa (recombinant protein C) has not been found to be helpful, and has recently been withdrawn from sale.

[0138] In addition to symptoms related to the provoking infection, sepsis is characterized by presence of acute inflammation present throughout the entire body, and is, therefore, frequently associated with fever and elevated white blood cell count (leukocytosis) or low white blood cell count (leukopenia) and lower-than-average temperature, and vomiting. The modern concept of sepsis is that the host's immune response to the infection causes most of the symptoms of sepsis, resulting in hemodynamic consequences and damage to organs. This host response has been termed systemic inflammatory response syndrome (SIRS) and is characterized by an elevated heart rate (above 90 beats per minute), high respiratory rate (above 20 breaths per minute or a partial pressure of carbon dioxide in the blood of less than 32), abnormal white blood cell count (above 12,000, lower than 4,000, or greater than 10% band forms) and elevated or lowered body temperature, i.e. under 36° C. (96.8° F.) or over 38° C. (100.4° F.). Sepsis is differentiated from SIRS by the presence of a known or suspected pathogen. For example SIRS and a positive blood culture for a pathogen indicates the presence of sepsis. However, in many cases of sepsis no specific pathogen is identified.

[0139] This immunological response causes widespread activation of acute-phase proteins, affecting the complement system and the coagulation pathways, which then cause damage to the vasculature as well as to the organs. Various neuroendocrine counter-regulatory systems are then activated as well, often compounding the problem. Even with immediate and aggressive treatment, this may progress to multiple organ dysfunction syndrome and eventually death.

[0140] The term "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to a sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule. Thus, the term "amino acid" comprises any synthetic or naturally occurring amino carboxylic acid, including any amino acid occurring in peptides and polypeptides including proteins and enzymes synthesized in vivo thus including modifications of the amino acids. The term amino acid is herein used synonymously with the term "amino acid residue" which is meant to encompass amino acids as stated which have been reacted with at least one other species, such as 2, for example 3, such as more than 3 other species. The generic term amino acid comprises both natural and non-natural amino acids any of which may be in the "D" or "L" isomeric form.

One-letter symbol	Three-letter symbol	Amino acid (trivial name)
A	Ala	alanine
B	Asx	aspartic acid or asparagine
C	Cys	cysteine
D	Asp	aspartic acid
E	Glu	glutamic acid
F	Phe	phenylalanine

-continued

One-letter symbol	Three-letter symbol	Amino acid (trivial name)
G	Gly	glycine
H	His	histidine
I	Ile	isoleucine
K	Lys	lysine
L	Leu	leucine
M	Met	methionine
N	Asn	asparagine
P	Pro	proline
Q	Gln	glutamine
R	Arg	arginine
S	Ser	serine
T	Thr	threonine
U*	Sec	selenocysteine
V	Val	valine
W	Trp	tryptophan
X	Xaa	unknown or other amino acid, i.e. X can be any of the conventional amino acids.
Y	Tyr	Tyrosine
Z	Glx	glutamic acid or glutamine (or substances such as 4-carboxyglutamic acid and 5-oxoproline that yield glutamic acid on acid hydrolysis of peptides)

[0141] The term "polypeptide" refers to a peptide having at least two, and preferably more than two amino acids. "Monomeric polypeptide" refers to a polypeptide that is a monomer as opposed to a dimer, trimer or polymer in the sense that the monomeric polypeptide is not crosslinked or otherwise bonded to another polypeptide chain. The term "dimer" thus refers to a moiety wherein two monomeric polypeptides are crosslinked to each other. In the same way, a trimeric polypetide refers to a moiety wherein three monomeric polypeptides are crosslinked to each other, while the term "polymer" or "multimer" refers to a moiety wherein at least two polypeptides, and preferably more than three polypeptides are crosslinked to each other.

[0142] The expression "cross-linker" or "cross-linking moiety" refers to a linking moiety conferred by an external cross-linking agent used to crosslink one polypeptide with one or more polypeptides as described further in detail herein below.

[0143] The term "homology" refers to sequence similarity or, interchangeably, sequence identity, between two or more polynucleotide sequences or two or more polypeptide sequences.

[0144] The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the charge and hydrophobicity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

[0145] "Percent identity" may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 6, at least 8,

at least 10, at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

[0146] The term "carrier" refers to a compound that is conjugated to the polypeptide(s) either to increase the number of polypeptides, for increasing activity or immunosuppressive effect of the polypeptide(s), to confer stability to the molecules, to increase the biological activity of the peptides, or to increase its serum half-life. The "carrier" may be a protein carrier or a non-protein carrier. Non-limiting examples of non-protein carriers include liposomes, micelles, polymeric nanoparticles and diaminoethane. The liposome may comprise glycosaminoglycan hyaluronan (HA) and/or PEG. In one embodiment, the carrier is an immunoliposome. Other carriers include protamines,or polysaccharides e.g. aminodextran or chitosan. Non-limiting examples of protein carriers include, keyhole limpet hemocyanin, serum proteins such as transferrin, bovine serum albumin, human serum albumin, whale myoglobin, ovalbumn, immunoglobulins, lysozyme, carbonic anhydrase, or hormones, such as insulin. In other embodiments of the present invention, the carrier may be a pharmaceutical acceptable carrier as described herein below. The immunosuppressive peptides of the present invention may be coupled to the carrier by means of cross-linking as further described herein below.

[0147] The terms "protein modification", "protein stability" and "peptide stability" is used to describe the state of the immunosuppressive proteins and peptides, in particular the state wherein said proteins and/or peptides are more resistant to degradation and/or have increased properties towards hydrolysis and/or proteolysis. In particular, proteolytic stability refers to the resistance toward the action of proteolytic enzymes, also known as proteases, i.e. enzymes that catalyzes the hydrolysis of the amide/peptide-bond of the protein or peptide. Moreover, the present invention also encompasses polypeptides, wherein one or more amino acid residues are modified, wherein said one or more modification(s) are preferably selected from the group consisting of in vivo or in vitro chemical derivatization, such as but not limited to acetylation or carboxylation, glycosylation, such as glycosylation resulting from exposing the polypeptide to enzymes which affect glycosylation, for example mammalian glycosylating or deglycosylating enzymes, phosphorylation, such as modification of amino acid residues which results in phosphorylated amino acid residues, for example phosphotyrosine, phosphoserine and phosphothreonine. The polypeptide according to the invention can comprise one or more amino acids independently selected from the group consisting of naturally occurring L-amino acids, naturally occurring D-amino acids as well as non-naturally occurring, synthetic amino acids. One or more amino acid residues of the polypeptide of the present invention are modified so as to preferably improve the resistance to proteolytic degradation and stability or to optimize solubility properties or to render the polypeptide more suitable as a therapeutic agent. The invention also relates to polypeptides of the invention where blocking groups are introduced in order to protect and/or stabilize the N-and/or C-termini of the polypeptide from undesirable degradation. Such blocking groups may be selected from the group comprising but not limited to branched or non-branched alkyl groups and acyl groups, such as formyl and acetyl groups, as well substituted forms thereof, such as acetamidomethyl. The invention also relates to the following: The polypeptides according to present invention, wherein the one or more blocking groups are selected from N-terminal blocking groups comprising desamino analogs of amino acids, which are either coupled to the N-terminus of the peptide or used in place of the N-terminal amino acid residue. The polypeptide according to present invention, but not limited to wherein the one or more blocking groups are selected from C-terminal blocking groups wherein the carboxyl group of the C-terminus is either incorporated or not, such as esters, ketones, and amides, as well as descarboxylated amino acid analogues. The polypeptide according to present invention, wherein the one or more blocking groups are selected from C-terminal blocking groups comprising ester or ketoneforming alkyl groups, such as lower (C1 to C6) alkyl groups, for example methyl, ethyl and propyl, and amide-forming amino groups, such as primary amines (-NH2), and mono- and dialkylamino groups, such as methylamino, ethylamino, dimethylamino, diethylamino, methylethylamino, and the like. The polypeptide according to present invention, wherein free amino group(s) at the N-terminal end and free carboxyl group(s) at the termini can be removed altogether from the polypeptide to yield desamino and descarboxylated forms thereof without significantly affecting the biological activity of the polypeptide. The increased properties may be achieved for example by chemical protection, i.e. by reacting the proteins and peptides of the present invention with protecting chemical groups, or by the incorporation of non-naturally occurring amino acids, e.g. D-amino acids, with the result of prolonging the half-life of the proteins and peptides of the present invention.

[0148] The term "penetration promoting" or "penetration enhancing" as used herein refers to compounds that facilitate the delivery of the immunosuppressive peptides of the present invention to the target site of action. In particular the term refers to the transcutaneous delivery of the immunosuppressive peptides. Simple topical application of the present invention may not always yield an adequate result, as the outermost layer of the skin provides an outstanding barrier against the external environment. While single penetration enhancers can aid topical delivery, combinations of several penetration enhancers may most effective. The amount of penetration enhancer which may be used in the invention varies from about 1 to 100 percent although adequate enhancement of penetration is generally found to occur in the range of about 1 to about 10 percent by weight of the formulation to be delivered. Non-limiting examples of penetration enahancers are entities that falls within liposomes, transferosomes niosomes and ethosomes, but may also be any of the many hundred known chemical prentration enhancers, of which sulfoxides, azones, pyrrolidones, fatty acids, terpenes and terpenoids, oxazolidinones and urea are non-limiting examples.

[0149] The term "immuno-modulation" as used herein refers to the process of where an immune response is either suppressed, partly or completely, or triggered or induced or enhanced. Likewise, the term "growth-modulation" as used herein refers to the process of were the cell proliferation is either suppressed, partly or completely, or where cell proliferation is induced or enhanced or promoted.

[0150] The term "substance" as used anywhere herein comprises any form of substance suitable for comprising the immunosuppressive polypeptides of the present invention.

[0151] Non-limiting examples of such substances are creams, lotions, shake lostions, ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosoloes as well as transdermal patches and bandages.

[0152] The term "treatment", as used anywhere herein comprises any type of therapy, which aims at terminating, preventing, ameliorating and/or reducing the susceptibility to a clinical condition as described herein. In a preferred embodiment, the term treatment relates to prophylactic treatment, i.e. a therapy to reduce the susceptibility of a clinical condition, a disorder or condition as defined herein.

[0153] Thus, "treatment," "treating," and the like, as used herein, refer to obtaining a desired pharmacologic and/or physiologic effect, covering any treatment of a pathological condition or disorder in a mammal, including a human. The effect may be prophylactic in terms of completely or partially preventing a disorder or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for a disorder and/or adverse affect attributable to the disorder. That is, "treatment" includes (1) preventing the disorder from occurring or recurring in a subject, (2) inhibiting the disorder, such as arresting its development, (3) stopping or terminating the disorder or at least symptoms associated therewith, so that the host no longer suffers from the disorder or its symptoms, such as causing regression of the disorder or its symptoms, for example, by restoring or repairing a lost, missing or defective function, or stimulating an inefficient process, or (4) relieving, alleviating, or ameliorating the disorder, or symptoms associated therewith, where ameliorating is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, such as inflammation, pain, and/or immune deficiency.

[0154] The term "animal" as used herein may be defined to include humans, domestic or agricultural (cats, dogs, cows, sheep, horses, pigs, etc.) or test species such as mouse, rats, rabbits and the like. Thus the anamals may also be of bovine, equine, porcine, human, ovine, caprine or cervidae origin.

[0155] According to an embodiment, the present invention concerns an immune suppressive domain for use as a medicament.

[0156] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is the fusion peptide of an envelope protein.

[0157] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is the fusion peptide of a virus.

[0158] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is the fusion peptide of an enveloped RNA virus.

[0159] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is from a virus.

[0160] The inventors have inter alia identified three new groups of enveloped RNA viruses with immunosuppressive domains in their fusion protein:

[0161] 1: The inventors have identified immunosuppressive domains among enveloped RNA viruses with type II fusion mechanism. Hitherto, immunosuppressive domains have not been described for any enveloped RNA viruses with a type II fusion mechanism. Immunosuppressive domains have been identified by the inventors at two positions in two different groups of viruses:

[0162] i. Co-localizing with the fusion peptide exemplified by the identification of an common immunosuppressive domain in the fusion peptide of Flavirius (Dengue virus, west Nile virus etc), and

[0163] ii. In the hydrophobic alpha helix N-terminal of the transmembrane domain in the fusion protein exemplified by the finding of an immunosuppressive domain in said helixes of all flaviridae e.g. Hepatitis C virus, Dengue, west nile etc.

[0164] 2: The inventors have identified immunosuppressive domains in the fusion protein among enveloped RNA viruses with type I fusion mechanism (excluding lentivirus, retrovirus and filovirus).

[0165] This position co-localizes with the fusion peptide of said fusion protein as demonstrated by the identification of a common immunosuppressive domain in the fusion peptide of all Influenza A and B types.

[0166] 3: The inventors have identified potential immunosuppressive domains located at various positions of type I enveloped RNA viruses (excluding lentivirus, retrovirus and filovirus) as well as in enveloped RNA viruses featuring a fusion protein with neither a type I nor a type II fusion structure.

[0167] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is from an influenza virus.

[0168] According to an embodiment, the invention concerns the immune suppressive domain, wherein said domain is derived from an enveloped RNA virus.

[0169] The expression "derived from a virus" means that the domain is substantially identical to the immune suppressive domain of the virus, optionally with mutations, insertions or deletions.

[0170] According to an embodiment, the invention concerns the immune suppressive domain, subject to the proviso that said immune suppressive domain is different from immunosuppressive domains obeying the conditions of:

[0171] i) being from a virus selected among the group consisting of gammaretrovirus, HIV and filovirus;

[0172] ii) being located in the linker between the two heptad repeat structures just N-terminal of the transmembrane domain in the fusion protein; and

[0173] iii) including at least some of the first 22 amino acids located N-terminal to the first cysteine residue of the two well conserved cystein residues, located between 4 and 6 amino acid residues from one another and further located just N-terminal of the transmembrane spanning domain of the fusion protein.

[0174] The immunosuppressive domains of lentivirus, retroviruses and filoviruses show large structural similarity. Furthermore the immunosuppressive domain of these viruses are all located at the same position in the structure of the fusion protein, more precisely in the linker between the two heptad repeat structures just N-terminal of the transmembrane domain in the fusion protein. These heptad repeat regions constitute two alpha helices that play a critical role in the active mechanism of membrane fusion by these proteins. The immune suppressive domains can be located in

relation to two well conserved cystein residues that are found in these structures. These cystein residues are between 4 and 6 amino acid residues from one another and in many cases are believed to form disulfide bridges that stabilize the fusion proteins. The immune suppressive domains in all three cases include at least some of the first 22 amino acids that are located N-terminal to the first cysteine residue.

[0175] According to an embodiment, the invention concerns the immune suppressive domain, subject to the proviso, that said immune suppressive domain is different from immunosuppressive domains obeying the conditions of:

[0176] i) being from a virus selected among the group consisting of gammaretrovirus, HIV and filovirus; and

[0177] ii) being located in the linker between the two heptad repeat structures just N-terminal of the transmembrane domain in the fusion protein.

[0178] The in this context relevant immunosuppressive domains are all located at a very well-defined structure within their fusion proteins, at the bend in the heptad repeat just N-terminale of the transmembrane structure in the fusion protein.

[0179] According to an embodiment, the invention concerns the immune suppressive domain, wherein said immune suppressive domain is different from immunosuppressive domains from a virus selected among the group consisting of gammaretrovirus, HIV and filovirus.

[0180] According to an embodiment, the invention concerns the immune suppressive domain, wherein the domain is selected among the sequences of Table 1 or sequences seqid 1 to seqid 287.

[0181] According to an embodiment, the invention concerns the immune suppressive domain, wherein the domain is obtainable from the sequences of Table 1 or the sequences seqid 1 to seqid 287, by at least one mutation, deletion or insertion.

[0182] According to an embodiment, the invention concerns the immune suppressive domain, wherein the total number of mutations, deletions or insertions is selected among 1, 2, 3 and 4.

[0183] The term "mutation" is used with a number about this number of point mutation(s), i.e. 3 mutations mean 3 point mutations. The term "deletion" is used with a number about the deletion of this number of amino acid(s), i.e. 2 deletions means the deletion of 2 amino acids. The term "insertion" is used with a number about insertion of this number of amino acid(s), i.e. 1 insertion means the insertion of 1 amino acid.

[0184] According to an embodiment, the invention concerns the immune suppressive domain, wherein the total number of mutations, deletions or insertions is more than 4.

[0185] According to an embodiment, the invention concerns the immune suppressive domain, whereby the obtained immune suppressive domain have abrogated immunosuppressive properties for use in a vaccine against Porcine Reproductive and Respiratory Syndrom (PRRS).

[0186] According to an embodiment, the invention concerns the immune suppressive domain for use in surgery, prophylaxis, therapy, or a diagnostic method.

[0187] According to an embodiment, the invention concerns the immune suppressive domain, wherein the domain is selected among the group consisting of segid 4 and seqid 119 to seqid 126.

[0188] According to an embodiment, the invention concerns the immune suppressive domain, wherein the domain is homologous to seqid 4.

[0189] According to an embodiment, the invention concerns the immune suppressive domain, which is a monomeric peptide.

[0190] According to an embodiment, the invention concerns the immune suppressive domain, cross-linked to at least one additional immunosuppressive peptide.

[0191] According to an embodiment, the invention concerns the immune suppressive domain, connected to at least one additional immunosuppressive peptide to form a dimer.

[0192] According to an embodiment, the invention concerns the immune suppressive domain, wherein said dimer is homologous and comprises at least two immunosuppressive peptides with SEQ ID NO. 4, which are cross-linked by a disulfide bond, N-terminal to N-terminal or C-terminal to C-terminal.

[0193] According to an embodiment, the invention concerns the immune suppressive domain, wherein said dimer is homologous and comprises at least two immunosuppressive peptides selected from SEQ ID NO. 119 to seqid 126, which are cross-linked by a disulfide bond, N-terminal to N-terminal or C-terminal to C-terminal.

[0194] According to an embodiment, the invention concerns the immune suppressive domain, connected to at least one additional immunosuppressive peptide to form a heterologous dimer.

[0195] According to an embodiment, the invention concerns the immune suppressive domain, connected to at least two additional immunosuppressive peptides to form a multimer.

[0196] According to an embodiment, the invention concerns the immune suppressive domain, wherein said immunosuppressive peptides comprises one or more modifications.

[0197] According to an embodiment, the invention concerns the immune suppressive domain, wherein said modifications are selected from the group consisting of chemical derivatizations, L-amino acid substitutions, D-amino acid substitutions, synthetic amino acid substitutions, deaminations and decarboxylations.

[0198] According to an embodiment, the invention concerns the immune suppressive domain, wherein the peptides or proteins have increased resistance against proteolysis compared to peptides or proteins not comprising said at least one modification.

[0199] According to an embodiment, the invention concerns the immune suppressive domain or an immune suppressive peptide according to the invention, for use in diagnostics and/or treatment and/or prevention and/or amelioration of disease.

[0200] According to an embodiment, the invention concerns the immune suppressive domain, wherein the subject is a human or an animal.

[0201] According to an embodiment, the invention concerns the immune suppressive domain, for use on an organ.

[0202] It is envisaged that an ISD may be used for treating an organ, e.g. before transplantation.

[0203] According to an embodiment, the invention concerns the immune suppressive domain for immune suppression.

[0204] According to an embodiment, the invention concerns the immune suppressive domain for the preparation or treatment of transplantation patients.

[0205] According to an embodiment, the invention concerns the immune suppressive domain for a use comprising treatment and/or prevention and/or amelioration of an autoimmune or inflammatory disease.

[0206] According to an embodiment, the invention concerns the immune suppressive domain for a use comprising prophylaxis or treatment of a condition selected among Acute disseminated encephalomyelitis (ADEM), Addison's disease, Agammaglobulinemia, Alopecia areata, Amyotrophic Lateral Sclerosis, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Atopic allergy, Atopic dermatitis, Autoimmune aplastic anemia, Autoimmune cardiomyopathy, Autoimmune enteropathy, Autoimmune hemolytic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune lymphoproliferative syndrome, Autoimmune peripheral neuropathy, Autoimmune pancreatitis, Autoimmune polyendocrine syndrome, Autoimmune progesterone dermatitis, Autoimmune thrombocytopenic purpura, Autoimmune urticaria, Autoimmune uveitis, Balo disease/Balo concentric sclerosis, Behçet's disease, Berger's disease, Bickerstaff's encephalitis, Blau syndrome, Bullous pemphigoid, Cancer, Castleman's disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy, Chronic recurrent multifocal osteomyelitis, Chronic obstructive pulmonary disease, Churg-Strauss syndrome, Cicatricial pemphigoid, Cogan syndrome, Cold agglutinin disease, Complement component 2 deficiency, Contact dermatitis, Cranial arteritis, CREST syndrome, Crohn's disease, Cushing's Syndrome, Cutaneous leukocytoclastic angiitis, Dego's disease, Dercum's disease, Dermatitis herpetiformis, Dermatomyositis, Diabetes mellitus type 1, Diffuse cutaneous systemic sclerosis, Dressler's syndrome, Drug-induced lupus, Discoid lupus erythematosus, Eczema, Endometriosis, Enthesitis-related arthritis, Eosinophilic fasciitis, Eosinophilic gastroenteritis, Epidermolysis bullosa acquisita, Erythema nodosum, Erythroblastosis fetalis, Essential mixed cryoglobulinemia, Evan's syndrome, Fibrodysplasia ossificans progressiva, Fibrosing alveolitis, Gastritis, Gastrointestinal pemphigoid, Glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, Hidradenitis suppurativa, Hughes-Stovin syndrome, Hypogammaglobulinemia, Idiopathic inflammatory demyelinating diseases, Idiopathic pulmonary fibrosis, Idiopathic thrombocytopenic purpura, IgA nephropathy, Inclusion body myositis, Chronic inflammatory demyelinating polyneuropathy, Interstitial cystitis, Juvenile idiopathic arthritis, Kawasaki's disease, Lambert-Eaton myasthenic syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Linear IgA disease (LAD), Lou Gehrig's disease, Lupoid hepatitis, Lupus erythematosus, Majeed syndrome, Ménière's disease, Microscopic polyangiitis, Miller-Fisher syndrome, Mixed connective tissue disease, Morphea, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica, Neuromyotonia, Occular cicatricial pemphigoid, Opsoclonus myoclonus syndrome, Ord's thyroiditis, Palindromic rheumatism, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonage-Turner syndrome, Pars planitis, Pemphigus vulgaris, Pernicious anaemia, Perivenous encephalomyelitis, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progressive inflammatory neuropathy, Psoriasis, Psoriatic arthritis, Pyoderma gangrenosum, Pure red cell aplasia, Rasmussen's encephalitis, Raynaud phenomenon, Relapsing polychondritis, Reiter's syndrome, Restless leg syndrome, Retroperitoneal fibrosis, Rheumatoid arthritis, Rheumatic fever, Sarcoidosis, Schizophrenia, Schmidt syndrome, Schnitzler syndrome, Scleritis, Scleroderma, Serum Sickness, Sjogren's syndrome, Spondyloarthropathy, Still's disease, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sweet's syndrome, Sydenham chorea, Sympathetic ophthalmia, Systemic lupus erythematosis, Takayasu's arteritis, Temporal arteritis, Thrombocytopenia, Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease, Undifferentiated spondyloarthropathy, Urticarial vasculitis, Vasculitis, Vitiligo, and Wegener's granulomatosis.

[0207] According to an embodiment, the invention concerns the immune suppressive domain for the treatment or prevention of acute or chronic inflammation.

[0208] According to an embodiment, the invention concerns the immune suppressive domain for the treatment or prevention of a disorder associated with inflammation.

[0209] According to an embodiment, the invention concerns the immune suppressive domain for the treatment or prevention of a disorder selected among Acne vulgaris, Allergy, Allergic rhinitis, Asthma, Atherosclerosis, Autoimmune disease, Celiac disease, Chronic prostatitis, Glomerulonephritis, Hypersensitivities, Inflammatory bowel diseases, Pelvic inflammatory disease, Reperfusion injury, Rheumatoid arthritis, Sarcoidosis, Transplant rejection, Vasculitis, interstitial cystitis, Cancer, Depression, Myopathies, and Leukocyte defects. These conditions are examples of diseases or conditions associated with inflammation.

[0210] According to an embodiment, the invention concerns the immune suppressive domain for a use comprising prophylaxis or treatment of sepsis.

[0211] According to an embodiment, the invention concerns the immune suppressive domain for a use comprising prophylaxis or treatment of asthma.

[0212] According to an embodiment, the invention concerns the immune suppressive domain for a use comprising prophylaxis or treatment of allergy.

[0213] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for immune suppression.

[0214] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for the preparation or treatment of transplantation patients.

[0215] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of an autoimmune or inflammatory disease.

[0216] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of a condition selected among Acute disseminated encephalomyelitis (ADEM), Addison's disease, Agammaglobuline-

mia, Alopecia areata, Amyotrophic Lateral Sclerosis, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Atopic allergy, Atopic dermatitis, Autoimmune aplastic anemia, Autoimmune cardiomyopathy, Autoimmune enteropathy, Autoimmune hemolytic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune lymphoproliferative syndrome, Autoimmune peripheral neuropathy, Autoimmune pancreatitis, Autoimmune polyendocrine syndrome, Autoimmune progesterone dermatitis, Autoimmune thrombocytopenic purpura, Autoimmune urticaria, Autoimmune uveitis, Balo disease/Balo concentric sclerosis, Behçet's disease, Berger's disease, Bickerstaff's encephalitis, Blau syndrome, Bullous pemphigoid, Cancer, Castleman's disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy, Chronic recurrent multifocal osteomyelitis, Chronic obstructive pulmonary disease, Churg-Strauss syndrome, Cicatricial pemphigoid, Cogan syndrome, Cold agglutinin disease, Complement component 2 deficiency, Contact dermatitis, Cranial arteritis, CREST syndrome, Crohn's disease, Cushing's Syndrome, Cutaneous leukocytoclastic angiitis, Dego's disease, Dercum's disease, Dermatitis herpetiformis, Dermatomyositis, Diabetes mellitus type 1, Diffuse cutaneous systemic sclerosis, Dressler's syndrome, Drug-induced lupus, Discoid lupus erythematosus, Eczema, Endometriosis, Enthesitis-related arthritis, Eosinophilic fasciitis, Eosinophilic gastroenteritis, Epidermolysis bullosa acquisita, Erythema nodosum, Erythroblastosis fetalis, Essential mixed cryoglobulinemia, Evan's syndrome, Fibrodysplasia ossificans progressiva, Fibrosing alveolitis, Gastritis, Gastrointestinal pemphigoid, Glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barre syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, Hidradenitis suppurativa, Hughes-Stovin syndrome, Hypogammaglobulinemia, Idiopathic inflammatory demyelinating diseases, Idiopathic pulmonary fibrosis, Idiopathic thrombocytopenic purpura, IgA nephropathy, Inclusion body myositis, Chronic inflammatory demyelinating polyneuropathy, Interstitial cystitis, Juvenile idiopathic arthritis, Kawasaki's disease, Lambert-Eaton myasthenic syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Linear IgA disease (LAD), Lou Gehrig's disease, Lupoid hepatitis, Lupus erythematosus, Majeed syndrome, Ménière's disease, Microscopic polyangiitis, Miller-Fisher syndrome, Mixed connective tissue disease, Morphea, Mucha-Habermann disease, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica, Neuromyotonia, Occular cicatricial pemphigoid, Opsoclonus myoclonus syndrome, Ord's thyroiditis, Palindromic rheumatism, PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcus), Paraneoplastic cerebellar degeneration, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonage-Turner syndrome, Pars planitis, Pemphigus vulgaris, Pernicious anaemia, Perivenous encephalomyelitis, POEMS syndrome, Polyarteritis nodosa, Polymyalgia rheumatica, Polymyositis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Progressive inflammatory neuropathy, Psoriasis, Psoriatic arthritis, Pyoderma gangrenosum, Pure red cell aplasia, Rasmussen's encephalitis, Raynaud phenomenon, Relapsing polychondritis, Reiter's syndrome, Restless leg syndrome, Retroperitoneal fibrosis, Rheumatoid arthritis, Rheumatic fever, Sarcoidosis, Schizophrenia, Schmidt syndrome, Schnitzler syndrome, Scleritis, Scleroderma, Serum Sickness, Sjogren's syndrome, Spondyloarthropathy, Still's disease, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sweet's syndrome, Sydenham chorea, Sympathetic ophthalmia, Systemic lupus erythematosis, Takayasu's arteritis, Temporal arteritis, Thrombocytopenia, Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease, Undifferentiated spondyloarthropathy, Urticarial vasculitis, Vasculitis, Vitiligo, and Wegener's granulomatosis.

[0217] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of a condition selected among acute or chronic inflammation.

[0218] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of a condition associated with inflammation.

[0219] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of a condition selected among Acne vulgaris, Allergy, Allergic rhinitis, Asthma, Atherosclerosis, Autoimmune disease, Celiac disease, Chronic prostatitis, Glomerulonephritis, Hypersensitivities, Inflammatory bowel diseases, Pelvic inflammatory disease, Reperfusion injury, Rheumatoid arthritis, Sarcoidosis, Transplant rejection, Vasculitis, interstitial cystitis, Cancer, Depression, Myopathies, and Leukocyte defects.

[0220] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of Sepsis.

[0221] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of asthma.

[0222] According to an embodiment, the invention concerns the use of an immune suppressive domain for the manufacture of a medicament for prophylaxis or treatment of allergy.

[0223] According to an embodiment, the invention concerns a method for the preparation of a pharmaceutical composition comprising the steps of:

[0224] a. Providing one or more immunosuppressive peptides selected from Seqid 1 to Seqid 287, and optionally cross-linking said one or more immunosuppressive peptides;

[0225] b. Optionally providing a carrier;

[0226] c. Providing a substance;

[0227] d. Mixing the provided one or more peptides with any carrier of optional step b. and the substance of step d. to obtain the pharmaceutical composition.

[0228] According to an embodiment, the invention concerns the method, wherein said substance of step c. is selected from the group consisting of creams, lotions, shake lotions, ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosols, transdermal patches and bandages.

[0229] According to an embodiment, the invention concerns a pharmaceutical composition obtainable according to the invention.

[0230] According to an embodiment, the invention concerns a pharmaceutical composition comprising an immune suppressive domain as an active substance.

[0231] According to an embodiment, the invention concerns the pharmaceutical composition, wherein said immune suppressive domain is selected among the immune suppressive domains of the invention.

[0232] According to an embodiment, the invention concerns the pharmaceutical composition, further comprising at least one carrier.

[0233] According to an embodiment, the invention concerns the pharmaceutical composition, wherein said at least one carrier is a non-protein carrier and/or a protein carrier.

[0234] According to an embodiment, the invention concerns a use of the composition according to the invention, for treatment of a disease by IV injection.

[0235] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a disease by direct injection at a site of inflammation.

[0236] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a disease by inhalation.

[0237] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a disease by oral delivery.

[0238] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a disease by anal delivery.

[0239] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a condition selected among a skin disease, Psoriasis, Arthritis, Asthma, Sepsis and inflammatory bowel disease.

[0240] According to an embodiment, the invention concerns the use of a composition of the invention for administration in a way selected among IV, IP, and IM.

[0241] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of Arthritis wherein the composition is injected directly at site of inflammation.

[0242] According to an embodiment, the invention concerns the use of a composition of the invention for treatment of a condition selected among Gastrointestinal hyperresponsiveness, Food Allergy, Food intolerance and inflammatory bowel disease, wherein the composition is delivered orally.

[0243] According to an embodiment, the invention concerns the use of a composition of the invention for treatment Asthma where the composition is delivered by inhalation.

[0244] According to an embodiment, the invention concerns the use of a composition of the invention for coating of nanoparticles and biomaterials. The immune suppressive domain may aid in suppressing any immune response e.g. from a patient treated with or subjected to nanoparticles, e.g. for drug delivery or diagnostics, or biomaterials.

[0245] According to an embodiment, the invention concerns the use of a composition of the invention to aid in suppressing any immune response to nanoparticles or biomaterials.

[0246] According to an embodiment, the invention concerns the use of a composition of the invention to increase the half-life of nanoparticles or biomaterials in vivo in a patient.

[0247] According to an embodiment, the invention concerns a vaccine comprising an immune suppressive domain, optionally mutated, for systemic immune suppression.

[0248] According to an embodiment, the invention concerns a vaccine comprising an immune suppressive domain selected among Seqid 275 to 287 against PRRS.

[0249] According to an embodiment, the invention concerns a vaccine comprising a peptide, obtained by performing at least one mutation, insertion or deletion of an immune suppressive domain selected among Seqid 275 to 287.

[0250] According to an embodiment, the invention concerns a vaccine against PRRS comprising a mutated immunosuppressive domain selected among seqid 275 to seqid 287, subject to the proviso that the immunosuppressive properties of said domain have been abrogated.

[0251] According to an embodiment, the invention concerns a peptide having the sequence of the Immune Suppressive Domain according to the invention.

[0252] According to an embodiment, the invention concerns the peptide having the sequence of the Immune Suppressive Domain according to the invention, modified by a number of point mutations selected among 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[0253] According to an embodiment, the invention concerns the peptide having the sequence of the Immune Suppressive Domain according to the invention, modified by a number of point deletions selected among 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[0254] According to an embodiment, the invention concerns the peptide having the sequence of the Immune Suppressive Domain according to the invention, modified by a number of point insertions selected among 1, 2, 3, 4, 5, 6, 7, 8, 9, and 10.

[0255] According to an embodiment, the invention concerns the peptide according to the invention, capable of an inhibition selected among at least 5% inhibition of T-lymphocyte proliferation, at least 10%, at least 20%, such as at least 30%, at least 40%, at least 50%, such as at least 60%, such as at least 70% inhibition of T-lymphocyte proliferation, at least 75% inhibition of T-lymphocyte proliferation, at least 80%, such as at least 85%, at least 90%, such as at least 95%, at least 97%, such as at least 99%, and at least 100% inhibition of T-lymphocyte proliferation.

[0256] According to an embodiment, the invention concerns a peptide according to the invention, capable of suppressing the immune response in an animal, preferably according to the TPA model.

[0257] According to an embodiment, the invention concerns the use of a peptide according to the invention, for a use selected among any of the uses of the invention.

[0258] According to an embodiment, the invention concerns a method of treatment of an indication selected among the indications of the present application and the viral infections of Table 1 comprising administration of an effective amount of an entity selected among the Immune Suppressive Domains of the invention, the compositions of the invention, and the peptides of the invention.

[0259] The co-pending patent application PCT/DK2012/050381 provides a number of immunosuppressive domains. Table 1 is provided below. Sequences of the table are applicable for the purposes of the present invention. Vira of the table provide examples of relevant indications for the present invention.

TABLE 1

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssive domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protein	IU ggroup and fusion type
Flavi-viridae	Flavi-virus	Aroa virus	Bussuquara virus guape virus Naranjal virus	seqid85 NRGWNNGCGLFGKG * * * * * * * * * * * * * * seqid7 GDAAWDFGSVGGVFNSLGK * * o * * * * o * * * * * oo * o * *		envelope protein prME fusion pretein E	Group 1 Type II Fusion mechanism
		Dengue virus	Dengue 1	seqid8 GGTAWDFGSIGGVFTSVGK *o**********	seqid2 DRGWGNGCGLFGKG ********** seqid172 KGS SIGKMFESTYRGAKRMAILG		
			Dengue 2	seqid9 GDTAWDFGSLGGVFTSVGK **********o** seqid173 KGS SIGKMFEATARGARRMAILG	seqid2 DRGWGNGCGLFGKG **********		
			Dengue 3	seqid174 KGSSIGQMFETTMRGAKRMAILG	seqid2 DRGWGNGCGLFGKG ********** seqid204 GDTAWDFGSVGGVLNSLGK **********		
			Dengue 4	seqid10 GETAWDFGSVGGLLTSLGK **********oo***** seqid173 KGSSIGKMFEATARGARRMAILG	seqid2 DRGWGNGCGLFGKG **********		
		Japanese encephalitis virus group	Japanese encephalitis virus	seqid11 LGDTAWDFGSIGGVFNSIG ***o**********	seqid2 DRGWGNGCGLFGKG **********		
			Koutango virus	seqid12 LGDTAWDFGSVGGIFTSLG	seqid2 DRGWGNGCGLFGKG **********		
			Murray Valley encephalitis virus	seqid13 LGDTAWDFGSVGGVFNSIG	seqid2 DRGWGNGCGLFGKG **********		
			St. Louis encephalitis virus	seqid11 LGDTAWDFGSIGGVFNSIG **********	seqid2 DRGWGNGCGLFGKG **********		
			Usutu virus	seqid14 LGDTAWDFGSVGGIFNSVG **********	seqid2 DRGWGNGCGLFGKG **********		
			West Nile virus	seqid15 LGDTAWDFGSVGGVFTSVG **********o********	seqid2 DRGWGNGCGLFGKG **********		
		Kokobera virus group	Kokobera virus unclassified Kokobera virus group	seqid16 IGDDAWDFGSVGGILNSVG	seqid2 DRGWGNGCGLFGKG		
		Modoc virus group	Modoc virus	seqid17 VGSAFWNSDQRFSAINLMD seqid18 DRGWGNGCALFGKG			
			Cowbone Ridge virus Jutiapa virus Sal Vieja virus San Perlita virus				
		mosquito-borne viruses	Ilheus virus	seqid84 LGDTAWDFGSVGGIFNSIG	seqid2 DRGWGNGCGLFGKG		
			Sepik virus	seqid19 TGEHSWDFGSTGGFFASVG	seqid2 DRGWGNGCGLFGKG		
		Ntaya virus group	Bagaza virus	seqid20 LGDTAWDFGSVGGFFTSLG	seqid2 DRGWGNGCGLFGKG		
			Tembusu virus	seqid83 LGDTAWDFGSVGGVLTSIG	seqid2 DRGWGNGCGLFGKG		
			Yokose virus	seqid21 IGDDAWDFGSTGGIFNTIG	seqid2 DRGWGNGCGLFGKG		
		Rio Bravo virus group	Apoi virus	seqid22 SSAFWNSDEPFHFSNLISII	seqid2 DRGWGNGCGLFGKG		
			Entebbe bat virus	seqid23 GDDAWDFGSTGGIFNTIGKA	seqid2 DRGWGNGCGLFGKG		
			Rio Bravo virus	seqid24 SSAYWSSSEPFTSAGIMRIL	seqid2 DRGWGNGCGLFGKG		
			Saboya virus	seqid18 DRGWGNGCALFGKG seqid25 GSSSWDFSSAGGFFGSIGKA			
		Seaborne tick-borne virus group	Meaban virus	seqid26 GDAAWDFGSVGGFMTSIGRA seqid27 DRGWGNHCGLFGKG			
			Saumarez Reef virus	seqid28 GETAWDFGSAGGFFTSVGRG seqid27 DRGWGNHCGLFGKG			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssive domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			Tyuleniy virus	seqid29 GEAAWDFGSAGGFFQSVGRG seqid27 DRGWGNHCGLFGKG			
		Spondweni virus group	Zika virus	seqid30 LGDTAWDFGSVGGVFNSLGK ***********oo**o**	seqid2 DRGWGNGCGLFGKG		
			Kyasanur forest disease virus	seqid31 VGEHAWDFGSVGGMLSSVG **********o***** seqid27 DRGWGNHCGLFGKG			
			Langat virus	seqid32 VLGEHAWDFGSVGGVMTSIG seqid27 DRGWGNHCGLFGKG			
			Louping ill virus	seqid33 IGEHAWDFGSAGGFFSSIG **********o***oo*o* seqid27 DRGWGNHCGLFGKG			
			Omsk hemorrhagic fever virus	seqid34 LGEHAWDFGSTGGFLSSIG seqid27 DRGWGNHCGLFGKG			
			Powassan virus	seqid35 VGEHAWDFGSVGGILSSVG **********o***** seqid36 DRGWGNHCGFFGKG **********			
			Royal Farm virus	seqid27 DRGWGNHCGLFGKG			
			Tick-borne encephalitis virus	seqid37 IGEHAWDFGSAGGFLSSIG seqid38 IGEHAWDFGSTGGFLTSVG seqid39 IGEHAWDFGSTGGFLASVG seqid27 DRGWGNHCGLFGKG			
		Yaounde virus		seqid40 LGDTAWDFGSIGGVFTSLG	seqid2 DRGWGNGCGLFGKG		
		Yellow fever virus group	Banzi virus	seqid41 VGSSSWDFSSTSGFFSSVG	seqid2 DRGWGNGCGLFGKG		
			Bouboui virus	seqid42 VGRSSWDFSSAGGFFSSVG	seqid2 DRGWGNGCGLFGKG		
			Edge Hill virus Uganda S virus Wesselsbron virus				
			Yellow fever virus	seqid43 MGDTAWDFSSAGGFFTSVG ***o***************	seqid2 DRGWGNGCGLFGKG		
		unclassified Flavivirus	Batu Cave virus Cacipacore virus Calbertado virus Cell fusing agent virus Chaoyang virus Chimeric Tick-borne encephalitis virus/Dengue virus 4 Culex theileri flavivirus Donggang virus Duck hemorrhagic ovaritis virus Flavivirus Aedes/MO-Ac/ITA/2009 Flavivirus Anopheles/PV-Am/ITA/2009 Flavivirus CbaAr4001 Flavivirus FSME Flavivirus Phlebotomine/76/Arrabida/2007 Gadgets Gully virus Greek goat encephalitis virus Jugra virus Kadam virus Kamiti River virus Kedougou virus Montana myotis leukoencephalitis virus Mosquito flavivirus Ngoye virus Nounane virus Phlebotomus flavivirus Alg_F19 Phlebotomus flavivirus Alg_F8 Quang Binh virus Russian Spring-Summer encephalitis virus Sokoluk virus Spanish sheep encephalitis virus T'Ho virus Tai forest virus B31 Tamana bat virus Tick-borne flavivirus Wang Thong virus Flavivirus sp.	seqid44 NRGWGTGCFKWGIG seqid45 NRGWGTGCFEWGLG	seqid2 DRGWGNGCGLFGKG		
			Aedes flavivirus	seqid45 NRGWGTGCFEWGLG seqid46 HVAGRYSKHGMAGIGSVWEDLVR			
			Culex flavivirus	seqid44 NRGWGTGCFKWGIG seqid47 VDKYRRFGTAGVGG			
Hepa civi	Hepatitis C	Hepatitis C virus genotype 1 a			seqid3 GLIHLHQNIVDVQYLYG	E1/E2	

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
	rus	virus			seqid175 PALSTGLIHLHQNIVDVQ		
			Hepatitis C virus genotype 1b	seqid48 GLIHLHRNIVDVQYLYG seqid176 PALSTGLIHLHRNIVDVQ			
			Hepatitis C virus genotype 2	seqid49 GLIHLHQNIVDVQYMYG seqid175 PALSTGLIHLHQNIVDVQ			
			Hepatitis C virus genotype 3	seqid175 PALSTGLIHLHQNIVDVQ	seqid3 GLIHLHQNIVDVQYLYG		
			Hepatitis C virus genotype 4	seqid175 PALSTGLIHLHQNIVDVQ	seqid3 GLIHLHQNIVDVQYLYG		
			Hepatitis C virus genotype 5	seqid50 GLIHLHQNIVDTQYLYG seqid177 PALSTGLIHLHQNIVDTQ			
			Hepatitis C virus genotype 6	seqid175 PALSTGLIHLHQNIVDVQ	seqid3 GLIHLHQNIVDVQYLYG		
			All Hepatitis C virus		seqid3 GLIHLHQNIVDVQYLYG		
		Border disease virus	Border disease virus - Border disease virus - X818 Border disease virus 1 Border disease virus 2 Border disease virus 3 Border disease virus isolates	seqid51 NTTLLNGSAFQLICPYGWVGRVEC seqid52 SYFQQYMLKGQYQYWFDLE			
		Bovine viral diarrhea virus 1	Bovine viral diarrhea virus 1-CP7 Bovine viral diarrhea virus 1-NADL Bovine viral diarrhea virus 1-Osloss Bovine viral diarrhea virus 1-SD1 Bovine viral diarrhea virus isolates and strains Bovine viral diarrhea virus type 1a Bovine viral diarrhea virus type 1b Pestivirus isolate 97-360 Pestivirus isolate Hay 87/2210 Pestivirus strain mousedeer Pestivirus type 1 isolates	seqid53 NTTLLNGPAFQMVCPLGWTGTVSC seqid54 SYFQQYMLKGEYQYWFDLE			
		Bovine viral diarrhea virus 2 (BVDV-2)	Bovine viral diarrhea virus 2 Pestivirus sp. strain 178003 Pestivirus sp. strain 5250Giessen-3 Bovine viral diarrhea virus-2 isolate SCP	seqid55 SLLNGPAFQMVCPQGWTGTIEC seqid56 DRYFQQYMLKGKWQYWFDLD			
		Classical swine fever virus	Classical swine fever virus Hog cholera virus strain Zoelen	seqid57 TLLNGSAFYLVCPIGWTGVIEC seqid58 SYFQQYMLKGEYQYWFDLD			
		unclassified Pestivirus	Bovine viral diarrhea virus 3	seqid59 TLLNGPAFQLVCPYGWTGTIEC seqid60 DNYFQQYMLKGKYQYWFDLEATD			
			Chamois pestivirus 1	seqid61 TLLNGSAFQMVCPFGWTGQVEC seqid62 DSYFQQYMLKGEYQYWFDLDAKD			
			Porcine pestivirus isolate Bungowannah	seqid205 TLLNGPAFQLVCPYGWTGTIECDSYYQQYII KSGYQYWFDLTAKD			
	Unnclassi-fied Flaviviridae		Barkedji virus Canine hepacivirus AAK-2011 GB virus A Douroucouli hepatitis GB virus A GBV-A-like agents GB virus D GBV-C/HGV group GB virus C Hepatitis GB virus C-like virus Hepatitis GB virus B Lammi virus Marmoset hepatitis GB virus A Nakiwogo virus Turkey meningoencephalitis virus				
Togaviridae	Alpha-virus	Aura virus Barmah Forest virus Middelburg virus Ndumu virus Salmon pancreas disease virus		seqid63 GVYPFMWGGAYCFCDTENTQVS **********o****o**o*o* seqid64 APFGCEIYTNPIRAENCAVGSIP *****o*ooo*o**oo*oo*oo* seqid65 SDFGGIATVKYSASKSGKCAVH o***oooooo*ooooo*o*oo* seqid66 FSTANIHPEFRLQICTSYVTCKGDCHPP *oooooooo*oooo*ooooo*ooo*o**			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
		Getah virus Mayaro virus Trocara virus EEEV complex					
		WEEV complex	Fort Morgan virus Highlands J virus Sindbis virus Western equine encephalomyelitis virus Whataroa virus				
		VEEV complex	Cabassou virus Mucambo virus Pixuna virus				
			Venezuelan equine encephalitis virus	seqid67 GVYPFMWGGAYCFCD ********** seqid68 GDCHPPKDHIVTHPQYHAQ **********o**o*o* seqid69 AVSKTAWTWLTS *********oo*			
		SFV complex	Bebaru virus O'nyong-nyong virus Ross River virus Semliki forest virus Una virus	seqid63 GVYPFMWGGAYCFCDTENTQVS **********o****o**o*o* seqid64 APFGCEIYTNPIRAENCAVGSIP *****o*ooo*o**oo*oo*oo* seqid65 SDFGGIATVKYSASKSGKCAVH o***oooooo*ooooo*o*oo* seqid66 FSTANIHPEFRLQICTSYVTCKGDCHPP *oooooooo*oooo*ooooo*ooo*o**			
			Chikungunya virus	seqid67 GVYPFMWGGAYCFCD ********** seqid70 VHCAAECHPPKDHIVNY oo*o*o**o******** seqid71 PASHTTLGVQDISATAMSWV o****oo******o******			
Rubivirus	Rubella virus	Rubella virus (strain BRD1) Rubella virus (strain BRDII) Rubella virus (strain Cendehill) Rubella virus (strain M33) Rubella virus (strain RN-UK86) Rubella virus (strain THERIEN) Rubella virus (strain TO-336 vaccine) Rubella virus (strain TO-336) Rubella virus (vaccine strain RA27/3)		seqid72 ACTFWAVNAYSSGGYAQLASYFNPGGSYYK ***o*o****o**oo****o**o******o seqid73 QYHPTACEVEPAFGHSDAACWGFPTDT ***o*o*o*o****o********o*** seqid74 MSVFALASYVQHPHKTVRVKFHT ***oo*****o**o**o****** seqid159 ETRTVWQLSVAGVSC o*o* ********oo* seqid76 NVTTEHPFCNMPHGQLEVQVPP o*o*o**oo*o*o****o*oo* seqid77 DPGDLVEYIMNYTGNQQSRW ****o******o*o****** seqid78 GSPNCHGPDWASPVCQRHSPDCS ****o***o********** seqid79 RLVGATPERPRLRLV o***o**o**o**** seqid80 DADDPLLRTAPGP *oo********** seqid81 GEVWVTPVIGSQARKCGL oo*o**o**o*****o** seqid86 HIRAGPYGHATVEM oo**********o seqid87 PEWIHAHTTSDPWHP o**oooo*o***o*o seqid88 PGPLGLKFKTVRPVALPR ****o***o**o*oo*** seqid89 ALAPPRNVRVTGCYQCGTPAL oooo**o*o*o**o******* seqid90 EGLAPGGGNCHLTVNGEDVG ***o*****o**oo*o*oo* seqid207 LLNTPPPYQVSCGG ******o*o*o*** 46 seqid92 RASARVIDPAAQSFTGWYGTHT		

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssive domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
				o*oo*o********** seqid93 TAVSETRQTWAEWAAAHWWQLTLG o*******ooo*****o*******			
Bunya-viridae	Hanta-virus (continued on next page)	Amur virus Bayou virus Black Creek Canal virus Cano Delgadito virus Calabazo virus Catacamas virus Choclo virus Dobrava-Belgrade virus El Moro Canyon virus Hantaan virus Isla Vista virus Khabarovsk virus Laguna Negra virus Limestone Canyon virus Monongahe-la virus Muleshoe virus Muju virus New York virus Oran virus Playa de Oro virus Prospect Hill virus Puumala virus Rio Mamore virus Rio Segundo virus Saaremaa virus Seoul virus Sin Nombre virus Soochong virus Thailand		seqid94 NPPDCPGVGTGCTACGVYLD **o****o********o*** seqid95 RKVCIQLGTEQTCKTIDSNDC *oo*o*o*o*oo**oo*o*** seqid96 DTLLFLGPLEEGGMIFKQWCTTTCQFGDPGD IM seqid97 GSFRKKCSFATLPSCQYDGNTVSG *o***o*o***o*o*ooo**oo** seqid98 ATKDSFQSFNITEPH **o****o**oooo* seqid99 GSGVGFNLVCSVSLTEC ******o*o*ooo**** seqid100 KACDSAMCYGSSTANLVRGQNT ****o*o***ooooo*o**o** seqid101 GKGGHSGSKFMCCHDKKCSATGLVAAAPHL ********o*o***ooo*ooo**o*oo*** seqid102 DDGAPQCGVHCWFKKSGEW ***o*o*ooo***oo****			Gn(G2)/Gc (G1)

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
		virus Thottapa-layam virus Topografov virus Tula virus					
	Ortho-bunya-virus	Anopheles A virus Anopheles B virus Bakau virus Batama virus Bwamba virus Caraparu virus Kaeng Khoi virus Kairi virus Madrid virus Main Drain virus Marituba virus Nyando virus Oriboca virus Oropouche virus Sathuperi virus Shamonda virus Shuni virus Simbu virus Tacaiuma virus Tete virus Turlock virus unclassified Orthobunya-virus		seqid103 KHDELCTGPCPVNINHQTGWLT *o*o***o**oooooooo*o*o seqid104 WGCEEFGCLAVSDGCVFGSCQD **o*oo**o*ooo**oo***** seqid105 GNGVPRFDYLCHLASRKEVIVRKC *o*ooo*ooo*oooo*ooooo*o* seqid106 SCAGCINCFQNIHC *o**ooooooooo*			
	Akabane virus		Sabo virus Tinaroo virus Yaba-7 virus				
	Bunyam-wera virus		Batai virus Birao virus Bozo virus Cache Valley virus Fort Sherman virus Germiston virus Guaroa virus Iaco virus Ilesha virus Lokern virus Maguari virus Mboke virus Ngari virus Northway virus Playas virus Potosi virus Shokwe virus Tensaw virus Tlacotalpan virus Xingu virus			
	California Encephalitis virus		California encephalitis serogroup virus LEIV California encephalitis virus - BFS-283 Chatanga virus Inkoo virus Jamestown Canyon virus				

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			Jamestown Canyon-like virus Jerry Slough virus Keystone virus La Crosse virus Lumbo virus Melao virus Morro Bay virus San Angelo virus Serra do Navio virus Snowshoe hare virus South River virus Tahyna virus Trivittatus virus				
		Caraparu virus	Apeu virus Bruconha virus Ossa virus Vinces virus				
		Manzanilla virus	Buttonwillow virus Ingwavuma virus Mermet virus				
		Marituba virus	Gumbo Limbo virus Murutucu virus Nepuyo virus Restan virus				
		Wyeomyia virus	Anhembi virus BeAr328208 virus Macaua virus Sororoca virus Taiassui virus				
	Phlebovirus	Bujaru virus Candiru-virus Chilibre virus Frijoles virus Punta Tor ⊔Saleha-bad virus Sandflyfever Naples virus Uukuniemi viruso virus					
		Rift Valley fever virus		seqid107 KTVSSELSCREGQSYWT **oo**oo*o**o*o** seqidl08 GSFSPKCLSSRRC *******oooooo seqid109 ENKCFEQCGGWGCGCFNVNPSCLFVHT **o*o**o*oo*oo***ooo***o**o seqid110 WGSVSLSLDAEGISGSNSFSF **ooo*o**o*o*o*o*oo** seqid111 RQGFLGEIRCNSE *o*****o**oo* seqid112 AHESCLRAPNLVSYKPMIDQLEC *oo**oo**oooo*o*oo*ooo* seqid113 DPFWFERGSLPQTR **ooo*oo*o***o* seqid114 QAFSKGSVQADLTLMFD **ooo*ooo*oooooo* seqidll5 CDAAFLNLTGCYSCNAG *o*o*o*oo*****oo* seqid116 CQILHFTVPEVEEEFMYSC *ooo*ooo*ooooooo*o* seqid117 STVVNPKSGSWN *o*o**oooooo seqid118 FFDWFSGLMSWFGGPLK *o***oo*o**oooooo			
	Unclassified Phelobvirus (continued on next page)	Anhanga virus Arumowot virus Chagres virus Corfou virus Gabek Forest virus Itaporanga virus Phlebovirus Adria/ALB1/2005 Phlebovirus Adria/ALB5/2005 Phlebovirus AH12 Phlebovirus AH12/China/2010 Phlebovirus AH15/China/2010 Phlebovirus B105-05 Phlebovirus B151-04 Phlebovirus B43-02 Phlebovirus B68-03 Phlebovirus B79-02 Phlebovirus Chios-A Phlebovirus Cyprus Phlebovirus HB29/ China/2010 Phlebovirus HN13/China/2010 Phlebovirus HN6/China/2010 Phlebovirus Hu/					

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			Xinyang1/China/2010 Phlebovirus Hu/Xinyang2/ China/2010 Phlebovirus IB13-04 Phlebovirus JS2007-01 Phlebovirus JS24 Phlebovirus JS26 Phlebovirus JS3/China/2010 Phlebovirus JS4/China/ 2010 Phlebovirus JS6 Phlebovirus JSD1 Phlebovirus LN2/China/2010 Phlebovirus LN3/China/2010 Phlebovirus sandflies/Gr29/Spain/2004 Phlebovirus sandflies/Gr36/Spain/2004 Phlebovirus sandflies/ Gr44/Spain/2004 Phlebovirus sandflies/Gr49/Spain/ 2004 Phlebovirus sandflies/Gr52/Spain/2004 Phlebovirus sandflies/Gr65/Spain/2004 Phlebovirus sandflies/Gr98/Spain/2004 Phlebovirus SD24/China/ 2010 Phlebovirus SD4/China/2010 Phlebovirus tick/ XCQ-2011 Phlebovirus XLL/China/2009 Rio Grande virus Salobo virus Sandfly fever sicilian virus Sandfly Sicilian Turkey virus Utique virus Phlebovirus sp. Phlebovirus sp. Be An 24262 Phlebovirus sp. Be An 356637 Phlebovirus sp. Be An 416992 Phlebovirus sp. Be An 578142 Phlebovirus sp. Be Ar 371637 Phlebovirus sp. Co Ar 170255 Phlebovirus sp. Co Ar 171616 Phlebovirus sp. GML 902878 Phlebovirus sp. Pa Ar 2381 Phlebovirus sp. PAN 479603 Phlebovirus sp. PAN 483391 Phlebovirus sp. VP-161A Phlebovirus sp. VP-334K Phlebovirus sp. VP-366G				
Orthomyxo-viridae	Influenza-virus A	Influenza A virus	INFA H1	seqid119 GLFGAIAGFIEGGWTG seqid178 WTYNAELLVLLENERTLD seqid179 NAELLVLLENERTLDYHD		INF F#2 DELTA6: seqid201 GLFGAAG-FIENG-WEG InFAHI-3: seq1d203	HA (Ha1/ HA2)
			INFA H2	seqid120 GLFGAIAGFIEGGWQG seqid180 WTYNAELLVLMENERTLD seqid181 NAELLVLMENERTLDYHD			
			INFA H3	seqid121 GIFGAIAGFIENGWEG seqid182 WSYNAELLVALENQHTID seqid183 NAELLVALENQHTIDLTD	seqid4 GLFGAIAGFIENGWEG		
			INFA H4	seqid122 GLFGAIAGFIENGWQG seqid182 WSYNAELLVALENQHTID seqid184 NAELLVALENQHTIDVTD			
			INFA H5	seqid120 GLFGAIAGFIEGGWQG seqid180 WTYNAELLVLMENERTLD seqidl85 NAELLVLMENERTLDFHD			
			INFA H6	seqid123 GIFGAIAGFIEGGWTG seqid119 GLFGAIAGFIEGGWTG seqid178 WTYNAELLVLLENERTLD seqid186 NAELLVLLENERTLDMHD			
			INFA H7	seqid187 WSYNAELLVAMENQHTID seqid208 WSYNAELLVAMENQHLAD	seqid4 GLFGAIAGFIENGWEG		
			INFA H8	seqid124 GLFGAIAGFIEGGWSG seqid189 WAYNAELLVLLENQKTLD seqid190 NAELLVLLENQKTLDEHD			
			INFA H9	seqid125 GLFGAIAGFIEGGWPG seqid124			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssive domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
				GLFGAIAGFIEGGWSG seqid189 WAYNAELLVLLENQKTLD seqid190 NAELLVLLENQKTLDEHD			
			INFA H10	seqid191 WTYQAELLVAMENQHTID seqid192 QAELLVAMENQHTIDMAD	seqid4 GLFGAIAGFIENGWEG		
			INFA H11	seqid125 GLFGAIAGFIEGGWPG seqid193 WSYNAQLLVLLENEKTLD seqid194 NAQLLVLLENEKTLDLHD			
			INFA H12	seqid125 GLFGAIAGFIEGGWPG seqid189 WAYNAELLVLLENQKTLD seqid190 NAELLVLLENQKTLDEHD			
			INFA H13	seqid125 GLFGAIAGFIEGGWPG seqid195 WSYNAKLLVLLENDKTLD seqid196 NAKLLVLLENDKTLDMHD			
			INFA H14	seqid122 GLFGAIAGFIENGWQG seqid182 WSYNAELLVALENQHTID seqid184 NAELLVALENQHTIDVTD			
			INFA H15	seqid187 WSYNAELLVAMENQHTID seqid188 NAELLVAMENQHTIDLAD	seqid4 GLFGAIAGFIENGWEG		
			INFA H16	seqid125 GLFGAIAGFIEGGWPG seqid197 WSYNAKLLVLIENDRTLD seqid198 NAKLLVLIENDRTLDLHD			
	Influenza-virus B	Influenza B virus	All strains	seqid126 GFFGAIAGFLEGGWEG seqid199 ISSQIELAVLLSNEGIIN seqid200 QIELAVLLSNEGIINSED			
	Influenza-virus C	Influenza C virus					
Paramyxo-viridae		Avulavirus	Avian paramyxovirus 2 Yucaipa virus Avian paramyxovirus 3 Avian paramyxovirus 3b Avian paramyxovirus 4 Avian paramyxovirus 5 Avian paramyxovirus 6 Avian paramyxovirus 7 Avian paramyxovirus 8 Avian paramyxovirus 9 Newcastle disease virus Pigeon paramyxovirus 1 unclassified Avulavirus Avian paramyxovirus 10_Avian paramyxovirus duck/Miyagi/885/05 Avian paramyxovirus penguin/Falkland Islands/324/2007 Goosramyxovirus HZ Goose paramyxovirus JS/1/97/Go Goose paramyxovirus SF02	seqid127 GAIALGVATAAAVTAG oooo*o*oo*o*oo**		F0 (F2/F1)
		Henipavirus	Hendra virus Hendra virus horse/Australia/Hendra/1994 Nipah virus unclassified Henipavirus Bat paramyxovirus Eid.hel/GH45/2008				
		Morbilli-virus	Canine distemper virus Cetacean morbillivirus_Dolphin morbillivirus_Pilot whale morbillivirus Porpoise morbillivirus Measles virus Peste-des-petits-ruminants virus Phocine distemper virus Phocine distemper virus 1 Phocine distemper virus-2 Rinderpest virus				
		Respiro-virus	Bovine parainfluenza virus 3 Porcine paramyxovirus strain Frost Porcine paramyxovirus strain Texas Human parainfluenza virus 1 Human parainfluenza virus 3 Simian Agent 10 Sendai virus unclassified Respirovirus Atlantic salmon respirovirus Guinea pig parainfluenza virus TS-9 Pacific salmon				

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			paramyxovirus Trask River 1983 Swine parainfluenza virus 3 Tursiops truncatus parainfluenza virus 1				
		Rubulavirus	Human parainfluenza virus 2 Human parainfluenza virus 2 (strain Greer) Human parainfluenza virus 2 (strain Toshiba) Human parainfluenza virus 4 Human parainfluenza virus 4a Human parainfluenza virus 4b Mapuera virus Mumps virus Parainfluenza virus 5 Porcine rubulavirus Simian virus 41 unclassified Rubulavirus Porcine parainfluenza virus Tuhoko virus 1 Tuhoko virus 2 Tuhoko virus 3				
		unclassified Paramyxo-virinae	Atlantic salmon paramyxovirus Beilong virus Canine parainfluenza virus Chimeric human parainfluenza virus rPIV3-2 Fer-de-lance virus J-virus Menangle virus Mossman virus Murayama virus Ovine parainfluenza virus 3 Pacific salmon paramyxovirus Paramyxovirus GonoGER85 Recombinant PIV3/ PIV1 virus Reptilian paramyxovirus Salem virus Salmo salar paramyxovirus Snake ATCC-VR-1408 paramyxovirus Snake ATCC-VR-1409 paramyxovirus Tioman virus Tupaia paramyxovirus				
	Pneumo-virus	Human respiratory syncytial virus	Human respiratory syncytial virus A Human respiratory syncytial virus (strain RSB1734) Human respiratory syncytial virus (strain RSB5857) Human respiratory syncytial virus (strain RSB6190) Human respiratory syncytial virus (strain RSB6256) Human respiratory syncytial virus (strain RSB642) Human respiratory syncytial virus (strain RSB6614) Human respiratory syncytial virus A strain Long LinkOut Human respiratory syncytial virus A2 Human respiratory syncytial virus B Human respiratory syncytial virus (subgroup B / strain 18537) Human respiratory syncytial virus (subgroup B / strain 8/60) Human Respiratory syncytial virus 9320 Human respiratory syncytial virus B1 Human respiratory syncytial virus S2 Human respiratory syncytial virus strain RSS-2 unclassified Human respiratory syncytial virus	seqid128 FLGLILGLGAAVTAGVA ***oo**o*o*ooo*o* seqid129 TNEAWSLTNGMSVL **o*****o**o*** seqid130 VIRFQQLNKRLLE **o***o*o**** seqid131 REFSSNAGLT ****o***o* seqid132 MLTDRELTSIVGGM ***oo**o*oooo* seqid133 YVIQLPLFGVMDTDCW *oo***oo**o**o** seqid134 CLARADNGWYCHNAGSLSYFP **ooo*o**o*o****o*o** seqid135 DTLKSLTVPVTSRECN **oo***o*ooooo** seqid136 YDCKISTSKTYVSTAVLTTMG *o*o*o***ooo*oo*o*oo* seqid137 VSCYGHNSCTVIN *****ooo**oo* Seqid75 GIIRTLPDGCHYISNKGVDRVQVGNTVYYLS KEVGK ***o*ooo**o*o**o*o*o*o****o**oo *oo** seqid139 PLSFPDDKFDVAIRDVEHSINQTRTFLKASD QLL **o**o*o*ooo*oo*ooo***ooo*ooo** o** seqid140 KIMTSKTDISSSVITSIGAIVSCYG o*o***ooo*oo*o*oo*oo*****			
		Bovine respiratory syncytial virus	All strains	seqid128 FLGLILGLGAAVTAGVA ***oo**o*o*ooo*o* seqid134 CLARADNGWYCHNAGSLSYFP **ooo*o**o*o****o*o** seqid133 YVIQLPLFGVMDTDCW *oo***oo**o**o**			
	Metapneu-movirus	Avian metapneu-mo-virus	All strains				
		Human metapneu-mo-virus	All strains				
Coronaviri-dae	Coronaviri-nae	Alphacoro-navirus	Alphacoronavirus 1 Coronavirus group 1b Human coronavirus 229E Human coronavirus NL63 Miniopterus bat coronavirus 1 Miniopterus bat coronavirus HKU8 Porcine epidemic diarrhea virus				S (S1/S2)

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			Rhinolophus bat coronavirus HKU2 Scotophilus bat coronavirus 512 unclassified Alphacoronavirus				
		Betacorona-virus	Betacoronavirus 1 Coronavirus group 2b Coronavirus group 2c Human coronavirus HKU1 Murine coronavirus Pipistrellus bat coronavirus HKU5 Rousettus bat coronavirus HKU9 Severe acute respiratory syndrome-related coronavirus recombinant SARSr-CoV SARS coronavirus Tylonycteris bat coronavirus HKU4 unclassified Betacoronavirus				
		Gammacor-ona-virus	Avian coronavirus Beluga Whale coronavirus SW1				
		unclassified coronaviru-ses	Alpaca coronavirus CA08-1/2008 Bat coronavirus Bird droppings coronavirus Bovine respiratory coronavirus Chicken enteric coronavirus Coronavirus Anas Coronavirus oystercatcher/p17/2006/GBR Coronavirus red knot/p60/2006/GBR Ferret enteric coronavirus 1202 Ferret systemic coronavirus MSU-S Ferret systemic coronavirus WADL Guangxi coronaviridae Human coronavirus NO Human enteric coronavirus strain 4408 Kenya bat coronavirus Mink coronavirus strain WD1133 Parrot coronavirus AV71/99 Quail coronavirus Italy/Elvia/2005 Tai Forest coronavirus unidentified coronavirus unidentified human coronavirus	seqid141 RSAIEDLLFDKVKLSDVG **oo****oo**ooo*o* seqid142 VPFYLNVQYRINGLGVT 0**00000**0**0*** seqid143 VLSQNQKLIANAFNNALHAIQ **00***0*000*00*000** seqid144 TNSALVKIQAVVNANA *oo**o*o*o***oo* seqid145 AEAQIDRLINGRLTALNAYVSQQL *oo******o***oo*oo*oo*** seqid146 SAAQAMEKVNECVKSQSSRINFCGNGNHIIS 0*00*00*00***00*00*00***0*0*00* seqid147 APYGLYFIHFNYVP **o*oo*o*oo*o* seqid148 LQEAIKVLNHSYINLKDIGTYEYYVKWPWYV W 00*00*0**0*000*000*00*0*0*****0 * seqid209 EVFAQVKQMYKT PTLKYFGGFNFSQIL seqid210 EVFAQVKQMYKT PAIKDFGGFNFSQIL Segid211 SFIEDLLFNKVTLADAGF Segid212 SAIEDLLFNKVRLSDVGF Seqid213 SLLEDLLFNKVKLSDVGF Seqid214 SAIEDLLFSKVKLADVGF Seqid215 SAIEDLLFDKVKLSDVGF			
Arena-viridae	Arean-virus	LCMV-Lassa virus (Old World) complex	Ippy virus Lassa virus Lujo virus Lymphocytic choriomeningitis virus Mobala virus Mopeia virus	seqid149 NALINDQLIMKNHLRDIMGIPYC *o**o***o*o***o*o**o*** seqid150 FTWTLSDSEGKDTPGGYCLT 00*000*00*000***0**0 seqid151 KCFGNTAIAKCNQKHDEEFCDMLRLFDFN ***0*000****00*00****000*000* seqid152 MLQKEYMERQGKTPLGLVDLFVFS *000*00**00**00*0*0000*0			GpC (Gp1/Gp2)
		Tacaribe virus (New World) complex	Amapari virus Chapare virus Flexal virus Guanarito virus Junin virus Latino virus Machupo virus Oliveros virus Paraná virus Pichinde virus Pirital virus Sabiá virus Tacaribe virus Tamiami virus Whitewater Arroyo virus	seqid150 FTWTLSDSEGKDTPGGYCLT 00*000*00*000***0**0 seqid151 KCFGNTAIAKCNQKHDEEFCDMLRLFDFN ***o*ooo****oo*oo****ooo*ooo* seqid152 MLQKEYMERQGKTPLGLVDLFVFS *000*00**00**00*0*0000*0			
Hepadnaviri-dae	Genus Orthohepad-navirus	Hepatitis B virus	HBV genotype A HBV genotype B HBV genotype C HBV genotype D HBV genotype E HBV genotype F HBV genotype G HBV genotype H Hepatitis B virus alphal				L and M and S Where S mediates
			Hepatitis B virus LSH/chimpanzee Hepatitis B virus strain cpz Hepatitis B virus subtype adr Hepatitis B virus subtype adw Hepatitis B virus subtype adyw Hepatitis B virus subtype ayw	seqid153 FNPLGFFPSHQLDPLF o***o*o*o*o*o*o* seqid154 ADWDKNPNKDPWP o*o*o*oo*oooo seqid155 MESITSGFLGPLLVLQAVFF			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssive domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
				oooooooo*ooooo**oooo seqid156 LLTRILTIPQSLDSWWTSLNFLGGA ooooo*oooo*oooo***o*o*oo seqid157 CPPTCPGYRWMC oo*o*****o*o seqid158 LFILLLCLIFLLVLLDYQ *oo*ooo*oo*oo*oooo			
Rhabdoviri-dae	Dimarhab-dovirus	Ephemero-virus	Bovine ephemeral fever virus	seqid160 LDGYLCRKQKWEVTCTETWYFVTD *o*oo****o*ooo*o*****o*o seqid161 KYQIIEVIPTENEC o***o**o*oooo* seqid162 LKGEYIPPYYPPTNCVWNAIDTQE oo*oo*******oo*o**oooo** seqid163 IEDPVTMTLMDSKFTKPC ooo*oooooo**o*oo** seqid164 LHCQIKSWECIPV o**oo*o****o* seqid165 SHRNMMEALYLESPD *oo*oo*o*oo*o** seqid166 LTFCGYNGILLDNGEWWSIY o****oo**oooo***** seqid167 ELEHEKCLGTLEKLQNGE *****o**o*oo*oo*o* seqid168 LDLSYLSPSNPGKHYAY **o***o*oo**oo*** seqid169 IRAVCYYHTFSMNLD o**o*o*oo*oooo*			Glyoprotein G
		Vesiculo-virus	Carajas virus Chandipura virus Cocal virus Isfahan virus Maraba virus Piry virus recombinant Vesiculovirus Spring viraemia of carp virus Vesicular stomatitis Alagoas virus Vesicular stomatitis Indiana virus Vesicular stomatitis New Jersey virus	seqid170 EWKTTCDYRWYGPQYITHSI o*o****o*****o*o*o* seqid171 LGFPPQSCGWASVTT o****oo**oooooo seqid1 VQVTPHHVLVDEYTGEWVDSQFINGKC ooooo*o*oooo*o*o*o*oooooooo			
	Lyssavirus	Aravan virus Australian bat lyssavirus Duvenhage virus European bat lyssavirus 1 European bat lyssavirus 2 Irkut virus Khujand virus Lagos bat virus Mokola virus West Caucasian bat virus					
		Rabies virus	Rabies virus AB21 Rabies virus AB22 Rabies virus AVO1 Rabies virus BNG4 Rabies virus BNG5 Rabies virus China/DRV Rabies virus China/MRV Rabies virus CVS-11 Rabies virus ERA Rabies virus Eth2003 Rabies virus HEP-FLURY Rabies virus India Rabies virus Nishigahara RCEH Rabies virus Ontario fox Rabies virus Ontario skunk Rabies virus PM Rabies virus red fox/08RS-1981/Udine/2008 Rabies virus SAD B19 Rabies virus silver-haired	seqid5 GFTCTGVVTEAETYTNFVGYVT *o****o**o*oo*oooo*** seqid6 SLHNPYPDYRWLRTVKTT *ooooooooooo***o* Seqid138 ESLVIISPSVADLDPYDRSLHS *ooo***oooo*o**ooo Seqid91 CKLKLCGVLGLRLMDGT *ooo****oooo*ooo* Seqid206 ILGPDGNVLIPEMQSS o**o*ooo*******o seqid82 QHMELLESSVIPLVHPL *ooo**o*ooo**oo**			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
			bat-associated SHBRV Rabies virus strain Pasteur vaccin Rabies virus strain Street Rabies virus vnukovo-32 Thailand genotype 1 dog lyssavirus				
		unclassified Lyssavirus	Bokeloh bat lyssavirus European bat lyssavirus Lyssavirus Ozernoe Shimoni bat virus				
	Novirhabdo-virus	Hirame rhabdovirus Infectious hematopoie-tic necrosis virus Snakehead rhabdovirus Viral hemorrhagic septicemia virus					
	unassigned Rhabdoviri-dae	Bangoran virus Bimbo virus Bivens Arm virus Flanders virus Garba virus Klamath virus Malpais Spring virus Nasoule virus Ngaingan virus Ouango virus Sigma virus Tupaia virus Wongabel virus					
Filoviridae			Lloviu virus (LLOV) Bundibugyo virus (BDBV; previously BEBOV) Reston virus (RESTV; previously REBOV) Sudan virus (SUDV; previously SEBOV) Tai Forest virus (TAFV; previously CIEBOV) Ebola virus (EBOV; previously ZEBOV) Marburg virus (MARV) Ravn virus (RAW)	Seqid216 GAALGLAWIPYFGPAAE oo*o*oo***o***ooo seqid217 GAAVGLAWIPYFGPAAE Seqid218 GAAAGLAWIPYFGPAAE Seqid219 DLAAGLSWIPFFGPGIE Seqid220 HNAAGIAWIPYFGPGAE			
Lentivirisae	Hiv1			Seqid221 AVGLGALFLGFLGAAGSTMGAAS oooo**ooo*o*oo*****o**o seqid222 LTLTGQARQLLS o***o*o*o*oo seqid223 GIVQQQSNLLQAIEAQQ o*****o***o*****o seqid224 GLGAMFLGFLGAAGSTMGAASLTLTVQARQL LS Seqid225 GIGAMFLGLLSAAGSTMSAAAITLTVQTRQL LS Seqid226 GIGAMFLGLLSAAGSTMGAAAITLTVQTRQL LS Seqid227			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
				GIGAVFLGFLGAAGSTMGAASITLTVQARQL LS Seqid228 GVGALFLGFLSAAGSTMGAASITLTVQARQL LS Seqid229 GIGAMILGFLGAAGSTMGAASITLTVQARQL LS Seqid230 GLGAMFLGFLGAAGSTMGAASITLTVQARQL LS Seqid231 GFGAMFLGFLGAAGSTMGAASITLTVQARQL LS Seqid232 TLGAMFLGFLGAAGSTMGAASMTLTVQARQL LS Seqid233 GLGAVFLGFLGAAGSTMGAASITLTVQARQL LS Seqid234 TIGAMFLGFLGAAGSTMGAASITLTVQARRL LS Seqid235 TIGAMFLGFLGAAGSTMGAASMTLTVQARLL LS Seqid236 TLGAMFLGFLGAAGSTMGAASMTLTVQARLL FS Seqid237 TLGAMFLGFLGAAGSTMGAASLTLTVQARLL LS Seqid238 GVGAMFLGFLGAAGSTMGAASLTLTVQARQL LS Seqid239 GLGAMFLGFLGAAGSTMGAASITLTVQARLL LS Seqid240 TLGAVFLGFLGAAGSTMGAASLTLTVQARLL LS Seqid241 GIGAVFLGFLGAAGSTMGAASITLTVQARKL LS Seqid242 GIGALFLGFLGAAGSTMGAASVTLTVQARQL LS Seqid243 GLGALFLGFLGAAGSTMGAASVTLTVQARQL LS Seqid244 GIGAMFLGFLGAAGSTMGAASITLTVQARLL LS Seqid245 GIGAMFLGFLGAAGSTMGAASVTLTVQARLL LS Seqid246 AIGALFLGFLGAAGSTMGAASVTLTVQARLL LS Seqid247 TLGAMFLGFLGAAGSTMGAASLTLTVQARQL LS Seqid248 GIGALFLGFLGAAGSTMGAASMTLTVQARQL LS Seqid249 GIGAMFLGFLGAAGSTMGAASLTLTVQARQL LS Seqid250 GIGAVFLGFLGAAGSTMGAASMTLTVQARLL LS Seqid251 GIGALFLGFLGAAGSTMGAASLTLTVQARQL LS Seqid252 GIGAVFLGILGAAGSTMGAASITLTVQARQL LS Seqid253 GIGAVFLGFLGAAGSTMGAASVTLTVQARQL LF Seqid254 GLGAMFFGFLGAAGSTMGAASVTLTVQARQL LS Seqid255			

TABLE 1-continued

family	genus	Species (group)	Species (Strain)	Putative ISU as identified using the criteria described in this application fir udentification of immubosupprssivc domains	Peptides from domains from fusion proteins exhibiting immunosuppressive activity (ISU)	Name of envelope attachment / fusion protcin	IU ggroup and fusion type
				GIGALFLGFLGAAGSTMGAASITLTVQARLL LS Seqid256 GLGALFVGFLGAAGSTMGAASITLTVQARQL LS Seqid257 GIGALFLGFLGTAGSTMGAASVTLTVQARQL LS Seqid258 GIGAMIFGFLGAAGSTMGAASITLTVQARQL LS Seqid259 GLGAVLLGFLGTAGSTMGAASLTLTVQVRQL LS Seqid260 GIGAVLFGFLGAAGSTMGAASITLTVQVRQL LS Seqid261 GLGALFLGFLGAAGSTMGAASLTLTGQARQL LS oo**ooo*o*oo*****o**oo***o*o*o* oo Seqid262 GTLGAMFLGFLGAAGSTMGAASMTLTVQARQ LL Seqid263 GTIGAMFLGFLGAAGSTMGAASITLTVQARR LL Seqid264 GTIGAMFLGFLGAAGSTMGAASMTLTVQARL LL Seqid265 IGALFLGFLGAAGSTMGAASVTLTVQARLLL SG			
			Bovine lentivirus group	Seqid266 AVGMVIFLLVLAIMAMTASVTAA ***oo**********o*o*oo**			
			Equine lentivirus group	Seqid267 FGISAIVAAIVAATAIAASA **o*ooo**********o*o			
			Feline lentivirus group	Seqid268 TLALVTATTAGLIGTTTGTSA Seqid269 HVMLALATVLSMAGAGTGATA			
			Ovine/caprine lentivirus group	Seqid270 GIGLVIMLVTMAIVAAAGAS *o***oo*oo***o*o***o			
			Human immunodeficiency virus 2	Seqid271 GVMVLGFLGFLAMAGSAMGA ooo***o**oooo*oooooo			
			Simian immunodeficiency virus	Seqid272 GVFVLGFLGFLATAGSAMGA oooo**oo*o*oo**ooooo			
			Simian immunodeficiency virus others	Seqid273 GAIVLGLLGFLGLAGSAMG *ooooooo*o*ooo**ooo			
			Ovine lentivirus	Seqid274 GIGLVIVLAIMAIIAAAGAGLGVANAVQ			
Arteriviri-dae		Porcint Reproduc-tions og Respirations Syndrome (PRRS)	PRRS Type I	seqid275 SRKLGRSLIPHSCFWWLFLLC seqid276 GNGNSSTYQYIYNLTIC seqid277 GTAWLSTHFSWAVETFVLYHILSL seqid278 GFLTTSHFFDTLGLGAVSITGFC seqid279 RYAHTRFTNFIVDDRGRIHRW			
			PRRS Type II	seqid280 SNNNSSHIQLIYNLTLC seqid281 GTDWLAQKFDWAVETFVIFPVLTH seqid282 GALTTSHFLDTVGLATVSTAGYY seqid283 IYAVCALAALICFVIRLAKNC seqid284 VSTAGYYHGRYVLSSIYAVCALAALICFVIR L			

[0260] All cited references are incorporated by reference.

[0261] The accompanying Figures and Examples are provided to explain rather than limit the present invention. It will be clear to the person skilled in the art that aspects, embodiments and claims of the present invention may be combined.

EXAMPLES

Example 1: ELISA

TNF-α ELISA assay

[0262] The supernatant from THP-1 cells treated with peptides was assayed on human TNF-α ELISA Max™ Deluxe Set (Biolegend, #430205). ELISA assay was performed according to the manufacturer's protocol, as follows. Each incubation step was followed by sealing and shaking on the rotating table at 150-200 rpm, except the overnight incubation with the Capture Antibody, where plates were not shaken. One day prior running ELISA the 96-well assay plates were covered with the Capture Antibody, diluted 1:200 in 1x Coating Buffer (5x Coating Buffer diluted in ddH_2O). 100 μL of this Capture Antibody solution was added into all wells, sealed and incubated overnight (16-18 hrs) at 4° C. The next day all reagents from the set were brought to the room temperature (RT) before use. The plate was washed 4 times with minimum 300 μL Wash Buffer (1x PBS, 0,05% Tween 20) per well. The residual buffer in the following washing was removed by blotting the plates against the absorbent paper. Next 200 μL of the 1x Assay Diluent A (5x Assay Diluent A diluted in PBS pH = 7.4) was added for 1 h to block non-specific binding. While the plate was being blocked, all samples and standards (mandatory for each plate) were prepared. Standards and samples were run in triplicates. 1 mL of the top standard 250 pg/mL was prepared in 1x Assay Diluent A (1x AD) from the TNF-α stock solution (55 ng/ mL). The six two-fold serial dilutions of the 250 pg/mL top standard were performed, with the human TNF-α standard concentration: 250 pg/mL, 125 pg/mL, 62.5 pg/mL, 31.2 pg/mL, 15.6 pg/mL, 7.8 pg/mL and 3.9 pg/mL, respectively. 1x AD serves as the zero standard (0 pg/mL). After blocking the plate, washing was performed and 100 μL standards and samples were assayed in triplicates and incubated for 2 h in RT. Samples were not diluted, the whole supernatant from the THP-1 cells was assayed. After washing, 100 μL of the Detection Antibody was applied to each well, diluted 1:200 in 1x AD, and incubated for 1 hour. Plate was washed and followed by 30 minutes incubation with 100 μL of Avidin-HRP solution per well, diluted 1:1000 in 1x AD. The final washing was performed 5 times with at least 30 seconds interval between the washings, to decrease the background. Next 100 μL of the freshly mixed TMB Substrate Solution (10 mL per plate, 5 mL of each from 2 substrates provided in the set) was applied and left in the dark for 15 min. It needs to be observed to prevent signal saturation, positive wells turned blue. After incubation in the dark the reaction was stopped with 100 μL of 2N H_2SO_4 per well. Positive wells turned yellow. Absorbance was read at 450 nm and 570 nm (background) within 30 minutes. The data were analyzed in the Microsoft Excel 2010 program.

Example 2: Effect of Peptides on Cytokine and Transcription Factor mRNA Level Measurements by QPCT

Cell Culture

[0263] THP-1 cells were cultured in RPMI medium supplemented with 10% fetal bovine serum 2 mM glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin and used before passage 10. Cells were cultured in a humidified atmosphere in 95% air, 5% CO_2 at 37° C.

RNA Isolation

[0264] RNAs from THP-1 cells were isolated using RNeasy ® Plus Mini Kit (Qiagen, DK) according to the manufacturer's protocol. Quality and integrity of isolated RNA samples was controlled by determining A_{260}/A_{280}, A_{260}/A_{230} absorbance ratios and 28S/18S rRNA ratios followed by rigorous DNase I (Ambion® TURBO DNA-free™) treatments.

Quantitative Real-Time RT-PCR

[0265] 500 ng total RNA was used for cDNA synthesis using iScript™ cDNA synthesis kit (Bio-Rad, CA USA) according to the instructions of the manufacturers. Real-time Q-PCR analysis was performed using a LightCycler 480 cycler (Roche Diagnostics, DK). 2 μl of cDNA (from a total 20 μl reaction volume) was used in a 20 μl reaction. The real-time Q-PCR reactions contained 10 μl SybrGreen 2x Master Mix (Roche Diagnostics, DK), 2 μl forward primer (5 pmol/μl), 2 μl reverse primer (5 pmol/μl) and 4 μl water. After initial denaturation at 95° C. for 10 minutes, PCR amplifications were performed for 45 cycles. The primer sequences used in this study are shown in Table 1. The crossing point (CP) for each transcript was measured and defined at constant fluorescence level in Light Cycler 480 software. The mRNA levels for the test gene were normalized to the RPL13a or RPL37A value and relative quantification was determined using the ΔCt model presented by PE Applied Biosystems (Perkins Elmer, Foster City, CA USA). For quantitative real-time RT-PCR analysis, standard deviations were calculated and a T-test was employed to compare expression levels. P-values ≤ 0.05 were considered statistically significant.

Target gene/primer name	Primer sequence 5′-3′
IL-2 β forward	GTGGCAATGAGGATGACTTGTTC (SEQ ID NO:288)
IL-2 β reverse	TAGTGGTGGTCGGAGATTCGTA (SEQ ID NO:289)
IL-6 forward	AGCCACTCACCTCTTCAGAAC (SEQ ID NO:290)
IL-6 reverse	GCCTCTTTGCTGCTTTCACAC (SEQ ID NO:291)
IL-10 forward	GTGATGCCCCAAGCTGAGA (SEQ ID NO:292)
IL-10 reverse	CACGGCCTTGCTCTTGTTTT (SEQ ID NO:293)
TNF-alpha forward	CTGCTGCACTTTGGAGTGAT (SEQ ID NO:294)
TNF-alpha reverse	AGATGATCTGACTGCCTGGG (SEQ ID NO:295)
NF-κB forward	TGAGTCCTGCTCCTTCCA (SEQ ID NO:296)
NF-κB reverse	GCTTCGGTGTAGCCCATT (SEQ ID NO:297)

-continued

Target gene/primer name	Primer sequence 5′-3′
RPL13a forward	CATCGTGGCTAAACAGGTACTG (SEQ ID NO:298)
RPL13a reverse	GCACGACCTTGAGGGCAGCA (SEQ ID NO:299)
RPL37A forward	ATTGAAATCAGCCAGCACGC (SEQ ID NO:300)
RPL37A reverse	AGGAACCACAGTGCCAGATCC (SEQ ID NO:301)

Treatment of Cells/Induction of Cytokines

[0266] Pro-and anti-inflammatory cytokine gene expression was analyzed in un-differentiated THP-1 cells, designed as THP-1 monocytes. LPS is widely used as a potent and prototypical inducer of cytokine production in innate immunity which begins with the orchestration of monocytes. Pathogen associated molecular patterns (PAMPs), like lipopolysaccharide (LPS), play a pivotal role in initiation of variety of host responses caused by infection with Gram-negative bacteria. Such action leads to systemic inflammatory response, for instance up-regulation of pro-and anti- inflammatory cytokines, resulting in secretion of cytokine proteins into the blood stream.

[0267] THP-1 cells (1.0 x 10^6) were cultured in a 24-well tissue culture plate (Corning). Cells were cultured with stimulant LPS at 1 μg/ml with or without indicated peptides (at the indicated concentrations) for 4 h. LPS and peptides concentrations were chosen according to our preliminary optimization studies. RPMI 1640 medium containing 10% fetal bovine serum, 2 mM glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin was used as a control. To investigate gene expression and cytokine secretion cells were harvested at 4 h time point, while cell-free culture supernatants were collected and stored at -80° C. The time point of 4 h has been chosen based on the previously published gene expression and cytokine secretion kinetics of THP-1 monocytes stimulated with LPS[1]. The experiments were performed by two independent biological replications, started from a new batch of cells.

[0268] 1. Wasaporn Chanput, Jurriaan Mes, Robert A.M. Vreeburg, Huub F.J. Savelkoul and Harry J. Wichers. Transcriptional profiles of LPS-stimulated THP-1 monocytes and macrophages: a tool to study inflammation modulating effects of food-derived compounds. Food Funct., 2010, 1, 254-261.

Example 3

[0269] Inflammatory shock as a consequence of LPS release remains a serious clinical concern. In humans, inflammatory responses to LPS result in the release of cytokines and other cell mediators from monocytes and macrophages, which can cause fever, shock, organ failure and death. Here we present data that show that pretreatment of cells with INF F#2 results in a decrease in the release of cytokines including pro-inflammatory cytokines such as TNFalpha and IL-6. Therefore, treatment of patients, in the risk of developing sepsis, with INF F#2 could act beneficially to decrease production of proinflammatory cytokines and hereby lessen the risk of developing shock, organ failure and death. See FIG. **8**.

[0270] The content of the ASCII text file of the sequence listing named "Sequence-Listing-as-filed-12397-0802", having a size of 257 kb and a creation date of 13 Dec. 2022, and electronically submitted via EFS-Web on 13 Dec. 2022, is incorporated herein by reference in its entirety.

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NRGWNNGCGL FGKG	14
SEQ ID NO: 86	moltype = AA length = 14
FEATURE	Location/Qualifiers
source	1..14
	mol_type = protein
	organism = unidentified
SEQ ID NO: 86	
HIRAGPYGHA TVEM	14
SEQ ID NO: 87	moltype = AA length = 15
FEATURE	Location/Qualifiers
source	1..15
	mol_type = protein
	organism = unidentified
SEQ ID NO: 87	
PEWIHAHTTS DPWHP	15
SEQ ID NO: 88	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 88	
PGPLGLKFKT VRPVALPR	18
SEQ ID NO: 89	moltype = AA length = 21
FEATURE	Location/Qualifiers
source	1..21
	mol_type = protein
	organism = unidentified
SEQ ID NO: 89	
ALAPPRNVRV TGCYQCGTPA L	21
SEQ ID NO: 90	moltype = AA length = 20
FEATURE	Location/Qualifiers
source	1..20
	mol_type = protein
	organism = unidentified
SEQ ID NO: 90	
EGLAPGGGNC HLTVNGEDVG	20
SEQ ID NO: 91	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = unidentified
SEQ ID NO: 91	
CKLKLCGVLG LRLMDGT	17
SEQ ID NO: 92	moltype = AA length = 23

-continued

FEATURE	Location/Qualifiers	
source	1..23	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 92		
RASARVIDPA AQSFTGVVYG THT		23
SEQ ID NO: 93	moltype = AA length = 24	
FEATURE	Location/Qualifiers	
source	1..24	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 93		
TAVSETRQTW AEWAAAHWWQ LTLG		24
SEQ ID NO: 94	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 94		
NPPDCPGVGT GCTACGVYLD		20
SEQ ID NO: 95	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 95		
RKVCIQLGTE QTCKTIDSND C		21
SEQ ID NO: 96	moltype = AA length = 33	
FEATURE	Location/Qualifiers	
source	1..33	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 96		
DTLLFLGPLE EGGMIFKQWC TTTCQFGDPG DIM		33
SEQ ID NO: 97	moltype = AA length = 24	
FEATURE	Location/Qualifiers	
source	1..24	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 97		
GSFRKKCSFA TLPSCQYDGN TVSG		24
SEQ ID NO: 98	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 98		
ATKDSFQSFN ITEPH		15
SEQ ID NO: 99	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 99		
GSGVGFNLVC SVSLTEC		17
SEQ ID NO: 100	moltype = AA length = 22	
FEATURE	Location/Qualifiers	
source	1..22	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 100		
KACDSAMCYG SSTANLVRGQ NT		22
SEQ ID NO: 101	moltype = AA length = 30	

-continued

FEATURE Location/Qualifiers
source 1..30
mol_type = protein
organism = unidentified
SEQ ID NO: 101
GKGGHSGSKF MCCHDKKCSA TGLVAAAPHL 30
SEQ ID NO: 102 moltype = AA length = 19
FEATURE Location/Qualifiers
source 1..19
mol_type = protein
organism = unidentified
SEQ ID NO: 102
DDGAPQCGVH CWFKKSGEW 19
SEQ ID NO: 103 moltype = AA length = 22
FEATURE Location/Qualifiers
source 1..22
mol_type = protein
organism = unidentified
SEQ ID NO: 103
KHDELCTGPC PVNINHQTGW LT 22
SEQ ID NO: 104 moltype = AA length = 22
FEATURE Location/Qualifiers
source 1..22
mol_type = protein
organism = unidentified
SEQ ID NO: 104
WGCEEFGCLA VSDGCVFGSC QD 22
SEQ ID NO: 105 moltype = AA length = 24
FEATURE Location/Qualifiers
source 1..24
mol_type = protein
organism = unidentified
SEQ ID NO: 105
GNGVPRFDYL CHLASRKEVI VRKC 24
SEQ ID NO: 106 moltype = AA length = 14
FEATURE Location/Qualifiers
source 1..14
mol_type = protein
organism = unidentified
SEQ ID NO: 106
SCAGCINCFQ NIHC 14
SEQ ID NO: 107 moltype = AA length = 17
FEATURE Location/Qualifiers
source 1..17
mol_type = protein
organism = unidentified
SEQ ID NO: 107
KTVSSELSCR EGQSYWT 17
SEQ ID NO: 108 moltype = AA length = 13
FEATURE Location/Qualifiers
source 1..13
mol_type = protein
organism = unidentified
SEQ ID NO: 108
GSFSPKCLSS RRC 13
SEQ ID NO: 109 moltype = AA length = 27
FEATURE Location/Qualifiers
source 1..27
mol_type = protein
organism = unidentified
SEQ ID NO: 109
ENKCFEQCGG WGCGCFNVNP SCLFVHT 27
SEQ ID NO: 110 moltype = AA length = 21
FEATURE Location/Qualifiers
source 1..21
mol_type = protein
organism = unidentified
SEQ ID NO: 110
WGSVSLSLDA EGISGSNSFS F 21
SEQ ID NO: 111 moltype = AA length = 13

-continued

FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 111		
RQGFLGEIRC NSE		13
SEQ ID NO: 112	moltype = AA length = 23	
FEATURE	Location/Qualifiers	
source	1..23	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 112		
AHESCLRAPN LVSYKPMIDQ LEC		23
SEQ ID NO: 113	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 113		
DPFVVFERGS LPQTR		15
SEQ ID NO: 114	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 114		
QAFSKGSVQA DLTLMFD		17
SEQ ID NO: 115	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 115		
CDAAFLNLTG CYSCNAG		17
SEQ ID NO: 116	moltype = AA length = 19	
FEATURE	Location/Qualifiers	
source	1..19	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 116		
CQILHFTVPE VEEEFMYSC		19
SEQ ID NO: 117	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 117		
STVVNPKSGS WN		12
SEQ ID NO: 118	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 118		
FFDWFSGLMS WFGGPLK		17
SEQ ID NO: 119	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 119		
GLFGAIAGFI EGGWTG		16
SEQ ID NO: 120	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 120		
GLFGAIAGFI EGGWQG		16
SEQ ID NO: 121	moltype = AA length = 16	

-continued

FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 121		
GIFGAIAGFI ENGWEG		16
SEQ ID NO: 122	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 122		
GLFGAIAGFI ENGWQG		16
SEQ ID NO: 123	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 123		
GIFGAIAGFI EGGWTG		16
SEQ ID NO: 124	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 124		
GLFGAIAGFI EGGWSG		16
SEQ ID NO: 125	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 125		
GLFGAIAGFI EGGWPG		16
SEQ ID NO: 126	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 126		
GFFGAIAGFL EGGWEG		16
SEQ ID NO: 127	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 127		
GAIALGVATA AAVTAG		16
SEQ ID NO: 128	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 128		
FLGLILGLGA AVTAGVA		17
SEQ ID NO: 129	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 129		
TNEAVVSLTN GMSVL		15
SEQ ID NO: 130	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 130		
VIRFQQLNKR LLE		13
SEQ ID NO: 131	moltype = AA length = 10	

-continued

FEATURE	Location/Qualifiers	
source	1..10	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 131		
REFSSNAGLT		10
SEQ ID NO: 132	moltype = AA length = 14	
FEATURE	Location/Qualifiers	
source	1..14	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 132		
MLTDRELTSI VGGM		14
SEQ ID NO: 133	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 133		
YVIQLPLFGV MDTDCW		16
SEQ ID NO: 134	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 134		
CLARADNGWY CHNAGSLSYF P		21
SEQ ID NO: 135	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 135		
DTLKSLTVPV TSRECN		16
SEQ ID NO: 136	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 136		
YDCKISTSKT YVSTAVLTTM G		21
SEQ ID NO: 137	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 137		
VSCYGHNSCT VIN		13
SEQ ID NO: 138	moltype = AA length = 22	
FEATURE	Location/Qualifiers	
source	1..22	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 138		
ESLVIISPSV ADLDPYDRSL HS		22
SEQ ID NO: 139	moltype = AA length = 34	
FEATURE	Location/Qualifiers	
source	1..34	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 139		
PLSFPDDKFD VAIRDVEHSI NQTRTFLKAS DQLL		34
SEQ ID NO: 140	moltype = AA length = 25	
FEATURE	Location/Qualifiers	
source	1..25	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 140		
KIMTSKTDIS SSVITSIGAI VSCYG		25
SEQ ID NO: 141	moltype = AA length = 18	

-continued

FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 141		
RSAIEDLLFD KVKLSDVG		18
SEQ ID NO: 142	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 142		
VPFYLNVQYR INGLGVT		17
SEQ ID NO: 143	moltype = AA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 143		
VLSQNQKLIA NAFNNALHAI Q		21
SEQ ID NO: 144	moltype = AA length = 16	
FEATURE	Location/Qualifiers	
source	1..16	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 144		
TNSALVKIQA VVNANA		16
SEQ ID NO: 145	moltype = AA length = 24	
FEATURE	Location/Qualifiers	
source	1..24	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 145		
AEAQIDRLIN GRLTALNAYV SQQL		24
SEQ ID NO: 146	moltype = AA length = 31	
FEATURE	Location/Qualifiers	
source	1..31	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 146		
SAAQAMEKVN ECVKSQSSRI NFCGNGNHII S		31
SEQ ID NO: 147	moltype = AA length = 14	
FEATURE	Location/Qualifiers	
source	1..14	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 147		
APYGLYFIHF NYVP		14
SEQ ID NO: 148	moltype = AA length = 32	
FEATURE	Location/Qualifiers	
source	1..32	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 148		
LQEAIKVLNH SYINLKDIGT YEYYVKWPWY VW		32
SEQ ID NO: 149	moltype = AA length = 23	
FEATURE	Location/Qualifiers	
source	1..23	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 149		
NALINDQLIM KNHLRDIMGI PYC		23
SEQ ID NO: 150	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 150		
FTWTLSDSEG KDTPGGYCLT		20
SEQ ID NO: 151	moltype = AA length = 29	

-continued

FEATURE Location/Qualifiers
source 1..29
mol_type = protein
organism = unidentified
SEQ ID NO: 151
KCFGNTAIAK CNQKHDEEFC DMLRLFDFN 29
SEQ ID NO: 152 moltype = AA length = 24
FEATURE Location/Qualifiers
source 1..24
mol_type = protein
organism = unidentified
SEQ ID NO: 152
MLQKEYMERQ GKTPLGLVDL FVFS 24
SEQ ID NO: 153 moltype = AA length = 16
FEATURE Location/Qualifiers
source 1..16
mol_type = protein
organism = unidentified
SEQ ID NO: 153
FNPLGFFPSH QLDPLF 16
SEQ ID NO: 154 moltype = AA length = 13
FEATURE Location/Qualifiers
source 1..13
mol_type = protein
organism = unidentified
SEQ ID NO: 154
ADWDKNPNKD PWP 13
SEQ ID NO: 155 moltype = AA length = 20
FEATURE Location/Qualifiers
source 1..20
mol_type = protein
organism = unidentified
SEQ ID NO: 155
MESITSGFLG PLLVLQAVFF 20
SEQ ID NO: 156 moltype = AA length = 25
FEATURE Location/Qualifiers
source 1..25
mol_type = protein
organism = unidentified
SEQ ID NO: 156
LLTRILTIPQ SLDSWWTSLN FLGGA 25
SEQ ID NO: 157 moltype = AA length = 12
FEATURE Location/Qualifiers
source 1..12
mol_type = protein
organism = unidentified
SEQ ID NO: 157
CPPTCPGYRW MC 12
SEQ ID NO: 158 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 158
LFILLLCLIF LLVLLDYQ 18
SEQ ID NO: 159 moltype = AA length = 15
FEATURE Location/Qualifiers
source 1..15
mol_type = protein
organism = unidentified
SEQ ID NO: 159
ETRTVWQLSV AGVSC 15
SEQ ID NO: 160 moltype = AA length = 24
FEATURE Location/Qualifiers
source 1..24
mol_type = protein
organism = unidentified
SEQ ID NO: 160
LDGYLCRKQK WEVTCTETWY FVTD 24
SEQ ID NO: 161 moltype = AA length = 14

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FEATURE	Location/Qualifiers	
source	1..14	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 161		
KYQIIEVIPT ENEC		14
SEQ ID NO: 162	moltype = AA length = 24	
FEATURE	Location/Qualifiers	
source	1..24	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 162		
LKGEYIPPYY PPTNCVWNAI DTQE		24
SEQ ID NO: 163	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 163		
IEDPVTMTLM DSKFTKPC		18
SEQ ID NO: 164	moltype = AA length = 13	
FEATURE	Location/Qualifiers	
source	1..13	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 164		
LHCQIKSWEC IPV		13
SEQ ID NO: 165	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 165		
SHRNMMEALY LESPD		15
SEQ ID NO: 166	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 166		
LTFCGYNGIL LDNGEWWSIY		20
SEQ ID NO: 167	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 167		
ELEHEKCLGT LEKLQNGE		18
SEQ ID NO: 168	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 168		
LDLSYLSPSN PGKHYAY		17
SEQ ID NO: 169	moltype = AA length = 15	
FEATURE	Location/Qualifiers	
source	1..15	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 169		
IRAVCYYHTF SMNLD		15
SEQ ID NO: 170	moltype = AA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 170		
EWKTTCDYRW YGPQYITHSI		20
SEQ ID NO: 171	moltype = AA length = 15	

-continued

FEATURE Location/Qualifiers
source 1..15
mol_type = protein
organism = unidentified
SEQ ID NO: 171
LGFPPQSCGW ASVTT 15
SEQ ID NO: 172 moltype = AA length = 23
FEATURE Location/Qualifiers
source 1..23
mol_type = protein
organism = unidentified
SEQ ID NO: 172
KGSSIGKMFE STYRGAKRMA ILG 23
SEQ ID NO: 173 moltype = AA length = 23
FEATURE Location/Qualifiers
source 1..23
mol_type = protein
organism = unidentified
SEQ ID NO: 173
KGSSIGKMFE ATARGARRMA ILG 23
SEQ ID NO: 174 moltype = AA length = 23
FEATURE Location/Qualifiers
source 1..23
mol_type = protein
organism = unidentified
SEQ ID NO: 174
KGSSIGQMFE TTMRGAKRMA ILG 23
SEQ ID NO: 175 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 175
PALSTGLIHL HQNIVDVQ 18
SEQ ID NO: 176 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 176
PALSTGLIHL HRNIVDVQ 18
SEQ ID NO: 177 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 177
PALSTGLIHL HQNIVDTQ 18
SEQ ID NO: 178 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 178
WTYNAELLVL LENERTLD 18
SEQ ID NO: 179 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 179
NAELLVLLEN ERTLDYHD 18
SEQ ID NO: 180 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 180
WTYNAELLVL MENERTLD 18
SEQ ID NO: 181 moltype = AA length = 18

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FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 181		
NAELLVLMEN ERTLDYHD		18
SEQ ID NO: 182	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 182		
WSYNAELLVA LENQHTID		18
SEQ ID NO: 183	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 183		
NAELLVALEN QHTIDLTD		18
SEQ ID NO: 184	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 184		
NAELLVALEN QHTIDVTD		18
SEQ ID NO: 185	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 185		
NAELLVLMEN ERTLDFHD		18
SEQ ID NO: 186	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 186		
NAELLVLLEN ERTLDMHD		18
SEQ ID NO: 187	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 187		
WSYNAELLVA MENQHTID		18
SEQ ID NO: 188	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 188		
NAELLVAMEN QHTIDLAD		18
SEQ ID NO: 189	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 189		
WAYNAELLVL LENQKTLD		18
SEQ ID NO: 190	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 190		
NAELLVLLEN QKTLDEHD		18
SEQ ID NO: 191	moltype = AA length = 18	

-continued

FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 191		
WTYQAELLVA MENQHTID		18
SEQ ID NO: 192	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 192		
QAELLVAMEN QHTIDMAD		18
SEQ ID NO: 193	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 193		
WSYNAQLLVL LENEKTLD		18
SEQ ID NO: 194	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 194		
NAQLLVLLEN EKTLDLHD		18
SEQ ID NO: 195	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 195		
WSYNAKLLVL LENDKTLD		18
SEQ ID NO: 196	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 196		
NAKLLVLLEN DKTLDMHD		18
SEQ ID NO: 197	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 197		
WSYNAKLLVL IENDRTLD		18
SEQ ID NO: 198	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 198		
NAKLLVLIEN DRTLDLHD		18
SEQ ID NO: 199	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 199		
ISSQIELAVL LSNEGIIN		18
SEQ ID NO: 200	moltype = AA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = protein	
	organism = unidentified	

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SEQ ID NO: 200
QIELAVLLSN EGIINSED 18

SEQ ID NO: 201 moltype = AA length = 15
FEATURE Location/Qualifiers
source 1..15
mol_type = protein
organism = unidentified
SEQ ID NO: 201
GLFGAAGFIE NGWEG 15

SEQ ID NO: 202 moltype = AA length = 14
FEATURE Location/Qualifiers
source 1..14
mol_type = protein
organism = unidentified
SEQ ID NO: 202
DRGWGNGCGD FGKG 14

SEQ ID NO: 203 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 203
NAELLVLLEN ERTLDFHD 18

SEQ ID NO: 204 moltype = AA length = 19
FEATURE Location/Qualifiers
source 1..19
mol_type = protein
organism = unidentified
SEQ ID NO: 204
GDTAWDFGSV GGVLNSLGK 19

SEQ ID NO: 205 moltype = AA length = 27
FEATURE Location/Qualifiers
source 1..27
mol_type = protein
organism = unidentified
SEQ ID NO: 205
TLLNGPAFQL VCPYGWTGTI ECDSYYQ 27

SEQ ID NO: 206 moltype = AA length = 16
FEATURE Location/Qualifiers
source 1..16
mol_type = protein
organism = unidentified
SEQ ID NO: 206
ILGPDGNVLI PEMQSS 16

SEQ ID NO: 207 moltype = AA length = 14
FEATURE Location/Qualifiers
source 1..14
mol_type = protein
organism = unidentified
SEQ ID NO: 207
LLNTPPPYQV SCGG 14

SEQ ID NO: 208 moltype = AA length = 18
FEATURE Location/Qualifiers
source 1..18
mol_type = protein
organism = unidentified
SEQ ID NO: 208
WSYNAELLVA MENQHLAD 18

SEQ ID NO: 209 moltype = AA length = 27
FEATURE Location/Qualifiers
source 1..27

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	mol_type = protein
	organism = unidentified
SEQ ID NO: 209	
EVFAQVKQMY KTPTLKYFGG FNFSQIL	27
SEQ ID NO: 210	moltype = AA length = 27
FEATURE	Location/Qualifiers
source	1..27
	mol_type = protein
	organism = unidentified
SEQ ID NO: 210	
EVFAQVKQMY KTPAIKDFGG FNFSQIL	27
SEQ ID NO: 211	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 211	
SFIEDLLFNK VTLADAGF	18
SEQ ID NO: 212	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 212	
SAIEDLLFNK VRLSDVGF	18
SEQ ID NO: 213	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 213	
SLLEDLLFNK VKLSDVGF	18
SEQ ID NO: 214	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 214	
SAIEDLLFSK VKLADVGF	18
SEQ ID NO: 215	moltype = AA length = 18
FEATURE	Location/Qualifiers
source	1..18
	mol_type = protein
	organism = unidentified
SEQ ID NO: 215	
SAIEDLLFDK VKLSDVGF	18
SEQ ID NO: 216	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = unidentified
SEQ ID NO: 216	
GAAIGLAWIP YFGPAAE	17
SEQ ID NO: 217	moltype = AA length = 17
FEATURE	Location/Qualifiers
source	1..17
	mol_type = protein
	organism = unidentified
SEQ ID NO: 217	
GAAVGLAWIP YFGPAAE	17
SEQ ID NO: 218	moltype = AA length = 17

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FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 218		
GAAAGLAWIP YFGPAAE		17
SEQ ID NO: 219	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 219		
DLAAGLSWIP FFGPGIE		17
SEQ ID NO: 220	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 220		
HNAAGIAWIP YFGPGAE		17
SEQ ID NO: 221	moltype = AA length = 23	
FEATURE	Location/Qualifiers	
source	1..23	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 221		
AVGLGALFLG FLGAAGSTMG AAS		23
SEQ ID NO: 222	moltype = AA length = 12	
FEATURE	Location/Qualifiers	
source	1..12	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 222		
LTLTGQARQL LS		12
SEQ ID NO: 223	moltype = AA length = 17	
FEATURE	Location/Qualifiers	
source	1..17	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 223		
GIVQQQSNLL QAIEAQQ		17
SEQ ID NO: 224	moltype = AA length = 33	
FEATURE	Location/Qualifiers	
source	1..33	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 224		
GLGAMFLGFL GAAGSTMGAA SLTLTVQARQ LLS		33
SEQ ID NO: 225	moltype = AA length = 33	
FEATURE	Location/Qualifiers	
source	1..33	
	mol_type = protein	
	organism = unidentified	
SEQ ID NO: 225		
GIGAMFLGLL SAAGSTMSAA AITLTVQTRQ LLS		33
SEQ ID NO: 226	moltype = AA length = 33	
FEATURE	Location/Qualifiers	
source	1..33	
	mol_type = protein	
	organism = unidentified	

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SEQ ID NO: 226
GIGAMFLGLL SAAGSTMGAA AITLTVQTRQ LLS 33

SEQ ID NO: 227 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 227
GIGAVFLGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 228 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 228
GVGALFLGFL SAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 229 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 229
GIGAMILGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 230 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 230
GLGAMFLGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 231 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 231
GFGAMFLGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 232 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 232
TLGAMFLGFL GAAGSTMGAA SMTLTVQARQ LLS 33

SEQ ID NO: 233 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 233
GLGAVFLGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 234 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 234
TIGAMFLGFL GAAGSTMGAA SITLTVQARR LLS 33

SEQ ID NO: 235 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33

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                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 235
TIGAMFLGFL GAAGSTMGAA SMTLTVQARL LLS                              33

SEQ ID NO: 236       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 236
TLGAMFLGFL GAAGSTMGAA SMTLTVQARL LFS                              33

SEQ ID NO: 237       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 237
TLGAMFLGFL GAAGSTMGAA SLTLTVQARL LLS                              33

SEQ ID NO: 238       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 238
GVGAMFLGFL GAAGSTMGAA SLTLTVQARQ LLS                              33

SEQ ID NO: 239       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 239
GLGAMFLGFL GAAGSTMGAA SITLTVQARL LLS                              33

SEQ ID NO: 240       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 240
TLGAVFLGFL GAAGSTMGAA SLTLTVQARL LLS                              33

SEQ ID NO: 241       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 241
GIGAVFLGFL GAAGSTMGAA SITLTVQARK LLS                              33

SEQ ID NO: 242       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 242
GIGALFLGFL GAAGSTMGAA SVTLTVQARQ LLS                              33

SEQ ID NO: 243       moltype = AA  length = 33
FEATURE              Location/Qualifiers
source               1..33
                     mol_type = protein
                     organism = unidentified
SEQ ID NO: 243
GLGALFLGFL GAAGSTMGAA SVTLTVQARQ LLS                              33

SEQ ID NO: 244       moltype = AA  length = 33
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FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 244
GIGAMFLGFL GAAGSTMGAA SITLTVQARL LLS 33

SEQ ID NO: 245 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 245
GIGAMFLGFL GAAGSTMGAA SVTLTVQARL LLS 33

SEQ ID NO: 246 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 246
AIGALFLGFL GAAGSTMGAA SVTLTVQARL LLS 33

SEQ ID NO: 247 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 247
TLGAMFLGFL GAAGSTMGAA SLTLTVQARQ LLS 33

SEQ ID NO: 248 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 248
GIGALFLGFL GAAGSTMGAA SMTLTVQARQ LLS 33

SEQ ID NO: 249 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 249
GIGAMFLGFL GAAGSTMGAA SLTLTVQARQ LLS 33

SEQ ID NO: 250 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 250
GIGAVFLGFL GAAGSTMGAA SMTLTVQARL LLS 33

SEQ ID NO: 251 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 251
GIGALFLGFL GAAGSTMGAA SLTLTVQARQ LLS 33

SEQ ID NO: 252 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified

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SEQ ID NO: 252
GIGAVFLGIL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 253 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 253
GIGAVFLGFL GAAGSTMGAA SVTLTVQARQ LLF 33

SEQ ID NO: 254 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 254
GLGAMFFGFL GAAGSTMGAA SVTLTVQARQ LLS 33

SEQ ID NO: 255 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 255
GIGALFLGFL GAAGSTMGAA SITLTVQARL LLS 33

SEQ ID NO: 256 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 256
GLGALFVGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 257 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 257
GIGALFLGFL GTAGSTMGAA SVTLTVQARQ LLS 33

SEQ ID NO: 258 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 258
GIGAMIFGFL GAAGSTMGAA SITLTVQARQ LLS 33

SEQ ID NO: 259 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 259
GLGAVLLGFL GTAGSTMGAA SLTLTVQVRQ LLS 33

SEQ ID NO: 260 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33
mol_type = protein
organism = unidentified
SEQ ID NO: 260
GIGAVLFGFL GAAGSTMGAA SITLTVQVRQ LLS 33

SEQ ID NO: 261 moltype = AA length = 33
FEATURE Location/Qualifiers
source 1..33

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	mol_type = protein
	organism = unidentified
SEQ ID NO: 261	
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SEQ ID NO: 262	moltype = AA length = 33
FEATURE	Location/Qualifiers
source	1..33
	mol_type = protein
	organism = unidentified
SEQ ID NO: 262	
GTLGAMFLGF LGAAGSTMGA ASMTLTVQAR QLL	33
SEQ ID NO: 263	moltype = AA length = 33
FEATURE	Location/Qualifiers
source	1..33
	mol_type = protein
	organism = unidentified
SEQ ID NO: 263	
GTIGAMFLGF LGAAGSTMGA ASITLTVQAR RLL	33
SEQ ID NO: 264	moltype = AA length = 33
FEATURE	Location/Qualifiers
source	1..33
	mol_type = protein
	organism = unidentified
SEQ ID NO: 264	
GTIGAMFLGF LGAAGSTMGA ASMTLTVQAR LLL	33
SEQ ID NO: 265	moltype = AA length = 33
FEATURE	Location/Qualifiers
source	1..33
	mol_type = protein
	organism = unidentified
SEQ ID NO: 265	
IGALFLGFLG AAGSTMGAAS VTLTVQARLL LSG	33
SEQ ID NO: 266	moltype = AA length = 23
FEATURE	Location/Qualifiers
source	1..23
	mol_type = protein
	organism = unidentified
SEQ ID NO: 266	
AVGMVIFLLV LAIMAMTASV TAA	23
SEQ ID NO: 267	moltype = AA length = 20
FEATURE	Location/Qualifiers
source	1..20
	mol_type = protein
	organism = unidentified
SEQ ID NO: 267	
FGISAIVAAI VAATAIAASA	20
SEQ ID NO: 268	moltype = AA length = 21
FEATURE	Location/Qualifiers
source	1..21
	mol_type = protein
	organism = unidentified
SEQ ID NO: 268	
TLALVTATTA GLIGTTTGTS A	21
SEQ ID NO: 269	moltype = AA length = 21
FEATURE	Location/Qualifiers
source	1..21
	mol_type = protein
	organism = unidentified
SEQ ID NO: 269	
HVMLALATVL SMAGAGTGAT A	21
SEQ ID NO: 270	moltype = AA length = 20

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FEATURE Location/Qualifiers
source 1..20
mol_type = protein
organism = unidentified
SEQ ID NO: 270
GIGLVIMLVT MAIVAAAGAS 20

SEQ ID NO: 271 moltype = AA length = 20
FEATURE Location/Qualifiers
source 1..20
mol_type = protein
organism = unidentified
SEQ ID NO: 271
GVMVLGFLGF LAMAGSAMGA 20

SEQ ID NO: 272 moltype = AA length = 20
FEATURE Location/Qualifiers
source 1..20
mol_type = protein
organism = unidentified
SEQ ID NO: 272
GVFVLGFLGF LATAGSAMGA 20

SEQ ID NO: 273 moltype = AA length = 19
FEATURE Location/Qualifiers
source 1..19
mol_type = protein
organism = unidentified
SEQ ID NO: 273
GAIVLGLLGF LGLAGSAMG 19

SEQ ID NO: 274 moltype = AA length = 28
FEATURE Location/Qualifiers
source 1..28
mol_type = protein
organism = unidentified
SEQ ID NO: 274
GIGLVIVLAI MAIIAAAGAG LGVANAVQ 28

SEQ ID NO: 275 moltype = AA length = 21
FEATURE Location/Qualifiers
source 1..21
mol_type = protein
organism = unidentified
SEQ ID NO: 275
SRKLGRSLIP HSCFWWLFLL C 21

SEQ ID NO: 276 moltype = AA length = 17
FEATURE Location/Qualifiers
source 1..17
mol_type = protein
organism = unidentified
SEQ ID NO: 276
GNGNSSTYQY IYNLTIC 17

SEQ ID NO: 277 moltype = AA length = 24
FEATURE Location/Qualifiers
source 1..24
mol_type = protein
organism = unidentified
SEQ ID NO: 277
GTAWLSTHFS WAVETFVLYH ILSL 24

SEQ ID NO: 278 moltype = AA length = 23
FEATURE Location/Qualifiers
source 1..23
mol_type = protein
organism = unidentified

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SEQ ID NO: 278
GFLTTSHFFD TLGLGAVSIT GFC 23

SEQ ID NO: 279 moltype = AA length = 21
FEATURE Location/Qualifiers
source 1..21
mol_type = protein
organism = unidentified
SEQ ID NO: 279
RYAHTRFTNF IVDDRGRIHR W 21

SEQ ID NO: 280 moltype = AA length = 17
FEATURE Location/Qualifiers
source 1..17
mol_type = protein
organism = unidentified
SEQ ID NO: 280
SNNNSSHIQL IYNLTLC 17

SEQ ID NO: 281 moltype = AA length = 24
FEATURE Location/Qualifiers
source 1..24
mol_type = protein
organism = unidentified
SEQ ID NO: 281
GTDWLAQKFD WAVETFVIFP VLTH 24

SEQ ID NO: 282 moltype = AA length = 23
FEATURE Location/Qualifiers
source 1..23
mol_type = protein
organism = unidentified
SEQ ID NO: 282
GALTTSHFLD TVGLATVSTA GYY 23

SEQ ID NO: 283 moltype = AA length = 21
FEATURE Location/Qualifiers
source 1..21
mol_type = protein
organism = unidentified
SEQ ID NO: 283
IYAVCALAAL ICFVIRLAKN C 21

SEQ ID NO: 284 moltype = AA length = 32
FEATURE Location/Qualifiers
source 1..32
mol_type = protein
organism = unidentified
SEQ ID NO: 284
VSTAGYYHGR YVLSSIYAVC ALAALICFVI RL 32

SEQ ID NO: 285 moltype = AA length = 29
FEATURE Location/Qualifiers
source 1..29
mol_type = protein
organism = unidentified
SEQ ID NO: 285
AEVQIDRLIT GRLQSLQTYV CGGEKEKEK 29

SEQ ID NO: 286 moltype = AA length = 26
FEATURE Location/Qualifiers
source 1..26
mol_type = protein
organism = unidentified
SEQ ID NO: 286
GAAIGLAWIP YFGPAAECGG EKEKEK 26

SEQ ID NO: 287 moltype = AA length = 25
FEATURE Location/Qualifiers
source 1..25

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mol_type = protein	
organism = unidentified	
SEQ ID NO: 287	
GLFGAIAGFI ENGWEGCGGE KEKEK	25
SEQ ID NO: 288 moltype = DNA length = 23	
FEATURE Location/Qualifiers	
source 1..23	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 288	
gtggcaatga ggatgacttg ttc	23
SEQ ID NO: 289 moltype = DNA length = 22	
FEATURE Location/Qualifiers	
source 1..22	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 289	
tagtggtggt cggagattcg ta	22
SEQ ID NO: 290 moltype = DNA length = 21	
FEATURE Location/Qualifiers	
source 1..21	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 290	
agccactcac ctcttcagaa c	21
SEQ ID NO: 291 moltype = DNA length = 21	
FEATURE Location/Qualifiers	
source 1..21	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 291	
gcctctttgc tgctttcaca c	21
SEQ ID NO: 292 moltype = DNA length = 19	
FEATURE Location/Qualifiers	
source 1..19	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 292	
gtgatgcccc aagctgaga	19
SEQ ID NO: 293 moltype = DNA length = 20	
FEATURE Location/Qualifiers	
source 1..20	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 293	
cacggccttg ctcttgtttt	20
SEQ ID NO: 294 moltype = DNA length = 20	
FEATURE Location/Qualifiers	
source 1..20	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 294	
ctgctgcact ttggagtgat	20
SEQ ID NO: 295 moltype = DNA length = 20	
FEATURE Location/Qualifiers	
source 1..20	
mol_type = unassigned DNA	
organism = unidentified	
SEQ ID NO: 295	
agatgatctg actgcctggg	20
SEQ ID NO: 296 moltype = DNA length = 18	

-continued

FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 296		
tgagtcctgc tccttcca		18
SEQ ID NO: 297	moltype = DNA length = 18	
FEATURE	Location/Qualifiers	
source	1..18	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 297		
gcttcggtgt agcccatt		18
SEQ ID NO: 298	moltype = DNA length = 22	
FEATURE	Location/Qualifiers	
source	1..22	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 298		
catcgtggct aaacaggtac tg		22
SEQ ID NO: 299	moltype = DNA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 299		
gcacgacctt gagggcagca		20
SEQ ID NO: 300	moltype = DNA length = 20	
FEATURE	Location/Qualifiers	
source	1..20	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 300		
attgaaatca gccagcacgc		20
SEQ ID NO: 301	moltype = DNA length = 21	
FEATURE	Location/Qualifiers	
source	1..21	
	mol_type = unassigned DNA	
	organism = unidentified	
SEQ ID NO: 301		
aggaaccaca gtgccagatc c		21

1. Pharmaceutical product comprising an immune suppressive domain from a virus fusion protein as an active substance, wherein said immune suppressive domain is from a virus of the Orthomyxoviridae family.

2. The pharmaceutical composition according to claim **1**, wherein said pharmaceutical composition further comprises at least one pharmaceutically acceptable carrier, preservative, buffer, and/or surfactant.

3. The pharmaceutical composition according to claim **1**, wherein said immune suppressive domain is from a virus of the Influenza virus A genus.

4. The pharmaceutical composition according to claim **1**, wherein said immune suppressive domain comprises SEQ ID NO: 4 and/or SEQ ID NO: 287.

5. The pharmaceutical composition according to claim **1**, wherein said immune suppressive domain is connected to at least one additional immune suppressive domain to form a dimer.

6. The pharmaceutical composition according to claim **5**, wherein said dimer is a homodimer and comprises at least two immune suppressive domains with SEQ ID NO. 4, wherein said immune suppressive domains are cross-linked by a disulfide bond at the N-terminal or the C-terminal.

7. A pharmaceutical composition comprising an immunosuppressive polypeptide that is a dimer formed by two peptides comprising SEQ ID NO: 4 as an active substance subject to at least one of the following provisos:

(i) said pharmaceutical composition is a parenteral, subcutaneous or oral formulation;

(ii) said pharmaceutical composition is an injection liquid or infusion liquid;

(iii) said pharmaceutical composition comprises a pharmaceutically acceptable carrier selected from solid, semisolid and liquid;

(iv) said pharmaceutical composition is a suspension, solution, emulsion, gel, cream, or powder;

(v) said pharmaceutical composition comprises 0.5-25% by weight of said peptides in solution; or

(vi) said two peptides comprise SEQ ID NO: 4 and an additional cysteine at the C-terminal or N-terminal end of

SEQ ID NO: 4, wherein said cysteine residues crosslink the two peptides via a disulfide bond.

8. The pharmaceutical composition according to claim **7**, wherein said pharmaceutical composition is selected from a parenteral composition, a subcutaneous formulation, and an oral composition.

9. The pharmaceutical composition according to claim **7**, wherein said pharmaceutical composition is suitable for IV, oral, parenteral, intraperitoneal, subcutaneous or intramuscular administration.

10. A pharmaceutical composition according to claim **7**, wherein said pharmaceutical composition is packaged in unit-dose or multi-dose sealed containers, and/or packaged in ampoules and/or vials.

11. The pharmaceutical composition according to claim **7**, wherein said pharmaceutical composition is a vaccine.

12. The pharmaceutical composition according to claim **7** obtainable by freeze-drying or which is suitable to be stored in a freeze-dried (lyophilized) condition.

13. The pharmaceutical composition according to claim **7** comprising a pharmaceutically acceptable carrier, preservative, buffer, and/or surfactant.

14. A pharmaceutical composition according to claim **7**, wherein one or more amino acid residues in said polypeptide are modified by in vitro or in vivo chemical derivatization, wherein said chemical derivatization is selected from acetylation, carboxylation, glycosylation and phosphorylation, or wherein said polypeptide comprises blocking groups and wherein said blocking groups are either coupled to the N-terminus or used in place of the N-terminal amino acid residue of said polypeptide and/or coupled to the C-terminus or used in place of the C-terminal amino acid residue of said polypeptide.

15. The pharmaceutical composition according to claim **7**, wherein the two peptides comprise a cysteine residue at a C-terminal end of SEQ ID NO. 4.

16. The pharmaceutical composition according to claim **7**, wherein each of the two peptides consists of SEQ ID NO. 287.

17. The pharmaceutical composition according to claim **7**, wherein said immune suppressive domains are cross-linked by a disulfide bond at the N-terminal or the C-terminal.

18. The pharmaceutical composition according to claim **7**, wherein said dimer is a homodimer.

19. The pharmaceutical composition of claim **7**, wherein said composition contains from 0.5 to 25% by weight of the active substance in solution.

20. A peptide comprising SEQ ID NO. 287.

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