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(54) Titre : UTILISATION DE PROTEINES ET DE PEPTIDES IMMUNOSUPPRESSEURS HUMAINS COMME
MEDICAMENTS

(54) Title: USE OF HUMAN DERIVED IMMUNOSUPPRESSIVE PROTEINS AND PEPTIDES AS MEDICAMENTS

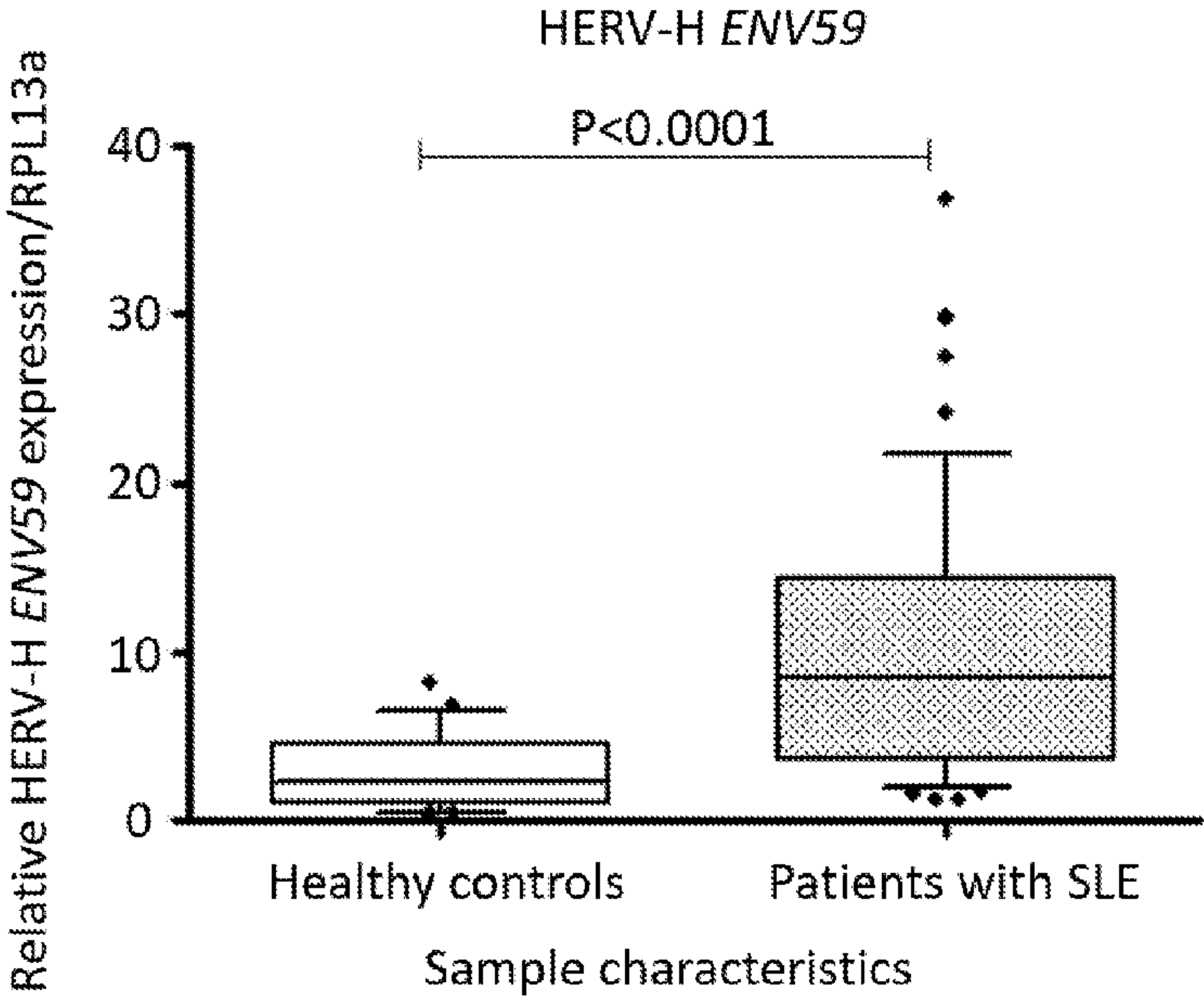


Fig. 1

(57) **Abrégé/Abstract:**
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(74) Agent: INSPICOS P/S; Kogle Allé 2, 2970 Hørsholm (DK).

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(71) Applicant: STEMGUARD A/S [DK/DK]; Åbogade 15, 8200 Aarhus N (DK).

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(72) Inventors: LASKA, Magdalena Janina; Thunøgade 26 st. tv, 8000 Aarhus C (DK). TROLDBORG, Anne Margrethe; Klokkefaldet 22, 8210 Aarhus V (DK). STENGAARD-PEDERSEN, Kristian; Sejrs Allé 17, 8240 Risskov (DK). BAHRAMI, Shervin; Stenkelbjergvej 15, 8381 Tilst (DK).

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(54) Title: USE OF HUMAN DERIVED IMMUNOSUPPRESSIVE PROTEINS AND PEPTIDES AS MEDICAMENTS

(57) Abstract: The present invention concerns uses of immune modulating and immune suppressing peptides from human endogenous retroviruses. In particular, the present invention concerns a use of an immune suppressive peptide for immune suppression and for reduction of inflammation.

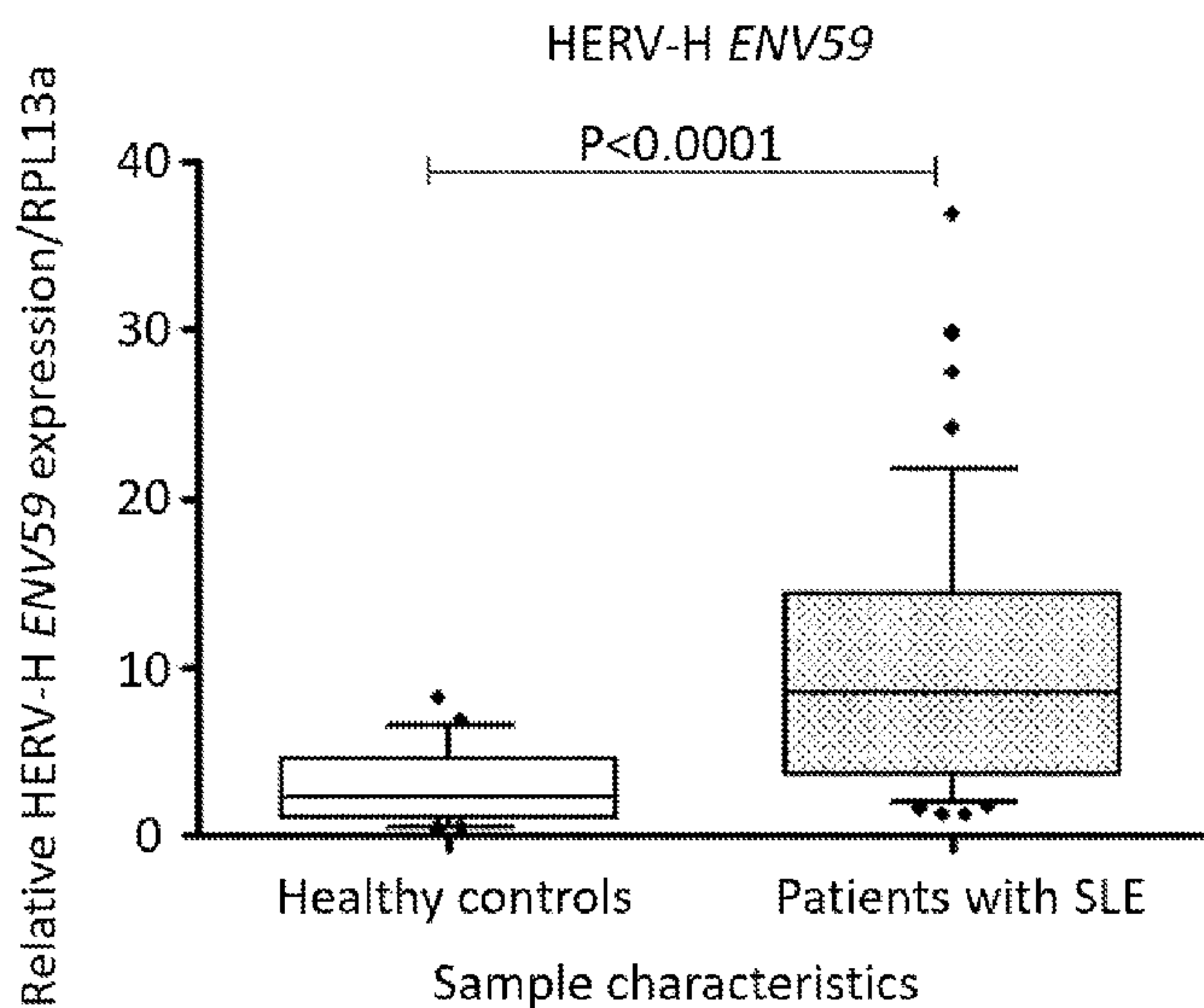


Fig. 1

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Use of human derived immunosuppressive proteins and peptides as Medicaments

The present invention relates to proteins related to human endogenous retrovirus and peptides derived from such proteins and use of the same for therapeutic applications. In particular, the present invention relates to immune modulating activity and immune suppressive domains (ISDs) related to human
 5 endogenous retrovirus and their use for immune modulation and for reduction of inflammation. Further, the invention relates to a class of multifunctional drugs for treatment of autoimmune diseases as well as inflammatory diseases. Additionally, the invention relates to pharmaceutical compositions comprising immune modulating proteins and peptides (proteins and peptides hereinafter generically referred to as polypeptides) that are derived from endogenous retroviruses.

10 Additionally the present invention relates to materials, surfaces and/or particles that are coupled to such a polypeptide. The present invention further relates to methods for producing the proteins, peptides and pharmaceutical compositions, as well as the usage of the same.

Technical Background

Retroviruses are a group of viruses that are characterized by containing an RNA genome, which upon
 15 infection is reverse transcribed into a DNA copy, which is subsequently integrated into the genome of the host cells. As a consequence hereof, all the progeny of such an infected cell will contain the viral genome (referred to as a pro-virus). All retroviruses include the following three genes/coding sequences: *gag* – which contains the structural proteins of the virus, *pol* – which contains the enzymes including the reverse transcriptase, and finally *env* – which encodes the viral surface glycoprotein, which is primarily responsible
 20 for viral entry into host cells as well as the immune suppressive activity demonstrated by many retroviruses. The present invention primarily relates the *env* gene and its protein product the ENV protein, derivatives thereof, peptides derived from this as well as the use of any of these compounds or entities.

Human Endogenous Retro Viruses (HERVs) are ancient retroviral integrations, which have been permanently fixed in the genome of humans. Although most of HERVs elements have accumulated
 25 numerous mutations and deletions, the existence of functional proteins for most viral components of HERVs have been demonstrated, including the viral protease and the envelope surface protein (Schmitt, Reichrath, Roesch, Meese, & Mayer, 2013; Tonjes et al., 1996; Willer et al., 1997). The selective pressure obviously exerted by evolution to maintain some functional HERV envelope open reading frames (ORFs) and restrict their expression to specific tissues suggests that HERV derived proteins may have developed to
 30 exhibit a significant physiological potential. For example, HERV derived envelope glycoproteins are abundantly expressed in placenta tissue (Boyd, Bax, Bax, Bloxam, & Weiss, 1993) and have been proposed

to participate in syncytiotrophoblast differentiation by fusing the underlying cytotrophoblast cell layer (Venables, Brookes, Griffiths, Weiss, & Boyd, 1995).

Retroviral infections in general can cause significant immunosuppression. In particular some human endogenous retroviruses show immune suppressive activity and can for example antagonize the immune-
5 dependent elimination of tumor cells transplanted into immunocompetent mice after transduction of these tumor cells by an envelope-expression vector (Mangenev & Heidmann, 1998).

The HERV-H family is one of the most abundant groups among human endogenous retroviruses, with approximately 1000 elements per haploid genome. Most of the HERV-H proviruses include deletions and/or mutations, rendering them without significant open reading frame activity. However, a small subset are
10 structurally intact and have full-length *gag*, *pol*, and *env* domains. Among the approximately 100 HERV-H derived envelope genes, only three, including HERV-H Env59 (hereafter also referred to as "Env 59"), have the capacity to encode a large protein encompassing an immune suppressive domain (hereafter also referred to as an ISU domain or just ISD). Previous knowledge regarding ISD or ISU sequences derives primarily from exogenous murine gamma retroviruses. In this case the the ISU sequence is located close to
15 the C-terminal of the envelope protein.

The immune suppressive domain constitutes a small segment of the viral glycoprotein and is a major mediator of immune suppression by retroviruses. It is well known that retroviral envelope proteins have significant immunosuppressive activity. In gamma retroviruses, this activity is located to a well-defined structure (the so called ISD) in the retroviral transmembrane (TM) protein which is conserved among
20 retroviruses of several species (including murine, feline, and human retroviruses including human T-cell leukemia virus).

Autoimmunity and autoimmune diseases

Autoimmunity is the system of immune responses of an organism against its own healthy cells and tissues. While low levels of autoimmunity help the body maintenance, high levels of autoimmunity may cause
25 disease. Any disease that results from such an aberrant immune response is termed an autoimmune disease. Autoimmune diseases have a wide variety of different effects. However the occurrence of one of three following characteristic pathological effects define a disease as autoimmune: damage to or destruction of tissue, altered organ growth or altered organ function.

There are more than 80 illnesses caused by autoimmunity and autoimmune diseases affects approximately
30 2-5% of the western world's population. Thus a substantial minority of the population suffers from these diseases, which are often chronic, debilitating, and life-threatening. Women are found to be more

commonly affected than men and it has been estimated that autoimmune diseases are among the leading causes of death among women in the United States in all age groups up to 65 years. Environmental events can trigger some cases of autoimmune diseases such as exposure to radiation or certain drugs, which can damage tissues of the body. Infections can also be a trigger of some autoimmune diseases for example
5 Lupus which is thought to be a milder version of an idiopathic disorder causing increased production of antihistone antibodies.

The treatment of autoimmune diseases is typically involves immunosuppressive medication that decreases the immune response. Novel treatments include Cytokine Blockade (therapeutic inhibition of cytokine signaling pathways), removal of effector T-cells and B-cells (e.g. anti-CD20 therapy can be effective at
10 removing instigating B-cells) and intravenous immunoglobulin, which has been helpful in treating some antibody mediated autoimmune diseases as well.

A large number of autoimmune diseases have been recognized. Due to genome wide association scans, new insight into the underlying pathophysiology of autoimmune diseases has been obtainable. As an example, this technique have identified a striking degree of genetic sharing among the autoimmune
15 diseases.

Arthritis

Arthritis is a form of joint disorder that involves inflammation of one or more joints.

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
20 rheumatoid arthritis, psoriatic arthritis, and related autoimmune diseases. Septic arthritis is caused by joint infection.

A denominator of 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
25 joints and fatigue.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a long lasting autoimmune disorder that primarily affects joints. It typically results in warm, swollen, and painful joints. Pain and stiffness often worsen following rest. Most commonly the wrist and hands are involved with typically the same joints involved on both sides of the body. The
30 disease may also affect other parts of the body. This may result in low red blood cells, inflammation around

the lungs, and inflammation around the heart. Fever and low energy may also be present. Often symptoms come on gradually over weeks to months.

While the cause of rheumatoid arthritis is not clear, it is believed to involve a combination of genetic and environmental factors. The underlying mechanism involves the body's immune system attacking the joints.

5 This results in inflammation and thickening of the joint capsule. It also affects the underlying bone and cartilage. The diagnosis is made mostly on the basis of a person's physical signs and symptoms, while X-rays and laboratory testing may support a diagnosis or exclude other diseases with similar symptoms. Other diseases that may present similarly include systemic lupus erythematosus, psoriatic arthritis, and fibromyalgia among others.

10 The goal of treatment is to decrease pain and inflammation, and improve a person's overall functioning. This may be helped by balancing rest and exercise, the use of splints and braces, or the use of assistive devices. Pain medications, steroids, and NSAIDs are frequently used to help with symptoms. A group of medications called disease-modifying antirheumatic drugs (DMARDs) may be used to try to slow the progression of disease. They include the medications hydroxychloroquine and methotrexate Biological
15 DMARDs may be used when disease does not respond to other treatments. However, they may have a greater rate of adverse effects. Surgery to repair, replace, or fusion joints may help in certain situations. Most alternative medicine treatments are not supported by evidence.

RA affects between 0.5 and 1% of adults in the developed world with between 5 and 50 per 100,000 people newly developing the condition each year. Onset is most frequent during middle age and women are
20 affected 2.5 times as frequently as men. In 2013 it resulted in 38,000 deaths up from 28,000 deaths in 1990. The term rheumatoid arthritis is based on the Greek for watery and inflamed joints.

Inflammatory synovitis in rheumatoid arthritis (and possibly in other inflammatory arthritides) 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. In RA, several cytokines, e.g.
25 interleukin (IL)-1, IL-6, IL-8, IL-12, IL-17, tumour necrosis factor- α (TNF- α), interferon- γ (IFN- γ) and granulocyte-macrophage colony-stimulating factor (GM-CSF), are involved in almost all aspects of articular inflammation and destruction.

Interleukin 6 (IL-6) plays a pivotal role in the pathophysiology of rheumatoid arthritis (RA). It is found in abundance in the synovial fluid and serum of patients with RA and the level correlates with the disease
30 activity and joint destruction. IL-6 can promote synovitis and joint destruction by stimulating neutrophil migration, osteoclast maturation and vascular endothelial growth factor (VEGF)-stimulated pannus proliferation. IL-6 may also be mediating many of the systematic manifestations of RA including inducing

the acute-phase reaction [including C-reactive protein (CRP)], anaemia through hecipidin production, fatigue via the hypothalamic—pituitary—adrenal (HPA) axis) and osteoporosis from its effect on osteoclasts. In addition, IL-6 may contribute to the induction and maintenance of the autoimmune process through B-cell maturation and TH-17 differentiation. All of the above makes IL-6 blockade a desirable therapeutic option in the treatment of RA. Following successful animal studies, a humanized anti-interleukin-6 receptor (anti-IL-6R) monoclonal antibody, tocilizumab (TCZ), entered into clinical trials and it has been shown to be an effective treatment in several large phase III clinical trials in RA with rapid and sustained improvement in disease activity, reducing radiographic joint damage and improving physical function(Srirangan & Choy, 2010).

10 **Systemic Lupus Erythematosus (SLE)**

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of generalized autoimmunity characterized by B cell hyperactivity, abnormally activated T cells and defects in the clearance of apoptotic cells and immune complexes. The pathogenesis is still unclear, but a myriad of innate and adaptive immune system aberrations in SLE have been identified as major contributors of the disease.

15 An association between IL-6 and progression of lupus has been published for several murine models of SLE. Additionally data from several studies suggest that IL-6 plays a critical role in the B cell hyperactivity and immunopathology of human SLE, and may have direct role in mediating tissue damage. Lupus patients have elevated levels of serum IL-6 that correlated with disease activity or anti-DNA (anti-nuclear antibodies) levels in some, but not all studies (Peterson, Robertson, & Emlen, 1996). The most compelling evidence supporting a critical role for IL-6 in the pathogenesis of SLE was demonstrated by the beneficial effects of IL-6 receptor blockade and the exacerbating effect of IL-6 in NZB/WF₁ mice (Mihara, Takagi, Takeda, & Ohnishi, 1998).

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine.

25 Crohn's disease and ulcerative colitis are the principal types of inflammatory bowel disease. It is important to note that not only does Crohn's disease affect the small intestine and large intestine, it can also affect the mouth, esophagus, stomach and the anus whereas ulcerative colitis primarily affects the colon and the rectum

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 anti-inflammatory 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 (Rogler & Andus, 1998).

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.

There is growing evidence that the pro-inflammatory cytokine interleukin IL-6 plays a crucial part in the uncontrolled intestinal inflammatory process, which is a main characteristic of IBD. There is elevated production of IL-6 and its soluble receptor (sIL-6R) by intestinal macrophages and CD4+T-cells. The increased formation of IL-6-sIL-6R complexes that interact with gp130 on the membrane of CD4+T-cells (trans-signaling) lead to an increased expression and nuclear translocation of STAT3, which causes the induction of anti-apoptotic genes, such as Bcl-xl. This leads to an augmented resistance of lamina propria T-cells to apoptosis. The ensuing T-cell expansion contributes to the perpetuation of chronic intestinal inflammation. This understanding concerning the predominant pathogenic role of an IL-6-dependent inflammatory cascade may lead to the development of new therapeutic strategies in the treatment of this disease.

Sepsis

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.

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;

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

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
15 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
20 lowered body temperature, i.e. under 36 °C (96.8 °F) or over 38 °C (100.4 °F).

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
25 organ dysfunction syndrome and eventually death.

Proinflammatory cytokines play a major role in the complications caused by sepsis.

In one study 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 targets for downregulation by immunosuppressive peptides (Hillenbrand et al., 2010).

30 In a second study a prospective observational study was used to determine the predictive role of Tumor Necrosis Factor alpha (TNF- α), Interleukin (IL)-1 β and IL-6 as three main pro-inflammatory cytokines in mortality of critically ill patients with severe sepsis.

It was found that among the 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. Results of this study suggest that IL-6 is a useful cytokine in prediction of mortality and clinical evaluation of severe septic patients(Hamishehkar et al., 2010).

5 Autoimmune diseases also include Acute disseminated encephalomyelitis (ADEM), Addison's disease, Agammaglobulinemia, Alopecia areata, Amyotrophic Lateral Sclerosis, ANCA Vasculitis, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Arteriosclerosis, Atopic allergy, Atopic dermatitis, Autoimmune aplastic anemia, Autoimmune cardiomyopathy, Autoimmune enteropathy, Autoimmune hemolytic anemia, Autoimmune hepatitis, Autoimmune inner ear disease, Autoimmune
10 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
15 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 leukocytoclasticangitis, Dego's disease, Dercum's disease, Dermatitis herpetiformis, Dermatomyositis, Diabetes mellitus type 1, Diffuse cutaneous systemic sclerosis, Dressler's syndrome,
20 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-Barré syndrome (GBS), Hashimoto's
25 encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, hepatitis, 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,
30 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, non-alcoholic

steatohepatitis (NASH), Occularcicatricial 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, 5 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 10 syndrome, Schnitzler syndrome, Scleritis, Scleroderma, Serum Sickness, Sjögren'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 erythematosus, Takayasu's arteritis, Temporal arteritis, Thrombocytopenia, Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease, Undifferentiated spondyloarthropathy, 15 Urticarial vasculitis, Vasculitis, Vitiligo, and Wegener's granulomatosis.

SUMMARY OF THE INVENTION

The inventors of the present invention have been able to show that proinflammatory cytokines, such as IL-6 20 and TNF- α , may be suppressed or activated by peptides and proteins of the present invention. Peptides and proteins of the present invention may provide active ingredients for the prophylaxis or treatment of conditions associated with autoimmune diseases or for immunotherapy e.g. when used as vaccine adjuvants.

According to an aspect, the present invention concerns a polypeptide consisting of or comprising a 25 sequence having at least 62%, more preferred at least 75%, preferably at least 87%, more preferred 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26).

According to an another aspect, the present invention concerns a polypeptide which includes a peptide 30 sequence having at least 70% sequence identity or homology to the sequence LSILLNEE (SEQ ID NO: 26), and derivatives thereof, fragments thereof, complexes thereof, any tertiary structures thereof in the form of monomers, dimers, trimers, multimeres, helix structur and globular structures, and crosslinkings, and any chemical modifications thereof to increase physical chemical form and properties and bioavailability.

A polypeptide of the invention may e.g. be in the form of or part of a single peptide chain, an aggregate, complex and/or nanoparticle.

According to an aspect, the present invention concerns a protein comprising a polypeptide according to the invention.

5 According to an aspect, the present invention concerns an isolated nucleic acid coding for a polypeptide or protein according to the invention.

According to an aspect, the present invention concerns an expression vector, said vector comprising a nucleic acid of the invention as well as the elements necessary for the expression of said nucleic acid.

10 According to an aspect, the present invention concerns a recombinant cell, said cell comprising a nucleic acid according to the invention, and/or an expression vector according to the invention.

According to an aspect, the present invention concerns a pharmaceutical composition comprising at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to the invention, and further at least one diluent, carrier, binder, solvent or excipient.

15 According to an aspect, the present invention concerns a method for the preparation of a pharmaceutical composition comprising the steps of:

- a. Providing one or more polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to the invention, and optionally cross-linking said one or more polypeptides;
- b. Optionally providing a diluent, carrier, binder, solvent or excipient;
- c. Providing a substance;
- 20 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.

According to an aspect, the present invention concerns a pharmaceutical composition obtainable according to the invention.

25 According to an aspect, the present invention concerns a biomaterial comprising a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention.

According to an aspect, the present invention concerns a medical use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or biomaterial according to the invention.

According to an aspect, the present invention concerns a use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of an anti-inflammatory medicament or a medicament for immune suppression or immune modulation.

5 According to an aspect, the present invention concerns a method of prophylactically or therapeutically treating an autoimmune disease and/or an inflammatory condition by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention through one or more or several administrations.

10 According to an aspect, the present invention concerns a method of immune therapy for treating cancer or other diseases by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention through one or more or several administrations.

According to an aspect, the present invention concerns an adjuvant for use in combination with a vaccine
15 or other immunogens in order to increase the immunogenicity of said vaccine or immunogen by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention through one or more or several administrations.

According to an aspect, the present invention concerns a pharmaceutical composition including an active
20 component wherein the active component includes a peptide sequence having at least 70% sequence identity or homology to the sequence LSILLNEE (SEQ ID NO: 26) or derivatives thereof, fragments thereof, as well as the HERV-H Env59 proteins from which it was derived, derivatives thereof, fragments thereof, complexes thereof, any tertiary structures thereof in the form of monomers, dimers, trimers, multimeres, helix structures and globular structures, crosslinkings, and any chemical modifications thereof which
25 increase physical and/or chemical form, properties and bioavailability of the compound.

According to an aspect, the present invention concerns a pharmaceutical composition, wherein the active component includes a peptide sequence and/or is a chemical derivative thereof and/or is part of a larger polypeptide or protein including as a monomer, dimer or as a whole or partly takes part of tertiary structures such as globular or helical structure(s) including monomers, dimers, trimers, multimers including
30 helical structures, beta-sheets, triple helical structures all in whole or in part.

According to an aspect, the present invention concerns a pharmaceutical composition, wherein the active component or peptide is part of an aggregate, complex or nanoparticle.

According to an aspect, the present invention concerns a pharmaceutical composition for injectional, topical, transdermal or oral application.

5 According to an aspect, the present invention concerns a pharmaceutical composition for immune therapy treatment of cancer or other diseases.

According to an aspect, the present invention concerns a pharmaceutical composition for use in vaccination.

10 According to an aspect, the present invention concerns a pharmaceutical composition for the treatment or prophylaxis of an autoimmune disease.

According to an aspect, the present invention concerns a pharmaceutical composition for the treatment or prophylaxis of an inflammatory condition.

15 According to an aspect, the present invention concerns a pharmaceutical composition for the treatment or prophylaxis of an autoimmune disease, wherein the autoimmune disease is SLE or arthritis including rheumatoid arthritis

According to an aspect, the present invention concerns a pharmaceutical composition including a peptide sequence and/or derivatives thereof selected among the groups consisting of GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

20 According to an aspect, the present invention concerns a polypeptide as above including a peptide sequence selected among GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

25 According to an aspect, the present invention concerns a polypeptide sequence, which contains the sequence LSILLNEE (SEQ ID NO: 26) attached to a sequence or a fragment thereof chosen among Seq ID 1 to Seq ID 1043. The attachment can be through N-terminal, C-terminal peptide bonds or any other chemical covalent and/or non-covalent bonds between any chemical moieties in either peptide fragment.

30 According to an aspect, the present invention concerns an expression vector including a nucleic acid sequence encoding a peptide having at least 70% sequence identity or homology to the sequence LSILLNEE (SEQ ID NO: 26).

According to an aspect, the present invention concerns an expression vector including a nucleic acid sequence encoding any of the peptides of the invention.

According to an aspect, the present invention concerns an expression vector as above, which utilizes an expression system based on a microorganism such as a retrovirus, an adeno virus, a pox virus, a measles
5 virus, or a salmonella, E.coli or yeast based vector.

According to an aspect, the present invention concerns a pharmaceutical composition including any expression vector of the invention.

According to an aspect, the present invention concerns a method of prophylactically or therapeutically treating an autoimmune disease and/or an inflammatory condition by administering to a subject in need
10 thereof a prophylactically or therapeutically effective amount of a pharmaceutical composition of the invention through one or more administration routes.

According to an aspect, the present invention concerns a biomaterial, such as a surface, particle, mesh, device, tube, etc., which contains a polypeptide of the invention. The polypeptide can be chemically bound to the biomaterial or be physically associated with it such as within its interior.

15 In yet another aspect, the present invention relates to diagnosis of SLE by means of measuring the expression level of HERV-H DNA. The expression level may be expressed by mean copy number or mean RNA.

In yet another aspect, the present invention relates to diagnosis of SLE by means of measuring the expression level of ENV-59 DNA and/or RNA.

20 In yet another aspect, the present invention relates to the use of a human endogenous retrovirus which is wholly or partly transcribed into RNA and which has either lower or higher transcription level in persons with a condition as compared to persons without said condition, for the treatment or diagnosis of said condition.

25 In yet another aspect, the present invention relates to the use of a human endogenous retrovirus which is wholly or partly transcribed into RNA and which has either lower or higher transcription level in persons with an autoimmune condition as compared to persons without said condition, for treatment or diagnosis of said autoimmune condition.

30 In yet another aspect, the present invention relates to the use of a human HERV-H which is wholly or partly transcribed into RNA and which has either lower or higher transcription level in persons with a condition as compared to persons without said condition, for treatment for diagnosis of said condition or disease.

In yet another aspect, the present invention relates to the use of HERV-H 59 derived DNA, RNA or proteins for diagnosis of the said condition or disease. An ENV 59 peptide sequence is provided as SEQ ID NO: 1044, an ENV 59 DNA sequence is provided as SEQ ID NO: 1045, and an HERV-H 59 complete provirus sequence is provided as SEQ ID NO: 1046.

- 5 According to an aspect, the invention concerns a polypeptide comprising a peptide sequence having at least 62,5%, more preferred 75%, more preferred 87,5%, more preferred at least 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26).

According to an aspect, the invention concerns polypeptide as above comprising one or more peptide sequences having at least 70%, preferably at least 76%, more preferred at least 82%, preferably at least
10 88%, more preferred at least 94%, preferably 100% sequence identity to sequences selected among LQNRRGLGLSILLNEEC (SEQ ID NO: 1), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

According to an aspect, the invention concerns a polypeptide as any above, said polypeptide comprising a
15 peptide sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to a sequence selected among the sequences SEQ ID NO: 1 – 41.

According to an aspect, the invention concerns a polypeptide as above selected among polypeptides having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably
20 100% sequence identity to sequences selected among LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

According to an aspect, the invention concerns a polypeptide of claim 1 selected among LSILLNEE (SEQ ID
25 NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

According to an aspect, the invention concerns a polypeptide entity comprising a polypeptide as any above, said polypeptide entity comprising less than 250 aminoacids, preferably less than 200 amino acids, more
30 preferred less than 175 amino acids, preferably less than 150 amino acids, more preferred less than 125 amino acids, preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less

than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids.

According to an aspect, the invention concerns a polypeptide entity comprising a polypeptide as any above, said polypeptide entity comprising at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more preferred at least 16, preferably at least 17, more preferred at least 18, preferably at least 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids.

According to an aspect, the invention concerns a polypeptide with a length of 17 amino acids, wherein the sequence of the first 7 amino acids is identical to the sequence of the first 7 amino acids of a sequence selected among the sequences of SEQ ID NO: 26 - 1027, and wherein the last 10 amino acids are GLSILLNEEC (SEQ ID NO: 25).

According to an aspect, the invention concerns the polypeptide as above, comprising 1, 2, 3 or 4 point mutations.

According to an aspect, the invention concerns the polypeptide as any above, which is glycolysed.

According to an aspect, the invention concerns the polypeptide as any above, which is acylated.

According to an aspect, the invention concerns the polypeptide as any above, which is a monomer.

According to an aspect, the invention concerns the polypeptide as any above, which is dimerized or trimerized.

According to an aspect, the invention concerns a protein comprising a polypeptide as any above, wherein said protein comprises less than 250 amino acids, preferably less than 200 amino acids, more preferred less than 175 amino acids, preferably less than 150 amino acids, more preferred less than 125 amino acids,

- preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids.
- 10 According to an aspect, the invention concerns a protein or polypeptide as any above or a protein comprising a polypeptide as any above, said protein or polypeptide comprising at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more preferred at least 16, preferably at least 17, more preferred at least 18, 15 preferably at least 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids.
- According to an aspect, the invention concerns a protein comprising a polypeptide as any above, wherein 20 said protein is not fusion active.
- According to an aspect, the invention concerns the polypeptide or protein as any above, wherein said polypeptide or protein inhibits IL-6 expression in a mammalian cell system or an animal model.
- According to an aspect, the invention concerns an isolated nucleic acid coding for a polypeptide or protein according to any of the preceding claims.
- 25 According to an aspect, the invention concerns an expression vector, said vector comprising a nucleic acid as above as well as the elements necessary for the expression of said nucleic acid.
- According to an aspect, the invention concerns an expression vector as above, wherein said vector is an eukaryotic or prokaryotic or viral expression vector.
- According to an aspect, the invention concerns an expression vector as above, wherein said vector is 30 selected among the group consisting of yeast, e-coli and baculo.

According to an aspect, the invention concerns a pharmaceutical composition comprising at least one polypeptide, protein, nucleic acid, or expression vector according to any of the preceding claims, and further at least one diluent, carrier, binder, solvent or excipient.

According to an aspect, the invention concerns the pharmaceutical composition according to any of the claims, wherein said at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell is the active ingredient or sole active ingredient of said pharmaceutical product.

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

a. Providing one or more polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to any of the preceding claims, and optionally cross-linking said one or more polypeptides;

b. Optionally providing a diluent, carrier, binder, solvent or excipient;

c. Providing a substance;

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.

According to an aspect, the invention concerns the method as above, wherein said substance of step c. is selected from the group consisting of creams, lotions, ointments, gels, balms, salves, oils, foams, and shampoos.

According to an aspect, the invention concerns a pharmaceutical composition obtainable as above.

According to an aspect, the invention concerns a pharmaceutical composition as any above, wherein said pharmaceutical composition is selected among the group consisting of creams, lotions, shake lotions, ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosols, transdermal patches and bandages.

According to an aspect, the invention concerns a medical use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims.

According to an aspect, the invention concerns a use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for immune suppression or immune modulation.

According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for use in surgery, prophylaxis, therapy, a diagnostic method, treatment and/or amelioration of disease.

5 According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for the treatment, amelioration or prophylaxis of an autoimmune disease.

10 According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition as above, wherein the autoimmune disease is SLE (systemic lupus erythematosus) or arthritis, such as rheumatoid arthritis, spondyloarthritis, or multiple sclerosis (MS).

According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for the treatment, amelioration or prophylaxis of an inflammatory condition or a disorder associated with inflammation, such as acute or chronic inflammation.

15 According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for use as a medicament.

20 According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition for a use according to any of the preceding claims, comprising prophylaxis or treatment of sepsis.

According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition for a use according to any of the preceding claims, comprising prophylaxis or treatment of spondyloarthritis.

25 According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition for a use according to any of the preceding claims, comprising prophylaxis or treatment of asthma and/or allergy.

According to an aspect, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims for a use in as an adjuvant, such as in a vaccine.

According to an aspect, the invention concerns a method of prophylactically or therapeutically treating an autoimmune disease and/or an inflammatory condition by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding
5 claims through one or more or several administrations.

According to an aspect, the invention concerns a use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims, for prophylaxis or treatment of a condition or disease by an administration route selected among injection, inhalation, topical, transdermal, oral, nasal, vaginal, or anal delivery.

10 According to an aspect, the invention concerns the use as above, wherein the mode of injection is selected among intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and (intramuscular) IM.

According to an aspect, the invention concerns the use as above, for treatment of a disease by direct injection at a site affected by a disorder, such as inflammation.

15 According to an aspect, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims, for treatment of Arthritis where the composition is injected directly at site of inflammation.

DETAILED DISCLOSURE

The present invention is *inter alia* the result of studying the involvement of the HERV genes and their influence on the immunological response in autoimmune diseases. It was found that in patients with SLE, the
20 expression of HERV-H *Env59* mRNA is negatively correlated with the levels of IL-6 and TLR7 expression ($p=0.0065$, $p=0.02$, respectively). It was demonstrated that HERV-H *Env59* encodes a functional membrane glycoprotein and make infectious pseudotyped virions with a lentiviral vector system. Moreover an ISD in ENV-59 with a unique sequence compared to known ISDs or ISD like sequences was identified.

This ENV-59 ISD seems to be unique to humans (although a similar ISD with one point mutation is also
25 found in chimpanzees and might be present in other primates).

The peptide, GLSILLNEEC (SEQ ID NO: 25), derived from the *Env59* ISU domain has significant immune regulatory activity both *in vitro*, *ex vivo* and *in vivo*. Surprisingly the virus-derived immunosuppressive peptide inhibits, among other effects, the production of IL-6, confirming the negative correlation seen between IL-6 and ENV59 expression levels in SLE patients. This further suggests that that the endogenous
30 envelope protein has adapted to perform a pivotal role in the human immune system and has an advantageous function in controlling autoimmune diseases.

In vivo the ISD peptide is capable of strongly reducing the symptoms of arthritis induced in two validated and recognized animal models, namely the Sakaguchi mice model and the Collagen Induced Arthritis – CIA-mouse model. This highly suggests a potential for the ISD peptide to have anti-Rheumatoid-Arthritis activity in humans;

5 According to an embodiment the invention relates to the peptide sequence LSILLNEE (SEQ ID NO: 26), or derivatives thereof, fragments thereof, as well as the HERV-H Env59 proteins from which it was derived, derivatives thereof, fragments thereof, complexes thereof, any tertiary structures thereof in the form of monomers, dimers, trimers, multimeres, helix structur and globular structures, crosslinkings, and any chemical modifications thereof which increase physical and/or chemical form, properties and bioavailability
10 of the compound of the present invention or each separately or in any compination the polypeptides or peptides of the invention. Additionally the invention also relates to any pharmaceutical formulations suitable for the application of the above described peptide and proteins to a patient in need thereof.

According to an embodiment, the invention concerns a polypeptide consisting of or comprising a sequence having at least 62%, more preferred at least 75%, preferably at least 87%, more preferred 100% sequence
15 identity to the sequence LSILLNEE (SEQ ID NO: 26).

According to an embodiment, a polypeptide of the invention is glycolysed.

According to an embodiment, a polypeptide of the invention is acylated.

According to an embodiment, a polypeptide of the invention is dimerized or trimerized.

A polypeptide is obtainable from the sequence e.g. by 1, 2 or 3 point deletions, point insertions and/or
20 point mutations. A point mutation is used here about a change of a single amino acid, a point insertion is the insertion of a single amino acid, and a point deletion is the removal of a single amino acid.

The invention also concerns a polypeptide which includes a peptide sequence having at least 70% sequence identity or homology to the sequence LSILLNEE (SEQ ID NO: 26), and derivatives thereof, fragments thereof, complexes thereof, any tertiary structures thereof in the form of monomers, dimers, trimers, multimeres,
25 helix structur and globular structures, and crosslinkings, and any chemical modifications thereof to increase physical chemical form and properties and bioavailability.

A polypeptide of the invention may e.g. be in the form of or part of a single peptide chain, an aggregate, complex and/or nanoparticle.

According to an embodiment, the invention concerns the polypeptide, said polypeptide comprising the sequence LSILLNEE (SEQ ID NO: 26) attached to a sequence or a fragment thereof chosen among Seq ID 1 to Seq ID 1043.

The attachment can be through N-terminal, C-terminal peptide bonds or any other chemical covalent and/or non-covalent bonds between any chemical moieties in either peptide fragment.

According to an embodiment, the polypeptide comprises or consists of a peptide sequence selected among GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

According to an embodiment, the polypeptide comprises or consists of a sequence having at least 70% sequence identity to the sequence: LQNRRGLGLSILLNEEC (SEQ ID NO: 1).

According to an embodiment, the polypeptide comprises or consists of a sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to SEQ ID NO: 1.

According to an embodiment, the polypeptide comprises or consists of a sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to a sequence selected among the sequences SEQ ID NO: 1 – 41.

According to an embodiment, the polypeptide comprises less than 250 amino acids, preferably less than 200 amino acids, more preferred less than 175 amino acids, preferably less than 150 amino acids, more preferred less than 125 amino acids, preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids.

According to an embodiment, the polypeptide comprises at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more

preferred at least 16, preferably at least 17, more preferred at least 18, preferably at least 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids.

According to an embodiment, the polypeptide has a length of 17 amino acids, wherein the sequence of the first 7 amino acids is identical to the sequence of the first 7 amino acids of a sequence selected among the sequences of SEQ ID NO: 42 - 1043, and wherein the last 10 amino acids are GLSILLNEEC (SEQ ID NO: 25).

According to an embodiment, the polypeptide has 1, 2, 3 or 4 point mutations.

According to an embodiment, the polypeptide is or acts as an immune suppressive domain. Such a polypeptide may be referred to as an immunosuppressive peptide. According to an embodiment, the immune suppressive domain is obtainable from a polypeptide according to the invention, by at least one point mutation, deletion or insertion. According to an embodiment, the total number of point mutations, deletions or insertions is selected among 1, 2, 3 and 4. According to an embodiment, the total number of point mutations, deletions or insertions is more than 4. According to an embodiment, the polypeptide is a monomeric peptide. According to an embodiment, the polypeptide is cross-linked to at least one additional immunosuppressive peptide and/or connected to a protein, said protein being connected to at least one additional immune suppressive domain. According to an embodiment, the polypeptide is connected to at least one additional immunosuppressive peptide to form a dimer. According to an embodiment, the dimer is homologous and comprises at least two immunosuppressive peptides, which are cross-linked by a disulfide bond, N-terminal to N-terminal or C-terminal to C-terminal, and/or a tandem repeat. According to an embodiment, the polypeptide is connected to at least one additional immunosuppressive peptide to form a heterologous dimer or a homologous dimer. According to an embodiment, the polypeptide is connected to at least two additional immunosuppressive peptides to form a multimer or polymer.

According to an embodiment, the polypeptide comprises one or more modifications. According to an embodiment, the 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. According to an embodiment, the polypeptide has increased resistance against proteolysis compared to peptides or proteins not comprising said at least one modification.

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, or 11, or 10, or 9, or 8, or 7, 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 known ISD. 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 1043, 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.

According to an embodiment additional aminoacids or molecules may be added or linked to an immunosuppressive peptide in order to improve the solubility characteristics of said immusuppressive peptide.

According to an embodiment, the invention concerns a protein comprising a polypeptide according to the invention.

According to an embodiment, the protein is an envelope protein.

According to an embodiment, the protein is not a functional membrane glycoprotein.

According to an embodiment, the protein is not fusion active. The expression "not fusion active" means the protein is not capable of mediating fusion of two biological membranes.

According to an embodiment, the protein is not bound or linked to a membrane.

According to an embodiment, the protein is not a membrane integral protein.

According to an embodiment, the polypeptide or protein according to the invention inhibits IL-6 expression in a mammalian cell system or an animal model.

According to an embodiment, the polypeptide or protein according to the invention induces IL-6 expression in a mammalian cell system or an animal model.

According to an embodiment, the invention concerns an isolated nucleic acid coding for a polypeptide or protein according to the invention.

According to an embodiment, the invention concerns an expression vector, said vector comprising a nucleic acid of the invention as well as the elements necessary for the expression of said nucleic acid.

According to an embodiment, the invention concerns an expression vector, wherein said vector is an eukaryotic or prokaryotic or viral expression vector.

According to an embodiment, the invention concerns an expression vector including a nucleic acid sequence encoding for a peptide having at least 62% sequence identity or homology to the sequence
5 LSILLNEE (SEQ ID NO: 26).

According to an embodiment, the invention concerns an expression vector including a nucleic acid sequence encoding for a polypeptide or protein according to the invention.

The expression vector may be based upon a microorganism such as a retrovirus, an adeno virus, a pox virus, a measles virus, a salmonella based vector, an E coli vector, yeast.

10 According to an embodiment, the invention concerns a recombinant cell, said cell comprising a nucleic acid according of the invention, and/or an expression vector according to the invention.

According to an embodiment, the invention concerns a pharmaceutical composition comprising at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to the invention, and further at least one diluent, carrier, binder, solvent or excipient.

15 **Administration forms, formulations and dosage regimes**

Pharmaceutically useful compositions comprising the compounds of the invention may be formulated according to known methods such as by the admixture of a pharmaceutically acceptable carriers and/or additional active compounds. Examples of such carriers and methods of formulation may be found in Remington's Pharmaceutical Sciences. To form a pharmaceutically acceptable composition suitable for
20 effective administration, such compositions will contain an effective amount of a compound of the invention. Such compositions may also contain more than one compound of the invention.

Pharmaceutical compositions or compounds of the invention are administered to an individual in therapeutic effective amounts. The effective amount may vary according to a variety of factors such as the individual's condition, weight, sex and age. Other factors include the mode of administration. Generally, the
25 compositions will be administered in dosages ranging from about 1 µg to about 100 mg, and especially from about 10 µg to about 10 mg.

The pharmaceutical compositions may be provided to the individual by a variety of routes and especially such as, subcutaneous, topical, oral, mucosal, intravenous, parenterally, and intramuscular.

Such formulations are generally safe, do not have toxic side effects; can be administered by an effective
30 route; are stable; and are compatible with the pharmaceutically carriers.

The pharmaceutical formulations and compounds of the invention may be used in dosage forms such as capsules, suspensions, elixirs, or liquid solutions.

The pharmaceutical formulations and compounds of the invention may be administered in single or multiple doses.

5

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 an entity of the present invention or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier therefore.

10

Pharmaceutically acceptable salts of the instant compositions, where they can be prepared, are also intended to be covered by this invention.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell is the active ingredient or sole active ingredient of said pharmaceutical product.

15

A pharmaceutical composition of the invention may include as the active component a peptide sequence and/or a chemical derivative thereof, and said sequence or derivative thereof may be part of a larger polypeptide or protein, e.g. as a monomer, dimer, or may as a whole or partly take part of tertiary structures such as globular or helical structure(s), including as monomers, dimers, trimers, multimers, and including helical structures, beta-sheets, triple helical structures, all in whole or in part.

20

A pharmaceutical composition of the invention may include as the active component a peptide, which is part of an aggregate, complex or nanoparticle.

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

25

- a. Providing one or more polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to the invention, and optionally cross-linking said one or more polypeptides;
- b. Optionally providing a diluent, carrier, binder, solvent or excipient;
- c. Providing a substance;

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.

According to an embodiment, the invention concerns the method, wherein said substance of step c. is selected from the group consisting of creams, lotions, ointments, gels, balms, salves, oils, foams, and
5 shampoos.

According to an embodiment, the invention concerns the pharmaceutical composition obtainable according to a method of the invention.

According to an embodiment, the invention concerns the pharmaceutical composition, wherein said pharmaceutical composition is selected among the group consisting of creams, lotions, shake lotions,
10 ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosols, transdermal patches and bandages.

According to an embodiment, the invention concerns a biomaterial comprising a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention.

According to an embodiment, the invention concerns the biomaterial, wherein said biomaterial is selected
15 among a surface, particle, mesh, device, tube, or an implant.

The polypeptide can be chemically bound to the biomaterial or be physically associated with it such as in its interior.

According to an embodiment, the invention concerns a medical use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or biomaterial according to
20 the invention.

According to an embodiment, the invention concerns a use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for immune suppression or immune modulation.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression
25 vector, recombinant cell, pharmaceutical composition, or implant according to the invention for use in surgery, prophylaxis, therapy, a diagnostic method, treatment and/or amelioration of disease.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the treatment, amelioration or prophylaxis of an autoimmune disease.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant, wherein the autoimmune disease is SLE (systemic lupus erythematosus) or arthritis, such as rheumatoid arthritis.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression
5 vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the treatment, amelioration or prophylaxis of an inflammatory condition or a disorder associated with inflammation, such as acute or chronic inflammation.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for use as a
10 medicament.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, wherein the subject is a human or an animal.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression
15 vector, recombinant cell, pharmaceutical composition, or implant according to the invention, for use on an organ.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention, in the preparation or treatment of transplantation patients.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression
20 vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, 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
25 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
30 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-Barré syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, hepatitis, 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, non-alcoholic steatohepatitis (NASH), 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, Sjögren'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 erythematosus, 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.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, 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.

10 According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, comprising prophylaxis or treatment of sepsis.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, 15 comprising prophylaxis or treatment of spondyloarthritis.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, comprising prophylaxis or treatment of asthma and/or allergy.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression 20 vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, comprising prophylaxis or treatment of cancer.

According to an embodiment, the invention concerns the polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to the invention, comprising enhancing the immunogenicity of vaccines or any antigen including those used in vaccines.

25 According to an embodiment, the invention concerns the polypeptide, wherein said polypeptide is or acts as an immune suppressive domain, for use in a method of prophylaxis or treatment or amelioration of a condition associated with an autoimmune disease, wherein a gene sequence expressing said immune suppressive domain exhibits increased or decreased expression in a group of patients suffering from said autoimmune disease as compared to a healthy control group. According to an embodiment, the invention 30 concerns the polypeptide, wherein said immune suppressive domain is from an endogenous retrovirus, preferably a human endogenous retrovirus. According to an embodiment, the invention concerns the

polypeptide, wherein said immune suppressive domain is selected among the sequences of SEQ ID NO: NO: 1 – 1043.

According to an embodiment, the invention concerns a use of a polypeptide selected among the sequences of SEQ ID NO: NO: 1 – 1043 for the prophylaxis or treatment or amelioration of an autoimmune disease or
5 at least one symptom associated with said autoimmune disease.

According to an embodiment, the invention concerns a use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of an anti-inflammatory medicament or a medicament for immune suppression or immune modulation.

10 According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of a medicament for the preparation or treatment of transplantation patients.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for
15 the manufacture of a medicament for prophylaxis or treatment of an autoimmune or inflammatory disease.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of a medicament for prophylaxis or treatment of a condition selected among Acute disseminated encephalomyelitis (ADEM), Addison's disease, Agammaglobulinemia, Alopecia areata,
20 Amyotrophic Lateral Sclerosis, ANCA Vasculitis, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Arteriosclerosis, 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
25 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
30 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, 5 Glomerulonephritis, Goodpasture's syndrome, Graves' disease, Guillain-Barré syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, hepatitis, 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 10 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, non-alcoholic 15 steatohepatitis (NASH), 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, 20 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, Sjögren's syndrome, 25 Spondyloarthropathy, Still's disease, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sweet's syndrome, Sydenham chorea, Sympathetic ophthalmia, Systemic lupus erythematosus, 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.

30 According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of a medicament for prophylaxis or treatment of inflammation or a condition associated with inflammation, such as acute or chronic inflammation.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention, 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
 5 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.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for
 10 the manufacture of a medicament for prophylaxis or treatment of at least condition selection among sepsis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and spondyloarthritis.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of a medicament for prophylaxis or treatment of asthma and/or allergy.

15 According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to the invention for the manufacture of an adjuvant.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for coating
 20 of nanoparticles and/or biomaterials.

A biomaterial is any matter, surface, particle or construct that interacts with biological systems.

Biomaterials can be derived either from nature or synthesized in the laboratory using a variety of chemical approaches utilizing metallic components, ceramic, polymers or composite materials. Some biomaterials consist of inorganic crystallization within a largely organic matrix of naturally occurring compounds.

25 Biomaterials are often used and/or adapted for a medical application, and thus comprise 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 hydroxy-apatite coated hip implants. Biomaterials are also used every day in dental applications, surgery, and drug delivery such as in the form of nanoparticles. A construct with impregnated
 30 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.

Biomaterials are used for example in: Joint replacements, bone plates, bone cement, artificial ligaments and tendons, dental implants for tooth fixation, blood vessel prostheses, heart valves, skin repair devices
5 (artificial tissue), cochlear replacements, contact lenses, breast implants.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for at least partial suppression of an immune response to at least one nanoparticle or biomaterial.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid,
10 expression vector, recombinant cell, or pharmaceutical composition according to the invention, to increase the *in vivo* half-life of nanoparticles and/or biomaterials and/or medical devices and/or implants in the patient.

According to an embodiment, the invention concerns the use of an endogenous retrovirus for diagnosis of a disease.

15 According to an embodiment, the invention concerns the use of an endogenous retrovirus whose expression level or copy number is different in a subject with a condition as compared to a subject without said condition for diagnosis of a disease.

According to an embodiment, the invention concerns the use of an endogenous retrovirus whose expression level or copy number is different in a subject with an autoimmune condition as compared to a
20 subject without the said condition for diagnosis of a disease.

According to an embodiment, the invention concerns the use of single nucleotide polymorphisms associated with HERV-H 59 for diagnosis of a disease.

According to an embodiment, the invention concerns the use of HERV-H 59 for diagnosis of SLE.

According to an embodiment, the invention concerns a method of prophylactically or therapeutically
25 treating an autoimmune disease and/or an inflammatory condition by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention through one or more or several administrations.

According to an embodiment, the invention concerns a method of prophylaxis or treatment or amelioration
30 of a condition associated with an autoimmune disease, comprising:

- 5 a. Measuring the expression or copy number of at least one endogenous retrovirus in a group of patients suffering from said autoimmune disease;
- b. Comparing said expression with the expression of said at least one endogenous retrovirus in a healthy control group;
- 5 c. Identifying at least one endogenous retrovirus having different expression in said group of patients;
- d. Optionally identifying at least one immune suppressive domain in said at least one endogenous retrovirus;
- 10 e. Treating at least one patient suffering from said condition by administration of at least one immune suppressive domain preferably contained in a protein containing said at least one immune suppressive domain and/or a protein expressed by said endogenous retrovirus.

According to an embodiment, the invention concerns a method of prophylaxis or treatment or amelioration of a condition associated with an autoimmune disease, comprising:

- 15 f. Measuring the concentration of at least one protein or polypeptide comprising at least one immune suppressive domain in a group of patients suffering from said autoimmune disease;
- g. Comparing said concentraion with the concentration in a healthy control group;
- h. Identifying at least one immune suppressive domain having different expression in said group of patients;
- 20 i. Treating at least one patient suffering from said condition by administration of said at least one immune suppressive domain and/or a protein comprising said at least one immune suppressive domain.

According to an embodiment, the invention concerns the method, wherein said different expression is selected among increased and decreased expression.

- 25 According to an embodiment, the invention concerns the method, wherein said endogenous retrovirus is a human endogenous retrovirus.

According to an embodiment, the invention concerns the method, wherein said human endogenous retrovirus belongs to the HERV-H subfamily or the HERV-K subfamily.

According to an embodiment, the invention concerns the method, wherein said endogenous retrovirus contains at least one open reading frame capable of encoding a protein.

According to an embodiment, the invention concerns the method, wherein said at least one open reading frame has a length of at least 50, preferably at least 100, more preferred at least 150, preferably at least 200, more preferred at least 250, preferably at least 300, more preferred at least 350, preferably at least 400 nucleotides.

According to an embodiment, the invention concerns a use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for prophylaxis or treatment of a condition or disease by an administration route selected among injection, inhalation, topical, transdermal, oral, nasal, vaginal, or anal delivery.

According to an embodiment, the invention concerns the use, wherein the mode of injection is selected among intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and (intramuscular) IM.

According to an embodiment, the invention concerns the use, for treatment of a disease by direct injection at a site affected by a disorder, such as inflammation.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for treatment of a condition selected among a skin disease, Psoriasis, Arthritis, Asthma, Sepsis, inflammatory bowel disease, rheumatoid arthritis, SLE, and spondyloarthritis.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for treatment of Arthritis where the composition is injected directly at site of inflammation.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for treatment of a condition selected among Gastrointestinal hyperresponsiveness, Food Allergy, Food intolerance and inflammatory bowel disease, preferably wherein the composition is delivered orally.

According to an embodiment, the invention concerns the use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to the invention, for treatment Asthma where the composition is delivered by inhalation.

According to an embodiment of the present invention, the entitie(s) (polypeptide(s), protein(s), nucleic acid(s), expression vector(s), recombinant cell(s), pharmaceutical composition(s) and/or implant(s)) of the

present invention can be used to reduce or ameliorate the effects of inflammation and/or inflammatory and autoimmune diseases.

The entities of the present invention may for example exercise their immune modulatory activity through binding to a protein on or inside lymphocytes, monocytes or other cells of the immune system. Such proteins or receptors can belong to any protein family including but not limited to Toll like receptors (TLRs), G-protein coupled receptors (GPCRs), antibodies, adhesion molecules, transporters (including but not limited to amino acid, inorganic ion, organic ion or sugar transporters, transmembrane pumps, transporter proteins, escort proteins, acid transport proteins, cation transport proteins, or anion transport proteins), channel proteins such as ion-channels including but not limited to sodium channels, potassium channels, calcium channels, phosphate channels and any other cation or anion transporters. Especially calcium and calcium activated potassium channels, which are involved in activation of lymphocytes and monocytes may be targeted by ISD peptides.

The entities of the present invention may also exercise their immune modulatory activity through introducing changes to the cellular membranes such as changing the membrane curvature or permeabilize or destabilize the membrane allowing metabolites or other molecules and ions to pass through, thereby disrupting the biologically relevant concentrations of such molecules inside the cells or interrupting gradients of such molecules across membranes, which might be important for the normal function of the cells. Other mechanisms may exist.

The Sakaguchi mice model and the Collagen Induced Arthritis – CIA - mouse model models (predictive for anti-Rheumatoid Arthritis activity of the ISD peptide in humans) and the in vivo validation of the peptides, proteins and pharmaceutical formulations of the invention:

SKG mice spontaneously develop T cell-mediated chronic autoimmune arthritis. This is due to a mutation of the gene encoding a Src homology 2 (SH2) domain of ζ -associated protein of 70 kDa (ZAP-70), which is a key signal transduction molecule in T cells (Sakaguchi et al., Nature 2003). This mutation impairs positive and negative selection of T cells in the thymus, leading to thymic production of arthritogenic T cells.

Clinically, joint swelling begins in small joints of the digits, progressing in a symmetrical fashion to larger joints including wrists and ankles. Histologically, the swollen joints show severe synovitis with formation of pannus invading and eroding adjacent cartilage and subchondral bone. SKG mice develop extra-articular lesions, such as interstitial pneumonitis, vasculitides, and subcutaneous necrobiotic nodules not unlike rheumatoid nodules in RA. Serologically, they develop high titers of RF and autoantibodies specific for type II collagen. Furthermore, CD4⁺ T cells can adoptively transfer arthritis in SKG mice, which have a BALB/c genetic background, to T cell-deficient BALB/c nude or T cell/B cell-deficient SCID mice, which indicates

that the disease is a T cell-mediated autoimmune disease. In addition to the causative gene, the polymorphism of the *MHC* gene also contributes to the occurrence of SKG arthritis depending on environmental conditions. Thus, this spontaneous autoimmune arthritis in mice resembles human RA in clinical and histological characteristics of articular and extra-articular lesions, in serological characteristics, and in the key role of CD4⁺ T cells in initiating arthritis (Sakaguchi et al Nature 2003).

Cytokines play key roles in spontaneous CD4⁺ T cell-mediated chronic autoimmune arthritis in SKG mice. A study conducted by Hata et al. (J Clin Invest 2004) show that genetic deficiency in IL-6 completely suppressed the development of arthritis in SKG mice, irrespective of the persistence of circulating rheumatoid factor. Either IL-1 or TNF- α deficiency retarded the onset of arthritis and substantially reduced its incidence and severity. IL-10 deficiency, on the other hand, exacerbated disease, whereas IL-4 or IFN- γ deficiency did not alter the disease course. Synovial fluid of arthritic SKG mice contained high amounts of IL-6, TNF- α , and IL-1, in accordance with active transcription of these cytokine genes in the afflicted joints. Notably, immunohistochemistry revealed that distinct subsets of synovial cells produced different cytokines in the inflamed synovium: the superficial synovial lining cells mainly produced IL-1 and TNF- α , whereas scattered subsynovial cells produced IL-6. Thus, IL-6, IL-1, TNF- α , and IL-10 play distinct roles in the development of SKG arthritis.. The results also indicate that targeting not only each cytokine but also each cell population secreting distinct cytokines could be an effective treatment of rheumatoid arthritis (Hata et al. j. Clin Invest 2004).

According to an embodiment of the present invention the entities of the present invention are capable of suppressing the development of inflammation, specially joint inflammation, in the Sakaguchi (SKG) mouse model for arthritis. According to the present invention, the entities of the present invention are capable of reducing the arthritis score in such animals, the score being reduced with at least 5%, such as at 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 the score upon induction of inflammation by mannan injection.

The entities of the present invention are capable suppressing the immune response in an animal suffering from a general inflammation according to the SKG mouse model. According to the present invention, the entities of the present invention are capable of reducing IL-6 levels in Sakaguchi mice challenged with mannan, the IL-6 levels being reduced with at least 5%, such as at 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 the IL-6 levels in mannan challenged SKG-mice.

The collagen-induced arthritis (CIA) mouse model is the most commonly studied autoimmune model of rheumatoid arthritis. Autoimmune arthritis is induced in this model by immunization with an emulsion of complete Freund's adjuvant and type II collagen (CII).

The model shares several pathological features with RA, and type II collagen (CII) is a major protein in cartilage, the target tissue of RA. Additionally, of the antigen-defined models that are based on cartilage proteins, the CIA mouse model has the shortest duration between immunization and disease manifestation. The CIA model has been used extensively to identify potential pathogenic mechanisms of autoimmunity, including the role of individual cell types in disease onset and progression, as well as to design and test new therapeutics. In recent years, the CIA model has been instrumental in the testing and development of the new biologically based therapeutics, such as those that target tumor necrosis factor- α , a cytokine produced by macrophages and T cells that is a dominant inflammatory mediator in the pathogenesis of RA.

CIA is elicited in genetically susceptible strains of mice by immunization with CII emulsified in complete Freund's adjuvant (CFA). The ensuing pathogenesis shares several pathological features with RA, including synovial hyperplasia, mononuclear cell infiltration, cartilage degradation, and, like RA, susceptibility is linked to the expression of specific MHC class II genes. The most notable differences between this model and RA are that rheumatoid factor is not present in CIA, there is little or no sex bias in CIA and that the experimental disease is generally monophasic, although some relapsing mouse models of CIA have been described. While the presence of T-cell and B-cell immunity to CII has been reported in RA, it is not clear if this is a causative factor or a result of the pathogenesis associated with this disease. The original "gold standard" of the CIA model was the DBA/1 (H-2q) mouse strain; however, in recent years, several HLA-DR mouse models have been established in which transgenic expression of the HLA-DR1 or DR4 class II genes associated with susceptibility to RA confers susceptibility to CIA in the recipient mouse strain. These data indicate that the DR molecules associated with susceptibility to RA are at least involved in the immune response to CII.

The immunopathogenesis of CIA involves both a T-cell and B-cell specific response to CII. The immunodominant T-cell determinants of CII that mediate CIA have been identified for most of the class II molecules that are associated with susceptibility to this experimental disease, and a few have been studied in detail for their interaction with the class II molecule and T-cell receptor. Similarly, B-cell determinants

targeted by the antibody response to CII have also been identified, and there is some evidence that antibodies from RA patients target the same areas of the CII molecule as those from CIA. Identification of pathogenic B-cell determinants has proven to be more difficult owing to the requirement that the pathogenic antibodies must be able to bind to the triple helical native CII. Unlike other autoimmune models such as experimental autoimmune encephalomyelitis (EAE), where T cells are the primary pathogenic mechanism, the pathogenesis of CIA is mediated, in a large part, by CII-specific antibodies that binds to the cartilage and is capable of fixing complement. Collectively, these data have enabled researchers to study a wide range of pathogenic mechanisms in this model, as well as to design and test novel therapeutics (Brand, Latham, & Rosloniec, 2007).

TNF- α plays an important role in CIA. Studies have shown that suppression of collagenarthritis was achieved both with neutralizing antibodies against TNF α and with soluble TNF receptors. Intriguingly, it was found that TNF α was crucial at the onset of the arthritis but appeared less dominant in the later stages. In fact, studies in TNF receptor knockout mice demonstrated that the incidence and severity of arthritis were less in such mice; once the joints became affected, however, full progression to erosive damage was noted in an apparently TNF-independent fashion.

Likewise, in CIA, it was shown that treatment with a set of neutralizing antibodies against both IL-1 α and IL-1 β was still highly effective in established arthritis, reducing both inflammation and the progression of cartilage destruction. Studies with antibodies to separate IL-1 isoforms revealed that IL-1 β is more crucial. This is in line with the clear efficacy in this model of ICE (IL-1 β -converting enzyme) inhibitors and the observation of reduced CIA in ICE-deficient mice. Similarly, the local overexpression of IL-1 α by retroviral gene transfer in inflamed knee joints was effective at the site. In line with the identification of TNF α and IL-1 β as separate targets in animal models of arthritis, it has been convincingly demonstrated that combination therapy with both TNF and IL-1 blockers provides optimal protection.

IL-6 also plays an important role in the development of CIA, IL-6 $^{-/-}$ mice are completely protected from CIA, accompanied by a reduced antibody response to type II collagen and the absence of inflammatory cells and tissue damage in knee joints. Both suppression of specific immune responses to CII and a tendency to a shift toward a Th2 cytokine profile might contribute in part to the attenuation of CIA in IL-6 $^{-/-}$ mice (Sasai et al., 1999).

According to an additional embodiment of the present invention the entities of the present invention are capable of suppressing the development of inflammation, specially joint inflammation, in the Collagen Induced Arthritis (CIA) mouse model for arthritis.

According to an embodiment of the present invention, the immunosuppressive polypeptides of the invention are capable of reducing the arthritis score in such animals, the score 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 the score from induction of inflammation by collagen injection.

Protein and peptides

In one embodiment of the present invention, the polypeptides are monomeric. In another embodiment of the present invention the polypeptides are dimeric. In another embodiment of the present invention the polypeptides are trimeric. In yet another embodiment of the present invention the polypeptides are multimeric. Thus, according to the present invention the polypeptides may be monomeric, homologous dimeric, heterologous dimeric, homologous trimeric, heterologous trimeric, homologous multimeric and/or heterologous multimeric. In a particular preferred embodiment the polypeptides of the present invention are homologous dimeric.

Additionally, the present invention may comprise combinations of di-, tri-and/or multimeric polypeptides. 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, homologous dimeric with heterologous trimeric, heterologous dimeric with homologous trimeric, heterologous dimeric with heterologous trimeric, homologous dimeric with homologous multimeric, heterologous dimeric with heterologous 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 immunosuppressive peptides.

In certain embodiments of the present invention the polypeptides are homologous dimers, such as homologous dimers formed by two of the peptides selected among SEQ ID NO: 1-1043.

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. In a preferred embodiment the peptides are cross-linked via a disulfide bond wherein the peptides are cross-linked C-terminal to C-terminal.

In an embodiment, a polypeptide of the invention is linked to at least one protein, which may act as a carrier protein. A multimer may be formed by linking to a carrier protein or other molecule and/or by linking several peptides to said carrier protein.

In one embodiment the monomeric peptides are chemically linked to a protein (such as a carrier protein) or any other molecule that can be coupled to more than one of peptide. The coupling can be through a covalent bond or through weaker bonds such as hydrogen bonds or van der Waals bonds. The peptides can be coupled through in its N-terminal, C-terminal or anywhere inside the peptide sequence. Any method described here in for cross-linking of peptides can be used to couple the peptide to the protein or the carrier molecule resulting in a molecule that contains several copies of the said peptide.

10 The 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.

15 According to an embodiment, the polypeptide or the sequence of said polypeptide may form part of a larger peptide or molecule and still retain its biological properties. According to an embodiment additional aminoacids or molecules may be added to an immunosuppressive peptide in order to improve the solubility and/or bioavailability characteristics of said immusuppressive 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 20 phosphotyrosine, phosphoserine and phosphothreonine. The polypeptides according to the invention can comprise one or more amino acids independently selected from the group consisting of naturally occurring L-amino acids, 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

5 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

10 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 di-alkylamino 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

15 altogether from the polypeptide to yield desamino and descarboxylated forms thereof without significantly affecting the biological activity of the polypeptide. The desirable 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.

20 According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments. Endogenous retroviruses are remnants of ancient retroviral integrations and readily identifiable because of their sequence homology to other retroviruses to a person who is skilled-in-the-art.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which are transcribed to RNA.

25 According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which are transcribed into RNA and whose transcription level is correlated to the transcription level of other genes involved in a disease or condition.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which are transcribed into RNA and whose transcription level is correlated to the transcription

30 level of other genes involved in autoimmunity.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which are transcribed into RNA and whose transcription level is different in subjects with a

condition as compared to subjects without such a condition. Such conditions can be diseases such as autoimmune diseases or congenital diseases.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which are transcribed into RNA and whose transcription level is different in subjects with an autoimmune condition as compared to subjects without such a condition. Such conditions include SLE, Rheumatoid Arthritis, IBD and others.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have different copy numbers in different individuals.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have different copy numbers in individuals with a disease or condition as compared to individuals without said disease or condition

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have different copy numbers in individuals with autoimmunity as compared to individuals without autoimmune conditions

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have different copy numbers in individuals with autoimmunity or congenital diseases as compared to individuals without autoimmune conditions or congenital diseases.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have different copy numbers in individuals with conditions such as SLE, Rheumatoid Arthritis, IBD and others as compared to individuals without such conditions

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which contain single nucleotide polymorphisms (SNPs) in different individuals.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have single nucleotide polymorphisms (SNPs) correlated with occurrence of a disease or condition as compared to individuals without said disease or condition

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have SNPs correlated with occurrence of autoimmunity as compared to individuals without autoimmune conditions

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have SNPs which occur more or less frequently in individuals with autoimmunity or congenital diseases as compared to individuals without autoimmune conditions or congenital diseases.

According to an embodiment, the present invention concerns endogenous retrovirus derived genes or gene segments which have SNPs correlated with occurrence of conditions such as SLE, Rheumatoid Arthritis, IBD and others as compared to individuals without such conditions

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.

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.

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.

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.

Some definitions

Protein and peptides

The terms "peptide" and "polypeptide" refers to any molecule containing at least three amino acid residues coupled through peptide bonds. The term "polypeptide" is used here for peptides and/or proteins without
 5 necessasrily being constricted to a specific lenth of said polypeptide.

The term "protein" is used interchangeably with polypeptide and is not limited to any specific length or size. Polypeptides and proteins can be in the form of fragments or complexes or can have any primary, secondary, tertiary or quartenary structure such as but not limited to monomer, dimer, trimer, tetramer or multimer, alpha helix, beta sheet or any other helix structures and/or globular structures. Polypeptides and
 10 proteins can contain crosslinkings or any chemical modifications.

Polypeptides and proteins can be modified. As non-restricting examples, a polypeptide of the invention may be glycolysed, acylased and/or dimerized or trimerized, but does not need to be glycolysed, acylased and/or dimerized or trimerized.

Polypeptides and proteins can comprise one or more amino acids independently selected from the group
 15 consisting of naturally occurring L-amino acids, D-amino acids as well as non-naturally occurring, synthetic amino acids.

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.

20 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, or to reduce it'simmunogenecity. 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
 25 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
 30 embodiments of the present invention, the carrier may be a pharmaceutical acceptable carrier as described

herein below. The immune modulating peptides of the present invention may be coupled to the carrier by means of cross-linking as further described herein below.

The terms "protein modification", "protein stability" and "peptide stability" is used to describe the state of the proteins and peptides, in particular the state wherein said proteins and/or peptides are more resistant to degradation, fibrillation, and aggregation and/or have increased properties towards hydrolysis and/or proteolysis or have improved shelf-life. 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 di-alkylamino 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.

Single nucleotide polymorphism (SNP):

A single nucleotide polymorphism, also known as simple nucleotide polymorphism, (SNP, pronounced snip; plural snips) is a DNA sequence variation occurring commonly within a population (e.g. 1%) in which a single nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes. For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide. In this case we say that there are two alleles. Almost all common SNPs have only two alleles. The genomic distribution of SNPs is not homogenous; SNPs occur in non-coding regions more frequently than in coding regions or, in general, where natural selection is acting and 'fixing' the allele (eliminating other variants) of the SNP that constitutes the most favorable genetic adaptation. Other factors, like genetic recombination and mutation rate, can also determine SNP density.

SNP density can be predicted by the presence of microsatellites: AT microsatellites in particular are potent predictors of SNP density, with long (AT)(n) repeat tracts tending to be found in regions of significantly reduced SNP density and low GC content.

Within a population, SNPs can be assigned a minor allele frequency — the lowest allele frequency at a locus that is observed in a particular population. This is simply the lesser of the two allele frequencies for single-nucleotide polymorphisms. There are variations between human populations, so a SNP allele that is common in one geographical or ethnic group may be much rarer in another.

These genetic variations between individuals (particularly in non-coding parts of the genome) are sometimes exploited in DNA fingerprinting, which is used in forensic science. Also, these genetic variations underlie differences in our susceptibility to disease. The severity of illness and the way our body responds to treatments are also manifestations of genetic variations. For example, a single base mutation in the APOE (apolipoprotein E) gene is associated with a higher risk for Alzheimer disease.

Homology and identity

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

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.

"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.

Other terms

An adjuvant is a component that potentiates the immune responses to an antigen and/or modulates it towards the desired immune responses. An adjuvant is defined as any substance that acts to accelerate, prolong, or enhance antigen-specific immune responses when used in combination with specific vaccine antigens.

The term Immunotherapy refers to the treatment of disease by inducing, enhancing, or suppressing an immune response. Immunotherapies designed to elicit or amplify an immune response are classified as activation immunotherapies, while immunotherapies that reduce or suppress are classified as suppression immunotherapies.

The term "immunosuppressive polypeptides" is used about polypeptides, which may exhibit immune suppressive activity. The term "immunosuppressive polypeptides of the invention" is used about polypeptides of the invention, which may exhibit immune suppressive activity.

The term "immune modulation" is used here about alteration of the immune system or of an immune response by agent(s) that activate or suppress its function. The term "immuno-modulation" might refer to

the process of an immune response being either suppressed, partly or completely, or triggered or induced or enhanced. This may include immunization or administration of immunomodulatory drugs.

The term "immune modulating peptides" is used about polypeptides, which may exhibit immune modulating activity. The term "immune modulating polypeptides of the invention" is used about
5 polypeptides of the invention, which may exhibit immune modulating activity.

Likewise, the term "growth-modulation" as used herein refers to the process of where the cell proliferation is either suppressed, partly or completely, or where cell proliferation is induced or enhanced or promoted.

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

10 Non-limiting examples of such substances are creams, lotions, shake lotions, ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosols as well as transdermal patches and bandages.

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
15 susceptibility of a clinical condition, a disorder or condition as defined herein.

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
20 adverse effect 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,
25 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.

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 animals
30 may also be of bovine, equine, porcine, human, ovine, caprine or cervidae origin.

The expression “derived from an endogenous retrovirus” means that the domain is substantially identical to the immune suppressive domain of the endogenous retrovirus, optionally with mutations, insertions or deletions.

All cited references are incorporated by reference.

- 5 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, items and claims of the present invention may be combined; also with features of the technical background and the cited references.

Example 1: The HERV-Env 59 is overexpressed in SLE patients as compared to healthy individuals

- 10 Here we present data on investigating HERV-Env59 gene expression in PBMCs (peripheral blood mononuclear cells) from 45 healthy individuals and from 45 patients with Systemic Lupus Erythematosus here SLE, by real-time RT-PCR. The data was normalized to RPL13a or RPL37A housekeeping genes. Venous blood samples were collected in CPT™ tubes (BD Vacutainers®, BD Diagnostics, NJ USA), and processed within 1h. Tube/blood samples were centrifuged at room temperature in a horizontal rotor for a minimum
- 15 of 30 minutes at 1800 g (relative centrifuge force). After centrifugation, mononuclear cell layers were collected and transferred to 15ml size conical tubes. Following two washing steps, cell pellets were resuspended in the desired medium for subsequent RNA extraction. RNAs from peripheral blood samples 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
- 20 and 28S/18S rRNA ratios. 200ng total RNA purified from PBMCs 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 Light Cycler 480 cycler (Roche Diagnostics, DK). 2µl of cDNA (from a total 20µl reaction volume) was used in 20µl reaction. The real-time Q-PCR reactions contained 10µl SybrGreen 2x Master Mix (Roche Diagnostics, DK), 2µl forward primer (5pmol/µl), 2 µl reverse primer (5pmol/µl) and
- 25 4µl water. After initial denaturation at 95°C for 10 minutes, PCR amplifications were performed for 45 cycles. 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* value and relative quantification was determined using the ΔC_t model presented by PE Applied Biosystems (Perkins Elmer, Foster City, CA USA).
- 30 A specific amplification product (primer sets: Env 3 forward set 1 and Env 3 reverse set 1, ISD 59 forward and ISD59 reverse, EnvH3 forward and EnvH3 reverse)was observed in all SLE samples as well as in healthy

controls. The relative HERV-Env 59 mRNA expression levels were significantly higher in patients with SLE than in healthy controls ($P < 0.001$) Figure 1. The bars show the median values and SD. The P value shows statistical differences (< 0.05) between samples. The P value was calculated using nonparametric Mann-Whitney U test. Furthermore significant variation in the HERV-Env59 mRNA expression level was observed in PBMCs samples obtained from patients with SLE. Differences were not due to the quality of retrotranscription, since the analysis of RNA *RPL13a* or *RPL37A* expression levels confirmed that total cDNA quantity was identical over all the samples tested.

The results are presented in Figure 1.

Example 2: Correlation between IL-6 and/or TLR-7 mRNA and HERV-Env 59 expression levels in patients with SLE.

Here we present data on investigating a correlation between IL-6 and/or TLR7 mRNA and HERV-Env59 mRNA expression levels in patients with SLE. Among the sample population used in the study of Env59 expression levels, we examined IL-6 mRNA expression levels in PBMCs from patients with SLE by real-time RT-PCR (for details on the assay see Example 1). Additionally, we assessed TLR-7 mRNA expression levels in PBMCs from patients with SLE. The data were normalized to housekeeping gene *RPL13a* mRNA expression levels. We next performed a Spearman correlation analysis between the expression of HERV-Env 59 mRNA and *IL-6* mRNA or *TLR-7* mRNA, both of which showed a distinctive modulation. Figure 2a and 2b shows the HERV-Env59 gene expression levels, evaluated by real-time RT-PCR, in PBMCs obtained from patients with SLE, plotted against *IL-6* or *TLR-7* gene expressions. Statistical analysis demonstrated a significant negative correlation between the mRNA expressions of HERV-Env59 and *IL-6* ($P = 0.0065$, $r = -0.5400$) or *TLR-7* ($P = 0.02$, $r = -0.38$) in the SLE group. Thus, the correlation analysis suggests that higher levels of HERV-Env 59 are associated to lower levels of IL-6 or TLR-7 in SLE patients.

The results are presented in Figure 2a and 2b.

Example 3: Characterization of a functional envelope protein from the HERV-H3/Env-59 locus

Here we present data on characterization of a functional envelope protein from HERV-Env 59 locus. The structural organization of the HERV-Env 59 was recognized previously, disclosing hydrophobicity profile as well as other characteristic feature of retroviral envelopes, i.e., a putative signal peptide located downstream of the M2 methionine, a CWLC motif, a furin cleavage site at the junction of the SU and TM subunits followed by hydrophobic fusion peptide and a hydrophobic membrane-spanning domain. In order to study the expression and activity of this protein further, the coding HERV-Env 59 cDNA was cloned into an expression vector, driven by a human cytomegalovirus (CMV) promoter. An HA-tag was added to the N-

terminal of the protein after the putative signal peptide identified through *in silico* methods. The PUC57Env59 plasmid was constructed by Genscript (NJ, USA), with a synthesized *Env59* insert cloned into *EcoRV* site of PUC57 plasmid. Due to lack of commercial antibodies, the gene was fused to C-terminal HA-tag. For expression studies, *Env59* was inserted into the 867 p-IRES-puro vector using *EcoRI* and *NotI* restriction sites to obtain final pEnv59IRESpuro construct. The correctness of the sequences was verified by sequencing.

Expression of HERV- Env 59 gene was confirmed using a monoclonal antibody against the HA-tag in western blot in transiently transfected HEK293 or NIH3T3 cells using Lipofectamine LTX[®] or Lipofectamine 2000[®] reagent (ThermoFisher Scientific) (Figure 3a). 48h after transfection cells were lysed and processed for Western blotting. Whole-cell extracts were prepared after lysis in NP-40 lysis buffer (10mM Tris-HCL pH7.4, 137 mMNaCl, 10%v/v glycerol, 1% v/v Nonidet P-40) containing a protease inhibitor cocktail (Roche Diagnostics, DK). Cell debris were removed by centrifugation at 10.00 x g for 25min at 4°C and protein concentration determined by BCA assay (Pierce, VWR/ Bie&Berntsen, DK). Equal amounts of protein (20µg/sample) were separated by SDS-polyacrylamide gel electrophoresis, transferred to nitrocellulose membranes, and incubated with specific antibodies, followed by incubation with HRP-conjugated secondary antibody. Immunoblots were developed by enhanced chemiluminescence using proprietary reagents (Millipore, DK).

As clearly evident, a band, corresponding to the molecular masses of ca. 62 kDa, was only detected in HEK293 and NIH3T3 cells transfected with the HERV-Env 59 expression vector, demonstrating that the HERV-*Env* 59 gene has the coding capacity for a full length protein and could be expressed *ex vivo*.

In order to determine correct surface expression of the envelope protein, we performed immunofluorescence confocal microscopy in transiently transfected HEK293 cells using a fluorescently labeled anti HA antibody. To visualize HERV-H Env59 surface expression in HEK293 cells transfected with the pEnv59IRESpuro and pcDNA-eGFP constructs by immunofluorescence, we stained formaldehyde-fixed, not permeabilized cells, with mouse anti-HA-tag antibody followed by fluorescence-labelled anti-mouse antibody, Alexa Fluor 568nm. In all experiments, HERV-H Env59 detection was performed on cells grown on glass coverslips approximately 36-48h posttransfection. Cells nuclei were stained using DAPI (4',6-diamidino-2-phenylindole). No signal was detected with cells transfected with an irrelevant expression vector. Observations were made under a Zeiss LSM 510 laser scanning confocal microscope.

Staining of on nonpermeabilized cells showed that the HERV-Env 59 protein could be detected on the cell surface, confirming correct intracellular transport of the protein consistent with a retroviral envelope protein (Figure 3b).

Figure 3a depicts detection of HA-tag envelope glycoprotein in HERV-H Env59 HA-tag transfected cells.

Human HEK293 or mouse NIH3T3 cells were transfected with plasmids expressing either HERV-H Env59 HA-tag cDNA or control plasmid pcDNA 3.1 eGFP, or left untransfected in culture medium. 48h later, the Env59-transfected cells, pcDNA 3.1 eGFP-transfected cells and untransfected cells were lysed and then proceed
5 for Western blotting with antibodies (Ab) against HA-tag or tubulin.

Figure 3b depicts expression of the HERV-Env59 protein. HERV-H Env59 proteins could be detected at the cell surface, a result consistent with the expected localization of a functional Env.

Confocal microscopy images from immunofluorescence analysis of human HEK293 cells transiently transfected with expression vector of the fully coding HERV-H Env59 gene (red) and control pcDNA 3.1
10 eGFP vector (green). Detection was performed on fixed and non-permeabilized HEK293 cells grown on glass coverslips approximately 36h posttransfection. HERV-H Env59 was detected (red) using a mouse anti HA-tag antibody. Cells nuclei are stained with DAPI.

Example 4: HERV-Env 59 encodes a functional envelope protein

Here we present data on investigating functional properties of HERV-Env59 encoded protein. We
15 investigated whether this envelope protein is still fusion active through pseudotyping of this protein with lentiviral core particles. Pseudotyped lentiviral/HERV-Env 59 particles were formed using a three plasmid vector system that includes a viral transfer vector encoding the eGFP protein. When co-transfected these three plasmids produce lentiviral particles that can be decorated with a surface protein if a fourth plasmid encoding such a protein is included in the transfection mixture. The plasmids for lentiviral vector packaging
20 were kindly provided by Professor Jacob Giehm Mikkelsen. Lentiviral vectors pseudotyped with the vesicular stomatitis virus G-protein (VSV-G) encoded by pMD.2G, or pEnv59IRESpuro, or control pcDNA 3.1 were generated using the four plasmid expression lentiviral system containing the pCCL/PGK-eGFP.pMDLg/p-RRE.pRSV-REV. In our system, to further decrease the risk of recombination and production of replication-competent viruses, the Rev gene was inserted on the pRSV-REV plasmid. Virus was produced
25 by transient transfection into 293T cells using standard calcium phosphate-mediated method. The total amount of DNA used per 6-well plate was 4µg of lentiviral vector plasmids 1,59µg of pCCL/PGK-eGFP, 1,59µg of pMDLg/p-RRE, 0,37µg of pRSV-Rev and 0,46µg of pMDM.2G/pEnv59IRESpuro/pcDNA3.1. Forty eight hours after transfection, the vector-containing medium was collected and spun at 500 x g for 5 min, filtered through a 0,45-µ pore size filter (Corning, NY USA) and used fresh for transduction of target cells .
30 Lentiviral titers were determined by seeding HEK293 cells in six-well plates at 5×10^5 cells per well the day before infection with serial dilutions of the concentrated viral stock in the presence of polybrene (8µg/ml). After 12h incubation, the culture medium was changed and the cells were incubated for additional time.

Cells expressing EGFP were identified using fluorescence microscopy (Figure 4). As evident in Figure 4, VSV-g pseudotyped particles infect all cell types showing that the assay is capable of detecting infection in all cell types, whereas the undecorated naked particles are not infectious. Most interestingly, ENV59 pseudotyped particles are only able to infect the HEK293 cells. The titers on human HEK293 cells were in the range of 3500- to 5000- CFU/ml range, which is quite significant. This suggests that ENV59 is incorporated into budding virions and constitutes an active fusion capable envelope protein. Furthermore, it seems that this envelope protein uses a receptor that is only found on HEK293 cells and not on murine NIH3T3 or HeLa cells.

Infection assay of the HERV-H Env59 envelope. Formation of the infectious HERV-H Env59 hybrid viral particles. Lentiviral vectors pseudotyped with the vesicular stomatitis virus G-protein (VSV-G) encoded by pMD.2G, or pEnv59IRESpuro, or control pcDNA 3.1 were generated using the four plasmid expression lentiviral system. Pseudotyped virions were assayed for infectivity and the target cells were human HEK293 cells. Viral titers are the means from two independent experiments.

Example 5: Immunomodulatory function induced by HERV-Env 59 retroviral peptide with impact on the pathogenesis of SLE and other autoimmune diseases.

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. Pro-and anti- 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.

Here we present data showing that pretreatment of cells with ENV59 peptide results in a decrease in the release of cytokines including pro-inflammatory cytokines such as IL-6. Therefore, treatment of patients, in the risk of developing sepsis or other inflammatory condition, with ENV59 peptide could act beneficially to decrease production of proinflammatory cytokines and hereby lessen the risk of developing shock, organ failure and death. Here, we examined the modulatory function of Env 59 ISD on the expression levels of IL-6 in human acute monocytic leukemia cell line THP-1 and PBMCs obtained from healthy donors or patients with SLE. THP-1 cells and PBMCs were maintained in RPMI 1640 supplemented with 10% FBS, 100U/ml penicillin, 100 µg/ml streptomycin and 2mM L-glutamine at 37°C in a 5% CO₂ incubator. THP-1 cells are known to induce IL-6 mRNA and protein in response to lipopolysaccharide (LPS) treatment. THP-1 cells were

left untreated or incubated with 0 uM, 30µM or 60µM of Env-59 ISD and stimulated with 1µg/µl LPS for 4h, based on the previous analyses to find the optimal dose and incubation times. Figure 5a and 5b are representative for the results of real-time RT-PCR (for assay details see example 1) and ELISA analyses on stimulant-induced IL-6 mRNA protein expression.

5 For IL-6 ELISA analyses the supernatant from THP-1 cells or PBMCs (Figure 5 c and d) treated with peptides was assayed on human IL-6 ELISA MaxTM Deluxe Set (Biolegend, #430505). 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
 10 Capture Antibody, diluted 1:200 in 1x Coating Buffer (5x Coating Buffer diluted in ddH₂O). 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
 15 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 IL-6 stock solution. The six two-fold serial dilutions of the 250 pg/mL top standard were performed, with the human IL-6 standard concentration: 250 pg/mL, 125 pg/mL, 62.5
 20 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 or PBMCs 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
 25 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
 30 2N H₂SO₄ 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.

The results are presented in Figure 5A-D.

Figure 5A and 5B. Inhibitory effect of Env59 (ISU) peptide on expression of IL-6 mRNA and IL-6 protein in LPS-stimulated THP-1 cells. THP-1 cells were incubated with either complete growth medium, or 30μM Env59 peptide, 60μM Env59 peptide, 30μM control peptide, 60μM control peptide, and simultaneously stimulated for 4h with 1μg/ml LPS. After incubation samples were proceed for RNA extraction and supernatant was used for ELISA experiments. The experiment was repeated five times and one of the five typical results is shown in the Figure 5A and 5B. Incubation time and peptides concentrations were optimized in time course and dose-response curve experiment (Wasaporn 2010).

Figure 5C and 5D. Inhibitory effect of Env59 (ISU) peptides on IL-6 protein and INF-gamma protein in PMA/ionomycin stimulated human PBMCs. Human PBMCs obtained from healthy donors or patients with SLE, were incubated with either complete growth medium, or 30μM Env59-H6 peptide, 60μM Env59-H6 peptide, 30μM Env59-GP3 peptide, 60μM Env59-GP3 peptide, 30μM control peptide, 60μM control peptide, and simultaneously stimulated for 4h with 50ng/ml PMA and 1μg/ml ionomycin. After incubation supernatants were collected and used for ELISA experiments. The experiment was repeated five times and one of the five typical results is shown in the Figure 5C and 5D. Incubation time and peptides concentrations were optimized in time course and dose-response curve experiment.

Env 59 ISD suppressed strongly the expression of the mRNA and protein for IL-6 in LPS-stimulated THP-1 cells. The control peptide showed no suppressive effect on either the IL-6 mRNA or protein expression levels. The expression of IL-6 protein was minimal in THP-1 cells incubated with medium alone (Figure 5B). The level of housekeeping gene RPL13a was used for mRNA normalization was not influenced by peptides and/or LPS treatment. The ability of Env 59 ISD to inhibit IL-6 in a cell line is very significant since IL-6 is believed to be involved in SLE and its reduction is expected to constitute a novel treatment strategy for autoimmune diseases. PBMCs were stimulated with 50 ng/ml PMA plus 1μg/ml ionomycin. This stimulation was selected as giving the most consistent results for IL-6 protein induction in human PBMCs (data not shown). Real-time RT-PCR quantification was not performed due to low concentration of purified RNA which is obtainable from PBMCs. The results are shown in Figure 5C. The IL-6 levels were significantly lower in PBMCs incubated with of any of the Env-59 ISD peptides. The control peptide had no effect on the synthesis of IL-6 protein. The level of IL-6 protein was below lowest detection limit in PBMCs incubated with medium alone. In the last series of experiments we were interested to see if Env 59 ISD had an effect on the production of other inflammatory cytokines. e.g. interferon gamma (IFN-gamma). Excessive production of IFN-gamma has been implicated in the pathogenesis of systemic lupus erythematosus, and a deficiency in INF-gamma receptor totally abates the disease process. The synthetic Env 59 ISD peptides inhibit the production of INF-gamma by PMA/ionomycin-stimulated human PBMCs (Figure 5D) although on

different levels. In those studies inhibition of effector molecules was not merely secondary to a nonspecific toxicity of the peptides to PBMCs as assessed by trypan blue dye exclusion.

Example 6: Immunomodulatory function induced by SG#1-SG#17 (ID1031 to ID1047).

Pretreatment of cells with peptides SG#1 to SG#17 (ID1031 to ID1047) affects the release of cytokines including pro-inflammatory cytokines such as IL-6, TNF-alpha, IL-10 and IL-8.

Here, we examined the modulatory function of peptides, peptides SG#1 to SG#17 (here ID1031 to ID1047) on the expression levels of IL-6, TNF-alpha, IL-10 and IL-8 in human acute monocytic leukemia cell line THP-1. THP-1 cells were maintained in RPMI 1640 supplemented with 10% FBS, 100U/ml penicillin, 100 µg/ml streptomycin and 2mM L-glutamine at 37°C in a 5% CO₂ incubator. THP-1 cells are known to induce IL-6, TNF-alpha, IL-10 and IL-8 mRNA and protein in response to lipopolysaccharide (LPS) treatment. THP-1 cells were left untreated or incubated with 0 uM, 7,5µM, 15µM, 30µM, 60µM or 100µm of each of the peptides, peptides SG#1 to SG#17 (here ID1031 to ID1047), and stimulated with 1µg/µl LPS for 6h, based on the previous analyses to find the optimal dose and incubation times.

Table 1: Modulatory function of peptides, peptides SG#1 to SG#17 (here ID1031 to ID1047) on the expression levels of IL-6 in human acute monocytic leukemia cell line THP-1. (-) inhibition indicates percentage (%) of inhibition as compared to only LPS treated samples (arbitrary set at 100%). As such (-) 98.93875 for SG#17 at 100µM indicates that compared to only LPS treated cells, 98.93875 percenatage (%) of IL-6 secretion was inhibited (or less than 0.1%IL-6 was secreted) by the treatment with a peptide SG#17 (ID1047). Accordingly (+) 36.9828 percentage (%) for SG#13 at 100µM indicates that the level of secreted cytokine was 36.9828 percentage (%) above the only LPS treated samples (100%) or 136,98285%.

Name	7.5µM	15µM	30µM	60µM	100µM
SG#1	(+)0,6842	(+)7,19017	(-) 3,53917	(-)25,11339	(-)26,67839
SG#2	(-)15,6948	(-)25,9059	(-)30,5144	(-)51,3958	(-)73,1873
SG#3	(-)2,24997	(-)10,222	(-)12,2657	(-)37,5909	(-)39,5264
SG#4	(+)12,98853	(+)20,76308	(+)38,19179	(+)36,39436	(+)13,26897
SG#5	(-)7,63816	(-)4,51669	(-)9,3891	(-)50,4993	(-)61,1801
SG#6	(+)3,08227	(+)15,47627	(-)2,16739	(-)13,4223	(-)28,9119
SG#7	N.D	N.D	N.D	N.D	N.D
SG#8	(+)1,471583	(+)14,54056	(+)6,835367	(+)7,654897	(+)20,85891
SG#9	(+)3,354645	(+)2,904014	(+)2,63574	(-)9,23121	N.D.
SG#10	(-)6,0571	(+)8,264384	(+)18,28915	(+)5,122111	(-)0,45913
SG#11	(+)12,10097	(-)15,0445	(-)3,07211	(-)15,9818	(-)0,73926
SG#12	N.D.	N.D.	N.D.	N.D	N.D.
SG#13	(-)5,76479	(+)6,907031	(-)5,28609	(+)8,616429	(+)36,9828
SG#14	(-)2,98108	(-)0,44762	(+)0,740257	(+)28,51696	(+)15,20844
SG#15	(-)14,0971	(-)3,04025	(-)28,6554	(-)78,1353	(-)99,0097
SG#16	(+)1,082038	(-)2,72293	(+)3,642883	(+)4,832977	(-)19,1099
SG#17	(-)42,71029	(-)41,98221	(-) 52,01779	(-) 69,48402	(-) 98,93875

Table 1

Fig. 6 (A, B, C, D): Immunomodulatory function induced by SG#2, SG#3, SG#15, SG#15 (ID1032, ID1033, ID1035 and ID1045) on the expression levels of TNF-alpha protein secretion.

Fig. 7 (A, B, C, D): Immunomodulatory function induced by SG#2, SG#3, SG#15, SG#15 (ID1032, ID1033, ID1035 and ID1045) on the expression levels of IL-10.

Fig. 8 (A, B, C, D): Immunomodulatory function induced by SG#2, SG#3, SG#15, SG#15 (ID1032, ID1033, ID1035 and ID1045) on the expression levels of IL-8.

Procedure for IL-6, TNF-alpha, IL-10 and IL8 ELISA quantification

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 ddH₂O). 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 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 concentration (250 pg/mL or 300 pg/mL for IL-10 quantification) was prepared in 1x Assay Diluent A (1x AD) from the relevant IL-6, TNF-alpha, IL-10 or IL-8 stock solution. The six two-fold serial dilutions of the 250 pg/mL (or 300 pg/mL for IL-10 quantification) top standard were performed, with the human IL-6, TNF-alpha or IL-8 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 as well as with the IL-10 standard concentration: 300 pg/mL, 150 pg/mL, 75 pg/mL, 37.5 pg/mL, 18.75 pg/mL, 9.375 pg/mL and 4.6875 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 or PBMCs 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 H₂SO₄ per well. Positive wells turned yellow. Absorbance was measured at 450 nm and 570 nm (background) within 30 minutes. The data were analyzed in the Microsoft Excel 2010 program. Statistical analyses were performed using Microsoft Excell 2010 program.

Example 7: The effect of the peptides on arthritis score and SAA-3 expression in Sakaguchi mice model (spontaneous CD4+T cell-mediated chronic autoimmune arthritis).

Here we present data on investigating *in vivo* effect of the HERV-Env59 peptide. The effect of the Env59 ISU peptides on disease development is compared with a scrambled peptide or saline treated control group. Arthritis was induced by intrapenile injection of 220µl mannan at concentration 90µg/ml. Animals were treated daily by subcutaneous injections with indicated concentration of Env-59 peptide, scrambled peptide control or NaCl saline control. Joint swelling was monitored by inspection and scored as follows: 0, no joint swelling; 0.1, swelling of one finger joint; 0.5, mild swelling of wrist or ankle; 1.0, severe swelling of wrist or ankle. Scores for all digits, wrists, and ankles were totaled for each mouse in Figure 9A.

Figure 9A

Development of arthritis in SKG mice. Vertical bars represent the means + SD of the whole group of mice (5 animals each group). Arthritis scores are significantly different between Env3 peptide and NaCl control treated mice. Peptides or control saline NaCl were administrated subcutaneously 5 times a week starting with Day (-1, one day pre-treatment).

Mouse Serum Amyloid A-3 ELISA

Acute-phase serum amyloid A proteins (A-SAAs) are secreted during the acute phase of inflammation.

Similar to CRP, levels of acute-phase SAA increase within hours after inflammatory stimulus, and the magnitude of increase may be greater than that of CRP. SAA3 gene is regulated by proinflammatory cytokine IL-6. Quality of ELISA assay has been verified by including two reference QC samples (included in the kit with known expected range). Plasma samples were analyzed in duplicate for the presence of SAA3 using an ELISA according to the manufacturer's protocol (Millipore). Concentrations of SAA3 were determined in plasma collected the same time point when animals were bled and sacrificed (day 28 of trial) (Figure 9B). Differences in medians were detected among treatment groups. SAA3 levels were elevated in SKG mice treated with saline NaCl as compared to animals treated with HERV-Env59 derived peptide. Next, we examined the correlation of circulating SAA3 levels with arthritis scores regardless of treatment group. There was a positive correlation between SAA3 plasma concentration and arthritis score using linear regression (Figure 9). However, the relationship appears curvilinear and best fits a semi-logarithmic (log-X, linear-Y) model ($R^2=0.73$). This suggests that log increases in circulating SAA3 corresponds to unit changes in arthritis score.

Results are presented in Figure 9b and 9c.

Example 8: List of primers used for real time RT-PCR analysis (table 2)

Target gene/primer name	Primer sequence 5'-3'
Env 3 forward set 1	Agggtaaaggtgagggctgt
Env 3 reverse set 1	agcaaacaactgctggcttt

IL-6 forward	AGCCACTCACCTCTTCAGAAC
IL-6 reverse	GCCTCTTTGCTGCTTTCACAC
ISD 59 forward	AGAGCTCCCTGTTCCCCTTA
ISD 59 reverse	CATTAGACGGGCTACGGAAG
RPL13a forward	CATCGTGGCTAAACAGGTACTG
RPL13a reverse	GCACGACCTTGAGGGCAGCA
RPL37A forward	ATTGAAATCAGCCAGCACGC
RPL37A reverse	AGGAACCACAGTGCCAGATCC
EnvH3 forward	gttgggctttggagatgg
EnvH3 reverse	ccctcctccacatttatttg

Table 2

Example 9: The effect of the peptides on arthritis scores in Collagen-Induced Arthritis Model (CIA model).

The CIA model is the “standard” animal model for evaluation of anti-arthritic activity based on immunization with bovine collagen to develop antibodies against bone and cartilage.

Here we present data on investigating *in vivo* effect of the HERV-Env59 peptide. The aim was to determine anti-arthritic dosing paradigm in a murine model of collagen-induced arthritis. This study was carried out in female DBA/1J mice. The effect of the Env59 ISU peptides on disease development is compared with a methotrexate MTX (positive control) or saline treated control group.

Summary of procedure:

Day 0: The mice were weighted and injected subcutaneously at the nape of the neck as in the table below (table 3):

Group	No. mice	Treatment	Dose
1	10	saline	10ml/kg
2	10	HERV-Env59 peptide	4µg/mouse
3	5	Methotrexate	3mg/kg

Table 3

An hour later, the mice were injected subcutaneously at the base of the tail with 50 µl of the collagen/CFA emulsion.

Mice were scored for signs of arthritis every Monday, Wednesday, and Friday during the next 41 days as follows:

- Each paw receives a score
- 0 = no visible effects of arthritis
- 1 = edema and/or erythema of 1 digit
- 2 = edema and/or erythema of 2 digits
- 3 = edema and/or erythema of more than 2 digits
- 4 = severe arthritis of entire paw and digits

5

The Arthritic Index (AI) was calculated by the addition of individual paw scores.

Day 42 The mice were weighted and scored for signs of arthritis.

Table 4 and Fig. 10 show the effect of treatment on average disease development based on AI.

10 Table 5 shows the effect of treatment on average terminal individual paw scores

		STUDY DAY											
Group	Mouse	21	22	25	27	29	32	34	36	38	41	42	
1	Mean	0	0.7	1.3	2.3	2.9	4.9	6.6	7.9	9.1	9.9	10.5	
	SEM	0	0.5	1.0	1.1	1.0	0.9	0.7	0.5	0.4	0.3	0.4	
2	Mean	0	0	0.8	1.1	1.2	2.0	2.1	2.7	3.1	3.2	3.3	
	SEM	0	0	0.7	1.0	1.0	1.2	1.1	1.2	1.2	1.2	1.2	
	p-value	1.00	0.17	0.68	0.42	0.25	0.06	0.003	0.001	0.0002	4x10 ⁻⁵	2x10 ⁻⁵	
3	Mean	0	0	0	0	0	0	0	0	0	0	0	
	SEM	0	0	0	0	0	0	0	0	0	0	0	
	p-value	1.00	0.34	0.38	0.16	0.07	0.002	9x10 ⁻⁶	4x10 ⁻⁸	9x10 ⁻¹⁰	4x10 ⁻¹¹	5x10 ⁻¹¹	

Table 4

Group	Mouse	Front right	Front left	Rear right	Rear left
1	Mean	1.7	2.6	2.9	3.1
	SEM	0.2	0.3	0.3	0.2
2	Mean	0.8	0.3	1.5	0.7
	SEM	0.4	0.3	0.6	0.5
	p-value	0.05	2×10^{-5}	0.04	7×10^{-5}
3	Mean	0	0	0	0
	SEM	0	0	0	0
	p-value	3×10^{-5}	3×10^{-6}	2×10^{-6}	3×10^{-10}

Table 5

Summary of results: Prophylactic daily subcutaneous injection with 4 µg/mouse HERV-Env59 peptide resulted in 70% incidence of disease and a 70% reduction in disease severity.

Conclusion: Once daily subcutaneous injection with 4 µg/mouse of the test compound, starting one hour prior to disease induction resulted only 70% incidence on disease which was associated with a significant 70% reduction in disease severity at the termination of the study.

Example 10: Hemolysis assay on red blood cells.

Drug-induced hemolysis is a relatively rare but serious toxicity liability. It occurs by two mechanisms:

Toxic hemolysis- direct toxicity of the drug, its metabolite, or an excipient in the formulation.

Allergic hemolysis- toxicity caused by an immunological reaction in patients previously sensitized to a drug.

Although the majority of normal individuals may suffer toxic hemolysis at sufficiently high concentrations of hemolytic drugs, for most drugs toxic hemolysis involves lower doses given to individuals who are genetically predisposed to hemolysis. The US FDA recommends that for excipients intended for injectable use, an in vitro hemolysis study should be performed at the indicated concentration for IV administration to test for hemolytic potential. In the hemolysis assay, human red blood cells and test materials are co-

incubated in buffers at defined pHs that mimic extracellular, early endosomal, and late endo-lysosomal environments. Following a centrifugation step to pellet intact red blood cells, the amount of hemoglobin released into the medium is spectrophotometrically measured (405 nm for best dynamic range). The percent red blood cell disruption is then quantified relative to positive control samples lysed with a detergent. In this model system the erythrocyte membrane serves as a surrogate for the lipid bilayer membrane that encloses endo-lysosomal vesicles. The desired result is negligible hemolysis at physiologic pH (7.4) and robust hemolysis in the endo-lysosomal pH range from approximately pH 5-6.8.

Here we present data on investigating hemolysis as a function of Env 59 peptide concentration, using red blood cells from chicken. The hemolytic activity of Env3 peptide after 1h incubation time at 37°C is shown in Figure 6. The concentration-response curves of peptides for percentage lysis of chicken red blood cells (RBC) are shown. Included as positive control, peptide from the glycoprotein of the Ebola virus, here assigned as Ebo Z. The control for 100% hemolysis was a sample of erythrocytes treated with NP-40 detergent. The peptide concentration is reported as µM.

The results are presented in Figure 11.

Example 11: Toxicity profile for peptides SG#1 to SG#17 ((ID1031 to ID1047)

Here, we examined the cytotoxicity effect of peptides SG#1 to SG#17 (ID1031 to ID1047) on two human cell lines THP-1 or HT-1080 cells.

The CellTiter-Blue® Cell Viability Assay provides a homogenous, fluorometric method for estimating the number of viable cells present in multiwell plates. It uses the indicator dye resazurin to measure the metabolic capacity of cells – an indicator of cell viability. Viable cells retain the ability to reduce resazurin into resorufin, which is highly fluorescent.

The CellTiter-Blue® Reagent is a buffered solution containing highly purified resazurin. Resazurin is dark blue in color and has little intrinsic fluorescence. However, when it is reduced to resorufin, it becomes pink and highly fluorescent (579_{EX}/584_{EM}).

Example Procedure:

1. Set up 96-well assay plates containing cells in culture medium. For HT-1080, plate 1.6×10^4 cells per well on the Day 1 of the experiment. Cells are plated in 100µl complete culture medium (DMEM) per well.

2. On day 2, gently remove medium and add 50µl of complete DMEM medium, add peptides and vehicle controls to appropriate wells so the final volume is 100µl in each well. Supplement with complete DMEM where necessary.
3. Culture cells for the desired test exposure period, about 20h.
4. On day 3, remove assay plates from 37°C incubator and add 20µl/well of CellTiter-Blue® Reagent.
5. Shake for 10 seconds.
6. Incubate using standard cell culture conditions for 4 hours.
7. Shake plate for 10 seconds and record fluorescence at 560/590nm

Results:

- 10 Toxicity profile for peptides SG#1 to SG#17 (ID1031 to ID1047). All peptides were tested at the dosage increment (10nm, 30nM, 100nM, 1µM, 10µM, 30µM, 100µM and 300µM). A cytotoxic cell penetrating peptide with IC50 of 1µM was included as a positive control at the same dosage increment.

None of the tested peptides SG#1 to SG#17 (ID1031 to ID1047) show signs of toxic effect on THP-1 or HT-1080 cells at the dosage increment (10nm, 30nM, 100nM, 1µM, 10µM, 30µM, 100µM and 300µM). Fig. 12 is a representative graph for SG#16 (ID1046).

	Toxicity yes/no at the 300µM conc.
SG#1	No
SG#2	No
SG#3	No
SG#4	No
SG#5	No
SG#6	No
SG#8	No
SG#9	No
SG#10	No

SG#11	No
SG#12	No
SG#13	No
SG#14	No
SG#15	No
SG#16	No
SG#17	No

EC50 is not calculated since none of the peptides SG#1 to SG#17 (ID1031 to ID1047) show signs of toxic effect on THP-1 or HT-1080 cells at the dosage increment (10nm, 30nM, 100nM, 1µM, 10µM, 30µM, 100µM and 300µM).

- 5 Example 12: The effect of the peptides on arthritis scores in Collagen-Induced Arthritis Model (CIA model), study number 2.

The CIA model as described in an Example 9 is the “standard” animal model for evaluation of anti-arthritic activity based on immunization with bovine collagen to develop antibodies against bone and cartilage.

- 10 Here we present data on investigating *in vivo* effect of the HERV-Env59, SG#2, and SG#5 and SG#15 peptides. The aim was to determine anti-arthritic dosing paradigm in a murine model of collagen-induced arthritis. This study was carried out in female DBA/1J mice. The effect of the Env59 ISU peptide, SG#2, SG#5 or SG#15 peptide on disease development is compared with a methotrexate MTX (positive control) or saline treated control group.

Summary of procedure:

- 15 Day 0: The mice were weighted and injected subcutaneously at the nape of the neck as in the table below (table 6):

Group	No. mice	Treatment	Dose
1	8	saline	10ml/kg
2	5	Methotrexate	1mg/kg
3	8	SG#2	4µg/mouse

4	8	SG#5	4µg/mouse
5	8	SG#15	4µg/mouse
6	8	HERV-Env59 peptide	4µg/mouse

Table 6

An hour later, the mice were injected subcutaneously at the base of the tail with 50 µl of the collagen/CFA emulsion.

- 5 Mice were scored for signs of arthritis every Monday, Wednesday, and Friday during the next 41 days as follows:

- Each paw receives a score
- 0 = no visible effects of arthritis
- 1 = edema and/or erythema of 1 digit
- 2 = edema and/or erythema of 2 digits
- 3 = edema and/or erythema of more than 2 digits
- 4 = severe arthritis of entire paw and digits

10

The Arthritic Index (AI) was calculated by the addition of individual paw scores.

Day 42 The mice were weighted and scored for signs of arthritis.

- 15 Table 7 and Fig. 13 show the effect of treatment on average disease development based on AI.

Table 8 shows the effect of treatment on average terminal individual paw scores

Table 7

Effect of Treatment on Avarage Disease Development (AI):

Effect of Treatment on Average Disease Development (AI):

Group	Mouse	STUDY DAY										
		14	21	25	27	29	32	34	36	39	41	42
1	Mean	0	0	0.3	1.1	2.1	3.9	7.5	9.3	12.1	12.4	12.5
	SEM	0	0	0.3	0.5	0.7	0.7	0.5	0.4	0.4	0.5	0.4
2	Mean	0	0	0	0	0	0	0	0	0	0	0
	SEM	0	0	0	0	0	0	0	0	0	0	0
	p-value	1.00	1.00	0.45	0.14	0.05	0.0009	7x10 ⁻⁸	2x10 ⁻⁹	9x10 ⁻¹¹	8x10 ⁻¹⁰	1x10 ⁻¹⁰
	Mean	0	0	0	0.4	0.4	0.9	0.9	0.9	0.9	1.0	1.4
	SEM	0	0	0	0.4	0.4	0.6	0.6	0.6	0.6	0.6	0.7
	p-value	1.00	1.00	0.33	0.28	0.05	0.004	4x10 ⁻⁷	1x10 ⁻⁸	2x10 ⁻¹⁰	5x10 ⁻¹⁰	1x10 ⁻⁹
4	Mean	0	0	0	0.0	0.9	1.1	1.3	2.1	3.3	3.5	3.6
	SEM	0	0	0	0.0	0.5	0.6	0.6	1.0	1.1	1.1	1.2
	p-value	1.00	1.00	0.33	0.06	0.18	0.008	2x10 ⁻⁶	9x10 ⁻⁶	2x10 ⁻⁶	5x10 ⁻⁶	7x10 ⁻⁶
	Mean	0	0	0	0.1	0.1	0.1	0.3	0.3	0.3	0.3	0.4
	SEM	0	0	0	0.1	0.1	0.1	0.2	0.2	0.2	0.2	0.2
	p-value	1.00	1.00	0.33	0.10	0.02	7x10 ⁻⁵	6x10 ⁻¹⁰	9x10 ⁻¹²	1x10 ⁻¹³	1x10 ⁻¹²	3x10 ⁻¹³
6	Mean	0	0	0.1	0.1	0.9	1.0	2.3	2.9	3.9	4.3	4.6
	SEM	0	0	0.1	0.1	0.5	0.6	1.2	1.6	1.6	1.6	1.7
	p-value	1.00	1.00	0.66	0.10	0.18	0.005	0.001	0.001	0.0002	0.0003	0.0005

Table 8 Effect of Treatment on Average Terminal Individual Paw Scores:

Group	Mouse	Front right	Front left	Rear right	Rear left
1	Mean	3.0	3.5	3.0	3.0
	SEM	0.3	0.3	0.3	0.0
2	Mean	0	0	0	0
	SEM	0	0	0	0
	p-value	2×10^{-5}	6×10^{-7}	3×10^{-6}	9×10^{-10}
3	Mean	0.4	0.4	0.5	0.1
	SEM	0.4	0.4	0.5	0.1
	p-value	0.0001	9×10^{-6}	0.0006	2×10^{-12}
4	Mean	1.1	1.3	1.0	0.3
	SEM	0.4	0.5	0.4	0.2
	p-value	0.004	0.002	0.001	1×10^{-10}
5	Mean	0	0.1	0	0.3
	SEM	0	0.1	0	0.2
	p-value	3×10^{-7}	2×10^{-8}	2×10^{-8}	1×10^{-10}
6	Mean	1.1	1.1	1.1	1.3
	SEM	0.5	0.5	0.5	0.5
	p-value	0.01	0.002	0.008	0.002

Summary of Results and Conclusion:

Effect of Prophylactic Treatment with SG#2 peptide (Group 3):

- 5 Once daily subcutaneous injection with 4 µg/mouse of SG#2 peptide, starting one hour prior to disease induction resulted in only 30% incidence of disease which was associated with a significant 90% reduction in disease severity at the termination of the study. This treatment regimen had no effect on diseased mouse weight.

Effect of Prophylactic Treatment with SG#5 peptide (Group 4):

- 10 Once daily subcutaneous injection with 4 µg/mouse of SG#5 peptide, starting one hour prior to disease induction resulted in 80% incidence of disease which was associated with a significant 70% reduction in disease severity at the termination of the study. This treatment regimen had no effect on diseased mouse weight.

Effect of Prophylactic Treatment with SG#15 peptide (Group 5):

- 15 Once daily subcutaneous injection with 4 µg/mouse of SG#15 peptide, starting one hour prior to disease induction resulted in only 30% incidence of disease which was associated with a significant 97% reduction in disease severity at the termination of the study. This treatment regimen had no effect on diseased mouse weight.

Effect of Prophylactic Treatment with HERV-Env59 peptide (Group 6):

Once daily subcutaneous injection with 4 µg/mouse of test compound 4, starting one hour prior to disease induction resulted in 80% incidence of disease which was associated with a significant 67% reduction in disease severity at the termination of the study. This treatment regimen had no effect on diseased mouse weight.

5

Sequences

SEQ ID NO: 1	LQNRRGLGLSILLNEEC	
SEQ ID NO: 2	XQNRRGLGLSILLNEEC	
SEQ ID NO: 3	LXNRRGLGLSILLNEEC	
SEQ ID NO: 4	LQXRRGLGLSILLNEEC	
SEQ ID NO: 5	LQNXRGLGLSILLNEEC	
SEQ ID NO: 6	LQNRXGLGLSILLNEEC	
SEQ ID NO: 7	LQNRRXLGLSILLNEEC	
SEQ ID NO: 8	LQNRRGXGLSILLNEEC	
SEQ ID NO: 9	LQNRRGLXLSILLNEEC	
SEQ ID NO: 10	LQNRRGLGXSILLNEEC	
SEQ ID NO: 11	LQNRRGLGLXILLNEEC	
SEQ ID NO: 12	LQNRRGLGLSXLLNEEC	
SEQ ID NO: 13	LQNRRGLGLSIXLNEEC	
SEQ ID NO: 14	LQNRRGLGLSILXNEEC	
SEQ ID NO: 15	LQNRRGLGLSILLXEEC	
SEQ ID NO: 16	LQNRRGLGLSILLNXEC	
SEQ ID NO: 17	LQNRRGLGLSILLNEXC	
SEQ ID NO: 18	LQNRRGLGLSILLNEEX	
SEQ ID NO: 19	LQNRRGLGLSILLNEECGPGPGP	SG#17 C-terminal amid Dimerized
SEQ ID NO: 20	LQNRRGLGLSILLNEECGGGPGPGP	
SEQ ID NO: 21	LQNRRGLGLSILLNEECHHHHHH	
SEQ ID NO: 22	LQNRRGLGLSILLNEECGGHHHHHH	
SEQ ID NO: 23	LQNRRGLGLSILLNEECGGEKEKEK	
SEQ ID NO: 24	LQNRRGLGLSIFLNEEC	
SEQ ID NO: 25	GLSILLNEEC	
SEQ ID NO: 26	LSILLNEE	
SEQ ID NO: 27	LQNRRGLGLSILLNEECEEGPGPGP	SG#2 Dimerized
SEQ ID NO: 28	LQNRRGLDLSILLNEECGPGPGP	SG#3 Dimerized
SEQ ID NO: 29	GLSILLNEECGPGPGP	SG#5 Dimerized
SEQ ID NO: 30	LQNRRGLLQNRRGLGLSILLNEE	SG#15 Monomeric
SEQ ID NO: 31	LQNRRGLGLSILLNEECKKGPGPGP	SG#1 Dimerized
SEQ ID NO: 32	LQNRRGLGLSILLNC	SG#4 Dimerized
SEQ ID NO: 33	LNRKAIGLSILLNEECGPGPGP	SG#6 Dimerized
SEQ ID NO: 34	LQARILAGLSILLNEECGPGPGP	SG#7 Dimerized
SEQ ID NO: 35	LQNKRLGLSILLNEECGPGPGP	SG#8 Dimerized

SEQ ID NO: 36	LQNKKGGLGLSILLNEECGP GPGP	SG#9	Dimerized
SEQ ID NO: 37	LQNRRGLGLSILLNEECGPKK	SG#11	Dimerized
SEQ ID NO: 38	LQNRRGLGLSILLNEELQNRRGLC	SG#12	Dimerized
SEQ ID NO: 39	LQNRRGLGLSILLNEE	SG#13	Monomeric
SEQ ID NO: 40	LQNRRGLGLSILLNEELQNRRGL	SG#14	Monomeric
SEQ ID NO: 41	LQNRRGLLQNRRGLGLSILLNEEC		Dimeric

SG#16 has the structure of a branched peptide with two LQNRRGL peptides coupled C-terminally to α - and ϵ -amino groups of the Lysine residue in the peptide KGLSILLNEE. One way of depicting such a structure is as follows: (LQNRRGL)₂(>K)GLSILLNEE

- 5 SG#10 has the sequence LQNRRGLGLSILLNEECGP GPGP which is identical to SG#17 but has an extra NH₂ group coupled to its C-terminal.

The One-letter and Three-letter symbols for amino acids are provided in Table 1 below.

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
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 glutamic acid or glutamine (or substances such as
Z	Glx	4-carboxyglutamic acid and 5-oxoproline that yield glutamic acid on acid hydrolysis of peptides)

Table 1

Items

1. A polypeptide consisting of or comprising a sequence having at least 62%, more preferred at least 75%, preferably at least 87%, more preferred 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26).
2. The polypeptide according to item 1, said polypeptide comprising the sequence LSILLNEE (SEQ ID NO: 26) attached to a sequence or a fragment thereof chosen among Seq ID 1 to Seq ID 1043.
3. The polypeptide of any of the preceding items, wherein said polypeptide comprises or consists of a peptide sequence selected among GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).
4. The polypeptide according to any of the preceding items, said polypeptide consisting of or comprising a sequence having at least 70% sequence identity to the sequence: LQNRRGLGLSILLNEEC (SEQ ID NO: 1).
5. The polypeptide according to any of the preceding items, said polypeptide consisting of or comprising a sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to SEQ ID NO: 1.
6. The polypeptide according to any of the preceding items, said polypeptide consisting of or comprising a sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to a sequence selected among the sequences SEQ ID NO: 1 – 25.
7. The polypeptide of any of the preceding items, said polypeptide comprising less than 250 aminoacids, preferably less than 200 amino acids, more preferred less than 175 amino acids,

preferably less than 150 amino acids, more preferred less than 125 amino acids, preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids.

8. The polypeptide of any of the preceding items, said polypeptide comprising at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more preferred at least 16, preferably at least 17, more preferred at least 18, preferably at least 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids.

9. A polypeptide with a length of 17 amino acids, wherein the sequence of the first 7 amino acids is identical to the sequence of the first 7 amino acids of a sequence selected among the sequences of SEQ ID NO: 26 - 1043, and wherein the last 10 amino acids are GLSILLNEEC (SEQ ID NO: 25).

10. The polypeptide according to item 8, comprising 1, 2, 3 or 4 point mutations.

11. The polypeptide according to any of the preceding items, wherein said polypeptide is or acts as an immune suppressive domain.

12. The polypeptide according to item 11, wherein the domain is obtainable from a polypeptide according to any of the items 1 - 9, by at least one point mutation, deletion or insertion.

13. The polypeptide according to item 11, wherein the total number of point mutations, deletions or insertions is selected among 1, 2, 3 and 4.

14. The polypeptide according to item 11, wherein the total number of point mutations, deletions or insertions is more than 4.

15. The polypeptide according to any of the items 11 - 14, which is a monomeric peptide.

16. The polypeptide according to any of the items 11 - 15, cross-linked to at least one additional immunosuppressive peptide and/or connected to a protein, said protein being connected to at least one additional immune suppressive domain according to any of the preceding items.

17. The polypeptide according to any of the items 11 - 16, connected to at least one additional immunosuppressive peptide to form a dimer.

18. The polypeptide according to item 17, wherein said dimer is homologous and comprises at least two immunosuppressive peptides according to any of the items 11 - 16, which are cross-linked by a disulfide bond, N-terminal to N-terminal or C-terminal to C-terminal, and/or a tandem repeat.

19. The polypeptide according to item 17 or 18, connected to at least one additional immunosuppressive peptide to form a heterologous dimer or a homologous dimer.

20. The polypeptide according to any of the items 11 - 19, connected to at least two additional immunosuppressive peptides to form a multimer or polymer.

21. The polypeptide according to any of the items 11 - 20, wherein said polypeptide comprises one or more modifications.

22. The polypeptide according to item 21, 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.

23. The polypeptide according to item 21 or 22, wherein the peptides or proteins have increased resistance against proteolysis compared to peptides or proteins not comprising said at least one modification.

24. A protein comprising a polypeptide according to any of the preceding items.

25. The protein according to item 24, which is an envelope protein.

26. A protein comprising a polypeptide according to any of the items 1 - 14, wherein said protein is not a functional membrane glycoprotein.

27. A protein comprising a polypeptide according to any of the items 1 - 14, wherein said protein is not fusion active.

28. A protein comprising a polypeptide according to any of the items 1 - 14, wherein said protein is not bound or linked to a membrane.

29. The polypeptide or protein according to any of the preceding items, wherein said polypeptide or protein inhibits IL-6 expression in a mammalian cell system or an animal model.

30. An isolated nucleic acid coding for a polypeptide or protein according to any of the preceding items.

31. An expression vector, said vector comprising a nucleic acid according to item 30 as well as the elements necessary for the expression of said nucleic acid.

32. An expression vector according to item 31, wherein said vector is an eukaryotic or prokaryotic or viral expression vector.

33. An expression vector including a nucleic acid sequence encoding for a peptide having at least 62% sequence identity or homology to the sequence LSILLNEE (SEQ ID NO: 26).

34. An expression vector including a nucleic acid sequence encoding for a polypeptide or protein according to any of the items 1 - 29.

35. A recombinant cell, said cell comprising a nucleic acid according to item 18, and/or an expression vector according to any of the items 31 - 34.

36. A pharmaceutical composition comprising at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to any of the preceding items, and further at least one diluent, carrier, binder, solvent or excipient.

37. The pharmaceutical composition according to item 36, wherein said at least one polypeptide, protein, nucleic acid, expression vector, or recombinant cell is the active ingredient or sole active ingredient of said pharmaceutical product.

38. A method for the preparation of a pharmaceutical composition comprising the steps of:

a. Providing one or more polypeptide, protein, nucleic acid, expression vector, or recombinant cell according to any of the preceding items, and optionally cross-linking said one or more polypeptides;

b. Optionally providing a diluent, carrier, binder, solvent or excipient;

5 c. Providing a substance;

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.

10 39. The method of item 38, wherein said substance of step c. is selected from the group consisting of creams, lotions, ointments, gels, balms, salves, oils, foams, and shampoos.

40. A pharmaceutical composition obtainable according to item 38 or 39.

15 41. A pharmaceutical composition according to any of the items 36, 37 or 40, wherein said pharmaceutical composition is selected among the group consisting of creams, lotions, shake lotions, ointments, gels, balms, salves, oils, foams, shampoos, sprays, aerosols, transdermal patches and bandages.

20 42. A biomaterial comprising a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items.

43. The biomaterial according to item 42, wherein said biomaterial is selected among a surface, particle, mesh, device, tube, or an implant.

25 44. A medical use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or biomaterial according to any of the preceding items.

45. A use of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for immune suppression or immune modulation.

5 46. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for use in surgery, prophylaxis, therapy, a diagnostic method, treatment and/or amelioration of disease.

10 47. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the treatment, amelioration or prophylaxis of an autoimmune disease.

15 48. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to item 47, wherein the autoimmune disease is SLE (systemic lupus erythematosus) or arthritis, such as rheumatoid arthritis.

20 49. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the treatment, amelioration or prophylaxis of an inflammatory condition or a disorder associated with inflammation, such as acute or chronic inflammation.

50. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for use as a medicament

25 51. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, wherein the subject is a human or an animal.

52. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items, for use on an organ.
53. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items, in the preparation or treatment of transplantation patients.
54. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, 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-Barré syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, hepatitis, 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, non-alcoholic steatohepatitis (NASH), 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, Sjögren'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 erythematosus, 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.

55. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, 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.

56. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, comprising prophylaxis or treatment of sepsis.

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57. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, comprising prophylaxis or treatment of spondyloarthritis.

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58. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant for a use according to any of the preceding items, comprising prophylaxis or treatment of asthma and/or allergy.

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59. The polypeptide according to any of the items 11 - 23 for use in a method of prophylaxis or treatment or amelioration of a condition associated with an autoimmune disease, wherein a gene sequence expressing said immune suppressive domain exhibits increased or decreased expression in a group of patients suffering from said autoimmune disease as compared to a healthy control group.

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60. The polypeptide according to item 59, wherein said immune suppressive domain is from an endogenous retrovirus, preferably a human endogenous retrovirus.

61. The polypeptide according to item 59 or 60, wherein said immune suppressive domain is selected among the sequences of SEQ ID NO: NO: 1 – 1043.

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62. Use of a polypeptide selected among the sequences of SEQ ID NO: NO: 1 – 1043 for the prophylaxis or treatment or amelioration of an autoimmune disease or at least one symptom associated with said autoimmune disease.

63. A use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of an anti-inflammatory medicament or a medicament for immune suppression or immune modulation.

5 64. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a medicament for the preparation or treatment of transplantation patients.

10 65. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a medicament for prophylaxis or treatment of an autoimmune or inflammatory disease.

15 66. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a medicament for prophylaxis or treatment of a condition selected among Acute disseminated encephalomyelitis (ADEM), Addison's disease, Agammaglobulinemia, Alopecia areata, Amyotrophic Lateral Sclerosis, ANCA Vasculitis, Ankylosing Spondylitis, Antiphospholipid syndrome, Antisynthetase syndrome, Arteriosclerosis, 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,

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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-Barré syndrome (GBS), Hashimoto's encephalopathy, Hashimoto's thyroiditis, Henoch-Schonlein purpura, Herpes gestationis, hepatitis, 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, non-alcoholic steatohepatitis (NASH), 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, Sjögren'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 erythematosus, 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.

67. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a

medicament for prophylaxis or treatment of inflammation or a condition associated with inflammation, such as acute or chronic inflammation.

68. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to item 67, 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.

69. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a medicament for prophylaxis or treatment of at least condition selection among sepsis, rheumatoid arthritis, systemic lupus erythematosus (SLE), and spondyloarthritis.

70. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, pharmaceutical composition, or implant according to any of the preceding items for the manufacture of a medicament for prophylaxis or treatment of asthma and/or allergy.

71. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for coating of nanoparticles and/or biomaterials.

72. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for at least partial suppression of an immune response to at least one nanoparticle or biomaterial.

73. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, to increase the *in vivo* half-life of nanoparticles and/or biomaterials and/or medical devices and/or implants in the patient.

5 74. The use of an endogenous retrovirus for diagnosis of a disease.

75. The use of an endogenous retrovirus whose expression level or copy number is different in a subject with a condition as compared to a subject without said condition for diagnosis of a disease.

10 76. The use of an endogenous retrovirus whose expression level or copy number is different in a subject with an autoimmune condition as compared to a subject without the said condition for diagnosis of a disease.

77. The use of single nucleotide polymorphisms associated with HERV-H 59 for diagnosis of a disease.

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78. The use of HERV-H 59 for diagnosis of SLE.

79. A method of prophylactically or therapeutically treating an autoimmune disease and/or an inflammatory condition by administering to a subject in need thereof a prophylactically or therapeutically effective amount of at least one polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items through one or more or several administrations.

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80. Method of prophylaxis or treatment or amelioration of a condition associated with an autoimmune disease, comprising:

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- a. Measuring the expression or copy number of at least one endogenous retrovirus in a group of patients suffering from said autoimmune disease;

- b. Comparing said expression with the expression of said at least one endogenous retrovirus in a healthy control group;
- c. Identifying at least one endogenous retrovirus having different expression in said group of patients;
- d. Optionally identifying at least one immune suppressive domain in said at least one endogenous retrovirus;
- e. Treating at least one patient suffering from said condition by administration of at least one immune suppressive domain preferably contained in a protein containing said at least one immune suppressive domain and/or a protein expressed by said endogenous retrovirus.

81. Method of prophylaxis or treatment or amelioration of a condition associated with an autoimmune disease, comprising:

- f. Measuring the concentration of at least one protein or polypeptide comprising at least one immune suppressive domain in a group of patients suffering from said autoimmune disease;
- g. Comparing said concentraion with the concentration in a healthy control group;
- h. Identifying at least one immune suppressive domain having different expression in said group of patients;
- i. Treating at least one patient suffering from said condition by administration of said at least one immune suppressive domain and/or a protein comprising said at least one immune suppressive domain.

82. Method according to item 80 or 81, wherein said different expression is selected among increased and decreased expression.

83. Method according to any of the items 80 - 82, wherein said endogenous retrovirus is a human endogenous retrovirus.

84. Method according to item 83, wherein said human endogenous retrovirus belongs to the HERV-H subfamily or the HERV-K subfamily.

85. Method according to any of the items 80 - 84, wherein said endogenous retrovirus contains at least one open reading frame capable of encoding a protein.

86. Method according to item 85, wherein said at least one open reading frame has a length of at least 50, preferably at least 100, more preferred at least 150, preferably at least 200, more preferred at least 250, preferably at least 300, more preferred at least 350, preferably at least 400 nucleotides.

87. A use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for prophylaxis or treatment of a condition or disease by an administration route selected among injection, inhalation, topical, transdermal, oral, nasal, vaginal, or anal delivery.

88. The use according to item 87, wherein the mode of injection is selected among intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and (intramuscular) IM.

89. The use according to item 88, for treatment of a disease by direct injection at a site affected by a disorder, such as inflammation.

90. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for treatment of a condition selected among a skin disease, Psoriasis, Arthritis, Asthma, Sepsis, inflammatory bowel disease, rheumatoid arthritis, SLE, and spondyloarthritis.

91. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for treatment of Arthritis where the composition is injected directly at site of inflammation.

92. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for treatment of a condition selected among Gastrointestinal hyperresponsiveness, Food Allergy, Food intolerance and inflammatory bowel disease, preferably wherein the composition is delivered orally.

93. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding items, for treatment Asthma where the composition is delivered by inhalation.

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CLAIMS

1. A polypeptide having a maximum length of 130 amino acids comprising a peptide sequence having at least 62,5%, more preferred 75%, more preferred 87,5%, more preferred at least 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26) for use in suppression immune therapy.
2. A polypeptide for use according to claim 1 comprising one or more peptide sequences having at least 70%, preferably at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to sequences selected among LQNRRGLGLSILLNEEC (SEQ ID NO: 1), LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).
3. A polypeptide for use according to claim 1 or 2, said polypeptide comprising a peptide sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to a sequence selected among the sequences SEQ ID NO: 1 - 25 and 27 - 41.
4. A polypeptide for use according to claim 1 selected among polypeptides having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to sequences selected among LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).
5. A polypeptide for use of claim 1 selected among LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).
6. A polypeptide entity for use in suppression immunotherapy comprising a polypeptide defined in any of the preceding claims, said polypeptide entity comprising less than 250 amino acids, preferably less than 200 amino acids, more preferred less than 175 amino acids, preferably less than 150 amino acids, more preferred less than 125 amino acids, preferably

less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids.

7. A polypeptide entity for use in suppression immunotherapy comprising a polypeptide defined in any of the preceding claims, said polypeptide entity comprising at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more preferred at least 16, preferably at least 17, more preferred at least 18, preferably at least 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids.

8. A polypeptide with a length of 17 amino acids, wherein the sequence of the first 7 amino acids is identical to the sequence of the first 7 amino acids of a sequence selected among the sequences of SEQ ID NO: 42 - 1043, and wherein the last 10 amino acids are GLSILLNEEC (SEQ ID NO: 25), for use in suppression immunotherapy.

9. The polypeptide for use according to claim 1, said polypeptide comprising a sequence having at least 62,5%, more preferred 75%, more preferred 87,5%, more preferred at least 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26) attached to a sequence or a fragment thereof chosen among Seq ID 1 to Seq ID 1043.

10. The polypeptide for use according to claim 8 or 9, comprising 1, 2, 3 or 4 point mutations.

11. The polypeptide for use according to any of the preceding claims, which is glycosylated.

12. The polypeptide for use according to any of the preceding claims, which is acylated.

13. The polypeptide for use according to any of the preceding claims, which is a monomer.

14. The polypeptide for use according to any of the preceding claims, which is dimerized, trimerized or multimerized.

5 15. A protein comprising a polypeptide defined in any of the preceding claims, wherein said protein comprises less than 250 amino acids, preferably less than 200 amino acids, more preferred less than 175 amino acids, preferably less than 150 amino acids, more preferred less than 125 amino acids, preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids,
10 preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino
15 acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids, more preferred less than 9 amino acids, preferably less than 8 amino acids, more preferred less than 7 amino acids, preferably less than 6 amino acids, for use in suppression immunotherapy.

16. A protein or polypeptide defined in any of the preceding claims or a protein
20 comprising a polypeptide defined in any of the preceding claims, said protein or polypeptide comprising at least 5, more preferred at least 6, preferably at least 7, more preferred at least 8, preferably at least 9, more preferred at least 10, preferably at least 11, more preferred at least 12, preferably at least 13, more preferred at least 14, preferably at least 15, more preferred at least 16, preferably at least 17, more preferred at least 18, preferably at least
25 19, more preferred at least 20, preferably at least 25, more preferred at least 30, preferably at least 35, more preferred at least 40, preferably at least 50, more preferred at least 60, preferably at least 75, more preferred at least 100, preferably at least 125, more preferred at least 150, preferably at least 175, more preferred at least 200, preferably at least 250 amino acids, for use in suppression immunotherapy.

30 17. A protein comprising a polypeptide according to any of the claims 1 - 16, wherein said protein is not fusion active, for use in suppression immunotherapy.

18. The polypeptide or protein for use according to any of the preceding claims, wherein said polypeptide or protein inhibits IL-6 expression in a mammalian cell system or an animal model.

19. An isolated nucleic acid coding for a polypeptide or protein defined in any of the preceding claims, for use in suppression immunotherapy.

20. An expression vector, said vector comprising a nucleic acid defined in claim 19 as well as the elements necessary for the expression of said nucleic acid, for use in suppression
5 immunotherapy.

21. An expression vector for the use according to claim 20, wherein said vector is an eukaryotic or prokaryotic or viral expression vector.

22. An expression vector for the use according to claim 20 or 21, wherein said vector is selected among the group consisting of yeast, e-coli and baculoviruses.

10 23. A pharmaceutical composition comprising a polypeptide comprising a peptide sequence having at least 62,5%, more preferred 75%, more preferred 87,5%, more preferred at least 100% sequence identity to the sequence LSILLNEE (SEQ ID NO: 26), and further at least one diluent, carrier, binder, solvent or excipient, for use in suppression immunotherapy.

15 24. A pharmaceutical composition for the use according to claim 23 comprising one or more peptide sequences having at least 70%, preferably at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to sequences selected among LQNRRGLGLSILLNEEC (SEQ ID NO: 1),
LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25),
20 LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30), and further at least one diluent, carrier, binder, solvent or excipient.

25 25. A pharmaceutical composition for the use according to claim 23 or 24, wherein said polypeptide comprising a peptide sequence having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to a sequence selected among the sequences SEQ ID NO: 1 – 41), and further at least one diluent, carrier, binder, solvent or excipient.

30 26. A pharmaceutical composition for the use according to claim 25 comprising a polypeptide selected among polypeptides having at least 76%, more preferred at least 82%, preferably at least 88%, more preferred at least 94%, preferably 100% sequence identity to sequences selected among LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25),

LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30)), and further at least one diluent, carrier, binder, solvent or excipient.

27. A pharmaceutical composition for the use comprising a polypeptide selected among
5 LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1),
LQNRRGLGLSILLNEECGPGPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25),
LQNRRGLGLSILLNEECEEGPGPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGPGPGP (SEQ ID
NO: 28), GLSILLNEECGPGPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID
NO: 30)), and further at least one diluent, carrier, binder, solvent or excipient .

10 28. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for the use according to any of the preceding claims, where the
use is for the treatment, amelioration or prophylaxis of an autoimmune disease.

15 29. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for the use according to claim 28, wherein the autoimmune
disease is SLE (systemic lupus erythematosus) or arthritis, such as rheumatoid arthritis,
spondyloarthritis, or multiple sclerosis (MS).

20 30. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for the use according to any of 1-27 for the treatment,
amelioration or prophylaxis of an inflammatory condition or a disorder associated with
inflammation, such as acute or chronic inflammation.

31. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for a use according to any of claims 1-27, comprising prophylaxis
or treatment of sepsis.

25 32. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for a use according to any of claims 1-27, comprising prophylaxis
or treatment of spondyloarthritis.

33. The polypeptide, protein, nucleic acid, expression vector, recombinant cell, or
pharmaceutical composition for a use according to any of claims 1-27, comprising prophylaxis
or treatment of asthma and/or allergy.

30 34. A polypeptide having a maximum length of 130 amino acids and comprising a
peptide sequence among LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1),

LQNRRGLGLSILLNEECGP GPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGP GPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGP GPGP (SEQ ID NO: 28), GLSILLNEECGP GPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID NO: 30).

5 35. The polypeptide according to claim 34, wherein the maximum length is less than 125 amino acids, preferably less than 100 amino acids, more preferred less than 75 amino acids, preferably less than 60 amino acids, more preferred less than 50 amino acids, preferably less than 40 amino acids, more preferred less than 35 amino acids, preferably less than 30 amino acids, more preferred less than 25 amino acids, preferably less than 20 amino
10 acids, more preferred less than 19 amino acids, preferably less than 18 amino acids, more preferred less than 17 amino acids, preferably less than 16 amino acids, more preferred less than 15 amino acids, preferably less than 14 amino acids, more preferred less than 13 amino acids, preferably less than 12 amino acids, more preferred less than 11 amino acids, preferably less than 10 amino acids.

15 36. The polypeptide according to claim 34 consisting of a peptide sequence selected from LSILLNEE (SEQ ID NO: 26), LQNRRGLGLSILLNEEC (SEQ ID NO: 1), LQNRRGLGLSILLNEECGP GPGP (SEQ ID NO: 19), GLSILLNEEC (SEQ ID NO: 25), LQNRRGLGLSILLNEECEEGP GPGP (SEQ ID NO: 27), LQNRRGLDLSILLNEECGP GPGP (SEQ ID NO: 28), GLSILLNEECGP GPGP (SEQ ID NO: 29) and LQNRRGLLQNRRGLGLSILLNEE (SEQ ID
20 NO: 30).

37. The polypeptide according to any one of claims 34-36, which is glycosylated.

38. The polypeptide for use according to any one of claims 34-37, which is acylated.

39. A dimer, trimer or multimer of the peptide according to any one of claims 34-38.

40. A pharmaceutical composition comprising a polypeptide according to any one of
25 claims 34-38 or a dimer, trimer or multimer according to claim 39, and further at least one diluent, carrier, binder, solvent or excipient.

41. An isolated nucleic acid coding for a polypeptide or protein defined in any one of claims 34-38.

42. An expression vector, said vector comprising a nucleic acid defined in claim 41 as
30 well as the elements necessary for the expression of said nucleic acid, for use in suppression immunotherapy.

43. An expression vector for the use according to claim 42, wherein said vector is an eukaryotic or prokaryotic or viral expression vector.

44. An expression vector for the use according to claim 42 or 43, wherein said vector is selected among the group consisting of yeast, E. coli and baculoviruses.

vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims through one or more or several administrations.

5 41. A use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims, for prophylaxis or treatment of a condition or disease by an administration route selected among injection, inhalation, topical, transdermal, oral, nasal, vaginal, or anal delivery.

10 42. The use according to claim 41, wherein the mode of injection is selected among intravenous (IV), intraperitoneal (IP), subcutaneous (SC) and (intramuscular) IM.

43. The use according to claim 42, for treatment of a disease by direct injection at a site affected by a disorder, such as inflammation.

15 44. The use of a polypeptide, protein, nucleic acid, expression vector, recombinant cell, or pharmaceutical composition according to any of the preceding claims, for treatment of Arthritis where the composition is injected directly at site of inflammation.

20

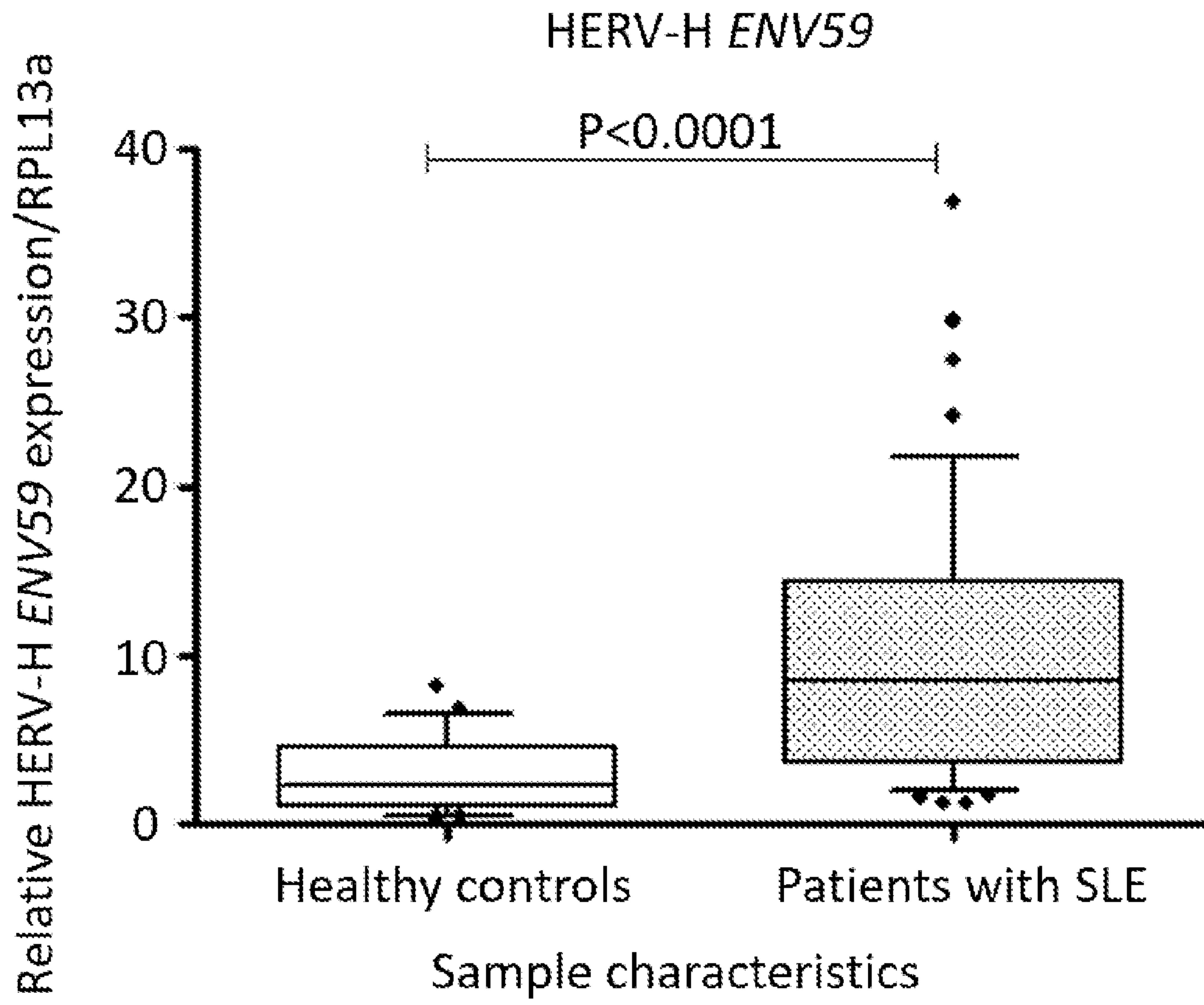


Fig. 1

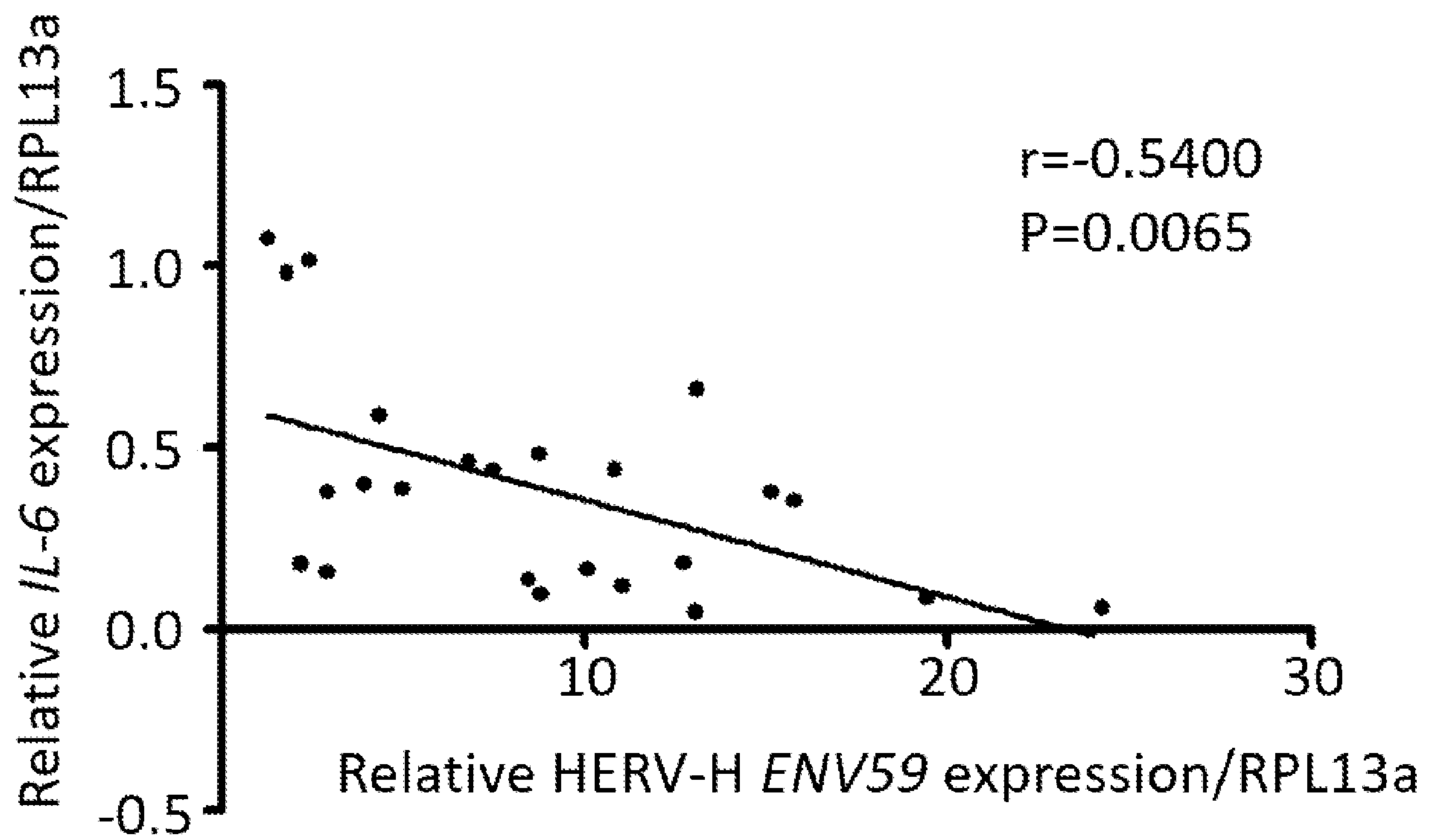


Fig. 2a

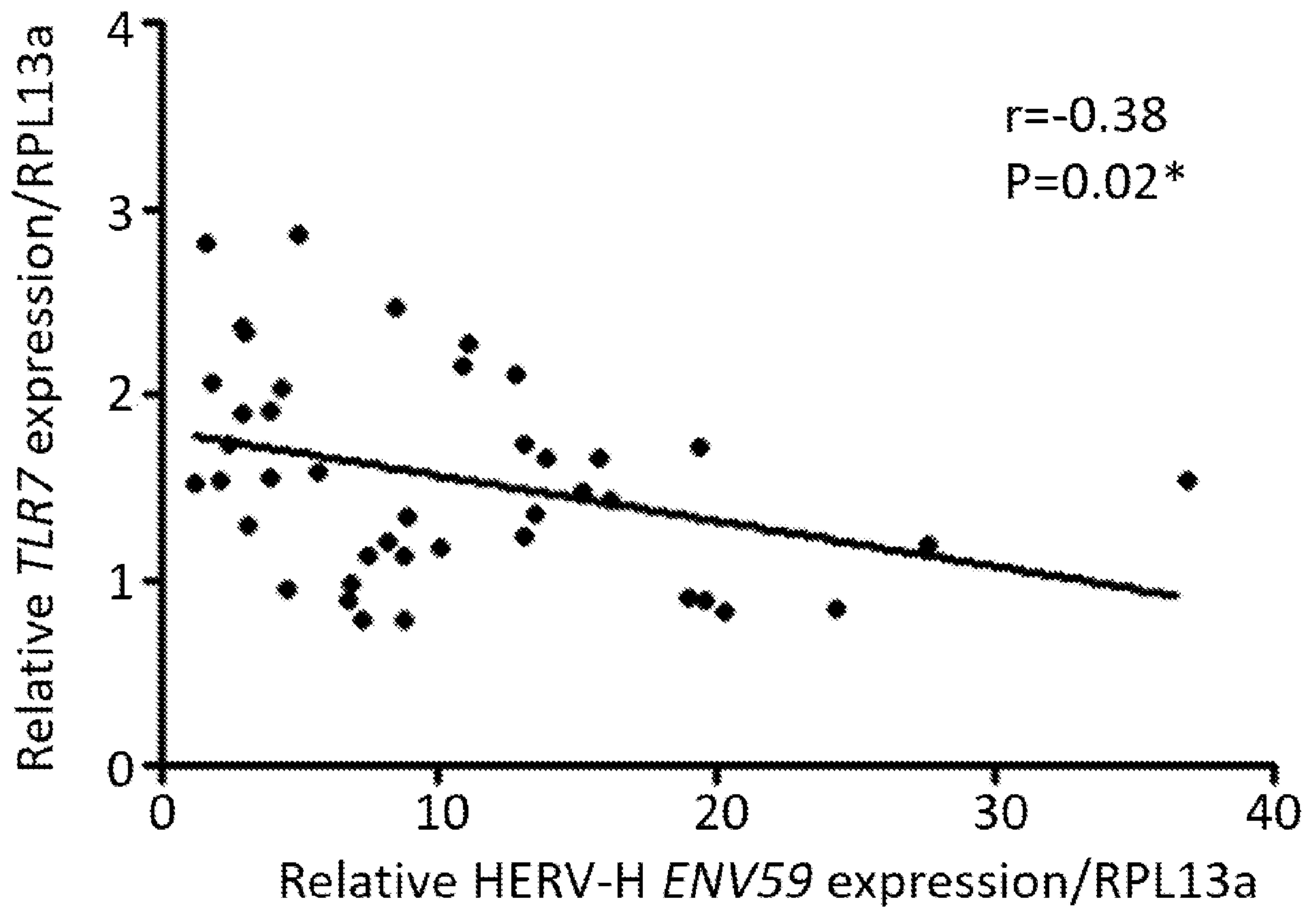


Fig. 2b

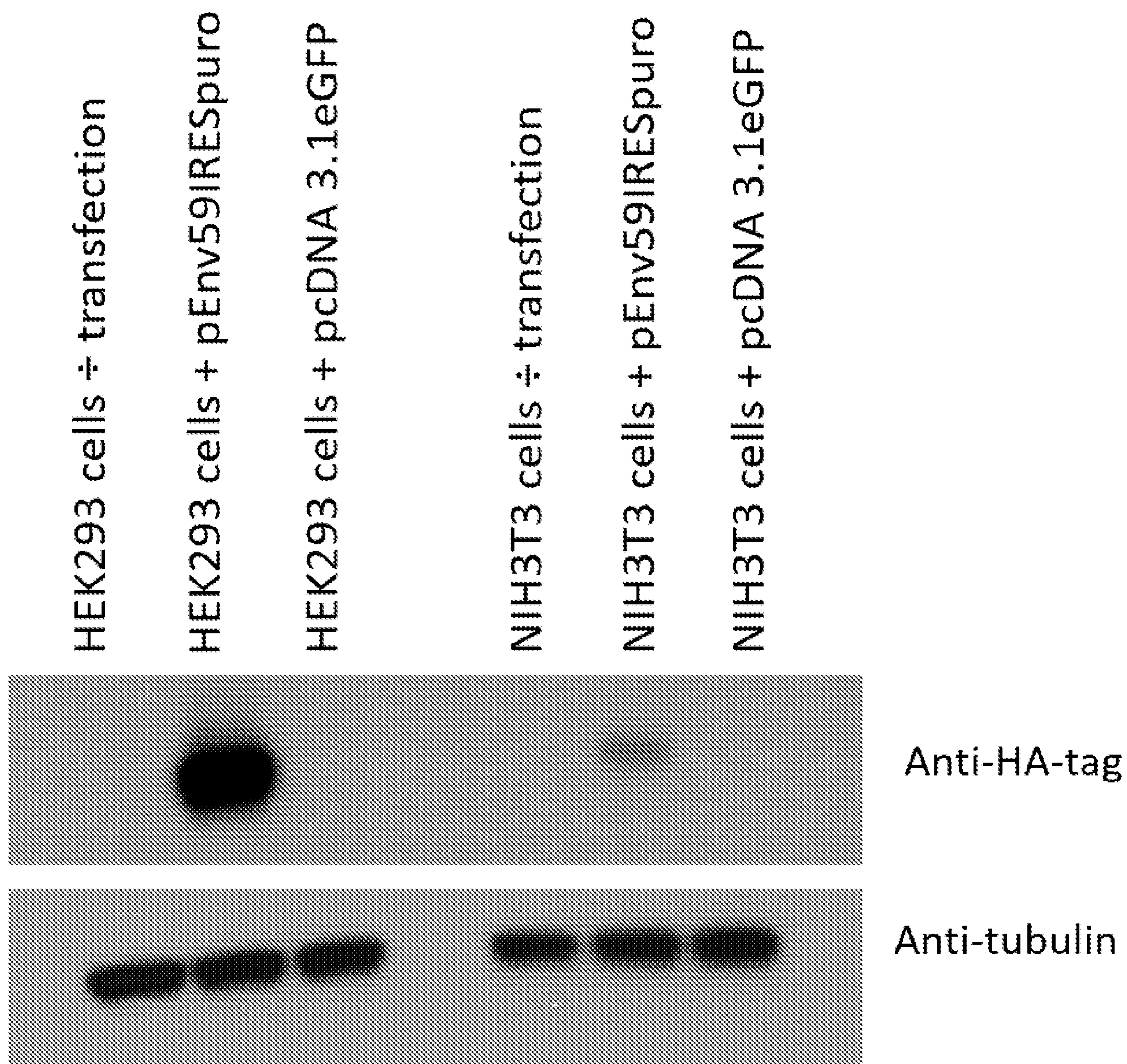


Fig. 3a

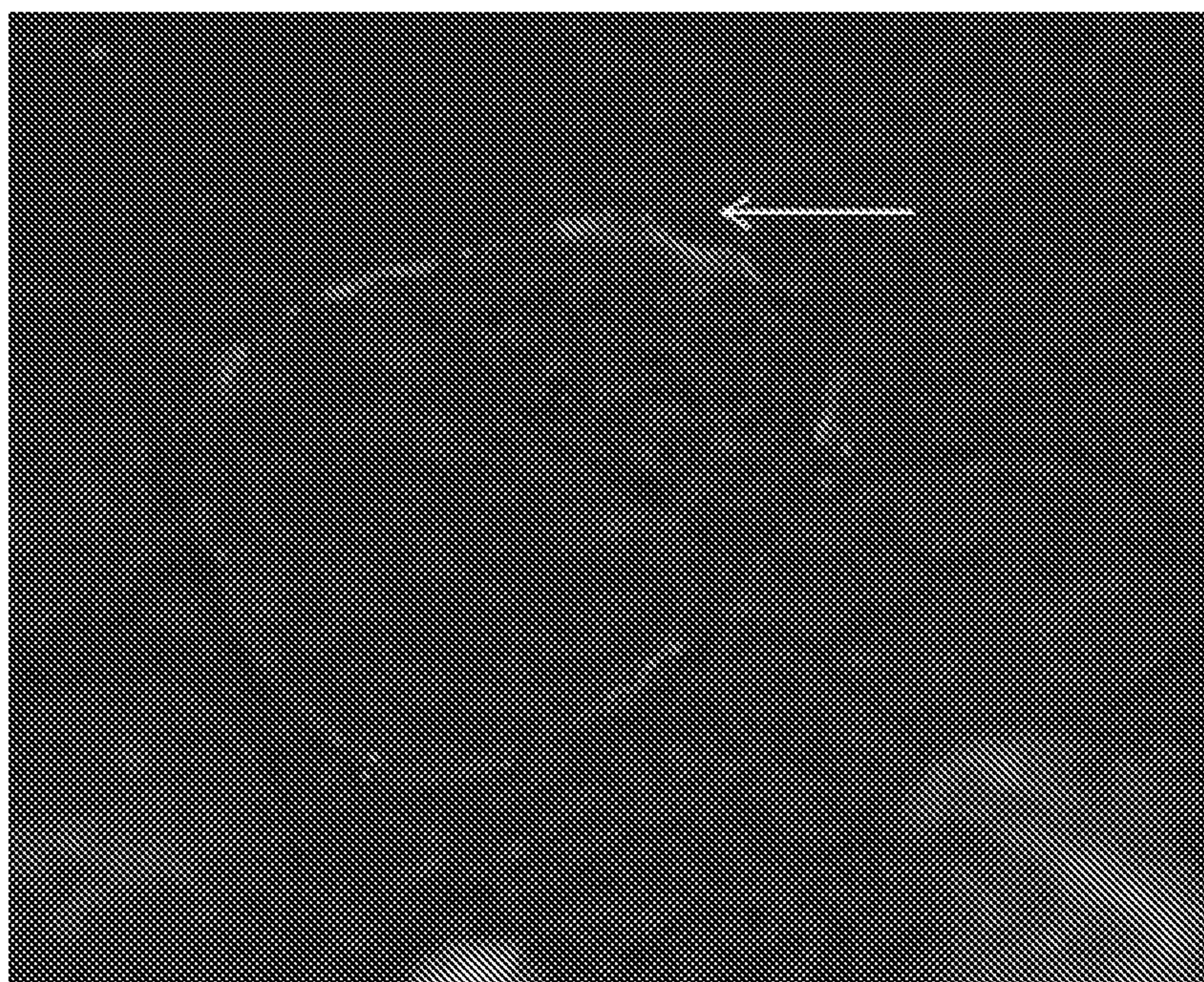
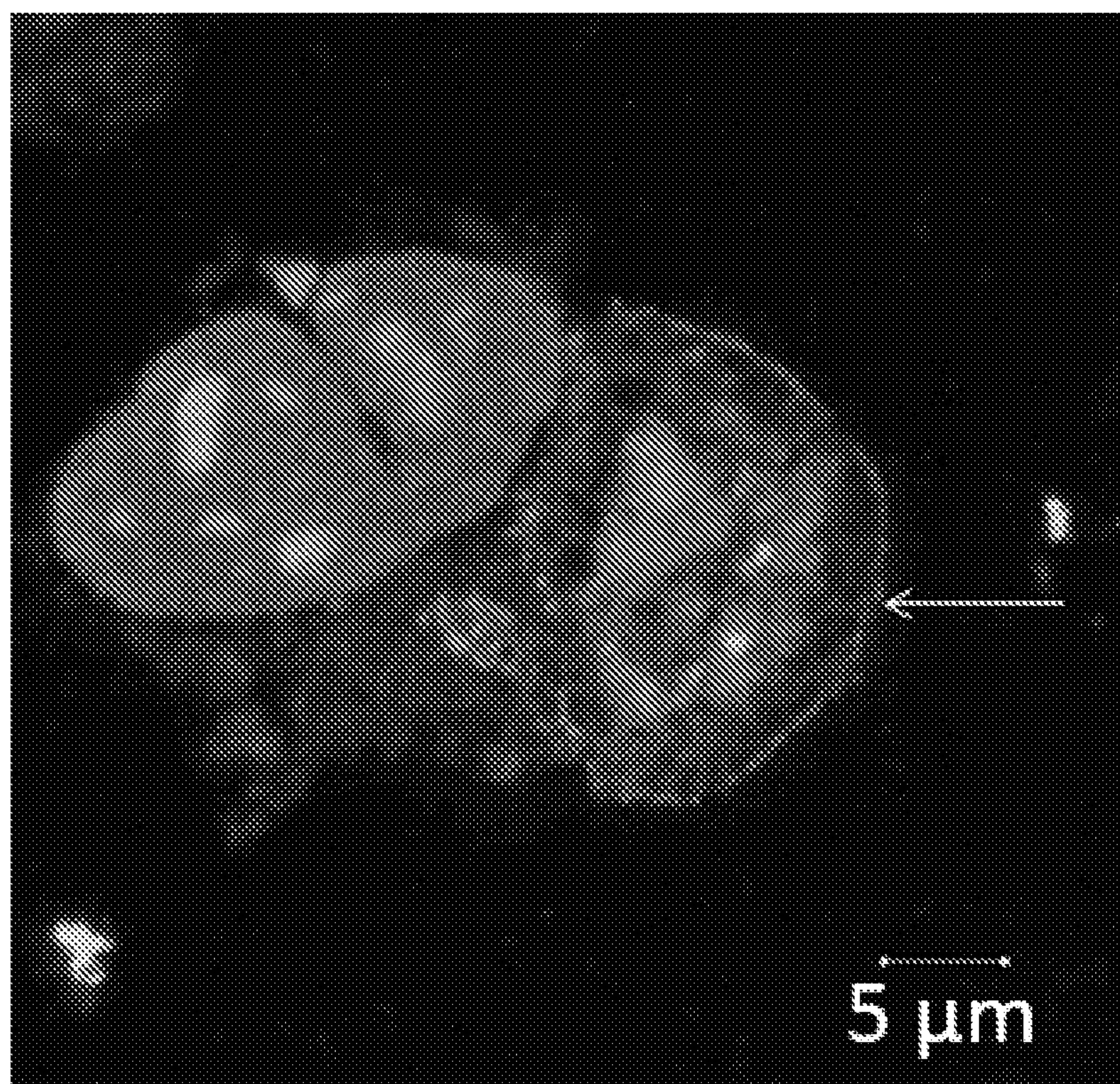


Fig. 3b

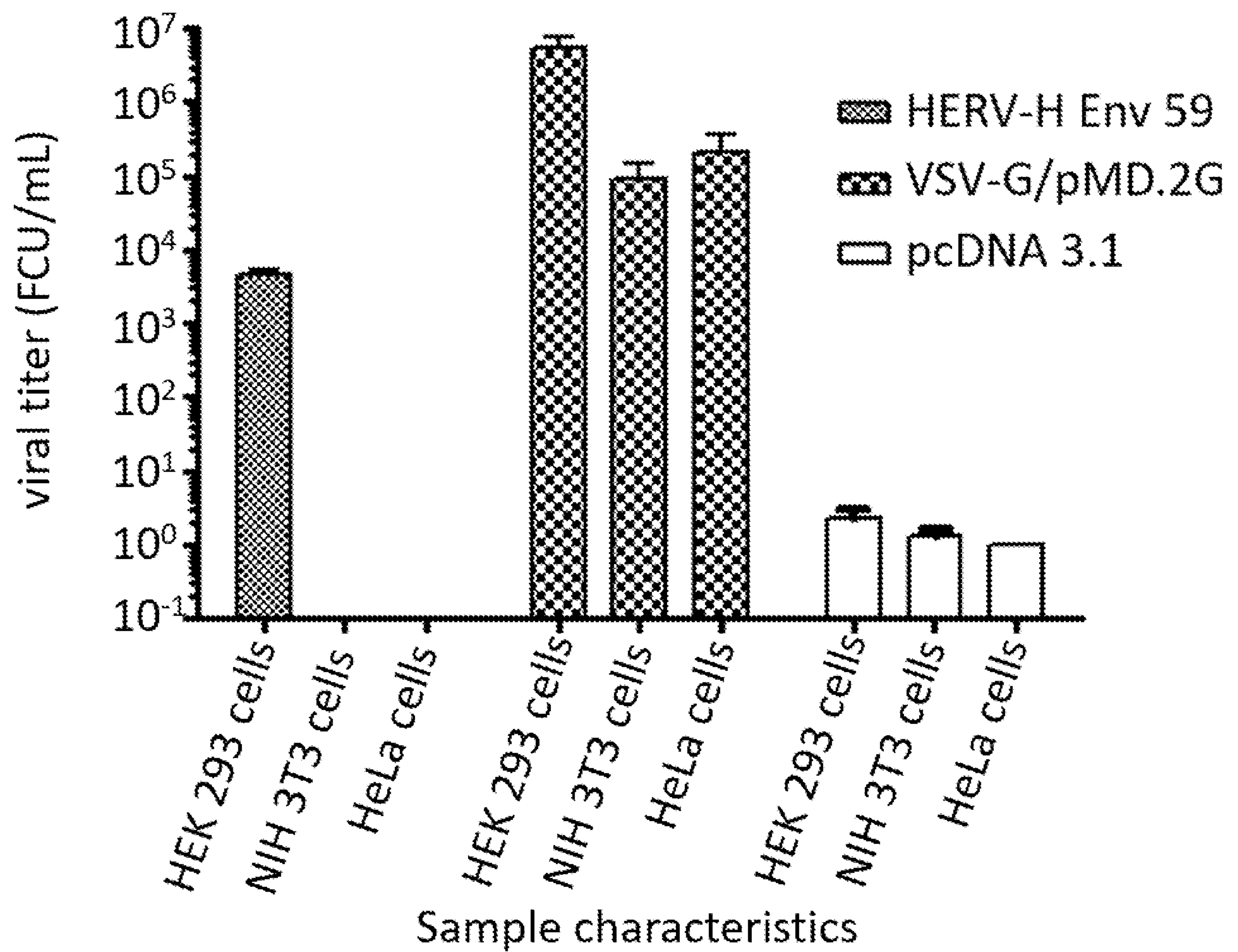


Fig. 4

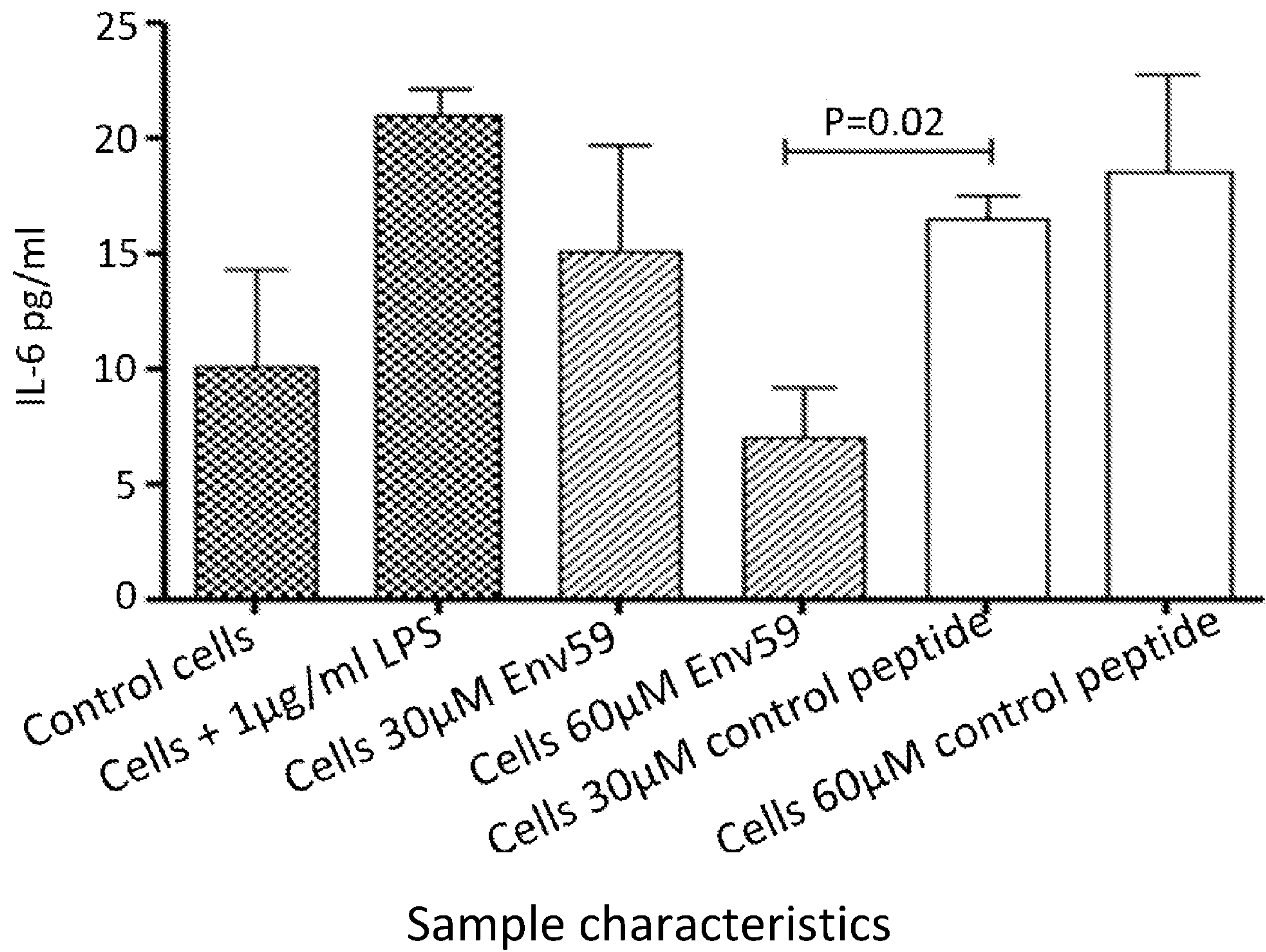


Fig. 5A

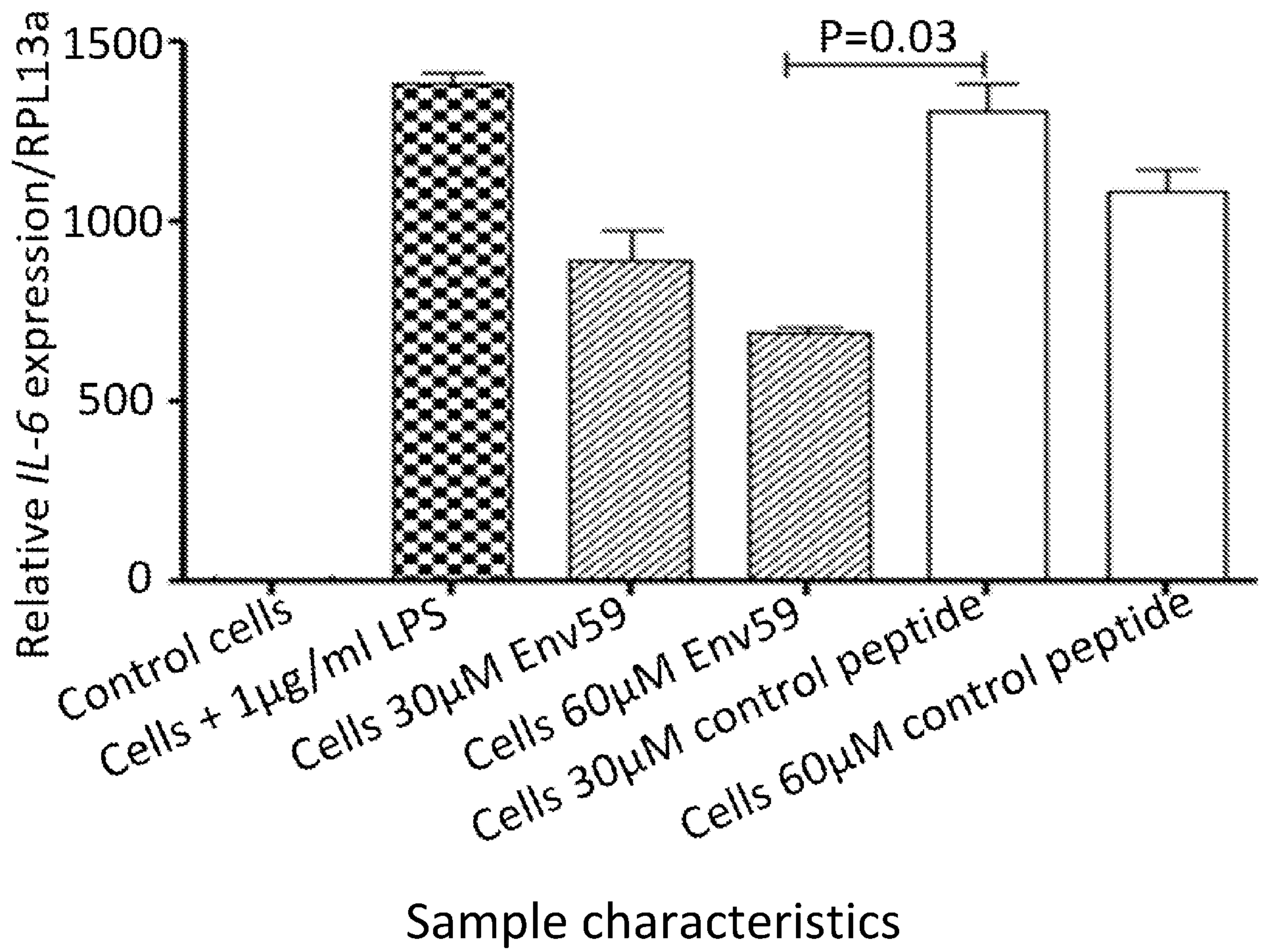


Fig. 5B

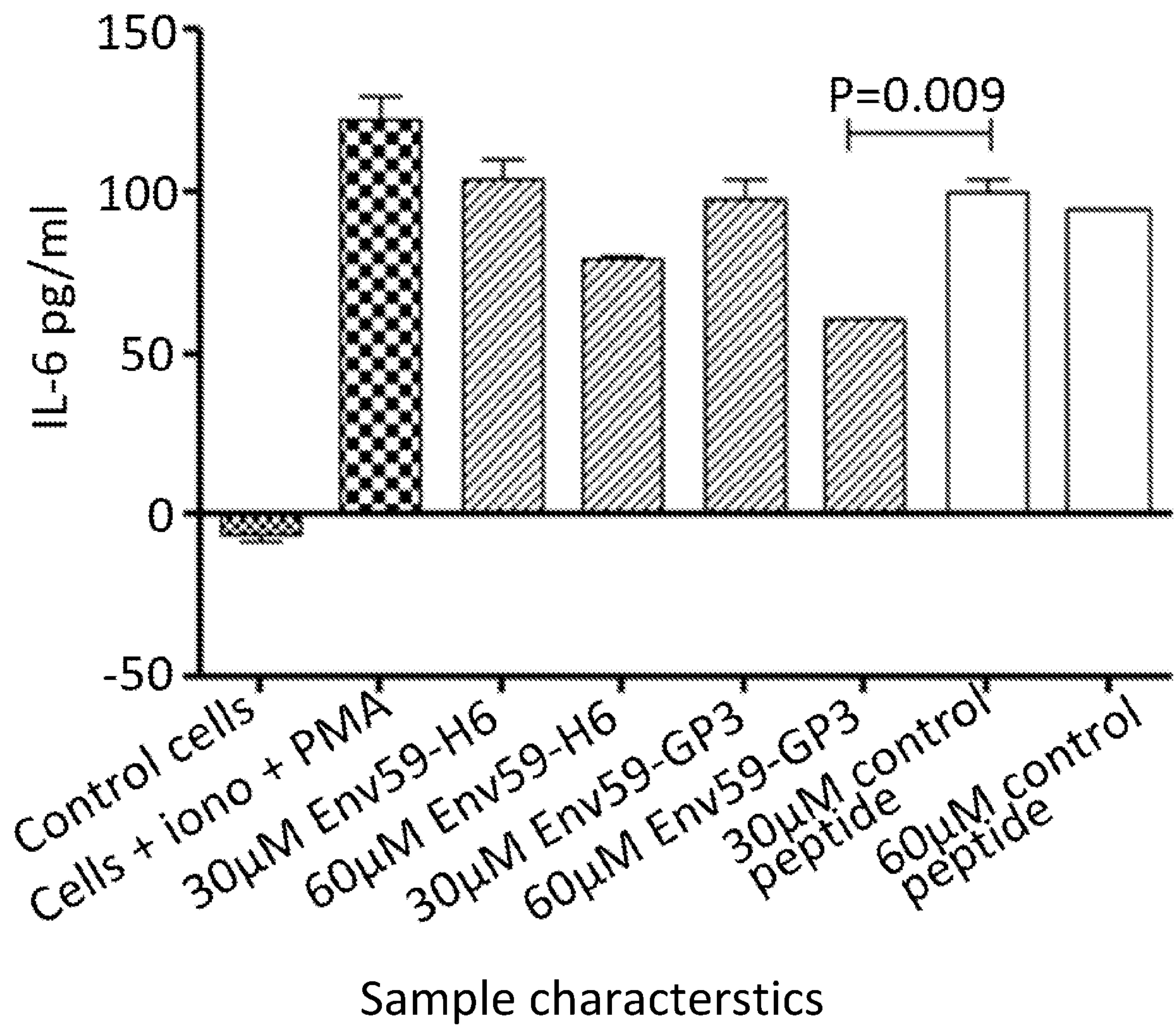


Fig. 5C

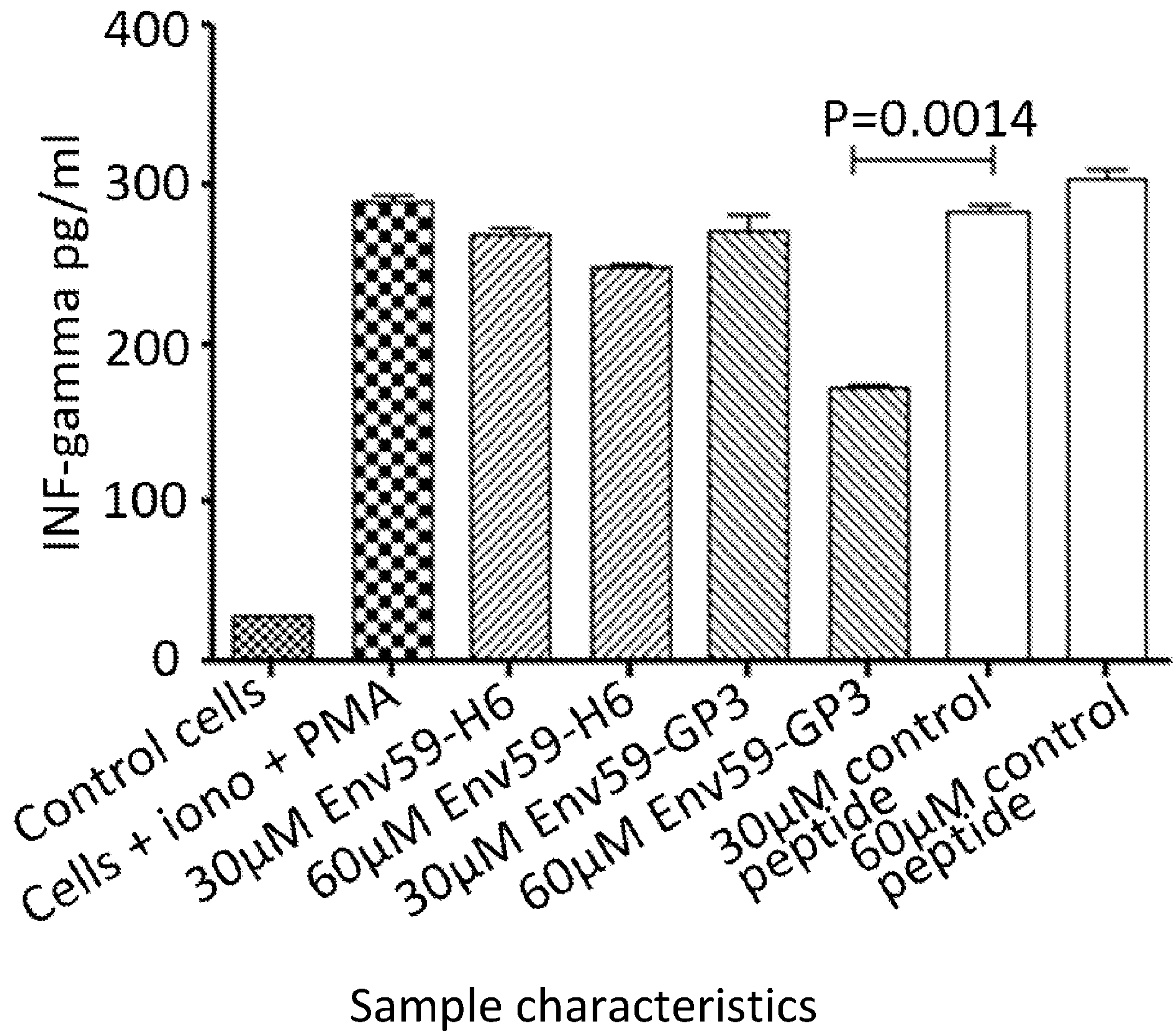


Fig. 5D

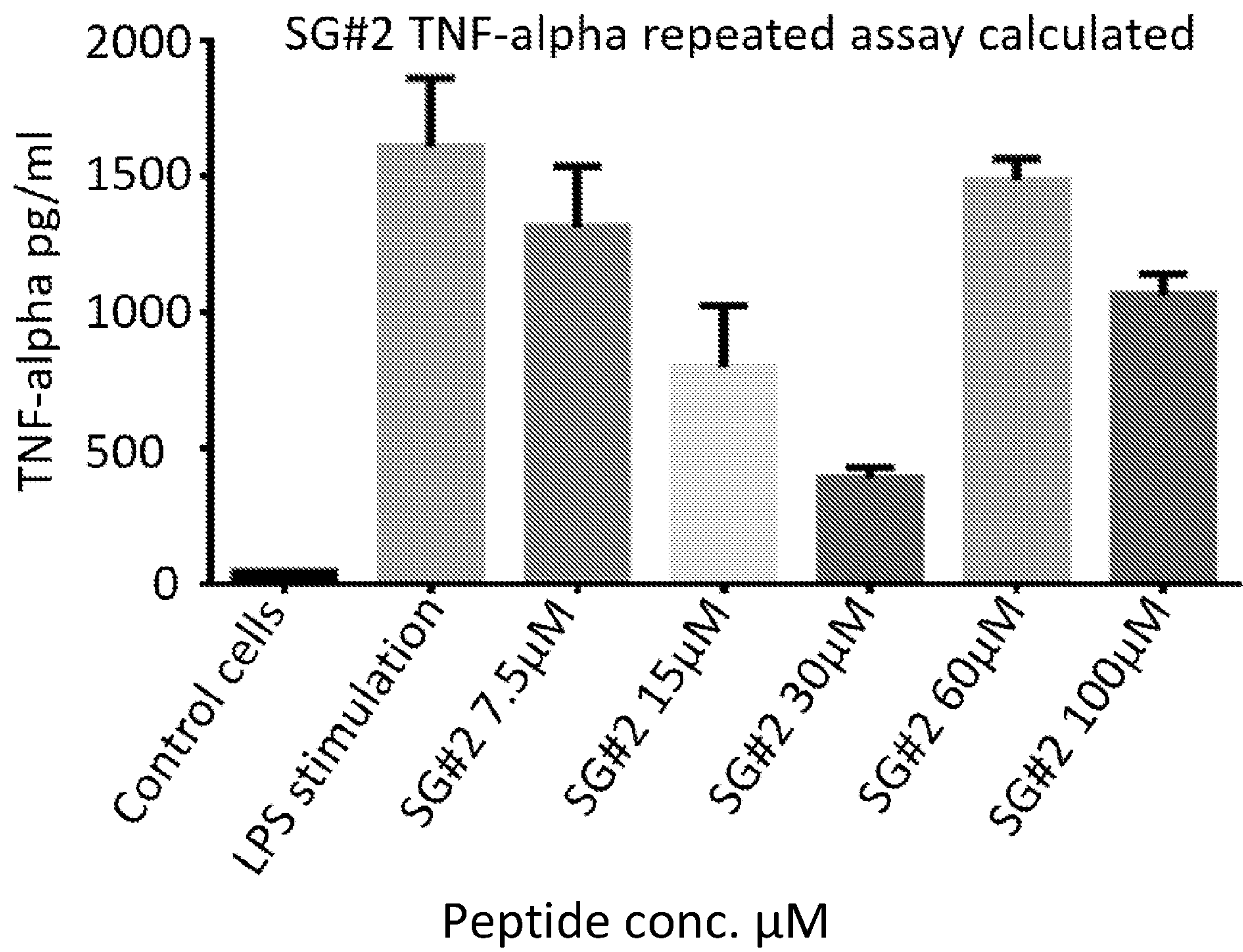


Fig. 6A

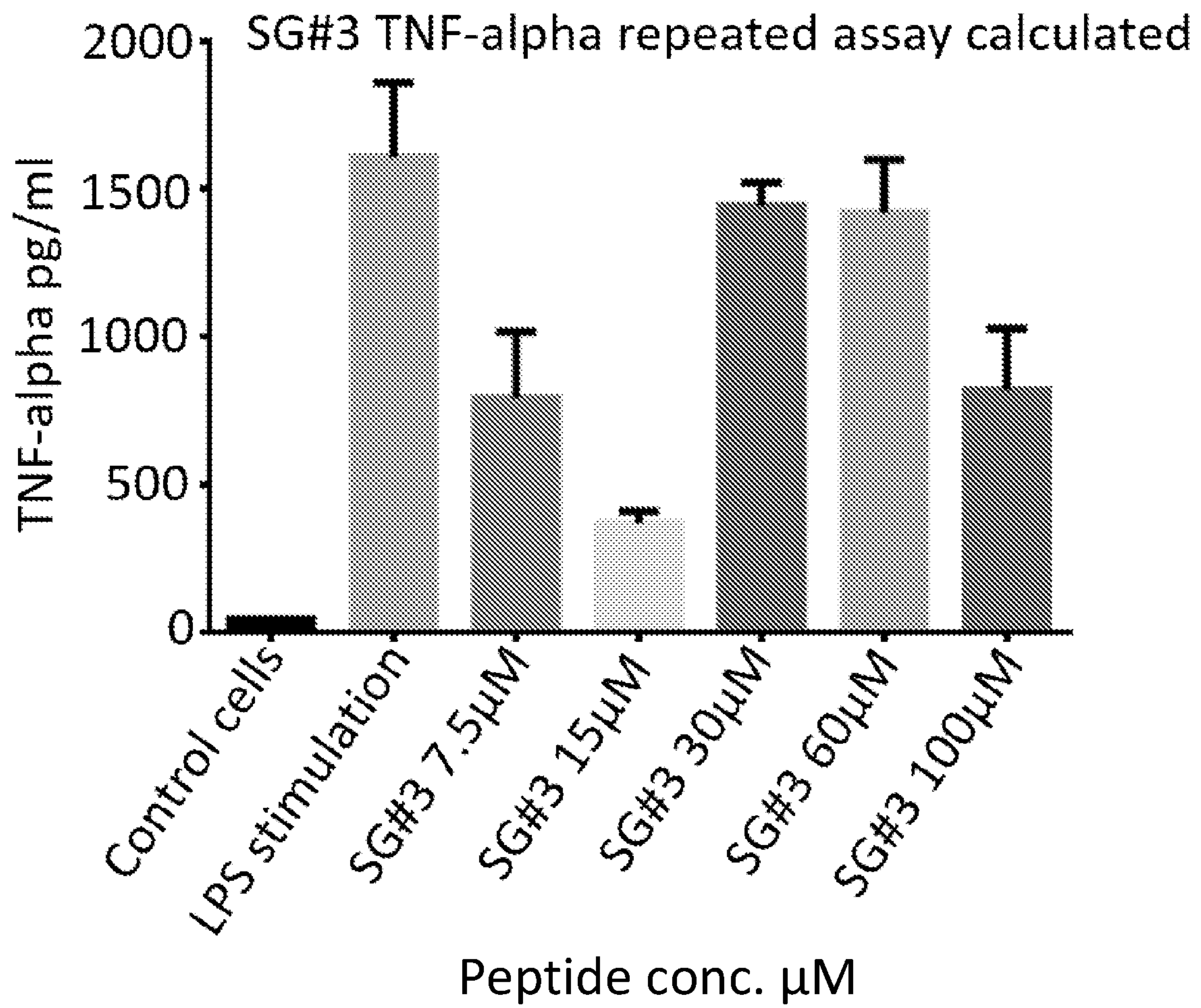


Fig. 6B

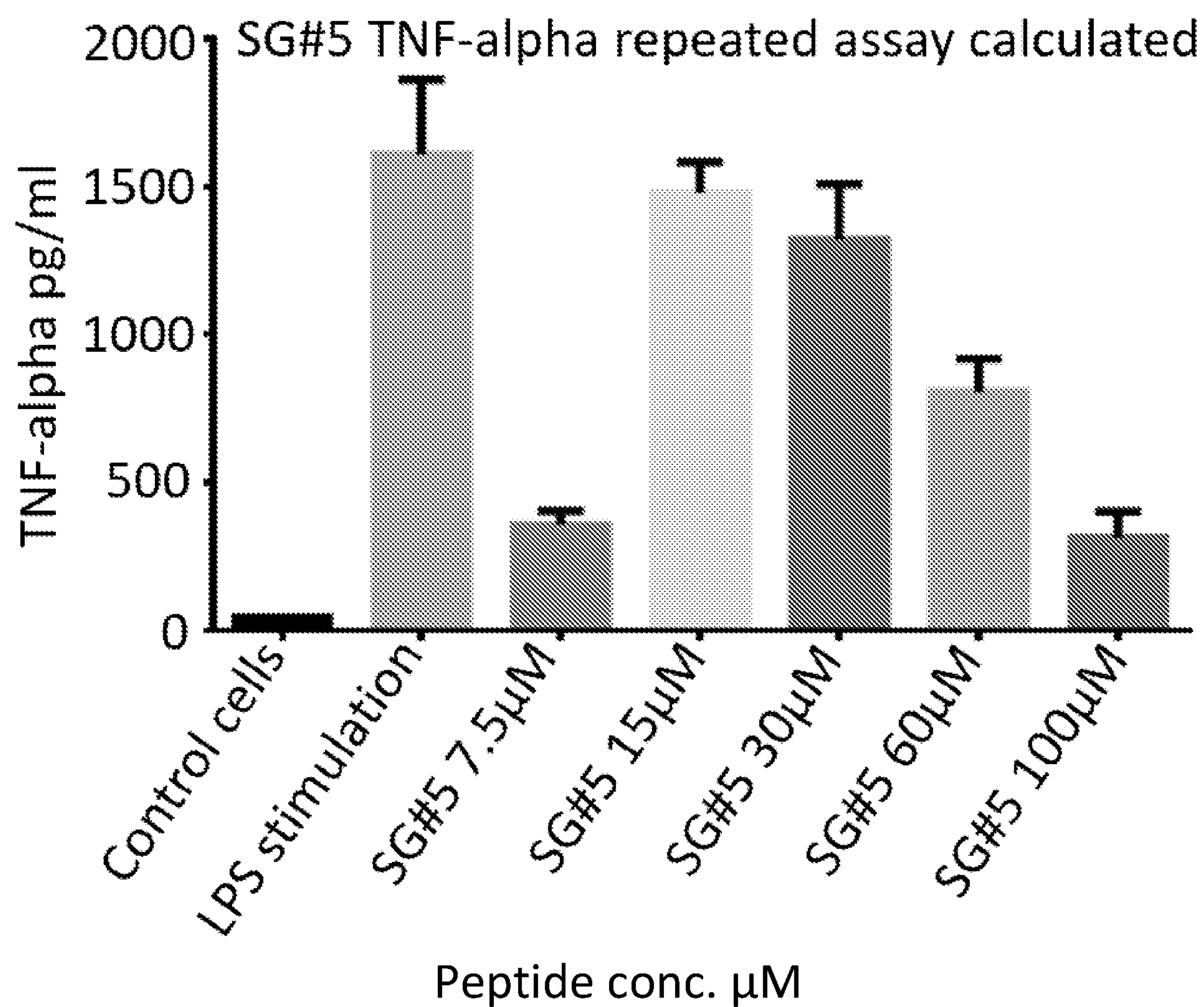


Fig. 6C

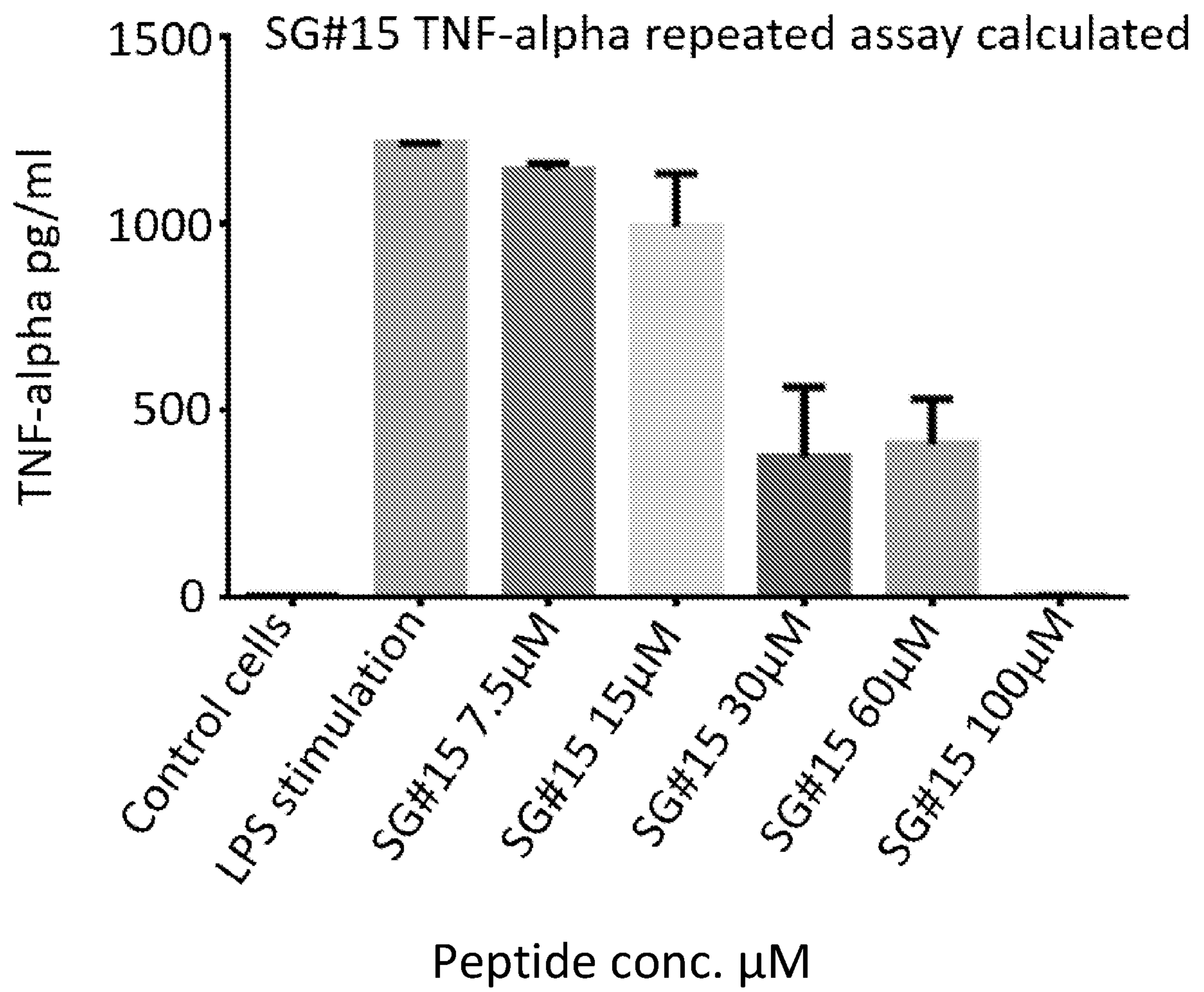


Fig. 6D

Fig. 7A

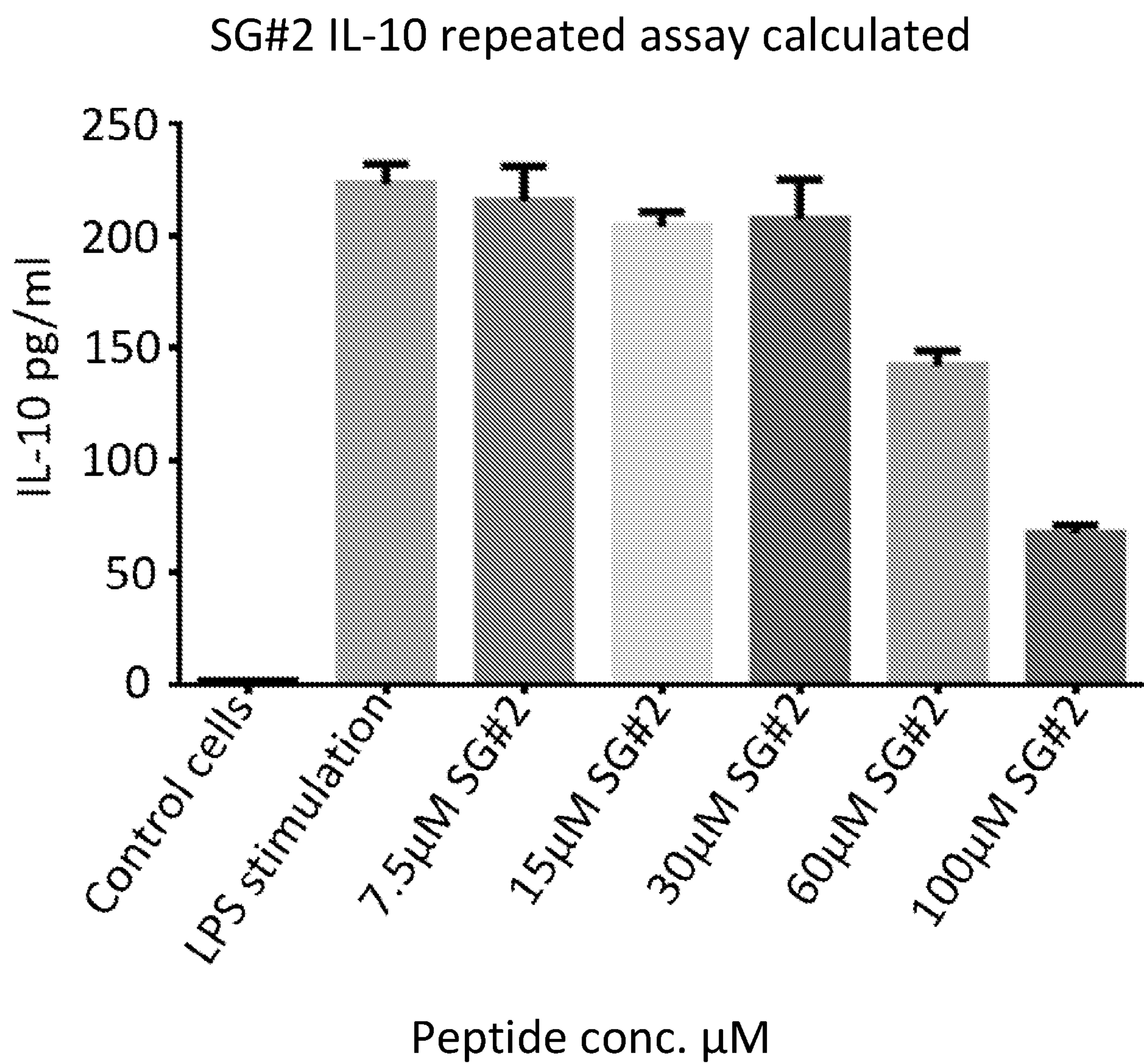


Fig. 7B

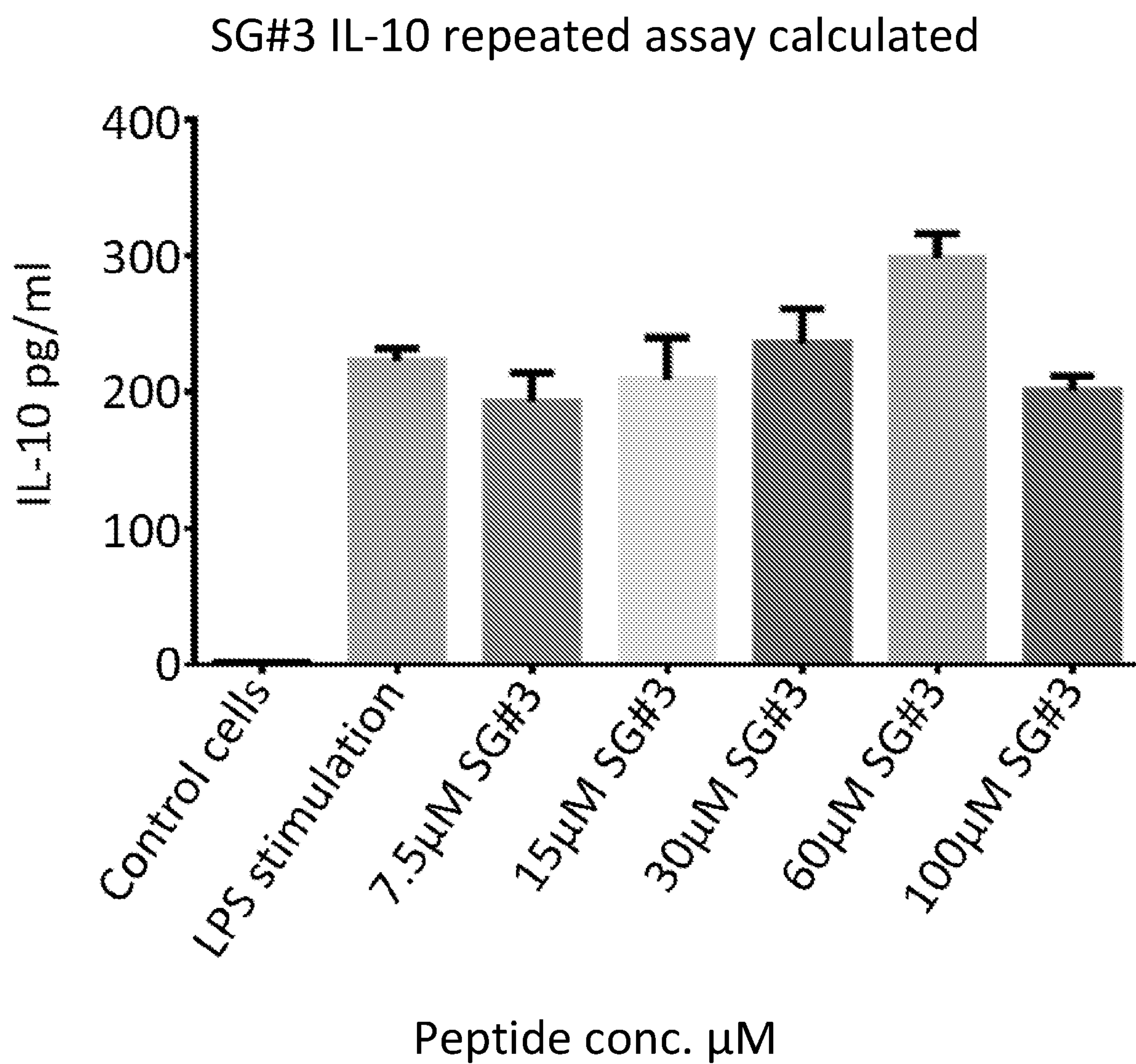


Fig. 7C

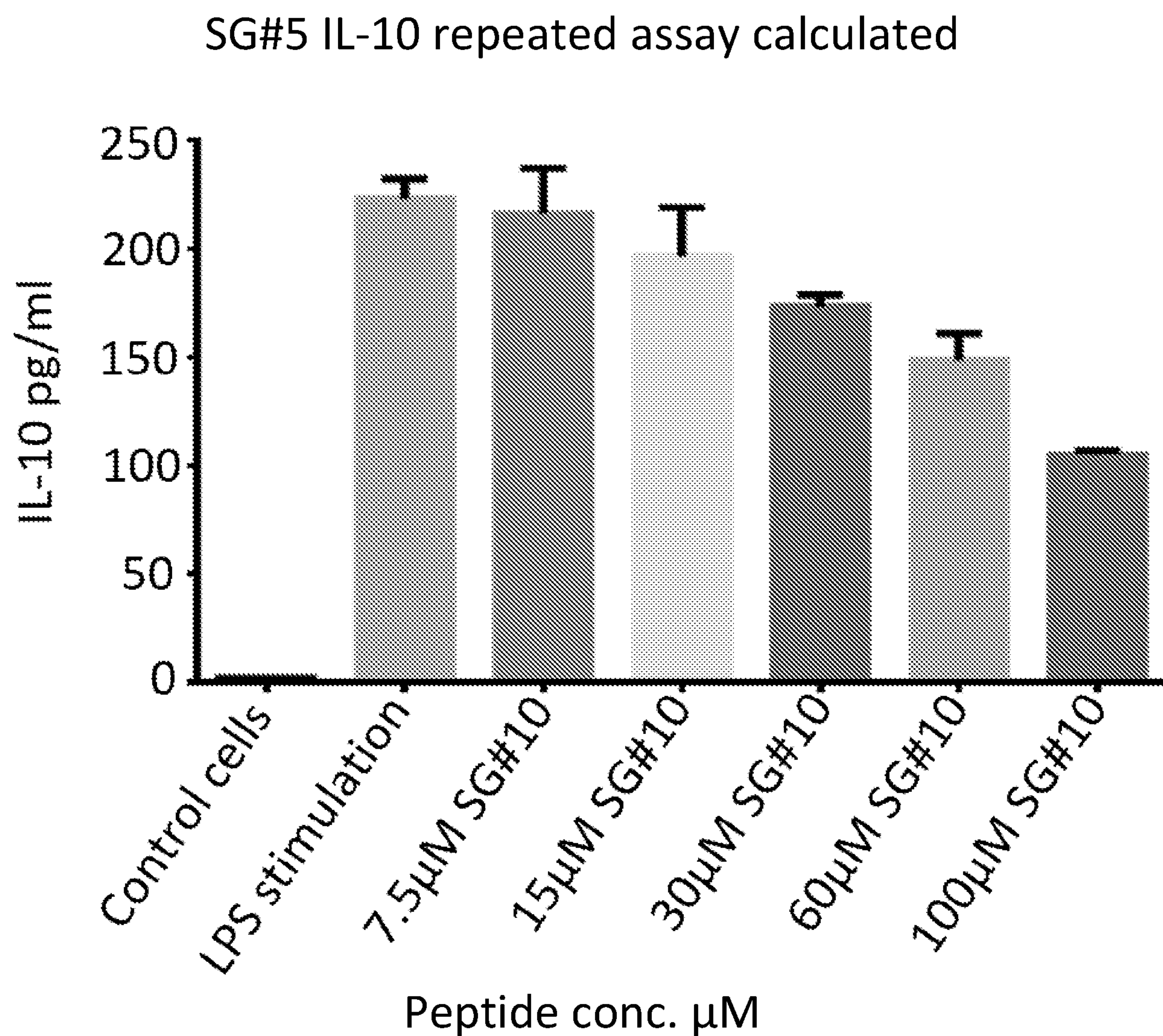
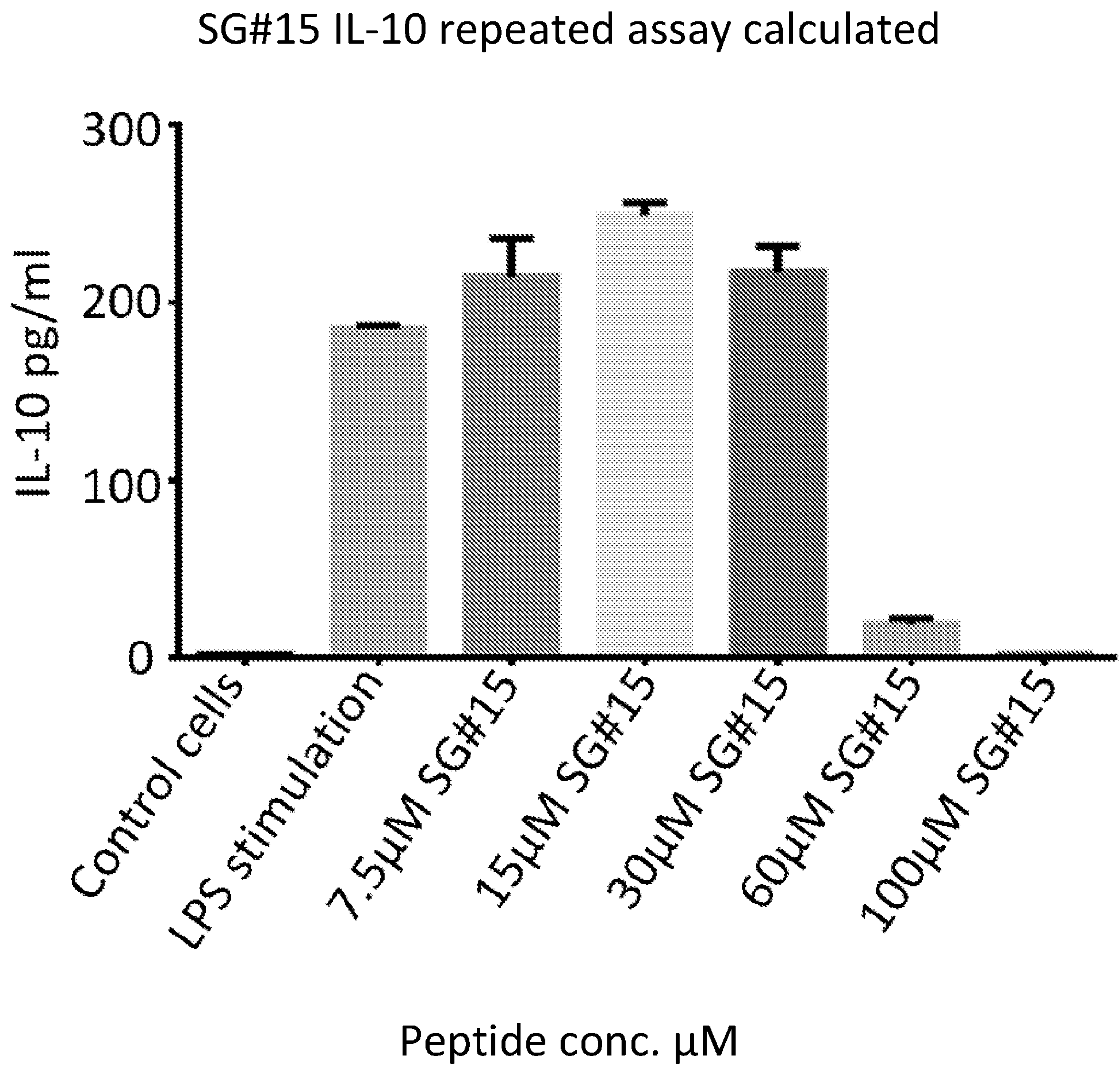


Fig. 7D



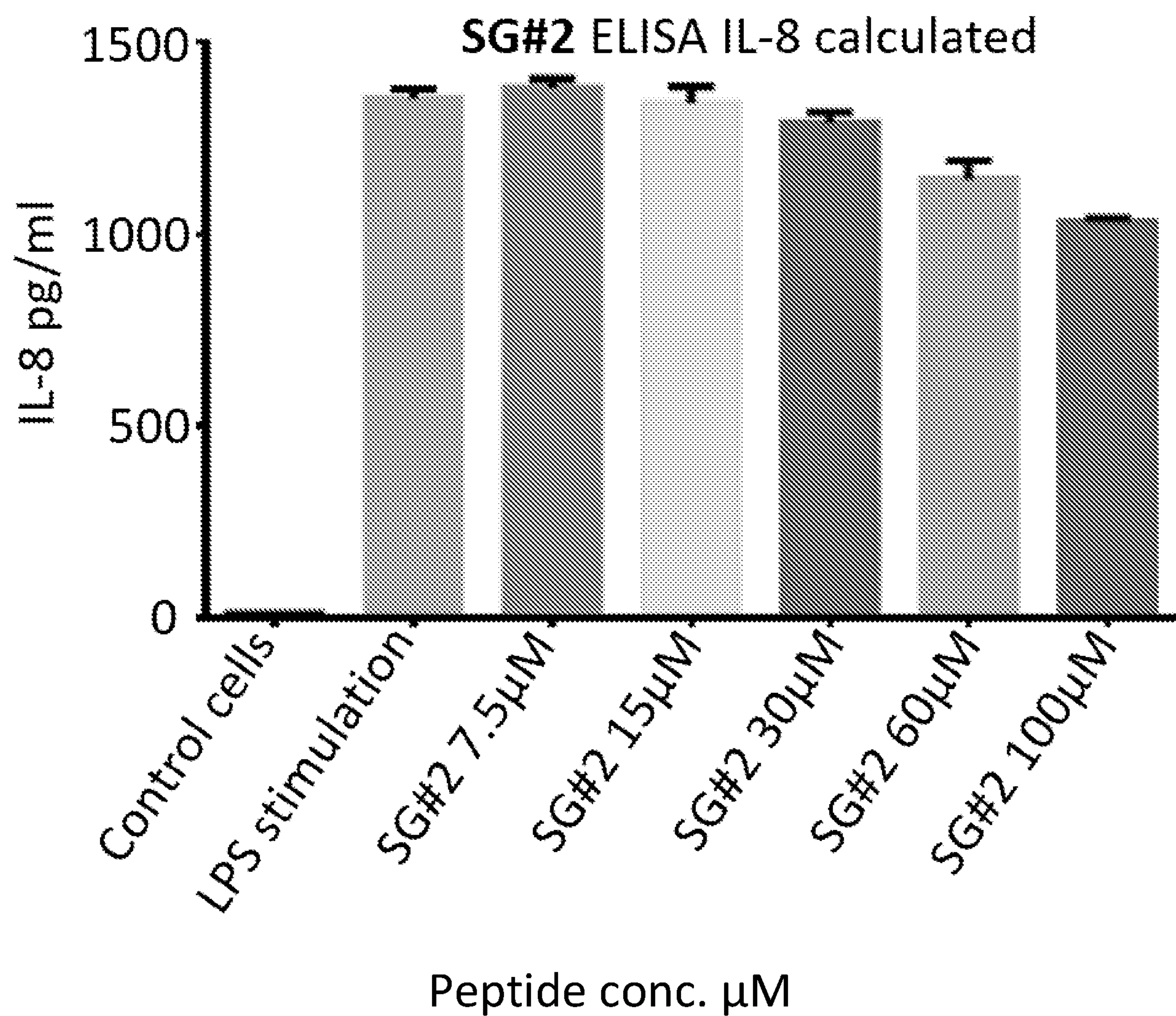


Fig. 8A

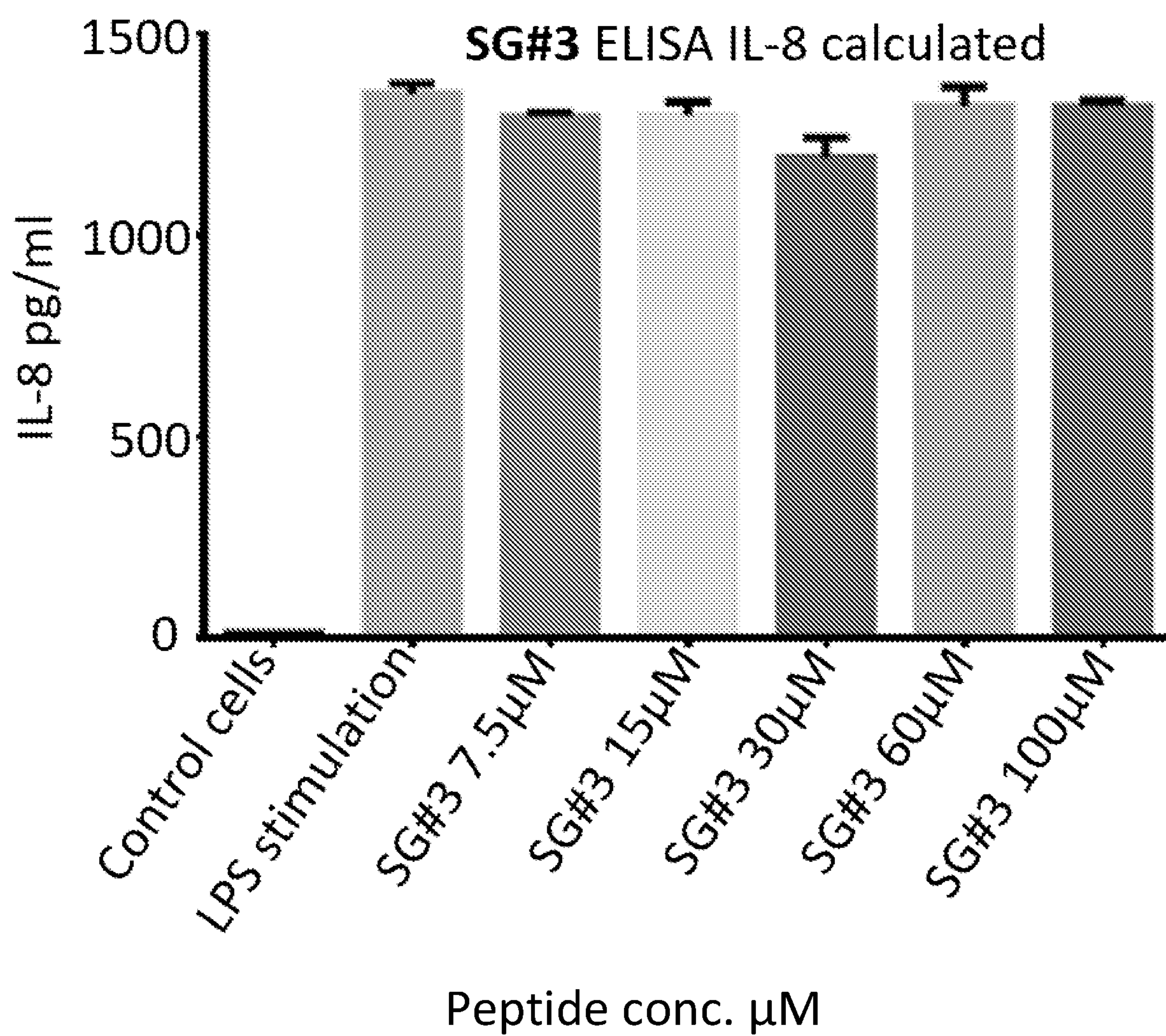


Fig. 8B

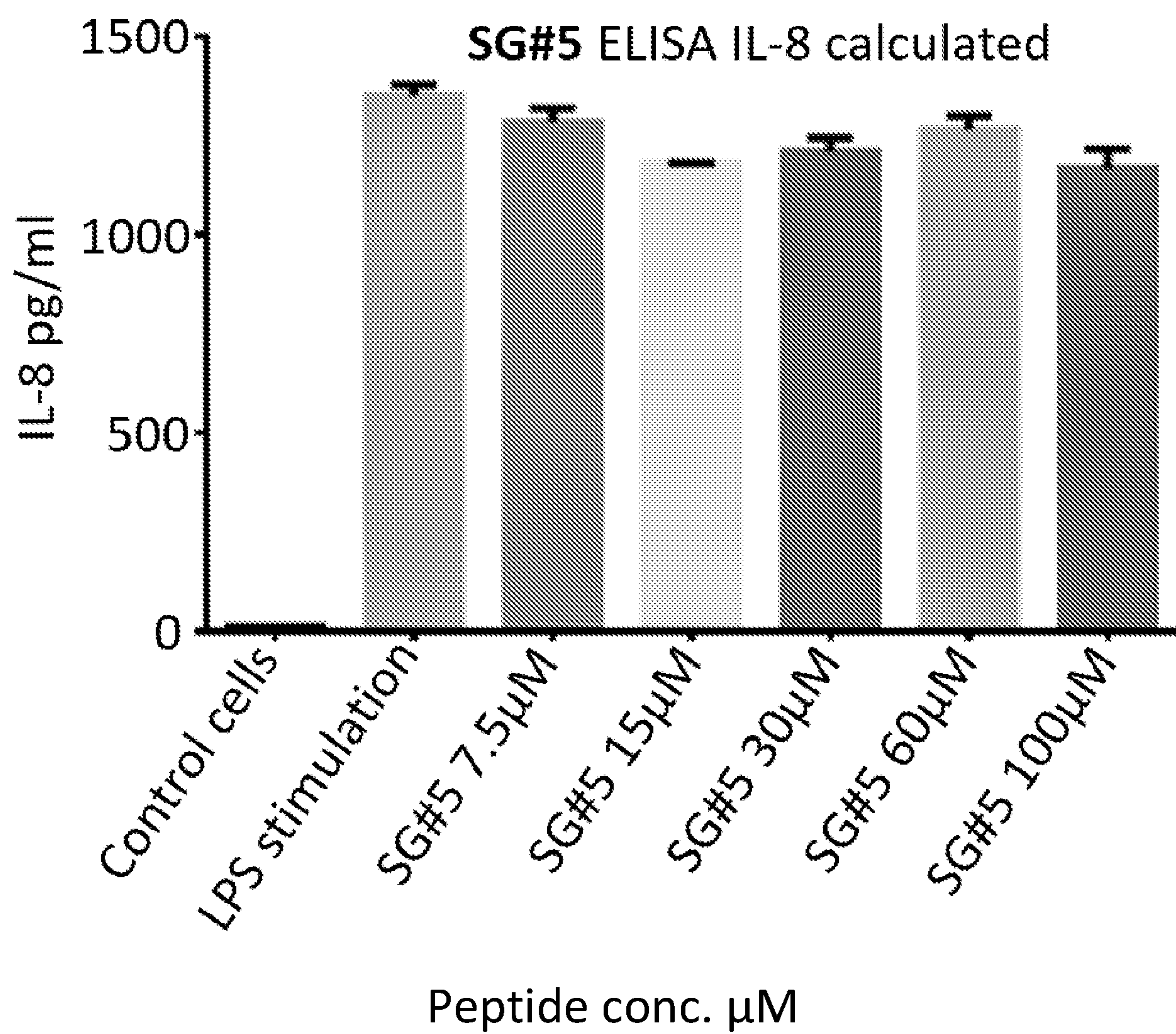


Fig. 8C

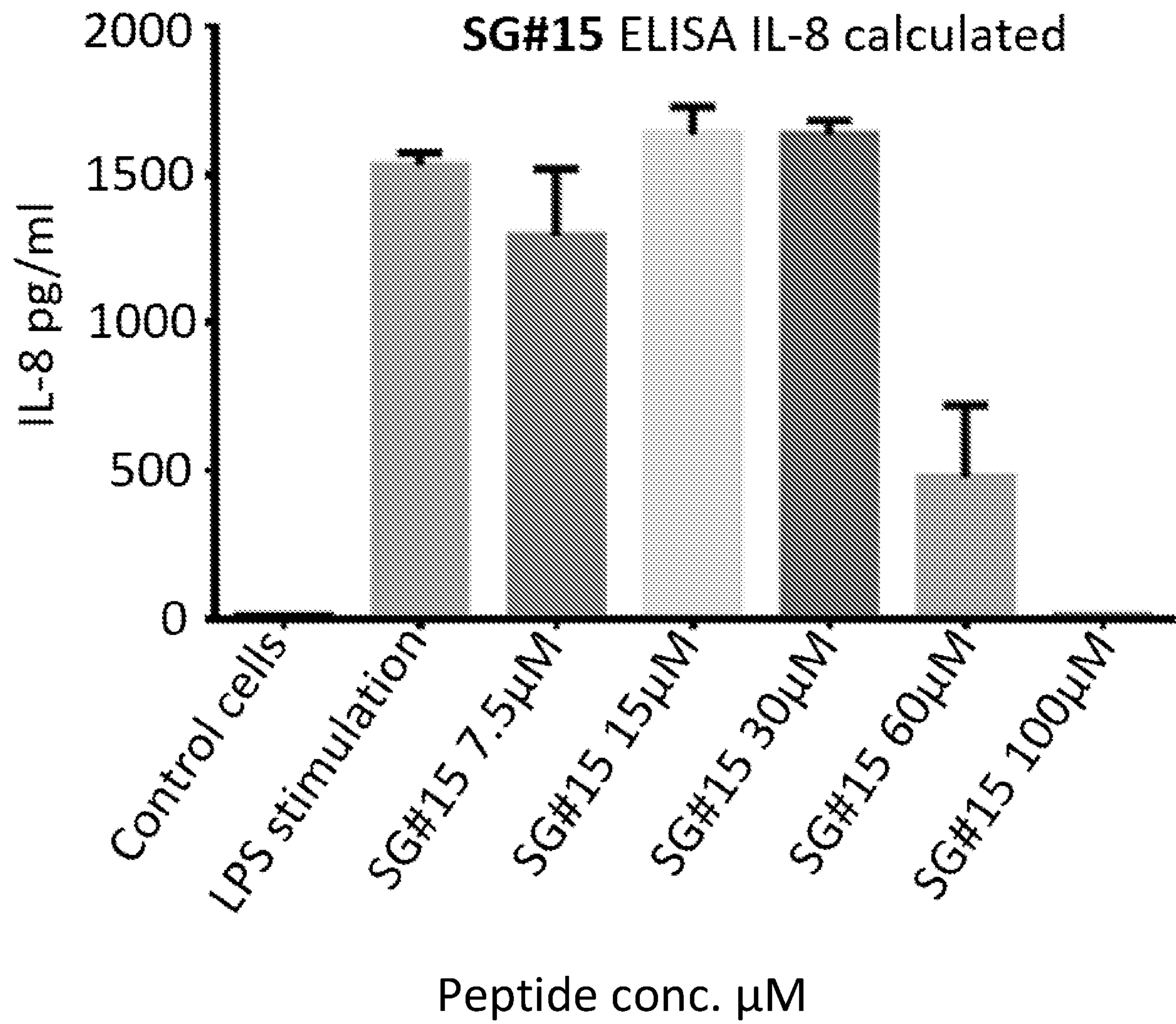


Fig. 8D

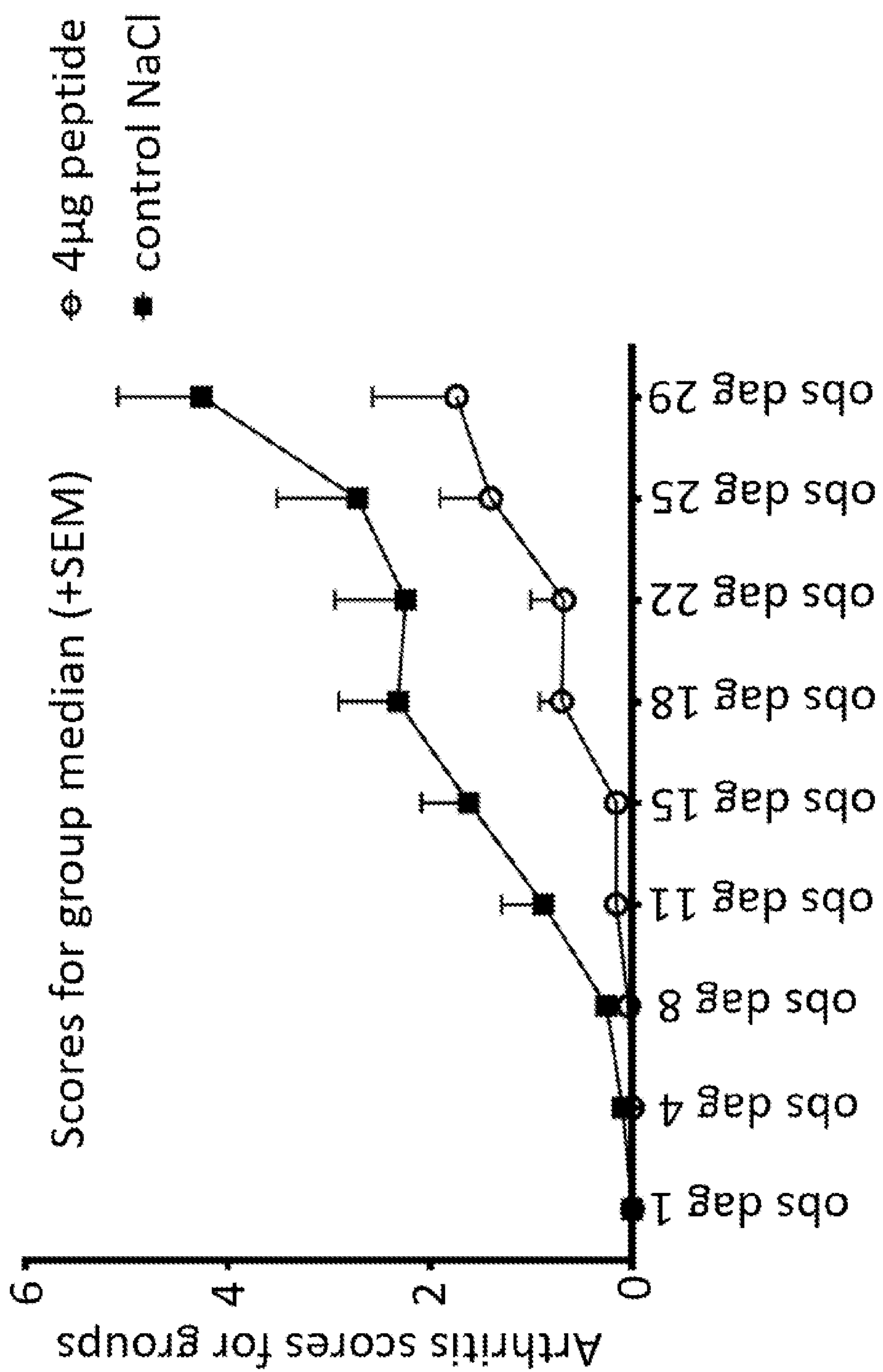


Fig. 9a

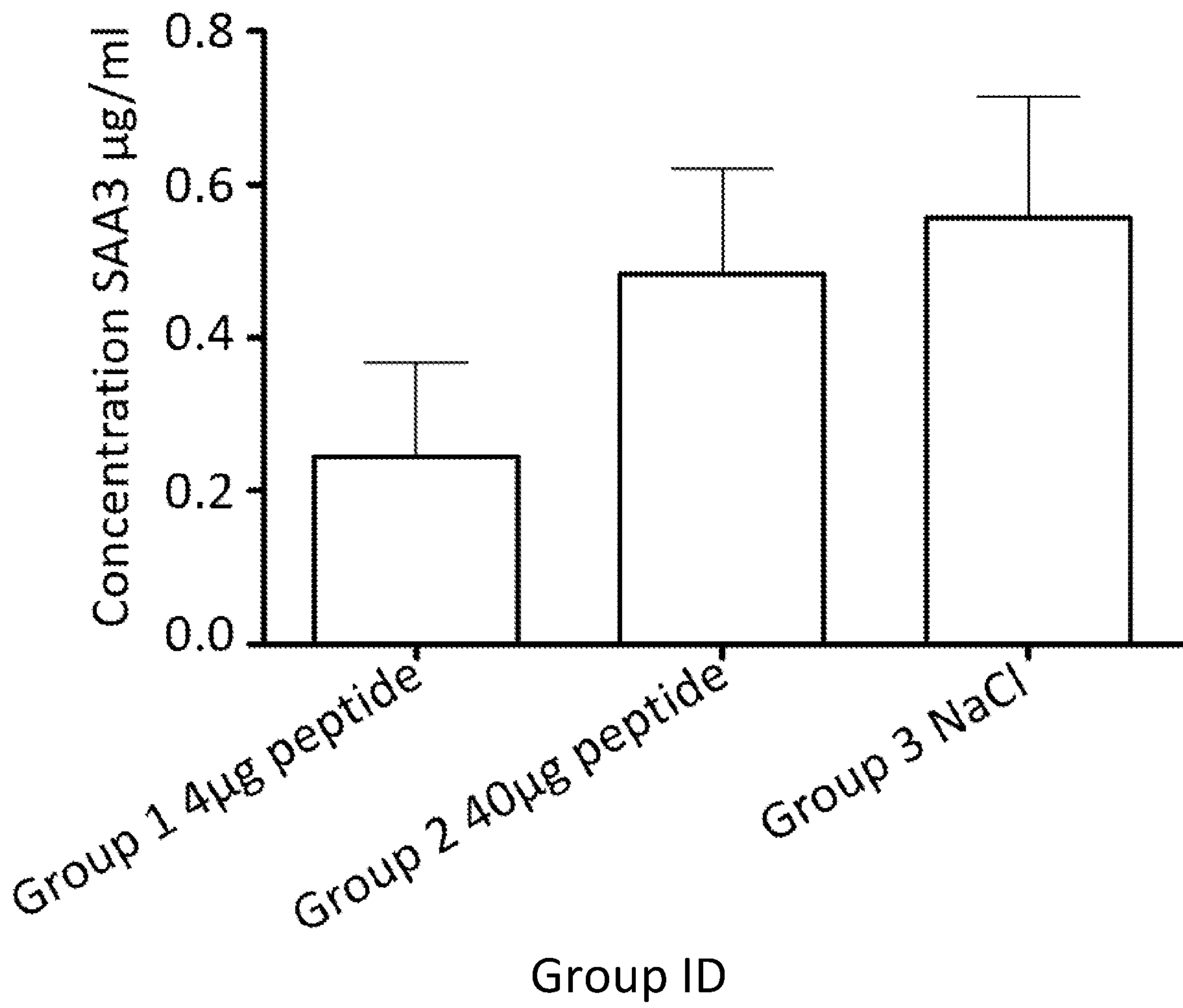


Fig. 9b

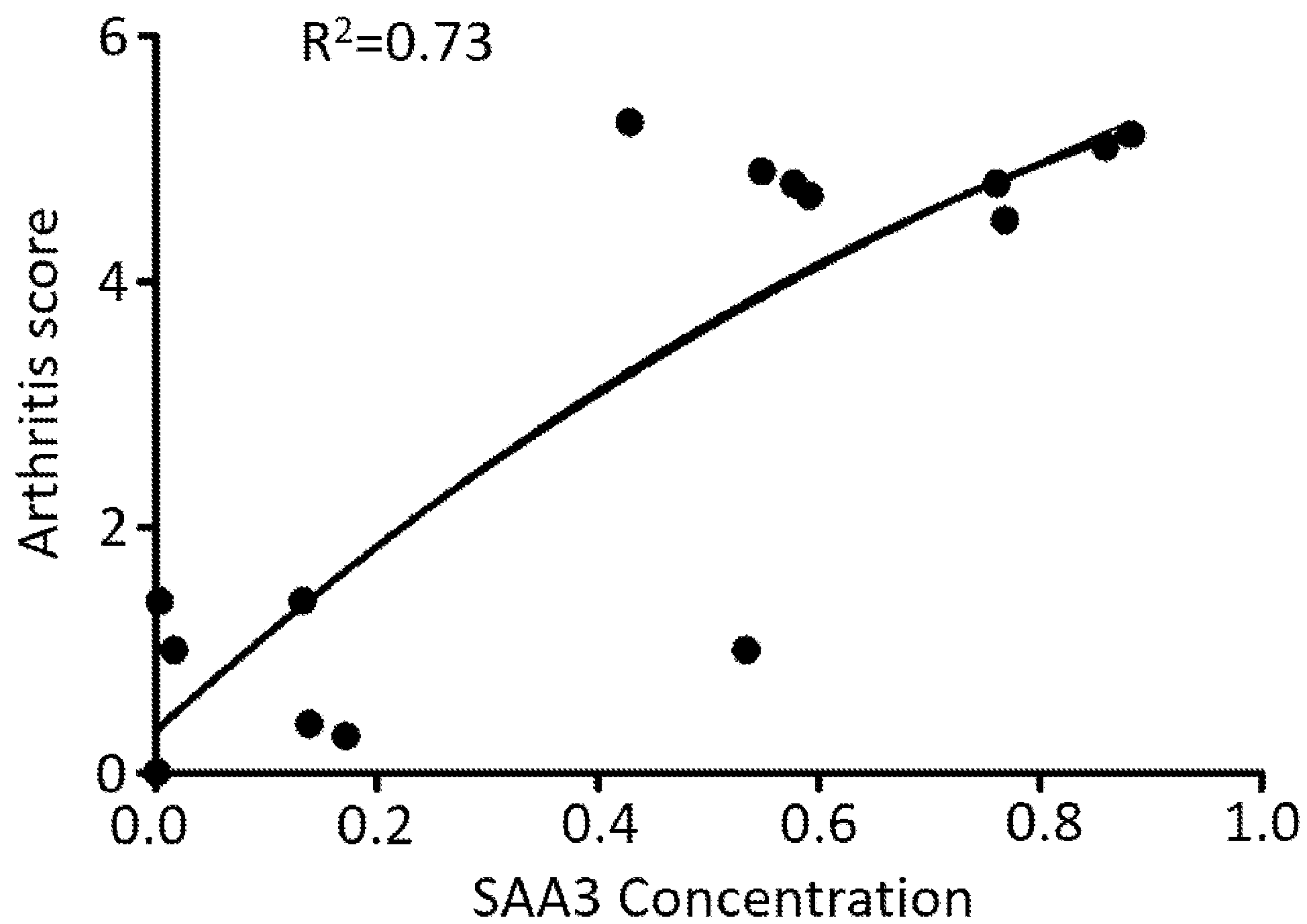
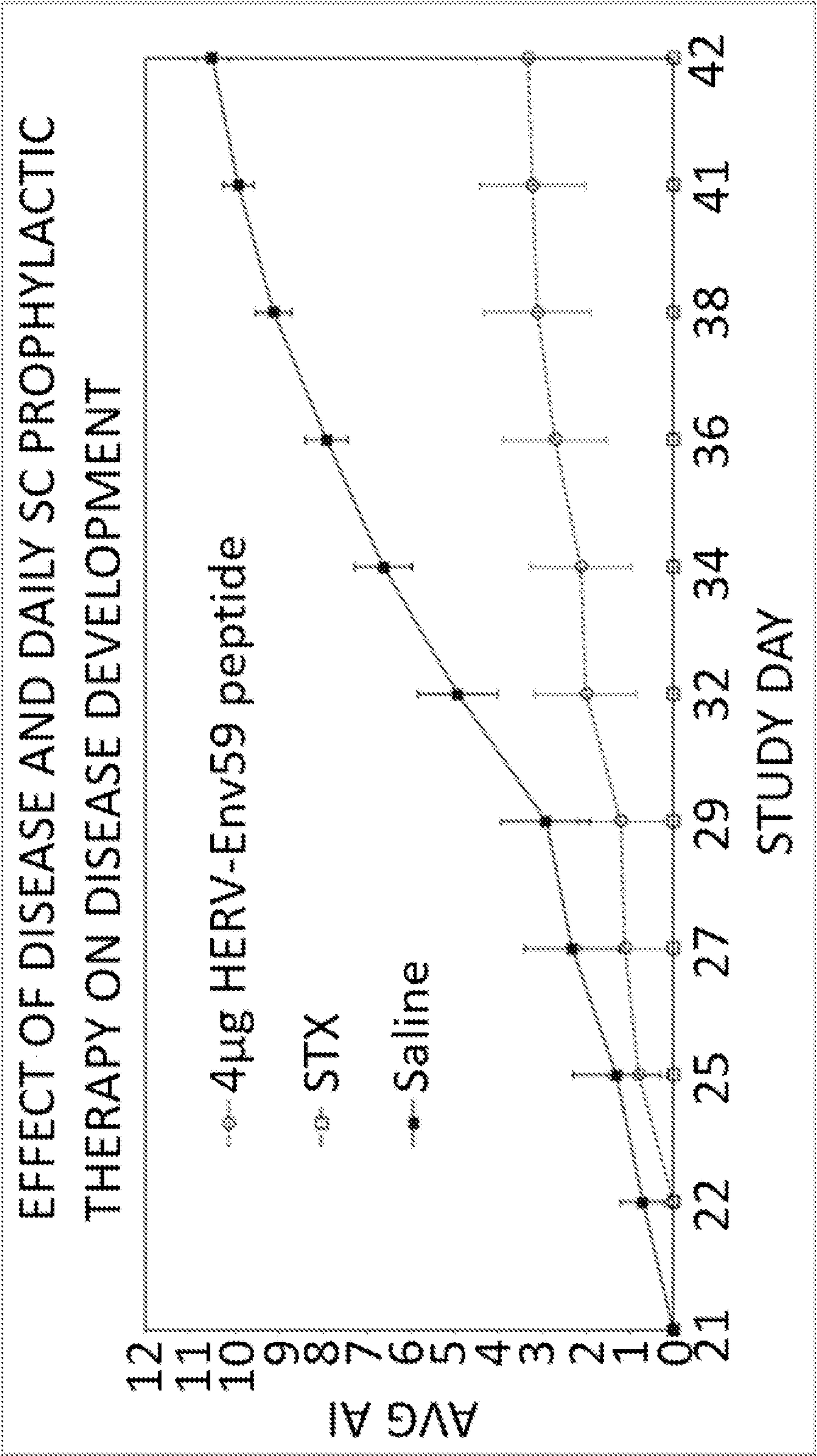


Fig. 9c

Fig. 10



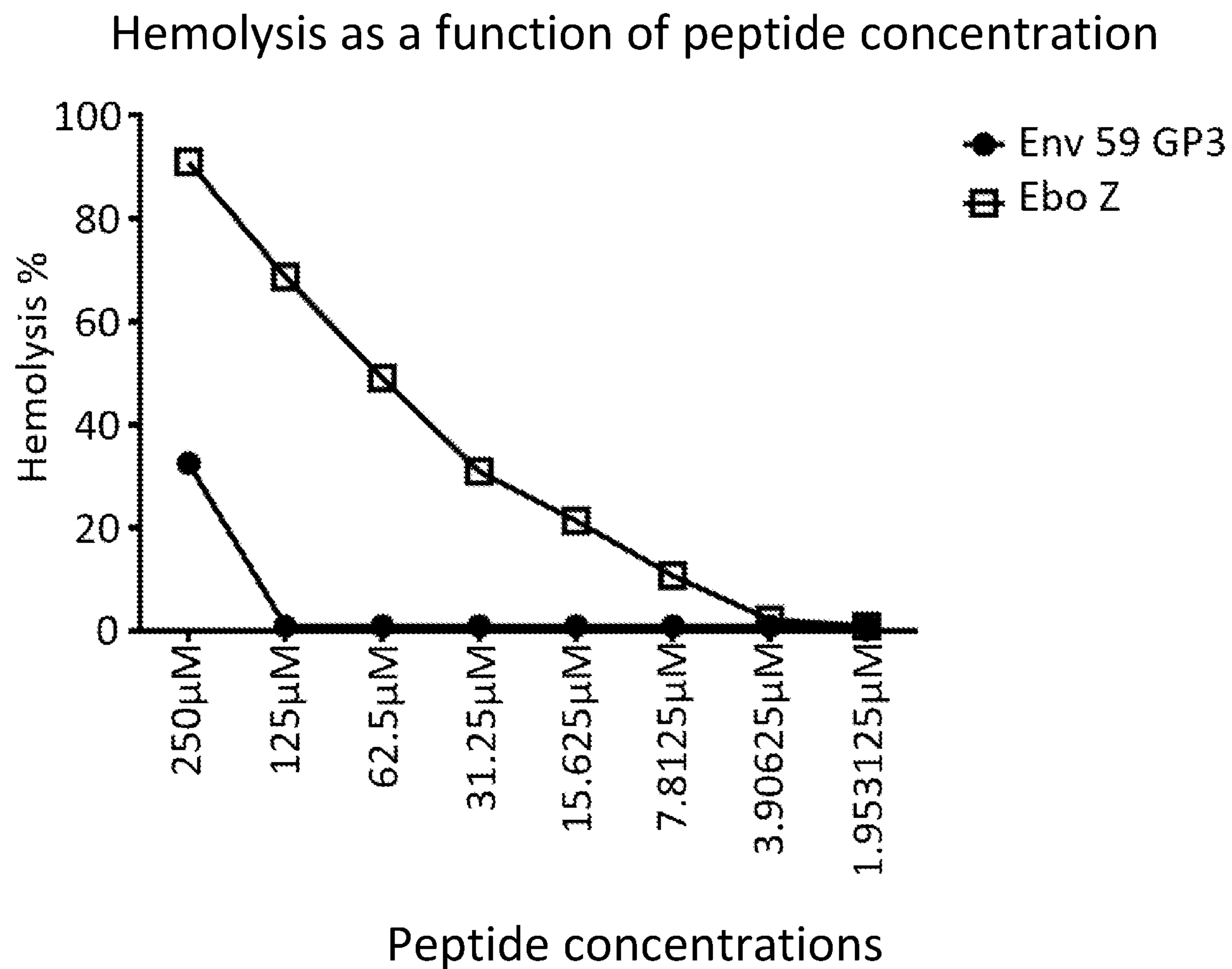


Fig. 11

Cell viability SG#16

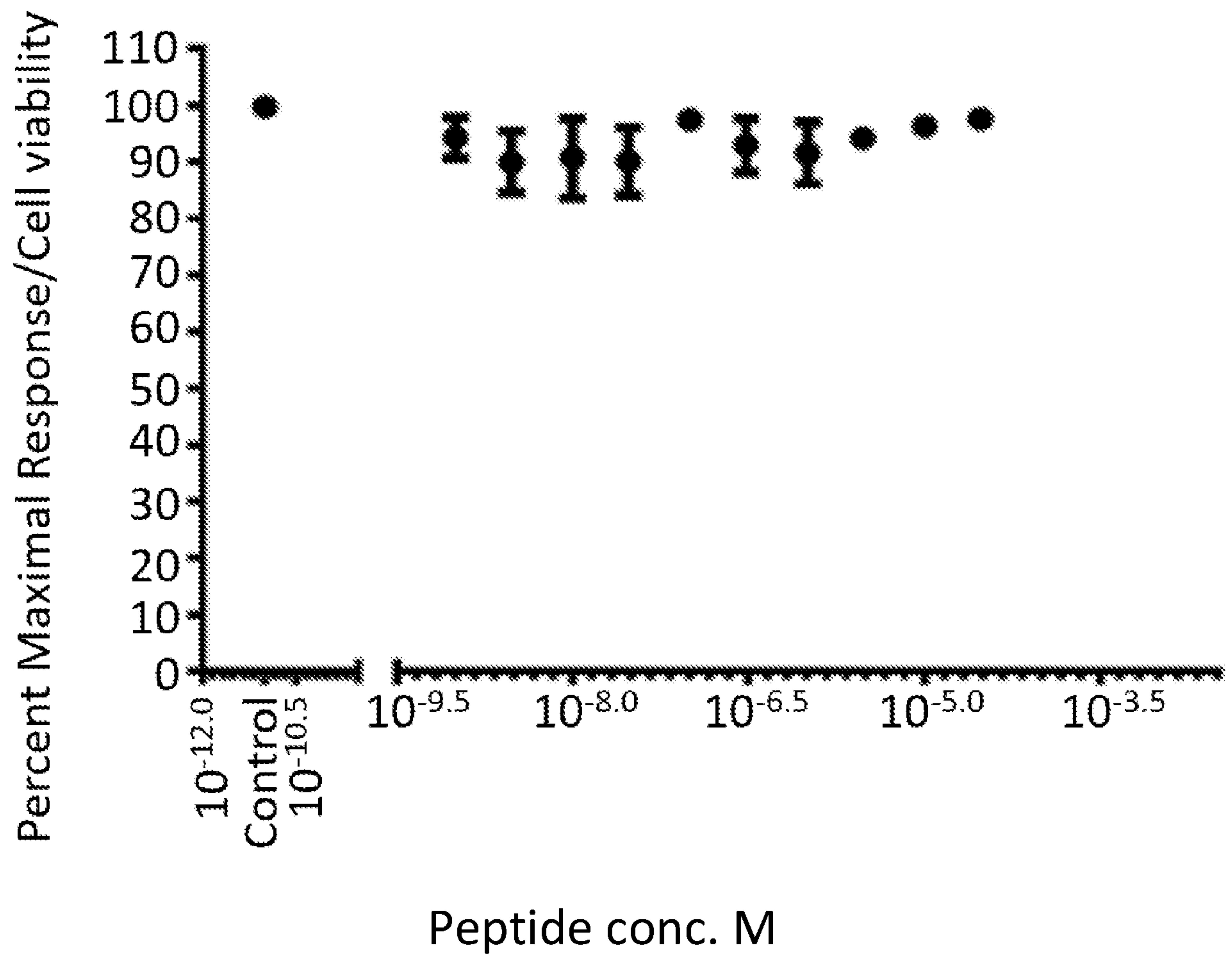
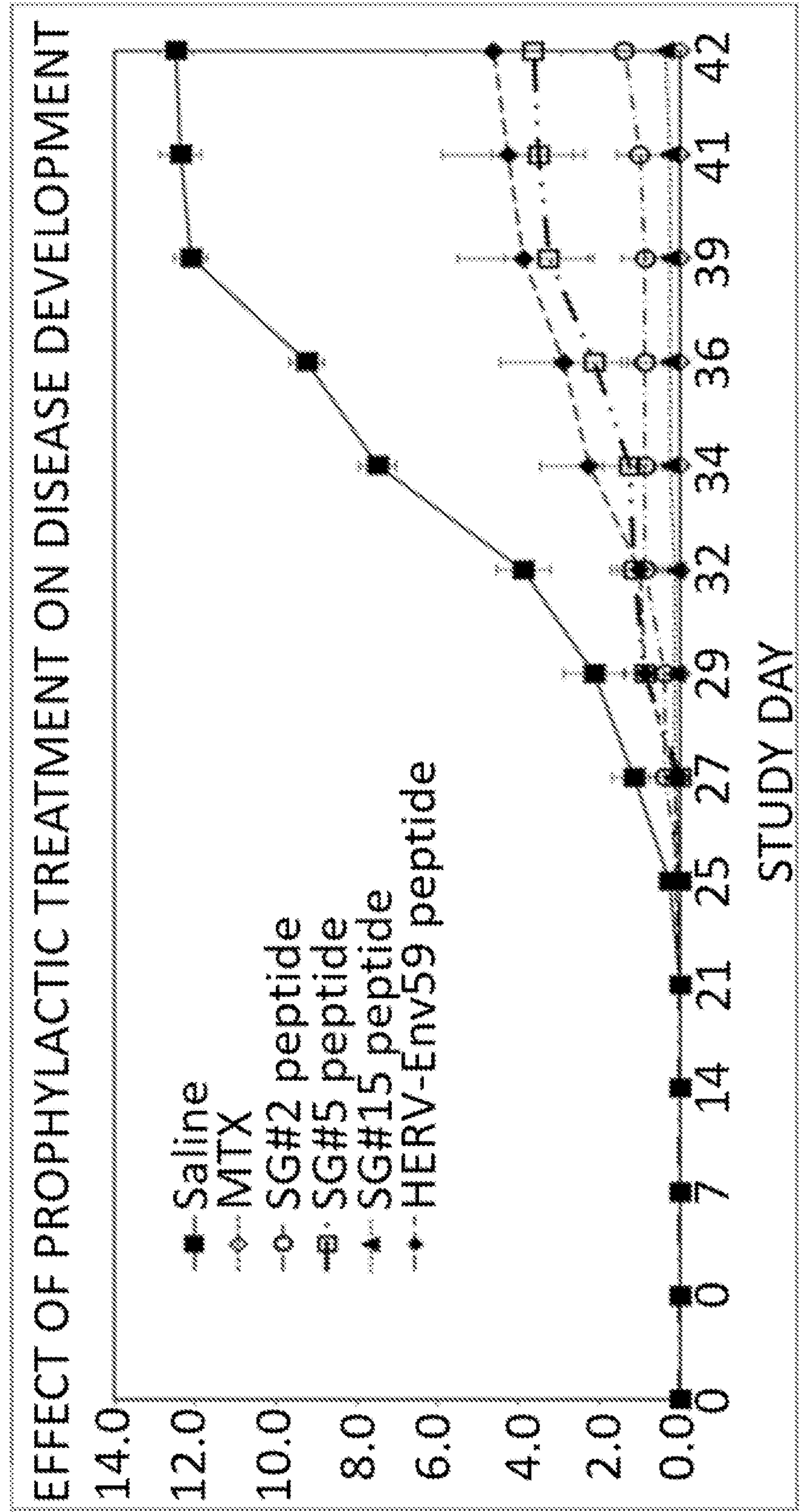


Fig. 12

Fig.13



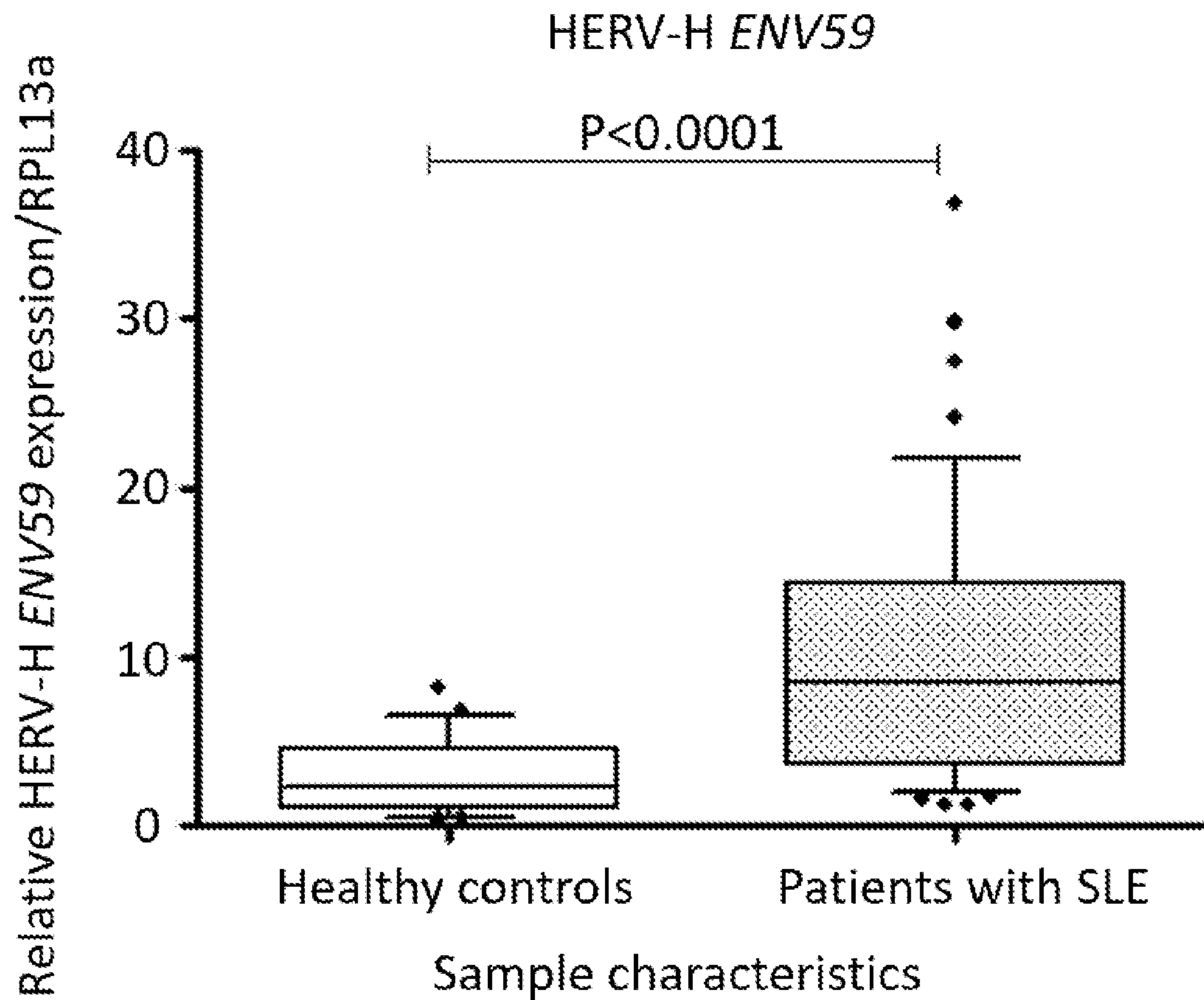


Fig. 1