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WO-A1-2013/014247
US-B1- 7 255 861
YOKOYAMA T ET AL: "Antigen-independent development of Foxp3<+> regulatory T cells suppressing autoantibody production in experimental pemphigus vulgaris", INTERNATIONAL IMMUNOLOGY 2011 OXFORD UNIVERSITY PRESS GBR, Bd. 23, Nr. 6, 2011, Seiten 365-373, XP05147631, ISSN: 0953-8178
TOMOAKI YOKOYAMA ET AL: "Immune dysregulation of pemphigus in humans and mice", JOURNAL OF DERMATOLOGY., Bd. 37, Nr. 3, 26. Februar 2010 (2010-02-26), Seiten 205-213, XP055147632, JP ISSN: 0385-2407, DOI: 10.1111/j.1346-8138.2009.00797.x

Description

[0001] The present invention relates to a T cell-based immunotherapy of antibody-mediated autoimmune diseases in mammals, in particular in humans, and in particular the use of peptides derived from human desmoglein 3 (Dsg 3) for the treatment of the disease Pemphigus vulgaris (PV). The application of a medical preparation comprising a peptide or a combination of the peptides Seq-ID 1-5 induces a desmoglein 3-specific immunotolerance in a human.

[0002] The present invention also relates to a T cell-based immunotherapy of antibody-mediated autoimmune diseases in dogs or horses, and in particular the use of peptides of the species-specific desmoglein 3 (Dsg 3) for the treatment of the disease Pemphigus vulgaris (PV). The application of one or a combination of the peptides Seq-ID 1-5 induces a desmoglein 3-specific immunotolerance in dogs or horses.

[0003] Antibodies are proteins from class of globulins which are formed by humans or animals in reaction to antigens and which are also designated as immunoglobulins.

[0004] Epitopes are those regions of an antigen to which an antibody or a T cell receptor specifically binds.

[0005] Autoantibodies are antibodies that are formed by humans or animals in response to the body's own antigens (autoantigens). Autoantibodies are characteristic of autoimmune diseases.

[0006] The HLA system (human leukocyte antigen system) describes a group of genes that are essential for the function of the human immune system. These genes are located on chromosome 6 in humans and can be divided into two classes: Class I with the isotypes A, B and C and class II with the isotypes DR, DP and DQ. These genes encode the MHC protein complexes which present antigens on the surface of body cells (for example leukocytes) and serve to identify the body's own cells.

Description of the general field of the invention

[0007] Pemphigus vulgaris (PV, ICD-10 classification L10.0) is an autoimmune disease of the skin and the mucous membranes close to the skin and belongs to the group of autoimmune blistering dermatoses. The disease is caused by the body's own antibodies (IgG autoantibodies) which are directed against the body's own protein desmoglein 3. Desmoglein 3 thus functions as an autoantigen. Desmoglein 3 is a protein component of the desmosome. Desmosomes are cell structures in epithelial cells that create a mechanical cohesion, e.g. between two epidermal keratinocytes of the skin or epithelial cells of the mucosa, respectively.

[0008] IgG autoantibodies against desmoglein 3 induce different effects at the cellular and molecular level which ultimately interfere with the intercellular binding of the desmogleins and cause a loss of adhesion of epidermal keratinocytes, thereby causing the clinical symptoms of Pemphigus vulgaris, i.e. the formation of blisters and erosions.

[0009] Autoaggressive CD4⁺ T cells, i.e. CD4⁺ T cells directed against the body's own structures, are essential initiators of the autoimmune response in the disease Pemphigus vulgaris for activating autoantibody-producing B cells. CD4⁺ T cells recognize epitopes of desmoglein 3 in association with the Pemphigus vulgaris-associated human leukocyte antigen (HLA)-class II alleles HLA-DRB1*04:02 and HLA-DQB1*05:03. Tolerance induction, i.e. the specific inhibition of autoreactive CD4⁺ T cells, i.e. CD4⁺ T cells directed against the body's own proteins, requires knowledge of the desmoglein 3 epitopes that lead to the stimulation of autoaggressive CD4⁺ T cells.

State of the art

[0010] The currently common therapy of the disease Pemphigus vulgaris consists of the systemic administration of high-dose glucocorticoids, for example prednisolone, as well as immunosuppressive drugs, for example azathioprine. Importantly, this normally is a long-term therapy which means that the potential side effects of the glucocorticoids and the immunosuppressive drugs can severely impair the success of the therapy as the duration of the disease increases and lead to considerable comorbidity (concomitant diseases). These include, amongst others, osteoporosis, diabetes mellitus, arterial hypertension, Cushing's syndrome, hepatitis, pancytopenia, opportunistic infections and thromboembolism.

[0011] Another therapeutic option is adjuvant immune adsorption, i.e. an immune adsorption applied in addition to immunosuppressive medication, which aims at the selective removal of the IgG antibodies circulating in the patient's blood and thus also the desmoglein 3-reactive autoantibodies from the patient's body using a binding column. This therapy is limited by the fact that it may only lead to clinical remission in the short term and is associated with potential side effects when using a central venous catheter, e.g. thrombembolic events and bacterial infections up to sepsis.

[0012] High-dose intravenous immunoglobulins are also used in the therapy of Pemphigus vulgaris and lead to a reduction of circulating desmoglein 3-specific autoantibodies via mechanisms that have not yet been fully clarified. Possible complications are thrombosis, aseptic meningitis and leukopenia.

[0013] Since 15th March 2019 the biotechnologically produced chimeric monoclonal antibody Rituximab, which is directed against the surface receptor CD20 on B-lymphocytes, has been approved by the European Parliament for the treatment of moderate to severe Pemphigus vulgaris. Rituximab is associated with the risk of severe bacterial and viral infections, including potentially life-threatening progressive multifocal leukoencephalopathy (PML) as potential complications.

[0014] Yokoyama T. et al. describe in their publication "Antigen-independent development of Foxp3+ regulatory T cells suppressing autoantibody production in experimental Pemphigus vulgaris" (International Immunology 2011 Oxford University Press GBR, Vol. 23, No. 6, 2011, pages 365-373) the development of Fox3+ regulatory T cells (Tregs) for the suppression of autoantibodies in Pemphigus vulgaris. The authors point to the important role of Tregs in the control of Dsg3-reactive lymphocytes.

[0015] Yokoyama T. and Amagai M. describe in their publication "Immune dysregulation of Pemphigus in humans and mice" (Journal of Dermatology, Vol. 37, No. 3, 2010, pages 205-213) the immunological dysregulation in Pemphigus vulgaris in humans and mice, wherein autoreactive lymphocytes are suppressed by regulatory T cell subunits such as CD4+, CD25+, Treg and IL-10 producing cells (Tr1).

[0016] In patent application WO 2013/014247 A1 the inventors claim peptides as part of an epitope of antigens from a group of polypeptides, including amongst others those of

desmoglein 3, for the treatment of autoimmune diseases such as Pemphigus. However, they do not point to a peptide or a combination of peptides which induce desmoglein 3-specific immunotolerance.

[0017] Patent document US 7 255 861 B1 discloses isolated peptides in connection with Pemphigus vulgaris and multiple sclerosis, wherein in the case of Pemphigus these are parts or epitopes of the human protein desmoglein 3. However, these peptides are not coupled to a carrier.

Objective

[0018] The objective of the present invention is to provide a medical preparation by use of which a more specific and better tolerable therapy of the disease Pemphigus vulgaris can be achieved.

Solution of the problem

[0019] The problem of the invention is solved by the claims.

[0020] The invention comprises the provision of a medical preparation for use in mammals, in particular humans, suffering from Pemphigus vulgaris (PV). The medical preparation comprises at least one or a combination of the peptides Seq-ID 1-5 of the immunodominant CD4+ T cell epitopes of the human protein desmoglein 3, which are coupled to suitable carriers in such a way that CD4+ T cells are activated. Suitable carriers are nanoparticles or mononuclear cells or erythrocytes or dendritic cells. These peptides induce an antigen-specific immunotolerance to desmoglein 3 in mammals, in particular in humans, wherein peptides Seq-ID 1-5 act as nominal antigens and induce an immunotolerance in the patient.

[0021] The invention further comprises the use of a medical preparation in the treatment of the disease Pemphigus vulgaris (PV) in humans.

[0022] The invention further comprises the provision of a medical preparation for use in dogs or horses suffering from Pemphigus vulgaris (PV). The medical preparation comprises at least one or a combination of the peptides Seq-ID 1-5 of the immunodominant CD4+ T cell epitopes of the canine or equine protein desmoglein 3, which are coupled to suitable carriers

in such a way that CD4+ T cells are activated. Suitable carriers are nanoparticles or mononuclear cells or erythrocytes or dendritic cells. These peptides induce an antigen-specific immunotolerance to desmoglein 3 in dogs or horses, wherein the peptides Seq-ID 1-5 act as nominal antigens and induce immunotolerance in the patient.

[0023] The invention further comprises the use of a medical preparation in the treatment of the disease Pemphigus vulgaris (PV) in dogs or horses.

[0024] By administration of a medical preparation comprising one or more HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (SEQ ID 1-5) under immunotolerance-producing conditions in patients with Pemphigus vulgaris, immunological tolerance to these CD4+ T cell epitopes of desmoglein 3 (SEQ ID 1-5) is induced so that the activation of autoaggressive T cells is inhibited. As a result, a T cell-dependent activation of desmoglein 3-specific B-cells does not take place, so that patients suffering from Pemphigus vulgaris no longer produce autoantibodies against the autoantigen desmoglein 3 (Seq-ID 1-5), thus bringing the disease Pemphigus vulgaris to a halt. It is therefore essential for the solution of the problem to provide a medical preparation that influences the function of desmoglein 3-reactive CD4+ T cells in such a way that an immunotolerance to desmoglein 3 is generated in patients with Pemphigus vulgaris.

[0025] The administration of one or more of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq ID 1-5) under immunotolerance-producing conditions in patients with Pemphigus vulgaris develops an immunotolerance to human desmoglein 3, thereby depriving Pemphigus vulgaris of its basis.

[0026] By administration of one or more of HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq ID 1-5) under immunotolerance-producing conditions in patients with Pemphigus vulgaris, the number of desmoglein 3-specific autoreactive CD4+ T cells in the peripheral blood of patients with Pemphigus vulgaris decreases, and the titers of desmoglein 3-specific autoantibodies in the serum of these patients decrease. Thus, the clinical symptoms improve and the consumption of the applied systemic glucocorticoids or immunosuppressants is reduced.

Exemplary embodiments

[0027] In own experiments, desmoglein 3-specific CD4+ T cell clones were isolated from the peripheral blood of Pemphigus vulgaris patients and five CD4+ T cell epitopes of human desmoglein 3 were identified in T cell proliferation assays (Seq-ID 1-5). The five epitopes show defined binding motifs for the restricting HLA-DRB1*04:02 allele. It was also shown that the recognition of these five CD4+ T cell epitopes of desmoglein 3 by autoreactive CD4+ T cells is also restricted, i.e. limited, by a second HLA class II allele which is associated with Pemphigus vulgaris, namely HLA-DQB1*05:03. Both HLA-DRB1*04:02 and HLA-DQB1*05:03 have a negative charge at positions 70 and 71 of the β 1 chain. This negative charge at the so-called p4 binding site of the HLA molecule is essential for the binding of the five CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5). By binding the five CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) to HLA-DRB1*04:02 and HLA-DQB1*05:03, the five CD4+ T cell epitopes of human desmoglein 3 (SEQ ID 1-5) are presented to autoaggressive T cells and these desmoglein 3-specific CD4+ T cells are activated, which is essential for the production of desmoglein 3-specific autoantibodies and thus for the development of Pemphigus vulgaris.

1. Mouse model for detecting the activation of CD4+ T cells by the five CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5)

[0028] In an HLA-DRB1*04:02 transgenic mouse model of the disease Pemphigus vulgaris it was shown that the activation of CD4+ T cells by the five CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) leads to the induction of pathogenic desmoglein 3-specific autoantibodies which are ultimately responsible for the disease Pemphigus vulgaris.

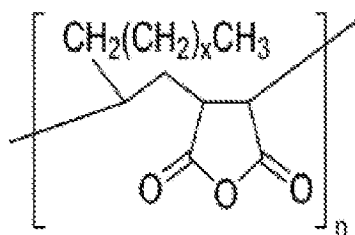
[0029] After immunization of the transgenic mice with recombinant human desmoglein 3, CD4+ T cells were generated that recognize the epitopes of human desmoglein 3 in conjunction with HLA-DRB1*04:02. Immunization of HLA-DRB1*04:02 transgenic mice with the five CD4+ T cell epitopes of desmoglein 3 (Seq-ID 1-5) leads to the induction of pathogenic desmoglein 3 reactive IgG autoantibodies. This is the first in vivo proof that desmoglein 3-specific CD4+ T cells, which recognize immunodominant epitopes of the human autoantigen in the context of the disease-associated HLA-DRB1*04:02, play a central role in the production of desmoglein 3-specific autoantibodies and therefore in the pathogenesis of Pemphigus vulgaris.

2. Preparation and administration of a medical preparation comprising one or more HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq ID 1-5) under immunotolerance-producing conditions for the treatment of patients with Pemphigus vulgaris

[0030] The following options are available for the administration of one or more of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) under immunotolerance-producing conditions in patients with Pemphigus vulgaris:

2.1 Medical preparation comprising conjugates of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of desmoglein 3 (Seq-ID 1-5) with nanoparticles:

[0031] HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) coupled to suitable nanoparticles are administered intravenously (i.v.) to a patient. An example of suitable nanoparticles are nanoparticles coated with polymers to which peptides are coupled. These nanoparticles can be, for example, superparamagnetic iron oxide nanocrystals which can be labeled with ^{59}Fe . Another example of suitable nanoparticles are nanoparticles coated with polymers in the form of quantum dots. These quantum dots can consist of a core of cadmium selenide, a first shell of cadmium sulfide and a second shell of zinc sulfide (CdSe/Cd/S/ZnS core-shell-shell quantum dots). The polymer suitable for coating the nanoparticles can be an amphiphilic polymer. An example of an amphiphilic polymer is poly(maleic anhydride-*alt*-1-octadecene) (maleic acid copolymer, maleated polymer).



[0032] The coupling of suitable nanoparticles with the peptides (HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq ID 1-5)) can be performed with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC). For this purpose, suitable nanoparticles can be used in a concentration of 6 $\mu\text{mol/l}$ and EDC in a concentration of 6 mmol/l . For incubation of the peptides (HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5)), EDC can be used overnight in a 100 to 1000-fold excess.

2.2 Medical preparation, as well as its preparation and administration comprising conjugates of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) with mononuclear cells of the peripheral blood or with erythrocytes:

[0033] HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (SEQ ID 1-5) are coupled with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) to the patient's own mononuclear cells or erythrocytes and administered intravenously to the patient. Intravenous administration may be a short infusion.

[0034] HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq ID 1-5) are coupled to cell surfaces of the patient's own (autologous) mononuclear cells or erythrocytes using a 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) treatment. The dose of the patient's own mononuclear cells or erythrocytes prepared in this way for the therapy of Pemphigus vulgaris is between 1×10^3 to 3×10^9 cells and can be varied in the course of therapy.

2.3 Medical preparation, its preparation and administration comprising conjugates of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) with dendritic cells:

[0035] Dendritic cells are very efficient, antigen-presenting immune cells which are of great interest in immunotherapeutic research, and in particular in the context of tumor and autoimmune diseases, due to their immunomodulatory properties. Due to the special ability of dendritic cells to induce both immune responses and immunological tolerance, they play a central role in the control of adaptive immune responses. For the treatment of Pemphigus vulgaris, dendritic cells are first generated from blood monocytes of patients, and these dendritic

cells are then loaded with one or more of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5). The dendritic cells loaded ex vivo with the human desmoglein 3 epitopes (Seq-ID 1-5) are administered to Pemphigus vulgaris patients under immunotolerance-producing conditions comparable to a vaccine, for example by intramuscular or subcutaneous injection. Immunotolerance-producing conditions are understood to mean that the dendritic cells are maintained in as immature a stage as possible.

3. Administration of a medical preparation comprising one or more HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of animal desmoglein 3 under immunotolerance-producing conditions in animal patients for the treatment of Pemphigus vulgaris

[0036] The medicinal preparations described in item 2 are also applicable to animals with Pemphigus vulgaris, for example dogs or horses. Instead of the human desmoglein 3 epitopes (Seq-ID 1-5), the medicinal preparation comprises the respective canine (for dogs) or equine (for horses) desmoglein 3 epitopes. When used in animals other than dogs or horses, the medicinal preparations described in item 2 include the species-specific desmoglein 3 epitopes.

4. Characterization of immunodominant epitopes using desmoglein 3-reactive T cell hybridomas

[0037] The functional characterization of the HLA-DRB1*04:02- and HLA-DQB1*05:03-binding CD4+ T cell epitopes of human desmoglein 3 (Seq-ID 1-5) is exemplary shown for a HLA-DRB1*4:02-restricted CD4+ T cell epitope of human desmoglein 3 with the sequence aa 505-521, SSPSVVVSARTLNNRYT (Seq-ID 6). This characterization was performed using immortalized CD4+ T cell hybridomas. The T cell hybridomas were generated after immunization of HLA transgenic mice with recombinant human desmoglein 3 protein. Fusion of desmoglein 3-specific CD4+ T cells from efferent regional lymph nodes of desmoglein 3-immunized HLA-transgenic mice with the murine thymus cell line BW5147 leads to desmoglein 3-specific hybridomas, which secrete interleukin-2 (IL-2) after antigen-specific activation. The results of the desmoglein 3-reactive T cell hybridomas, which is specific for the HLA-DRB1*04:02-restricted CD4+ T cell epitope of desmoglein 3 with sequence aa 505-521, SSPSVVVSARTLNNRYT (Seq-ID 6) are shown in Figure 1. By using shortened vari-

ants of the native desmoglein 3 epitope with the sequence aa 505-521, SSPSVVVSARTLNNRYT (Seq-ID 6) it is possible to define the so-called core epitope of the epitope; in this case the core epitope has the sequence VVVSARTLN (core epitope of Seq-ID 6). The core epitope is the region of the epitope that interacts with the binding groove of the HLA-DRB1*04:02 molecule. The core epitope is the peptide region required for T cell activation.

Figure legend

[0038] Figure 1 shows the concentration of the T cell growth factor interleukin-2 (IL-2), which was secreted by the desmoglein 3 reactive cell hybridoma after antigen-specific activation, in the culture supernatant. This is specific for the HLA-DRB1*04:02-binding CD4+ T cell epitope of human desmoglein 3 with the sequence aa 505-521, SSPSVVVSARTLNNRYT. The quantification of the interleukin 2 concentrations in the culture supernatants was performed by an interleukin 2 enzyme linked immunosorbent assay (ELISA) and is expressed as optical density (OD) at 450 nm wavelength. On the y-axis the shortened variants of the desmoglein 3 epitope are listed (aa 505-521, SSPSVVVSARTLNNRYT).

[0039]

<110> Philipps University Marburg

<120> Peptides of the Desmoglein 3 for Pemphigus vulgaris

<130> TM819

<140> EP

<141> 2014-07-21

<160> 6

<170> PatentIn version 3.5

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<211> 15

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<213> Homo sapiens

<220>

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11

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<223> Dsg3 15-mer peptide which binds to HLA-DRB1*04:02 and HLA-DQB1*05:03

<400> 1

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<210> 2

<211> 15

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<213> homo sapiens

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<400> 2

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1			5					10					15	

<210> 3

<211> 15

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<213> homo sapiens

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<223> Dsg3 15-mer peptide which binds to HLA-DRB1*04:02 and HLA-DQB1*05:03

<400> 3

Thr	Pro	Met	Phe	Leu	Leu	Ser	Arg	Asn	Thr	Gly	Glu	Val	Arg	Thr
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<400> 4

Cys	Glu	Cys	Asn	Ile	Lys	Val	Lys	Asp	Val	Asn	Asp	Asn	Phe	Pro
1				5					10					15

<210> 5

<211> 17

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<220>

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<222> (1)..(17)

<223> Dsg3 17-mer peptide which binds to HLA-DRB1*04:02 and HLA-DQB1*05:03

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Ile	Asn	Val	Arg	Glu	Gly	Ile	Ala	Phe	Arg	Pro	Ala	Ser	Lys	Thr	Phe
1				5					10					15	

Thr

<210> 6

<211> 17

<212> PRT

<213> homo sapiens

<220>

<221> core epitope

<222> (5)..(13)

<223> core epitope, region of the peptide that interacts with the binding groove of the HLA-DRβ1*04:02 molecule; the peptide region required for T cell activation.

<220>

<221> peptide T cell receptor binding site

<222> (5)..(8)

<223> peptide T cell receptor binding site at position 5 and position 8

<220>

<221> peptide HLA-DRB1*04:02 binding site

<222> (7)..(13)

<223> peptide HLA-DRB1*04:02 binding site at position 7, position 10, position 12, position 13

<400> 6

Ser Ser Pro Ser Val Val Val Ser Ala Arg Thr Leu Asn Asn Arg Tyr
 1 5 10 15

Thr

Organization Applicant

[0040]

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Application Project

[0041]

<120> Title : Peptide des Desmoglein3 bei Pemphigus vulgaris
 <130> AppFileReference : TM819
 <140> CurrentAppNumber : EP
 <141> CurrentFilingDate : 2014-07-21

Sequence

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Feature

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Sequence

[0044]

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[0045]

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Sequence

[0046]

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Feature

[0047]

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Sequence

[0048]

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Feature

[0049]

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sequence

[0050]

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<212> Type : PRT

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Feature

[0051]

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<222> LocationFrom : 1

<222> LocationTo : 17 Other Information : Dsg3 17-mer peptide which binds to HLA-DRB1*04:02 and HLA-DQB1*05:03 CDSJoin : No

Sequence

[0052]

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<400> PreSequenceString : SSPSVVVSAR TLNNRYT 17

<212> Type : PRT

<211> Length : 17 SequenceName : Dsg3 (aa505-521) SequenceDescription :

Feature

[0053]

Sequence: Dsg3 (aa505-521):

<221> FeatureKey : core epitope

<222> LocationFrom : 5

<222> LocationTo : 13 other Information : core epitope, region of the peptide that interacts with the binding groove of the HLA-DR β 1*04:02 molecule; the peptide region required for T cell activation. CDSJoin : No

Feature

[0054]

Sequence: Dsg3 (aa505-521):

<221> FeatureKey : peptide HLA-DRB1*04:02 binding site

<222> LocationFrom : 7

<222> LocationTo : 13 other Information : peptide HLA-DRB1*04:02 binding site at position 7, position 10, position 12, position 13 CDSJoin : No

Feature

[0055]

Sequence: Dsg3 (aa505-521):

<221> FeatureKey : peptide T cell receptor binding site

<222> LocationFrom : 5

<222> LocationTo : 8 other Information : peptide T cell receptor binding site at position 5 and position 8 CDSJoin : No

P A T E N T K R A V

1. Medicinsk præparat til anvendelse i pattedyr, især i mennesker, som lider af pemphigus vulgaris (PV), der omfatter mindst ét eller en kombination af peptiderne Seq-ID 1 – 5 af de immundominante CD4⁺-T-celleepitoper af det humane protein desmoglein-3 koblet til egnede bærere således at CD4⁺-T-celler aktiveres, **kendetegnet ved, at** de egnede bærere er nanopartikler eller mononukleære celler eller erythrocytter eller dendritiske celler og at disse peptider inducerer en antigenspecifik immuntolerance overfor desmoglein-3 i pattedyr, især i mennesker, hvor peptiderne Seq-ID 1 – 5 virker som nominele antigener og inducerer en immuntolerance i patienten.
2. Medicinsk præparat til anvendelse i hunde eller heste som lider af pemphigus vulgaris (PV), der omfatter mindst ét eller en kombination af peptiderne Seq-ID 1 – 5 af de immundominante CD4⁺-T-celleepitoper af hunde- eller hesteproteinet desmoglein-3 koblet til egnede bærere, **kendetegnet ved, at** de egnede bærere er nanopartikler eller mononukleære celler eller erythrocytter eller dendritiske celler og at disse peptider inducerer en antigenspecifik immuntolerance overfor desmoglein-3 i hunde eller heste, hvor peptiderne Seq-ID 1 – 5 virker som nominele antigener og inducerer en immuntolerance i patienten.
3. Medicinsk præparat ifølge krav 1 til anvendelse ved behandling af sygdommen pemphigus vulgaris (PV) i mennesker.
4. Medicinsk præparat ifølge krav 2 til anvendelse ved behandling af sygdommen pemphigus vulgaris (PV) i hunde eller heste.

Figur 1

