

selected from the group of retrovirus, adenovirus, lentivirus, herpes simplex virus, vaccinia, pox virus, and adeno-associated virus.

The terms "inhibit", "neutralize" or "block" as used herein, have to be understood as synonyms which mean reducing a molecule, a reaction, an interaction, a gene expression, an mRNA, and/or a protein's expression, stability, function or activity by a measurable amount or to prevent entirely. Inhibitors are compounds that, e.g., bind to, partially or totally block stimulation, decrease, prevent, delay activation, inactivate, desensitize, or down regulate a protein, a gene, and an mRNA stability, expression, function and activity, e.g., antagonists.

The term "antisense expression vector" refers to an expression vector, which encodes for single-stranded or double-stranded RNA that is complementary to a messenger RNA (mRNA) strand and which inhibits translation of said mRNA into amino acids. The term antisense RNA comprises asRNA, siRNA, shRNA, microRNA.

The term "gene therapy" as used herein means the use of DNA, e.g. an expression vector, as a pharmaceutical agent to treat a disease as disclosed herein.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides the use of an IL-18 inhibitor, or a composition comprising IL-18BP in the manufacture of a medicament for the treatment of an IL-18 associated disease or disorder in a subject suffering from such a disease or disorder, wherein the body fluids of said subject have been quantified to have abnormal levels of free IL-18, which exceed the level of free IL-18 in body fluids of a healthy control subject, using an assay capable of detecting free IL-18 in body fluids, said assay comprising IL-18BP and wherein said IL-18 inhibitor or composition comprises N-terminal and/or C-terminal deletion variants of IL-18BP in an amount of less than 40%, wherein said deletion variants comprise deletions of between 1 and 5 amino acid residues at the C-terminal end of the IL-18BP and/or between 1 and 30 amino acid residues at the N-terminal end of the IL-18BP and wherein IL-18BP is human IL-18BP selected from isoform a, b, c and d of human IL-18BP as shown in SEQ ID NO: 7, or SEQ ID NOs: 388-390 and wherein said IL-18 associated disease or disorder is one selected from the group consisting of chronic obstructive pulmonary disease (COPD), transfusion-related lung injury, bronchopulmonary dysplasia (BPD), acute respiratory distress syndrome (ARDS), Still's disease, adult Still's disease, juvenile Still's disease, juvenile rheumatoid arthritis (JRA), juvenile idiopathic arthritis (JIA), systemic onset juvenile idiopathic arthritis (SoJIA), systemic juvenile idiopathic arthritis (sJIA), interstitial lung disease (ILD), macrophage activation syndrome (MAS) including primary, secondary and recurrent MAS, hemophagocytic lymphohistiocytosis (HLH), familial (hereditary) hemophagocytic lymphohistiocytosis (FHLH) associated with gene defects in perforin, munc 13-4 and 18-2, synthaxin 11, immune deficiencies such as Chédiak-Higashi syndrome (CHS), Griscelli syndrome (GS), X-linked lymphoproliferative syndrome (XLP2), X-linked inhibitor of apoptosis protein deficiency (XIAP), acquired hemophagocytic lymphohistiocytosis associated with infectious conditions especially Herpes virus such as Epstein-Barr virus (EBV) and other pathogens, autoinflammatory syndrome associated with *NLR4* mutations, Giant Cell Arteritis (GCA), pyogenic arthritis, pyoderma

gangrenosum, and acne (PAPA), pulmonary sarcoidosis, heart failure, ischemic heart disease, dry eye disease (DED), keratitis, corneal ulcer and abrasion, iritis, glaucoma, Sjögren's syndrome, autoimmune uveitis, Behçet's disease, conjunctivitis, allergic conjunctivitis, diabetes type 2, solid organ and hematologic stem cell transplantation, ischemia reperfusion injury, familial Mediterranean fever (FMF), tumor necrosis factor receptor 1-associated periodic syndromes (TRAPS), hyper-IgD syndromes (mevalonate kinase gene mutation), gout, Schnitzler syndrome, Wegener's granulomatosis also called granulomatosis with polyangiitis (GPA), Hashimoto's thyroiditis, Crohn's disease, early onset inflammatory bowel disease (EOIBD), very EOIBD (VEOIBD), infantile IBD, neonatal IBD, ulcerative colitis and Blau syndrome (NOD-2 mutation).

In another aspect, the present invention provides use of IL-18BP, or a composition as defined the pending claim set in the manufacture of a medicament for the treatment of a pediatric autoinflammatory disease or condition, wherein the pediatric autoinflammatory disease or condition is a MAS-like pediatric disease or condition including primary, secondary and recurrent MAS and wherein the MAS-like pediatric disease or condition is an IL-18 associated, pediatric autoinflammatory disease or condition with severe systemic inflammation.

In yet another aspect, the present invention provides use of the IL-18 inhibitor or the composition as defined in the pending claim set in the manufacture of a medicament for the treatment of early onset severe pyogenic arthritis, pyoderma gangrenosum and acne (PAPA).

In yet another aspect, the present invention provides use of the IL-18 inhibitor or the composition as defined in the pending claim set in the manufacture of a medicament for the treatment of early onset inflammatory bowel disease (EOIBD), very EOIBD (VEOIBD), infantile IBD and neonatal IBD.

EMBODIMENTS

1. A composition comprising IL-18BP or an active fragment thereof for use in the treatment of an IL-18 associated disease or disorder in a subject suffering from such a disease or disorder, wherein the body fluids of said subject have been quantified to have abnormal levels of free IL-18, which exceed the level of free IL-18 in body fluids of a healthy control subject, particularly by 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more than 100%, using an assay capable of detecting free IL-18 in body fluids, said assay comprising IL-18BP or an antibody or a functional part thereof, which antibody or active part thereof binds to IL-18 at the binding site of IL-18BP or in the vicinity of the binding site of IL-18BP, but does not bind IL-18/IL-18BP complexes and wherein said composition is substantially free of N- terminal and/or C-terminal deletion variants of IL-18BP, which are present in an amount of less than 30%, particularly less than 20%, particularly less than 15%, particularly less than 10%, particularly less than 7.5%, particularly less than 5%, particularly less than 2.5%, particularly less than 1%, particularly less than 0.5%, particularly less than 0.25%, particularly less than 0.1%.

2. A composition comprising an IL-18 inhibitor or an active fragment thereof for use in the treatment of an IL-18 associated disease or disorder in a subject suffering from such a disease, wherein the body fluids of said subject have been quantified to have abnormal levels of free IL-18, which exceed the level of free IL-18 in body fluids of a healthy control subject, particularly by 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or

CLAIMS

1. Use of an IL-18 inhibitor, or a composition comprising IL-18BP in the manufacture of a medicament for the treatment of an IL-18 associated disease or disorder in a subject suffering from such a disease or disorder, wherein the body fluids of said subject have been quantified to have abnormal levels of free IL-18, which exceed the level of free IL-18 in body fluids of a healthy control subject, using an assay capable of detecting free IL-18 in body fluids, said assay comprising IL-18BP and wherein said IL-18 inhibitor or composition comprises N-terminal and/or C-terminal deletion variants of IL-18BP in an amount of less than 40%, wherein said deletion variants comprise deletions of between 1 and 5 amino acid residues at the C-terminal end of the IL-18BP and/or between 1 and 30 amino acid residues at the N-terminal end of the IL-18BP and wherein IL-18BP is human IL-18BP selected from isoform a, b, c and d of human IL-18BP as shown in SEQ ID NO: 7, or SEQ ID NOs: 388-390 and wherein said IL-18 associated disease or disorder is one selected from the group consisting of chronic obstructive pulmonary disease (COPD), transfusion-related lung injury, bronchopulmonary dysplasia (BPD), acute respiratory distress syndrome (ARDS), Still's disease, adult Still's disease, juvenile Still's disease, juvenile rheumatoid arthritis (JRA), juvenile idiopathic arthritis (JIA), systemic onset juvenile idiopathic arthritis (SoJIA), systemic juvenile idiopathic arthritis (sJIA), interstitial lung disease (ILD), macrophage activation syndrome (MAS) including primary, secondary and recurrent MAS, hemophagocytic lymphohistiocytosis (HLH), familial (hereditary) hemophagocytic lymphohistiocytosis (FHLH) associated with gene defects in perforin, munc 13-4 and 18-2, syntaxin 11, immune deficiencies such as Chédiak-Higashi syndrome (CHS), Griscelli syndrome (GS), X-linked lymphoproliferative syndrome (XLP2), X-linked inhibitor of apoptosis protein deficiency (XIAP), acquired hemophagocytic lymphohistiocytosis associated with infectious conditions especially Herpes virus such as Epstein-Barr virus (EBV) and other pathogens, autoinflammatory syndrome associated with *NLR4* mutations, Giant Cell Arteritis (GCA), pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA), pulmonary sarcoidosis, heart failure, ischemic heart disease, dry eye disease (DED), keratitis, corneal ulcer and abrasion, iritis, glaucoma, Sjögren's syndrome, autoimmune uveitis, Behçet's disease, conjunctivitis, allergic conjunctivitis, diabetes type 2, solid organ and hematologic stem cell transplantation, ischemia reperfusion injury, familial Mediterranean fever (FMF), tumor necrosis factor receptor 1-associated periodic syndromes (TRAPS), hyper-IgD syndromes (mevalonate kinase gene mutation), gout, Schnitzler syndrome, Wegener's granulomatosis also called granulomatosis with polyangitis (GPA), Hashimoto's thyroiditis, Crohn's disease, early onset inflammatory bowel disease (EOIBD), very

EOIBD (VEOIBD), infantile IBD, neonatal IBD, ulcerative colitis and Blau syndrome (NOD-2 mutation).

2. The use according to claim 1, wherein the level of free IL-18 in the body fluids has been determined to be ≥ 5 pg/mL as compared to ≤ 4 pg/mL in the healthy control.
3. The use according to claim 1 or 2, wherein the proportion of the deletion variants in the composition is less than 30%.
4. The use according to any one of claims 1-3, wherein the assay for quantifying the level of free IL-18 in the body fluids includes the steps of:
 - a) bringing a sample of body fluid suspected to contain free IL-18 into contact with IL-18BP which functions as the capturing molecule for free IL-18;
 - b) allowing the IL-18BP to bind to free IL-18;
 - c) detecting the binding of the IL-18BP and determining the amount of free IL-18 in the sample.
5. Use of IL-18BP, or a composition as defined in any one of claims 1-4 in the manufacture of a medicament for the treatment of a pediatric autoinflammatory disease or condition, wherein the pediatric autoinflammatory disease or condition is a MAS-like pediatric disease or condition including primary, secondary and recurrent MAS and wherein the MAS-like pediatric disease or condition is an IL-18 associated, pediatric autoinflammatory disease or condition with severe systemic inflammation.
6. The use according to claim 5, wherein said autoinflammatory disease or condition with severe systemic inflammation is caused by NLRC4 mutation.
7. The use according to claim 5, wherein said autoinflammatory disease or condition with severe systemic inflammation is associated with XIAP deficiency.
8. The use according to claim 7, wherein said XIAP deficiency is caused by mutation in XIAP/BIRC4.
9. The use according to claim 7 or claim 8, for the treatment of X-linked inhibitor of apoptosis protein deficiency (XIAP) and/or X-linked lymphoproliferative syndrome 2 (XLP2), particularly when caused by mutations in XIAP/BIRC4.
10. The use according to claim 9, for the treatment of severe early onset hemophagocytic lymphohistiocytosis/MAS (HLH/MAS) associated with a monogenic XIAP deficiency caused by mutations of XIAP/BIRC4.

11. The use according to claim 10, for the treatment of enterocolitis, particularly of Crohn's-like enterocolitis, caused by or associated with XIAP deficiency.
12. The use according to any one of claims 7 to 11, for reducing susceptibility to viral infections, particularly EBV and/or cytomegalovirus (CMV) infections, in patients suffering from XIAP deficiency before viral infection has occurred or after virus clearance through treatment with an antiviral agent.
13. The use according to any one of claims 5-12, wherein said autoinflammatory disease or condition with severe systemic inflammation is accompanied with high levels of IL-18 and free IL-18.
14. Use of the IL-18 inhibitor or the composition as defined in any one of claims 1-4 in the manufacture of a medicament for the treatment of early onset severe pyogenic arthritis, pyoderma gangrenosum and acne (PAPA).
15. Use of the IL-18 inhibitor or the composition as defined in any one of claims 1-4 in the manufacture of a medicament for the treatment of early onset inflammatory bowel disease (EOIBD), very EOIBD (VEOIBD), infantile IBD and neonatal IBD.
16. The use according to any one of claims 1-15, wherein the subject to be treated has been exposed to one or more compounds selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDs), Prednisone; synthetic Disease-modifying anti-rheumatic drugs (sDMARDs), immunosuppressors and biologic immunosuppressors, but has not shown a response to treatment or an incomplete response to treatment, particularly to non-steroidal anti-inflammatory drugs (NSAIDs), and Prednisone, at a dose of at least 5mg/day for ≥ 1 month, and/or to synthetic Disease-modifying anti-rheumatic drugs (sDMARDs) at a dose of at least 10mg/day for ≥ 3 months.
17. The use according to any one of claims 1-16, wherein said IL-18 inhibitor or composition is to be administered to a subject in need thereof in multiple doses/day, in multiple doses/week or in multiple doses/month.
18. The use according to any one of the claims 1-17, wherein said IL-18 inhibitor or composition is to be administered in one dose per week, in two doses per week, three doses per week, four doses per week.
19. The use according to any one of claims 1-18, wherein said IL-18 inhibitor or composition is to be administered every 24 h to 48 h.
20. The use according to any one of claims 1-19, wherein a single dose comprises between 0.5 mg and 600 mg IL-18BP.

21. The use according to claim 20, wherein a single dose comprises between 0.5 mg of IL-18 inhibitor/kg body weight and 10 mg IL-18 inhibitor /kg body weight.
22. The use according to any one of claims 1-21, wherein a single dose of between 0.5 mg IL-18 inhibitor /kg body weight and 5 mg IL-18 inhibitor /kg body weight is to be administered every 24 or 48 h.
23. The use according to claim 1, wherein the Adult Still's disease treatment is to be continued at least until the treated subject shows a therapeutic response characterized by
 - (a) Normalization of body temperature (Normal range between 36.3 and 37.4°C measured in the armpit, in the absence of NSAIDs 24h prior to measurement
 - (b) Improvement in joint swelling and tenderness ($\geq 20\%$) and,
 - (c) Decrease of CRP $\geq 70\%$ or normalization of CRP and ferritin to reference values.