CLAIMS

1. Use of ~~An~~ an IL-18 inhibitor in the manufacture of a medicament for ~~for use in the treatment of~~treating an IL-18 associated disease or disorder in a population of subjects diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in body samples, particularly in body fluids, compared to the levels in body fluids of a healthy control subject.

2. The ~~IL-18 inhibitor for~~ use according to claim 1, wherein said abnormal level of free IL-18 in the body fluids exceeds the level in body fluids of a healthy control subject by 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more than 100%.

3. The ~~IL-18 inhibitor for~~ use ~~in~~ of any one of the preceding claims, wherein the subject to be treated belongs to a group of subjects which have been determined to have elevated levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP (IL-18BP) in 18BP in body samples, particularly in a sample selected from the group consisting of broncho-alveolar lavage fluid (BALF) circulation fluids, secretion fluids, biopsy and homogenized tissue, particularly serum, urine, tear, saliva, bile, sweat, exhalation, expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa, and tissue secretion compared to the levels in the body fluids of a healthy subject.

4. The ~~IL-18 inhibitor for~~ use ~~in~~ of claims 2 or 3, wherein said elevated levels of free IL-18 in serum are ≥5 pg/mL and, particularly, up to 10000 pg/mL, whereas the amount of free IL-18 in serum of healthy subject, particularly a healthy human is ≤4 pg/mL.

5. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, 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), Adult Still's disease, juvenile Still's disease, interstitial lung disease (ILD), idiopathic pulmonary fibrosis, cystic fibrosis, pulmonary arterial hypertension, asthma, bronchiectasis, heart failure, amyotrophic lateral sclerosis (ALS), dry eye disease (DED), keratitis, corneal ulcer and abrasion, corneal neovascularization, pathological intraocular neovascularization, iritis, glaucoma, macular degeneration, Sjögren's syndrome, autoimmune uveitis, Behçet's disease, conjunctivitis, allergic conjunctivitis,

dermatitis of eyelid, diabetes type 2, non-alcoholic fatty liver disease (NAFLD), steato hepatitis, solid organ and hematologic transplantation, ischemia reperfusion injury, familial Mediterranean fever, tumor necrosis factor receptor 1-associated periodic syndromes, cryopyrin-associated periodic fever syndromes, hyper-IgD syndromes, gout, Schnitzler syndrome, Wegener's granulomatosis also called granulomatosis with polyangitis (GPA), Hashimoto's thyroiditis, Crohn's disease, ulcerative colitis, immunoglobulin-4 (IgG4)-related diseases and stem cell therapies.

6. The IL-18 inhibitor for use according to any one of the preceding claims, wherein said IL-18 associated disease or disorder is induced by smoking or second-hand smoke exposure, in particular tobacco smoke exposure.

7. The IL-18 inhibitor for use according to any one of the preceding claims, wherein said IL-18 associated disease or disorder is induced by viral infection.

8. The IL-18 inhibitor for use according to any one of the preceding claims, wherein said IL-18 associated disease or disorder is an IL-18 induced systemic manifestation of inflammation and associated comorbidities selected from the group consisting of emphysema, tissue inflammation, tissue destruction, lung resection, disappearance of the vasculature, apoptosis of endothelial cells, mucos metaplasia, cardiac hypertrophy, decrease of VEGF in the lung tissue, pulmonary vessel loss, vessel muscularization,, vascular remodeling, collagen deposition, aberrant elastin layers in the lung, fibrotic airway remodeling, airspace enlargement, chronic remodeling of the airways and pulmonary vessels and decreased pulmonary function.

9. The IL-18 inhibitor for use according to any one of the preceding claims, wherein treatment comprises prevention, halting, alleviation or reversion of symptoms associated with said disease or disorder.

10. The IL-18 inhibitor for use according to any one of the preceding claims, wherein IL-18 binding is restricted or inhibited, particularly binding of free IL-18 to IL-18R.

11. The IL-18 inhibitor for use according to claim 10, wherein binding of free IL-18 to IL-18Rα is restricted or inhibited.

12. The IL-18 inhibitor for use according to any one of the preceding claims, wherein IL-18-dependent downstream signaling pathways are modified, particularly inhibited.

13. The IL-18 inhibitor for use according to any one of the preceding claims, wherein increased expression of IFNγ, IL-13 or IL-17A is modified, particularly inhibited, compared to untreated subjects suffering from said disease or disorder.

14. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 inhibitor compensates the IL-18/IL-18BP imbalance by trapping and neutralizing the excess of free IL-18 in tissue and circulation.

15. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 inhibitor inhibits infiltration of neutrophils into the lung, particularly through mitigation of G-CSF release in the lung airways.

16. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for ~~the treatment of~~treating chronic obstructive pulmonary disease (COPD), heart disease, amyotrophic lateral sclerosis (ALS), dry eye disease and/or diabetes type II.

17. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for ~~the treatment of~~treating chronic obstructive pulmonary disease (COPD).

18. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for treating~~the treatment of~~ heart disease.

19. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for treating~~the treatment of~~ amyotrophic lateral sclerosis (ALS).

20. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for treating~~the treatment of~~ dry eye disease.

21. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims for treating~~the treatment of~~ diabetes type II.

22. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein said disease or disorder is induced by smoking or second-hand smoke exposure, in particular tobacco smoke exposure.

23. The ~~IL-18 inhibitor of for~~ use according to any one of the preceding claims, wherein said disease or disorder is induced by viral infection.

24. The ~~IL- IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein said disease or disorder is an IL-18 induced systemic manifestation of inflammation and associated comorbidities selected from the group consisting of emphysema, tissue inflammation, tissue destruction, lung resection, disappearance of the vasculature, mucos metaplasia, cardiac hypertrophy, decrease of VEGF in the lung tissue, pulmonary vessel loss, vessel muscularization, collagen deposition, aberrant elastin layers in the lung, fibrotic airway remodeling, airspace enlargement, chronic remodeling of the airways and pulmonary vessels and decreased pulmonary function.

25. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein IL-18 binding is restricted or inhibited, particularly binding of free IL-18 to IL-18R, but especially free IL-18 binding to IL-18Rα.

26. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 inhibitor reduces binding of IL-18 to IL-18 receptor, particularly binding to IL-18Rα by at least 5%, particularly by at least 10%, particularly by at least 15%, particularly by at least 20%, particularly by at least 25%, particularly by at least 30%, particularly by at least 40%, particularly by at least 45%, particularly by at least 50%, particularly by at least 55%, particularly by at least 60%, particularly by at least 65%, particularly by at least 70, particularly by at least 75, particularly by at least 80, particularly by at least 85%, particularly by at least 90%, particularly by at least 95%, particularly by 100%.

27. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 inhibitor neutralizes free IL-18 by restricting or preventing IL-18 binding to IL-18 receptor (IL-18R), especially free IL-18 binding to IL-18Rα.

28. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the inhibitor is an IL-18 binding molecule, particularly an IL-18 binding molecule specifically binding free IL-18, particularly an IL-18 binding molecule which prevents binding of free IL-18 to IL-18 receptor, especially free IL-18 binding to IL-18Rα.

29. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 binding molecule is IL-18BP, particularly human IL-18BP (hIL-18BP), particularly IL-18BP including any functional equivalents or parts thereof, particularly an IL-18BP as shown in SEQ ID NO: 7.

30. The ~~IL-18 inhibitor~~use of claim 28 or 29 ~~for use according to any one of the preceding claims~~, ~~which~~ wherein the IL-18 inhibitor is a full-length protein or a mutein, functional derivative, functional fragment, biologically active peptide, fraction, circularly permuted derivative, fused protein, isoform or a salt thereof.

31. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein the IL-18 binding molecule is an antibody including any functionally equivalent antibody or parts thereof, particularly an antibody specific for free IL-18, particularly an antagonistic antibody, which prevents binding of free IL-18 to IL-18 receptor, especially free IL-18 binding to IL-18Rα.

32. The ~~IL-18 inhibitor~~use of claim 31 ~~or 32 for use according to any one of the preceding claims~~, wherein the IL-18 specific antibody including any functionally equivalent

antibody or parts thereof binds to IL-18 at the binding site of IL-18BP or in the vicinity of the binding site of IL-18BP, but not IL-18/IL-18BP complexes.

33. The ~~IL-18 inhibitor~~ use of claim 31 or 32 ~~for use according to any one of the preceding claims~~, wherein the IL-18 specific antibody including any functionally equivalent antibody or parts thereof is a monoclonal antibody or a polyclonal antibody.

34. The ~~IL-18 inhibitor~~use of claim 31 or 32 for use according to any one of the preceding claims, wherein the IL-18 specific antibody including any functionally equivalent antibody or parts thereof is a chimeric, single chain, bispecific, simianized, human and humanized antibody.

35. The ~~IL-18 inhibitor~~use of any one of claims 31-34 ~~for use according to any one of the preceding claims~~, wherein the IL-18 specific antibody including any functionally equivalent antibody or parts thereof binds to human IL-18.

36. The ~~IL-18 inhibitor for~~ use according to any one of the preceding claims, wherein said abnormal levels of free IL-18 in body samples, particularly in body fluids, have been determined by use of an IL-18 binding molecule as defined in any one of claims 28-35.

37. A pharmaceutical composition for use in the treatment of an IL-18 associated disease or disorder in a population of subjects diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in the body fluids compared to the levels in body fluids of a healthy control subject or having a predisposition to develop such a disease or disorder as defined in any one of claims 1-27, wherein said composition comprises the IL-18 inhibitor as defined in any one of the preceding claims, particularly the IL-18 inhibitor as defined in claims 28-35, particularly in a prophylactically and/or therapeutically effective amount.

38. The pharmaceutical composition of claim 37 for use in the treatment of the disease or disorder as defined in any one of claims 1-27, wherein said composition comprises the IL-18 inhibitor as defined in any one of claims 29 and 30, particularly in a prophylactically and/or therapeutically effective amount.

39. The pharmaceutical composition of claim 36 for use in the treatment of the disease or disorder as defined in any one of claims 1-27, wherein said composition comprises the IL-18 inhibitor as defined in any one of claims 31-35, particularly in a prophylactically and/or therapeutically effective amount.

40. The pharmaceutical composition of any one of claims 37-39 for use in the treatment of the disease or disorder as defined in any one of claims 1-27, wherein said composition optionally further provides another inhibitor of a pro-inflammatory cytokine or functional

fragment thereof, or a regulatory factor, which induces in-situ expression of said inhibitor of pro-inflammatory cytokine or functional fragment thereof, co-therapeutic agents such as anti-inflammatory, bronchodilatory, antihistamine, decongestant or anti-tussive drug substances.

41. The pharmaceutical composition of any one of claims 37-40 for use in the treatment of the disease or disorder as defined in any one of claims 1-27, comprising a pharmaceutically acceptable carrier and/or excipient.

42. An expression vector comprising a coding sequence of the IL-18 inhibitor according to any one of claims 28-35, which upon administration to a subject suffering from a disease or disorder or having a predisposition to develop such a disease or disorder as defined in the preceding claims leads to in situ expression of IL-18 inhibitor for use in the treatment of the disease or disorder as defined in any one of claims 1-27.

43. The expression vector of claim 42 for use in the treatment of the disease or disorder as defined in any one of claims 1-27, wherein said expression vector is administered to a subject suffering from such a disease or disorder, or having a predisposition to develop such a disease or disorder, alone or in combination with the IL-18 inhibitor according to any one of claims 28-35, or the pharmaceutical composition according to any one of claims 37-41.

44. The expression vector of any one of claims 42-43 comprising the coding sequence of IL-18BP according to claims 29-30, which upon administration to a subject suffering from a disease or disorder or having a predisposition to develop such a disease or disorder as defined in the preceding claims, leads to in situ expression of IL-18BP for use in the treatment of the disease or disorder as defined in any one of claims 1-27.

45. The ~~IL-18 inhibitor~~ use of any one of claims 28-35, the pharmaceutical composition of any one of claims 37-41, or the expression vector of any one of claims 42-44 for use according to any one of claims 1-27, comprising administering to a subject in need thereof a prophylactically and/or therapeutically effective amount of said IL-18 inhibitor, IL-18BP, pharmaceutical composition, or expression vector, particularly by systemic, intranasal, buccal, oral, transmucosal, intratracheal, intravenous, subcutaneous, intraurinary tract, intravaginal, sublingual, intrabronchial, intrapulmonary, transdermal or intramuscular administration, in particular broncho-pulmonary administration.

46. The ~~IL-18 inhibitor~~use, the pharmaceutical composition or the expression vector for use according to claim 45, wherein said subject is a mammal, particularly said subject is a human.

47. Use of the IL-18 inhibitor as defined in any one of claims 28-35, the pharmaceutical composition of any one of claims 37-41, or the expression vector of any one of claims 42-44 in the manufacture of a medicament ~~A method~~ for treating an IL-18 associated disease or disorder in a population of subjects diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in the body fluids compared to the levels in body fluids of a healthy control subject, or having a predisposition to develop such a disease or disorder, comprising administering to said subject a therapeutically or prophylactically effective amount of the IL-18 inhibitor as defined in any one of claims 28-35, the pharmaceutical composition of any one of claims 37-41, or the expression vector of any one of claims 42-44, particularly by systemic, intranasal, buccal, oral, transmucosal, intratracheal, intravenous, subcutaneous, intraurinary tract, intravaginal, sublingual, intrabronchial, intrapulmonary, transdermal or intramuscular administration, in particular broncho-pulmonary administration.

48. A method of determining the amount of free IL-18 in a sample obtained from a subject ~~or *in situ*~~ comprising detecting the specific binding of the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35 to free IL-18 protein in the sample or *in situ* which includes the steps of:
    a) bringing a sample obtained from a subject~~or a specific body part or body area~~ suspected to contain free IL-18 into contact with of the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35, which specifically binds to free IL-18, but not to IL-18 bound in a complex and functions as the capturing molecule for free IL-18;
    b) allowing the IL- the IL-18 binding molecule, the 18BP or the antibody to bind to free IL-18;
    c) detecting the binding of IL-18 to the IL- the IL-18 binding molecule, 18BP or the antibody and determining the amount of free IL-18 in the sample.

49. A method of diagnosing an IL-18 associated disease or disorder, particularly an IL-18 associated disease or disorder as defined in any one of claims 1-27 in a patient comprising detecting the specific binding of the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35 to free IL-18 protein in a sample obtained from the patient~~or *in situ*~~ which includes the steps of:
    a) bringing a sample obtained from the patient ~~or a specific body part or body area~~ suspected to contain free IL-18 into contact with the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody

as defined in any one of claims 31-35, which specifically binds to free IL-18, but not to IL-18 bound in a complex and functions as the capturing molecule for free IL-18;

b) allowing the IL-18 binding molecule, IL-18BP or the antibody to bind to free IL-18;

c) detecting the binding of IL-18 to the IL-18 binding molecule, IL-18BP or the antibody and determining the amount of free IL-18 in the sample;

d) comparing the amount of free IL-18 in the sample of the subject suffering from the diseases or disorder as defined in any one of claims 1-27 to the amount in the sample of a healthy subject.

50. A method for diagnosing a predisposition to an IL-18 associated disease or disorder, particularly an IL-18 associated disease or disorder as defined in any one of claims 1-27 in a patient comprising detecting the specific binding of IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35 to free IL-18 protein in a sample obtained from the patient~~or *in situ*~~ which includes the steps of:

a) bringing a sample obtained from the patient~~or a specific body part or body area~~ suspected to contain free IL-18 into contact with the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35, which specifically binds to free IL-18, but not to IL-18 bound in a complex and functions as the capturing molecule for free IL-18;

b) allowing the IL-18 binding molecule, IL-18BP or the antibody to bind to free IL-18;

c) detecting the binding of IL-18 to the IL-18 binding molecule, IL-18BP or the antibody and determining the amount of free IL-18 in the sample;

d) comparing the amount of free IL-18 in the sample of the patient suffering from the diseases or disorder as defined in any one of claims 1-27 to the amount in the sample of a healthy patient;

wherein an increase in the amount of said free-IL-18 in the sample compared to a normal control value obtained from a healthy patient indicates that said patient is suffering from or is at risk of developing a disease or disorder as defined in any one of claims 1-27.

51. A method for monitoring minimal residual disease in a patient following treatment with the IL-18 inhibitor as defined in any one of claims 28-35, the pharmaceutical composition of any one of claims 37-41, or the expression vector of any one of claims 42-44, wherein said method comprises:

a) bringing a sample obtained from the patient ~~or a specific body part or body area~~ suspected to contain free IL-18 into contact with the IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35, which specifically binds to free IL-18, but not to IL-18 bound in a complex and functions as the capturing molecule for free IL-18;

b) allowing the IL-18 binding molecule, IL-18BP or the antibody to bind to free IL-18;

c) detecting the binding of IL-18 to the IL-18 binding molecule, IL-18BP or the antibody and determining the amount of free IL-18 in the sample;

d) comparing the amount of free IL-18 in the sample of the patient suffering from the diseases or disorder as defined in any one of claims 1-27 to the amount in the sample of a healthy patient;

wherein an increase in the amount of said free-IL-18 in the sample compared to a normal control value obtained from a healthy patient indicates that said patient is still suffering from a minimal residual disease.

52. A method for predicting responsiveness of a patient to a treatment with the IL-18 inhibitor of any one of claims 28-35, the pharmaceutical composition of any one of claims 37-41, or the expression vector of any one of claims 42-44, wherein said method comprises:

a) bringing a sample obtained from the patient ~~or a specific body part or body area~~ suspected to contain free IL-18 into contact with IL-18 binding molecule as defined in claim 28, particularly the IL-18BP as defined in any one of claims 29-30 or the antibody as defined in any one of claims 31-35, which specifically binds to free IL-18, but not to IL-18 bound in a complex and functions as the capturing molecule for free IL-18;

b) allowing the IL-18 binding molecule, IL-18BP or the antibody to bind to free IL-18;

c) detecting the binding of IL-18 to the IL-18 binding molecule, IL-18BP or the antibody and determining the amount of free IL-18 in the sample;