SUMMARY

In one aspect, the present invention refers to an *in vitro* method of determining the amount of free IL-18 in a sample obtained from a subject comprising detecting the specific binding of an IL-18 binding protein (IL-18BP) to free IL-18 protein in the sample which includes the steps of:

a) bringing a sample suspected to contain free IL-18 into contact with the IL-18BP 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-18BP to bind to free IL-18;

c) detecting the binding of IL-18 to the IL-18BP and determining the amount of free IL-18 in the sample using a detection assay.

In another aspect, the present invention refers to use of an IL-18 inhibitor in the manufacture of a pharmaceutical composition for treating an IL-18 associated disease or disorder in a subject diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in a sample obtained from the subject, compared to the levels in body fluids of a healthy control subject, wherein said abnormal level of free IL-18 in the body fluids:

a) 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%; and

b) 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,

wherein the subject diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in the sample, compared to the levels in body fluids of a healthy control subject has been determined using the method of the present invention; wherein said IL-18 associated disease or disorder is:

a) 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, 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, and ulcerative colitis;

b) induced by viral infection;

and/or

c) 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, mucous 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 and wherein treatment comprises prevention, halting, alleviation or reversion of symptoms associated with said disease or disorder. In yet another aspect, the present invention refers to a diagnostic kit for detecting free IL-18, comprising the IL-18 binding protein (IL-18BP) as defined in the present invention as the capturing molecule, and a second IL-18 specific binding molecule as the detection molecule and, optionally, a second IL-18 specific capturing molecule, wherein the detection molecule binds to different sites of IL-18 than the capturing molecule. In still another aspect, the present invention refers to the use of the diagnostic kit of the present invention.

In another aspect, the present invention refers to the use of a diagnostic kit for detecting free IL-18 in the method as described herein, wherein the diagnostic kit comprises the IL-18 binding protein (IL-18BP) as defined herein as the capturing molecule, and a second IL-18 specific binding molecule as the detection molecule, wherein the detection molecule binds to different sites of IL-18 than the capturing molecule.

DETAILED DESCRIPTION

The present invention now provides such detection means in form of an IL-18 binding molecule, particularly an IL-18 binding protein (IL-18BP) or an antibody, which specifically

binds to free IL-18, but not to IL-18 bound in a complex. Therefore, the present invention satisfies the need for an adequate means for the detection of free IL-18 and for diagnosis of diseases or disorders, which are associated with free IL-18 in the body fluids.

This opens the door for an efficient personalized medicine approach. In particular, it is now for the first time possible to identify the population of patients that are suffering from diseases or disorders, which are associated with free IL-18 in the body tissues, but particularly in the body fluids and to effectively treat said patients by administration of binding molecules which specifically bind free-IL18.

The present invention thus further provides effective therapeutic means for the treatment and prevention of IL-18 associated diseases or disorders in the population of patients that are suffering from diseases or disorders, which are associated with free IL-18 in the body tissues, but particularly in the body fluids. The present invention also satisfies the need for an effective treatment of diseases or disorders, which are associated with free IL-18 in the body tissues, particularly in the body fluids by providing IL-18 binding molecules, particularly (1) IL-18BP, and/or (2) antibodies, which are specific for free IL-18 and do not cross-react with IL-18 bound in a complex.

The IL-18 binding molecules, but particularly the IL-18BP and the IL-18 specific antibodies according to the present invention are able to reduce and/or abrogate the binding of free IL-18 to its receptor and to provide therapeutic benefits to patient suffering from an IL-18 associated disease or disorder.

Recent non-clinical and clinical investigations have defined a prominent role of the pro-inflammatory cytokine Interleukin 18 (IL-18) in the pathogenesis of Chronic Obstructive Pulmonary Disease, and suggest that IL-18 acts as the master regulator of destructive and remodeling processes.

Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive lung disease (COLD), chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD), is the occurrence of chronic bronchitis or emphysema, a pair of commonly co-existing diseases of the lungs in which the airways narrow over time. This leads to a limited airflow to and from the lung, which is considered as not fully reversible, but becomes rather becomes progressively worse over time. Smoking is responsible for 90% of COPD in the Europe and in the United States. Although not all tobacco smokers will develop COPD, it is estimated that 20% will. Smokers with COPD have higher death rates than nonsmokers with COPD. They also have more

CLAIMS

1. An *in vitro* method of determining the amount of free IL-18 in a sample obtained from a subject comprising detecting the specific binding of an IL-18 binding protein (IL-18BP) to free IL-18 protein in the sample which includes the steps of:

   a) bringing a sample suspected to contain free IL-18 into contact with the IL-18BP 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-18BP to bind to free IL-18;

   c) detecting the binding of IL-18 to the IL-18BP and determining the amount of free IL-18 in the sample using a detection assay.

2. The method of claim 1, wherein the detection assay comprises a detection molecule, which binds to different sites of IL-18 than the capturing molecule.

3. Use of an IL-18 inhibitor in the manufacture of a pharmaceutical composition for treating an IL-18 associated disease or disorder in a subject diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in a sample obtained from the subject, compared to the levels in body fluids of a healthy control subject, wherein said abnormal level of free IL-18 in the body fluids:

   a) 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%; and

   b) 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,

   wherein the subject diagnosed of having abnormal levels of free IL-18 and/or an abnormal ratio of free IL-18/IL-18BP in the sample, compared to the levels in body fluids of a healthy control subject has been determined using the method of claim 1;

   wherein said IL-18 associated disease or disorder is:

   a) 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, 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, and ulcerative colitis;

b) induced by viral infection;

and/or

c) 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, mucous 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 and wherein treatment comprises prevention, halting, alleviation or reversion of symptoms associated with said disease or disorder.

4. The use of claim 3, wherein the IL-18 inhibitor is IL-18BP.

5. The method of claim 1 or 2 or the use of claim 3, wherein IL-18BP is human IL-18BP (hIL-18BP).

6. The method of claim 1 or 2 or the use of claim 3, wherein IL-18BP is an IL-18BP as shown in SEQ ID NO: 7, or a functional fragment, biologically active peptide, fraction, fused protein, isoform or a salt thereof.

7. The use of claim 3, wherein the IL-18 inhibitor is an antibody including any functionally equivalent antibody or parts thereof.

8. The use of claim 7, wherein the antibody is an antibody specific for free IL-18.

9. The use of claim 8, wherein the antibody specific for free IL-18 is an antagonistic antibody which prevents binding of free IL-18 to IL-18 receptor (IL-18R).

10. The use of claim 9, wherein the antagonistic antibody which prevents binding of free IL-18 to IL-18 receptor (IL-18R) prevents binding either to IL-18Rα, IL-18Rβ or both.

11. The use of claim 8, wherein the antibody specific for free IL-18 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.

12. The use of any one of claims 3 to 11, 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 in a sample obtained from the subject compared to the levels in the body fluids of a healthy subject, wherein the sample is selected from the group consisting of broncho-alveolar lavage fluid (BALF) circulation fluids, secretion fluids, biopsy and homogenized tissue, particularly serum, plasma, urine, tear, saliva, bile, sweat, exhalation, expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa, and tissue secretion.

13. The use of any one of claims 3 to 12, wherein said pharmaceutical compositions further comprises 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, or anti-tussive drug substances.

14. The use of claim 3, wherein said IL-18 inhibitor is an antibody or part thereof that specifically binds to a single epitope, a combination of two epitopes or a combination of 3 epitopes, which epitope is:

a) comprised in a sequence selected from a group of sequences depicted in SEQ ID NO:1, SEQ ID NO: 2 and SEQ ID NO: 3; and/or

b) has a sequence which has 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% sequence identity to a sequence selected from a group of sequences depicted in SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6; and/or

c) is selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.

15. The use of claim 14, wherein said antibody or parts thereof:

a) specifically binds to a single epitope, a combination of two epitopes or a combination of 3 epitopes comprised in a sequence selected from a group of sequences depicted in SEQ ID NO:1, SEQ ID NO: 2 and SEQ ID NO: 3*;* and/or

b) specifically binds to an epitope, which has a sequence identity of 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% to the sequence depicted in SEQ ID NO: 4, SEQ ID NO:5 or SEQ ID NO: 6*;* and

c) specifically binds to IL-18 at the binding site of IL-18BP or in the vicinity of the binding site of IL-18BP; and

d) specifically binds to free IL-18 protein, but not IL-18/IL-18BP complexes; and

e) sterically hinders the binding of IL-18BP to IL-18; and

f) reduces binding of IL-18 to IL-18 receptor (IL-18R), particularly binding to either IL-18Rα, IL-18Rβ or both 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%.

16. The use according to claim 14 or 15, wherein said antibody including any functionally equivalent antibody or parts thereof or an antigen-binding portion thereof comprises:

a. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 9, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 10, respectively, including variants thereof; or

b. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 12, respectively, including variants thereof; or

c. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 13, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 14, respectively, including variants thereof; or

d. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO:

15, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 16, respectively, including variants thereof; or

e. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 15, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 17, respectively, including variants thereof; or

f. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 18, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 19, respectively, including variants thereof; or

g. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 20, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 22, respectively, including variants thereof; or

h. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 21, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 22, respectively, including variants thereof; or

i. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 23, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 24, respectively, including variants thereof; or

j. all three complementarity determining regions (CDRs) of the heavy chain variable region as shown in SEQ ID NO: 25, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region as shown in SEQ ID NO: 26, respectively, including variants thereof; or

k. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 107C6 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 107C6 as shown in Figure 11, respectively, including variants thereof; or

l. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 108F8 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 108F8 as shown in Figure 11, respectively, including variants thereof; or

m. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 109A6 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 109A6 as shown in Figure 11, respectively, including variants thereof; or

n. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 111A6 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 111A6 as shown in Figure 11, respectively, including variants thereof; or

o. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 131B4 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light

chain variable region antibody 131B4 as shown in Figure 11, respectively, including variants thereof; or

p. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 131E8 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 131E8 as shown in Figure 11, respectively, including variants thereof; or

q. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 131H1 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 131H1 as shown in Figure 11, respectively, including variants thereof; or

r. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 132H4 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 132H4 as shown in Figure 11, respectively, including variants thereof; or

s. all three complementarity determining regions (CDRs) of the heavy chain variable region of antibody 133A6 as shown in Figure 11, respectively, and all three complementarity determining regions (CDRs) of the light chain variable region antibody 133A6 as shown in Figure 11, respectively, including variants thereof;

wherein said antibody, equivalent antibody or antigen-binding portion thereof binds free IL-18 protein, particularly 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.

17. The use of claim 16, wherein said antibody comprises:

a. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 27, SEQ ID NO: 28, and SEQ ID NO: 29, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region

having the sequence as shown in SEQ ID NO: 30, SEQ ID NO: 31, and SEQ ID NO: 32, respectively; or

b. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 33, SEQ ID NO: 34, and SEQ ID NO: 35, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 36, SEQ ID NO: 37, and SEQ ID NO: 38, respectively; or

c. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 39, SEQ ID NO: 40, and SEQ ID NO: 41, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 42, SEQ ID NO: 43, and SEQ ID NO: 44, respectively; or

d. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 48, SEQ ID NO: 49, and SEQ ID NO: 50, respectively; or

e. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 45, SEQ ID NO: 46, and SEQ ID NO: 47, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 51, SEQ ID NO: 52, and SEQ ID NO: 53, respectively; or

f. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 54, SEQ ID NO: 55, and SEQ ID NO: 56, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 57, SEQ ID NO: 58, and SEQ ID NO: 59, respectively; or

g. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 60, SEQ ID NO: 61, and SEQ ID NO: 62, respectively; and

CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 66, SEQ ID NO: 67, and SEQ ID NO: 68, respectively; or

h. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 63, SEQ ID NO: 64, and SEQ ID NO: 65, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 66, SEQ ID NO: 67, and SEQ ID NO: 68, respectively; or

i. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 69, SEQ ID NO: 70, and SEQ ID NO: 71, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 72, SEQ ID NO: 73, and SEQ ID NO: 74, respectively; or

j. CDR1, CDR2, and CDR 3 of the heavy chain variable region having the sequence as shown in SEQ ID NO: 75, SEQ ID NO: 78, and SEQ ID NO: 77, respectively; and CDR1, CDR2, and CDR 3 of the light chain variable region having the sequence as shown in SEQ ID NO: 78, SEQ ID NO: 79, and SEQ ID NO: 80, respectively.

18. The use of any one of claims 14 to 17, wherein said antibody, including any functionally equivalent antibody or parts thereof or an antigen-binding portion thereof, comprises:

a. a light chain variable region that has at least 75%, 80%, 82%, 83%,84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% sequence identity to the sequence shown in SEQ ID NOs: 10, 12, 14, 16, 17, 19, 22, 24 or 26, and/or

b. a heavy chain variable region that has at least 75%, 80%, 82%, 83%,84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100% sequence identity to the sequence shown in SEQ ID NOs: 9, 11, 13, 15, 18, 20, 21, 23 or 25.

19. The use of any one of claims 14 to 17, wherein said antibody, including any functionally equivalent antibody or parts thereof or an antigen-binding portion thereof, comprises:

a. the heavy chain variable region as shown in SEQ ID NO: 9, respectively, and the light chain variable region as shown in SEQ ID NO: 10, respectively, including variants thereof; or

b. the heavy chain variable region as shown in SEQ ID NO: 11, respectively, and the light chain variable region as shown in SEQ ID NO: 12, respectively, including variants thereof; or

c. the heavy chain variable region as shown in SEQ ID NO: 13, respectively, and the light chain variable region as shown in SEQ ID NO: 14, respectively, including variants thereof; or

d. the heavy chain variable region as shown in SEQ ID NO: 15, respectively, and the light chain variable region as shown in SEQ ID NO: 16, respectively, including variants thereof; or

e. the heavy chain variable region as shown in SEQ ID NO: 15, respectively, and the light chain variable region as shown in SEQ ID NO: 17, respectively, including variants thereof; or

f. the heavy chain variable region as shown in SEQ ID NO: 18, respectively, and the light chain variable region as shown in SEQ ID NO: 19, respectively, including variants thereof; or

g. the heavy chain variable region as shown in SEQ ID NO: 20, respectively, and the light chain variable region as shown in SEQ ID NO: 22, respectively, including variants thereof; or

h. the heavy chain variable region as shown in SEQ ID NO: 21, respectively, and the light chain variable region as shown in SEQ ID NO: 22, respectively, including variants thereof; or

i. the heavy chain variable region as shown in SEQ ID NO: 23, respectively, and the light chain variable region as

shown in SEQ ID NO: 24, respectively, including variants thereof; or

j. the heavy chain variable region as shown in SEQ ID NO: 25, respectively, and the light chain variable region as shown in SEQ ID NO: 26, respectively, including variants thereof; or ;

k. the heavy chain variable region of antibody 107C6 as shown in Figure 11, and the light chain variable region of antibody 107C6 as shown in Figure 11 including variants thereof; or

l. the heavy chain variable region of antibody 108F8 as shown in Figure 11, and the light chain variable region of antibody 108F8 as shown in Figure 11 including variants thereof; or

m. the heavy chain variable region of antibody 109A6 as shown in Figure 11, and the light chain variable region of antibody 109A6 as shown in Figure 11 including variants thereof; or

n. the heavy chain variable region of antibody 111A6 as shown in Figure 11, and the light chain variable region of antibody 111A6 as shown in Figure 11 including variants thereof; or

o. the heavy chain variable region of antibody 131B4 as shown in Figure 11, and the light chain variable region of antibody 131B4 as shown in Figure 11 including variants thereof; or

p. the heavy chain variable region of antibody 131E8 as shown in Figure 11, and the light chain variable region of antibody 131E8 as shown in Figure 11 including variants thereof; or

q. the heavy chain variable region of antibody 131H1 as shown in Figure 11, and the light chain variable region of antibody 131H1 as shown in Figure 11 including variants thereof; or

r. the heavy chain variable region of antibody 132H4 as shown in Figure 11, and the light chain variable region of antibody 132H4 as shown in Figure 11 including variants thereof; or

s. the heavy chain variable region of antibody 133A6 as shown in Figure 11, and the light chain variable region of antibody 133A6 as shown in Figure 11 including variants thereof;

wherein said antibody, equivalent antibody or antigen-binding portion thereof binds free IL-18 protein, particularly 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.

20. The use of any one of claims 14 to 19, wherein said antibody is a monoclonal, polyclonal, chimeric, single chain, bispecific or bi-effective, simianized, human or humanized antibody.

21. Use of a diagnostic kit for detecting free IL-18 in the method of claim 2, wherein the diagnostic kit comprises the IL-18 binding protein (IL-18BP) as defined in any one of claims 5 to 6 as the capturing molecule, and a second IL-18 specific binding molecule as the detection molecule, wherein the detection molecule binds to different sites of IL-18 than the capturing molecule.