

It is therefore an objective of the present invention to provide means and methods useful to control side effects in CAR-T-cell therapy, particularly toxic side effects due to an overshooting of the immune system and/or a cytokine release syndrome.

The technical problem is solved by the examples provided herein, in particular as characterized in the claims.

SUMMARY

In one aspect, the present disclosure relates to use of an IL-18 binding molecule in the manufacture of a medicament for avoiding or minimizing side effects related to a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient diagnosed with a disease associated with expression of a tumor antigen.

In another aspect, the present disclosure relates to use of a pharmaceutical composition comprising an IL-18 binding molecule, particularly an IL-18 binding molecule defined in the present disclosure, in the manufacture of a medicament for avoiding or minimizing side effects related to a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient, diagnosed with a disease associated with expression of a tumor antigen, optionally wherein the composition comprises a pharmaceutically acceptable carrier and/or solvent and/or excipient.

Accordingly, the present disclosure relates to, inter alia, the following examples:

1. An IL-18 binding molecule for use in a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient diagnosed with a disease associated with expression of a tumor antigen to avoid or minimize side effects related to the CAR-T therapy.
2. The IL-18 binding molecule for use of example 1 as a modulator of IL-18 levels in the patient to avoid or minimize side effects related to the CAR-T therapy.
3. The IL-18 binding molecule for use of example 2, wherein the IL-18 levels are levels of free IL-18.
4. The IL-18 binding molecule for use of any one of examples 1 to 3, wherein the IL-18 binding molecule inhibits IFN-gamma secretion.
5. The IL-18 binding molecule for use of any one of examples 1 to 4, wherein the IL-18 binding molecule inhibits IL-18 mediated stimulation of IFN-gamma secretion, that is further elevated by IL-12.
6. The IL-18 binding molecule for use of any one of examples 1 to 5, wherein the disease associated with expression of a tumor antigen is a proliferative disease, a precancerous condition, a cancer, and/or a non-cancer related indication associated with expression of the tumor antigen.
7. The IL-18 binding molecule for use of any one of examples 1 to 6, wherein the patient has cancer, particularly a hematological cancer or a solid tumor, particularly a tumor expressing tumor-associated antigens.
8. The IL-18 binding molecule for use of example 7, wherein the cancer is a hematologic cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-

ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative condition, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, and Waldenstrom macroglobulinemia.

9. The IL-18 binding molecule for use of any one of examples 1 to 8, wherein a population of cells is used in the CAR-T therapy, which are engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain.
10. The IL-18 binding molecule for use of example 9, wherein the cells are further engineered to express IL-18.
11. The IL-18 binding molecule for use of any one of examples 1 to 10, wherein the side effects are due to an overshooting of the immune system and/or a cytokine release syndrome.
12. The IL-18 binding molecule for use of example 11, wherein the side effects are selected from the group consisting of unremitting fever, hypotension, hypoxia (lung involvement), other end-organ damage and dysfunction including but not limited to liver and kidney, cytopenias, coagulopathy, hemophagocytosis and neurologic toxicities.
13. The IL-18 binding molecule for use of any one of examples 1 to 12, as a modulator of free IL-18 levels in the patient.
14. The IL-18 binding molecule for use of any one of examples 1 to 13 for decreasing the IL-18 levels, particularly the free IL-18 levels, in the patient.
15. The IL-18 binding molecule for use of any one of examples 1 to 14, wherein the patient is an animal, particularly a human.
16. The IL-18 binding molecule for use of any one of examples 1 to 15, which is an IL-18 binding protein (IL-18BP), including any functional equivalent or functional part thereof which retains the modulator activity.

17. The IL-18 binding molecule for use of any one of examples 1 to 15, which is an IL-18 binding antibody that specifically binds to free IL-18, but not to IL-18 bound in a complex, including any functional equivalent or functional part thereof which retains the modulator activity.
18. The IL-18 binding molecule for use of example 16, which is a human IL-18BP (hIL-18 BP), preferably a recombinant human IL-18BP (rhIL-18 BP), including any functional equivalent or functional part thereof, which retains the modulator activity.
19. The IL-18 binding molecule for use of example 18, wherein said human IL-18BP is selected from isoform a, b, c and d of human IL-18BP, particularly isoform a as in SEQ ID NO: 2, isoform b as in SEQ ID NO: 3, isoform c as in SEQ ID NO: 4 or isoform d as in SEQ ID NO: 5, including any functional equivalent or functional part of isoforms a, b, c and/or d, which retains the modulator activity.
20. The IL-18 binding molecule for use of example 19, which is an IL-18BP as shown in SEQ ID NO: 2, including any functional equivalent or functional part thereof, which retains the modulator activity, preferably wherein the functional equivalent has a sequence identity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% to the sequence depicted in SEQ ID NO: 2 and retains the modulator activity.
21. The IL-18 binding molecule for use of example 20, wherein the functional equivalent or functional part thereof includes a mutein of IL-18BP, a fragment, a peptide, a functional derivative, a functional fragment, a fraction, a circularly permuted derivative, a fused protein comprising IL-18BP, an isoform or a salt thereof which retains the modulator activity.
22. A composition comprising the IL-18 binding molecule, particularly an IL-18 binding molecule of any one of examples 16 to 21, for use in a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient, diagnosed with a disease associated with expression of a tumor antigen, to avoid or minimize side effects related to the CAR-T therapy, optionally wherein the composition comprises a pharmaceutically acceptable carrier and/or solvent and/or excipient.
23. The composition for use of example 22, as a modulator of IL-18 levels in the patient to avoid or minimize side effects related to the CAR-T therapy.

24. The composition for use of example 22 or 23, wherein the side effects are due to an overshooting of the immune system and/or a cytokine release syndrome.
25. The composition for use of any one of examples 22 to 24, wherein the disease is a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.
26. The composition for use of any one of examples 22 to 25, wherein the patient has cancer, particularly a hematological cancer or a solid tumor, particularly a tumor expressing tumor-associated antigens.
27. The composition for use of example 26, wherein the cancer is a hematologic cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative condition, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, and Waldenstrom macroglobulinemia.
28. The composition for use of any one of examples 22 to 27, wherein the side effects are selected from the group consisting of unremitting fevers, hypotension, hypoxia (lung involvement), other end-organ damage and dysfunction including but not limited to liver and kidney, cytopenias, coagulopathy, hemophagocytosis and neurologic toxicities.
29. The composition for use of any one of examples 22 to 28 comprising
 - (i) a population of cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain, and
 - (ii) an IL-18 binding molecule, particularly the IL-18 binding molecule of any one of examples 15 to 20.
30. The composition for use of example 29, wherein the population of cells of (i) are further engineered to express IL-18.

31. The composition for use of any one of examples 22 to 30, wherein the IL-18 binding protein (IL-18BP) further comprises N-terminal and/or C-terminal deletion variants of IL-18BP.
32. The composition for use of any one of examples 22 to 31, wherein the patient is an animal, particularly a human.
33. The composition for use of any one of examples 22 to 32, comprising N- terminal and/or C-terminal deletion variants of IL-18BP in an amount of up to 40%, particularly up to 30%, particularly up to 20%, particularly up to 15%, particularly up to 10%, particularly up to 7.5%, particularly up to 5%, particularly up to 2.5%, particularly up to 1%, particularly up to 0.5%, particularly up to 0.25%, particularly up to 0.1%, particularly up to 0.05%, particularly up to 0.01%.
34. The composition for use of example 31 or 33, 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.
35. The composition for use of any one of examples 31 to 34, wherein said N- terminal and/or C-terminal deletion variants of IL-18BP are present in an amount of up to 40%, particularly in an amount of between 2% and 35%.
36. The IL-18 binding molecule of any one of examples 1 to 21 or the composition of any one of examples 22 to 35 for controlling and/or modulating, particularly decreasing, IL-18 levels, particularly free IL-18 levels, in the patient.
37. A method for modulating IL-18 levels in a patient under a Chimeric Antigen Receptor T-cell (CAR-T) therapy to avoid or minimize side effects, comprising administering to a patient in need thereof a therapeutically effective amount of an IL-18 binding molecule, particularly an IL-18 binding molecule according to any one of examples 16 to 21, or a therapeutically effective amount of a composition of any one of examples 22 to 35.
38. The method for use of examples 37, for modulating, particularly decreasing, IL-18 levels, particularly free IL-18 levels, in the patient.

39. The method for use of example 37 or 38, wherein the patient has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.
40. The method for use of example 39, wherein the patient has cancer, particularly a hematological cancer or a solid tumor, particularly a tumor expressing tumor-associated antigens.
41. The method for use of example 40, wherein the cancer is a hematologic cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, and Waldenstrom macroglobulinemia.
42. The method for use of any one of examples 37 to 41, wherein the patient is an animal, particularly a human.
43. The method of any one of examples 37 to 42, wherein the CAR-T-cells and the IL-18 binding molecule or the composition, respectively, are administered to the patient concomitantly.
44. The method of any one of examples 37 to 42, wherein the CAR-T-cells and the IL-18 binding molecule or the composition, respectively, are administered to the patient sequentially.
45. The method of any one of examples 37 to 44, wherein the IL-18 binding molecule or the composition, respectively, is administered to the patient as an acute intervention during the CAR-T therapy.
46. The IL-18 binding molecule for use of example 7 or the composition for use of example 26 or the method of example 40 wherein the cancer is a solid tumor,

particularly selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancer, combinations of said cancers, and metastatic lesions of said cancers.

47. The IL-18 binding molecule for use of any one of examples 1 to 21, 36 or 46 or the composition for use of any one of examples 22 to 35 or 46, or the method of any one of examples 37 to 46, wherein in a body fluid of the patient an abnormal level of free IL-18 has been determined, in particular wherein the level of free IL-18 exceeds 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 the IL-18 binding molecule as defined in any one of examples 16 to 21.
48. The IL-18 binding molecule for use, the composition for use or the method of example 47, wherein the assay for quantifying the level of free IL-18 in the body fluid(s) comprises the following steps:
 - a) bringing a sample of body fluid suspected to contain free IL-18 into contact with the IL-18 binding molecule as defined in any one of examples 16 to 21 as the capturing molecule for free IL-18;
 - b) allowing the IL-18 binding molecule to bind to free IL-18; and
 - c) detecting the binding of the IL-18 binding molecule and determining the amount of free IL-18 in the sample.
49. The IL-18 binding molecule for use, the composition for use or the method of any one of examples 47 or 48, wherein the body fluid is 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 or expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa and tissue secretion.

50. The IL-18 binding molecule for use of any one of examples 1 to 21, 36 or 46 to 49 or the composition for use of any one of examples 22 to 35 or 46 to 49, or the method of any one of examples 37 to 49, wherein the therapy of the patient further comprises the use of one or more check-point inhibitor(s).
51. The IL-18 binding molecule for use of example 50 or the composition for use of example 50, or the method of example 50, wherein the check-point inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor.

Accordingly, the disclosure relates to an IL-18 binding molecule, particularly the IL-18 binding protein (IL-18BP), for use as a co-medication in CAR-T therapy of a patient, who has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and/or a non-cancer related indication associated with expression of the tumor antigen; in particular as a modulator, particularly a modulator of IL-18, particularly a modulator of free IL-18 in body samples and/or the body fluids of the patient under CAR-T therapy, which IL-18 levels may be increased due to the cancer and/or CAR-T-cells engineered to secrete IL-18, to avoid or minimize side effects related to the CAR-T therapy.

The IL-18 binding molecule as used herein may inhibit IFN-gamma secretion. The IL-18 binding molecule as used herein may inhibit IL-18 mediated stimulation of IFN-gamma secretion, that is further elevated by IL-12.

In a specific example, by using the IL-18 binding molecule of the disclosure, in particular the IL-18BP of the disclosure, the IL-18 levels in the body fluids of the patient under CAR-T therapy are modulated, particularly decreased, in order to avoid or minimize side effects related to the CAR-T therapy, but particularly the risk of overshooting immune reactions and/or toxic side effects. The IL-18 levels may be free IL-18 levels.

In a specific example of the disclosure, the side effects are selected from the group consisting of unremitting fever, hypotension, hypoxia (lung involvement), other end-organ damage and dysfunction including but not limited to liver and kidney, cytopenias, coagulopathy, hemophagocytosis and neurologic toxicities.

Within the disclosure, a precise quantification of the free IL-18 level in a body sample and/or body fluids of the patient under CAR-T therapy may be made by using a quantification assay as described in WO 2015/032932 and/or WO 2016/139297, respectively. Dependent on the free IL-18 level determined in an assay described therein, the amount of IL-18 binding molecule may be determined that ensures an increase in the efficacy of the CAR-T therapy by avoiding or minimizing side effects, particularly side effects which are due to an overshooting of the immune system and/or a cytokine release syndrome.

Within the present disclosure, the assay may be used to ensure that only those patients are selected for CAR-T therapy that are in need of such a treatment, e.g., patients that have elevated levels of IL-18, particularly elevated levels of free IL-18, in their body fluids, and which are therefore likely to respond to a co-medication with an IL-18 binding molecule as defined herein, particularly an IL-18 binding protein (IL-18BP) as defined herein.

The assay may additionally or alternatively be used to monitor the efficacy of a CAR-T co-medication with an IL-18 binding molecule as defined herein, particularly an IL-18 binding protein (IL-18BP) as defined herein. As such, a decrease of elevated IL-18 levels, particularly of free IL-18 levels, in the body fluids of the treated patient indicates that the co-medication is efficient.

In particular, the assay that may be used for quantifying the levels of free IL-18 in the body samples and/or body fluids of a patient under CAR-T therapy may comprise the following steps:

- a) bringing a body sample or a sample of body fluid suspected to contain free IL-18 into contact with an IL-18 binding molecule, in particular an IL-18 binding molecule as defined herein as the capturing molecule for free IL-18;
- b) allowing the IL-18 binding molecule to bind to free IL-18;
- c) detecting the binding of the IL-18 binding molecule and determining the amount of free IL-18 in the sample.

Within the present disclosure, the body samples and/or body fluids may be 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 or expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa and tissue secretion.

In a specific example, the IL-18 binding molecule of the disclosure is an antibody that specifically binds to free IL-18, but not to IL-18 bound in a complex.

In another specific example, the IL-18 binding molecule of the disclosure is an IL-18 binding protein (IL-18BP), particularly human IL-

18BP (hIL-18BP), particularly recombinant human IL-18BP (rhIL-18BP), including any functional equivalent or functional part thereof, which retains the modulator activity of the reference molecule.

In another specific example, the IL-18BP is selected from isoform a, b, c and d of IL-18BP, particularly isoform a, particularly isoform c.

In another specific example, the IL-18BP is selected from isoform a, b, c and d IL-18BP as shown in SEQ ID NOs 2, and SEQ ID NOs: 3, 4 and 5, respectively, but especially isoform a of IL-18BP as shown in SEQ ID NO: 2, or isoform c as shown in SEQ ID NO: 4, including any functional equivalent or functional part thereof, which retains the modulator activity of the reference molecule.

Within the present disclosure, mixtures of the above isoforms in different combinations may be used in the composition of the disclosure, but particularly a mixture of isoform a and isoform c, including any functional equivalent or functional part thereof which retains the modulator activity of the reference molecule.

Within the present disclosure, the term “functional equivalent” or “functional part” is meant to relate to the equivalent or the part of the IL-18 binding reference molecule that has still retained the capability of selectively binding to free IL-18 and thus to function as a modulator in CAR-T therapy to avoid or minimize side effects.

Also comprised within the scope of the present disclosure is a functional mutein of IL-18BP, a functional fragment, a functional peptide, a functional derivative, a functional fragment, a functional fraction, a functional circularly permuted derivative, a functional fused protein comprising IL-18BP, an functional isoform or a functional salt thereof, which retains the capability of selectively binding to free IL-18 and thus to function in CAR-T therapy to avoid or minimize side effects, in particular to function as a modulator of free IL-18 levels in a patient under CAR-T therapy.

In one example, the disclosure relates to an IL-18BP, which is a fused protein comprising all or part of an IL-18BP, fused to all or part of an immunoglobulin, preferably to the constant region of an immunoglobulin, and wherein the fused protein is still capable of selectively binding to free IL-18, which fused protein retains the capability of selectively binding to free IL-18 and thus to function in CAR-T therapy to avoid or minimize side effects, in particular to function as a modulator of free IL-18 levels in a patient under CAR-T therapy. More specifically, the immunoglobulin may be of the IgG1 or IgG2 isotype, for use in a composition according to any one of the examples described herein.

In another example the disclosure relates to an IL-18BP, which is a fused protein comprising all or part of an IL-18BP, fused to all or part of a small molecule, particularly to all or part of a small molecular drug, optionally wherein the fusion is through a linker molecule and wherein the fused protein retains the capability of selectively binding to free IL-18 and

thus to function in CAR-T therapy to avoid or minimize side effects, in particular to function as a modulator of free IL-18 levels in a patient under CAR-T therapy.

In one example, the present disclosure provides the IL-18 binding molecule for use of any one of the examples described herein, wherein the inhibitor is an IL-18 binding protein (IL-18BP) which has a sequence identity of 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% to the sequence depicted in SEQ ID NO: 2 and SEQ ID NOs: 3, 4 and 5, but particularly to the sequence depicted in SEQ ID NO: 2 and SEQ ID NO: 4 and has retained the capability of selectively binding to free IL-18 and thus to function in CAR-T therapy to avoid or minimize side effects, in particular to function as a modulator of free IL-18 levels in a patient under CAR-T therapy.

In another example of the disclosure, the IL-18BP may be accompanied by N- terminal and/or C-terminal deletion variants of IL-18BP in an amount of up to 40%, particularly up to 30%, particularly up to 20%, particularly up to 15%, particularly up to 10%, particularly up to 7.5%, particularly up to 5%, particularly up to 2.5%, particularly up to 1%, particularly up to 0.5%, particularly up to 0.25%, particularly up to 0.1%, particularly up to 0.05%, particularly up to 0.01%.

In a specific example, said N- terminal and/or C-terminal deletion variants of IL-18BP are present in an amount of up to 40%, particularly in an amount of between 2% and 35%.

In particular, said deletion variants may 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.

Thus, in one example, the disclosure relates to a composition comprising the IL-18 binding molecule, particularly the IL-18 binding protein provided herein, for use in a Chimeric Antigen Receptor T-cell (CAR-T) therapy in a patient, who has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and/or a non-cancer related indication associated with expression of the tumor antigen,, in particular to increase efficacy of the treatment and/or as a modulator of IL-18 levels in the treated patient to avoid or minimize side effects, particularly side effects related to the CAR-T therapy, particularly side effects which are due to an overshooting of the immune system and/or a cytokine release syndrome.

In a specific example of the disclosure, the side effects are selected from the group consisting of unremitting fever, hypotension, hypoxia (lung involvement), other end-organ damage and dysfunction including but not limited to liver and kidney, cytopenias, coagulopathy, hemophagocytosis and neurologic toxicities.

In another example, the disclosure relates to a composition comprising an IL-18 binding

molecule, particularly the IL-18 binding protein provided herein and, in addition, N- terminal and/or C-terminal deletion variants of the IL-18BP provided herein, for use in a Chimeric Antigen Receptor T-cell (CAR-T) therapy in a patient in need thereof to increase efficacy of the treatment and/or for controlling, modulating, particularly decreasing, IL-18 levels, particularly free IL-18 levels, in the patient, particularly throughout the CAR-T therapy.

In particular, the IL-18 binding molecule and the composition comprising the IL-18 binding molecule according to the present disclosure may be used as a modulator, particularly a modulator of IL-18 levels in the treated patient, particularly a modulator of free IL-18 levels in the treated patient, to avoid or minimize side effects, particularly side effects related to the CAR-T therapy, particularly side effects which are due to an overshooting of the immune system and/or a cytokine release syndrome.

In particular, the composition of the disclosure may comprise

- (i) a population of cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain, and
- (ii) an IL-18 binding molecule, particularly the IL-18 binding protein provided herein.

In a specific example, the population of cells of (i) are further engineered to express IL-18.

In another specific example, the composition further comprises N- terminal and/or C-terminal deletion variants of IL-18BP, particularly N- terminal and/or C-terminal deletion variants of IL-18BP, in particular deletion variants as defined herein.

In another specific example, the above compositions further comprise a pharmaceutically acceptable carrier and/or excipient.

In various examples of the disclosure, the IL-18 binding molecule, particularly the IL-18BP of the disclosure as described herein, including any functional equivalent or functional part thereof, or the composition of the disclosure as described herein, comprising said IL-18 binding molecule, particularly the IL-18BP of the disclosure and, optionally, further comprising N- and C-terminal deletion variants of the IL-18BP, including any functional equivalent or functional part thereof, is used as a co-medication in CAR-T therapy, in particular as a modulator, to avoid or minimize side effects, particularly side effects which are due to an overshooting of the immune system and/or a cytokine release syndrome.

In particular, the CAR-T therapy is used in a patient, who has a disease associated with expression of a tumor antigen, e.g., a proliferative disease, a precancerous condition, a cancer, and/or a non-cancer related indication associated with expression of the tumor antigen.

In particular, the IL-18 binding molecule and the composition comprising the IL-18 binding molecule of the disclosure is used in CAR-T therapy in a mammal, particularly in a human.

In a specific example, the IL-18 binding molecule and the composition comprising the IL-18 binding molecule of the disclosure is used in CAR-T therapy, particularly for treating hematological tumors and/or solid tumors, particularly tumors expressing tumor-associated antigens.

In particular, the cancer may be a hematologic cancer, particularly a hematological cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemias, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom macroglobulinemia, and preleukemia.

In a specific example, the cancer may be a solid tumor, particularly a cancer selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancers, combinations of said cancers, and metastatic lesions of said cancers.

In one example, the IL-18 binding molecule and the composition comprising the IL-18 binding molecule of the disclosure, particular the composition of the disclosure comprising (i) a population of cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain and further to express IL-18, and (ii) an IL-18 binding molecule, particularly the IL-18 binding protein provided herein, is used in CAR-T therapy for treating solid tumors,

particularly tumors expressing tumor-associated antigens, particularly non-small cell lung cancer, malignant pleural mesothelioma, or multiform glioblastoma.

Therapy or treatment as used herein comprises prevention, halting, alleviation and/or reversion of symptoms associated with the disease or disorder to be treated.

Within the present disclosure, the therapy or treatment may be continued at least until the treated patient shows a therapeutic response.

In various further examples, the disclosure relates to the IL-18 binding molecule of the disclosure, particularly the IL-18BP of the disclosure as defined herein, or the composition comprising the IL-18 binding molecule of the disclosure, particularly the IL-18BP of the disclosure as defined herein, for use according to any one of the preceding examples, wherein

- increased expression of IFN γ , IL-13 and/or IL-17A is modified, particularly inhibited, compared to untreated subjects suffering from said disease or disorder; and/or
- binding of free IL-18 by the IL-18BP compensates the IL-18/IL-18BP imbalance by trapping and neutralizing the excess of free IL-18 in tissue and circulation; and/or
- IL-18 binding is restricted or inhibited, particularly binding of free IL-18 to IL-18 receptor (IL-18R), but especially free IL-18 binding to IL-18R α ; and/or
- the IL-18BP reduces binding of IL-18 to IL-18 receptor, particularly binding to IL-18R α 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%; and/or
- the IL-18BP neutralizes free IL-18 by restricting or preventing IL-18 binding to IL-18 receptor (IL-18R), especially free IL-18 binding to IL-18R α .

In one example, the disclosure relates to the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or to the composition comprising the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, for use according to any one of the preceding examples, wherein the level of free IL-18 in the body fluid(s) has been determined to be ≥ 5 pg/mL and, particularly, up to 10000 pg/mL as compared to ≤ 4 pg/mL in the healthy control.

In a specific example, the level of free IL-18 in the body fluid(s) is two to three times above normal.

The determination of free IL-18 in the body fluid(s) may be accomplished by using an assay for quantifying the level of free IL-18 in the body fluids, in a body sample or *in situ*, which includes the steps of:

- a) bringing a sample of body fluid or a body sample or body area suspected to contain free IL-18 into contact with an IL-18 binding molecule, particularly 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-18 binding molecule, particularly the IL-18BP to bind to free IL-18;
- c) detecting the binding of IL-18 to the IL-18 binding molecule, particularly the IL-18BP and determining the amount of free IL-18 in the sample or *in situ*.

In one example of the disclosure, the sample is selected from the group consisting of bronchoalveolar lavage fluid (BALF) circulation fluids, secretion fluids, biopsy, and homogenized tissue, particularly serum, urine, tear, saliva, bile, sweat, exhalation or expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa and tissue secretion.

For determining the presence or absence of free IL-18 in a sample according to the present disclosure, any immunoassay format known to those of ordinary skill in the art may be used such as, for example, assay formats which utilize indirect detection methods using secondary reagents for detection, in particular, ELISA's and immunoprecipitation and agglutination assays may be used. A detailed description of these assays is, for example, given in Harlow and Lane, *Antibodies: A Laboratory Manual* (Cold Spring Harbor Laboratory, New York 1988 555-612, WO96/13590 to Maertens and Stuyver, Zrein et al. (1998) and WO96/29605.

The sample may be a non-diluted or diluted biological fluid, such as, without being restricted thereto, serum, urine, tear, saliva, bile, sweat, exhalation or expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa or tissue secretion, biopsy, homogenized tissue.

For *in situ* diagnosis, the IL-18 binding molecule, particularly the IL-18BP or any active and functional part thereof may be administered to the subject to be diagnosed by methods known in the art such as, for example, intravenous, intranasal, intraperitoneal, intracerebral, intraarterial injection such that a specific binding between the IL-18BP with free IL-18 may occur. The IL-18 binding molecule, particularly the IL-18BP, or any active and functional part thereof may comprise a detectable label, as described further below.

In another aspect of the disclosure, detection of free IL-18 described herein may be accomplished by an immunoassay procedure. The immunoassay typically includes contacting a test sample with an IL-18 binding molecule, particularly the IL-18BP as described herein in

the various examples that specifically binds to free IL-18 and detecting the presence of the IL-18BP/free IL-18 complex in the sample. The immunoassay procedure may be selected from a wide variety of immunoassay procedures known to those skilled in the art such as, for example, competitive or non-competitive enzyme-based immunoassays, enzyme-linked immunosorbent assays (ELISA), radioimmunoassay (RIA), and Western blots, etc. Further, multiplex assays may be used, including arrays, wherein the IL-18 binding molecule, particularly the IL-18BP are placed on a support, such as a glass bead or plate, and reacted or otherwise contacted with the test sample.

Various chemical or biochemical derivatives of the IL-18 binding molecule, in particular the IL-18BP can be produced using known methods. One type of derivative which is diagnostically useful as an immunoconjugate comprising an IL-18 molecule, in particular IL-18BP is conjugated to a detectable label. However, in many examples, the IL-18 molecule, in particular IL-18BP is not labeled but in the course of an assay, it becomes indirectly labeled by binding to or being bound by another molecule that is labeled. The disclosure encompasses molecular complexes comprising an IL-18 molecule, in particular IL-18BP and a label.

Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β -galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferones, fluoresceins, fluorescein isothiocyanate, rhodamines, dichlorotriazinylamine fluorescein, dansyl chloride, phycoerythrins, Alexa Fluor 647, Alexa Fluor 680, DiI_{C19}(3), Rhodamine Red-X, Alexa Fluor 660, Alexa Fluor 546, Texas Red, YOYO-1 + DNA, tetramethylrhodamine, Alexa Fluor 594, BODIPY FL, Alexa Fluor 488, Fluorescein, BODIPY TR, BODIPY TMR, carboxy SNARF-1, FM 1-43, Fura-2, Indo-1, Cascade Blue, NBD, DAPI, Alexa Fluor 350, aminomethylcoumarin, Lucifer yellow, Propidium iodide, or dansylamide; an example of a luminescent material includes luminol; examples of bioluminescent materials include green fluorescent proteins, modified green fluorescent proteins, luciferase, luciferin, and aequorin, and examples of suitable radioactive material include ¹²⁵I, ¹³¹I, ³⁵S or ³H.

The immunoassays will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells, in the presence of a detectably labeled IL-18 molecule, in particular IL-18BP, and detecting the bound IL-18 molecule, in particular IL-18BP by any of a number of techniques well-known in the art. One way of measuring the level of free IL-18 with the IL-18BP is by enzyme immunoassay (EIA) such as an enzyme-linked immunosorbent assay (ELISA) (Voller, A. *et al.*, *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), *Enzyme*

Immunoassay, CRC Press, Boca Raton, FL, 1980). The enzyme, either conjugated to the IL-18 molecule, in particular IL-18BP or to a binding partner for the IL-18 molecule, in particular IL-18BP, when later exposed to an appropriate substrate, will react with the substrate in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, or fluorimetric means.

In a specific example of the disclosure, the IL-18 molecule, in particular IL-18BP used in any of the above formats, but particularly in an ELISA format is IL-18BP isoform a, b, c or d, or a functional equivalent or a functional derivate thereof, or a functional fragment thereof, particularly isoform a, particularly isoform c, or a derivate thereof, particularly isoform a, b, c or d as shown in SEQ ID NOs 2, and 3, 4 and 5, but especially the isoform a of IL-18BP as shown in SEQ ID NO: 2 or the isoform c as shown in SEQ ID NO 4.

Also, mixtures of the above isoforms may be used in the composition of the disclosure, but particularly a mixture of isoform a and isoform c.

The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled IL-18 binding molecule, particularly IL-18BP. The solid phase support may then be washed with the buffer a second time to remove unbound IL-18 binding molecule, particularly unbound IL-18BP. The amount of bound label on solid support may then be detected by conventional means. A well-known example of such a technique is Western blotting.

In various examples, the present disclosure provides compositions comprising labeled IL-18 molecule, in particular IL-18BP according to the disclosure as described herein.

In still another example, the disclosure relates to a method for modulating side effects in a Chimeric Antigen Receptor T-cell (CAR-T) cancer therapy, said method comprising:

- a. in a first optional step, quantifying the amount of free IL-18 in the body fluids of said subject using the method as described herein in the various examples;
- b. administering to a patient in need thereof a therapeutically effective amount of an IL-18 binding molecule, particularly an IL-18 binding protein as provided herein, or an effective amount of a composition as provided herein.

In particular, a patient in need of such a treatment is a patient, whose level of free IL-18 has been determined in a body sample or in the body fluids to exceed the level of free IL-18 in a body sample or the body fluids of a healthy control subject by 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%, or more than 100%.

A therapeutically or prophylactically effective amount of an IL-18 binding molecule or a composition comprising said IL-18 binding molecule as defined in any one of the preceeding examples, may be administered to the patient by systemic, intranasal, buccal, oral, transmucosal, intratracheal, intravenous, subcutaneous, intraurinary tract, intravaginal, sublingual, intrabronchial, intrapulmonary, transdermal or intramuscular administration, in particular broncho-pulmonary administration.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples is administered to a patient in need thereof in a suitable dosage form and/or unit and/or dosage interval.

In a specific example, the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, as defined herein, is formulated as a pharmaceutical composition, in particular a pharmaceutical composition comprising a sterile solution for injection, preferably further sodium chloride, and/or sodium hydroxide and/or sodium phosphate buffer, particularly in a concentration of between 0.01 M and 0.2 M, particularly between 0.01 M and 0.15 M. It is preferred herein to include sodium chloride and sodium phosphate buffer in the composition of the disclosure. In a preferred example, the composition of the disclosure, in particular the pharmaceutical composition, comprises about 0.12 M sodium chloride and about 0.02 M sodium phosphate buffer.

The IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or to the composition comprising the IL-18 binding molecule, particularly the IL-18BP of the disclosure, including any functional equivalent or functional part thereof, may be administered to a patient in need thereof in a single dose or dosage unit/day, in multiple doses or doseage units/day, in multiple doses or doseage units /week or in multiple doses or doseage units /month. The single dose or dosage unit may be split into several doses or dosage units and administered to the patient to be treated over several hours or a whole day.

In one example, the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or to the composition comprising the IL-18 binding molecule, particularly the IL-18BP of the disclosure, including any functional equivalent or functional part thereof, is administered every 48 hours.

In one example, the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or the composition according to the disclosure may be administered by s.c. injection. In particular, the site of the s.c. injection is alternated, particularly the site of injection is outside of the thighs and the various quadrants

of the anterior abdominal wall. The separate injections that constitute a single dosage of the composition of the disclosure is particularly administered within the same body region but not at the exact same injection site.

In one example, the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or the composition according to the disclosure may be administered intravenously. The formulation of the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or the composition according to the disclosure may be adapted for intravenous administration using methods known in the art.

In one example, the composition is brought to room temperature, particularly between 18 – 25°C, before administration.

In a specific example, a single dose of the composition of the disclosure and particularly the composition for use according to any one of the preceding examples comprises between 10 mg and 600 mg IL-18BP.

In particular, the single dose may comprise between 10 and 20 mg, between 20 and 40 mg, between 40 and 80 mg, between 80 and 160 mg, between 160 mg and 320 mg or between 320 mg and 600 mg IL-18BP.

In various examples of the disclosure, a single dose may comprise between 0.5 mg of IL-18 binding molecule/kg body weight and 10 mg IL-18 binding molecule /kg body weight, particularly between 1 mg IL-18 binding molecule /kg body weight and 8 mg IL-18 binding molecule /kg body weight, particularly between 1,5 mg IL-18 binding molecule /kg body weight and 6 mg IL-18 binding molecule /kg body weight, particularly between 2 mg IL-18 binding molecule /kg body weight and 4 mg IL-18 binding molecule /kg body weight.

In a specific example of the disclosure, a single dose may comprise between 2 mg of IL-18BP/kg body weight and 3 mg IL-18BP /kg body weight, particularly 2 mg of IL-18BP/kg body weight.

In a specific example, the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof, or the composition comprising the IL-18 binding molecule, particularly the IL-18BP, of the disclosure, including any functional equivalent or functional part thereof is administered in a dosage of between 0.5 mg IL-18 binding molecule /kg body weight and 5 mg IL-18 binding molecule /kg body weight every 24 or 48 h, particularly, a single dose of 2 mg IL-18 binding molecule /kg body weight is administered every 48 h.

In another specific example, human IL-18BP (rhIL-18 BP), including any functional equivalent or functional part thereof or the composition comprising a recombinant human IL-18BP (rhIL-18 BP), including any functional equivalent or functional part thereof, is

administered in a single dose every other day of 2 mg/kg body weight, for example over three weeks. However, it is preferred that the IL-18 binding molecule, in particular the IL-18 binding protein as provided herein, is administered depending on free IL-18 levels assumed or determined in a patient, in particular that the IL-18 molecule, IL-18 binding protein, is administered until free IL-18 levels are assumed or determined to be below a level that is thought to be acceptable, such as for example a level observed in a healthy subject.

The compositions of the disclosure may comprise additional medicinal agents, pharmaceutical agents, carriers, excipients, buffers, dispersing agents, diluents, and/or co-therapeutic agents such as anti-inflammatory, bronchodilatory, antihistamine, decongestant, anti-tussive drug substances, antiviral and/or immunosuppressant drugs, and/or anti-cancer agents, such as checkpoint inhibitors, and the like, depending on the intended use and application.

In one example of the present disclosure, the IL-18 binding molecule or the composition comprising the the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples, is administered prophylactically.

In another example of the present disclosure, the IL-18 binding molecule or the composition comprising the the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples is administered therapeutically.

In one example of the present disclosure, the IL-18 binding molecule or the composition comprising the the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples is administered to a patient in need thereof by systemic, intranasal, intraocular, intravitreal, eye drops, buccal, oral, transmucosal, intratracheal, intravenous, subcutaneous, intraurinary tract, intrarectal, intravaginal, sublingual, intrabronchial, intrapulmonary, transdermal or intramuscular administration. In particular, the administration is done by subcutaneous injection.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples may be provided as a liquid, liquid spray, microspheres, semisolid, gel, or powder for transmucosal administration, e.g. intranasal, buccal, oral transmucosal, intratracheal, intraurinary tract, intravaginal, sublingual, intrabronchial, intrapulmonary and/or transdermal administration. Further, the composition may be in a solid dosage form for buccal, oral transmucosal and/or sublingual administration. Intranasal, buccal, oral intratracheal, intraurinary tract, intravaginal, transmucosal and sublingual administrations lead to the disintegration of the composition as described herein in an oral cavity at body temperature and optionally may adhere to the body tissue of the oral cavity. Additionally, the composition as disclosed herein further may include one or more excipient, diluent, binder, lubricant, glidant, disintegrant, desensitizing agent, emulsifier,

mucosal adhesive, solubilizer, suspension agent, viscosity modifier, ionic tonicity agent, buffer, carrier, surfactant, flavor, or mixture thereof.

In a specific aspect of the present disclosure, the IL-18 binding molecule or the composition comprising the IL-18 binding molecule is formulated as a parenteral, or intravenous solution, suspension, emulsion, as a tablet, pill, bioadhesive patch, drops, sponge, film, lozenge, hard candy, wafer, sphere, lollipop, disc-shaped structure, suppository or spray.

Transmucosal administration is generally rapid because of the rich vascular supply to the mucosa and the lack of a stratum corneum in the epidermis. Such drug transport typically provides a rapid rise in blood concentrations, and similarly avoids the enterohepatic circulation and immediate destruction by gastric acid or partial first- pass effects of gut wall and hepatic metabolism. Drugs typically need to have prolonged exposure to a mucosal surface for significant drug absorption to occur.

The transmucosal routes can also be more effective than the oral route in that these routes can provide for relatively faster absorption and onset of therapeutic action. Further, the transmucosal routes can be preferred for use in treating patients who have difficulty in swallowing tablets, capsules, or other oral solids, or those who have disease-compromised intestinal absorption. Accordingly, there are many advantages to transmucosal administration of the IL-18 binding molecule, particularly the IL-18BP, or a composition comprising the IL-18 binding molecule, particularly the IL-18BP and a pharmaceutically acceptable carrier and/or excipient.

In either of the intranasal or buccal routes, drug absorption can be delayed or prolonged, or uptake may be almost as rapid as if an intravenous bolus were administered. Because of the high permeability of the rich blood supply, the sublingual route can provide a rapid onset of action.

The intranasal compositions can be administered by any appropriate method according to their form. A composition including microspheres or a powder can be administered using a nasal insufflator device. Examples of these devices are well known to those of skill in the art, and include commercial powder systems such as Fisons Lomudal System. An insufflator produces a finely divided cloud of the dry powder or microspheres. The insufflator is preferably provided with a mechanism to ensure administration of a substantially fixed amount of the composition. The powder or microspheres can be used directly with an insufflator, which is provided with a bottle or container for the powder or microspheres. Alternatively, the powder or microspheres can be filled into a capsule such as a gelatin capsule, or other single dose device adapted for nasal administration. The insufflator preferably has a mechanism to break open the capsule or other device. Further, the composition can provide an initial rapid release of the active ingredient followed by a sustained release of the active ingredient, for example, by providing more than one type of microsphere or powder. Further, alternative methods

suitable for administering a composition to the nasal cavity will be well known by the person of ordinary skill in the art. Any suitable method may be used. For a more detailed description of suitable methods reference is made to EP2112923, EP1635783, EP1648406, EP2112923 (the entire contents of which are incorporated by reference herein).

In one example of the present disclosure, the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples may be further administered intranasally, i.e. by inhalation and, thus, may be formulated in a form suitable for intranasal administration, i.e. as an aerosol, dry powder formulation or a liquid preparation. Examples of suitable pharmaceutical carriers, excipients and/or diluents are well known in the art and include, but are not limited to, a gum, a starch (e.g. corn starch, pregeletanized starch), a sugar (e.g., lactose, mannitol, sucrose, dextrose), a cellulosic material (e.g. microcrystalline cellulose), an acrylate (e.g. polymethylacrylate), calcium carbonate, magnesium oxide, talc, or mixtures thereof.

Pharmaceutically acceptable carriers for liquid formulation are aqueous or non-aqueous solutions, suspensions, dry powder formulations, emulsions or oils. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, and injectable organic esters such as ethyl oleate. Examples of oils are those of animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, olive oil, sunflower oil, fish-liver oil, another marine oil, or a lipid from milk or eggs.

The present disclosure also relates to transpulmonary administration by inhalation of the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples as a dry powder, gaseous or volatile formulation into systemic circulation via the respiratory tract. Absorption is virtually as rapid as the formulation can be delivered into the alveoli of the lungs, since the alveolar and vascular epithelial membranes are quite permeable, blood flow is abundant and there is a very large surface for adsorption. For instance, aerosols may be delivered from pressure-packaged, metered-dose inhalers (MDIs).

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples would generally be administered in a mixture with a suitable pharmaceutical excipient, diluent or carrier selected with regard to the chosen means of inhalation and standard pharmaceutical practice.

In another example of the disclosure, the IL-18 binding molecule, particularly the IL-18BP or the composition provided herein, is formulated as a dry powder, optionally together with at least one particulate pharmaceutically acceptable carrier, which may be one or more materials known as pharmaceutically acceptable carriers, preferably chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose,

glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran, mannitol or sorbitol. An especially preferred carrier is lactose, for example lactose monohydrate or anhydrous lactose. The dry powder may be contained as unit doses in capsules of, for example, gelatin or plastic, or in blisters (e.g. of aluminium or plastic), for use in a dry powder inhalation device, which may be a single dose or multiple dose device, preferably in dosage units together with the carrier in amounts to bring the total weight of powder per capsule to from 5 mg to 50 mg. Alternatively, the dry powder may be contained in a reservoir in a multi-dose dry powder inhalation (MDDPI) device adapted to deliver.

Any other therapeutically efficacious route of administration may be used, for example absorption through epithelial or endothelial tissues or by gene therapy wherein a DNA molecule encoding the active agent is administered to the patient (e.g. via an expression vector), which causes the active agent to be expressed and secreted *in vivo*.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples may be used for treatment of a cancer as described herein in the various examples in human and veterinary medicine for treating humans and animals, including avians, non-human primates, dogs, cats, pigs, goats, sheep, cattle, horses, mice, rats and rabbits.

In a specific example, the present disclosure provides the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples for use in the treatment of cancer as described herein in the various examples, wherein the subject is a mammal, in particular wherein the subject is a human.

Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media such as phosphate buffered saline solutions, water, emulsions, such as oil/water emulsions, various types of wetting agents, sterile solutions etc. Compositions comprising such carriers can be formulated by well known conventional methods. Suitable carriers may comprise any material which, when combined with the biologically active compound of the disclosure, the compound retains the biological activity.

Efforts have been made in the art to chemically modify the barrier properties of skin to permit the penetration of certain agents, enhance the effectiveness of the agent being delivered, enhance delivery times, reduce the dosages delivered, reduce the side effects from various delivery methods, reduce patient reactions, and so forth.

In this regard, penetration enhancers have been used to increase the permeability of the dermal surface to drugs and are often proton accepting solvents such as dimethyl sulfoxide (DMSO) and dimethylacetamide. Other penetration enhancers that have been studied and reported as effective include 2-pyrrolidine, N,N-diethyl-m-toluamide (Deet), 1-dodecylazacycloheptane-2-one, N,N-dimethylformamide, N-methyl-2-pyrrolidine, calcium

thioglycolate, hexanol, fatty acids and esters, pyrrolidone derivatives, derivatives of 1,3-dioxanes and 1,3-dioxolanes, 1-N-dodecyl-2-pyrrolidone-5-carboxylic acid, 2-pentyl-2-oxo-pyrrolidineacetic acid, 2-dodecyl-2-oxo-1-pyrrolidineacetic acid, 1-azacycloheptan-2-one-2-dodecylacetic acid, and aminoalcohol derivatives, including derivatives of 1,3-dioxanes, among others.

Preparations for transmucosal administration may include sterile aqueous or non-aqueous solutions, suspensions, dry powder formulations and emulsions. Examples of non-aqueous solvents are propylene glycol, polyethylene glycol, vegetable oils such as olive oil, and injectable organic esters such as ethyl oleate. Aqueous carriers include water, alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Transmucosal vehicles may include sodium chloride solution, Ringer's dextrose, dextrose and sodium chloride, lactated Ringer's, or fixed oils. Preservatives and other additives may also be present including, for example, antimicrobials, anti-oxidants, chelating agents, and inert gases and the like. In addition, the pharmaceutical composition of the present disclosure might comprise proteinaceous carriers, like, e.g., serum albumin or immunoglobulin, preferably of human origin.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples may be administered topically to body surfaces and, thus, be formulated in a form suitable for topical administration. Suitable topical formulations include gels, ointments, creams, lotions, drops and the like. For topical administration, the composition of the disclosure as disclosed herein in the various examples is prepared and applied as a solution, suspension, or emulsion in a physiologically acceptable diluent with or without a pharmaceutical carrier.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples may also be administered as controlled-release compositions, i.e. compositions in which the active ingredient is released over a period of time after administration. Controlled- or sustained-release compositions include formulation in lipophilic depots (e.g. fatty acids, waxes, oils). In another example, the composition is an immediate-release composition, i.e. a composition in which all the active ingredient is released immediately after administration.

Further examples for suitable formulations are provided in WO 2006/085983, the entire contents of which is herein incorporated by reference. For example, the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure and as disclosed herein in the various examples is of the present disclosure may be provided as liposomal formulations. The technology for forming liposomal suspensions is well known in the art. The lipid layer employed can be of any conventional composition and can either contain cholesterol or can be cholesterol-free. The liposomes can be reduced in size, as through the use of

standard sonication and homogenization techniques. Liposomal formulations containing the pharmaceutical composition of the disclosure as disclosed herein in the various examples can be lyophilized to produce a lyophilizate which can be reconstituted with a pharmaceutically acceptable carrier, such as water, to regenerate a liposomal suspension. The pharmaceutical composition of the disclosure as disclosed herein in the various examples can be administered to the subject at a suitable dose. The dosage regimen will be determined by the attending physician and clinical factors. As is well known in the medical arts, dosages for any one subject depend upon many factors, including the subject's size, body surface area, age, the particular compound to be administered, sex, time and route of administration, general health, and other drugs being administered concurrently.

The dosage of the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples will depend on the condition being treated, the particular composition used, and other clinical factors such as weight, size and condition of the subject, body surface area, the particular compound or composition to be administered, other drugs being administered concurrently, and the route of administration.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples may be administered in combination with other biologically active substances and procedures for the treatment of symptoms associated with cancer therapy. The other biologically active substances may be part of the same composition already comprising the composition according to the disclosure, in form of a mixture, wherein the composition of the disclosure and the other biologically active substance are intermixed in or with the same pharmaceutically acceptable solvent and/or carrier or may be provided separately as part of a separate compositions, which may be offered separately or together in form of a kit of parts. Within the present disclosure, the other biologically active substance may, for example, be a checkpoint inhibitor, such as a CTLA-4, PD-1 or PD-L1 inhibitor.

The IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples may be administered concomitantly with the other biologically active substance or substances, intermittently or sequentially. For example, the composition according to the disclosure may be administered simultaneously with a first additional biologically active substance or sequentially after or before administration of said composition. If an application scheme is chosen where more than one additional biologically active substance is administered and at least one composition according to the disclosure, the compounds or substances may be partially administered simultaneously, partially sequentially in various combinations.

The present disclosure thus provides for mixtures of the IL-18 binding molecule or the composition comprising the IL-18 binding molecule of the disclosure as disclosed herein in the various examples, optionally comprising, one or more further biologically active substances in a therapeutically or prophylactically effective amount, as well as to methods of using such a mixture for prevention and/or therapeutic treatment.

The other biologically active substance or compound may exert its biological effect by the same or a similar mechanism as the composition according to the disclosure or by an unrelated mechanism of action or by a multiplicity of related and/or unrelated mechanisms of action.

Suitable dosages of the composition of the disclosure as disclosed herein in the various examples will vary depending upon the condition, age and species of the subject, and can be readily determined by those skilled in the art. The total daily dosages of the employed in both veterinary and human medicine will suitably be in the range of 0.1 to 10 mg per kilogram.

Further, functional derivatives of the IL-18 binding molecule, particularly the IL-18BP, may be conjugated to polymers in order to improve the properties of the protein, such as the stability, half-life, bioavailability, tolerance by the human body, or immunogenicity. To achieve this goal, IL-18BP may be linked e.g. to Polyethyleneglycol (PEG). PEGylation may be carried out by known methods, described in WO 92/13095, for example.

Therefore, in another example of the present disclosure, IL-18BP is PEGylated.

In still another example of the disclosure, IL-18BP is a fused protein comprising all or part of an IL-18BP, which is fused to all or part of an immunoglobulin, preferably to the constant region (Fc) of an immunoglobulin, and wherein the fused protein is still capable of binding to IL-18. More specifically, the immunoglobulin may be of the IgG1 or IgG2 isotype.

In a further example of the disclosure, the IL-18BP is PEGylated, fused to all or part of an immunoglobulin, preferably to the constant region (Fc) of an immunoglobulin, and wherein the fused protein is still capable of binding to IL-18. More specifically, the immunoglobulin may be of the IgG1 or IgG2 isotype.

The person skilled in the art will understand that the resulting fusion protein retains the biological activity of IL-18BP, in particular the binding to IL-18. The fusion may be direct, or via a short linker peptide which can be as short as 1 to 3 amino acid residues in length or longer, for example, 13 amino acid residues in length. Said linker may be a tripeptide of the sequence E-F-M (Glu-Phe-Met), for example, or a 13-amino acid linker sequence comprising Glu-Phe-Gly-Ala-Gly-Leu-Val-Leu-Gly-Gly-Gln-Phe-Met (SEQ ID NO: 1) introduced between the IL-18BP sequence and the immunoglobulin sequence. The resulting fusion protein has improved properties, such as an extended residence time in body fluids (half-life), increased specific activity, increased expression level, or the purification of the fusion protein is facilitated.

Preferably, it is fused to heavy chain regions, like the CH2 and CH3 domains of human IgG1, for example. The generation of specific fusion proteins comprising IL-18BP and a portion of an immunoglobulin are described in example 11 of WO99/09063, for example. Other isoforms of Ig molecules are also suitable for the generation of fusion proteins according to the present disclosure, such as isoforms IgG2 or IgG4, or other Ig classes, like IgM or IgA, for example. Fusion proteins may be monomeric or multimeric, hetero or homomultimeric.

DEFINITIONS

The technical terms and expressions used within the scope of this application are generally to be given the meaning commonly applied to them in the pertinent art if not otherwise indicated herein below.

As used in this specification and the appended embodiments, the singular forms "a", "an", and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a compound" includes one or more compounds.

The terms "treatment", "treating" and the like are used herein to generally mean obtaining a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing a disease or symptom thereof and/or may be therapeutic in terms of partially or completely curing a disease and/or adverse effects attributed to the disease. The term "treatment" as used herein covers any treatment of a disease in a subject and includes: (a) preventing a disease, i.e. related to an undesired immune response from occurring in a subject which may be predisposed to the disease; (b) inhibiting the disease, i.e. arresting its development; or (c) relieving the disease, i.e. causing regression of the disease (d) reversing the disease symptoms, i.e. leading to recovery of damaged tissue.

The expression "IL-18 Binding Protein (IL-18BP)" as used herein includes the full-length protein, as well as a mutein, fragment, peptide, functional derivative, functional fragment, fraction, circularly permuted derivative, fused protein comprising IL-18BP, isoform or a salt thereof, which have retained the specific activity of the full-length reference protein, particularly the CAR-T modulating activity as described herein.

The term "free IL-18" as used herein means monomeric, soluble and non-complexed interleukin-18 protein.

The term "functional" and "active" are used herein synonymously and refers to a modified IL-18 binding molecule, particularly a modified IL-18BP, or to a part thereof, which still has the same or essentially the same biological, pharmacological and therapeutic properties as the unmodified or full length IL-18 binding molecule, particularly the unmodified IL-18BP, and can thus be used within the present invention for the treatment of the diseases and disorders as disclosed herein the same way as the unmodified or full length IL-18 binding molecule, particularly as the unmodified IL-18BP. In particular, by "functional" is meant that the modified

CLAIMS

1. Use of an IL-18 binding molecule in the manufacture of a medicament for avoiding or minimizing side effects related to a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient diagnosed with a disease associated with expression of a tumor antigen.
2. The use of claim 1, wherein the IL-18 binding molecule is a modulator of IL-18 levels in the patient to avoid or minimize side effects related to the CAR-T therapy.
3. The use of claim 2, wherein the IL-18 levels are levels of free IL-18.
4. The use of any one of claims 1 to 3, wherein the IL-18 binding molecule inhibits IFN-gamma secretion.
5. The use of any one of claims 1 to 4, wherein the IL-18 binding molecule inhibits IL-18 mediated stimulation of IFN-gamma secretion, that is further elevated by IL-12.
6. The use of any one of claims 1 to 5, wherein a population of cells is used in the CAR-T therapy, which are engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain.
7. The use of claim 6, wherein the cells are further engineered to express IL-18.
8. The use of any one of claims 1 to 7, wherein the IL-18 binding molecule
 - (a) is a modulator of free IL-18 levels in the patient; or
 - (b) decreases the IL-18 levels, particularly the free IL-18 levels, in the patient.
9. The use of any one of claims 1 to 15, wherein the IL-18 binding molecule is
 - (a) an IL-18 binding protein (IL-18BP), including any functional equivalent or functional part thereof which retains the modulator activity
 - (b) an IL-18 binding antibody that specifically binds to free IL-18, but not to IL-18 bound in a complex, including any functional equivalent or functional part thereof which retains the modulator activity;
 - (c) a human IL-18BP (hIL-18 BP), preferably a recombinant human IL-18BP (rhIL-18 BP), including any functional equivalent or functional part thereof, which retains the modulator activity;

- (d) a human IL-18BP is selected from isoform a, b, c and d of human IL-18BP, particularly isoform a as in SEQ ID NO: 2, isoform b as in SEQ ID NO: 3, isoform c as in SEQ ID NO: 4 or isoform d as in SEQ ID NO: 5, including any functional equivalent or functional part of isoforms a, b, c and/or d, which retains the modulator activity; or
- (e) an IL-18BP as shown in SEQ ID NO: 2, including any functional equivalent or functional part thereof, which retains the modulator activity, preferably wherein the functional equivalent has a sequence identity of 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% to the sequence depicted in SEQ ID NO: 2 and retains the modulator activity, optionally wherein the functional equivalent or functional part thereof includes a mutein of IL-18BP, a fragment, a peptide, a functional derivative, a functional fragment, a fraction, a circularly permuted derivative, a fused protein comprising IL-18BP, an isoform or a salt thereof which retains the modulator activity.
10. Use of a pharmaceutical composition comprising an IL-18 binding molecule, particularly an IL-18 binding molecule defined in claim 9, in the manufacture of a medicament for avoiding or minimizing side effects related to a Chimeric Antigen Receptor T-cell (CAR-T) therapy of a patient, diagnosed with a disease associated with expression of a tumor antigen, optionally wherein the composition comprises a pharmaceutically acceptable carrier and/or solvent and/or excipient.
 11. The use of claim 10, wherein the composition is a modulator of IL-18 levels in the patient to avoid or minimize side effects related to the CAR-T therapy.
 12. The use of claim 10 or 11, wherein the composition comprises
 - (i) a population of cells engineered to express a chimeric antigen receptor (CAR), wherein the CAR comprises an antigen-binding domain, a transmembrane domain, and an intracellular signaling domain, and
 - (ii) an IL-18 binding molecule, particularly the IL-18 binding molecule of any one of claims 15 to 20.
 13. The use of claim 12, wherein the population of cells of (i) are further engineered to express IL-18.
 14. The use of any one of claims 10-13, wherein the IL-18 binding protein (IL-18BP) further comprises N-terminal and/or C-terminal deletion variants of IL-18BP.
 15. The use of any one of claims 10-14, wherein the composition comprises N- terminal and/or C-terminal deletion variants of IL-18BP in an amount of up to 40%, particularly up to 30%, particularly up to 20%, particularly up to 15%, particularly up to 10%,

particularly up to 7.5%, particularly up to 5%, particularly up to 2.5%, particularly up to 1%, particularly up to 0.5%, particularly up to 0.25%, particularly up to 0.1%, particularly up to 0.05%, particularly up to 0.01%.

16. The use of claim 14 or 15, 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.
17. The use of any one of claims 14-16, wherein said N- terminal and/or C-terminal deletion variants of IL-18BP are present in an amount of up to 40%, particularly in an amount of between 2% and 35%.
18. The use of any one of claims 1-9 or 10-17, wherein the IL-18 binding molecule or composition control and/or modulates, particularly decreases IL-18 levels, particularly free IL-18 levels, in the patient.
19. The use of any one of claims 1-18, wherein the disease is a proliferative disease, a precancerous condition, a cancer, and a non-cancer related indication associated with expression of the tumor antigen.
20. The use of any one of claims 1-19, wherein the patient is an animal, particularly a human.
21. The use of any one of claims 1-20, wherein the patient has cancer, particularly a hematological cancer or a solid tumor, particularly a tumor expressing tumor-associated antigens.
22. The use of claim 21, wherein the cancer is a hematologic cancer selected from one or more of chronic lymphocytic leukemia (CLL), acute leukemia, acute lymphoid leukemia (ALL), B-cell acute lymphoid leukemia (B-ALL), T-cell acute lymphoid leukemia (T-ALL), chronic myelogenous leukemia (CML), B cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative condition, MALT lymphoma, mantle cell lymphoma, marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, and Waldenstrom macroglobulinemia; or

wherein the cancer is a solid tumor, particularly selected from the group consisting of colon cancer, rectal cancer, renal-cell carcinoma, liver cancer, non-small cell carcinoma of the lung, cancer of the small intestine, cancer of the esophagus, melanoma, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, uterine cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, solid tumors of childhood, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, environmentally induced cancer, combinations of said cancers, and metastatic lesions of said cancers.

23. The use of any one of claims 1-22, wherein the side effects are due to an overshooting of the immune system and/or a cytokine release syndrome, optionally wherein the side effects are selected from the group consisting of unremitting fevers, hypotension, hypoxia (lung involvement), other end-organ damage and dysfunction including but not limited to liver and kidney, cytopenias, coagulopathy, hemophagocytosis and neurologic toxicities.
24. The use of any one of claims 1-23 wherein in a body fluid of the patient an abnormal level of free IL-18 has been determined, in particular wherein the level of free IL-18 exceeds 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 the IL-18 binding molecule as defined in claim 9.
25. The use of claim 24, wherein the assay for quantifying the level of free IL-18 in the body fluid(s) comprises the following steps:
 - a) bringing a sample of body fluid suspected to contain free IL-18 into contact with the IL-18 binding molecule as defined in claim 9 as the capturing molecule for free IL-18;
 - b) allowing the IL-18 binding molecule to bind to free IL-18; and
 - c) detecting the binding of the IL-18 binding molecule and determining the amount of free IL-18 in the sample.

optionally wherein the body fluid is 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 or expiration, sputum, bronchoalveolar fluid, sebum, cellular, gland, mucosa and tissue secretion.

26. The use of any one of claims 1-25 wherein the therapy of the patient further comprises the use of one or more check-point inhibitor(s) optionally, wherein the check-point inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor or a PD-L1 inhibitor.