

BRIEF SUMMARY

[0008a] In an aspect of the present disclosure, there is provided a use of a binding protein in a manufacture of a medicament for removal or reducing the number of a disease-causing agent by targeted phagocytosis of the disease-causing agent, wherein the binding protein comprises a first binding domain that specifically binds to the agent, a second binding domain that binds to Dectin-1 expressed on a macrophage and induces phagocytosis activity of the macrophage by activating Dectin-1, and an immunoglobulin Fc domain.

[0009] The present disclosure relates to a method of removal and degradation the numbers of disease-causing agents including host cells, or host cells products, microbes or their products in a human subject upon administration of a molecule that comprises a first binding domain that specifically binds to the agent, a second binding domain that binds to a phagocytotic receptor, Dectin-1, expressed on a macrophage and induces phagocytosis, and an immunoglobulin Fc domain. In a specific embodimentexample, a method of the disclosure depletes or reduces the number of disease-causing agents in tissues, blood, and/or bone marrow by targeted phagocytosis.

[0010] In some embodimentexamples, provided herein is a method of reducing number of a disease-causing agent by targeted phagocytosis in a subject, comprising administering to said subject a binding protein comprising a first binding domain that specifically binds to the agent, and a second binding domain that binds to a phagocytotic receptor expressed on a macrophage, monocyte, and/or granulocyte and induces phagocytosis activity of the macrophage, monocyte, and/or granulocyte. In some embodimentexamples, the phagocytotic receptor is Dectin-1, *e.g.*, human Dectin-1. In some embodimentexamples, provided herein is a method of reducing number of a disease-causing agent in a subject, comprising administering to said subject a binding protein comprising a first binding domain that specifically binds to the agent and a second binding domain that binds to Dectin-1. In some embodimentexample, the binding protein further comprises an immunoglobulin Fc domain. In some embodimentexamples, the binding protein is an antibody (*e.g.*, a multispecific or bispecific antibody). In some embodimentexamples, the subject is a human. In some embodimentexamples, the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by the disease-causing agent. In some embodimentexamples, the subject is a human. In some embodimentexamples, the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by the disease-causing agent, wherein the bispecific antibody has a format shown and/or described in reference to **FIG. 1A**.

[0011] In some [embodimentexamples](#), administration of the binding protein reduces the number of the agent. In some [embodimentexamples](#), administration of the binding protein reduces the number of the agent to below the limit of detection. In some [embodimentexamples](#), administration of the binding protein reduces the number of the agent for at least about 1 week after dosing of the binding protein. In some [embodimentexamples](#), administration of the binding protein reduces the number of the agent within 12 hours, within 24 hours, within 36 hours, or within 48 hours after administration. In some [embodimentexamples](#), reduction of the disease-causing agent is reversible, *e.g.*, after

administration of the binding protein is ceased. In some [embodimentexamples](#), administration of the binding protein reduces severity and/or incidence of one or more symptoms in the subject.

[0012] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of one or more disease-associated proteins or protein aggregates. In some [embodimentexamples](#), the method results in inhibition of aberrant protein accumulation. In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of a disease, *e.g.*, a neurodegenerative disease, fibrosis, or amyloidosis. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target protein or protein aggregate.

[0013] In some [embodimentexamples](#), the method results in removal and/or reduction in number of cancer, tumor or lymphoma cells. In some [embodimentexamples](#), the method results in alleviating one or more symptoms of cancer and/or preventing progression of cancer. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a cancer cell (*e.g.*, a tumor antigen expressed on the surface of a cancer cell).

[0014] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of one or more microbes (*e.g.*, a bacterial cell, fungal cell, protozoan cell, or virus). In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of a disease or infection caused by a microbe (*e.g.*, a bacterial cell, fungal cell, protozoan cell, or virus). In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a bacterial cell (*e.g.*, an antigen expressed on the surface of a bacterial cell). In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a fungal cell (*e.g.*, an antigen expressed on the surface of a fungal cell). In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a protozoan cell (*e.g.*, an antigen expressed on the surface of a protozoan cell). In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a virus (*e.g.*, an antigen expressed on the surface of virus).

[0015] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of senescent cells and/or their product(s). In some [embodimentexamples](#), the method results in alleviating or preventing progression of ageing, *e.g.*, in one or more age-related symptoms or conditions. In

some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a senescent cell (*e.g.*, an antigen expressed on the surface of a senescent cell).

[0016] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of LDL and other agents that induce cardiovascular disease, *e.g.*, arteriosclerosis or familial hypercholesterolemia. In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of a cardiovascular disease, *e.g.*, arteriosclerosis or familial hypercholesterolemia. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a lipoprotein particle (*e.g.*, LDL).

[0017] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of mast cells. In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of a mast cell-related disease, *e.g.*, allergy, fibrosis, COPD, asthma, or other immunoproliferative, mast cell-related diseases. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by a mast cell (*e.g.*, an antigen expressed on the surface of a mast cell).

[0018] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of eosinophils. In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of an eosinophil-related disease, *e.g.*, allergy, fibrosis, COPD, asthma, or other immunoproliferative, eosinophil-related diseases. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by eosinophil (*e.g.*, an antigen expressed on the surface of an eosinophil).

[0019] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of ILC2 cells. In some [embodimentexamples](#), the method results in alleviating or preventing progression of one or more symptoms of an ILC2-related disease, *e.g.*, allergy, fibrosis, COPD, asthma, or other immunoproliferative, ILC2-related diseases. In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by an ILC2 cell (*e.g.*, an antigen expressed on the surface of an ILC2 cell).

[0020] In some [embodimentexamples](#), the method results in removal and/or reduction in levels of inflammatory immune cells, *e.g.*, in one or more tissues selected from the group consisting of muscles, GI tract, lungs, heart, joints, and brain. In some [embodimentexamples](#), the method results in

alleviating or preventing progression of one or more symptoms of myositis, IBD, RA, allergy, fibrosis, COPD, asthma, or other immunoproliferative, inflammatory immune cell-related diseases.

In some [embodimentexamples](#), the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin-1 and a second binding domain that binds to a target antigen expressed by an inflammatory immune cell (*e.g.*, an antigen expressed on the surface of an inflammatory immune cell).

[0021] In some [embodimentexamples](#), the binding protein is an antibody; two antibodies or IgGs that are covalently linked; IgG-scFv; intrabody; peptibody; nanobody; single domain antibody; SMTP; multispecific antibody (*e.g.*, bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFv, tandem tri-scFv, ADAPTIR); Fab, Fab', F(ab')₂, or Fv fragment; Fab'-SH or F(ab')₂ diabody; linear antibody; scFv antibodies; VH antibody; or multispecific antibody formed from antibody fragments. In some [embodimentexamples](#), one or more binding domain(s) of the binding protein are non-human, chimeric, humanized, or human. In some [embodimentexamples](#), one or more binding domain(s) of the binding protein are humanized or human. In some [embodimentexamples](#), both binding domains of the binding protein are non-human, chimeric, humanized, or human. In some [embodimentexamples](#), both binding domains of the binding protein are humanized or human.

[0022] It is to be understood that one, some, or all of the properties of the various [embodimentexamples](#) described herein may be combined to form other [embodimentexamples](#) of the present disclosure. These and other [aspectexamples](#) of the present disclosure will become apparent to one of skill in the art. These and other [embodimentexamples](#) of the present disclosure are further described by the detailed description that follows.

BRIEF DESCRIPTION OF THE DRAWINGS

[0023] **FIG. 1A** provides schematic diagrams of antibody molecules for targeted phagocytosis, in accordance with some embodiments. A bispecific antibody that binds to Dectin-1 (d) and a disease-causing agent (a) is shown in **FIG. 1A** at panel A. Examples of IgG-scFv molecules are shown in **FIG. 1A** at panels B and C. Two IgG molecules covalently coupled (IgG₂) are shown in **FIG. 1A** at panel D. An IgG that is specific for a disease-causing agent covalently attached to a β -1, 6-linked glucans containing carbohydrate such as curdlan (c).

[0024] **FIG. 1B** provides a schematic overview of the mechanism of action for the removal and degradation of disease-causing agent through phagocytosis by monocytes/macrophages. The present disclosure describes the development of a molecule, such as a bispecific antibody, that binds to the phagocytic receptor Dectin-1 on one arm and a disease-causing agent (*e.g.* tumor cells, bacteria, viruses, LDL, protein aggregates, etc.) on the other arm. Upon engagement, the disease-causing agent is engulfed by the phagocyte and eliminated through the endo-lysosomal

CLAIMS

What is claimed is:

1. ~~A method of Use of a binding protein in a manufacture of a medicament for~~ removal or reducing the number of a disease-causing agent by targeted phagocytosis ~~of the disease-causing agent, in a human subject comprising administering to said subject a~~wherein the binding protein comprises a first binding domain that specifically binds to the agent, a second binding domain that binds to ~~a phagocytotic receptor, Dectin-1,~~ expressed on a macrophage and induces phagocytosis activity of the macrophage ~~by activating Dectin-1,~~ and an immunoglobulin Fc domain.

2. The use of claim 1, wherein the binding protein is a bispecific antibody comprising the first and second binding domains, wherein the second binding domain binds to Dectin-1, and wherein the first binding domain binds to a target antigen expressed by the disease-causing agent.

~~2. The method of claim 1, wherein the administration of the antibody reduces the number of the agent below the limit of detection and the level remains below detection for at least about 1 week after dosing of the antibody.~~

~~3. The method of claim 1, wherein the reduction of the disease-causing agent takes place within the first 24 hours or 48 hours after administration.~~

~~4. The method of claim 1, wherein the reduction of the disease-causing agent is reversible.~~

~~5.3.~~ The method use of claim 1 or claim 2, wherein said reduction of the disease-causing agent leads to a reduction in symptoms.

4. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to a target protein aggregate, and the second binding domain binds to Dectin-1.

5. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to a tumor antigen expressed on the surface of a cancer cell, and the second binding domain binds to Dectin-1.

6. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of a bacterial cell, fungal cell, protozoan cell, or virus, and the second binding domain binds to Dectin-1.
7. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of a senescent cell, and the second binding domain binds to Dectin-1.
8. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an LDL lipoprotein particle, and the second binding domain binds to Dectin-1.
9. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of a mast cell, and the second binding domain binds to Dectin-1.
10. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of an eosinophil, and the second binding domain binds to Dectin-1.
11. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of an ILC2 cell, and the second binding domain binds to Dectin-1.
12. The use of claim 2 or claim 3, wherein the binding protein is a bispecific antibody wherein the first binding domain binds to an antigen expressed on the surface of an inflammatory immune cell, and the second binding domain binds to Dectin-1.
- ~~6. The method of any one of claims 1-5, wherein the method is used to remove disease-associated protein and protein aggregates to inhibit aberrant protein accumulation and therefore alleviating or preventing progression of the disease including neurodegenerative, fibrosis or amyloidoses.~~
- ~~7. The method of any one of claims 1-5, wherein the method is used to remove or reduce level of cancer, tumor or lymphoma cells and therefore inhibit or prevent progression of the disease.~~

8. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level a microbe (e.g., bacteria, fungus, virus), a protozoan parasite and therefore inhibit or prevent progression of the disease.~~
9. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of senescent cells and their products and therefore inhibit or prevent progression of ageing.~~
10. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level a microbe (e.g., bacteria, fungus, virus), a protozoan parasite and therefore inhibit or prevent progression of the disease.~~
11. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of LDL and other agents that induce cardiovascular diseases including arteriosclerosis or familial hypercholesterolemia and therefore inhibit or prevent progression of the diseases.~~
12. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of mast cells and therefore inhibit or prevent progression of allergy, fibrosis, COPD, asthma and other mast cells related disease including immunoproliferative diseases.~~
13. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of eosinophils and therefore inhibit or prevent progression of allergy, fibrosis, COPD, asthma and other eosinophil related disease including immunoproliferative diseases.~~
14. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of ILC2 cells and therefore inhibit or prevent progression of allergy, fibrosis, COPD, asthma and other ILC2 cells related disease including immunoproliferative diseases.~~
15. — ~~The method of any one of claims 1-5, wherein the method is used to remove or reduce level of inflammatory immune cells in muscles, GI tract, lungs, heart, joints, brain and other organs and therefore inhibit or prevent progression of myositis, IBD, RA, allergy, fibrosis, COPD, asthma and other immune cells related disease including immunoproliferative diseases.~~
- 16.13.** The method use of any one of ~~the preceding~~ claims 1-12, wherein the binding protein is selected from specific antibodies; comprises two antibodies or IgGs (IgG2) that are covalently linked; an IgG-scFv; an intrabodyies, peptibodyies, nanobodyies, single domain antibodyies, SMTPs, and a multispecific antibodyies (e.g., bispecific antibodies, diabodies, triabodies, tetrabodies, tandem di-scFV, tandem tri-scFv, ADAPTIR); a Fab, Fab', F(ab')₂, and or Fv

fragments; a Fab'-SH, or F(ab')₂, diabodyies,; linear antibodyies,; an scFv antibodyies,; a VH antibody,; and or a multispecific antibodyies formed from antibody fragments.

14. The use of claim 13, wherein the multispecific antibody is a bispecific antibody, diabody, triabody, tetrabody, tandem di-scFV, tandem tri-scFv, or ADAPTIR.

17.15. The ~~method-use~~ of claim ~~16~~13 or claim 14, wherein the binding domains of the binding protein is/are non-human, chimeric, humanized, or human, ~~preferably humanized or human.~~

16. The use of claim 15, wherein the binding domains of the binding protein is/are humanized or human.

18. —~~The method of any one of the preceding claims, wherein the binding protein is a bispecific antibody comprising a first binding domain that binds to Dectin 1 and a second binding domain that binds to a target antigen expressed by the disease-causing agent.~~