MULTIVALENT AND MULTISPECIFIC CYTOKINE ANTAGONISTS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/433,476 (filed on December 18, 2022), the disclosure of which is incorporated by reference herein in its entirety for all purposes.

SEQUENCE LISTING

[0002] The present specification makes reference to a Sequence listing which has been submitted electronically in XML format and is hereby incorporated by reference in its entirety. Said XML file, created on December 13, 2023, is named RBT-052WO_SL.xml, and is 330 kb in size.

BACKGROUND

[0003] Cytokines are small proteins which have diverse roles in controlling growth and activity of cells such as immune cells and tumor cells. Anti-cytokine therapy is an emerging treatment paradigm for a variety of human diseases and conditions, including cancer and autoimmune disease. One challenge faced by this treatment modality stems from the complex disease biology, which may involve multiple pathophysiological processes driven by distinct cytokines. Therefore, therapeutic agents which can only target an individual cytokine may lack efficacy.

[0004] There is a need for anti-cytokine therapeutics with improved efficacy.

SUMMARY

[0005] The present disclosure addresses this need with the provision of self-assembled polypeptide complexes whose specificities and valences can be tuned to enhance efficacy. In certain embodiments, the provided complexes are multispecific, e.g., capable of binding (e.g., specifically binding) to more than one cytokine. Provided self-assembled polypeptide complexes generally display one or more types of cytokine-binding moieties and optionally display one or more tumor-binding moieties. Such self-assembled polypeptide complexes may be used to sequester cytokines, thereby interfering with cytokine signaling. Also disclosed are related fusion proteins, complexes, compositions, and methods.

[0006] In one aspect, provided are fusion polypeptides comprising: (1) a cytokine-binding moiety and (2) a nanocage monomer or subunit thereof.

[0007] In some examples, the cytokine-binding moiety comprises an antibody or antigen-binding fragment thereof.

[0008] In some examples, the antibody or antigen-binding fragment thereof comprises an immunoglobulin heavy chain variable region (V_H) and an immunoglobulin light chain variable region (V_L or V_K).

[0009] In some examples, the antibody or antigen-binding fragment thereof comprises a Fab fragment.

[0010] In some examples, the Fab fragment is a single-chain Fab fragment (scFab).

[0011] In some examples, the cytokine-binding moiety is capable of binding to interleukin-6 (IL-6) or interleukin-11 (IL-11).

[0012] In some examples, the cytokine-binding moiety comprises an antibody fragment comprising a heavy chain variable region (V_H) and light chain variable region (V_L or V_K), wherein the CDRs of the V_H and the V_L or V_K (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) have sequences which each differ by at most two amino acids from the CDRs of an IL-6 or IL-11 antibody.

[0013] In some examples, the CDRs of the V_H and the V_L or V_K have sequences which are identical to those of the heavy and light chain CDRs of an IL-6 or IL-11 antibody, except for one or two amino acid substitutions total across all six CDRs.

[0014] In some examples, the CDRs of the V_H and the V_L or V_K are identical to those of the heavy and light chain CDRs of an IL-6 or IL-11 antibody.

[0015] In some examples, the cytokine-binding moiety comprises an antibody fragment comprising heavy and light chain variable regions with sequences that have at least 85% identity to those of the heavy and light chain variable regions of an IL-6 or IL-11 antibody.

[0016] In some examples, the cytokine-binding moiety is capable of binding to an epitope of interleukin-6 (IL-6), which epitope is involved in binding of IL-6 to IL-6 receptor (IL-6Rα).

[0017] In some examples, the cytokine-binding moiety is capable of binding to an epitope of IL-6 that is involved in binding of IL-6 to glycoprotein 130 (gp130).

[0018] In some examples, the nanocage monomer is a ferritin monomer or a subunit thereof.

[0019] In some examples, the ferritin monomer is a human ferritin monomer.

[0020] In some examples, the ferritin monomer is a ferritin light chain.

[0021] In some examples, the cytokine-binding moiety is linked via an amino acid linker to the nanocage monomer or subunit thereof.

[0022] In some examples, the cytokine-binding moiety is linked via the N-terminus of the nanocage monomer or subunit thereof.

[0023] In one aspect, provided are a self-assembled polypeptide complexes comprising: (a) a plurality of first cytokine-binding fusion polypeptides, each first cytokine-binding fusion polypeptide being a fusion polypeptide as disclosed herein; and (b) a plurality of Fc fusion polypeptides, each Fc fusion polypeptide comprising (1) an Fc polypeptide and (2) a nanocage monomer or subunit thereof.

[0024] In some examples, the self-assembled polypeptide complex further comprises (c) a plurality of second cytokine-binding fusion polypeptides, each second cytokine-binding fusion polypeptide being a fusion polypeptide as disclosed herein, wherein the first and second cytokine-binding fusion polypeptides comprise first and second cytokine-binding moieties, respectively, which are capable of binding to different epitopes.

[0025] In some examples, the first and second cytokine-binding moieties are capable of binding to different cytokines.

[0026] In some examples, the first cytokine-binding moiety is capable of binding to IL-6 and the second cytokine-binding moiety is capable of binding to IL-11.

[0027] In some examples, the self-assembled polypeptide complex further comprises (d) a plurality of tumor-binding fusion polypeptides, each tumor-binding fusion polypeptide comprising (1) tumor-binding moiety and (2) a nanocage monomer or subunit thereof.

[0028] In some examples, within each Fc fusion polypeptide, the Fc polypeptide is linked via an amino acid linker to the nanocage monomer or subunit thereof.

[0029] In some examples, the Fc polypeptide is linked via the N-terminus of the nanocage monomer or subunit thereof.

[0030] In some examples, the Fc polypeptide is linked via the C-terminus of the nanocage monomer or subunit thereof.

[0031] In some examples, within each tumor-binding fusion polypeptide, the tumor-binding moiety is linked via an amino acid linker to the nanocage monomer or subunit thereof.

[0032] In some examples, the tumor-binding moiety is linked via the N-terminus of the nanocage monomer or subunit thereof.

[0033] In some examples, the tumor-binding moiety comprises an antibody or antigen-binding fragment thereof.

[0034] In some examples, the antibody or antigen-binding fragment thereof comprises an immunoglobulin heavy chain variable region (V_H) and an immunoglobulin light chain variable region (V_L or V_K).

[0035] In some examples, the antibody or antigen-binding fragment thereof comprises a Fab fragment. In some examples, the Fab fragment is a single-chain Fab fragment (scFab).

[0036] In some examples, the tumor-binding moiety is a PD-L1-binding moiety.

[0037] In some examples, the tumor-binding moiety comprises an antibody fragment comprising a heavy chain variable region (V_H) and light chain variable region (V_L or V_K), wherein the CDRs of the V_H and the V_L or V_K (CDR-H1, CDR-H2, CDR-H3, CDR-L1, CDR-L2, and CDR-L3) have sequences which each differ by at most two amino acids from the CDRs of a PD-L1 antibody.

[0038] In some examples, the CDRs of the V_H and the V_L or V_K have sequences which are identical to those of the heavy and light chain CDRs of a PD-L1 antibody, except for one or two amino acid substitutions total across all six CDRs.

[0039] In some examples, the CDRs of the V_H and the V_L or V_K are identical to those of the heavy and light chain CDRs of a PD-L1 antibody.

[0040] In some examples, the tumor-binding moiety comprises an antibody fragment comprising heavy and light chain variable regions with sequences that have at least 85% identity to those of the heavy and light chain variable regions of a PD-L1 antibody.

[0041] In some examples, the nanocage monomers within each Fc fusion polypeptide, each cytokine-binding fusion polypeptide, and/or each tumor-binding fusion polypeptide are each a ferritin monomer or a subunit thereof.

[0042] In some examples, the ferritin monomer is a human ferritin monomer.

[0043] In some examples, the ferritin monomer is a ferritin light chain.

[0044] In some examples, the self-assembled polypeptide complex does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.

[0045] In some examples, the self-assembled polypeptide complex does not comprise any iron-binding moieties.

[0046] In one aspect, described are a pharmaceutical compositions comprising a self-assembled polypeptide complex as disclosed herein and a pharmaceutically acceptable excipient.

[0047] In one aspect, described are uses of a self-assembled polypeptide complex or a pharmaceutical composition as disclosed herein in the manufacture of a medicament for treating, ameliorating, or preventing a disease or condition in a subject.

[0048] In one example, described are a methods of treating, ameliorating, or preventing a disease or condition, the method comprising administering to a subject a self-assembled polypeptide complex or a pharmaceutical composition as disclosed herein.

[0049] In some examples, the subject is a mammal, e.g., a human.

[0050] In some examples, the disease or condition is cancer, e.g., a solid cancer or a hematological cancer.

[0051] In some examples, the disease or condition is an autoimmune disease or condition.

CLAIMS

1. A fusion polypeptide comprising: (1) a cytokine-binding moiety and (2) a nanocage monomer or subunit thereof.

2. The fusion polypeptide of claim 1, wherein the cytokine-binding moiety comprises an antibody or antigen-binding fragment thereof.

3. The fusion polypeptide of claim 2, wherein the antibody or antigen-binding fragment thereof comprises an immunoglobulin heavy chain variable region (V_H) and an immunoglobulin light chain variable region (V_L or V_K).

4. The fusion polypeptide of claim 3, wherein the antibody or antigen-binding fragment thereof comprises a Fab fragment.

5. The fusion polypeptide of claim 4, wherein the Fab fragment is a single-chain Fab fragment (scFab).

6. The fusion polypeptide of any one of claims 1-5, wherein the cytokine-binding moiety is capable of binding to interleukin-6 (IL-6) or interleukin-11 (IL-11).

7. The fusion polypeptide of any one of claims 1-6, wherein the cytokine-binding moiety is capable of binding to an epitope of interleukin-6 (IL-6), which epitope is involved in binding of IL-6 to IL-6 receptor (IL-6Rα).

8. The fusion polypeptide of claim 6 or 7, wherein the cytokine-binding moiety is capable of binding to an epitope of IL-6 that is involved in binding of IL-6 to glycoprotein 130 (gp130).

9. The fusion polypeptide of any one of claims 1-8, wherein the nanocage monomer is a ferritin monomer or a subunit thereof.

10. The fusion polypeptide of claim 9, wherein the ferritin monomer is a human ferritin monomer.

11. The fusion polypeptide of claim 9 or 10, wherein the ferritin monomer is a ferritin light chain.

12. A self-assembled polypeptide complex comprising:

(a) a plurality of first cytokine-binding fusion polypeptides, each first cytokine-binding fusion polypeptide being a fusion polypeptide of any one of claims 1-11; and

(b) a plurality of Fc fusion polypeptides, each Fc fusion polypeptide comprising (1) an Fc polypeptide and (2) a nanocage monomer or subunit thereof.

13. The self-assembled polypeptide complex of claim 12, further comprising

(c) a plurality of second cytokine-binding fusion polypeptides, each second cytokine-binding fusion polypeptide being a fusion polypeptide of any one of claims 1-11,

wherein the first and second cytokine-binding fusion polypeptides comprise first and second cytokine-binding moieties, respectively, which are capable of binding to different epitopes.

14. The self-assembled polypeptide complex of claim 13, wherein the first and second cytokine-binding moieties are capable of binding to different cytokines.

15. The self-assembled polypeptide complex of claim 14, wherein the first cytokine-binding moiety is capable of binding to IL-6 and the second cytokine-binding moiety is capable of binding to IL-11.

16. The self-assembled polypeptide complex of any one of claims 12-15, further comprising

(d) a plurality of tumor-binding fusion polypeptides, each tumor-binding fusion polypeptide comprising (1) tumor-binding moiety and (2) a nanocage monomer or subunit thereof.

17. The self-assembled polypeptide complex of claim 16, wherein the tumor-binding moiety comprises an antibody or antigen-binding fragment thereof.

18. The self-assembled polypeptide complex of claim 17, wherein the tumor-binding moiety is a PD-L1-binding moiety.

19. The self-assembled polypeptide complex of any one of claims 12-18, wherein the nanocage monomers within each Fc fusion polypeptide, each cytokine-binding fusion polypeptide, and/or each tumor-binding fusion polypeptide are each a ferritin monomer or a subunit thereof.

20. The self-assembled polypeptide complex of claim 19, wherein the ferritin monomer is a human ferritin monomer.

21. The self-assembled polypeptide complex of claim 19 or 20, wherein the ferritin monomer is a ferritin light chain.

22. The self-assembled polypeptide complex of claim 21, which does not comprise any ferritin heavy chains or subunits of ferritin heavy chains.

23. The self-assembled polypeptide complex of any one of claims 19-22, which does not comprise any iron-binding moieties.

24. A pharmaceutical composition comprising a self-assembled polypeptide complex of any one of claims 12-23 and a pharmaceutically acceptable excipient.

25. Use of the self-assembled polypeptide complex of any one of claims 12-23 or the pharmaceutical composition of claim 24 in the manufacture of a medicament for treating, ameliorating, or preventing a disease or condition in a subject.

26. The use of claim 25, wherein the subject is a mammal.

27. The use of claim 26, wherein the subject is human.

28. The use of any one of claims 25-27, wherein the disease or condition is cancer.

29. The use of any one of claims 25-27, wherein the disease or condition is an autoimmune disease or condition.