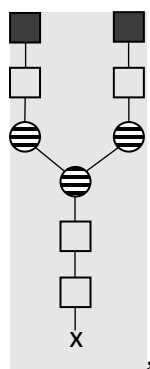


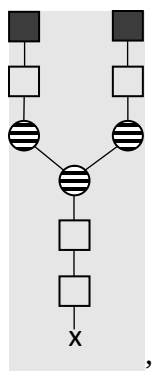
WHAT IS CLAIMED:

1. A glycoengineered bifunctional binding protein comprising: a first moiety that specifically binds to a target protein associated with a disease; and a second moiety that binds specifically to an endocytic carbohydrate-binding protein or receptor, wherein the second moiety comprises a glycan structure.
2. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising terminal GalNAc.
3. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising the structure:



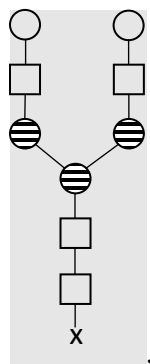
wherein the black square represents an N-acetyl galactosamine (GalNAc), the white square represents an N-acetylglucosamine (GlcNAc) residue and the black striped circle represents a mannose (Man) residue, and wherein X represents an amino acid residue of the bifunctional binding protein.

4. A glycoengineered bifunctional binding protein, wherein the bifunctional binding protein (i) specifically binds to a target protein and (ii) comprises an N-glycan of the structure:



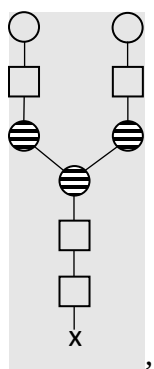
wherein the N-glycan is linked to the bifunctional binding protein at 1, 2, 3, 4 or 5 N-glycosylation sites.

5. The glycoengineered bifunctional binding protein of claim 3, wherein any branched structure of the N-glycan of the proximal GlcNAc can be included.
6. The glycoengineered bifunctional binding protein of claim 3, wherein the GlcNAc residue is fucosylated.
7. The glycoengineered bifunctional binding protein of claim 3, wherein the terminal N-glycan consists of GalNAc.
8. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising terminal Gal.
9. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising the structure:



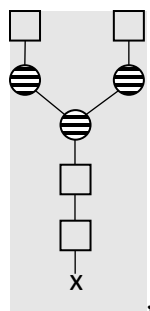
wherein the white circle represents a galactose (Gal) residue, the square represents an N-acetylglucosamine (GlcNAc) residue and the black striped circle represents a mannose (Man) residue, and wherein X represents an amino acid residue of the bifunctional binding protein.

10. A glycoengineered bifunctional binding protein, wherein the bifunctional binding protein (i) specifically binds to a target protein and (ii) comprises an N-glycan of the structure:



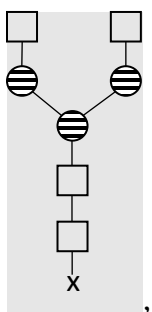
wherein the N-glycan is linked to the bifunctional binding protein at 1, 2, 3, 4 or 5 N-glycosylation sites.

11. The glycoengineered bifunctional binding protein of claim 10, wherein any branched structure of the N-glycan of the proximal GlcNAc can be included.
12. The glycoengineered bifunctional binding protein of claim 10, wherein the GlcNAc residue is fucosylated.
13. The glycoengineered bifunctional binding protein of claim 10, wherein the terminal N-glycan consists of Gal.
14. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising terminal GlcNAc.
15. A glycoengineered bifunctional binding protein comprising a first moiety that specifically binds to a target protein and a second moiety comprising a glycan comprising the structure:



wherein the square represents an N-acetylglucosamine (GlcNAc) residue and the black striped circle represents a mannose (Man) residue, and wherein X represents an amino acid residue of the bifunctional binding protein.

16. A glycoengineered bifunctional binding protein, wherein the bifunctional binding protein (i) specifically binds to a target protein and (ii) comprises an N-glycan of the structure:



wherein the N-glycan is linked to the bifunctional binding protein at 1, 2, 3, 4 or 5 N-glycosylation sites.

17. The glycoengineered bifunctional binding protein of any one of claims 3-6, 9-13, 15, and 14, wherein the amino acid residue is Asn.
18. The glycoengineered bifunctional binding protein of any one of claim 1 to 17, wherein the protein comprises 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more or 10 or more N-glycan structures.
19. The glycoengineered bifunctional binding protein of any one of claims 1 to 18, wherein the glycan structure comprises GlcNAc₂Man₃GlcNAc₂, GalNAc₂GlcNAc₂Man₃GlcNAc₂,

Gal2GlcNAc2Man3GlcNAc2, GlcNAc1Man3GlcNAc2, Gal2GlcNAc2Man3GlcNAc2, Gal1GlcNAc2Man3GlcNAc2, GalNAc1GlcNAc2Man3GlcNAc2, GlcNAc3Man3GlcNAc2, GlcNAc4Man3GlcNAc2, Gal3GlcNAc3Man3GlcNAc2, GalNAc3GlcNAc3Man3GlcNAc2, GalNAc4GlcNAc4Man3GlcNAc2, Gal4GlcNAc4Man3GlcNAc2, or Man-6-P-N-glycan.

20. The glycoengineered bifunctional binding protein of claim 19, wherein the glycan structure is GlcNAc2Man3GlcNAc2.

21. The glycoengineered bifunctional binding protein of claim 19, wherein the glycan structure is GalNAc2GlcNAc2Man3GlcNAc2.

22. The glycoengineered bifunctional binding protein of claim 19, wherein the glycan structure is Gal2GlcNAc2Man3GlcNAc2.

23. The glycoengineered bifunctional binding protein of any one of claims 1 to 22, wherein the bifunctional protein is an antibody or fragment thereof and comprises a heavy chain variable region or a light chain variable region.

24. The glycoengineered bifunctional binding protein of any one of claims 1 to 23, wherein the bifunctional protein is an antibody or fragment thereof and comprises a Fab fragment.

25. The glycoengineered bifunctional binding protein of any one of claims 1 to 24, wherein the glycoengineered bifunctional binding protein is an antibody.

26. The glycoengineered bifunctional binding protein of claim 25, wherein the antibody is: (i) a monoclonal or polyclonal antibody; (ii) recombinant; or (iii) humanized, chimeric or fully human.

27. The glycoengineered bifunctional binding protein of claim 25, wherein the antibody has a glycan to protein ratio of 2 to 1, 4 to 1, 6 to 1, 8 to 1, or 10 to 1.

28. The glycoengineered bifunctional binding protein of claim 25, wherein the antibody is glycosylated at a predetermined and specific residue.

29. The glycoengineered bifunctional binding protein of any one of claims 1 to 28, wherein the glycoengineered bifunctional binding protein binds to an autoantibody and comprises an autoantigen or immunogenic fragment thereof.
30. A population of the glycoengineered bifunctional binding protein of any one of claims 1 to 29, wherein at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99% or 100% of the glycans at a given glycosite are the same.
31. The glycoengineered bifunctional binding protein of any one of claims 1 to 29 or the population of claim 30, wherein the target protein is a cell surface molecule or a non-cell surface molecule, optionally wherein the cell surface molecule is a receptor, or optionally wherein the non-cell surface molecule is an extracellular protein.
32. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 32, wherein the target protein is bound by the first moiety.
33. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 32, wherein the target protein associated with a disease is upregulated or expressed in the disease compared to a non-disease state.
34. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 33, wherein the target protein associated with a disease is involved in cancer progression.
35. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 34, wherein the target protein associated with said disease comprises TNF α , HER2, EGFR, HER3, VEGFR, CD20, CD19, CD22, α v β 3 integrin, CEA, CXCR4, MUC1, LCAM1, EphA2, PD-1, PD-L1, TIGIT, TIM3, CTLA4, VISTA, Notch receptors, EGF, c-MET, CCL2, CCR2, Frizzled receptors, Wnt, LRP5/6, CSF-1R, SIRP α , CD38, CD73, or TGF- β , Bombesin R, CAIX, CD13, CD44, v6, Emmprin, Endoglin, EpCAM, EphA2, FAP- α , Folate R, GRP78, IGF-1R, Matriptase, Mesothelin, sMET/HGFR, MT1-MMP, MT6-MMP, PSCA, PSMA, Tn antigen, and uPAR, TSHR α , MOG, AChR- α 1, noncollagen domain 1 of the α 3 chain of type IV collagen (α 3NC1), ADAMTS13, Desmoglein-1/3, or GPIb/IX, GPIIb/IIIa, GPIa/IIa, NMDA receptor, glutamic acid decarboxylase (GAD), amphiphysin and gangliosides GM1, GD3, GQ1B,

LILRB1, LILRB2, VEGF-R, CXCR4, CXCL12, CSF-1, CD47, aggregated light chains or aggregated transthyretin.

36. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 33, wherein the target protein associated with said autoimmune disease is an antibody binding to TSHR α , MOG, AChR- α 1, noncollagen domain 1 of the α 3 chain of type IV collagen (α 3NC1), ADAMTS13, Desmoglein-1/3, or GPIb/IX, GPIIb/IIIa, GPIa/IIa, NMDA receptor, glutamic acid decarboxylase (GAD), amphiphysin, or gangliosides GM1, GD3 or GQ1B.

37. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 36, wherein the endocytic carbohydrate-binding protein or receptor comprises a DC-SIGN, L-SIGN, LSECTin, asialoglycoprotein receptor (ASGPR), mannose-6-phosphate receptor, mincle, dectin-1, dectin-2, langerin, cation-independent mannose 6-phosphate receptor (CI-MPR), macrophage mannose receptor 2, BDCA-2, MGL, MDL, MICL, CLEC2, DNGR1, or CLEC12B.

38. The glycoengineered bifunctional binding protein or population of any one of claims 1 to 37, wherein the disease comprises a cancer or an autoimmune disease.

39. Use of the glycoengineered bifunctional binding protein or population of any one of claims 1 to 38 in the manufacture of a medicament for delivering a target protein to a hepatocyte endosome, wherein the delivery comprises contacting the target protein with the glycoengineered bifunctional binding protein under conditions suitable to mediate endocytosis of the target protein.

40. The use of claim 39, wherein increasing the number of glycan structures on the protein increases the rate of delivery, optionally wherein the number of glycan structures comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more or 10 or more.

41. Use of the glycoengineered bifunctional binding protein or population of any one of claims 1 to 38 in the manufacture of a medicament for degrading a target protein, wherein the degrading comprises contacting the target protein with the glycoengineered bifunctional binding protein under conditions suitable to mediate lysosomal degradation of the target protein by a host cell.

42. The use of claim 41, wherein increasing the number of glycan structures on the protein increases the rate of lysosomal degradation, optionally wherein the number of glycan structures comprise 1 or more, 2 or more, 3 or more, 4 or more, 5 or more, 6 or more, 7 or more, 8 or more, 9 or more or 10 or more.
43. The use of claim 41, wherein the target protein is upregulated in cancer or involved in cancer progression, optionally wherein the target protein upregulated in cancer or involved in cancer progression comprises TNF α , HER2, EGFR, HER3, VEGFR CD20, CD19, CD22, α v β 3 integrin, CEA, CXCR4, MUC1, LCAM1, EphA2, PD-1, PD-L1, TIGIT, TIM3, CTLA4, VISTA, Notch receptors, EGF, c-MET, CCL2, CCR2, Frizzled receptors, Wnt, LRP5/6, CSF-1R, SIRP α , LILRB1, LILRB2, CD38, CD73, or TGF- β .
44. The use of claim 41, wherein the target protein is an autoantibody or an autoantigen in an autoimmune disease, optionally wherein the autoantibody in the autoimmune disease is an antibody binding to TSHR α , MOG, AChR- α 1, noncollagen domain 1 of the α 3 chain of type IV collagen (α 3NC1), ADAMTS13, Desmoglein-1/3, GPIb/IX, GPIIb/IIIa, GPIa/Iia, NMDA receptor, glutamic acid decarboxylase (GAD), amphiphysin, or gangliosides GM1, or GD3.
45. The use of claims 41, wherein the target protein is upregulated or expressed in a neurodegenerative disease, optionally wherein the target protein upregulated or expressed in a neurodegenerative disease is alpha-synuclein, amyloid beta or complement cascade component.
46. The use of claim 41, wherein the host cell is a liver cell, myeloid cell, an immune cell, an endothelial cell, a parenchymal cell or an epithelial cell, optionally wherein the immune cell is a dendritic cell, a macrophage, a monocyte, a microglia cell, a granulocyte or a B lymphocyte.
47. The use of claim 41, wherein the host cell is any cell.
48. The use of claim 41, wherein said glycoengineered bifunctional binding protein enhances degradation of the target protein relative to degradation of the target protein in the presence of a glycoengineered bifunctional binding protein comprising a different second moiety.
49. The use of claim 41, wherein said degradation is mediated by endocytosis or phagocytosis.

50. A pharmaceutical composition comprising the glycoengineered bifunctional binding protein or population of any one of claims 1 to 38 and a pharmaceutically acceptable carrier.

51. Use of the glycoengineered bifunctional binding protein or population of any one of claims 1 to 38 or the pharmaceutical composition of claim 50 in the manufacture of a medicament for treating or preventing a disease in a patient.

52. The use of claim 51, wherein the disease is an autoimmune disease, a cancer or tumor, a liver disease, an inflammatory disorder, or a blood coagulation disorder.

53. The use of claim 52, wherein:

a. the autoimmune disease is selected from Graves' Disease, Myelin oligodendrocyte glycoprotein antibody-associated disease, Myasthenia Gravis, Anti-GBM Disease, Immune Thrombotic Thrombocytopenic Purpura, Acquired Pemphigus Vulgaris, Immune Thrombocytopenia, autoimmune encephalitis, Guillain-Barré Syndrome, and Membranous Nephropathy; or

b. the cancer is selected from lung cancer (small cell or non-small cell), breast cancer, gastric cancer, colorectal cancer, bladder cancer, malignant melanoma, brain cancer (e.g., astrocytoma, glioma, meningioma, neuroblastoma, or others), bone cancer (e.g., osteosarcoma), cervical cancer, cholangiocarcinoma, digestive tract cancer (e.g., oral, esophageal, stomach, colon or rectal cancer), head and neck cancer, leiomyosarcoma, liposarcoma, liver cancer (e.g., hepatocellular carcinoma), mesothelioma, nasopharyngeal cancer, neuroendocrine cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cancer, rhabdomyosarcoma, salivary gland cancer, skin cancer, spindle cell carcinoma, testicular cancer, thyroid cancer, or uterine cancer (e.g., endometrial cancer).

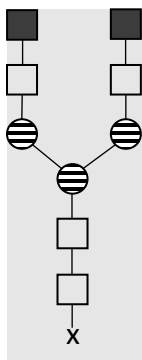
54. The use of claim 51, wherein treatment comprises reprogramming tumor associated macrophages (TAMs) by administering the bifunctional binding protein under conditions to mediate endocytosis of a target protein.

55. The use of claim 54, wherein the target protein is upregulated or expressed in TAMs, optionally wherein the target protein upregulated or expressed in TAMs comprises SIRP α , CCR2, CSF-1R, LILRB1, LILRB2, VEGF-R, CXCR4, CCL2, CXCL12, CSF-1 or CD47.

56. The use of claim 51, wherein the administration step comprises intravenous injection, intraperitoneal injection, subcutaneous injection, transdermal injection, or intramuscular injection.

57. A kit comprising the glycoengineered bifunctional binding protein or population of any one of claims 1 to 38, or the pharmaceutical composition of claim 50 and instructions for administering the glycoengineered bifunctional molecule or pharmaceutical composition to an individual in need thereof.

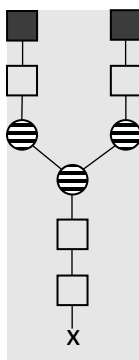
58. A bispecific binding protein capable of specifically binding to asialoglycoprotein receptor (ASGPR), wherein the protein (i) comprises an N-glycan of the structure:



wherein the black square represents N-acetylgalactosamine (GalNAc), the white square represents N-acetylglucosamine (GlcNAc), the black striped circle represents mannose (Man), and the X represents an amino acid residue in the protein; and (ii) specifically binds to a target protein.

59. Use of a bifunctional binding protein in the manufacture of a medicament for degrading a target protein in a subject, wherein the bifunctional binding protein specifically binds to the target protein and comprises a biantennary glycan comprising an N-terminal GalNAc capable of binding asialoglycoprotein receptor (ASGPR).

60. The use of claim 59, wherein the biantennary GalNAc has the following structure:

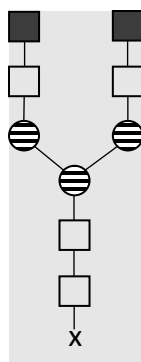


wherein the black square represents N-acetylgalactosamine (GalNAc), the white square represents N-acetylglucosamine (GlcNAc), the black striped circle represents mannose (Man), and the X represents an amino acid residue.

61. Use of a bifunctional binding protein in the manufacture of a medicament for treating an acute condition associated with increased levels of a target protein in a patient, wherein the bifunctional binding protein (i) specifically binds to the target protein and (ii) comprises an N-glycan, wherein the N-glycan is linked to the bifunctional binding protein at two or more glycosites such that the half-life of the target protein in the patient is at most 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or at most 2 hours.

62. Use of a bifunctional binding protein in the manufacture of a medicament for treating an acute condition associated with increased levels of a target protein in a patient, wherein the bifunctional binding protein (i) specifically binds to the target protein and (ii) comprises an N-glycan, wherein the N-glycan is linked to the bifunctional binding protein at two or more glycosites, such that the half-life is at most 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 99% of the half-life of the target protein in the patient in the absence of the bifunctional binding protein or in the absence of any treatment.

63. Use of a bifunctional binding protein in the manufacture of a medicament for treating an acute condition associated with increased levels of a target protein, wherein the bifunctional binding protein (i) specifically binds to the target protein and (ii) comprises an N-glycan, wherein the N-glycan has the structure of:



wherein the black square represents N-acetylgalactosamine (GalNAc), the white square represents N-acetylglucosamine (GlcNAc), the black striped circle represents mannose (Man), and the X represents an amino acid residue in the protein, and wherein the half-life of the target protein in the patient after said administering step is at most 15 minutes, 30 minutes, 45 minutes, 60 minutes, 90 minutes, or at most 2 hours.

64. Use of a bifunctional binding protein in the manufacture of a medicament for treating a chronic condition associated with increased levels of a target protein, wherein the bifunctional binding protein (i) specifically binds to the target protein and (ii) comprises an N-glycan wherein the N-glycan is linked to the bifunctional binding protein at most one or two glycosites, such that the half-life of the bispecific protein in the patient is at least 12 hours, 1 day, 2 days, 3 days, 4 days, 5 days, 6 days or 7 days.

65. Use of a bifunctional binding protein in the manufacture of a medicament for treating a chronic condition associated with increased levels of a target protein in a patient, wherein the bifunctional binding protein (i) specifically binds to the target protein and (ii) comprises an N-glycan wherein the N-glycan is linked to the bifunctional binding protein at most one or two glycosites, such that the half-life is at most 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% or 99% of the half-life of the target protein in the patient in the absence of the bifunctional binding protein or in the absence of any treatment.