

CLAIMS

~~A1.~~ An *in vitro* method of expressing a bivalent binding member in a cell of the nervous system, comprising introducing into the cell an expression cassette encoding a polypeptide comprising an antibody heavy chain variable domain (V_H), an antibody light chain variable domain (V_L), and an IgG Fc region,

~~1.~~ _____ wherein the V_H and the V_L form an antigen-binding site that binds specifically to a target protein, and upon expression in the cell, two molecules of the polypeptide form a disulfide-bonded homodimeric bivalent binding member specific for the target protein;

_____ wherein the bivalent binding member binds to neonatal Fc receptor (FcRn), but it does not bind to an Fc gamma receptor due to one or more mutations in the IgG Fc region.

~~2.~~ An expression construct for use in treating a human patient in need thereof, wherein the expression construct comprises an expression cassette encoding a polypeptide comprising an antibody heavy chain variable domain (V_H), an antibody light chain variable domain (V_L), and an IgG Fc region,

_____ wherein the V_H and the V_L form an antigen-binding site that binds specifically to a target protein, and upon expression in a cell of the nervous system in the human patient, two molecules of the polypeptide form a disulfide-bonded homodimeric bivalent binding member specific for the target protein,

_____ wherein the bivalent binding member binds to neonatal Fc receptor (FcRn), but it does not bind to an Fc gamma receptor due to one or more mutations in the IgG Fc region.

~~2.~~ 3. The method or expression construct for use of claim 1 or 2, wherein the cell of the nervous system is a neuron; a glial cell, optionally selected from an oligodendrocyte, an astrocyte, a pericyte, a Schwann cell, and a microglia cell; ependymal cells; and brain epithelial cells.

~~3.~~ ~~4.~~ The method ~~of claim 2, wherein the cell is a human cell.~~

~~The method or expression construct for use~~ of claim 3, wherein the cell is a human cell.

~~4.~~ 5. The expression construct for use of claim 2, wherein the cell is in the brain of a patient.

~~5.~~ 6. The method or expression construct for use of any one of claims 1-~~4~~5, wherein the target protein is a protein expressed in the brain.

~~6.~~ 7. The method or expression construct for use of claim ~~5~~6, wherein the protein is amyloid beta peptide (A β), tau, SOD-1, TDP-43, ApoE, or α -synuclein.

~~7.~~ 8. The method or expression construct for use of any one of claims 1-~~6~~7, wherein the polypeptide comprises, from N terminus to C terminus,

- (i) the V_H, a peptide linker, and the V_L; or the V_L, a peptide linker, and the V_H; and
- (ii) the IgG Fc region.

8. 9. The method or expression construct for use of claim ~~7~~8, wherein the peptide linker comprises the sequence GGGGS (SEQ ID NO: 3).

9. 10. The method or expression construct for use of any one of claims 1-~~8~~, ~~wherein the bivalent binding member binds to neonatal Fc receptor (FcRn), but it does not bind to an Fc gamma receptor due to 9, wherein the~~ one or more mutations in the IgG Fc region: are selected from C220S, C226S, C229S, N297Q, N297A, N297G, E233P, L234V, L234F, L234A, L235A, L235E, P331S, and P238S (Eu numbering).

~~10.~~ 11. The method or expression construct for use of any one of claims 1-~~9~~10, wherein the introducing step comprises administering a recombinant virus whose genome contains the expression cassette.

~~11.~~ 12. The method or expression construct for use of claim ~~10~~11, wherein the recombinant virus is introduced to the brain of a patient via intracranial injection, intrathecal injection, or intracisterna-magna injection.

~~12.~~ 13. The method or expression construct for use of claim ~~10 or 11~~ or 12, wherein the recombinant virus is a recombinant adeno-associated virus (AAV).

~~13.~~ 14. The method or expression construct for use of claim ~~12~~13, wherein the recombinant AAV is of serotype 1 or 2.

~~14.~~ 15. The method or expression construct for use of any one of claims 1-~~13~~14, wherein expression of the polypeptide is under the transcriptional control of a constitutively active promoter or an inducible promoter.

~~15.~~ 16. The ~~method~~expression construct for use of any one of ~~claims 4-14~~claims 2-15, wherein the patient has a neurodegenerative disease.

~~16.~~ 17. The ~~method~~expression construct for use of claim ~~15~~16, wherein the patient has Alzheimer's disease, cerebral amyloid angiopathy, ~~synucleopathy~~synucleinopathy, tauopathy, or amyotrophic lateral sclerosis.

~~17. — A bivalent binding member for use in treating a patient in need thereof in a method of any one of claims 4-16.~~

~~18. — Use of a bivalent binding member for the manufacture of a medicament for the treatment of a patient in need thereof in a method of any one of claims 4-16.~~