WHAT IS CLAIMED IS:

1. Use of an antibody in the manufacture of a medicament for transporting a compound across the blood-brain barrier; wherein the antibody binds with low affinity to a blood-brain barrier receptor (BBB-R) and is coupled to the compound, and wherein the antibody transports the compound coupled thereto across the blood-brain barrier.
2. Use of an antibody in the manufacture of a medicament for increasing exposure of the CNS to a compound, wherein the compound is coupled to the antibody, and wherein the antibody binds with low affinity to a BBB-R, thereby increasing the exposure of the CNS to the compound.
3. Use of an antibody in the manufacture of a medicament for decreasing clearance of a compound administered to a subject, wherein the compound is coupled to the antibody, and wherein the antibody binds with low affinity to a BBB-R, such that the clearance of the compound is decreased.
4. Use of an antibody in the manufacture of a medicament for increasing retention in the CNS of a compound administered to a subject, wherein the compound is coupled to the antibody, and wherein the antibody binds with low affinity to a BBB-R, such that the retention in the CNS of the compound is increased.
5. Use of an antibody in the manufacture of a medicament for optimizing the pharmcokinetics and/or pharmacodynamics of a compound to be efficacious in the CNS in a subject, wherein the compound is coupled to the antibody, wherein the antibody binds with low affinity to a BBB-R, and wherein the antibody is selected such that its affinity for the BBB-R after coupling to the compound results in an amount of transport of the antibody conjugated to the compound across the BBB that optimizes the pharmacokinetics and/or pharmacodynamics of the compound in the CNS.
6. Use of an antibody in the manufacture of a medicament for treating a neurological disorder in a mammal, wherein the antibody binds a BBB-R and is coupled to a compound and wherein the antibody has been selected to have a low affinity for the BBB-R and thereby improves CNS uptake of the antibody and coupled compound.
7. The use of any of claims 1-6, wherein the compound is a neurological disorder drug or an imaging agent.
8. The use of any of claims 2-4, wherein the increase or decrease is measured relative to a typical antibody not having lowered affinity for the BBB-R.

9. The use of any of claims 1-6, wherein the antibody is selected from the group consisting of:

(a) an antibody which does not impair the binding of the BBB-R to one or more of its native ligands;

(b) an antibody which has an IC50 for the BBB-R from about 1 nM to about 100 μM;

(c) an antibody which has an affinity for the BBB-R from about 5 nM to about 10 μM;

(d) an antibody coupled to the compound which has an affinity for the BBB-R from about 30 nM to about 1 μM;

(e) an antibody coupled to the compound which is to be administered at a therapeutic dose; and

(f) an antibody which is a multispecific antibody and wherein the compound optionally forms one portion of the multispecific antibody.

10. The use of any of claims 1-6, wherein the blood-brain barrier is in a mammal.

11. The use of claim 10, wherein the mammal is selected from the group consisting of: (a) a mammal which has a neurological disorder; and (b) a mammal which is a human.

12. The use of claim 11, wherein the neurological disorder is selected from the group consisting of Alzheimer's disease (AD), stroke, dementia, muscular dystrophy (MD),

multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), cystic fibrosis, Angelman's syndrome, Liddle syndrome, Parkinson's disease, Pick's disease, Paget's disease, cancer and traumatic brain injury.

13. The use of claim 8, wherein the IC50 is selected from the group consisting of:
    (a) an IC50 which is from about 5 nM to about 100μM;
    (b) an IC50 which is from about 50 nM to about 100μM; and
    (c) an IC50 which is from about 100 nM to about 100μM.
14. The use of any of claims 1-6, wherein the BBB-R is selected from the group consisting of transferrin receptor (TfR), insulin receptor, insulin-like growth factor receptor (IGF receptor), low density lipoprotein receptor-related protein 8 (LRP8), low density lipoprotein receptor-related protein 1 (LRP1), and heparin-binding epidermal growth factor-like growth factor (HB-EGF).
15. The use of claim 14, wherein the BBB-R is transferrin receptor.
16. The use of claim 15, wherein the antibody does not inhibit the binding of TfR to transferrin.
17. The use of claim 9(e), wherein the therapeutic dose is BBB-R-saturating.
18. The use of claim 9(f) wherein the multispecific antibody comprises a first antigen binding site which binds the BBB-R and a second antigen binding site which binds a brain antigen.
19. The use of claim 18, wherein the brain antigen is selected from the group consisting of: beta-secretase 1 (BACE1), Abeta, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, apolipoprotein E4 (ApoE4), alpha-synuclein, CD20, huntingtin, prion protein (PrP), leucine rich repeat kinase 2 (LRRK2),

parkin, presenilin 1, presenilin 2, gamma secretase, death receptor 6 (DR6), amyloid precursor protein (APP), p75 neurotrophin receptor (p75NTR), and caspase 6.

20. The use of claim 18, wherein the multispecific antibody is selected from the group consisting of: (a) a multispecific antibody which binds both TfR and BACE1; and

(b) a multispecific antibody which binds both TfR and Abeta.

21. A method of making an antibody useful for transporting a compound across the BBB comprising selecting an antibody specific for a blood-brain barrier receptor (BBB-R) because it has a desirably low affinity for the BBB-R.

22. The method of claim 21, wherein the affinity for the BBB-R is from about 5 nM to about 10 μM.

23. The method of claim 21, wherein the antibody is selected from the group consisting of: (a) an antibody which has an IC50 of from about 1nM to about 100 μM;

(b) an antibody which is selected from a panel of antibodies based upon the affinity of the selected antibody; and

(c) an antibody which is engineered to have the affinity.

24. The method of claim 21 comprising coupling the antibody with a therapeutic compound.

25. The method of claim 24 wherein the therapeutic compound is a neurological disorder drug.

26. The method of claim 21 comprising making a multispecific antibody which comprises a first antigen binding site which binds the BBB-R and a second antigen binding site which binds a brain antigen.

27. An antibody which binds to a BBB-R, wherein the affinity of the antibody for the BBB-R is from about 5 nM to about 10 μM.

28. The antibody of claim 27 wherein the affinity is from about 20 nM to about 1 μM.

29. The antibody of claim 27 wherein the BBB-R is selected from the group consisting of transferrin receptor (TfR), insulin receptor, insulin-like growth factor receptor (IGF receptor), low density lipoprotein receptor-related protein 8 (LRP8), low density lipoprotein receptor-related protein 1 (LRP1), and heparin-binding epidermal growth factor-like growth factor (HB-EGF).

30. The antibody of claim 29 wherein the BBB-R is transferrin receptor (TfR), or insulin receptor.

31. The antibody of claim 27 wherein the BBB-R is a human BBB-R.

32. The antibody of claim 27, wherein the antibody is selected from the group consisting of: (a) an antibody which is coupled with a neurological disorder drug; and (b) an antibody which is an antibody fragment with an antigen binding region that binds the BBB-R.

33. The antibody of claim 32 which is a multispecific antibody which comprises a first antigen binding site which binds the BBB-R and a second antigen binding site which binds a brain antigen.

34. The antibody of claim 33 wherein the brain antigen is selected from the group consisting of: beta-secretase 1 (BACE1), Abeta, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, apolipoprotein E4 (ApoE4), alpha-synuclein, CD20, huntingtin, prion protein (PrP), leucine rich repeat kinase 2 (LRRK2), parkin, presenilin 1, presenilin 2, gamma secretase, death receptor 6 (DR6), amyloid precursor protein (APP), p75 neurotrophin receptor (p75NTR), and caspase 6.

35. The antibody of claim 34 wherein the brain antigen is selected from the group consisting of BACE1 and Abeta.

36. The antibody fragment of claim 32(b) which is a Fab fragment.

37. The multispecific antibody of claim 33 which is a full-length antibody or an antibody fragment.

38. Use of an antibody that binds with low affinity to a BBB-R for the manufacture of a medicament for treating a neurological disorder.

39. Use of the antibody of any of claims 27-37 for the manufacture of a medicament for treating a neurological disorder.

WHAT IS CLAIMED IS:

1. A method of transporting a compound across the blood-brain barrier comprising exposing an antibody which binds with low affinity to the transferrin receptor (TfR) coupled to a compound to the blood-brain barrier such that the antibody transports the compound coupled thereto across the blood-brain barrier.

2. Use of an antibody in the manufacture of a medicament for treatment of a neurological disorder in a mammal wherein the antibody is one that binds TfR and is coupled to a compound, wherein the antibody has been selected to have a low affinity for TfR and thereby improves CNS uptake of the antibody and coupled compound.

3. An agent for use in the treatment of a neurological disorder in a mammal wherein the agent comprises an antibody that binds TfR and is coupled to a compound, wherein the antibody has been selected to have a low affinity for TfR and thereby improves CNS uptake of the antibody and coupled compound.

4. The use of claim 2 or agent of claim 3, wherein the compound is a neurological disorder drug or an imaging agent.

5. The use of claim 2 or agent of claim 3, wherein the antibody does not impair the binding of transferrin to the TfR.

6. The use of claim 2 or agent of claim 3, or use or agent of claims 4 or 5, wherein the neurological disorder is selected from the group consisting of Alzheimer's disease (AD), stroke, dementia, muscular dystrophy (MD), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), cystic fibrosis, Angelman's syndrome, Liddle syndrome, Parkinson's disease, Pick's disease, Paget's disease, cancer, and traumatic brain injury.

7. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 6, wherein the IC50 for TfR is from about 5 nM to about 100μM.

8. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 7, wherein the IC50 for TfR is from about 50 nM to about 100μM.

9. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 8, wherein the IC50 for TfR is from about 100 nM to about 100μM.

10. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 9, wherein the antibody has an affinity for TfR from about 5 nM to about 10 μM.

11. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 10, wherein the antibody coupled to the compound has an affinity for TfR from about 30 nM to about 1 μM.

12. The use of claim 2 or agent of claim 3, or use or agent of any one of claims 4 to 11, wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

13. The use or agent of claim 12 wherein the multispecific antibody comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

14. The use or agent of claim 13, wherein the brain antigen is selected from the group consisting of: beta-secretase 1 (BACEl), Abeta, epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), Tau, apolipoprotein E4 (ApoE4), alpha-synuclein, CD20, huntingtin, prion protein (PrP), leucine rich repeat kinase 2 (LRRK2), parkin, presenilin 1, presenilin 2, gamma secretase, death receptor 6 (DR6), amyloid precursor protein (APP), p75 neurotrophin receptor (p75NTR), and caspase 6.

15. The use or agent of any one of claims 12 to 14, wherein the multispecific antibody binds both TfR and BACE1.

16. The use or agent of any one of claims 12 to 14, wherein the multispecific antibody binds both TfR and Abeta.

17. The use or agent of any one of claims 12 to 16, wherein the multispecific antibody is a full-length antibody or an antibody fragment.