WHAT IS CLAIMED IS:

1. A method of transporting a compound across the blood-brain barrier in a subject comprising exposing an antibody which binds with low affinity to a blood-brain barrier receptor (BBB-R) coupled to a compound to the blood-brain barrier such that the antibody transports the compound coupled thereto across the blood-brain barrier, wherein reduction of red blood cell levels in the subject upon antibody administration to the subject is decreased or eliminated.
2. A method of increasing exposure of the CNS of a subject to a compound, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, thereby increasing the exposure of the CNS to the compound, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
3. A method of decreasing clearance of a compound administered to a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, such that the clearance of the compound is decreased, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
4. A method of increasing retention in the CNS of a compound administered to a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, such that the retention in the CNS of the compound is increased, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
5. A method of optimizing the pharmcokinetics and/or pharmacodynamics of a compound to be efficacious in the CNS in a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, and 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, wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
6. A method of treating a neurological disorder in a mammal comprising treating the mammal with an antibody that binds a BBB-R and is coupled to a compound, 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, and wherein reduction of red blood

cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.

7. The method 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF).
8. The method of claim 7, wherein the BBB-R is TfR.
9. The method of claim 8, wherein the red blood cells are immature red blood cells.
10. The method of claim 9, wherein the immature red blood cells are reticulocytes.
11. The method of claim 10, wherein reduction of reticulocyte levels is accompanied by acute clinical symptoms.
12. The method of claim 11, wherein one or more properties of the antibody have been modified to reduce the impact of the antibody on reticulocyte levels and/or reduce the severity or presence of acute clinical symptoms in the subject or mammal.
13. The method of claim 12, wherein the one or more properties are selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R.
14. The method of claim 13, wherein the one or more properties are selected from the effector function of the antibody Fc region and the complement activation function of the antibody, and wherein the effector function or complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype.
15. The method of claim 14, wherein the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region.
16. The method of claim 15, wherein the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur.
17. The method of claim 16, wherein the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically.

18. The method of claim 16, wherein the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position.

19. The method of claim 15, wherein the effector function is reduced or eliminated by at least one modification of the Fc region.

20. The method of claim 19, wherein the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region or non-Fc region competent for effector function or complement activation function.

21. The method of claim 19, wherein the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321; eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

22. The method of claim 11, wherein the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the red blood cells are exposed.

23. The method of claim 11, wherein the antibody is modified to comprise pH-sensitive binding to the BBB-R.

24. The method of claim 11, wherein a further compound is administered in addition to the antibody.

25. The method of claim 24, wherein the further compound is responsible for or contributes to the lack of reduction of reticulocyte levels.

26. The method of claim 25, wherein the further compound protects reticulocytes from antibody-related depletion or supports the growth, development, or reestablishment of reticulocytes.

27. The method of claim 26, wherein the further compound is selected from erythropoietin (EPO), an iron supplement, vitamin C, folic acid, and vitamin B12.

28. The method of claim 26, wherein the further compound is red blood cells or reticulocytes from the same or another subject.

29. The method of claim 13, wherein the affinity of the antibody for the BBB-R is further decreased.
30. The method of any of claims 1-29, further comprising the step of monitoring the subject for depletion of red blood cells.
31. The method of any of claims 1-30, wherein the compound is a neurological disorder drug or an imaging agent.
32. The method of any of claims 2-30, wherein the increase or decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.
33. The method of any of claims 1-30, wherein the antibody does not impair the binding of the BBB-R to one or more of its native ligands.
34. The method of any of claims 1-30, wherein the blood-brain barrier is in a mammal.
35. The method of claim 34, wherein the mammal has a neurological disorder.
36. The method of claim 35, 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.
37. The method of claim 34 wherein the mammal is a human.
38. The method of any of claims 1-30, wherein the antibody has an IC50 for the BBB-R from about 1 nM to about 100 μM.
39. The method of claim 38, wherein the IC50 is from about 5 nM to about 100μM.
40. The method of claim 38, wherein the IC50 is from about 50 nM to about 100μM.
41. The method of claim 38, wherein the IC50 is from about 100 nM to about 100μM.
42. The method of any of claims 1-30, wherein the antibody has an affinity for the BBB-R from about 5 nM to about 50 μM.
43. The method of any of claims 1-30, wherein the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM.
44. The method of any of claims 1-30, wherein the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 1 μM.
45. The method of any of claims 1-30, wherein the antibody coupled to the compound has a dissociation half-life for the BBB-R from about 30 seconds to about 5 minutes, or from about 30 seconds to about 2 minutes.
46. The method of claim 8, wherein the antibody does not inhibit the binding of TfR to transferrin.

47. The method of any of claims 1-30, wherein the antibody coupled to the compound is administered at a therapeutic dose.

48. The method of claim 47, wherein the therapeutic dose is BBB-R-saturating.

49. The method of any of claims 1-30, wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

50. The method of claim 49 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.

51. The method of claim 50, 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.

52. The method of claim 51, wherein the multispecific antibody binds both TfR and BACE1.

53. The method of claim 51, wherein the multispecific antibody binds both TfR and Abeta.

54. A method of improving the safety in a subject of an antibody that binds a BBB-R comprising modifying one or more properties of the antibody such that administration of the antibody decreases or eliminates reduction of red blood cell levels in the subject observed upon administration of the unmodified antibody.

55. A method of making an antibody useful for transporting a compound across the BBB with improved safety comprising selecting an antibody specific for a blood-brain barrier receptor (BBB-R) that has a desirably low affinity for the BBB-R, and modifying one or more properties of the antibody such that administration of the antibody decreases or eliminates reduction of red blood cell levels in the subject observed upon administration of the unmodified antibody.

56. The method of claims 54 or 55 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF).

57. The method of claim 56 wherein the BBB-R is transferrin receptor (TfR).

58. The method of claim 57, wherein the red blood cells are reticulocytes.

59. The method of claim 58, wherein reduction of reticulocyte levels is accompanied by acute clinical symptoms.

60. The method of claim 59, wherein the one or more properties is selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R.

61. The method of claim 60, wherein the one or more properties is selected from the effector function of the antibody Fc region and the complement activation function of the antibody, and wherein the effector function or the complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype.

62. The method of claim 61, wherein the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region.

63. The method of claim 62, wherein the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur.

64. The method of claim 63, wherein the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically.

65. The method of claim 63, wherein the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position

66. The method of claim 62, wherein the effector function or the complement activation function is reduced or eliminated by at least one modification of the Fc region or the non-Fc region of the antibody.

67. The method of claim 66, wherein the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region competent for effector function or complement activation function.

68. The method of claim 66, wherein the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair

binding to C1q selected from the following positions: 270, 322, 329, and 321, eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

69. The method of claim 59, wherein the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the red blood cells are exposed.

70. The method of claim 59, wherein the antibody is modified to comprise pH-sensitive binding to the BBB-R.

71. The method of claim 60, wherein the affinity of the antibody for the BBB-R is further decreased.

72. The method of claim 71, wherein the decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.

73. The method of claims 54 or 55, wherein the affinity for the BBB-R is from about 1 nM to about 100 μM.

74. The method of claim 73, wherein the antibody has an IC50 of from about 1nM to about 100 μM.

75. The method of claim 73, wherein the IC50 is from about 5 nM to about 100 μM.

76. The method of claim 73, wherein the IC50 is from about 50 nM to about 100 μM.

77. The method of claim 73, wherein the IC50 is from about 100 nM to about 100 μM.

78. The method of any of claims 54-71, wherein the antibody has an affinity for the BBB-R from about 5 nM to about 50 μM.

79. The method of any of claims 54-71, wherein the antibody has a dissociation half-life for the BBB-R from about 30 seconds to about 5 minutes, or from about 30 seconds to about 2 minutes.

80. The method of claims 54 or 55 wherein the antibody is selected from a panel of antibodies based upon the affinity of the selected antibody.

81. The method of claims 54 or 55, wherein the antibody is engineered to have the affinity.

82. The method of claims 54 or 55 comprising coupling the antibody with a therapeutic compound.

83. The method of claim 82 wherein the therapeutic compound is a neurological disorder drug.

84. The method of claim 82, wherein the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM.

85. The method of claim 83, wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

86. The method of claims 54 or 55 wherein the antibody 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.

87. The method of claim 86, 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.

88. The method of claim 87, wherein the multispecific antibody binds both TfR and BACE1.

89. The method of claim 87, wherein the multispecific antibody binds both TfR and Abeta.

90. The method of any of claims 54-88, wherein the antibody does not impair the binding of the BBB-R to one or more of its native ligands.

91. The method of claim 90, wherein the antibody does not inhibit the binding of TfR to transferrin.

92. 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 50 μM or the dissociation half-life of the antibody for the BBB-R is from about 30 seconds to about 2 minutes, and wherein one or more properties of the antibody have been modified to reduce at least one undesired side effect on red blood cells.

93. The antibody of claim 92 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF).

94. The antibody of claim 93 wherein the BBB-R is transferrin receptor (TfR).

95. The antibody of claim 94, wherein the red blood cells are reticulocytes.

96. The antibody of claim 95, wherein the at least one undesired side effect on red blood cells is selected from reduction of reticulocyte levels and acute clinical symptoms.

97. The antibody of claim 96, wherein the one or more properties is selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R.

98. The antibody of claim 97, wherein the one or more properties is selected from the effector function of the antibody Fc region and the complement activation function of the antibody,

and wherein the effector function or complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype.

99. The antibody of claim 98, wherein the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region.

100. The antibody of claim 99, wherein the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur.

101. The antibody of claim 100, wherein the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically.

102. The antibody of claim 100, wherein the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position.

103. The antibody of claim 99, wherein the effector function or complement activation function is reduced or eliminated by at least one modification of the Fc region or the non-Fc region.

104. The antibody of claim 103, wherein the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region competent for effector function.

105. The antibody of claim 103, wherein the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321; eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

106. The antibody of claim 97, wherein the antibody is modified to comprise pH-sensitive binding to the BBB-R.

107. The antibody of claim 97, wherein the affinity of the antibody for the BBB-R is further decreased.

108. The antibody of claim 107, wherein the decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.

109. The antibody of claim 92, wherein the affinity is measured as an IC50.

110. The antibody of claims 92 wherein the antibody is selected from a panel of antibodies based upon the affinity of the selected antibody.

111. The antibody of claim 92 wherein the antibody is engineered to have the affinity.

112. The antibody of claim 92, further coupled with a therapeutic compound.

113. The antibody of claim 112 wherein the therapeutic compound is a neurological disorder drug.

114. The antibody of claim 112, wherein the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM.

115. The antibody of claim 112, wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

116. The antibody of claim 92 wherein the antibody 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.

117. The antibody of claim 116, 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.

118. The antibody of claim 117, wherein the multispecific antibody binds both TfR and BACE1.

119. The antibody of claim 117, wherein the multispecific antibody binds both TfR and Abeta.

120. The antibody of any of claims 92-119, wherein the antibody does not impair the binding of the BBB-R to one or more of its native ligands.

121. The antibody of claim 120, wherein the antibody does not inhibit the binding of TfR to transferrin.

122. Use of an antibody that binds with low affinity to a BBB-R and that does not impact red blood cell levels for the manufacture of a medicament for treating a neurological disorder.

123. Use of the antibody of any of claims 92-121 for the manufacture of a medicament for treating a neurological disorder.

124. An antibody that binds with low affinity to a BBB-R and which does not impact red blood cell levels for use in treating a neurological disorder.

125. An antibody of any of claims 92-121 for use in treating a neurological disorder.

126. A method of treating a disease or disorder associated with or caused by elevated red blood cell levels in a subject comprising administering an anti-TfR antibody comprising at least partial effector function to the subject.

127. The method of claim 126, wherein the administering step is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

WHAT IS CLAIMED IS:

1. A method of transporting a compound across the blood-brain barrier in a subject comprising exposing an antibody which binds with low affinity to a blood-brain barrier receptor (BBB-R) coupled to a compound to the blood-brain barrier such that the antibody transports the compound coupled thereto across the blood-brain barrier, wherein reduction of red blood cell levels in the subject upon antibody administration to the subject is decreased or eliminated.
2. A method of increasing exposure of the CNS of a subject to a compound, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, thereby increasing the exposure of the CNS to the compound, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
3. A method of decreasing clearance of a compound administered to a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, such that the clearance of the compound is decreased, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
4. A method of increasing retention in the CNS of a compound administered to a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, such that the retention in the CNS of the compound is increased, and wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
5. A method of optimizing the pharmcokinetics and/or pharmacodynamics of a compound to be efficacious in the CNS in a subject, wherein the compound is coupled to an antibody which binds with low affinity to a BBB-R, and 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, wherein reduction of red blood cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.
6. Use of an antibody that binds a BBB-R and is coupled to a compound, 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, in the manufacture of a medicament for treatment of a neurological disorder in a mammal, wherein reduction of red blood

cell levels in the subject upon compound-coupled antibody administration to the subject is decreased or eliminated.

7. The method of any of claims 1-5 or the use of claim 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF),wherein:

i) optionally the BBB-R is TfR, or

ii) optionally the red blood cells are immature red blood cells, or

iii) optionally the immature red blood cells are reticulocytes, or

iv) optionally reduction of reticulocyte levels is accompanied by acute clinical symptoms, or

v) optionally one or more properties of the antibody have been modified to reduce the impact of the antibody on reticulocyte levels and/or reduce the severity or presence of acute clinical symptoms in the subject or mammal, or

vi) optionally the one or more properties are selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R, or

vii) optionally the one or more properties are selected from the effector function of the antibody Fc region and the complement activation function of the antibody, and wherein the effector function or complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype, or

viii) optionally the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region, or

ix) optionally the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur, or

x) optionally the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically, or

xi) optionally the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position.

8. The method of claim 7viii), wherein optionally the effector function is reduced or eliminated by at least one modification of the Fc region, or
wherein optionally the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region or non-Fc region competent for effector function or complement activation function, or
wherein the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 335, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321; eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

9. The method of claim 7iv), wherein: i) the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the red blood cells are exposed, or
ii) the antibody is modified to comprise pH-sensitive binding to the BBB-R, or
iii) a further compound is to be administered in addition to the antibody.

10. The method of claim 9iii), wherein i) the further compound is responsible for or contributes to the lack of reduction of reticulocyte levels, or
ii) optionally the further compound protects reticulocytes from antibody-related depletion or supports the growth, development, or reestablishment of reticulocytes.

11. The method of claim 10ii), wherein the further compound is selected from erythropoietin (EPO), an iron supplement, vitamin C, folic acid, and vitamin B12, or
wherein the further compound is red blood cells or reticulocytes from the same or another subject.

12. The method of claim 7vi), wherein the affinity of the antibody for the BBB-R is further decreased.

13. The method of any of claims 1-12, further comprising the step of monitoring the subject for depletion of red blood cells.

14. The method of any of claims 1-13, wherein: i) the compound is a neurological disorder drug or an imaging agent, or ii) the antibody does not impair the binding of the BBB-R to one or more of its native ligands, or iii) the blood-brain barrier is in a mammal, or iv) the antibody has an IC50 for the BBB-R from about 1 nM to about 100 μM, or v) the antibody has an affinity for the BBB-R from about 5 nM to about 50 μM, or vi) the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM, or vii) the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 1 μM, or viii) the antibody coupled to the compound has a dissociation half-life for the BBB-R from about 30 seconds to about 5 minutes, or from about 30 seconds to about 2 minutes, or ix) the antibody coupled to the compound is to be administered at a therapeutic dose, and or x) the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

15. The method of any of claims 2-13, wherein the increase or decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.

16. The method of claim 14iii), wherein the mammal has a neurological disorder, wherein optionally 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.

17. The method of claim 14iii) wherein the mammal is a human.

18. The method of claim 14iv), wherein the IC50 is from about 5 nM to about 100μM, or wherein the IC50 is from about 50 nM to about 100μM, or wherein the IC50 is from about 100 nM to about 100μM.

19. The method of claim 7i), wherein the antibody does not inhibit the binding of TfR to transferrin.

20. The method of claim 14ix), wherein the therapeutic dose is BBB-R-saturating.

21. The method of claim 14x) 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,

wherein optionally 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, or wherein optionally the multispecific antibody binds both TfR and BACE1, or wherein the multispecific antibody binds both TfR and Abeta.

22. A method of improving the safety in a subject of an antibody that binds a BBB-R comprising modifying one or more properties of the antibody such that administration of the antibody decreases or eliminates reduction of red blood cell levels in the subject observed upon administration of the unmodified antibody.

23. A method of making an antibody useful for transporting a compound across the BBB with improved safety comprising selecting an antibody specific for a blood-brain barrier receptor (BBB-R) that has a desirably low affinity for the BBB-R, and modifying one or more properties of the antibody such that administration of the antibody decreases or eliminates reduction of red blood cell levels in the subject observed upon administration of the unmodified antibody.

24. The method of claims 22 or 23 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF), wherein:

i) optionally the BBB-R is transferrin receptor (TfR), or

ii) optionally the red blood cells are reticulocytes, or

iii) optionally reduction of reticulocyte levels is accompanied by acute clinical symptoms, or

iv) optionally the one or more properties is selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R, or

v) optionally the one or more properties is selected from the effector function of the antibody Fc region and the complement activation function of the antibody, and wherein the effector function or the complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype, or

vi) optionally the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region, or

vii) optionally the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur, or

viii) optionally wherein the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically, or

ix) wherein the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position.

25. The method of claim 24vi), wherein the effector function or the complement activation function is reduced or eliminated by at least one modification of the Fc region or the non-Fc region of the antibody, wherein:

i) optionally the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region competent for effector function or complement activation function, or

ii) the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321, eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

26. The method of claim 24iii), wherein the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the red blood cells are exposed, or

wherein the antibody is modified to comprise pH-sensitive binding to the BBB-R.

27. The method of claim 24iv), wherein the affinity of the antibody for the BBB-R is further decreased,

wherein optionally the decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.

28. The method of claims 22 or 23, wherein: i) the affinity for the BBB-R is from about 1 nM to about 100 μM, or ii) the antibody is selected from a panel of antibodies based upon the affinity of the selected antibody, or iii) the antibody is engineered to have the

affinity, or iv) the antibody is coupled with a therapeutic compound, or v) the antibody 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.

29. The method of claim 28i), wherein the antibody has an IC50 of from about 1nM to about 100 μM, or

wherein the IC50 is from about 5 nM to about 100 μM, or

wherein the IC50 is from about 50 nM to about 100 μM, or

wherein the IC50 is from about 100 nM to about 100 μM.

30. The method of any of claims 22-27, wherein the antibody has an affinity for the BBB-R from about 5 nM to about 50 μM, or

wherein the antibody has a dissociation half-life for the BBB-R from about 30 seconds to about 5 minutes, or from about 30 seconds to about 2 minutes.

31. The method of claim 28iv) wherein: i) the therapeutic compound is a neurological disorder drug, or

ii) the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM.

32. The method of claim 31i), wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

33. The method of claim 28v), 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.

34. The method of claim 33, wherein (i) the multispecific antibody binds both TfR and BACE1, or

(ii) the multispecific antibody binds both TfR and Abeta.

35. The method of any of claims 22-34i), wherein the antibody does not impair the binding of the BBB-R to one or more of its native ligands,

wherein optionally the antibody does not inhibit the binding of TfR to transferrin.

36. 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 50 μM or the dissociation half-life of the antibody for the BBB-R is from about 30 seconds to about 2 minutes, and wherein one or more properties

of the antibody have been modified to reduce at least one undesired side effect on red blood cells.

37. The antibody of claim 36 wherein i) 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), glucose transporter 1 (Glut1) and heparin-binding epidermal growth factor-like growth factor (HB-EGF), wherein:
ii) optionally the BBB-R is transferrin receptor (TfR), or
iii) optionally the red blood cells are reticulocytes, or
iv) optionally at least one undesired side effect on red blood cells is selected from reduction of reticulocyte levels and acute clinical symptoms, or
v) optionally one or more properties is selected from the effector function of the antibody Fc region, the complement activation function of the antibody and the affinity of the antibody for the BBB-R, or
vi) optionally one or more properties is selected from the effector function of the antibody Fc region and the complement activation function of the antibody, and wherein the effector function or complement activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype, or
vii) optionally the effector function is reduced or eliminated by a method selected from reduction of glycosylation of the antibody, modification of the antibody isotype to an isotype that naturally has reduced or eliminated effector function, and modification of the Fc region, or
viii) optionally the glycosylation of the antibody is reduced by a method selected from: production of the antibody in an environment that does not permit wild-type glycosylation; removal of carbohydrate groups already present on the antibody; and modification of the antibody such that wild-type glycosylation does not occur, or
ix) optionally wherein the antibody is produced in a non-mammalian cell production system, or where the antibody is produced synthetically, or
x) wherein the Fc region of the antibody comprises a mutation at position 297 such that the wild-type asparagine residue at that position is replaced with another amino acid that interferes with glycosylation at that position.

38. The antibody of claim 37vii), wherein the effector function or complement activation function is reduced or eliminated by at least one modification of the Fc region or the non-Fc region,

wherein optionally the effector function or complement activation function is reduced or eliminated by deletion of all or a portion of the Fc region, or by engineering the antibody such that it does not include an Fc region competent for effector function, or

wherein the modification is selected from: a point mutation of the Fc region to impair binding to one or more Fc receptors selected from the following positions: 238, 239, 248, 249, 252, 254, 265, 268, 269, 270, 272, 278, 289, 292, 293, 294, 295, 296, 297, 298, 301, 303, 322, 324, 327, 329, 333, 338, 340, 373, 376, 382, 388, 389, 414, 416, 419, 434, 435, 437, 438, and 439; a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321; eliminating some or all of the Fc region, and a point mutation at position 132 of the CH1 domain.

39. The antibody of claim 37v), wherein: i) the antibody is modified to comprise pH-sensitive binding to the BBB-R, or

ii) the affinity of the antibody for the BBB-R is further decreased.

40. The antibody of claim 39ii), wherein the decrease is measured relative to a wild-type antibody of the same isotype not having lowered affinity for the BBB-R.

41. The antibody of claim 36, wherein: i) the affinity is measured as an IC50, or

ii) the antibody is selected from a panel of antibodies based upon the affinity of the selected antibody, or

iii) the antibody is engineered to have the affinity, or

iv) the antibody is further coupled with a therapeutic compound.

42. The antibody of claim 41iv) wherein the therapeutic compound is a neurological disorder drug, or

wherein the antibody coupled to the compound has an affinity for the BBB-R from about 30 nM to about 30 μM, or

wherein the antibody is a multispecific antibody and the compound optionally forms one portion of the multispecific antibody.

43. The antibody of claim 36 wherein the antibody 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.

44. The antibody of claim 43, 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.

45. The antibody of claim 44, wherein the multispecific antibody binds both TfR and BACE1, or

wherein the multispecific antibody binds both TfR and Abeta.

46. The antibody of any of claims 36-45, wherein the antibody does not impair the binding of the BBB-R to one or more of its native ligands.

47. The antibody of claim 46, wherein the antibody does not inhibit the binding of TfR to transferrin.

48. Use of an antibody that binds with low affinity to a BBB-R and that does not impact red blood cell levels for the manufacture of a medicament for treating a neurological disorder.

49. Use of the antibody of any of claims 36-47 for the manufacture of a medicament for treating a neurological disorder.

50. An antibody that binds with low affinity to a BBB-R and which does not impact red blood cell levels for use in treating a neurological disorder.

51. An antibody of any of claims 36-47 for use in treating a neurological disorder.

52. Use of an anti-TfR antibody comprising at least partial effector function in the manufacture of a medicament for treating a disease or disorder associated with or caused by elevated red blood cell levels,

53. The use of claim 52, wherein the antibody is to be administered at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.