BBB-R or anti-BBB-R/compound for the BBB-R is measured using BIACORE analysis. In another embodiment, the dissociation half-life of the anti-BBB-R or anti-BBB-R/compound for the BBB-R is measured using a competition binding assay, such as a competition ELISA.

In another embodiment, the antibody is selected from a panel of antibodies based upon the affinity of the selected antibody. In another embodiment, the antibody is engineered to have the desired affinity. In one such embodiment, the antibody is generated using any art-known protein engineering methodology including, but not limited to, phage display, yeast display, random mutagenesis, and site-directed mutagenesis.

In another embodiment, a compound is covalently coupled to the antibody. In one such embodiment, the compound is joined to the antibody by a linker. In one such embodiment, the linker is cleavable. In another such embodiment, the linker is not cleavable. In another such embodiment, the compound is directly linked to the antibody. In one such embodiment, the antibody is a multispecific antibody and the compound forms one portion of the multispecific antibody. In another such embodiment, 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. In another such embodiment, 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), interleukin 6 receptor (IL6R), TNF receptor 1 (TNFR1), interleukin 1 beta (IL1β), and caspase 6. In another such embodiment, the multispecific antibody binds both TfR and BACE1. In another such embodiment, the multispecific antibody binds both TfR and Abeta. In another such embodiment, the multispecific antibody is labeled. In another embodiment, the compound is reversibly coupled to the antibody such that the compound is released from the antibody concurrent with or after BBB transport.

It will be appreciated that any of the foregoing aspects may be applied singly or in combination with the foregoing embodiment.

In one aspect, there is provided use of an antibody that binds with low affinity to a TfR for the manufacture of a medicament for treating a neurological disorder, 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 a subject such that reduction of red blood cell levels in the subject upon antibody administration is decreased or eliminated, and wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen..

In one aspect, there is provided use of the antibody as described herein for the manufacture of a medicament for treating a neurological disorder, wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

In another embodiment, the disclosure provides the use of an antibody that binds with low affinity to a BBB-R and that does not reduce red blood cell levels for the manufacture of a medicament for treating a neurological disorder. Any of the foregoing described low-affinity anti-BBB-R antibodies or any of the low-affinity anti-BBB-R antibodies described elsewhere herein may be used in the method.

In one aspect, there is provided an antibody that binds with low affinity to a TfR for use in treating a neurological disorder, 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 a subject such that reduction of red blood cell levels in the subject upon antibody administration is decreased or eliminated, and wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

In one aspect, there is provided an antibody as described herein for use in treating a neurological disorder, wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

In another embodiment, the disclosure provides an antibody that binds with low affinity to a BBB-R and that does not reduce red blood cell levels for use in treating a neurological disorder. Any of the foregoing described low-affinity anti-BBB-R antibodies or any of the low-affinity anti-BBB-R antibodies described elsewhere herein may be used in the method.

In another embodiment, the disclosure provides a method of transporting a therapeutic compound, such as a neurological disorder drug, across the blood-brain barrier comprising exposing the anti-BBB-R antibody coupled with a neurological disorder drug to the blood-brain barrier such that the antibody transports the neurological disorder drug coupled thereto across the blood-brain barrier, wherein the antibody does not reduce red blood cell levels.

The disclosure additionally provides a method of treating a neurological disorder in a mammal comprising treating the mammal with a multispecific antibody that binds both a blood-brain barrier receptor (BBB-R) and a brain antigen, wherein the anti-BBB-R antibody has been selected to have a low affinity for the BBB-R and thereby improves brain uptake of the anti-brain antigen antibody, and wherein administration of the antibody does not decrease red blood cell levels.

The disclosure additionally provides 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. In one embodiment, the administering step is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

It will be understood that any of the foregoing methods and compositions of the disclosure may be combined with one another and/or with the further aspects and embodiments of the disclosure described in the specification herein.

BRIEF DESCRIPTION OF THE FIGURES

Figures 1A-1E depict the results of experiments assessing the affinities of anti-transferrin receptor ("TfR") and anti-TfR/beta-secretase ("BACE1") variants for TfR, as well as concentrations of the antibody and $A\beta_{1-40}$ after administration in mice, as described in Example 1. The competitive ELISA assay results in Figure 1A show that anti-TfR/BACE1 variants and anti-TfR variants have distinct affinities for TfR. Figures 1B and 1D show, respectively, mean serum and brain antibody concentrations in wild-type mice after a single 50 mg/kg intravenous injection of control IgG, anti-BACE1, or an anti-TfR/BACE1 variant (n= 6 per group). Figures 1C and 1E show, respectively, plasma and brain concentrations of $A\beta_{1-40}$ in these same treated mice, as a marker of the activity of the injected antibody.

53. The antibody of any one of claims 39 to 52, wherein the antibody does not inhibit the binding of TfR to transferrin.

54. Use of an antibody that binds with low affinity to a TfR for the manufacture of a medicament for treating a neurological disorder, 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 a subject such that reduction of red blood cell levels in the subject upon antibody administration is decreased or eliminated, and wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

55. Use of the antibody of any one of claims 39 to 53 for the manufacture of a medicament for treating a neurological disorder, wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

56. An antibody that binds with low affinity to a TfR for use in treating a neurological disorder, 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 a subject such that reduction of red blood cell levels in the subject upon antibody administration is decreased or eliminated, and wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.

57. An antibody of any one of claims 39 to 53 for use in treating a neurological disorder, wherein the antibody is coupled to a neurological disorder drug or the antibody is a multispecific antibody that comprises a first antigen binding site which binds the TfR and a second antigen binding site which binds a brain antigen.