blood-brain barrier (BBB). Past studies have shown that a very small percentage (approximately 0.1%) of an IgG circulating in the bloodstream crosses through the BBB into the CNS (Felgenhauer, Klin. Wschr. 52: 1158-1164 (1974)), where the CNS concentration of the antibody may be insufficient to permit a robust effect. It was previously found that the percentage of the antibody that distributes into the CNS could be improved by exploiting BBB receptors (ie, transferrin receptor, insulin receptorand the like) (see, e.g., WO9502421). For example, the anti-BBB receptor antibody can be made multispecific to target one or more desired antigens in the CNS, or one or more heterologous molecules can be coupled to the anti-BBB receptor antibody; in either case, the anti-BBB receptor antibody can assist in delivering a therapeutic molecule into the CNS across the BBB.

However, targeting a BBB receptor with a traditional specific high-affinity antibody generally resulted in limited increase in BBB transport. It was later found by Applicants that the magnitude of antibody uptake into and distribution in the CNS is inversely related to its binding affinity for the BBB receptor amongst the anti-BBB antibodies studied. For example, a low-affinity antibody to transferrin receptor (TfR) dosed at therapeutic dose levels greatly improves BBB transport and CNS retention of the anti-TfR antibody relative to a higher-affinity anti-TfR antibody, and makes it possible to more readily attain therapeutic concentrations in the CNS (Atwal et al., *Sci. Transl. Med.* **3**, 84ra43 (2011)). Proof of such BBB transport was achieved using a bispecific antibody that binds both TfR and the amyloid precursor protein (APP) cleavage enzyme, β-secretase (BACE1). A single systemic dose of the bispecific anti-TfR/BACE1 antibody engineered using the methodology of the ~~invention~~disclosure not only resulted in significant antibody uptake in brain, but also dramatically reduced levels of brain $A\beta_{1-40}$ compared to monospecific anti-BACE1 alone, suggesting that BBB penetrance affects the potency of anti-BACE1. (Atwal et al., *Sci. Transl. Med.* **3**, 84ra43 (2011); Yu et al., *Sci. Transl. Med.* **3**, 84ra44 (2011)).

Those data and experiments highlighted several causative mechanisms behind increasing uptake of an antibody into the CNS using a lower-affinity antibody approach. First, high affinity anti-BBB receptor (BBB-R) antibodies (e.g., anti-TfR^A from Atwal et al. and Yu et al., *supra*) limit brain uptake by quickly saturating the BBB-R in the brain vasculature, thus reducing the total amount of antibody taken up into the brain and also restricting its distribution to the vasculature. Strikingly, lowering affinity for the BBB-R improves brain uptake and distribution, with a robust shift observed in localization from the vasculature to neurons and associated neuropil distributed within the CNS. Second, the lower affinity of the antibody for the BBB-R is proposed to impair the ability of the antibody to return to the vascular side of the

BBB via the BBB-R from the CNS side of the membrane because the overall affinity of the antibody for the BBB-R is low and the local concentration of the antibody on the CNS side of the BBB is non-saturating due to the rapid dispersal of the antibody into the CNS compartment. Third, *in vivo*, and as observed for the TfR system, antibodies with less affinity for the BBB-R are not cleared from the system as efficiently as those with greater affinity for the BBB-R, and thus remain at higher circulating concentrations than their higher-affinity counterparts. This is advantageous because the circulating antibody levels of the lower-affinity antibody are sustained at therapeutic levels for a longer period of time than the higher-affinity antibody, which consequently improves uptake of antibody in brain for a longer period of time. Furthermore, this improvement in both plasma and brain exposure may reduce the frequency of dosing in the clinic, which would have potential benefit not only for patient compliance and convenience but also in lessening any potential side effects or off-target effects of the antibody and/or of a therapeutic compound coupled thereto.

The low-affinity BBB-R antibodies described in the above-referenced work were selected /engineered to avoid interference with the natural binding between transferrin and the TfR, and thus to avoid potential iron transport-related side effects. Nonetheless, upon administration of certain of these antibodies in mice, some marked side effects were observed. The mice displayed a primary response of robust depletion of reticulocyte populations accompanied by rapid onset acute clinical symptoms. Though the mice recovered from both the acute clinical symptoms and the decreased reticulocyte levels in due course, avoiding or otherwise mitigating this impact on reticulocytes is clearly desirable for an anti-TfR antibody to be able to be used safely as a therapeutic molecule. It was found that the primary response to anti-TfR administration (robust reticulocyte depletion and acute clinical signs) is driven in large part by the antibody-dependent cell-mediated cytotoxicity (ADCC) activity of the antibody, while the residual reticulocyte depletion effect is mediated by the complement pathway.

These prior studies utilized mouse antibodies which bound specifically to mouse TfR, but which did not specifically recognize primate or human TfR. Accordingly, the ~~invention~~disclosure provides antibodies and functional parts thereof which do specifically recognize both primate and human TfR, in order to facilitate safety and efficacy studies in primates with the antibodies prior to therapeutic or diagnostic use in humans. In vitro studies using a human erythroblast cell line and primary bone marrow cells treated with the anti-human TfR antibodies of the ~~invention~~disclosure demonstrated that a robust depletion of TfR-positive erythroid cells is also observable in human/primate cellular systems as it is in mice (see, e.g., Example 4).

Accordingly, also provided herein are modifications to the antibodies of the ~~invention~~disclosure to greatly reduce or eliminate the unwanted reduction in the TfR-expressing reticulocyte population upon anti-TfR administration while still enabling the enhanced BBB transport, increased CNS distribution and CNS retention provided by the anti-human/primate TfR antibodies administered at therapeutic concentrations. Several general approaches to mitigate the observed effect of the anti-TfR antibodies of the ~~invention~~disclosure on both the primary and residual reticulocyte depletion are provided herein, and may be used singly or in combination.

In one approach, the effector function of the anti-human/cyno TfR antibody is reduced or eliminated in order to reduce or eliminate ADCC activity. In another approach, the affinity of the anti-human/cyno TfR antibody for human or primate TfR is further lessened such that interactions of the antibody with the reticulocyte population are less detrimental to that population. A third approach is directed to reducing the amount of anti-human/cyno TfR antibody that is present in the plasma to reduce exposure of the reticulocyte population to potentially detrimental concentrations of the antibody. A fourth approach seeks to protect, stabilize and/or replenish reticulocyte populations such that any potential depletion of the reticulocyte population in circulation or in bone marrow by administration of the anti-human/cyno TfR antibody is avoided, lessened, or mitigated.

Effector function reduction or elimination, as described herein, may be accomplished by: (i) reduction or elimination of wild-type mammalian glycosylation of the antibody, (for example, by producing the antibody in an environment where such glycosylation cannot occur, by mutating one or more carbohydrate attachment points such that the antibody cannot be glycosylated, or by chemically or enzymatically removing one or more carbohydrates from the antibody after it has been glycosylated); (ii) by reduction or elimination of the Fc receptor-binding capability of the anti-human/cyno TfR antibody (for example, by mutation of the Fc region, by deletion within the Fc region or elimination of the Fc region); or (iii) by utilization of an antibody isotype known to have minimal or no effector function (ie., including but not limited to IgG4).

Decreasing antibody complement activation, as described herein, may be accomplished by reduction or elimination of the C1q binding capability of the anti-human/cyno TfR antibody (for example, by mutation of, deletion within or elimination of the Fc region, or by modifying the non-Fc portion of the anti-human/cyno TfR antibody), or by otherwise suppressing activation or activity of the complement system (for example, by co-administering one or more complement pathway activation or complement pathway activity inhibitors).

One of ordinary skill in the art will appreciate that any combination of the foregoing methods may be employed to engineer an antibody (and/or dosage regimen for same) with the optimum balance between (i) the desirably low affinity for primate or human TfR that will maximize transport of the antibody and any conjugated compounds into the CNS; (ii) the affinity of the conjugated compound (including as a nonlimiting example, a second or further antigen-binding specificity in the anti-human/cyno TfR antibody) for its CNS antigen, since this is relevant to the amount of the compound that needs to be present in the CNS to have a therapeutic effect; (iii) the clearance rate of the anti-human/cynoTfR antibody; (iv) the lability of the anti-TfR/conjugated compound at low pH to facilitate release of the conjugated compound on the CNS/brain side of the BBB, and (v) the impact on reticulocyte populations.

It will also be appreciated that the reticulocyte-depleting effect recognized herein of anti-TfR antibody administration may be useful in the treatment of any disease or disorder where overproliferation of reticulocytes is problematic. For example, in congenital polycythemia or neoplastic polycythemia vera, raised red blood cell counts due to hyperproliferation of, e.g., reticulocytes, results in thickening of blood and concomitant physiological symptoms. Administration of an anti-human/cyno TfR antibody of the ~~invention~~disclosure wherein at least partial effector function of the antibody was preserved would permit selective removal of immature reticulocyte populations without impacting normal transferrin transport into the CNS. Dosing of such an antibody could be modulated such that acute clinical symptoms could be minimized (ie, by dosing at a very low dose or at widely-spaced intervals), as well-understood in the art.

Anti-TfR/BACE1 and anti-TfR/Abeta are each promising and novel therapeutic candidates for the treatment of Alzheimer's disease. Furthermore, receptor mediated transport (RMT)-based bispecific targeting technology opens the door for a wide range of potential therapeutics for CNS diseases. The ~~invention~~disclosure provides methods of engineering BBB-penetrant therapeutics that greatly improve transport across the BBB and CNS distribution of the therapeutic without depletion of reticulocytes.

~~Accordingly, in a first embodiment, the invention provides~~In one aspect, there is provided an isolated antibody that binds to human transferrin receptor (TfR) and primate TfR, wherein the antibody does not inhibit the binding of transferrin to TfR. In one ~~aspect~~embodiment, the binding is specific binding. In another ~~aspect~~embodiment, the antibody further does not inhibit the binding of human hemachromatosis protein ("HFE") to TfR. In another aspect, there is provided an isolated antibody that binds to human TfR and primate TfR, wherein the antibody does not inhibit the binding of transferrin to TfR, and wherein one or more properties of the antibody have been modified to reduce or eliminate the impact of the antibody on reticulocytes and/or reduce the severity or presence of acute clinical symptoms in a subject or mammal treated with the antibody. In one ~~aspect~~embodiment, the binding is specific binding. In one ~~aspect~~embodiment, the antibody is a monoclonal antibody. In another ~~aspect~~embodiment, the antibody is a human antibody. In another ~~aspect~~embodiment, the antibody is a humanized antibody. In another ~~aspect~~embodiment, the antibody is a

chimeric antibody. In another ~~aspect~~embodiment, the antibody is an antibody fragment that binds human TfR and primate TfR. In another ~~aspect~~embodiment, the primate TfR is from cynomolgous monkey.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 36, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 36, 40 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 42, 43 and 44. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 46, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 62, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 68, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 73, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 79, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 79, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 87, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 93, 95 and

96. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 99, 101 and 102. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 127, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 156 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 157 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 155, 54 and 55

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2 and HVR-H3, respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 40 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 43 and 44. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 47, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and

HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 74, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 88, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 94, 95 and 96. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 100, 101 and 102. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 156 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 157 and 55.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 35, 30 and 36. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 41, 30 and 42. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 45, 30 and 46. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 56, 57 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 61 and 62. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 64 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and

HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 66, 67 and 68. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 71, 72 and 73. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs:77, 78 and 79. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 85, 86 and 87. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 91, 92 and 93. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 97, 98 and 99. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 127. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 155.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31 and HVR-H1, HVR-H2 and HVR-H3, respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 35, 30 and 36 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 35, 30 and 36 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 40 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 41, 30 and 42 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 43 and 44 In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 45, 30 and 46 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino

acid sequences of SEQ ID NOs: 47, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 56, 57 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 61 and 62 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 64 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 66, 67 and 68 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 71, 72 and 73 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 74, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs:77, 78 and 79 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2 and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 77, 78 and 79, and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 85, 86 and 87 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 88, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 91, 92 and 93 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 94, 95 and 96. In another ~~aspect of the above~~ embodiment, the antibody

comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 97, 98 and 99 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 100, 101 and 102. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 127 and HVR-H1, HVR-H2 and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52 and HVR-H1, HVR-H2 and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 156 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52 and HVR-H1, HVR-H2 and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 157 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 155 and HVR-H1, HVR-H2 and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 54 and 55.

In one ~~aspect of the above~~ embodiment, the antibody comprises at least one HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, or HVR-L3 sequence selected from the group of sequences consisting of an HVR-H1 sequence of SEQ ID NO: 47, 53, or 100; an HVR-H2 sequence of SEQ ID NO: 48, 69, 101, 156 or 157;an HVR-H3 sequence of SEQ ID NO: 49, 76, or 102; an HVR-L1 sequence of SEQ ID NO: 45, 66 or 97; an HVR-L2 sequence of SEQ ID NOs: 30, 67 or 98; and an HVR-L3 sequence of SEQ ID NOs: 46, 68 or 102.

In one ~~aspect of the above~~ embodiment, the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 15, 16, 17, 18, 20, 25, 26, 27, 28, 108, 114, 120, 126, 153 or 154; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:4, 5, 6, 11, 12, 13, 14, 19, 21, 22, 23, 24, 105, 111, 117, 123 or 151; or (c) a VH sequence as in (a) and a VL sequence as in (b). In one such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 4 and a VH sequence of SEQ ID NO: 7. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 5 and a VH sequence of SEQ ID NO: 8. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 5 and a VH sequence of SEQ ID NO: 9. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 6 and a VH sequence of SEQ ID NO: 10. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 11 and a VH sequence of SEQ ID NO: 15. In another such ~~aspect~~embodiment, the antibody comprises

a VL sequence of SEQ ID NO: 12 and a VH sequence of SEQ ID NO: 16. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 13 and a VH sequence of SEQ ID NO: 17. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 14 and a VH sequence of SEQ ID NO: 18. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 19 and a VH sequence of SEQ ID NO: 20. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 21 and a VH sequence of SEQ ID NO: 25. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 22 and a VH sequence of SEQ ID NO: 26. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 23 and a VH sequence of SEQ ID NO: 27. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 24 and a VH sequence of SEQ ID NO: 28. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 105 and a VH sequence of SEQ ID NO: 108. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 111 and a VH sequence of SEQ ID NO: 114. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 117 and a VH sequence of SEQ ID NO: 120. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 123 and a VH sequence of SEQ ID NO: 126. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 105 and a VH sequence of SEQ ID NO: 153. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 105 and a VH sequence of SEQ ID NO: 154. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 151 and a VH sequence of SEQ ID NO: 108. In another such ~~aspect~~embodiment, the antibody comprises a VH sequence of (a) SEQ ID NO: 108, (b) SEQ ID NO: 114, (c) SEQ ID NO: 120 or (d) SEQ ID NO: 126. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of (a) SEQ ID NO: 105, (b) SEQ ID NO: 111, (c) SEQ ID NO: 117, or (d) SEQ ID NO: 123.

In one ~~aspect of the~~ embodiment ~~above~~, the antibody is selected from the group consisting of antibodies 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, and 13D4. In one such ~~aspect~~embodiment, the antibody is 7A4. In another such ~~aspect~~embodiment, the antibody is 8A2. In another such ~~aspect~~embodiment, the antibody is 15D2. In another such ~~aspect~~embodiment, the antibody is 10D11. In another such ~~aspect~~embodiment, the antibody is 7B10. In another such ~~aspect~~embodiment, the antibody is 15G11. In another such ~~aspect~~embodiment, the antibody is 16G5. In another such ~~aspect~~embodiment, the antibody is 13C3. In another such ~~aspect~~embodiment, the antibody is 16G4. In another such ~~aspect~~embodiment, the antibody is 16F6. In another such ~~aspect~~embodiment, the antibody is 7G7. In another such ~~aspect~~embodiment, the antibody is 4C2. In another such ~~aspect~~embodiment, the antibody is 1B12. In another such ~~aspect~~embodiment, the antibody is 13D4.

In one ~~aspect~~embodiment of any of the foregoing, the antibody is further affinity matured. In one such ~~aspect~~embodiment, the antibody is selected from the group consisting of 15G11.v1, 15G11.v2, 15G11.v3, 15G11.v4, 15G11.v5, 7A4.v1; 7A4.v2, 7A4.v3, 7A4.v4, 7A4.v5, 7A4.v6, 7A4.v7, 7A4.v8, 7A4.v9, 7A4.v10, 7A4.v11, 7A4.v12, 7A4.v13, 7A4.v14, 7A4.v15, 7G7.v1, 16F6.v1, 16F6.v2, 16F6.v3, 16F6.v4, 15G11.N52A, 15G11.T53A and 15G11.W92A. In one such ~~aspect~~embodiment, the antibody is 15G11.v1. In another such ~~aspect~~embodiment, the antibody is 15G11.v2. In another such ~~aspect~~embodiment, the antibody is 15G11.v3. In another such ~~aspect~~embodiment, the antibody is 15G11.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.v5. In another such ~~aspect~~embodiment, the antibody is 7A4.v1. In another such ~~aspect~~embodiment, the antibody is 7A4.v2. In another such ~~aspect~~embodiment, the antibody is 7A4.v3. In another such ~~aspect~~embodiment, the antibody is 7A4.v4. In another such ~~aspect~~embodiment, the antibody is 7A4.v5. In another such ~~aspect~~embodiment, the antibody is 7A4.v6. In another such ~~aspect~~embodiment, the antibody is 7A4.v7. In another such ~~aspect~~embodiment, the antibody is 7A4.v8. In another such ~~aspect~~embodiment, the antibody is 7A4.v9. In another such ~~aspect~~embodiment, the antibody is 7A4.v10. In another such ~~aspect~~embodiment, the antibody is 7A4.v11. In another such ~~aspect~~embodiment, the antibody is 7A4.v12. In another such ~~aspect~~embodiment, the antibody is 7A4.v13. In another such ~~aspect~~embodiment, the antibody is 7A4.v14. In another such ~~aspect~~embodiment, the antibody is 7A4.v15. In another such ~~aspect~~embodiment, the antibody is 7G7.v1. In another such ~~aspect~~embodiment, the antibody is 16F6.v1. In another such ~~aspect~~embodiment, the antibody is 16F6.v2. In another such ~~aspect~~embodiment, the antibody is 16F6.v3. In another such ~~aspect~~embodiment, the antibody is 16F6.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.N52A. In another such ~~aspect~~embodiment, the antibody is 15G11.T53A. In another such ~~aspect~~embodiment, the antibody is 15G11.W92A.

In one ~~aspect of the above~~ embodiment, the antibody is modified at one or more amino acid positions in the VH or VL to the amino acid indicated for that position in Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises a sequence or one or more HVR sequences corresponding to that of or one or more of those set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises a VH or VL sequence corresponding to that of set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises one or more HVR sequences corresponding to one or more of those set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2.

In one ~~aspect of the above~~ embodiment, the antibody is coupled to a therapeutic compound. In another ~~aspect of the above~~ embodiment, the antibody is coupled to an imaging agent or a label. In one such ~~aspect~~embodiment, the antibody is a multispecific antibody and the therapeutic compound optionally forms one portion of the multispecific antibody. In one such

~~aspect~~embodiment, the multispecific antibody comprises a first antigen binding site which binds TfR and a second antigen binding site which binds a brain antigen. In one such ~~aspect~~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 E (ApoE), 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. In another such ~~aspect~~embodiment, the multispecific antibody binds both TfR and BACE1. In another such ~~aspect~~embodiment, the multispecific antibody binds both TfR and Abeta. In another such ~~aspect~~embodiment, the therapeutic compound is a neurological disorder drug.

In one ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides an isolated nucleic acid encoding any of the foregoing antibodies. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a host cell comprising such nucleic acid. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of producing any of the foregoing antibodies comprising culturing such host cell so that the antibody is produced and optionally further comprising recovering the antibody from the host cell.

In one ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides a pharmaceutical formulation comprising any of the foregoing antibodies and a pharmaceutically acceptable carrier.

In one ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides any of the foregoing antibodies for use as a medicament. In another ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides the use of any of the foregoing antibodies in the manufacture of a medicament for treating a neurological disorder. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

In another ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides any of the foregoing antibodies for use in treating a neurological disorder. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

In another ~~aspect of the above~~ embodiment, the ~~invention~~disclosure provides any of the foregoing antibodies for use in transporting one or more compounds across the BBB. In another ~~aspect of~~

~~the above~~ embodiment, use of any of the foregoing antibodies in the manufacture of a medicament for transporting one or more compounds across the BBB is provided.

In one ~~aspect of the above~~ embodiment, a method of transporting a compound across the BBB in a subject is provided, comprising exposing any of the foregoing antibodies to the BBB such that the antibody transports the compound coupled thereto across the BBB. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In another ~~aspect of the above~~ embodiment, a method of increasing exposure of the CNS of a subject to a compound is provided, comprising exposing any of the foregoing antibodies to the BBB such that the antibody transports the compound coupled thereto across the BBB. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In one ~~aspect of the above~~ embodiment, a method of increasing rentention in the CNS of a compound administered to a subject is provided, comprising exposing any of the foregoing antibodies to the BBB such that the retention in the CNS of the compound is increased. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is

at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In one ~~aspect of the above~~ embodiment, a method of treating a neurological disorder in a mammal is provided, comprising treating the mammal with any of the foregoing antibodies. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation. In another such ~~aspect~~embodiment, the neurological disorder is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the re blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In another embodiment, the ~~invention~~disclosure provides an isolated antibody that binds to human TfR and primate TfR, wherein the antibody does not inhibit the binding of transferrin to TfR, and wherein one or more properties of the antibody have been modified to reduce or eliminate the impact of the antibody on reticulocytes and/or reduce the severity or presence of acute clinical symptoms in a subject or mammal treated with the antibody. In one ~~aspect~~embodiment, the binding is specific binding. In another ~~aspect~~embodiment, the antibody further does not inhibit the binding of HFE to TfR. In one ~~aspect~~embodiment, the antibody is a monoclonal antibody. In another ~~aspect~~embodiment, the antibody is a human antibody. In another ~~aspect~~embodiment, the antibody is a humanized antibody. In another ~~aspect~~embodiment, the antibody is a chimeric antibody. In another ~~aspect~~embodiment, the antibody is an antibody fragment that binds human TfR and primate TfR. In another ~~aspect~~embodiment, the primate TfR is from cynomolgous monkey.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 36, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 36, 40 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 42, 43 and

44. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 31, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 46, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs:52, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 52, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 62, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs:52, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 68, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 73, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 79, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 79, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs:87, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 93, 95 and 96. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 99, 101 and 102. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L3, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 127, 33 and 34.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2 and HVR-H3, respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 40 and 34. In

another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 43 and 44. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 47, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 74, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 88, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 94, 95 and 96. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 100, 101 and 102.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 35, 30 and 36. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 41, 30 and 42. In

another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 45, 30 and 46. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 56, 57 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 61 and 62. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 64 and 52. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 66, 67 and 68. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 71, 72 and 73. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs:77, 78 and 79. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 85, 86 and 87. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 91, 92 and 93. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 97, 98 and 99. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 127.

In one ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31 and HVR-H1, HVR-H2 and HVR-H3, respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 35, 30 and 36 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 38 and 39. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid

sequences of SEQ ID NOs: 35, 30 and 36 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 40 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 41, 30 and 42 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 37, 43 and 44 In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 31 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 45, 30 and 46 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 47, 48 and 49. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 50, 51 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 54 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 56, 57 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 58 and 59. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 61 and 62 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 63 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 60, 64 and 52 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 65 and 55. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 66, 67 and 68 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 53, 69 and 70. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 71, 72 and 73 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 74, 75 and 76. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs:77, 78 and 79 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino

acid sequences of SEQ ID NOs: 80, 81 and 82. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2 and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 77, 78 and 79, and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 80, 83 and 84. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 85, 86 and 87 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 88, 89 and 90. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 91, 92 and 93 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 94, 95 and 96. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 97, 98 and 99 and HVR-H1, HVR-H2, and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 100, 101 and 102. In another ~~aspect of the above~~ embodiment, the antibody comprises HVR-L1, HVR-L2, and HVR-L3 respectively comprising the amino acid sequences of SEQ ID NOs: 29, 30 and 127 and HVR-H1, HVR-H2 and HVR-H3 respectively comprising the amino acid sequences of SEQ ID NOs: 32, 33 and 34.

In one ~~aspect of the above~~ embodiment, the antibody comprises at least one HVR-H1, HVR-H2, HVR-H3, HVR-L1, HVR-L2, or HVR-L3 sequence selected from the group of sequences consisting of an HVR-H1 sequence of SEQ ID NO: 47, 53, or 100; an HVR-H2 sequence of SEQ ID NO: 48, 69, or 101;an HVR-H3 sequence of SEQ ID NO: 49, 76, or 102; an HVR-L1 sequence of SEQ ID NO: 45, 66 or 97; an HVR-L2 sequence of SEQ ID NOs: 30, 67 or 98; and an HVR-L3 sequence of SEQ ID NOs: 46, 68 or 102.

In one ~~aspect of the above~~ embodiment, the antibody comprises (a) a VH sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO: 7, 8, 9, 10, 15, 16, 17, 18, 20, 25, 26, 27, 28, 108, 114, 120 or 126; (b) a VL sequence having at least 95% sequence identity to the amino acid sequence of SEQ ID NO:4, 5, 6, 11, 12, 13, 14, 19, 21, 22, 23, 24, 105, 111, 117 or 123; or (c) a VH sequence as in (a) and a VL sequence as in (b). In one such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 4 and a VH sequence of SEQ ID NO: 7. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 5 and a VH sequence of SEQ ID NO: 8. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 5 and a VH sequence of SEQ ID NO: 9. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 6 and a VH sequence of SEQ ID NO: 10. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 11 and a

VH sequence of SEQ ID NO: 15. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 12 and a VH sequence of SEQ ID NO: 16. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 13 and a VH sequence of SEQ ID NO: 17. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 14 and a VH sequence of SEQ ID NO: 18. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 19 and a VH sequence of SEQ ID NO: 20. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 21 and a VH sequence of SEQ ID NO: 25. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 22 and a VH sequence of SEQ ID NO: 26. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 23 and a VH sequence of SEQ ID NO: 27. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 24 and a VH sequence of SEQ ID NO: 28. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 105 and a VH sequence of SEQ ID NO: 108. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 111 and a VH sequence of SEQ ID NO: 114. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 117 and a VH sequence of SEQ ID NO: 120. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of SEQ ID NO: 123 and a VH sequence of SEQ ID NO: 126. In another such ~~aspect~~embodiment, the antibody comprises a VH sequence of (a) SEQ ID NO: 108, (b) SEQ ID NO: 114, (c) SEQ ID NO: 120 or (d) SEQ ID NO: 126. In another such ~~aspect~~embodiment, the antibody comprises a VL sequence of (a) SEQ ID NO: 105, (b) SEQ ID NO: 111, (c) SEQ ID NO: 117, or (d) SEQ ID NO: 123.

In another aspect, there is provided an antibody comprising:

a. a VH sequence of SEQ ID NO:108 and a VL sequence of SEQ ID NO:105;
b. a VH sequence of SEQ ID NO:114 and a VL sequence of SEQ ID NO: 111;
c. a VH sequence of SEQ ID NO:120 and a VL sequence of SEQ ID NO: 117;
d. a VH sequence of SEQ ID NO:126 and a VL sequence of SEQ ID NO: 123;
e. a VH sequence of SEQ ID NO: 153 and a VL sequence of SEQ ID NO: 105;
f. a VH sequence of SEQ ID NO: 154 and a VL sequence of SEQ ID NO: 105;
g. a VH sequence of SEQ ID NO: 108 and a VL sequence of SEQ ID NO: 155.

In one ~~aspect of the~~ embodiment ~~above~~, the antibody is selected from the group consisting of antibodies 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, and 13D4. In one such ~~aspect~~embodiment, the antibody is 7A4. In another such ~~aspect~~embodiment, the antibody is 8A2. In another such ~~aspect~~embodiment, the antibody is 15D2. In another such ~~aspect~~embodiment, the antibody is 10D11. In another such ~~aspect~~embodiment, the antibody is 7B10. In another such ~~aspect~~embodiment, the antibody is 15G11. In another such ~~aspect~~embodiment, the antibody is 16G5. In another such ~~aspect~~embodiment, the antibody is 13C3. In another such ~~aspect~~embodiment, the antibody is 16G4. In another such ~~aspect~~embodiment, the antibody is 16F6. In another such ~~aspect~~embodiment, the antibody is 7G7. In another such ~~aspect~~embodiment, the antibody is 4C2. In another such ~~aspect~~embodiment, the antibody is 1B12. In another such ~~aspect~~embodiment, the antibody is 13D4.

In one ~~aspect~~embodiment of any of the foregoing, the antibody is further affinity matured. In one such ~~aspect~~embodiment, the antibody is selected from the group consisting of 15G11.v1, 15G11.v2, 15G11.v3, 15G11.v4, 15G11.v5, 7A4.v1; 7A4.v2, 7A4.v3, 7A4.v4, 7A4.v5, 7A4.v6, 7A4.v7, 7A4.v8, 7A4.v9, 7A4.v10, 7A4.v11, 7A4.v12, 7A4.v13, 7A4.v14, 7A4.v15, 7G7.v1, 16F6.v1,

16F6.v2, 16F6.v3 and 16F6.v4. In one such ~~aspect~~embodiment, the antibody is 15G11.v1. In another such ~~aspect~~embodiment, the antibody is 15G11.v2. In another such ~~aspect~~embodiment, the antibody is 15G11.v3. In another such ~~aspect~~embodiment, the antibody is 15G11.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.v5. In another such ~~aspect~~embodiment, the antibody is 7A4.v1. In another such ~~aspect~~embodiment, the antibody is 7A4.v2. In another such ~~aspect~~embodiment, the antibody is 7A4.v3. In another such ~~aspect~~embodiment, the antibody is 7A4.v4. In another such ~~aspect~~embodiment, the antibody is 7A4.v5. In another such ~~aspect~~embodiment, the antibody is 7A4.v6. In another such ~~aspect~~embodiment, the antibody is 7A4.v7. In another such ~~aspect~~embodiment, the antibody is 7A4.v8. In another such ~~aspect~~embodiment, the antibody is 7A4.v9. In another such ~~aspect~~embodiment, the antibody is 7A4.v10. In another such ~~aspect~~embodiment, the antibody is 7A4.v11. In another such ~~aspect~~embodiment, the antibody is 7A4.v12. In another such ~~aspect~~embodiment, the antibody is 7A4.v13. In another such ~~aspect~~embodiment, the antibody is 7A4.v14. In another such ~~aspect~~embodiment, the antibody is 7A4.v15. In another such ~~aspect~~embodiment, the antibody is 7G7.v1. In another such ~~aspect~~embodiment, the antibody is 16F6.v1. In another such ~~aspect~~embodiment, the antibody is 16F6.v2. In another such ~~aspect~~embodiment, the antibody is 16F6.v3. In another such ~~aspect~~embodiment, the antibody is 16F6.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.N52A. In another such ~~aspect~~embodiment, the antibody is 16F6.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.T53A. In another such ~~aspect~~embodiment, the antibody is 16F6.v4. In another such ~~aspect~~embodiment, the antibody is 15G11.W92A. In another such ~~aspect~~embodiment, the antibody is 16F6.v4.

In another aspect, there is provided an isolated antibody that binds to the same epitope on TfR as an antibody selected from the group consisting of antibodies 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, 13D4, 15G11.v1, 15G11.v2, 15G11.v3, 15G11.v4, 15G11.v5, 7A4.v1; 7A4.v2, 7A4.v3, 7A4.v4, 7A4.v5, 7A4.v6, 7A4.v7, 7A4.v8, 7A4.v9, 7A4.v10, 7A4.v11, 7A4.v12, 7A4.v13, 7A4.v14, 7A4.v15, 7G7.v1, 16F6.v1, 16F6.v2, 16F6.v3, 16F6.v4, 15G11.N52A, 15G11.T53A or 15G11.W92A.

In one ~~aspect of the above~~ embodiment, the antibody is modified at one or more amino acid positions in the VH or VL to the amino acid indicated for that position in Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises a sequence or one or more HVR sequences corresponding to that of or one or more of those set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises a VH or VL sequence corresponding to that of set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2. In another ~~aspect of the above~~ embodiment, the antibody comprises one or more HVR sequences corresponding to one or more of those set forth for any one of the clones in Figures 3 and 4 and Figures 4E-1 and 4E-2.

In one ~~aspect of the above~~ embodiment, the one or more properties of the antibody 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 TfR. In one such ~~aspect~~embodiment, the property is the effector function of the antibody Fc region. In another such ~~aspect~~embodiment, the property is the complement activation function of the antibody. In another such ~~aspect~~embodiment, the property is the affinity of the antibody for TfR. In one such ~~aspect~~embodiment, the effector function or complement

activation function has been reduced or eliminated relative to a wild-type antibody of the same isotype. In one ~~aspect~~embodiment, 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.

In one such ~~aspect~~embodiment, the effector function is reduced or eliminated by reduction of glycosylation of the antibody. In one such ~~aspect~~embodiment, 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. In one such ~~aspect~~embodiment, the glycosylation of the antibody is reduced by a production of the antibody in an environment that does not permit wild-type glycosylation, such as production in a non-mammalian cell production system or where the antibody is produced synthetically. In one such ~~aspect~~embodiment, the antibody is produced in a non-mammalian cell production system. In another such ~~aspect~~embodiment, the antibody is produced synthetically. In another such ~~aspect~~embodiment, the glycosylation of the antibody is reduced by modification of the antibody such that wild-type glycosylation does not occur, such as 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.

In another such ~~aspect~~embodiment, the effector function is reduced or eliminated by at least one modification of the Fc region. In one such ~~aspect~~embodiment, 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. In another such ~~aspect~~embodiment, the at least one modification of the Fc region 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. In one such ~~aspect~~embodiment, the modification is a point mutation of the Fc region to impair binding to C1q selected from the following positions: 270, 322, 329, and 321. In another such ~~aspect~~embodiment, the modification is elimination of some or all of the Fc region. In another such ~~aspect~~embodiment, complement-triggering 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 that engages the complement pathway. In one such ~~aspect~~embodiment, the antibody is selected from a Fab or a single chain antibody. In another such ~~aspect~~embodiment, the non-Fc region of the antibody is modified to reduce or eliminate activation of the complement pathway by the antibody. In one such ~~aspect~~embodiment, the modification is a point mutation of the CH1 region to impair binding to C3. In one such ~~aspect~~embodiment, the point mutation is at position 132 (see, e.g., Vidarte et al., (2001) J. Biol. Chem. 276(41): 38217-38223).

In one ~~aspect~~embodiment, the antibody the half-life of the antibody is increased by a modification in the FcRn binding region. In one ~~aspect~~embodiment, the modification is a substitution in an amino acid selected from the following positions: 251 256, 285, 290, 308, 314, 385, 389, 428, 434, 436, 238, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434. In one ~~aspect~~embodiment the modification is a substitution selected from the following: M252Y, S254T, T256E, N434A and Y436I.

In one ~~aspect~~embodiment, the antibody is combined with a further compound that mitigates or contributes to the reduction of impact on reticulocyte levels or acute clinical symptoms. In one such ~~aspect~~embodiment, the further compound protects reticulocytes from antibody-related depletion or supports the growth, development, or reestablishment of reticulocytes. In another such ~~aspect~~embodiment, the further compound is selected from erythropoietin (EPO), an iron supplement, vitamin C, folic acid, and vitamin B12, or is red blood cells or reticulocytes.

In one ~~aspect of the above~~ embodiment, the affinity of the antibody for TfR is decreased, as measured relative to a wild-type antibody of the same isotype not having lowered affinity for TfR. In one such ~~aspect~~embodiment, the antibody has a KD or IC50 for TfR of about 1 pM to about 100 μM. In another ~~aspect~~embodiment, the dose amount and/or frequency of administration of the antibody is modulated to reduce the concentration of the antibody to which the red blood cells are exposed.

In one ~~aspect of the above~~ embodiment, the antibody is coupled to a therapeutic compound. In another ~~aspect of the above~~ embodiment, the antibody is coupled to an imaging agent or a label. In one such ~~aspect~~embodiment, the antibody is a multispecific antibody and the therapeutic compound optionally forms one portion of the multispecific antibody. In one such ~~aspect~~embodiment, the multispecific antibody comprises a first antigen binding site which binds TfR and a second antigen binding site which binds a brain antigen. In one such ~~aspect~~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 E (ApoE), 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. In another such ~~aspect~~embodiment, the multispecific antibody binds both TfR and BACE1. In another such ~~aspect~~embodiment, the multispecific antibody binds both TfR and Abeta. In another such ~~aspect~~embodiment, the therapeutic compound is a neurological disorder drug.

In one aspect, there is ~~of the above embodiment, the invention~~ provided~~s~~ an isolated nucleic acid encoding any of the foregoing antibodies. In another aspect, there is provided a host cell comprising the nucleic acid described herein. In another aspect, there is provided a method of producing an antibody comprising culturing the host cell described herein so that the antibody is produced and optionally further comprising recovering the antibody from the host cell. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a host cell comprising such nucleic acid. In another ~~aspect~~embodiment, the ~~invention~~disclosure provides a method of producing any of the foregoing antibodies comprising culturing such host cell so that the antibody is produced and optionally further comprising recovering the antibody from the host cell.

In one aspect ~~of the above embodiment~~, there is ~~invention~~ provided~~s~~ a pharmaceutical formulation comprising any of the foregoing antibodies and a pharmaceutically acceptable carrier.

In one aspect ~~of the above embodiment~~, there is ~~invention~~ provided~~s~~ any of the foregoing antibodies for use as a medicament. In another aspect ~~of the above embodiment~~, there is~~invention~~ provided~~s~~ the use of any of the foregoing antibodies in the manufacture of a medicament for ~~treating a~~the treatment of a neurological disorder. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

In another aspect ~~of the above embodiment~~, there is~~the invention~~ provided~~s~~ any of the foregoing antibodies for use in the treatment of~~treating~~ a neurological disorder. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

In another aspect ~~of the above embodiment~~, there is ~~invention~~ provided~~s~~ any of the foregoing antibodies for use in transporting one or more compounds across the BBB. In another aspect ~~of the above embodiment~~, use of any of the foregoing antibodies in the manufacture of a medicament for transporting one or more compounds across the BBB is provided.

In another aspect, there is provided use of an antibody described herein in the manufacture of a medicament for transporting a compound across the BBB in a subject, wherein the antibody is exposed to the BBB such that the antibody transports the compound coupled thereto across the BBB. In one ~~aspect of the above~~ embodiment, a method of transporting a compound across the BBB in a subject is provided, comprising exposing any of the foregoing antibodies to the BBB such that the antibody transports the compound coupled thereto across the BBB. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to

which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In another aspect, there is provided use of an antibody described herein in the manufacture of a medicament for increasing exposure of the CNS of a subject to a compound, wherein the antibody is exposed to the BBB such that the antibody transports the compound coupled thereto across the BBB. In another ~~aspect of the above~~ embodiment, a method of increasing exposure of the CNS of a subject to a compound is provided, comprising exposing any of the foregoing antibodies to the BBB such that the antibody transports the compound coupled thereto across the BBB. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In another aspect, there is provided use of an antibody described herein in the manufacture of a medicament for increasing retention in the CNS of a compound administered to a subject, wherein the antibody is exposed to the BBB such that the retention in the CNS of the compound is increased. In one ~~aspect of the above~~ embodiment, a method of increasing rentention in the CNS of a compound administered to a subject is provided, comprising exposing any of the foregoing antibodies to the BBB such that the retention in the CNS of the compound is increased. In another such ~~aspect~~embodiment, the BBB is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which red blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In one aspect, there is provided use of an antibody described herein in the manufacture of a medicament for treating a neurological disorder in a mammal. In one ~~aspect of the above~~ embodiment, a method of treating a neurological disorder in a mammal is provided, comprising treating the mammal with any of the foregoing antibodies. In one such ~~aspect~~embodiment, the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation. In another such ~~aspect~~embodiment, the neurological disorder

is in a human subject. In another such ~~aspect~~embodiment, the dose amount and/or frequency of administration is modulated to reduce the concentration of antibody to which the re blood cells are exposed. In another such ~~aspect~~embodiment, the method further comprises the step of monitoring the subject for depletion of red blood cells. In another such ~~aspect~~embodiment, the antibody coupled to the compound is administered at a therapeutic dose. In one such ~~aspect~~embodiment, the therapeutic dose is TfR-saturating. In another such ~~aspect~~embodiment, administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.

In another embodiment, the ~~invention~~disclosure provides an isolated antibody that binds to the same epitope on TfR as an antibody selected from the group consisting of antibodies 7A4, 8A2, 15D2, 10D11, 7B10, 15G11, 16G5, 13C3, 16G4, 16F6, 7G7, 4C2, 1B12, 13D4, 15G11.v1, 15G11.v2, 15G11.v3, 15G11.v4, 15G11.v5, 7A4.v1; 7A4.v2, 7A4.v3, 7A4.v4, 7A4.v5, 7A4.v6, 7A4.v7, 7A4.v8, 7A4.v9, 7A4.v10, 7A4.v11, 7A4.v12, 7A4.v13, 7A4.v14, 7A4.v15, 7G7.v1, 16F6.v1, 16F6.v2, 16F6.v3, 16F6.v4 15G11.N52A, 15G11.T53A and 15G11W92A.

In another embodiment, a method of decreasing clearance of a compound administered to a subject is provided, wherein the compound is coupled to an antibody which binds with low affinity to TfR, 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.

In another embodiment, a method of optimizing the pharmcokinetics and/or pharmacodynamics of a compound to be efficacious in the CNS in a subject is provided, wherein the compound is coupled to an antibody which binds with low affinity to TfR, and the antibody is selected such that its affinity for TfR 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.

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

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 depicts a three-dimensional crystal structure of a TfR dimer in complex with Tf, based on the pdb file 3SM9. The non-Tf-binding apical region of TfR is labeled.

55. A method of producing an antibody comprising culturing the host cell of claim 54 so that the antibody is produced and optionally further comprising recovering the antibody from the host cell.

56. A pharmaceutical formulation comprising the antibody of any of claims 1-55 and a pharmaceutically acceptable carrier.

57. The antibody of any of claims 1-52 for use as a medicament.

58. The antibody of claim 1 for use in ~~treating~~ the treatment of a neurological disorder.

59. The antibody of claim 58, wherein the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

60. The antibody of any of claims 1-52 for use in transporting one or more compounds across the BBB.

61. Use of the antibody of claim 1 in the manufacture of a medicament for the ~~treating~~ treatment of a neurological disorder.

62. The use of claim 61, wherein the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

63. Use of the antibody of claim 1 in the manufacture of a medicament for transporting one or more compounds across the BBB.

64. Use of an antibody of claim 46 in the manufacture of a medicament for ~~A method of~~ transporting a compound across the BBB in a subject, wherein the ~~comprising exposing an~~ antibody is exposed ~~of claim 46~~ to the BBB such that the antibody transports the compound coupled thereto across the BBB.

65. Use of an antibody of claim 46 in the manufacture of a medicament for~~A method of~~ increasing exposure of the CNS of a subject to a compound, wherein the ~~comprising exposing an~~ antibody is exposed ~~of claim 46~~ to the BBB such that the antibody transports the compound coupled thereto across the BBB.

66. Use of an antibody of claim 46 in the manufacture of a medicament for~~A method of~~ increasing retention in the CNS of a compound administered to a subject, wherein the~~comprising exposing an~~ antibody is exposed~~of claim 46~~ to the BBB such that the retention in the CNS of the compound is increased.

67. Use of an antibody of claim 46 in the manufacture of a medicament for~~A method of~~ treating a neurological disorder in a mammal ~~comprising treating the mammal with an antibody of claim 46~~.

68. The ~~method~~use of claim 67, wherein the neurological disorder is selected from the group consisting of a neuropathy disorder, a neurodegenerative disease, cancer, an ocular disease disorder, a seizure disorder, a lysosomal storage disease, amyloidosis, a viral or microbial disease, ischemia, a behavioral disorder, and CNS inflammation.

69. The ~~method~~use of any of claims 64-68, wherein the BBB or neurological disorder is in a human subject.

70. The ~~method~~use of claim 69, 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.

71. The ~~method~~use of claim 69, further comprising the step of monitoring the subject for depletion of red blood cells.

72. The ~~method~~use of claim 69, wherein the antibody coupled to the compound is administered at a therapeutic dose.

73. The ~~method~~use of claim 72, wherein the therapeutic dose is TfR-saturating.

74. The ~~method~~use of claim 69, wherein administration of the antibody is at a dose and/or dose frequency calibrated to minimize acute clinical symptoms of the antibody administration.