TRANSFERRIN RECEPTOR BINDING PROTEINS AND CONJUGATES

SEQUENCE LISTING

[0001] The present application is being filed along with a Sequence Listing in ST.26 XML format. The Sequence Listing is provided as a file titled "30369_WO" created 18-July-2023 and is 667 kilobytes in size. The Sequence Listing information in the ST.26 XML format is incorporated herein by reference in its entirety.

BACKGROUND

[0002] The blood brain barrier (BBB) is a selective semipermeable border of capillary endothelial cells that prevents solutes, including pathogens, from passing into the central nervous system (CNS). The BBB allows the passage of some small molecules by passive diffusion and the cells of BBB actively transport metabolic products crucial to neural function such as glucose and amino acids across the barrier using specific transport proteins. The BBB has neuroprotective function by tightly controlling access to the brain; but it also impedes access of therapeutic agents to CNS.

[0003] BBB shuttles for improving passage of the therapeutic agents across the blood brain barrier and into the CNS have been described. For example, WO2003/009815 describes the use of antibodies directed to transferrin receptor ("TfR") for modulating blood brain barrier transport. However, attempts at using anti-TfR antibodies to shuttle therapeutic agents across the BBB have proven challenging. To date, there are no approved TfR shuttles or conjugates for the treatment of CNS diseases.

[0004] Therefore, there remains a need for TfR binding proteins and conjugates that can deliver therapeutic agents across the BBB into the CNS for the treatment of various CNS diseases.

SUMMARY

[0005] Provided herein are proteins comprising one monovalent human TfR binding domain ("human TfR binding proteins"), proteins comprising one monovalent mouse TfR binding domain ("mouse TfR binding proteins"), conjugates comprising such human or mouse TfR binding proteins, e.g., human TfR binding proteins-dsRNA conjugates, pharmaceutical compositions comprising human TfR binding proteins or conjugates, and methods of treating

CNS diseases (e.g., neurodegenerative disease such as neurodegenerative synucleinopathy or tauopathy) using human TfR binding proteins or conjugates.

[0006] In one example, provided herein are proteins comprising one and only one monovalent human TfR binding domain ("human TfR binding proteins"). In some examples, the monovalent human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), and the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3. In some examples, the monovalent human TfR binding domain comprises a VH comprising HCDR1, HCDR2, and HCDR3 selected from Table 1, and/or a VL comprising LCDR1, LCDR2, and LCDR3 selected from Table 2. In some examples, the monovalent human TfR binding domain comprises a VH and/or a VL selected from Table 3.

[0007] In a first aspect of the present disclosure, there is provided a protein comprising one monovalent human TfR binding domain, wherein the human TfR binding domain comprises a VH and a VL, wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 21, HCDR3 comprises SEQ ID NO: 22, LCDR1 comprises SEQ ID NO: 23, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 24; or

(b) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 25, HCDR3 comprises SEQ ID NO: 26, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

[0008] In some examples, provided herein are proteins comprising one monovalent human TfR binding domain, wherein the human TfR binding domain comprises a VH and a VL, wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 3, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(b) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 7, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(c) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 8, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(d) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12;

(e) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 14, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;

(f) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18; or

(g) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 20, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

[0009] In some examples, provided herein are proteins comprising one monovalent human TfR binding domain, wherein the human TfR binding domain comprises a VH and a VL, and wherein the VH and VL comprise the following sequences:

(a) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 27 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(b) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 29 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(c) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 30 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 31;

(d) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 32 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 33;

(e) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 34 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 35;

(f) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 36 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37; or

(g) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 38 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37.

[00010] In some examples, provided herein are proteins comprising one monovalent human TfR binding domain, wherein the human TfR binding domain comprises a VH and a VL, and wherein the VH and VL comprise the following sequences:

(a) VH comprises SEQ ID NO: 27 and VL comprises SEQ ID NO: 28;

(b) VH comprises SEQ ID NO: 29 and VL comprises SEQ ID NO: 28;

(c) VH comprises SEQ ID NO: 30 and VL comprises SEQ ID NO: 31;

(d) VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33;

(e) VH comprises SEQ ID NO: 34 and VL comprises SEQ ID NO: 35;

(f) VH comprises SEQ ID NO: 36 and VL comprises SEQ ID NO: 37; or

(g) VH comprises SEQ ID NO: 38 and VL comprises SEQ ID NO: 37.

[00011] In some examples, the monovalent human TfR binding domain is an antibody fragment, e.g., Fab, scFv, Fv, or scFab (single chain Fab). In some examples, the monovalent human TfR binding domain is Fab. In some examples, the human TfR binding domain further comprises a heavy chain constant region and/or a light chain constant region.

[00012] In some examples, the human TfR binding proteins describe herein further comprise a half-life extender, e.g., an immunoglobulin Fc region or a VHH that binds human serum albumin (HSA).

[00013] In some examples, the human TfR binding proteins described herein comprise one or more engineered cysteine residues for conjugation. In some examples, the human TfR binding proteins described herein comprise one or more native cysteine residues for conjugation.

[00014] In some examples, the human TfR binding protein described herein is any one of the human TfR binding proteins in Table 6a and 6b. In some examples, the human TfR binding protein described herein has one heavy chain (HC) and one light chain (LC), e.g., TBP1, TBP2, TBP3, TBP4, TBP5, TBP6, TBP7, TBP8, or TBP9. In some examples, the human TfR binding protein has two heavy chains (HC1 and HC2) and two light chains (LC1 and LC2). In some examples, the human TfR binding protein described herein has a heterodimeric antibody format, e.g., TBP10, TBP11, TBP12, or TBP13.

[00015] In another aspect of the present disclosure, there is provided a protein comprising one monovalent human transferrin receptor (TfR) binding domain, wherein the human TfR binding domain binds an epitope comprising one or more residues in (a) residues 346-364 FGNMEGDCPSDWKTDSTCR (SEQ ID NO: 119), (b) residues 243-247 FEDLY (SEQ ID NO: 162) and residues 345-364 LFGNMEEGDCPSDWKTDSTCR) (SEQ ID NO: 163), or (c) residues 243-247 FEDLY (SEQ ID NO: 162), residues 259-263 AGKIT (SEQ ID NO: 164), and residues 532-538 (VEKLTLD) (SEQ ID NO: 165), of human TfR.

[00016] In another example, provided herein are proteins comprising one monovalent mouse TfR binding domain (“mouse TfR binding proteins”). These mouse TfR binding proteins can serve as surrogate molecules to the human TfR binding proteins in mouse models. In some examples, provided herein are proteins comprising one monovalent mouse TfR binding domain, wherein the mouse TfR binding domain comprises a VH and a VL, wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein HCDR1 comprises SEQ ID NO: 71, HCDR2 comprises SEQ ID NO: 72, HCDR3 comprises SEQ ID NO: 73, LCDR1 comprises SEQ ID NO: 74, LCDR2 comprises SEQ ID NO: 75, and LCDR3 comprises SEQ ID NO: 76. In some examples, provided herein are

proteins comprising one monovalent mouse TfR binding domain, wherein the mouse TfR binding domain comprises a VH comprising SEQ ID NO: 77 and a VL comprising SEQ ID NO: 78.

[00016a] In yet another aspect of the present disclosure, there is provided a protein comprising one monovalent mouse transferrin receptor (TfR) binding domain, wherein the mouse TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein HCDR1 comprises SEQ ID NO: 71, HCDR2 comprises SEQ ID NO: 72, HCDR3 comprises SEQ ID NO: 73, LCDR1 comprises SEQ ID NO: 74, LCDR2 comprises SEQ ID NO: 75, and LCDR3 comprises SEQ ID NO: 76.

[00017] Also provided herein are antibodies comprising a VH comprising HCDR1, HCDR2, and HCDR3 selected from Table 1, and/or a VL comprising LCDR1, LCDR2, and LCDR3 selected from Table 2. In some examples, such antibodies comprise a VH and/or a VL selected from Table 3.

[00018] In another example, provided herein are conjugates comprising human or mouse TfR binding proteins described herein and a therapeutic agent. In some examples, the therapeutic agent is selected from a double stranded RNA (e.g., siRNA, saRNA), oligonucleotide (e.g., antisense oligonucleotide), peptide, small molecule, nanoparticle, lipid nanoparticle, exosome, antibody or antigen binding fragment thereof, or a combination thereof. In some examples, the therapeutic agent is a double stranded RNA (dsRNA). In some examples, the dsRNA comprises a sense strand and an antisense stand, wherein the antisense strand is complementary to a target mRNA selected from SNCA, MAPT, APP, ATXN2, ATXN3, SARM1, APOE, BACE1, FMR1, LRRK2, HTT, SOD1, SCN10A, SCN9A or CACNA1B mRNA. In some examples, the therapeutic agent to protein ratio is about 1:1 to 3:1. In some examples, the therapeutic agent to protein ratio is about 1:1. In some examples, the therapeutic agent to protein ratio is about 2:1. In some examples, the therapeutic agent to protein ratio is about 3:1.

[00018a] In a further aspect of the present disclosure, there is provided a conjugate comprising the protein as disclosed herein and a therapeutic agent.

[00019] In some examples, the therapeutic agent is linked to the human or mouse TfR binding protein through a linker. In some examples, the linker is a Mal-Tet-TCO linker, SMCC linker, or GDM linker (structures of these linkers shown in Table 8).

[00020] In some examples, provided herein are conjugates of Formula (I): R-L-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human or mouse TfR binding domain; and wherein L is a linker, or optionally absent. In some examples, P is a human or mouse TfR binding protein described herein. In some examples, the R to P ratio is about 1:1 to 3:1. In some examples, the R to P ratio is about 1:1. In some examples, the R to P ratio is about 2:1. In some examples, the R to P ratio is about 3:1.

[00021] In some examples, provided herein are conjugates of Formula (II): $(R\text{-}L)_n\text{-}P$, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human or mouse TfR binding domain; wherein L is a linker, or optionally absent, and wherein n is 1 to 3. In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

[00022] In some examples, provided herein are conjugates of Formula (I): R-L-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, herein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 21, HCDR3 comprises SEQ ID NO: 22, LCDR1 comprises SEQ ID NO: 23, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 24; or

(b) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 25, HCDR3 comprises SEQ ID NO: 26, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

[00023] In some examples, provided herein are conjugates of Formula (I): R-L-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 3, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(b) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 7, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(c) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 8, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(d) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12;

(e) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 14, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;

(f) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18; or

(g) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 20, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

[00024] In some examples, provided herein are conjugates of Formula (I): R-L-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, herein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the following sequences:

(a) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 27 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(b) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 29 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(c) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 30 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 31;

(d) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 32 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 33;

(e) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 34 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 35;

(f) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 36 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37; or

(g) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 38 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37.

[00025] In some examples, provided herein are conjugates of Formula (I): R-L-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, herein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the following sequences:

(a) VH comprises SEQ ID NO: 27 and VL comprises SEQ ID NO: 28;

(b) VH comprises SEQ ID NO: 29 and VL comprises SEQ ID NO: 28;

(c) VH comprises SEQ ID NO: 30 and VL comprises SEQ ID NO: 31;

(d) VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33;

(e) VH comprises SEQ ID NO: 34 and VL comprises SEQ ID NO: 35;

(f) VH comprises SEQ ID NO: 36 and VL comprises SEQ ID NO: 37; or

(g) VH comprises SEQ ID NO: 38 and VL comprises SEQ ID NO: 37.

[00026] In another aspect of the present disclosure, there is provided a conjugate of Formula (II): $(R\text{-}L)_n\text{-}P$, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, herein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 21, HCDR3 comprises SEQ ID NO: 22, LCDR1 comprises SEQ ID NO: 23, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 24; or

(b) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 25, HCDR3 comprises SEQ ID NO: 26, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18,

and wherein n is 1 to 3.

[00027] In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

[00028] In some examples, provided herein are conjugates of Formula (II): $(R\text{-}L)_n\text{-}P$, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 3, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(b) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 7, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(c) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 8, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(d) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12;

(e) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 14, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;

(f) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18; or

(g) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 20, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18,

and wherein n is 1 to 3.

[00029] In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

[00030] In some examples, provided herein are conjugates of Formula (II): (R-L)n-P, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the following sequences:

(a) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 27 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(b) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 29 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 28;

(c) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 30 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 31;

(d) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 32 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 33;

(e) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 34 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 35;

(f) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 36 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37; or

(g) VH comprises a sequence having at least 95% sequence identity to SEQ ID NO: 38 and VL comprises a sequence having at least 95% sequence identity to SEQ ID NO: 37,

and wherein n is 1 to 3.

[00031] In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

[00032] In some examples, provided herein are conjugates of Formula (II): $(R\text{-}L)_n\text{-}P$, wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand; wherein P is a protein comprising one monovalent human TfR binding domain; and wherein L is a linker, or optionally absent, wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH and VL comprise the following sequences:

(a) VH comprises SEQ ID NO: 27 and VL comprises SEQ ID NO: 28;

(b) VH comprises SEQ ID NO: 29 and VL comprises SEQ ID NO: 28;

(c) VH comprises SEQ ID NO: 30 and VL comprises SEQ ID NO: 31;

(d) VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33;

(e) VH comprises SEQ ID NO: 34 and VL comprises SEQ ID NO: 35;

(f) VH comprises SEQ ID NO: 36 and VL comprises SEQ ID NO: 37; or

(g) VH comprises SEQ ID NO: 38 and VL comprises SEQ ID NO: 37,

and wherein n is 1 to 3.

[00033] In some examples, n is 1. In some examples, n is 2. In some examples, n is 3.

[00034] In some examples, the linker (L) is a Mal-Tet-TCO linker, SMCC linker, or GDM linker (see Table 8).

[00035] In some examples, the dsRNA comprises an antisense strand complementary to a target mRNA selected from SNCA, MAPT, APP, ATXN2, ATXN3, SARM1, APOE, BACE1, FMR1, LRRK2, HTT, SOD1, SCN10A, SCN9A or CACNA1B mRNA. In some examples, the dsRNA comprises an antisense strand complementary to SNCA mRNA. In some examples, the dsRNA comprises an antisense strand complementary to MAPT mRNA.

[00036] Exemplary unmodified sense strand and antisense strand sequences of dsRNA targeting human SNCA mRNA are provided in Table 9a. In some examples, the sense strand and the antisense strand of the dsRNA comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 81, and the antisense strand comprises SEQ ID NO: 82;

(b) the sense strand comprises SEQ ID NO: 83, and the antisense strand comprises SEQ ID NO: 84;

(c) the sense strand comprises SEQ ID NO: 85, and the antisense strand comprises SEQ ID NO: 86;

(d) the sense strand comprises SEQ ID NO: 87, and the antisense strand comprises SEQ ID NO: 88;

(e) the sense strand comprises SEQ ID NO: 89, and the antisense strand comprises SEQ ID NO: 90; and

(f) the sense strand comprises SEQ ID NO: 91, and the antisense strand comprises SEQ ID NO: 92;

(g) the sense strand comprises SEQ ID NO: 116, and the antisense strand comprises SEQ ID NO: 82,

[00037] wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages. In some examples, the sense strand comprises SEQ ID NO: 81, and the antisense strand comprises SEQ ID NO: 82.

[00038] Exemplary unmodified sense strand and antisense strand sequences of dsRNA targeting human MAPT mRNA are provided in Table 9b. In some examples, the sense strand and the antisense strand of the dsRNA comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 120, and the antisense strand comprises SEQ ID NO: 121;

(b) the sense strand comprises SEQ ID NO: 122, and the antisense strand comprises SEQ ID NO: 123; and

(c) the sense strand comprises SEQ ID NO: 124, and the antisense strand comprises SEQ ID NO: 125,

[00039] wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

[00040] The dsRNA can include modifications. The modifications can be made to one or more nucleotides of the sense and/or antisense strand or to the internucleotide linkages. In some examples, one or more nucleotides of the sense strand and/or the antisense strand are independently modified nucleotides, which means the sense strand and the antisense strand can have different modified nucleotides. In some examples, each nucleotide of the sense strand is a modified nucleotide. In some examples, each nucleotide of the antisense strand is a modified nucleotide. In some examples, the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide. In some examples, each nucleotide of the sense strand and the antisense strand is independently a modified nucleotide, e.g., a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide, or 2'-O-alkyl modified nucleotide.

[00041] In some examples, the sense strand has four 2'-fluoro modified nucleotides, e.g., at positions 7, 9, 10, 11 from the 5’ end of the sense strand. In some examples, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some examples, the antisense strand has four 2'-fluoro modified nucleotides, e.g., at positions 2, 6, 14, 16 from the 5’ end of the antisense strand. In some examples, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00042] In some examples, the sense strand has three 2'-fluoro modified nucleotides, e.g., at positions 9, 10, 11 from the 5’ end of the sense strand. In some examples, the other nucleotides of the sense strand are 2'-O-methyl modified nucleotides. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 7, 14, 16 from the 5’ end of the antisense strand. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 5, 8, 14, 16 from the 5’ end of the antisense strand. In some examples, the antisense strand has five 2'-fluoro modified nucleotides, e.g., at positions 2, 3, 7, 14, 16 from the 5’ end of the antisense strand. In some examples, the other nucleotides of the antisense strand are 2'-O-methyl modified nucleotides.

[00043] In some examples, the 5’ end of the antisense strand has a phosphate analog, e.g., 5’-vinylphosphonate (5’-VP).

[00044] In some examples, the sense strand or the antisense strand comprises an abasic moiety or inverted abasic moiety.

[00045] In some examples, the sense strand and the antisense strand have one or more modified internucleotide linkages. In some examples, the modified internucleotide linkage is phosphorothioate linkage. In some examples, the sense strand has four or five phosphorothioate linkages. In some examples, the antisense strand has four or five phosphorothioate linkages. In some examples, the sense strand and the antisense strand each has four or five phosphorothioate linkages. In some examples, the sense strand has four phosphorothioate linkages and the antisense strand has five phosphorothioate linkages.

[00046] Exemplary modified sense strand and antisense strand sequences of dsRNA targeting human SNCA mRNA are provided in Table 11a. Exemplary modified sense strand and antisense strand sequences of dsRNA targeting human MAPT mRNA are provided in Table 11b.

[00046a] In yet another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the protein as disclosed herein or the conjugate as disclosed herein, and a pharmaceutically acceptable carrier.

[00047] In another example, provided herein are methods of treating a CNS disease, e.g., a neurodegenerative disease, in a patient in need thereof, and such the method comprises

administering to the patient an effective amount of the human TfR binding protein or conjugate or a pharmaceutical composition described herein.

[00048] In a further example, provided herein are methods of treating a neurodegenerative synucleinopathy in a patient in need thereof, and such the method comprises administering to the patient an effective amount of the human TfR binding proteins or conjugate or a pharmaceutical composition described herein (e.g., a TBP-SNCA siRNA conjugate described herein or a pharmaceutical composition comprising such a TBP-SNCA siRNA conjugate). In some examples, the neurodegenerative synucleinopathy is selected from Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia. The human TfR binding protein or conjugate or a pharmaceutical composition can be administered to the patient intravenously or subcutaneously.

[00049] In a further example, provided herein are methods of treating a tauopathy in a patient in need thereof, and such the method comprises administering to the patient an effective amount of the human TfR binding proteins or conjugate or a pharmaceutical composition described herein (e.g., a TBP-MAPT siRNA conjugate described herein or a pharmaceutical composition comprising such a TBP-MAPT siRNA conjugate). In some examples, the tauopathy is selected from Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles,

postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT). The human TfR binding protein or conjugate or a pharmaceutical composition can be administered to the patient intravenously or subcutaneously.

[00050] In another example, provided herein are human TfR binding proteins or conjugates described herein or pharmaceutical compositions comprising such human TfR binding proteins or conjugates for use in a therapy. Also provided herein are human TfR binding proteins or conjugates described herein or pharmaceutical compositions comprising such human TfR binding proteins or conjugates (e.g., a TBP-SNCA siRNA conjugate described herein or a pharmaceutical composition comprising such a TBP-SNCA siRNA conjugate) for use in the treatment of a neurodegenerative synucleinopathy, e.g., Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia. Also provided herein are human TfR binding proteins or conjugates described herein or pharmaceutical compositions comprising such human TfR binding proteins or conjugates (e.g., a TBP-MAPT siRNA conjugate described herein or a pharmaceutical composition comprising such a TBP-MAPT siRNA conjugate) for use in the treatment of a tauopathy, e.g., e.g., Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease

type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

[00050a] In a further aspect of the present disclosure, there is provided the conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in a therapy.

[00050b] In another aspect of the present disclosure, there is provided the conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the treatment of a neurodegenerative synucleinopathy, optionally wherein the neurodegenerative synucleinopathy is selected from Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia.

[00050c] In yet another aspect of the present disclosure, there is provided the conjugate as disclosed herein, or the pharmaceutical composition as disclosed herein, for use in the treatment of a tauopathy, optionally wherein the tauopathy is selected from Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy,

myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

[00051] In another example, provided herein are uses of human TfR binding proteins or conjugates described herein in the manufacture of a medicament for treating a CNS disease, e.g., a neurodegenerative disease. In some examples, the neurodegenerative disease is a neurodegenerative synucleinopathy, e.g., Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia. In some examples, the neurodegenerative disease is a tauopathy, e.g., Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

[00051a] In a further aspect of the present disclosure, there is provided a use of the conjugate as disclosed herein in the manufacture of a medicament for treating a CNS disease.

[00051b] In another aspect of the present disclosure, there is provided a use of the conjugate as disclosed herein in the manufacture of a medicament for treating a neurodegenerative synucleinopathy, optionally wherein the neurodegenerative synucleinopathy is selected from Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia.

[00051c] In yet another aspect of the present disclosure, there is provided a use of the conjugate as disclosed herein in the manufacture of a medicament for treating a tauopathy, optionally wherein the tauopathy is selected from Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

CLAIMS

1. A protein comprising one monovalent human transferrin receptor (TfR) binding domain, wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:
   (a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 21, HCDR3 comprises SEQ ID NO: 22, LCDR1 comprises SEQ ID NO: 23, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 24; or
   (b) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 25, HCDR3 comprises SEQ ID NO: 26, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

2. The protein of claim 1, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:
   (a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 3, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;
   (b) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 7, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;
   (c) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 8, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;
   (d) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12;

(e) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 14, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;
(f) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18; or
(g) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 20, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

3. The protein of claim 1 or 2, wherein the VH and VL comprise the following sequences:
(a) VH comprises SEQ ID NO: 27 and VL comprises SEQ ID NO: 28;
(b) VH comprises SEQ ID NO: 29 and VL comprises SEQ ID NO: 28;
(c) VH comprises SEQ ID NO: 30 and VL comprises SEQ ID NO: 31;
(d) VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33;
(e) VH comprises SEQ ID NO: 34 and VL comprises SEQ ID NO: 35;
(f) VH comprises SEQ ID NO: 36 and VL comprises SEQ ID NO: 37; or
(g) VH comprises SEQ ID NO: 38 and VL comprises SEQ ID NO: 37.

4. The protein of any one of claims 1-3, wherein the human TfR binding domain is a Fab, scFv, Fv, or scFab.

5. The protein of any one of claims 1-4, wherein the human TfR binding domain further comprises:
(a) a heavy chain constant region comprising cysteine at residue 124 (according to the EU Index numbering), and/or
(b) a light chain constant region comprising cysteine at residue 156 (according to the EU Index numbering).

6. The protein of any one of claims 1-5 further comprising a half-life extender.

7. The protein of claim 6, wherein the half-life extender is an immunoglobulin Fc region, optionally wherein the Fc region is a modified human IgG4 Fc region.

8. The protein of claim 7, wherein the modified human IgG4 Fc region comprises proline at residue 228, and alanine at residues 234 and 235 (all residues are numbered according to the EU Index numbering).

9. The protein of claim 7 or 8, wherein the protein comprises an immunoglobulin Fc region comprising cysteine at residue 378 (according to the EU Index numbering).

10. The protein of any one of claims 7-9, wherein the Fc region comprises:
(a) a first Fc CH3 domain comprising a serine at position 349, a methionine at position 366, a tyrosine at position 370, and a valine at position 409; and a second Fc CH3 domain comprising a glycine at position 356, an aspartic acid at position 357, a glutamine at position 364, and an alanine at position 407 (all residues are numbered according to the EU Index numbering); or
(b) a first Fc CH3 domain comprising leucine at residue 405, and a second Fc CH3 domain comprising arginine at residue 409 (all residues are numbered according to the EU Index numbering).

11. The protein of any one of claims 1-9, wherein the protein comprises one heavy chain (HC) and one light chain (LC), wherein the HC and LC comprise the following sequences:
(a) HC comprises SEQ ID NO: 53 and LC comprises SEQ ID NO: 54;
(b) HC comprises SEQ ID NO: 55 and LC comprises SEQ ID NO: 54;
(c) HC comprises SEQ ID NO: 56 and LC comprises SEQ ID NO: 57;
(d) HC comprises SEQ ID NO: 58 and LC comprises SEQ ID NO: 59;
(e) HC comprises SEQ ID NO: 60 and LC comprises SEQ ID NO: 61;
(f) HC comprises SEQ ID NO: 62 and LC comprises SEQ ID NO: 63; or
(g) HC comprises SEQ ID NO: 64 and LC comprises SEQ ID NO: 63.

12. The protein of any one of claims 1-10, wherein the protein comprises two heavy chains HC1 and HC2 and one light chain LC1, wherein:

(a) HC1 comprises SEQ ID NO: 68, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 69;
(b) HC1 comprises SEQ ID NO: 138, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 139; or
(c) HC1 comprises SEQ ID NO: 166, LC1 comprises SEQ ID NO: 54, HC2 comprises SEQ ID NO: 167.

13. The protein of any one of claims 1-4, wherein the protein comprises one heavy chain (HC) and one light chain (LC), and wherein the HC comprises SEQ ID NO: 65 and the LC comprises SEQ ID NO: 59.

14. The protein of claim 6, wherein the half-life extender is a VHH that binds HSA.

15. The protein of claim 14, wherein the VHH comprises CDR1 comprising SEQ ID NO: 39, CDR2 comprising SEQ ID NO: 40, and CDR3 comprising SEQ ID NO: 41.

16. The protein of claim 14 or 15, wherein the VHH comprises SEQ ID NO: 42.

17. The protein of any one of claims 14-16, wherein the protein comprises one heavy chain (HC) and one light chain (LC), and wherein the HC comprises SEQ ID NO: 66 and the LC comprises SEQ ID NO: 67.

18. The protein of any one of claims 1-11, wherein the protein is a heterodimeric antibody that comprises a first arm comprising one monovalent human TfR binding domain and a second arm that is a null arm.

19. The protein of claim 18, wherein the second arm comprises a VH and a VL, wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein HCDR1 comprises SEQ ID NO: 43, HCDR2 comprises SEQ ID NO: 44, HCDR3 comprises SEQ ID NO: 45, LCDR1 comprises SEQ ID NO: 46, LCDR2 comprises SEQ ID NO: 47, and LCDR3 comprises SEQ ID NO: 48,

optionally wherein the VH comprises SEQ ID NO: 49 and the VL comprises SEQ ID NO: 50.

20. The protein of claim 18 or 19, wherein the protein comprises two heavy chains HC1 and HC2 and two light chains LC1 and LC2, wherein HC1, LC1, HC2, and LC2 comprise the following sequences:
    (a) HC1 comprises SEQ ID NO: 64, LC1 comprises SEQ ID NO: 63, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52;
    (b) HC1 comprises SEQ ID NO: 55, LC1 comprises SEQ ID NO: 54, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52;
    (c) HC1 comprises SEQ ID NO: 56, LC1 comprises SEQ ID NO: 57, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52; or
    (d) HC1 comprises SEQ ID NO: 58, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52.

21. A protein comprising one monovalent human transferrin receptor (TfR) binding domain, wherein the human TfR binding domain binds an epitope comprising one or more residues in (a) residues 346-364 FGNMEGDCPSDWKTDSTCR (SEQ ID NO: 119), (b) residues 243-247 FEDLY (SEQ ID NO: 162) and residues 345-364 LFGNMEEGDCPSDWKTDSTCR) (SEQ ID NO: 163), or (c) residues 243-247 FEDLY (SEQ ID NO: 162), residues 259-263 AGKIT (SEQ ID NO: 164), and residues 532-538 (VEKLTLD) (SEQ ID NO: 165), of human TfR.

22. A protein comprising one monovalent mouse transferrin receptor (TfR) binding domain, wherein the mouse TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein HCDR1 comprises SEQ ID NO: 71, HCDR2 comprises SEQ ID NO: 72, HCDR3 comprises SEQ ID NO: 73, LCDR1 comprises SEQ ID NO: 74, LCDR2 comprises SEQ ID NO: 75, and LCDR3 comprises SEQ ID NO: 76.

23. The protein of claim 22, wherein the VH comprising SEQ ID NO: 77 and the VL comprising SEQ ID NO: 78, optionally wherein the protein comprises a heavy chain (HC) comprising SEQ ID NO: 79 and a light chain (LC) comprising SEQ ID NO: 80.

24. The protein of claim 22 or 23, wherein the protein comprises two heavy chains HC1 and HC2 and two light chains LC1 and LC2, wherein HC1 comprises SEQ ID NO: 79, LC1 comprises SEQ ID NO: 80, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52.

25. A conjugate comprising the protein of any one of claims 1-24 and a therapeutic agent.

26. The conjugate of claim 25, wherein the therapeutic agent is selected from a double stranded RNA, oligonucleotide, peptide, small molecule, nanoparticle, lipid nanoparticle, exosome, antibody or antigen binding fragment thereof, or a combination thereof.

27. The conjugate of claim 25 or 26, wherein the therapeutic agent is linked to the protein through a linker, optionally wherein the linker is a Mal-Tet-TCO linker, SMCC linker, or GDM linker.

28. The conjugate of any one of claims 25-27, wherein the therapeutic agent is a double stranded RNA (dsRNA), wherein the dsRNA comprises a sense strand and an antisense stand, optionally wherein the antisense strand is complementary to a target mRNA selected from SNCA, MAPT, APP, ATXN2, ATXN3, SARM1, APOE, BACE1, FMR1, LRRK2, HTT, SOD1, SCN10A, SCN9A or CACNA1B mRNA.

29. The conjugate of claim 28, wherein the antisense strand is complementary to:
    (a) SNCA mRNA; or
    (b) MAPT mRNA.

30. The conjugate of any one of claims 25-29, wherein the therapeutic agent to protein ratio is about 1:1 to 3:1.

31. A conjugate of Formula (II): $(R\text{-}L)_n\text{-}P$,

wherein R is a double stranded RNA (dsRNA) comprising a sense stand and an antisense strand;

wherein P is a protein comprising one monovalent human TfR binding domain; and

wherein L is a linker, or optionally absent,

wherein the human TfR binding domain comprises a heavy chain variable region (VH) and a light chain variable region (VL), wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 21, HCDR3 comprises SEQ ID NO: 22, LCDR1 comprises SEQ ID NO: 23, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 24; or

(b) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 25, HCDR3 comprises SEQ ID NO: 26, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;

and wherein n is 1 to 3.

32. The conjugate of claim 31, wherein:

(a) n is 1; or

(b) n is 2.

33. The conjugate of claim 31 or 32, wherein the HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, and LCDR3 comprise the following sequences:

(a) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 3, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(b) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 7, LCDR1 comprises SEQ ID NO: 4, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(c) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 2, HCDR3 comprises SEQ ID NO: 8, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 6;

(d) HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12;

(e) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 14, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18;

(f) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 15, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18; or

(g) HCDR1 comprises SEQ ID NO: 13, HCDR2 comprises SEQ ID NO: 19, HCDR3 comprises SEQ ID NO: 20, LCDR1 comprises SEQ ID NO: 16, LCDR2 comprises SEQ ID NO: 17, and LCDR3 comprises SEQ ID NO: 18.

34. The conjugate of any one of claims 31-33, wherein the VH and VL comprise the following sequences:

(a) VH comprises SEQ ID NO: 27 and VL comprises SEQ ID NO: 28;

(b) VH comprises SEQ ID NO: 29 and VL comprises SEQ ID NO: 28;

(c) VH comprises SEQ ID NO: 30 and VL comprises SEQ ID NO: 31;

(d) VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33;

(e) VH comprises SEQ ID NO: 34 and VL comprises SEQ ID NO: 35;

(f) VH comprises SEQ ID NO: 36 and VL comprises SEQ ID NO: 37; or

(g) VH comprises SEQ ID NO: 38 and VL comprises SEQ ID NO: 37.

35. The conjugate of any one of claims 31-34, wherein HCDR1 comprises SEQ ID NO: 1, HCDR2 comprises SEQ ID NO: 10, HCDR3 comprises SEQ ID NO: 11, LCDR1 comprises SEQ ID NO: 9, LCDR2 comprises SEQ ID NO: 5, and LCDR3 comprises SEQ ID NO: 12.

36. The conjugate of any one of claims 31-35, wherein VH comprises SEQ ID NO: 32 and VL comprises SEQ ID NO: 33.

37. The conjugate of any one of claims 31-36, wherein the human TfR binding domain is a Fab, scFv, Fv, or scFab.

38. The conjugate of any one of claims 31-37, wherein the human TfR binding domain further comprises:
(a) a heavy chain constant region comprising cysteine at residue 124 (according to the EU Index numbering); and/or
(b) a light chain constant region comprising cysteine at residue 156 (according to the EU Index numbering).

39. The conjugate of any one of claims 31-38, wherein the protein further comprises a half-life extender.

40. The conjugate of claim 39, wherein the half-life extender is an immunoglobulin Fc region, optionally wherein the immunoglobulin Fc region is a modified human IgG4 Fc region.

41. The conjugate of claim 40, wherein the modified human IgG4 Fc region comprises proline at residue 228, and alanine at residues 234 and 235 (all residues are numbered according to the EU Index numbering).

42. The conjugate of any one of claims 39-41, wherein the protein comprises an immunoglobulin Fc region comprising cysteine at residue 378 (according to the EU Index numbering).

43. The conjugate of any one of claims 39-42, wherein the Fc region comprises:
(a) a first Fc CH3 domain comprising a serine at position 349, a methionine at position 366, a tyrosine at position 370, and a valine at position 409; and a second Fc CH3 domain comprising a glycine at position 356, an aspartic acid at position 357, a glutamine at

position 364, and an alanine at position 407 (all residues are numbered according to the EU Index numbering); or

(b) a first Fc CH3 domain comprising leucine at residue 405, and a second Fc CH3 domain comprising arginine at residue 409 (all residues are numbered according to the EU Index numbering).

44. The conjugate of any one of claims 31-43, wherein the protein comprises one heavy chain (HC) and one light chain (LC), wherein the HC and LC comprise the following sequences:
    (a) HC comprises SEQ ID NO: 53 and LC comprises SEQ ID NO: 54;
    (b) HC comprises SEQ ID NO: 55 and LC comprises SEQ ID NO: 54;
    (c) HC comprises SEQ ID NO: 56 and LC comprises SEQ ID NO: 57;
    (d) HC comprises SEQ ID NO: 58 and LC comprises SEQ ID NO: 59;
    (e) HC comprises SEQ ID NO: 60 and LC comprises SEQ ID NO: 61;
    (f) HC comprises SEQ ID NO: 62 and LC comprises SEQ ID NO: 63; or
    (g) HC comprises SEQ ID NO: 64 and LC comprises SEQ ID NO: 63.

45. The conjugate of any one of claims 31-44, wherein the protein comprises two heavy chains HC1 and HC2 and one light chain LC1, wherein:
    (a) HC1 comprises SEQ ID NO: 68, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 69;
    (b) HC1 comprises SEQ ID NO: 138, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 139; or
    (c) HC1 comprises SEQ ID NO: 166, LC1 comprises SEQ ID NO: 54, HC2 comprises SEQ ID NO: 167.

46. The conjugate of any one of claims 31-38, wherein the protein comprises one heavy chain (HC) and one light chain (LC), and wherein the HC comprises SEQ ID NO: 65 and the LC comprises SEQ ID NO: 59.

47. The conjugate of claim 39, wherein the half-life extender is a VHH that binds HSA.

48. The conjugate of claim 47, wherein the VHH comprises CDR1 comprising SEQ ID NO: 39, CDR2 comprising SEQ ID NO: 40, and CDR3 comprising SEQ ID NO: 41.

49. The conjugate of claim 47 or 48, wherein the VHH comprises SEQ ID NO: 42.

50. The conjugate of any one of claims 47-49, wherein the protein comprises one heavy chain (HC) and one light chain (LC), and wherein the HC comprises SEQ ID NO: 66 and the LC comprises SEQ ID NO: 67.

51. The conjugate of any one of claims 31-43, wherein the protein is a heterodimeric antibody that comprises a first arm comprising one monovalent human TfR binding domain and a second arm that is a null arm.

52. The conjugate of claim 51, wherein the second arm comprises a VH and a VL, wherein the VH comprises heavy chain complementarity determining regions HCDR1, HCDR2, and HCDR3, and the VL comprises light chain complementarity determining regions LCDR1, LCDR2, and LCDR3, and wherein HCDR1 comprises SEQ ID NO: 43, HCDR2 comprises SEQ ID NO: 44, HCDR3 comprises SEQ ID NO: 45, LCDR1 comprises SEQ ID NO: 46, LCDR2 comprises SEQ ID NO: 47, and LCDR3 comprises SEQ ID NO: 48, optionally wherein the VH comprises SEQ ID NO: 49 and the VL comprises SEQ ID NO: 50.

53. The conjugate of claim 51 or 52, wherein the protein comprises two heavy chains HC1 and HC2 and two light chains LC1 and LC2, wherein HC1, LC1, HC2, and LC2 comprise the following sequences:
    (a) HC1 comprises SEQ ID NO: 64, LC1 comprises SEQ ID NO: 63, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52;
    (b) HC1 comprises SEQ ID NO: 55, LC1 comprises SEQ ID NO: 54, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52;
    (c) HC1 comprises SEQ ID NO: 56, LC1 comprises SEQ ID NO: 57, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52; or
    (d) HC1 comprises SEQ ID NO: 58, LC1 comprises SEQ ID NO: 59, HC2 comprises SEQ ID NO: 51, and LC2 comprises SEQ ID NO: 52.

54. The conjugate of any one of claims 31-53, wherein the linker is a Mal-Tet-TCO linker, SMCC linker, or GDM linker.

55. The conjugate of any one of claims 31-54, wherein the antisense strand is complementary to a target mRNA selected from SNCA, MAPT, APP, ATXN2, ATXN3, SARM1, APOE, BACE1, FMR1, LRRK2, HTT, SOD1, SCN10A, SCN9A or CACNA1B mRNA.

56. The conjugate of claim 55, wherein the antisense strand is complementary to SNCA mRNA.

57. The conjugate of any one of claims 29-56, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 81, and the antisense strand comprises SEQ ID NO: 82;
(b) the sense strand comprises SEQ ID NO: 83, and the antisense strand comprises SEQ ID NO: 84;
(c) the sense strand comprises SEQ ID NO: 85, and the antisense strand comprises SEQ ID NO: 86;
(d) the sense strand comprises SEQ ID NO: 87, and the antisense strand comprises SEQ ID NO: 88;
(e) the sense strand comprises SEQ ID NO: 89, and the antisense strand comprises SEQ ID NO: 90;
(f) the sense strand comprises SEQ ID NO: 91, and the antisense strand comprises SEQ ID NO: 92; and
(g) the sense strand comprises SEQ ID NO: 116, and the antisense strand comprises SEQ ID NO: 82,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

58. The conjugate of claim 55, wherein the antisense strand is complementary to MAPT mRNA.

59. The conjugate of any one of claims 29-55 and 58, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 120, and the antisense strand comprises SEQ ID NO: 121;

(b) the sense strand comprises SEQ ID NO: 122, and the antisense strand comprises SEQ ID NO: 123; and

(c) the sense strand comprises SEQ ID NO: 124, and the antisense strand comprises SEQ ID NO: 125,

wherein optionally one or more nucleotides of the sense strand and the antisense strand are independently modified nucleotides, and wherein optionally one or more internucleotide linkages of the sense strand and the antisense strand are modified internucleotide linkages.

60. The conjugate of any one of claims 29-59, wherein one or more nucleotides of the sense strand or the antisense strand are modified nucleotides.

61. The conjugate of claim 60, wherein each nucleotide of the sense strand is a modified nucleotide.

62. The conjugate of claim 60, wherein each nucleotide of the antisense strand is a modified nucleotide.

63. The conjugate of any one of claims 60-62, wherein the modified nucleotide is a 2'-fluoro modified nucleotide, 2'-O-methyl modified nucleotide or 2'-O-alkyl modified nucleotide.

64. The conjugate of any one of claims 60-63, wherein the sense strand has: (a) four 2'-fluoro modified nucleotides at positions 7, 9, 10, and 11 from the 5’ end of the sense

strand; or (b) three 2'-fluoro modified nucleotides at positions 9, 10, and 11 from the 5' end of the sense strand.

65. The conjugate of any one of claims 60-64, wherein the antisense strand has: (a) four 2'-fluoro modified nucleotides at positions 2, 6, 14, and 16 from the 5' end of the antisense strand;

    (b) five 2'-fluoro modified nucleotides at positions 2, 5, 7, 14, and 16 from the 5' end of the antisense strand;
    (c) five 2'-fluoro modified nucleotides at positions 2, 5, 8, 14, and 16 from the 5' end of the antisense strand; or
    (d) five 2'-fluoro modified nucleotides at positions 2, 3, 7, 14, and 16 from the 5' end of the antisense strand.

66. The conjugate of claim 64 or 65, wherein nucleotides at positions other than the listed positions are 2'-O-methyl modified nucleotides.

67. The conjugate of any one of claims 29-66, wherein the sense strand and the antisense strand have one or more modified internucleotide linkages, optionally wherein the modified internucleotide linkage is phosphorothioate linkage.

68. The conjugate of claim 67, wherein:
    (a) the sense strand has four or five phosphorothioate linkages; and/or
    (b) the antisense strand has four or five phosphorothioate linkages.

69. The conjugate of any one of claims 29-68, wherein the antisense strand has a phosphate analog at 5' end, optionally wherein the phosphate analog is 5'-vinylphosphonate.

70. The conjugate of any one of claims 29-69, wherein the sense strand comprises an abasic moiety or inverted abasic moiety.

71. The conjugate of any one of claims 29-57 or 60-70, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 93 or 140, and the antisense strand comprises SEQ ID NO: 94;

(b) the sense strand comprises SEQ ID NO: 95 or 141, and the antisense strand comprises SEQ ID NO: 96;

(c) the sense strand comprises SEQ ID NO: 95 or 141, and the antisense strand comprises SEQ ID NO: 97;

(d) the sense strand comprises SEQ ID NO: 95 or 141, and the antisense strand comprises SEQ ID NO: 98;

(e) the sense strand comprises SEQ ID NO: 99 or 142, and the antisense strand comprises SEQ ID NO: 94;

(f) the sense strand comprises SEQ ID NO: 100 or 143, and the antisense strand comprises SEQ ID NO: 101;

(g) the sense strand comprises SEQ ID NO: 102 or 144, and the antisense strand comprises SEQ ID NO: 103;

(h) the sense strand comprises SEQ ID NO: 104 or 145, and the antisense strand comprises SEQ ID NO: 105;

(i) the sense strand comprises SEQ ID NO: 106 or 146, and the antisense strand comprises SEQ ID NO: 107;

(j) the sense strand comprises SEQ ID NO: 108 or 147, and the antisense strand comprises SEQ ID NO: 107;

(k) the sense strand comprises SEQ ID NO: 117 or 148, and the antisense strand comprises SEQ ID NO: 97; and

(l) the sense strand comprises SEQ ID NO: 118 or 149, and the antisense strand comprises SEQ ID NO: 97.

72. The conjugate of any one of claims 29-57 or 60-70, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand consists of SEQ ID NO: 93 or 140, and the antisense strand consists of SEQ ID NO: 94;
(b) the sense strand consists of SEQ ID NO: 95 or 141, and the antisense strand consists of SEQ ID NO: 96;
(c) the sense strand consists of SEQ ID NO: 95 or 141, and the antisense strand consists of SEQ ID NO: 97;
(d) the sense strand consists of SEQ ID NO: 95 or 141, and the antisense strand consists of SEQ ID NO: 98;
(e) the sense strand consists of SEQ ID NO: 99 or 142, and the antisense strand consists of SEQ ID NO: 94;
(f) the sense strand consists of SEQ ID NO: 100 or 143, and the antisense strand consists of SEQ ID NO: 101;
(g) the sense strand consists of SEQ ID NO: 102 or 144, and the antisense strand consists of SEQ ID NO: 103;
(h) the sense strand consists of SEQ ID NO: 104 or 145, and the antisense strand consists of SEQ ID NO: 105;
(i) the sense strand consists of SEQ ID NO: 106 or 146, and the antisense strand consists of SEQ ID NO: 107;
(j) the sense strand consists of SEQ ID NO: 108 or 147, and the antisense strand consists of SEQ ID NO: 107;
(k) the sense strand consists of SEQ ID NO: 117 or 148, and the antisense strand consists of SEQ ID NO: 97; and
(l) the sense strand consists of SEQ ID NO: 118 or 149, and the antisense strand consists of SEQ ID NO: 97.

73. The conjugate of any one of claims 29-55 or 58-70, wherein the sense strand and the antisense strand comprise a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand comprises SEQ ID NO: 126 or 150, and the antisense strand comprises SEQ ID NO: 127;

(b) the sense strand comprises SEQ ID NO: 128 or 151, and the antisense strand comprises SEQ ID NO: 129;

(c) the sense strand comprises SEQ ID NO: 130 or 152, and the antisense strand comprises SEQ ID NO: 131;

(d) the sense strand comprises SEQ ID NO: 132 or 153, and the antisense strand comprises SEQ ID NO: 133;

(e) the sense strand comprises SEQ ID NO: 134 or 154, and the antisense strand comprises SEQ ID NO: 135; and

(f) the sense strand comprises SEQ ID NO: 136 or 155, and the antisense strand comprises SEQ ID NO: 137.

74. The conjugate of any one of claims 29-55 or 58-70, wherein the sense strand and the antisense strand have a pair of nucleic acid sequences selected from the group consisting of:

(a) the sense strand consists of SEQ ID NO: 126 or 150, and the antisense strand consists of SEQ ID NO: 127;

(b) the sense strand consists of SEQ ID NO: 128 or 151, and the antisense strand consists of SEQ ID NO: 129;

(c) the sense strand consists of SEQ ID NO: 130 or 152, and the antisense strand consists of SEQ ID NO: 131;

(d) the sense strand consists of SEQ ID NO: 132 or 153, and the antisense strand consists of SEQ ID NO: 133;

(e) the sense strand consists of SEQ ID NO: 134 or 154, and the antisense strand consists of SEQ ID NO: 135; and

(f) the sense strand consists of SEQ ID NO: 136 or 155, and the antisense strand consists of SEQ ID NO: 137.

75. A pharmaceutical composition comprising the protein of any one of claims 1-21 or the conjugate of any one of claims 25-74, and a pharmaceutically acceptable carrier.

76. The conjugate of any one of claims 25-74, or the pharmaceutical composition of claim 75, for use in a therapy.

77. The conjugate of any one of claims 29(a), 30-57, or 60-72, or the pharmaceutical composition of claim 75, for use in the treatment of a neurodegenerative synucleinopathy, optionally wherein the neurodegenerative synucleinopathy is selected from Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia.

78. The conjugate of any one of claims 29(b), 30-55, 58-70, 73, or 74, or the pharmaceutical composition of claim 75, for use in the treatment of a tauopathy, optionally wherein the tauopathy is selected from Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).

79. Use of the conjugate of any one of claims 25-74 in the manufacture of a medicament for treating a CNS disease.

80. Use of the conjugate of any one of claims 29(a), 30-57, or 60-72 in the manufacture of a medicament for treating a neurodegenerative synucleinopathy, optionally wherein the neurodegenerative synucleinopathy is selected from Parkinson's disease, Alzheimer's disease, multiple system atrophy, or Lewy body dementia.

81. Use of the conjugate of any one of claims 29(b), 30-55, 58-70, 73, or 74 in the manufacture of a medicament for treating a tauopathy, optionally wherein the tauopathy is selected from Alzheimer's disease, frontotemporal dementia (FTD), frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17), frontotemporal lobar degeneration (FTLD), behavioral variant frontotemporal dementia (bvFTD), nonfluent variant primary progressive aphasia (nfvPPA), Parkinson's discase, Pick's disease (PiD), primary progressive aphasia - semantic (PPA-S), primary progressive aphasia - logopenic (PPA-L), multiple system tauopathy with presenile dementia (MSTD), neurofibrillary tangle (NFT) dementia, FTD with motor neuron disease, progressive supranuclear palsy (PSP), amyotrophic lateral sclerosis/parkinsonism-dementia complex (ALS-PDC), argyrophilic grain dementia (AGD), British type amyloid angiopathy, cerebral amyloid angiopathy, chronic traumatic encephalopathy (CTE), corticobasal degeneration (CBD), Creutzfeldt-Jakob disease (CJD), dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down's syndrome, epilepsy, Gerstmann-Straussler-Scheinker disease, Hallervorden-Spatz disease, Huntington's disease, inclusion body myositis, lead encephalopathy, Lytico-Bodig disease, meningioangiomatosis, multiple system atrophy, myotonic dystrophy, Niemann-Pick disease type C (NP-C), non-Guamanian motor neuron disease with neurofibrillary tangles, postencephalitic parkinsonism, prion protein cerebral amyloid angiopathy, progressive subcortical gliosis, tangle only dementia, tangle-predominant dementia, ganglioglioma, gangliocytoma, subacute sclerosingpan encephalitis, tuberous sclerosis, lipofuscinosis, primary age-related tauopathy (PART), or globular glial tauopathies (GGT).