CELL PENETRATING AGENTS AND USES THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of priority to U.S. Provisional Patent Application No. 63/538,600, filed on September 15, 2023, the content of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

This application contains a Sequence Listing that has been submitted electronically as an XML file named 50887-0048WO1_ST26_SL.XML." The XML file, created on September 5, 2024, is 373,575 bytes in size. The material in the XML file is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

This disclosure relates to the technical fields of immunology and medicine.

BACKGROUND

Inclusion body myositis (IBM), or sometimes referred to as sporadic inclusion body myositis (sIBM), is one of a group of muscle diseases known as the inflammatory myopathies. These myopathies are generally characterized by chronic, progressive muscle inflammation, and are usually accompanied by muscle weakness.

The onset of muscle weakness in IBM is generally gradual typically over months and years and affects both muscles throughout the body, however, in some instances muscle weakness can affect only one side of the body. Symptoms can begin with falling, tripping, and difficulty with motor tasks such as pinching, buttoning, and gripping objects. Often diagnosis does not occur until after the age of 50 and IBM is predominantly diagnosed in men, although women also suffer from IBM.

Although life-expectancy is generally not reduced in individuals suffering from IBM, the condition does progress over time which can result in the life style adaptions and mobility aids such as canes, walkers, or wheelchairs.

The cause or causes of IBM are poorly understood, however, one theory suggests IBM is an autoimmune disorder that results in inflammation in muscle cells. Prolonged inflammation leads to degeneration of muscle fiber and protein resulting in the symptoms

observed in patients as the disease progresses. Additionally and/or alternatively, IBM may be the result of aberrant beta-amyloid protein deposits in muscle cells.

The principal constituent of Aβ (Abeta) or β-amyloid deposits are peptides. Aβ peptide is a 4-kDa internal fragment of 39-43 amino acids of a larger transmembrane glycoprotein termed amyloid precursor protein (APP). As a result of proteolytic processing of APP by different secretase enzymes, Aβ is primarily found in both a short form, 40 amino acids in length, and a long form, ranging from 42-43 amino acids in length. Part of the hydrophobic transmembrane domain of APP is found at the carboxy end of Aβ, and may account for the ability of Aβ to aggregate into plaques, particularly in the case of the long form. Accumulation of amyloid deposits in the muscle are thought to play a role in the phenotypes associated with IBM (See, e.g., Benveniste, O., et al., Amyloid deposits and inflammatory infiltrates in sporadic inclusion body myositis: the inflammatory egg comes before the degenerative chicken, *Acta Neuropahol.*, 139(5): 611-624 (2015)). While the specific cause or causes of IBM are still unclear an beta amyloid vaccine has shown efficacy against IBM in mouse models (Kitazawa, M., et al., Immunization with amyloid-β attenuates inclusion body myositis-like myopathology and motor impairment in a transgenic mouse model, *The Journal of Neuroscience*, 29(19): 6132-41 (2009)), however, treatments for IBM are still needed in human patients.

SUMMARY

The present disclosure relates to cell penetrating agents ("CPAs") that include a cell internalization module ("CIM") and antibodies (and antigen binding antibody fragments) that specifically bind to Aβ. The present disclosure also features methods of producing such CPAs and associated nucleic acids, pharmaceutical formulations and compositions of CPAs including antibodies that show high affinity binding to Aβ for prophylactic and/or therapeutic use to, for example, treat, reduce the risk of or delay the outset of amyloidogenic disease, prevent, reduce or inhibit markers of amyloidogenic disease. In some examples, the amyloidogenic disease is Inclusion-body myositis (IBM), also referred to as sporadic IBM (sIBM).

The disclosure is based, at least in part, on the identification and characterization of antibodies that specifically bind to Aβ peptides and are effective at reducing deposit burden and neutralizing soluble Aβ species associated with IBM.

Thus, provided herein are anti-amyloid beta peptide (Aβ) cell penetrating agents (CPA) including: (i) a cell internalizing module and (ii) an antibody that specifically binds to amyloid beta (Aβ) peptide.

In some embodiments, the CIM includes a Cell Membrane Internalizing Peptide (CMIP).

In another aspect, the present disclosure provides a polypeptide of a formula selected from Formula (IA) to Formula (ID):

I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L (I-A) (SEQ ID 395);

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-X^{20}-F-X^{22}-S-X^{24}-L (I-B);

X^1-X^2-L-T-X^5-L-K-X^8-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L (I-C);

I-W-L-T-X^5-X^6-K-F-S-X^{10}-K-X^{12}-A-A-K-A-X^{17}-X^{18}-K-Q-F-L-X^{23}-X^{24}-X^{25} (I-D);

wherein:

X^1 is a hydrophobic amino acid residue or a positively-charged amino acid residue; X^2 is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue; X^3 is an aromatic amino acid residue, a hydrophobic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue; X^4 is a neutral hydrophilic amino acid residue or an aromatic amino acid residue; X^5 is a hydrophobic amino acid residue or an aromatic amino acid residue; X^6 is a hydrophobic amino acid residue; X^7 is a hydrophobic amino acid residue or a positively-charged amino acid; X^8 is an aromatic amino acid residue; X^9 is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue; X^{10} is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue; X^{11} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue; X^{12} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue; X^{13} is a neutral hydrophilic amino acid residue or a hydrophobic amino acid residue; X^{14} is a hydrophobic amino acid residue or a positively-charged amino acid; X^{15} is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue; X^{16} is a hydrophobic amino acid residue, an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue; X^{17} is a positively-charged amino acid residue or a negatively-charged amino acid residue; X^{18} is a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue; X^{19} is a hydrophobic amino acid residue or a positively-charged amino acid residue; X^{20} is a neutral hydrophilic amino acid residue or a negative-charged amino acid residue; X^{21} is a hydrophobic amino acid residue or an aromatic amino acid residue; X^{22} is

absent, a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue; X^{23} is absent, a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue; X^{24} is absent, an aromatic amino acid residue, or a positively-charged amino acid residue; and X^{25} is absent or a hydrophobic amino acid; or a pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IA):

$I\text{-}X^{2}\text{-}X^{3}\text{-}T\text{-}A\text{-}L\text{-}X^{7}\text{-}F\text{-}X^{9}\text{-}G\text{-}X^{11}\text{-}A\text{-}A\text{-}X^{14}\text{-}K\text{-}X^{16}\text{-}E\text{-}A\text{-}X^{19}\text{-}Q\text{-}F\text{-}L\text{-}X^{23}\text{-}X^{24}\text{-}L$ (IA)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IB):

$I\text{-}W\text{-}X^{3}\text{-}X^{4}\text{-}A\text{-}L\text{-}X^{7}\text{-}F\text{-}X^{9}\text{-}G\text{-}X^{11}\text{-}X^{12}\text{-}X^{13}\text{-}A\text{-}X^{15}\text{-}A\text{-}E\text{-}A\text{-}X^{19}\text{-}X^{20}\text{-}F\text{-}X^{22}\text{-}S\text{-}X^{24}\text{-}L$ (IB)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IC):

$X^{1}\text{-}X^{2}\text{-}L\text{-}T\text{-}X^{5}\text{-}L\text{-}K\text{-}X^{8}\text{-}S\text{-}X^{10}\text{-}K\text{-}A\text{-}A\text{-}A\text{-}X^{15}\text{-}A\text{-}E\text{-}A\text{-}K\text{-}Q\text{-}X^{21}\text{-}L\text{-}S\text{-}X^{24}\text{-}L$ (IC)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (ID):

$I\text{-}W\text{-}L\text{-}T\text{-}X^{5}\text{-}X^{6}\text{-}K\text{-}F\text{-}S\text{-}X^{10}\text{-}K\text{-}X^{12}\text{-}A\text{-}A\text{-}K\text{-}A\text{-}X^{17}\text{-}X^{18}\text{-}K\text{-}Q\text{-}F\text{-}L\text{-}X^{23}\text{-}X^{24}\text{-}X^{25}$ (ID)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP consists essentially of an amino acid sequence selected from Formula (IA) to (ID). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IA). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IB). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IC). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (ID).

In another aspect, the present disclosure provides a CMIP comprising an amino acid sequence having a formula selected from Formula (IIA) to Formula (IIC):

$I\text{-}X^{2}\text{-}X^{3}\text{-}T\text{-}A\text{-}L\text{-}X^{7}\text{-}F\text{-}X^{9}\text{-}G\text{-}X^{11}\text{-}A\text{-}A\text{-}X^{14}\text{-}K\text{-}X^{16}\text{-}E\text{-}A\text{-}X^{19}\text{-}Q\text{-}F\text{-}L\text{-}X^{23}\text{-}X^{24}\text{-}L$ (IIA) (SEQ ID NO: 399);

$I\text{-}W\text{-}X^{3}\text{-}X^{4}\text{-}A\text{-}L\text{-}X^{7}\text{-}F\text{-}X^{9}\text{-}G\text{-}X^{11}\text{-}X^{12}\text{-}X^{13}\text{-}A\text{-}X^{15}\text{-}A\text{-}E\text{-}A\text{-}X^{19}\text{-}Q\text{-}F\text{-}X^{22}\text{-}S\text{-}X^{24}\text{-}L$ (IIB) (SEQ ID NO: 400);

$X^{1}\text{-}X^{2}\text{-}L\text{-}T\text{-}A\text{-}L\text{-}K\text{-}F\text{-}S\text{-}X^{10}\text{-}K\text{-}A\text{-}A\text{-}A\text{-}X^{15}\text{-}A\text{-}E\text{-}A\text{-}K\text{-}Q\text{-}X^{21}\text{-}L\text{-}S\text{-}X^{24}\text{-}L$ (IIC) (SEQ ID NO: 401);

or pharmaceutically acceptable salt thereof; wherein X^{1} is isoleucine or lysine; X^{2} is arginine or tryptophan; X^{3} is arginine, glutamic acid, leucine, or tryptophan; X^{4} is threonine or tryptophan; X^{7} is arginine, isoleucine, or lysine; X^{9} is arginine, histidine, or serine; X^{10} is

glycine or tyrosine; X^{11} is arginine, isoleucine, lysine, or threonine; X^{12} is alanine or glutamine; X^{13} is alanine or serine; X^{14} is alanine, histidine, leucine, or valine; X^{15} is arginine, glutamic acid, or lysine; X^{16} is alanine or lysine; X^{18} is alanine, methionine, or tryptophan; X^{19} is arginine or lysine; X^{21} is arginine or phenylalanine; X^{22} is arginine, leucine, or tryptophan; X^{23} is arginine or serine; and X^{24} is arginine, lysine, or tryptophan.

In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIA). In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIB). In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIC).

In some embodiments, the CIM includes a wild-type M-lycotoxin peptide. In some embodiments, the CIM includes an M-lycotoxin derivative. In some embodiments, the CIM includes a polyarginine amino acid sequence. In some embodiments, the CIM includes more than one polyarginine amino acid sequence. In some embodiments, the CIM includes a TAT amino acid sequence. In some embodiments, the CIM includes more than one TAT amino acid sequence.

In some embodiments, the CIM includes a macrocycle. In some embodiments, the macrocycle is formed by a covalent bond between two amino acid residues of the CIM. In some embodiments, the macrocycle is formed by a disulfide bond between two cysteine residues of the CIM.

In some embodiments, the CIM includes a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 101-107, 110, and 116-338.

In some embodiments, the CIM includes one or more spacer regions. In some embodiments, at least one of the one or more spacer regions includes one or more amino acid residues. In some embodiments, at least one of the one or more spacer regions includes one or more glycine residues.

In some embodiments, the CIM is a polypeptide having an amino acid sequence selected from: SEQ ID NOs: 101-338.

In some embodiments, the CIM is covalently linked to the antibody. In some embodiments, the CIM is non-covalently linked to the antibody.

In some embodiments, the CPA includes a linker connecting the CIM to the antibody. In some embodiments, the linker is covalently linked to both the CIM and the antibody. In some embodiments, the linker is a cleavable linker. In some embodiments, the linker is a non-cleavable linker. In some embodiments, the linker includes a polypeptide. In some embodiments, the linker includes one or more glycine residues. In some embodiments, the

linker includes a polypeptide including an amino acid sequence selected from any one of SEQ ID NOs: 343-346.

In some embodiments, the antibody is linked to the C-terminus of the CIM. In some embodiments, the antibody is linked to the N-terminus of the CIM.

In some embodiments, the antibody includes a heavy chain or a portion thereof. In some embodiments, the CIM is covalently linked to a C-terminus of the heavy chain. In some embodiments, the CIM is covalently linked to a N-terminus of the heavy chain.

In some embodiments, the antibody includes a light chain or a portion thereof. In some embodiments, the CIM is covalently linked to a C-terminus of the light chain. In some embodiments, the CIM is covalently linked to a N-terminus of the light chain.

In some embodiments, the antibody competes with binding with a reference antibody including a heavy chain variable domain including heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain including light chain CDR1, CDR2 and CDR3, where the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1A and Table 1B.

In some embodiments, the antibody includes a heavy chain variable domain including heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain including light chain CDR1, CDR2 and CDR3, where the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1A and Table 1B.

In some embodiments, the antibody includes a heavy chain variable domain is as shown for one of the antibodies in Table 1A and Table 1B. In some embodiments, the antibody includes a light chain variable domain is as shown for one of the antibodies in Table 1A and Table 1B.

In some embodiments, the antibody includes a heavy chain variable domain including heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain including light chain CDR1, CDR2 and CDR3, where heavy chain CDR1 includes one of SEQ ID NO: 16, 19, or 20, heavy chain CDR2 includes one of SEQ ID NO: 20, 21, 22 or 23, heavy chain CDR3 includes one of SEQ ID NO: 18, 24, or 25, light chain CDR1 includes one of SEQ ID NO: 26, 29, 31, or 32, light chain CDR2 includes one of SEQ ID NO: 33, 34, 35 or 36, and light chain CDR3 includes one of SEQ ID NO: 28, 38 or 39.

In some embodiments, the heavy chain variable domain, excluding the CDRs, is at least 95% identical an amino acid sequence selected from SEQ ID NO: 3, 4, 5, 6, and 7 , and the light chain variable domain, excluding the CDRs, is at least 95% identical an amino acid sequence selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14, and 15.

In some embodiments, heavy chain variable domain, excluding the CDRs is at least 98% identical to an amino acid sequence selected from SEQ ID NOs: 3, 4, 5, 6, and 7, and the light chain variable domain, excluding the CDRs, is at least 98% identical to an amino acid sequence selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14 and 15.

In some embodiments, the heavy chain variable domain is selected from SEQ ID NOs: 3, 4, 5, 6, and 7, and the light chain variable domain is selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14 and 15.

In some embodiments, the antibody includes a heavy chain variable domain including heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain including light chain CDR1, CDR2 and CDR3, where: heavy chain CDR1 comprises amino acid sequence GFTFSNX^{A}GMS, wherein X^{A} is Y or F (SEQ ID NO: 88); heavy chain CDR2 comprises amino acid sequence SX^{A}RSGSGRTYYSDNVKG, wherein is X^{A} is I or V (SEQ ID NO: 89); heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90); light chain CDR1 comprises amino acid sequence KSSQSLLDYDGKTYLN (SEQ ID NO: 91); light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRDX^{C}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is S or T (SEQ ID NO: 92); and light chain CDR3 comprises amino acid sequence WQGTHFPRX^{A}, wherein X^{A} is S or T (SEQ ID NO: 93). In some embodiments, the light chain CDR3 comprises WQGTHFPRX^{A}FX^{B}, wherein X^{A} is S or T and X^{B} is F or Y (SEQ ID NO: 94).

In some embodiments, the antibody includes a heavy chain variable domain including heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain including light chain CDR1, CDR2 and CDR3, where: heavy chain CDR1 comprises amino acid sequence GFTFX^{A}NX^{B}GMS, wherein X^{A} is S or A, and X^{B} is Y or F (SEQ ID NO: 95); heavy chain CDR2 comprises amino acid sequence SX^{A}RSGX^{B}X^{C}RTYYSDNVKG, wherein is X^{A} is I or V, X^{B} is S or G and X^{C} is S or G (SEQ ID NO: 96); heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90); light chain CDR1 comprises amino acid sequence X^{A}SSQSLX^{B}DX^{C}DGKTYLN, wherein X^{A} is K or R, X^{B} is V, M or L, and X^{C} is Y, T or S (SEQ ID NO: 97); light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRX^{C}X^{D}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is E or D, and X^{D} is S or T (SEQ ID NO: 98). light chain CDR3 comprises amino acid sequence WQGX^{A}HFPRX^{B}, wherein X^{A} is S or T, and X^{B} is S or T (SEQ ID NO: 99). In some embodiments, light chain CDR3 includes WQGTHFPRX^{A}FX^{B}X^{C}, wherein X^{A} is S or T, X^{B} is S or T and X^{C} is F or Y (SEQ ID NO: 100).

In some embodiments, the antibody is humanized. In some embodiments, the antibody is human IgG1 isotype. In some embodiments, the antibody is a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody. In some embodiments, the fragment is a Fab, Fab', F(ab')2, Fabc, or Fv.

In some embodiments, the antibody includes a heavy chain constant domain including an amino acid sequence at least 95% identical to SEQ ID NO: 40. In some embodiments, the antibody includes light chain constant domain including an amino acid sequence at least 95% identical to SEQ ID NO: 41.

In some embodiments, the heavy chain variable domain is fused to a heavy chain constant domain and the light chain variable domain is fused to a light chain constant domain. In some embodiments, the heavy chain constant domain is a mutant form of a natural human heavy chain constant domain which has reduced binding to an Fcγ receptor relative to the natural heavy chain constant domain.

In some embodiments, the heavy chain constant domain is of IgG1 isotype.

In some embodiments, the antibody has at least one mutation in a constant domain. In some embodiments, the at least one mutation reduces complement fixation or activation by the constant domain. In some embodiments, the at least one mutation is at one or more positions of: 241, 264, 265, 270, 296, 297, 318, 320, 322, 329, and 331 by EU numbering. In some embodiments, the antibody has an alanine at positions 318, 320, and 322 by EU numbering.

In some embodiments, the antibody specifically binds to an epitope having an amino acid sequence including three or more amino acid positions from amino acids 1-7 of Aβ.

In some embodiments, the antibody is selected from aducanumab, lecanumab, bapineuzumab, solanezumab, gantererumab, crenezumab, and ponezumab.

In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394. In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394. In some embodiments, the anti-Aβ CPA includes a polypeptide sequence selected from any one of: SEQ ID NO: 349, SEQ

ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394.

In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393. In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393. In some embodiments, the anti-Aβ CPA comprises a polypeptide sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362 SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

In some embodiments, the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein: the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 349 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 350; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 351 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 352; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 353 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 354; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 355 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 356; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 357 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 358; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 359 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 360; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 361 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 362; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 363 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 364; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 365 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 366; the first polypeptide comprises a sequence that is at least 95% identical to

SEQ ID NO: 367 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 368; or the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 394 and the second polypeptide comprises a sequence that is at least 95% identical to any one of SEQ ID NOs: 369-393.

In some embodiments, the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein: the first polypeptide comprises SEQ ID NO: 349 and the second polypeptide comprises SEQ ID NO: 350; the first polypeptide comprises SEQ ID NO: 351 and the second polypeptide comprises SEQ ID NO: 352; the first polypeptide comprises SEQ ID NO: 353 and the second polypeptide comprises SEQ ID NO: 354; the first polypeptide comprises SEQ ID NO: 355 and the second polypeptide comprises SEQ ID NO: 356; the first polypeptide comprises SEQ ID NO: 357 and the second polypeptide comprises SEQ ID NO: 358; the first polypeptide comprises SEQ ID NO: 359 and the second polypeptide comprises SEQ ID NO: 360; the first polypeptide comprises SEQ ID NO: 361 and the second polypeptide comprises SEQ ID NO: 362; the first polypeptide comprises SEQ ID NO: 363 and the second polypeptide comprises SEQ ID NO: 364; the first polypeptide comprises SEQ ID NO: 365 and the second polypeptide comprises SEQ ID NO: 366; the first polypeptide comprises SEQ ID NO: 367 and the second polypeptide comprises SEQ ID NO: 368; or the first polypeptide comprises SEQ ID NO: 394 and the second polypeptide comprises any one of SEQ ID NOs: 369-393.

In some embodiments, wherein the antibody is conjugated to a therapeutic, cytotoxic, cytostatic, immunomodulatory, neurotrophic, or neuroprotective agent.

In some embodiments, the heavy chain does not comprise a C-terminal lysine residue.

Also provided herein are pharmaceutical compositions including any of the anti-Aβ CPAs described herein and a pharmaceutically acceptable carrier or diluent.

Also provided herein are nucleic acids encoding at least a portion of any of the anti-Aβ CPAs described herein. In some embodiments, the nucleic acid encodes for the CIM or a portion thereof. In some embodiments, the nucleic acid encodes for the CIM or a portion thereof and at least one of a heavy chain variable domain of the antibody and a light chain variable domain of the antibody. In some embodiments, the nucleic acid encodes for the CIM or a portion thereof and a heavy chain variable domain of the antibody or a portion thereof. In some embodiments, the nucleic acid encodes for the CIM or a portion thereof and a light chain variable domain of the antibody or a portion thereof.

Also provided herein are vectors including any of the nucleic acids described herein operably linked to one or more regulatory sequences to effect expression in a mammalian cell

of any of the cell penetrating agents described herein. In some embodiments, the one or more regulatory sequences include one or more of an enhancer, ribosome binding site, transcription termination signal, and promoter, optionally, where the promoter is a eukaryotic promoter. In some embodiments, the nucleic acid is codon-optimized for expression in a host cell.

Also provided herein are host cells transformed with any of the vectors described herein.

Also provided herein are host cells including any of the nucleic acids described herein.

Also provided herein are methods of delivering the antibody that specifically binds to Aβ into a cell, including contacting any of the anti-Aβ CPAs described herein with the cell, thereby resulting in the internalization into the cell of, at a minimum, an antigen-binding fragment of the antibody. In some embodiments, the method includes transfer of, at a minimum, an antigen-binding fragment of the antibody, to the cytosol of the cell.

Also provided herein are methods of binding an intracellular Aβ protein in a cell, the method including contacting any of the anti-Aβ CPAs described herein with the cell, thereby resulting in the internalization of and transfer to the cytosol of, at a minimum, an antigen-binding fragment of the antibody. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is in a subject.

Also provided herein are methods of inhibiting or reducing aggregation of Aβ in a subject having or at risk of developing a Aβ-related disease, including administering to the subject an effective amount of any of the anti-Aβ CPAs described herein, thereby inhibiting or reducing aggregation of Aβ in the subject.

Also provided herein are methods of treating or effecting prophylaxis of a Aβ-related disease in a subject, including administering a therapeutically effective amount of any of the cell penetrating agents described herein, thereby treating or effecting prophylaxis of the Aβ-associated disease. In some embodiments, the Aβ-related disease is Inclusion-Body Myositis.

Also provided herein are methods of detecting Aβ deposits in a subject having or at risk of developing a Aβ-related disease, including administering to a subject any of the cell penetrating agents described herein, and detecting the antibody bound to Aβ in the subject.

Also provided herein are methods of detecting Aβ in a sample obtained from a patient having or at risk of developing a Aβ related disease, including contacting the sample with any of the cell penetrating agents described herein, and detecting the binding of the antibody to Aβ in the sample.

In some embodiments, the antibody is labeled. In some embodiments, the antibody is labeled with a fluorescent label, a paramagnetic label, or a radioactive label. In some embodiments, the radioactive label is detected using positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, patent application, or item of information was specifically and individually indicated to be incorporated by reference. To the extent publications, patents, patent applications, and items of information incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

Where values are described in terms of ranges, it should be understood that the description includes the disclosure of all possible sub-ranges within such ranges, as well as specific numerical values that fall within such ranges irrespective of whether a specific numerical value or specific sub-range is expressly stated.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings illustrate certain embodiments of the features and advantages of this disclosure. These embodiments are not intended to limit the scope of the appended claims in any manner. Like reference symbols in the drawings indicate like elements.

Figures 1A-C are graphs showing the results of Aβ model cells treated with anti-Aβ cell penetrating agents on foci area (Figure 1A), foci count (Figure 1B), and mean focus area (Figure 1C).

Figures 2A-C are graphs showing the results of Aβ model cells treated with anti-Aβ cell penetrating agents compared to an isotype control on foci area (Figure 2A), foci count (Figure 2B), and mean focus area (Figure 2C).

Figures 3A-C are graphs showing the results of Aβ model cells treated with anti-Aβ cell penetrating agents compared to an isotype control on foci area (Figure 3A), foci count (Figure 3B), and mean focus area (Figure 3C).

Figures 4A-C are graphs showing the results of Aβ model cells treated with anti-Aβ cell penetrating agents including FcK or FcRn mutations on the total Aβ foci area per cell (Figure 4A), the number of Aβ foci area per cell (Figure 4B), and cell penetrating agent internalization per cell (Figure 4C).

Figures 5A-C are graphs showing results of Aβ model cells treated with an anti-Aβ cell penetrating agent (mzd-2931-CMIP4) on foci area (Figure 5A), foci number per cell (Figure 5B), and antibody or cell penetrating agent internalization per cell (Figure 5C).

Figures 6A-C are graphs showing the results of Aβ model cells treated with CMIP-4 derived cell internalizing modules on total Aβ foci area per cell (Figure 6A), average number of Aβ foci per cell (Figure 6B), and antibody or cell penetrating agent internalization (Figure 6C).

Figures 7A-C are images showing the results on Aβ aggregates in model Aβ cells that were either untreated (Figure 7A), treated with an untagged antibody (Figure 7B), or with an anti-Aβ cell penetrating agent (Figure 7C).

Figures 8A-C are graphs showing the results of Aβ model cells treated with anti-Aβ cell penetrating agents on total Aβ foci area per cell (Figure 8A), foci count (Figure 8B), and internalization (Figure 8C).

Figures 9A-B show staining of Aβ aggregates with two different antibodies (Figure 9A) and a graph showing the percentage of stable cells having Aβ aggregates as compared to a control sample (Figure 9B).

Figures 10A-C are graphs showing the results of Aβ model cells treated with murinized cell penetrating agents on total Aβ foci area per cell (Figure 10A), the number of Aβ foci per cell (Figure 10B), and cell penetrating agent internalization (Figure 10C).

DETAILED DESCRIPTION

The present disclosure provides systems and methods for the delivery of antibodies into a cell. More specifically, the present disclosure provided systems and methods for delivering anti-amyloid beta (Aβ) cell penetrating agents into a cell. Also provided are pharmaceutical compositions including these cell penetrating agents and a pharmaceutically acceptable carrier, nucleic acids and/or vectors encoding these cell penetrating agents, and host cells expressing the aforementioned nucleic acids and/or vectors. The specific examples and embodiments disclosed herein are not limiting and are merely illustrative of the breadth of the approach.

In some aspects, the present disclosure provides a cell penetrating agent ("CPA") including (i) a Cell Internalizing Module ("CIM") and (ii) an antibody that specifically binds to Aβ peptide. The CIM facilitates the internalization of the cell penetrating agent into the cell. In some embodiments, the CIM further facilitates the transfer of the cell penetrating

agent from the internalization vesicle (e.g., endosome) to the cytosol. In some embodiments, the CIM disrupts the membrane of the internalization vesicle, leading to vesicle rupture and facilitating transfer of the cell penetrating agent out of the vesicle and into the cytosol.

Monoclonal antibodies (mAbs) targeting the N-terminus of amyloid beta (Aβ) have been demonstrated clinically to reduce amyloid plaque burden and one such antibody, aducanumab, showed that significant reduction in plaque burden. Preclinical studies have also indicated that monoclonal antibodies (mAbs) targeting N-terminal epitopes of Aβ elicit an antibody-dependent microglial-mediated Aβ-plaque clearance and neutralization of soluble toxic Aβ oligomers both *in vitro* and *in vivo*. It is hypothesized that administration of a cell penetrating agent comprising Aβ targeting mAbs can slow disease progression via clearance of intracellular Aβ plaques in patient with IBM.

Accordingly, the disclosure provides antibodies (and antigen biding antibody fragments), nucleic acids encoding and/or vectors, and methods of producing such antibodies and antibody fragments, pharmaceutical compositions, and methods for preventing or treating amyloidogenic disease, such as Inclusion Body Myositis.

The disclosure is based, at least in part, on the characterization of a genus of monoclonal antibodies effective at binding beta amyloid protein (Aβ) (*e.g.*, binding soluble and/or aggregated Aβ), mediating phagocytosis (*e.g.*, of aggregated Aβ), reducing plaque burden and/or reducing neuritic dystrophy (*e.g.*, in patient), neutralizing soluble, toxic Aβ species. The antibodies and fragments of the disclosure exhibit greater binding strength (affinity and/or avidity) for pathologic fibrillar Aβ than reported current experimental therapies, and high affinity for soluble toxic Aβ forms. These antibodies may enable more convenient dosing strategies and enhanced patient access.

I. Definitions

The term "antibody" includes intact antibodies and binding fragments thereof. Typically, fragments compete with the intact antibody from which they were derived for specific binding to the target. Fragments include separate heavy chains, light chains Fab, Fab′, $F(ab')_2$, F(ab)c, Fv and single domain antibodies. Single (variable) domain antibodies include VH regions separated from their VL partners (or vice versa) in conventional antibodies (Ward et al., 1989, Nature 341: 544-546) as well as VH regions (sometimes known as VHH) from species such as Camelidae or cartilaginous fish (e.g., a nurse shark) in which VH regions are not associated with VL regions (see, e.g., WO 9404678). Single domain antibodies in which one chain is separated from its natural partners

are sometimes known as Dabs and single domain antibodies from Caemelidae or cartilaginous fish are sometimes known as nanobodies. Constant regions or parts of constant regions may or may not be present in single domain antibodies. For example, natural single variable region antibodies from Camelidae include a VHH variable region, and CH2 and CH3 constant regions. Single domain antibodies can be subject of humanization by analogous approaches to conventional antibodies. The Dabs type of antibodies are usually obtained from antibodies of human origin. NANOBODY types of antibody are of Camelidae or shark origin and can be subject to humanization. Fragments can be produced by recombinant DNA techniques, or by enzymatic or chemical separation of intact immunoglobulins. The term "antibody" also includes a bispecific antibody. A bispecific or bifunctional antibody is an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites (see, e.g., Songsivilai and Lachmann, Clin. Exp. Immunol., 79:315-321 (1990); Kostelny et al., J. Immunol., 148:1547-53 (1992)).

The term "amyloidogenic disease" refers to Inclusion Body Myositis (IBM) or sporadic Inclusion Body Myositis (sIBM). Accordingly, IBM or sIBM are examples of a "disease characterized by deposits of Aβ" or a "disease associated with deposits of Aβ", e.g., in the muscles of a subject or patient. The terms "β-amyloid protein", "β-amyloid peptide", "β-amyloid", "Aβ" and "Aβ peptide" are used interchangeably herein.

As used herein a "Cell-Penetrating Agent" (also referred to herein as a "CPA") refers to an agent (e.g., a molecule and/or molecular complex) capable of entering a cell (e.g., a mammalian cell in vitro and/or in vivo). In some embodiments, the CPA enters the cell and is transferred to the cytosol following internalization by the cell. In some embodiments, the CPA comprises a Cell Internalizing Module (CIM) that facilitates the internalization of the CPA by the cell. In some cases, the CPA comprises a CIM that facilitates the internalization of the CPA the transfer of the CPA the cytosol. In some embodiments, the CPA further comprises an anti-Aβ antibody that is linked (e.g., covalently or non-covalently) to the CIM. In some embodiments, the CPA comprises a CIM covalently linked to the anti-Aβ antibody (e.g., via a linker between the CIM and the anti-Aβ antibody). In other embodiments, the CPA comprises a CIM non-covalently linked to the anti-Aβ antibody (e.g., via a streptavidin-biotin interaction), such that the CIM remains linked to the anti-Aβ antibody in relevant conditions (e.g., blood plasma). In some embodiments, the CPA further comprises a linker connecting the CIM to the anti-Aβ antibody. In various cases, linkers can be cleavable or non-cleavable and/or can connect the CIM to the anti-Aβ antibody covalently or non-covalently. In some embodiments, the CPA comprising the anti-Aβ antibody has enhanced

cell penetration compared to a reference anti-Aβ antibody that is not part of a CPA. In some embodiments, the CPA comprises two or more anti-Aβ antibodies and/or two or more CIMs (e.g., the CPA comprising a dendrimer linked to a plurality of CIMs and/or anti-Aβ antibodies). Non-limiting features and examples of cell penetrating agents are described herein.

As used herein a "Cell Internalizing Module" (also referred to herein as a "CIM") refers to a portion of the CPA that facilitates the internalization of the CPA (and by extension, the anti-Aβ antibody) by the cell. In various embodiments, the CIM may utilize one or more cellular internalization processes, including both active and passive cellular internalization, to effect internalization. Exemplary processes include, without limitation, endocytosis (e.g., Receptor Mediated Endocytosis (RME), phagocytosis, pinocytosis) and membrane translocation (e.g., direct penetration and/or energy-independent internalization). In various non-limiting embodiments, the CIM comprises, for example, a Cell-Membrane Internalizing Peptide (CMIP), a small molecule ligand (e.g., vitamin, fatty acids, integrin binding ligand, etc.), a portion of an antibody (e.g., an scFv portion that binds an internalizing cell surface target), or a decoy receptor ligand (e.g., a cytokine or derivative thereof). In some embodiments, the CIM comprises a Cell-Membrane Internalizing Peptide (CMIP). Non-limiting features and examples of cell internalizing modules are described herein.

As used herein a "Cell Membrane Internalizing Peptide" (also referred to herein as a CMIP"), is a sequence of three or more naturally occurring or non-naturally-occurring amino acids that, when covalently or non-covalently linked to an anti-Aβ antibody, results in the internalization into a mammalian cell of, at a minimum, the anti-Aβ antibody or an active fragment of the anti-Aβ antibody. In various embodiments, the CMIP may utilize one or more cellular internalization processes, including both active and passive cellular internalization, to effect internalization. Exemplary processes include, without limitation, endocytosis and membrane translocation. In some embodiments, the CMIP interacts with the cell membrane, and/or a cell surface antigen, leading to internalization of the CPA or a portion thereof (e.g., a portion comprising the anti-Aβ antibody or a functional portion thereof) via an endocytic vesicle. In some embodiments, the CMIP further facilitates the transfer of the CPA or portion thereof out of the endocytic vesicle and into the cytoplasm of the cell. In some cases, the CMIP further interacts with the membrane of the endocytic vesicle, leading to vesicle rupture and endosomal escape of the CPA or portion thereof into the cytosol. Thus, in some embodiments, the CMIP facilitates both the internalization of the anti-Aβ antibody or functional portion thereof into the cell, as well as transfer of the anti-Aβ

antibody or functional portion thereof into the cytosol. Non-limiting examples of CMIPs include, for example, cationic peptides (including, for example, M-lycotoxin, TAT peptides, penetratin, and polyarginine peptides, as well as derivatives thereof), amphipathic peptides (including, for example, MPG peptides, Pep-1 peptides, transportan peptides, as well as derivative thereof), and proline-rich peptides (including, for example, Bac7 peptides and derivatives thereof). In some embodiments, CMIPs include cell penetrating peptides and derivatives thereof, including, for example, those described in I. Ruseska and A. Zimmer, Internalization mechanisms of cell penetrating peptides, BEILSTEIN J. NANOTECHOL. 202; 11:101-123. Non-limiting features and examples of CMIPs are described herein.

The term "epitope" refers to a site on an antigen to which an antibody binds. An epitope can be formed from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of one or more proteins. Epitopes formed from contiguous amino acids (also known as linear epitopes) are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding (also known as conformational epitopes) are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. *See, e.g.*, Epitope Mapping Protocols, in Methods in Molecular Biology, Vol. 66, Glenn E. Morris, Ed. (1996).

Antibodies that recognize the same or overlapping epitopes can be identified in a simple immunoassay showing the ability of one antibody to compete with the binding of another antibody to a target antigen. The epitope of an antibody can also be defined X-ray crystallography of the antibody bound to its antigen to identify contact residues. Alternatively, two antibodies have the same epitope if all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

The term "humanized immunoglobulin" or "humanized antibody" refers to an immunoglobulin or antibody that includes at least one humanized immunoglobulin or antibody chain (i.e., at least one humanized light or heavy chain). The term "humanized immunoglobulin chain" or "humanized antibody chain" (i.e., a "humanized immunoglobulin light chain" or "humanized immunoglobulin heavy chain") refers to an immunoglobulin or antibody chain (i.e., a light or heavy chain, respectively) having a variable domain that includes a variable framework region substantially from a human immunoglobulin or

antibody and complementarity determining regions (CDRs) (e.g., at least one CDR, preferably two CDRs, more preferably three CDRs) substantially from a non-human immunoglobulin or antibody, and further includes constant regions (e.g., at least one constant region or portion thereof, in the case of a light chain, and preferably three constant regions in the case of a heavy chain). The term "humanized variable region" (e.g., "humanized light chain variable region" or "humanized heavy chain variable region") refers to a variable region that includes a variable framework region substantially from a human immunoglobulin or antibody and complementarity determining regions (CDRs) substantially from a non-human immunoglobulin or antibody.

Competition between antibodies is determined by an assay in which an antibody under test inhibits specific binding of a reference antibody (e.g., 3D6, aducanumab, bapineuzumab) to a common antigen (see, e.g., Junghans et al., Cancer Res. 50:1495, 1990). A test antibody competes with a reference antibody if an excess of a test antibody (e.g., at least 2×, 5×, 10×, 20× or 100×) inhibits binding of the reference antibody by at least 50% but preferably 75%, 90% or 99% as measured in a competitive binding assay. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

An immunoglobulin light or heavy chain variable region (also sometimes referred to herein as a "light chain variable domain" ("VL domain") or "heavy chain variable domain" ("VH domain"), respectively) consists of a "framework" region interrupted by three "complementarity determining regions" or "CDRs." The framework regions serve to align the CDRs for specific binding to an epitope of an antigen. The CDRs include the amino acid residues of an antibody that are primarily responsible for antigen binding. From amino-terminus to carboxyl-terminus, both VL and VH domains comprise the following framework (FR) and CDR regions: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. CDRs 1, 2, and 3 of a VL domain are also sometimes referred to herein, respectively, as CDR-L1, CDR-L2, and CDR-L3; CDRs 1, 2, and 3 of a VH domain are also sometimes referred to herein, respectively, as CDR-H1, CDR-H2, and CDR-H3. When the application discloses a VL sequence with R as the C-terminal residue, the R can alternatively be considered as being the N-terminal residue of the light chain constant domain. Thus, the application should also be understood as disclosing the VL sequence without the C-terminal R.

The assignment of amino acids to each VL and VH domain is in accordance with any conventional definition of CDRs. Conventional definitions include, the Kabat definition (Kabat, Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, MD, 1987 and 1991), the Chothia definition (Chothia & Lesk, J. Mol. Biol. 196:901-917, 1987; Chothia et al., Nature 342:878-883, 1989); a composite of Chothia Kabat CDR in which CDR-H1 is a composite of Chothia and Kabat CDRs; the AbM definition used by Oxford Molecular's antibody modelling software; and, the contact definition of Martin et al (bioinfo.org.uk/abs) (see Table A). Kabat provides a widely used numbering convention (Kabat numbering) in which corresponding residues between different heavy chains or between different light chains are assigned the same number. When an antibody is said to comprise CDRs by a certain definition of CDRs (e.g., Kabat) that definition specifies the minimum number of CDR residues present in the antibody (i.e., the Kabat CDRs). It does not exclude that other residues falling within another conventional CDR definition but outside the specified definition are also present. For example, an antibody comprising CDRs defined by Kabat includes among other possibilities, an antibody in which the CDRs contain Kabat CDR residues and no other CDR residues, and an antibody in which CDR H1 is a composite Chothia-Kabat CDR H1 and other CDRs contain Kabat CDR residues and no additional CDR residues based on other definitions.

Table A

Conventional Definitions of CDRs Using Kabat Numbering

Loop	**Kabat**	**Chothia**	**Composite of Chothia & Kabat**	**AbM**	**Contact**
L1	L24--L34	L24--L34	L24--L34	L24--L34	L30--L36
L2	L50--L56	L50--L56	L50--L56	L50--L56	L46--L55
L3	L89--L97	L89--L97	L89--L97	L89--L97	L89--L96
H1	H31--H35B	H26--H32..H34*	H26--H35B*	H26--H35B	H30--H35B

Conventional Definitions of CDRs Using Kabat Numbering

Loop	Kabat	Chothia	Composite of Chothia & Kabat	AbM	Contact
H2	H50--H65	H52--H56	H50--H65	H50--H58	H47--H58
H3	H95--H102	H95--H102	H95--H102	H95--H102	H93--H101

*CDR-H1 by Chothia can end at H32, H33, or H34 (depending on the length of the loop). This is because the Kabat numbering scheme places insertions of extra residues at 35A and 35B, whereas Chothia numbering places them at 31A and 31B. If neither H35A nor H35B (Kabat numbering) is present, the Chothia CDR-H1 loop ends at H32. If only H35A is present, it ends at H33. If both H35A and H35B are present, it ends at H34.

In some embodiments, the CDRs of the humanized antibodies of the present disclosure are of a definition selected from the group of Kabat, Chothia, Kabat/Chothia Composite, AbM and Contact.

One or several amino acids at the amino or carboxy terminus of the light and/or heavy chain, such as a C-terminal lysine of the heavy chain, may be missing or derivatized in a proportion or all of the molecules. Substitutions can be made in the constant domains to reduce or increase effector function such as complement-mediated cytotoxicity or ADCC (see, e.g., Winter et al., US Patent No. 5,624,821; Tso et al., US Patent No. 5,834,597; and Lazar et al., Proc. Natl. Acad. Sci. USA 103:4005, 2006), or to prolong half-life in humans (see, e.g., Hinton et al., J. Biol. Chem. 279:6213, 2004). Exemplary substitutions include a Gln at position 250 and/or a Leu at position 428 (EU numbering is used in this paragraph for the constant domain) for increasing the half-life of an antibody. Substitution at any or all of positions 234, 235, 236 and/or 237 reduce affinity for Fcγ receptors, particularly FcγRI receptor (see, e.g., US 6,624,821). An alanine substitution at positions 234, 235, and 237 of human IgG1 can be used for reducing effector functions. Some antibodies have alanine substitution at positions 234, 235 and 237 of human IgG1 for reducing effector functions. Optionally, positions 234, 236 and/or 237 in human IgG2 are substituted with alanine and position 235 with glutamine (see, e.g., US 5,624,821). In some antibodies, a mutation at one or more of positions 241, 264, 265, 270, 296, 297, 322, 329, and 331 by EU numbering of

human IgG1 is used. In some antibodies, a mutation at one or more of positions 318, 320, and 322 by EU numbering of human IgG1 is used. In some antibodies, positions 234 and/or 235 are substituted with alanine and/or position 329 is substituted with glycine. In some antibodies, positions 234 and 235 are substituted with alanine. In some antibodies, the isotype is human IgG2 or IgG4.

As used herein a "linker" refers a chemical moiety that does not have catalytic or therapeutic activity in a mammalian cell that is used to covalently link two different functional molecules (e.g., a cell internalization module and a an Aβ antibody). For example, a linker can be a peptide of about 3 amino acids to about 25 amino acids (e.g., about 3 amino acids to about 20, or about 3 amino acids to about 12 amino acids). In other examples, a linker can be a bond (e.g., an amide bond, an ester bond, an ether bond, and a disulfide bond). In some examples, a linker can comprise a pair of affinity domains (e.g., a first domain of the pair of affinity domains can be interleukin-15 and a second domain of the pair of affinity domains can be a sushi domain of interleukin-15 receptor alpha). In some examples, a linker is a glycine residue followed by a serine residue (GS). In some examples, a linker is three consecutive glycine residues (e.g., GGG). In some examples, a linker is any one of SEQ ID NOs: 343-346.

The term "pharmaceutically acceptable" means that the carrier, diluent, excipient, or auxiliary is compatible with the other ingredients of the formulation and not substantially deleterious to the recipient thereof.

As used herein a "M-lycotoxin derivative" is a peptide comprising three or more amino acids (naturally-occurring or non-naturally-occurring) that was designed based on a starting M-lycotoxin peptide. In some embodiments, the "M-lycotoxin derivative" is a polypeptide having, e.g., between 60% and 99% sequence homology to wild-type M-lycotoxin. Additional non-limiting aspects and examples of M-lycotoxin derivatives are described herein.

As used herein, the term "macromolecule" refers to a molecule having either a molecular weight of at least 5 kDa and/or a hydrodynamic radius of at least 1.0 nm. As used herein, the term "macromolecules" includes biomolecules, organic polymers, and organometallic complexes.

As used herein a "spacer" or "spacer region" refers to an amino acid that does not have catalytic or therapeutic activity in a mammalian cell. For example, a spacer can be a peptide of 1 amino acid to about 10 amino acids (e.g., 1 to about 8 amino acids, 1 to about 6 amino acids, or 1 to about 4 amino acids). In some examples, one or more spacer regions are

included in the cell internalizing module. For example, a spacer region can separate amino acids within a cell internalizing module, e.g., a spacer can be disposed after the first amino acid of a CIM. In some examples, a spacer can be disposed before the final amino acid of a CIM. In some examples, a CIM can have two or more spacer regions (e.g., two spacer regions, three space sequences, four spacer regions, five spacer regions or more). In some examples, a spacer region is a single glycine residue. In some examples, a spacer region is a pair of glycine residues. In some examples, a spacer region is three glycine residues. In some examples, a spacer region is four glycine residues. In some examples, a spacer region is four glycine residues followed by a serine residue. In some examples, a spacer region is any one of SEQ ID NOs: 339-342.

The term "patient" or "subject" includes human and other mammalian subjects (e.g., human) that receive either prophylactic or therapeutic treatment.

An individual is at increased risk of a disease if the subject has at least one known risk factor (e.g., genetic, biochemical, family history, and situational exposure) placing individuals with that risk factor at a statistically significant greater risk of developing the disease than individuals without the risk factor.

The term "biological sample" refers to a sample of biological material within or obtainable from a biological source, for example a human or mammalian subject. Such samples can be organs, organelles, tissues, sections of tissues, bodily fluids, peripheral blood, blood plasma, blood serum, cells, molecules such as proteins and peptides, and any parts or combinations derived therefrom. The term biological sample can also encompass any material derived by processing the sample. Derived material can include cells or their progeny. Processing of the biological sample may involve one or more of filtration, distillation, extraction, concentration, fixation, inactivation of interfering components, and the like.

The term "control sample" refers to a biological sample not known or suspected to include Aβ affected regions, or at least not known or suspect to include diseased regions of a given type. Control samples can be obtained from individuals not afflicted with the Aβ-related disease. Alternatively, control samples can be obtained from patients afflicted with the Aβ-related disease. Such samples can be obtained at the same time as a biological sample thought to comprise the Aβ-related disease or on a different occasion. A biological sample and a control sample can both be obtained from the same tissue. Preferably, control samples consist essentially or entirely of normal, healthy regions and can be used in comparison to a biological sample thought to comprise Aβ-related disease-affected regions. Preferably, the

tissue in the control sample is the same type as the tissue in the biological sample. Preferably, the Aβ-related disease-affected cells thought to be in the biological sample arise from the same cell type (e.g., neurons or glia) as the type of cells in the control sample.

For purposes of classifying amino acids substitutions as conservative or nonconservative, amino acids are grouped as follows: Group I (hydrophobic side chains): Met, Ala, Val, Leu, Ile; Group II (neutral hydrophilic side chains): Cys, Ser, Thr; Group III (acidic side chains): Asp, Glu; Group IV (basic side chains): Asn, Gln, His, Lys, Arg; Group V (residues influencing chain orientation): Gly, Pro; and Group VI (aromatic side chains): Trp, Tyr, Phe. Conservative substitutions involve substitutions between amino acids in the same class. Non-conservative substitutions constitute exchanging a member of one of these classes for a member of another.

Percentage sequence identities are determined with antibody sequences maximally aligned by the Kabat numbering convention. After alignment, if a subject antibody region *(e.g.,* the entire mature variable region of a heavy or light chain) is being compared with the same region of a reference antibody, the percentage sequence identity between the subject and reference antibody regions is the number of positions occupied by the same amino acid in both the subject and reference antibody region divided by the total number of aligned positions of the two regions, with gaps not counted, multiplied by 100 to convert to percentage.

Unless otherwise apparent from the context, the term "about" encompasses insubstantial variations, such as values within a standard margin of error of measurement *(e.g.,* SEM) of a stated value.

The phrase "substantially from a human immunoglobulin or antibody" means that, when aligned to a human immunoglobulin or antibody amino sequence for comparison purposes, the region shares at least 80-90%, preferably 90-95%, more preferably 95-99% identity (*i.e.*, local sequence identity) with the human framework or constant region sequence, allowing, for example, for conservative substitutions, consensus sequence substitutions, germline substitutions, backmutations, and the like. The introduction of conservative substitutions, consensus sequence substitutions, germline substitutions, backmutations, and the like, is often referred to as "optimization" of a humanized antibody or chain. The phrase "substantially from a non-human immunoglobulin or antibody" or "substantially non-human" means having an immunoglobulin or antibody sequence at least 80-95%, preferably 90-95%, more preferably, 96%, 97%, 98%, or 99% identical to that of a non-human organism, *e.g.*, a non-human mammal.

Accordingly, all regions or residues of a humanized immunoglobulin or antibody, or of a humanized immunoglobulin or antibody chain, except possibly the CDRs, are substantially identical to the corresponding regions or residues of one or more native human immunoglobulin sequences. The term "corresponding region" or "corresponding residue" refers to a region or residue on a second amino acid or nucleotide sequence which occupies the same (*i.e.*, equivalent) position as a region or residue on a first amino acid or nucleotide sequence, when the first and second sequences are optimally aligned for comparison purposes.

"Specific binding" of an antibody mean that the antibody exhibits appreciable affinity for antigen or a preferred epitope and, preferably, does not exhibit significant cross reactivity. "Appreciable" or preferred binding include binding with an affinity of at least 10^6, 10^7, 10^8, 10^9 M^{-1}, or 10^{10} M^{-1}. Affinities greater 10^7 M^{-1}, preferably greater than 10^8 M^{-1} are more preferred. Values intermediate of those set forth herein are also intended to be within the scope of the present disclosure and a preferred binding affinity can be indicated as a range of affinities, for example, 10^6 to 10^{10} M^{-1}, preferably 10^7 to 10^{10} M^{-1}, more preferably 10^8 to 10^{10} M^{-1}. An antibody that "does not exhibit significant cross reactivity" is one that will not appreciably bind to an undesirable entity (e.g., an undesirable proteinaceous entity). For example, an antibody that specifically binds to Aβ will appreciably bind Aβ but will not significantly react with non-Aβ proteins or peptides (e.g., non-Aβ proteins or peptides included in plaques). An antibody specific for a preferred epitope will, for example, not significantly cross-react with remote epitopes on the same protein or peptide. Specific binding can be determined according to any art-recognized means for determining such binding. Preferably, specific binding is determined according to Scatchard analysis and/or competitive binding assays.

II. Beta Amyloid

Aβ (also referred to herein as beta amyloid peptide and A-beta) peptide is about a 4-kDa internal fragment of 39-43 amino acids of APP (referred to as Aβ39, Aβ40, Aβ41, Aβ42, and Aβ43, respectively). Aβ40, for example, consists of residues 672-711 of APP and Aβ42 consists of residues 673-713 of APP. As a result of proteolytic processing of APP by different secretase enzymes *in vivo* or *in situ*, Aβ is found in both a "short form", 40 amino acids in length, and a "long form", ranging from 42-43 amino acids in length. Preferred epitopes or antigenic determinants, as described herein, are located within the N-terminus of the Aβ

peptide and include residues within amino acids 1-10 of Aβ, preferably from residues 1-3, 1-4, 1-5, 1-6, 1-7, or 3-7 of Aβ42. Additional referred epitopes or antigenic determinants include residues 2-4, 5, 6, 7, or 8 of Aβ, residues 3-5, 6, 7, 8, or 9 of Aβ, or residues 4-7, 8, 9, or 10 of Aβ42.

Unless otherwise apparent from context, reference to Aβ, or its fragments includes the natural human amino acid sequences including isoforms, mutants, and allelic variants thereof. The ability of an antibody or antigen-binding antibody fragment to bind to Aβ can be determined using, e.g., surface plasmon resonance.

III. Anti-Aβ Cell Penetrating Agents

The present disclosure provides cell penetrating agents (as described herein) that include a cell internalization moiety and an antibody or an antigen-binding fragment thereof that specifically binds to Aβ (e.g., human Aβ). Further, the present disclosure relates to cell penetrating agents that include a cell internalization moiety and an antibody that specifically binds to human Aβ, compositions comprising these cell penetrating agents, and methods of using these cell penetrating agents to treat Aβ related diseases, including Inclusion Body Myositis.

Throughout the present disclosure, references to the anti-Aβ CPA and/or anti-Aβ antibody will be made in the context of cell internalization and/or intracellular function, but one of ordinary skill will understand such references to include intact anti-Aβ CPA and/or anti-Aβ antibody, chemically modified (e.g., oxidized, reduced) anti-Aβ CPA and/or anti-Aβ antibody, as well as partially degraded functional fragments thereof (intact anti-Aβ CPA, CPA fragment, intact anti-Aβ antibody, and/or anti-Aβ antibody fragment, etc.). Thus, references to internalization of, cytosolic transfer of, and target engagement by either the anti-Aβ CPA or the anti-Aβ antibody will include references to intact anti-Aβ CPA and/or anti-Aβ antibody, chemically modified anti-Aβ CPA and/or anti-Aβ antibody, and partially degraded functional fragments thereof. For example, methods of the present disclosure may refer to internalization of and/or transfer to the cytosol of anti-Aβ antibody, but it will be understood that such a reference encompasses the transfer of an intact anti-Aβ CPA and/or a functional fragment of the anti-Aβ CPA comprising the anti-Aβ antibody or a portion thereof, as well as chemically modified derivatives thereof.

Cell penetrating agents of the present disclosure may utilize one or more of several biochemical processes to achieve internalization of the anti-Aβ antibody. In various

embodiments, the anti-Aβ CPAs of the present disclosure may utilize passive internalization, active internalization, or a combination thereof. In some embodiments, the anti-Aβ CPA utilizes active internalization (e.g., endocytosis) to achieve intracellular delivery of the anti-Aβ antibody.

In various embodiments, the anti-Aβ CPA is internalized into the cell via endocytosis. Following internalization, the anti-Aβ CPA achieves endosomal escape. In such embodiments, the anti-Aβ CPA is thereby transferred to the cytosol, where the anti-Aβ antibody can bind to Aβ (e.g., human Aβ). In some embodiments, endosomal escape of the anti-Aβ CPA is achieved by interaction of the CIM with the membrane of the endosome, thereby leading to disruption of the endosomal membrane. The CIM may utilize one or more methods to achieve endosomal escape. For example, the CIM may comprise a cationic portion (e.g., positively charged amino acids, a cationic polymer and/or oligomer, cationic lipid). In some of such embodiments, the cationic portion can interact with the negatively charged phospholipids that comprise the endosomal membrane, thereby disrupting the endosomal membrane, and achieving endosomal escape of the anti-Aβ CPA. anti-Aβ CPAs of the present disclosure may also comprise a CIM having an amphiphilic portion (e.g., an amphiphilic peptide). In some of such embodiments, the amphiphilic portion can interact with the endosomal membrane via hydrophobic interactions with the membrane lipids, thereby disrupting the endosomal membrane, and achieving endosomal escape of the anti-Aβ CPA. Following endosomal escape of the anti-Aβ antibody, the anti-Aβ antibody is then transferred to the cytosol, where it can bind to Aβ (e.g., human Aβ). Further examples of internalization mechanisms that can be utilized by CPAs are described in detail herein.

Thus, provided herein are cell penetrating agents that include: (i) a cell internalizing module (CIM) and (ii) an antibody that specifically binds to Aβ (e.g., human Aβ). Various aspects of cell penetrating agents of the present disclosure are described below, including examples of Cell Internalizing Moieties, anti-Aβ antibodies, and/or optional linkers. One of ordinary skill will understand how to combine the various CIM, anti-Aβ antibodies, and optional linkers disclosed herein. Such examples are merely illustrative of the scope of the present disclosure and are non-limiting.

Anti-Aβ Antibodies

Cell-penetrating agents and methods of the present disclosure facilitate the cellular internalization and/or cytosolic release of a wide range of anti-Aβ antibodies including a cell penetrating agent comprising an antibody or fragment thereof that that specifically binds to

Aβ peptide. The antibody or fragment includes the heavy chain CDRs and the light chain CDRs from one of the constructs identified herein as h2726, h2731, h2831, h2931, h2926, h4921, h2828, h2929, h3818G, h2927, h49k3G, h4917G h2727, and h4918G. Particular monoclonal antibodies of the disclosure may bind to an epitope within residues 1-6 of Aβ (with the first N terminal residue of natural Aβ designated 1). Some monoclonal antibodies bind to an epitope within amino acids 1-6, some to an epitope within 1-5, and some to an epitope within 1-4. Some antibodies bind to epitopes within amino acids 1-3, 2-5, 3-5, 2-4, 2-5, 2-6, 3-5, or 3-6. When an antibody is said to bind to an epitope within specified residues, such as Aβ 1-6 for example, what is meant is that the antibody specifically binds to a polypeptide containing the specified residues (i.e., Aβ 1-6 in this an example); such antibody does not necessarily contact every residue within Aβ 1-6.

In another aspect, the antibody or fragment includes a heavy chain variable region having a heavy chain CDR1, CDR2 and CDR3 and a light chain variable region comprising a light chain CDR1, CDR2 and CDR3 from the constructs show in Table 1A.

Table 1A

Construct ID	VH/VL Sequences		SEQ ID	CDR Sequences		SEQ ID
h2726	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNYGMSWVRQAPG KGLEWVASIRSGSG RTYYSDNVKGRFTI SRDNSKNTLYLQMN SLRAEDTAVYYCVR YDHYSGSSDYWGQ GTLVTVSS	3	1	GFTFS NYGMS	16
				2	SIRSG SGRTY YSDNV KG	20
				3	YDHYS GSSDY	18
	VL	DVVMTQSPLSLPVT PGEPASISCKSSQSL LDYDGKTYLNWLL QKPGQSPQRLIYKV SNRDSGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRTFGQGTKVEIK	8	1	KSSQS LLDYD GKTYL N	29
				2	KVSNR DS	33
				3	WQGTH FPRT	28
h2731	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNYGMSWVRQAPG KGLEWVASIRSGSG RTYYSDNVKGRFTI SRDNSKNTLYLQMN SLRAEDTAVYYCVR YDHYSGSSDYWGQ GTLVTVSS	3	1	GFTFS NYGMS	16
				2	SIRSG SGRTY YSDNV KG	20
				3	YDHYS GSSDY	18
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL LDYDGKTYLNWLL QKPGQSPQRLIYRV	9	1	KSSQS LLDYD GKTYL N	29
				2	RVTNR DT	34
				3	WQGTH FPRS	38

		TNRDTGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRSFGQGTKVEIK				
h2831	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTI SRDNSKNTLYLQMN SLRAEDTAVYYCVR YDHYSGTSDYWGQ GTLVTVSS	4	1 2 3	GFTFS NFGMS SVRSG SGRTY YSDNV KG YDHYS GTSDY	19 21 24
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL LDYDGKTYLNWLL QKPGQSPQRLIYRV TNRDTGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRSFGQGTKVEIK	9	1 2 3	KSSQS LLDYD GKTYL N RVTNR DT WQGTH FPRS	29 34 38
h2931	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTI SRDNSKNTLYLQMN SLRAEDTAVYYCVR YDHYTGTSDYWGQ GTLVTVSS	5	1 2 3	GFTFS NFGMS SVRSG SGRTY YSDNV KG YDHYT GTSDY	19 21 25
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL LDYDGKTYLNWLL	9	1 2 3	KSSQS LLDYD GKTYL N RVTNR DT WQGTH FPRS	29 34 38

		QKPGQSPQRLIYRV TNRDTGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRSFGQGTKVEIK				
h2926	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTI SRDNSKNTLYLQMN SLRAEDTAVYYCVR YDHYTGTSDYWGQ GTLVTVSS	5	1 2 3	GFTFS NFGMS SVRSG SGRTY YSDNV KG YDHYT GTSDY	19 21 25
	VL	DVVMTQSPLSLPVT PGEPASISCKSSQSL LDYDGKTYLNWLL QKPGQSPQRLIYKV SNRDSGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRTFGQGTKVEIK	8	1 2 3	KSSQS LLDYD GKTYL N KVSNR DS WQGTH FPRT	29 33 28
h4921G	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGG GRTYYSDNVKGRFT ISRDNSKNTLYLQM NSLRAEDTAVYYCV RYDHYSGTSDYWG QGTLVTVSS	6	1 2 3	GFTFS NFGMS SVRSG GGRTY YSDNV KG YDHYS GTSDY	19 22 24
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL	10	1 2	KSSQS LLDSD GKTYL N RVTNR DT	26 34

		LDSDGKTYLNWLL QKPGQSPQRLIYRV TNRDTGVPDRFSGS GSGTDFTLKISRVEA EDVGVYYCWQGTH FPRTFGQGTKVEIK		3	WQGTH FPRT	28
h2826	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCVRY DHYSGTSDYWGQG TLVTVSS	4	1	GFTFS NFGMS	19
				2	SVRSG SGRTY YSDNV KG	21
				3	YDHYS GTSDY	24
	VL	DVVMTQSPLSLPVT PGEPASISCKSSQSLL DYDGKTYLNWLLQ KPGQSPQRLIYKVSN RDSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RTFGQGTKVEIK	8	1	KSSQS LLDYD GKTYL N	29
				2	KVSNR DS	33
				3	WQGTH FPRT	28
h2929	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCVRY DHYTGTSDYWGQG TLVTVSS	5	1	GFTFS NFGMS	19
				2	SVRSG SGRTY YSDNV KG	21
				3	YDHYT GTSDY	25
	VL		11	1	RSSQS LVDYD GKTYL N	31

		DVVMTQSPLSLPVT PGEPASISCRSSQSL VDYDGKTYLNWLL QRPGQSPQRLIYKVS NRDSGVPDRFSGSG SGTDFTLKISRVEAE DVGVYYCWQGSHF PRSYGQGTKVEIK		2 3	KVSNR DS WQGSH FPRS	33 39
h3818G	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF ANYGMSWVRQAPG KGLEWVASVRSGGS RTYYSDNVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCVRY DHYSGSSDYWGQG TLVTVSS	7	1 2 3	GFTFA NYGMS SVRSG GSRTY YSDNV KG YDHYS GSSDY	20 23 18
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL MDTDGKTYLNWLL QKPGQSPQRLIYKVS NRESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RTFGQGTKVEIK	12	1 2 3	KSSQS LMDTD GKTYL N KVSNR ES WQGTH FPRT	32 35 28
h2927	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGSG RTYYSDNVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCVRY	5	1 2 3	GFTFS NFGMS SVRSG SGRTY YSDNV KG YDHYT GTSDY	19 21 25

		DHYTGTSDYWGQG TLVTVSS				
	VL	DVVMTQSPLSLPVT PGEPASISCKSSQSLL DYDGKTYLNWLLQ KPGQSPQRLIYKVSN RDSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RSFGQGTKVEIK	13	1 2 3	KSSQS LLDYD GKTYL N KVSNR DS WQGTH FPRS	29 33 38
h49k3G	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGG GRTYYSDNVKGRFT ISRDNSKNTLYLQM NSLRAEDTAVYYCV RYDHYSGTSDYWG QGTLVTVSS	6	1 2 3	GFTFS NFGMS SVRSG GGRTY YSDNV KG YDHYS GTSDY	19 22 24
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL LDSDGKTYLNWLLQ KPGQSPQRLIYKVSN RDSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RTFGQGTKVEIK	14	1 2 3	KSSQS LLDSD GKTYL N KVSNR DS WQGTH FPRT	26 33 28
h4917G	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGG GRTYYSDNVKGRFT ISRDNSKNTLYLQM	6	1 2 3	GFTFS NFGMS SVRSG GGRTY YSDNV KG YDHYS GTSDY	19 22 24

		NSLRAEDTAVYYCV RYDHYSGTSDYWG QGTLVTVSS				
	VL	DVVMTQSPLSLPVT **L**GEPASISCKSSQSL LDSDGKTYLNWLLQ KPGQSPQRLIYKVT NRESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RSFGQGTKVEIK	15	1	KSSQS LLDSD GKTYL N	26
				2	KVTNR ES	36
				3	WQGTH FPRS	38
h2727	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNYGMSWVRQAPG KGLEWVASIRSGSG RTYYSDNVKGRFTIS RDNSKNTLYLQMNS LRAEDTAVYYCVRY DHYSGSSDYWGQG TLVTVSS	3	1	GFTFS NYGMS	16
				2	SIRSG SGRTY YSDNV KG	20
				3	YDHYS GSSDY	18
	VL	DVVMTQSPLSLPVT PGEPASISCKSSQSLL DYDGKTYLNWLLQ KPGQSPQRLIYKVSN RDSGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RSFGQGTKVEIK	13	1	KSSQS LLDYD GKTYL N	29
				2	KVSNR DS	33
				3	WQGTH FPRS	38
h4918G	VH	EVQLLESGGGLVQP GGSLRLSCAASGFTF SNFGMSWVRQAPG KGLEWVASVRSGG GRTYYSDNVKGRFT	6	1	GFTFS NFGMS	19
				2	SVRSG GGRTY YSDNV	22
				3	KG YDHYS GTSDY	24

		ISRDNSKNTLYLQM NSLRAEDTAVYYCV RYDHYSGTSDYWG QGTLVTVSS				
	VL	DVVMTQSPLSLPVT LGEPASISCKSSQSL MDTDGKTYLNWLL QKPGQSPQRLIYKVS NRESGVPDRFSGSGS GTDFTLKISRVEAED VGVYYCWQGTHFP RTFGQGTKVEIK	12	1	KSSQS LMDTD GKTYL N	32
				2	KVSNR ES	25
				3	WQGTH FPRT	28

In another aspect the antibody or fragment of the disclosure includes a heavy chain variable region (VH) as shown for one of the constructs in Table 1A. The antibody or fragment may also include light chain variable region (VL) as shown for one of the constructs in Table 1A.

In one aspect, the disclosure is directed an antibody or fragment thereof including a heavy chain CDR1, CDR2, and CDR3, wherein CDR1 may be selected from any one of SEQ ID NOS: 16, 19 and 20, wherein CDR2 may be selected from any one of SEQ ID NOS: 17, 20, 21 22, and 23 and wherein CDR3 may be selected from any one of SEQ ID NOS: 18, 24, 25. In addition, the antibody or fragment thereof includes a light chain CDR1, CDR2, and CDR3, wherein CDR1 may be selected from any one of SEQ ID NOS: 26, 29, 31, and 32, wherein CDR2 may be selected from any one of SEQ ID NOS: 27, 33, 34 and 35, and wherein CDR3 may be selected from any one of SEQ ID NOS: 28, 38 and 39. In each of these embodiments, the heavy chain CDRs and the light chain CDRs are not, in combination, simultaneously SEQ ID NOS: 16, 17, 18, 26, 27 and 28.

Analysis of protein modeling information for the antibodies described above identified two changes in the CDRs that, among others, were the contributors to increased avidity/affinity characteristics of the antibodies of the disclosure: CDR-L1: S32Y (Ser to Tyr at position 32), and CDR-H2: G55S (Gly to Ser at position 54). Anti-Aβ antibodies with Tyr at position 32 in CDR-L1 and Ser at position 54 in CDR-H2 that bind the same epitope bound by antibodies listed herein are expected to have the same properties as the listed identified

antibodies (*See* Table 1A). Antibodies disclosed that do not have Tyr at position 32 in CDR-L1 and Ser at position 55 in CDR-H2 can be modified to possess Tyr at position 32 in CDR-L1 and Ser at position 55 in CDR-H2 and can be expected to confer similar binding properties to such antibodies identified herein.

Examples of a CDR-L1 with Tyr at position 32 include SEQ NOs: 29 and 31. Examples of a CDR-H2 with Ser at position 55 include SEQ Nos: 20 and 21. As examples, antibodies comprising a CDR-L1 with Tyr at position 32 and a CDR-H2 with Ser at position 55 include antibodies with the CDRs of h2726, h2731, h2727, h2826, h2831, h2926, h2927, h2931, h2929 (See Table 1A). Additional such antibodies include antibodies comprising LC CDRs 1, 2, 3 and HC CDRs 1, 2, 3 as set forth in the table below in Table 1B.

Table 1B

Antibody	**HC/LC**	**CDR Sequences (HC 1, 2, 3; LC 1, 2, 3)**		**SEQ ID**
h2729	HC	1	GFTFS NYGMS	16
		2	SIRSG SGRTY YSDNV KG	20
		3	YDHYS GSSDY	18
	LC	1	RSSQS LVDYD GKTYL N	31
		2	KVSNR DS	33
		3	WQGSH FPRS	39
h2829	HC	1	GFTFS NFGMS	19
		2	SVRSG SGRTY YSDNV KG	21
		3	YDHYS GTSDY	24
	LC	1	RSSQS LVDYD GKTYL N	31
		2	KVSNR DS	33
		3	WQGSH FPRS	39
h2827	HC	1	GFTFS NFGMS	19
		2	SVRSG SGRTY YSDNV KG	21
		3	YDHYS GTSDY	24
	LC	1	KSSQS LLDYD GKTYL N	29
		2	RVTNR DT	33
		3	WQGTH FPRS	38
	HC	1	GFTFS NYGMS	16

HC-S55/ LC-Y32		2	SIRSG SGRTY YSDNV KG	20
		3	YDHYS GSSDY	18
	LC	1	KSSQS LLDYD GKTYL N	29
		2	LVSKL DS	27
		3	WQGTH FPRT	28

In view of the binding properties identified for the antibodies identified herein, consensus sequences can be identified that would be expected to provide similar binding properties. For example, in embodiments of the disclosure, antibodies or binding fragments thereof that that specifically bind to Aβ peptide may include heavy chain variable regions having heavy chain CDR1, CDR2 and CDR3 and a light chain variable regions having light chain CDR1, CDR2 and CDR3, as follows: heavy chain CDR1 comprises amino acid sequence GFTFSNX^{A}GMS, wherein X^{A} is Y or F (SEQ ID NO: 88); heavy chain CDR2 comprises amino acid sequence SX^{A}RSGSGRTYYSDNVKG, wherein is X^{A} is I or V (SEQ ID NO: 89); heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90); light chain CDR1 comprises amino acid sequence KSSQSLLDYDGKTYLN (SEQ ID NO: 91); light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRDX^{C}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is S or T (SEQ ID NO: 92); and light chain CDR3 comprises amino acid sequence WQGTHFPRX^{A}, wherein X^{A} is S or T (SEQ ID NO: 93).

In some embodiments, the light chain CDR3 comprises WQGTHFPRX^{A}FX^{B}, wherein X^{A} is S or T and X^{B} is F or Y (SEQ ID NO: 94).

Similar consensus sequences that may be expected to provide binding properties similar to the antibodies described herein include a heavy chain variable region having heavy chain CDR1, CDR2 and CDR3 and a light chain variable region having light chain CDR1, CDR2 and CDR3, as follows: heavy chain CDR1 comprises amino acid sequence GFTFX^{A}NX^{B}GMS, wherein X^{A} is S or A, and X^{B} is Y or F (SEQ ID NO: 95); heavy chain CDR2 comprises amino acid sequence SX^{A}RSGX^{B}X^{C}RTYYSDNVKG, wherein is X^{A} is I or V, X^{B} is S or G and X^{C} is S or G (SEQ ID NO: 96); heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90); light chain CDR1 comprises amino acid sequence X^{A}SSQSLX^{B}DX^{C}DGKTYLN, wherein X^{A} is K or R, X^{B} is V, M or L, and X^{C} is Y, T or S (SEQ ID NO: 97); light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRX^{C}X^{D}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is E or D,

and X^D is S or T (SEQ ID NO: 98); and light chain CDR3 comprises amino acid sequence $WQGX^AHFPRX^B$, wherein X^A is S or T, and X^B is S or T (SEQ ID NO: 99).

In some embodiments, the light chain CDR3 comprises $WQGTHFPRX^AFX^BX^C$, wherein X^A is S or T, X^B is S or T and X^C is F or Y (SEQ ID NO: 100).

In addition, the light and heavy variable regions may be at least at least 75% identical to the light and heavy chain variable regions show in Table 1A. For example, the light and heavy chain variable regions may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to VH and/or VL sequences identified in Table 1A. In various aspects, any sequence variation in the VH and VL may be present outside the CDRs so that the VH and VL sequences of the disclosure include the CDRs identified in Table 1A, but the regions of the VH and VL sequences outside of the CDRs may be at least 75% identical to the regions outside the CDRs of the VH and VL sequences in Table 1A.

For example, the antibody or fragment of the disclosure may include a heavy chain variable region, excluding the CDRS, that is at least 95% identical to one of SEQ ID NOS: 3, 4, 5, 6 and 7, and the light chain variable region, excluding the CDRs, that is at least 95% identical to one of SEQ ID NOS: 8, 9, 10, 11, 12, 13, 14 and 15.

The antibodies and fragments of the disclosure may also include a heavy chain constant region that is at least 75% identical to SEQ ID NO: 40. For example, the heavy chain constant region may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 40.

The antibodies and fragments of the disclosure may also include a light chain constant region that is at least 75% identical to SEQ ID NO: 41. For example, the heavy chain constant region may be 75% identical, 80%, identical, 85% identical, 90% identical, 95% identical, 96% identical, 97% identical, 98% identical, 99% identical, of 100% identical to SEQ ID NO: 41.

A variant antibodies or fragments that are less than 100% identical to the sequences described in Table 1A (plus any constant region) can differ from an anti-Aβ antibody of Table 1A by as few as 1 to 15 amino acid residues, as few as 1 to 10 amino acid residues, such as 6-10, as few as 5, as few as 4, 3, 2, or even 1 amino acid residue. A "conservative amino acid substitution" is one in which the amino acid residue is replaced with an amino acid residue having a side chain with a similar charge. Families of amino acid residues having side chains with similar charges have been defined in the art. These families include amino

acids with basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (e.g., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Alternatively, mutations can be introduced randomly along all or part of the coding sequence, such as by saturation mutagenesis, and the resultant mutants can be screened for biological activity to identify mutants that retain activity (e.g., the ability to bind an Aβ polypeptide).

For example, it is possible to introduce mutations only in framework regions of the antibody molecules. Introduced mutations can be silent or neutral missense mutations, i.e., have no, or little, effect on an antibody's ability to bind antigen. These types of mutations can be useful to optimize codon usage or improve a hybridoma's antibody production. Alternatively, non-neutral missense mutations can alter an antibody's ability to bind antigen. One of skill in the art would be able to design and test mutant molecules with desired properties such as no alteration in antigen binding activity or alteration in binding activity (e.g., improvements in antigen binding activity or change in antibody specificity). Following mutagenesis, the encoded protein can routinely be expressed and the functional and/or biological activity of the encoded protein, (e.g., ability to immunospecifically bind at least one epitope of an Aβ polypeptide) can be determined using techniques described herein or by routinely modifying techniques known in the art.

In each of the foregoing embodiments, the antibody or fragment of the disclosure may be a humanized antibody as described herein. For example, the antibody may be a human IgG1 antibody. In addition, the antibody may a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody. Fragments of the antibody may be a Fab, Fab', F(ab')2, Fabc, or Fv. Fragments are produced by recombinant DNA techniques, or by enzymatic or chemical separation of intact immunoglobulins.

Other exemplary Aβ antibodies can be used in the cell penetrating agents described herein. For example, anti-Aβ antibodies such as aducanumab, lecanumab, bapineuzumab, solanezumab, gantererumab, crenezumab, donanemab, and ponezumab can be used in the cell penetrating agents described herein. Additional Aβ antibodies are available from Novus Biologicals (Cat. No. NBP2-13075); Cell Signalling Technology (Cat. No. 2454); Santa Cruz Biotechnology (Cat. No. sc-28365); LS Bio (Cat. No. LS-C186426), abcam (Cat. No. ab11132); and Invitrogen (Cat. No. MAI-24966).

Other Aβ antibodies that can be used in the cell penetrating agents described herein include those described U.S. Patent No. 8,491,903; U.S. Patent No. 8,323,654; U.S. Patent No. 8,614,298; U.S. Patent No. 11,655,289; U.S. Patent Application Publication No. 2022/02181963; U.S. Patent Application Publication No. U.S. 2022/0372123 and those described in the following references: Karran, E. and Strooper B., The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. *Nat Rev Drug Discov*. 21(4):306-318 (2022); Imbimbo, B.P., et al., Role of monomeric amyloid-β in cognitive performance in Alzheimer's disease: Insights from clinical trials with secretase inhibitors and monoclonal antibodies, *Pharmacol Res*. Jan. (2023); Vitek, G.E., et al., An anti-beta-amyloid monoclonal antibody for the treatment of Alzheimer disease, *Expert Opin Investig Drugs*, 32(2):89-94 (2023); and Panza, F. et al., Anti-β-amyloid monoclonal antibodies for the treatment of Alzheimer's disease, *Immunotherapy*. 2(6):767-82 (2010), each of which is incorporated herein by reference in their entireties.

The antibody or binding fragments, variant, or derivative disclosed herein can be said to bind to Aβ) or a fragment or variant thereof with an off rate (k(off)) of less than or equal to 5×10^{-2} sec^{-1}, 10^{-2} sec^{-1}, 5×10^{-3} sec^{-1} or 10^{-3} sec^{-1}. In certain embodiments, an antibody of the disclosure can be said to bind Aβ or a fragment or variant thereof with an off rate (k(off)) less than or equal to 5×10^{4} sec^{-1}, 10^{-4} sec^{-1}, 5×10^{-5} sec^{-1}, or 10^{-5} sec^{-1}, 5×10^{-6} sec^{-1}, 10^{-6} sec^{-1}, 5×10^{-7} sec^{-1} or 10^{-7} sec^{-1}.

An antibody or antigen-binding fragment, variant, or derivative disclosed herein can be said to bind a target polypeptide disclosed herein (e.g., Aβ) or a fragment or variant thereof with an on rate (k(on)) of greater than or equal to 10^{3} M−1 sec−1, 5×10^{3} M−1 sec−1, 10^{4} M−1 sec−1 or 5×10^{4} M−1 sec−1. In certain embodiments, an antibody of the disclosure can be said to bind a target polypeptide disclosed herein (e.g., Aβ) or a fragment or variant thereof with an on rate (k(on)) greater than or equal to 10^{5} M−1 sec−1, 5×10^{5} M−1 sec−1, 10^{6} M−1 sec−1, or 5×10^{6} M−1 sec−1 or 10^{7} M−1 sec−1.

Anti-Aβ antibodies or antigen-binding fragments, variants or derivatives thereof, as described herein can also be described or specified in terms of their binding affinity Aβ. Binding affinities can include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The humanized mature heavy chain of the antibody described herein can include a lysine residue at their C-terminus. However, in some embodiments, the humanized mature

heavy chain (e.g., any of the mature heavy chains described herein) does not include the C-terminal lysine residue.

The humanized mature light chain variable domains described herein can include a lysine residue at their C-terminus. However, in some embodiments, the humanized mature heavy chain (e.g., any of the mature heavy chains described herein) does not include the C-terminal lysine residue. For example, any one of the mature heavy chains of SEQ ID NOs: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, or SEQ ID NO: 394 can lack the C-terminal lysine residue.

In some embodiments, the humanized antibody has a melting temperature of about 55 °C or greater. In some embodiments, the humanized antibody has a melting temperature of about 56 °C or greater, about 57 °C or greater, about 58° C or greater, about 59 °C or greater, about 60 °C or greater, about 61 °C or greater, about 62 °C or greater, about 63 °C or greater, about 64 °C or greater, about 65 °C or greater, about 66 °C or greater, about 67 °C or greater, about 68 °C or greater, about 69 °C or greater, about 70 °C or greater, about 71 °C or greater, about 72 °C or greater, about 73 °C or greater, about 74 °C or greater, about 75 °C or greater, about 76 °C or greater, about 77 °C or greater, about 78 °C or greater, about 79 °C or greater, about 80 °C or greater, about 81 °C or greater, about 82 °C or greater, about 83 °C or greater, about 84 °C or greater, or about 85 °C or greater. In some embodiments, the humanized antibody has a melting temperature of at least about 55 °C, at least about 56 °C, at least about 57 °C, at least about 58 °C, at least about 59 °C, at least about 60 °C, at least about 61 °C, at least about 62 °C, at least about 63 °C, at least about 64 °C, at least about 65 °C, at least about 66 °C, at least about 67 °C, at least about 68 °C, at least about 69 °C, at least about 70 °C, at least about 71 °C, at least about 72 °C, at least about 73 °C, at least about 74 °C, at least about 75 °C, at least about 76 °C, at least about 77 °C, at least about 78 °C, at least about 79 °C, at least about 80 °C, at least about 81 °C, at least about 82 °C, at least about 83 °C, at least about 84 °C, or at least about 85 °C. In some embodiments, the humanized antibody has a melting temperature of about 55 °C to about 85 °C, about 55 °C to about 80 °C, about 55 °C to about 75 °C, about 55 °C to about 70 °C, about 55 °C to about 65 °C, about 55 °C to about 63 °C, about 55 °C to about 61 °C, about 55 °C to about 59 °C, about 55 °C to about 57 °C, about 57 °C to about 85 °C, about 57 °C to about 80 °C, about 57 °C to about 75 °C, about 57 °C to about 70 °C, about 57 °C to about 65 °C, about 57 °C to about 63 °C, about 57 °C to about 61 °C, about 57 °C to about 59 °C, about 59 °C to about 85 °C, about 59 °C to about 80 °C, about 59 °C to about 75 °C, about 59 °C to about 70 °C, about 59

°C to about 65 °C, about 59 °C to about 63 °C, about 59 °C to about 61 °C, about 61 °C to about 85 °C, about 61 °C to about 80 °C, about 61 °C to about 75 °C, about 61 °C to about 70 °C, about 61 °C to about 65 °C, about 61 °C to about 63 °C, about 63 °C to about 85 °C, about 63 °C to about 80 °C, about 63 °C to about 75 °C, about 63 °C to about 70 °C, about 63 °C to about 65 °C, about 65 °C to about 85 °C, about 65 °C to about 80 °C, about 65 °C to about 75 °C, about 65 °C to about 70 °C, about 70 °C to about 85 °C, about 70 °C to about 80 °C, about 70 °C to about 75 °C, about 75 °C to about 85 °C, about 75 °C to about 80 °C, or about 80 °C to about 85 °C.

In some embodiments, the antibody of the cell penetrating agent is an intact antibody. In some embodiments, the antibody has a human IgG1 isotype.

In some embodiments, the heavy chain variable domain is fused to a heavy chain constant region (e.g., any of the heavy chain constant regions described herein) and the light chain variable domain is fused to a light chain constant region (e.g., any of the light chain constant regions described herein).

In some embodiments, the heavy chain constant region is a mutant form of a natural human heavy chain constant region which has reduced binding to an Fcγ receptor relative to the natural heavy chain constant region. In some embodiments, the heavy chain constant region is of IgG1 isotype. In some embodiments, the antibody has at least one mutation in a constant region. In some embodiments, the at least one mutation reduces complement fixation or activation by the constant region. In some embodiments, the at least one mutation is at one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11) positions of: 241, 264, 265, 270, 296, 297, 318, 320, 322, 329, and 331 by EU numbering. In some embodiments, the antibody has an alanine at positions 318, 320, and 322 by EU numbering.

In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent binds to phosphorylated Aβ (e.g., human Aβ) with greater (e.g., at least 10-fold, at least 20-fold, at least 30-fold, at least 40-fold, at least 50-fold, at least 100-fold, at least 150-fold, at least 200-fold, at least 250-fold, at least 300-fold, at least 350-fold, at least 400-fold, at least 450-fold, at least 500-fold, at least 550-fold, at least 600-fold, at least 650-fold, at least 700-fold, at least 750-fold, at least 800-fold, at least 850-fold, at least 900-fold, at least 950-fold, at least 1,000-fold, at least 1,050-fold, at least 1,100-fold, at least 1,150-fold, at least 1,200-fold, at least 1,250-fold, at least 1,300-fold, at least 1,350-fold, at least 1,400-fold, at least 1,450-fold, or at least 1,500-fold greater, or about 10-fold to about 1,500-fold, about 10-fold to 1,400-fold greater, about 10-fold to about 1,300-fold, about 10-fold to about 1,200-fold, about 10-fold to about 1,100-fold, about 10-fold to about 1,000-fold, about

10-fold to about 900-fold, about 10-fold to about 800-fold, about 10-fold to about 700-fold, about 10-fold to about 600-fold, about 10-fold to about 500-fold, about 10-fold to about 400-fold, about 10-fold to about 300-fold, about 10-fold to about 200-fold, about 10-fold to about 100-fold, about 10-fold to about 50-fold, about 50-fold to about 1,500-fold, about 50-fold to 1,400-fold greater, about 50-fold to about 1,300-fold, about 50-fold to about 1,200-fold, about 50-fold to about 1,100-fold, about 50-fold to about 1,000-fold, about 50-fold to about 900-fold, about 50-fold to about 800-fold, about 50-fold to about 700-fold, about 50-fold to about 600-fold, about 50-fold to about 500-fold, about 50-fold to about 400-fold, about 50-fold to about 300-fold, about 50-fold to about 200-fold, about 50-fold to about 100-fold, about 100-fold to about 1,500-fold, about 100-fold to 1,400-fold greater, about 100-fold to about 1,300-fold, about 100-fold to about 1,200-fold, about 100-fold to about 1,100-fold, about 100-fold to about 1,000-fold, about 100-fold to about 900-fold, about 100-fold to about 800-fold, about 100-fold to about 700-fold, about 100-fold to about 600-fold, about 100-fold to about 500-fold, about 100-fold to about 400-fold, about 100-fold to about 300-fold, about 100-fold to about 200-fold, about 200-fold to about 1,500-fold, about 200-fold to 1,400-fold greater, about 200-fold to about 1,300-fold, about 200-fold to about 1,200-fold, about 200-fold to about 1,100-fold, about 200-fold to about 1,000-fold, about 200-fold to about 900-fold, about 200-fold to about 800-fold, about 200-fold to about 700-fold, about 200-fold to about 600-fold, about 200-fold to about 500-fold, about 200-fold to about 400-fold, about 200-fold to about 300-fold, about 500-fold to about 1,500-fold, about 500-fold to 1,400-fold greater, about 500-fold to about 1,300-fold, about 500-fold to about 1,200-fold, about 500-fold to about 1,100-fold, about 500-fold to about 1,000-fold, about 500-fold to about 900-fold, about 500-fold to about 800-fold, about 500-fold to about 700-fold, about 500-fold to about 600-fold, about 800-fold to about 1,500-fold, about 800-fold to 1,400-fold greater, about 800-fold to about 1,300-fold, about 800-fold to about 1,200-fold, about 800-fold to about 1,100-fold, about 800-fold to about 1,000-fold, about 800-fold to about 900-fold, about 1,000-fold to about 1,500-fold, about 1,000-fold to 1,400-fold greater, about 1,000-fold to about 1,300-fold, about 1,000-fold to about 1,200-fold, or about 1,000-fold to about 1,100-fold) affinity than unphosphorylated Aβ (e.g., human Aβ).

In some embodiments, the antibody, or fragment thereof, of the cell penetrating agent selectively binds to cytoplasmic aggregates of Aβ (e.g., cytoplasmic aggregates of human Aβ). In some embodiments, the antibody, or fragment thereof, of the cell penetrating agent selectively binds to cytoplasmic aggregates of Aβ (e.g., cytoplasmic aggregates of human Aβ) compared to nuclear Aβ (e.g., nuclear human Aβ).

The heavy and light chain variable regions present in the cell penetrating agents can be linked to at least a portion of a human constant region. The choice of constant region depends, in part, whether antibody conjugate-dependent cell-mediated cytotoxicity, antibody conjugate dependent cellular phagocytosis and/or complement dependent cytotoxicity are desired. For example, human isotypes IgG1 and IgG3 have complement-dependent cytotoxicity and human isotypes IgG2 and IgG4 do not. Human IgG1 and IgG3 also induce stronger cell mediated effector functions than human IgG2 and IgG4. Light chain constant regions can be lambda or kappa. Numbering conventions for constant regions include EU numbering (Edelman, G.M. et al., *Proc. Natl. Acad. Sci. U.S.A.* 63:78-85 (1969)), Kabat numbering (Kabat, *Sequences of Proteins of Immunological Interest* (National Institutes of Health, Bethesda, MD, 1991, IMGT unique numbering (Lefranc M.-P. et al., IMGT unique numbering for immunoglobulin and T cell receptor constant domains and Ig superfamily C-like domains, *Dev. Comp. Immunol.* 29:185- 203 (2005), and IMGT exon numbering (Lefranc, supra).

One or several amino acids at the amino or carboxy terminus of the light and/or heavy chain, such as the C-terminal lysine of the heavy chain, may be missing or derivatized in a proportion or all of the molecules. Substitutions can be made in the constant regions to reduce or increase effector function such as complement-mediated cytotoxicity or ADCC (see, e.g., Winter et al., U.S. Patent No. 5,624,821; Tso et al., US Patent No. 5,834,597; and Lazar et al., *Proc. Natl. Acad. Sci. U.S.A.* 103:4005 (2006)), or to prolong half-life in humans (see, e.g., Hinton et al., *J. Biol. Chem.* 279:6213 (2004)). Exemplary substitutions include a Gln at position 250 and/or a Leu at position 428 (EU numbering is used in this paragraph for the constant region) for increasing the half-life of an antibody. Substitution at any or all of positions 234, 235, 236 and/or 237 reduce affinity for Fey receptors, particularly FcyRI receptor (see, e.g., U.S. Patent No. 6,624,821). An alanine substitution at positions 234, 235, and 237 of human IgG 1 can be used for reducing effector functions. Some antibodies have alanine substitution at positions 234, 235 and 237 of human IgG 1 for reducing effector functions. Optionally, positions 234, 236 and/or 237 in human IgG2 are substituted with alanine and position 235 with glutamine (see, e.g., U.S. Patent No. 5,624,821). In some antibodies, a mutation at one or more (e.g., 2, 3, 4, 5, 6, 7, 8, or 9) of positions 241, 264, 265, 270, 296, 297, 322, 329, and 331 by EU numbering of human IgG 1 is used. In some antibodies, a mutation at one or more (e.g., 2 or 3) of positions 318, 320, and 322 by EU numbering of human IgG1 is used. In some antibodies, positions 234 and/or 235 are substituted with alanine and/or position 329 is substituted with glycine. In some antibodies,

positions 234 and 235 are substituted with alanine. In some antibodies, the isotype is human IgG2 or IgG4.

Antibodies can be expressed as tetramers containing two light and two heavy chains, as separate heavy chains, light chains, as Fab, Fab', $F(ab')_2$, and Fv, or as single chain antibodies in which heavy and light chain mature variable domains are linked through a spacer.

Human constant regions show allotypic variation and isoallotypic variation between different individuals, that is, the constant regions can differ in different individuals at one or more polymorphic positions. Isoallotypes differ from allotypes in that sera recognizing an isoallotype bind to a non-polymorphic region of a one or more other isotypes. Thus, for example, another heavy chain constant region is of IgG1 Glm3 with or without the C-terminal lysine. Reference to a human constant region includes a constant region with any natural allotype or any permutation of residues occupying positions in natural allotypes.

Cell Internalizing Modules

As used herein a "cell internalizing module" or "CIM" is a composition that, when covalently or non-covalently linked to an anti-Aβ antibody molecule, results in the internalization into a cell of, at a minimum, the anti-Aβ antibody or an active fragment thereof. Non-limiting features and examples of cell internalizing modules are described herein.

In some embodiments, a CIM is a peptide (e.g., an amino acid sequence). In such examples, the CIM can also be referred to as a cell membrane internalizing peptide or "CMIP" as further defined herein. Exemplary cell membrane internalizing peptides include naturally occurring peptides, and derivatives thereof, as well as, synthetic peptides. Non-limiting examples of CMIPs include M-lycotoxin and derivatives thereof, TAT and derivatives thereof, PEPTH, polyarginine sequences, Penetratin, DPT-C9h, DPT-C9, Transportan, Xentry, Pep-1, Pep-7, Aurein 1.2, MTS, GFWFG, DPV1047, MPG, pVEC, ARF(1_22), BPrPr, MAP, p28, VT5, Bac7, C105Y, PFVYLI, and BR2. In some embodiments, CMIPs include any one of SEQ ID NOs: 101-338.

In some embodiments, a CIM is a non-peptide moiety (e.g., a ligand) that is internalized by a cell (e.g., a mammalian cell). In such examples, a ligand can induce receptor-mediated internalization of an anti-Aβ antibody. Generally, ligand internalization is a receptor-mediated endocytic process in which cells intake extracellular molecules

(including therapeutics) if the ligand binds to its cognate receptor protein on the cell's surface. Receptor-mediated internalization also includes transcytosis.

CIMs can effectuate the internalization of anti-Aβ antibody into a mammalian cell. In general, the process of cellular internalization is broadly classified as endocytosis. Typically, endocytosis pathways can be subdivided into two broader categories phagocytosis and pinocytosis. During pinocytosis the plasma membrane absorbs solutes while during phagocytosis the cell internalizes much larger vesicles. Pinocytosis is generally further subdivided into macropinocytosis, clathrin-dependent endocytosis (e.g., receptor-mediated endocytosis), caveolin-dependent endocytosis, and clathrin/caveolin-independent endocytosis. (See e.g., Marsh, M. Endocytosis, Oxford University Press (2001); Doherty, G.J., and McMahon, H.T., Mechanisms of Endocytosis, Annu. Rev. Biochem., 78:31.1-31.46 (2009); and Xu, Y., et al., Endocytosis and membrane receptor internalization: implication of F-BAR protein Carom, Front Biosci, 22: 1439-1457 (2017), each of which is incorporated herein by reference in their entireties).

Ligand mediated endocytosis is the mechanism by which cells internalize specific macromolecules. In some examples, the cell membrane (e.g., plasma membrane) includes clathrin pits which protrude from the cell membrane to form small vesicles called clathrin-coated vesicles. These clathrin-coated vesicles contain the receptors and the bound macromolecules, i.e., ligands. Then the clathrin-coated vesicles fuse with the early endosomes (vesicles consisting of tubular extensions residing at the periphery of the cell). The endosomes have an acidic environment (pH 6.0-6.2) that facilitates the dissociation of receptors from the ligands. Then, the ingested content is sorted out for either recycling to the plasma membrane or transport to lysosomes for degradation.

Peptide based CIMs (e.g., CMIPs) internalize anti-Aβ antibodies through a variety of mechanisms. In general, CMIPs have been shown to use either endocytosis (e.g., energy-dependent internalization) as described above or direct penetration (e.g., translocation) (energy-independent internalization) as the two major internalization mechanisms. For direct penetration, various mechanisms have been described including the carpet-like model (membrane destabilization) and the pore formation model (barrel-stave). Positively charged CMIPs can interact with negatively charged membrane components such as the phospholipid bilayer, followed by destabilization of the membrane, and crossing of the CMIP and anti-Aβ antibody through the lipid bilayer. Studies have shown that several CMIPs are able to induce and shift between different uptake mechanisms depending on their concentration, cargo,

and/or the cell line used (See e.g., Ruseska, I. and Zimmer, A., Internalization mechanisms of cell penetrating peptides, Beilstein J Nanotechnol, 11: 101-123, (2020)).

Once internalized into a cell, anti-Aβ antibody typically need to escape the endosomal pathway. In general, the endocytic pathway of mammalian cells consists of distinct membrane compartments, which internalize molecules (i.e., cell penetrating agents) from the plasma membrane and recycle membrane-bound receptors back to the surface or sort internalized molecules to various degradation pathways. The main components of the endocytic pathway include early endosomes which are the first compartment of the endocytic pathway. Early endosomes are usually located in the periphery of the cell and receive most types of vesicles coming from the cell surface. They have a characteristic tubulo-vesicular structure and a mildly acidic pH. Early endosomes are principally sorting organelles where many endocytosed ligands dissociate from their receptors in the acid pH of the compartment and are recycled to the cell surface. Early endosomes also sort into transcytotic pathway to later compartments (e.g., late endosomes or lysosomes) via transvesicular compartments.

Late endosomes generally receive endocytosed material *en route* to lysosomes, usually from early endosomes in the endocytic pathway, from trans-Golgi network (TGN) in the biosynthetic pathway, and from phagosomes in the phagocytic pathway. They are acidic (approx. pH 5.5) and are generally thought to mediate a final sorting prior the delivery of material to lysosomes. Lysosomes are the last compartment of the endocytic pathway. Lysosomes break down cellular waste products, fats, carbohydrates, proteins, and other macromolecules into simple compounds which are returned to the cytoplasm as new cell-building materials. Lysosomes include many different types of hydrolytic enzymes which function in an acidic environment (e.g., pH of approximately 4.8).

In some embodiments, the CIM (as defined herein) includes a Cell Membrane Internalizing Peptide (e.g., CMIP4, SEQ ID NO: 143). In some embodiments, the CIM includes a wild-type M-lycotoxin peptide. In some embodiments, the CIM includes an M-lycotoxin derivative (e.g., SEQ ID NO: 104). In some embodiments, the CIM includes a Penetratin amino acid sequence or a derivative thereof (e.g., SEQ ID NO: 110). In some embodiments, the CIM includes a Pepth amino acid sequence or a derivative thereof (e.g., SEQ ID NO: 107). In some embodiments, the CIM includes a polyarginine amino acid sequence (e.g., SEQ ID NO: 113, SEQ ID NO: 114, and/or SEQ ID NO: 115). In some embodiments, the CIM includes more than one polyarginine amino acid sequence (e.g., 2, 3, 4, 5 or more polyarginine amino acid sequences). In some embodiments, the CIM includes three polyarginine amino acid sequences. In some embodiments, the CIM includes a TAT

amino acid sequence (e.g., SEQ ID NO: 101, SEQ ID NO: 102, SEQ ID NO: 109, and/or SEQ ID NO: 117). In some embodiments, the CIM includes more than one TAT amino acid sequence or derivatives thereof (e.g., 2, 3, 4, 5 or more TAT amino acid sequences or derivatives thereof). In some embodiments, the CIM includes three TAT amino acid sequences.

In some embodiments, the CIM includes a macrocycle. Generally, macrocycles are molecules and ions containing a ring of twelve or more atoms. Classic examples include the crown ethers, calixarenes, porphyrins, and cyclodextrins. In some embodiments, the macrocycle is formed by a covalent bond between two amino acid residues of the CIM. In some embodiments, the macrocycle is formed by a disulfide bond between two cysteine residues of the CIM.

In some embodiments, the CIM includes one or more histidine residues.

In some embodiments, the CIM includes a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 101-338. In some embodiments, the CIM is a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 1101-338.

In some embodiments, the CIM is covalently linked to the antibody or antigen-binding antibody fragment thereof. In some embodiments, the CIM is non-covalently linked to the antibody or antigen-binding fragment antibody thereof. In some embodiments, the cell penetrating agent includes a linker connecting the CIM to the antibody. In some embodiments, the linker is covalently linked to both the CIM and the antibody. In some embodiments, the linker is a cleavable linker (e.g., a photocleavable linker, a chemical linker, an enzymatic-cleavable linker, etc.). In some embodiments, the linker is a non-cleavable linker. In some embodiments, the linker includes a polypeptide. In some embodiments, the linker includes one or more glycine residues (e.g., 2, 3, 4, 5 or more glycine residues). In some examples, a linker is a glycine residue followed by a serine residue (GS). In some embodiments, the linker includes a polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 343-346. In some embodiments, the linker is a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 343-346.

In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the C-terminus of the CIM. In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the N-terminus of the CIM. In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the C-terminus of the heavy chain of the CIM. In some

embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the N-terminus of the heavy chain of the CIM. In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the C-terminus of the light chain of the CIM. In some embodiments, the antibody or antigen-binding antibody fragment of the cell penetrating agent is linked to the N-terminus of the light chain of the CIM.

Table 2 below shows a non-limiting, exemplary list of CMIPs including M-lycotoxin and derivatives thereof, TAT and derivatives thereof, PEPTH, polyarginine sequences, Pep1, Pep-7, and others that can be included in any of the CIMs.

Table 2

SEQ ID NO: 101	TAT	GRKKRRQRRRPPQ
SEQ ID NO: 102	TAT 49_57	RKKRRQRRR
SEQ ID NO: 103	WT M-Lyco	IWLTALKFLGKHAAKHLAKQQLSKL
SEQ ID NO: 104	L17E_M-Lyco	IWLTALKFLGKHAAKHEAKQQLSKL
SEQ ID NO: 105	L17D_M-Lyco	IWLTALKFLGKHAAKHDAKQQLSKL
SEQ ID NO: 106	L17Aad	IWLTALKFLGKHAAKHXAKQQLSKL
SEQ ID NO: 107	PEPTH	VKKKKIKAEIKIG
SEQ ID NO: 108	cycR9	CG*RRRRRRRRRG*C
SEQ ID NO: 109	cycTAT1	CG*GRKKRRQRRRPQG*C
SEQ ID NO: 110	Penetratin	RQIKIWFQNRRMKWKK
SEQ ID NO: 111	Penetratin – spacer	RQIKIWFQNRRMKWKKG*
SEQ ID NO: 112	TAT3	GRKKRRQRRRPQGRKKRRQRRRPQGRKKRRQRRRPQG*G*
SEQ ID NO: 113	cycTAT3	CG*G*GRKKRRQRRRPQGRKKRRQRRRPQGRKKRRQRRRPQG*G*C
SEQ ID NO: 114	cycR8 x 3	CG*G*G*RRRRRRRRG*G*G*RRRRRRRRG*G*G*RRRRRRRRG*G*G*C
SEQ ID NO: 115	R8 x 3	CG*G*G*RRRRRRRRG*G*G*RRRRRRRRG*G*G*RRRRRRRRG*G*G*C

SEQ ID NO: 116	R6H4	RRRRRRHHHH
SEQ ID NO: 117	TAT-H4	GRKKRRQRRRPHHHH
SEQ ID NO: 118	DPT-C9h	VKKKKIKREIKI YVETLDDIFEQWAHSEDL
SEQ ID NO: 119	DPC-C9	VKKKKIKREIKI YIETLDGILEQWARSEDL
SEQ ID NO: 120	Transportan	GWTLNSAGYLLGKINLKALAALAKKIL
SEQ ID NO: 121	Xentry	LCLRPVG
SEQ ID NO: 122	HA-TAT	GDIMGEWGNEIFGAIAGFLGYGRKKRRQRRR
SEQ ID NO: 123	Pep-1	KETWWETWWTEWSQPKKKRKV
SEQ ID NO: 124	Aurein 1.2	GLFDIIKKIAESF
SEQ ID NO: 125	MTS	KGEGAAVLLPVLLAAPG
SEQ ID NO: 126	GFWFG	GFWFG
SEQ ID NO: 127	DPV1047	VKRGLKLRHVRPRVTRMDV
SEQ ID NO: 128	MPG	GALFLGFLGAAGSTMGAWSQPKKKRKV
SEQ ID NO: 129	pVEC	LLIILRRRIRKQAHAHSK
SEQ ID NO: 130	ARF(1_22)	MVRRFLVTLRIRRACGPPRVRV
SEQ ID NO: 131	BPrPr	MVKSKIGSWILVLFVAMWSDVGLCKKRP
SEQ ID NO: 132	MAP	KLALKLALKALKAALKLA
SEQ ID NO: 133	p28	LSTAADMQGVVTDGMASGLDKDYLKPDD
SEQ ID NO: 134	VT5	DPKGDPKGVTVTVTVTVTGKGDPKPD
SEQ ID NO: 135	Bac 7	RRIRPRPPRLPRPRPRPLPFPRPG
SEQ ID NO: 136	C105Y	CSIPPEVKFNKPFVYLI
SEQ ID NO: 137	PFVYLI	PFVYLI
SEQ ID NO: 138	Pep-7	SDLWEMMMVSLACQY
SEQ ID NO: 139	BR2	RAGLQFPVGRLLRRLLR

Spacer regions or amino acids are denoted with an asterisk (*) following the amino acid residue (e.g., G).

The present disclosure further provides improved CMIPs for use, among other things, in the context of developing novel cell penetrating agents.

In some embodiments, the CIM includes one or more spacer regions. For example, CIMs comprising any one of SEQ ID NOs: 108, 109, and 111-115 include one or more spacer regions. In some embodiments, the CIM does not include a spacer region. For example, CIMs comprising a polypeptide amino acid sequence selected from: 101-107, 110, and 116-338 do not include a spacer region.

As used herein a spacer refers to an amino acid that does not have catalytic or therapeutic activity in a mammalian cell. For example, a spacer can be a peptide of 1 amino acid to about 10 amino acids (e.g., 1 to about 8 amino acids, 1 to about 6 amino acids, or 1 to about 4 amino acids). In some examples, spacer regions are included in the cell internalizing module sequences. For example, a spacer region can separate amino acids within a cell internalizing module (CIM), e.g., a spacer can be disposed after the first amino acid of a CIM. In some examples, a spacer can be disposed before the final amino acid of a CIM. In some examples, a CIM can have one or more spacer regions (e.g., two spacer regions, three space sequences, four spacer regions, five spacer regions or more). In some examples, a spacer region is a single glycine residue. In some examples, a spacer region is a pair of glycine residues. In some examples, a spacer region is three glycine residues. In some examples, a spacer region is four glycine residues. In some examples, a spacer region is four glycine residues followed by a serine residue. In some embodiments, at least one of the one or more spacer regions includes an amino acid sequence selected from any one of SEQ ID NOs: 339-342. In some embodiments, each of the one or more spacer regions includes an amino acid sequence selected from any one of SEQ ID NOs: 339-3342.

In some embodiments, the CIM comprises a spacer. In some embodiments, the spacer is a spacer in **Table 3**.

Table 3

SEQ ID NO: 339	G
SEQ ID NO: 340	GG
SEQ ID NO: 341	GGG
SEQ ID NO: 342	GGGGS

The present disclosure further provides CMIPs for use, among other things, in the context of developing novel cell-penetrating agents. In some embodiments, the cell-internalizing effects of CMIPs can be improved by designing CMIPs having an α-helical conformation.

In another aspect, the present disclosure provides a polypeptide of a formula selected from Formula (IA) to Formula (ID):

I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L (I-A) (SEQ ID NO: 395);

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-X^{20}-F-X^{22}-S-X^{24}-L (I-B) (SEQ ID NO: 396);

X^1-X^2-L-T-X^5-L-K-X^8-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L (I-C) (SEQ ID NO: 397);

I-W-L-T-X^5-X^6-K-F-S-X^{10}-K-X^{12}-A-A-K-A-X^{17}-X^{18}-K-Q-F-L-X^{23}-X^{24}-X^{25} (I-D) (SEQ ID NO: 395);

wherein:

X^1 is a hydrophobic amino acid residue or a positively-charged amino acid residue;

X^2 is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^3 is an aromatic amino acid residue, a hydrophobic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^4 is a neutral hydrophilic amino acid residue or an aromatic amino acid residue;

X^5 is a hydrophobic amino acid residue or an aromatic amino acid residue;

X^6 is a hydrophobic amino acid residue;

X^7 is a hydrophobic amino acid residue or a positively-charged amino acid;

X^8 is an aromatic amino acid residue;

X^9 is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{10} is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{11} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue;

X^{12} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue;

X^{13} is a neutral hydrophilic amino acid residue or a hydrophobic amino acid residue;

X^{14} is a hydrophobic amino acid residue or a positively-charged amino acid;

X^{15} is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^{16} is a hydrophobic amino acid residue, an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^{17} is a positively-charged amino acid residue or a negatively-charged amino acid residue;

X^{18} is a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{19} is a hydrophobic amino acid residue or a positively-charged amino acid residue;

X^{20} is a neutral hydrophilic amino acid residue or a negative-charged amino acid residue;

X^{21} is a hydrophobic amino acid residue or an aromatic amino acid residue;

X^{22} is absent, a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{23} is absent, a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{24} is absent, an aromatic amino acid residue, or a positively-charged amino acid residue; and

X^{25} is absent or a hydrophobic amino acid; or a pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IA):

I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L (IA) (SEQ ID NO: 395)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IB):

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-X^{20}-F-X^{22}-S-X^{24}-L (IB) (SEQ ID NO: 396)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (IC):

X^1-X^2-L-T-X^5-L-K-X^8-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L (IC) (SEQ ID NO: 397)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP comprises Formula (ID):

I-W-L-T-X^5-X^6-K-F-S-X^{10}-K-X^{12}-A-A-K-A-X^{17}-X^{18}-K-Q-F-L-X^{23}-X^{24}-X^{25} (ID) (SEQ ID NO: 398)

or pharmaceutically acceptable salt thereof.

In some embodiments, the CMIP consists essentially of an amino acid sequence selected from Formula (IA) to (ID). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IA). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IB). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (IC). In some embodiments, the CMIP consists essentially of the amino acid sequence of Formula (ID).

In some embodiments, the CMIP consists of an amino acid sequence selected from Formulas (IA) to (ID). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IA). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IB). In some embodiments, the CMIP consists of the amino acid sequence of

Formulas (IC). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (ID).

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), the polypeptide comprises at least three positively-charged amino acid residues, each of which occupies a position corresponding to X^7, X^{11}, X^{15}, X^{19}, or X^{24}. In some embodiments, the polypeptide comprises at least four positively-charged amino acid residues, each of which occupies a position corresponding to X^7, X^{11}, X^{15}, X^{19}, or X^{24}. In some embodiments, the polypeptide comprises five positively-charged amino acid residues, each of which occupies a position corresponding to X^7, X^{11}, X^{15}, X^{19}, or X^{24}.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), the polypeptide comprises at least four hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}. In some embodiments, the polypeptide comprises at least five hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}. In some embodiments, the polypeptide comprises at least six hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}. In some embodiments, the polypeptide comprises at least seven hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}. In some embodiments, the polypeptide comprises at least eight hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}. In some embodiments, the polypeptide comprises nine hydrophobic amino acid residues, each of which occupies a position corresponding to X^3, X^5, X^6, X^8, X^{13}, X^{14}, X^{16}, X^{18}, or X^{22}.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^1 is a hydrophobic amino acid residue or a positively-charged amino acid residue. In some embodiments, X^1 is a hydrophobic amino acid residue. In some embodiments, X^1 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^1 is an amino acid residue selected from alanine, arginine, aspartic acid, isoleucine, and lysine. In some embodiments, X^1 is isoleucine or lysine. In some embodiments, X^1 is isoleucine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^2 is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue. In some embodiments, X^2 is an aromatic amino acid residue. In

some embodiments, X^2 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^2 is an amino acid residue selected from alanine, arginine, aspartic acid, phenylalanine, tryptophan, and tyrosine. In some embodiments, X^2 is arginine, aspartic acid, phenylalanine, tryptophan, or tyrosine. In some embodiments, X^2 is tryptophan.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^3 is an aromatic amino acid residue, a hydrophobic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue. In some embodiments, X^3 is a hydrophobic amino acid residue. In some embodiments, X^3 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^3 is an amino acid residue selected from alanine, arginine, glutamic acid, leucine, lysine, phenylalanine, and tryptophan. In some embodiments, arginine, glutamic acid, leucine, phenylalanine, or tryptophan. In some embodiments, X^3 is leucine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^4 is a neutral hydrophilic amino acid residue or an aromatic amino acid residue. In some embodiments, X^4 is a neutral hydrophilic amino acid residue. In some embodiments, X^4 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^4 is an amino acid residue selected from alanine, histidine, phenylalanine, threonine, and tryptophan. In some embodiments, X^4 is threonine or tryptophan. In some embodiments, X^4 is threonine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^5 is a hydrophobic amino acid residue or an aromatic amino acid residue. In some embodiments, X^5 is a hydrophobic amino acid residue. In some embodiments, X^5 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^5 is an amino acid residue selected from alanine, arginine, histidine, phenylalanine, and tryptophan. In some embodiments, X^5 is alanine or phenylalanine. In some embodiments, X^5 is alanine.

In some embodiments, X^5 is histidine. In some embodiments, X^5 is histidine; and X^3 is an amino acid residue selected from alanine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^5 is histidine; and X^3 is an amino acid residue selected from alanine, glutamic acid, leucine, lysine, phenylalanine, and tryptophan.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^6 is a hydrophobic amino acid residue. In some embodiments, X^6 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^6 is an amino acid residue selected from alanine, arginine, glutamic acid, isoleucine, and leucine. In some embodiments, X^6 is leucine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^7 is a hydrophobic amino acid residue or a positively charged amino acid. In some embodiments, X^7 is a positively charged amino acid. In some embodiments, X^7 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^7 is an amino acid residue selected from alanine, arginine, aspartic acid, isoleucine, leucine, lysine, and phenylalanine. In some embodiments, X^7 is arginine, isoleucine, leucine, or lysine. In some embodiments, X^7 is lysine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^8 is an aromatic amino acid residue. In some embodiments, X^8 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^8 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, glutamine, histidine, lysine, phenylalanine, serine, and tryptophan. In some embodiments, X^8 is phenylalanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^9 is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively charged amino acid residue. In some embodiments, X^9 is a neutral hydrophilic amino acid residue. In some embodiments, X^9 is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine,

leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^9 is an amino acid residue selected from alanine, arginine, histidine, leucine, phenylalanine, serine, and tryptophan. In some embodiments, X^9 is arginine, histidine, phenylalanine, or serine. In some embodiments, X^9 is serine.

In some embodiments, X^9 is serine; and X^{12} is not histidine. In some embodiments, X^9 is serine; and X^{12} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^9 is serine; and X^{12} is an amino acid residue selected from alanine, arginine, glutamic acid, glutamine, phenylalanine, and tryptophan.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{10} is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{10} is a neutral, hydrophilic amino acid residue. In some embodiments, X^{10} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{10} is an amino acid residue selected from alanine, arginine, glycine, tryptophan, and tyrosine. In some embodiments, X^{10} is arginine, glycine, or tyrosine. In some embodiments, X^{10} is glycine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{11} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{11} is a positively-charged amino acid residue. In some embodiments, X^{11} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{11} is an amino acid residue selected from alanine, arginine, asparagine, glutamic acid, isoleucine, lysine, threonine, and tryptophan. In some embodiments, X^{11} is arginine, isoleucine, lysine, or threonine. In some embodiments, X^{11} is lysine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{12} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{12} is a hydrophobic amino acid residue. In some embodiments, X^{12} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine,

leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{12} is an amino acid residue selected from alanine, glutamic acid, glutamine, histidine, phenylalanine, and tryptophan. In some embodiments, X^{12} is alanine or glutamine. In some embodiments, X^{12} is alanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{13} is a neutral hydrophilic amino acid residue or a hydrophobic amino acid residue. In some embodiments, X^{13} is a hydrophobic amino acid residue. In some embodiments, X^{13} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{13} is an amino acid residue selected from alanine, arginine, aspartic acid, glutamic acid, glycine, leucine, phenylalanine, serine, and tryptophan. In some embodiments, X^{13} is alanine or serine. In some embodiments, X^{13} is alanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{14} is a hydrophobic amino acid residue or a positively-charged amino acid. In some embodiments, X^{14} is a hydrophobic amino acid residue. In some embodiments, X^{14} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{14} is an amino acid residue selected from alanine, arginine, glutamic acid, histidine, isoleucine, leucine, phenylalanine, tryptophan, tyrosine, and valine. In some embodiments, X^{14} is alanine, histidine, leucine, or valine. In some embodiments, X^{14} is alanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{15} is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue. In some embodiments, X^{15} is a positively-charged amino acid residue. In some embodiments, X^{15} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{15} is an amino acid residue selected from alanine, arginine, glutamic acid, lysine, threonine, and tryptophan. In some embodiments, X^{15} is arginine, glutamic acid, or lysine. In some embodiments, X^{15} is lysine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{16} is a hydrophobic amino acid residue, an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue. In some embodiments, X^{16} is a

hydrophobic amino acid residue. In some embodiments, X^{16} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{16} is an amino acid residue selected from alanine, arginine, glutamic acid, glutamine, histidine, lysine, serine, and tryptophan. In some embodiments, X^{16} is not histidine. In some embodiments, X^{16} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{16} is an amino acid residue selected from alanine, arginine, glutamic acid, glutamine, lysine, serine, and tryptophan. In some embodiments, X^{16} is alanine, glutamic acid, or lysine. In some embodiments, X^{16} is alanine.

In some embodiments, for the CMIP of for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{17} is a positively-charged amino acid residue or a negatively-charged amino acid residue. In some embodiments, X^{17} is a negatively-charged amino acid residue. In some embodiments, X^{17} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{17} is an amino acid residue selected from alanine, arginine, aspartic acid, glutamic acid, leucine, phenylalanine, and tryptophan. In some embodiments, X^{17} is arginine or glutamic acid. In some embodiments, X^{17} is glutamic acid.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{18} is a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{18} is a hydrophobic amino acid residue. In some embodiments, X^{18} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{18} is an amino acid residue selected from alanine, arginine, glutamic acid, leucine, methionine, and tryptophan. In some embodiments, X^{18} is alanine, glutamic acid, methionine, or tryptophan. In some embodiments, X^{18} is alanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{19} is a hydrophobic amino acid residue or a positively-charged amino acid residue. In some embodiments, X^{19} is a positively-charged amino acid residue. In some embodiments, X^{19} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine,

phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{19} is an amino acid residue selected from alanine, arginine, leucine, lysine, threonine, and tryptophan. In some embodiments, X^{19} is arginine, leucine, or lysine. In some embodiments, X^{19} is lysine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{20} is a neutral hydrophilic amino acid residue or a negative-charged amino acid residue. In some embodiments, X^{20} is a neutral hydrophilic amino acid residue. In some embodiments, X^{20} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{20} is an amino acid residue selected from alanine, arginine, glutamic acid, glutamine, methionine, serine, and tryptophan. In some embodiments, X^{20} is glutamic acid or glutamine. In some embodiments, X^{20} is glutamine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{21} is a hydrophobic amino acid residue or an aromatic amino acid residue. In some embodiments, X^{21} is an aromatic amino acid residue. In some embodiments, X^{21} is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{21} is an amino acid residue selected from alanine, arginine, glutamic acid, glutamine, lysine, phenylalanine, and tryptophan. In some embodiments, X^{21} is an amino acid residue selected from alanine, arginine, lysine, phenylalanine, and tryptophan. In some embodiments, X^{21} is arginine, phenylalanine, or tryptophan. In some embodiments, X^{21} is phenylalanine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), is absent, a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{22} is a hydrophobic amino acid residue. In some embodiments, X^{22} is either absent or an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{22} is either absent or an amino acid residue selected from alanine, arginine, aspartic acid, leucine, and lysine. In some embodiments, X^{22} is either absent or is leucine. In some embodiments, X^{22} is absent. In some embodiments, X^{22} is Arginine, leucine, or tryptophan. In some embodiments, X^{22} is leucine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{23} is absent, a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue. In some embodiments, wherein X^{23} is a neutral hydrophilic amino acid residue. In some embodiments, X^{23} is either absent or an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{23} is either absent or an amino acid residue selected from alanine, arginine, aspartic acid, glutamic acid, leucine, lysine, threonine, tryptophan, and valine. In some embodiments, X^{23} is either absent or is serine. In some embodiments, X^{23} is absent. In some embodiments, X^{23} is absent, or is arginine, methionine, serine, or tryptophan. In some embodiments, X^{23} is serine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{24} is absent, an aromatic amino acid residue, or a positively-charged amino acid residue. In some embodiments, X^{24} is a positively-charged amino acid residue. In some embodiments, X^{24} is either absent or an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{24} is either absent or an amino acid residue selected from alanine, arginine, and lysine. In some embodiments, X^{24} is either absent or is lysine. In some embodiments, X^{24} is absent. In some embodiments, X^{24} is absent, or is arginine, lysine, or tryptophan. In some embodiments, X^{24} is lysine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{25} is absent or a hydrophobic amino acid. In some embodiments, X^{25} is a hydrophobic amino acid. In some embodiments, X^{25} is either absent or is an amino acid residue selected from alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. In some embodiments, X^{25} is either absent or an amino acid residue selected from alanine, arginine, leucine, and lysine. In some embodiments, X^{25} is either absent or is leucine. In some embodiments, X^{25} is absent. In some embodiments, X^{25} is leucine.

In some embodiments, for the CMIP of Formula (IA), (IB), (IC), and (ID), X^{22}, X^{23}, X^{24}, and X^{25} are each absent.

In another aspect, the present disclosure provides a CMIP comprising an amino acid sequence having a formula selected from Formula (IIA) to Formula (IIC) (SEQ ID NO: 395:

I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L (IIA);

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-Q-F-X^{22}-S-X^{24}-L (IIB);

X^1-X^2-L-T-A-L-K-F-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L (IIC);

or pharmaceutically acceptable salt thereof; wherein X^1 is isoleucine or lysine; X^2 is arginine or tryptophan; X^3 is arginine, glutamic acid, leucine, or tryptophan; X^4 is threonine or tryptophan; X^7 is arginine, isoleucine, or lysine; X^9 is arginine, histidine, or serine; X^{10} is glycine or tyrosine; X^{11} is arginine, isoleucine, lysine, or threonine; X^{12} is alanine or glutamine; X^{13} is alanine or serine; X^{14} is alanine, histidine, leucine, or valine; X^{15} is arginine, glutamic acid, or lysine; X^{16} is alanine or lysine; X^{18} is alanine, methionine, or tryptophan; X^{19} is arginine or lysine; X^{21} is arginine or phenylalanine; X^{22} is arginine, leucine, or tryptophan; X^{23} is arginine or serine; and X^{24} is arginine, lysine, or tryptophan.

In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIA). In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIB). In some embodiments, the CMIP comprises the amino acid sequence of Formulas (IIC).

In some embodiments, the CMIP consists of an amino acid sequence selected from Formulas (IIA) to (IIC). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIA). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIB). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIC).

In some embodiments, the CMIP consists of an amino acid sequence selected from Formulas (IIA) to (IIC). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIA). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIB). In some embodiments, the CMIP consists of the amino acid sequence of Formulas (IIC).

In some embodiments, for the CMIP of Formula (IIA), (IIB), and (IIC), X^1 is Isoleucine. In some embodiments, X^2 is tryptophan. In some embodiments, X^3 is leucine. In some embodiments, X^4 is threonine. In some embodiments, X^7 is lysine. In some embodiments, X^9 is serine. In some embodiments, X^{10} is glycine. In some embodiments, X^{11} is lysine. In some embodiments, X^{12} is alanine. In some embodiments, X^{13} is alanine. In some embodiments, X^{14} is alanine. In some embodiments, X^{15} is lysine. In some embodiments, X^{16} is alanine. In some embodiments, X^{18} is alanine. In some embodiments, X^{19} is lysine. In some embodiments, X^{21} is phenylalanine. In some embodiments, X^{22} is leucine. In some embodiments, X^{23} is serine. In some embodiments, X^{24} is lysine.

Table 4 below shows a non-limiting, exemplary list of CMIPs of the present disclosure. In some embodiments, the CMIP is selected from a CMIP of **Table 4**.

Table 4

SEQ ID NO: 140	CMIP1	IWLTALKFLGKAAAKAEAKQQLSKL
SEQ ID NO: 141	CMIP2:	IWLTALKFSGKAAAKAEAKQQLSKL
SEQ ID NO: 142	CMIP3	IWLTASKFSGKAAAKAEAKQQLSKL
SEQ ID NO: 143	CMIP4	IWLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 144	CMIP5	IWLTALKFSGKAAAKAEAKQWLSKL
SEQ ID NO: 145	CMIP4-1	AWLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 146	CMIP4-2	IALTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 147	CMIP4-3	IWATALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 148	CMIP4-4	IWLAALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 149	CMIP4-5	IWLTGLKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 150	CMIP4-6	IWLTAAKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 151	CMIP4-7	IWLTALAFSGKAAAKAEAKQFLSKL
SEQ ID NO: 152	CMIP4-8	IWLTALKASGKAAAKAEAKQFLSKL
SEQ ID NO: 153	CMIP4-9	IWLTALKFAGKAAAKAEAKQFLSKL
SEQ ID NO: 154	CMIP4-10	IWLTALKFSAKAAAKAEAKQFLSKL
SEQ ID NO: 155	CMIP4-11	IWLTALKFSGAAAAKAEAKQFLSKL
SEQ ID NO: 156	CMIP4-12	IWLTALKFSGKGAAKAEAKQFLSKL
SEQ ID NO: 157	CMIP4-13	IWLTALKFSGKAGAKAEAKQFLSKL
SEQ ID NO: 158	CMIP4-14	IWLTALKFSGKAAGKAEAKQFLSKL
SEQ ID NO: 159	CMIP4-15	IWLTALKFSGKAAAAAEAKQFLSKL
SEQ ID NO: 160	CMIP4-16	IWLTALKFSGKAAAKGEAKQFLSKL
SEQ ID NO: 161	CMIP4-17	IWLTALKFSGKAAAKAAAKQFLSKL
SEQ ID NO: 162	CMIP4-18	IWLTALKFSGKAAAKAEGKQFLSKL
SEQ ID NO: 163	CMIP4-19	IWLTALKFSGKAAAKAEAAQFLSKL
SEQ ID NO: 164	CMIP4-20	IWLTALKFSGKAAAKAEAKAFLSKL
SEQ ID NO: 165	CMIP4-21	IWLTALKFSGKAAAKAEAKQALSKL
SEQ ID NO: 166	CMIP4-22	IWLTALKFSGKAAAKAEAKQFASKL
SEQ ID NO: 167	CMIP4-23	IWLTALKFSGKAAAKAEAKQFLAKL

SEQ ID NO: 168	CMIP4-24	IWLTALKFSGKAAAKAEAKQFLSAL
SEQ ID NO: 169	CMIP4-25	IWLTALKFSGKAAAKAEAKQFLSKA
SEQ ID NO: 170	CMIP4-26b	IWLTALAFSGKAAAKAEAKAFLSKL
SEQ ID NO: 171	CMIP4-27b	IWLTALAFSGKAAAKAEAKQFLSKA
SEQ ID NO: 172	CMIP4-28b	IWLTALKFSGKAAAKAEAKAFLSKA
SEQ ID NO: 173	CMIP4-29b	IWLTALAFSGKAAAKAEAKAFLSKA
SEQ ID NO: 174	CMIP30:	IWLTALRFSGKAAAKAEAKQFLSKL
SEQ ID NO: 175	CMIP31:	IWLTALKFSGRAAAKAEAKQFLSKL
SEQ ID NO: 176	CMIP32:	IWLTALKFSGKAAARAEAKQFLSKL
SEQ ID NO: 177	CMIP33:	IWLTALKFSGKAAAKAEARQFLSKL
SEQ ID NO: 178	CMIP34:	IWLTALKFSGKAAAKAEAKQFLSRL
SEQ ID NO: 179	CMIP35:	IWLTALRFSGRAAAKAEAKQFLSKL
SEQ ID NO: 180	CMIP36:	IWLTALKFSGKAAAKAEARQFLSRL
SEQ ID NO: 181	CMIP37:	IWLTALRFSGRAAARAEAKQFLSKL
SEQ ID NO: 182	CMIP38:	IWLTALKFSGKAAARAEARQFLSRL
SEQ ID NO: 183	CMIP39:	IWLTALRFSGKAAAKAEAKQFLSRL
SEQ ID NO: 184	CMIP40:	IWLTALKFSGKAAAKAEAKQFLRRL
SEQ ID NO: 185	CMIP41:	IWLTALKFSGKAAAKAEAKQFKRRL
SEQ ID NO: 186	CMIP42:	IWLTALKFSGKAAAKAEAKQFKRRK
SEQ ID NO: 187	CMIP43:	IWLTALKFSGKAAAKAEAKQFKRRR
SEQ ID NO: 188	CMIP44:	IWLTALKFSGKAAAKAEAKQFRRRR
SEQ ID NO: 189	CMIP45:	IWLTALKFSGKAAAKADAKQFRRRR
SEQ ID NO: 190	CMIP46:	IWLTALKFSGKAEAKAEAKQELSKE
SEQ ID NO: 191	CMIP47:	IWLTALKFSGKARAKARAKQRLSKR
SEQ ID NO: 192	CMIP48:	SWLTALFSLGKHAITQDAKRRTSRR
SEQ ID NO: 193	CMIP49:	SWLTALFSLGKHAITQEAKRRTSRR
SEQ ID NO: 194	CMIP50:	SWLTALFSLGKHAITQDAKRR
SEQ ID NO: 195	CMIP51:	SWLTALFSLGKHAITQDAKRR
SEQ ID NO: 196	CMIP58	IWLTHLKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 197	CMIP59:	IWLTALKFSGKAAAKKEAKQFLSKL
SEQ ID NO: 198	CMIP60	IWLTHLKFSGKAAAKHE
SEQ ID NO: 199	CMIP61	IWRTALKFSGKAAAKAE

SEQ ID NO: 200	CMIP62:	IWRTARKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 201	CMIP63	IWRTARKFSGKAAAKAEAKQKLSKL
SEQ ID NO: 202	CMIP64:	IWWTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 203	CMIP65	IWLTALKFSWKAAAKAEAKQFLSKL
SEQ ID NO: 204	CMIP66:	IWLTALKFSGKAAVKAE
SEQ ID NO: 205	CMIP67:	IWLTALIFSGKAAAKAEAKQFLSKL
SEQ ID NO: 206	CMIP68	IWLTALKFSGKAAAKAEAKQRLSKL
SEQ ID NO: 207	CMIP69	IWLTALKRSGKAAAKAEAKQFLSKL
SEQ ID NO: 208	CMIP70:	IWLTALKFSGKAALKAEAKQFLSKL
SEQ ID NO: 209	CMIP71	IWLTALLFSGKAAAKAEAKQFLSKL
SEQ ID NO: 210	CMIP72:	IWLTALKFSGKAAAKAFAKQFLSKL
SEQ ID NO: 211	CMIP73:	IWLTALKFRGKAAAKAEAKQFLSKL
SEQ ID NO: 212	CMIP74:	IWLTALKFHGKAAAKAEAKQFLSKL
SEQ ID NO: 213	CMIP75	IWLTALKFHGKHAAKAEAKQFLSKL
SEQ ID NO: 214	CMIP76	IWLTALKFSGKAAAKAEAKQFRSKL
SEQ ID NO: 215	CMIP77:	IWLTALKFSGKAAAKAEAKQFDSKL
SEQ ID NO: 216	CMIP78	IWLTALKFSGKAAAKAEALQFLSKL
SEQ ID NO: 217	CMIP79	IWLTALKFSGKAAAKAEWKQFLSKL
SEQ ID NO: 218	CMIP80	IWLTALKFSGIAAAKAEAKQFLSKL
SEQ ID NO: 219	CMIP81	IWLTALKFSGKAAAKALAKQFLSKL
SEQ ID NO: 220	CMIP82:	IWLTALKFSGKADAKAEAKQFLSKL
SEQ ID NO: 221	CMIP83:	IRLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 222	CMIP84:	IYLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 223	CMIP85	IWLTALKFSGTAAAKAEAKQFLSKL
SEQ ID NO: 224	CMIP86:	IWLTALKFSGKASAKAEAKQFLSKL
SEQ ID NO: 225	CMIP87	IWLTALKFSGKAAHKAEAKQFLSKL
SEQ ID NO: 226	CMIP88	IWLTALKQSGKAAAKAEAKQFLSKL
SEQ ID NO: 227	CMIP89	IWLTALKFSGKQAAKAEAKQFLSKL
SEQ ID NO: 228	CMIP90	IWLTALKFSGKAAAKAEAKQFLMKL
SEQ ID NO: 229	CMIP91:	IWLTALKFSGKAAAKAEAKQFLSK
SEQ ID NO: 230	CMIP92:	IWLTALKFSGKAAAKAEAKQFLM
SEQ ID NO: 231	CMIP93:	IWLTALKFSGKAAAKAEMKQFL

SEQ ID NO: 232	CMIP94	IWLTALKFSGKAAAEAEMKQF
SEQ ID NO: 233	CMIP95	IWLTALFKSGWAAAEAIMKQF
SEQ ID NO: 234	CMIP96	RRLTALFKSGWAAAEAIMKQF
SEQ ID NO: 235	CMIP97	RRLTALFKSGWHAAEAIMKQF
SEQ ID NO: 236	CMIP98	RRLTALFKSGWHAAEHIMKQF
SEQ ID NO: 237	CMIP99	RRLTALFKSGWRAAEHIMKQF
SEQ ID NO: 238	CMIP100	RRLTHLFKSGWRAAEHIMKQF
SEQ ID NO: 239	CMIP101	RRLTRLFKSGWRAAEHIMKQF
SEQ ID NO: 240	CMIP102	RRLTRLFKHGWRAAEHIMKQF
SEQ ID NO: 241	CMIP103	RRLTRLFKHGWRAAEHIWKQF
SEQ ID NO: 242	CMIP104	RRLTRLFKHGWRAAEHIWKSF
SEQ ID NO: 243	CMIP105	RRLTRLFKHGWRFAEHIWKSF
SEQ ID NO: 244	CMIP106	RRLTRLFKHGARFAEHIWKSF
SEQ ID NO: 245	CMIP107	RRLTRLFKHGARFAEHIWTSF
SEQ ID NO: 246	CMIP108	RRLTRLFKHGARGAEHIWTSF
SEQ ID NO: 247	CMIP109	RRLTRLFKHGARGAESIWTSF
SEQ ID NO: 248	CMIP110	RRLTRLFKHGARGLESIWTSF
SEQ ID NO: 249	CMIP111	KWLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 250	CMIP112	IDLTALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 251	CMIP113	IWETALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 252	CMIP114	IWLWALKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 253	CMIP115	IWLTFLKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 254	CMIP116	IWLTAEKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 255	CMIP117	IWLTALLDSGKAAAKAEAKQFESKL
SEQ ID NO: 256	CMIP118	IWLTALKFLGKAAAKAEAKQFLSKL
SEQ ID NO: 257	CMIP119	IWLTALKFSYKAAAKAEAKQFLSKL
SEQ ID NO: 258	CMIP120	IWLTAIKFSGIAAAKAEAKQFVSKL
SEQ ID NO: 259	CMIP121	IWLTALKFSYKAAAKAEAKMFLSKL
SEQ ID NO: 260	CMIP122	IWLTALKFSYKAAYKAEAKQFLSKL
SEQ ID NO: 261	CMIP123	IWLTALKFSYKALAKAEAKQFLSKL
SEQ ID NO: 262	CMIP124	IWLTALKFFGIAAAKAEAKQFLSKL
SEQ ID NO: 263	CMIP125	IWLTALKFSGIFAAKAEAKQFLSKL

SEQ ID NO: 264	CMIP126	IWLTALKFSGIAAFKAEAKQFLSKL
SEQ ID NO: 265	CMIP127	IWLTALKFSGIAFAKAEAKQFLSKL
SEQ ID NO: 266	CMIP128	KWLTALKFSGKAAAKAEAKQFESKL
SEQ ID NO: 267	CMIP129	IDLTALKFSGKAAAKAEAKQELSKL
SEQ ID NO: 268	CMIP130	IWLTALLFSGKAAAKEEAKQFLSKL
SEQ ID NO: 269	CMIP131	IWLTARKFLGKAAAKAEAKQRRSKL
SEQ ID NO: 270	CMIP132	IWLTALKFSYKAAAEAEAKQFLSKL
SEQ ID NO: 271	CMIP133	IWLTALKFSGIAAEKAEAKQFLSKL
SEQ ID NO: 272	CMIP134	IWLTALKFSYKAEAKAEAKMFLSKL
SEQ ID NO: 273	CMIP135	IWLTALKFSYKEAYKAEAKQFLSKL
SEQ ID NO: 274	CMIP136	IWLTALKFSYEALAKAEAKQFLSKL
SEQ ID NO: 275	CMIP137	KWLTALKFSGKAAAKAEAKQFLSKW
SEQ ID NO: 276	CMIP138	IDLTALKFSGKAAAKAEAKQFLSWL
SEQ ID NO: 277	CMIP139	IWETALKFSGKAAAKAEAKQFLWKL
SEQ ID NO: 278	CMIP140	IWLTALLFSGKAAAKAEAWQFLSKL
SEQ ID NO: 279	CMIP141	IWLTALKFLGKAAAKAEWKQFLSKL
SEQ ID NO: 280	CMIP142	IWLTALKFSYKAAAKAWAKQFLSKL
SEQ ID NO: 281	CMIP143	IWLTALKFFGIWAAKAEAKQFLSKL
SEQ ID NO: 282	CMIP144	IWLTALKFSGWFAAKAEAKQFLSKL
SEQ ID NO: 283	CMIP145	IWLTALKFSWIAAFKAEAKQFLSKL
SEQ ID NO: 284	CMIP146	IWLTALKFWGIAFAKAEAKQFLSKL
SEQ ID NO: 285	CMIP147	KWLTALKWSGKAAAKAEAKQFESKL
SEQ ID NO: 286	CMIP148	IDLTALWFSGKAAAKAEAKQELSKL
SEQ ID NO: 287	CMIP149	IWWTAEKFSGKAAAKAFAKQFLSKL
SEQ ID NO: 288	CMIP150	IFLTALLFSGKAAAKEEAKQFLSKL
SEQ ID NO: 289	CMIP151	IWFTALKFLGKAAAKAEAKQFLSKL
SEQ ID NO: 290	CMIP152	IWLTAFKFSYKAEAKAEAKMFLSKL
SEQ ID NO: 291	CMIP153	IWLTALFFSYKEAYKAEAKQFLSKL
SEQ ID NO: 292	CMIP154	IWLTALKHSYEALAKAEAKQFLSKL
SEQ ID NO: 293	CMIP155	RWLTAEKFSGKAAAKAFAKQFLSKL
SEQ ID NO: 294	CMIP156	IRLTALLFSGKAAAKEEAKQFLSKL
SEQ ID NO: 295	CMIP157	IWRTALKFLGKAAAKAEAKQFLSKL

SEQ ID NO: 296	CMIP158	IWLTALKRSYEALAKAEAKQFLSKL
SEQ ID NO: 297	CMIP159	KWLTALKFRGKAAAKAEAKQFLSKW
SEQ ID NO: 298	CMIP160	IDLTALKFSRKAAAKAEAKQFLSWL
SEQ ID NO: 299	CMIP161	IWETALKFSGRAAAKAEAKQFLWKL
SEQ ID NO: 300	CMIP162	IWLTALLFSGKAAARAEAWQFLSKL
SEQ ID NO: 301	CMIP163	IWLTALKFLGKAAAKREWKQFLSKL
SEQ ID NO: 302	CMIP164	IWLTALKFSYKHAAKARAKQFLSKL
SEQ ID NO: 303	CMIP165	IWLTALKFSGIAAAKWERKQFLSKL
SEQ ID NO: 304	CMIP166	IWLTALKFFGIWAAKAEAKQFRSKL
SEQ ID NO: 305	CMIP167	IWLTALKFSGWFAAKAEAKQFLRKL
SEQ ID NO: 306	CMIP168	IWLTALKFWGIAFAKAEAKQFLSKR
SEQ ID NO: 307	CMIP169	IWETALKFSGKAAAKAEAKEFLSKL
SEQ ID NO: 308	CMIP170	IWLWALKFSGKAAAKAEAEQFLSKL
SEQ ID NO: 309	CMIP171	IWLTFLKFSGKAAAKAEEKQFLSKL
SEQ ID NO: 310	CMIP172	IWLTAEKFSGKHAAKAFAKQFLSKL
SEQ ID NO: 311	CMIP173	IWLWALKFSGKAAAKAEAKQFWSKL
SEQ ID NO: 312	CMIP174	IWLTFLKFSGKAAAKAEAKQWLSKL
SEQ ID NO: 313	CMIP175	IWLTAEKFSGKHAAKAEAKWFLSKL
SEQ ID NO: 314	CMIP176	IWLTALKFSGIAAAKWEAKQFLSKL
SEQ ID NO: 315	CMIP177	IWLTALKFSYKAAAWAEAKMFLSKL
SEQ ID NO: 316	CMIP178	IWLTALKFSYKAAWKAEAKQFLSKL
SEQ ID NO: 317	CMIP179	IWLTALKFSYKAWAKAEAKQFLSKL
SEQ ID NO: 318	CMIP180	IWETAWKFSGKAAAKAEAKEFLSKL
SEQ ID NO: 319	CMIP181	IWLWWLKFSGKAAAKAEAEQFLSKL
SEQ ID NO: 320	CMIP182	IWLWFLKFSGKHAAKAEEKQFLSKL
SEQ ID NO: 321	CMIP183	IWLFALKFSYKAAAEAEAKQFLSKL
SEQ ID NO: 322	CMIP184	IWLTFLKFSGIAAEKAEAKQFLSKL
SEQ ID NO: 323	CMIP185	IWLRALKFSYKAAAEAEAKQFLSKL
SEQ ID NO: 324	CMIP186	IWLTRLKFSGIAAEKAEAKQFLSKL
SEQ ID NO: 325	CMIP187	IWLTARKFSYKAEAKAEAKMFLSKL
SEQ ID NO: 326	CMIP188	IWLTALDFSYKEAYKAEAKQFLSKL
SEQ ID NO: 327	CMIP189	IWLWALKFSGKRAAKAEAKQFWSKL

SEQ ID NO: 328	CMIP190	IWLTFLKFSGKARAKAEAKQWLSKL
SEQ ID NO: 329	CMIP191	IWLTAEKFSGKAARKAEAKWFLSKL
SEQ ID NO: 330	CMIP192	IWLTALKFSYKAAAWAEARMFLSKL
SEQ ID NO: 331	CMIP193	IWLTALKFSYKAAWKAEAKRFLSKL
SEQ ID NO: 332	CMIP194	IWLTALKFSYKAWAKAEAKQRLSKL
SEQ ID NO: 333	CMIP195	IWLTALKFSWIAAFKAEAKQFLSRL
SEQ ID NO: 334	CMIP196	DWETADKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 335	CMIP197	IWLTALKFSGKAAAKAEAKQEDSKD
SEQ ID NO: 336	CMIP198	RWKTARKFSGKAAAKAEAKQFLSKL
SEQ ID NO: 337	CMIP199	IWLTALKFSGKAAAKAEAKQKRSKR
SEQ ID NO: 338	CMIP200	IWRTAKKRSGKAAAKAEAKQRLSKL

In some embodiments, CMIPs of the present disclosure provide the additional benefit of having reduced predicted immunogenicity compared to other cell-penetrating peptides. One method of calculating immunogenicity of CMIP sequences is to assign each sequence an Immunogenicity Units (IU), as explained in Example 2, below. In some embodiments, the CMIP comprises an immunogenicity value of 2.0 IU or less (e.g., 1.8 IU or less, 1.6 IU or less, 1.4 IU or less, 1.2 IU or less, or 1.0 IU or less). In some embodiments, the CMIP comprises an immunogenicity value of 1.6 IU or less. In some embodiments, the CMIP comprises an immunogenicity value of from 0 to 2.0 IU (e.g., from 0 to 1.8 IU, from 0 to 1.6 IU, from 0 to 1.4 IU, from 0 to 1.2 IU, from 0 to 1.0 IU, from 0 to 0.8 IU, from 0 to 0.6 IU, from 0 to 0.4 IU, from 0 to 0.2 IU). In some embodiments, the CMIP comprises an immunogenicity value of from 0 to 1.6 IU.

Linkers

In various aspects of the present disclosure, the anti-Aβ cell penetrating agents further comprise a linker connecting the CIM to the anti-Aβ antibody. Linkers of the present disclosure may connect the CIM to the anti-Aβ antibody via either a covalent linkage or a non-covalent linkage. In some embodiments, the CIM is covalently linked to the anti-Aβ antibody via a linker (i.e., a covalent linker). In some embodiments, the CIM is non-covalently linked to the anti-Aβ antibody via the linker (i.e., a non-covalent linker). In some embodiments, the CIM is covalently linked to the linker. In some embodiments, the anti-Aβ

antibody is covalently linked to the linker. In some embodiments, the linker is covalently linked to both the CPP and the anti-Aβ antibody.

In some embodiments, the linker is a non-covalent linker. A non-covalent linkage can be achieved using an affinity pair that interact strongly in a noncovalent manner (e.g., by hydrogen bonding, ionic bonding, van Der Waals interactions, or any combination thereof). Numerous examples of non-covalent linkages are known in the art. For example, biotin and a biotin-binding agent (e.g., streptavidin) are one example of an affinity pair. For example, by connecting biotin to one side of the CPA (e.g., the CIM), and connecting the biotin-binding agent to the other side of the CPA (e.g., the anti-Aβ antibody), a non-covalent linkage can be achieved between the CIM and the anti-Aβ antibody. In some embodiments, a linker comprises a pair of affinity domains (e.g., a first domain of the pair of affinity domains can be interleukin-15 and a second domain of the pair of affinity domains can be a sushi domain of interleukin-15 receptor alpha).

In some embodiments, the linker is a covalent linker. Many covalent linkers are known in the art. For example, in some embodiments, the covalent linker comprises an organic linker (e.g., an alkylene chain, a polyethylene glycol chain, a polyacrylamides, a polyacrylic acid, a polyvinyl alcohol, or a polyethyleneimine chain). In some cases, the covalent linker comprises an unsubstituted or substituted alkylene chain (including, for example, a polyvinyl alcohol chain, a polyacrylamide chain, or a polyacrylic acid chain). In some cases, the covalent linker comprises an unsubstituted or substituted heteroalkylene chain (e.g., a polyethylene glycol chain or a polyethyleneimine chain). In various embodiments, the linker is a straight chain linker or a branched linker. In some such embodiments, the branched linker allows incorporation of two or more CIMs and/or anti-Aβ antibodies into a CPA (e.g., a dendrimer linker structure).

In some embodiments, the linker comprises an amino acid residue. In some embodiments, the linker comprises a polypeptide. In some exemplary embodiments, a linker can be a peptide of about 1 amino acids to about 50 amino acids (e.g., about 1 amino acids to about 40, or about 1 amino acids to about 30 amino acids). In some exemplary embodiments, a linker can be a peptide of about 1 amino acids to about 25 amino acids (e.g., about 1 amino acids to about 20, or about 1 amino acids to about 12 amino acids). In some exemplary embodiments, a linker can be a peptide of about 1 amino acids to about 10 amino acids (e.g., about 1 amino acids to about 6, or about 1 amino acids to about 7 amino acids). In some exemplary embodiments, a linker can be a peptide of about 1 amino acids to about 5 amino acids (e.g., about 1 amino acids to about 4, or about 1 amino acids to about 3 amino acids).

In some exemplary embodiments, a linker can be a peptide of about 3 amino acids to about 20 amino acids (e.g., about 3 amino acids to about 15, or about 3 amino acids to about 12 amino acids). In some exemplary embodiments, a linker can be a peptide of about 3 amino acids to about 10 amino acids (e.g., about 3 amino acids to about 8, or about 3 amino acids to about 6 amino acids).

In some embodiments, the linker comprises a glycine residue. In some embodiments, the linker comprises two or more glycine residues. In some embodiments, the linker comprises two or more consecutive glycine residues (e.g., two to three consecutive glycine residues, two to four consecutive glycine residues, two to five consecutive glycine residues, or two to six consecutive glycine residues. In some embodiments, the linker comprises two, three, four, five, or six consecutive glycine residues. In some embodiments, the linker comprises a serine residue. In some embodiments, the linker comprises an amino acid sequence selected from GS, GGG, GGGGS, and GGGGSGGGGS. In some embodiments, the linker comprises an amino acid sequence of GGGGS.

In some embodiments, the CIM comprises a linker. In some embodiments, the linker is a linker in **Table 5**.

Table 5.

SEQ ID NO: 343	GS
SEQ ID NO: 344	GGG
SEQ ID NO: 345	GGGGS
SEQ ID NO: 346	GGGGSGGGGS

Exemplary Anti-Aβ Cell Penetrating Agents

Various components of cell penetrating agents have been disclosed herein, including anti-Aβ antibodies, linkers and cell internalizing moieties (e.g., CMIPs). One of ordinary skill will understand how to combine these features to arrive a functional anti-Aβ cell penetrating agents. Also described herein are cell penetrating agents having the CMIP, the optional linker, and the light and/or heavy chain of the anti-Aβ antibody expressed as a single polypeptide (i.e., a fusion protein).

In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394. In some

embodiments, the anti-Aβ CPA includes a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394. In some embodiments, the anti-Aβ CPA includes a polypeptide sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394.

In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393. In some embodiments, the anti-Aβ CPA includes a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393. In some embodiments, the anti-Aβ CPA comprises a polypeptide sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

In some embodiments, the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein: the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 349 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 350; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 351 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 352; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 353 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 354; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 355 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 356; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 357 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 358; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 359 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 360; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 361 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 362;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 363 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 364; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 365 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 366; the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 367 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 368; or the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 394 and the second polypeptide comprises a sequence that is at least 95% identical to any one of SEQ ID NOs: 369-393.

In some embodiments, the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein: the first polypeptide comprises SEQ ID NO: 349 and the second polypeptide comprises SEQ ID NO: 350; the first polypeptide comprises SEQ ID NO: 351 and the second polypeptide comprises SEQ ID NO: 352; the first polypeptide comprises SEQ ID NO: 353 and the second polypeptide comprises SEQ ID NO: 354; the first polypeptide comprises SEQ ID NO: 355 and the second polypeptide comprises SEQ ID NO: 356; the first polypeptide comprises SEQ ID NO: 357 and the second polypeptide comprises SEQ ID NO: 358; the first polypeptide comprises SEQ ID NO: 359 and the second polypeptide comprises SEQ ID NO: 360; the first polypeptide comprises SEQ ID NO: 361 and the second polypeptide comprises SEQ ID NO: 362; the first polypeptide comprises SEQ ID NO: 363 and the second polypeptide comprises SEQ ID NO: 364; the first polypeptide comprises SEQ ID NO: 365 and the second polypeptide comprises SEQ ID NO: 366; the first polypeptide comprises SEQ ID NO: 367 and the second polypeptide comprises SEQ ID NO: 368; or the first polypeptide comprises SEQ ID NO: 394 and the second polypeptide comprises any one of SEQ ID NOs: 369-393.

Cell-penetrating agents can also be administered in the form of nucleic acids encoding the cell penetrating agent or the antibody present within a cell penetrating agent. If both heavy and light chains are present, the chains are preferably linked as a single chain antibody.

IV. Nucleic Acids, Vectors, and Host Cells

The present disclosure provides nucleic acids encoding at least a portion of any of the cell penetrating agents described herein. For example, the nucleic acids can encode any of the CIMs, linkers, and/or spacers described herein in addition to any of the heavy chains and/or light chains described herein. In some embodiments, the nucleic acids encodes a first

polypeptide comprising a heavy chain of an antibody that binds specifically to Aβ, the first polypeptide comprising any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394. In some embodiments, the nucleic acids encode a second polypeptide comprising a light chain of an antibody that binds specifically to Aβ, the second polypeptide comprising any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

In some embodiments, the nucleic acids encodes a first polypeptide comprising a heavy chain of an antibody that binds specifically to Aβ, the first polypeptide comprising any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394 and a second polypeptide comprising a light chain of an antibody that binds specifically to Aβ, the second polypeptide comprising any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 349 and a second polypeptide comprising SEQ ID NO: 350. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 351 and a second polypeptide comprising SEQ ID NO: 352. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 353 and a second polypeptide comprising SEQ ID NO: 354. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 355 and a second polypeptide comprising SEQ ID NO: 356. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 357 and a second polypeptide comprising SEQ ID NO: 358. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 359 and a second polypeptide comprising SEQ ID NO: 360. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 361 and a second polypeptide comprising SEQ ID NO: 362. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 363 and a second polypeptide comprising SEQ ID NO: 364. In some embodiments,

the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 365 and a second polypeptide comprising SEQ ID NO: 366. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 367 and a second polypeptide comprising SEQ ID NO: 368. In some embodiments, the nucleic acid encodes a cell penetrating agent comprising a first polypeptide comprising SEQ ID NO: 394 and a second polypeptide comprising any one of SEQ ID NOs: 369-393.

Optionally, the nucleic acids further encode a signal peptide and can be expressed with the signal peptide linked to the constant region (with or without a CMIP). Coding sequences of nucleic acids can be operably linked with regulatory sequences to ensure expression of the coding sequences, such as a promoter, enhancer, ribosome binding site, transcription termination signal, and the like. The nucleic acids encoding heavy and light chains can occur in isolated form or can be cloned into one or more vectors. The nucleic acids can be synthesized by, for example, solid state synthesis or PCR of overlapping oligonucleotides. Nucleic acids encoding heavy and light chains can be joined as one contiguous nucleic acid, e.g., within an expression vector, or can be separate, e.g., each cloned into its own expression vector. In some embodiments, the nucleic acid is codon-optimized for expression in a host cell.

A number of methods are known for producing chimeric and humanized antibodies using an antibody-expressing cell line *(e.g.,* hybridoma) that can be used for the production of anti-Aβ CPAs of the present disclosure. For example, the immunoglobulin variable regions of antibodies can be cloned and sequenced using well known methods. In one method, the heavy chain variable VH region is cloned by RT-PCR using mRNA prepared from hybridoma cells. Consensus primers are employed to the VH region leader peptide encompassing the translation initiation codon as the 5' primer and a g2b constant regions specific 3' primer. Exemplary primers are described in U.S. patent publication US 2005/0009150 by Schenk et al. (hereinafter "Schenk"). The sequences from multiple, independently derive clones can be compared to ensure no changes are introduced during amplification. The sequence of the VH region can also be determined or confirmed by sequencing a VH fragment obtained by 5' RACE RT-PCR methodology and the 3' g2b specific primer.

The light chain variable VL region for anti-Aβ CPAs can be cloned in an analogous manner. In one approach, a consensus primer set is designed for amplification of VL regions using a 5' primer designed to hybridize to the VL region encompassing the translation

initiation codon and a 3' primer specific for the Ck region downstream of the V-J joining region. In a second approach, 5'RACE RT-PCR methodology is employed to clone a VL encoding cDNA. Exemplary primers are described in Schenk, supra. The cloned sequences are then combined with sequences encoding human (or other non-human species) constant regions.

Also provided herein are vectors including any of the nucleic acids described herein operably linked to one or more regulatory sequences to effect expression in a mammalian cell of any of the cell penetrating agents described herein.

Also provided herein are vectors including a nucleic acid encoding a mature heavy chain variable domain (e.g., any of the heavy chain variable domains described herein with or without the CMIP) and a light chain variable domain (e.g., any of the light chain variable domains described herein with or without the CMIP) operably linked to one or more regulatory sequences to effect expression in a mammalian cell of any of the antibodies or antigen-binding fragments described herein.

In one approach, the heavy and light chain variable regions are re-engineered to encode splice donor sequences downstream of the respective VDJ or VJ junctions and are cloned into a mammalian expression vector, such as pCMV-hγ1 for the heavy chain and pCMV-Mcl for the light chain. These vectors encode human γ1 and Ck constant regions as exonic fragments downstream of the inserted variable region cassette. Following sequence verification, the heavy chain and light chain expression vectors can be co-transfected into CHO cells to produce chimeric antibodies. Conditioned media is collected 48 hours post-transfection and assayed by western blot analysis for antibody production or ELISA for antigen binding. The chimeric antibodies are humanized as described above.

Chimeric, veneered, humanized, and human antibodies are typically produced by recombinant expression, which can be used for the production of anti-Aβ CPAs of the present disclosure. Recombinant polynucleotide constructs typically include an expression control sequence operably linked to the coding sequences of antibody chains, including naturally associated or heterologous expression control elements, such as a promoter. The expression control sequences can be promoter systems in vectors capable of transforming or transfecting eukaryotic or prokaryotic host cells. Once the vector has been incorporated into the appropriate host, the host is maintained under conditions suitable for high level expression of the nucleotide sequences and the collection and purification of the cross-reacting antibodies.

Thus, provided herein are host cells transformed with any of the vectors described herein. Also provided herein are host cells including any of the nucleic acids described herein.

Expression vectors are typically replicable in the host organisms either as episomes or as an integral part of the host chromosomal DNA. Commonly, expression vectors contain selection markers, e.g., ampicillin resistance or hygromycin resistance, to permit detection of those cells transformed with the desired DNA sequences.

E. coli is one prokaryotic host useful for expressing antibodies, particularly antibody fragments. Microbes, such as yeast, are also useful for expression. *Saccharomyces* is a yeast host with suitable vectors having expression control sequences, an origin of replication, termination sequences, and the like as desired. Typical promoters include 3-phosphoglycerate kinase and other glycolytic enzymes. Inducible yeast promoters include, among others, promoters from alcohol dehydrogenase, isocytochrome C, and enzymes responsible for maltose and galactose utilization.

Mammalian cells can be used for expressing nucleotide segments encoding immunoglobulins or fragments thereof. See, Winnacker, From Genes to Clones, (VCH Publishers, NY, 1987). A number of suitable host cell lines capable of secreting intact heterologous proteins have been developed, and include CHO cell lines, various COS cell lines, HeLa cells, HEK293 cells, L cells, and non-antibody-producing myelomas including Sp2/0 and NS0. The cells can be non-human. Expression vectors for these cells can include expression control sequences, such as an origin of replication, a promoter, an enhancer (Queen *et al., Immunol. Rev.* 89:49 (1986)), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. Expression control sequences can include promoters derived from endogenous genes, cytomegalovirus, SV 40, adenovirus, bovine papillomavirus, and the like. *See* Co *et al., J. Immunol.* 148: 1149 (1992). In some embodiments, the promoter is a eukaryotic promoter.

Alternatively, antibody coding sequences can be incorporated in transgenes for introduction into the genome of a transgenic animal and subsequent expression in the milk of the transgenic animal (see, e.g., U.S. Pat. No. 5,741,957; U.S. Pat. No. 5,304,489; and U.S. Pat. No. 5,849,992). Suitable transgenes include coding sequences for light and/or heavy chains operably linked with a promoter and enhancer from a mammary gland specific gene, such as casein or beta lactoglobulin.

The vectors containing the DNA segments of interest can be transferred into the host cell by methods depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment, electroporation, lipofection, biolistics, or viral-based transfection can be used for other cellular hosts. Other methods used to transform mammalian cells include the use of polybrene, protoplast fusion, liposomes, electroporation, and micro injection. For production of transgenic animals, trans genes can be microinjected into fertilized oocytes or can be incorporated into the genome of embryonic stem cells, and the nuclei of such cells transferred into enucleated oocytes.

Having introduced vector(s) encoding antibody heavy and light chains into cell culture, cell pools can be screened for growth productivity and product quality in serum-free media. Top-producing cell pools can then be subjected of FACS-based single-cell cloning to generate monoclonal lines. Specific productivities above 50 pg or 100 pg per cell per day, which correspond to product titers of greater than 7.5 g/L culture, can be used. Antibodies produced by single cell clones can also be tested for turbidity, filtration properties, PAGE, IEF, UV scan, HPSEC, carbohydrate-oligosaccharide mapping, mass spectrometry, and binding assay, such as ELISA or Biacore. A selected clone can then be banked in multiple vials and stored frozen for subsequent use.

Once expressed, antibodies can be purified according to standard procedures of the art, including protein A capture, HPLC purification, column chromatography, gel electrophoresis and the like (See generally, Scopes, *Protein Purification* (Springer-Verlag, NY, 1982)).

Methodology for commercial production of antibodies can be employed for the production of anti-Aβ CPAs of the present disclosure, including codon optimization, selection of promoters, selection of transcription elements, selection of terminators, serum-free single cell cloning, cell banking, use of selection markers for amplification of copy number, CHO terminator, or improvement of protein titers (see, e.g., U.S. Patent No. 5,786,464; U.S. Patent No. 6,114,148; US 6,063,598; U.S. Patent No. 7,569,339; W02004/050884; W02008/012142; W02008/012142; W02005/019442; W02008/107388; W02009/027471; and U.S. Patent No. 5,888,809).

The DNA can be delivered in naked form (i.e., without colloidal or encapsulating materials). Alternatively, a number of viral vector systems can be used including retro viral systems (see, e.g., Lawrie and Tumin, Cur. Opin. Genet. Develop. 3, 102-109 (1993)); adenoviral vectors (see, e.g., Bett et al, J. Virol. 67, 591 1 (1993)); adeno-associated virus

vectors (see, e.g., Zhou et al., J. Exp. Med. 179, 1867 (1994)), viral vectors from the pox family including vaccinia virus and the avian pox viruses, viral vectors from the alpha virus genus such as those derived from Sindbis and Semliki Forest Viruses (see, e.g., Dubensky et al., J. Virol. 70, 508-519 (1996)), Venezuelan equine encephalitis virus (see U.S. Patent No. 5,643,576) and rhabdoviruses, such as vesicular stomatitis virus (see WO 96/34625) and papillomaviruses (Ohe et al., *Human Gene Therapy* 6:325-333 (1995); Woo et al., WO 94/12629 and Xiao & Brandsma, *Nucleic Acids. Res.* 24:2630-2622 (1996)).

DNA encoding an immunogen, or a vector containing the same, can be packaged into liposomes. Suitable lipids and related analogs are described by U.S. Patent No. 5,208,036, U.S. Patent No. 5,264,618, U.S. Patent No. 5,279,833, and U.S. Patent No. 5,283,185. Vectors and DNA encoding an immunogen can also be adsorbed to or associated with particulate carriers, examples of which include polymethyl methacrylate polymers and polylactides and poly(lactide-co-glycolides) (see, e.g., McGee et al., *J. Micro Encap.* 1996).

V. Additional Conjugates

Cell penetrating agents of the present disclosure comprising conjugated antibodies and antigen-binding antibody fragments that specifically bind to antigens such as Aβ (e.g., human Aβ), are useful in detecting the presence of Aβ; monitoring and evaluating the efficacy of therapeutic agents being used to treat patients diagnosed with Inclusion Body Myositis (IBM) or sporadic Inclusion Body Myositis (sIBM) in a patient.

The cell penetrating agents described herein, can be further conjugated with other therapeutic moieties, other proteins, other antibodies, and/or detectable labels. See WO 03/057838; U.S. Patent No. 8,455,622. Such therapeutic moieties can be any agent that can be used to treat, combat, ameliorate, prevent, or improve an unwanted condition or disease in a patient, such as Inclusion Body Myositis.

For example, such cell penetrating agents can be linked to radioisotopes. Examples of radioisotopes include, for example, yttrium^{90} (90Y), indium^{111} (111In), ^{131}1, ^{99}mTc, radiosilver-111, radiosilver-199, and Bismuth^{213}. Linkage of radioisotopes to antibodies or antigen-binding antibody fragments may be performed with conventional bifunction chelates. For radiosilver-111 and radiosilver-199 linkage, sulfur-based linkers may be used. See Hazra et al., *Cell Biophys.* 24-25:1-7 (1994). Linkage of silver radioisotopes may involve reducing the immunoglobulin with ascorbic acid. For radioisotopes such as 111In and 90Y, ibritumomab tiuxetan can be used and will react with such isotopes to form 111In -

ibritumomab tiuxetan and 90Y-ibritumomab tiuxetan, respectively. See Witzig, *Cancer Chemother. Pharmacol.*, 48(Suppl 1):S91-S95 (2001).

Some such antibodies or antigen-binding antibody fragments can be linked to other therapeutic moieties. Such therapeutic moieties can be, for example, cytotoxic, cytostatic, immunomodulatory, neurotrophic, or neuroprotective. For example, antibodies and antigen-binding antibody fragments can be conjugated with toxic chemotherapeutic drugs such as maytansine, geldanamycin, tubulin inhibitors such as tubulin binding agents *(e.g.,* auristatins), or minor groove binding agents such as calicheamicin. Other representative therapeutic moieties include agents known to be useful for treatment, management, or amelioration of Inclusion Body Myositis.

Antibodies or antigen-binding antibody fragments can also be coupled with a detectable label. Such antibodies and antigen-binding antibody fragments can be used, for example, for diagnosing Inclusion Body Myositis. Representative detectable labels that may be coupled or linked to an antibody or antigen-binding antibody fragment include various enzymes, such as horseradish peroxidase, alkaline phosphatase, betagalactosidase, or acetylcholinesterase; prosthetic groups, such streptavidin/biotin and avidin/biotin; fluorescent materials, such as umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as luminol; bioluminescent materials, such as luciferase, luciferin, and aequorin; radioactive materials, such as radiosilver-111, radiosilver-199, Bismuth^{213}, iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{5}S), tritium (^{3}H), indium (^{115}In ^{113}In ^{112}In ^{111}In), technetium (^{99}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru, ^{68}Ge, ^{57}Co, ^{65}ZN, ^{85}SR, ^{32}P, ^{153}Gd, ^{169}Yb, ^{51}CR, ^{54}Mn, ^{75}Se, ^{113}Sn, and ^{117}Sn; positron emitting metals using various positron emission tomographies; nonradioactive paramagnetic metal ions; and molecules that are radiolabelled or conjugated to specific radioisotopes.

Therapeutic moieties, other proteins, other antibodies, and/or detectable labels may be coupled or conjugated, directly or indirectly through an intermediate *(e.g.,* a linker), to an antibody or antigen-binding antibody fragment of the invention. See e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting of Drugs in Cancer Therapy," in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery," in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers of

Cytotoxic Agents in Cancer Therapy: A Review," in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475- 506 (1985); "Analysis, Results, and Future Prospective of The Therapeutic Use of Radio labeled Antibody in Cancer Therapy," in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985); and Thorpe et al., *Immunol. Rev.*, 62:119-58 (1982). Suitable linkers include, for example, cleavable and noncleavable linkers. Different linkers that release the coupled therapeutic moieties, proteins, antibodies, and/or detectable labels under acidic or reducing conditions, on exposure to specific proteases, or under other defined conditions can be employed.

In some embodiments, the cell penetrating agent is also conjugated to a therapeutic, cytotoxic, cytostatic, immunomodulatory, neurotrophic, or neuroprotective agent as described herein. For example, antibodies present in the cell penetrating agent can be coupled (i.e., conjugated) with a therapeutic moiety, such as a cytotoxic agent, a radiotherapeutic agent, an immunomodulator, or a second antibody (*e.g.*, to form an antibody heteroconjugate). Representative therapeutic moieties include agents known to be useful for treatment, management, or amelioration of Aβ-related diseases or symptoms of Aβ-related diseases.

Therapeutic moieties and/or detectable substances may be coupled or conjugated directly to any of the murine, chimeric, or humanized antibodies described herein through an intermediate (*e.g.*, a linker) using techniques known in the art. See e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy," in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery," in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review," in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy," in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., Immunol. Rev., 1982, 62:119-58.

Cell-penetrating agents used in the disclosed formulations also include modified forms of murine, chimeric, or humanized antibodies, which have increased *in vivo* half-lives relative to the corresponding unmodified antibodies. Such modified forms may be prepared, for example, by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a

cellular ligand or other protein, etc. As one example, representative methods for antibody half-life extension are described in PCT International Publication No. WO 02/060919.

VI. Pharmaceutical Compositions

The present disclosure also provides pharmaceutical compositions and products. Thus, provided herein are pharmaceutical compositions including any of the cell penetrating agents described herein and a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions for parenteral administration are preferably sterile and substantially isotonic and manufactured under GMP conditions. Pharmaceutical compositions can be provided in unit dosage form (i.e., the dosage for a single administration). Pharmaceutical compositions can be formulated using one or more physiologically acceptable carriers, diluents, excipients or auxiliaries. The formulation depends on the route of administration chosen. For injection, cell penetrating agents can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hank's solution, Ringer's solution, or physiological saline or acetate buffer (to reduce discomfort at the site of injection). The solution can contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, cell penetrating agents can be in lyophilized form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

The anti-Aβ cell penetrating agents described herein can be present in any pharmaceutically acceptable excipient or carrier. For example, the anti-Aβ cell penetrating agents described herein can be present in a buffer. The buffer can have a pH from about 6 to about 7. Typically, the formulations are sterile, for example, as accomplished by sterile filtration using a 0.2 μm or a 0.22 μm filter. The formulations disclosed herein are also generally stable upon freezing and thawing.

In some embodiments, it can be desirable to use a pharmaceutical composition comprising any of the cell penetrating agents described herein in an *ex vivo* or *in vitro* method. For example, the method can be for a non-diagnostic and/or non-therapeutic purposes. In such instances, samples such as cells, tissues, and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising any of the cell penetrating agents described herein.

In prophylactic applications, a cell penetrating agent (e.g., or a nucleic acid or a vector encoding any of the cell penetrating agent) or a pharmaceutical composition of the same is administered to a patient susceptible to, or otherwise at risk of a disease such IBM in regime

(dose, frequency and route of administration) effective to reduce the risk, lessen the severity, or delay the onset of at least one sign or symptom of the amyloidogenic disease (e.g., IBM). In particular, the regime is preferably effective to inhibit or delay Aβ aggregates (e.g., human Aβ aggregates) in muscle tissue, and/or inhibit or delay its toxic effects and/or inhibit/or delay development of motor skill deficits.

In therapeutic applications, a cell penetrating agent is administered to a patient suspected of, or already suffering from a disease (e.g., IBM) in a regime (dose, frequency and route of administration) effective to ameliorate or at least inhibit further deterioration of at least one sign or symptom of the disease. In particular, the regime is preferably effective to reduce or at least inhibit further increase of cytoplasmic levels of Aβ (e.g., human Aβ) and/or aggregates formed from it, associated toxicities and/or motor skill deficits.

A regime is considered therapeutically or prophylactically effective if an individual treated patient achieves an outcome more favorable than the mean outcome in a control population of comparable patients not treated by methods disclosed herein.

VII. Treatment Regimens

As used herein, the terms "treat" and "treatment" refer to the alleviation or amelioration of one or more symptoms or effects associated with the disease, prevention, inhibition or delay of the onset of one or more symptoms or effects of the disease, lessening of the severity or frequency of one or more symptoms or effects of the disease, and/or increasing or trending toward desired outcomes as described herein.

Desired outcomes of the treatments disclosed herein vary according to the patient profile and are readily determinable to those skilled in the art. Desired outcomes include an improvement in the patient's health status. Generally, desired outcomes include measurable indices such as reduction or clearance of pathologic Aβ in IBM disease.

Provided herein are methods of delivering the antibody that specifically binds to Aβ into a cell, including contacting any of the anti-Aβ CPAs described herein with the cell, thereby resulting in the internalization into the cell of, at a minimum, an antigen-binding fragment of the antibody. In some embodiments, the method includes transfer of, at a minimum, an antigen-binding fragment of the antibody, to the cytosol of the cell.

Also provided herein are method of binding an intracellular Aβ protein in a cell, the method including contacting any of the anti-Aβ CPAs described herein with the cell, thereby resulting in the internalization of and transfer to the cytosol of, at a minimum, an antigen-

binding fragment of the antibody. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is *in vitro*. In some embodiments, the cell is in a subject.

Also provided herein are methods of inhibiting or reducing aggregation of Aβ in a subject having or at risk of developing a Aβ-related disease, including administering to the subject an effective amount of any of the anti-Aβ CPAs described herein, thereby inhibiting or reducing aggregation of Aβ in the subject.

Also provided herein are methods of treating or effecting prophylaxis of a Aβ-related disease in a subject, including administering a therapeutically effective amount of any of the cell penetrating agents described herein, thereby treating or effecting prophylaxis of the Aβ-associated disease.

In some embodiments, the AB-related disease is IBM.

Also provided herein are methods of detecting Aβ deposits in a subject having or at risk of developing a Aβ-related disease, including administering to a subject any of the cell penetrating agents described herein, and detecting the antibody bound to Aβ in the subject.

Also provided herein are methods of detecting Aβ in a sample obtained from a patient having or at risk of developing a Aβ related disease, including contacting the sample with any of the cell penetrating agents described herein, and detecting the binding of the antibody to Aβ in the sample. In some embodiments, the cell penetrating agent is administered by intravenous injection into the body of the subject. In some embodiments, the cell penetrating agent or the antibody in the cell penetrating agent is labeled. In some embodiments, the cell penetrating agent is labeled with a fluorescent label, a paramagnetic label, or a radioactive label. In some embodiments, the radioactive label is detected using positron emission tomography (PET) or single-photon emission computed tomography (SPECT).

The cell penetrating agents are administered in an effective regime meaning a dosage, route of administration and frequency of administration that delays the onset, reduces the severity, inhibits further deterioration, and/or ameliorates at least one sign or symptom of a disorder being treated. If a patient is already suffering from a disorder, the regime can be referred to as a therapeutically effective regime. If the patient is at elevated risk of the disorder relative to the general population but is not yet experiencing symptoms, the regime can be referred to as a prophylactically effective regime. In some instances, therapeutic or prophylactic efficacy can be observed in an individual patient relative to historical controls or past experience in the same patient. In other instances, therapeutic or prophylactic efficacy can be demonstrated in a preclinical or clinical trial in a population of treated patients relative to a control population of untreated patients.

Administration can be parenteral, intravenous, oral, subcutaneous, intra-arterial, intracranial, intrathecal, intraperitoneal, topical, intranasal or intramuscular. Some cell penetrating agents can be administered into the systemic circulation by intravenous or subcutaneous administration.

The cell penetrating agent formulation can be administered intravenously or subcutaneously in dosage ranges from about 0.5 mg/kg to about 30 mg/kg of the host body weight. For example, dosages can be about 0.5 mg/kg body weight, about 1.0 mg/kg, about 1.5 mg/kg, about 2.0 mg/kg, about 4.0 mg/kg, about 5.0 mg/kg, about 8.0 mg/kg, about 10 mg/kg, about 15 mg/kg, about 16 mg/kg, about 20 mg/kg, about 24 mg/kg, about 25 mg/kg, or about 30 mg/kg body weight. The dosages can also be administered according to body surface area from about 0.5 mg/m^2 to about 500 mg/m^2, for example, 0.5, 5, 10, 50, 100, 250 or 500 mg/m^2. For intravenous dosing, an amount of the cell penetrating agent formulation sufficient to achieve the desired dosage for the individual patient is transferred from one or more vials to one or more intravenous bags containing a liquid (e.g., saline) and administered to the patient.

Cell-penetrating agents are usually administered on multiple occasions. The frequency of administration depends on the half-life of the cell penetrating agent in circulation, the condition of the patient and the route of administration among other factors. The frequency can be daily, weekly, monthly, quarterly, or at irregular intervals in response to changes in the patient's condition or progression of the disorder being treated.

An exemplary treatment regimen entails administration once per every two weeks, once a month, or once every 3 to 6 months. The number of dosages administered depends on whether the disorder is acute or chronic and the response of the disorder to the treatment. The dosing frequency can be adjusted depending on the pharmacokinetic profile of the antibody formulation in the patient. For example, the half-life of the cell penetrating agent may warrant a two week frequency of dosing. In some embodiments disclosed herein, the cell penetrating agent is administered to the patient for at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, 5 years, 10 years, or for the life of the patient.

Normal levels of Aβ (e.g., human Aβ) can be determined in the muscles of a representative sample of individuals in the general population who have not been diagnosed with IBM and are not considered at elevated risk of developing such disease (e.g., a representative sample of disease-free individuals over 50 years of age). Alternatively, a normal level can be recognized in an individual patient if a PET signal according to the

present methods in muscles in which Aβ aggregates (e.g., human Aβ aggregates) are known to develop is not different (within the accuracy of measurement) from the signal from muscles in which it is known that such deposits do not normally develop. An elevated level in an individual can be recognized by comparison to the normal levels (e.g., outside mean and variance of a standard deviation) or simply from an elevated signal beyond experimental error in muscles associated with Aβ aggregates (e.g., human Aβ aggregates) compared with a region not known to be associated with deposits. For purposes of comparing the levels of Aβ aggregates (e.g., human Aβ aggregates) in an individual and population, the Aβ aggregates should preferably be determined in the same region(s) of the muscle, these regions including at least one region in which Aβ aggregates associated with a particular disease (e.g., IBM) are known to form (e.g., in the cytoplasm).

A patient having an elevated level of Aβ aggregates (e.g., human Aβ aggregates) is a candidate for commencing immunotherapy. After commencing immunotherapy, a decrease in the level of Aβ 3 aggregates (e.g., human Aβ aggregates) can be first seen as an indication that the treatment is having the desired effect. The observed decrease can be, for example, in the range of 1-100%, 1-50%, or 1-25% of the baseline value. Such effects can be measured in one or more muscles in which deposits are known to form or can be measured from an average of such regions. The total effect of treatment can be approximated by adding the percentage reduction relative to baseline to the increase in Aβ aggregates (e.g., human Aβ aggregates) that would otherwise occur in an average untreated patient.

Maintenance of Aβ aggregates (e.g., human Aβ aggregates) at an approximately constant level or even a small increase in Aβ aggregates (e.g., human Aβ aggregates) can also be an indication of response to treatment albeit a suboptimal response. Such responses can be compared with a time course of levels of Aβ aggregates (e.g., human Aβ aggregates) in patients with a particular disease (e.g., IBM) that did not receive treatment, to determine whether the immunotherapy is having an effect in inhibiting further increases of Aβ aggregates (e.g., human Aβ aggregates).

VIII. Kits

The present disclosure further provides kits (*e.g.,* containers) comprising any of the cell penetrating agents described herein and related materials, such as instructions for use (*e.g.,* package insert). The instructions for use can contain, for example, instructions for administration of the cell penetrating agent and optionally one or more additional agents.

The containers of cell penetrating agents may be unit doses, bulk packages (*e.g.*, multi-dose packages), or sub-unit doses.

IX. Methods of Detection

In some aspects, the cell penetrating agents of the present disclosure further provides methods of detecting Aβ in a sample. For example, in some embodiments, the present disclosure provides a method of detecting Aβ in a sample comprising contacting a cell penetrating agent of the present disclosure with the sample and detecting the binding of the cell penetrating agent or the antibody to Aβ. For example, such methods can be an *ex vivo* or *in vitro* method. In some embodiments, the sample is a biological sample derived from a subject (e.g., a human subject). In some embodiments, the subject is a human. In some embodiments, the subject is a patient having or at risk of having a Aβ related disease. In such instances, samples such as cells, tissues, and/or organs that have been removed from the patient are exposed to an antibody or antigen-binding fragments described herein. In some embodiments, the sample comprises cells derived from the patient and the cells are lysed prior to administration of the antibody or antigen-binding fragments described herein.

EXAMPLES

The following examples have been included to illustrate modes disclosed herein. Certain aspects of the following examples are described in terms of techniques and procedures found or contemplated by the present co-inventors to work well in the practice disclosed herein. In light of the present disclosure and the general level of skill in the art, those of skill appreciate that the following examples are intended to be exemplary only and that numerous changes, modifications, and alterations may be employed without departing from the scope of the disclosure.

Example 1: Cellular Internalization of Anti-GFP Cell-Penetrating Agents Comprising Selected CMIPs

To demonstrate the capacity for CMIPs of the present disclosure to be internalized by cells, a panel of exemplary CMIPs (shown in Table 5, below) was assessed for internalization. A panel of anti-GFP cell-penetrating agents was expressed, with each CPA comprising an anti-GFP antibody having a CMIP of Table 5 attached to the C-terminus of the light chain via a polypeptide linker having a GGSSS sequence (SEQ ID NO: 256). The anti-

GFP antibody comprised the heavy chain variable region and light chain variable regions of the ScFv disclosed in WO 2022/053642 A1.

HEK cells were transiently transfected with Htt-exon1-Q103-eGFP, to express GFP within the cytosol of the cell. After 24 hours, the cells were incubated with 11 ug/ml of anti-GFP CPA for another 24 hours (n=2 per CPA). Cells were then washed, fixed/permeabilized, and stained with AF647-conjugated anti-human secondary antibodies to stain the intracellular CPAs. Stained cells were imaged by high content imaging (Operetta system) with 40x water objective (30 fields/well). The amount of intracellular CPA detected via secondary antibody was quantified and the number normalized to the value observed for the CPA comprising CMIP4 (SEQ ID NO: 143). Quantitative analyses were carried out with Harmony software.

Table 6 provides relative internalization efficiency (normalized to CMIP4) for exemplary CMIPs for the present disclosure. This internalization efficiency was assessed in the manner described above.

Table 6

SEQ ID NO:	Name	Internalization (Normalized)	SEQ ID NO:	Name	Internalization (Normalized)
143	CMIP4	100	256	CMIP118	56.5
174	CMIP30	97.0	257	CMIP119	--
175	CMIP31	97.0	258	CMIP120	21.5
176	CMIP32	98.6	259	CMIP121	--
177	CMIP33	94.6	260	CMIP122	--
178	CMIP34	106.2	261	CMIP123	--
179	CMIP35	95.0	262	CMIP124	97.2
180	CMIP36	108.7	263	CMIP125	--
181	CMIP37	128.0	264	CMIP126	--
182	CMIP38	147.3	265	CMIP127	--
183	CMIP39	115.1	266	CMIP128	79.0
184	CMIP40	115.5	267	CMIP129	43.2
185	CMIP41	42.9	268	CMIP130	75.7
186	CMIP42	15.8	269	CMIP131	10.1
187	CMIP43	28.8	270	CMIP132	136.9
188	CMIP44	15.4	271	CMIP133	78.3
189	CMIP45	14.8	272	CMIP134	--
190	CMIP46	10.6	273	CMIP135	--
191	CMIP47	38.4	274	CMIP136	--
192	CMIP48	5.5	275	CMIP137	11.6
193	CMIP49	2.5	276	CMIP138	163.9
194	CMIP50	3.3	277	CMIP139	164.3
195	CMIP51	4.1	278	CMIP140	--
196	CMIP58	71.7	279	CMIP141	70.6
197	CMIP59	95.0	280	CMIP142	--
198	CMIP60	77.7	281	CMIP143	--

199	CMIP61	115.1
200	CMIP62	20.3
201	CMIP63	19.0
202	CMIP64	152.2
203	CMIP65	--
204	CMIP66	129.2
205	CMIP67	109.7
206	CMIP68	102.5
207	CMIP69	13.8
208	CMIP70	126.4
209	CMIP71	89.6
210	CMIP72	97.2
211	CMIP73	110.4
212	CMIP74	123.6
213	CMIP75	128.6
214	CMIP76	143.4
215	CMIP77	67.9
216	CMIP78	117.9
217	CMIP79	171.4
218	CMIP80	120.1
219	CMIP81	45.6
220	CMIP82	78.5
221	CMIP83	113.1
222	CMIP84	94.0
223	CMIP85	89.7
224	CMIP86	103.0
225	CMIP87	98.5
226	CMIP88	22.0
227	CMIP89	104.9
228	CMIP90	122.6
229	CMIP91	24.4
230	CMIP92	116.5
231	CMIP93	147.1
232	CMIP94	6.6
233	CMIP95	15.7
234	CMIP96	48.2
235	CMIP97	6.4
236	CMIP98	5.9
237	CMIP99	8.9
238	CMIP100	15.7
239	CMIP101	6.3
240	CMIP102	11.7
241	CMIP103	18.8
242	CMIP104	16.7
243	CMIP105	--
244	CMIP106	19.8
245	CMIP107	14.1
246	CMIP108	10.3

282	CMIP144	--
283	CMIP145	--
284	CMIP146	--
285	CMIP147	71.3
286	CMIP148	17.1
287	CMIP149	18.4
288	CMIP150	88.7
289	CMIP151	90.0
290	CMIP152	--
291	CMIP153	--
292	CMIP154	40.6
293	CMIP155	13.2
294	CMIP156	110.6
295	CMIP157	132.0
296	CMIP158	41.9
297	CMIP159	13.3
298	CMIP160	159.1
299	CMIP161	173.7
300	CMIP162	--
301	CMIP163	55.3
302	CMIP164	95.8
303	CMIP165	--
304	CMIP166	--
305	CMIP167	--
306	CMIP168	--
307	CMIP169	90.7
308	CMIP170	69.7
309	CMIP171	92.3
310	CMIP172	20.8
311	CMIP173	134.6
312	CMIP174	108.8
313	CMIP175	20.2
314	CMIP176	--
315	CMIP177	--
316	CMIP178	--
317	CMIP179	--
318	CMIP180	12.9
319	CMIP181	18.3
320	CMIP182	62.2
321	CMIP183	--
322	CMIP184	62.8
323	CMIP185	92.5
324	CMIP186	157.3
325	CMIP187	--
326	CMIP188	44.8
327	CMIP189	118.0
328	CMIP190	97.6
329	CMIP191	18.7

247	CMIP109	15.2
248	CMIP110	24.7
249	CMIP111	147.3
250	CMIP112	80.4
251	CMIP113	123.9
252	CMIP114	120.2
253	CMIP115	88.0
254	CMIP116	11.9
255	CMIP117	2.9

330	CMIP192	--
331	CMIP193	--
332	CMIP194	--
333	CMIP195	--
334	CMIP196	3.9
335	CMIP197	2.9
336	CMIP198	--
337	CMIP199	--
338	CMIP200	--

Example 2: Immunogenicity of CMIPs

To understand the therapeutic potential for cell-penetrating agents of the present disclosure, the immunogenicity of exemplary CMIPs was assessed. Qualitative immunogenicity profiles for CMIP sequences were generated using the EpiQuest program, which provides a matrix of predicted probability of CTL epitopes for each CMIP sequence analyzed. Using the EpiQuest software, each amino acid residue of the sequence is given a position along the X-axis, and each amino acid residue is provided a predicted immunogenicity (PI) value as an integer along the Y-axis. A positive PI value indicates a probability for an immunogenic epitope comprising the amino acid residue at that position, and a negative PI value indicates a low probability for an immunogenic epitope comprising that the amino acid residue at that position. These values across all amino acid residues in the CMIP sequence are combined resulting in an immunogenicity profile for each CMIP sequence analyzed.

To compare potential immunogenicity across the CMIPs, the immunogenicity profiles generated by the EpiQuest program were converted to an Immunogenicity Unit (IU) scale of 0 through 10 IU. The EpiQuest immunogenicity profiles were generated using the default EpiQuest threshold, and were converted to an IU value in the following manner:

First, each residue is assigned an IU value based on the PI value provided by the EpiQuest program. For each residue having a positive PI value, a score of 0.2 Immunogenicity Units (IU) is assigned a for each shaded tile between 0 to 5 (for example, if a residue has all five vertical tiles shaded from 0 to 5, an IU of 1 is assigned to that residue). In addition to the vertical tiles from 1 to 5, any vertical tile that is shaded from 6 to 10 is assigned an additional IU score of 0.4 for each shaded tile. Similarly, any shaded vertical tile from 11 to15 is assigned a IU score of 0.6 for each shaded tile. For example, if an amino acid residue has a PI value of 12 (indicated by 12 vertical shaded tiles), then it would be assigned a IU score of 4.2 IU (add 0.2 for each of the five shaded tiles from 1 to 5 for a total of 1.0;

add 0.4 for each of the five shaded tiles from 6 to 10 for a total of 2.0; and add 0.6 for each of the two shaded tiles from 11 to 12 for a total of 1.2).

Second, a penalty score is added to the IU score based on the number of continuous amino acid residues assessed as having a positive PI value. A penalty of 1 IU is imposed for three or more contiguous amino acid residues having PI values from 1 to 5 (indicated by positive shaded tiles for three or more continuous residues). No additional penalty is imposed even if all contiguous tiles have PI values of five. A penalty score of 2 is imposed for three or more contiguous amino acid residues having PI values from 6 to 10. Additionally, A penalty score of 3 is imposed for three or more contiguous amino acid residues having PI values from 11 to 15. A molecule will be assigned a maximum score 10 even if calculated score is higher.

Table 7 provides IU scores for exemplary CMIPs for the present disclosure. These IU scores were calculated in the manner described above.

Table 7

SEQ ID NO:	Name	IU Score	SEQ ID NO:	Name	IU Score
143	CMIP4	1.6	256	CMIP118	7.5
174	CMIP30	1.2	257	CMIP119	0.6
175	CMIP31	1.6	258	CMIP120	0.5
176	CMIP32	1.6	259	CMIP121	10
177	CMIP33	1.6	260	CMIP122	8.5
178	CMIP34	1.2	261	CMIP123	9
179	CMIP35	0.4	262	CMIP124	10
180	CMIP36	0.2	263	CMIP125	4.4
181	CMIP37	0.2	264	CMIP126	1.6
182	CMIP38	0.2	265	CMIP127	1.6
183	CMIP39	0	266	CMIP128	0.2
184	CMIP40	0.2	267	CMIP129	0.4
185	CMIP41	0.2	268	CMIP130	10
186	CMIP42	0.2	269	CMIP131	0.2
187	CMIP43	0.2	270	CMIP132	1.8
188	CMIP44	0.2	271	CMIP133	1.6
189	CMIP45	0.2	272	CMIP134	10
190	CMIP46	0.2	273	CMIP135	1.8
191	CMIP47	0.2	274	CMIP136	3.4
192	CMIP48	10	275	CMIP137	0
193	CMIP49	10	276	CMIP138	3.8
194	CMIP50	10	277	CMIP139	10
195	CMIP51	10	278	CMIP140	10
196	CMIP58	0.6	279	CMIP141	3.8
197	CMIP59	1.4	280	CMIP142	1.8
198	CMIP560	1.2	281	CMIP143	10
199	CMIP61	1.2	282	CMIP144	2.2

200	CMIP62	1.2
201	CMIP63	0.4
202	CMIP64	1.2
203	CMIP65	1.8
204	CMIP66	1.6
205	CMIP67	1.6
206	CMIP68	1.6
207	CMIP69	1.2
208	CMIP70	1.6
209	CMIP71	10
210	CMIP72	1.6
211	CMIP73	1.2
212	CMIP74	1.2
213	CMIP75	1.2
214	CMIP76	0.6
215	CMIP77	0.6
216	CMIP78	5
217	CMIP79	1.6
218	CMIP80	1.6
219	CMIP81	2.2
220	CMIP82	1.6
221	CMIP83	1.2
222	CMIP84	2.6
223	CMIP85	1.6
224	CMIP86	1.6
225	CMIP87	1.6
226	CMIP88	1.2
227	CMIP89	1.6
228	CMIP90	10
229	CMIP91	0.6
230	CMIP92	10
231	CMIP93	1.4
232	CMIP94	0.4
233	CMIP95	10
234	CMIP96	0
235	CMIP97	0
236	CMIP98	0
237	CMIP99	0
238	CMIP100	0
239	CMIP101	0
240	CMIP102	0
241	CMIP103	0
242	CMIP104	0
243	CMIP105	0
244	CMIP106	0
245	CMIP107	0
246	CMIP108	0
247	CMIP109	0

283	CMIP145	1.8
284	CMIP146	10
285	CMIP147	0.2
286	CMIP148	9.5
287	CMIP149	1.2
288	CMIP150	10
289	CMIP151	9.5
290	CMIP152	10
291	CMIP153	10
292	CMIP154	1.2
293	CMIP155	1.2
294	CMIP156	4.4
295	CMIP157	1.2
296	CMIP158	1.2
297	CMIP159	0
298	CMIP160	3.8
299	CMIP161	10
300	CMIP162	10
301	CMIP163	3.8
302	CMIP164	1.8
303	CMIP165	1.6
304	CMIP166	10
305	CMIP167	1.2
306	CMIP168	10
307	CMIP169	2.2
308	CMIP170	2.6
309	CMIP171	2.6
310	CMIP172	1.2
311	CMIP173	1.4
312	CMIP174	2.6
313	CMIP175	2.2
314	CMIP176	1.6
315	CMIP177	10
316	CMIP178	1.8
317	CMIP179	1.8
318	CMIP180	1.4
319	CMIP181	1.4
320	CMIP182	3.2
321	CMIP183	3.6
322	CMIP184	5.6
323	CMIP185	1.2
324	CMIP186	10
325	CMIP187	10
326	CMIP188	10
327	CMIP189	1.4
328	CMIP190	2
329	CMIP191	3.2
330	CMIP192	4.4

248	CMIP110	0
249	CMIP111	1.2
250	CMIP112	0.6
251	CMIP113	0.6
252	CMIP114	1
253	CMIP115	4.5
254	CMIP116	0.5
255	CMIP117	10

331	CMIP193	4.6
332	CMIP194	0.8
333	CMIP195	0.6
334	CMIP196	1.2
335	CMIP197	1.2
336	CMIP198	1.2
337	CMIP199	0.4
338	CMIP200	0.2

Example 3. M-Lycotoxin Cell Penetrating Agents Reduce Aβ Foci Area and Count

HEK cells were initially transfected with APP770sw [K670N-M671L_Swedish] which is a model for analyzing Aβ-related diseases. After 24 hours, the cells were subjected to separate 24-hour incubations with cell penetrating agent (h2931_ML (L17E linked to the C-terminus of the light chain)) at concentrations of 1, 10, and 100 μg/ml, respectively. Subsequently, the cells were washed, fixed, permeabilized, and stained using m3D6 anti-Aβ antibody and AF647-conjugated anti-mouse secondary antibodies. Stained cells were imaged by high content imaging (Operetta system) with a 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 1A is a graph showing the total Aβ foci area (px^2). The data demonstrate that incubation with h2931-M-Lycotoxin cell penetrating agent (e.g., an anti-Aβ cell penetrating agent) resulted in a lower total Aβ foci area in a concentration dependent manner. The data also showed a reduction in total Aβ foci area at each concentration as compared to the control sample. Figure 1B is a graph showing Aβ focus count which shows that incubation with the h2931-M-Lycotoxin cell penetrating agent resulted in a lower number of Aβ foci in a concentration dependent manner compared to the control. Figure 1C is a graph showing the mean focus area for Aβ foci in cells treated with h2931 or h2931 cell penetrating agent. Thus, Figures 1A-C demonstrate that the h2931 cell penetrating agents (i.e., cell penetrating agents) interfere with Aβ aggregation in a concentration-dependent manner.

Example 4. M-Lycotoxin Cell Penetrating Agents Reduce Aβ Foci Area and Count Compared to Isotype Controls

HEK cells were transiently transfected with APP770sw [K670N-M671L_Swedish]. 24 hours later, cells were incubated with either 10 μg/ml or 100 μg/ml h2931_ML (L17E linked to the C-terminus of the light chain), or with 100 ug/ml h2931 untagged antibody for 24 hours, respectively. The cells were then washed, fixed, permeabilized, and stained with

m3D6 anti-Aβ antibody and AF647-conjugated anti-mouse secondary antibodies. The stained cells were imaged by high content imaging (Operetta system) with a 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 2A is a graph showing total Aβ foci area. The data demonstrate that incubation with the h2931-M-Lycotoxin cell penetrating agent (e.g., an anti-Aβ cell penetrating agent) resulted in reduced total Aβ foci area in a concentration dependent manner as compared to the untreated and IgG isotype controls. Figure 2B is a graph showing Aβ foci count demonstrating that incubation with the h2931-M-Lycotoxin cell penetrating agent resulted in a lower number of Aβ foci in a concentration dependent manner as compared to the untreated and IgG isotype controls. Figure 2C is a graph showing the mean focus area for Aβ foci in cells treated with h2931 or h2931 cell penetrating agent. Collectively, Figures 2A-C demonstrate that h2931 cell penetrating agents interfere with Aβ aggregation in a concentration-dependent manner.

Additionally, HEK cells were transiently transfected with APP770sw [K670N-M671L_Swedish]. After 24 hours, transfected HEK cells were incubated with five different concentrations of a h2931-M-Lycotoxin (L17E linked to the C-terminus of the light chain) cell-penetrating agent (e.g., an anti-Aβ cell penetrating agent) at 1, 2.5, 5, 10 and 100 μg/ml. Cells treated with 100 ug/ml untagged h2931 were used as controls. The cells were then fixed, permeabilized, and stained with m3D6 anti-Aβ antibody and AF647-conjugated anti-mouse secondary antibodies. The stained cells were imaged by high content imaging (Operetta system) with a 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 3A is a graph showing the total Aβ foci area. The data demonstrate that incubation with the h2931-M-Lycotoxin cell penetrating agent (e.g., an anti-Aβ cell penetrating agent) resulted in a reduced total Aβ foci area in a concentration dependent manner as compared to the untreated and IgG isotype controls. Figure 3B a graph showing the Aβ focus count, demonstrating that incubation with the h2931-M-Lycotoxin cell penetrating agent resulted in a lower number of Aβ foci in a concentration dependent manner compared to the untreated and IgG isotype controls. Figure 3C is a graph showing the mean focus area for Aβ foci in cells treated with either h2931 (i.e., untagged) or h2931 cell penetrating agents. Thus, Figures 3A-C demonstrate that h2931 cell penetrating agents interfere with Aβ aggregation in a concentration-dependent manner.

Example 5. M-Lycotoxin Cell Penetrating Agents Disrupt Aβ Deposits In the Absence of Functioning FcK or FcRn Regions

HEK cells were transiently transfected with APP770sw [K670N-M671L_Swedish]. After 24 hours, transfected HEK cells were incubated with various h2931-CMIP4 cell penetrating agents including h2931 (i.e., untagged antibody), h2931 with a disrupted Fcγ function (L234A/L325A mutation), or an h2931 antibody having a mutation in the FcRn region (H310A/H435Q mutation) for another 24 hours, each at a concentration of 100 ug/ml. For each of h2931_CMIP4, h2931_CMIP4_LALA, and h2931_CMIP4_ H310A_H435Q CMIP4 is linked to the C-terminus of the light chain. Subsequently, the cells were fixed, permeabilized, and stained using the primary m3D6 anti-Aβ antibody, followed by the secondary antibodies AF647-conjugated anti-mouse and AF568-conjugated anti-human. Stained cells were imaged by high content imaging (Operetta system) with 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 4A is a graph showing the total Aβ foci area per cell. The data demonstrate that incubation with the h2931 cell penetrating agents resulted in a reduced total Aβ foci area per cell as compared to the untreated and IgG isotype controls, regardless of Fcγ or FcRn function. That is, the h2931 cell penetrating agents (e.g., anti-Aβ cell penetrating agents) are able to disrupt Aβ deposits intracellularly without the function of either a FcK domain or a FcRn region. Figure 4B is a graph showing the number of Aβ foci area per cell, demonstrating that incubation with the h2931 cell penetrating agents resulted in a lower number of Aβ foci per cell compared to the untreated and IgG isotype controls, regardless of Fcγ or FcRn function. Figure 4C is a graph showing the antibody (i.e., anti-Aβ cell penetrating agents) internalization per cell, demonstrating that incubation with the h2931 cell penetrating agents resulted in increased antibody internalization per cell as compared to the untagged h2931 antibody, regardless of Fcγ or FcRn function. Thus, Figures 4A-C demonstrate that the h2931 cell penetrating agents interfere with intracellular Aβ deposits even when Fcγ or FcRn function is abrogated through mutation.

Example 6. CMIP-4 Cell Penetrating Agents Reduce Aβ Foci Area and Count

HEK cells were transiently transfected with APP770sw [K670N-M671L_Swedish]. After 24 hours, the transfected HEK cells were incubated with either 100 μg/ml untagged murinized 2931 antibody (mzd-2931) or 100 μg/ml mzd-2931-CMIP4 cell penetrating agent (i.e., an anti-Aβ cell penetrating agent) for an additional 24 hours. For mzd-2931_CMIP4 CMIP4 linked to the C-terminus of the light chain. The cells were fixed, permeabilized,

stained using the primary m3D6 anti-Aβ antibody, followed by secondary antibodies AF647-conjugated anti-mouse and AF568-conjugated anti-human. The stained cells were imaged by high content imaging (Operetta system) with a 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 5A is a graph showing the total Aβ foci area per cell, demonstrating that incubation with the mzd-2931-CMIP4 cell penetrating agent resulted in a reduced total Aβ foci area per cell as compared to cells treated with untagged mzd-2931 antibody (i.e., no cell internalizing module). Figure 5B is a graph showing the number of Aβ foci per cell, demonstrating that incubation with the mzd-2931-CMIP4 cell penetrating agent resulted in a lower number of Aβ foci area per cell as compared to cells treated with untagged mzd-2931 antibody. Figure 5C is a graph showing the antibody or cell penetrating agent internalization per cell. The data demonstrate that incubation with the mzd-2931-CMIP4 cell penetrating agent resulted in a greater internalization into these cells compared to the cells treated with untagged mzd-2931. Thus, Figures 5A-C demonstrates that cell penetrating agents of the present disclosure are internalized by disrupt Aβ aggregation, even when the cell penetrating agents comprise murinized antibodies.

Example 7. Anti-Aβ Cell-Penetrating Agents

HEK cells were transiently transfected with APP770sw [K670N-M671L_Swedish]. After the initial 24 hours, the transfected HEK cells were exposed to different treatments for an additional 24 hours. These treatments included untagged h2931 antibody, h2931-CMIP4, and h2931 conjugated with CMIP4-derived peptides, each at a concentration of 100 µg/ml. For each of h2931_CMIP4-1 through h2931-CMIP4-25, CMIP4 is linked at the C-terminus of the light chain. Following this, the cells were fixed, permeabilized, and stained using m3D6 anti-Aβ antibody along with AF647-conjugated anti-mouse and AF568-conjugated anti-human secondary antibodies. The stained cells were then imaged using the high content imaging Operetta system with a 40x water objective. Quantitative analyses were performed using Harmony software.

Figure 6A is a graph showing the total Aβ foci area per cell. The data demonstrate that cell penetrating agents of the present disclosure significantly reduced the total area of Aβ foci per cell as compared to untreated cells and cells treated with either IgG isotype or untagged h2931 antibody (i.e., no cell internalizing module). Figure 6B is a graph showing the average number of Aβ foci area per cell which shows that cell penetrating agents (e.g.,

cell penetrating agents) of the present disclosure significantly reduced the number of Aβ foci per cell as compared to untreated cells and cells treated with either IgG isotype or untagged h2931 antibody. Figure 6C is a graph showing antibody or cell penetrating agent internalization per cell. The data demonstrates that cell penetrating agents of the present disclosure were readily internalized into transfected HEK cells, leading to higher signals as compared to untreated cells and cells treated with either IgG isotype or untagged h2931 antibody. Thus, Figures 6A-C demonstrates that cell penetrating agents comprising anti-Aβ antibodies effectively internalize and bind to Aβ peptides, effectively disrupting intracellular Aβ aggregates. Figures 6A-C further shows that this effect is observed in cell penetrating agents comprising a variety of CMIPs.

Example 8. Anti-Aβ Cell-Penetrating Agents Reduce Aβ Aggregates in Aβ Model Cells

HEK cells were transduced with lentivirus vectors comprising APP770sw [K670N-M671L_Swedish]. After 48 hours the transduced HEK cells were subjected to a further 24 hour incubation with various treatments as follow: either untagged h2931 antibody or h2931-CMIP4 antibody each at a concentration of 100 μg/ml. Following incubation, the cells were fixed, permeabilized, and stained using m3D6 anti-Aβ antibody along with AF647-conjugated anti-mouse and AF568-conjugated anti-human secondary antibodies. The stained cells were then imaged using the high content imaging Operetta system with a 40x water objective. Quantitative analyses were performed using Harmony software.

Figure 7A is an image of untreated HEK cells expressing APPsw following lentiviral transfection. Cells are shown in grey and Aβ aggregates are shown in white. Figure 7A demonstrates substantial Aβ production and aggregation for untreated HEK cells. Figure 7B is an image of HEK cells expressing APPsw following lentiviral transfection and incubation with untagged h2931 antibody. Cells are shown in grey and Aβ aggregates are shown in white. Figure 7B demonstrates reduced Aβ aggregation for h2931 treated HEK cells. Figure 7C is an image of HEK cells expressing APPsw following lentiviral transfection and incubation with h2931-CMIP4 cell penetrating agent. CMIP4 is linked to the C-terminus of the light chain. Cells are shown in grey, with Aβ aggregates shown in white. Figure 7C demonstrates substantially reduced Aβ aggregation for h2931-CMIP4 cell penetrating agent treated HEK cells.

Example 9. CMIP-4 Cell Penetrating Agents Reduce Aβ Foci Area and Count and are Internalized by HEK Cells

HEK cells were transduced with lentivirus vectors comprising APP770sw [K670N-M671L_Swedish] at MOI (multiplicity of infection) = 10. After 48 hours, the transduced HEK cells were subjected to a further 24 hour incubation with either untagged h2931 antibody or h2931-CMIP4 antibody each at a concentration of 100 µg/ml. CMIP4 is linked to the C-terminus of the light chain. Following incubation, the cells were fixed, permeabilized, and stained using m3D6 anti-Aβ antibody along with AF647-conjugated anti-mouse and AF568-conjugated anti-human secondary antibodies. The stained cells were then imaged using the high content imaging Operetta system with a 40x water objective. Quantitative analyses were performed using Harmony software.

Figure 8A is a graph showing the total Aβ foci area per cell, demonstrating that incubation with the h2931-CMIP4 cell penetrating agent resulted in a lower total Aβ foci area per cell in lenti-APPsw transduced HEK-293 cells compared to untreated cells and cells treated with untagged h2931 antibody. Figure 8B is a graph showing the number of Aβ foci per cell, demonstrating that incubation with the h2931-CMIP4 cell penetrating agent resulted in a lower number of Aβ foci area per cell compared to untreated cells and cells treated with untagged h2931 antibody. Figure 8C is a graph showing antibody or cell penetrating agent internalization per cell, demonstrating that incubation with the h2931-CMIP4 cell penetrating agent resulted in increased internalization as compared to untreated cells and cells treated with untagged h2931 antibody alone.

Example 10. HEK Cells Stably Express $A\beta_{1-42}$ and Form Aβ Aggregates

HEK cells were initially transduced with lentivirus vectors containing APP770sw [K670N-M671L_Swedish] at a MOI (multiplicity of infection) of 10. Following transduction, a dose-dependent puromycin selection process was employed to eliminate non-transduced cells and enrich for those that successfully integrated the lentiviral construct. To achieve stable expression of APPsw, the surviving cells underwent two additional rounds of lentiviral transduction and puromycin selection. Subsequently, the cells were fixed, permeabilized, and stained using primary antibodies m3D6 anti-Aβ, CT695, and LN27 anti-APP. Secondary antibodies AF647-conjugated anti-mouse and AF568-conjugated anti-rabbit were utilized to bind the primary antibody. High content imaging was performed using the Operetta system

with a 40x water objective, and quantitative analyses were conducted using Harmony software.

Figure 9A shows high content images of stable APPsw-HEK cells stained with either anti-Aβ antibody m3D6 (*left*) or anti-Aβ antibody CT695 (*right*). Cell bodies are shown as grey rounded structures and Aβ aggregates are shown as diffuse grey structures with exemplary aggregates identified with white arrows. Figure 9A shows that stable APPsw-HEK cells are expressing substantial amounts of Aβ, leading to aggregation. Figure 9B is a graph showing the percentage of stable APPsw-HEK cells having Aβ aggregates compared to untransfected HEK cells (control), as measured by either anti-Aβ antibody m3D6 (*left*) or anti-Aβ antibody CT695 (*right*). Under both measures, about 80% of stable APPsw-HEK cells include Aβ1-42 aggregates. Thus, Figures 9A-B demonstrates that stable APPsw-HEK cells express Aβ and lead to substantial $A\beta_{1-42}$ aggregation.

Example 11. Murinized CMIP-4 Cell Penetrating Agents Reduce Aβ Foci Area and Count and are Internalized by HEK Cells

HEK cells were initially transduced with lentivirus vectors containing APP770sw [K670N-M671L_Swedish] at a MOI (multiplicity of infection) of 10. Following transduction, a dose-dependent puromycin selection process was employed to eliminate non-transduced cells and enrich for those that successfully integrated the lentiviral construct. To achieve stable expression of APPsw, the surviving cells underwent two additional rounds of lentiviral transduction and puromycin selection. Subsequently, the APPsw stable cells were exposed to untagged mzd-2931 and mzd-2931-CMIP4 cell penetrating agents separately for a 24-hour incubation each at a concentration of 100 μg/ml. Cells were then fixed, permeabilized, and stained using h2931 anti-Aβ antibody along with AF647-conjugated anti-mouse and AF568-conjugated anti-human secondary antibodies. The stained cells were imaged by high content imaging (Operetta system) with a 40x water objective. Quantitative analyses were carried out with Harmony software.

Figure 10A is a graph showing the total Aβ foci area per cell demonstrating that incubation with the mzd2931-CMIP4 cell penetrating agent (e.g., an anti-Aβ cell penetrating agent) resulted in a lower total Aβ foci area per cell in lenti-APPsw transduced HEK-293 cells as compared to untreated cells and cells treated with untagged mzd2931 antibody. Figure 10B is a graph showing the number of Aβ foci per cell, demonstrating that incubation with the mzd2931-CMIP4 cell penetrating agent resulted in a lower number of Aβ foci area

per cell as compared to untreated cells and cells treated with untagged mzd2931 antibody. Figure 10C is a graph showing cell penetrating agent internalization per cell, demonstrating that incubation with the mzd2931-CMIP4 cell penetrating agent resulted in greater cell penetrating agent internalization compared to untreated cells and cells treated with untagged mzd2931 antibody. CMIP4 is linked to the C-terminus of the light chain.

All publications (including GenBank Accession numbers, UniProtKB/Swiss-Prot accession numbers and the like), patents and patent applications cited are herein incorporated by reference in their entirety for all purposes to the same extent as if each individual publication, patent and patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes. In the event of any variance in sequences associated with Genbank and UniProtKB/Swiss-Prot accession numbers and the like, the application refers to the sequences associated with the cited accession numbers as of the effective filing date of the application meaning the actual filing date or earlier date of a priority application disclosing the relevant accession number. Any feature, step, element, embodiment, or aspect of the disclosure can be used in combination with any other unless specifically indicated otherwise. Although the present disclosure has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be apparent that certain changes and modifications may be practiced within the scope of the appended claims.

SEQUENCE APPENDIX

SEQ ID NO. 1:
DVVMTQSPLSLPVTLGQPASISCRSSQSLVHSDGNTYLNWFQQRPGQSPQRLIYKVSNRDSGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCMQGTHWPWTFGQGTKVEIK

SEQ ID NO. 2:
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDSDGKTYLNWLLQKPGQSPQRLIYLVSKLDSGVPDRFSGS
GSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGQGTKVEIK

SEQ ID NO. 40: huIgG1 Constant
ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVV
TVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRT
PEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKC
KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENN
YKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO. 41: huKappa Constant
RTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLS
STLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SEQ ID NO. 42: h2726_VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTTCTGGAGAGCGGGGGCGGCCTGGTGCAGCCGGGCGGATCCCTGAGACTGTCCTG
TGCCGCGTCCGGTTTTACCTTCTCCAACTACGGAATGTCATGGGTCCGCCAAGCACCCGGAAAGGG
ATTGGAATGGGTGGCTTCGATCCGGTCCGGCTCGGGACGGACCTACTACTCCGATAACGTCAAGG
GCAGATTCACTATTAGCCGGGACAACAGCAAGAATACCCTGTACCTCCAAATGAACTCCCTGAGG
GCCGAGGACACCGCCGTGTATTACTGCGTGCGCTACGACCACTACTCGGGTTCCTCTGATTACTGG
GGACAGGGGACCCTCGTGACTGTGTCAAGC

SEQ ID NO. 43: h2726_VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACCCAGTCACCACTGTCCCTTCCTGTGACTCCCGGAGAACCGGCGTCCATTTCG
TGCAAGAGCAGCCAGTCCCTGCTCGATTATGACGGAAAGACCTACCTGAACTGGTTGCTCCAAAA
GCCTGGGCAGAGCCCCCAGAGACTGATCTACAAAGTGTCCAACAGGGACTCGGGCGTGCCGGACC
GCTTCTCGGGGTCCGGTTCCGGTACCGACTTTACGCTGAAGATCTCACGGGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGCACTCACTTCCCGCGGACCTTCGGACAAGGCACCAAGGTC
GAGATCAAG

SEQ ID NO. 44: h2931_VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTCCTGGAGTCCGGGGGTGGACTGGTGCAGCCCGGGGGCAGCCTGAGGCTGAGCTG
CGCCGCGTCAGGATTCACCTTCTCCAACTTCGGAATGTCCTGGGTCAGACAGGCCCCGGGAAAGG
GCCTTGAATGGGTGGCTAGCGTGCGCTCCGGTTCCGGACGGACCTACTACTCGGACAACGTGAAG
GGCCGGTTTACTATCTCCCGGGACAATTCGAAGAACACCCTGTACCTCCAAATGAACTCCTTGCGC
GCCGAGGATACCGCAGTGTATTACTGCGTGCGCTACGACCACTACTCTGGCACTAGCGATTACTGG
GGCCAGGGAACTCTGGTCACCGTGTCGTCA

SEQ ID NO. 45: h2931_VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCACCTCTGTCCCTGCCTGTGACCCTTGGGGAACCCGCCTCGATCTCGT
GCAAGAGCTCCCAGAGCCTGCTCGACTATGATGGAAAGACCTACCTGAACTGGTTGCTCCAAAAG
CCGGGCCAGAGCCCCCAGAGGCTGATCTACCGCGTGACCAACCGCGACACCGGGGTGCCGGACCG
GTTCTCCGGATCCGGCAGCGGCACTGACTTCACCCTGAAAATTTCCAGAGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGTACTCACTTTCCACGGTCCTTCGGTCAAGGAACCAAGGTCG
AGATCAAG

SEQ ID NO. 46: h2731_VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTTCTGGAGAGCGGGGGCGGCCTGGTGCAGCCGGGCGGATCCCTGAGACTGTCCTG
TGCCGCGTCCGGTTTTACCTTCTCCAACTACGGAATGTCATGGGTCCGCCAAGCACCCGGAAAGGG
ATTGGAATGGGTGGCTTCGATCCGGTCCGGCTCGGGACGGACCTACTACTCCGATAACGTCAAGG
GCAGATTCACTATTAGCCGGGACAACAGCAAGAATACCCTGTACCTCCAAATGAACTCCCTGAGG
GCCGAGGACACCGCCGTGTATTACTGCGTGCGCTACGACCACTACTCGGGTTCCTCTGATTACTGG
GGACAGGGGACCCTCGTGACTGTGTCAAGC

SEQ ID NO. 47: h2731_VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCACCTCTGTCCCTGCCTGTGACCCTTGGGGAACCCGCCTCGATCTCGT
GCAAGAGCTCCCAGAGCCTGCTCGACTATGATGGAAAGACCTACCTGAACTGGTTGCTCCAAAAG
CCGGGCCAGAGCCCCCAGAGGCTGATCTACCGCGTGACCAACCGCGACACCGGGGTGCCGGACCG
GTTCTCCGGATCCGGCAGCGGCACTGACTTCACCCTGAAAATTTCCAGAGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGTACTCACTTTCCACGGTCCTTCGGTCAAGGAACCAAGGTCG
AGATCAAG

SEQ ID NO. 48: h2831_VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTGCTGGAGTCTGGCGGCGGACTGGTGCAGCCCGGGGGATCCCTGCGGCTTTCCTG
CGCCGCATCCGGCTTCACCTTTTCAAACTTCGGAATGTCGTGGGTCAGACAGGCCCCGGGAAAGGG
TCTGGAATGGGTGGCCTCAGTGCGGTCCGGATCGGGTAGAACCTACTACAGCGATAACGTGAAGG
GCCGGTTCACGATCTCCCGCGACAACTCCAAGAACACCCTGTACTTGCAAATGAATAGCCTCAGGG
CTGAGGATACCGCGGTCTACTACTGTGTGCGCTATGACCACTACACTGGAACTAGCGACTACTGGG
GCCAGGGGACCCTCGTGACTGTGTCGTCC

SEQ ID NO. 49: h2831_VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCACCTCTGTCCCTGCCTGTGACCCTTGGGGAACCCGCCTCGATCTCGT
GCAAGAGCTCCCAGAGCCTGCTCGACTATGATGGAAAGACCTACCTGAACTGGTTGCTCCAAAAG
CCGGGCCAGAGCCCCCAGAGGCTGATCTACCGCGTGACCAACCGCGACACCGGGGTGCCGGACCG

GTTCTCCGGATCCGGCAGCGGCACTGACTTCACCCTGAAAATTTCCAGAGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGTACTCACTTTCCACGGTCCTTCGGTCAAGGAACCAAGGTCG
AGATCAAG

SEQ ID NO. 50: h2926_VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTCCTGGAGTCCGGGGGTGGACTGGTGCAGCCCGGGGGCAGCCTGAGGCTGAGCTG
CGCCGCGTCAGGATTCACCTTCTCCAACTTCGGAATGTCCTGGGTCAGACAGGCCCCGGGAAAGG
GCCTTGAATGGGTGGCTAGCGTGCGCTCCGGTTCCGGACGGACCTACTACTCGGACAACGTGAAG
GGCCGGTTTACTATCTCCCGGGACAATTCGAAGAACACCCTGTACCTCCAAATGAACTCCTTGCGC
GCCGAGGATACCGCAGTGTATTACTGCGTGCGCTACGACCACTACTCTGGCACTAGCGATTACTGG
GGCCAGGGAACTCTGGTCACCGTGTCGTCA

SEQ ID NO. 51: h2926_VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACCCAGTCACCACTGTCCCTTCCTGTGACTCCCGGAGAACCGGCGTCCATTTCG
TGCAAGAGCAGCCAGTCCCTGCTCGATTATGACGGAAAGACCTACCTGAACTGGTTGCTCCAAAA
GCCTGGGCAGAGCCCCCAGAGACTGATCTACAAAGTGTCCAACAGGGACTCGGGCGTGCCGGACC
GCTTCTCGGGGTCCGGTTCCGGTACCGACTTTACGCTGAAGATCTCACGGGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGCACTCACTTCCCGCGGACCTTCGGACAAGGCACCAAGGTC
GAGATCAAG

SEQ ID NO. 52: h4921G VH (Variable Heavy) Nucleotide Sequence
GAGGTGCAGCTGCTGGAGTCGGGGGGGGGACTCGTGCAGCCCGGGGGCTCCCTGAGACTCTCTTG
TGCCGCCTCCGGCTTCACTTTTTCAAACTTCGGAATGTCCTGGGTCCGCCAAGCACCGGGAAAGGG
TCTGGAATGGGTCGCCAGCGTGCGGTCCGGCGGCGGACGGACTTACTACTCCGACAACGTGAAGG
GCCGGTTCACCATCTCAAGGGATAACTCCAAGAATACTCTGTACTTGCAAATGAACTCGCTGCGCG
CTGAAGATACCGCGGTGTACTATTGCGTGCGCTACGACCACTACTCCGGTACCAGCGACTACTGGG
GACAGGGAACCCTTGTGACCGTGTCGAGC

SEQ ID NO. 53: h4921G VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCGCCCCTCTCCCTGCCTGTGACTCTGGGGGAACCCGCGTCCATTTCGT
GCAAGAGCAGCCAGTCCCTGTTGGACTCAGACGGAAAGACCTACCTTAACTGGCTGCTGCAAAAG
CCAGGACAGAGCCCGCAGAGGCTGATCTACCGCGTGACCAACCGGGATACGGGAGTGCCGGACA
GATTCAGCGGCTCGGGTTCCGGCACCGACTTCACCCTCAAAATCTCCCGCGTCGAGGCCGAGGACG
TGGGCGTGTATTACTGTTGGCAGGGAACCCACTTTCCTCGGACCTTCGGTCAAGGGACTAAGGTCG
AAATCAAG

SEQ ID NO. 54: h2826 VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTGCTGGAGTCTGGCGGCGGACTGGTGCAGCCCGGGGGATCCCTGCGGCTTTCCTG
CGCCGCATCCGGCTTCACCTTTTCAAACTTCGGAATGTCGTGGGTCAGACAGGCCCCGGGAAAGGG
TCTGGAATGGGTGGCCTCAGTGCGGTCCGGATCGGGTAGAACCTACTACAGCGATAACGTGAAGG
GCCGGTTCACGATCTCCCGCGACAACTCCAAGAACACCCTGTACTTGCAAATGAATAGCCTCAGGG
CTGAGGATACCGCGGTCTACTACTGTGTGCGCTATGACCACTACACTGGAACTAGCGACTACTGGG
GCCAGGGGACCCTCGTGACTGTGTCGTCC

SEQ ID NO. 55: h2826 VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACCCAGTCACCACTGTCCCTTCCTGTGACTCCCGGAGAACCGGCGTCCATTTCG
TGCAAGAGCAGCCAGTCCCTGCTCGATTATGACGGAAAGACCTACCTGAACTGGTTGCTCCAAAA
GCCTGGGCAGAGCCCCCAGAGACTGATCTACAAAGTGTCCAACAGGGACTCGGGCGTGCCGGACC
GCTTCTCGGGGTCCGGTTCCGGTACCGACTTTACGCTGAAGATCTCACGGGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGCACTCACTTCCCGCGGACCTTCGGACAAGGCACCAAGGTC
GAGATCAAG

SEQ ID NO. 56: h2929 VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTCCTGGAGTCCGGGGGTGGACTGGTGCAGCCCGGGGGCAGCCTGAGGCTGAGCTG
CGCCGCGTCAGGATTCACCTTCTCCAACTTCGGAATGTCCTGGGTCAGACAGGCCCCGGGAAAGG
GCCTTGAATGGGTGGCTAGCGTGCGCTCCGGTTCCGGACGGACCTACTACTCGGACAACGTGAAG
GGCCGGTTTACTATCTCCCGGGACAATTCGAAGAACACCCTGTACCTCCAAATGAACTCCTTGCGC
GCCGAGGATACCGCAGTGTATTACTGCGTGCGCTACGACCACTACTCTGGCACTAGCGATTACTGG
GGCCAGGGAACTCTGGTCACCGTGTCGTCA

SEQ ID NO. 57: h2929 VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACCCAAAGCCCCCTGTCCCTCCCTGTGACTCCTGGAGAGCCGGCGTCCATTTCC
TGCCGGTCAAGCCAGTCCTTGGTGGACTACGACGGAAAGACCTACCTCAACTGGCTGCTGCAGCG
CCCCGGGCAGTCGCCGCAGCGGCTTATCTACAAAGTGTCCAACCGCGACTCGGGCGTGCCGGATA
GGTTTTCGGGTTCCGGAAGCGGCACCGACTTCACCCTGAAAATCTCCAGAGTGGAAGCCGAGGAC
GTGGGAGTGTACTACTGTTGGCAGGGTTCTCACTTCCCACGGTCATATGGCCAAGGGACTAAGGTC
GAAATCAAG

SEQ ID NO. 58: h3818G VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTCCTGGAGTCCGGCGGTGGACTGGTGCAGCCGGGCGGATCCCTGAGACTGTCCTG
CGCCGCGTCGGGCTTTACTTTCGCAAATTACGGCATGAGCTGGGTCAGACAGGCCCCCGGGAAGG
GTCTGGAATGGGTGGCCAGCGTCCGGAGCGGGGGATCCCGGACCTATTACTCCGACAACGTGAAG
GGCCGCTTCACCATCTCAAGGGACAACTCCAAGAACACCCTGTACTTGCAAATGAACAGCCTTCGG
GCTGAGGATACTGCCGTGTACTACTGCGTGCGCTACGACCACTACTCCGGATCCTCGGATTACTGG
GGACAGGGAACCCTCGTGACCGTGTCATCG

SEQ ID NO. 59: h3818G VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCGCCCCTCTCCCTGCCTGTGACTCTGGGGGAACCCGCGTCCATTTCGT
GCAAGAGCAGCCAGTCCCTGATGGACACCGACGGAAAGACCTACCTTAACTGGCTGCTGCAAAAG
CCAGGACAGAGCCCGCAGAGGCTGATCTACAAAGTGTCAAACCGGGAGTCCGGAGTGCCGGACA
GATTCAGCGGCTCGGGTTCCGGCACCGACTTCACCCTCAAAATCTCCCGCGTCGAGGCCGAGGACG
TGGGCGTGTATTACTGTTGGCAGGGAACCCACTTTCCTCGGACCTTCGGTCAAGGGACTAAGGTCG
AAATCAAG

SEQ ID NO. 60: h2927 VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTCCTGGAGTCCGGGGGTGGACTGGTGCAGCCCGGGGGCAGCCTGAGGCTGAGCTG
CGCCGCGTCAGGATTCACCTTCTCCAACTTCGGAATGTCCTGGGTCAGACAGGCCCCGGGAAAGG
GCCTTGAATGGGTGGCTAGCGTGCGCTCCGGTTCCGGACGGACCTACTACTCGGACAACGTGAAG
GGCCGGTTTACTATCTCCCGGGACAATTCGAAGAACACCCTGTACCTCCAAATGAACTCCTTGCGC
GCCGAGGATACCGCAGTGTATTACTGCGTGCGCTACGACCACTACTCTGGCACTAGCGATTACTGG
GGCCAGGGAACTCTGGTCACCGTGTCGTCA

SEQ ID NO. 61: h2927 VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCACCGCTCTCCCTCCCTGTGACCCCGGGCGAACCAGCGTCGATCTCC
TGCAAGAGCAGCCAATCATTGCTGGACTACGACGGAAAGACCTATCTTAACTGGCTGCTGCAGAA
GCCCGGGCAGAGCCCGCAGCGCCTGATCTACAAAGTGTCCAACAGAGACTCCGGAGTGCCTGATA
GGTTCTCGGGTTCCGGCTCCGGTACCGACTTCACTCTGAAAATTTCCCGGGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGCACCCACTTCCCCCGGTCGTTTGGACAAGGGACCAAGGTCG
AGATCAAG

SEQ ID NO. 62: h49K3G VH (Variable Heavy) Nucleotide Sequence
GAGGTGCAGCTGCTGGAGTCGGGGGGGGGACTCGTGCAGCCCGGGGGCTCCCTGAGACTCTCTTG
TGCCGCCTCCGGCTTCACTTTTTCAAACTTCGGAATGTCCTGGGTCCGCCAAGCACCGGGAAAGGG
TCTGGAATGGGTCGCCAGCGTGCGGTCCGGCGGCGGACGGACTTACTACTCCGACAACGTGAAGG
GCCGGTTCACCATCTCAAGGGATAACTCCAAGAATACTCTGTACTTGCAAATGAACTCGCTGCGCG
CTGAAGATACCGCGGTGTACTATTGCGTGCGCTACGACCACTACTCCGGTACCAGCGACTACTGGG
GACAGGGAACCCTTGTGACCGTGTCGAGC

SEQ ID NO. 63: h49K3G VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCGCCCCTCTCCCTGCCTGTGACTCTGGGGGAACCCGCGTCCATTTCGT
GCAAGAGCAGCCAGTCCCTGTTGGACTCAGACGGAAAGACCTACCTTAACTGGCTGCTGCAAAAG
CCAGGACAGAGCCCGCAGAGGCTGATCTACAAAGTGTCAAACCGGGATTCCGGAGTGCCGGACAG
ATTCAGCGGCTCGGGTTCCGGCACCGACTTCACCCTCAAAATCTCCCGCGTCGAGGCCGAGGACGT
GGGCGTGTATTACTGTTGGCAGGGAACCCACTTTCCTCGGACCTTCGGTCAAGGGACTAAGGTCGA
AATCAAG

SEQ ID NO. 64: h4917G VH (Variable Heavy) Nucleotide Sequence
GAGGTGCAGCTGCTGGAGTCGGGGGGGGGACTCGTGCAGCCCGGGGGCTCCCTGAGACTCTCTTG
TGCCGCCTCCGGCTTCACTTTTTCAAACTTCGGAATGTCCTGGGTCCGCCAAGCACCGGGAAAGGG
TCTGGAATGGGTCGCCAGCGTGCGGTCCGGCGGCGGACGGACTTACTACTCCGACAACGTGAAGG

GCCGGTTCACCATCTCAAGGGATAACTCCAAGAATACTCTGTACTTGCAAATGAACTCGCTGCGCG
CTGAAGATACCGCGGTGTACTATTGCGTGCGCTACGACCACTACTCCGGTACCAGCGACTACTGGG
GACAGGGAACCCTTGTGACCGTGTCGAGC

SEQ ID NO. 65: h4917G VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCGCCCCTCTCCCTGCCTGTGACTCTGGGGGAACCCGCGTCCATTTCGT
GCAAGAGCAGCCAGTCCCTGTTGGACTCAGACGGAAAGACCTACCTTAACTGGCTGCTGCAAAAG
CCAGGACAGAGCCCGCAGAGGCTGATCTACAAAGTGACCAACCGGGAGTCCGGAGTGCCGGACA
GATTCAGCGGCTCGGGTTCCGGCACCGACTTCACCCTCAAAATCTCCCGCGTCGAGGCCGAGGACG
TGGGCGTGTATTACTGTTGGCAGGGAACCCACTTTCCTCGGTCATTCGGTCAAGGGACTAAGGTCG
AAATCAAG

SEQ ID NO. 66: h2727 VH (Variable Heavy) Nucleotide Sequence
GAAGTGCAGCTTCTGGAGAGCGGGGGCGGCCTGGTGCAGCCGGGCGGATCCCTGAGACTGTCCTG
TGCCGCGTCCGGTTTTACCTTCTCCAACTACGGAATGTCATGGGTCCGCCAAGCACCCGGAAAGGG
ATTGGAATGGGTGGCTTCGATCCGGTCCGGCTCGGGACGGACCTACTACTCCGATAACGTCAAGG
GCAGATTCACTATTAGCCGGGACAACAGCAAGAATACCCTGTACCTCCAAATGAACTCCCTGAGG
GCCGAGGACACCGCCGTGTATTACTGCGTGCGCTACGACCACTACTCGGGTTCCTCTGATTACTGG
GGACAGGGGACCCTCGTGACTGTGTCAAGC

SEQ ID NO. 67: h2727 VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCACCGCTCTCCCTCCCTGTGACCCCGGGCGAACCAGCGTCGATCTCC
TGCAAGAGCAGCCAATCATTGCTGGACTACGACGGAAAGACCTATCTTAACTGGCTGCTGCAGAA
GCCCGGGCAGAGCCCGCAGCGCCTGATCTACAAAGTGTCCAACAGAGACTCCGGAGTGCCTGATA
GGTTCTCGGGTTCCGGCTCCGGTACCGACTTCACTCTGAAAATTTCCCGGGTGGAAGCCGAGGACG
TGGGAGTGTACTACTGTTGGCAGGGCACCCACTTCCCCCGGTCGTTTGGACAAGGGACCAAGGTCG
AGATCAAG

SEQ ID NO. 68: h4918G VH (Variable Heavy) Nucleotide Sequence
GAGGTGCAGCTGCTGGAGTCGGGGGGGGGGACTCGTGCAGCCCGGGGGCTCCCTGAGACTCTCTTG
TGCCGCCTCCGGCTTCACTTTTTCAAACTTCGGAATGTCCTGGGTCCGCCAAGCACCGGGAAAGGG
TCTGGAATGGGTCGCCAGCGTGCGGTCCGGCGGCGGACGGACTTACTACTCCGACAACGTGAAGG
GCCGGTTCACCATCTCAAGGGATAACTCCAAGAATACTCTGTACTTGCAAATGAACTCGCTGCGCG
CTGAAGATACCGCGGTGTACTATTGCGTGCGCTACGACCACTACTCCGGTACCAGCGACTACTGGG
GACAGGGAACCCTTGTGACCGTGTCGAGC

SEQ ID NO. 69: h4918G VL (Variable Light) Nucleotide Sequence
GATGTCGTGATGACTCAGTCGCCCCTCTCCCTGCCTGTGACTCTGGGGGAACCCGCGTCCATTTCGT
GCAAGAGCAGCCAGTCCCTGATGGACACCGACGGAAAGACCTACCTTAACTGGCTGCTGCAAAAG
CCAGGACAGAGCCCGCAGAGGCTGATCTACAAAGTGTCAAACCGGGAGTCCGGAGTGCCGGACA
GATTCAGCGGCTCGGGTTCCGGCACCGACTTCACCCTCAAAATCTCCCGCGTCGAGGCCGAGGACG
TGGGCGTGTATTACTGTTGGCAGGGAACCCACTTTCCTCGGACCTTCGGTCAAGGGACTAAGGTCG
AAATCAAG

SEQ ID NO. 70: Aducanumab Heavy Chain:
QVQLVESGGGVVQPGRSLRLSCAASGFAFSSYGMHWVRQAPGKGLEWVAVIWFDGTKKYYTDSVKG
RFTISRDNSKNTLYLQMNTLRAEDTAVYYCARDRGIGARRGPYYMDVWGKGTTVTVSSASTKGPSVF
PLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQ
TYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVD
VSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAP
IEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDS
DGSFFLYSKLTVDKSRWQQGNVFSCSVMIIEALIINIIYTQKSLSLSPGK

SEQ ID NO. 71: Aducanumab Light Chain:
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQSYSTPLTFGGGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP
REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSF
NRGEC

SEQ ID NO. 72: Bapineuzumab HC (Heavy Chain)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGGGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO. 73: Bapineuzumab VH (Variable Heavy)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNYGMSWVRQAPGKGLEWVASIRSGGGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYSGSSDYWGQGTLVTVSS

SEQ ID NO: 16: VH CDR1 GFTFSNYGMS
SEQ ID NO: 17: VH CDR2 SIRSGGGRTYYSNDYNVKG
SEQ ID NO: 18: VH CDR3 YDHYSGSSDY

SEQ ID NO. 77: Bapineuzumab LC (Light Chain)
DVVMTQSPLSLPVTPGEPASISCKSSQSLLDSDGKTYLNWLLQKPGQSPQRLIYLVSKLDSGVPDRFSGS
GSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVC
LLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGL
SSPVTKSFNRGEC

SEQ ID NO. 78: Bapineuzumab VL (Variable Light)
DVVMTQSPLSLPVTPGEPASISCKSSQSLLDSDGKTYLNWLLQKPGQSPQRLIYLVSKLDSGVPDRFSGS
GSGTDFTLKISRVEAEDVGVYYCWQGTHFPRTFGQGTKVEIK

SEQ ID NO: 26: VL CDR1 KSSQSLLDSDGKTYLN
SEQ ID NO: 27: VL CDR2 LVSSKLDS
SEQ ID NO: 28: VL CDR3 WQGTHFPRT

SEQ ID NO. 82: Gantenerumab IIC amino acid sequence:
QVELVESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSAINASGTRTYYADSVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCARGKGNTHKPYGYVRYFDVWGQGTLVTVSSASTKGPSV
FPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGT
QTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVV
DVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALP
APIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLD
SDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO. 83: Gantenerumab LC amino acid sequence:
DIVLTQSPATLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYGASSRATGVPARFSGSGSGT
DFTLTISSLEPEDFATYYCLQIYNMPITFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKS
FNRGEC

SEQ ID NO. 84: Amyloid Beta (Aβ) 1-42:
DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIA

SEQ ID NO. 85: Amyloid Beta (Aβ) Precursor Protein:
MLPGLALLLLAAWTARALEVPTDGNAGLLAEPQIAMFCGRLNMHMNVQNGKWDSDPSGTKTCIDTK
EGILQYCQEVYPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYRCLVGEFVSDALLVPDKCKF
LHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPCGIDKFRGVEFVCCPLAEESDNVDSADAE
EDDSDVWWGGADTDYADGSEDKVVEVAEEEEVAEVEEEEADDDEDDEDGDEVEEEAEEPYEEATER
TTSIATTTTTTTESVEEVVREVCSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYC
MAVCGSAMSQSLLKTTQEPLARDPVKLPTTAASTPDAVDKYLETPGDENEHAHFQKAKERLEAKHRE
RMSQVMREWEEAERQAKNLPKADKKAVIQHFQEKVESLEQEAANERQQLVETHMARVEAMLNDRR
RLALENYITALQAVPPRPRHVFNMLKKYVRAEQKDRQHTLKHFEHVRMVDPKKAAQIRSQVMTHLR
VIYERMNQSLSLLYNVPAVAEEIQDEVDELLQKEQNYSDDVLANMISEPRISYGNDALMPSLTETKTTV
ELLPVNGEFSLDDLQPWHSFGADSVPANTENEVEPVDARPAADRGLTTRPGSGLTNIKTEEISEVKMDA

EFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVVIATVIVITLVMLKKKQYTSIHHGVVEVDAA
VTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID NO. 86: huIgG1 Constant Nucleotide Sequence
GCCAGCACTAAGGGGCCTAGCGTCTTTCCGCTGGCCCCGTCCTCCAAGTCCACTTCGGGTGGAACC
GCGGCACTGGGGTGCCTCGTGAAGGACTACTTCCCCGAGCCGGTCACCGTGTCCTGGAACTCGGG
AGCCCTGACCTCCGGAGTGCATACTTTCCCTGCGGTGCTGCAGTCCTCCGGGCTCTACTCGCTGTCA
AGCGTGGTCACCGTCCCGAGCTCATCCCTGGGTACTCAGACCTACATTTGCAACGTGAACCACAAA
CCTTCCAACACCAAGGTCGACAAGAAAGTGGAGCCTAAGAGCTGCGACAAGACCCACACCTGTCC
CCCGTGTCCCGCCCCTGAGCTGCTGGGCGGCCCCAGCGTGTTCCTCTTCCCGCCTAAGCCGAAGGA
CACTCTGATGATCTCGAGAACCCCTGAAGTGACCTGTGTGGTGGTGGATGTGTCCCACGAGGATCC
GGAAGTGAAGTTCAATTGGTACGTGGACGGAGTGGAAGTCCATAACGCCAAGACCAAGCCCCGCG
AGGAACAGTACAACTCAACTTACCGGGTGGTGTCAGTGCTGACCGTGCTGCACCAAGATTGGCTG
AACGGGAAGGAGTACAAGTGCAAAGTCTCCAACAAGGCGCTGCCGGCCCCCATTGAAAAGACCAT
CAGCAAGGCTAAGGGCCAGCCCCGGGAACCACAGGTCTACACCTTGCCCCCTTCCCGGGAGGAAA
TGACCAAGAACCAAGTGTCGCTGACGTGCCTGGTCAAGGGCTTTTATCCATCTGACATCGCCGTGG
AGTGGGAAAGCAACGGCCAGCCGGAAAACAACTACAAGACTACCCCGCCTGTGCTGGACTCCGAC
GGCTCGTTCTTCCTGTATTCCAAGCTCACCGTGGATAAGTCCAGATGGCAGCAGGGCAATGTGTTC
AGCTGCAGCGTGATGCATGAGGCCCTGCACAACCACTACACTCAGAAATCACTGTCCCTTTCCCCC
GGAAAGTAA

SEQ ID NO. 87: huKappa Constant Nucleotide Sequence
CGAACTGTGGCTGCACCATCTGTCTTCATCTTCCCGCCATCTGATGAGCAGTTGAAATCTGGAACT
GCCTCTGTTGTGTGCCTGCTGAATAACTTCTATCCCAGAGAGGCCAAAGTACAGTGGAAGGTGGAT
AACGCCCTCCAATCGGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACAGCAAGGACAGCACCTA
CAGCCTCAGCAGCACCCTGACGCTGAGCAAAGCAGACTACGAGAAACACAAAGTCTACGCCTGCG
AAGTCACCCATCAGGGCCTGAGCTCGCCCGTCACAAAGAGCTTCAACAGGGGAGAGTGTTAA

SEQ ID NO: 347 h2931 Untagged Antibody Heavy chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 348 h2931 Untagged Antibody Light chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

SEQ ID NO: 349 h2931_Ab_LC-Ct-CMIP4 Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 350 h2931_Ab_LC-Ct-CMIP4 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 351 h2931_Ab_LC-Ct-L17E-Mycotoxin Heavy Chain

EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 352 h2931_Ab_LC-Ct-L17E-MLycotoxin Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFLGKHAAKHEAKQQLSKL

SEQ ID NO: 353 h2931_Ab_LC-Ct-cycR8 Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 354 h2931_Ab_LC-Ct-cycR8 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**CRRRRRRRRC

SEQ ID NO: 355 h2931_Ab_LC-Ct-cycTAT Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 356 h2931_Ab_LC-Ct-cycTAT Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**CYGRKKRRQRRRC

SEQ ID NO: 357 h2931_Ab_LC-Ct-R8 Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 358 h2931_Ab_LC-Ct-R8 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**RRRRRRRR

SEQ ID NO: 359 h2931_Ab_LC-Ct-TAT Heavy Chain

EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SEQ ID NO: 360 h2931_Ab_LC-Ct-TAT Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**YGRKKRRQRRR

SEQ ID NO: 361 h2931_Ab_HC-H433A_LC-Ct-CMIP4 (effector function null cell penetrating agent) Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALANHYTQKSLSLSPGK

SEQ ID NO: 362 h2931_Ab_HC-H433A_LC-Ct-CMIP4 (effector function null cell penetrating agent) Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 363 mzd-2931-CMIP4 Heavy Chain
EVQLVESGGGLVKPGGSLKLSCAASGFTFSNFGMSWVRQAPEKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNAKNTLFLQMTSLRSEDTALYYCVRYDHYTGTSDYWGQGTSVTVSSAKTTAPSVYPLAPVCG
DTTGSSVTLGCLVKGYFPEPVTLTWNSGSLSSGVHTFPAVLQSDLYTLSSSVTVTSSTWPSQSITCNVAH
PASSTKVDKKIEPRGPTIKPCPPCKCPAPNAAGGPSVFIFPPKIKDVLMISLSPIVTCVVVDVSEDDPDVQI
SWFVNNVEVHTAQTQTHREDYNSTLRVVSALPIQHQDWMSGKEFKCKVNNKDLPAPIERTISKPKGSV
RAPQVYVLPPPEEEMTKKQVTLTCMVTDFMPEDIYVEWTNNGKTELNYKNTEPVLDSDGSYFMYSKL
RVEKKNWVERNSYSCSVVHEGLHNHHTTKSFSRTPGK

SEQ ID NO: 364 mzd-2931-CMIP4 Light Chain
DVVMTQTPLTLSVTIGQPASISCKSSQSLLDYDGKTYLNWLLQRPGQSPKRLIYRVTNRDTGVPDRFTG
SGSGTDFTLKISRVEAEDLGVYYCWQGTHFPRSFGSGTKLEIKADAAPTVSIFPPSSEQLTSGGASVVCF
LNNFYPKDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKDEYERHNSYTCEATHKTSTS
PIVKSFNRNEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 365 h2931-CMIP4-LALA Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK*

SEQ ID NO: 366 h2931-CMIP4-LALA Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKL*

SEQ ID NO: 367 h2931-CMIP4-H310A_H435Q Heavy Chain
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLAQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNQYTQKSLSLSPGK*

SEQ ID NO: 368 h2931-CMIP4-H310A_H435Q Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKL*

SEQ ID NO: 369 h2931-CMIP4-1 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**AWLTALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 370 h2931-CMIP4-2 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IALTALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 371 h2931-CMIP4-3 Light-Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWATALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 372 h2931-CMIP4-4 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLAALKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 373 h2931-CMIP4-5 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTGLKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 374 h2931-CMIP4-6 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTAAKFSGKAAAKAEAKQFLSKL

SEQ ID NO: 375 h2931-CMIP4-7 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALAFSGKAAAKAEAKQFLSKL

SEQ ID NO: 376 h2931-CMIP4-8 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV

CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKASGKAAAKAEAKQFLSKL

SEQ ID NO: 377 h2931-CMIP4-9 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFAGKAAAKAEAKQFLSKL

SEQ ID NO: 378 h2931-CMIP4-10 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSAKAAAKAEAKQFLSKL

SEQ ID NO: 379 h2931-CMIP4-11 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGAAAAKAEAKQFLSKL

SEQ ID NO: 380 h2931-CMIP4-12 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKGAAKAEAKQFLSKL

SEQ ID NO: 381 h2931-CMIP4-13 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAGAKAEAKQFLSKL

SEQ ID NO: 382 h2931-CMIP4-14 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAGKAEAKQFLSKL

SEQ ID NO: 383 h2931-CMIP4-15 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAAAEAKQFLSKL

SEQ ID NO: 384 h2931-CMIP4-16 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKGEAKQFLSKL

SEQ ID NO: 385 h2931-CMIP4-17 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAAAKQFLSKL

SEQ ID NO: 386 h2931-CMIP4-18 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEGKQFLSKL

SEQ ID NO: 387 h2931-CMIP4-19 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAAQFLSKL

SEQ ID NO: 388 h2931-CMIP4-20 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKAFLSKL

SEQ ID NO: 389 h2931-CMIP4-21 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQALSKL

SEQ ID NO: 390 h2931-CMIP4-22 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFASKL

SEQ ID NO: 391 h2931-CMIP4-23 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLAKL

SEQ ID NO: 392 h2931-CMIP4-24 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSAL

SEQ ID NO: 393 h2931-CMIP4-25 Light Chain
DVVMTQSPLSLPVTLGEPASISCKSSQSLLDYDGKTYLNWLLQKPGQSPQRLIYRVTNRDTGVPDRFSG
SGSGTDFTLKISRVEAEDVGVYYCWQGTHFPRSFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVV
CLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC**GGGGSGGGGS**IWLTALKFSGKAAAKAEAKQFLSKA

SEQ ID NO: 394 H2931_Heavy Chain (common to all CMIP4-1-25 (SEQ ID NOs: 369-393))
EVQLLESGGGLVQPGGSLRLSCAASGFTFSNFGMSWVRQAPGKGLEWVASVRSGSGRTYYSDNVKGR
FTISRDNSKNTLYLQMNSLRAEDTAVYYCVRYDHYTGTSDYWGQGTLVTVSSASTKGPSVFPLAPSSK
STSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNV
NHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDP
EVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISK
AKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLY
SKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

The following applies to SEQ ID NOs: 347-394
Linker sequences are denoted in bold font.
Cell internalizing modules are denoted with double-underlining.
Constant domains are denoted by underlining.

SEQ ID NO: 395 Formula IA
I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L

SEQ ID NO: 396 Formula IB

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-X^{20}-F-X^{22}-S-X^{24}-L

SEQ ID NO: 397 Formula IC
X^1-X^2-L-T-X^5-L-K-X^8-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L

SEQ ID NO: 398 Formula ID
I-W-L-T-X^5-X^6-K-F-S-X^{10}-K-X^{12}-A-A-K-A-X^{17}-X^{18}-K-Q-F-L-X^{23}-X^{24}-X^{25}

SEQ ID NO: 399 Formula (IIA)
I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L

SEQ ID NO: 400 Formula (IIB)
I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-Q-F-X^{22}-S-X^{24}-L

SEQ ID NO: 401 (Formula IIC)
X^1-X^2-L-T-A-L-K-F-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L

WHAT IS CLAIMED IS:

1. An anti-amyloid beta peptide (Aβ) cell penetrating agent (CPA) comprising: (i) a cell internalizing module (CIM) and (ii) an antibody that specifically binds to amyloid beta (Aβ) peptide.

2. The anti-Aβ CPA of claim 1, wherein the CIM comprises a Cell Membrane Internalizing Peptide (CMIP).

3. The anti-Aβ CPA of claim 2, wherein the CMIP comprises an amino acid sequence selected from Formula (IA) to Formula (ID):

I-X^2-X^3-T-A-L-X^7-F-X^9-G-X^{11}-A-A-X^{14}-K-X^{16}-E-A-X^{19}-Q-F-L-X^{23}-X^{24}-L (I-A) (SEQ ID NO: 395);

I-W-X^3-X^4-A-L-X^7-F-X^9-G-X^{11}-X^{12}-X^{13}-A-X^{15}-A-E-A-X^{19}-X^{20}-F-X^{22}-S-X^{24}-L (I-B) (SEQ ID NO: 396);

X^1-X^2-L-T-X^5-L-K-X^8-S-X^{10}-K-A-A-A-X^{15}-A-E-A-K-Q-X^{21}-L-S-X^{24}-L (I-C) (SEQ ID NO: 397);

I-W-L-T-X^5-X^6-K-F-S-X^{10}-K-X^{12}-A-A-K-A-X^{17}-X^{18}-K-Q-F-L-X^{23}-X^{24}-X^{25} (I-D) (SEQ ID NO: 398);

wherein:

X^1 is a hydrophobic amino acid residue or a positively-charged amino acid residue;

X^2 is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^3 is an aromatic amino acid residue, a hydrophobic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^4 is a neutral hydrophilic amino acid residue or an aromatic amino acid residue;

X^5 is a hydrophobic amino acid residue or an aromatic amino acid residue;

X^6 is a hydrophobic amino acid residue;

X^7 is a hydrophobic amino acid residue or a positively-charged amino acid;

X^8 is an aromatic amino acid residue;

X^9 is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{10} is a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{11} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue;

X^{12} is a neutral hydrophilic amino acid residue, a hydrophobic amino acid residue, or a positively-charged amino acid residue;

X^{13} is a neutral hydrophilic amino acid residue or a hydrophobic amino acid residue;

X^{14} is a hydrophobic amino acid residue or a positively-charged amino acid;

X^{15} is an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^{16} is a hydrophobic amino acid residue, an aromatic amino acid residue, a positively-charged amino acid residue, or a negatively-charged amino acid residue;

X^{17} is a positively-charged amino acid residue or a negatively-charged amino acid residue;

X^{18} is a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{19} is a hydrophobic amino acid residue or a positively-charged amino acid residue;

X^{20} is a neutral hydrophilic amino acid residue or a negative-charged amino acid residue;

X^{21} is a hydrophobic amino acid residue or an aromatic amino acid residue;

X^{22} is absent, a hydrophobic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{23} is absent, a neutral hydrophilic amino acid residue, an aromatic amino acid residue, or a positively-charged amino acid residue;

X^{24} is absent, an aromatic amino acid residue, or a positively-charged amino acid residue; and

X^{25} is absent or a hydrophobic amino acid; or a pharmaceutically acceptable salt thereof.

4. The anti-Aβ CPA of claim 1 or 2, wherein the CIM comprises a wild-type M-lycotoxin peptide.

5. The anti-Aβ CPA of claim 1 or 2, wherein the CIM comprises an M-lycotoxin derivative.

6. The anti-Aβ CPA of claim 1 or 2, wherein the CIM comprises a polyarginine amino acid sequence.

7. The anti-Aβ CPA of any one of claims 1, 2, and 6, wherein the CIM comprises more than one polyarginine amino acid sequence.

8. The anti-Aβ CPA of claim 1 or 2, wherein the CIM comprises a TAT amino acid sequence.

9. The anti-Aβ CPA of any one of claims 1, 2, and 8, wherein the CIM comprises more than one TAT amino acid sequence.

10. The anti-Aβ CPA of any one of claims 1-9, wherein the CIM comprises a macrocycle.
11. The anti-Aβ CPA of claim 10, wherein the macrocycle is formed by a covalent bond between two amino acid residues of the CIM.

12. The anti-Aβ CPA of claim 10 or 11, wherein the macrocycle is formed by a disulfide bond between two cysteine residues of the CIM.

13. The anti-Aβ of any one of claims 1-2 or 4-12, wherein the CIM comprises a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 101-107, 110, and 116-338.

14. The anti-Aβ CPA of any one of claims 1-13, wherein the CIM further comprises one or more spacer regions.

15. The anti-Aβ CPA of claim 14, wherein at least one of the one or more spacer regions comprises one or more amino acid residues.

16. The anti-Aβ CPA of claim 14 or 15, wherein at least one of the one or more spacer regions comprises one or more glycine residue.

17. The anti-Aβ CPA of claim 1, wherein the CIM is a polypeptide having an amino acid sequence selected from any one of SEQ ID NOs: 101-338.

18. The anti-Aβ CPA of any one of claims 1-17, wherein the CIM is covalently linked to the antibody.

19. The anti-Aβ CPA of any one of claims 1-17, wherein the CIM is non-covalently linked to the antibody.

20. The anti-Aβ CPA of any one of claims 1-19, wherein the CPA further comprises a linker connecting the CIM to the antibody.

21. The anti-Aβ CPA of claim 20, wherein the linker is covalently linked to both the CIM and the antibody.

22. The anti-Aβ CPA of claim 20 or 21, wherein the linker is a cleavable linker.

23. The anti-Aβ CPA of claim 20 or 21, wherein the linker is a non-cleavable linker.

24. The anti-Aβ CPA of any one of claims 20-23, wherein the linker comprises a polypeptide.

25. The anti-Aβ CPA of any one of claims 20-24, wherein the linker comprises one or more glycine residues.

26. The anti-Aβ CPA of any one of claims 20-25, wherein the linker is a polypeptide comprising an amino acid sequence selected from any one of SEQ ID NOs: 343-346.

27. The anti-Aβ CPA of any one of claims 1-26, wherein the antibody is linked to the C-terminus of the CIM.

28. The anti-Aβ CPA of any one of claims 1-26, wherein the antibody is linked to the N-terminus of the CIM.

29. The anti-Aβ CPA of any one of claims 1-28, wherein the antibody comprises a heavy chain or a portion thereof.

30. The anti-Aβ CPA of claim 29, wherein the CIM is covalently linked to a C-terminus of the heavy chain.

31. The anti-Aβ CPA of claim 29, wherein the CIM is covalently linked to a N-terminus of the heavy chain.

32. The anti-Aβ CPA of any one of claims 1-31, wherein the antibody comprises a light chain or a portion thereof.

33. The anti-Aβ CPA of claim 32, wherein the CIM is covalently linked to a C-terminus of the light chain.

34. The anti-Aβ CPA of claim 32, wherein the CIM is covalently linked to a N-terminus of the light chain.

35. The anti-Aβ CPA of any one of claims 1-34, wherein the antibody competes with binding with a reference antibody comprising a heavy chain variable domain comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain comprising light chain CDR1, CDR2 and CDR3, wherein the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1A and Table 1B.

36. The anti-Aβ CPA of any one of claims 1-35, wherein the antibody comprises a heavy chain variable domain comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain comprising light chain CDR1, CDR2 and CDR3, wherein the heavy chain CDR1, CDR2 and CDR3 and the light chain CDR1, CDR2 and CDR3 are as shown for one of the antibodies in Table 1A and Table 1B.

37. The anti-Aβ CPA of any one of claims 1-36, wherein the antibody comprises a heavy chain variable domain is as shown for one of the antibodies in Table 1A and Table 1B.

38. The anti-Aβ CPA of any one of claims 1-37, wherein the antibody comprises a light chain variable domain is as shown for one of the antibodies in Table 1A and Table 1B.

39. The anti-Aβ CPA of any one of claims 1-35, wherein the antibody comprises a heavy chain variable domain comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain comprising light chain CDR1, CDR2 and CDR3, wherein

heavy chain CDR1 comprises one of SEQ ID NO: 16, 19, or 20,

heavy chain CDR2 comprises one of SEQ ID NO: 20, 21, 22 or 23,

heavy chain CDR3 comprises one of SEQ ID NO: 18, 24, or 25,

light chain CDR1 comprises one of SEQ ID NO: 26, 29, 31, or 32,
light chain CDR2 comprises one of SEQ ID NO: 33, 34, 35 or 36, and
light chain CDR3 comprises one of SEQ ID NO: 28, 38 or 39.

40. The anti-Aβ CPA of claim 35 or claim 39, wherein the heavy chain variable domain, excluding the CDRs, is at least 95% identical an amino acid sequence selected from SEQ ID NO: 3, 4, 5, 6, and 7 , and the light chain variable domain, excluding the CDRs, is at least 95% identical an amino acid sequence selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14, and 15.

41. The anti-Aβ CPA of claim 40, wherein the heavy chain variable domain, excluding the CDRs is at least 98% identical to an amino acid sequence selected from SEQ ID NOs: 3, 4, 5, 6, and 7, and the light chain variable domain, excluding the CDRs, is at least 98% identical to an amino acid sequence selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14 and 15.

42. The anti-Aβ CPA of claim 41, wherein the heavy chain variable domain is selected from SEQ ID NOs: 3, 4, 5, 6, and 7, and the light chain variable domain is selected from SEQ ID NO: 8, 9, 10, 11, 12, 13, 14 and 15.

43. The anti-Aβ CPA of any one of claims 1-35, wherein the antibody comprises a heavy chain variable domain comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain comprising light chain CDR1, CDR2 and CDR3, wherein:
heavy chain CDR1 comprises amino acid sequence GFTFSNX^{A}GMS, wherein X^{A} is Y or F (SEQ ID NO: 88);
heavy chain CDR2 comprises amino acid sequence SX^{A}RSGSGRTYYSDNVKG, wherein is X^{A} is I or V (SEQ ID NO: 89);
heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90);
light chain CDR1 comprises amino acid sequence KSSQSLLDYDGKTYLN (SEQ ID NO: 91);
light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRDX^{C}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is S or T (SEQ ID NO: 92); and

light chain CDR3 comprises amino acid sequence WQGTHFPRX^{A}, wherein X^{A} is S or T (SEQ ID NO: 93).

44. The anti-Aβ CPA of claim 43, wherein light chain CDR3 comprises WQGTHFPRX^{A}FX^{B}, wherein X^{A} is S or T and X^{B} is F or Y (SEQ ID NO: 94).

45. The anti-Aβ CPA of any one of claims 1-35, wherein the antibody comprises a heavy chain variable domain comprising heavy chain CDR1, CDR2 and CDR3 and a light chain variable domain comprising light chain CDR1, CDR2 and CDR3, wherein:
heavy chain CDR1 comprises amino acid sequence GFTFX^{A}NX^{B}GMS, wherein X^{A} is S or A, and X^{B} is Y or F (SEQ ID NO: 95);
heavy chain CDR2 comprises amino acid sequence SX^{A}RSGX^{B}X^{C}RTYYSDNVKG, wherein is X^{A} is I or V, X^{B} is S or G and X^{C} is S or G (SEQ ID NO: 96);
heavy chain CDR3 comprises amino acid sequence YDHYX^{A}GX^{B}SDY, wherein X^{A} is S or T and X^{B} is S or T (SEQ ID NO: 90);
light chain CDR1 comprises amino acid sequence X^{A}SSQSLX^{B}DX^{C}DGKTYLN, wherein X^{A} is K or R, X^{B} is V, M or L, and X^{C} is Y, T or S (SEQ ID NO: 97);
light chain CDR2 comprises amino acid sequence X^{A}VX^{B}NRX^{C}X^{D}, wherein X^{A} is K or R, X^{B} is S or T, and X^{C} is E or D, and X^{D} is S or T (SEQ ID NO: 98); and
light chain CDR3 comprises amino acid sequence WQGX^{A}HFPRX^{B}, wherein X^{A} is S or T, and X^{B} is S or T (SEQ ID NO: 99).

46. The anti-Aβ CPA of claim 45, wherein light chain CDR3 comprises WQGTHFPRX^{A}FX^{B}X^{C}, wherein X^{A} is S or T, X^{B} is S or T and X^{C} is F or Y (SEQ ID NO: 100).

47. The anti-Aβ CPA of any one of claims 1-46, wherein the antibody is humanized.

48. The anti-Aβ CPA of any one of claims 1-47, wherein the antibody is human IgG1 isotype.

49. The anti-Aβ CPA of any one of claims 1-48, wherein the antibody is a full antibody, a chimeric antibody, a CDR-grafted antibody, or a recombinant antibody.

50. The anti-Aβ CPA of any one of claims 1-48, wherein the fragment is a Fab, Fab', F(ab')2, Fabc, or Fv.

51. The anti-Aβ CPA of any one of claims 1-50, wherein the antibody further comprises a heavy chain constant domain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 40.

52. The anti-Aβ CPA of any one of claims 1-51, wherein the antibody further comprises light chain constant domain comprising an amino acid sequence at least 95% identical to SEQ ID NO: 41.

53. The anti-Aβ CPA of any one of claims 1-52, wherein the heavy chain variable domain is fused to a heavy chain constant domain and the light chain variable domain is fused to a light chain constant domain.

54. The anti-Aβ CPA of claim 55, wherein the heavy chain constant domain is a mutant form of a natural human heavy chain constant domain which has reduced binding to an Fcγ receptor relative to the natural heavy chain constant domain.

55. The anti-Aβ CPA of claim 52 or 53 wherein the heavy chain constant domain is of IgG1 isotype.

56. The anti-Aβ CPA of any one of claims 1-54, wherein the antibody has at least one mutation in a constant domain.

57. The anti-Aβ CPA of claim 55, wherein the at least one mutation reduces complement fixation or activation by the constant domain.

58. The anti-Aβ CPA of claim 57, where the at least one mutation is at one or more positions of: 241, 264, 265, 270, 296, 297, 318, 320, 322, 329, and 331 by EU numbering.

59. The anti-Aβ CPA of claim 57, wherein the antibody has an alanine at positions 318, 320, and 322 by EU numbering.

60. The anti-Aβ CPA of any one of claims 1-59, wherein the antibody specifically binds to an epitope having an amino acid sequence including three or more amino acid positions from amino acids 1-7 of Aβ.

61. The anti-Aβ CPA of any one of claims 1-34, wherein the antibody is selected from aducanumab, lecanumab, bapineuzumab, solanezumab, gantererumab, crenezumab, and ponezumab.

62. The anti-Aβ CPA of claim 1, wherein the anti-Aβ CPA comprises a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394.

63. The anti-Aβ CPA of claim 1 or 62, wherein the anti-Aβ CPA comprises a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394.

64. The anti-Aβ CPA of any one of claims 1, 62, or 63, wherein the anti-Aβ CPA comprises a polypeptide sequence selected from any one of: SEQ ID NO: 349, SEQ ID NO: 351, SEQ ID NO: 353, SEQ ID NO: 355, SEQ ID NO: 357, SEQ ID NO: 359, SEQ ID NO: 361, SEQ ID NO: 363, SEQ ID NO: 365, SEQ ID NO: 367, and SEQ ID NO: 394.

65. The anti-Aβ CPA of claim 1 or 62-64, wherein the anti-Aβ CPA comprises a polypeptide that is at least 95% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

66. The anti-Aβ CPA of claim 1 or 62-65, wherein the anti-Aβ CPA comprises a polypeptide that is at least 98% identical to a sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

67. The anti-Aβ CPA of claim 1 or 62-66, wherein the anti-Aβ CPA comprises a polypeptide sequence selected from any one of: SEQ ID NO: 350, SEQ ID NO: 352, SEQ ID NO: 354, SEQ ID NO: 356, SEQ ID NO: 358, SEQ ID NO: 360, SEQ ID NO: 362, SEQ ID NO: 364, SEQ ID NO: 366, and SEQ ID NOs: 368-393.

68. The anti-Aβ CPA of claim 1, wherein the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein:

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 349 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 350;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 351 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 352;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 353 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 354;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 355 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 356;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 357 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 358;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 359 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 360;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 361 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 362;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 363 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 364;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 365 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 366;

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 367 and the second polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 368; or

the first polypeptide comprises a sequence that is at least 95% identical to SEQ ID NO: 394 and the second polypeptide comprises a sequence that is at least 95% identical to any one of SEQ ID NOs: 369-393.

69. The anti-Aβ CPA of claim 1, wherein the anti-Aβ CPA comprises a first polypeptide and a second polypeptide, further wherein:

the first polypeptide comprises SEQ ID NO: 349 and the second polypeptide comprises SEQ ID NO: 350;

the first polypeptide comprises SEQ ID NO: 351 and the second polypeptide comprises SEQ ID NO: 352;

the first polypeptide comprises SEQ ID NO: 353 and the second polypeptide comprises SEQ ID NO: 354;

the first polypeptide comprises SEQ ID NO: 355 and the second polypeptide comprises SEQ ID NO: 356;

the first polypeptide comprises SEQ ID NO: 357 and the second polypeptide comprises SEQ ID NO: 358;

the first polypeptide comprises SEQ ID NO: 359 and the second polypeptide comprises SEQ ID NO: 360; or

the first polypeptide comprises SEQ ID NO: 361 and the second polypeptide comprises SEQ ID NO: 362;

the first polypeptide comprises SEQ ID NO: 363 and the second polypeptide comprises SEQ ID NO: 364;

the first polypeptide comprises SEQ ID NO: 365 and the second polypeptide comprises SEQ ID NO: 366;

the first polypeptide comprises SEQ ID NO: 367 and the second polypeptide comprises SEQ ID NO: 368; or

the first polypeptide comprises SEQ ID NO: 394 and the second polypeptide comprises any one of SEQ ID NOs: 369-393.

70. The anti-Aβ CPA of any one of claims 1-69, wherein the antibody is conjugated to a therapeutic, cytotoxic, cytostatic, immunomodulatory, neurotrophic, or neuroprotective agent.

71. The cell penetrating agent of any one of claims 1-70, wherein the heavy chain does not comprise a C-terminal lysine residue.

72. A pharmaceutical composition comprising the anti-Aβ CPA of any one of claims 1-71 and a pharmaceutically acceptable carrier or diluent.

73. A nucleic acid encoding at least a portion of the anti-Aβ CPA of any one of claims 1-71.

74. The nucleic acid of claim 73, wherein the nucleic acid encodes for the CIM or a portion thereof.

75. The nucleic acid of claim 73 or 74, wherein the nucleic acid encodes for the CIM or a portion thereof and at least one of a heavy chain variable domain of the antibody and a light chain variable domain of the antibody.

76. The nucleic acid of any one of claims 73-75, wherein the nucleic acid encodes for the CIM or a portion thereof and a heavy chain variable domain of the antibody or a portion thereof.

77. The nucleic acid of any one of claims 73-75, wherein the nucleic acid encodes for the CIM or a portion thereof and a light chain variable domain of the antibody or a portion thereof.

78. A vector comprising the nucleic acid of any one of claims 73-77 operably linked to one or more regulatory sequences to effect expression in a mammalian cell of the cell penetrating agent of any one of claims 1 to 71.

5

79. The vector of claim 78, wherein the one or more regulatory sequences comprise one or more of an enhancer, ribosome binding site, transcription termination signal, and promoter, optionally, wherein the promoter is a eukaryotic promoter.

80. The vector of claim 78 or 79, wherein the nucleic acid is codon-optimized for expression in a host cell.

81. A host cell transformed with the vector of any one of claims 78-80.

82. A host cell comprising the nucleic acid of any one of claims 73-77.

83. A method of delivering the antibody that specifically binds to Aβ into a cell, comprising contacting the anti-Aβ CPA of any one of claims 1 to 71 with the cell, thereby resulting in the internalization into the cell of, at a minimum, an antigen-binding fragment of the antibody.

84. The method of claim 83, the method further comprising transfer of, at a minimum, an antigen-binding fragment of the antibody, to the cytosol of the cell.

85. A method of binding an intracellular Aβ protein in a cell, the method comprising: contacting the anti-Aβ CPA of any one of claims 1 to 71 with the cell, thereby resulting in the internalization of and transfer to the cytosol of, at a minimum, an antigen-binding fragment of the antibody.

86. The method of any one of claims 83-85, wherein the cell is a mammalian cell.

87. The method of any one of claims 83-86, wherein the cell is in vitro.

88. The method of any one of claims 83-86, wherein the cell is in a subject.

89. A method of inhibiting or reducing aggregation of Aβ in a subject having or at risk of developing a Aβ-related disease, comprising administering to the subject an effective amount of the anti-Aβ CPA of any one of claims 1 to 71, thereby inhibiting or reducing aggregation of Aβ in the subject.

90. A method of treating or effecting prophylaxis of a Aβ-related disease in a subject, comprising administering a therapeutically effective amount of the cell penetrating agent of any one of claims 1 to 71, thereby treating or effecting prophylaxis of the Aβ-associated disease.

91. The method of claim 90, wherein the Aβ-related disease is Inclusion-Body Myositis.

5

92. A method of detecting Aβ deposits in a subject having or at risk of developing a Aβ-related disease, comprising administering to a subject the cell penetrating agent of any one of claims 1 to 71, and detecting the antibody bound to Aβ in the subject.

93. A method of detecting Aβ in a sample obtained from a patient having or at risk of developing a Aβ related disease, comprising contacting the sample with the cell penetrating agent of any one of claims 1 to 71, and detecting the binding of the antibody to Aβ in the sample.

94. The method of claim 92 or 93, wherein the antibody is labeled.

95. The method of claim 94, wherein the antibody is labeled with a fluorescent label, a paramagnetic label, or a radioactive label.

96. The method of claim 95, wherein the radioactive label is detected using positron emission tomography (PET) or single-photon emission computed tomography (SPECT).