Claims

1. A polypeptide comprising a variant of a starting amino acid sequence, wherein the starting amino acid sequence is amino acids 1-217 of SEQ ID NO:1, wherein:

(a) the polypeptide binds to and/or disaggregates amyloid;

(b) the polypeptide has reduced immunogenicity as compared to a polypeptide comprising the starting amino acid sequence;

(c) the variant has from 1 to 9 amino acid substitutions as compared to the starting amino acid sequence, wherein each amino acid substitution is selected from the group of amino acid substitutions set forth below:

Amino Acid #	Amino Acid present in the Starting Amino Acid Sequence	Amino Acid Substitutions in the Variant
48	G	H, K, R, S, T, D, P
50	E	G, H, K, P, R
51	T	G, H, K, R, P, Q, N, W
53	C	F, H, K, N, Q, R, W, Y
54	Y	G, H, K, R, P
56	T	G, H, K, R, P
135	M	A, D, G, K, N, T, H, R, C, E, P, Q, S
137	Q	D, E
138	N	D, E, G, H, P, Q, S, T
140	R	D, E, H, Q, A, G, M, N, P, S, Y
141	F	D, E
143	N	A, G
173	S	G, P, K, D, H, R, T
174	K	R
175	A	G, H, K, P, R
176	M	G, H, K, N, R, P, Q, W
178	D	G, N, Q, S, T, F, H, K, R, W, Y
179	A	H, K, P, R
181	W	G, H, K, R, P
215	V	S, T, C, D, E, F, H, K, N, P, Q, R

and

(d) the variant optionally further comprises one or more of the following modifications as compared to the starting amino acid sequence:

(i) substitution of VVV at amino acids 43-45 with AAA;

(ii) substitution C53W;

(iii) deletion of amino acids 96-103;

(iv) substitution of QPP at amino acids 212-214 with AGA;

(v) substitutions W181A, F190A and F194A;

(vi) deletion of amino acid 1; and

(vii) deletion of amino acids 1 and 2.

2. A polypeptide comprising a variant of a starting amino acid sequence, wherein the starting amino acid sequence is amino acids 1-217 of SEQ ID NO:3, wherein:

(a) the polypeptide binds to and/or disaggregates amyloid;

(b) the polypeptide has reduced immunogenicity as compared to a polypeptide comprising the starting amino acid sequence;

(c) the variant has from 1 to 9 amino acid substitutions as compared to the starting amino acid sequence, wherein each amino acid substitution is selected from the group of amino acid substitutions set forth below:

Amino Acid #	Amino Acid present in the Starting Amino Acid Sequence	Amino Acid Substitutions in the Variant
48	G	H, K, R, S, T, D, P
50	E	G, H, K, P, R
51	T	G, H, K, R, P, Q, N, W
53	C	F, H, K, N, Q, R, W, Y
54	Y	G, H, K, R, P
56	T	G, H, K, R, P
135	M	A, D, G, K, N, T, H, R, C, E, P, Q, S
137	Q	D, E
138	N	D, E, G, H, P, Q, S, T
140	R	D, E, H, Q, A, G, M, N, P, S, Y
141	F	D, E
143	N	A, G
173	S	G, P, K, D, H, R, T
174	K	R
175	A	G, H, K, P, R
176	M	G, H, K, N, R, P, Q, W
178	D	G, N, Q, S, T, F, H, K, R, W, Y
179	A	H, K, P, R
181	W	G, H, K, R, P

and

(d) the variant optionally further comprises one or more of the following modifications as compared to the starting amino acid sequence:

(i) substitution of VVV at amino acids 43-45 with AAA;

(ii) substitution C53W;

(iii) deletion of amino acids 96-103;

(iv) substitution of QPP at amino acids 212-214 with AGA;

(v) substitutions W181A, F190A and F194A;

(vi) deletion of amino acid 1; and

(vii) deletion of amino acids 1 and 2.

3. A polypeptide comprising a variant of a starting amino acid sequence, wherein the starting amino acid sequence is amino acids 1-217 of SEQ ID NO:7, wherein:

(a) the polypeptide binds to and/or disaggregates amyloid;

(b) the polypeptide has reduced immunogenicity as compared to a polypeptide comprising the starting amino acid sequence;

(c) the variant has from 1 to 9 amino acid substitutions as compared to the starting amino acid sequence, wherein each amino acid substitution is selected from the group of amino acid substitutions set forth below:

Amino Acid #	Amino Acid present in the Starting Amino Acid Sequence	Amino Acid Substitutions in the Variant
48	G	H, K, R, S, T, D, P
50	E	G, H, K, P, R
51	T	G, H, K, R, P, Q, N, W
53	C	F, H, K, N, Q, R, W, Y
54	Y	G, H, K, R, P
56	T	G, H, K, R, P
135	M	A, D, G, K, N, T, H, R, C, E, P, Q, S
137	Q	D, E
138	N	D, E, G, H, P, Q, S, T
140	R	D, E, H, Q, A, G, M, N, P, S, Y
141	F	D, E
143	N	A, G
173	S	G, P, K, D, H, R, T

174	K	R
175	A	G, H, K, P, R
176	M	G, H, K, N, R, P, Q, W
178	D	G, N, Q, S, T, F, H, K, R, W, Y
179	A	H, K, P, R
181	W	G, H, K, R, P

and

(d) the variant optionally further comprises one or more of the following modifications as compared to the starting amino acid sequence:

(i) substitution of VVV at amino acids 43-45 with AAA;

(ii) substitution C53W;

(iii) deletion of amino acids 96-103;

(iv) substitution of QPP at amino acids 212-214 with AGA;

(v) substitutions W181A, F190A and F194A;

(vi) deletion of amino acid 1; and

(vii) deletion of amino acids 1 and 2.

4. The polypeptide of any one of claims 1-3, wherein each of the 1 to 9 amino acid substitutions in the variant as compared to the starting amino acid sequence is selected from the group of amino acid substitutions set forth below:

Amino Acid #	Amino Acid present in the Starting Amino Acid Sequence	Amino Acid Substitutions in the Variant
48	G	H, K, R, S, T
51	T	G, H, K, R, P, Q, N
54	Y	G, H, K, R, P
56	T	G, H, K, R, P
135	M	A, D, G, K, N, T, H, R
140	R	D, E, H, Q, A, G
141	F	D, E
143	N	A, G
173	S	G, P, K
174	K	R
176	M	G, H, K, N, R
178	D	G, N, Q, S, T

181	W	G, H, K, R

5. The polypeptide of any one of claims 1-4, wherein the variant amino acid sequence has 2 to 9 amino acid substitutions relative to the starting amino acid sequence, and wherein at least one substitution is present in at least two of: epitope 1, comprising amino acids 48-56 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7; epitope 2, comprising amino acids 135-143 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7; and epitope 3, comprising amino acids 173-181 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7.

6. The polypeptide of claim 5, wherein the variant amino acid sequence has only two amino acid substitutions, and wherein the substitutions are selected from the group of two amino acid substitutions set forth below:

Y54K and M135K	Y54K and M135T	Y54K and R140Q	Y54R and M135K
Y54R and M135T	Y54R and R140Q	T56H and M135K	T56H and M135T
T56H and R140Q	T56K and M135K	T56K and M135T	T56K and R140Q
Y54K and D178N	Y54K and W181H	Y54K and W181R	Y54K and K174R
Y54R and D178N	Y54R and W181H	Y54R and W181R	Y54R and K174R
T56H and D178N	T56H and W181H	T56H and W181R	T56H and K174R
T56K and D178N	T56K and W181H	T56K and W181R	T56K and K174R
M135K and D178N	M135K and W181H	M135K and W181R	M135K and K174R
M135T and D178N	M135T and W181H	M135T and W181R	M135T and K174R
R140Q and D178N	R140Q and W181H	R140Q and W181R	R140Q and K174R

7. The polypeptide of any one of claims 1-4, wherein the variant amino acid sequence has 3 to 9 amino acid substitutions relative to the starting amino acid sequence, and wherein at least one substitution is in each of epitope 1, comprising amino acids 48-56 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7; epitope 2, comprising amino acids 135-143 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7; and epitope 3, comprising amino acids 173-181 of SEQ ID NO:1, SEQ ID NO:3 or SEQ ID NO:7.

8. The polypeptide of claim 7, wherein the variant amino acid sequence has only three amino acid substitutions compared to the starting amino acid sequence, and wherein the substitutions are selected from any of the following sets of amino acid substitutions: T56H, M135K and D178N; T56K, M135K and D178N; T56K, M135T and D178N; T56H, M135K and W181R; T56H, M135T

and W181R; Y54K, M135T and K174R; Y54R, M135K and K174R;Y54R, M135T and K174R; T56H, M135K and K174R; and T56H, M135T and K174R.

9. The polypeptide of any one of claims 1 to 8, consisting essentially of a human or humanized immunoglobulin Fc polypeptide sequence fused either via a peptide linker or directly to the C-terminus of the variant amino acid sequence.

10. The polypeptide of claim 9, wherein the immunoglobulin Fc polypeptide sequence is the Fc portion of a human IgG.

11. The polypeptide of claim 10, wherein the amino acid sequence of the peptide linker and Fc portion of human IgG is selected from amino acids 218-488 of SEQ ID NO:1, amino acids 218-486 of SEQ ID NO:3, and amino acids 218-488 of SEQ ID NO:7.

12. A polypeptide variant consisting of a modified starting sequence, wherein the starting sequence is selected from SEQ ID NO:3 or SEQ ID NO:7 and the modification is two or three amino acid substitutions, the polypeptide being selected from any one of the polypeptides set forth below:

Polypeptide No.	Starting Sequence	Epitope 1 Substitution	Epitope 2 Substitution	Epitope 3 Substitution
63	SEQ ID NO:3	Y54K	M135K	None
64	SEQ ID NO:3	Y54K	M135T	None
65	SEQ ID NO:3	Y54K	R140Q	None
66	SEQ ID NO:3	Y54R	M135K	None
67	SEQ ID NO:3	Y54R	M135T	None
68	SEQ ID NO:3	Y54R	R140Q	None
69	SEQ ID NO:3	T56H	M135K	None
70	SEQ ID NO:3	T56H	M135T	None
71	SEQ ID NO:3	T56H	R140Q	None
72	SEQ ID NO:3	T56K	M135K	None
73	SEQ ID NO:3	T56K	M135T	None
74	SEQ ID NO:3	T56K	R140Q	None
75	SEQ ID NO:3	Y54K	None	D178N
76	SEQ ID NO:3	Y54K	None	W181H
77	SEQ ID NO:3	Y54K	None	W181R
78	SEQ ID NO:3	Y54K	None	K174R
79	SEQ ID NO:3	Y54R	None	D178N
80	SEQ ID NO:3	Y54R	None	W181H
81	SEQ ID NO:3	Y54R	None	W181R
82	SEQ ID NO:3	Y54R	None	K174R
83	SEQ ID NO:3	T56H	None	D178N

Polypeptide No.	Starting Sequence	Epitope 1 Substitution	Epitope 2 Substitution	Epitope 3 Substitution
84	SEQ ID NO:3	T56H	None	W181H
85	SEQ ID NO:3	T56H	None	W181R
86	SEQ ID NO:3	T56H	None	K174R
87	SEQ ID NO:3	T56K	None	D178N
88	SEQ ID NO:3	T56K	None	W181H
89	SEQ ID NO:3	T56K	None	W181R
90	SEQ ID NO:3	T56K	None	K174R
91	SEQ ID NO:3	None	M135K	D178N
92	SEQ ID NO:3	None	M135K	W181H
93	SEQ ID NO:3	None	M135K	W181R
94	SEQ ID NO:3	None	M135K	K174R
95	SEQ ID NO:3	None	M135T	D178N
96	SEQ ID NO:3	None	M135T	W181H
97	SEQ ID NO:3	None	M135T	W181R
98	SEQ ID NO:3	None	M135T	K174R
99	SEQ ID NO:3	None	R140Q	D178N
100	SEQ ID NO:3	None	R140Q	W181H
101	SEQ ID NO:3	None	R140Q	W181R
102	SEQ ID NO:3	None	R140Q	K174R
110	SEQ ID NO:7	T56H	M135K	D178N
111	SEQ ID NO:7	T56H	M135K	W181H
112	SEQ ID NO:7	T56H	M135K	W181R
113	SEQ ID NO:7	T56H	M135K	K174R
114	SEQ ID NO:7	T56H	M135T	D178N
115	SEQ ID NO:7	T56H	M135T	W181H
116	SEQ ID NO:7	T56H	M135T	W181R
117	SEQ ID NO:7	T56H	M135T	K174R
118	SEQ ID NO:7	T56K	M135K	D178N
119	SEQ ID NO:7	T56K	M135K	W181H
120	SEQ ID NO:7	T56K	M135K	W181R
121	SEQ ID NO:7	T56K	M135K	K174R
122	SEQ ID NO:7	T56K	M135T	D178N
123	SEQ ID NO:7	T56K	M135T	W181H
124	SEQ ID NO:7	T56K	M135T	W181R
125	SEQ ID NO:7	T56K	M135T	K174R
126	SEQ ID NO:7	Y54K	M135K	K174R
127	SEQ ID NO:7	Y54K	M135T	K174R
128	SEQ ID NO:7	Y54R	M135K	K174R
129	SEQ ID NO:7	Y54R	M135T	K174R
130	SEQ ID NO:7	T56H	None	D178N
131	SEQ ID NO:7	T56H	None	W181H
132	SEQ ID NO:7	T56H	None	W181R
133	SEQ ID NO:7	T56H	None	K174R

Polypeptide No.	Starting Sequence	Epitope 1 Substitution	Epitope 2 Substitution	Epitope 3 Substitution
134	SEQ ID NO:7	T56K	None	D178N
135	SEQ ID NO:7	T56K	None	W181H
136	SEQ ID NO:7	T56K	None	W181R
137	SEQ ID NO:7	T56K	None	K174R

13. The polypeptide of claim 12, selected from any one of Polypeptide Nos. 110, 112, 113, 116, 117, 118, 122, 127, 128, and 129.

14. A pharmaceutical composition comprising the polypeptide of any one of claims 1-13 and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14 for use in treating a disease characterized by the presence of amyloid or tau protein aggregates.

16. The pharmaceutical composition of claim 14 for use according to claim 15, wherein the use comprises treating a patient that is positive for the biomarker florbetapir when that biomarker is used as an imaging agent in positron emission tomography.

17. The pharmaceutical composition of claim 14 for use according to either of claims 15 or 16, wherein the disease to be treated is selected from Alzheimer’s disease, early onset Alzheimer's disease, late onset Alzheimer's disease, presymptomatic Alzheimer's disease, Parkinson’s disease, SAA amyloidosis, cystatin C, hereditary Icelandic syndrome, senility, multiple myeloma, prion diseases, kuru, Creutzfeldt-Jakob disease (CJD), Gerstmann-Straussler-Scheinker disease (GSS), fatal familial insomnia (FFI), scrapie, bovine spongiform encephalitis (BSE), amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA1, SCA3, SCA6, or SCA7), Huntington’s disease, dentatorubral-pallidoluysian atrophy, spinal and bulbar muscular atrophy, hereditary cerebral amyloid angiopathy, familial amyloidosis, British/Danish dementia, familial encephalopathy, Amyotrophic lateral sclerosis/parkinsonism-dementia complex, Argyrophilic grain dementia, Corticobasal degeneration, Dementia pugilistica, diffuse neurofibrillary tangles with calcification, Down’s syndrome, Gerstmann-Sträussler-Scheinker disease, Hallervorden-Spatz disease, Myotonic dystrophy, Niemann-Pick disease type C, Non-Guamanian motor neuron disease with neurofibrillary tangles, Pick’s disease, Postencephalitic parkinsonism, Prion protein cerebral amyloid angiopathy, Progressive subcortical gliosis, Progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only

dementia, frontotemporal lobar degenerations (FTLDs), and frontotemporal lobe dementia (FTD) including a patient having one or more of the following clinical syndromes: behavioral variant FTD (bvFTD), progressive non-fluent aphasia (PNFA), frontotemporal dementia with parkinsonism linked to chromosome 17, Progressive Supranuclear Palsey (PSP), and semantic dementia (SD).

18. A nucleic acid sequence encoding any one of the polypeptides of claims 1-13.

19. A vector comprising a nucleic acid sequence of claim 18, wherein the nucleic acid sequence is operatively linked to an expression control sequence in the vector.

20. A host cell containing the vector of claim 19.

21. A method of making a polypeptide of any one of claims 1-13 comprising the steps of expressing the protein encoded by the nucleic acid sequence of claim 18 or culturing the host cell of claim 20 under conditions sufficient to allow expression of the polypeptide; and isolating the expressed polypeptide.