ANTI-TAU ANTIBODIES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority of US Provisional Application No. 62/171,693, filed June 5, 2015, which is incorporated by reference herein in its entirety for any purpose.

FIELD OF THE INVENTION

[0002] The present invention relates to anti-Tau antibodies and methods of using the same.

BACKGROUND

[0003] Neurofibrillary tangles and neuropil threads (NTs) are the major neuropathological hallmarks of Alzheimer's Disease (AD). NTs are composed of the microtubule-associated Tau protein that has undergone post-translational modifications including phosphorylation, and develop by aggregation of hyperphosphorylated Tau conformers. AD shares this pathology with many neurodegenerative tauopathies, in particularly with certain types of frontotemporal dementia (FTD). Tau protein appears to be a major player in the cognitive demise in AD and related neurodegenerative tauopathies.

[0004] Therapeutic approaches that target Tau protein are scarce and comprise mainly inhibitors of the kinases that are thought to increase the phosphorylation of Tau to pathological levels, and compounds that block the cytoplasmic aggregation of hyper-phosphorylated Tau protein. These approaches suffer various draw-backs of specificity and efficacy. There is a need for additional therapeutic agents that target the pathological protein conformers that are known or presumed to cause neurodegenerative disorders.

SUMMARY

[0005] The disclosure provides anti-Tau antibodies and methods of using the same.

[0005a] In one aspect, the disclosure provides an isolated antibody that binds to human Tau, wherein the antibody comprises:

a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147;

b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167; or

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247.

[0006] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some examples, the antibody binds an epitope within amino acids 2 to 24 of mature human Tau. In some examples, the antibody is a monoclonal antibody. In some examples, the antibody is a human, humanized, or chimeric

antibody. In some examples, the antibody is an antibody fragment that binds human Tau. In some examples, the human Tau comprises the sequence of SEQ ID NO: 2.

[0007] In some examples, the antibody comprises:

a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; and HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344; or

b) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; and HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304;

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44;

d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64;

e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214;

f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34; or

g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54.

[0008] In some examples, the antibody comprises:

a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347;

b) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307;

c) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47;

d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67;

e) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217

f) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37; or

g) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[0009] In some examples, the antibody comprises:

a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344; HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347;

b) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304; HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; HVR-

L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307;

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47;

d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67;

e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217;

f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37; or

g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[0010] In some examples, the antibody comprises:

s) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 50;

t) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 51; or

u) a VH as in (s) and a VL as in (t).

[0011] In some examples, the antibody comprises:

a) a heavy chain variable region (VH) comprising a sequence selected from SEQ ID NOs: 10, 20, 280, 290, and 340;

b) a light chain variable region (VL) comprising a sequence selected from SEQ ID NOs: 11, 21, 281, 291, and 341;

c) a VH as in (a) and a VL as in (b);

d) a heavy chain variable region (VH) comprising a sequence selected from SEQ ID NOs: 70, 300, and 452 to 459;

e) a light chain variable region (VL) comprising a sequence selected from SEQ ID NOs: 71, 301, and 460 to 467;

f) a VH as in (d) and a VL as in (e);

g) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 40;

h) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 41;

i) a VH as in (g) and a VL as in (h);

j) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 60;

k) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 61;

l) a VH as in (j) and a VL as in (k);

m) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 210;

n) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 211;

o) a VH as in (m) and a VL as in (n);

p) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 30;

q) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 31;

r) a VH as in (p) and a VL as in (q);

s) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 50;

t) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 51; or

u) a VH as in (s) and a VL as in (t).

[0012] In some examples, the antibody comprises HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

[0013] In some examples, the antibody comprises a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 340 and a light chain variable region comprising the amino acid sequence of SEQ ID NO: 341.

[0014] In some examples, the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349.

[0015] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 348 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain comprising the amino acid sequence of SEQ ID NO: 602 and a light chain comprising the amino acid sequence of SEQ ID NO: 349. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain consisting of the amino acid sequence of SEQ ID NO: 349. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 348 and a light

chain consisting of the amino acid sequence of SEQ ID NO: 349. In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody comprises a heavy chain consisting of the amino acid sequence of SEQ ID NO: 602 and a light chain consisting of the amino acid sequence of SEQ ID NO: 349.

[0016] In some examples, an isolated antibody that binds to human Tau is provided, wherein the antibody binds an epitope within amino acids 19 to 33, 19 to 42, 28 to 44, 37 to 51, 100 to 114, 109 to 123, 118 to 132, 154 to 168, 172 to 177, 217 to 231, or 397 to 411 of mature human Tau.

[0017] In some examples, the antibody comprises:

a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114;

b) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 132;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 133; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 134;

c) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144;

d) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 152;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 153; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154;

e) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164;

f) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 252;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 253; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254;

g) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 272;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 273; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 274;

h) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 102;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 103; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104;

s) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; and
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264.

[0018] In some examples, the antibody comprises:

a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 116; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 117;
b) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 135;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 136; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 137;
c) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147;
d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 155;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 156; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 157;
e) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167;
f) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 255;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 256; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 257;
g) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 275;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277;
h) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 105;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 106; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 107;
i) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 175;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 176; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 177;
j) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 195;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 196; and
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 197;

k) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247;

l) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 85, 315, 325, and 335; HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 86, 316, 326, and 336; and HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 87, 317, 327, and 337;

m) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 95; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 96; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 97;

n) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 125; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 126; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 127;

o) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 185; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 186; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 187;

p) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 205; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 206; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 207;

q) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 225; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 226; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 227;

r) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237; or

s) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 265; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 266; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 267.

[0019] In some examples, the antibody comprises:

a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115;

r) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 232; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 233; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237; or

s) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264; HVR-L1 comprising the amino acid sequence of SEQ ID NO: 265; HVR-L2 comprising the amino acid sequence of SEQ ID NO: 266; and HVR-L3 comprising the amino acid sequence of SEQ ID NO: 267.

[0020] In some examples, the antibody comprises:

a) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 110;

b) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 111;

c) a VH as in (a) and a VL as in (b);

d) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 130;

e) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 131;

f) a VH as in (d) and a VL as in (e);

g) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 140;

h) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 141;

i) a VH as in (g) and a VL as in (h);

j) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 150;

k) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 151;

l) a VH as in (j) and a VL as in (k);

zz) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 230;

aaa) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 231;

bbb) a VH as in (zz) and a VL as in (aaa);

ccc) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 260;

ddd) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 261; or

eee) a VH as in (ccc) and a VL as in (ddd).

[0021] In some examples, the antibody comprises:

a) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 110;

b) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 111;

c) a VH as in (a) and a VL as in (b);

d) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 130;

e) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 131;

f) a VH as in (d) and a VL as in (e);

g) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 140;

h) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 141;

i) a VH as in (g) and a VL as in (h);

j) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 150;

k) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 151;

l) a VH as in (j) and a VL as in (k);

m) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 160;

bbb) a VH as in (zz) and a VL as in (aaa);

ccc) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 260;

ddd) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 261; or

eee) a VH as in (ccc) and a VL as in (ddd).

[0022] In any of the examples described herein, the antibody may be an IgG1 or an IgG4 antibody. In any of the examples described herein, the antibody may be an IgG4 antibody. In some such examples, the antibody comprises M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may comprise an S228P mutation. In any of the examples described herein, the antibody may comprise S228P, M252Y, S254T, and T256E mutations. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations. In some examples, the antibody is an antibody fragment. In any of the examples described herein, the antibody may be an IgG4 antibody comprising S228P, M252Y, S254T, and T256E mutations, and lacking the C-terminal lysine (des-K) of the heavy chain constant region. The C-terminal lysine of the heavy chain constant region may be removed, for example, during purification of the antibody or by recombinant engineering of the nucleic acid encoding the antibody such that the C-terminal lysine is not encoded.

[0023] In some examples, an isolated antibody that binds human Tau is provided, wherein the antibody binds each of monomeric Tau, phosphorylated Tau, non-phosphorylated Tau, and oligomeric Tau with a K_D of less than 100 nM, less than 75 nM, or less than 50 nM. In some examples, the antibody binds cynomolgus monkey Tau (SEQ ID NO: 4).

[0024] In one aspect, the disclosure provides an isolated nucleic acid that encodes the antibody as disclosed herein. In some examples, an isolated nucleic acid is provided, wherein the isolated nucleic acid encodes an antibody described herein. In one aspect, the disclosure provides a host cell comprising the nucleic acid as disclosed herein. In some examples, a host cell is provided, wherein the host cell comprises an isolated nucleic acid that encodes an antibody described herein. In one aspect, the disclosure provides a method of producing an antibody comprising culturing the host cell as disclosed herein under conditions suitable for producing the antibody. In some examples, a method of producing an antibody is provided, comprising culturing the host cell under conditions suitable for producing the antibody.

[0025] In one aspect, the disclosure provides an immunoconjugate comprising the isolated antibody as disclosed herein and a second therapeutic agent. In some examples, an immunoconjugate is provided, wherein the immunoconjugate comprises an isolated antibody described herein and a therapeutic agent. In one aspect, the disclosure provides a labeled antibody comprising the antibody as disclosed herein and a detectable label. In some examples, a labeled antibody is provided, comprising an antibody described herein and a detectable label.

[0026] In one aspect, the disclosure provides a pharmaceutical composition comprising the isolated antibody as disclosed herein and a pharmaceutically acceptable carrier. In some examples, a pharmaceutical composition is provided, comprising an isolated antibody described herein and a pharmaceutically acceptable carrier.

[0027] In some examples, a method of treating a Tau protein associated disease is provided, comprising administering to an individual with a Tau protein related disease an antibody described herein or a pharmaceutical composition comprising an antibody described herein. In some examples, the Tau protein associated disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotetemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0028] In some examples, a method of retaining or increasing cognitive memory capacity or slowing memory loss in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0029] In some examples, a method of reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual is provided, comprising administering an antibody described herein or a pharmaceutical composition comprising an antibody described herein.

[0030] In some examples, an isolated antibody described herein is provided for use as a medicament. In some examples, an isolated antibody described herein is provided for use in treating a tauopathy in an individual. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal

degeneration, diffuse neurofibrillary tangles with calcification, frontotetemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0031] In some examples, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual. In some examples, an isolated antibody described herein is provided for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual.

[0032] In some examples, use of an antibody described herein is provided for manufacture of a medicament for treating a Tau protein associated disease in an individual. In some examples, the Tau protein associate disease is a tauopathy. In some examples, the tauopathy is a neurodegenerative tauopathy. In some examples, the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down's Syndrome, Gerstmann-Sträussler-Scheinker disease, inclusion-body myositis, prion protein cerebral amyloid angiopathy, traumatic brain injury, amyotrophic lateral sclerosis/parkinsonism-dementia complex of Guam, Non-Guamanian motor neuron disease with neurofibrillary tangles, argyrophilic grain dementia, corticobasal degeneration, diffuse neurofibrillary tangles with calcification, frontotetemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallevorden-Spatz disease, multiple system atrophy, Niemann-Pick disease type C, Pallido-ponto-nigral degeneration, Pick's disease, progressive subcortical gliosis, progressive supranuclear palsy, Subacute sclerosing panencephalitis, Tangle only dementia, Postencephalitic Parkinsonism, and Myotonic dystrophy. In some examples, the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

[0033] In some examples, use of an antibody described herein is provided for manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual.

[0034] In some examples, a method of detecting neurofibrillary tangles, neuropil threads, or dystrophic neuritis is provided, comprising contacting a sample with an antibody

described herein. In some examples, the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.

[0035] In any of the examples described herein, a method or use may comprise administering an antibody described herein in combination with at least one additional therapy. Non-limiting examples of additional therapies include neurological drugs, corticosteroids, antibiotics, antiviral agents, and other therapeutic agents. Such other therapeutic agents include, but are not limited to, other anti-Tau antibodies, antibodies against amyloid-beta, antibodies against beta-secretase 1 ("BACE1"), and inhibitors of beta-secretase 1.

BRIEF DESCRIPTION OF THE FIGURES

[0036] Figure 1A-F. Binding of antibodies to hyperphosphorylated Tau (pTau) was compared to non-phosphorylated Tau using an ELISA. Results are expressed in optical densities (O.D.).

[0037] Figure 2A-E. Binding of antibodies to oligomeric Tau was assessed using an oligo- and monoTau capture ELISA. Results are expressed in optical densities (O.D.).

[0038] Figure 3. The three panTau antibodies tested show binding to soluble Tau in brain lysates from Alzheimer's disease (AD) and matched control donors using a Western blot (WB) assay. Protein extracts from AD and control brain lysates, and six isoforms of recombinant human Tau, were run on SDS-PAGE and membranes blotted with three panTau antibodies (37D3-H9, 94B2-C1, and 125B11-H3). Lanes with AD samples are labeled as AD18, AD24, and AD27, and lanes with control samples are labeled as C25 and C21. The lanes run with six isoforms of recombinant human Tau are labeled as hTau ladder.

[0039] Figure 4A-C. PanTau antibodies show binding to soluble Tau in brain lysates from AD and matched control donors using a Tau capture ELISA. Data is shown for three panTau antibodies, 37D3-H9, 94B2-C1, and 125B11-H3. Results are expressed in optical densities (O.D.), with mean values ±SD, N=2.

[0040] Figure 5. Sensorgrams showing 37D3-H9 binding as a Fab (left panel) and as an IgG (right panel) to human Tau monomer covalently coupled to a Biacore chip surface. A 1:1 binding model has been applied and is shown as an overlay. The x-axis indicates time (units=seconds). The y-axis indicated Resonance Units (RU).

[0041] Figure 6. Overlaid sensorgrams showing binding of hu37D3-H9.v5 samples t=0 (left panel) and t=2 weeks (right panel) to human Tau monomer at 3.1, 6.3, 12.5, 25, 25, 50 and 100 nM. A 1:1 binding model has been applied and is also shown in this figure. The x-axis indicates time (units=seconds). The y-axis indicated Resonance Units (RU).