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.

[0006] Disclosed is 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.

[0009a] In one aspect, there is provided an isolated monoclonal antibody that binds to human Tau, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau, wherein 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 an amino acid sequence selected from SEQ ID NOs: 345, 15, 468 to 478, 495 to 517, 522 to 534, 536 to 539, and 543 to 556; 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.

[0010] In some examples, the antibody comprises:

a) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 10, 20, 280, 290, and 340;
b) a light chain variable region (VL) comprising a sequence that is at least 95% identical to 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 that is at least 95% identical to a sequence selected from SEQ ID NOs: 70, 300, and 452 to 459;
e) a light chain variable region (VL) comprising a sequence that is at least 95% identical to 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 a sequence that is at least 95% identical to SEQ ID NO: 40;
h) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 41;
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: 60;
k) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 61;
l) a VH as in (j) and a VL as in (k);
m) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 210;
n) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 211;
o) a VH as in (m) and a VL as in (n);
p) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 30;
q) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 31;
r) a VH as in (p) and a VL as in (q);

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 one aspect, 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 one aspect, 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;

i) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 172; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174;

j) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 192; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194;

k) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244;

l) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; and HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334;

m) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 92; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94;

n) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 122; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124;

o) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 182; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 183; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184;

p) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 202; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204;

q) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 222; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224;

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; and HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234; 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; 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;

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

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;
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154;
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-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;

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;
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254;
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; or

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;
HVR-L1 comprising the amino acid sequence of SEQ ID NO: 275;
HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276;
HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277;

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;
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104;
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-H1 comprising the amino acid sequence of SEQ ID NO: 172;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173;
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174;
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-H1 comprising the amino acid sequence of SEQ ID NO: 192;
HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193;
HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194;
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; or

k) 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;

l) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334; 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-H1 comprising the amino acid sequence of SEQ ID NO: 92; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94; 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-H1 comprising the amino acid sequence of SEQ ID NO: 122; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124; 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-H1 comprising the amino acid sequence of SEQ ID NO: 182; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 183; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184; 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-H1 comprising the amino acid sequence of SEQ ID NO: 202; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204; 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-H1 comprising the amino acid sequence of SEQ ID NO: 222; HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224; 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-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);

m) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 160;

n) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 161; or

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

p) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 250;

q) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 251;

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

s) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 270;

t) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 271;

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

v) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 100;

w) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 101; or

x) a VH as in (v) and a VL as in (w);

y) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 170;

z) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 171;

aa) a VH as in (y) and a VL as in (z);

bb) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 190;

cc) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 191;

dd) a VH as in (bb) and a VL as in (cc);

ee) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 240;

ff) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 241; or

gg) a VH as in (ee) and a VL as in (ff);

hh) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 80, 310, 320, 330, and 446 to 451;

ii) a light chain variable region (VL) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 81, 311, 321, 331, and 442 to 445;

jj) a VH as in (hh) and a VL as in (ii);

kk) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 90;

ll) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 91;

mm) a VH as in (kk) and a VL as in (ll);

nn) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 120;

oo) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 121;

pp) a VH as in (nn) and a VL as in (oo);

qq) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 180;

rr) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 181;

ss) a VH as in (qq) and a VL as in (rr);

tt) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 200;

uu) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 201;

vv) a VH as in (tt) and a VL as in (uu);

ww) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 220;

xx) a light chain variable region (VL) comprising a sequence that is at least 95% identical to SEQ ID NO: 221;

yy) a VH as in (ww) and a VL as in (xx);

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;

n) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 161; or

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: 250;

q) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 251;

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: 270;

t) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 271; or

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

v) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 100;

w) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 101; or

x) a VH as in (v) and a VL as in (w);

y) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 170;

z) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 171;

aa) a VH as in (y) and a VL as in (z);

bb) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 190;

cc) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 191;

dd) a VH as in (bb) and a VL as in (cc);

ee) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 240;

ff) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 241;

gg) a VH as in (ee) and a VL as in (ff);

hh) a heavy chain variable region (VH) comprising a sequence selected from SEQ ID NOs: 80, 310, 320, 330, and 446 to 451;

ii) a light chain variable region (VL) comprising a sequence selected from SEQ ID NOs: 81, 311, 321, 331, and 442 to 445;

jj) a VH as in (hh) and a VL as in (ii);

kk) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 90;

ll) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 91;

mm) a VH as in (kk) and a VL as in (ll);

nn) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 120;

oo) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 121;

pp) a VH as in (nn) and a VL as in (oo);

qq) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 180;

rr) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 181;

ss) a VH as in (qq) and a VL as in (rr);

tt) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 200;

uu) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 201;

vv) a VH as in (tt) and a VL as in (uu);

ww) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 220;

xx) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 221;

yy) a VH as in (ww) and a VL as in (xx);

zz) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 230;

aaa) a light chain variable region (VL) comprising the sequence of SEQ ID NO: 231;

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, an isolated nucleic acid is provided, wherein the isolated nucleic acid encodes an antibody described herein. In one aspect, a host cell is provided, wherein the host cell comprises an isolated nucleic acid that encodes an antibody described herein. In one aspect, a method of producing an antibody is provided, comprising culturing the host cell described herein under conditions suitable for producing the antibody.

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

[0026] In one aspect, 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 one aspect, an isolated antibody described herein is provided for use as a medicament. In one aspect, 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 one aspect, an isolated antibody described herein is provided for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease. In one aspect, 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 with a Tau protein associated disease.

[0032] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the 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 one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

[0033a] In one aspect, use of an antibody or pharmaceutical composition described herein is provided in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

[0034] In one aspect, 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).

[0042] Figure 7. Binding of hu37D3-H9.v5 and hu37D3-H9.v5 N28D to monomeric Tau individually (left panel shows hu37D3-H9.v5 and middle panel shows hu37D3-H9.v5 N28D) and mixed at a 1:1 ratio (right panel). The x-axis indicates time (units=seconds). The y-axis indicated Resonance Units (RU).

[0043] Figure 8A-D. Affinity, stability index and sequences of the ninety 37D3-H9 variants screened for potential improved stability. For clarity, values obtained with an unstressed control antibody (hu37D3-H9.v5 hIgG1) run at the beginning, middle and end of each experiment are shown in both sections of the table.

[0044] Figure 9. Structural model of the 37D3-H9 Fv region showing the positions of residues 28 to 33 (NGNTYF motif) of the light chain and relative positions of residues 28 and 33. Note that residue 33, mutated in hu37D3.v28.A4 to Leu, is not nearby the unstable Asn-28 residue. The dotted line shows a hydrogen bond between residues Asn-28 and Tyr-32. Figure generated using MOE software package (Chemical Computing Group).

[0045] Figure 10 shows pharmacokinetics of anti-Tau antibody 37D3-H9 in mice following a single 10 mg/kg intravenous or intraperitoneal injection.

[0046] Figure 11 shows pharmacokinetics of hu37D3.v28.A4 hIgG4-S228P and hu37D3.v28.A4 hIgG4-S228P.YTE in cynomolgus monkeys following a single IV bolus injection at a dose of 1 mg/kg.

[0047] Figure 12A-C. Binding of certain anti-Tau antibodies to Tau fragments. (A) Binding of certain anti-Tau antibodies to Tau fragments 1-15, 10-24, 19-33, 28-42, 37-51, and 46-60 is shown. (B) Binding of antibody 37D3-H9 mIgG2a to Tau fragments 10-44, 10-24, 2-24, 2-34, and full-length Tau. (C) Binding of antibody hu37D3-H9.v5 hIgG1 to Tau fragments 10-44, 10-24, 2-24, 2-34, and full-length Tau.

[0048] Figure 13A-B. Effect of effector function on Tau toxicity in neuron-microglia co-cultures. (A) Percent MAP2 fragmentation in co-cultures contacted with various antibodies and oligomeric Tau. (B) Images of neurons (top panels) and neuron-microglia co-cultures (bottom panels) contacted with various antibodies and oligomeric Tau.

[0049] Figure 14. pTau212/214 levels in the hippocampus of mice administered anti-tau 37D3-H9 WT IgG2a or anti-tau 37D3-H9 DANG IgG2.

[0050] Figure 15. Comparison of human and cynomolgus monkey Tau sequences. The epitope for antibody 37D3-H9 is indicated.

[0051] Figure 16 shows pharmacokinetics of anti-Tau antibody 94B2-C1 in mice following a single 10 mg/kg intravenous or intraperitoneal injection.

[0052] Figure 17 shows pharmacokinetics of anti-Tau antibody 125B11-H3 in mice following a single 10 mg/kg intravenous or intraperitoneal injection.

[0053] Figure 18 shows an alignment of the kappa 1 light chain variable regions of hu37D3-H9.v1, hu37D3-H9.v39, hu37D3-H9.v40, and hu37D3-H9.v41.

[0054] Figure 19A-B show plasma antibody concentration (A) and CSF antibody concentration (B) in cynomolgus monkeys following a single IV injection of the indicated antibody at 50 mg/kg.

[0055] Figure 20 shows plasma total Tau concerntration and plasma antibody concentration in cynomolgus monkeys following a single IV injection of the indicated antibody at 50 mg/kg.

[0056] Figures 21A-D show antibody concentration in various regions of cynomolgus monkey brain 2 days and 10 days following a single IV injection of hu37D3.v28.A4 hIgG4-S228P (A) and hu37D3.v28.A4 hIgG4-S228P.YTE (B) at 50 mg/kg; average antibody concentration in brain (C); % brain:plasma antibody concentration (D).

[0057] Figures 22A-B show the concentration of antibody in cynomolgus monkey brain at various time points following a single IV injection of the indicated antibody at 50 mg/kg, plotted in logarithmic (A) and linear (B) scale.

[0058] Figures 23A-E show show the concentration of antibody in the hippocampus (A), cerebellum (B), frontal cortex (C), CSF (D), and plasma (E) of cynomolgus monkeys at various time points following a single IV injection of the indicated antibody at 50 mg/kg.

[0059] Figures 24A-B show average (A) and individual (B) plasma total Tau concentration over time in cynomolgus monkeys following a single IV injection of the indicated antibody at 50 mg/kg.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

I. DEFINITIONS

[0060] An "acceptor human framework" for the purposes herein is a framework comprising the amino acid sequence of a light chain variable domain (VL) framework or a heavy chain variable domain (VH) framework derived from a human immunoglobulin framework or a human consensus framework, as defined below. An acceptor human framework "derived from" a human immunoglobulin framework or a human consensus framework may comprise the same amino acid sequence thereof, or it may contain amino acid sequence changes. In some embodiments, the number of amino acid changes are 10 or less, 9 or less, 8 or less, 7 or less, 6 or less, 5 or less, 4 or less, 3 or less, or 2 or less. In some

embodiments, the VL acceptor human framework is identical in sequence to the VL human immunoglobulin framework sequence or human consensus framework sequence.

[0061] "Affinity" refers to the strength of the sum total of noncovalent interactions between a single binding site of a molecule (*e.g.*, an antibody) and its binding partner (*e.g.*, an antigen). Unless indicated otherwise, as used herein, "binding affinity" refers to intrinsic binding affinity which reflects a 1:1 interaction between members of a binding pair (*e.g.*, antibody and antigen). The affinity of a molecule X for its partner Y can generally be represented by the dissociation constant (K_D). Affinity can be measured by common methods known in the art, including those described herein. Specific illustrative and exemplary embodiments for measuring binding affinity are described in the following.

[0062] An "affinity matured" antibody refers to an antibody with one or more alterations in one or more hypervariable regions (HVRs), compared to a parent antibody which does not possess such alterations, such alterations resulting in an improvement in the affinity of the antibody for antigen.

[0063] The terms "anti-Tau antibody" and "an antibody that binds to Tau" refer to an antibody that is capable of binding Tau with sufficient affinity such that the antibody is useful as a diagnostic and/or therapeutic agent in targeting Tau. In some embodiments, the extent of binding of an anti-Tau antibody to an unrelated, non-Tau protein is less than about 10% of the binding of the antibody to Tau as measured, *e.g.*, by a radioimmunoassay (RIA). In certain embodiments, an antibody that binds to Tau has a dissociation constant (K_D) of $\leq$ 1μM, $\leq$ 100 nM, $\leq$ 10 nM, $\leq$ 1 nM, $\leq$ 0.1 nM, $\leq$ 0.01 nM, or $\leq$ 0.001 nM (*e.g.* 10^{-8} M or less, *e.g.* from 10^{-8} M to 10^{-13} M, *e.g.*, from 10^{-9} M to 10^{-13} M). In certain embodiments, an anti-Tau antibody binds to an epitope of Tau that is conserved among Tau from different species. The term "anti-Tau antibody" and "antibody that binds to Tau," as used herein, refers to an antibody that binds monomeric Tau, oligomeric Tau, and/or phosphorylated Tau, unless specifically indicated otherwise. In some such embodiments, the anti-Tau antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau with comparable affinities, such as with affinities that differ by no more than 50-fold from one another. In some embodiments, an antibody that binds monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau is referred to as a "pan-Tau antibody."

[0064] The term "antibody" herein is used in the broadest sense and encompasses various antibody structures, including but not limited to monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), and antibody fragments so long as they exhibit the desired antigen-binding activity.

[0065] An "antibody fragment" refers to a molecule other than an intact antibody that comprises a portion of an intact antibody that binds the antigen to which the intact antibody binds. Examples of antibody fragments include but are not limited to Fv, Fab, Fab', Fab'-SH, $F(ab')_2$; diabodies; linear antibodies; single-chain antibody molecules (*e.g.* scFv); and multispecific antibodies formed from antibody fragments.

[0066] An "antibody that binds to the same epitope" as a reference antibody refers to an antibody that blocks binding of the reference antibody to its antigen in a competition assay by 50% or more, and conversely, the reference antibody blocks binding of the antibody to its antigen in a competition assay by 50% or more. An exemplary competition assay is provided herein.

[0067] The term "chimeric" antibody refers to an antibody in which a portion of the heavy and/or light chain is derived from a particular source or species, while the remainder of the heavy and/or light chain is derived from a different source or species.

[0068] The "class" of an antibody refers to the type of constant domain or constant region possessed by its heavy chain. There are five major classes of antibodies: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), *e.g.*, IgG_1, IgG_2, IgG_3, IgG_4, IgA_1, and IgA_2. The heavy chain constant domains that correspond to the different classes of immunoglobulins are called α, δ, ε, γ, and μ, respectively.

[0069] The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents a cellular function and/or causes cell death or destruction. Cytotoxic agents include, but are not limited to, radioactive isotopes (*e.g.*, At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu); chemotherapeutic agents or drugs (*e.g.*, methotrexate, adriamicin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents); growth inhibitory agents; enzymes and fragments thereof such as nucleolytic enzymes; antibiotics; toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof; and the various antitumor or anticancer agents disclosed below.

[0070] "Effector functions" refer to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.* B cell receptor); and B cell activation.

[0071] An "effective amount" of an agent, *e.g.*, a pharmaceutical formulation, refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic or prophylactic result.

[0072] The term "Fc region" herein is used to define a C-terminal region of an immunoglobulin heavy chain that contains at least a portion of the constant region. The term includes native sequence Fc regions and variant Fc regions. In some embodiments, a human IgG heavy chain Fc region extends from Cys226, or from Pro230, to the carboxyl-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region or constant region is according to the EU numbering system, also called the EU index, as described in Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD, 1991.

[0073] "Framework" or "FR" refers to variable domain residues other than hypervariable region (HVR) residues. The FR of a variable domain generally consists of four FR domains: FR1, FR2, FR3, and FR4. Accordingly, the HVR and FR sequences generally appear in the following sequence in VH (or VL): FR1-H1(L1)-FR2-H2(L2)-FR3-H3(L3)-FR4.

[0074] The terms "full length antibody," "intact antibody," and "whole antibody" are used herein interchangeably to refer to an antibody having a structure substantially similar to a native antibody structure or having heavy chains that contain an Fc region as defined herein.

[0075] The terms "host cell," "host cell line," and "host cell culture" are used interchangeably and refer to cells into which exogenous nucleic acid has been introduced, including the progeny of such cells. Host cells include "transformants" and "transformed cells," which include the primary transformed cell and progeny derived therefrom without regard to the number of passages. Progeny may not be completely identical in nucleic acid content to a parent cell, but may contain mutations. Mutant progeny that have the same function or biological activity as screened or selected for in the originally transformed cell are included herein.

[0076] A "human antibody" is one which possesses an amino acid sequence which corresponds to that of an antibody produced by a human or a human cell or derived from a non-human source that utilizes human antibody repertoires or other human antibody-encoding sequences. This definition of a human antibody specifically excludes a humanized antibody comprising non-human antigen-binding residues.

[0077] The term "variable region" or "variable domain" refers to the domain of an antibody heavy or light chain that is involved in binding the antibody to antigen. The variable

domains of the heavy chain and light chain (VH and VL, respectively) of a native antibody generally have similar structures, with each domain comprising four conserved framework regions (FRs) and three hypervariable regions (HVRs). (See, *e.g.*, Kindt et al. *Kuby Immunology*, 6th ed., W.H. Freeman and Co., page 91 (2007).) A single VH or VL domain may be sufficient to confer antigen-binding specificity. Furthermore, antibodies that bind a particular antigen may be isolated using a VH or VL domain from an antibody that binds the antigen to screen a library of complementary VL or VH domains, respectively. *See, e.g.*, Portolano et al., *J. Immunol.* 150:880-887 (1993); Clarkson et al., *Nature* 352:624-628 (1991).

[0078] A "human consensus framework" is a framework which represents the most commonly occurring amino acid residues in a selection of human immunoglobulin VL or VH framework sequences. Generally, the selection of human immunoglobulin VL or VH sequences is from a subgroup of variable domain sequences. Generally, the subgroup of sequences is a subgroup as in Kabat et al., *Sequences of Proteins of Immunological Interest*, Fifth Edition, NIH Publication 91-3242, Bethesda MD (1991), vols. 1-3. In some embodiments, for the VL, the subgroup is subgroup kappa I as in Kabat et al., *supra.* In some embodiments, for the VH, the subgroup is subgroup III as in Kabat et al., *supra.*

[0079] A "humanized" antibody refers to a chimeric antibody comprising amino acid residues from non-human HVRs and amino acid residues from human FRs. In certain embodiments, a humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the HVRs (*e.g.*, CDRs) correspond to those of a non-human antibody, and all or substantially all of the FRs correspond to those of a human antibody. A humanized antibody optionally may comprise at least a portion of an antibody constant region derived from a human antibody. A "humanized form" of an antibody, *e.g.*, a non-human antibody, refers to an antibody that has undergone humanization.

[0080] The term "hypervariable region" or "HVR" as used herein refers to each of the regions of an antibody variable domain which are hypervariable in sequence ("complementarity determining regions" or "CDRs") and/or form structurally defined loops ("hypervariable loops") and/or contain the antigen-contacting residues ("antigen contacts"). Generally, antibodies comprise six HVRs: three in the VH (H1, H2, H3), and three in the VL (L1, L2, L3). Exemplary HVRs herein include:

(a) hypervariable loops occurring at amino acid residues 26-32 (L1), 50-52 (L2), 91-96 (L3), 26-32 (H1), 53-55 (H2), and 96-101 (H3) (Chothia and Lesk, *J. Mol. Biol.* 196:901-917 (1987));

(b) CDRs occurring at amino acid residues 24-34 (L1), 50-56 (L2), 89-97 (L3), 31-35b (H1), 50-65 (H2), and 95-102 (H3) (Kabat et al., *Sequences of Proteins of Immunological Interest*, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD (1991));

(c) antigen contacts occurring at amino acid residues 27c-36 (L1), 46-55 (L2), 89-96 (L3), 30-35b (H1), 47-58 (H2), and 93-101 (H3) (MacCallum et al. *J. Mol. Biol.* 262: 732-745 (1996)); and

(d) combinations of (a), (b), and/or (c), including HVR amino acid residues 46-56 (L2), 47-56 (L2), 48-56 (L2), 49-56 (L2), 26-35 (H1), 26-35b (H1), 49-65 (H2), 93-102 (H3), and 94-102 (H3).

[0081] Unless otherwise indicated, HVR residues and other residues in the variable domain (*e.g.*, FR residues) are numbered herein according to Kabat et al., *supra.*

[0082] An "immunoconjugate" is an antibody conjugated to one or more heterologous molecule(s), including but not limited to a cytotoxic agent.

[0083] An "individual" or "subject" is a mammal. Mammals include, but are not limited to, domesticated animals (*e.g.*, cows, sheep, cats, dogs, and horses), primates (*e.g.*, humans and non-human primates such as monkeys), rabbits, and rodents (*e.g.*, mice and rats). In certain embodiments, the individual or subject is a human.

[0084] An "isolated" antibody is one which has been separated from a component of its natural environment. In some embodiments, an antibody is purified to greater than 95% or 99% purity as determined by, for example, electrophoretic (*e.g.*, SDS-PAGE, isoelectric focusing (IEF), capillary electrophoresis) or chromatographic (*e.g.*, ion exchange or reverse phase HPLC). For review of methods for assessment of antibody purity, see, *e.g.*, Flatman et al., *J. Chromatogr. B* 848:79-87 (2007).

[0085] An "isolated" nucleic acid refers to a nucleic acid molecule that has been separated from a component of its natural environment. An isolated nucleic acid includes a nucleic acid molecule contained in cells that ordinarily contain the nucleic acid molecule, but the nucleic acid molecule is present extrachromosomally or at a chromosomal location that is different from its natural chromosomal location.

[0086] "Isolated nucleic acid encoding an anti-Tau antibody" refers to one or more nucleic acid molecules encoding antibody heavy and light chains (or fragments thereof), including such nucleic acid molecule(s) in a single vector or separate vectors, and such nucleic acid molecule(s) present at one or more locations in a host cell.

[0087] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies

comprising the population are identical and/or bind the same epitope, except for possible variant antibodies, *e.g.*, containing naturally occurring mutations or arising during production of a monoclonal antibody preparation, such variants generally being present in minor amounts. In contrast to polyclonal antibody preparations, which typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody of a monoclonal antibody preparation is directed against a single determinant on an antigen. Thus, the modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by a variety of techniques, including but not limited to the hybridoma method, recombinant DNA methods, phage-display methods, and methods utilizing transgenic animals containing all or part of the human immunoglobulin loci, such methods and other exemplary methods for making monoclonal antibodies being described herein.

[0088] A "naked antibody" refers to an antibody that is not conjugated to a heterologous moiety (*e.g.*, a cytotoxic moiety) or radiolabel. The naked antibody may be present in a pharmaceutical formulation.

[0089] "Native antibodies" refer to naturally occurring immunoglobulin molecules with varying structures. For example, native IgG antibodies are heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light chains and two identical heavy chains that are disulfide-bonded. From N- to C-terminus, each heavy chain has a variable region (VH), also called a variable heavy domain or a heavy chain variable domain, followed by three constant domains (CH1, CH2, and CH3). Similarly, from N- to C-terminus, each light chain has a variable region (VL), also called a variable light domain or a light chain variable domain, followed by a constant light (CL) domain. The light chain of an antibody may be assigned to one of two types, called kappa (κ) and lambda (λ), based on the amino acid sequence of its constant domain.

[0090] The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, combination therapy, contraindications and/or warnings concerning the use of such therapeutic products.

[0091] "Percent (%) amino acid sequence identity" with respect to a reference polypeptide sequence is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the reference polypeptide sequence,

after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for aligning sequences, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc., and the source code has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available from Genentech, Inc., South San Francisco, California, or may be compiled from the source code. The ALIGN-2 program should be compiled for use on a UNIX operating system, including digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

[0092] In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

100 times the fraction X/Y

where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

[0093] The term "pharmaceutical formulation" refers to a preparation which is in such form as to permit the biological activity of an active ingredient contained therein to be

effective, and which contains no additional components which are unacceptably toxic to a subject to which the formulation would be administered.

[0094] A "pharmaceutically acceptable carrier" refers to an ingredient in a pharmaceutical formulation, other than an active ingredient, which is nontoxic to a subject. A pharmaceutically acceptable carrier includes, but is not limited to, a buffer, excipient, stabilizer, or preservative.

[0095] The term "Tau," as used herein, refers to any native Tau protein from any vertebrate source, including mammals such as primates (*e.g.*, humans) and rodents (*e.g.*, mice and rats), unless otherwise indicated. The term encompasses "full-length," unprocessed Tau as well as any form of Tau that results from processing in the cell. The term also encompasses naturally occurring variants of Tau, *e.g.*, splice variants or allelic variants.

[0096] The term "pTau," as used herein, refers to Tau in which a serine, a threonine or a tyrosine residue is phosphorylated by a protein kinase by the addition of a covalently bound phosphate group. In some embodiments, pTau is phosphorylated on a serine or on a threonine residue. In some embodiments, pTau is phosphorylated on Serine at position 409 and/or Serine at position 404. In some embodiments, pTau is phosphorylated on Serine at position 409.

[0097] The terms "soluble Tau" or "soluble Tau protein," as used herein, refer to proteins consisting of both completely solubilized Tau protein/peptide monomers or of Tau-like peptides/proteins, or of modified or truncated Tau peptides/proteins or of other derivates of Tau peptides/proteins monomers, and of Tau protein oligomers. "Soluble Tau" excludes particularly neurofibrillary tangles (NFT).

[0098] The term "insoluble Tau," as used herein, refers to multiple aggregated monomers of Tau peptides or proteins, or of Tau-like peptides/proteins, or of modified or truncated Tau peptides/proteins or of other derivates of Tau peptides/proteins forming oligomeric or polymeric structures which are insoluble both *in vitro* in aqueous medium and *in vivo* in the mammalian or human body more particularly in the brain, but particularly to multiple aggregated monomers of Tau or of modified or truncated Tau peptides/proteins or of derivatives thereof, which are insoluble in the mammalian or human body more particularly in the brain, respectively. "Insoluble Tau" particularly includes neurofibrillary tangles (NFT).

[0099] The terms "monomeric Tau" or "Tau monomer," as used herein, refer to completely solubilized Tau proteins without aggregated complexes in aqueous medium.

[00100] The terms "aggregated Tau", "oligomeric Tau" and "Tau oligomer," as used herein, refer to multiple aggregated monomers of Tau peptides or proteins, or of Tau-like

peptides/proteins, or of modified or truncated Tau peptides/proteins or of other derivates of Tau peptides/proteins forming oligomeric or polymeric structures which are insoluble or soluble both *in vitro* in aqueous medium and *in vivo* in the mammalian or human body more particularly in the brain, but particularly to multiple aggregated monomers of Tau or of modified or truncated Tau peptides/proteins or of derivatives thereof, which are insoluble or soluble in the mammalian or human body more particularly in the brain, respectively.

[00101] The terms "pTau PHF", "PHF", and "paired helical filaments," are used herein synonymously, refer to pairs of filaments wound into helices with a periodicity of 160 nm visible on electron microscopy. Width varies between 10 and 22 nm. PHF are the predominant structures in neurofibrillary tangles of Alzheimer's Disease (AD) and neuropil threads. PHF may also be seen in some but not all dystrophic neurites associated with neuritic plaques. The major component of PHF is a hyperphosphorylated form of microtubule-associated protein tau. PHF may be partially composed of disulfide-linked antiparallel hyper-phosphorylated Tau proteins. PHF Tau may be truncated of its C-terminal 20 amino acid residues. The mechanisms underlying PHF formation are uncertain but hyper-phosphorylation of Tau may disengage it from microtubules, increasing the soluble pool of Tau from which PHF can be formed inside neurons.

[00102] As used herein, "treatment" (and grammatical variations thereof such as "treat" or "treating") refers to clinical intervention in an attempt to alter the natural course of the individual being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies of the invention are used to delay development of a disease or to slow the progression of a disease.

[00103] The term "early Alzheimer's Disease" or "early AD" as used herein (e.g., a "patient diagnosed with early AD" or a "patient suffering from early AD") includes patients with mild cognitive impairement, such as a memory deficit, due to AD and patients having AD biomarkers, for example amyloid positive patients.

[00104] The term "mild Alzheimer's Disease" or "mild AD" as used herein (e.g., a "patient diagnosed with mild AD") refers to a stage of AD characterized by an MMSE score of 20 to 26.

[00105] The term "mild to moderate Alzheimer's Disease" or "mild to moderate AD" as used herein encompasses both mild and moderate AD, and is characterized by an MMSE score of 18 to 26.

[00106] The term "moderate Alzheimer's Disease" or "moderate AD" as used herein (e.g., a "patient diagnosed with moderate AD") refers to a stage of AD characterized by an MMSE score of 18 to 19.

[00107] The term "MMSE" refers to the Mini Mental State Examination, which provides a score between 1 and 30. See Folstein, et al., 1975, J. Psychiatr. Res. 12:189–98. Scores of 26 and lower are generally considered to be indicative of a deficit. The lower the numerical score on the MMSE, the greater the tested patient's deficit or impairment relative to another individual with a lower score. An increase in MMSE score may be indicative of improvement in the patient's condition, whereas a decrease in MMSE score may denote worsening in the patient's condition.

[00108] The term "vector," as used herein, refers to a nucleic acid molecule capable of propagating another nucleic acid to which it is linked. The term includes the vector as a self-replicating nucleic acid structure as well as the vector incorporated into the genome of a host cell into which it has been introduced. Certain vectors are capable of directing the expression of nucleic acids to which they are operatively linked. Such vectors are referred to herein as "expression vectors."

II. COMPOSITIONS AND METHODS

[00109] Antibodies that bind Tau are provided. In some embodiments, an antibody of the invention binds Tau binds monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some embodiments, an antibody of the invention binds to an epitope within amino acids 2 to 24 of mature human Tau. In some embodiments, an antibody of the invention binds to an epitope within Tau amino acids 2 to 24 and binds monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau. In some embodiments, an antibody binds an epitope of human Tau having, or consisting of, the sequence AEPRQEFEVMEDHAGTYGLGDRK (SEQ ID NO: 2). In some embodiments, an antibody binds an epitope of cynomolgus monkey Tau having, or consisting of, the sequence AEPRQEFDVMEDHAGTYGLGDRK (SEQ ID NO: 4). In some embodiments, an antibody binds an epitope of human Tau having, or consisting of, the sequence AEPRQEFEVMEDHAGTYGLGDRK (SEQ ID NO: 2) and an epitope of cynomolgus monkey Tau having, or consisting of, the sequence AEPRQEFDVMEDHAGTYGLGDRK (SEQ ID NO: 4). In some embodiments, an antibody of the invention binds to an epitope

within amino acids 19 to 33, 19 to 42, 37 to 51, 100 to 114, 118 to 132, or 172 to 177 of mature human Tau. In some embodiments, an antibody of the invention binds to an epitope within amino acids 19 to 33, 19 to 42, 37 to 51, 100 to 114, 118 to 132, or 172 to 177 of mature human Tau and binds monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau.

[00110] Antibodies of the invention are useful, *e.g.*, for the diagnosis or treatment of neurodegenerative diseases.

A. Exemplary Anti-Tau Antibodies

[00111] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; (e) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347.

[00112] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

[00113] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; (e) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307.

[00114] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 85, 315, 325, and 335; (e) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 86, 316, 326, and 336; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 87, 317, 327, and 337.

[00115] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

[00116] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00117] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[00118] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67.

[00119] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 72; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 73; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 74; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77.

[00120] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 82; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 83; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 84; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 85; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 86; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 87.

[00121] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 92; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 95; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 96; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 97.

[00122] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 102; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 103; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 105; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 106; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 107.

[00123] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 116; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 117.

[00124] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence

of SEQ ID NO: 122; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 125; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 126; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 127.

[00125] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 132; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 133; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 134; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 135; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 136; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 137.

[00126] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147.

[00127] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 152; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 153; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 155; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 156; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 157.

[00128] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167.

[00129] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 175; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 176; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 177.

[00130] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 182; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 183; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 185; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 186; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 187.

[00131] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 192; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 195; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 196; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 197.

[00132] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 202; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 205; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 206; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 207.

[00133] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; (e) HVR-L2 comprising the amino

acid sequence of SEQ ID NO: 216; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217.

[00134] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 222; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 225; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 226; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 227.

[00135] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 233; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237.

[00136] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247.

[00137] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 252; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 253; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 255; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 256; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 257.

[00138] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264; (d) HVR-L1

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

[00139] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 272; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 273; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 274; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 275; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277.

[00140] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 282; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 283; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 284; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 285; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 286; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 287.

[00141] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 292; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 293; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 294; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 295; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 296; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 297.

[00142] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 302; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 303; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 304; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 305; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 306; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 307.

[00143] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 312; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 313;

(c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 314; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 315; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 316; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 317.

[00144] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 322; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 323; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 324; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 325; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 326; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 327.

[00145] In some embodiments, an anti-Tau antibody comprises at least one, two, three, four, five, or six HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 333; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 334; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 335; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 336; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 337.

[00146] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344.

[00147] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344. In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344.

[00148] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304.

[00149] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; and (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334.

[00150] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34.

[00151] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44.

[00152] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; and (c) HVR-H3

comprising the amino acid sequence of SEQ ID NO: 54. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54.

[00153] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64.

[00154] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 72; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 73; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 74. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 72; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 73; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 74.

[00155] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 82; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 83; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 84. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 82; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 83; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 84.

[00156] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 92; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 92; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94.

[00157] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO:

102; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 103; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 102; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 103; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104.

[00158] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114.

[00159] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 122; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 122; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124.

[00160] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 132; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 133; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 134. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 132; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 133; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 134.

[00161] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144.

[00162] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 152; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 153; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 152; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 153; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154.

[00163] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164.

[00164] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174.

[00165] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 182; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 183; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 182; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 183; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184.

[00166] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 192; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 192; (b)

HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194.

[00167] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 202; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 202; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204.

[00168] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214.

[00169] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 222; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 222; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224.

[00170] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 233; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 233; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234.

[00171] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244. In some embodiments, an anti-Tau

antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244.

[00172] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 252; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 253; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 252; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 253; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254.

[00173] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264.

[00174] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 272; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 273; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 274. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 272; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 273; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 274.

[00175] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 282; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 283; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 284. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 282; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 283; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 284.

[00176] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 292; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 293; and (c) HVR-H3

comprising the amino acid sequence of SEQ ID NO: 294. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 292; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 293; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 294.

[00177] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 302; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 303; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 304. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 302; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 303; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 304.

[00178] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 312; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 313; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 314. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 312; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 313; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 314.

[00179] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 322; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 323; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 324. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 322; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 323; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 324.

[00180] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 333; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 334. In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 333; and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 334.

[00181] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising an amino acid sequence selected from

SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347.

[00182] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

[00183] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 76 and 306; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 77 and 307.

[00184] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 85, 315, 325, and 335; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 86, 316, 326, and 336; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 87, 317, 327, and 337. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 85, 315, 325, and 335; (b) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 86, 316, 326, and 336; and (c) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 87, 317, 327, and 337.

[00185] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:

35; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

[00186] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00187] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[00188] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67.

[00189] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77.

[00190] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 85; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 86; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 87. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 85; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 86; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 87.

[00191] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 95; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 96; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 97. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 95; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 96; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 97.

[00192] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 105; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 106; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 107. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 105; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 106; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 107.

[00193] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 116; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 117. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 116; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 117.

[00194] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 125; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 126; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 127. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 125; (b)

HVR-L2 comprising the amino acid sequence of SEQ ID NO: 126; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 127.

[00195] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 135; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 136; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 137. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 135; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 136; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 137.

[00196] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147.

[00197] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 155; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 156; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 157. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 155; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 156; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 157.

[00198] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167.

[00199] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 175; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 176; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 177. In some embodiments, an anti-Tau

antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 175; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 176; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 177.

[00200] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 185; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 186; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 187. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 185; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 186; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 187.

[00201] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 195; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 196; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 197. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 195; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 196; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 197.

[00202] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 205; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 206; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 207. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 205; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 206; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 207.

[00203] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217.

[00204] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 225; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 226; and (c) HVR-L3

comprising the amino acid sequence of SEQ ID NO: 227. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 225; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 226; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 227.

[00205] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237.

[00206] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247.

[00207] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 255; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 256; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 257. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 255; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 256; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 257.

[00208] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 265; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 266; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 267. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 265; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 266; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 267.

[00209] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO:

275; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 275; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277.

[00210] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 285; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 286; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 287. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 285; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 286; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 287.

[00211] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 295; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 296; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 297. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 295; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 296; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 297.

[00212] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 305; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 306; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 307. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 305; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 306; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 307.

[00213] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 315; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 316; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 317. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 315; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 316; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 317.

[00214] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 325; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 326; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 327. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 325; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 326; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 327.

[00215] In some embodiments, an anti-Tau antibody comprises at least one, two, or three HVRs selected from (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 335; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 336; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 337. In some embodiments, an anti-Tau antibody comprises (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 335; (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 336; and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 337.

[00216] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 12, 22, 282, 292, and 342; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 13, 23, 283, 293, and 343; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 14, 24, 284, 294, and 344; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 15, 25, 285, 295, 345, and 468 to 556; (e) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 16, 26, 286, 296, and 346; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 17, 27, 287, 297, and 347.

[00217] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 342; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 343; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 344; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 345; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 346; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 347.

[00218] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 72 and 302; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 73 and 303; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 74 and 304; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 75 and 305; (e) HVR-L2

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

[00219] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising an amino acid sequence selected from SEQ ID NOs: 82, 312, 322, and 332; (b) HVR-H2 comprising an amino acid sequence selected from SEQ ID NOs: 83, 313, 323, and 333; (c) HVR-H3 comprising an amino acid sequence selected from SEQ ID NOs: 84, 314, 324, and 334; (d) HVR-L1 comprising an amino acid sequence selected from SEQ ID NOs: 85, 315, 325, and 335; (e) HVR-L2 comprising an amino acid sequence selected from SEQ ID NOs: 86, 316, 326, and 336; and (f) HVR-L3 comprising an amino acid sequence selected from SEQ ID NOs: 87, 317, 327, and 337.

[00220] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 32; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 33; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 34; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 35; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 36; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 37.

[00221] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 42; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 43; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 44; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 45; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 46; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 47.

[00222] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 52; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 53; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 54; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 55; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 56; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 57.

[00223] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 62; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 63; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 64; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 65; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 66; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 67.

[00224] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 72; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 73; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 74; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 75; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 76; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 77.

[00225] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 82; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 83; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 84; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 85; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 86; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 87.

[00226] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 92; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 93; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 94; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 95; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 96; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 97.

[00227] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 102; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 103; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 104; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 105; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 106; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 107.

[00228] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 112; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 113; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 114; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 115; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 116; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 117.

[00229] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 122; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 123; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 124; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 125; (e) HVR-

L2 comprising the amino acid sequence of SEQ ID NO: 126; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 127.

[00230] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 132; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 133; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 134; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 135; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 136; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 137.

[00231] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 142; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 143; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 144; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 145; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 146; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 147.

[00232] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 152; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 153; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 154; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 155; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 156; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 157.

[00233] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 162; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 163; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 164; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 165; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 166; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 167.

[00234] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 172; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 173; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 174; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 175; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 176; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 177.

[00235] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 182; (b) HVR-H2 comprising the amino

acid sequence of SEQ ID NO: 183; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 184; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 185; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 186; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 187.

[00236] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 192; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 193; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 194; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 195; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 196; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 197.

[00237] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 202; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 203; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 204; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 205; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 206; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 207.

[00238] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 212; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 213; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 214; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 215; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 216; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 217.

[00239] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 222; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 223; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 224; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 225; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 226; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 227.

[00240] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 232; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 233; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 234; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 235; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 236; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 237.

[00241] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 242; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 243; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 244; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 245; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 246; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 247.

[00242] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 252; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 253; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 254; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 255; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 256; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 257.

[00243] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 262; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 263; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 264; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 265; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 266; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 267.

[00244] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 272; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 273; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 274; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 275; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 276; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 277.

[00245] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 282; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 283; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 284; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 285; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 286; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 287.

[00246] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 292; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 293; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 294; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 295; (e) HVR-

L2 comprising the amino acid sequence of SEQ ID NO: 296; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 297.

[00247] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 302; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 303; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 304; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 305; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 306; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 307.

[00248] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 312; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 313; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 314; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 315; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 316; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 317.

[00249] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 322; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 323; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 324; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 325; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 326; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 327.

[00250] In some embodiments, an anti-Tau antibody comprises (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 332; (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 333; (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 334; (d) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 335; (e) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 336; and (f) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 337.

[00251] In any of the above embodiments, an anti-Tau antibody is humanized. In some embodiments, an anti-Tau antibody comprises HVRs as in any of the above embodiments, and further comprises an acceptor human framework, e.g. a human immunoglobulin framework or a human consensus framework.

[00252] In another aspect, an anti-Tau antibody comprises a heavy chain variable domain (VH) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230,

240, 250, 260, 270, 280, 290, 300, 310, 320, 330, or 340. In certain embodiments, a VH sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Tau antibody comprising that sequence retains the ability to bind to Tau. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, or 340. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-Tau antibody comprises the VH sequence in SEQ ID NO: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, or 340, including post-translational modifications of that sequence. In a particular embodiment, the VH comprises one, two or three HVRs selected from: (a) HVR-H1 comprising the amino acid sequence of SEQ ID NO: 12, 22, 32, 42, 52, 62, 72, 82, 92, 102, 112, 122, 132, 142, 152, 162, 172, 182, 192, 202, 212, 222, 232, 242, 252, 262, 272, 282, 292, 302, 312, 322, 332, or 342, (b) HVR-H2 comprising the amino acid sequence of SEQ ID NO: 13, 23, 33, 43, 53, 63, 73, 83, 93, 100, 113, 123, 133, 143, 153, 163, 173, 183, 193, 203, 213, 223, 233, 243, 253, 263, 273, 283, 293, 303, 313, 323, 333, or 343, and (c) HVR-H3 comprising the amino acid sequence of SEQ ID NO: 14, 24, 34, 44, 54, 64, 74, 84, 94, 104, 114, 124, 134, 144, 154, 164, 174, 184, 194, 204, 214, 224, 234, 244, 254, 264, 274, 284, 294, 304, 314, 324, 334, or 344.

[00253] In another aspect, an anti-Tau antibody comprises a light chain variable domain (VL) sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, or 341. In certain embodiments, a VL sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% identity contains substitutions (*e.g.*, conservative substitutions), insertions, or deletions relative to the reference sequence, but an anti-Tau antibody comprising that sequence retains the ability to bind to Tau. In certain embodiments, a total of 1 to 10 amino acids have been substituted, inserted and/or deleted in SEQ ID NO: 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201, 211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, or 341. In certain embodiments, substitutions, insertions, or deletions occur in regions outside the HVRs (i.e., in the FRs). Optionally, the anti-Tau antibody comprises the VL sequence in SEQ ID NO: 11, 21, 31, 41, 51, 61, 71, 81, 91, 101, 111, 121, 131, 141, 151, 161, 171, 181, 191, 201,

211, 221, 231, 241, 251, 261, 271, 281, 291, 301, 311, 321, 331, or 341, including post-translational modifications of that sequence. In a particular embodiment, the VL comprises one, two or three HVRs selected from: (a) HVR-L1 comprising the amino acid sequence of SEQ ID NO: 15, 25, 35, 45, 55, 65, 75, 85, 95, 105, 115, 125, 135, 145, 155, 165, 175, 185, 195, 205, 215, 225, 235, 245, 255, 265, 275, 285, 295, 305, 315, 325, 335, or 345, (b) HVR-L2 comprising the amino acid sequence of SEQ ID NO: 16, 26, 36, 46, 56, 66, 76, 86, 96, 106, 116, 126, 136, 146, 156, 166, 176, 186, 196, 206, 216, 226, 236, 246, 266, 266, 276, 286, 296, 306, 316, 326, 336, or 346, and (c) HVR-L3 comprising the amino acid sequence of SEQ ID NO: 17, 27, 37, 47, 57, 67, 77, 87, 97, 107, 117, 127, 137, 147, 157, 167, 177, 187, 197, 207, 217, 227, 237, 247, 267, 277, 277, 287, 297, 307, 317, 327, 337, or 347.

[00254] In another aspect, an anti-Tau antibody is provided, wherein the antibody comprises a VH as in any of the embodiments provided above, and a VL as in any of the embodiments provided above. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 280 and SEQ ID NO: 281, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 290 and SEQ ID NO: 291, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 300 and SEQ ID NO: 301, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 310 and SEQ ID NO: 311, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 320 and SEQ ID NO: 321, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 330 and SEQ ID NO: 331, respectively, including post-translational modifications of those sequences. In some embodiments, the antibody comprises the VH and VL sequences in SEQ ID NO: 340 and SEQ ID NO: 341, respectively, including post-translational modifications of those sequences.

[00255] In some embodiments, an anti-Tau antibody 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 embodiments, an anti-Tau antibody 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.

[00256] In a further aspect, the invention provides an antibody that binds to the same epitope as an anti-Tau antibody provided herein. For example, in certain embodiments, an antibody is provided that binds to the same epitope as an antibody selected from 94B2-C1, 125B11-H3, 37D3-H9, and hu37D3-H9.v28.A4. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 2-24 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 7-24 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 7-20 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 10-24 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 7-21 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 8-22 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to an epitope within a fragment of Tau consisting of amino acids 11-25 of SEQ ID NO: 2. In certain embodiments, an antibody is provided that binds to one or more, or all, of the following fragments of Tau: 2-24, 7-24, 7-20, 10-24, 7-21, 8-22, and 11-25. In some embodiments, an antibody is provided that binds to a peptide having the sequence of SEQ ID NO: 593, but does not bind to a peptide having the sequence of SEQ ID NO: 596 or SEQ ID NO: 597.

[00257] In a further aspect of the invention, an anti-Tau antibody according to any of the above embodiments is a monoclonal antibody, including a chimeric, humanized or human antibody. In one embodiment, an anti-Tau antibody is an antibody fragment, *e.g.*, a Fv, Fab, Fab', scFv, diabody, or $F(ab')_2$ fragment. In another embodiment, the antibody is a full length antibody, *e.g.*, an intact IgG1 or IgG4 antibody or other antibody class or isotype as defined herein.

[00258] In a further aspect, an anti-Tau antibody according to any of the above embodiments may incorporate any of the features, singly or in combination, as described in Sections 1-7 below:

1. Antibody Affinity

[00259] In certain embodiments, an antibody provided herein has a dissociation constant (K_D) of $\leq$ 1μM, $\leq$ 100 nM, $\leq$ 10 nM, $\leq$ 1 nM, $\leq$ 0.1 nM, $\leq$ 0.01 nM, or $\leq$ 0.001 nM (*e.g.* 10^{-8} M or less, *e.g.* from 10^{-8} M to 10^{-13} M, *e.g.*, from 10^{-9} M to 10^{-13} M).

[00260] In some embodiments, K_D is measured by a radiolabeled antigen binding assay (RIA). In some embodiments, an RIA is performed with the Fab version of an antibody of interest and its antigen. For example, solution binding affinity of Fabs for antigen is measured by equilibrating Fab with a minimal concentration of (^{125}I)-labeled antigen in the presence of a titration series of unlabeled antigen, then capturing bound antigen with an anti-Fab antibody-coated plate (see, *e.g.*, Chen et al., *J. Mol. Biol.* 293:865-881(1999)). To establish conditions for the assay, MICROTITER® multi-well plates (Thermo Scientific) are coated overnight with 5 μg/ml of a capturing anti-Fab antibody (Cappel Labs) in 50 mM sodium carbonate (pH 9.6), and subsequently blocked with 2% (w/v) bovine serum albumin in PBS for two to five hours at room temperature (approximately 23°C). In a non-adsorbent plate (Nunc #269620), 100 pM or 26 pM [^{125}I]-antigen are mixed with serial dilutions of a Fab of interest (*e.g.*, consistent with assessment of the anti-VEGF antibody, Fab-12, in Presta et al., *Cancer Res.* 57:4593-4599 (1997)). The Fab of interest is then incubated overnight; however, the incubation may continue for a longer period (*e.g.*, about 65 hours) to ensure that equilibrium is reached. Thereafter, the mixtures are transferred to the capture plate for incubation at room temperature (*e.g.*, for one hour). The solution is then removed and the plate washed eight times with 0.1% polysorbate 20 (TWEEN-20®) in PBS. When the plates have dried, 150 μl/well of scintillant (MICROSCINT-20 ™; Packard) is added, and the plates are counted on a TOPCOUNT ™ gamma counter (Packard) for ten minutes. Concentrations of each Fab that give less than or equal to 20% of maximal binding are chosen for use in competitive binding assays.

[00261] According to another embodiment, K_D is measured using a BIACORE® surface plasmon resonance assay. For example, an assay using a BIACORE®-2000 or a BIACORE ®-3000 (BIAcore, Inc., Piscataway, NJ) is performed at 25°C with immobilized antigen CM5 chips at ~10 resonance units (RU). In some embodiments, carboxymethylated dextran biosensor chips (CM5, BIACORE, Inc.) are activated with *N*-ethyl-*N*'- (3-dimethylaminopropyl)-carbodiimide hydrochloride (EDC) and *N*-hydroxysuccinimide (NHS) according to the supplier's instructions. Antigen is diluted with 10 mM sodium acetate, pH 4.8, to 5 μg/ml (~0.2 μM) before injection at a flow rate of 5 μl/minute to achieve approximately 10 resonance units (RU) of coupled protein. Following the injection of antigen, 1 M ethanolamine is injected to block unreacted groups. For kinetics measurements, two-fold serial dilutions of Fab (0.78 nM to 500 nM) are injected in PBS with 0.05% polysorbate 20 (TWEEN-20™) surfactant (PBST) at 25°C at a flow rate of approximately 25 μl/min. Association rates (k_{on}) and dissociation rates (k_{off}) are calculated using a simple one-to-one

Langmuir binding model (BIACORE® Evaluation Software version 3.2) by simultaneously fitting the association and dissociation sensorgrams. The equilibrium dissociation constant (K_D) is calculated as the ratio k_{off}/k_{on}. See, *e.g.*, Chen et al., *J. Mol. Biol.* 293:865-881 (1999). If the on-rate exceeds 10^6 M^{-1} s^{-1} by the surface plasmon resonance assay above, then the on-rate can be determined by using a fluorescent quenching technique that measures the increase or decrease in fluorescence emission intensity (excitation = 295 nm; emission = 340 nm, 16 nm band-pass) at 25°C of a 20 nM anti-antigen antibody (Fab form) in PBS, pH 7.2, in the presence of increasing concentrations of antigen as measured in a spectrometer, such as a stop-flow equipped spectrophometer (Aviv Instruments) or a 8000-series SLM-AMINCO™ spectrophotometer (ThermoSpectronic) with a stirred cuvette.

2. Antibody Fragments

[00262] In certain embodiments, an antibody provided herein is an antibody fragment. Antibody fragments include, but are not limited to, Fab, Fab', Fab'-SH, $F(ab')_2$, Fv, and scFv fragments, and other fragments described below. For a review of certain antibody fragments, see Hudson et al. *Nat. Med.* 9:129-134 (2003). For a review of scFv fragments, see, *e.g.*, Pluckthün, in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenburg and Moore eds., (Springer-Verlag, New York), pp. 269-315 (1994); see also WO 93/16185; and U.S. Patent Nos. 5,571,894 and 5,587,458. For discussion of Fab and $F(ab')_2$ fragments comprising salvage receptor binding epitope residues and having increased *in vivo* half-life, see U.S. Patent No. 5,869,046.

[00263] Diabodies are antibody fragments with two antigen-binding sites that may be bivalent or bispecific. See, for example, EP 404,097; WO 1993/01161; Hudson et al., *Nat. Med.* 9:129-134 (2003); and Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90: 6444-6448 (1993). Triabodies and tetrabodies are also described in Hudson et al., *Nat. Med.* 9:129-134 (2003).

[00264] Single-domain antibodies are antibody fragments comprising all or a portion of the heavy chain variable domain or all or a portion of the light chain variable domain of an antibody. In certain embodiments, a single-domain antibody is a human single-domain antibody (Domantis, Inc., Waltham, MA; *see, e.g.*, U.S. Patent No. 6,248,516 B1).

[00265] Antibody fragments can be made by various techniques, including but not limited to proteolytic digestion of an intact antibody as well as production by recombinant host cells (*e.g. E. coli* or phage), as described herein.

3. Chimeric and Humanized Antibodies

[00266] In certain embodiments, an antibody provided herein is a chimeric antibody. Certain chimeric antibodies are described, *e.g.*, in U.S. Patent No. 4,816,567; and Morrison et al., *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). In one example, a chimeric antibody comprises a non-human variable region (*e.g.*, a variable region derived from a mouse, rat, hamster, rabbit, or non-human primate, such as a monkey) and a human constant region. In a further example, a chimeric antibody is a "class switched" antibody in which the class or subclass has been changed from that of the parent antibody. Chimeric antibodies include antigen-binding fragments thereof.

[00267] In certain embodiments, a chimeric antibody is a humanized antibody. Typically, a non-human antibody is humanized to reduce immunogenicity to humans, while retaining the specificity and affinity of the parental non-human antibody. Generally, a humanized antibody comprises one or more variable domains in which HVRs, *e.g.*, CDRs, (or portions thereof) are derived from a non-human antibody, and FRs (or portions thereof) are derived from human antibody sequences. A humanized antibody optionally will also comprise at least a portion of a human constant region. In some embodiments, some FR residues in a humanized antibody are substituted with corresponding residues from a non-human antibody (*e.g.*, the antibody from which the HVR residues are derived), *e.g.*, to restore or improve antibody specificity or affinity.

[00268] Humanized antibodies and methods of making them are reviewed, *e.g.*, in Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008), and are further described, *e.g.*, in Riechmann et al., *Nature* 332:323-329 (1988); Queen et al., *Proc. Nat'l Acad. Sci. USA* 86:10029-10033 (1989); US Patent Nos. 5, 821,337, 7,527,791, 6,982,321, and 7,087,409; Kashmiri *et al.*, *Methods* 36:25-34 (2005) (describing specificity determining region (SDR) grafting); Padlan, *Mol. Immunol.* 28:489-498 (1991) (describing "resurfacing"); Dall'Acqua et al., *Methods* 36:43-60 (2005) (describing "FR shuffling"); and Osbourn et al., *Methods* 36:61-68 (2005) and Klimka et al., *Br. J. Cancer*, 83:252-260 (2000) (describing the "guided selection" approach to FR shuffling).

[00269] Human framework regions that may be used for humanization include but are not limited to: framework regions selected using the "best-fit" method (see, *e.g.*, Sims et al. *J. Immunol.* 151:2296 (1993)); framework regions derived from the consensus sequence of human antibodies of a particular subgroup of light or heavy chain variable regions (see, *e.g.*, Carter et al. *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); and Presta et al. *J. Immunol.*, 151:2623 (1993)); human mature (somatically mutated) framework regions or human germline

framework regions (see, *e.g.*, Almagro and Fransson, *Front. Biosci.* 13:1619-1633 (2008)); and framework regions derived from screening FR libraries (see, *e.g.*, Baca et al., *J. Biol. Chem.* 272:10678-10684 (1997) and Rosok et al., *J. Biol. Chem.* 271:22611-22618 (1996)).

4. Human Antibodies

[00270] In certain embodiments, an antibody provided herein is a human antibody. Human antibodies can be produced using various techniques known in the art. Human antibodies are described generally in van Dijk and van de Winkel, *Curr. Opin. Pharmacol.* 5: 368-74 (2001) and Lonberg, *Curr. Opin. Immunol.* 20:450-459 (2008).

[00271] Human antibodies may be prepared by administering an immunogen to a transgenic animal that has been modified to produce intact human antibodies or intact antibodies with human variable regions in response to antigenic challenge. Such animals typically contain all or a portion of the human immunoglobulin loci, which replace the endogenous immunoglobulin loci, or which are present extrachromosomally or integrated randomly into the animal's chromosomes. In such transgenic mice, the endogenous immunoglobulin loci have generally been inactivated. For review of methods for obtaining human antibodies from transgenic animals, see Lonberg, *Nat. Biotech.* 23:1117-1125 (2005). See also, *e.g.*, U.S. Patent Nos. 6,075,181 and 6,150,584 describing XENOMOUSE™ technology; U.S. Patent No. 5,770,429 describing HUMAB® technology; U.S. Patent No. 7,041,870 describing K-M MOUSE® technology, and U.S. Patent Application Publication No. US 2007/0061900, describing VELOCIMOUSE® technology). Human variable regions from intact antibodies generated by such animals may be further modified, *e.g.*, by combining with a different human constant region.

[00272] Human antibodies can also be made by hybridoma-based methods. Human myeloma and mouse-human heteromyeloma cell lines for the production of human monoclonal antibodies have been described. (See, *e.g.*, Kozbor *J. Immunol.*, 133: 3001 (1984); Brodeur et al., *Monoclonal Antibody Production Techniques and Applications*, pp. 51-63 (Marcel Dekker, Inc., New York, 1987); and Boerner et al., *J. Immunol.*, 147: 86 (1991).) Human antibodies generated via human B-cell hybridoma technology are also described in Li et al., *Proc. Natl. Acad. Sci. USA*, 103:3557-3562 (2006). Additional methods include those described, for example, in U.S. Patent No. 7,189,826 (describing production of monoclonal human IgM antibodies from hybridoma cell lines) and Ni, *Xiandai Mianyixue*, 26(4):265-268 (2006) (describing human-human hybridomas). Human hybridoma technology (Trioma technology) is also described in Vollmers and Brandlein, *Histology and Histopathology*,

20(3):927-937 (2005) and Vollmers and Brandlein, *Methods and Findings in Experimental and Clinical Pharmacology*, 27(3):185-91 (2005).

[00273] Human antibodies may also be generated by isolating Fv clone variable domain sequences selected from human-derived phage display libraries. Such variable domain sequences may then be combined with a desired human constant domain. Techniques for selecting human antibodies from antibody libraries are described below.

5. Library-Derived Antibodies

[00274] Antibodies of the invention may be isolated by screening combinatorial libraries for antibodies with the desired activity or activities. For example, a variety of methods are known in the art for generating phage display libraries and screening such libraries for antibodies possessing the desired binding characteristics. Such methods are reviewed, *e.g.*, in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, 2001) and further described, *e.g.*, in the McCafferty et al., *Nature* 348:552-554; Clackson et al., *Nature* 352: 624-628 (1991); Marks et al., *J. Mol. Biol.* 222: 581-597 (1992); Marks and Bradbury, in *Methods in Molecular Biology* 248:161-175 (Lo, ed., Human Press, Totowa, NJ, 2003); Sidhu et al., *J. Mol. Biol.* 338(2): 299-310 (2004); Lee et al., *J. Mol. Biol.* 340(5): 1073-1093 (2004); Fellouse, *Proc. Natl. Acad. Sci. USA* 101(34): 12467-12472 (2004); and Lee et al., *J. Immunol. Methods* 284(1-2): 119-132(2004).

[00275] In certain phage display methods, repertoires of VH and VL genes are separately cloned by polymerase chain reaction (PCR) and recombined randomly in phage libraries, which can then be screened for antigen-binding phage as described in Winter et al., *Ann. Rev. Immunol.*, 12: 433-455 (1994). Phage typically display antibody fragments, either as single-chain Fv (scFv) fragments or as Fab fragments. Libraries from immunized sources provide high-affinity antibodies to the immunogen without the requirement of constructing hybridomas. Alternatively, the naive repertoire can be cloned (*e.g.*, from human) to provide a single source of antibodies to a wide range of non-self and also self antigens without any immunization as described by Griffiths et al., *EMBO J,* 12: 725-734 (1993). Finally, naive libraries can also be made synthetically by cloning unrearranged V-gene segments from stem cells, and using PCR primers containing random sequence to encode the highly variable CDR3 regions and to accomplish rearrangement *in vitro*, as described by Hoogenboom and Winter, *J. Mol. Biol.*, 227: 381-388 (1992). Patent publications describing human antibody phage libraries include, for example: US Patent No. 5,750,373, and US Patent Publication Nos. 2005/0079574, 2005/0119455, 2005/0266000, 2007/0117126, 2007/0160598, 2007/0237764, 2007/0292936, and 2009/0002360.

[00276] Antibodies or antibody fragments isolated from human antibody libraries are considered human antibodies or human antibody fragments herein.

6. Multispecific Antibodies

[00277] In certain embodiments, an antibody provided herein is a multispecific antibody, *e.g.* a bispecific antibody. Multispecific antibodies are monoclonal antibodies that have binding specificities for at least two different sites. In certain embodiments, one of the binding specificities is for Tau and the other is for any other antigen. In certain embodiments, one of the binding specificities is for Tau and the other is for amyloid beta. In certain embodiments, bispecific antibodies may bind to two different epitopes of Tau. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express Tau. Bispecific antibodies can be prepared as full length antibodies or antibody fragments.

[00278] Techniques for making multispecific antibodies include, but are not limited to, recombinant co-expression of two immunoglobulin heavy chain-light chain pairs having different specificities (see Milstein and Cuello, *Nature* 305: 537 (1983)), WO 93/08829, and Traunecker et al., *EMBO J.* 10: 3655 (1991)), and "knob-in-hole" engineering (see, *e.g.*, U.S. Patent No. 5,731,168). Multi-specific antibodies may also be made by engineering electrostatic steering effects for making antibody Fc-heterodimeric molecules (WO 2009/089004A1); cross-linking two or more antibodies or fragments (see, *e.g.*, US Patent No. 4,676,980, and Brennan et al., *Science*, 229: 81 (1985)); using leucine zippers to produce bi-specific antibodies (see, *e.g.*, Kostelny et al., *J. Immunol.*, 148(5):1547-1553 (1992)); using "diabody" technology for making bispecific antibody fragments (see, *e.g.*, Hollinger et al., *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993)); and using single-chain Fv (sFv) dimers (see,*e.g.* Gruber et al., *J. Immunol.*, 152:5368 (1994)); and preparing trispecific antibodies as described, *e.g.*, in Tutt et al. *J. Immunol.* 147: 60 (1991).

[00279] Engineered antibodies with three or more functional antigen binding sites, including "Octopus antibodies," are also included herein (see, *e.g.* US 2006/0025576A1).

[00280] The antibody or fragment herein also includes a "Dual Acting FAb" or "DAF" comprising an antigen binding site that binds to Tau as well as another, different antigen (see, US 2008/0069820, for example).

7. Antibody Variants

[00281] In certain embodiments, amino acid sequence variants of the antibodies provided herein are contemplated. For example, it may be desirable to improve the binding affinity and/or other biological properties of the antibody. Amino acid sequence variants of an

antibody may be prepared by introducing appropriate modifications into the nucleotide sequence encoding the antibody, or by peptide synthesis. Such modifications include, for example, deletions from, and/or insertions into and/or substitutions of residues within the amino acid sequences of the antibody. Any combination of deletion, insertion, and substitution can be made to arrive at the final construct, provided that the final construct possesses the desired characteristics, *e.g.*, antigen-binding.

a) Substitution, Insertion, and Deletion Variants

[00282] In certain embodiments, antibody variants having one or more amino acid substitutions are provided. Sites of interest for substitutional mutagenesis include the HVRs and FRs. Conservative substitutions are shown in Table 1 under the heading of "preferred substitutions." More substantial changes are provided in Table 1 under the heading of "exemplary substitutions," and as further described below in reference to amino acid side chain classes. Amino acid substitutions may be introduced into an antibody of interest and the products screened for a desired activity, *e.g.*, retained/improved antigen binding, decreased immunogenicity, or improved ADCC or CDC.

TABLE 1

Original Residue	Exemplary Substitutions	Preferred Substitutions
Ala (A)	Val; Leu; Ile	Val
Arg (R)	Lys; Gln; Asn	Lys
Asn (N)	Gln; His; Asp, Lys; Arg	Gln
Asp (D)	Glu; Asn	Glu
Cys (C)	Ser; Ala	Ser
Gln (Q)	Asn; Glu	Asn
Glu (E)	Asp; Gln	Asp
Gly (G)	Ala	Ala
His (H)	Asn; Gln; Lys; Arg	Arg
Ile (I)	Leu; Val; Met; Ala; Phe; Norleucine	Leu
Leu (L)	Norleucine; Ile; Val; Met; Ala; Phe	Ile
Lys (K)	Arg; Gln; Asn	Arg
Met (M)	Leu; Phe; Ile	Leu
Phe (F)	Trp; Leu; Val; Ile; Ala; Tyr	Tyr
Pro (P)	Ala	Ala
Ser (S)	Thr	Thr

Original Residue	Exemplary Substitutions	Preferred Substitutions
Thr (T)	Val; Ser	Ser
Trp (W)	Tyr; Phe	Tyr
Tyr (Y)	Trp; Phe; Thr; Ser	Phe
Val (V)	Ile; Leu; Met; Phe; Ala; Norleucine	Leu

Amino acids may be grouped according to common side-chain properties:

(1) hydrophobic: Norleucine, Met, Ala, Val, Leu, Ile;

(2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

(3) acidic: Asp, Glu;

(4) basic: His, Lys, Arg;

(5) residues that influence chain orientation: Gly, Pro;

(6) aromatic: Trp, Tyr, Phe.

[00283] Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

[00284] One type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (*e.g.* a humanized or human antibody). Generally, the resulting variant(s) selected for further study will have modifications (*e.g.*, improvements) in certain biological properties (*e.g.*, increased affinity, reduced immunogenicity) relative to the parent antibody and/or will have substantially retained certain biological properties of the parent antibody. An exemplary substitutional variant is an affinity matured antibody, which may be conveniently generated, *e.g.*, using phage display-based affinity maturation techniques such as those described herein. Briefly, one or more HVR residues are mutated and the variant antibodies displayed on phage and screened for a particular biological activity (*e.g.* binding affinity).

[00285] Alterations (*e.g.*, substitutions) may be made in HVRs, *e.g.*, to improve antibody affinity. Such alterations may be made in HVR "hotspots," i.e., residues encoded by codons that undergo mutation at high frequency during the somatic maturation process (see, *e.g.*, Chowdhury, *Methods Mol. Biol.* 207:179-196 (2008)), and/or residues that contact antigen, with the resulting variant VH or VL being tested for binding affinity. Affinity maturation by constructing and reselecting from secondary libraries has been described, *e.g.*, in Hoogenboom et al. in *Methods in Molecular Biology* 178:1-37 (O'Brien et al., ed., Human Press, Totowa, NJ, (2001).) In some embodiments of affinity maturation, diversity is introduced into the variable genes chosen for maturation by any of a variety of methods (*e.g.*,

error-prone PCR, chain shuffling, or oligonucleotide-directed mutagenesis). A secondary library is then created. The library is then screened to identify any antibody variants with the desired affinity. Another method to introduce diversity involves HVR-directed approaches, in which several HVR residues (*e.g.*, 4-6 residues at a time) are randomized. HVR residues involved in antigen binding may be specifically identified, *e.g.*, using alanine scanning mutagenesis or modeling. CDR-H3 and CDR-L3 in particular are often targeted.

[00286] In certain embodiments, substitutions, insertions, or deletions may occur within one or more HVRs so long as such alterations do not substantially reduce the ability of the antibody to bind antigen. For example, conservative alterations (*e.g.*, conservative substitutions as provided herein) that do not substantially reduce binding affinity may be made in HVRs. Such alterations may, for example, be outside of antigen contacting residues in the HVRs. In certain embodiments of the variant VH and VL sequences provided above, each HVR either is unaltered, or contains no more than one, two or three amino acid substitutions.

[00287] A useful method for identification of residues or regions of an antibody that may be targeted for mutagenesis is called "alanine scanning mutagenesis" as described by Cunningham and Wells (1989) *Science*, 244:1081-1085. In this method, a residue or group of target residues (*e.g.*, charged residues such as arg, asp, his, lys, and glu) are identified and replaced by a neutral or negatively charged amino acid (*e.g.*, alanine or polyalanine) to determine whether the interaction of the antibody with antigen is affected. Further substitutions may be introduced at the amino acid locations demonstrating functional sensitivity to the initial substitutions. Alternatively, or additionally, a crystal structure of an antigen-antibody complex to identify contact points between the antibody and antigen. Such contact residues and neighboring residues may be targeted or eliminated as candidates for substitution. Variants may be screened to determine whether they contain the desired properties.

[00288] Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Examples of terminal insertions include an antibody with an N-terminal methionyl residue. Other insertional variants of the antibody molecule include the fusion to the N- or C-terminus of the antibody to an enzyme (*e.g.* for ADEPT) or a polypeptide which increases the serum half-life of the antibody.

b) **Glycosylation variants**

[00289] In certain embodiments, an antibody provided herein is altered to increase or decrease the extent to which the antibody is glycosylated. Addition or deletion of glycosylation sites to an antibody may be conveniently accomplished by altering the amino acid sequence such that one or more glycosylation sites is created or removed.

[00290] Where the antibody comprises an Fc region, the carbohydrate attached thereto may be altered. Native antibodies produced by mammalian cells typically comprise a branched, biantennary oligosaccharide that is generally attached by an N-linkage to Asn297 of the CH2 domain of the Fc region. See, *e.g.*, Wright et al. *TIBTECH* 15:26-32 (1997). The oligosaccharide may include various carbohydrates, *e.g.*, mannose, N-acetyl glucosamine (GlcNAc), galactose, and sialic acid, as well as a fucose attached to a GlcNAc in the "stem" of the biantennary oligosaccharide structure. In some embodiments, modifications of the oligosaccharide in an antibody of the invention may be made in order to create antibody variants with certain improved properties.

[00291] In some embodiments, antibody variants are provided having a carbohydrate structure that lacks fucose attached (directly or indirectly) to an Fc region. For example, the amount of fucose in such antibody may be from 1% to 80%, from 1% to 65%, from 5% to 65% or from 20% to 40%. The amount of fucose is determined by calculating the average amount of fucose within the sugar chain at Asn297, relative to the sum of all glycostructures attached to Asn 297 (e. g. complex, hybrid and high mannose structures) as measured by MALDI-TOF mass spectrometry, as described in WO 2008/077546, for example. Asn297 refers to the asparagine residue located at about position 297 in the Fc region (Eu numbering of Fc region residues); however, Asn297 may also be located about ± 3 amino acids upstream or downstream of position 297, i.e., between positions 294 and 300, due to minor sequence variations in antibodies. Such fucosylation variants may have improved ADCC function. See, *e.g.*, US Patent Publication Nos. US 2003/0157108 (Presta, L.); US 2004/0093621 (Kyowa Hakko Kogyo Co., Ltd). Examples of publications related to "defucosylated" or "fucose-deficient" antibody variants include: US 2003/0157108; WO 2000/61739; WO 2001/29246; US 2003/0115614; US 2002/0164328; US 2004/0093621; US 2004/0132140; US 2004/0110704; US 2004/0110282; US 2004/0109865; WO 2003/085119; WO 2003/084570; WO 2005/035586; WO 2005/035778; WO2005/053742; WO2002/031140; Okazaki et al. *J. Mol. Biol.* 336:1239-1249 (2004); Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004). Examples of cell lines capable of producing defucosylated antibodies include Lec13 CHO cells deficient in protein fucosylation (Ripka et al. *Arch. Biochem. Biophys.*

249:533-545 (1986); US Pat Appl No US 2003/0157108 A1, Presta, L; and WO 2004/056312 A1, Adams *et al.*, especially at Example 11), and knockout cell lines, such as alpha-1,6-fucosyltransferase gene, *FUT8,* knockout CHO cells (see, *e.g.*, Yamane-Ohnuki et al. *Biotech. Bioeng.* 87: 614 (2004); Kanda, Y. et al., *Biotechnol. Bioeng.*, 94(4):680-688 (2006); and WO2003/085107).

[00292] Antibodies variants are further provided with bisected oligosaccharides, *e.g.*, in which a biantennary oligosaccharide attached to the Fc region of the antibody is bisected by GlcNAc. Such antibody variants may have reduced fucosylation and/or improved ADCC function. Examples of such antibody variants are described, *e.g.*, in WO 2003/011878 (Jean-Mairet et al.); US Patent No. 6,602,684 (Umana et al.); and US 2005/0123546 (Umana *et al.*). Antibody variants with at least one galactose residue in the oligosaccharide attached to the Fc region are also provided. Such antibody variants may have improved CDC function. Such antibody variants are described, *e.g.*, in WO 1997/30087 (Patel et al.); WO 1998/58964 (Raju, S.); and WO 1999/22764 (Raju, S.).

c) Fc region variants

[00293] In certain embodiments, one or more amino acid modifications may be introduced into the Fc region of an antibody provided herein, thereby generating an Fc region variant. The Fc region variant may comprise a human Fc region sequence (*e.g.*, a human IgG1, IgG2, IgG3 or IgG4 Fc region) comprising an amino acid modification (*e.g.* a substitution) at one or more amino acid positions.

[00294] In certain embodiments, the invention contemplates an antibody variant that possesses some but not all effector functions, which make it a desirable candidate for applications in which the half life of the antibody *in vivo* is important yet certain effector functions (such as complement and ADCC) are unnecessary or deleterious. *In vitro* and/or *in vivo* cytotoxicity assays can be conducted to confirm the reduction/depletion of CDC and/or ADCC activities. For example, Fc receptor (FcR) binding assays can be conducted to ensure that the antibody lacks FcγR binding (hence likely lacking ADCC activity), but retains FcRn binding ability. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII and FcγRIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-492 (1991). Non-limiting examples of *in vitro* assays to assess ADCC activity of a molecule of interest is described in U.S. Patent No. 5,500,362 (see, *e.g.* Hellstrom, I. et al. *Proc. Nat'l Acad. Sci. USA* 83:7059-7063 (1986)) and Hellstrom, I et al., *Proc. Nat'l Acad. Sci. USA*

82:1499-1502 (1985); 5,821,337 (see Bruggemann, M. et al., *J. Exp. Med.* 166:1351-1361 (1987)). Alternatively, non-radioactive assays methods may be employed (see, for example, ACTI™ non-radioactive cytotoxicity assay for flow cytometry (CellTechnology, Inc. Mountain View, CA; and CytoTox 96® non-radioactive cytotoxicity assay (Promega, Madison, WI). Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in a animal model such as that disclosed in Clynes et al. *Proc. Nat'l Acad. Sci. USA* 95:652-656 (1998). C1q binding assays may also be carried out to confirm that the antibody is unable to bind C1q and hence lacks CDC activity. See, *e.g.*, C1q and C3c binding ELISA in WO 2006/029879 and WO 2005/100402. To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro *et al.*, *J. Immunol. Methods* 202:163 (1996); Cragg, M.S. et al., *Blood* 101:1045-1052 (2003); and Cragg, M.S. and M.J. Glennie, *Blood* 103:2738-2743 (2004)). FcRn binding and *in vivo* clearance/half life determinations can also be performed using methods known in the art (see, *e.g.*, Petkova, S.B. et al., *Int'l. Immunol.* 18(12):1759-1769 (2006)).

[00295] Antibodies with reduced effector function include those with substitution of one or more of Fc region residues 238, 265, 269, 270, 297, 327 and 329 (U.S. Patent No. 6,737,056). Such Fc mutants include Fc mutants with substitutions at two or more of amino acid positions 265, 269, 270, 297 and 327, including the so-called "DANA" Fc mutant with substitution of residues 265 and 297 to alanine (US Patent No. 7,332,581).

[00296] Certain antibody variants with improved or diminished binding to FcRs are described. (See, *e.g.*, U.S. Patent No. 6,737,056; WO 2004/056312, and Shields et al., *J. Biol. Chem.* 9(2): 6591-6604 (2001).)

[00297] In certain embodiments, an antibody variant comprises an Fc region with one or more amino acid substitutions which improve ADCC, *e.g.*, substitutions at positions 298, 333, and/or 334 of the Fc region (EU numbering of residues).

[00298] In some embodiments, alterations are made in the Fc region that result in altered (*i.e.*, either improved or diminished) C1q binding and/or Complement Dependent Cytotoxicity (CDC), *e.g.*, as described in US Patent No. 6,194,551, WO 99/51642, and Idusogie et al. *J. Immunol.* 164: 4178-4184 (2000).

[00299] Antibodies with increased half lives and improved binding to the neonatal Fc receptor (FcRn), which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., *J. Immunol.* 117:587 (1976) and Kim et al., *J. Immunol.* 24:249 (1994)), are described in US2005/0014934A1 (Hinton et al.). Those antibodies comprise an Fc region with

one or more substitutions therein which improve binding of the Fc region to FcRn. Such Fc variants include those with substitutions at one or more of Fc region residues: 238, 256, 265, 272, 286, 303, 305, 307, 311, 312, 317, 340, 356, 360, 362, 376, 378, 380, 382, 413, 424 or 434, *e.g.*, substitution of Fc region residue 434 (US Patent No. 7,371,826).

[00300] See also Duncan & Winter, *Nature* 322:738-40 (1988); U.S. Patent No. 5,648,260; U.S. Patent No. 5,624,821; and WO 94/29351 concerning other examples of Fc region variants.

d) Cysteine engineered antibody variants

[00301] In certain embodiments, it may be desirable to create cysteine engineered antibodies, *e.g.*, "thioMAbs," in which one or more residues of an antibody are substituted with cysteine residues. In particular embodiments, the substituted residues occur at accessible sites of the antibody. By substituting those residues with cysteine, reactive thiol groups are thereby positioned at accessible sites of the antibody and may be used to conjugate the antibody to other moieties, such as drug moieties or linker-drug moieties, to create an immunoconjugate, as described further herein. In certain embodiments, any one or more of the following residues may be substituted with cysteine: V205 (Kabat numbering) of the light chain; A118 (EU numbering) of the heavy chain; and S400 (EU numbering) of the heavy chain Fc region. Cysteine engineered antibodies may be generated as described, *e.g.*, in U.S. Patent No. 7,521,541.

e) Antibody Derivatives

[00302] In certain embodiments, an antibody provided herein may be further modified to contain additional nonproteinaceous moieties that are known in the art and readily available. The moieties suitable for derivatization of the antibody include but are not limited to water soluble polymers. Non-limiting examples of water soluble polymers include, but are not limited to, polyethylene glycol (PEG), copolymers of ethylene glycol/propylene glycol, carboxymethylcellulose, dextran, polyvinyl alcohol, polyvinyl pyrrolidone, poly-1, 3-dioxolane, poly-1,3,6-trioxane, ethylene/maleic anhydride copolymer, polyaminoacids (either homopolymers or random copolymers), and dextran or poly(n-vinyl pyrrolidone)polyethylene glycol, propropylene glycol homopolymers, prolypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols (*e.g.*, glycerol), polyvinyl alcohol, and mixtures thereof. Polyethylene glycol propionaldehyde may have advantages in manufacturing due to its stability in water. The polymer may be of any molecular weight, and may be branched or unbranched. The number of polymers attached to the antibody may vary, and if more than one

polymer are attached, they can be the same or different molecules. In general, the number and/or type of polymers used for derivatization can be determined based on considerations including, but not limited to, the particular properties or functions of the antibody to be improved, whether the antibody derivative will be used in a therapy under defined conditions, etc.

[00303] In another embodiment, conjugates of an antibody and nonproteinaceous moiety that may be selectively heated by exposure to radiation are provided. In some embodiments, the nonproteinaceous moiety is a carbon nanotube (Kam et al., *Proc. Natl. Acad. Sci. USA* 102: 11600-11605 (2005)). The radiation may be of any wavelength, and includes, but is not limited to, wavelengths that do not harm ordinary cells, but which heat the nonproteinaceous moiety to a temperature at which cells proximal to the antibody-nonproteinaceous moiety are killed.

B. Recombinant Methods and Compositions

[00304] Antibodies may be produced using recombinant methods and compositions, *e.g.*, as described in U.S. Patent No. 4,816,567. In some embodiments, isolated nucleic acid encoding an anti-Tau antibody described herein is provided. Such nucleic acid may encode an amino acid sequence comprising the VL and/or an amino acid sequence comprising the VH of the antibody (*e.g.*, the light and/or heavy chains of the antibody). In a further embodiment, one or more vectors (*e.g.*, expression vectors) comprising such nucleic acid are provided. In a further embodiment, a host cell comprising such nucleic acid is provided. In one such embodiment, a host cell comprises (*e.g.*, has been transformed with): (1) a vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and an amino acid sequence comprising the VH of the antibody, or (2) a first vector comprising a nucleic acid that encodes an amino acid sequence comprising the VL of the antibody and a second vector comprising a nucleic acid that encodes an amino acid sequence comprising the VH of the antibody. In some embodiments, the host cell is eukaryotic, *e.g.* a Chinese Hamster Ovary (CHO) cell or lymphoid cell (*e.g.*, Y0, NS0, Sp20 cell). In some embodiments, a method of making an anti-Tau antibody is provided, wherein the method comprises culturing a host cell comprising a nucleic acid encoding the antibody, as provided above, under conditions suitable for expression of the antibody, and optionally recovering the antibody from the host cell (or host cell culture medium).

[00305] For recombinant production of an anti-Tau antibody, nucleic acid encoding an antibody, *e.g.*, as described above, is isolated and inserted into one or more

vectors for further cloning and/or expression in a host cell. Such nucleic acid may be readily isolated and sequenced using conventional procedures (*e.g.*, by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of the antibody).

[00306] Suitable host cells for cloning or expression of antibody-encoding vectors include prokaryotic or eukaryotic cells described herein. For example, antibodies may be produced in bacteria, in particular when glycosylation and Fc effector function are not needed. For expression of antibody fragments and polypeptides in bacteria, see, *e.g.*, U.S. Patent Nos. 5,648,237, 5,789,199, and 5,840,523. (See also Charlton, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ, 2003), pp. 245-254, describing expression of antibody fragments in *E. coli*.) After expression, the antibody may be isolated from the bacterial cell paste in a soluble fraction and can be further purified.

[00307] In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for antibody-encoding vectors, including fungi and yeast strains whose glycosylation pathways have been "humanized," resulting in the production of an antibody with a partially or fully human glycosylation pattern. See Gerngross, *Nat. Biotech.* 22:1409-1414 (2004), and Li et al., *Nat. Biotech.* 24:210-215 (2006).

[00308] Suitable host cells for the expression of glycosylated antibody are also derived from multicellular organisms (invertebrates and vertebrates). Examples of invertebrate cells include plant and insect cells. Numerous baculoviral strains have been identified which may be used in conjunction with insect cells, particularly for transfection of *Spodoptera frugiperda* cells.

[00309] Plant cell cultures can also be utilized as hosts. *See, e.g.*, US Patent Nos. 5,959,177, 6,040,498, 6,420,548, 7,125,978, and 6,417,429 (describing PLANTIBODIES™ technology for producing antibodies in transgenic plants).

[00310] Vertebrate cells may also be used as hosts. For example, mammalian cell lines that are adapted to grow in suspension may be useful. Other examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7); human embryonic kidney line (293 or 293 cells as described, *e.g.*, in Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK); mouse sertoli cells (TM4 cells as described, *e.g.*, in Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1); African green monkey kidney cells (VERO-76); human cervical carcinoma cells (HELA); canine kidney cells (MDCK; buffalo rat liver cells (BRL 3A); human lung cells (W138); human liver cells (Hep G2); mouse mammary tumor (MMT 060562); TRI cells, as described, *e.g.*, in Mather et al.,

Annals N.Y. Acad. Sci. 383:44-68 (1982); MRC 5 cells; and FS4 cells. Other useful mammalian host cell lines include Chinese hamster ovary (CHO) cells, including DHFR$^-$ CHO cells (Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); and myeloma cell lines such as Y0, NS0 and Sp2/0. For a review of certain mammalian host cell lines suitable for antibody production, see, *e.g.*, Yazaki and Wu, *Methods in Molecular Biology, Vol. 248* (B.K.C. Lo, ed., Humana Press, Totowa, NJ), pp. 255-268 (2003).

C. Assays

[00311] Anti-Tau antibodies provided herein may be identified, screened for, or characterized for their physical/chemical properties and/or biological activities by various assays known in the art.

1. Binding assays and other assays

[00312] In one aspect, an antibody of the invention is tested for its antigen binding activity, *e.g.*, by known methods such as ELISA, Western blot, etc.

[00313] In another aspect, competition assays may be used to identify an antibody that competes with an antibody described herein for binding to Tau. In certain embodiments, such a competing antibody binds to the same epitope (*e.g.*, a linear or a conformational epitope) that is bound by 94B2-C1, 125B11-H3, 37D3-H9, or hu37D3-H9.v28.A4. Detailed exemplary methods for mapping an epitope to which an antibody binds are provided in Morris (1996) "Epitope Mapping Protocols," in *Methods in Molecular Biology* vol. 66 (Humana Press, Totowa, NJ).

[00314] In an exemplary competition assay, immobilized Tau (such as monomeric Tau) is incubated in a solution comprising a first labeled antibody that binds to Tau (*e.g.*, any antibody described herein, such as hu37D3-H9.v28.A4) and a second unlabeled antibody that is being tested for its ability to compete with the first antibody for binding to Tau. The second antibody may be present in a hybridoma supernatant. As a control, immobilized Tau is incubated in a solution comprising the first labeled antibody but not the second unlabeled antibody. After incubation under conditions permissive for binding of the first antibody to Tau, excess unbound antibody is removed, and the amount of label associated with immobilized Tau is measured. If the amount of label associated with immobilized Tau is substantially reduced in the test sample relative to the control sample, then that indicates that the second antibody is competing with the first antibody for binding to Tau. See Harlow and Lane (1988) *Antibodies: A Laboratory Manual* ch.14 (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY).

2. Activity assays

[00315] In one aspect, assays are provided for identifying anti-Tau (*e.g.*, pan-Tau) antibodies thereof having biological activity. Biological activity may include, *e.g.*, binding of such antibodies to multiple forms of Tau (*e.g.*, monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau) and reducing the level of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble non-phosphorylated Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble non-phosphorylated Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau, in the brain, *e.g.*, in the brain cortex and/or hippocampus). Antibodies having such biological activity *in vivo* and/or *in vitro* are also provided.

[00316] In certain embodiments, an antibody of the invention is tested for such biological activity. For example, an animal model of tauopathy, such as a Tau transgenic mice (*e.g.*, P301L), can be used to detect binding of anti-Tau antibodies to brain sections, and for example, to neurofibrillary tangles in the brains of the transgenic mice. Further, an animal model of tauopathy, such as a Tau transgenic mice (*e.g.*, P301L), can be treated with anti-Tau antibodies and experimental techniques known in the art can be used to assess whether such treatment reduces the level of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, soluble non-phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, insoluble non-phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau) in the mouse brain (*e.g.*, in the brain cortex and/or hippocampus).

D. Immunoconjugates

[00317] The invention also provides immunoconjugates comprising an anti-Tau antibody herein conjugated to one or more other therapeutic agents or radioactive isotopes.

[00318] In another embodiment, an immunoconjugate comprises an antibody as described herein conjugated to a radioactive atom to form a radioconjugate. A variety of radioactive isotopes are available for the production of radioconjugates. Examples include At^{211}, I^{131}, I^{125}, Y^{90}, Re^{186}, Re^{188}, Sm^{153}, Bi^{212}, P^{32}, Pb^{212} and radioactive isotopes of Lu. When the radioconjugate is used for detection, it may comprise a radioactive atom for scintigraphic studies, for example tc99m or I123, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

[00319] Conjugates of an antibody may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridyldithio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate (SMCC), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCl), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of a cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Res.* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

[00320] The immunuoconjugates or ADCs herein expressly contemplate, but are not limited to such conjugates prepared with cross-linker reagents including, but not limited to, BMPS, EMCS, GMBS, HBVS, LC-SMCC, MBS, MPBH, SBAP, SIA, SIAB, SMCC, SMPB, SMPH, sulfo-EMCS, sulfo-GMBS, sulfo-KMUS, sulfo-MBS, sulfo-SIAB, sulfo-SMCC, and sulfo-SMPB, and SVSB (succinimidyl-(4-vinylsulfone)benzoate) which are commercially available (*e.g.*, from Pierce Biotechnology, Inc., Rockford, IL., U.S.A).

E. Methods and Compositions for Diagnostics and Detection

[00321] In certain embodiments, any of the anti-Tau antibodies provided herein is useful for detecting the presence of Tau in a biological sample. The term "detecting" as used herein encompasses quantitative or qualitative detection. In certain embodiments, a biological sample comprises a cell or tissue, such as cerebrospinal fluid, a cell or tissue of the brain (e.g., brain cortex or hippocampus), or blood. In some embodiments, a biological sample is cerebrospinal fluid.

[00322] In some embodiments, an anti-Tau antibody for use in a method of diagnosis or detection is provided. In a further aspect, a method of detecting the presence of Tau in a biological sample is provided. In certain embodiments, the method comprises contacting the biological sample with an anti-Tau antibody as described herein under conditions permissive for binding of the anti-Tau antibody to Tau, and detecting whether a

complex is formed between the anti-Tau antibody and Tau. Such method may be an *in vitro* or *in vivo* method. Further, the complex formed between the anti-Tau antibody and Tau in a test biological sample can be compared to the complex formed in a control biological sample (e.g., a biological sample from a healthy subject or subjects). The amount of the complex formed between the anti-Tau antibody and Tau in a test biological sample can also be quantified and compared to the amount of the complex formed in a control biological sample (e.g., a biological sample from a healthy subject or subjects) or to the average amount of the complex known to be formed in healthy subjects.

[00323] In some embodiments, an anti-Tau antibody is used to select subjects eligible for therapy with an anti-Tau antibody, *e.g.* where Tau is a biomarker for selection of patients. For example, in some embodiments, an anti-Tau (e.g., pan-Tau) antibody is used to detect whether the subject has a Tau protein disease or disorder, or whether the subject is at high risk (or predisposed to) a Tau protein disease or disorder.

[00324] Exemplary diseases or disorders that may be diagnosed using an antibody of the invention include Tau protein associated diseases or disorders, and diseases or disorders caused by or associated with the formation of neurofibrillary tangles or neuropil threads. In some embodiments, diseases or disorders that may be diagnosed using an antibody of the invention include Tau protein associated diseases or disorders that are manifested in an impairment or loss of cognitive functions including reasoning, situational judgement, memory capacity, learning, and/or special navigation. In particular, diseases or disorders that may be diagnosed using an antibody of the invention include tauopathies such as neurodegenerative tauopathies. Exemplary diseases or disorders that may be diagnosed using an antibody of the invention include, but are not limited to, Alzheimer'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 embodiments, a disorder that may be diagnosed using an antibody of the invention is Alzheimer's Disease (AD).

[00325] In certain embodiments, labeled anti-Tau antibodies are provided. Labels include, but are not limited to, labels or moieties that are detected directly (such as fluorescent, chromophoric, electron-dense, chemiluminescent, and radioactive labels), as well as moieties, such as enzymes or ligands, that are detected indirectly, *e.g.*, through an enzymatic reaction or molecular interaction. Exemplary labels include, but are not limited to, the radioisotopes ^{32}P, ^{14}C, ^{125}I, ^{3}H, and ^{131}I, fluorophores such as rare earth chelates or fluorescein and its derivatives, rhodamine and its derivatives, dansyl, umbelliferone, luceriferases, *e.g.*, firefly luciferase and bacterial luciferase (U.S. Patent No. 4,737,456), luciferin, 2,3-dihydrophthalazinediones, horseradish peroxidase (HRP), alkaline phosphatase, β-galactosidase, glucoamylase, lysozyme, saccharide oxidases, *e.g.*, glucose oxidase, galactose oxidase, and glucose-6-phosphate dehydrogenase, heterocyclic oxidases such as uricase and xanthine oxidase, coupled with an enzyme that employs hydrogen peroxide to oxidize a dye precursor such as HRP, lactoperoxidase, or microperoxidase, biotin/avidin, spin labels, bacteriophage labels, stable free radicals, and the like.

F. Pharmaceutical Formulations

[00326] Pharmaceutical formulations of an anti-Tau antibody as described herein are prepared by mixing such antibody having the desired degree of purity with one or more optional pharmaceutically acceptable carriers, diluents, and/or excipients (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Pharmaceutically acceptable carriers, diluents, and excipients are generally nontoxic to recipients at the dosages and concentrations employed, and include, but are not limited to: sterile water, buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride; benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.* Zn-protein complexes); and/or non-ionic surfactants such as polyethylene glycol (PEG). Exemplary pharmaceutically acceptable

carriers herein further include insterstitial drug dispersion agents such as soluble neutral-active hyaluronidase glycoproteins (sHASEGP), for example, human soluble PH-20 hyaluronidase glycoproteins, such as rHuPH20 (HYLENEX®, Baxter International, Inc.). Certain exemplary sHASEGPs and methods of use, including rHuPH20, are described in US Patent Publication Nos. 2005/0260186 and 2006/0104968. In one aspect, a sHASEGP is combined with one or more additional glycosaminoglycanases such as chondroitinases.

[00327] Exemplary lyophilized antibody formulations are described in US Patent No. 6,267,958. Aqueous antibody formulations include those described in US Patent No. 6,171,586 and WO2006/044908, the latter formulations including a histidine-acetate buffer.

[00328] The formulation herein may also contain more than one active ingredients as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such active ingredients are suitably present in combination in amounts that are effective for the purpose intended.

[00329] Active ingredients may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in *Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980).

[00330] Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, *e.g.* films, or microcapsules.

[00331] The formulations to be used for *in vivo* administration are generally sterile. Sterility may be readily accomplished, *e.g.*, by filtration through sterile filtration membranes.

G. Therapeutic Methods and Compositions

[00332] Any of the anti-Tau antibodies provided herein may be used in therapeutic methods.

[00333] In one aspect, an anti-Tau antibody for use as a medicament is provided. In further aspects, an anti-Tau antibody for use in treating a Tau protein associated disease or disorder is provided. In some embodiments, an anti-Tau antibody for use in treating diseases

or disorders caused by or associated with the formation of neurofibrillary tangles or neuropil threads is provided. In particular embodiments, an anti-Tau antibody for use in treating a tauopathy such as a neurodegenerative tauopathy is provided. Exemplary Tau protein associated diseases or disorders that can be treated that can be treated with anti-tau antibodies include, without limitation, 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 embodiments, an anti-Tau antibody for use in treating Alzheimer's Disease (AD) is provided herein. In some embodiments, an anti-Tau antibody for use in treating moderate AD, mild to moderate AD, mild AD, early AD, or prodromal AD is provided herein. Further, Tau protein associated diseases or disorders that can be treated with an anti-Tau antibody include diseases or disorders that are manifested in an impairment or loss of a cognitive function such as reasoning, situational judgement, memory capacity, learning, and/or special navigation. In certain embodiments, an anti-Tau antibody for use in a method of treatment is provided. In certain embodiments, the invention provides an anti-Tau antibody for use in a method of treating an individual, having any one of the Tau associated diseases or disorders described above, comprising administering to the individual an effective amount of the anti-Tau antibody. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, *e.g.*, as described below.

[00334] In some embodiments, the antibody of the invention is used to treat an individual having an MMSE score of between 20 and 30, between 20 and 26, between 24 and 30, between 21and 26, between 22 and 26, between 22 and 28, between 23 and 26, between 24 and 26, or between 25 and 26. In some embodiments, the patient has an MMSE score between 22 and 26. As used herein, an MMSE score between two numbers includes the numbers at each end of the range. For example, an MMSE score between 22 and 26 includes MMSE scores of 22 and 26.

[00335] In some embodiments, the antibodies of the invention are used to treat an individual who is 'tau positive,' e.g., a patient having brain tau deposits that are typical of Tau protein associated disorders, e.g., a patient having a positive Tau PET scan.

[00336] In further embodiments, the invention provides an anti-Tau antibody for use in reducing the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau) in an individual. For example such reduction can occur in the brain (*e.g.*, in the brain cortex and/or hippocampus). In some embodiments, the invention provides an anti-Tau antibody for use in reducing the levels of phosphorylated Tau. In some embodiments, the invention provides an anti-Tau antibody for use in reducing the levels of insoluble Tau (*e.g.*, insoluble phosphorylated Tau). In some embodiments, the invention provides an anti-Tau antibody for use in reducing the levels of hyperphosphorylated Tau. In some embodiments, the invention provides an anti-Tau antibody for use in reducing the levels of paired helical filaments (*e.g.*, paired helical filaments containing hyperphosphorylated Tau) in a brain tissue (*e.g.*, in the brain cortex and/or hippocampus). In certain embodiments, the invention provides an anti-Tau antibody for use in a method of reducing the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau) in the brain (*e.g.*, in the brain cortex and/or hippocampus) in an individual comprising administering to the individual an effective amount of the anti-Tau antibody to reduce the levels of Tau protein. An "individual" according to any of the above embodiments is a mammal, preferably a human.

[00337] In some embodiments, the invention provides an anti-Tau antibody for use in modulating the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau), for example, in the brain (*e.g.*, in the brain cortex and/or hippocampus) of an individual.

[00338] In a further aspect, the invention provides for the use of an anti-Tau antibody in the manufacture or preparation of a medicament. In some embodiments, the medicament is for treatment of a Tau protein associated disease or disorder. The Tau protein associated disease or disorder can be a disease or disorders caused by or associated with the formation of neurofibrillary tangles or neuropil threads. In particular embodiments, the medicament is for treatment of a tauopathy such as a neurodegenerative tauopathy. In specific embodiments, the medicament is for treatment of diseases or disorders selected from the group

consisting of: Alzheimer's Disease (AD), 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 embodiments, the medicament is for treatment of AD. In particular embodiments, the medicament is for treatment of a Tau associated disease or disorder that is manifested in an impairment or loss of a cognitive function such as reasoning, situational judgement, memory capacity, learning, or special navigation. In a further embodiment, the medicament is for use in a method of treating one of the above-listed diseases (*e.g.*, a tauopathy such as AD) comprising administering to an individual having such disease an effective amount of the medicament. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, *e.g.*, as described below.

[00339] In a further embodiment, the medicament is for reducing the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble non-phorphorylated Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, insoluble non-phorphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau). For example, such reducing of Tau protein can be observed in the brain (*e.g.*, in the brain cortex and/or hippocampus) or in cerebrospinal fluid of an individual. In some embodiments, the medicament is for reducing the levels of paired helical filaments. In a further embodiment, the medicament is for use in a method of reducing the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau) in an individual comprising administering to the individual an effective amount of the medicament to reducing the levels of Tau protein. An "individual" according to any of the above embodiments is a mammal, preferably, a human.

[00340] In a further aspect, the invention provides a method for treating a Tau protein associated disease or disorder. Tau protein associated disease or disorder that can be

treated in accordance with the methods provided herein include diseases or disorders caused by or associated with the formation of neurofibrillary tangles or neuropil threads. In particular embodiments, the invention provides a method for treating a tauopathy such as a neurodegenerative tauopathy. In specific embodiments, the invention provides a method for treating a disease or disorder selected from the group consisting of: Alzheimer'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 embodiments, the invention provides a method for treating Alzheimer's Disease (AD). In particular embodiments, the invention provides a method for treating a Tau protein associated disease or disorder that is manifested in an impairment or loss of a cognitive function such as reasoning, situational judgement, memory capacity, learning, or special navigation. In some embodiments, the method comprises administering to an individual, having any one of the diseases or disorders described above, an effective amount of an anti-Tau antibody. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, *e.g.*, as described below. In some embodiments, the method comprises administering to an individual having one of the diseases described herein an effective amount of an anti-Tau antibody. In one such embodiment, the method further comprises administering to the individual an effective amount of at least one additional therapeutic agent, as described below. An "individual" according to any of the above embodiments may be a human.

[00341] In a further aspect, the invention provides a method for reducing the levels of Tau protein (*e.g.*, total Tau, total soluble Tau, soluble phosphorylated Tau, total insoluble Tau, insoluble phosphorylated Tau, hyperphosphorylated Tau, or paired helical filaments containing hyperphosphorylated Tau) in an individual. For example, such reducing of the levels of Tau protein can be observed in the brain (*e.g.*, brain cortex and/or hippocampus) or cerebrospinal fluid of an individual. In some embodiments, the invention

provides a method for reducing the levels of paired helical filaments. In some embodiments, the method comprises administering to the individual an effective amount of an anti-Tau antibody to reduce the levels of Tau protein. In some embodiments, an "individual" is a human.

[00342] In some aspects, the invention provides a method for alleviating one or more symptoms of a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for alleviating one or more symptoms of a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). In some aspects, the invention provides a method for reducing the number of symptoms or the severity of one or more symptoms of a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for reducing the number of symptoms or the severity of one or more symptoms of a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). In a particular embodiment, the symptom of a Tau protein associated disease or disorder is an impairment in cognition. In a specific embodiment, the symptom of a Tau protein associated disease or disorder is an impairment in learning and/or memory. In a specific embodiment, the symptom of a Tau protein associated disease or disorder is a long-term memory loss. In a specific embodiment, the symptom of a Tau protein associated disease or disorder is dementia. In some embodiments, the symptom of a Tau protein associated disease or disorder is confusion, irritability, aggression, mood swings, or a language impairment. In some embodiments, the symptom of a Tau protein associated disease or disorder is an impairment or loss of one or more cognitive functions such as reasoning, situational judgment, memory capacity, and/or learning. The methods provided herein comprise administration of an amount (*e.g.*, therapeutically effective amount) of an anti-Tau antibody to an individual (*e.g.*, who displays one or more symptoms of a Tau protein associated disease or disorder).

[00343] In specific aspects, the invention provides a method for retaining or increasing cognitive memory capacity, or for slowing down memory loss associated with a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for retaining or increasing cognitive memory capacity or for slowing down memory loss associated with a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). The methods provided herein comprise administration of an amount (*e.g.*, therapeutically effective amount) of an anti-Tau

antibody to an individual (*e.g.*, who displays one or more symptoms of memory loss or a decrease of memory capacity).

[00344] In some aspects, the invention provides a method for decreasing the rate of progression of a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for decreasing the rate of progression of a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). The methods provided herein comprise administration of an amount (*e.g.*, therapeutically effective amount) of an anti-Tau antibody to an individual (*e.g.*, who displays one or more symptoms of a Tau protein associated disease or disorder).

[00345] In some aspects, the invention provides a method for preventing the development of a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for preventing the development of a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). The methods provided herein comprise administration of an amount (*e.g.*, therapeutically effective amount) of an anti-Tau antibody to an individual (*e.g.*, who is at risk of a Tau protein associated disease or disorder).

[00346] In some aspects, the invention provides a method for delaying the development of a Tau protein associated disease or disorder; or an anti-Tau antibody or a medicament comprising anti-Tau antibody for delaying the development of a Tau protein associated disease or disorder (such as any of the diseases or disorders described herein, for example, AD). The methods provided herein comprise administration of an amount (*e.g.*, therapeutically effective amount) of an anti-Tau antibody to an individual (*e.g.*, who displays one or more symptoms of a Tau protein associated disease or disorder).

[00347] In a further aspect, the invention provides pharmaceutical formulations comprising any of the anti-Tau antibodies provided herein, *e.g.*, for use in any of the above therapeutic methods. In some embodiments, a pharmaceutical formulation comprises any of the anti-Tau antibodies provided herein and a pharmaceutically acceptable carrier. In another embodiment, a pharmaceutical formulation comprises any of the anti-Tau antibodies provided herein and at least one additional therapeutic agent, *e.g.*, as described below.

[00348] Antibodies of the invention can be used either alone or in combination with other agents in a therapy. For instance, an antibody of the invention may be co-administered with at least one additional therapeutic agent.

[00349] For example, the composition according to the invention may be administered in combination with other compositions comprising an additional therapeutic

agent, such as a biologically active substance or compound such as, for example, a known compound used in the medication of tauopathies and/or of amyloidoses, a group of diseases and disorders associated with amyloid or amyloid-like protein such as the amyloid β protein involved in Alzheimer's Disease.

[00350] Generally, the other biologically active compound may include neuron-transmission enhancers, psychotherapeutic drugs, acetylcholine esterase inhibitors, calcium-channel blockers, biogenic amines, benzodiazepine tranquillizers, acetylcholine synthesis, storage or release enhancers, acetylcholine postsynaptic receptor agonists, monoamine oxidase-A or –B inhibitors, N-methyl-D-aspartate glutamate receptor antagonists, non-steroidal anti-inflammatory drugs, antioxidants, serotonergic receptor antagonists, or other therapeutic agents. In particular, the biologically active agent or compound may comprise at least one compound selected from compounds against oxidative stress, anti-apoptotic compounds, metal chelators, inhibitors of DNA repair such as pirenzepine and metabolites, 3-amino-1-propanesulfonic acid (3APS), 1,3-propanedisulfonate (1,3PDS), secretase activators, beta- and gamma-secretase inhibitors, tau proteins, anti-Tau antibodies (including, but not limited to, antibodies disclosed in WO2012049570, WO2014028777, WO2014165271, WO2014100600, WO2015200806, US8980270, and US8980271), neurotransmitter, beta-sheet breakers, antiinflammatory molecules, "atypical antipsychotics" such as, for example clozapine, ziprasidone, risperidone, aripiprazole or olanzapine or cholinesterase inhibitors (ChEIs) such as tacrine, rivastigmine, donepezil, and/or galantamine and other drugs and nutritive supplements such as, for example, vitamin B 12, cysteine, a precursor of acetylcholine, lecithin, choline, Ginkgo biloba, acyetyl-L-carnitine, idebenone, propentofylline, or a xanthine derivative, together with a binding peptide according to the invention including antibodies, particularly monoclonal antibodies and active fragments thereof, and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient and instructions for the treatment of diseases.

[00351] In some embodiments, an antibody of the invention may be administered in combination with a neurological drug. Such neurological drugs include, but are not limited to, an antibody or other binding molecule (including, but not limited to a small molecule, a peptide, an aptamer, or other protein binder) that specifically binds to a target selected from: beta secretase, presenilin, amyloid precursor protein or portions thereof, amyloid beta peptide or oligomers or fibrils thereof, death receptor 6 (DR6), receptor for advanced glycation endproducts (RAGE), parkin, and huntingtin; an NMDA receptor antagonist (*i.e.*, memantine), a monoamine depletor (*i.e.*, tetrabenazine); an ergoloid mesylate; an anticholinergic

antiparkinsonism agent (*i.e.*, procyclidine, diphenhydramine, trihexylphenidyl, benztropine, biperiden and trihexyphenidyl); a dopaminergic antiparkinsonism agent (*i.e.*, entacapone, selegiline, pramipexole, bromocriptine, rotigotine, selegiline, ropinirole, rasagiline, apomorphine, carbidopa, levodopa, pergolide, tolcapone and amantadine); a tetrabenazine; an anti-inflammatory (including, but not limited to, a nonsteroidal anti-inflammatory drug (*i.e.*, indomethicin and other compounds listed above); a hormone (*i.e.*, estrogen, progesterone and leuprolide); a vitamin (*i.e.*, folate and nicotinamide); a dimebolin; a homotaurine (*i.e.*, 3-aminopropanesulfonic acid; 3APS); a serotonin receptor activity modulator (*i.e.*, xaliproden); an, an interferon, and a glucocorticoid or corticosteroid. The term "corticosteroid" includes, but is not limited to, fluticasone (including fluticasone propionate (FP)), beclometasone, budesonide, ciclesonide, mometasone, flunisolide, betamethasone and triamcinolone. "Inhalable corticosteroid" means a corticosteroid that is suitable for delivery by inhalation. Exemplary inhalable corticosteroids are fluticasone, beclomethasone dipropionate, budenoside, mometasone furoate, ciclesonide, flunisolide, and triamcinolone acetonide.

[00352] In some embodiments, one or more anti-amyloid beta (anti-Abeta) antibodies may be administered with an anti-Tau antibody provided herein. Non-limiting examples of such anti-Abeta antibodies include crenezumab, solanezumab, bapineuzumab, aducanumab, gantenerumab, and BAN-2401 (Biogen, Eisai Co., Ltd.). In some embodiments, one or more beta-amyloid aggregation inhibitors may be administered with an anti-Tau antibody provided herein. Nonlimiting exemplary beta-amyloid aggregation inhibitors include ELND-005 (also referred to as AZD-103 or scyllo-inositol), tramiprosate, and PTI-80 (Exebryl-1®; ProteoTech). In some embodiments, one or more BACE inhibitors may be administered with an anti-Tau antibody provided herein. Non-limiting examples of such BACE inhibitors include E-2609 (Biogen, Eisai Co., Ltd.), AZD3293 (also known as LY3314814; AstraZeneca, Eli Lilly & Co.), MK-8931 (verubecestat), and JNJ-54861911 (Janssen, Shionogi Pharma). In some embodiments, one or more Tau inhibitors may be administered with an anti-Tau antibody provided herein. Non-limiting examples of such Tau inhibitors include methylthioninium, LMTX (also known as leuco-methylthioninium or Trx-0237; TauRx Therapeutics Ltd.), Rember™ (methylene blue or methylthioninium chloride [MTC]; Trx-0014; TauRx Therapeutics Ltd), PBT2 (Prana Biotechnology), and PTI-51-CH3 (TauPro™; ProteoTech). In some embodiments, one or more other anti-Tau antibodies may be administered with an anti-Tau antibody provided herein. Non-limiting examples of such other anti-Tau antibodies include BMS-986168 (Bristol-Myers Squibb) and C2N-8E12 (AbbVie, C2N Diagnostics, LLC). In some embodiments, a general misfolding inhibitor, such as

NPT088 (NeuroPhage Pharmaceuticals), may be administered with an anti-Tau antibody provided herein.

[00353] In some embodiments, the composition according to the invention may comprise niacin or memantine together with a chimeric antibody or a humanized antibody according to the invention including antibodies, particularly monoclonal antibodies and active fragments thereof, and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

[00354] In some embodiments, compositions are provided that comprise "atypical antipsychotics" such as, for example clozapine, ziprasidone, risperidone, aripiprazole or olanzapine for the treatment of positive and negative psychotic symptoms including hallucinations, delusions, thought disorders (manifested by marked incoherence, derailment, tangentiality), and bizarre or disorganized behavior, as well as anhedonia, flattened affect, apathy, and social withdrawal, together with the chimeric antibody or the humanized antibody according to the invention or active fragments thereof, and, optionally, a pharmaceutically acceptable carrier and/or a diluent and/or an excipient.

[00355] Other compounds that can be suitably used in compositions in addition to chimeric antibody or humanized antibody according to the invention, are those disclosed, for example, in WO 2004/058258 (see especially pages 16 and 17) including therapeutic drug targets (page 36-39), alkanesulfonic acids and alkanolsulfuric acid (pages 39-51), cholinesterase inhibitors (pages 51-56), NMDA receptor antagonists (pages 56-58), estrogens (pages 58-59), non-steroidal anti-inflammatory drugs (pages 60-61), antioxidants (pages 61-62), peroxisome proliferators-activated receptors (PPAR) agonists (pages 63-67), cholesterol–lowering agents (pages 68-75); amyloid inhibitors (pages 75-77), amyloid formation inhibitors (pages 77-78), metal chelators (pages 78-79), anti-psychotics and anti-depressants (pages 80-82), nutritional supplements (pages 83-89) and compounds increasing the availability of biologically active substances in the brain (see pages 89-93) and prodrugs (pages 93 and 94), which document is incorporated herein by reference, but especially the compounds mentioned on the pages indicated above.

[00356] Such combination therapies noted above encompass combined administration (where two or more therapeutic agents are included in the same or separate formulations), and separate administration, in which case, administration of the antibody of the invention can occur prior to, simultaneously, and/or following, administration of the additional therapeutic agent or agents. In some embodiments, administration of the anti-Tau antibody and administration of an additional therapeutic agent occur within about one month, or within

about one, two or three weeks, or within about one, two, three, four, five, or six days, of each other.

[00357] An antibody of the invention (and any additional therapeutic agent) can be administered by any suitable means, including parenteral, intrapulmonary, and intranasal, and, if desired for local treatment, intralesional administration. Parenteral infusions include intramuscular, intravenous, intraarterial, intraperitoneal, or subcutaneous administration. Dosing can be by any suitable route, *e.g.* by injections, such as intravenous or subcutaneous injections, depending in part on whether the administration is brief or chronic. Various dosing schedules including but not limited to single or multiple administrations over various time-points, bolus administration, and pulse infusion are contemplated herein.

[00358] Antibodies of the invention would be formulated, dosed, and administered in a fashion consistent with good medical practice. Factors for consideration in this context include the particular disorder being treated, the particular mammal being treated, the clinical condition of the individual patient, the cause of the disorder, the site of delivery of the agent, the method of administration, the scheduling of administration, and other factors known to medical practitioners. The antibody need not be, but is optionally formulated with one or more agents currently used to prevent or treat the disorder in question. The effective amount of such other agents depends on the amount of antibody present in the formulation, the type of disorder or treatment, and other factors discussed above. These are generally used in the same dosages and with administration routes as described herein, or about from 1 to 99% of the dosages described herein, or in any dosage and by any route that is empirically/clinically determined to be appropriate.

[00359] For the prevention or treatment of disease, the appropriate dosage of an antibody of the invention (when used alone or in combination with one or more other additional therapeutic agents) will depend on the type of disease to be treated, the type of antibody, the severity and course of the disease, whether the antibody is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, and the discretion of the attending physician. The antibody is suitably administered to the patient at one time or over a series of treatments. Depending on the type and severity of the disease, about 1 μg/kg to 15 mg/kg (*e.g.* 0.1mg/kg-10mg/kg) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. One typical daily dosage might range from about 1 μg/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition,

the treatment would generally be sustained until a desired suppression of disease symptoms occurs. One exemplary dosage of the antibody would be in the range from about 0.05 mg/kg to about 10 mg/kg. Thus, one or more doses of about 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg or 10 mg/kg (or any combination thereof) may be administered to the patient. Such doses may be administered intermittently, *e.g.* every week or every three weeks (*e.g.* such that the patient receives from about two to about twenty, or *e.g.* about six doses of the antibody). An initial higher loading dose, followed by one or more lower doses may be administered. However, other dosage regimens may be useful. The progress of this therapy is easily monitored by conventional techniques and assays.

[00360] It is understood that any of the above formulations or therapeutic methods may be carried out using an immunoconjugate of the invention in place of or in addition to an anti-Tau antibody.

H. Articles of Manufacture

[00361] In another aspect of the invention, an article of manufacture containing materials useful for the treatment, prevention and/or diagnosis of the disorders described above is provided. The article of manufacture comprises a container and a label or package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, IV solution bags, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is by itself or combined with another composition effective for treating, preventing and/or diagnosing the condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an antibody of the invention. The label or package insert indicates that the composition is used for treating the condition of choice. Moreover, the article of manufacture may comprise (a) a first container with a composition contained therein, wherein the composition comprises an antibody of the invention; and (b) a second container with a composition contained therein, wherein the composition comprises a further cytotoxic or otherwise therapeutic agent. The article of manufacture in this embodiment of the invention may further comprise a package insert indicating that the compositions can be used to treat a particular condition. Alternatively, or additionally, the article of manufacture may further comprise a second (or third) container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and

dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

[00362] It is understood that any of the above articles of manufacture may include an immunoconjugate of the invention in place of or in addition to an anti-Tau antibody.

III. EXAMPLES

[00363] The following are examples of methods and compositions of the invention. It is understood that various other embodiments may be practiced, given the general description provided above.

Example 1: Generation of Tau for Immunization

Generation of monomeric recombinant Tau

[00364] The recombinant human Tau construct, 2N4R isoform (amino acids 2-441), was fused to a N-terminal His-tag to facilitate purification and characterization. *See, e.g.*, Figure 15. The fusion construct was cloned into the pET52b vector (Novagen) and expressed in *E. coli*. Cells were harvested and lysed under denaturing condition using 7M guanidinium chloride overnight at 4°C with stirring. Cell debris was pelleted at 40,000 rpm for 1 hour. The recombinant, His-tagged protein was isolated by nickel affinity chromatography (Ni Sepharose excel affinity resin, GE Healthcare Life Sciences) followed by size-exclusion chromatography (Superdex 200 resin, GE Healthcare Life Sciences) under denaturing condition. Guanidinium chloride was removed by dialyzing the recovered protein into 20mM MES, 50mM NaCl, and 1mM TCEP at pH 6.8. The His-tag was subsequently removed using TEV protease, followed by final purification using cation exchange chromatography (Mono S column, GE Healthcare Life Sciences) to remove the cleaved His-tag. The purification buffer contained 0.1% Triton x-114 (v/v) to remove endotoxin. Purified protein was exchanged into PBS with 1mM TCEP. The purity and monomeric state were analyzed by SDS-PAGE and SEC-MALLS. Identity was confirmed by mass spectrometry. Protein concentration was determined by UV absorption at 280 nm. The final product was free of endotoxin (<0.5 EU/mg), as determined by Kinetic Limulus Amebocyte Lysate (LAL) assay.

Generation of phosphorylated Tau

[00365] Phosphorylated Tau was generated using the Tau 2-441 construct prepared using the method described above. The protein construct was phosphorylated using 0.5 μM PKA kinase (Life Technologies), which phosphorylates serine 409, among other residues. The reaction mixture was incubated with 1mM ATP, 5mM $MgCl_2$, at room temperature for 72 hours. Phosphorylation was confirmed by mass spectrometry. Size-

exclusion chromatography (Superdex 75, GE Healthcare Life Sciences) was used to remove the kinase. The purity, monomeric state, and endotoxin level of the phosphorylated protein preparation were analyzed substantially as described above.

In vitro oligomeriztion of monomeric Tau

[00366] Oligomeric Tau was generated using the monomeric Tau 2-441 construct. The monomeric protein was first exchanged into 20mM N,N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 25mM NaCl, pH 7.4, followed by oligomeriztion using 75 μM arachidonic acid (Cayman Chemicals) and 18 kDa Heparin (Sigma Aldrich), at equimolar concentration with protein at 37°C for 3 days. Oligomerization was confirmed by thioflavin T fluorescence assay, dynamic light scattering (DLS), and analytical size-exclusion chromatography. Oligomeric Tau is in some instances referred to as "oligoTau."

Example 2: Generation of anti-Tau Antibodies

Methods

Generation of hybridomas

[00367] Female C57BL/6JOlaHsd (C57BL/6) and BALB/c OlaHsd (Balb/c) wild-type mice (Harlan, USA) were received at 9 weeks of age. Tau knock-out mice (B6.129-Mapttm1Hnd/J; The Jackson Laboratory, USA) were received at 6 and 9 weeks of age. Vaccinations started at 12 to 15 weeks of age. Mice were vaccinated with oligomerized human Tau. Before vaccination, the oligoTau was mixed with one of two adjuvants used in this study, Ribi Adjuvant System (Ribi; Sigma-Aldrich, Switzerland) at 50% v/v, or a combination of CpG single-stranded synthetic DNA oligodeoxynucleotides (CpG; Microsynth, Switzerland) and aluminium hydroxide (Al; Brenntag, Switzerland). Ribi is 2% squalene oil-in-water emulsion containing monophosphoryl lipid A (isolated from *Salmonella minnesota*) and synthetic trehalose dicorynomycolate (isolated from the cord factor of the *Tubercle bacillus*) in squalene oil, 0.2% Tween-80, and water.

[00368] Mice were vaccinated by subcutaneous injection (s.c.), except groups D and G, which received a combination of intraperitoneal (i.p.) and hock administrations. Mice in group D were administered 50 μg of oligoTau i.p. and 10 μg of oligoTau as hock injection. Mice in group G were administered 8 μg of oligoTau i.p. and 2 μg of oligoTau as hock injection. *See* Table 2.

For vaccinations containing CpG and Al (CpG/Al) as adjuvant, each injection of 200 μL contained 60 μg (30 nmol) CpG, 1 mg Al, and 50 μg oligoTau. For all study groups, mice were injected on days 0, 14, 35, and 56. Mice used for myeloma fusion (Nanotools,

Germany) were additionally vaccinated with three daily booster injections of oligoTau (50 µg per i.p. injection) without adjuvant added.

Table 2. Mice and vaccination protocols

Study group	Mouse strain	Total oligoTau dose (µg/injection)	Adjuvant	Vaccination route
A	C57BL/6	50	CpG/Al	s.c.
B	C57BL/6	50	Ribi	s.c.
C	Balb/c	50	CpG/Al	s.c.
D	Balb/c	60	CpG/Al	hock+i.p.
E	Balb/c	5	CpG/Al	s.c.
F	Balb/c	50	Ribi	s.c.
G	Tau knock-out	10	Ribi	hock+i.p.

[00369] Mice were bled and sacrificed one day following the last of three booster injections, and splenocytes were fused with myeloma cells to generate antibody producing hybridomas.

Selection of hybridomas for subcloning

[00370] For fusions, mice were divided into three groups, for a total of 10 fusions (2 fusions in one group, four fusions in the second group, and four fusions in the third group), generating 299 hybridomas. Viable hybridomas were grown using serum-containing selection media, and the best hybridomas were then selected for subcloning, using ELISA assays for full-length human Tau and oligoTau binding as described below. Following limiting dilution, the final hybridomas were then grown in serum-free medium and media was collected from stable colonies for antibody screening and selection.

ELISA screening assays

[00371] Serum-free supernatants were harvested from stable hybridomas. The supernatants containing antibodies of interest were then screened by ELISA assays to characterize antibody properties and select antibodies for further development. The ELISA assays were used to determine the following: binding to full-length human Tau (flTau; SignalChem, Canada), binding to hyperphosphorylated flTau (Genentech, USA), binding to oligomeric versus monomeric preparations of flTau, and binding to certain antibody Tau epitope(s). Briefly, 96-well MaxiSorp ELISA plates (Nunc, Denmark) were coated with one of the targets as shown in Table 3.

Table 3. Targets used for the ELISA screening assays.

Assay	ELISA setup	Target
Binding to flTau	Direct ELISA	Full-length human Tau (flTau) coated at 1 µg/mL
Binding to pTau	Direct ELISA	Full-length human Tau phosphorylated *in vitro* using 4 kinases (GSK3β, Cdk5, PKA, and CK1δ; hyper-phosphorylated Tau or pTau) purified and coated at 1 µg/mL
Epitope mapping	Direct ELISA	Biotinylated 15-mer peptides spanning the 441 amino acids (aa) of human Tau with 9 aa offset and 6 aa overlap coated at 10 µg/mL on a streptavidin 96-well plate
Binding to oligoTau	Capture ELISA	AVI-tag biotinylated oligomeric and monomeric flTau captured in solution by anti-IgG immobilized antibodies being tested

[00372] Coating was done overnight in phosphate-buffered saline (PBS) at 4°C. Plates were washed thoroughly with 0.05% Tween-20/PBS and then blocked with 1% bovine serum albumin (BSA) in 0.05% Tween-20/PBS for 1 hr at 37°C. The antibody contained in the hybridoma supernatant was then added at the indicated dilutions, and incubated for 2 hrs at 37°C after which the plates were washed as described previously.

[00373] For the direct ELISAs, an AP-conjugated anti-mouse IgG secondary antibody (Jackson ImmunoResearch Laboratories, United Kingdom) was added at 1/6000 dilution in 0.05% Tween-20/PBS for 2 hr at 37°C. After the final wash, plates were incubated with p-nitrophenyl phosphate disodium hexahydrate (pNPP; Sigma-Aldrich, Switzerland) phosphatase substrate solution, and read at 405 nm using an ELISA plate reader (Tecan, Switzerland). Results are expressed as optical densities (O.D.).

[00374] For the oligoTau and monoTau capture ELISAs, antibodies contained in serum-free sterile hybridoma supernatants were immobilized on an anti-IgG coated plate at 500-fold dilution, followed by the incubation of oligoTau or monoTau, both with site-specific biotinylation via an AVI-tag. The target incubations started at 5 µg/mL and then were diluted 8- or 16-fold. Streptavidin-HRP and ABTS substrate was used for signal quantitation in a plate reader (Tecan, Switzerland). Results are expressed as O.D.

Affinity estimates

[00375] Affinity of non-purified antibodies in serum-free hybridoma supernatants was estimated by surface plasmon resonance using a Biacore T-100 instrument (GE Healthcare, United Kingdom). Antibodies were immobilized onto an anti-IgG biosensor chip, and flTau (SignalChem, Canada) was used as the target analyte. Kinetic analysis was done using a 1:1 Langmuir fit model.

SDS-PAGE and Western-blot assays

[00376] The binding of selected panTau antibodies to Tau in human brain was tested in a Western-blot (WB) using brain lysates from three AD and two age-matched non-AD control donors (Tissue Solutions, United Kingdom). The lysates were processed to obtain a detergent-free soluble Tau fraction. Processed lysates were loaded onto 4-12% bis-tris gels (Novex, Life Technologies, Switzerland) and transferred onto Immobilon PVDF membranes and blotted with antibodies being tested with and an IRDye 800CW goat anti-mouse secondary antibody (Li-Cor, USA).

ELISA assay using human brain lysates

[00377] To assess the binding of selected antibodies to non-denatured human Tau in AD and control brain lysates, antibodies from hybridoma supernatants, or a negative and positive control antibodies, were immobilized on a 96-well plate as described above. Tau in soluble human brain lysates from AD or age-matched control subjects (400 μg/mL protein; all from Tissue Solutions, United Kingdom) was then captured and detection was performed using a polyclonal rabbit panTau antibody (AbCam, United Kingdom) followed by an Fc-γ fragment specific anti-rabbit IgG-AP (Jackson ImmunoResearch, USA). Brain lysate from Tau knock-out mouse was used as a negative sample control. Plates were incubated with pNPP (Sigma-Aldrich) phosphatase substrate solution, and read at 405 nm using an ELISA plate reader (Tecan, Switzerland). Results are expressed as optical densities (O.D.).

Sequencing of antibody hybridomas

[00378] Hybridoma cell lysates were supplied to Antitope (Antitope, United Kingdom) for variable region gene sequencing. Briefly, RT-PCR was performed using degenerate primer pools for murine signal sequences together with constant region primers for each of IgG variable heavy (VH), IgM VH, Ig kappa variable light (KVL) and Ig λ VL chains. Heavy chain V-region mRNA was amplified using a set of six degenerate primer pools (HA to HF) specific for VH signal sequences together with either IgM or IgG-specific constant region primers. The light chain V-region mRNA was amplified using a set of eight signal sequence-specific degenerate primer pools, seven for the κ cluster (KA to KG) and one for the λ cluster (LA), together with either κ or λ constant region primers. The PCR products obtained from successful amplification were purified, cloned into a 'TA' cloning vector (pGEM-T Easy, Promega), transformed into E.coli and individual colonies sequenced. The nucleotide and amino acid sequences of the antibody VH and VL regions were determined with the sequences for 27 antibody hybridomas.

Results

Selection of hybridomas for subcloning

[00379] Hybridomas that were generated from each of the three rounds of fusions, a total of 299 hybridomas derived from ten fusions, were initially assayed for binding to flTau, with selected hybridomas additionally assayed for binding to pTau and oligomerized Tau. The aim was to select antibodies that bind equally well to Tau and to Tau modified post-translationally, such as phosphorylated or oligomeric Tau. For this, assays were run on hybridomas to select for the best panTau properties. To determine antibody binding region and the specific Tau epitope, the binding region was first determined using different Tau fragments and then a library of 15-mer overlapping Tau peptides spanning the full 441 amino acids (aa) sequence of the longest human Tau isoform. A group of antibodies binding to pre-determined regions of Tau were intentionally avoided with the aim to maximize binding to different post-translationally modified forms of Tau and to all the six different human Tau isoforms present in humans.

[00380] The three fusion series resulted in the generation of 133 subcloned stable hybridomas that were screened for the best panTau properties. A combination of different screening assays was used to narrow down the number of antibody hybridomas having the preferred properties for a panTau antibody. For comparing flTau and pTau binding, 90 hybridomas were assayed with the results of 24 hybridomas shown in Figure 1A-F. As an initial screen had been performed using Tau fragments to avoid selecting antibodies binding to regions of Tau known to have high density of residues that are phosphorylated in Alzheimer's disease (AD) and other tauopathies, most antibodies tested bound to both flTau and pTau with similar binding properties as determined by this ELISA.

[00381] In some embodiments, it is desirable that a panTau antibody bind to both monomeric and oligomeric forms of Tau without a strong preference to one or the other. A capture ELISA was set up to determine if antibodies bound to both monomeric and oligomeric forms of flTau. An ELISA run in capture mode preserves the oligomer conformation of pre-oligomerized Tau and the monomeric state of monoTau better than when run as a direct ELISA with the targets immobilized onto an ELISA plate.

[00382] Each assay was run by directly comparing the binding of the two forms of Tau to all 90 antibodies tested. Antibodies known to have preferred binding to either oligoTau or that do not discriminate between the two forms of Tau were used as controls in each assay. The results of 18 hybridomas are shown in Figure 2A-E.

[00383] Mapping the epitopes is important for selecting antibodies with good panTau properties, as antibodies that bind to regions with high density of potential pTau

residues (Ser, Thr, and Tyr) can be avoided. Binding to all six isoforms of human Tau was also used as a selection criterion for a panTau antibody. The panTau epitopes of antibodies that had been initially selected were verified and determined with improved accuracy using a library of 49 peptides each having 15 amino acids (aa) spanning the full length of human Tau, with an overlap of 6 aa residues and an offset of 9 aa. The residue numbers are based on the longest isoform of human Tau (441 aa). Non-purified antibdies were used at high 1/10 dilution to verify binding versus no binding to all peptides. Screening of antibodies from 112 hybridomas previously selected by ELISA indicated binding to 20 different Tau epitopes (Table 4).

Table 4: Tau epitopes for antibodies

Antibody	Tau epitope (aa)
14F5-D9	1-15
94B2-B12	1-15
94B2-C1	1-15
10A1-A6	10-24
10A1-D8	10-24
11E10-B8	10-24
17G12-C11	10-24
17G12-D5	10-24
19H6-A1	10-24
19H6-F7	10-24
19H6-G8	10-24
37D3-H12	10-24
37D3-H9	10-24
37E8-B4	10-24
37E8-C2	10-24
3A4-H4	10-24
3H10-E12(A)	10-24
3H10-G12	10-24
44B7-A9	10-24
44B7-B1	10-24
54C1-H11	10-24
61E7-B11	10-24
61H10-B4	10-24
61H10-H3	10-24
127G7-A5	10-24
127G7-E7	10-24
115A4-A3	10-24
115A4-B1	10-24
125B11-B6	10-24
73C8-A5	10-24
73C8-G4	10-24
76B4-D9	10-24
76B4-H7	10-24

Antibody	Tau epitope (aa)
30A1-C9	73-87
30A1-D11	73-87
28F5-G8	82-96
28F5-H8	82-96
33G9-A11	100-114
33G9-B9	100-114
52F2-E12	100-114
52F2-E8	100-114
52F6-B3	100-114
52F6-F11	100-114
56D3-C8	100-114
56D3-E9	100-114
70B10-B6B2	100-114
70B10-B6G12	100-114
78E4-D11	100-114
78E4-G4	100-114
30G1-B2	109-123
30G1-C11	109-123
49G10-F4	109-123
49G10-H1	109-123
65B1-A2	109-123
65B1-A7	109-123
73H6-B8	109-123
113F5-A8	109-123
113F5-F7	109-123
125B11-H3	109-123
26C1-B11	118-132
26C1-C8	118-132
74H10-A3	118-132
74H10-C3	118-132
78F3-B2	118-132
78F3-E7C6	118-132
78F3-E7H7	118-132

123E9-B3	19-33
15C6-A7	19-33
19F8-B1	19-33
24A11-D5	19-33
63H3-B2	19-33
63H3-D8	19-33
64B9-E11	19-33
64B9-F12	19-33
45D2-C9	19-33
45D2-F4	19-33
72E12-B2	19-33
72G10-A7	19-33
72G10-B6	19-33
123E9-A1	19-42
19F8-C11	19-42
7A11-C12	19-42
89F4-A2	28-42
89F4-A1	28-44
12A10-E8	37-51
55E7-B12	37-51
72E12-H9	37-51
55E7-F11	37-51
30D12-B5	64-78
21C1-D8	64-78
21C1-G6	64-78
30D12-F6	64-78
31A3-A4	64-78
31A3-A7	64-78
77D1-D2	64-78
77D1-E6	64-78
126H12-G6	136-150
126H12-H7	136-150
22G7-C9	154-168
22G7-G9	154-168
111B8-C4	163-177
111B8-F10	163-177
66F5-A1	172-177
66F5-F2	172-177
71H8-A1	190-204
71H8-D6	190-204
83E10-D10	190-204
83E10-D6	190-204
126F11-B3	217-231
126F11-G11	217-231
93A8-C9	397-411
93A8-D2	397-411

[00384] For affinity measurements to flTau, 46 antibodies were measured using SPR on a Biacore instrument, with the K_Ds determined. Biacore affinity measurements were done by immobilizing antibodies on an anti-IgG chip and using flTau as the target analyte. Results for 32 antibodies are shown in Table 5, with antibodies ranked based on affinity to flTau. Of the antibodies measured for affinty to flTau, 22 antibodies had affinities better than 20 nM, of which 14 antibodies had K_Ds under 5 nM with antibody 37D3-H9 having a K_D (affinity) of 1 nM.

Table 5: Affinity for flTau

Antibody	K_D (nM)
37D3-H9	1
54C1-H11	1.5
3A4-H4	7.8
52F6-F11	8.4

123E9-A1	1.8	3A4-A12	10.1
94B2-C1	1.9	44B7-B1	14.7
24A11-D5	2	3H10-E12	19.4
113F5-F7	2.4	10A1-D8	19.6
89F4-A1	2.9	52F2-E8	26
19F8-B1	2.9	19H6-F7	39
61E7-C4	3.3	34H4-F5	43
126F11-G11	4.2	19H6-A1	56
26C1-C8	4.3	34H4-B10	69
93A8-D2	4.3	17G12-C11	118
37E8-B4	4.4	45H12-C4	139
61E7-B11	4.8	17G12-D5	161
125B11-H3	6	61H10-H3	177
54C1-C3	6.8	11E10-C3	399

[00385] To verify the binding of selected antibodies to all six isoforms of human Tau, an SDS-PAGE was run with a recombinant Tau ladder containing all six isoforms and Western-blot (WB) done using three selected Tau antibodies. All three panTau antibodies bind to all six Tau isoforms (Figure 3). Furthermore, brain homogenates from three AD and two age-matched controls were simultaneously run for comparison. As expected, and based on the mapped epitopes, all three antibodies tested in this assay showed binding to all six Tau isoforms. The difference observed in band patterns between human AD and control donors may represent the greater phosphorylation and/or SDS-stable Tau aggregates that would be expected to be present in AD subjects.

[00386] Human Alzheimer's disease (AD) and control samples were additionally run in a non-denaturing ELISA capture assay to verify binding to Tau in human brains. Samples lysates processed for soluble Tau from two AD and two non-AD age-matched control subjects were run at 8 dilutions testing three antibodies (Figure 4A-C).

[00387] Antibody variable chain sequences were determined for 27 hybridomas (Antitope, United Kingdom). Protein sequences for certain heavy and light chain variable domains and hypervariable regions (HVRs) are shown in the Table of Sequences.

Example 3: Characterization anti-Tau Antibodies

[00388] Antibody heavy and light chains were constructed via gene synthesis and subcloning of the resulting DNA into murine IgG2a (heavy chain) and murine kappa (light

chain) mammalian expression vectors. Antibodies were expressed in CHO or 293T cells by transient co-transfection of the heavy chain and light chain plasmids and were purified with affinity resin MabSelectSure (GE Healthcare Life Sciences). Purified recombinant antibodies were screened for binding to Tau monomer protein on a Biacore T200 surface plasmon resonance instrument using a mouse IgG capture kit and a Series S CM5 chip. Antibodies in mIgG2a format diluted in 10mM HEPES pH7.4, 150 mM NaCl, 0.05% Tween 20 (running buffer, HBSP) were captured for 30 or 45 seconds at a concentration of 1 µg/ml (antibodies 26C1, 94B2-C1, 52F6-F11.v1, 52F6-F11.v2, 11E10-B8, 55E7-F11, 125B11-H3, 123E9-A1, 30G1-B2, 66F5-A1, 89F4-A1, 93A8-D2 and 126F11-G11) or for 70 or 150 seconds at a concentration of 0.1 µg/ml (antibodies 19H6-F7, 3A4-H4, 54C1-H11 and 37D3-H9) using a flow rate of 10 µl/min. Binding of Tau monomer in HBSP was monitored at 25°C using a flow rate of 30 µl/min and concentrations of 16, 31, 63, 125, 125, 250 and 500 nM for antibodies 26C1 and 94B2; 16, 31, 63, 125, 125, 250, 500 and 1000 nM for antibodies 52F6-F11.v1 and 52F6-F11.v2; 6, 19, 56, 56, 167 and 500 nM for antibodies 11E10-B8, 55E7-F11 and 125B11-H3; 5, 16, 49, 148, 148, 444, 1333 and 4000 nM for antibodies 123E9-A1, 30G1-B2, 66F5-A1, 89F4-A1, 93A8-D2 and 126F11-G11; 0.4, 1.6, 6.3, 2.5, 100 and 400 nM for 19H6-F7; and 0.2, 0.8, 4, 4, 20 and 100 nM for 3A4-H4, 54C1-H11 and 37D3-H9. Association and dissociation times were monitored for 180-480 seconds and for 300-600 seconds respectively. Antibody 37D3-H9 was selected for further analysis due to the high affinity (Table 6) and the absence of NXS/T glycosylation motifs in the CDRs.

Table 6: K_D (nM) of murine antibodies to human Tau monomer. Data shown represent output of a 1:1 binding model.

Antibody	K_D (nM)	k_{on} (1/Ms)	k_{off} (1/s)
26C1	17	4×10^{4}	7×10^{-4}
94B2-C1	6	5×10^{4}	3×10^{-4}
54C1-H11	0.6	3×10^{5}	2×10^{-4}
3A4-H4	12	3×10^{4}	3×10^{-4}
37D3-H9	1.6	1×10^{5}	1×10^{-4}
19H6-F7	10	2×10^{5}	2×10^{-3}
11E10-B8	108	2×10^{5}	2×10^{-2}
55E7-F11	171	2×10^{5}	4×10^{-2}
125B11-H3	5	5×10^{4}	3×10^{-4}
123E9-A1	52	4×10^{5}	2×10^{-2}

30G1-B2	20	4×10^{5}	8×10^{-3}
66F5-A1	105	8×10^{4}	8×10^{-3}
89F4-A1	27	3×10^{5}	7×10^{-3}
93A8-D2	6	3×10^{5}	2×10^{-3}
126F11-G11	3	2×10^{6}	4×10^{-3}
52F6-F11.v1	15	5×10^{4}	7×10^{-4}
52F6-F11.v2	5	7×10^{4}	4×10^{-4}

37D3-H9 demonstrates avidity when binding to Tau protein

[00389] Human monomer Tau protein was covalently coupled to a Biacore Series S CM5 chip using the Biacore Amine Coupling Kit (GE Life Sciences), resulting in immobilization to a level of approximately 128 RU. Direct binding of 37D3-H9 in both Fab and IgG formats was monitored using the single-cycle kinetics experimental format with five association periods of 300s each and antibody concentrations of 1, 2, 4, 8 and 16 nM (IgG) or 5, 10, 20, 40 and 80 nM (Fab). Dissociation was monitored for 7200 seconds (Fab) or for 14400 seconds (IgG). A value for the dissociation rate was calculated by fitting a 1:1 binding model to the data. Calculated dissociation rates were 5.0×10^{-4} for 37D3-H9 Fab and 1.1×10^{-5} for 37D3-H9 IgG, a 45-fold difference. Figure 5 illustrates the difference in the dissociation rates of Fab (left panel) and IgG (right panel), indicating that 37D3-H9 IgG is demonstrating avidity.

Example 4: Humanization of anti-Tau Antibodies

[00390] Antibody 37D3-H9 was humanized by grafting the antibody CDRs and selected variable region framework residues onto human antibody consensus frameworks (Dennis, M.S. (2010). CDR repair: A novel approach to antibody humanization. In Current Trends in Monoclonal Antibody Development and Manufacturing, S.J. Shire, W. Gombotz, K. Bechtold-Peters and J. Andya, eds. (Springer, New York), pp. 9–28). Grafting onto consensus VH3, Vκ2 and Vκ1 frameworks was assessed. The heavy chain graft included murine residue at position 49 (Kabat numbering system). The Vκ2 graft included murine residues in framework positions 2 and 4. The Vκ1 graft included murine residues in framework positions 2, 4 and 43. Humanized variants were constructed by gene synthesis and subcloning into human IgG1 or IgG4 and Kappa chain mammalian expression vectors. Antibodies were expressed by co-transfection of the heavy and light chain plasmids into CHO cells and purified

with affinity resin MabSelect Sure. Humanized variants were screened for affinity to human Tau monomer using the Biacore human IgG capture kit, a Series S CM5 chip and a Biacore T200 instrument. Antibodies were diluted to 2 µg/ml and captured for 15 seconds at 10 µl/min. Association and dissociation of 100, 33, 11 and 3.7 nM human Tau monomer in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) was monitored for 180 seconds and 600 seconds respectively at a flow rate of 30 µl/min. A 1:1 binding model was applied to the results (Table 7).

Table 7: Affinity screening of humanized variants for monomeric human Tau

Antibody variant	Light chain framework	K_D (nM)
hu37D3-H9.v1	Kappa1	4.1
hu37D3-H9.v2	Kappa1	5.6
hu37D3-H9.v3	Kappa1	8.8
hu37D3-H9.v4	Kappa1	8.2
hu37D3-H9.v5	Kappa2	1.9
hu37D3-H9.v6	Kappa2	3.5
hu37D3-H9.v7	Kappa2	27.0
hu37D3-H9.v8	Kappa2	10.2
hu37D3-H9.v9	Kappa2	13.2
hu37D3-H9.v10	Kappa2	14.3
hu37D3-H9.v11	Kappa2	74.8
hu37D3-H9.v12	Kappa2	21.6
hu37D3-H9.v13	Kappa2	9.0
hu37D3-H9.v14	Kappa2	10.8
hu37D3-H9.v15	Kappa2	19.0
hu37D3-H9.v16	Kappa2	27.2
hu37D3-H9.v17	Kappa2	8.1
hu37D3-H9.v18	Kappa2	13.4
hu37D3-H9.v19	Kappa2	55.7
hu37D3-H9.v20	Kappa2	36.9
hu37D3-H9.v21	Kappa2	38.1
hu37D3-H9.v22	Kappa2	36.6
hu37D3-H9.v23	Kappa2	81.1
hu37D3-H9.v24	Kappa2	56.6

[00391] Antibody variants hu37D3-H9.v1, hu37D3-H9.v2, hu37D3-H9.v5 and hu37D3-H9.v6 were characterized further by surface plasmon resonance with additional antibody concentrations and longer association/dissociation times. These variants were analyzed with a broader range of human Tau monomer concentrations (1.2, 3.7, 11.1, 11.1,

33.3, 100 nM) and increased association (300 seconds) and dissociation (1200 seconds) periods. A 1:1 binding model was applied to the results (Table 8).

Table 8: Detailed analysis of binding kinetics of selected variants to human Tau by surface plasmon resonance

Antibody variant	Light chain framework	K_D (nM)
hu37D3-H9.v1	Kappa1	1.1 nM, 1.0 nM
hu37D3-H9.v2	Kappa1	1.2 nM
hu37D3-H9.v5	Kappa2	0.8 nM
hu37D3-H9.v6	Kappa2	1.4 nM

[00392] A YTE (M252Y/S254T/T256E) mutation was incorporated into certain IgG4 antibodies. Fc Receptor-neonate (FcRn) binding domain mutations such as M252Y, S254T and T256E (YTE) have been described to increase FcRn binding and thus increase the half-life of antibodies. *See* U.S. Published Patent Application No. 2003/0190311 and Dall'Acqua *et al.*, *J. Biol. Chem.* 281:23514-23524 (2006).

[00393] Antibody 125B11-H3 was humanized onto VH3 and Vκ1 consensus frameworks. The heavy chain graft included murine residues at position 78 (Kabat numbering system). The Vκ1 graft included murine residues in framework positions 43 and 87. The light chain of 113F5-F7 was also humanized onto the Vκ1 framework, with additional murine residues at framework positions 43 and 87. Humanized variant heavy chains (125B11) and light chains (125B11 and 113F5-F7) were co-transfected in multiple combinations and purified in 96-well format as described above. Humanized variants were then screened for affinity for human Tau monomer using the Biacore human IgG capture kit, a Series S CM5 chip and a Biacore T200 instrument. Antibodies were diluted to 2 μg/ml and captured for 15 seconds at 10 μl/min. Association and dissociation of 0, 100 and 500 nM human Tau monomer in HBSP was monitored for 180s and 300s respectively at a flow rate of 40 μl/min. A 1:1 binding model was applied to the results (Table 9).

Table 9: Screening of 125B11-H3 and 113F5-F7 humanization variants by surface plasmon resonance

Screening K_D (nM)		125B11 heavy chain humanization variant					
		HC1	HC2	HC3	HC4	HC5	HC6
125B11 light chain humanization variant	LC1	16, 19	18	18	15	85	-
	LC2	20	20	19	14	-*	NT
	LC3	21	23	20	15	-	-

	LC4	23	22	20	17	>100	>100
113F5-F7 light chain humanization variant	LC1	57	61	54	44	-	-
	LC2	67	68	55	47	-	-
	LC3	61	64	54	47	>100	-
	LC4	71	77	65	51	-	-

* Minimal binding to Tau monomer.
NT, not tested.

[00394] Variants hu125B11.v17 (HC3+LC1), hu125B11.v26 (HC4+LC2) and hu125B11.v28 (HC4+LC4) were selected for high-resolution kinetic analysis based on the affinity screen (Table 10). Antibody 94B2-C1 was humanized onto VH1 and Vκ2 frameworks. The heavy chain graft also included murine residues at position 28, 29, 67, 69, 71, and 73 (Kabat numbering system). The Vκ2 graft also included murine residues in framework positions 2, 36, and 46. Combinations of eight heavy chains and eight light chains were expressed, purified and screened by surface plasmon resonance (SPR) as described for 125B11 above. Results of the SPR screen are shown in Table 11. Variant hu94B2.v105 (heavy chain variant 94B2.HC1, light chain variant 94B2.LC13) was selected for detailed SPR characterization (Table 11).

Table 10: Kinetic data for selected humanized anti-Tau antibody variants

Antibody	Isotype	K_D (nM)	k_{on} (1/Ms)	k_{off} (1/s)
hu125B11.v17	hIgG1	10.5	0.8×10^5	0.8×10^{-3}
hu125B11.v26	hIgG1	9.5	0.7×10^5	0.7×10^{-3}
hu125B11.v28	hIgG1	10.2	0.7×10^5	0.7×10^{-3}
hu94B2.v105	hIgG1	3.7	0.8×10^5	0.3×10^{-3}

Table 11: Screening of 94B2 humanization variants by surface plasmon resonance

Screening K_D (nM)		94B2 Light Chain humanization variant:							
		LC9	LC10	LC11	LC12	LC13	LC14	LC15	LC16
94B2 Heavy Chain humanization variant:	HC1	3.8*	§	91.5	§	4.1¶	§	104.0	§
	HC2	5.7	§	89.6	§	7.4	NT	99.6	§
	HC3	2.0	§	69.3	§	3.8	§	64.1	§
	HC4	61.9	§	§	§	64.1	§	§	§
	HC5	2.7	§	62.6	§	4.0	§	72.6	§
	HC6	0.9	§	70.1	§	3.0	§	74.1	§
	HC7	52.9	§	§	§	57.8	§	§	§

	HC8	1.0	§	44.3	§	2.4	§	51.5	§

* Mean of n=3 repeats.
¶ hu94B2.v105.
§ Minimal binding to Tau monomer observed.
NT, not tested.

Example 5: Stability Analysis of Humanized anti-Tau Antibodies

Identification of chemical instability

[00395] Antibody samples were thermally stressed to mimic stability over the shelf life of the product. Samples were buffer exchanged into 20mM Acetate buffer, pH 5.5, or phosphate buffer, pH 7.4, and diluted to a concentration of 1 mg/ml. One ml of sample was stressed at 40°C for 2 weeks and a second was stored at -70°C as a control. Both samples were then digested using trypsin to create peptides that could be analyzed using liquid chromatography (LC) - mass spectrometry (MS) analysis. For each peptide in the sample retention time, from the LC as well as high resolution accurate mass and peptide ion fragmentation information (amino acid sequence information) were acquired in the MS. Extracted ion chromatograms (XIC) were taken for peptides of interest (native and modified peptide ions) from the data sets at a window of ±10 ppm and peaks were integrated to determine area. Relative percentages of modification were calculated for each sample by taking the (area of the modified peptide) divided by (area of the modified peptide plus the area of the native peptide) multiplied by 100. These relative percentages were then compared between the control (t=0) and the stressed (t=2weeks) samples. Percentages shown represent the control (t=0) value subtracted from the stressed (t=2weeks) value. Deamidation analysis of antibodies hu37D3-H9.v1 and hu37D3-H9.v5 led to the observation that the sequence $N^{28}G^{29}N^{30}$ (Kabat numbering) within the light chain CDR-1 was susceptible to deamidation. The increase in deamidated $N^{28}G^{29}N^{30}$ was found to be 16.5% for hu37D3-H9.v1 and 11% for hu37D3-H9.v5.

Impact of deamidation on antibody binding to antigen

[00396] To assess the impact of N^{28} deamidation on the affinity for human Tau, it was desirable to obtain two samples with widely separated N^{28} deamidation status. Hu37D3-H9.v5 hIgG4.S228P was incubated at 40°C for two weeks at a concentration of 1 mg/ml in Phosphate Buffered Saline, pH 7.4. Deamidation of the $N^{28}G^{29}$ motif was measured using LC-MS/MS. The t = 2 week stressed sample had a 43.1% increase deamidation relative to the t = 0 unstressed sample. The stressed and unstressed antibodies were analyzed for Tau binding by surface plasmon resonance (Biacore) using the GE Biacore human IgG capture kit and a Series

S CM5 chip. The hIgG were diluted to 2 µg/ml in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) and captured at a flow rate of 10 µl/min for 15 seconds (t0 sample) or 17 seconds (t2 sample). Kinetic data was collected for Human Tau monomer injected at concentrations of 0, 3.1, 6.3, 12.5, 25, 25, 50 & 100 nM in HBSP, using a flow rate of 30 µl/min, a 300 s association phase and an 1800 s dissociation phase. Between cycles the surface was regenerated using a 30 second injection of 3M Magnesium Chloride at 10 µl/min. A 1:1 binding model was fitted to the data using instrument defaults, including local fitting of the "RI" parameter. Results shown in Figure 6 and Table 12 demonstrate that although the stressed antibody immobilized at greater levels than the unstressed antibody in this experiment, the magnitude of the Tau binding signal (as represented by the magnitude of the parameter Rmax) was noticeably lower. After normalizing the Rmax value for the differences in capture level, the stressed (t=2weeks) sample appeared to show approximately half the total Tau binding capacity of the unstressed sample (indicated by a 56% reduction in the Normalized Rmax). The calculated affinity did not appear to change: in this analysis the difference in K_D between the t=0 and the t=2weeks samples was less than 2% (K_D = 0.7nM for t=0 and t=2weeks). The results are consistent with the t=2weeks sample containing a significantly reduced population of high affinity antibody.

Table 12: Relative binding of stressed and unstressed hu37D3-H9.v5 samples to monomeric Tau by surface plasmon resonance

hu37D3-H9.v5 hIgG4.S228P sample	**Ligand Level (RU)**	**Rmax (RU)**	**Normalized Rmax (= Rmax / Ligand Level)**	**Change in Normalized Rmax**
Control (t=0)	102.9	47.7	0.46	N/A
Stressed (t=2weeks)	146.8	30.2	0.21	- 56%

Impact of deamidation on antibody binding to antigen and calculation of "Normalized Rmax"

[00397] Given that asparagine deamidation is expected to result in aspartic acid and iso-aspartic acid products (Bischoff R. & Kolbe H.V.J. (1994). *J. Chromat.* 5, 662, p261-278) the impact of replacing N^{28} with D^{28} (variant hu37D3-H9.v5 N28D) on affinity for human Tau monomer was analyzed. Affinity was assessed at 25°C using a Biacore T200 instrument, the GE Biacore human IgG capture kit and a CM5 Series S chip. The hIgG were diluted to 2 µg/ml in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) and captured at a flow rate of 10 µl/min for 22 seconds. Kinetic data was collected for human Tau monomer injected at concentrations of 0, 6.3, 12.5, 25, 25, 50, 100, 200, and 400 nM in HBSP, using a flow rate of 30 µl/min, a 300 second association phase and a 600 second dissociation

phase. Between cycles the surface was regenerated using a 30 second injection of 3M Magnesium Chloride at 10 µl/min. A 1:1 binding model was fitted to the data and affinities for hu37D3-H9.v5 and hu37D3-H9.v5.3 (also referred to herein as hu37D3-H9.v5 N28D) calculated using kinetic analysis. Parameters used for the 1:1 fitting included the Instrument default of local fitting for the "RI" parameter. The results are shown in Figure 7 and Table 13.

[00398] Calculated K_D for the hu37D3-H9.v5 N28D variant was 160 x 10^{-9} M, compared to 1.5 x10^{-9} M (mean, n = 4 intra-experiment determinations) for hu37D3-H9.v5 analyzed under the same conditions. Therefore, conversion of N^{28} to D^{28} causes > 100-fold reduction in affinity. Given the comparatively low affinity of the hu37D3-H9.v5 N28D variant, and the comparatively rapid kinetics, we reasoned that the kinetics analysis of a mixture of the N^{28} and D^{28} variants would be dominated by the higher affinity population, and that presence of the lower affinity variants might be reflected by a reduction in the Normalized Rmax. To validate this reasoning, the Tau-binding profile of antibody variants hu37D3-H9.v5 and hu37D3-H9.v5 N28D were compared to that of the two antibodies mixed together in equal quantities. Compared to hu37D3-H9.v5 alone, a 1:1 mix of hu37D3-H9.v5 and hu37D3-H9.v5 N28D resulted in a 45% reduction in Normalized Rmax (Table 13). We concluded that changes in Normalized Rmax upon thermal stress may be indicative of a reduced population of high affinity antibody in the stressed sample. We reasoned that changes in Normalized Rmax could therefore be used to screen variants of hu37D3-H9 for improved stability.

Table 13: Changes in Normalized Rmax observed upon thermal stress of hu37D3-H9.v5 and upon mixing of hu37D3-H9.v5 with anticipated deamidation product hu37D3-H9.v5 N28D

Sample	**K_D (nM)**	**Rmax (RU)**	**Decrease in Normalized Rmax compared to Reference***	**Comments**
hu37D3-H9.v5 hIgG1	1.5 ± 0.2	76.1 ± 0.4	Reference	Mean +/- Standard Deviation of four intra-experiment analyses
hu37D3-H9.v5 N28D hIgG1	160	81.0	4%	
hu37D3-H9.v5 & hu37D3-H9.v5 N28D hIgG1	2.0	46.4	45%	Two antibodies mixed at a 1:1 ratio
hu37D3-H9.v5 hIgG4.S228P, t=0	1.5	68.8	3%	Control for Stressed sample
hu37D3-H9.v5 hIgG4.S228P, t=2weeks	1.5	33.4	54%	Stressed sample

*Normalized Rmax = Rmax (RU) / Ligand Level (RU). Normalized Rmax for reference antibody = 0.33 (mean of four intra-experiment determinations, standard deviation < 0.01).

Antibody optimization and selection

[00399] Ninety 37D3-H9 variants were assessed by Biacore to compare their functional stability with or without a two-week 40°C thermal stress period. The variants included most single mutations of the $N^{28}G^{29}N^{30}T^{31}$ motif, double mutants containing the G29A mutation, double mutations of Asn-28 and Tyr-32 that might functionally replace these to hydrogen-bonded residues, as well as all possible permutations of residues 2, 4, 33, and 93 as either the residues present in the original 37D3-H9 antibody or the corresponding germline residue variant. In addition, mutations were tested in the context of residue 1 being Asp or Glu, which does not impact affinity or stability of the Asn-28 residue.

[00400] Antibodies were expressed by transient transfection of Expi293 cells in 96-well format and automated purification performed on a Tecan freedom EVO 200 liquid handling system with a 500 µL MCA96 head. Briefly, IgGs in 1 mL culuture were captured using tip columns that were custom packed with 20 µL MabSelect SuRe resin (Glygen Corp & GE Healthcare). After washing with 1X PBS pH 7.4, IgGs were eluted into 160 µL of 50 mM phosphoric acid pH 3 and neutralized with 12 µL of 20X PBS pH 11. MabSelect SuRe tip columns were stripped in 0.1 M NaOH and regenerated with 1X PBS pH 7.4 for consecutive use of up to 15 times. Purified antibodies in 96-well format were normalized to 0.1 mg/ml using a Hamilton Star liquid handling robot. The "pre-stress" samples were kept at approximately 4°C and the "post-stress" samples were incubated at 40°C for two weeks in a PCR machine. Functional stability of the variants was compared by running surface plasmon resonance kinetics experiments with the "pre-stress" and "post-stress" antibody preps. The antibodies were assessed using a human antibody capture CM5 Series S chip generated using the GE Biacore human IgG capture kit and a Biacore T200 instrument. Antibodies diluted to 2 µg/ml were immobilized using a 15 second injection time and 10 µl/min flow rate. Binding to Tau monomer at 0 nM, 26.5 nM and 265 nM, at 25°C, using a flow rate of 40 µl/min, was monitored for a 180 second association phase followed by a 300 second dissociation phase. Samples were run in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (HBSP) using a multi-cycle kinetics format. Data was analyzed using BIAevaluation software, fitting a 1:1 binding model. The resulting affinity (K_D) values are shown in Figure 8A-D. A Stability Index was also calculated, using the rationale that affinity-compromised antibodies (due for example to deamidation of key residues) are expected to contribute equally to the IgG capture level ("Ligand Level") but to contribute less to the measured Tau binding, and that this would

be reflected in the experimentally derived value for Rmax. To account for variations in the amount of each antibody captured, Rmax was normalized for the antibody capture level (as measured by "Ligand Level", Response Units immobilized during antibody capture). Thus Normalized Rmax is calculated as the experimental Rmax (units=RU) divided by the "Ligand Level" (Evaluation output representing the RU captured during the hIgG capture step, units=RU), and Stability Index is calculated here as Normalized Rmax (post-stress) divided by Normalized Rmax (pre-stress).

[00401] Selected antibodies were expressed by transient transfection of CHO cells and purified. The antibodies were then stressed for two weeks at 1 mg/ml and deamidation analyzed by LC-MS/MS, using RCM tryptic peptide mapping with DTT reduction, IAA capping and pH 8.2 digestion. Results (Table 14) demonstrated that variant hu37D3-H9.v28.A4 had reduced susceptibility to deamidation on the $N^{28}G^{29}N^{30}$ motif. The reduced deamidation of the hu37D3-H9.v28.A4 was unexpected, as the residue is not located in the immediate vicinity of the Asn-28 residue (Figure 9) and it is not clear how the F33L mutation might stabilize Asn-28.

Table 14: Stability of the hu37D3-H9.v28.A4 variants in stress tests for deamidation

Antibody		**Thermal Stress Conditions**	**Increase in deamidation of light chain $N^{28}G^{29}N^{30}$**
hu37D3-H9.v1	hIgG1	40°C in Acetate Buffer, pH 5.5	16.5%
hu37D3-H9.v5	hIgG1	40°C in Acetate Buffer, pH 5.5	11%
hu37D3-H9.v28.A4	hIgG1	40°C in Acetate Buffer, pH 5.5	N^{28}: 2.8% N^{30}: 0.2%
		37°C in PBS pH 7.4	N^{28}: 5.3% N^{30}: ND
	hIgG4.S228P.YTE	40°C in Acetate Buffer, pH 5.5	N^{28}: 0% N^{30}: 0%
		37°C in PBS pH 7.4	N^{28}: 10.4% N^{30}: 2.0%

Example 6: Humanized Anti-Tau Antibody Selection and Characterization

Antibody selection and characterization: binding to human Tau protein

[00402] Affinity of selected antibodies was assessed at 25°C using a Biacore T200 instrument, the GE Biacore human IgG capture kit and a CM5 Series S chip. The hIgG

were diluted to 0.25 µg/ml in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) and captured at a flow rate of 10 µl/min for 150 seconds. Kinetic data was collected for Human Tau monomer injected at concentrations of 0, 0.4, 1.2, 3.7, 11, 11, 33 and 100 nM in HBSP, using a flow rate of 30 µl/min, a 300 second association phase and a 600 second dissociation phase. Between cycles the surface was regenerated using two sequential 30 second injections of 3M MgCl at 10 µl/min. Data was fit to a 1:1 binding model (Table 15).

Table 15: Kinetic data for selected humanized anti-Tau antibody variants

Antibody	Isotype	K_D (nM)	k_{on} (1/Ms)	k_{off} (1/s)
hu37D3-H9.v28.A4	hIgG1	1.5	6.9×10^{5}	1.1×10^{-3}
hu37D3-H9.v5	hIgG1	1.0	7.5×10^{5}	0.8×10^{-3}
hu37D3-H9.v5	hIgG4.S228P	1.3	7.1×10^{5}	0.9×10^{-3}
hu37D3-H9.v1	hIgG4.S228P	2.0	6.7×10^{5}	1.3×10^{-3}

Antibody characterization: Binding to human Tau protein in hIgG4.S228P.YTE format

[00403] Affinity was assessed at 25°C using a Biacore T200 instrument, the GE Biacore human FAb capture kit and a CM5 Series S chip. The hIgG were diluted to 0.5 µg/ml in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) and captured at a flow rate of 10 µl/min for 180 seconds. Kinetic data was collected for Human Tau monomer injected at concentrations of 0, 0.4, 1.2, 3.7, 11, 11, 33 and 100 nM in HBSP, using a flow rate of 30 µl/min, a 300 second association phase and a 600 second dissociation phase. Between cycles the surface was regenerated using two sequential 60 second injections of 10 mM Glycine pH 2.1. Data was fit to a 1:1 binding model. Kinetic data are shown in Table 16.

Table 16: Binding kinetics of hu37D3-H9.v28.A4 hIgG4.S228P.YTE to monomeric human Tau by surface plasmon resonance

Antibody	Antibody preparation	K_D (nM)	k_{on} (1/Ms)	k_{off} (1/s)
hu37D3-H9.v28.A4 hIgG4.S228P.YTE	Prep 1	1.4	6×10^{5}	9×10^{-4}
	Prep 2	1.4	6×10^{5}	9×10^{-4}

Antibody characterization: Binding to cynomolgus monkey Tau protein

[00404] Affinity was assessed at 25°C using a Biacore T200 instrument, the GE Biacore human IgG capture kit and a CM5 Series S chip. The hIgG were diluted to 2 µg/ml in 10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20 (running buffer, HBSP) and captured at a flow rate of 10 µl/min for 15 seconds. Kinetic data was collected for Human Tau monomer injected at a minimum of five different non-zero concentrations between 1.2 and 100 nM, with one replicate concentration. Kinetics were assessed using a flow rate of 30 µl/min, a 300 second association phase and a 600 second dissociation phase. Between cycles a 30 second regeneration injection of 3M Magnesium Chloride was performed at a flow rate of 10 µl/min. The results were fit to a 1:1 binding model. Kinetic data are shown in Table 17.

Table 17: Affinity of humanized anti-Tau antibodies for monomeric cynomolgus monkey Tau

Antibody	Ligand Level (RU)	Rmax (RU)	K_D (nM)	k_{on} (1/Ms)	k_{off} (1/s)
hu37D3.v28.A4	113.9	62.6	0.7	17×10^5	1×10^{-3}
hu37D3.v28.F1	126.9	61.2	1.3	12×10^5	2×10^{-3}
hu37D3.v28.A12	162.6	85.2	1.0	17×10^5	2×10^{-3}
hu37D3.v29.2	168.6	86.0	1.4	17×10^5	2×10^{-3}
hu37D3-H9.v5	125.1	55.5	0.6	15×10^5	1×10^{-3}
hu37D3-H9.v1	130.2	51.7	0.8	20×10^5	1×10^{-3}

[00405] Humanized antibodies hu37D3.v28.A4 and hu37D3.v28.F1 also bind to phosphorylated Tau (pTau).

Example 7: Pharmacokinetics of Anti-Tau Antibody

[00406] To evaluate the pharmacokinetics of the anti-Tau 37D3-H9 mIgG2a antibody *in vivo*, C57BL/6 mice were administered a single intravenous (IV) or intraperitoneal (IP) bolus injection at a dose of 10 mg/kg to conscious mice. At various time points up to 28 days post-dose, plasma samples were collected to determined anti-Tau antibody concentrations.

[00407] The concentrations of the dosed antibody in mouse plasma were measured with a generic ELISA using a mouse anti-muIgG2a antibody coat, followed by adding plasma samples starting at a dilution of 1:100, and finished by adding a mouse anti-muIgG2a-biotin conjugate, and then streptavidin conjugated to horseradish peroxidase for

detection. The assay had a standard curve range of 1.56-200 ng/mL and a limit of detection of 0.16 µg/mL. Results below this limit of detection were reported as less than reportable (LTR).

[00408] Figure 10 shows the results of the pharmacokinetic analysis for anti-Tau 37D3-H9 mIgG2a. Anti-Tau 37D3-H9 mIgG2a had similar exposure and clearance in wild-type C57BL/6 mice as isotype control antibodies, with a clearance of 6.31 mL/day/kg.

[00409] To evaluate the pharmacokinetics of anti-Tau 94B2-C1 mIgG2a and anti-tau 125B11-H3 mIgG2a *in vivo*, a single IP bolus injection of antibody was administered at a dose of 10 mg/kg to conscious C57BL/6 mice. At various time points up to 28 days post-dose, plasma samples were collected to determined anti-Tau antibody concentrations.

[00410] The concentrations of the dosed antibody in mouse plasma and was measured with a generic ELISA using a mouse anti-muIgG2a antibody coat, followed by adding plasma samples starting at a dilution of 1:100, and finished by adding a mouse anti-muIgG2a-biotin conjugate, and then streptavidin conjugated to horseradish peroxidase for detection. The assay had a standard curve range of 0.78-100 ng/mL and a limit of detection of 0.078 µg/mL. The concentrations were also measured with a specific ELISA using recombinant Tau as the coat, followed by adding plasma samples starting at a dilution of 1:10, and finished by adding goat anti-mIgG2a conjugated to horseradish peroxidase for detection. The assay had a standard curve range of 0.078-10 ng/mL and a limit of detection of 0.0008 µg/mL. Results below this limit of detection were reported as less than reportable (LTR).

[00411] The results of those experiments are shown in Figures 16 and 17. Anti-Tau 94B2 mIgG2a had similar exposure and clearance in wild-type C57BL/6 mice as an isotype control antibody when concentrations were analyzed using a generic assay, but lower exposure and faster clearance when concentrations were analyzed using a specific assay. *See* Figure 16. The clearance determined by the generic assay was 4.06 mL/day/kg and that determined by the specific assay was 7.53 mL/day/kg. These results suggest that the antibody may undergo *in vivo* changes over time that compromise its ability to recognize its target. Anti-Tau 125B11-H3 mIgG2a had similar exposure and clearance in wild-type C57BL/6 mice as an isotype control antibody, regardless of which assay generated the concentrations. *See* Figure 17. The clearance determined by the generic assay is 4.96 mL/day/kg and that determined by the specific assay is 4.90 mL/day/kg.

[00412] Table 18 shows the pharmacokinetic parameters for anti-Tau antibodies 37D3-H9, 94B2-C1, and 125B11-H3 in mice.

Table 18: Pharmacokinetic parameters for anti-Tau antibodies

	Administratio	**Assay**	**Cmax**	**AUCinf**	**CL or CL/F**

	n Route		(µg/mL)	(µg/mL*day)	(mL/day/kg)
37D3-H9	IV	Generic	185	1590	6.31
	IP	Generic	107	1680	6.76
94B2-C1	IP	Generic	151	2460	4.06
	IP	Specific	141	1330	4.91
125B11-H3	IP	Generic	127	2020	4.96
	IP	Specific	151	2040	4.90

[00413] To evaluate the pharmacokinetics of hu37D3.v28.A4 hIgG4.S228P and hu37D3.v28.A4 hIgG4-S228P.YTE antibodies *in vivo*, cynomolgus monkeys (*Macaca fascicularis*) were administered a single IV bolus injection at a dose of 1 mg/kg to conscious moneys. At various time points up to 49 days post-dose, plasma samples were collected to determined anti-Tau antibody concentrations.

[00414] The concentrations of the dosed antibody in monkey plasma and was measured with a generic ELISA using a sheep anti-human IgG antibody coat, followed by adding plasma samples starting at a dilution of 1:100, and finished by adding goat anti-human IgG conjugated to horseradish peroxidase for detection. The assay had a standard curve range of 0.156-20 ng/mL and a limit of detection of 0.02 µg/mL. Results below this limit of detection were reported as less than reportable (LTR).

[00415] Figure 11 shows the results of the pharmacokinetic analysis for hu37D3.v28.A4 hIgG4.S228P and hu37D3.v28.A4 hIgG4-S228P.YTE. In Figure 11, each set of datapoints represents one animal and the lines represent the average for all animals in the antibody and assay group. Table 19 shows the pharmacokinetic parameters for hu37D3.v28.A4 hIgG4.S228P and hu37D3.v28.A4 hIgG4-S228P.YTE in cynomolgus monkeys.

Table 19: Pharmacokinetic parameters for hu37D3.v28.A4 hIgG4.S228P and hu37D3.v28.A4 hIgG4-S228P.YTE in cynomolgus monkeys

Antibody	Assay	Cmax (µg/mL)	AUCinf (day*µg/mL)	CL (mL/day/kg)	Vss (mL/kg)
anti-gD hIgG4	Generic	34.6	386	2.66	55.5
hu37D3.v28.A4 hIgG4.S228P	Generic	35.7 ± 2.59	559 ± 209	1.97 ± 0.743	71.9 ± 16.0
	Specific	35.4 ± 1.37	419 ± 89.9	2.47 ± 0.581	60.8 ± 3.49
hu37D3.v28.A4 hIgG4.S228P.YTE	Generic	34.5 ± 5.23	578 ± 43.5	1.74 ± 0.125	60.5 ± 1.87
	Specific	33.5 ± 2.72	520 ± 39.0	1.93 ± 0.139	56.5 ± 4.90

Example 8: Further Epitope Characterization of Anti-Tau Antibody

[00416] Following a comparison of 37D3-H9 binding to biotinylated Tau monomer and biotinylated peptide (MAPT_10-24), binding of 37D3-H9 to additional biotinylated peptides was also assessed. Nunc maxisorp 96-well microplates were coated at 4°C for > 12 hours with Neutravidin diluted to 2 µg/ml in 50 mM Sodium Carbonate Buffer, pH 9.6. All subsequent incubations were performed at room temperature. After coating, plates were blocked with Superblock™ (PBS) Blocking Buffer (Thermo Fisher Scientific) for two hours then washed thoroughly with PBS, 0.05% Polysorbate 20. Wells were then exposed to biotinylated Tau peptides (Table 20) or Avi-tag biotinylated Tau monomer at 1 µg/ml for one hour and washed as previously. Peptides were synthesized using standard solid-phase Fmoc chemistry (*see, e.g.*, Fmoc solid phase peptide synthesis: A practical approach; Chan, W. C., White, P. D., Eds.; Oxford University Press: New York, 2000). Antibodies 37D3-H9 mIgG2a and hu37D3-H9.v5 hIgG1, serially diluted from 500 nM to 50 pM in 90% Superblock™ (PBS) Blocking Buffer, were allowed to bind biotinylated-Tau coated wells for 90 minutes. Wells were washed as previously and bound antibody detected with peroxidase-conjugated secondary antibody (Invitrogen / Life Technologies) diluted 1/1000 in Superblock™ Blocking Buffer (Rabbit anti-Mouse IgG or Goat Anti-Human IgG (H+L) respectively). After twenty minutes wells were washed as previously and signal developed with TMB Microwell 2-Component Substrate (KPL). Reactions were stopped by addition of 1M Phosphoric Acid and absorbance at 450 nm was measured with a SpectraMax M2 platereader.

Table 20: Peptide Sequences

MAPT sequence	**Peptide sequence**	**SEQ ID NO:**
MAPT(10-24)	VMEDHAGTYGLGDRK	592
MAPT(2-24)	AEPRQEFEVMEDHAGTYGLGDRK	593
MAPT(2-34)	AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQD	594
MAPT(10-44)	VMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLK	595

[00417] The results of that experiment are shown in Figure 12. Figure 12A shows binding of each of the indicated antibodies for the indicated peptides. Antibodies 37D3-H9 and 94B2-C1 both showed strong binding to fragment 10-24 in that experiment, and antibody 94B2-C1 also showed strong binding to fragment 1-15. Antibodies 19F8-C11 and 123E9-A1 showed strong binding to fragment 19-33, while antibody 89F4-A1 showed strong binding to fragments 28-42 and 37-51. *See* Figure 12A. Antibodies 37D3-H9 mIgG2a and

hu37D3-H9.v5 hIgG1 both showed strong binding to Tau fragments 2-24 and 2-34 and weaker binding to fragment 10-24. *See* Figures 12B and 12C. These results suggest that antibodies 37D3-H9 mIgG2a and hu37D3-H9.v5 hIgG1 bind an epitope of Tau within amino acids 2-24 of the mature protein.

[00418] In an alanine scanning substitution experiment, mutations Y18A and L20A were found to abrogate binding by murine antibody 37D3-H9 to a Tau fragment (fragment 2-21), suggesting that the antibody contacts these Tau residues. Using a series of 15mer offset peptides, it was found that murine antibody 37D3-H9 showed similar binding to fragment 9-23 as to fragment 10-24, and also showed moderate binding to fragments 7-21, 8-22, and 11-25.

Example 9: Cell-based characterization of 37D3-H9 humanized antibodies

Methods

Primary hippocampal and microglial culture and hippocampal-microglial co-culture

[00419] Dissociated primary hippocampal neurons were prepared from embryonic day 16-17 wild-type C57BL/6N mice. Cells were plated onto PDL/laminin-coated 8-well chamber slides (Biocoat, 354688 Corning) at 25,000 cells/well. Cells were plated and maintained in NbActiv4 (BrainBits) and half of the media was replaced twice a week. Recombinant tau and antibodies were applied to the culture at 18 cell divisions.

[00420] For microglial culture, cortices and hippocampi from postnatal day 1-2 C57BL/6N mice were dissociated and grown in 10% FBS in DMEM in 225 mm^2 culture flasks for 10-12 days. The culture flasks were gently shaken to dissociate microglia and the cells in 10% FBS in DMEM were replated onto either PDL/laminin-coated 8-well chamber slides at 30,000 cells/well for imaging or uncoated 48-well plates (3548, Corning) at 100,000 cells/well for cytokine assay. 4-5 hours after plating, cells were switched to serum-free low-glucose DMEM and maintained overnight before treatment with recombinant tau and antibodies.

[00421] Hippocampal-microglial co-cultures were prepared by replating microglia dissociated from 225 mm^2 culture flasks onto 18 DIV primary hippocampal neurons in 8-well slide chambers (12,500 microglia and 25,000 neurons per one well). Co-cultures were treated with recombinant tau and antibodies 4 hours after microglia plating.

In vitro treatment of recombinant tau and antibodies

[00422] For 18 DIV hippocampal cultures or hippocampal-microglial co-cultures, recombinant human oligomeric tau and antibodies (500 nM each at 1:1 ratio) or controls were pre-incubated in neuron culture medium (conditioned medium from 18DIV

hippocampal culture:fresh NbActiv4 at 1:1) for 1 hour at 37°C before they were added to the cells. Cells were incubated with the tau-antibody mix or control in the media for 72 hours (hippocampal culture) or 48 hours (hippocampal-microglial co-culture). Cells were washed with PBS three times before fixation.

[00423] For microglia culture, recombinant human oligomeric tau and antibodies or controls were pre-incubated at 125 nM each (immunocytochemistry/imaging) or 250 nM each (cytokine assay) in low-glucose DMEM in the absence of serum for 1 hour at 37°C prior to the addition to the cells. For immunocytochemistry/imaging, cells were incubated with the tau-antibody mix or controls for 10 minutes and washed three times with PBS before fixation. For cytokine assay, cells were incubated with the tau-antibody mix or control for 24 hours and medium of each well was collected for cytokine assay.

Immunocytochemistry, imaging, and quanitificaton

[00424] Cells were fixed with 4% paraformaldehyde in PBS for 15 min and permeabilized with 0.1% Triton X-100 in PBS for 10 minutes. 10% donkey serum was used for blocking and cells were incubated with primary antibodies in PBS overnight at 4°C, followed by incubation with Alexa-fluorophore-labeled secondary antibodies against appropriate species developed in donkey (Invitrogen). Primary antibodies used were anti-tau (DAKO), rabbit anti-human tau developed against the human tau N-terminal region spanning amino acids 11-24, anti-MAP2 (ab5392, Abcam), and anti-Iba-1 (ab5076, Abcam). The slides were mounted with Prolong Gold DAPI (P36935, Invitrogen) and no.1 coverslips.

[00425] Confocal fluorescent imaging was performed with a LSM780 (Carl Zeiss, Inc.) using Zen 2010 software (Carl Zeiss, Inc.). For imaging of hippocampal cultures and hippocampal-microglial co-cultures, 5 z-stack images at 0.98 μm intervals were collected using Plan Apochromat 20x/0.8 M27 objective lens. For the MAP2 fragmentation assay, a maximum intensity z projection was created for the image stack and analyzed using Metamorph (Molecular Devices, Sunnyvale, CA). A median filter and nearest neighbor deconvolution were used for noise reduction. Neurite and cell body lengths were analyzed using the neurite outgrowth module followed by morphological processing. Fragments less than 15 pixels (6.225 μm) were normalized to total signal length to obtain a measure of MAP2 fragmentation.

[00426] Microglia were imaged with α-Plan Apochromat 100x/1.46 M27 objective. Quantification of recombinant tau uptake in the cells was performed with Image J (1.43u, 64-bit, National Institute of Health). ROIs of cell area were drawn manually using Iba-1 signal as a reference. Area and integrated intensity of tau immunoreactivity of ROI were

measured to obtain tau immunoreactivity normalized to area. All analyses were performed blinded to experimental conditions.

Results

[00427] The results of the experiment are shown in Figure 13. As shown in Figure 13A, antibodies with full effector function were not protective against Tau toxicity in the neuron-microglia co-cultures. Figure 13B shows images of neuron-microglia co-cultures contacted with oligomeric Tau and antibodies (bottom panels). Antibody 37D3-H9 hIgG4 and hu37D3-H9 hIgG1 (N297G), which lack effector function, were protective against Tau toxicity, while 37D3-H9 hIgG1 was not.

Example 10: Dose-dependent reduction of Tau pathology in Tau Tg mice administered 37D3-H9 IgG2a or 37D3-H9 IgG2a DANG

[00428] Transgenic mice expressing human Tau P301L under the Thy1 promoter (Tau P301L-Tg) were maintained on a C57BL/6N (Charles River) background. Tau P301L-Tg and wild type littermate mice were assigned to treatment groups and dosed once weekly intraperitoneally (i.p.) with either IgG2a-control (anti-gp120) at 30 mg/kg, anti-tau 37D3-H9 WT IgG2a at 3, 10 or 30 mg/kg, anti-tau 37D3-H9 DANG IgG2a at 3, 10 or 30 mg/kg. DANG refers to D265A/N297G mutations in IgG2a, which abrogate effector function. All antibody-dosing solutions were prepared in 10 mM histidine pH 5.8, 6% sucrose, 0.02% Tween 20 at a concentration of 10 mg/ml. Treatment started at 13 weeks of age. The mouse groups in the *in vivo* study were males and staggered into 3 cohorts. In addition, 3 TauP301L-Tg mice were harvested at age 3 months without undergoing any treatment in order to determine the baseline level of pathology at the time of treatment initiation.

[00429] To harvest tissue, mice were anesthetized with 2.5% tribromoethanol (0.5ml per 25g body weight) and transcardially perfused with PBS. Brains were harvested and bisected. Right hemispheres were fixed in 4% paraformaldehyde overnight at 4°C then transferred to phosphate buffered saline prior to processing for immunohistochemistry. Left hemispheres were sub-dissected on ice then frozen at -80°C for biochemical analysis. Tail clips were taken from all mice to confirm genotypes.

[00430] Hemibrains were multiply embedded into a gelatin matrix using MultiBrain® blocks (NeuroScience Associates, Knoxville, TN) and sectioned coronally at 25 µm thickness. Within each block, the brain position was randomized relative to genotype and treatment. Free-floating sections of individual mouse hemibrains or of MultiBrain® blocks were stained as previously described (Le Pichon et al., 2013, PLoS One, 8(4): e62342), but

with washes in PBS instead of Tris buffered saline and primary antibody incubations at 4°C instead of room temperature. Primary antibody was rabbit anti-pTau212/214 (generated in-house; 0.01 µg/ml). To avoid high background staining, in the case of mouse primary antibodies that were subtype specific, we used the corresponding subtype-specific secondary antibody (eg. Biotinylated anti-mouse IgG3, Bethyl A90-111B).

[00431] Immunohistochemically stained slides were imaged using the Leica SCN400 (Leica Microsystems; Buffalo Grove, IL) whole slide scanning system at 200x magnification with a resolution of 0.5 µm/pixel. Regions of interest (ROIs) were manually drawn on 4 matched hippocampal levels per animal, and the amount of staining in these ROIs was quantified in an automated fashion using the two endpoints described below. All image analysis was performed blind to genotype and treatment groups. For positive pixel area analysis for quantitation of IHC stains, digital images of antibody-labeled brain sections were analyzed as previously described (Le Pichon et al., 2013). The percent area stained was calculated by normalizing the total positive pixels to the total pixel area of the ROI. The integrated intensity was calculated using the Beer-Lambert law, *absorbance = −log(transmitted light intensity / incident light intensity)*, for the positive pixel areas only.

[00432] The results of that experiment are shown in Figure 14. Administration of anti-tau 37D3-H9 WT IgG2a or anti-tau 37D3-H9 DANG IgG2a resulted in a dose-dependent reduction of pTau212/214 in the hippocampus.

Example 11: Humanized 37D3-H9 kappa 1 variants

[00433] Humanized antibody variants based on hu37D3-H9.v1, which has a kappa 1 light chain, were made and tested for N^{28} stability. An alignment of the light chain variable region of the three variants tested with hu37D3-H9.v1 is shown in Figure 18. The three variants differ from each other in the light chain variable region: hu37D3.v39 contains the mutation F33L, hu37D3.v40 contains the mutation G29T and hu37D3.v41 contains the mutation N30Q.

[00434] Antibody samples were thermally stressed, as follows. Samples were buffer exchanged into 20mM histidine acetate, 240mM sucrose, pH 5.5 and diluted to a concentration of 1 mg/ml. One ml of sample was stressed at 40°C for 2 weeks and a second was stored at -70°C as a control. Both samples were then digested using trypsin to create peptides that could be analyzed using liquid chromatography (LC) - mass spectrometry (MS) analysis. For each peptide in the sample retention time, from the LC as well as high resolution

accurate mass and peptide ion fragmentation information (amino acid sequence information) were acquired in the MS. Extracted ion chromatograms (XIC) were taken for peptides of interest (native and modified peptide ions) from the data sets at a window of ±10 ppm and peaks were integrated to determine area. Relative percentages of modification were calculated for each sample by taking the (area of the modified peptide) divided by (area of the modified peptide plus the area of the native peptide) multiplied by 100. These relative percentages were then compared between the control (t=0) and the stressed (t=2weeks) samples. Percentages shown represent the control (t=0) value subtracted from the stressed (t=2weeks) value. The results are shown in Table 21. The results demonstrate that the F33L mutation is effective for reducing deamidation in a kappa 1 humanized light chains.

Table 21 – Stability of the hu37D3-H9.v1 variants in stress tests for deamidation.

Antibody		**Increase in deamidation of light chain $N^{28}G^{29}N^{30}$**
hu37D3.v39	hIgG4.S228P.YTE	N^{28}: 2.7 % N^{30}: No significant increase detected
hu37D3.v40	hIgG4.S228P.YTE	N^{28}: 12.1 % N^{30}: 3.9 %
hu37D3.v41	hIgG4.S228P.YTE	N^{28}: 6.0 % N^{30}: Residue replaced with glutamine

[00435] Affinity of the humanized antibody variants was measured at 25°C using a Biacore T200 instrument, the GE Biacore human FAb capture kit, and a CM5 Series S chip. Antibodies were diluted to 1 µg/ml in HBSP (10mM HEPES pH7.4, 150mM NaCl, 0.05% Tween 20) and captured at a flow rate of 10 µl/min for 180 seconds. Kinetic data were collected for human Tau monomer injected at 1.2, 3.7, 11, 33 and 100 nM in HBSP using the Single Cycle Kinetics methodology and a flow rate of 30 µl/min. Each concentration of Tau monomer was injected for a period of 3 minutes and dissociation was monitored for ten minutes. Between cycles, the surface was regenerated with two sequential one-minute injections of 10 mM glycine pH2.1. Data was fit to a 1:1 binding model using BIAEvaluation software. Each antibody was analyzed twice within the experiment; data in Table 22 are shown as mean ± range.

Table 22: Affinities of hu37D3-H9.v1 variants for monomeric Tau

	K_D (nM)	**k_{on} (1/Ms)**	**K_{off} (1/s)**
hu37D3.v1 hIgG1	2.3 ± 0.3	$6 \pm 0.5 \times 10^{5}$	$1 \pm 0.1 \times 10^{-3}$

hu37D3.v1 hIgG4	2.3 ± 0.3	6 ± 0.2 x10^5	1 ± 0.1 x10^{-3}
hu37D3.v39 hIgG4.YTE	1.9 ± 0.2	6 ± 0.6 x10^5	1 ± 0.02 x10^{-3}
hu37D3.v40 hIgG4.YTE	4.4 ± 0.5	8 ± 0.9 x10^5	3 ± 0.02 x10^{-3}
hu37D3.v41 hIgG4.YTE	5.4 ± 0.3	9 ± 1.2 x10^5	5 ± 0.3 x10^{-3}

Example 12: Pharmacokinetics and pharmacodynamics of hu37D3.v28.A4 hIgG4-S228P and hu37D3.v28.A4 hIgG4-S228P.YTE in cynomolgus monkeys

[00436] To evaluate the pharmacokinetics and pharmacodynamics of hu37D3.v28.A4 hIgG4.S228P and hu37D3.v28.A4 hIgG4-S228P.YTE antibodies *in vivo*, five conscious cynomolgus monkeys (*Macaca fascicularis*) per group were administered a single IV bolus injection at a dose of 50 mg/kg in the first phase. Anti-gD hIgG4 was used as a control, also at a dose of 50 mg/kg. At various time points up to 35 days post-dose, plasma and CSF samples were collected to determine anti-Tau antibody concentrations. After the final sample collection, the animals were allowed to recover for 63-64 days before initiation of the second phase. In the second phase, the 15 animals from the first phase, plus 3 additional animals, were divided into two groups; the first group (n=9) was administered antibody hu37D3.v28.A4 hIgG4.S228P and the second group (n=9) was administered hu37D3.v28.A4 hIgG4-S228P.YTE antibody, both at 50 mg/kg. Brains of 4 or 5 animals per group were harvested at 2 days and 10 days post-dose.

[00437] Human IgG4 antibodies in cynomolgus monkey plasma, CSF, and brain homogenate (described below) were measured with an ELISA using a sheep anti-human IgG monkey adsorbed antibody coat, followed by adding plasma samples starting at a dilution of 1:100, CSF samples starting at a dilution of 1:20, or brain homogenate samples starting at a dilution of 1:10, and finished by adding a goat anti-human IgG antibody conjugated to horseradish peroxidase monkey adsorbed for detection. Color was developed using 3,3',5,5'-tetramethylbenzidine and neutralized using 1M phosphoric acid. Samples were read at 450/620 nm. The assay has a standard curve range of 0.156-20 ng/mL and a limit of detection of 0.02 ug/mL for plasma, 0.003 µg/mL for CSF, and 0.002 µg/mL for brain homogenate. Results below this concentration were reported as less than reportable (LTR).

[00438] The results of the pharmacokinetic analysis are shown in Figure 19A (plasma) and 19B (CSF), and in Tables 23 and 24. Animals that were suspected of being anti-therapeutic antibody positive (ATA+) were excluded from the analysis. These data show that introducing the YTE mutations in the Fc region of hu37D3.v28.A4 hIgG4.S228P slowed the peripheral and CSF clearance rates of the antibody by about two fold.

Table 23: Mean (± SD) plasma clearance and C_{max} estimates following single IV bolus dose

Antibody	Plasma clearance (mL/day/kg)	C_{max} (µg/mL)
anti-gD hIgG4	1.67 ± 0.415	1950 ± 174
hu37D3.v28.A4 hIgG4.S228P	2.09 ± 0.229	1970 ± 144
hu37D3.v28.A4 hIgG4-S228P.YTE	1.12 ± 0.233	1850 ± 156

Table 24: Mean (± SD) CSF C_{max} estimates following single IV bolus dose

Antibody	C_{max} (µg/mL)
anti-gD hIgG4	1.39 ± 0.751
hu37D3.v28.A4 hIgG4.S228P	0.910 ± 0.552
hu37D3.v28.A4 hIgG4-S228P.YTE	2.51 ± 1.93

[00439] The brain concentration of the antibodies at 2 and 10 days post-injection was determined as follows. Brain tissue was weighed and then homogenized in 1% NP-40 in phosphate-buffered saline containing cOmplete™, Mini, EDTA-free protease inhibitor cocktail tablets. The homogenized brain samples were then rotated at 4°C for 1 hour before spinning at 14,000 rpm for 20 minutes. The supernatant was isolated for brain antibody measurement by ELISA, as described above. The results of that experiment are shown in Figures 21A-D. The concentration of antibody hu37D3.v28.A4 hIgG4-S228P.YTE in the brain, and the ratio of brain:plasma concentration for antibody hu37D3.v28.A4 hIgG4-S228P.YTE trended higher than antibody hu37D3.v28.A4 hIgG4.S228P.

[00440] The pharmacodynamics response in plasma was also determined. The concentration of total Tau in K_2EDTA plasma was determined using an electrochemiluminescence (ECL) immunoassay (Roche Professional Diagnostics (RPD), Penzberg, Germany). The Elecsys® immunoassay is validated for the quantification of total Tau in human CSF, and because of the similarity between human and cynomolgus monkey Tau, was considered acceptable for the measurement of cynomolgus monkey Tau in CSF and plasma. The assay captures and detects amino acids 159-224 of human and cynomolgus monkey Tau, a region present in all known isoforms, independent of phosphorylation state. The lower detection limit (LDL) of the assay is 1.01 pg/mL. The assay is tolerant to 15.0 mg/mL of hu37D3.v28.A4 hIgG4-S228P.YTE.

[00441] The results of the pharmacodynamic analysis are shown in Figure 20. There were 3 animals per group after excluding animals suspected of being ATA+, and another animal that lacked baseline values. Surprisingly, within the first day of dosing, plasma Tau

levels rise to a greater degree in the animals treated with the YTE variant versus the non-YTE variant. Further, that result is not predicted from the pharmacokinetics response (Figure 20), as the PK is similar between the variants at the early time points. A more robust response is sustained in the animals treated with the YTE variant for the entire duration of sampling.

Example 13: Pharmacokinetics and pharmacodynamics of hu37D3.v28.A4 hIgG4-S228P.YTE in cynomolgus monkey brain

[00442] To assess antibody pharmacokinetics in brain, twelve conscious cynomolgus monkeys (*Macaca fascicularis*) per group were administered a single IV bolus injection of hu37D3.v28.A4 hIgG4-S228P.YTE at a dose of 50 mg/kg. Anti-gD hIgG4 was used as a control, also at a dose of 50 mg/kg. At various time points up to 42 days post-dose, plasma samples were collected to determine anti-Tau antibody concentrations. In addition, at various time points up to 42 days, 2 monkeys were sacrificed and brain and CSF concentrations of antibody were determined.

[00443] Antibody concentrations were determined substantially as described in Example 12.

[00444] Figure 22A-B show the concentration of antibody in cynomolgus monkey brain at various time points post-dose, plotted in logarithmic (A) and linear (B) scale. Table 25 shows the brain concentration parameters.

Table 25: Mean (± SD) brain PK parameter estimates following single IV bolus dose

Group	Cmax (µg/ml)	AUCall (day*µg/ml)
anti-gD hIgG4	0.175±0.02	4.26±0.35
hu37D3.v28.A4 hIgG4-S228P.YTE	0.12.±0.03	3.88±0.89

The hu37D3.v28.A4 hIgG4-S228P.YTE antibody showed increased brain concentration at the terminal timepoint, compared to anti-gD.

[00445] The concentration of the antibodies in various regions of the brain, including hippocampus, cerebellum, and frontal cortex, was also determined. Figure 23A-C and Tables 26 to 28 show the results of that analysis.

Table 26: Mean hippocampus PK parameter estimates following single IV bolus dose

Group	Cmax (µg/ml)	AUCall (day*µg/ml)
anti-gD hIgG4	0.159	3.95
hu37D3.v28.A4 hIgG4-S228P.YTE	0.087	2.87

Table 27: Mean cerebellum PK parameter estimates following single IV bolus dose

Group	Cmax (μg/ml)	AUCall (day*μg/ml)
anti-gD hIgG4	0.196	4.30
hu37D3.v28.A4 hIgG4-S228P.YTE	0.139	4.56

Table 28: Mean frontal cortex PK parameter estimates following single IV bolus dose

Group	Cmax (μg/ml)	AUCall (day*μg/ml)
anti-gD hIgG4	0.17	4.65
hu37D3.v28.A4 hIgG4-S228P.YTE	0.138	4.22

[00446] The results of that experiment show exposure of various regions of the brain to antibody hu37D3.v28.A4 hIgG4-S228P.YTE following a single IV injection. Overall exposures in brain were comparable across the two groups, however, similar to the observations in plasma, there was about a two-fold increase in antibody concentrations in the brain at the terminal timepoint in animals dosed with antibody hu37D3.v28.A4 hIgG4-S228P.YTE, compared to anti-gD. *See* Figure 23. These results suggest maintenance of higher trough (terminal) concentrations in brain after dosing with the YTE antibody.

[00447] The concentration of the antibodies in CSF and plasma over time was also determined. Figures 23D (CSF) and 23E (plasma) and Tables 29 and 30 show the results of that analysis.

Table 29: Mean CSF PK parameter estimates following single IV bolus dose

Group	Cmax (μg/ml)	AUCall (day*μg/ml)
anti-gD hIgG4	1.270	18.400
hu37D3.v28.A4 hIgG4-S228P.YTE	3.980	21.100

Table 30: Mean plasma PK parameter estimates following single IV bolus dose

Group	Cmax (μg/ml)	Tmax Day	AUCall (day*μg/ml)	Terminal (Day 43) μg/mL
anti-gD hIgG4	0.175±0.02	2	4.26±0.35	36.3±14.1
hu37D3.v28.A4 hIgG4-S228P.YTE	0.12.±0.03	3	3.88±0.89	89.4±42.3

[00448] Again, similar to the plasma and brain pharmacokinetics, there was about a two-fold increased antibody concentration in CSF and plasma at the terminal timepoint in animals dosed with antibody hu37D3.v28.A4 hIgG4-S228P.YTE, compared to anti-gD. *See* Figure 23.

[00449] Using the collected plasma samples from the cynomolgus monkeys, the plasma pharmacodynamics of antibody hu37D3.v28.A4 hIgG4-S228P.YTE and control antibody following a single IV 50 mg/kg dose were assessed. Plasma Tau was quantitated using the Elecsys® immunoassay discussed in Example 12.

[00450] The results of the pharmacodynamics analysis are shown in Figure 24A-B. Figure 24A shows the mean total plasma Tau concerntration, normalized to baseline. Figure 24B shows the total plasma Tau concerntration in individual monkeys in the study, normalized to baseline. Similar to the results observed in Example 12, administration of antibody hu37D3.v28.A4 hIgG4-S228P.YTE resulted in significantly increased plasma Tau levels. While not intending to be bound by any particular theory, these data suggest that hu37D3.v28.A4 hIgG4-S228P.YTE binds to Tau in the brain, and consequently Tau is cleared from the brain into the periphery. These results are consistent with target engagement in the brain by hu37D3.v28.A4 hIgG4-S228P.YTE.

[00451] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, the descriptions and examples should not be construed as limiting the scope of the invention. The disclosures of all patent and scientific literature cited herein are expressly incorporated in their entirety by reference.

Table of Sequences

SEQ ID NO	Description	Sequence
2	Human Tau epitope (2-24)	AEPRQEFEVMEDHAGTYGLGDRK
4	Cynomolgus monkey Tau epitope (2-24)	AEPRQEFDVMEDHAGTYGLGDRK
10	37D3-H9 heavy chain variable region (VH)	EVQLVESGGD LAKPGGSLKL SCTASGLIFR SYGMSWVRQT PDKRLEWVAT INSGGTYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYYCANSY SGAMDYWGQG TSVTVSS
11	37D3-H9 light chain variable region (VL)	DDLLTQTPLS LPVSLGDPAS ISCRSSQSIV HSNGNTYFEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSLVP WTFGGGTKLE IK
12	37D3-H9 HVR-H1	SYGMS
13	37D3-H9 HVR-H2	TINSGGTYTYYPDSVKG
14	37D3-H9 HVR-H3	SYSGAMDY
15	37D3-H9 HVR-L1	RSSQSIVHSNGNTYFE
16	37D3-H9 HVR-L2	KVSNRFS
17	37D3-H9 HVR-L3	FQGSLVPWT
20	37D3-H9b heavy chain variable region (VH)	EVQLVESGGD LAKPGGSLKL SCTASGLIFR SYGMSWVRQT PDKRLEWVAT INSGGTYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYYCANSY SGAMDYWGQG TSVTVSS
21	37D3-H9b light chain variable region (VL)	EDLLTQTPLS LPVSLGDPAS ISCRSSQSIV HSNGNTYFEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSLVP WTFGGGTKLE IK
22	37D3-H9b HVR-H1	SYGMS
23	37D3-H9b HVR-H2	TINSGGTYTYYPDSVKG
24	37D3-H9b HVR-H3	SYSGAMDY
25	37D3-H9b HVR-L1	RSSQSIVHSNGNTYFE
26	37D3-H9b HVR-L2	KVSNRFS
27	37D3-H9b HVR-L3	FQGSLVPWT
30	11E10-B8 heavy chain variable region (VH)	EVQLVESGGD LVKPGGSLKL SCAASGFTFR SYGMSWVRQT PDKRLEWVAT ISGGGSYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYYCAVSY DGAMDYWGQG TSVTVSS
31	11E10-B8 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGL YYCFQGSHVP WTFGGGTKLE IK
32	11E10-B8 HVR-H1	SYGMS
33	11E10-B8 HVR-H2	TISGGGSYTYYPDSVKG

34	11E10-B8 HVR-H3	SYDGAMDY
35	11E10-B8 HVR-L1	RSSQSIVHSNGNTYLE
36	11E10-B8 HVR-L2	KVSNRFS
37	11E10-B8 HVR-L3	FQGSHVPWT
40	54C1-H11 and 61E7-C4 heavy chain variable region (VH)	EVQLVESGGD LVKPGGSLKV SCVASGFTFR SYGMSWVRQT PDKRLDWVAT ISSGGNYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYYCASSY SGAMDYWGQG TSVTVSS
41	54C1-H11 and 61E7-C4 light chain variable region (VL)	DTVMTQSPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYTVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSHVP WTFGGGTKLE IK
42	54C1-H11 and 61E7-C4 HVR-H1	SYGMS
43	54C1-H11 and 61E7-C4 HVR-H2	TISSGGNYTYYPDSVKG
44	54C1-H11 and 61E7-C4 HVR-H3	SYSGAMDY
45	54C1-H11 and 61E7-C4 HVR-L1	RSSQSIVHSNGNTYLE
46	54C1-H11 and 61E7-C4 HVR-L2	TVSNRFS
47	54C1-H11 and 61E7-C4 HVR-L3	FQGSHVPWT
50	3A4-H4 heavy chain variable region (VH)	EVQLVESGGD LVKPGGSLKL SCAASGFTFS SYGMSWVRQT PDKRLEWVAT ISSGGTYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYFCATSY DGAMDYWGQG TSVTVSS
51	3A4-H4 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQNIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGTLVP WTFGGGTKLE IK
52	3A4-H4 HVR-H1	SYGMS
53	3A4-H4 HVR-H2	TISSGGTYTYYPDSVKG
54	3A4-H4 HVR-H3	SYDGAMDY
55	3A4-H4 HVR-L1	RSSQNIVHSNGNTYLE
56	3A4-H4 HVR-L2	KVSNRFS
57	3A4-H4 HVR-L3	FQGTLVPWT
60	19H6-F7 heavy chain variable region (VH)	EVQLVESGGD LVKPGGSLKL SCAASGFTFS SYGMSWVRQT PDKRLEWVAT ISSGGTYTYY PDSVKGRFTI SRDNAKNTLY LQMSSLKSED TAMYYCAPSY DGAMDYWGQG TSVTVSS
61	19H6-F7 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSLVP WTFGGGTKLE IK
62	19H6-F7 HVR-H1	SYGMS

63	19H6-F7 HVR-H2	TISSGGTYTYYPDSVKG
64	19H6-F7 HVR-H3	SYDGAMDY
65	19H6-F7 HVR-L1	RSSQSIVHSNGNTYLE
66	19H6-F7 HVR-L2	KVSNRFS
67	19H6-F7 HVR-L3	FQGSLVPWT
70	94B2-C1 heavy chain variable region (VH)	EVQLQQSGPE LVKPGASMKI SCKASGYSLT GYTMNWVKQS HGKNLEWIGL ISPYNGVTSY NQKFKGKATL TVDKSSNTAY MELLSLTFED SAVYYCARQG AYWGQGTLVT VSA
71	94B2-C1 light chain variable region (VL)	DVVMTQTPLT LSVTIGQPAS ISCKSSQSLL DSDGKTYLNW LLQRPGQSPK RLIYLVSKLD SGVPDRFTGS GSGTDFTLKI SRVEAEDLGV YYCWQGTHFP WTFGGGTKLE IK
72	94B2-C1 HVR-H1	GYTMN
73	94B2-C1 HVR-H2	LISPYNGVTSYNQKFKG
74	94B2-C1 HVR-H3	QGAY
75	94B2-C1 HVR-L1	KSSQSLLDSDGKTYLN
76	94B2-C1 HVR-L2	LVSKLDS
77	94B2-C1 HVR-L3	WQGTHFPWT
80	125B11-H3 heavy chain variable region (VH)	EVKLEESGGG LVQPGGSMKL SCVASRFIFS NYWMNWVRQS PEKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKSS VYLQMNNLRA EDTGIYYCTG GTTYWGQGTT LTVSS
81	125B11-H3 light chain variable region (VL)	DIVMTQSQKF LSTSVGDRVN ITCKASQNVG TAVAWYQQKP GQSPGLLIYS ASIRYTGVPD RFTGNGSGTD FTLTISDMQS EDLADYFCQQ FRTYPYTFGG GTKLEIK
82	125B11-H3 HVR-H1	NYWMN
83	125B11-H3 HVR-H2	QIRLKSDNYA THYAESVKG
84	125B11-H3 HVR-H3	GTTY
85	125B11-H3 HVR-L1	KASQNVGTAVA
86	125B11-H3 HVR-L2	SASIRYT
87	125B11-H3 HVR-L3	QQFRTYPYT
90	113F5-F7 heavy chain variable region (VH)	EVKLEESGGG LVQPGGSMRL SCVASEFTFS NYWMNWIRQS PEKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDASNFS VYLQMNNLRA EDTGIYYCTG GTSYWGQGTT LTVSS
91	113F5-F7 light chain variable region (VL)	DIVMTQSQKI MSTSVGDRVS ITCKASQNVG TAVAWYQQRP GHSPKLLIYS ASRRFSGVPD RFTGSGSGTD FTLTIINVQS EDLADYFCQQ FSTYPYTFGV GTKLEIK
92	113F5-F7 HVR-H1	NYWMN
93	113F5-F7 HVR-H2	QIRLKSDNYATHYAESVKG

94	113F5-F7 HVR-H3	GTSY
95	113F5-F7 HVR-L1	KASQNVGTAVA
96	113F5-F7 HVR-L2	SASRRFS
97	113F5-F7 HVR-L3	QQFSTYPYT
100	26C1-B11 heavy chain variable region (VH)	EVHLQQSGAE LVRSGASVKL SCTASGFNIK DYYMYWVKQR PEQGLEWIGW IDPENGDTEY FPKFQGKATM TADTSSKTAY LQLSSLTSED TAVYYCNAWR ARATNSALDY WGQGTSVTVS S
101	26C1-B11 light chain variable region (VL)	DVVMTQTPLT LSVTIGQPAS ISCKSSQSLL DSDGKTYLNW LLRRPGQSPK RLIYLVSKLD SGVPDRFTGS GSGTDFTLKI SRVEAEDLGV YYCWQGTHFP WTFGGGTKLE IK
102	26C1-B11 HVR-H1	DYYMY
103	26C1-B11 HVR-H2	WIDPENGDTE YFPKFQG
104	26C1-B11 HVR-H3	WRARATNSAL DY
105	26C1-B11 HVR-L1	KSSQSLLDSD GKTYLN
106	26C1-B11 HVR-L2	LVSKLDS
107	26C1-B11 HVR-L3	WQGTHFPWT
110	26C1-C8 heavy chain variable region (VH)	EVHLQQSGAE LVRSGASVKL SCTASGFNIK DYYMYWVKQR PEQGLEWIGW IDPENGDTEY FPKFQGKATM TADTSSKTAY LQLSSLTSED TAVYYCNAWR ARATNSALDY WGQGTSVTVS S
111	26C1-C8 light chain variable region (VL)	DVVMTQTPLT LSVTIGQPAS ISCKSSQSLL DSDGKTYLNW LLRRPGQSPK RLIYLVSKLD SGVPDRFTGS GSGTDFTLKI SRVEAEDLGV YYCWQGTHFP WTFGGGTKLE IK
112	26C1-C8 HVR-H1	DYYMY
113	26C1-C8 HVR-H2	WIDPENGDTE YFPKFQG
114	26C1-C8 HVR-H3	WRARATNSAL DY
115	26C1-C8 HVR-L1	KSSQSLLDSD GKTYLN
116	26C1-C8 HVR-L2	LVSKLDS
117	26C1-C8 HVR-L3	WQGTHFPWT
120	30G1-B2 heavy chain	QVQLQQSGAE LVRPGASVTL SCKASGYTFT DYEMYWVKQT PVHGLEWIGA IDPETGDTAY NQKFKGKATL TADKSSNTAY

	variable region (VH)	MELRSLTSED SAVYYCIRQY GNWFPYWGQG TLVTVSA
121	30G1-B2 light chain variable region (VL)	DVVMTQTPLS LPVSLGDQAS ISCRSSQSLV HANGNTYLHW FLQKPGLSPK LLIYKVSNRF SGVPDRFSGG GSGTDFTLKI TRLEAEDLGV YFCSQSTHVP FTFGSGTKLE IK
122	30G1-B2 HVR-H1	DYEMY
123	30G1-B2 HVR-H2	AIDPETGDTAYNQKFKG
124	30G1-B2 HVR-H3	QYGNWFPY
125	30G1-B2 HVR-L1	RSSQSLVHANGNTYLH
126	30G1-B2 HVR-L2	KVSNRFS
127	30G1-B2 HVR-L3	SQSTHVPFT
130	66F5-A1 heavy chain variable region (VH)	QVQLQQSGAE LVRPGASVTL SCKASGYTFI DYEMNWVKQT PVHGLEWIGA IDPENGGTAY NQKFKGKAIV TADKSSSTAY MELRSLTSED SAVYYCSGPH FDYWGQGTTL TVSS
131	66F5-A1 light chain variable region (VL)	DIVMTQSPSS LAMSVGQKVT MSCKSSQSLL NSSTQKNYLA WYQQKPGQSP KLLVYFASTR ESGVPDRFIG SGSGTDFTLT ISSVQAEDLA DYFCQQHYST PYTFGGGTKL EIK
132	66F5-A1 HVR-H1	DYEMN
133	66F5-A1 HVR-H2	AIDPENGGTA YNQKFKG
134	66F5-A1 HVR-H3	PHFDY
135	66F5-A1 HVR-L1	KSSQSLLNSS TQKNYLA
136	66F5-A1 HVR-L2	FASTRES
137	66F5-A1 HVR-L3	QQHYSTPYT
140	123E9-A1 heavy chain variable region (VH)	EVQLQQSGPE LVKPGASVKM SCKASGYTFT DYYMKWVKQS HGKSLEWIGD IDPNNGGTSY NQKFKGKATL TVDKSSSTAY MQLNSLTSED SAVYYCARSA GFGDSFSFWG LGTLVTVSA
141	123E9-A1 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGF YYCFQGSHVP PTFGGGTKLE IK
142	123E9-A1 HVR-H1	DYYMK
143	123E9-A1 HVR-H2	DIDPNNGGTSYNQKFKG

144	123E9-A1 HVR-H3	SAGFGDSFSF
145	123E9-A1 HVR-L1	RSSQSIVHSNGNTYLE
146	123E9-A1 HVR-L2	KVSNRFS
147	123E9-A1 HVR-L3	FQGSHVPPT
150	15C6-A7 heavy chain variable region (VH)	EVQLQQSGPE LVKPGASVMM TCKASGYTFT DYYMKWVKQS NGKSLEWIGD LDPYTGGANY NQKFKGKATL TVDKSSSTAY MHLNSLTSED SAVYYCARSR GYGDSFAYWG QGTLVTVSA
151	15C6-A7 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQNIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDKFSGS GSGTDFTLKI SRVEAEDLGV YFCFQGSHVP PTFGGGTKLE IK
152	15C6-A7 HVR-H1	DYYMK
153	15C6-A7 HVR-H2	DLDPYTGGAN YNQKFKG
154	15C6-A7 HVR-H3	SRGYGDSFAY
155	15C6-A7 HVR-L1	RSSQNIVHSN GNTYLE
156	15C6-A7 HVR-L2	KVSNRFS
157	15C6-A7 HVR-L3	FQGSHVPPT
160	19F8-B1 heavy chain variable region (VH)	EVQLQQSGPE LVKPGASVKM SCKASGYTFT DYYMKWVKQS HGKSLEWIGD LNPNNGGTLY NQKFKGQATL TVDKSSSTAY MQFNSLTSED SAVYYCARSA GYGDSFAYWG QGTLVTVSA
161	19F8-B1 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQNIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGI YFCFQGSHVP PTFGGGTKLE IK
162	19F8-B1 HVR-H1	DYYMK
163	19F8-B1 HVR-H2	DLNPNNGGTL YNQKFKG
164	19F8-B1 HVR-H3	SAGYGDSFAY
165	19F8-B1 HVR-L1	RSSQNIVHSN GNTYLE
166	19F8-B1 HVR-L2	KVSNRFS
167	19F8-B1 HVR-L3	FQGSHVPPT

170	24A11-D5 heavy chain variable region (VH)	EVQLQQSGPE LVKPGASVKM SCKASGYTFT DYYMKWVKQS HGKSLEWIGD LNPKNGGIIY NQKFKGQATL TVDKSSSTAY MQLNSLTSED SAVFYCARSG GYGDSFAYWG QGTLVTVSA
171	24A11-D5 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQNIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGI YFCFQGSHVP PTFGGGTKLE IK
172	24A11-D5 HVR-H1	DYYMK
173	24A11-D5 HVR-H2	DLNPKNGGII YNQKFKG
174	24A11-D5 HVR-H3	SGGYGDSFAY
175	24A11-D5 HVR-L1	RSSQNIVHSN GNTYLE
176	24A11-D5 HVR-L2	KVSNRFS
177	24A11-D5 HVR-L3	FQGSHVPPT
180	126F11-G11 heavy chain variable region (VH)	EVQLQQSGAE LVRPGASVKL SCTASGFNIK DDYMHWVKQR PEQGLEWIGW IDPENGDTEY ASKFQGKATI TTDTSSNTAY LQLSSLTSED TAVYYCLDFA YGYWGQGTTL TVSS
181	126F11-G11 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YYCFQGSHVP PAFGGGTKLE IK
182	126F11-G11 HVR-H1	DDYMH
183	126F11-G11 HVR-H2	WIDPENGDTE YASKFQG
184	126F11-G11 HVR-H3	FAYGY
185	126F11-G11 HVR-L1	RSSQSIVHSN GNTYLE
186	126F11-G11 HVR-L2	KVSNRFS
187	126F11-G11 HVR-L3	FQGSHVPPA
190	89F4-A1 heavy chain variable region (VH)	EVQLVESGGG LVQPKGSLKL SCAASGFTFN TYAMNWVRQA PGKGLEWVAR IRSKSNNYAA YFADSVKDRF TISRDDSQTM LYLQMNNLKS EDTAMYYCVS GGNYVPFAYW GQGTLVTVSA
191	89F4-A1 light chain variable region (VL)	NIMMTQSPSS LAVSAGEKVT MSCKSSQSVF YSSEQRNYLA WYQQKPGQSP KLLISWASTR ESGVPDRFTG SGSGTDFTLT ISSVQGEDLA VYYCHQYLSS FTFGSGTKLE IK
192	89F4-A1 HVR-H1	TYAMN
193	89F4-A1 HVR-H2	RIRSKSNNYA AYFADSVKD
194	89F4-A1 HVR-H3	GGNYVPFAY
195	89F4-A1 HVR-L1	KSSQSVFYSS EQRNYLA

196	89F4-A1 HVR-L2	WASTRES
197	89F4-A1 HVR-L3	HQYLSSFT
200	93A8-D2 heavy chain variable region (VH)	EVQLQQSGPV LVKPGASVKM SCKASGYTFT DYYVNWVKQS HGKGLEWIGL INPNNGRTSY NQNFNDKATL TVDKSSSTAF MDLNSLTSED SAVYYCTREG GTGYWGQGTT LSVSS
201	93A8-D2 light chain variable region (VL)	DVVMTQTPLT LSVTIGQPAS ISCKSSQSLL DSDGKTYLNW LLQRPGQSPR RLIYLVSKLD SGVPDRFTGS GSGTDFTLKI SRVAAEDLGV YYCWQGTHFP RTFGGGTKLE IK
202	93A8-D2 HVR-H1	DYYVN
203	93A8-D2 HVR-H2	LINPNNGRTSYNQNFND
204	93A8-D2 HVR-H3	EGGTGY
205	93A8-D2 HVR-L1	KSSQSLLDSDGKTYLN
206	93A8-D2 HVR-L2	LVSKLDS
207	93A8-D2 HVR-L3	WQGTHFPRT
210	14F5-D9 heavy chain variable region (VH)	EVKLVESGGG LVQPGGSLRL SCATSGFTFS DFYMEWVRQS PGKRLEWIAA SKNKANDYTT EYNASVKDRF FVSRDTSQSI LYLQMNALRA EDTAIYYCAR DALGTVFAYW GQGTLVTVSA
211	14F5-D9 light chain variable region (VL)	DVVMTQTPLS LPVSLGDQAS ISCRSSQSLV HSNGNTYLHW YLQKPGQSPK LLIYKVFNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTLVP LTFGAGTKLE LK
212	14F5-D9 HVR-H1	DFYME
213	14F5-D9 HVR-H2	ASKNKANDYT TEYNASVKD
214	14F5-D9 HVR-H3	DALGTVFAY
215	14F5-D9 HVR-L1	RSSQSLVHSN GNTYLH
216	14F5-D9 HVR-L2	KVFNRFS
217	14F5-D9 HVR-L3	SQSTLVPLT
220	73H6-B8 heavy chain variable region (VH)	QVQLKESGPG LVAPSQSLSI TCTISGFSLT SYGVHWVRQP PGKGLEWLVV IWSDGSTTYN SALKSRLSIS KDNSKSQVFL KMNSLQTDDT AMYYCARQGG FITTAYYAMD YWGQGTSVTV SS
221	73H6-B8 light chain variable region (VL)	DIVMSQSPSS LAVSAGEKVT MSCKSSQSLL NSRTRKNYLA WYQQKPGQSP KLLIYWASTR ESGVPDRFTG SGSGTDFTLT ISSVQAEDLA VYYCKQSYNL YTFGGGTKLE IK
222	73H6-B8 HVR-H1	SYGVH
223	73H6-B8 HVR-H2	VIWSDGSTTY NSALKS
224	73H6-B8 HVR-H3	QGGFITTAYY AMDY
225	73H6-B8 HVR-L1	KSSQSLLNSR TRKNYLA
226	73H6-B8 HVR-L2	WASTRES
227	73H6-B8 HVR-L3	KQSYNLYT

230	22G7-C9 heavy chain variable region (VH)	QIQLVQSGPE LKKPGETVKI SCKASGYTFT DCSIHWVKQA PGEGLKWMGW INTETGEPSY ADDFKGRFAF SLETSASTAF LQINNLKSED TASYFCGTAY YRYDGALDYW GQGTSVTVSS
231	22G7-C9 light chain variable region (VL)	DIVLTQSPAS LAVSLGQRAT ISCRASQSVS TSSYSYMHWF QQKPGQPPKL LIKYASNLES GVPARFSGSG SGTDFTLNIH PVEEEDTATY YCQHSWELPW TFGGGTKLEI K
232	22G7-C9 HVR-H1	DCSIH
233	22G7-C9 HVR-H2	WINTETGEPS YADDFKG
234	22G7-C9 HVR-H3	AYYRYDGALD Y
235	22G7-C9 HVR-L1	RASQSVSTSS YSYMH
236	22G7-C9 HVR-L2	YASNLES
237	22G7-C9 HVR-L3	QHSWELPWT
240	7A11-C12 heavy chain variable region (VH)	QIQLVQSGPD LKKPGETVKI SCKASGYTFT NYGMNWVKQA PGKGLKWMGW INTNTGEPTY AEEFKGRFAF SLETSASTAY LQIDNLKNED TATYFCARGT VSFPYWGQGT LVTVSA
241	7A11-C12 light chain variable region (VL)	DVVMSQTPLS LPVSLGDHAS ISCRSSQNLV HSDGNTYLHW YLQKPGQSPK LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVI FTFGSGTKLE IK
242	7A11-C12 HVR-H1	NYGMN
243	7A11-C12 HVR-H2	WINTNTGEPT YAEEFKG
244	7A11-C12 HVR-H3	GTVSFPY
245	7A11-C12 HVR-L1	RSSQNLVHSD GNTYLH
246	7A11-C12 HVR-L2	KVSNRFS
247	7A11-C12 HVR-L3	SQSTHVIFT
250	12A10-E8 heavy chain variable region (VH)	QIQLVQSGPE LKKPGETVKI SCKASGYTFT NYGMNWVKQA PGKGLKWMGW INMYTGEPTY GDDFKGRFVF SLETSVSTVY LQINNLKKED TATFFCARGG RPDYWGQGTS VTVSS
251	12A10-E8 light chain variable region (VL)	DVLMTQTPLS LPVSLGDQAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPK LLIYKVFNRF SGVPDRFSGS GSGTDFTLKI NRVEAEDLGV YYCLQGSHVP YTFGGGTKLE IK
252	12A10-E8 HVR-H1	NYGMN
253	12A10-E8 HVR-H2	WINMYTGEPT YGDDFKG
254	12A10-E8 HVR-H3	GGRPDY
255	12A10-E8 HVR-L1	RSSQSIVHSN GNTYLE
256	1 2A10-E8 HVR-L2	KVFNRFS
257	12A10-E8 HVR-L3	LQGSHVPYT
260	55E7-F11 heavy chain variable region (VH)	EVKLEESGGG LVQPGGSMKL SCVASGFTFS NYWMNWVRQS PEKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKSS VYLQMNNLRA EDTGIYYCAG YFYGGYFDVW GTGTTVTVSS

261	55E7-F11 light chain variable region (VL)	ELVLTQSPTT MAASPGKKIT ITCSASSSIS SNYLHWYQQK PGFSPKLLIY RTSNLASGVP ARFSGSGSGT SYSLTIGTME AEDVATYYCQ QGSSLPFTFG SGTKLEIK
262	55E7-F11 HVR-H1	NYWMN
263	55E7-F11 HVR-H2	QIRLKSDNYA THYAESVKG
264	55E7-F11 HVR-H3	YFYGGYFDV
265	55E7-F11 HVR-L1	SASSSISSNY LH
266	55E7-F11 HVR-L2	RTSNLAS
267	55E7-F11 HVR-L3	QQGSSLPFT
270	52F6-F11 heavy chain variable region (VH)	QVQLQQSGTE LAKPGASVKL SCKASGYTFT HYWMHWIKQR PGQGLEWIGY IYPTNDYTKY NQNFRDKATL TADESSNSAY MQLNSLTYED SAVYYCARAG NRVFDFWGQG TTLTVSS
271	52F6-F11 light chain variable region (VL)	QAVVTQESAL TTSPGETVTL TCRSSTGAVT TSNFANWVQE KPDHLFTGLI GGTNNRAPGV PARFSGSLIG DKAALTITGA QTEDEAIYFC ALWYSNLWVF GGGTKLTVL
272	52F6-F11 HVR-H1	HYWMH
273	52F6-F11 HVR-H2	YIYPTNDYTK YNQNFRD
274	52F6-F11 HVR-H3	AGNRVFDF
275	52F6-F11 HVR-L1	RSSTGAVTTS NFAN
276	52F6-F11 HVR-L2	GTNNRAP
277	52F6-F11 HVR-L3	ALWYSNLWV
280	Hu37D3-H9.v1 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
281	Hu37D3-H9.v1 light chain variable region (VL)	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IK
282	Hu37D3-H9.v1 HVR-H1	SYGMS
283	Hu37D3-H9.v1 HVR-H2	TINSGGTYTYYPDSVKG
284	Hu37D3-H9.v1 HVR-H3	SYSGAMDY
285	Hu37D3-H9.v1 HVR-L1	RSSQSIVHSNGNTYFE
286	Hu37D3-H9.v1 HVR-L2	KVSNRFS
287	Hu37D3-H9.v1 HVR-L3	FQGSLVPWT
288	Hu37D3-H9.v1 IgG1 heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK

		CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK
289	Hu37D3-H9.v1 IgG1 light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
290	Hu37D3-H9.v5 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
291	Hu37D3-H9.v5 light chain variable region (VL)	EDVLTQTPLS LPVTPGQPAS ISCRSSQSIV HSNGNTYFEW YLQKPGQSPQ LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQGSLVP WTFGQGTKVE IK
292	Hu37D3-H9.v5 HVR-H1	SYGMS
293	Hu37D3-H9.v5 HVR-H2	TINSGGTYTYYPDSVKG
294	Hu37D3-H9.v5 HVR-H3	SYSGAMDY
295	Hu37D3-H9.v5 HVR-L1	RSSQSIVHSNGNTYFE
296	Hu37D3-H9.v5 HVR-L2	KVSNRFS
297	Hu37D3-H9.v5 HVR-L3	FQGSLVPWT
300	Hu94B2.v105 heavy chain variable region (VH)	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRATL TVDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
301	Hu94B2.v105 light chain variable region (VL)	DIVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
302	Hu94B2.v105 HVR-H1	GYTMN
303	Hu94B2.v105 HVR-H2	LISPYNGVTSYNQKFKG
304	Hu94B2.v105 HVR-H3	QGAY
305	Hu94B2.v105 HVR-L1	KSSQSLLDSDGKTYLN
306	Hu94B2.v105 HVR-L2	LVSKLDS
307	Hu94B2.v105 HVR-L3	WQGTHFPWT
310	hu125B11.v17 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKNT LYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
311	hu125B11.v17 light chain variable region (VL)	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKSPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FRTYPYTFGQ GTKVEIK
312	hu125B11.v17 HVR-H1	NYWMN

313	hu125B11.v17 HVR-H2	QIRLKSDNYATHYAESVKG
314	hu125B11.v17 HVR-H3	GTTY
315	hu125B11.v17 HVR-L1	KASQNVGTAVA
316	hu125B11.v17 HVR-L2	SASIRYT
317	hu125B11.v17 HVR-L3	QQFRTYPYT
320	hu125B11.v26 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDNSKNT LYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
321	hu125B11.v26 light chain variable region (VL)	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FRTYPYTFGQ GTKVEIK
322	hu125B11.v26 HVR-H1	NYWMN
323	hu125B11.v26 HVR-H2	QIRLKSDNYATHYAESVKG
324	hu125B11.v26 HVR-H3	GTTY
325	hu125B11.v26 HVR-L1	KASQNVGTAVA
326	hu125B11.v26 HVR-L2	SASIRYT
327	hu125B11.v26 HVR-L3	QQFRTYPYT
330	hu125B11.v28 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDNSKNT LYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
331	hu125B11.v28 light chain variable region (VL)	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FRTYPYTFGQ GTKVEIK
332	hu125B11.v28 HVR-H1	NYWMN
333	hu125B11.v28 HVR-H2	QIRLKSDNYATHYAESVKG
334	hu125B11.v28 HVR-H3	GTTY
335	hu125B11.v28 HVR-L1	KASQNVGTAVA
336	hu125B11.v28 HVR-L2	SASIRYT
337	hu125B11.v28 HVR-L3	QQFRTYPYT
340	Hu37D3-H9.v28.A4 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
341	Hu37D3-H9.v28.A4 light chain variable region (VL)	DDVLTQTPLS LPVTPGQPAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPQ LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQGSLVP WTFGQGTKVE IK

342	Hu37D3-H9.v28.A4 HVR-H1	SYGMS
343	Hu37D3-H9.v28.A4 HVR-H2	TINSGGTYTYYPDSVKG
344	Hu37D3-H9.v28.A4 HVR-H3	SYSGAMDY
345	Hu37D3-H9.v28.A4 HVR-L1	RSSQSIVHSNGNTYLE
346	Hu37D3-H9.v28.A4 HVR-L2	KVSNRFS
347	Hu37D3-H9.v28.A4 HVR-L3	FQGSLVPWT
348	Hu37D3-H9.v28.A4 IgG4-S228P.YTE heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLYI TREPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
602	Hu37D3-H9.v28.A4 IgG4-S228P.YTE des-K heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLYI TREPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLG
349	Hu37D3-H9.v28.A4 IgG4-S228P.YTE light chain	DDVLTQTPLS LPVTPGQPAS ISCRSSQSIV HSNGNTYLEW YLQKPGQSPQ LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
442	hu125B11-H3.LC1	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKSPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FRTYPYTFGQ GTKVEIK
443	hu125B11-H3.LC2	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FRTYPYTFGQ GTKVEIK
444	hu125B11-H3.LC3	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKSPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FRTYPYTFGQ GTKVEIK
445	hu125B11-H3.LC4	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASIRYTGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FRTYPYTFGQ GTKVEIK
446	hu125B11-H3.HC1	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKNT VYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS

447	hu125B11-H3.HC2	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDNSKNT VYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
448	hu125B11-H3.HC3	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKNT LYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
449	hu125B11-H3.HC4	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYWMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDNSKNT LYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
450	hu125B11-H3.HC5	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYYMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKNT VYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
451	hu125B11-H3.HC6	EVQLVESGGG LVQPGGSLRL SCAASRFIFS NYFMNWVRQA PGKGLEWVAQ IRLKSDNYAT HYAESVKGRF TISRDDSKNT VYLQMNSLRA EDTAVYYCTG GTTYWGQGTL VTVSS
452	Hu94B2.HC1	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRATL TVDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
453	Hu94B2.HC2	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRVTL TVDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
454	Hu94B2.HC3	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRATI TVDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
455	Hu94B2.HC4	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRATL TRDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
456	Hu94B2.HC5	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRATL TVDTSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
457	Hu94B2.HC6	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRVTI TVDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
458	Hu94B2.HC7	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRVTI TRDKSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
459	Hu94B2.HC8	EVQLVQSGAE VKKPGASVKV SCKASGYSLT GYTMNWVRQA PGQGLEWIGL ISPYNGVTSY NQKFKGRVTI TVDTSTSTAY LELSSLRSED TAVYYCARQG AYWGQGTLVT VSS
460	Hu94B2.LC9	DVVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
461	Hu94B2.LC10	DVVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ LLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
462	Hu94B2.LC11	DVVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW YLQKPGQSPQ RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
463	Hu94B2.LC12	DVVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW YLQKPGQSPQ LLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
464	Hu94B2.LC13	DIVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
465	Hu94B2.LC14	DIVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW LLQKPGQSPQ LLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
466	Hu94B2.LC15	DIVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW YLQKPGQSPQ RLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK

467	Hu94B2.LC16	DIVMTQTPLS LPVTPGQPAS ISCKSSQSLL DSDGKTYLNW YLQKPGQSPQ LLIYLVSKLD SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCWQGTHFP WTFGQGTKVE IK
468	Hu37D3-H9.v5.1 HVR-L1	RSSQSIVHSNANTYFE
469	Hu37D3-H9.v5.2 HVR-L1	RSSQSIVHSSGNTYFE
470	Hu37D3-H9.v5.3 HVR-L1	RSSQSIVHSDGNTYFE
471	Hu37D3-H9.v5.4 HVR-L1	RSSQSIVHSQGNTYFE
472	Hu37D3-H9.v5.5 HVR-L1	RSSQSIVHSEGNTYFE
473	Hu37D3-H9.v5.6 HVR-L1	RSSQSIVHSAGNTYFE
474	Hu37D3-H9.v5.7 HVR-L1	RSSQSIVHSNGDTYFE
475	Hu37D3-H9.v5.8 HVR-L1	RSSQSIVHSNGQTYFE
476	Hu37D3-H9.v5.9 HVR-L1	RSSQSIVHSNGETYFE
477	Hu37D3-H9.v5.10 HVR-L1	RSSQSIVHSNGATYFE
478	Hu37D3-H9.v5.11 HVR-L1	RSSQSIVHSNGSTYFE
479	Hu37D3.v28 HVR-L1	RSSQSIVHSNGNTYFE
480	Hu37D3.v28.A2 HVR-L1	RSSQSIVHSNGNTYFE
481	Hu37D3.v28.A4 HVR-L1	RSSQSIVHSNGNTYLE
482	Hu37D3.v28.A6 HVR-L1	RSSQSIVHSNGNTYLE
483	Hu37D3.v28.A8 HVR-L1	RSSQSIVHSNGNTYFE
484	Hu37D3.v28.A10 HVR-L1	RSSQSIVHSNGNTYFE
485	Hu37D3.v28.A12 HVR-L1	RSSQSIVHSNGNTYLE
486	Hu37D3.v28.A14 HVR-L1	RSSQSIVHSNGNTYLE
487	Hu37D3.v28.A16 HVR-L1	RSSQSIVHSNGNTYFE
488	Hu37D3.v28.A18 HVR-L1	RSSQSIVHSNGNTYFE
489	Hu37D3.v28.A20 HVR-L1	RSSQSIVHSNGNTYLE
490	Hu37D3.v28.A22 HVR-L1	RSSQSIVHSNGNTYLE
491	Hu37D3.v28.A24 HVR-L1	RSSQSIVHSNGNTYFE

492	Hu37D3.v28.A26 HVR-L1	RSSQSIVHSNGNTYFE
493	Hu37D3.v28.A28 HVR-L1	RSSQSIVHSNGNTYLE
494	Hu37D3.v28.A30 HVR-L1	RSSQSIVHSNGNTYLE
495	Hu37D3.v28.B1 HVR-L1	RSSQSIVHSIGNTFFE
496	Hu37D3.v28.B2 HVR-L1	RSSQSIVHSMGNTFFE
497	Hu37D3.v28.B3 HVR-L1	RSSQSIVHSQGNTWFE
498	Hu37D3.v28.B4 HVR-L1	RSSQSIVHSQGNTHFE
499	Hu37D3.v28.B6 HVR-L1	RSSQSIVHSDGNTRFE
500	Hu37D3.v28.B7 HVR-L1	RSSQSIVHSDGNTKFE
501	Hu37D3.v28.B8 HVR-L1	RSSQSIVHSEGNTRFE
502	Hu37D3.v28.C1 HVR-L1	RSSQSIVHSNNNTYFE
503	Hu37D3.v28.C2 HVR-L1	RSSQSIVHSNDNTYFE
504	Hu37D3.v28.D1 HVR-L1	RSSQSIVHANGNTYFE
505	Hu37D3.v28.E1 HVR-L1	RSSQSIVNSNGNTYFE
506	Hu37D3.v28.E2 HVR-L1	RSSQSIVQSNGNTYFE
507	Hu37D3.v28.E3 HVR-L1	RSSQSIVDSDGNTYFE
508	Hu37D3.v28.F1 HVR-L1	RSSQSIVHSNTNTYFE
509	Hu37D3.v28.F2 HVR-L1	RSSQSIVHTNGNTYFE
510	Hu37D3.v28.F3 HVR-L1	RSSQSIVHTNANTYFE
511	Hu37D3.v28.51 HVR-L1	RSSQSIVHSHGNTYFE
512	Hu37D3.v28.52 HVR-L1	RSSQSIVHSKGNTYFE
513	Hu37D3.v28.53 HVR-L1	RSSQSIVHSRGNTYFE
514	Hu37D3.v28.54 HVR-L1	RSSQSIVHSLGNTYFE
515	Hu37D3.v28.55 HVR-L1	RSSQSIVHSNQNTYFE
516	Hu37D3.v28.56 HVR-L1	RSSQSIVHSNYNTYFE
517	Hu37D3.v28.57 HVR-L1	RSSQSIVHSNFNTYFE
518	Hu37D3.v29.1 HVR-L1	RSSQSIVHSNGDTYFE
519	Hu37D3.v29.2 HVR-L1	RSSQSIVHSNGQTYFE
520	Hu37D3.v29.3 HVR-L1	RSSQSIVHSNGETYFE
521	Hu37D3.v29.4 HVR-L1	RSSQSIVHSNGATYFE
522	Hu37D3.v29.5 HVR-L1	RSSQSIVHSNGHTYFE

523	Hu37D3.v29.6 HVR-L1	RSSQSIVHSNGKTYFE
524	Hu37D3.v29.7 HVR-L1	RSSQSIVHSNGLTYFE
525	Hu37D3.v29.8 HVR-L1	RSSQSIVHSNADTYFE
526	Hu37D3.v29.9 HVR-L1	RSSQSIVHSNAQTYFE
527	Hu37D3.v29.10 HVR-L1	RSSQSIVHSNAETYFE
528	Hu37D3.v29.11 HVR-L1	RSSQSIVHSNAATYFE
529	Hu37D3.v29.12 HVR-L1	RSSQSIVHSNAHTYFE
530	Hu37D3.v29.13 HVR-L1	RSSQSIVHSNAKTYFE
531	Hu37D3.v29.14 HVR-L1	RSSQSIVHSNALTYFE
532	Hu37D3-H9.v30.1 HVR-L1	RSSQSIVHSGGNTYFE
533	Hu37D3-H9.v30.2 HVR-L1	RSSQSIVHSTGNTYFE
534	Hu37D3-H9.v30.3 HVR-L1	RSSQSIVHSVGNTYFE
535	Hu37D3-H9.v30.4 HVR-L1	RSSQSIVHSLGNTYFE
536	Hu37D3-H9.v30.5 HVR-L1	RSSQSIVHSIGNTYFE
537	Hu37D3-H9.v30.6 HVR-L1	RSSQSIVHSPGNTYFE
538	Hu37D3-H9.v30.7 HVR-L1	RSSQSIVHSFGNTYFE
539	Hu37D3-H9.v30.8 HVR-L1	RSSQSIVHSYGNTYFE
540	Hu37D3-H9.v30.9 HVR-L1	RSSQSIVHSHGNTYFE
541	Hu37D3-H9.v30.10 HVR-L1	RSSQSIVHSKGNTYFE
542	Hu37D3-H9.v30.11 HVR-L1	RSSQSIVHSRGNTYFE
543	Hu37D3-H9.v31.1 HVR-L1	RSSQSIVHSNAGTYFE
544	Hu37D3-H9.v31.2 HVR-L1	RSSQSIVHSNAVTYFE
545	Hu37D3-H9.v31.3 HVR-L1	RSSQSIVHSNAITYFE
546	Hu37D3-H9.v31.4 HVR-L1	RSSQSIVHSNAPTYFE
547	Hu37D3-H9.v31.5 HVR-L1	RSSQSIVHSNAFTYFE
548	Hu37D3-H9.v31.6 HVR-L1	RSSQSIVHSNAYTYFE
549	Hu37D3-H9.v31.7 HVR-	RSSQSIVHSNARTYFE

	L1	
550	Hu37D3-H9.v31.8 HVR-L1	RSSQSIVHSNANVYFE
551	Hu37D3-H9.v31.9 HVR-L1	RSSQSIVHSNANIYFE
552	Hu37D3-H9.v31.10 HVR-L1	RSSQSIVHSNANPYFE
553	Hu37D3-H9.v31.11 HVR-L1	RSSQSIVHSNANFYFE
554	Hu37D3-H9.v31.12 HVR-L1	RSSQSIVHSNANYYFE
555	Hu37D3-H9.v31.13 HVR-L1	RSSQSIVHSNANNYFE
556	Hu37D3-H9.v31.14 HVR-L1	RSSQSIVHSNANRYFE
557	Human Tau 7-24 peptide	EFEVMEDHAGTYGLGDRK
558	Human Tau 7-20 peptide	EFEVMEDHAGTYGL
560	Hu37D3.v39 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
561	Hu37D3.v39 light chain variable region (VL)	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTYLEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IK
562	Hu37D3.v39 HVR-H1	SYGMS
563	Hu37D3.v39 HVR-H2	TINSGGTYTYYPDSVKG
564	Hu37D3.v39 HVR-H3	SYSGAMDY
565	Hu37D3.v39 HVR-L1	RSSQSIVHSNGNTYLE
566	Hu37D3.v39 HVR-L2	KVSNRFS
567	Hu37D3.v39 HVR-L3	FQGSLVPWT
568	Hu37D3.v39 IgG4-S228P.YTE heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLYI TREPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
569	Hu37D3.v39 IgG4-S228P.YTE light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTYLEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
570	Hu37D3.v40 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
571	Hu37D3.v40 light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNTNTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI

	variable region (VL)	SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IK
572	Hu37D3.v40 HVR-H1	SYGMS
573	Hu37D3.v40 HVR-H2	TINSGGTYTYYPDSVKG
574	Hu37D3.v40 HVR-H3	SYSGAMDY
575	Hu37D3.v40 HVR-L1	RSSQSIVHSNTNTYFE
576	Hu37D3.v40 HVR-L2	KVSNRFS
577	Hu37D3.v40 HVR-L3	FQGSLVPWT
578	Hu37D3.v40 IgG4-S228P.YTE heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLYI TREPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
579	Hu37D3.v40 IgG4-S228P.YTE light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNTNTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
580	Hu37D3.v41 heavy chain variable region (VH)	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSS
581	Hu37D3.v41 light chain variable region (VL)	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGQTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IK
582	Hu37D3.v41 HVR-H1	SYGMS
583	Hu37D3.v41 HVR-H2	TINSGGTYTYYPDSVKG
584	Hu37D3.v41 HVR-H3	SYSGAMDY
585	Hu37D3.v41 HVR-L1	RSSQSIVHSNGQTYFE
586	Hu37D3.v41 HVR-L2	KVSNRFS
587	Hu37D3.v41 HVR-L3	FQGSLVPWT
588	Hu37D3.v41 IgG4-S228P.YTE heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLYI TREPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
589	Hu37D3.v41 IgG4-S228P.YTE light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGQTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ

		SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
590	Hu37D3-H9.v1 IgG4-S228P heavy chain	EVQLVESGGG LVQPGGSLRL SCAASGLIFR SYGMSWVRQA PGKGLEWVAT INSGGTYTYY PDSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCANSY SGAMDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK
591	Hu37D3-H9.v1 IgG4 light chain	EDQLTQSPSS LSASVGDRVT ITCRSSQSIV HSNGNTYFEW YQQKPGKSPK LLIYKVSNRF SGVPSRFSGS GSGTDFTLTI SSLQPEDFAT YYCFQGSLVP WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC
592	MAPT(10-24)	VMEDHAGTYGLGDRK
593	MAPT(2-24)	AEPRQEFEVMEDHAGTYGLGDRK
594	MAPT(2-34)	AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQD
595	MAPT(10-44)	VMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLK
596	MAPT(2-24)Y18A	AEPRQEFEVMEDHAGTAGLGDRK
597	MAPT(2-24)L20A	AEPRQEFEVMEDHAGTYGAGDRK
598	hu113F5-F7.LC1	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKSPKLLIYS ASRRFSGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FSTYPYTFGQ GTKVEIK
599	hu113F5-F7.LC2	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASRRFSGVPS RFSGSGSGTD FTLTISSLQP EDFATYFCQQ FSTYPYTFGQ GTKVEIK
600	hu113F5-F7.LC3	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKSPKLLIYS ASRRFSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FSTYPYTFGQ GTKVEIK
601	hu113F5-F7.LC4	DIQMTQSPSS LSASVGDRVT ITCKASQNVG TAVAWYQQKP GKAPKLLIYS ASRRFSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FSTYPYTFGQ GTKVEIK

WHAT IS CLAIMED IS:

1. An isolated monoclonal antibody that binds to human Tau, wherein the antibody binds to monomeric Tau, oligomeric Tau, non-phosphorylated Tau, and phosphorylated Tau, wherein 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 an amino acid sequence selected from SEQ ID NOs: 345, 15, 468 to 478, 495 to 517, 522 to 534, 536 to 539, and 543 to 556; 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.

2. The antibody of claim 1, wherein the antibody comprises:

a) a heavy chain variable region (VH) comprising a sequence that is at least 95% identical to SEQ ID NO: 340 or 10; and

b) a light chain variable region (VL) comprising a sequence that is at least 95% identical to a sequence selected from SEQ ID NOs: 341, 11, 21, 281, 291, 561, 571, and 581.

3. The antibody of claim 1, wherein the antibody comprises:

a) a heavy chain variable region (VH) comprising the sequence of SEQ ID NO: 340 or 10; and

b) a light chain variable region (VL) comprising a sequence selected from SEQ ID NOs: 341, 11, 21, 281, 291, 561, 571, and 581.

4. The isolated antibody of any one of the preceding claims, wherein 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.

5. The isolated antibody of any one of the preceding claims, wherein 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.

6. The isolated antibody of any one of the preceding claims, wherein the antibody comprises:

a) a heavy chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 348 or SEQ ID NO: 602 and a light chain comprising an amino acid sequence that is at least 95%, at least 97%, or at least 99% identical to the sequence of SEQ ID NO: 349; or

b) 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.

7. An isolated antibody that binds to human Tau, 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.

8. An isolated antibody that binds to human Tau, 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.

9. The isolated antibody of any one of the preceding claims, wherein the antibody is a humanized antibody.

10. The isolated antibody of any one of the preceding claims, wherein the antibody is an IgG1 or an IgG4 antibody.

11. The isolated antibody of claim 10, wherein the antibody is an IgG4 antibody.

12. The isolated antibody of claim 11, wherein the antibody comprises M252Y, S254T, and T256E mutations.

13. The isolated antibody of claim 11 or claim 12, wherein the antibody comprises an S228P mutation.

14. The isolated antibody of any one of claims 1 to 9, which is an antibody fragment.

15. The isolated antibody of any one of the preceding claims, 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.

16. The isolated antibody of any one of the preceding claims, wherein the human Tau comprises the sequence of SEQ ID NO: 2.

17. The isolated antibody of any one of the preceding claims, which binds cynomolgus monkey Tau (SEQ ID NO: 4).

18. An isolated nucleic acid that encodes the antibody of any one of the preceding claims.

19. A host cell comprising the nucleic acid of claim 18.

20. A method of producing an antibody comprising culturing the host cell of claim 19 under conditions suitable for producing the antibody.

21. An immunoconjugate comprising the isolated antibody of any one of claims 1 to 17 and a second therapeutic agent.

22. A labeled antibody comprising the antibody of any one of claims 1 to 17 and a detectable label.

23. A pharmaceutical composition comprising the isolated antibody of any one of claims 1 to 17 and a pharmaceutically acceptable carrier.

24. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for treating a Tau protein associated disease in an individual.

25. The use of claim 24, wherein the Tau protein associated disease is a tauopathy.

26. The use of claim 25, wherein the tauopathy is a neurodegenerative tauopathy.

27. The use of claim 25 or claim 26, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down 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, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallervorden-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.

28. The use of any one of claims 25 to 27, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

29. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

30. Use of the antibody of any one of claims 1 to 17 or the pharmaceutical composition of claim 23 in the manufacture of a medicament for reducing the level of Tau protein, non-phosphorylated Tau protein, phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

31. The use of any one of claims 24 to 30, wherein the medicament is to be administered with at least one additional therapy.

32. The use of claim 31, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, Tau inhibitors, anti-amyloid beta antibodies, beta-amyloid aggregation inhibitors, anti-BACE1 antibodies, and BACE1 inhibitors.

33. The isolated antibody of any one of claims 1 to 17 for use as a medicament.

34. The isolated antibody of any one of claims 1 to 17 for use in treating a tauopathy in an individual.

35. The isolated antibody for use of claim 34, wherein the tauopathy is a neurodegenerative tauopathy.

36. The isolated antibody for use of claim 34 or claim 35, wherein the tauopathy is selected from Alzheimer's Disease, amyotrophic lateral sclerosis, Parkinson's disease, Creutzfeldt-Jacob disease, Dementia pugilistica, Down 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, frontotemporal dementia, frontotemporal dementia with parkinsonism linked to chromosome 17, Hallervorden-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.

37. The isolated antibody for use of any one of claims 34 to 36, wherein the tauopathy is Alzheimer's disease or progressive supranuclear palsy.

38. An isolated antibody of any one of claims 1 to 17 for use in retaining or increasing cognitive memory capacity or slowing memory loss in an individual with a Tau protein associated disease.

39. An isolated antibody of any one of claims 1 to 17 for use in reducing the level of Tau protein, phosphorylated Tau protein, non-phosphorylated Tau protein, or hyperphosphorylated Tau protein in an individual with a Tau protein associated disease.

40. The isolated antibody for use of any one of claims 34 to 39, wherein the antibody is for use with at least one additional therapy.

41. The isolated antibody for use of claim 40, wherein the additional therapy is selected from neurological drugs, corticosteroids, antibiotics, antiviral agents, anti-Tau antibodies, anti-amyloid beta antibodies, anti-BACE1 antibodies, and BACE1 inhibitors.

42. A method of detecting neurofibrillary tangles, neurophil threads, or dystrophic neuritis comprising contacting a sample with the antibody of any one of claims 1 to 17.

43. The method of claim 42, wherein the sample is a brain sample, a cerebrospinal fluid sample, or a blood sample.