A NI-105.4E4-VH (variable heavy chain sequence VH; SEQ ID NO: 9)

FR1----------CDR1-FR2----------CDR2---------
EVQLVESGGGLVQPGGSLKLSCAASGFNFNISAIHWVRQASGKGLEWVGRIRSKSHNYATLY

------FR3----------CDR3------FR4--------
AASLKGRFTLSRDDSRNTAYLQMSSLQTEDMAVYYCTVLSANYDTFDYWGQGTLVTVSS

NI-105.4E4-VL (variable light chain sequence VL; SEQ ID NO: 11)

FR1----------CDR1-------FR2----------CDR2---FR3----
SYELTQPPSVSVSPGQTARISCFGDTLPKQYTYWYQQKPGQAPVLVIYKDTERPSGIPERFS
LPV
----------CDR3------FR4-------
GSSSGTTVTLTISGVQAEDEADYYCLSADNSATWVFGGGTKVTVL

B NI-105.24B2-VH (variable heavy chain sequence VH; SEQ ID NO: 13)

FR1----------CDR1-FR2----------CDR2---------
QVQLVQSGAEVKKPGASVKVSCKASGYTFVNYIIHWVRQAPGQGLEWMGIINPNGGNTSYAE
E
----FR3----------CDR3--FR4--------
KFQARVTLTSDTSTSTVYMDLSSLTSEDTAVYYCAVLSPSNPWGQGTTVTVSS

NI-105.24B2-VL (variable light chain sequence VL; SEQ ID NO: 15)

FR1----------CDR1-------FR2----------CDR2---FR3----
SY**E**LTQPPSVSVSPGQTAGITCSGDALPKQFVYWYQKKPGQAPVLLIYKDTERPSRIPERFS
V
----------CDR3-------FR4-------
GSTSGTTVALTINGVQAEDEADYYCQSADRSGALWVFGGGTKLTVL

C NI-105.4A3-VH (variable heavy chain sequence VH; SEQ ID NO: 17)

FR1----------CDR1-FR2----------CDR2---------
QVQLVE**S**GGGAVQPGGSLRLSCAASGFTFSDYAMHWVRQAPGKGLQWVAVISYEGTYKYYAD
E **T**
----FR3----------CDR3----------FR4------
SVKGRFTISRDNSKNTLNLQMSSLRVEDTAVYFCVKARAFASGQRSTSTVPDYWGQGTLVTV

SS

NI-105.4A3-VL (variable light chain sequence VL; SEQ ID NO: 19)

FR1----------CDR1-------FR2----------CDR2---FR3----
SYELTQPPSVSVSPGQTARITCSGDALPKKYAYWYQQKSGQAPVLVIYEDNKRPSGIPERFS

----------CDR3-------FR4-------
GSSSGTVATLTISGAQVDDEADYYCYSTDISGDLRVFGGGTKLTVL

FIG. 1

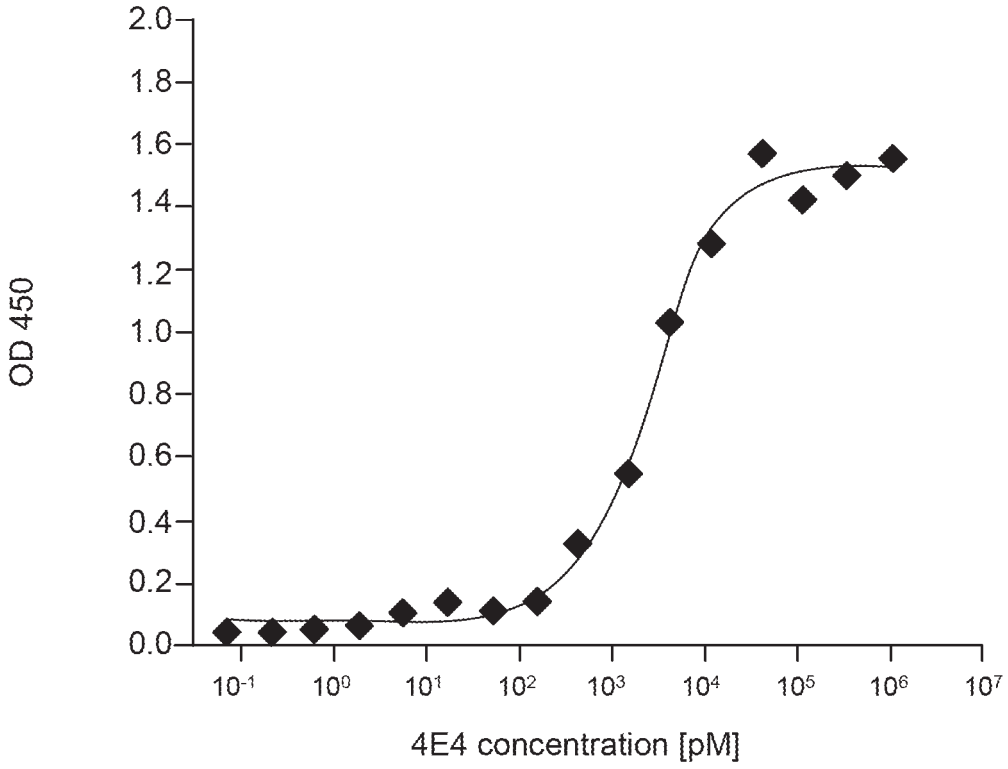

2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
OD 450
10-1
100
101
102
103
104
105
106
107
4E4 concentration [pM]

FIG. 2

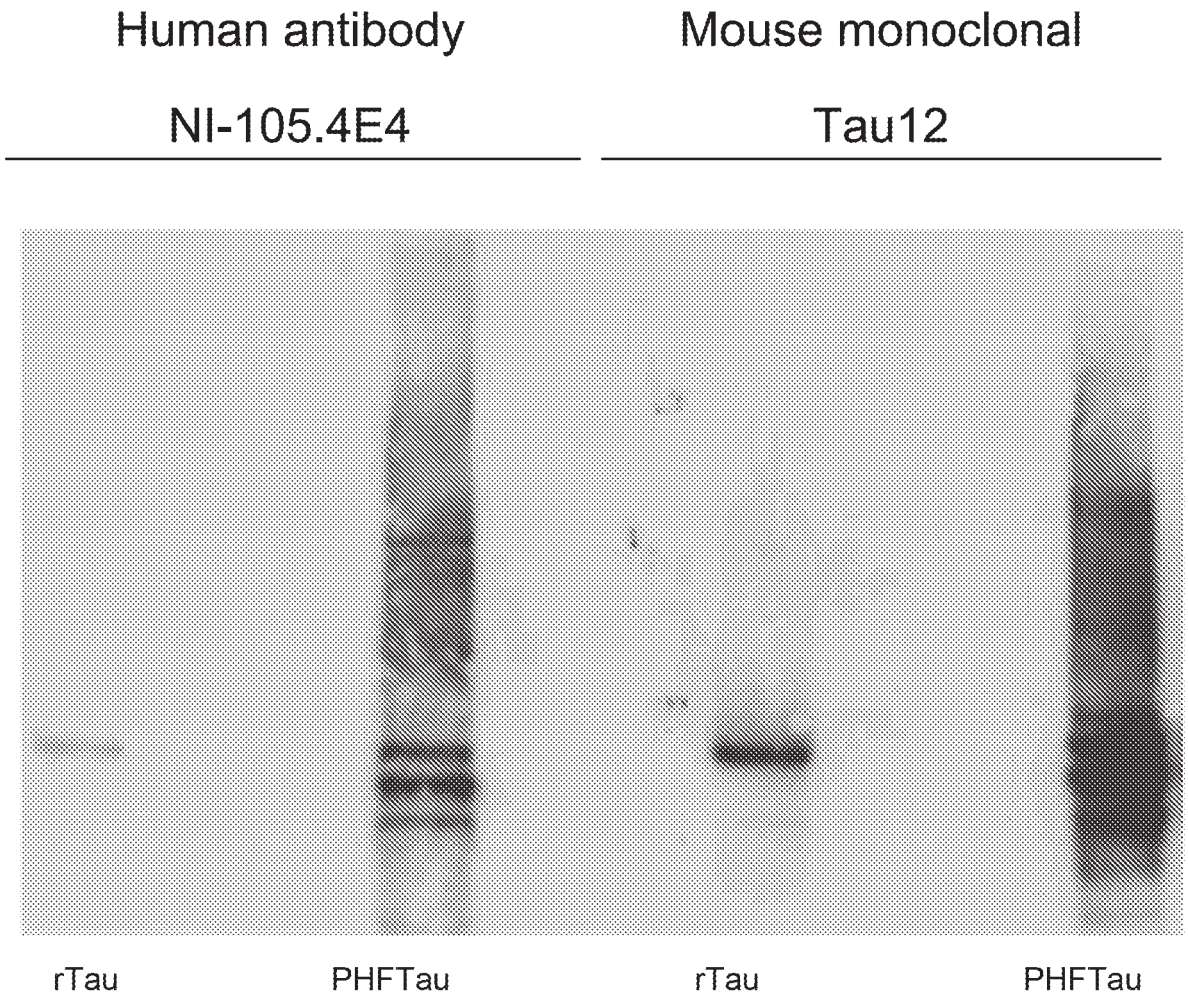

Human antibody
NI-105.4E4
Mouse monoclonal
Tau12
rTau
PHFTau
rTau
PHFTau

FIG. 3

FIG. 4A

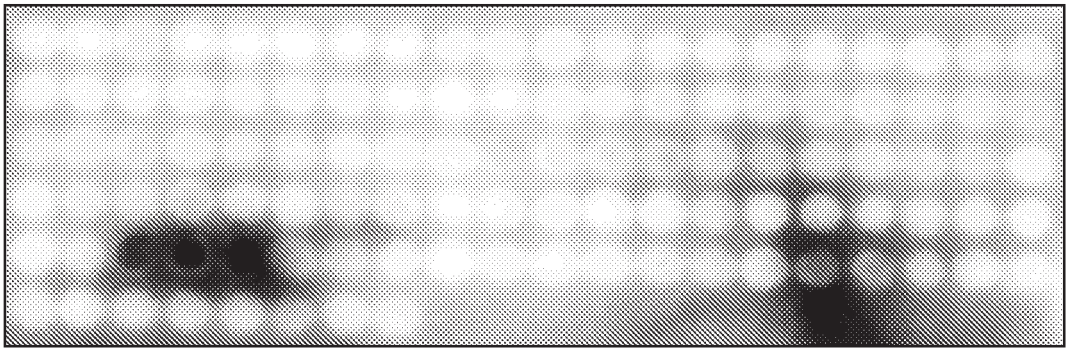


FIG. 4A'

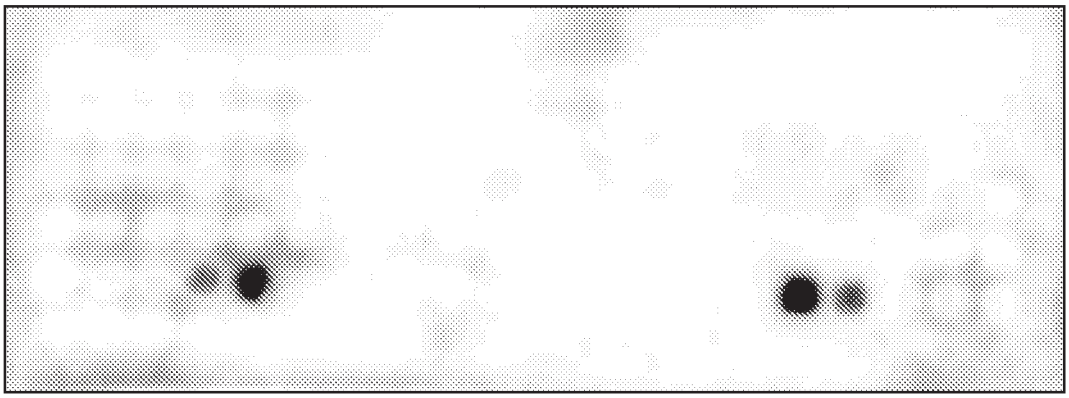


FIG. 4B

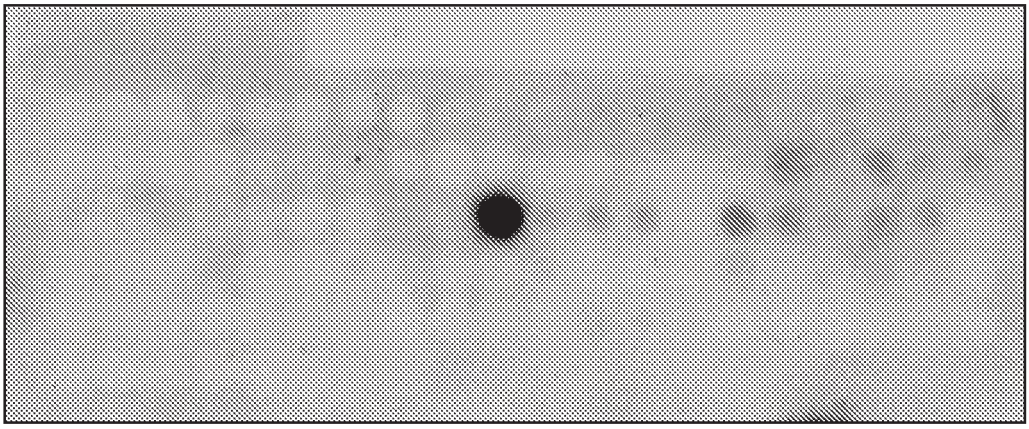


FIG. 4C

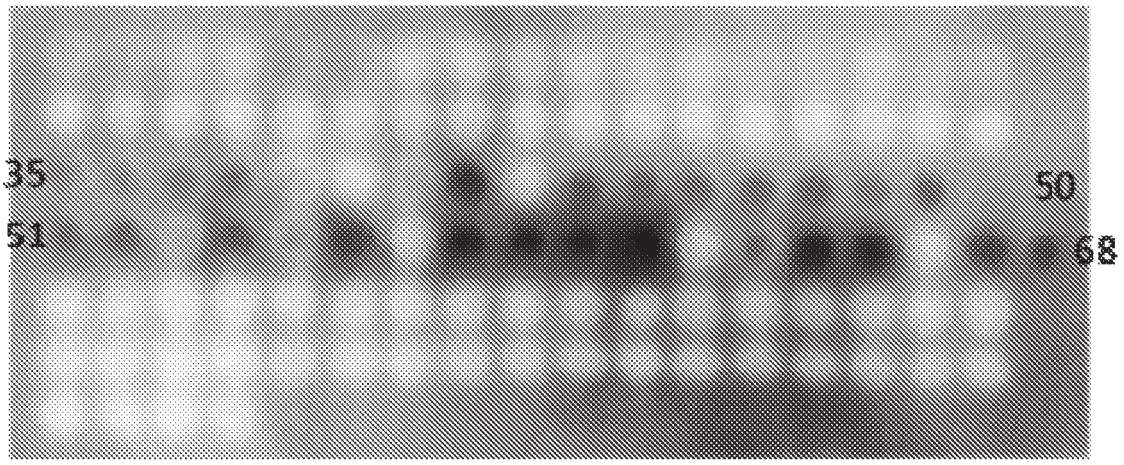


FIG. 4D

Alanine mutagenesis table 4E4 epitope

$_{335}$GQVEVK SEKLDFKDR$_{349}$

35	G	Q	V	E	V	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 43
36	**A**	Q	V	E	V	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 44
37	G	**A**	V	E	V	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 45
38	G	Q	**A**	E	V	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 46
39	G	Q	V	**A**	V	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 47
40	G	Q	V	E	**A**	K	S	E	K	L	D	F	K	D	R	SEQ ID NO: 48
41	G	Q	V	E	V	**A**	S	E	K	L	D	F	K	D	R	SEQ ID NO: 49
42	G	Q	V	E	V	K	**A**	E	K	L	D	F	K	D	R	SEQ ID NO: 50
43	G	Q	V	E	V	K	S	**A**	K	L	D	F	K	D	R	SEQ ID NO: 51
44	G	Q	V	E	V	K	S	E	**A**	L	D	F	K	D	R	SEQ ID NO: 52
45	G	Q	V	E	V	K	S	E	K	**A**	D	F	K	D	R	SEQ ID NO: 53
46	G	Q	V	E	V	K	S	E	K	L	**A**	F	K	D	R	SEQ ID NO: 54
47	G	Q	V	E	V	K	S	E	K	L	D	**A**	K	D	R	SEQ ID NO: 55
48	G	Q	V	E	V	K	S	E	K	L	D	F	**A**	D	R	SEQ ID NO: 56
49	G	Q	V	E	V	K	S	E	K	L	D	F	K	**A**	R	SEQ ID NO: 57
50	G	Q	V	E	V	K	S	E	K	L	D	F	K	D	**A**	SEQ ID NO: 58

FIG. 4E

Alanine mutagenesis table 4E4 epitope

383 KAKT**D**HGA **E**IVY**K**SP 397

51	K	A	K	T	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 59
52	**A**	A	K	T	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 60
53	K	**G**	K	T	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 61
54	K	**P**	K	T	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 62
55	K	A	**A**	T	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 63
56	K	A	K	**A**	D	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 64
57	K	A	K	T	**A**	H	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 65
58	K	A	K	T	D	**A**	G	A	E	I	V	Y	K	S	P	SEQ ID NO: 66
59	K	A	K	T	D	H	**A**	A	E	I	V	Y	K	S	P	SEQ ID NO: 67
60	K	A	K	T	D	H	G	**G**	E	I	V	Y	K	S	P	SEQ ID NO: 68
61	K	A	K	T	D	H	G	**P**	E	I	V	Y	K	S	P	SEQ ID NO: 69
62	K	A	K	T	D	H	G	A	**A**	I	V	Y	K	S	P	SEQ ID NO: 70
63	K	A	K	T	D	H	G	A	E	**A**	V	Y	K	S	P	SEQ ID NO: 71
64	K	A	K	T	D	H	G	A	E	I	**A**	Y	K	S	P	SEQ ID NO: 72
65	K	A	K	T	D	H	G	A	E	I	V	**A**	K	S	P	SEQ ID NO: 73
66	K	A	K	T	D	H	G	A	E	I	V	Y	**A**	S	P	SEQ ID NO: 74
67	K	A	K	T	D	H	G	A	E	I	V	Y	K	**A**	P	SEQ ID NO: 75
68	K	A	K	T	D	H	G	A	E	I	V	Y	K	S	**A**	SEQ ID NO: 76

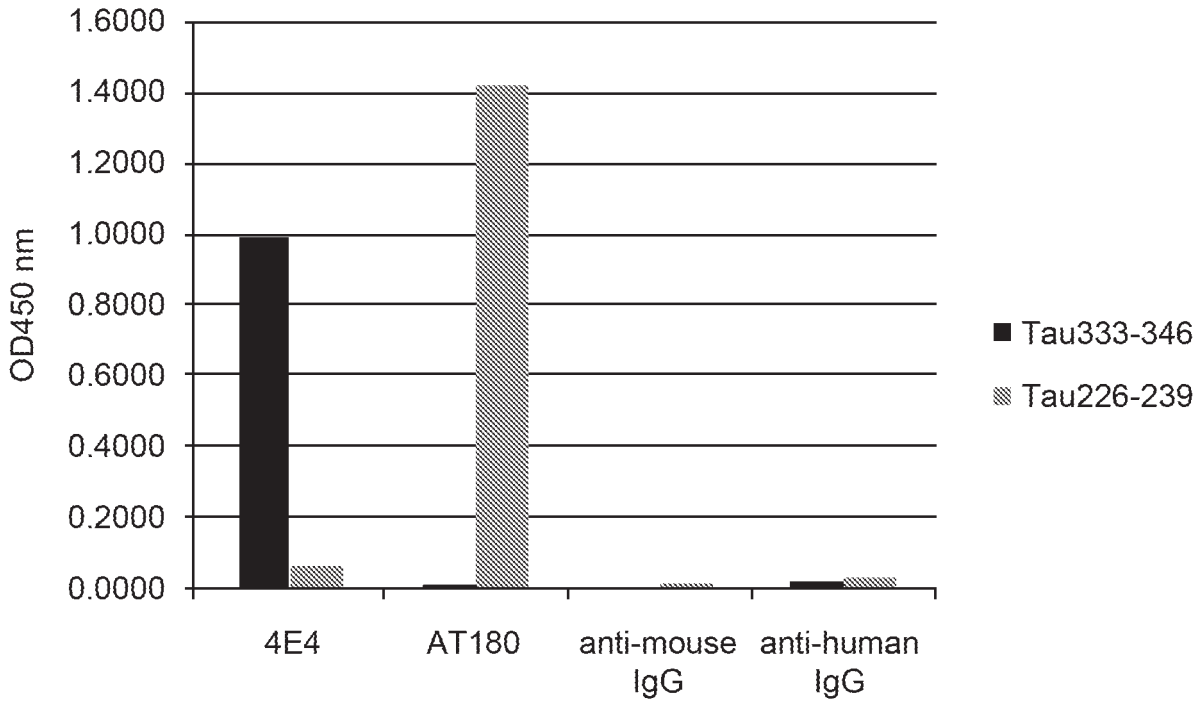

1.6000
1.4000
1.2000
1.0000
0.8000
0.6000
0.4000
0.2000
0.0000
OD450 nm
4E4
AT180
anti-mouse IgG
anti-human IgG
Tau333-346
Tau226-239

FIG. 5

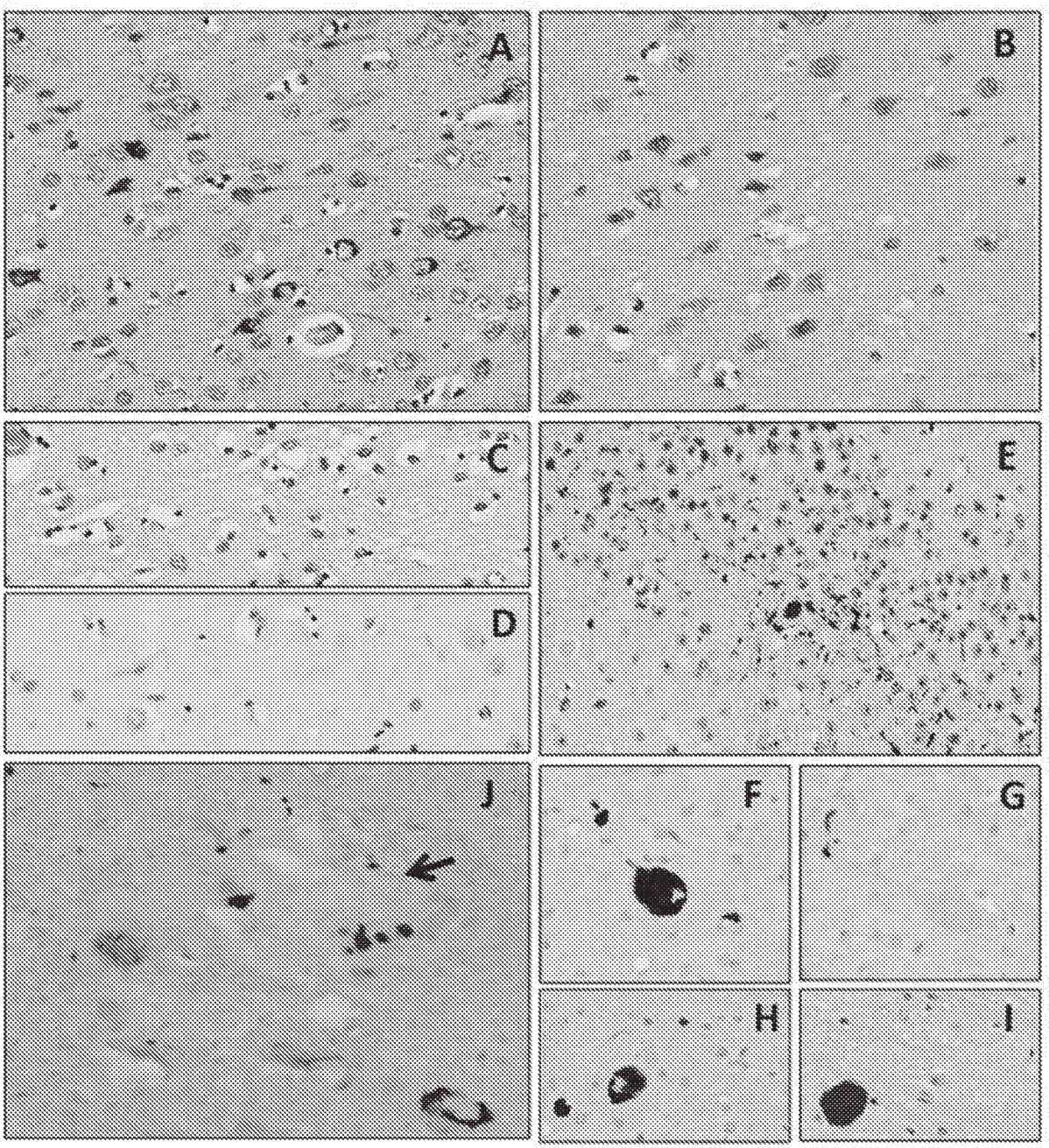


FIG. 6

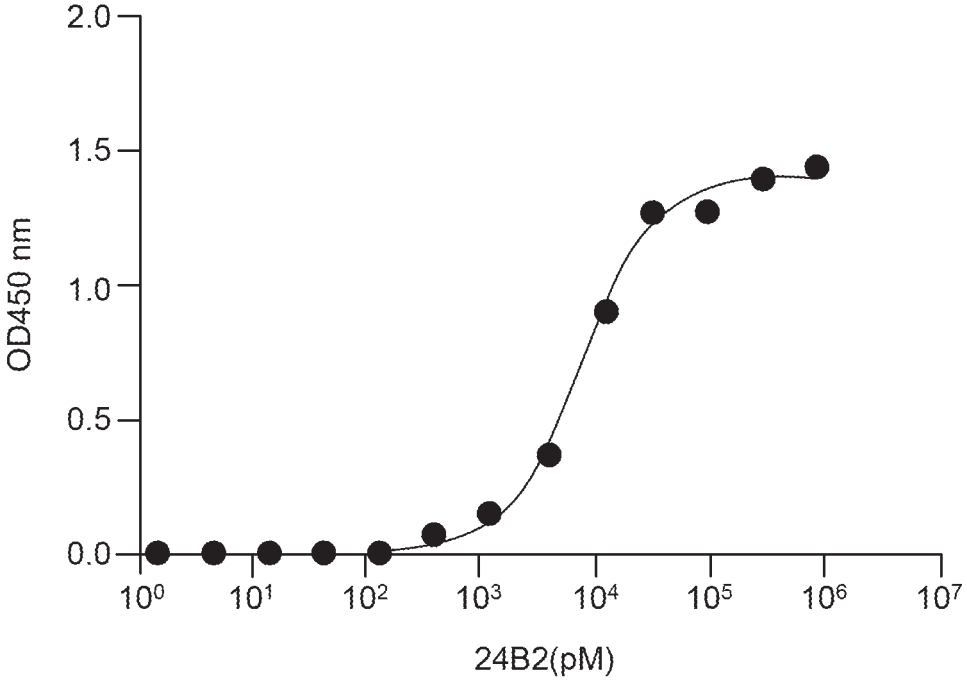


FIG. 7

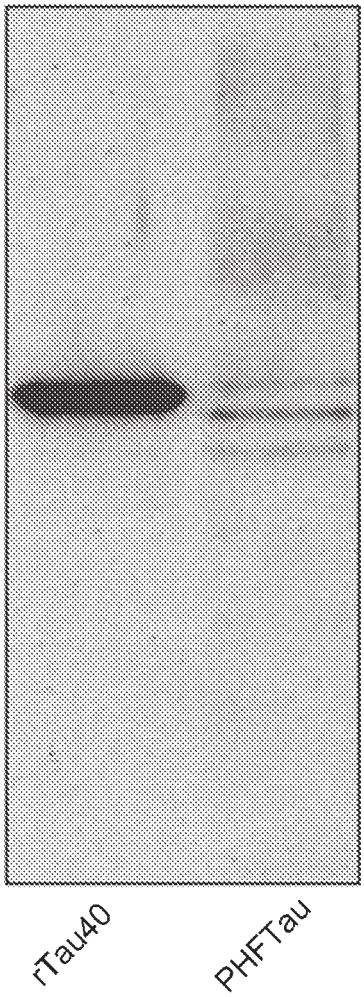


FIG. 8

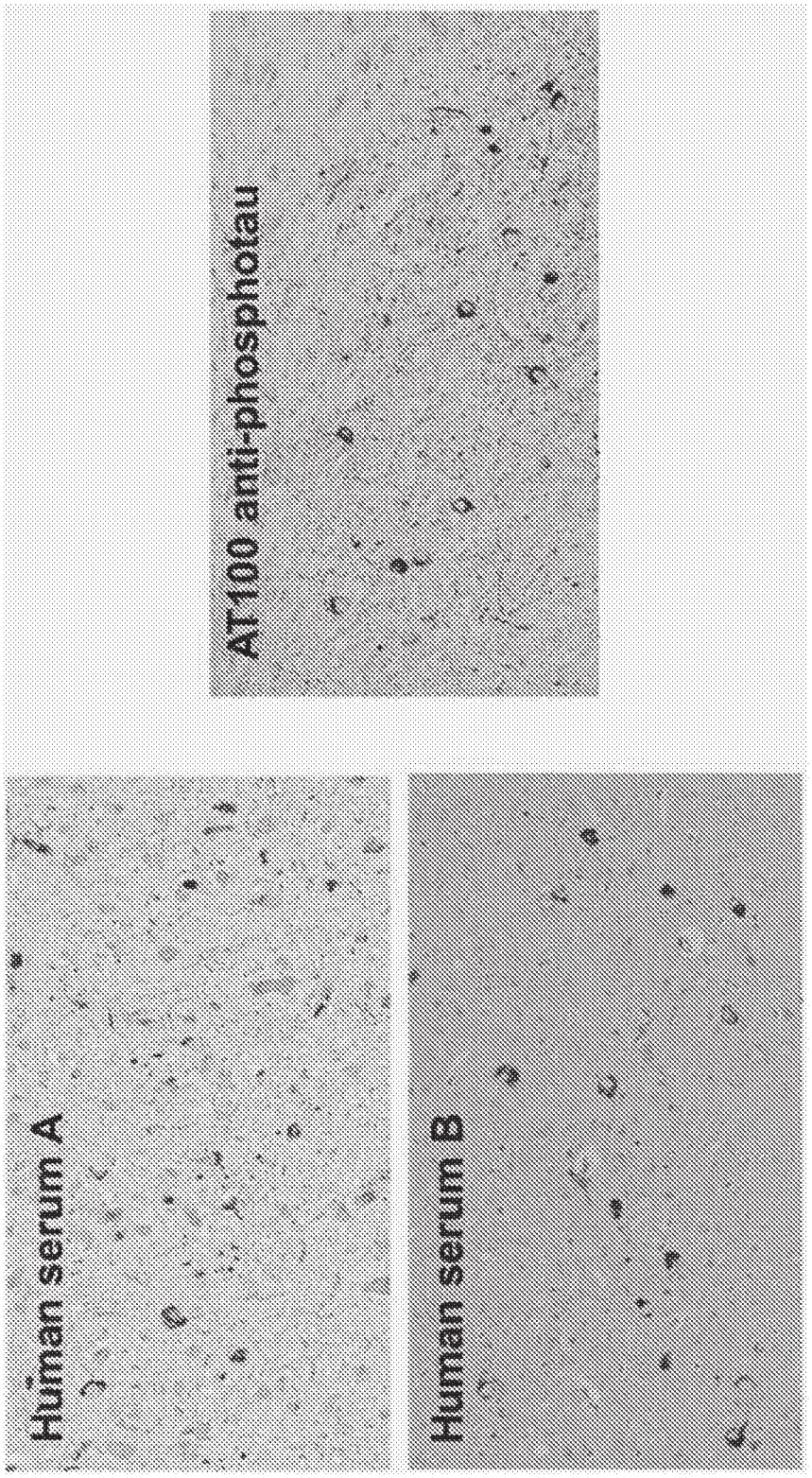


FIG. 9

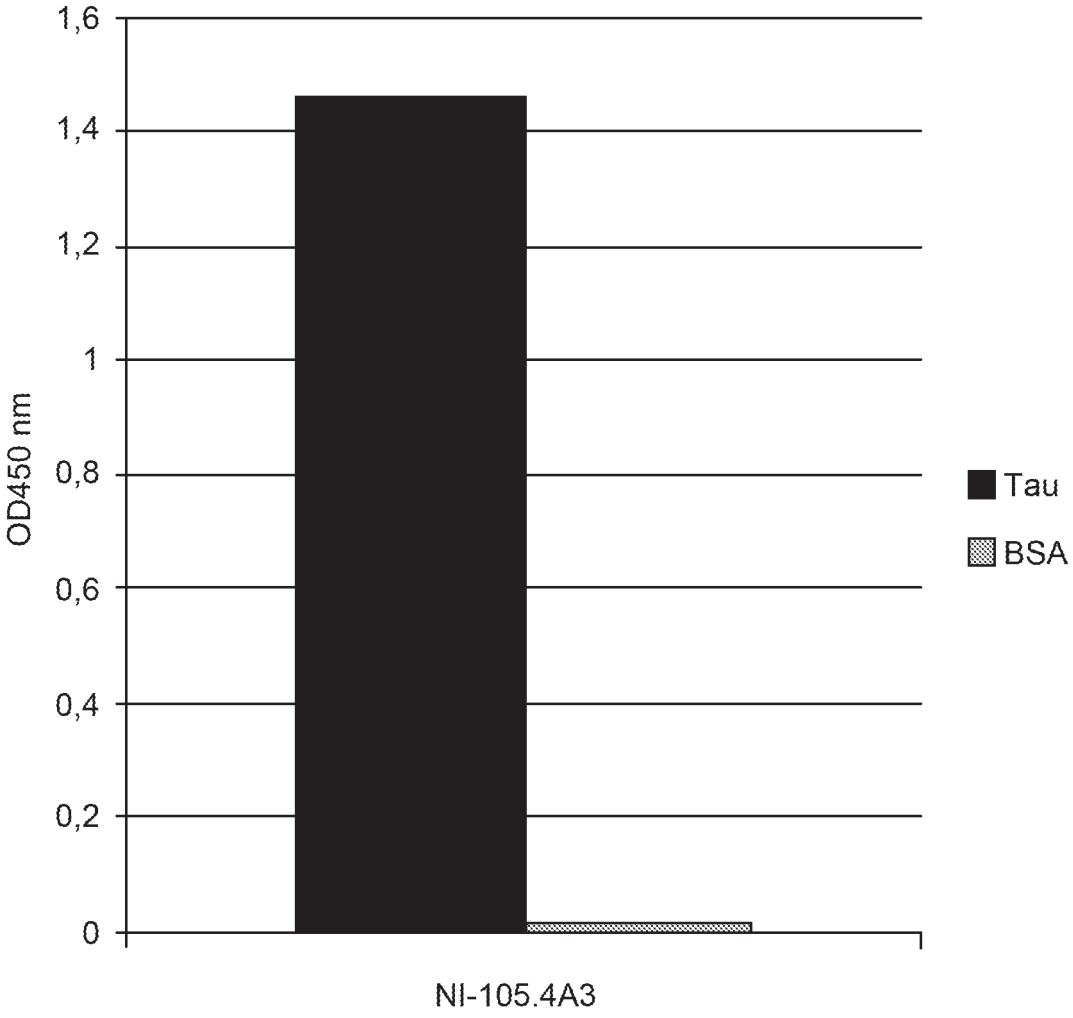


FIG. 10

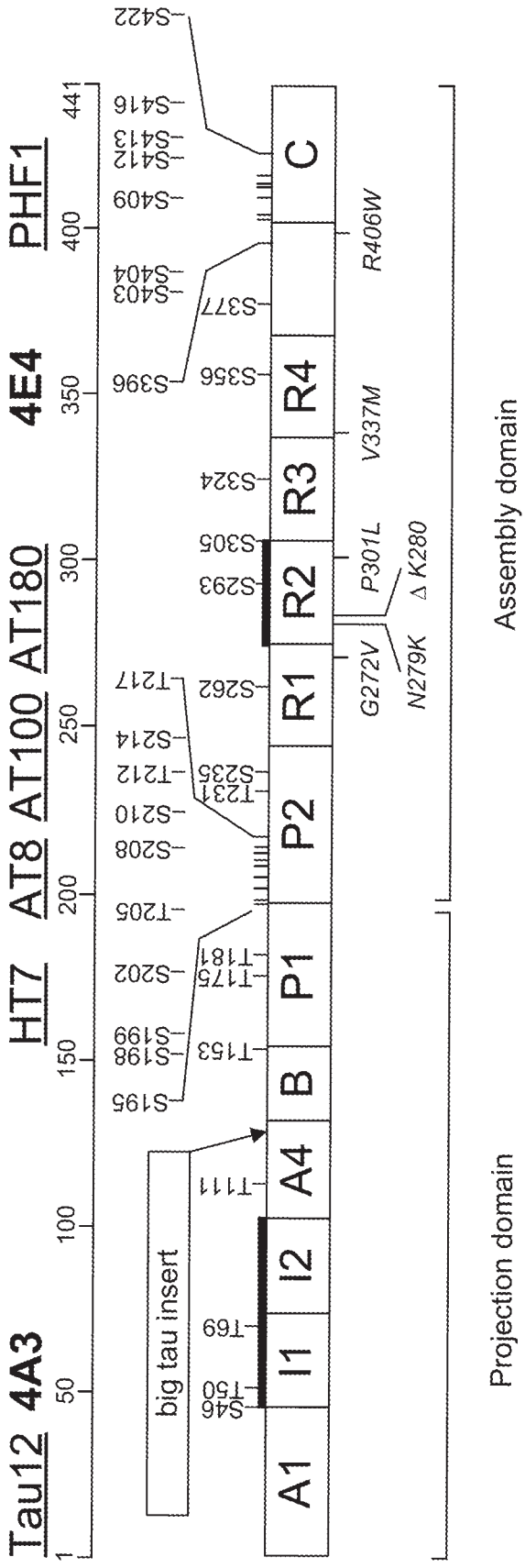

Tau12 4A3 HT7 AT8 AT100 AT180 4E4 PHF1
1 50 100 150 200 250 300 350 400 441
A1 I1 I2 A4 B P1 P2 R1 R2 R3 R4 C
big tau insert
S46 T50 T69 T111 S195 T153 S198 S199 T175 T181 S202 T205 S208 T212 T231 S235 S210 S214 T217 S262 S293 S305 S324 S356 S377 S396 S403 S404 S409 S412 S413 S416 S422
G272V N279K P301L Δ K280 V337M R406W
Assembly domain
Projection domain

FIG. 11

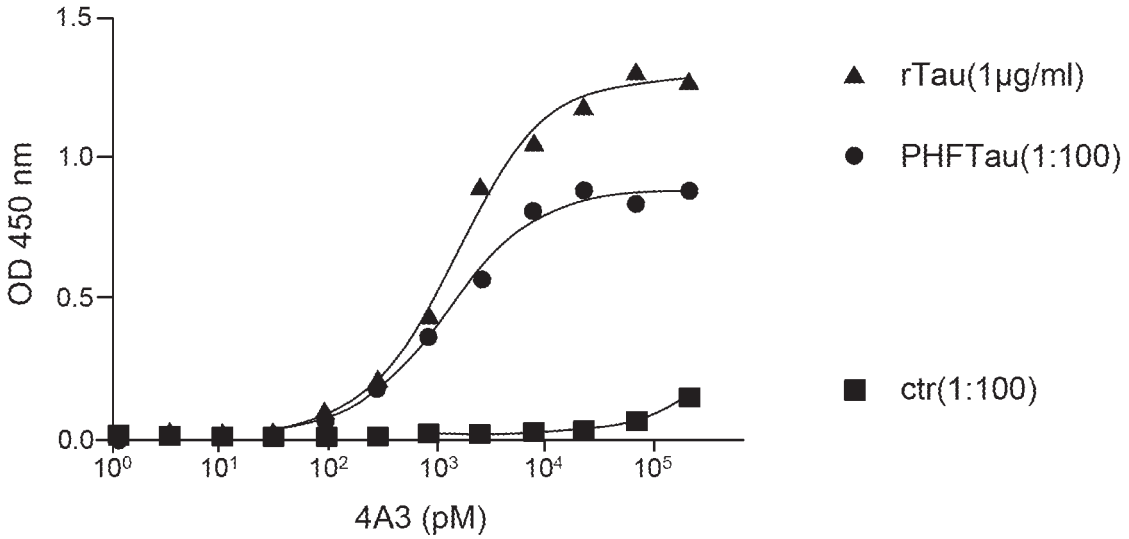

1.5
1.0
0.5
0.0
OD 450 nm
10^0
10^1
10^2
10^3
10^4
10^5
4A3 (pM)
rTau(1µg/ml)
PHFTau(1:100)
ctr(1:100)

FIG. 12

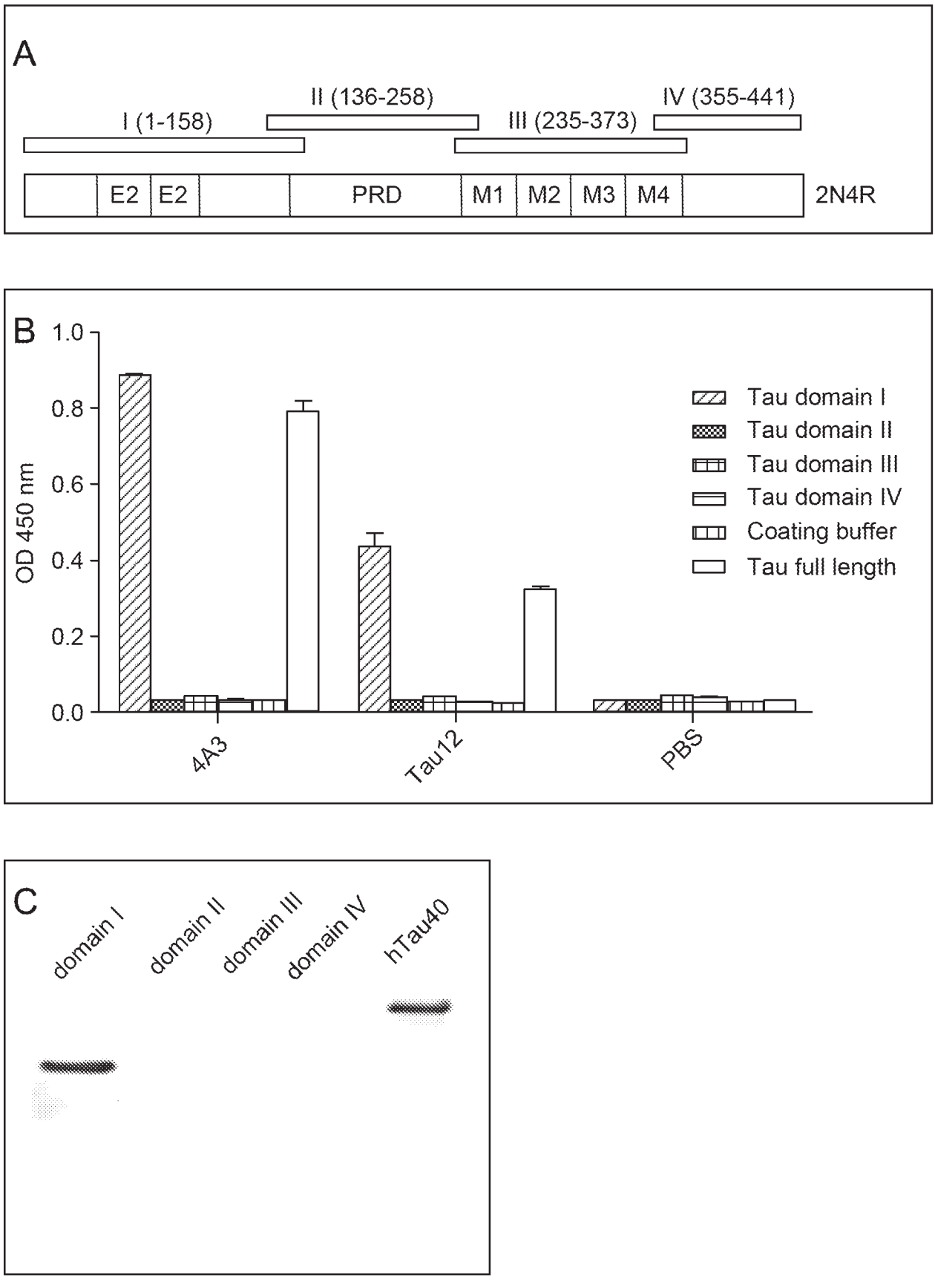
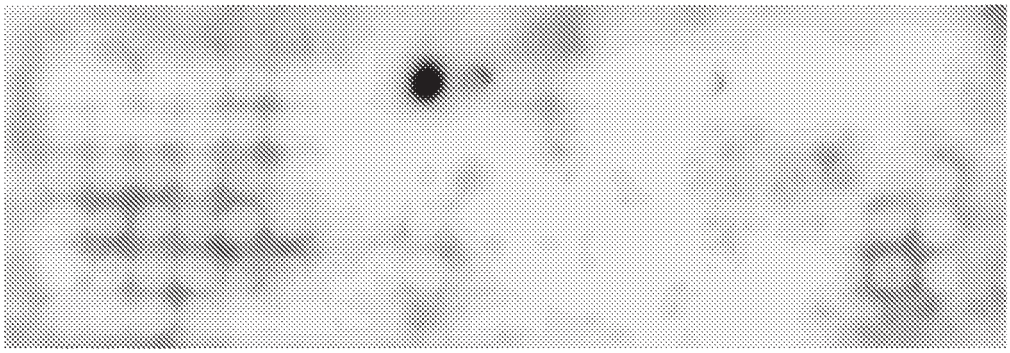
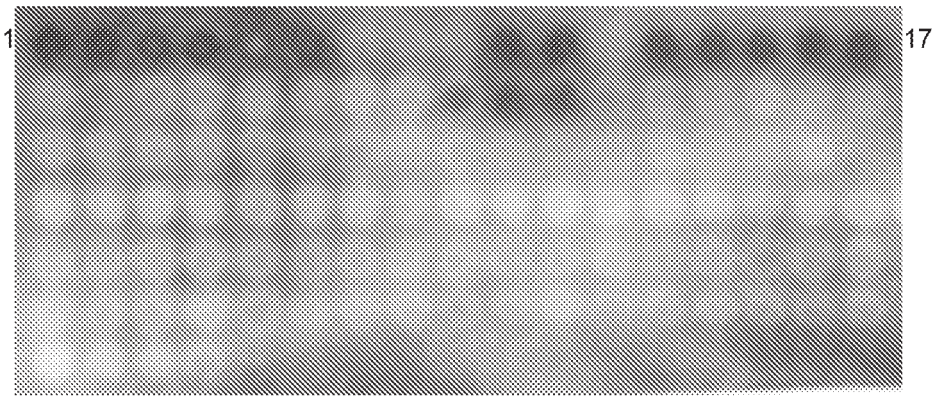

A
I (1-158)
II (136-258)
III (235-373)
IV (355-441)
E2
E2
PRD
M1
M2
M3
M4
2N4R
B
OD 450 nm
1.0
0.8
0.6
0.4
0.2
0.0
Tau domain I
Tau domain II
Tau domain III
Tau domain IV
Coating buffer
Tau full length
4A3
Tau12
PBS
C
domain I
domain II
domain III
domain IV
hTau40

FIG. 13

A



B



C

Alanine Mutagenesis Table

1	Q	E	G	D	T	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 42
2	**A**	E	G	D	T	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 77
3	Q	**A**	G	D	T	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 78
4	Q	E	**A**	D	T	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 79
5	Q	E	G	**A**	T	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 80
6	Q	E	G	D	**A**	D	A	G	L	K	E	S	P	L	Q	SEE ID NO: 81
7	Q	E	G	D	T	**A**	A	G	L	K	E	S	P	L	Q	SEE ID NO: 82
8	Q	E	G	D	T	D	**G**	G	L	K	E	S	P	L	Q	SEE ID NO: 83
9	Q	E	G	D	T	D	**P**	G	L	K	E	S	P	L	Q	SEE ID NO: 84
10	Q	E	G	D	T	D	A	**A**	L	K	E	S	P	L	Q	SEE ID NO: 85
11	Q	E	G	D	T	D	A	G	**A**	K	E	S	P	L	Q	SEE ID NO: 86
12	Q	E	G	D	T	D	A	G	L	**A**	E	S	P	L	Q	SEE ID NO: 87
13	Q	E	G	D	T	D	A	G	L	K	**A**	S	P	L	Q	SEE ID NO: 88
14	Q	E	G	D	T	D	A	G	L	K	E	**A**	P	L	Q	SEE ID NO: 89
15	Q	E	G	D	T	D	A	G	L	K	E	S	**A**	L	Q	SEE ID NO: 90
16	Q	E	G	D	T	D	A	G	L	K	E	S	P	**A**	Q	SEE ID NO: 91
17	Q	E	G	D	T	D	A	G	L	K	E	S	P	L	**A**	SEE ID NO: 92

FIG. 14

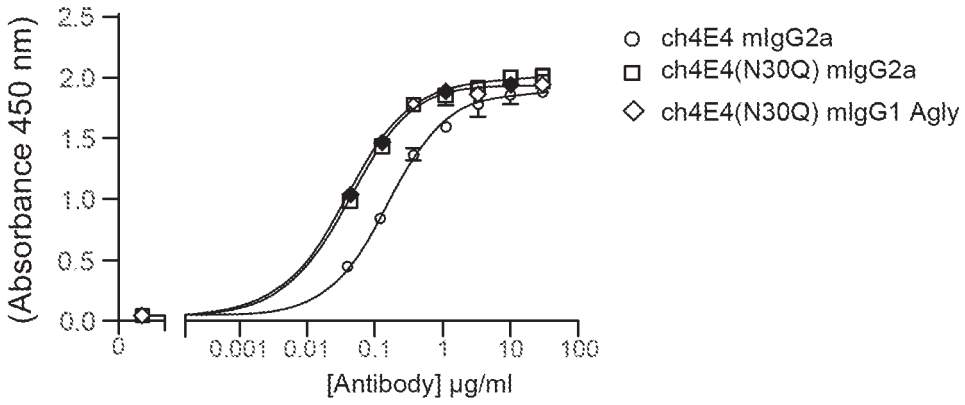

(Absorbance 450 nm)
2.5
2.0
1.5
1.0
0.5
0.0
0
0.001
0.01
0.1
1
10
100
[Antibody] µg/ml
ch4E4 mIgG2a
ch4E4(N30Q) mIgG2a
ch4E4(N30Q) mIgG1 Agly

FIG. 15

FIG. 16

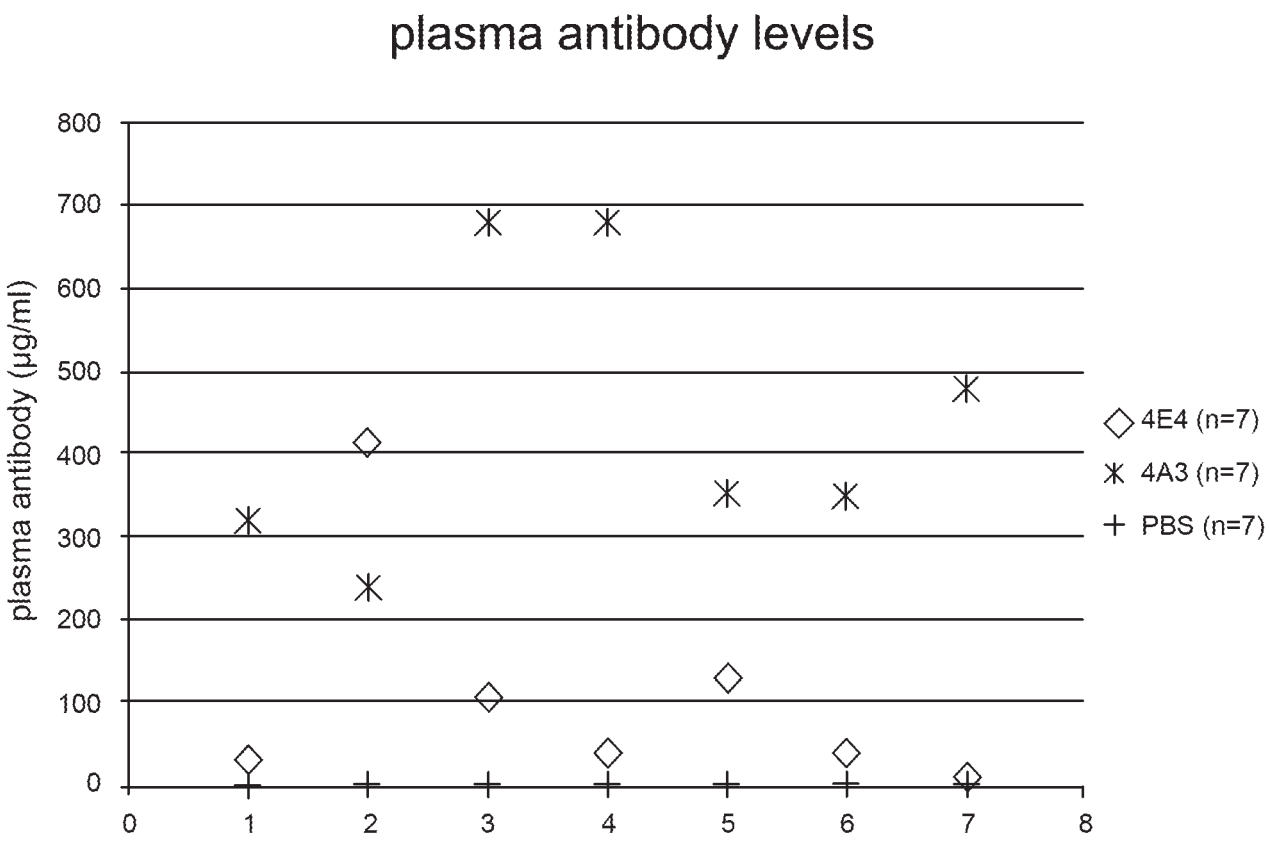
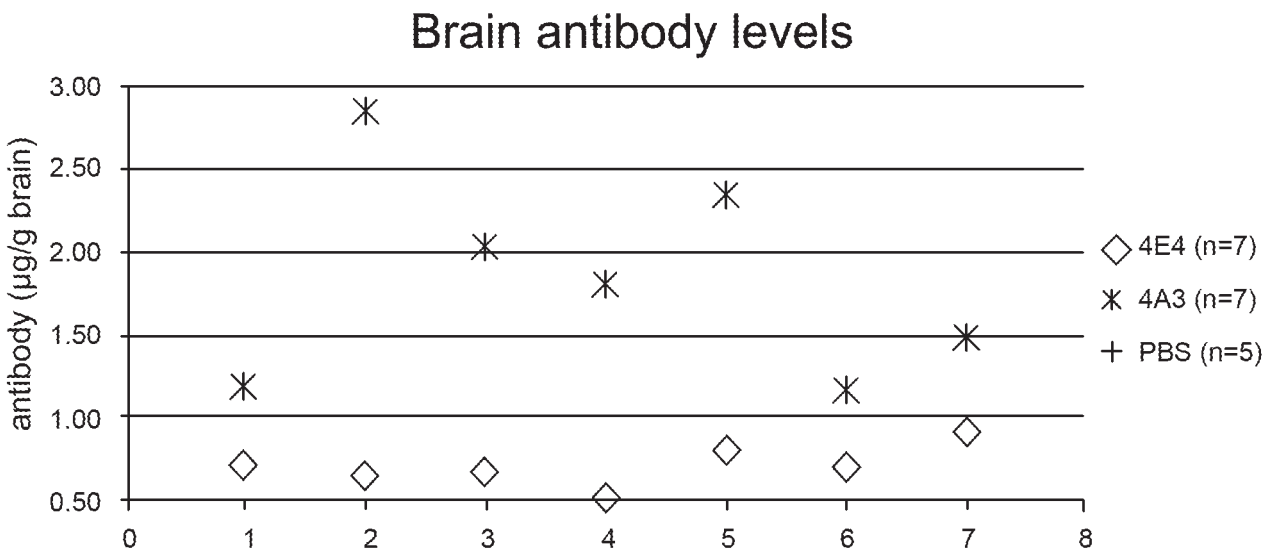

plasma antibody levels
plasma antibody (µg/ml)
800
700
600
500
400
300
200
100
0
0 1 2 3 4 5 6 7 8
4E4 (n=7)
4A3 (n=7)
PBS (n=7)

FIG. 17


Brain antibody levels
antibody (µg/g brain)
3.00
2.50
2.00
1.50
1.00
0.50
0 1 2 3 4 5 6 7 8
4E4 (n=7)
4A3 (n=7)
PBS (n=5)