SUBSTITUTE SHEET (RULE 26)

Hybridoma IPN001 Heavy Chain Sequences

```
        E  V  Q  L   V  E  S   G  E  D   L  V  K  P   G  G  S   L  K  L
1   GAGGTGCAGT TGGTGGAGTC TGGGGAAGAC TTAGTGAAGC CTGGAGGGTC CCTGAAACTC
2

        S  C  V  A   S  G  F   A  F  S   S  Y  G  M   S  W  V   R  Q  T
61  TCCTGTGTCG CTTCTGGATT CGCTTTCAGT AGCTATGGCA TGTCTTGGGT TCGCCAGACT

        P  D  M  R   L  E  W   V  A  T   I  S  S  S   G  S  R   T  Y  F
121 CCAGACATGA GGCTGGAGTG GGTCGCAACA ATTAGTAGCA GTGGTAGTCG CACCTACTTT

        P  D  S  V   K  G  R   L  T  I   S  R  D  N   D  K  N   I  L  Y
181 CCAGACAGTG TGAAGGGGCG ACTCACCATC TCCAGAGACA ATGACAAGAA CATCCTATAC

        L  Q  M  S   S  L  R   S  E  D   T  A  M  Y   Y  C  T   I  T  W
241 CTACAAATGA GCAGTCTGAG GTCTGAGGAC ACAGCCATGT ACTATTGTAC GATTACCTGG

        D  G  A  M   D  Y  W   G  R  G   I  S  V  T   V  S  S (SEQ ID NO:14)
301 GACGGTGCTA TGGACTACTG GGGTCGTGGA ATATCAGTCA CCGTCTCCTC A (SEQ ID NO:18)
```

CDR definitions and protein sequence numbering according to Kabat numbering system.
CDRs, and nucleotide sequences encoding the CDRs, are in bold text and underlined.

FIG. 1A

SUBSTITUTE SHEET (RULE 26)

Hybridoma IPN001 Light Chain Sequences

```
        D  V  L  M   T  Q  T   P  L  S   L  A  V  N   L  G  D   Q  A  S
1   GATGTTTTGA TGACCCAAAC TCCGCTCTCC CTGGCAGTCA ATCTTGGAGA TCAAGCCTCC

        L  S  C  R   S  S  Q   T  I  L   H  S  N  G   N  T  Y   L  E  W
61  CTCTCTTGCA GATCGAGTCA GACTATTTTA CATAGTAATG GAAATACCTA TTTAGAATGG

        Y  L  Q  K   P  G  Q   S  P  R   L  L  I  Y   K  V  S   K  R  F
121 TATTTGCAGA AACCAGGCCA GTCTCCAAGA CTCCTGATCT ACAAAGTTTC TAAACGATTT

        S  G  V  P   D  R  F   S  G  S   G  S  G  T   D  F  T   L  K  I
181 TCTGGGGTCC CAGACAGGTT CAGTGGCAGT GGATCAGGGA CAGATTTCAC ACTCAAGATC

        S  R  V  E   A  D  D   L  G  I   Y  Y  C  F   Q  G  S   L  V  P
241 AGCAGAGTGG AGGCTGACGA TCTGGGAATT TATTACTGCT TCAAGGTTC ACTTGTTCCT

        W  A  F  G   G  G  T   K  L  E   I  K  (SEQ ID NO:13)
301 TGGGCGTTCG GTGGAGGCAC CAAGCTGGAA ATCAAA (SEQ ID NO:17)
```

CDR definitions and protein sequence numbering according to Kabat numbering system.
CDRs, and nucleotide sequences encoding the CDRs, are in bold text and underlined.

FIG. 1B

SUBSTITUTE SHEET (RULE 26)

Hybridoma IPN002 Heavy Chain Sequences

```
        E  V  H  L  V  E  S  G  G  A  L  V  K  P  G  G  S  L  K  L
1   GAGGTTCATC TGGTGGAGTC TGGGGGAGCC TTAGTGAAGC CTGGAGGGTC CCTGAAACTC

        S  C  A  A  S  G  F  S  F  S  K  Y  G  M  S  W  V  R  Q  T
61  TCCTGTGCAG CCTCTGGATT CAGTTTCAGT AAATATGGCA TGTCTTGGGT TCGCCAGACT

        P  D  K  R  L  E  W  V  A  T  I  S  S  S  G  S  R  T  Y  Y
121 CCAGACAAGA GGCTGGAGTG GGTCGCAACC ATTAGTAGTA GTGGGAGTCG CACCTACTAT

        P  D  S  V  K  G  Q  F  T  I  S  R  D  N  A  K  N  T  L  Y
181 CCAGACAGTG TGAAGGGCCA ATTCACCATC TCCAGAGACA ATGCCAAGAA CACCCTGTAC

        L  Q  M  S  S  L  K  S  E  D  T  A  M  Y  Y  C  S  I  S  W
241 CTGCAAATGA GCAGTCTGAA GTCTGAGGAC ACAGCCATGT ATTACTGTTC AATTAGCTGG

        D  G  A  M  D  Y  W  G  Q  G  T  S  V  T  V  S  S (SEQ ID NO:16)
301 GACGGTGCTA TGGACTACTG GGGTCAAGGG ACCTCAGTCA CCGTCTCCTC A (SEQ ID NO:20)
```

CDR definitions and protein sequence numbering according to Kabat numbering system.
CDRs, and nucleotide sequences encoding the CDRs, are in bold text and underlined.

FIG. 2A

SUBSTITUTE SHEET (RULE 26)

Hybridoma IPN002 Light Chain Sequences

```
          D  V  L  M   T  Q  T   P  L  S   L  P  V  S   L  G  D   Q  A  S
    1     GATGTTTTGA TGACCCAAAC TCCACTCTCC CTGCCTGTCA GTCTTGGAGA TCAAGCCTCC

          I  S  C  K   S  S  Q   S  I  V   H  S  N  G   N  T  Y   L  E  W
   61     ATCTCTTGCA AATCTAGTCA GAGCATTGTA CATAGTAATG GAAACACCTA TTTAGAATGG

          Y  L  Q  K   P  G  Q   S  P  K   L  L  V  Y   K  V  S   N  R  F
  121     TACCTGCAGA AACCAGGCCA GTCTCCAAAG CTCCTGGTCT ACAAAGTTTC CAATCGATTT

          S  G  V  P   D  R  F   S  G  S   G  S  G  T   D  F  T   L  K  I
  181     TCTGGGGTCC CAGACAGGTT CAGTGGCAGT GGATCAGGGA CAGATTTCAC ACTCAAGATC

          S  R  V  E   A  E  D   L  G  T   Y  Y  C  F   Q  G  S   L  V  P
  241     AGCAGAGTGG AGGCTGAGGA TCTGGGAACT TATTACTGCT TCAAGGTTC ACTTGTTCCT

          W  A  F  G   G  G  T   K  L  E   I  K  (SEQ ID NO:15)
  301     TGGGCGTTCG GTGGAGGCAC CAAGCTGGAA ATCAAA (SEQ ID NO:19)
```

CDR definitions and protein sequence numbering according to Kabat numbering system.
CDRs, and nucleotide sequences encoding the CDRs, are in bold text and underlined.

FIG. 2B

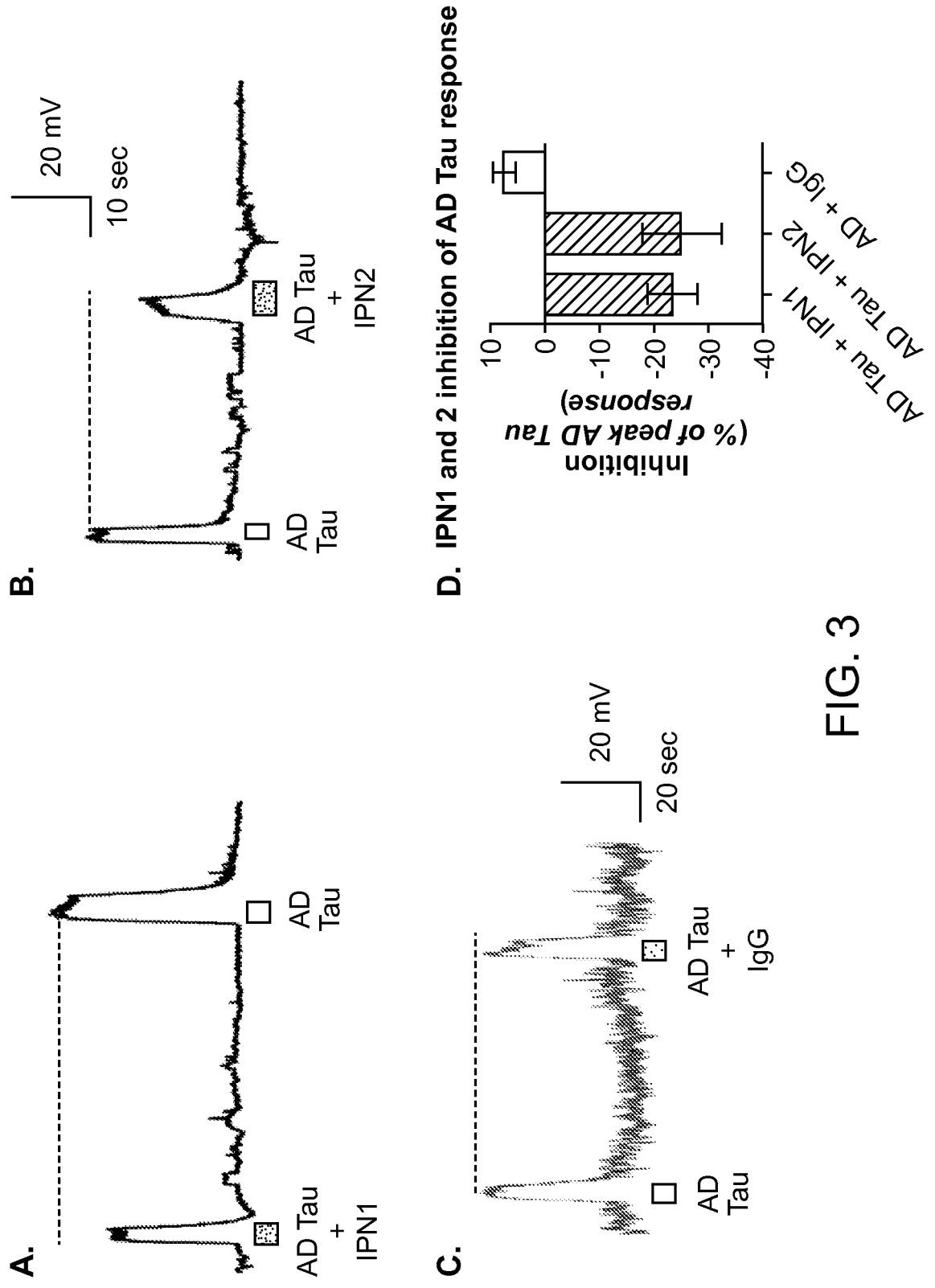

A.
AD Tau
+
IPN1
AD
Tau
B.
20 mV
10 sec
AD Tau
+
IPN2
AD
Tau
C.
20 mV
20 sec
AD Tau
+
IgG
AD
Tau
D. IPN1 and 2 inhibition of AD Tau response
Inhibition
(% of peak AD Tau
response)
10
0
-10
-20
-30
-40
AD Tau + IPN1
AD Tau + IPN2
AD + IgG

FIG. 3

SUBSTITUTE SHEET (RULE 26)

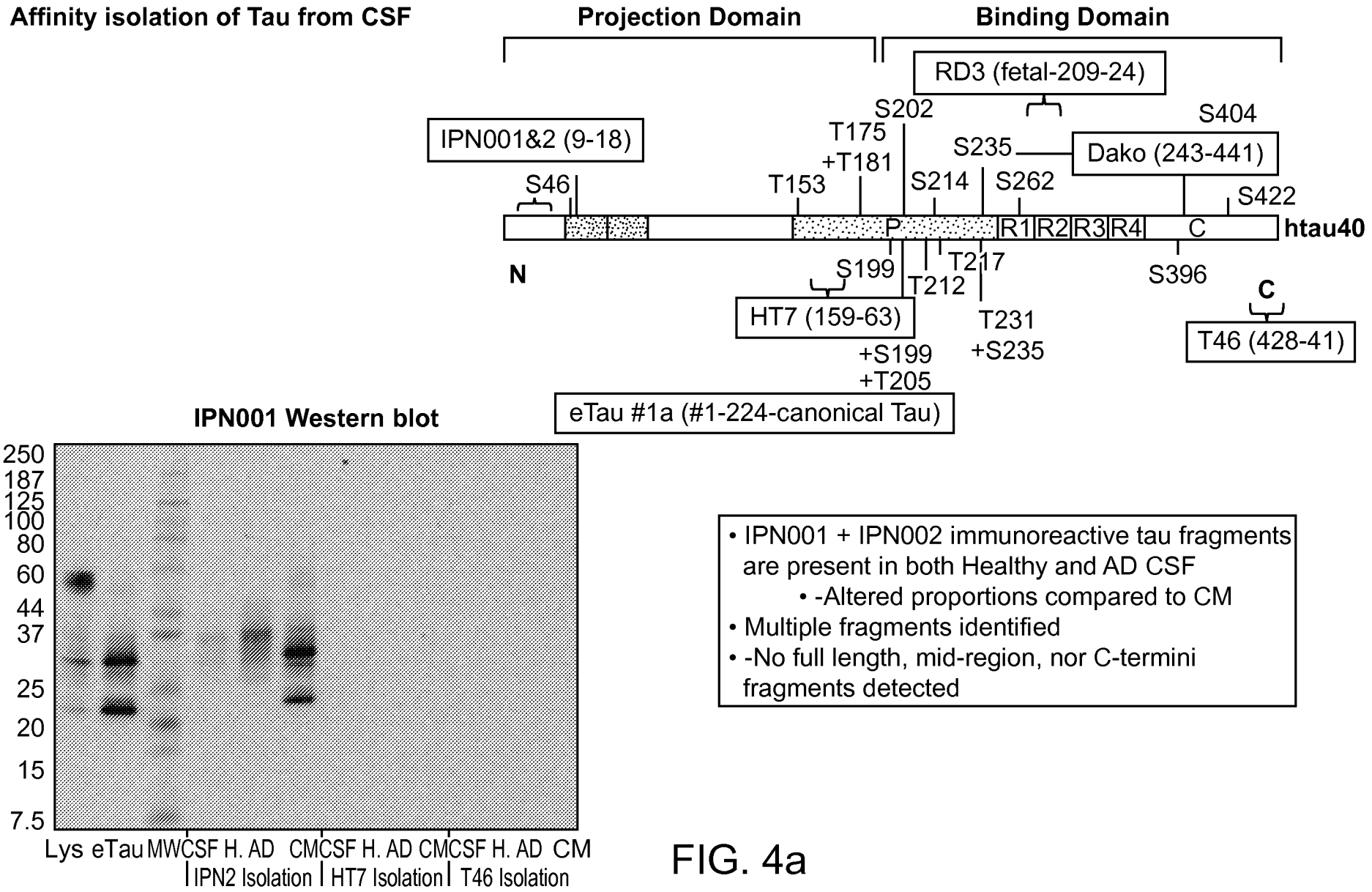


FIG. 4a

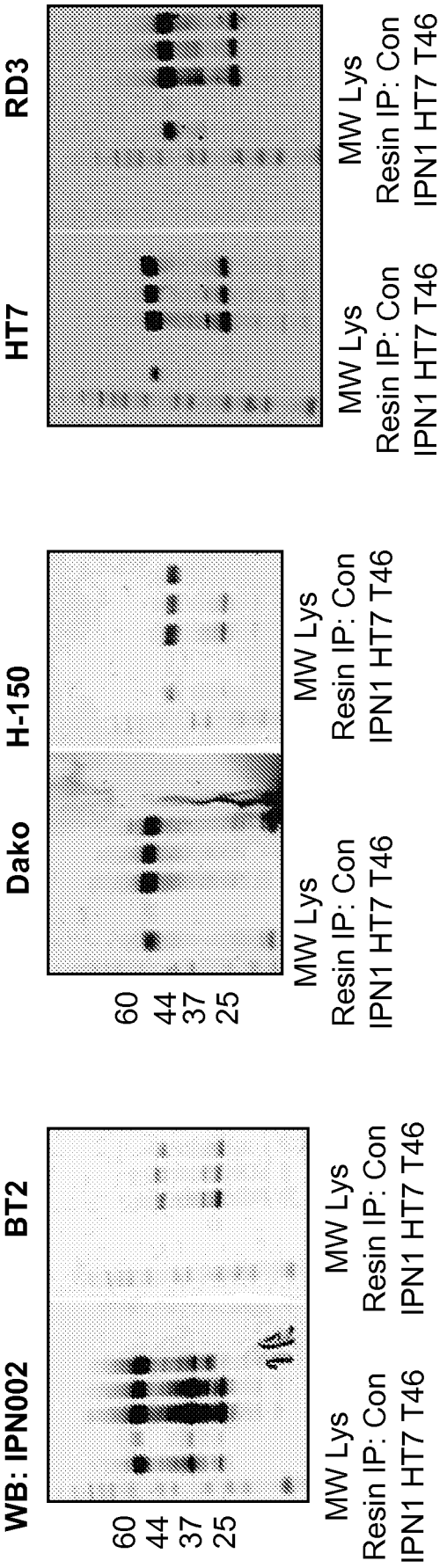

WB: IPN002
BT2
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
Dako
H-150
MW Lys
Resin IP: Con
IPN1 HT7 T46
HT7
RD3
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4a (Cont.)

SUBSTITUTE SHEET (RULE 26)

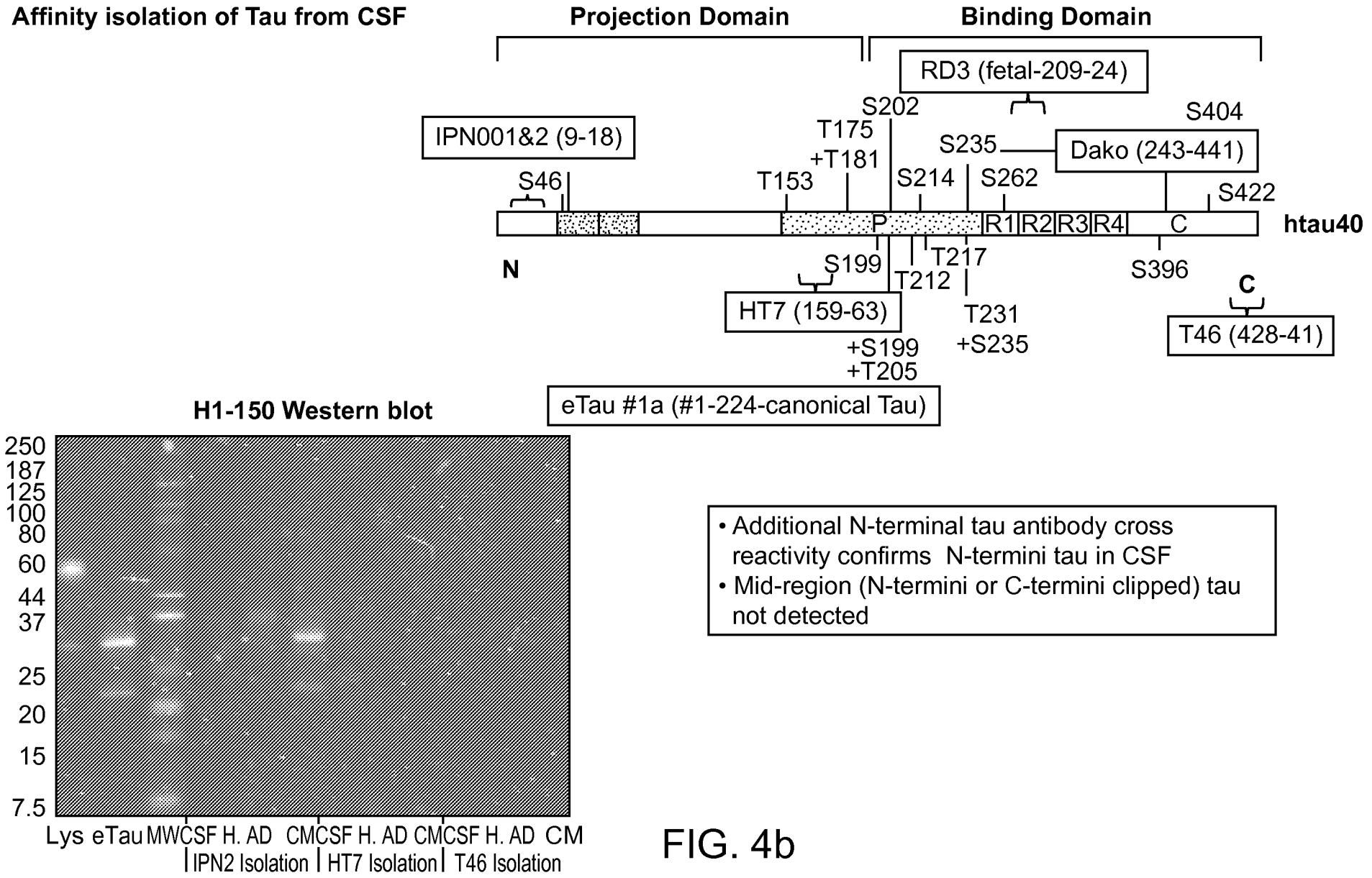


FIG. 4b

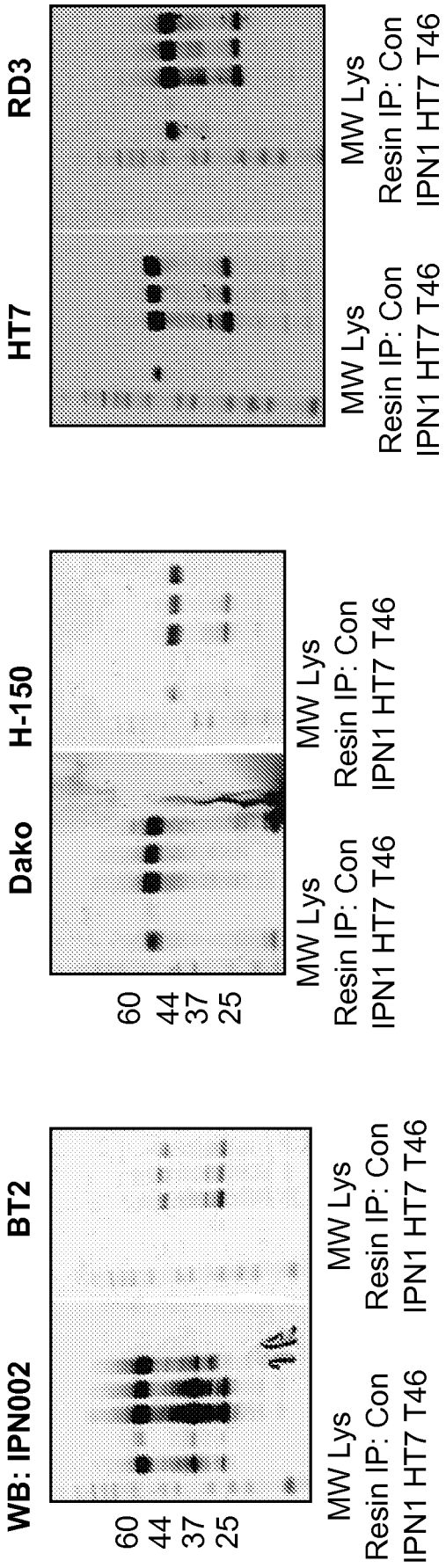

WB: IPN002
BT2
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
Dako
H-150
MW Lys
Resin IP: Con
IPN1 HT7 T46
HT7
RD3
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4b (Cont.)

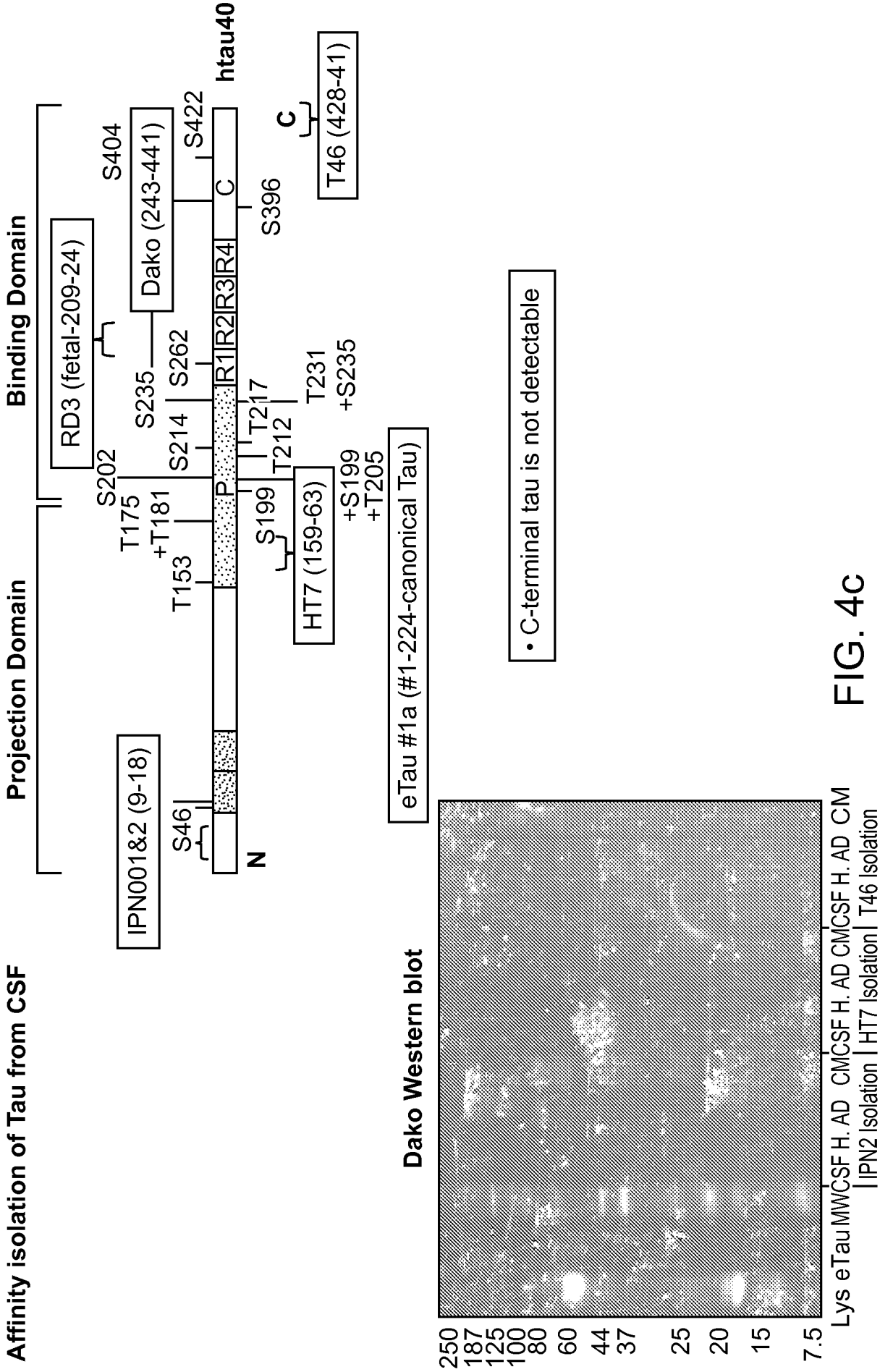

Affinity isolation of Tau from CSF
Projection Domain
Binding Domain
IPN001&2 (9-18)
RD3 (fetal-209-24)
Dako (243-441)
htau40
N
C
P
R1
R2
R3
R4
C
S46
T153
T175
+T181
S202
S214
S235
S262
S404
S422
S396
T46 (428-41)
S199
T212
T217
T231
+S235
HT7 (159-63)
+S199
+T205
eTau #1a (#1-224-canonical Tau)
• C-terminal tau is not detectable
Dako Western blot
250
187
125
100
80
60
44
37
25
20
15
7.5
Lys eTau MW CSF H. AD CM CSF H. AD CM CSF H. AD CM
IPN2 Isolation
HT7 Isolation
T46 Isolation

FIG. 4c

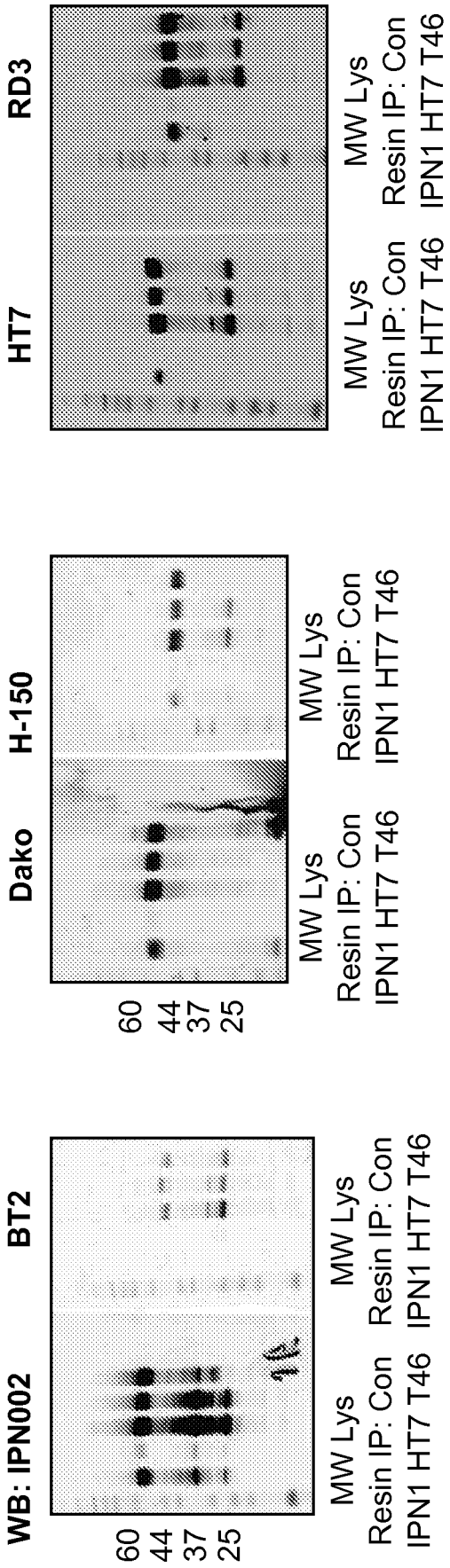

WB: IPN002
BT2
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
Dako
H-150
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
HT7
RD3
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4c (Cont.)

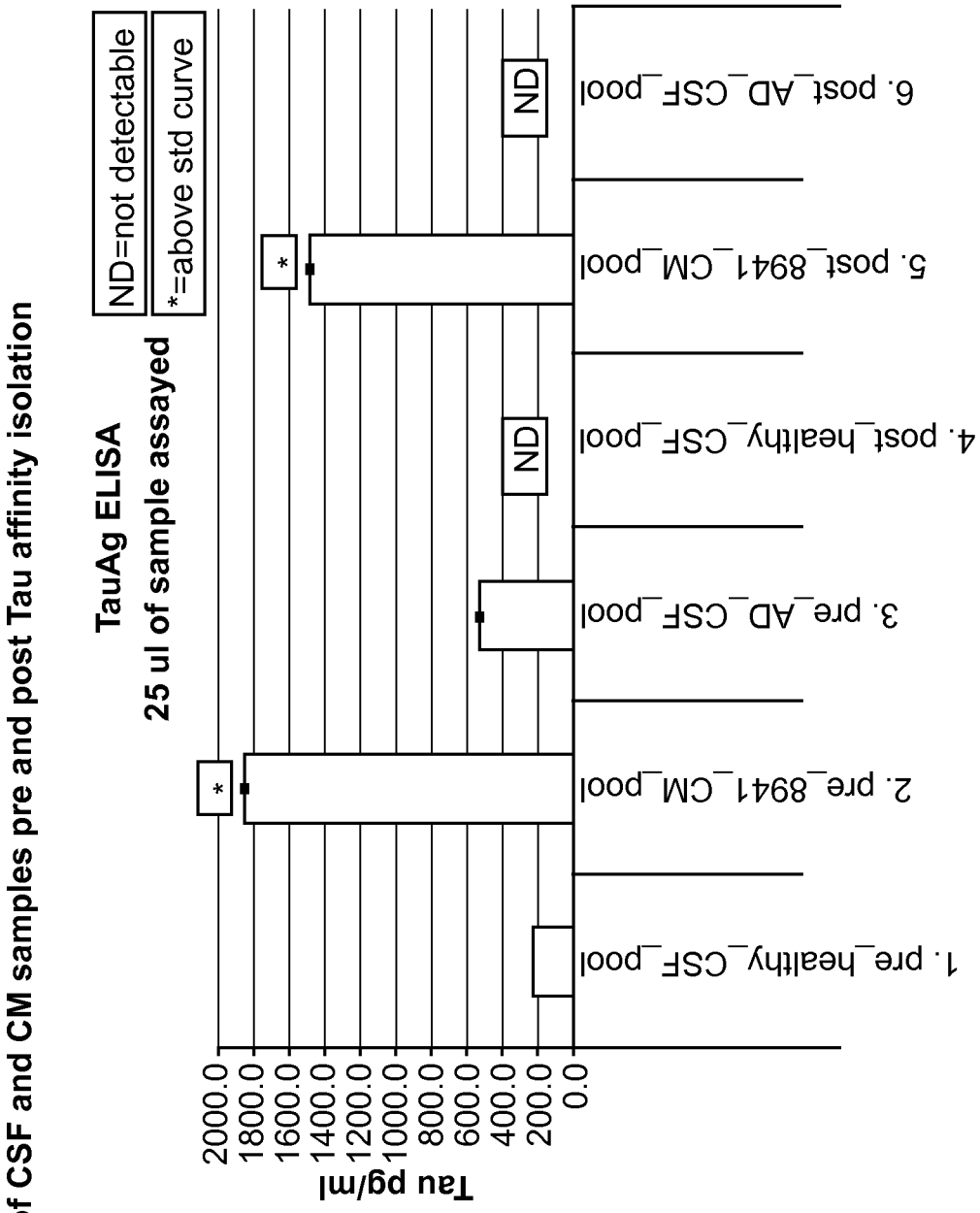

Quantification of CSF and CM samples pre and post Tau affinity isolation
TauAg ELISA
25 ul of sample assayed
ND=not detectable
*=above std curve
Tau pg/ml
2000.0
1800.0
1600.0
1400.0
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
1. pre_healthy_CSF_pool
2. pre_8941_CM_pool
3. pre_AD_CSF_pool
4. post_healthy_CSF_pool
5. post_8941_CM_pool
6. post_AD_CSF_pool
1. pre_healthy_CSF_pool
2. pre_8941_CM_pool
3. pre_AD_CSF_pool
4. post_healthy_CSF_pool
5. post_8941_CM_pool
6. post_AD_CSF_pool
*
*
ND
ND

FIG. 5

SUBSTITUTE SHEET (RULE 26)

Human tau isoforms

```
isoform 2       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG 60
isoform 3       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLK---------------- 44
isoform 4       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLK---------------- 44
isoform 5       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG 60
isoform 6       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG 60
isoform 1       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKESPLQTPTEDGSEEPG 60
fetal           MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLK----------------
                ****************************************

isoform 2       SETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAG 120
isoform 3       -----------------------------------------AEEAGIGDTPSLEDEAAG 62
isoform 4       -----------------------------------------AEEAGIGDTPSLEDEAAG 62
isoform 5       SETSDAKSTP------------------------------TAEAEEAGIGDTPSLEDEAAG 91
isoform 6       SETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAG 120
isoform 1       SETSDAKSTPTAEDVTAPLVDEGAPGKQAAAQPHTEIPEGTTAEEAGIGDTPSLEDEAAG 120
fetal           -----------------------------------------AEEAGIGDTPSLEDEAAG
                                                          ******************

isoform 2       HVTQ---------------------------------------------------------- 124
isoform 3       HVTQ---------------------------------------------------------- 66
isoform 4       HVTQ---------------------------------------------------------- 66
isoform 5       HVTQ---------------------------------------------------------- 95
isoform 6       HVTQEPESGKVVQEGFLREPGPPGLSHQLMSGMPGAPLLPEGPREATRQPSGTGPEDTEG 180
isoform 1       HVTQEPESGKVVQEGFLREPGPPGLSHQLMSGMPGAPLLPEGPREATRQPSGTGPEDTEG 180
fetal           HVTQ----------------------------------------------------------
                ****
```

FIG. 6A

```
isoform 2  ------------------------------------------------------------
isoform 3  ------------------------------------------------------------
isoform 4  ------------------------------------------------------------
isoform 5  ------------------------------------------------------------
isoform 6  GRHAPELLKHQLLGDLHQEGPPLKGAGGKERPGSKEEVDEDRDVDESSPQDSPPSKASPA 240
isoform 1  GRHAPELLKHQLLGDLHQEGPPLKGAGGKERPGSKEEVDEDRDVDESSPQDSPPSKASPA 240
fetal      ------------------------------------------------------------

isoform 2  ------------------------------------------------------------
isoform 3  ------------------------------------------------------------
isoform 4  ------------------------------------------------------------
isoform 5  ------------------------------------------------------------
isoform 6  QDGRPPQTAAREATSIPGFPAEGAIPLPVDFLSKVSTEIPASEPDGPSVGRAKGQDAPLE 300
isoform 1  QDGRPPQTAAREATSIPGFPAEGAIPLPVDFLSKVSTEIPASEPDGPSVGRAKGQDAPLE 300
fetal      ------------------------------------------------------------

isoform 2  ------------------------------------------------------------
isoform 3  ------------------------------------------------------------
isoform 4  ------------------------------------------------------------
isoform 5  ------------------------------------------------------------
isoform 6  FTFHVEITPNVQKEQAHSEEHLGRAAFPGAPGEGPEARGPSLGEDTKEADLPEPSEKQPA 360
isoform 1  FTFHVEITPNVQKEQAHSEEHLGRAAFPGAPGEGPEARGPSLGEDTKEADLPEPSEKQPA 360
fetal      ------------------------------------------------------------

isoform 2  ----------ARMVSKSKDGTGSDDKKAK------------------------------ 143
isoform 3  ----------ARMVSKSKDGTGSDDKKAK------------------------------ 85
isoform 4  ----------ARMVSKSKDGTGSDDKKAK------------------------------ 85
isoform 5  ----------ARMVSKSKDGTGSDDKKAK------------------------------ 114
isoform 6  AAPRGKPVSRVPQLKARMVSKSKDGTGSDDKKAKTSTRSSAKTLKNRPCLSPKHPTPGSS 420
isoform 1  AAPRGKPVSRVPQLKARMVSKSKDGTGSDDKKAKTSTRSSAKTLKNRPCLSPKHPTPGSS 420
fetal      ----------ARMVSKSKDGTGSDDKKAK------------------------------
                     **********
```

FIG. 6B

```
isoform 2  ----------------------------------------GADGKTKIATPRGAAPPGQK 163
isoform 3  ----------------------------------------GADGKTKIATPRGAAPPGQK 105
isoform 4  ----------------------------------------GADGKTKIATPRGAAPPGQK 105
isoform 5  ----------------------------------------GADGKTKIATPRGAAPPGQK 134
isoform 6  DPLIQPSSPAVCPEPPSSPKHVSSVTSRTGSSGAKEMKLKGADGKTKIATPRGAAPPGQK 480
isoform 1  DPLIQPSSPAVCPEPPSSPKHVSSVTSRTGSSGAKEMKLKGADGKTKIATPRGAAPPGQK 480
fetal      ----------------------------------------GADGKTKIATPRGAAPPGQK
                                                    ********************

isoform 2  GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT 205
isoform 3  GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT 147
isoform 4  GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT 147
isoform 5  GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT 176
isoform 6  GQANATRIPAKTPPAPKTPPSSATKQVQRRPPPAGPRSERGEPPKSGDRSGYSSPGSPGT 540
isoform 1  GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT 522
fetal      GQANATRIPAKTPPAPKTPPSS----------------------GEPPKSGDRSGYSSPGSPGT
           ********************                         **********************

isoform 2  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 265
isoform 3  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 207
isoform 4  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 207
isoform 5  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 236
isoform 6  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 600
isoform 1  PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN 582
fetal      PGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSAKSRLQTAPVPMPDLKNVKSKIGSTEN
           ************************************************************
```

FIG. 6C

SUBSTITUTE SHEET (RULE 26)

```
isoform 2       LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSL 325
isoform 3       LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSL 267
isoform 4       LKHQPGGGK------------------------------VQIVYKPVDLSKVTSKCGSL 236
isoform 5       LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSL 296
isoform 6       LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSL 660
isoform 1       LKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSL 642
fetal           LKHQPGGGK------------------------------VQIVYKPVDLSKVTSKCGSL
                *********                                ********************

isoform 2       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 385
isoform 3       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 327
isoform 4       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 296
isoform 5       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 356
isoform 6       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 720
isoform 1       GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK 702
fetal           GNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAK
                ************************************************************

isoform 2       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 441 (SEQ ID NO:21)
isoform 3       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 383 (SEQ ID NO:22)
isoform 4       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 352 (SEQ ID NO:23)
isoform 5       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 412 (SEQ ID NO:24)
isoform 6       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 776 (SEQ ID NO:25)
isoform 1       TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL 758 (SEQ ID NO:26)
fetal           TDHGAEIVYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL (SEQ ID NO:27)
                ************************************************************
```

FIG. 6D

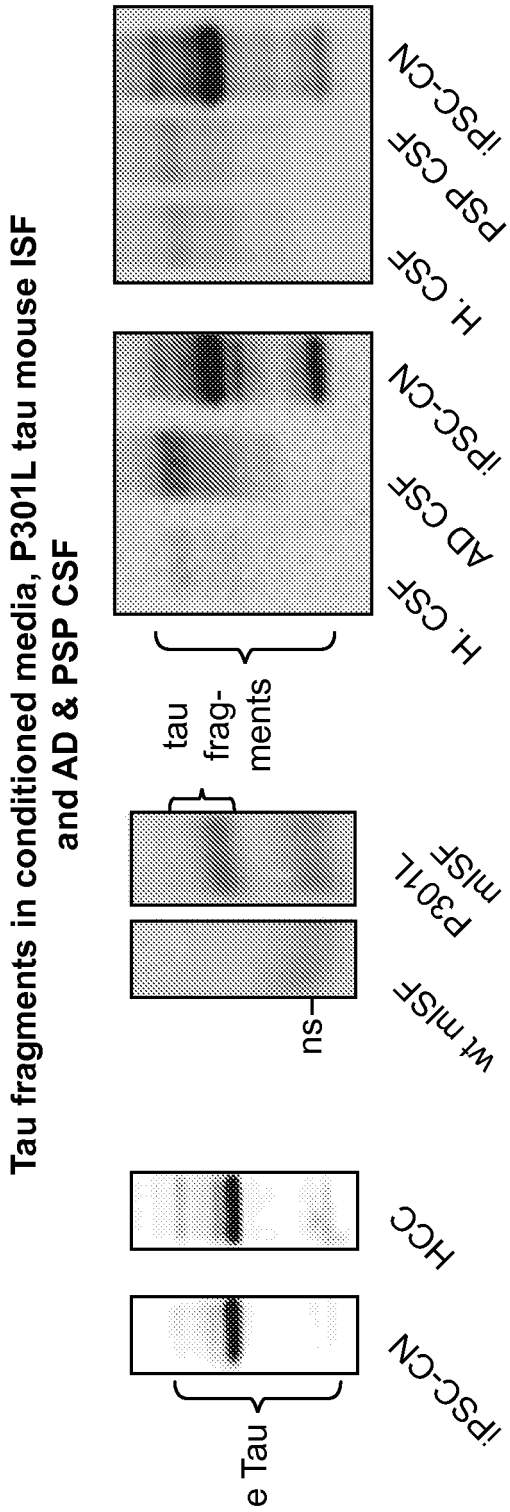

Tau fragments in conditioned media, P301L tau mouse ISF and AD & PSP CSF
iPSC-CN
HCC
iPSC-CN
wt mISF
P301L mISF
iPSC-CN
AD CSF
H. CSF
iPSC-CN
PSP CSF
H. CSF
e Tau
ns
tau frag-ments

FIG. 7

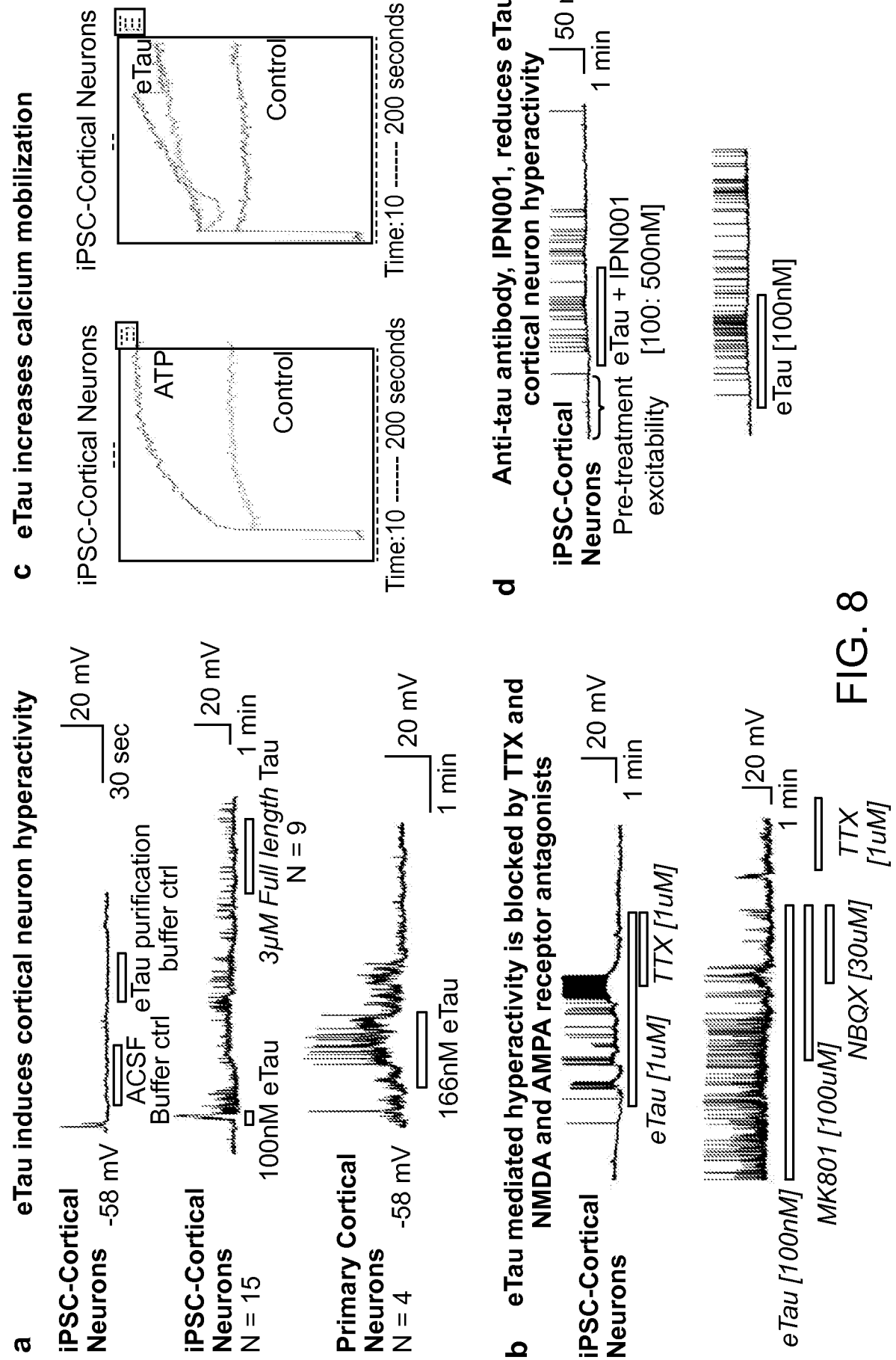

a
eTau induces cortical neuron hyperactivity
iPSC-Cortical Neurons
-58 mV
20 mV
30 sec
ACSF
Buffer ctrl
eTau purification buffer ctrl
iPSC-Cortical Neurons
N = 15
100nM eTau
3μM Full length Tau
N = 9
20 mV
1 min
Primary Cortical Neurons
N = 4
-58 mV
166nM eTau
20 mV
1 min
b
eTau mediated hyperactivity is blocked by TTX and NMDA and AMPA receptor antagonists
iPSC-Cortical Neurons
eTau [1uM]
TTX [1uM]
20 mV
1 min
eTau [100nM]
MK801 [100uM]
NBQX [30uM]
TTX [1uM]
20 mV
1 min
c
eTau increases calcium mobilization
iPSC-Cortical Neurons
ATP
Control
Time:10 ----- 200 seconds
iPSC-Cortical Neurons
eTau
Control
Time:10 ----- 200 seconds
d
Anti-tau antibody, IPN001, reduces eTau's cortical neuron hyperactivity
iPSC-Cortical Neurons
Pre-treatment excitability
eTau + IPN001 [100: 500nM]
50 mV
1 min
eTau [100nM]

FIG. 8

IPN002 VH Variant 1

```
         10        20        30        40        50        60        70        80        90        100
GAGGTTCATCTGGTGGAGTCTGGGGGAGCCTTAGTGAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGTTTCAGTAAATATGGCA
 E  V  H  L  V  E  S  G  G  A  L  V  K  P  G  G  S  L  R  L  S  C  A  A  S  G  F  S  F  S  K  Y  G
                          10                        20                        30

       110       120       130       140       150       160       170       180       190       200
TGTCTTGGGTTCGCCAGGCCCCAGGCAAGGGCCTGGAGTGGGTCGCAACCATTAGTAGTAGTGGGAGTCGCACCTACTATCCAGACAGTGTGAAGGGCAG
 M  S  W  V  R  Q  A  P  G  K  G  L  E  W  V  A  T  I  S  S  S  G  S  R  T  Y  Y  P  D  S  V  K  G  R
                40                            50    52  A                     60

       210       220       230       240       250       260       270       280       290       300
ATTCACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTGCAAATGAGCAGTCTGAAGTCTGAGGACACAGCCATGTATTACTGTTCAATTAGCTGG
  F  T  I  S  R  D  N  A  K  N  T  L  Y  L  Q  M  S  S  L  K  S  E  D  T  A  M  Y  Y  C  S  I  S  W
          70                            80    82  A  B  C                     90

       310       320       330       340       350
GACGGTGCTATGGACTACTGGGGTCAAGGGACCTCAGTCACCGTCTCCTCA (SEQ ID NO:28)
 D  G  A  M  D  Y  W  G  Q  G  T  S  V  T  V  S  S  (SEQ ID NO:36)
         100                           110       113
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 9

SUBSTITUTE SHEET (RULE 26)

IPN002 VH Variant 2

```
        10        20        30        40        50        60        70        80        90        100
GAGGTTCATCTGGTGGAGTCTGGGGGAGCCTTAGTGAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGTTTCAGTAAATATGGCA
 E  V  H  L  V  E  S  G  G  A  L  V  K  P  G  G  S  L  R  L  S  C  A  A  S  G  F  S  F  S  K  Y  G
                          10                                20                                30

      110       120       130       140       150       160       170       180       190       200
TGTCTTGGGTTCGCCAGGCCCCAGGCAAGGGCCTGGAGTGGGTCGCAACCATTAGTAGTAGTGGGAGTCGCACCTACTATCCAGACAGTGTGAAGGGCAG
M  S  W  V  R  Q  A  P  G  K  G  L  E  W  V  A  T  I  S  S  S  S  G  S  R  T  Y  Y  P  D  S  V  K  G  R
               40                                50    52  A                   60

      210       220       230       240       250       260       270       280       290       300
ATTCACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTGCAAATGAACAGTCTGAGAGCCGAGGACACAGCCATGTATTACTGTTCAATTAGCTGG
  F  T  I  S  R  D  N  A  K  N  T  L  Y  L  Q  M  N  S  L  R  A  E  D  T  A  M  Y  Y  C  S  I  S  W
         70                                80    82  A  B  C                   90

      310       320       330       340       350
GACGGTGCTATGGACTACTGGGGTCAAGGGACCACCGTCACCGTCTCCTCA (SEQ ID NO:29)
 D  G  A  M  D  Y  W  G  Q  G  T  T  V  T  V  S  S   (SEQ ID NO:37)
        100                         110       113
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 10

IPN002 VH Variant 3

```
        10        20        30        40        50        60        70        80        90        100
GAGGTTCAGCTGGTGGAGTCTGGGGGAGCCTTAGTGAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGTTTCAGTAAATATGGCA
 E  V  Q  L  V  E  S  G  G  A  L  V  K  P  G  G  S  L  R  L  S  C  A  A  S  G  F  S  F  S  K  Y  G
                           10                                20                                30

       110       120       130       140       150       160       170       180       190       200
TGTCTTGGGTTCGCCAGGCCCCAGGCAAGGGCCTGGAGTGGGTCGCAACCATTAGTAGTAGTGGGAGTCGCACCTACTATCCAGACAGTGTGAAGGGCAG
 M  S  W  V  R  Q  A  P  G  K  G  L  E  W  V  A  T  I  S  S  S  G  S  R  T  Y  Y  P  D  S  V  K  G  R
                  40                                50    52  A                     60

       210       220       230       240       250       260       270       280       290       300
ATTCACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTGCAAATGAACAGTCTGAGAGCCGAGGACACAGCCATGTATTACTGTTCAATTAGCTGG
  F  T  I  S  R  D  N  A  K  N  T  L  Y  L  Q  M  N  S  L  R  A  E  D  T  A  M  Y  Y  C  S  I  S  W
           70                                80    82  A  B  C                     90

       310       320       330       340       350
GACGGTGCTATGGACTACTGGGGTCAAGGGACCACCGTCACCGTCTCCTCA (SEQ ID NO:30)
 D  G  A  M  D  Y  W  G  Q  G  T  T  V  T  V  S  S   (SEQ ID NO:38)
        100                          110       113
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 11

IPN002 VH Variant 4

```
        10        20        30        40        50        60        70        80        90        100
GAGGTTCAGCTGGTGGAGTCTGGGGGAGCCTTAGTGAAGCCTGGAGGGTCCCTGAGACTCTCCTGTGCAGCCTCTGGATTCAGTTTCAGTAAATATGGCA
 E  V  Q  L  V  E  S  G  G  A  L  V  K  P  G  G  S  L  R  L  S  C  A  A  S  G  F  S  F  S  K  Y  G
                          10                                20                                30

       110       120       130       140       150       160       170       180       190       200
TGTCTTGGGTTCGCCAGGCCCCAGGCAAGGGCCTGGAGTGGGTCGCAACCATTAGTAGTAGTGGGAGTCGCACCTACTATCCAGACAGTGTGAAGGGCAG
M  S  W  V  R  Q  A  P  G  K  G  L  E  W  V  A  T  I  S  S  S  S  G  S  R  T  Y  Y  P  D  S  V  K  G  R
                 40                                50    52  A                   60

       210       220       230       240       250       260       270       280       290       300
ATTCACCATCTCCAGAGACAATGCCAAGAACACCCTGTACCTGCAAATGAACAGTCTGAGAGCCGAGGACACAGCCATGTATTACTGTGCCATTAGCTGG
  F  T  I  S  R  D  N  A  K  N  T  L  Y  L  Q  M  N  S  L  R  A  E  D  T  A  M  Y  Y  C  A  I  S  W
         70                          80    82  A  B  C                   90

       310       320       330       340       350
GACGGTGCTATGGACTACTGGGGTCAAGGGACCACCGTCACCGTCTCCTCA (SEQ ID NO:31)
 D  G  A  M  D  Y  W  G  Q  G  T  T  V  T  V  S  S   (SEQ ID NO:39)
        100                         110       113
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 12

SUBSTITUTE SHEET (RULE 26)

IPN002 Vk Variant 1

```
        10        20        30        40        50        60        70        80        90        100
GATGTTTTGATGACCCAAAGCCCACTCTCCCTGCCTGTCACCCTTGGACAGCCCGCCTCCATCTCTTGCAAATCTAGTCAGAGCATTGTACATAGTAATG
 D  V  L  M  T  Q  S  P  L  S  L  P  V  T  L  G  Q  P  A  S  I  S  C  K  S  S  Q  S  I  V  H  S  N
                          10                                20                   27  A  B  C  D  E

      110       120       130       140       150       160       170       180       190       200
GAAACACCTATTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCACAGCTCCTGGTCTACAAAGTTTCCAATCGATTTTCTGGGGTCCCAGACAGATT
G  N  T  Y  L  E  W  Y  L  Q  K  P  G  Q  S  P  Q  L  L  V  Y  K  V  S  N  R  F  S  G  V  P  D  R  F
  30                          40                          50                          60

      210       220       230       240       250       260       270       280       290       300
CAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATGTGGGAACTTATTACTGCTTTCAAGGCTCACTTGTTCCT
 S  G  S  G  S  G  T  D  F  T  L  K  I  S  R  V  E  A  E  D  V  G  T  Y  Y  C  F  Q  G  S  L  V  P
                   70                          80                          90

      310       320
TGGGCGTTCGGTGGAGGCACCAAGGTGGAAATCAAA (SEQ ID NO:32)
 W  A  F  G  G  G  T  K  V  E  I  K   (SEQ ID NO:40)
          100               106  A
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 13

IPN002 Vk Variant 2

```
        10        20        30        40        50        60        70        80        90        100
GATGTTGTGATGACCCAAAGCCCACTCTCCCTGCCTGTCACCCTTGGACAGCCCGCCTCCATCTCTTGCAAATCTAGTCAGAGCATTGTACATAGTAATG
 D  V  V  M  T  Q  S  P  L  S  L  P  V  T  L  G  Q  P  A  S  I  S  C  K  S  S  Q  S  I  V  H  S  N
                          10                                20                   27  A  B  C  D  E

      110       120       130       140       150       160       170       180       190       200
GAAACACCTATTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCACAGCTCCTGGTCTACAAAGTTTCCAATCGATTTTCTGGGGTCCCAGACAGATT
G  N  T  Y  L  E  W  Y  L  Q  K  P  G  Q  S  P  Q  L  L  V  Y  K  V  S  N  R  F  S  G  V  P  D  R  F
  30                          40                          50                          60

      210       220       230       240       250       260       270       280       290       300
CAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATGTGGGAACTTATTACTGCTTTCAAGGCTCACTTGTTCCT
 S  G  S  G  S  G  T  D  F  T  L  K  I  S  R  V  E  A  E  D  V  G  T  Y  Y  C  F  Q  G  S  L  V  P
                   70                          80                          90

      310       320
TGGGCGTTCGGTGGAGGCACCAAGGTGGAAATCAAA (SEQ ID NO:33)
 W  A  F  G  G  G  T  K  V  E  I  K   (SEQ ID NO:41)
          100               106  A
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 14

IPN002 Vk Variant 3

```
        10        20        30        40        50        60        70        80        90        100
GATGTTGTGATGACCCAAAGCCCACTCTCCCTGCCTGTCACCCTTGGACAGCCCGCCTCCATCTCTTGCAAATCTAGTCAGAGCATTGTACATAGTAATG
 D  V  V  M  T  Q  S  P  L  S  L  P  V  T  L  G  Q  P  A  S  I  S  C  K  S  S  Q  S  I  V  H  S  N
                          10                                20                   27  A  B  C  D  E

       110       120       130       140       150       160       170       180       190       200
GAAACACCTATTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCACAGCTCCTGGTCTACAAAGTTTCCAATCGATTTTCTGGGGTCCCAGACAGATT
G  N  T  Y  L  E  W  Y  L  Q  K  P  G  Q  S  P  Q  L  L  V  Y  K  V  S  N  R  F  S  G  V  P  D  R  F
  30                            40                            50                            60

       210       220       230       240       250       260       270       280       290       300
CAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATGTGGGAGTGTATTACTGCTTTCAAGGCTCACTTGTTCCT
 S  G  S  G  S  G  T  D  F  T  L  K  I  S  R  V  E  A  E  D  V  G  V  Y  Y  C  F  Q  G  S  L  V  P
                    70                            80                            90

       310       320
TGGGCGTTCGGTGGAGGCACCAAGGTGGAAATCAAA (SEQ ID NO:34)
 W  A  F  G  G  G  T  K  V  E  I  K   (SEQ ID NO:42)
          100               106  A
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 15

IPN002 Vk Variant 4

```
        10        20        30        40        50        60        70        80        90        100
GATGTTGTGATGACCCAAAGCCCACTCTCCCTGCCTGTCACCCTTGGACAGCCCGCCTCCATCTCTTGCAAATCTAGTCAGAGCATTGTACATAGTAATG
 D  V  V  M  T  Q  S  P  L  S  L  P  V  T  L  G  Q  P  A  S  I  S  C  K  S  S  Q  S  I  V  H  S  N
                          10                                20                   27  A  B  C  D  E

       110       120       130       140       150       160       170       180       190       200
GAAACACCTATTTAGAATGGTACCTGCAGAAACCAGGCCAGTCTCCACAGCTCCTGATCTACAAAGTTTCCAATCGATTTTCTGGGGTCCCAGACAGATT
G  N  T  Y  L  E  W  Y  L  Q  K  P  G  Q  S  P  Q  L  L  I  Y  K  V  S  N  R  F  S  G  V  P  D  R  F
  30                          40                          50                          60

       210       220       230       240       250       260       270       280       290       300
CAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATGTGGGAGTGTATTACTGCTTTCAAGGCTCACTTGTTCCT
 S  G  S  G  S  G  T  D  F  T  L  K  I  S  R  V  E  A  E  D  V  G  V  Y  Y  C  F  Q  G  S  L  V  P
                    70                          80                          90

       310       320
TGGGCGTTCGGTGGAGGCACCAAGGTGGAAATCAAA (SEQ ID NO:35)
 W  A  F  G  G  G  T  K  V  E  I  K  (SEQ ID NO:43)
          100               106  A
```

CDR definitions and protein sequence numbering according to Kabat. CDR nucleotide and amino acid sequences are underlined.

FIG. 16

Table 4: Binding of IPN002 variants to Tau proteins

	K_D values (M)					
Antibody	rTau383	eTau 1a	eTau 1b	eTau 2	eTau 4	eTau 4
VH1/Vk1	1.83E-10	2.94E-10	7.37E-10	4.65E-10	3.58E-10	5.77E-10
VH1/Vk2	1.21E-10	2.12E-10	5.58E-10	3.61E-10	3.21E-10	6.33E-10
VH1/Vk3	1.75E-10	2.91E-10	5.90E-10	4.44E-10	4.78E-10	7.61E-10
VH1/Vk4	2.86E-10	2.52E-10	5.97E-10	4.27E-10	2.69E-10	8.69E-10
VH2/Vk1	2.42E-10	2.81E-10	2.15E-10	2.25E-10	3.69E-10	3.21E-10
VH2/Vk2	1.99E-10	3.27E-10	2.29E-10	2.83E-10	2.94E-10	3.94E-10
VH2/Vk3	2.23E-10	3.27E-10	2.87E-10	2.61E-10	2.19E-10	4.11E-10
VH2/Vk4	2.48E-10	3.43E-10	5.20E-10	3.54E-10	4.18E-10	6.71E-10
VH3/Vk1	2.36E-10	2.41E-10	5.29E-10	7.05E-10	4.54E-10	9.21E-10
VH3/Vk2	2.58E-10	2.82E-10	6.14E-10	4.08E-10	5.89E-10	7.01E-10
VH3/Vk3	2.24E-10	2.20E-10	6.89E-10	4.71E-10	4.69E-10	6.65E-10
VH3/Vk4	2.55E-10	2.16E-10	3.82E-10	4.47E-10	3.81E-10	5.86E-10
VH4/Vk1	1.87E-10	1.98E-10	3.59E-10	4.05E-10	2.80E-10	4.98E-10
VH4/Vk2	1.60E-10	1.91E-10	4.83E-10	4.51E-10	2.91E-10	4.67E-10
VH4/Vk3	2.76E-10	1.78E-10	3.13E-10	4.73E-10	6.36E-10	6.29E-10
VH4/Vk4	3.79E-10	3.25E-10	5.35E-10	5.64E-10	4.62E-10	1.03E-09

FIG. 17

SUBSTITUTE SHEET (RULE 26)

Table 5: Binding of humanized IPN002 variants to Tau383

Antibody	K_D (M)	k_{on} (1/Ms)	k_{dis} (1/s)
VH1/VK1	4.26E-11	2.06E+05	8.75E-06
VH1/VK2	4.46E-10	1.96E+05	8.74E-05
VH1/VK3	1.28E-09	1.82E+05	2.33E-04
VH1/VK4	5.71E-10	1.67E+05	9.52E-05
VH2/VK1	4.67E-10	2.14E+05	1.00E-05
VH2/VK2	2.32E-10	2.05E+05	4.75E-05
VH2/VK3	1.73E-09	1.34E+05	2.32E-04
VH2/VK4	1.66E-09	1.42E+05	2.36E-04
VH3/VK1	1.99E-09	1.29E+05	2.57E-04
VH3/VK2	5.77E-10	1.85E+05	1.07E-04
VH3/VK3	1.69E-10	1.87E+05	3.15E-05
VH3/VK4	4.75E-10	2.11E+05	1.00E-04
VH4/VK1	2.12E-09	1.40E+05	2.97E-04
VH4/VK2	1.88E-09	1.63E+05	3.07E-04
VH4/VK3	5.71E-10	1.64E+05	9.39E-05
VH4/VK4	8.12E-10	1.56E+05	1.26E-04
IPN002	2.06E-10	2.33E+05	4.78E-05

FIG. 18

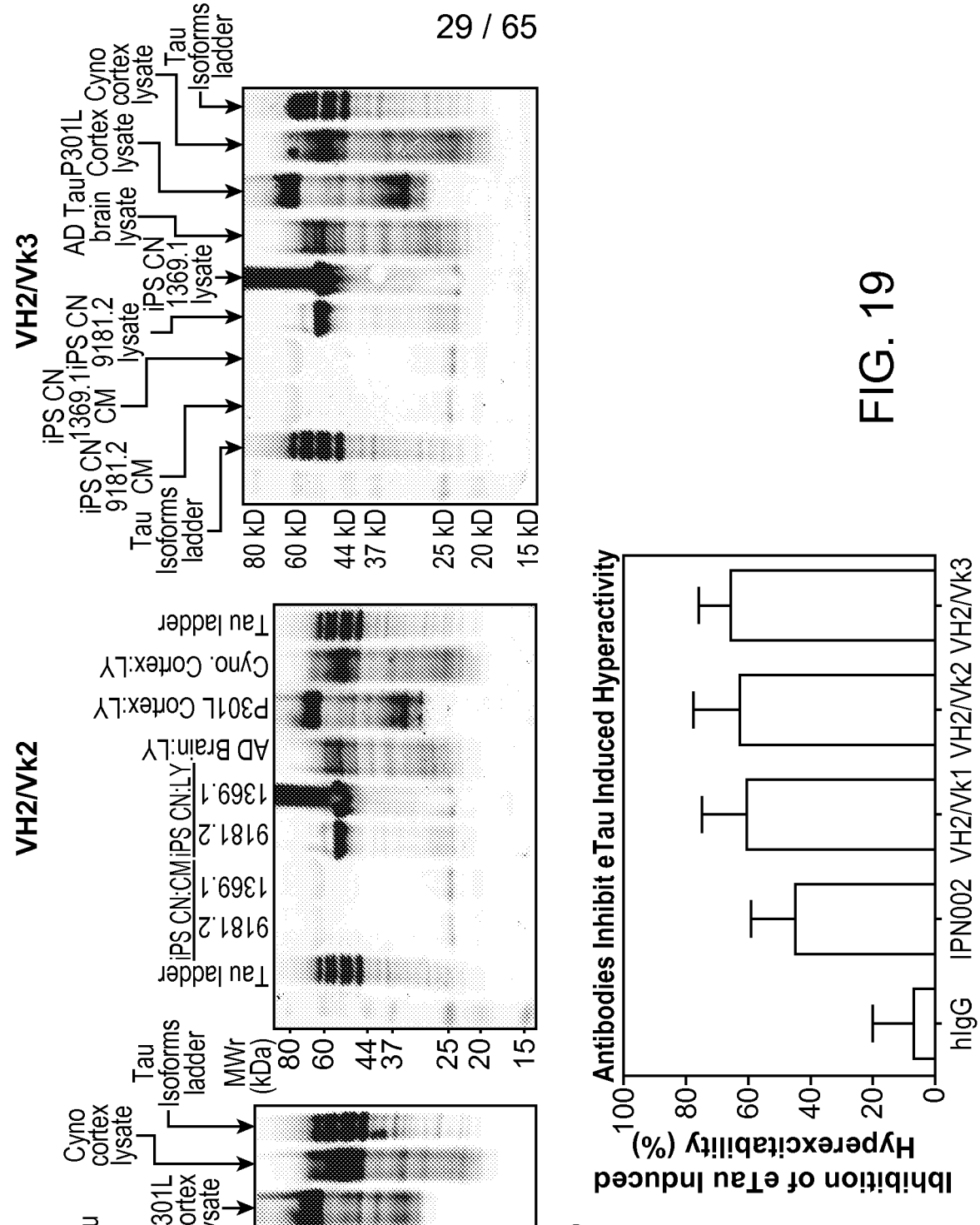

a
VH2/Vk1
VH2/Vk2
VH2/Vk3
iPS CN 9181.2 CM
iPS CN 1369.1 CM
iPS CN 9181.2 lysate
iPS CN 1369.1 lysate
AD Tau brain lysate
P301L Cortex lysate
Cyno cortex lysate
Tau Isoforms ladder
MWr (kDa)
80 kD
60 kD
44 kD
37 kD
25 kD
20 kD
15 kD
Tau ladder
iPS CN:CM
iPS CN:LY
AD Brain:LY
P301L Cortex:LY
Cyno. Cortex:LY
b
Antibodies Inhibit eTau Induced Hyperactivity
Inhibition of eTau Induced Hyperexcitability (%)
hIgG
IPN002
VH2/Vk1
VH2/Vk2
VH2/Vk3
Antibody

FIG. 19

```
fetal       MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA
#2           AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA
#3           AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA
#4           AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA
eTau 2-172   AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA
eTau 2-176   AEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEGDTDAGLKAEEAGIGDTPSLEDEA

fetal        AGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPA
#2           AGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPA
#3           AGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPA
#4           AGHVTQAR (68)(SEQ ID NO:48)
eTau 2-172   AGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPA
eTau 2-176   AGHVTQARMVSKSKDGTGSDDKKAKGADGKTKIATPRGAAPPGQKGQANATRIPAKTPPA

fetal        PKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPKSPSSA
#2           PKTPPSSGEPPKSGDRSGYSSPGSPGTPGSR (151)(SEQ ID NO:46)
#3           PK (122)(SEQ ID NO:47)
eTau 2-172   PKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVR  (SEQ ID NO:44)
eTau 2-176   PKTPPSSGEPPKSGDRSGYSSPGSPGTPGSRSRTPSLPTPPTREPKKVAVVRTPPK (SEQ ID NO:45)

fetal        KSRLQTAPVPMPDLKNVKSKIGSTENLKHQPGGGKVQIVYKPVDLSKVTSKCGSLGNIHHK

fetal        PGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGNKKIETHKLTFRENAKAKTDHGAEI

fetal        VYKSPVVSGDTSPRHLSNVSSTGSIDMVDSPQLATLADEVSASLAKQGL (SEQ ID NO:27)
```

FIG. 20

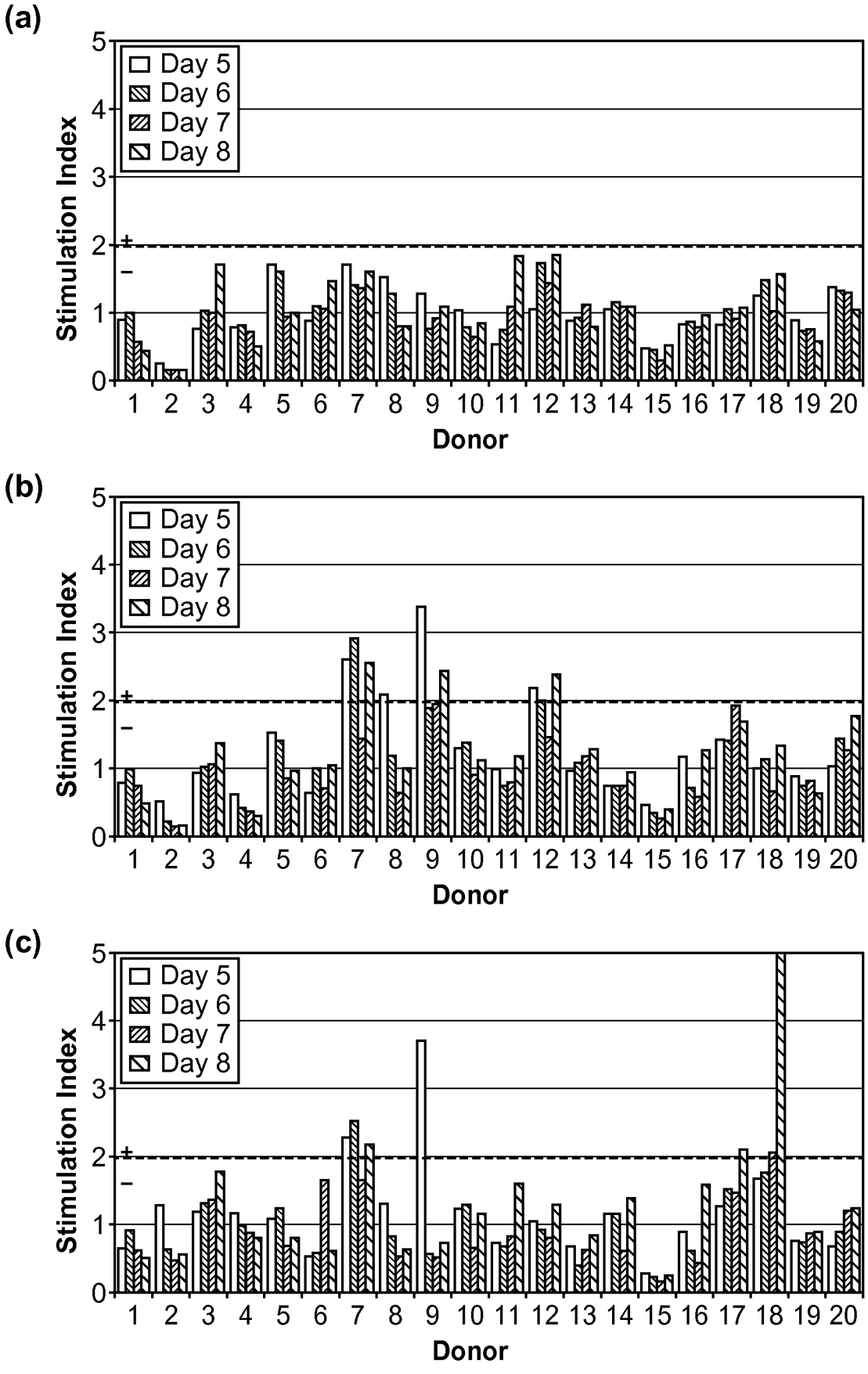

(a)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Donor
(b)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Donor
(c)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Donor

FIG. 21

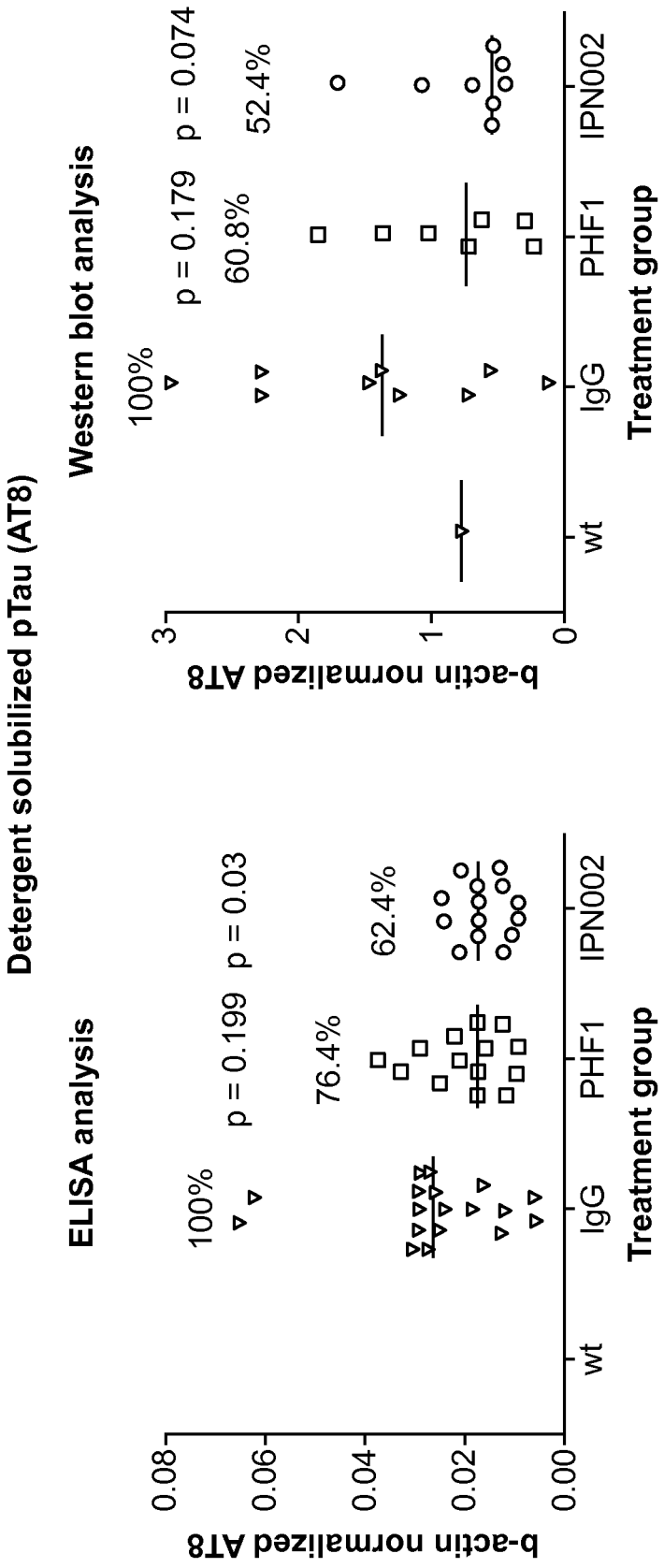

Detergent solubilized pTau (AT8)
ELISA analysis
b-actin normalized AT8
0.00
0.02
0.04
0.06
0.08
100%
p = 0.199
p = 0.03
76.4%
62.4%
wt
IgG
PHF1
IPN002
Treatment group
Western blot analysis
b-actin normalized AT8
0
1
2
3
100%
p = 0.179
p = 0.074
60.8%
52.4%
wt
IgG
PHF1
IPN002
Treatment group

FIG. 22

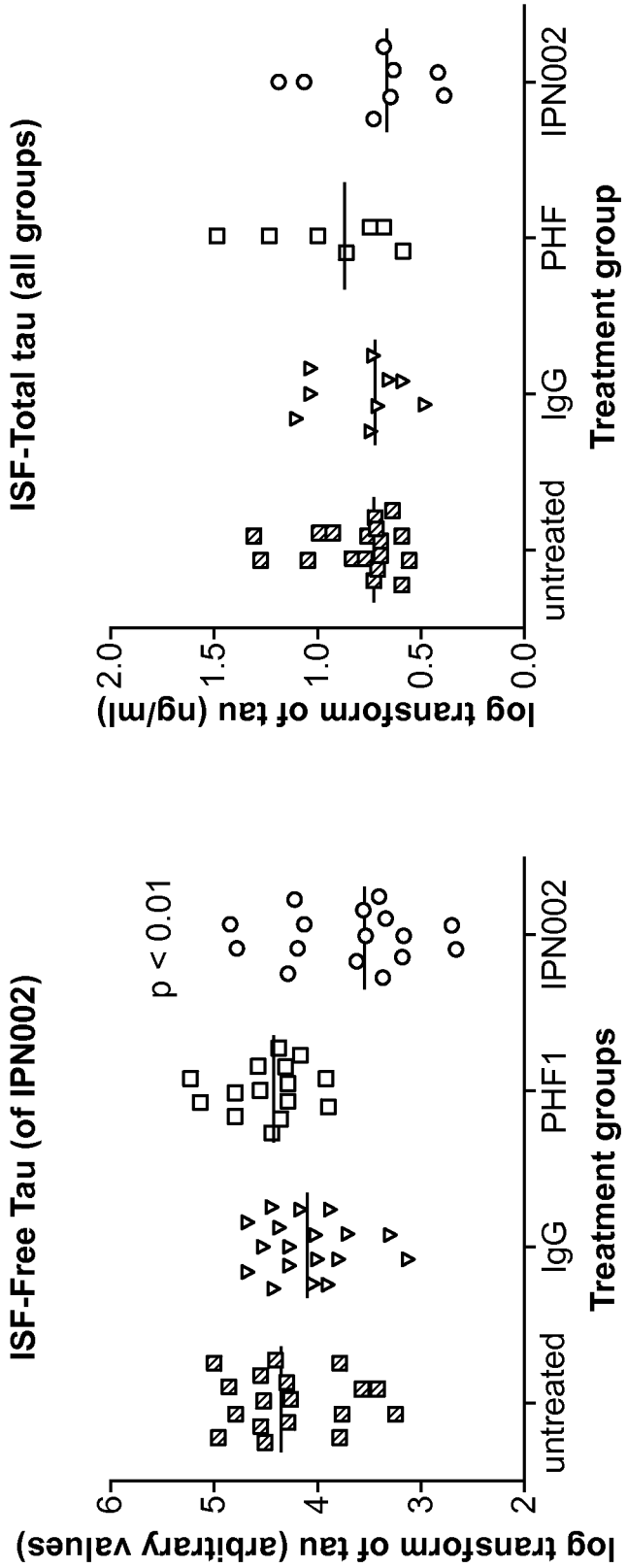
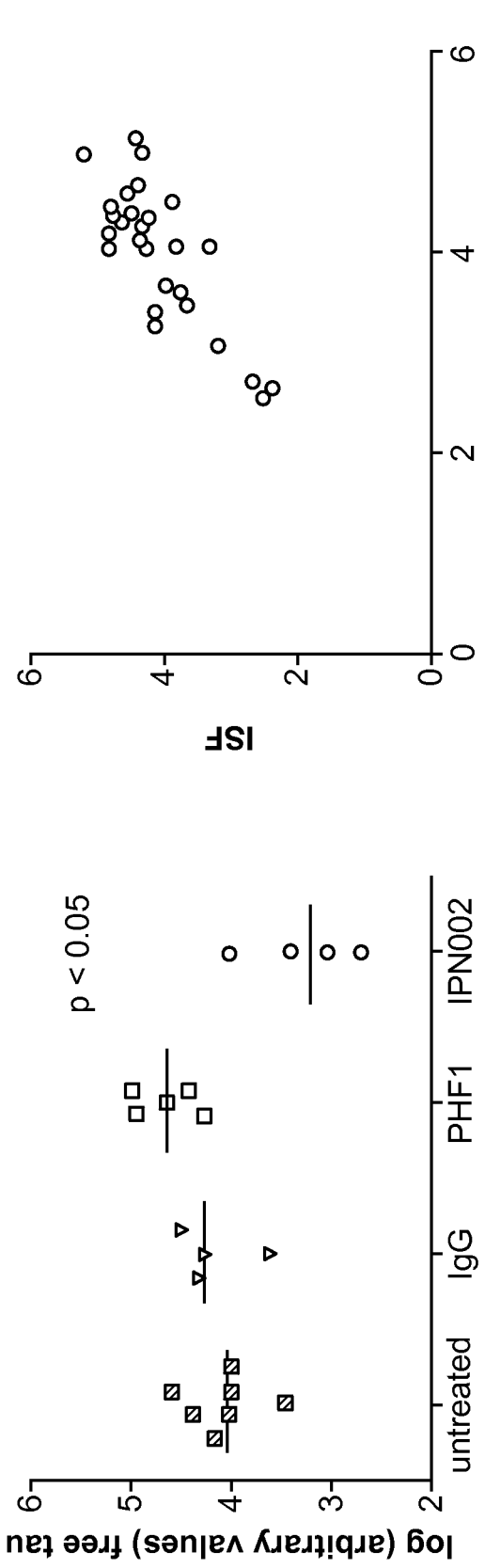

ISF-Free Tau (of IPN002)
log transform of tau (arbitrary values)
p < 0.01
6
5
4
3
2
untreated
IgG
PHF1
IPN002
Treatment groups
ISF-Total tau (all groups)
log transform of tau (ng/ml)
2.0
1.5
1.0
0.5
0.0
untreated
IgG
PHF
IPN002
Treatment group

FIG. 23



Number of XY Pairs	27
Pearson r	0.8094
95% confidence interval	0.6200 to 0.9096
P value (two-tailed)	< 0.0001
P value summary	****
Is the correlation significant? (alpha=0.05)	Yes
R square	0.6551

FIG. 24

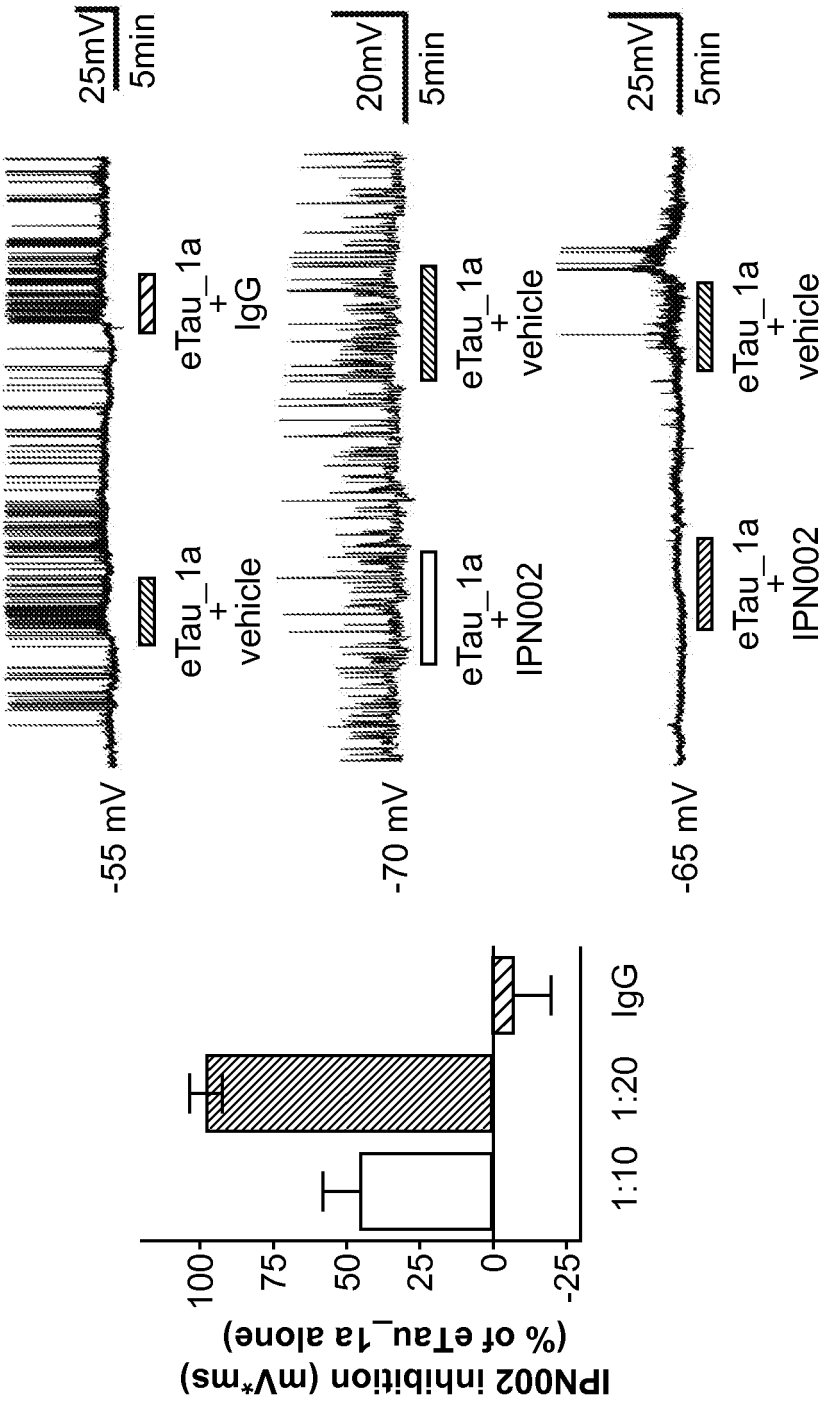

-55 mV
eTau_1a + vehicle
eTau_1a + IgG
25mV
5min
-70 mV
eTau_1a + IPN002
eTau_1a + vehicle
20mV
5min
-65 mV
eTau_1a + IPN002
eTau_1a + vehicle
25mV
5min
IPN002 inhibition (mV*ms)
(% of eTau_1a alone)
100
75
50
25
0
-25
1:10
1:20
IgG

FIG. 25

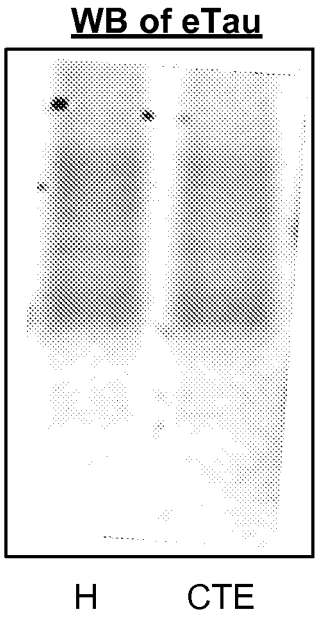
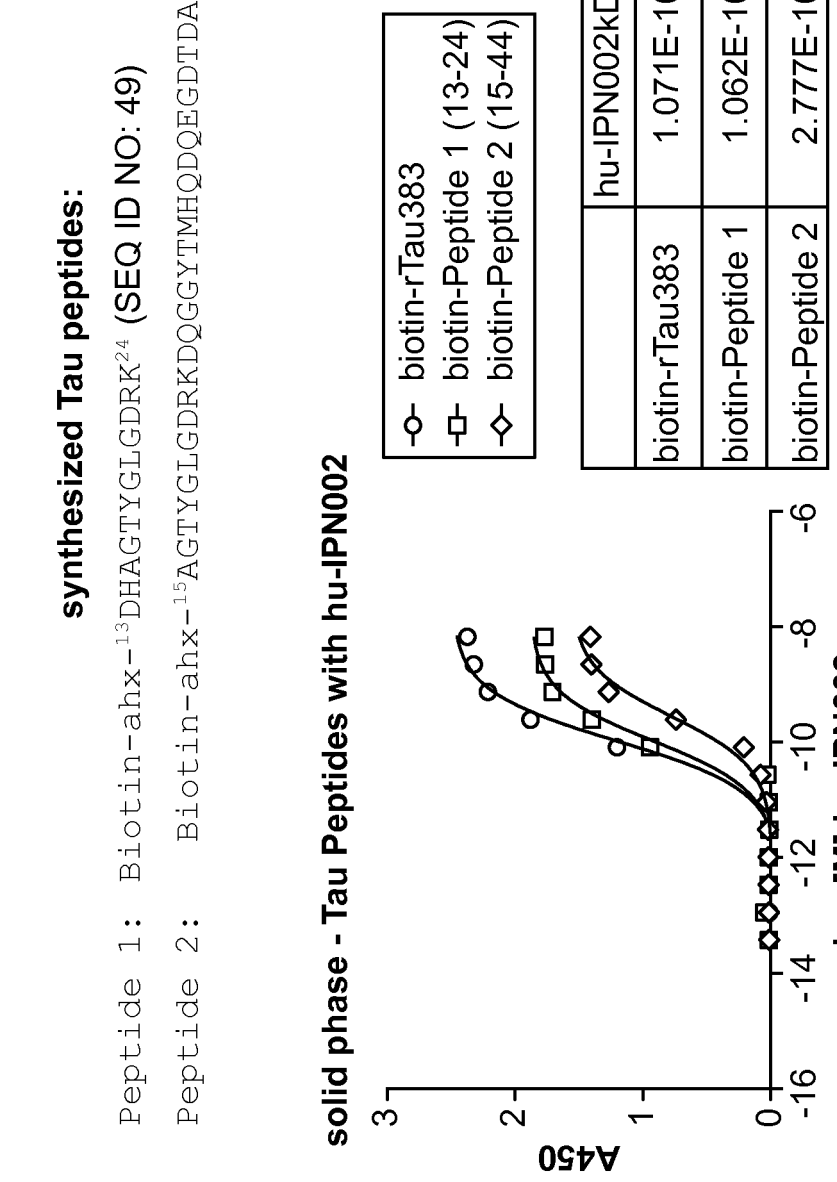


FIG. 26

synthesized Tau peptides:

Peptide 1: Biotin-ahx-^{13}DHAGTYGLGDRK^{24} (SEQ ID NO: 49)

Peptide 2: Biotin-ahx-^{15}AGTYGLGDRKDQGGYTMHQDQEGDTDAGLK^{44} (SEQ ID NO: 50)



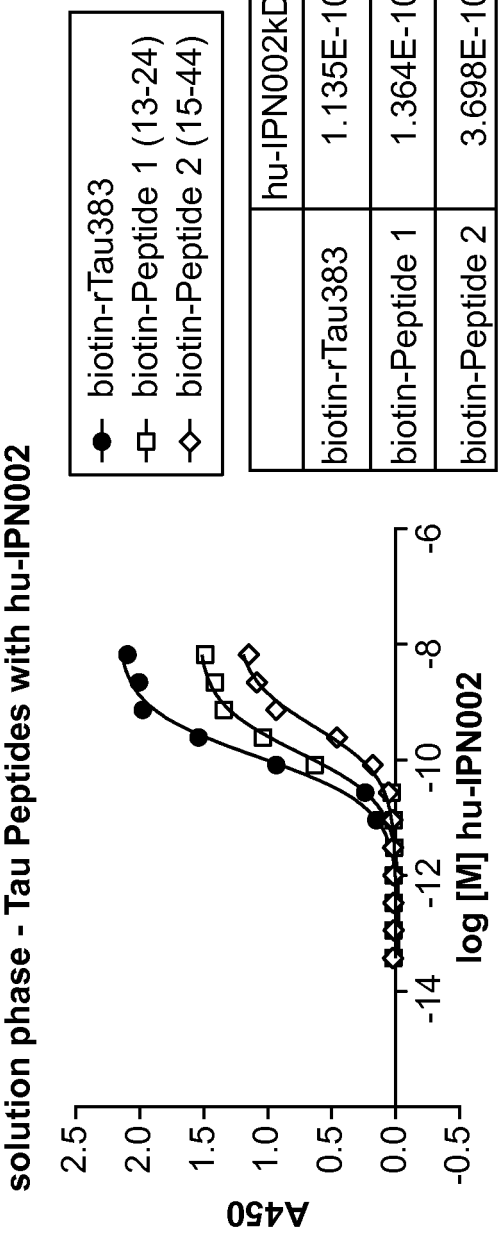
	hu-IPN002kD [M]
biotin-rTau383	1.071E-10
biotin-Peptide 1	1.062E-10
biotin-Peptide 2	2.777E-10

FIG. 27

synthesized Tau peptides:

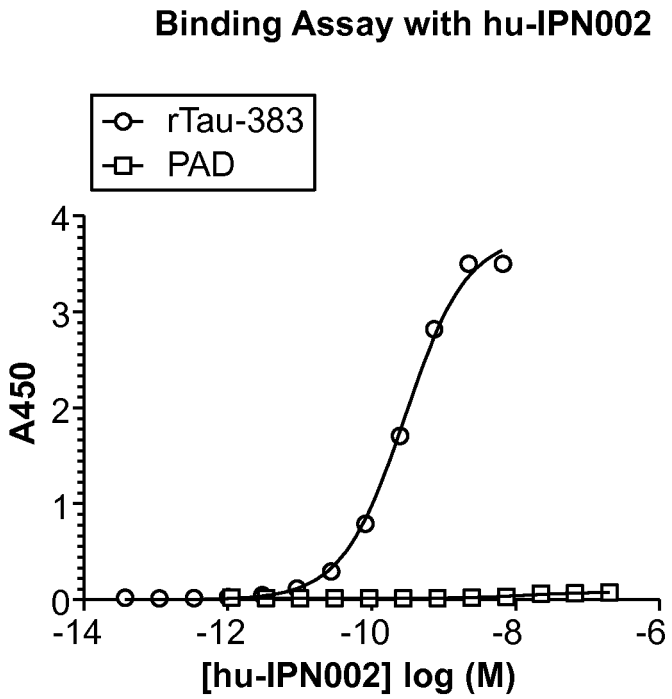
Peptide 1: Biotin-ahx-^{13}DHAGTYGLGDRK^{24} (SEQ ID NO: 49)

Peptide 2: Biotin-ahx-^{15}AGTYGLGDRKDQGGYTMHQDQEGDTDAGLK^{44} (SEQ ID NO: 50)



	hu-IPN002kD [M]
biotin-rTau383	1.135E-10
biotin-Peptide 1	1.364E-10
biotin-Peptide 2	3.698E-10

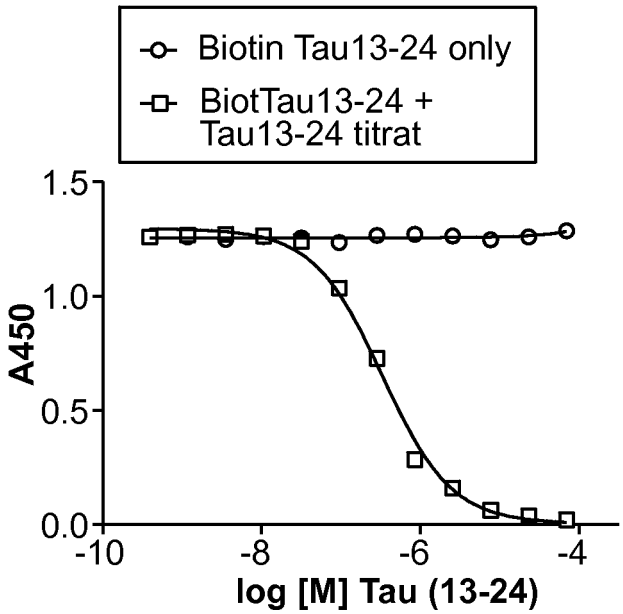
FIG. 28



	Hu-IPN002k_D [M]
rTau383	2.88E-10
PAD	n.a.

FIG. 29

Competition Assay of Biotin-Tau (13-24) vs. Tau (13-24) for hu-IPN002



Competition Assay of Biotin-Tau (15-44) vs. Tau (15-44) for hu-IPN002

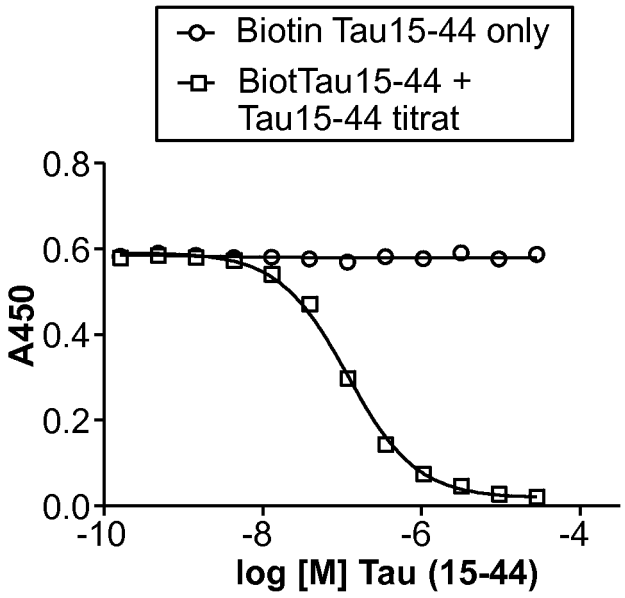


FIG. 30

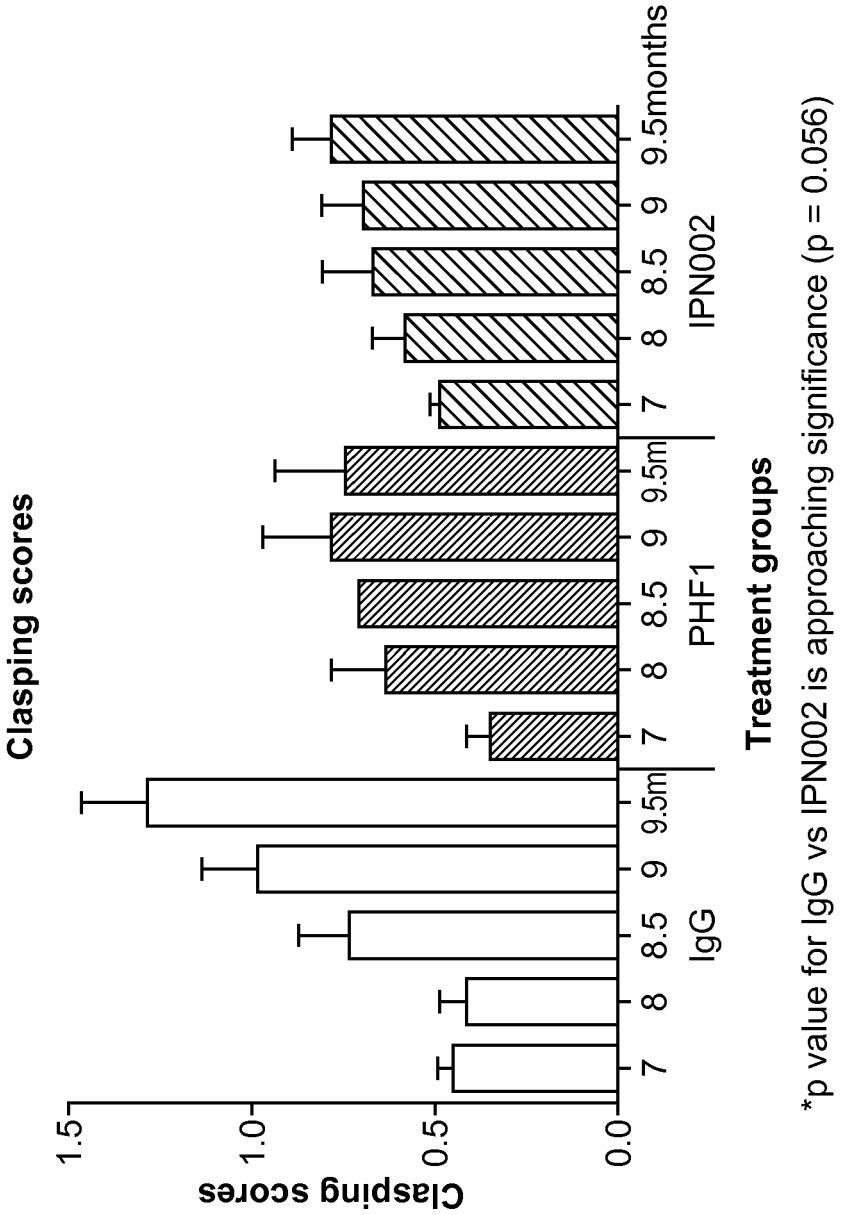

Clasping scores
1.5
1.0
0.5
0.0
Clasping scores
7
8
8.5
9
9.5m
IgG
7
8
8.5
9
9.5m
PHF1
7
8
8.5
9
9.5
months
IPN002
Treatment groups
*p value for IgG vs IPN002 is approaching significance (p = 0.056)

FIG. 31

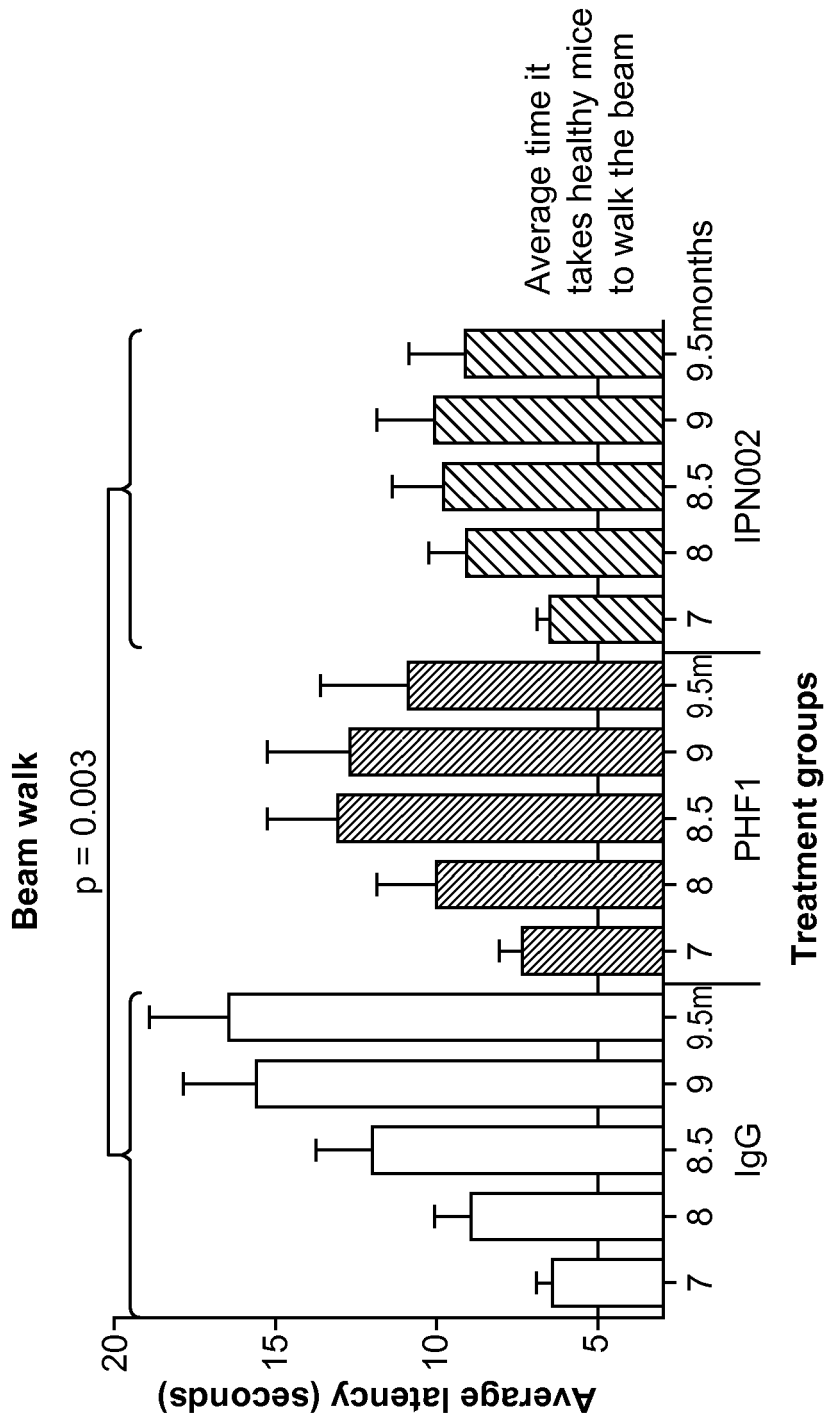

Beam walk
p = 0.003
Average latency (seconds)
20
15
10
5
7
8
8.5
9
9.5m
IgG
PHF1
IPN002
Treatment groups
Average time it takes healthy mice to walk the beam
9.5months

FIG. 32

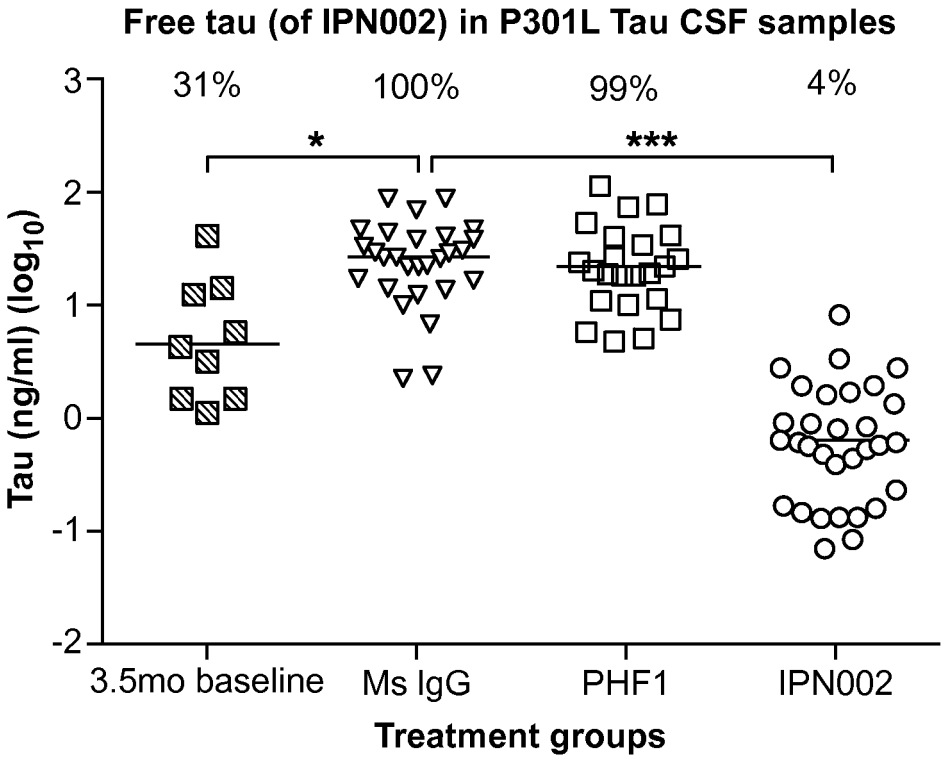
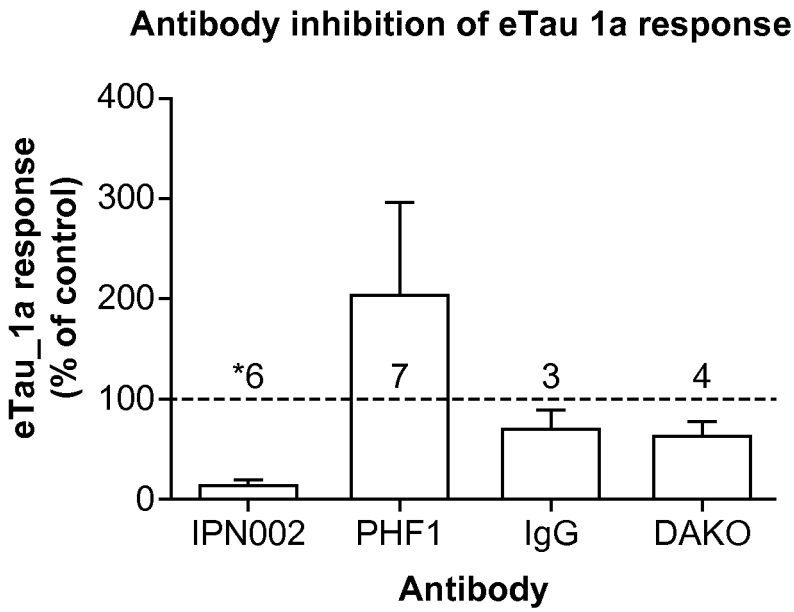

Free tau (of IPN002) in P301L Tau CSF samples
31%
100%
99%
4%
*
***
3
2
1
0
-1
-2
Tau (ng/ml) (log10)
3.5mo baseline
Ms IgG
PHF1
IPN002
Treatment groups

FIG. 33



*Values in graph represent number of neurons tested for each antibody

FIG. 34

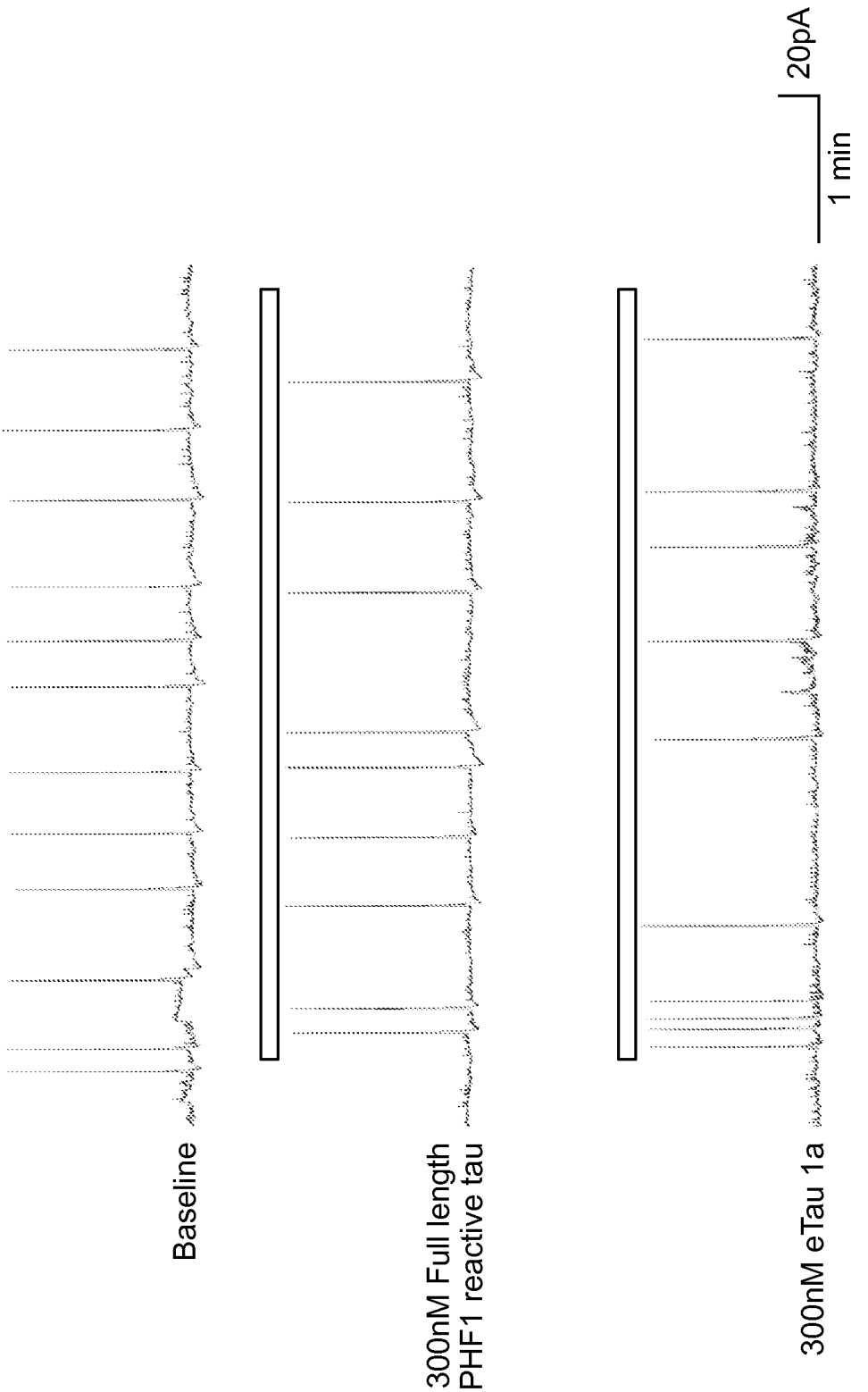

20pA
1 min
Baseline
300nM Full length PHF1 reactive tau
300nM eTau 1a

FIG. 35

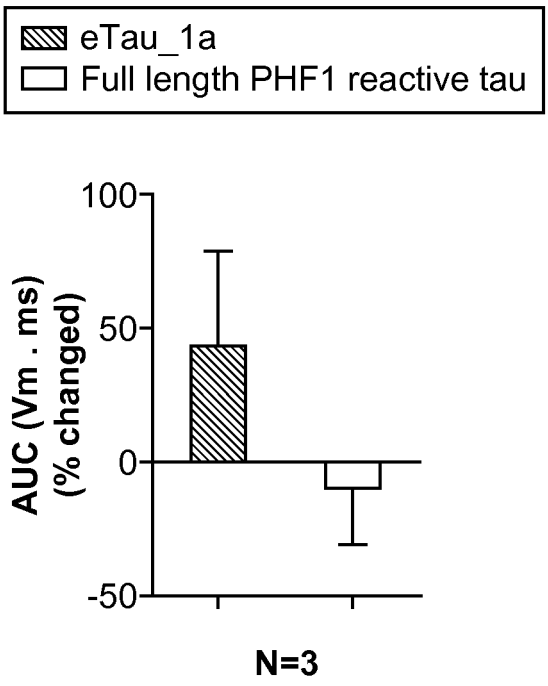

eTau_1a
Full length PHF1 reactive tau
100
50
0
-50
AUC (Vm . ms)
(% changed)
N=3

FIG. 36

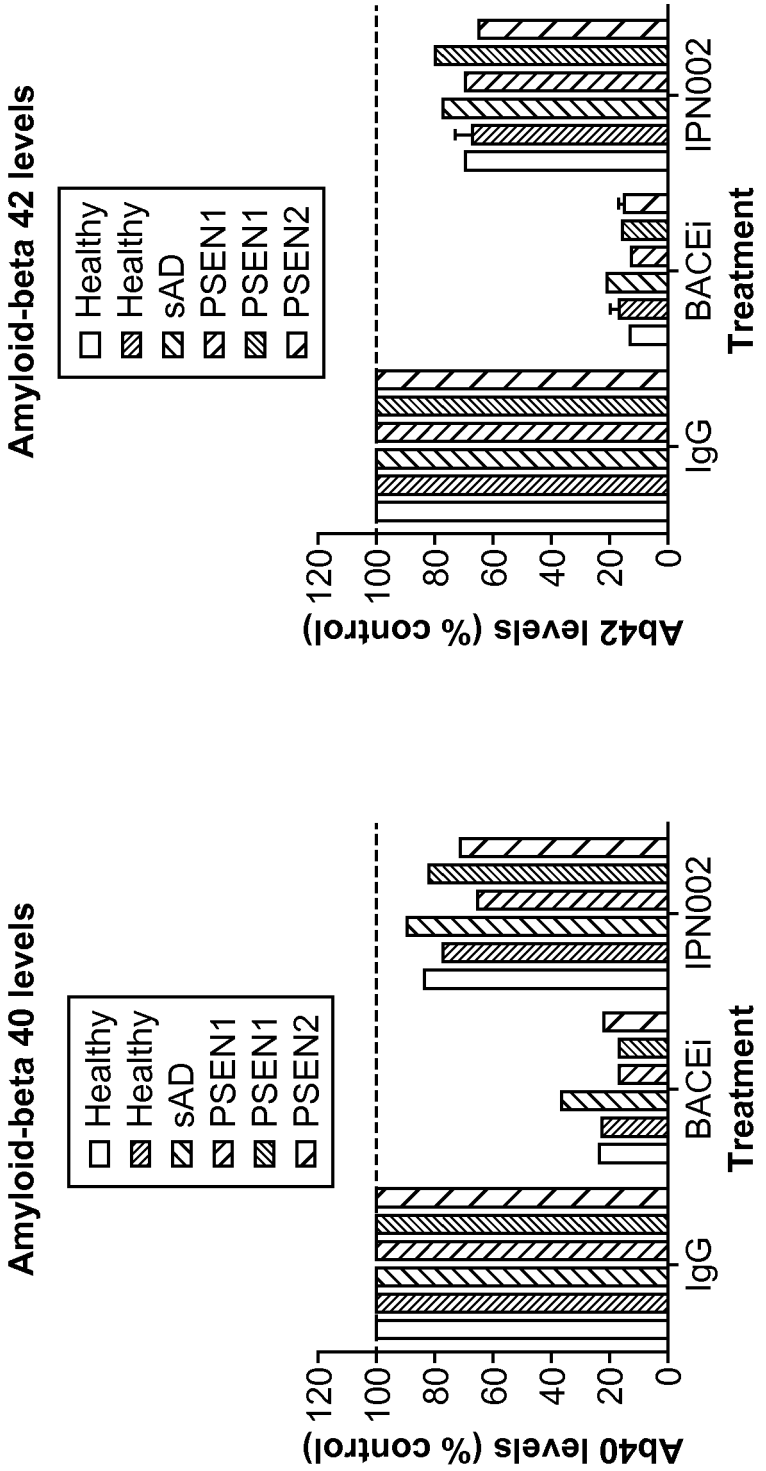

Amyloid-beta 42 levels
Healthy
Healthy
sAD
PSEN1
PSEN1
PSEN2
Ab42 levels (% control)
120
100
80
60
40
20
0
IgG
BACEi
IPN002
Treatment
Amyloid-beta 40 levels
Healthy
Healthy
sAD
PSEN1
PSEN1
PSEN2
Ab40 levels (% control)
120
100
80
60
40
20
0
IgG
BACEi
IPN002
Treatment

FIG. 37

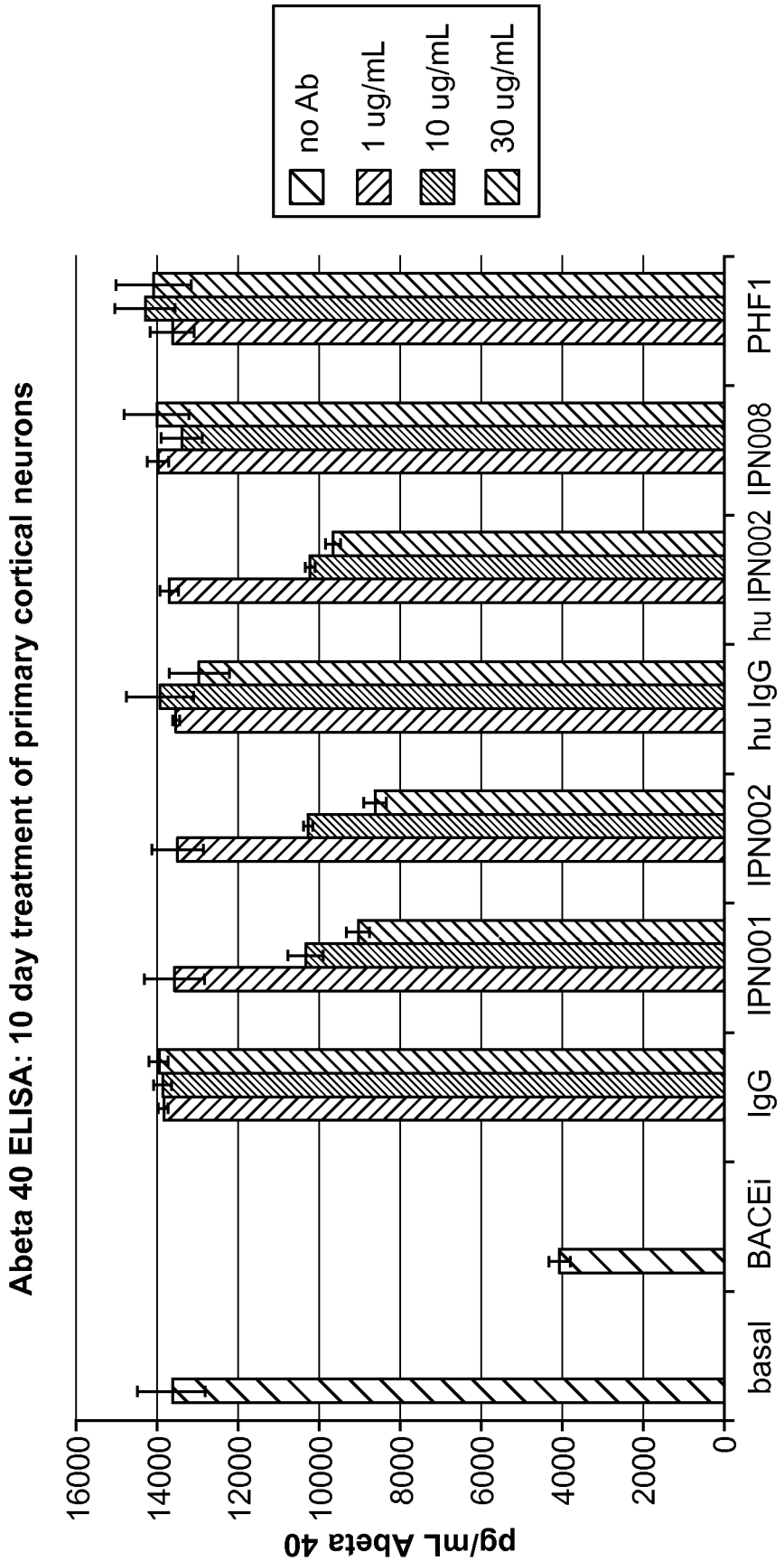

Abeta 40 ELISA: 10 day treatment of primary cortical neurons
pg/mL Abeta 40
16000
14000
12000
10000
8000
6000
4000
2000
0
no Ab
1 ug/mL
10 ug/mL
30 ug/mL
basal
BACEi
IgG
IPN001
IPN002
hu IgG
hu IPN002
IPN008
PHF1

FIG. 38

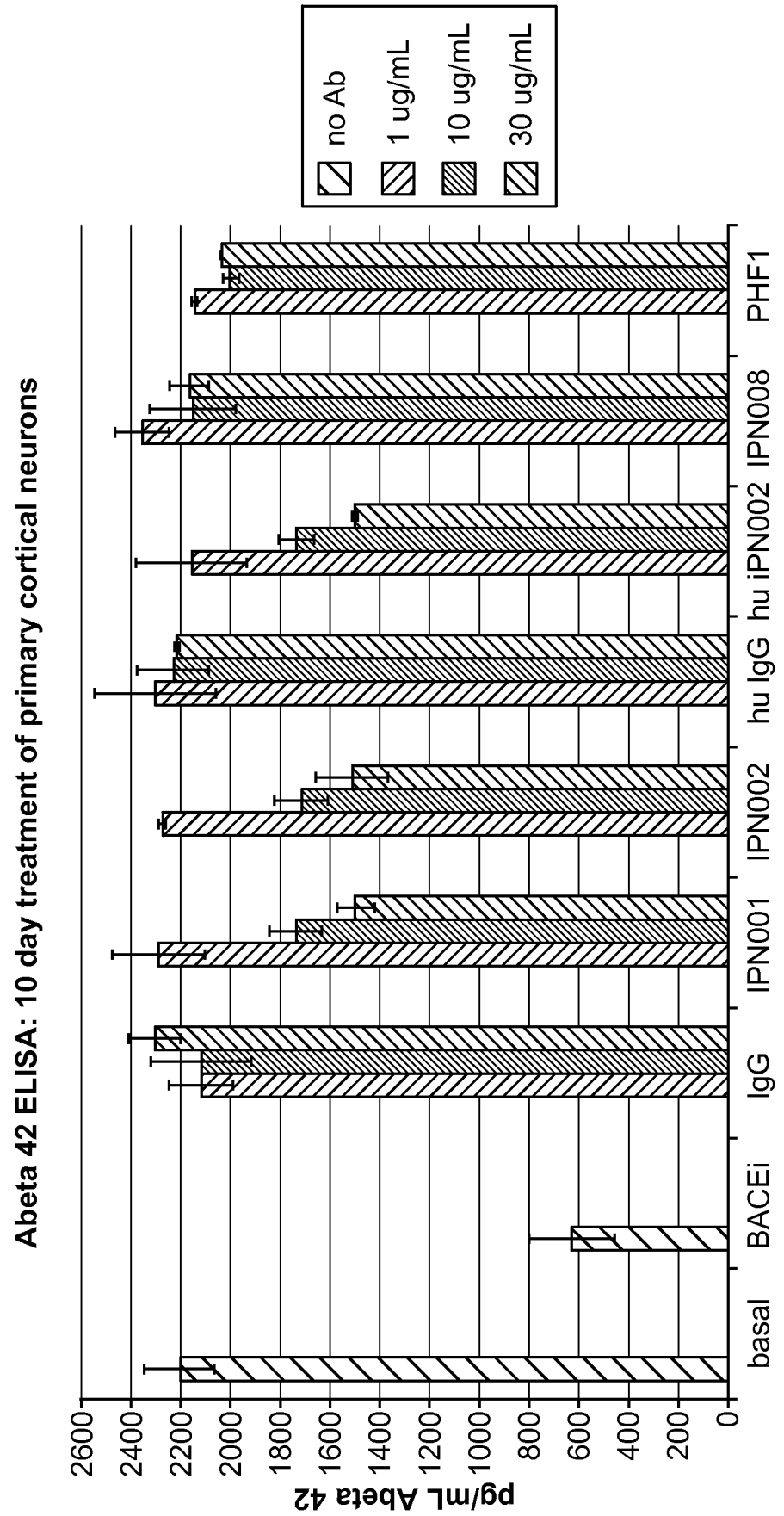

Abeta 42 ELISA: 10 day treatment of primary cortical neurons
pg/mL Abeta 42
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
no Ab
1 ug/mL
10 ug/mL
30 ug/mL
basal
BACEi
IgG
IPN001
IPN002
hu IgG
hu iPN002
IPN008
PHF1

FIG. 39

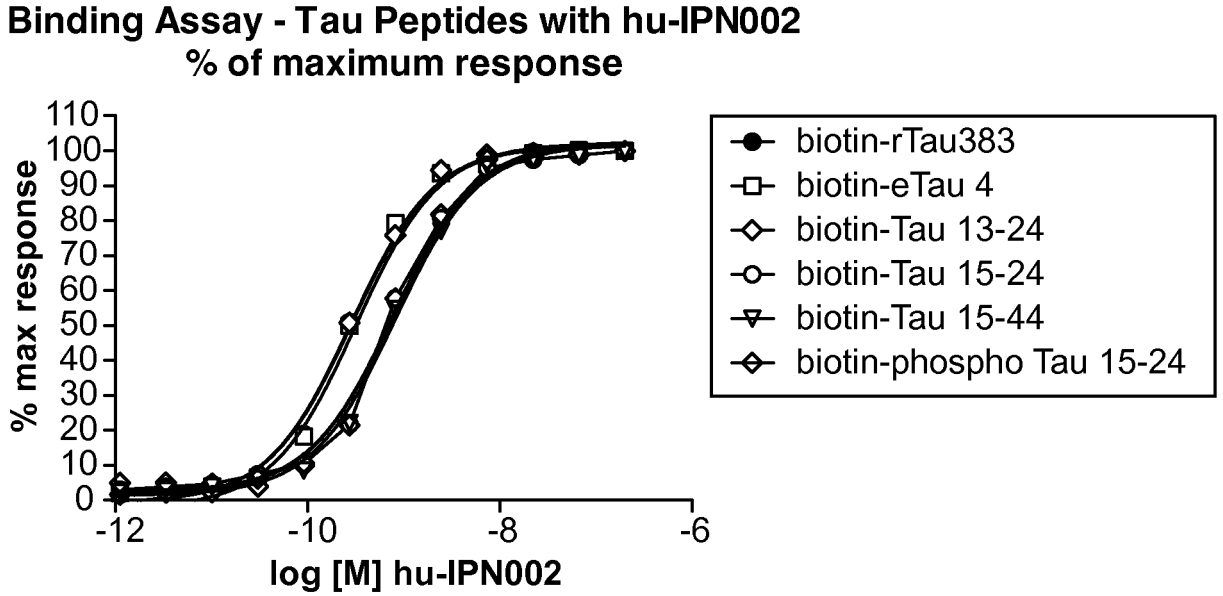
SUBSTITUTE SHEET (RULE 26)

Biotin-ahx-^{13}DHAGTYGLGDRK^{24} (SEQ ID NO: 49)

Biotin-ahx-^{15}AGTYGLGDRK^{24} (SEQ ID NO: 51)

Biotin-ahx-^{15}AGTYGLGDRKDQGGYTMHQDQEGDTDAGLK^{44} (SEQ ID NO: 50)

Biotin-ahx-^{15}AGTY(phospho)GLGDRK^{24} (SEQ ID NO: 52)



sample	k_D [M]
biotin-rTau383	2.83E-10
biotin-eTau 4	2.89E-10
biotin-Tau 13-24	3.18E-10
biotin-Tau 15-24	7.54E-10
biotin-Tau 15-44	8.13E-10
biotin-Tau 15-24 PHOSPHO	7.68E-10

FIG. 40

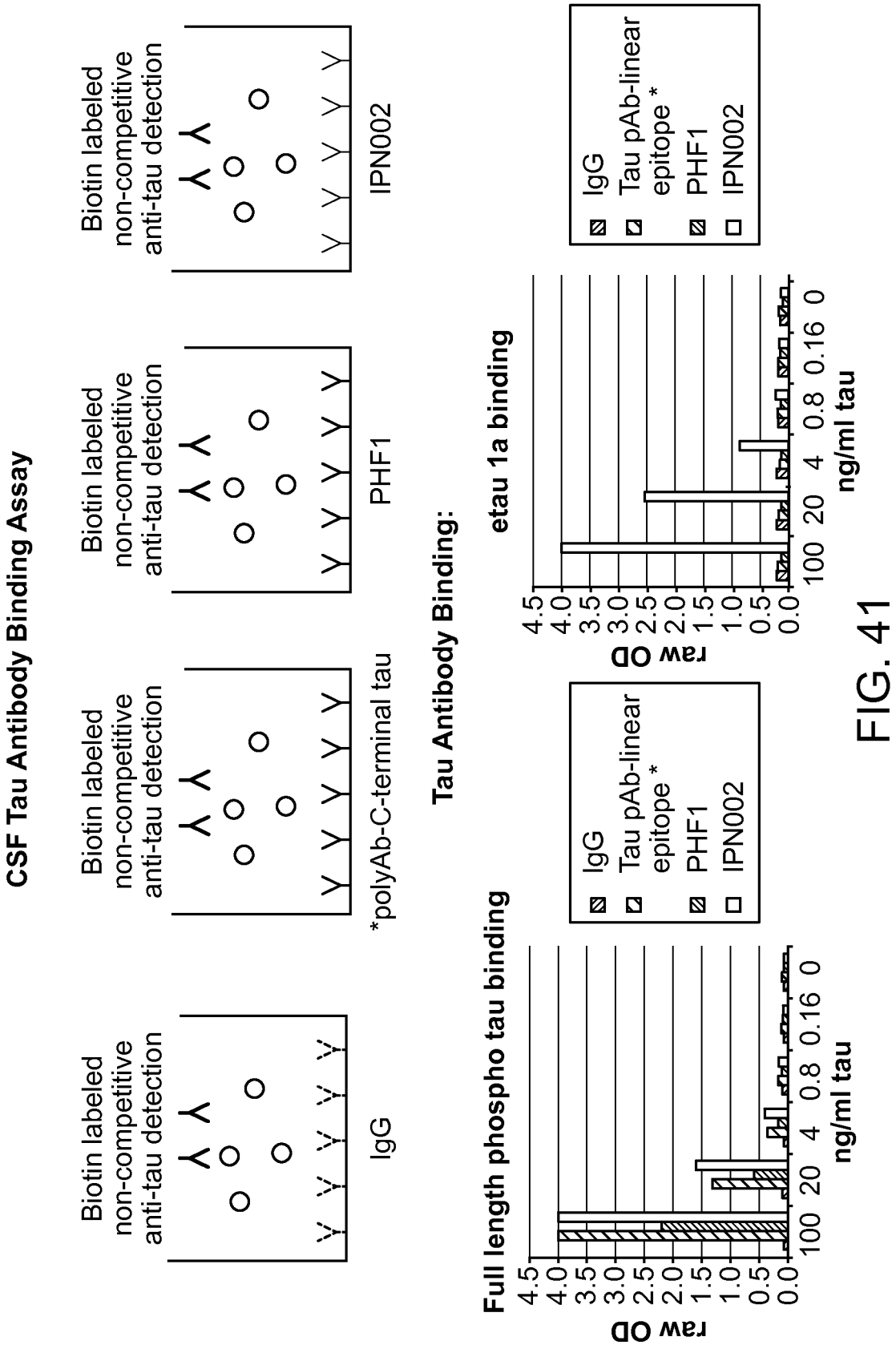

CSF Tau Antibody Binding Assay
Biotin labeled non-competitive anti-tau detection
IgG
*polyAb-C-terminal tau
PHF1
IPN002
Tau Antibody Binding:
Full length phospho tau binding
etau 1a binding
raw OD
ng/ml tau
100 20 4 0.8 0.16 0
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5
IgG
Tau pAb-linear epitope *
PHF1
IPN002

FIG. 41

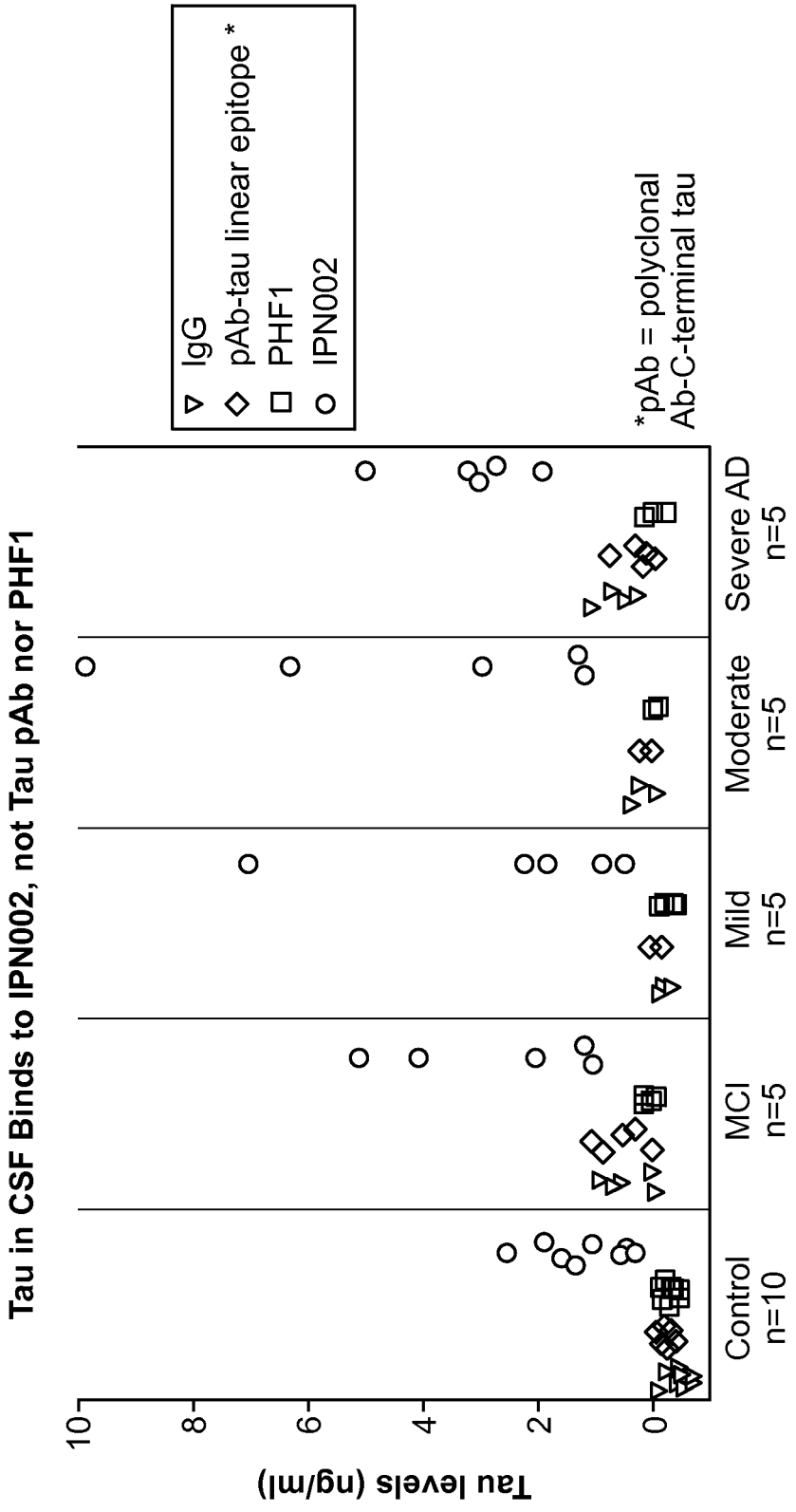

Tau in CSF Binds to IPN002, not Tau pAb nor PHF1
Tau levels (ng/ml)
0
2
4
6
8
10
Control n=10
MCI n=5
Mild n=5
Moderate n=5
Severe AD n=5
IgG
pAb-tau linear epitope *
PHF1
IPN002
*pAb = polyclonal Ab-C-terminal tau

FIG. 42

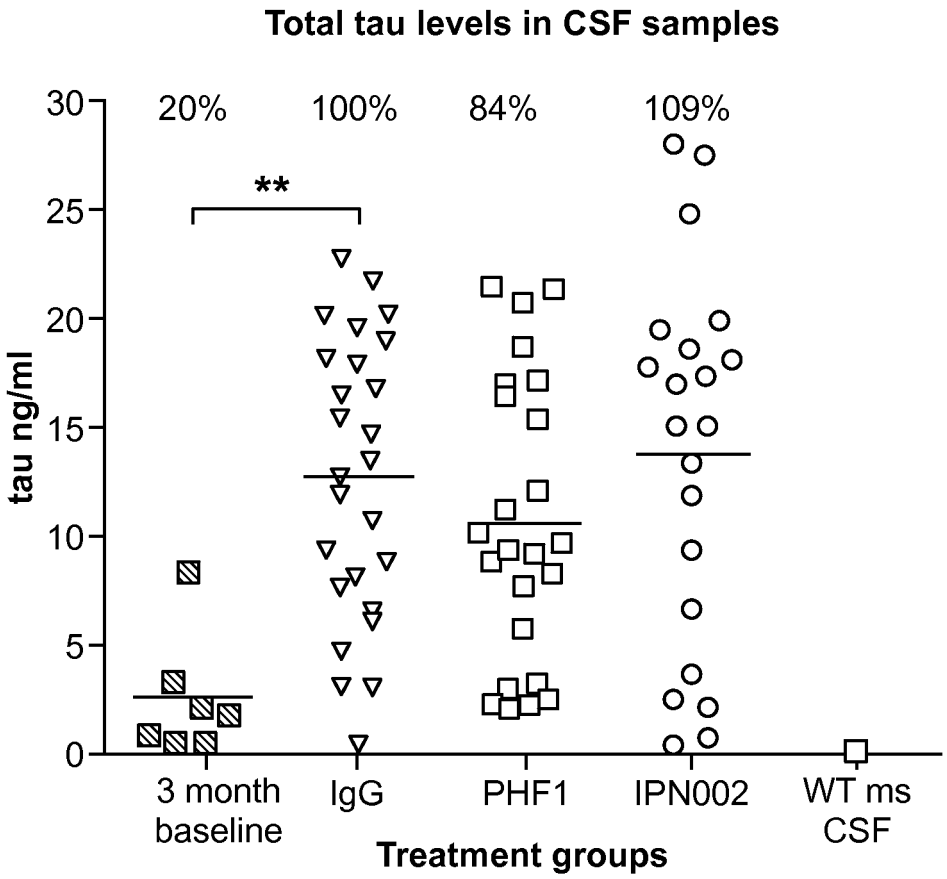

Total tau levels in CSF samples
20%
100%
84%
109%
**
30
25
20
15
10
5
0
tau ng/ml
3 month baseline
IgG
PHF1
IPN002
WT ms CSF
Treatment groups

FIG. 43

*p < 0.05
**p < 0.01
***p < 0.001
****p < 0.0001

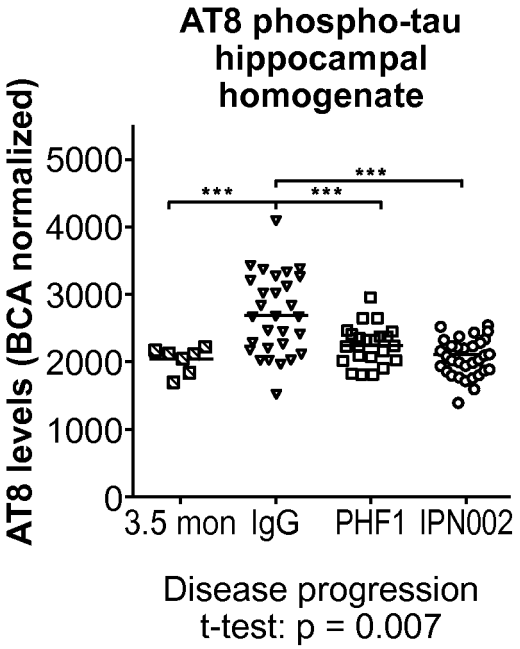


FIG. 44A

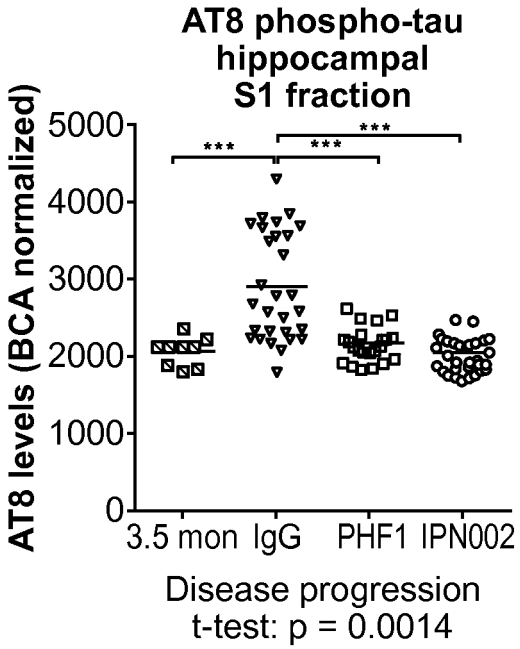


FIG. 44B

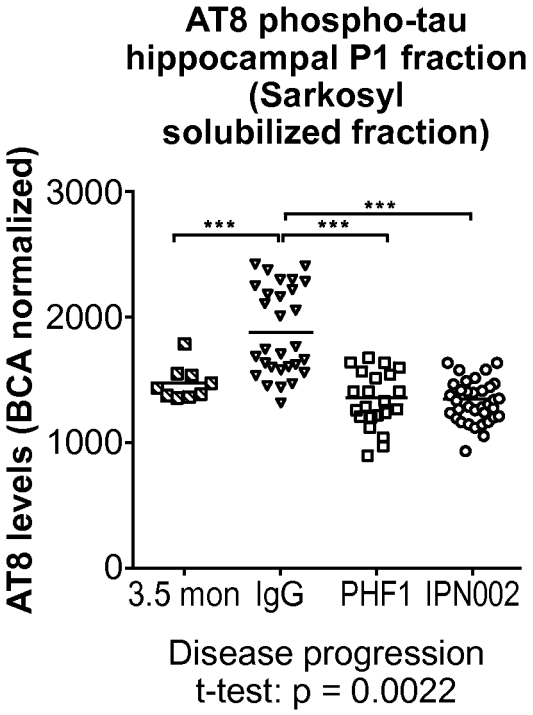


FIG. 44C

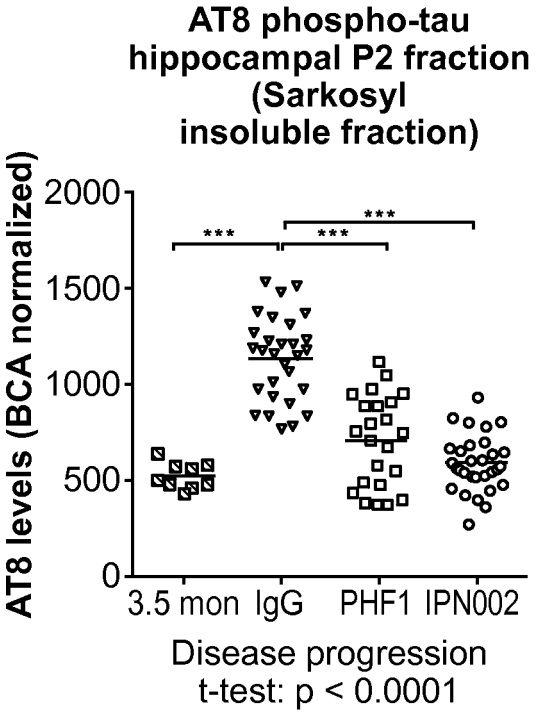


FIG. 44D

One way ANOVA followed by
Dunnett's multiple comparison test
*=p<.05
**=p<.01
***=p<.001

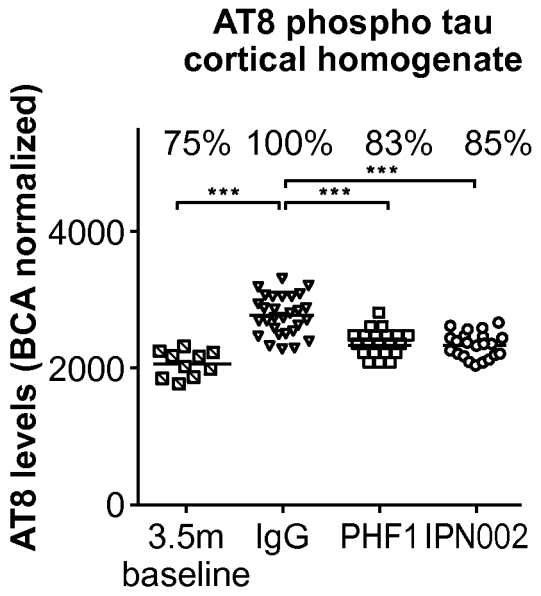


FIG. 44E

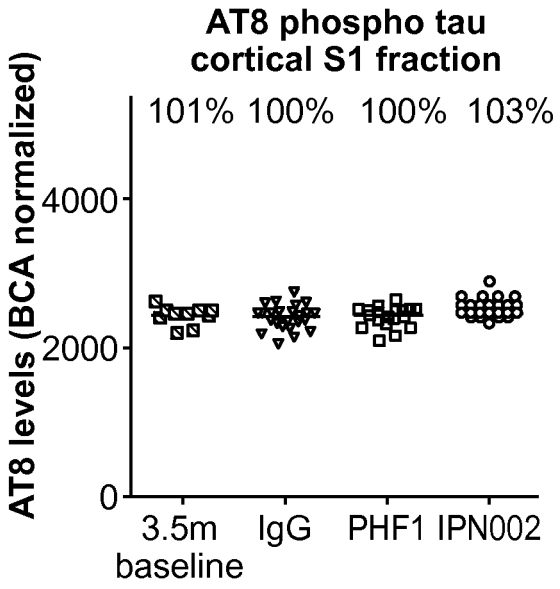


FIG. 44F

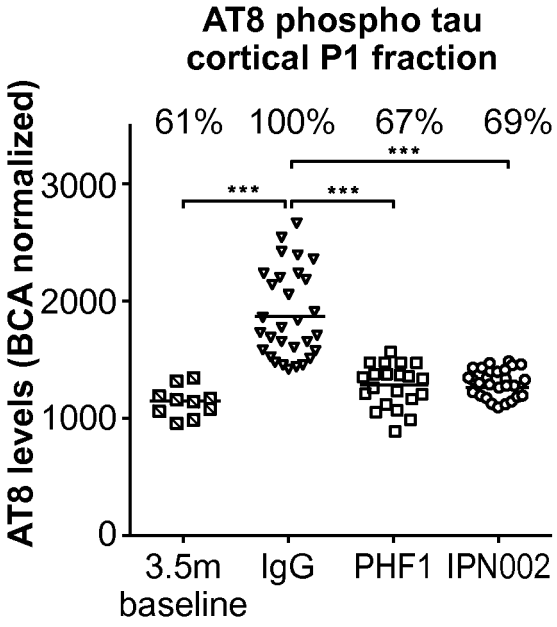


FIG. 44G

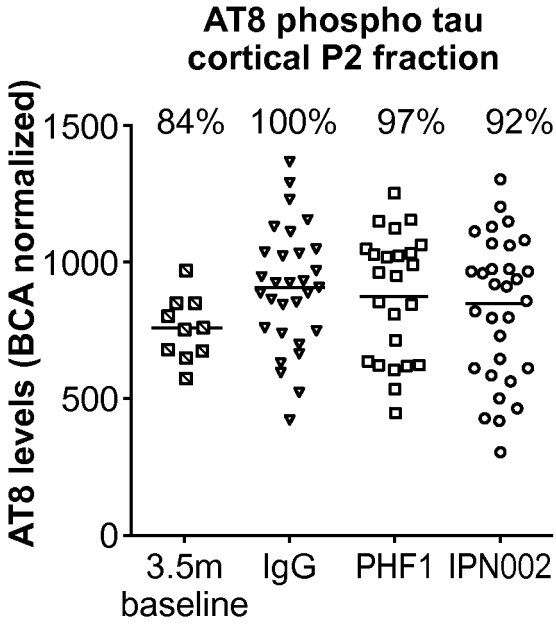


FIG. 44H

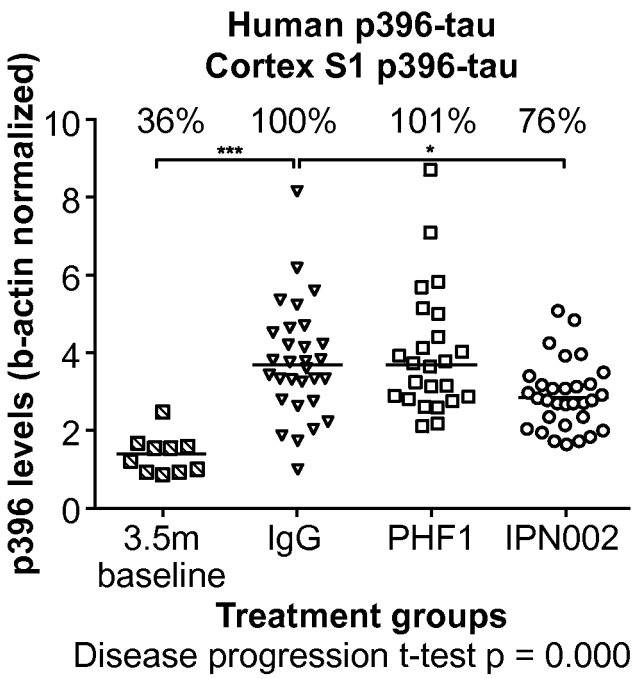


FIG. 45A

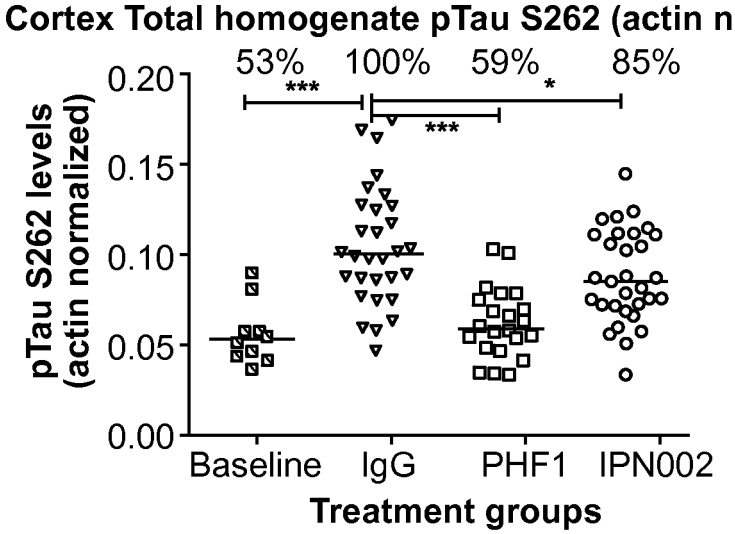


FIG. 45B

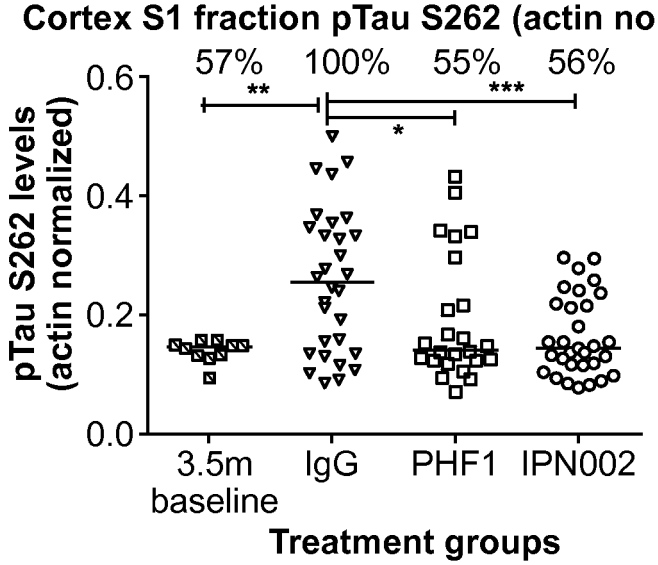
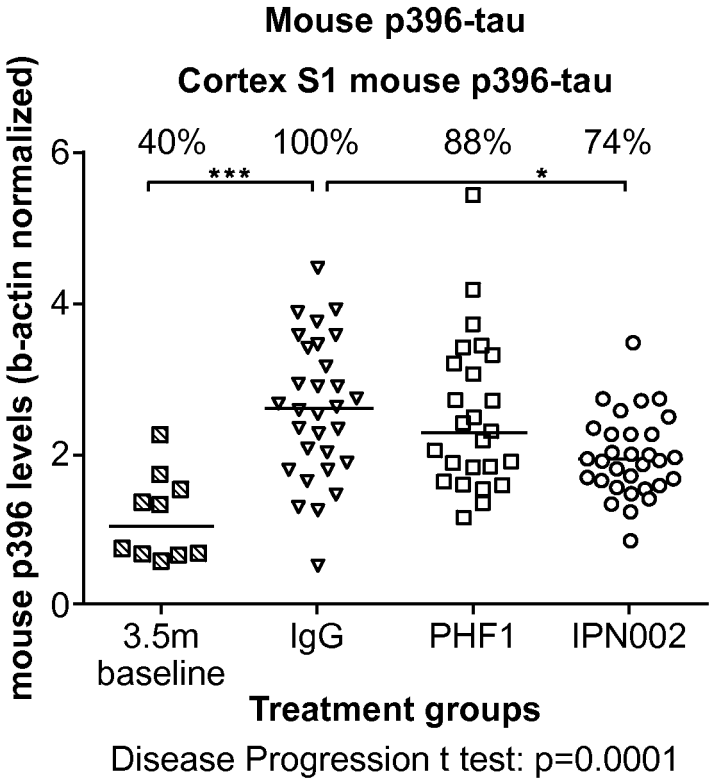
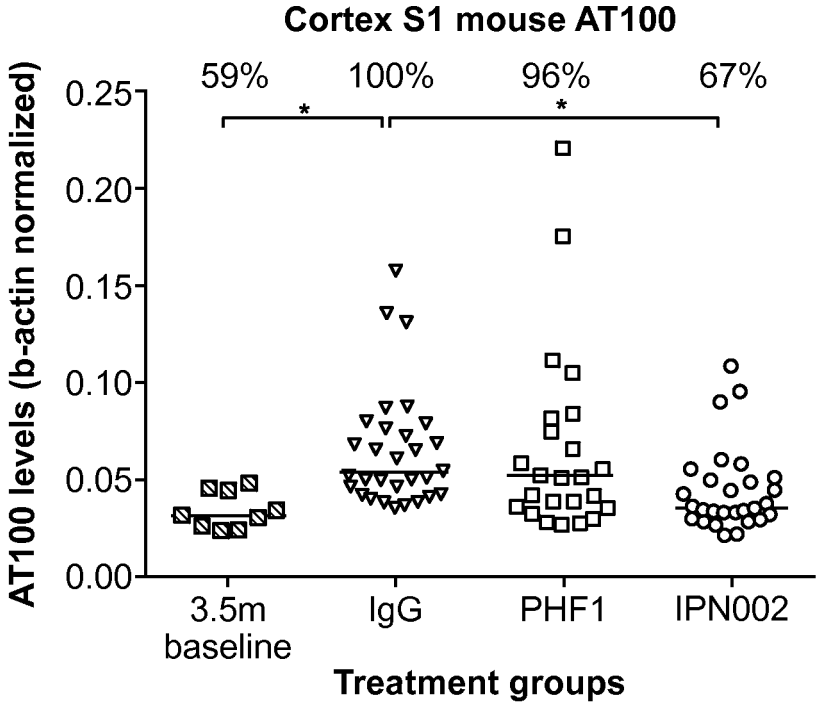


FIG. 45C



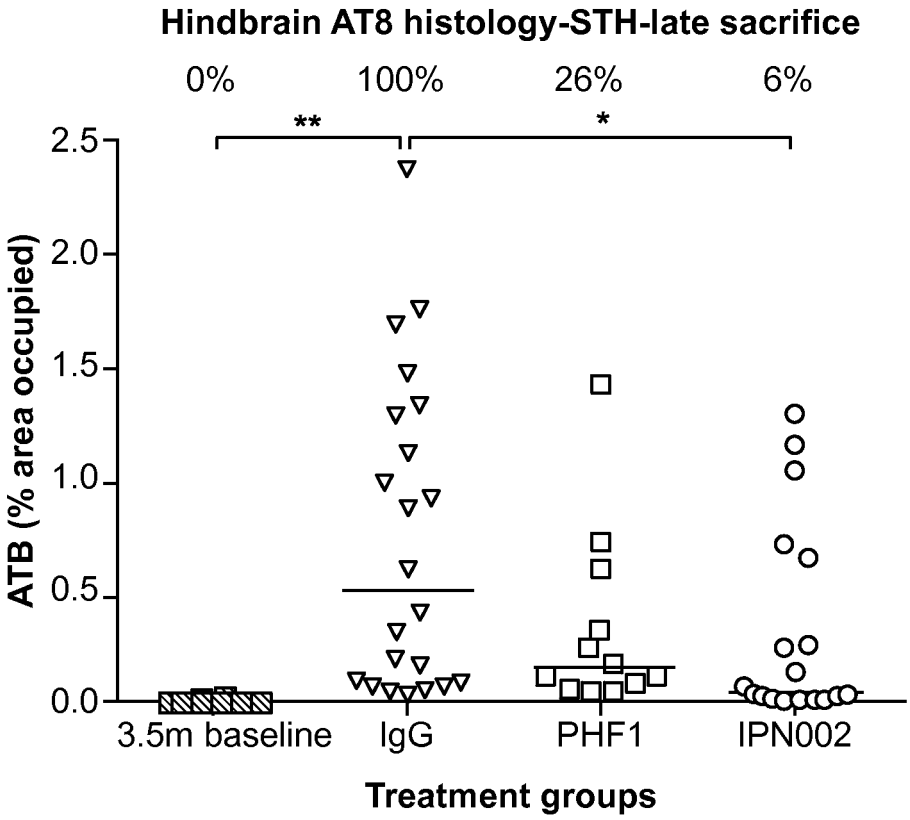
Disease Progression t test: p=0.0001

FIG. 45D



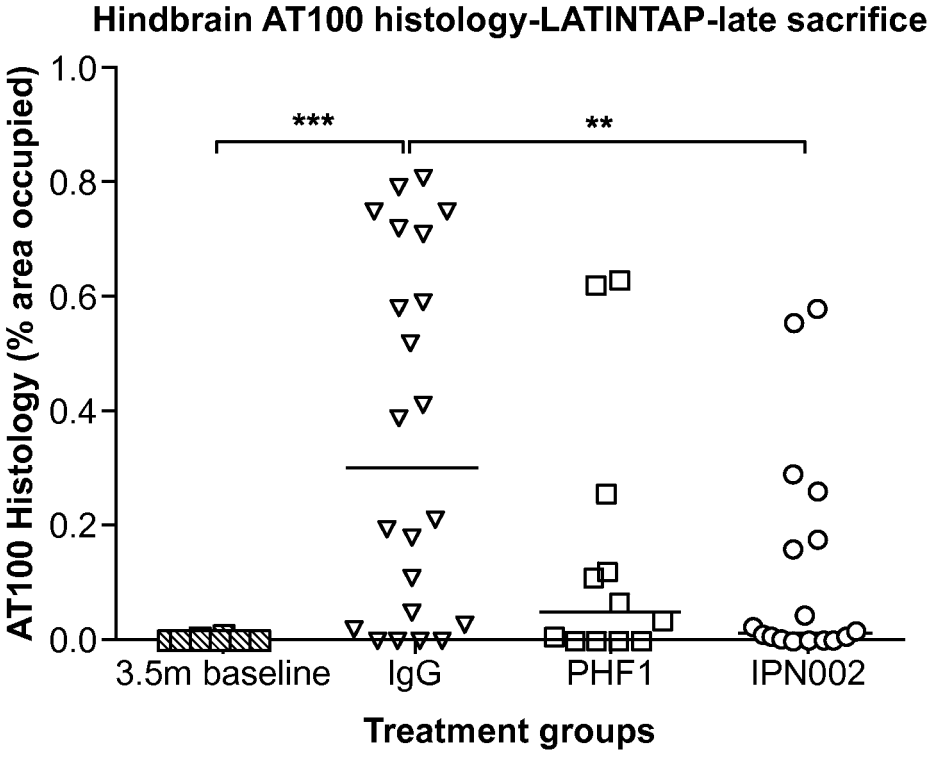
Disease progression t-test: p = 0.005

FIG. 45E



Disease progression t-test: $p < 0.0028$

FIG. 46



Disease progression t-test: $p < 0.0014$

FIG. 47

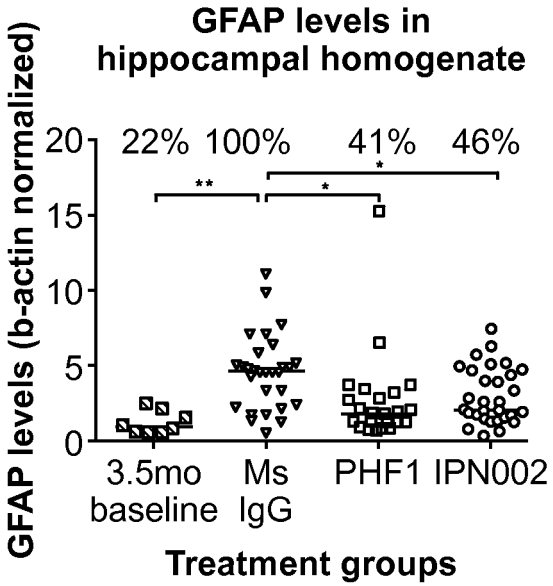
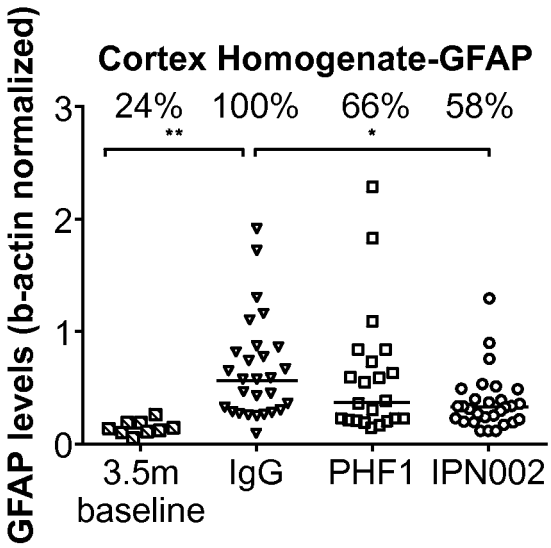


FIG. 48A



Disease progression
t-test p = 0.0019

FIG. 48B

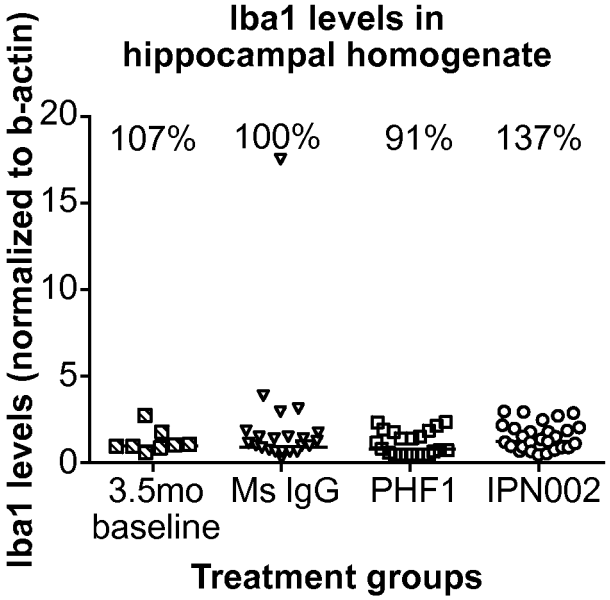
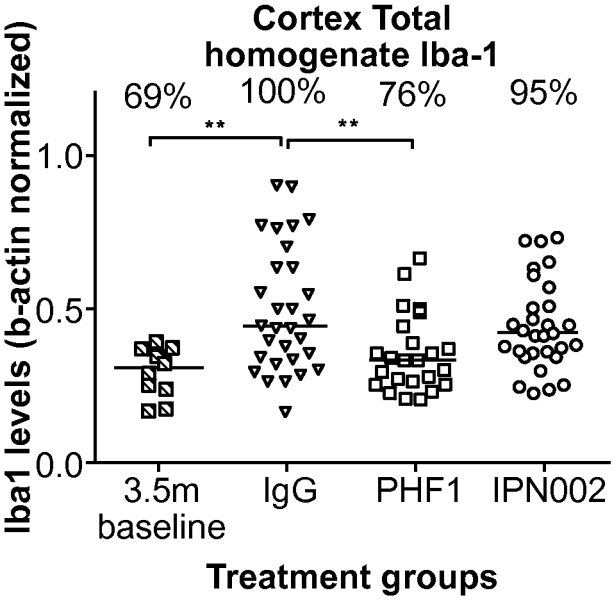


FIG. 49A



Disease progression
t-test p = 0.0041

FIG. 49B

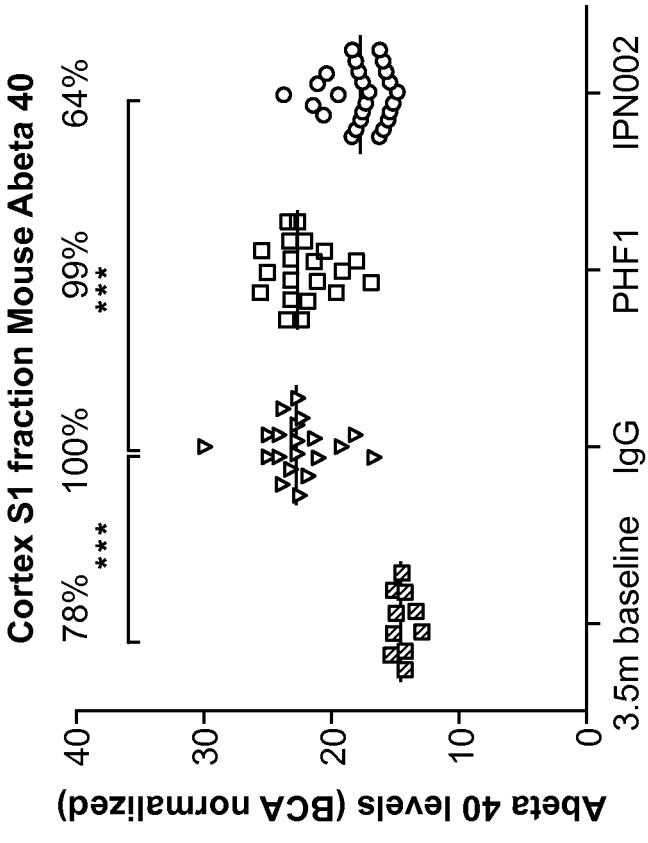


FIG. 50B

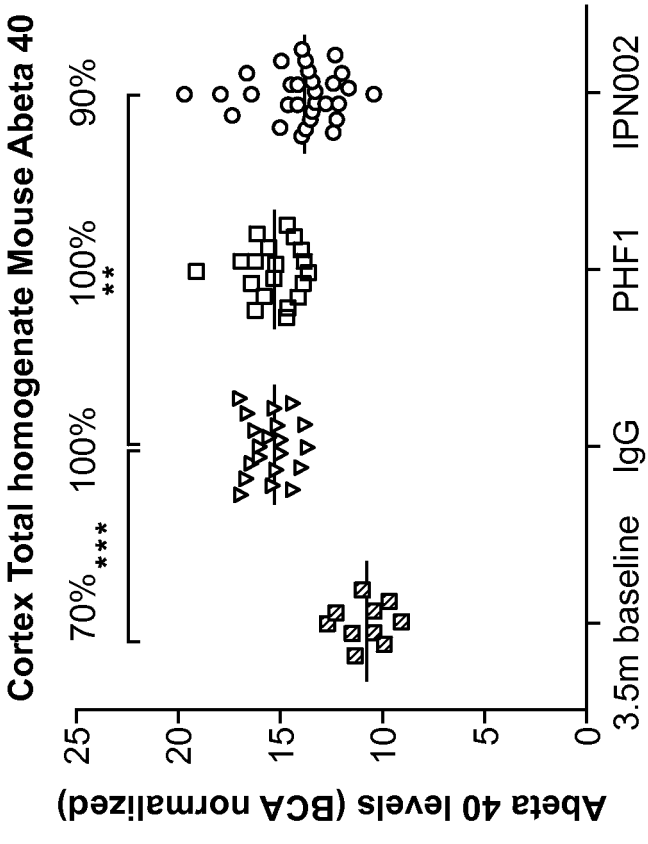


FIG. 50A

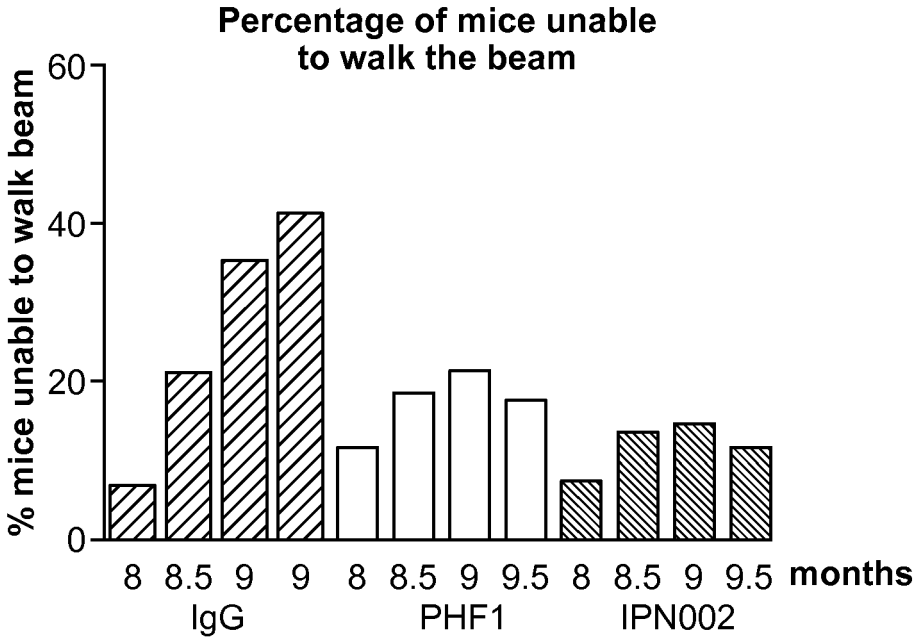
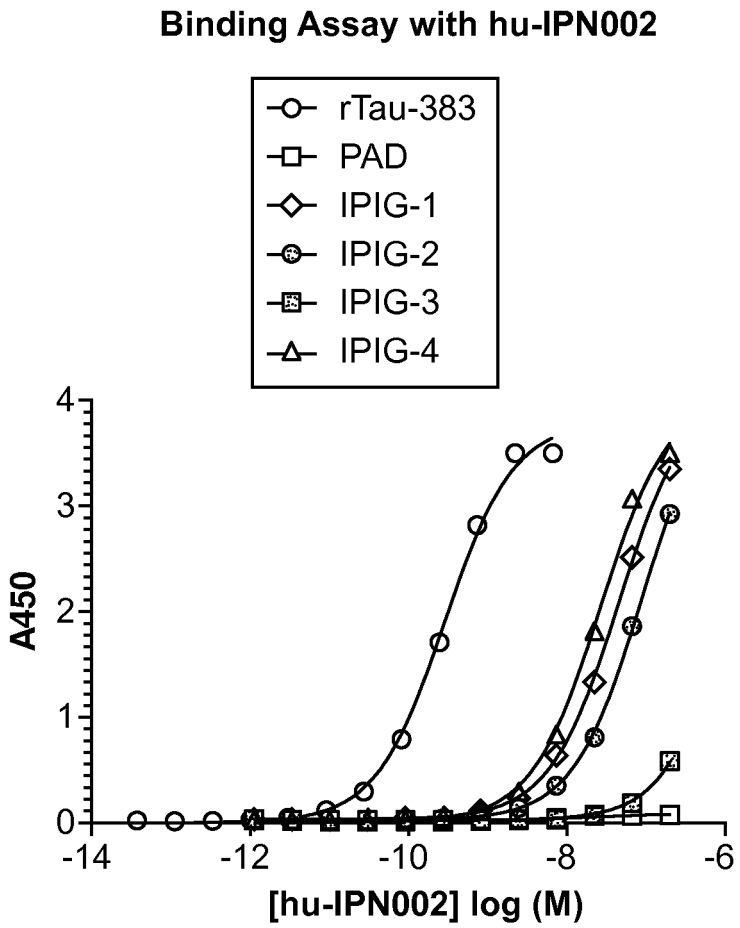
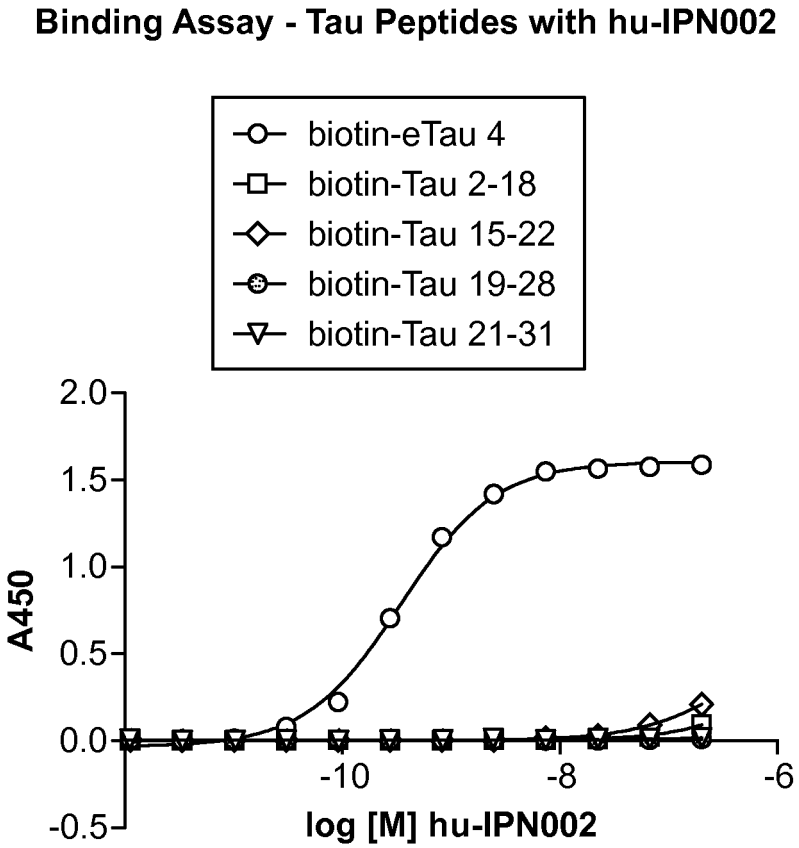

Percentage of mice unable to walk the beam
% mice unable to walk beam
60
40
20
0
8 8.5 9 9 8 8.5 9 9.5 8 8.5 9 9.5
months
IgG
PHF1
IPN002

FIG. 51



	hu-IPN002 k_D [M]
rTau-383	2.88E-10
PAD (2-18)	n.a.
IPIG-1 (9-24)	4.52E-08
IPIG-2 (13-24)	9.03E-08
IPIG-3 (15-22)	n.a.
IPIG-4 (15-44)	2.65E-08

FIG. 52



sample	k_D [M]
biotin-eTau 4	3.447E-10
biotin-Tau 2-18	n.a.
biotin-Tau 15-22	incomplete
biotin-Tau 19-28	n.a.
biotin-Tau 21-31	n.a.

FIG. 53

A.
Free Tau (of IPN002) Assay
1. IPN002 competitive capture antibody, IPN001, to tau
2. IPN002 + tau
3. Biotin labelled anti-tau, HT7, detection
FRET detection
B.
Bound Tau (to IPN002) Assay
1. Non-IPN002 competitive Rb, PA5-27287, capture antibody to tau
2. IPN002 + tau
3. Biotin anti-mouse/ human Ab detection
Strep-HRP

FIG. 54