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

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

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

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

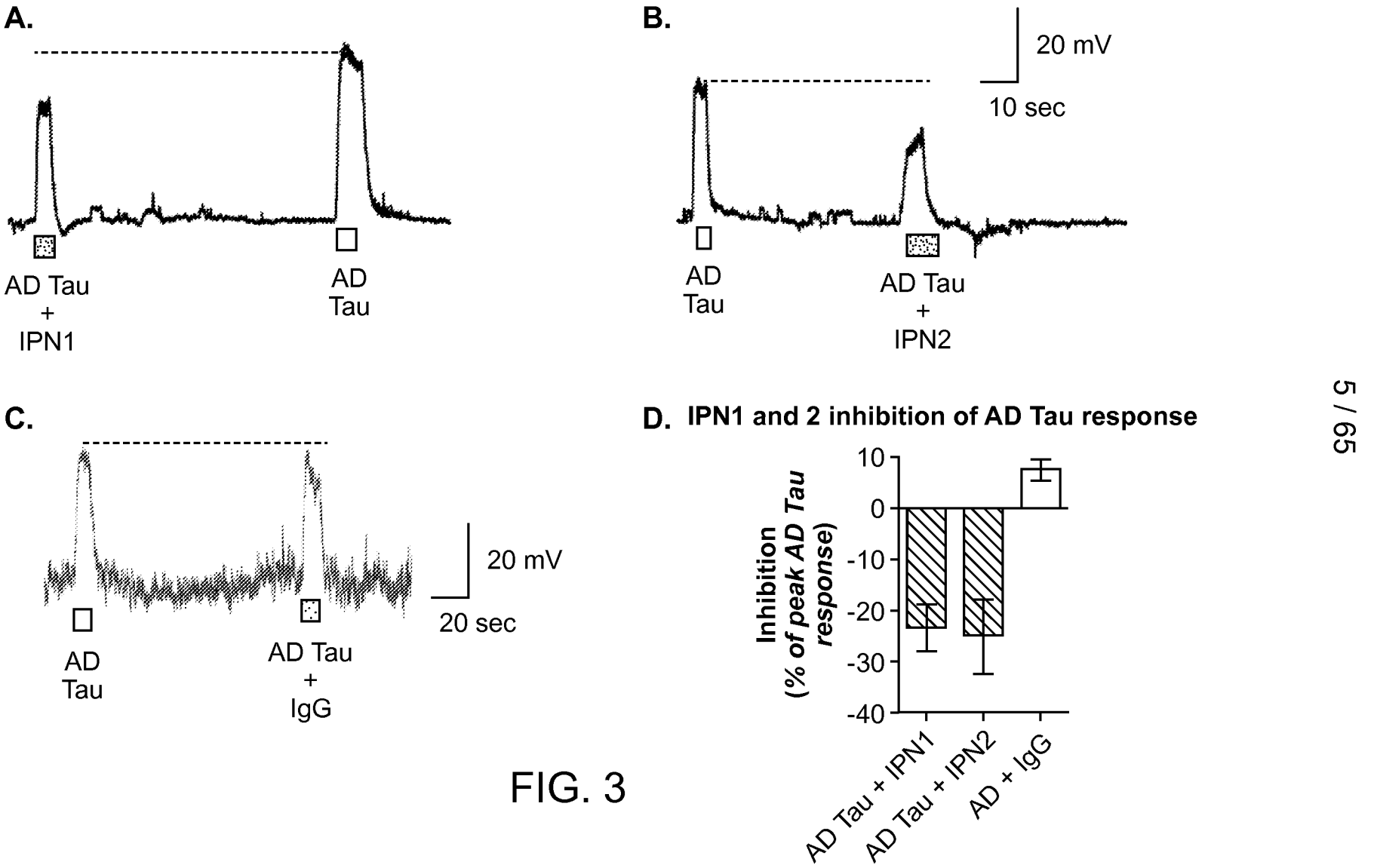

A.
AD Tau
+
IPN1
AD
Tau
B.
20 mV
10 sec
AD
Tau
AD Tau
+
IPN2
C.
20 mV
20 sec
AD
Tau
AD Tau
+
IgG
D. IPN1 and 2 inhibition of AD Tau response
Inhibition
(% of peak AD Tau
response)
10
0
-10
-20
-30
-40
AD Tau + IPN1
AD Tau + IPN2
AD + IgG

FIG. 3

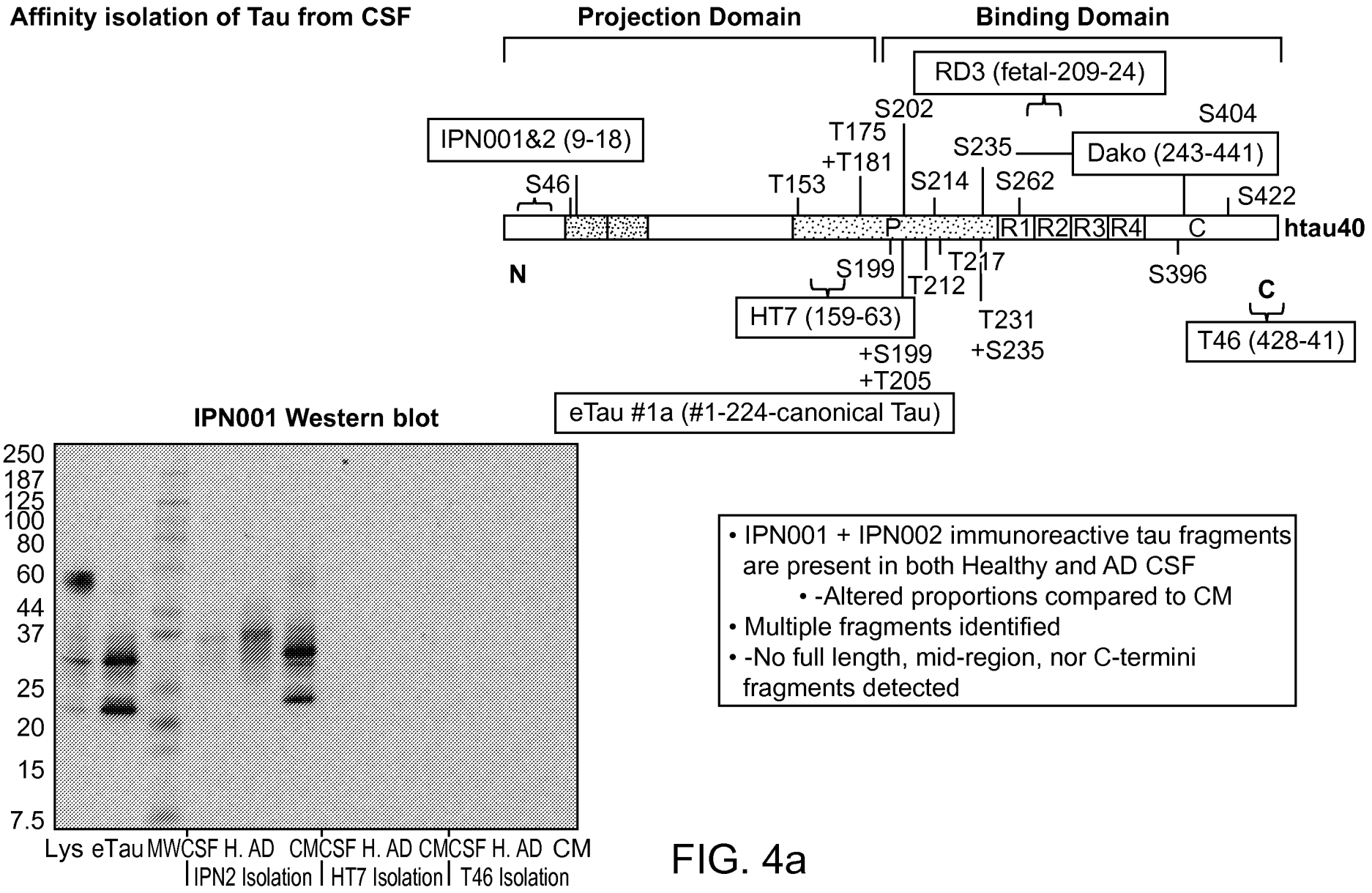

Affinity isolation of Tau from CSF
Projection Domain
Binding Domain
RD3 (fetal-209-24)
S202
S404
IPN001&2 (9-18)
T175
+T181
S235
Dako (243-441)
S46
T153
S214
S262
S422
P
R1
R2
R3
R4
C
htau40
N
S199
T212
T217
S396
C
HT7 (159-63)
T231
+S235
T46 (428-41)
+S199
+T205
eTau #1a (#1-224-canonical Tau)
IPN001 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
• IPN001 + IPN002 immunoreactive tau fragments are present in both Healthy and AD CSF
• -Altered proportions compared to CM
• Multiple fragments identified
• -No full length, mid-region, nor C-termini fragments detected

FIG. 4a

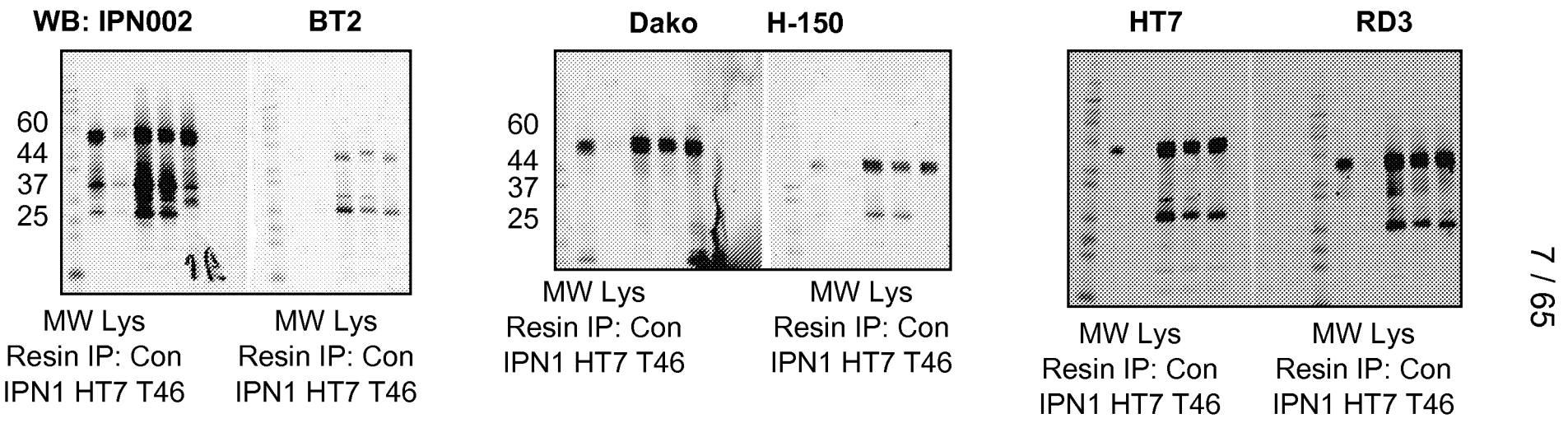

WB: IPN002
BT2
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
Dako
H-150
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
HT7
RD3
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4a (Cont.)

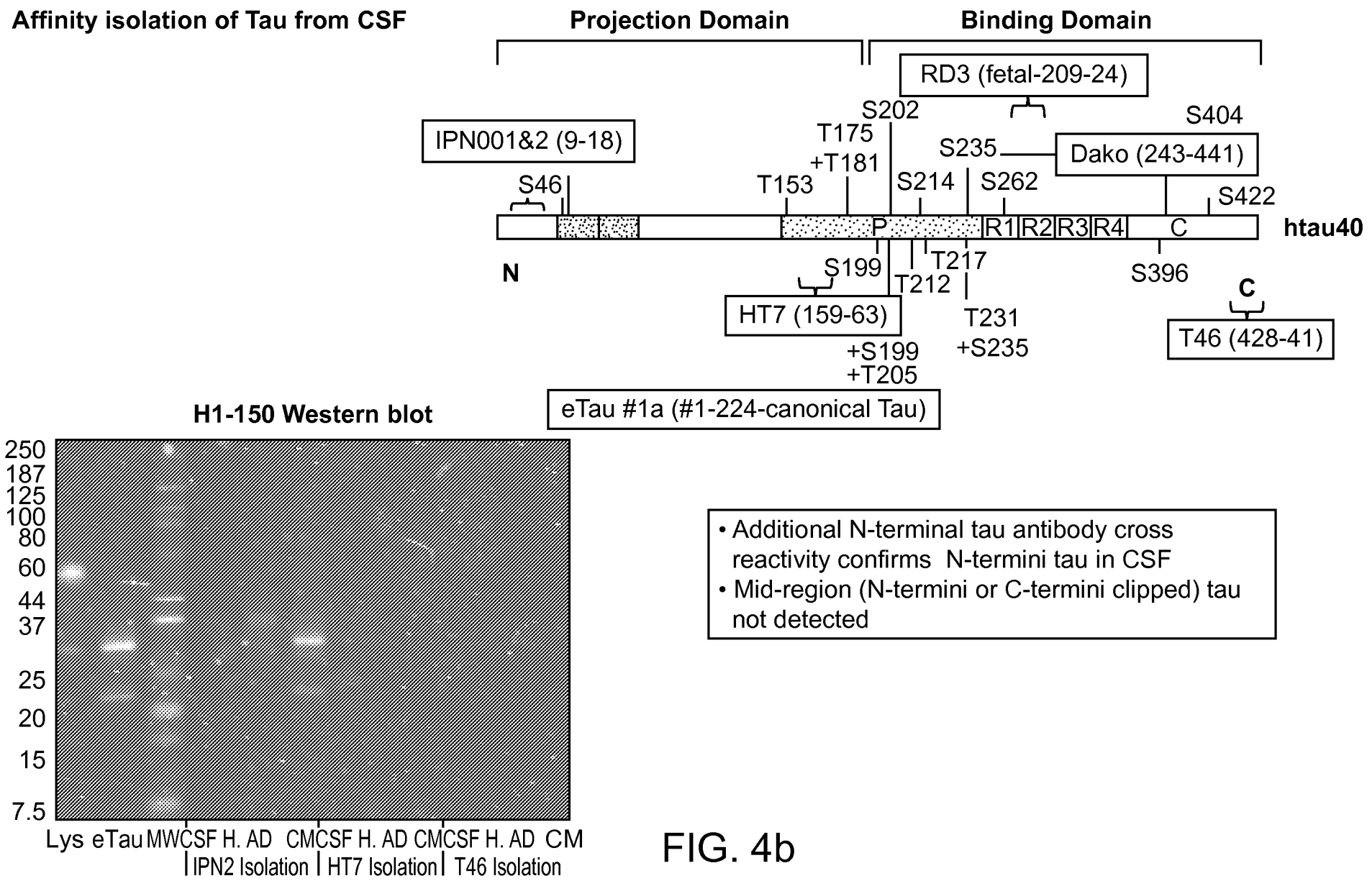

Affinity isolation of Tau from CSF
Projection Domain
Binding Domain
RD3 (fetal-209-24)
S202
S404
IPN001&2 (9-18)
T175
+T181
S235
Dako (243-441)
S46
T153
S214
S262
S422
P
R1
R2
R3
R4
C
htau40
N
S199
T217
T212
S396
C
HT7 (159-63)
T231
+S235
T46 (428-41)
+S199
+T205
eTau #1a (#1-224-canonical Tau)
H1-150 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
• Additional N-terminal tau antibody cross reactivity confirms N-termini tau in CSF
• Mid-region (N-termini or C-termini clipped) tau not detected

FIG. 4b

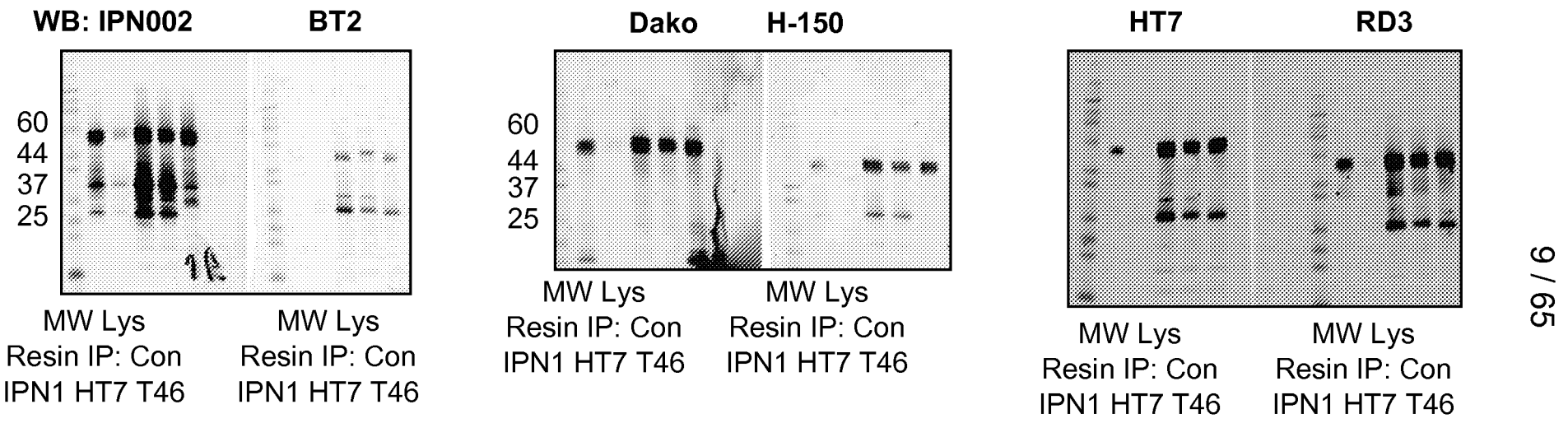

WB: IPN002
BT2
Dako
H-150
HT7
RD3
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4b (Cont.)

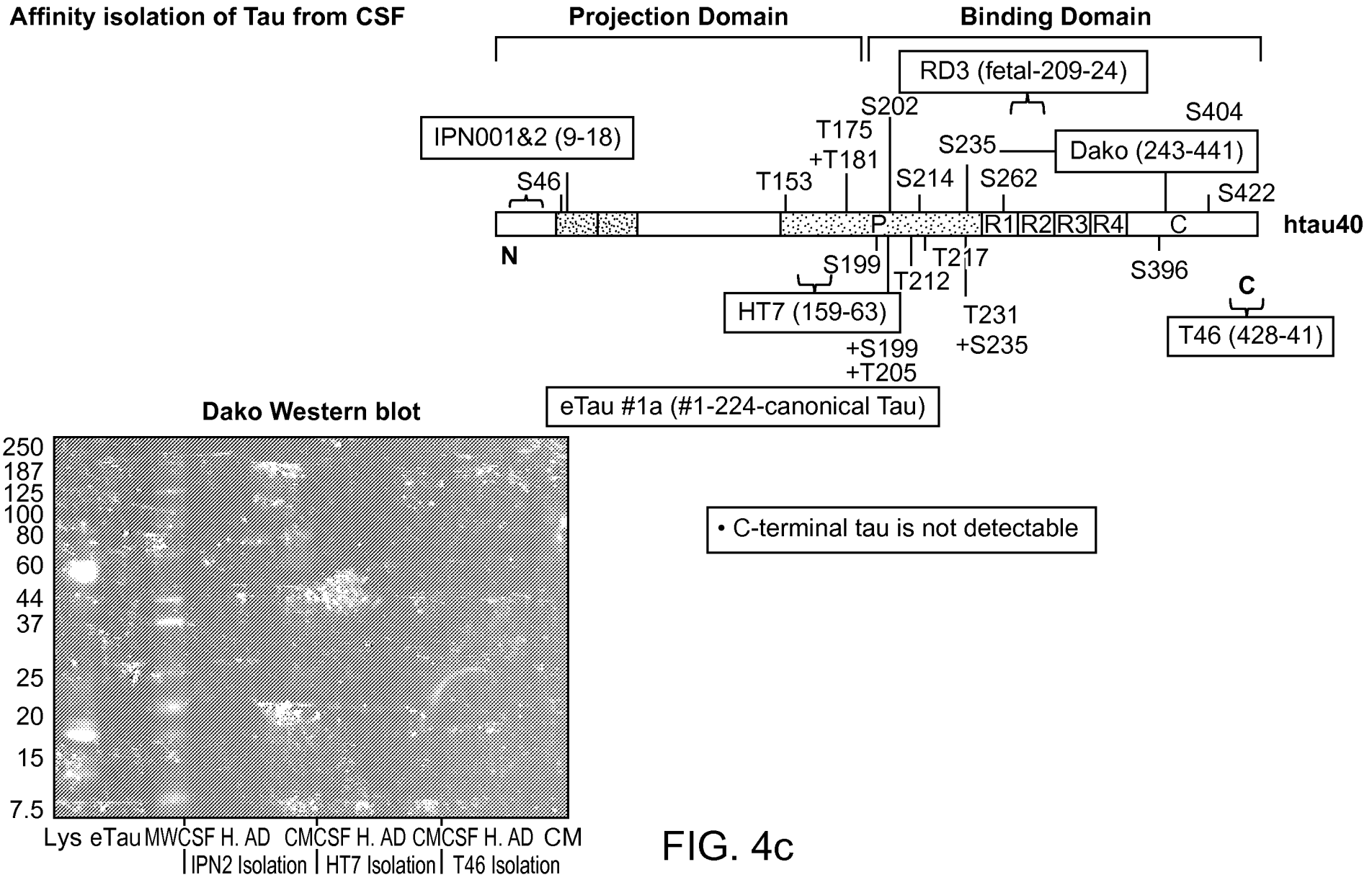

Affinity isolation of Tau from CSF
Projection Domain
Binding Domain
RD3 (fetal-209-24)
S202
S404
IPN001&2 (9-18)
T175
+T181
S235
Dako (243-441)
S46
T153
S214
S262
S422
P
R1
R2
R3
R4
C
htau40
N
S199
T217
T212
S396
C
HT7 (159-63)
T231
+S235
T46 (428-41)
+S199
+T205
eTau #1a (#1-224-canonical Tau)
Dako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

FIG. 4c

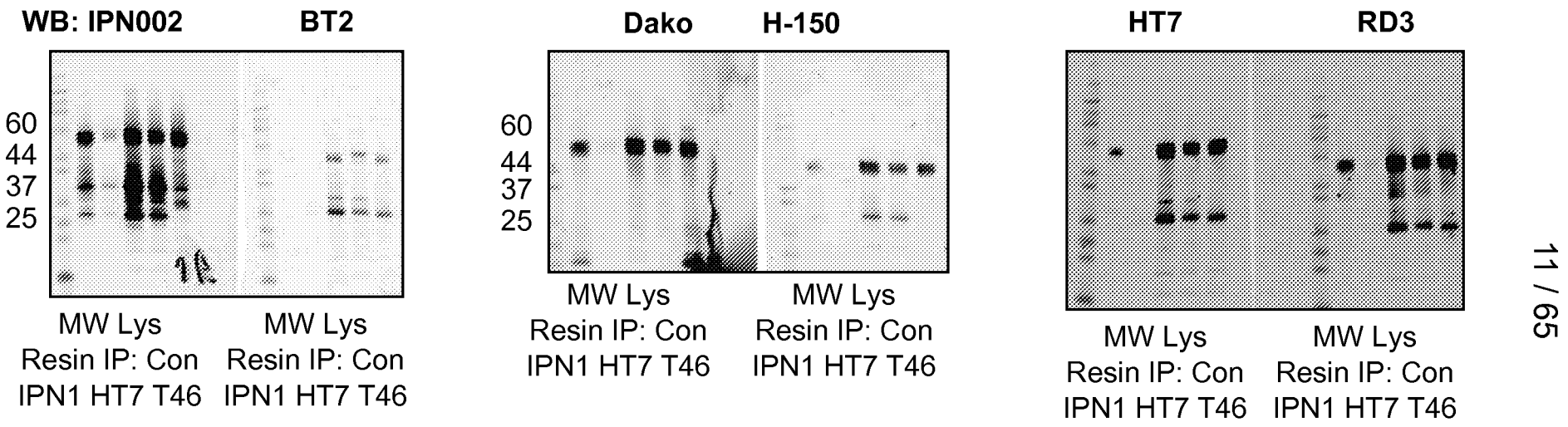

WB: IPN002
BT2
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
Dako
H-150
60
44
37
25
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46
HT7
RD3
MW Lys
Resin IP: Con
IPN1 HT7 T46
MW Lys
Resin IP: Con
IPN1 HT7 T46

FIG. 4c (Cont.)

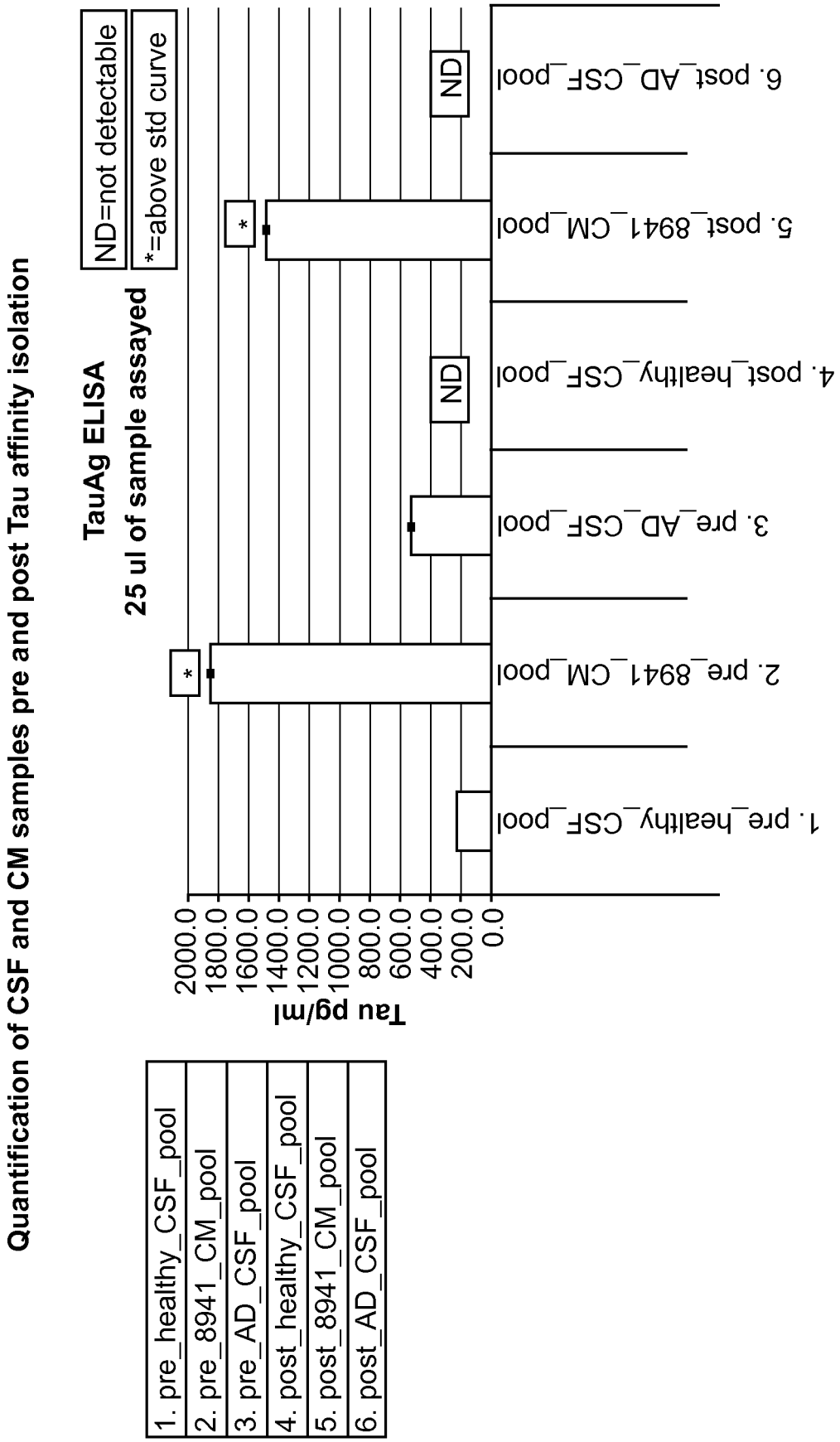

Quantification of CSF and CM samples pre and post Tau affinity isolation
TauAg ELISA
25 ul of sample assayed
ND=not detectable
*=above std curve
Tau pg/ml
2000.0
1800.0
1600.0
1400.0
1200.0
1000.0
800.0
600.0
400.0
200.0
0.0
1. pre_healthy_CSF_pool
2. pre_8941_CM_pool
3. pre_AD_CSF_pool
4. post_healthy_CSF_pool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

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

```
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

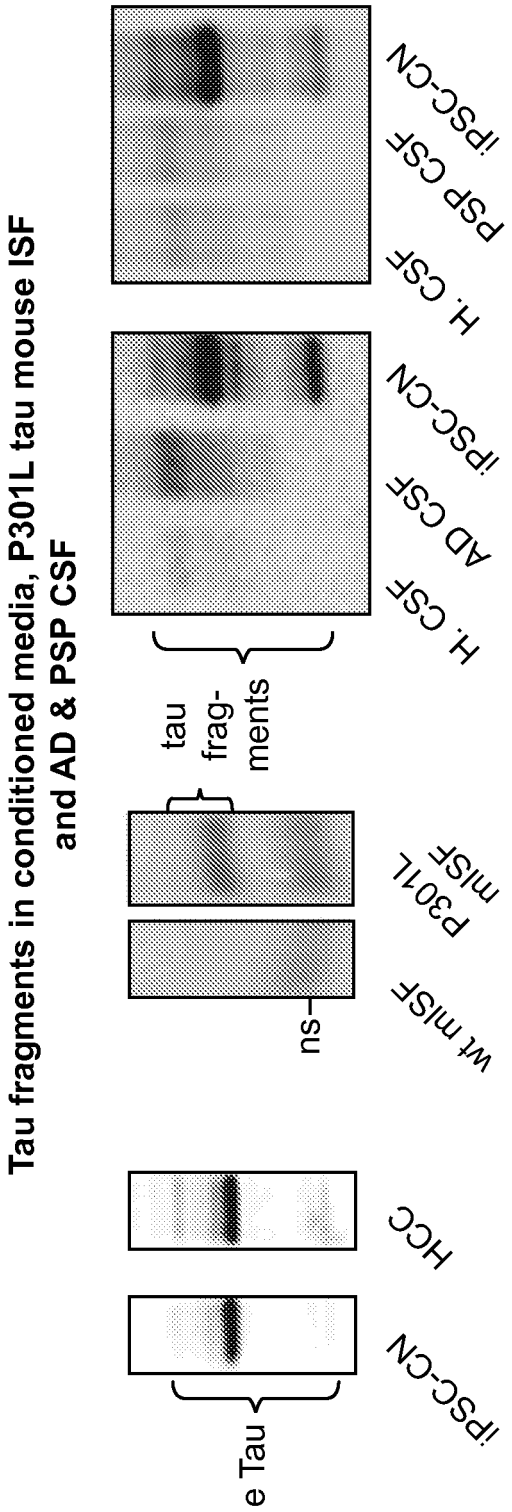

Tau fragments in conditioned media, P301L tau mouse ISF and AD & PSP CSF
iPSC-CN
HCC
wt mISF
P301L mISF
H. CSF
AD CSF
iPSC-CN
H. CSF
PSP CSF
iPSC-CN
e Tau
ns
tau frag-ments

FIG. 7

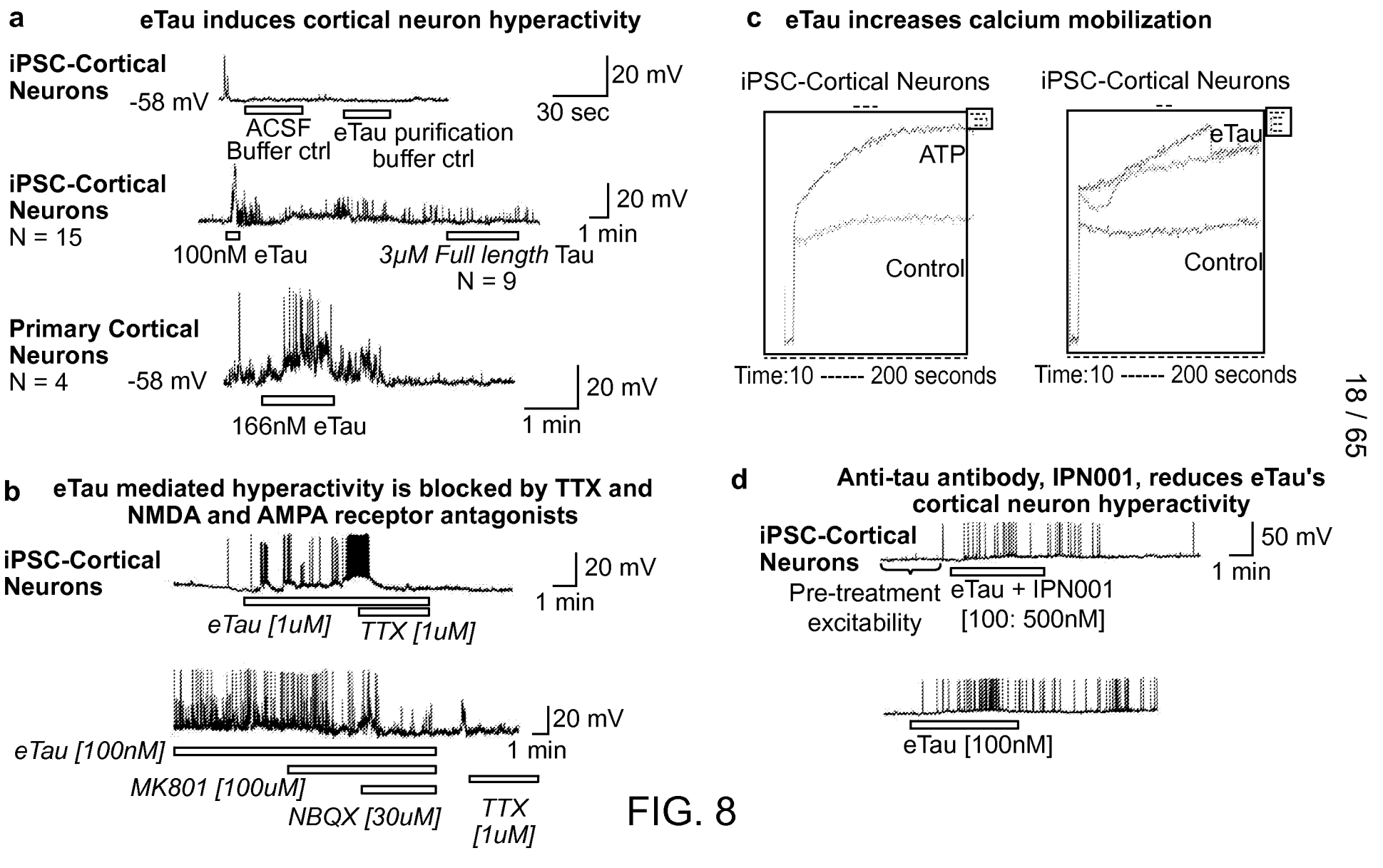

a
eTau induces cortical neuron hyperactivity
iPSC-Cortical Neurons
-58 mV
20 mV
30 sec
ACSF Buffer ctrl
eTau purification buffer ctrl
iPSC-Cortical Neurons
N = 15
20 mV
1 min
100nM eTau
3μM Full length Tau
N = 9
Primary Cortical Neurons
N = 4
-58 mV
20 mV
1 min
166nM eTau
b
eTau mediated hyperactivity is blocked by TTX and NMDA and AMPA receptor antagonists
iPSC-Cortical Neurons
20 mV
1 min
eTau [1uM]
TTX [1uM]
20 mV
1 min
eTau [100nM]
MK801 [100uM]
NBQX [30uM]
TTX [1uM]
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
50 mV
1 min
Pre-treatment excitability
eTau + IPN001 [100: 500nM]
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

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

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

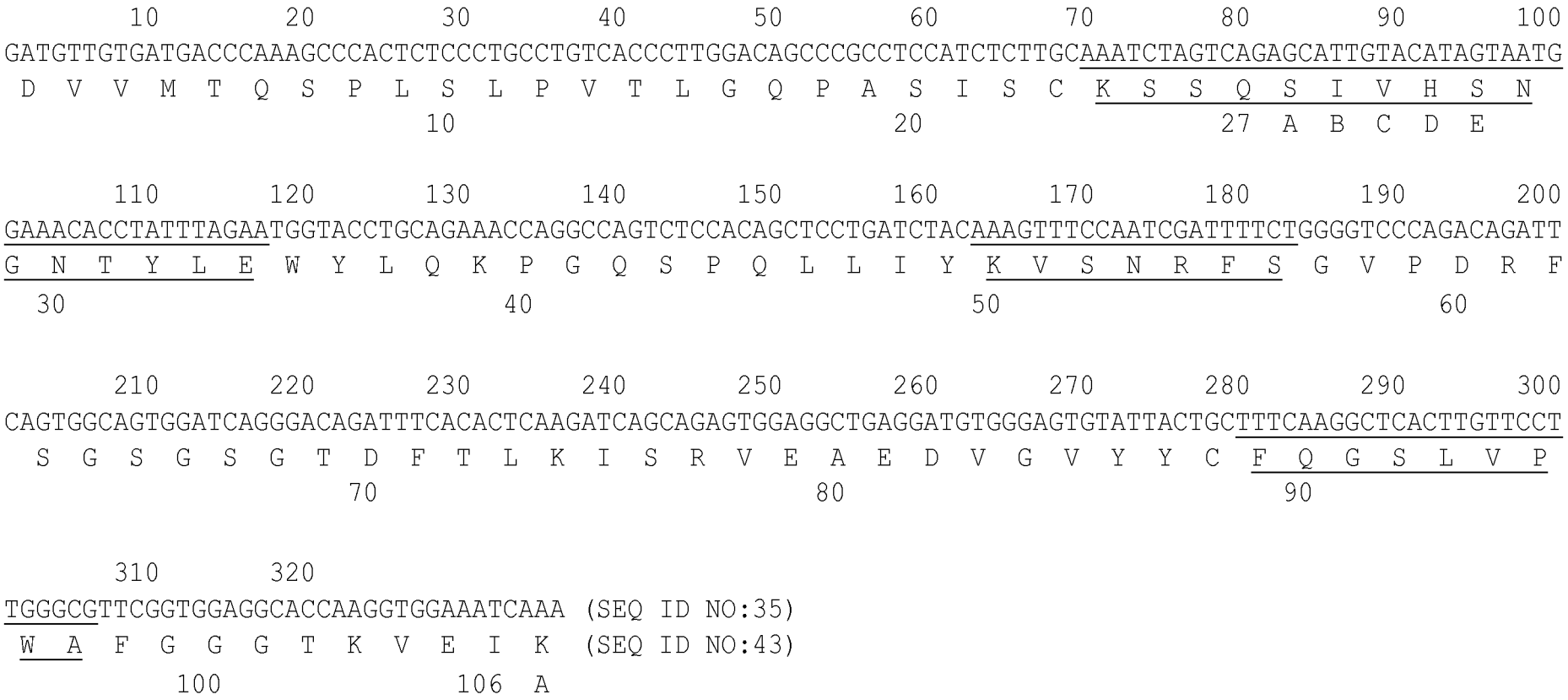
       210       220       230       240       250       260       270       280       290       300
CAGTGGCAGTGGATCAGGGACAGATTTCACACTCAAGATCAGCAGAGTGGAGGCTGAGGATGTGGGAGTGTATTACTGCTTTCAAGGCTCACTTGTTCCT
  S  G  S  G  S  G  T  D  F  T  L  K  I  S  R  V  E  A  E  D  V  G  V  Y  Y  C  F  Q  G  S  L  V  P
     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



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

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

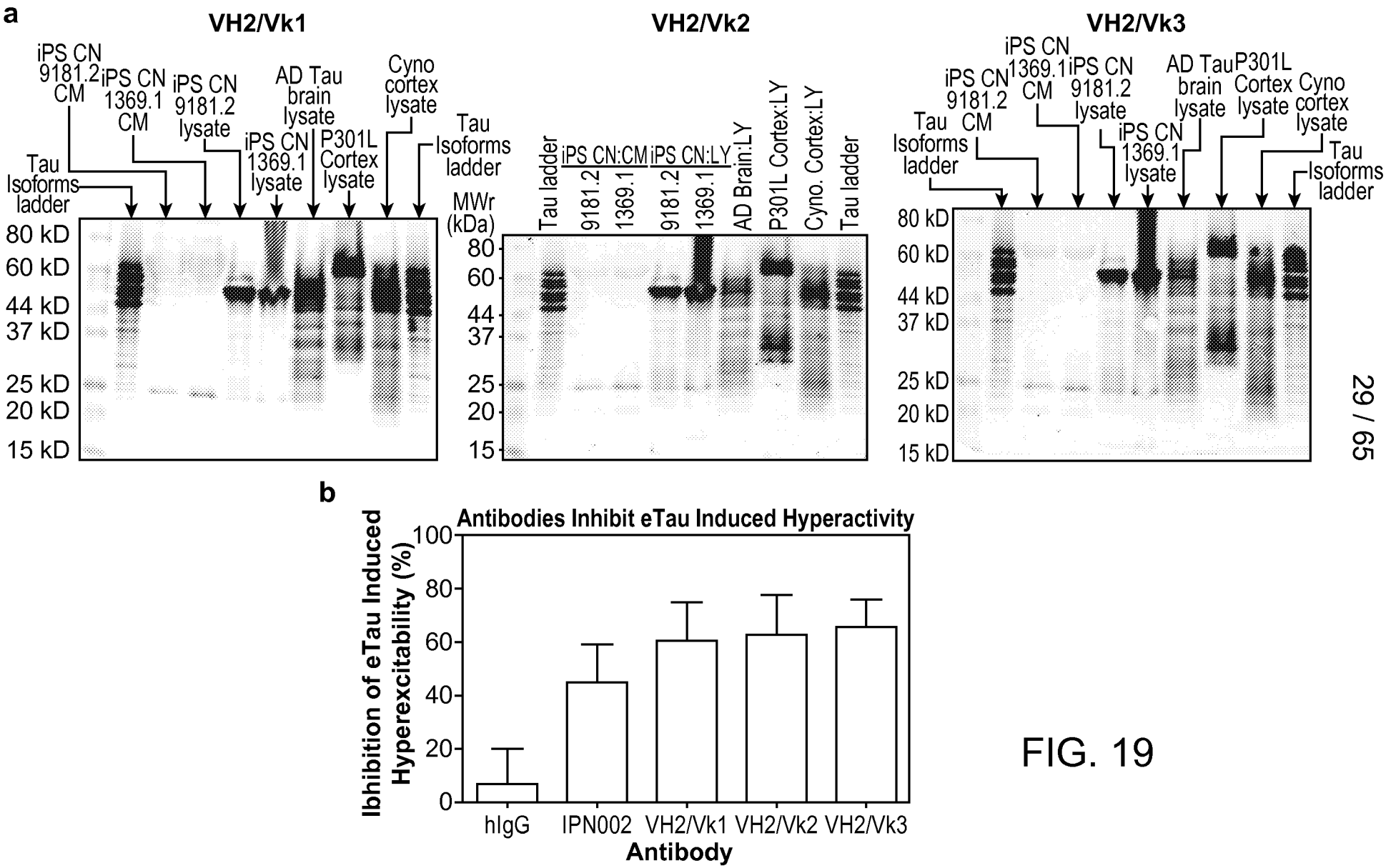

a
VH2/Vk1
VH2/Vk2
VH2/Vk3
iPS CN 9181.2 CM
iPS CN 1369.1 CM
iPS CN 9181.2 lysate
iPS CN 1369.1 lysate
AD Tau brain lysate
P301L Cortex lysate
Cyno cortex lysate
Tau Isoforms ladder
MWr (kDa)
80 kD
60 kD
44 kD
37 kD
25 kD
20 kD
15 kD
Tau ladder
iPS CN:CM
iPS CN:LY
9181.2
1369.1
AD Brain:LY
P301L Cortex:LY
Cyno. Cortex:LY
b
Antibodies Inhibit eTau Induced Hyperactivity
Ibhibition of eTau Induced Hyperexcitability (%)
100
80
60
40
20
0
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

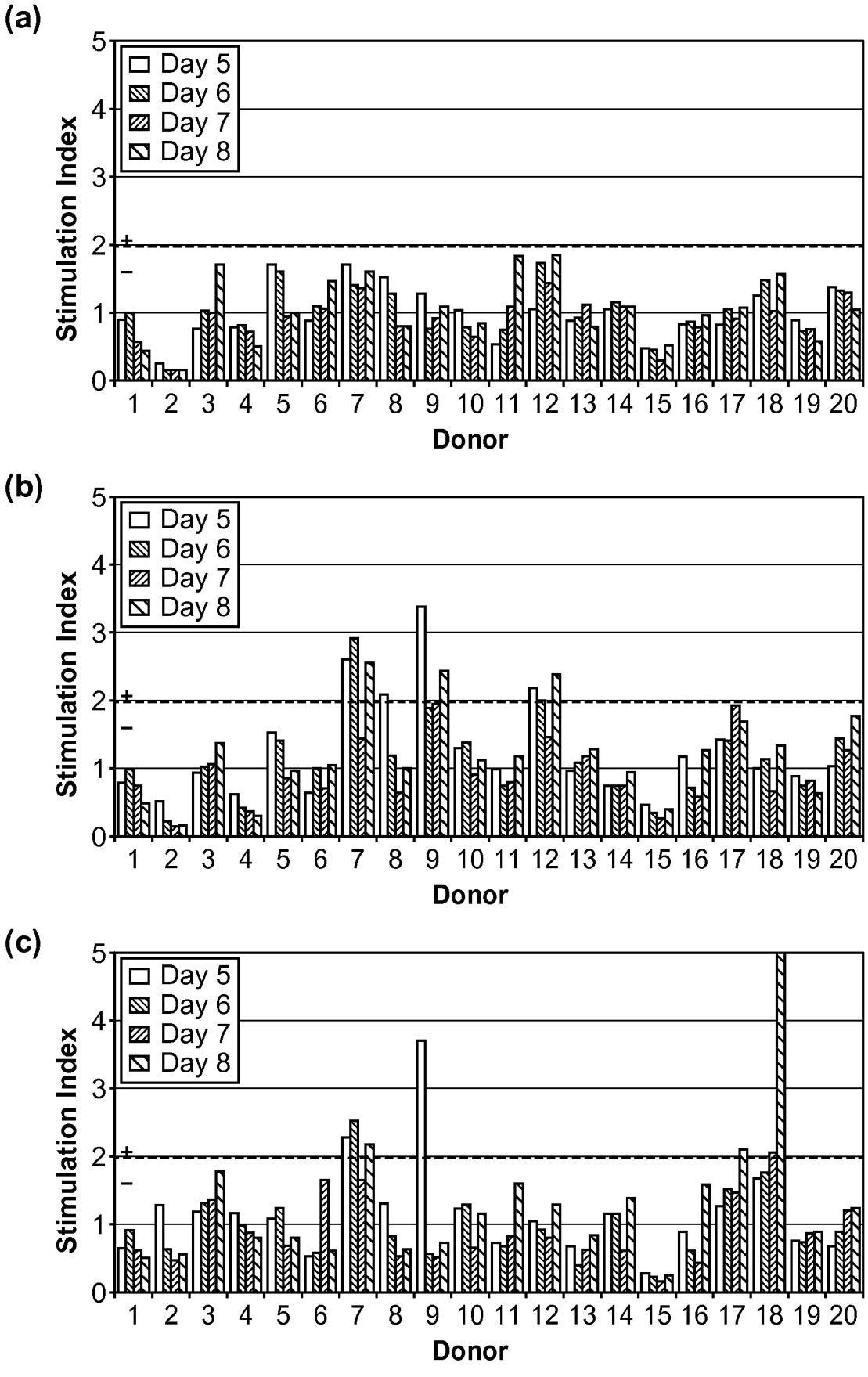

(a)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Donor
(b)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Donor
(c)
Day 5
Day 6
Day 7
Day 8
Stimulation Index
0
1
2
3
4
5
+
–
1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

FIG. 21

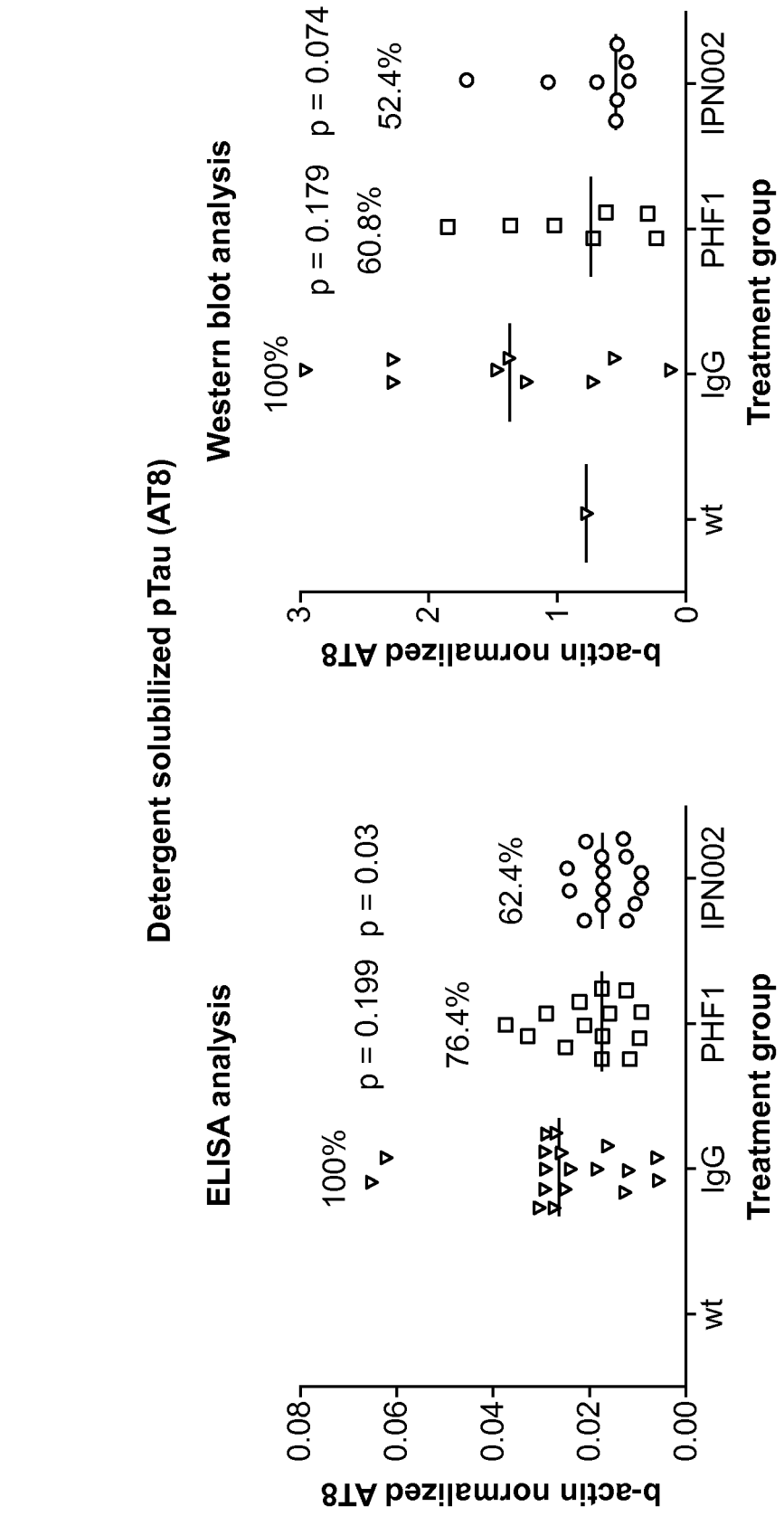

Detergent solubilized pTau (AT8)
ELISA analysis
b-actin normalized AT8
0.08
0.06
0.04
0.02
0.00
100%
p = 0.199
p = 0.03
76.4%
62.4%
wt
IgG
PHF1
IPN002
Treatment group
Western blot analysis
b-actin normalized AT8
3
2
1
0
100%
p = 0.179
p = 0.074
60.8%
52.4%
wt
IgG
PHF1
IPN002
Treatment group

FIG. 22

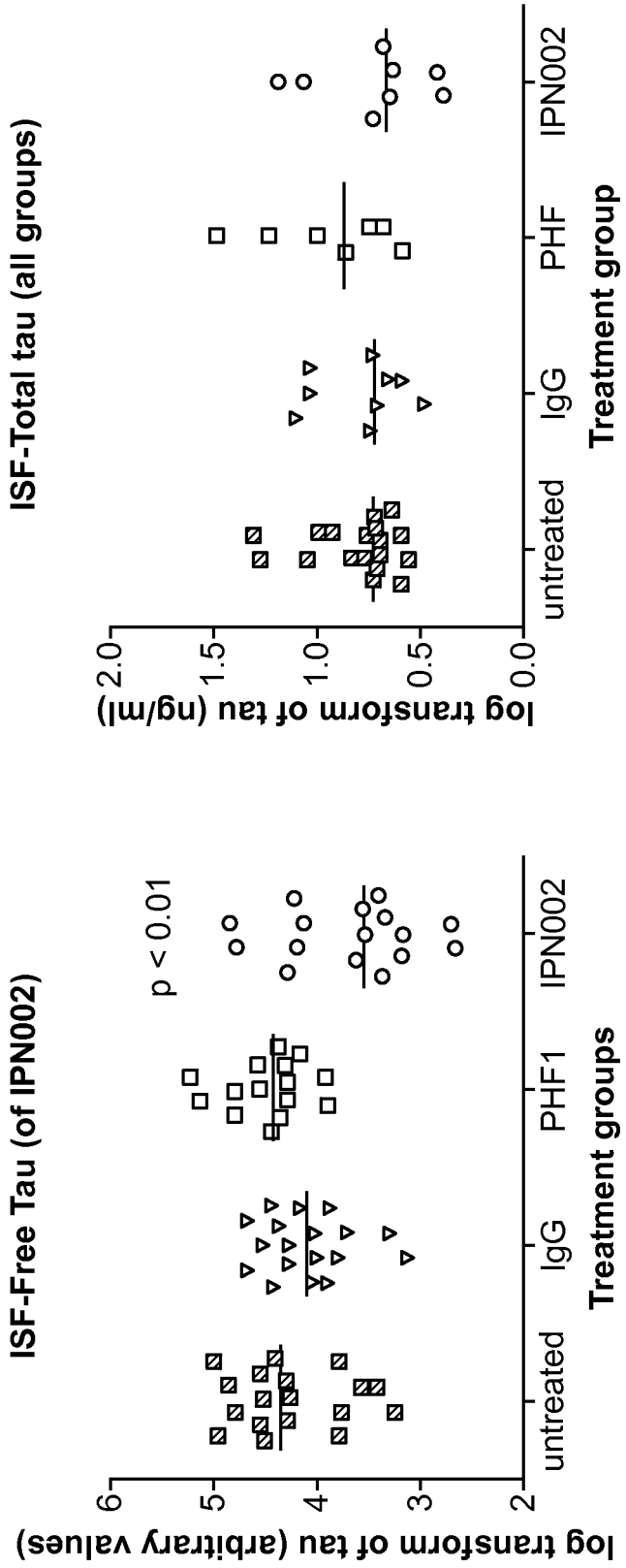
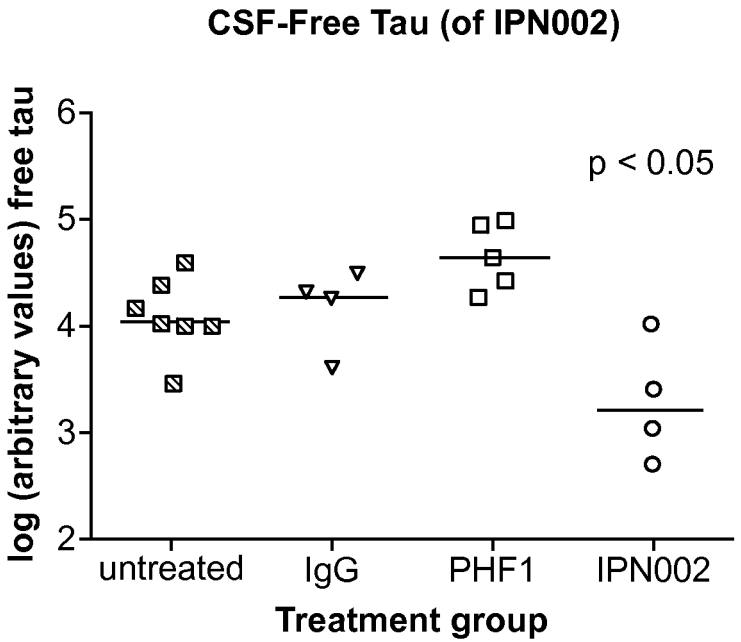
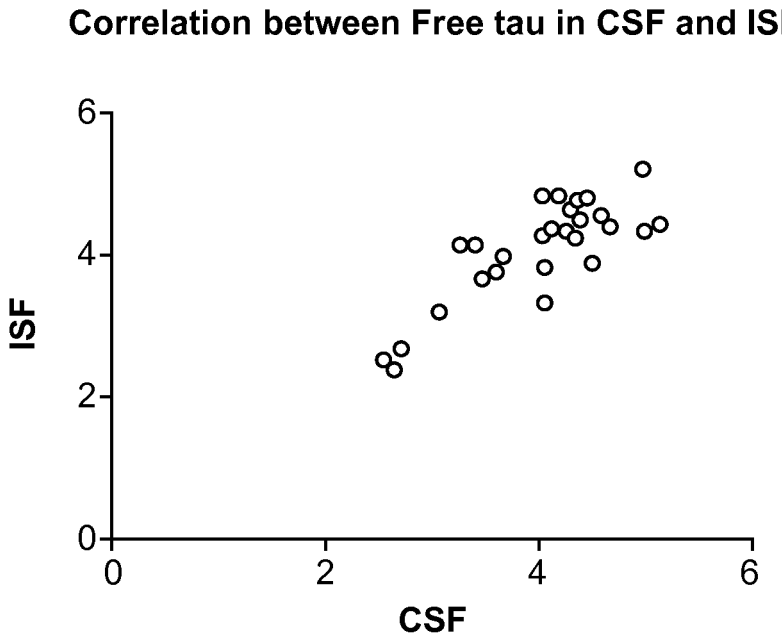

ISF-Free Tau (of IPN002)
log transform of tau (arbitrary values)
p < 0.01
6
5
4
3
2
untreated
IgG
PHF1
IPN002
Treatment groups
ISF-Total tau (all groups)
log transform of tau (ng/ml)
2.0
1.5
1.0
0.5
0.0
untreated
IgG
PHF
IPN002
Treatment group

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

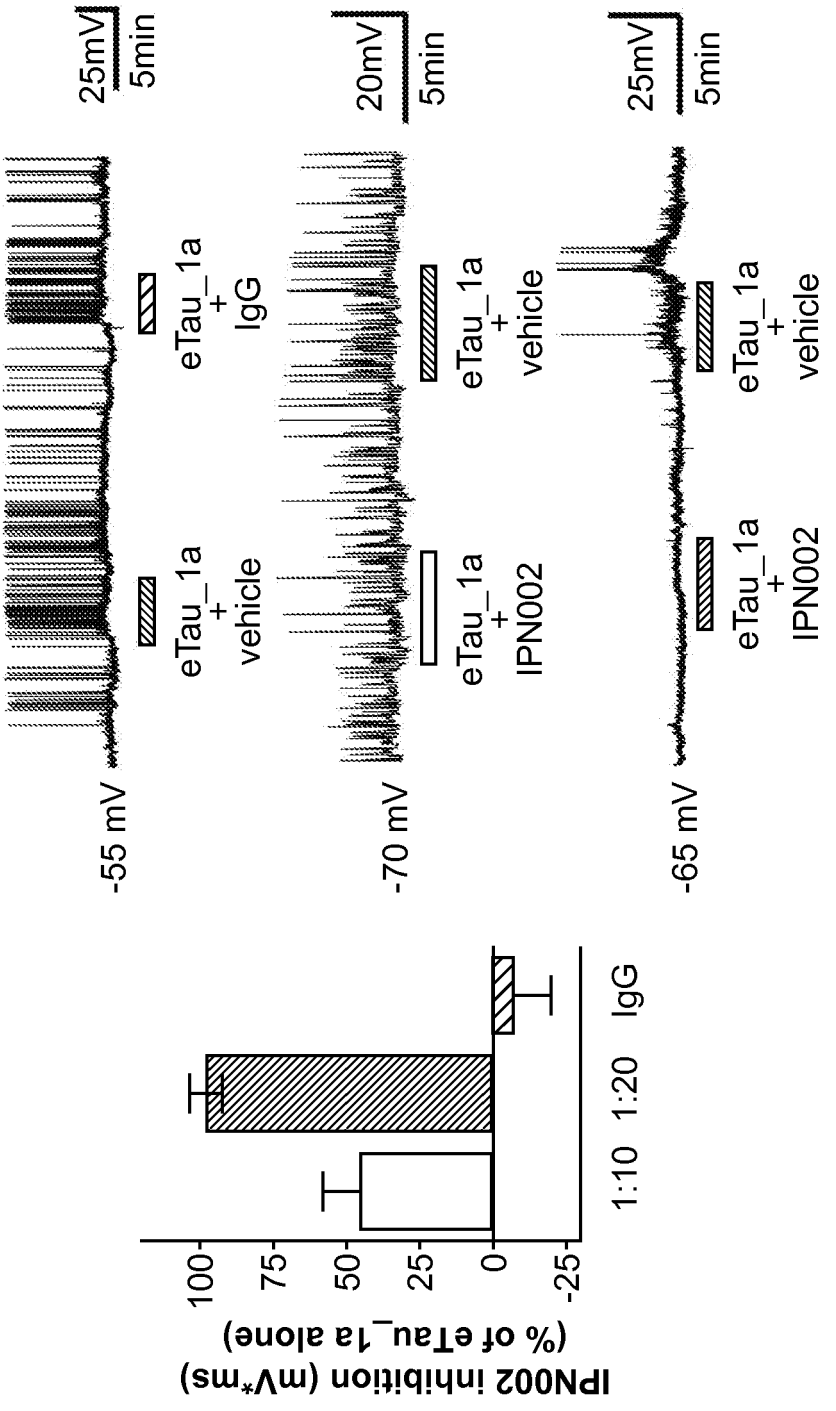

IPN002 inhibition (mV*ms)
(% of eTau_1a alone)
100
75
50
25
0
-25
1:10
1:20
IgG
-55 mV
eTau_1a
+
vehicle
eTau_1a
+
IgG
25mV
5min
-70 mV
eTau_1a
+
IPN002
eTau_1a
+
vehicle
20mV
5min
-65 mV
eTau_1a
+
IPN002
eTau_1a
+
vehicle
25mV
5min

FIG. 25

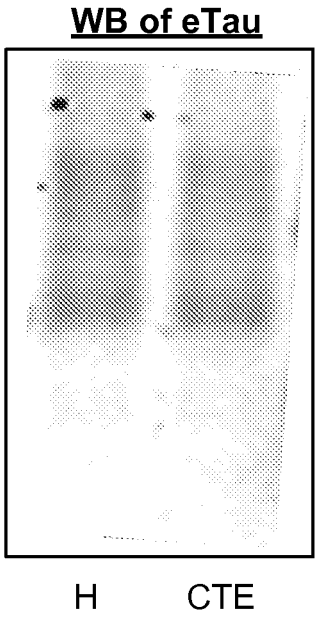
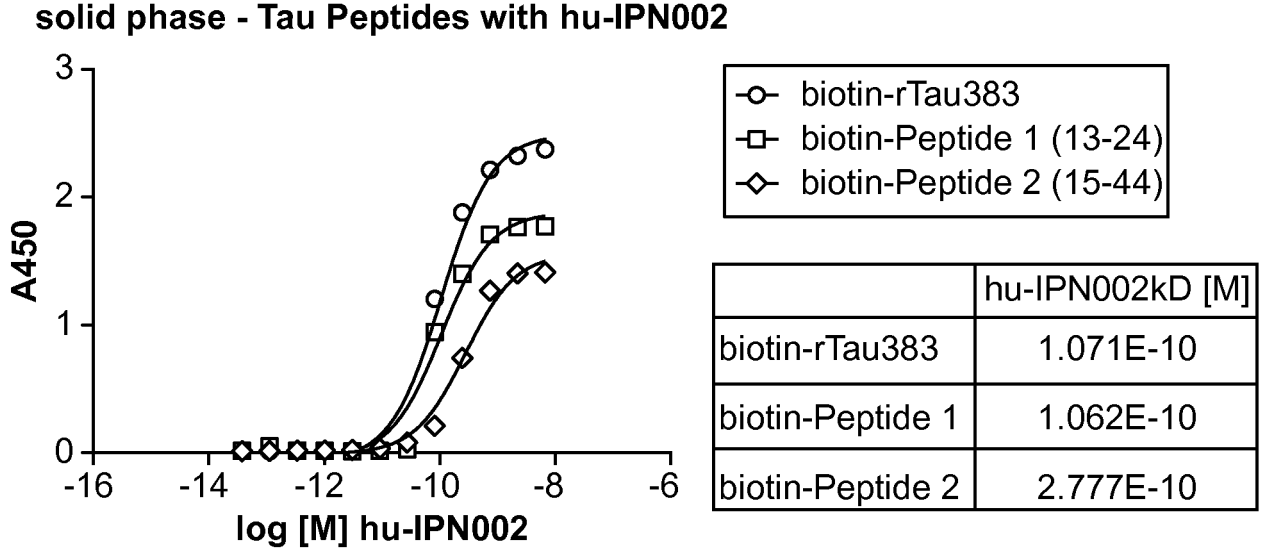


FIG. 26

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)



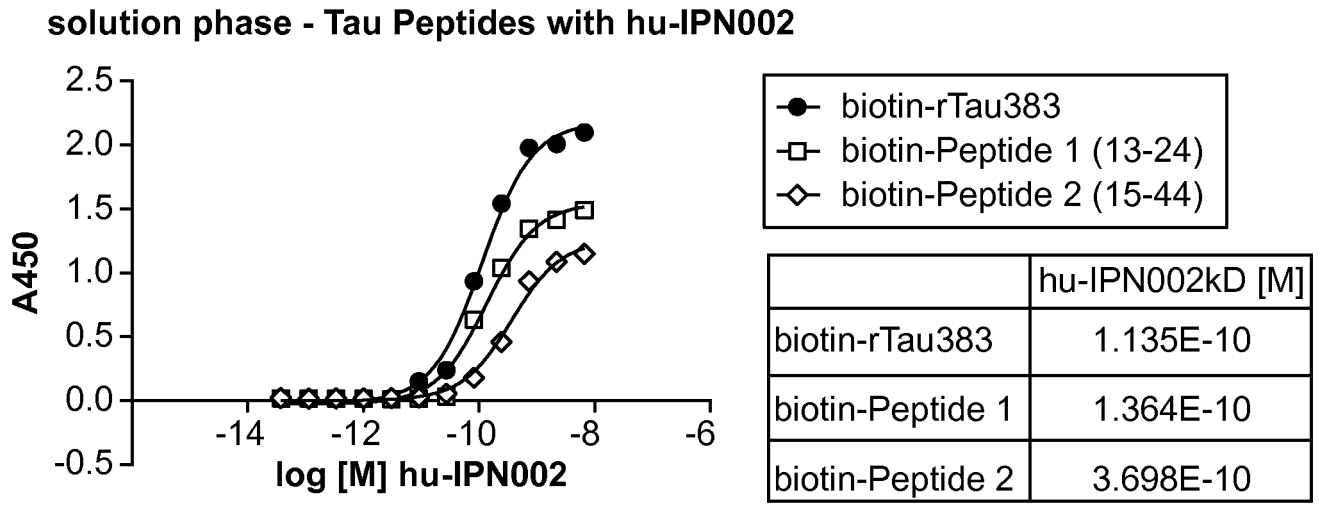
	hu-IPN002kD [M]
biotin-rTau383	1.071E-10
biotin-Peptide 1	1.062E-10
biotin-Peptide 2	2.777E-10

FIG. 27

synthesized Tau peptides:

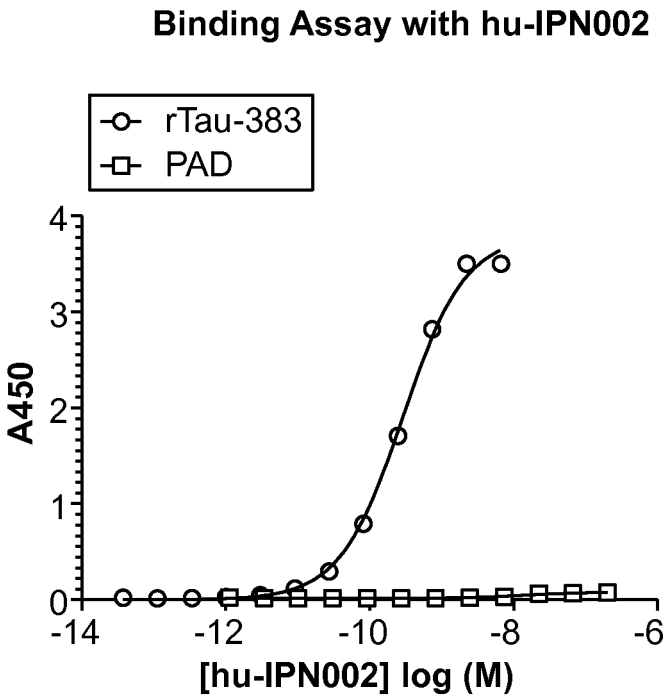
Peptide 1: Biotin-ahx-^{13}DHAGTYGLGDRK^{24} (SEQ ID NO: 49)

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

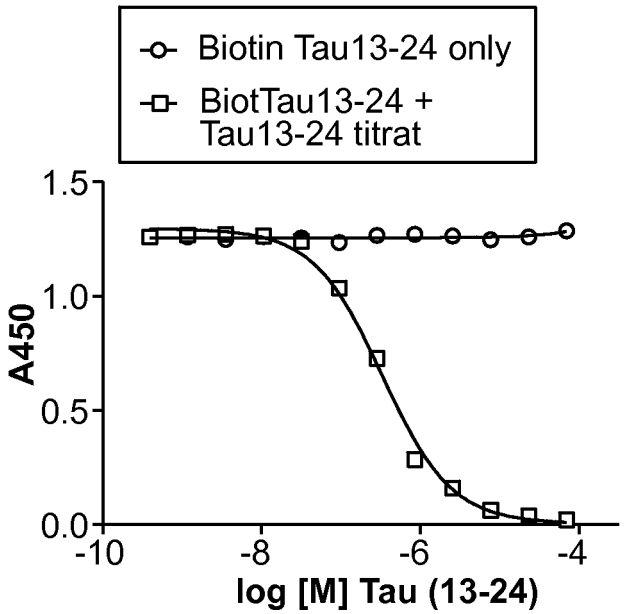
FIG. 28



	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

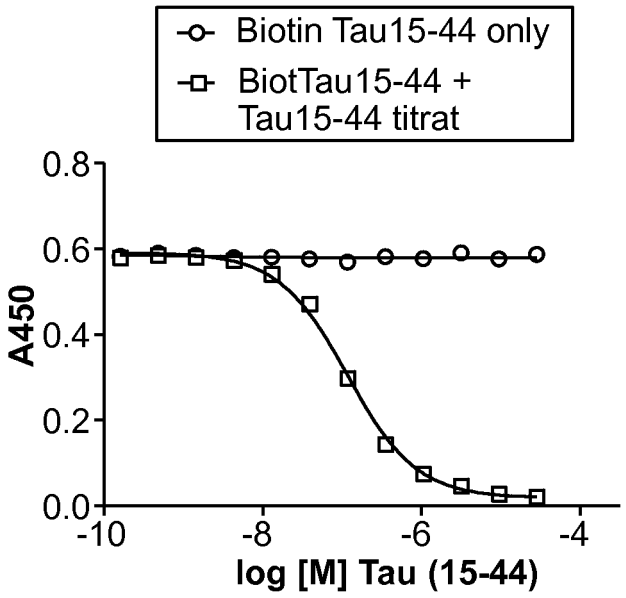


FIG. 30

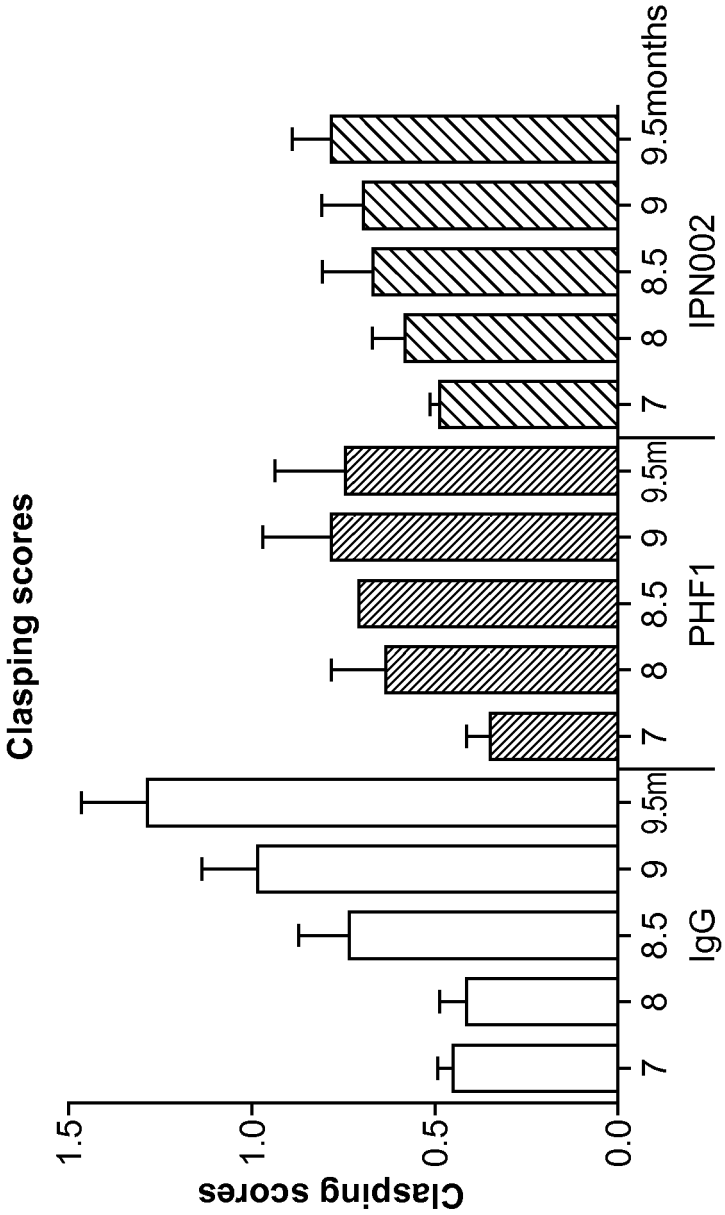

Clasping scores
Clasping scores
1.5
1.0
0.5
0.0
7
8
8.5
9
9.5m
IgG
7
8
8.5
9
9.5m
PHF1
7
8
8.5
9
9.5months
IPN002
Treatment groups
*p value for IgG vs IPN002 is approaching significance (p = 0.056)

FIG. 31

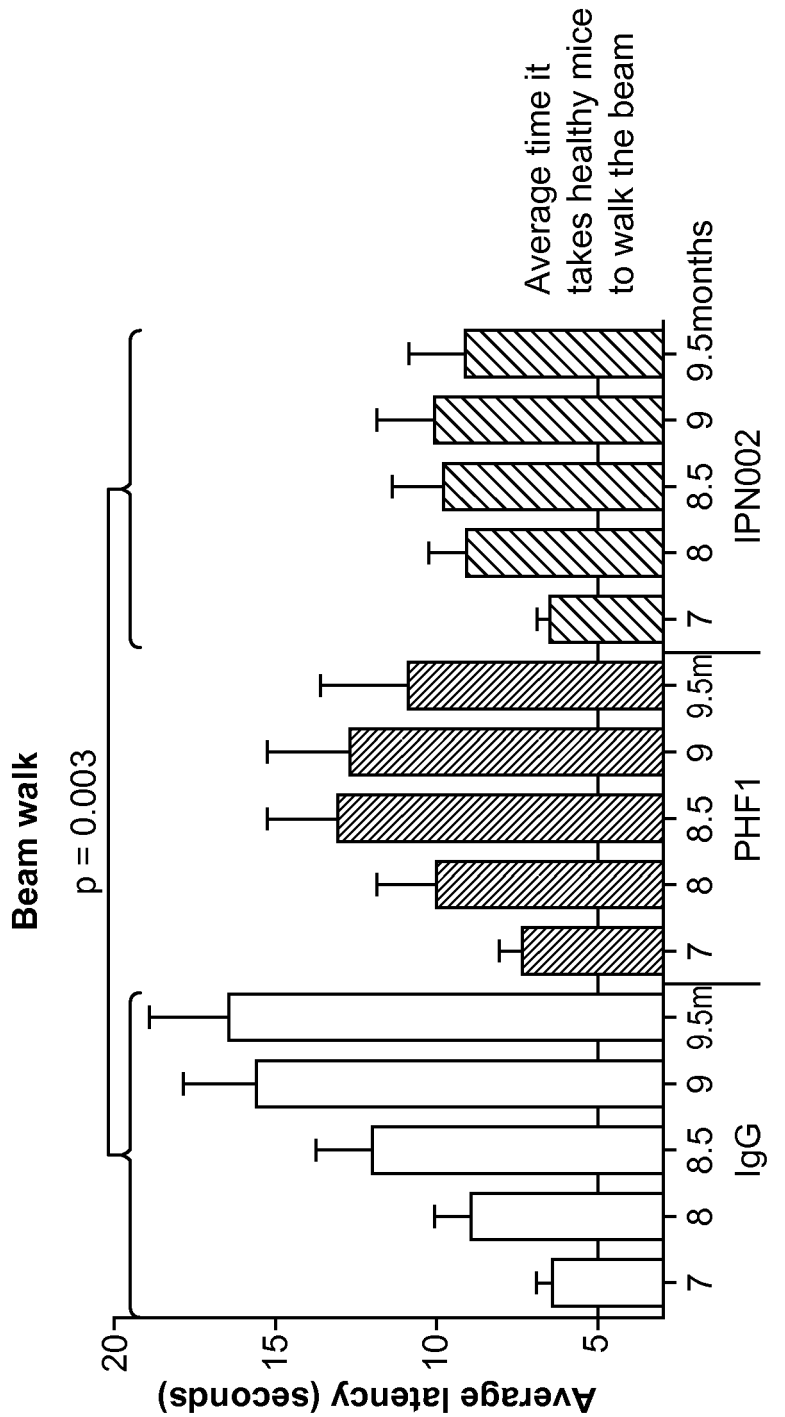

Beam walk
p = 0.003
Average latency (seconds)
20
15
10
5
7
8
8.5
9
9.5m
IgG
PHF1
IPN002
Treatment groups
Average time it takes healthy mice to walk the beam
9.5months

FIG. 32

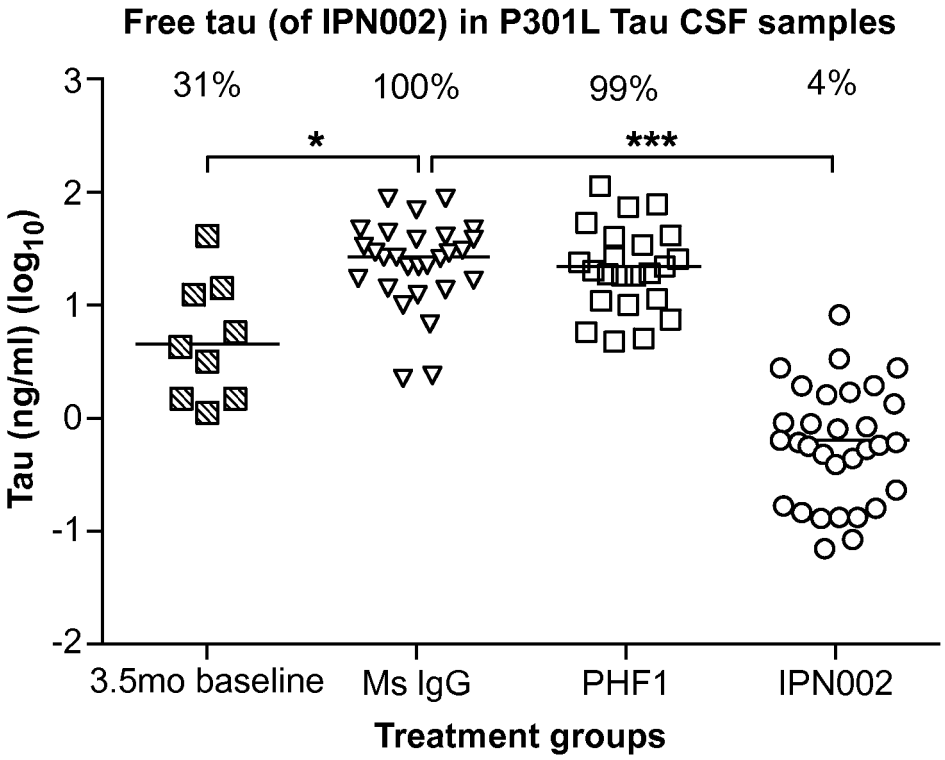
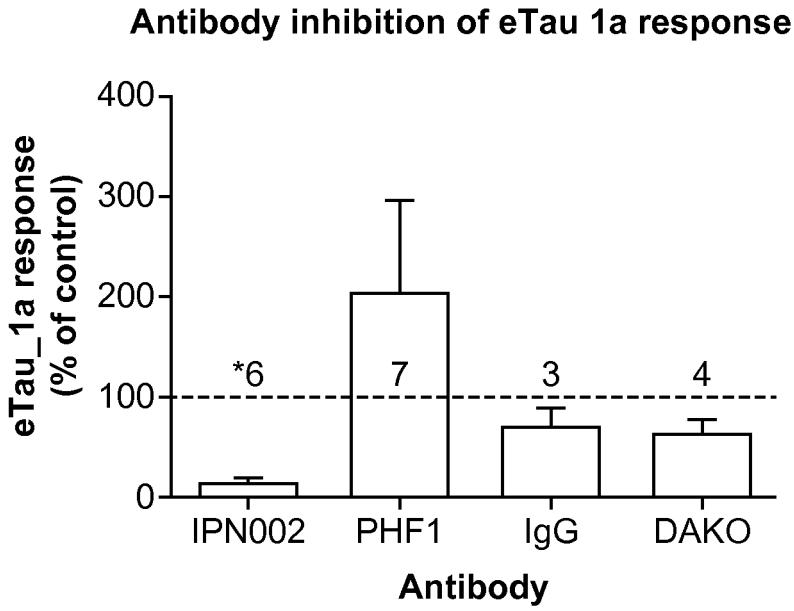

Free tau (of IPN002) in P301L Tau CSF samples
31%
100%
99%
4%
*
***
3
2
1
0
-1
-2
Tau (ng/ml) (log10)
3.5mo baseline
Ms IgG
PHF1
IPN002
Treatment groups

FIG. 33



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

FIG. 34

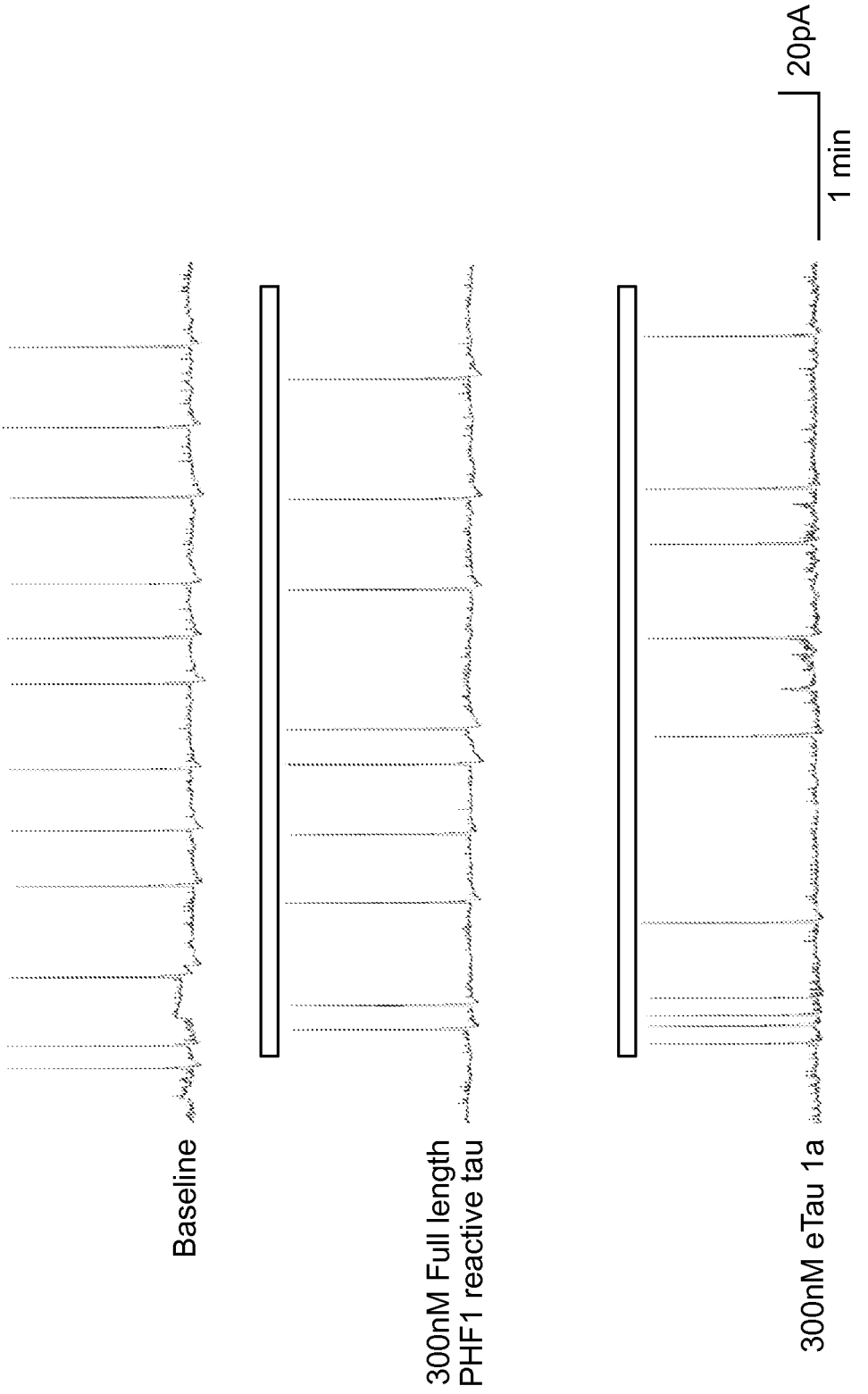

Baseline
300nM Full length
PHF1 reactive tau
300nM eTau 1a
20pA
1 min

FIG. 35

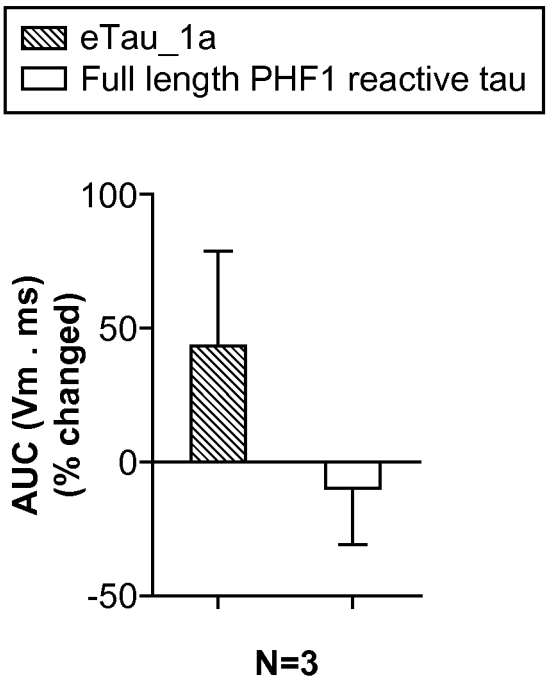

eTau_1a
Full length PHF1 reactive tau
100
50
0
-50
AUC (Vm . ms)
(% changed)
N=3

FIG. 36

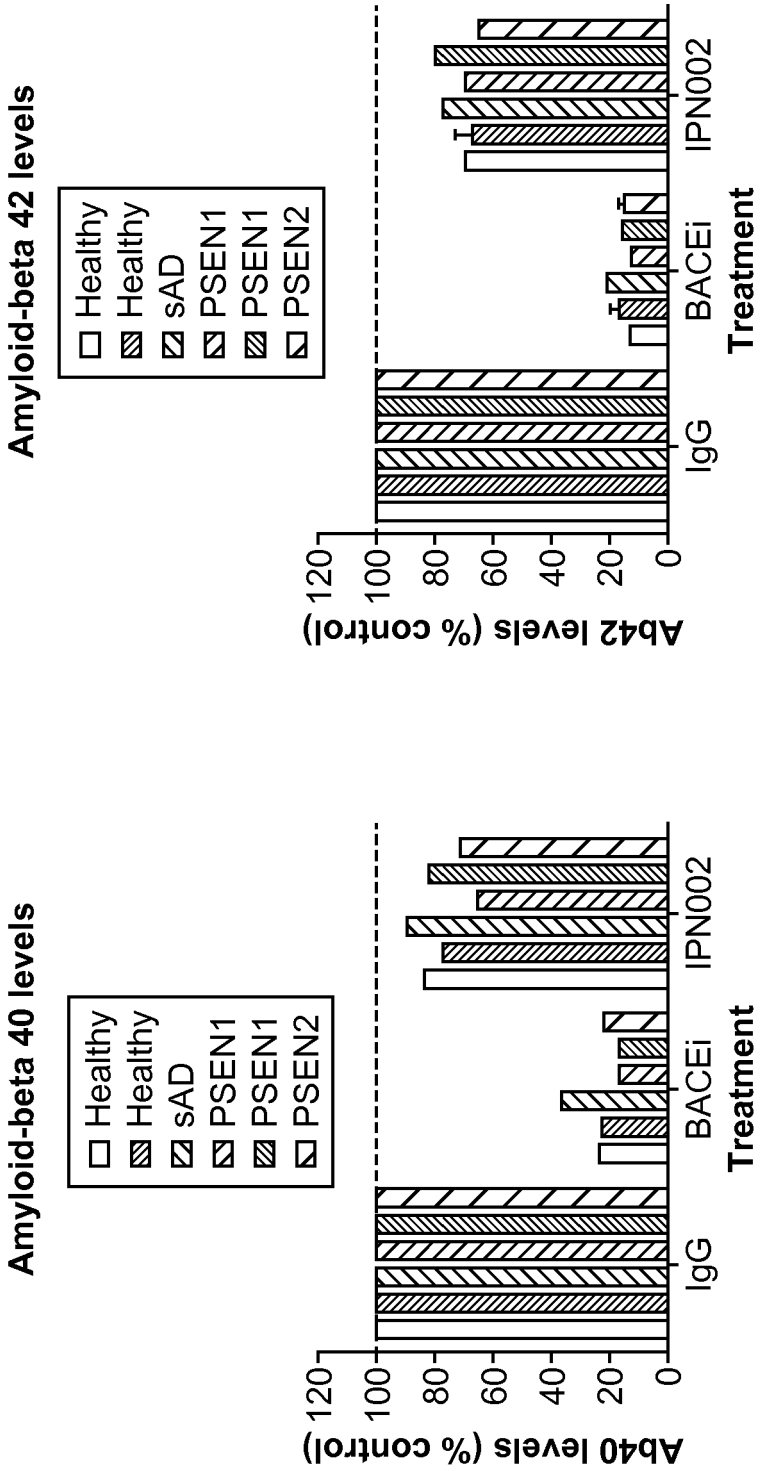

Amyloid-beta 40 levels
Healthy
Healthy
sAD
PSEN1
PSEN1
PSEN2
Aβ40 levels (% control)
120
100
80
60
40
20
0
IgG
BACEi
IPN002
Treatment
Amyloid-beta 42 levels
Healthy
Healthy
sAD
PSEN1
PSEN1
PSEN2
Aβ42 levels (% control)
120
100
80
60
40
20
0
IgG
BACEi
IPN002
Treatment

FIG. 37

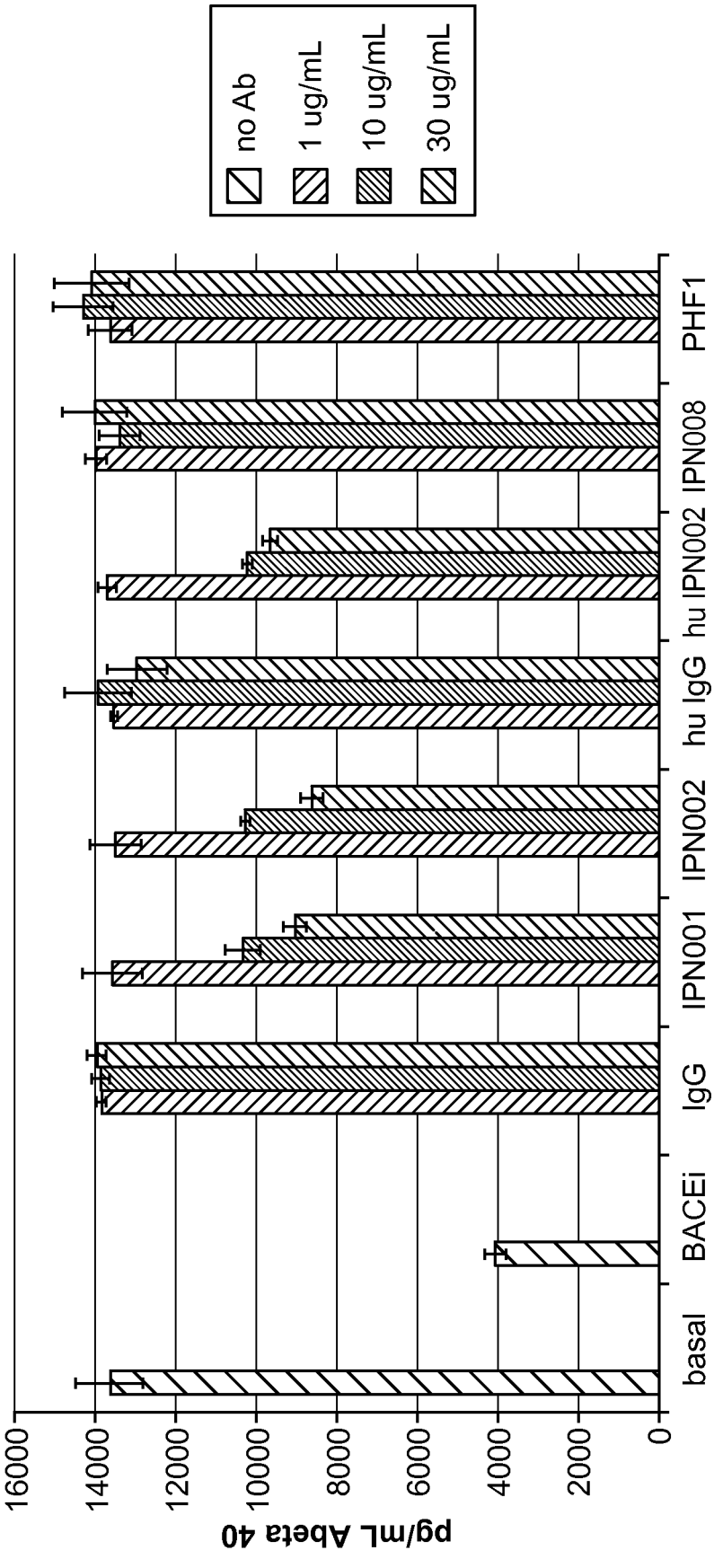

Abeta 40 ELISA: 10 day treatment of primary cortical neurons
pg/mL Abeta 40
16000
14000
12000
10000
8000
6000
4000
2000
0
no Ab
1 ug/mL
10 ug/mL
30 ug/mL
basal
BACEi
IgG
IPN001
IPN002
hu IgG
hu IPN002
IPN008
PHF1

FIG. 38

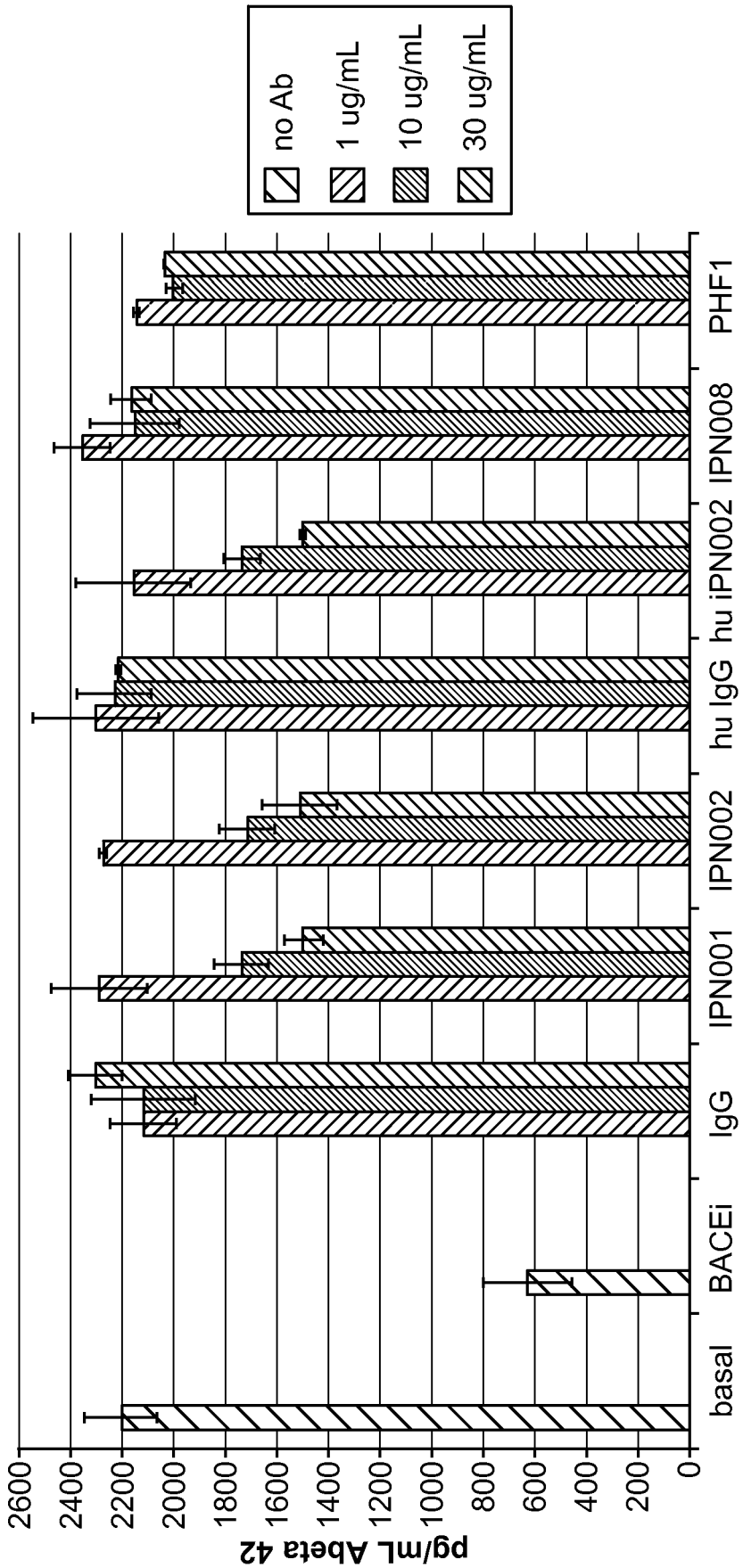

Abeta 42 ELISA: 10 day treatment of primary cortical neurons
pg/mL Abeta 42
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
no Ab
1 ug/mL
10 ug/mL
30 ug/mL
basal
BACEi
IgG
IPN001
IPN002
hu IgG
hu iPN002
IPN008
PHF1

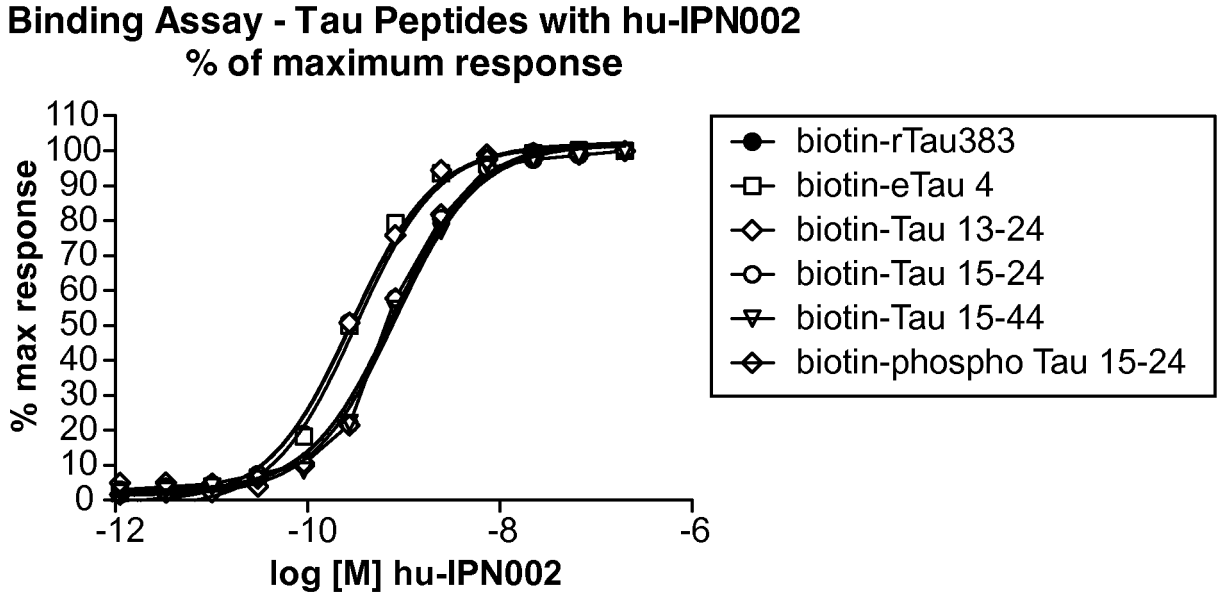
FIG. 39

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

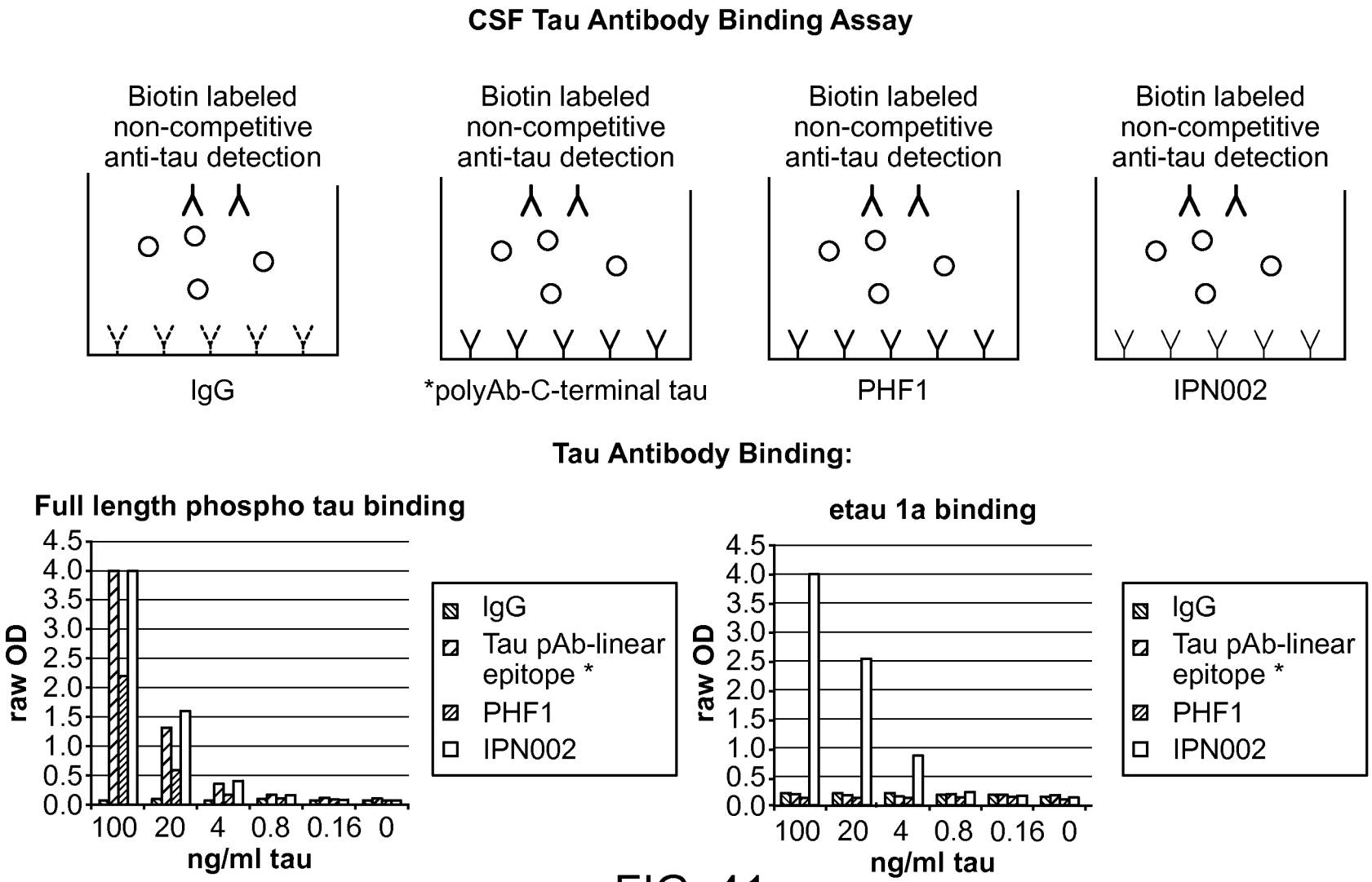

CSF Tau Antibody Binding Assay
Biotin labeled non-competitive anti-tau detection
IgG
*polyAb-C-terminal tau
PHF1
IPN002
Tau Antibody Binding:
Full length phospho tau binding
raw OD
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
100 20 4 0.8 0.16 0
ng/ml tau
IgG
Tau pAb-linear epitope *
PHF1
IPN002
etau 1a binding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

FIG. 41

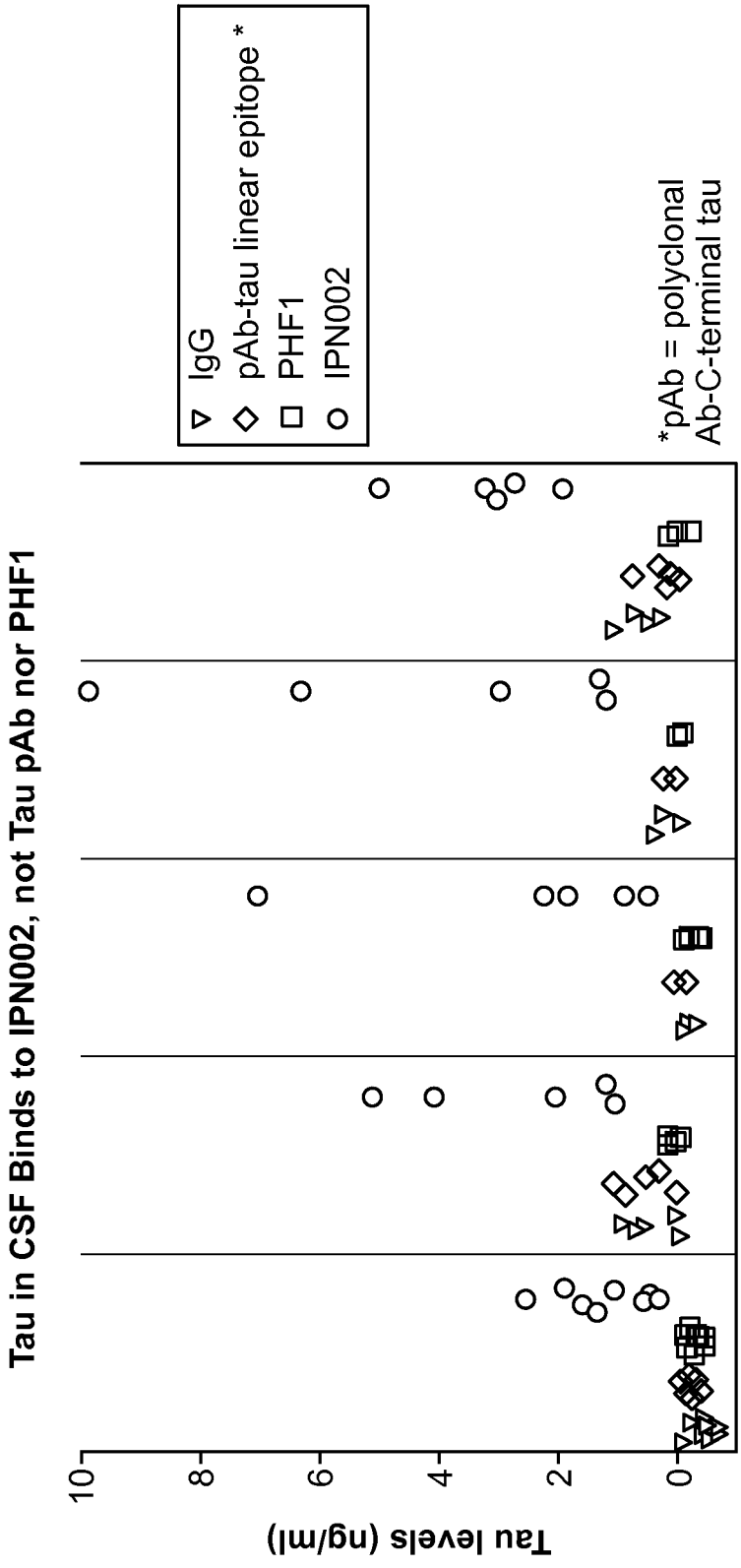

Tau in CSF Binds to IPN002, not Tau pAb nor PHF1
Tau levels (ng/ml)
0
2
4
6
8
10
Control n=10
MCI n=5
Mild n=5
Moderate n=5
Severe AD n=5
IgG
pAb-tau linear epitope *
PHF1
IPN002
*pAb = polyclonal Ab-C-terminal tau

FIG. 42

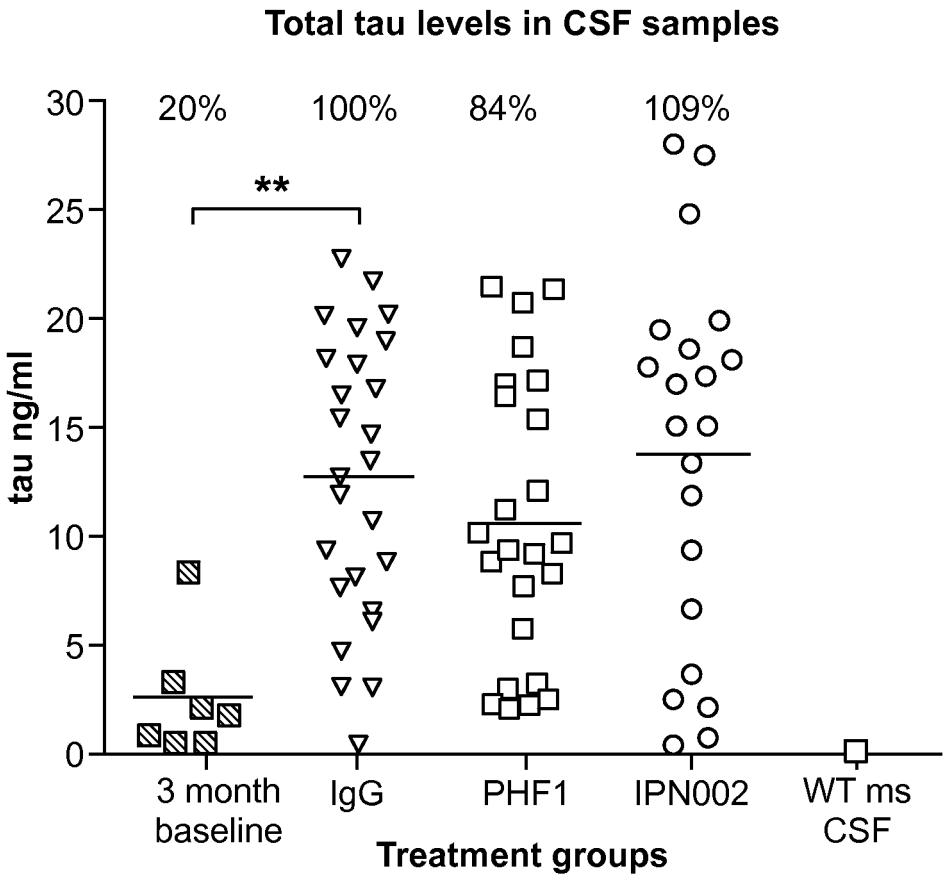

Total tau levels in CSF samples
20%
100%
84%
109%
**
30
25
20
15
10
5
0
tau ng/ml
3 month baseline
IgG
PHF1
IPN002
WT ms CSF
Treatment groups

FIG. 43

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

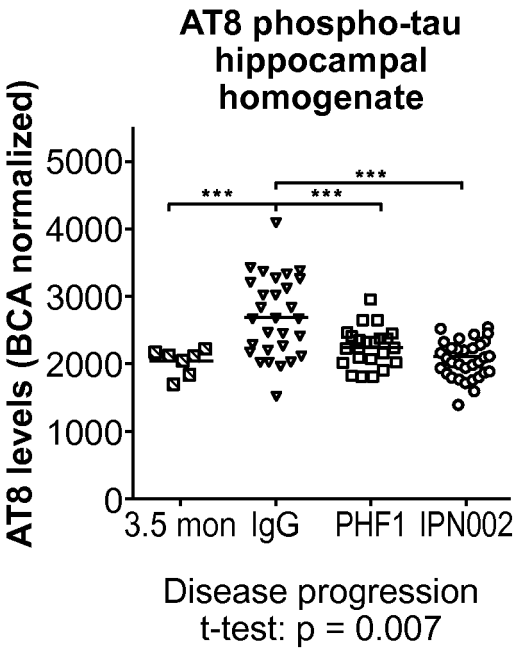


FIG. 44A

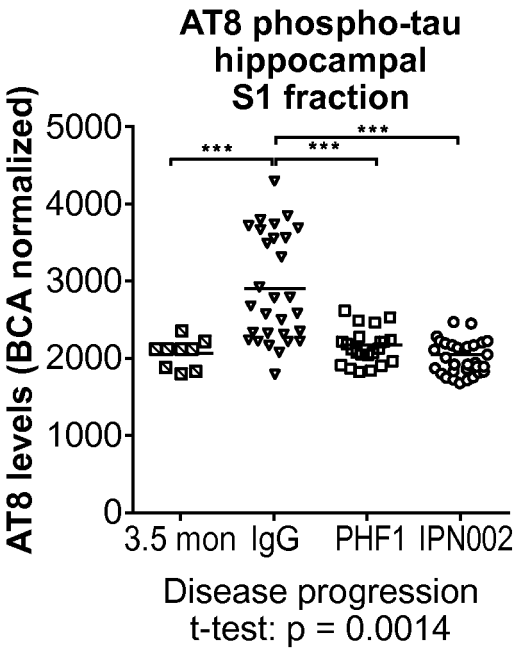


FIG. 44B

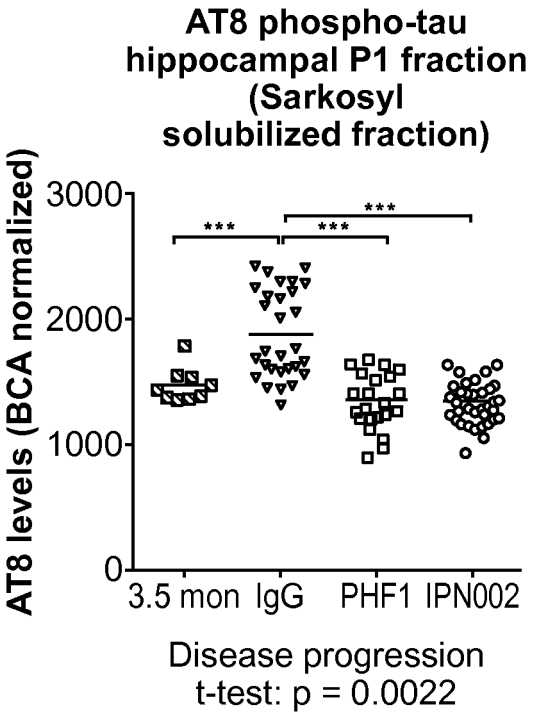


FIG. 44C

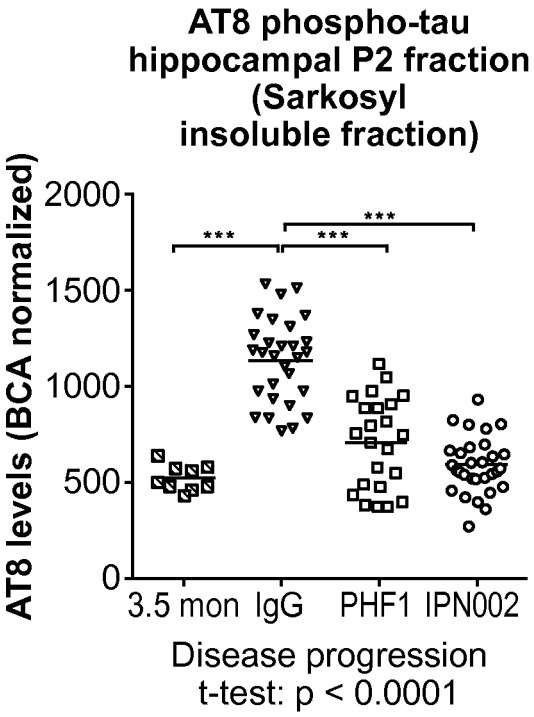


FIG. 44D

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

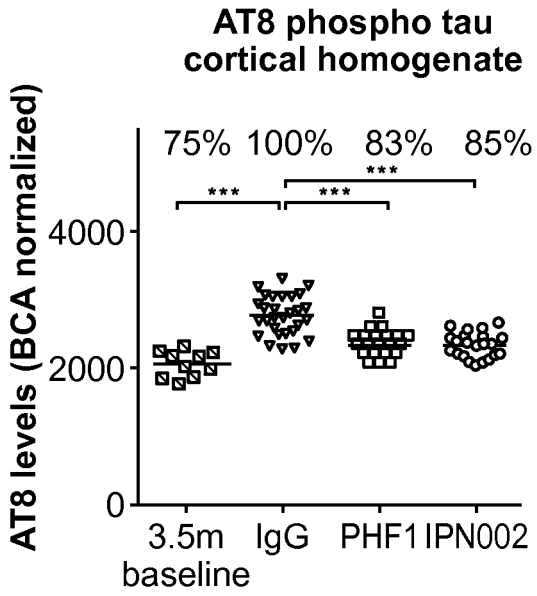


FIG. 44E

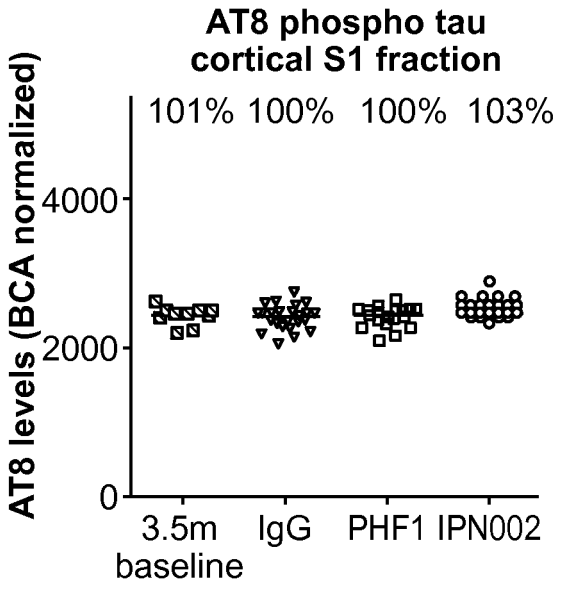


FIG. 44F

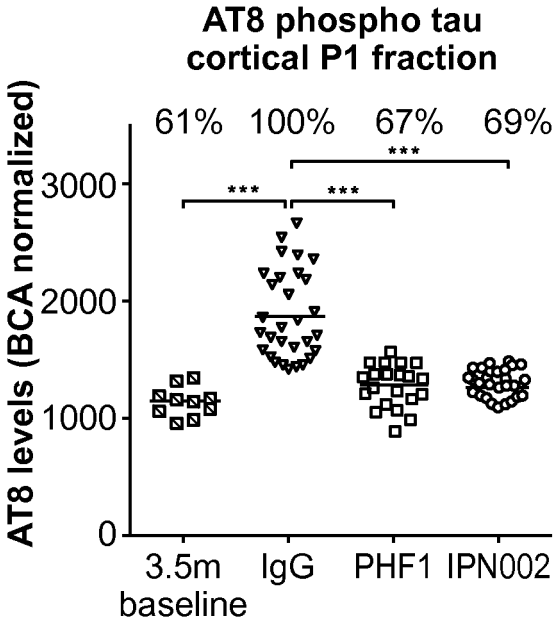


FIG. 44G

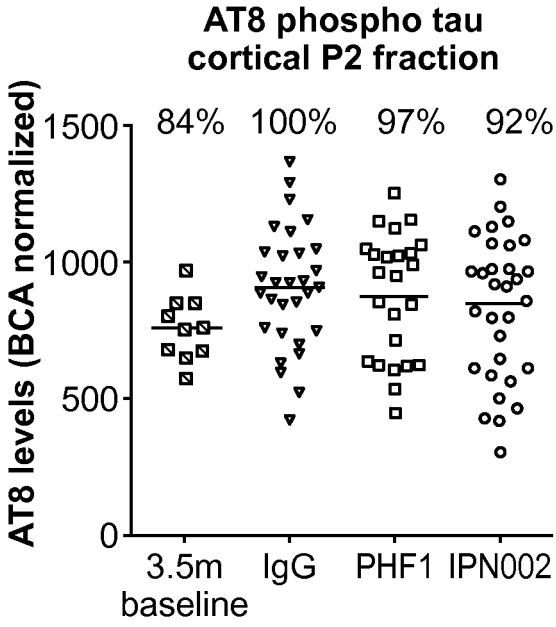


FIG. 44H

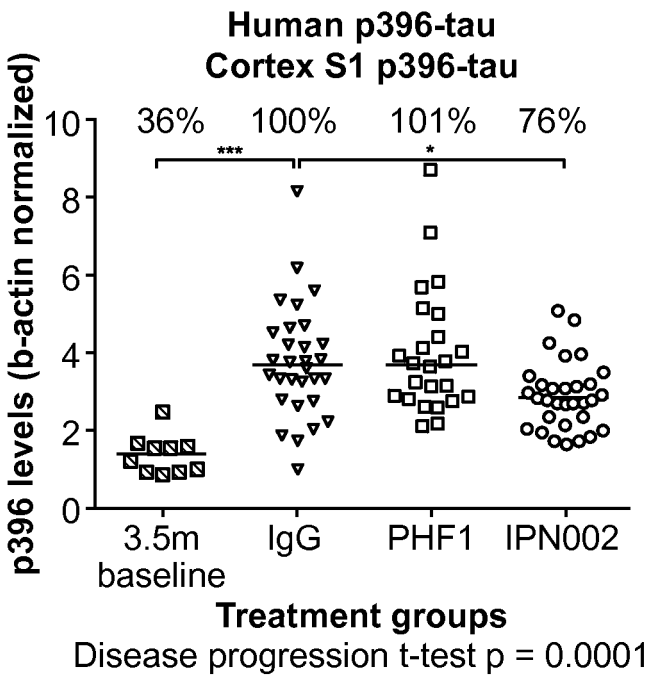


FIG. 45A

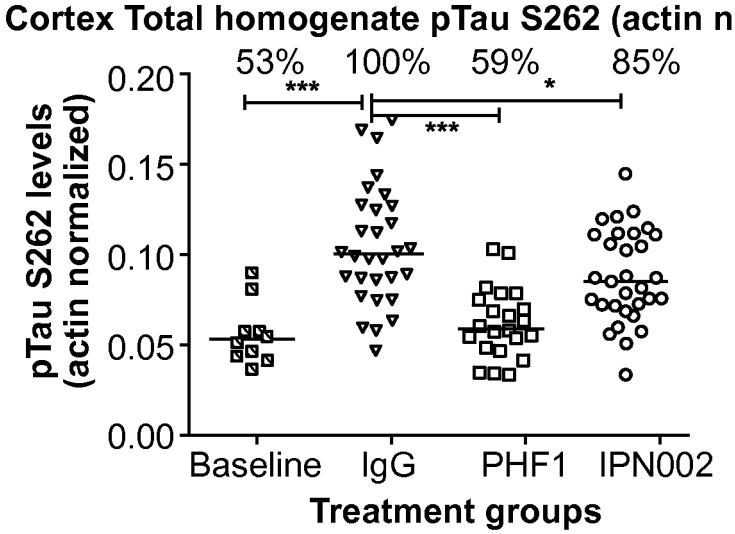


FIG. 45B

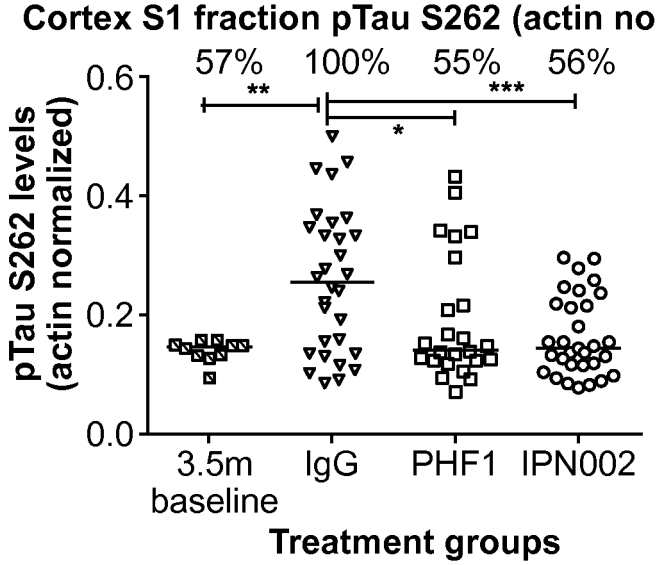
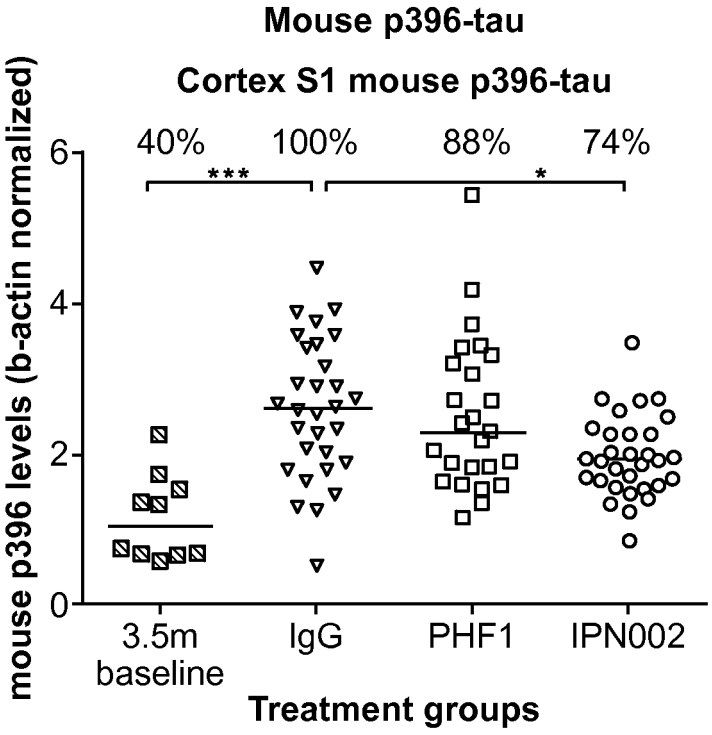
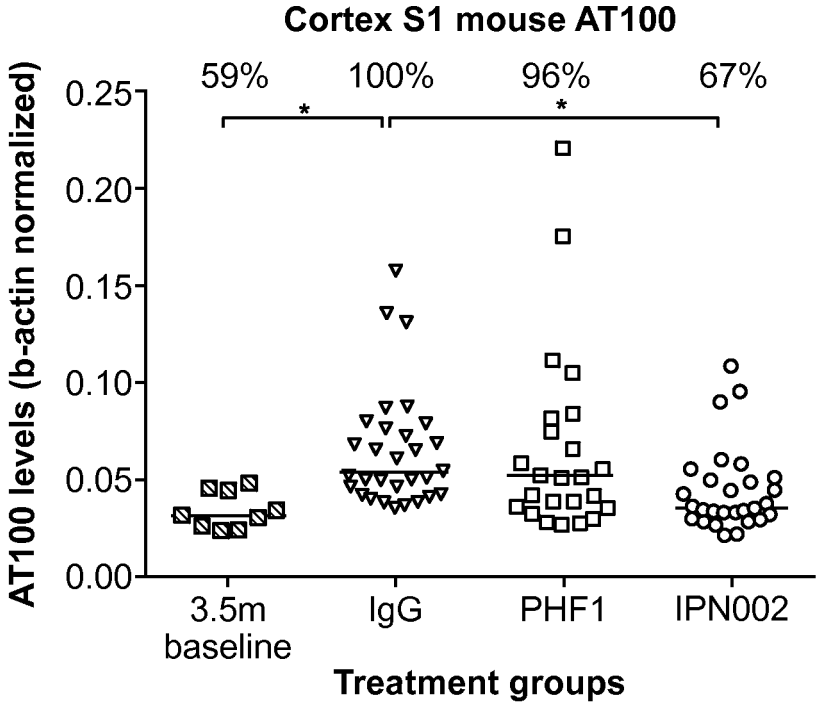


FIG. 45C



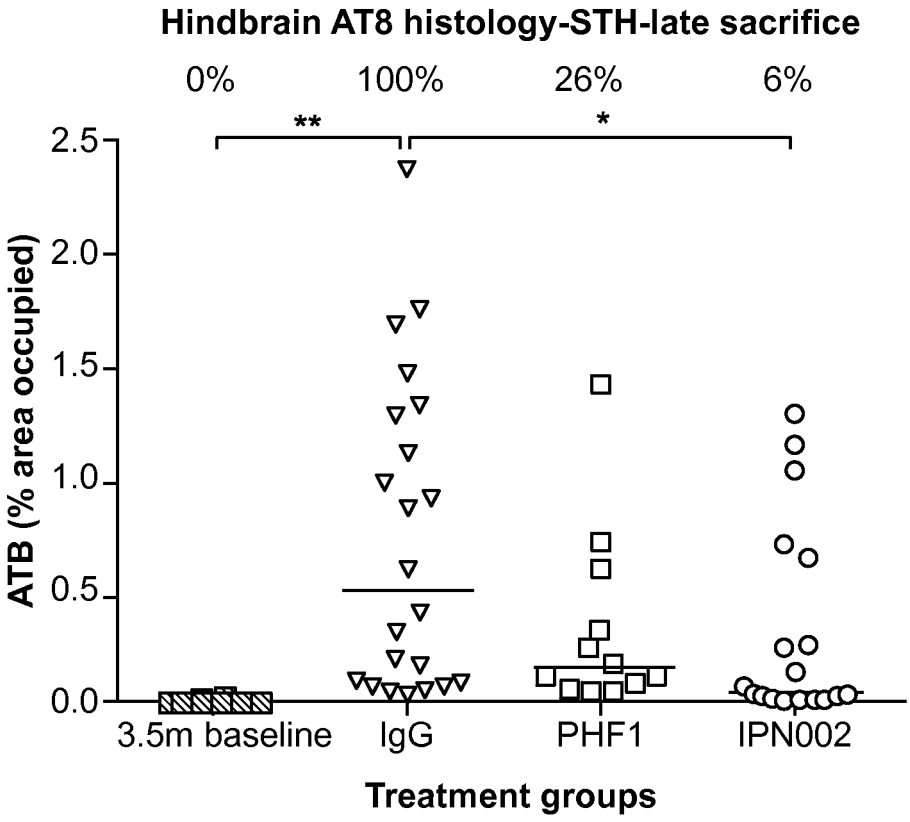
Disease Progression t test: p=0.0001

FIG. 45D



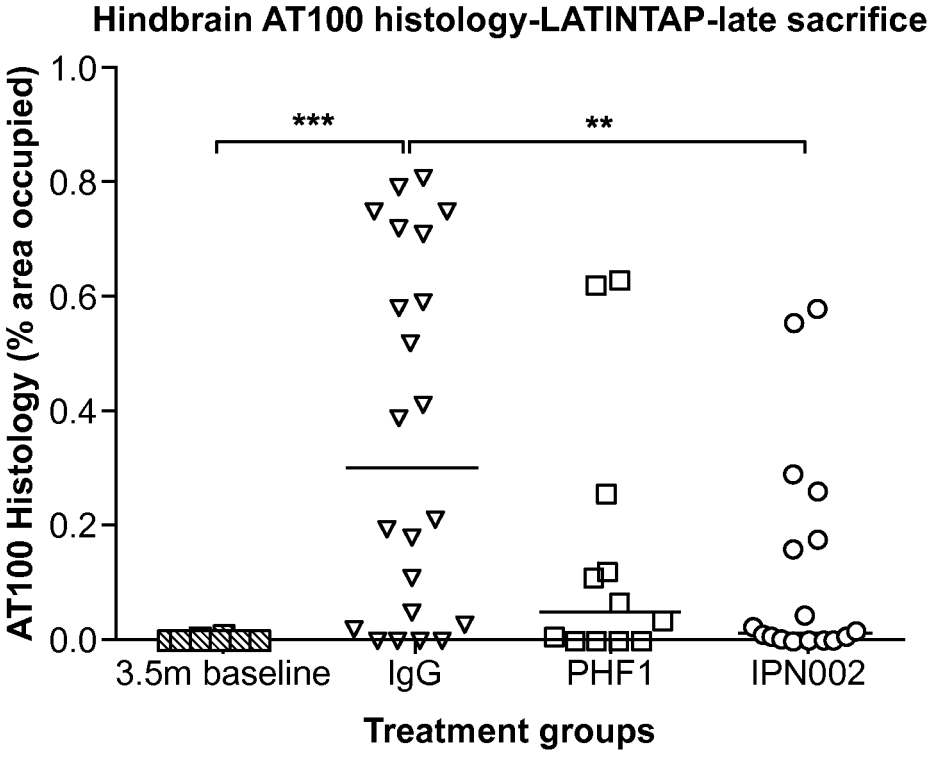
Disease progression t-test: p = 0.005

FIG. 45E



Disease progression t-test: $p < 0.0028$

FIG. 46



Disease progression t-test: $p < 0.0014$

FIG. 47

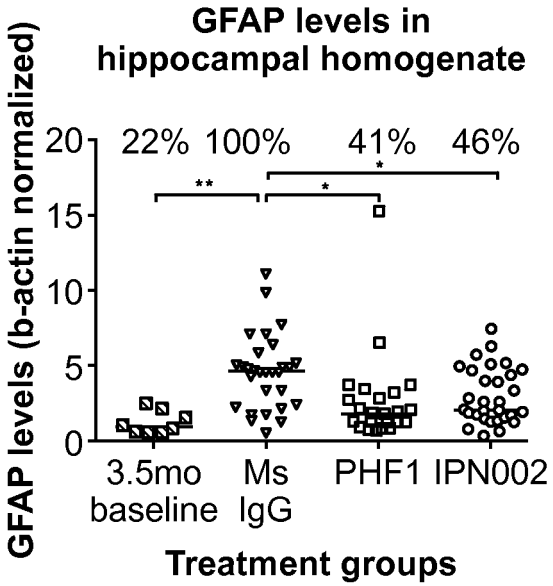
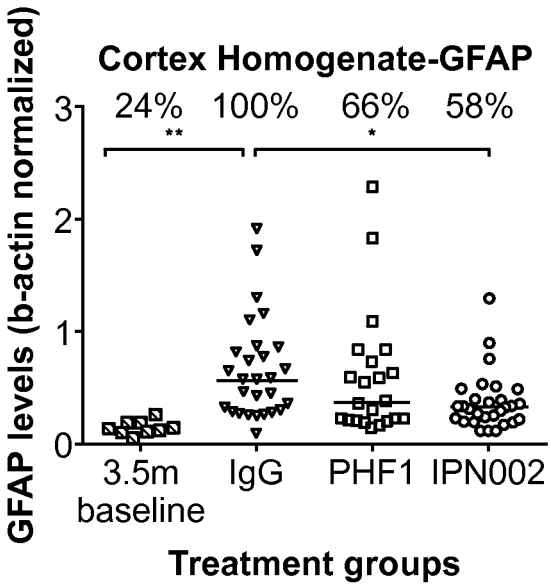


FIG. 48A



Disease progression
t-test p = 0.0019

FIG. 48B

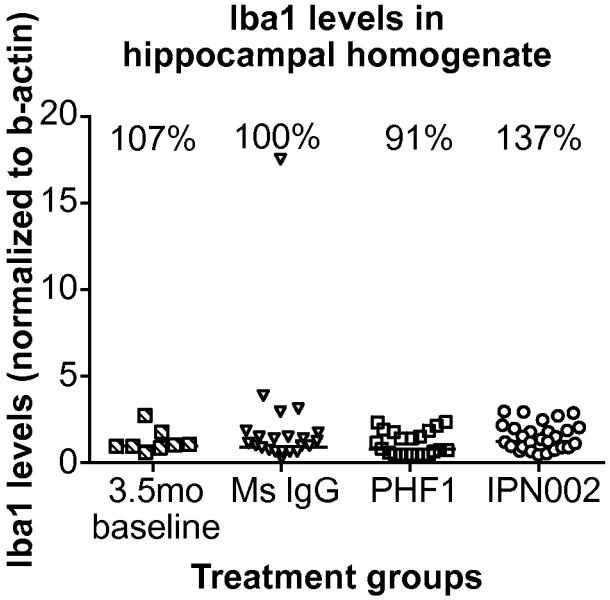
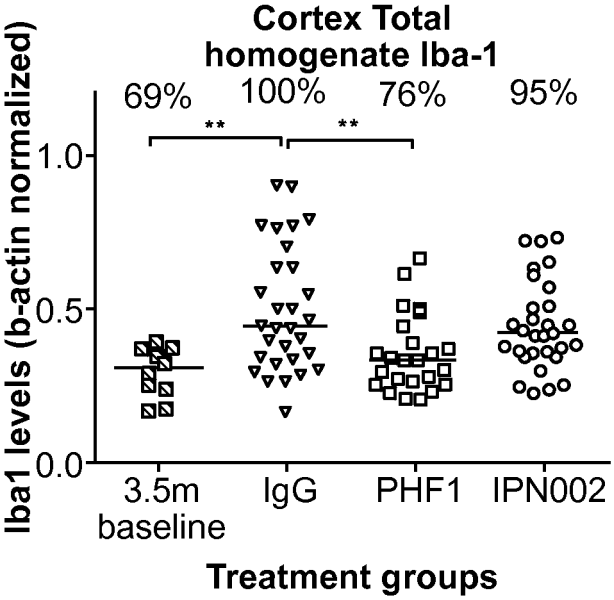


FIG. 49A



Disease progression
t-test p = 0.0041

FIG. 49B

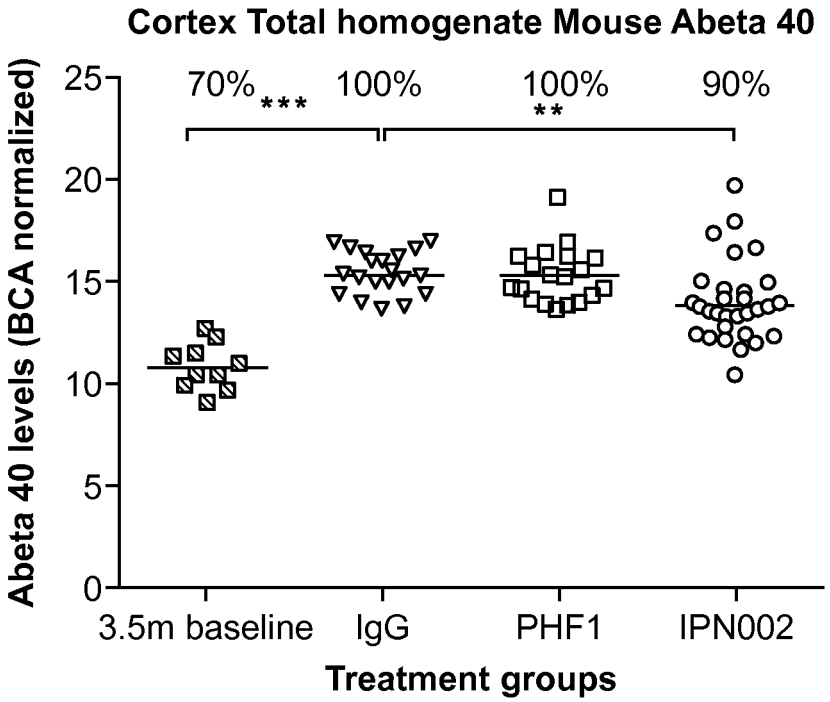


FIG. 50A

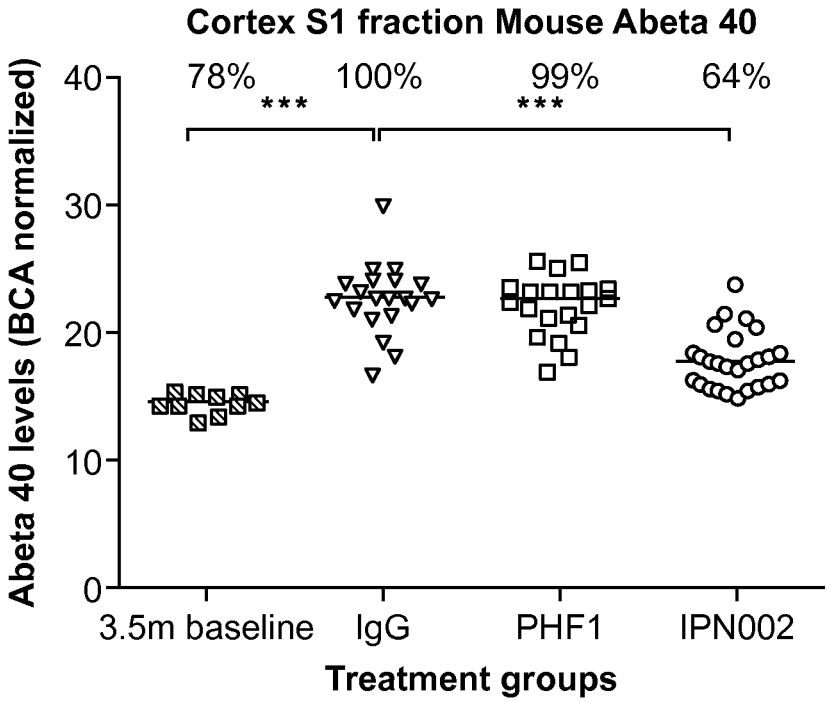


FIG. 50B

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

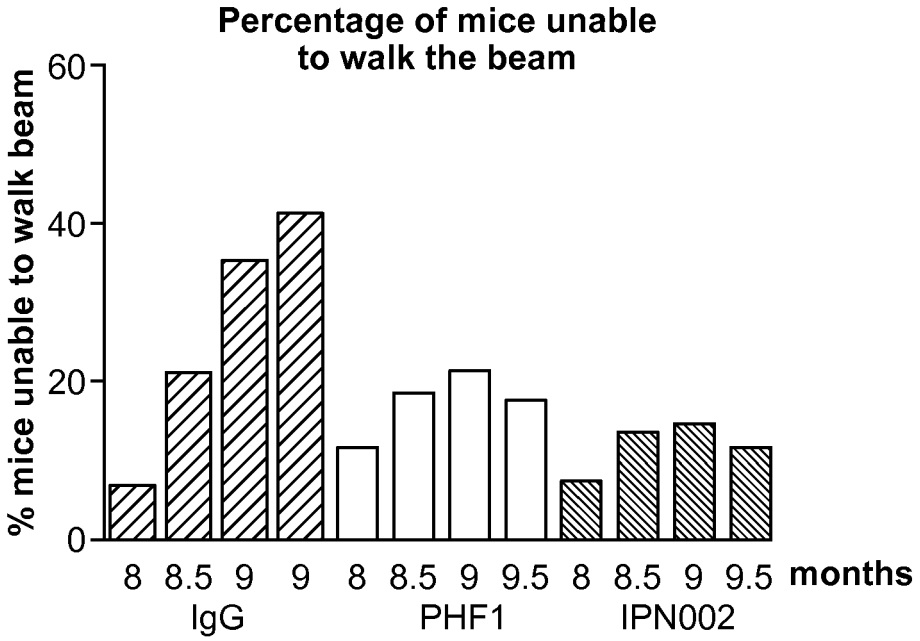
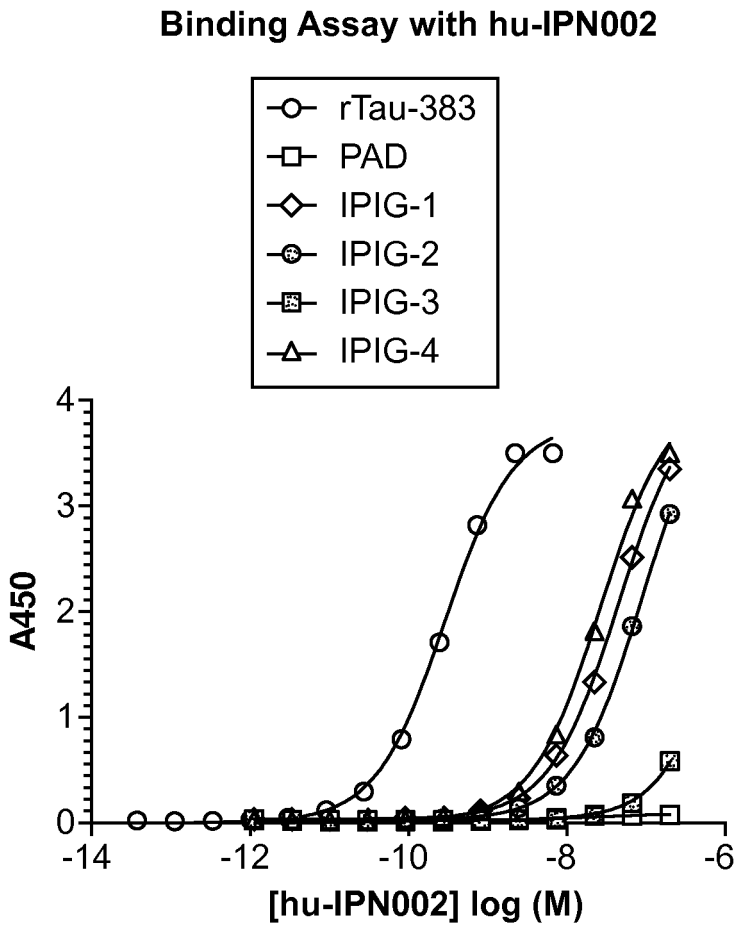
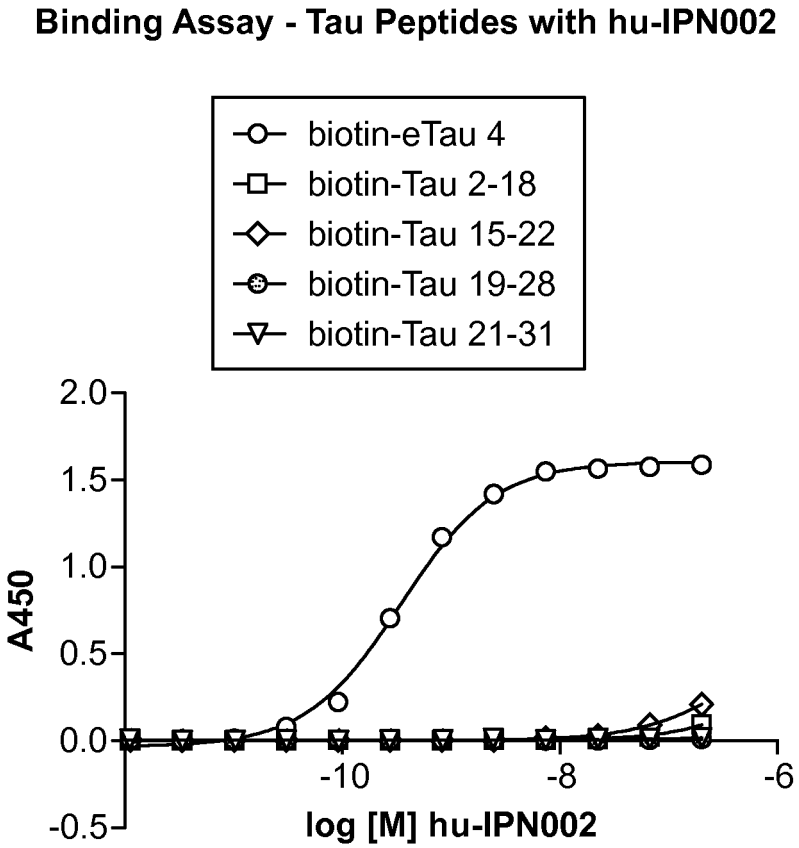

Percentage of mice unable to walk the beam
% mice unable to walk beam
60
40
20
0
8 8.5 9 9 8 8.5 9 9.5 8 8.5 9 9.5
months
IgG
PHF1
IPN002

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

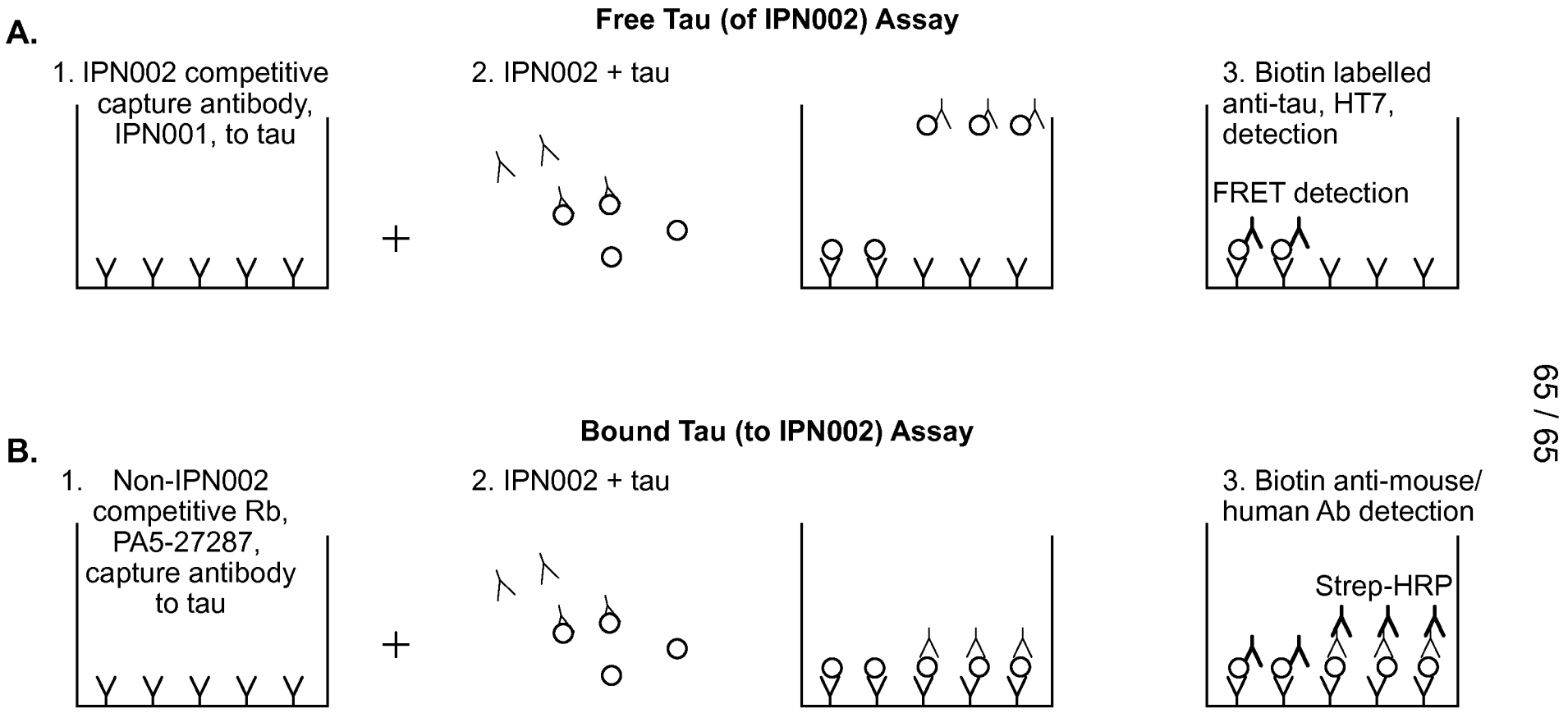

A.
Free Tau (of IPN002) Assay
1. IPN002 competitive capture antibody, IPN001, to tau
2. IPN002 + tau
3. Biotin labelled anti-tau, HT7, detection
FRET detection
B.
Bound Tau (to IPN002) Assay
1. Non-IPN002 competitive Rb, PA5-27287, capture antibody to tau
2. IPN002 + tau
3. Biotin anti-mouse/ human Ab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

FIG. 54

SEQUENCE LISTING

<110> Griswold-Prenner, Irene
Stagliano, Nancy E.
Dang, Vu

<120> METHODS OF TREATING A TAUOPATHY

<130> IPRN-745WO

<150> US 61/833,355
<151> 2013-06-10

<150> US 61/833,355
<151> 2013-04-19

<150> US 61/833,355
<151> 2013-03-14

<150> US 61/754,085
<151> 2013-01-18

<150> US 61/683,902
<151> 2012-08-16

<160> 86

<170> PatentIn version 3.5

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1 5

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Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Phe Pro Asp Ser Val Lys
1 5 10 15

Gly

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Thr Trp Asp Gly Ala Met Asp Tyr
1 5

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Lys Ser Ser Gln Ser Ile Val His Ser Asn Gly Asn Thr Tyr Leu Glu
1 5 10 15

<210> 8
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Lys Val Ser Asn Arg Phe Ser
1   5

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Phe Gln Gly Ser Leu Val Pro Trp Ala
1   5

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Lys Tyr Gly Met Ser
1   5

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<211> 17
<212> PRT
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Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val Lys
1   5   10   15

Gly

<210> 12
<211> 8
<212> PRT
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<400> 12

Ser Trp Asp Gly Ala Met Asp Tyr
1   5

<210> 13
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<400> 13

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Ala Val Asn Leu Gly
1 5 10 15

Asp Gln Ala Ser Leu Ser Cys Arg Ser Ser Gln Thr Ile Leu His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Arg Leu Leu Ile Tyr Lys Val Ser Lys Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Asp Asp Leu Gly Ile Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
100 105 110

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Glu Val Gln Leu Val Glu Ser Gly Glu Asp Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Lys Leu Ser Cys Val Ala Ser Gly Phe Ala Phe Ser Ser Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Met Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Phe Pro Asp Ser Val
50 55 60

Lys Gly Arg Leu Thr Ile Ser Arg Asp Asn Asp Lys Asn Ile Leu Tyr
65 70 75 80

```
Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Met Tyr Tyr Cys
                85                  90                  95


Thr Ile Thr Trp Asp Gly Ala Met Asp Tyr Trp Gly Arg Gly Ile Ser
            100                 105                 110


Val Thr Val Ser Ser
        115


<210>  15
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<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic amino acid sequence

<400>  15

Asp Val Leu Met Thr Gln Thr Pro Leu Ser Leu Pro Val Ser Leu Gly
1               5                   10                  15


Asp Gln Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30


Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45


Pro Lys Leu Leu Val Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60


Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80


Ser Arg Val Glu Ala Glu Asp Leu Gly Thr Tyr Tyr Cys Phe Gln Gly
                85                  90                  95


Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys
            100                 105                 110


<210>  16
<211>  117
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic amino acid sequence

<400>  16

Glu Val His Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1               5                   10                  15


Ser Leu Lys Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Tyr
            20                  25                  30
```

Gly Met Ser Trp Val Arg Gln Thr Pro Asp Lys Arg Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Gln Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ser Ile Ser Trp Asp Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 17
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

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ctctcttgca gatcgagtca gactatttta catagtaatg gaaataccta tttagaatgg 120

tatttgcaga aaccaggcca gtctccaaga ctcctgatct acaaagtttc taaacgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgacga tctgggaatt tattactgct ttcaaggttc acttgttcct 300

tgggcgttcg gtggaggcac caagctggaa atcaaa 336

<210> 18
<211> 351
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 18
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tcctgtgtcg cttctggatt cgctttcagt agctatggca tgtcttgggt tcgccagact 120

ccagacatga ggctggagtg ggtcgcaaca attagtagca gtggtagtcg cacctacttt 180

ccagacagtg tgaaggggcg actcaccatc tccagagaca atgacaagaa catcctatac 240

ctacaaatga gcagtctgag gtctgaggac acagccatgt actattgtac gattacctgg 300

gacggtgcta tggactactg gggtcgtgga atatcagtca ccgtctcctc a 351

<210> 19
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 19
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atctcttgca aatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccaaag ctcctggtct acaaagtttc caatcgattt 180

tctggggtcc cagacaggtt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tctgggaact tattactgct ttcaaggttc acttgttcct 300

tgggcgttcg gtggaggcac caagctggaa atcaaa 336

<210> 20
<211> 351
<212> DNA
<213> Artificial sequence

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<400> 20
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tcctgtgcag cctctggatt cagtttcagt aaatatggca tgtcttgggt tcgccagact 120

ccagacaaga ggctggagtg ggtcgcaacc attagtagta gtgggagtcg cacctactat 180

ccagacagtg tgaagggcca attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgttc aattagctgg 300

gacggtgcta tggactactg gggtcaaggg acctcagtca ccgtctcctc a 351

<210> 21
<211> 441
<212> PRT
<213> Artificial sequence

<220>
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<400> 21

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
35 40 45

Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser

50 55 60

Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val
65 70 75 80

Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala Ala Gln Pro His Thr Glu
85 90 95

Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro
100 105 110

Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Ala Arg Met Val
115 120 125

Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Gly
130 135 140

Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro
145 150 155 160

Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro
165 170 175

Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro Lys Ser Gly
180 185 190

Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser
195 200 205

Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys
210 215 220

Lys Val Ala Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys
225 230 235 240

Ser Arg Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val
245 250 255

Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly
260 265 270

Gly Lys Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln
275 280 285

Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly
290 295 300

Ser Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser
305 310 315 320

Lys Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln

325 330 335

Val Glu Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser
340 345 350

Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn
355 360 365

Lys Lys Ile Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala
370 375 380

Lys Thr Asp His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser
385 390 395 400

Gly Asp Thr Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser
405 410 415

Ile Asp Met Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val
420 425 430

Ser Ala Ser Leu Ala Lys Gln Gly Leu
435 440

<210> 22
<211> 383
<212> PRT
<213> Artificial sequence

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<223> Synthetic amino acid sequence

<400> 22

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala
35 40 45

Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val
50 55 60

Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp
65 70 75 80

Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro
85 90 95

Arg Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg
100 105 110

```
Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly
        115                 120                 125

Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser
    130                 135                 140

Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro
145                 150                 155                 160

Pro Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys
                165                 170                 175

Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met
            180                 185                 190

Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu
        195                 200                 205

Lys His Gln Pro Gly Gly Gly Lys Val Gln Ile Ile Asn Lys Lys Leu
    210                 215                 220

Asp Leu Ser Asn Val Gln Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys
225                 230                 235                 240

His Val Pro Gly Gly Gly Ser Val Gln Ile Val Tyr Lys Pro Val Asp
                245                 250                 255

Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His His
            260                 265                 270

Lys Pro Gly Gly Gly Gln Val Glu Val Lys Ser Glu Lys Leu Asp Phe
        275                 280                 285

Lys Asp Arg Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr His
    290                 295                 300

Val Pro Gly Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr Phe
305                 310                 315                 320

Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val Tyr
                325                 330                 335

Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser Asn
            340                 345                 350

Val Ser Ser Thr Gly Ser Ile Asp Met Val Asp Ser Pro Gln Leu Ala
        355                 360                 365

Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu
    370                 375                 380
```

<210> 23
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<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 23

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1               5                  10                  15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
            20                  25                  30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala
        35                  40                  45

Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val
    50                  55                  60

Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp
65                  70                  75                  80

Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro
                85                  90                  95

Arg Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg
            100                 105                 110

Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly
        115                 120                 125

Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser
    130                 135                 140

Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro
145                 150                 155                 160

Pro Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys
                165                 170                 175

Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met
            180                 185                 190

Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu
        195                 200                 205

Lys His Gln Pro Gly Gly Gly Lys Val Gln Ile Val Tyr Lys Pro Val
    210                 215                 220

Asp Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His
```

225 230 235 240

His Lys Pro Gly Gly Gly Gln Val Glu Val Lys Ser Glu Lys Leu Asp
245 250 255

Phe Lys Asp Arg Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr
260 265 270

His Val Pro Gly Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr
275 280 285

Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val
290 295 300

Tyr Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser
305 310 315 320

Asn Val Ser Ser Thr Gly Ser Ile Asp Met Val Asp Ser Pro Gln Leu
325 330 335

Ala Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu
340 345 350

<210> 24
<211> 412
<212> PRT
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<400> 24

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1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
35 40 45

Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser
50 55 60

Asp Ala Lys Ser Thr Pro Thr Ala Glu Ala Glu Glu Ala Gly Ile Gly
65 70 75 80

Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Ala
85 90 95

Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp Lys Lys
100 105 110

```
Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala
        115                 120                 125

Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala
    130                 135                 140

Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro
145                 150                 155                 160

Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr
                165                 170                 175

Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg
            180                 185                 190

Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys Ser Pro Ser
        195                 200                 205

Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu
    210                 215                 220

Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln
225                 230                 235                 240

Pro Gly Gly Gly Lys Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser
                245                 250                 255

Asn Val Gln Ser Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro
            260                 265                 270

Gly Gly Gly Ser Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys
        275                 280                 285

Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly
    290                 295                 300

Gly Gly Gln Val Glu Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg
305                 310                 315                 320

Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly
                325                 330                 335

Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr Phe Arg Glu Asn
            340                 345                 350

Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val Tyr Lys Ser Pro
        355                 360                 365

Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser Asn Val Ser Ser
    370                 375                 380
```

```
Thr Gly Ser Ile Asp Met Val Asp Ser Pro Gln Leu Ala Thr Leu Ala
385                 390                 395                 400


Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu
                405                 410


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<211>  776
<212>  PRT
<213>  Artificial sequence

<220>
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<400>  25

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1               5                   10                  15


Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
            20                  25                  30


Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
        35                  40                  45


Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser
    50                  55                  60


Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val
65                  70                  75                  80


Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala Ala Gln Pro His Thr Glu
                85                  90                  95


Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro
            100                 105                 110


Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Glu Pro Glu Ser
        115                 120                 125


Gly Lys Val Val Gln Glu Gly Phe Leu Arg Glu Pro Gly Pro Pro Gly
    130                 135                 140


Leu Ser His Gln Leu Met Ser Gly Met Pro Gly Ala Pro Leu Leu Pro
145                 150                 155                 160


Glu Gly Pro Arg Glu Ala Thr Arg Gln Pro Ser Gly Thr Gly Pro Glu
                165                 170                 175


Asp Thr Glu Gly Gly Arg His Ala Pro Glu Leu Leu Lys His Gln Leu
            180                 185                 190


Leu Gly Asp Leu His Gln Glu Gly Pro Pro Leu Lys Gly Ala Gly Gly
```

195 200 205

Lys Glu Arg Pro Gly Ser Lys Glu Glu Val Asp Glu Asp Arg Asp Val
210 215 220

Asp Glu Ser Ser Pro Gln Asp Ser Pro Pro Ser Lys Ala Ser Pro Ala
225 230 235 240

Gln Asp Gly Arg Pro Pro Gln Thr Ala Ala Arg Glu Ala Thr Ser Ile
245 250 255

Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro Leu Pro Val Asp Phe Leu
260 265 270

Ser Lys Val Ser Thr Glu Ile Pro Ala Ser Glu Pro Asp Gly Pro Ser
275 280 285

Val Gly Arg Ala Lys Gly Gln Asp Ala Pro Leu Glu Phe Thr Phe His
290 295 300

Val Glu Ile Thr Pro Asn Val Gln Lys Glu Gln Ala His Ser Glu Glu
305 310 315 320

His Leu Gly Arg Ala Ala Phe Pro Gly Ala Pro Gly Glu Gly Pro Glu
325 330 335

Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr Lys Glu Ala Asp Leu Pro
340 345 350

Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala Pro Arg Gly Lys Pro Val
355 360 365

Ser Arg Val Pro Gln Leu Lys Ala Arg Met Val Ser Lys Ser Lys Asp
370 375 380

Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Thr Ser Thr Arg Ser Ser
385 390 395 400

Ala Lys Thr Leu Lys Asn Arg Pro Cys Leu Ser Pro Lys His Pro Thr
405 410 415

Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro Ser Ser Pro Ala Val Cys
420 425 430

Pro Glu Pro Pro Ser Ser Pro Lys His Val Ser Ser Val Thr Ser Arg
435 440 445

Thr Gly Ser Ser Gly Ala Lys Glu Met Lys Leu Lys Gly Ala Asp Gly
450 455 460

Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys

```
465                 470                 475                 480

Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro
                485                 490                 495

Lys Thr Pro Pro Ser Ser Ala Thr Lys Gln Val Gln Arg Arg Pro Pro
            500                 505                 510

Pro Ala Gly Pro Arg Ser Glu Arg Gly Glu Pro Pro Lys Ser Gly Asp
        515                 520                 525

Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg
    530                 535                 540

Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys
545                 550                 555                 560

Val Ala Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser
                565                 570                 575

Arg Leu Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys
            580                 585                 590

Ser Lys Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly
        595                 600                 605

Lys Val Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser
    610                 615                 620

Lys Cys Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser
625                 630                 635                 640

Val Gln Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys
                645                 650                 655

Cys Gly Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val
            660                 665                 670

Glu Val Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys
        675                 680                 685

Ile Gly Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys
    690                 695                 700

Lys Ile Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys
705                 710                 715                 720

Thr Asp His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly
                725                 730                 735

Asp Thr Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile
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740 745 750

Asp Met Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser
755 760 765

Ala Ser Leu Ala Lys Gln Gly Leu
770 775

<210> 26
<211> 758
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 26

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Glu Ser Pro Leu
35 40 45

Gln Thr Pro Thr Glu Asp Gly Ser Glu Glu Pro Gly Ser Glu Thr Ser
50 55 60

Asp Ala Lys Ser Thr Pro Thr Ala Glu Asp Val Thr Ala Pro Leu Val
65 70 75 80

Asp Glu Gly Ala Pro Gly Lys Gln Ala Ala Ala Gln Pro His Thr Glu
85 90 95

Ile Pro Glu Gly Thr Thr Ala Glu Glu Ala Gly Ile Gly Asp Thr Pro
100 105 110

Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr Gln Glu Pro Glu Ser
115 120 125

Gly Lys Val Val Gln Glu Gly Phe Leu Arg Glu Pro Gly Pro Pro Gly
130 135 140

Leu Ser His Gln Leu Met Ser Gly Met Pro Gly Ala Pro Leu Leu Pro
145 150 155 160

Glu Gly Pro Arg Glu Ala Thr Arg Gln Pro Ser Gly Thr Gly Pro Glu
165 170 175

Asp Thr Glu Gly Gly Arg His Ala Pro Glu Leu Leu Lys His Gln Leu
180 185 190

```
Leu Gly Asp Leu His Gln Glu Gly Pro Pro Leu Lys Gly Ala Gly Gly
        195                 200                 205

Lys Glu Arg Pro Gly Ser Lys Glu Glu Val Asp Glu Asp Arg Asp Val
    210                 215                 220

Asp Glu Ser Ser Pro Gln Asp Ser Pro Pro Ser Lys Ala Ser Pro Ala
225                 230                 235                 240

Gln Asp Gly Arg Pro Pro Gln Thr Ala Ala Arg Glu Ala Thr Ser Ile
                245                 250                 255

Pro Gly Phe Pro Ala Glu Gly Ala Ile Pro Leu Pro Val Asp Phe Leu
            260                 265                 270

Ser Lys Val Ser Thr Glu Ile Pro Ala Ser Glu Pro Asp Gly Pro Ser
        275                 280                 285

Val Gly Arg Ala Lys Gly Gln Asp Ala Pro Leu Glu Phe Thr Phe His
    290                 295                 300

Val Glu Ile Thr Pro Asn Val Gln Lys Glu Gln Ala His Ser Glu Glu
305                 310                 315                 320

His Leu Gly Arg Ala Ala Phe Pro Gly Ala Pro Gly Glu Gly Pro Glu
                325                 330                 335

Ala Arg Gly Pro Ser Leu Gly Glu Asp Thr Lys Glu Ala Asp Leu Pro
            340                 345                 350

Glu Pro Ser Glu Lys Gln Pro Ala Ala Ala Pro Arg Gly Lys Pro Val
        355                 360                 365

Ser Arg Val Pro Gln Leu Lys Ala Arg Met Val Ser Lys Ser Lys Asp
    370                 375                 380

Gly Thr Gly Ser Asp Asp Lys Lys Ala Lys Thr Ser Thr Arg Ser Ser
385                 390                 395                 400

Ala Lys Thr Leu Lys Asn Arg Pro Cys Leu Ser Pro Lys His Pro Thr
                405                 410                 415

Pro Gly Ser Ser Asp Pro Leu Ile Gln Pro Ser Ser Pro Ala Val Cys
            420                 425                 430

Pro Glu Pro Pro Ser Ser Pro Lys His Val Ser Ser Val Thr Ser Arg
        435                 440                 445

Thr Gly Ser Ser Gly Ala Lys Glu Met Lys Leu Lys Gly Ala Asp Gly
    450                 455                 460
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Lys Thr Lys Ile Ala Thr Pro Arg Gly Ala Ala Pro Pro Gly Gln Lys
465                 470                 475                 480

Gly Gln Ala Asn Ala Thr Arg Ile Pro Ala Lys Thr Pro Pro Ala Pro
                485                 490                 495

Lys Thr Pro Pro Ser Ser Gly Glu Pro Pro Lys Ser Gly Asp Arg Ser
            500                 505                 510

Gly Tyr Ser Ser Pro Gly Ser Pro Gly Thr Pro Gly Ser Arg Ser Arg
        515                 520                 525

Thr Pro Ser Leu Pro Thr Pro Pro Thr Arg Glu Pro Lys Lys Val Ala
    530                 535                 540

Val Val Arg Thr Pro Pro Lys Ser Pro Ser Ser Ala Lys Ser Arg Leu
545                 550                 555                 560

Gln Thr Ala Pro Val Pro Met Pro Asp Leu Lys Asn Val Lys Ser Lys
                565                 570                 575

Ile Gly Ser Thr Glu Asn Leu Lys His Gln Pro Gly Gly Gly Lys Val
            580                 585                 590

Gln Ile Ile Asn Lys Lys Leu Asp Leu Ser Asn Val Gln Ser Lys Cys
        595                 600                 605

Gly Ser Lys Asp Asn Ile Lys His Val Pro Gly Gly Gly Ser Val Gln
    610                 615                 620

Ile Val Tyr Lys Pro Val Asp Leu Ser Lys Val Thr Ser Lys Cys Gly
625                 630                 635                 640

Ser Leu Gly Asn Ile His His Lys Pro Gly Gly Gly Gln Val Glu Val
                645                 650                 655

Lys Ser Glu Lys Leu Asp Phe Lys Asp Arg Val Gln Ser Lys Ile Gly
            660                 665                 670

Ser Leu Asp Asn Ile Thr His Val Pro Gly Gly Gly Asn Lys Lys Ile
        675                 680                 685

Glu Thr His Lys Leu Thr Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp
    690                 695                 700

His Gly Ala Glu Ile Val Tyr Lys Ser Pro Val Val Ser Gly Asp Thr
705                 710                 715                 720

Ser Pro Arg His Leu Ser Asn Val Ser Ser Thr Gly Ser Ile Asp Met
                725                 730                 735
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Val Asp Ser Pro Gln Leu Ala Thr Leu Ala Asp Glu Val Ser Ala Ser
740 745 750

Leu Ala Lys Gln Gly Leu
755

<210> 27
<211> 352
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 27

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His
20 25 30

Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala
35 40 45

Gly Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val
50 55 60

Thr Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp
65 70 75 80

Asp Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro
85 90 95

Arg Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg
100 105 110

Ile Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly
115 120 125

Glu Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser
130 135 140

Pro Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro
145 150 155 160

Pro Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys
165 170 175

Ser Pro Ser Ser Ala Lys Ser Arg Leu Gln Thr Ala Pro Val Pro Met
180 185 190

Pro Asp Leu Lys Asn Val Lys Ser Lys Ile Gly Ser Thr Glu Asn Leu

195 200 205

Lys His Gln Pro Gly Gly Gly Lys Val Gln Ile Val Tyr Lys Pro Val
210 215 220

Asp Leu Ser Lys Val Thr Ser Lys Cys Gly Ser Leu Gly Asn Ile His
225 230 235 240

His Lys Pro Gly Gly Gly Gln Val Glu Val Lys Ser Glu Lys Leu Asp
245 250 255

Phe Lys Asp Arg Val Gln Ser Lys Ile Gly Ser Leu Asp Asn Ile Thr
260 265 270

His Val Pro Gly Gly Gly Asn Lys Lys Ile Glu Thr His Lys Leu Thr
275 280 285

Phe Arg Glu Asn Ala Lys Ala Lys Thr Asp His Gly Ala Glu Ile Val
290 295 300

Tyr Lys Ser Pro Val Val Ser Gly Asp Thr Ser Pro Arg His Leu Ser
305 310 315 320

Asn Val Ser Ser Thr Gly Ser Ile Asp Met Val Asp Ser Pro Gln Leu
325 330 335

Ala Thr Leu Ala Asp Glu Val Ser Ala Ser Leu Ala Lys Gln Gly Leu
340 345 350

<210> 28
<211> 351
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 28
gaggttcatc tggtggagtc tgggggagcc ttagtgaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt cagtttcagt aaatatggca tgtcttgggt tcgccaggcc 120

ccaggcaagg gcctggagtg ggtcgcaacc attagtagta gtgggagtcg cacctactat 180

ccagacagtg tgaagggcag attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga gcagtctgaa gtctgaggac acagccatgt attactgttc aattagctgg 300

gacggtgcta tggactactg gggtcaaggg acctcagtca ccgtctcctc a 351

<210> 29
<211> 351
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 29
gaggttcatc tggtggagtc tgggggagcc ttagtgaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt cagtttcagt aaatatggca tgtcttgggt tcgccaggcc 120

ccaggcaagg gcctggagtg ggtcgcaacc attagtagta gtgggagtcg cacctactat 180

ccagacagtg tgaagggcag attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga acagtctgag agccgaggac acagccatgt attactgttc aattagctgg 300

gacggtgcta tggactactg gggtcaaggg accaccgtca ccgtctcctc a 351

<210> 30
<211> 351
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 30
gaggttcagc tggtggagtc tgggggagcc ttagtgaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt cagtttcagt aaatatggca tgtcttgggt tcgccaggcc 120

ccaggcaagg gcctggagtg ggtcgcaacc attagtagta gtgggagtcg cacctactat 180

ccagacagtg tgaagggcag attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga acagtctgag agccgaggac acagccatgt attactgttc aattagctgg 300

gacggtgcta tggactactg gggtcaaggg accaccgtca ccgtctcctc a 351

<210> 31
<211> 351
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 31
gaggttcagc tggtggagtc tgggggagcc ttagtgaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt cagtttcagt aaatatggca tgtcttgggt tcgccaggcc 120

ccaggcaagg gcctggagtg ggtcgcaacc attagtagta gtgggagtcg cacctactat 180

ccagacagtg tgaagggcag attcaccatc tccagagaca atgccaagaa caccctgtac 240

ctgcaaatga acagtctgag agccgaggac acagccatgt attactgtgc cattagctgg 300

gacggtgcta tggactactg gggtcaaggg accaccgtca ccgtctcctc a 351

<210> 32
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 32

gatgttttga tgacccaaag cccactctcc ctgcctgtca cccttggaca gcccgcctcc 60

atctcttgca aatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccacag ctcctggtct acaaagtttc caatcgattt 180

tctggggtcc cagacagatt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tgtgggaact tattactgct ttcaaggctc acttgttcct 300

tgggcgttcg gtggaggcac caaggtggaa atcaaa 336

<210> 33
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 33
gatgttgtga tgacccaaag cccactctcc ctgcctgtca cccttggaca gcccgcctcc 60

atctcttgca aatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccacag ctcctggtct acaaagtttc caatcgattt 180

tctggggtcc cagacagatt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tgtgggaact tattactgct ttcaaggctc acttgttcct 300

tgggcgttcg gtggaggcac caaggtggaa atcaaa 336

<210> 34
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 34
gatgttgtga tgacccaaag cccactctcc ctgcctgtca cccttggaca gcccgcctcc 60

atctcttgca aatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccacag ctcctggtct acaaagtttc caatcgattt 180

tctggggtcc cagacagatt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tgtgggagtg tattactgct ttcaaggctc acttgttcct 300

tgggcgttcg gtggaggcac caaggtggaa atcaaa 336

<210> 35
<211> 336
<212> DNA
<213> Artificial sequence

<220>
<223> Synthetic nucleic acid sequence

<400> 35
gatgttgtga tgacccaaag cccactctcc ctgcctgtca cccttggaca gcccgcctcc 60

atctcttgca aatctagtca gagcattgta catagtaatg gaaacaccta tttagaatgg 120

tacctgcaga aaccaggcca gtctccacag ctcctgatct acaaagtttc caatcgattt 180

tctggggtcc cagacagatt cagtggcagt ggatcaggga cagatttcac actcaagatc 240

agcagagtgg aggctgagga tgtgggagtg tattactgct ttcaaggctc acttgttcct 300

tgggcgttcg gtggaggcac caaggtggaa atcaaa 336

<210> 36
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 36

Glu Val His Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Ser Ser Leu Lys Ser Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ser Ile Ser Trp Asp Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Ser
100 105 110

Val Thr Val Ser Ser
115

<210> 37
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 37

Glu Val His Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Tyr

20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ser Ile Ser Trp Asp Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 38
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 38

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ser Ile Ser Trp Asp Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 39
<211> 117
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 39

Glu Val Gln Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser Lys Tyr
20 25 30

Gly Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Thr Ile Ser Ser Ser Gly Ser Arg Thr Tyr Tyr Pro Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Met Tyr Tyr Cys
85 90 95

Ala Ile Ser Trp Asp Gly Ala Met Asp Tyr Trp Gly Gln Gly Thr Thr
100 105 110

Val Thr Val Ser Ser
115

<210> 40
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 40

Asp Val Leu Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Val Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Thr Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 41
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 41

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
20 25 30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Val Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Thr Tyr Tyr Cys Phe Gln Gly
85 90 95

Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> 42
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 42

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
20 25 30

```
Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Val Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
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<210> 43
<211> 112
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 43

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Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1               5                   10                  15

Gln Pro Ala Ser Ile Ser Cys Lys Ser Ser Gln Ser Ile Val His Ser
            20                  25                  30

Asn Gly Asn Thr Tyr Leu Glu Trp Tyr Leu Gln Lys Pro Gly Gln Ser
        35                  40                  45

Pro Gln Leu Leu Ile Tyr Lys Val Ser Asn Arg Phe Ser Gly Val Pro
    50                  55                  60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65                  70                  75                  80

Ser Arg Val Glu Ala Glu Asp Val Gly Val Tyr Tyr Cys Phe Gln Gly
                85                  90                  95

Ser Leu Val Pro Trp Ala Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105                 110
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<210> 44
<211> 171
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 44

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Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1               5                   10                  15

Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His Gln
            20                  25                  30

Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala Gly
        35                  40                  45

Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr
    50                  55                  60

Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp
65                  70                  75                  80

Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg
                85                  90                  95

Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile
            100                 105                 110

Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu
        115                 120                 125

Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro
    130                 135                 140

Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro
145                 150                 155                 160

Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg
                165                 170


<210>  45
<211>  175
<212>  PRT
<213>  Artificial sequence

<220>
<223>  Synthetic amino acid sequence

<400>  45

Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1               5                   10                  15

Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His Gln
            20                  25                  30

Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala Gly
        35                  40                  45

Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr
```

50 55 60

Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp
65 70 75 80

Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg
85 90 95

Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile
100 105 110

Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu
115 120 125

Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro
130 135 140

Gly Thr Pro Gly Ser Arg Ser Arg Thr Pro Ser Leu Pro Thr Pro Pro
145 150 155 160

Thr Arg Glu Pro Lys Lys Val Ala Val Val Arg Thr Pro Pro Lys
165 170 175

<210> 46
<211> 150
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 46

Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1 5 10 15

Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His Gln
20 25 30

Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala Gly
35 40 45

Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr
50 55 60

Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp
65 70 75 80

Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg
85 90 95

Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile
100 105 110

Pro Ala Lys Thr Pro Pro Ala Pro Lys Thr Pro Pro Ser Ser Gly Glu
115 120 125

Pro Pro Lys Ser Gly Asp Arg Ser Gly Tyr Ser Ser Pro Gly Ser Pro
130 135 140

Gly Thr Pro Gly Ser Arg
145 150

<210> 47
<211> 121
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 47

Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1 5 10 15

Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His Gln
20 25 30

Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala Gly
35 40 45

Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr
50 55 60

Gln Ala Arg Met Val Ser Lys Ser Lys Asp Gly Thr Gly Ser Asp Asp
65 70 75 80

Lys Lys Ala Lys Gly Ala Asp Gly Lys Thr Lys Ile Ala Thr Pro Arg
85 90 95

Gly Ala Ala Pro Pro Gly Gln Lys Gly Gln Ala Asn Ala Thr Arg Ile
100 105 110

Pro Ala Lys Thr Pro Pro Ala Pro Lys
115 120

<210> 48
<211> 67
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 48

Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1 5 10 15

Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr Met His Gln
            20   25   30

Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys Ala Glu Glu Ala Gly
        35   40   45

Ile Gly Asp Thr Pro Ser Leu Glu Asp Glu Ala Ala Gly His Val Thr
    50   55   60

Gln Ala Arg
65

<210> 49
<211> 12
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 49

Asp His Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys
1   5   10

<210> 50
<211> 30
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 50

Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys Asp Gln Gly Gly Tyr Thr
1   5   10   15

Met His Gln Asp Gln Glu Gly Asp Thr Asp Ala Gly Leu Lys
            20   25   30

<210> 51
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 51

Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys
1   5   10

<210> 52
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (4)..(4)
<223> The amino acid at this position is phosphorylated

<400> 52

Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys
1 5 10

<210> 53
<211> 18
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 53

Met Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly
1 5 10 15

Thr Tyr

<210> 54
<211> 23
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> X at this position is L or V

<400> 54

Asp Val Xaa Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys
20

<210> 55
<211> 15
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE

<222> (14)..(14)
<223> X at this position is V or I

<400> 55

Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Xaa Tyr
1 5 10 15

<210> 56
<211> 32
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (29)..(29)
<223> X at this position is T or V

<400> 56

Gly Val Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr
1 5 10 15

Leu Lys Ile Ser Arg Val Glu Ala Glu Asp Val Gly Xaa Tyr Tyr Cys
20 25 30

<210> 57
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 57

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
1 5 10

<210> 58
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 58

Gly Ser Gly Gly Ser
1 5

<210> 59
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 59

Gly Gly Gly Ser
1

<210> 60
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 60

Gly Gly Ser Gly
1

<210> 61
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 61

Gly Gly Ser Gly Gly
1 5

<210> 62
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 62

Gly Ser Gly Ser Gly
1 5

<210> 63
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 63

Gly Ser Gly Gly Gly
1 5

<210> 64
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 64

Gly Gly Gly Ser Gly
1   5

<210> 65
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 65

Gly Ser Ser Ser Gly
1   5

<210> 66
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 66

His His His His His
1   5

<210> 67
<211> 6
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 67

His His His His His His
1   5

<210> 68
<211> 10
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 68

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu
1   5   10

<210> 69
<211> 8
<212> PRT

<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 69

Asp Tyr Lys Asp Asp Asp Asp Lys
1 5

<210> 70
<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 70

Trp Ser His Pro Gln Phe Glu Lys
1 5

<210> 71
<211> 9
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 71

Tyr Pro Tyr Asp Val Pro Asp Tyr Ala
1 5

<210> 72
<211> 5
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 72

Arg Tyr Ile Arg Ser
1 5

<210> 73
<211> 4
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 73

Phe His His Thr
1

<210> 74

<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 74

Trp Glu Ala Ala Ala Arg Glu Ala Cys Cys Arg Glu Cys Cys Ala Arg
1 5 10 15

Ala

<210> 75
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 75

Thr Phe Phe Tyr Gly Gly Cys Arg Gly Lys Arg Asn Asn Phe Lys Thr
1 5 10 15

Glu Glu Tyr

<210> 76
<211> 19
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 76

Thr Phe Phe Tyr Gly Gly Ser Arg Gly Lys Arg Asn Asn Phe Lys Thr
1 5 10 15

Glu Glu Tyr

<210> 77
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 77

Cys Thr Phe Phe Tyr Gly Gly Ser Arg Gly Lys Arg Asn Asn Phe Lys
1 5 10 15

Thr Glu Glu Tyr

20

<210> 78
<211> 20
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 78

Thr Phe Phe Tyr Gly Gly Ser Arg Gly Lys Arg Asn Asn Phe Lys Thr
1 5 10 15

Glu Glu Tyr Cys
20

<210> 79
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 79

Thr Phe Val Tyr Gly Gly Cys Arg Ala Lys Arg Asn Asn Phe Lys Ser
1 5 10 15

<210> 80
<211> 17
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 80

Ala Glu Pro Arg Gln Glu Phe Glu Val Met Glu Asp His Ala Gly Thr
1 5 10 15

Tyr

<210> 81
<211> 16
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 81

Glu Val Met Glu Asp His Ala Gly Thr Tyr Gly Leu Gly Asp Arg Lys
1 5 10 15

<210> 82

<211> 8
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 82

Ala Gly Thr Tyr Gly Leu Gly Asp
1 5

<210> 83
<211> 30
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (3)..(3)
<223> X at this position is an H or Q

<400> 83

Glu Val Xaa Leu Val Glu Ser Gly Gly Ala Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Phe Ser
20 25 30

<210> 84
<211> 14
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<400> 84

Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val Ala
1 5 10

<210> 85
<211> 32
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (18)..(18)
<223> X at this position is an S or N

<220>
<221> MISC_FEATURE
<222> (20)..(20)

<223> X at this position is an S or L

<220>
<221> MISC_FEATURE
<222> (21)..(21)
<223> X at this position is a K or R

<220>
<221> MISC_FEATURE
<222> (22)..(22)
<223> X at this position is a S or A

<220>
<221> MISC_FEATURE
<222> (31)..(31)
<223> X at this position is a S or A

<400> 85

Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr Leu Gln
1 5 10 15

Met Xaa Ser Xaa Xaa Xaa Glu Asp Thr Ala Met Tyr Tyr Cys Xaa Ile
20 25 30

<210> 86
<211> 11
<212> PRT
<213> Artificial sequence

<220>
<223> Synthetic amino acid sequence

<220>
<221> MISC_FEATURE
<222> (6)..(6)
<223> X at this position is an S or T

<400> 86

Trp Gly Gln Gly Thr Xaa Val Thr Val Ser Ser
1 5 10