FIGURE 1

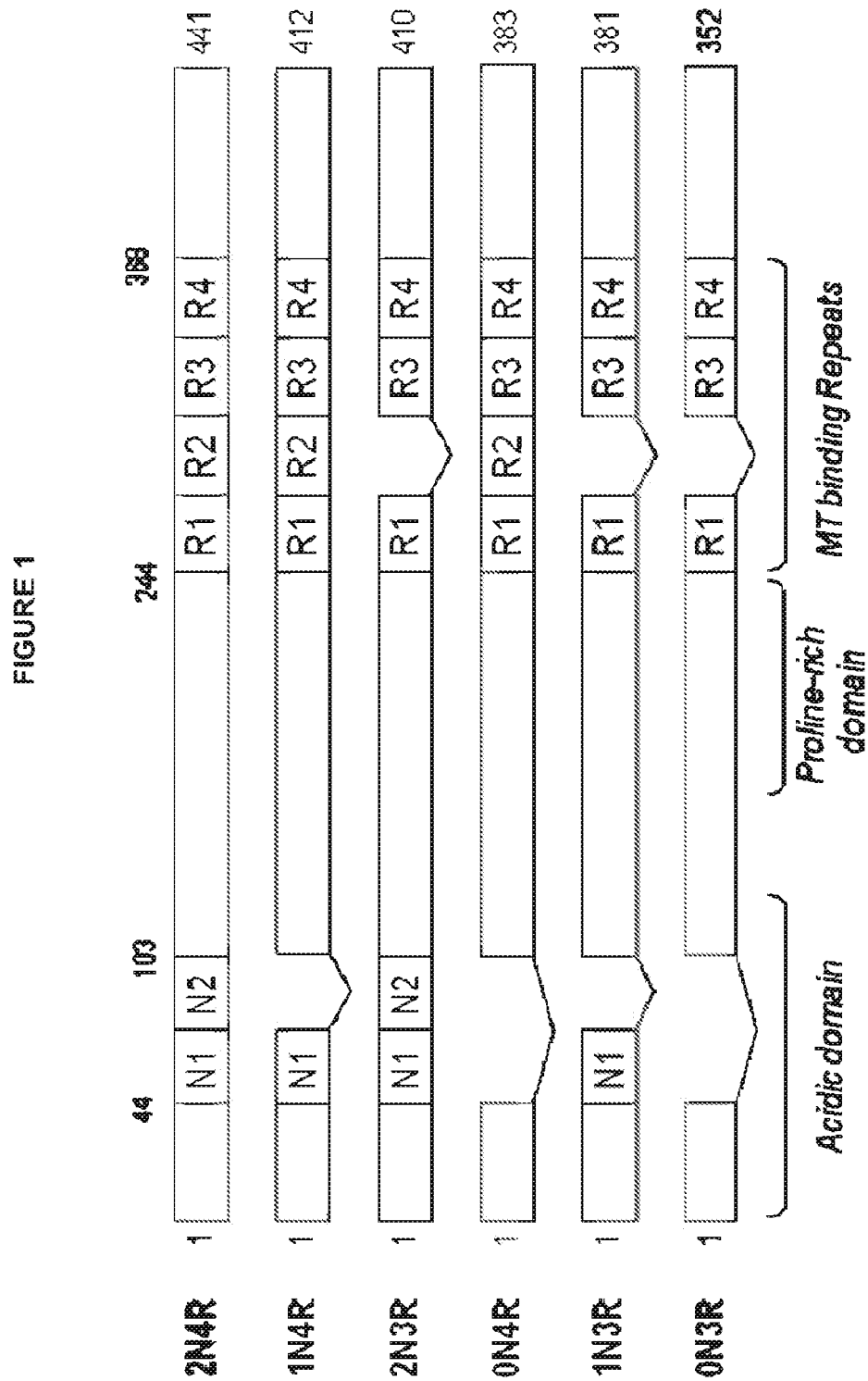

2N4R
1N4R
2N3R
0N4R
1N3R
0N3R
1
44
103
244
383
N1
N2
R1
R2
R3
R4
441
412
410
383
381
352
Acidic domain
Proline-rich domain
MT binding Repeats

FIGURE 2

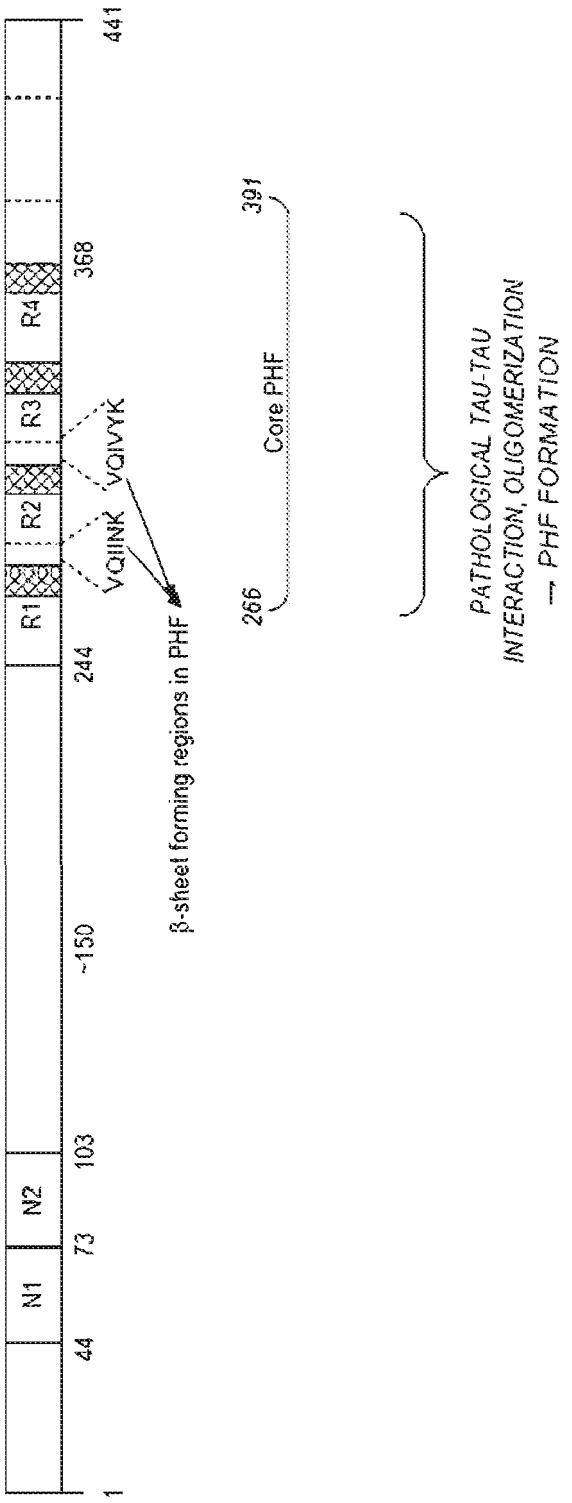

N1
N2
R1
R2
R3
R4
1
44
73
103
~150
244
266
368
391
441
VQIINK
VQIVYK
β-sheet forming regions in PHF
Core PHF
PATHOLOGICAL TAU-TAU
INTERACTION, OLIGOMERIZATION
→ PHF FORMATION

FIGURE 3

A. Nucleotide sequence of DC8E8 variable light chain (VL):

GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGAGAAGGTCACTATGAGCTGCAAATCCAGTCAGAGTCTGCTC
AACAGTAGAACCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCTAAACTGCTGATCTACTGGGCATCCACTAGG
GAATCTGGGGTCCCTGATCGCTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTGTGCAGGCTGAAGACCTGGCA
GTTTATTACTGCAAGCAATCTTTTTATCTTCGGACGTTCGGTGGAGGCACCAAGCTGGACATCAAA

B. Amino acid sequence of DC8E8 variable light chain (VL):

DIVMSQSPSSLAVSAGEKVTMSCKSSQSLLNSRTRKNYLAWYQQKPGQSPKLLIYWASTRESGVPDRFTGSGSGTDFTLTISSVQAEDLA
VYYCKQSFYLRTFGGGTKLDIK

CDR1: QSLLNSRTRKNY
CDR2: WAS
CDR3: KQSFYLRT

C. Alignment of DC8E8 (VL) sequence with the closest mouse germline sequence IGKV8-21*01:

V-gene (298/301; 99.0% sequence identity):

```
DC8E8 light    GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGA
IGKV8-21*01    GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGA
               **************************************************

DC8E8 light    GAAGGTCACTATGAGCTGCAAATCCAGTCAGAGTCTGCTCAACAGTAGAA
IGKV8-21*01    GAAGGTCACTATGAGCTGCAAATCCAGTCAGAGTCTGCTCAACAGTAGAA
               **************************************************

DC8E8 light    CCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCT
IGKV8-21*01    CCCGAAAGAACTACTTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCT
               ************** ***********************************

DC8E8 light    AAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCG
IGKV8-21*01    AAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCG
               **************************************************
DC8E8 light    CTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTG
IGKV8-21*01    CTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTG
               **************************************************
```

```
DC8E8 light    TGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTTTTATCTT
IGKV8-21*01    TGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTATAATCTT
               ****************************************** * *****

DC8E8 light    C
IGKV8-21*01    C
               *
```

J-gene (35/36; 97.2% sequence identity):

```
DC8E8 light    GGACGTTCGGTGGAGGCACCAAGCTGGACATCAAAC
IGKJ1*01       GGACGTTCGGTGGAGGCACCAAGCTGGAAATCAAAC
               ***************************** *******
```

D. Nucleotide sequence of DC8E8 heavy chain variable region (VH):

CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGGACTTCAGTGAAGATGCCCTGTAAGGCTTCTGGATACATATTCACT
GACTATGTCATAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAGATTTTTCCTAGAAGTGGTAGTACTTACTAC
AATGAGAAGTTCAAGGGCAAGGCCACACTGACTGCAGACAAATCCTCCAACACAGCCTACATGCAGCTCAGCAGCGTGACATCTGAGGAC
TCTGCGGTCTATTTCTGTGCAAGAGATTACTACGGTACTTCATTTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

E. Amino acid sequence of DC8E8 heavy chain variable region (VH):

QVQLQQSGPELVKPGTSVKMPCKASGYIFTDYVISWVKQRTGQGLEWIGEIFPRSGSTYYNEKFKGKATLTADKSSNTAYMQLSSVTSED
SAVYFCARDYYGTSFAMDYWGQGTSVTVSS

CDR1: GYIFTDYVIS
CDR2: IFPRSGST
CDR3: ARDYYGTSFAMDY

F. Alignment of DC8E8 (VH) sequence with the closest mouse germline sequence IGKV8-81*01:

V-gene (269/294; 91.5% sequence identity):

```
DC8E8 heavy    CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGGACTTC
IGHV1-81*01    CAGGTTCAGCTGCAGCAGTCTGGAGCTGAGCTGGCGAGGCCTGGGGCTTC
               ***** **  ************** ********* ** ******* ****
```

```
DC8E8 heavy   AGTGAAGATGCCCTGTAAGGCTTCTGGATACATATTCACTGACTATGTCA
IGHV1-81*01   AGTGAAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACAAGCTATGGTA
              *******  **  *****  ***********  ****   *****    *

DC8E8 heavy   TAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAG
IGHV1-81*01   TAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAG
              **********************************************

DC8E8 heavy   ATTTTTCCTAGAAGTGGTAGTACTTACTACAATGAGAAGTTCAAGGGCAA
IGHV1-81*01   ATTTATCCTAGAAGTGGTAATACTTACTACAATGAGAAGTTCAAGGGCAA
              ****  ********************  ********************

DC8E8 heavy   GGCCACACTGACTGCAGACAAAATCCTCCAACACAGCCTACATGCAGCTCA
IGHV1-81*01   GGCCACACTGACTGCAGACAAATCCTCCAGCACAGCGTACATGGAGCTCC
              **********************  *******  *******  *****

DC8E8 heavy   GCAGCGTGACATCTGAGGACTCTGCGGTCTATTTCTGTGCAAGA
IGHV1-81*01   GCAGCCTGACATCTGAGGACTCTGCGGTCTATTTCTGTGCAAGA
                ******  ************************************

D-gene (12/15; 80.0% sequence identity):

DC8E8 heavy   GATTACTAC-GGTAC
IGHD2-14*01   GACTACTATAGGTAC
              **  ******  *****

J-gene (50/53; 94.3% sequence identity):

DC8E8 heavy   TTCATTTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
IGHJ4*01      TTACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
              **  *  ************************************

DC8E8 heavy   TCAG
IGHJ4*01      TCAG
              ****
```

G. Nucleotide sequence of the DC8E8 kappa light chain constant region:

gggctgatgctgcaccaacactgtatccatcttcccaccatccagtgagcagttaacatcttggaggtgcctcagtcgtgtgcttctttgaaca
acttctaccccaaagacatcaatgtcaggtggaagattgatggcagtgaacgacaaaatggcgtccttgaacagttggactgatcaggaca
gcaaagacagcacctacagcatgagcaccctcacgttgaccaaggacgagtatgaacgacataacagctataccttgtgaggcca

H. Nucleotide sequence of the DC8E8 heavy chain constant region CH1:

ccaaaacgacacccccatctgtctatccactggcccctggatctgctgcccaaactaactcccatggtgaccctgggatgcctggtcaagg
gctatttccctgagccagtgacagtgacctggaactctggatccctgtccagcggtgtgcacaccttcccagctgtcctgcagtctgacc
tctacactctgagcagctcagtgactgtccctccagcacctggcccagcgagaccgtcacctgcaacgttgcccacccggccagcagca
ccaagg

FIGURE 4

V-gene (242/301; 80.4 % sequence identity):

```
DC8E8                    GACATTGTGATGTCACAGTCTCCATCCTCCCTGGCTGTGTCAGCAGGAGA
IGKV4-1*01_Homo+sapiens  GACATCGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTCTGGGCGA
                         ***** ****** * *********  ***************    ** **

DC8E8                    GAAGGTCACTATGAGCTGCAAATCCAGTCAGAGTCTGCTCAACAGTAGAA
IGKV4-1*01_Homo+sapiens  GAGGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGCTCCA
                         ** ** *** ** * ****** ***** ****** *  *  ****    *

DC8E8                    CCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACCAGGGCAGTCTCCT
IGKV4-1*01_Homo+sapiens  ACAATAAGAACTACTTAGCTTGGTACCAGCAGAAACCAGGACAGCCTCCT
                         *   ********** * ************************ *** *****

DC8E8                    AAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCG
IGKV4-1*01_Homo+sapiens  AAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGGTCCCTGACCG
                         ** ***** ** ************ **  ******* ************ **

DC8E8                    CTTCACAGGCAGTGGATCTGGGACAGATTTCACTCTCACCATCAGCAGTG
IGKV4-1*01_Homo+sapiens  ATTCAGTGGCAGCGGGTCTGGGACAGATTTCACTCTCACCATCAGCAGCC
                         ****  ***** ** **********************************

DC8E8                    TGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTTTTATCTT
IGKV4-1*01_Homo+sapiens  TGCAGGCTGAAGATGTGGCAGTTTATTACTGTCAGCAATATTATAGTACT
                         *************  ****************  ****** ** *  *  *

DC8E8                    C----
IGKV4-1*01_Homo+sapiens  CCTCC
                         *
```

J-gene (30/36; 83.3 % sequence identity):

```
DC8E8                              --GGACGTTCGGTGGAGGCACCAAGCTGGACATCAAAC
IGKJ1*01_Homo+sapiens_J-REGION GTGGACGTTCGGCCAAGGGACCAAGGTGGAAATCAAAC
                                 **********   *** ****** **** *******
```

FIGURE 5

V-gene (219/294; 74.5% sequence identity):

```
DC8E8_heavy_V             CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGGACTTC
IGHV1-69*10_Homo+sapiens  CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTC
                          ********  **  *********  ***** **  ********** * **

DC8E8_heavy_V             AGTGAAGATGCCCTGTAAGGCTTCTGGATACATATTCACTGACTATGTCA
IGHV1-69*10_Homo+sapiens  AGTGAAGGTCTCCTGCAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
                          ******* *  **** ************  **  ****    *****  *

DC8E8_heavy_V             TAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAG
IGHV1-69*10_Homo+sapiens  TCAGCTGGGTGCGACAGGCCCCTGGACAAGGGCTTGAGTGGATGGGAGGG
                          * *********   ***    ******* ** ********** **** *

DC8E8_heavy_V             ATTTTTCCTAGAAGTGGTAGTACTTACTACAATGAGAAGTTCAAGGGCAA
IGHV1-69*10_Homo+sapiens  ATCATCCCTATCCTTGGTATAGCAAACTACGCACAGAAGTTCCAGGGCAG
                          **  * ****    *****   *  *****    ******** ******

DC8E8_heavy_V             GGCCACACTGACTGCAGACAAATCCTCCAACACAGCCTACATGCAGCTCA
IGHV1-69*10_Homo+sapiens  AGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGA
                          * ***  * ** ** ********* * * ************* **** *

DC8E8_heavy_V             GCAGCGTGACATCTGAGGACTCTGCGGTCTATTTCTGTGCAAGA--
IGHV1-69*10_Homo+sapiens  GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGAGAGA
                          ***** *** ********** * ** ** **** ****** ***
```

D-gene (9/14; 64.3 % sequence identity):

```
DC8E8                -------GATTACTACGGTAC-----------------------------------
IGHD7-27*01_Homo+sapiens CTGAGCTGAGAACCACTGTGCTAACTGGGGACACAGTGATTGGCAGCTCT
                           **  ** ** ** *

DC8E8                -
IGHD7-27*01_Homo+sapiens A
```

J-gene (35/53; 66.0 % sequence identity):

```
DC8E8                TTCATTTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCT
IGHJ3*01_Homo+sapiens ---TGATGCTTTTTGATGTCTGGGGCCAAGGGACAATGGTCACCGTCTCTT
                        **** * **   ****** ***** **    **********  *

DC8E8                CAG
IGHJ3*01_Homo+sapiens CAG
                     ***
```

FIGURE 6A

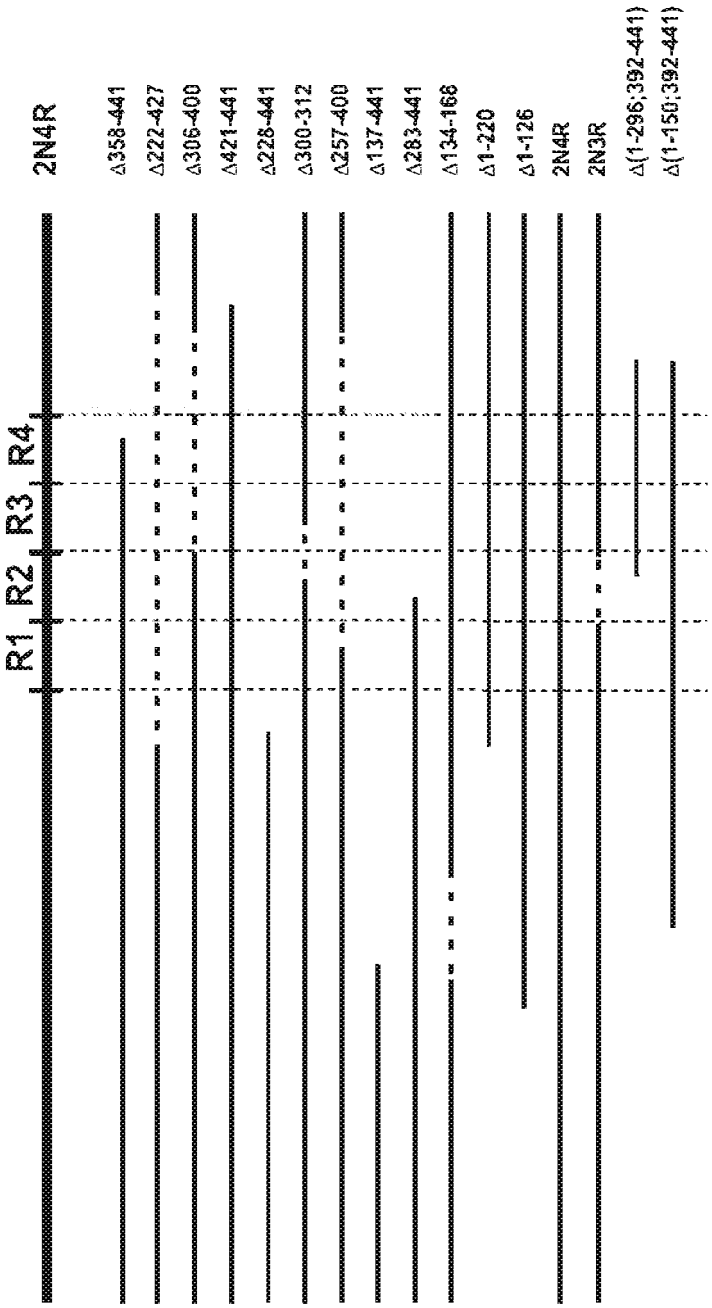

R1
R2
R3
R4
2N4R
Δ358-441
Δ222-427
Δ306-400
Δ421-441
Δ228-441
Δ300-312
Δ257-400
Δ137-441
Δ283-441
Δ134-168
Δ1-220
Δ1-126
2N4R
2N3R
Δ(1-296;392-441)
Δ(1-150;392-441)

FIGURE 6B

Δ358-441

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSVQIVY KPVDLSKVTS KCGSLGNIHH KPGGGQVEVK SEKLDFKDRV QSKIGSL
```

Δ222-427

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT RLADEVSASL AKQGL
```

Δ306-400

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSGDTSP RHLSNVSSTG SIDMVDSPQL ATLADEVSAS LAKQGL
```

Δ421-441

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSVQIVY KPVDLSKVTS KCGSLGNIHH KPGGGQVEVK SEKLDFKDRV QSKIGSLDNI
361 THVPGGGNKK IETHKLTFRE NAKAKTDHGA EIVYKSPVVS GDTSPRHLSN VSSTGSIDMV
```

Δ228-441

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVA
```

Δ300-312

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 DLSKVTSKCG SLGNIHHKPG GGQVEVKSEK LDFKDRVQSK IGSLDNITHV PGGGNKKIET
361 HKLTFRENAK AKTDHGAEIV YKSPVVSGDT SPRHLSNVSS TGSIDMVDSP QLATLADEVS
421 ASLAKQGL
```

Δ257-400

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVGDTS PRHLSNVSST GSIDMVDSPQ LATLADEVSA SLAKQGL
```

Δ137-441

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTG
```

Δ283-441

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KL
```

Δ134-168

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDTRIPAKT PPAPKTPPSS GEPPKSGDRS GYSSPGSPGT PGSRSRTPSL
181 PTPPTREPKK VAVVRTPPKS PSSAKSRLQT APVPMPDLKN VKSKIGSTEN LKHQPGGGKV
241 QIINKKLDLS NVQSKCGSKD NIKHVPGGGS VQIVYKPVDL SKVTSKCGSL GNIHHKPGGG
301 QVEVKSEKLD FKDRVQSKIG SLDNITHVPG GGNKKIETHK LTFRENAKAK TDHGAEIVYK
361 SPVVSGDTSP RHLSNVSSTG SIDMVDSPQL ATLADEVSAS LAKQGL
```

Δ1-220

```
1   MREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVKSK IGSTENLKHQ PGGGKVQIIN
61  KKLDLSNVQS KCGSKDNIKH VPGGGSVQIV YKPVDLSKVT SKCGSLGNIH HKPGGGQVEV
121 KSEKLDFKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG AEIVYKSPVV
181 SGDTSPRHLS NVSSTGSIDM VDSPQLATLA DEVSASLAKQ GL
```

Δ1-126

```
1   MVSKSKDGTG SDDKKAKGAD GKTKIATPRG AAPPGQKGQA NATRIPAKTP PAPKTPPSSG
61  EPPKSGDRSG YSSPGSPGTP GSRSRTPSLP TPPTREPKKV AVVRTPPKSP SSAKSRLQTA
121 PVPMPDLKNV KSKIGSTENL KHQPGGGKVQ IINKKLDLSN VQSKCGSKDN IKHVPGGGSV
181 QIVYKPVDLS KVTSKCGSLG NIHHKPGGGQ VEVKSEKLDF KDRVQSKIGS LDNITHVPGG
241 GNKKIETHKL TFRENAKAKT DHGAEIVYKS PVVSGDTSPR HLSNVSSTGS IDMVDSPQLA
301 TLADEVSASL AKQGL
```

4R2N

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSVQIVY KPVDLSKVTS KCGSLGNIHH KPGGGQVEVK SEKLDFKDRV QSKIGSLDNI
361 THVPGGGNKK IETHKLTFRE NAKAKTDHGA EIVYKSPVVS GDTSPRHLSN VSSTGSIDMV
421 DSPQLATLAD EVSASLAKQG L
```

3R2N

```
1   MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
61  SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEEAGIGD TPSLEDEAAG
121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRS RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
241 SRLQTAPVPM PDLKNVKSKI GSTENLKHQP GGGKVQIVYK PVDLSKVTSK CGSLGNIHHK
301 PGGGQVEVKS EKLDFKDRVQ SKIGSLDNIT HVPGGGNKKI ETHKLTFREN AKAKTDHGAE
361 IVYKSPVVSG DTSPRHLSNV SSTGSIDMVD SPQLATLADE VSASLAKQGL
```

Δ(1-296;392-441)

```
1   MIKHVPGGGS VQIVYKPVDL SKVTSKCGSL GNIHHKPGGG QVEVKSEKLD FKDRVQSKIG
61  SLDNITHVPG GGNKKIETHK LTFRENAKAK TDHGAE
```

Δ(1-150;392-441)

```
1   MIATPRGAAP PGQKGQANAT RIPAKTPPAP KTPPSSGEPP KSGDRSGYSS PGSPGTPGSR
61  SRTPSLPTPP TREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVKSK IGSTENLKHQ
121 PGGGKVQIIN KKLDLSNVQS KCGSKDNIKH VPGGGSVQIV YKPVDLSKVT SKCGSLGNIH
181 HKPGGGQVEV KSEKLDFKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG
241 AE
```

Note

The Methionine (M) at the position 1 in the tau deletion constructs Δ1-220, Δ(1-296;392-441) and Δ(1-150;392-441) is not part of the natural human tau sequence. It was added in order to provide a start codon for the bacterial translational machinery.

FIGURE 6C

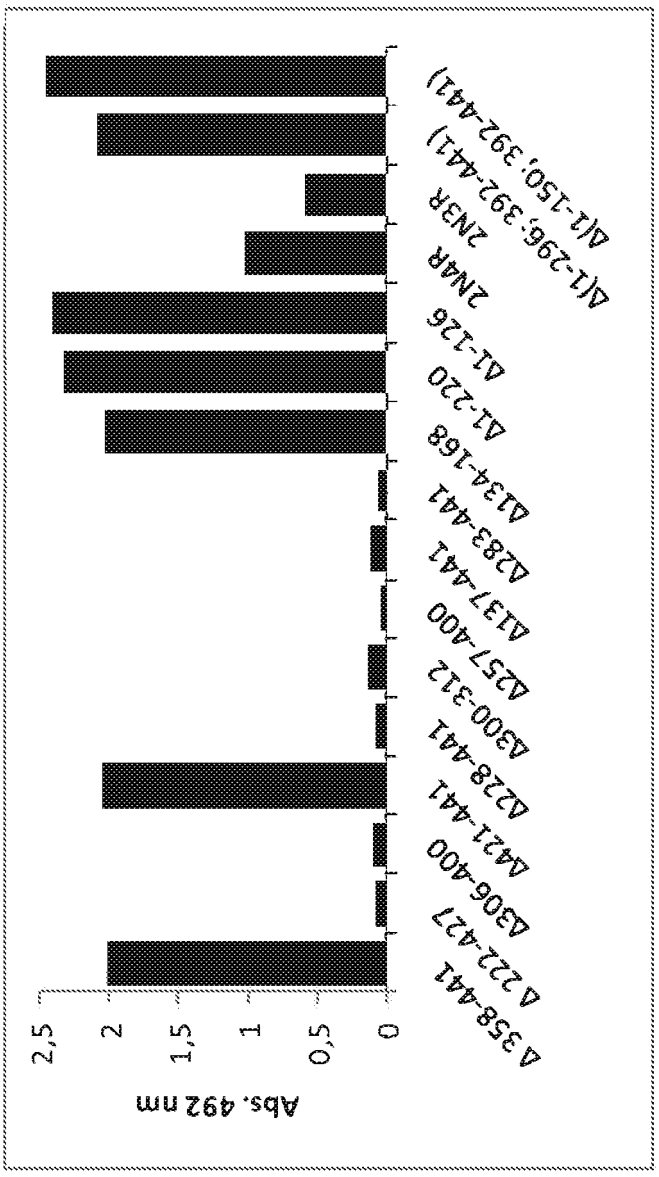

Abs. 492 nm
2,5
2
1,5
1
0,5
0
A358-441
A 222-427
A306-400
A421-441
A228-441
A300-312
A257-400
A137-441
A283-441
A134-168
A1-220
A1-126
2N4R
2N3R
Δ(1-296; 392-441)
Δ(1-150; 392-441)

FIGURE 7A

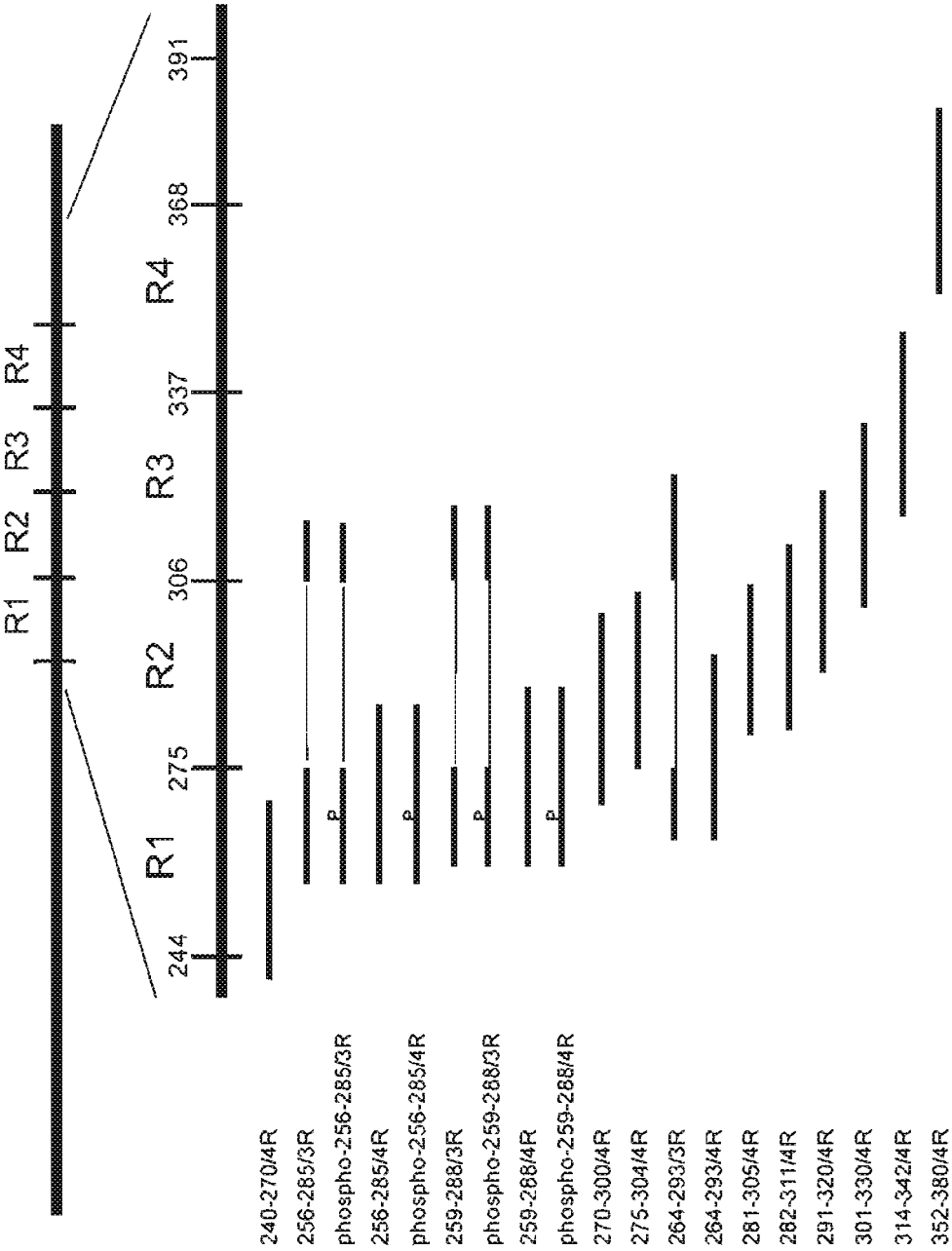

R1
R2
R3
R4
244
275
306
337
368
391
240-270/4R
256-285/3R
phospho-256-285/3R
256-285/4R
phospho-256-285/4R
259-288/3R
phospho-259-288/3R
259-288/4R
phospho-259-288/4R
270-300/4R
275-304/4R
264-293/3R
264-293/4R
281-305/4R
282-311/4R
291-320/4R
301-330/4R
314-342/4R
352-380/4R
P

FIGURE 7B

Synthetic peptide	Sequence
240-270/4R	KSRLQTAPVPMPDLKNVKSKIGSTENLKHQP
256-285/3R	VKSKIGSTENLKHQPGGGKVQIVYKPVDLS
phospho 256-285/3R (pSer262)	VKSKIGpSTENLKHQPGGGKVQIVYKPVDLS
256-285/4R	VKSKIGSTENLKHQPGGGKVQIINKKLDLS
phospho 256-285/4R (pSer262)	VKSKIGpSTENLKHQPGGGKVQIINKKLDLS
259-288/3R	KIGSTENLKHQPGGGKVQIVYKPVDLSKVT
phospho 259-288/3R (pSer262)	KIGpSTENLKHQPGGGKVQIVYKPVDLSKVT
259-288/4R	KIGSTENLKHQPGGGKVQIINKKLDLSNVQ
phospho 259-288/4R (pSer262)	KIGpSTENLKHQPGGGKVQIINKKLDLSNVQ
270-300/4R	PGGGKVQIINKKLDLSNVQSKCGSKDNIKHV
275-304/4R	VQIINKKLDLSNVQSKCGSKDNIKHVPGGG
264-293/3R	ENLKHQPGGGKVQIVYKPVDLSKVTSKCGS
264-293/4R	ENLKHQPGGGKVQIINKKLDLSNVQSKCGS
281-305/4R	KLDLSNVQSKCGSKDNIKHVPGGGS
282-311/4R	LDLSNVQSKCGSKDNIKHVPGGGSVQIVYK
291-320/4R	CGSKDNIKHVPGGGSVQIVYKPVDLSKVTS
301-330/4R	PGGGSVQIVYKPVDLSKVTSKCGSLGNIHH
314-342/4R	DLSKVTSKCGSLGNIHHKPGGGQVEVKSE
352-380/4R	SKIGSLDNITHVPGGGNKKIETHKLTFREN

FIGURE 7C

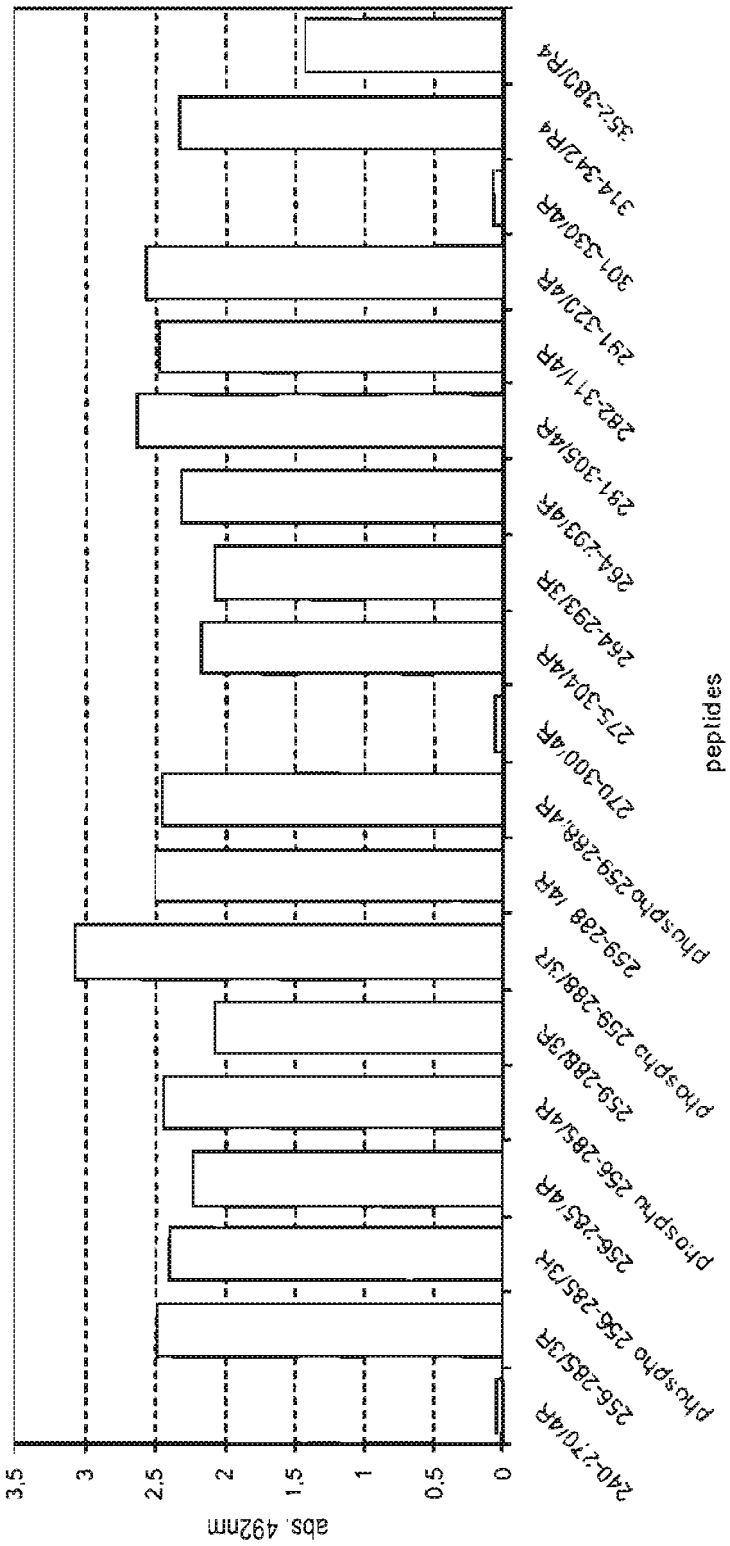

abs. 492nm
3.5
3
2.5
2
1.5
1
0.5
0
peptides
240-270/4R
256-285/3R
phosphn 256-285/3R
256-285/4R
phosphn 256-285/4R
259-288/3R
phosphn 259-288/3R
259-288 4R
phosphn 259-288.4R
270-300/4R
275-304/4R
264-293/3R
264-293/4R
291-305/4R
282-311/4R
291-320/4R
301-330/4R
314-342/R4
352-380/R4

FIGURE 7D

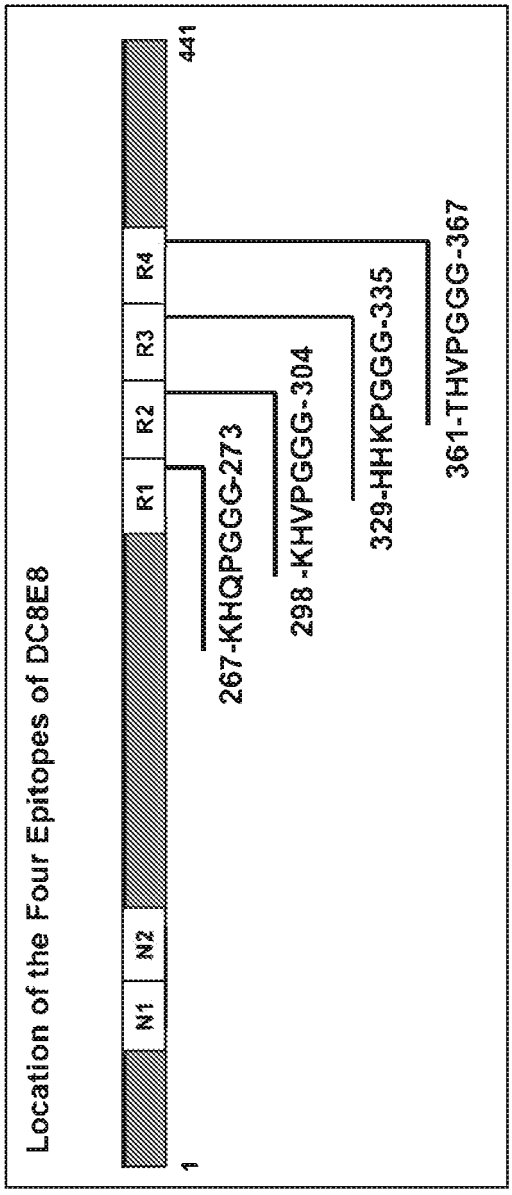

Location of the Four Epitopes of DC8E8
N1
N2
R1
R2
R3
R4
1
441
267-KHQPGGG-273
298-KHVPGGG-304
329-HHKPGGG-335
361-THVPGGG-367

FIGURE 8A

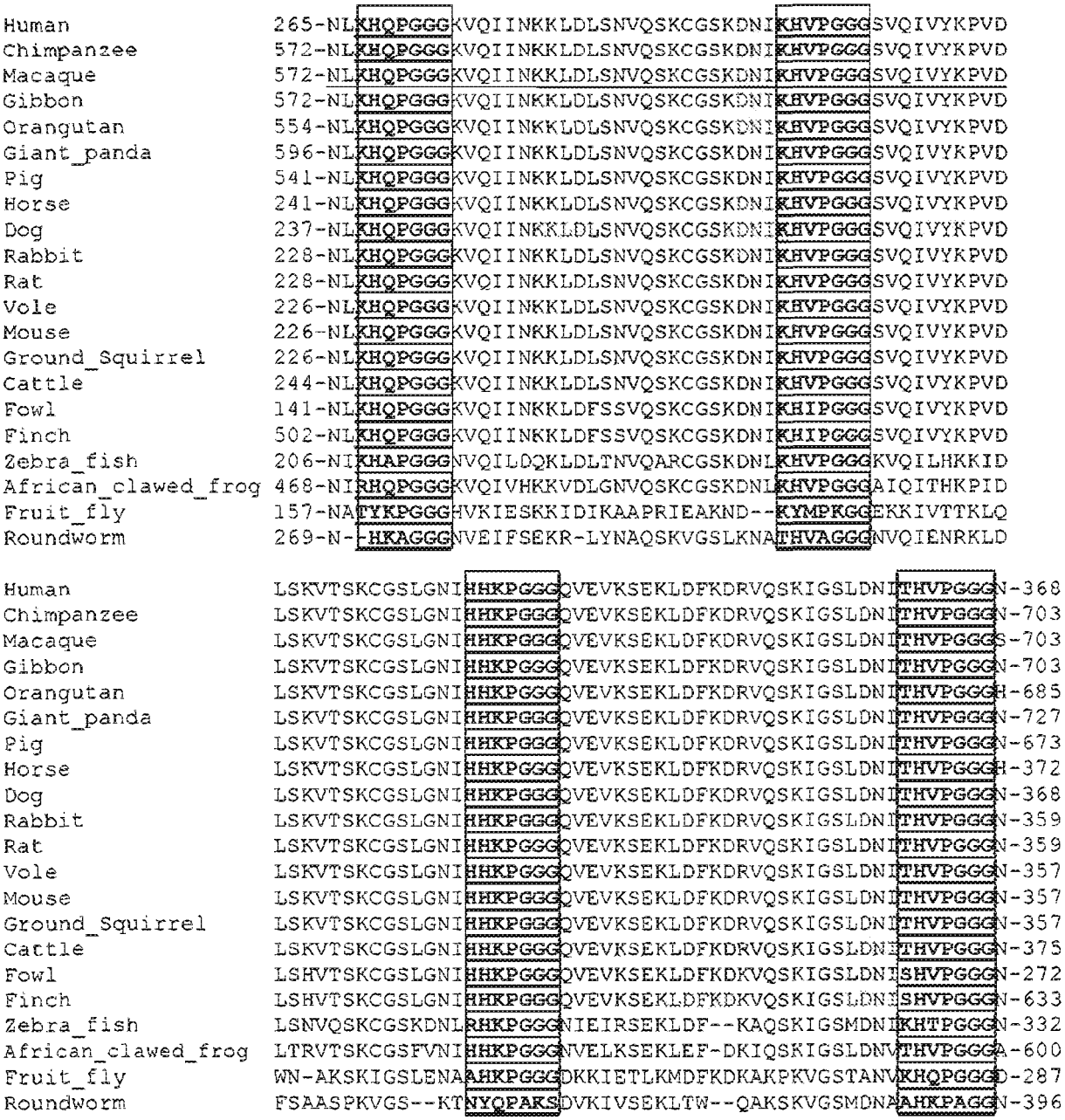

Human 265-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Chimpanzee 572-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Macaque 572-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Gibbon 572-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Orangutan 554-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Giant_panda 596-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Pig 541-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Horse 241-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Dog 237-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Rabbit 228-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Rat 228-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Vole 226-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Mouse 226-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Ground_Squirrel 226-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Cattle 244-NLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVD
Fowl 141-NLKHQPGGGKVQIINKKLDFSSVQSKCGSKDNIKHIPGGGSVQIVYKPVD
Finch 502-NLKHQPGGGKVQIINKKLDFSSVQSKCGSKDNIKHIPGGGSVQIVYKPVD
Zebra_fish 206-NIKHAPGGGNVQILDQKLDLTNVQARCGSKDNLKHVPGGGKVQILHKKID
African_clawed_frog 468-NIRHQPGGGKVQIVHKKVDLGNVQSKCGSKDNLKHVPGGGAIQITHKPID
Fruit_fly 157-NATYKPGGGHVKIESKKIDIKAAPRIEAKND--KYMPKGGEKKIVTTKLQ
Roundworm 269-N--HKAGGGNVEIFSEKR-LYNAQSKVGSLKNATHVAGGGNVQIENRKLD
Human LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-368
Chimpanzee LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-703
Macaque LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGS-703
Gibbon LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-703
Orangutan LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGH-685
Giant_panda LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-727
Pig LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-673
Horse LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGH-372
Dog LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-368
Rabbit LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-359
Rat LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-359
Vole LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-357
Mouse LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-357
Ground_Squirrel LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-357
Cattle LSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN-375
Fowl LSHVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDKVQSKIGSLDNISHVPGGGN-272
Finch LSHVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDKVQSKIGSLDNISHVPGGGN-633
Zebra_fish LSNVQSKCGSKDNLRHKPGGGNIEIRSEKLDF--KAQSKIGSMDNIKHTPGGGN-332
African_clawed_frog LTRVTSKCGSFVNIHHKPGGGNVELKSEKLEF-DKIQSKIGSLDNVTHVPGGGA-600
Fruit_fly WN-AKSKIGSLENAAHKPGGGDKKIETLKMDFKDKAKPKVGSTANVKHQPGGGD-287
Roundworm FSAASPKVGS--KTNYQPAKSDVKIVSEKLTW--QAKSKVGSMDNAAHKPAGGN-396

FIGURE 8B

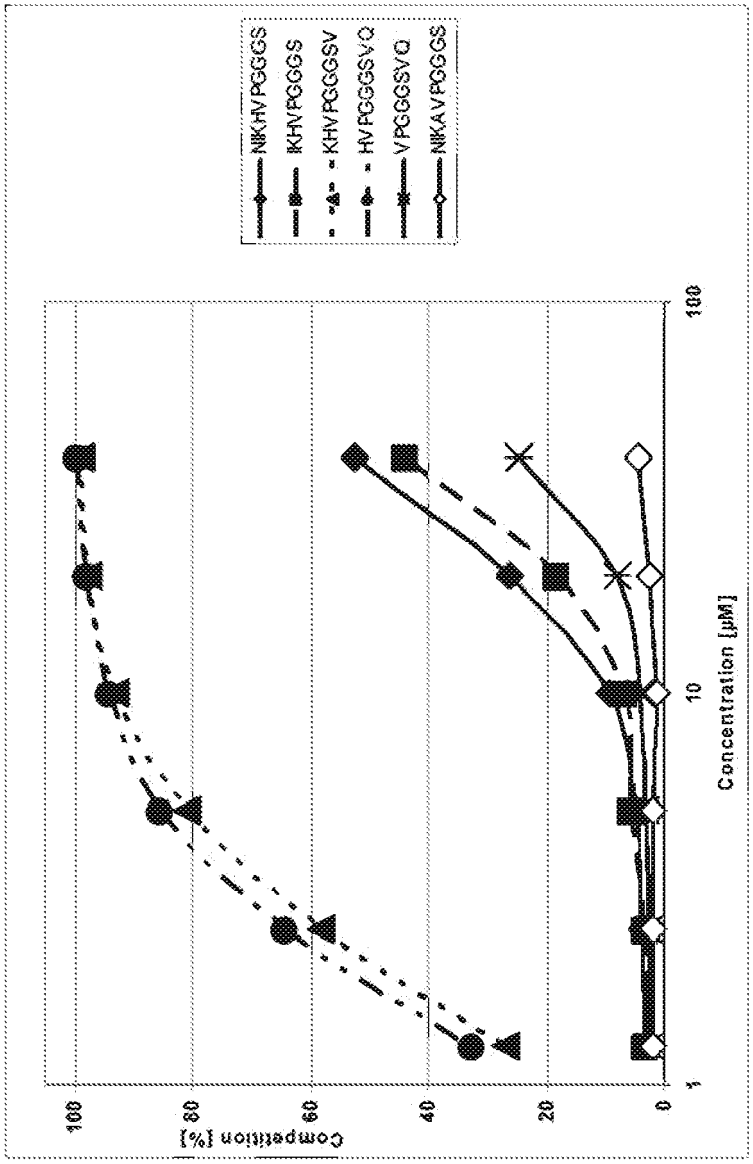

NIKHVPGGGS
IKHVPGGGS
KHVPGGGSV
HVPGGGSVQ
VPGGGSVQ
NIKAVPGGGS
Competition [%]
100
80
60
40
20
0
1
10
100
Concentration [µM]

FIGURE 8C

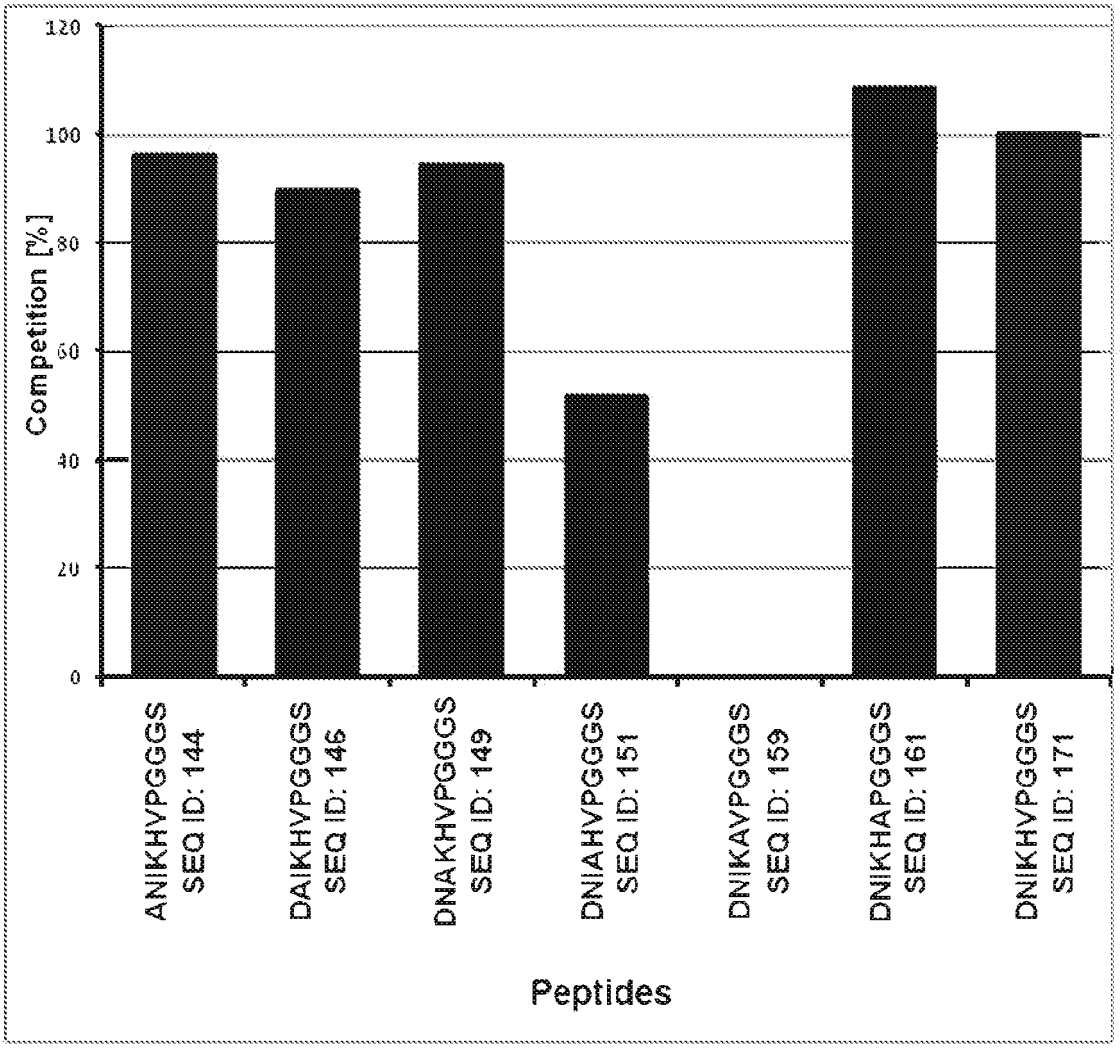
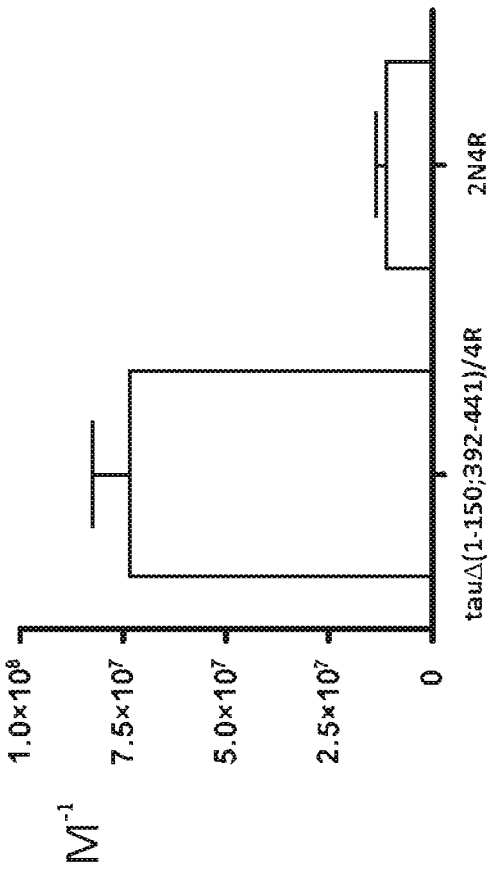
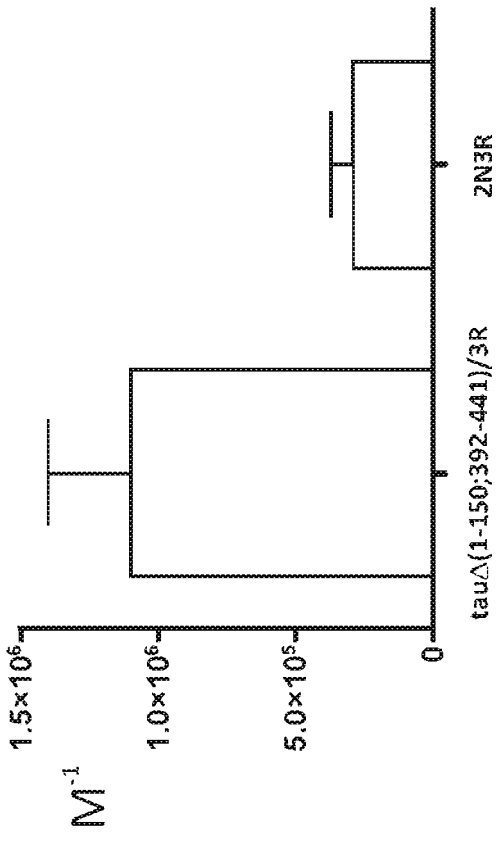

120
100
80
60
40
20
0
Competition [%]
ANIKHVPGGGS SEQ ID: 144
DAIKHVPGGGS SEQ ID: 146
DNAKHVPGGGS SEQ ID: 149
DNIAHVPGGGS SEQ ID: 151
DNIKAVPGGGS SEQ ID: 159
DNIKHAPGGGS SEQ ID: 161
DNIKHVPGGGS SEQ ID: 171
Peptides

FIGURE 9A



	K_A
tauΔ(1-150;392-441)/4R	7.3±0.9 x10^7 M^-1
2N4R	1.1±0.3 x10^7 M^-1

FIGURE 9B



	K_A
tauΔ(1-150;392-441)/3R	1.1±0.3 x10^6 M^{-1}
2N3R	2.9±0.8 x10^5 M^{-1}

FIGURE 10A

	k_{ON} (s^{-1} M^{-1})	k_{OFF} (s^{-1})
tauΔ(1-150;392-441)/4R	2.6±0.5 x10^{6}	0.04±0.01
2N4R	4.6±1.4 x10^{5}	0.04±0.01

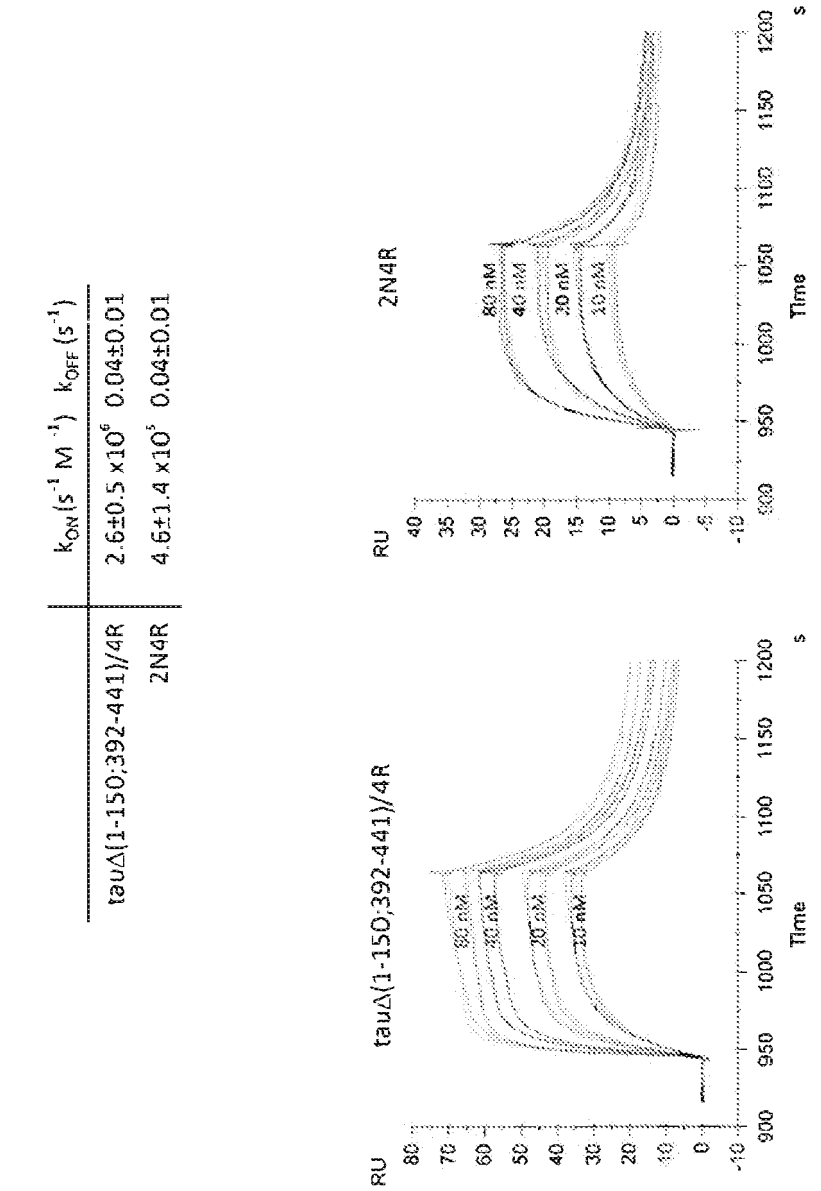


FIGURE 10B

	k_{ON} (s^{-1} M^{-1})	k_{Off} (s^{-1})
tauΔ(1-150;392-441)/3R	4.9±1.4 x10^5	0.5±0.1
2N3R	1.4±0.4 x10^5	0.5±0.1

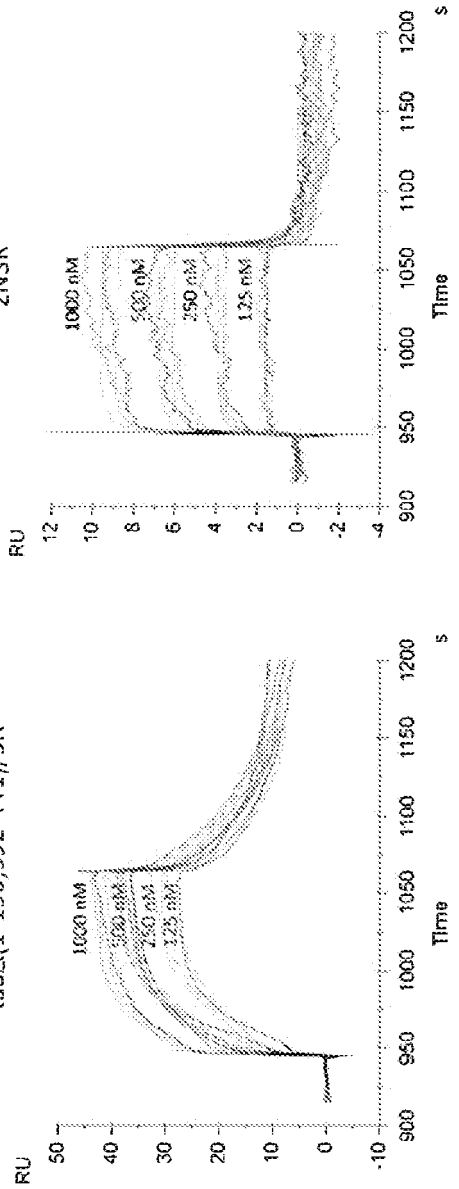


FIGURE 11

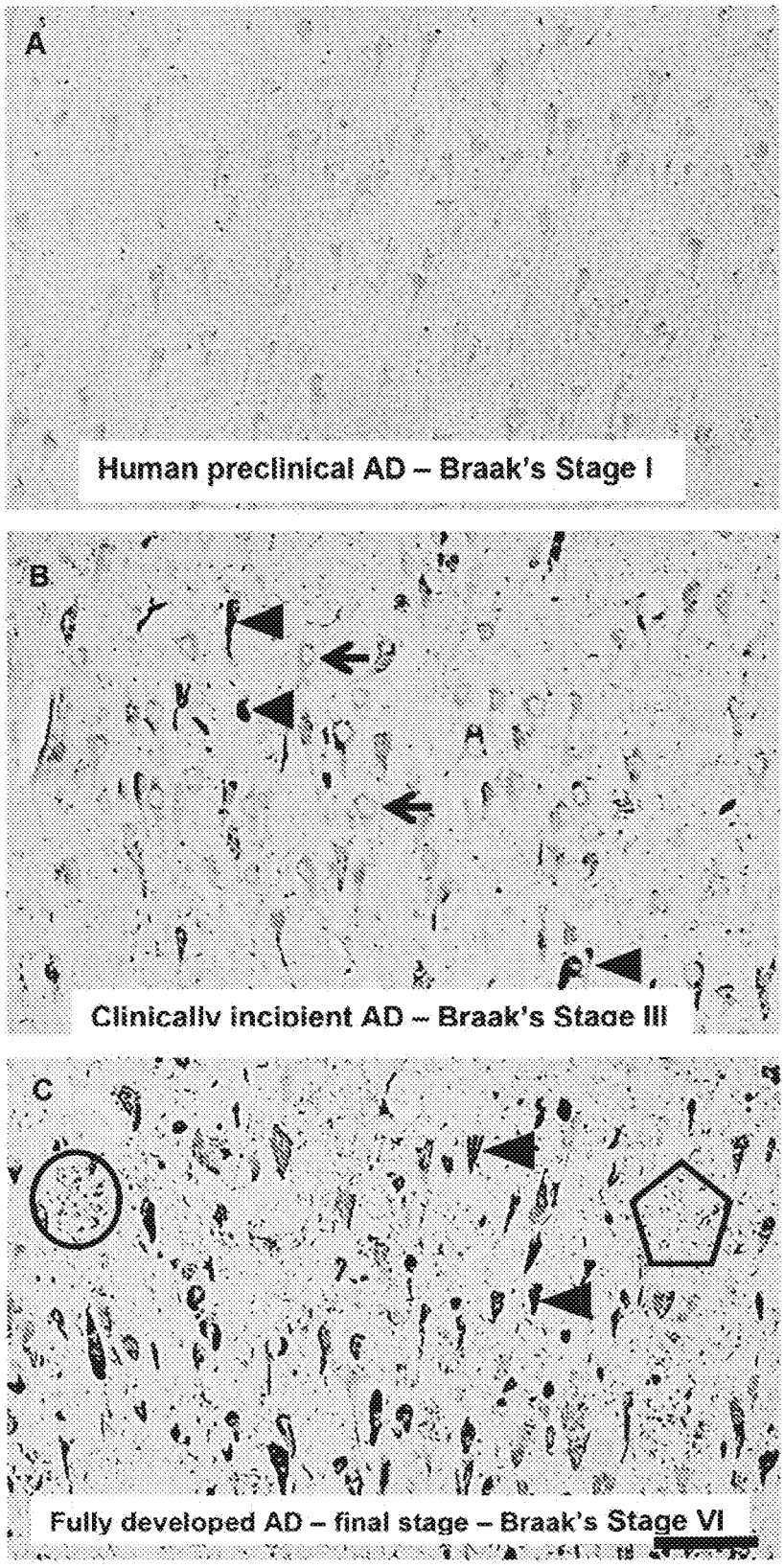

A
Human preclinical AD – Braak's Stage I
B
A
A'
Clinically incipient AD – Braak's Stage III
C
B
Fully developed AD – final stage – Braak's Stage VI

FIGURE 11D

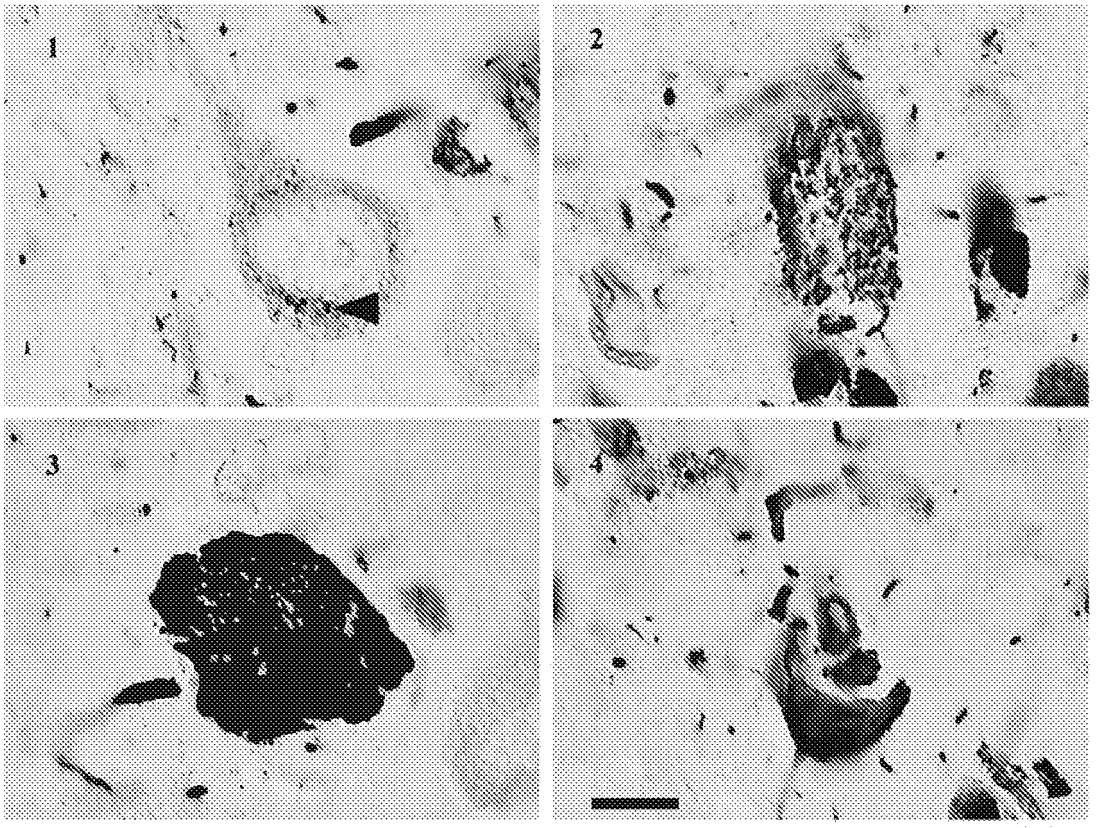


FIGURE 12A AND FIGURE 12B

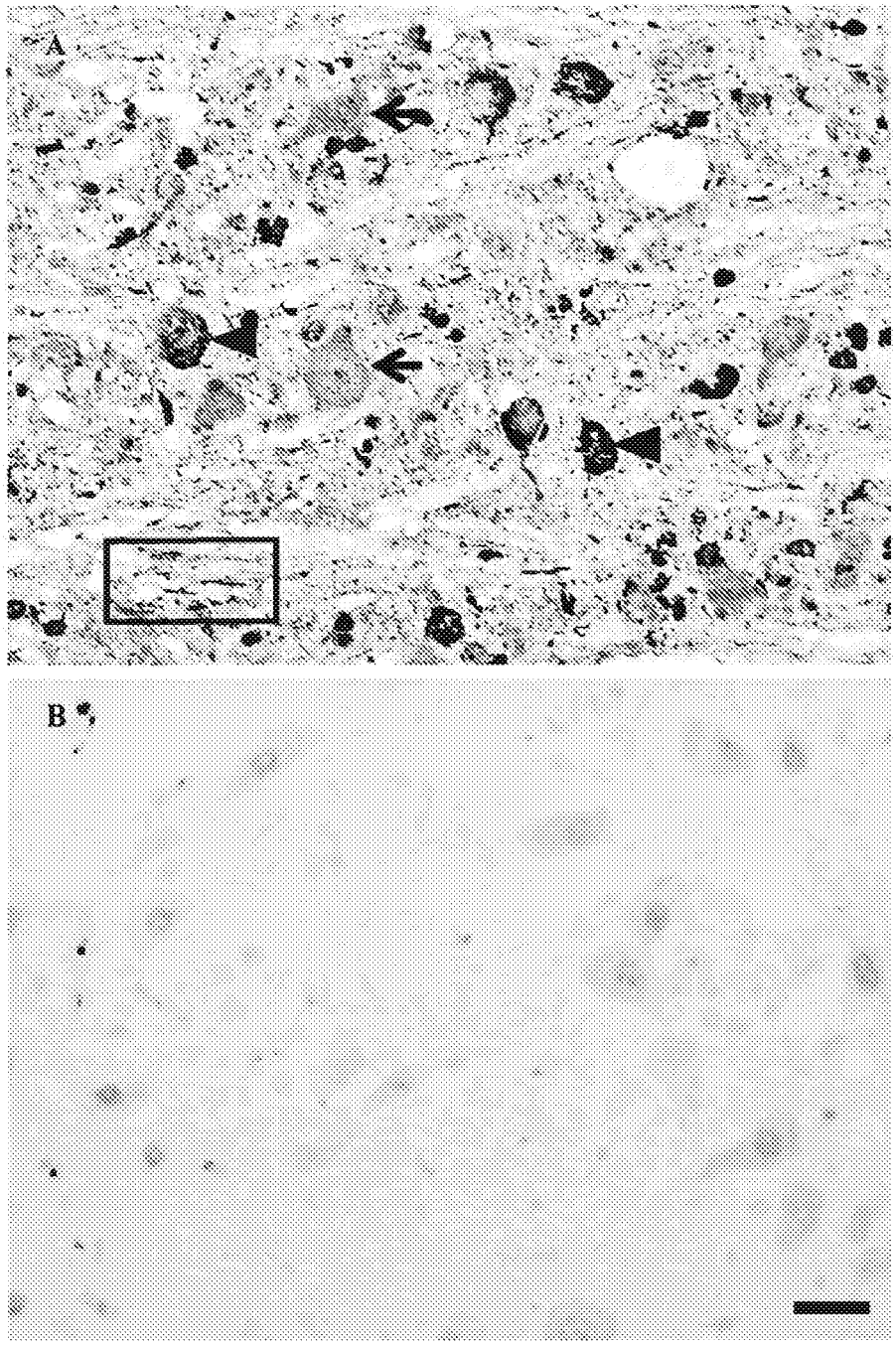


FIGURE 12C THROUGH FIGURE 12F

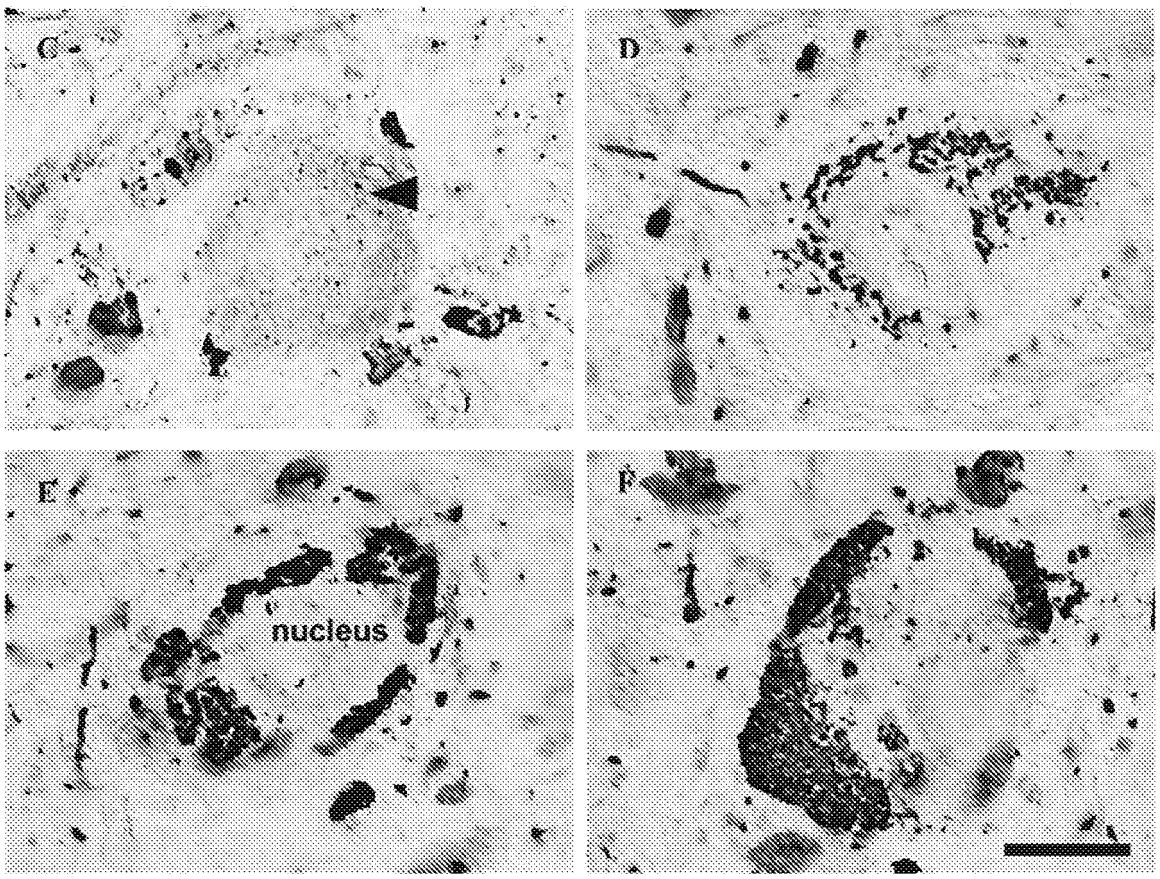


FIGURE 13

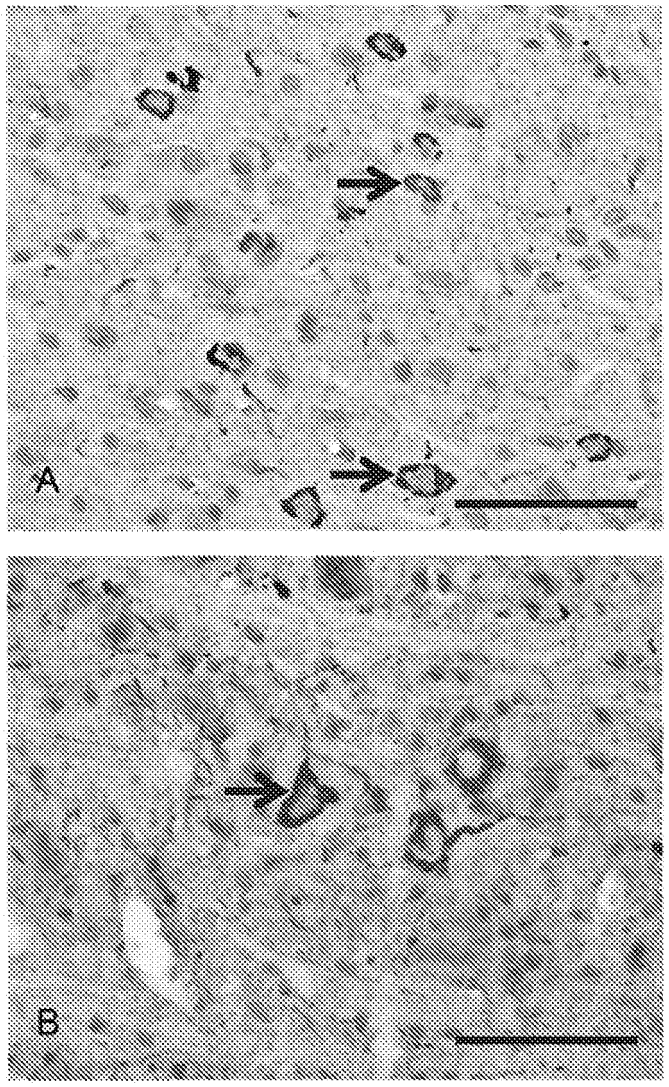


FIGURE 14A and 14B

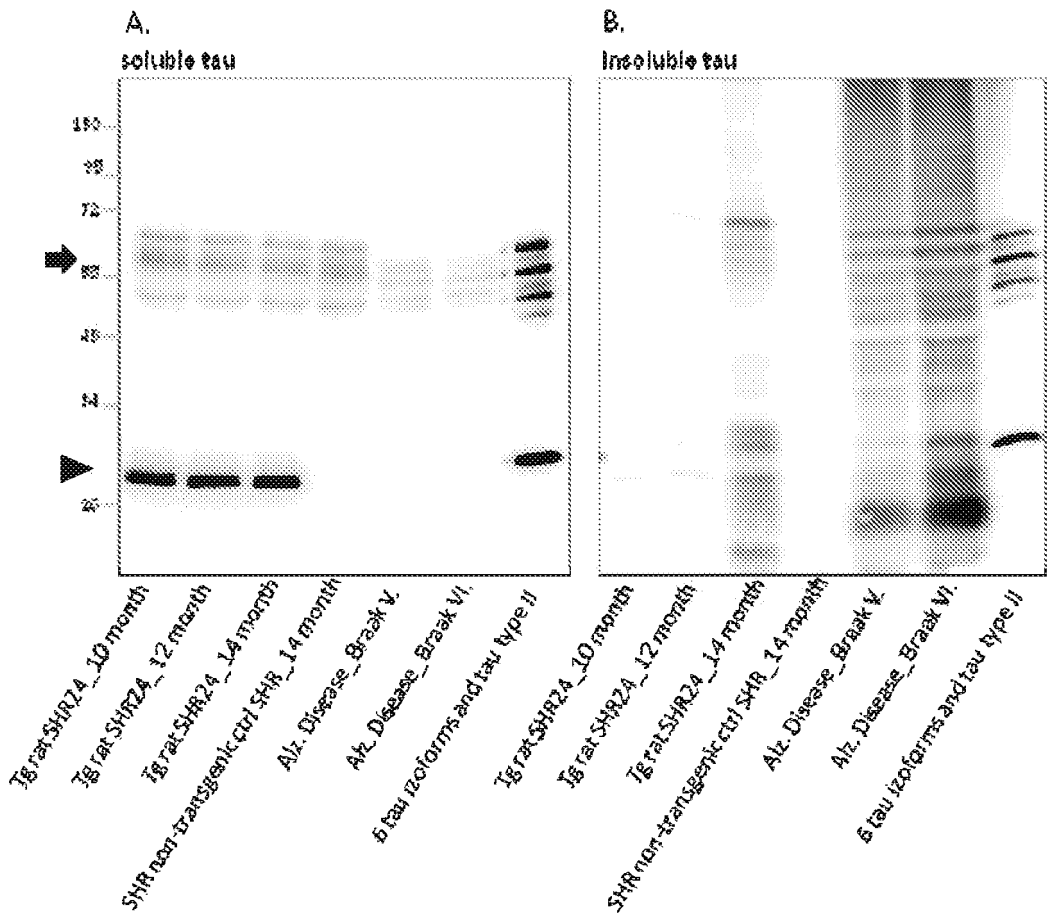


FIGURE 14C and 14D

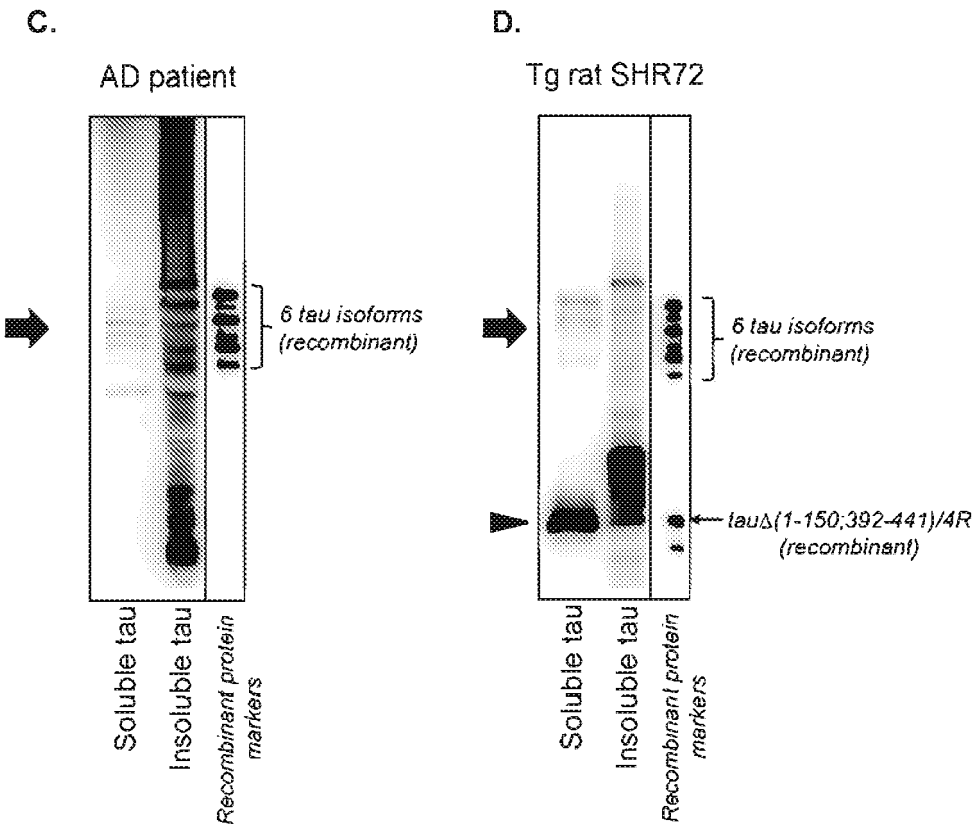


FIGURE 15A

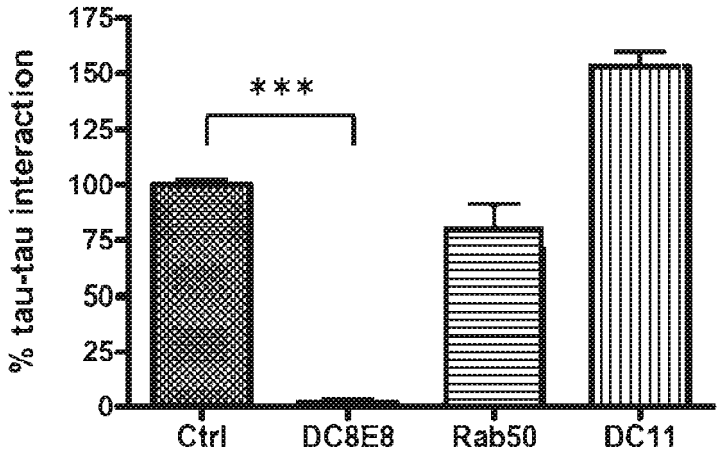


FIGURE 15B

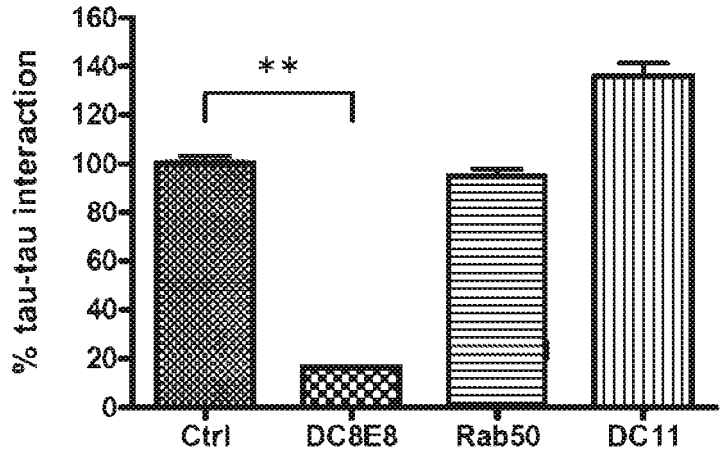


FIGURE 16

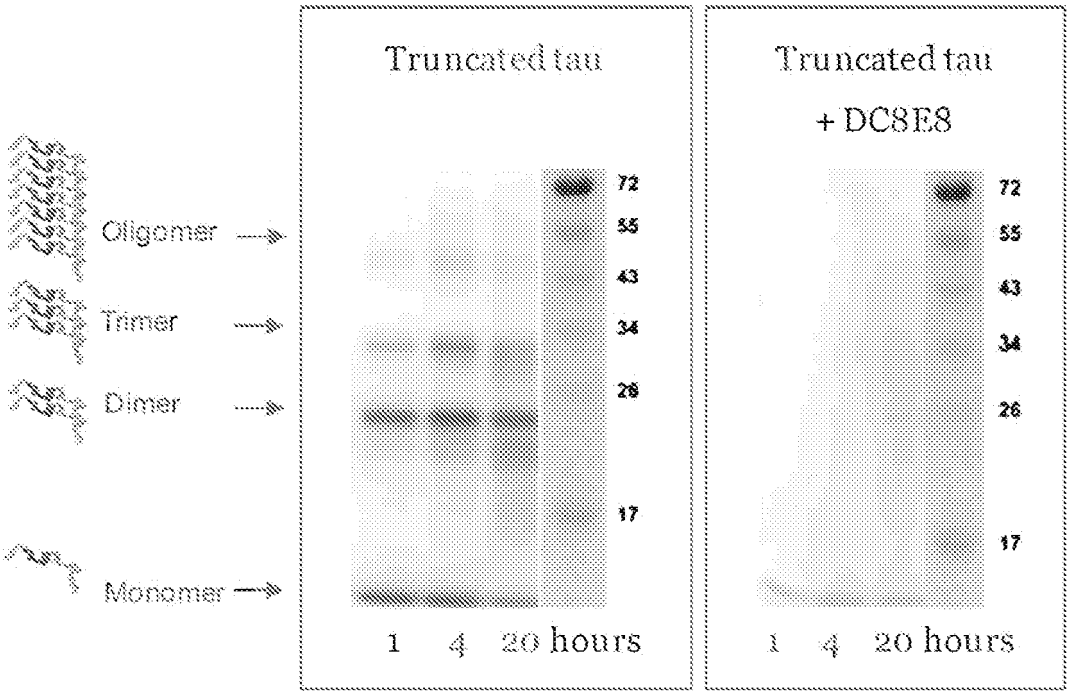

Oligomer
Trimer
Dimer
Monomer
Truncated tau
72
55
43
34
26
17
1 4 20 hours
Truncated tau
+ DC8E8
72
55
43
34
26
17
1 4 20 hours

FIGURE17A

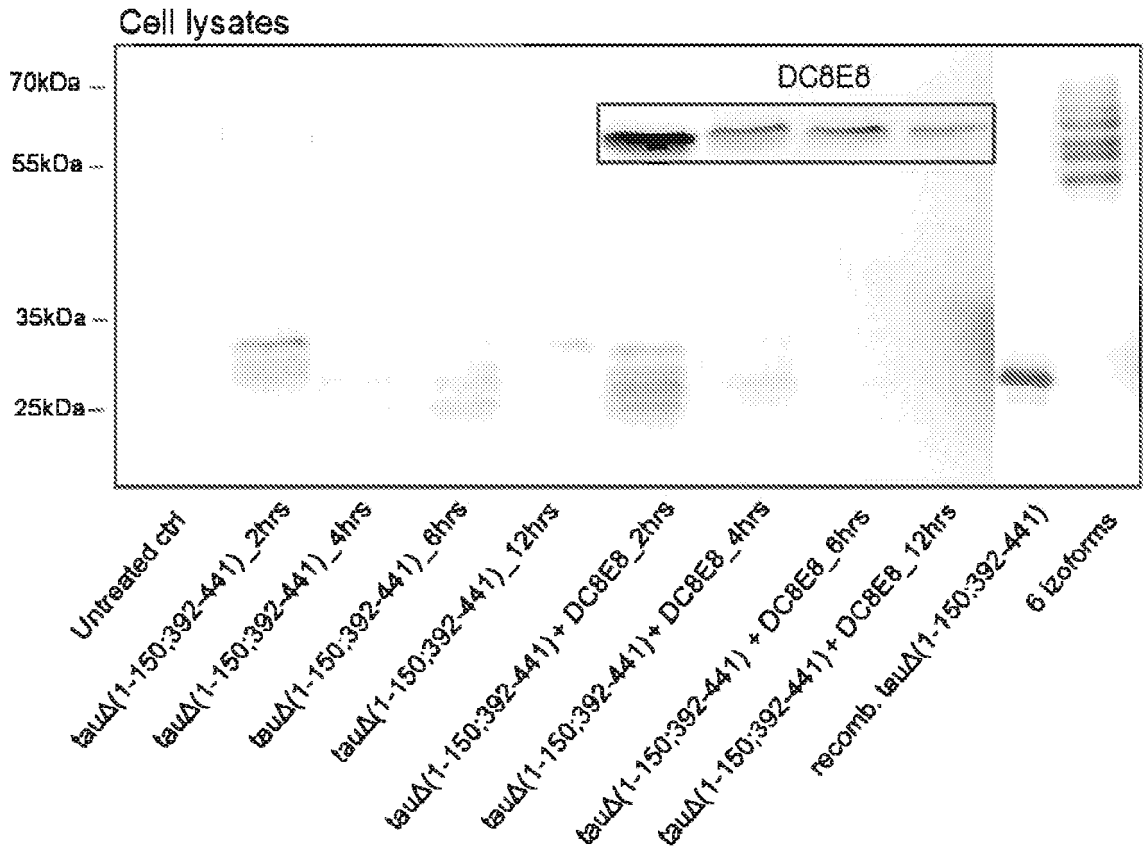

Cell lysates
70kDa
55kDa
35kDa
25kDa
DC8E8
Untreated ctrl
tauΔ(1-150;392-441)_2hrs
tauΔ(1-150;392-441)_4hrs
tauΔ(1-150;392-441)_6hrs
tauΔ(1-150;392-441)_12hrs
tauΔ(1-150;392-441)+ DC8E8_2hrs
tauΔ(1-150;392-441)+ DC8E8_4hrs
tauΔ(1-150;392-441) + DC8E8_6hrs
tauΔ(1-150;392-441)+ DC8E8_12hrs
recomb. tauΔ(1-150;392-441)
6 Izoforms

FIGURE 17B

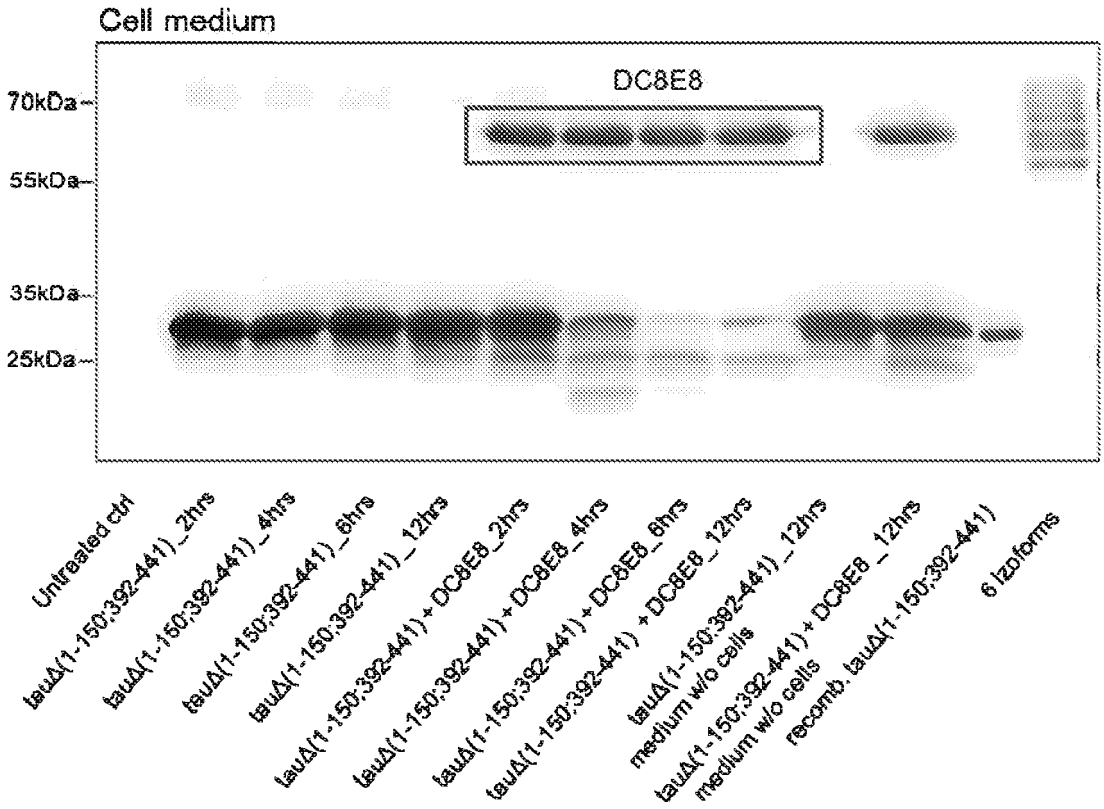

Cell medium
DC8E8
70kDa
55kDa
35kDa
25kDa
Untreated ctrl
tauΔ(1-150;392-441)_2hrs
tauΔ(1-150;392-441)_4hrs
tauΔ(1-150;392-441)_6hrs
tauΔ(1-150;392-441)_12hrs
tauΔ(1-150;392-441)+DC8E8_2hrs
tauΔ(1-150;392-441)+DC8E8_4hrs
tauΔ(1-150;392-441)+DC8E8_6hrs
tauΔ(1-150;392-441)+DC8E8_12hrs
tauΔ(1-150;392-441)_12hrs medium w/o cells
tauΔ(1-150;392-441)+DC8E8_12hrs medium w/o cells
recomb. tauΔ(1-150;392-441) 6 isoforms

FIGURE 18

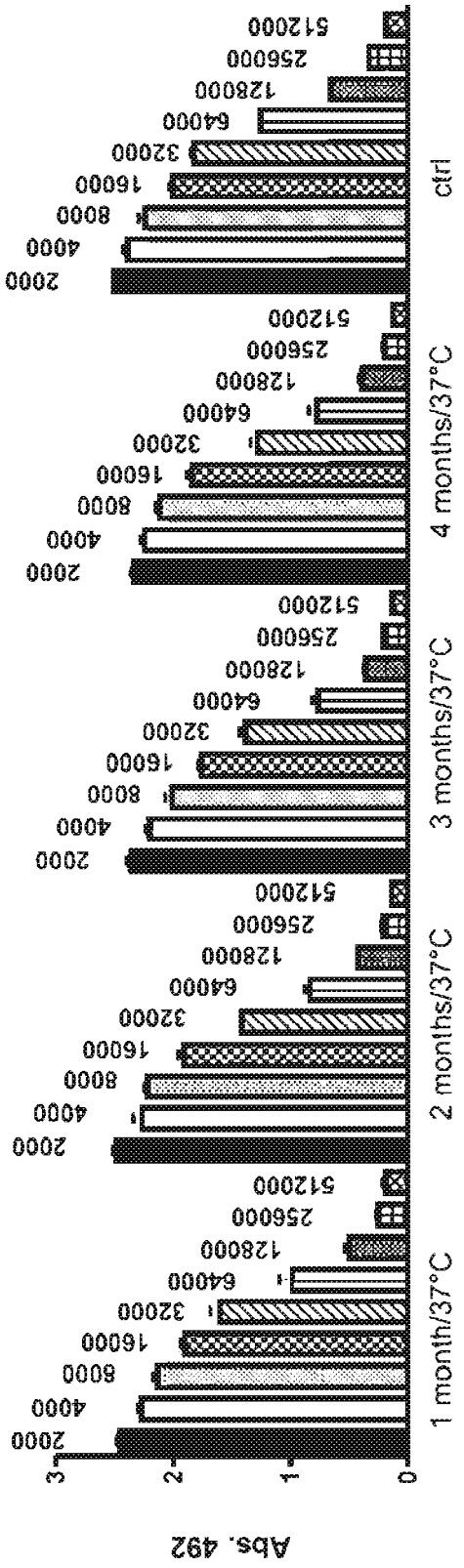

Abs. 492
0
1
2
3
1 month/37°C
2 months/37°C
3 months/37°C
4 months/37°C
ctrl
2000
4000
8000
16000
32000
64000
128000
256000
512000

FIGURE 19

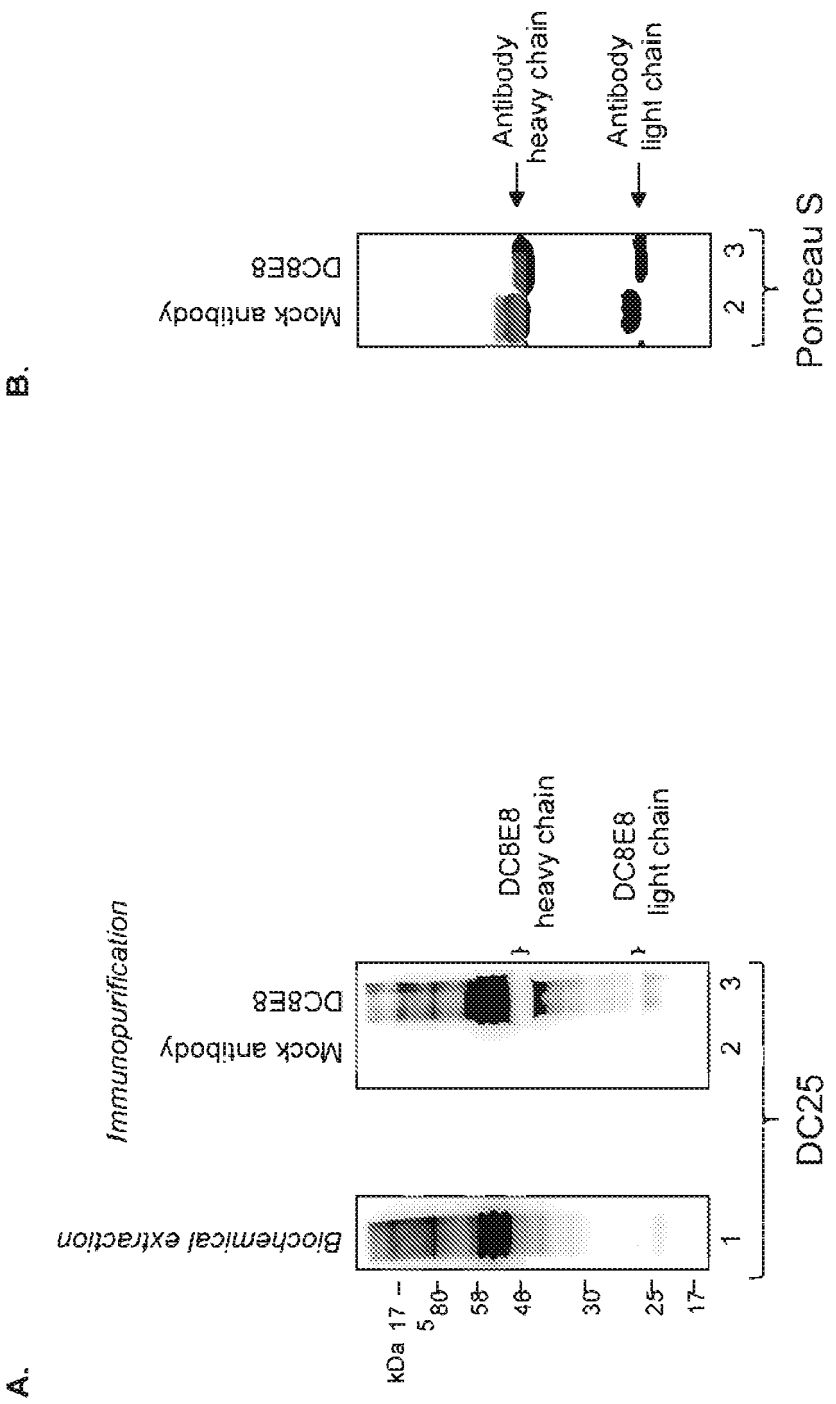
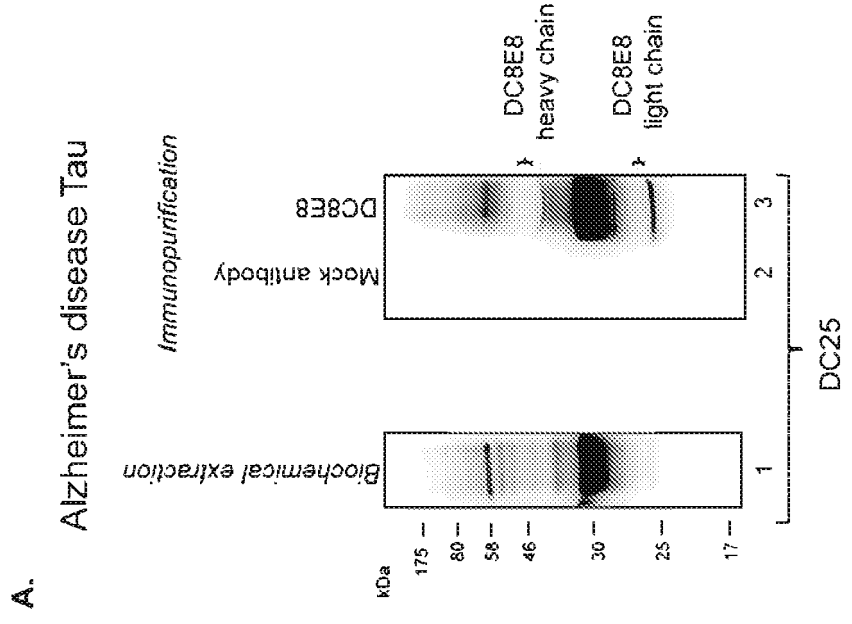

A.
Biochemical extraction
Immunopurification
Mock antibody
DC8E8
DC8E8 heavy chain
DC8E8 light chain
DC25
1
2
3
kDa
17
5
80
58
46
30
25
17
B.
Mock antibody
DC8E8
Antibody heavy chain
Antibody light chain
2
3
Ponceau S

FIGURE 20


A.
Alzheimer's disease Tau
Immunopurification
Biochemical extraction
Mock antibody
DC8E8
DC8E8 heavy chain
DC8E8 light chain
DC25
kDa
175
80
58
46
30
25
17
1
2
3

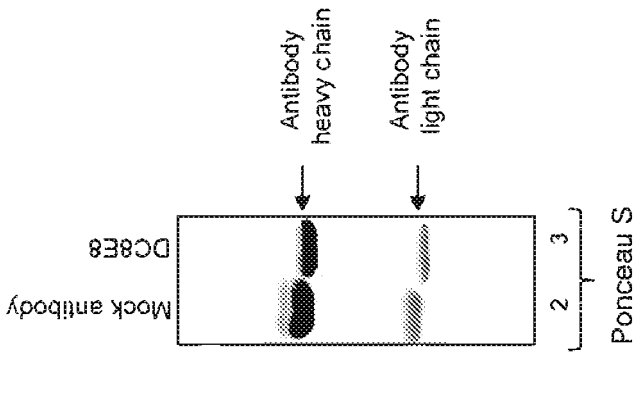

B.
Antibody heavy chain
Antibody light chain
Mock antibody
DC8E8
2
3
Ponceau S

FIGURE 21A

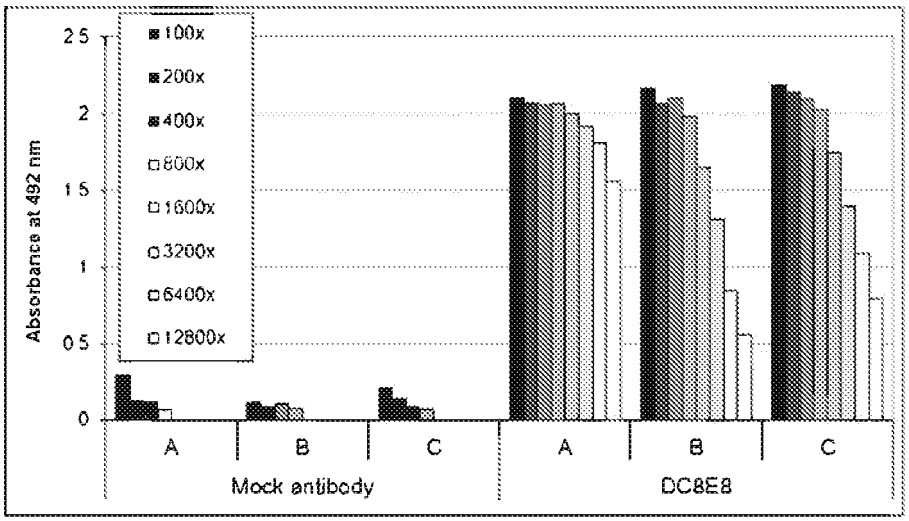


FIGURE 21B

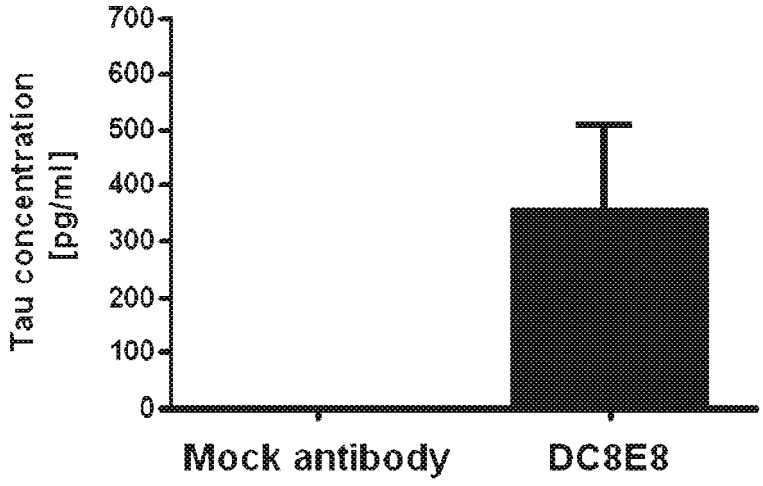


FIGURE 22A

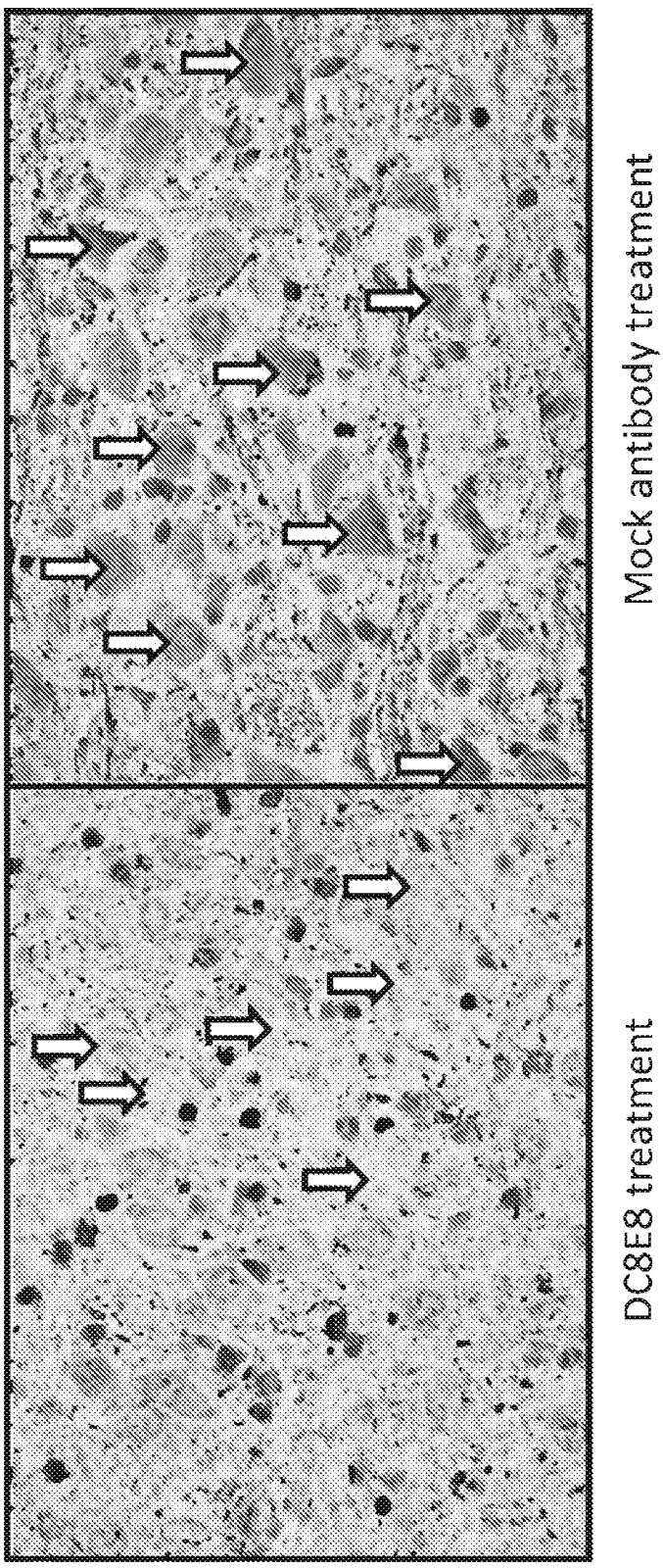


FIGURE 22B

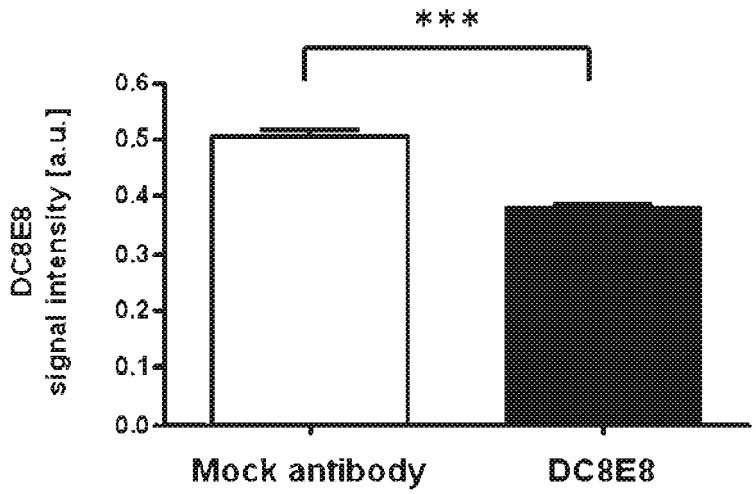

***
DC8E8
signal intensity [a.u.]
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Mock antibody
DC8E8

FIGURE 23

FIGURE 23A.

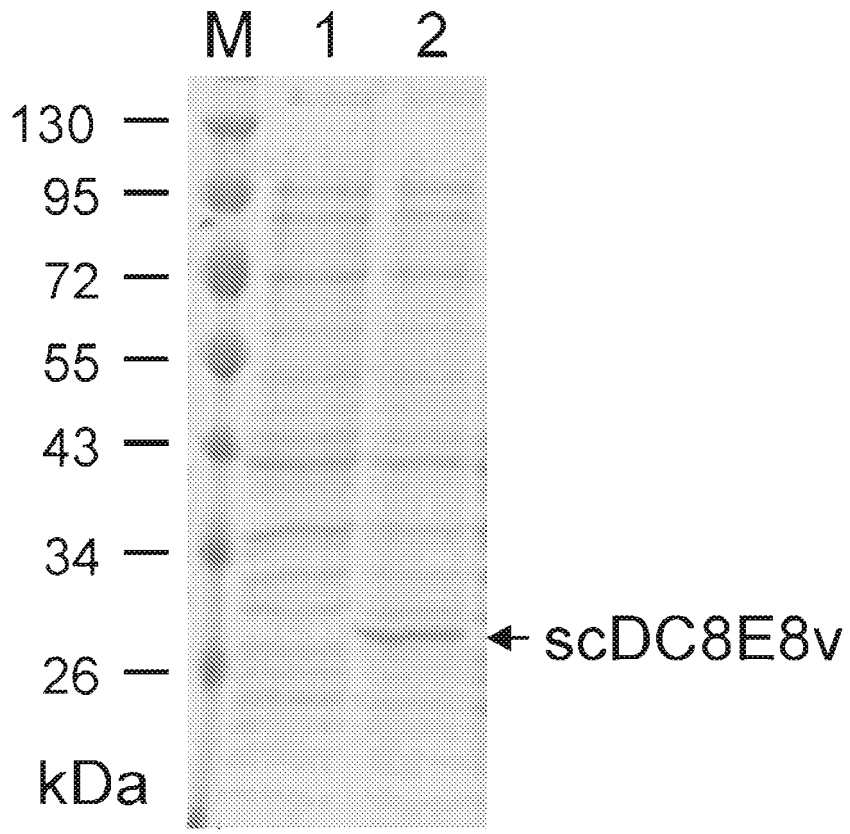


FIGURE 23B.

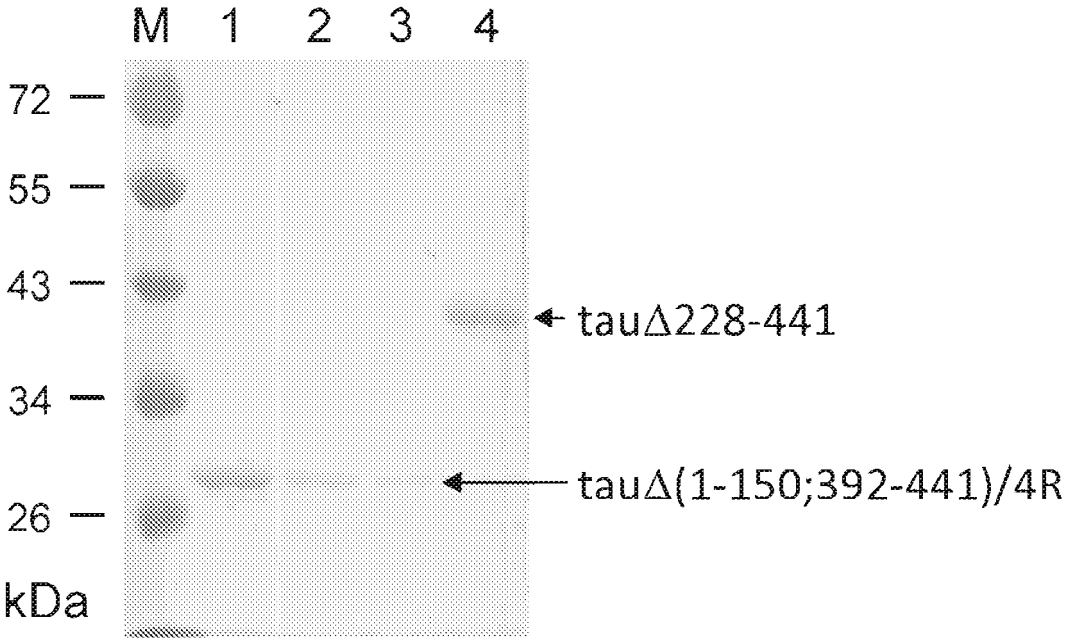


FIGURE 23C

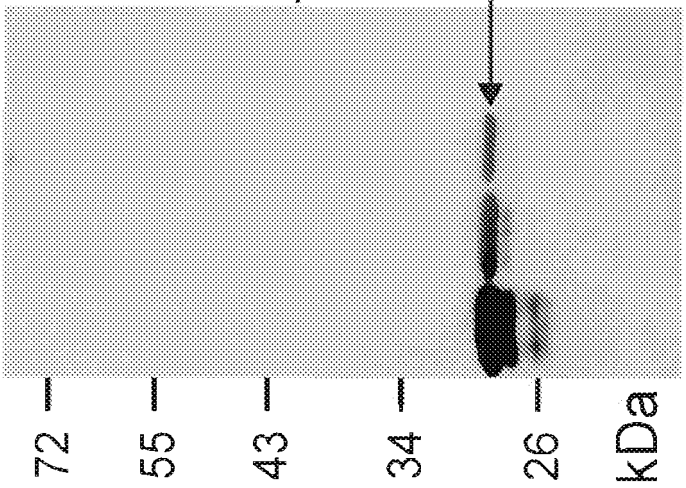


FIGURE 23D

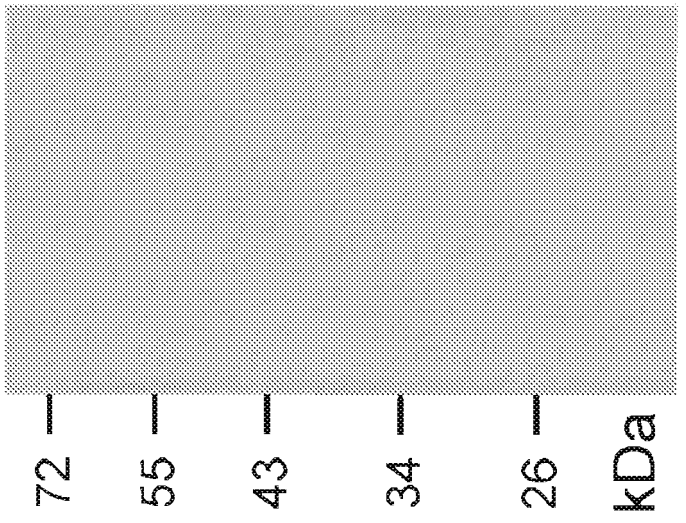


FIGURE 24A

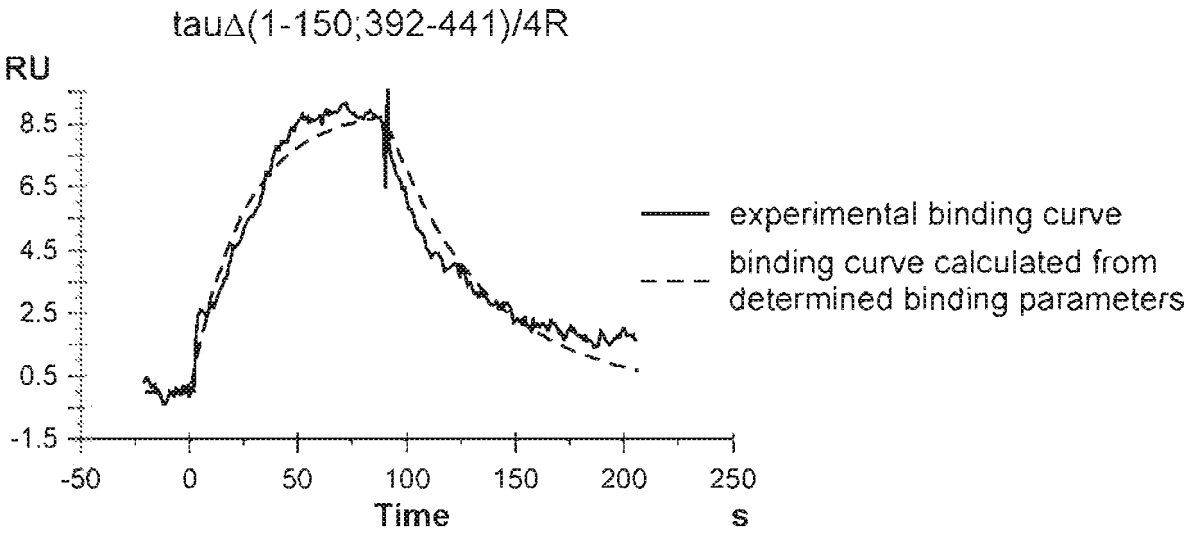


FIGURE 24B

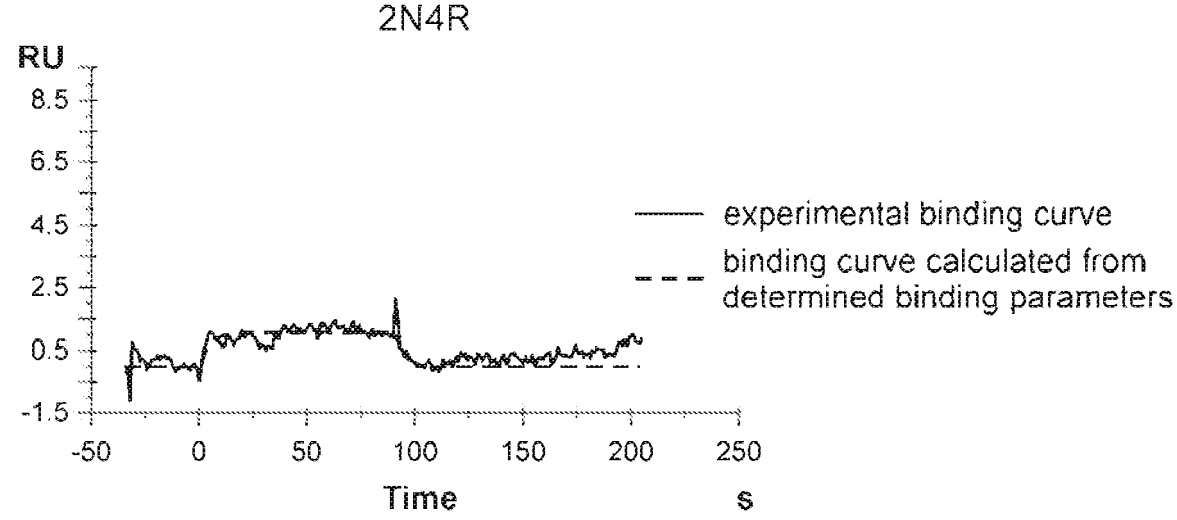


FIGURE 24C

	$k_{ON}(s^{-1} M^{-1})$	$k_{OFF}(s^{-1})$	$K_A(M^{-1})$
tauΔ(1-150;392-441)/4R	$1.8x10^5$	0.02	$8.1x10^6$
2N4R	$5.7x10^4$	0.2	$2.7x10^5$

FIGURE 25A

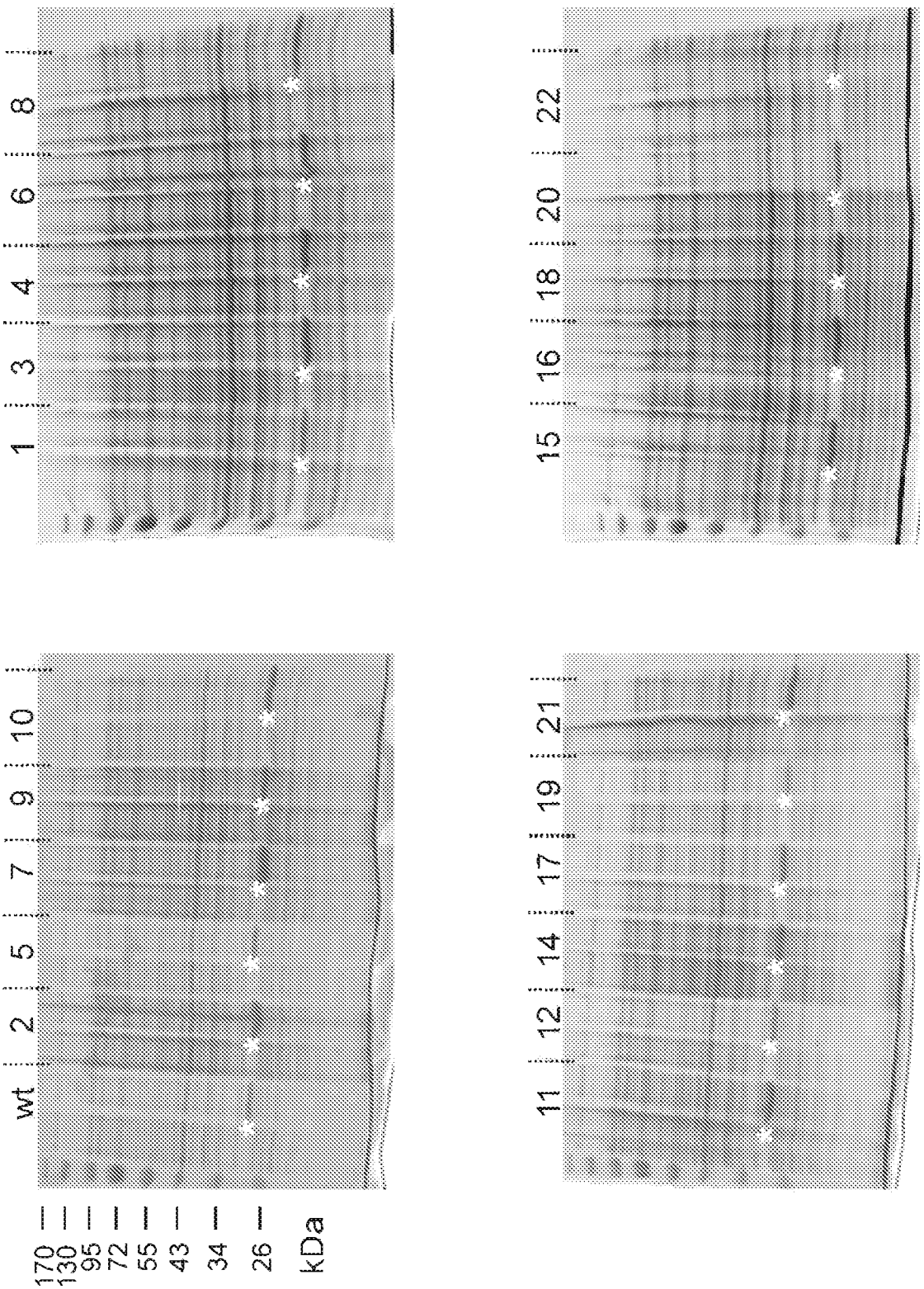

wt
2
5
7
9
10
1
3
4
6
8
11
12
14
17
19
21
15
16
18
20
22
170
130
95
72
55
43
34
26
kDa

FIGURE 25B

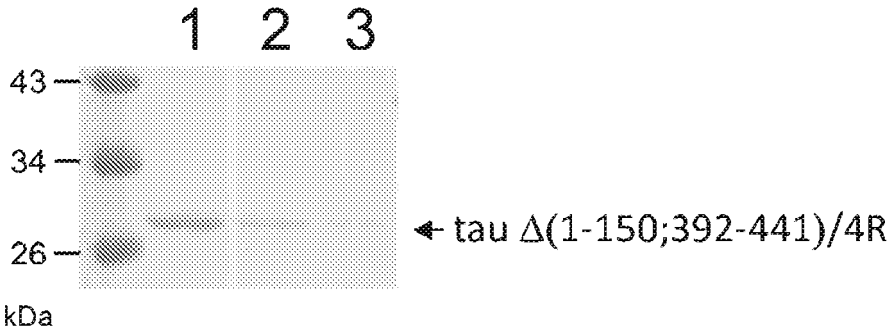


FIGURE 25C

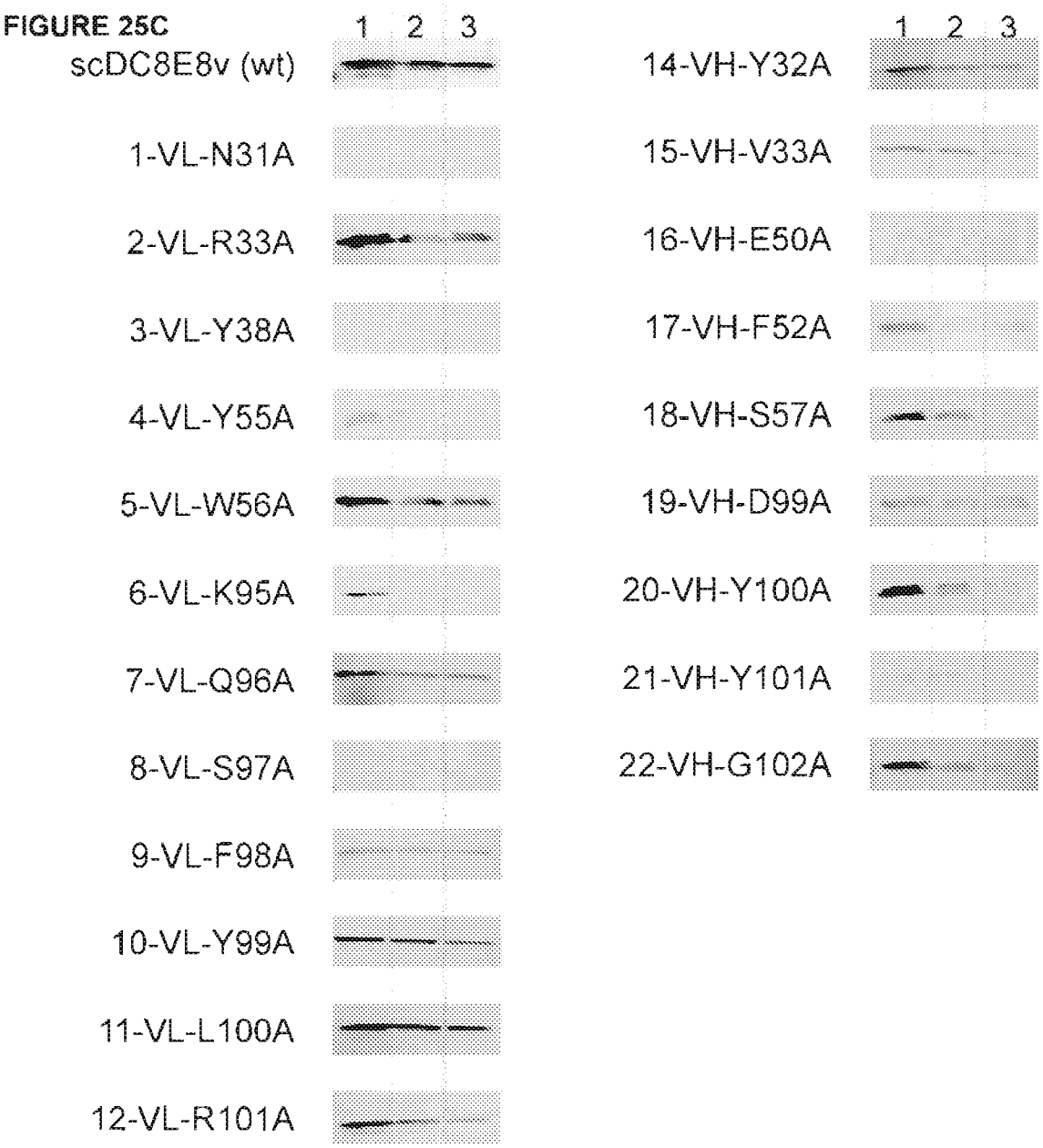


FIGURE26A

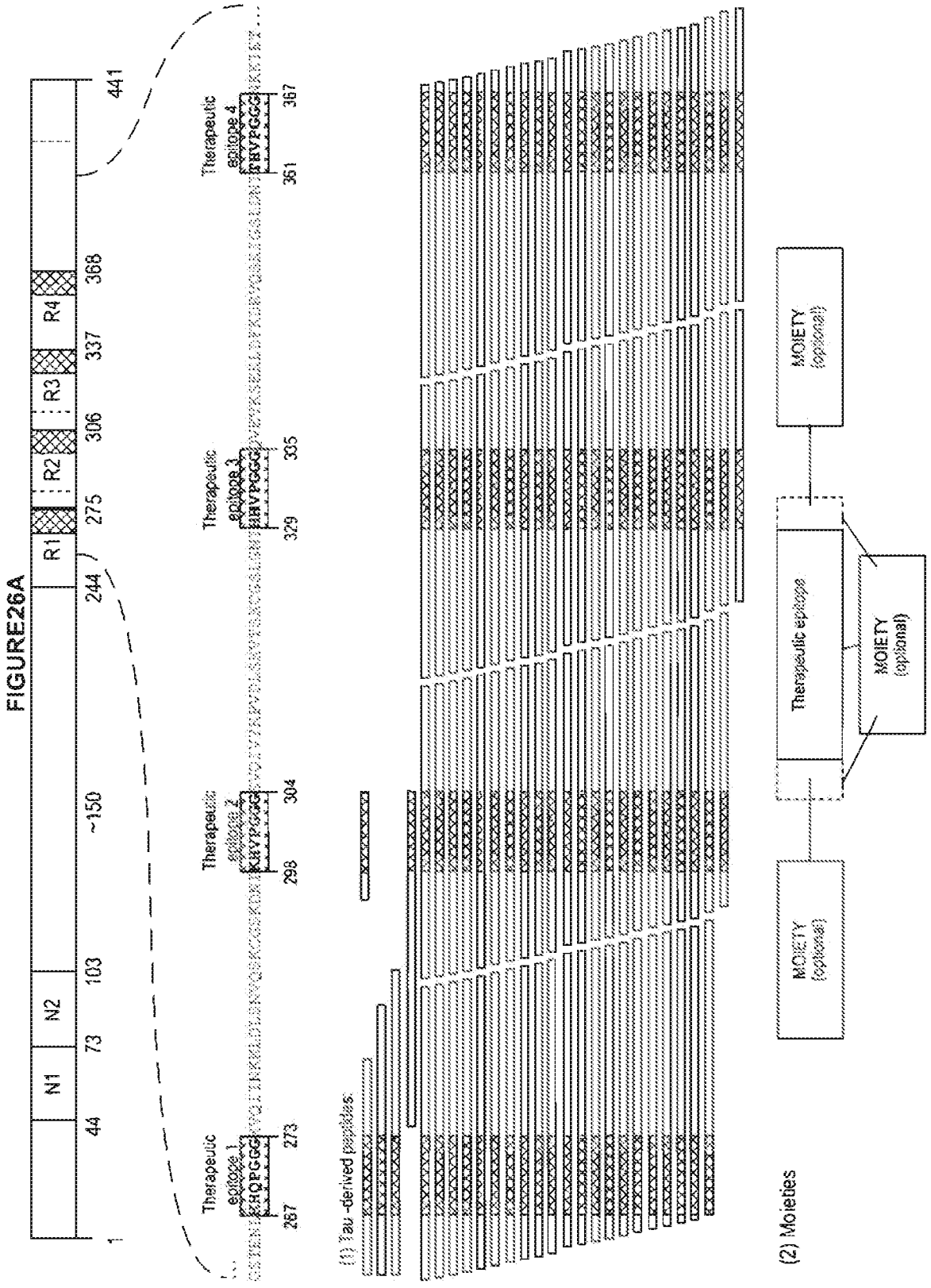

N1
N2
R1
R2
R3
R4
44
73
103
~150
244
275
306
337
368
441
Therapeutic epitope 1
EHQPGGG
267
273
Therapeutic epitope 2
EHVPGGG
298
304
Therapeutic epitope 3
EHVPGGG
329
335
Therapeutic epitope 4
EHVPGGG
361
367
(1) Tau -derived peptides
(2) Moieties
MOIETY (optional)
Therapeutic epitope
MOIETY (optional)
MOIETY (optional)

FIGURE 26B

SEQ ID NO	Immunogen	Reduction of insoluble tau (%) AD-relevant epitopes				
		347-353	pT217	pT231	pS202/pT205	pT181
SEQ ID NO: 1	Tau251-280	71	42	11	ND	58
SEQ ID NO: 2	Tau 256-285	41	72	64	80	74
SEQ ID NO: 2	Tau 256-285/pS262	46	73	85	82	82
SEQ ID NO: 3	Tau 259-288	40	30	63	61	74
SEQ ID NO: 4	Tau 275-304	63	92	95	95	87
SEQ ID NO:108	Tau 294-305	70	96	97	98	94
SEQ ID NO: 5	Tau 201-230/pT217	1	-11	33	-31	30
SEQ ID NO: 6	Tau 379-408/pS396/pS404	-87	-33	-44	19	-7
SEQ ID NO: 7	Tau 181-210/pS202/pT205	-6	-3	-11	-41	-7
SEQ ID NO: 8	Tau 300-317	-82	9	-60	17	-10

FIGURE 26C

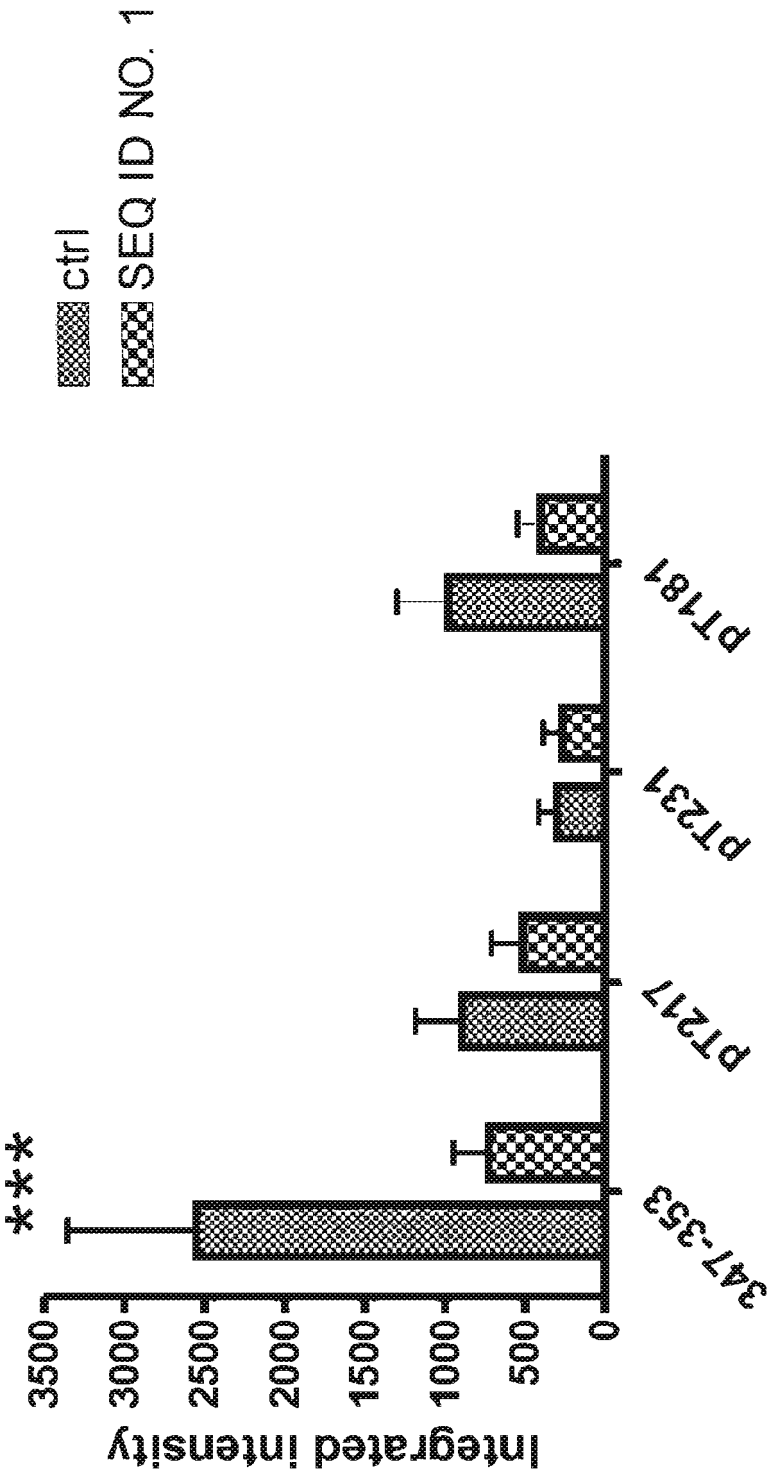
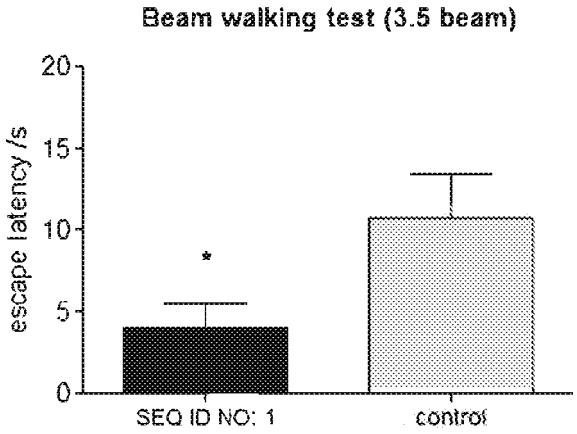
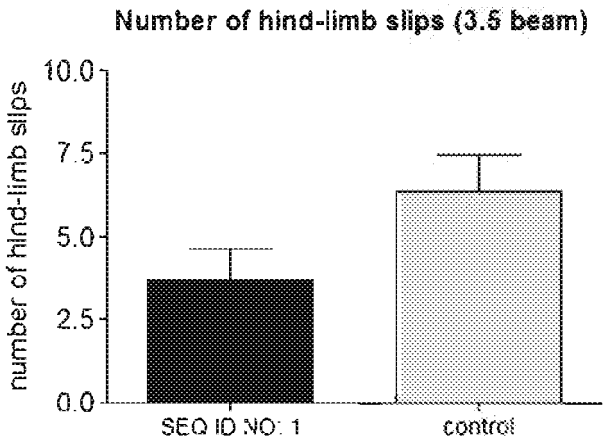

ctrl
SEQ ID NO. 1
Integrated intensity
3500
3000
2500
2000
1500
1000
500
0
***
347-353
PT217
PT231
PT181

FIGURE 27

A



B



C

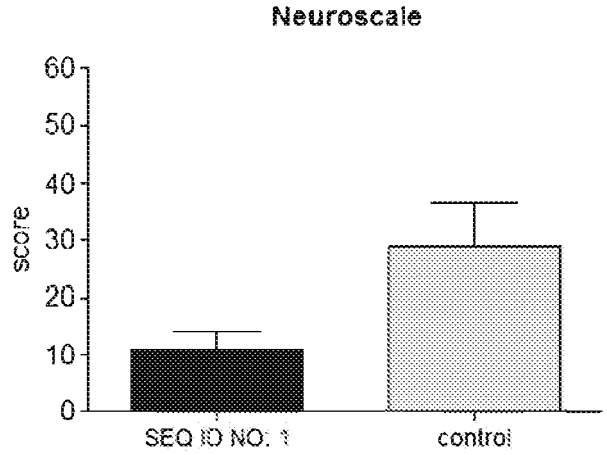


FIGURE 28

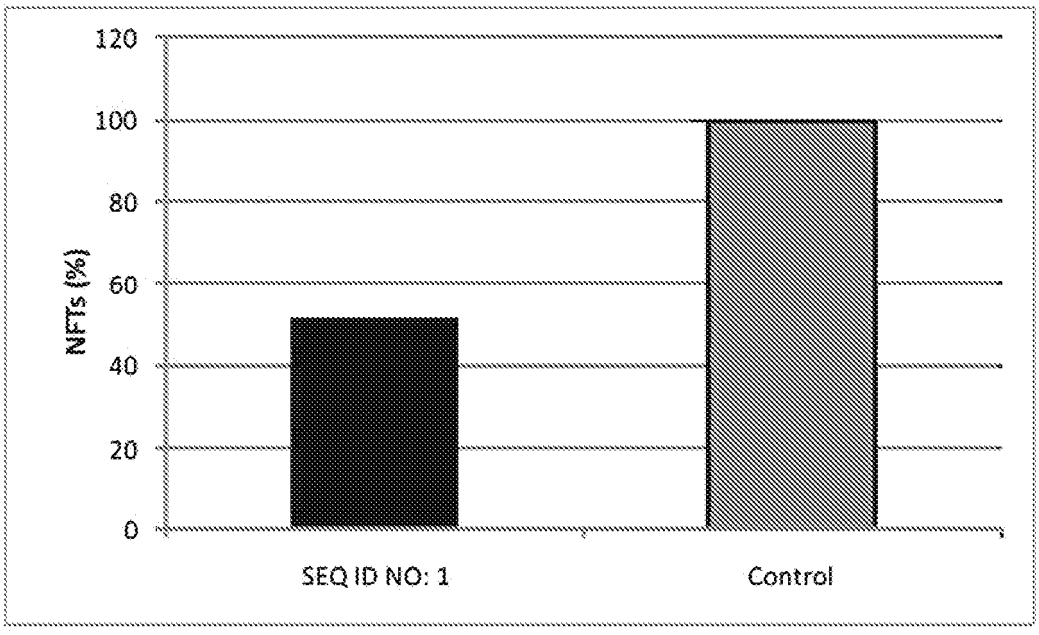


FIGURE 29

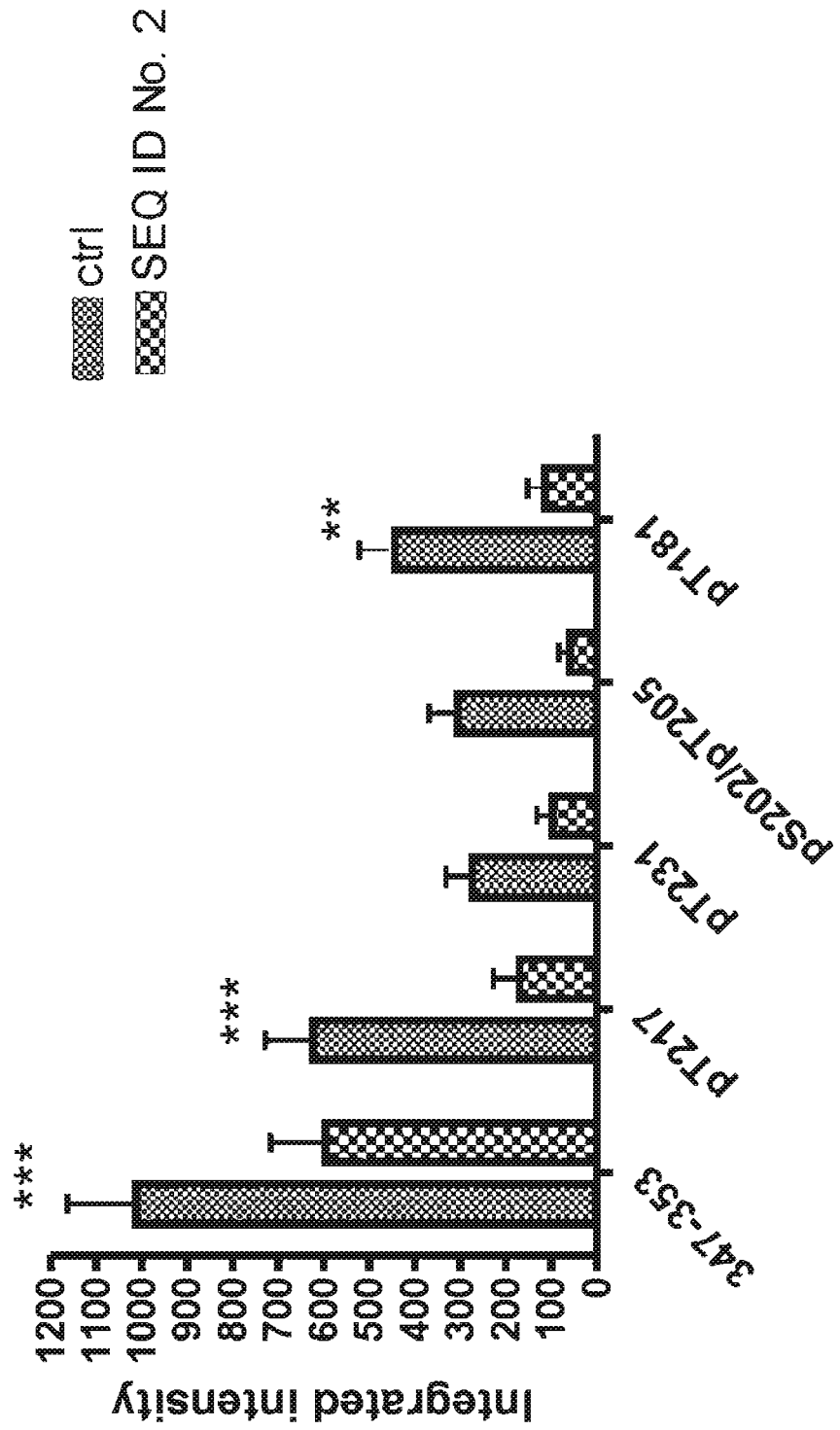
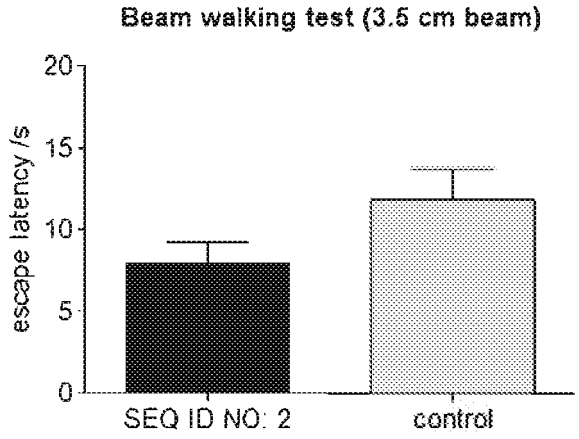
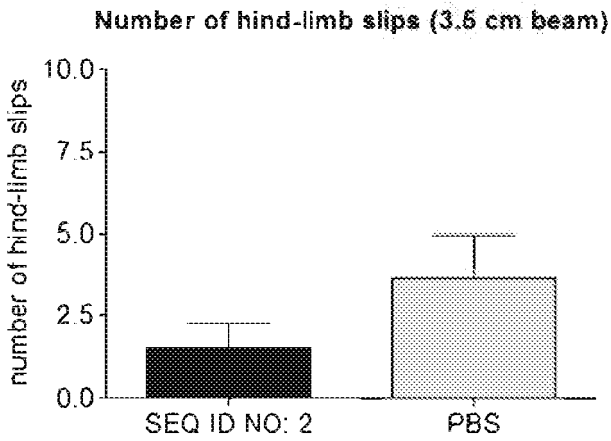

ctrl
SEQ ID No. 2
Integrated intensity
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
***
***
**
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 30

A.



B.



C.

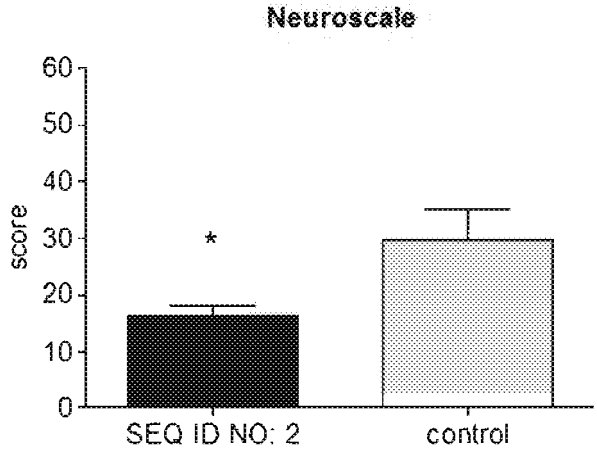


FIGURE 31

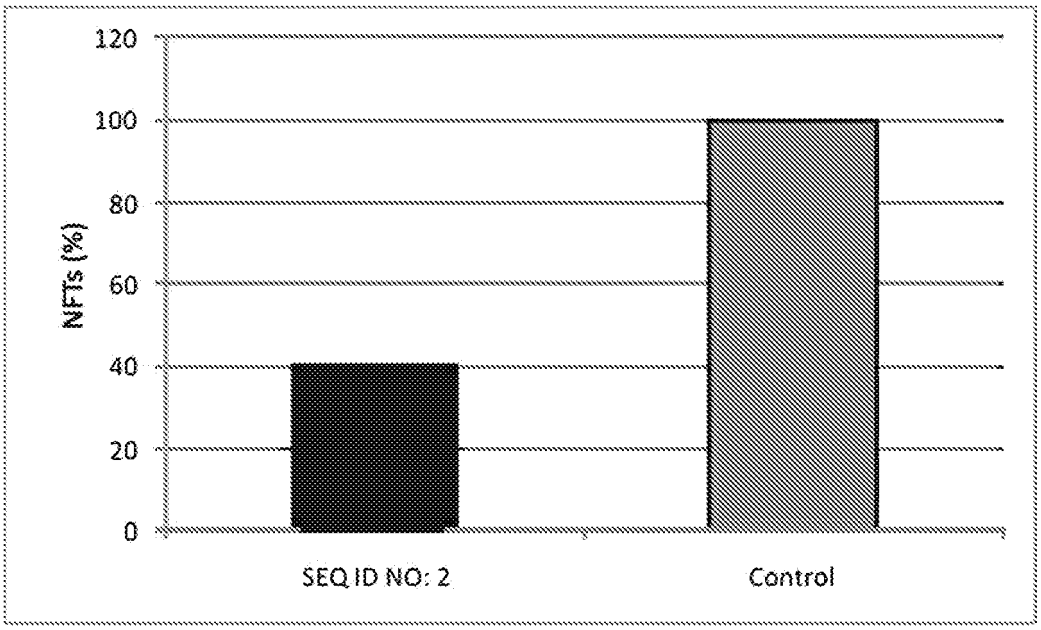


FIGURE 32

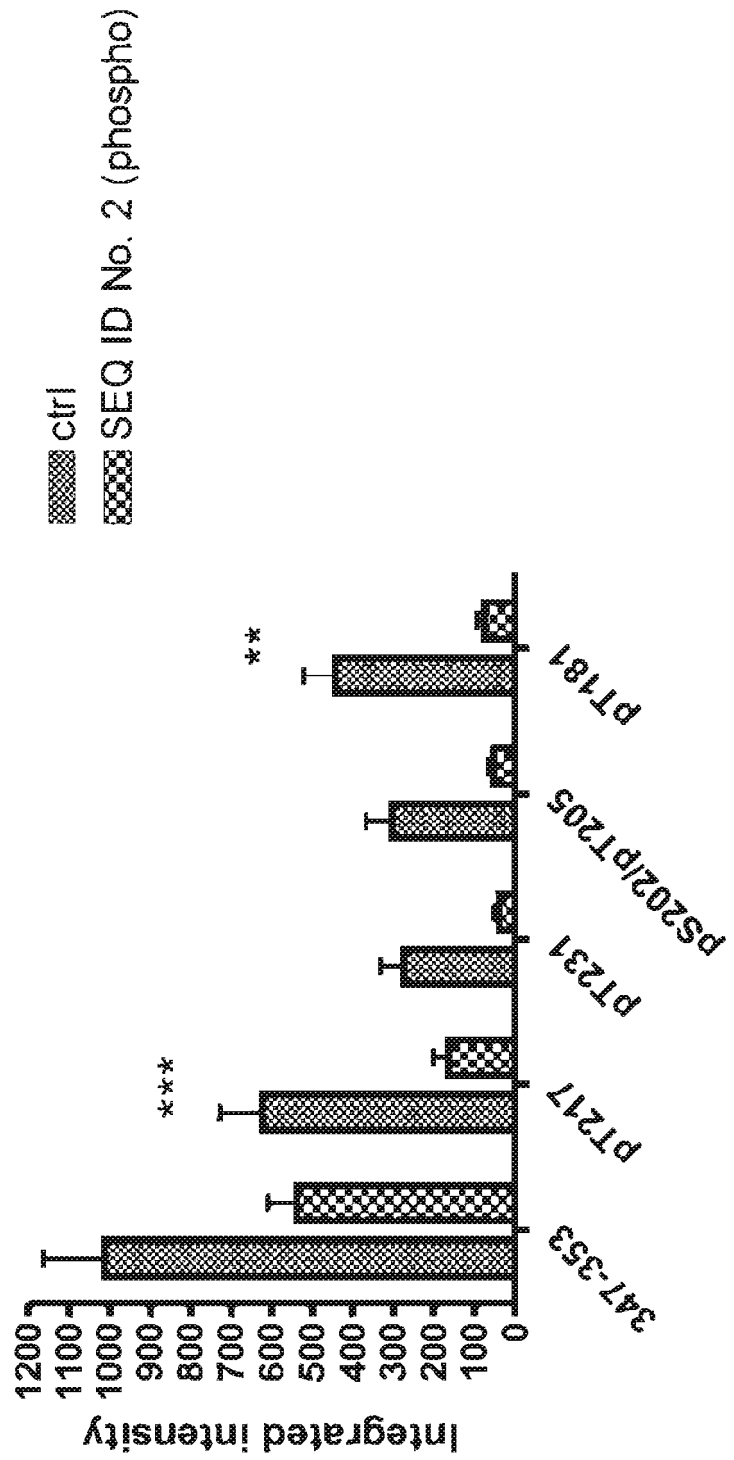

ctrl
SEQ ID No. 2 (phospho)
Integrated intensity
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
***
***
**
3AT-353
PT247
PT231
PS202/PT205
PT181

FIGURE 33

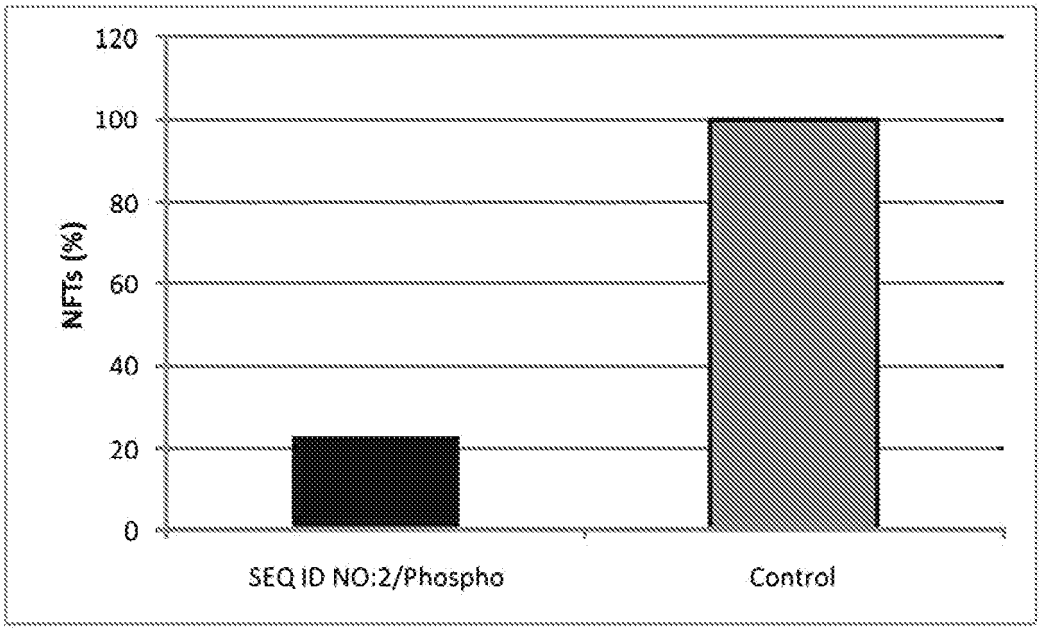


FIGURE 34

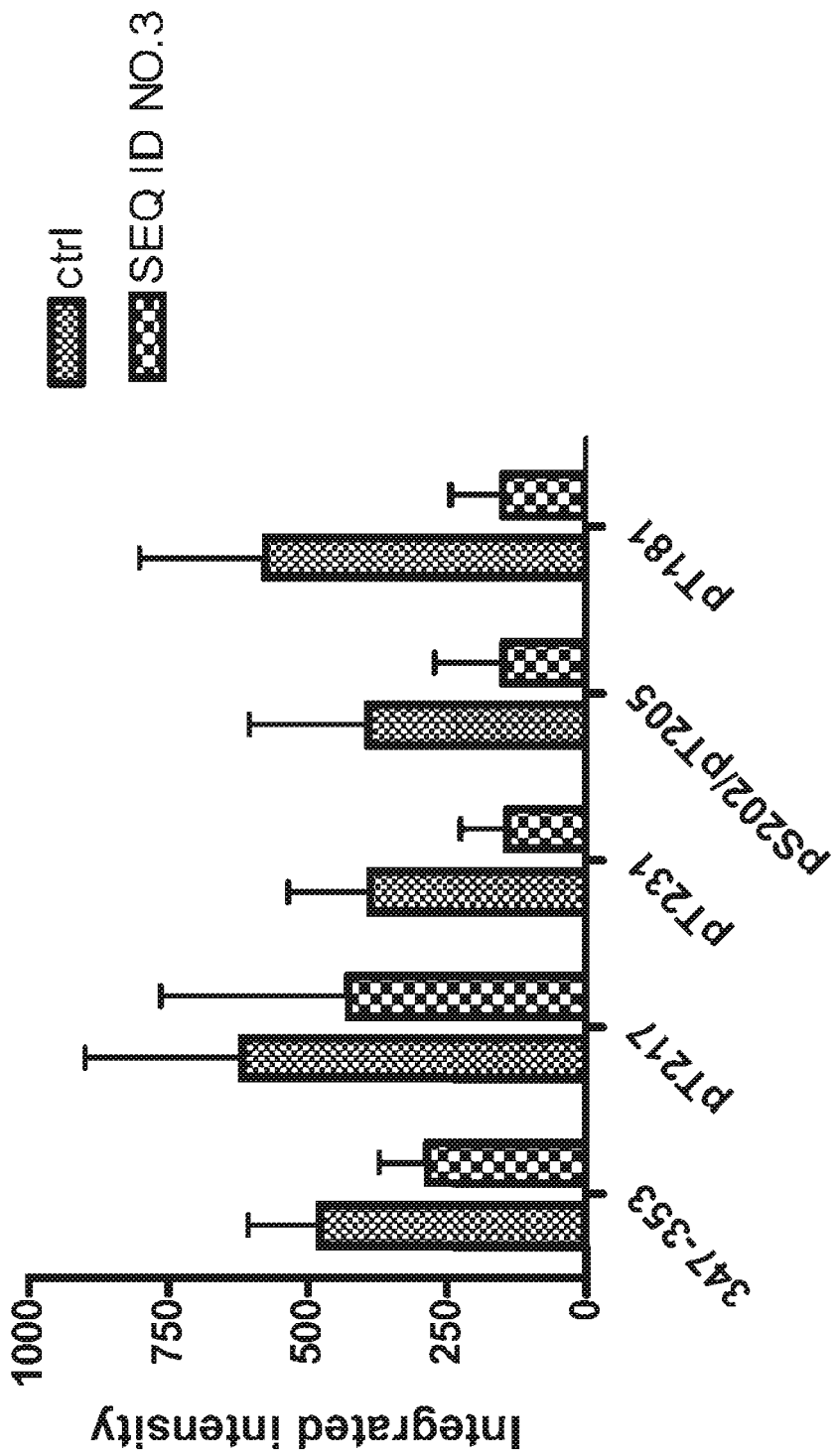
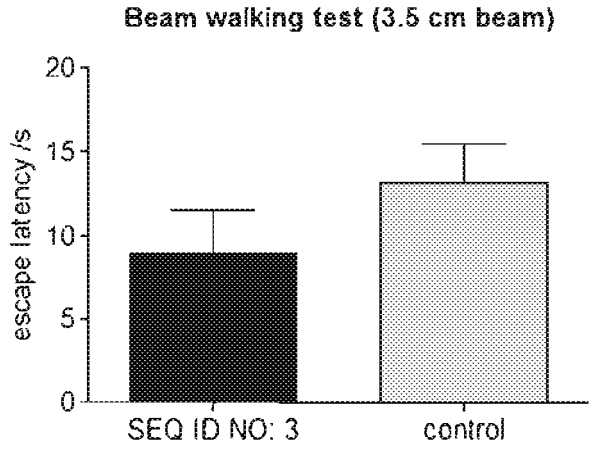
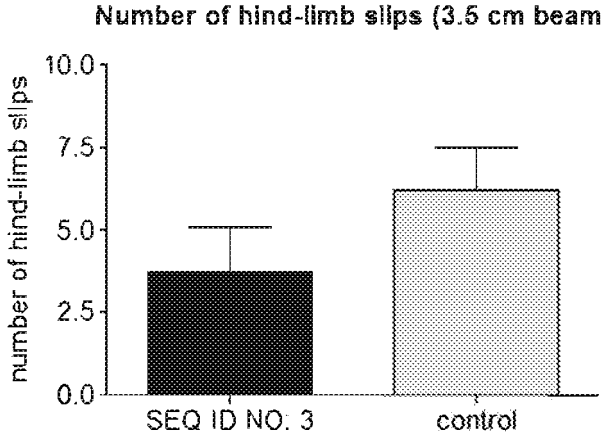

ctrl
SEQ ID NO.3
Integrated intensity
1000
750
500
250
0
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 35

A.



B.



C.

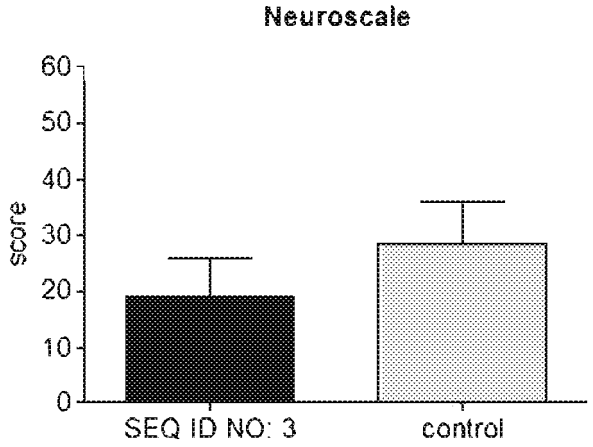


FIGURE 36

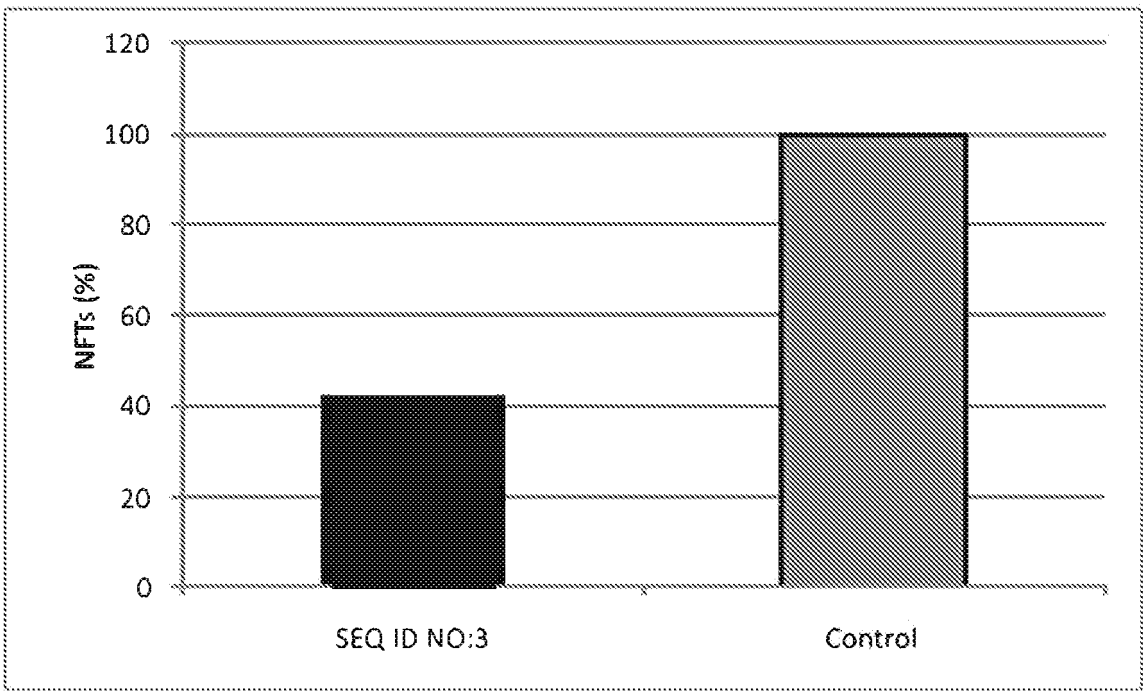


FIGURE 37

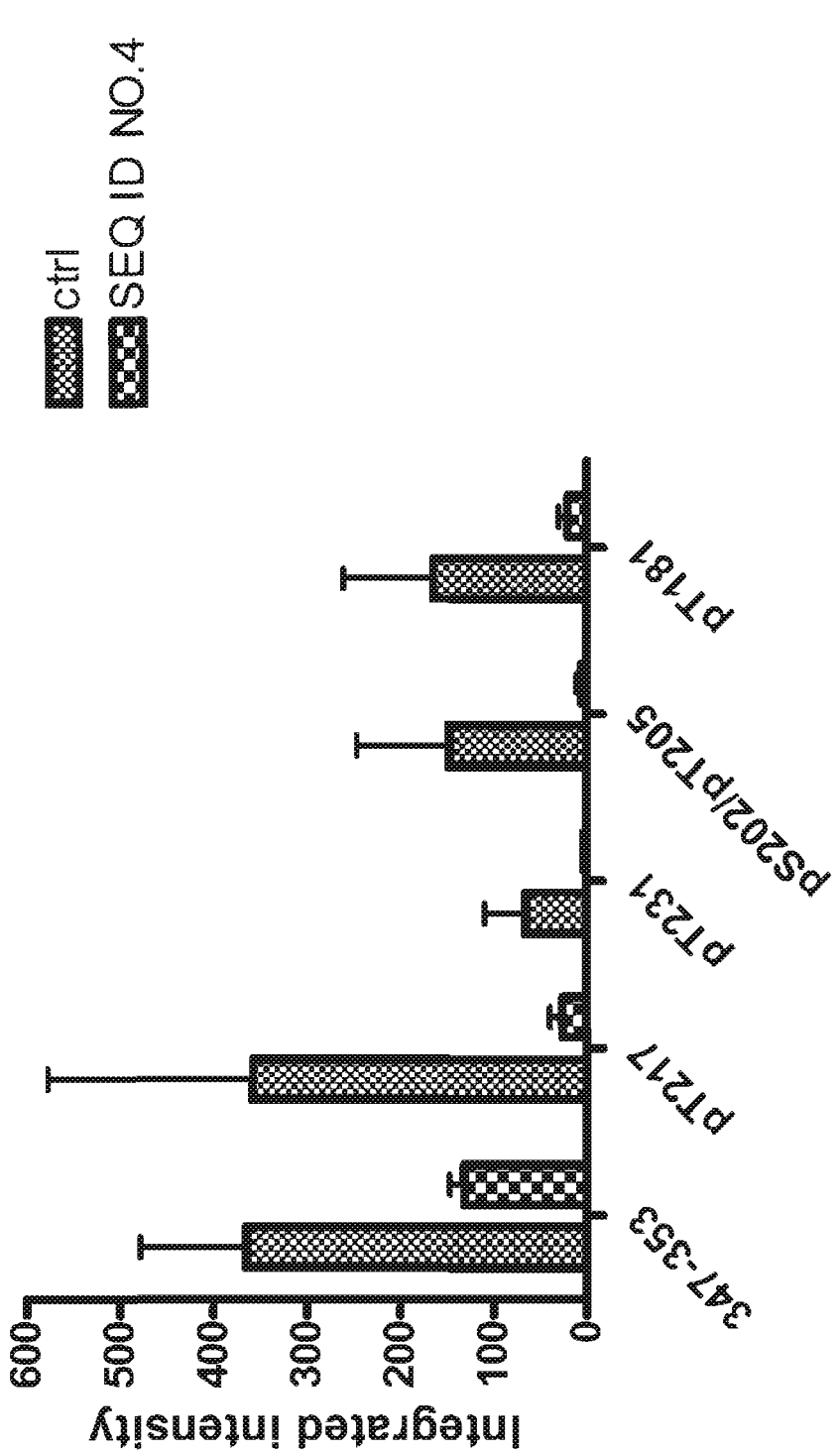
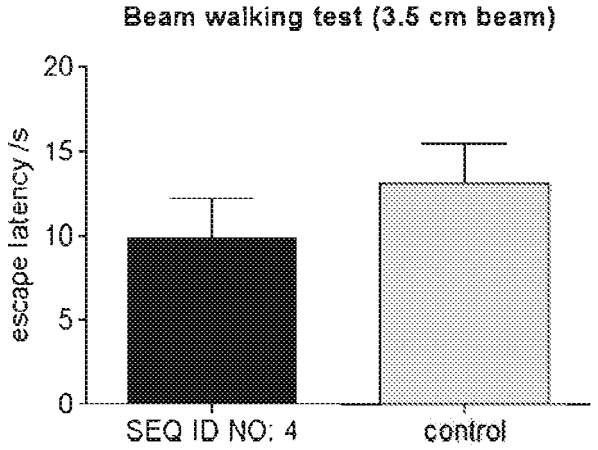
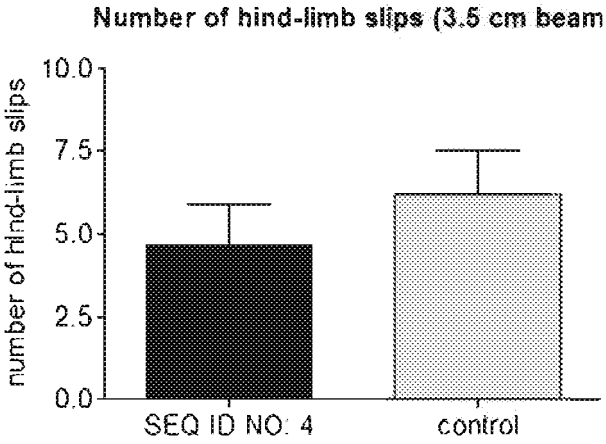

ctrl
SEQ ID NO.4
Integrated intensity
600
500
400
300
200
100
0
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 38

A



B



C

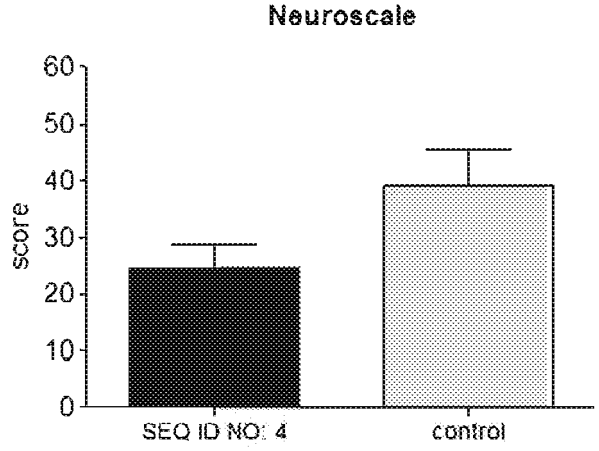


FIGURE 39

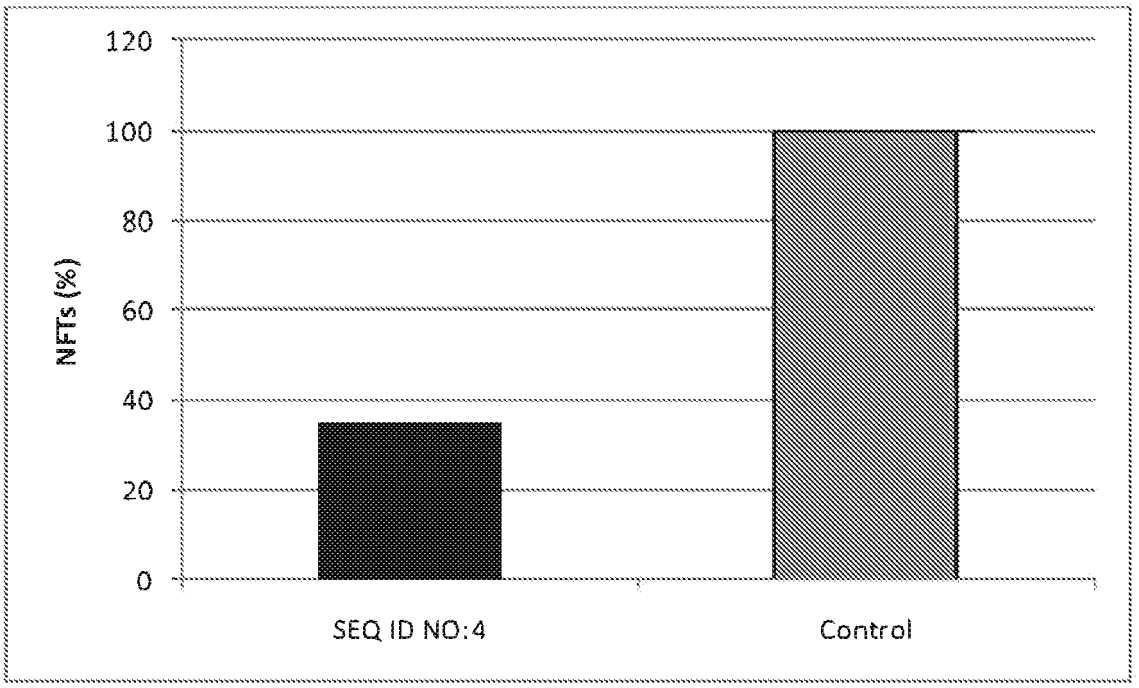


FIGURE 40

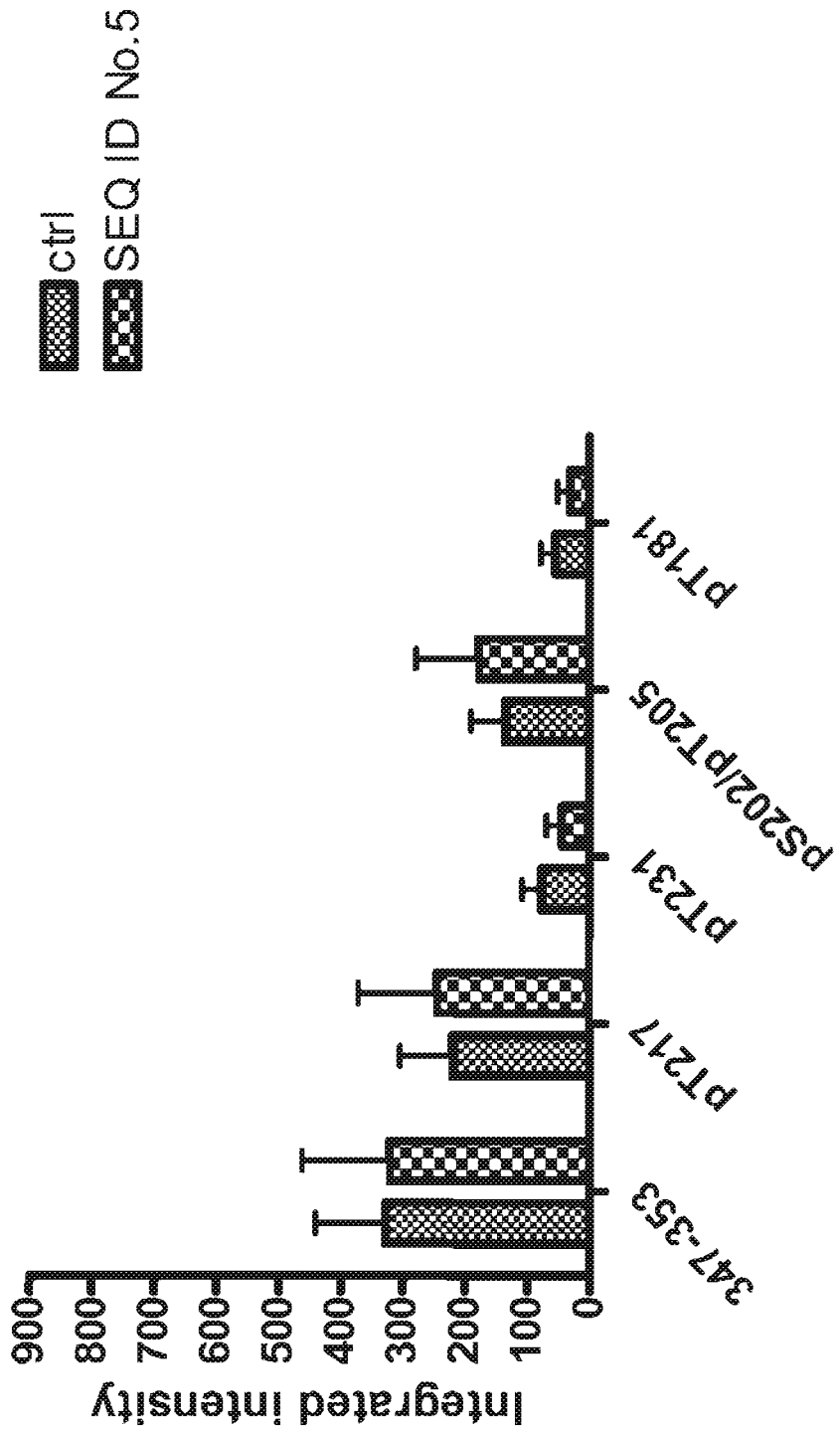
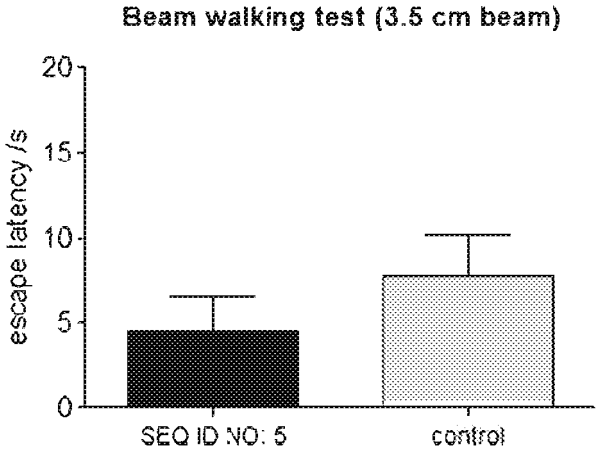
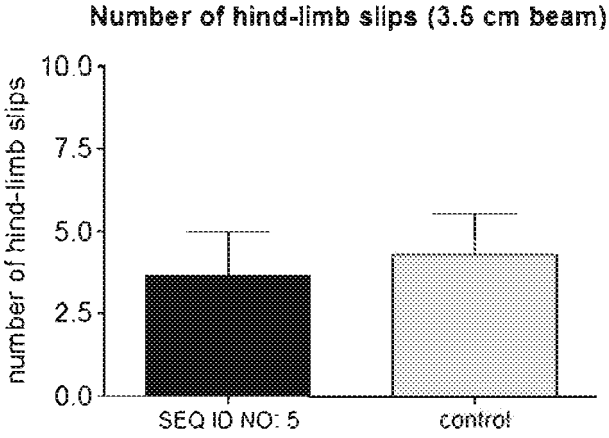

ctrl
SEQ ID No.5
Integrated intensity
900
800
700
600
500
400
300
200
100
0
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 41

A.



B.



C.

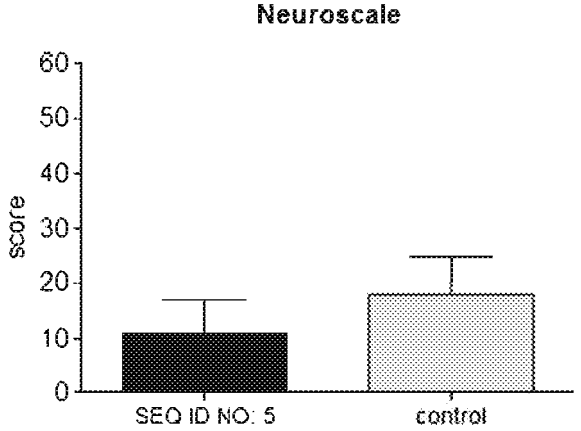


FIGURE 42

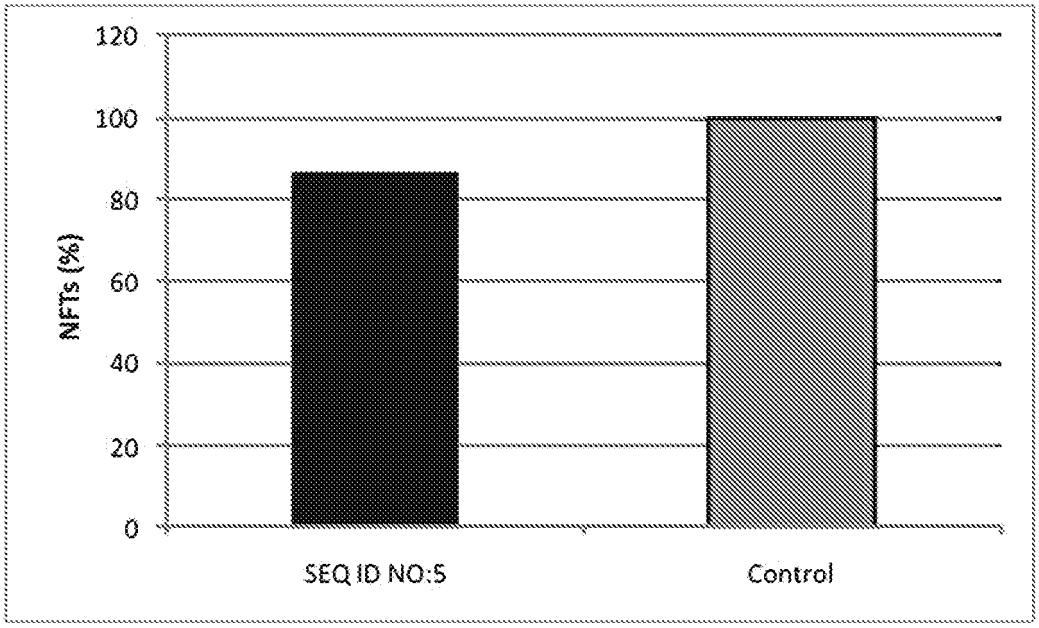


FIGURE 43

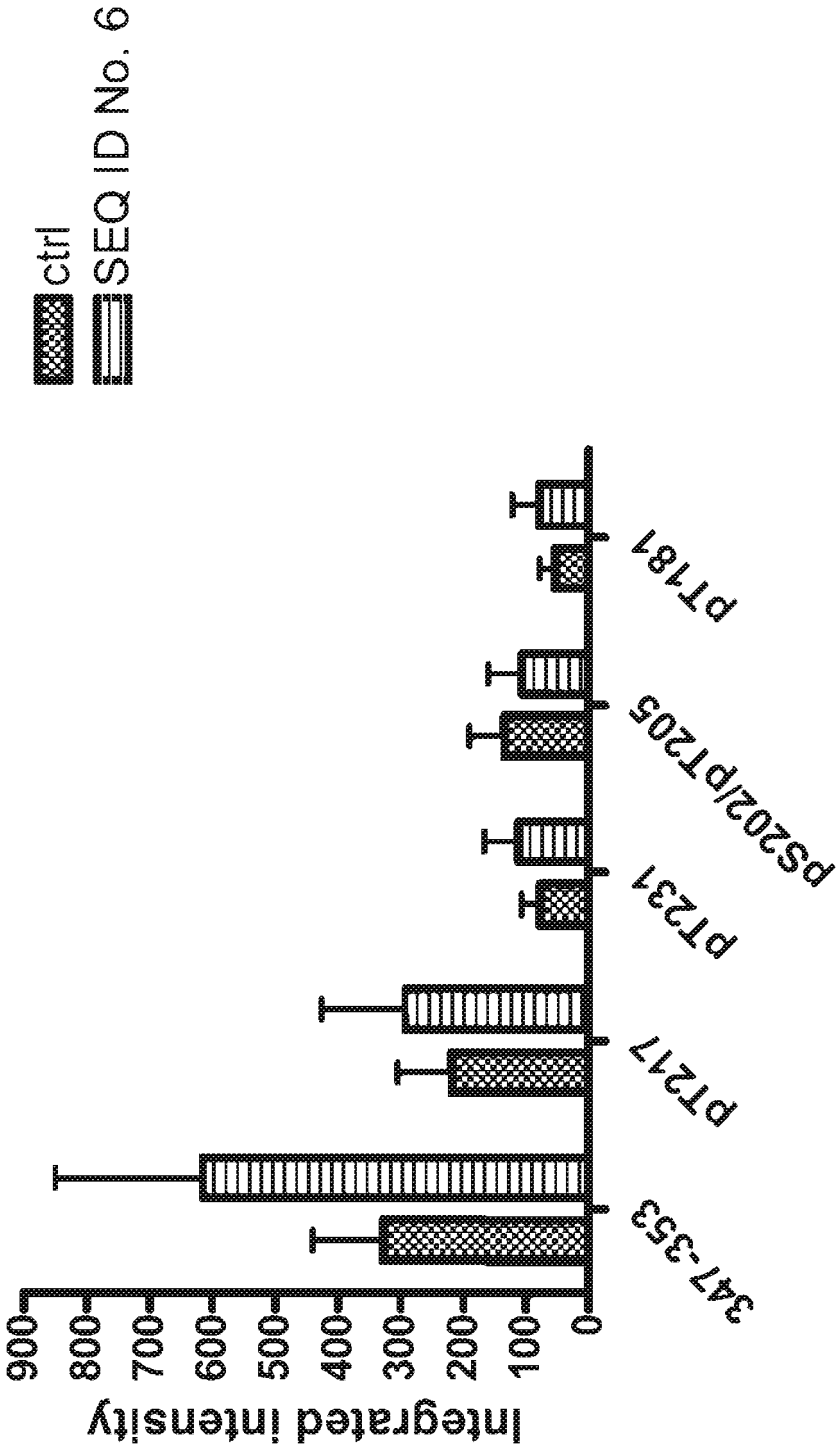
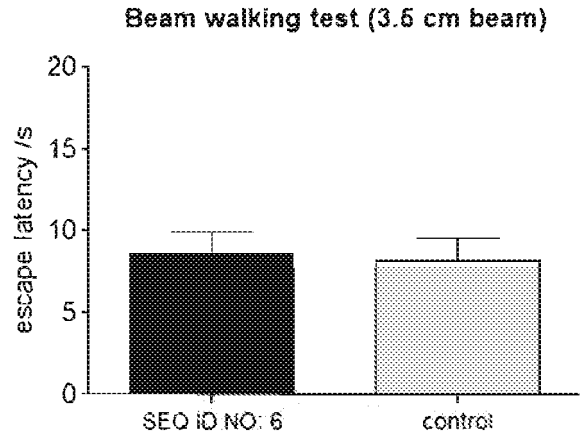
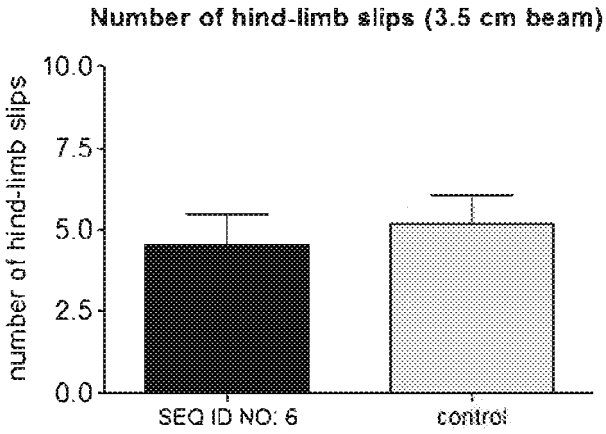

ctrl
SEQ ID No. 6
Integrated intensity
0
100
200
300
400
500
600
700
800
900
347-353
PT217
PT231
PS202/PT205
PT181

FIGURE 44

A.



B.



C.

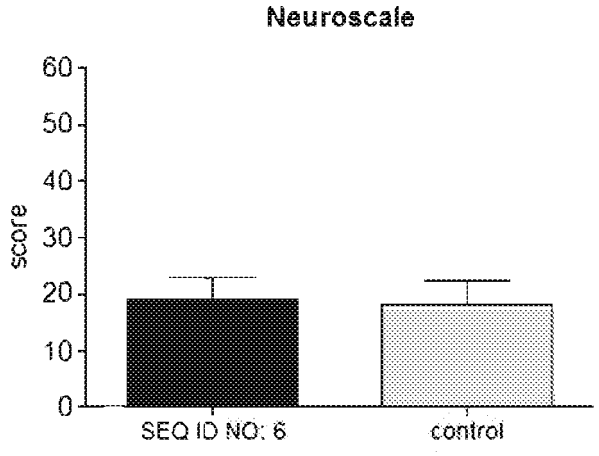


FIGURE 45

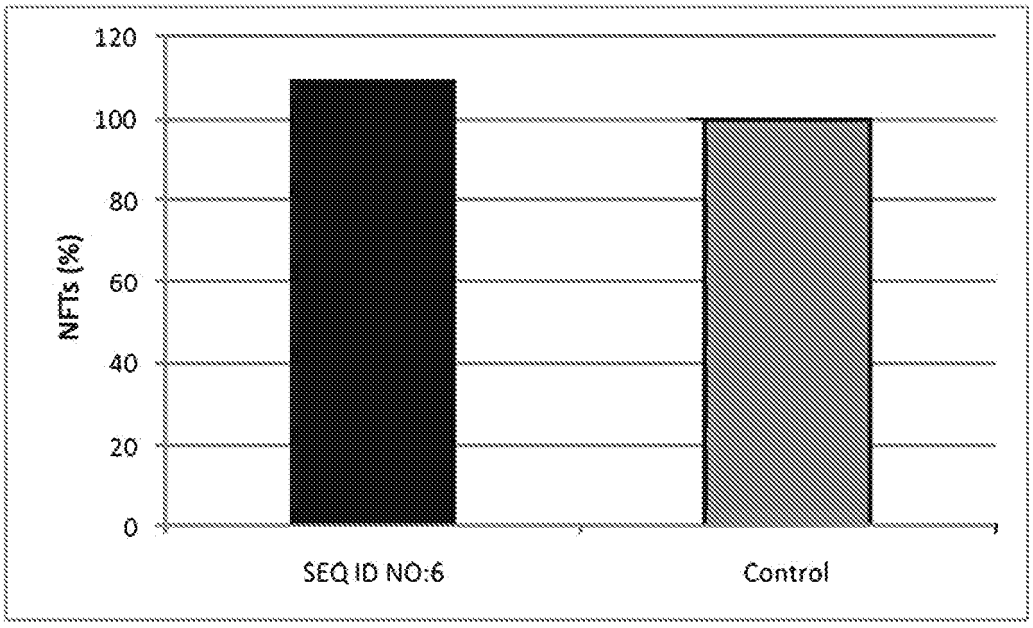


FIGURE 46

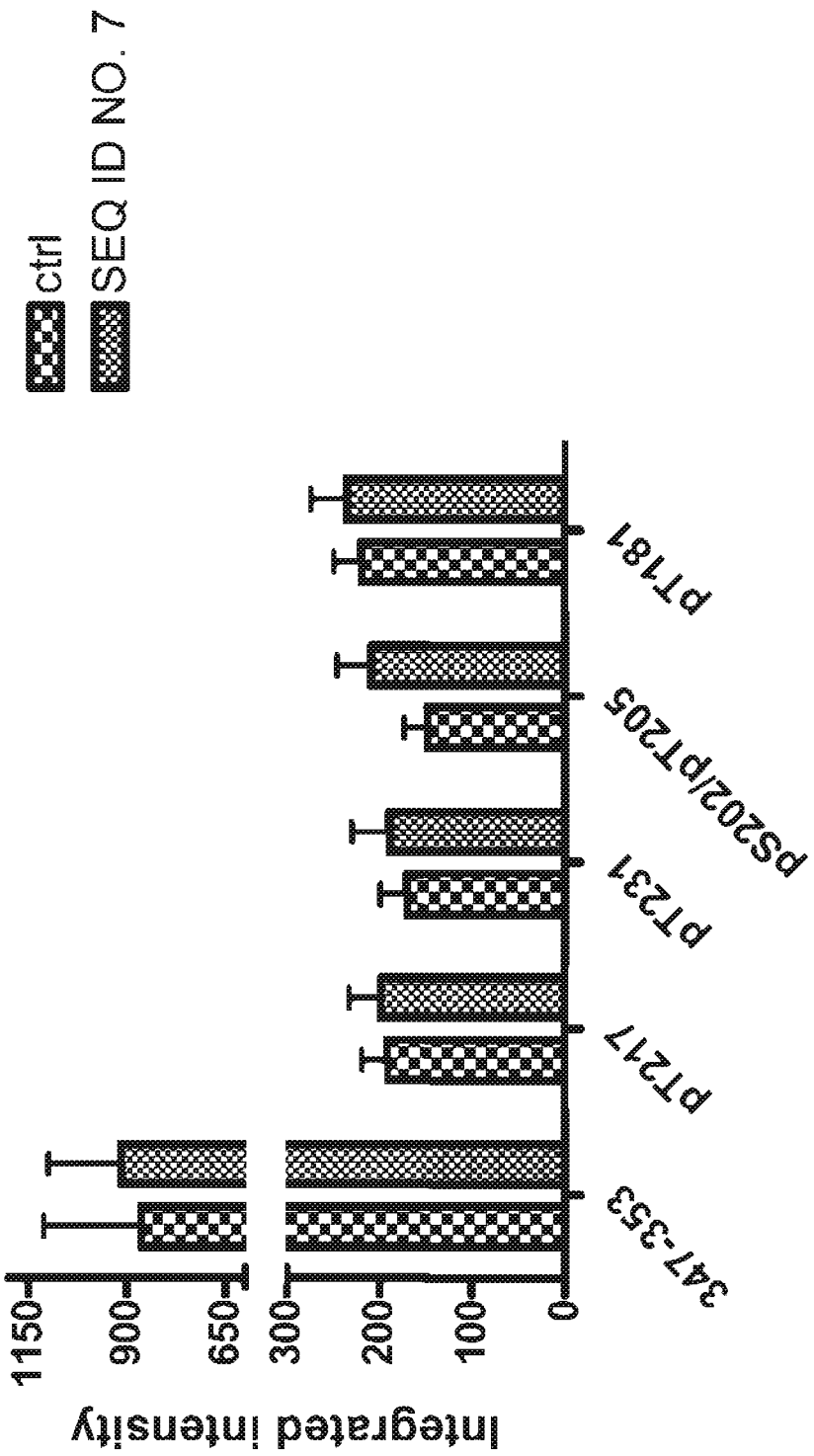
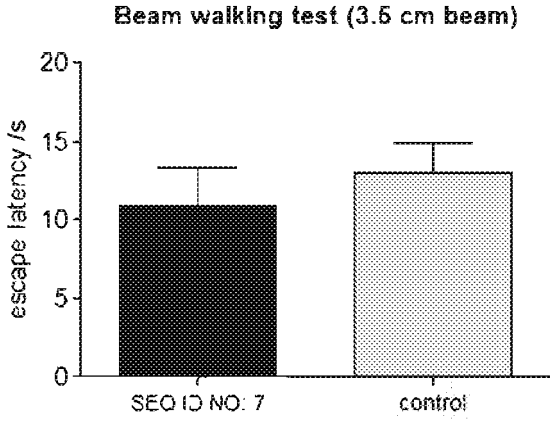
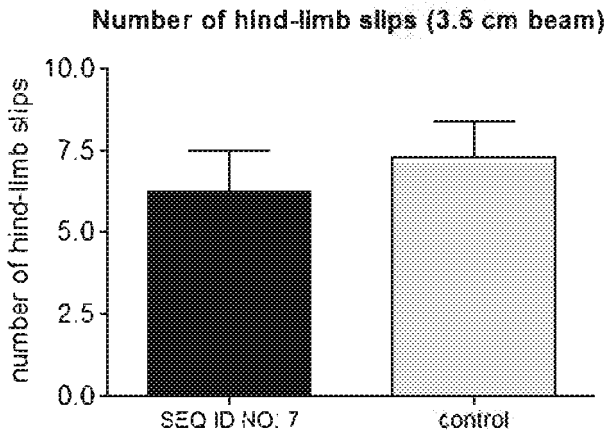

ctrl
SEQ ID NO. 7
Integrated intensity
1150
900
650
300
200
100
0
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 47

A.



B.



C.

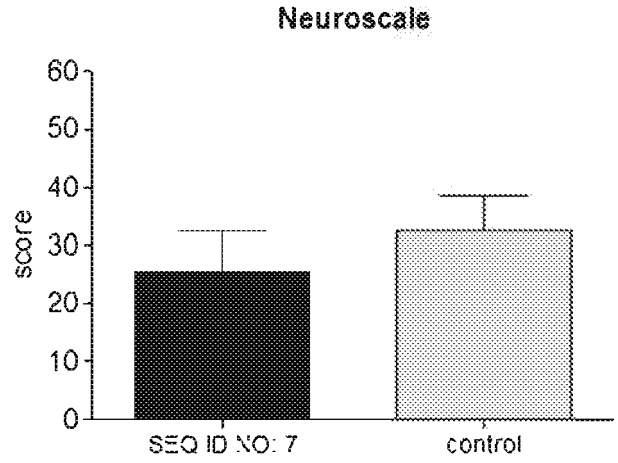


FIGURE 48

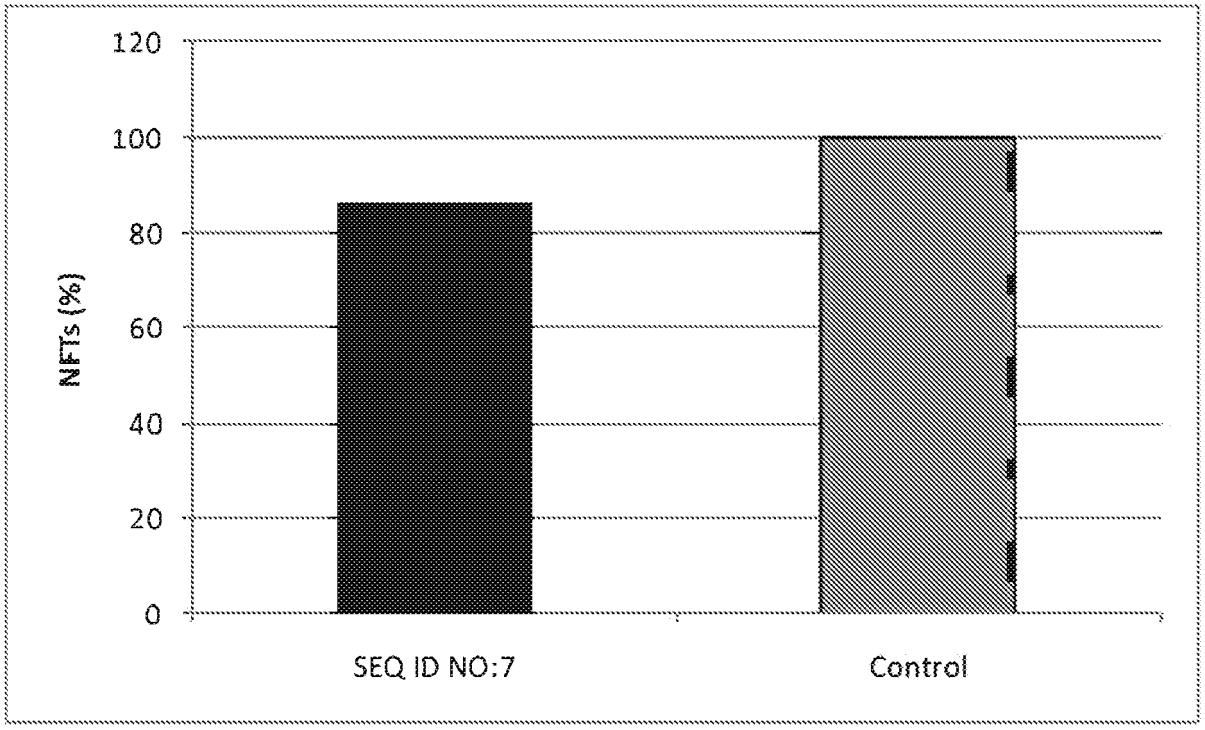


FIGURE 49

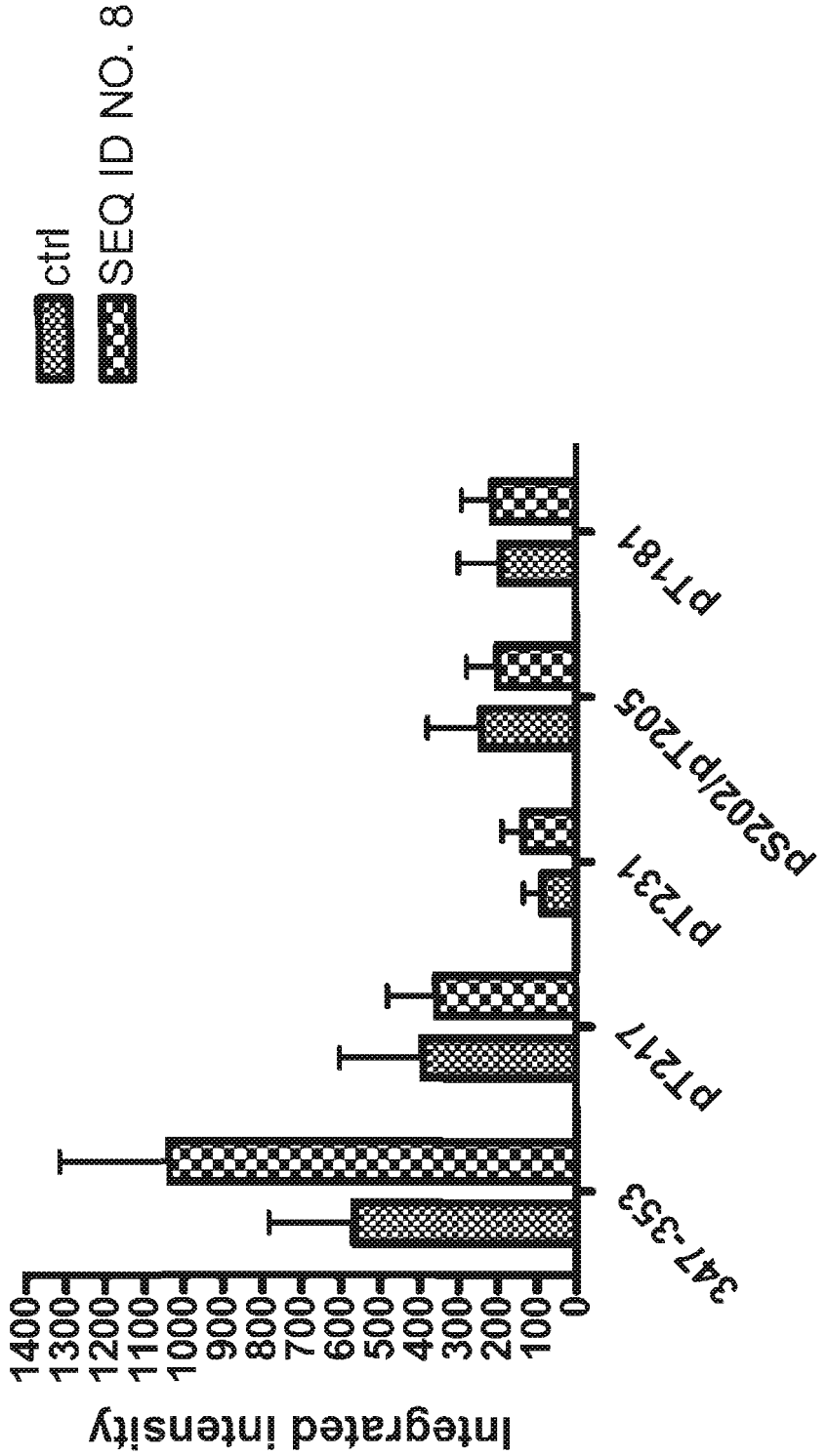
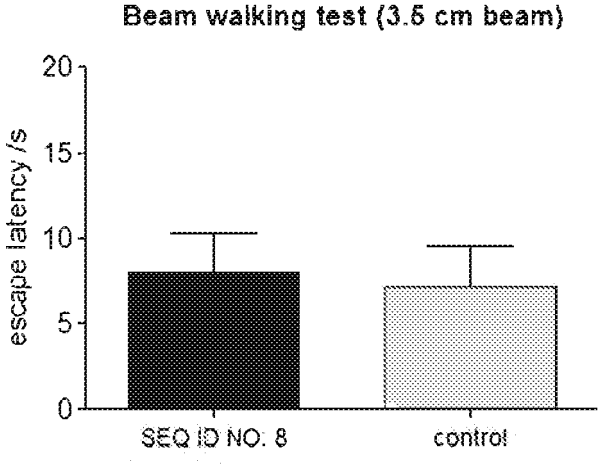
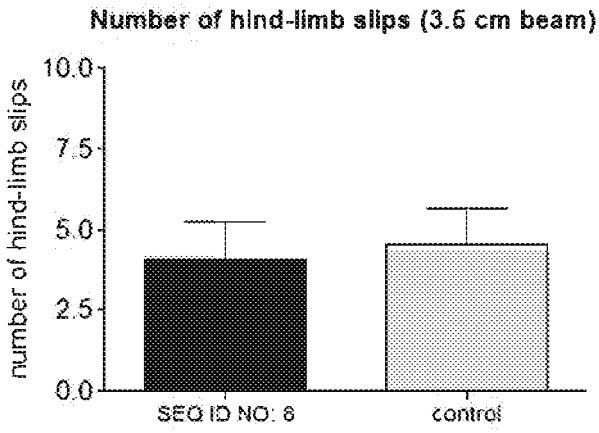

ctrl
SEQ ID NO. 8
Integrated intensity
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
347-353
pT217
pT231
pS202/pT205
pT181

FIGURE 50

A.



B.



C.

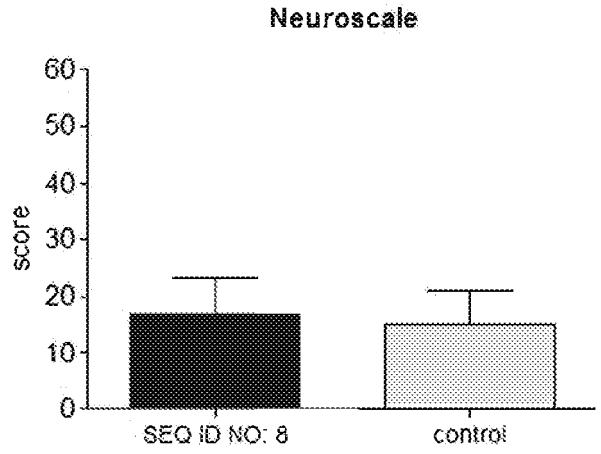


FIGURE 51

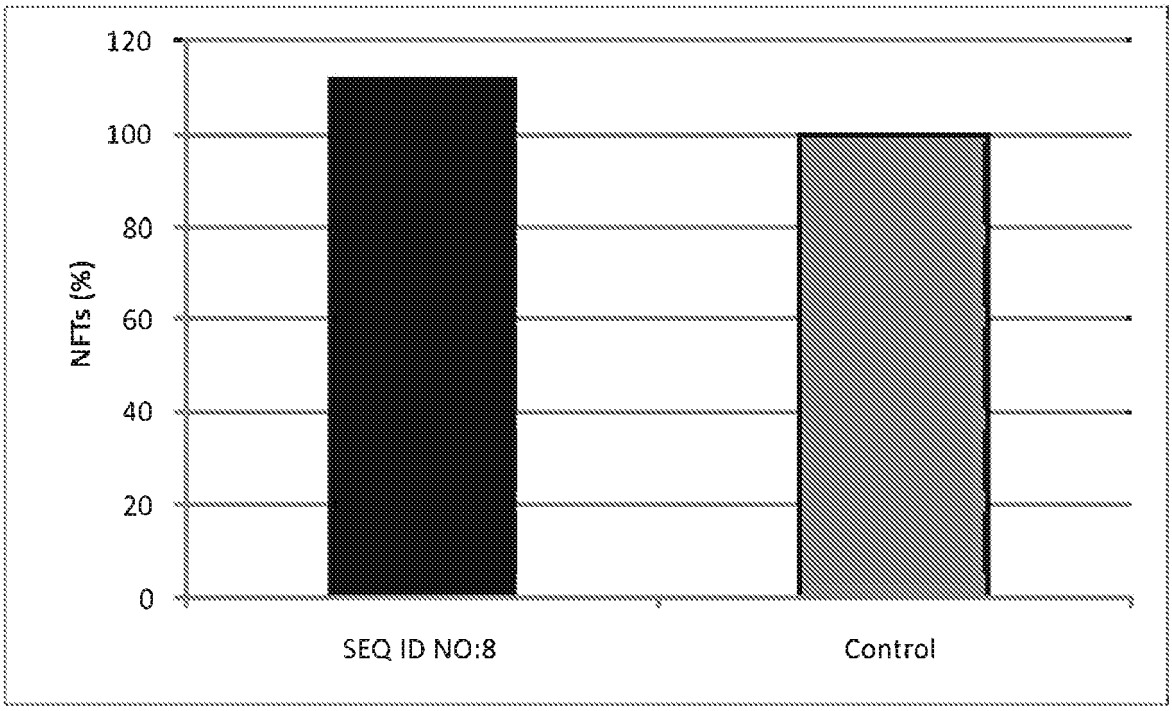


FIGURE 52

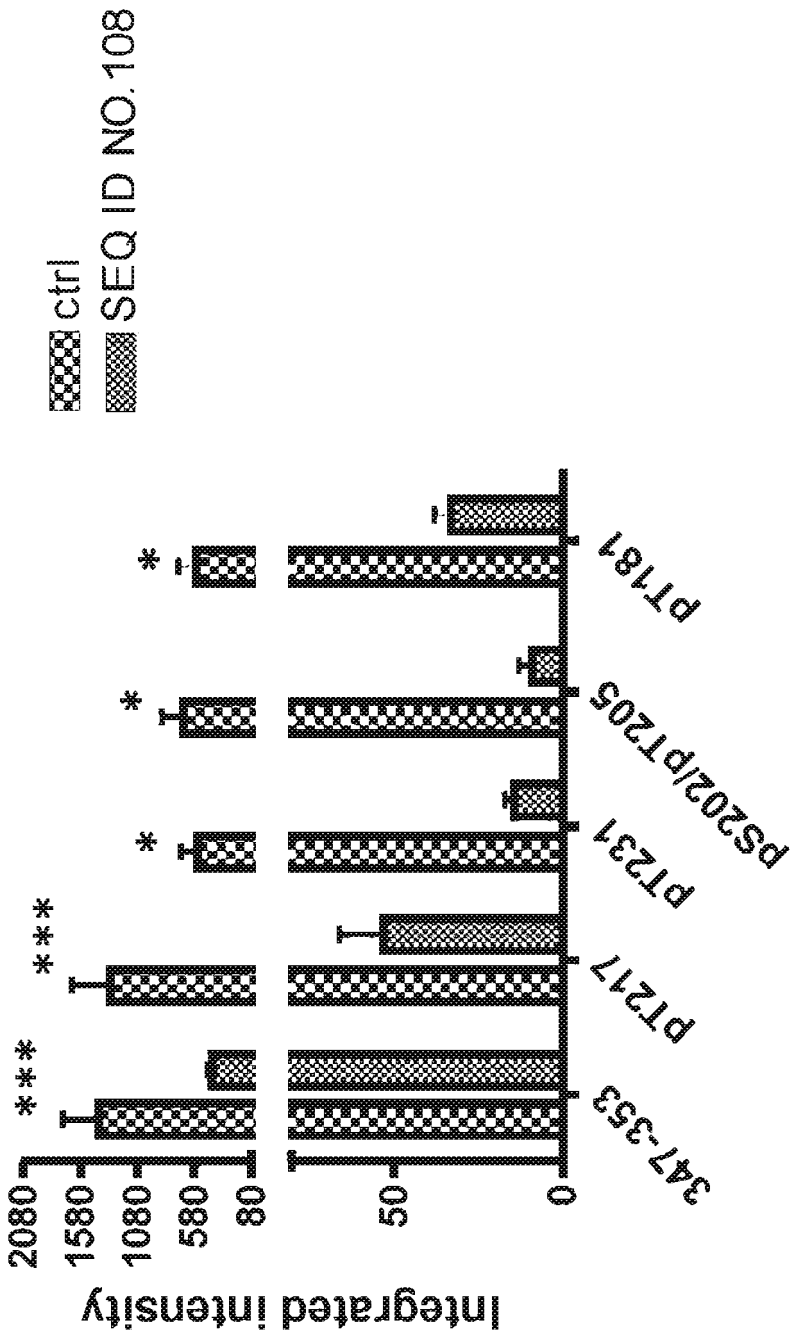
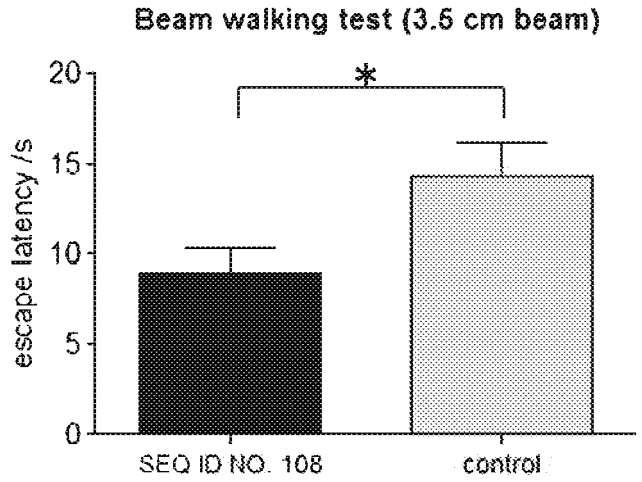
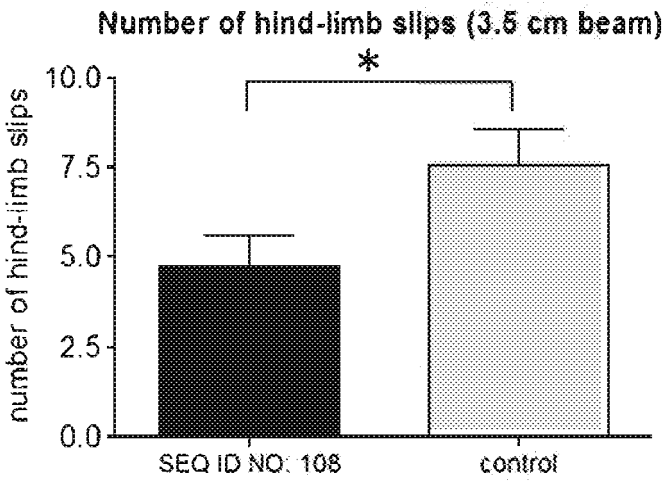

ctrl
SEQ ID NO.108
Integrated intensity
2080
1580
1080
580
80
50
0
****
****
*
*
*
-
-
-
347-353
PT217
PT231
PS202/PT205
PT181

FIGURE 53

A



B



C

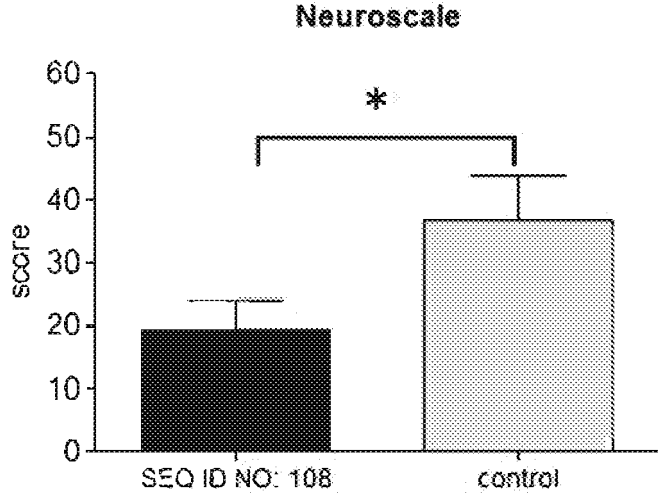


FIGURE 54

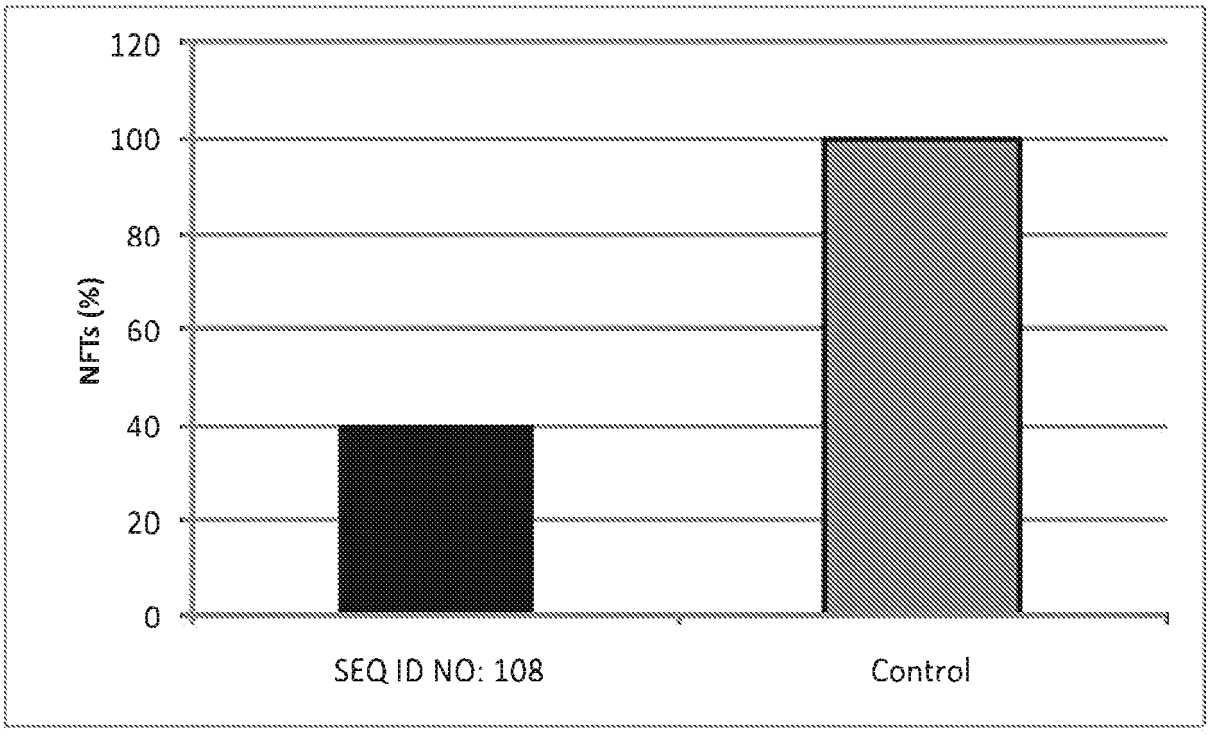


FIGURE 55

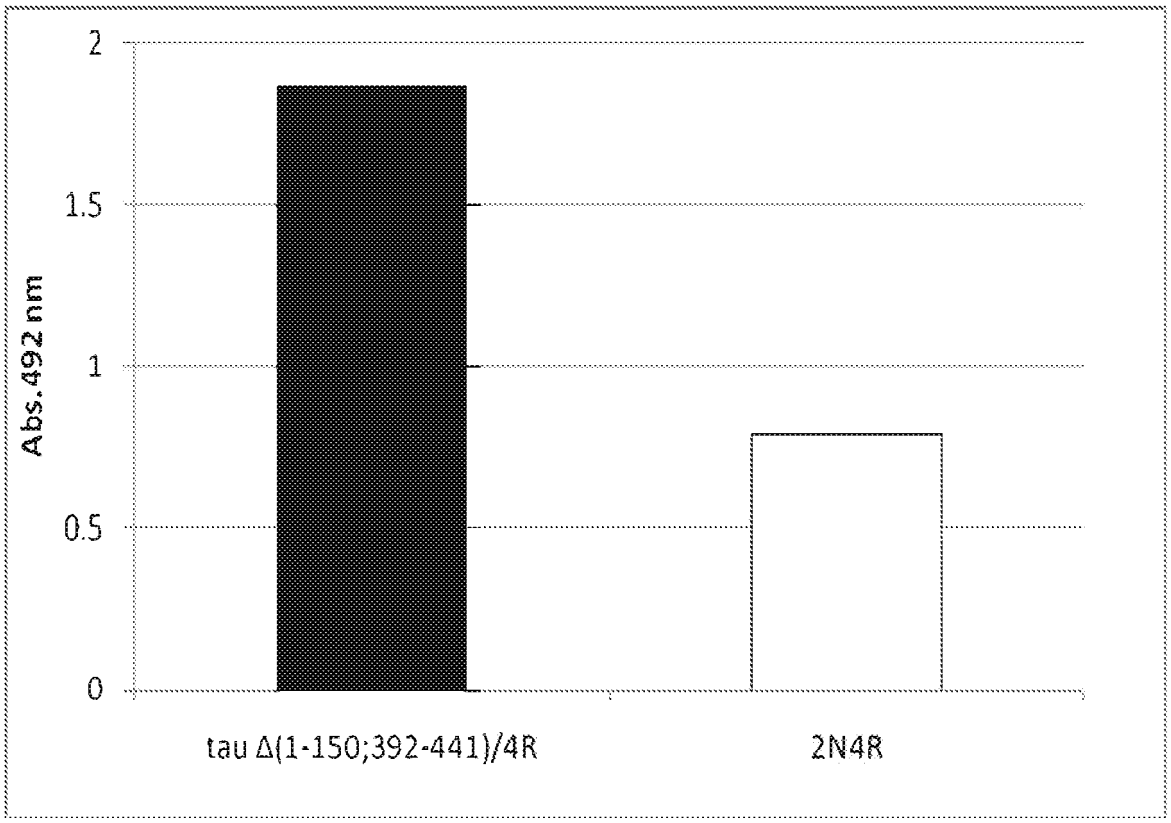


FIGURE 56

Geometric mean antibody titers			
	Solid phase		
Serum dilutions	Peptide SEQ ID NO:108	Tau Δ(1-150;392-441)/4R	Tau 2N4R
100	0[a]	0	0
200	0	0	0
400	0	0	0
800	0	0	2
1 600	0	0	1
3 200	1	0	3
6 400	0	4	1
12 800	2	2	1
25 600	5	4	2
51 200	2	0	0
GMT[b]	20800	12800	4200

Footnotes:

[a] Number of responders

[b] Geometric mean titre

FIGURE 57

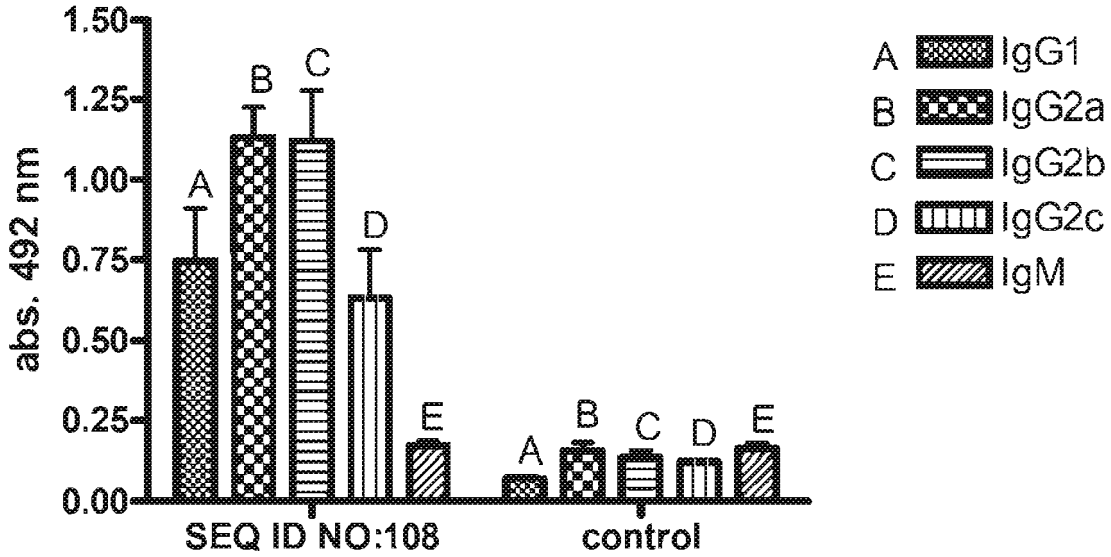
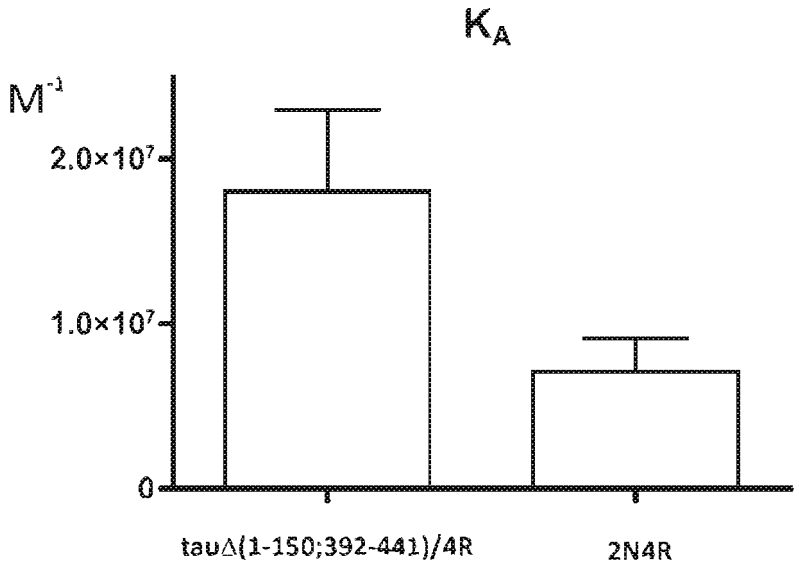

1.50
1.25
1.00
0.75
0.50
0.25
0.00
abs. 492 nm
A
B
C
D
E
A
B
C
D
E
SEQ ID NO:108
control
A IgG1
B IgG2a
C IgG2b
D IgG2c
E IgM

FIGURE 58



	K_A
tauΔ(1-150;392-441)/4R	$1.8\pm0.5 \times10^7 M^{-1}$
2N4R	$7.1\pm2 \times10^6 M^{-1}$

FIGURE 59

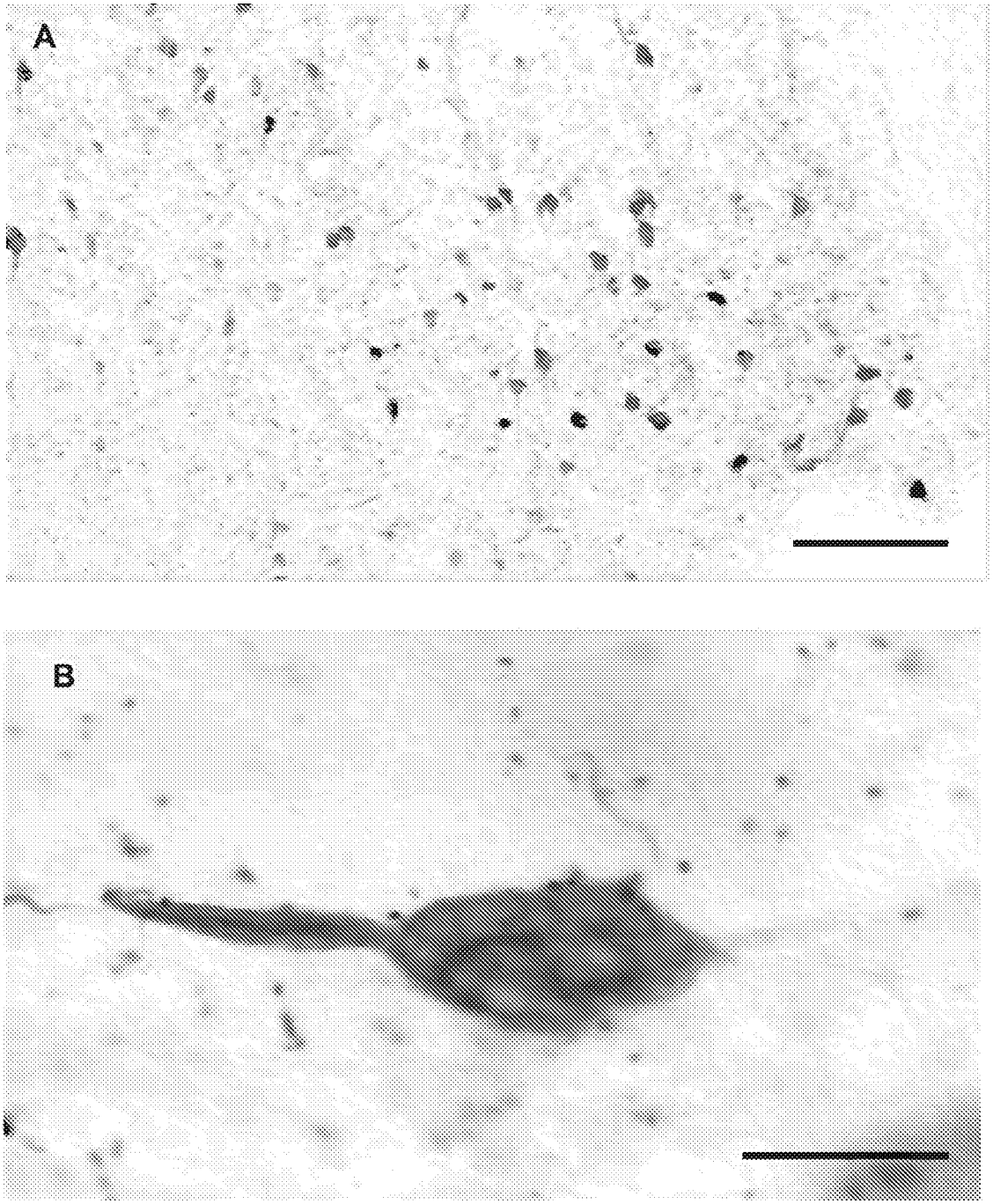


FIGURE 60

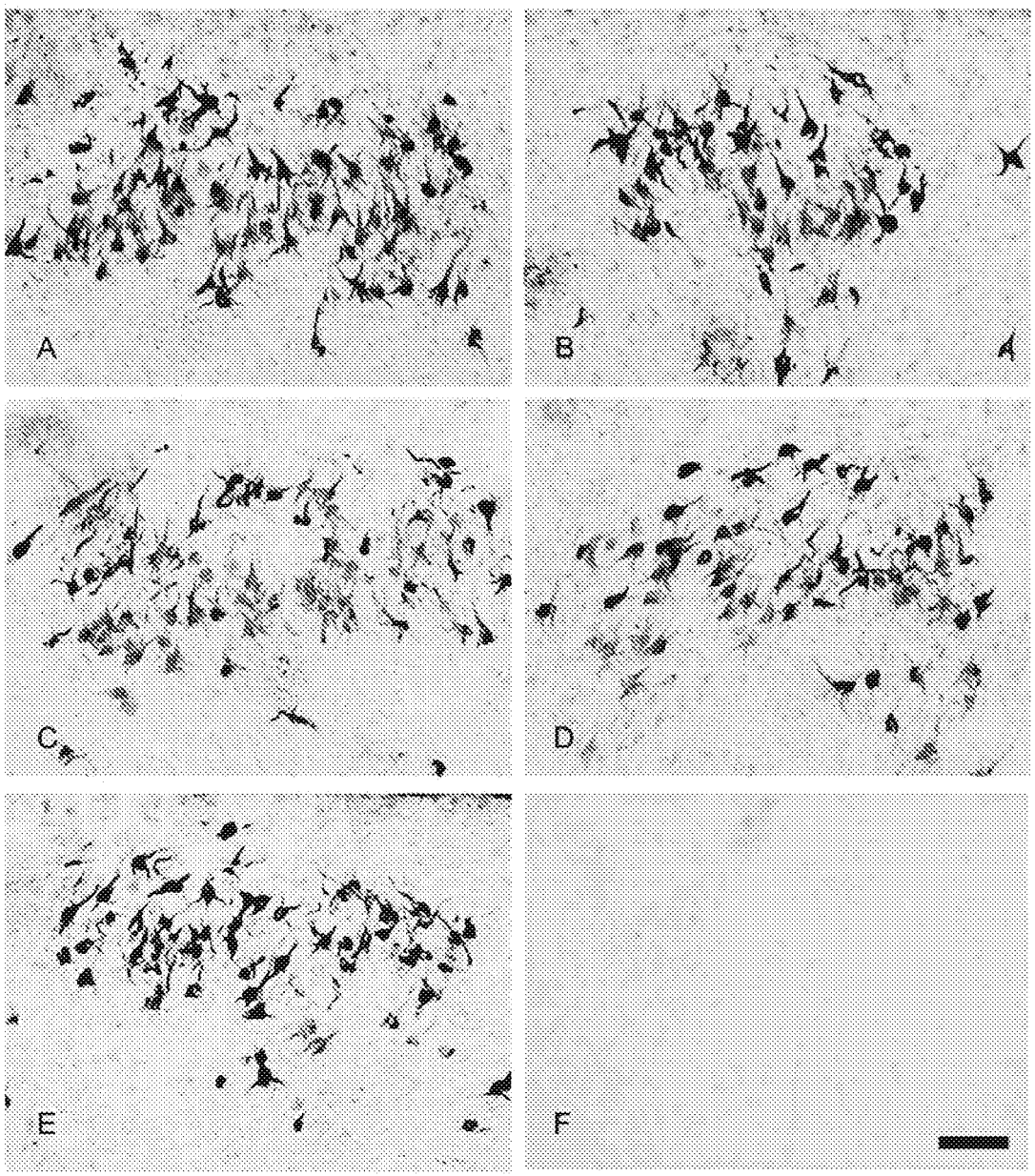


FIGURE 61

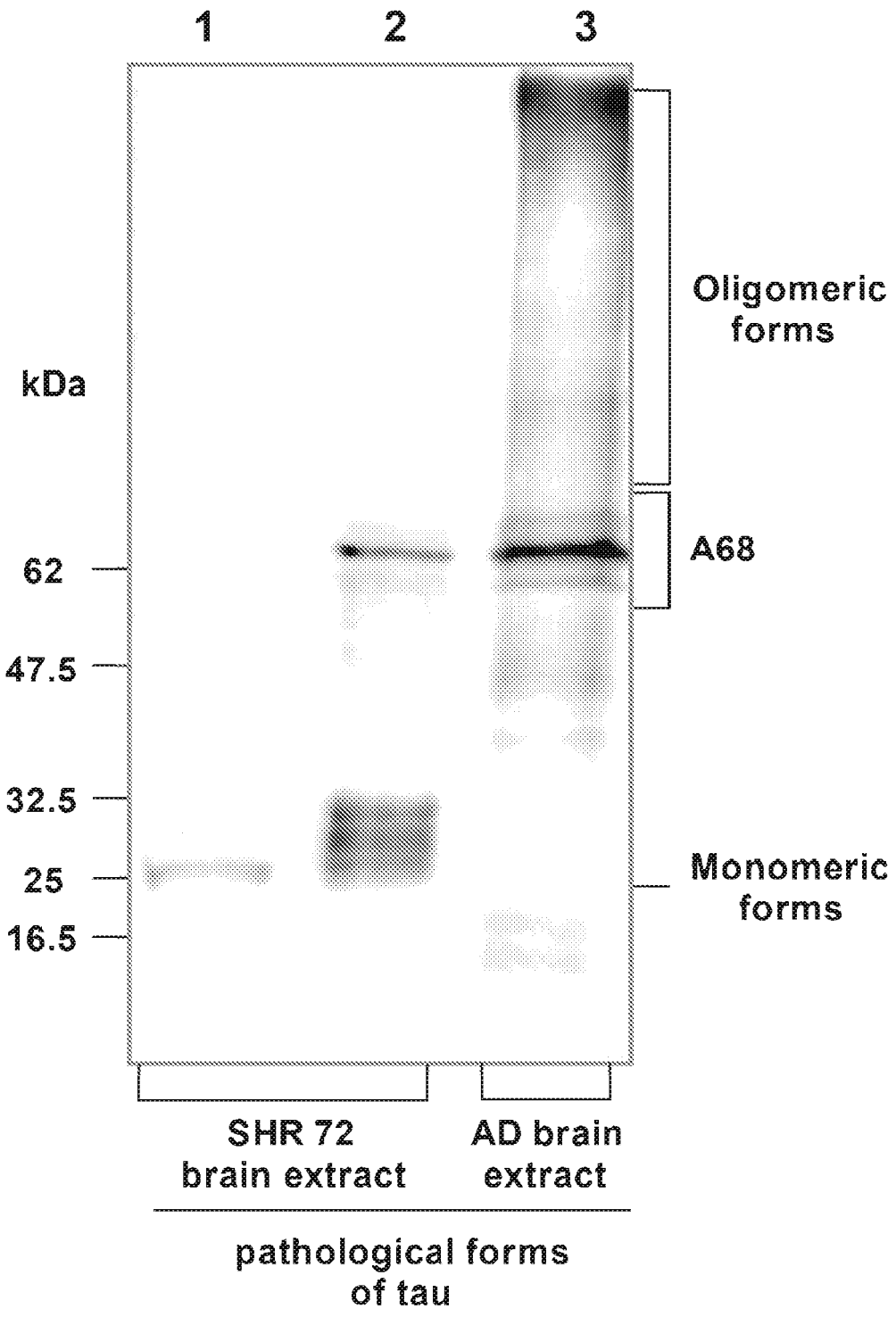

1
2
3
kDa
62
47.5
32.5
25
16.5
Oligomeric forms
A68
Monomeric forms
SHR 72 brain extract
AD brain extract
pathological forms of tau

FIGURE 62

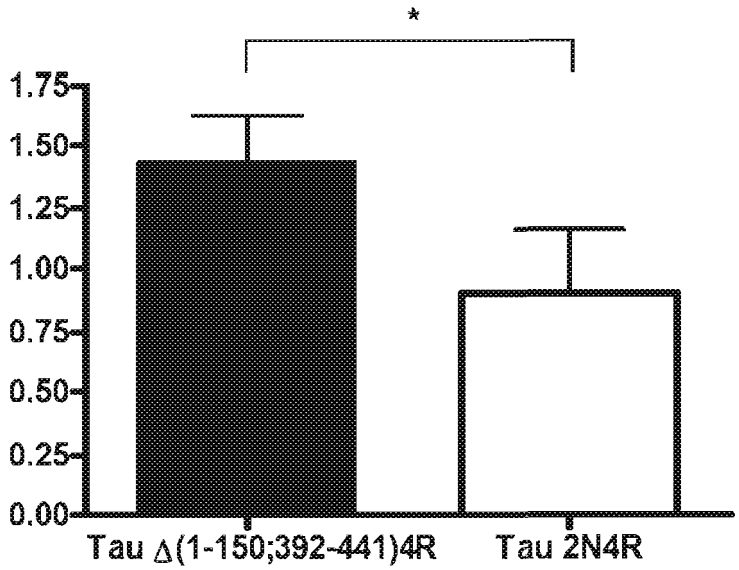


FIGURE 63

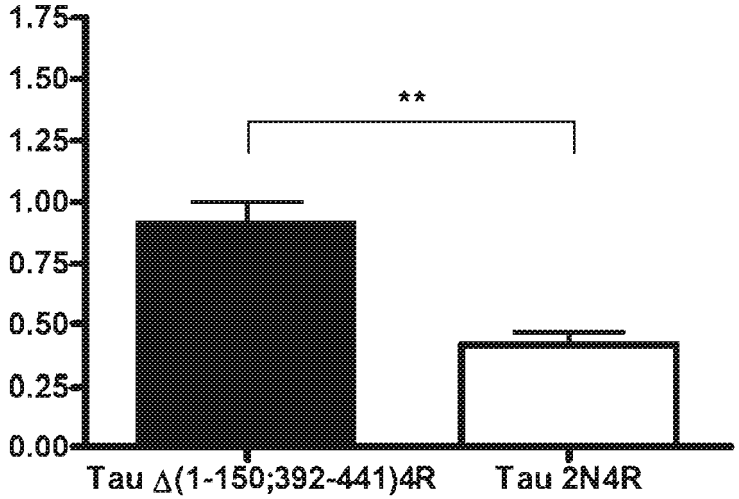


FIGURE 64

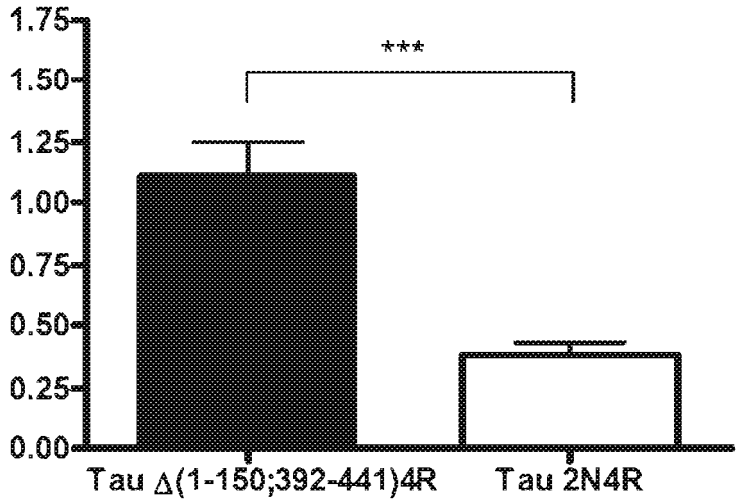


FIGURE 65

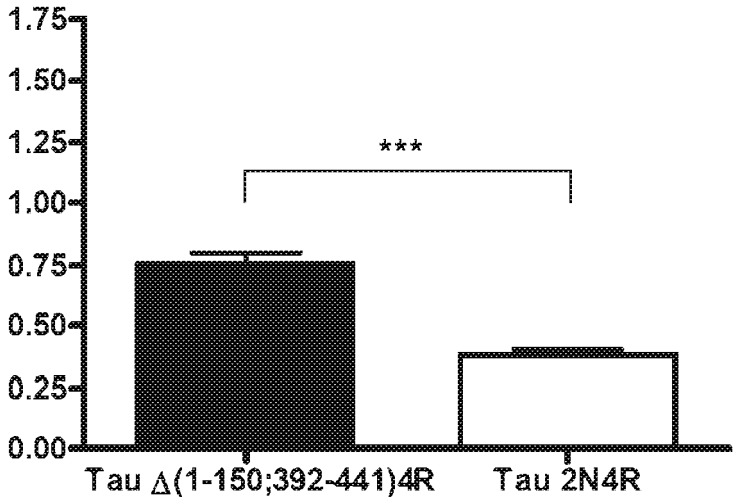


FIGURE 66

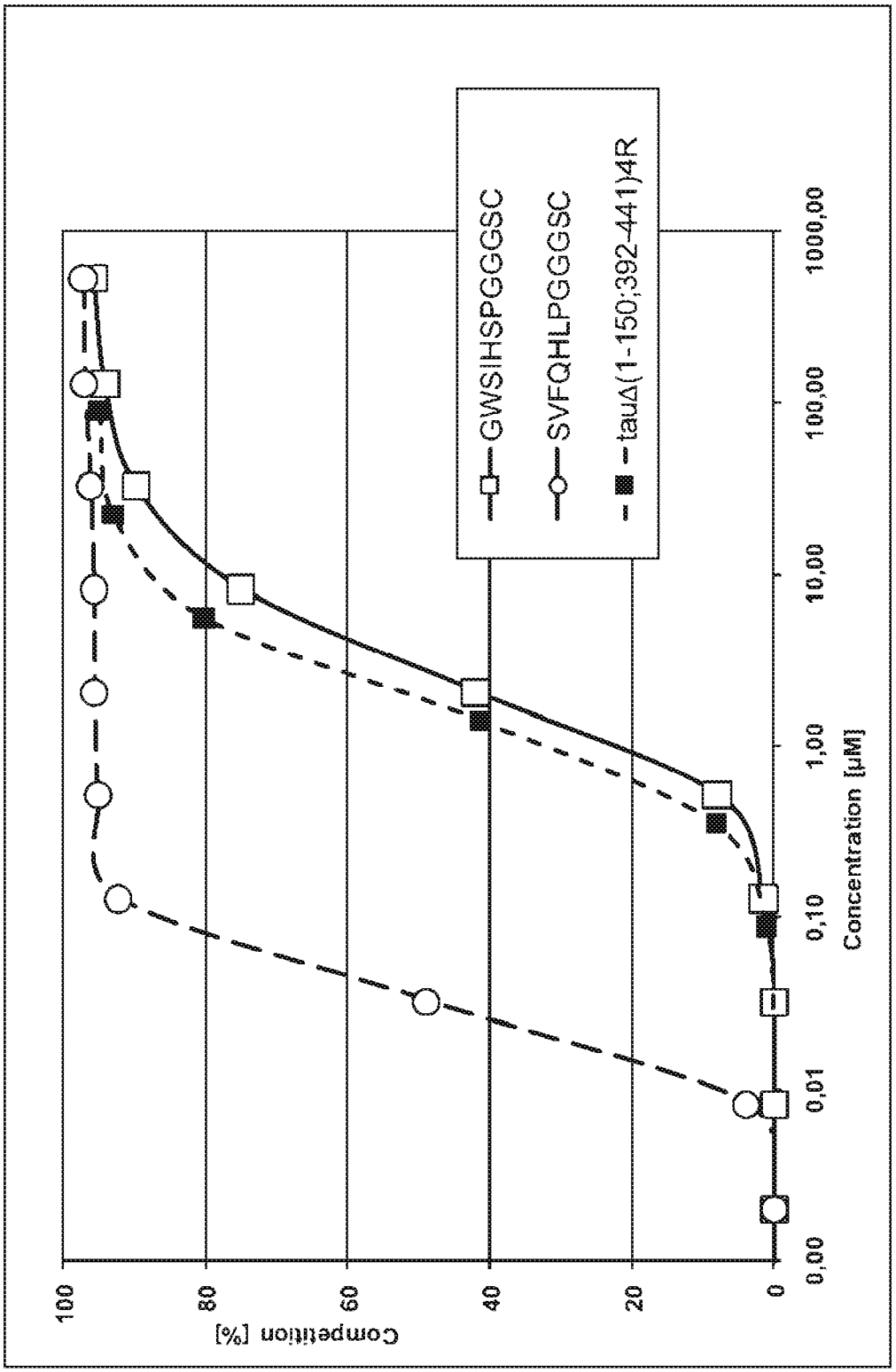

GWSIHSPGGGSC
SVFQHLPGGGSC
tauΔ(1-150;392-441)4R
Competition [%]
100
80
60
40
20
0
0,00
0,01
0,10
1,00
10,00
100,00
1000,00
Concentration [µM]

FIGURE 67

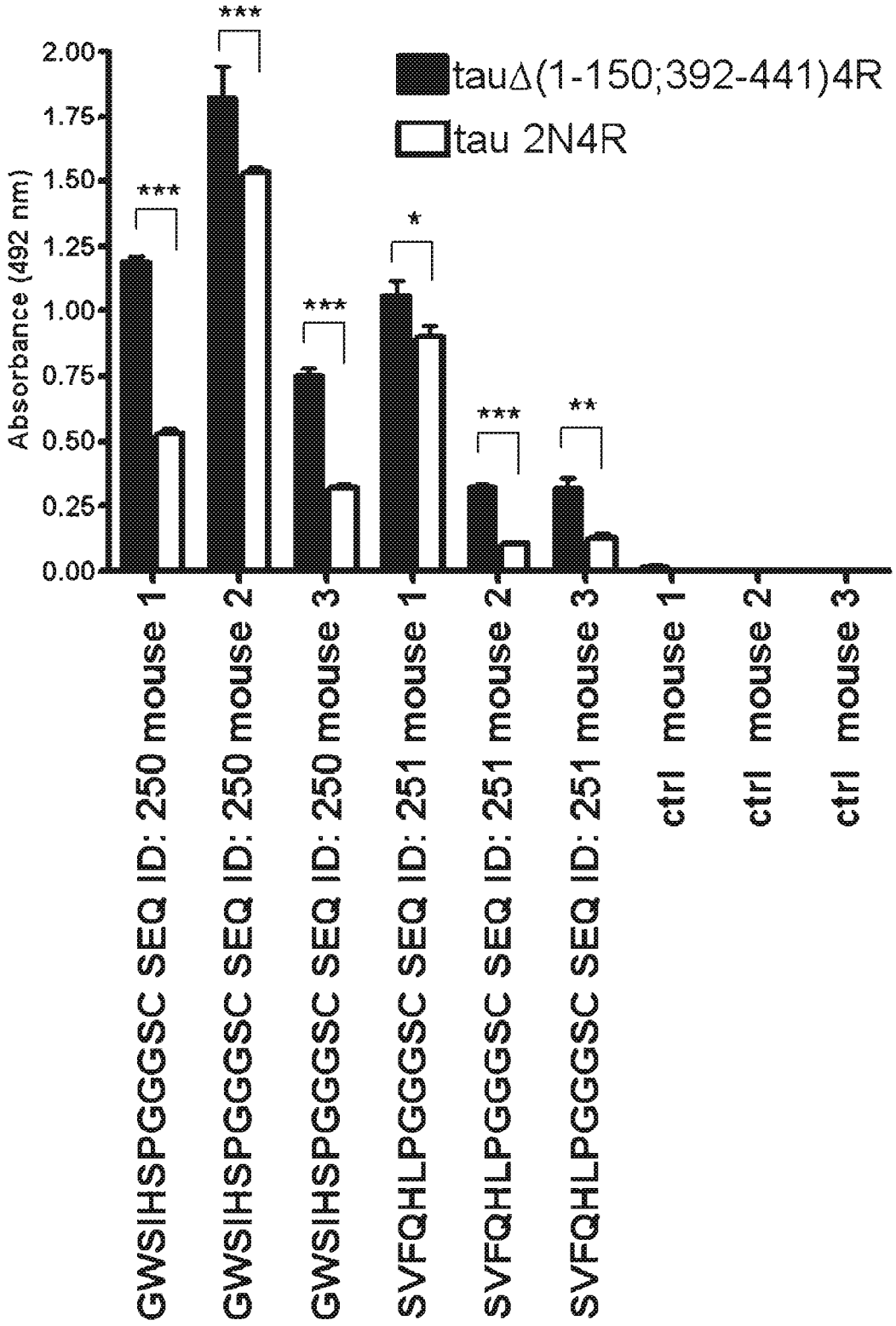

tauΔ(1-150;392-441)4R
tau 2N4R
Absorbance (492 nm)
2.00
1.75
1.50
1.25
1.00
0.75
0.50
0.25
0.00
***
***
***
*
***
**
GWSIHSPGGGSC SEQ ID: 250 mouse 1
GWSIHSPGGGSC SEQ ID: 250 mouse 2
GWSIHSPGGGSC SEQ ID: 250 mouse 3
SVFQHLPGGGSC SEQ ID: 251 mouse 1
SVFQHLPGGGSC SEQ ID: 251 mouse 2
SVFQHLPGGGSC SEQ ID: 251 mouse 3
ctrl mouse 1
ctrl mouse 2
ctrl mouse 3

FIGURE 68

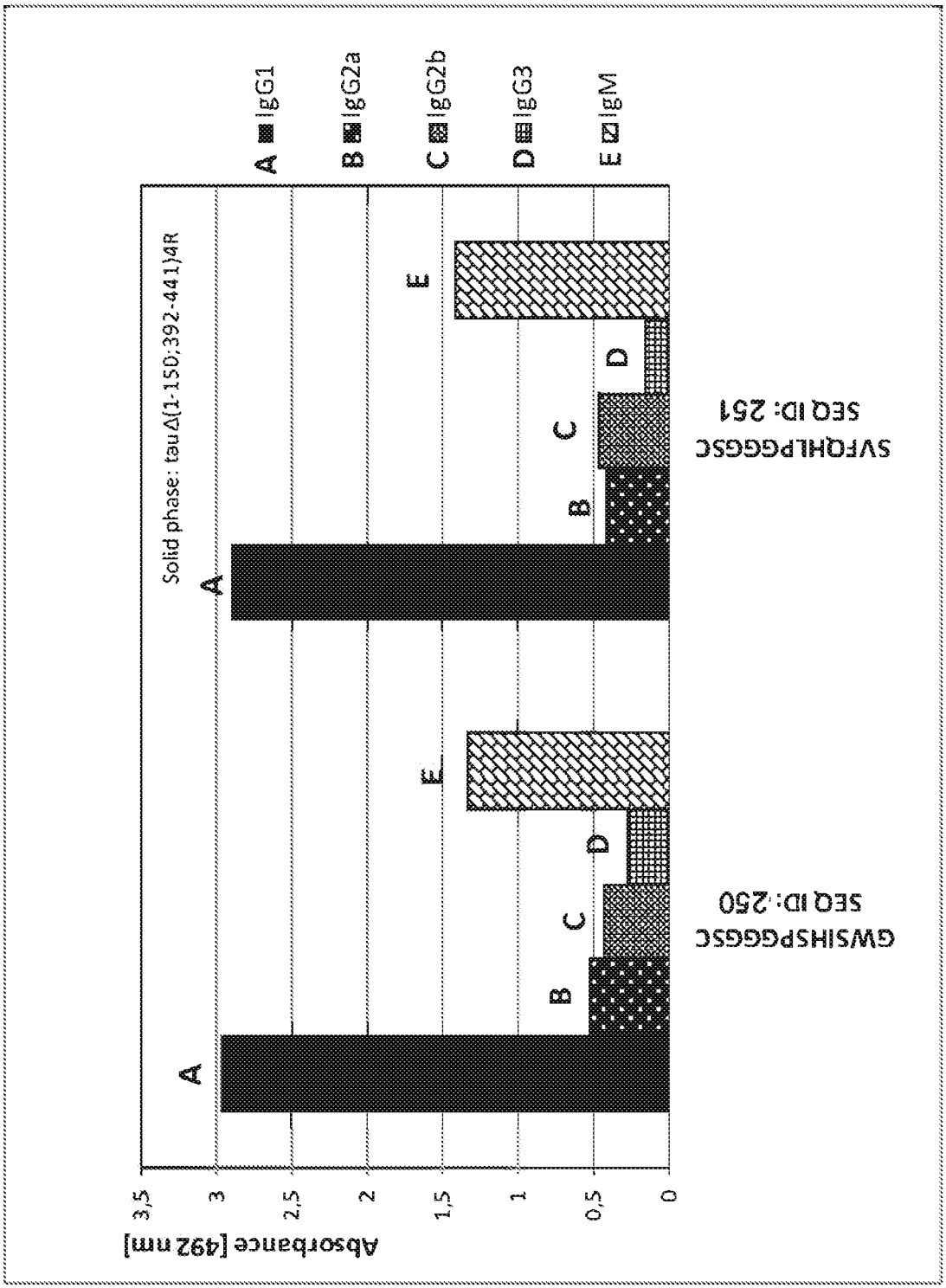
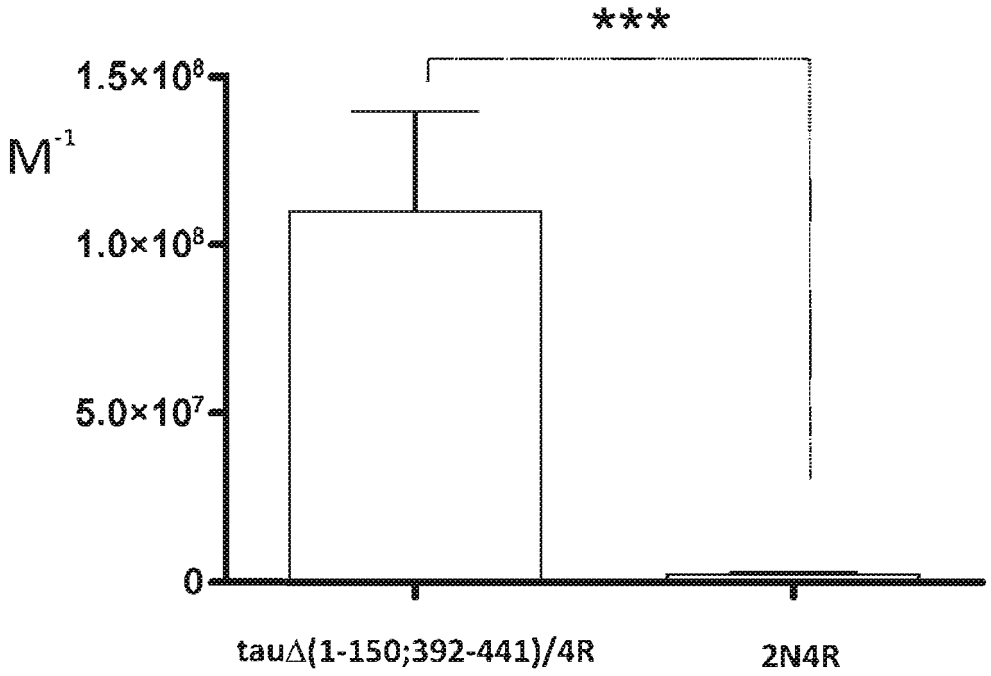

Absorbance [492 nm]
3,5
3
2,5
2
1,5
1
0,5
0
A IgG1
B IgG2a
C IgG2b
D IgG3
E IgM
Solid phase: tauΔ(1-150;392-441)4R
A
B
C
D
E
GWSIHSPGGGSC
SEQ ID: 250
SVFQHLPGGGSC
SEQ ID: 251

FIGURE 69A

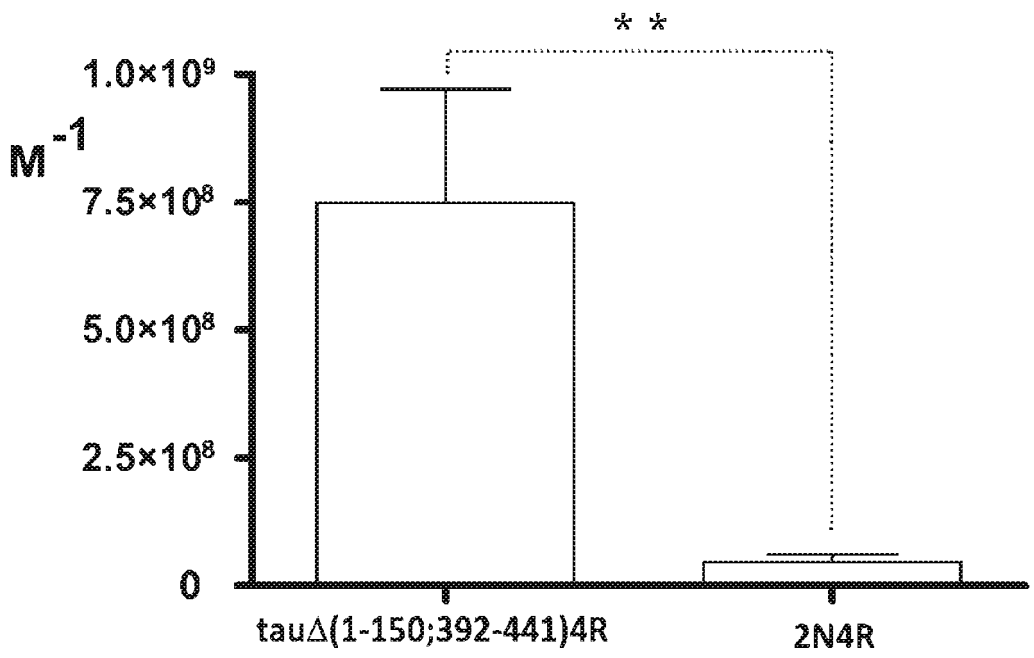
[GWSIHSPGGGSC (SEQ ID: 250)]



	K_A
tauΔ(1-150;392-441)4R	1.1±0.3x10^{8}M^{-1}
2N4R	2.3±0.7x10^{6}M^{-1}

FIGURE 69B

[SVFQHLPGGGSC (SEQ ID: 251)]



	K_A
tauΔ(1-150;392-441)4R	$7.5\pm2.2 \times 10^8 M^{-1}$
2N4R	$4.7\pm1.4 \times 10^7 M^{-1}$

FIGURE 70-A through F

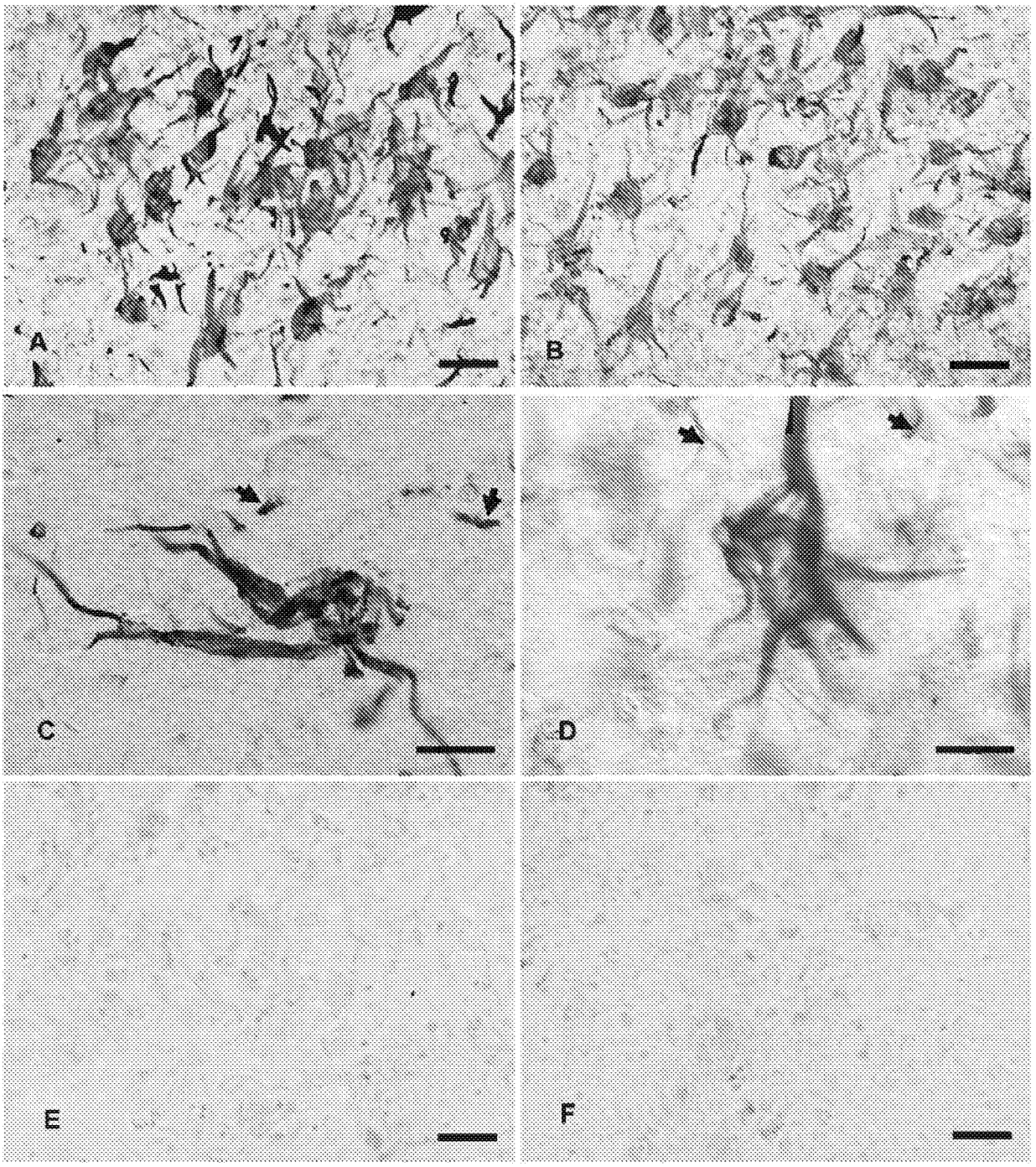


FIGURE 70 G-J

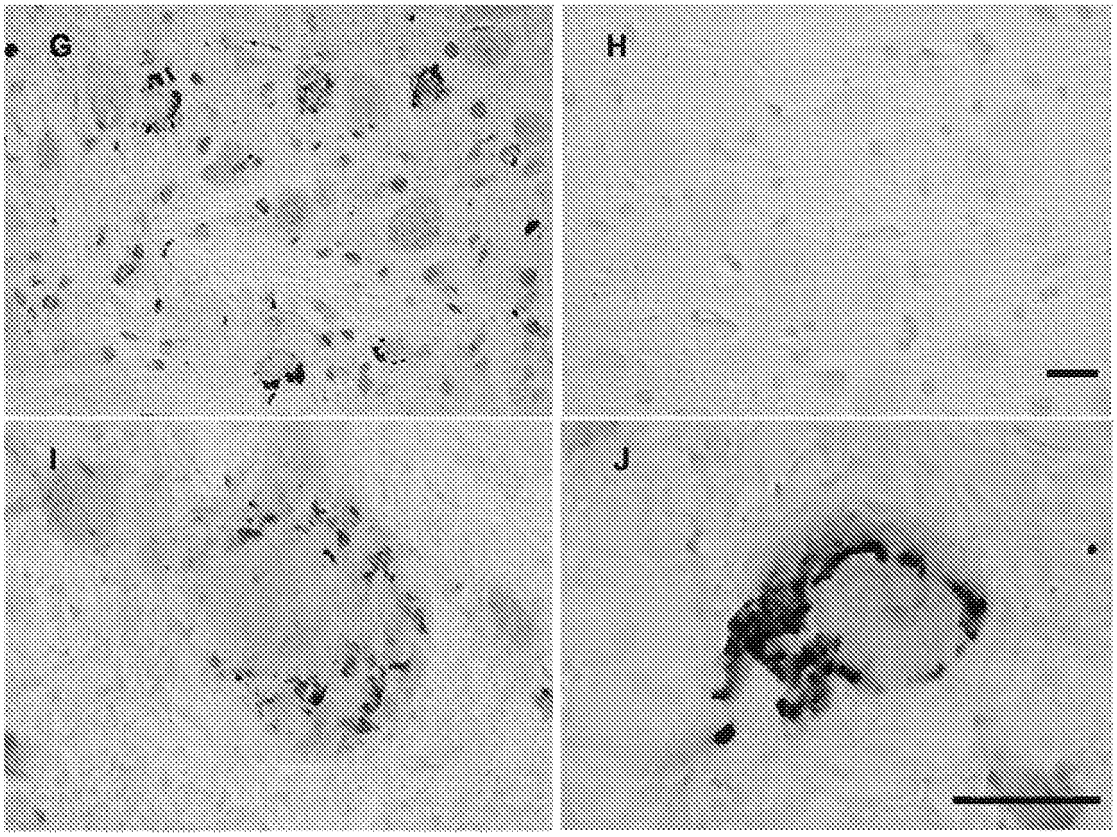


FIGURE 71

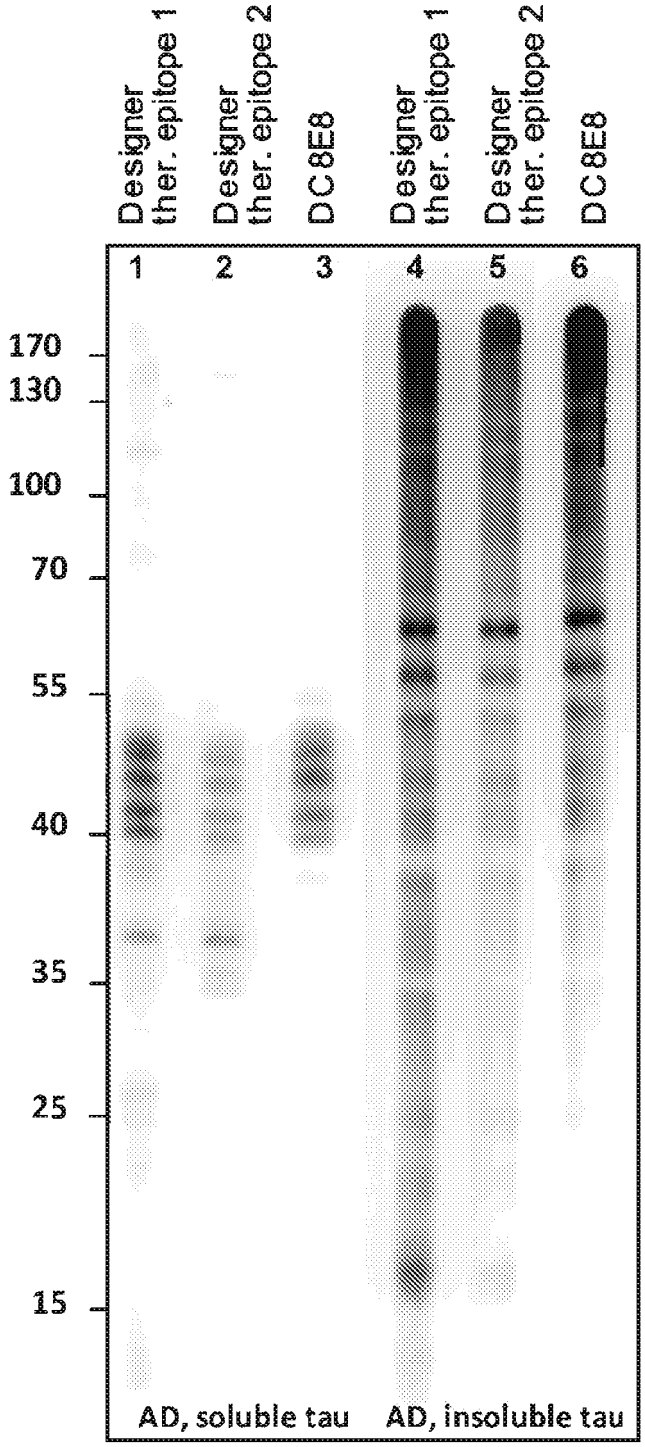

Designer ther. epitope 1
Designer ther. epitope 2
DC8E8
Designer ther. epitope 1
Designer ther. epitope 2
DC8E8
1
2
3
4
5
6
170
130
100
70
55
40
35
25
15
AD, soluble tau
AD, insoluble tau

FIGURE 72

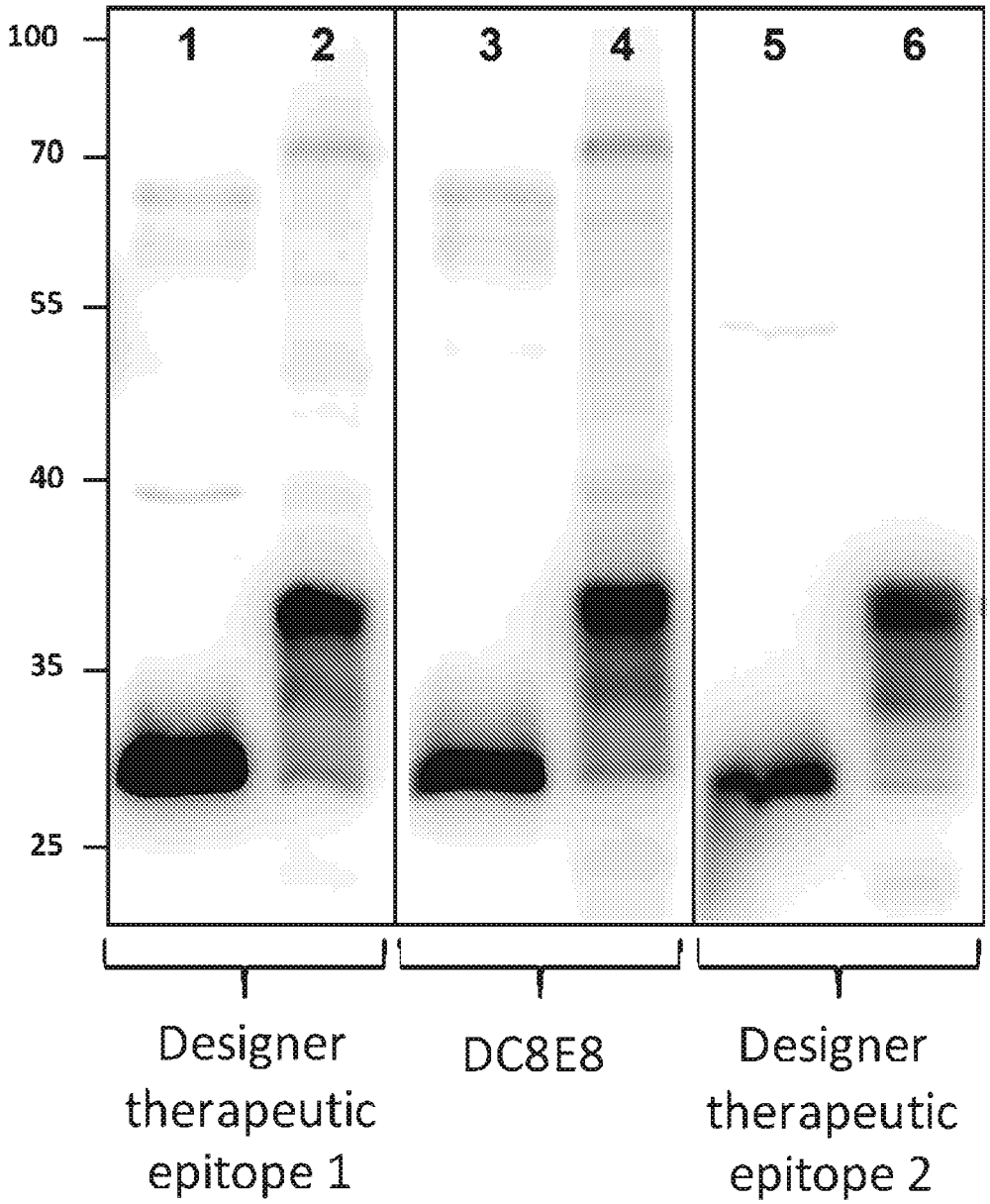
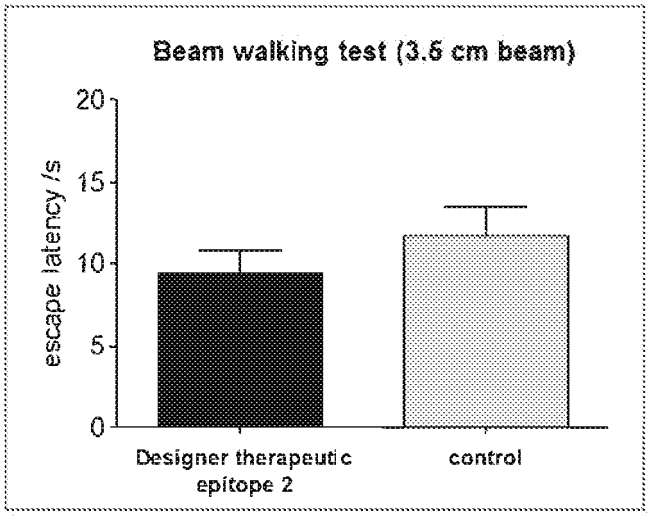
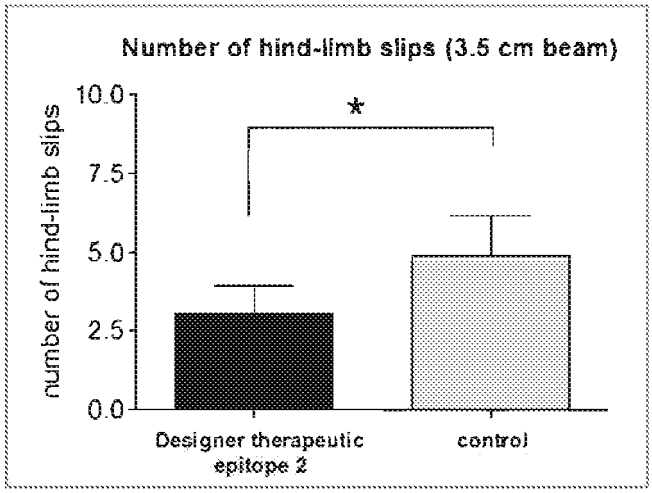

100
70
55
40
35
25
1
2
3
4
5
6
Designer therapeutic epitope 1
DC8E8
Designer therapeutic epitope 2

FIGURE 73

A.



B.



C.

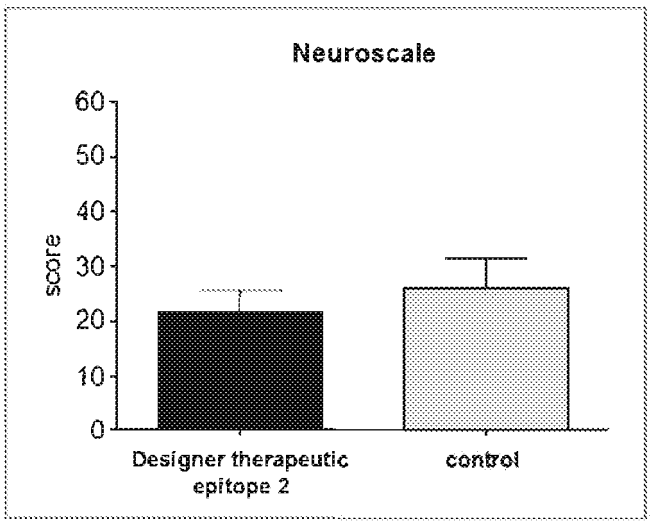
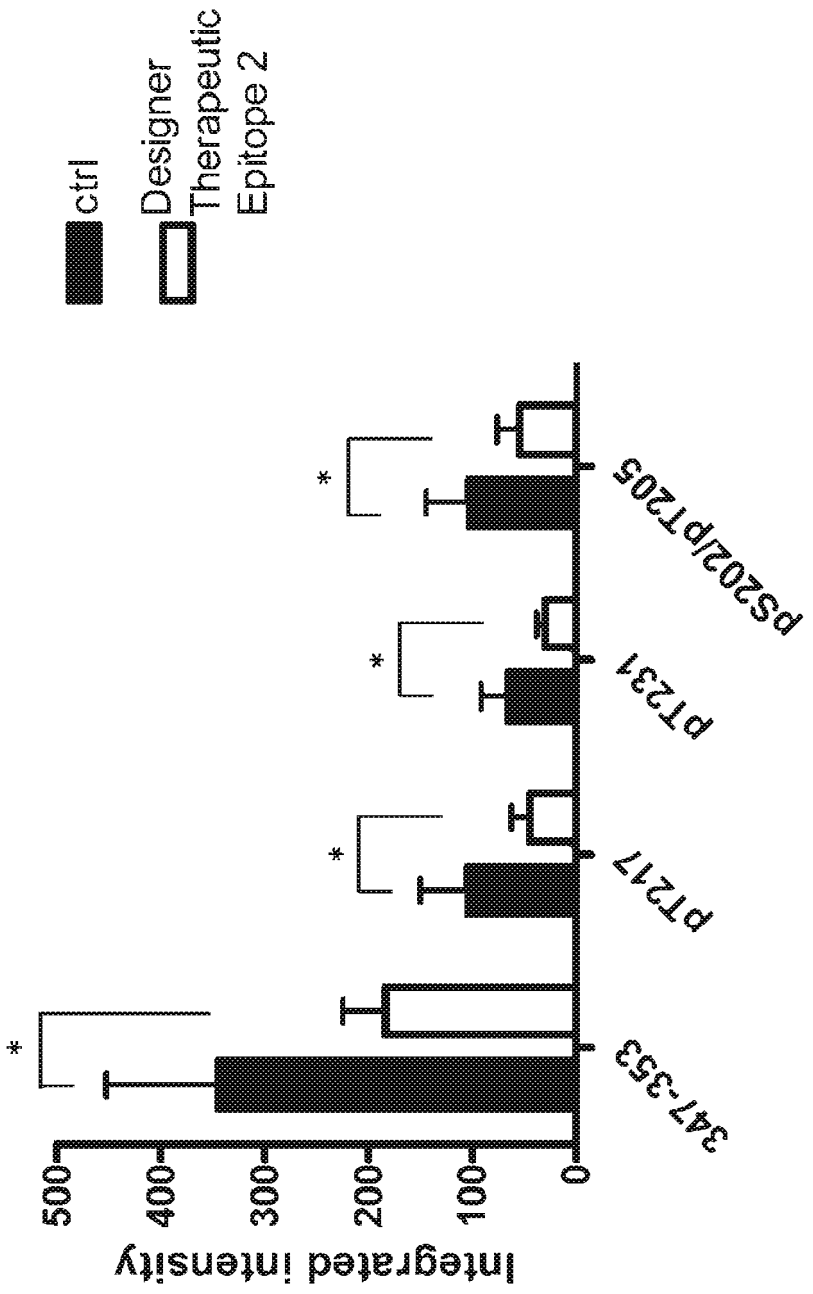


FIGURE 74


ctrl
Designer Therapeutic Epitope 2
Integrated intensity
0
100
200
300
400
500
347-353
pT217
pT231
pS202/pT205
*
*
*
*

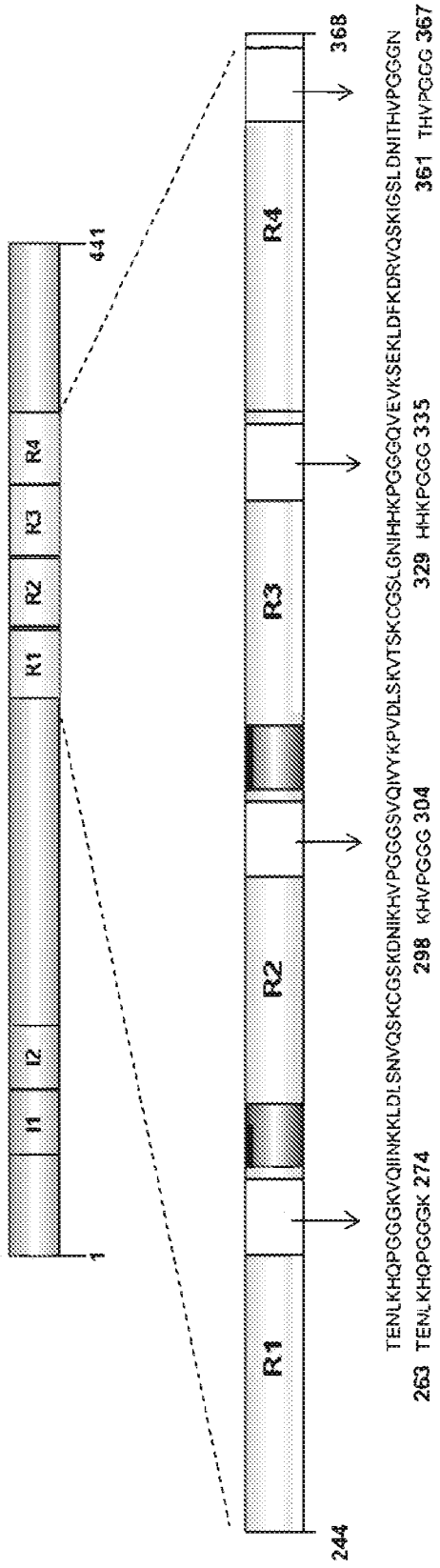

I1
I2
R1
R2
R3
R4
1
441
244
368
TENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGSVQIVYKPVDLSKVTSKCGSLGNIHHKPGGGQVEVKSEKLDFKDRVQSKIGSLDNITHVPGGGN
263 TENLKHQPGGGK 274
267 KHQPGGG 273
268 HQPGGG 273
268 HQPGG 272
269 QPGGG 273
264 ENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGS 305
298 KHVPGGG 304
299 HVPGGG 304
299 HVPGG 303
300 VPGGG 304
295 DNIKHVPGGGSVQIVYKPV 313
329 HHKPGGG 335
330 HKPGGG 335
361 THVPGGG 367

FIGURE 75A

FIGURE 75B

Synthetic peptide	SEQ ID NO	Sequence
Tau263-274	SEQ ID NO: 270	TENLKHQPGGGK
Tau267-273	SEQ ID NO: 271	KHQPGGG
Tau268-273	SEQ ID NO: 272	HQPGGG
Tau268-272	SEQ ID NO: 273	HQPGG
Tau269-273	SEQ ID NO: 274	QPGGG
Tau264-305	SEQ ID NO: 275	ENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPGGGS
Tau298-304	SEQ ID NO: 276	KHVPGGG
Tau299-304	SEQ ID NO: 277	HVPGGG
Tau299-303	SEQ ID NO: 278	HVPGG
Tau300-304	SEQ ID NO: 279	VPGGG
Tau295-313	SEQ ID NO: 280	DNIKHVPGGGSVQIVYKPV
Tau329-335	SEQ ID NO: 281	HHKPGGG
Tau330-335	SEQ ID NO: 282	HKPGGG
Tau361-367	SEQ ID NO: 283	THVPGGG

FIGURE 76

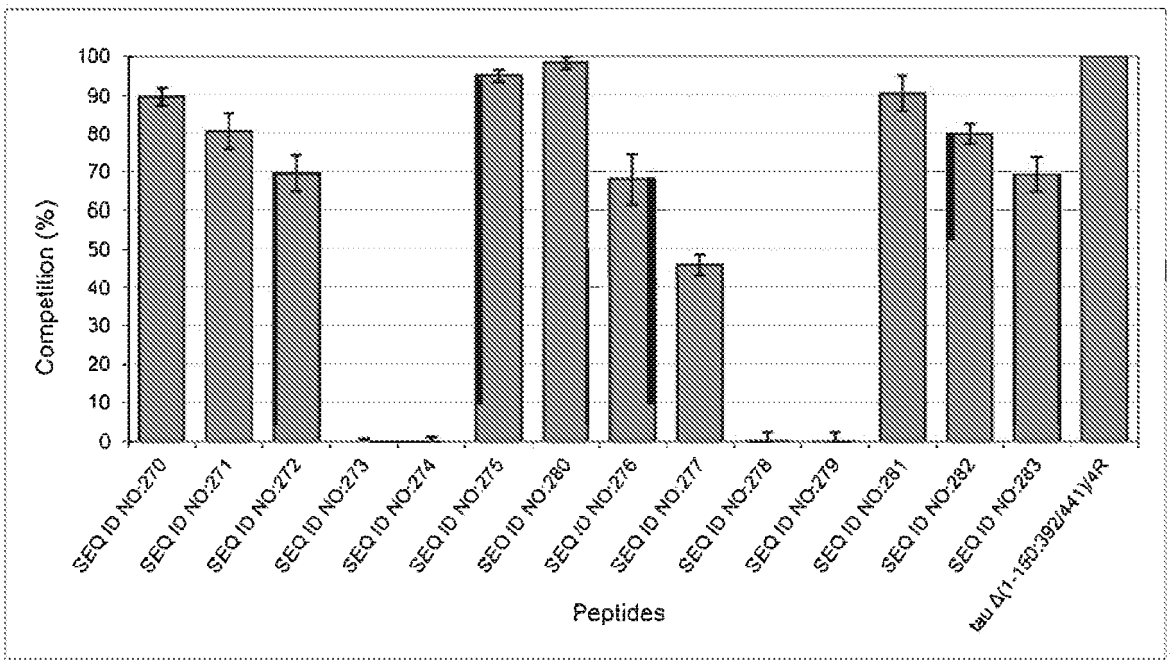

Competition (%)
100
90
80
70
60
50
40
30
20
10
0
SEQ ID NO:270
SEQ ID NO:271
SEQ ID NO:272
SEQ ID NO:273
SEQ ID NO:274
SEQ ID NO:275
SEQ ID NO:280
SEQ ID NO:276
SEQ ID NO:277
SEQ ID NO:278
SEQ ID NO:279
SEQ ID NO:281
SEQ ID NO:282
SEQ ID NO:283
tau Δ(1-150;392/441)4R
Peptides

Figure 77A

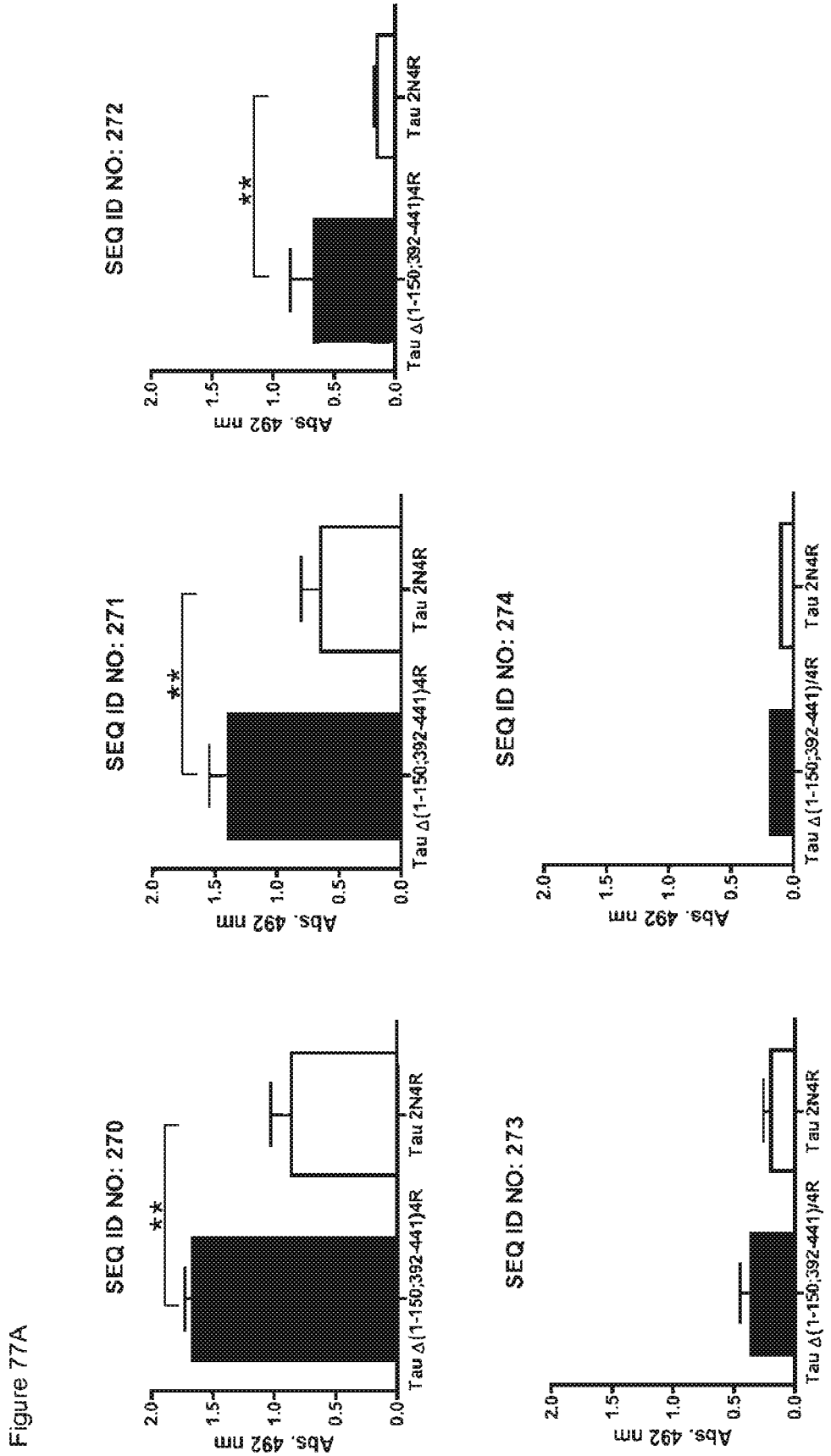
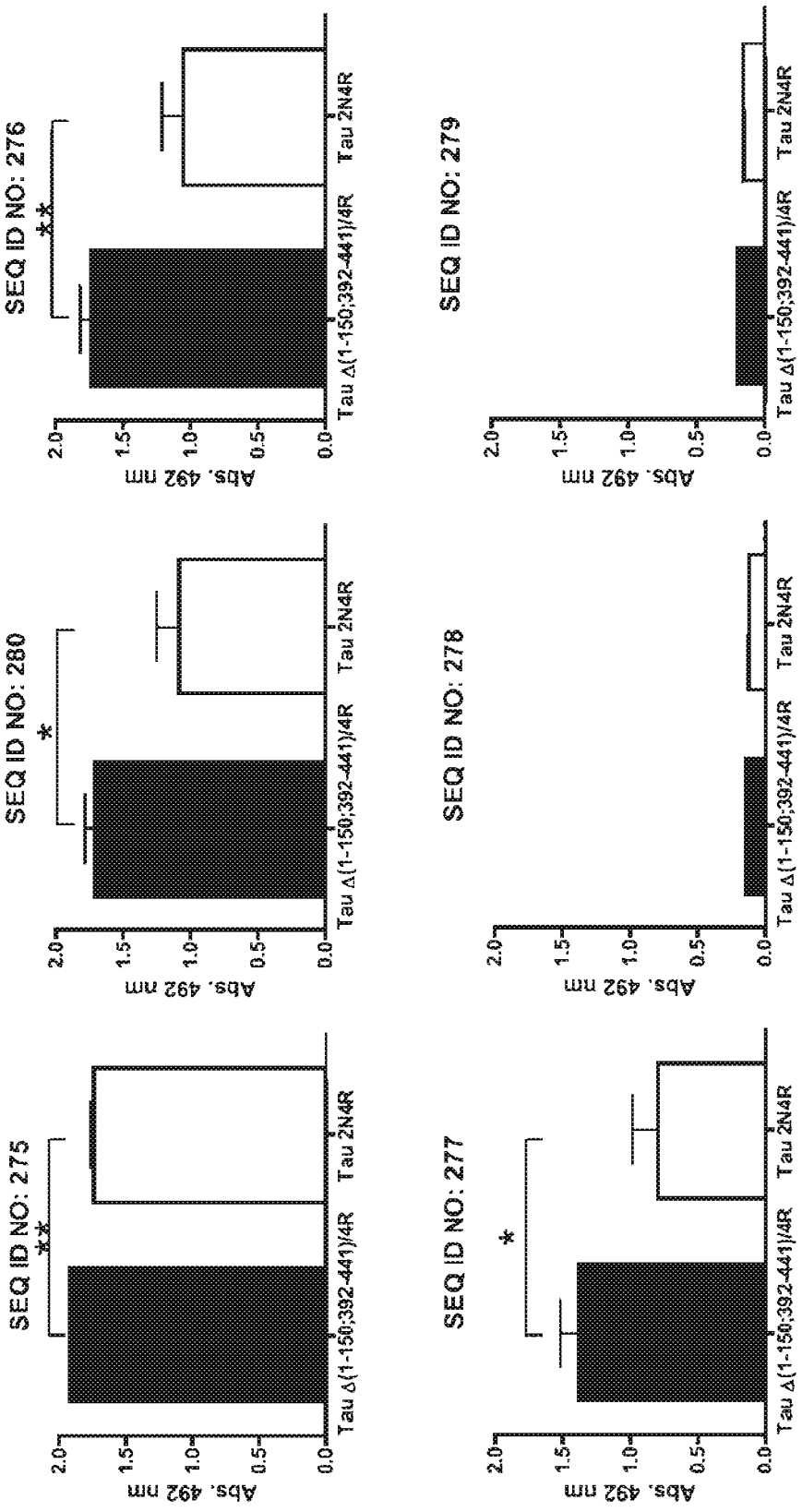

SEQ ID NO: 270
SEQ ID NO: 271
SEQ ID NO: 272
SEQ ID NO: 273
SEQ ID NO: 274
Abs. 492 nm
2.0
1.5
1.0
0.5
0.0
**
Tau Δ(1-150;392-441)4R
Tau 2N4R

FIGURE 77B


SEQ ID NO: 276
SEQ ID NO: 279
SEQ ID NO: 280
SEQ ID NO: 278
SEQ ID NO: 275
SEQ ID NO: 277
Abs. 492 nm
2.0
1.5
1.0
0.5
0.0
Tau Δ(1-150;392-441)/4R
Tau 2N4R

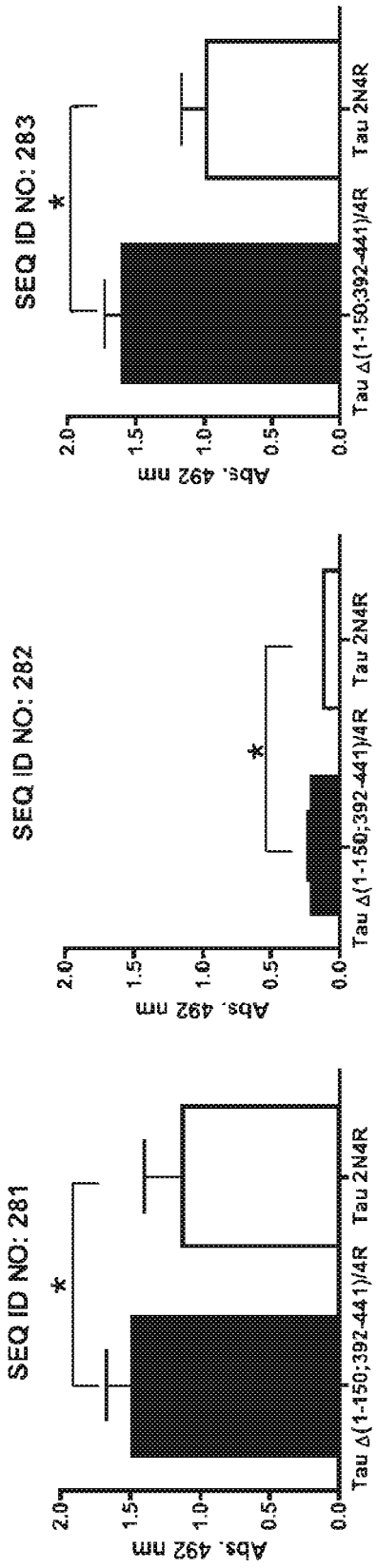

SEQ ID NO: 281
SEQ ID NO: 282
SEQ ID NO: 283
Abs. 492 nm
2.0
1.5
1.0
0.5
0.0
*
Tau Δ(1-150;392-441)/4R
Tau 2N4R

FIGURE 77C

FIGURE 78

Geometric mean antibody titers		
	solid phase	
Peptides	Tau Δ(1-150; 392-441)/4R	Tau 2N4R
SEQ ID NO: 270	22286	4222
SEQ ID NO: 271	12800	3200
SEQ ID NO: 272	2786	264
SEQ ID NO: 273	400	<100
SEQ ID NO: 274	152	0
SEQ ID NO: 275	>51200	16890
SEQ ID NO: 280	51200	12800
SEQ ID NO: 276	22286	4038
SEQ ID NO: 277	12800	3805
SEQ ID NO: 278	277	383
SEQ ID NO: 279	<100	<100
SEQ ID NO: 281	8445	2425
SEQ ID NO: 282	174	<100
SEQ ID NO: 283	14703	4222

FIGURE 79A

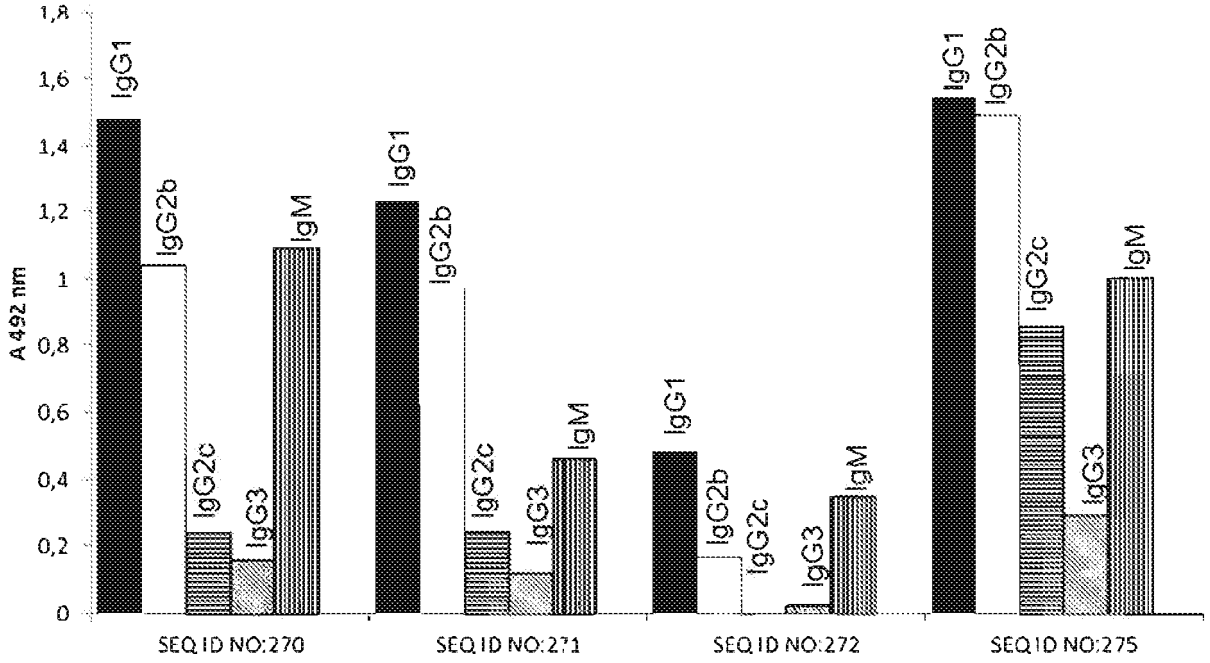

A 492 nm
1,8
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
IgG1
IgG2b
IgG2c
IgG3
IgM
SEQ ID NO:270
SEQ ID NO:271
SEQ ID NO:272
SEQ ID NO:275

FIGURE 79B

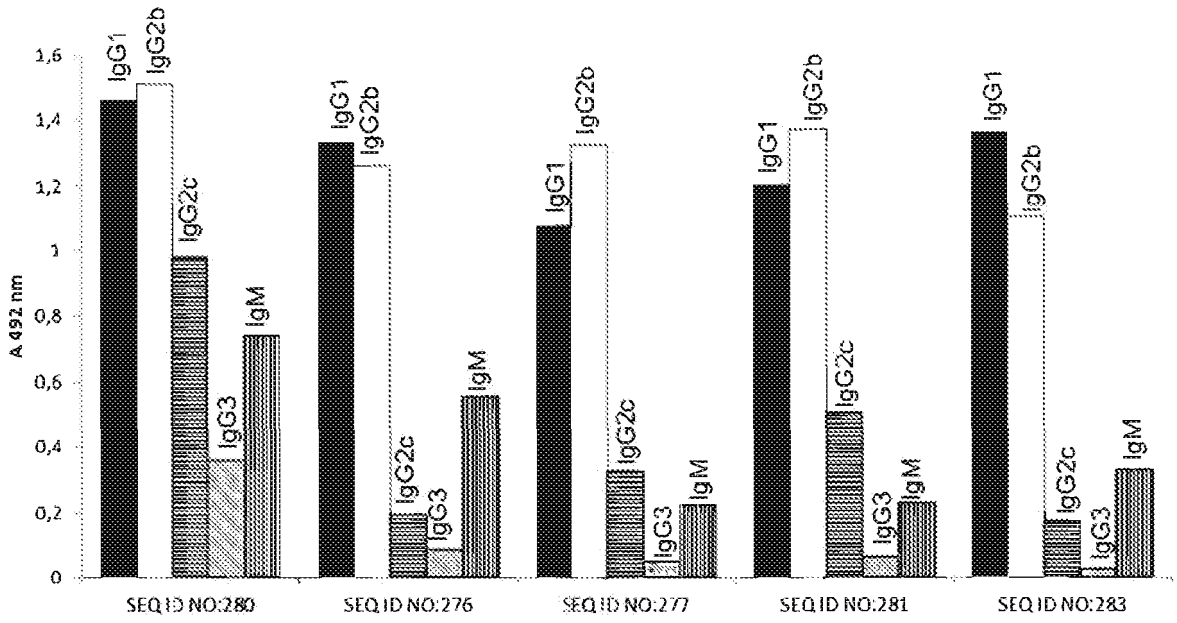

A 492 nm
1,6
1,4
1,2
1
0,8
0,6
0,4
0,2
0
IgG1
IgG2b
IgG2c
IgG3
IgM
SEQ ID NO:280
SEQ ID NO:276
SEQ ID NO:277
SEQ ID NO:281
SEQ ID NO:283

FIGURE 80

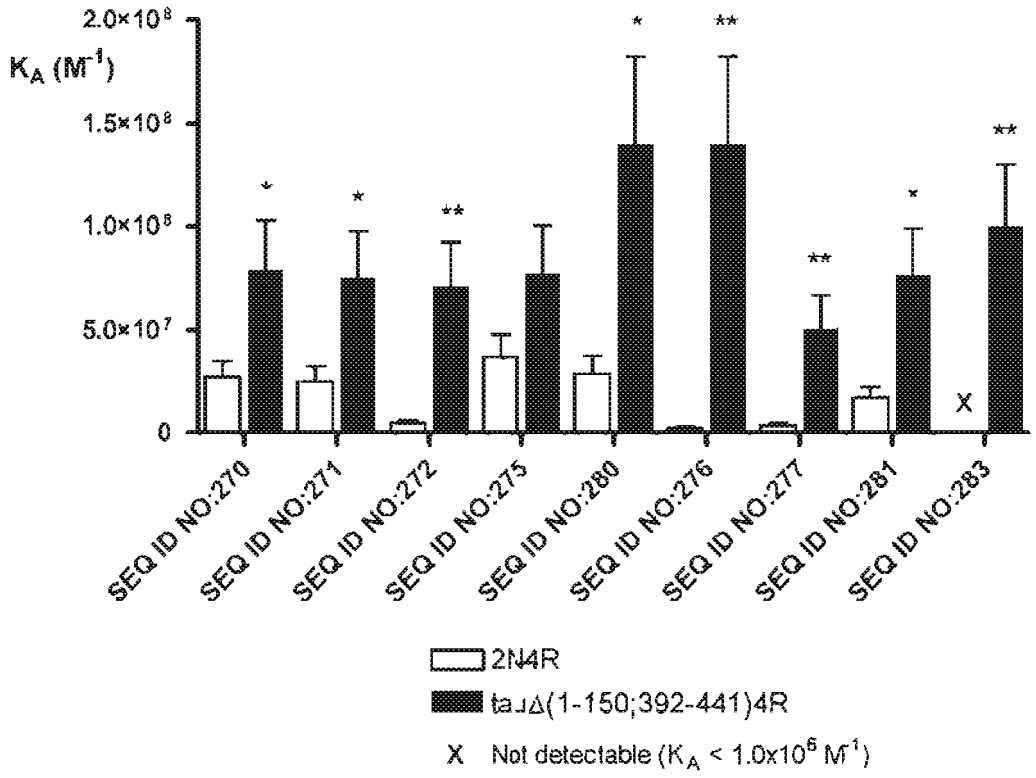

2.0×10⁸
K_A (M⁻¹)
1.5×10⁸
1.0×10⁸
5.0×10⁷
0
*
*
**
*
**
**
*
**
*
X
SEQ ID NO:270
SEQ ID NO:271
SEQ ID NO:272
SEQ ID NO:275
SEQ ID NO:280
SEQ ID NO:276
SEQ ID NO:277
SEQ ID NO:281
SEQ ID NO:283
2N4R
tauΔ(1-150;392-441)4R
X Not detectable (K_A < 1.0x10⁶ M⁻¹)

FIGURE 81

Pathological forms of tau recognized by tau peptides-induced antibodies in Western blot

Peptides	SHR 72 brain extract	AD brain extract
SEQ ID NO: 270	-	+
SEQ ID NO: 271	-	+
SEQ ID NO: 272	-	+
SEQ ID NO: 273	-	-
SEQ ID NO: 274	-	-
SEQ ID NO: 275	-	+
SEQ ID NO: 276	-	+
SEQ ID NO: 277	-	+
SEQ ID NO: 278	-	-
SEQ ID NO: 279	-	-
SEQ ID NO: 280	-	+
SEQ ID NO: 281	-	+
SEQ ID NO: 282	-	-
SEQ ID NO: 283	-	+

+ positive
- negative

FIGURE 82A

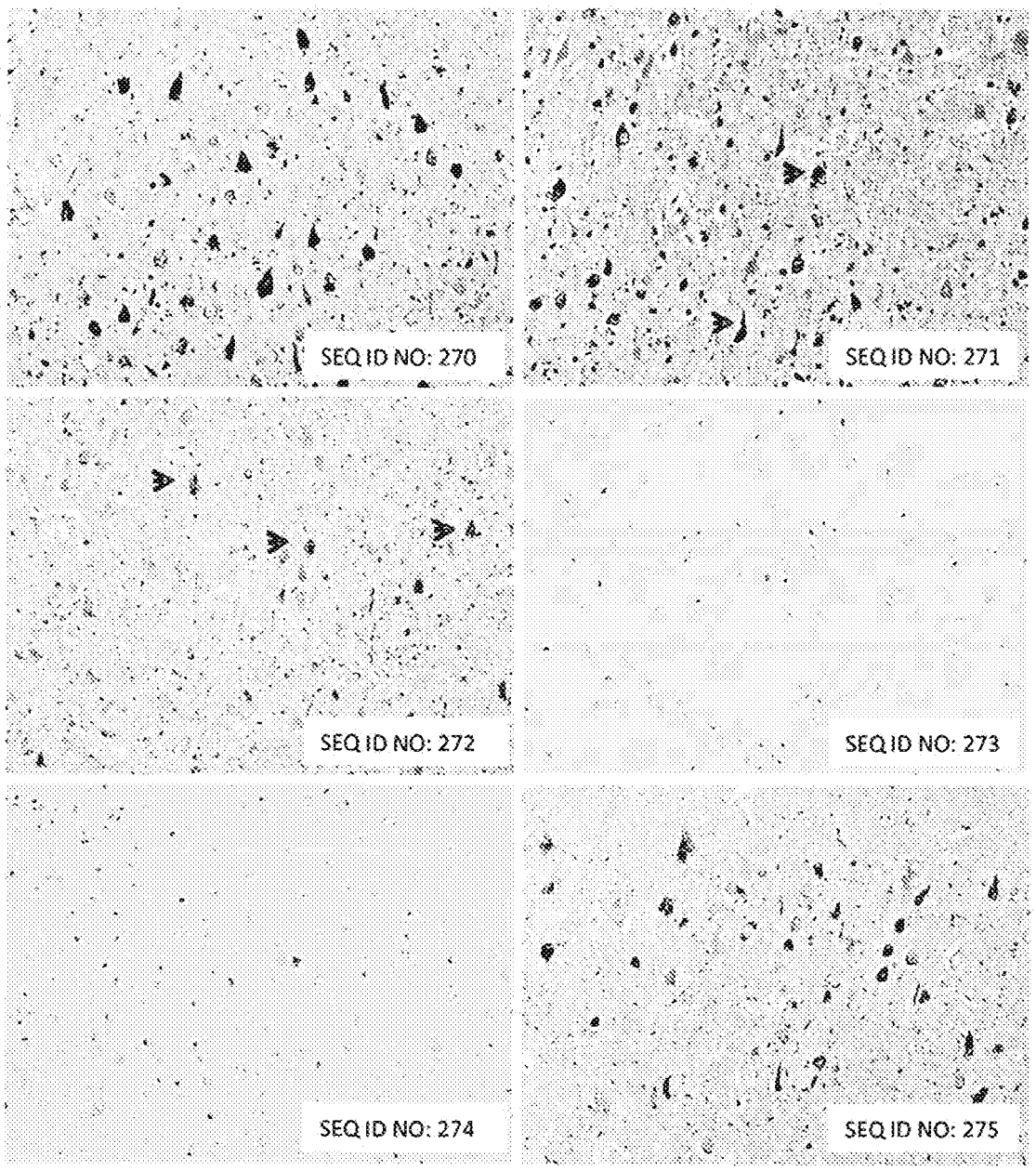

SEQ ID NO: 270
SEQ ID NO: 271
SEQ ID NO: 272
SEQ ID NO: 273
SEQ ID NO: 274
SEQ ID NO: 275

FIGURE 82B

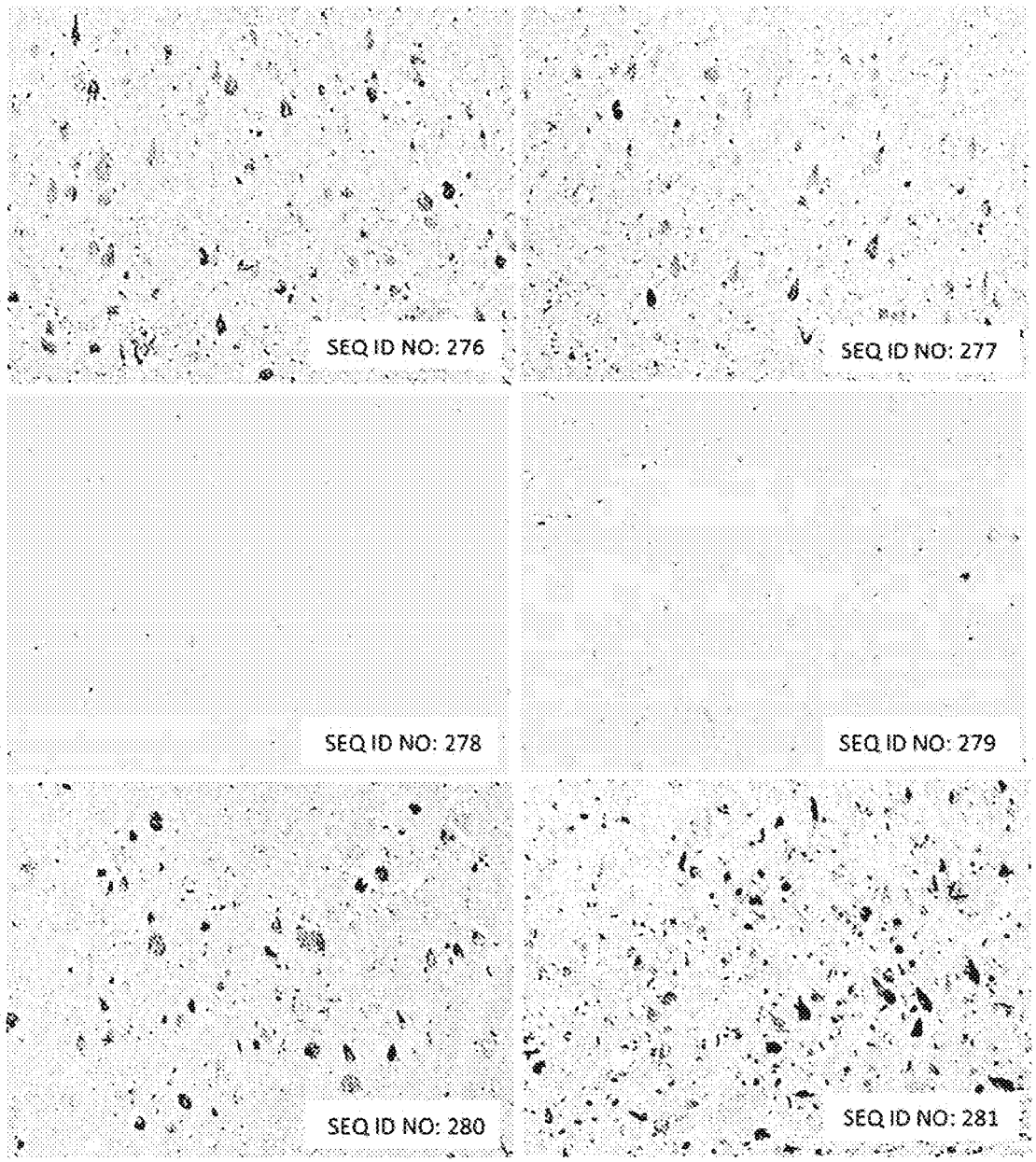

SEQ ID NO: 276
SEQ ID NO: 277
SEQ ID NO: 278
SEQ ID NO: 279
SEQ ID NO: 280
SEQ ID NO: 281

FIGURE 82C

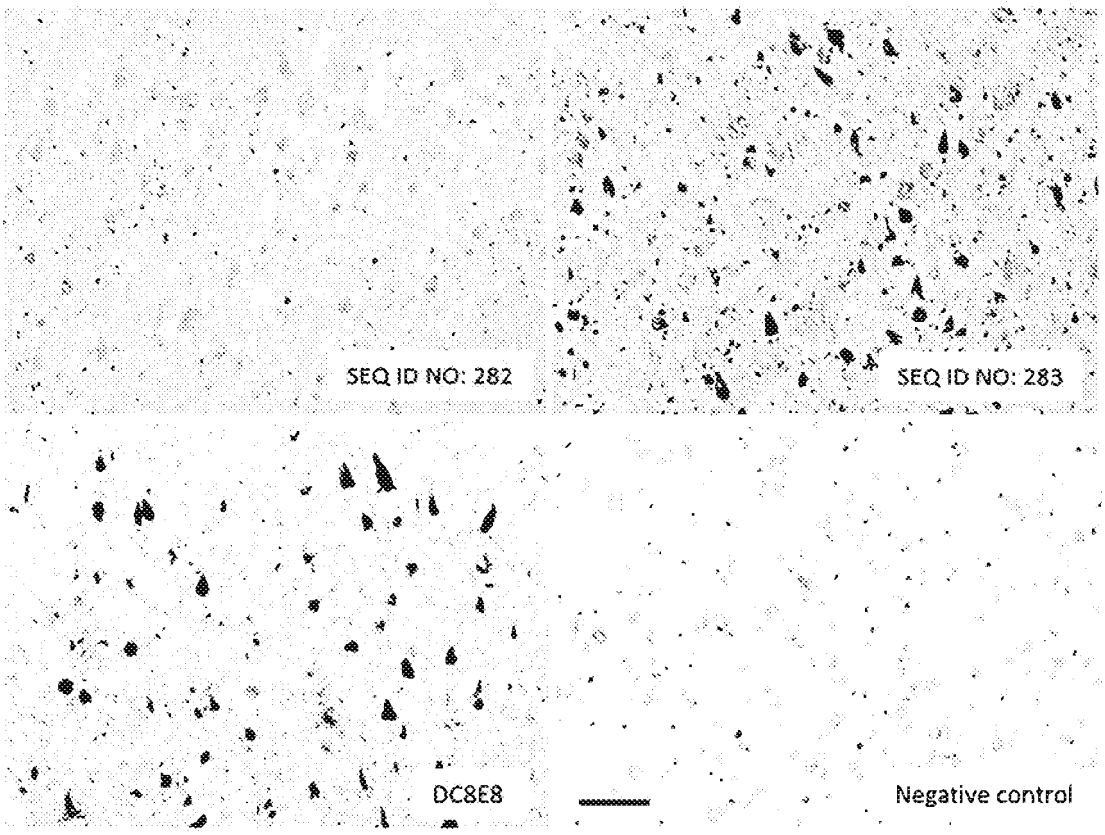


FIGURE 83

Neurofibrillary tangles recognized by tau peptide-induced antibodies in human AD brain tissues

Peptides	Intensity of staining	Number of NFTs
SEQ ID NO: 270	Very intensive staining of NFTs	+++
SEQ ID NO: 271	Intensive staining of NFTs	++
SEQ ID NO: 272	Weak staining of few NFTs	+
SEQ ID NO: 273	No NFT staining	-
SEQ ID NO: 274	No NFT staining	-
SEQ ID NO: 275	Very intensive staining of NFTs	+++
SEQ ID NO: 280	Intensive staining of NFTs	+++
SEQ ID NO: 276	Intensive staining of NFTs	+++
SEQ ID NO: 277	Weak staining of NFTs	++
SEQ ID NO: 278	No NFT staining	-
SEQ ID NO: 279	No NFT staining	-
SEQ ID NO: 281	Intensive staining of NFTs	++
SEQ ID NO: 282	No NFT staining	-
SEQ ID NO: 283	Very intensive staining of NFTs	+++