

FIGURE 1

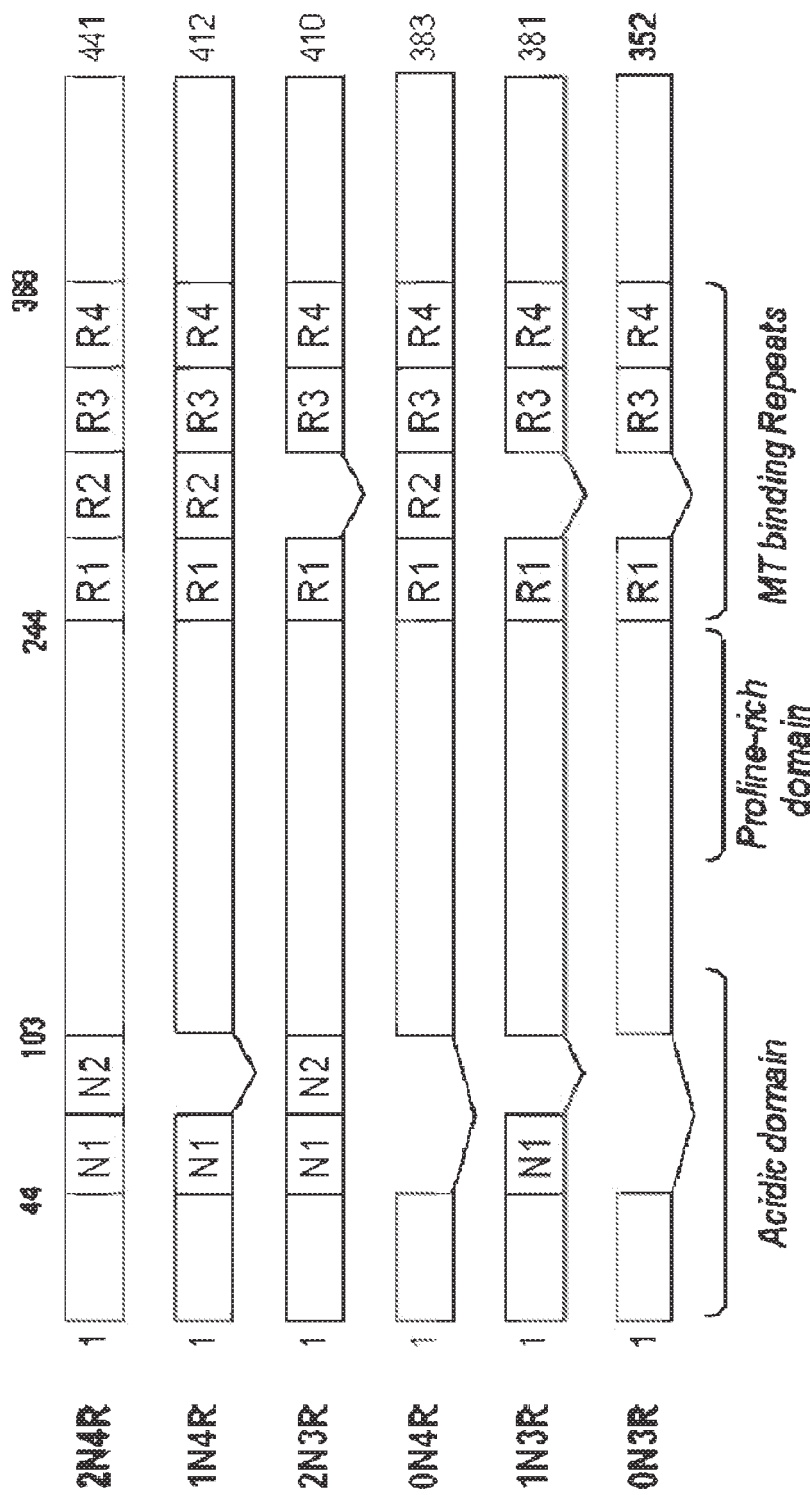


FIGURE 2

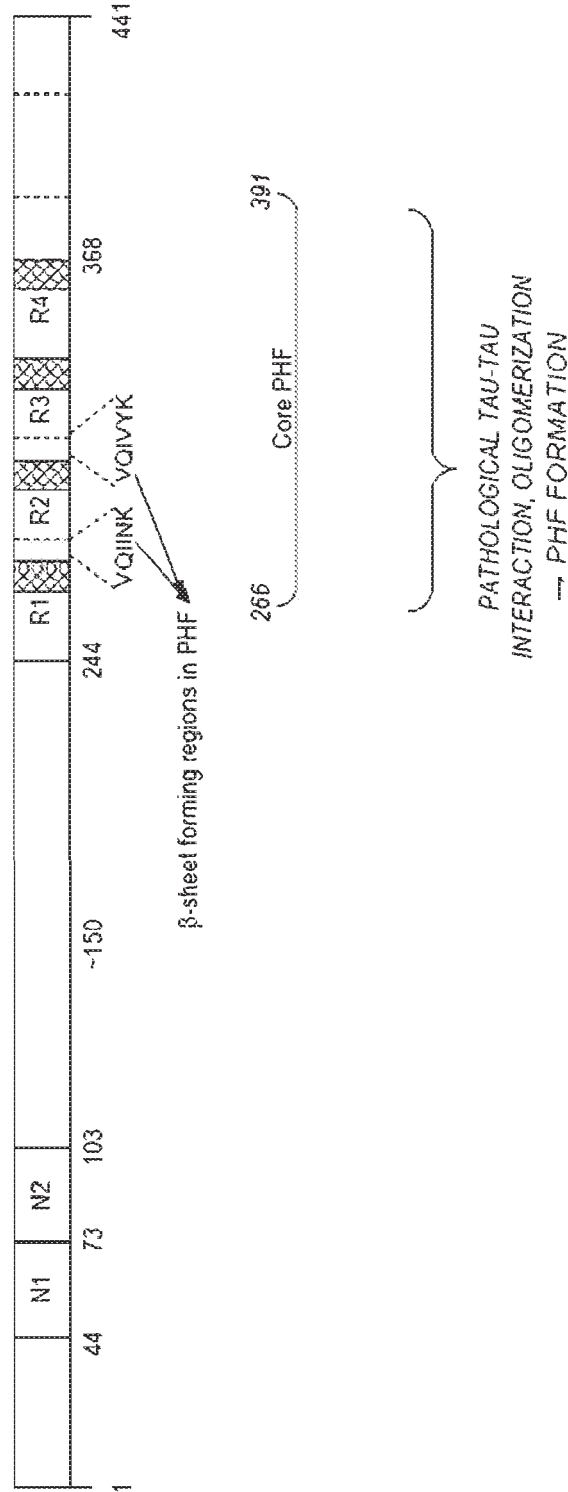


FIGURE 3

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

GACATTGTGATGTCAAGTCTCCATCCCTCGCTGTGTGACAGGAGAGAGGTCACTATGAGCTGCAAAATCCAGTCAGAGTCTGCTC
 AACAGTAGAACCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACACAGGCAGTCTCTAACTGCTGATCTACTGGGCATCCACTAGG
 GAATCTGGGGTCCCTGATCGCTTCAACAGGACGTGATCTGGGACAGATTTCACCTCTCACCATCAGCAGTGTGCAAGGCTGAAGACCTGGCA
 GTTTATTACTGCAAGCAATCTTTTATCTTCGACGTTCCGGTGGAGGCCAACCAAGCTGGACATCAAA

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

DIVMSQSPSSLA~~V~~SA~~G~~GEKVTMSCKSSQSL~~L~~NSRTRK~~N~~YLAWYQQKPGQSPKLLIYWASTRESGV~~P~~DRFTGSGSGTDFTLTIS~~S~~VQAEDLA
 VY~~Y~~CKQSEFYLR~~T~~FGG~~T~~KL~~D~~IK

CDR1: QSLNSRTRKNY

CDR2: WAS

CDR3: KQSFYLR

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 GACATTGTGATGTCAAGTCTCCATCCCTCGCTGTGTGTCAGCAGGAGA

IGKV8-21*01 GACATTGTGATGTCAAGTCTCCATCCCTCGCTGTGTGTCAGCAGGAGA

DC8E8 light

GAAGTCACTATGAGCTGCAAAATCCAGTCAGAGTCTGCTCAACAGTAGAA

IGKV8-21*01

GAAGTCACTATGAGCTGCAAAATCCAGTCAGAGTCTGCTCAACAGTAGAA

DC8E8 light

CCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACAGGGCAGTCTCT

IGKV8-21*01

CCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACAGGGCAGTCTCT

DC8E8 light

AAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCIGATCG

IGKV8-21*01

AAACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCIGATCG

DC8E8 light

CTTCACAGGCAGTGGATCTGGGACAGATTTCACCTCTCACCATCAGCAGTG

IGKV8-21*01

CTTCACAGGCAGTGGATCTGGGACAGATTTCACCTCTCACCATCAGCAGTG

DC8E8 light TGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTTTATCTT
 IGKV8-21*01 TGCAGGCTGAAGACCTGGCAGTTTATTACTGCAAGCAATCTTATAATCTT

DC8E8 light C
 IGKV8-21*01 C
 *

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

DC8E8 light GGACGTTCCGGTGGAGGCACCAAGCTGGACATCAAAC
 IGKJ1*01 GGACGTTCCGGTGGAGGCACCAAGCTGGAAATCAAAC

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

CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCTGGACTTCAGTGAAGATGCCCTGTAAAGCTTCTGGATACATATTCAC
 GACTATGTCATAAGCTGGTGAAGCAGAGAACTGGACAGGGCCTTGAGTGGATTGGAGAGATTTTCTAGAAAGTGGTAGTACTTACTAC
 AATGAGAAAGTTCAAGGCAAGGCCACACTGACTGCAGACAAATCCTCCAACACAGCCTACATGCAGCTCAGCAGCGTGACATCTGAGGAC
 TCTGCGGTCTATTCTGTGCAAGAGATTACTACGGTACTTTCATTTGCTATGGACTACTGGGTCAAGGAACCTCAGTCACCGTCTCCTCA

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

QVQLQQSGPELVKPGTSVKMPCKASGYIFTDYVISWVKQRTGQGLEWIGEIFPRSGSTYYNEKFKGKATLTADKSSNTAYMQLSSVTSED
 SAVYFCARDYYGTSFAMDYWGQTSVTVSS

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 CAGGTTCAAGTCCAGCAGTCTGGAGCTGAGCTGGCGAGGCCCTGGGGCTTC

DC8E8 heavy AGTGAAGATGCCCTGTAAAGGCTTCTGGATACATATTCAGTACTATGTCA
IGHV1-81*01 AGTGAAGCTGTCTGCAAGGCTTCTGGCTACACCTTCACAAGCTATGGTA
***** ** ***** ***** ***** ***** *

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

DC8E8 heavy ATTTTTCCTAGAAAGTGGTAGTACTTACTACAAATGAGAAAGTTCAAGGGCAA
IGHV1-81*01 ATTTATCCTAGAAAGTGGTAATACTTACTACAAATGAGAAAGTTCAAGGGCAA
***** ***** ***** ***** ***** *****

DC8E8 heavy GGCCACACTGACTGCAGACAAATCCTCCAACACAGCCTACATGCAGCTCA
IGHV1-81*01 GGCCACACTGACTGCAGACAAATCCTCCAACACAGCCTACATGCAGCTCC
***** ***** ***** ***** ***** *****

DC8E8 heavy GCAGCGTGACATCTGAGGACTCTGCGGTCTATTCTGTGCAAGA
IGHV1-81*01 GCAGCGTGACATCTGAGGACTCTGCGGTCTATTCTGTGCAAGA
***** ***** ***** ***** ***** *****

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 TTCATTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
IGHJ4*01 TTACTATGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCC
** * ***** ***** ***** ***** ***** *****

DC8E8 heavy TCAG
IGHJ4*01 TCAG

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

gggctgctgcacaaactgtatccatcttcccaccatccagtgagcagttaacatctggaggtgcctcagtcgctgtgttgaaca
acttctaccccaagacatcaatgtcaggtggaagattgatggcagtgaaacgacaaaaatggcgtcctgaaacagttggactgatcaggaca
gcaaagacagcacctacagcatgagcagcacctcacgttgaccaaggacgagtatgaaacgacataaacagctatatacctgtgaggcca

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

ccaaaacgacaccccccatctgtctatccactggccccctggatctgtgccccaaactaaactccatggtgaccctgggatgcctggtcaagg
gctatttccctgagccagtgacagtgacctctggatccctgtccagcgggtgtgcacaccttcccagctgtcctgcagctctgacc
tctacactctgagcagctcagtgactgtccccctccagcacctggccccagcgagacogtcacctgcaacgttgccccccggccagcagca
ccaagg

FIGURE 4

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

DC8E8 GACATTGTGATGTCACAGTCTCCATCCCTGGCTGTGTCTGACAGGAGA
 IGKV4-1*01_Homo+sapiens GACATCGTGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTGCGCGA
 ***** * ***** * ***** * ***** * ***** * ***** *

DC8E8 GAAGTCACTATGAGCTGCAAAATCCAGTCAGAGTCTGCTCAACAGTAGAA
 IGKV4-1*01_Homo+sapiens GAGGCCACCATCAACTGCAAGTCCAGCCAGAGTGTTTTATACAGTCCA
 ** ** ** *

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

DC8E8 AACTGCTGATCTACTGGGCATCCACTAGGGAATCTGGGGTCCCTGATCG
 IGKV4-1*01_Homo+sapiens AAGCTGCTCATTTACTGGGCATCTACCCGGGAATCCGGGTCCCTGACCG
 ** ***** ** ***** * * * * * * * * * * * * * * * * * *

DC8E8 CTTACAGGCAGTGGATCTGGGACAGATTTCACCTCACCATCAGCAGTG
 IGKV4-1*01_Homo+sapiens ATTACAGTGGCAGCGGTCTGGGACAGATTTCACCTCACCATCAGCAGCC
 **** *

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

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

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

DC8E8 --GGACGTTCTGGTGGAGGCCACCAAGCTGGACATCAAAC
 IGKJ1*01_Homo+sapiens_J-REGION GTGGACGTTCTGGCCCAAGGACCAAGCTGGAAATCAAAC
 ***** *

FIGURE 5

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

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DC8E8 heavy_V      CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCCTGGGACTTC
IGHV1-69*10_Homo+sapiens CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCTGGGTCCTC
***** ** ***** ** ***** ** ***** * **
DC8E8 heavy_V      AGTGAAGATGCCCTGTAAAGCTTCTGGATACATATTCACTGACTATGTCA
IGHV1-69*10_Homo+sapiens AGTGAAGGTCTCCTGCAAGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
***** * **** ***** ** ***** ** ***** *
DC8E8 heavy_V      TAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCCTTGAGTGGATTGGAGAG
IGHV1-69*10_Homo+sapiens TCAGCTGGGTCCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGAGGG
***** ** ***** ** ***** ** ***** *
DC8E8 heavy_V      ATTTTCCTAGAAGTGGTAGTACTTACTACAAATGAGAAGTTCAGGGCAA
IGHV1-69*10_Homo+sapiens ATCATCCCTATCCTTGGTATAGCAAACTACGCCACAGAAGTTCAGGGCAG
** * **** * **** * ***** *****
DC8E8 heavy_V      GGGCACACTGACTGCAGACAAATCCTCCAAACACAGCCTACATCCAGCTCA
IGHV1-69*10_Homo+sapiens AGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGAGAGTGA
* *** * ** ** ***** * * ***** ***** *
DC8E8 heavy_V      GCAGCGTGACATCTGAGGACTCTGCGGTCATTTCGTGCAAGA--
IGHV1-69*10_Homo+sapiens GCAGCCTGAGATCTGAGGACACGCGCGTGTATTACTGTGCGGAGAGA
***** *** ***** * ** ** ***** ***

```

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

DC8E8 -----GATTACTACGGTAC-----
IGHD7-27*01_Homo+sapiens CTGAGCTGAGAACCACTGTGCTAACTGGGGACACACTGATTGGCAGCTCT
** **

DC8E8 -
IGHD7-27*01_Homo+sapiens A

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

DC8E8 TTCATTGCTATGGACTACTGGGGTCAAGGAACCTCAGTCACCGTCTCCT
IGHJ3*01_Homo+sapiens ---TGATGCTTTTGATGTCTGGGGCCCAAGGACAATGGTCACCGTCTCTT
*** * * * * ***** *

DC8E8 CAG
IGHJ3*01_Homo+sapiens CAG

FIGURE 6A

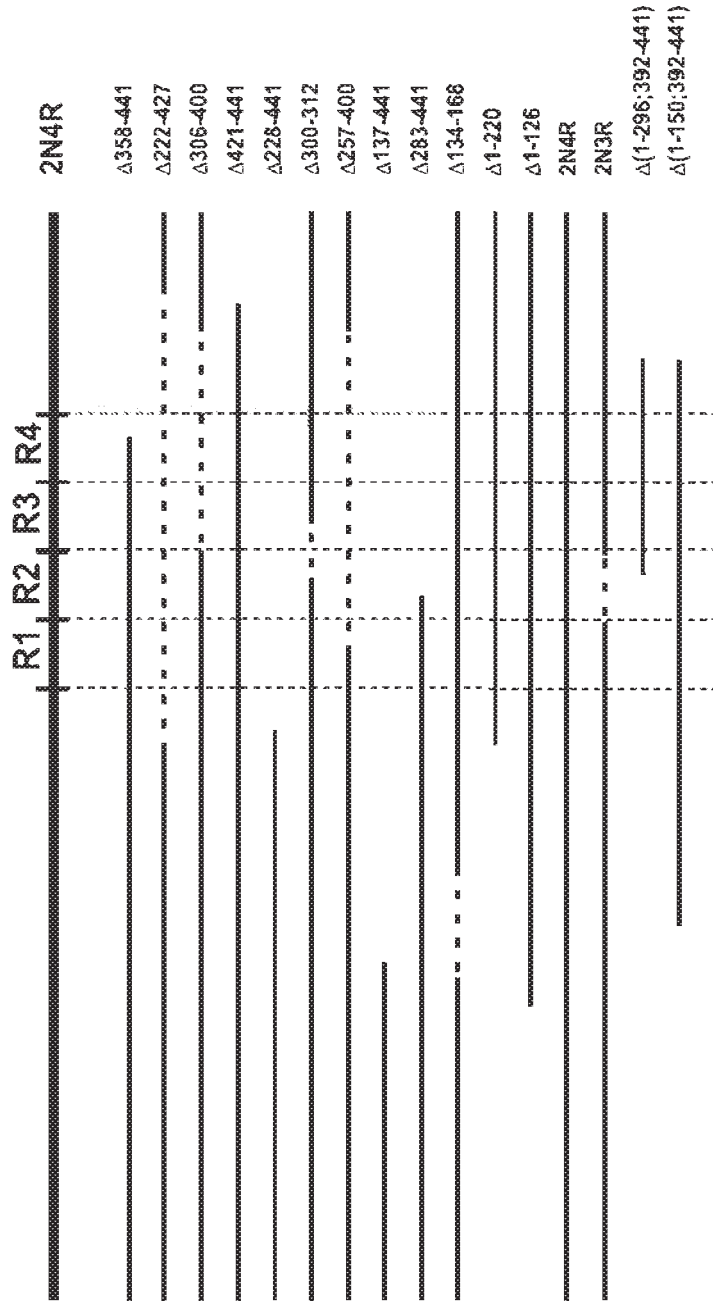


FIGURE 6B

 $\Delta 358-441$

```

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

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 $\Delta 222-427$

```

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

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 $\Delta 306-400$

```

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

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 $\Delta 421-441$

```

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

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 $\Delta 228-441$

```

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

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12/115

Δ300-312

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRs RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVSKSI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
 301 DLSKVTSCG SLGNHHKPG GGQVEVKSEK LDFKDRVQSK IGSLDNITHV PGGGNKKIET
 361 HKLTFRENAK AKTDHGAEIV YKSPVVS GDT SPRHLSNVSS TGSIDMVDSF QLATLADEVs
 421 ASLAKQGL

Δ257-400

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSRs RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVGDTS PRHLSNVsST GSIDMVDSFQ LATLADEVSA SLAKQGL

Δ137-441

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

Δ283-441

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

Δ134-168

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDTRIPAKT PPAPKTPPSS GEPPKSGDRS GYSSPGSPGT PGSRSRTPSL
 181 PTPPTREPCK VAVVRTPPKS PSSAKSRLQT APVPM PDLKN VKSKIGSTEN LKHQPGGGKV
 241 QIINKKLDLS NVQSKCGSKD NIKHVPGGGS VQIVYKPVDL SKVTSKCGSL GNIHHKPGGG
 301 QVEVKSEKLD FKDRVQSKIG SLDNITHVPG GGNKKIETHK LTFRENAKAK TDHGAEIVYK
 361 SPVVS GDTSP RHLSNVsSTG SIDMVDSFQL ATLADEVsSAS LAKQGL

Δ1-220

1 MREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVSK IGSTENLKHQ PGGGVQIIN
 61 KKLDLSNVQS KCGSKDNIKH VPGGGSVQIV YKPVDSLKVTSKCGSLGNH HKPGGGQVEV
 121 KSEKLDKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG AEIVYKSPVV
 181 SGDTSPRHLS NVsSTGSIDM VDSPQLATLA DEVsSASLAKQ GL

Δ 1-126

1 MVSKSKDGTG SDDKKAKGAD GGTKIATPRG AAPPGQKGQA NATRIPAKTP PAPKTPPSSG
 61 EPPKSGDRSG YSSPGSPGTP GSRRTPSLP TPPTREPKKV AVVRTPPKSP SSAKSRLQTA
 121 PVPMPDLKNV KSKIGSTENL KHQPGGGKVQ IINKKLDLSN VQSKCGSKDN IKHVPGGGSV
 181 QIVYKPVDLK KVTSCGSLG NIHHKPGGGQ VEVKSEKLDF KDRVQSKIGS LDNITHVPPG
 241 GNKKIETHKL TFRENAKAKT DHGAEIVYKS PVSOGDTSPR HLSNVSSSTGS IDMVDSPQLA
 301 TLADEVASL AKQGL

4R2N

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAEAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSR RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVSKSI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
 301 PGGGSVQIVY KPVDSLKVTS KCGSLGNIH 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 TTAEAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSR RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVSKSI GSTENLKHQP GGGKVQIVYK PVDLSKVTSK CGLGNIHHK
 301 PGGGQVEVKS EKLDFKDRVQ SKIGSLDNIT HVPGGGNKKI ETHKLTFREN AKAKTDHGAE
 361 IVYKSPVVS GDTSPRHLSN VSSTGSIDMV 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 SRTPSLPTP TREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVSK IGSTENLKHQ
 121 PGGGKVQIIN KKLDLSNVQS KCGSKDNIH VPGGGSVQIV YKPVDSLKVTSK SKCGSLGNIH
 181 HKPGGGQVEV KSEKLDFKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG
 241 AE

Note

The Methionine (M) at the position 1 in the tau deletion constructs Δ 1-220, 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

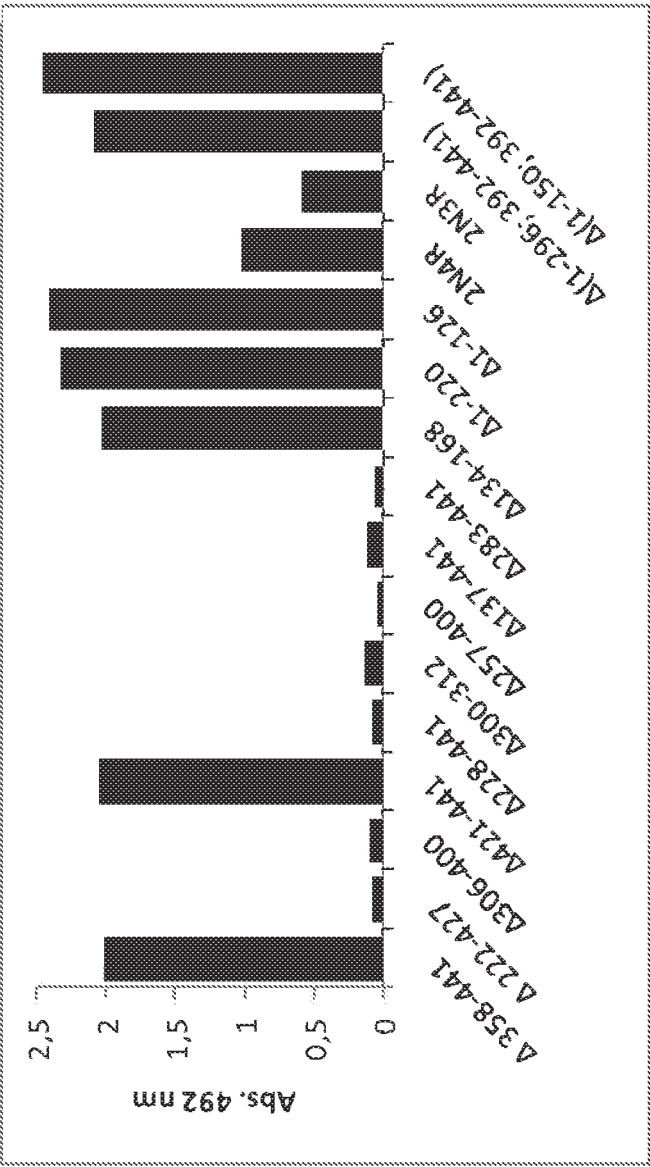


FIGURE 7A

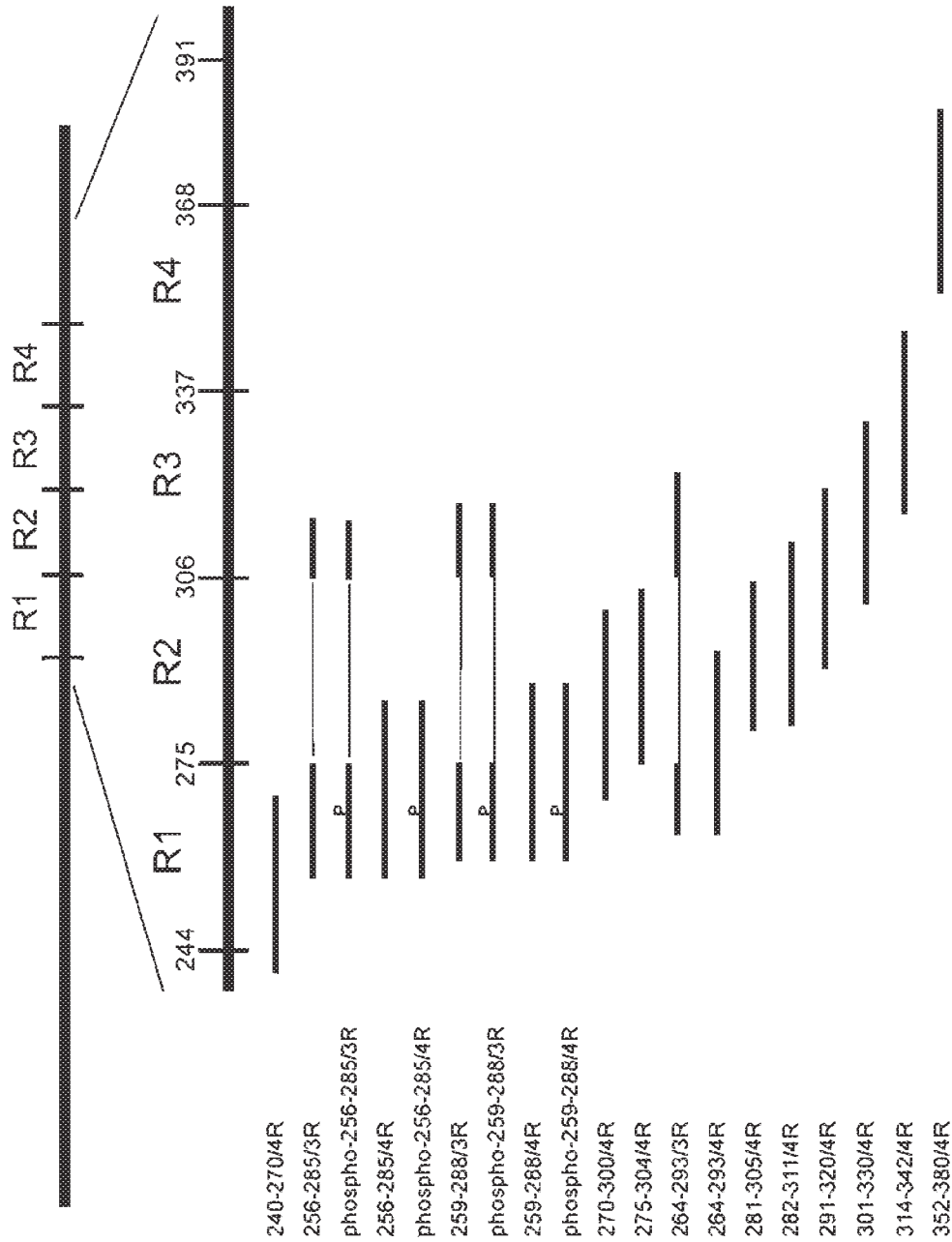


FIGURE 7B

Synthetic peptide	Sequence
240-270/4R	KSRLQTAPVMPDLKNVKSIGSTENLKHQP
256-285/3R	VKSIGSTENLKHQPGGGKVQIVYKPPVDLS
phospho 256-285/3R (pSer262)	VKSIGpSTENLKHQPGGGKVQIVYKPPVDLS
256-285/4R	VKSIGSTENLKHQPGGGKVQIINKKLDLS
phospho 256-285/4R (pSer262)	VKSIGpSTENLKHQPGGGKVQIINKKLDLS
259-288/3R	KIGSTENLKHQPGGGKVQIVYKPPVDLSKVT
phospho 259-288/3R (pSer262)	KIGpSTENLKHQPGGGKVQIVYKPPVDLSKVT
259-288/4R	KIGSTENLKHQPGGGKVQIINKKLDLSNVQ
phospho 259-288/4R (pSer262)	KIGpSTENLKHQPGGGKVQIINKKLDLSNVQ
270-300/4R	PGGGKVQIINKKLDLSNVQSKCGSKDNIKHV
275-304/4R	VQIINKKLDLSNVQSKCGSKDNIKHVPGGG
264-293/3R	ENLKHQPGGGKVQIVYKPPVDLSKVTSCGGS
264-293/4R	ENLKHQPGGGKVQIINKKLDLSNVQSKCGGS
281-305/4R	KLDLSNVQSKCGSKDNIKHVPGGGGS
282-311/4R	LDLSNVQSKCGSKDNIKHVPGGGSVQIVYK
291-320/4R	CGSKDNIKHVPGGGSVQIVYKPPVDLSKVT
301-330/4R	PGGGSVQIVYKPPVDLSKVTSCGSLGNIHH
314-342/4R	DLSKVTSCGSLGNIHHKPGGGQVEVKSE
352-380/4R	SKIGSLDNITHVPGGGNKKIETHKLTFRN

FIGURE 7C

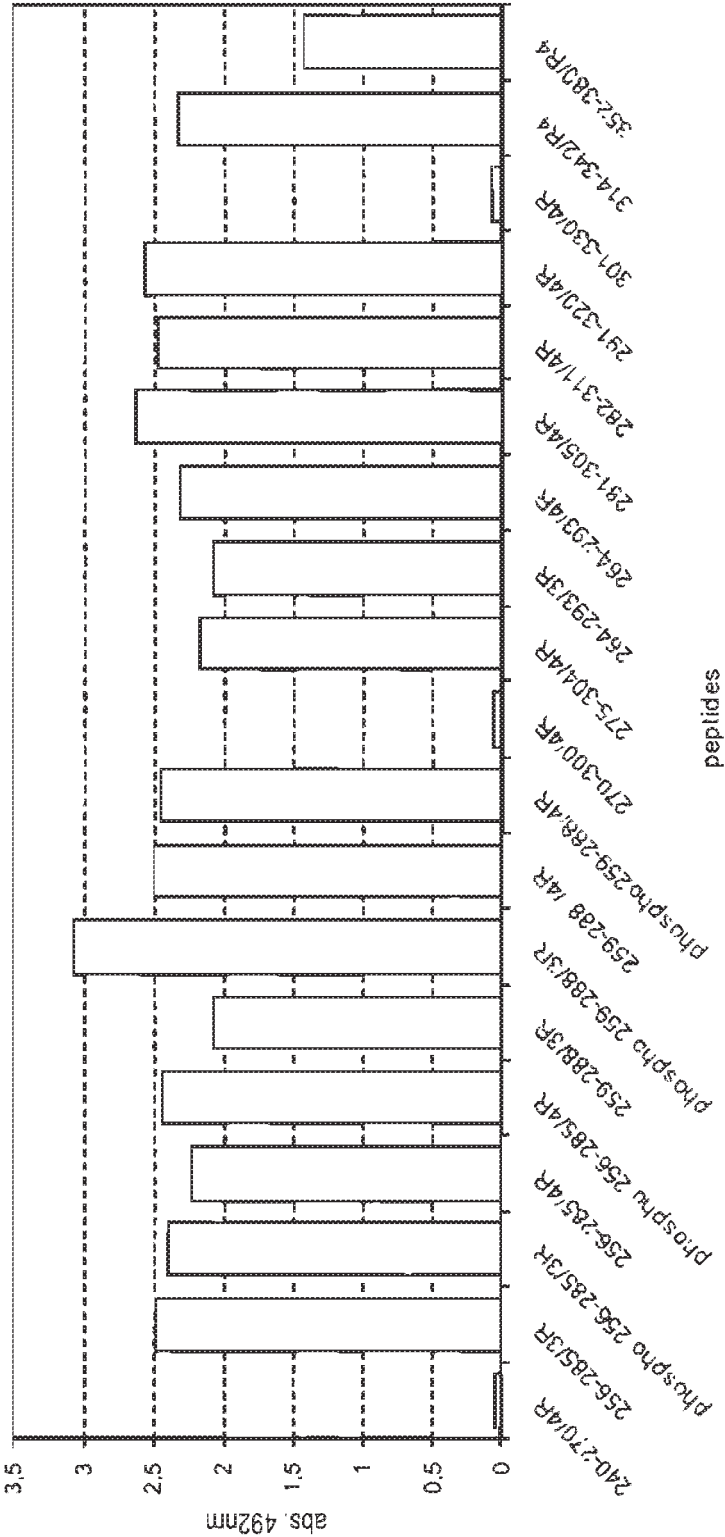


FIGURE 7D

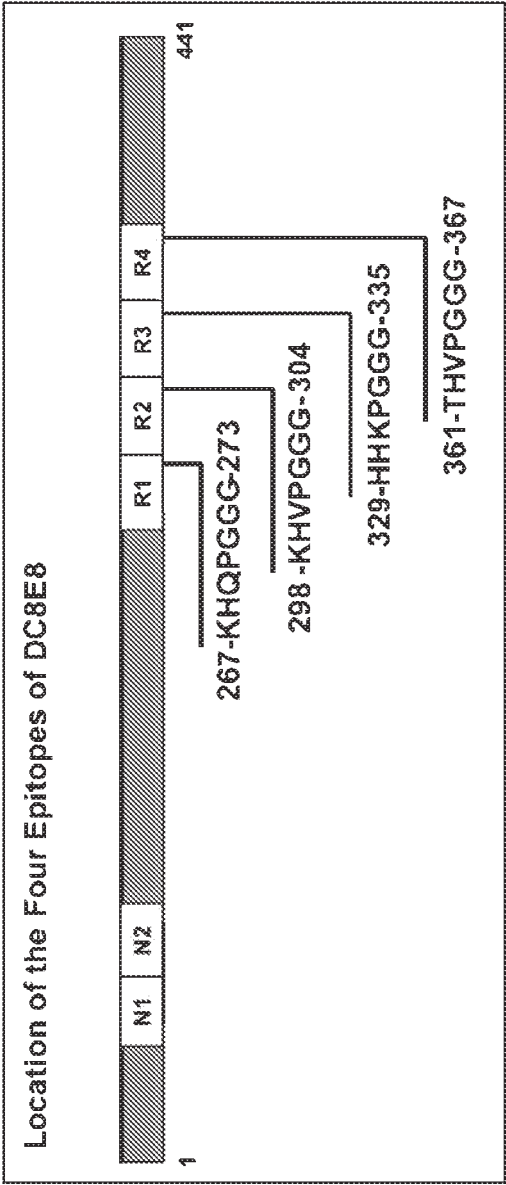


FIGURE 8A

Human	265-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Chimpanzee	572-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Macaque	572-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Gibbon	572-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Orangutan	554-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Giant_panda	596-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Pig	541-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Horse	241-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Dog	237-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Rabbit	228-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Rat	228-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Vole	226-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Mouse	226-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Ground_Squirrel	226-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Cattle	244-NL	KHQP	GGG	KVQI	I	NKKL	DLSNVQ	SKCG	SKDNI	KHVP	GGG	SVQI	IVYK	PVD
Fowl	141-NL	KHQP	GGG	KVQI	I	NKKL	DFSSVQ	SKCG	SKDNI	KHIP	GGG	SVQI	IVYK	PVD
Finch	502-NL	KHQP	GGG	KVQI	I	NKKL	DFSSVQ	SKCG	SKDNI	KHIP	GGG	SVQI	IVYK	PVD
Zebra_fish	206-NI	KHAP	GGG	NVQI	L	DQK	LDTNVQ	ARC	SGSKDNI	KHVP	GGG	KVQI	LHKK	ID
African_clawed_frog	468-NI	RHQP	GGG	KVQI	I	VHKK	VDLGNVQ	SKCG	SKDNI	KHVP	GGG	AIQI	THKP	ID
Fruit_fly	157-NA	TYKP	GGG	HVKI	E	SKKID	IKAAPRI	EAKND	--	KYMP	RGG	EKKI	VT	TKLQ
Roundworm	269-N-	HKAG	GGG	NVEI	F	SEKR	-LYNAQ	SKVGS	SLKNA	THVAG	GGG	NVQI	ENRK	L

Human	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-368	
Chimpanzee	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703	
Macaque	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703	
Gibbon	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703	
Orangutan	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-685	
Giant_panda	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-727	
Pig	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-673	
Horse	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-372	
Dog	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-368	
Rabbit	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-359	
Rat	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-359	
Vole	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357	
Mouse	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357	
Ground_Squirrel	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357	
Cattle	LSKVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-375	
Fowl	LSHVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DKVQ	SKIG	SLDNI	SHVP	GGG	N-272	
Finch	LSHVTSKCGSLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DKVQ	SKIG	SLDNI	SHVP	GGG	N-633	
Zebra_fish	LSNVQSKCGSKDNI	HHKP	GGG	NIEI	RSEK	LDF--	KAQ	SKIG	SMDNI	KHTP	GGG	N-332	
African_clawed_frog	LTRVTSKCGSFVNI	HHKP	GGG	NVEL	KSEK	LEF-D	KIQ	SKIG	SLDNI	THVP	GGG	N-600	
Fruit_fly	WN-AKSKIGSLENA	HHKP	GGG	DKKI	ETL	KMDF	KDKAK	PKVG	STANV	KHQP	GGG	N-287	
Roundworm	FSAASPKVGS--KT	NYQP	AKS	QV	KIV	SEK	LTV--	QAK	SKVGS	SMDNA	HHKP	GGG	N-396

FIGURE 8B

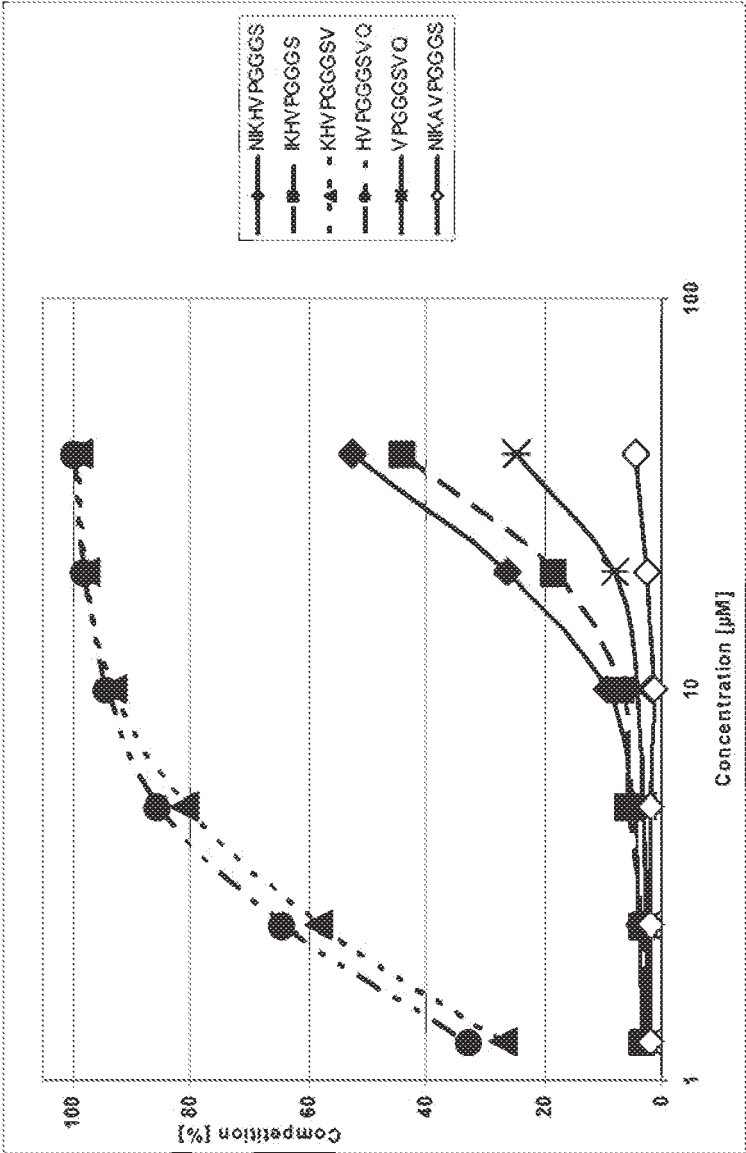


FIGURE 8C

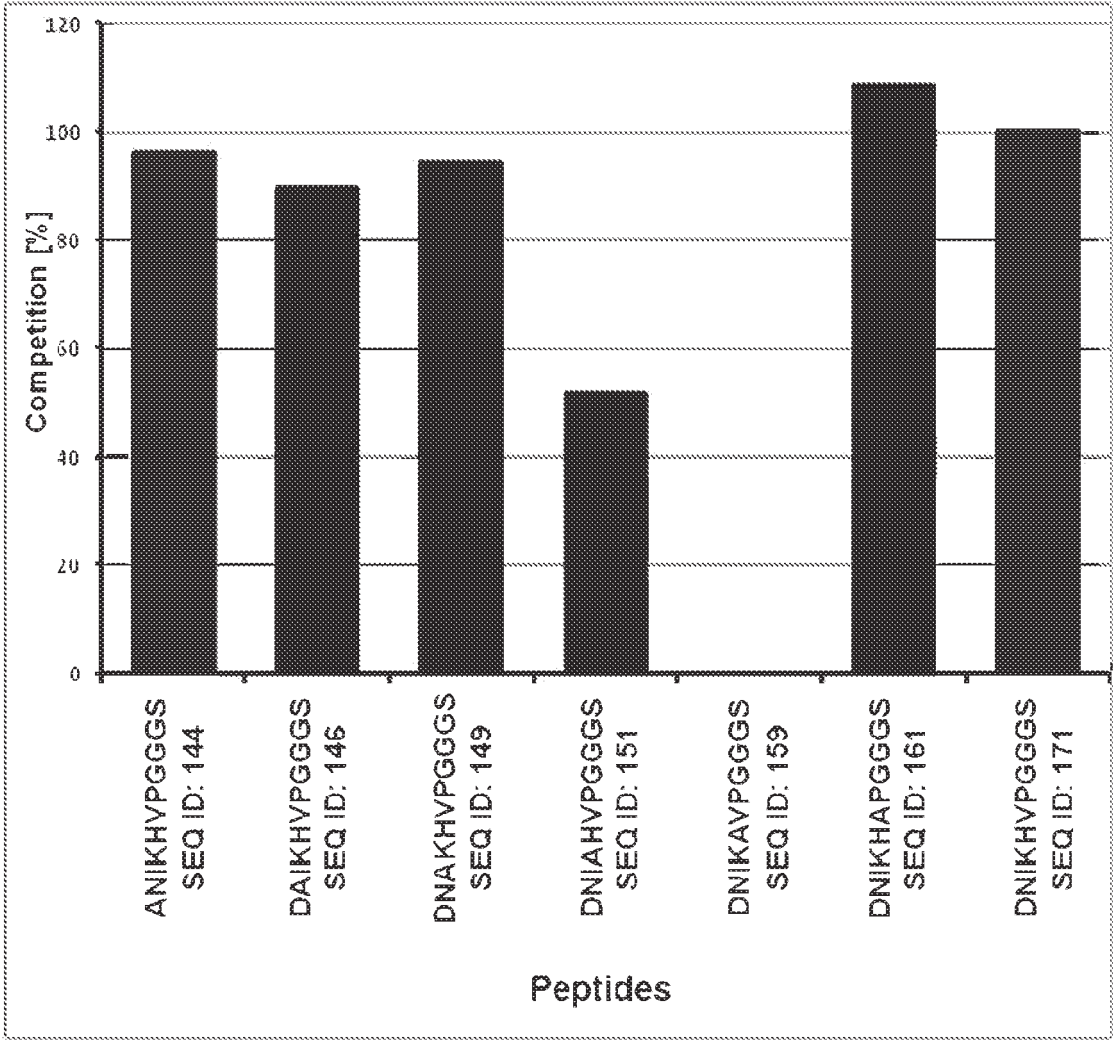


FIGURE 9A

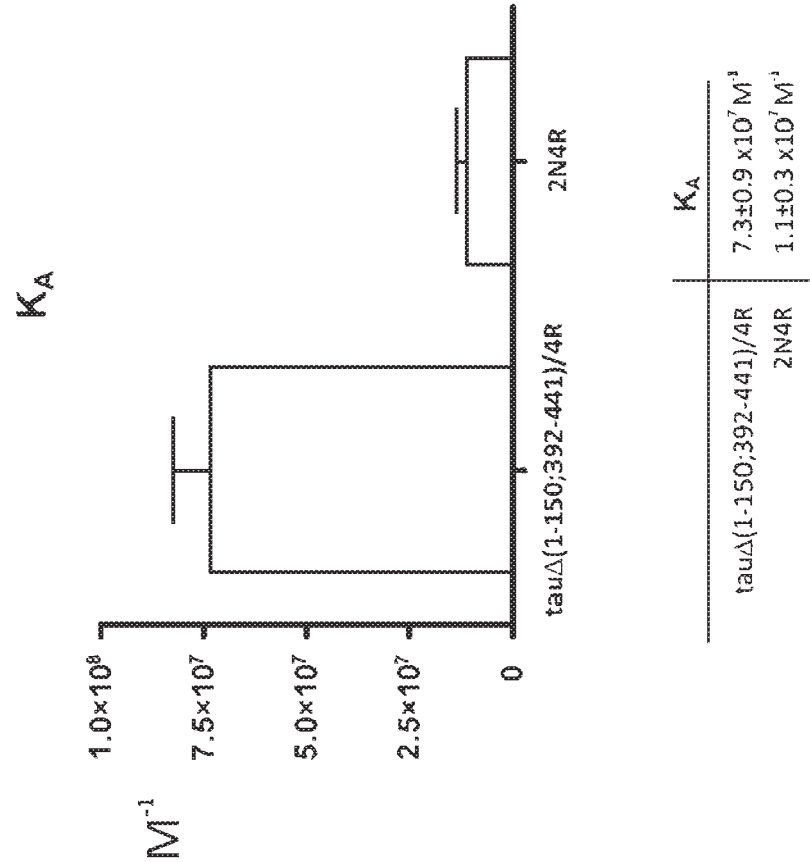


FIGURE 9B

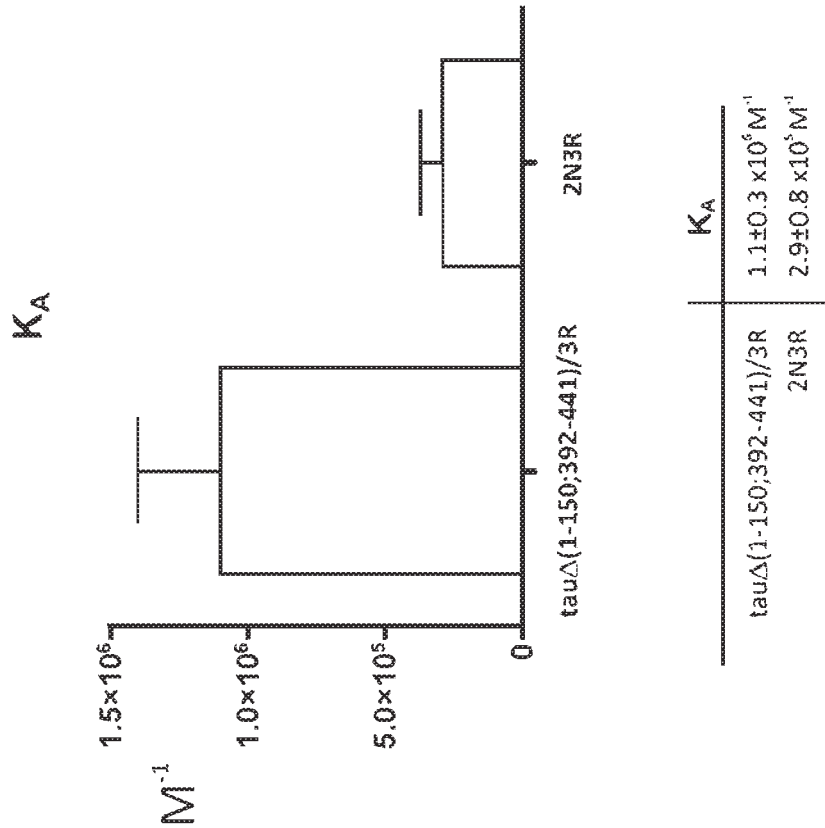


FIGURE 10A

	$k_{ON} (s^{-1} M^{-1})$	$k_{OFF} (s^{-1})$
$\tau_{au\Delta}(1-150:392-441)/4R$	$2.6 \pm 0.5 \times 10^6$	0.04 ± 0.01
2N4R	$4.6 \pm 1.4 \times 10^5$	0.04 ± 0.01

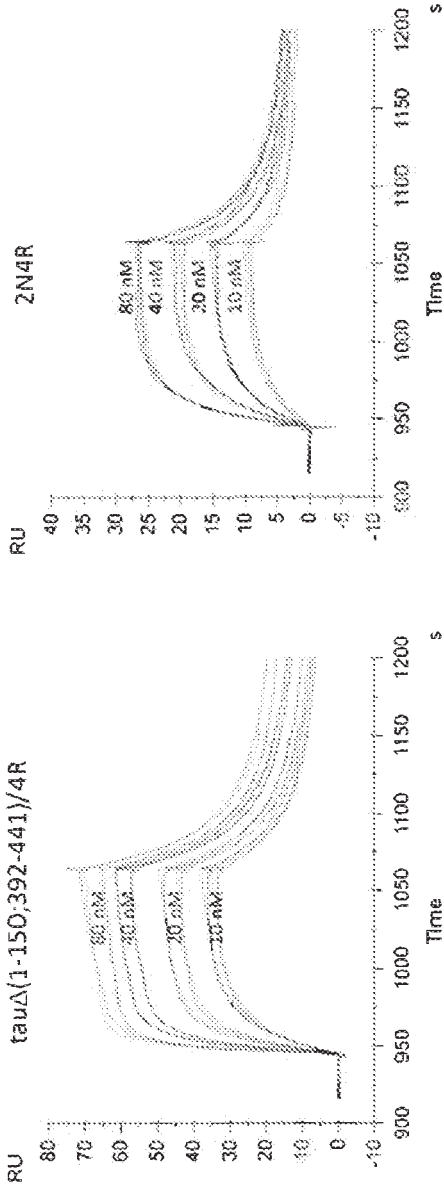


FIGURE 10B

	$k_{ON}(s^{-1} M^{-1})$	$k_{OFF}(s^{-1})$
$\tau_{au\Delta}(1-150;392-441)/3R$	$4.9 \pm 1.4 \times 10^5$	0.5 ± 0.1
2N3R	$1.4 \pm 0.4 \times 10^5$	0.5 ± 0.1

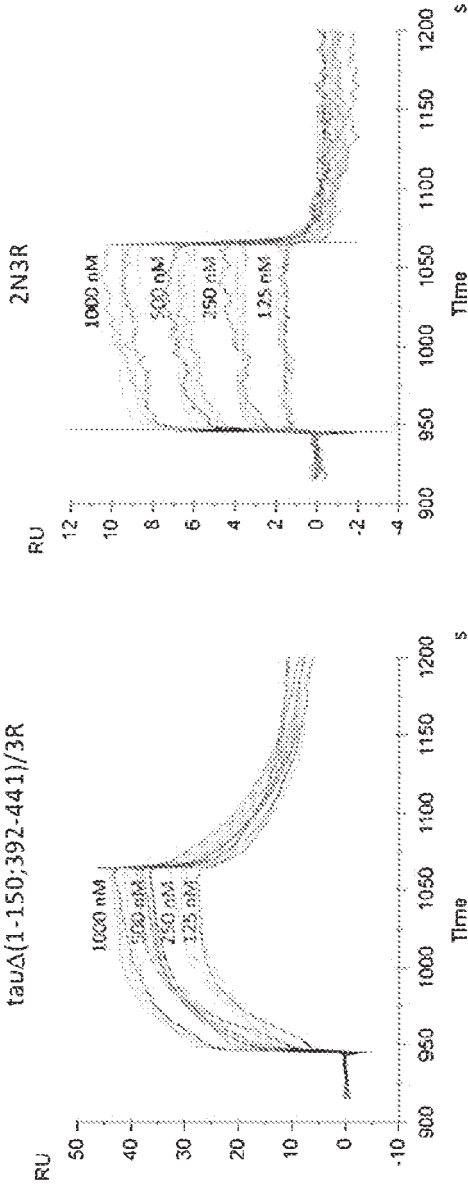
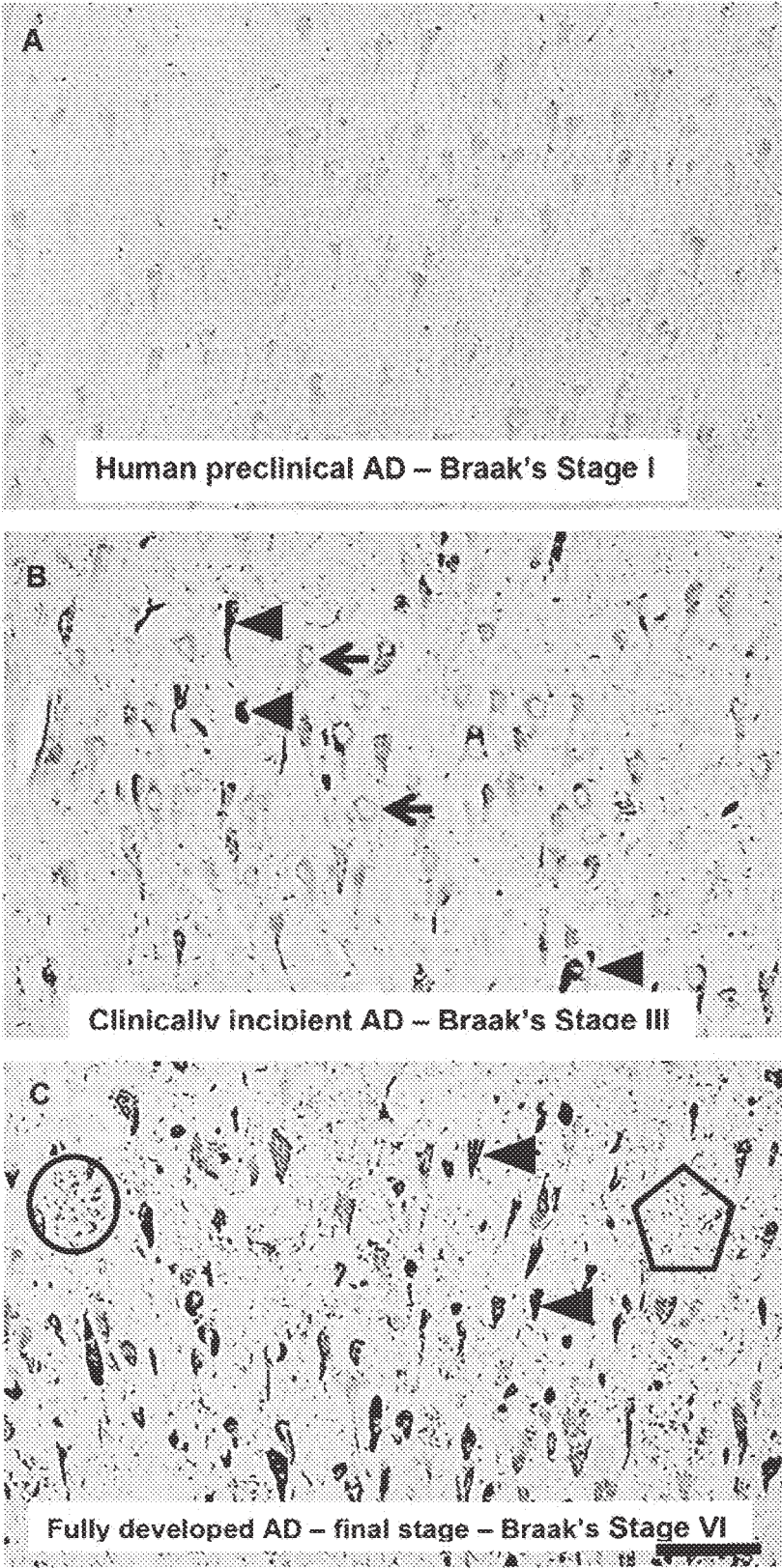


FIGURE 11



27/115

FIGURE 11D

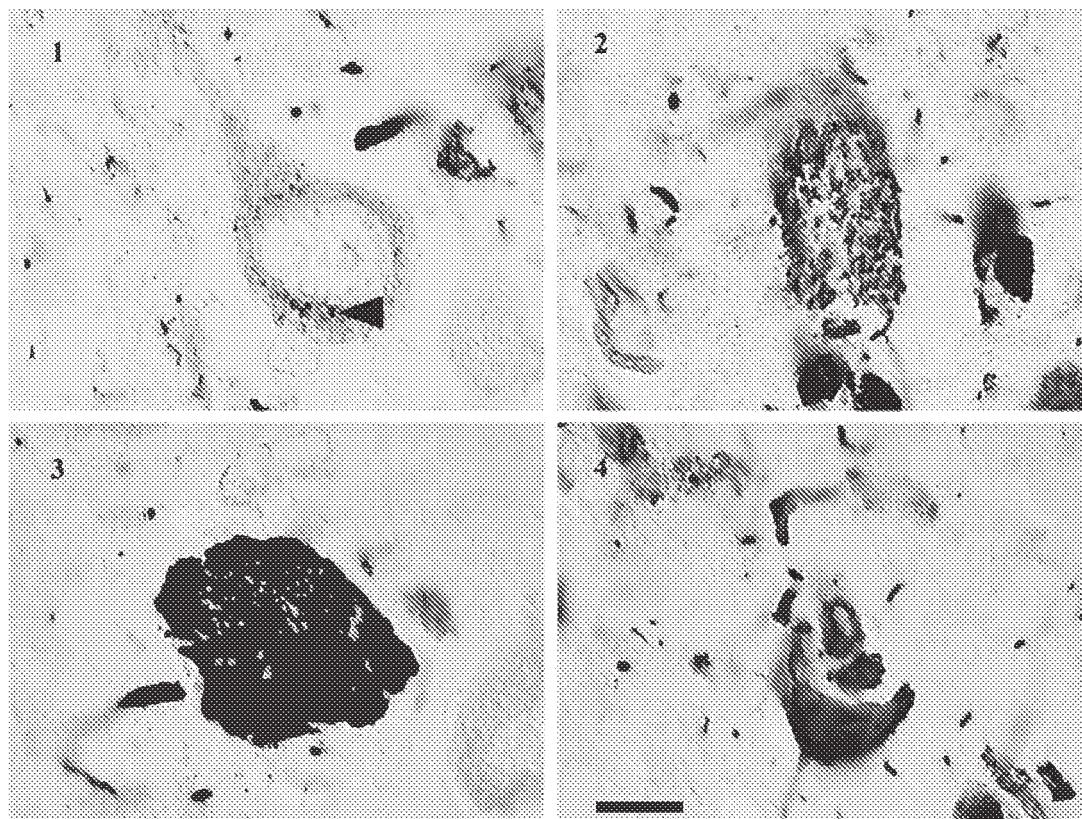


FIGURE 12A AND FIGURE 12B

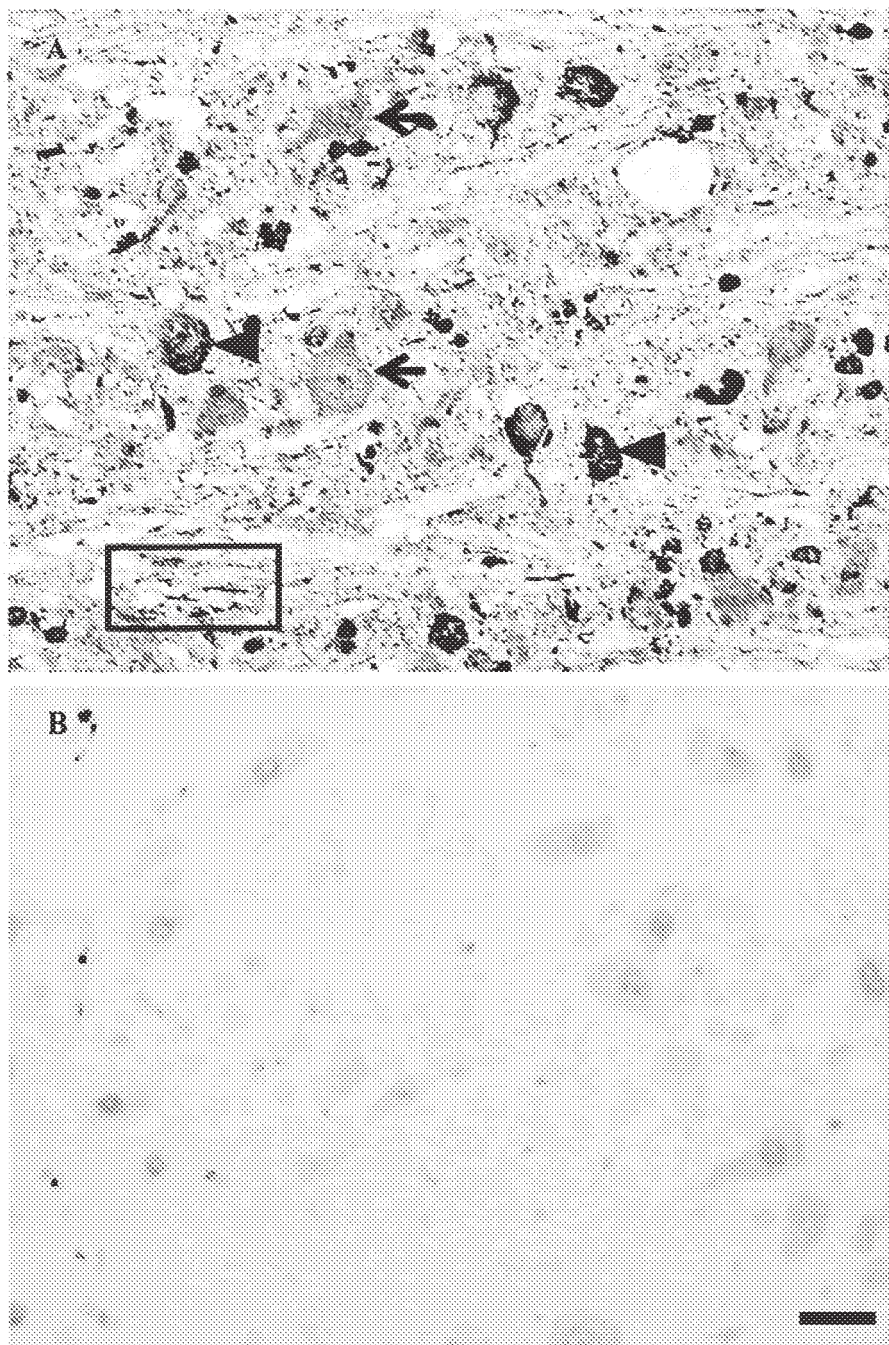


FIGURE 12C THROUGH FIGURE 12F

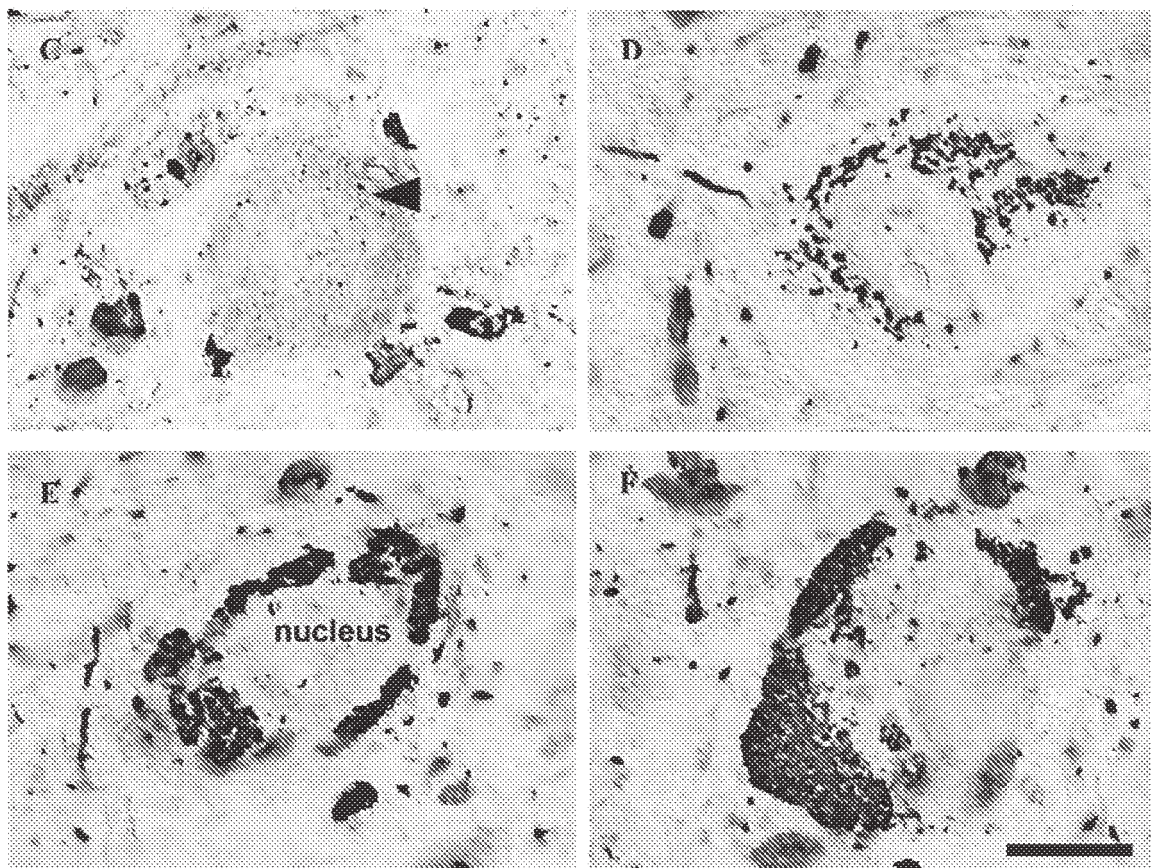


FIGURE 13

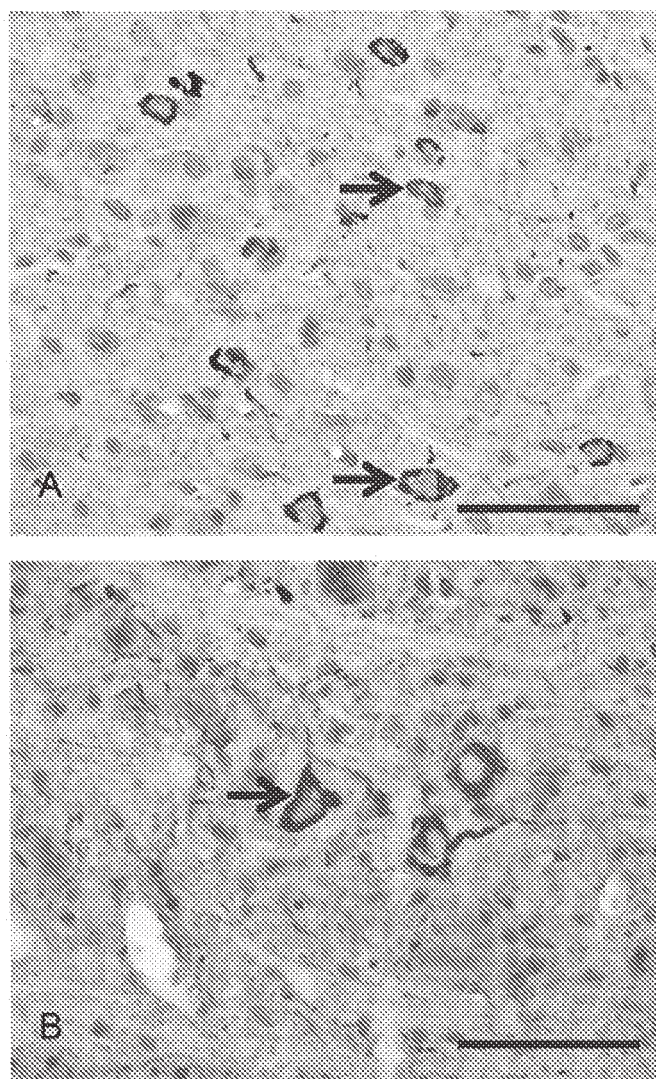


FIGURE 14A and 14B

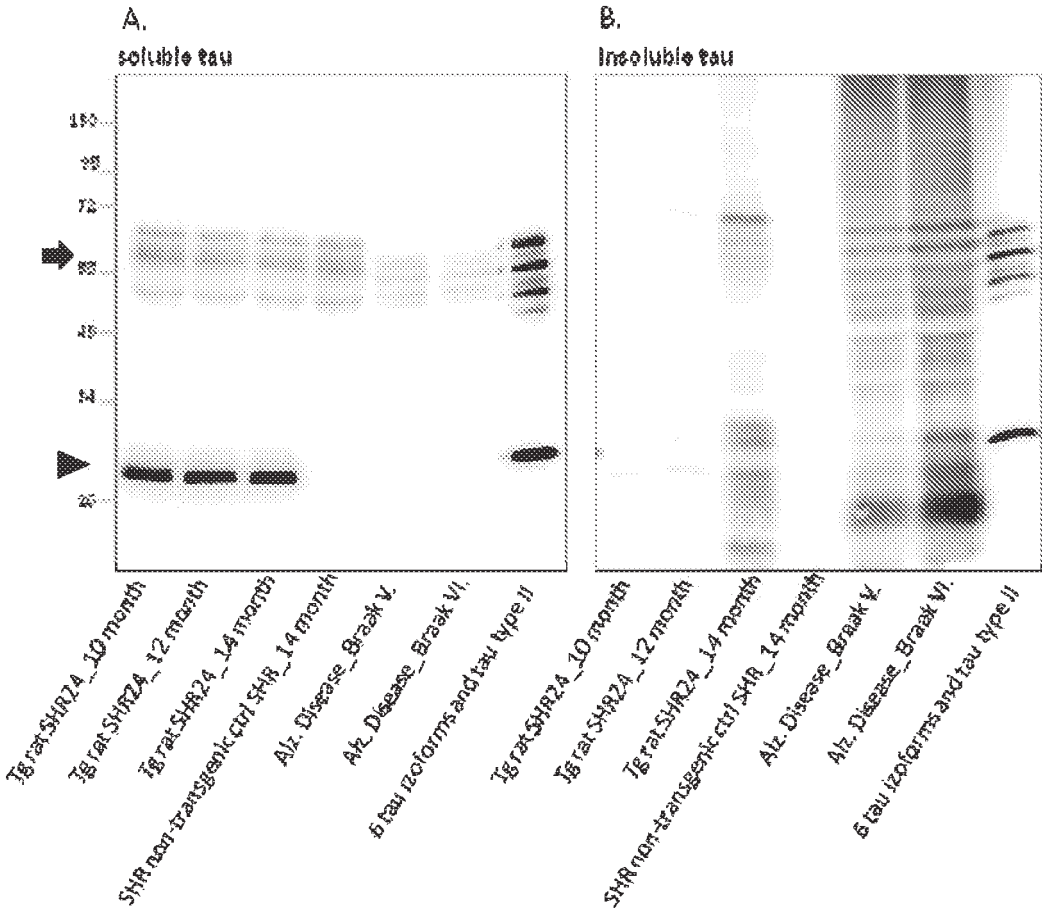


FIGURE 14C and 14D

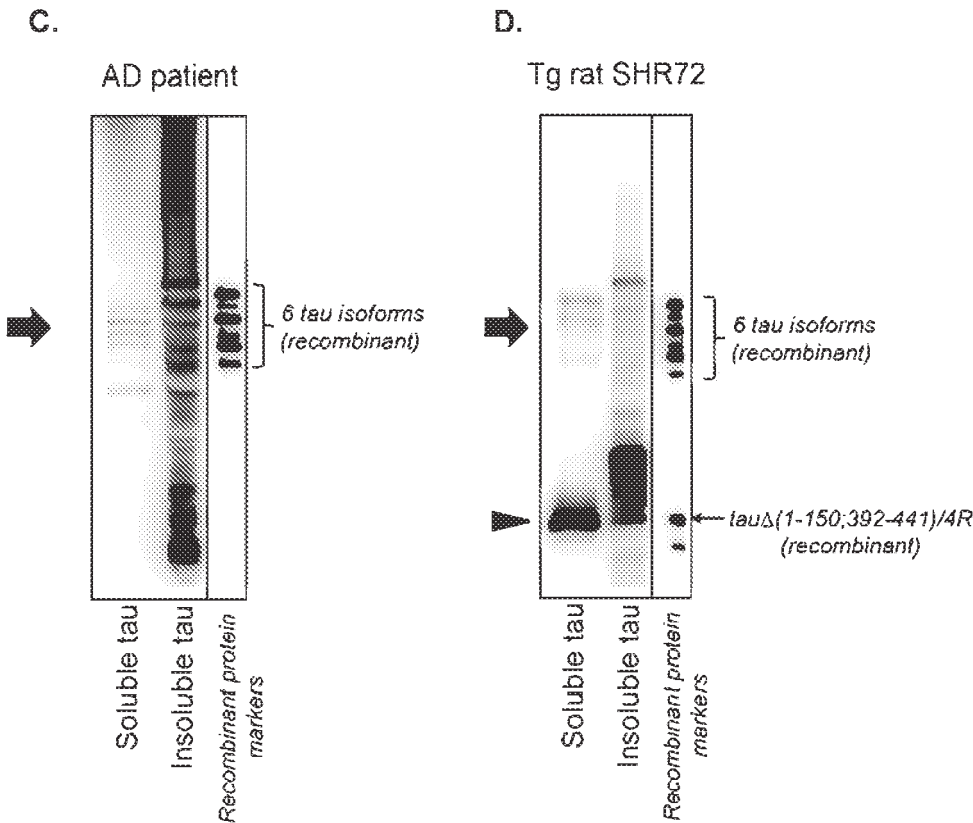


FIGURE 15A

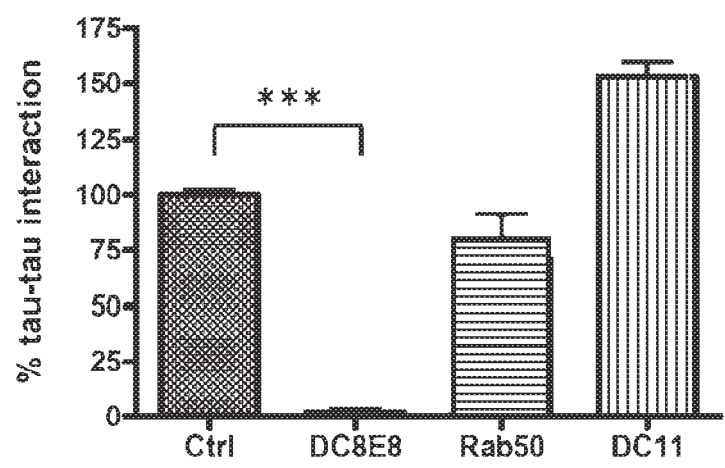


FIGURE 15B

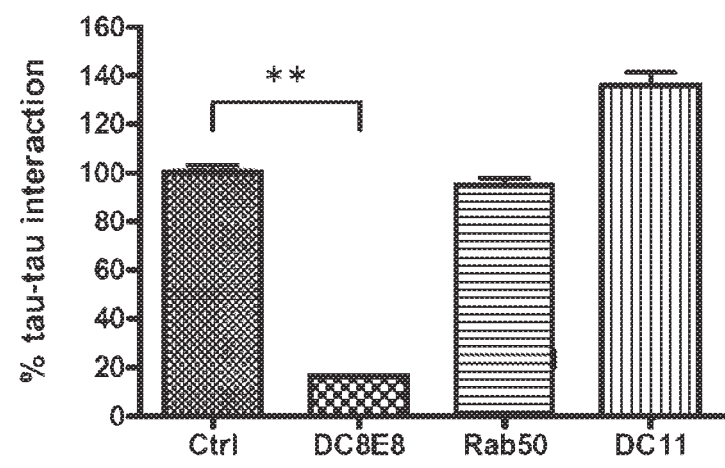


FIGURE 16

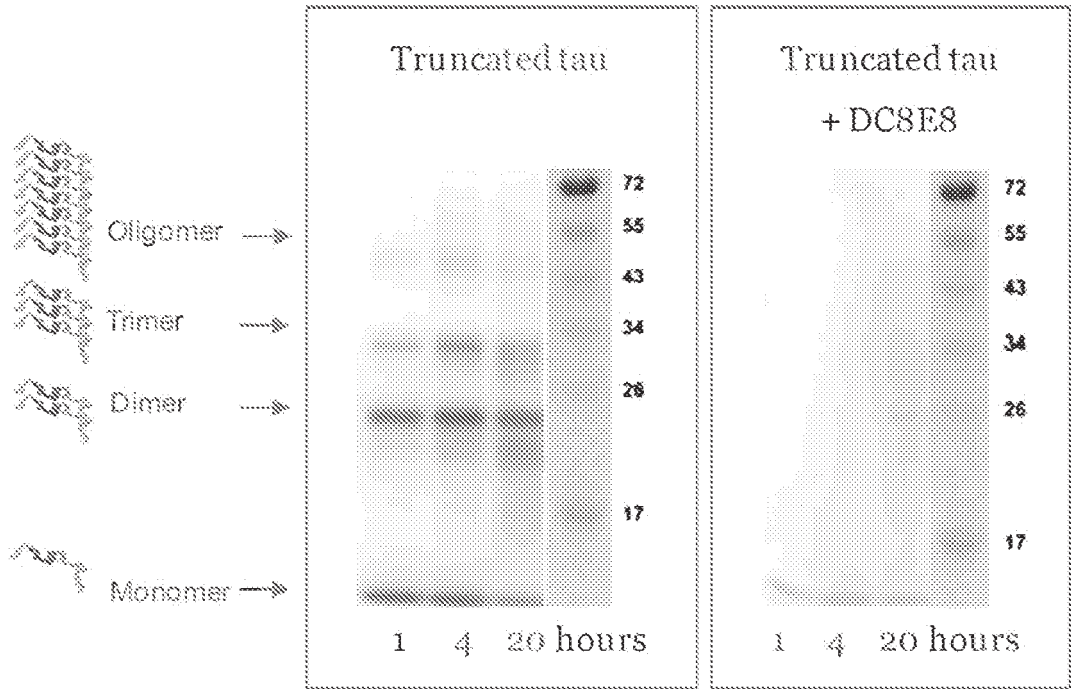


FIGURE17A

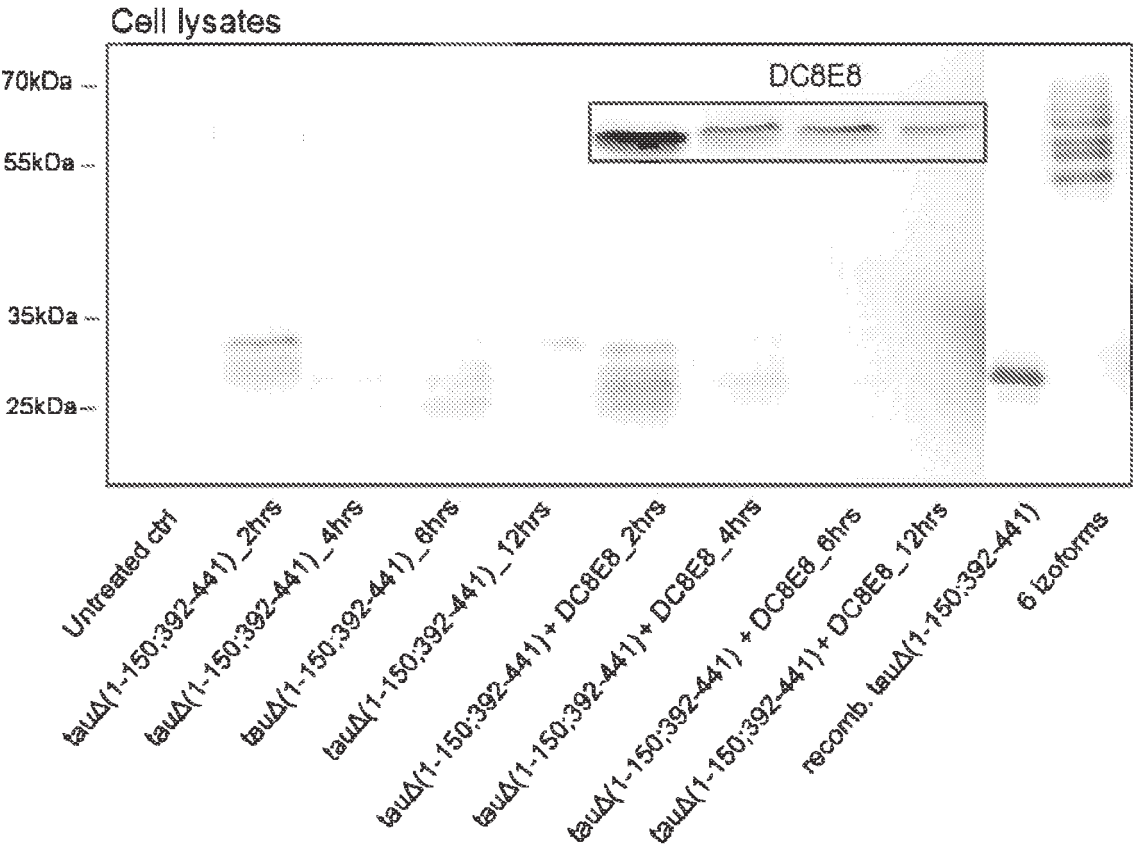
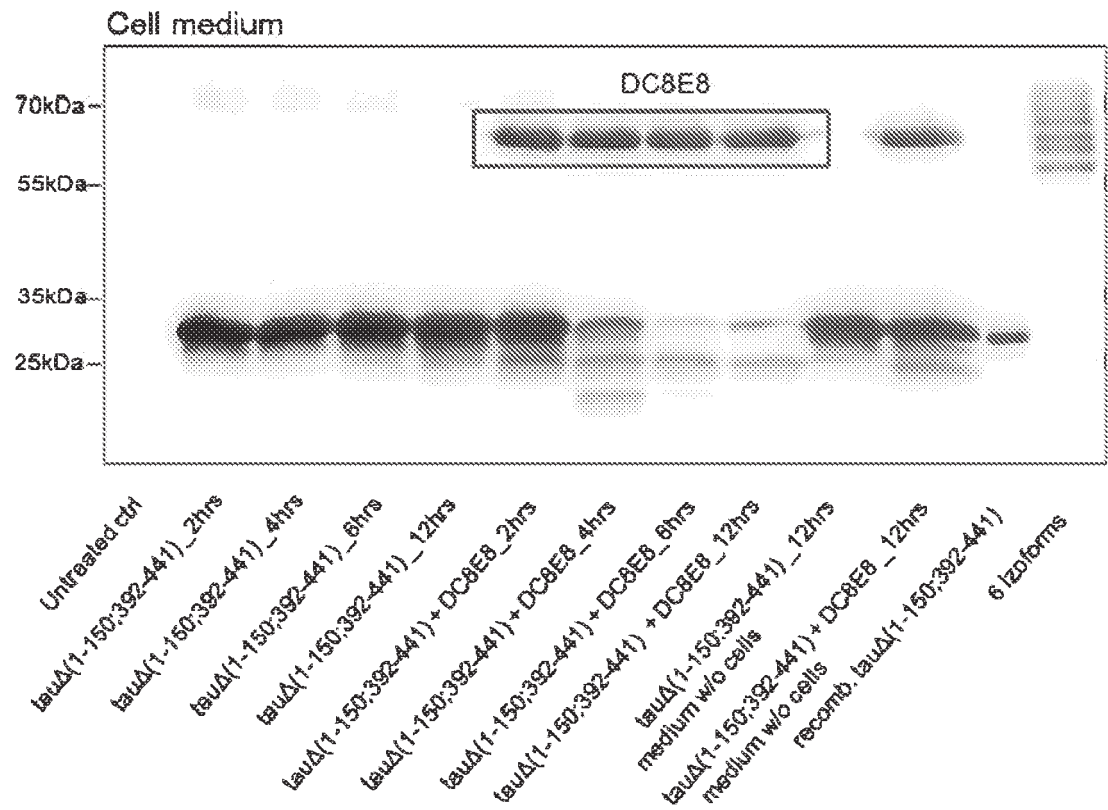


FIGURE 17B



37/115

FIGURE 18

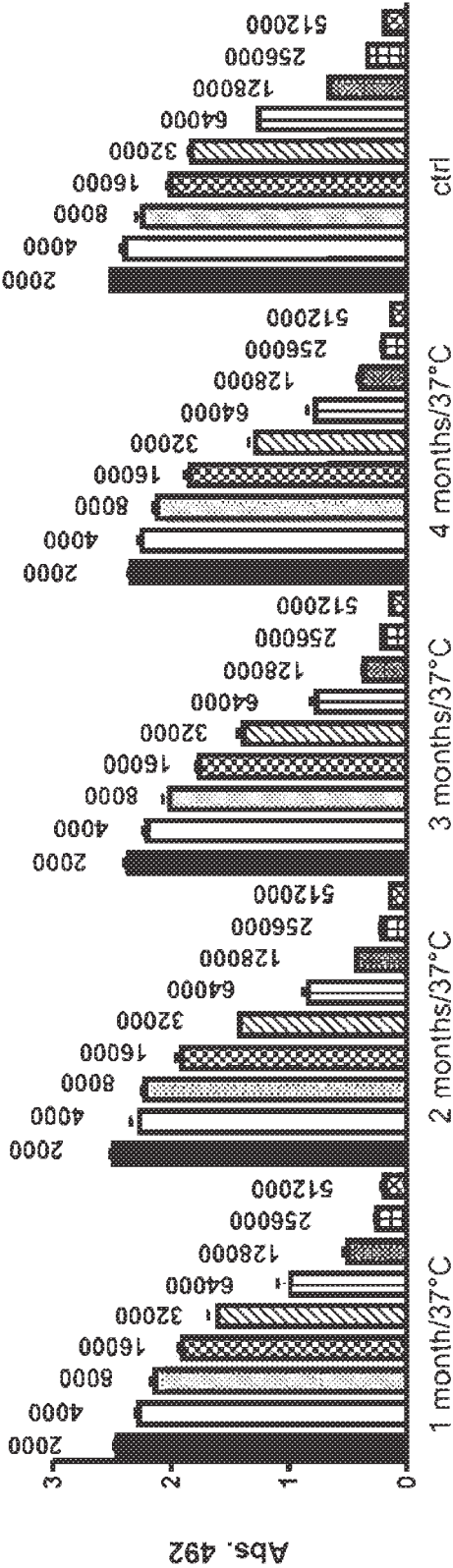


FIGURE 19

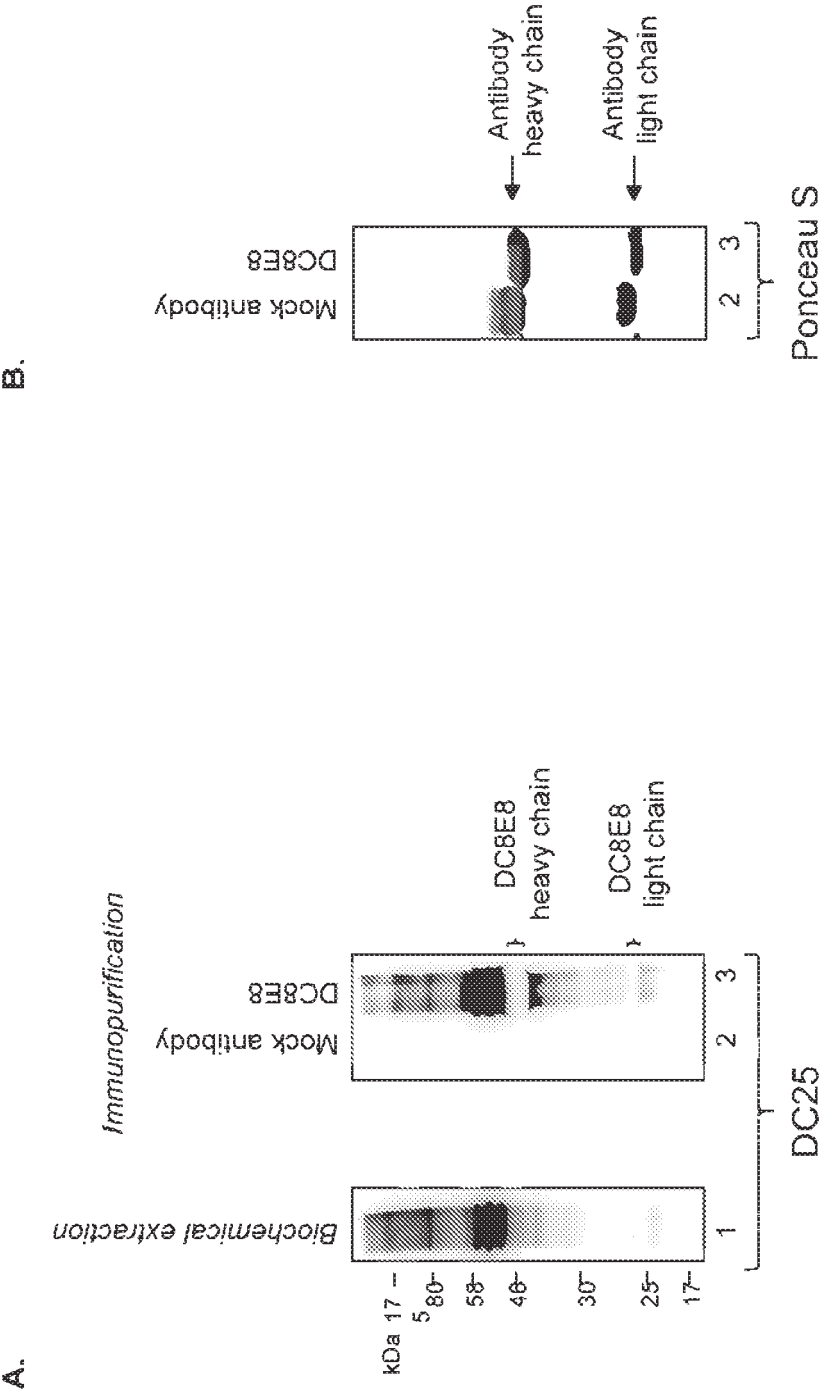


FIGURE 20

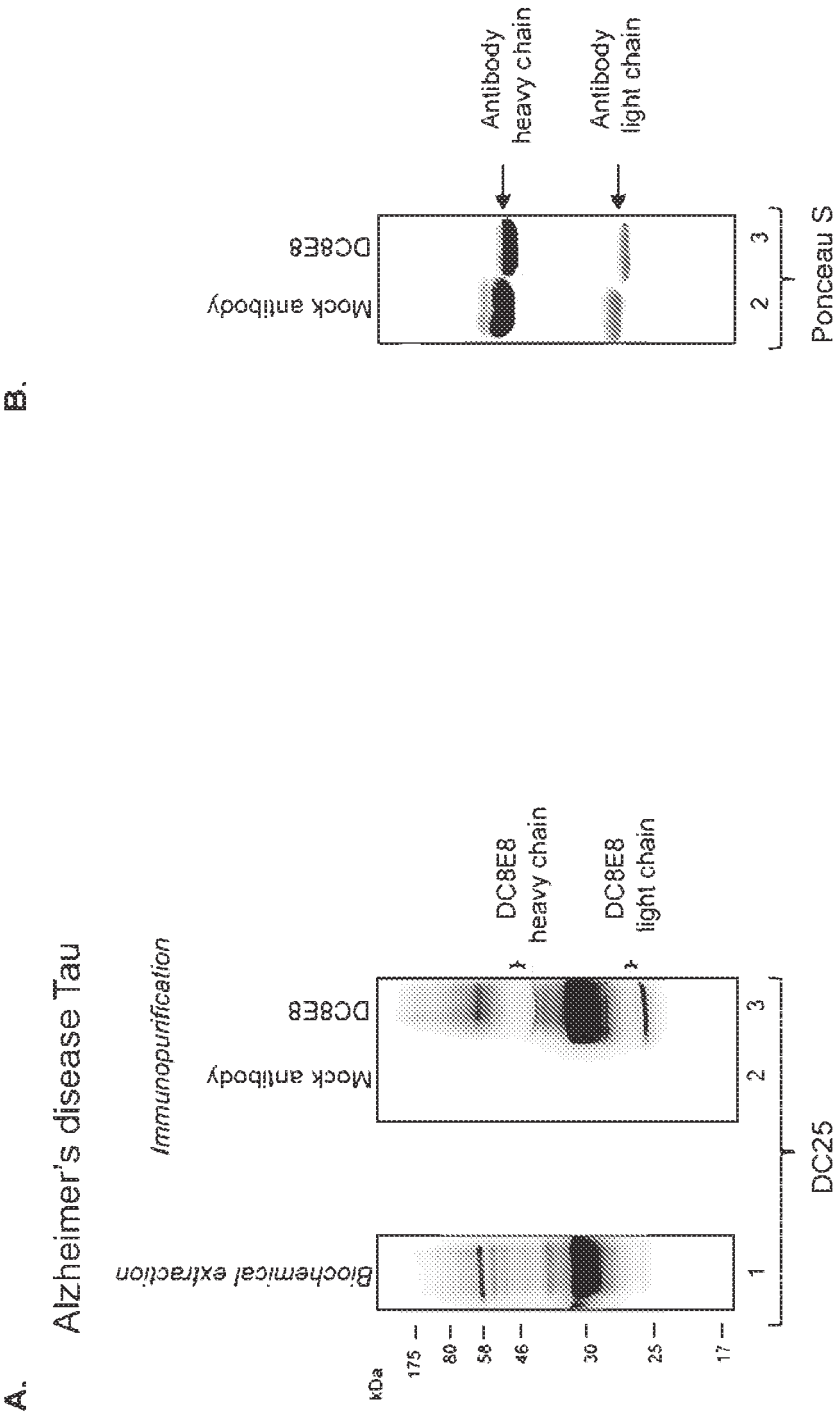


FIGURE 21A

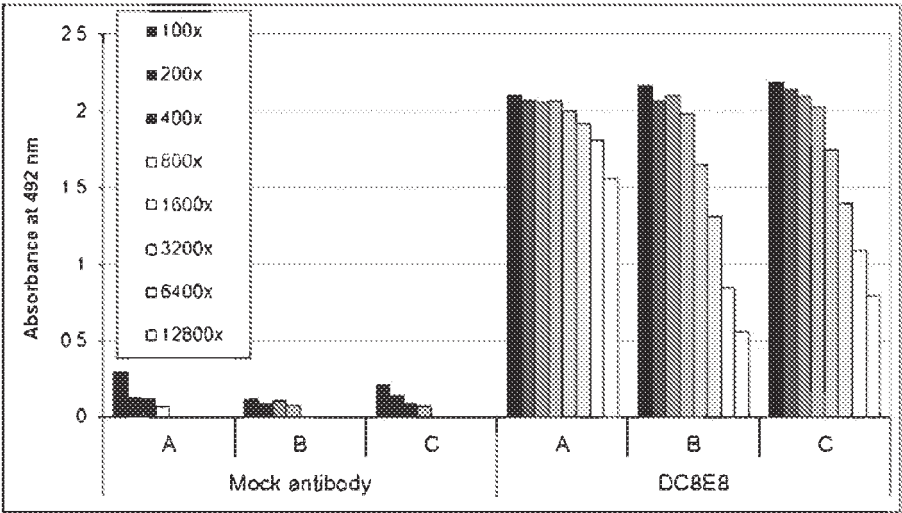


FIGURE 21B

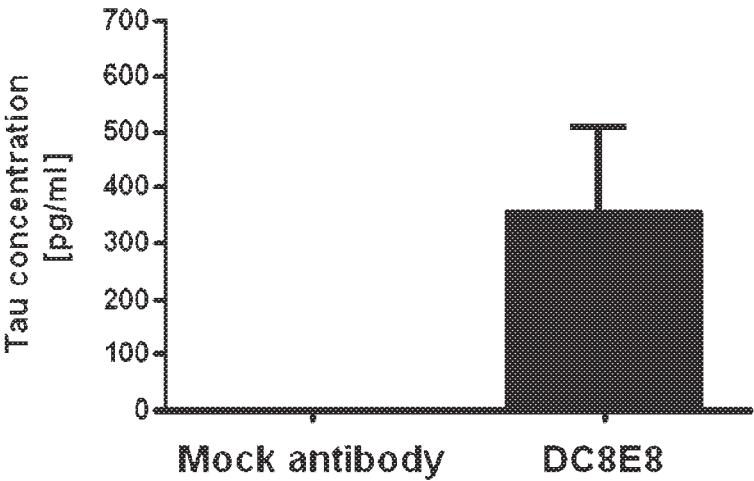
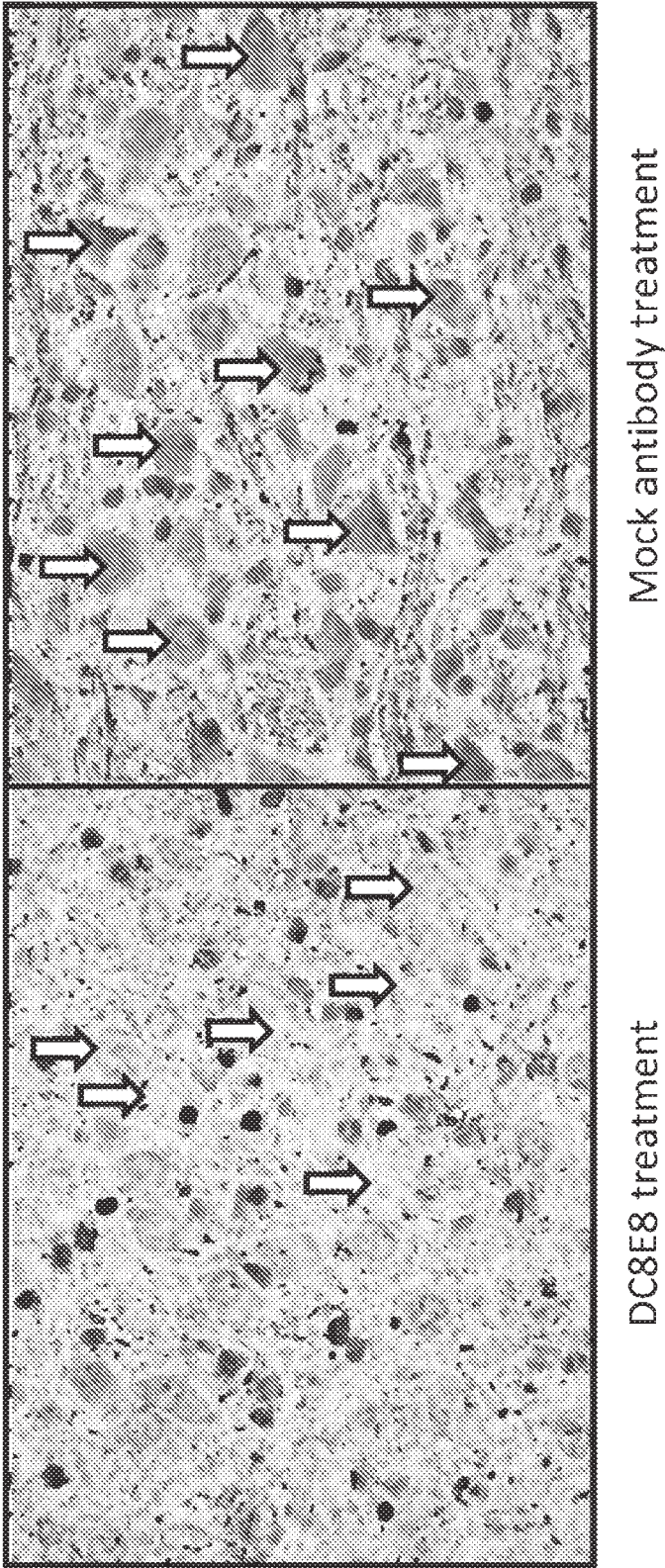


FIGURE 22A



42/115

FIGURE 22B

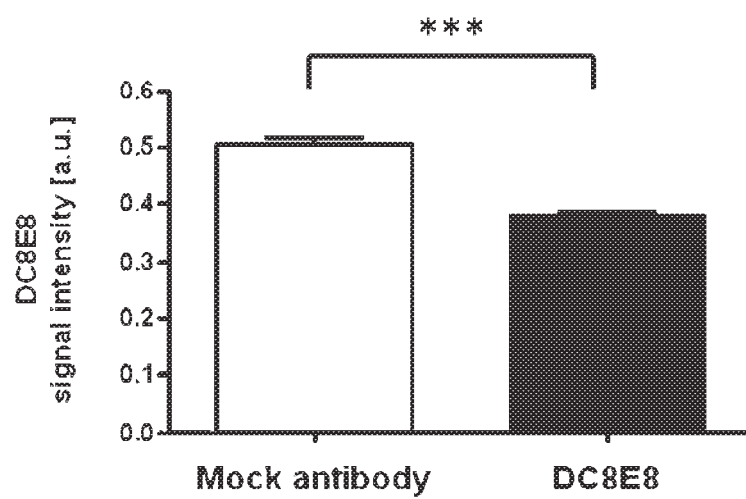


FIGURE 23

FIGURE 23A.

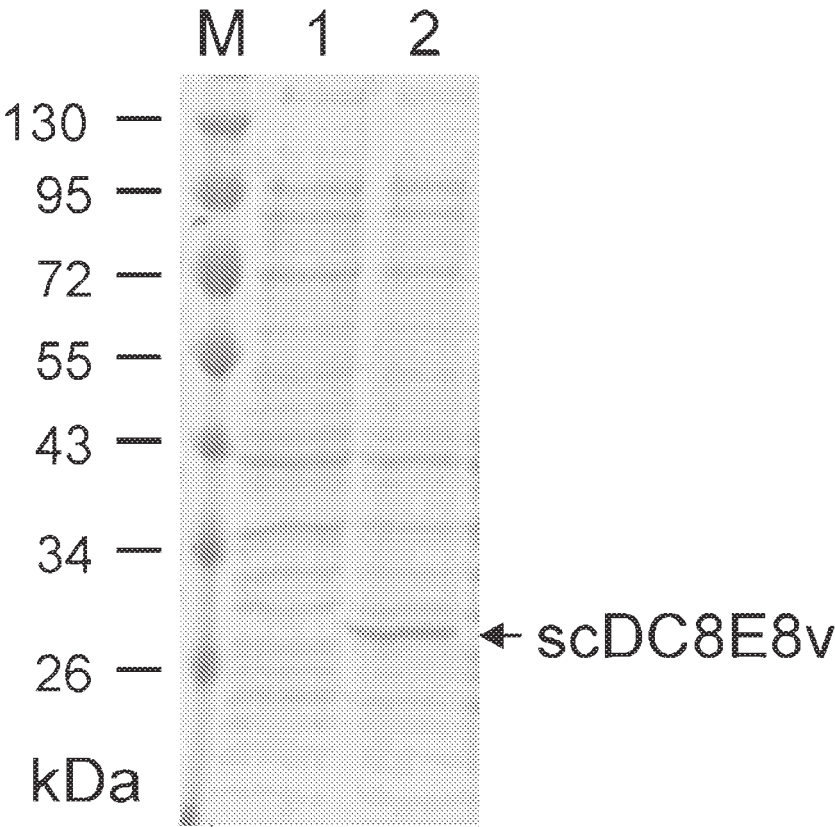


FIGURE 23B.

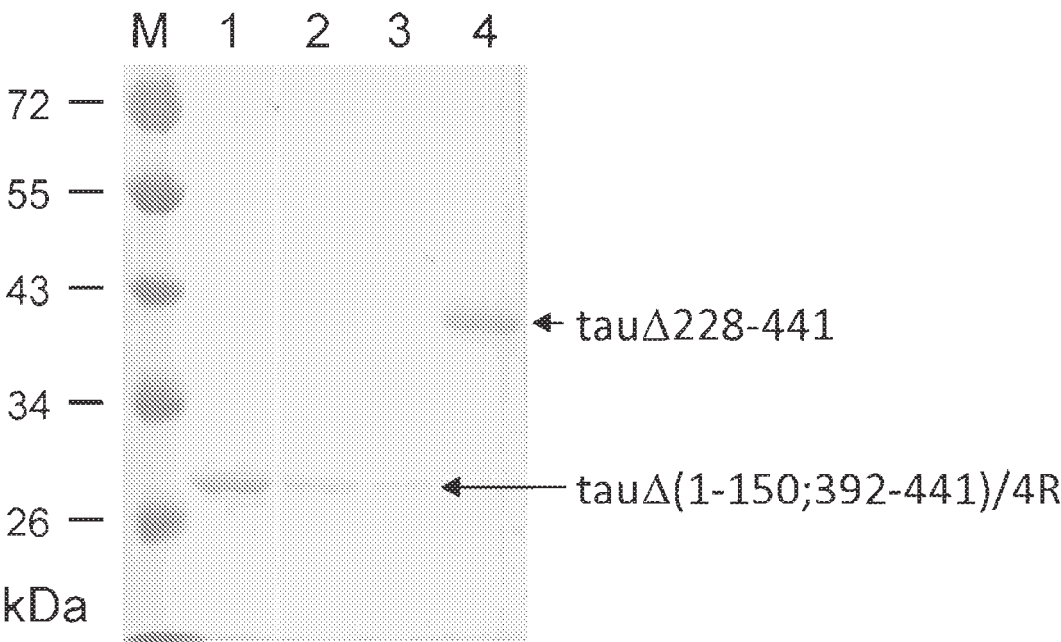


FIGURE 23D

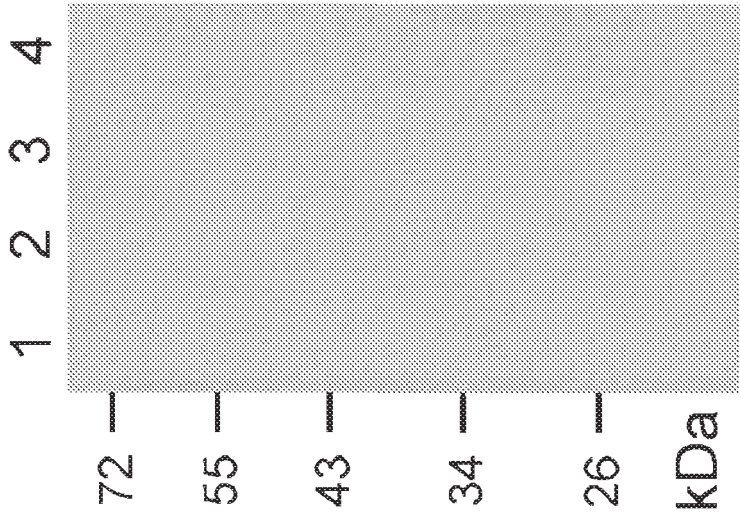


FIGURE 23C

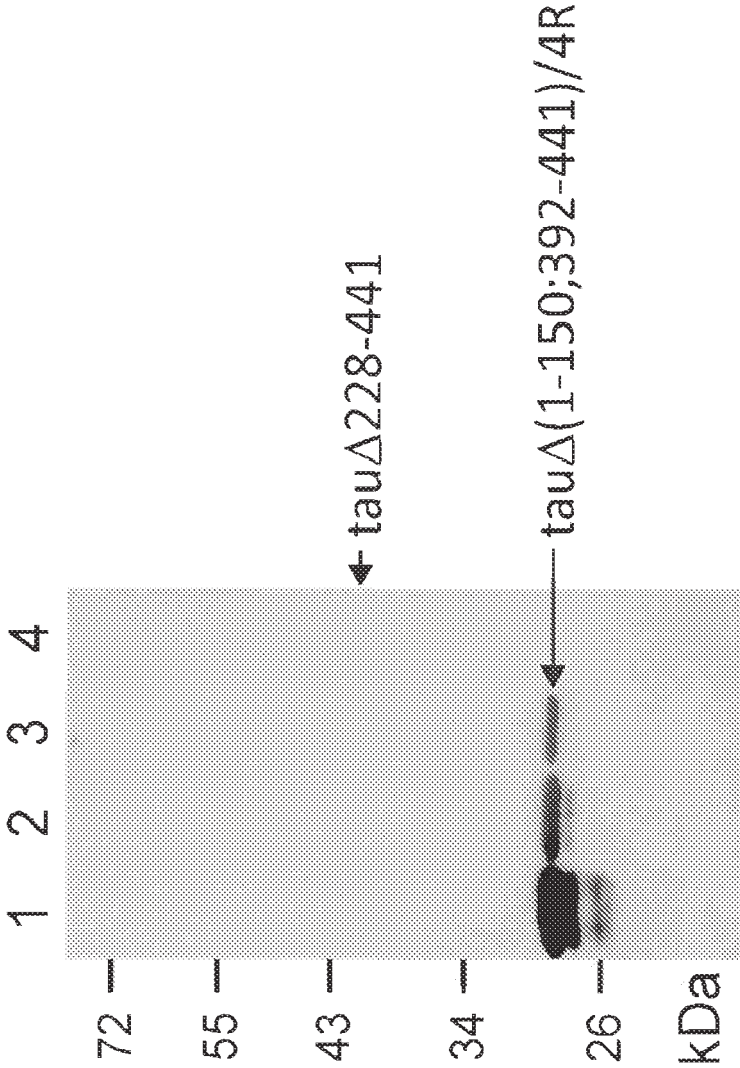


FIGURE 24A

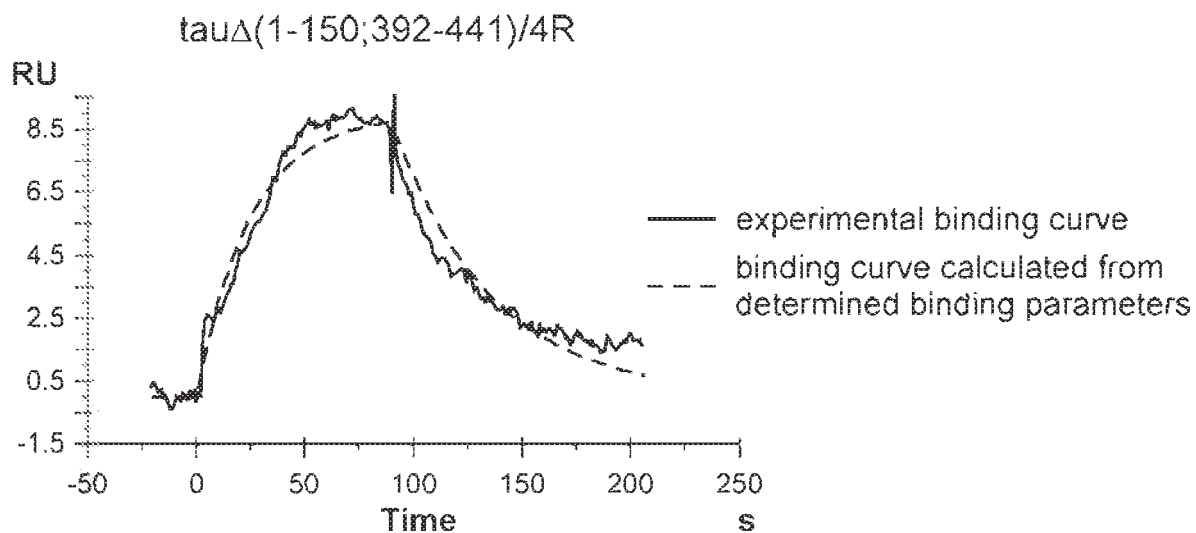


FIGURE 24B

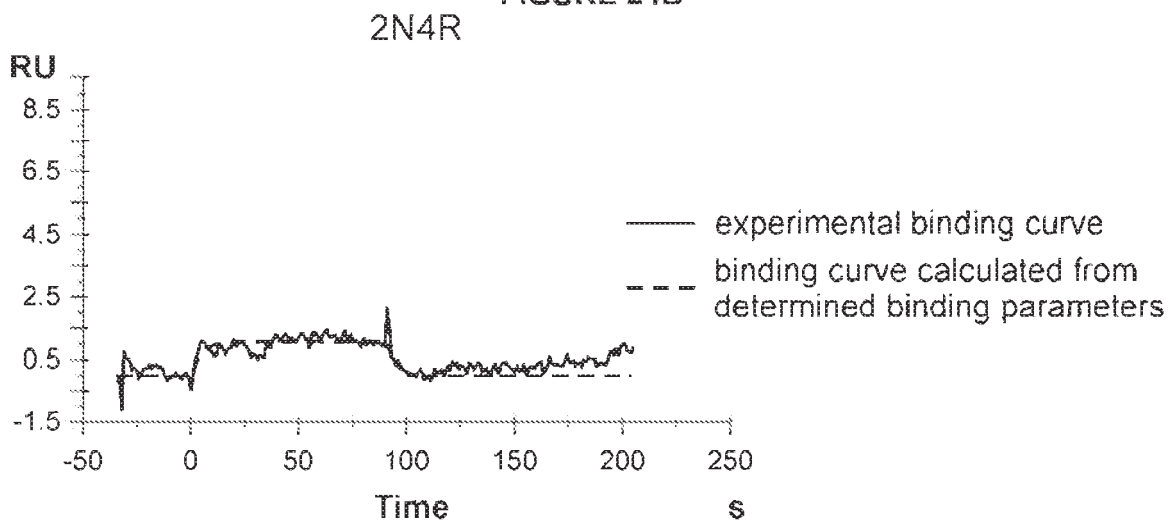


FIGURE 24C

	$k_{\text{ON}}(\text{s}^{-1} \text{M}^{-1})$	$k_{\text{OFF}}(\text{s}^{-1})$	$K_{\text{A}}(\text{M}^{-1})$
$\text{tau}\Delta(1-150;392-441)/4R$	1.8×10^5	0.02	8.1×10^6
2N4R	5.7×10^4	0.2	2.7×10^5

FIGURE 25A

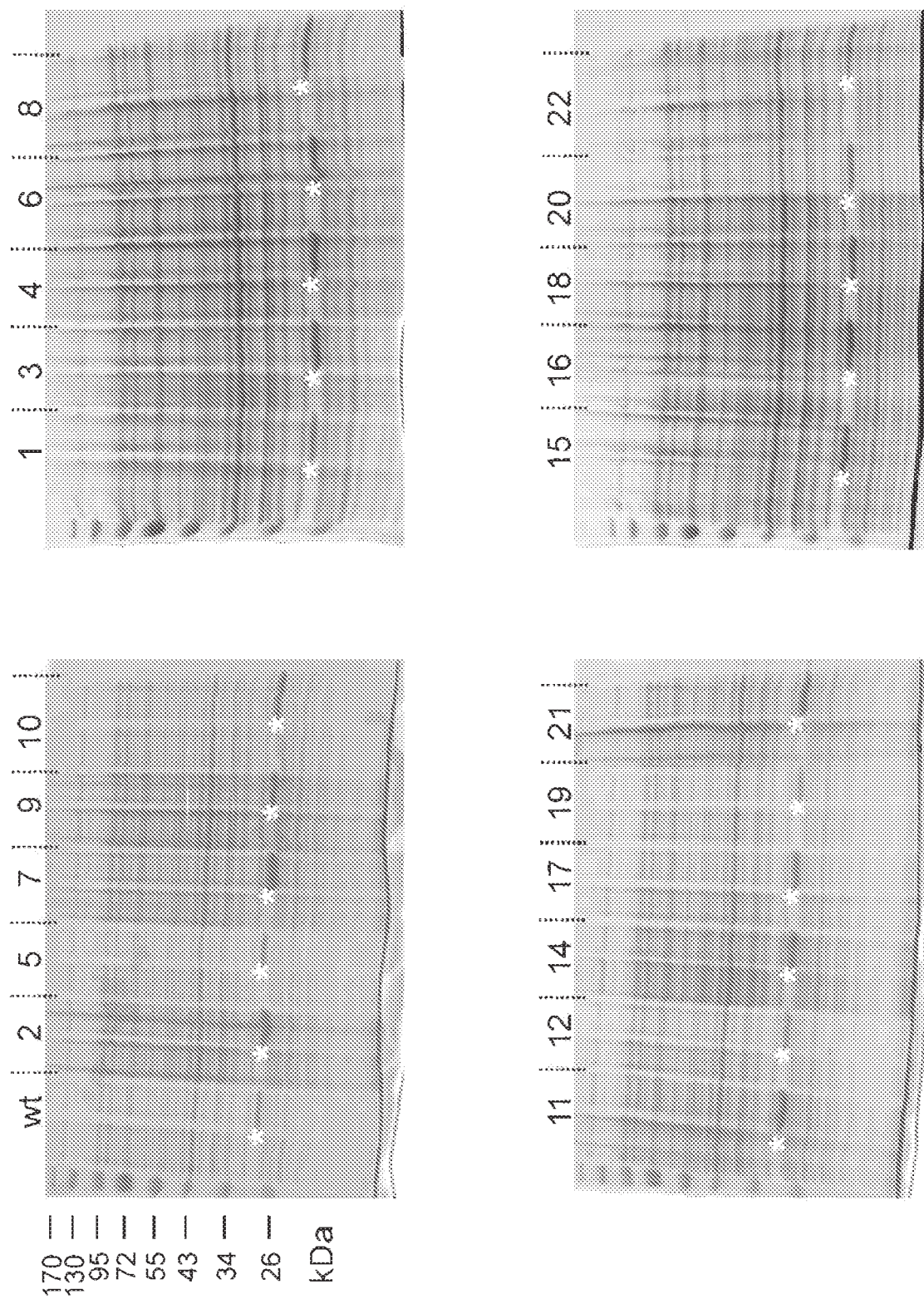


FIGURE 25B

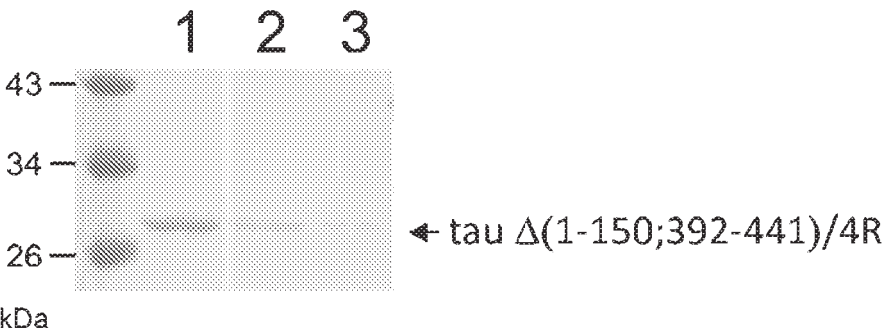


FIGURE 25C

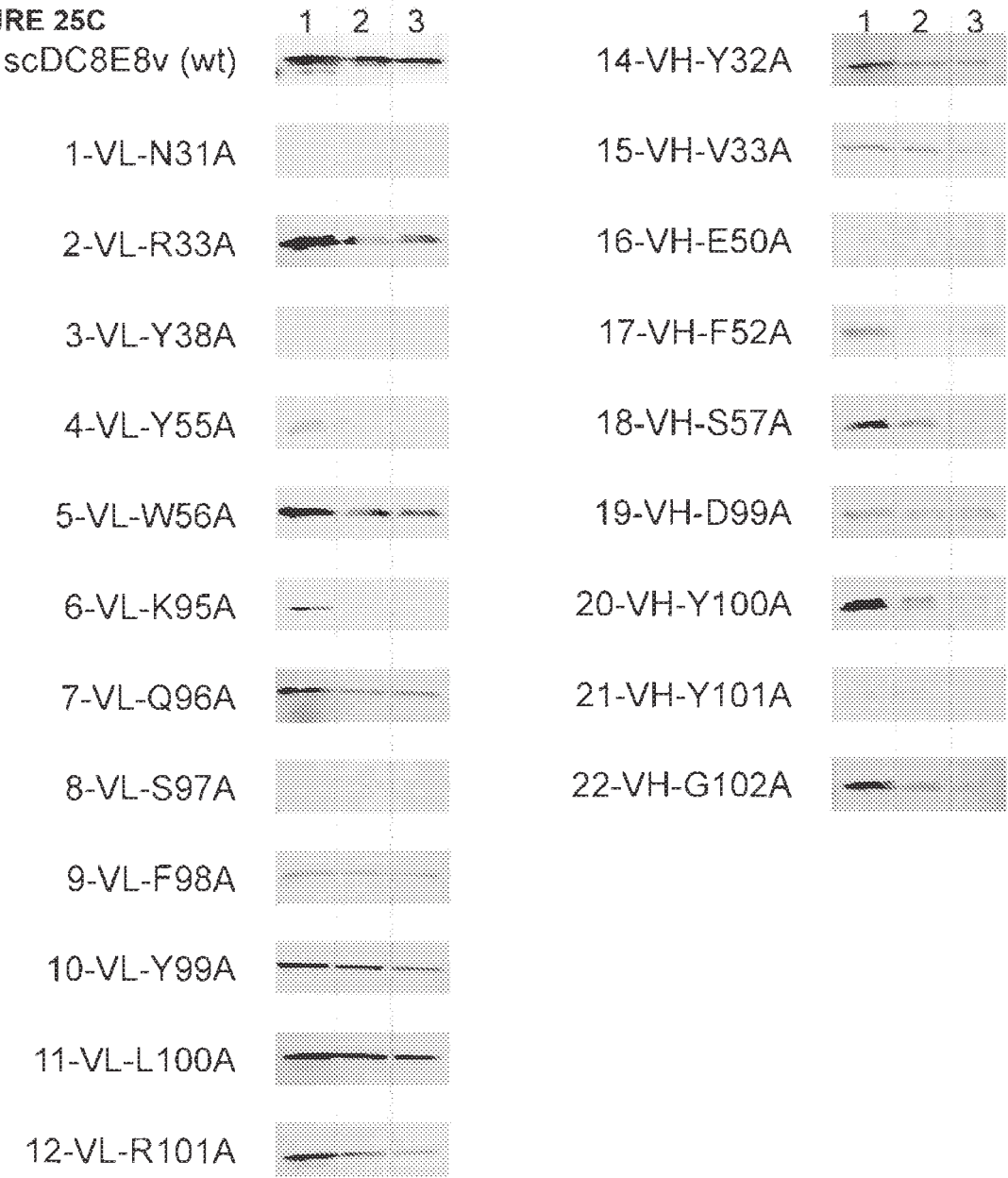


FIGURE 26A

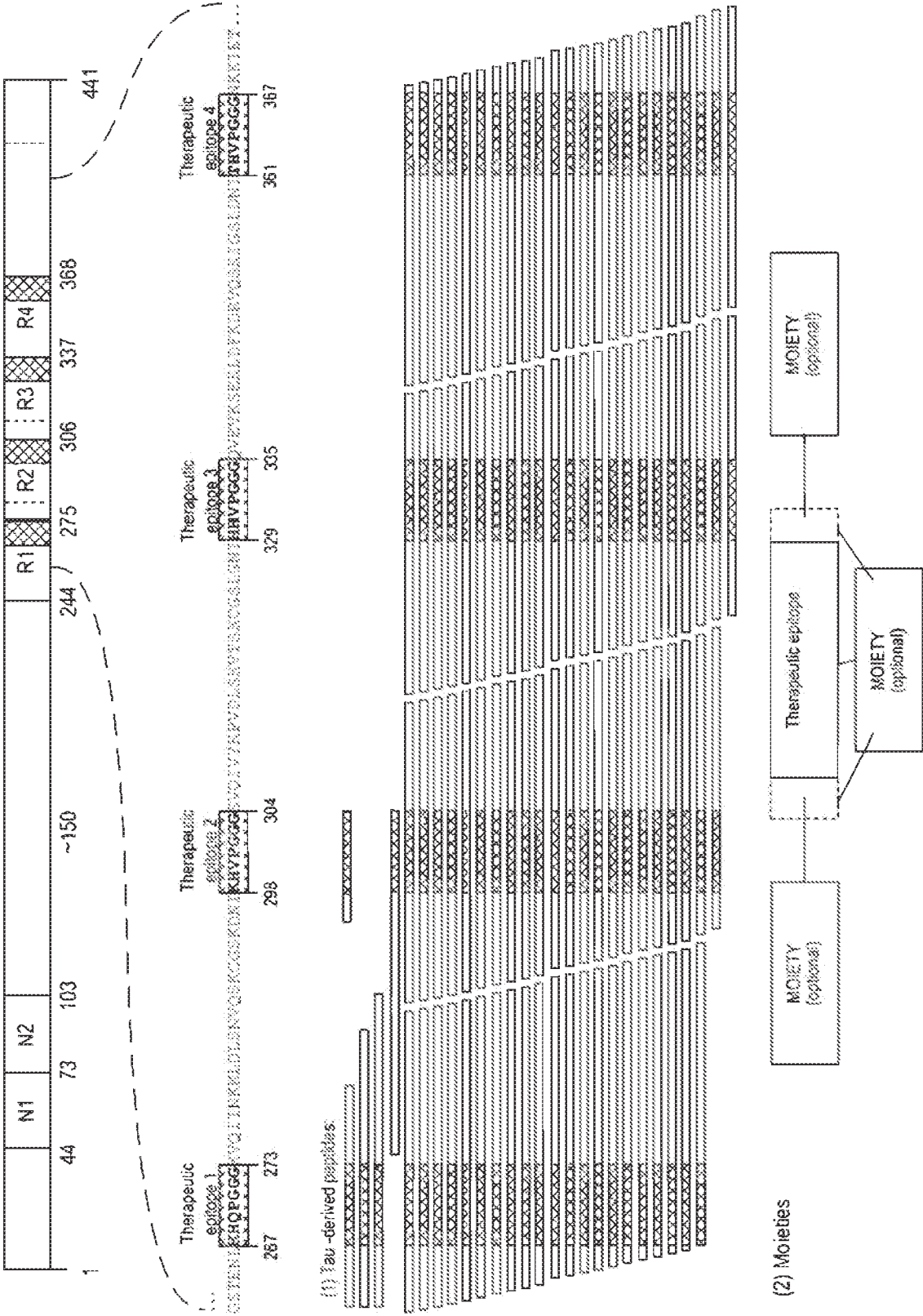
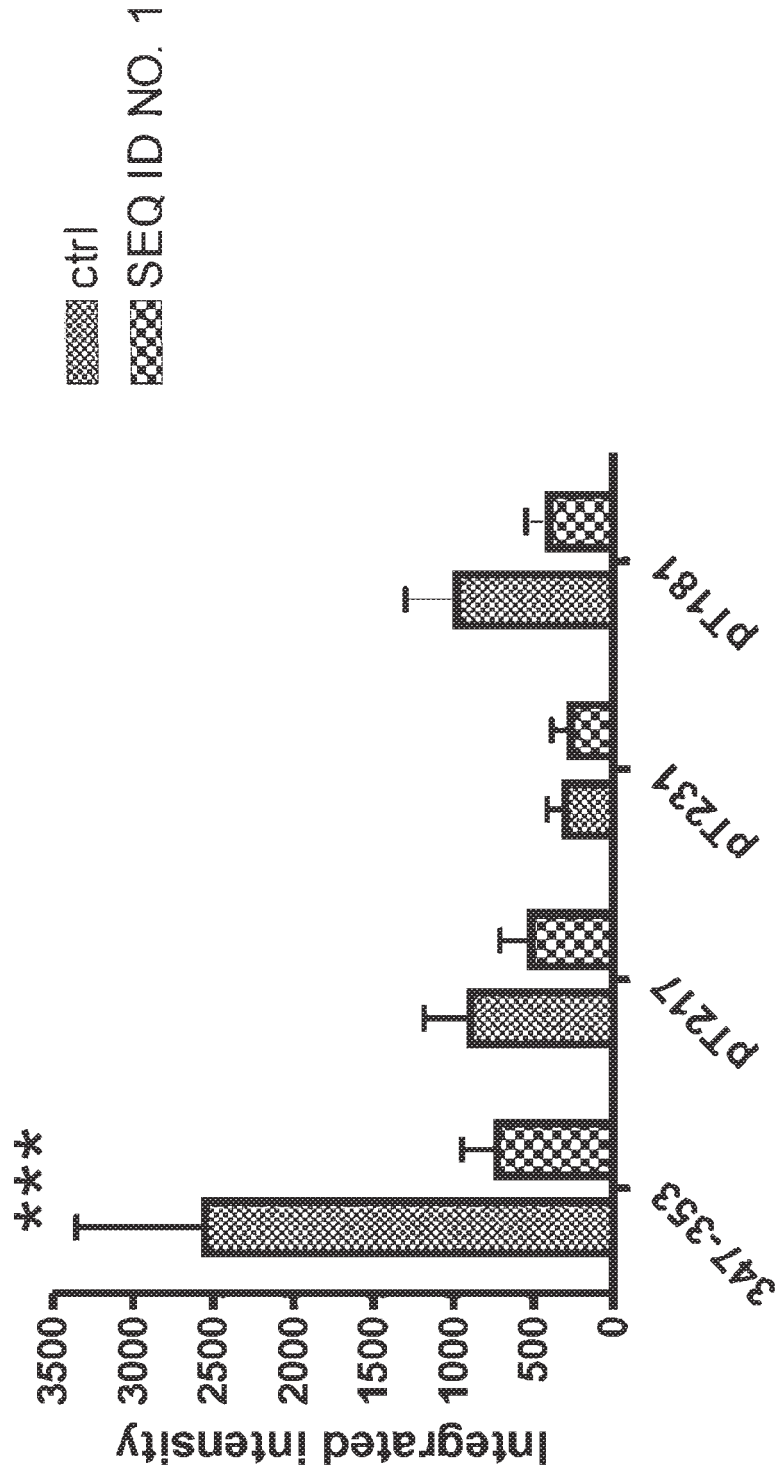


FIGURE 26B

SEQ ID NO	Immunogen	Reduction of insoluble tau (%) AD-relevant epitopes					
		347-353	pT217	pT231	pS202/pT205	pT181	
SEQ ID NO:1	Tau 251-280	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	

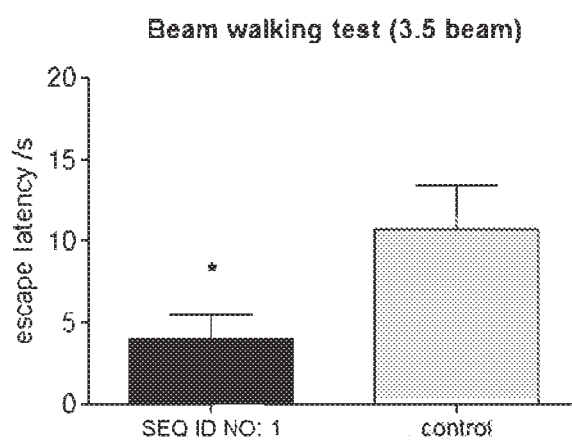
FIGURE 26C



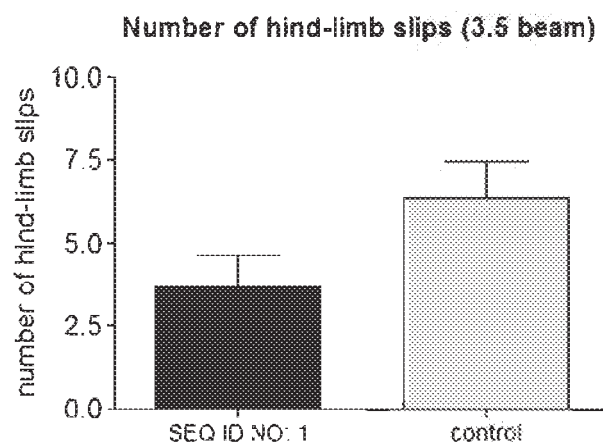
51/115

FIGURE 27

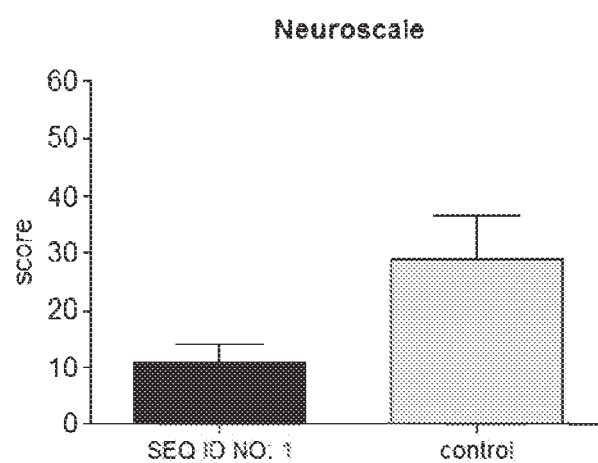
A



B



C



52/115

FIGURE 28

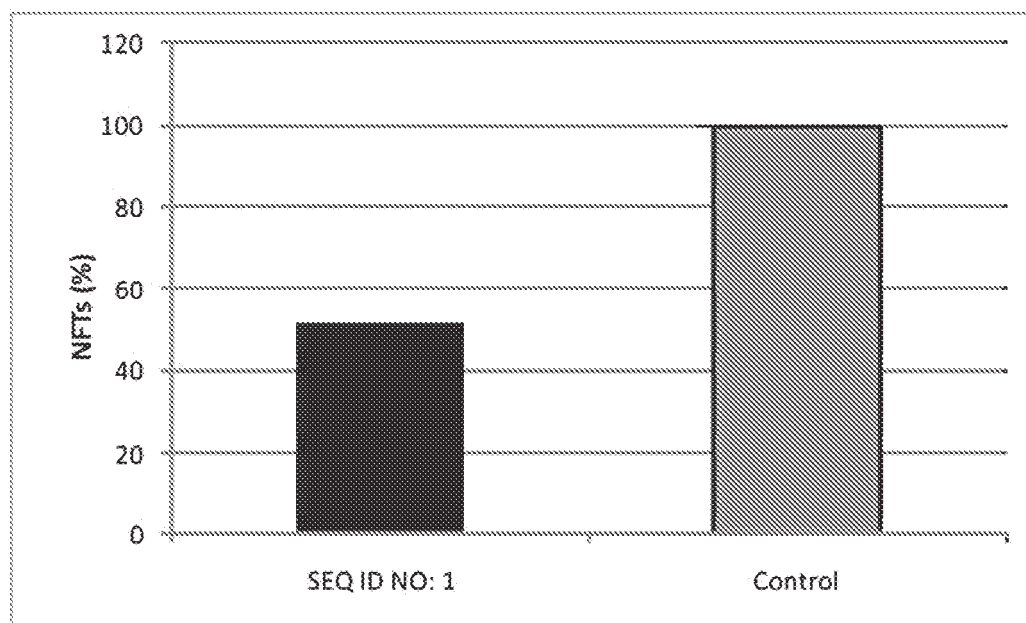
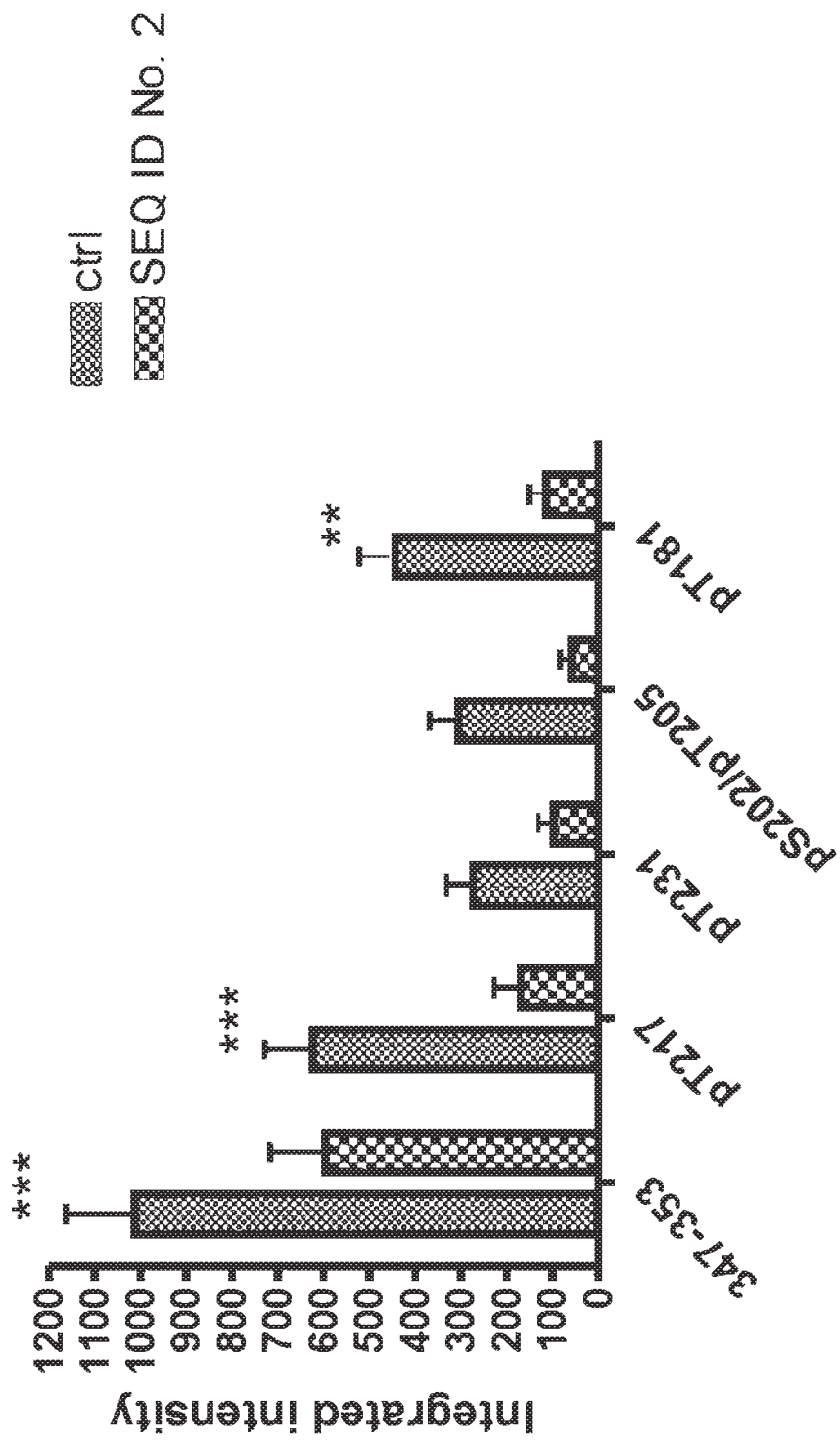


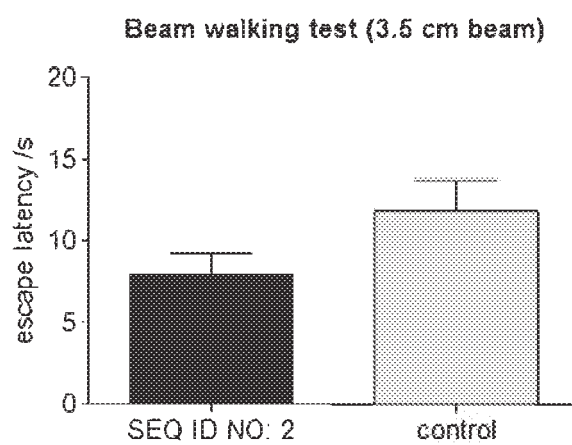
FIGURE 29



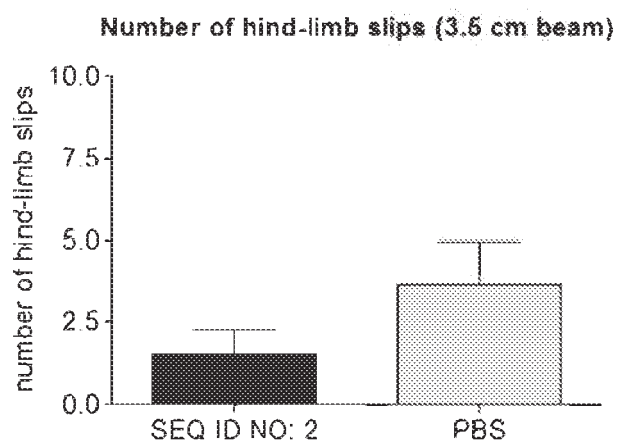
54/115

FIGURE 30

A.



B.



C.

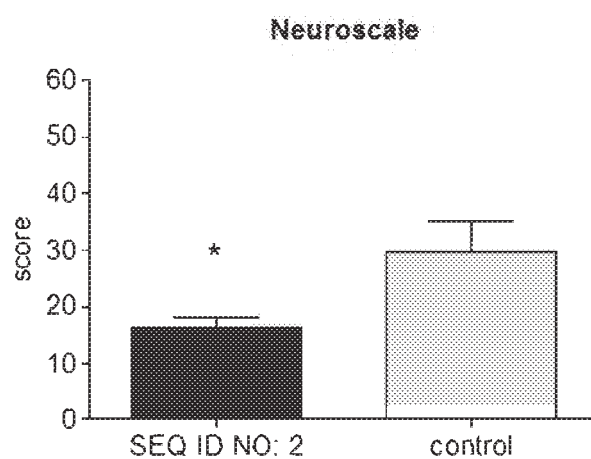


FIGURE 31

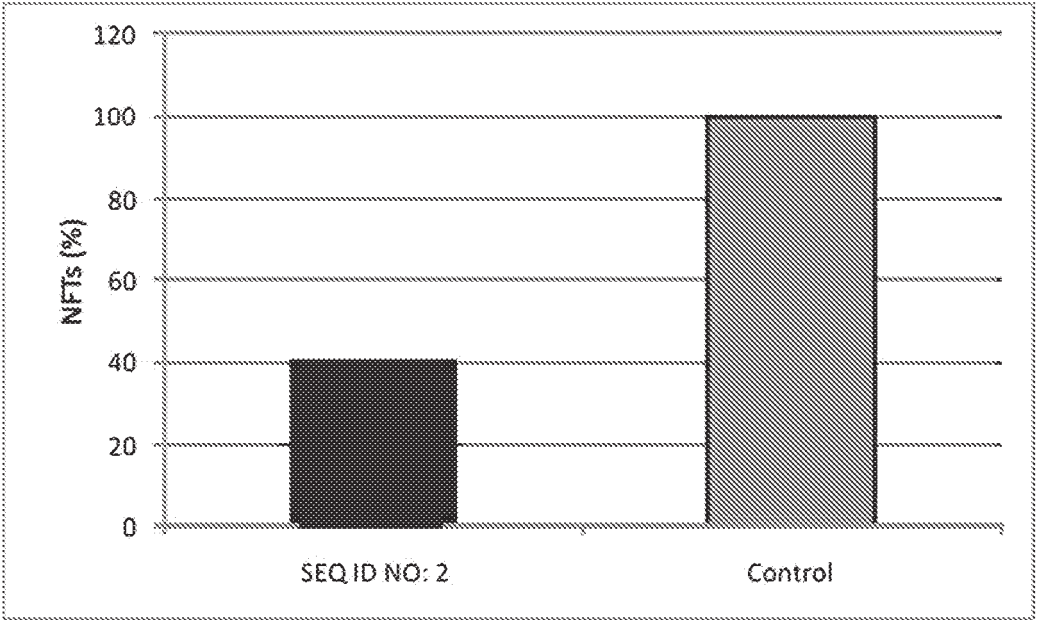
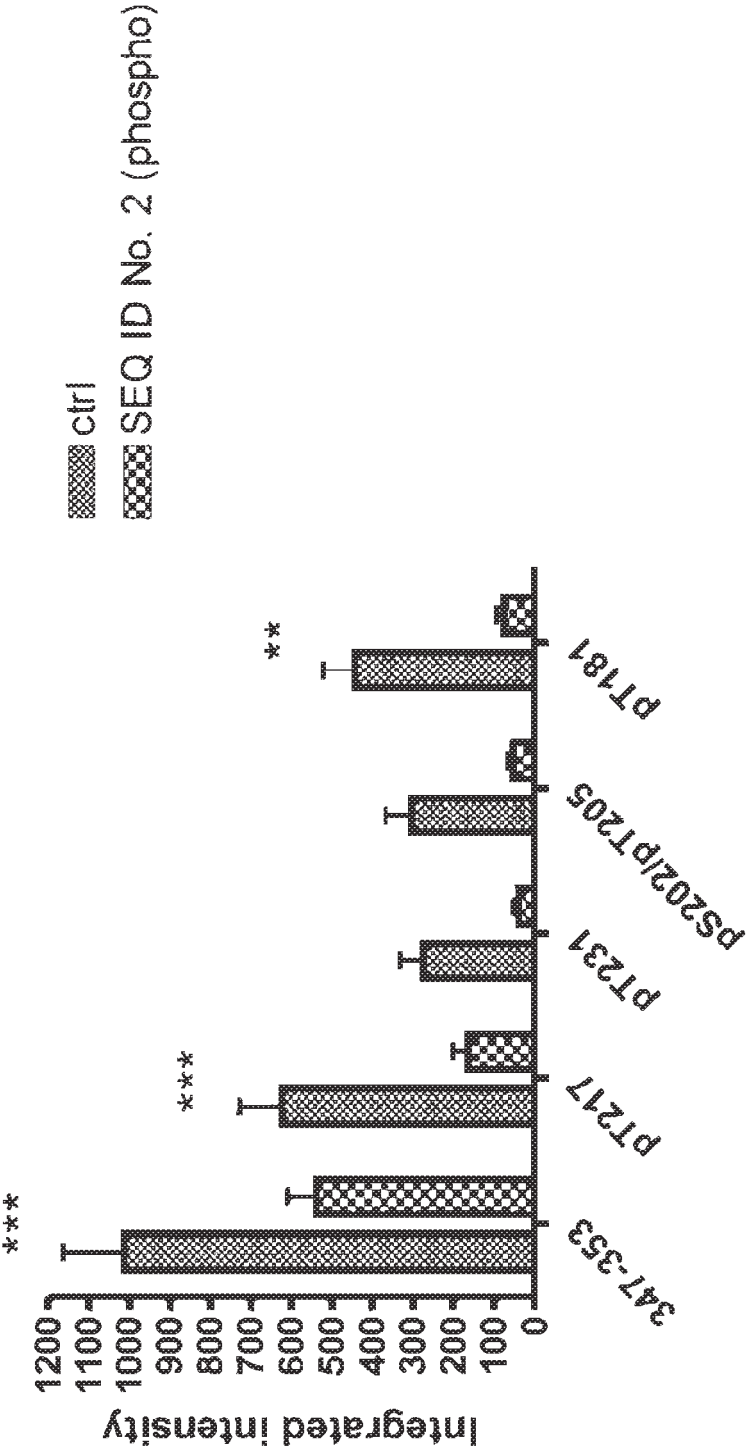


FIGURE 32



57/115

FIGURE 33

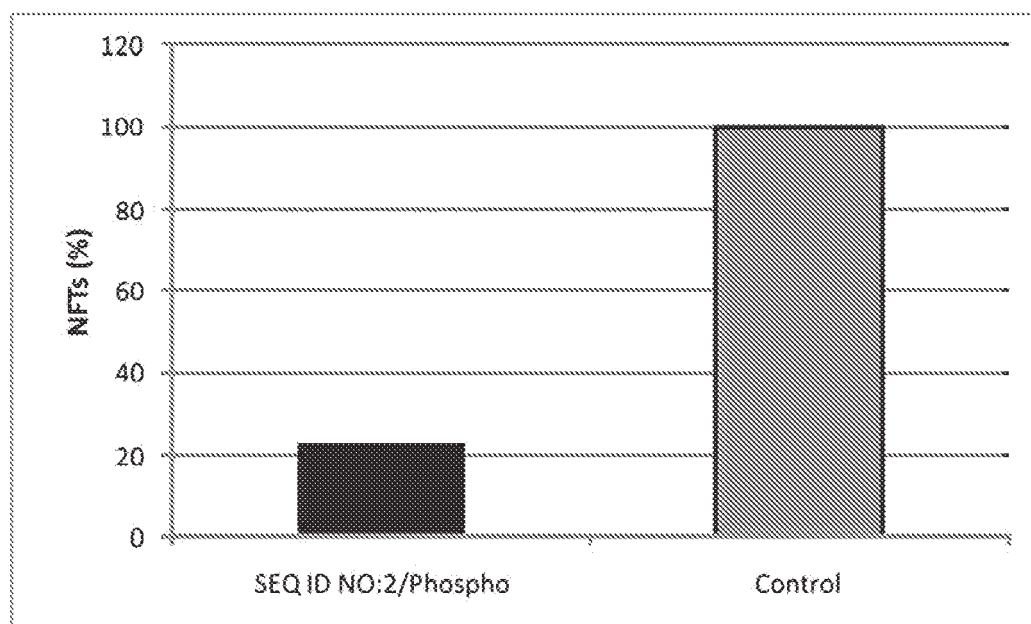
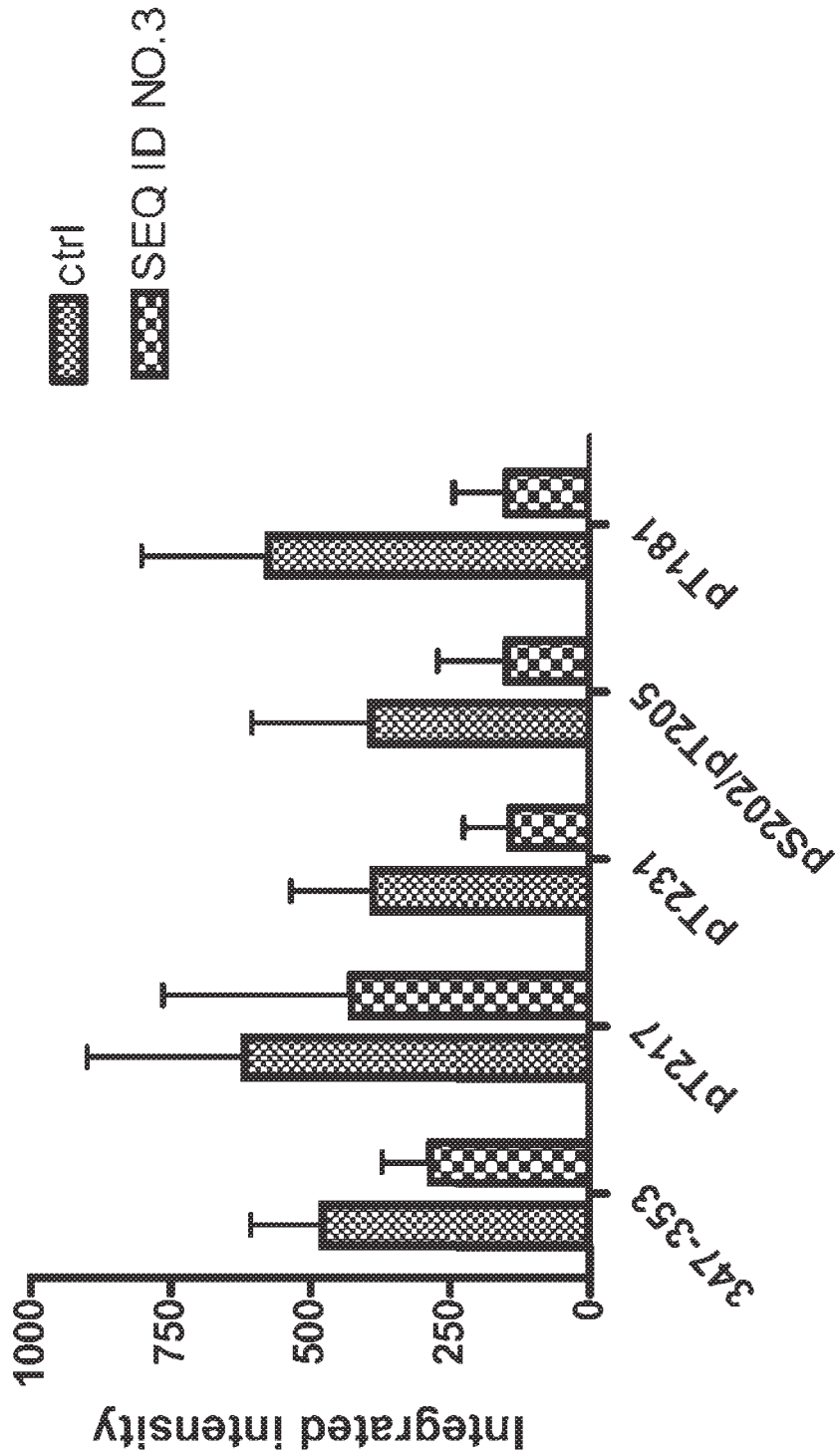


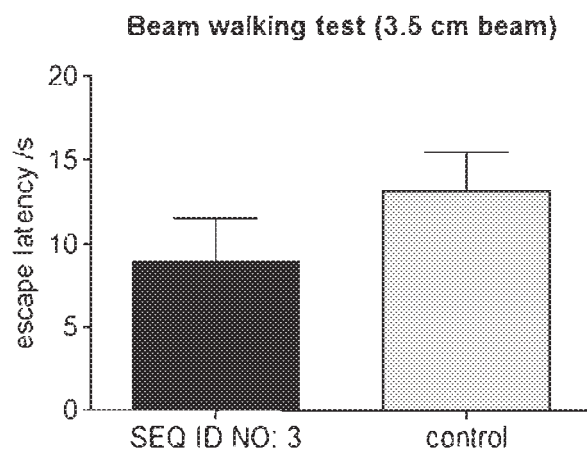
FIGURE 34



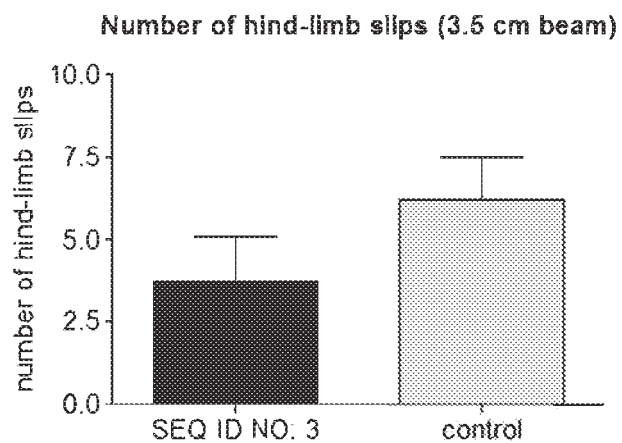
59/115

FIGURE 35

A.



B.



C.

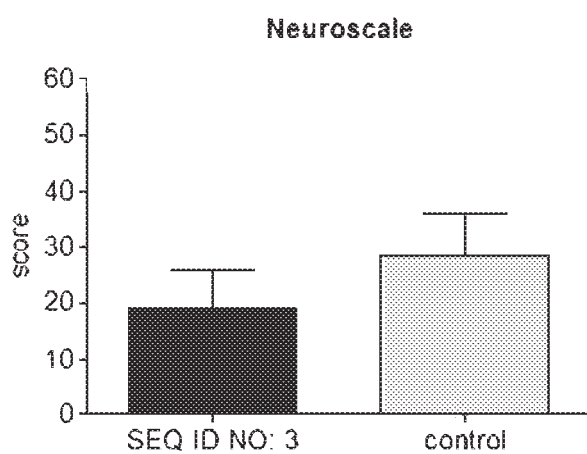


FIGURE 36

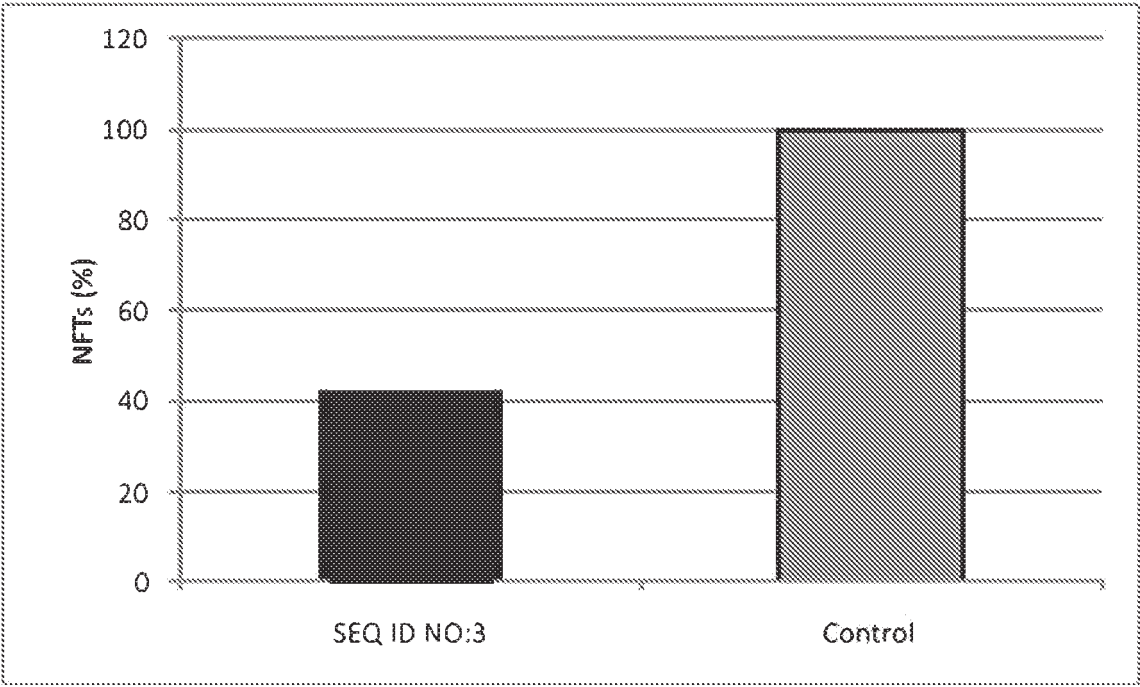


FIGURE 37

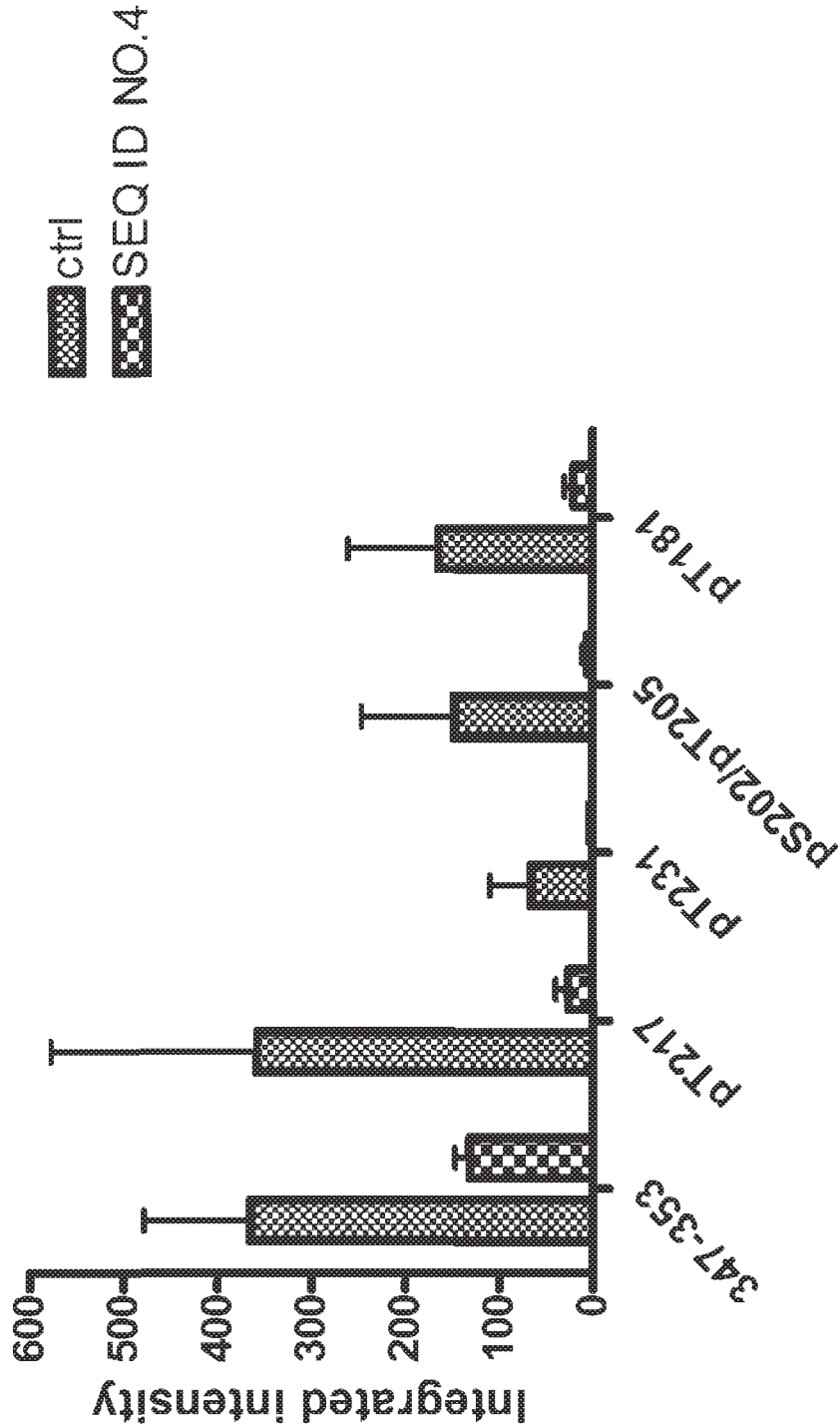
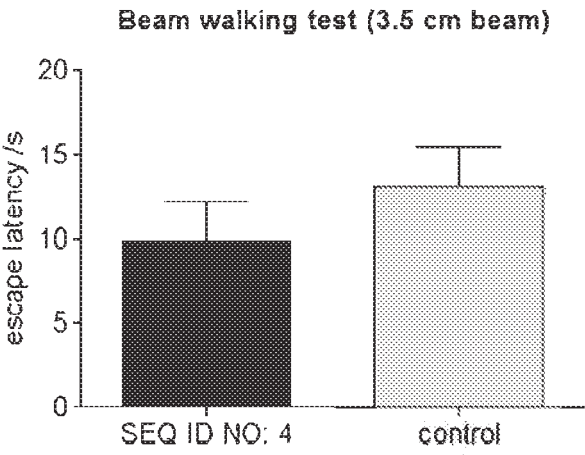
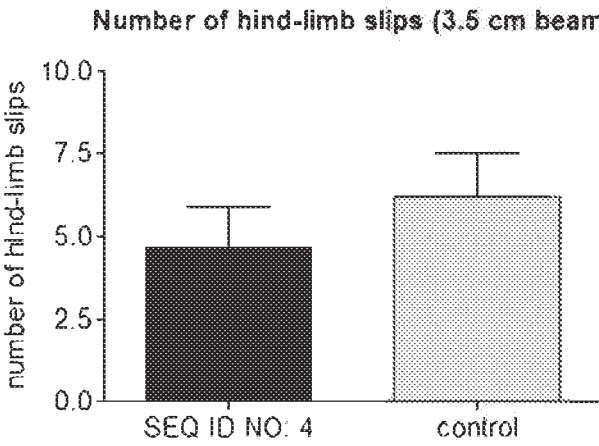


FIGURE 38

A



B



C

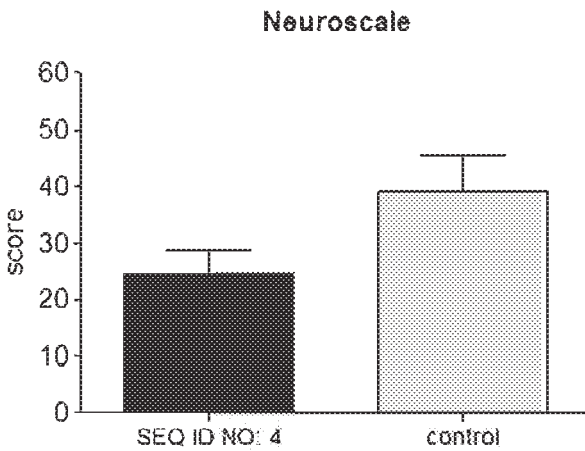


FIGURE 39

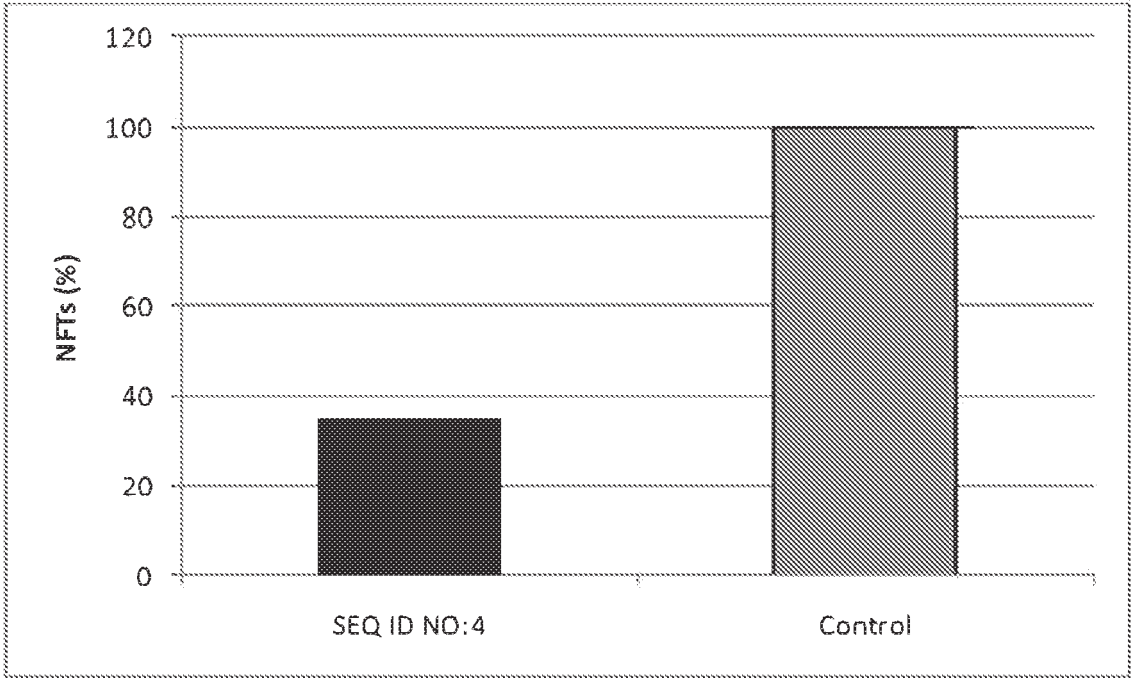
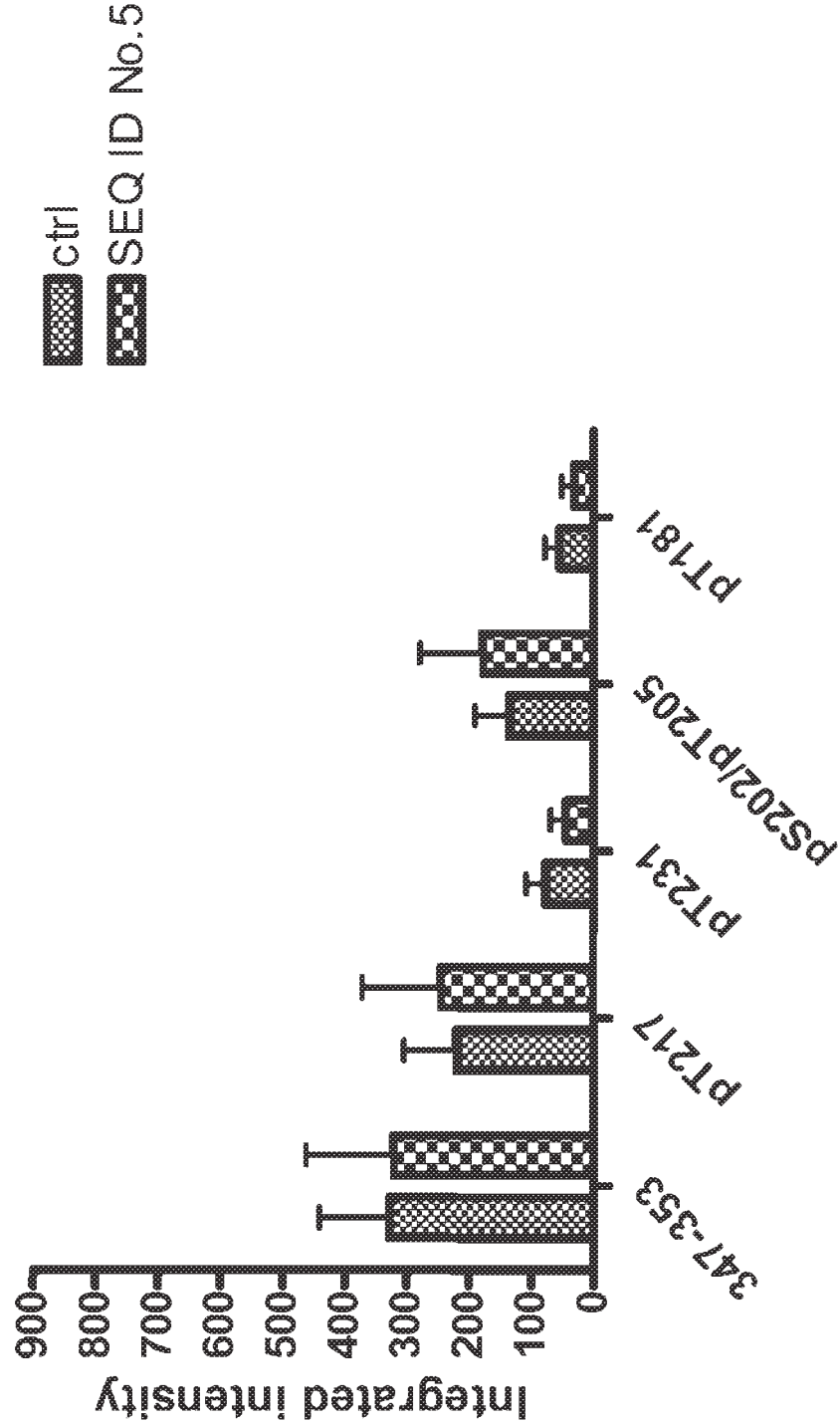


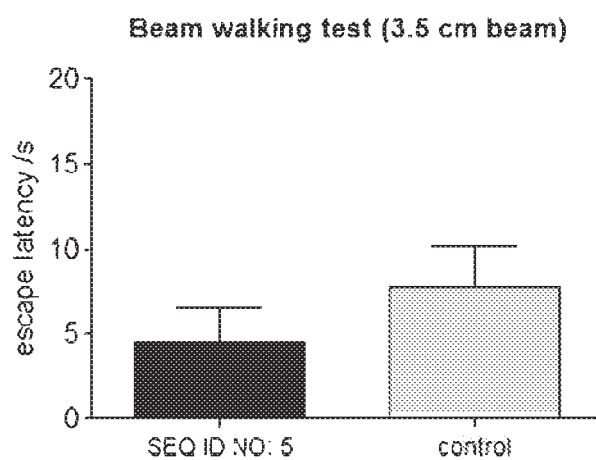
FIGURE 40



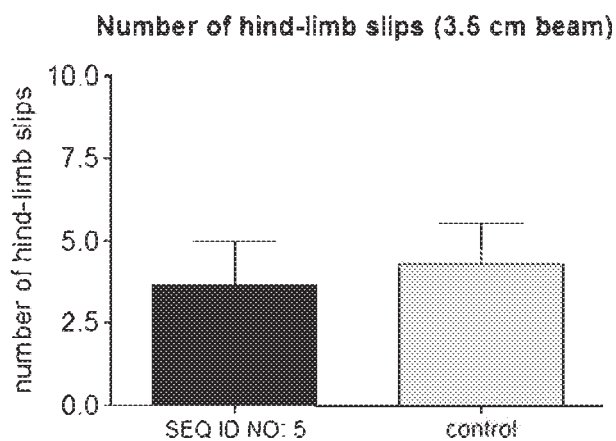
65/115

FIGURE 41

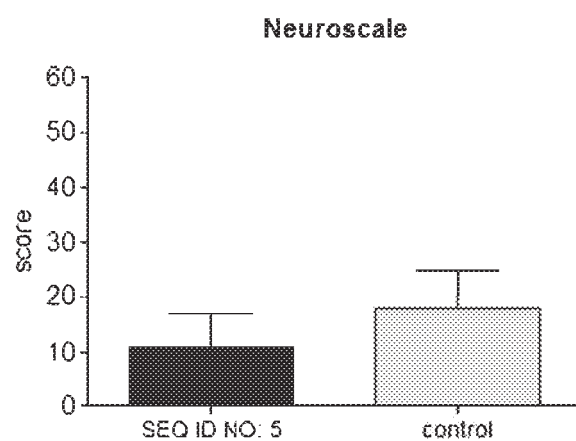
A.



B.



C.



66/115

FIGURE 42

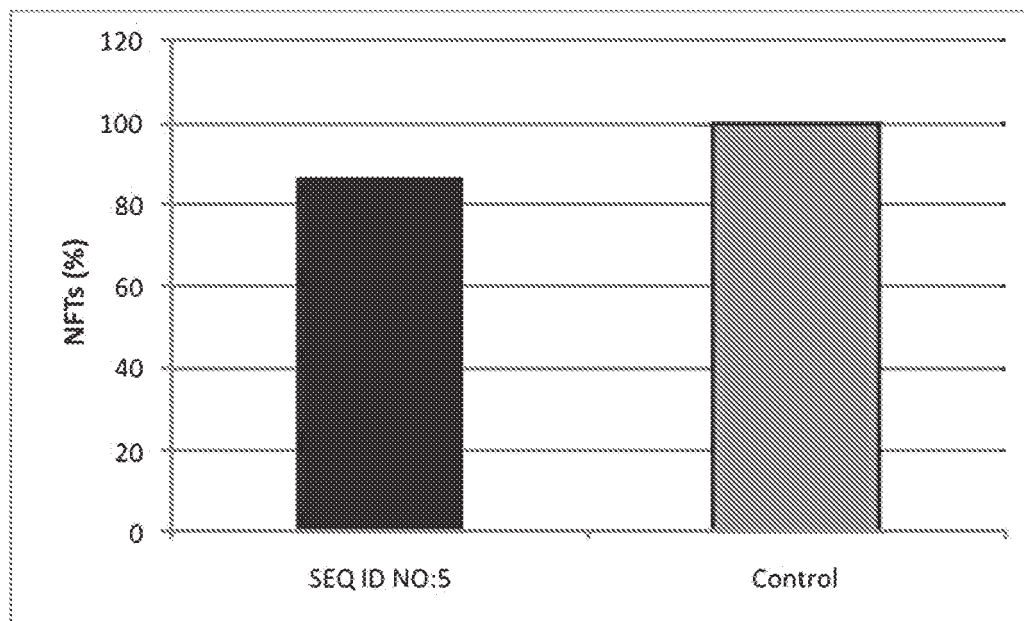
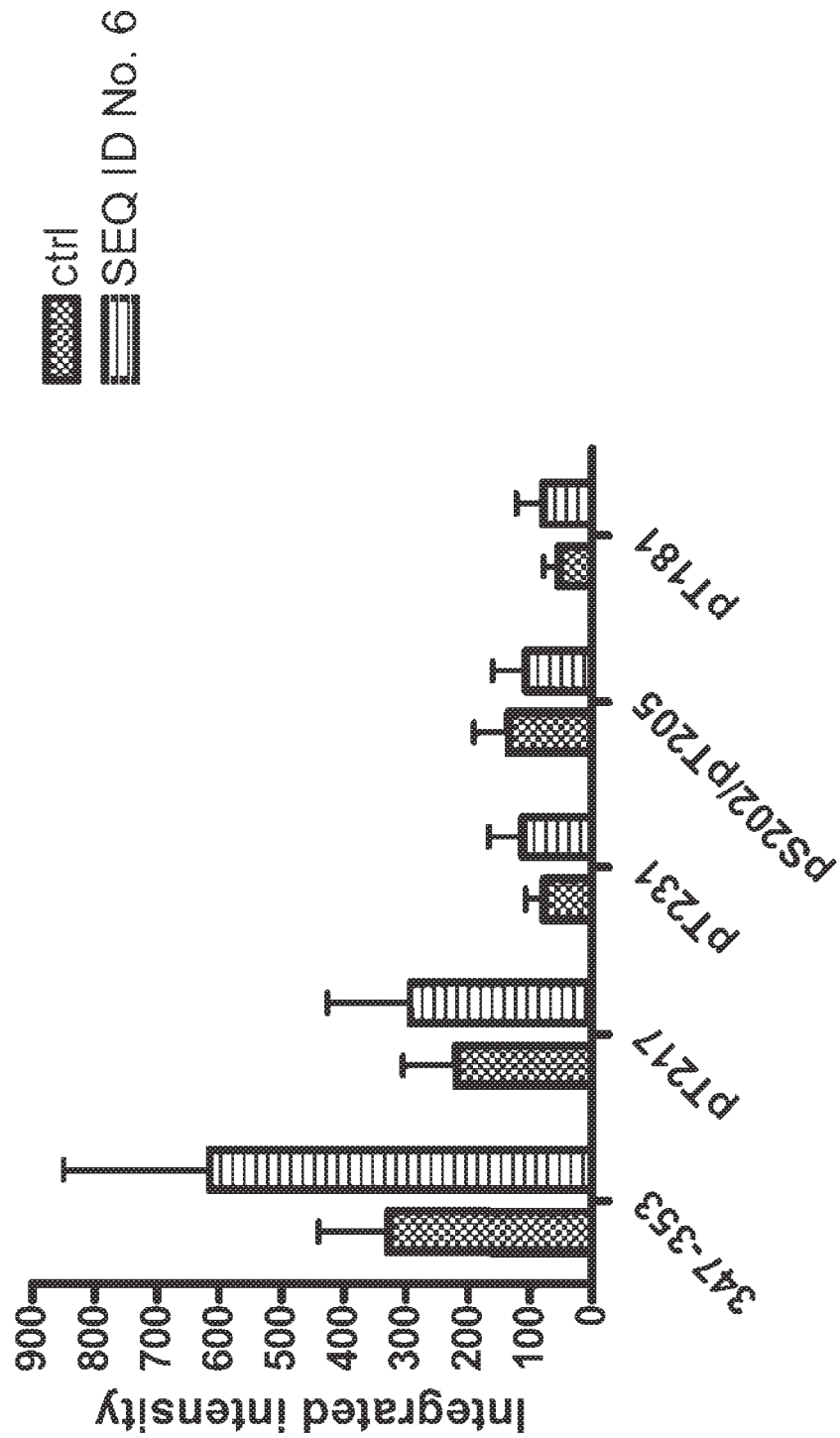


FIGURE 43

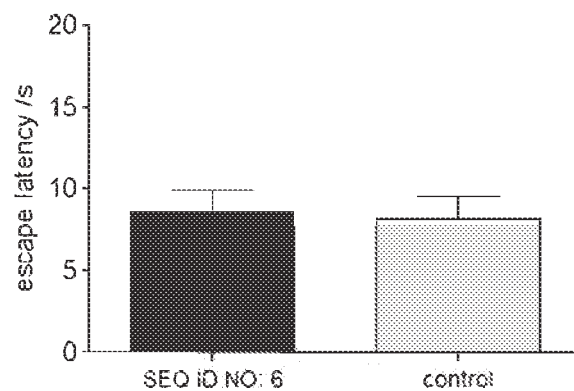


68/115

FIGURE 44

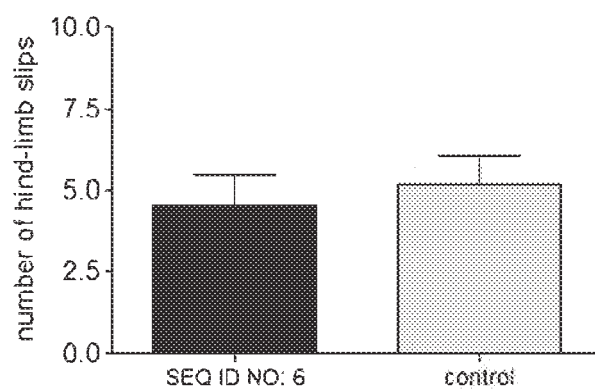
A.

Beam walking test (3.5 cm beam)



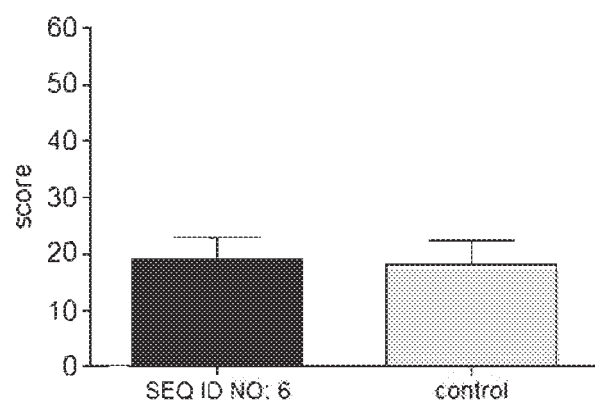
B.

Number of hind-limb slips (3.5 cm beam)



C.

Neuroscale



69/115

FIGURE 45

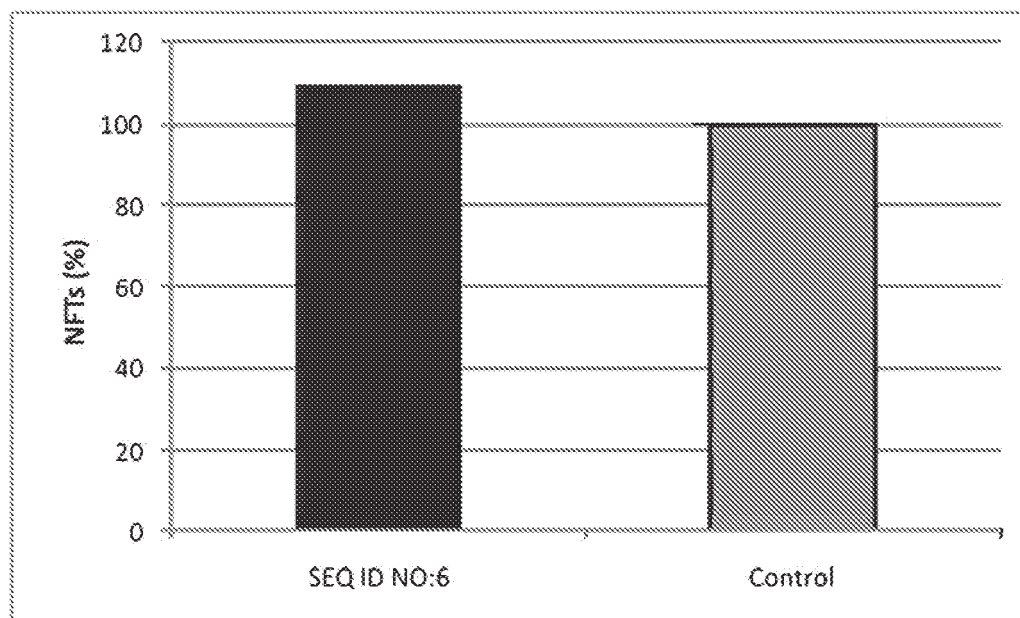


FIGURE 46

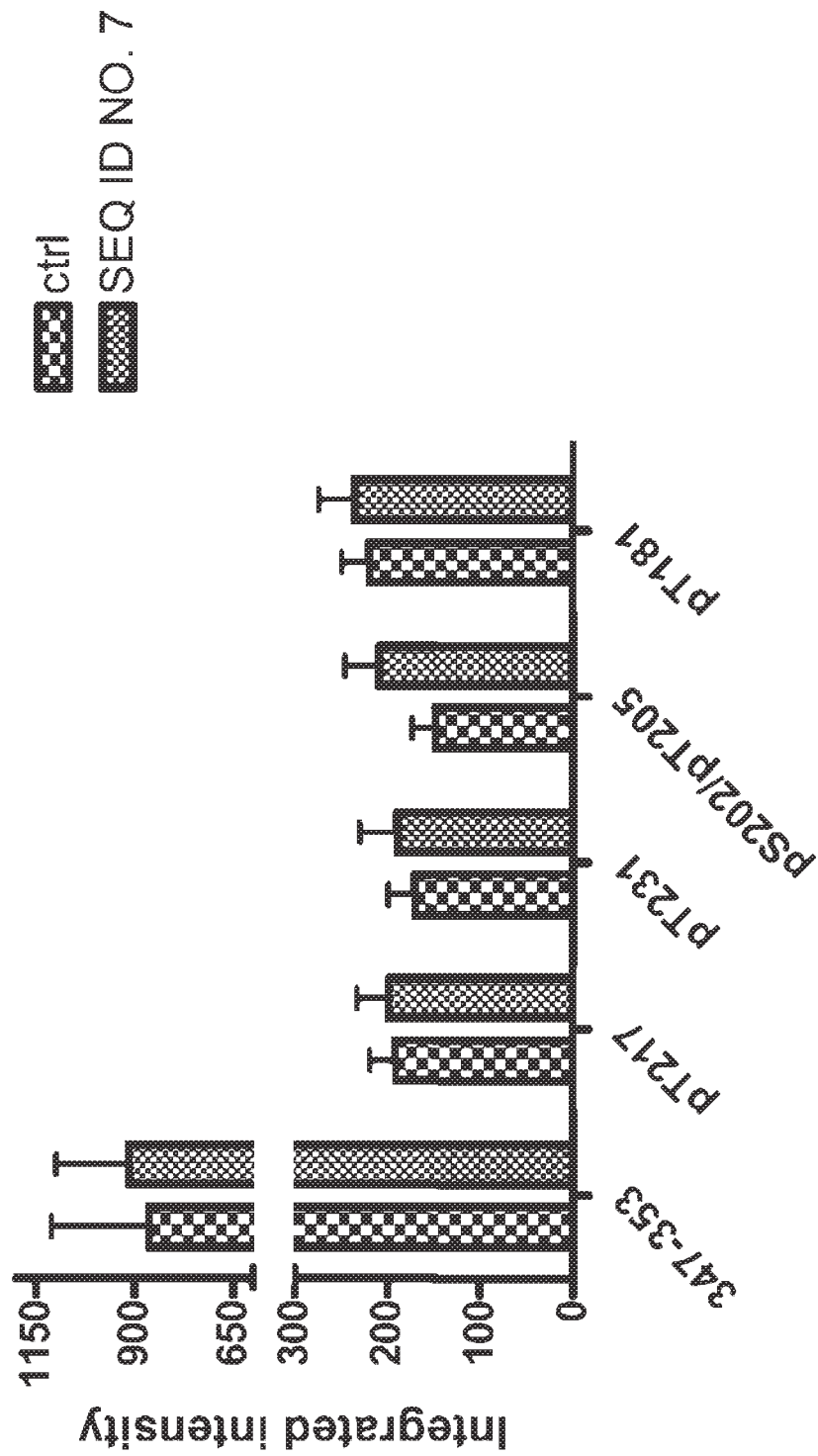
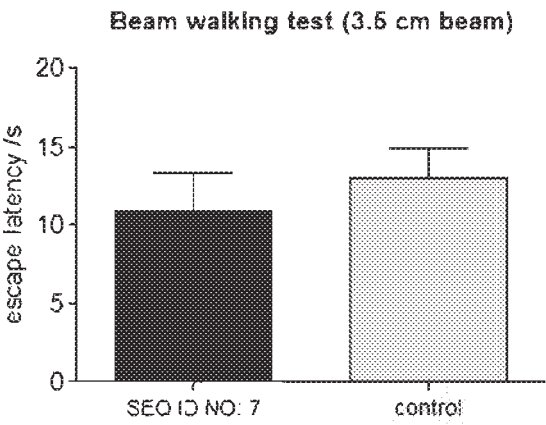
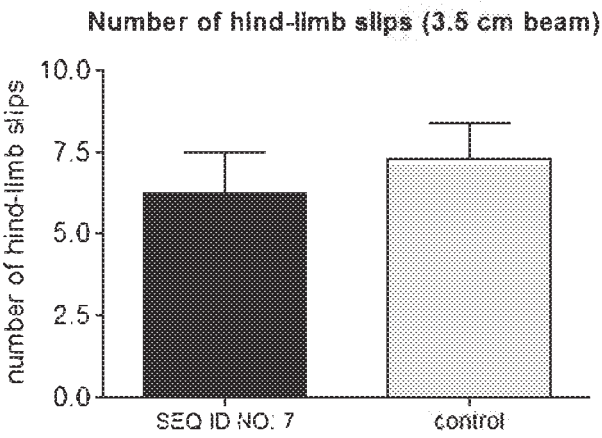


FIGURE 47

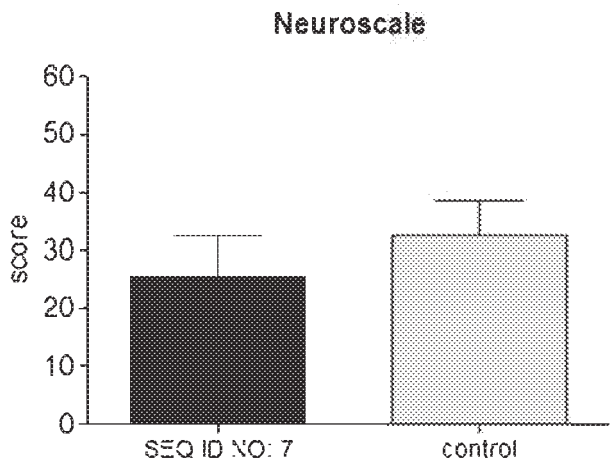
A.



B.



C.



72/115

FIGURE 48

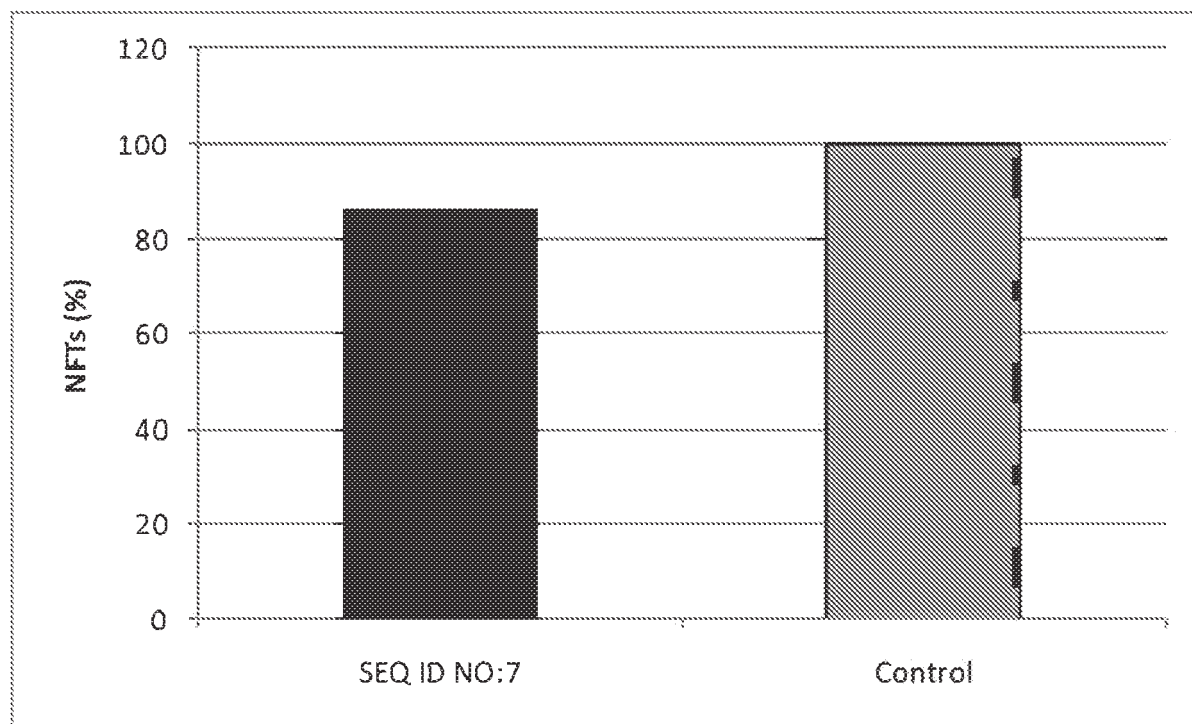
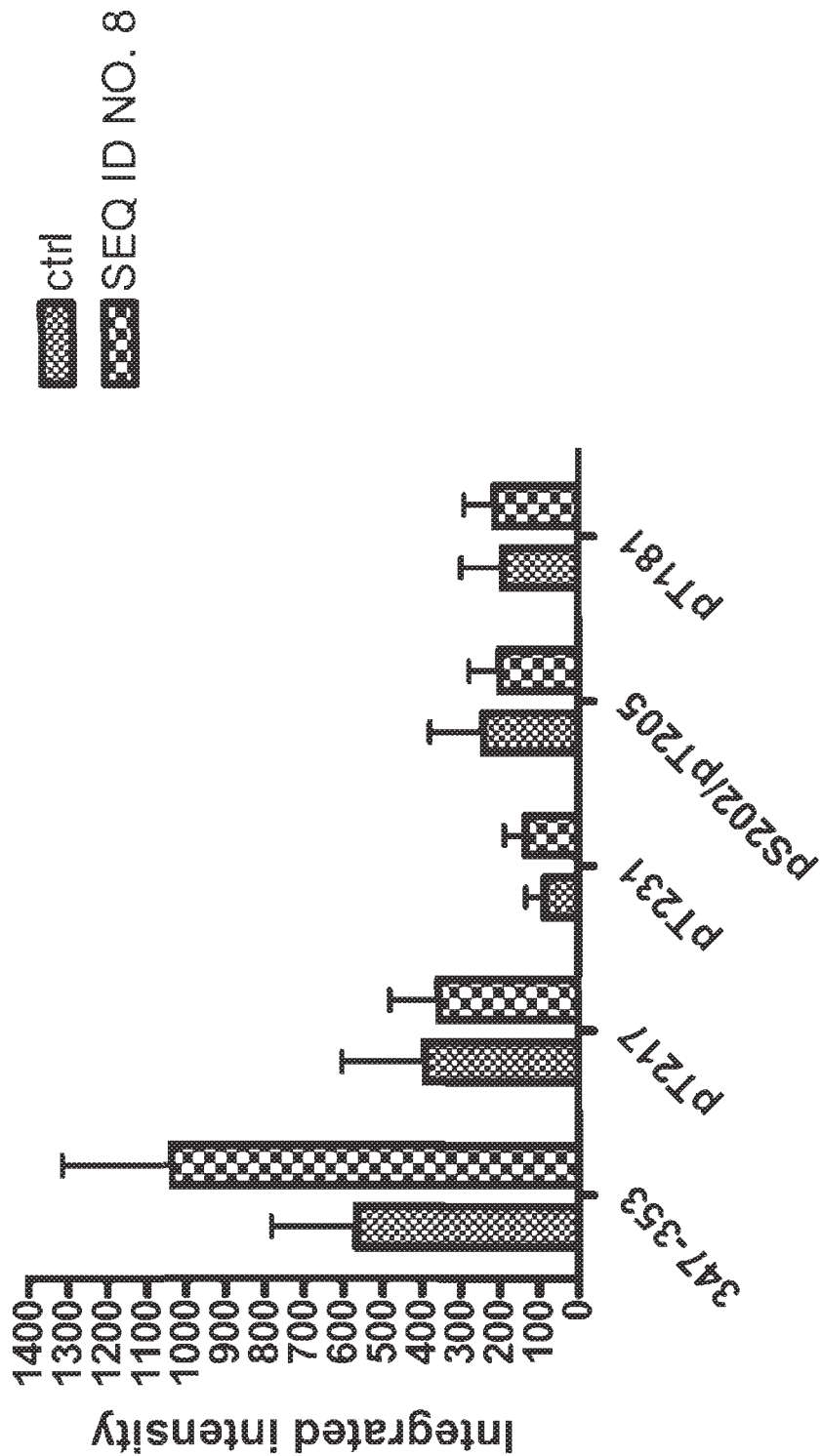


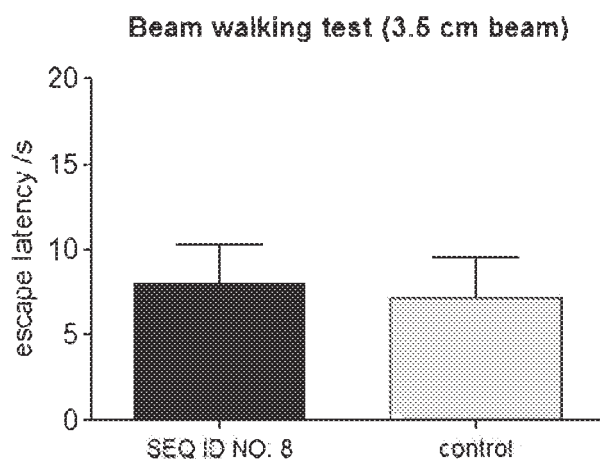
FIGURE 49



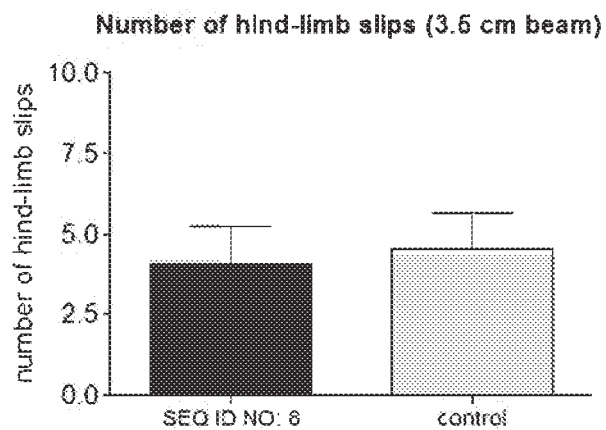
74/115

FIGURE 50

A.



B.



C.

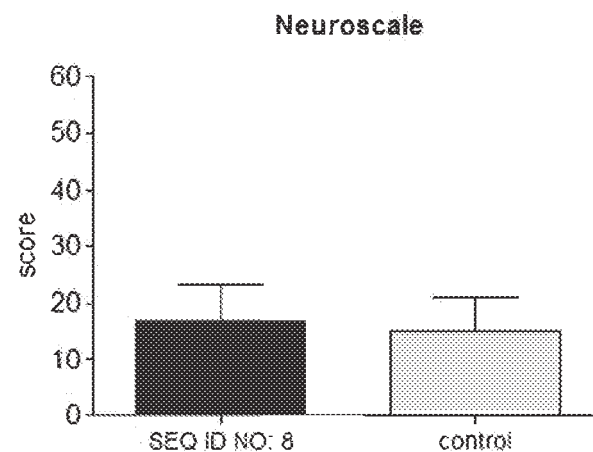


FIGURE 51

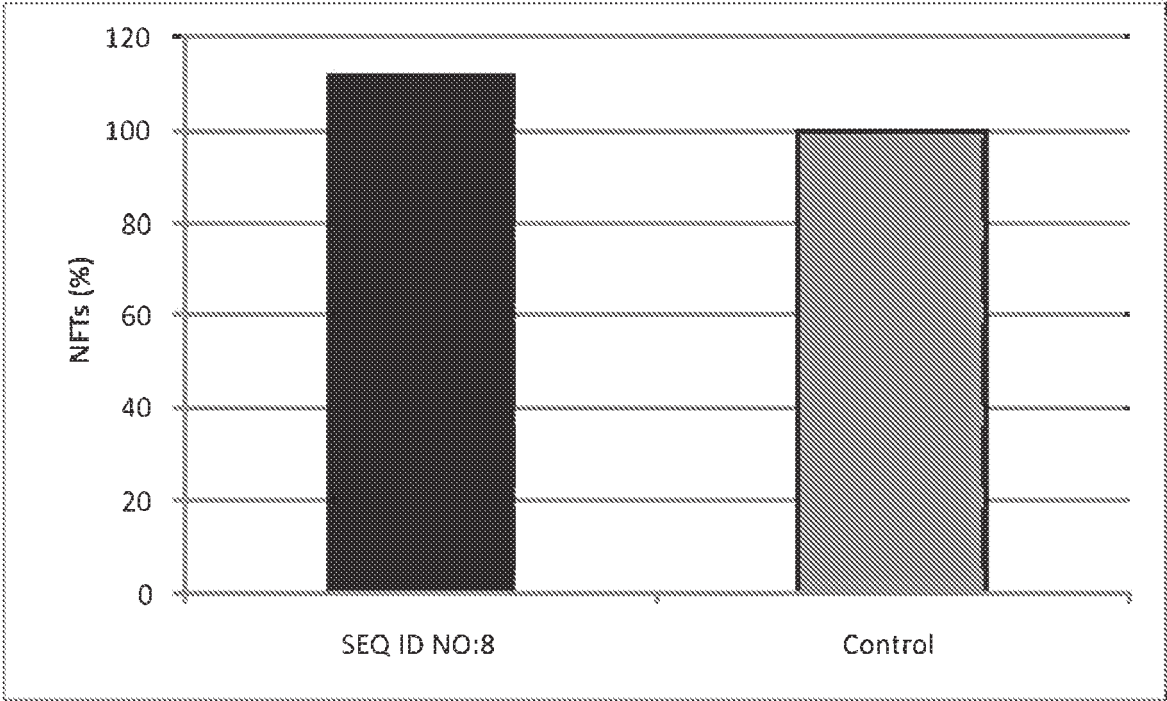
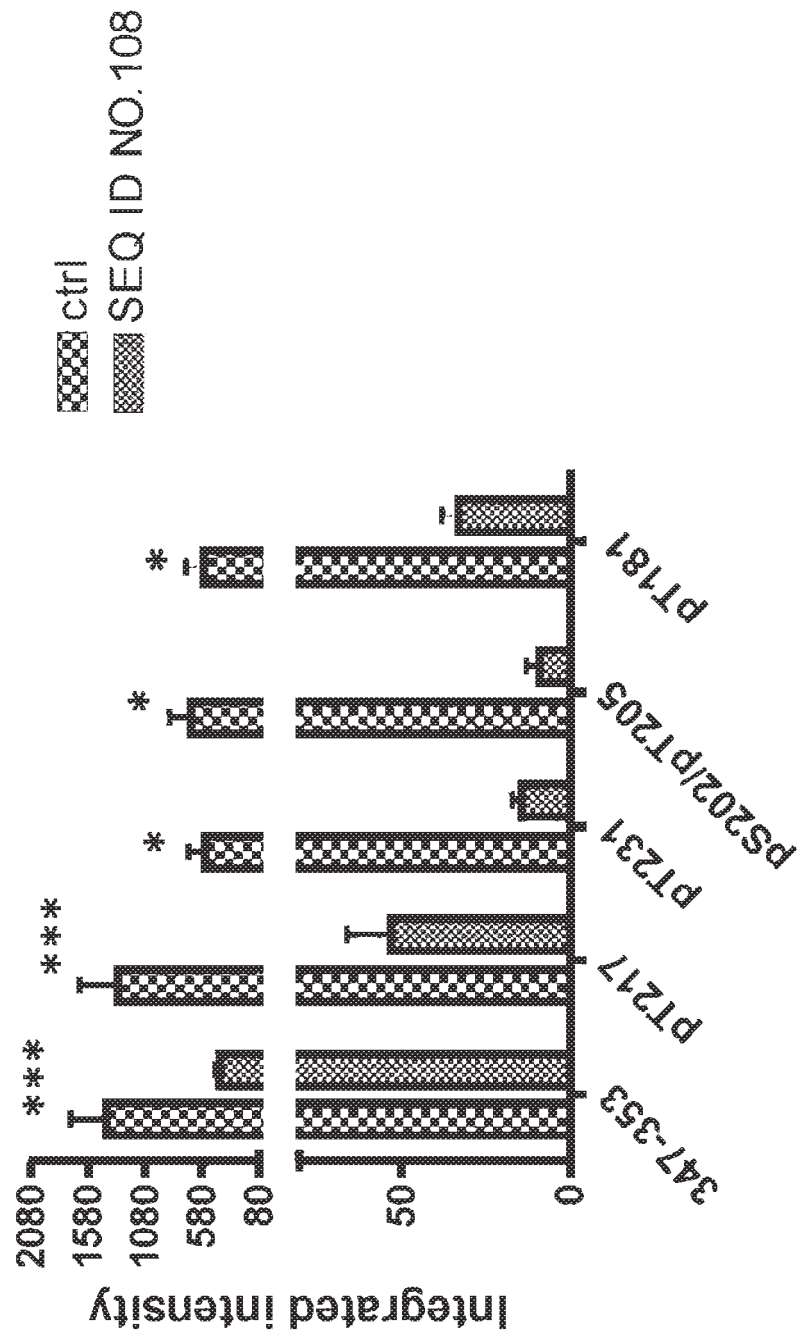


FIGURE 52

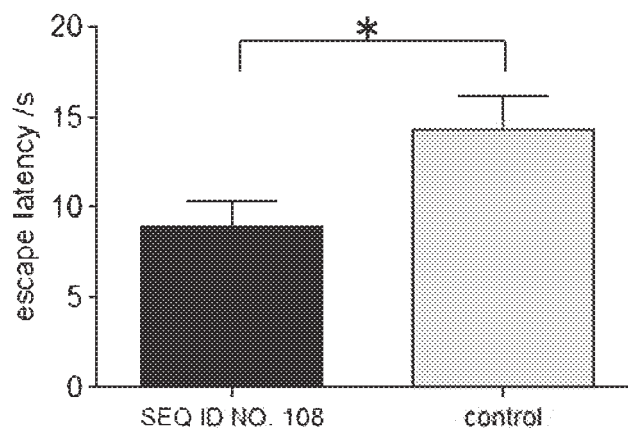


77/115

FIGURE 53

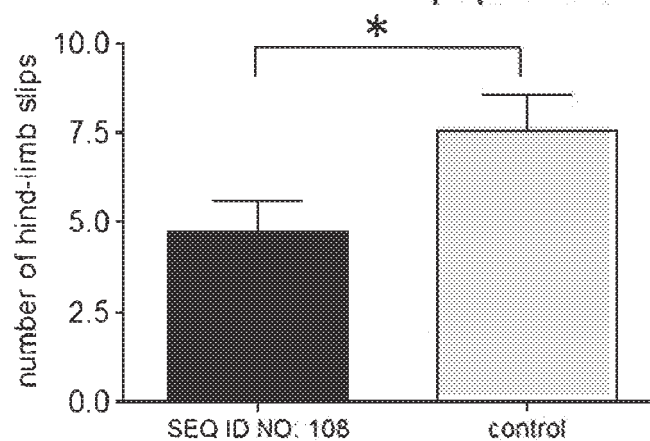
A

Beam walking test (3.5 cm beam)



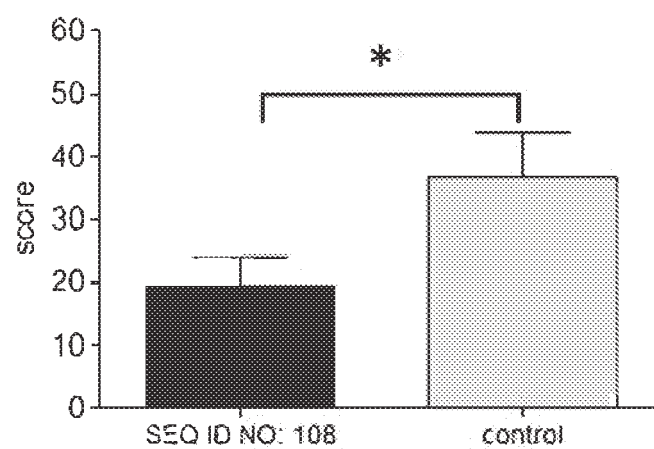
B

Number of hind-limb slips (3.5 cm beam)



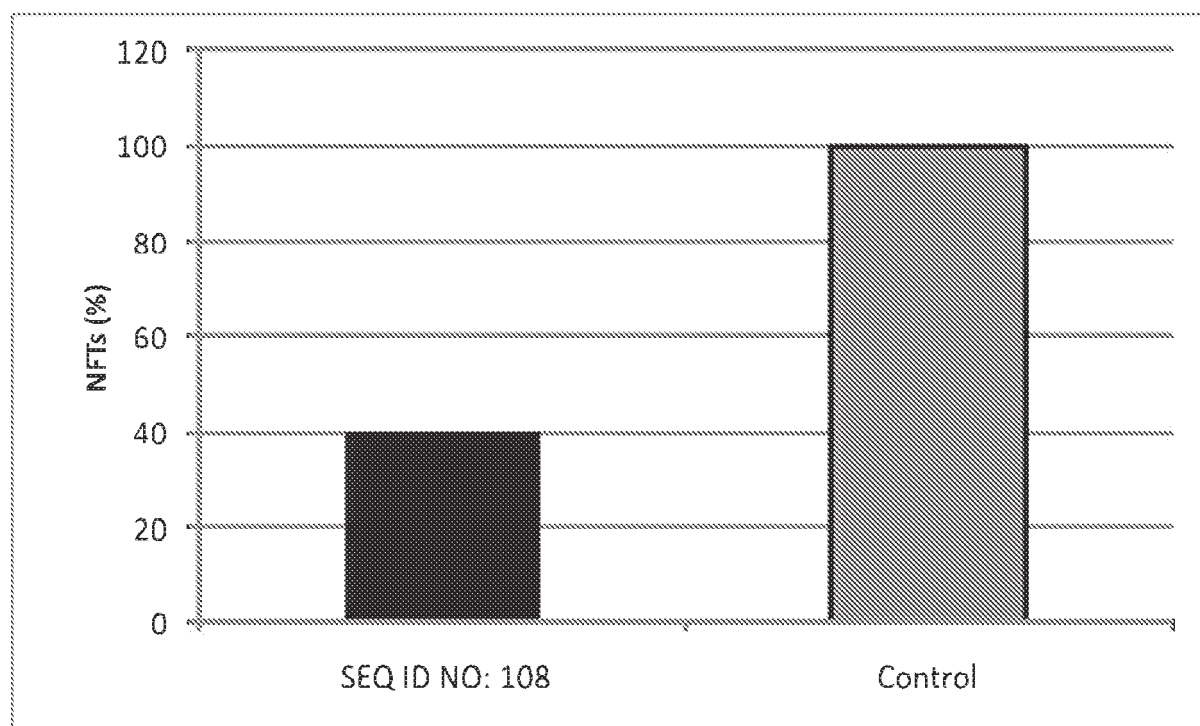
C

Neuroscale



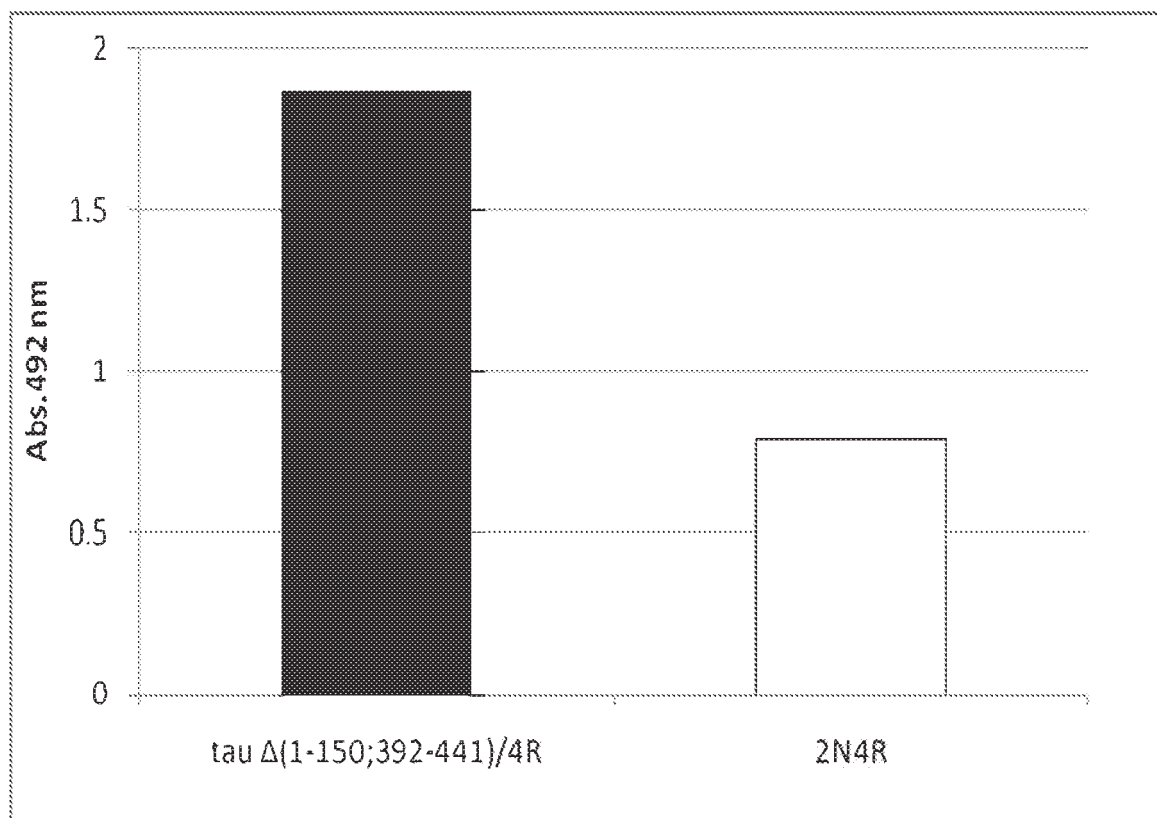
78/115

FIGURE 54



79/115

FIGURE 55



80/115

FIGURE 56

Geometric mean antibody titers			
Serum dilutions	Solid phase		
	Peptide SEQ ID NO:108	Tau $\Delta(1-150;392-441)/4R$	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

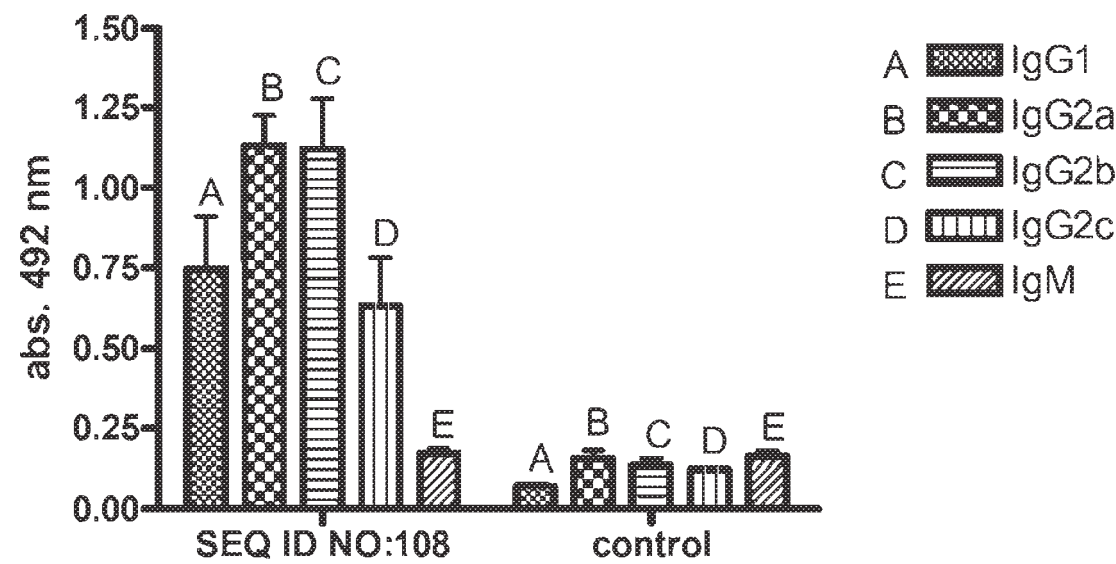
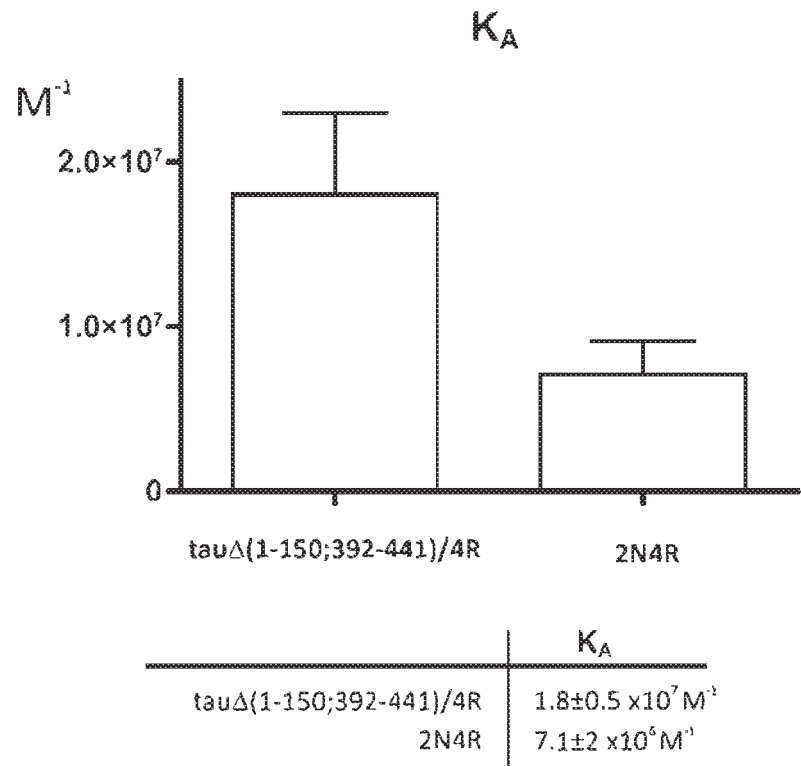


FIGURE 58



83/115

FIGURE 59

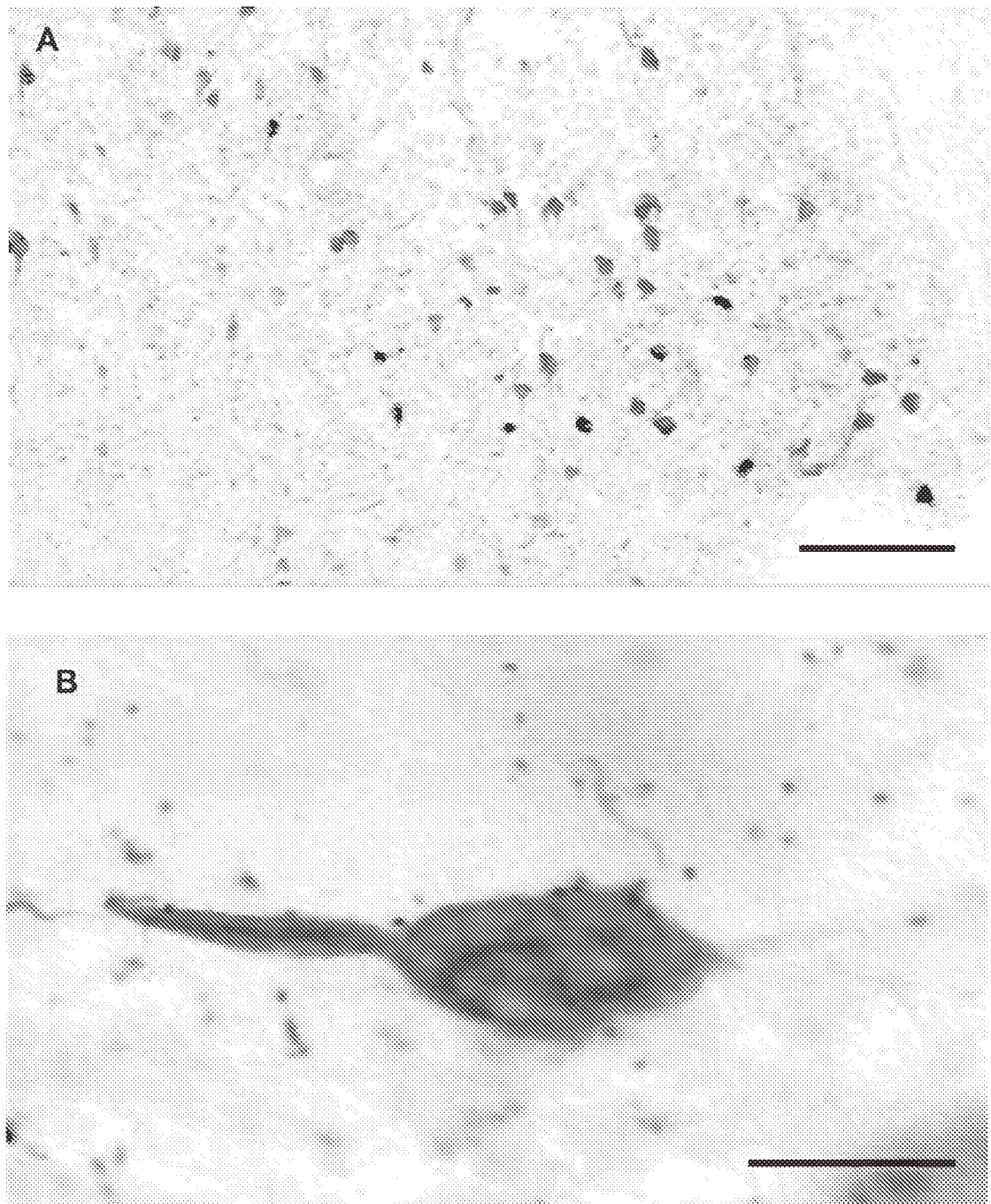


FIGURE 60

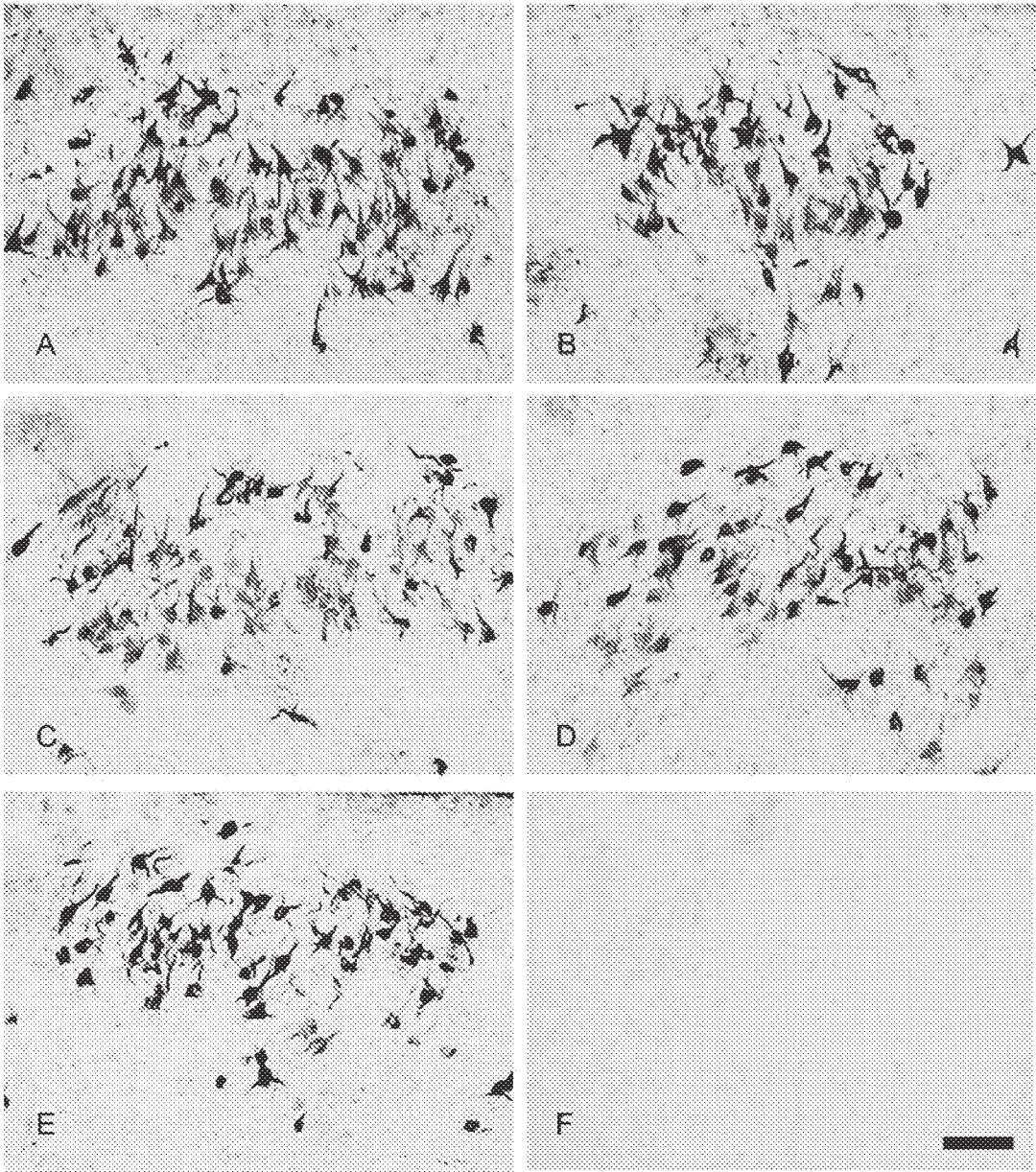
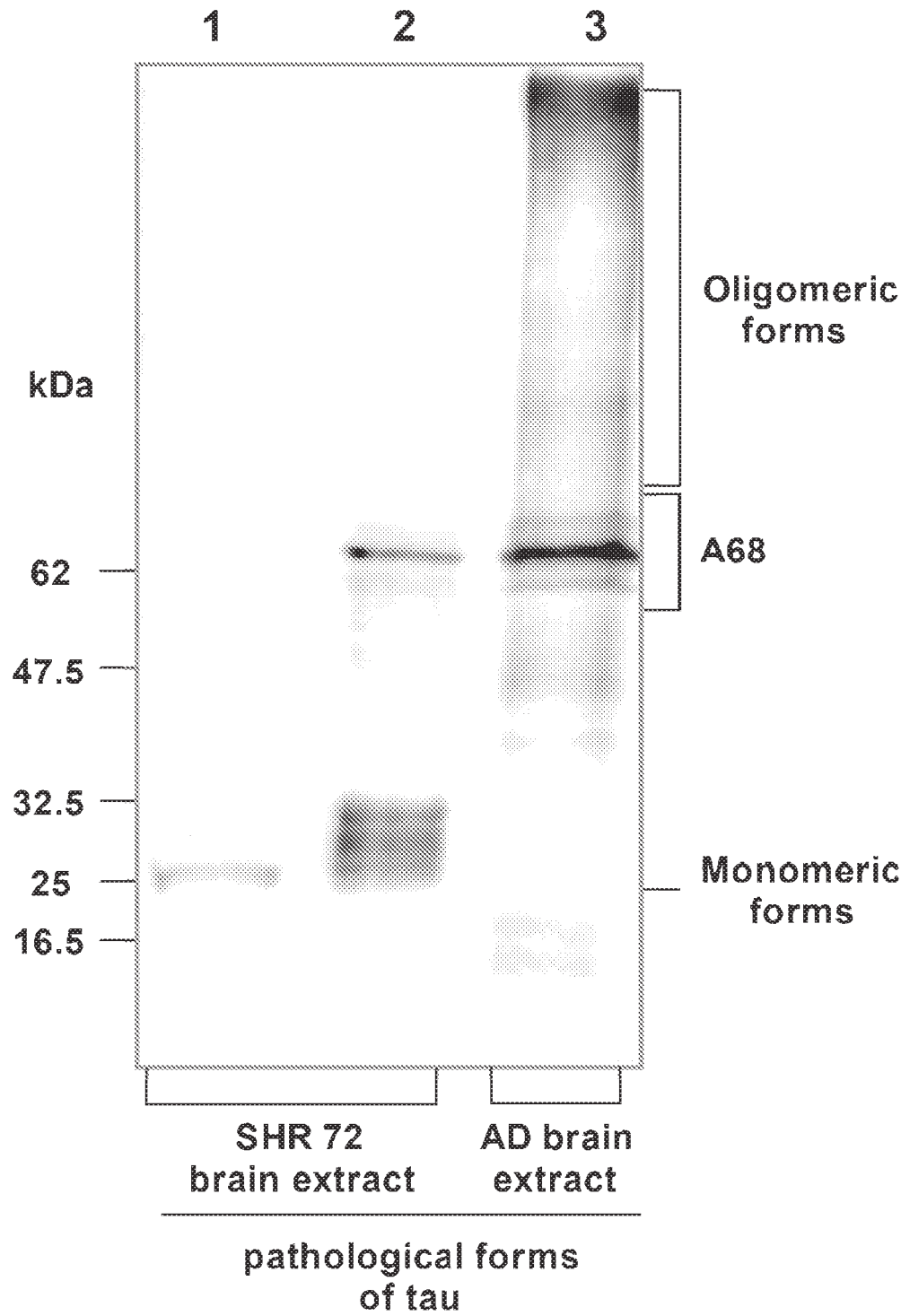
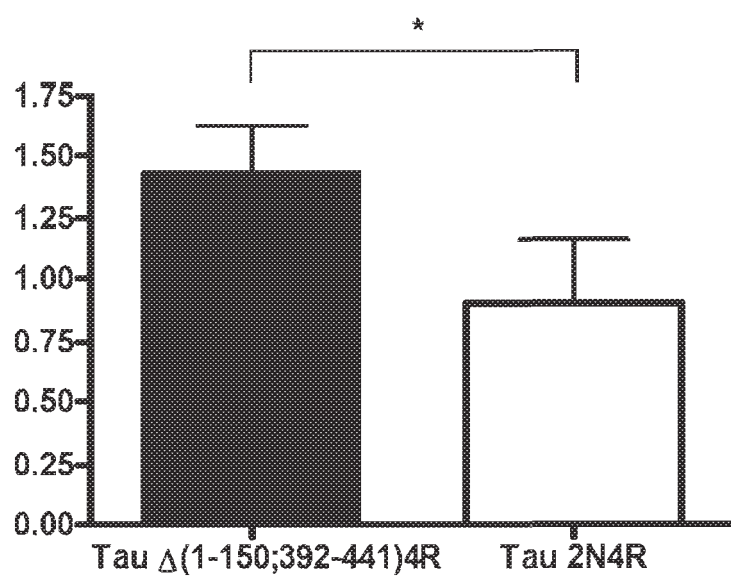


FIGURE 61



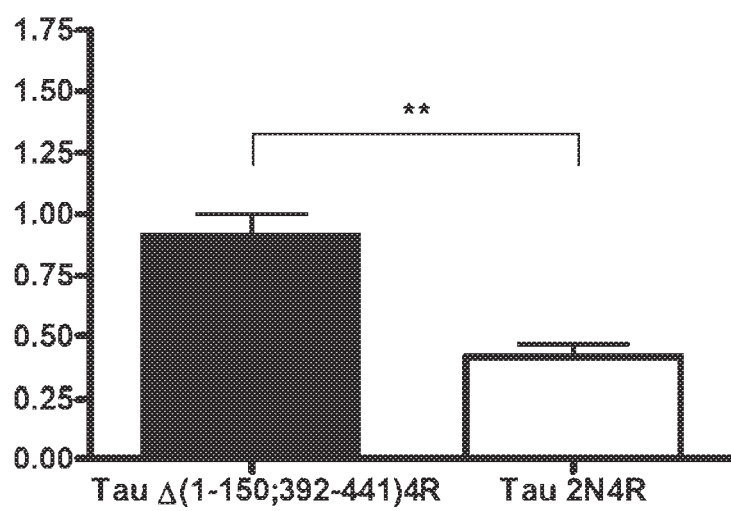
86/115

FIGURE 62



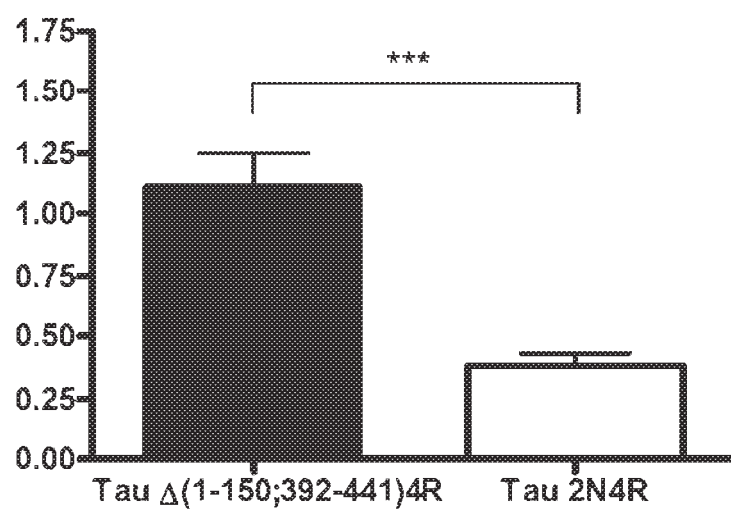
87/115

FIGURE 63



88/115

FIGURE 64



89/115

FIGURE 65

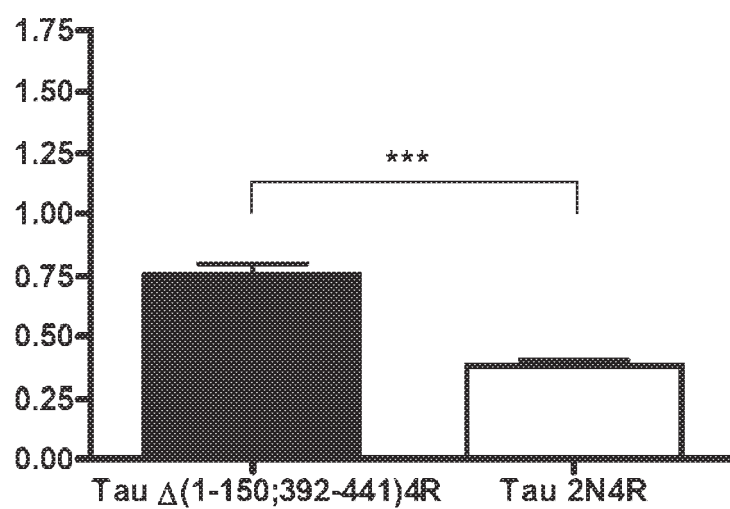


FIGURE 66

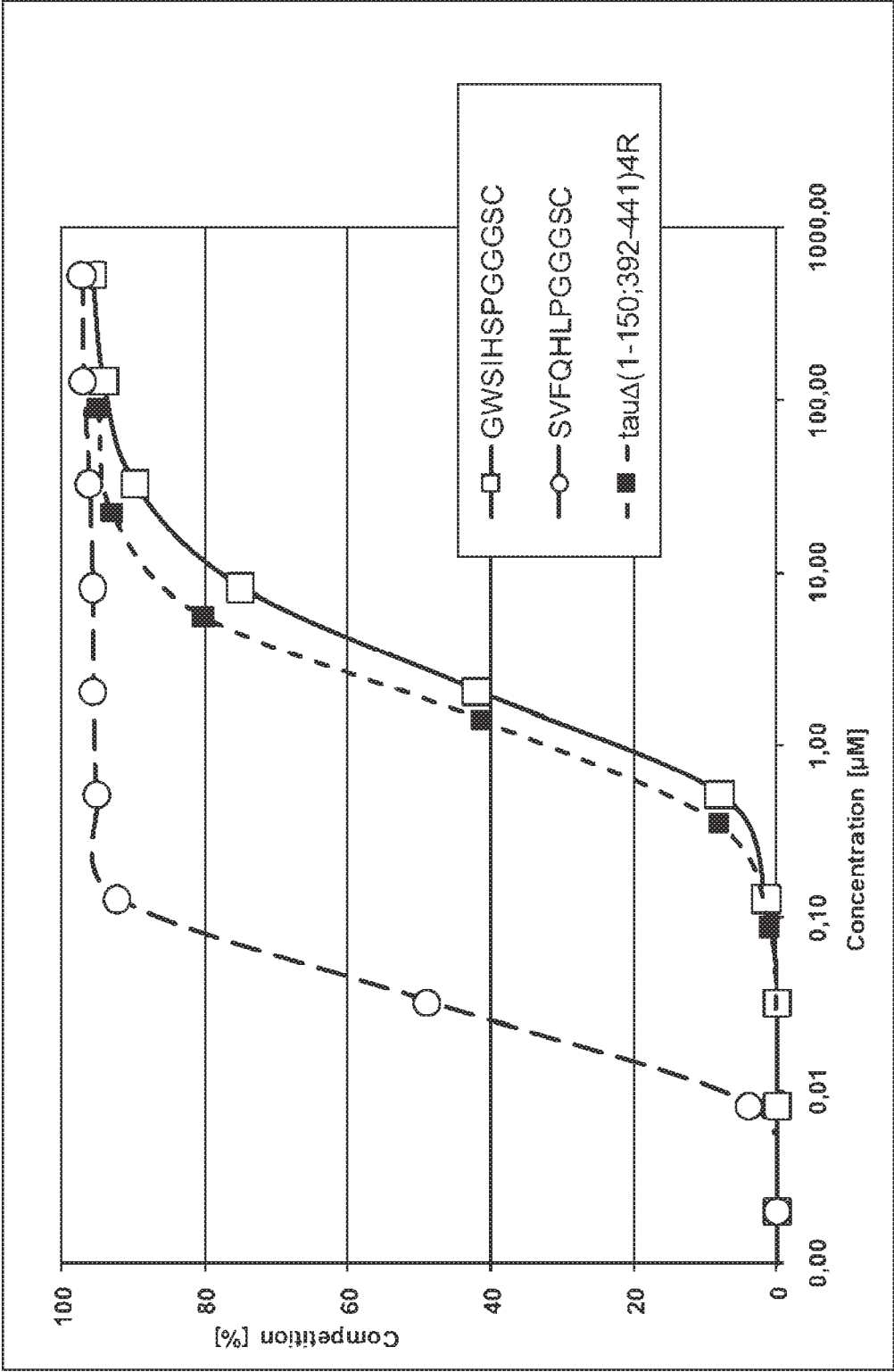


FIGURE 67

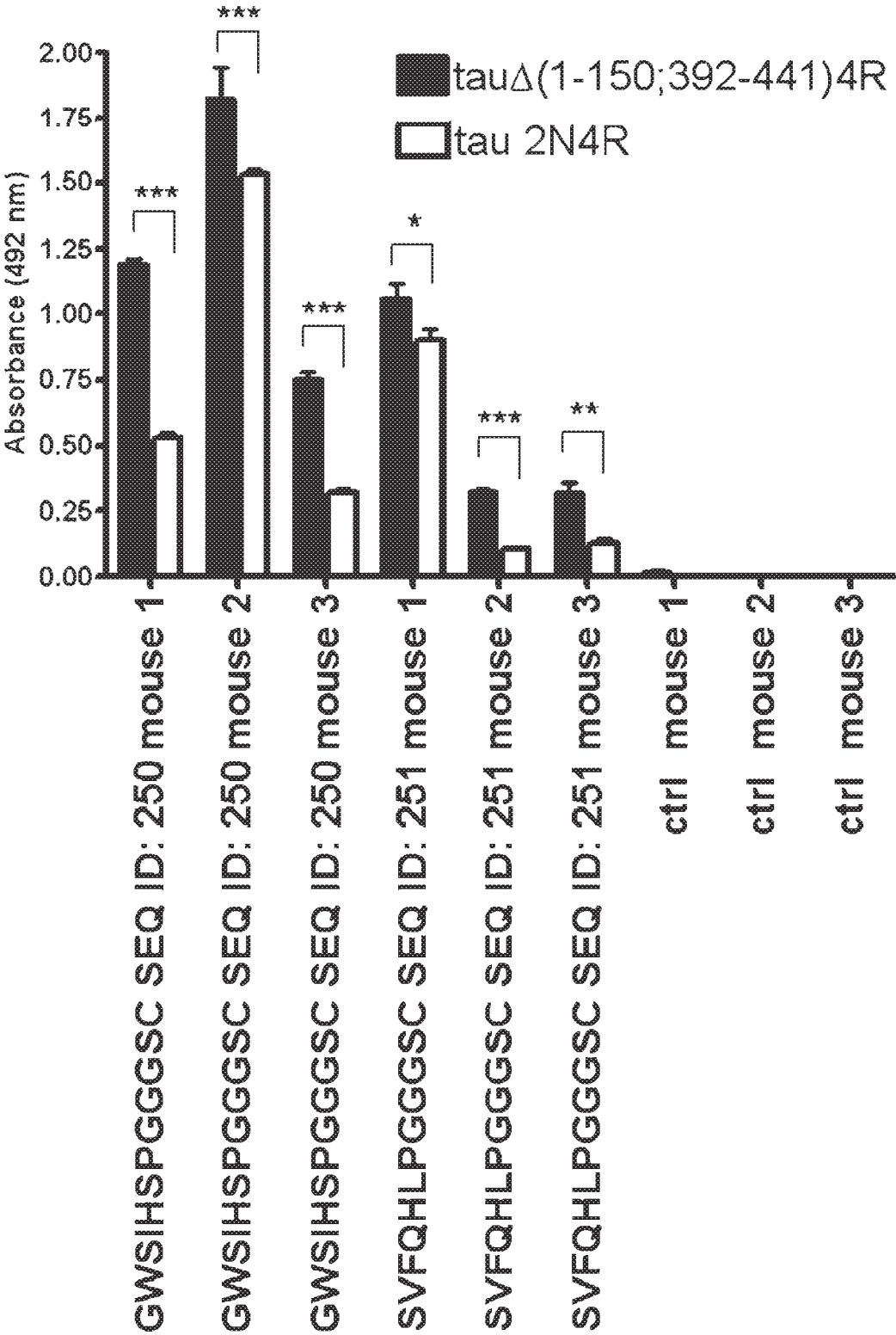


FIGURE 68

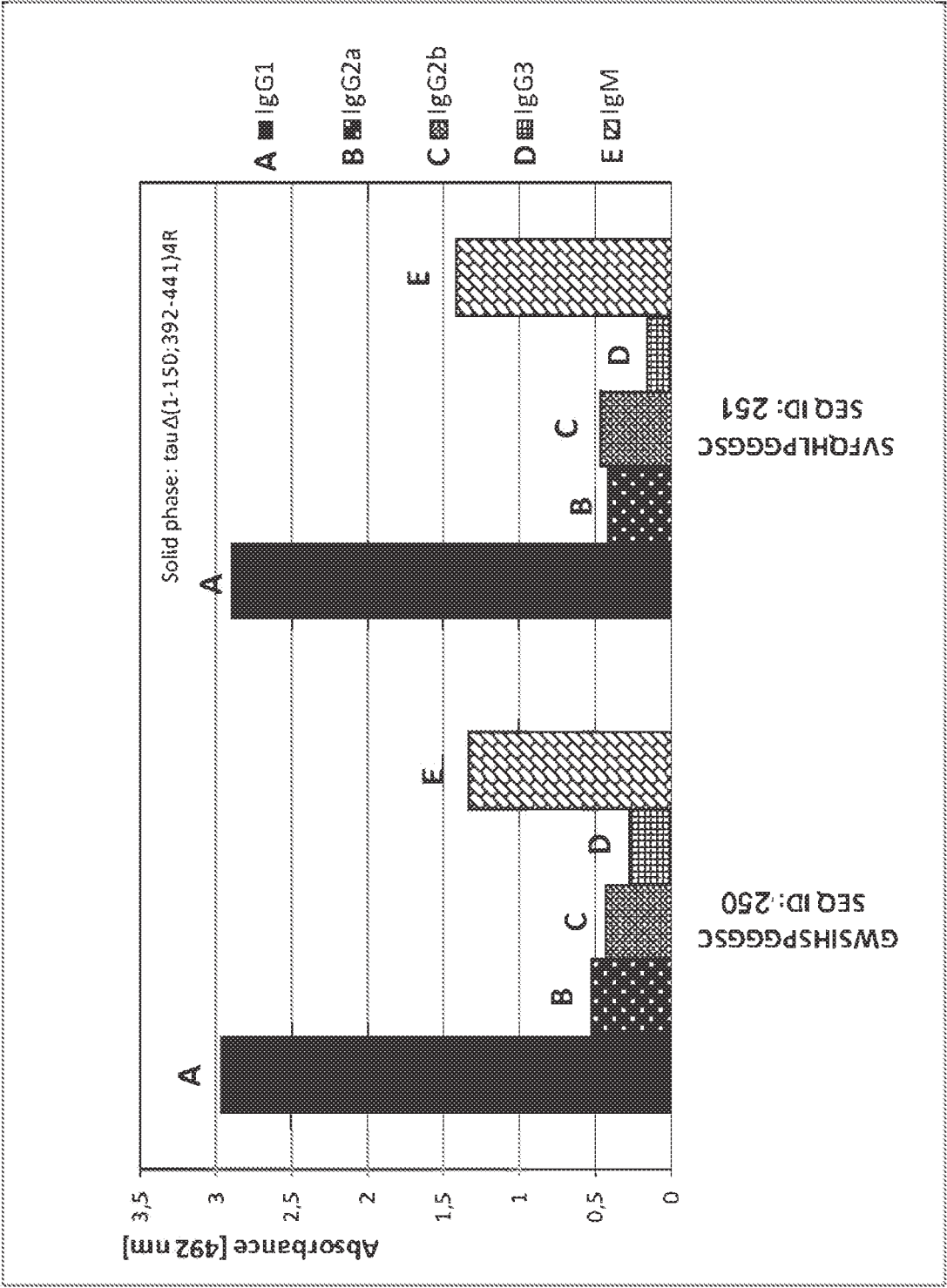
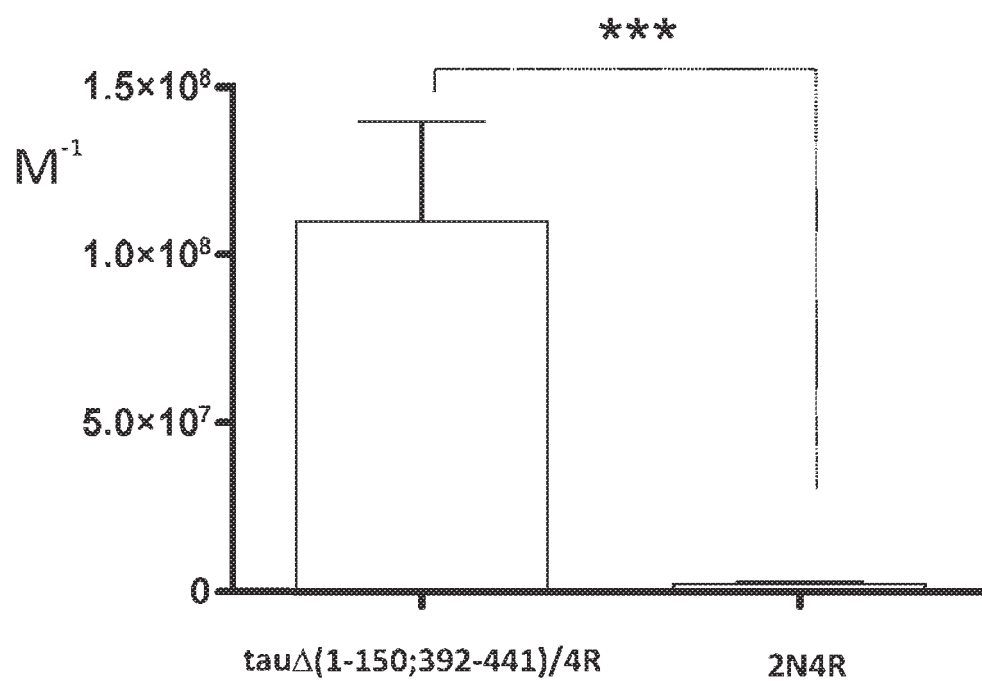


FIGURE 69A

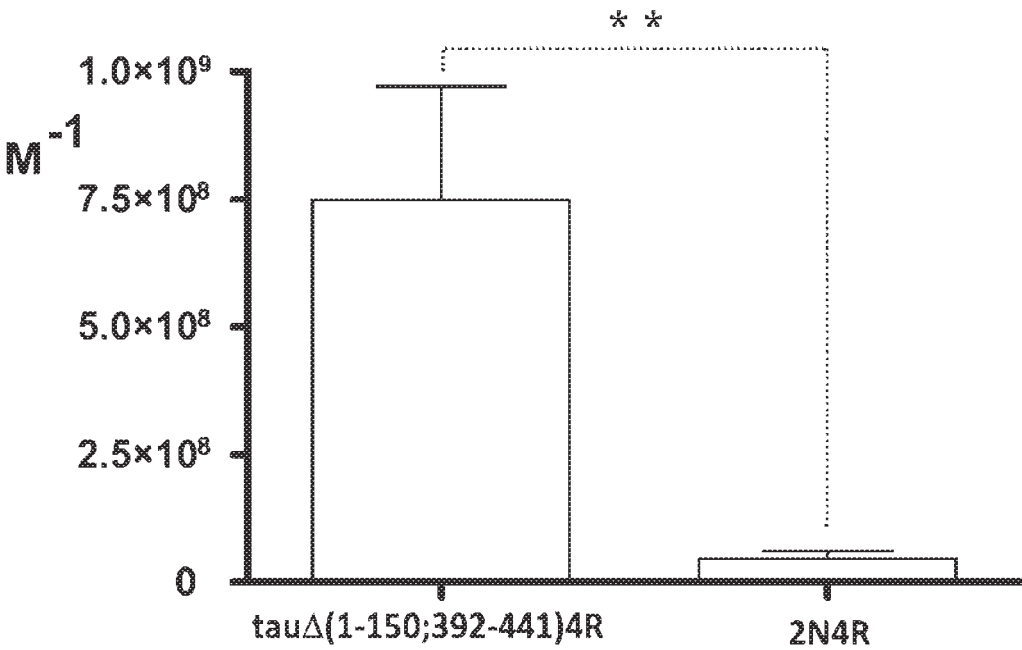
[GWSIHSPGGGSC (SEQ ID: 250)]



	K_A
$\text{tau}\Delta(1-150;392-441)/4R$	$1.1 \pm 0.3 \times 10^8 M^{-1}$
$2N4R$	$2.3 \pm 0.7 \times 10^6 M^{-1}$

FIGURE 69B

[SVFQHLPGGGSC (SEQ ID: 251)]



	K_A
$\text{tau}\Delta(1-150;392-441)4R$	$7.5 \pm 2.2 \times 10^8 M^{-1}$
$2N4R$	$4.7 \pm 1.4 \times 10^7 M^{-1}$

FIGURE 70-A through F

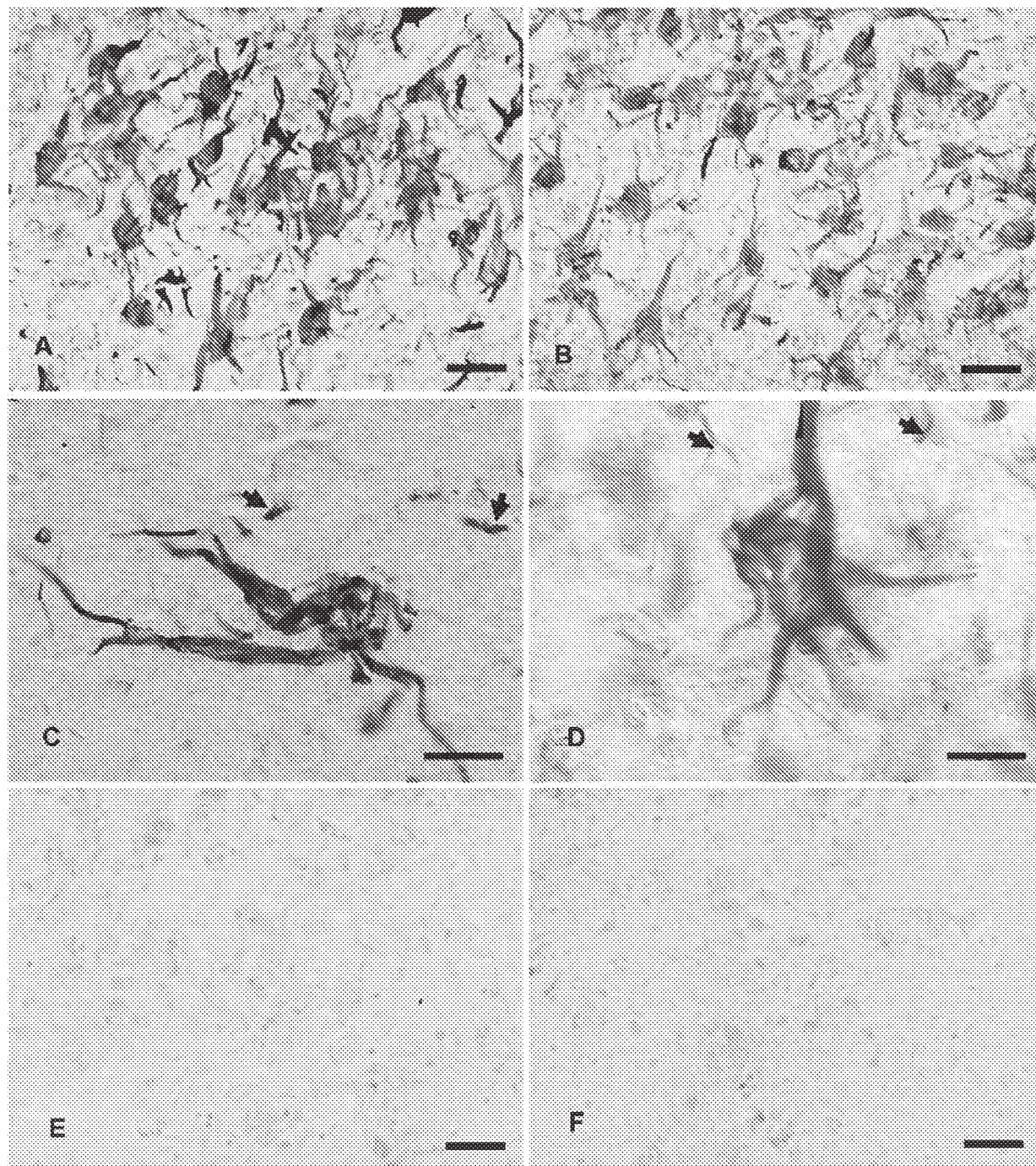


FIGURE 70 G-J

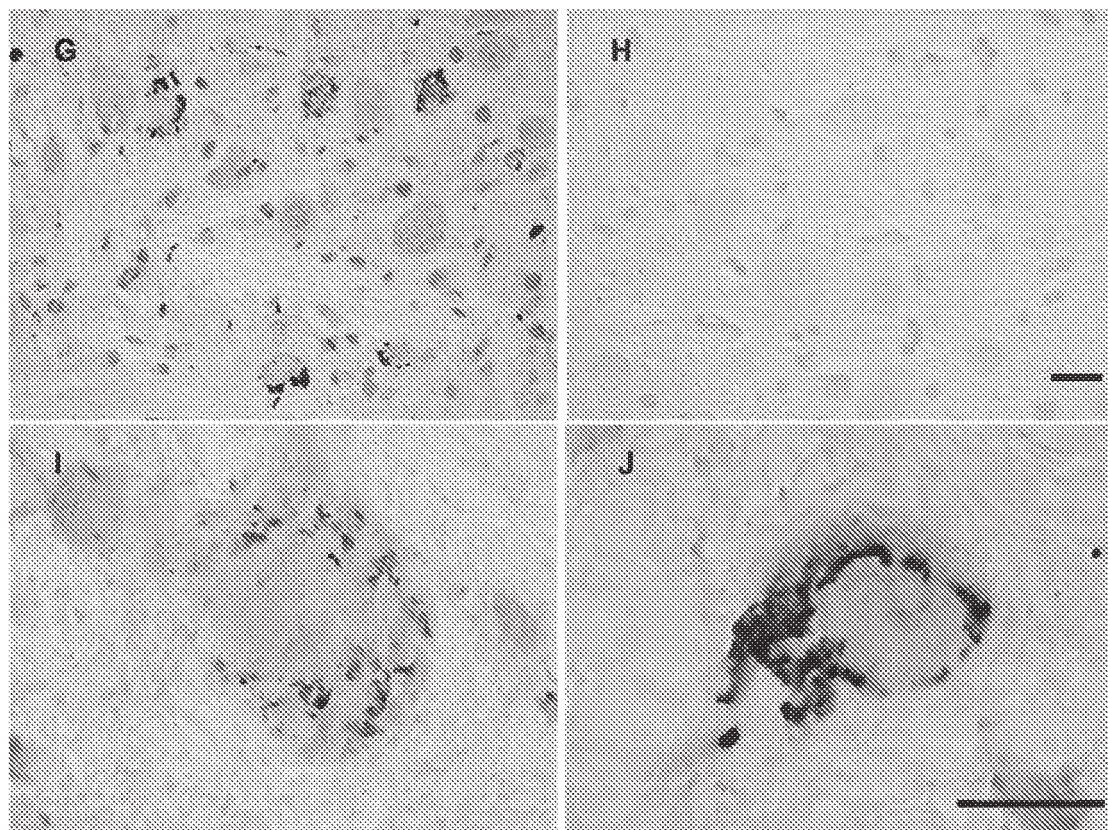


FIGURE 71

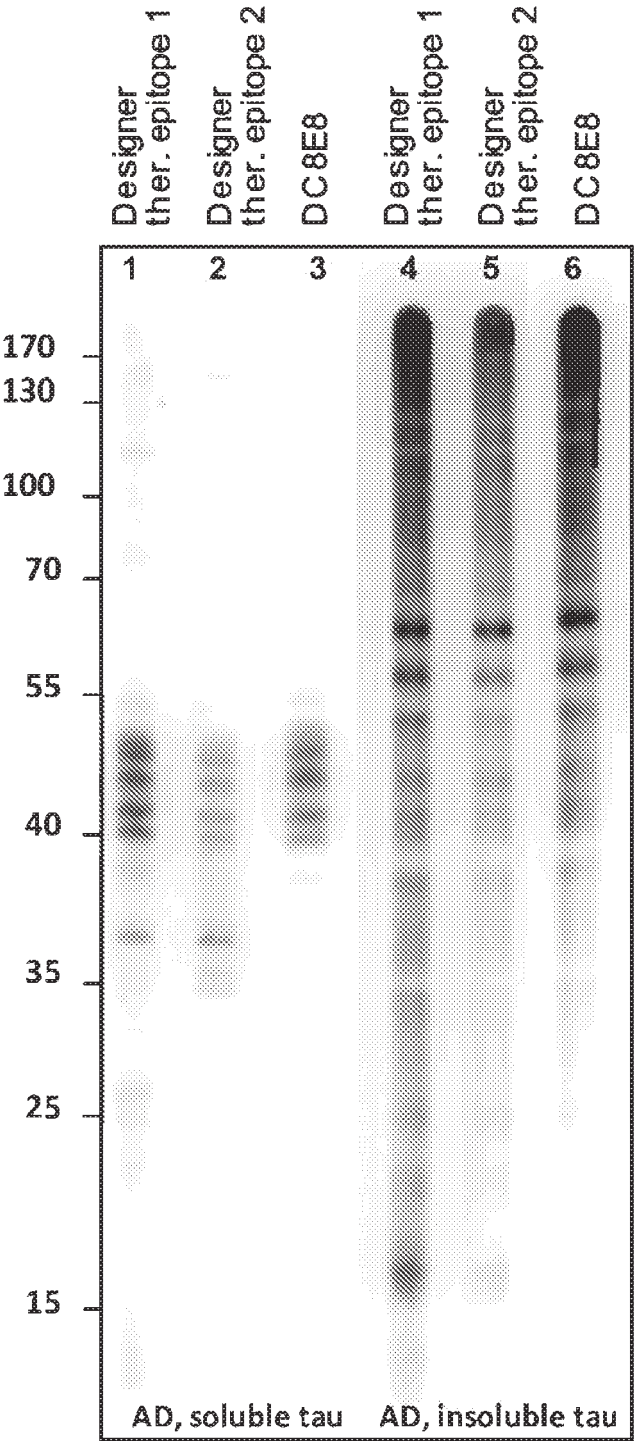


FIGURE 72

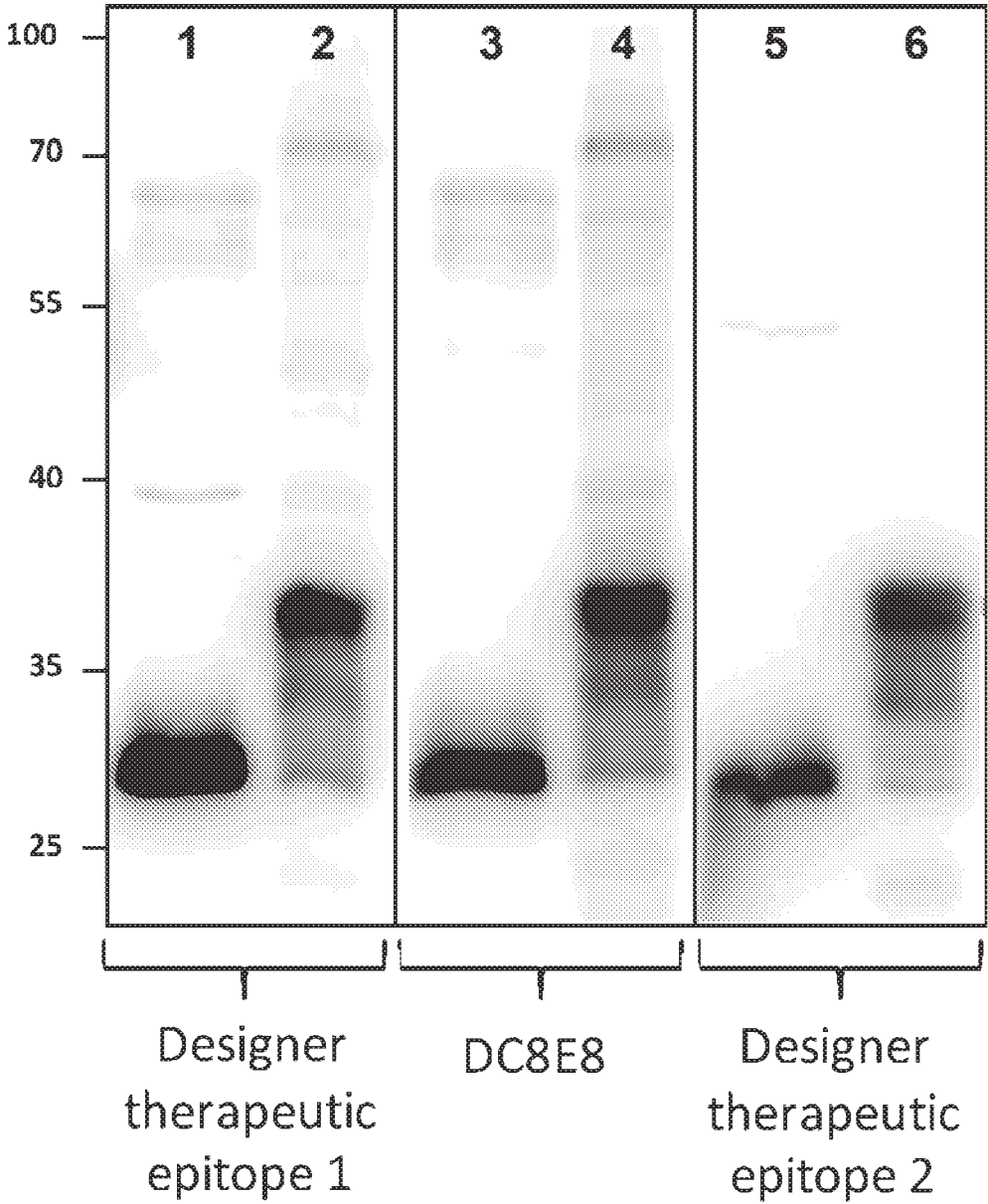
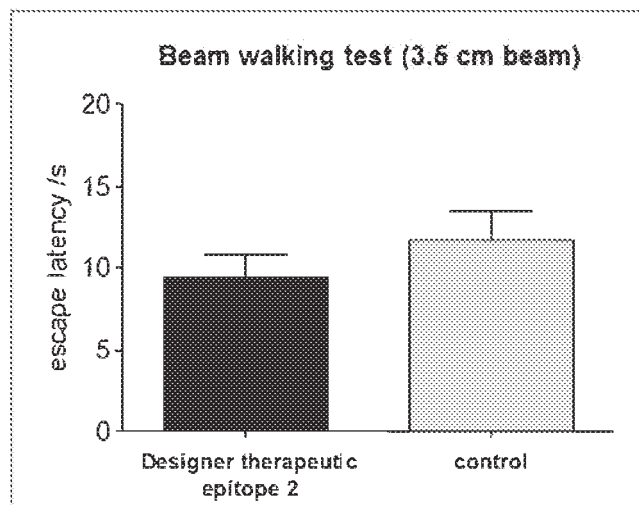
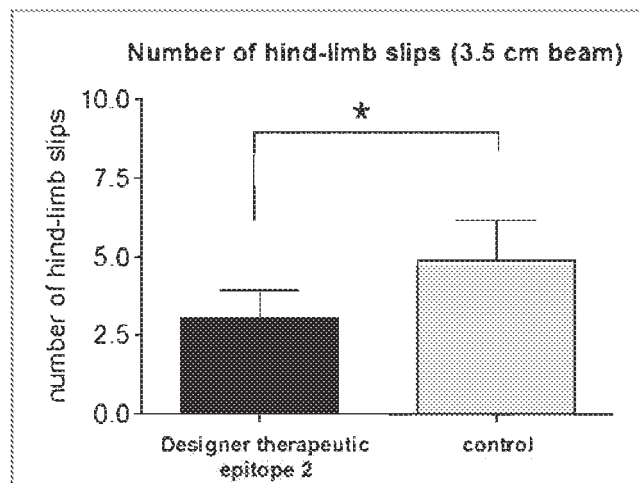


FIGURE 73

A.



B.



C.

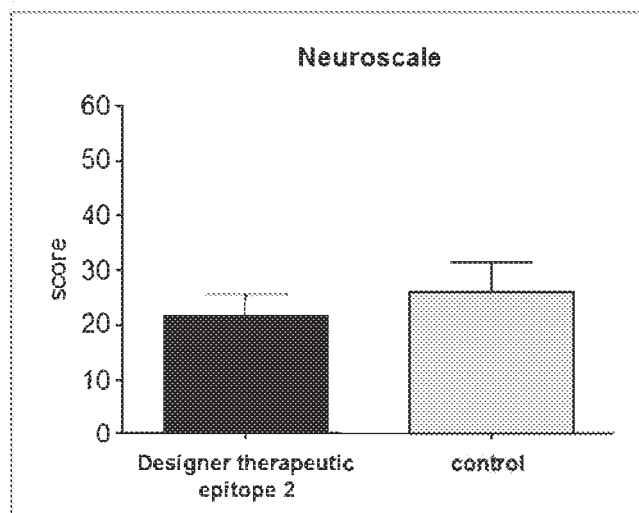


FIGURE 74

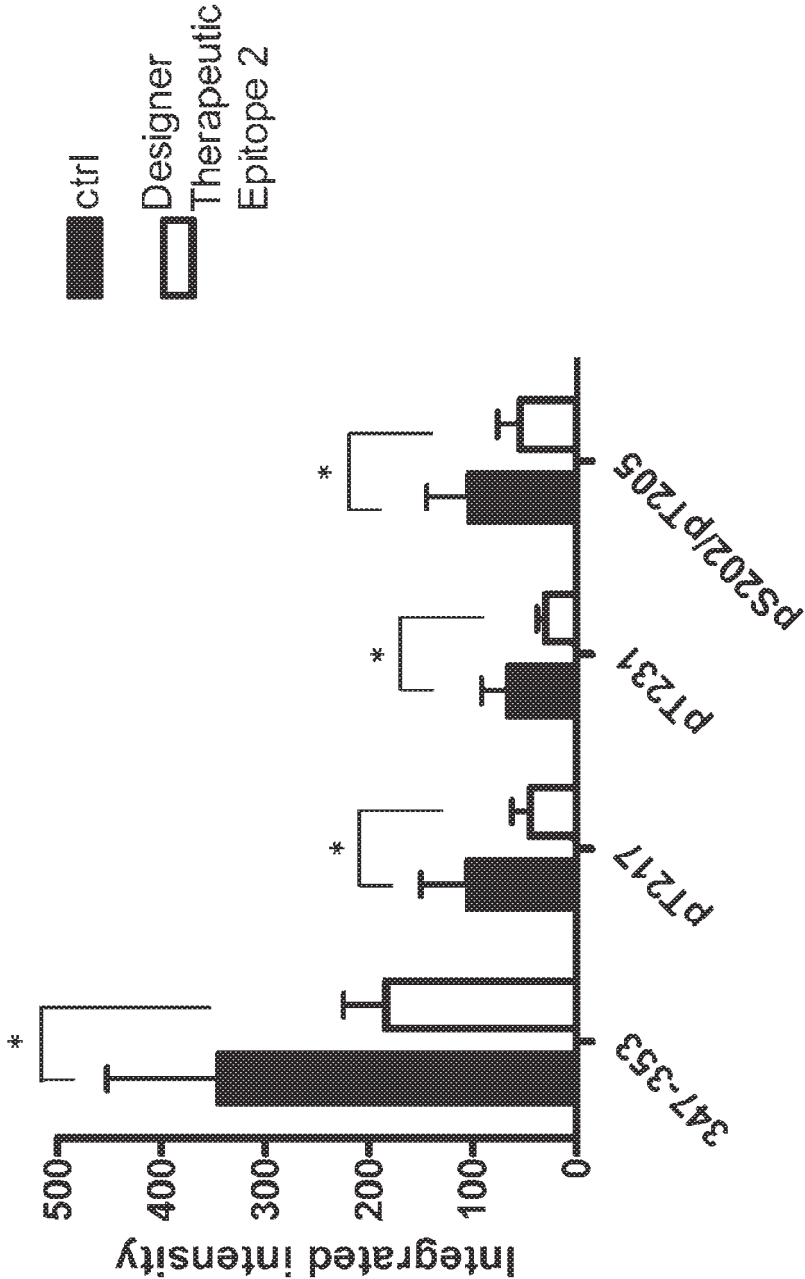


FIGURE 75A

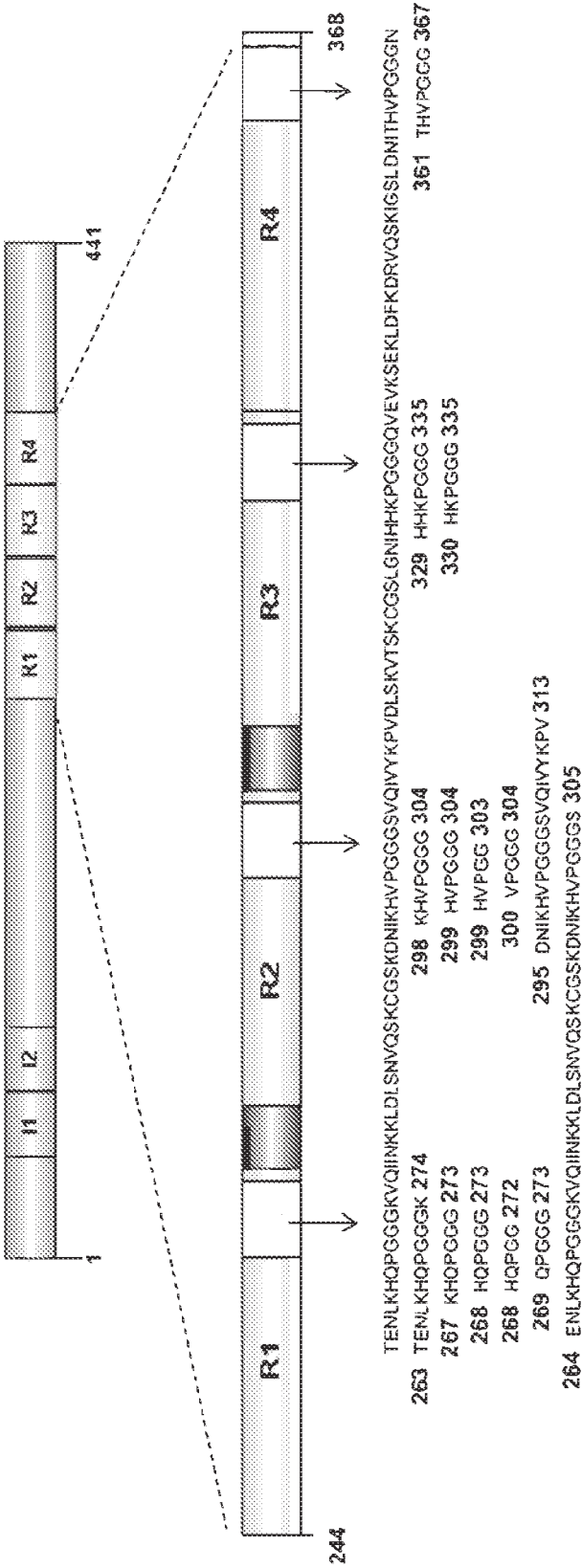


FIGURE 75B

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	ENLKHQPGGGKVQIINKKLDLSNVQSKCGSKDNIKHVPPGGGS
Tau298-304	SEQ ID NO: 276	KHVPPGGG
Tau299-304	SEQ ID NO: 277	HVPPGGG
Tau299-303	SEQ ID NO: 278	HVPPG
Tau300-304	SEQ ID NO: 279	VPGGG
Tau295-313	SEQ ID NO: 280	DNIKHVPPGGGSVQIVYKPV
Tau329-335	SEQ ID NO: 281	HHKPPGGG
Tau330-335	SEQ ID NO: 282	HKPPGGG
Tau361-367	SEQ ID NO: 283	THVPPGGG

FIGURE 76

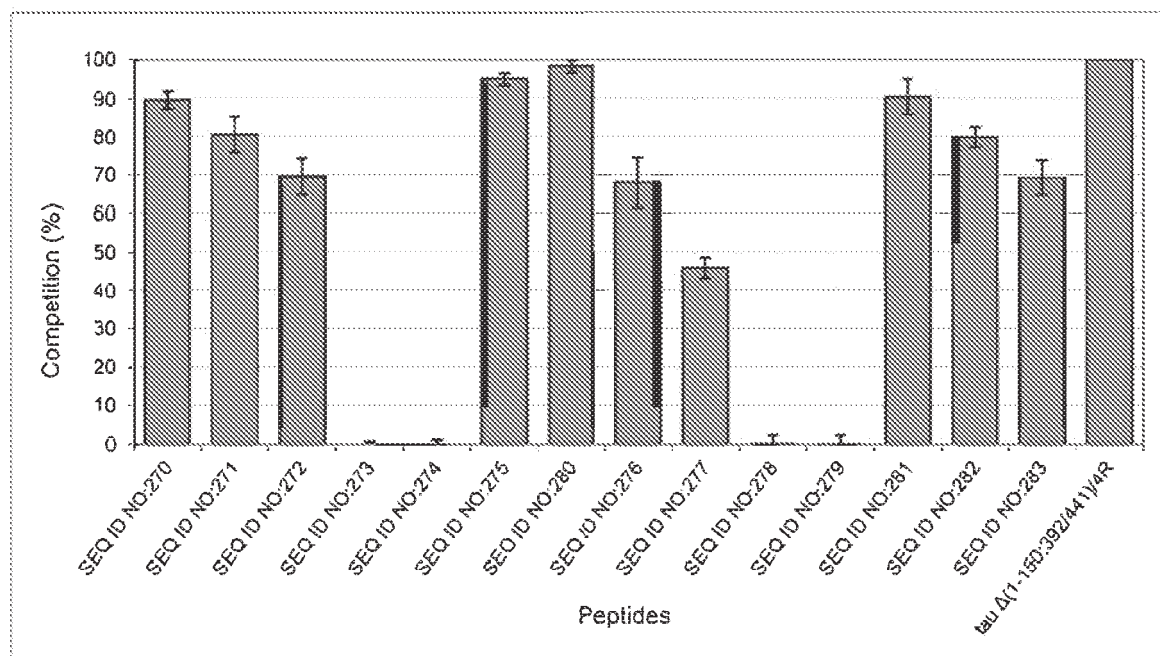


Figure 77A

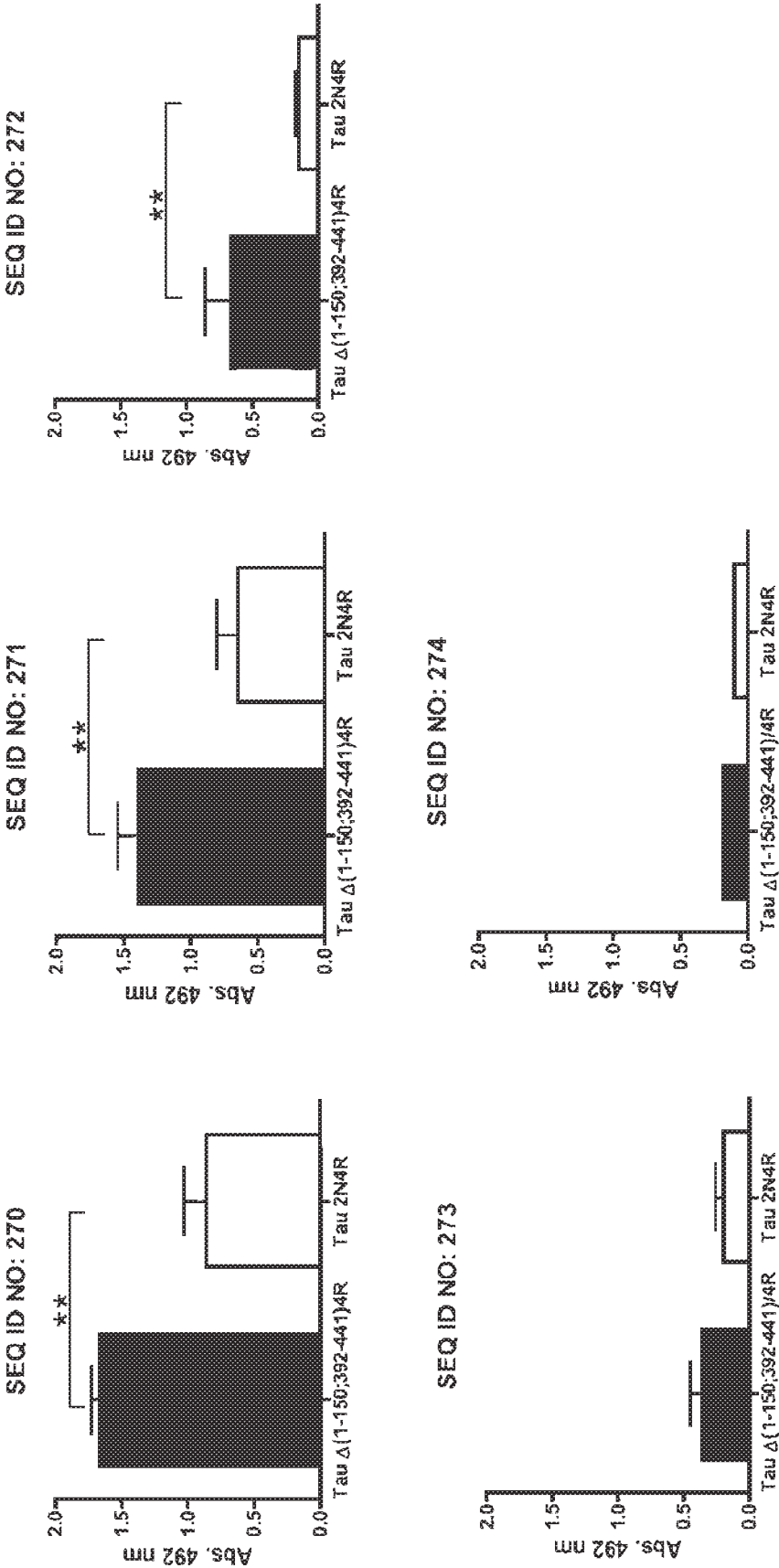


FIGURE 77B

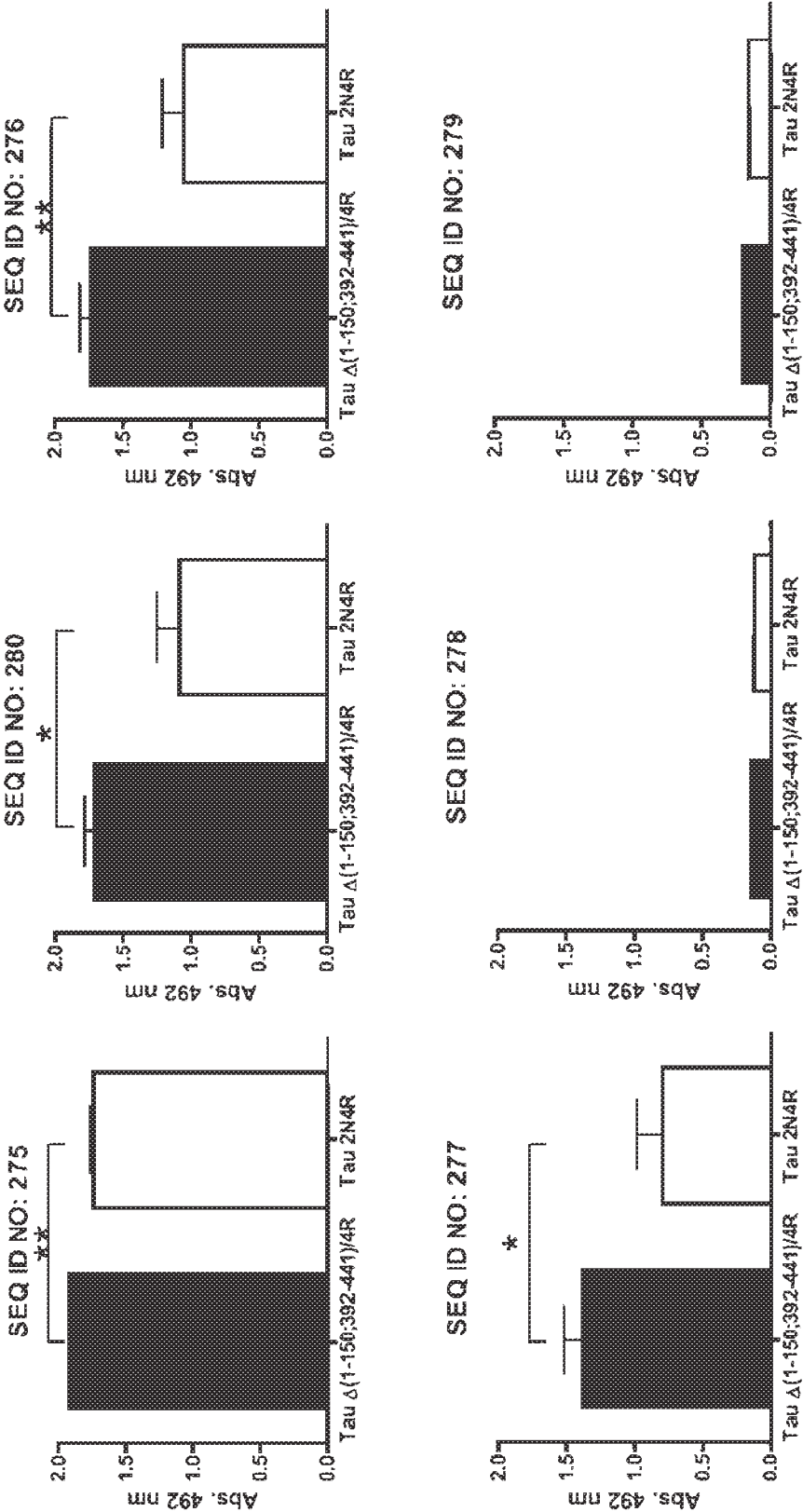
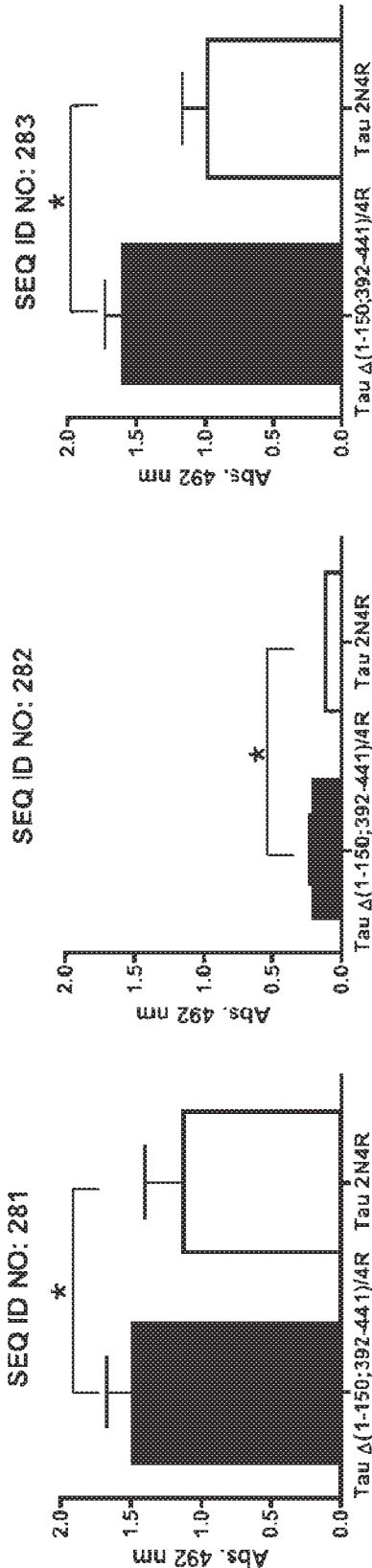


FIGURE 77C



107/115

FIGURE 78

Peptides	Geometric mean antibody titers	
	solid phase	
	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

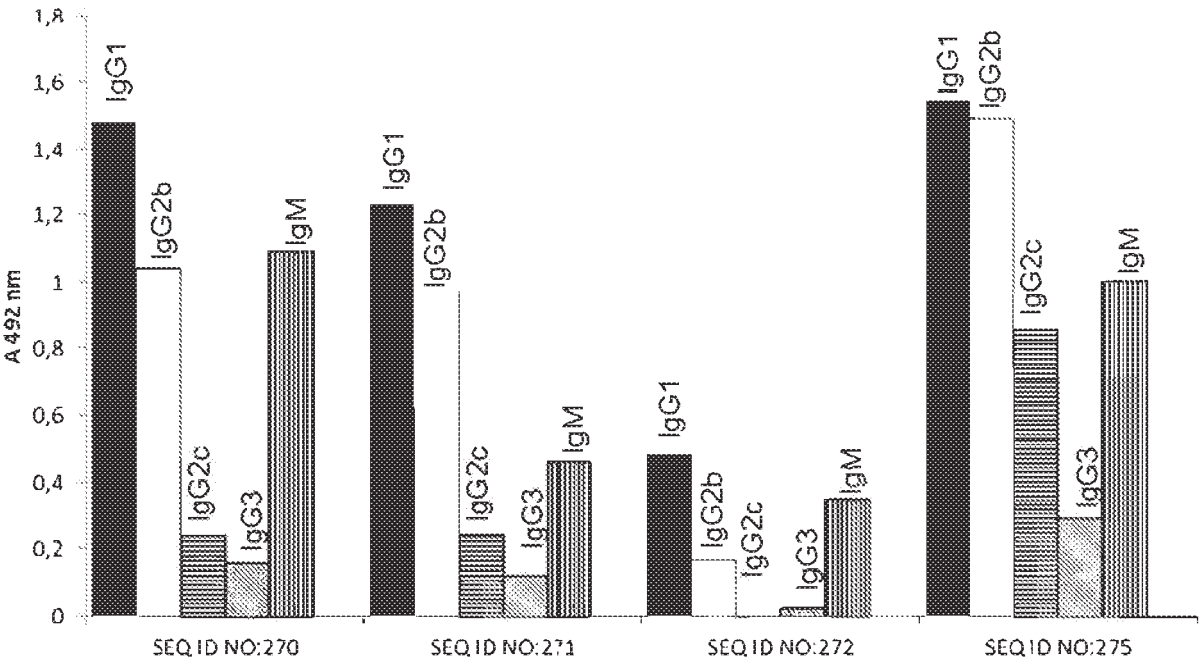


FIGURE 79B

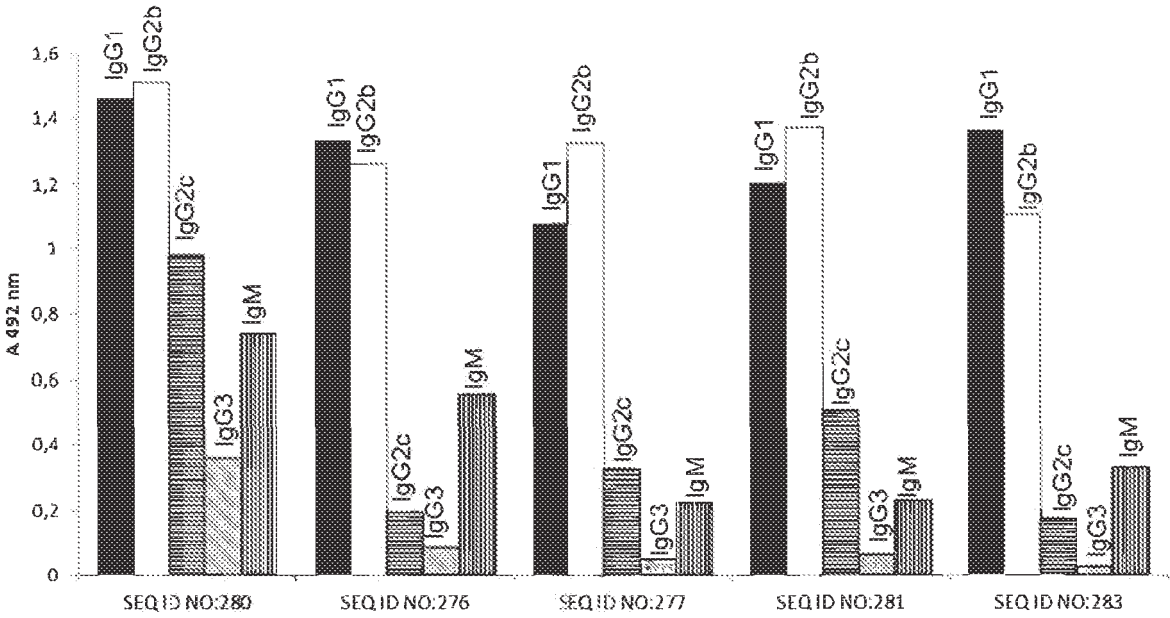
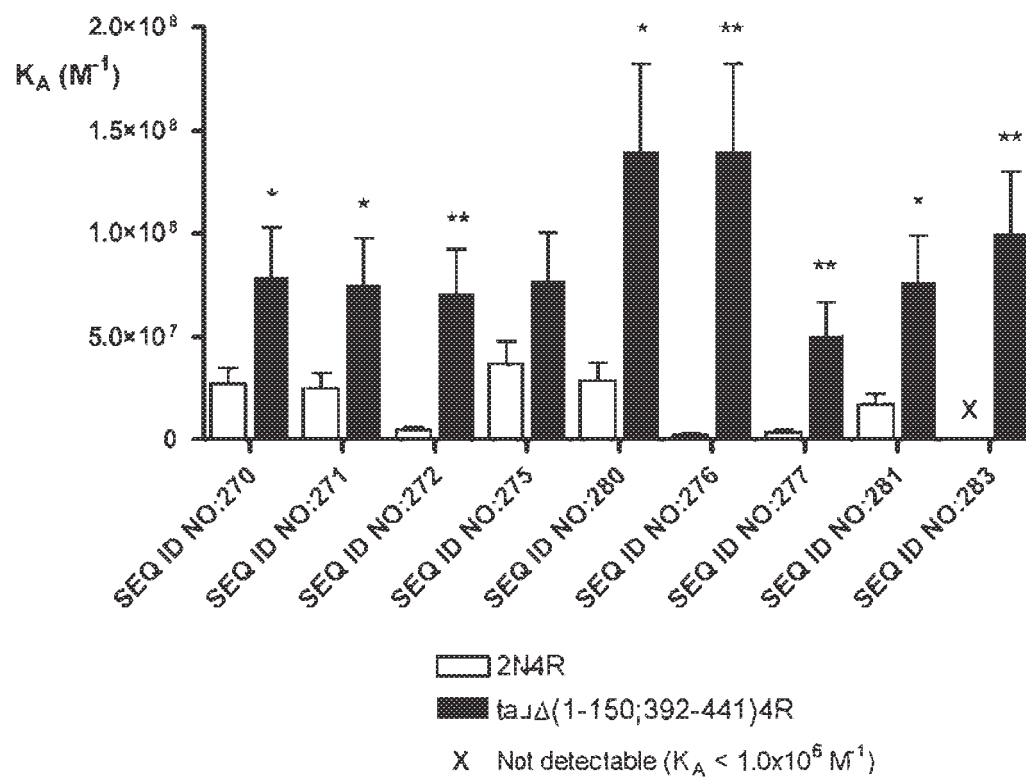


FIGURE 80



111/115

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

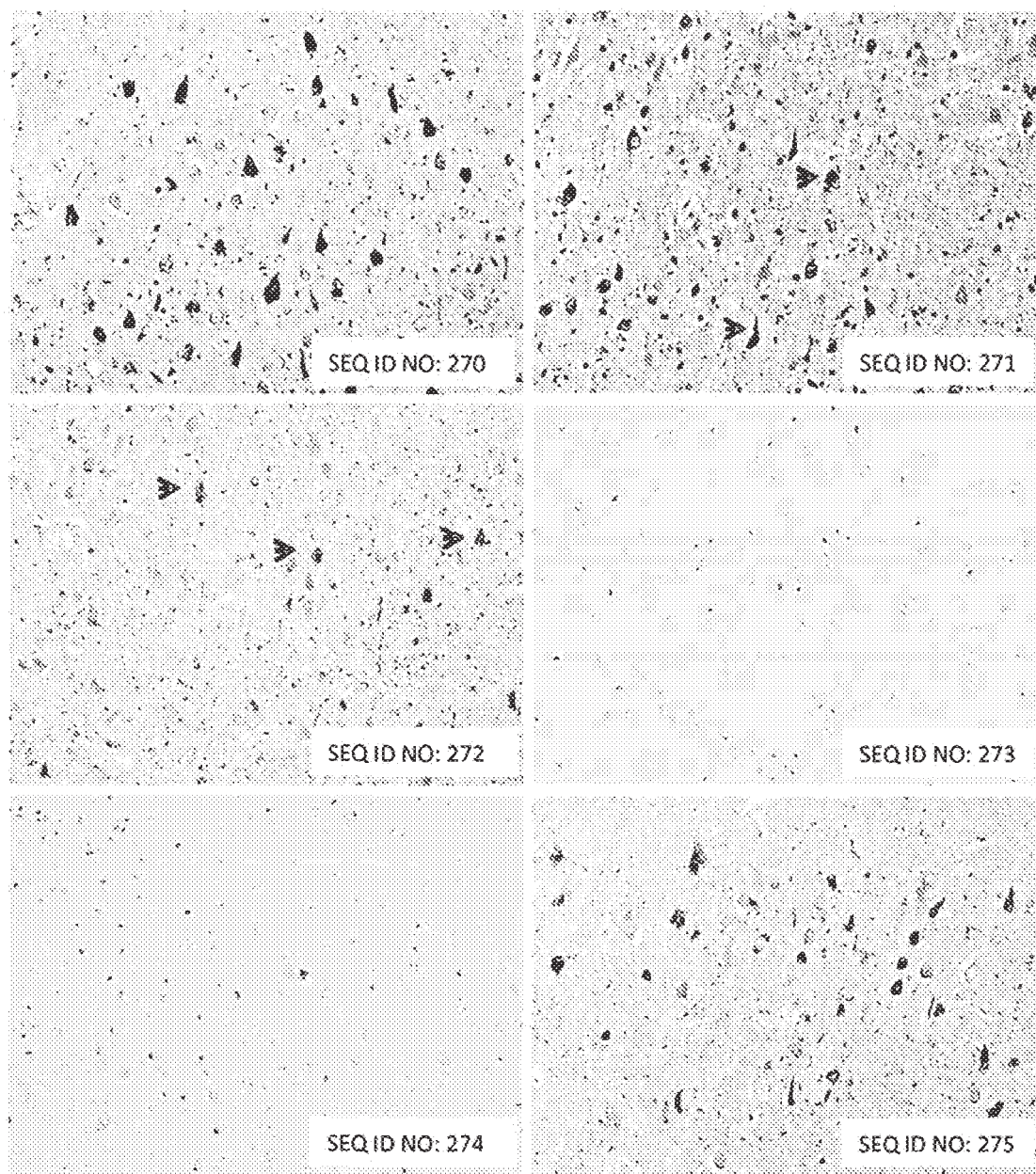


FIGURE 82B

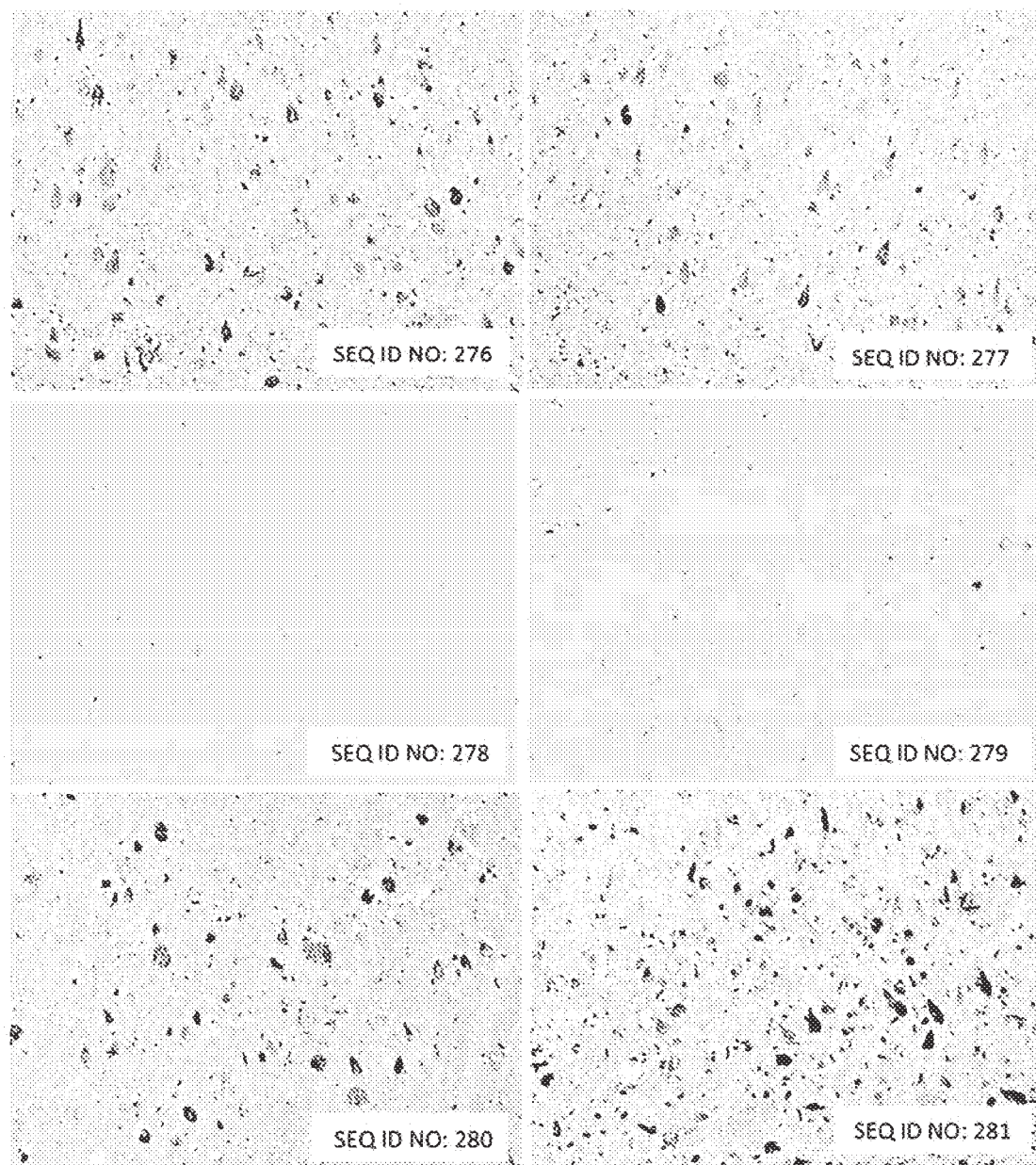


FIGURE 82C

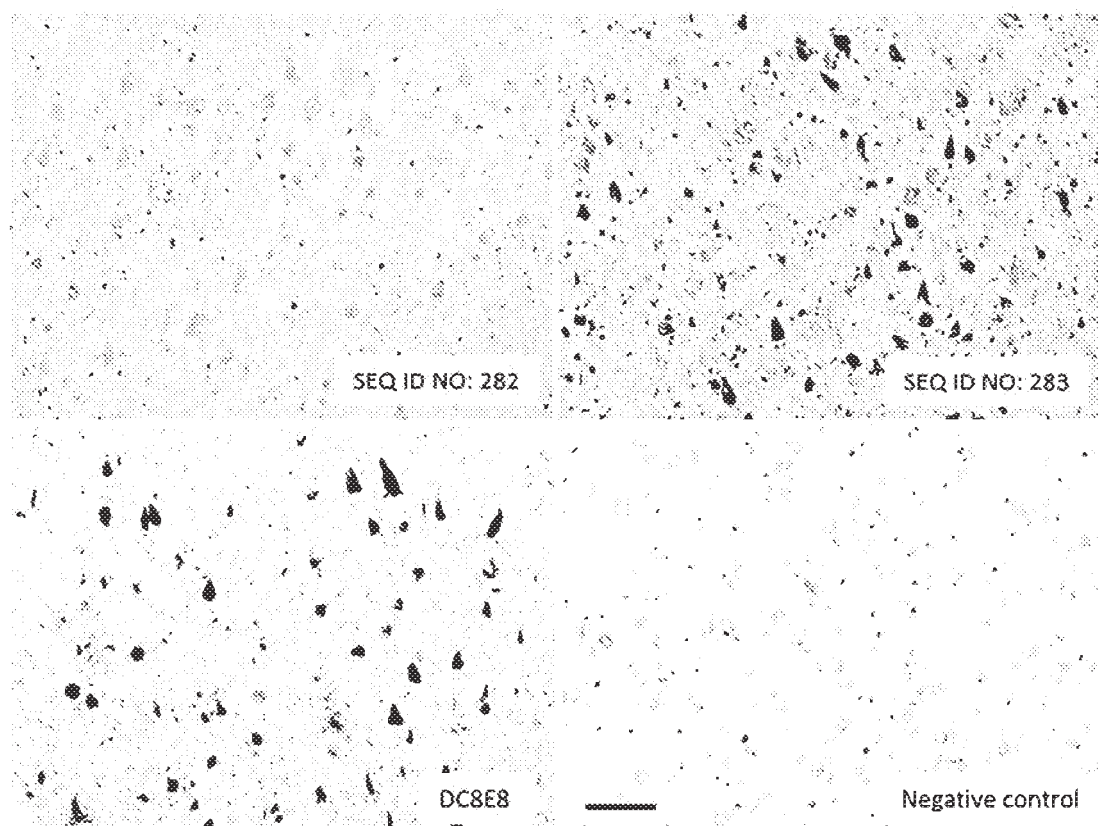


FIGURE 83

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	+++