

FIGURE 1

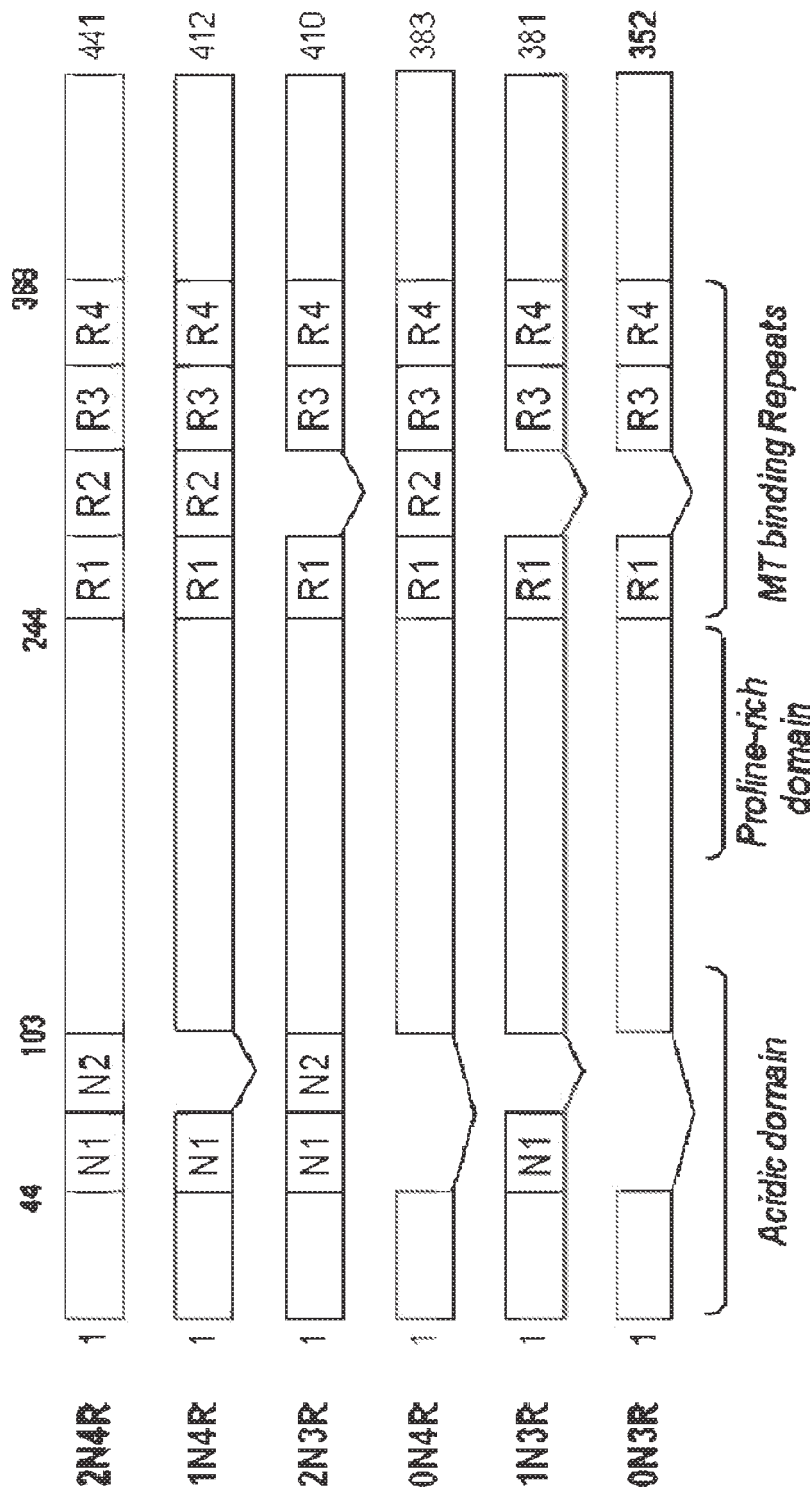


FIGURE 2

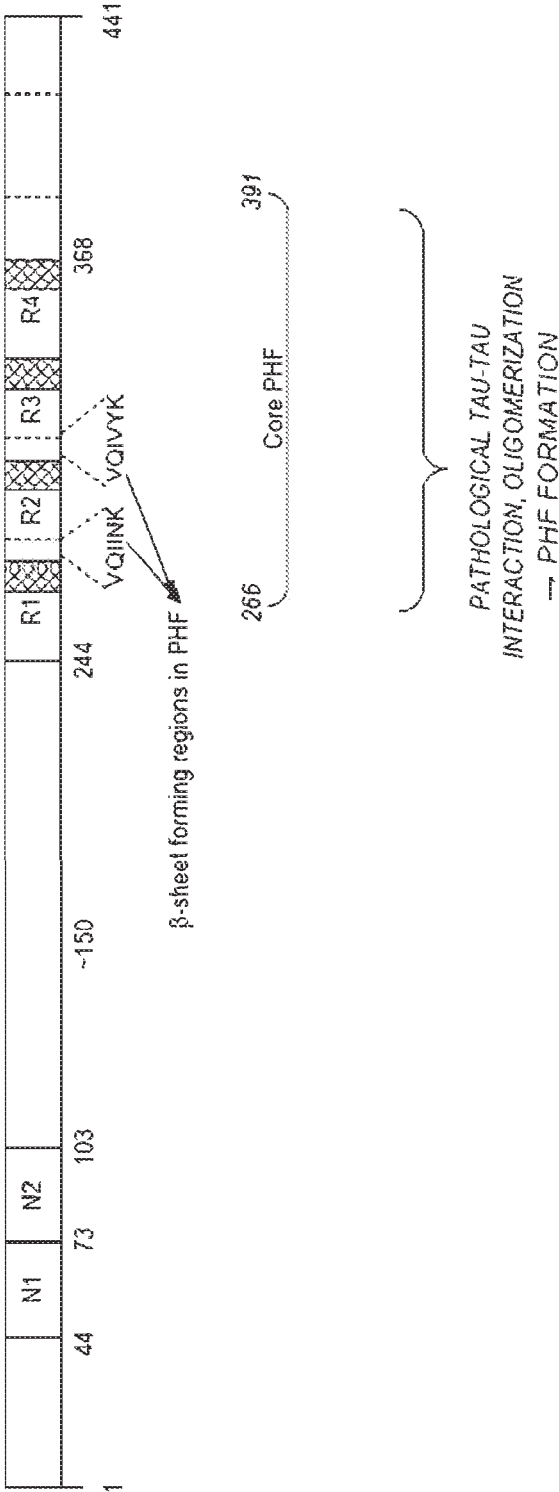


FIGURE 3

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

GACATTGTGATGTCAAGTCTCCATCCCTCCCTGGCTGTGTACAGCAGAGAGAGGTCATATGAGCTGC AAAATCCAGTCAGAGTCTGCTC
AACAGTAGAACCCGAAAGAACTACCTGGCTTGGTACACAGCAGAAACACAGGCAGTCTCCTAAACTGCTGATCTACTGGGCATCCACTAGG
GAATCTGGGGTCCCTGATCGCTTCAACAGGACGTGATCTGGGACAGATTTCACCTCTCACCATCAGCAGTGTGCAAGGCTGAAGACCTGGCA
GTTTATTACTGCAAGCAATCTTTTATCTTCGACGTTCCGGTGGAGGCCACCAAGCTGGACATCAAA

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

DIVMSQSPSSLA VSAAGEKVTMSCKSSQSLNLSRTRKNYLAWYQQKPGQSPKLLIYWASTRESGVDPDRFTGSGSGTDFLTLTISSVQAEDLA
VYYCKQSEFYLRTFGGGTKLDIK

CDR1 : QSLNLSRTRKNY

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 GACATTGTGATGTCAAGTCTCCATCCCTCCCTGGCTGTGTGTCAGCAGGAGA

IGKV8-21*01 GACATTGTGATGTCAAGTCTCCATCCCTCCCTGGCTGTGTGTCAGCAGGAGA

DC8E8 light

IGKV8-21*01 GAAGGTCACTATGAGCTGC AAAATCCAGTCAGAGTCTGCTCAACAGTAGAA

DC8E8 light

IGKV8-21*01 CCCGAAAGAACTACCTGGCTTGGTACCAGCAGAAACACAGGCAGTCTCCT

DC8E8 light

IGKV8-21*01 AAACGTCTGATCTACTGGGCATCCACTAGGGAATCTGSGGTCCCIGATCG

DC8E8 light

IGKV8-21*01 CTTACAGGCAGTGGATCTGGGACAGATTTCACCTCTCACCATCAGCAGTG

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
 SAVYFCARDYYGTSEAMDYWGQTSVTVSS

CDR1: GYIFTDYVIS
 CDR2: IFPRSGST
 CDR3: ARDYYGTSEAMDY

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 AGTGAAGCTGTCCTGCAAGGCTTCTGGCTACACCTTCACAAGCTATGGTA
***** ** ***** ***** ***** ***** *

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

DC8E8 heavy ATTTTTCCTAGAAGTGGTAGTACTTACTACAAATGAGAAAGTTCAAGGGCAA
IGHV1-81*01 ATTTATCCTAGAAGTGGTAATACTTACTACAAATGAGAAAGTTCAAGGGCAA
***** ***** ***** ***** ***** *****

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
acttctaccccaagacatcaatgtcaggtggaagattgatggcagtgaaacgacaaaatggcgtcctgaaacagttggactgatcaggaca
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 GACATTGTGATGTCACAGTCTCCATCCCTGGCTGTGTCTGAGCAGGAGA
 IGKV4-1*01_Homo+sapiens GACATCGTGTGATGACCCAGTCTCCAGACTCCCTGGCTGTGTCTGAGCAGGAGA
 ***** * ***** * ***** * ***** * ***** * ***** *

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

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

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

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

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 --GGACGTTCTGGTGGAGGCACCAAGCTGGACATCAAAC
 IGKJ1*01_Homo+sapiens_J-REGION GTGGACGTTCTGGCCAAGGACCAAGCTGGAAATCAAAC
 ***** *

FIGURE 5

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

```

DC8E8 heavy_V      CAGGTCCAATTGCAGCAGTCTGGACCTGAGCTGGTGAAGCCCTGGGACTTC
IGHV1-69*10_Homo+sapiens CAGGTCCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCCTGGGTCCTC
***** ** ***** ** ***** ** ***** * **
DC8E8 heavy_V      AGTGAAGATGCCCTGTAAAGCTTCTGGATACATATTCACTGACTATGTCA
IGHV1-69*10_Homo+sapiens AGTGAAGGTCTCTGCAAGCTTCTGGAGGCACCTTCAGCAGCTATGCTA
***** * **** ***** ** ***** ** ***** *
DC8E8 heavy_V      TAAGCTGGGTGAAGCAGAGAACTGGACAGGGCCCTTGAGTGGATTGGAGAG
IGHV1-69*10_Homo+sapiens TCAGCTGGGTCCGACAGGCCCTGGACAAGGGCTTGAGTGGATGGAGGG
* ***** ** ***** ** ***** ***** *
DC8E8 heavy_V      ATTTTCCTAGAAGTGGTAGTACTTACTACAAATGAGAAGTTCGAAGGCCAA
IGHV1-69*10_Homo+sapiens ATCATCCCTATCCTTGGTATAGCAAACTACGCCACAGAAGTTCAGGGCAG
** * **** * **** * ***** *****
DC8E8 heavy_V      GGCCACACTGACTGCAGACAAATCCTCCAAACACAGCCTACATCCAGCTCA
IGHV1-69*10_Homo+sapiens AGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGAGAGTGA
* *** * ** ** ***** * * ***** ***** *
DC8E8 heavy_V      GCAGCGTGACATCTGAGGACTCTGCGGTCATTTCTGTGCAAGA--
IGHV1-69*10_Homo+sapiens GCAGCCTGAGATCTGAGGACACGGCCGTGTATTACTGTGCGGAGAGA
***** *** ***** * ** ** ***** ***

```

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

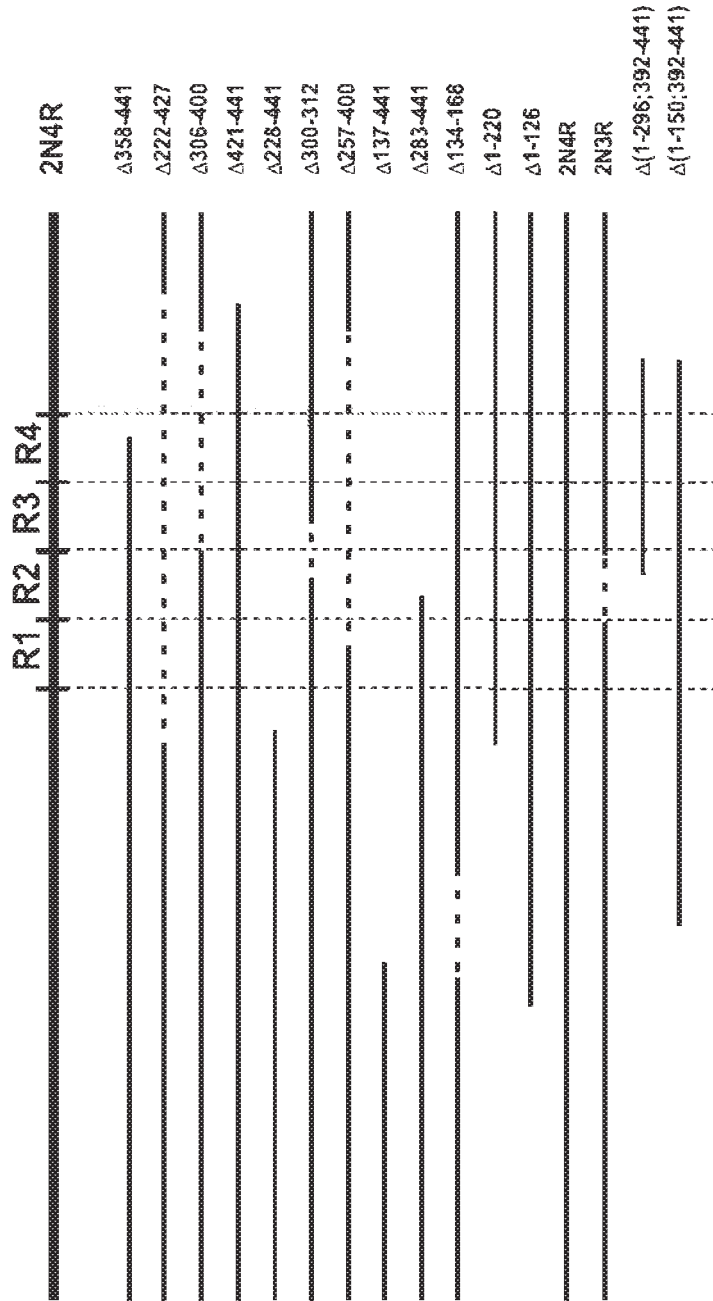


FIGURE 6B

 $\Delta 358-441$

```

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 PDLKNVYSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSGVQIVY KPVDSLKVTS KCGSLGNIHH KPGGGQVEVK SEKLDKDRV QSKIGSL

```

 $\Delta 222-427$

```

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 RLADSVSASL AKQGL

```

 $\Delta 306-400$

```

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 PDLKNVYSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSGDTSP RHLSNVSTG SIDMVDSPQL ATLADEVSA LAKQGL

```

 $\Delta 421-441$

```

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 PDLKNVYSKI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
301 PGGGSGVQIVY KPVDSLKVTS KCGSLGNIHH KPGGGQVEVK SEKLDKDRV QSKIGSLDNI
361 THVPGGGNKK IETHKLTFR NAKARTDHGA EIVYKSPVVS GDTSPRHLSN VSSTGSIDMV

```

 $\Delta 228-441$

```

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 TTAE EAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSR S RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVSKSI GSTENLKHQP GGGKVQIINK KLDLSNVQSK CGSKDNIKHV
 301 DLSKVTSCG SLGNIIHKPG GGQVEVKSEK LDFKDRVQSK IGSLDNITHV PGGGNKKIET
 361 HKLTFRENAK AKTDHGAEIV YKSPVVSGDT SPRHLSNVSS TGSIDMVDSP QLATLADEV S
 421 ASLAKQGL

Δ257-400

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAE EAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDGTGSDDK KAKGADGKTK IATPRGAAPP GQKGQANATR IPAKTPPAPK
 181 TPPSSGEPPK SGDRSGYSSP GSPGTPGSR S RTPSLPTPPT REPKKVAVVR TPPKSPSSAK
 241 SRLQTAPVPM PDLKNVGDTS PRHLSNV SST GSIDMVDSPQ LATLADEVSA SLAKQGL

Δ137-441

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

Δ283-441

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

Δ134-168

1 MAEPRQEFEV MEDHAGTYGL GDRKDQGGYT MHQDQEGDTD AGLKESPLQT PTEDGSEEPG
 61 SETSDAKSTP TAEDVTAPLV DEGAPGKQAA AQPHTEIPEG TTAE EAGIGD TPSLEDEAAG
 121 HVTQARMVSK SKDTRIPAKT PPAPKTPPSS GEPPKSGDRS GYSSPGSPGT PGSRSRTPSL
 181 PTPPTREP KK VAVVRTPPKS PSSAKSRLQT APVPM PDLKN VKSKIGSTEN LKHQPGGGKV
 241 QIINKKLDLS NVQSKCGSKD NIKHVPGGGS VQIVYKPV DL SKVTSKCGSL GNIHHPGGG
 301 QVEVKSEKLD FKDRVQSKIG SLDNITHVPG GGNKKIETHK LTFRENAKAK TDHGAEIVYK
 361 SPVVSGDTSP RHLSNV SSTG SIDMVDSPQL ATLADEV SAS LAKQGL

Δ1-220

1 MREP KK VAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVSK IGSTENLKHQ PGGGVQIIN
 61 KKLDLSNVQS KCGSKDNIKH VPGGGSVQIV YKPV DLSKVT SKCGSLGNII HKPGGGQVEV
 121 KSEKLD FKDR VQSKIGSLDN ITHVPGGGNK KIETHKLTFR ENAKAKTDHG AEIVYKSPVV
 181 SGDTSPRHLS NVSSTGSIDM VDSPQLATLA DEV SASLAKQ GL

Δ 1-126

1 MVSKSKDGTG SDDKKAKGAD GGTKIATPRG AAPPGQKGQA NATRIPAKTP PAPKTPPSSG
 61 EPPKSGDRSG YSSPGSPGTP GSRSRTPSLP TPPTREPKKV AVVRTPPKSP SSAKSRLQTA
 121 PVPMPDLKNV KSKIGSTENL KHQPGGGKVQ IINKKLDLSN VQSKCGSKDN IKHVPGGGSV
 181 QIVYKPV DLS KVTSCGSLG NIHHKPGGGQ VEVKSEKLDF KDRVQSKIGS LDNITHVPPG
 241 GNKKIETHKL TFRENAKAKT DHGAEIVYKS PVSVDGTSR HLNSVSSSTGS IDMVDSPLA
 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 KPVDLSKVT 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 PVDLSKVT SKCGSLGNIH
 301 PGGGQVEVKS EKLDKDFKDRV SKIGSLDNIT HVPGGGNKKI ETHKLTFRENAKAKTDHGA
 361 IVYKSPVVS DTSRHLNSV SSTGSIDMV SPQLATLADEVASLAKQGL

 Δ (1-296;392-441)

1 MIKHVPGGGS VQIVYKPV DLS SKVTSCGSL GNIHHKPGGG QVEVKSEKLD FKDRVQSKIG
 61 SLDNITHVPG GGNKKIETHK LTFRENAKAK TDHGA

 Δ (1-150;392-441)

1 MIATPRGAAP PGQKGQANAT RIPAKTPPAP KTPPSSGEPP KSGDRSGYSS PGSPGTPGSR
 61 SRTPSLPTP TREPKKVAVV RTPPKSPSSA KSRLQTAPVP MPDLKNVSK IGSTENLKHQ
 121 PGGGKVQIIN KKLDLSNVQS KCGSKDNIH VPGGGSVQIV YKPVDLSKVT SKCGSLGNIH
 181 HKPGGGQVEV KSEKLDFKDR VQSKIGSLDN ITHVPGGGNKKI ETHKLTFRENAKAKTDHG
 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

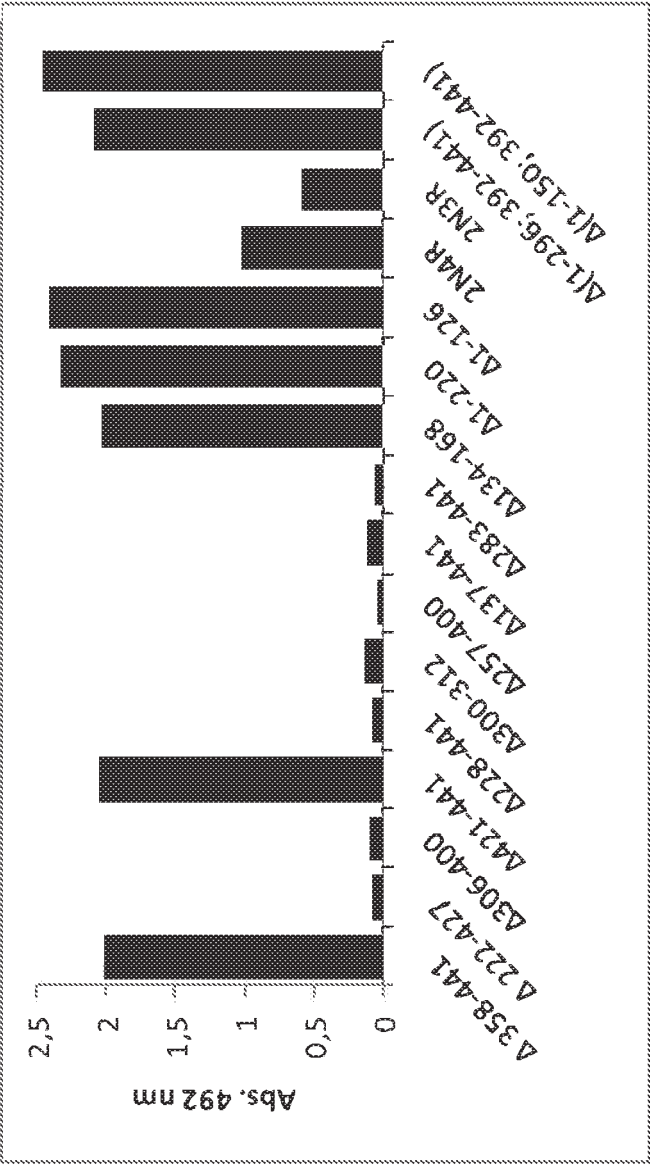


FIGURE 7A

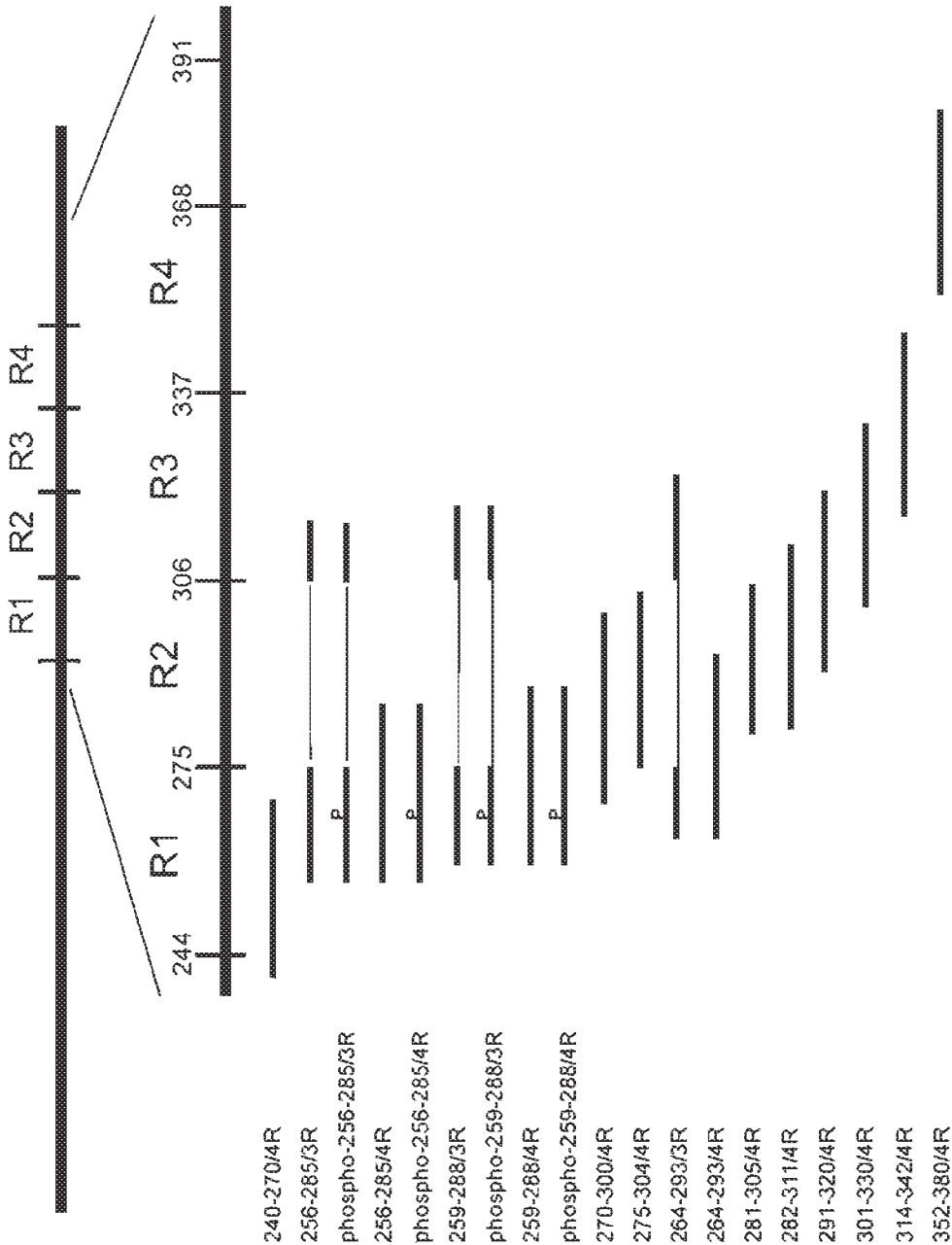


FIGURE 7B

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

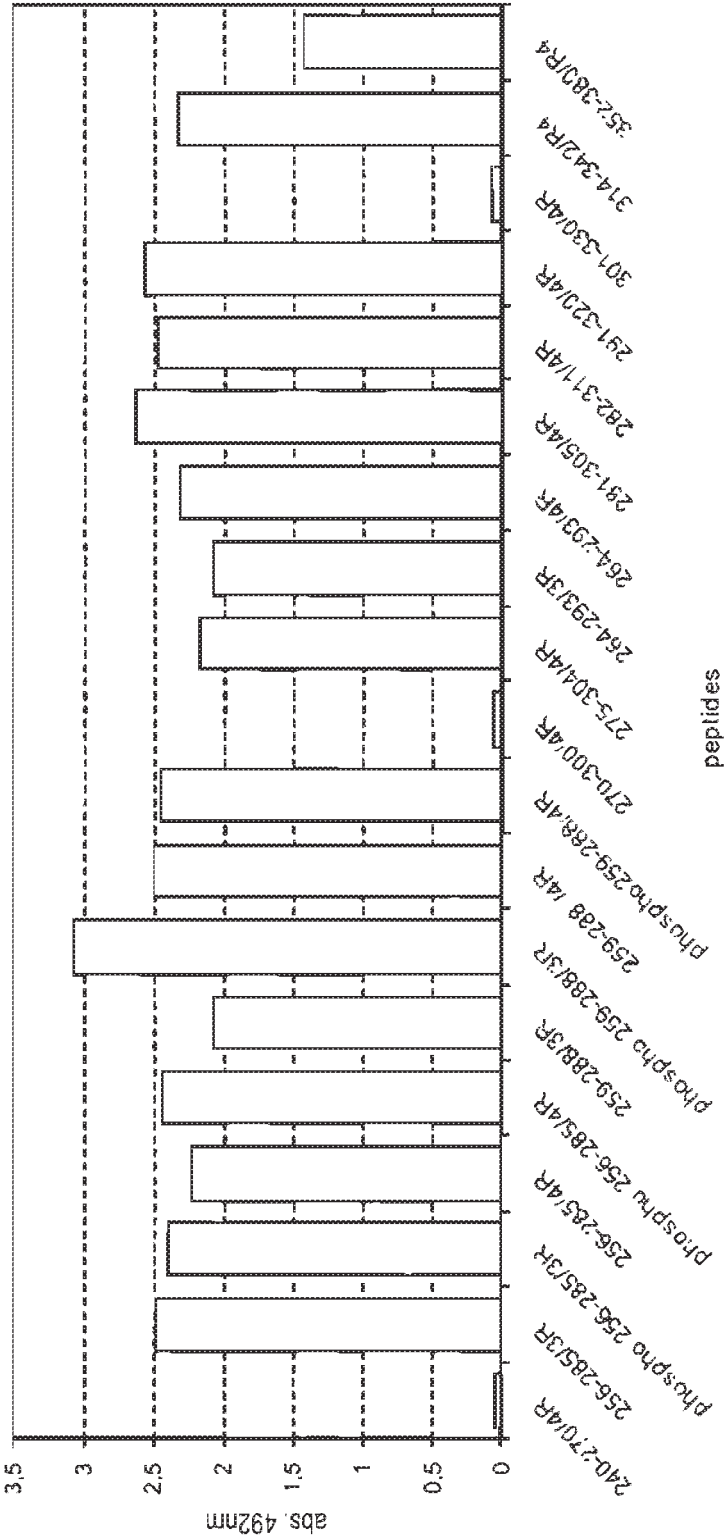


FIGURE 7D

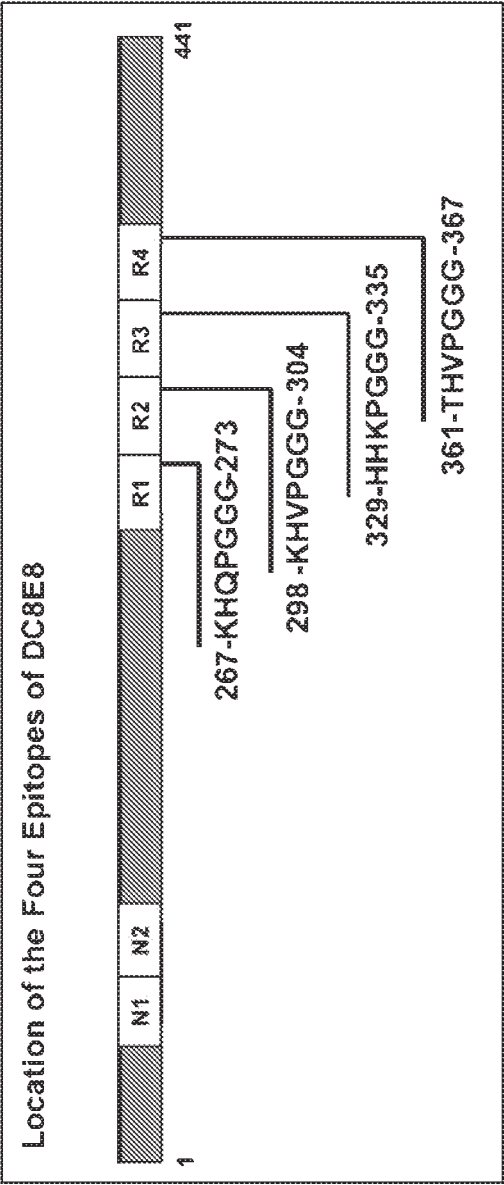


FIGURE 8A

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	LDLT	NVQAR	CGSKDNI	KHVP	GGG	KVQI	LHKK	ID
African_clawed_frog	468-NI	RHQP	GGG	KVQI	V	HKKV	D	LG	NVQSKCGSKDNI	KHVP	GGG	AIQI	THK	PID
Fruit_fly	157-NA	TYKP	GGG	HKV	I	ESK	I	DIK	AA	PRIEAKND--	KYMP	RGG	EKKI	VT
Roundworm	269-N-	HKAG	GGG	NVEI	F	SEKR	-	LYNA	QSKVGS	SLKNA	THVAG	GGG	NVQI	ENR

Human	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-368
Chimpanzee	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703
Macaque	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703
Gibbon	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-703
Orangutan	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-685
Giant_panda	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-727
Pig	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-673
Horse	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-372
Dog	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-368
Rabbit	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-359
Rat	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-359
Vole	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357
Mouse	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357
Ground_Squirrel	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-357
Cattle	LSKV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DRVQ	SKIG	SLDNI	THVP	GGG	N-375
Fowl	LSHV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DKVQ	SKIG	SLDNI	SHVP	GGG	N-272
Finch	LSHV	TSKCG	SLGNI	HHKP	GGG	QVEV	KSEK	LDFK	DKVQ	SKIG	SLDNI	SHVP	GGG	N-633
Zebra_fish	LSNV	QSKCG	SKDNI	HHKP	GGG	NIEI	RSEK	LDF--	KAQ	SKIG	SMDNI	KHTP	GGG	N-332
African_clawed_frog	LTRV	TSKCG	SFVNI	HHKP	GGG	NVEL	KSEK	LEF-	DKI	QSKIG	SLDNI	THVP	GGG	N-600
Fruit_fly	WN-AK	SKIG	SENA	HHKP	GGG	DKKI	ETL	KMD	FKD	KAKP	KGSTANV	KHQP	GGG	N-287
Roundworm	FSAAS	PKVGS--	KT	NYQP	AKS	DKV	KIV	SEK	L	TW--	QAK	SKVGS	SMDNA	HHKP

FIGURE 8B

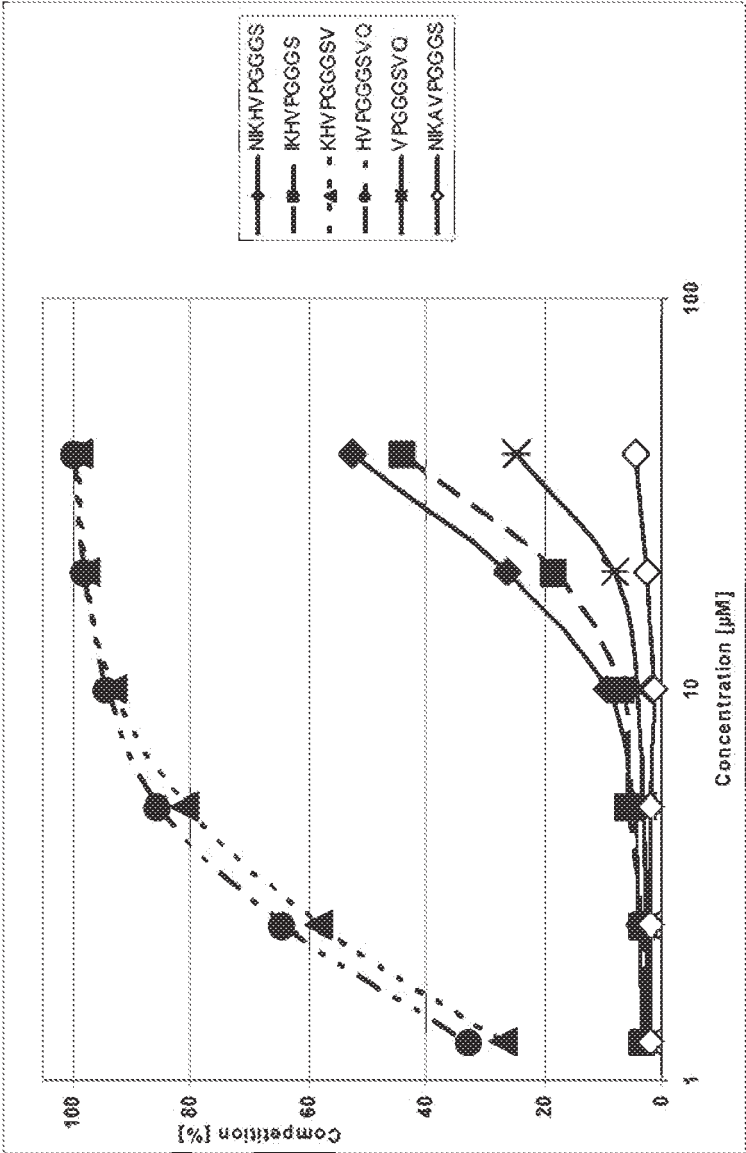


FIGURE 8C

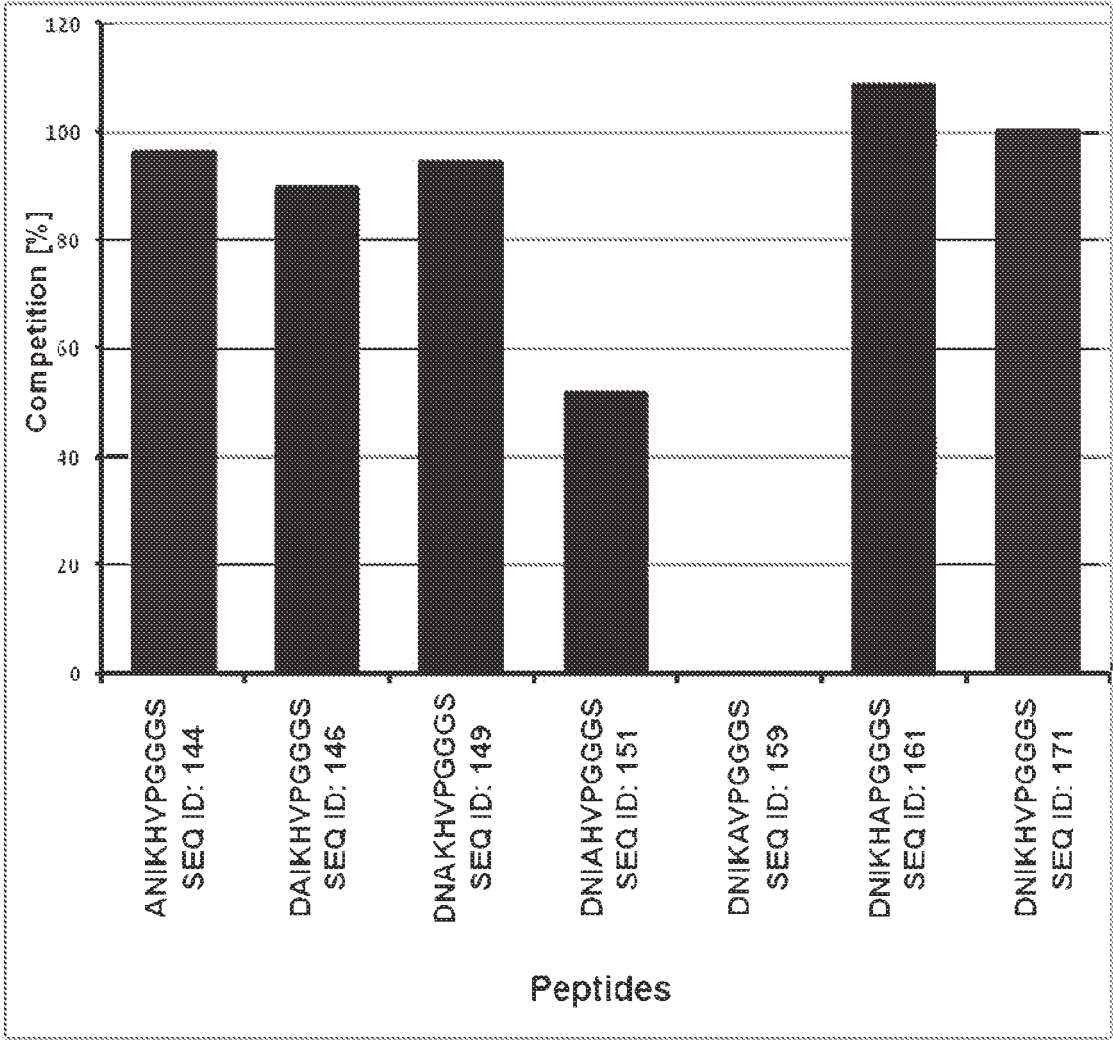


FIGURE 9A

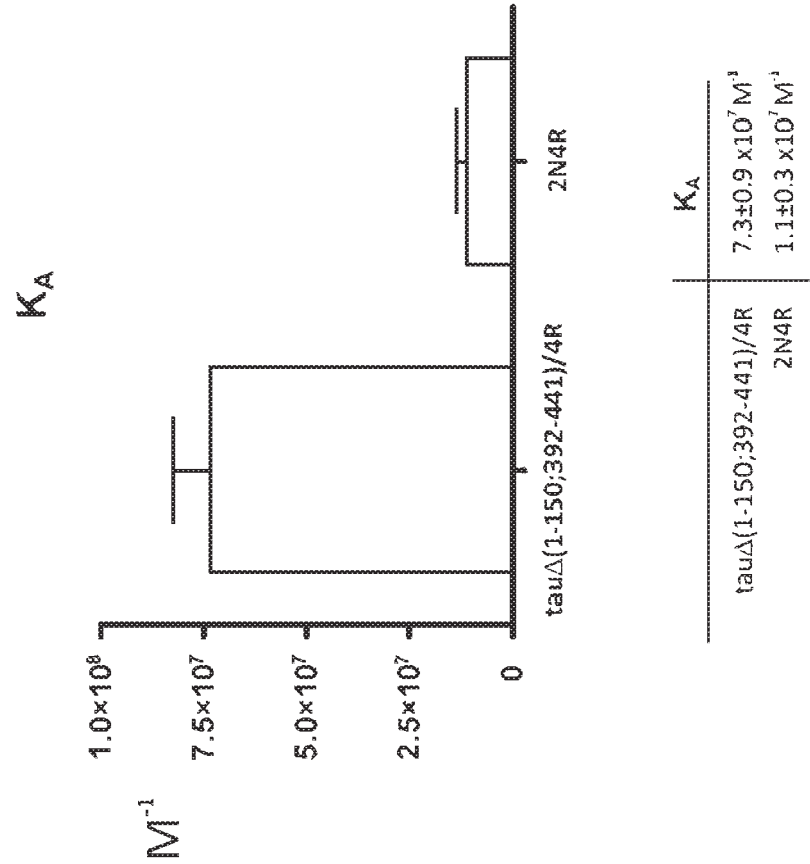


FIGURE 9B

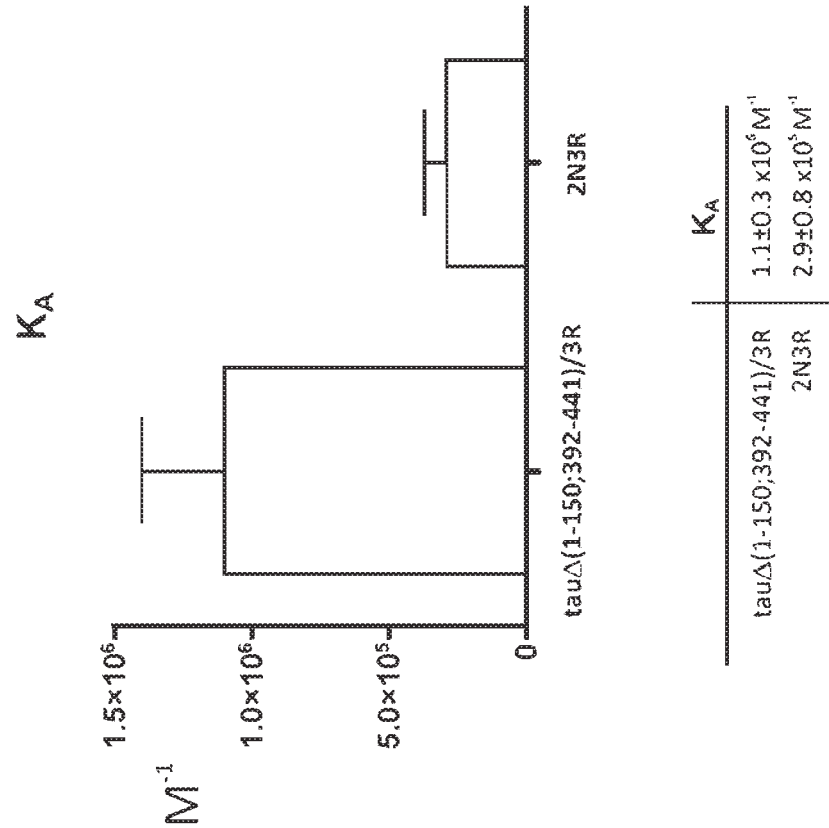


FIGURE 10A

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

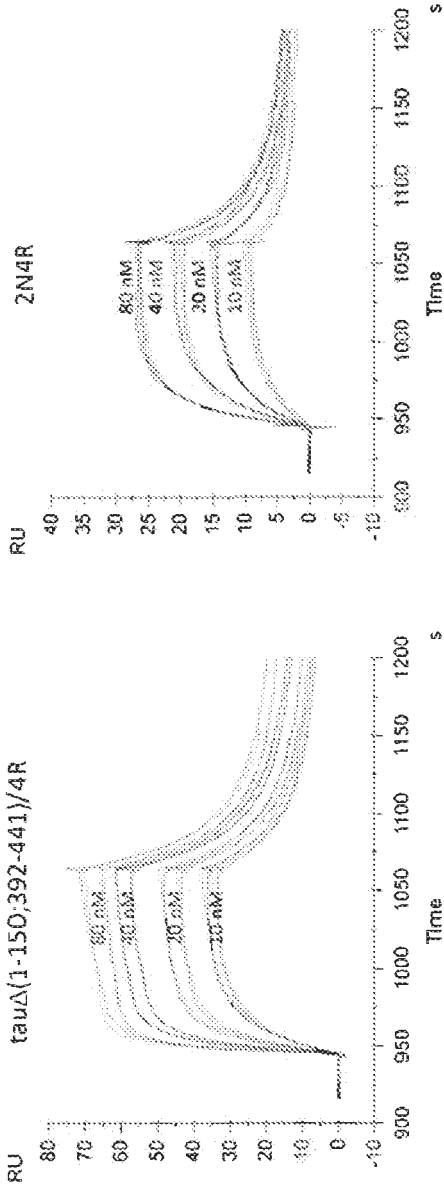


FIGURE 10B

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

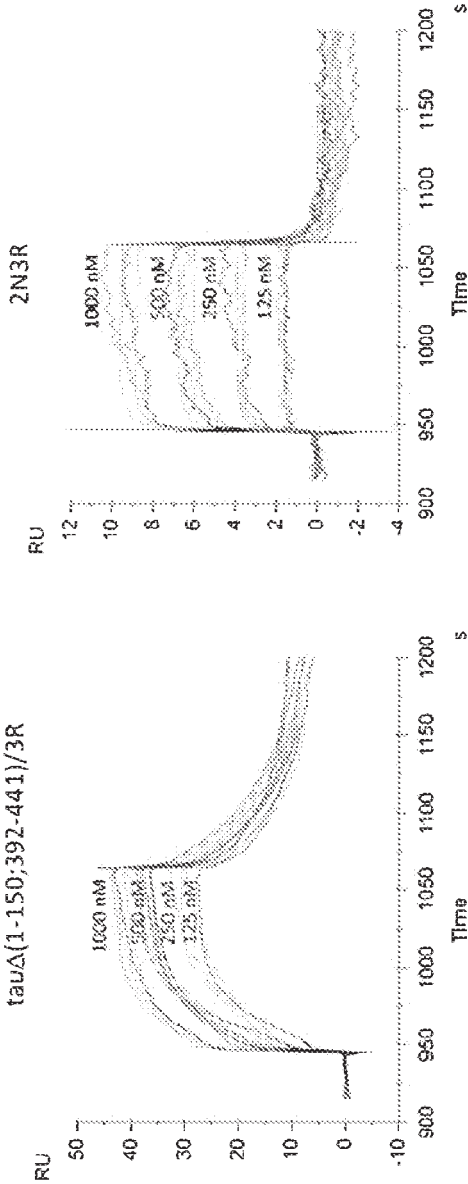
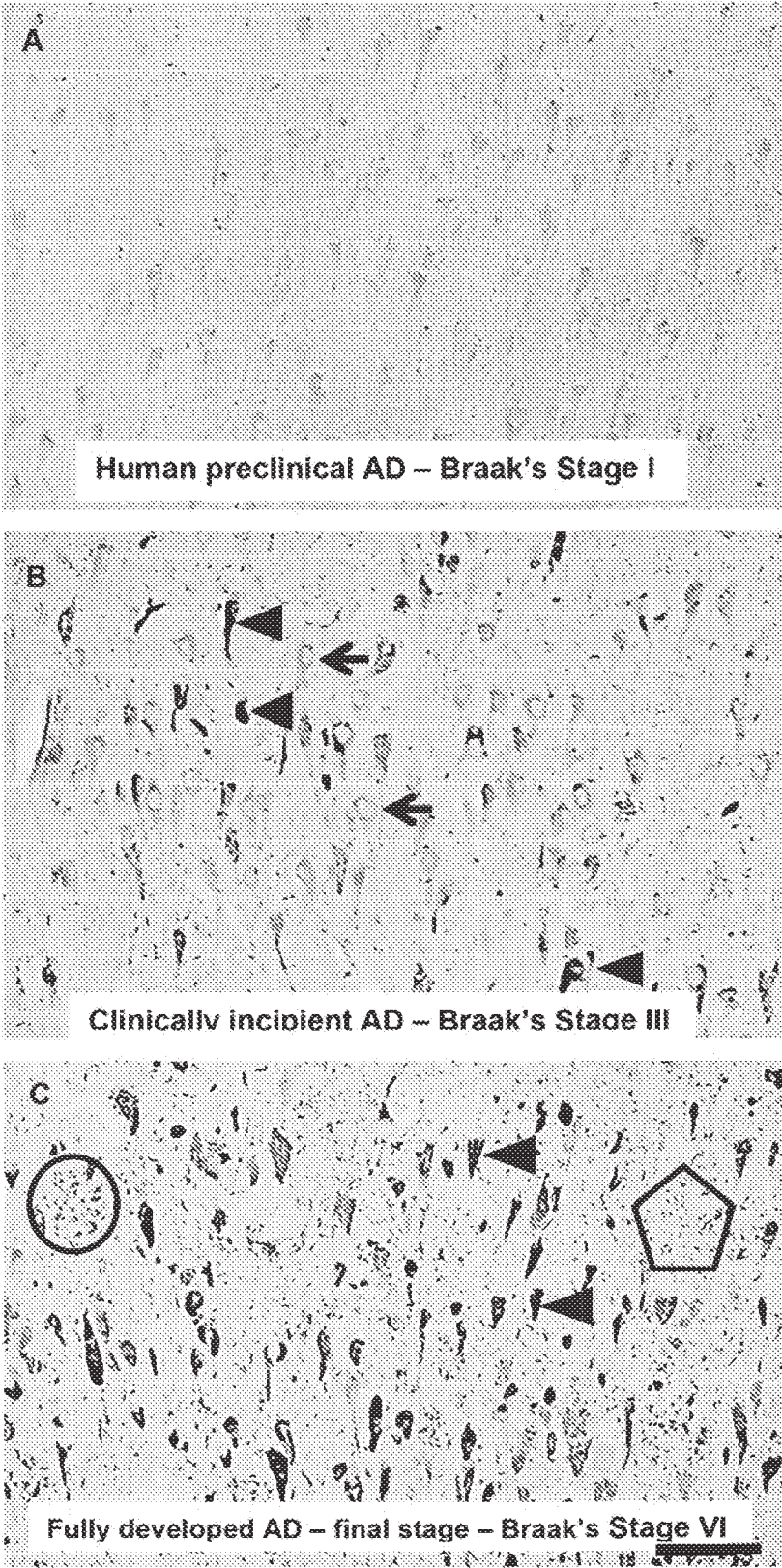


FIGURE 11



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FIGURE 11D

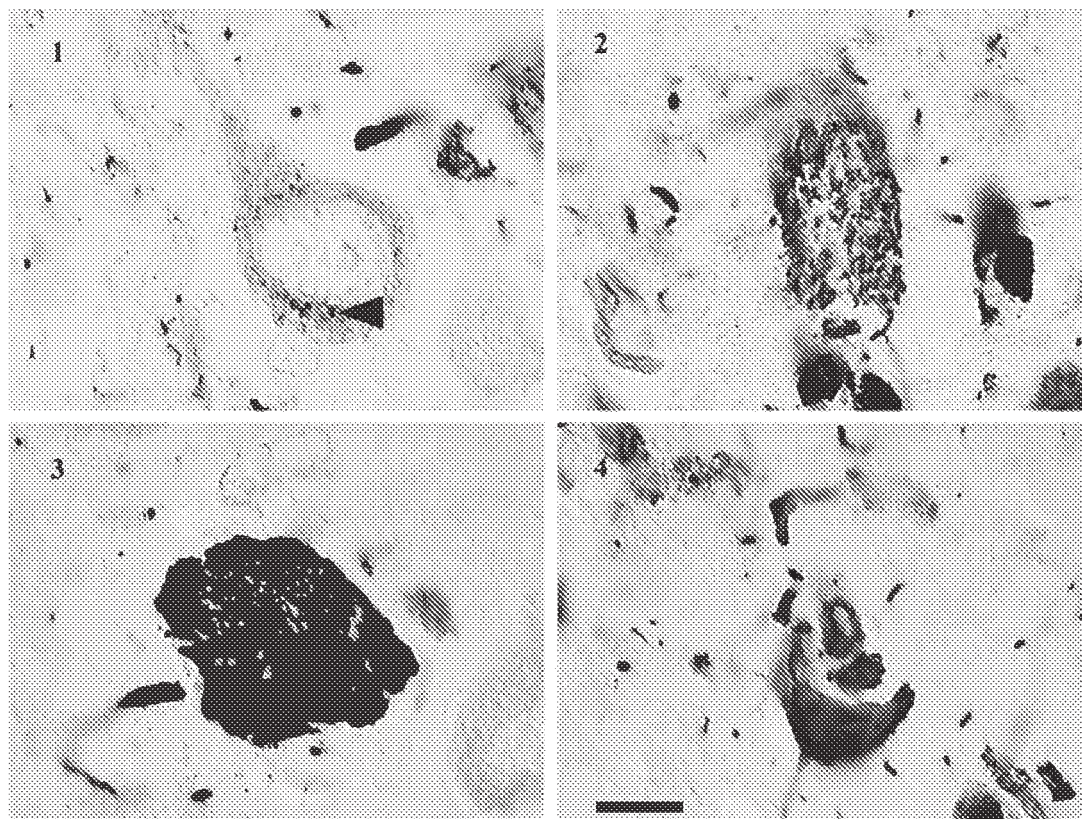


FIGURE 12A AND FIGURE 12B

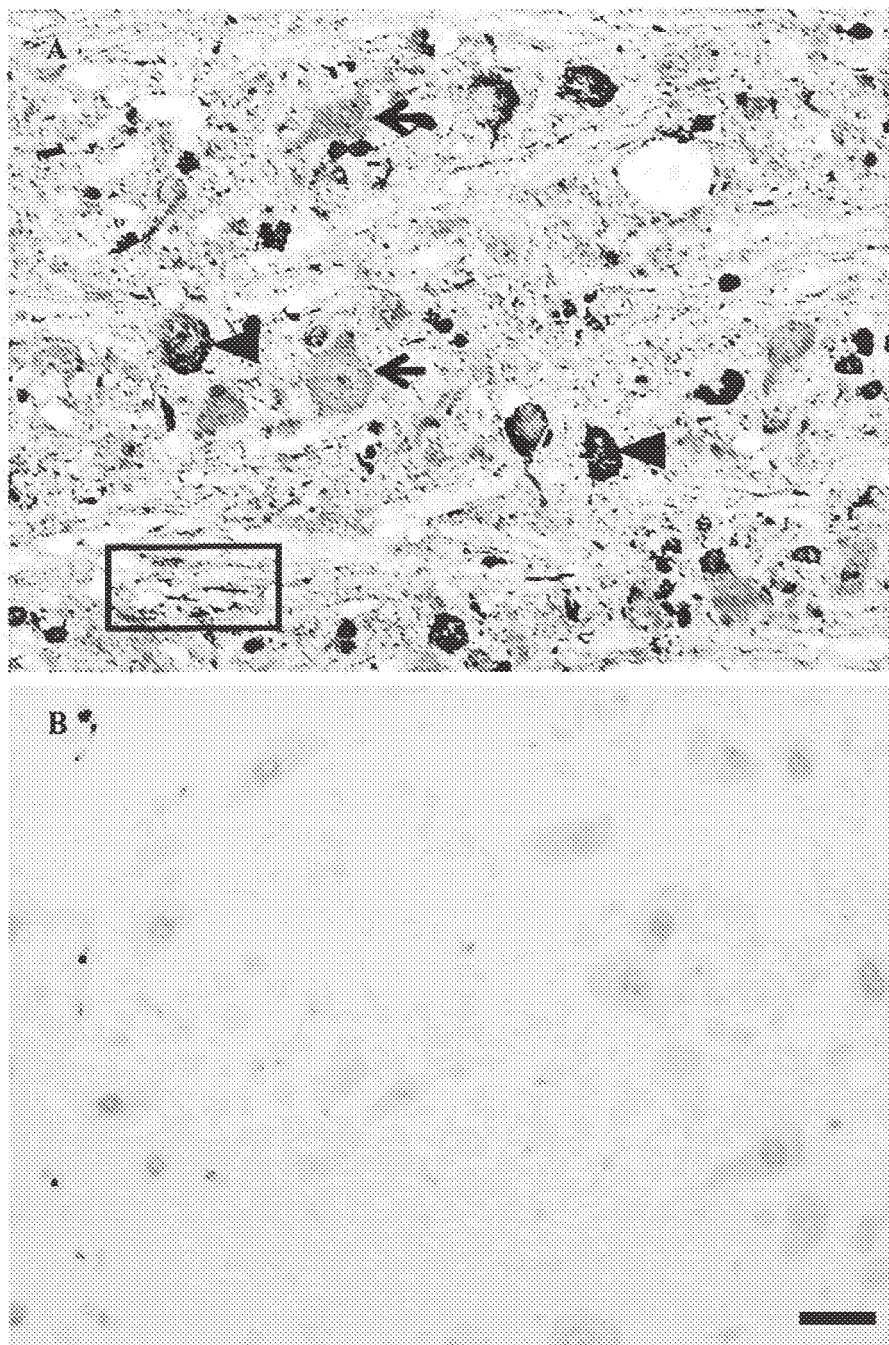


FIGURE 12C THROUGH FIGURE 12F

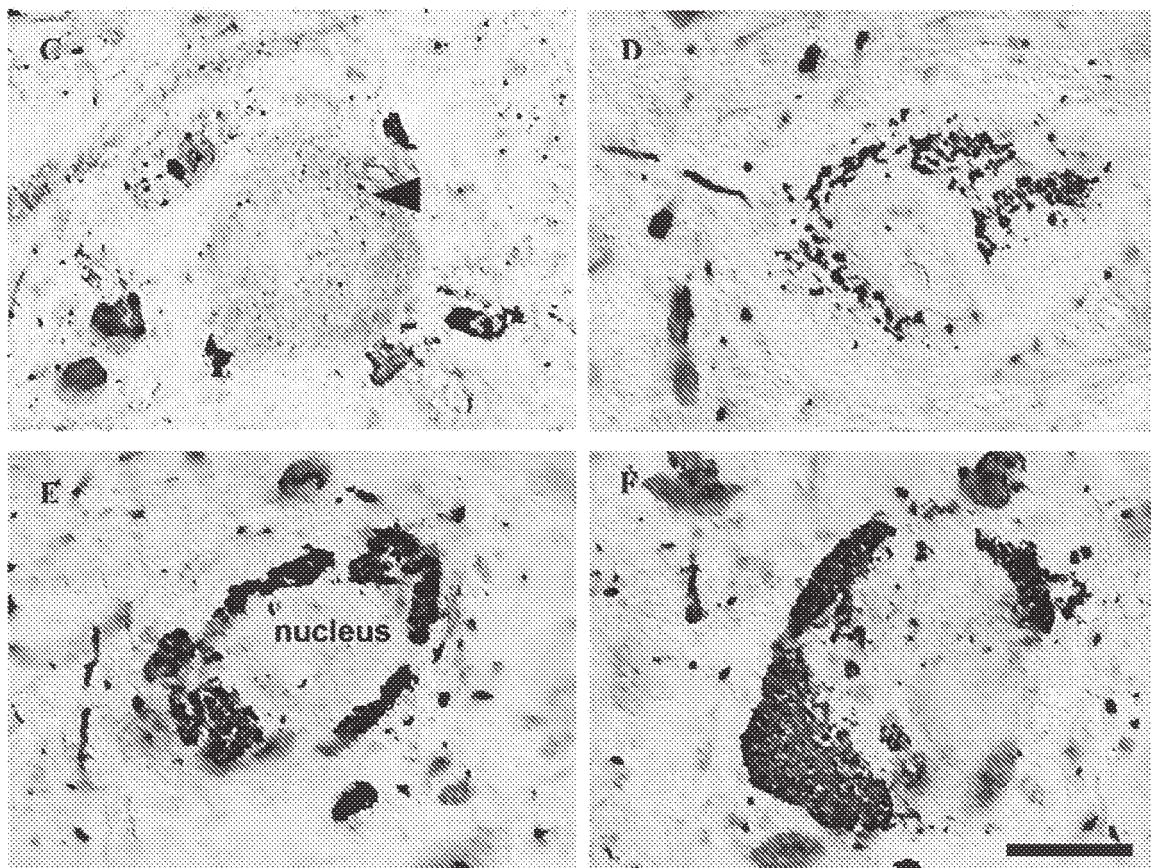


FIGURE 13

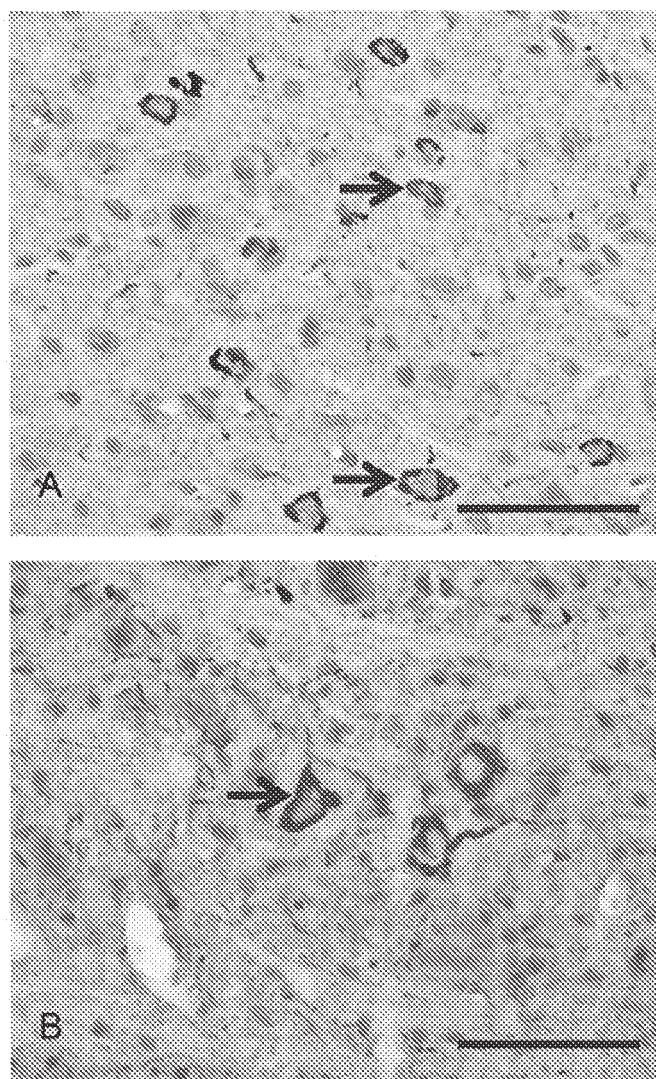


FIGURE 14A and 14B

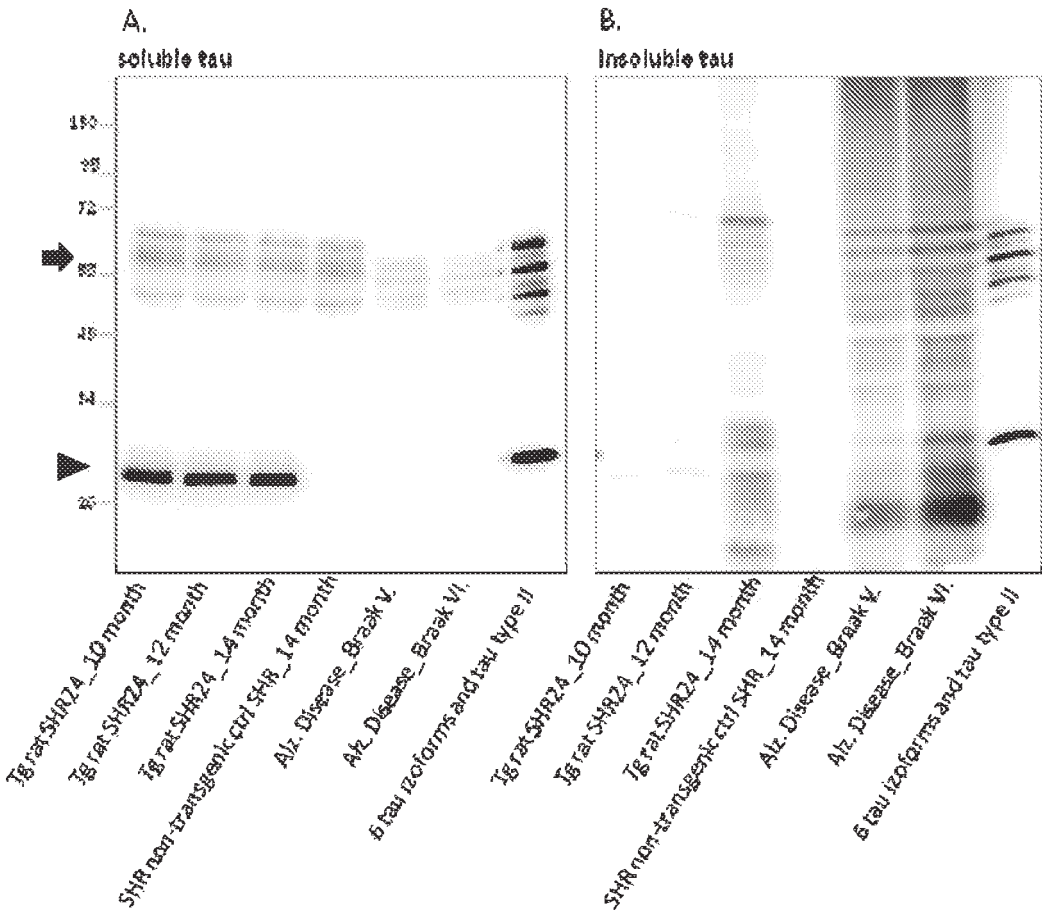


FIGURE 14C and 14D

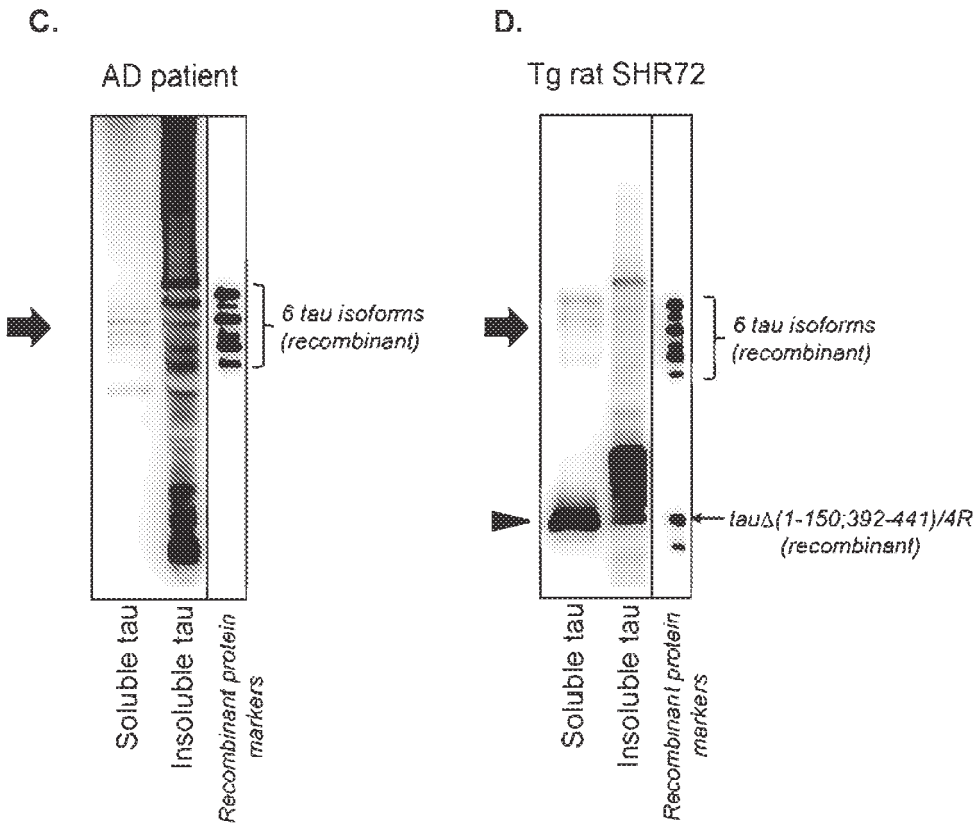


FIGURE 15A

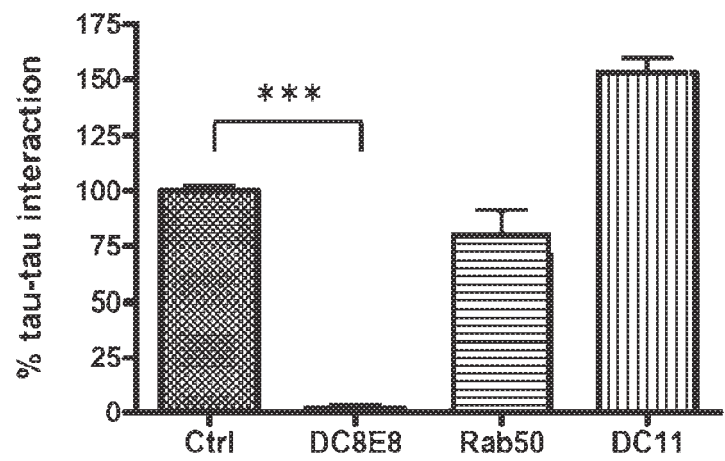


FIGURE 15B

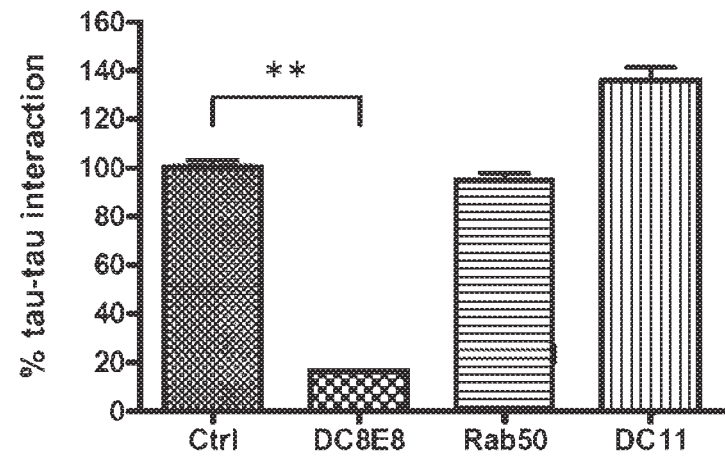


FIGURE 16

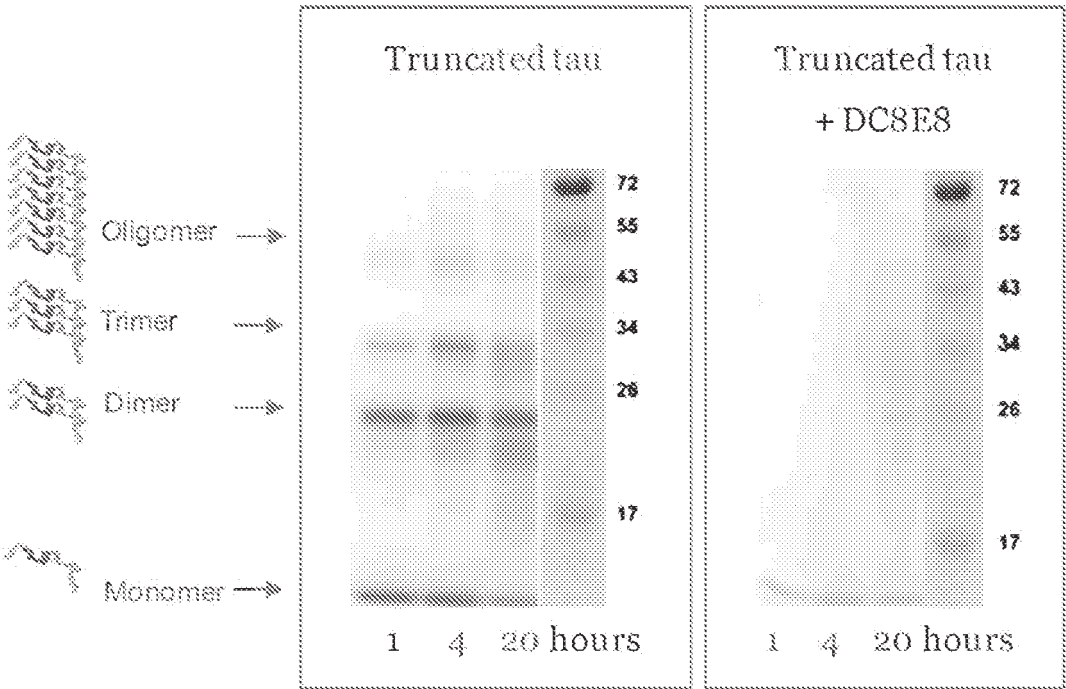


FIGURE17A

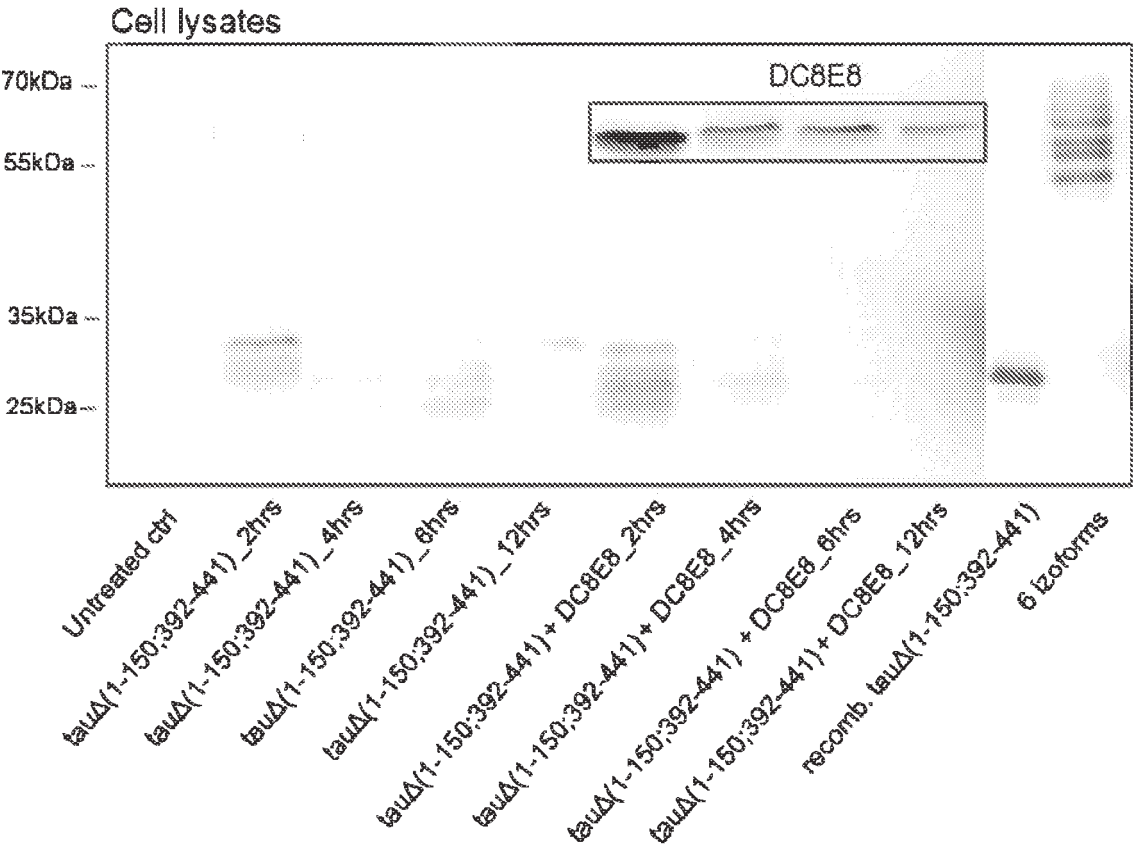
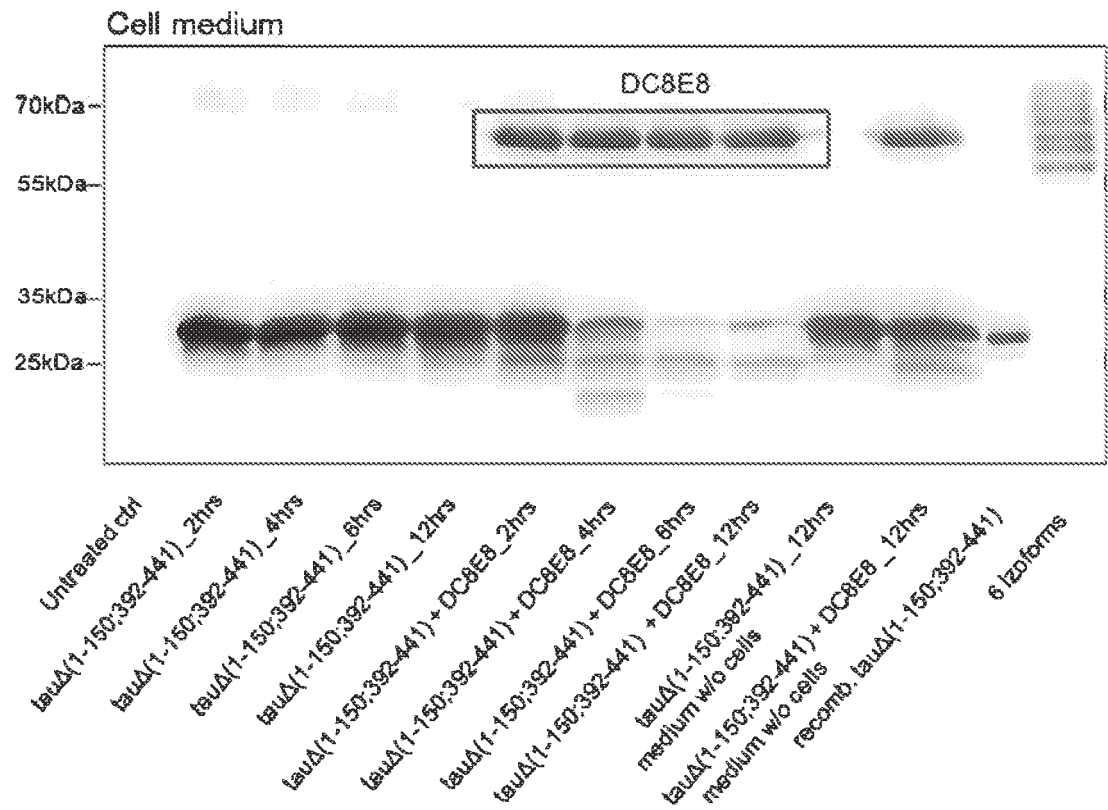


FIGURE 17B



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FIGURE 18

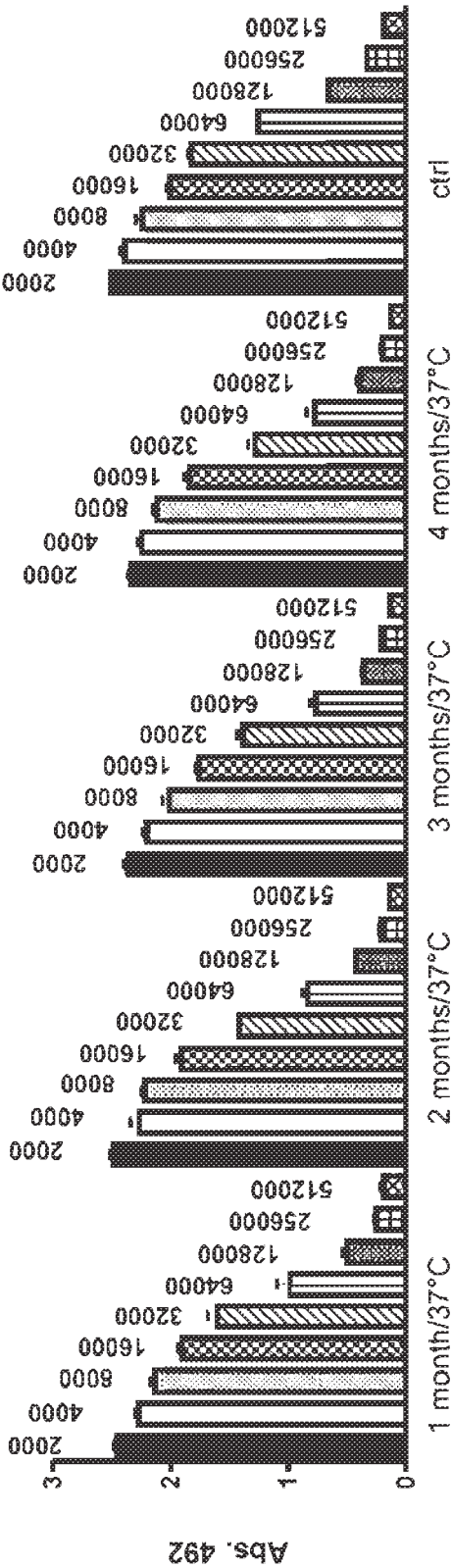


FIGURE 19

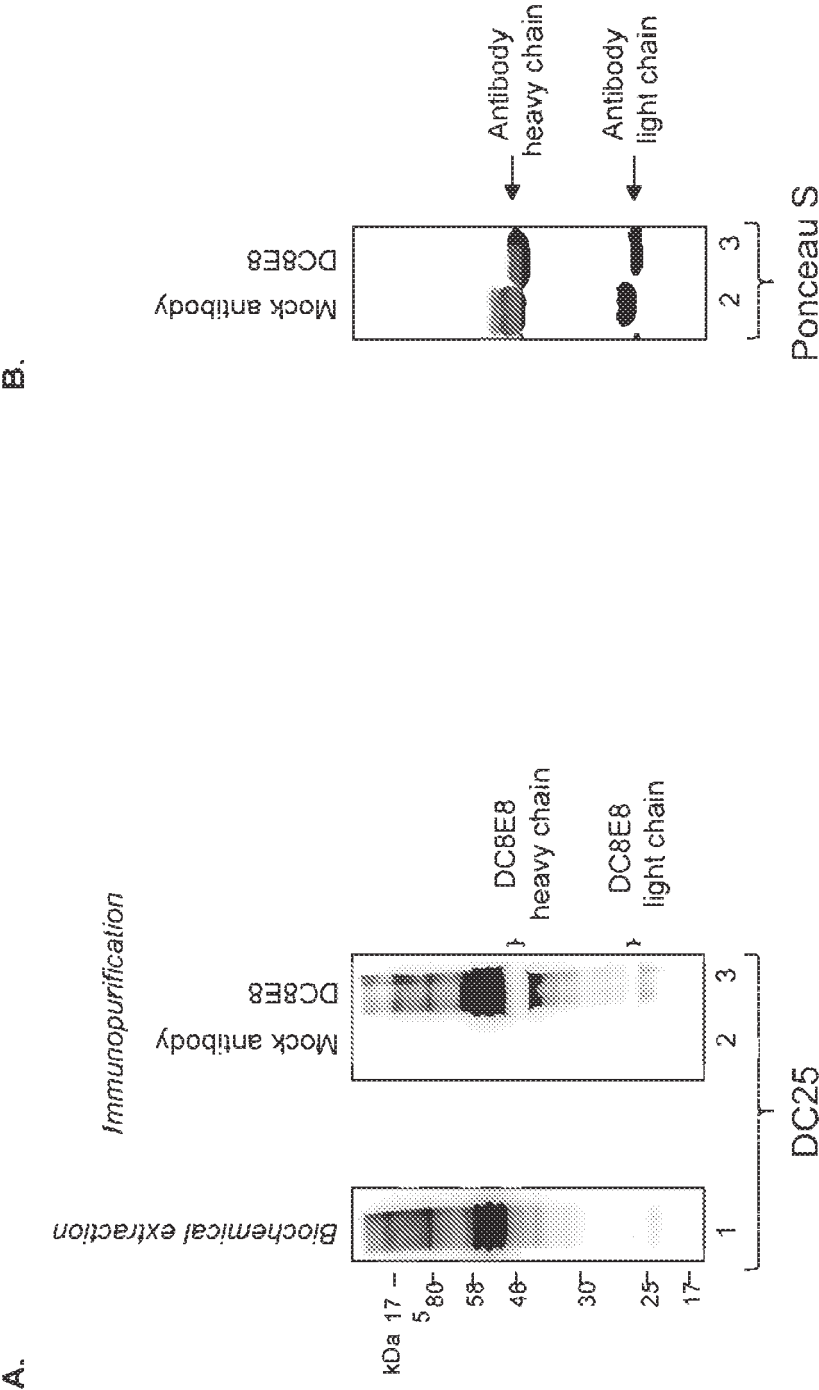


FIGURE 20

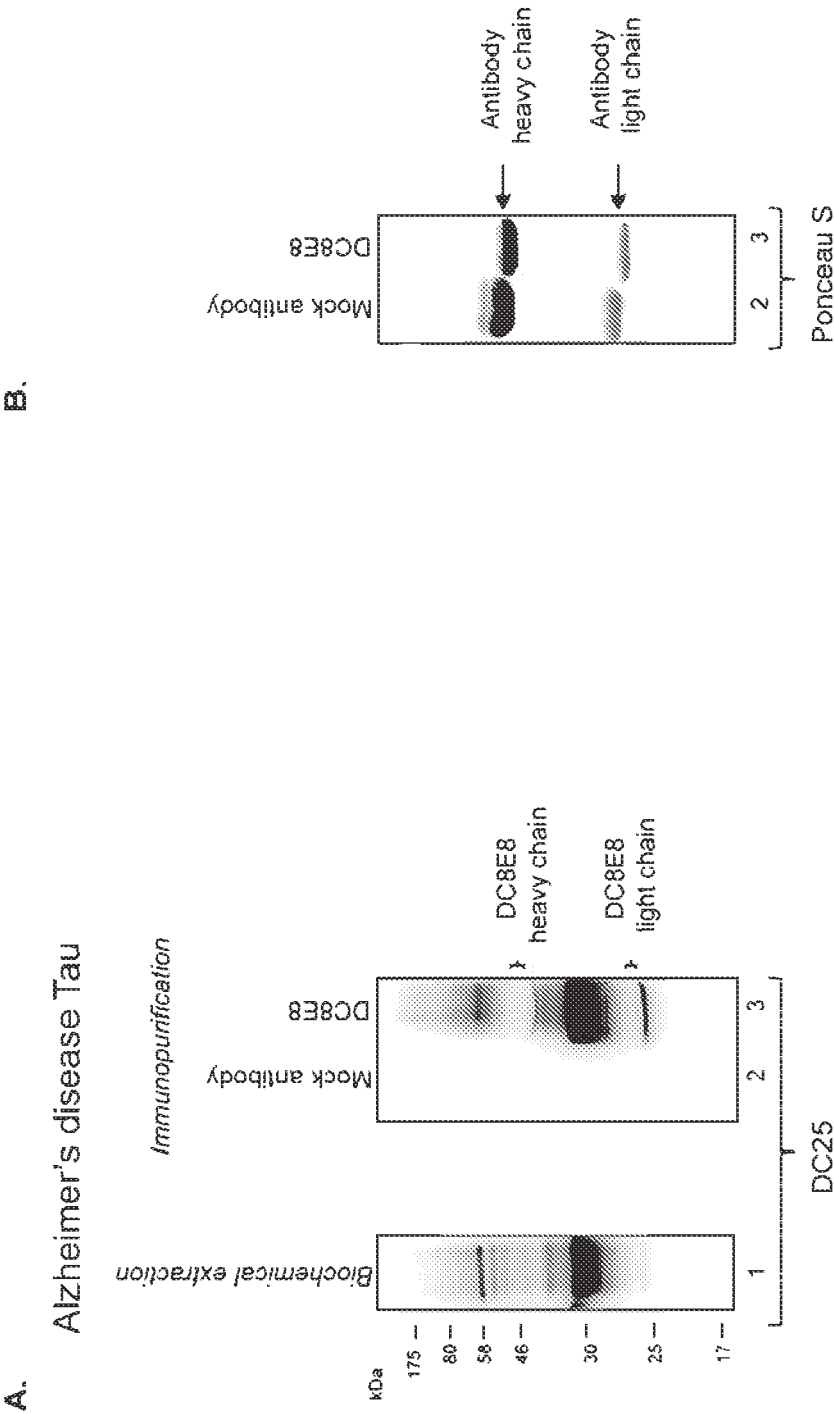


FIGURE 21A

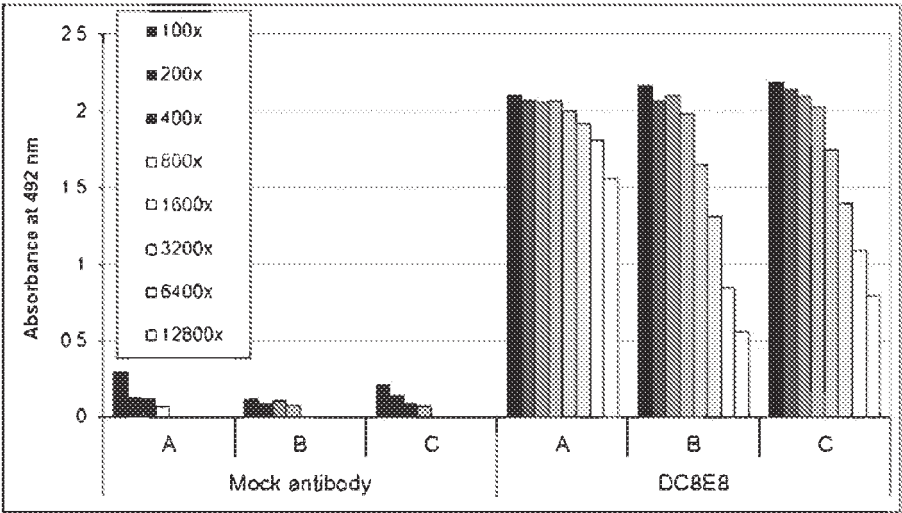


FIGURE 21B

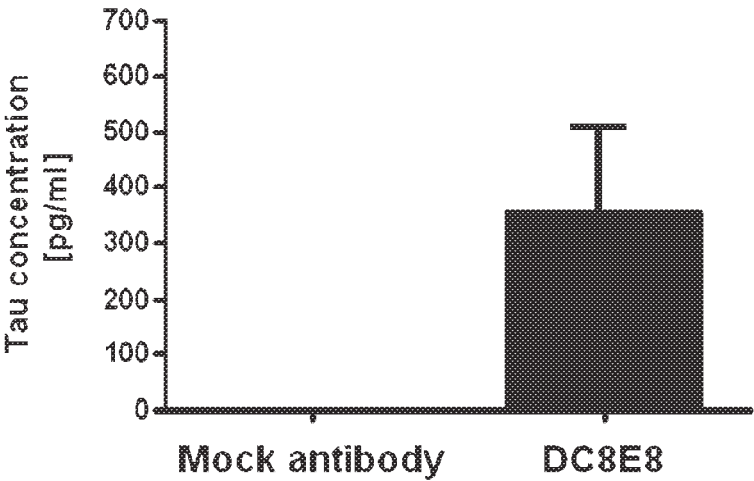
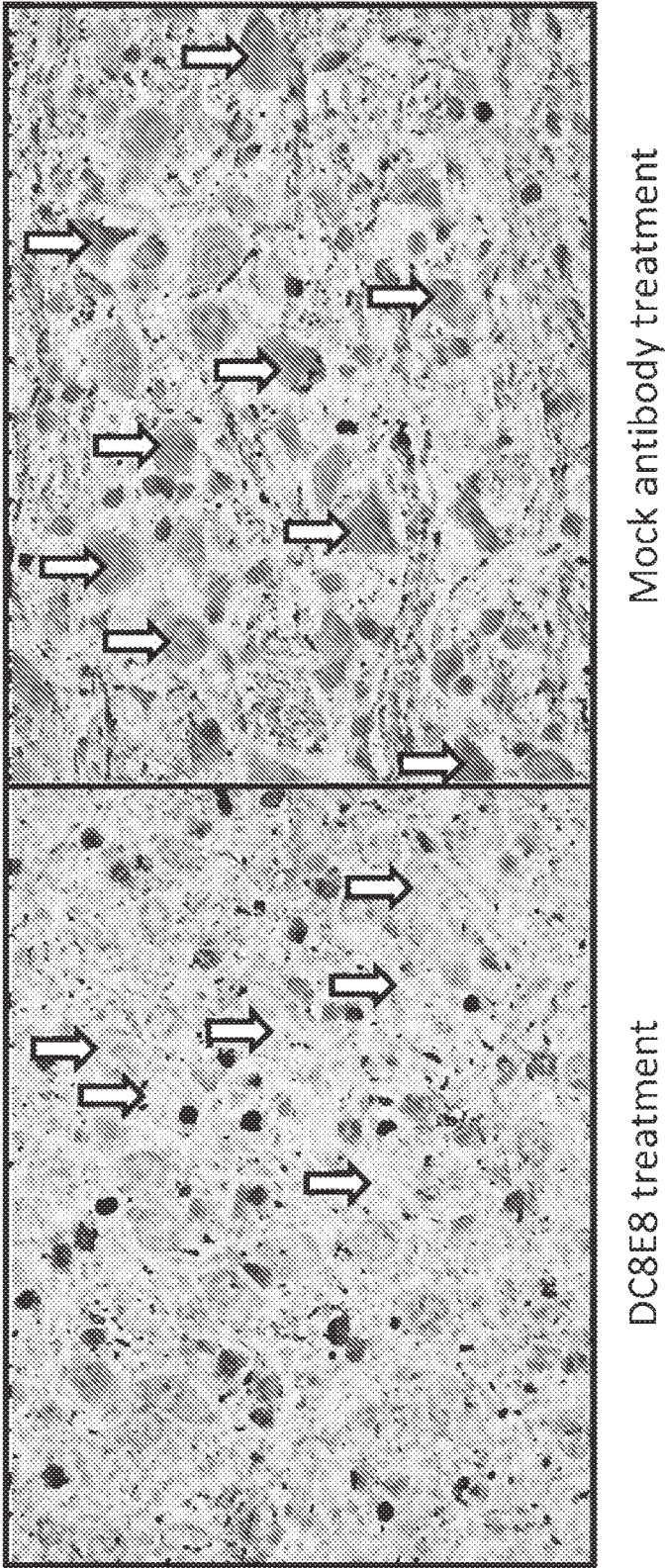


FIGURE 22A



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FIGURE 22B

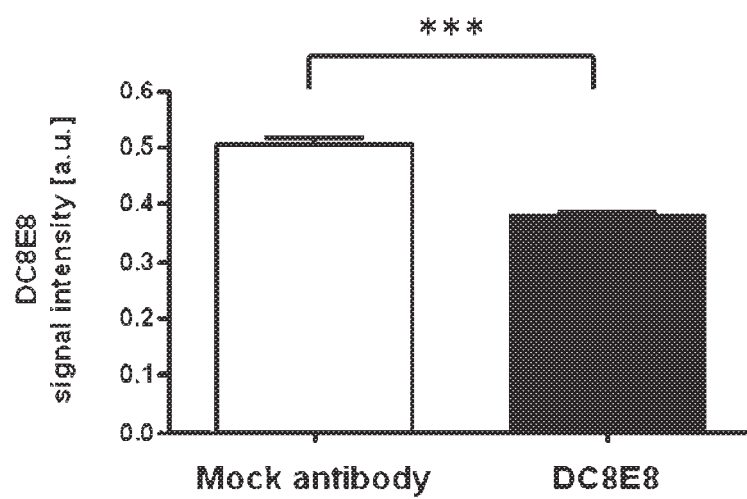


FIGURE 23

FIGURE 23A.

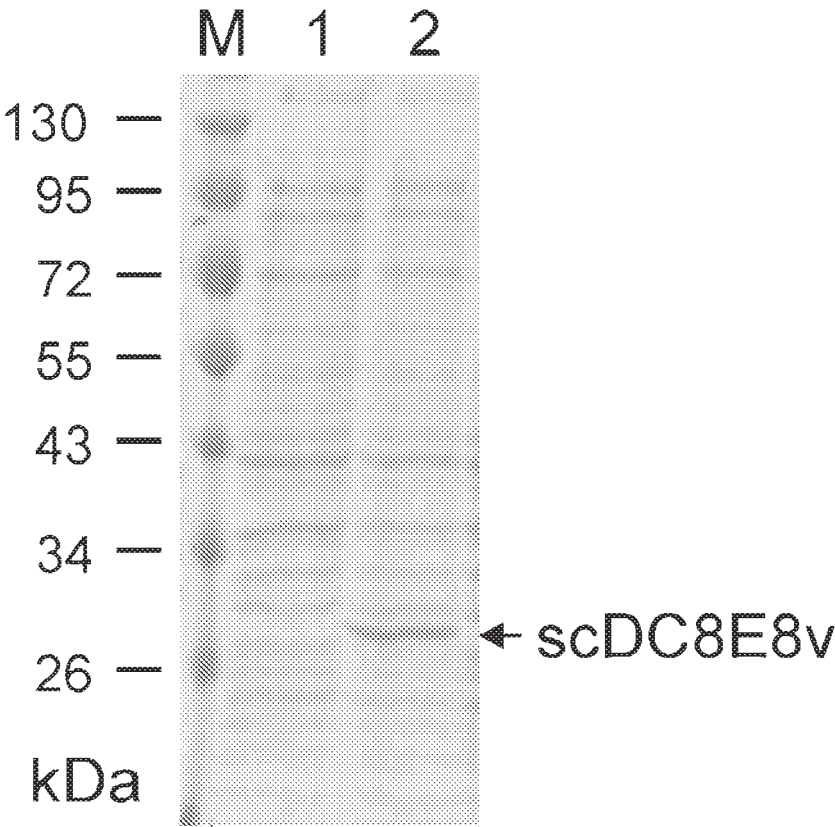


FIGURE 23B.

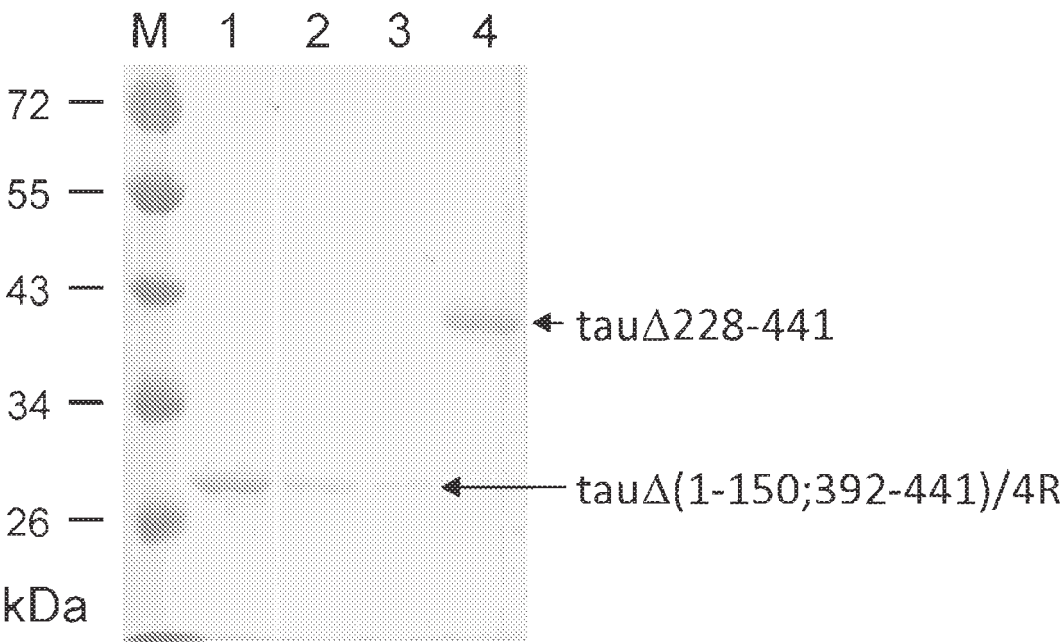


FIGURE 23D

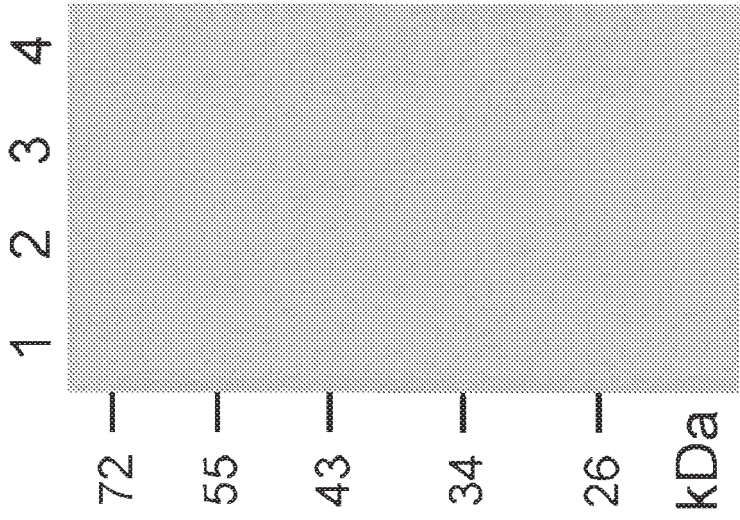


FIGURE 23C

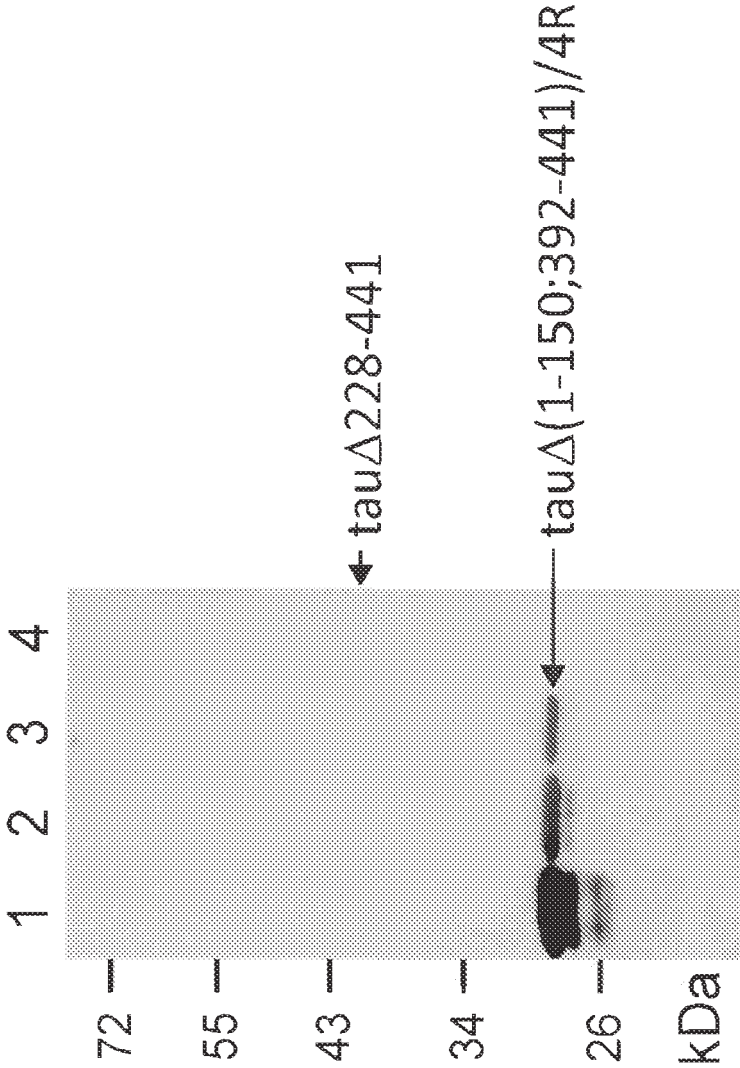


FIGURE 24A

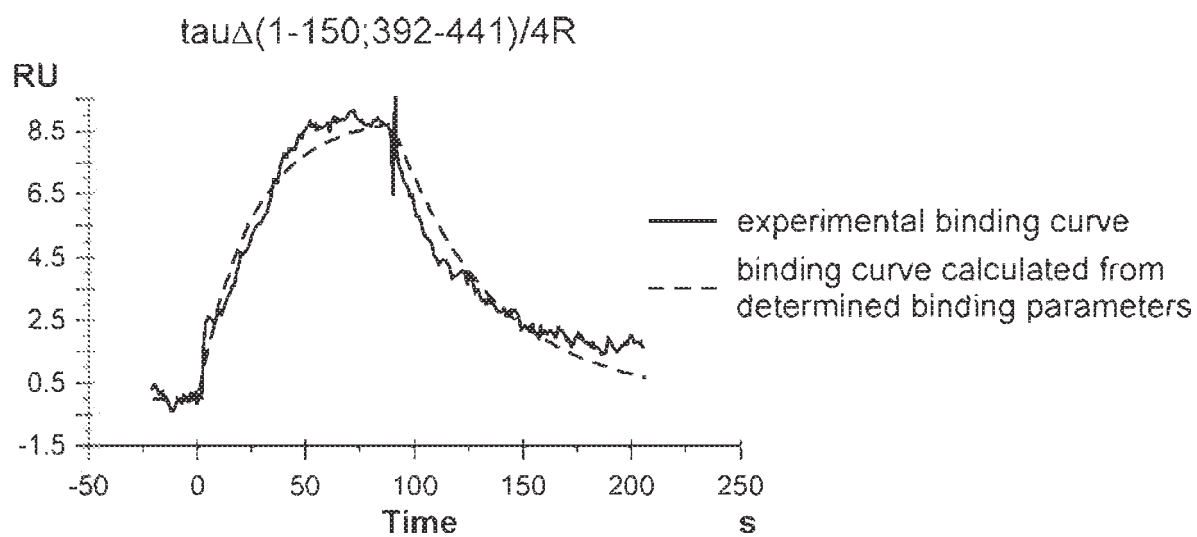


FIGURE 24B

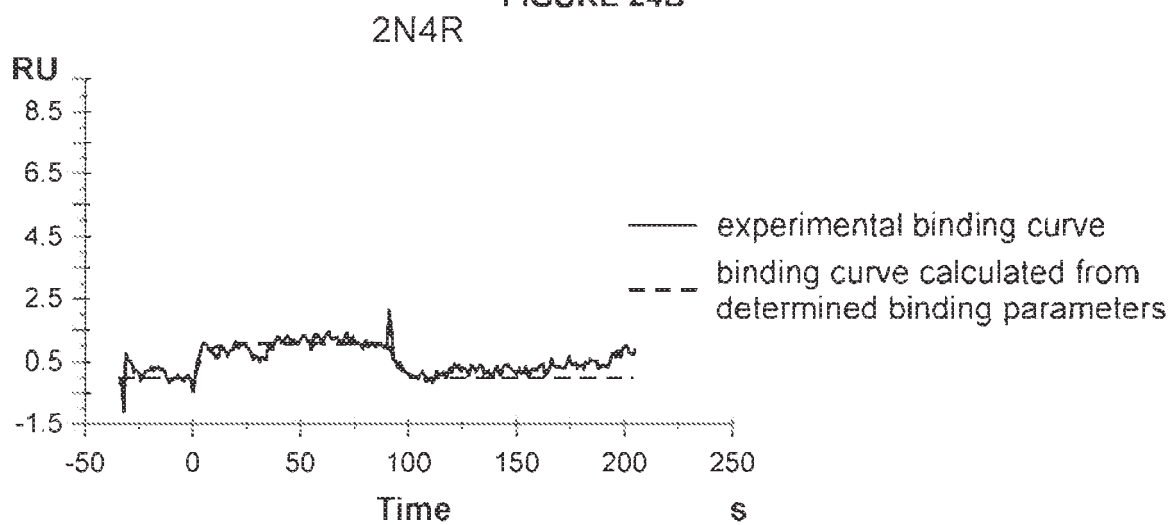


FIGURE 24C

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

FIGURE 25A

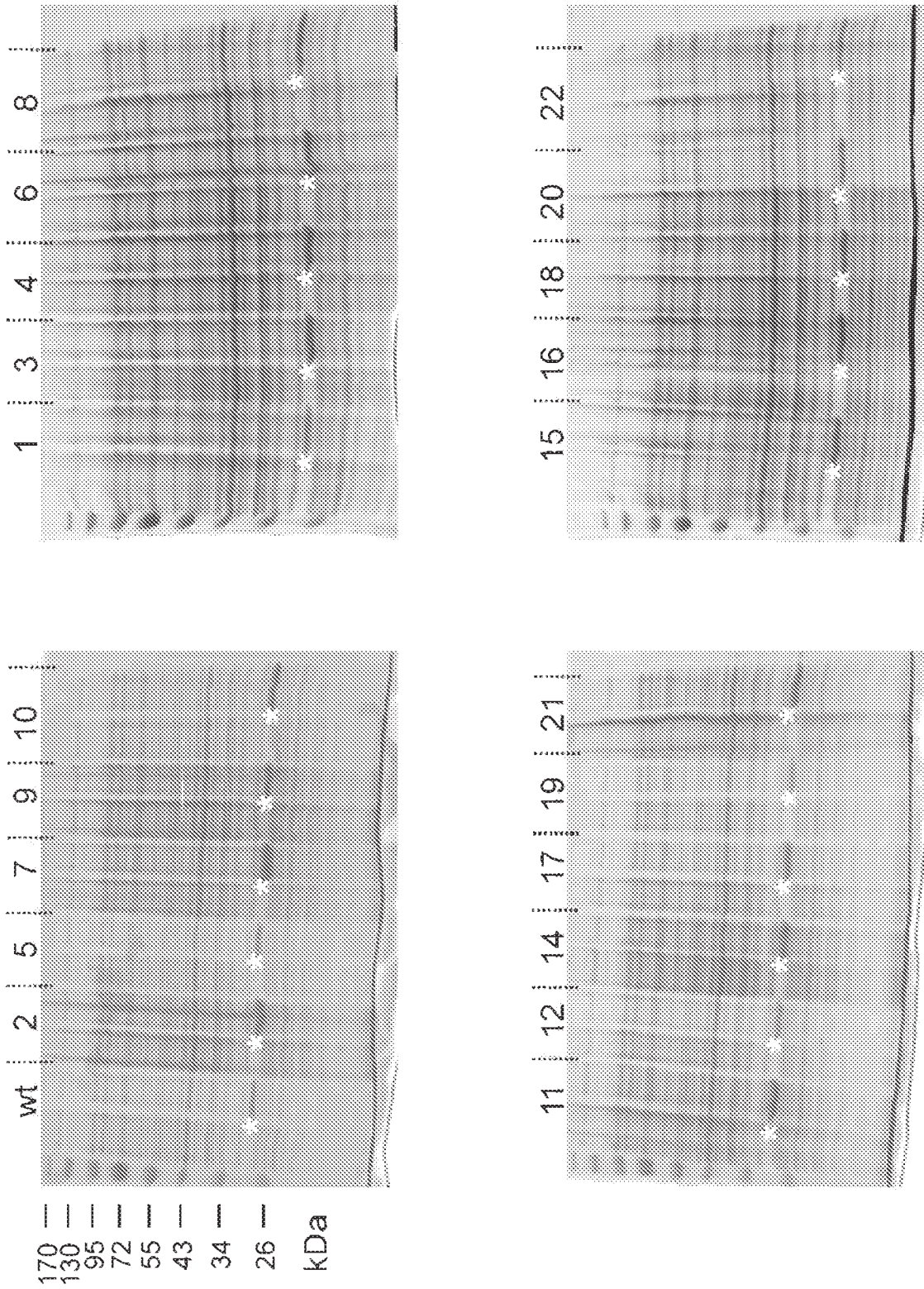


FIGURE 25B

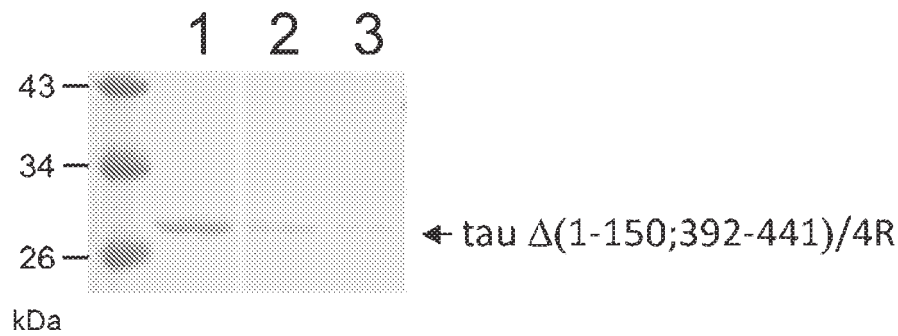


FIGURE 25C

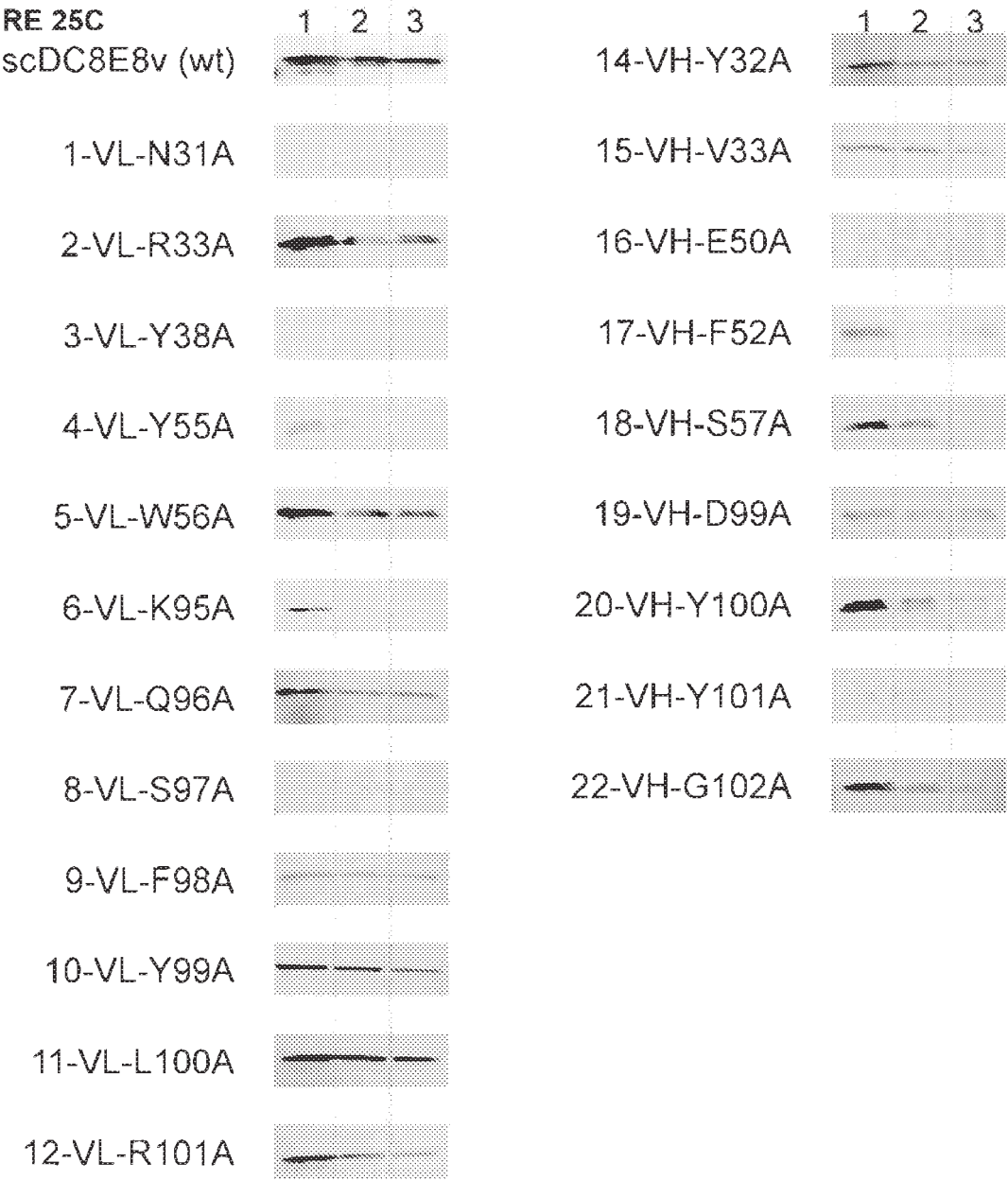


FIGURE 26A

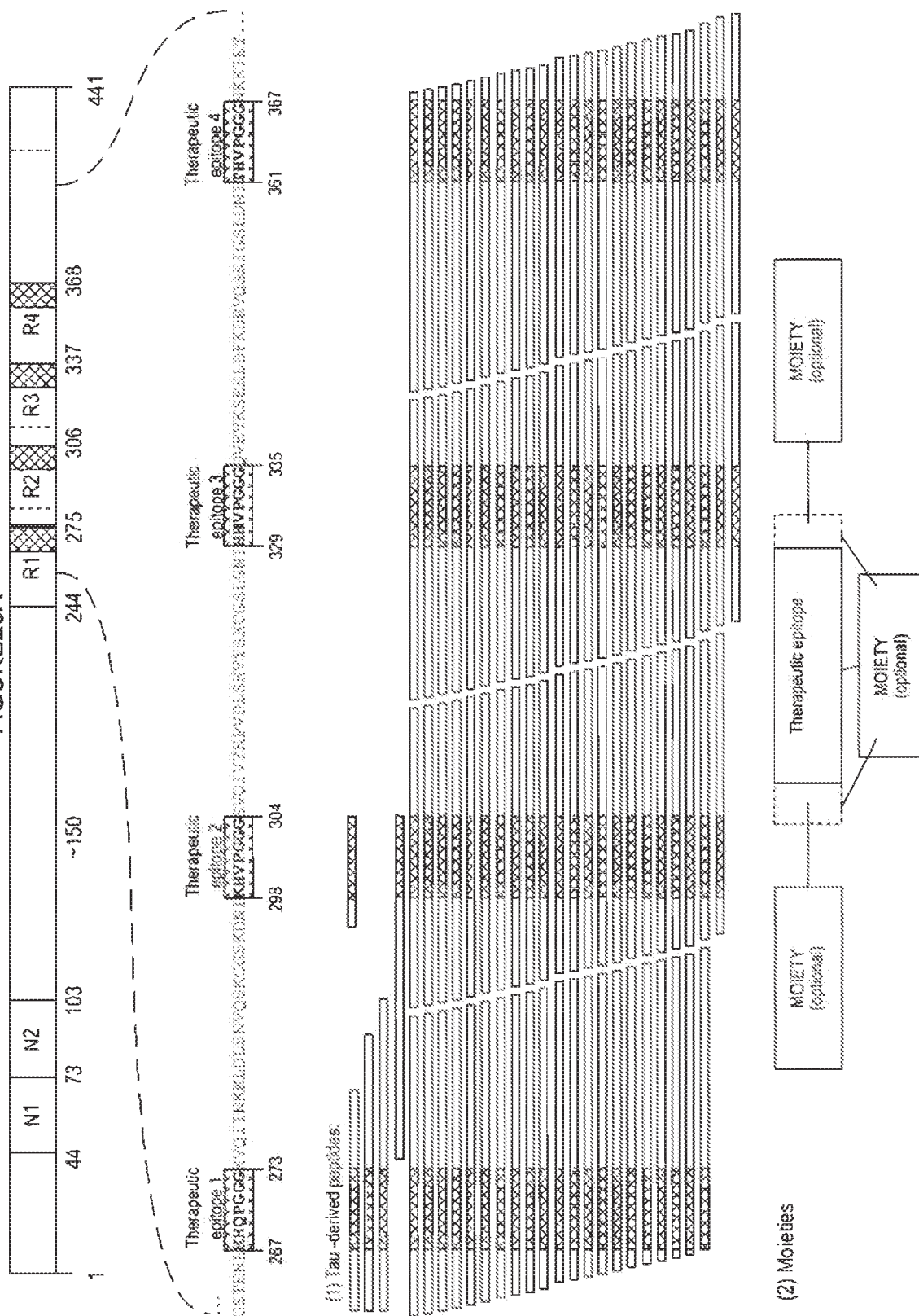
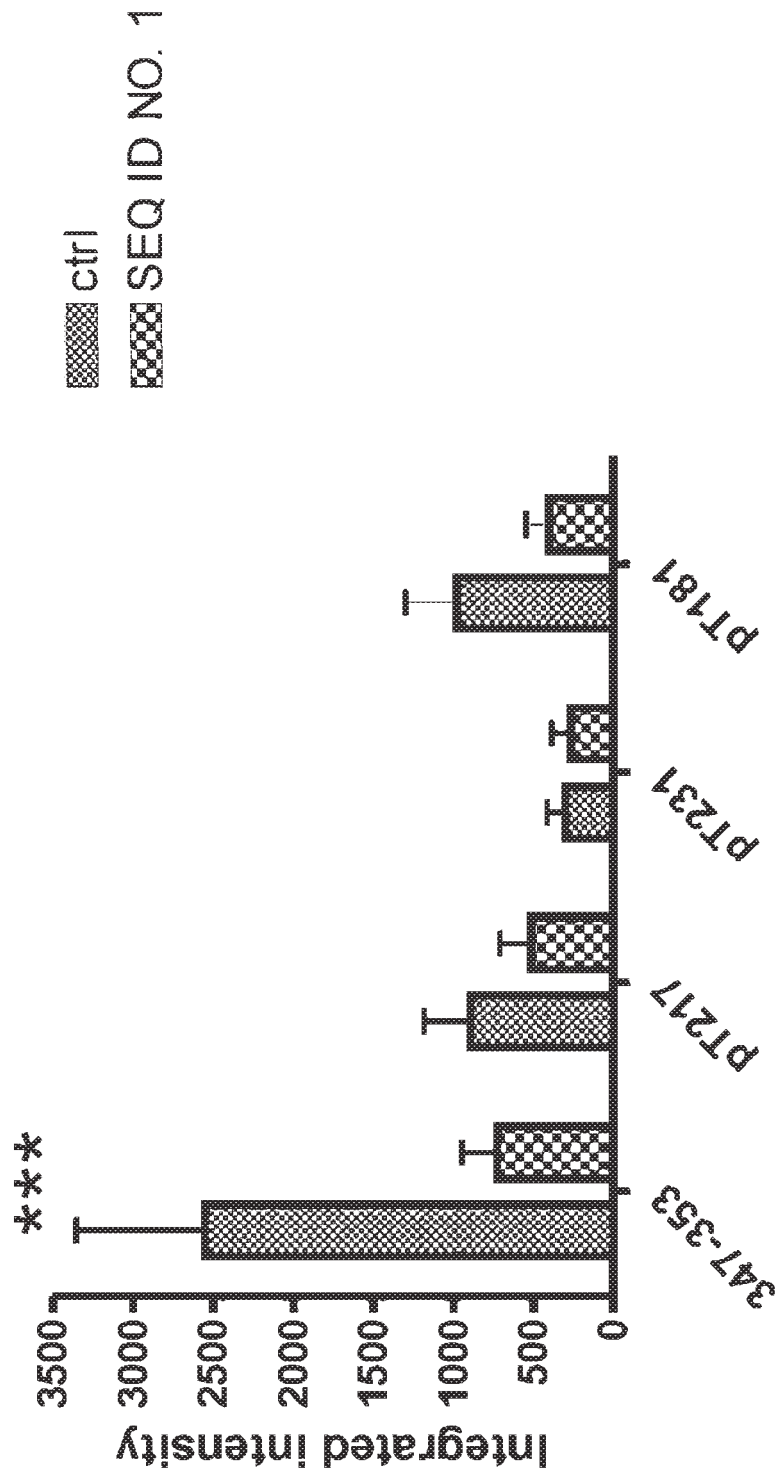


FIGURE 26B

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	

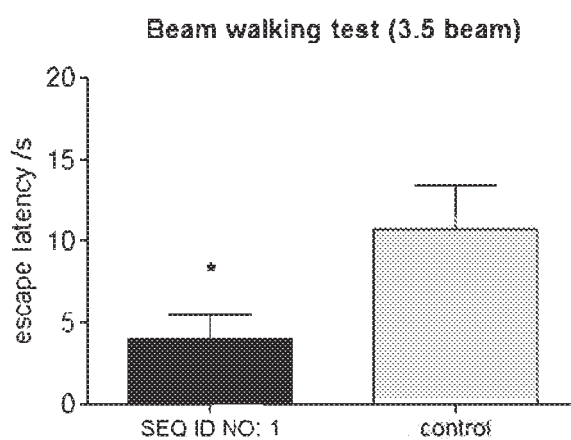
FIGURE 26C



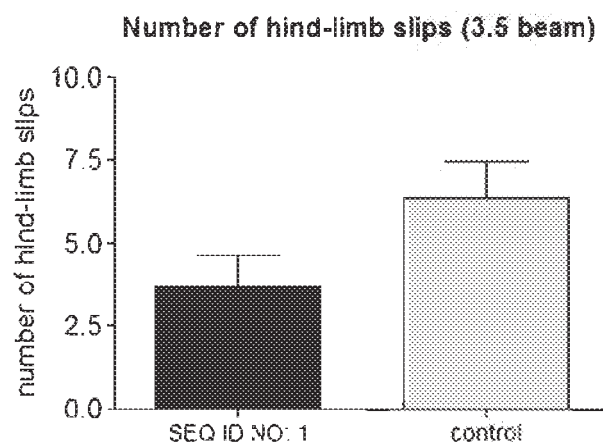
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FIGURE 27

A



B



C

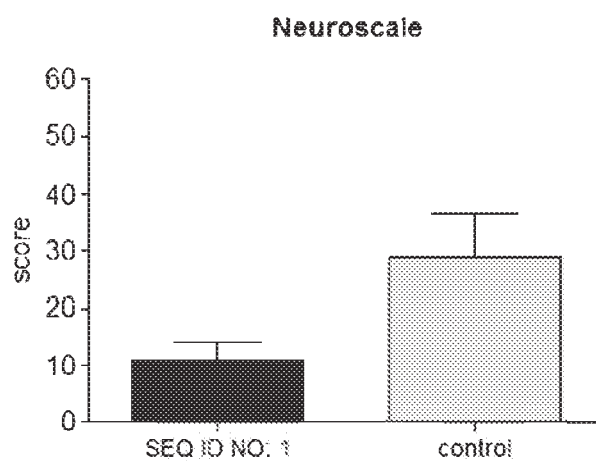


FIGURE 28

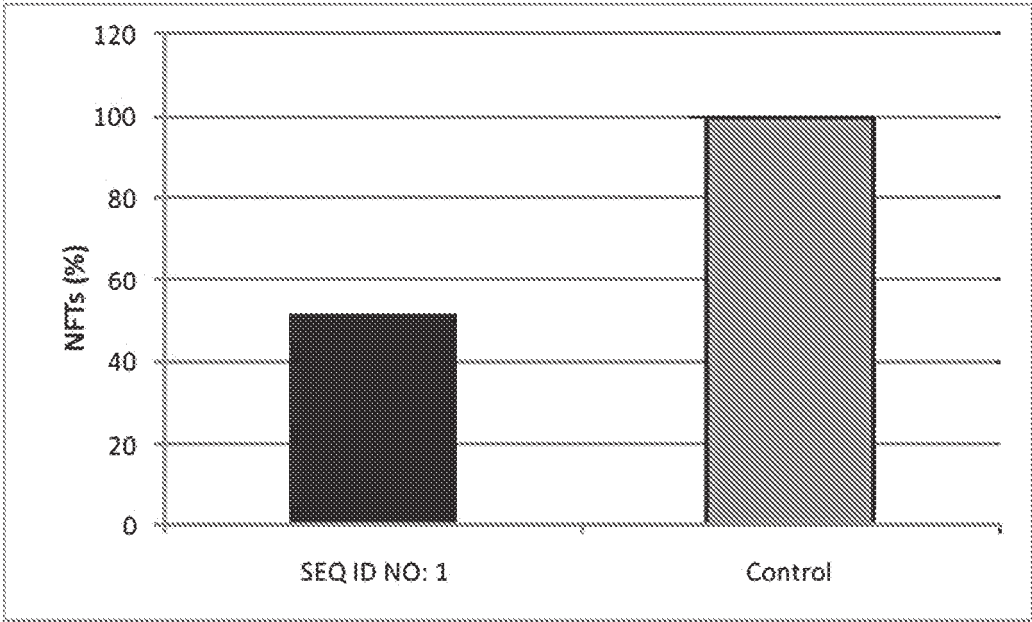
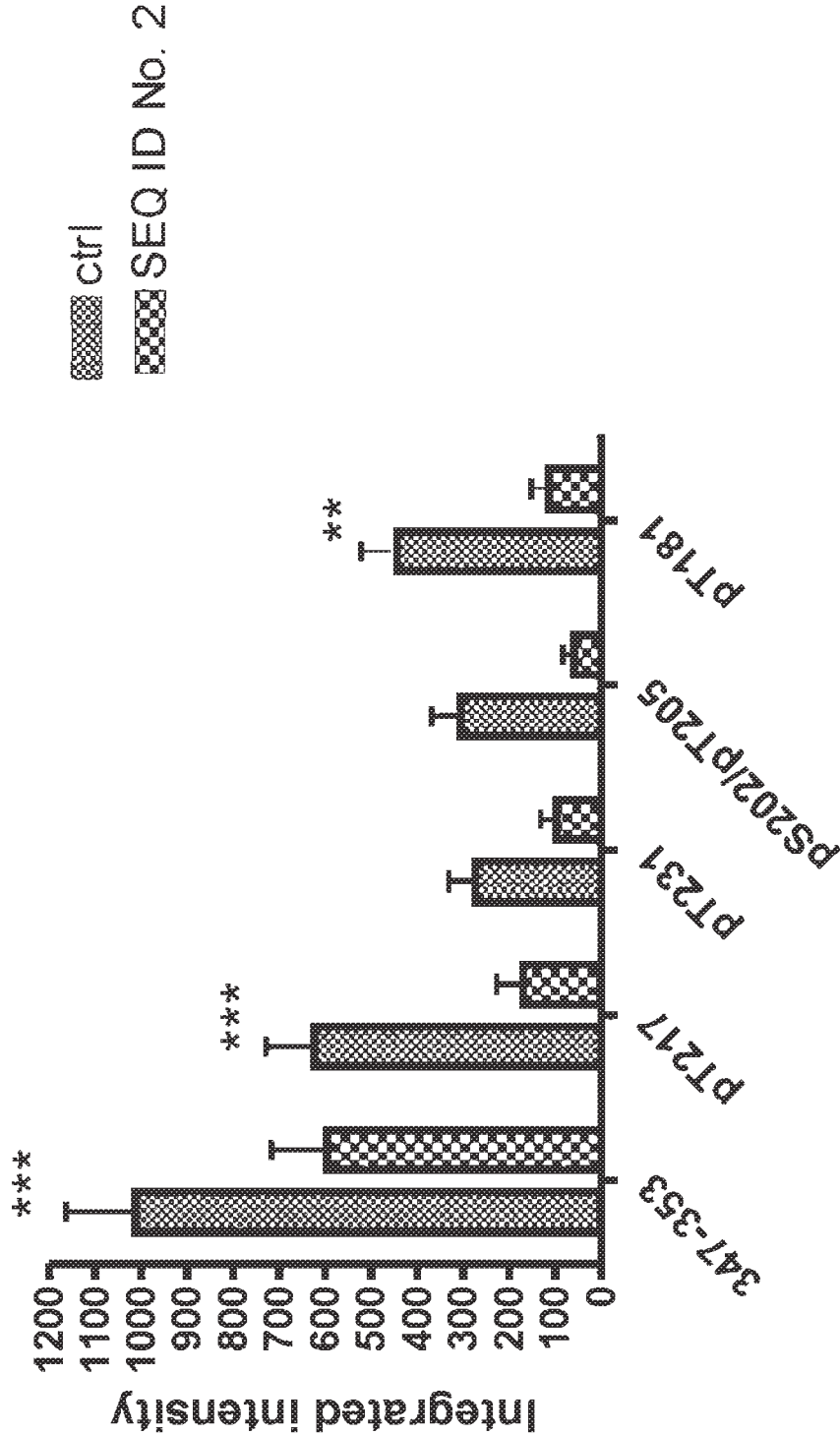


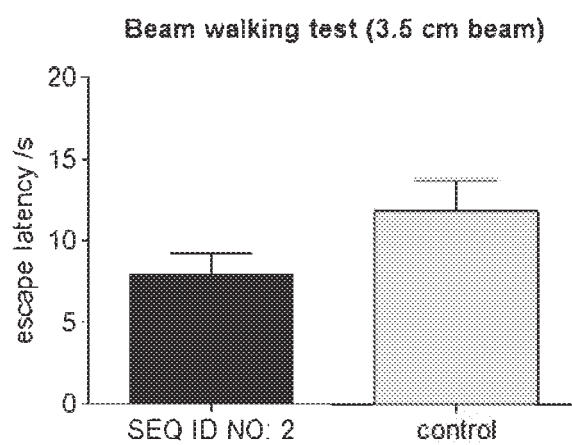
FIGURE 29



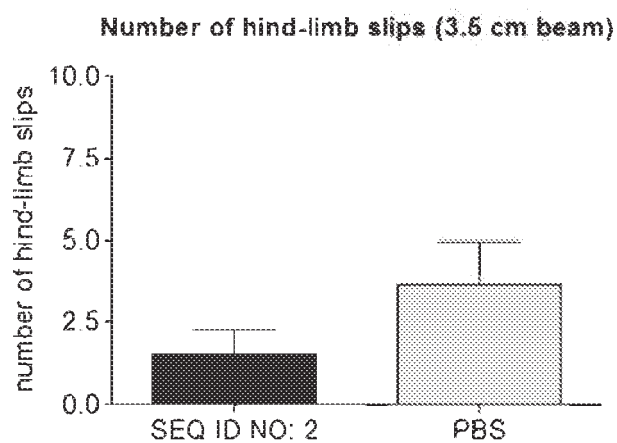
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FIGURE 30

A.



B.



C.

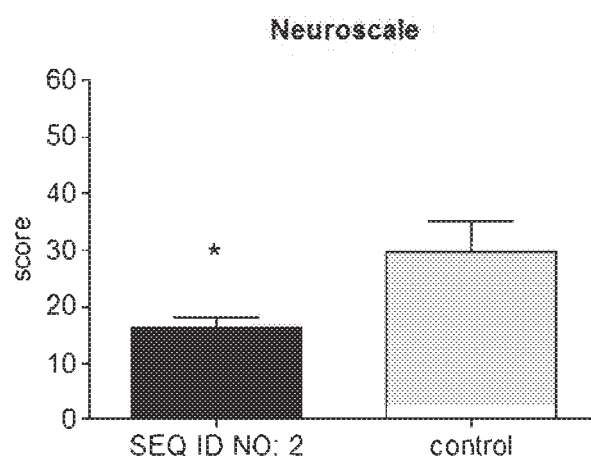


FIGURE 31

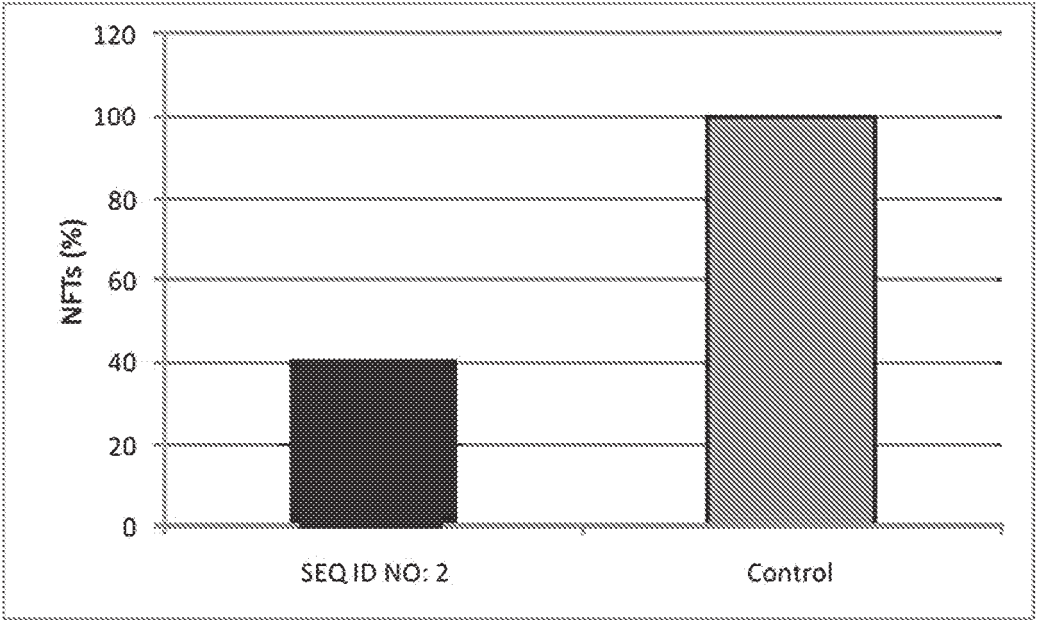
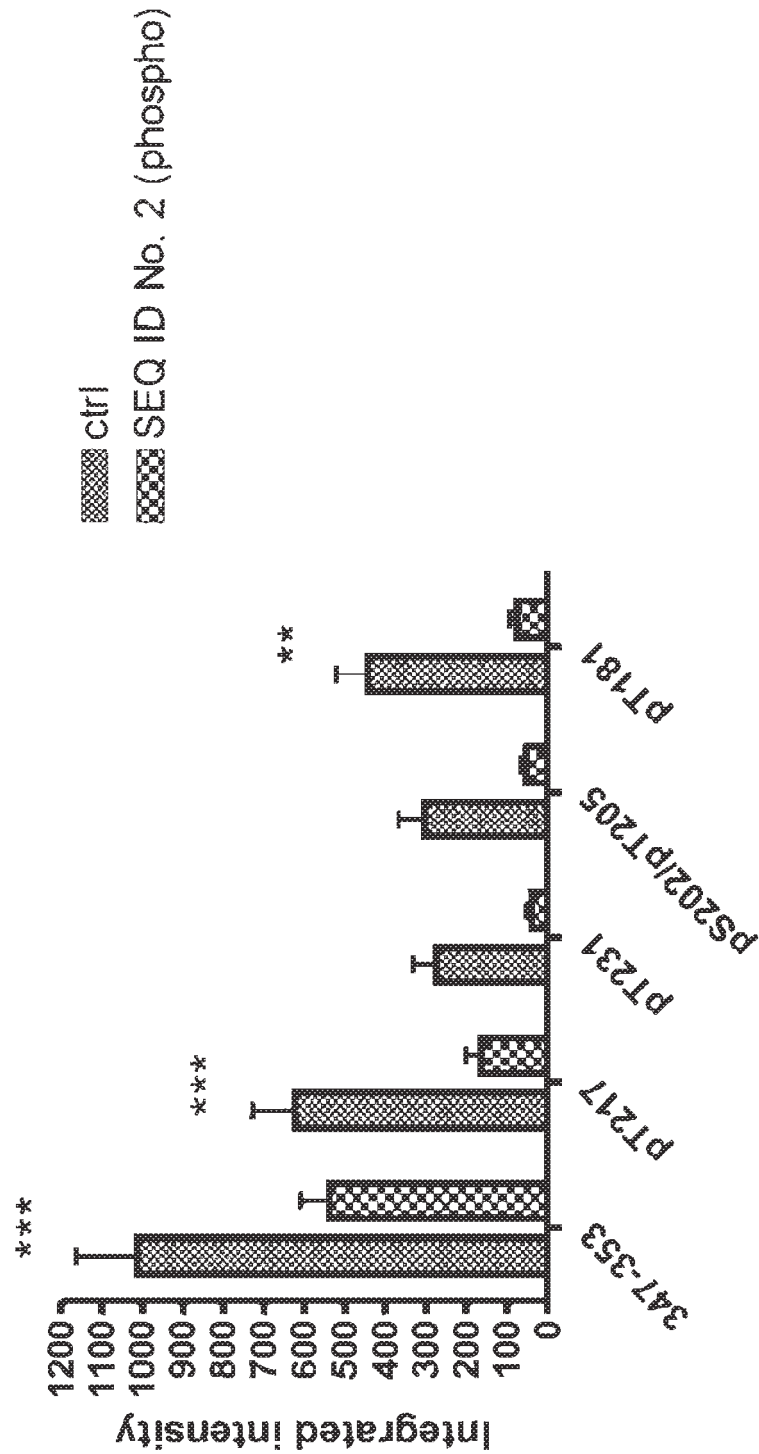


FIGURE 32



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FIGURE 33

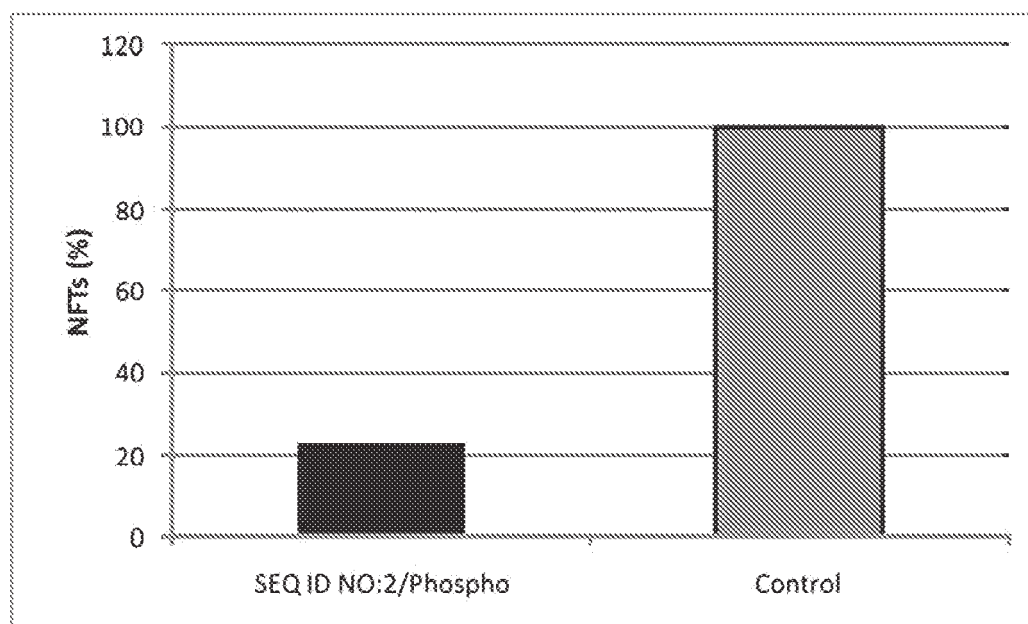


FIGURE 34

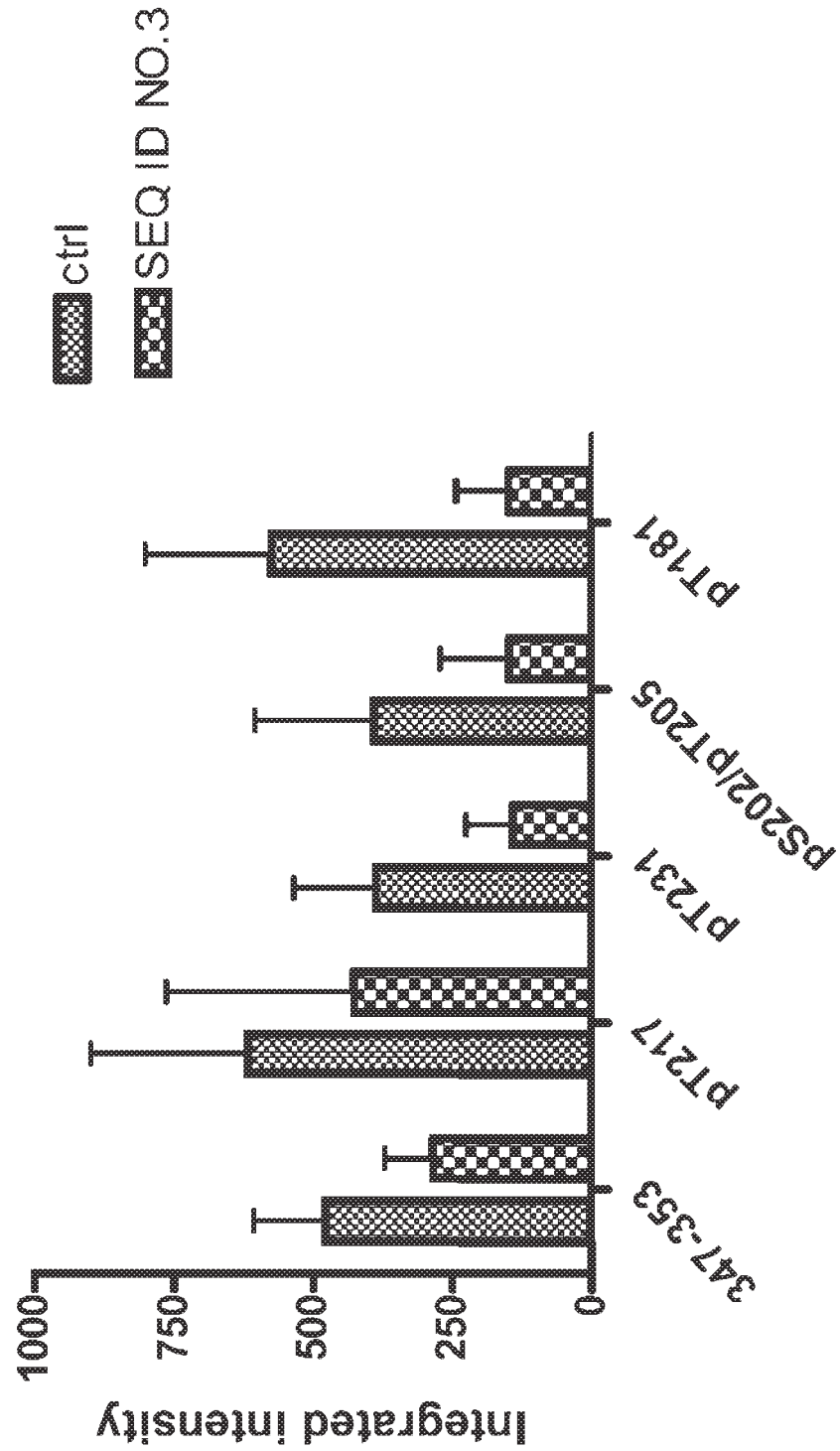
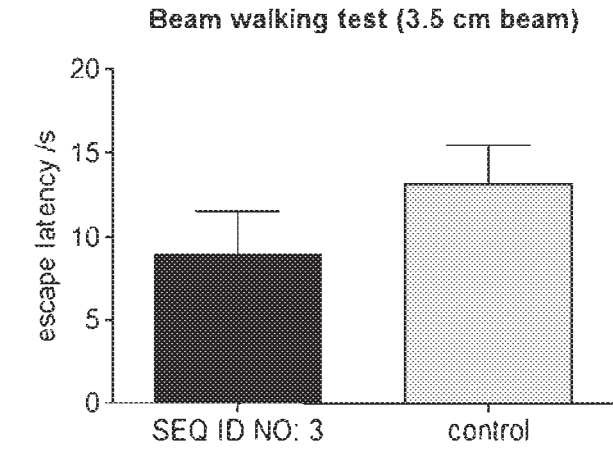
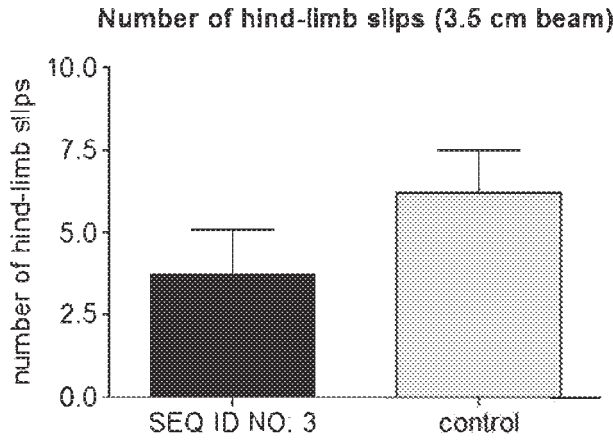


FIGURE 35

A.



B.



C.

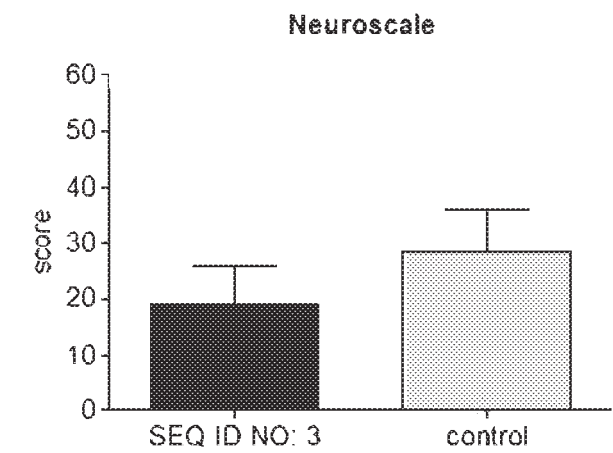


FIGURE 36

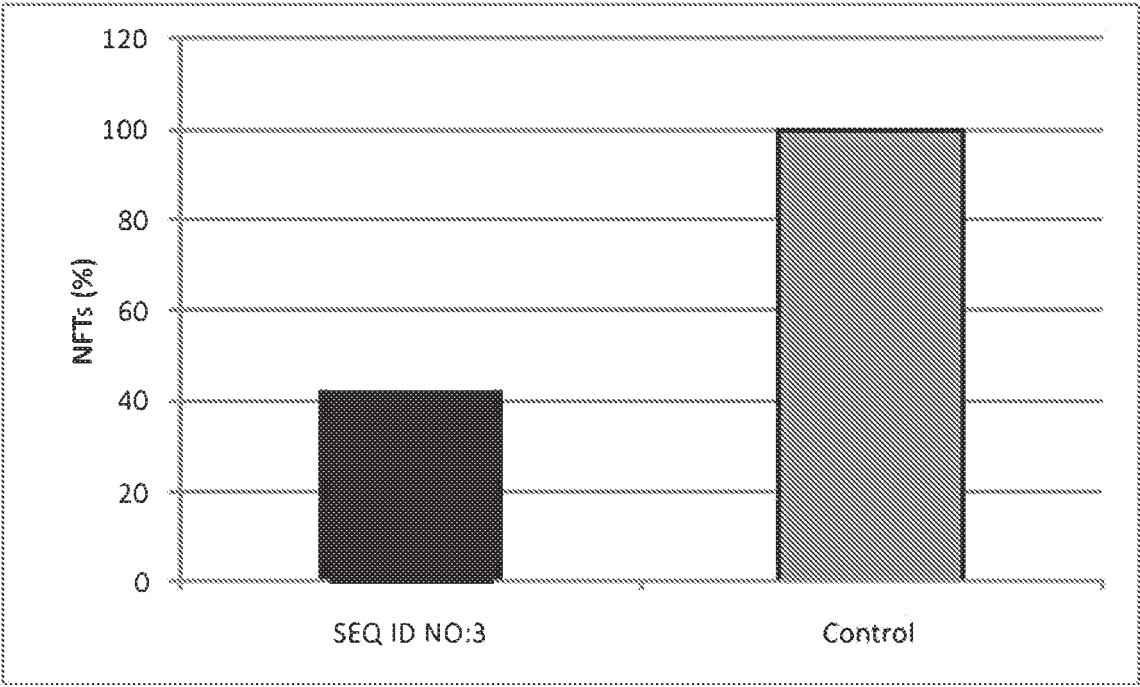


FIGURE 37

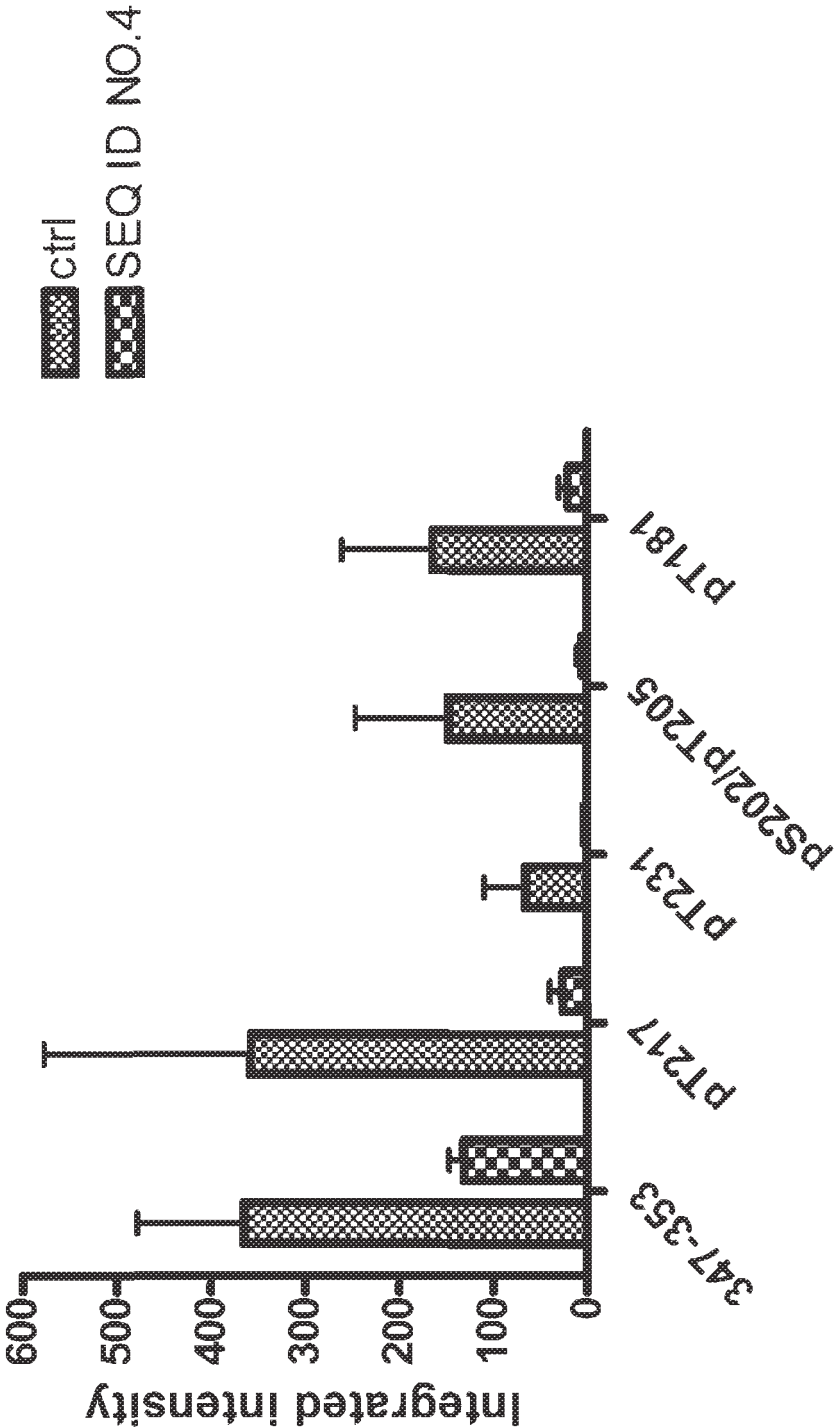
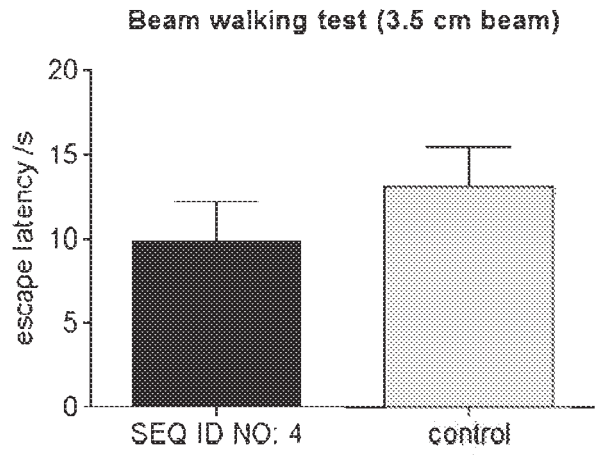
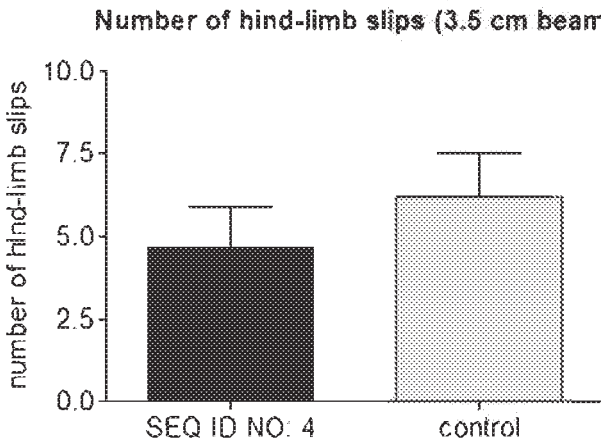


FIGURE 38

A



B



C

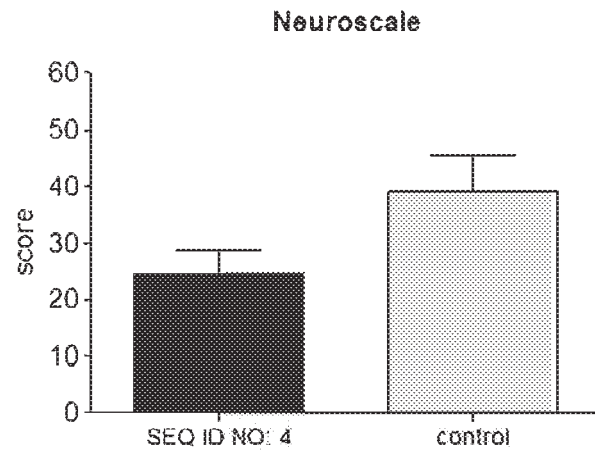


FIGURE 39

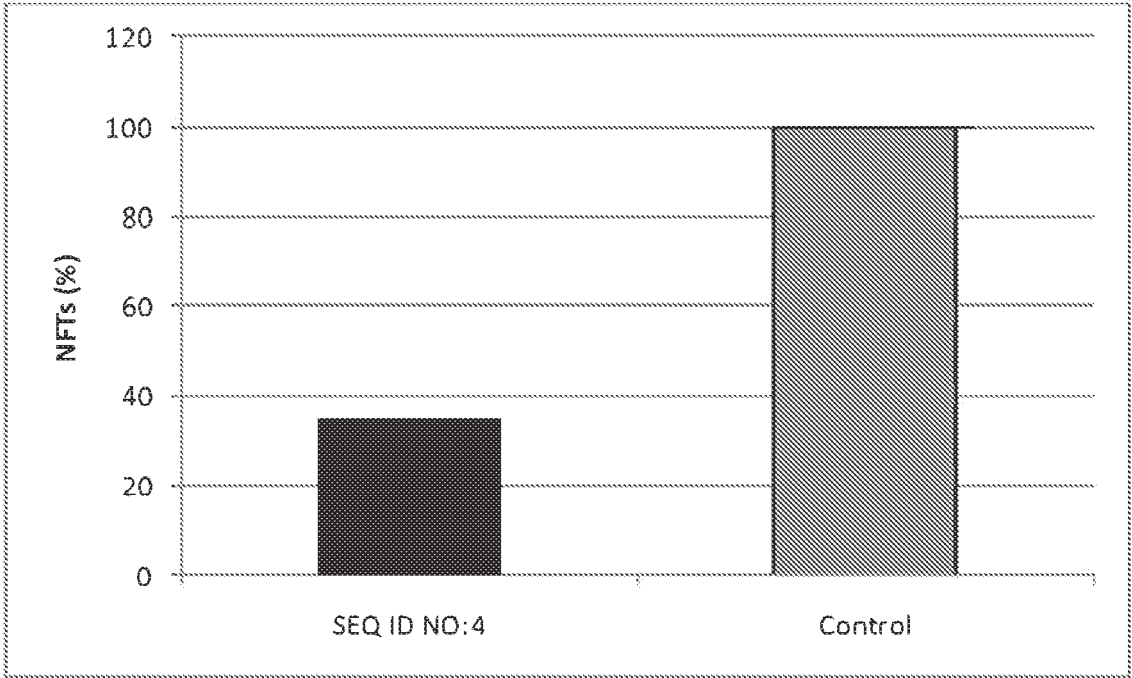
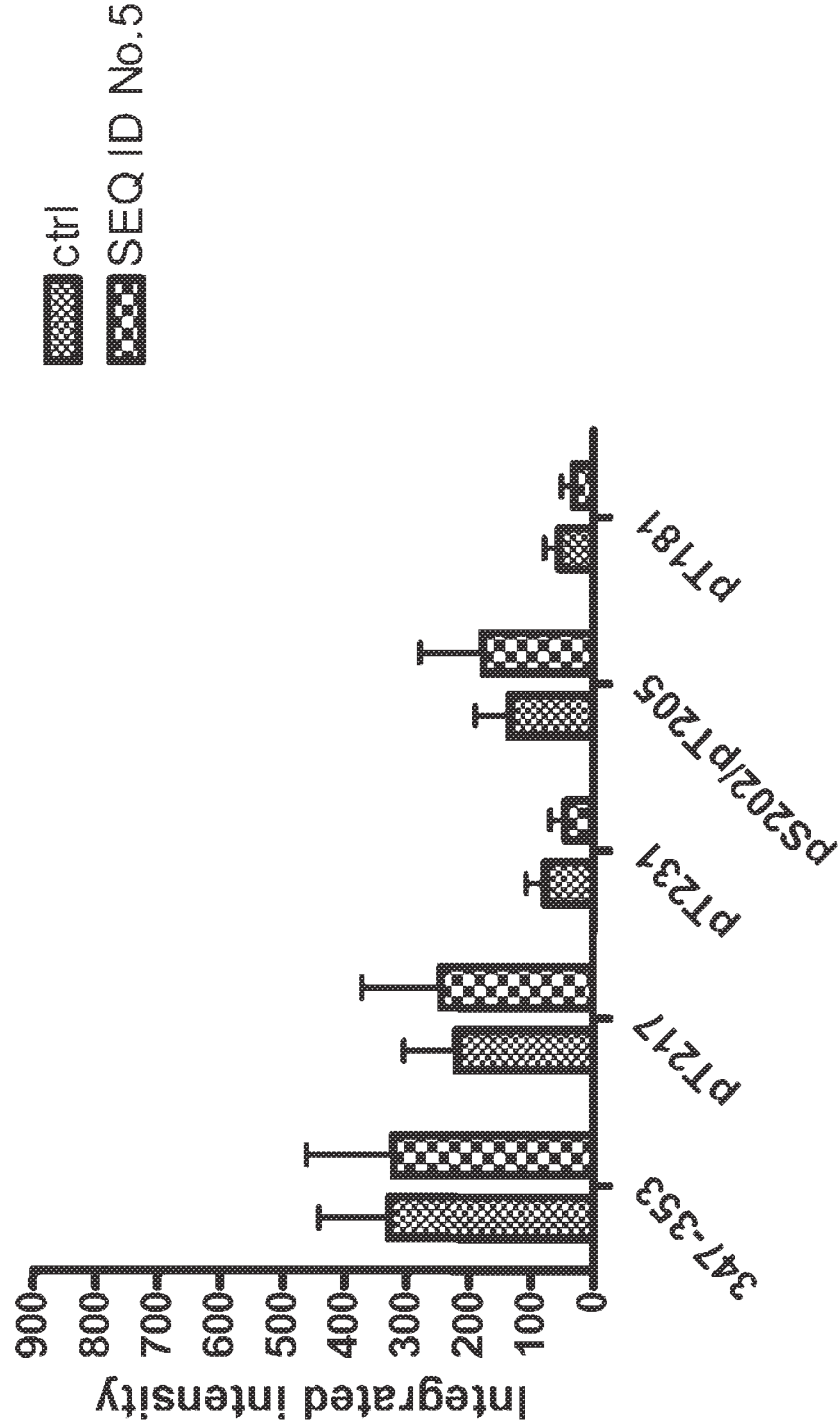


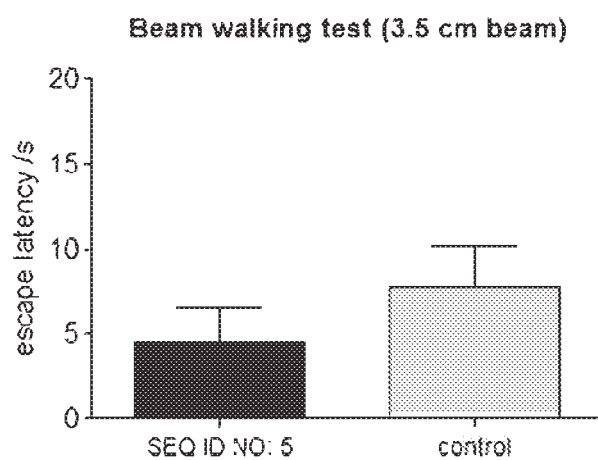
FIGURE 40



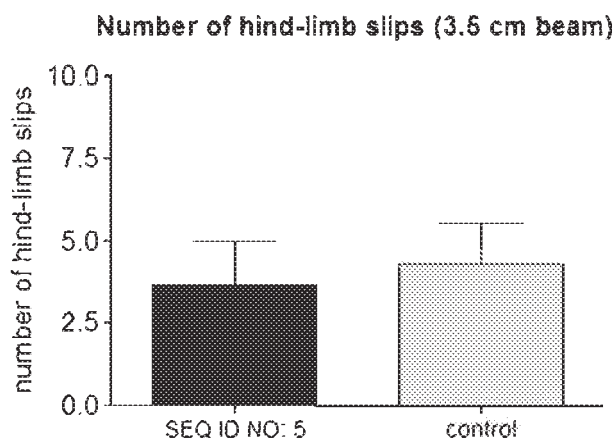
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FIGURE 41

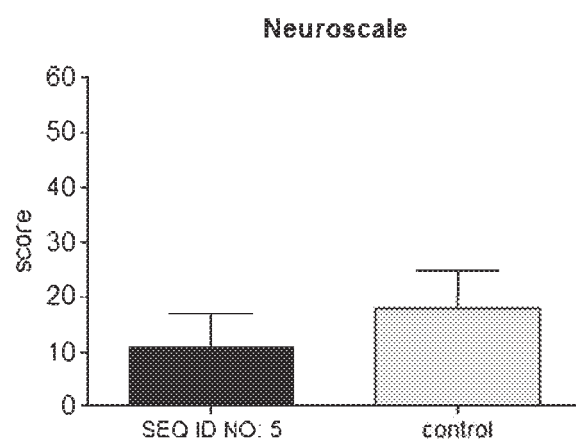
A.



B.



C.



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FIGURE 42

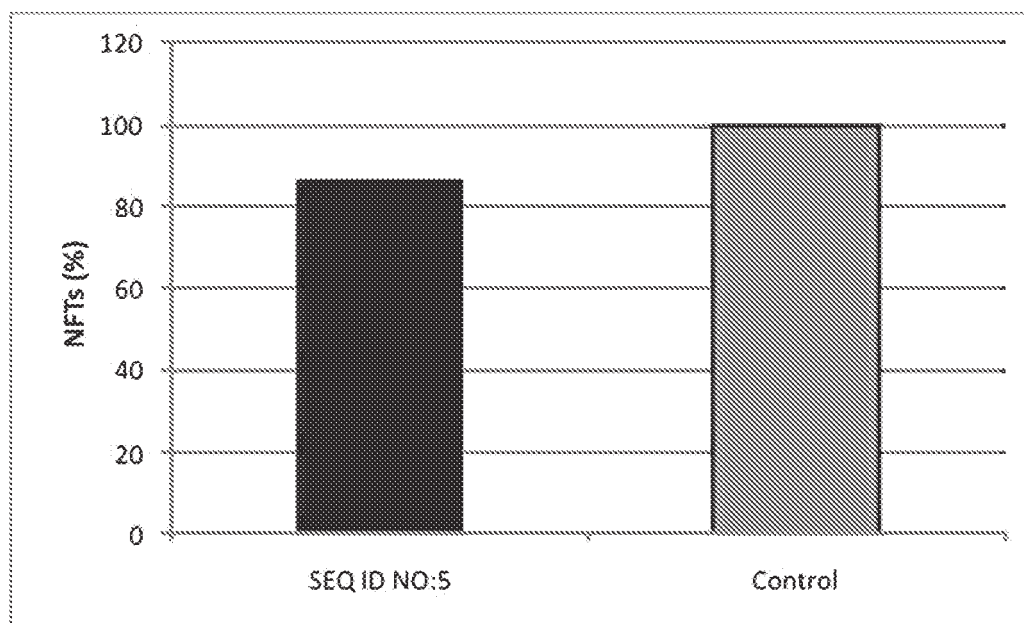
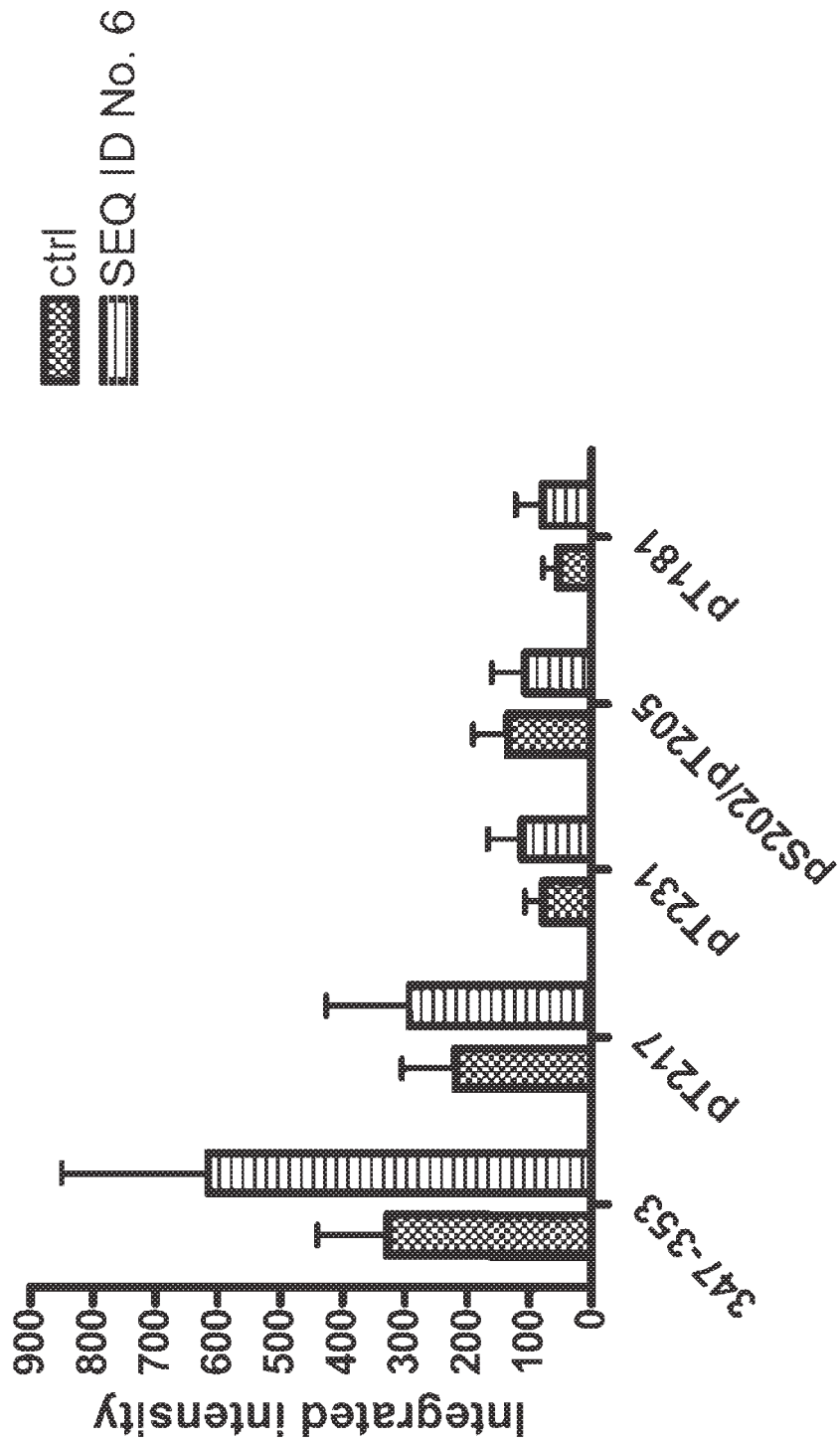


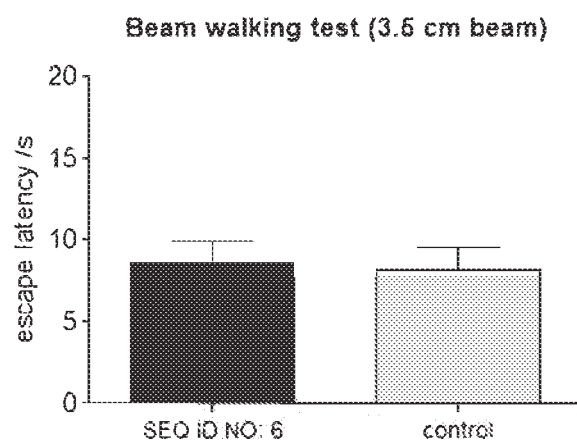
FIGURE 43



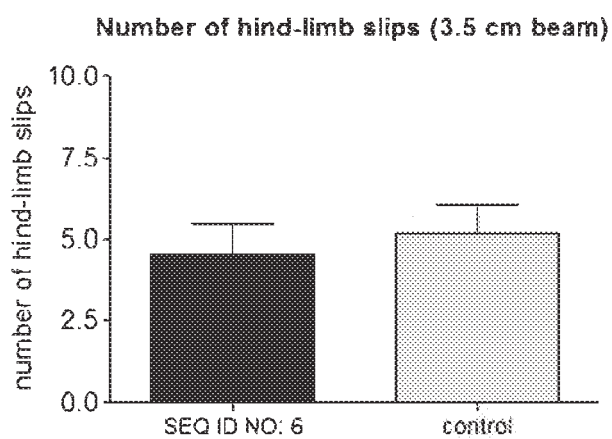
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FIGURE 44

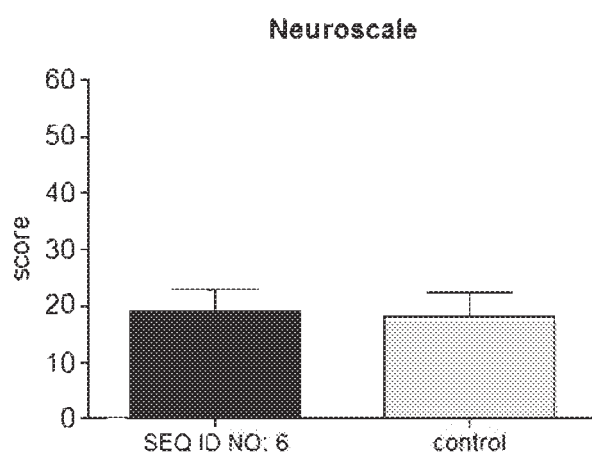
A.



B.



C.



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FIGURE 45

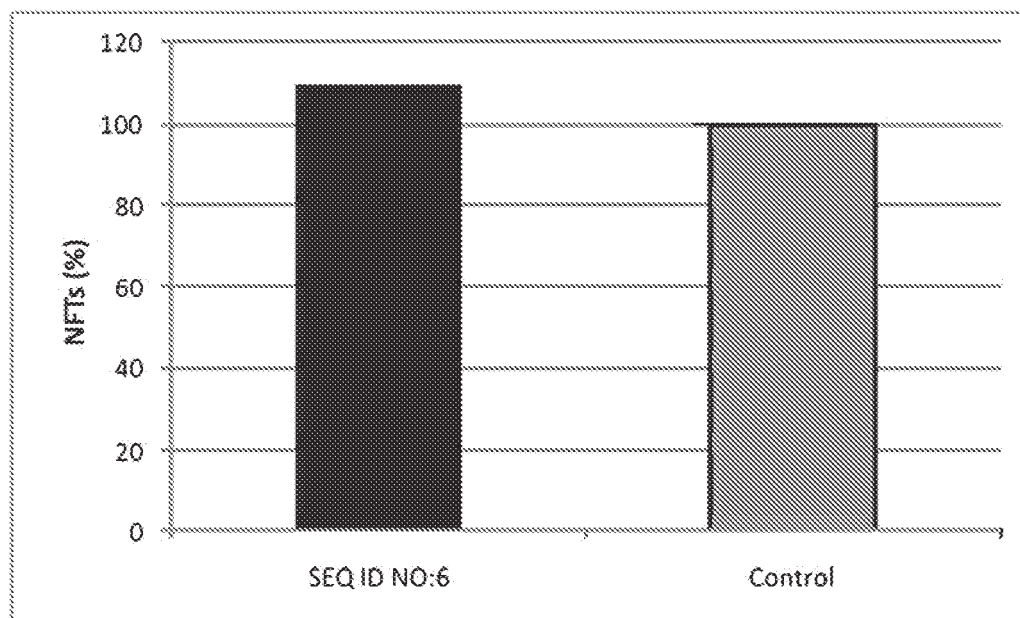
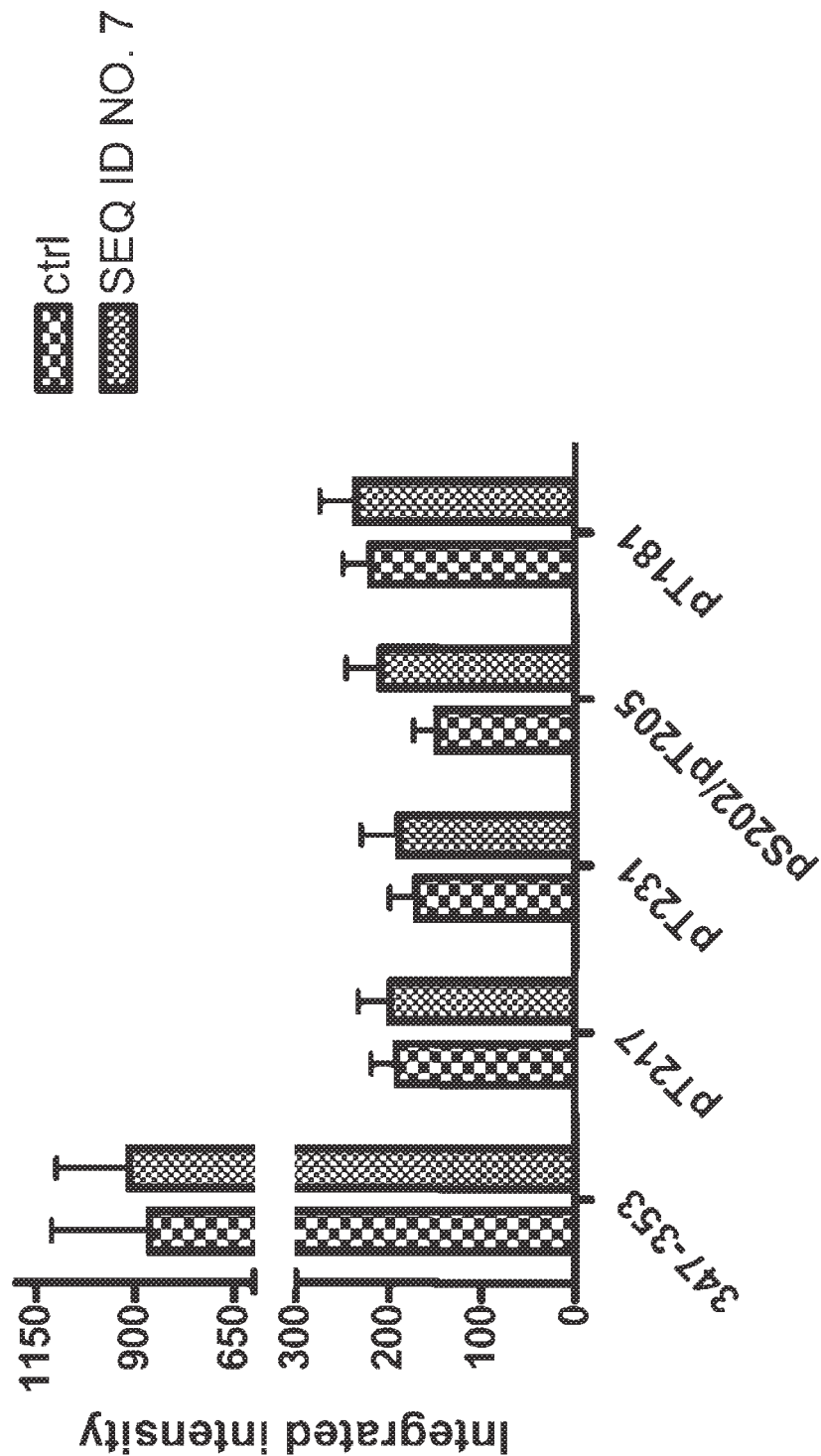


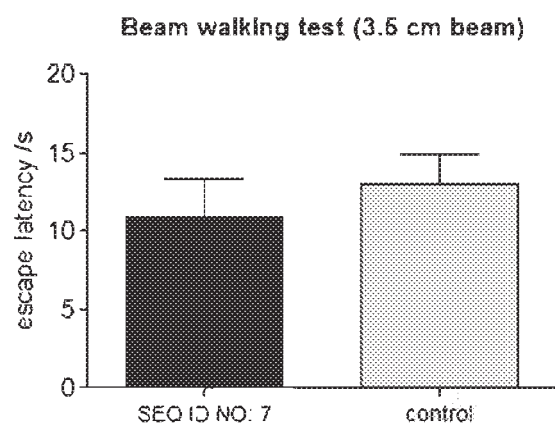
FIGURE 46



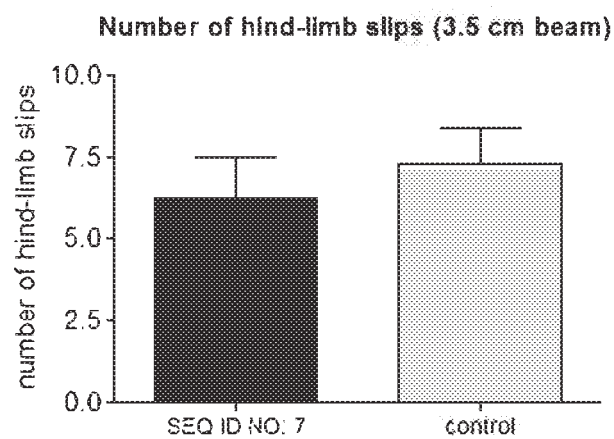
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FIGURE 47

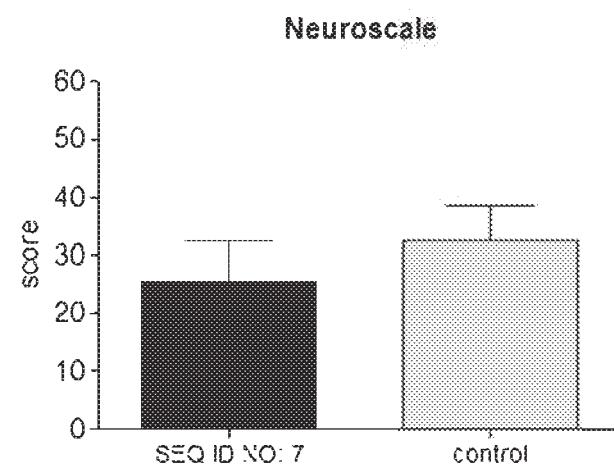
A.



B.



C.



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FIGURE 48

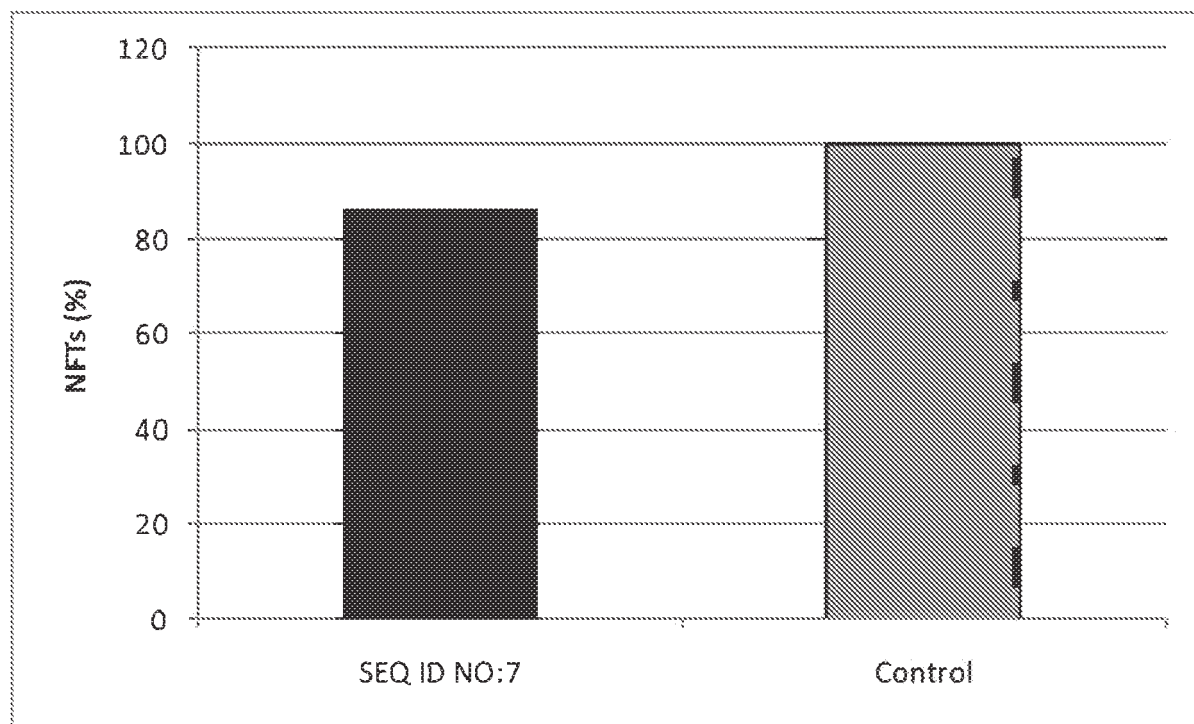
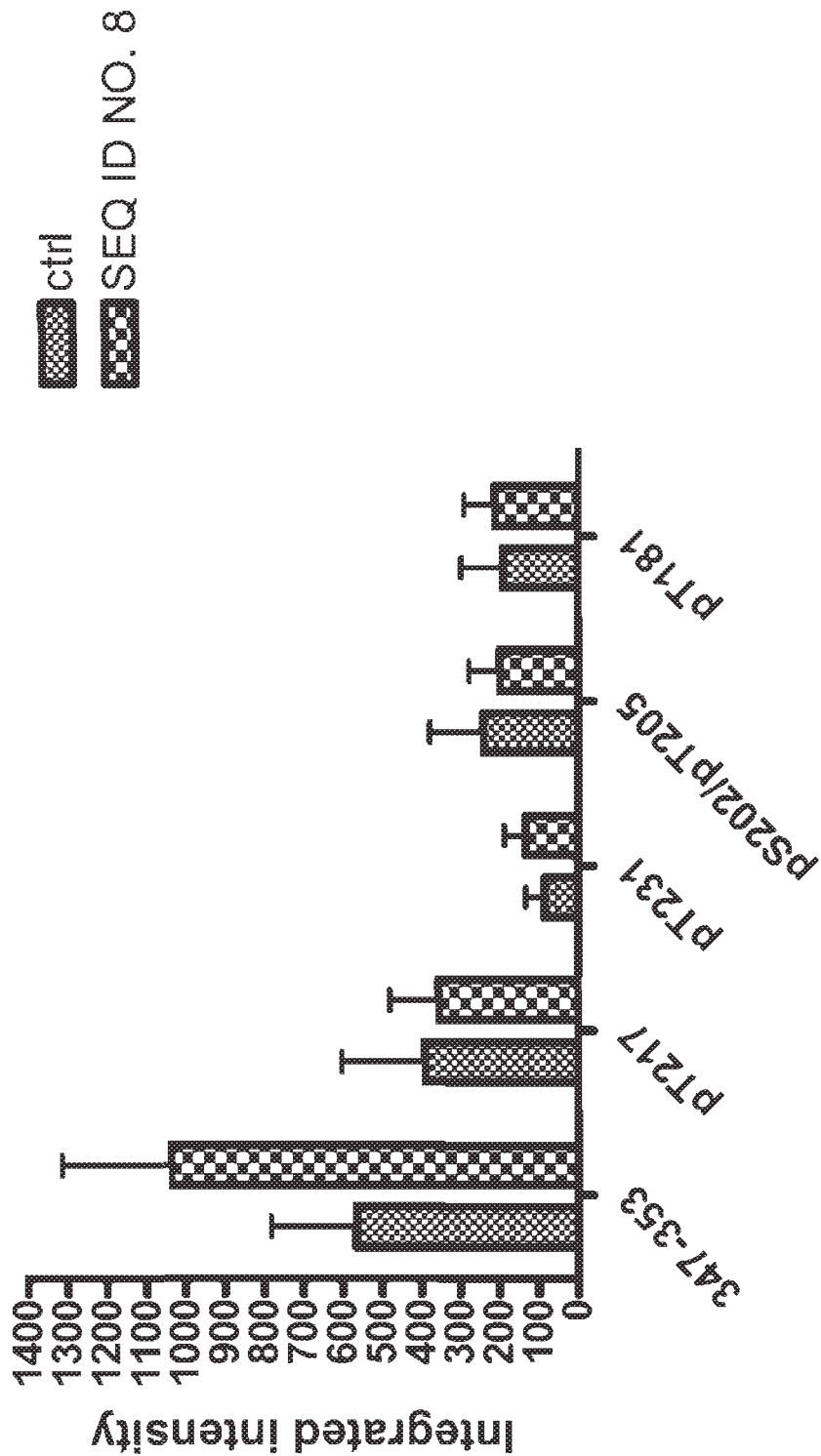


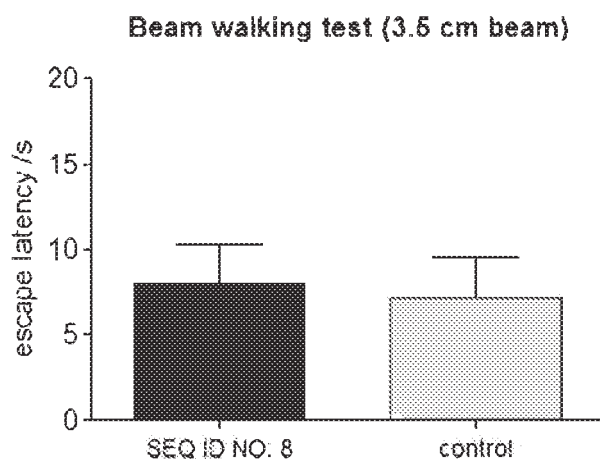
FIGURE 49



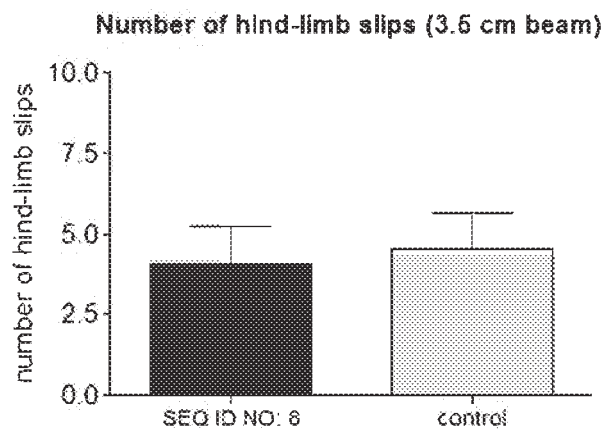
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FIGURE 50

A.



B.



C.

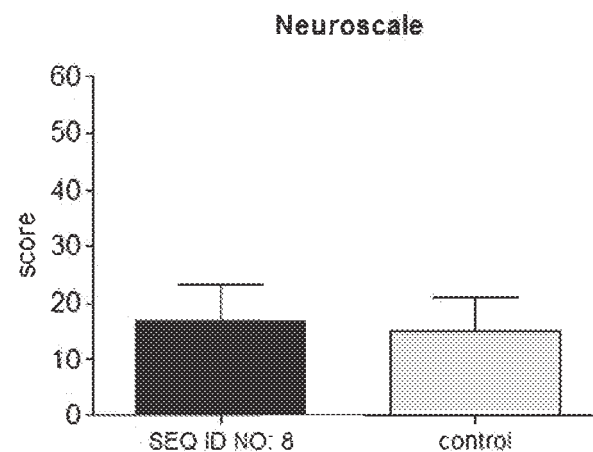


FIGURE 51

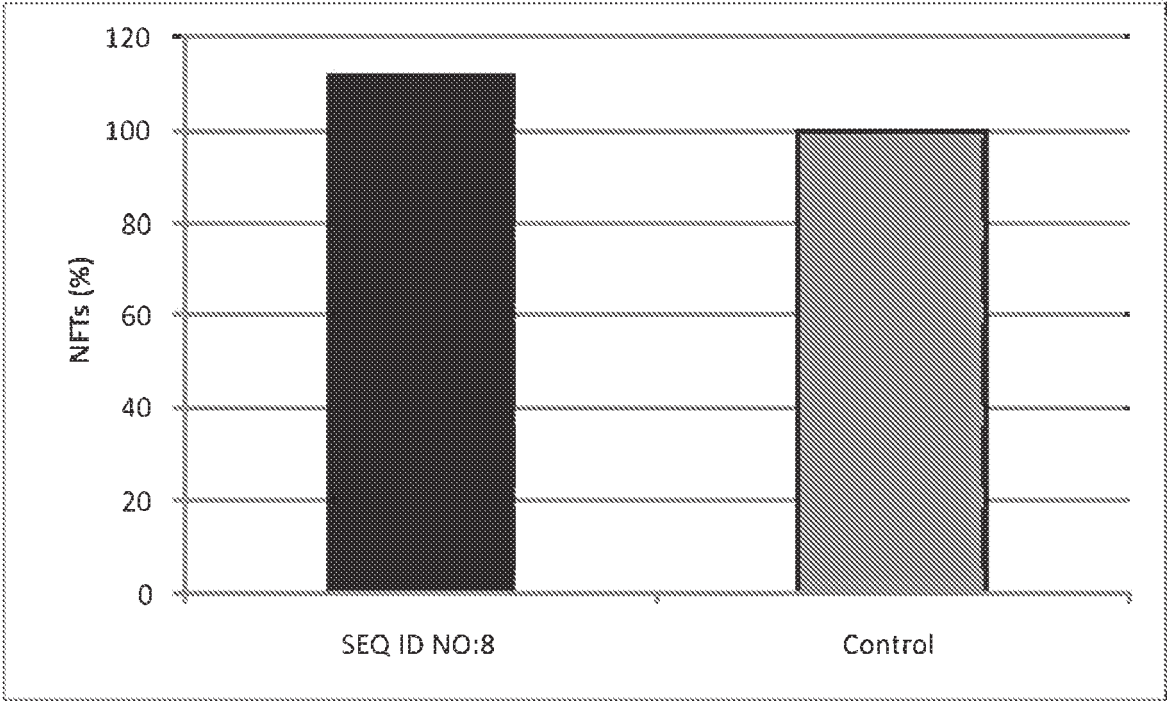
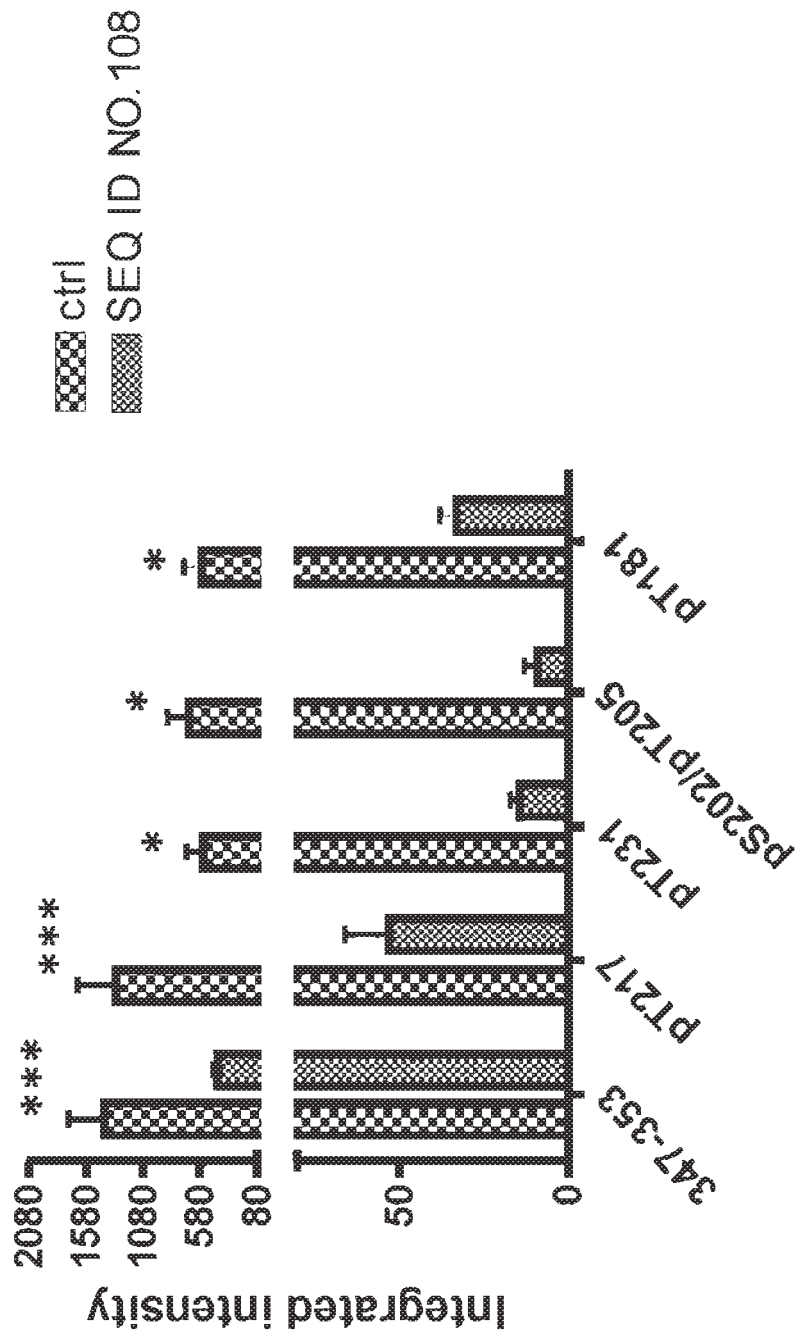


FIGURE 52

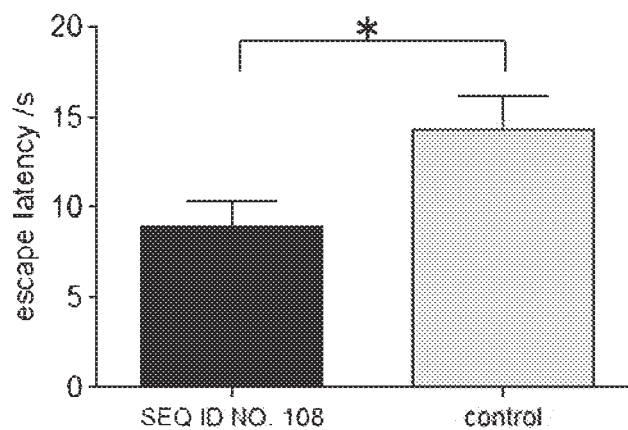


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FIGURE 53

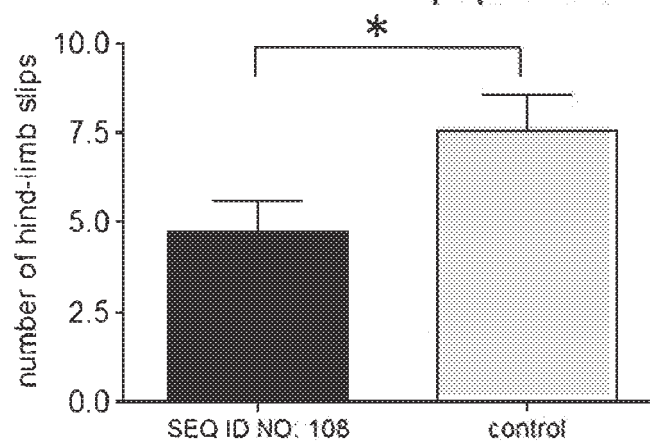
A

Beam walking test (3.5 cm beam)



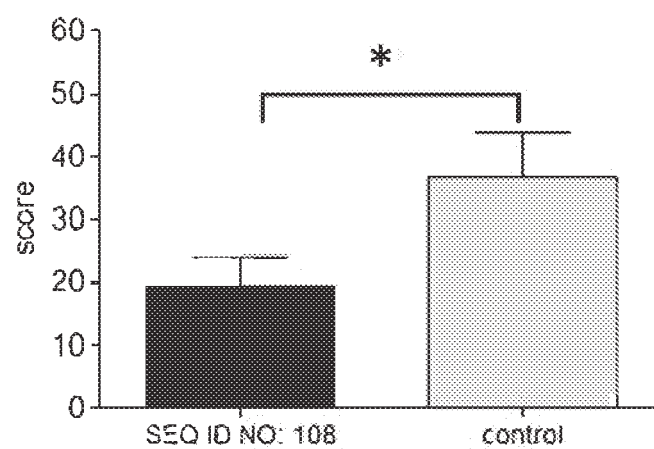
B

Number of hind-limb slips (3.5 cm beam)



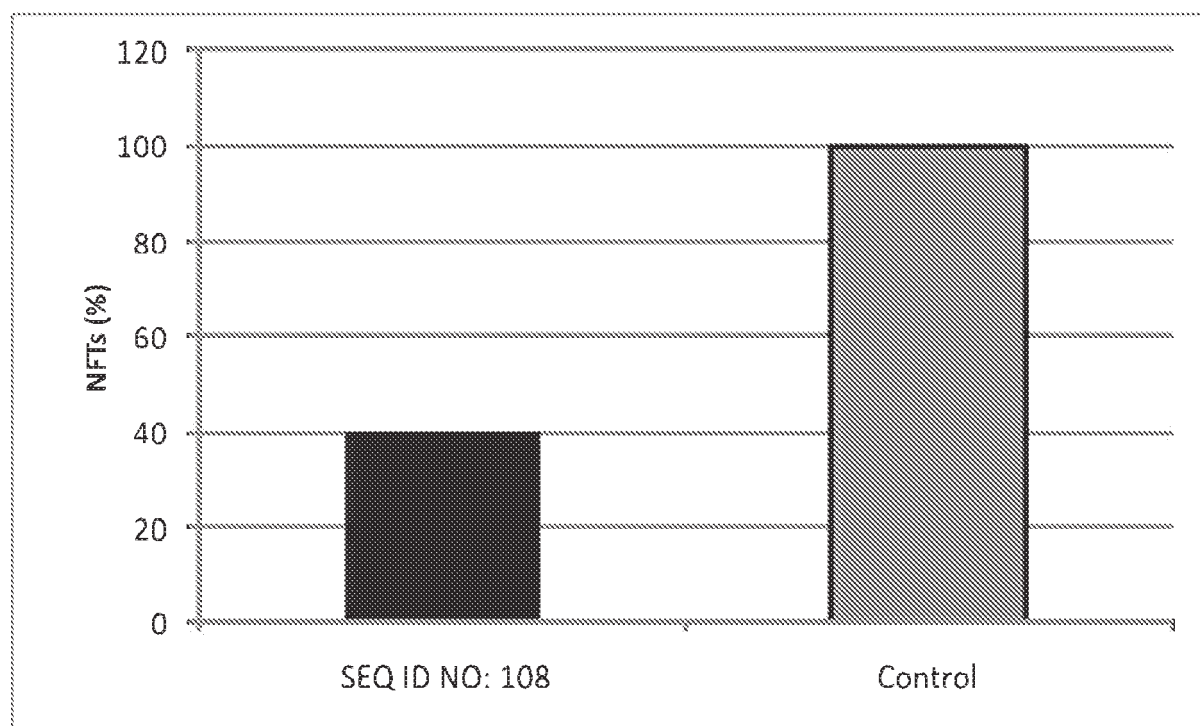
C

Neuroscale



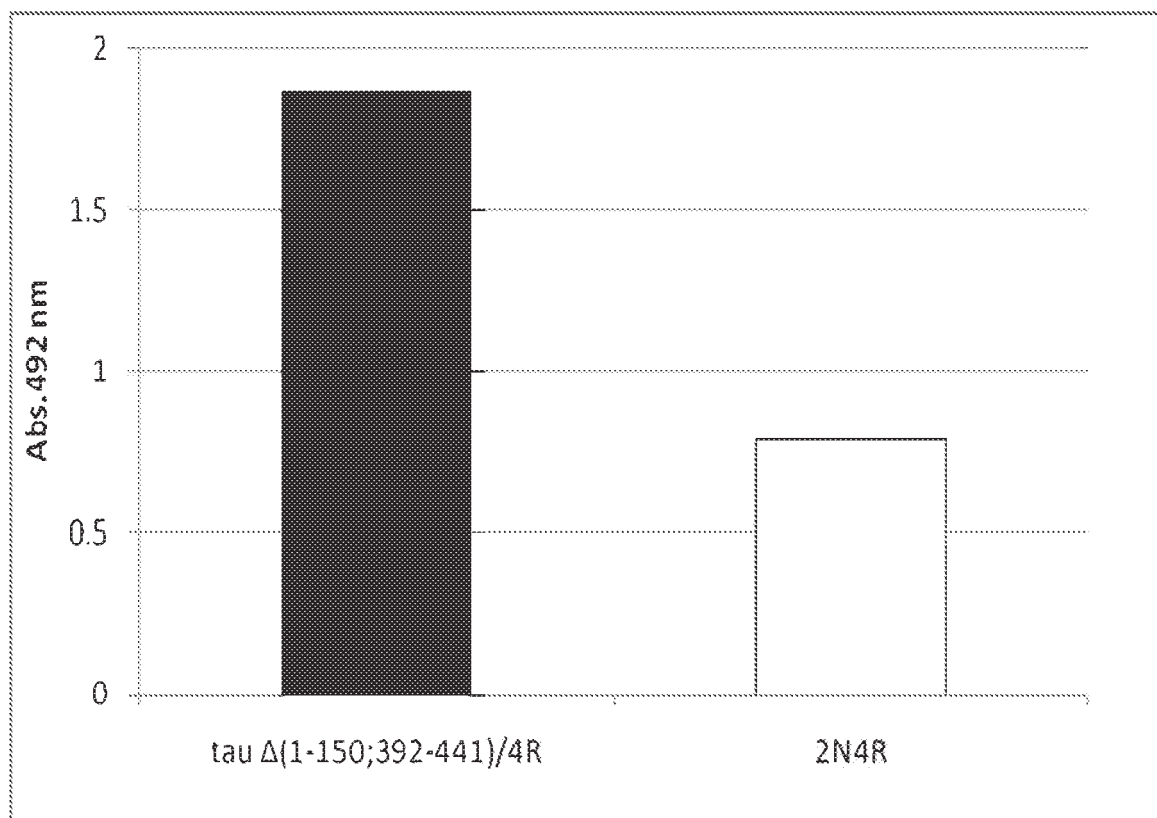
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FIGURE 54



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FIGURE 55



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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

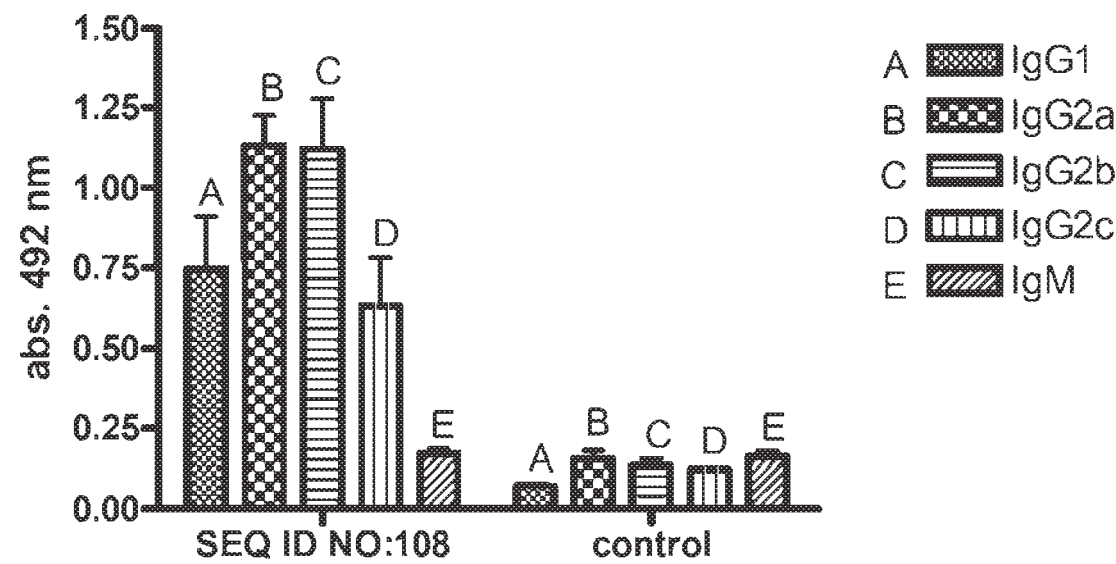


FIGURE 58

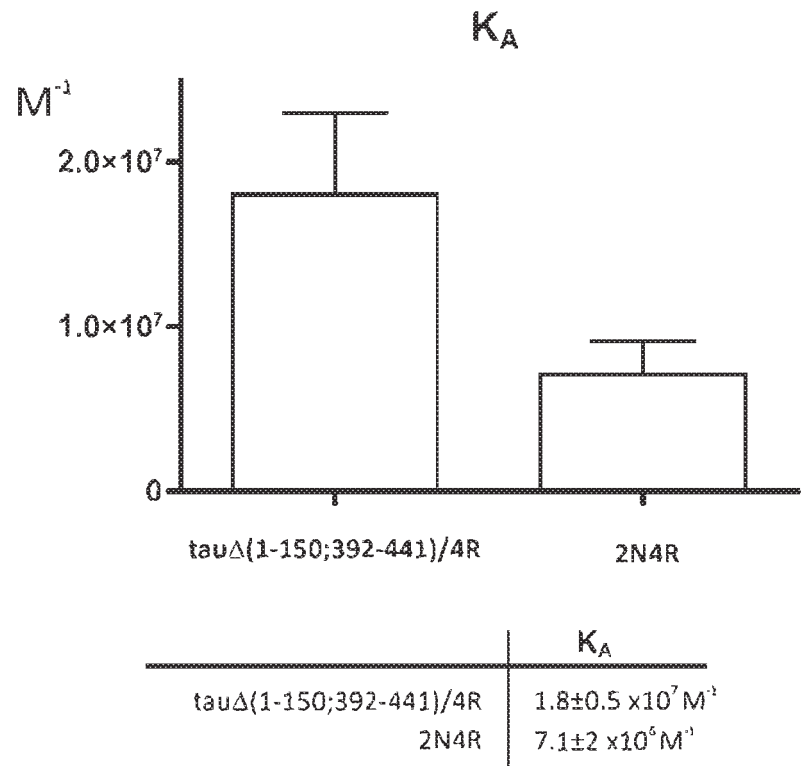


FIGURE 59

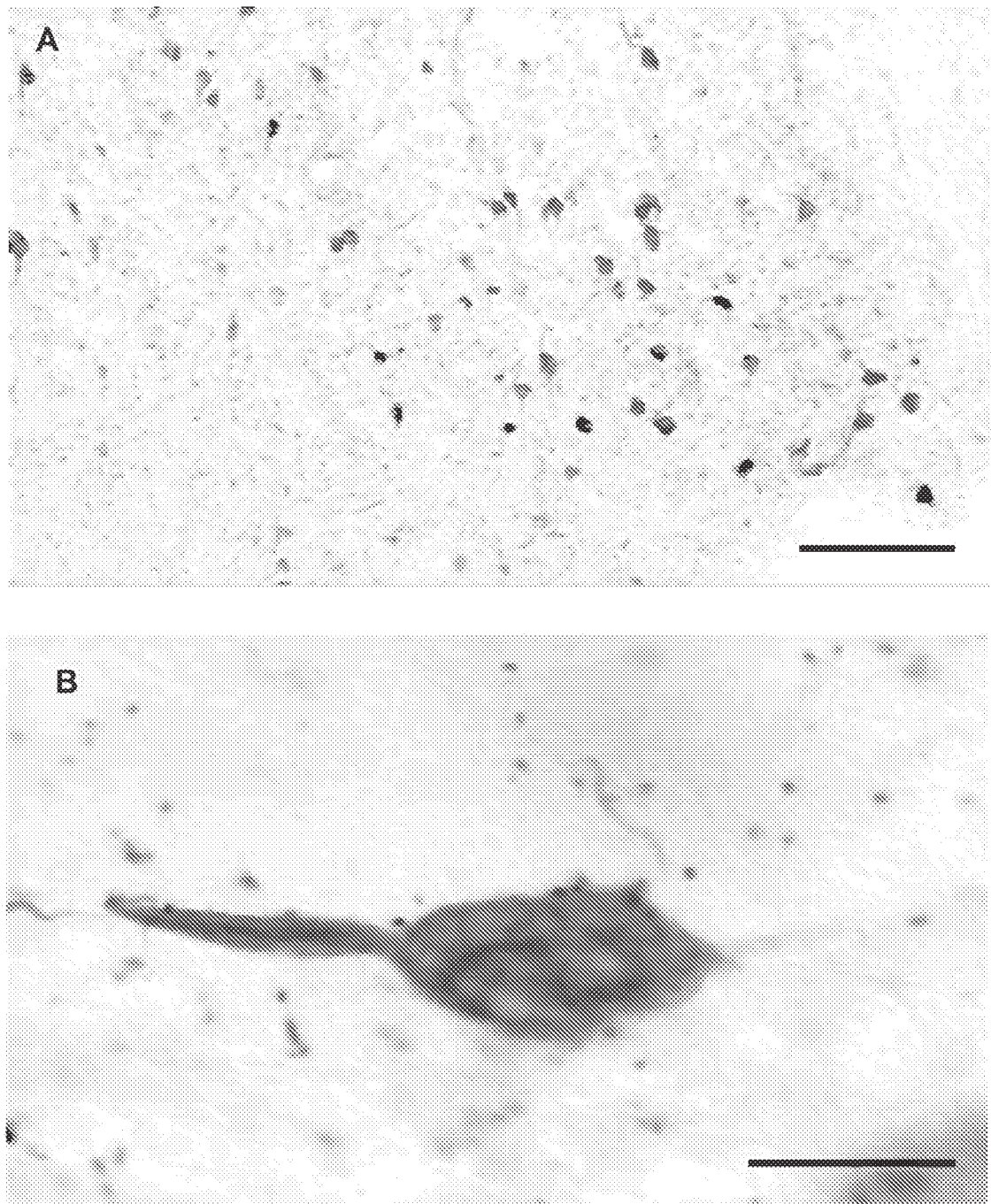


FIGURE 60

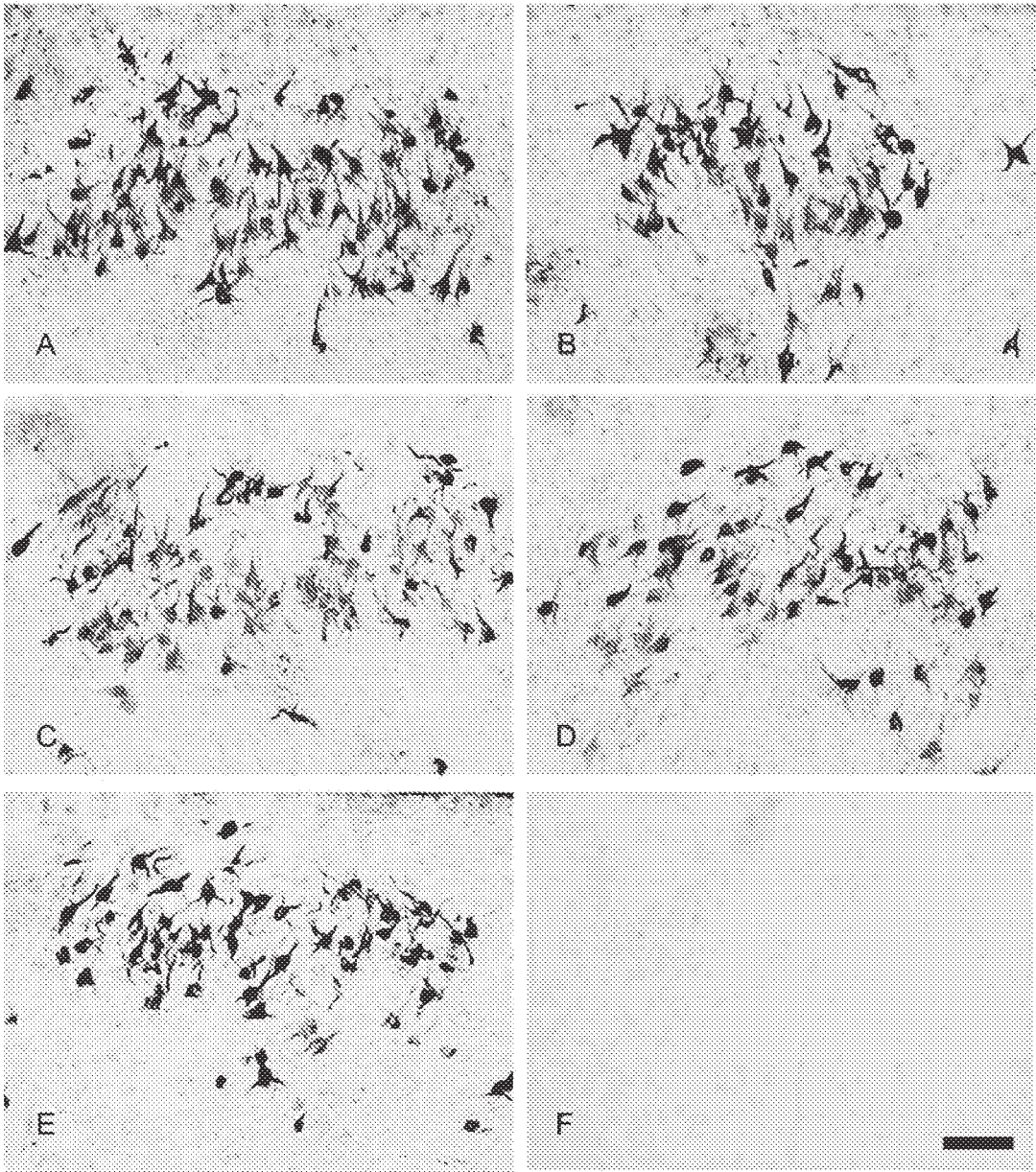
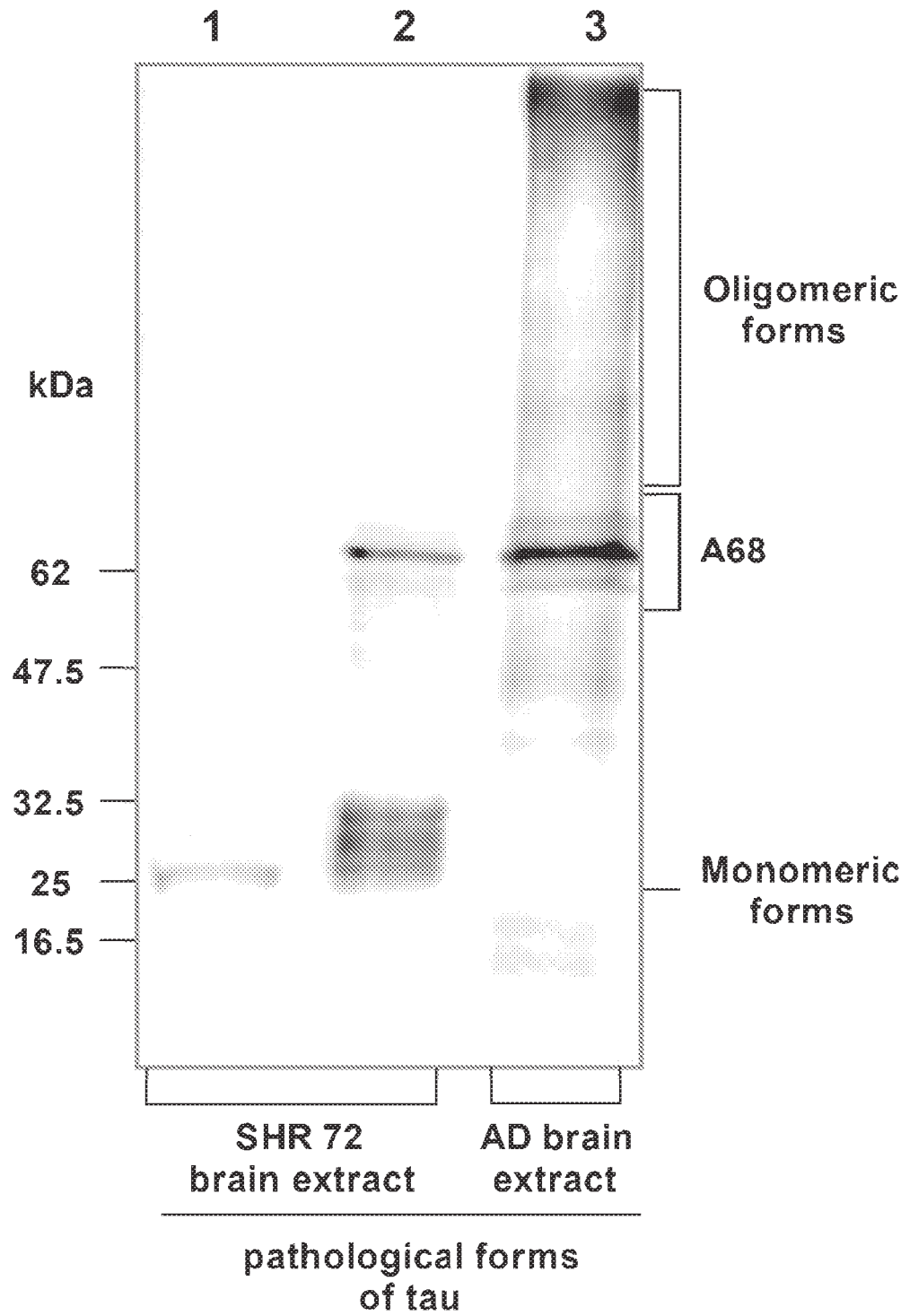
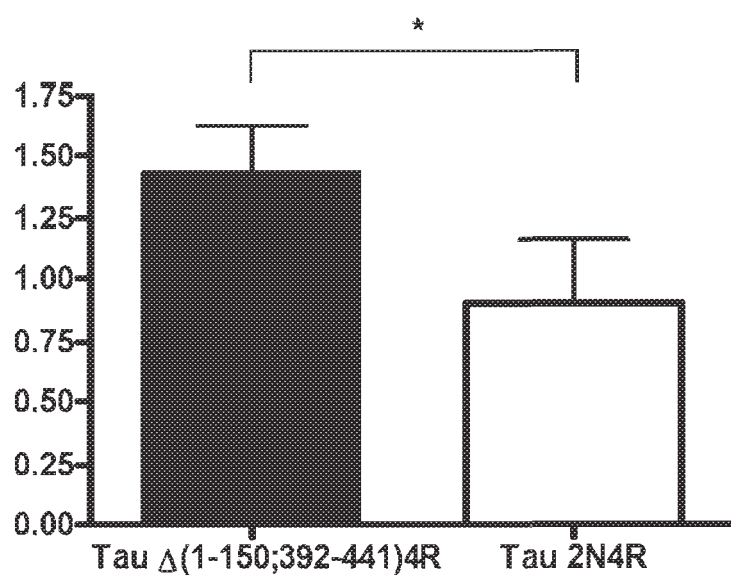


FIGURE 61



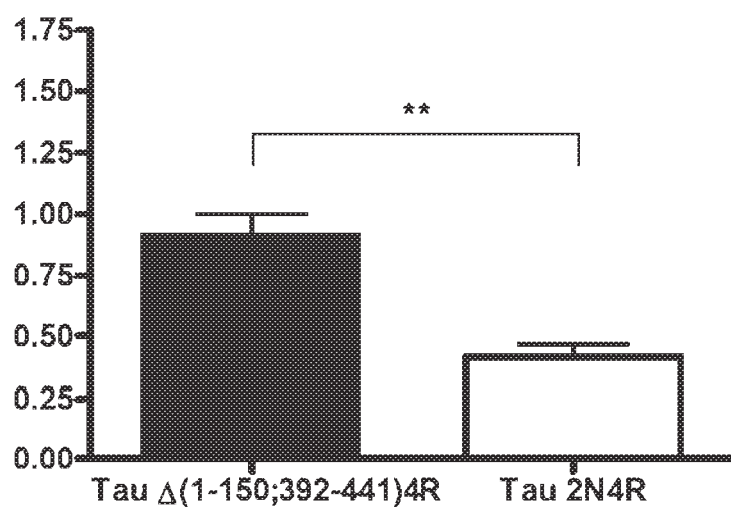
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FIGURE 62



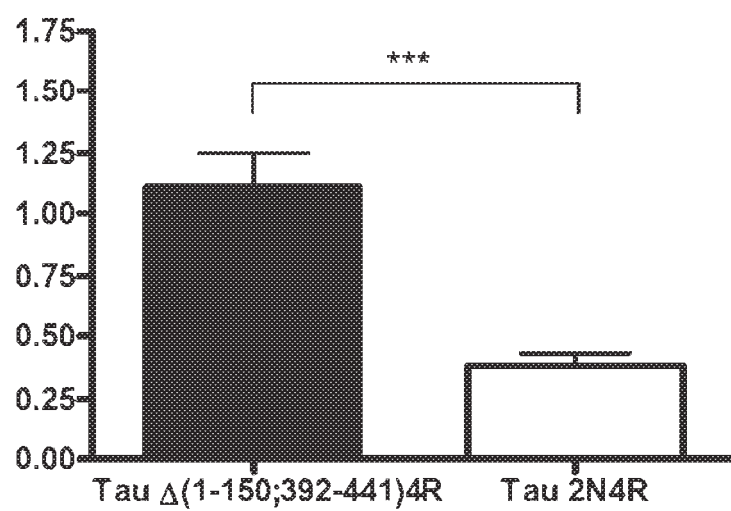
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FIGURE 63



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FIGURE 64



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FIGURE 65

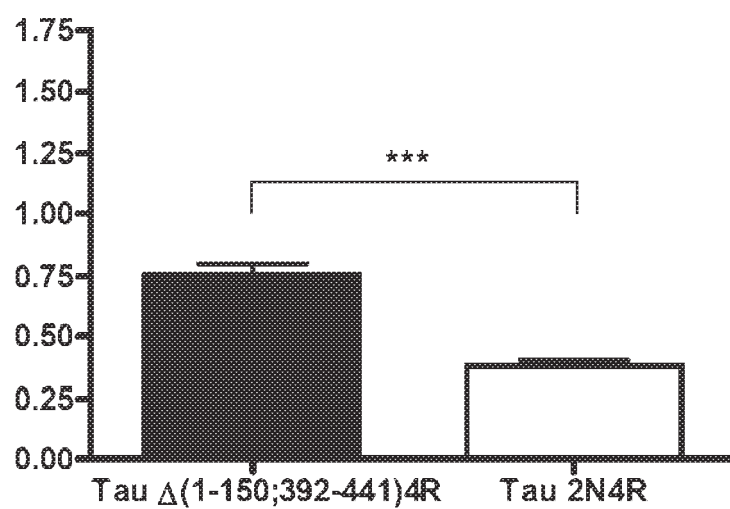


FIGURE 66

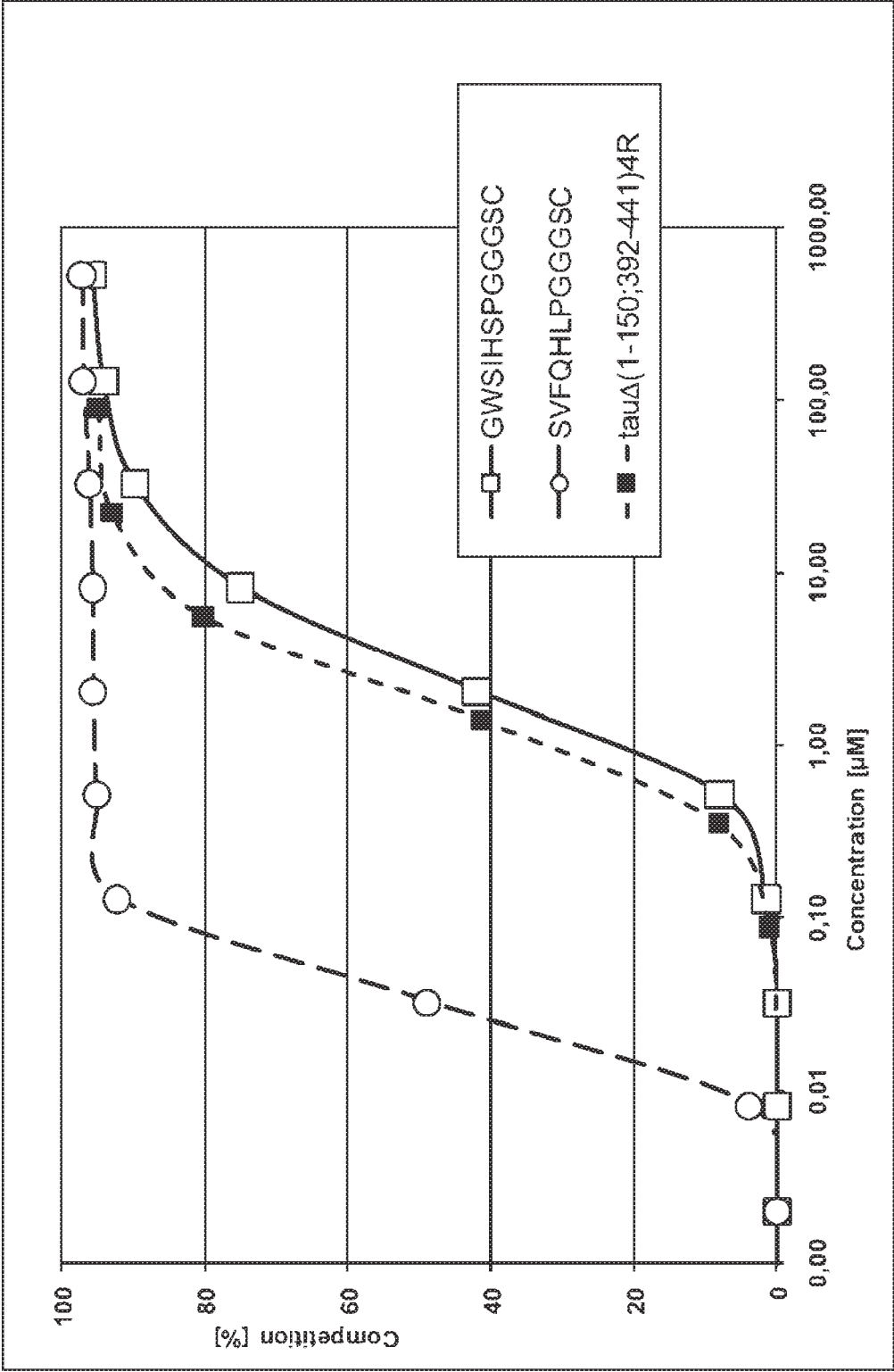


FIGURE 67

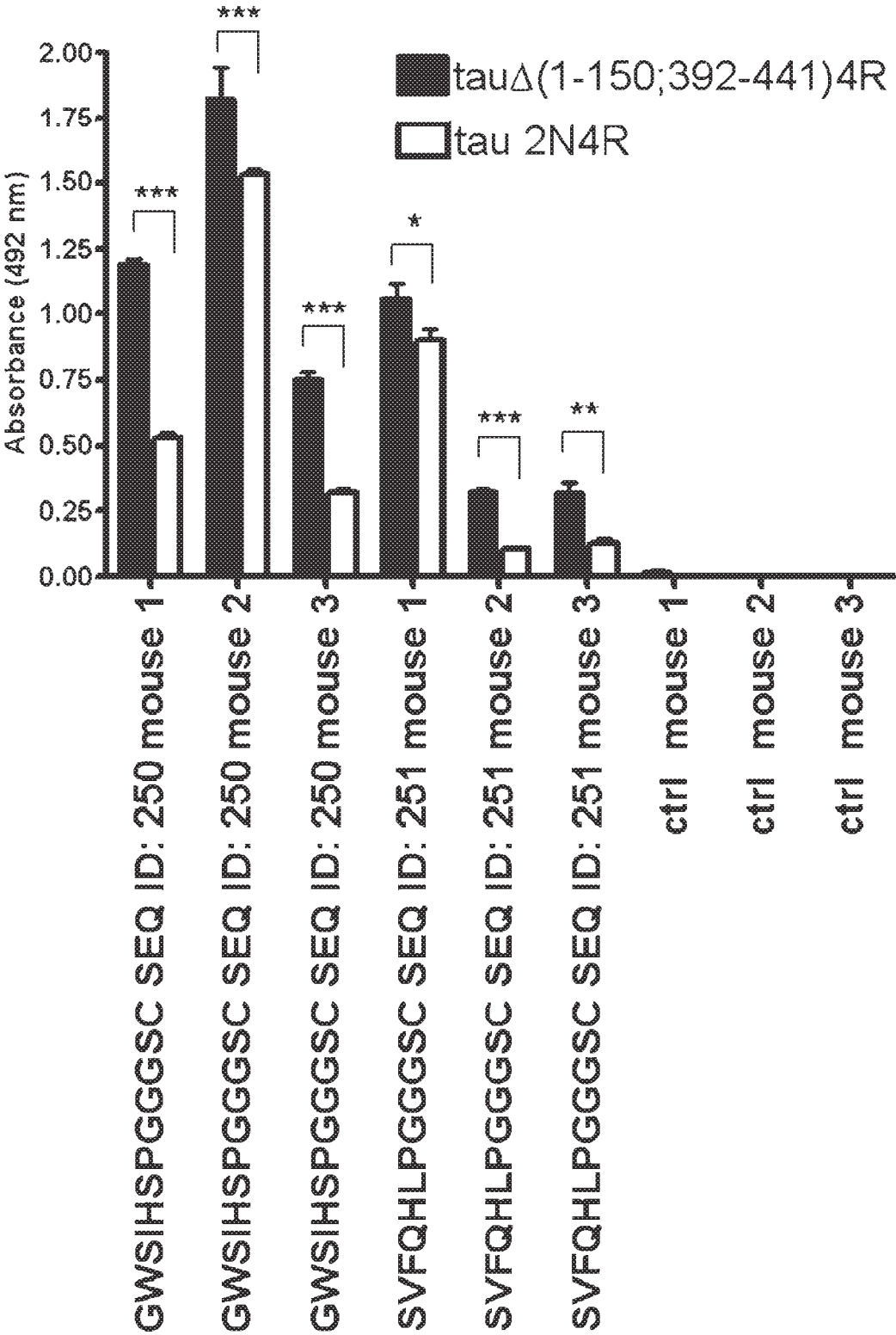


FIGURE 68

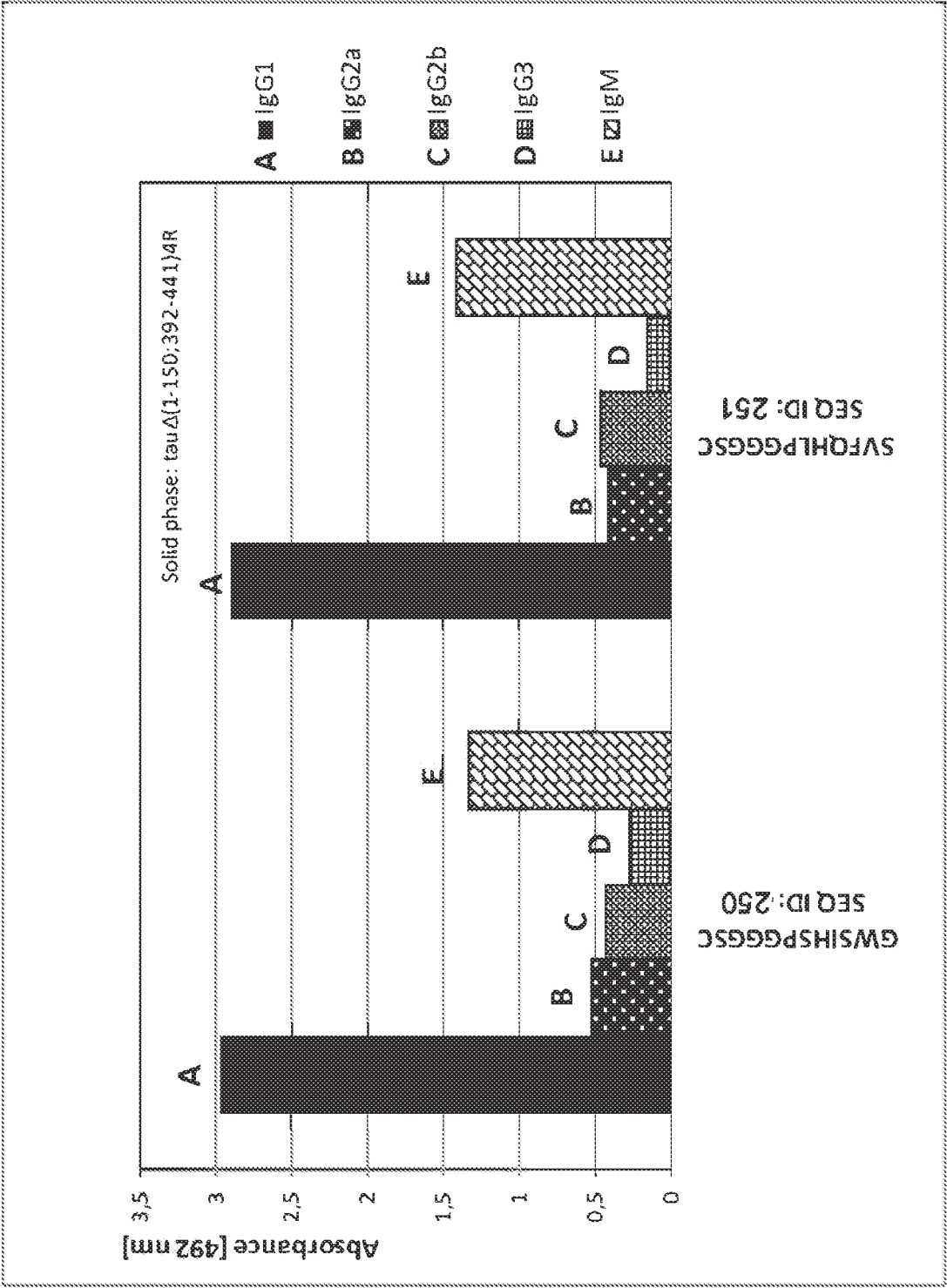
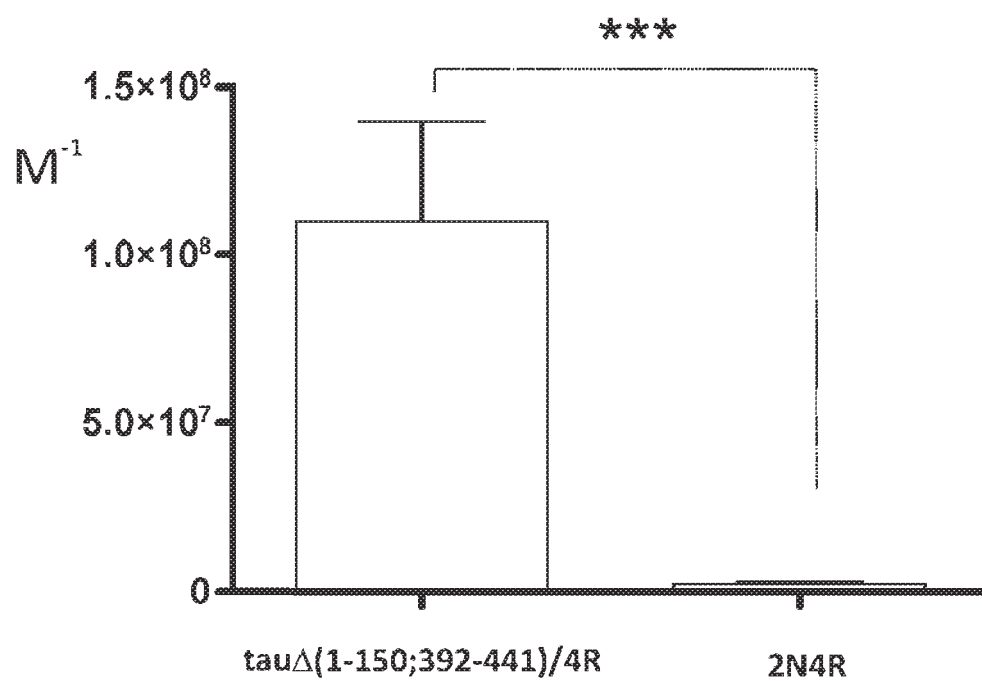


FIGURE 69A

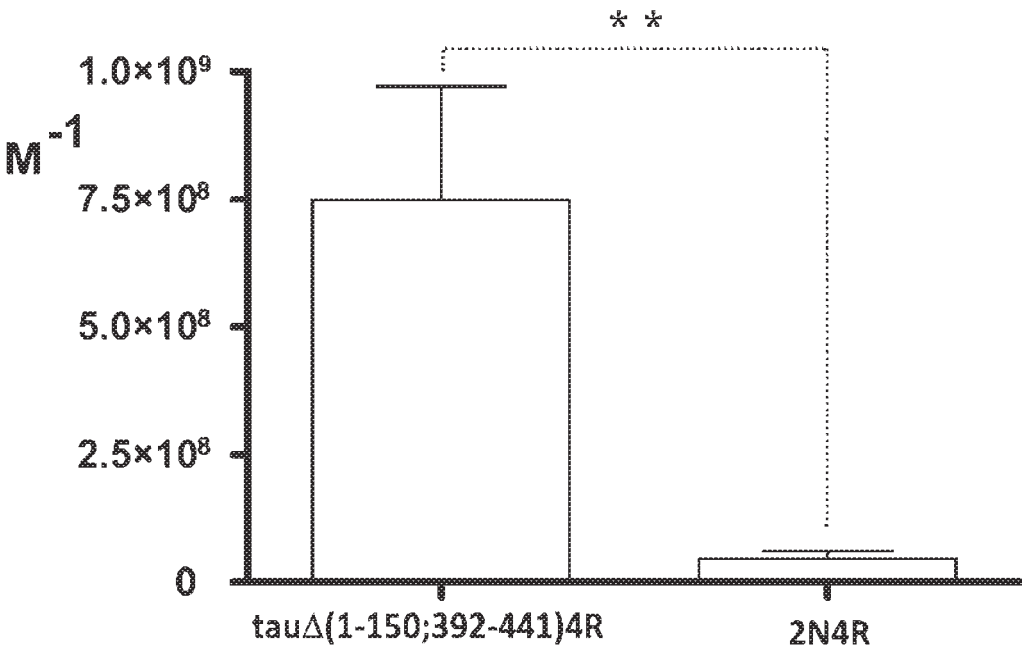
[GWSIHSPGGGSC (SEQ ID: 250)]



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

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

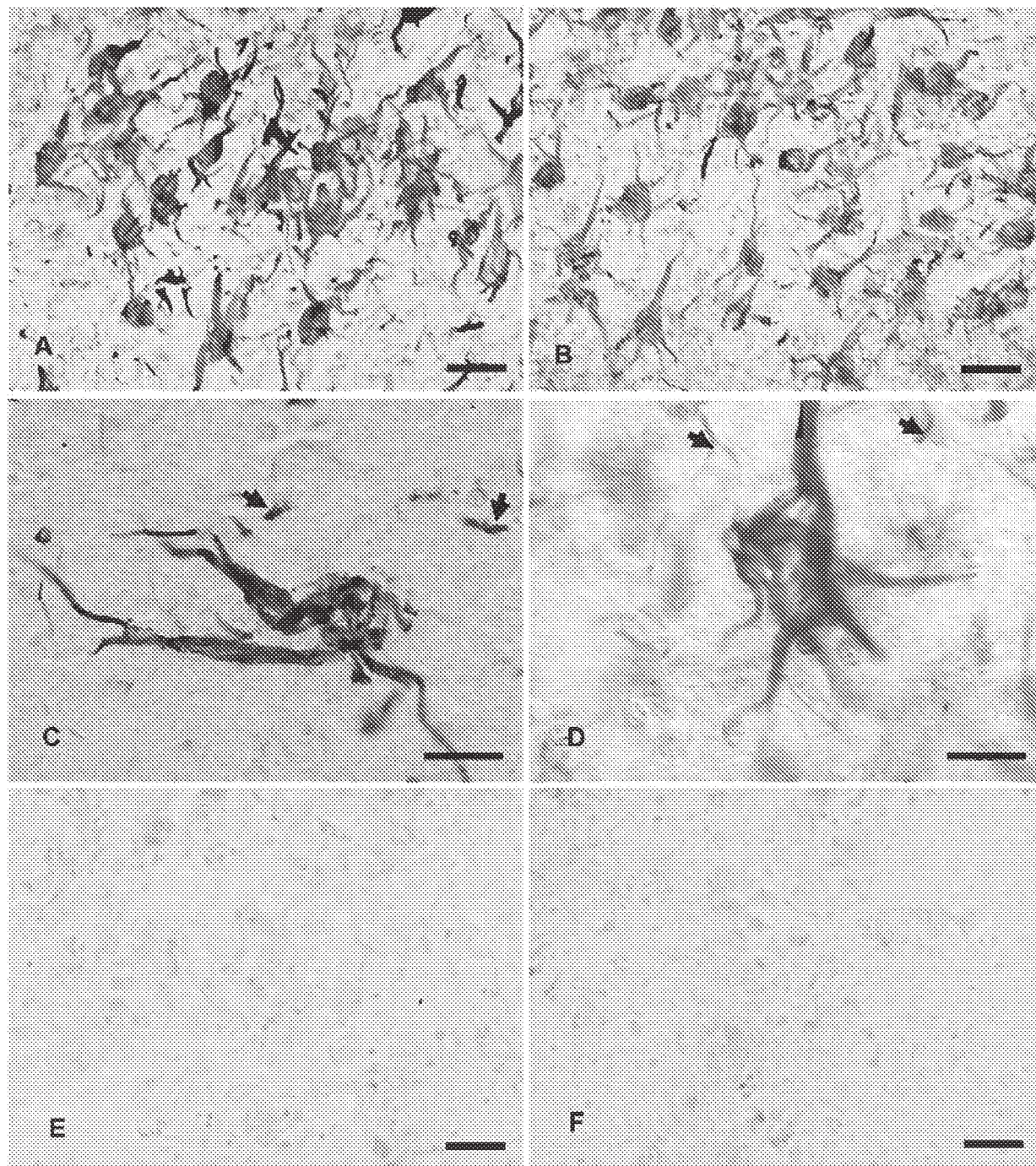


FIGURE 70 G-J

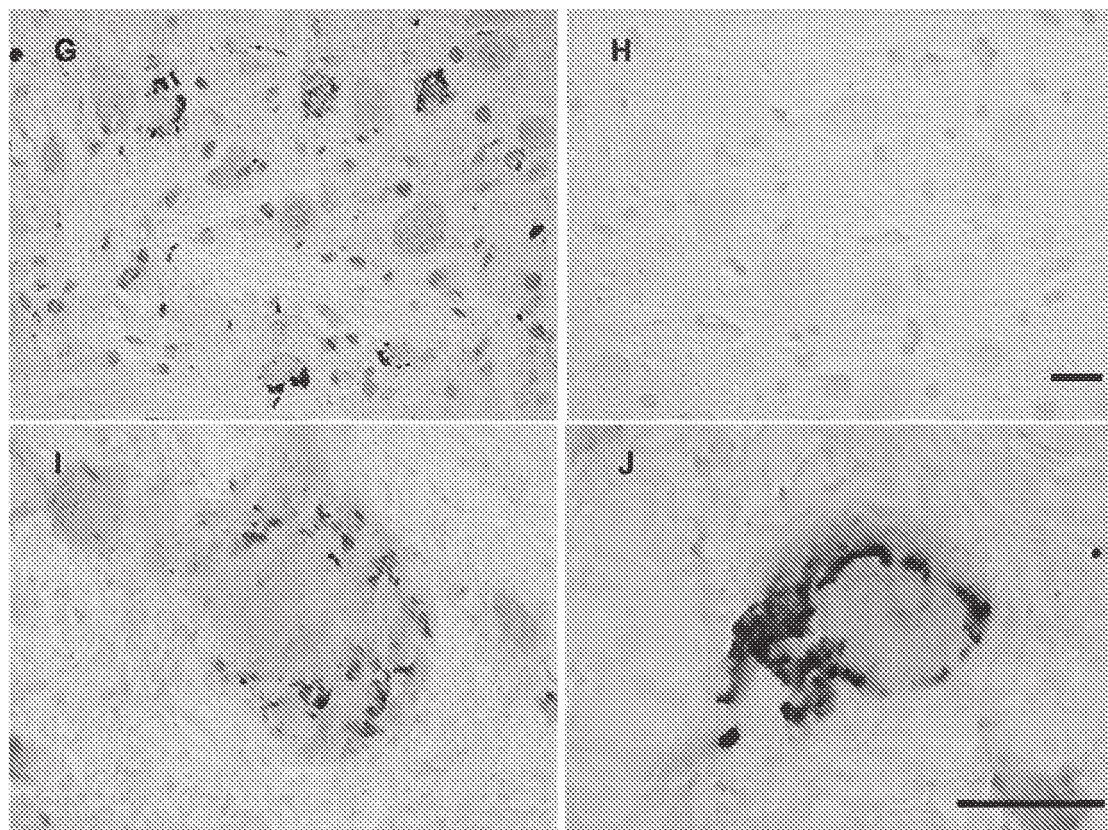


FIGURE 71

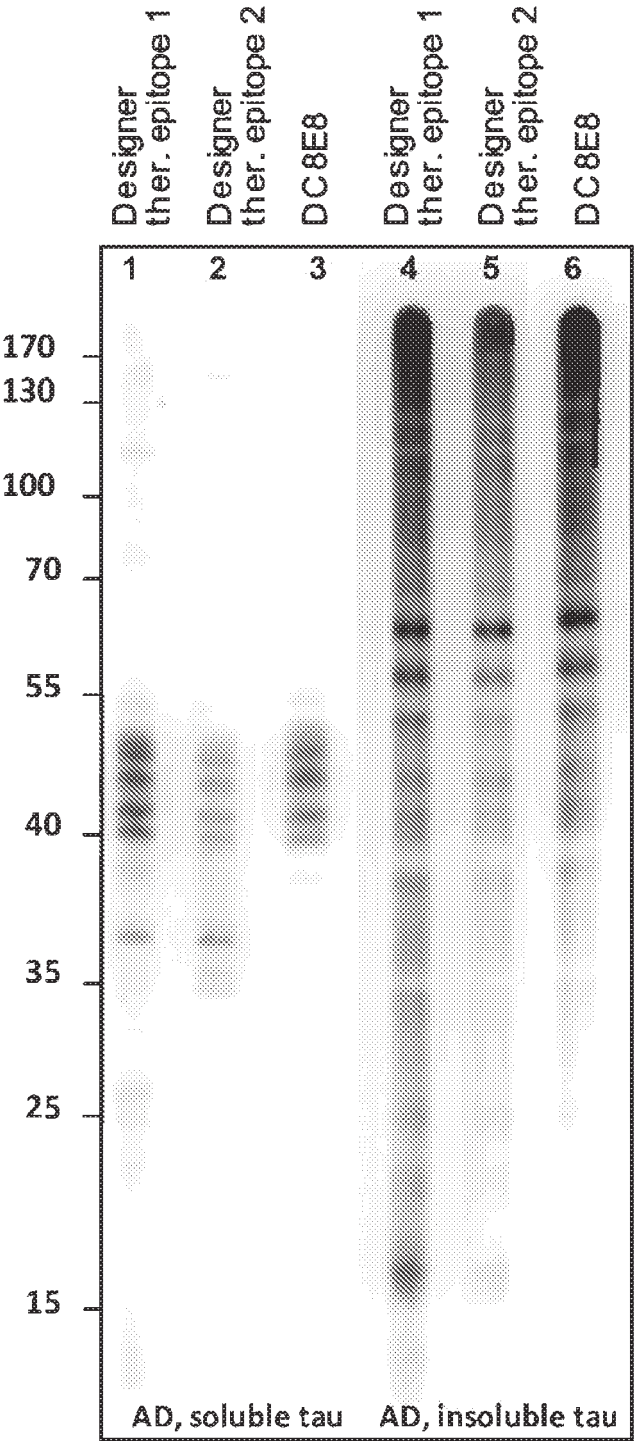


FIGURE 72

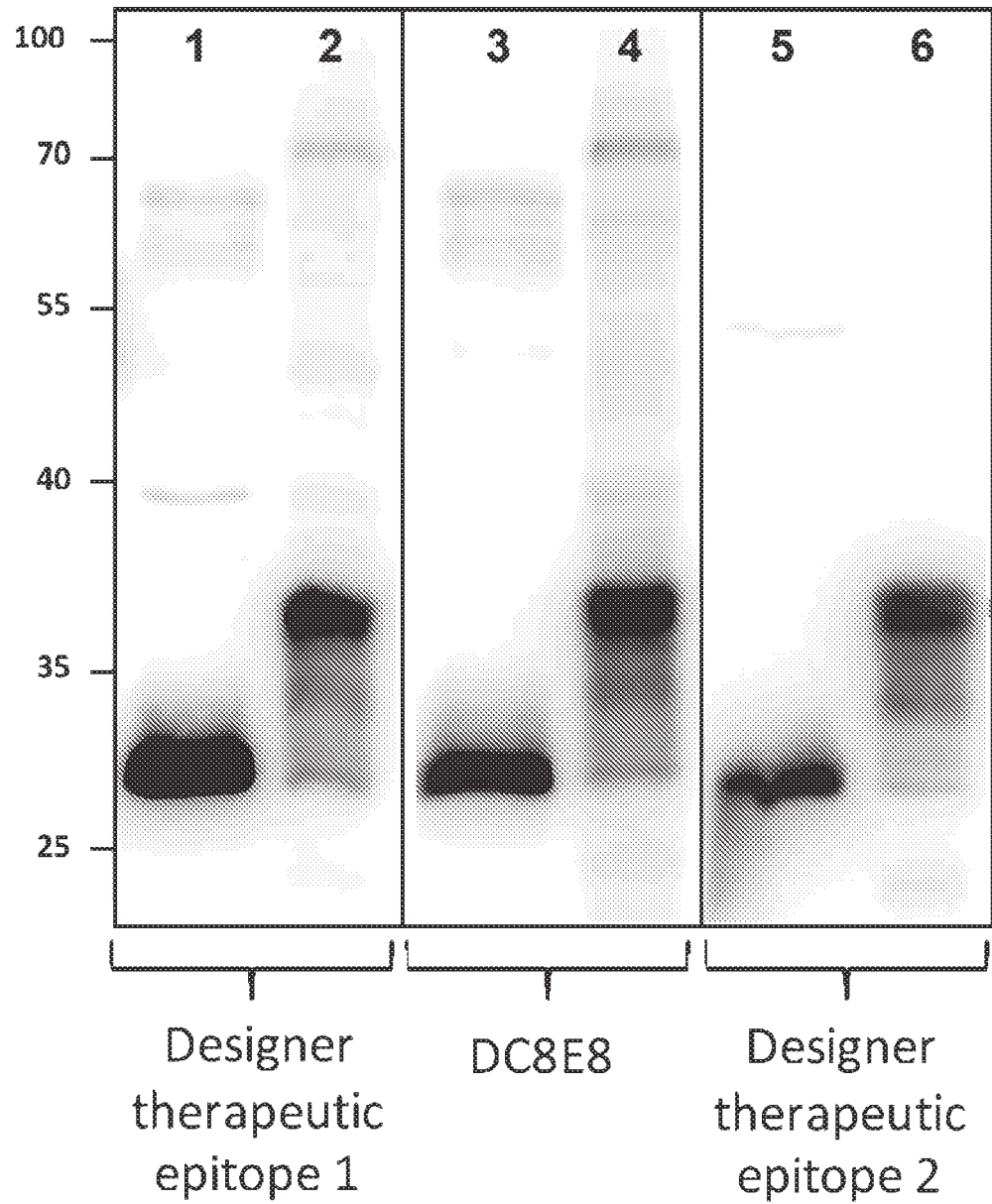
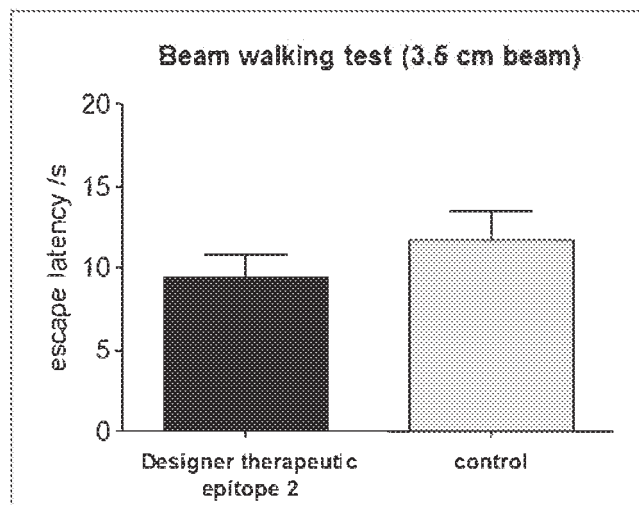
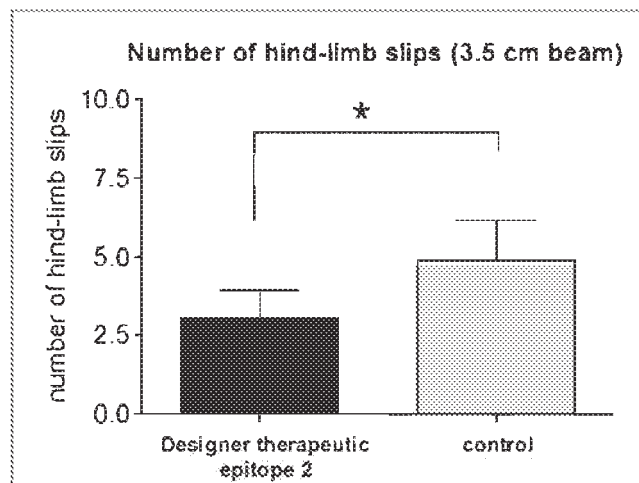


FIGURE 73

A.



B.



C.

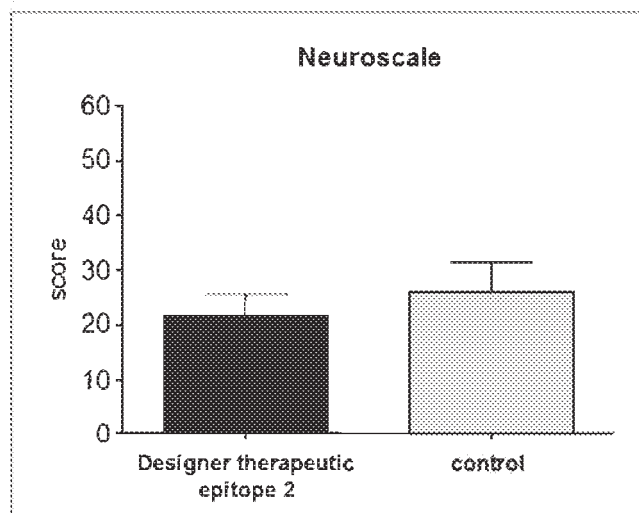


FIGURE 74

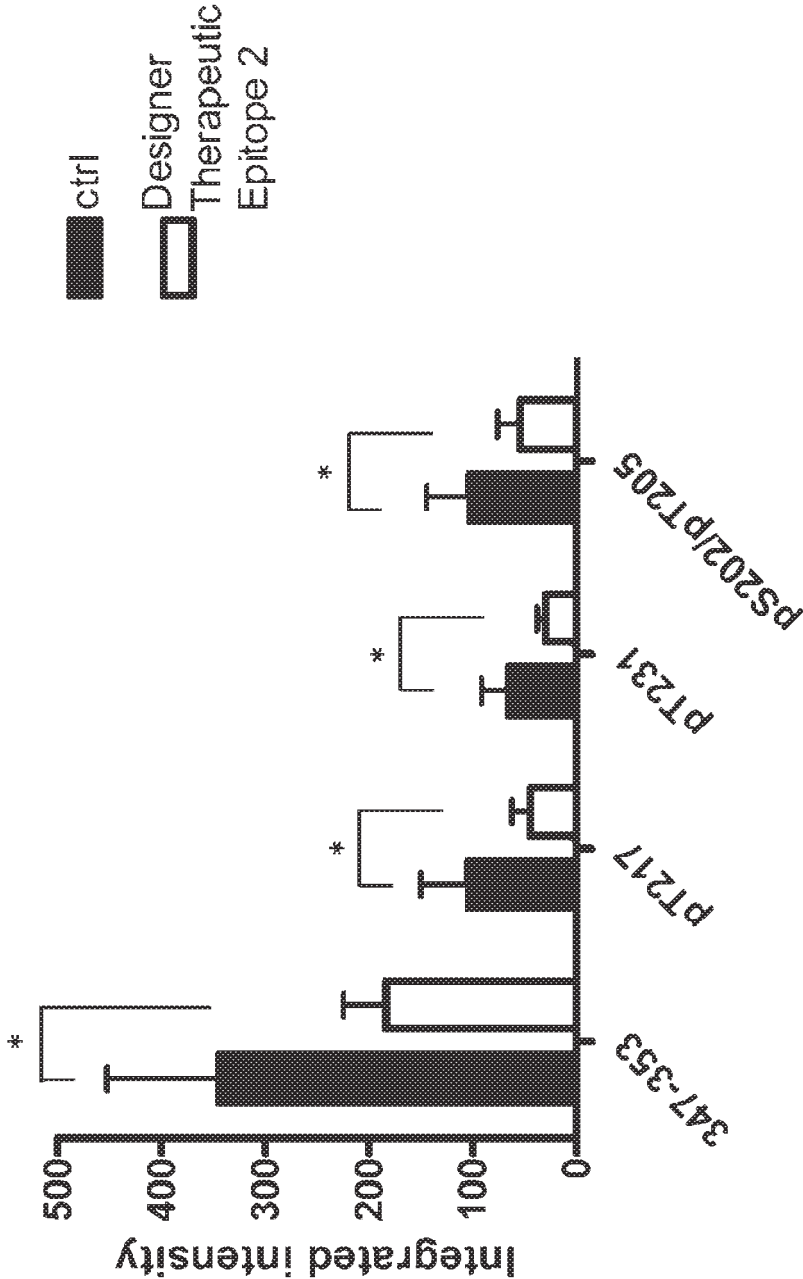


FIGURE 75A

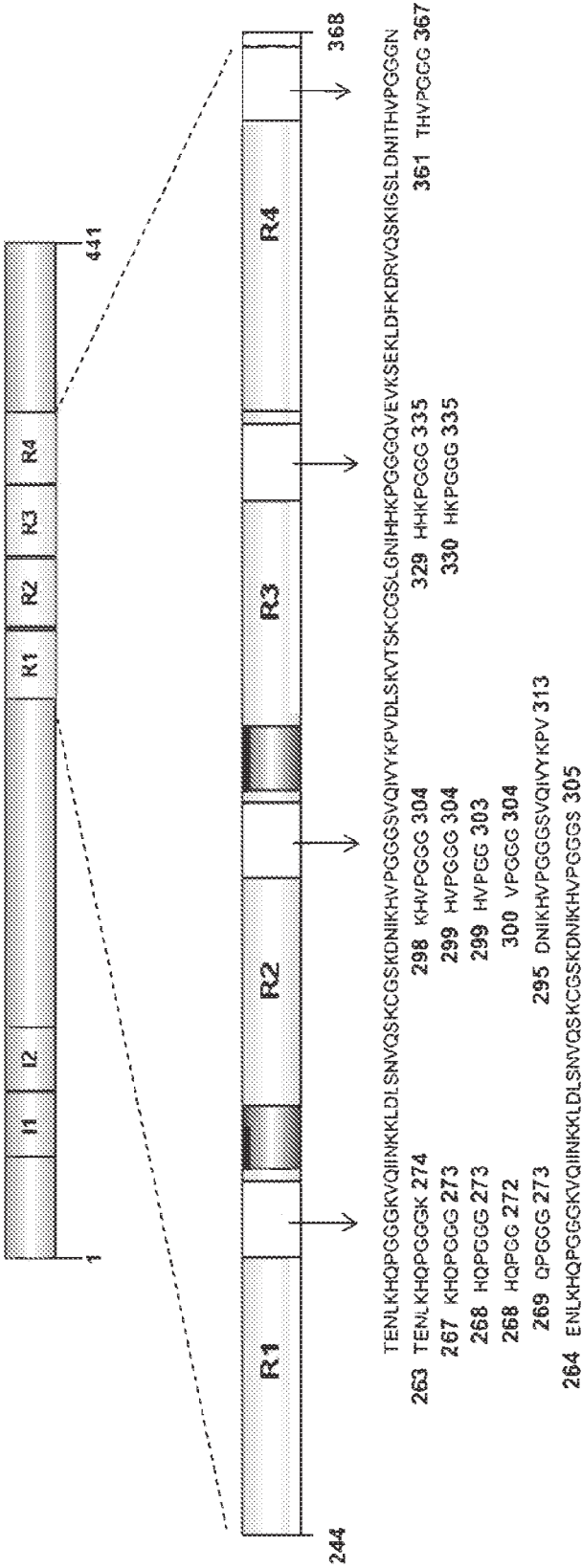
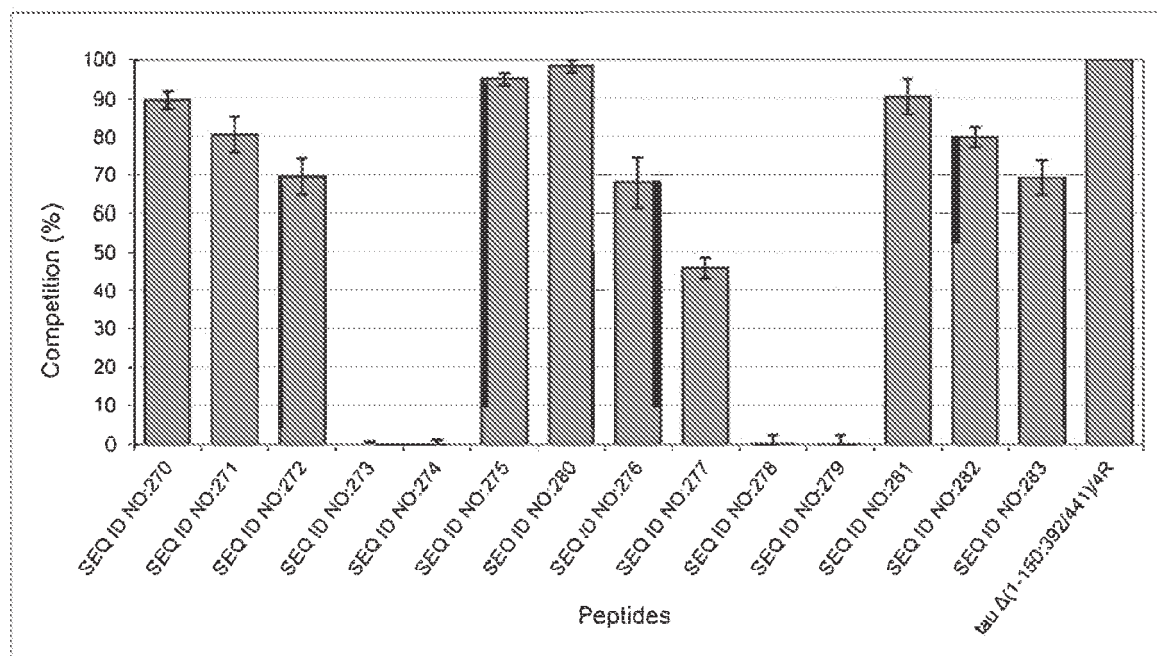


FIGURE 75B

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	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



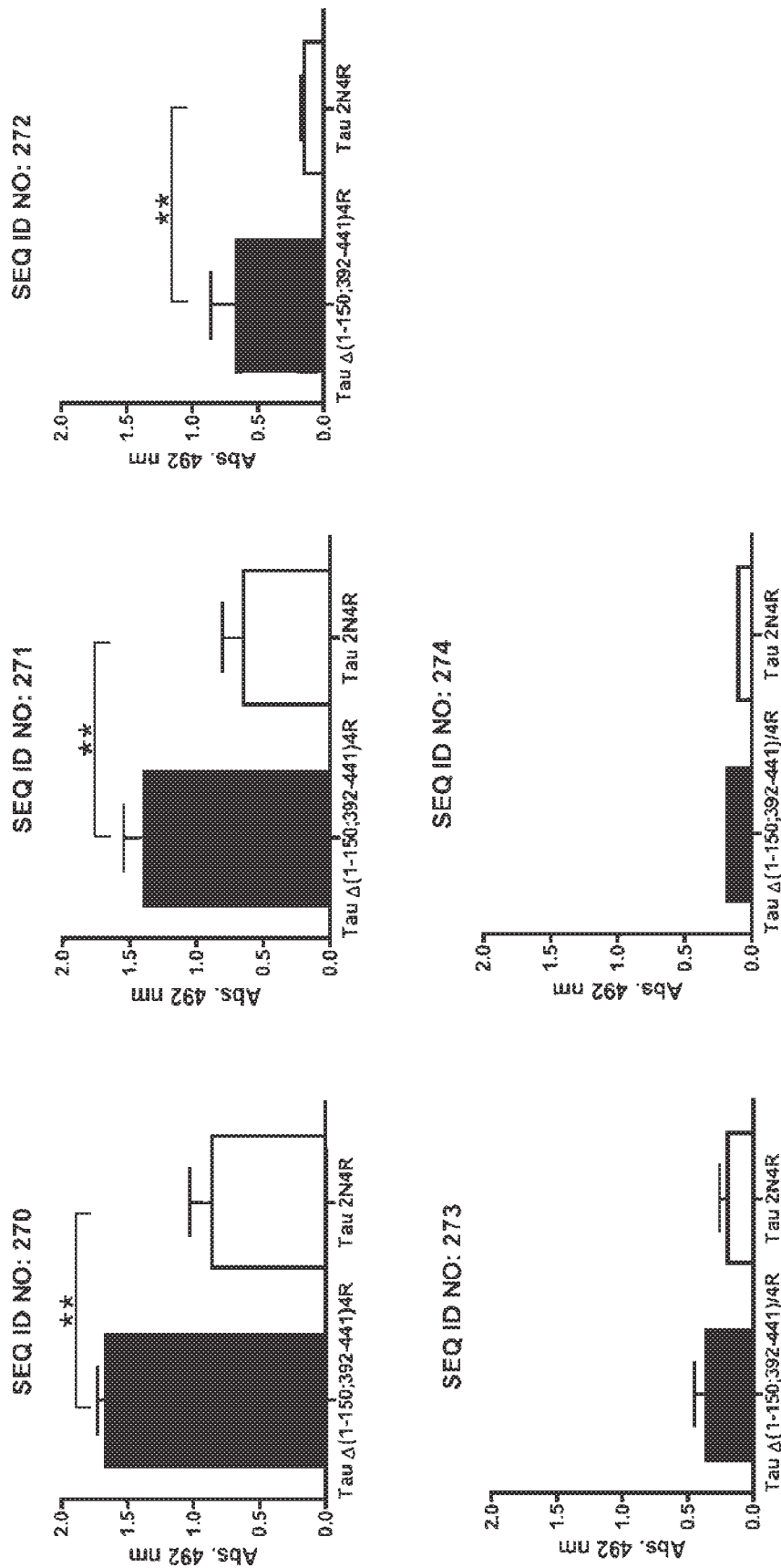


Figure 77A

FIGURE 77B

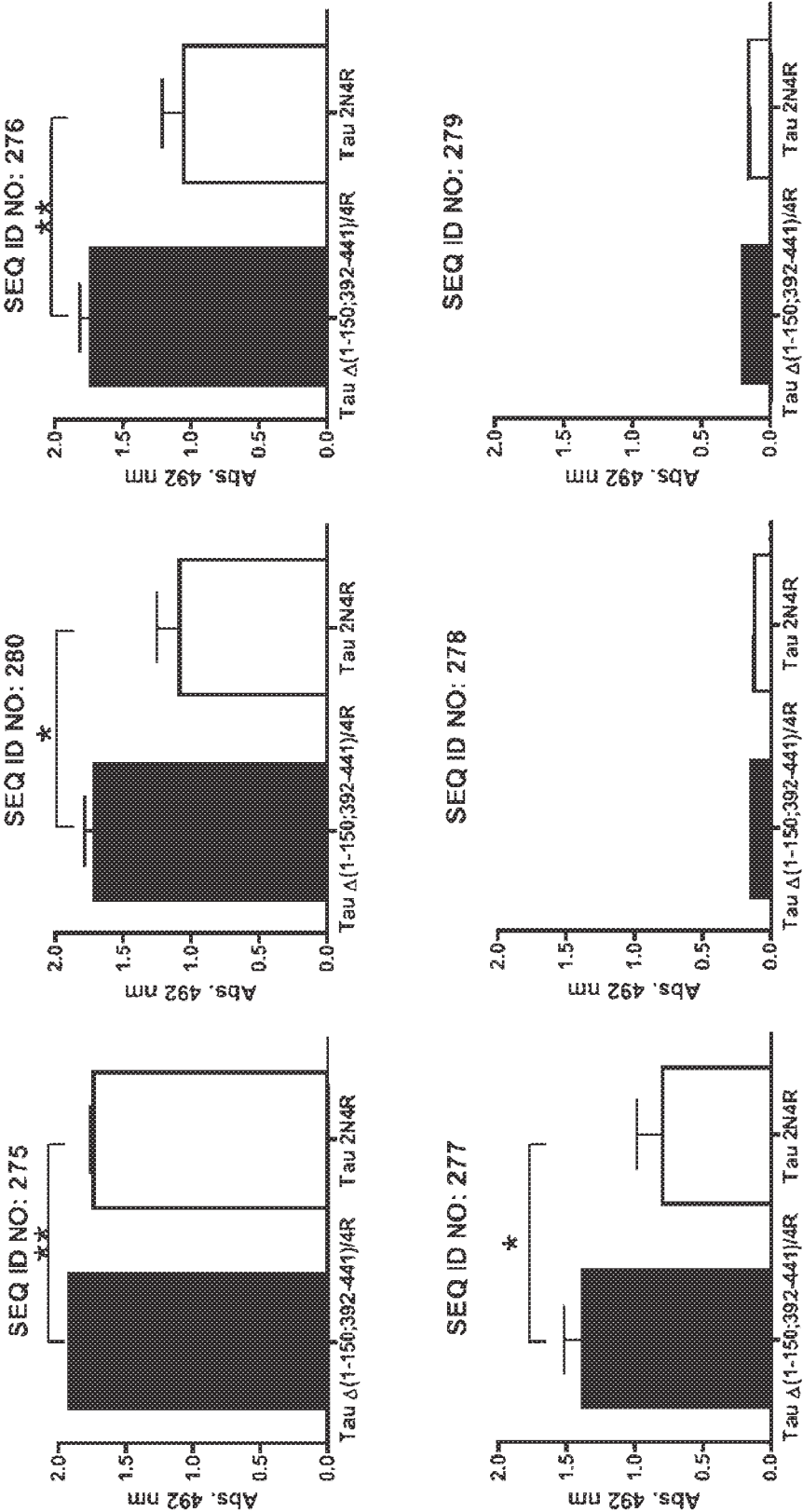
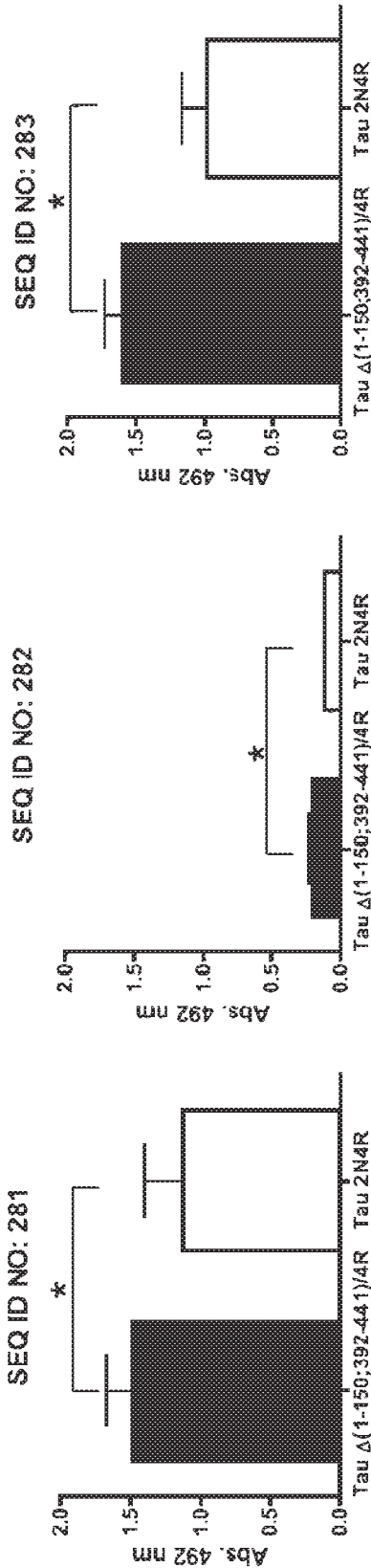


FIGURE 77C



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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

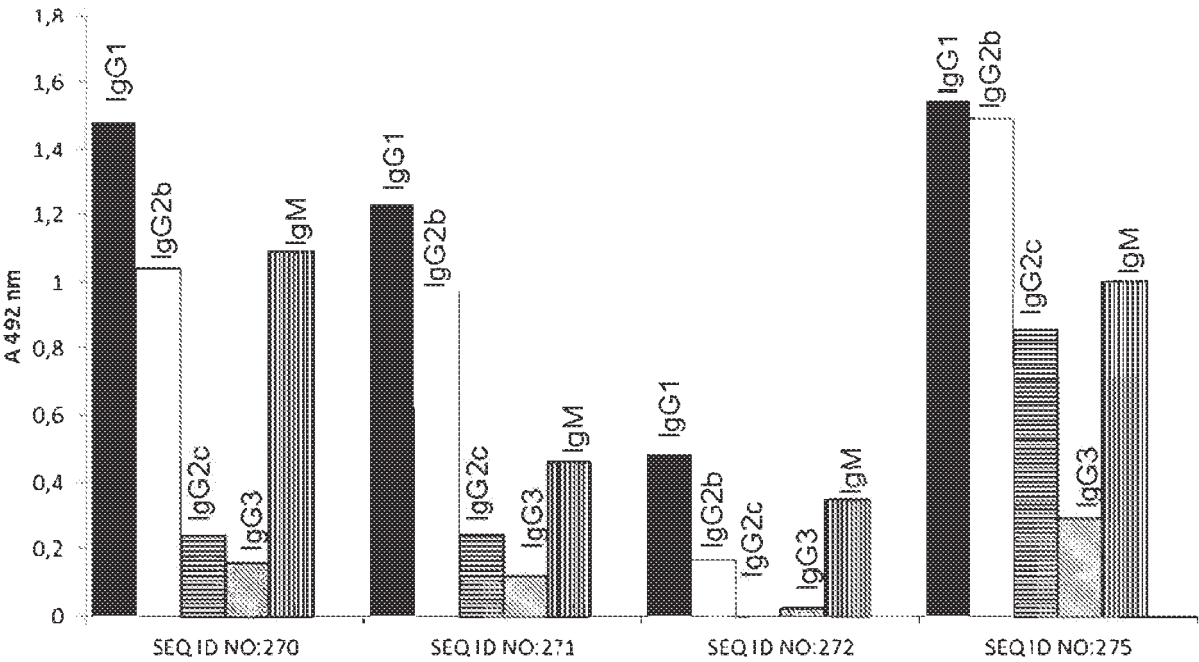


FIGURE 79B

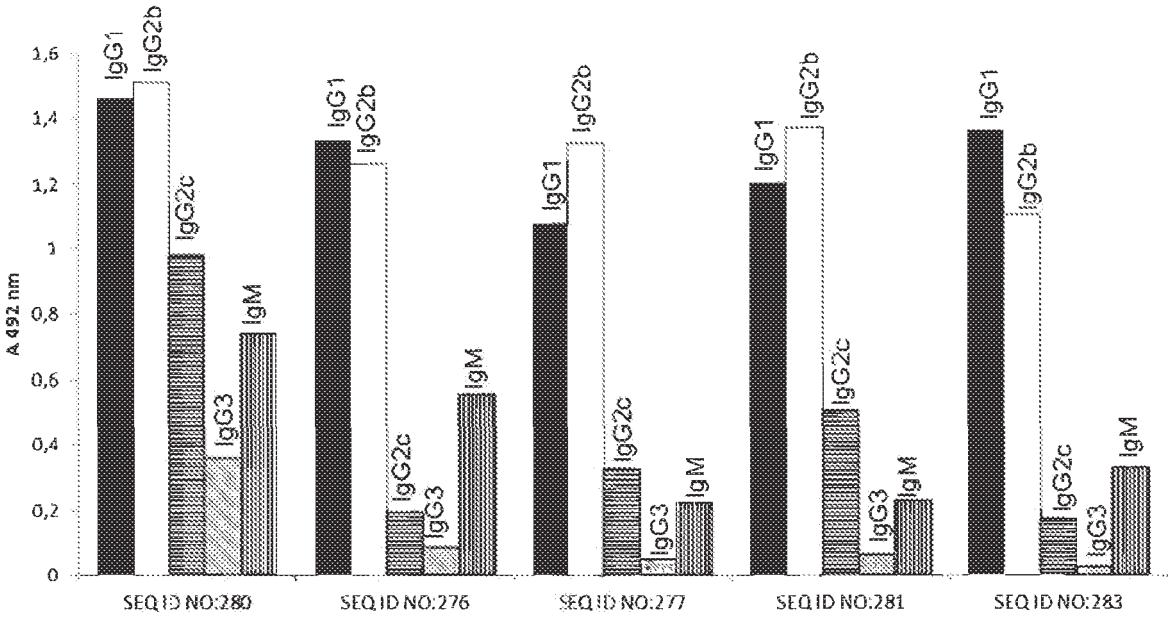


FIGURE 80

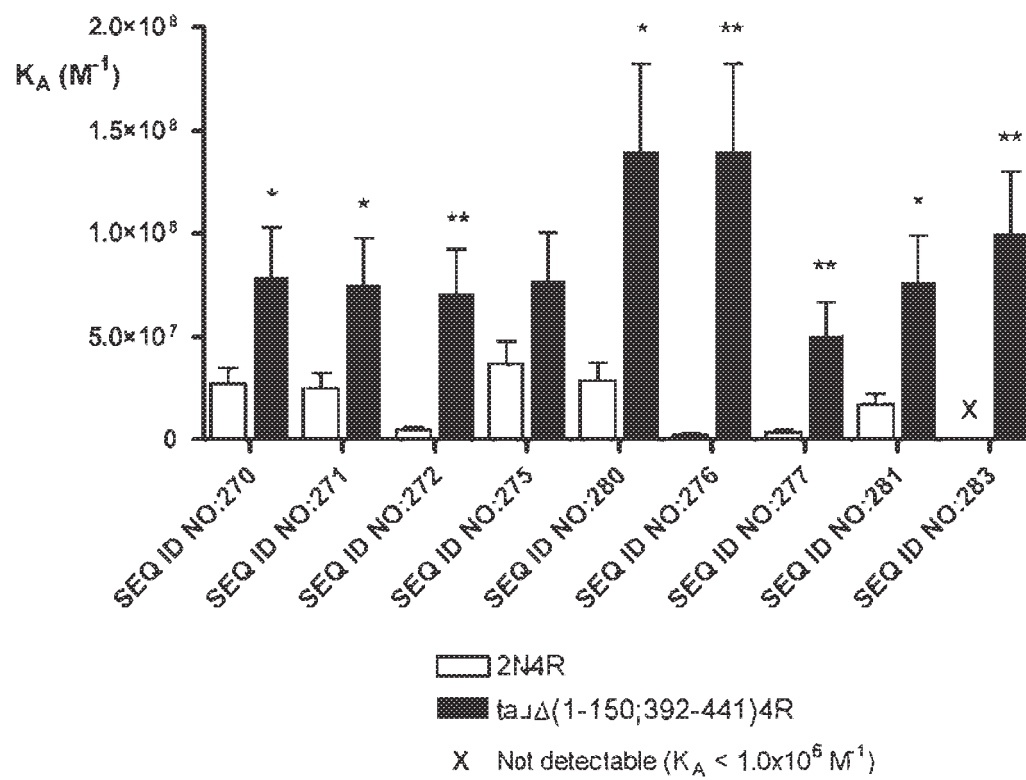


FIGURE 81

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

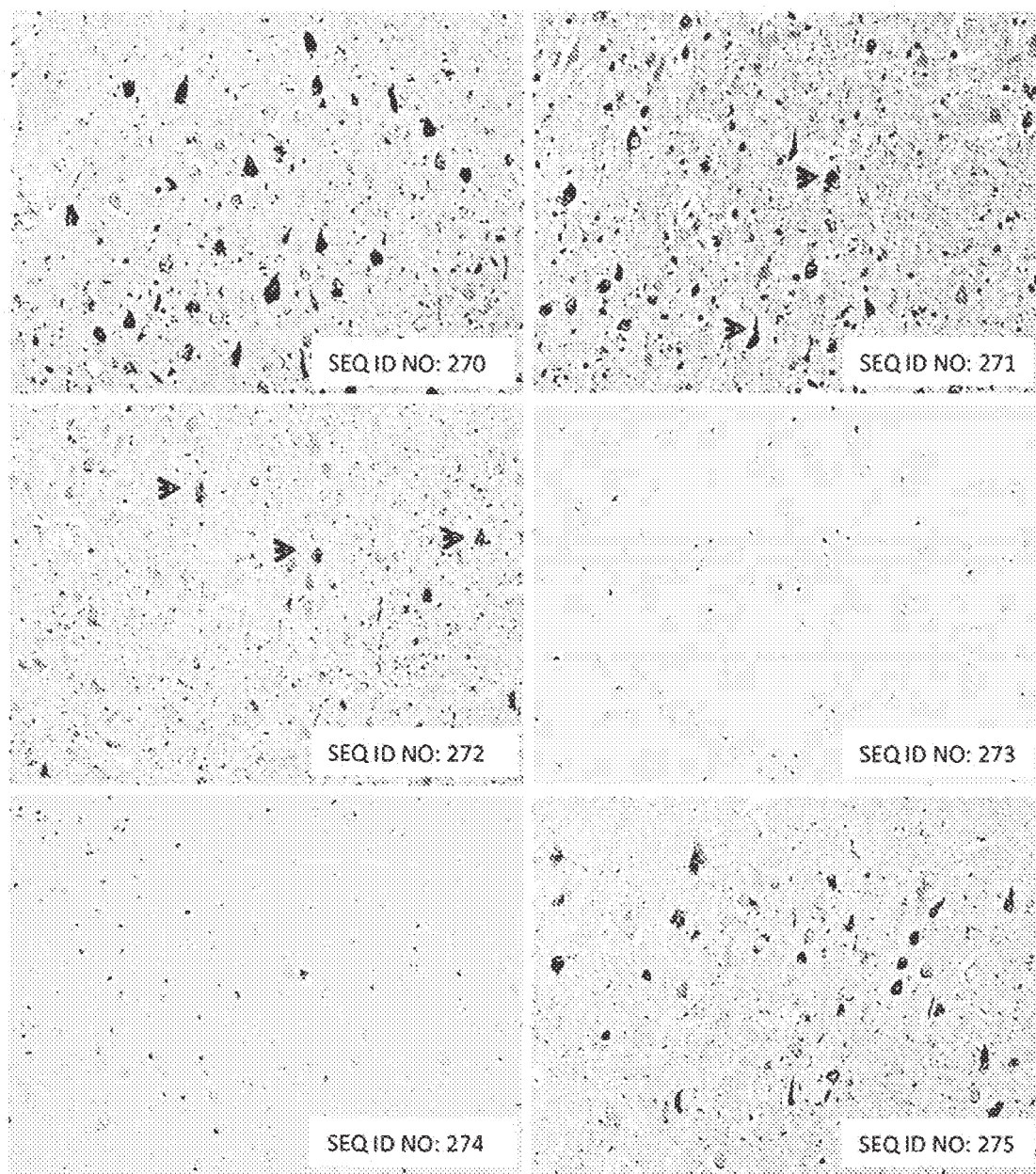


FIGURE 82B

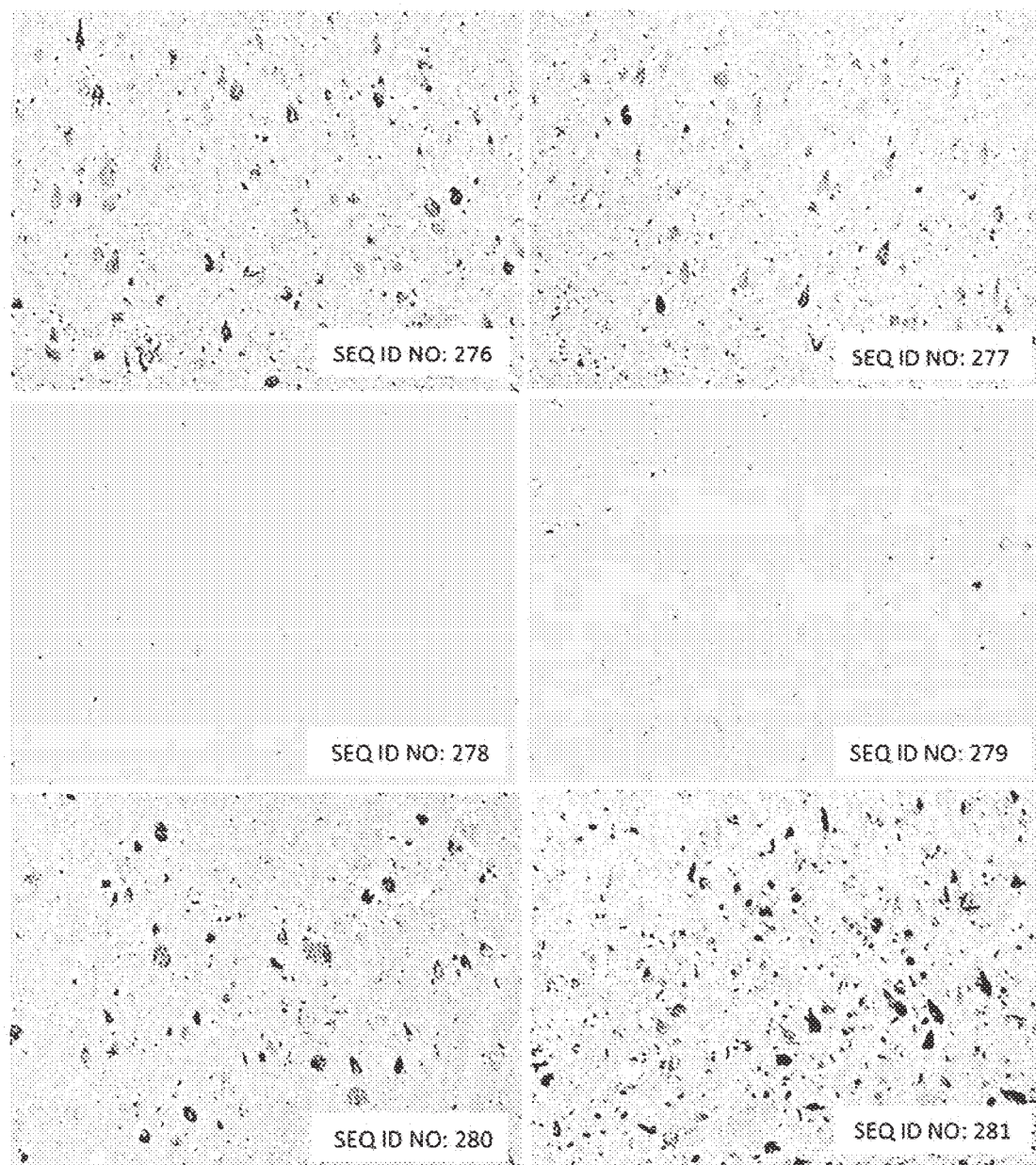


FIGURE 82C

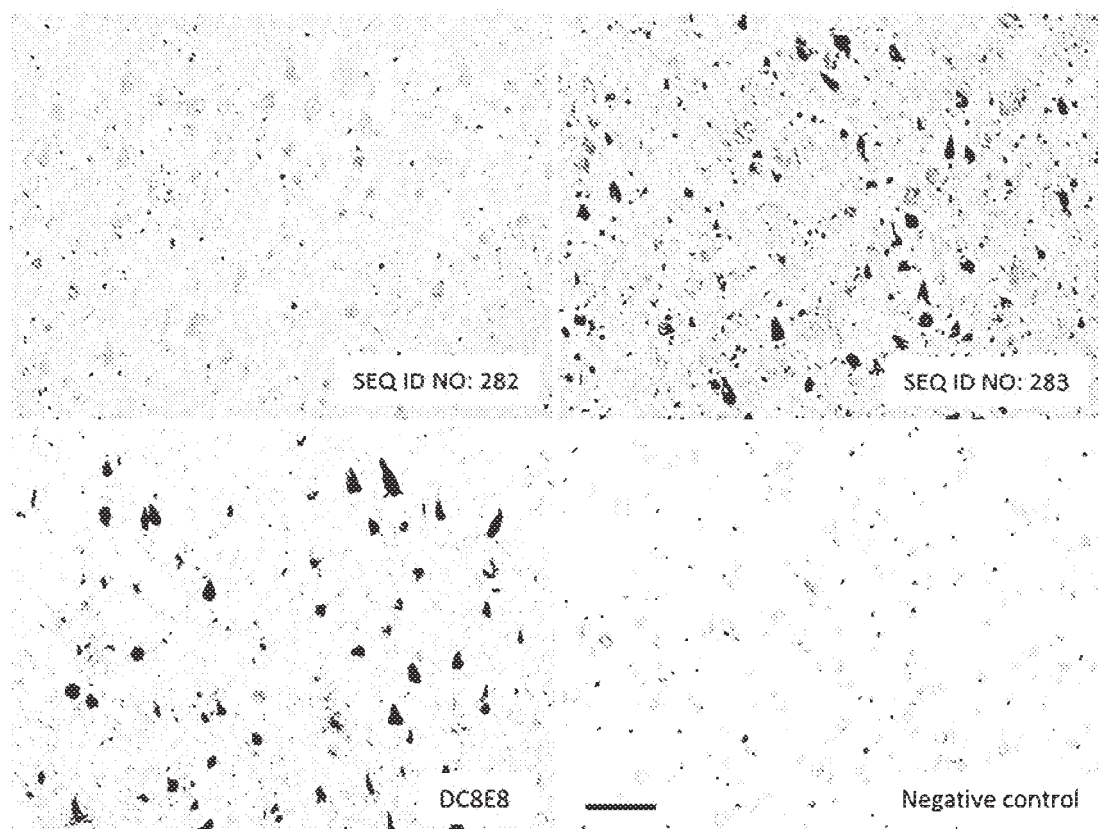


FIGURE 83

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	+++