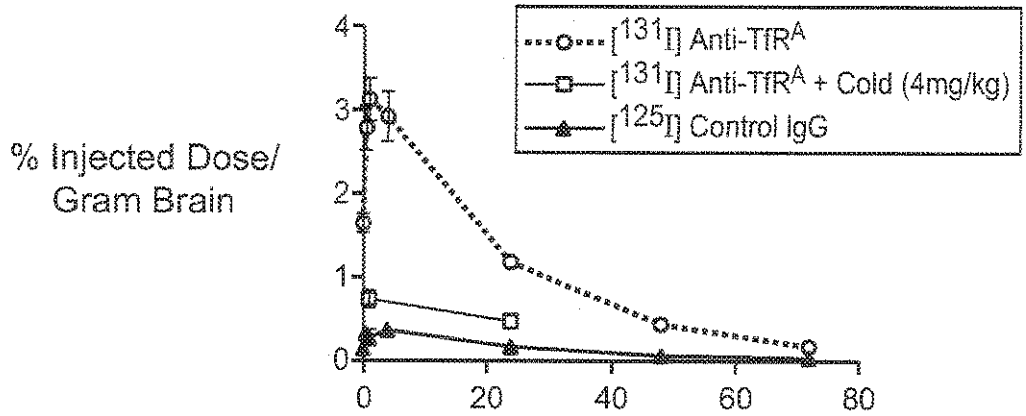


FIG. 1A

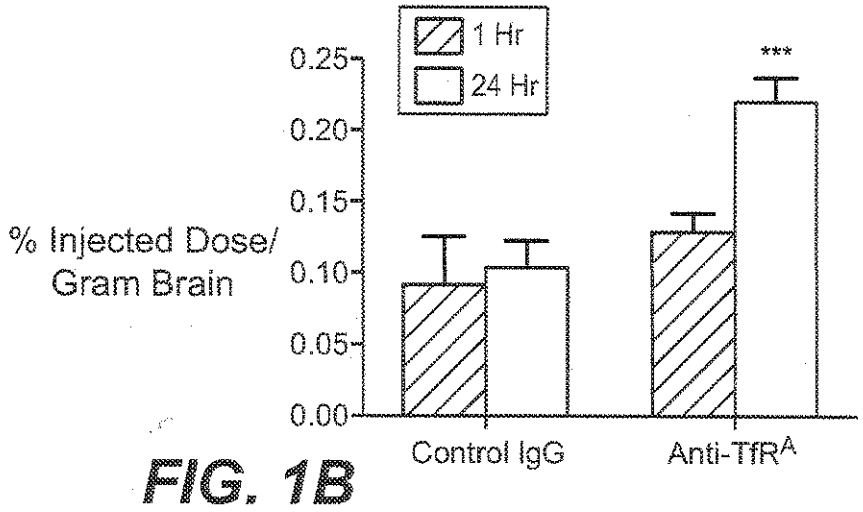


FIG. 1B

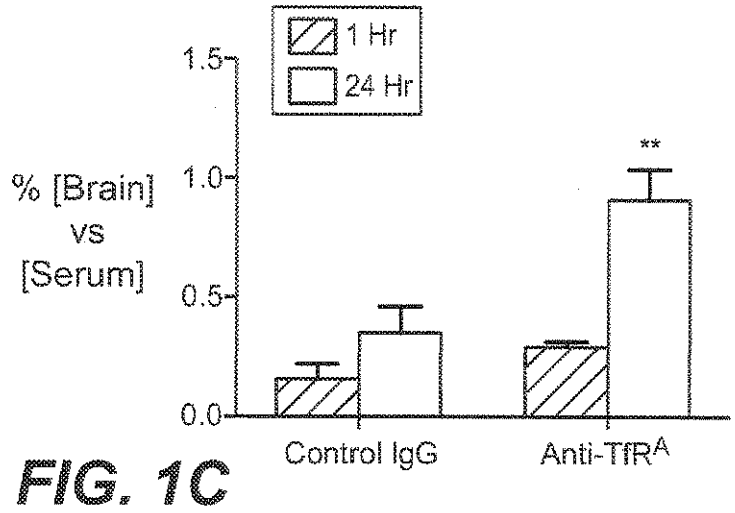


FIG. 1C

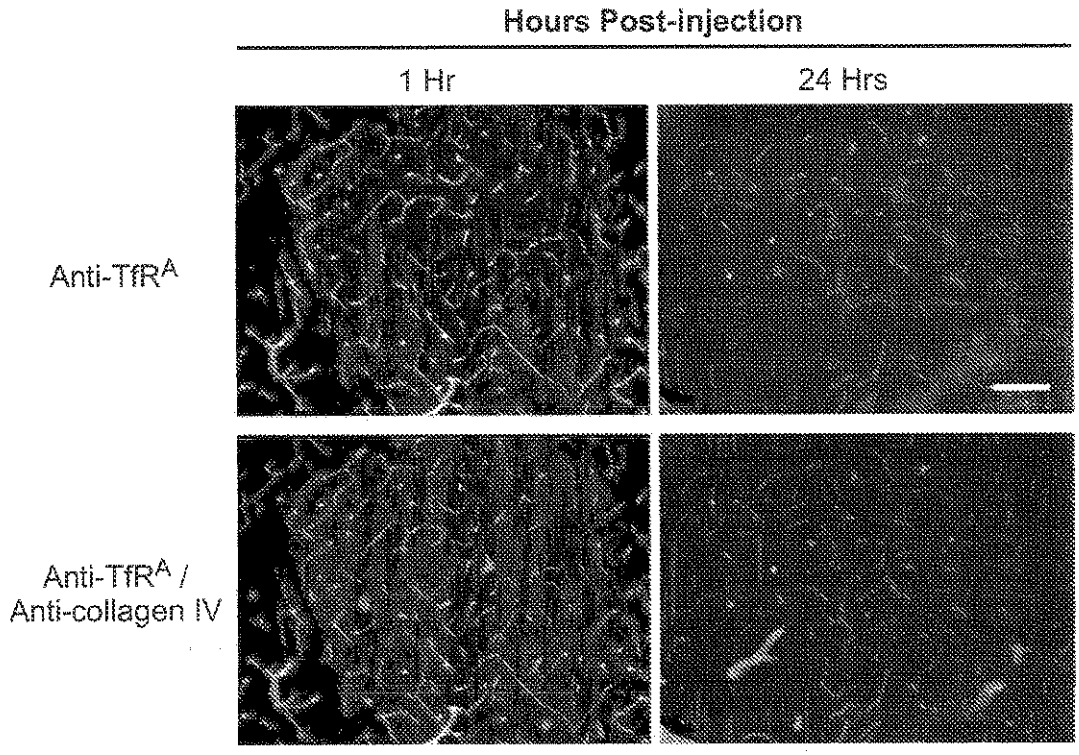

Hours Post-injection
1 Hr
24 Hrs
Anti-TfR^A
Anti-TfR^A / Anti-collagen IV

FIG. 1D

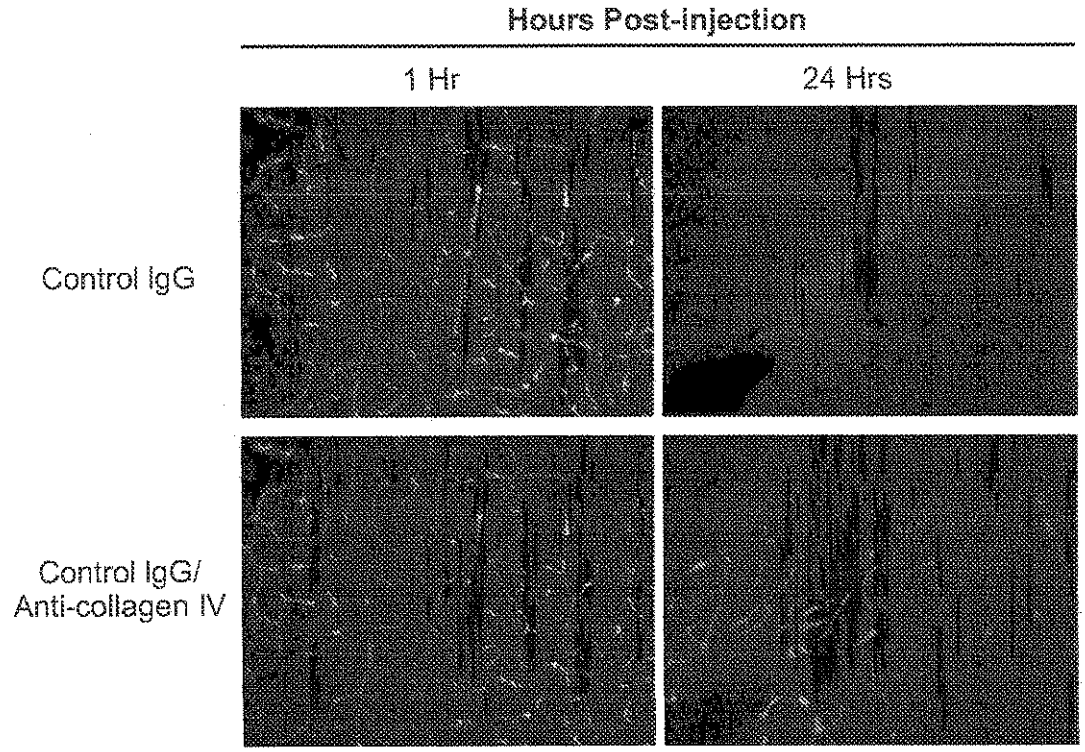

Hours Post-injection
1 Hr
24 Hrs
Control IgG
Control IgG/ Anti-collagen IV

FIG. 1E

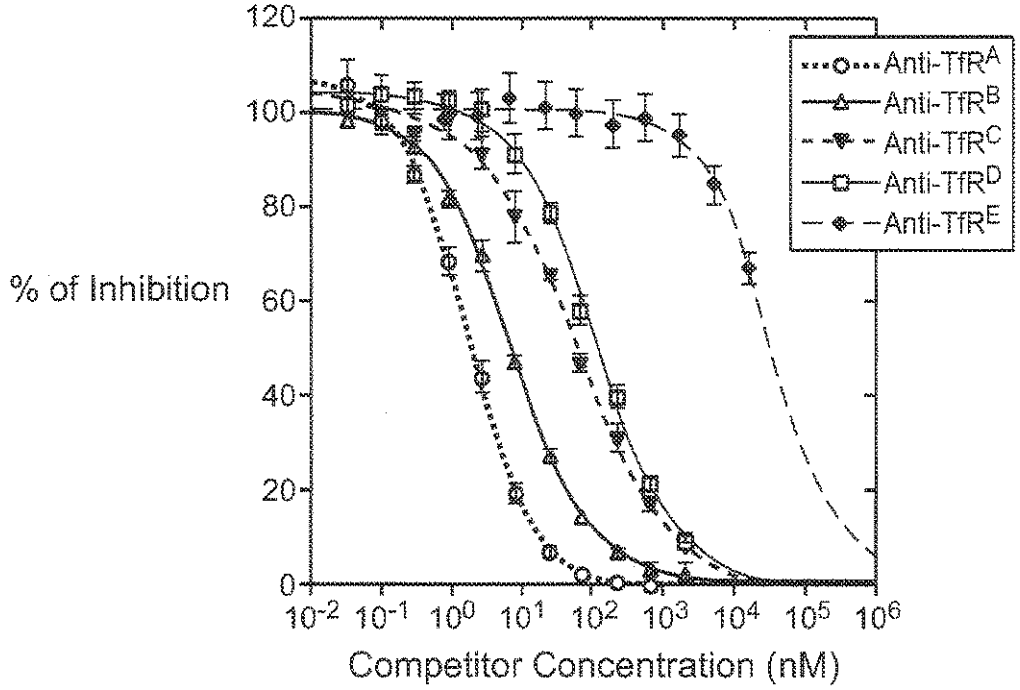

% of Inhibition
120
100
80
60
40
20
0
10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4} 10^{5} 10^{6}
Competitor Concentration (nM)
Anti-TfR^{A}
Anti-TfR^{B}
Anti-TfR^{C}
Anti-TfR^{D}
Anti-TfR^{E}

FIG. 2A

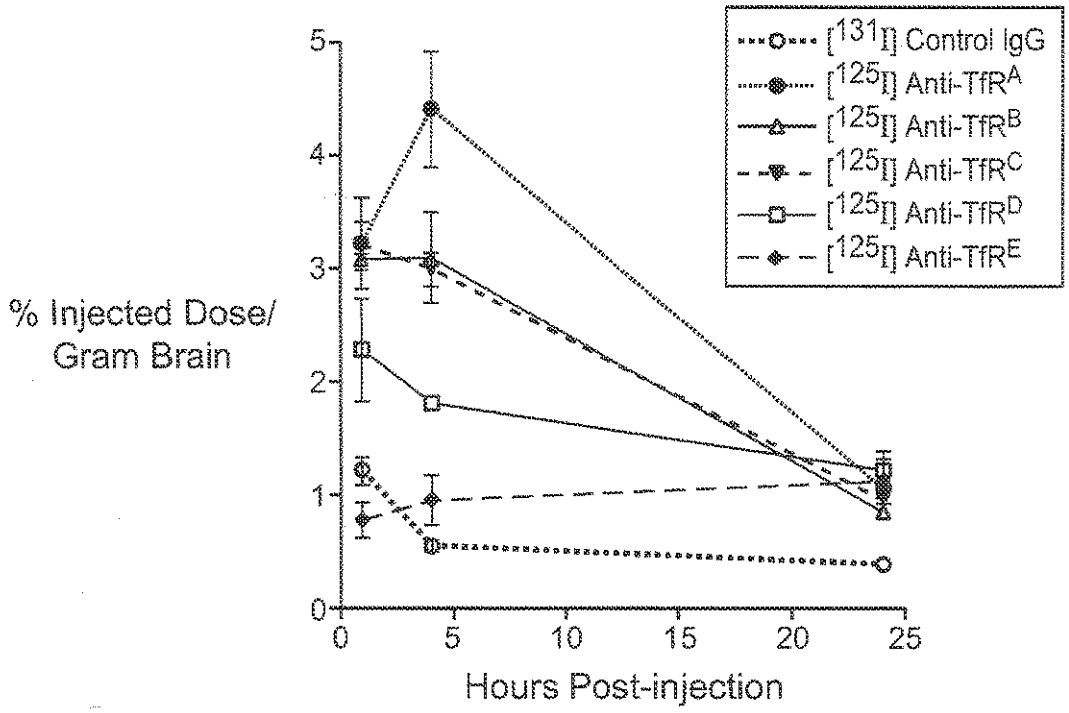

% Injected Dose/ Gram Brain
5
4
3
2
1
0
0 5 10 15 20 25
Hours Post-injection
[^{131}I] Control IgG
[^{125}I] Anti-TfR^{A}
[^{125}I] Anti-TfR^{B}
[^{125}I] Anti-TfR^{C}
[^{125}I] Anti-TfR^{D}
[^{125}I] Anti-TfR^{E}

FIG. 2B

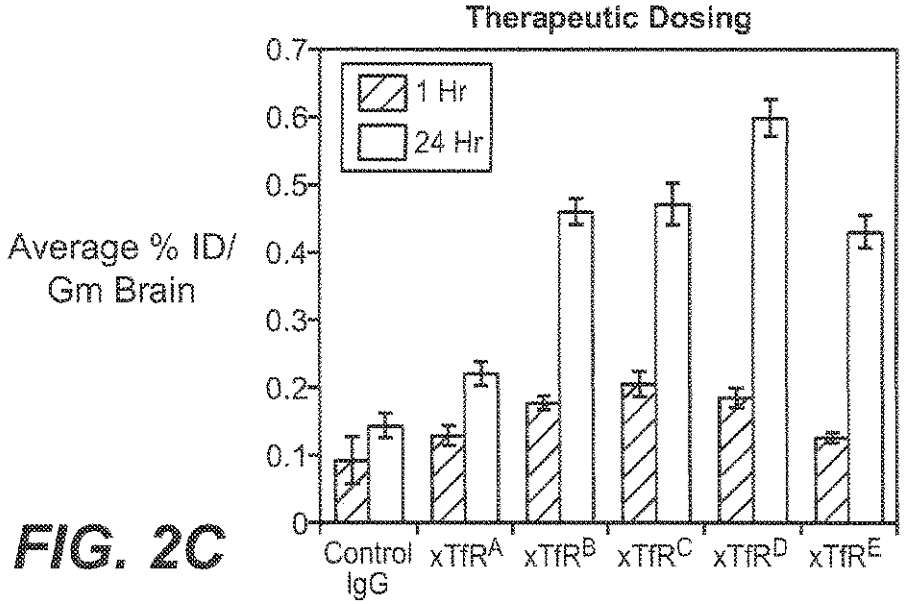

Therapeutic Dosing
Average % ID/ Gm Brain
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1 Hr
24 Hr
Control IgG
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E

FIG. 2C

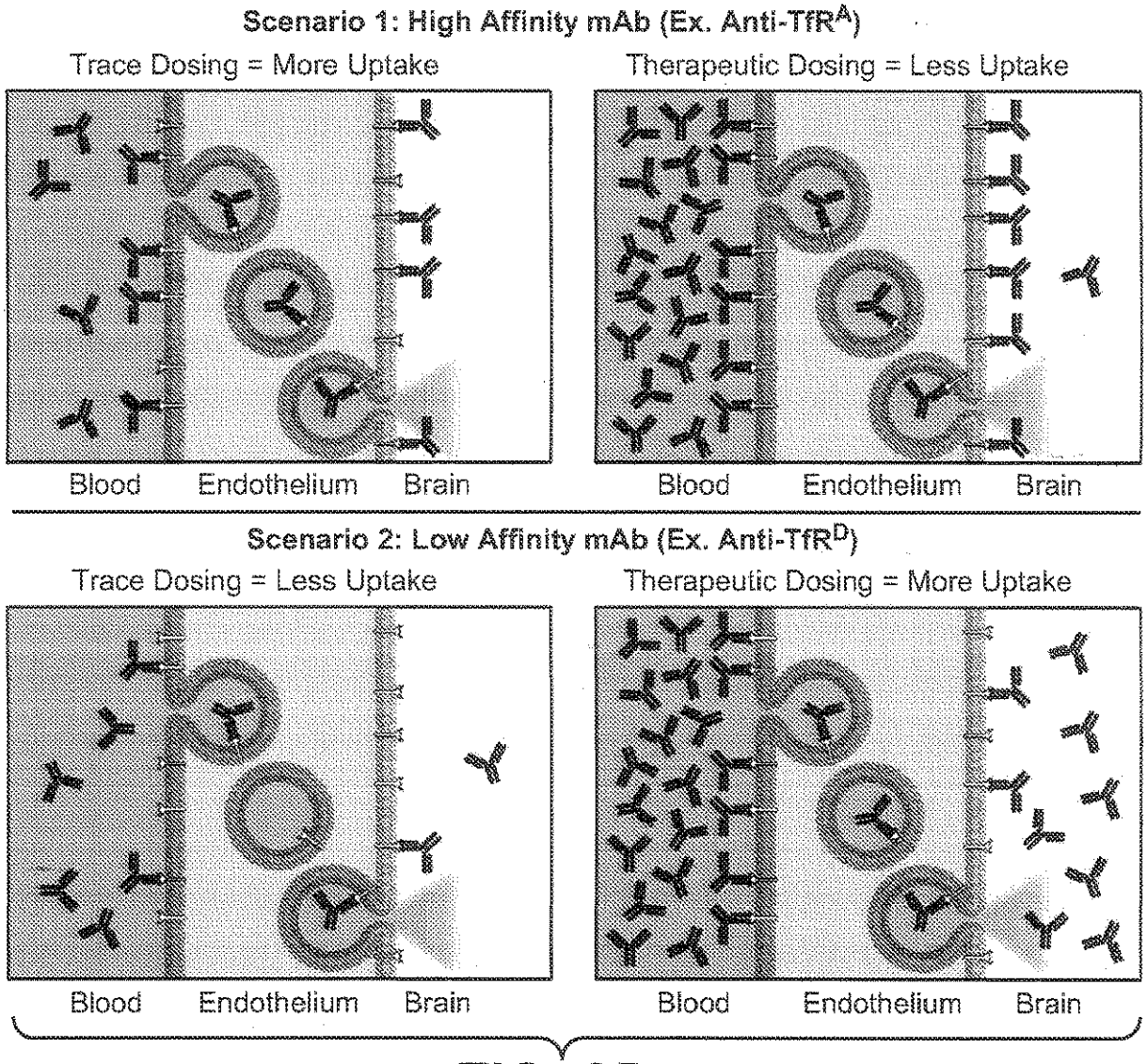

Scenario 1: High Affinity mAb (Ex. Anti-TfR^A)
Trace Dosing = More Uptake
Therapeutic Dosing = Less Uptake
Blood
Endothelium
Brain
Blood
Endothelium
Brain
Scenario 2: Low Affinity mAb (Ex. Anti-TfR^D)
Trace Dosing = Less Uptake
Therapeutic Dosing = More Uptake
Blood
Endothelium
Brain
Blood
Endothelium
Brain

FIG. 2D

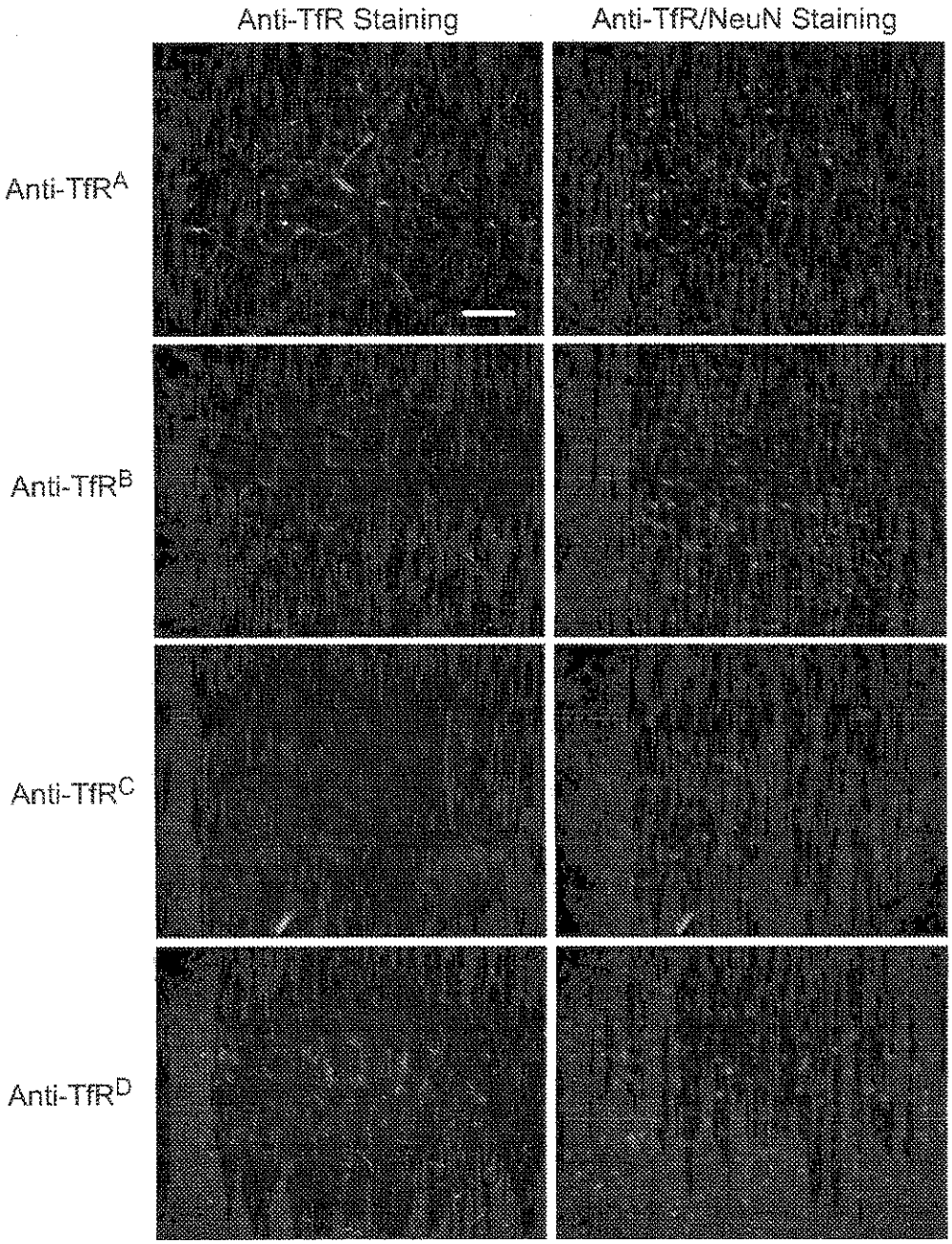

Anti-TfR Staining
Anti-TfR/NeuN Staining
Anti-TfR^A
Anti-TfR^B
Anti-TfR^C
Anti-TfR^D

FIG. 2E

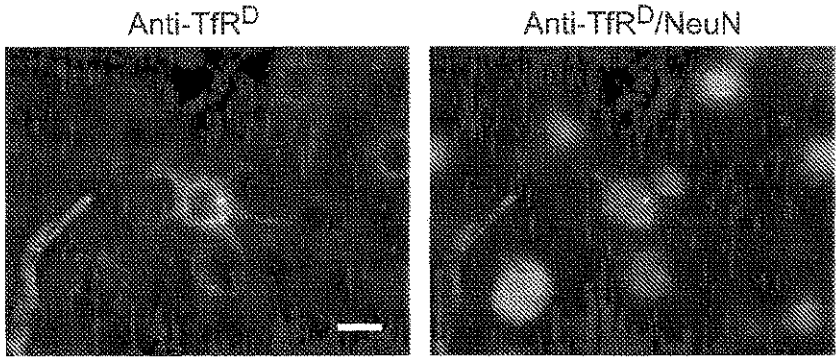

Anti-TfR^D
Anti-TfR^D/NeuN

FIG. 2F

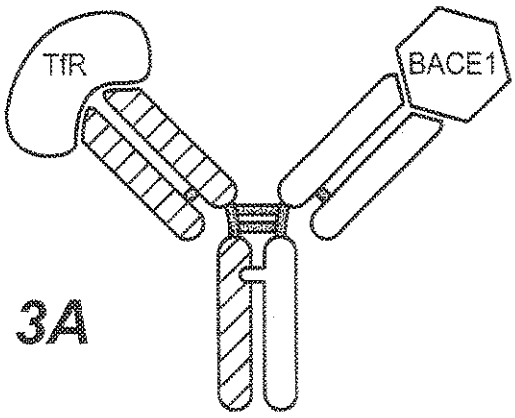


FIG. 3A

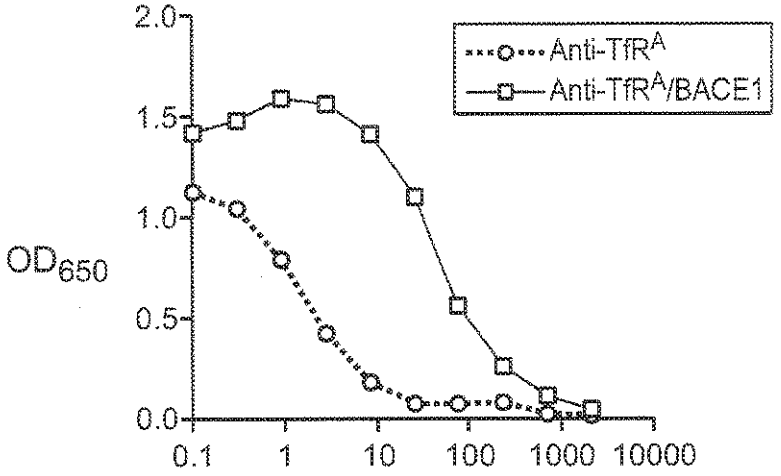


FIG. 3B Antibody Concentration (nM)

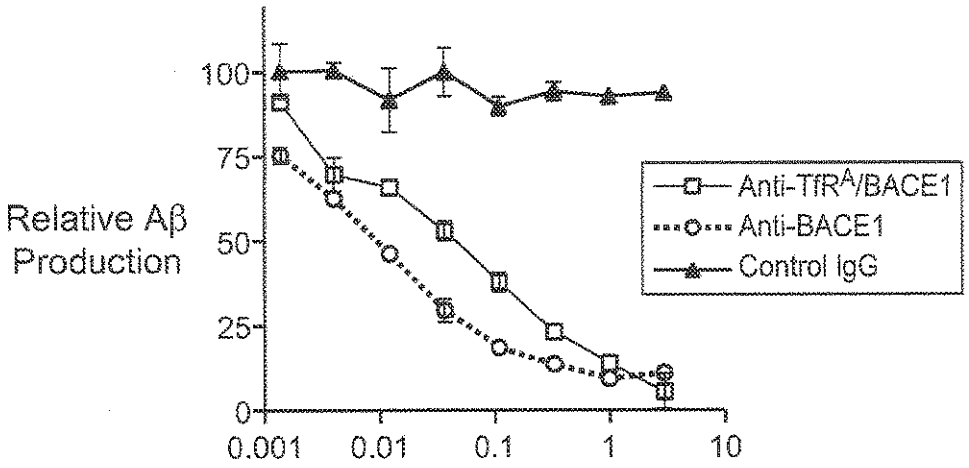


FIG. 3C Antibody Concentration (μM)

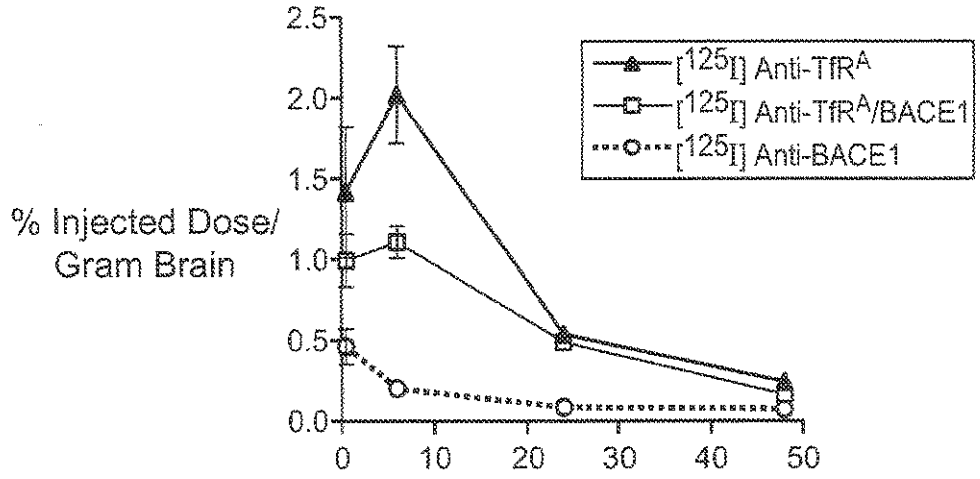


FIG. 3D

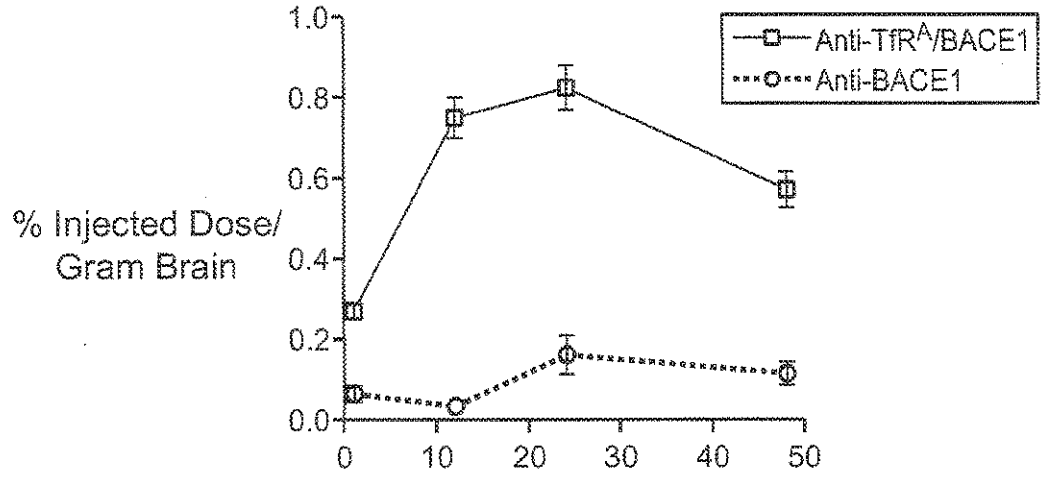


FIG. 3E

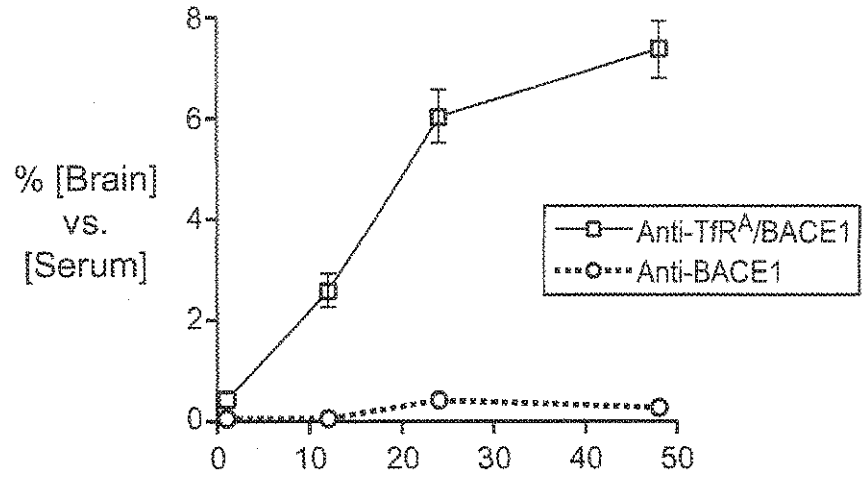


FIG. 3F

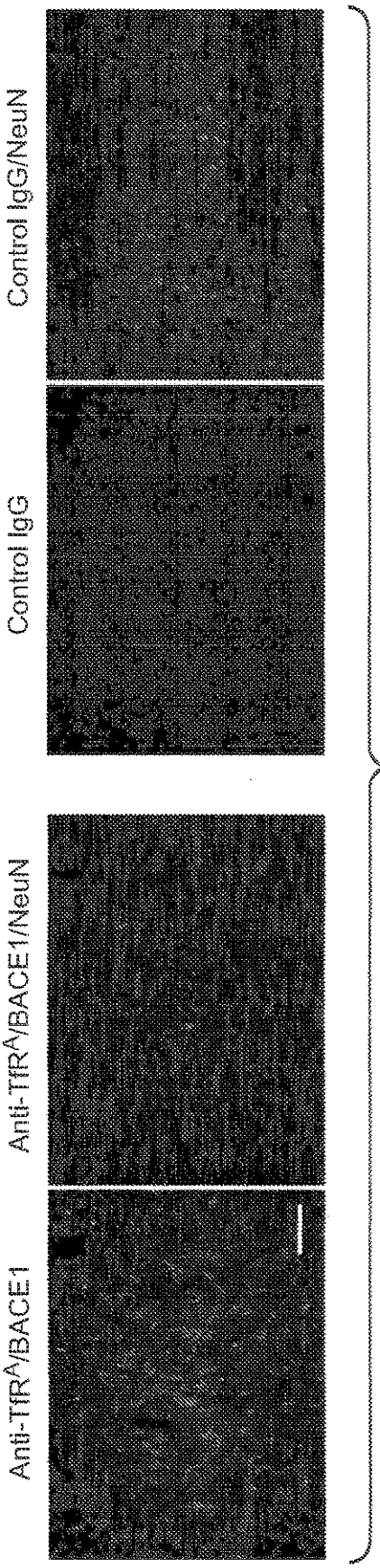

Anti-TfR^A/BACE1
Anti-TfR^A/BACE1/NeuN
Control IgG
Control IgG/NeuN

FIG. 3G

FIG. 4A

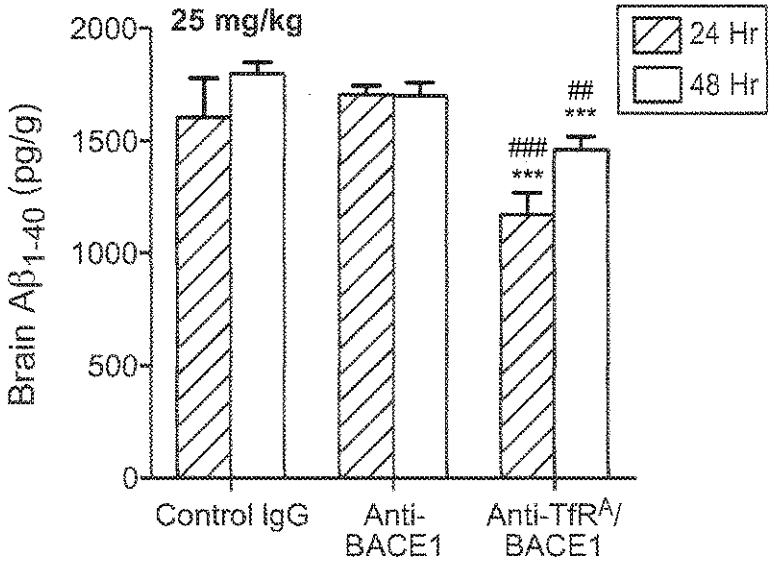


FIG. 4B

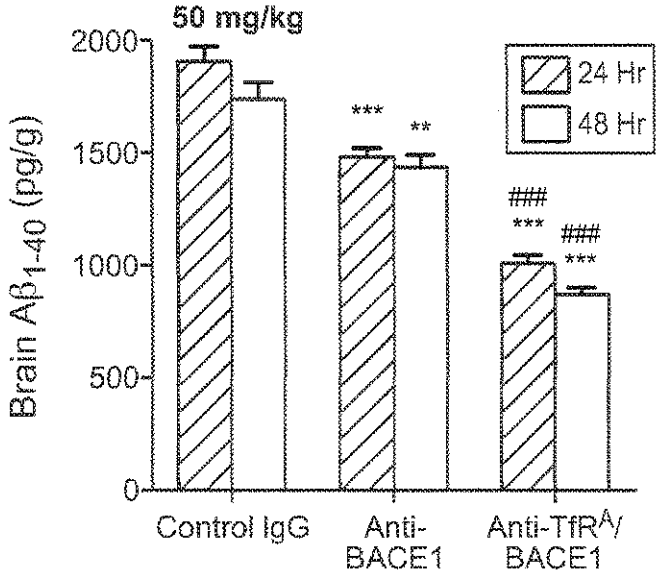


FIG. 4C

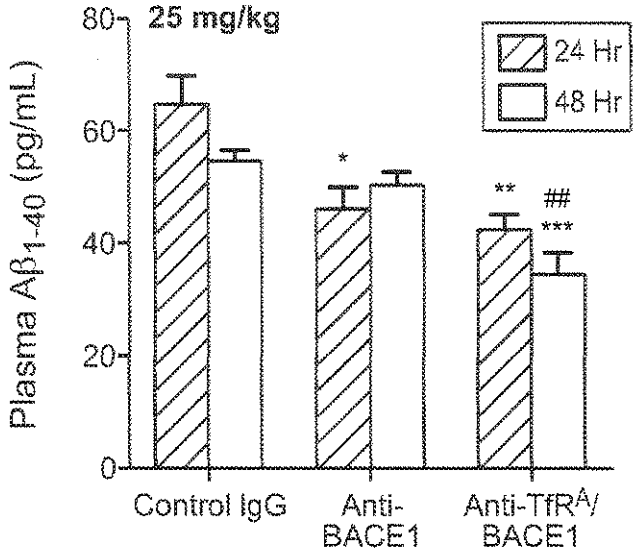


FIG. 4D

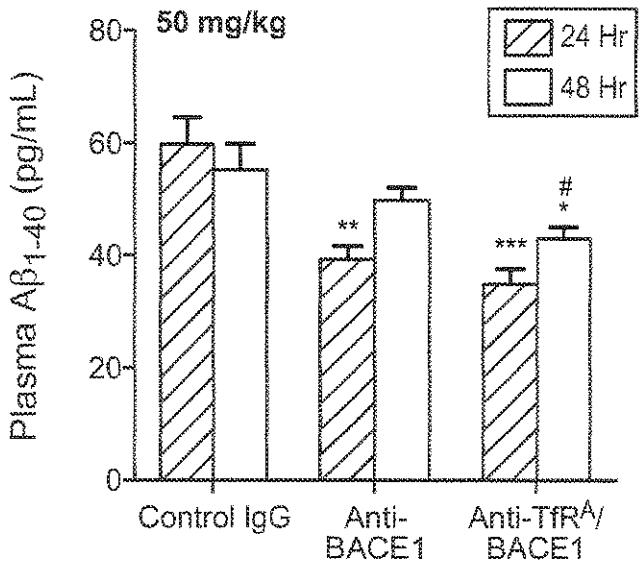
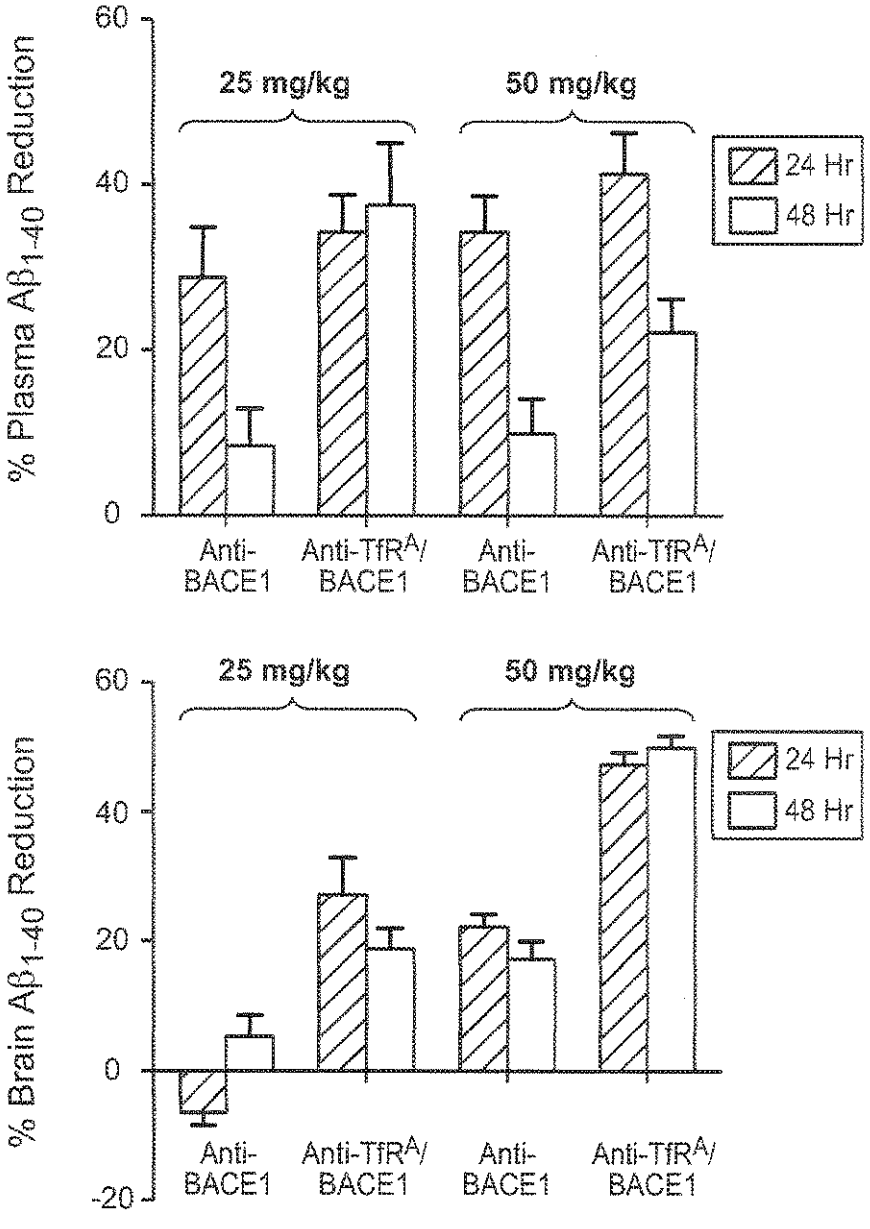

50 mg/kg
24 Hr
48 Hr
Plasma $A\beta_{1-40}$ (pg/mL)
80
60
40
20
0
**
***
#
*
Control IgG
Anti-BACE1
Anti-TfR^A/BACE1

FIG. 4E


% Plasma $A\beta_{1-40}$ Reduction
% Brain $A\beta_{1-40}$ Reduction
25 mg/kg
50 mg/kg
24 Hr
48 Hr
60
40
20
0
-20
Anti-BACE1
Anti-TfR^A/BACE1
Anti-BACE1
Anti-TfR^A/BACE1

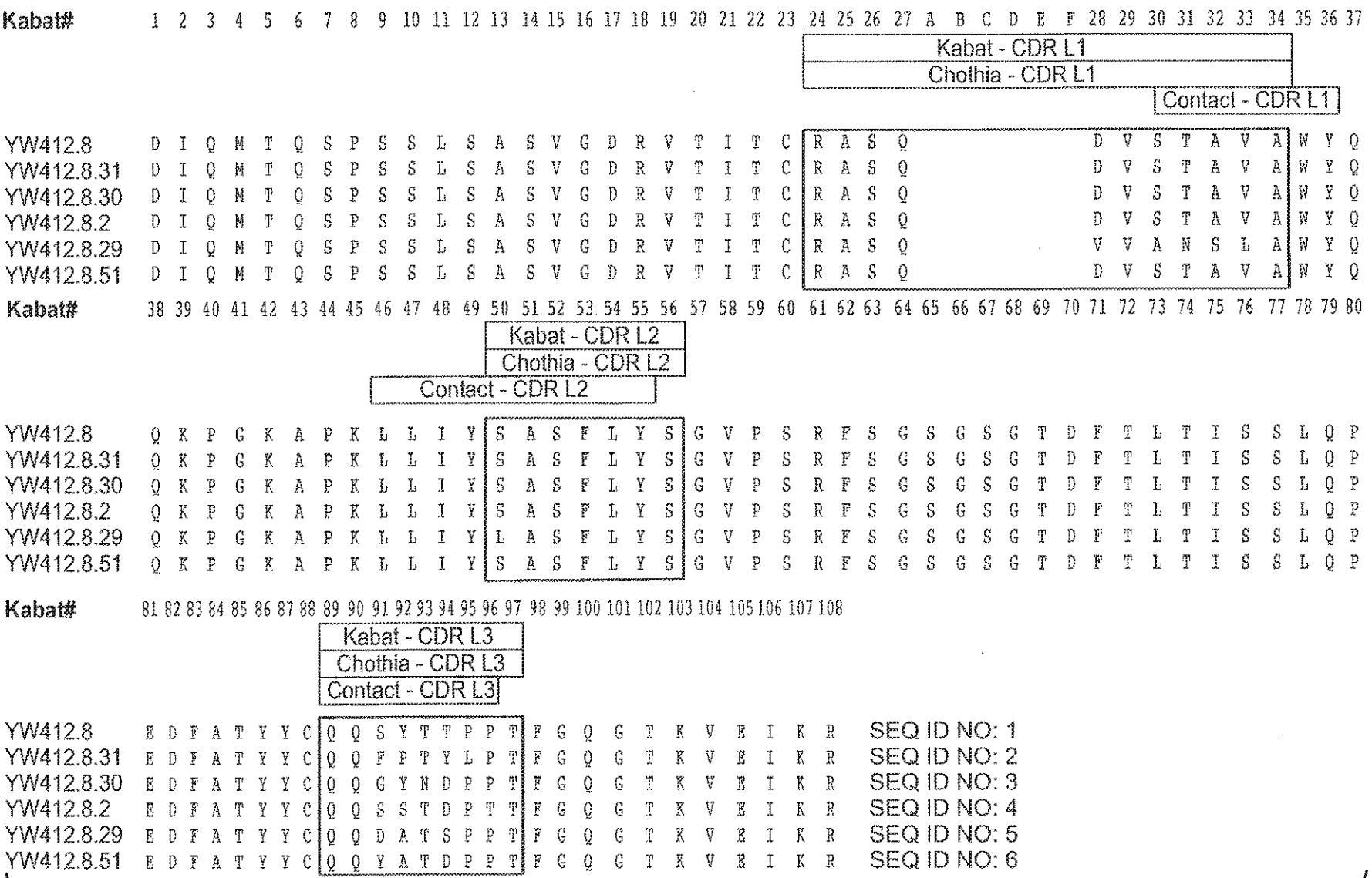

Kabat#
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Kabat - CDR L1
Chothia - CDR L1
Contact - CDR L1
YW412.8 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q
YW412.8.31 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q
YW412.8.30 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q
YW412.8.2 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q
YW412.8.29 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q V V A N S L A W Y Q
YW412.8.51 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q D V S T A V A W Y Q
Kabat#
38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
Kabat - CDR L2
Chothia - CDR L2
Contact - CDR L2
YW412.8 Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P
YW412.8.31 Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P
YW412.8.30 Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P
YW412.8.2 Q K P G K A P K L L I Y S A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P
YW412.8.29 Q K P G K A P K L L I Y L A S F L Y S G V P S R F S G S G S G T D F T L T I S S L Q P
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Kabat#
81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 101 102 103 104 105 106 107 108
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Chothia - CDR L3
Contact - CDR L3
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YW412.8.51 E D F A T Y Y C Q Q Y A T D P P T F G Q G T K V E I K R SEQ ID NO: 6

FIG. 5A

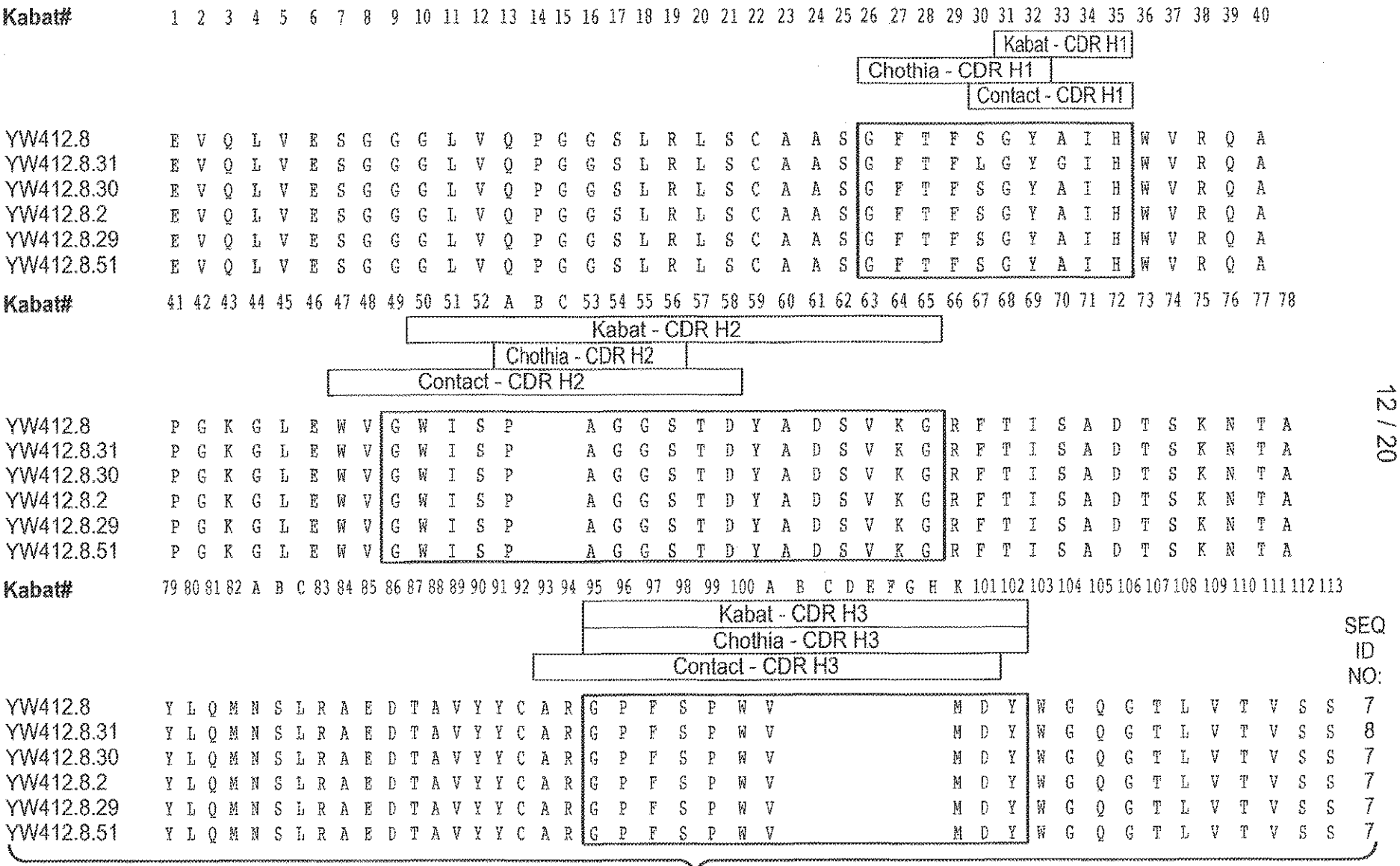

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Kabat - CDR H1
Chothia - CDR H1
Contact - CDR H1
YW412.8 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
YW412.8.31 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F L G Y G I H W V R Q A
YW412.8.30 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
YW412.8.2 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
YW412.8.29 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
YW412.8.51 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
Kabat#
41 42 43 44 45 46 47 48 49 50 51 52 A B C 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78
Kabat - CDR H2
Chothia - CDR H2
Contact - CDR H2
YW412.8 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
YW412.8.31 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
YW412.8.30 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
YW412.8.2 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
YW412.8.29 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
YW412.8.51 P G K G L E W V G W I S P A G G S T D Y A D S V K G R F T I S A D T S K N T A
Kabat#
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Kabat - CDR H3
Chothia - CDR H3
Contact - CDR H3
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FIG. 5B

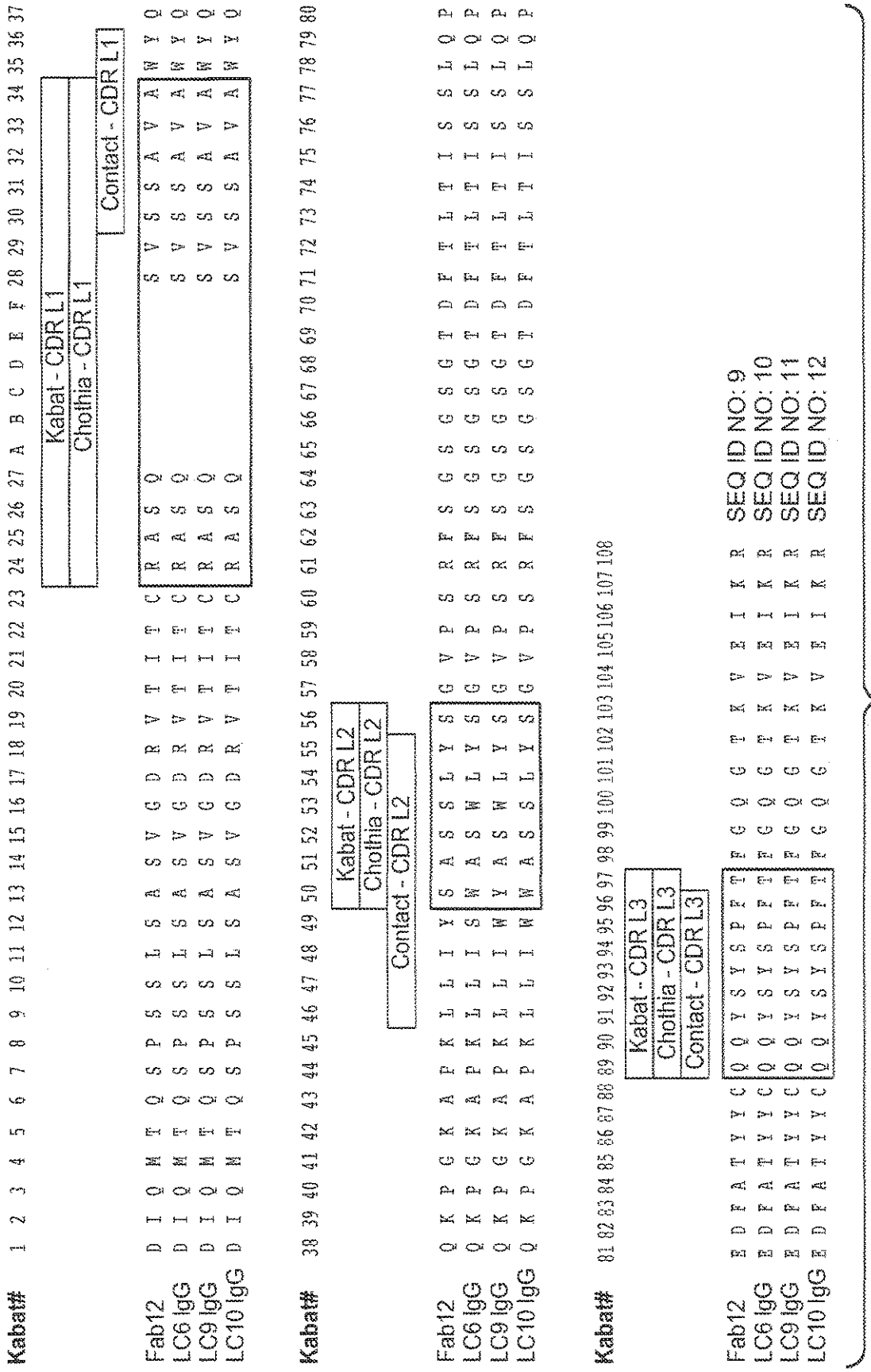

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Chothia - CDR L1
Contact - CDR L1
Kabat - CDR L2
Chothia - CDR L2
Contact - CDR L2
Kabat - CDR L3
Chothia - CDR L3
Contact - CDR L3
SEQ ID NO: 9
SEQ ID NO: 10
SEQ ID NO: 11
SEQ ID NO: 12

FIG. 6A

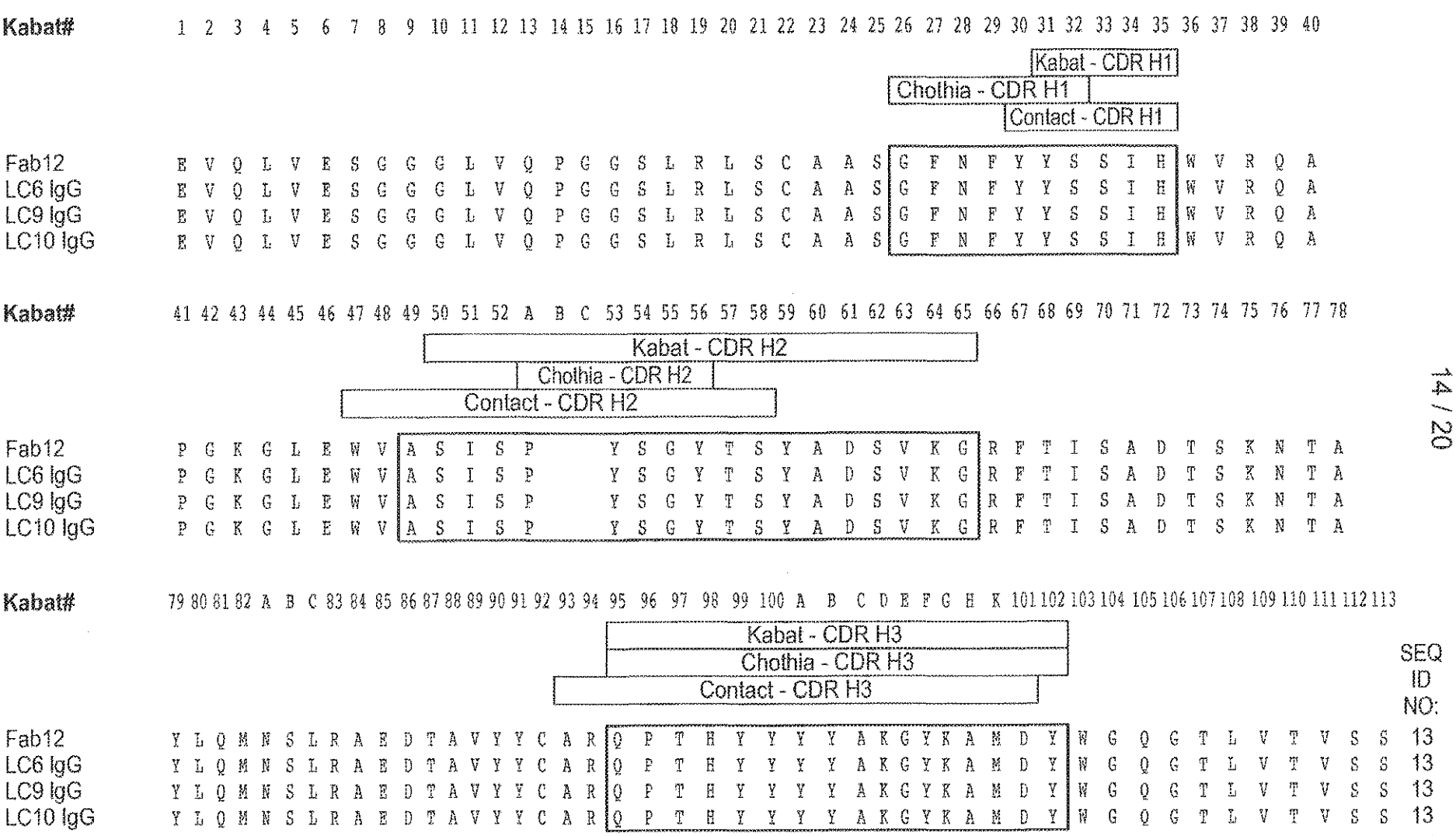

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Chothia - CDR H1
Contact - CDR H1
Fab12 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N F Y Y S S I H W V R Q A
LC6 IgG E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N F Y Y S S I H W V R Q A
LC9 IgG E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N F Y Y S S I H W V R Q A
LC10 IgG E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N F Y Y S S I H W V R Q A
Kabat#
41 42 43 44 45 46 47 48 49 50 51 52 A B C 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78
Kabat - CDR H2
Chothia - CDR H2
Contact - CDR H2
Fab12 P G K G L E W V A S I S P Y S G Y T S Y A D S V K G R F T I S A D T S K N T A
LC6 IgG P G K G L E W V A S I S P Y S G Y T S Y A D S V K G R F T I S A D T S K N T A
LC9 IgG P G K G L E W V A S I S P Y S G Y T S Y A D S V K G R F T I S A D T S K N T A
LC10 IgG P G K G L E W V A S I S P Y S G Y T S Y A D S V K G R F T I S A D T S K N T A
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Kabat - CDR H3
Chothia - CDR H3
Contact - CDR H3
SEQ ID NO:
Fab12 Y L Q M N S L R A E D T A V Y Y C A R Q P T H Y Y Y Y A K G Y K A M D Y W G Q G T L V T V S S 13
LC6 IgG Y L Q M N S L R A E D T A V Y Y C A R Q P T H Y Y Y Y A K G Y K A M D Y W G Q G T L V T V S S 13
LC9 IgG Y L Q M N S L R A E D T A V Y Y C A R Q P T H Y Y Y Y A K G Y K A M D Y W G Q G T L V T V S S 13
LC10 IgG Y L Q M N S L R A E D T A V Y Y C A R Q P T H Y Y Y Y A K G Y K A M D Y W G Q G T L V T V S S 13

FIG. 6B

```
  1 EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYGMSWVRQA PGKGLELVAS
 51 INSNGGSTYY PDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCASGD
101 YWGQGTTVTV SSASTKGPSV FPLAPCSRST SESTAALGCL VKDYFPEPVT
151 VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT KTYTCNVDHK
201 PSNTKVDKRV ESKYGPPCPP CPAPEFLGGP SVFLFPPKPK DTLMISRTPE
251 VTCVVVDVSQ EDPEVQFNWY VDGVEVHNAK TKPREEQFNS TYRVVSVLTV
301 LHQDWLNGKE YKCKVSNKGL PSSIEKTISK AKGQPREPQV YTLPPSQEEM
351 TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL DSDGSFFLYS
401 RLTVDKSRWQ EGNVFSCSVM HEALHNHYTQ KSLSLSLG (SEQ ID NO: 14)
```

FIG. 7A

```
  1 DIVMTQSPLS LPVTPGEPAS ISCRSSQSLV YSNGDTYLHW YLQKPGQSPQ
 51 LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHVP
101 WTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
151 VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
201 VTHQGLSSPV TKSFNRGEC (SEQ ID NO: 15)
```

FIG. 7B

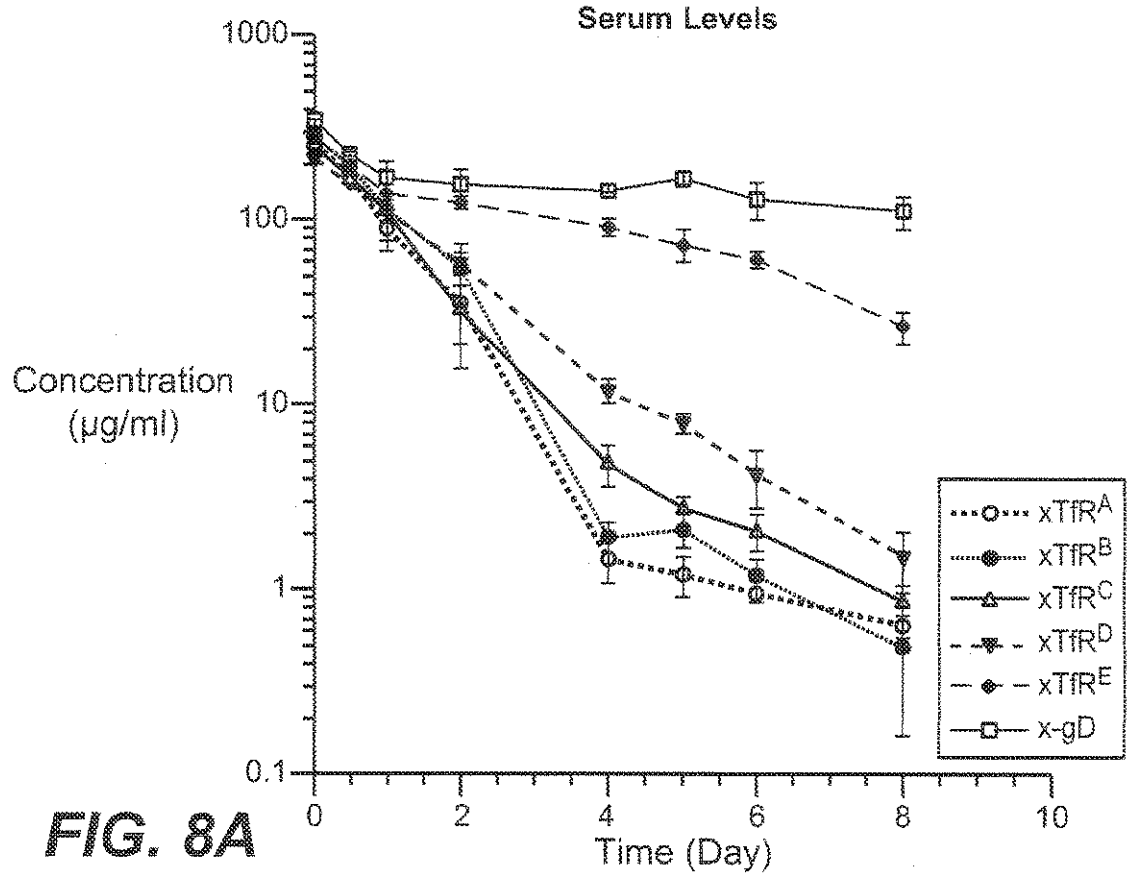

Serum Levels
1000
100
10
1
0.1
Concentration (µg/ml)
0
2
4
6
8
10
Time (Day)
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E
x-gD

FIG. 8A

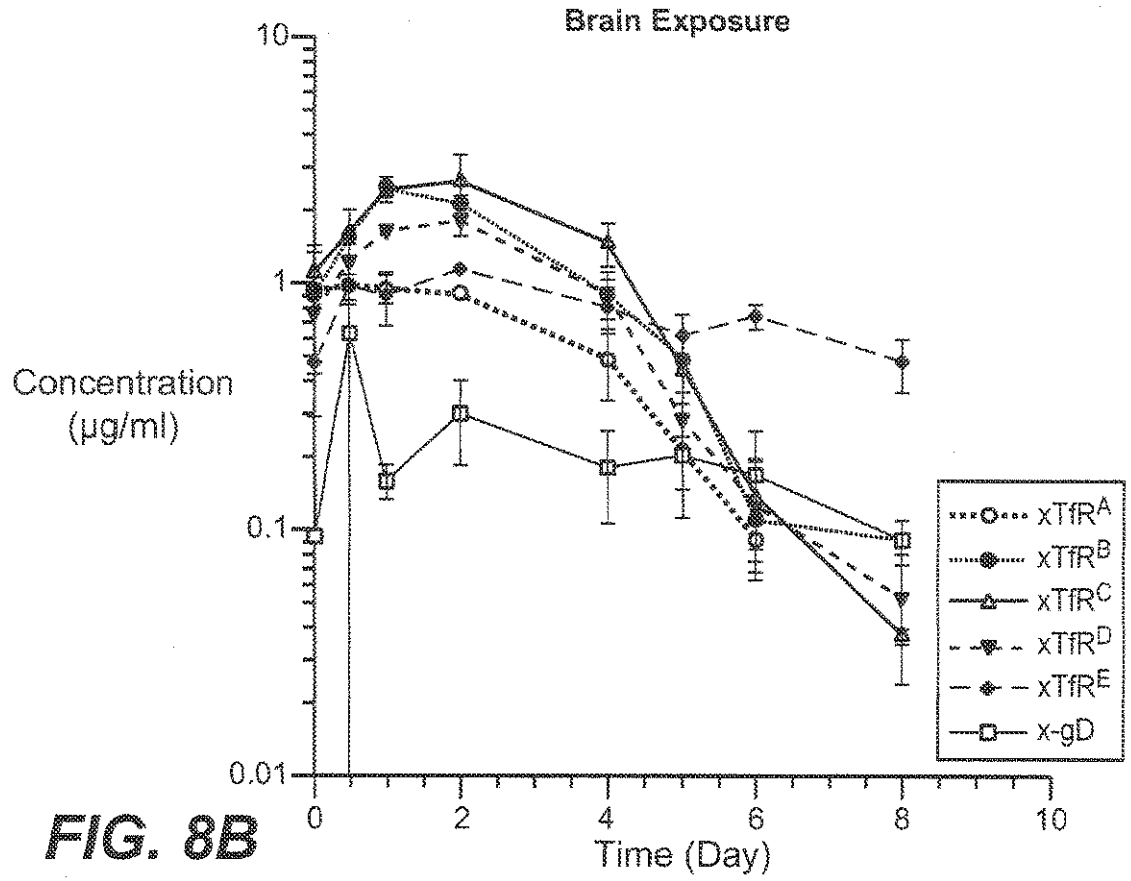

Brain Exposure
10
1
0.1
0.01
Concentration (µg/ml)
0
2
4
6
8
10
Time (Day)
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E
x-gD

FIG. 8B

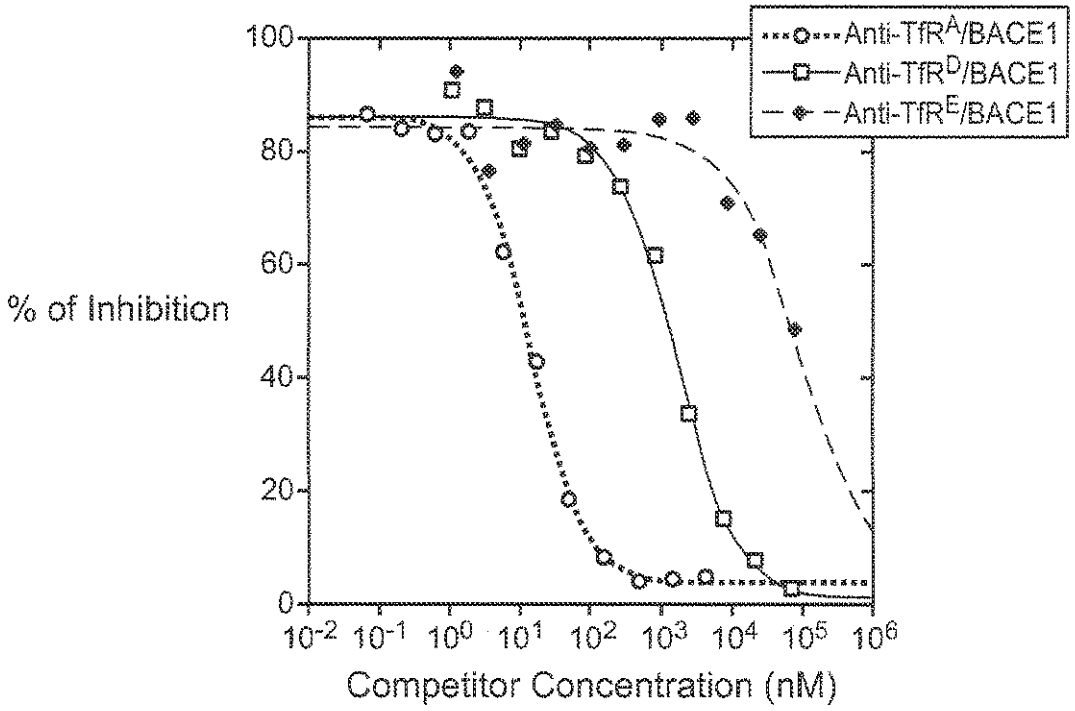

Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1
% of Inhibition
100
80
60
40
20
0
10^-2 10^-1 10^0 10^1 10^2 10^3 10^4 10^5 10^6
Competitor Concentration (nM)

FIG. 9A

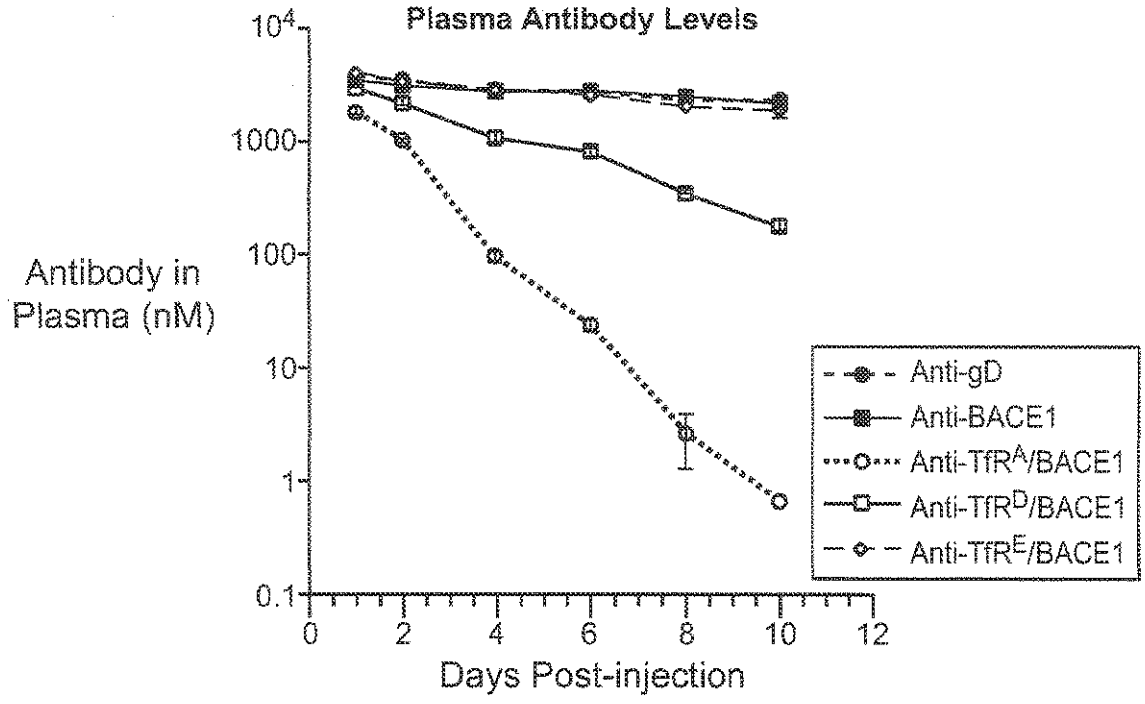

Plasma Antibody Levels
Antibody in Plasma (nM)
10^4
1000
100
10
1
0.1
0 2 4 6 8 10 12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9B

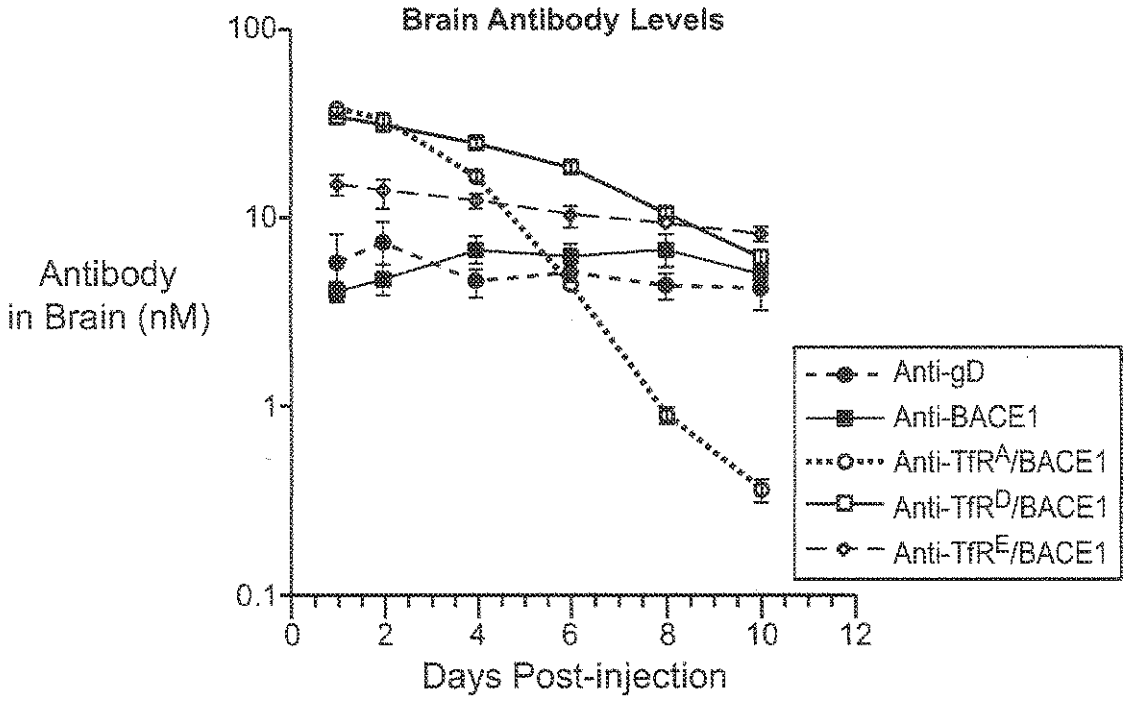

Brain Antibody Levels
Antibody in Brain (nM)
100
10
1
0.1
0
2
4
6
8
10
12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9C

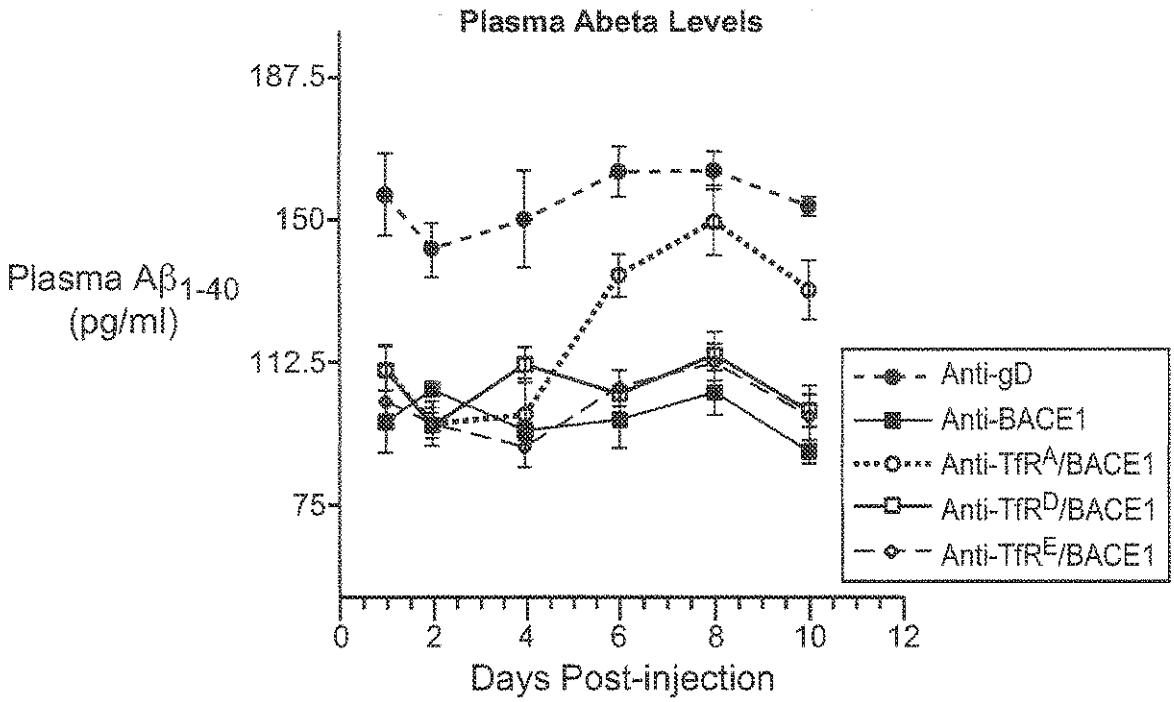

Plasma Abeta Levels
Plasma Aβ1-40 (pg/ml)
187.5
150
112.5
75
0
2
4
6
8
10
12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9D

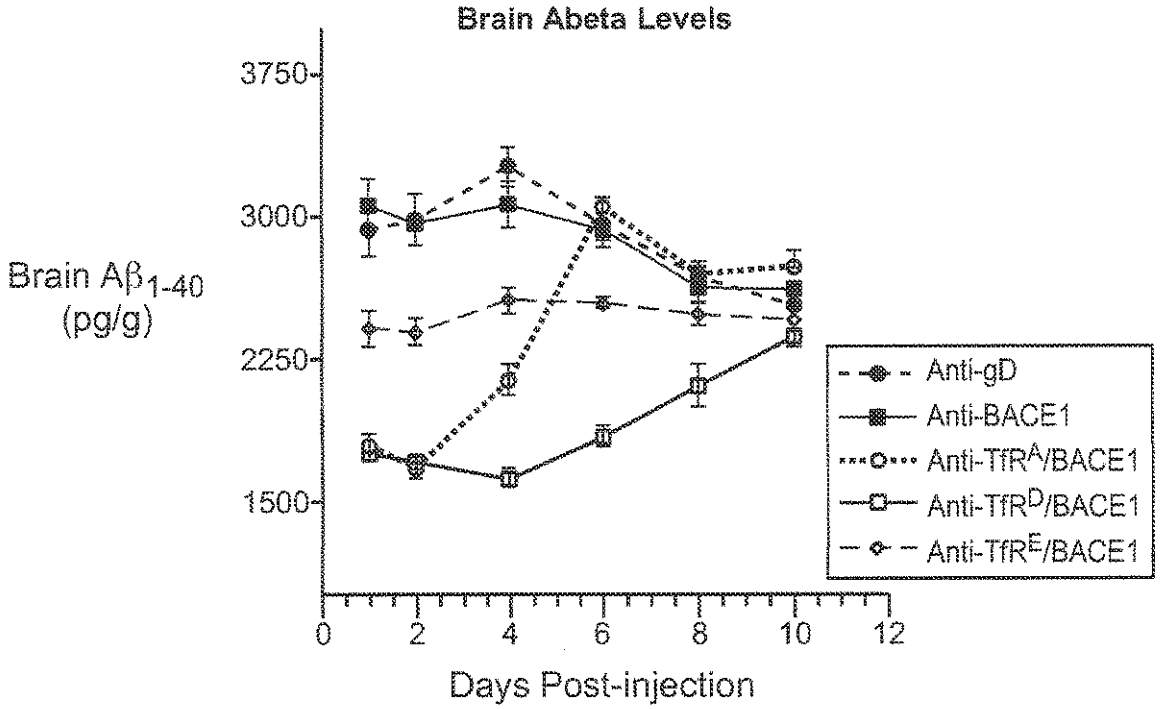


FIG. 9E

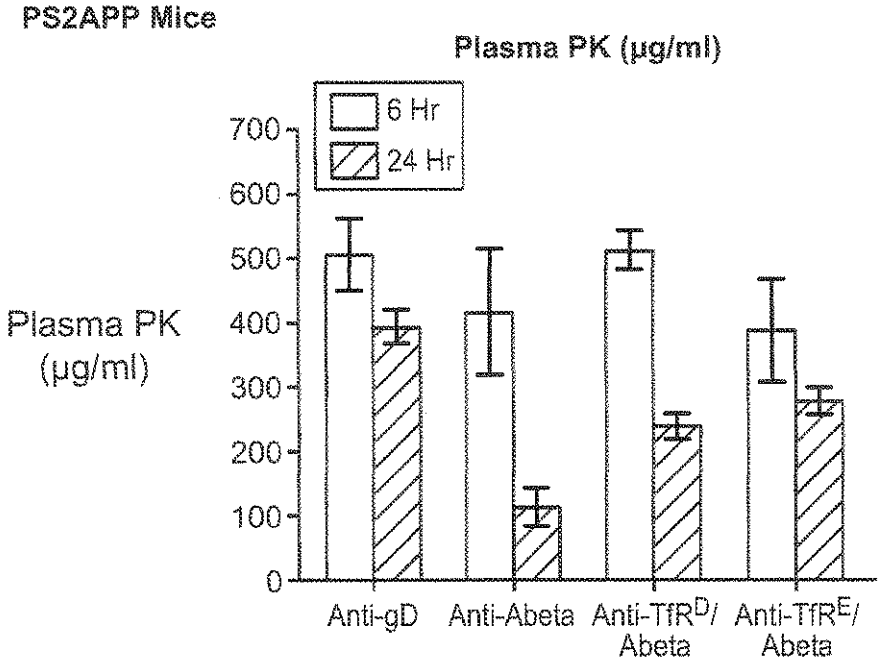


FIG. 10A

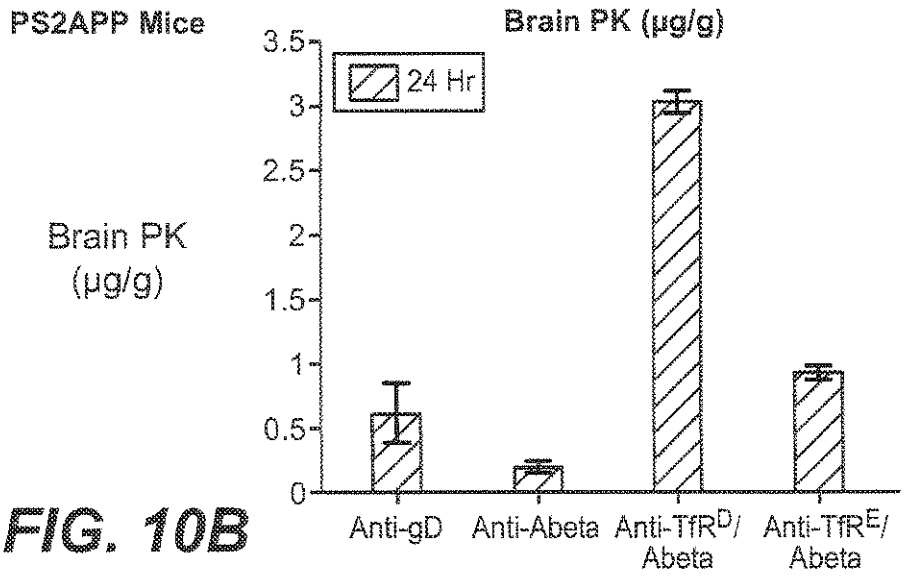


FIG. 10B

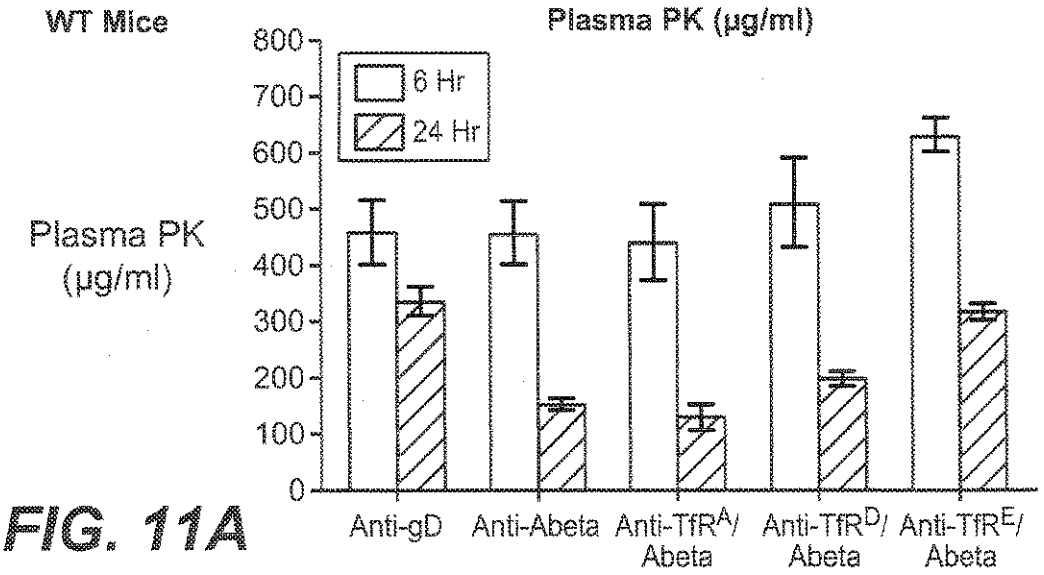


FIG. 11A

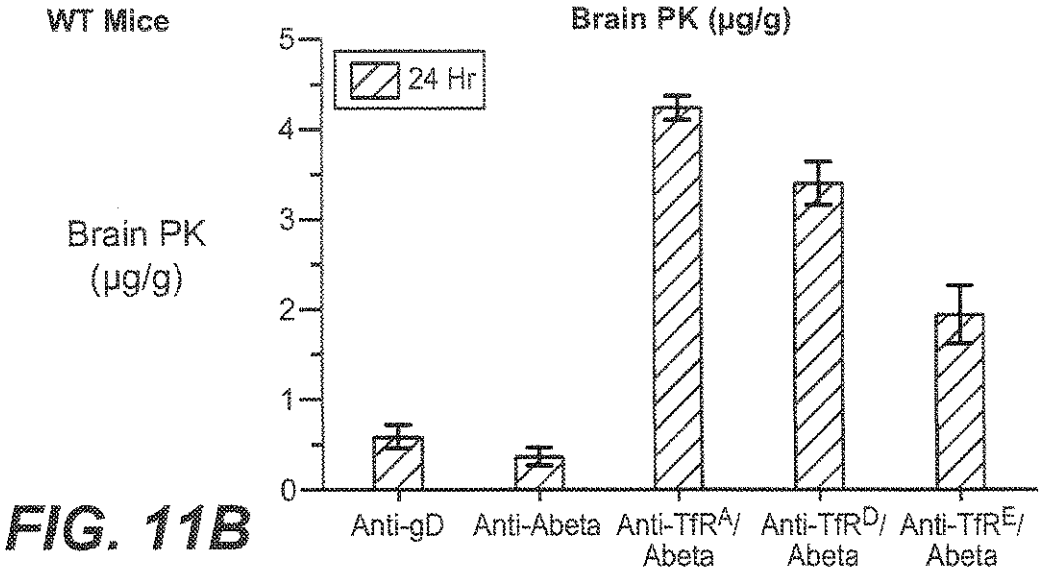


FIG. 11B