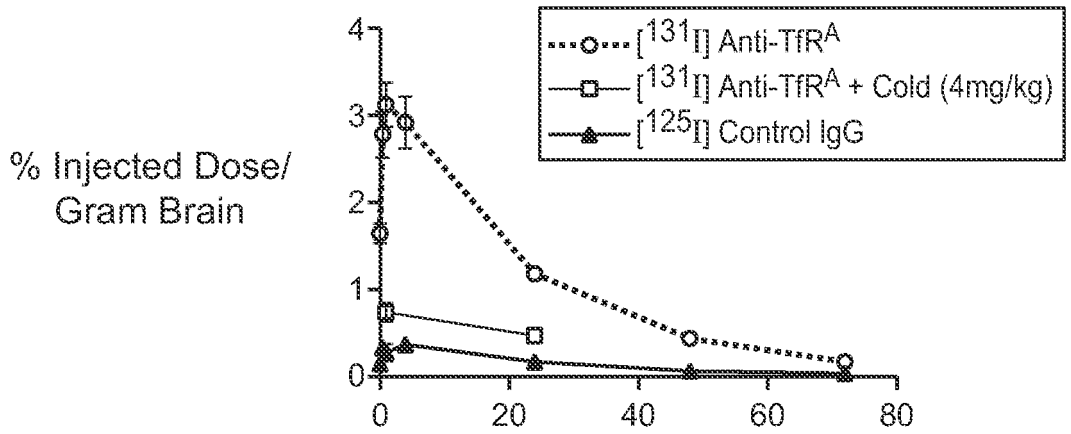


FIG. 1A

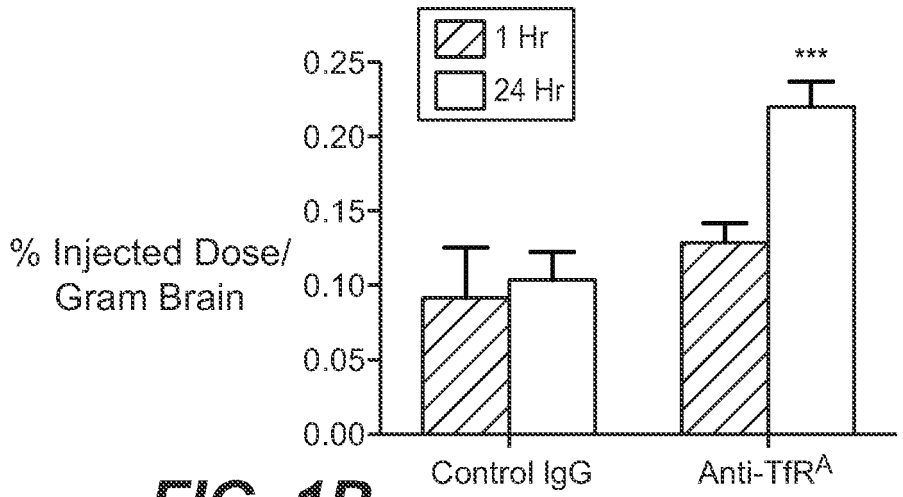


FIG. 1B

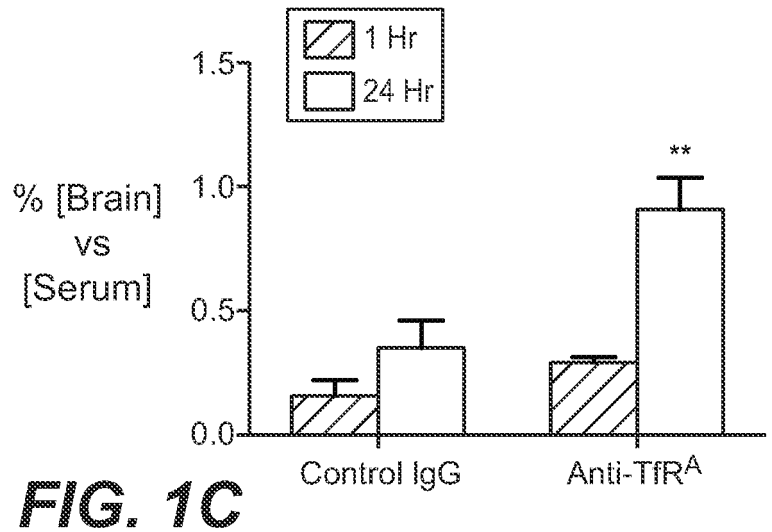


FIG. 1C

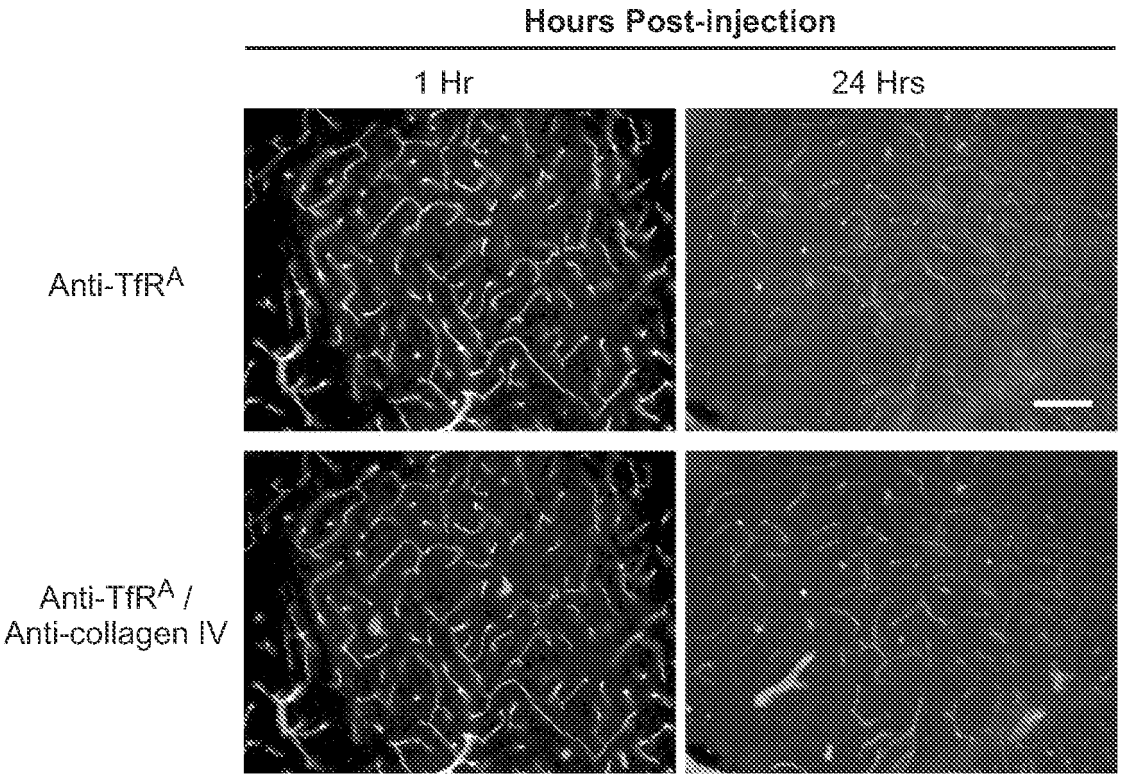

Hours Post-injection
1 Hr
24 Hrs
Anti-TfR^A
Anti-TfR^A / Anti-collagen IV

FIG. 1D

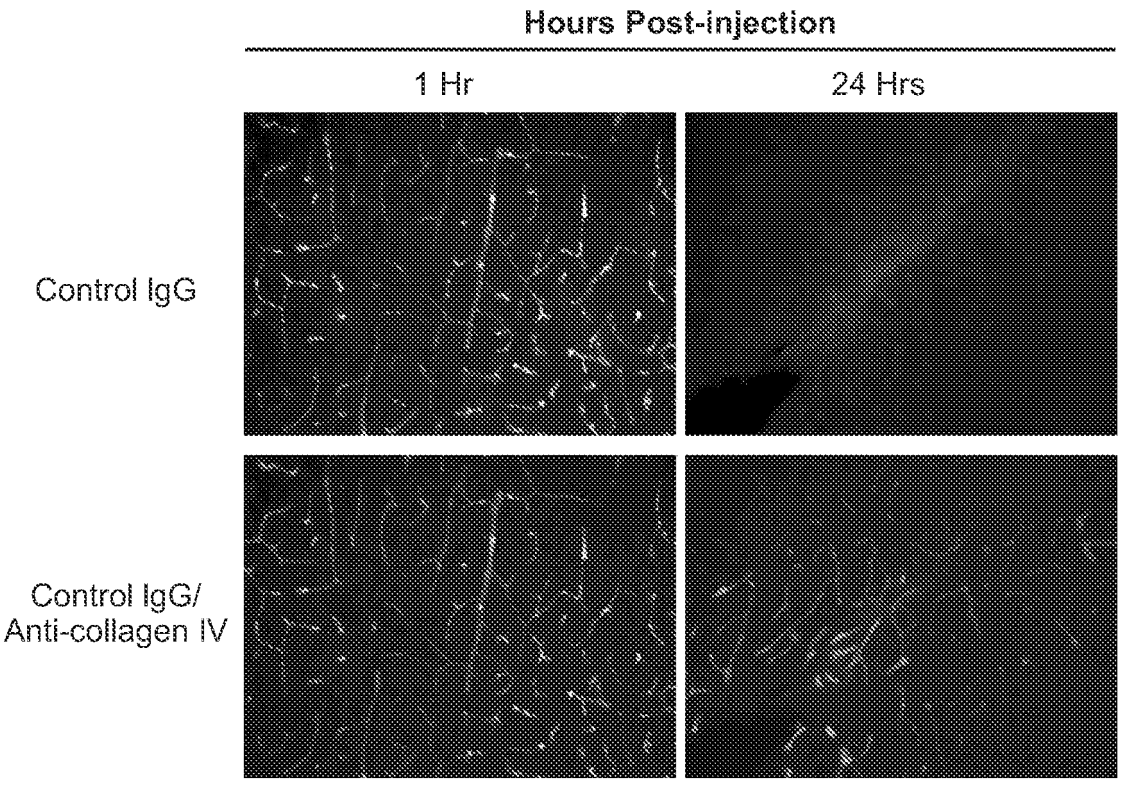

Hours Post-injection
1 Hr
24 Hrs
Control IgG
Control IgG/ Anti-collagen IV

FIG. 1E

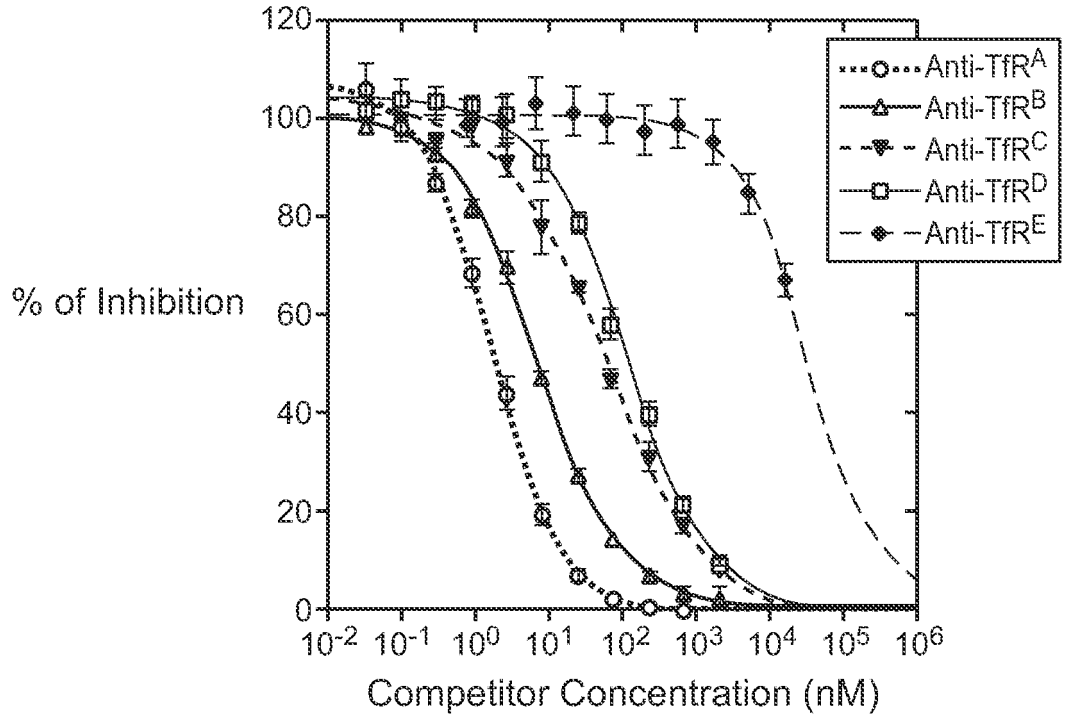

% of Inhibition
120
100
80
60
40
20
0
10^{-2} 10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4} 10^{5} 10^{6}
Competitor Concentration (nM)
Anti-TfR^{A}
Anti-TfR^{B}
Anti-TfR^{C}
Anti-TfR^{D}
Anti-TfR^{E}

FIG. 2A

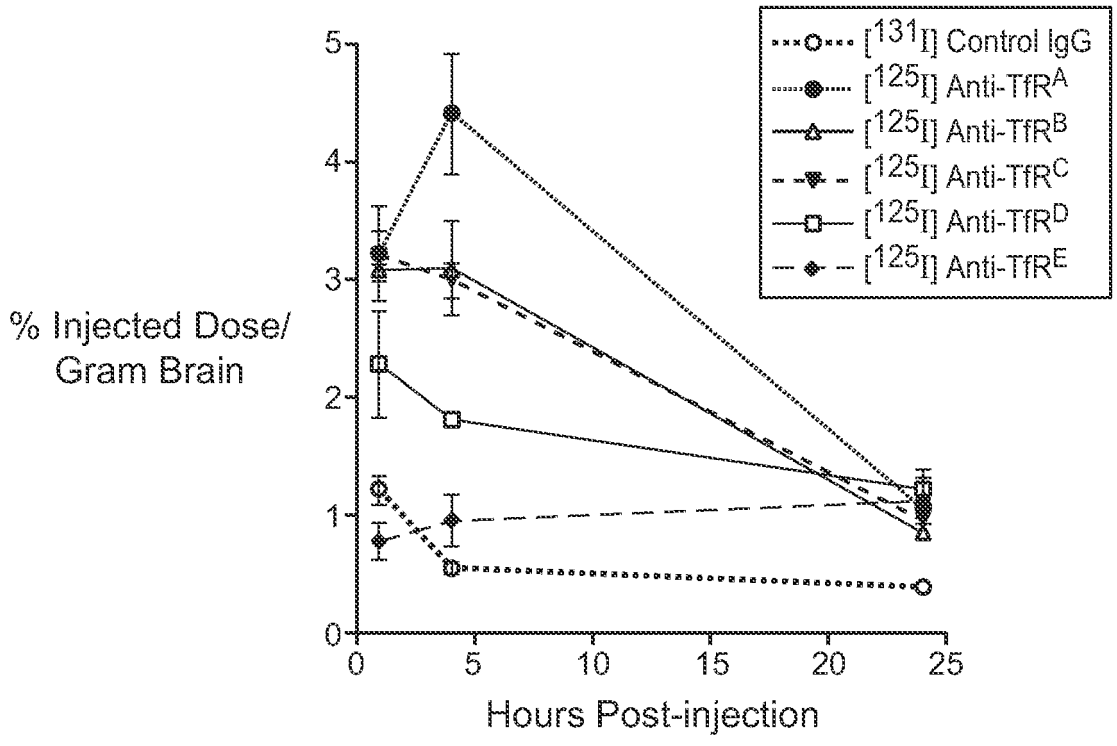

% Injected Dose/
Gram Brain
5
4
3
2
1
0
0 5 10 15 20 25
Hours Post-injection
[^{131}I] Control IgG
[^{125}I] Anti-TfR^{A}
[^{125}I] Anti-TfR^{B}
[^{125}I] Anti-TfR^{C}
[^{125}I] Anti-TfR^{D}
[^{125}I] Anti-TfR^{E}

FIG. 2B

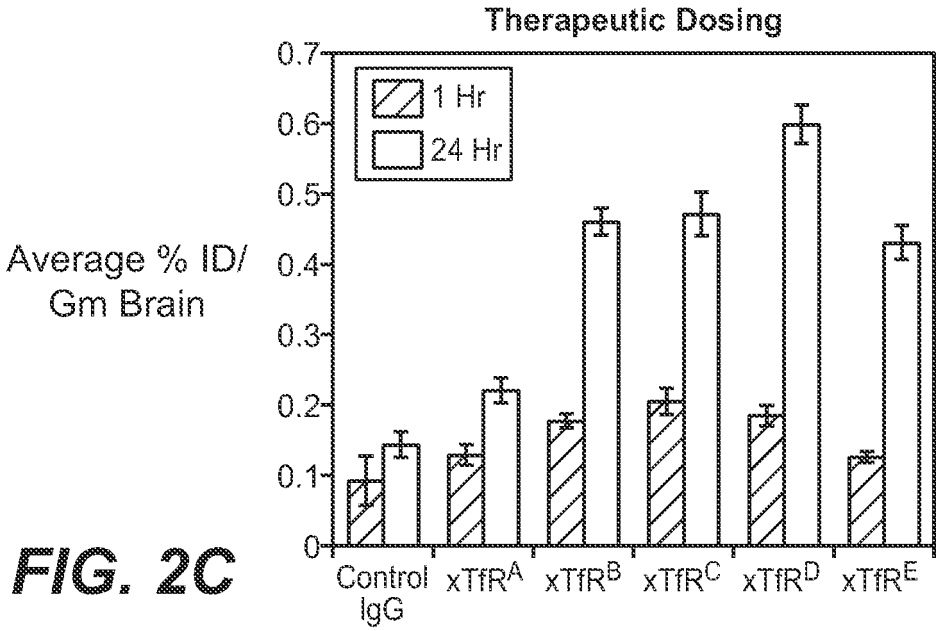

Therapeutic Dosing
Average % ID/ Gm Brain
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1 Hr
24 Hr
Control IgG
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E

FIG. 2C

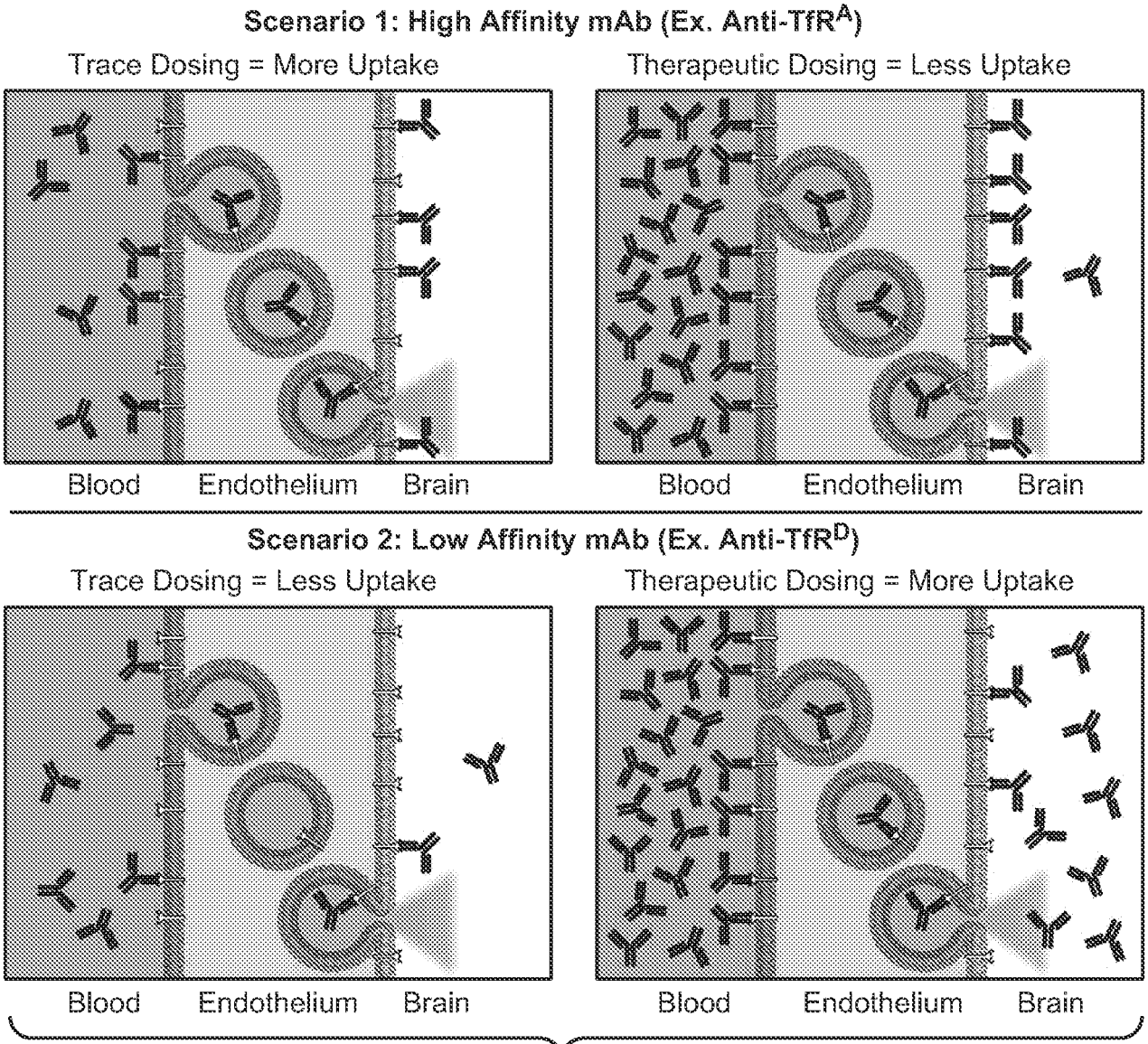

Scenario 1: High Affinity mAb (Ex. Anti-TfR^A)
Trace Dosing = More Uptake
Therapeutic Dosing = Less Uptake
Blood
Endothelium
Brain
Blood
Endothelium
Brain
Scenario 2: Low Affinity mAb (Ex. Anti-TfR^D)
Trace Dosing = Less Uptake
Therapeutic Dosing = More Uptake
Blood
Endothelium
Brain
Blood
Endothelium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

FIG. 2D

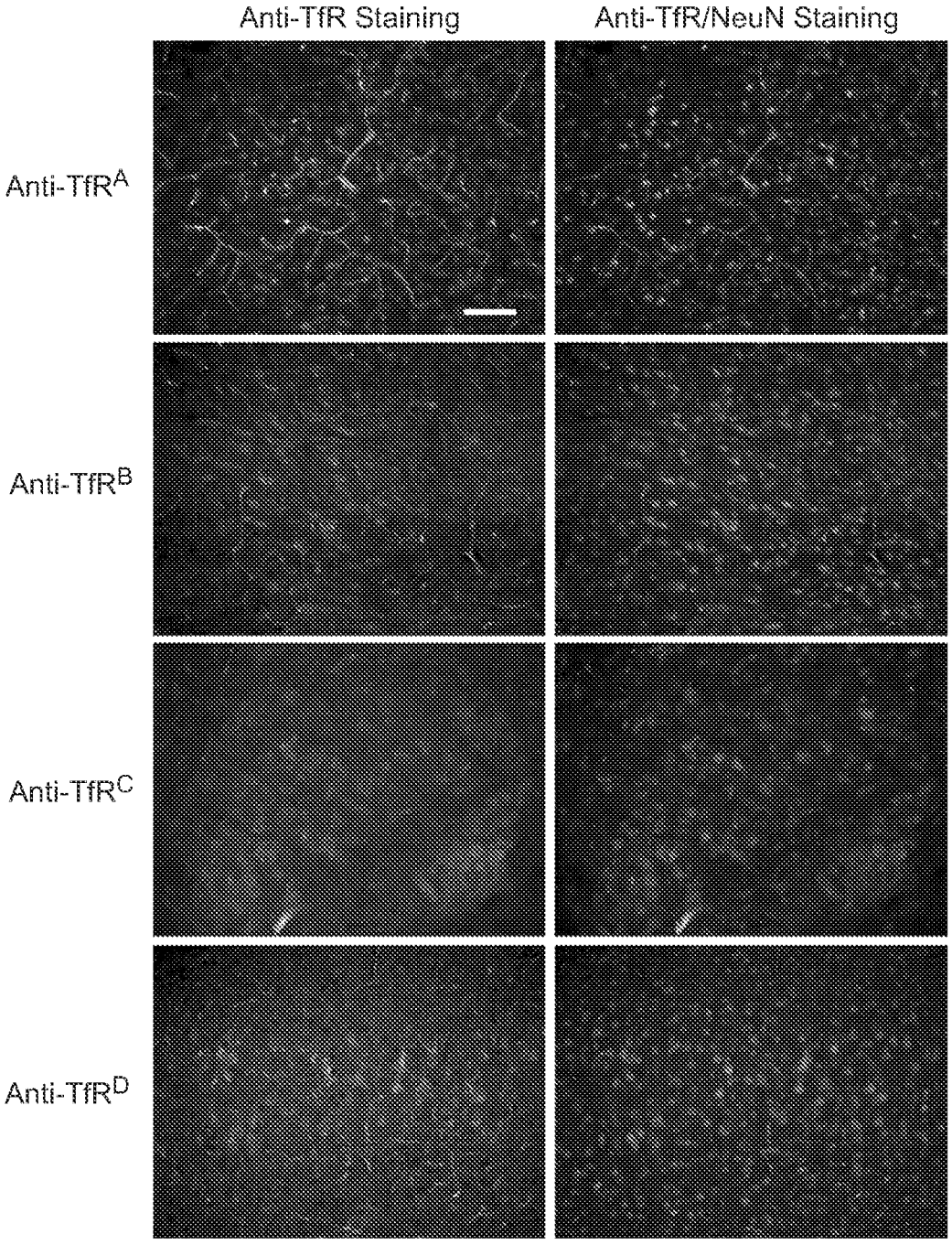

Anti-TfR Staining
Anti-TfR/NeuN Staining
Anti-TfR^{A}
Anti-TfR^{B}
Anti-TfR^{C}
Anti-TfR^{D}

FIG. 2E

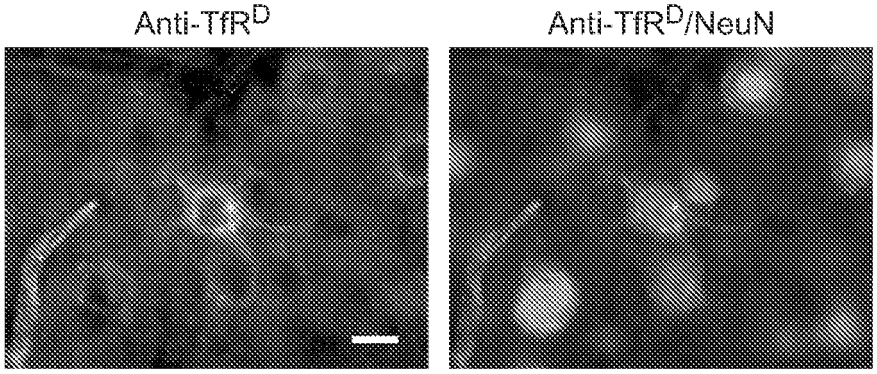

Anti-TfR^{D}
Anti-TfR^{D}/NeuN

FIG. 2F

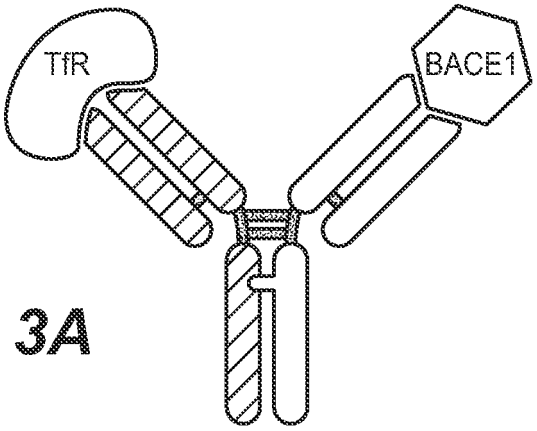


FIG. 3A

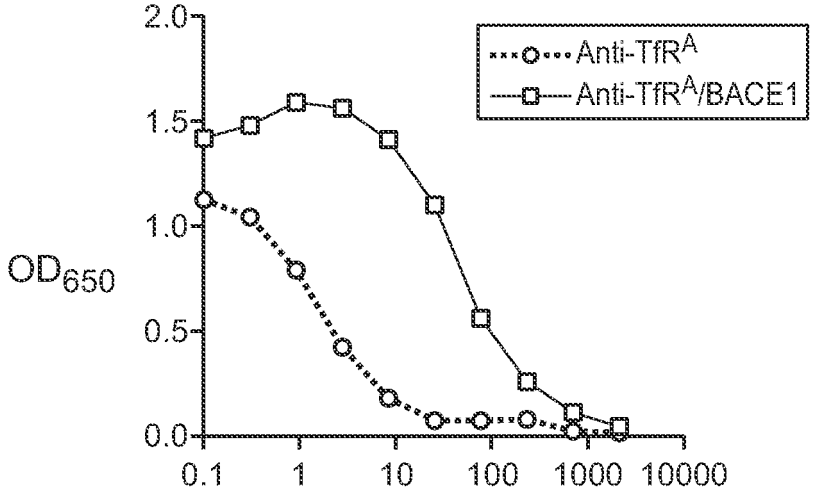


FIG. 3B

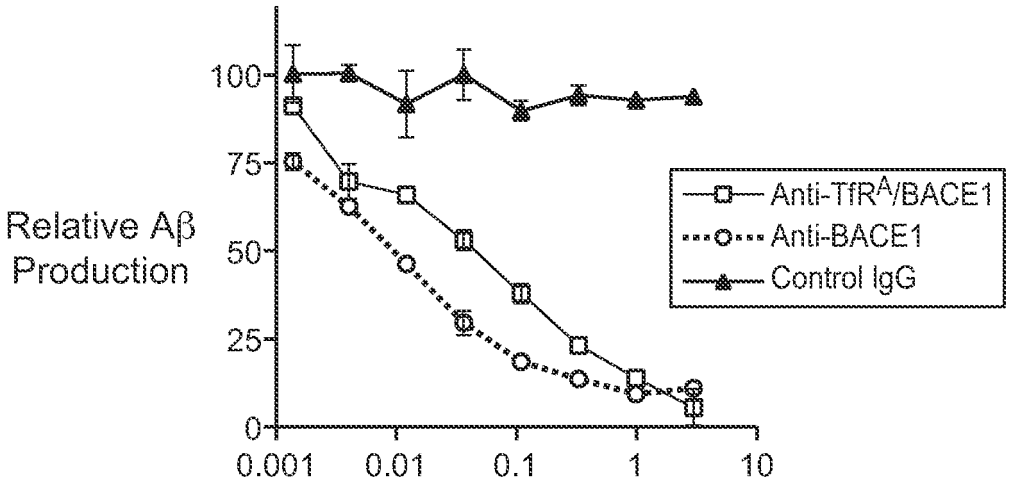


FIG. 3C

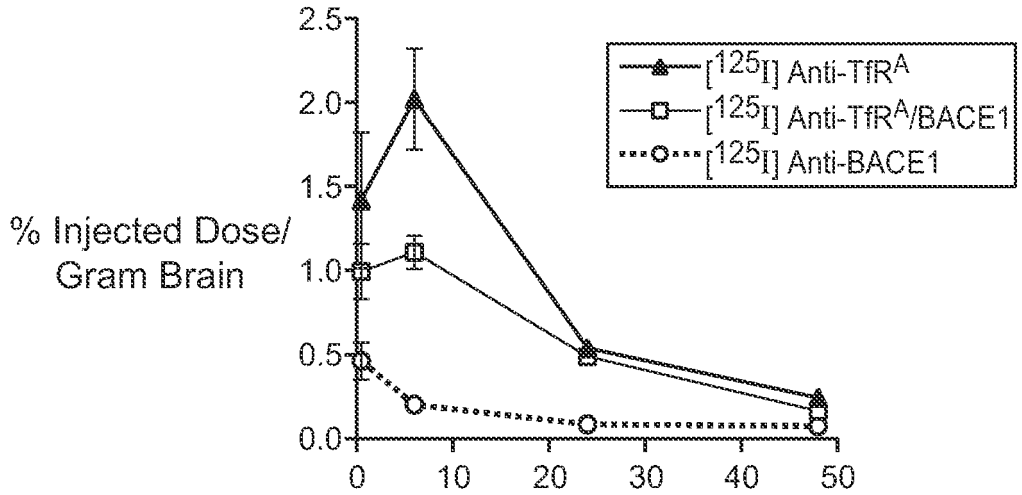


FIG. 3D

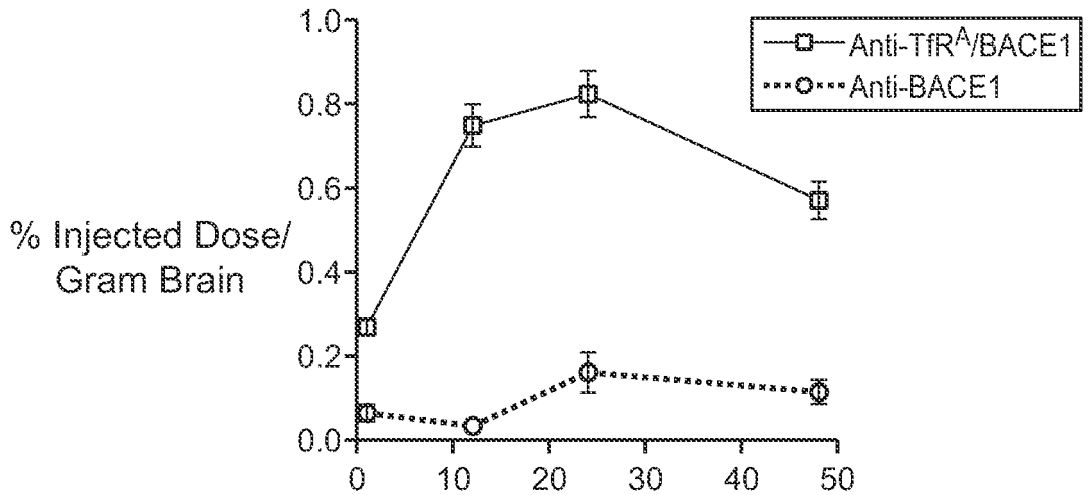


FIG. 3E

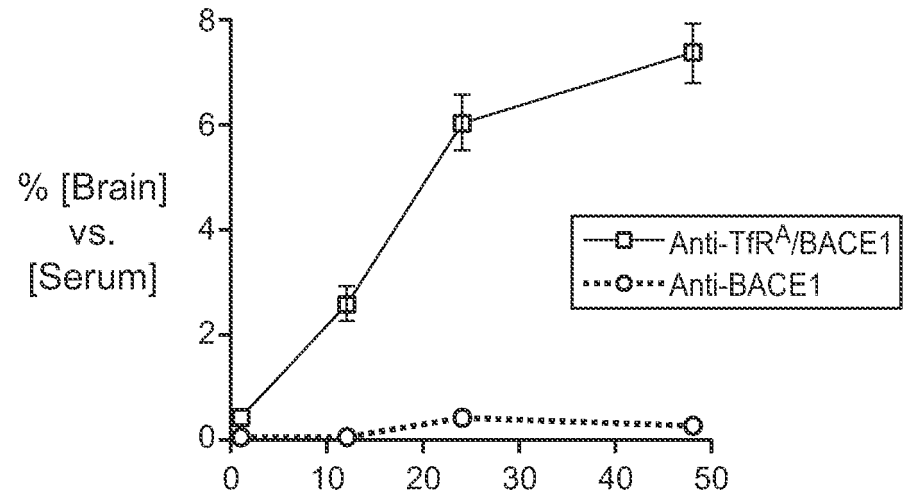


FIG. 3F

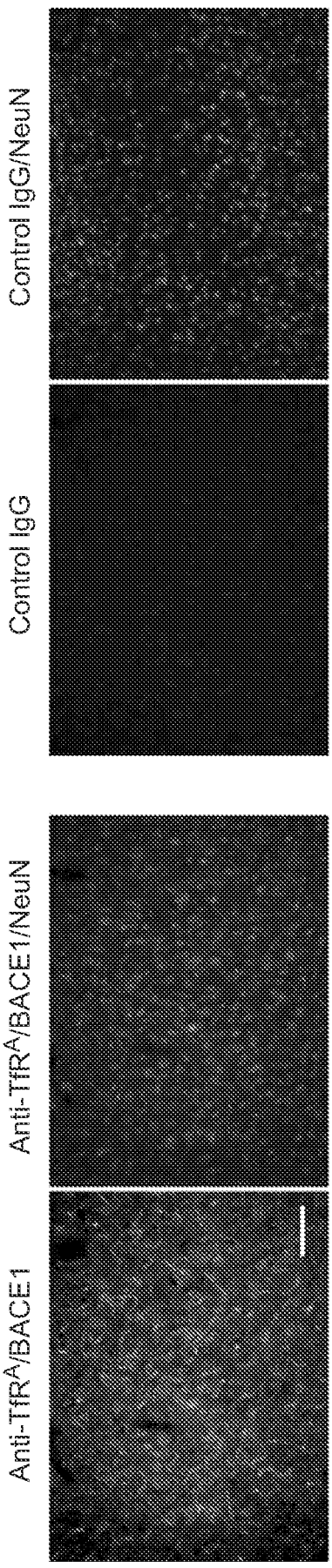

Anti-TfR^A/BACE1
Anti-TfR^A/BACE1/NeuN
Control IgG
Control IgG/NeuN

FIG. 3G

FIG. 4A

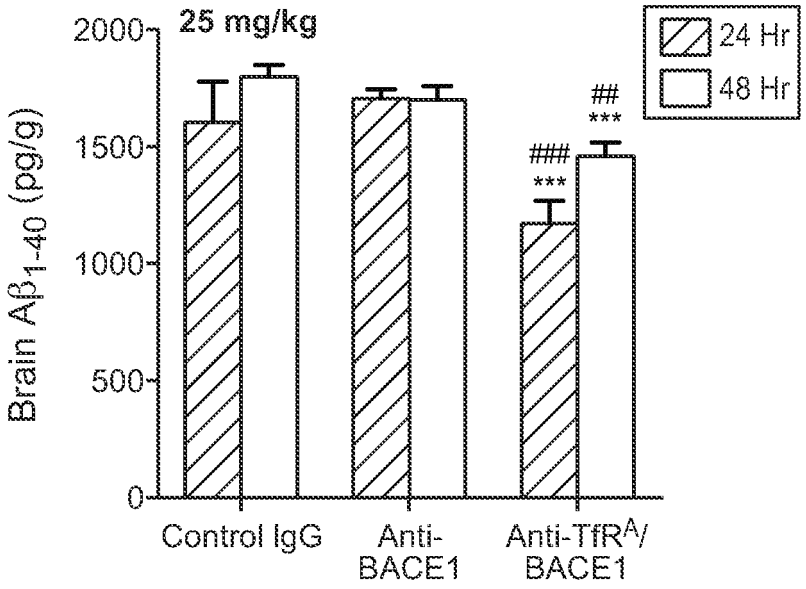


FIG. 4B

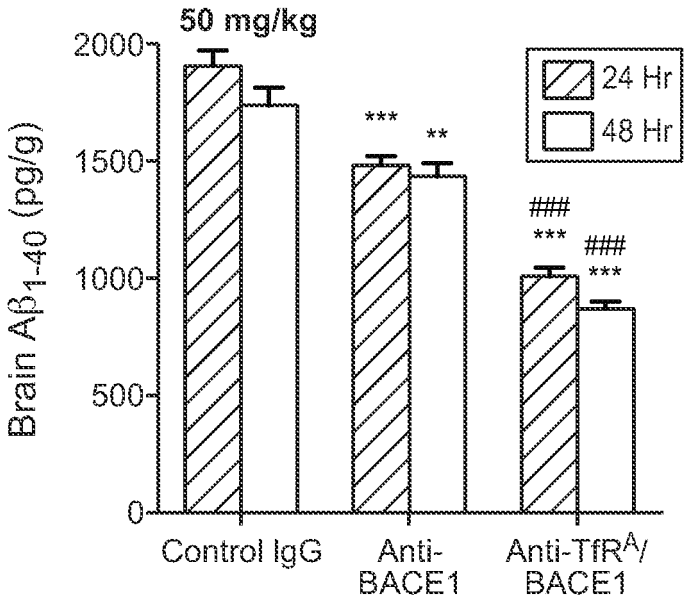


FIG. 4C

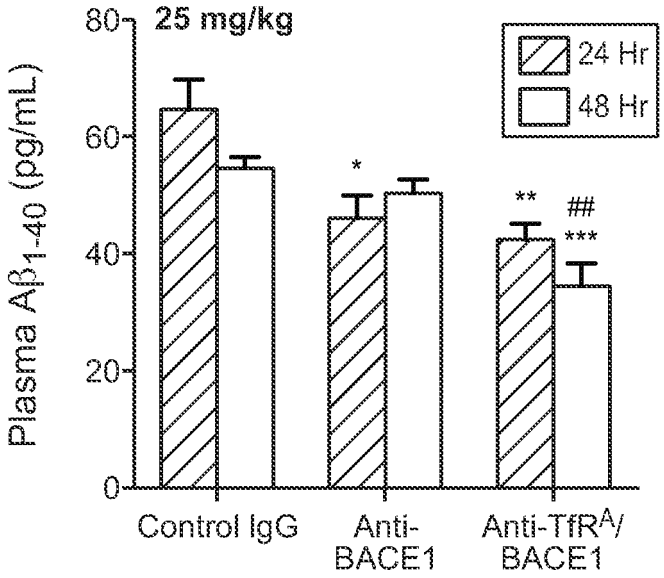


FIG. 4D

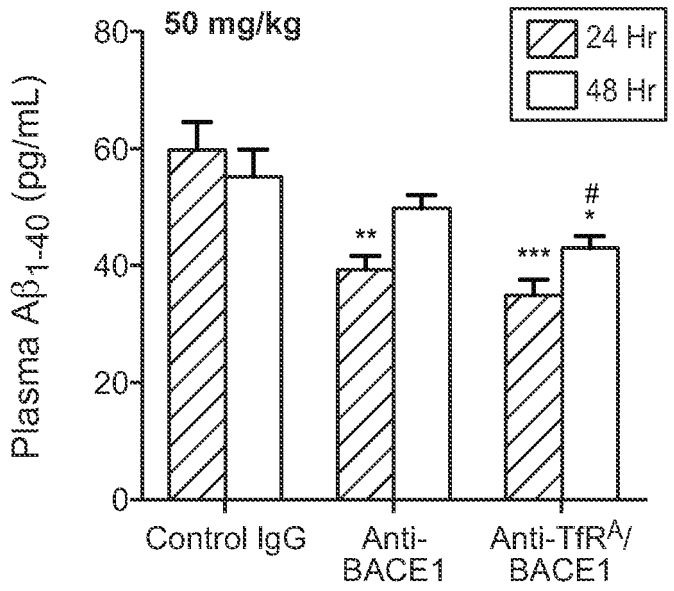
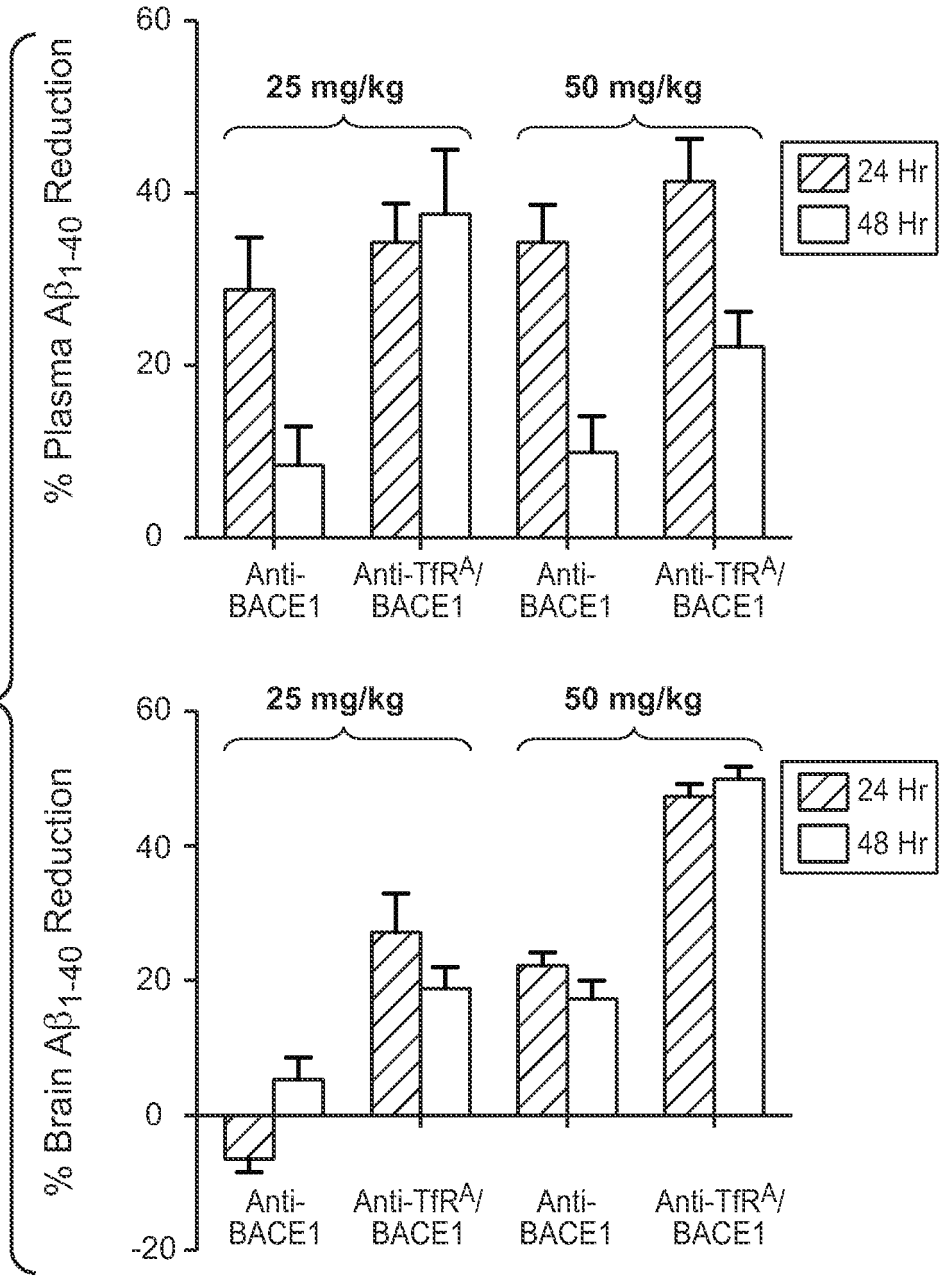

50 mg/kg
24 Hr
48 Hr
Plasma $A\beta_{1-40}$ (pg/mL)
80
60
40
20
0
**
***
#
*
Control IgG
Anti-BACE1
Anti-TfR^A/BACE1

FIG. 4E


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

Kabat#	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	A	B	C	D	E	F	28	29	30	31	32	33	34	35	36	37
																								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
YW412.8.51	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
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																	
									Kabat - CDR L3																																			
									Chothia - CDR L3																																			
									Contact - CDR L3																																			
YW412.8	E	D	F	A	T	Y	Y	C	Q	Q	S	Y	T	T	P	P	T	F	G	Q	G	T	K	V	E	I	K	R																	
YW412.8.31	E	D	F	A	T	Y	Y	C	Q	Q	F	P	P	T	Y	L	P	T	F	G	Q	G	T	K	V	E	I	K	R																	
YW412.8.30	E	D	F	A	T	Y	Y	C	Q	Q	G	Y	N	D	P	P	T	F	G	Q	G	T	K	V	E	I	K	R																	
YW412.8.2	E	D	F	A	T	Y	Y	C	Q	Q	S	S	T	D	P	P	T	F	G	Q	G	T	K	V	E	I	K	R																	
YW412.8.29	E	D	F	A	T	Y	Y	C	Q	Q	D	A	T	S	P	P	T	F	G	Q	G	T	K	V	E	I	K	R																	
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																	

YW412.8	SEQ ID NO: 1
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YW412.8.30	SEQ ID NO: 3
YW412.8.2	SEQ ID NO: 4
YW412.8.29	SEQ ID NO: 5
YW412.8.51	SEQ ID NO: 6

FIG. 5A

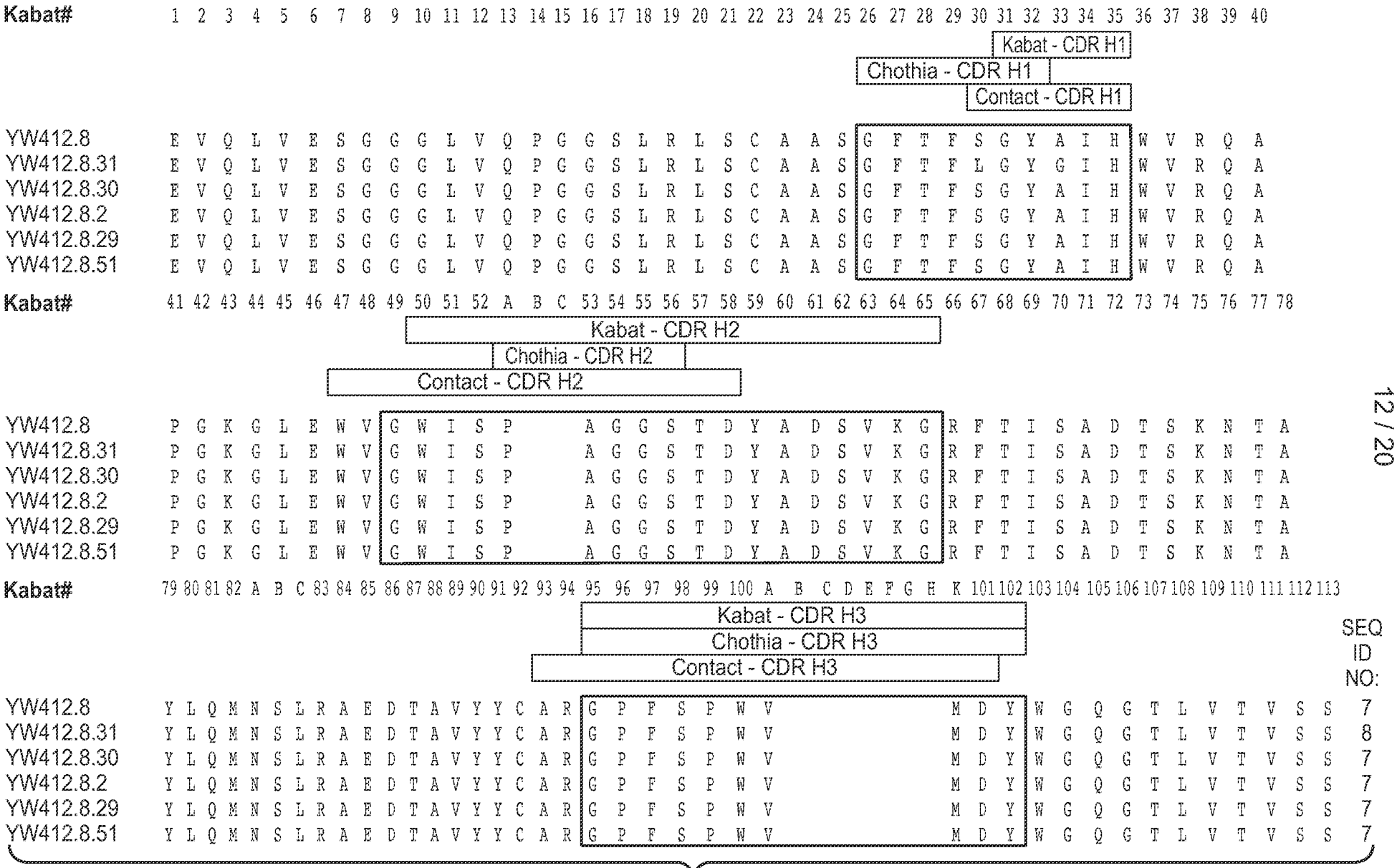

Kabat#
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Kabat - CDR H1
Chothia - CDR H1
Contact - CDR H1
YW412.8 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F T F S G Y A I H W V R Q A
YW412.8.31 E V Q L V E S G G G L V Q P G G S L 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#
79 80 81 82 A B C 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 A B C D E F G H K 101 102 103 104 105 106 107 108 109 110 111 112 113
Kabat - CDR H3
Chothia - CDR H3
Contact - CDR H3
SEQ ID NO:
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YW412.8.31 Y L Q M N S L R A E D T A V Y Y C A R G P F S P W V M D Y W G Q G T L V T V S S 8
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FIG. 5B

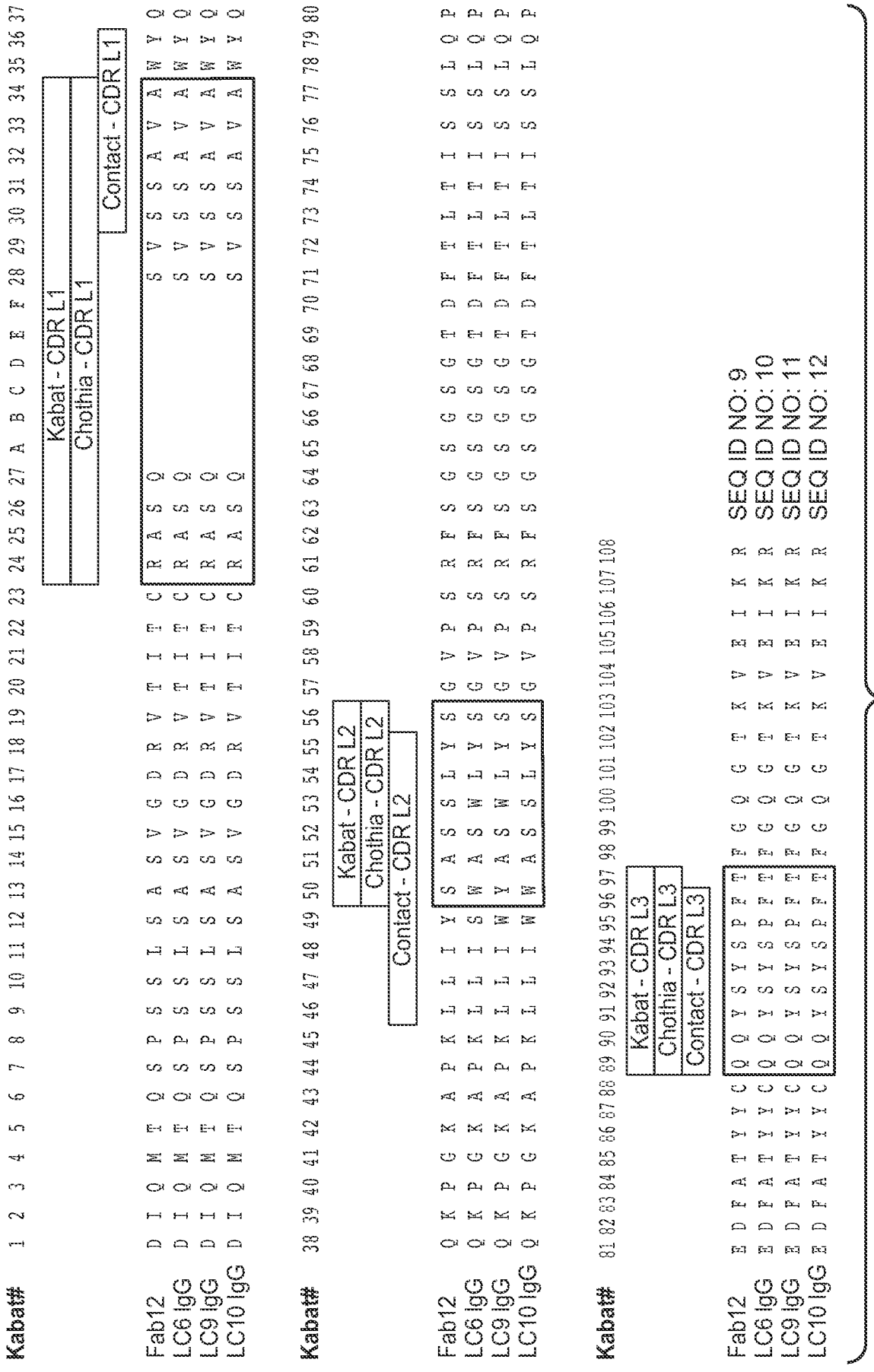

Kabat - CDR L1
Chothia - CDR L1
Contact - CDR L1
Kabat - CDR L2
Chothia - CDR L2
Contact - CDR L2
Kabat - CDR L3
Chothia - CDR L3
Contact - CDR L3
Kabat# 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 A B C D E F 28 29 30 31 32 33 34 35 36 37
Fab12 D I Q M T Q S P S S L S A S V G D R V T I T C R A S Q S V S S A V A W Y Q
LC6 IgG 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 S V S S A V A W Y Q
LC9 IgG 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 S V S S A V A W Y Q
LC10 IgG 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 S V S S 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
Fab12 Q K P G K A P K L L I Y S A S S 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
LC6 IgG Q K P G K A P K L L I S W A S W 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
LC9 IgG Q K P G K A P K L L I W Y A S W 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
LC10 IgG Q K P G K A P K L L I W W A S S 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
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
Fab12 E D F A T Y Y C Q Q Y S Y S P F T F G Q G T K V E I K R SEQ ID NO: 9
LC6 IgG E D F A T Y Y C Q Q Y S Y S P F T F G Q G T K V E I K R SEQ ID NO: 10
LC9 IgG E D F A T Y Y C Q Q Y S Y S P F T F G Q G T K V E I K R SEQ ID NO: 11
LC10 IgG E D F A T Y Y C Q Q Y S Y S P F T F G Q G T K V E I K R SEQ ID NO: 12

FIG. 6A

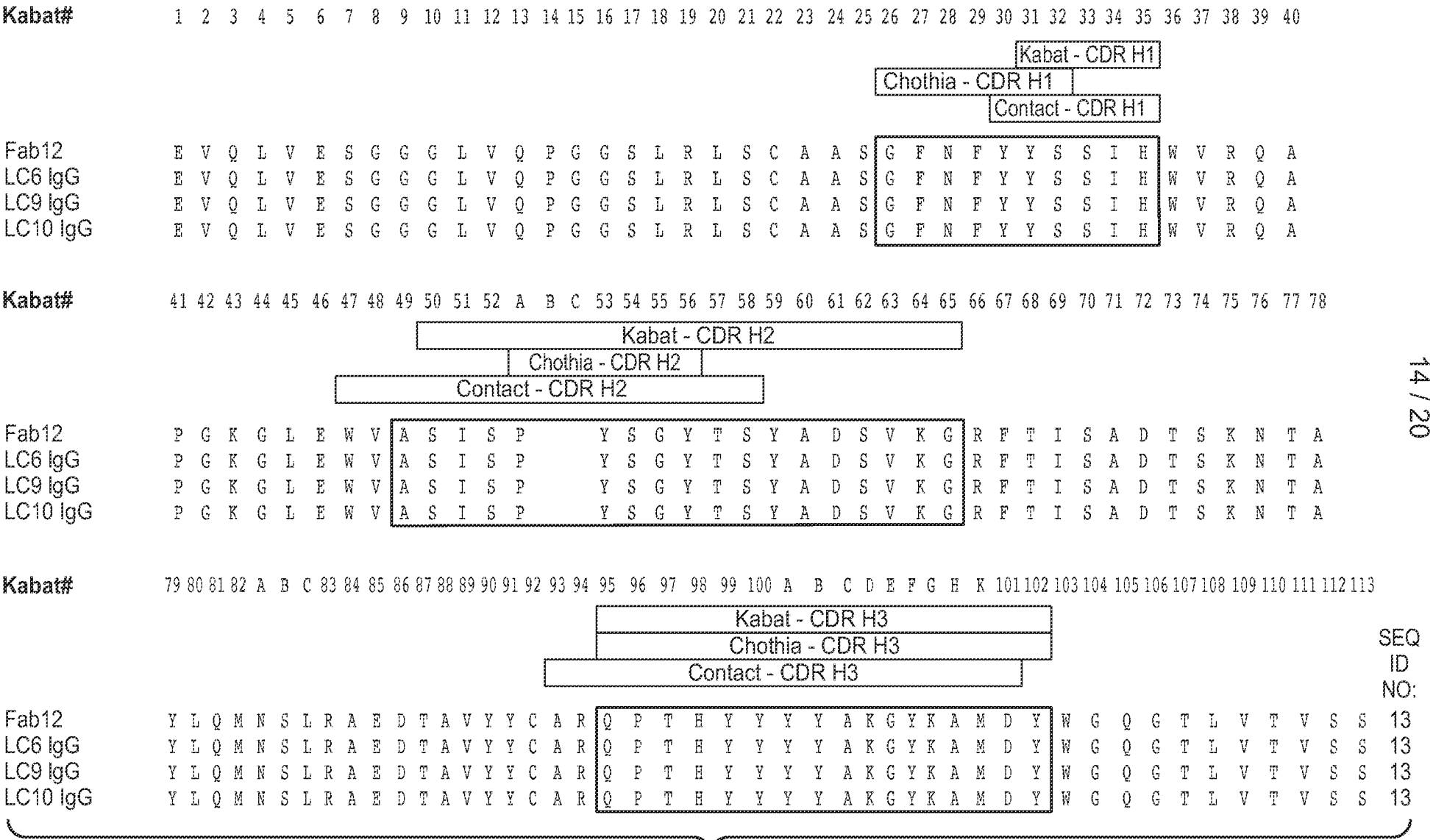

Kabat#
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
Kabat - CDR H1
Chothia - CDR H1
Contact - CDR H1
Fab12 E V Q L V E S G G G L V Q P G G S L R L S C A A S G F N F Y Y S S I H W V R Q A
LC6 IgG E V Q L V E S G G G L V Q P G G S L R L 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
Kabat#
79 80 81 82 A B C 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100 A B C D E F G H K 101 102 103 104 105 106 107 108 109 110 111 112 113
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

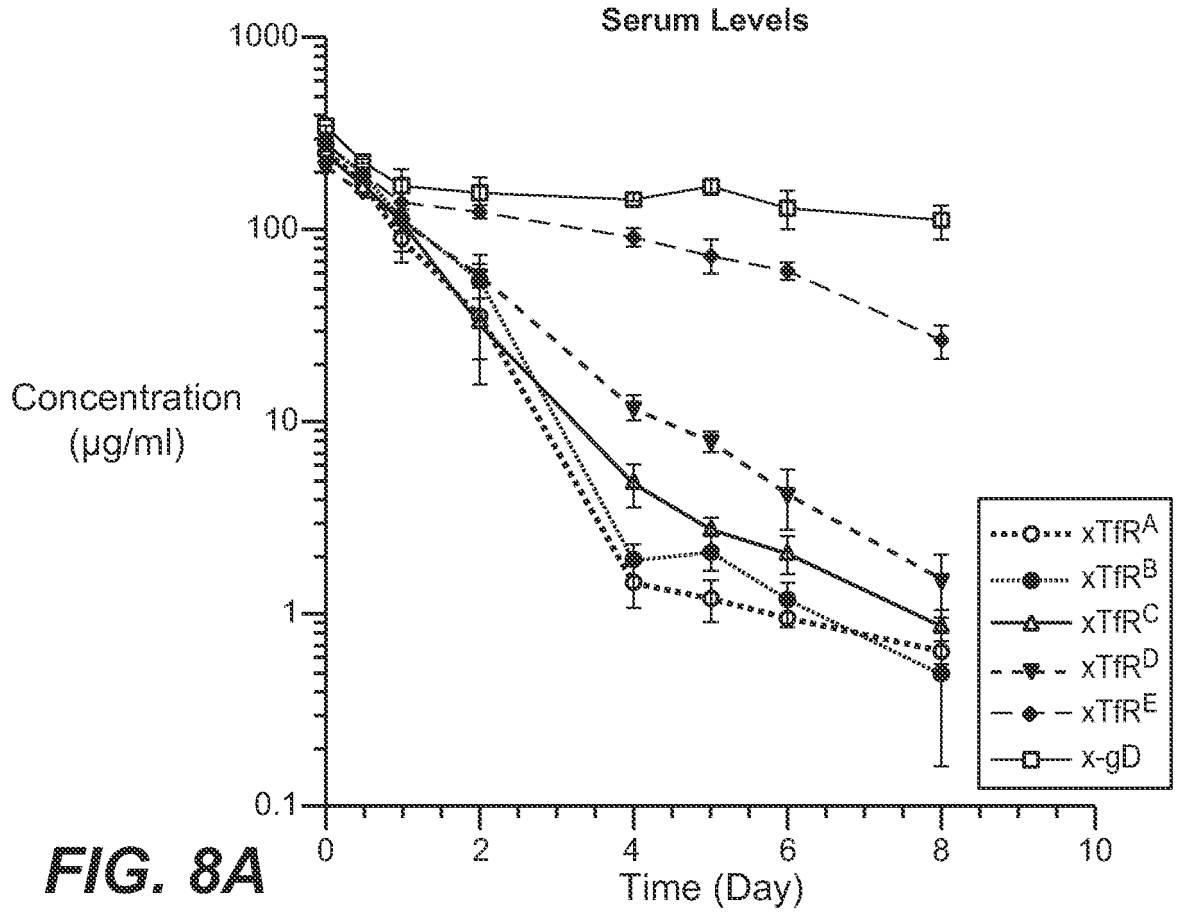

Serum Levels
1000
100
10
1
0.1
Concentration (µg/ml)
0
2
4
6
8
10
Time (Day)
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E
x-gD

FIG. 8A

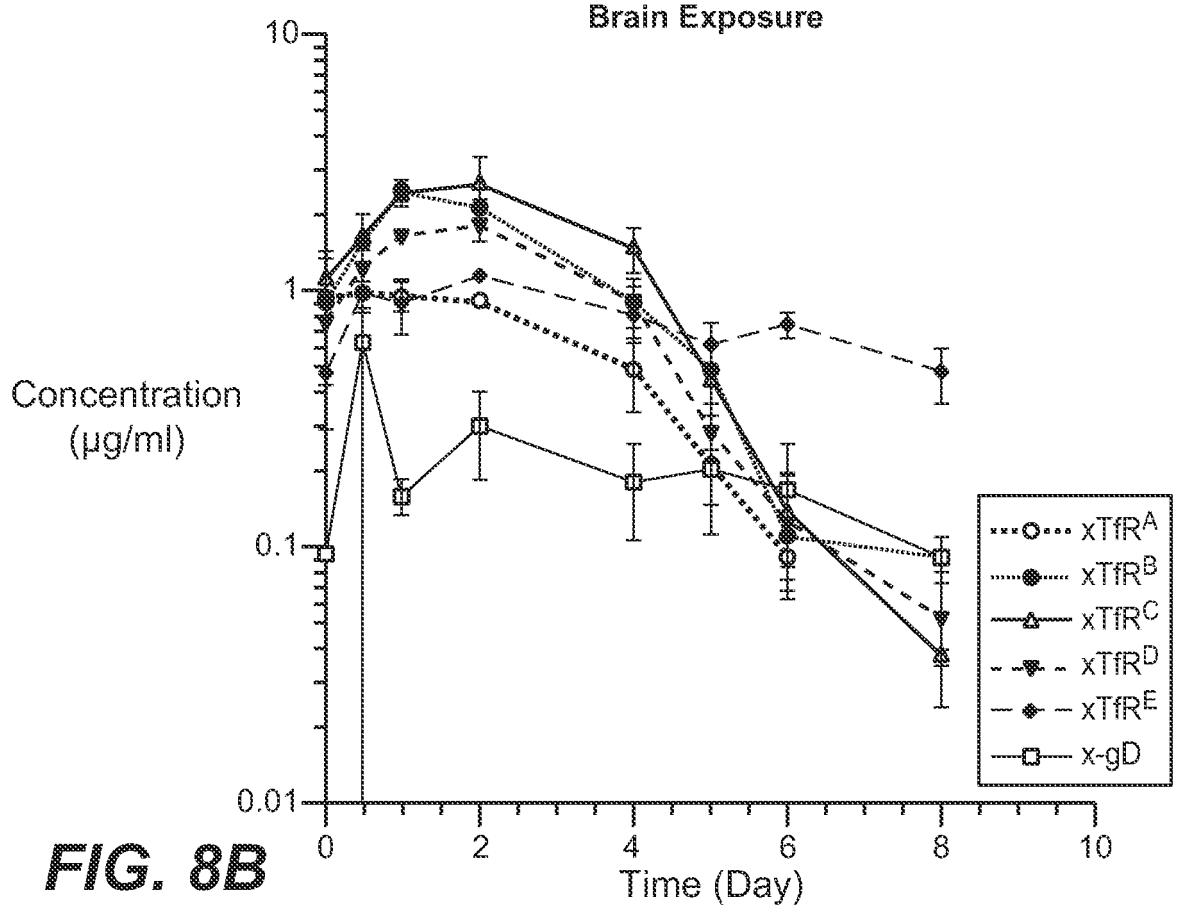

Brain Exposure
10
1
0.1
0.01
Concentration (µg/ml)
0
2
4
6
8
10
Time (Day)
xTfR^A
xTfR^B
xTfR^C
xTfR^D
xTfR^E
x-gD

FIG. 8B

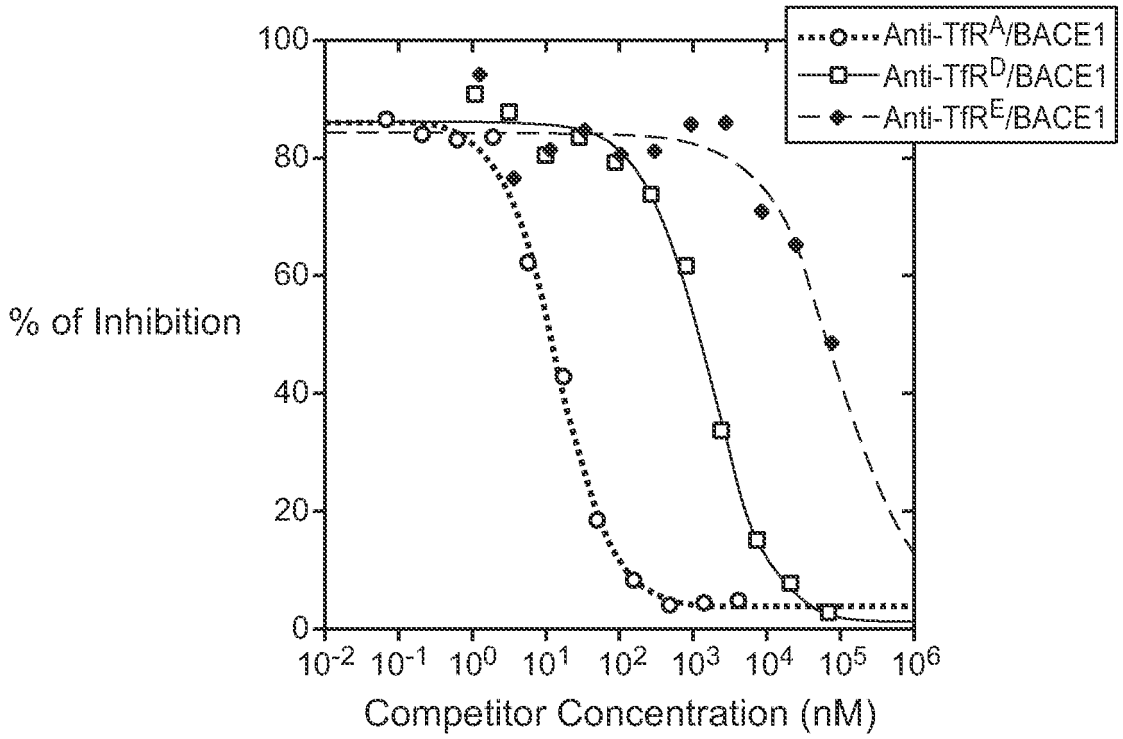

Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1
% of Inhibition
100
80
60
40
20
0
10^-2 10^-1 10^0 10^1 10^2 10^3 10^4 10^5 10^6
Competitor Concentration (nM)

FIG. 9A

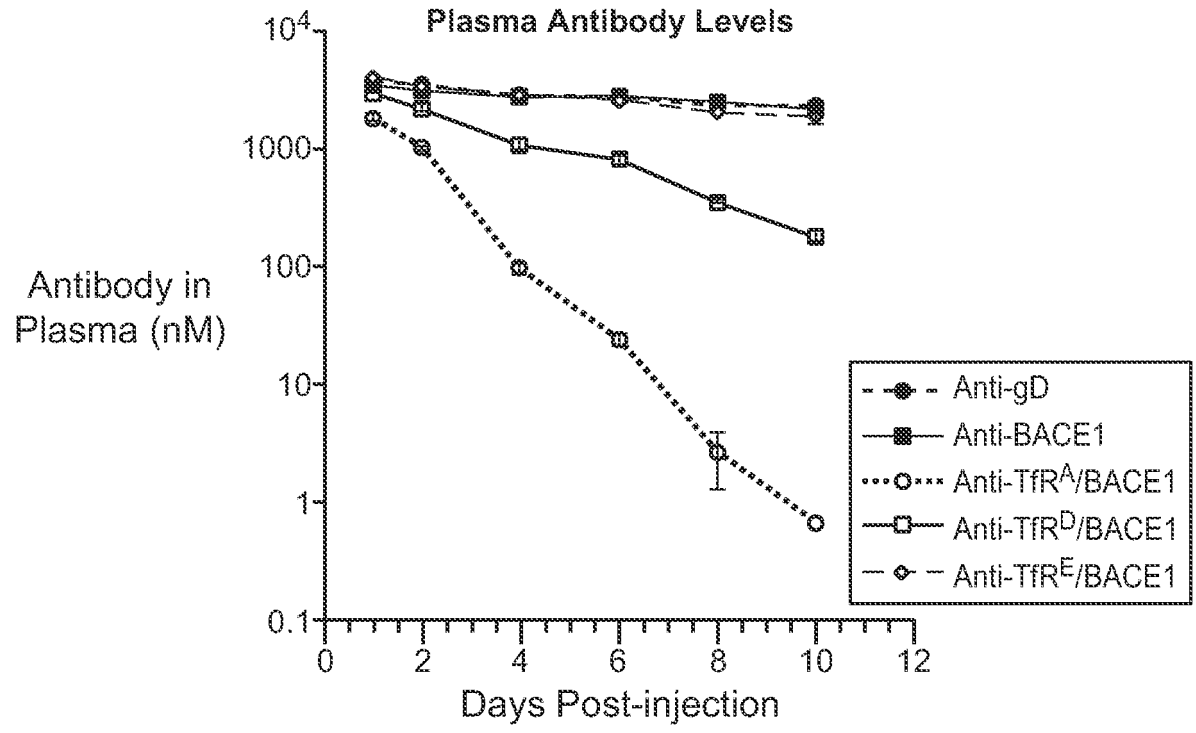

Plasma Antibody Levels
Antibody in Plasma (nM)
10^4
1000
100
10
1
0.1
0 2 4 6 8 10 12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9B

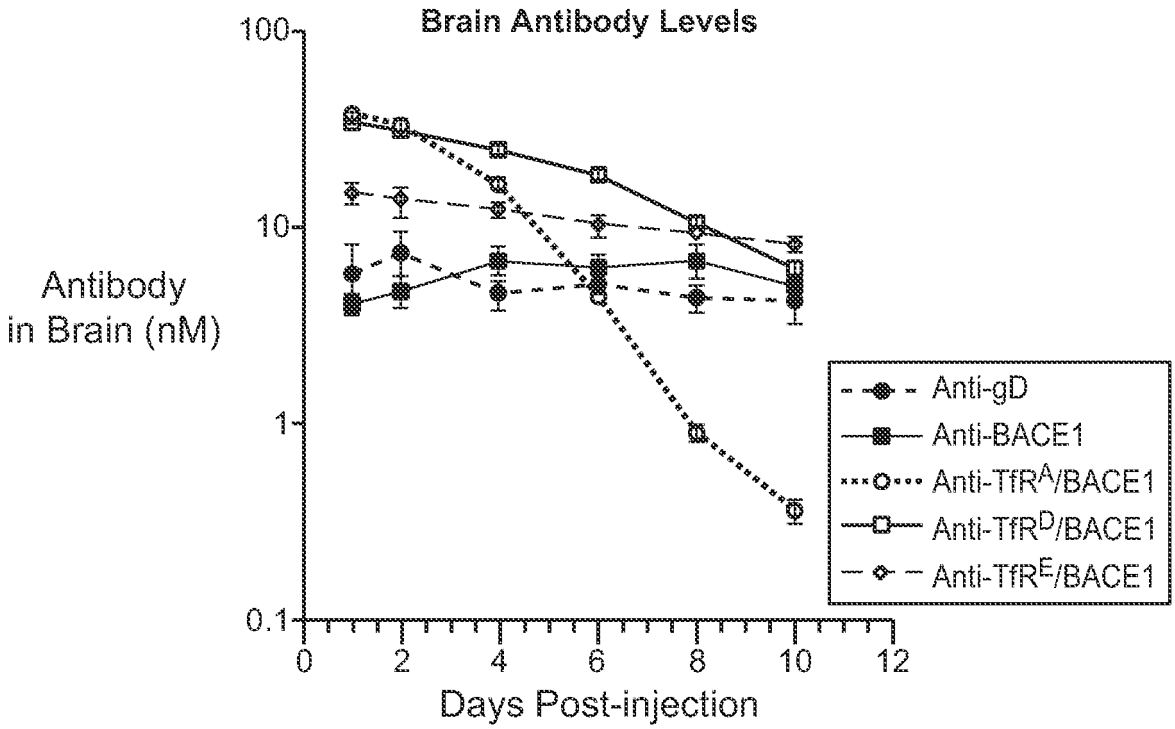

Brain Antibody Levels
Antibody in Brain (nM)
100
10
1
0.1
0
2
4
6
8
10
12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9C

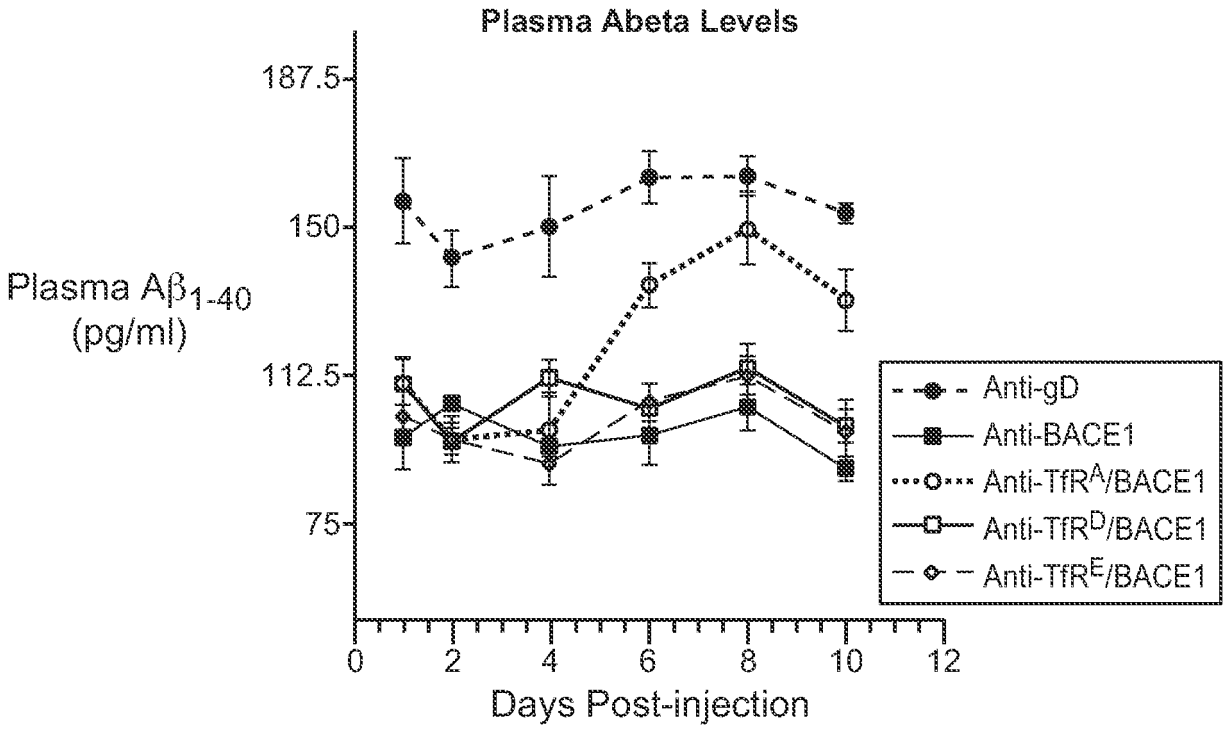

Plasma Abeta Levels
Plasma Aβ1-40 (pg/ml)
187.5
150
112.5
75
0
2
4
6
8
10
12
Days Post-injection
Anti-gD
Anti-BACE1
Anti-TfR^A/BACE1
Anti-TfR^D/BACE1
Anti-TfR^E/BACE1

FIG. 9D

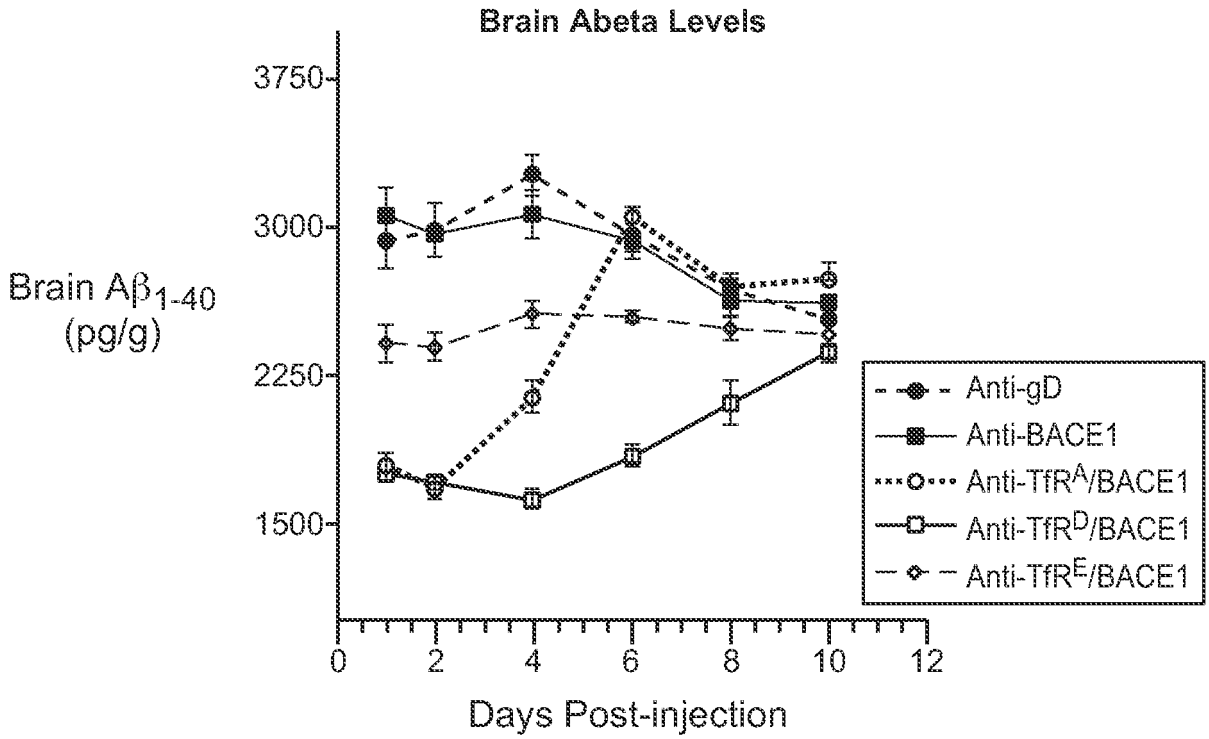


FIG. 9E

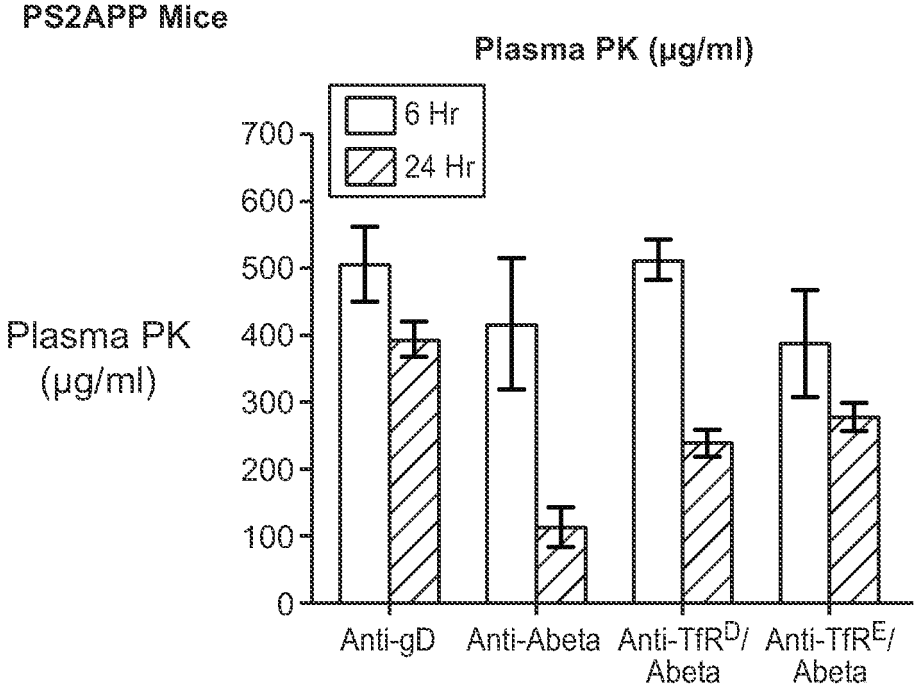


FIG. 10A

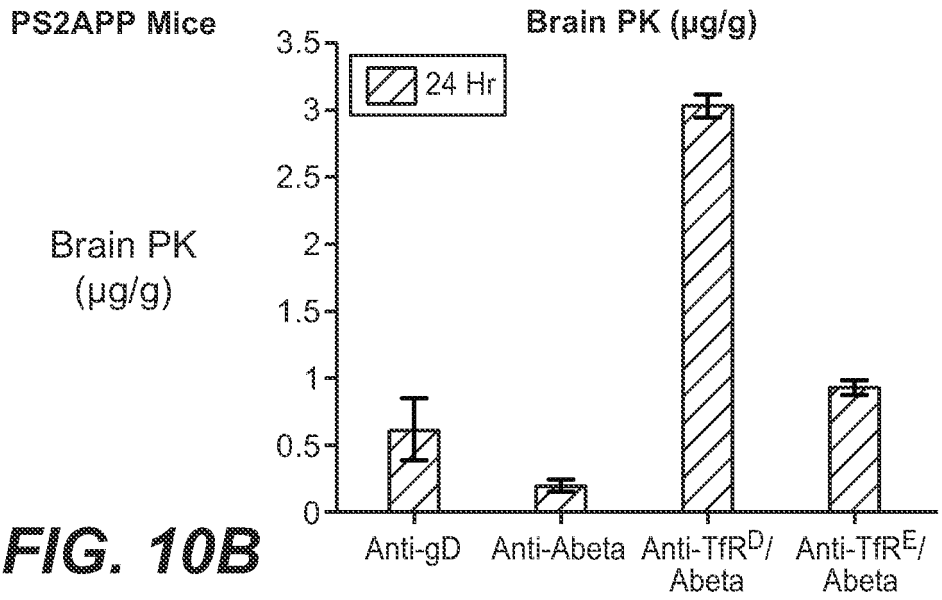


FIG. 10B

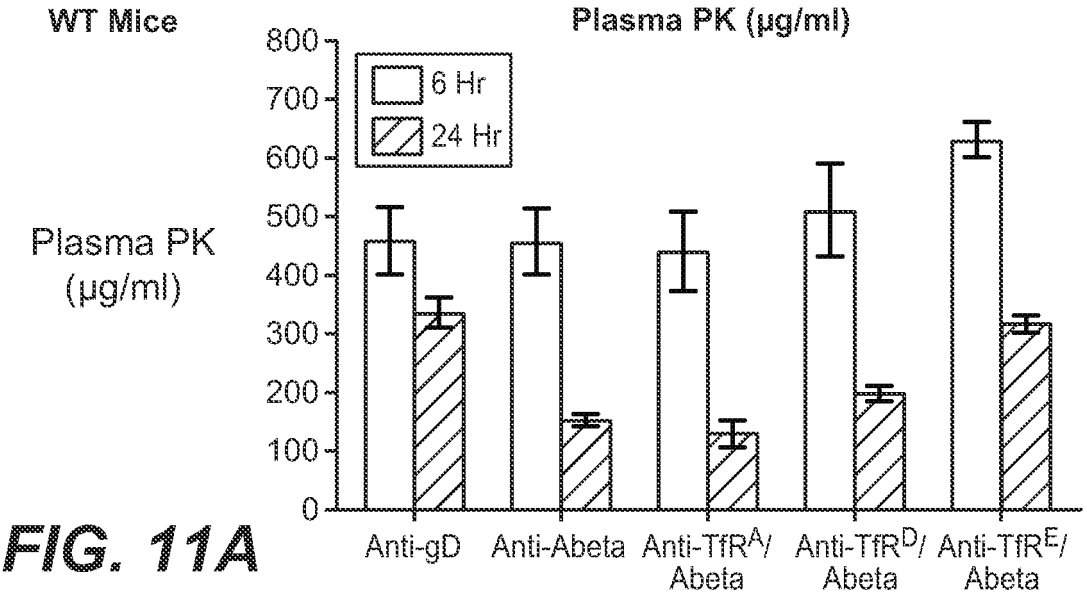


FIG. 11A

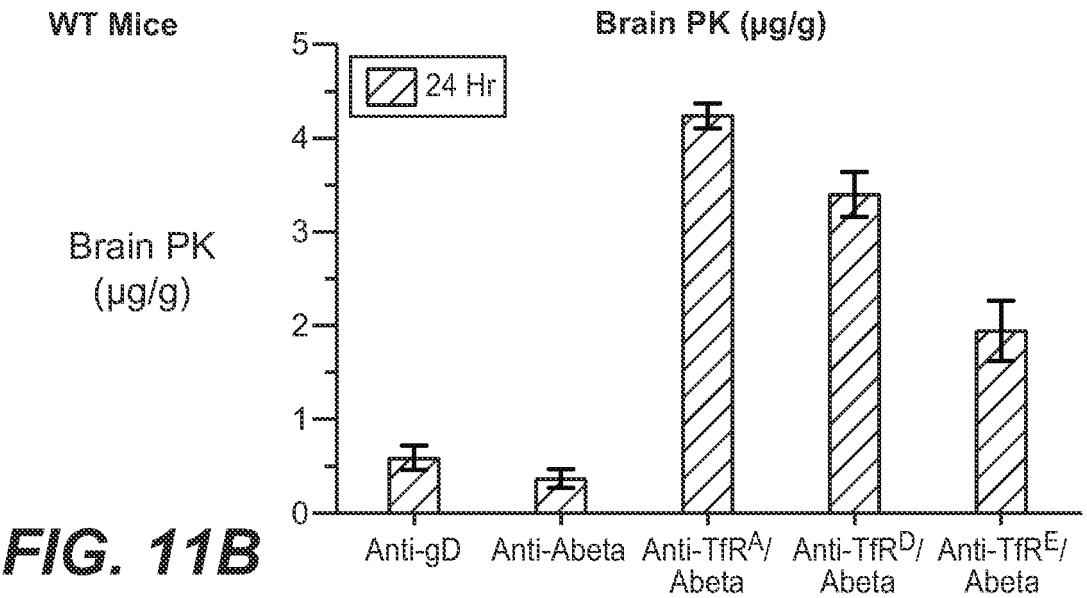


FIG. 11B