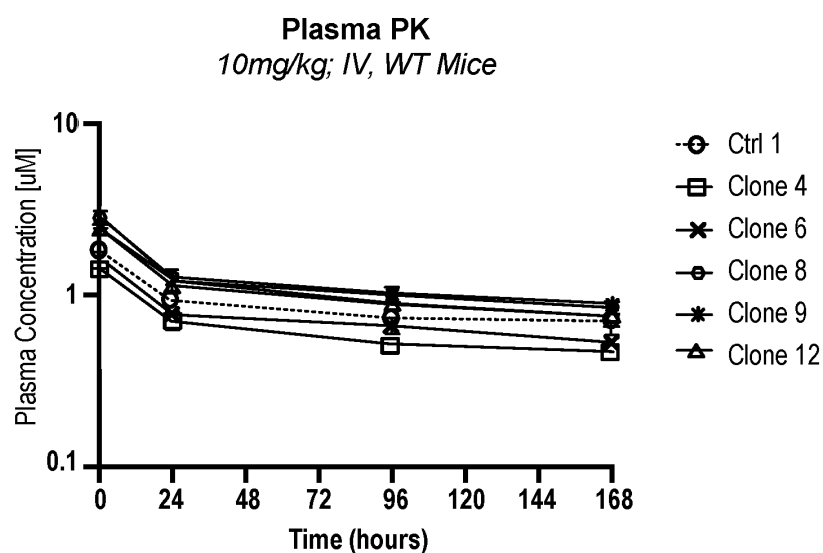


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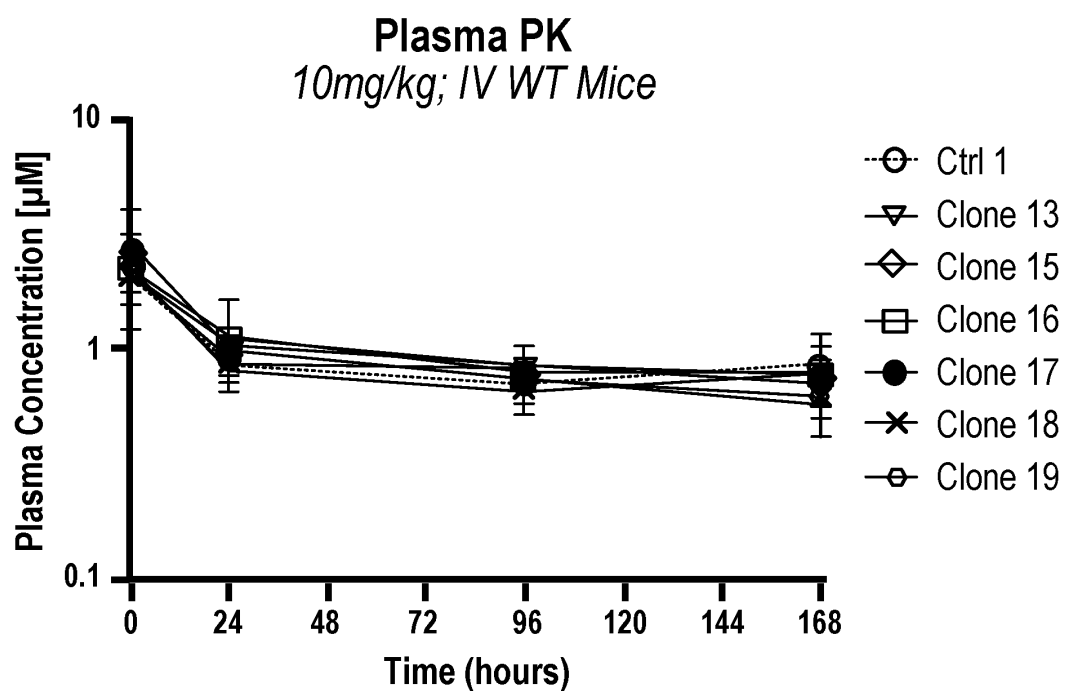


Clone#	Clone name	CD98hc binding valency	Fabs	EF status	C ₀ (uM)	AUC _{0-t} (hr*uM)	CL (mL/d/kg)
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	1.77 ± 0.19	142.8 ± 16.8	3.5 ± 1.6
Clone 4	LLB1-3 D380E	Bivalent	NBF	+	1.42 ± 0.05	104.0 ± 4.5	6.9 ± 1.4
Clone 6	LLB1-3 D380E	Monovalent	NBF	+	1.62 ± 0.17	121.5 ± 8.1	5.0 ± 0.1
Clone 8	LLB2-10-6	Monovalent	NBF	+	2.87 ± 0.26	195.6 ± 4.5	3.2 ± 0.9
Clone 9	LLB2-10-8	Monovalent	NBF	+	2.49 ± 0.21	190.1 ± 19.1	2.8 ± 0.3
Clone 12	LLB2-10-28	Monovalent	NBF	+	2.47 ± 0.22	173.1 ± 14.8	3.8 ± 1.1

FIG. 1

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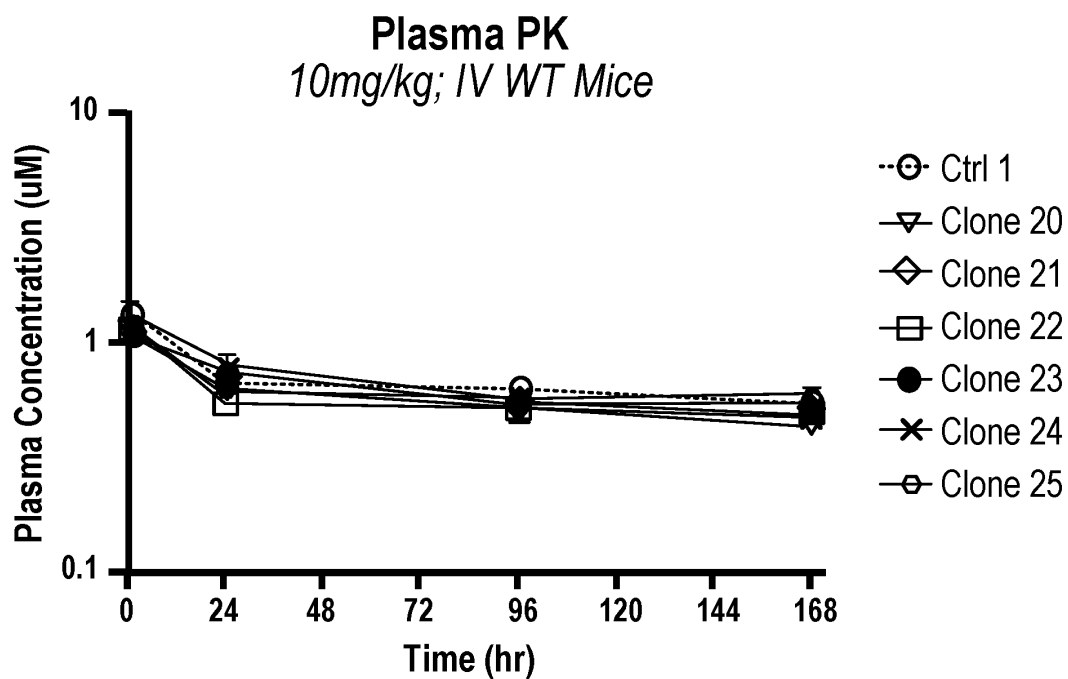


Clone#	Clone name	CD98hc binding valency	Fabs	EF status	C_0 (μM)	AUC_{0-t} ($\text{hr} \cdot \mu\text{M}$)	CL (mL/d/kg)
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	1.77 ± 0.19	142.8 ± 16.8	3.5 ± 1.6
Clone 13	LLB1-3-16	Monovalent	NBF	+	2.04 ± 0.25	144 ± 17	4.25 ± 1.8
Clone 15	LLB1-3-25-1	Monovalent	NBF	+	2.87 ± 1.3	152 ± 4.4	3.86 ± 0.52
Clone 16	LLB2-10-8-1	Monovalent	NBF	+	2.26 ± 1.0	166 ± 37	2.62 ± 1.5
Clone 17	LLB2-31	Monovalent	NBF	+	2.40 ± 0.24	155 ± 23	2.92 ± 0.94
Clone 18	LLB2-37	Monovalent	NBF	+	2.16 ± 0.18	162 ± 6.4	2.78 ± 0.99
Clone 19	LLB2-10-12	Monovalent	NBF	+	2.24 ± 0.30	134 ± 19	3.99 ± 1.5

FIG. 2

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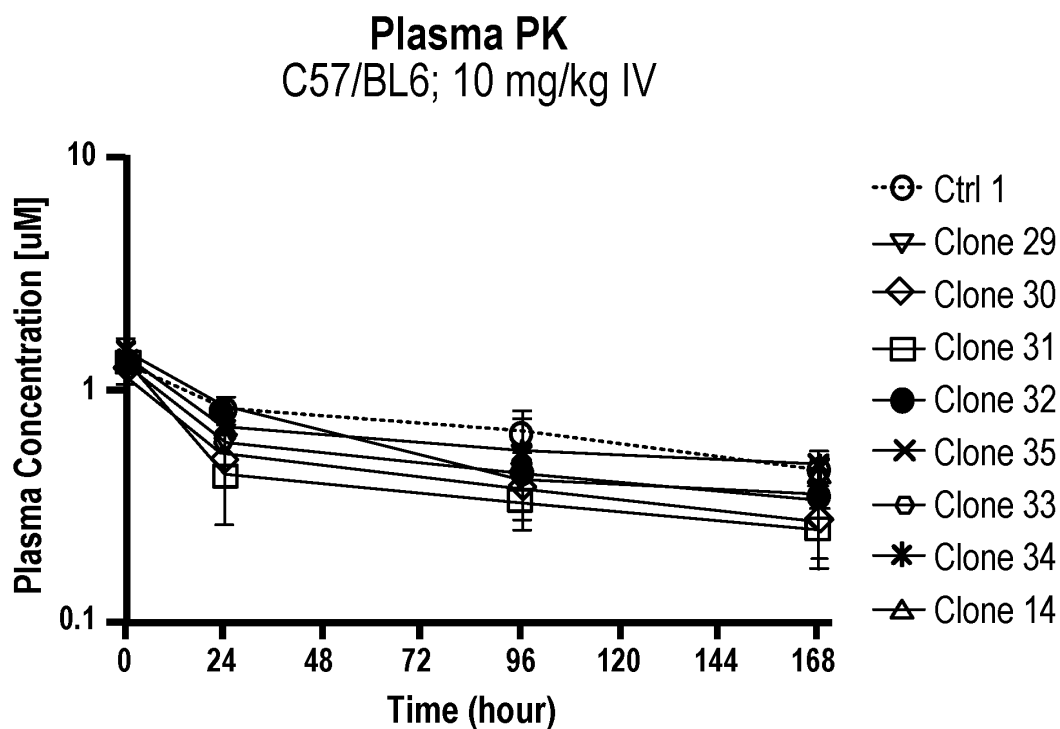


Clone#	Clone name	CD98hc binding valency	Fabs	EF status	C ₀ (uM)	AUC _{0-t} (hr*uM)	CL (mL/d/kg)
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	1.42 ± 0.16	116 ± 3.6	5.60 ± 1.9
Clone 20	LLB2.10.8.12.5	Monovalent	NBF	+	1.36 ± 0.15	120 ± 6.3	6.26 ± 0.73
Clone 21	LLB2.10.8.4.12	Monovalent	NBF	+	1.15 ± 0.12	98.6 ± 4.9	5.86 ± 0.76
Clone 22	LLB2.10.8.14.3	Monovalent	NBF	+	1.26 ± 0.24	96.9 ± 4.5	2.48 ± 1.2
Clone 23	LLB2.10.8.10.1	Monovalent	NBF	+	1.08 ± 0.097	108 ± 13	4.87 ± 1.1
Clone 24	LLB2.10.8.10.3	Monovalent	NBF	+	1.27 ± 0.21	104 ± 5.2	6.52 ± 1.4
Clone 25	LLB2.10.8.10.8	Monovalent	NBF	+	1.37 ± 0.084	110 ± 5.9	9.42 ± 4.7

FIG. 3

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Clone#	Clone name	CD98hc binding valency	Fabs	EF status	C ₀ (uM)	AUC _{0-t} (hr*uM)	CL (mL/d/kg)
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	1.35 ± 0.11	118 ± 5	7.36 ± 0.99
Clone 29	LLB2-10-8-d3	Monovalent	NBF	+	1.36 ± 0.15	97.0 ± 17.2	12.1 ± 3.7
Clone 30	LLB2-10-8-d6	Monovalent	NBF	+	1.20 ± 0.08	75.2 ± 13.7	13.1 ± 5.5
Clone 31	LLB2-10-8-d1	Bivalent	NBF	+	1.40 ± 0.31	68.4 ± 17.0	15.1 ± 5.2
Clone 32	LLB2-10-8-d3	Bivalent	NBF	+	1.30 ± 0.15	86.7 ± 14.4	8.97 ± 1.76
Clone 35	LLB2-10-8-d18	Bivalent	NBF	+	1.50 ± 0.18	105 ± 9	5.20 ± 2.35
Clone 33	LLB2-10-8-d6	Bivalent	NBF	+	1.45 ± 0.14	81.1 ± 4.7	10.4 ± 1.5
Clone 34	LLB2-10-8-d12	Bivalent	NBF	+	1.55 ± 0.04	118 ± 10	7.55 ± 1.24
Clone 14	LLB1-3-16-2	Monovalent	NBF	+	1.21 ± 0.08	88.9 ± 16.7	8.96 ± 0.79

FIG. 4

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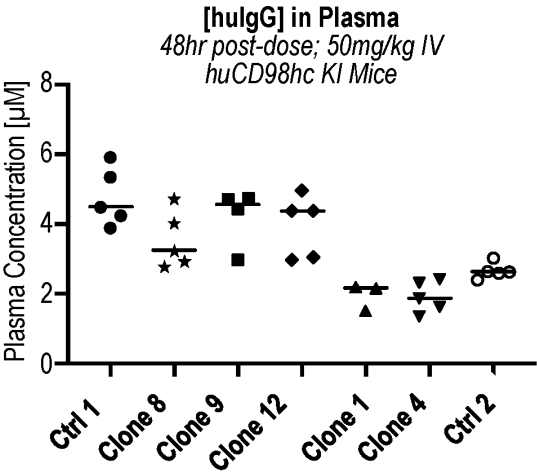


FIG. 5A

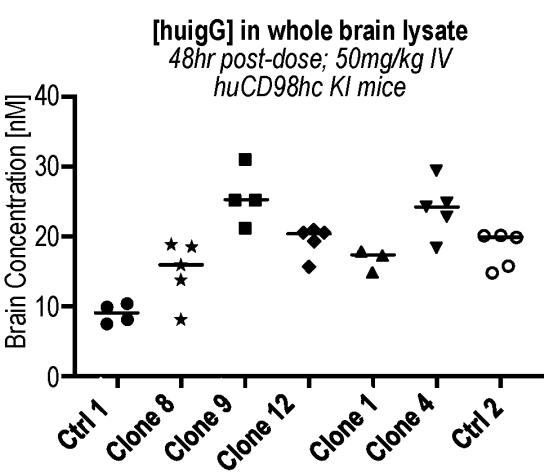


FIG. 5B

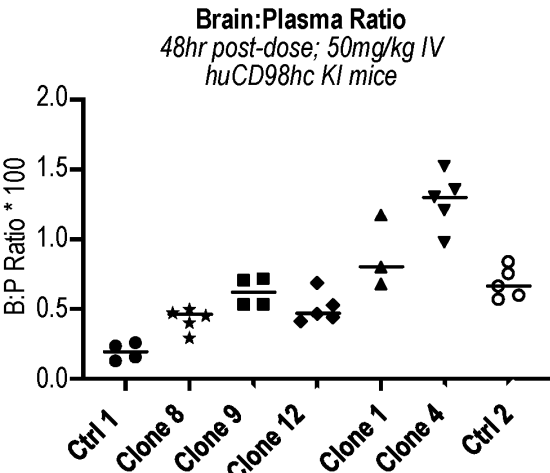


FIG. 5C

Clone#	Clone name	CD98hc binding valency	Fabs	EF status	Hu CD98hc Affinity	[Brain] nM ± SD
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	-	8.98 ± 1.4
Clone 8	LLB2-10-6	Monovalent	NBF	+	230nM	15.1 ± 4.4
Clone 9	LLB2-10-8	Monovalent	NBF	+	100-200nM	25.7 ± 4.1
Clone 12	LLB2-10-28	Monovalent	NBF	+	150nM	19.4 ± 2.2
Clone 1	LLB2-10-8	Bivalent	NBF	+	100-200nM	16.7 ± 1.6
Clone 4	LLB1-3 D380E	Bivalent	NBF	+	1uM	23.8 ± 3.9
Ctrl 2	CD98/BACE1 (pos. control mAb)	Monovalent	-	+	80nM	18.1 ± 2.6

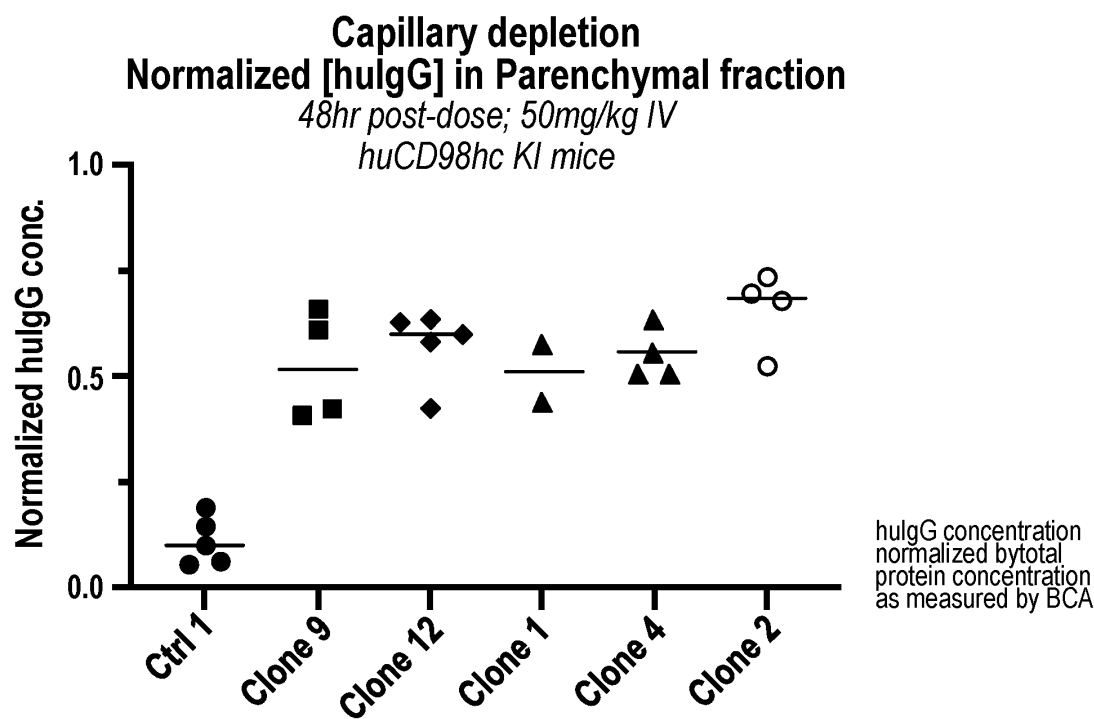


FIG. 6

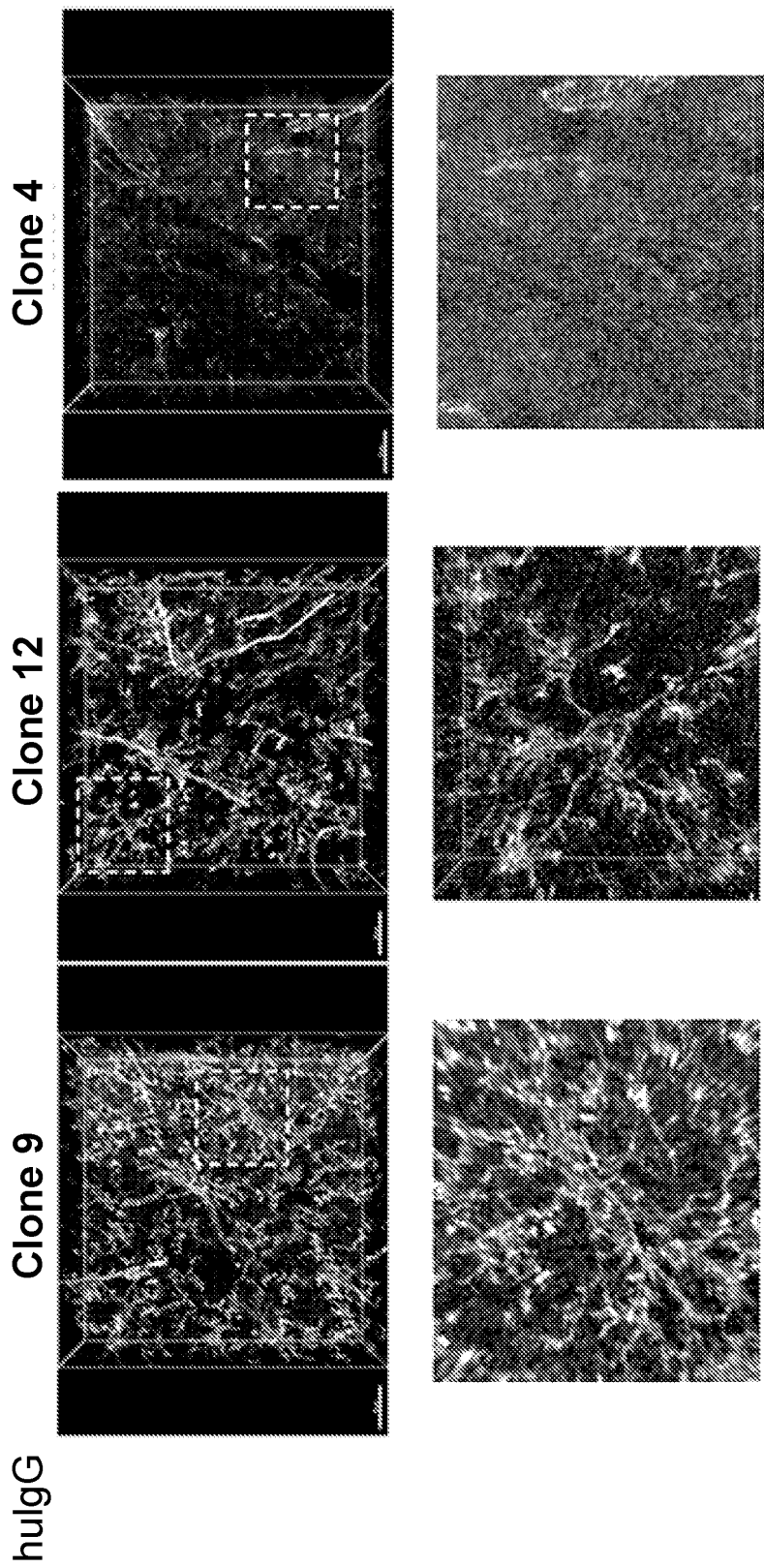
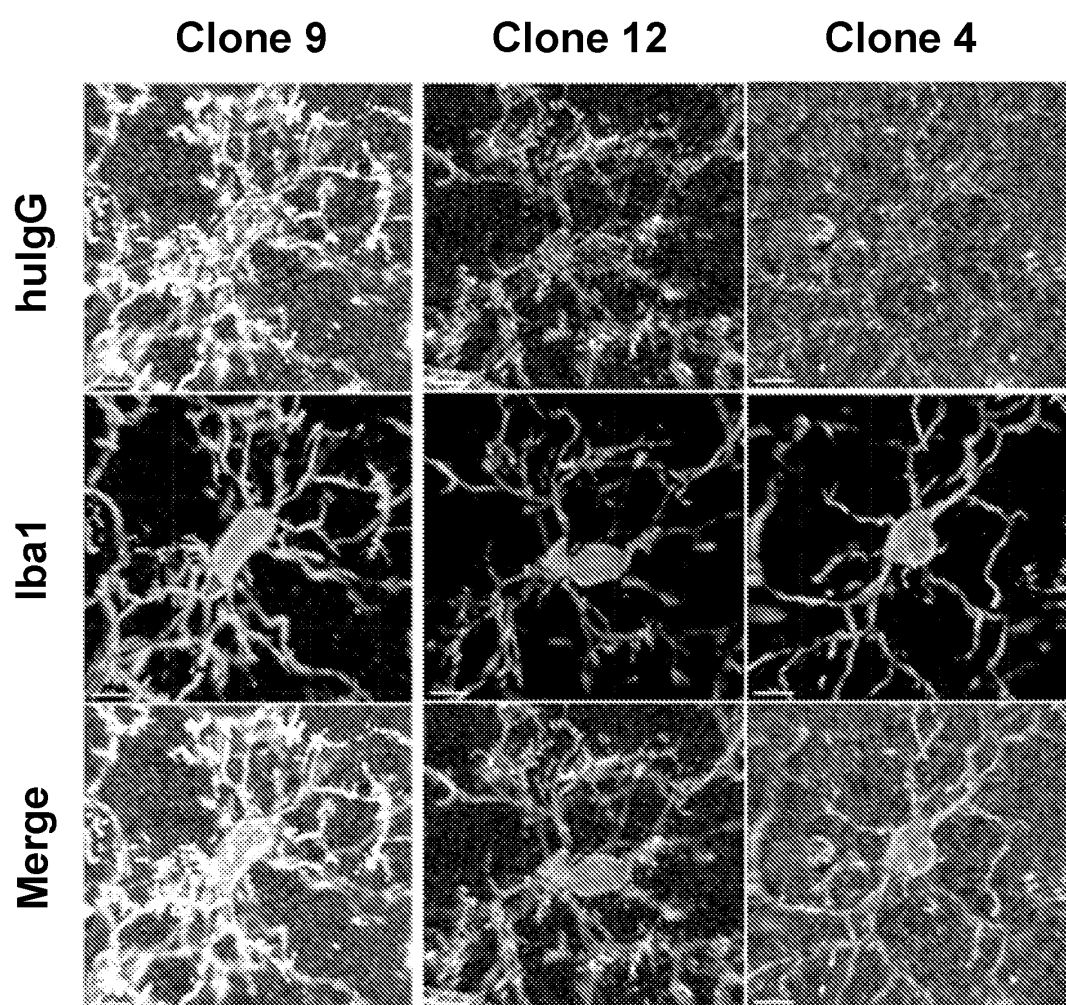
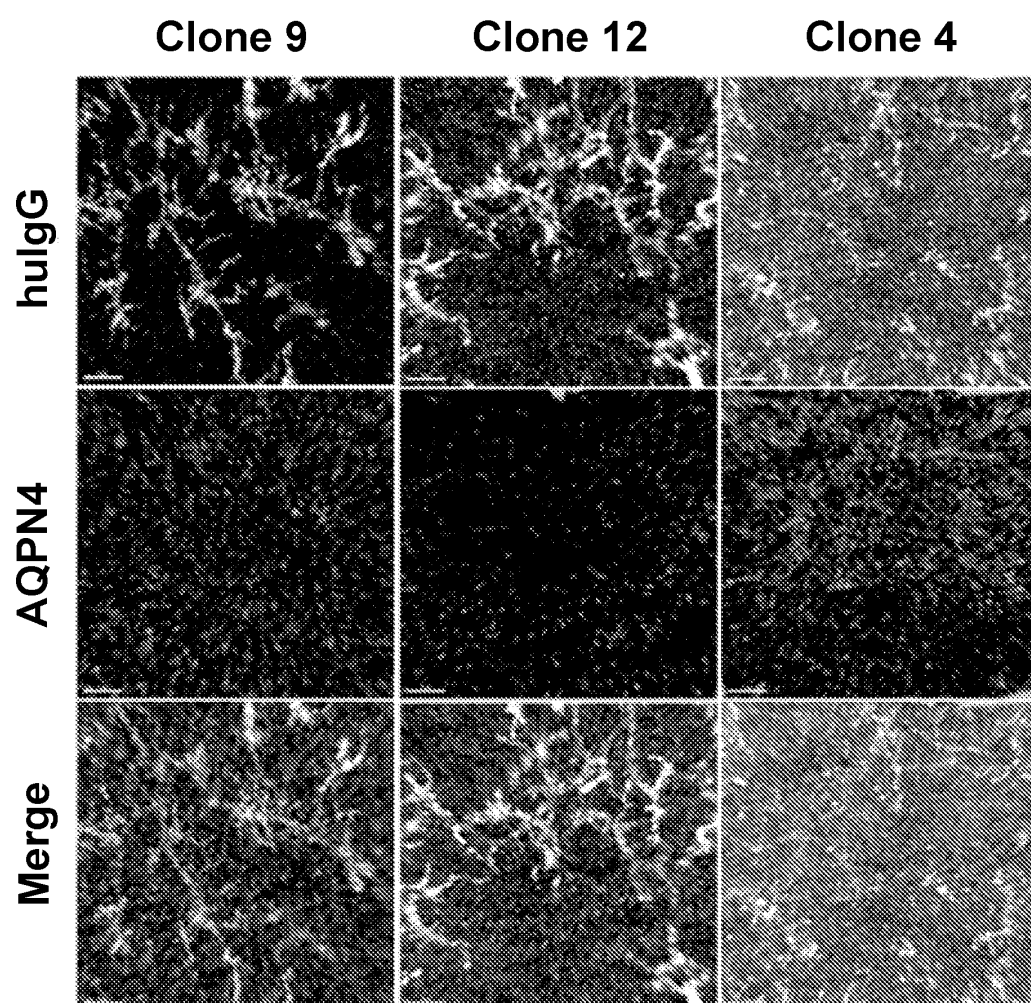


FIG. 7

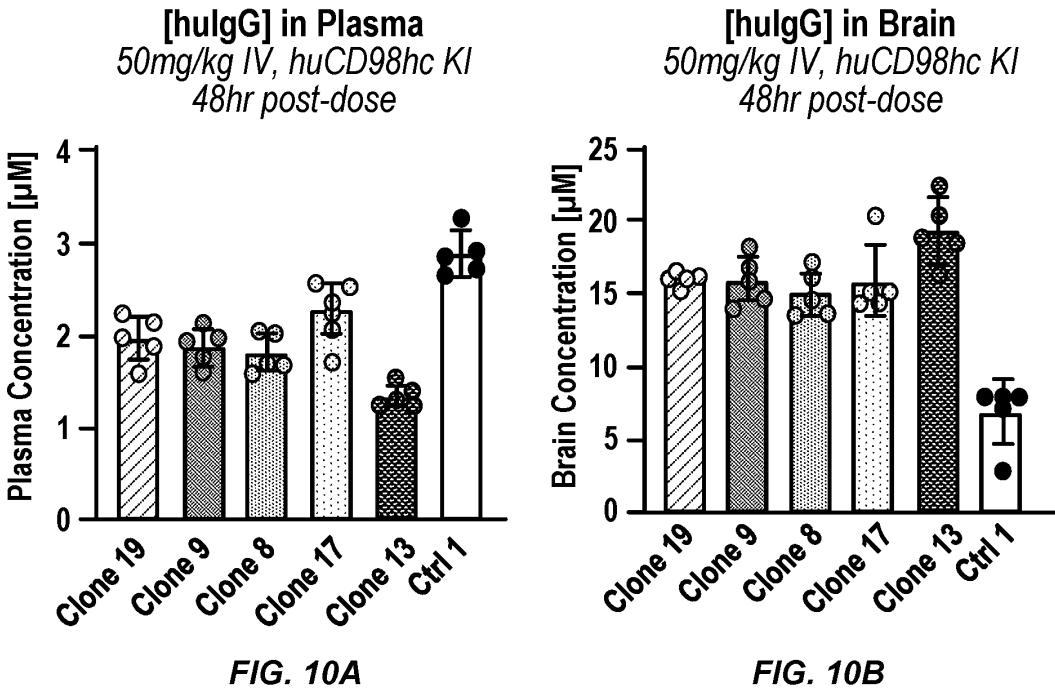
**FIG. 8**

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**FIG. 9**

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Clone#	Clone name	CD98hc binding valency	Fabs	EF status	Hu CD98hc Affinity	[Brain] nM ± SD
Ctrl 1	Non-binding Fab (negative control)	-	NBF	+	-	6.80 ± 2.3
Clone 19	LLB2-10-12	Monovalent	NBF	+	130	15.9 ± 0.45
Clone 9	LLB2-10-8	Monovalent	NBF	+	100-200	15.9 ± 1.6
Clone 8	LLB2-10-86	Monovalent	NBF	+	260	15.0 ± 1.5
Clone 17	LLB2-31	Monovalent	NBF	+	270	15.9 ± 2.5
Clone 13	LLB1-3-16	Monovalent	NBF	+	32	19.3 ± 2.3

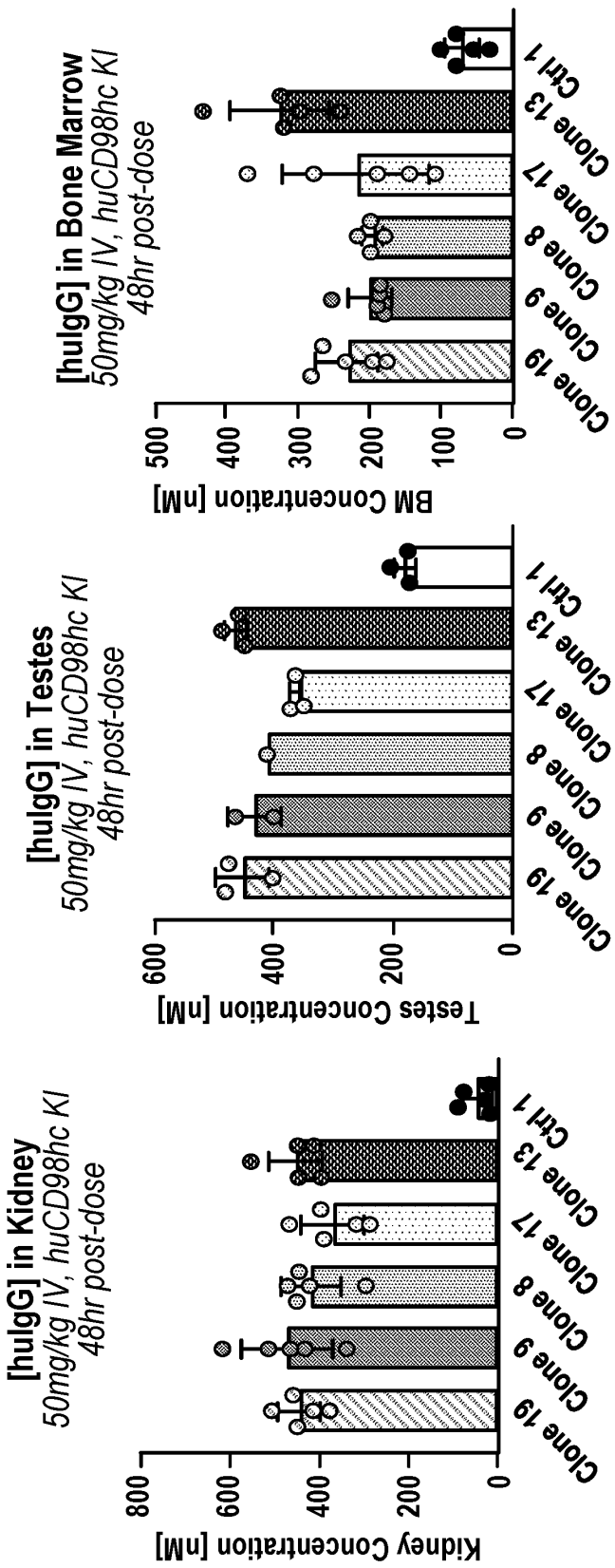


FIG. 11A

FIG. 11B

FIG. 11C

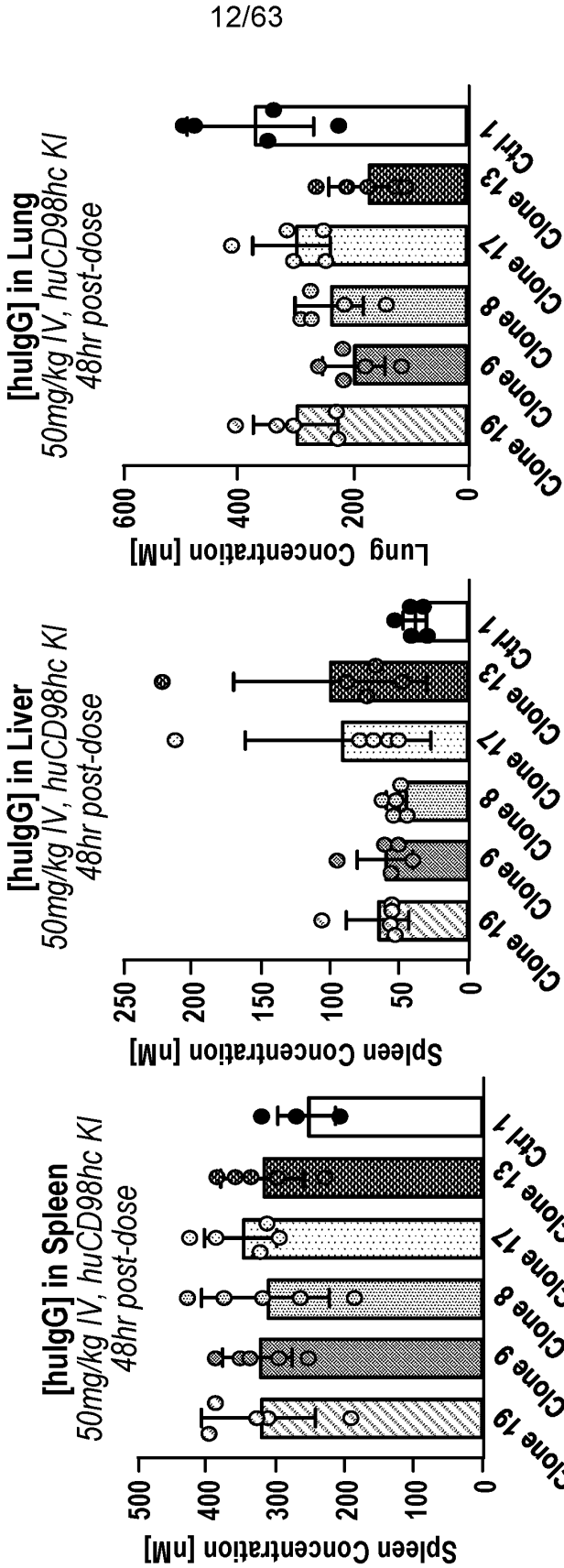


FIG. 11F

FIG. 11E

FIG. 11D

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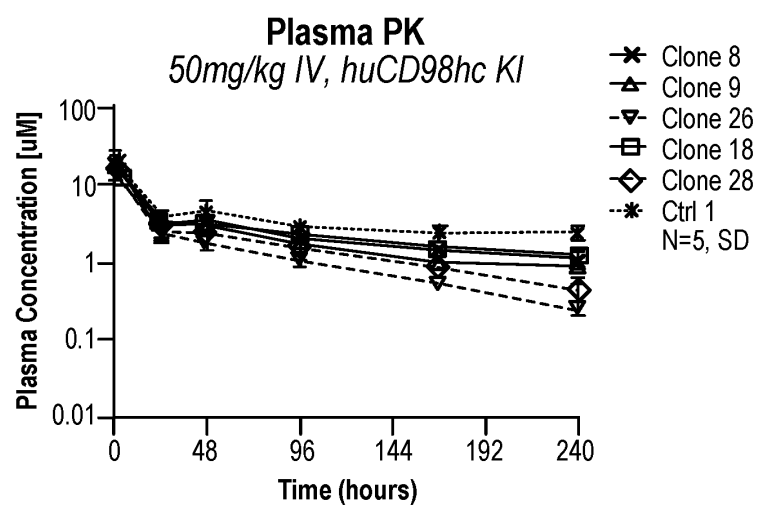


FIG. 12A

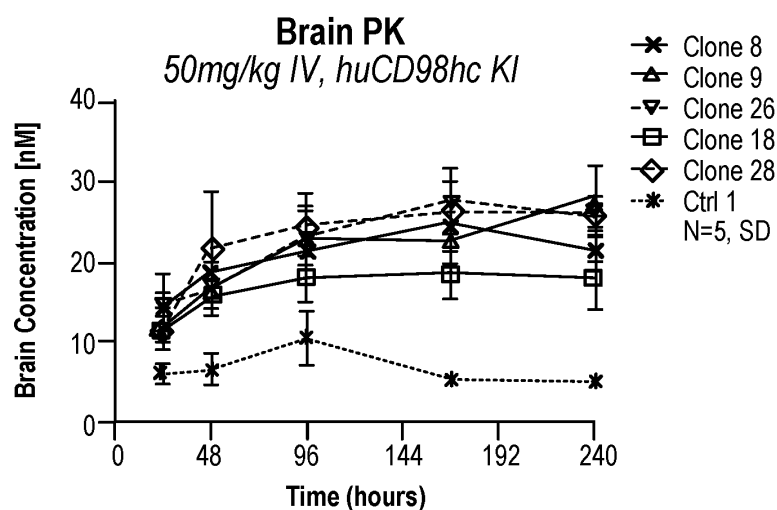
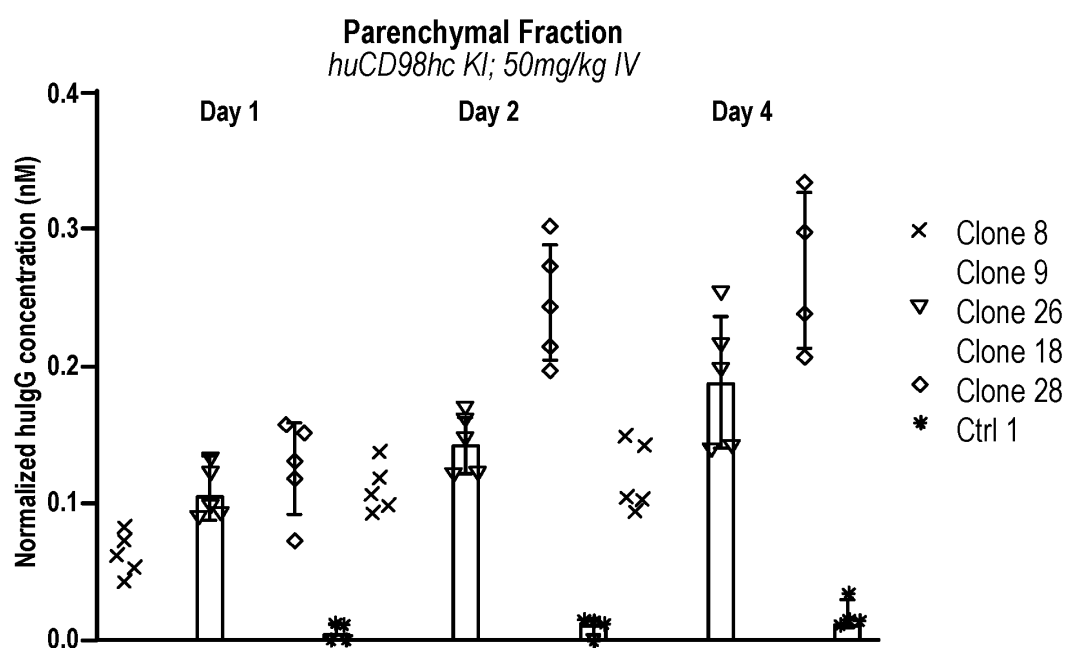


FIG. 12B

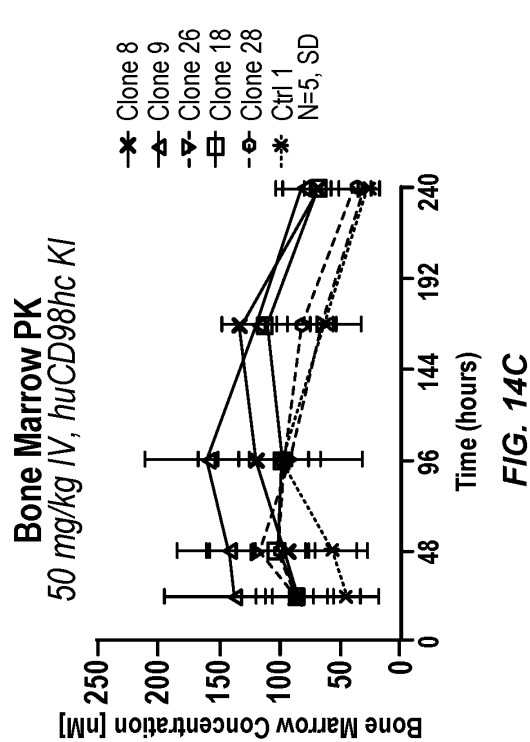
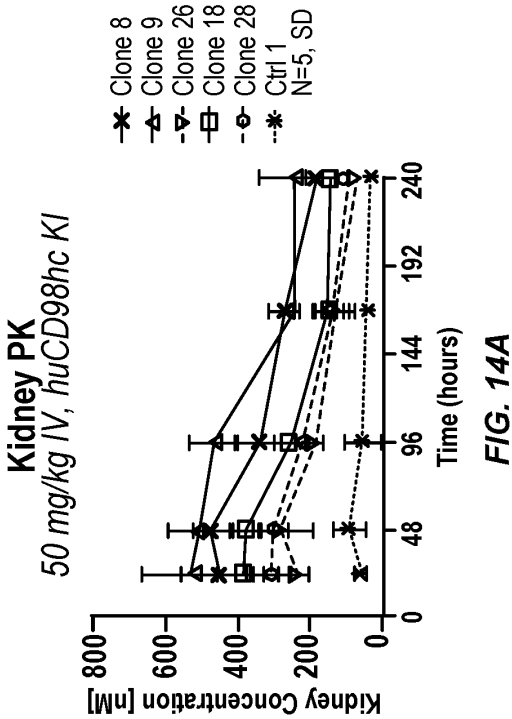
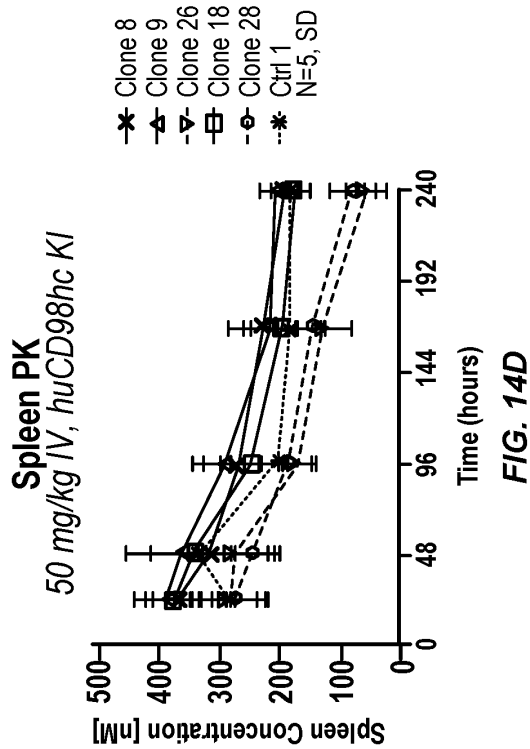
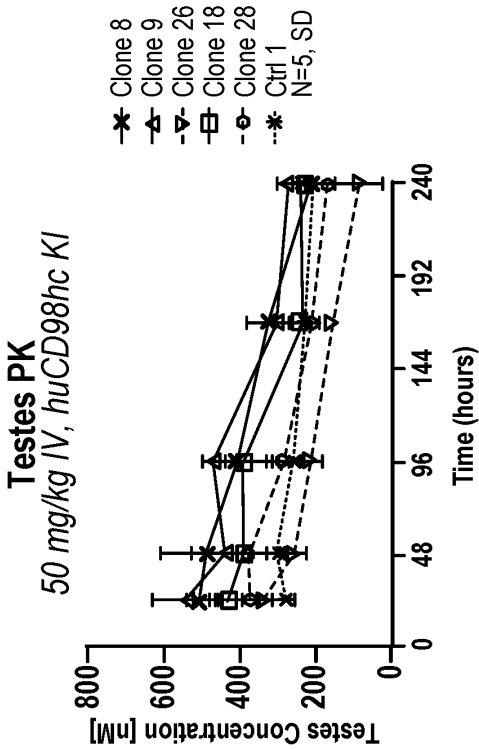
Clone #	Clone Name	CD98hc binding valency	Fabs	EF status	Affinity (nM)	Plasma					Brain				C ₀ (uM)
						C ₀ (uM)	AUC ₀₋₁ (uM*hr)	V (L/kg)	CL (mL/d/kg)		C _{max} (nM)	AUC ₀₋₁ (uM*hr)	T _{max} (hr)	%Extr ap AUC	
Clone 8	LLB2-10-6	Mono	NBF	+	260	20.8	641	0.0724	9.35		24.9	4880	168	76	20.8
Clone 9	LLB2-10-8	Mono	NBF	+	100-200	17.2	567	0.0641	11.9		28.1	5070	240	132	17.2
Clone 26	LLB2-10-8	Bi	NBF	+	100-200	15.6	373	0.0628	20.9		27.7	5440	168	118	15.6
Clone 18	LLB2-37	Mono	NBF	+	390	19.7	652	0.0727	8.91		18.8	4060	168	100	19.7
Clone 28	LLB2-37	Bi	NBF	+	390	19.0	456	0.0647	16.4		26.5	5470	168	109	19.0
Ctrl 1	Non-binding Fab (neg ctrl)	-	NBF	+	N/A	22.8	902	0.0666	4.64		10.5	1780	96	80	22.8

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**FIG. 13**

SUBSTITUTE SHEET (RULE 26)



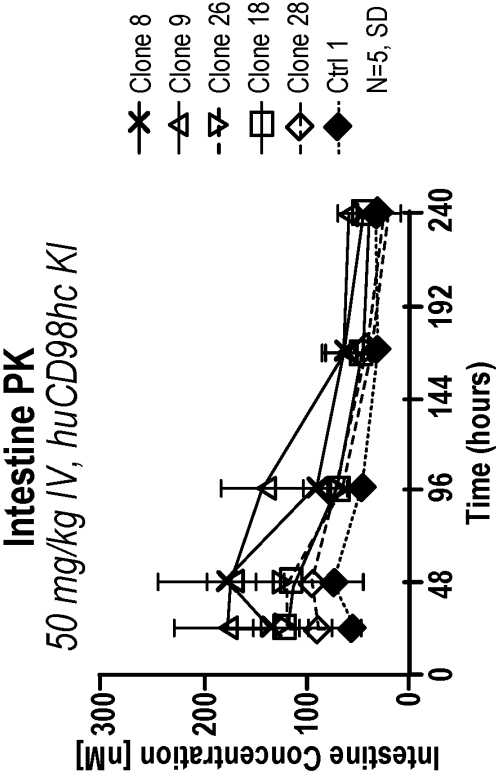


FIG. 14F

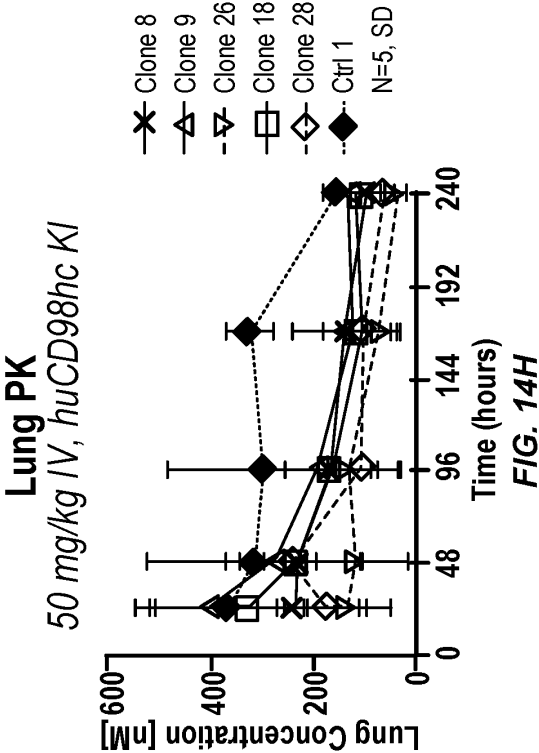


FIG. 14H

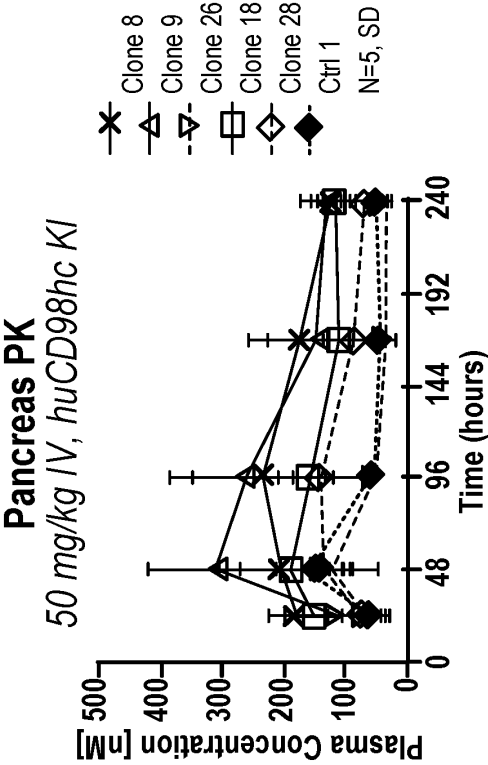


FIG. 14E

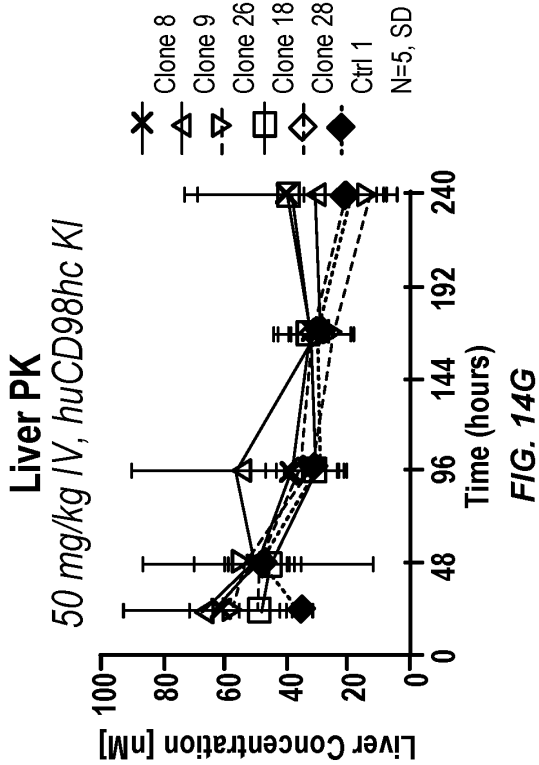


FIG. 14G

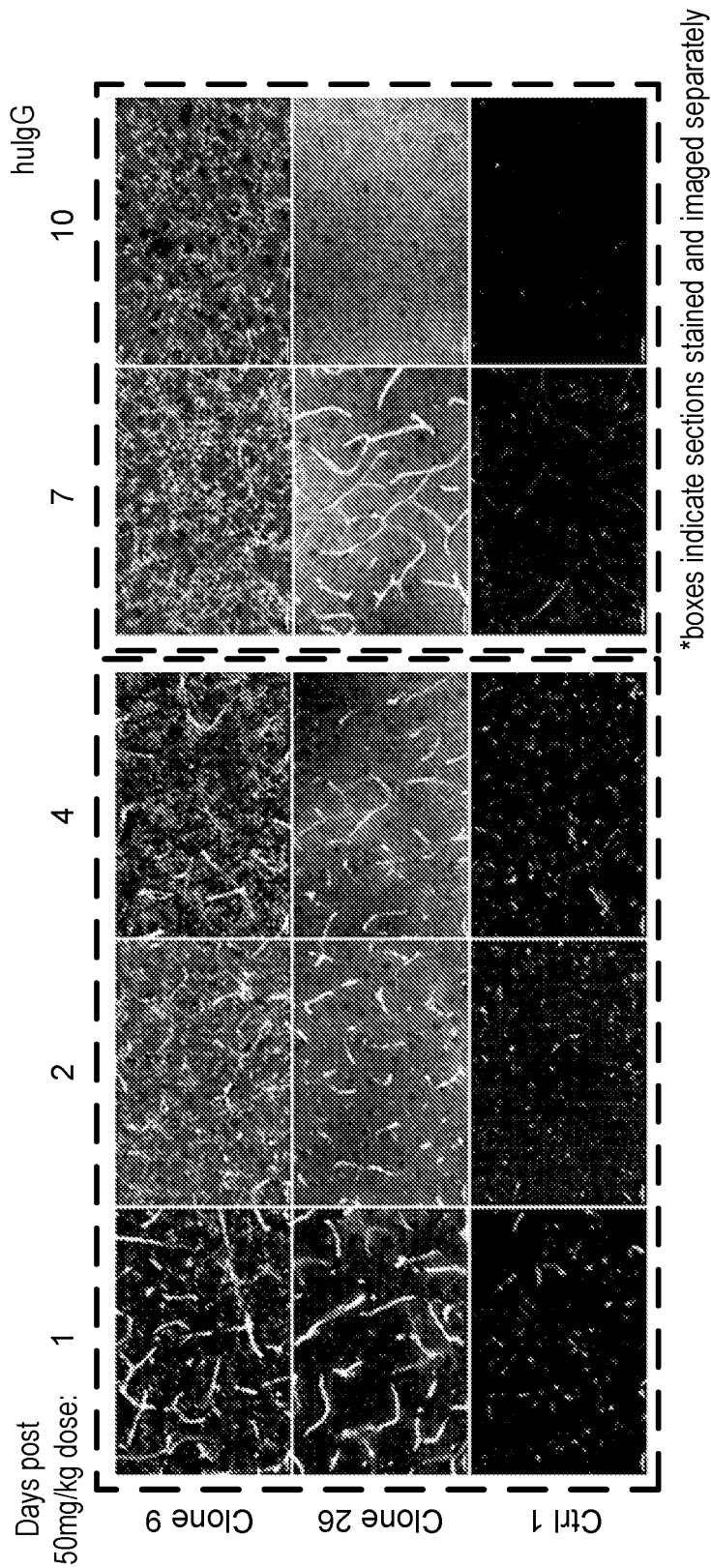


FIG. 15

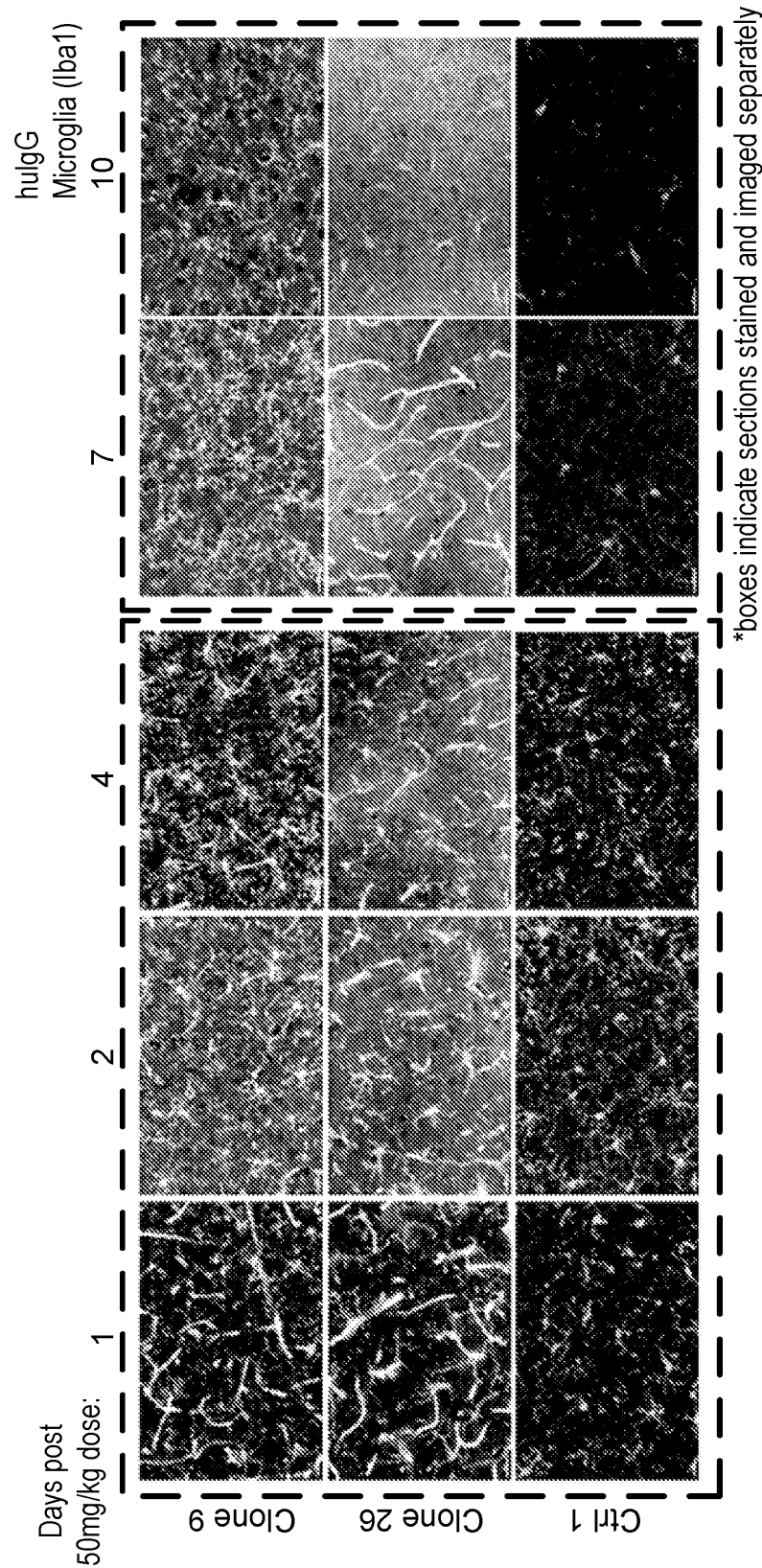


FIG. 16

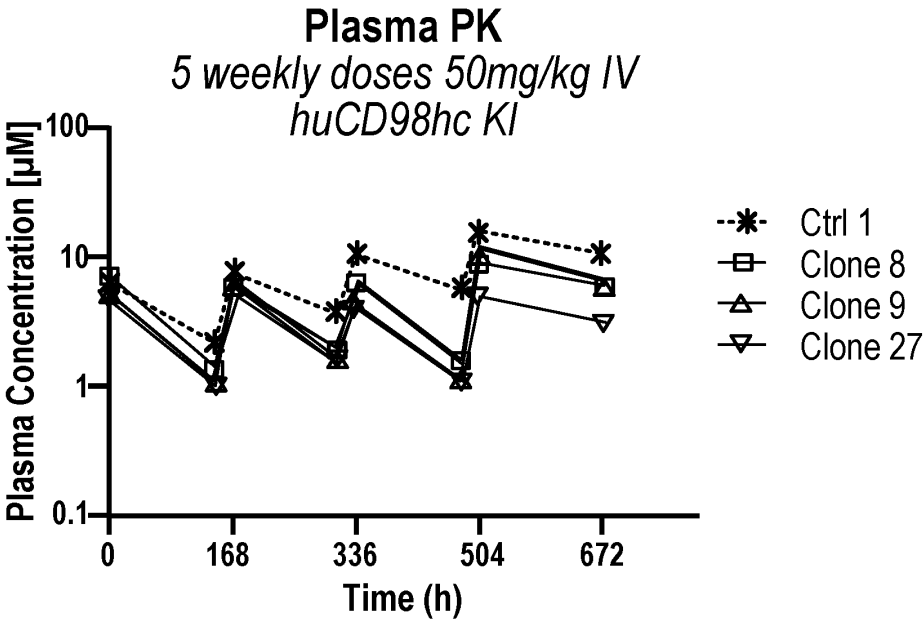


FIG. 17A

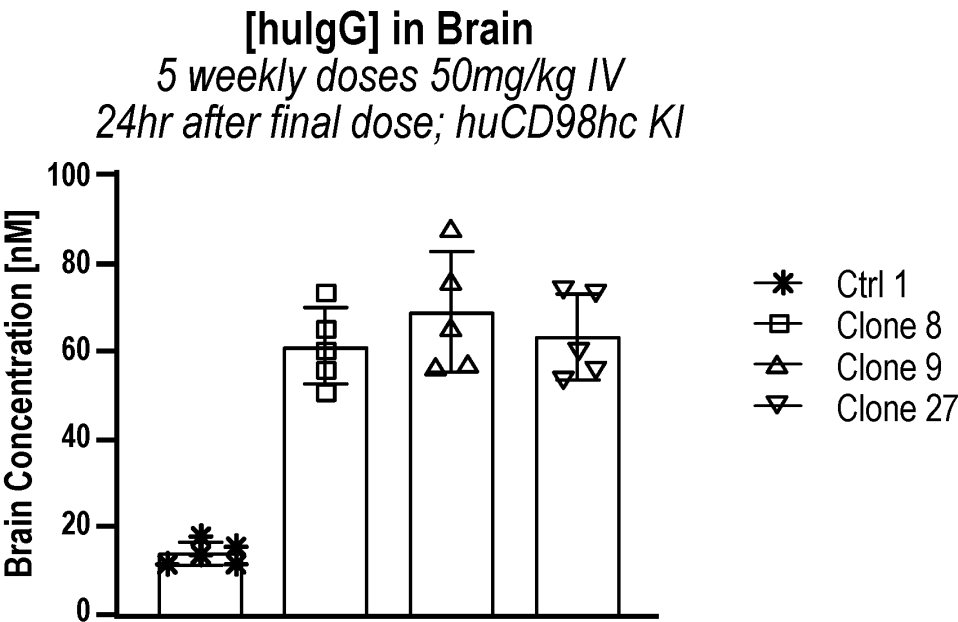


FIG. 17B

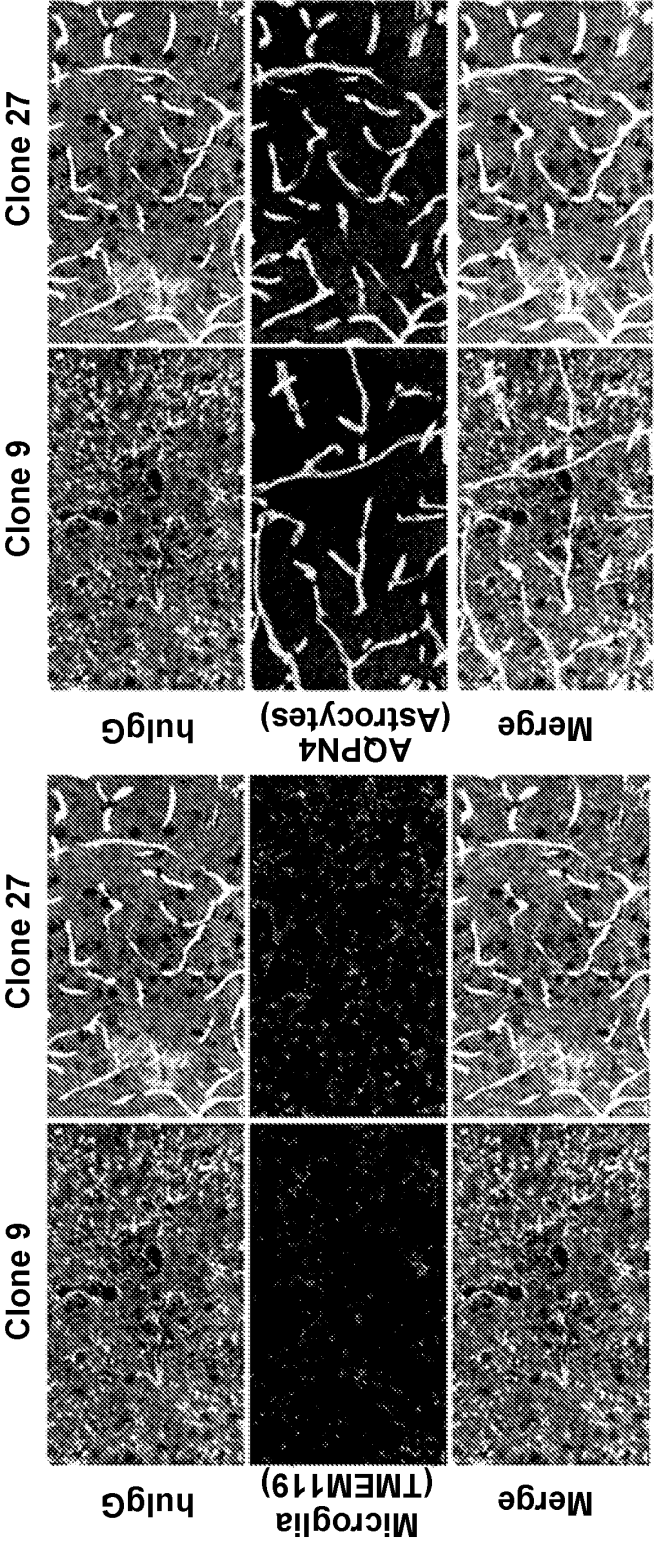


FIG. 18

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FIG. 19A



Library residues

FIG. 19B

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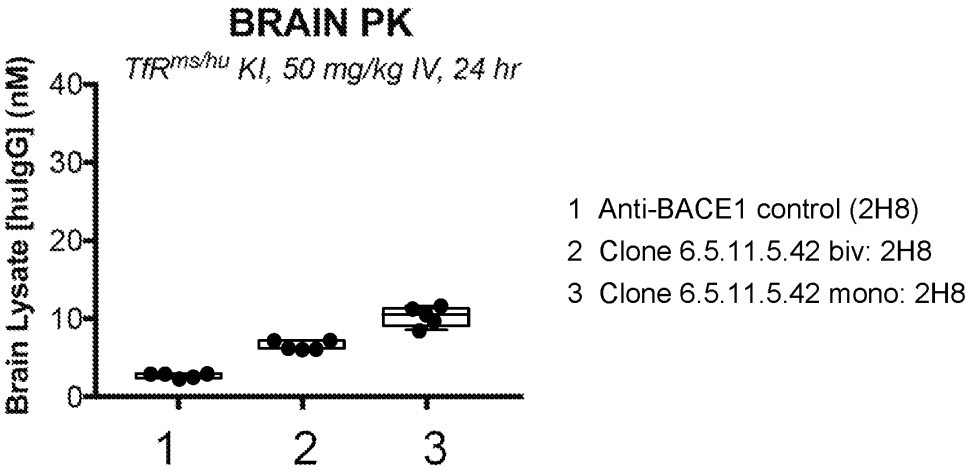


FIG. 20A

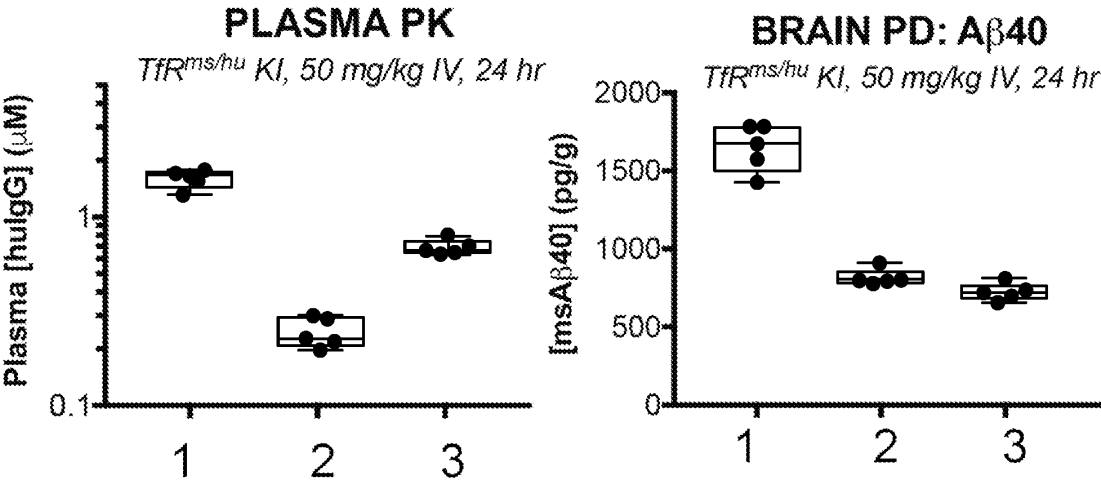


FIG. 20B

FIG. 20C

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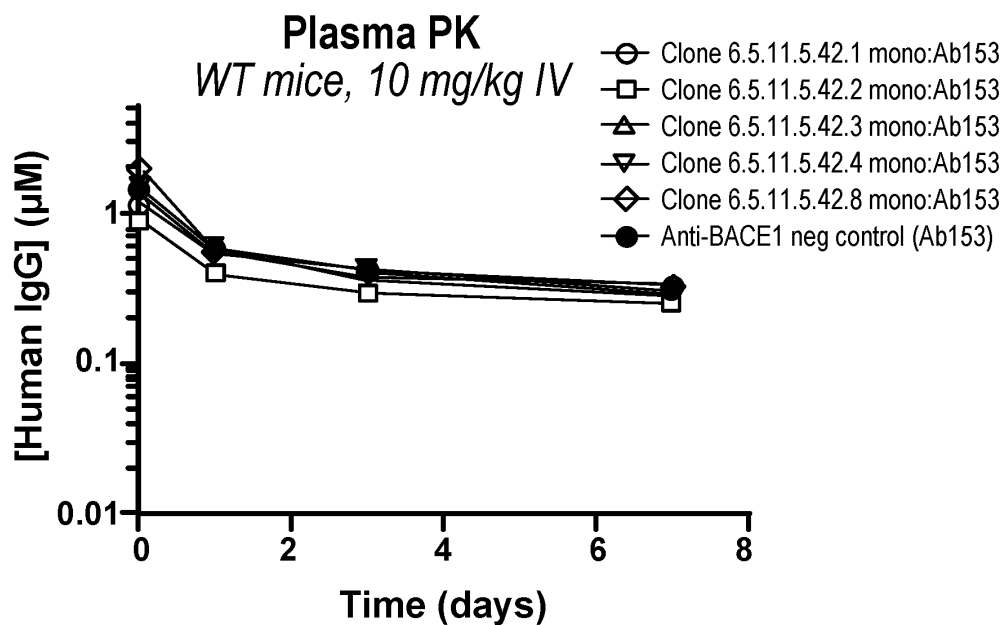


FIG. 21A

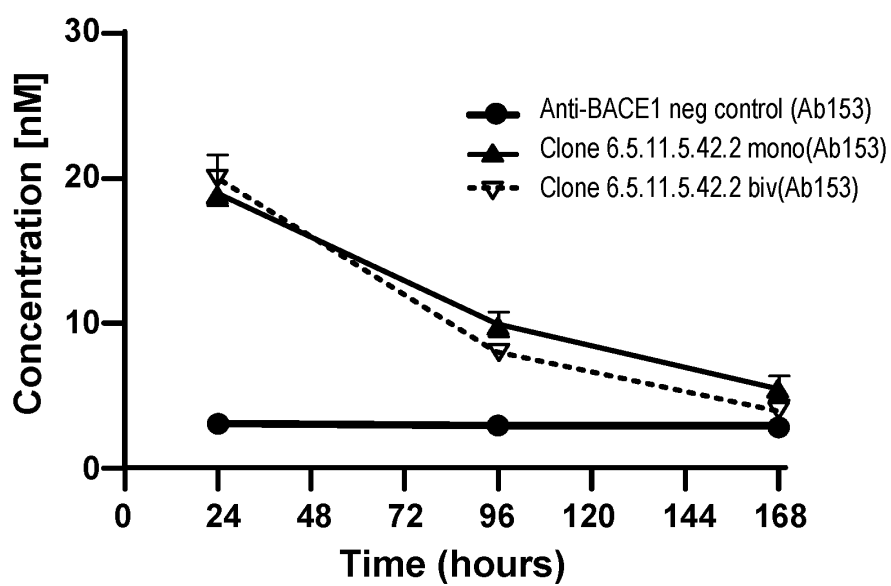


FIG. 21B

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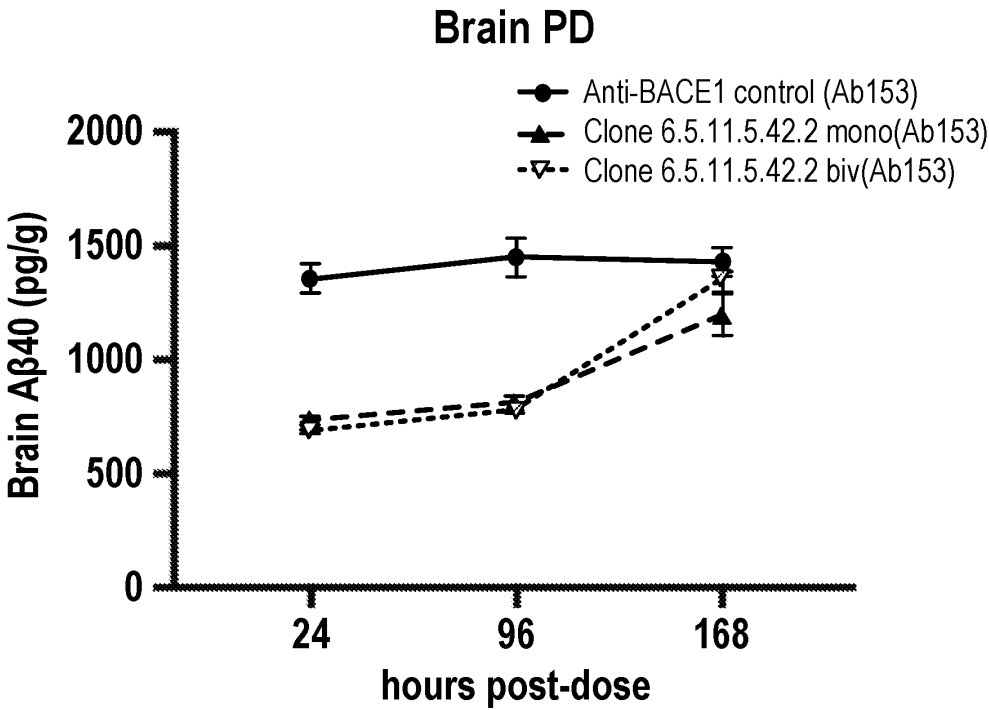


FIG. 21C

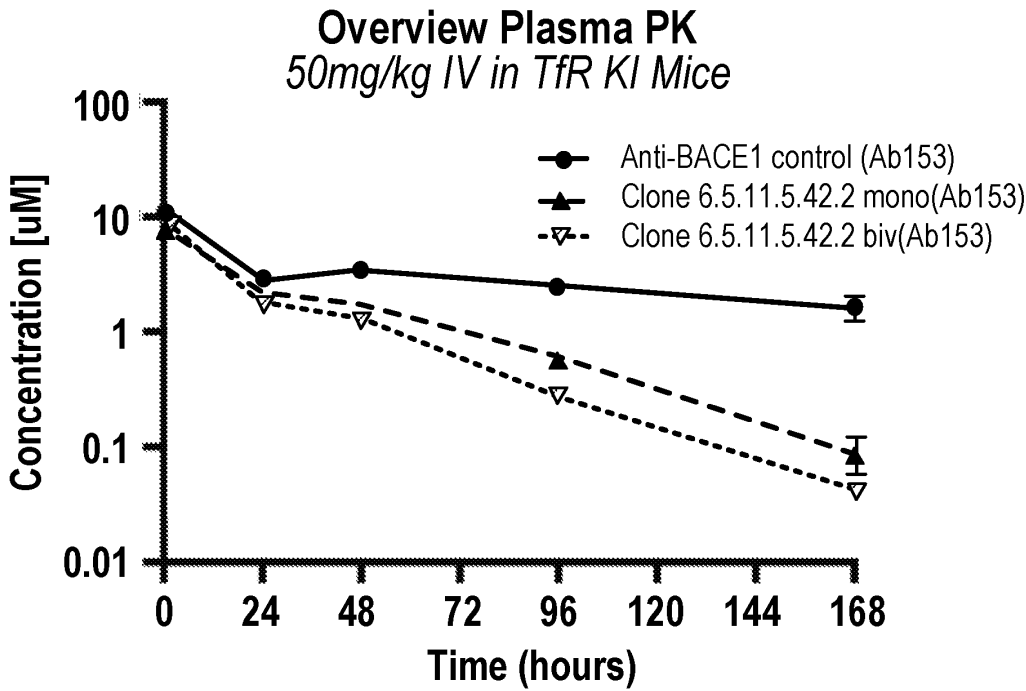
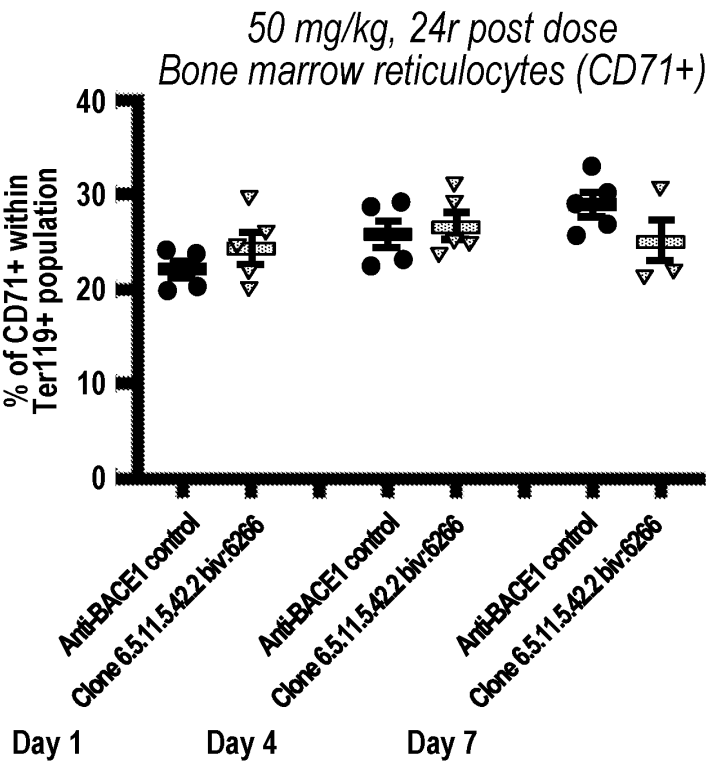
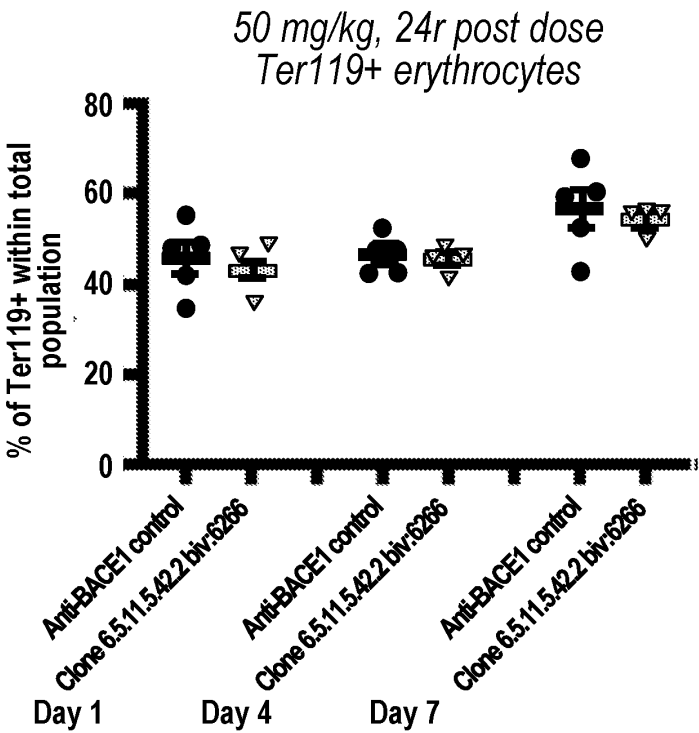
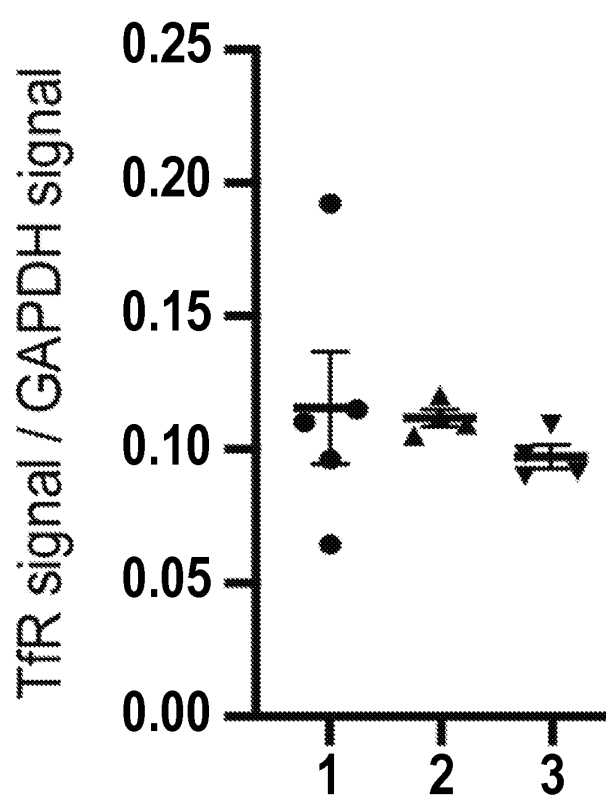


FIG. 21D

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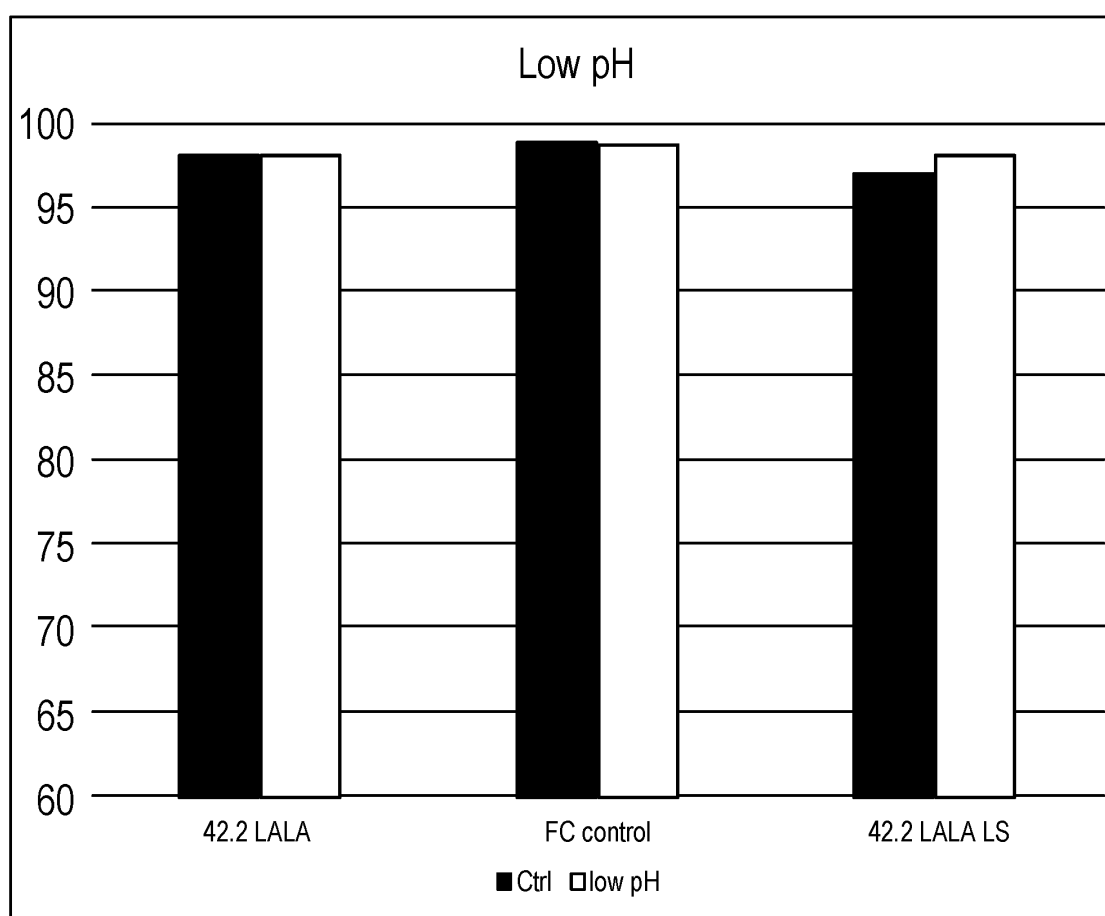


1. Anti-BACE1 control (Ab153)
2. Clone 6.5.11.5.42.2 mono:Ab153
3. Clone 6.5.11.5.42.2 biv:Ab153

FIG. 21G

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**FIG.22**

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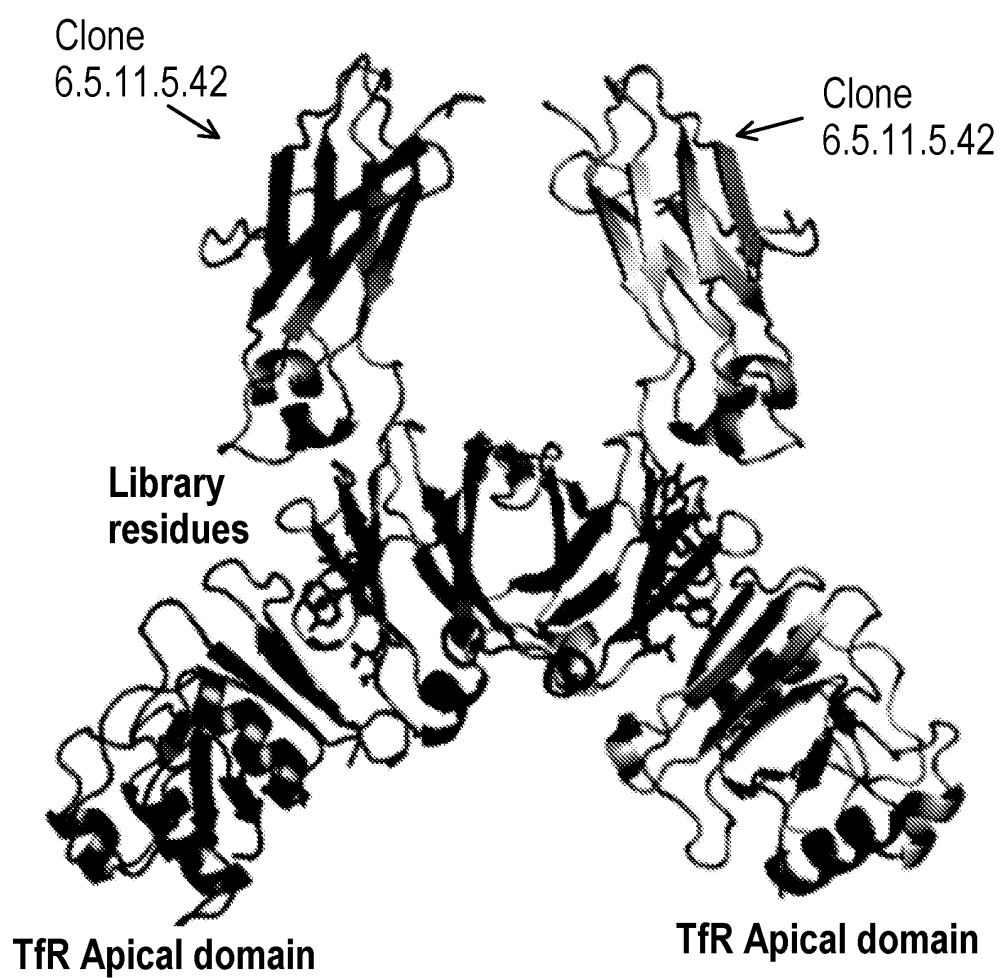


FIG. 23A

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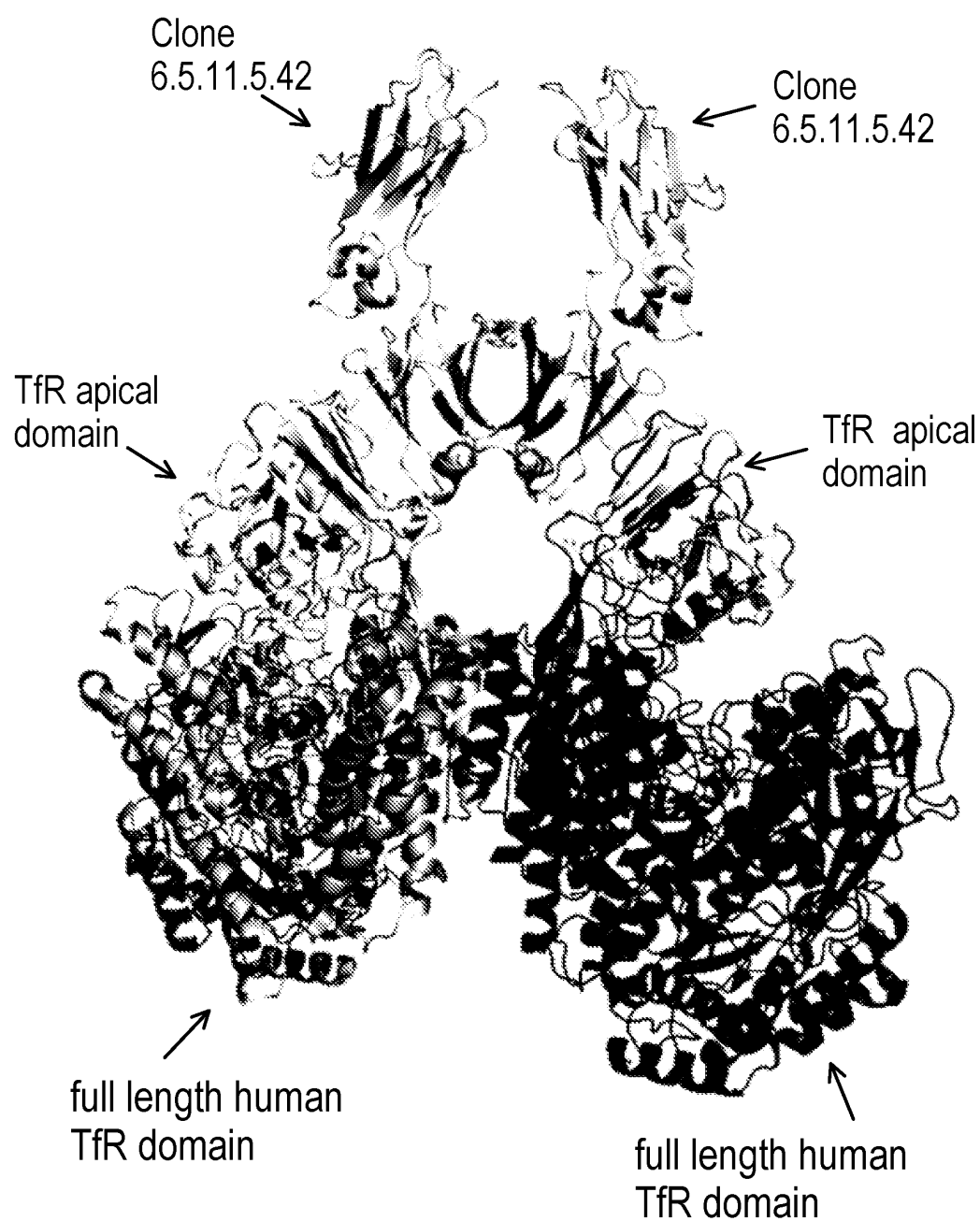


FIG. 23B

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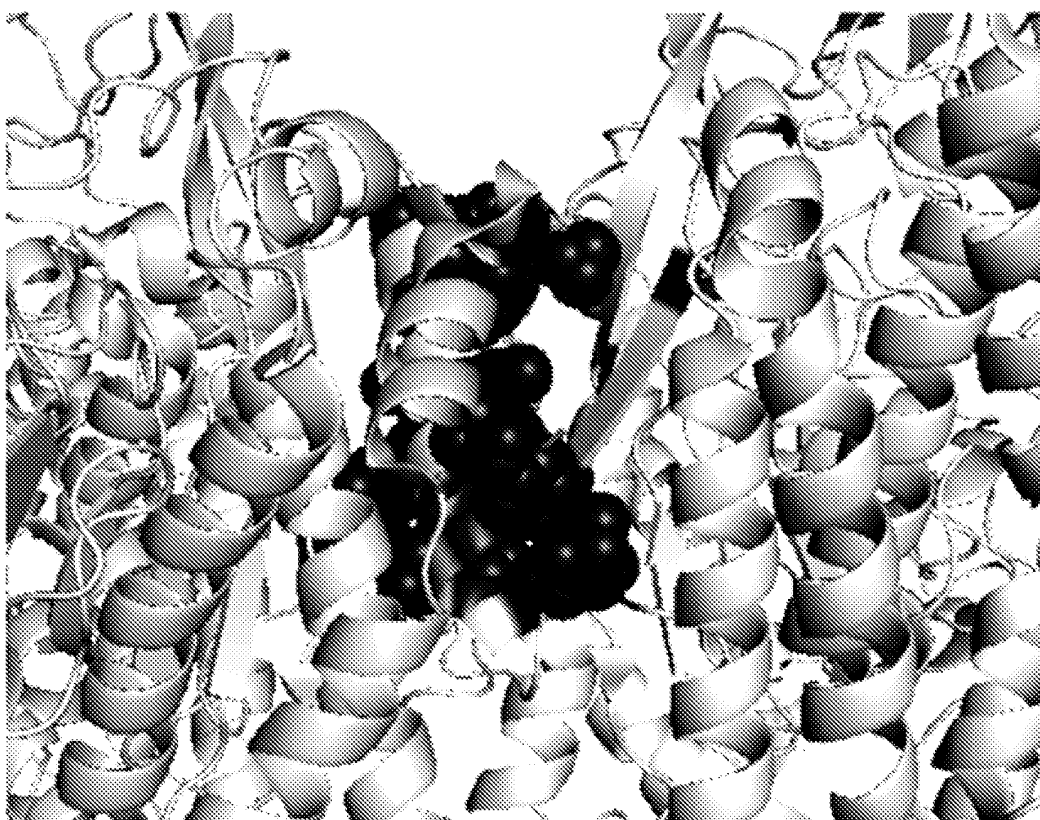


FIG. 23C

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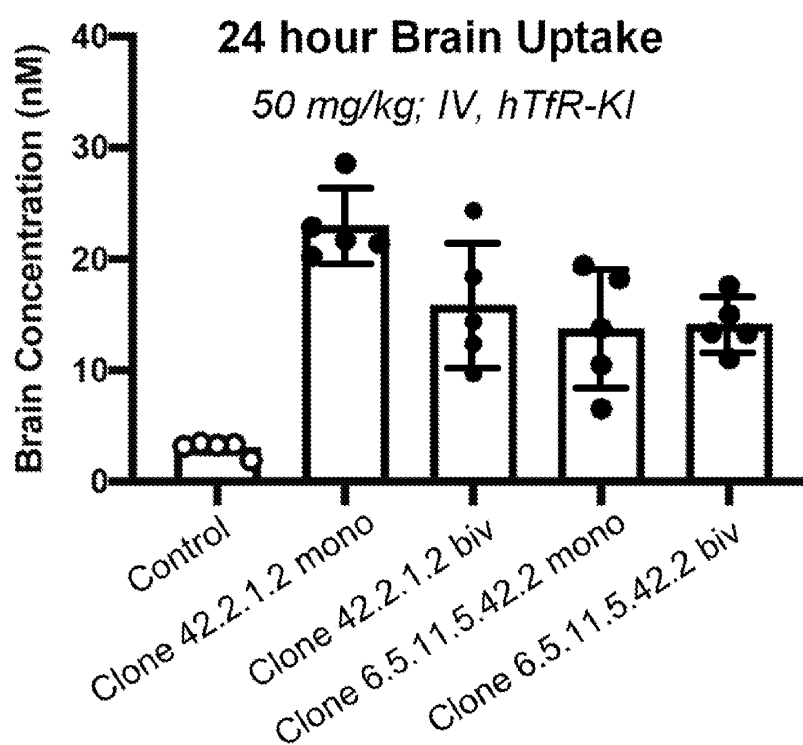


FIG. 24A

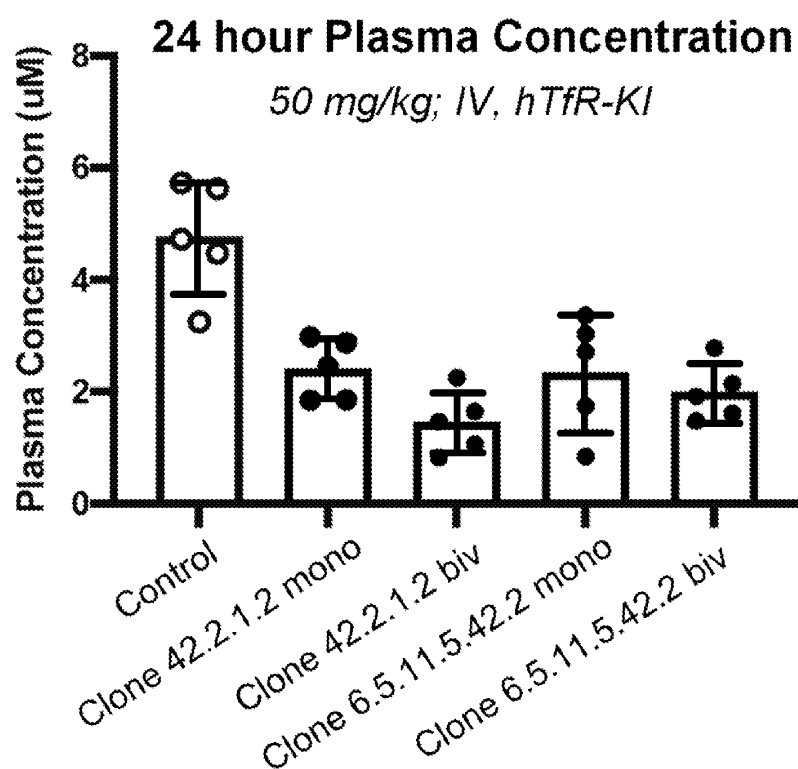
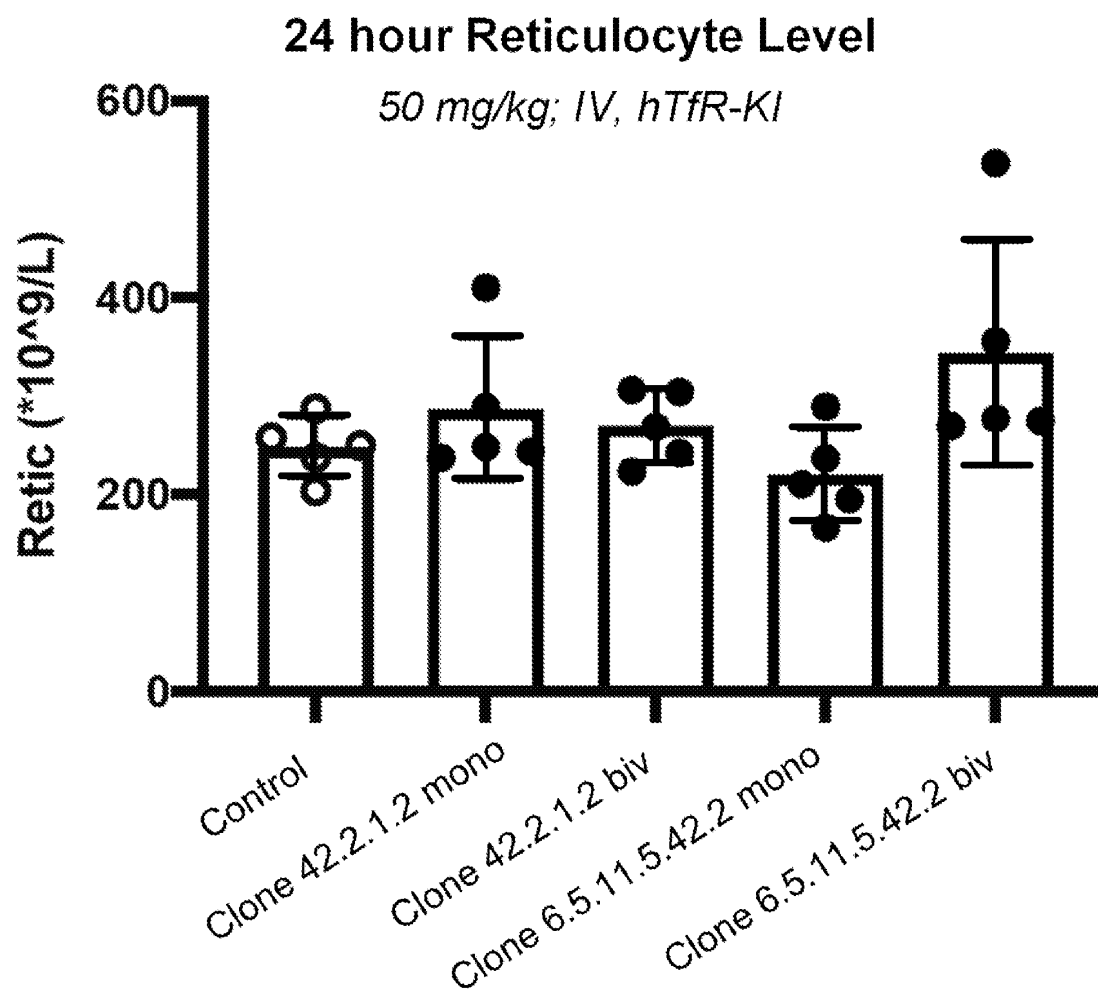


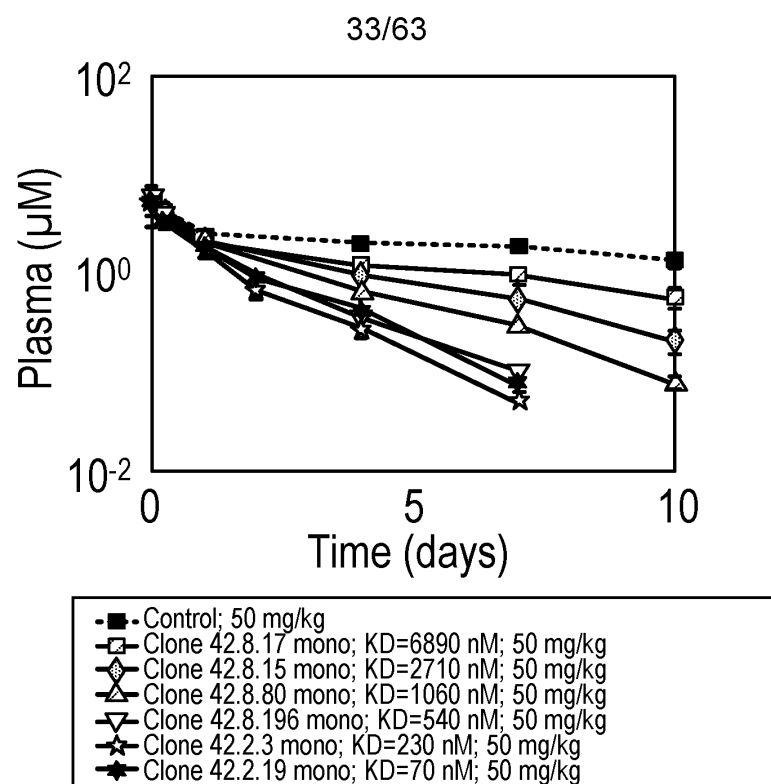
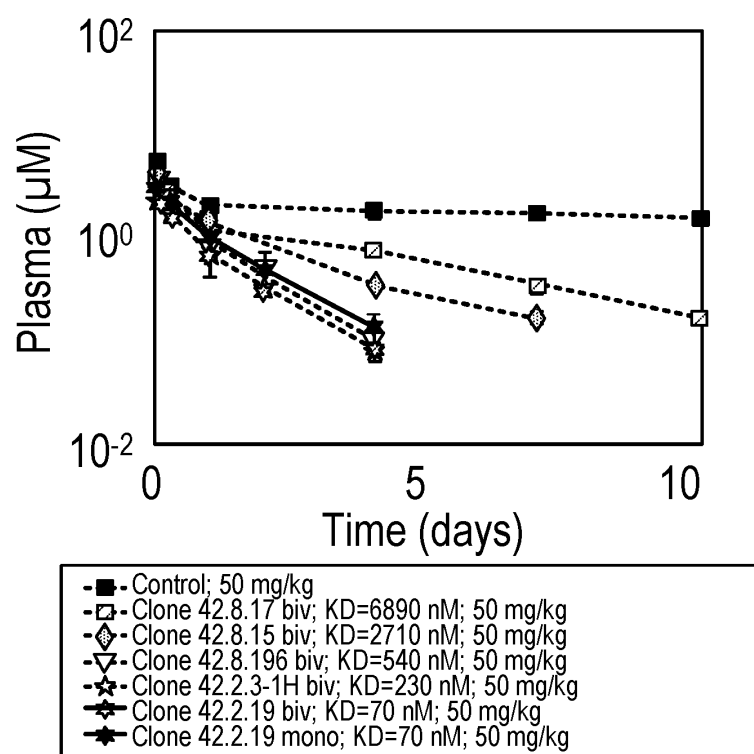
FIG. 24B

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**FIG. 25**

SUBSTITUTE SHEET (RULE 26)

**FIG. 26A****FIG. 26B**

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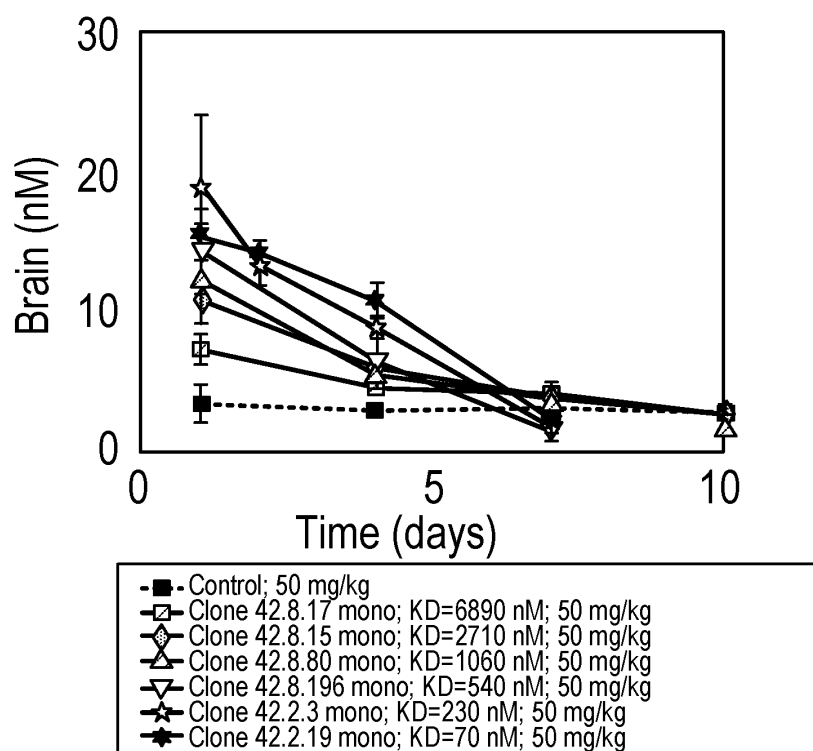


FIG. 26C

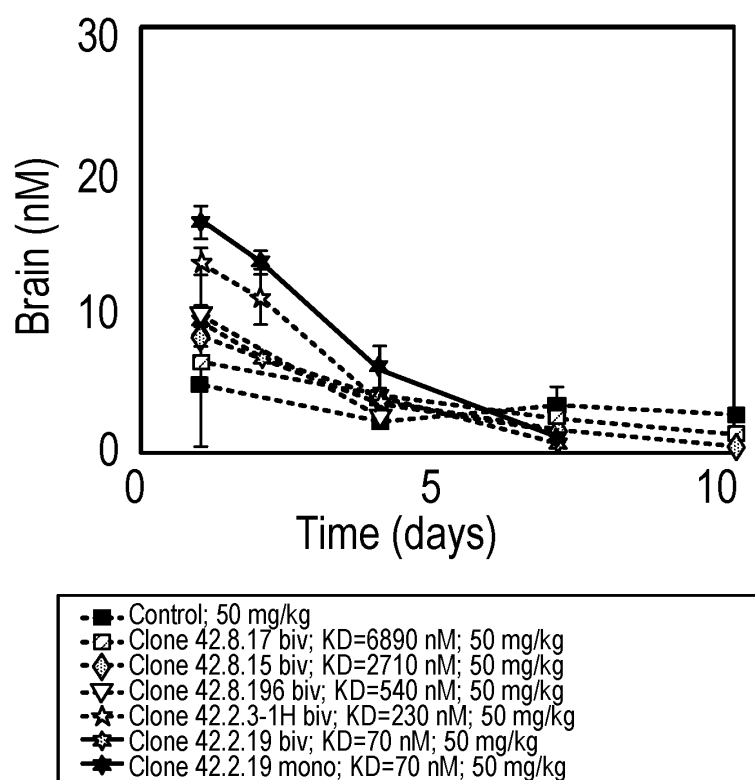


FIG. 26D

SUBSTITUTE SHEET (RULE 26)

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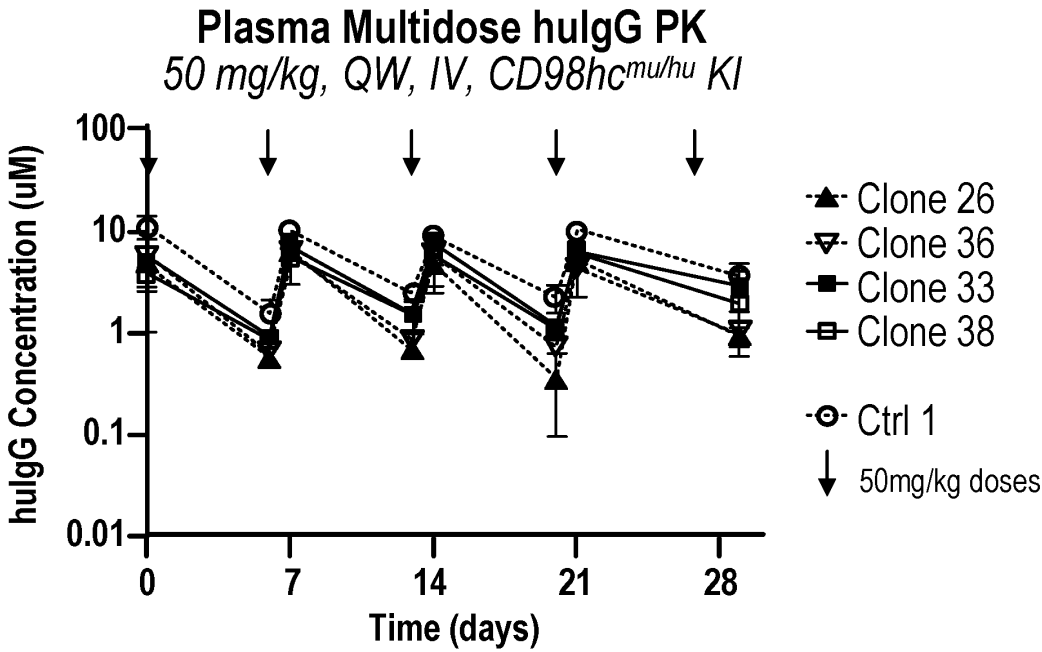


FIG. 27A

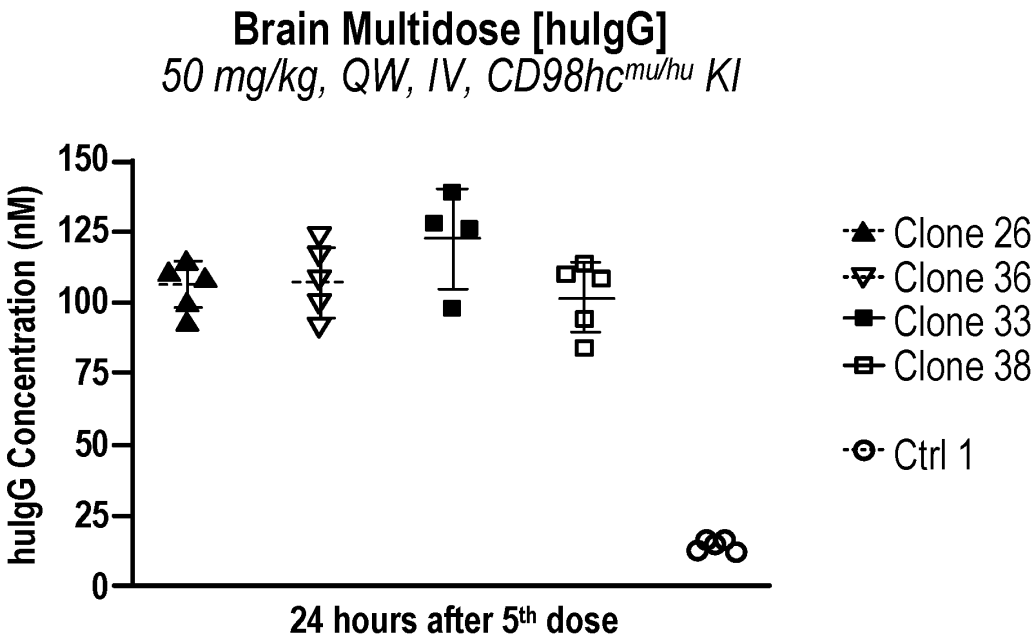


FIG. 27B

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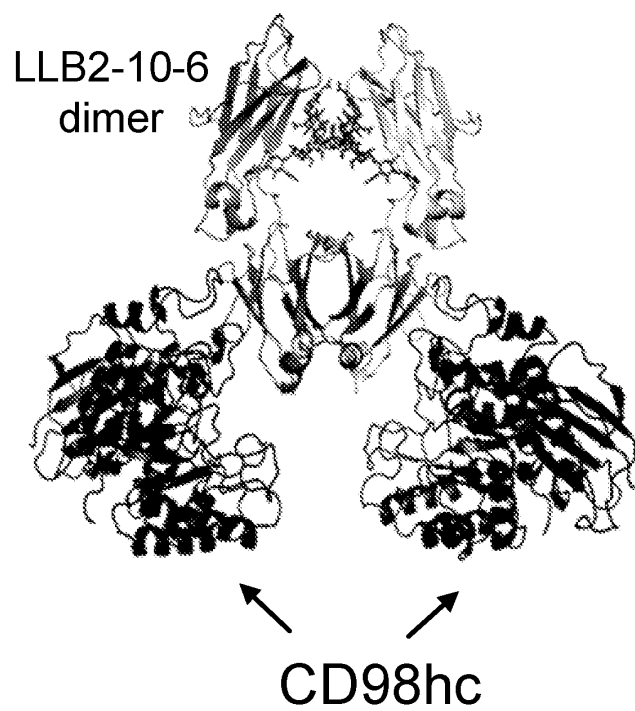


FIG. 28A

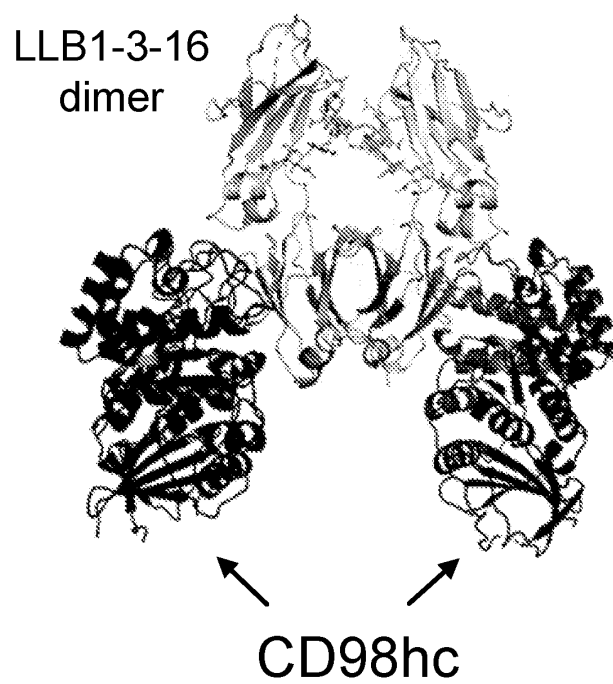


FIG. 28B

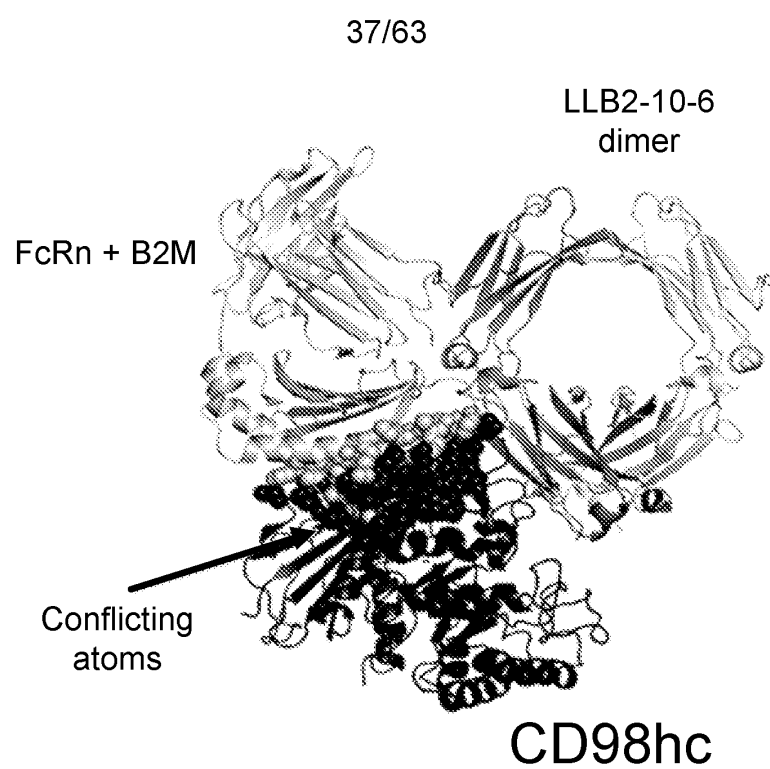


FIG. 29A

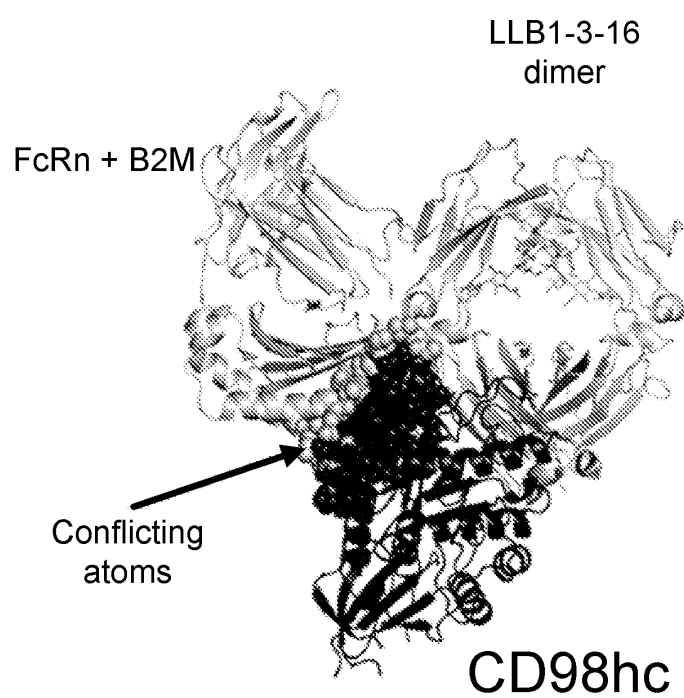


FIG. 29B

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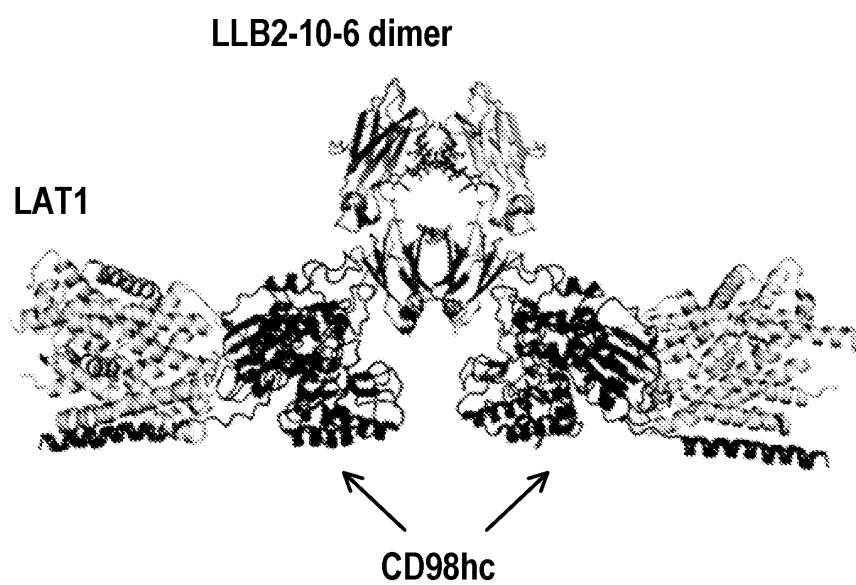


FIG. 30A

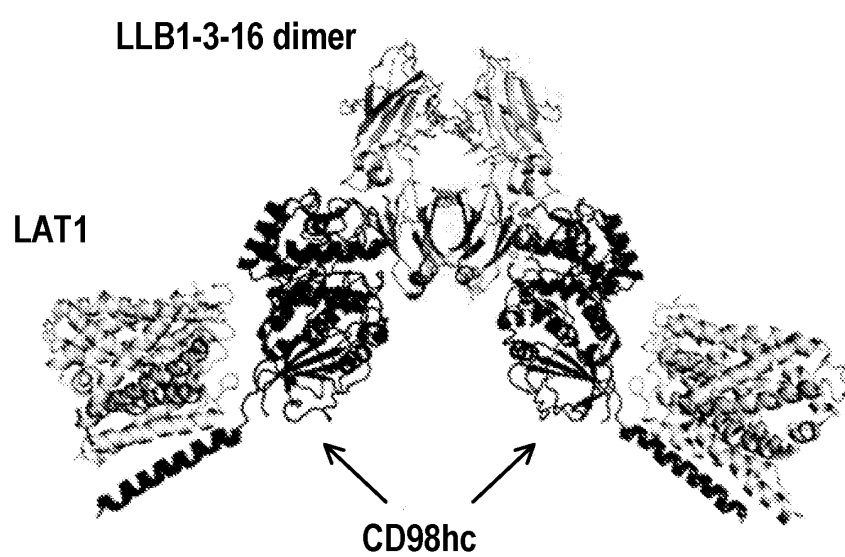


FIG. 30B

SUBSTITUTE SHEET (RULE 26)

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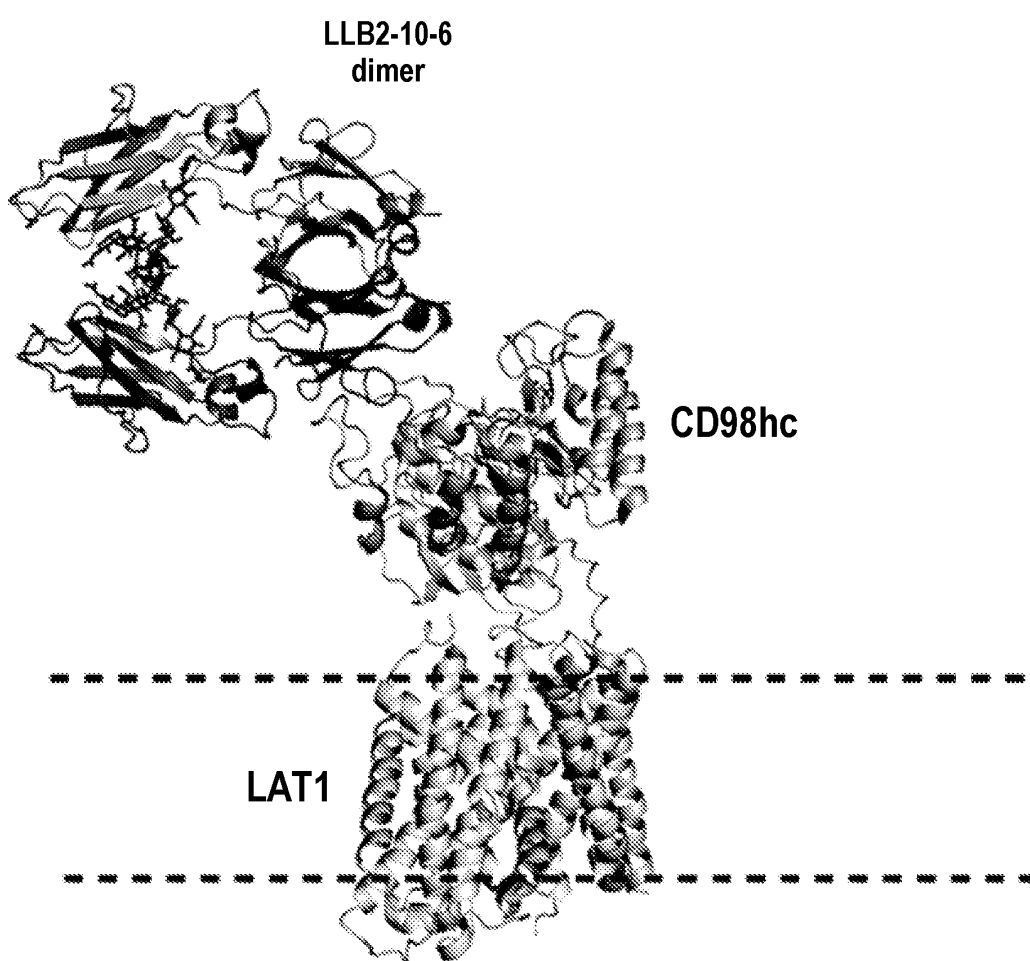


FIG. 30C

SUBSTITUTE SHEET (RULE 26)

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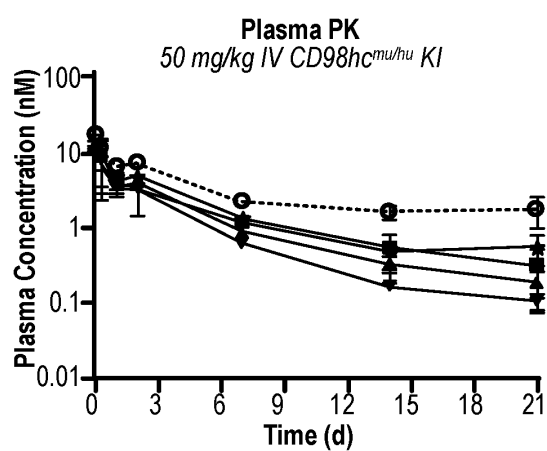


FIG. 31A

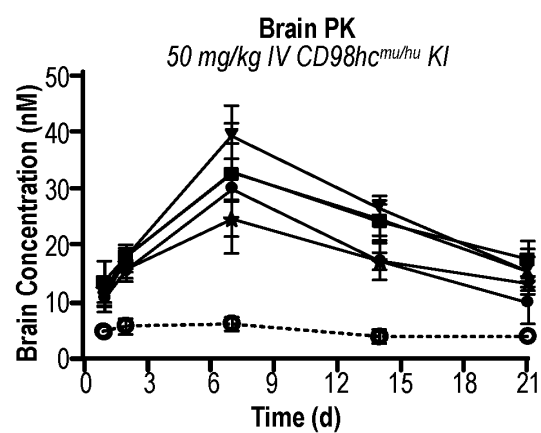


FIG. 31B

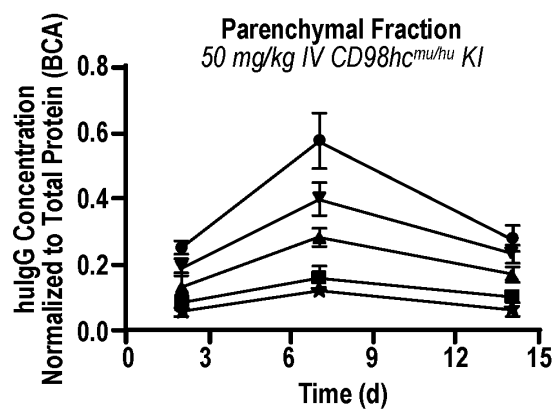
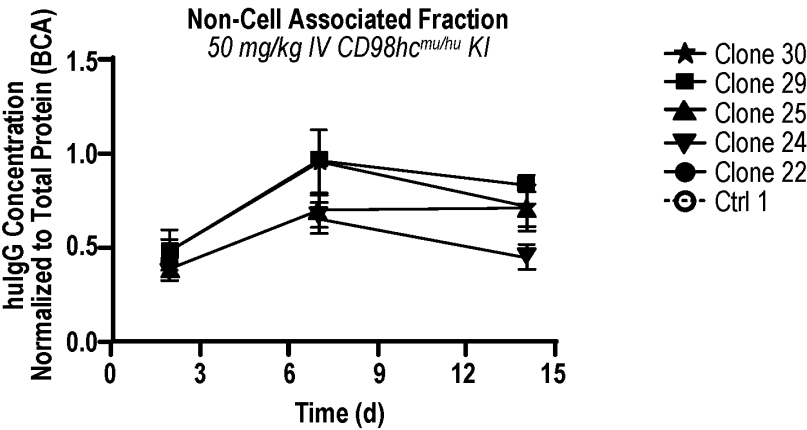
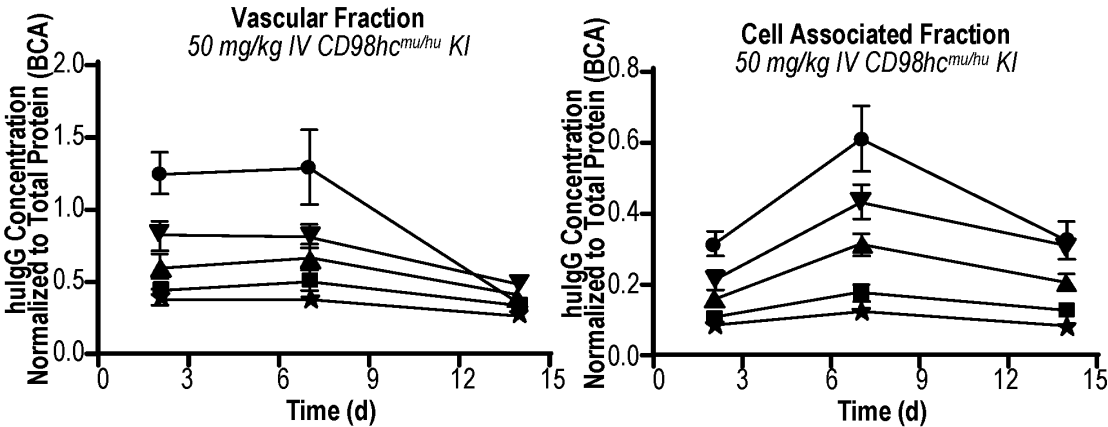


FIG. 31C

- ★ Clone 30
- Clone 29
- ▲ Clone 25
- ▼ Clone 24
- Clone 22
- Ctrl 1



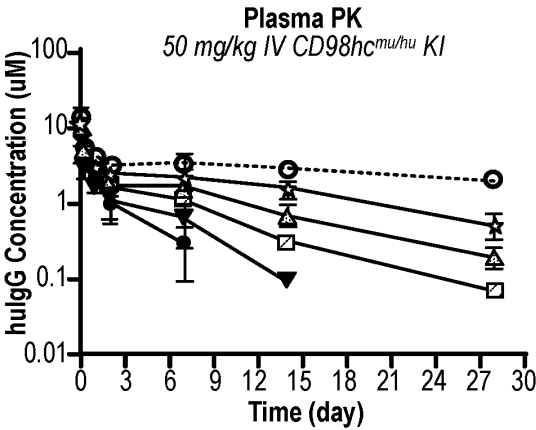


FIG. 32A

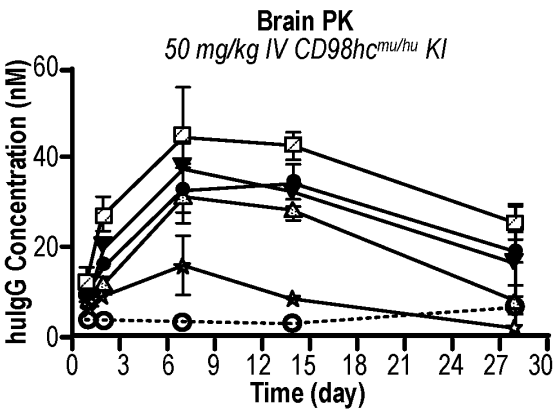


FIG. 32B

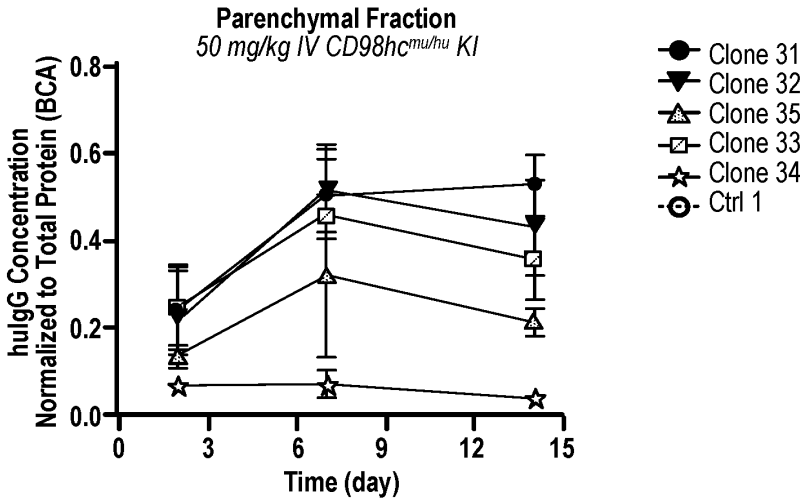


FIG. 32C

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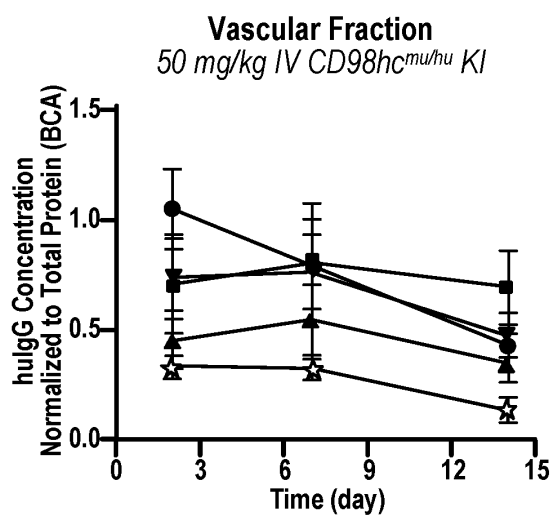


FIG. 32D

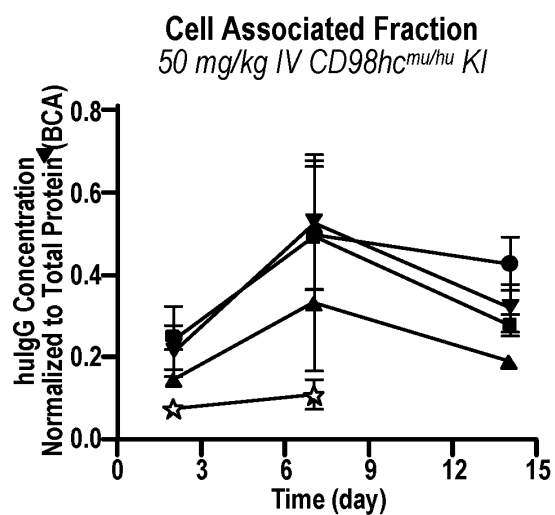


FIG. 32E

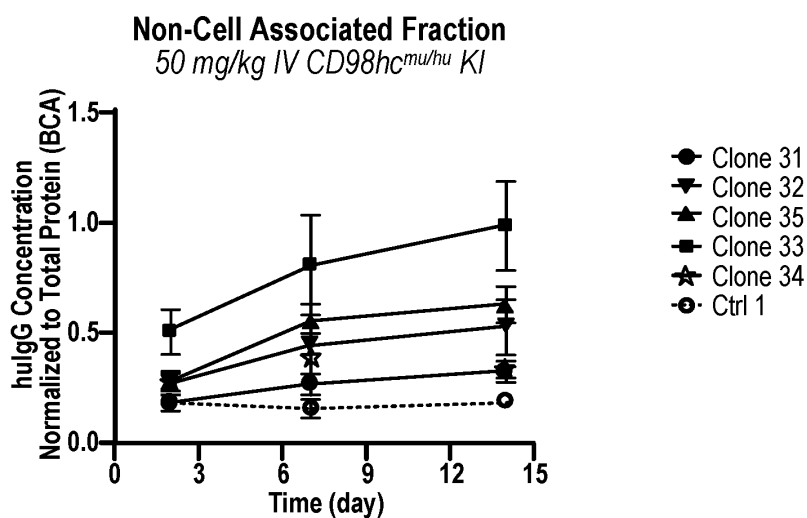


FIG. 32F

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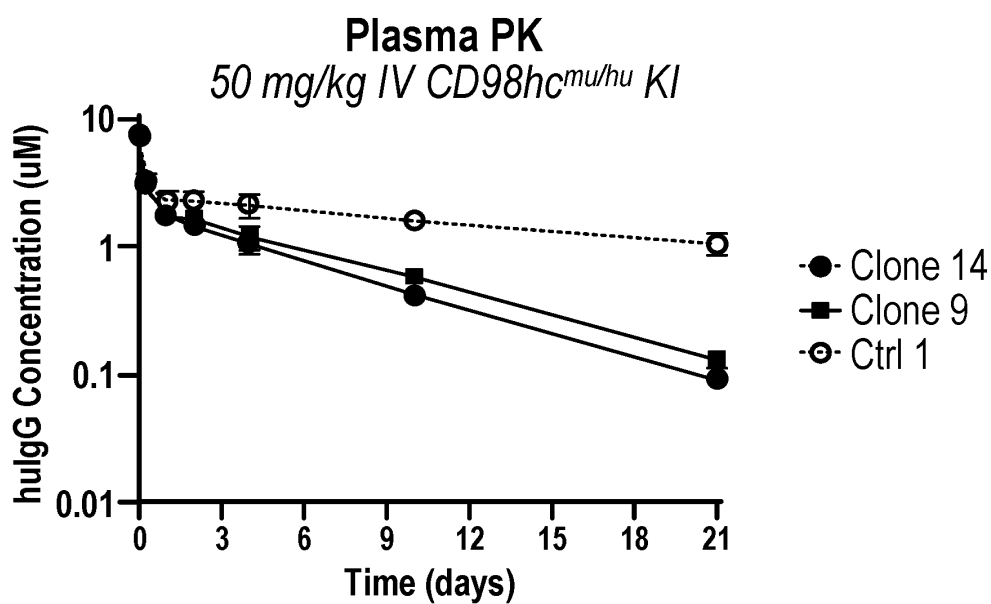


FIG. 33A

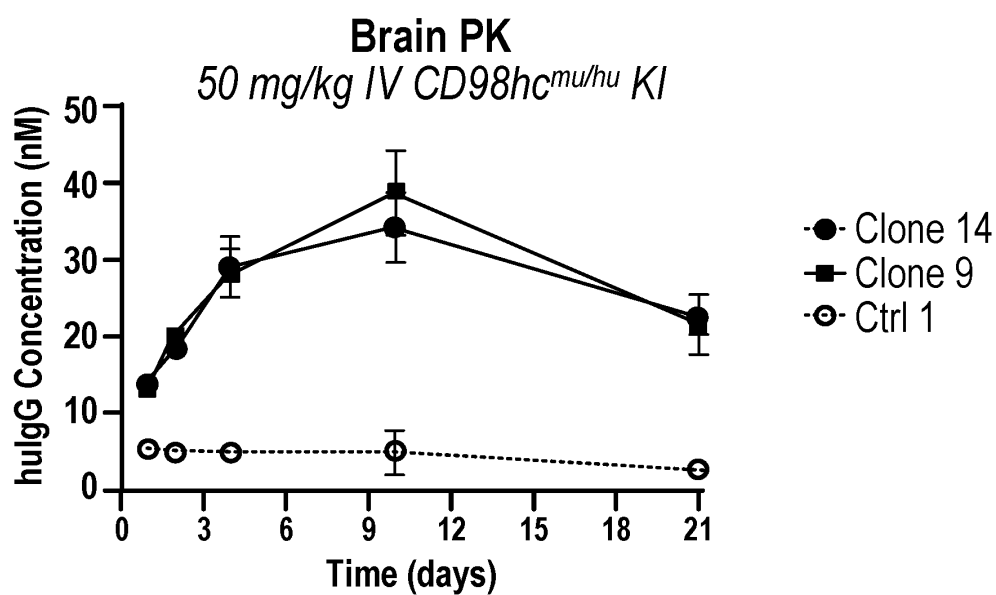


FIG. 33B

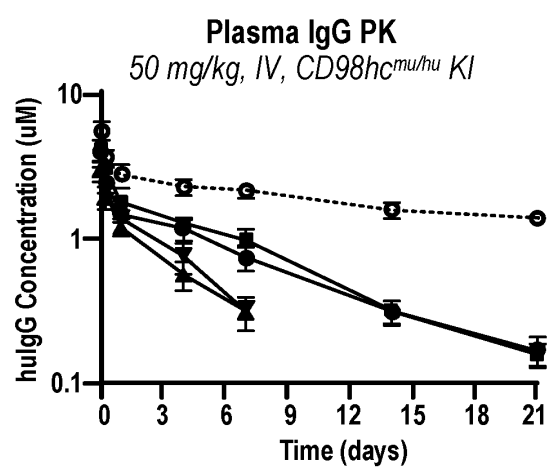


FIG. 34A

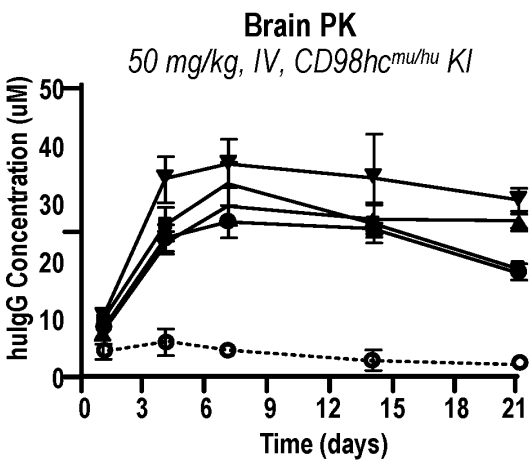


FIG. 34B

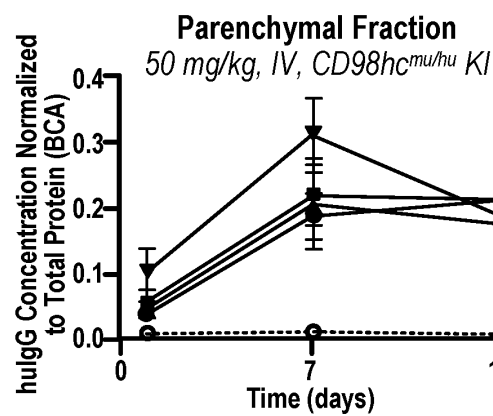


FIG. 34C

- Clone 27
- Clone 9
- ▲ Clone 37
- ▼ Clone 26
- Ctrl 1

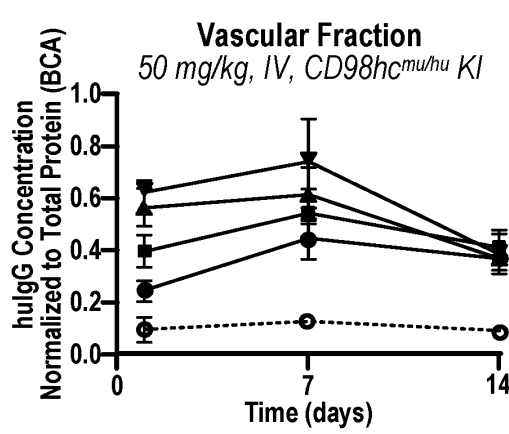


FIG. 34D

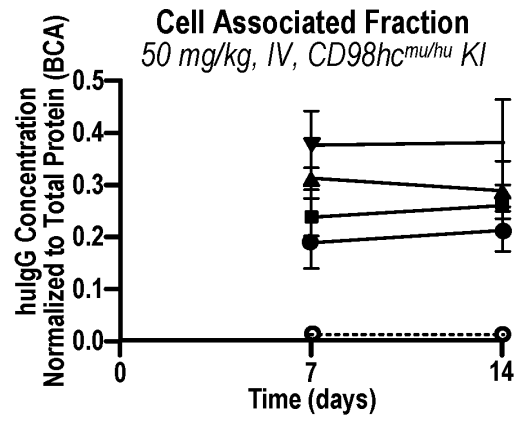


FIG. 34E

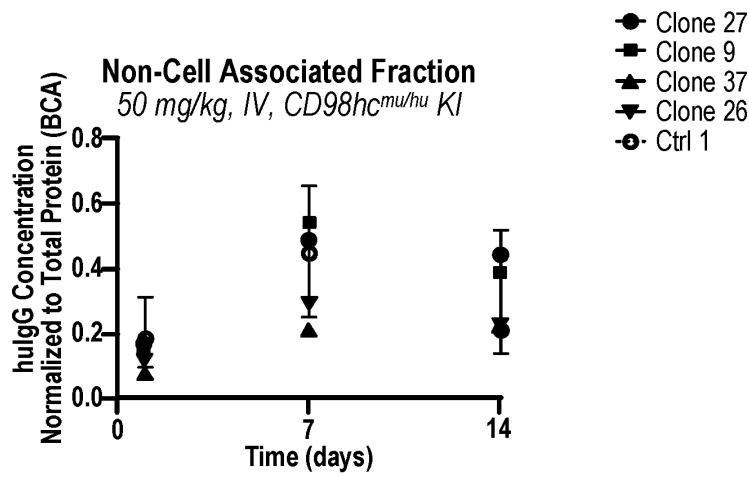
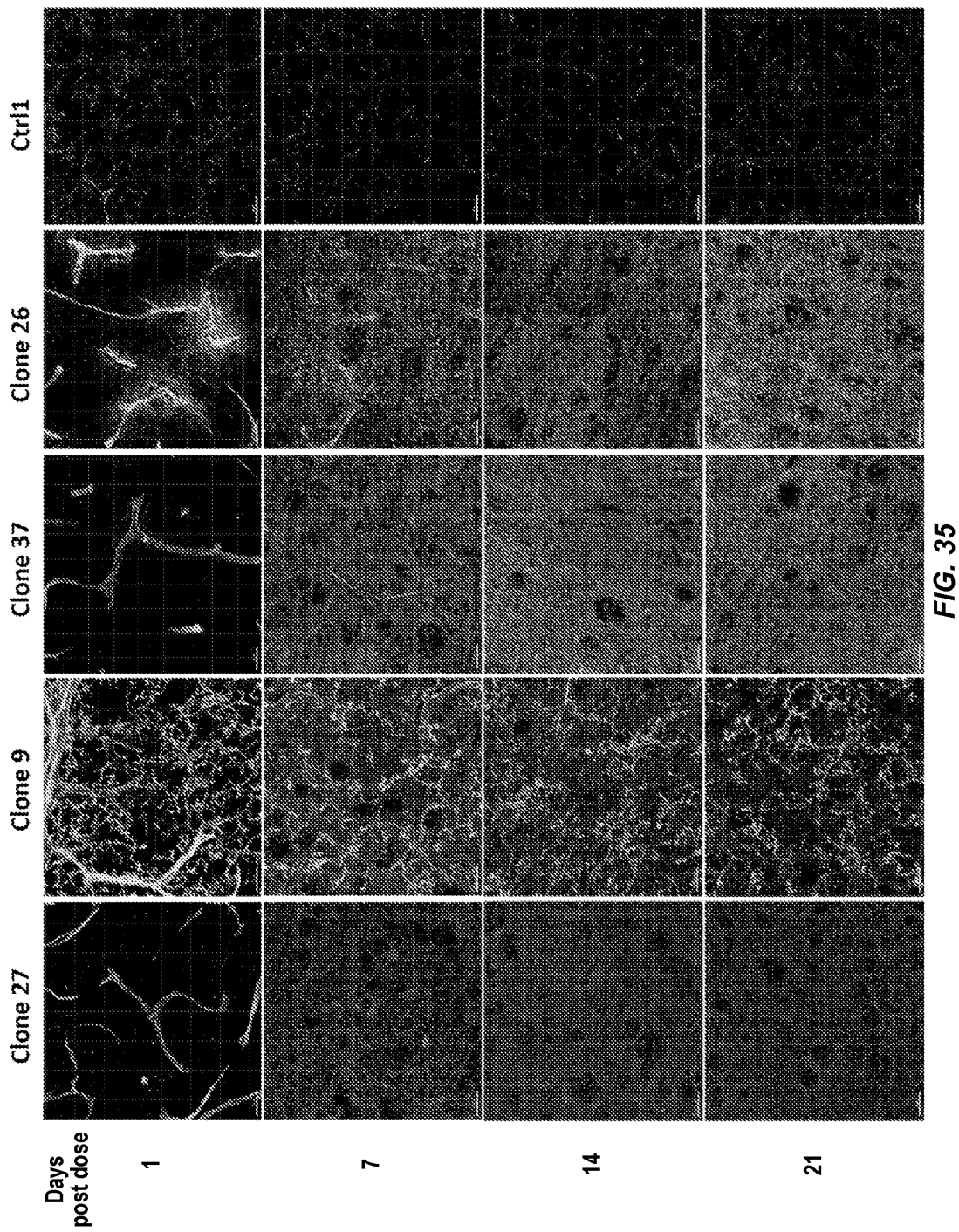
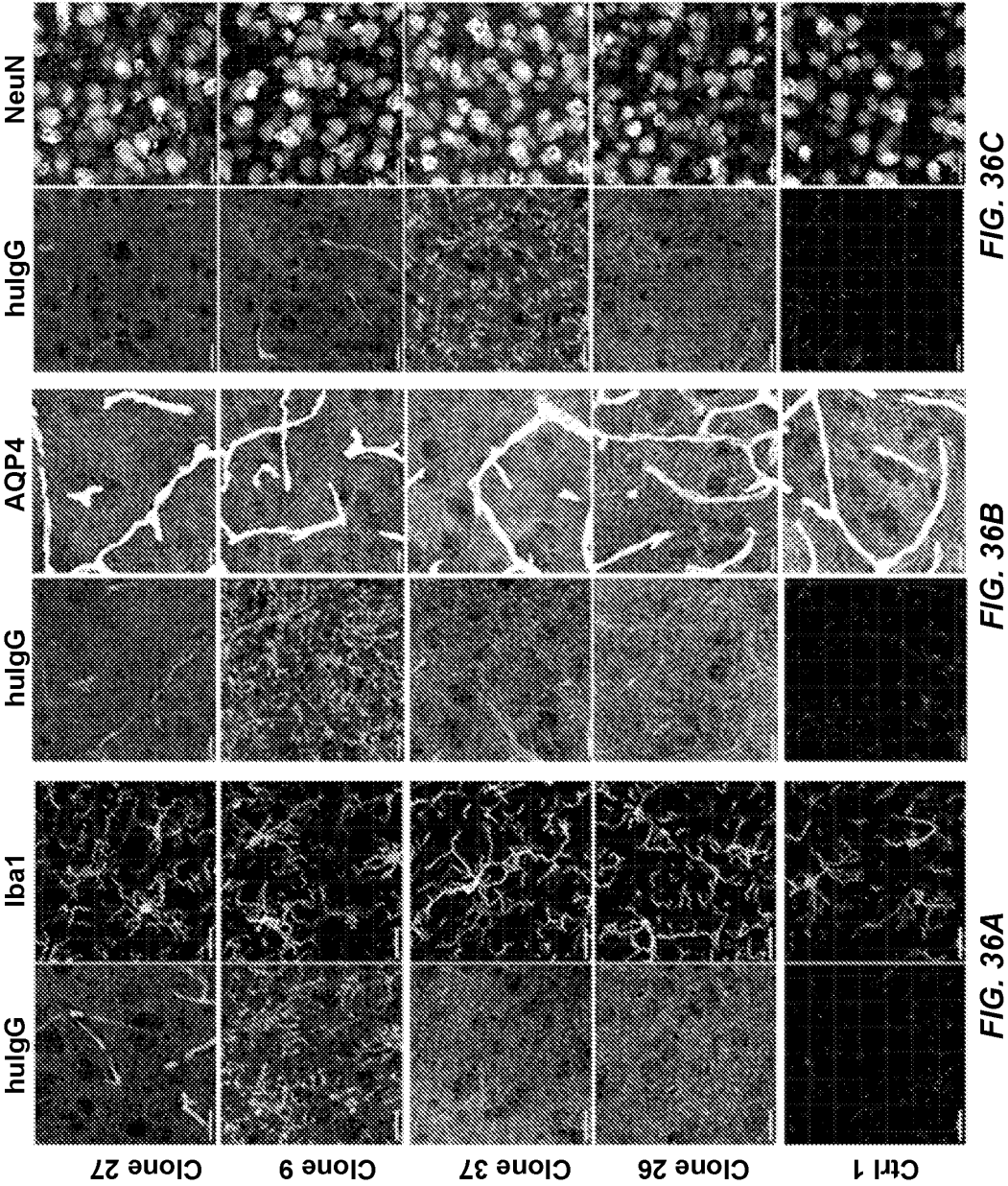


FIG. 34F

- Clone 27
- Clone 9
- ▲ Clone 37
- ▼ Clone 26
- ◆ Ctrl 1





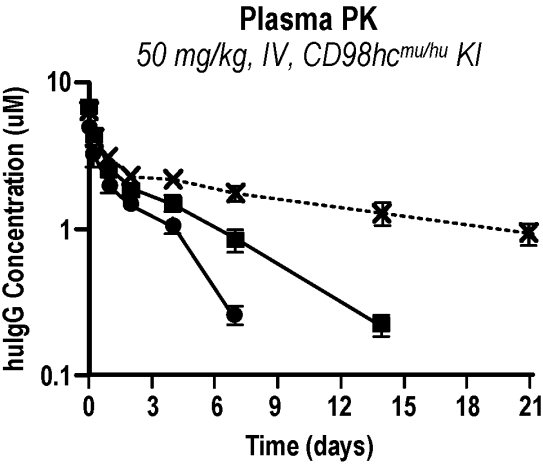


FIG. 37A

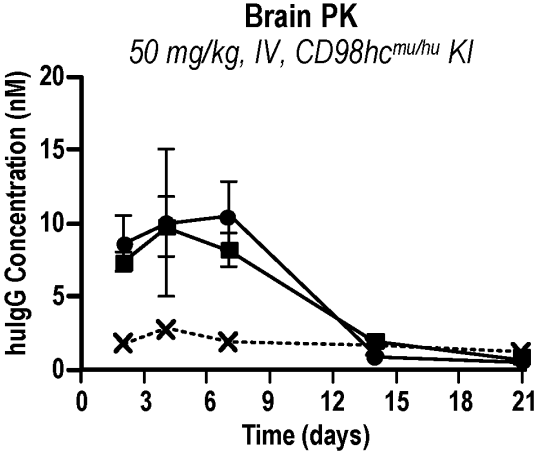


FIG. 37B

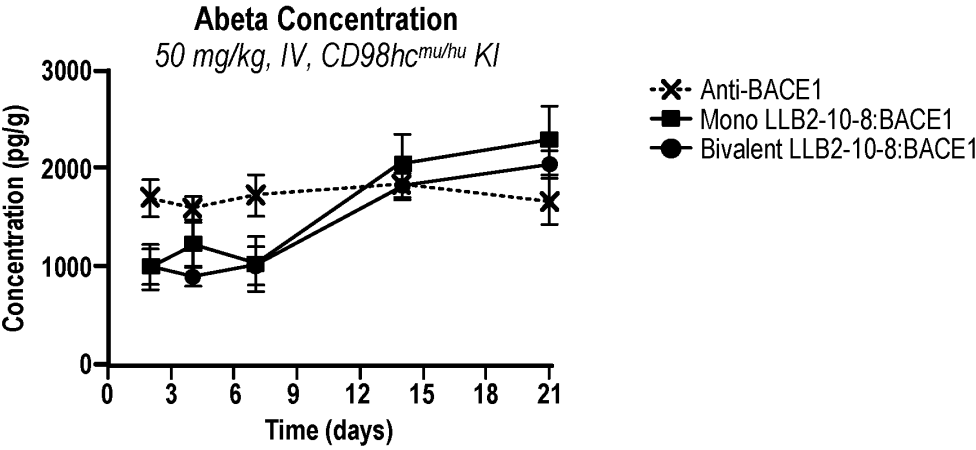


FIG. 37C

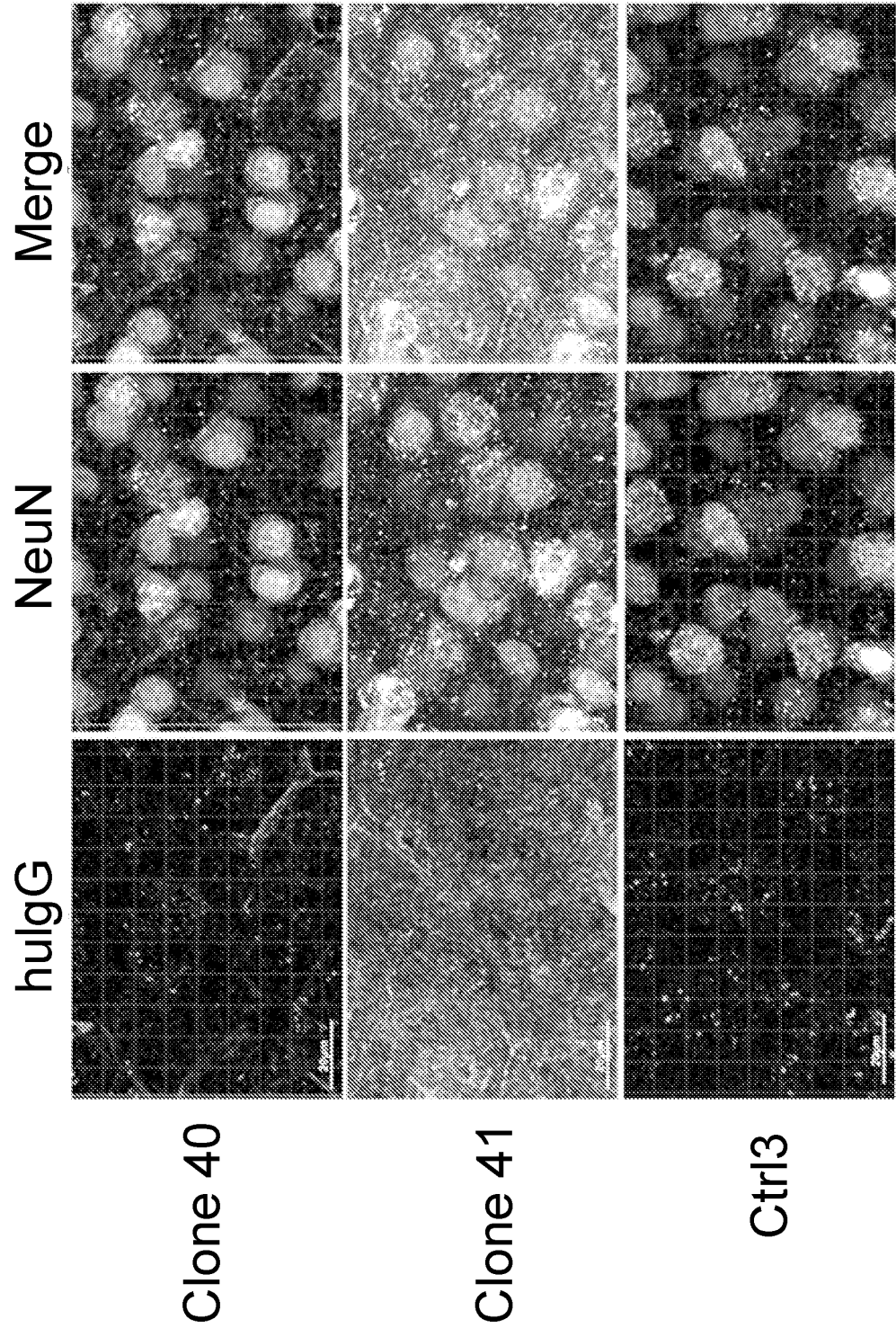


FIG. 38A

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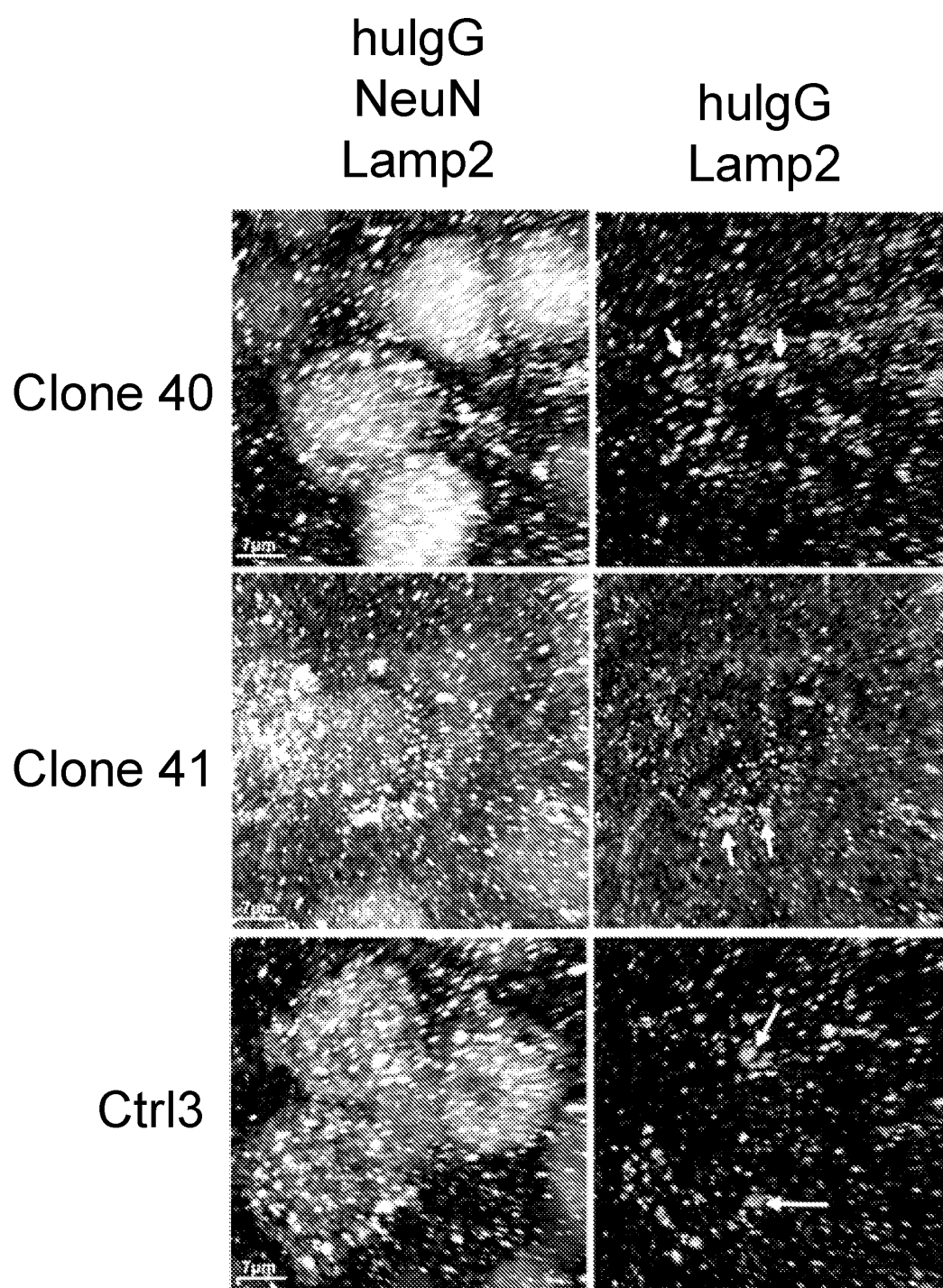
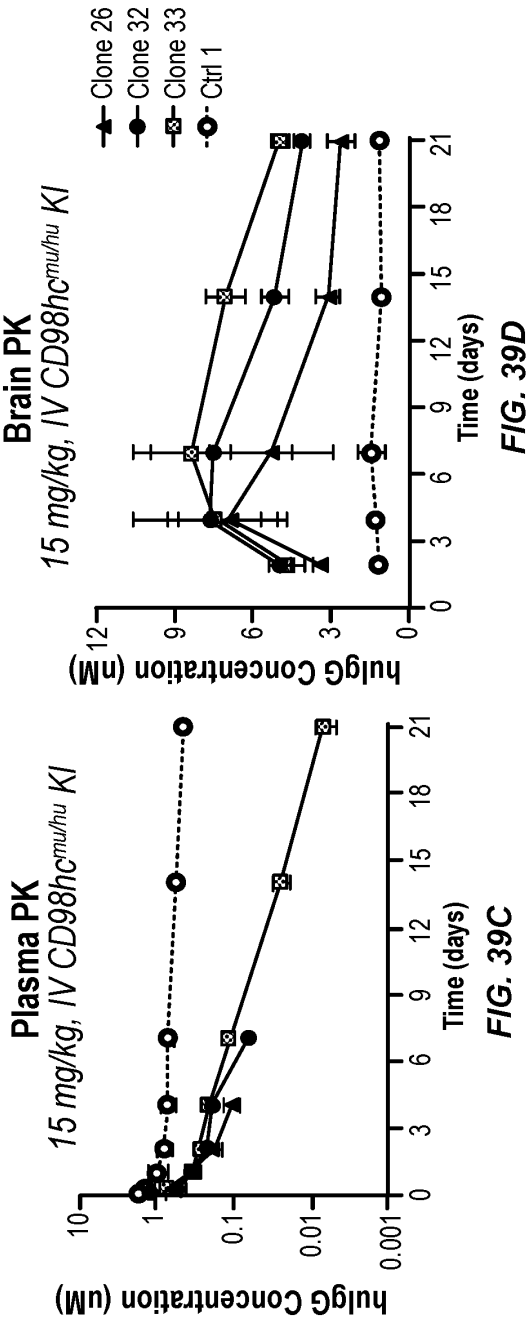
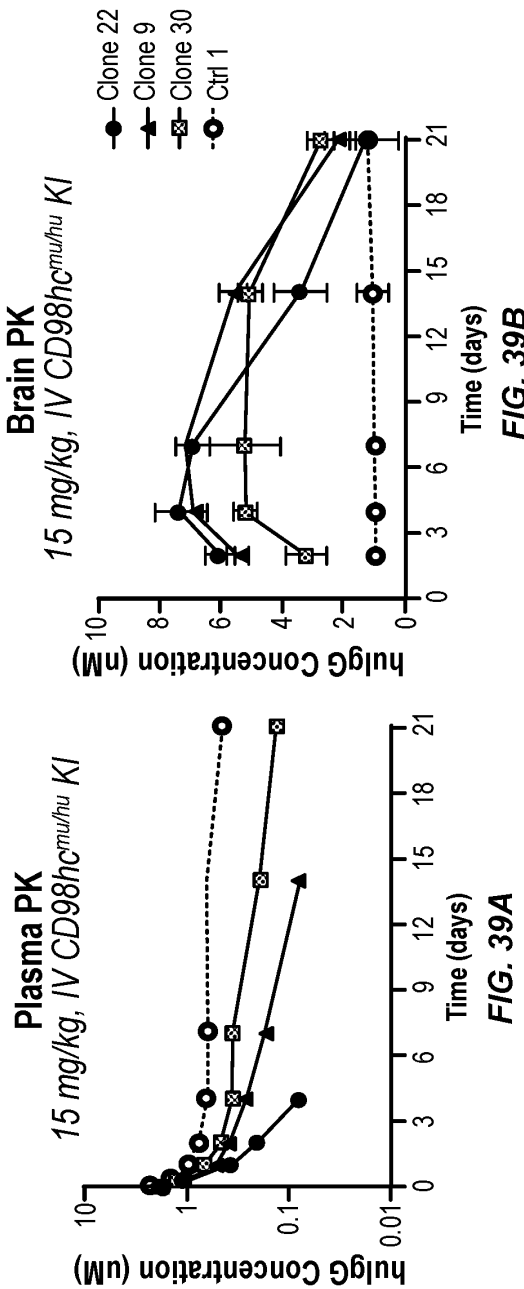


FIG. 38B

SUBSTITUTE SHEET (RULE 26)



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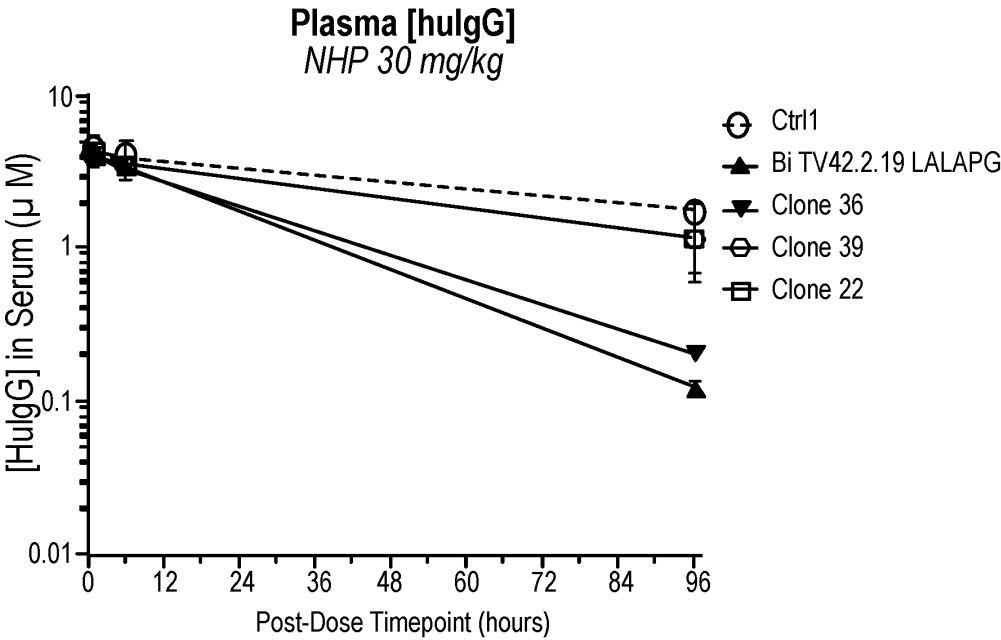


FIG. 40A

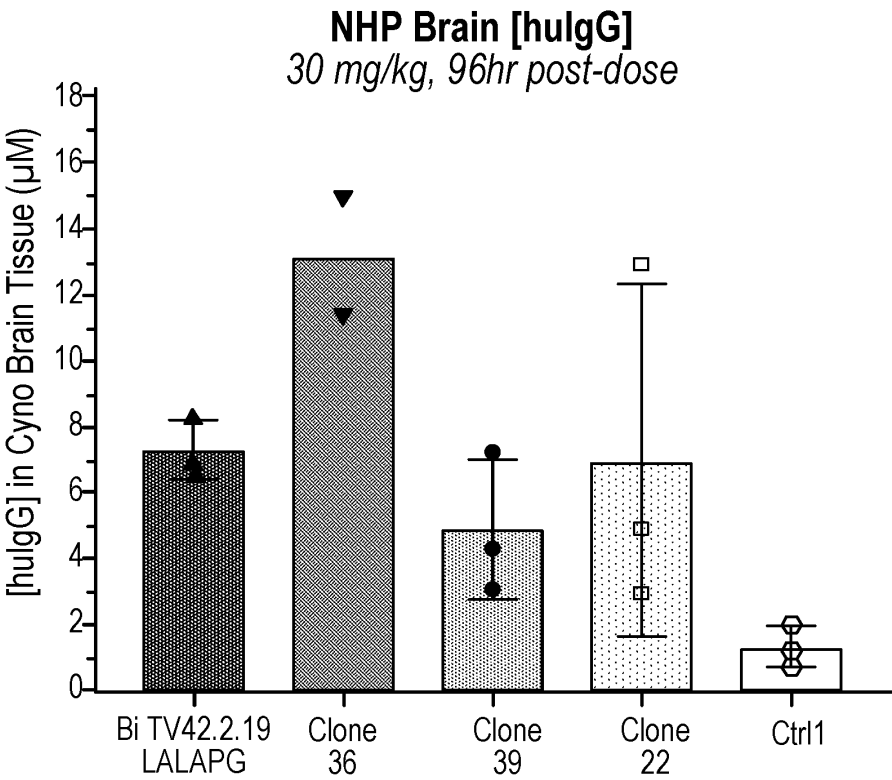


FIG. 40B

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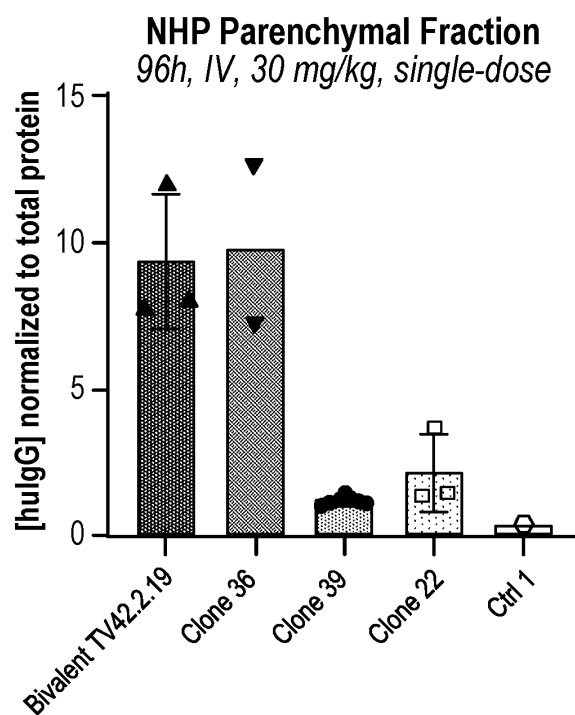


FIG. 40C

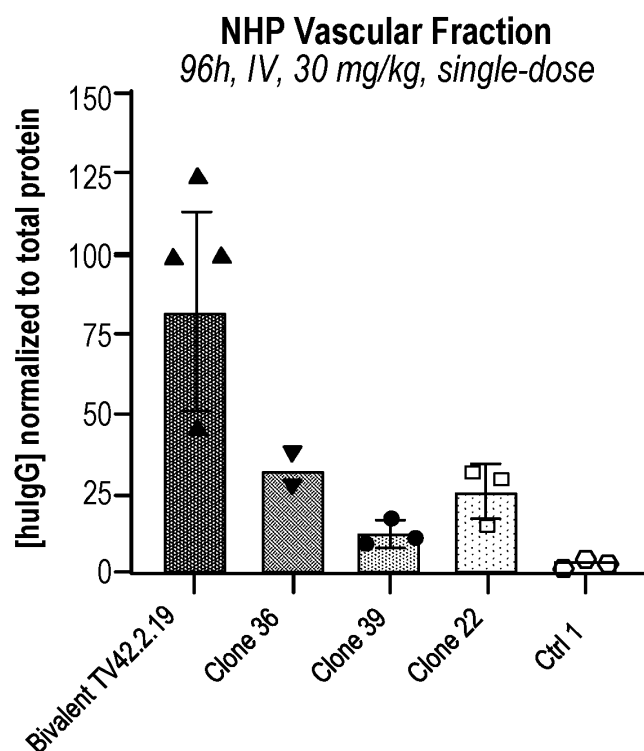
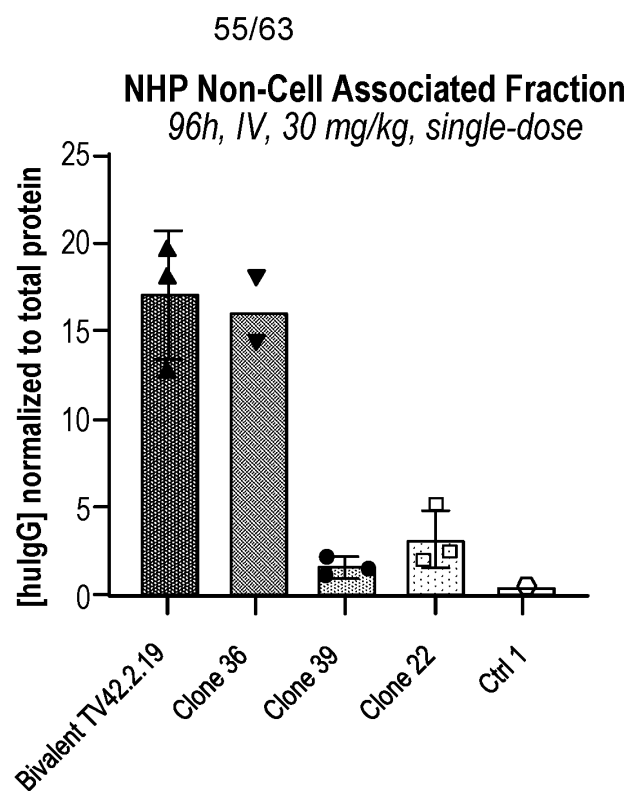
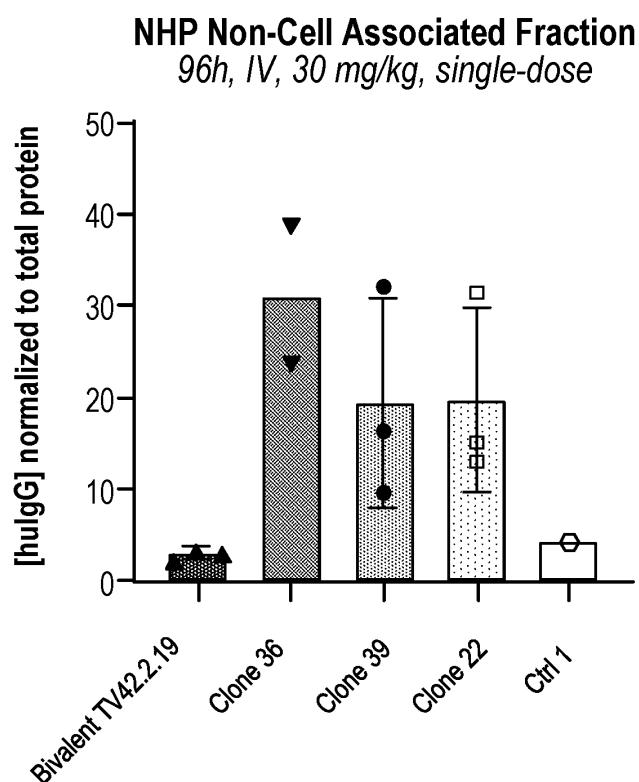
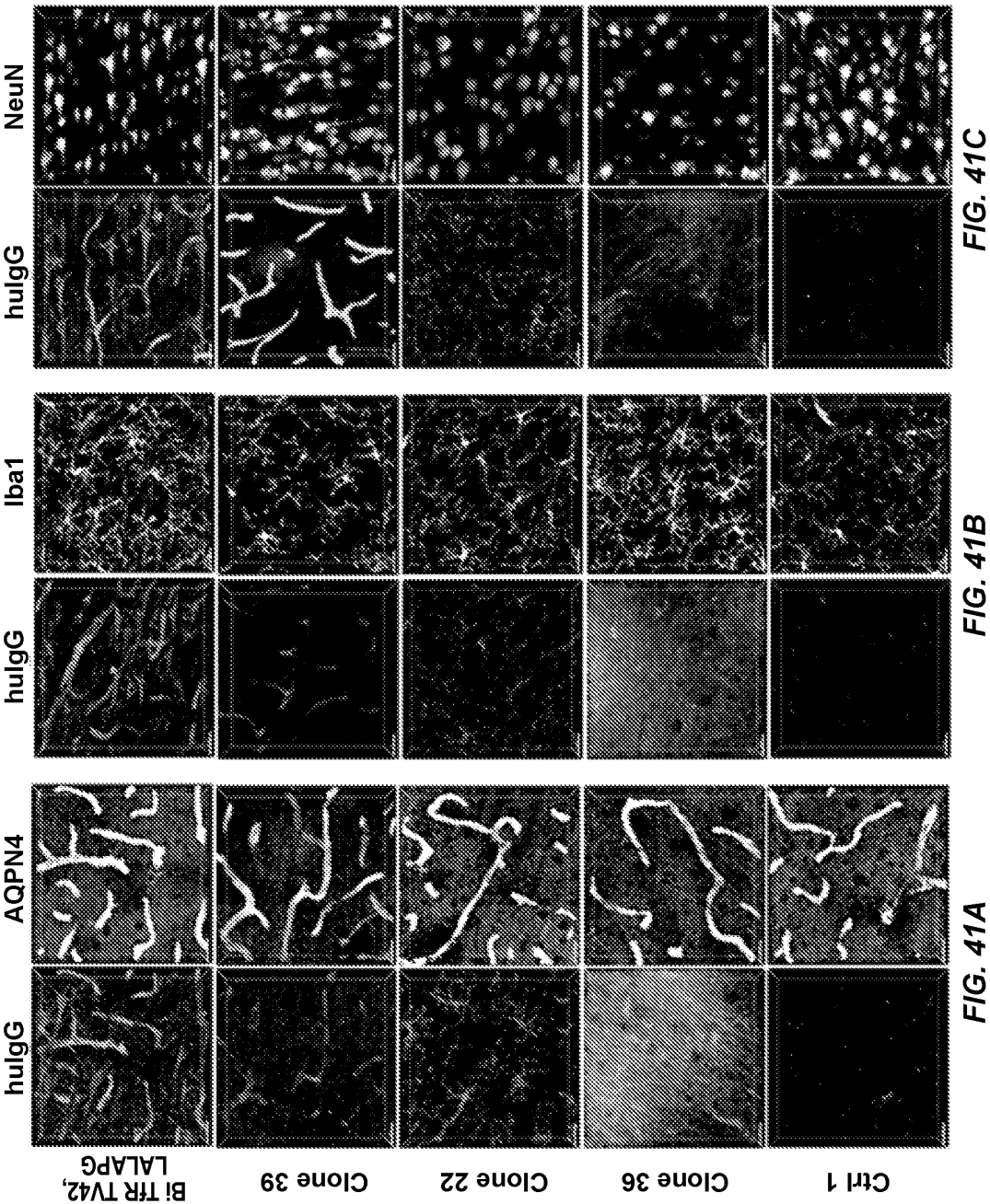
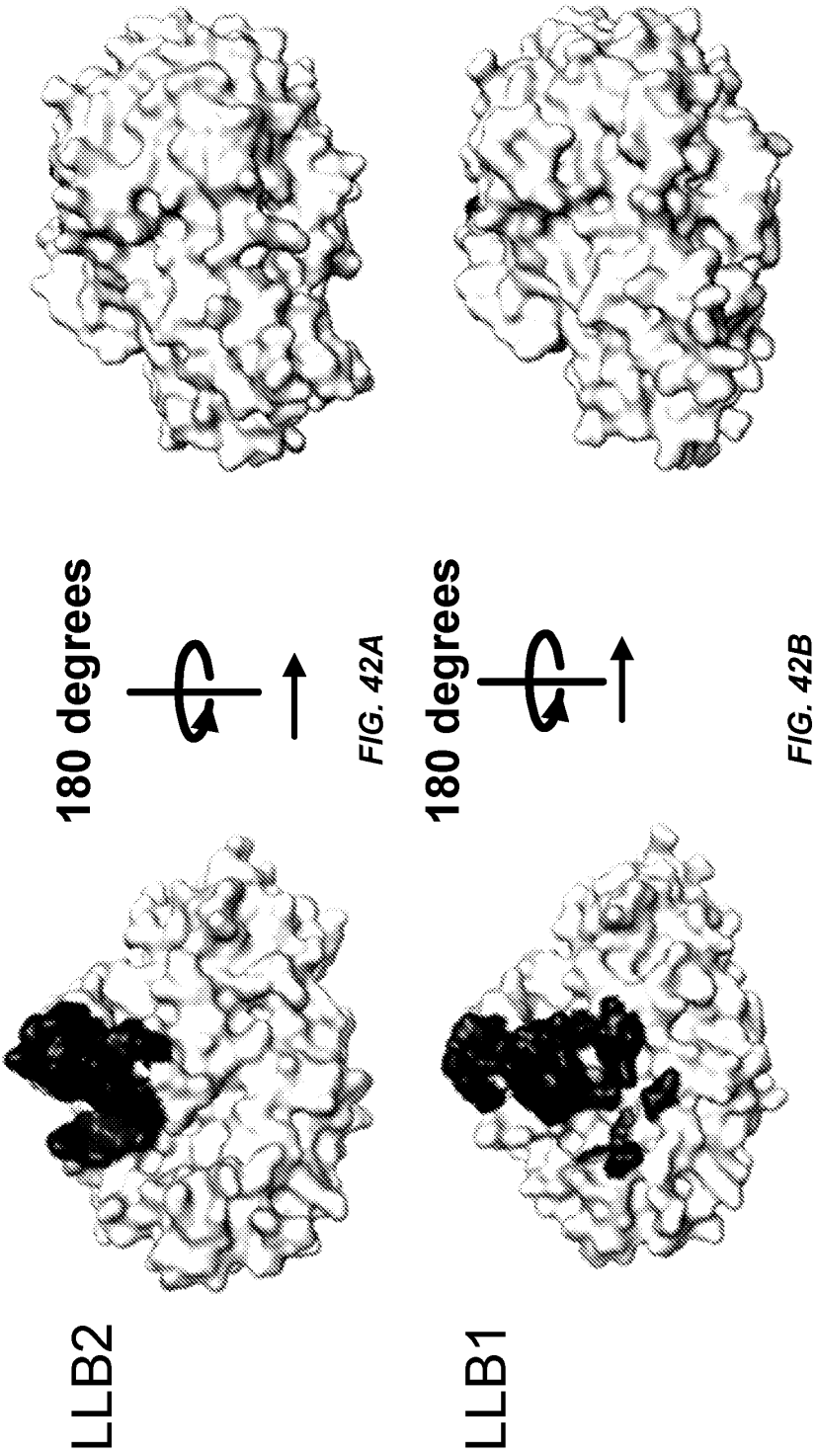


FIG. 40D

**FIG. 40E****FIG. 40F**





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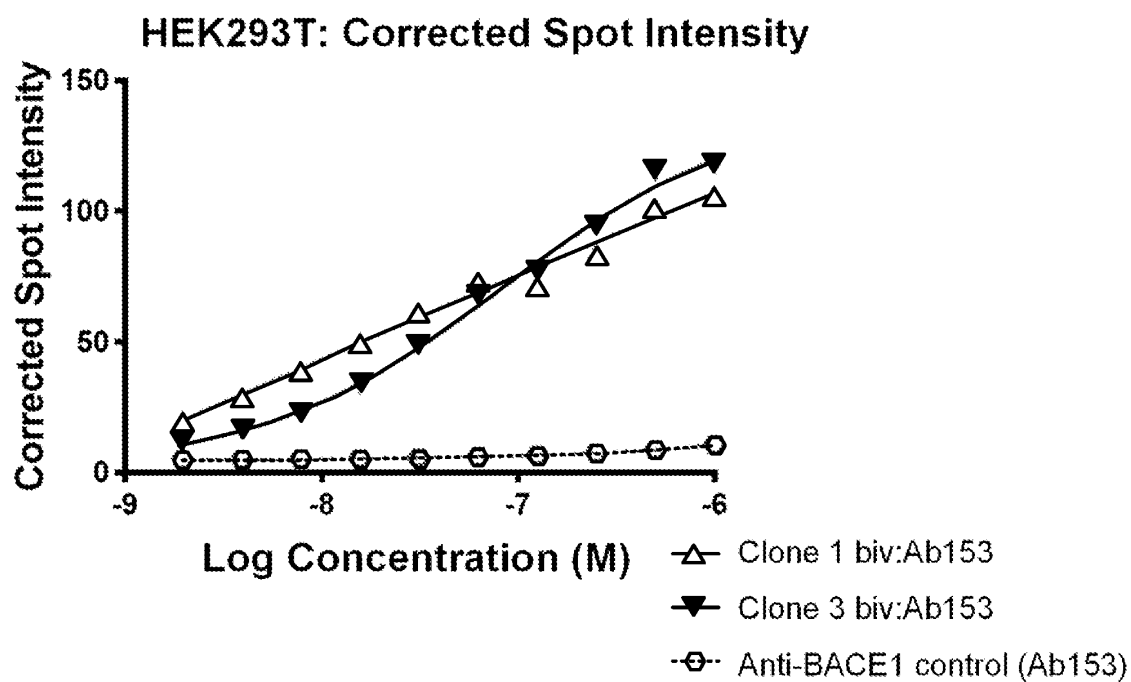


FIG. 43A

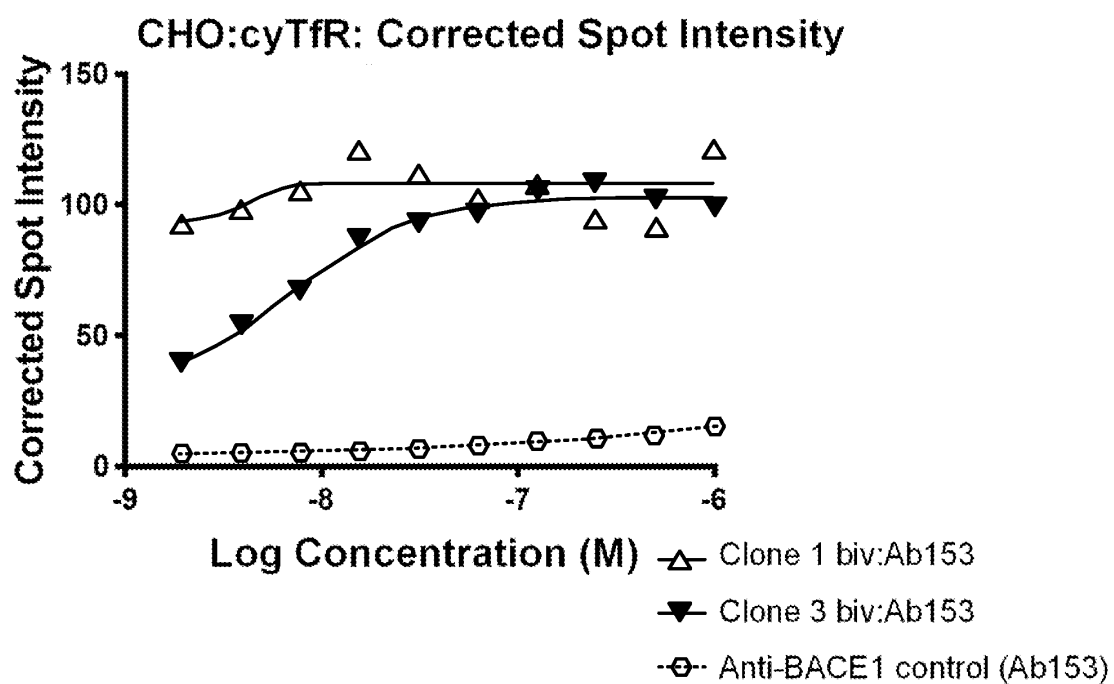


FIG. 43B

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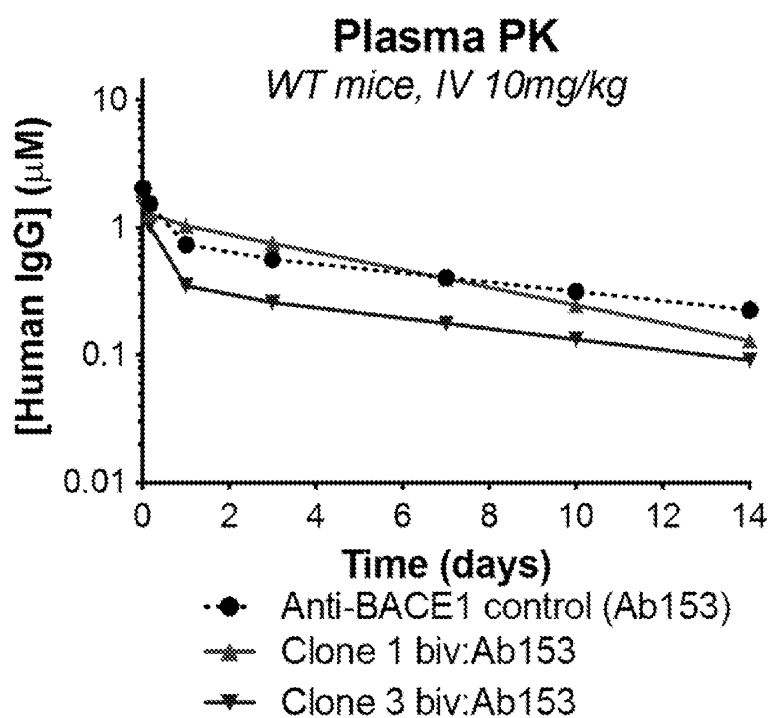


FIG. 44

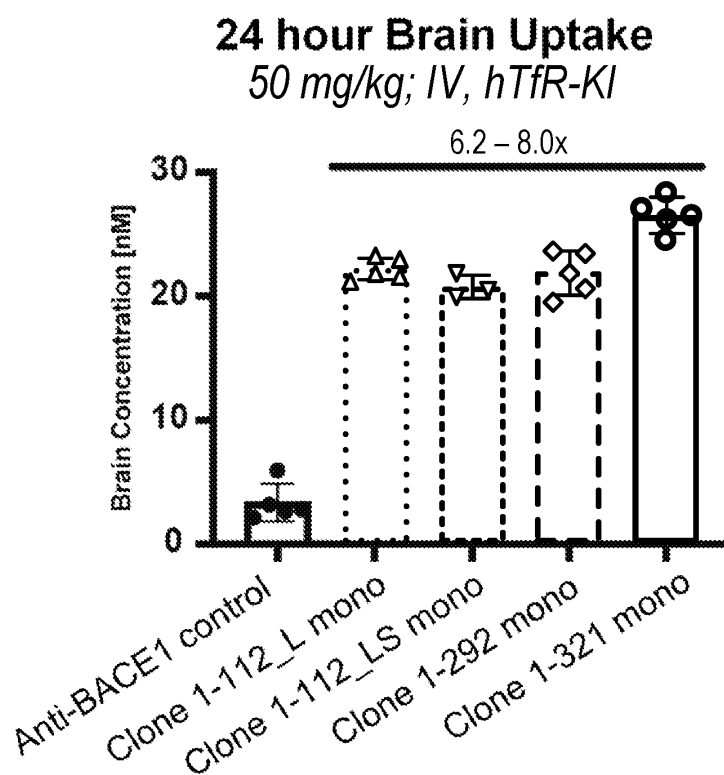
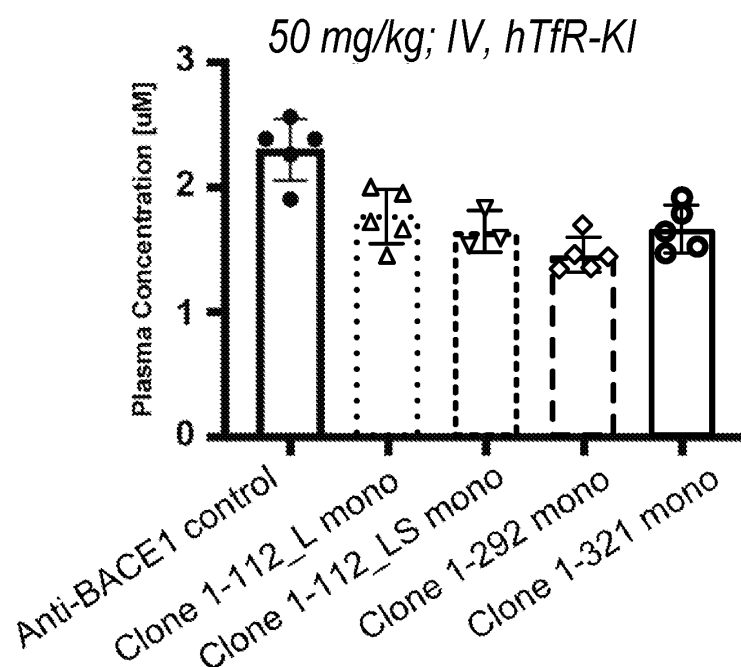
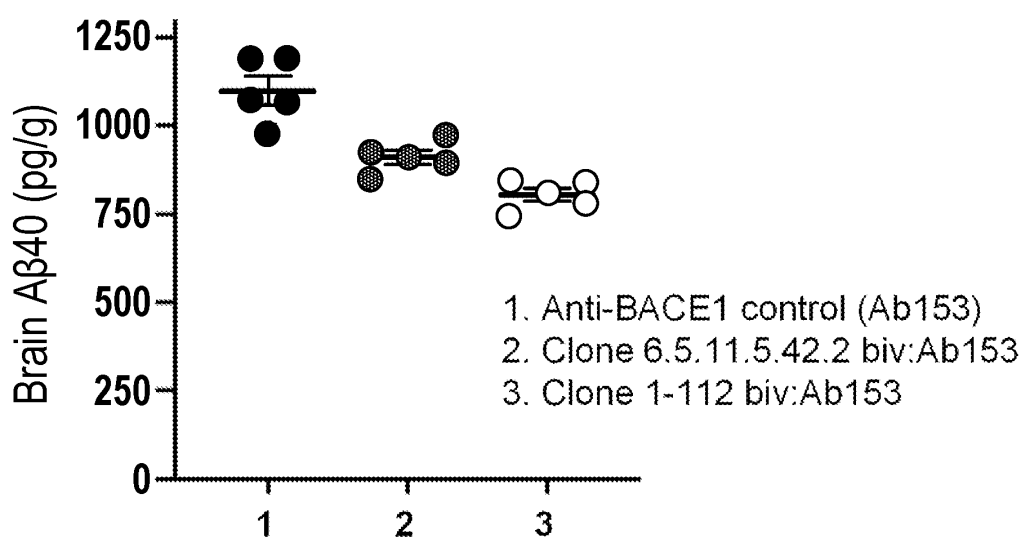


FIG. 45A

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24 hour Plasma Concentration**FIG. 45B**

*TfR ms/hu KI, 50mg/kg i.p. Day 0, 3, 5
Day 6 (24 h post-last-dose)*

**FIG. 46**

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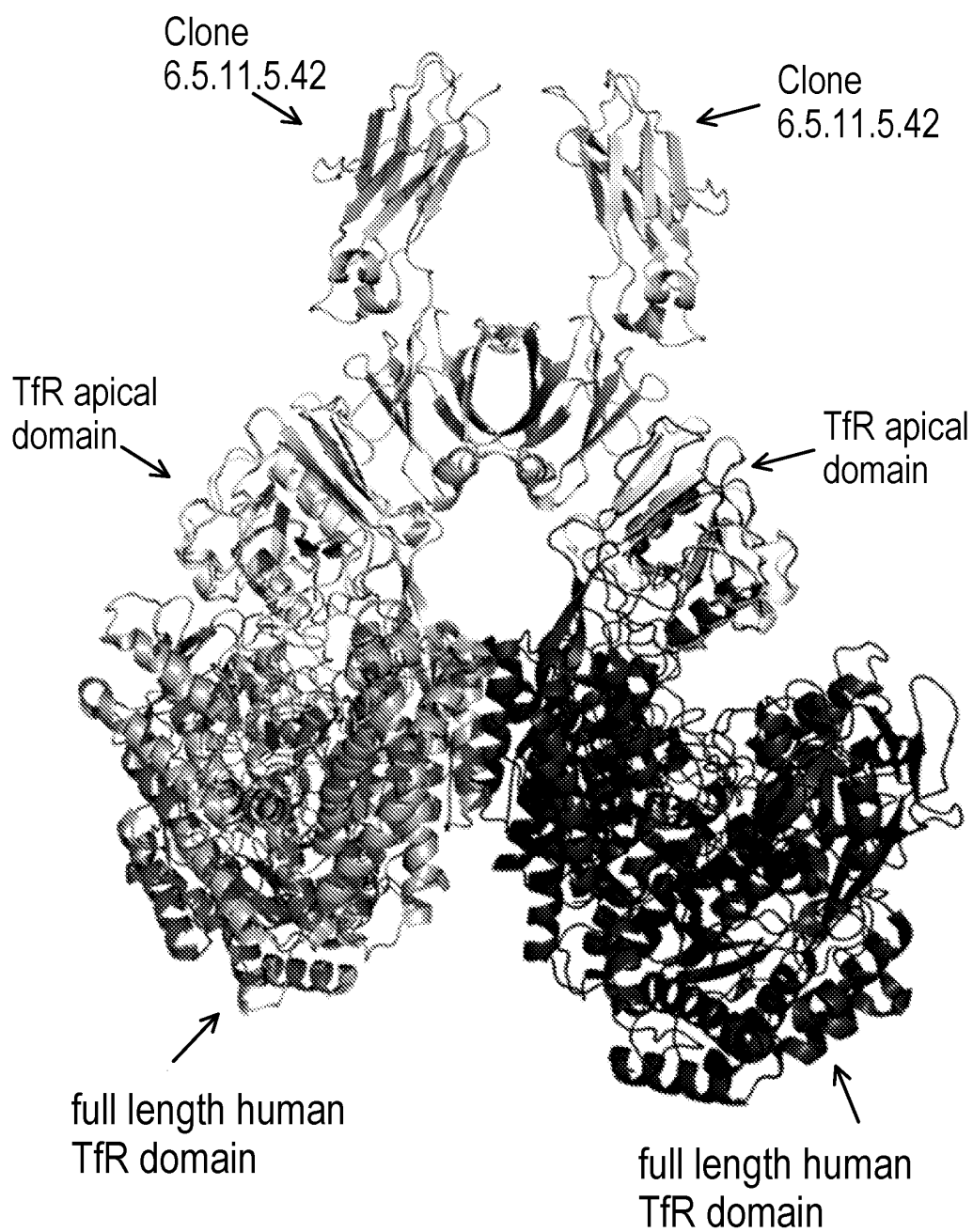


FIG. 47A

SUBSTITUTE SHEET (RULE 26)

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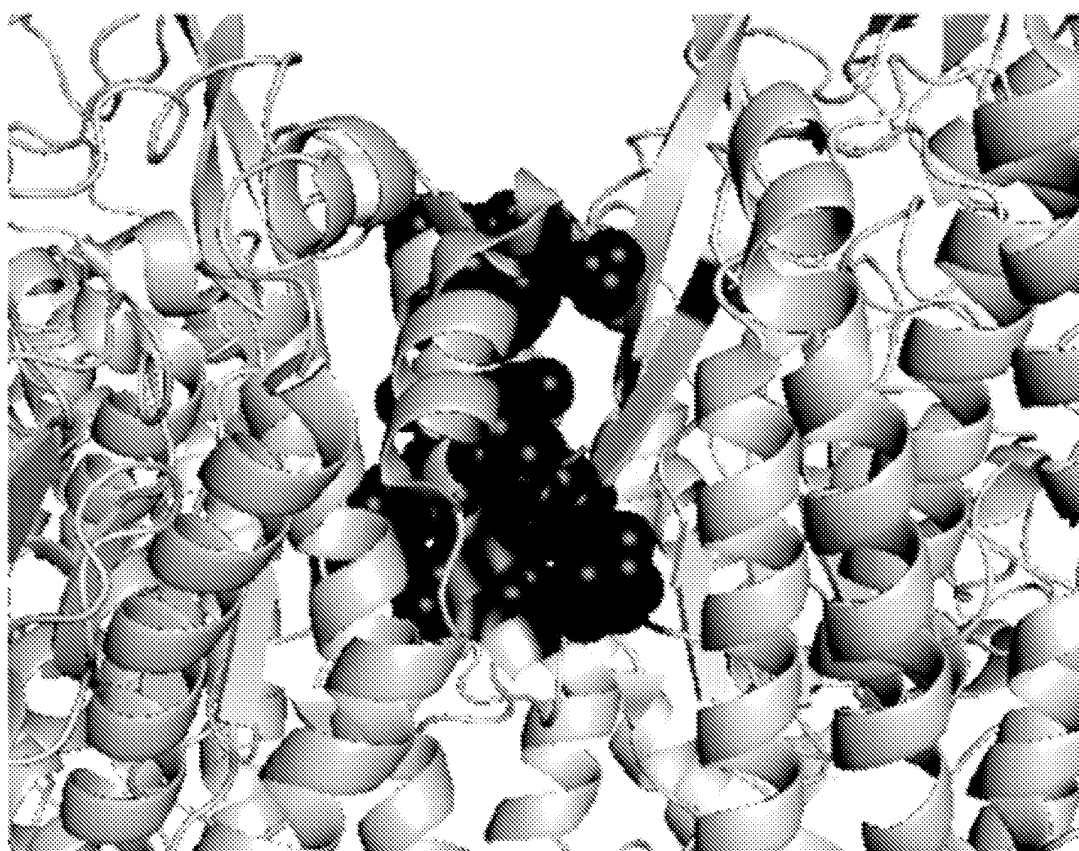


FIG. 47B

SUBSTITUTE SHEET (RULE 26)

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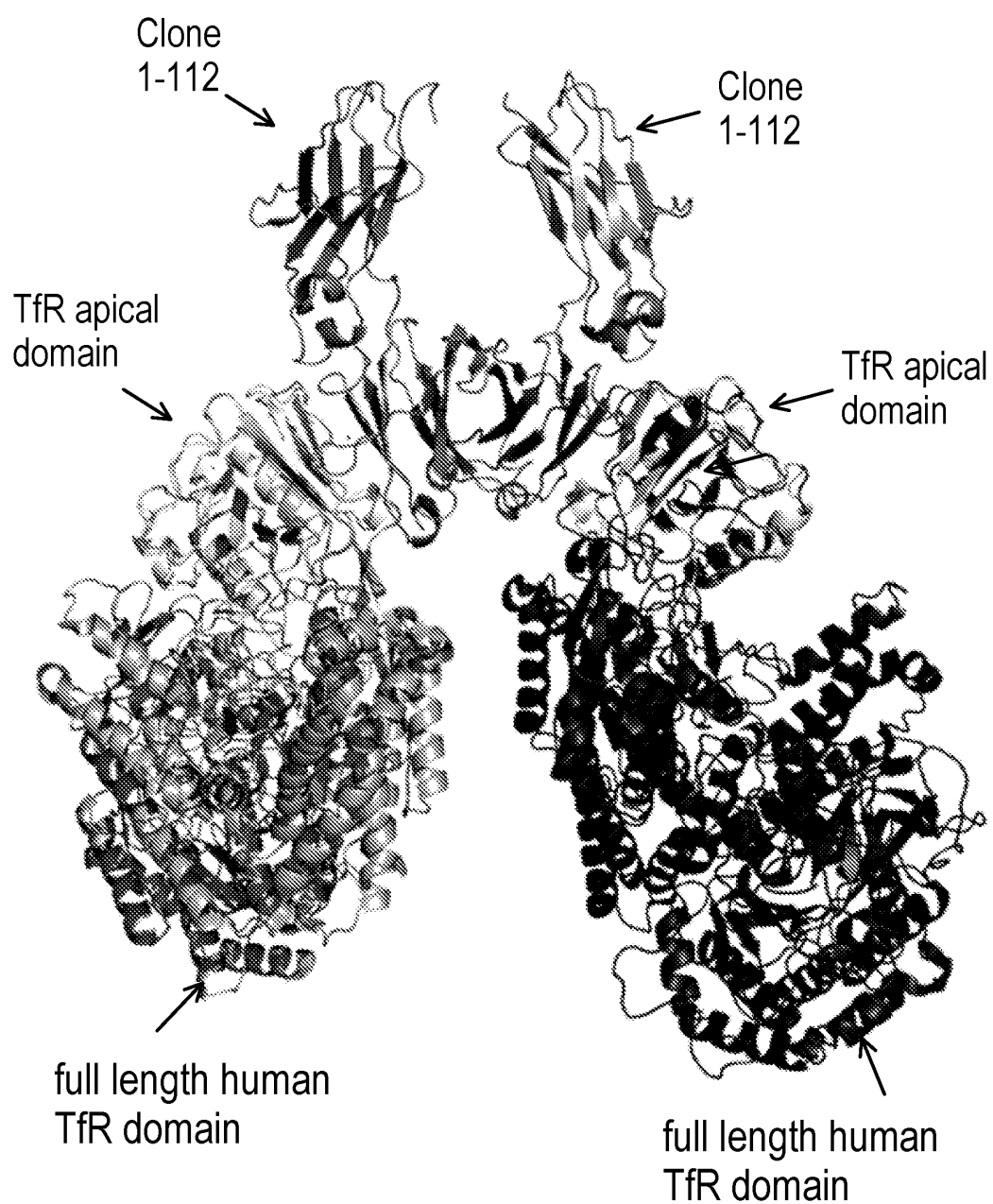


FIG. 47C

SUBSTITUTE SHEET (RULE 26)