

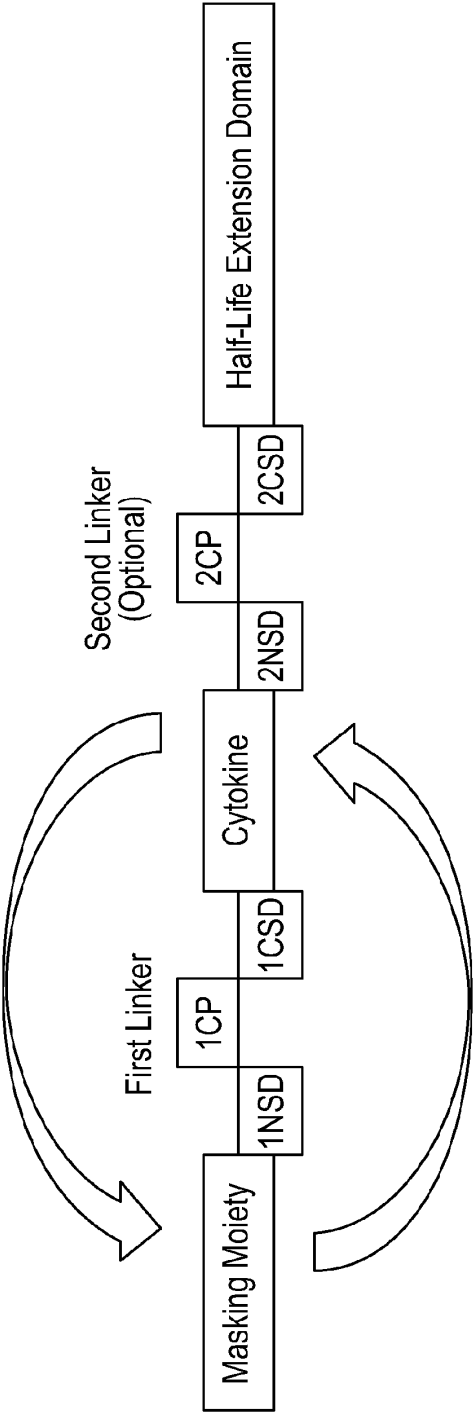


FIG. 1

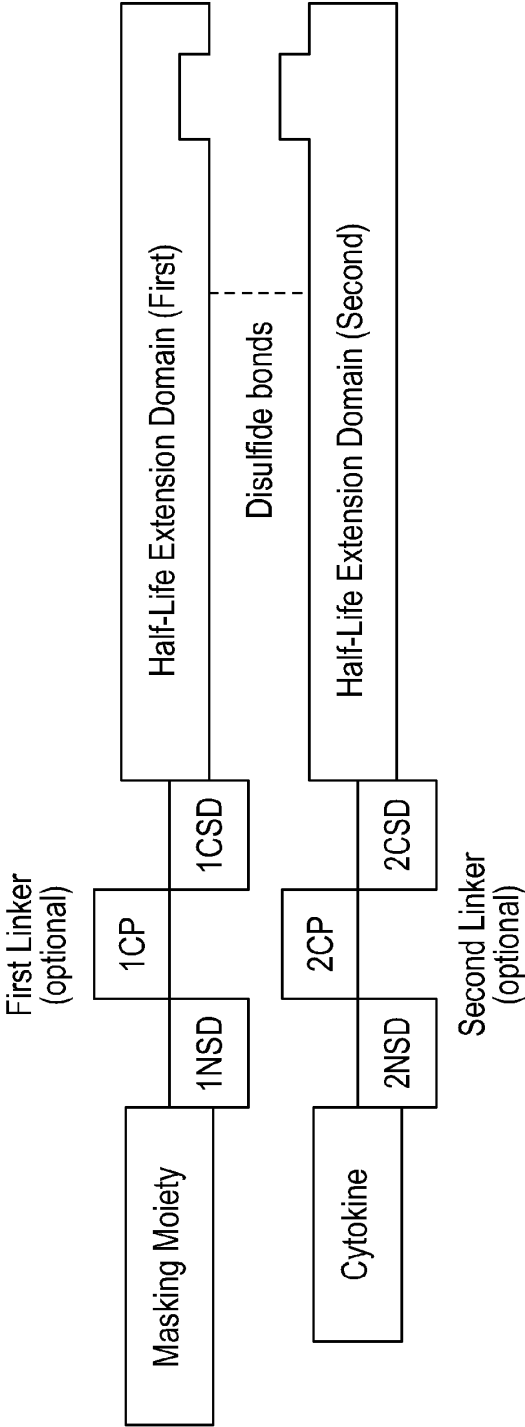
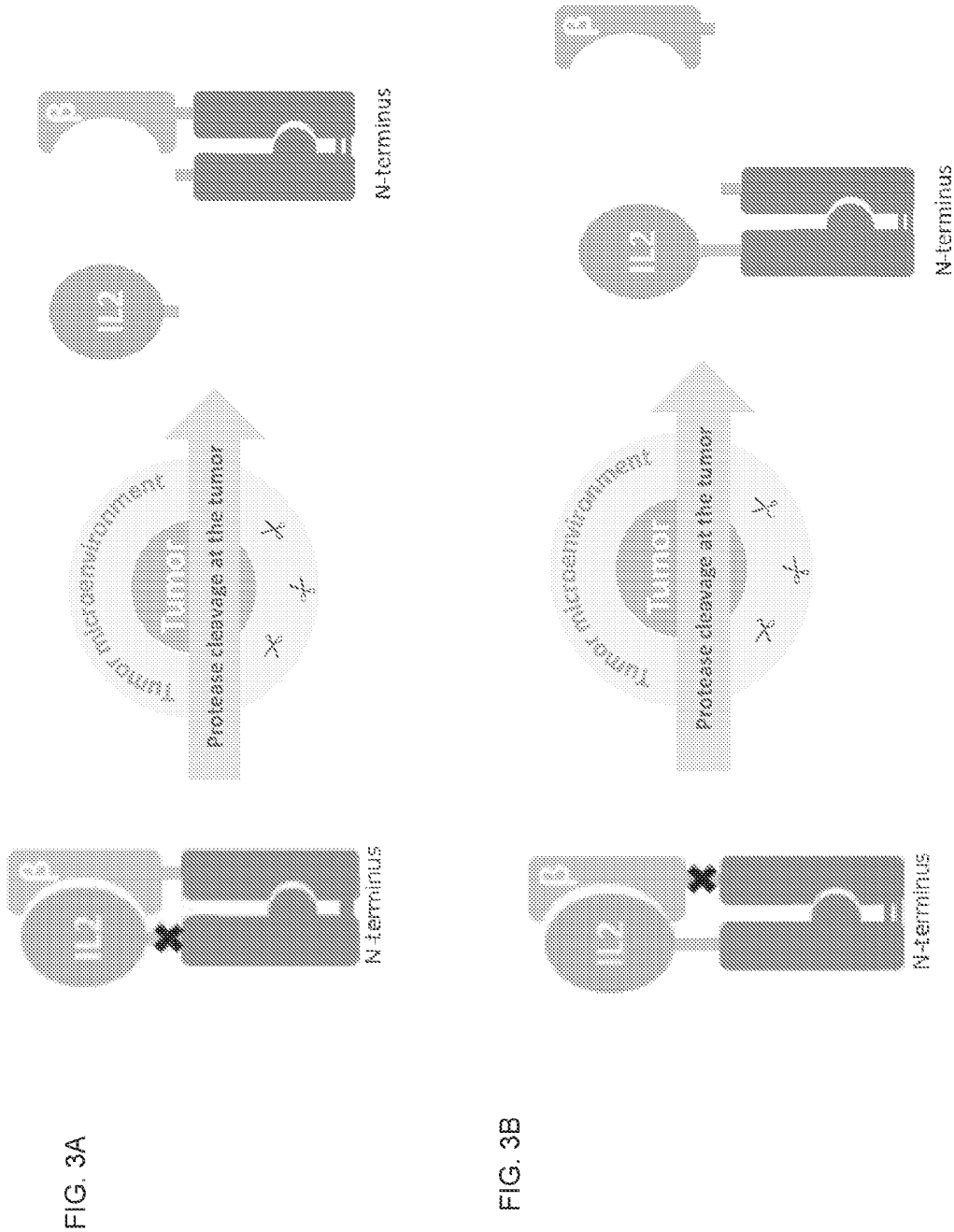


FIG. 2



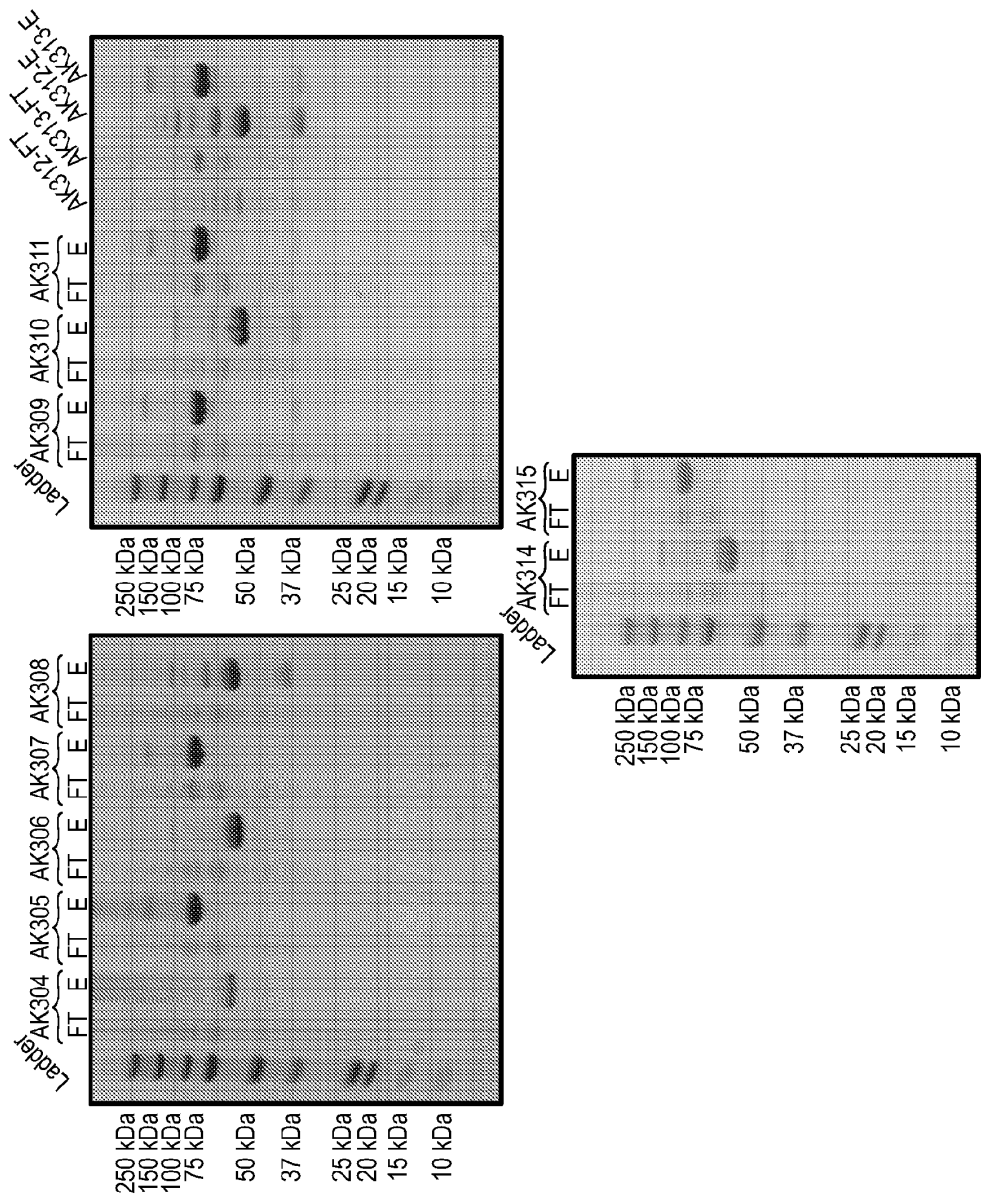
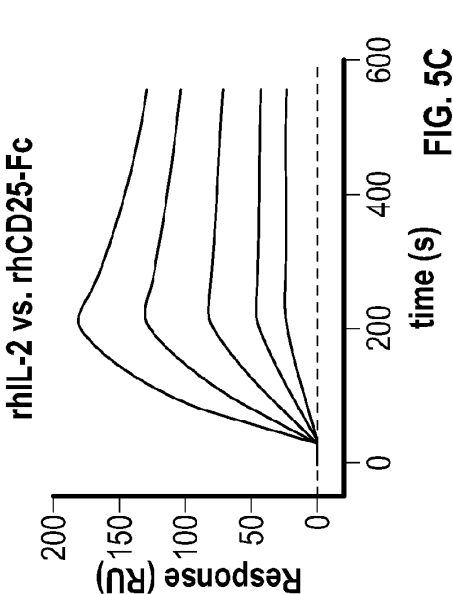
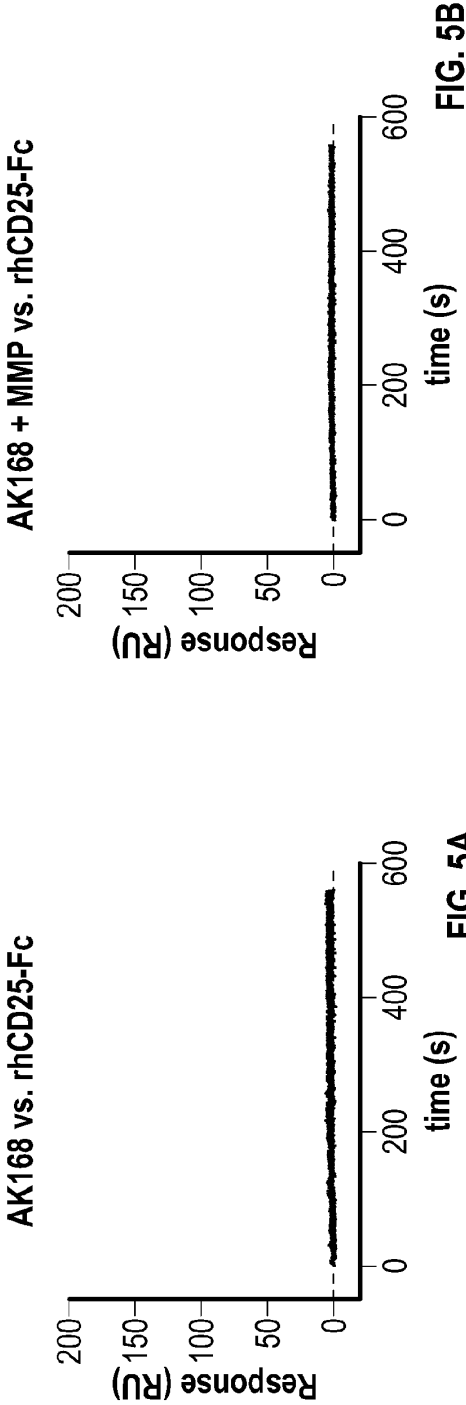
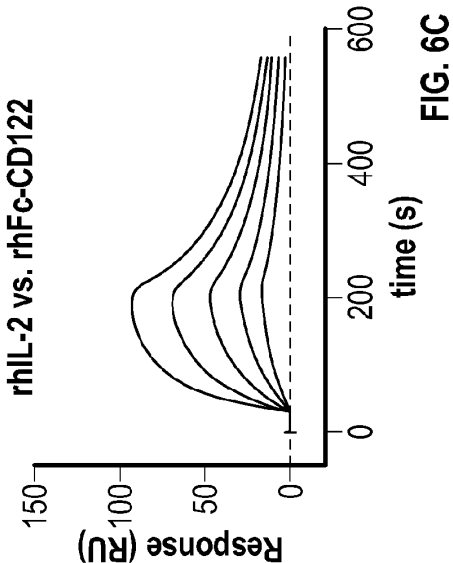
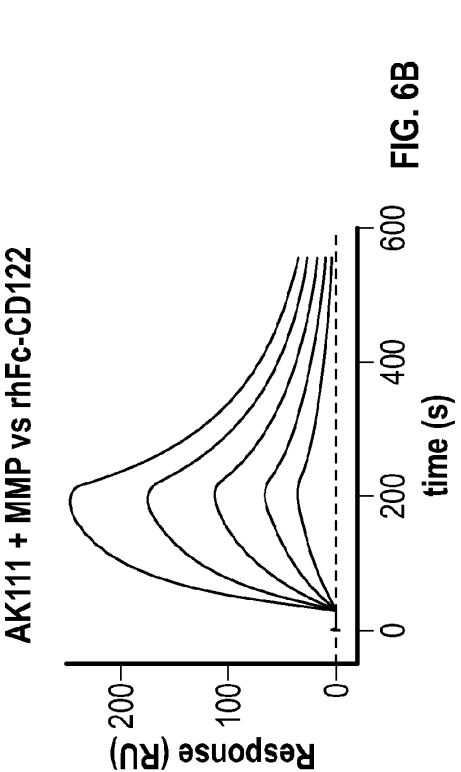
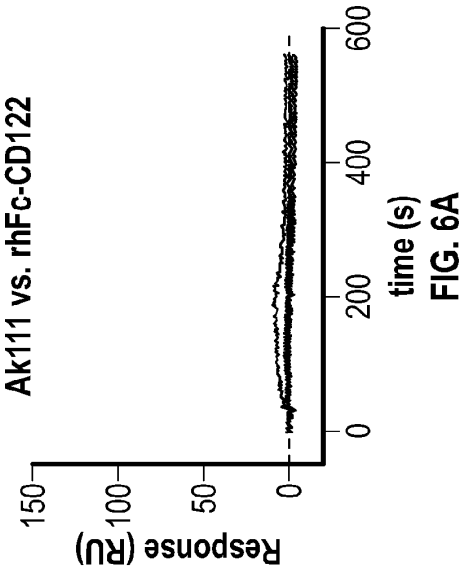


FIG. 4



Sample	k_a ($1/(M \cdot s)$)	k_d (1/s)	KD	Chi2	U-Value: k_d (%)
AK168	ND	ND	ND	ND	ND
AK168+ MMP	ND	ND	ND	ND	ND
rhIL-2	$8.30e+5$	$7.29e-4$	0.878 nM	7.01	3.1

FIG. 5D



Sample	k_a ($1/(M \cdot s)$)	k_d (1/s)	KD	Chi2	U-Value: k_d (%)
AK111	ND	ND	ND	ND	ND
AK111+ MMP	2.64e+4	6.21e-3	235 nM	9.82	0.6
rhIL-2	4.17e+4	5.17e-3	124 nM	2.09	0.8

FIG. 6D

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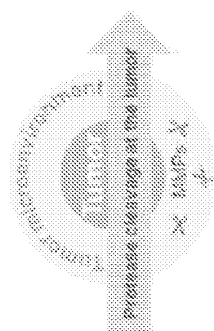
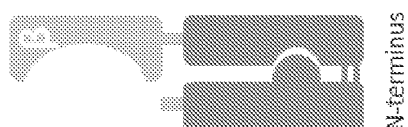
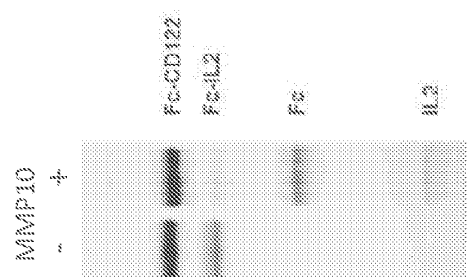
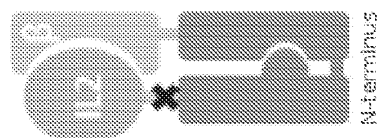


FIG. 7A



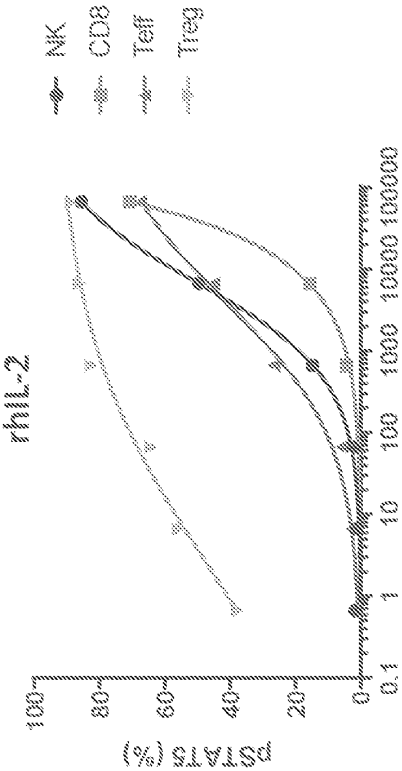


FIG. 8A

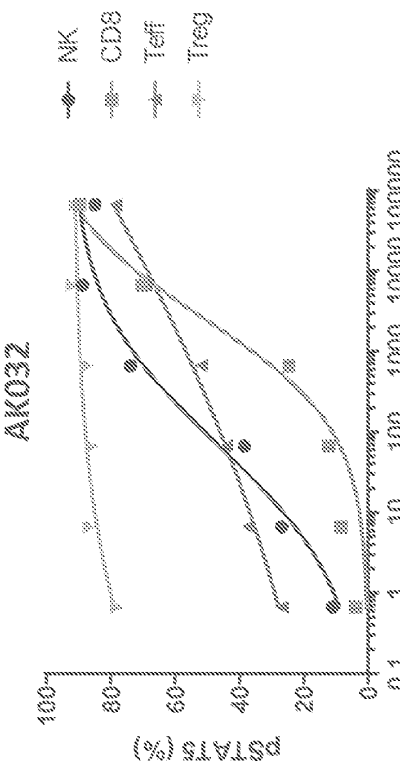


FIG. 8B

FIG. 8C

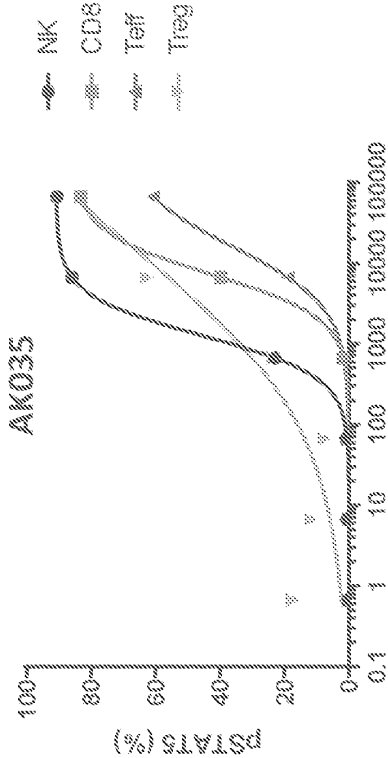


FIG. 8D

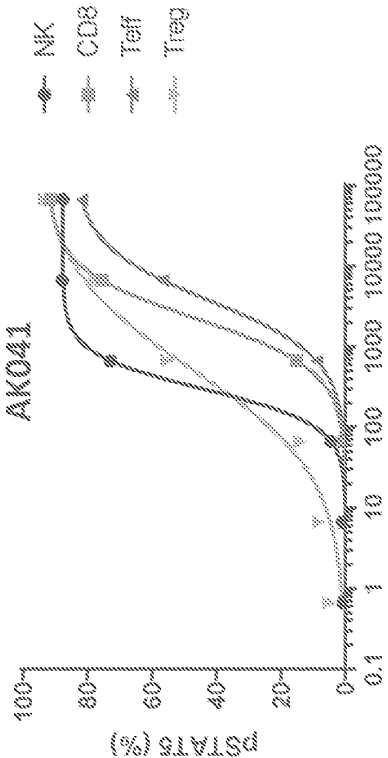


FIG. 9A

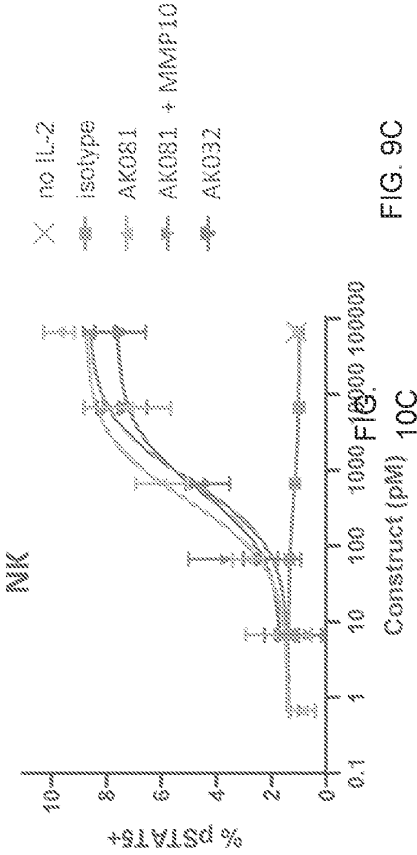


FIG. 9B

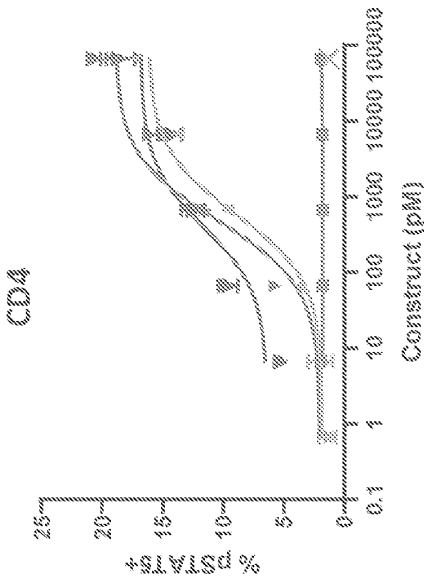


FIG. 9C

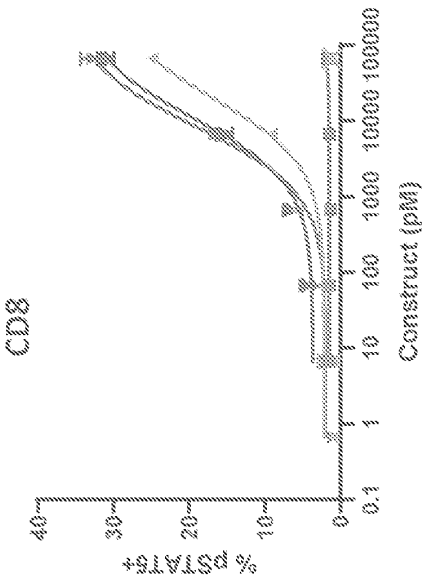


FIG. 10A

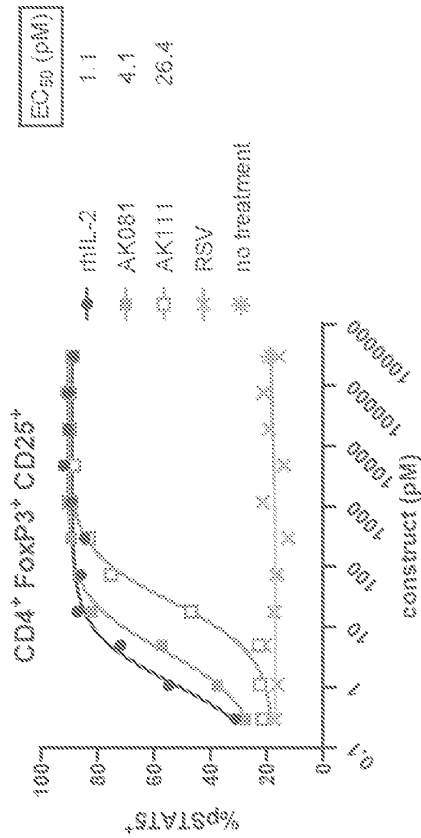


FIG. 10B

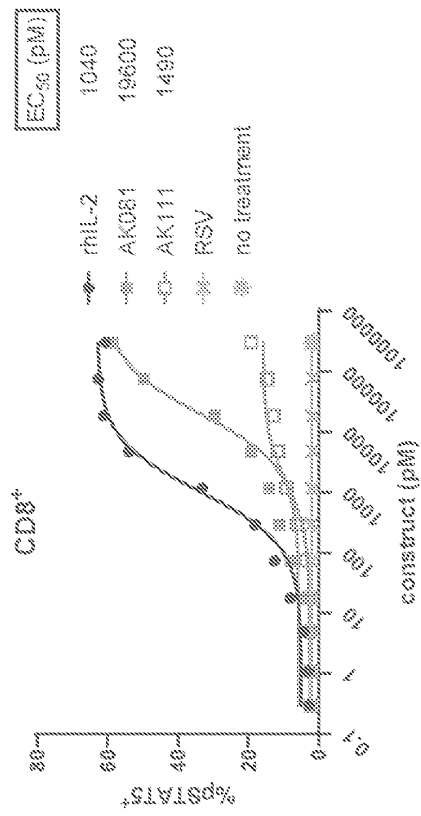


FIG. 10C

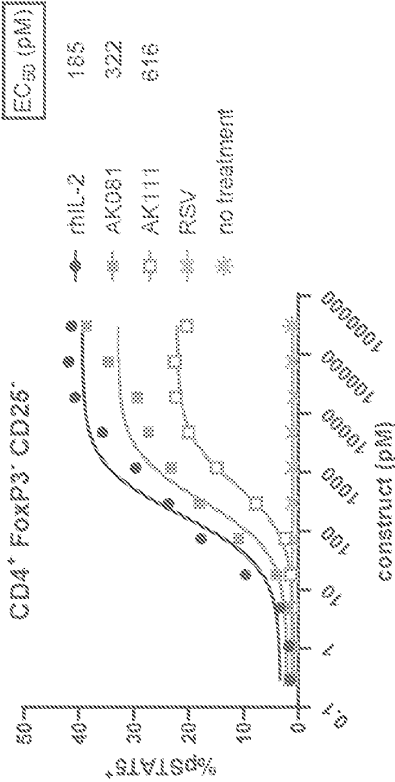


FIG. 10D

Construct	FoxP3 ⁺ T _{reg}		CD4 ⁺ T _{help}		CD8 ⁺ T _{cyto}	
	EC ₅₀ (pM)	Fold-change	EC ₅₀ (pM)	Fold-change	EC ₅₀ (pM)	Fold-change
rhIL-2	1.1		1040		185	
AK081	4.1	3.7	19600	18.8	322	1.7
AK111	26.4	24.0	1490*	1.4*	616	3.3

*Prism was able to find a best fit value, but was unable to calculate a complete confidence interval. This best fit value should be interpreted with caution.

FIG. 11A

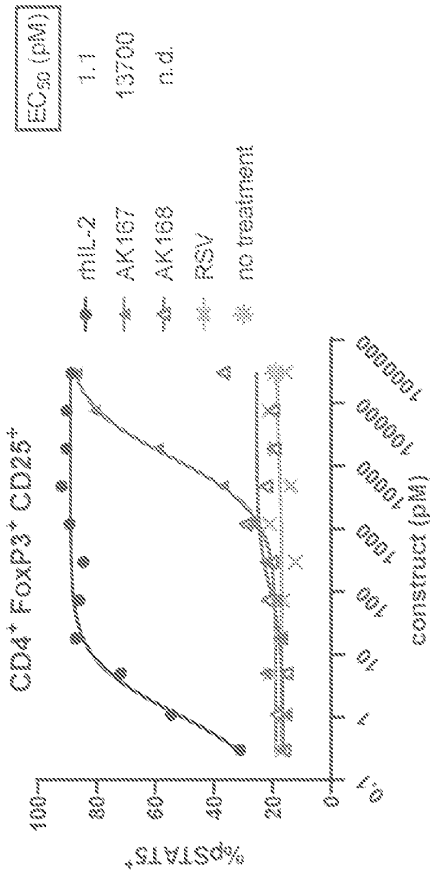


FIG. 11B

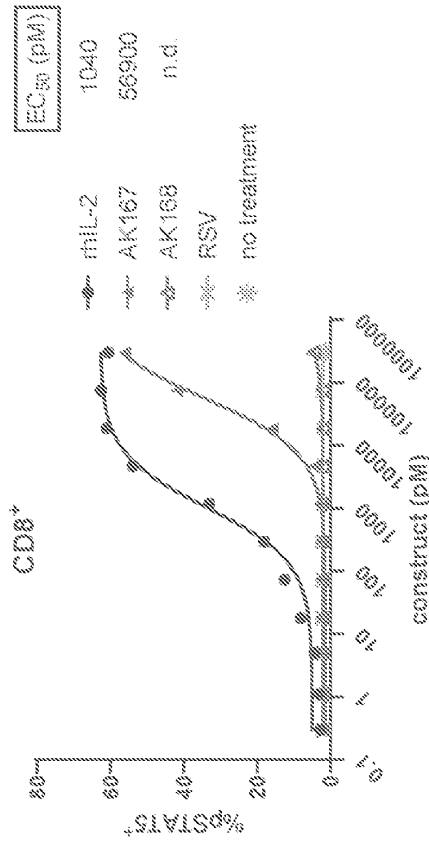


FIG. 11C

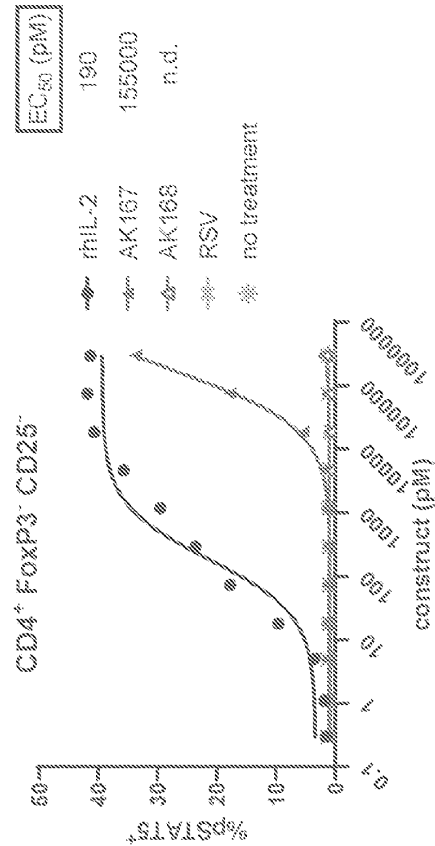


FIG. 11D

Construct	FoxP3 ⁺ T _{reg}		CD4 ⁺ T _{help}		CD8 ⁺ T _{cyt}	
	EC ₅₀ (pM)	Fold-change	EC ₅₀ (pM)	Fold-change	EC ₅₀ (pM)	Fold-change
rhIL-2	1.1		1040		190	
AK167	13700	12455	56900	55	155000	816
AK168	n.d.		n.d.		n.d.	

FIG. 12A

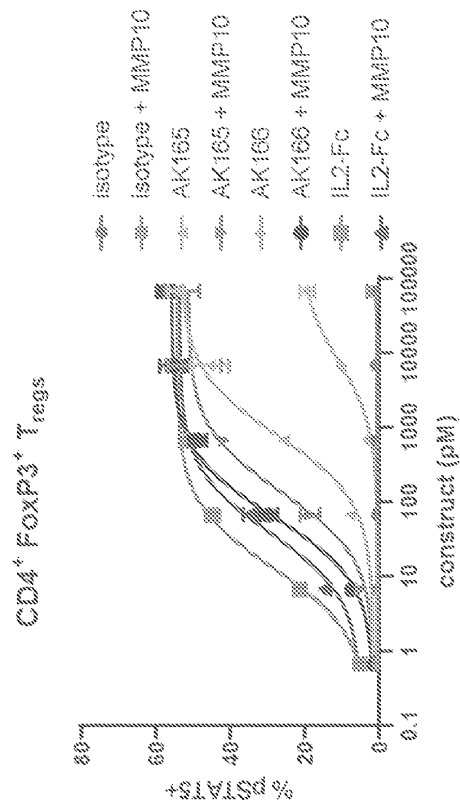


FIG. 12B

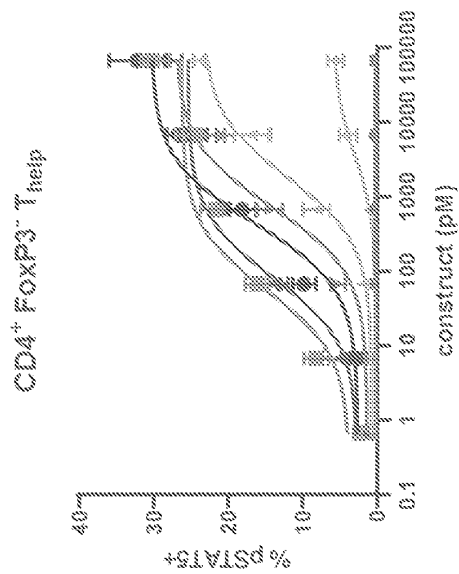


FIG. 12C

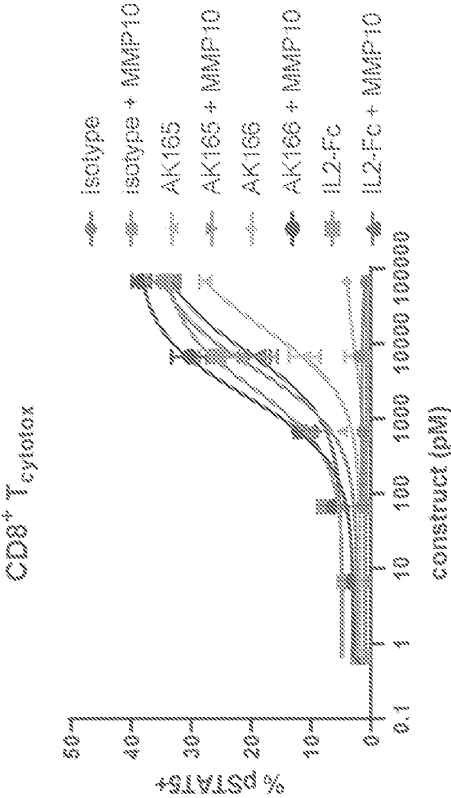


FIG. 12D

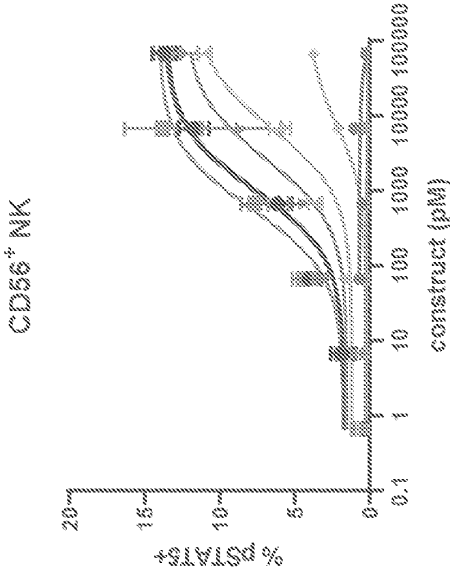


FIG. 13A

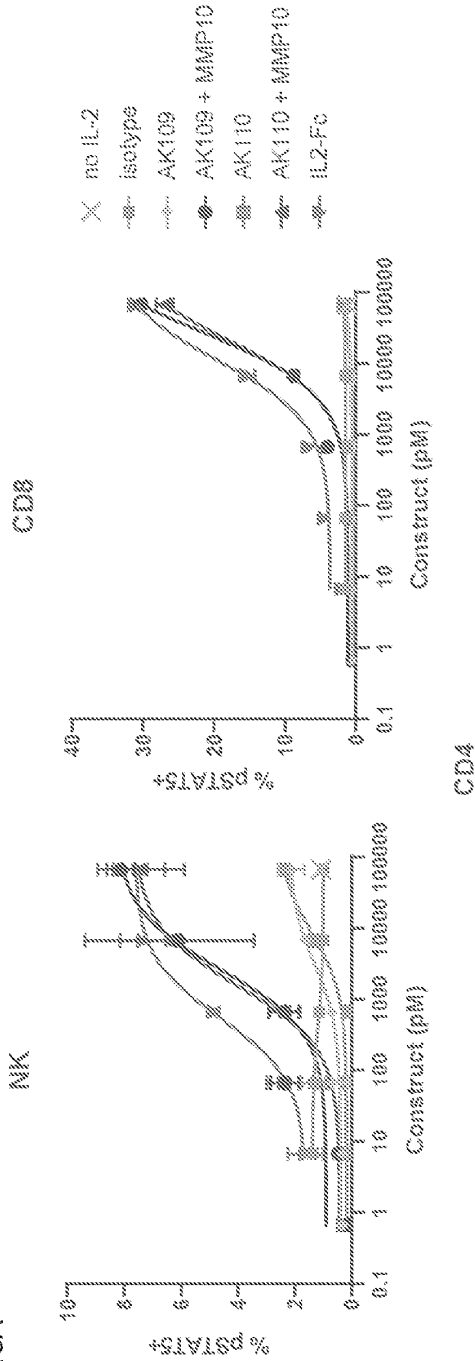
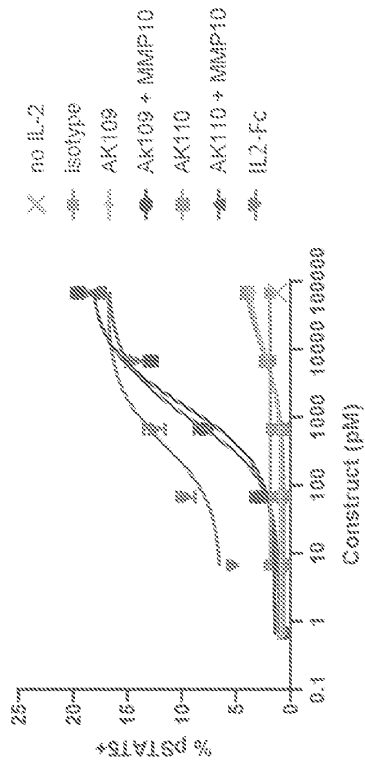
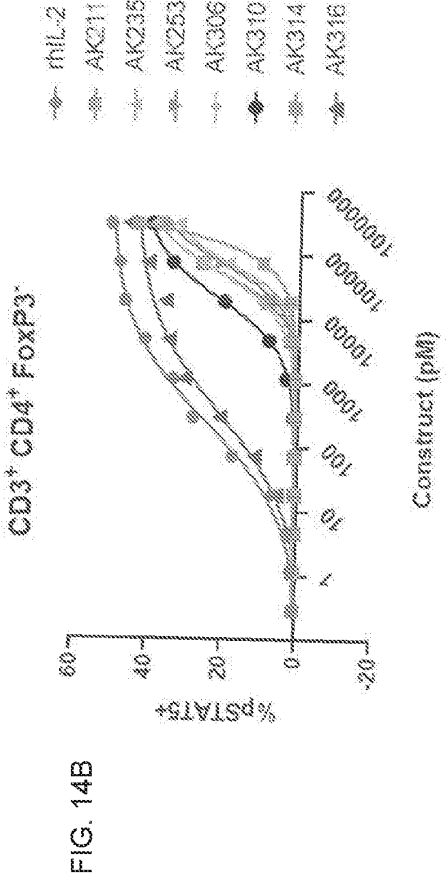
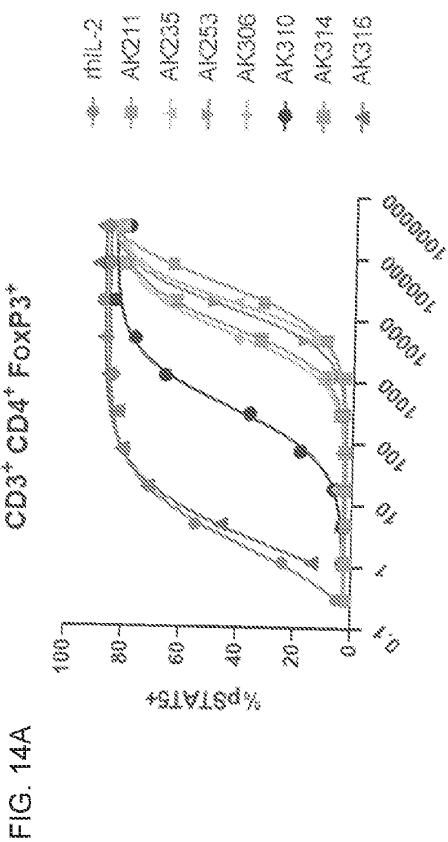
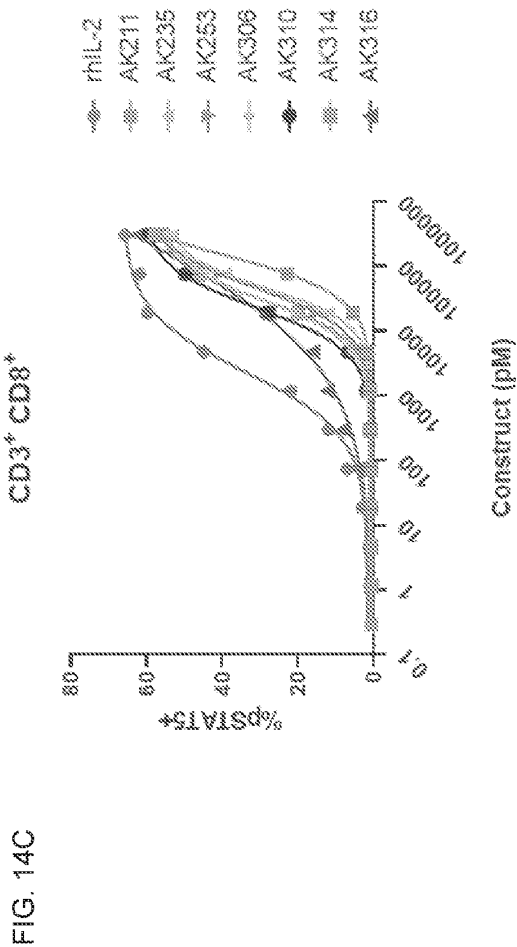


FIG. 13C

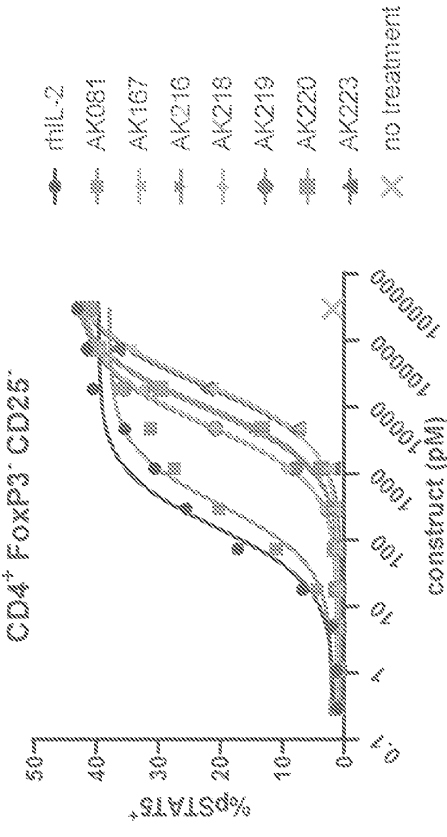
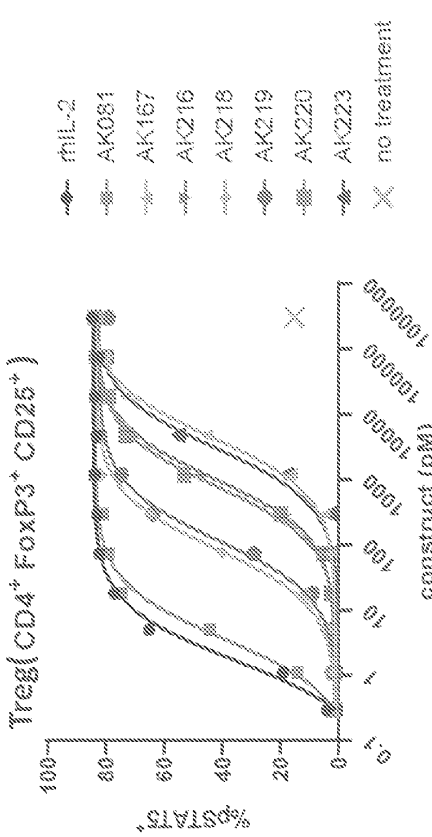






Construct	CD3 ⁺ CD4 ⁺ FoxP3 ⁺ EC ₅₀ (pM)	CD3 ⁺ CD4 ⁺ FoxP3 ⁻ EC ₅₀ (pM)	CD3 ⁺ CD8 ⁺ EC ₅₀ (pM)
rhIL-2	1.94	247	2300
AK211	39500	*	164000
AK253	15400	75100	46400
AK235	19200	69500	44100
AK314	7250	49400	29500
AK306	5680	56300	28800
AK310	373	20800	22300
AK316	1.73	331	167000*

FIG. 14D



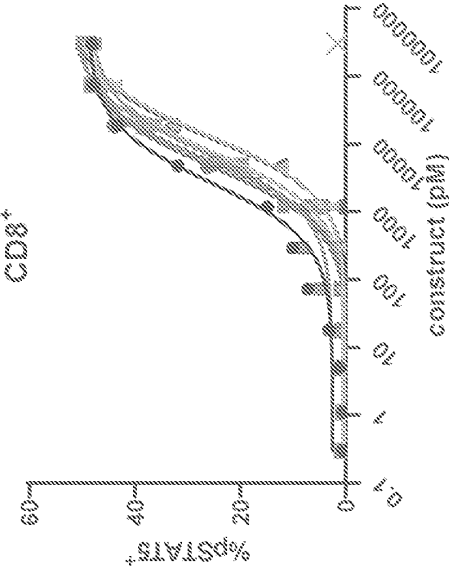


FIG. 15D

Construct	Foxp3 ⁺ T _{reg} EC ₅₀ (pM)	CD4 ⁺ T _{help} EC ₅₀ (pM)	CD8 ⁺ T _{cyto} EC ₅₀ (pM)
Phil-2	1.67	154	2710
AK081	3.59	332	6700
AK167	4390	22900	13200
AK216	1020	9200	5490
AK218	86.7	5270	7550
AK219	117	5030	4570
AK220	782	10900	7650
AK223	3040	20200	12600

FIG. 16A

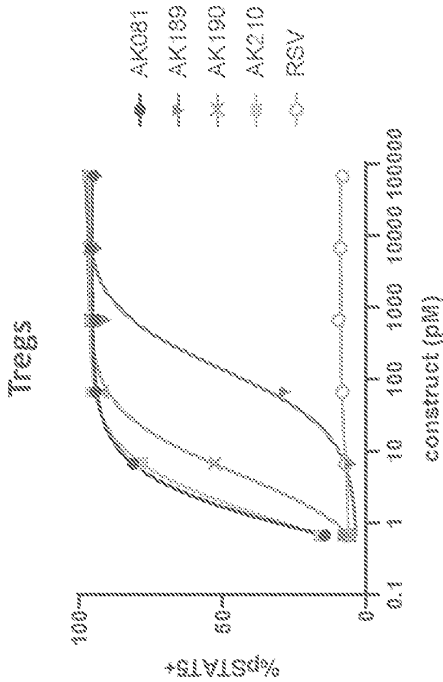


FIG. 16B

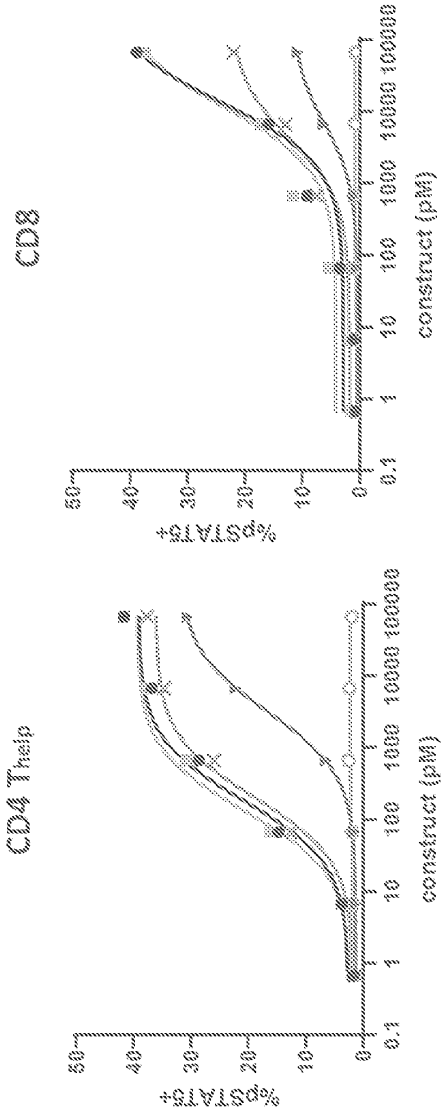


FIG. 16C

FIG. 17A

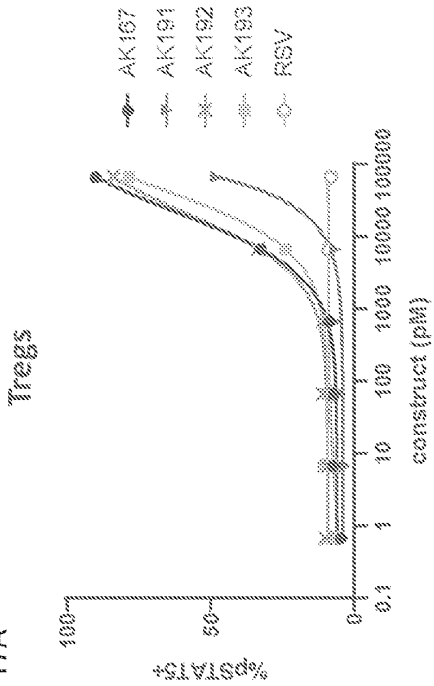


FIG. 17B

CD4^{Th1p}

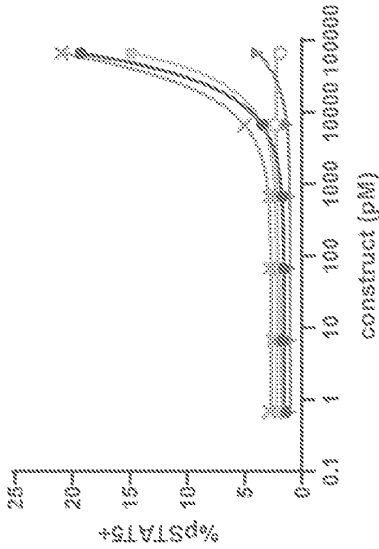


FIG. 17C

CD8

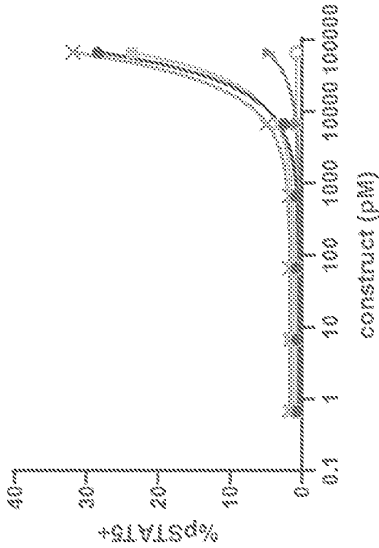


FIG. 18A

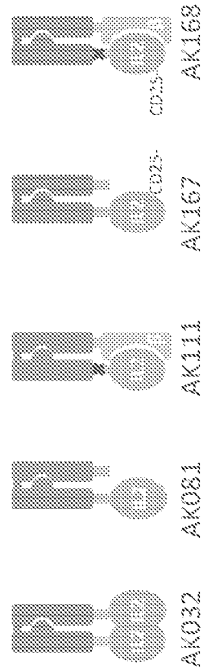


FIG. 18B

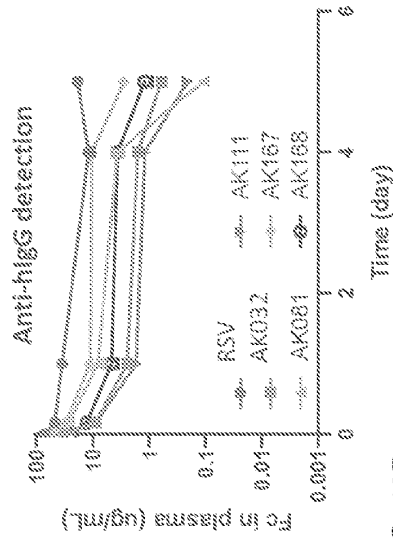


FIG. 18C

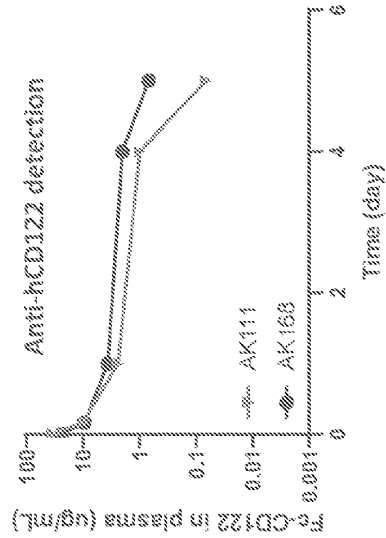
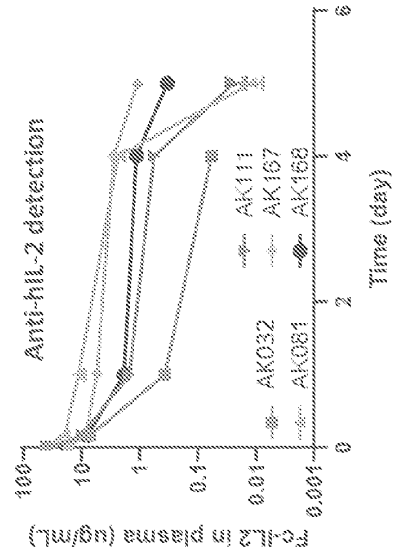
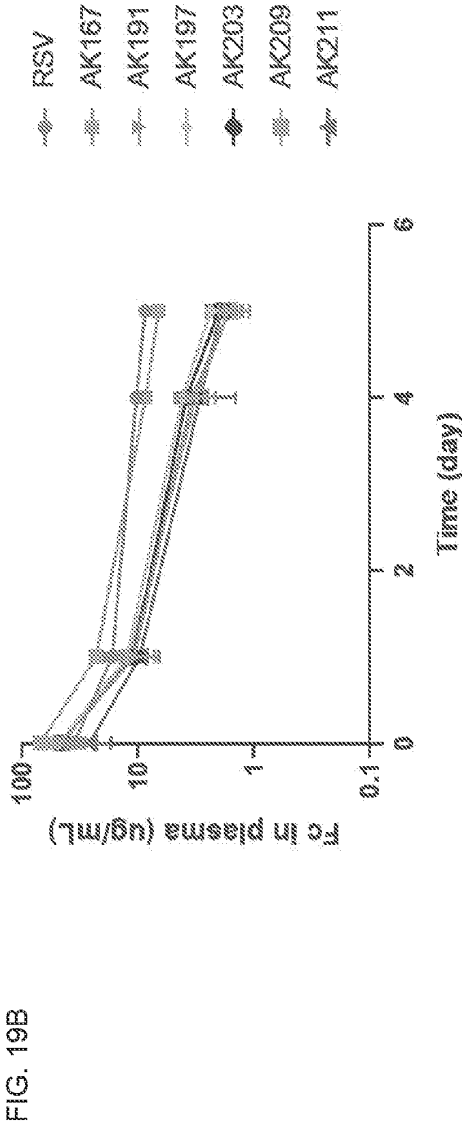
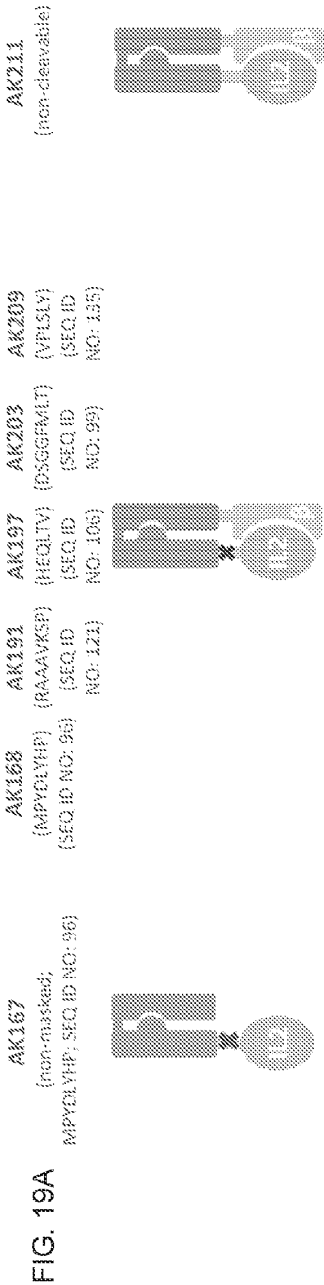
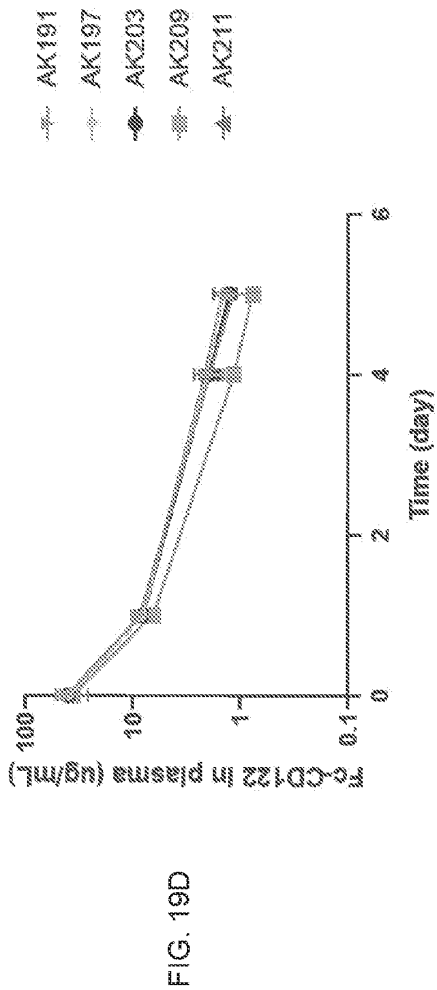
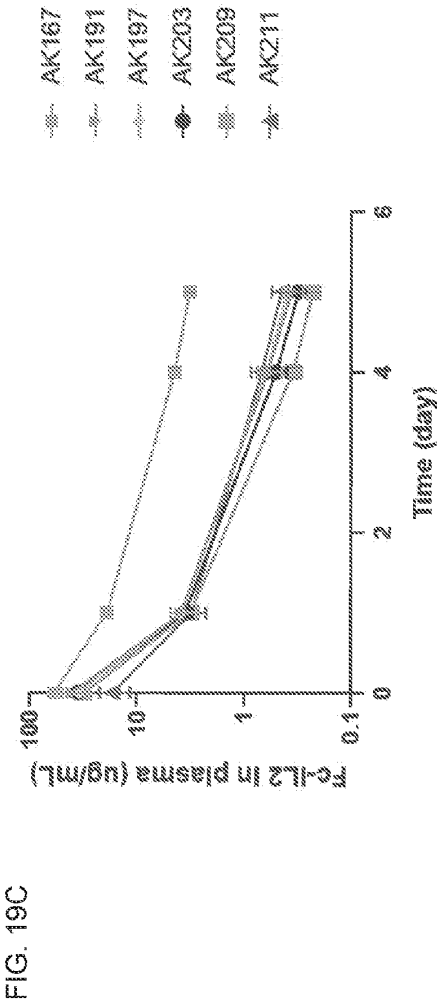


FIG. 18D







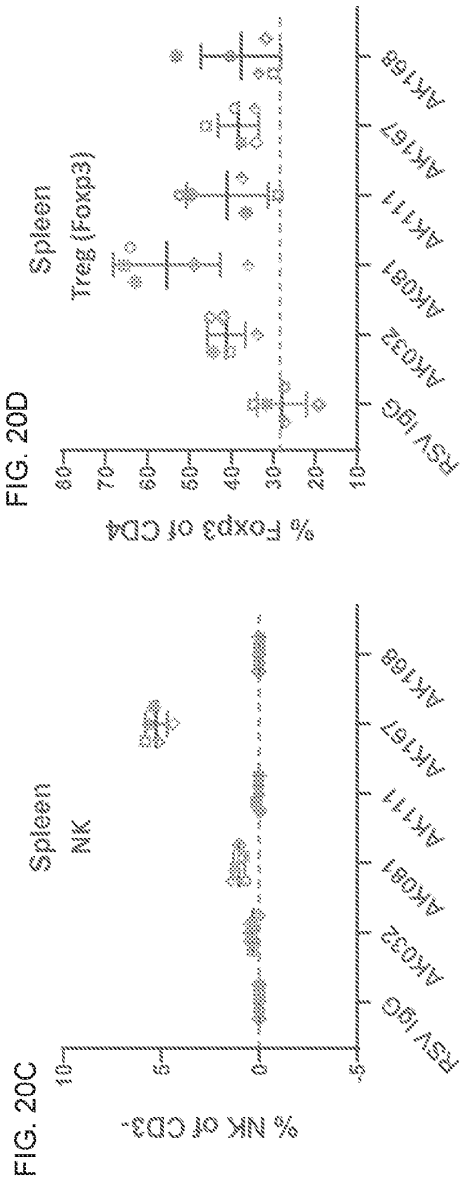
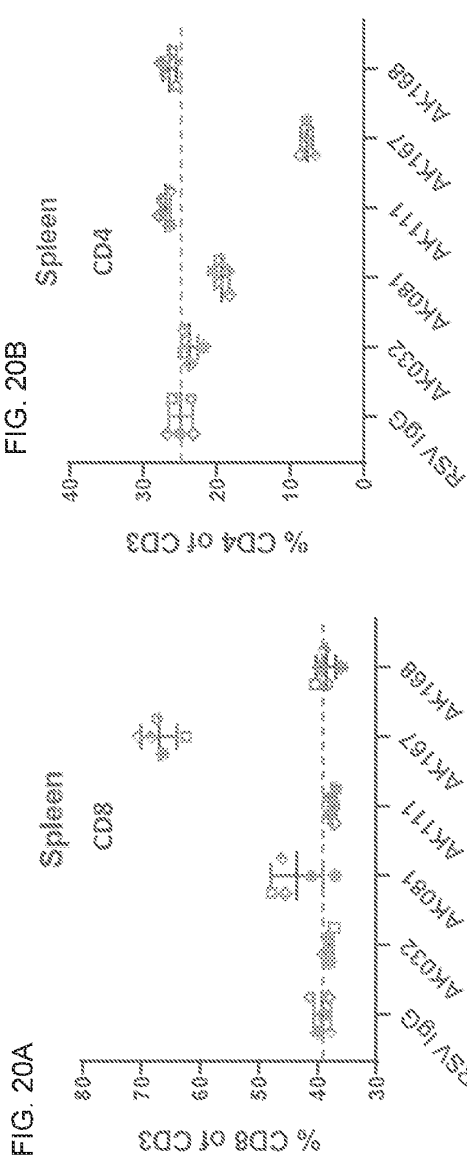


FIG. 20B

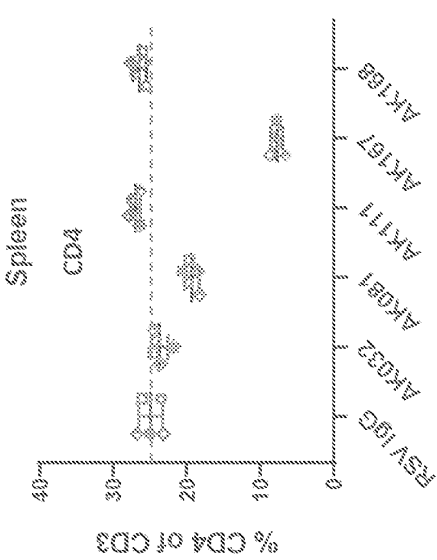


FIG. 20D

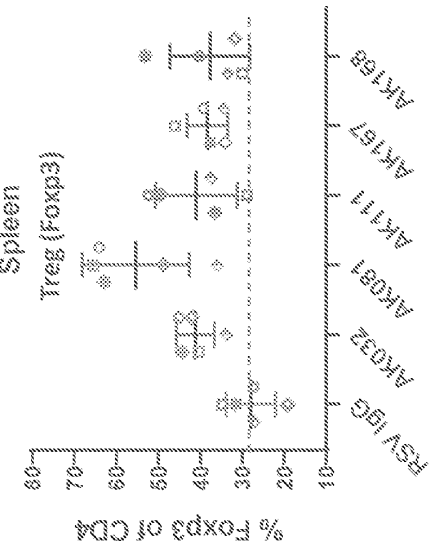


FIG. 20F

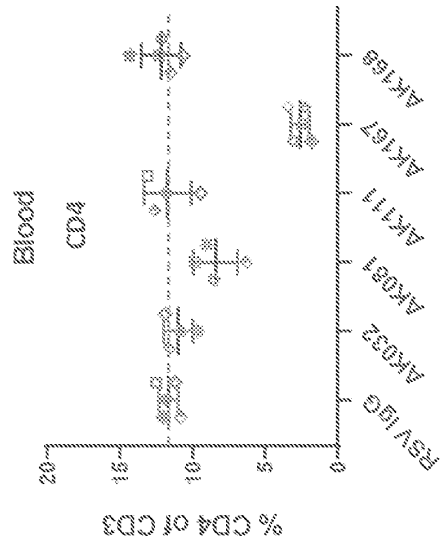


FIG. 20H

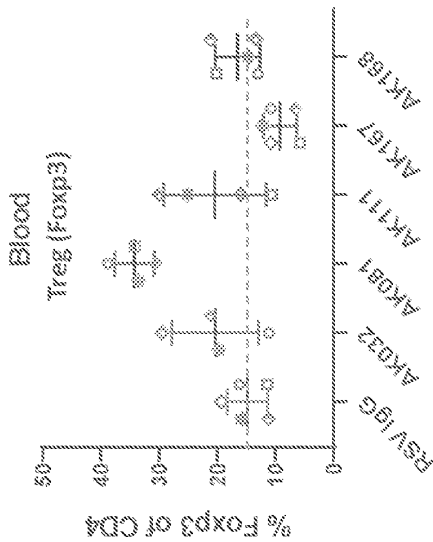


FIG. 20E

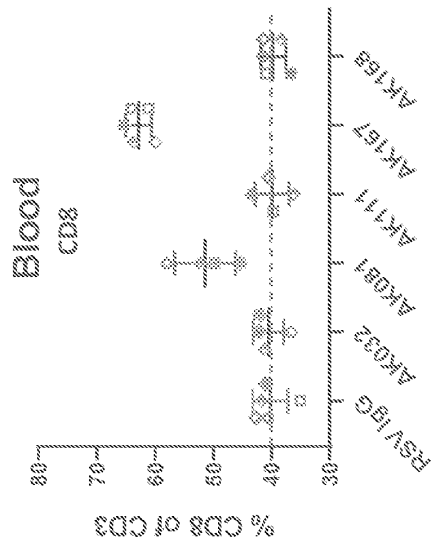


FIG. 20G

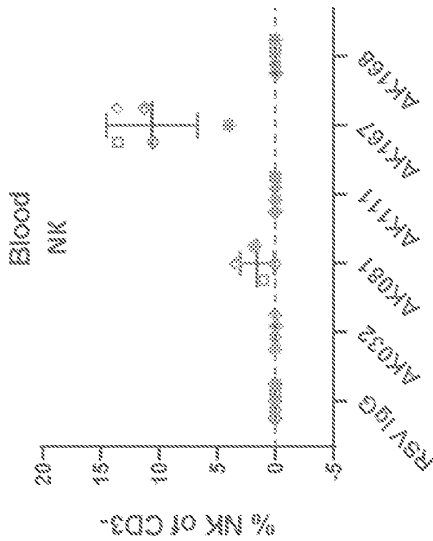


FIG. 20J

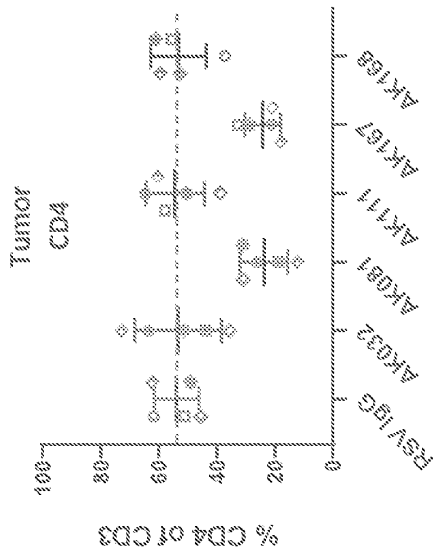


FIG. 20L

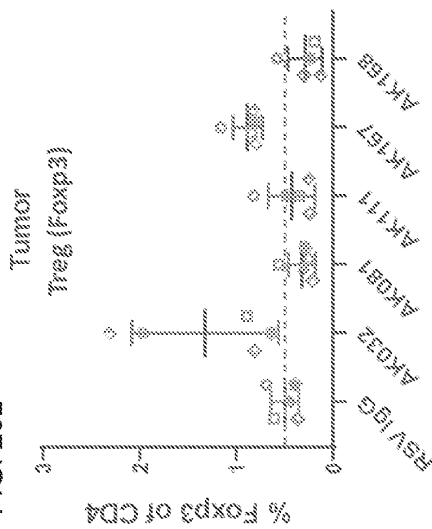


FIG. 20I

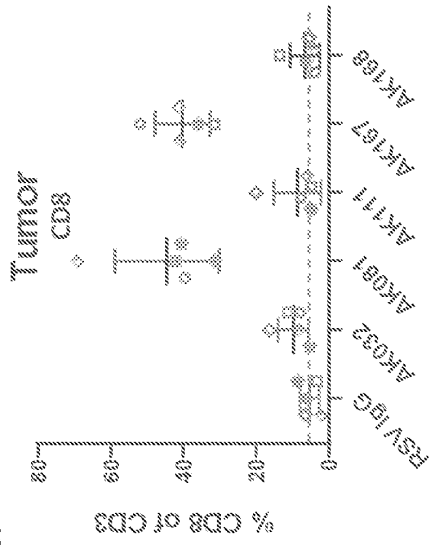


FIG. 20K

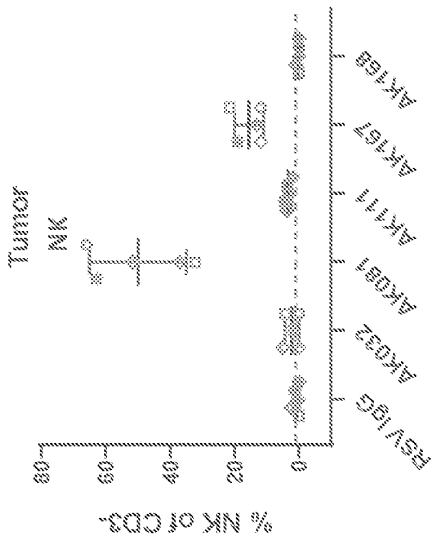


FIG. 21B

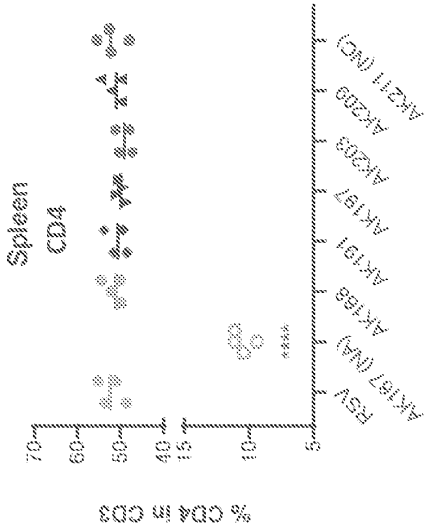


FIG. 21D

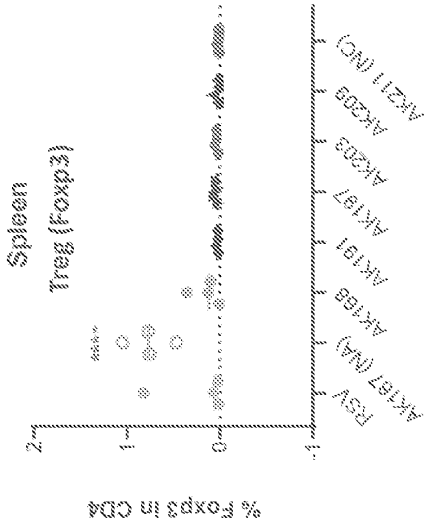


FIG. 21A

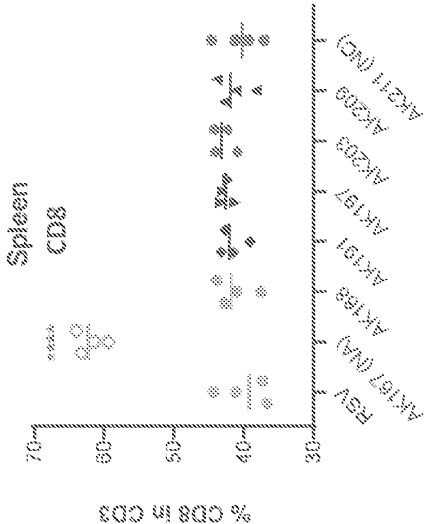


FIG. 21C

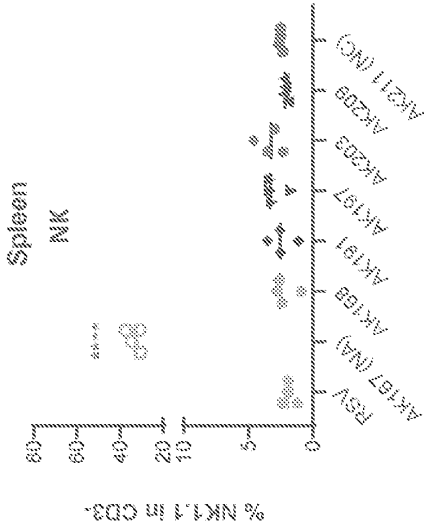


FIG. 21F

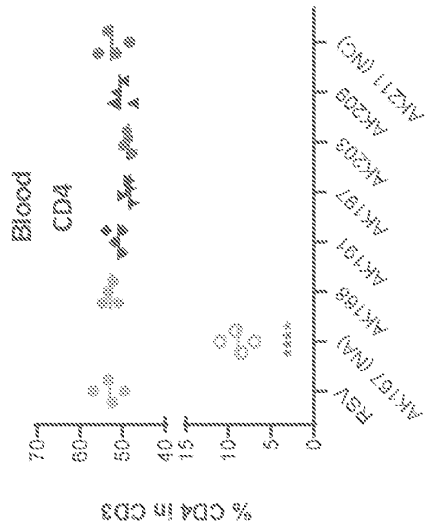


FIG. 21H

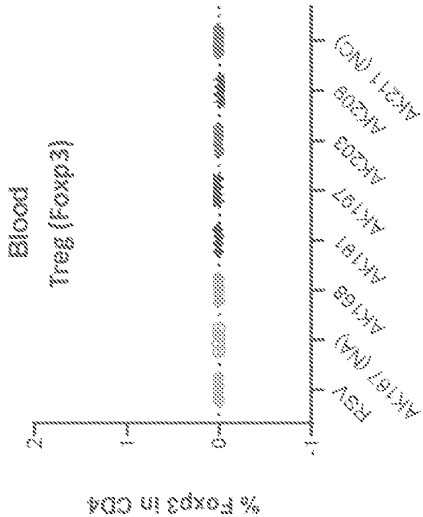


FIG. 21E

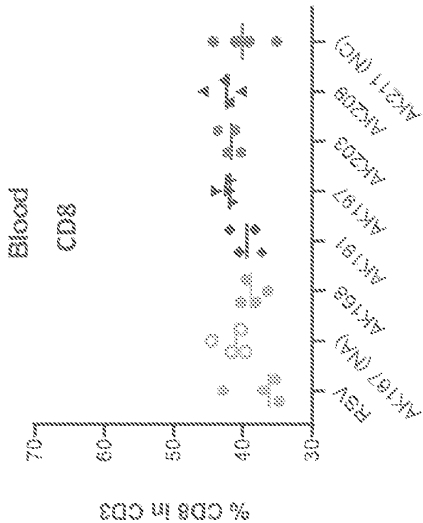


FIG. 21G

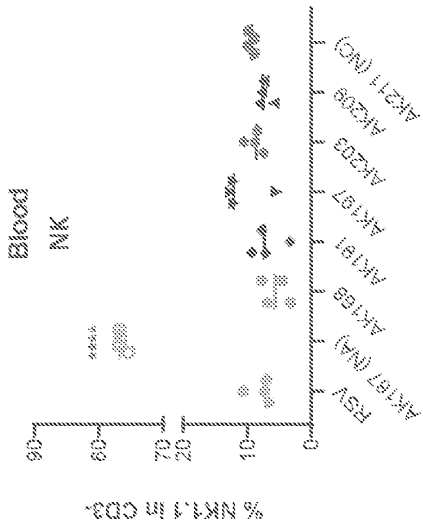


FIG. 21J

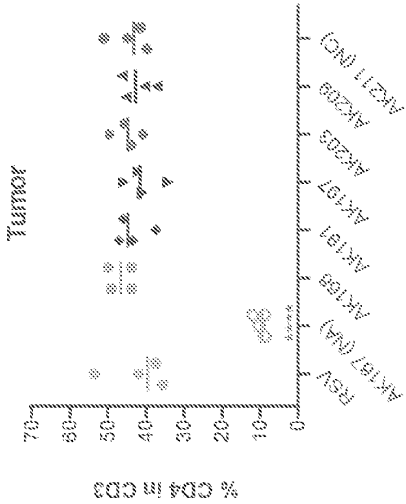


FIG. 21L

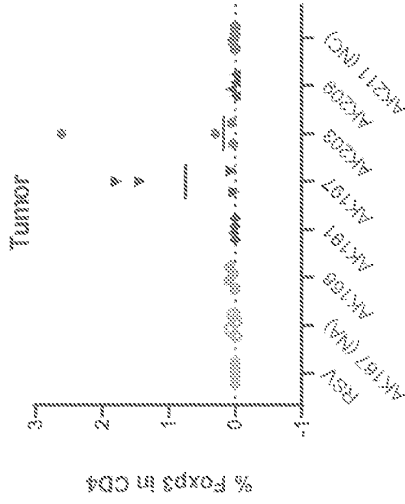


FIG. 21I

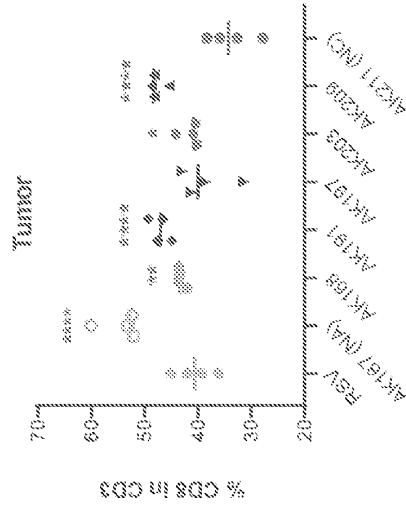


FIG. 21K

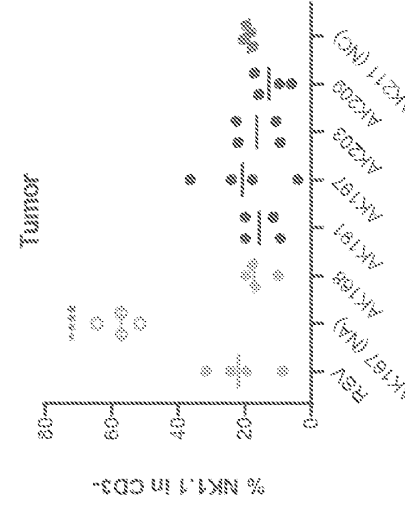


FIG. 22A

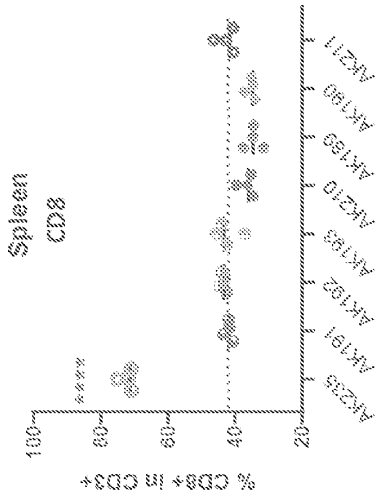


FIG. 22B

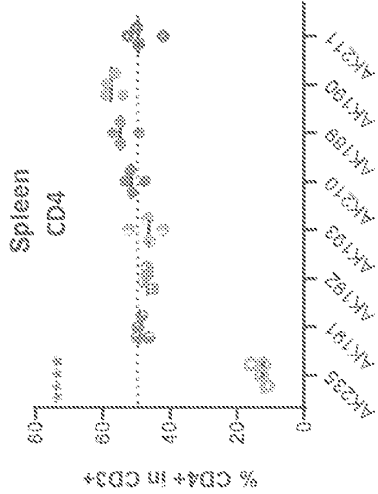


FIG. 22C

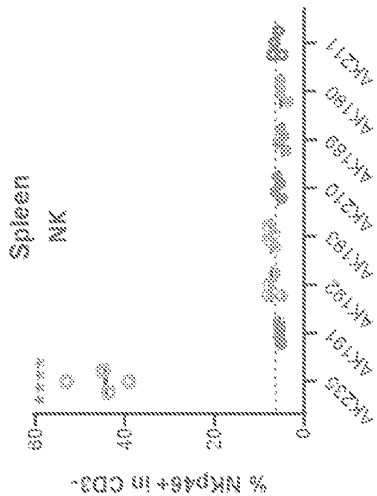


FIG. 22D

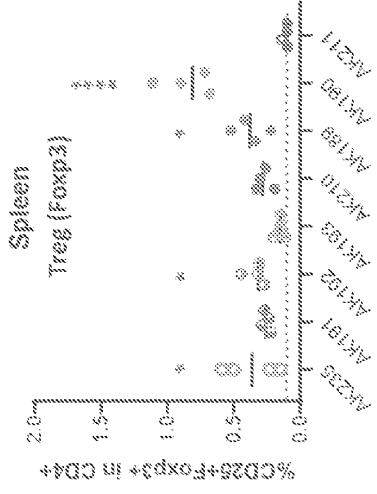


FIG. 22E

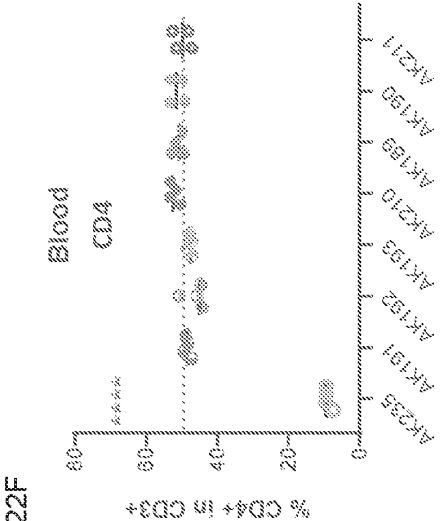
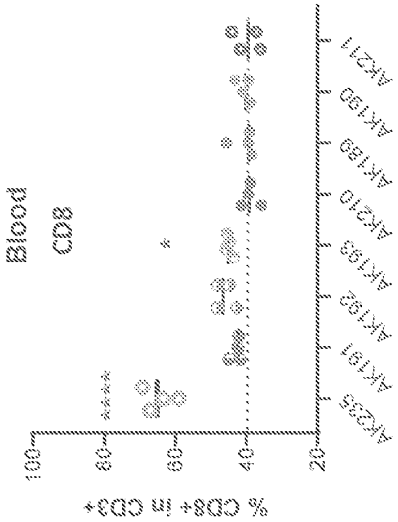


FIG. 22G

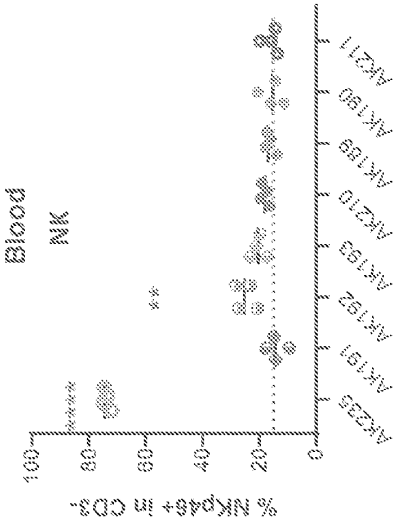


FIG. 22H

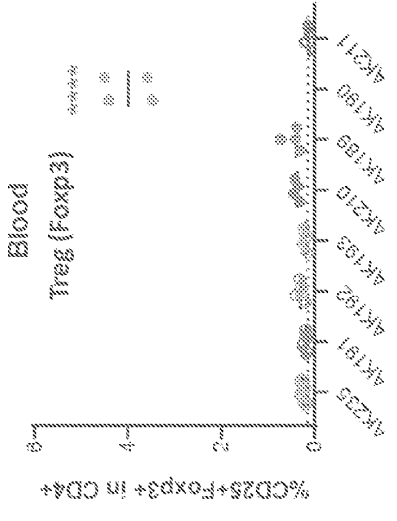


FIG. 22J

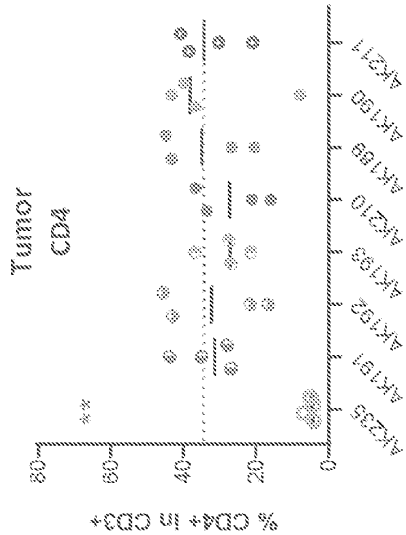


FIG. 22L

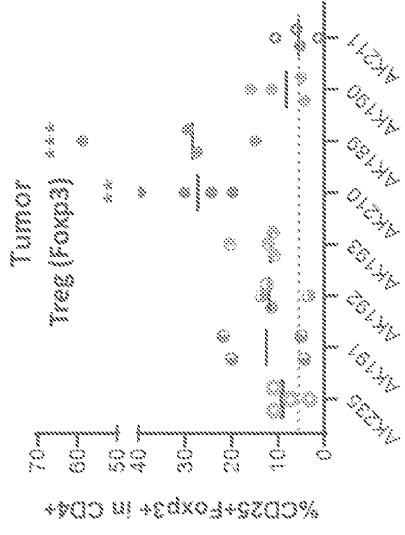


FIG. 22I

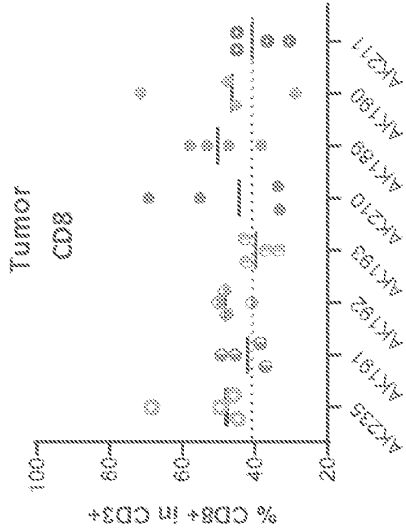


FIG. 22K

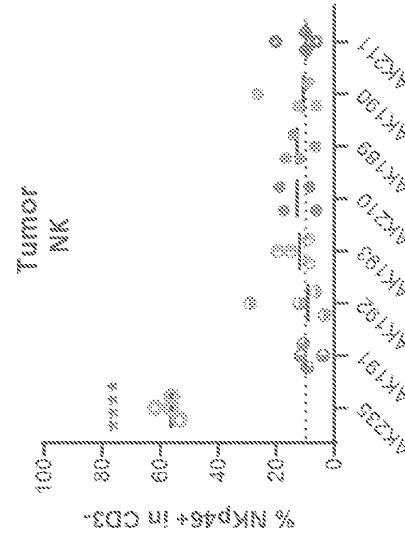


FIG. 23B

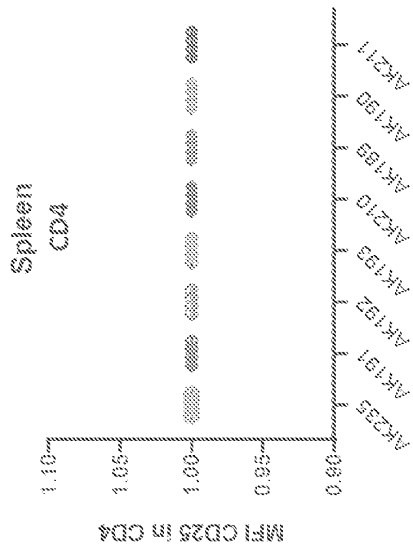


FIG. 23A

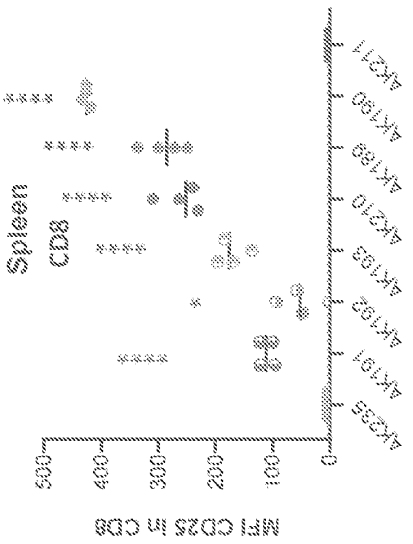


FIG. 23C

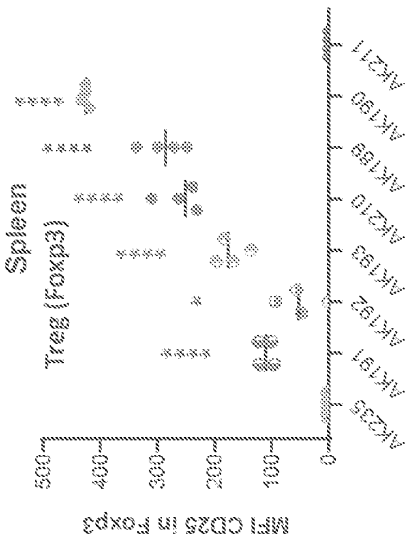


FIG. 23E

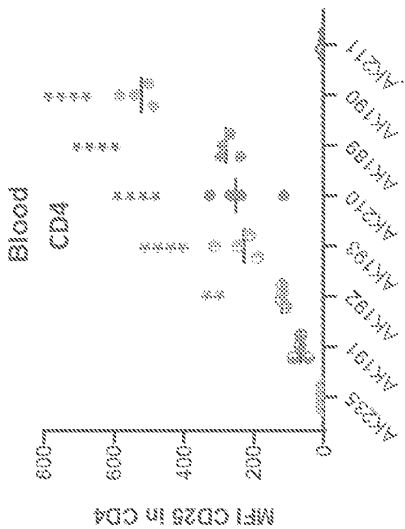


FIG. 23D

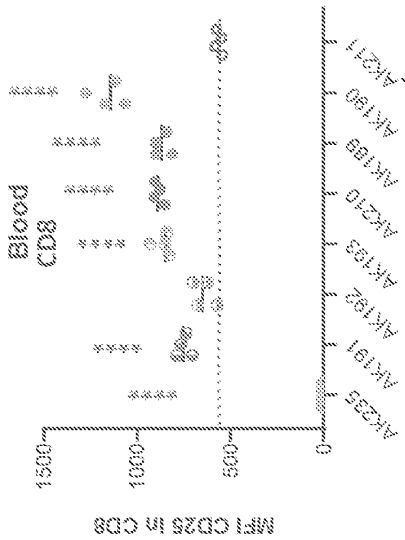


FIG. 23F

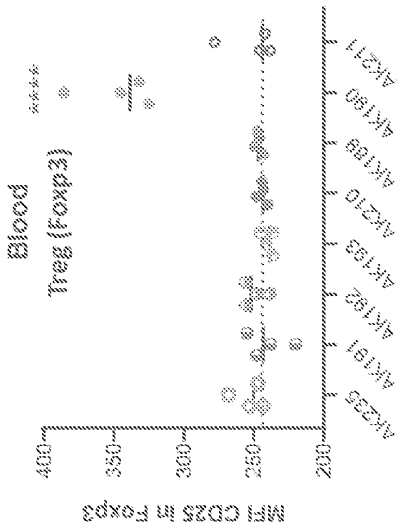


FIG. 23H

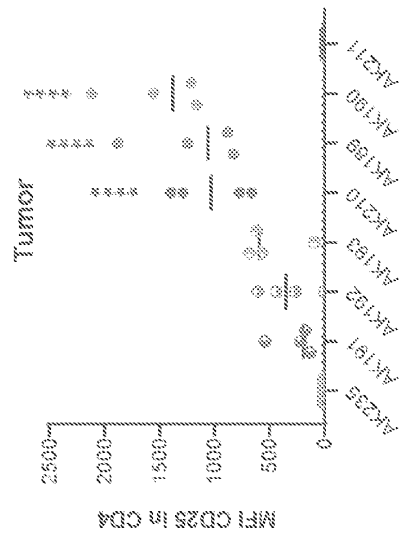


FIG. 23G

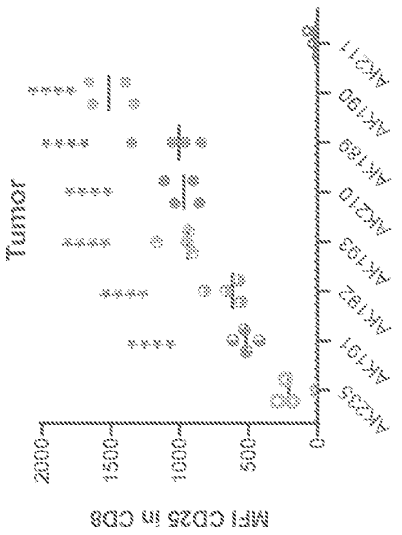
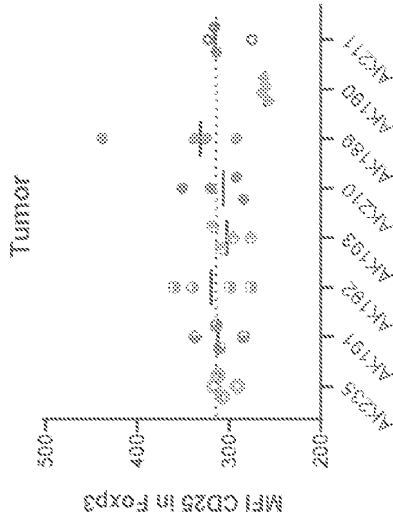
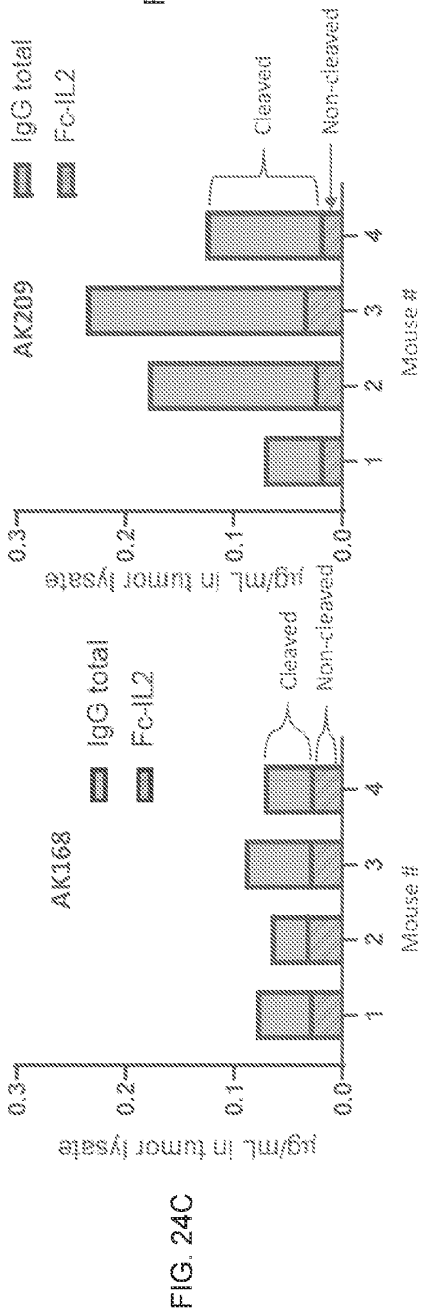
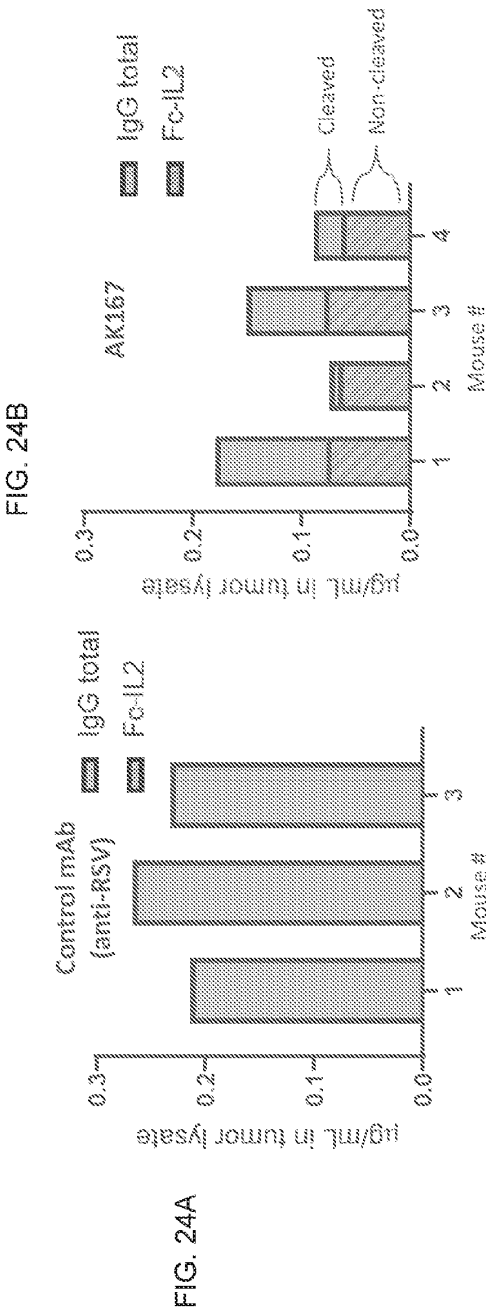


FIG. 23I





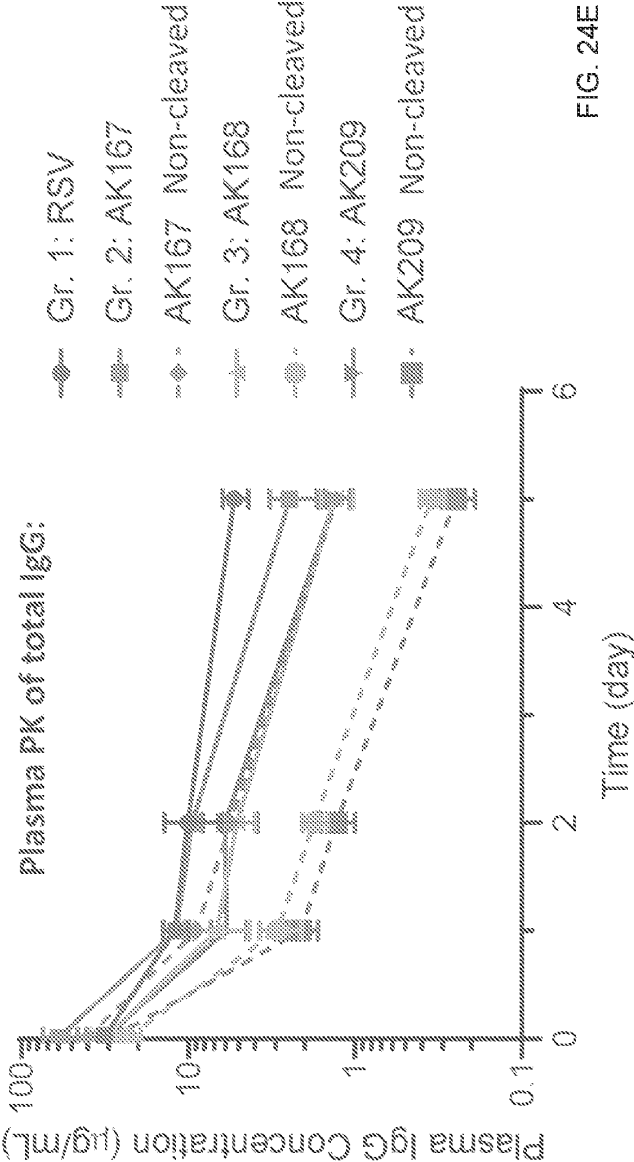


FIG. 24E

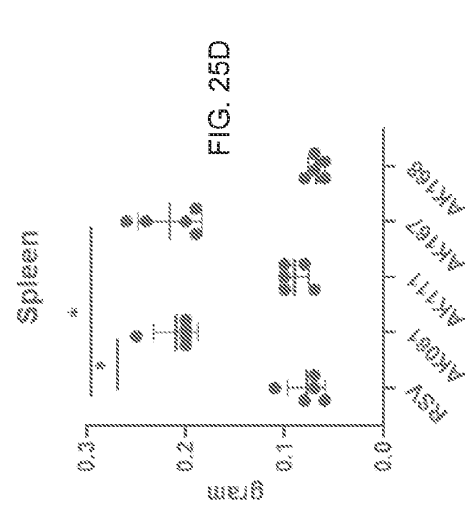
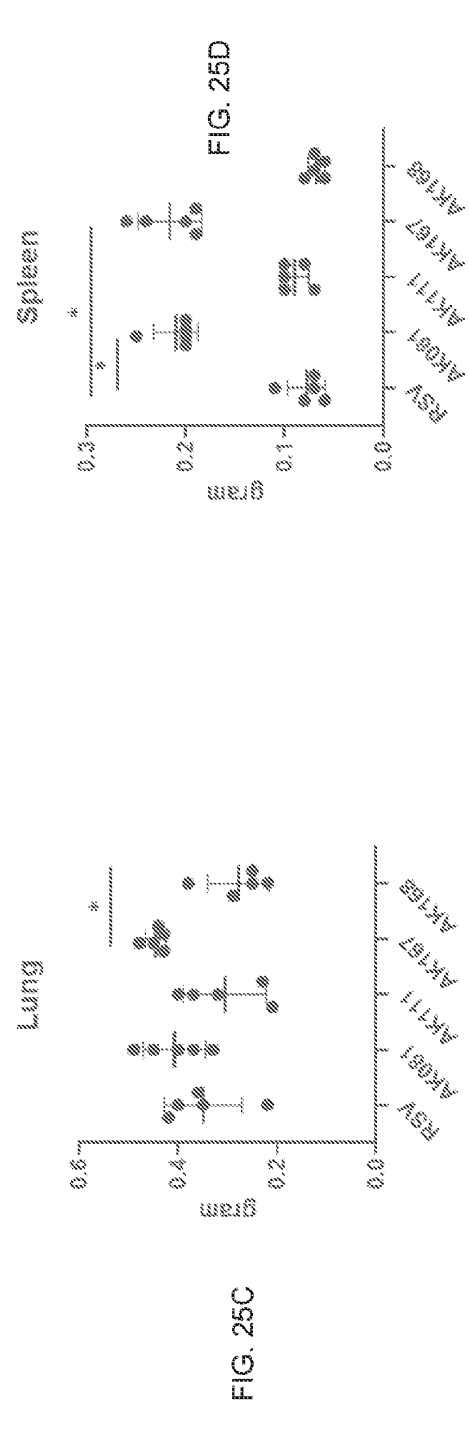
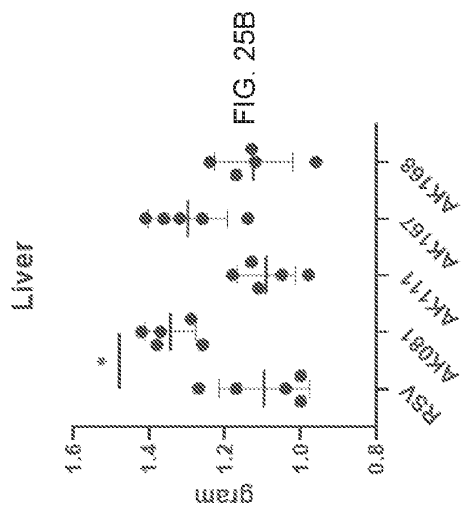
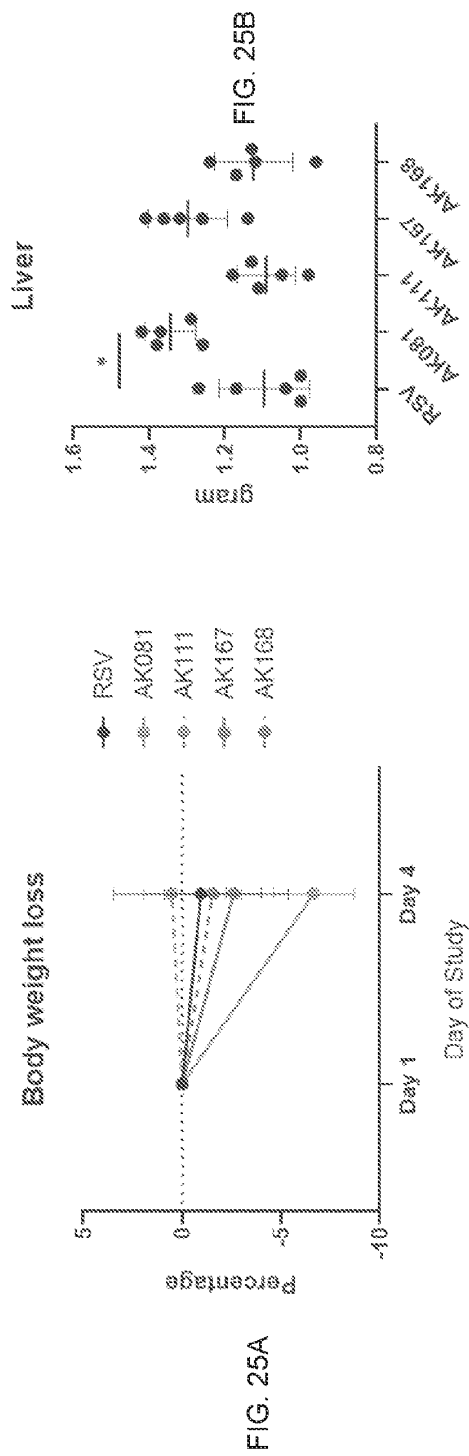


FIG. 26B

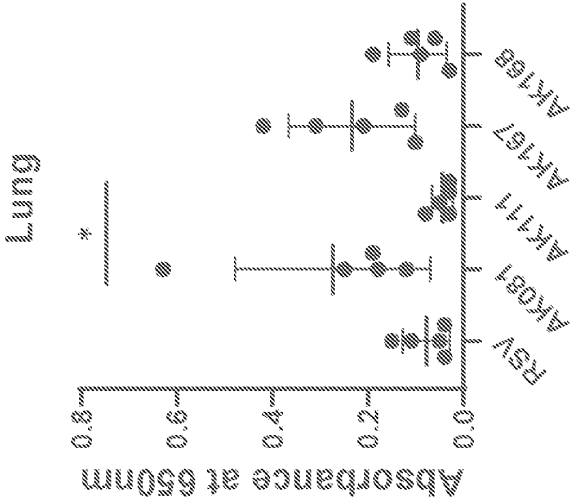


FIG. 26A

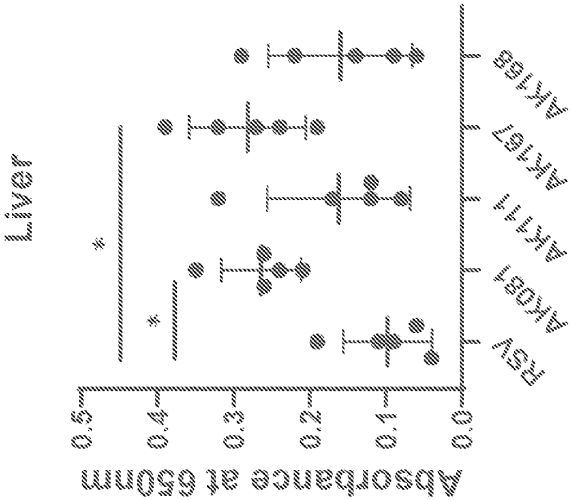


FIG. 27A

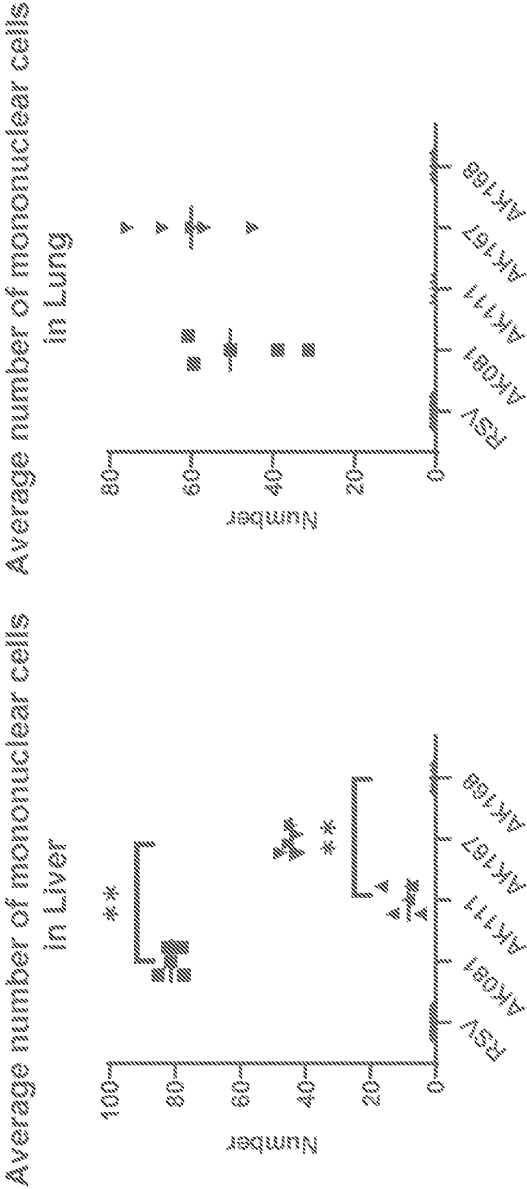


FIG. 27B

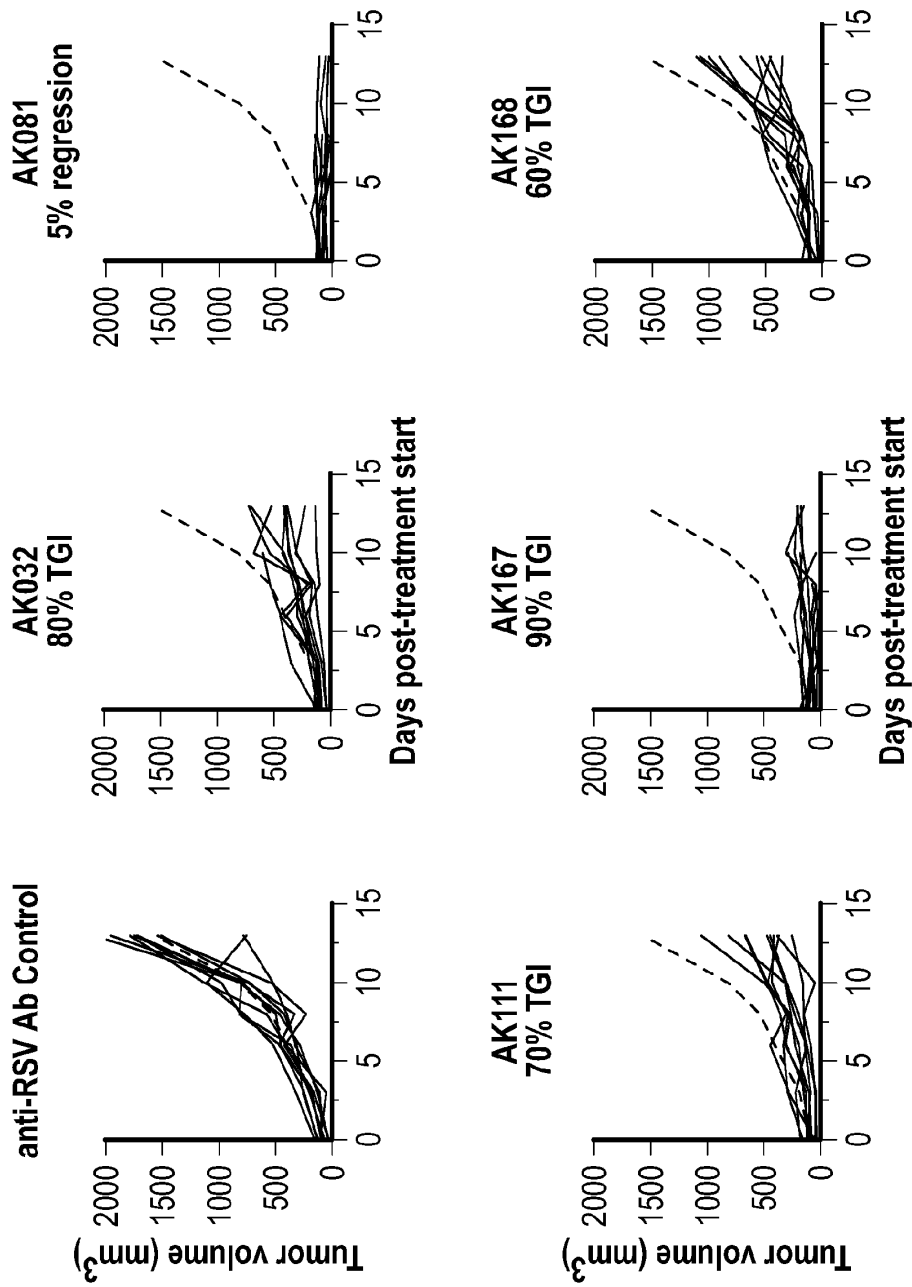


FIG. 28A

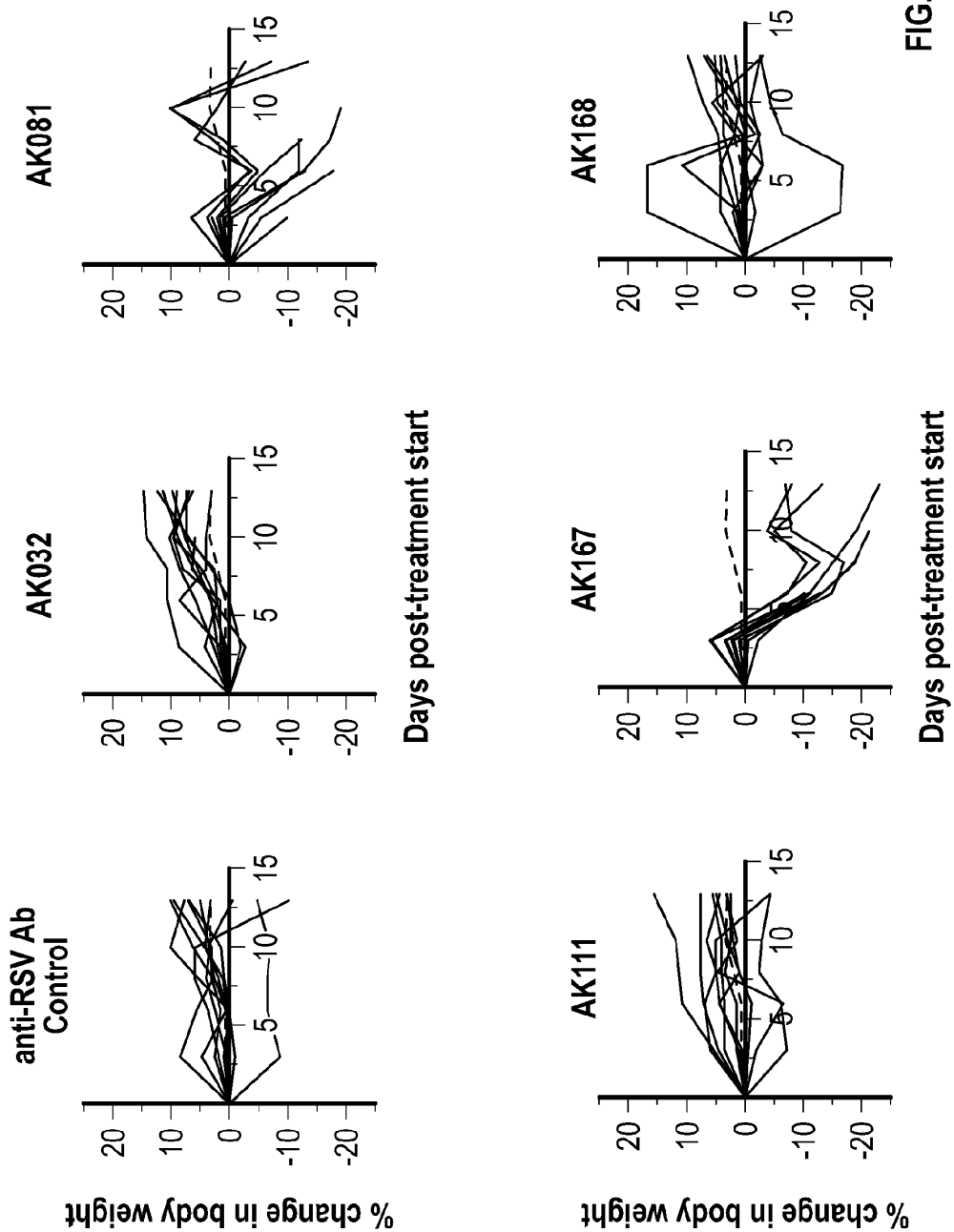


FIG. 28B

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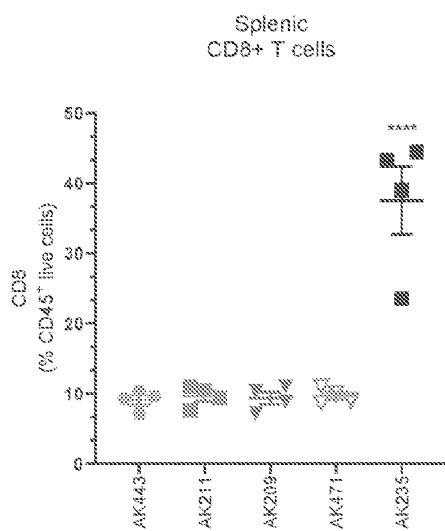


FIG. 29A

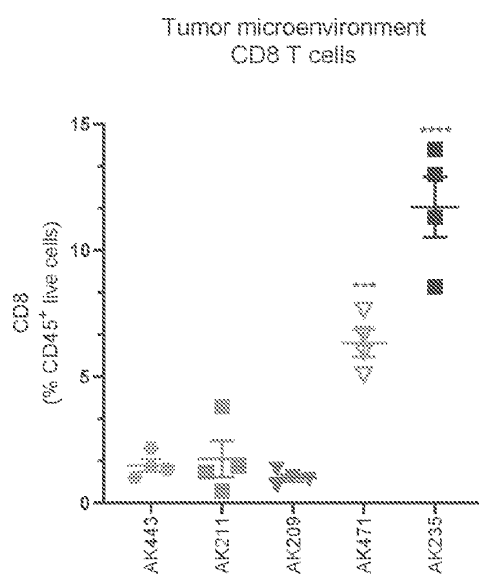
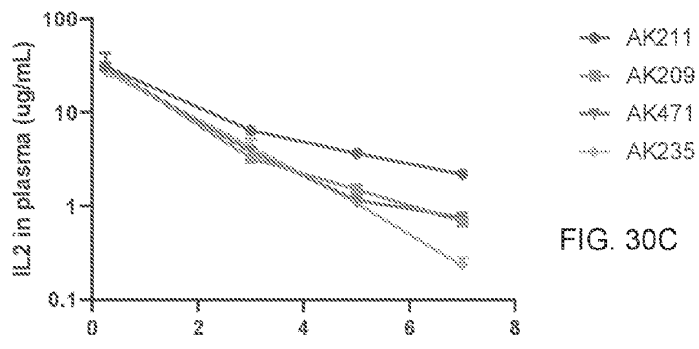
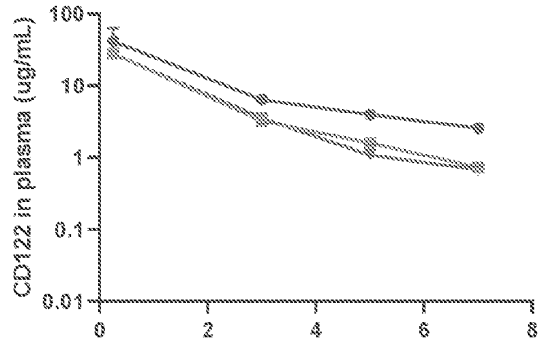
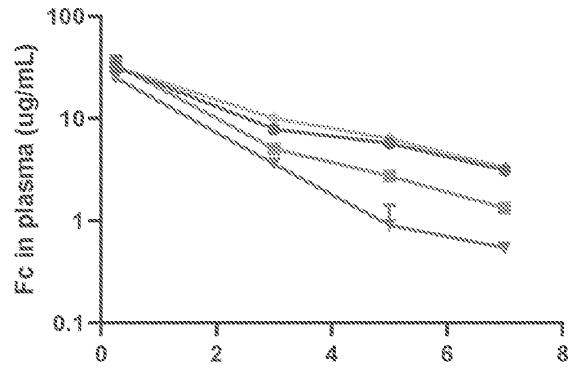


FIG. 29B



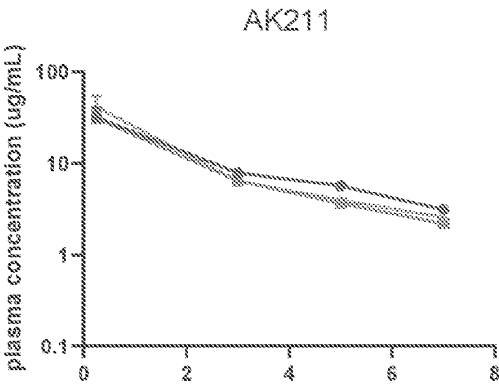


FIG. 31A

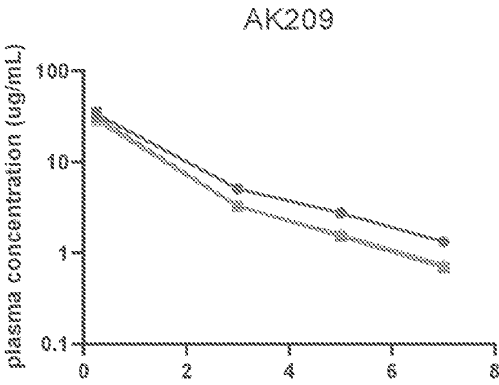


FIG. 31B

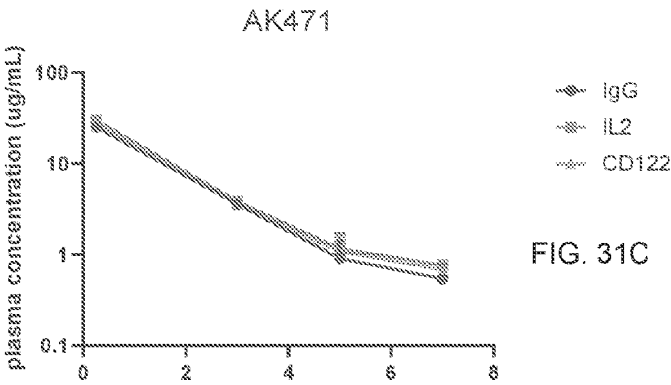


FIG. 31C

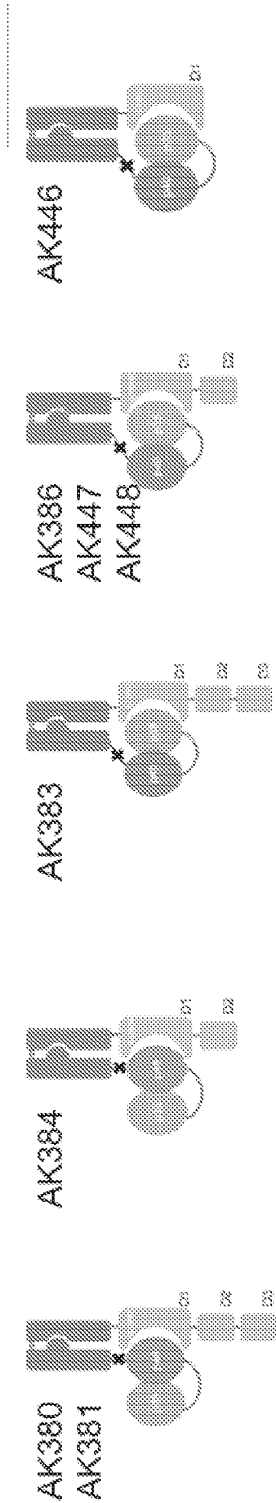


FIG.32

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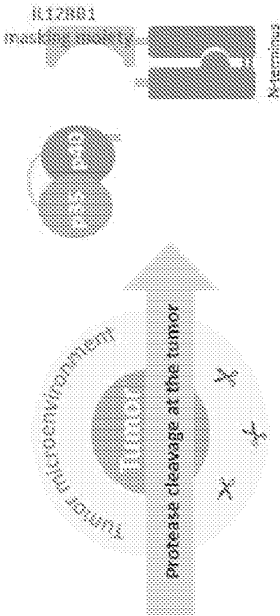
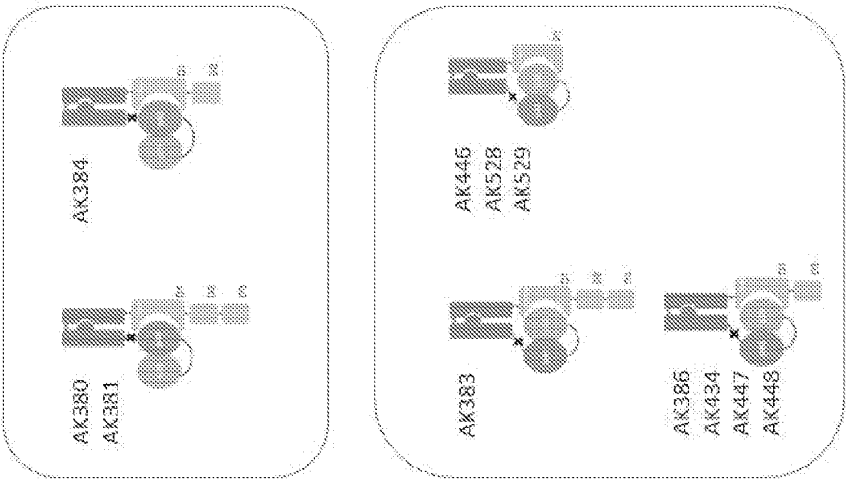


FIG33A

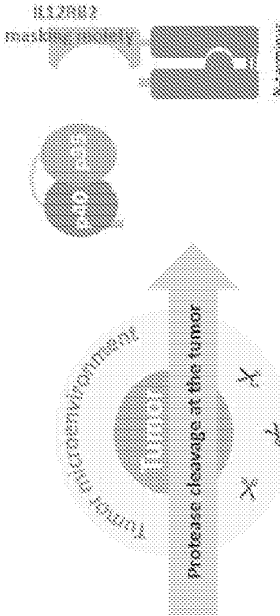
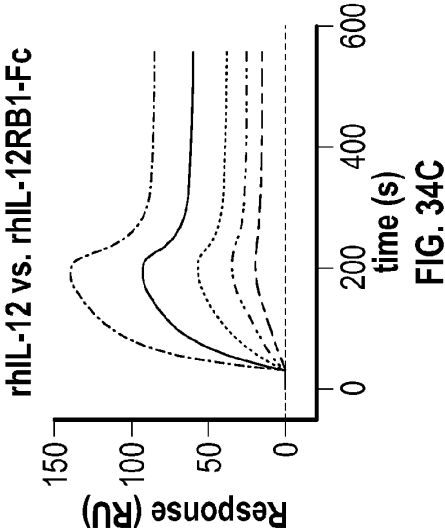
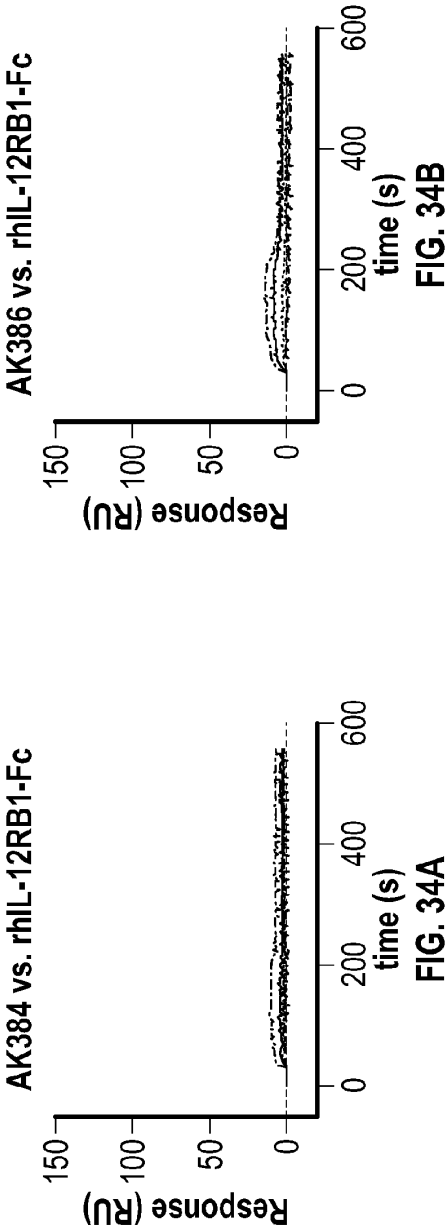
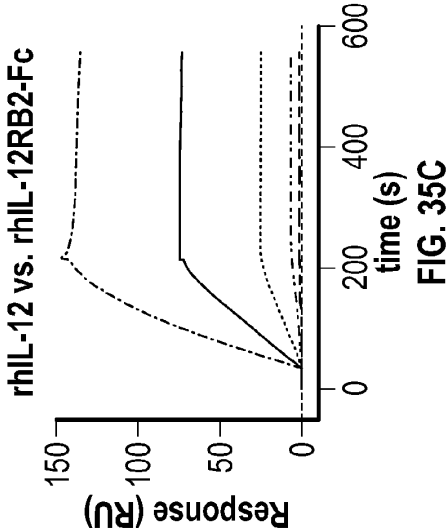
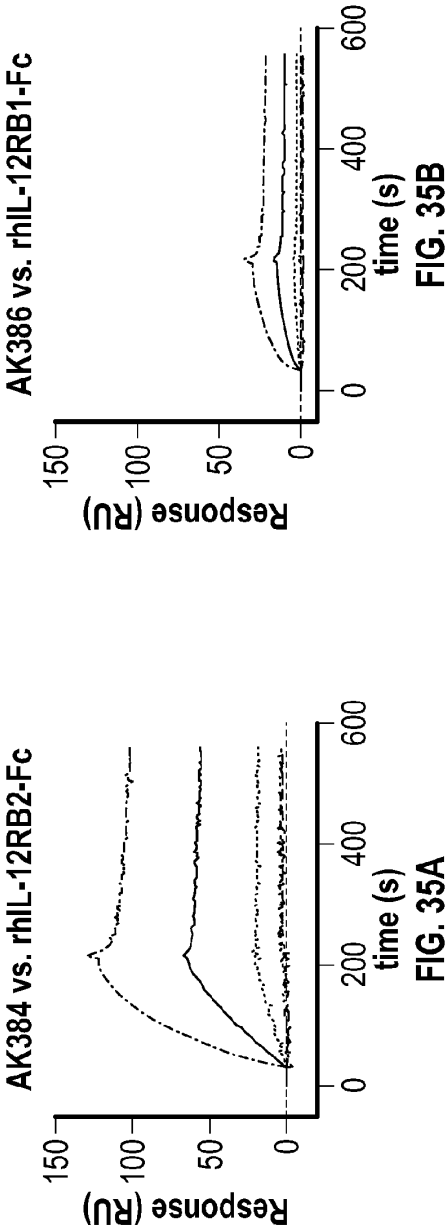


FIG33B



Sample	k_a ($1/(M^+s)$)	k_d (1/s)	KD	Chi2	U-value: k_d (%)
AK384	ND	ND	ND	ND	ND
AK386	ND	ND	ND	ND	ND
rhIL-12	N/A	N/A	60.1 nM	N/A	N/A

FIG. 34D



Sample	k_a ($1/(M \cdot s)$)	k_d (1/s)	KD	Chi2	U-value: k_d (%)
AK384	$2.31e+5$	$3.92e-4$	1.70 nM	1.21	2.10
AK386	ND	ND	ND	ND	ND
rhIL-12	$2.21e+5$	$1.37e-4$	0.617 nM	18.42	10.5

FIG. 35D

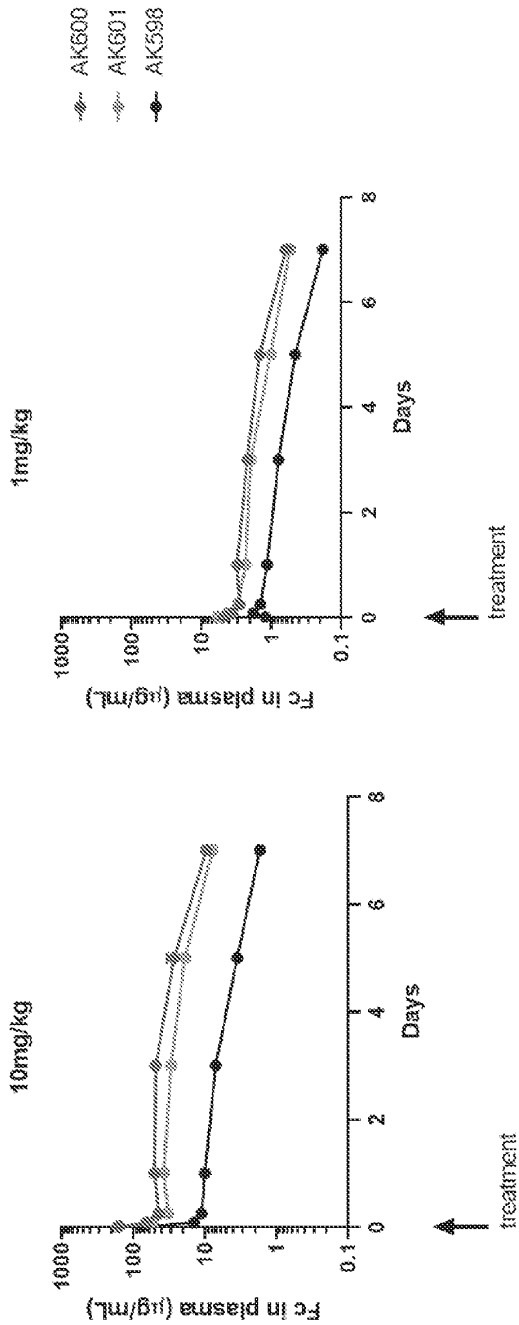
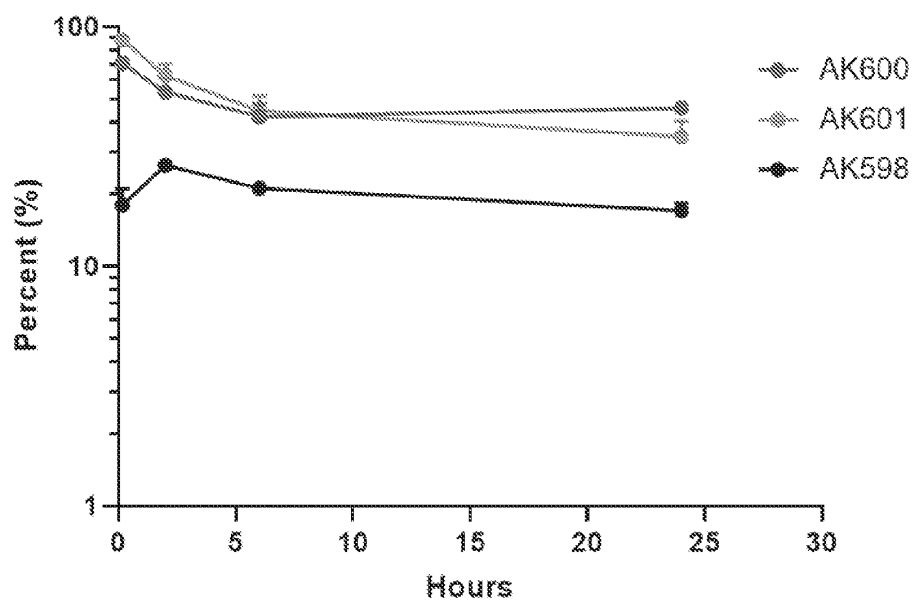


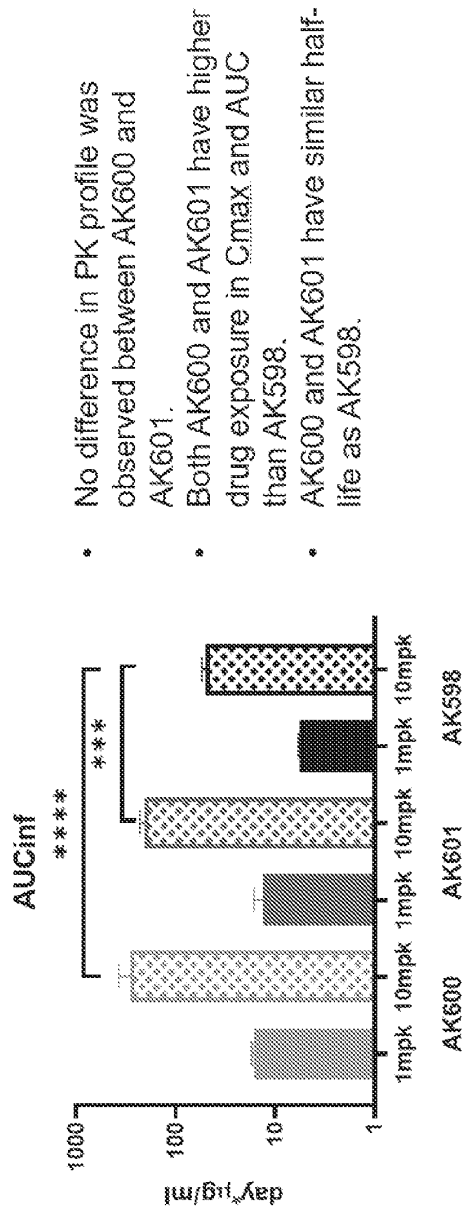
FIG 36

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FIG 37



- C57BL/6 mice
- 20 μ g
- Single i.v.
- Capture: anti-human IgG
- Detect: anti-human IgG



- No difference in PK profile was observed between AK600 and AK601.
- Both AK600 and AK601 have higher drug exposure in C_{max} and AUC than AK598.
- AK600 and AK601 have similar half-life as AK598.

AK600											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)
2.486	4.767	0.007	14.03	16.276	16.276	1.714	166.486	0.007	261.314	285.263	285.263
AK601											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)
2.031	5.994	0.007	11.692	13.291	13.291	2.199	154.814	0.007	181.3	206.2	206.2
AK598											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	Half-life (day)	C _{max} (ug/ml)	T _{max} (day)	AUC _{last} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)	AUC _{inf_obs} (day*ug/ml)
2.013	1.793	0.083	5.097	5.639	5.639	1.954	73.45	0.007	45.573	50.403	50.403

FIG. 38

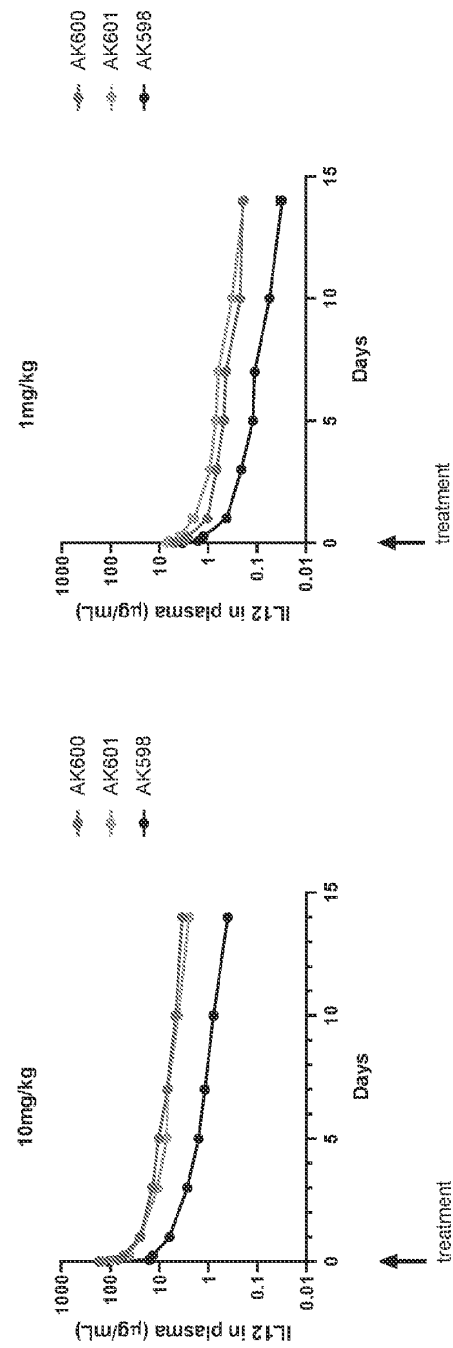


FIG. 39

AK600											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)	Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)
5.651	4.925	7.021	9.359	107.083	871.266	6.052	169.773	160.198	190.176	53.938	474.291
AK601											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)	Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)
4.168	7.193	11.542	12.653	82.775	505.09	5.455	147.612	138.749	158.338	63.786	505.923
AK598											
1 mg/kg						10 mg/kg					
Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)	Half-life (day)	C _{max} (ug/ml)	AUC _{last} (day*ug/ml)	AUCIN _{F_obs} (day*ug/ml)	Cl _{obs} (ml/day/kg)	Vz _{obs} (ml/kg)
4.136	3.368	2.59	2.784	363.913	2123.945	4.7	107.585	34.501	37.38	268.073	1818.55

FIG 40

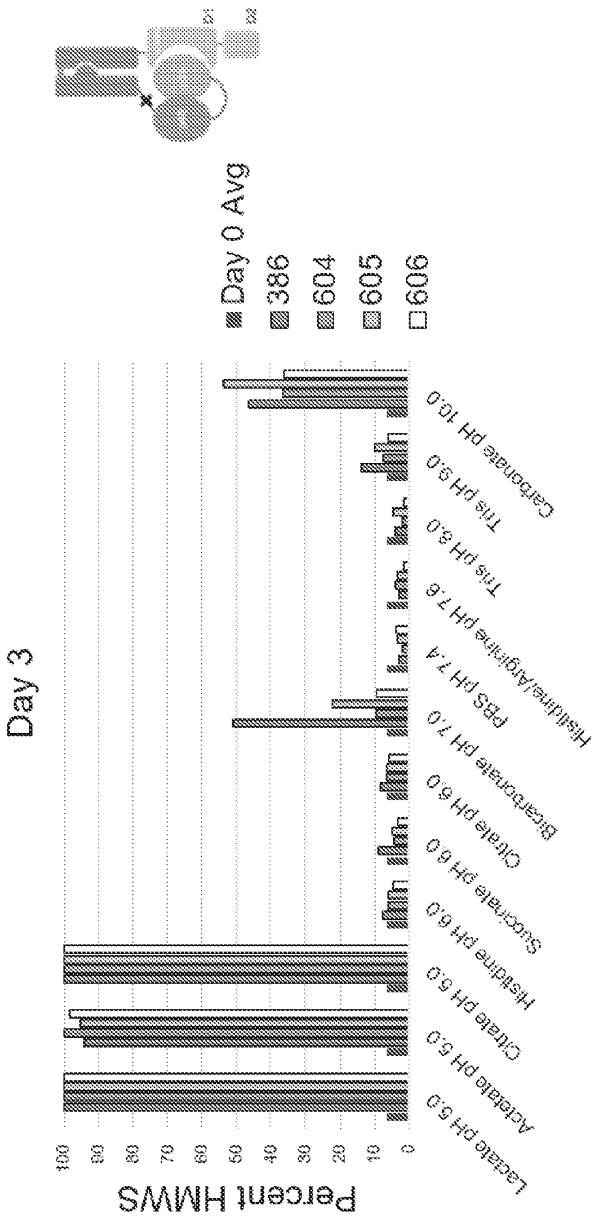
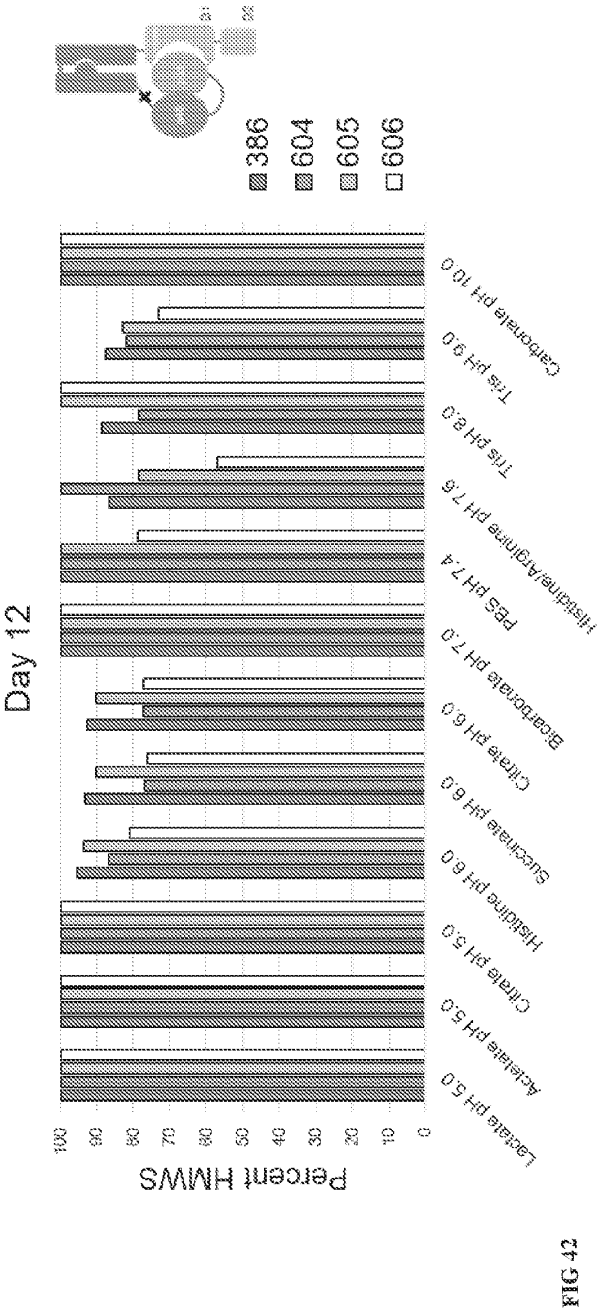
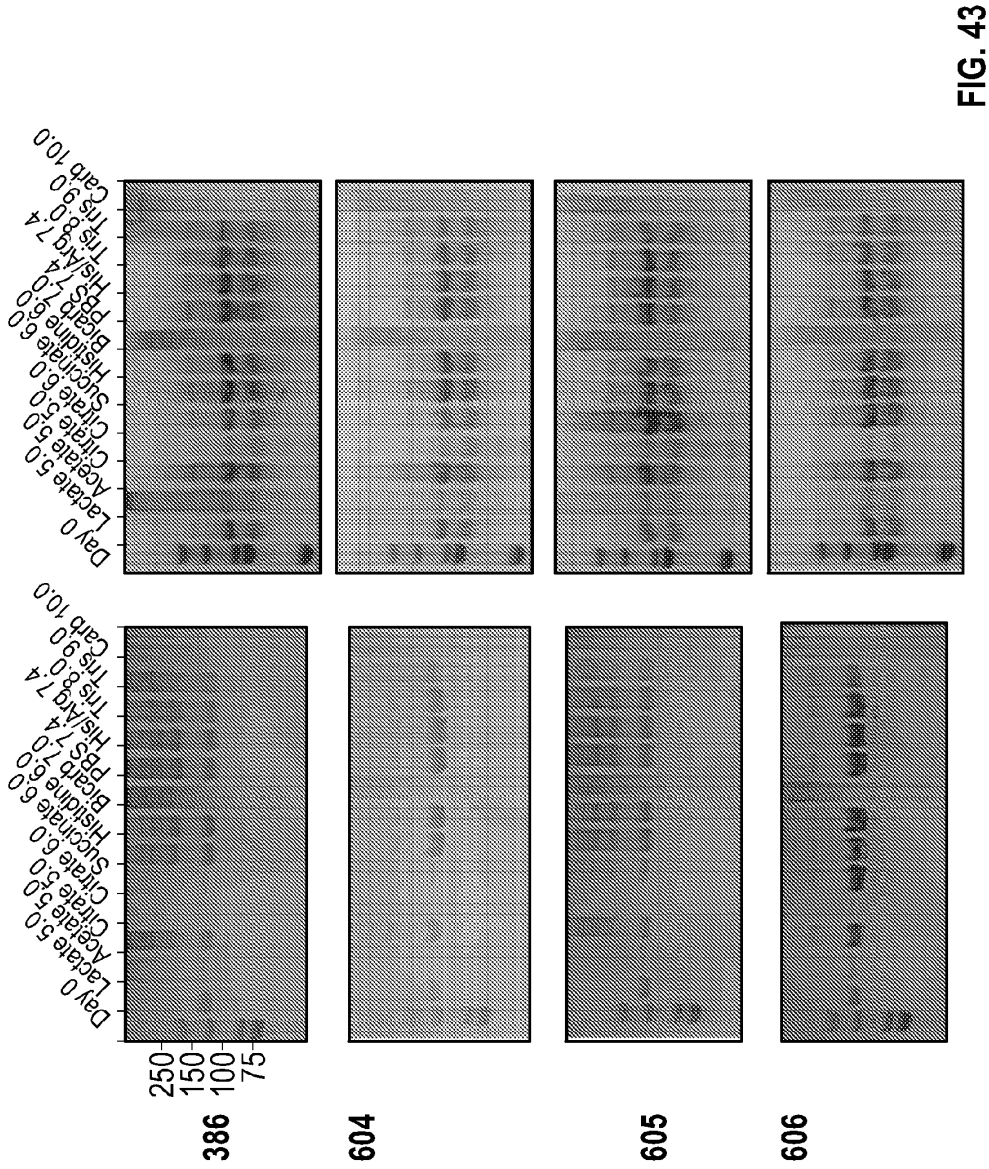


FIG 41





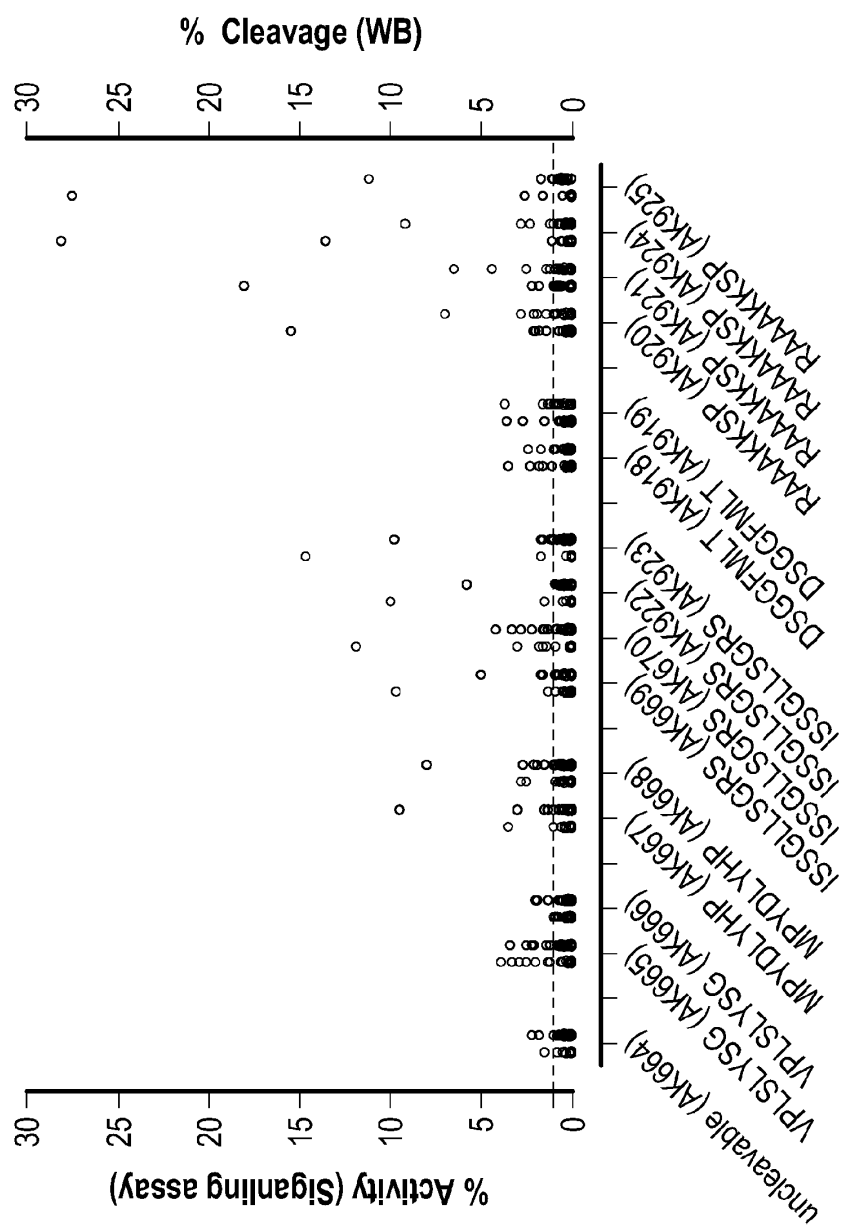


FIG. 44

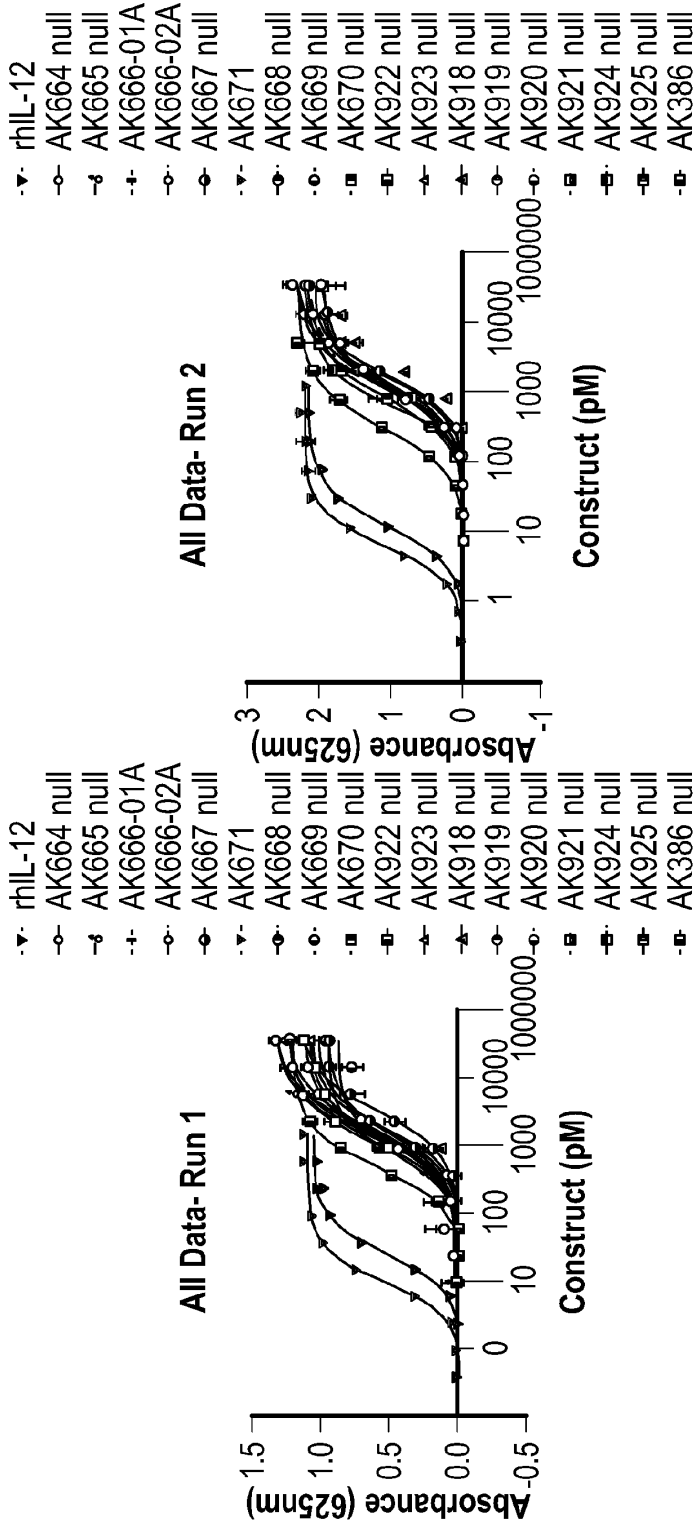


FIG. 45

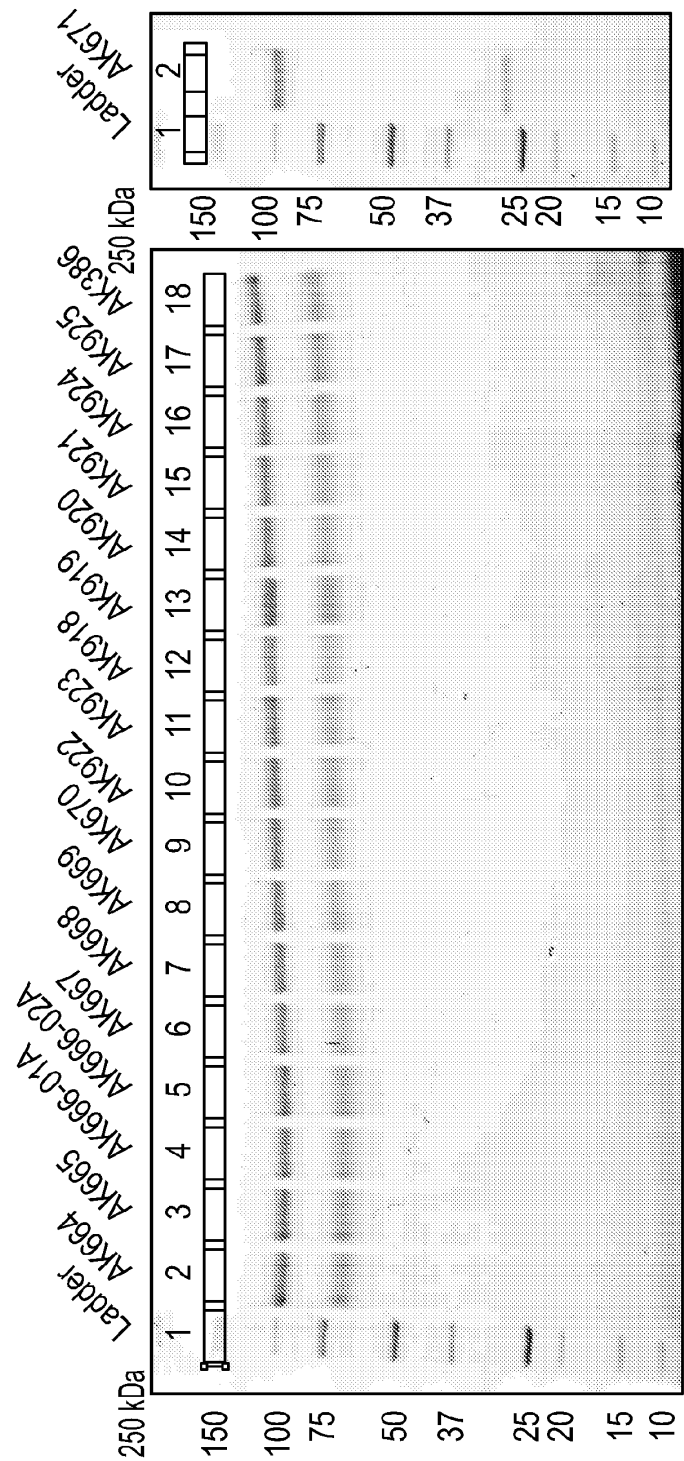


FIG. 46A

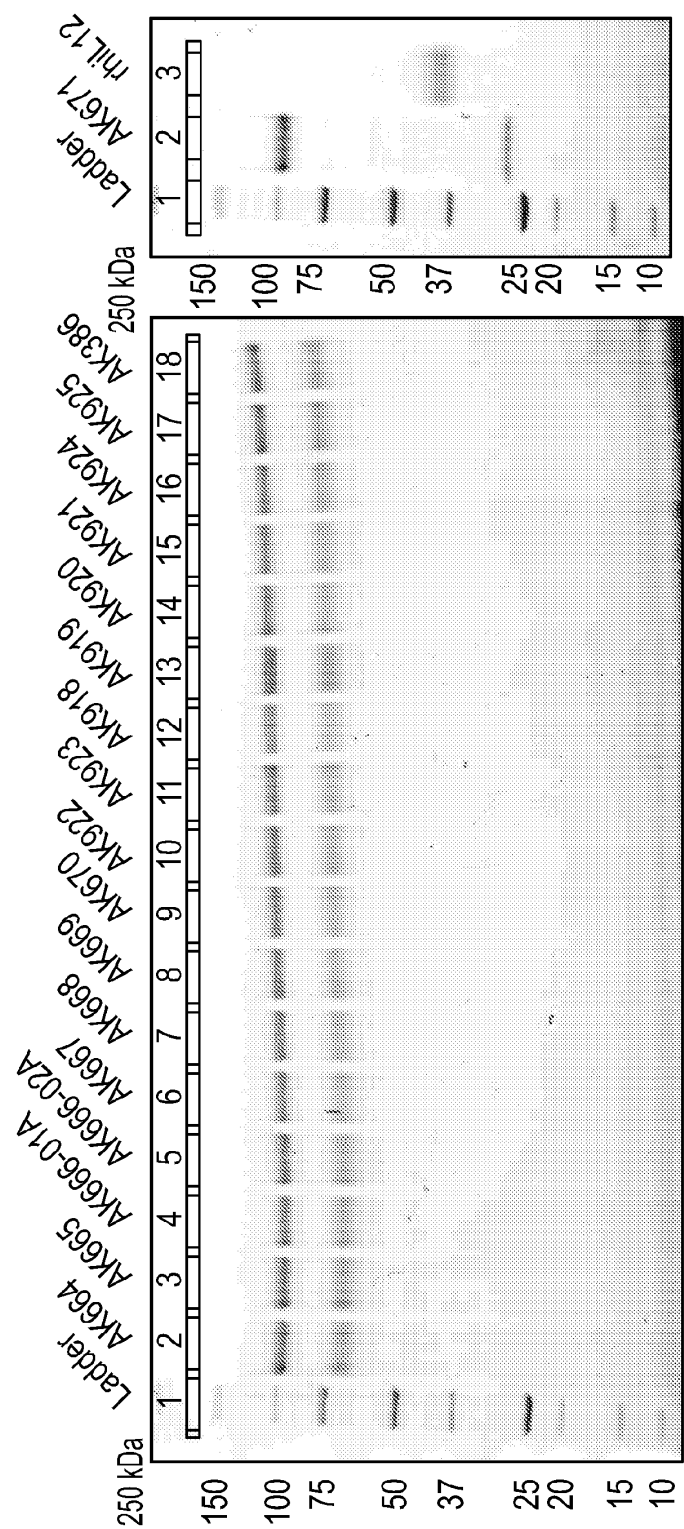


FIG. 46B

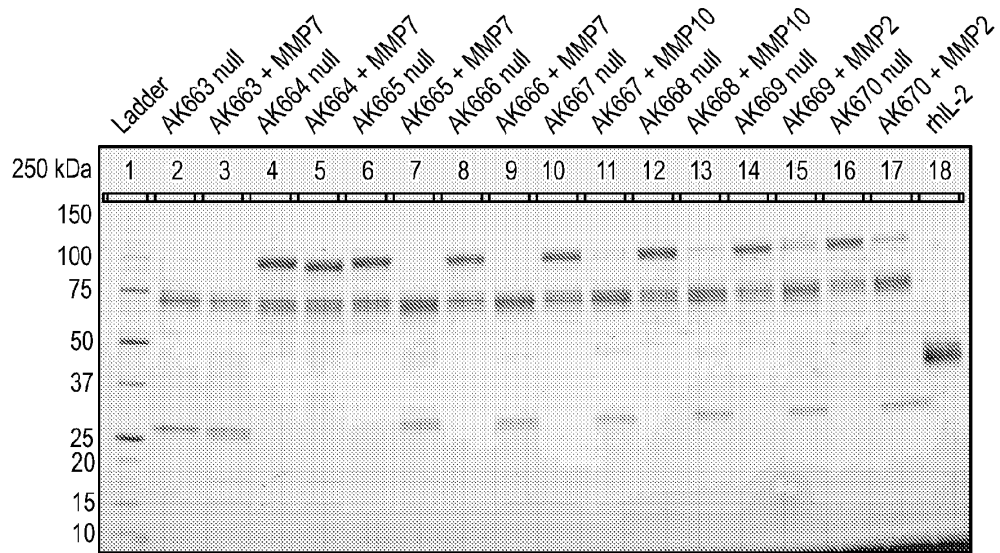


FIG. 47A

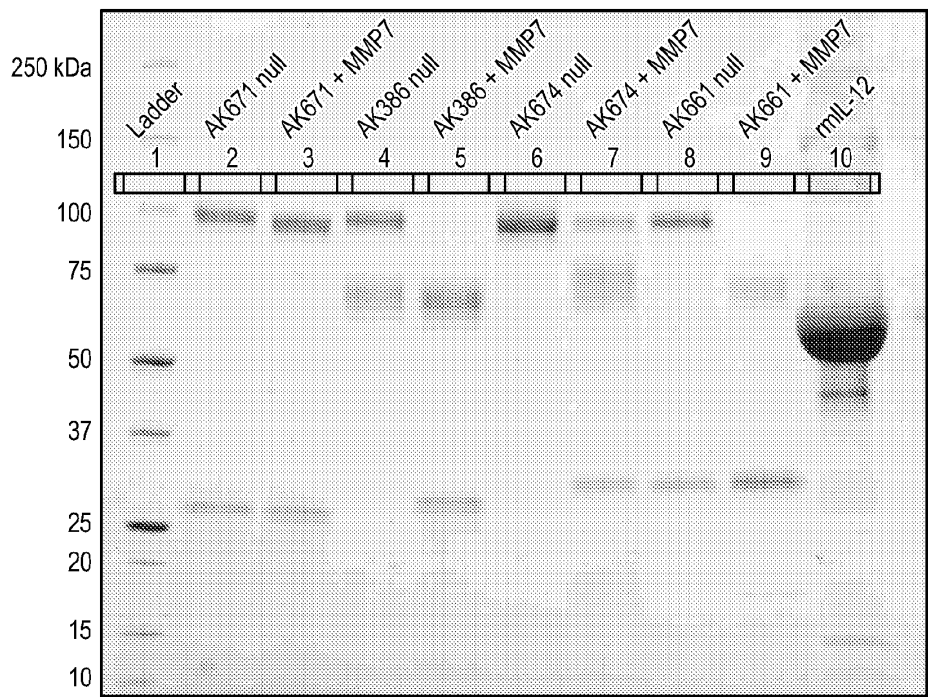
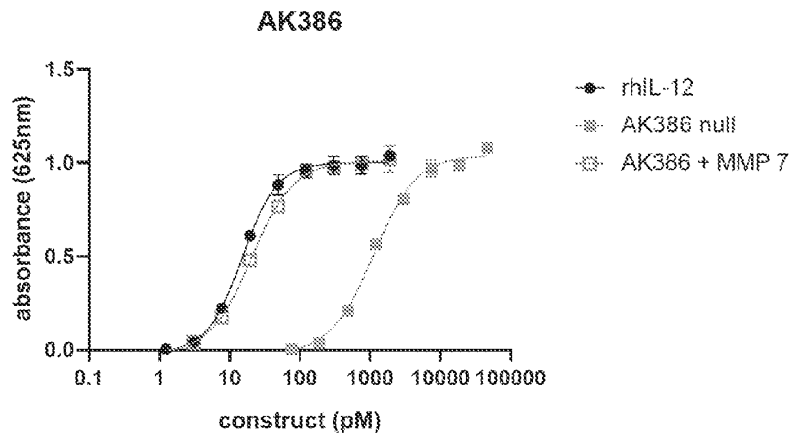


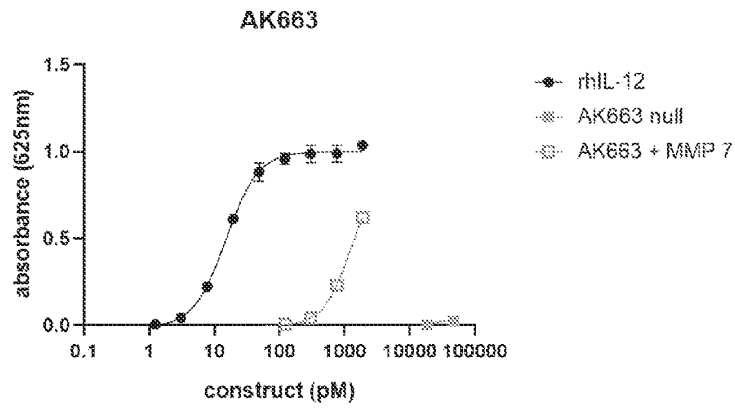
FIG. 47B

FIG 48A



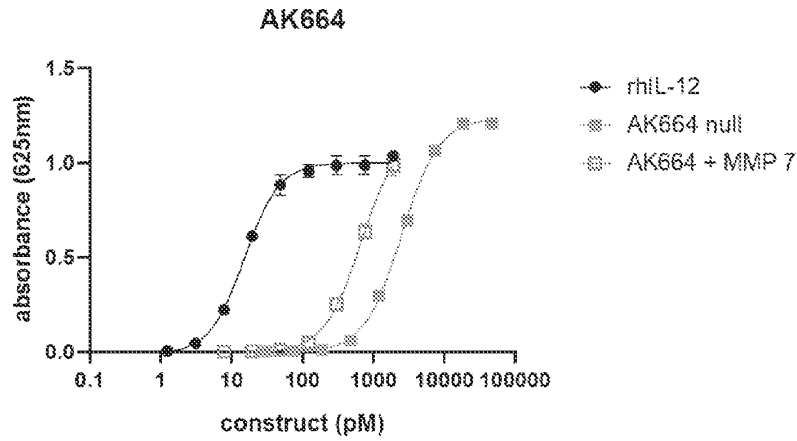
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK386 null	1123	74.2
AK386 + MMP 7	20.64	1.4

FIG 48B



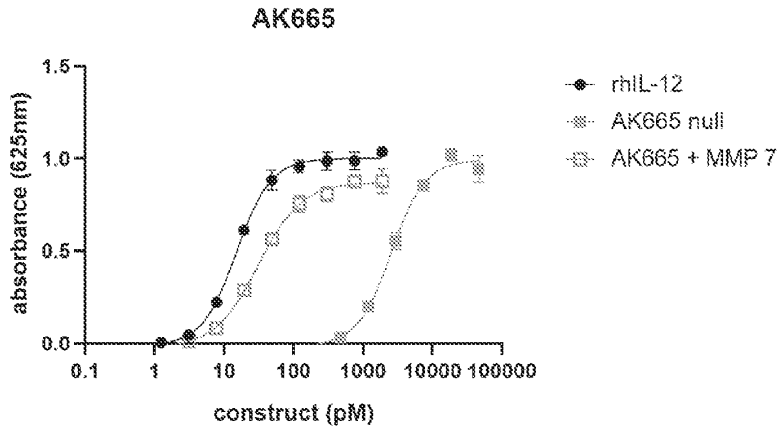
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK663 null	~ 21100	N/A
AK663 + MMP 7	1240	82.0

FIG 48C



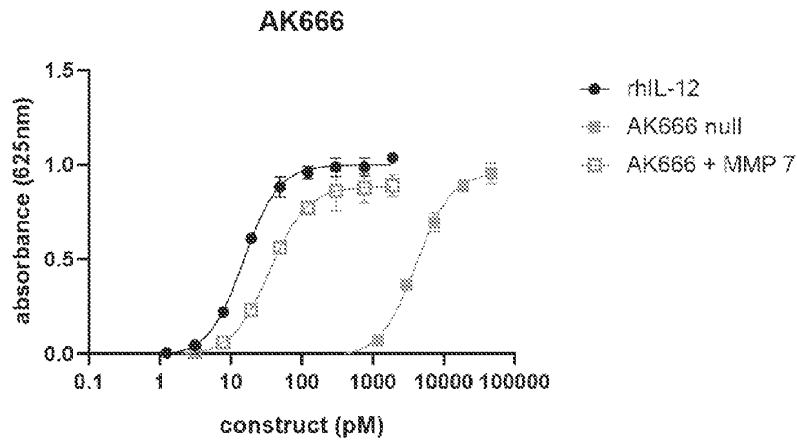
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK664 null	2485	164.2
AK664 + MMP 7	667.4	44.1

FIG 48D



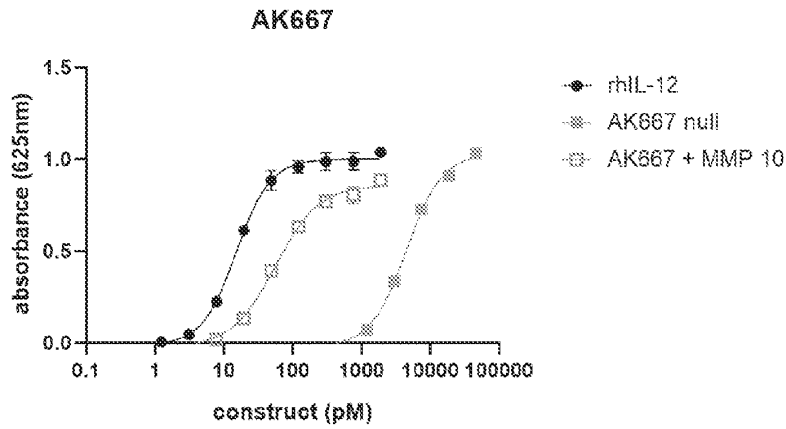
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK665 null	2555	168.9
AK665 + MMP 7	31.21	2.1

FIG 48E



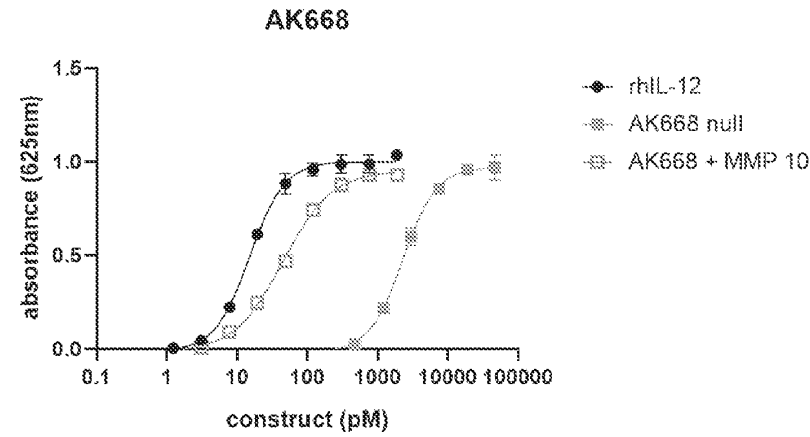
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK666 null	4061	268.4
AK666 + MMP 7	35.09	2.3

FIG 48F



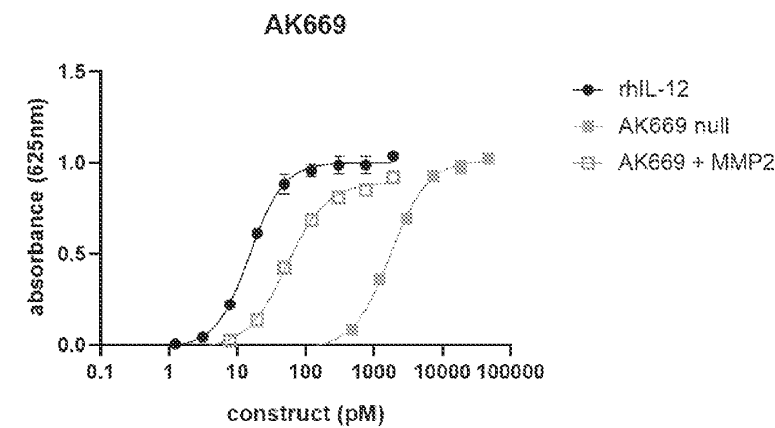
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK667 null	4497	297.2
AK667 + MMP 10	55.77	3.7

FIG 48G



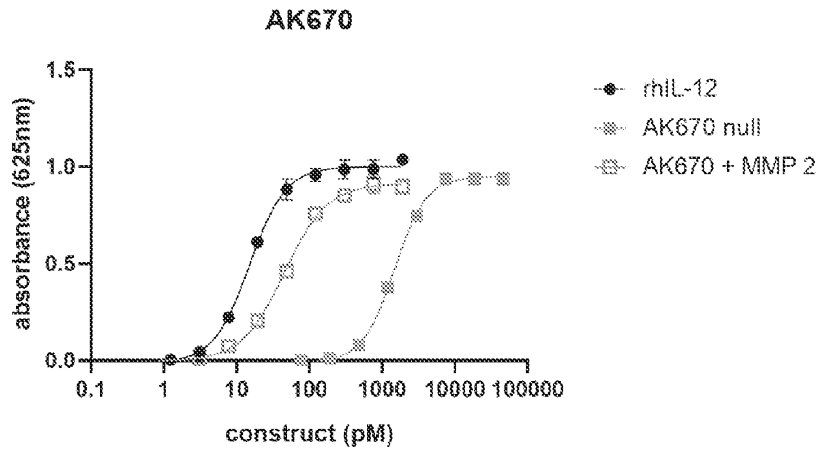
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK668 null	2293	151.6
AK668 + MMP 10	45.05	3.0

FIG 48H



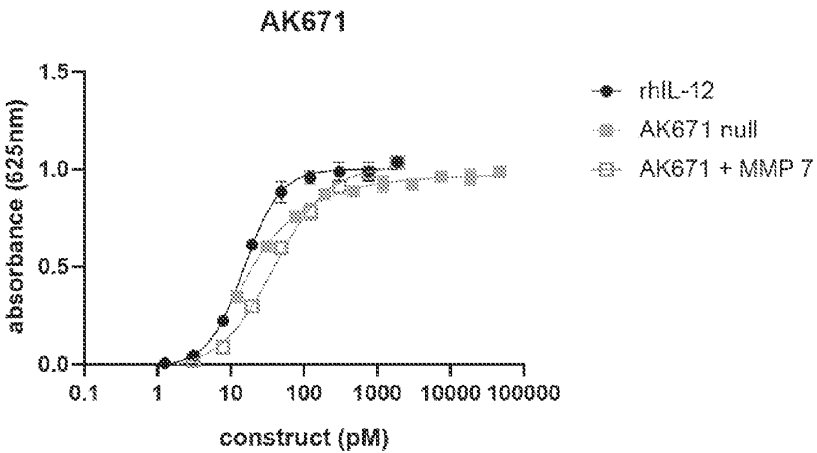
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK669 null	1751	115.7
AK669 + MMP2	52.7	3.5

FIG 48I



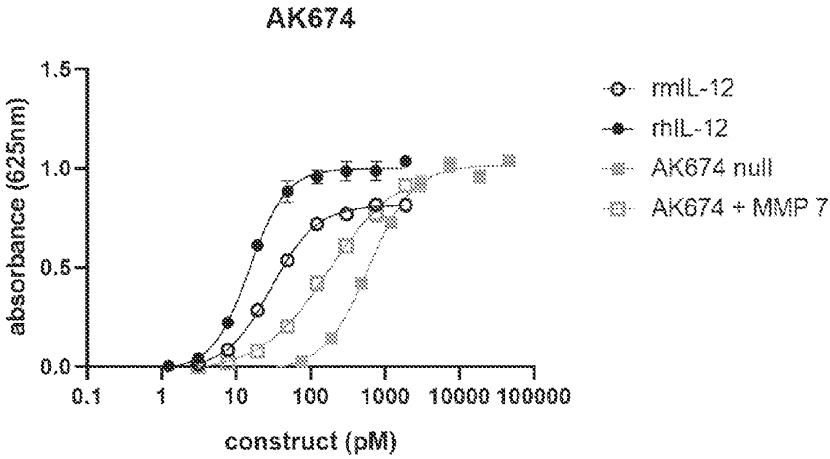
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK670 null	1478	97.7
AK670 + MMP 2	45.49	3.0

FIG 48J



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	15.13	
AK671 null	~ 0.0003067*	N/A
AK671 + MMP 7	38.44	2.5

FIG 48K



Construct	EC50 (pM)	Fold-Aklusion
rmlL-12	29.82	
AK674 null	603.8	20.2
AK674 + MMP 7	177.2	5.9

FIG 49A

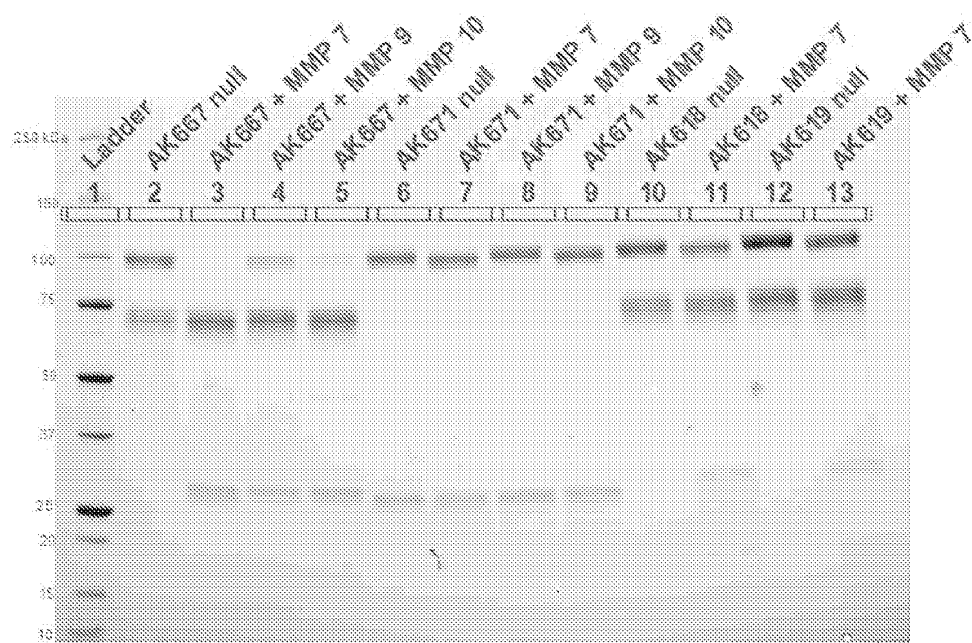


FIG49B

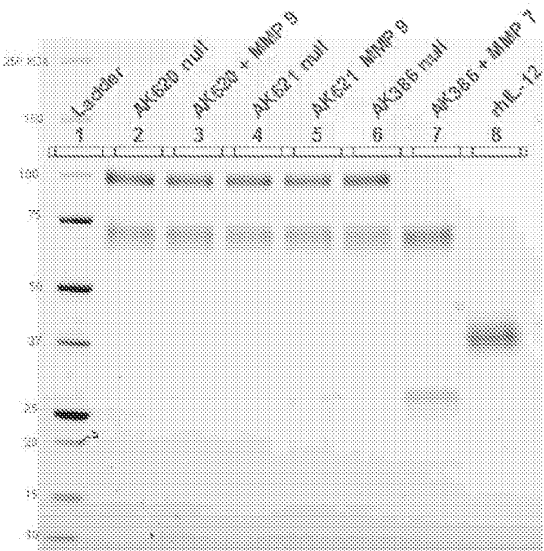
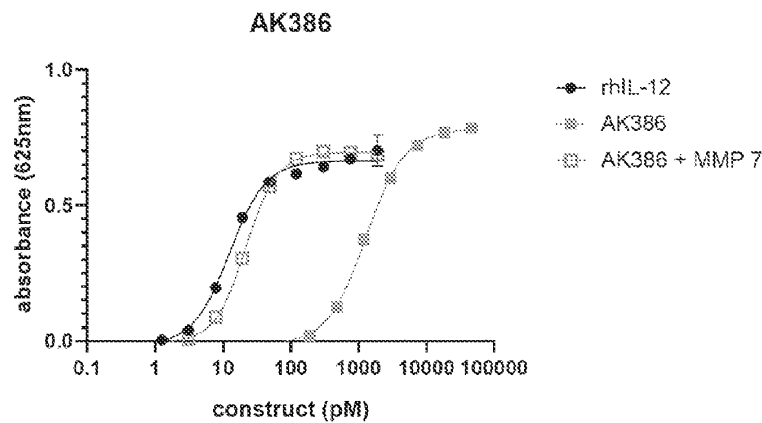
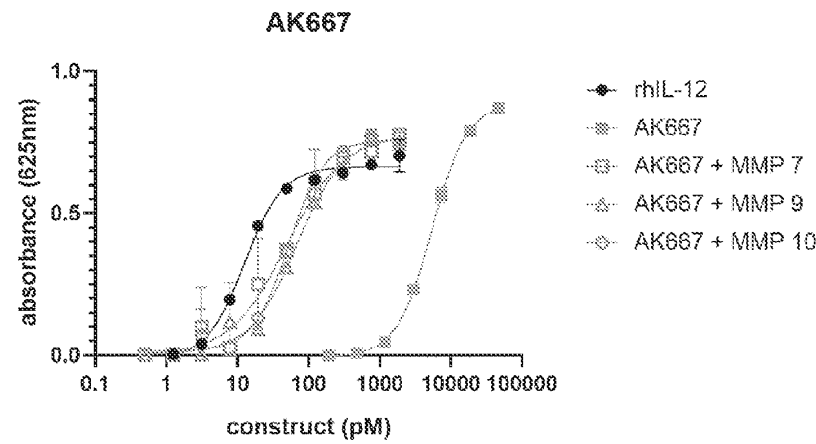


FIG 50A



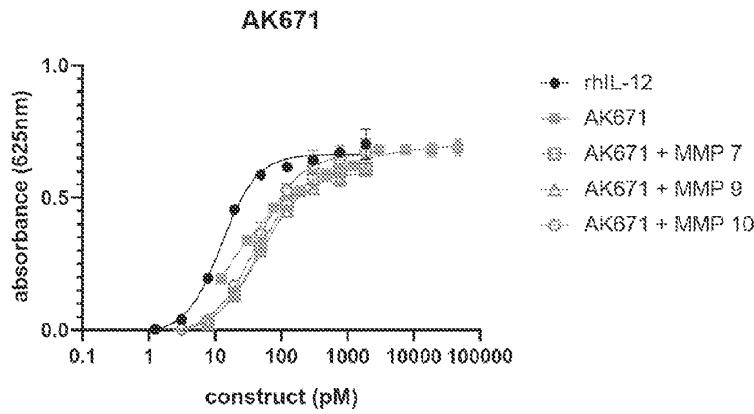
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK386	1294	103.1
AK386 + MMP 7	21.76	1.7

FIG 50B



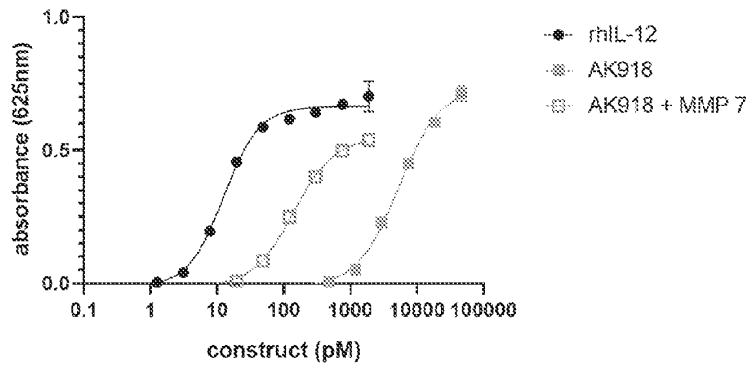
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK667	5412	431.2
AK667 + MMP 7	49.24	3.9
AK667 + MMP 9	67.88	5.4
AK667 + MMP 10	52.29	4.2

FIG 50C



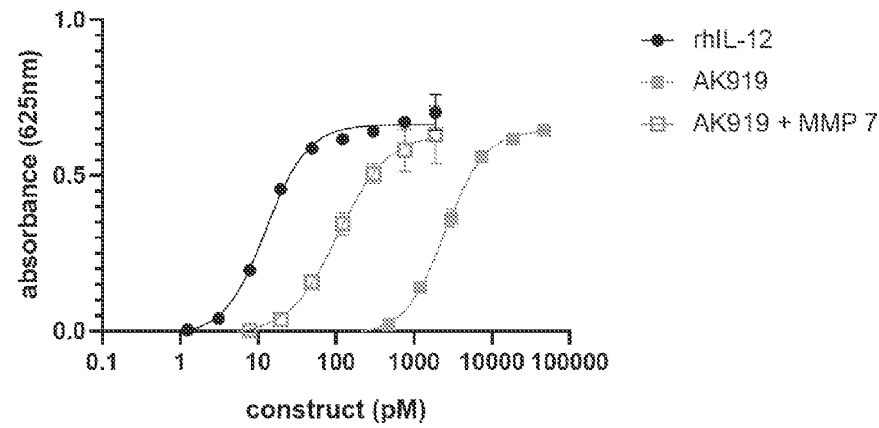
Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK671	1.36*	0.1*
AK671 + MMP 7	46.04	3.7
AK671 + MMP 9	46.42	3.9
AK671 + MMP 10	42.47	3.4

FIG 50D (AK918)



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK918	5372	428.0
AK918 + MMP 7	141	11.2

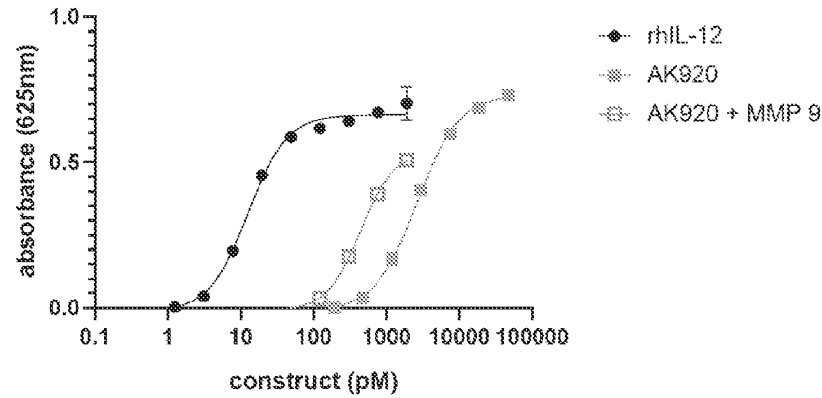
FIG 50E (AK919)



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK919	2506	199.7
AK919 + MMP 7	106.5	8.5

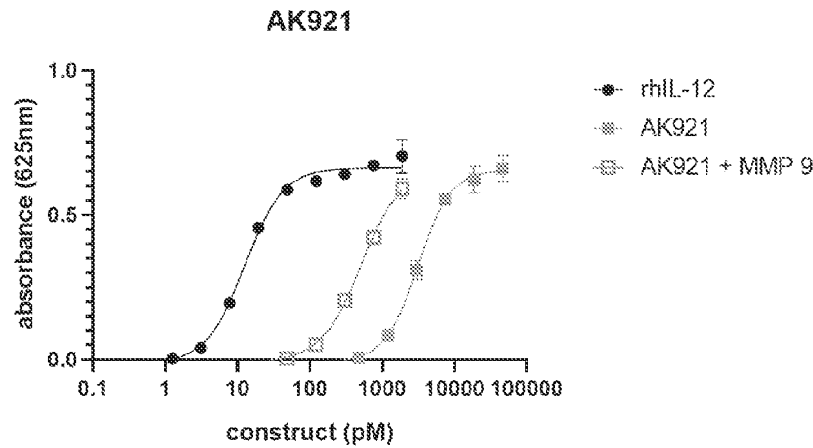
FIG 50F

AK920



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK920	2600	207.2
AK920 + MMP 9	442.9	35.3

FIG 50G



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	12.55	N/A
AK921	3119	248.5
AK921 + MMP 9	518.4	41.3

FIG 51

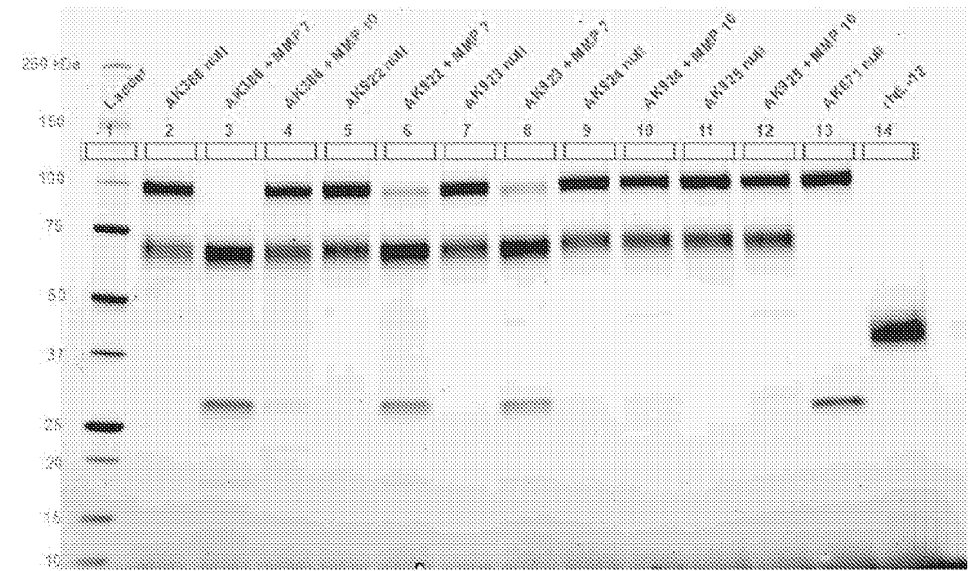


FIG 52A

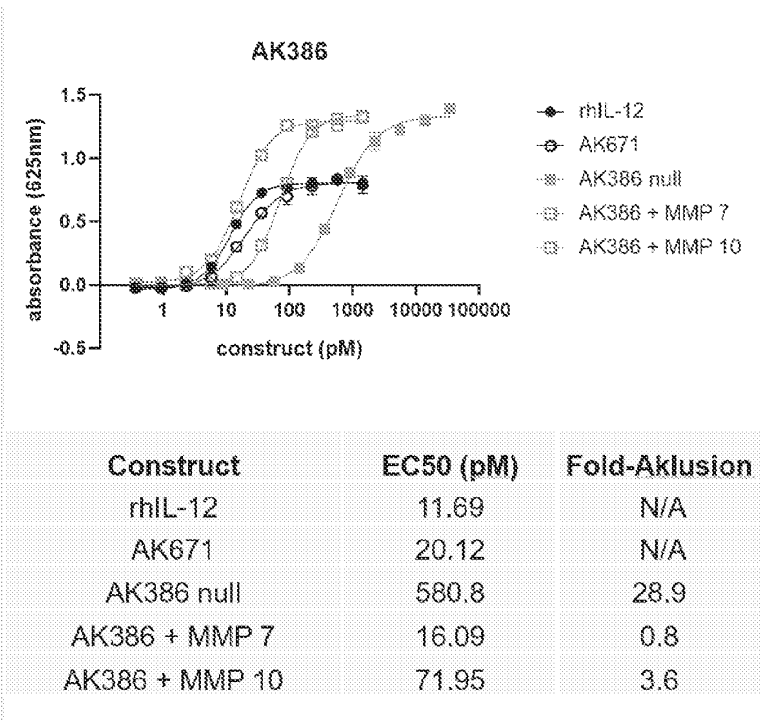
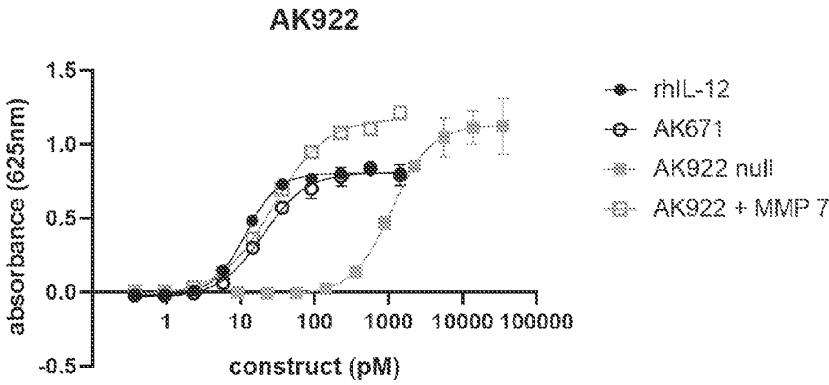
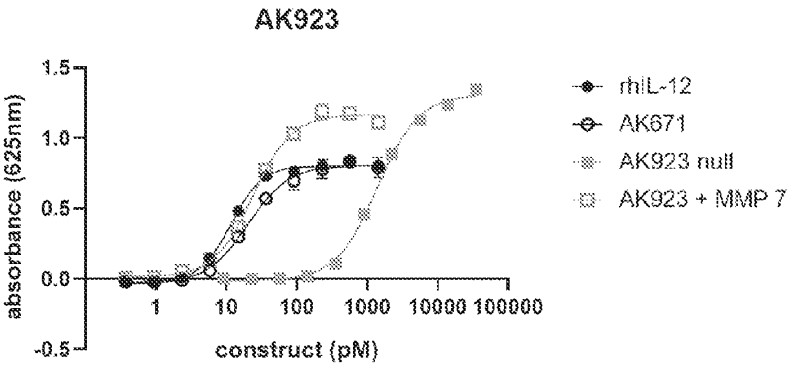


FIG 52B



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	11.69	
AK671	20.12	
AK922 null	1102	54.8
AK922 + MMP 7	27.5	1.4

FIG 52C



Construct	EC50 (pM)	Fold-Aklusion
rhIL-12	11.69	
AK671	20.12	
AK923 null	1393	69.2
AK923 + MMP 7	23.84	1.2

FIG 52D

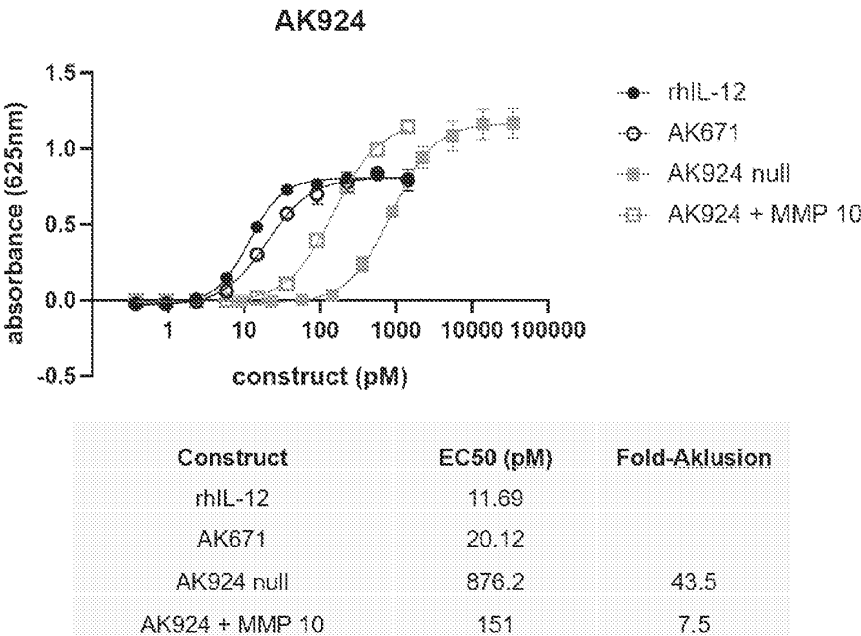
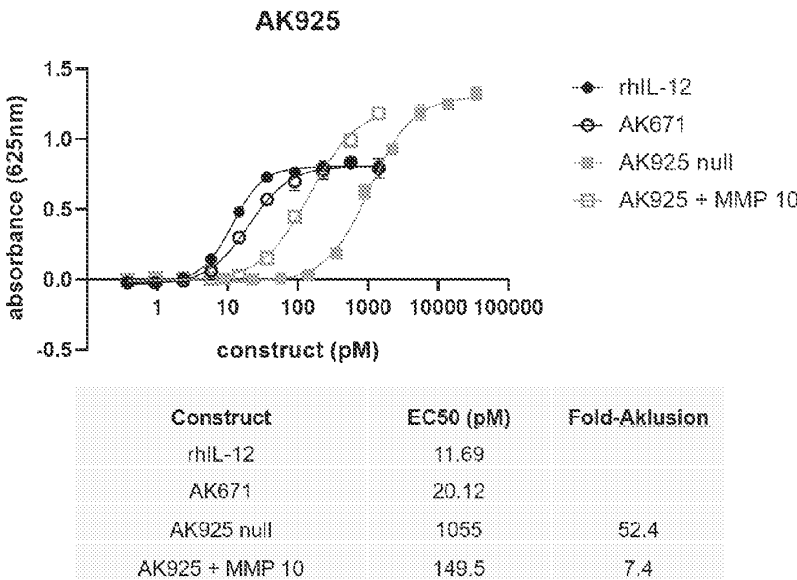


FIG 52E



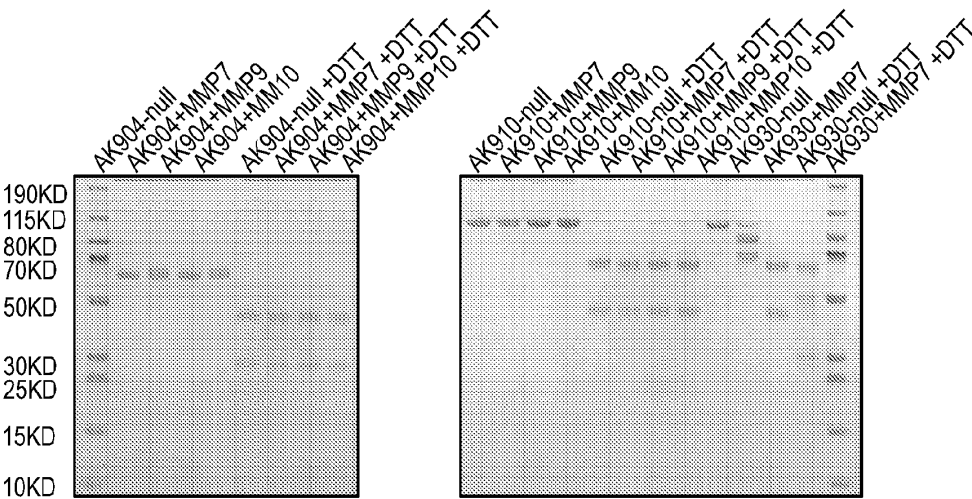


FIG. 53A

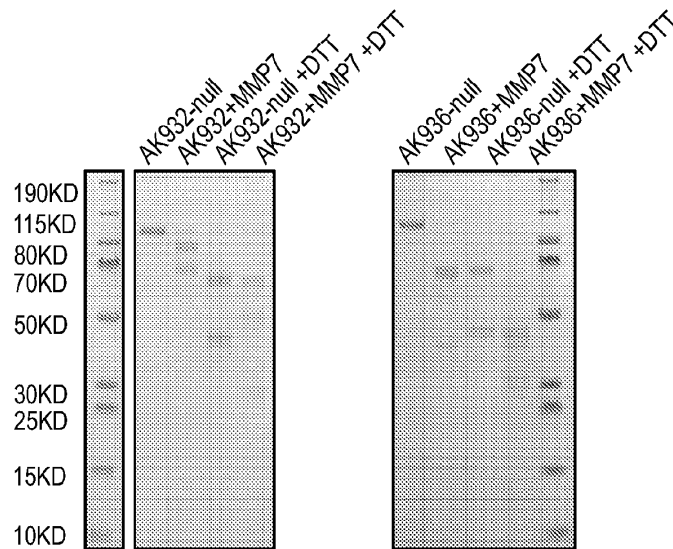


FIG. 53B

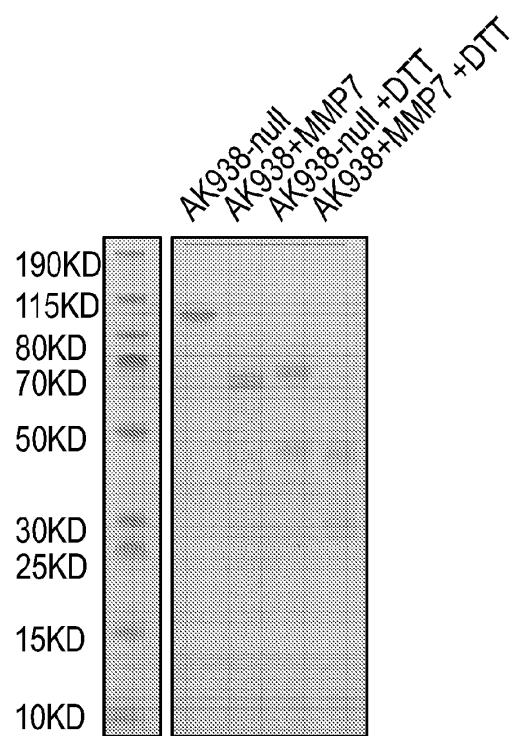


FIG. 53C

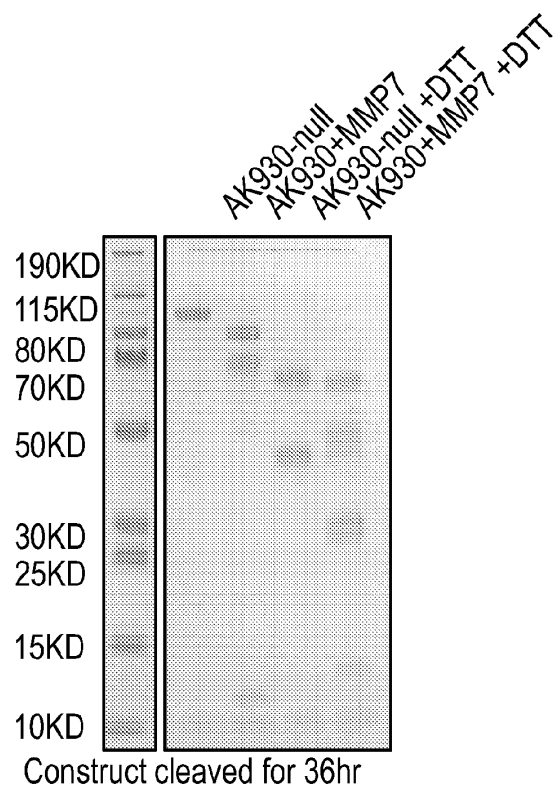


FIG. 53D

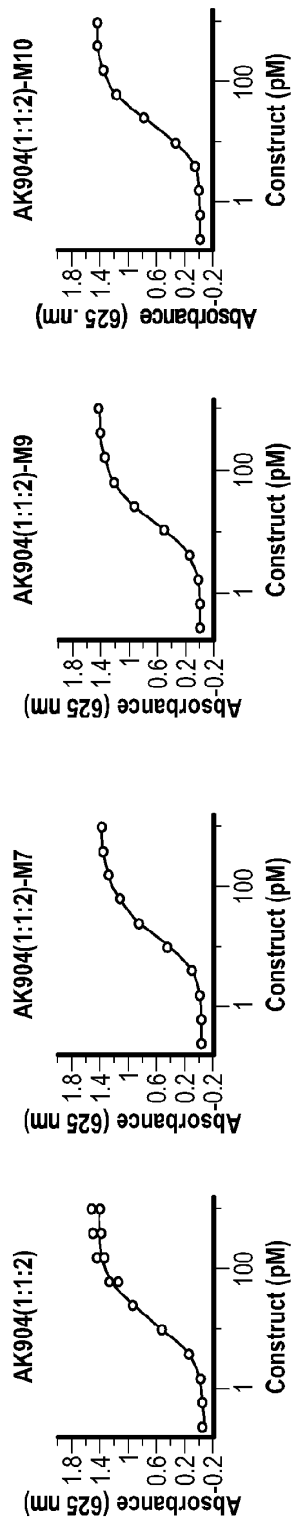


FIG. 54A (AK904)

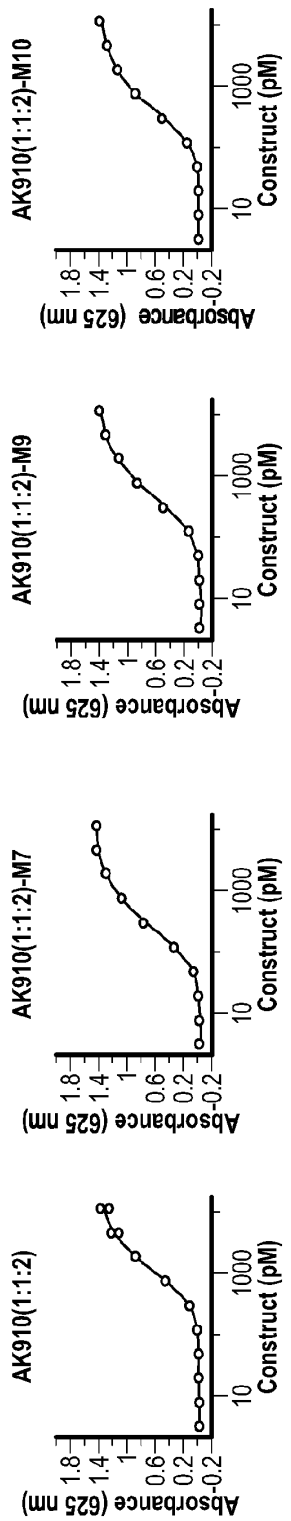


FIG. 54B (AK910)

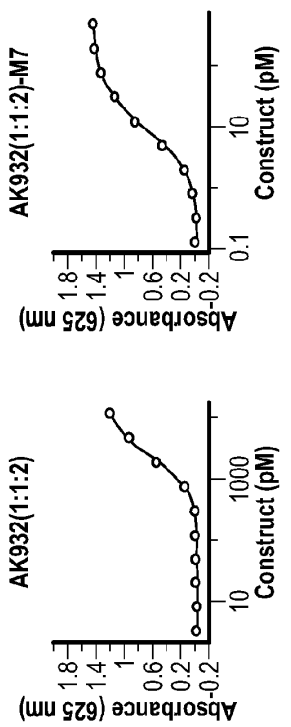


FIG. 54C (AK932)

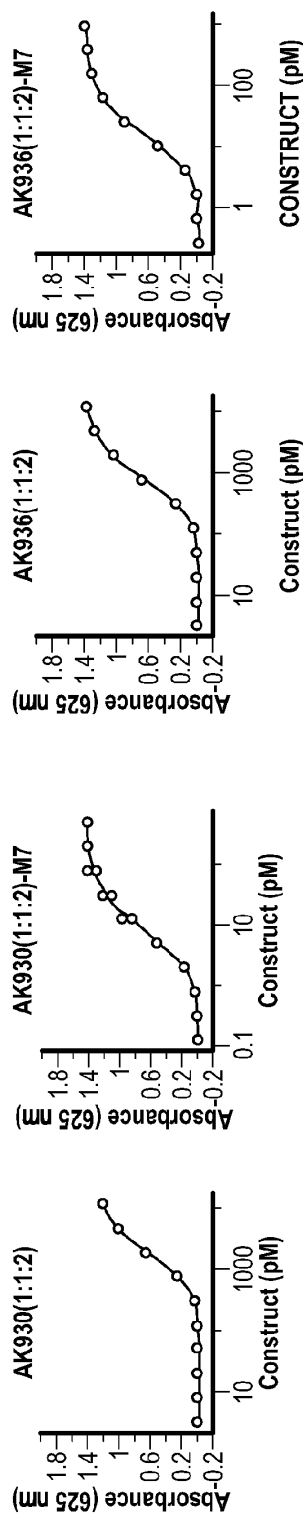


FIG. 54D (AK936)

FIG. 54F (AK930)

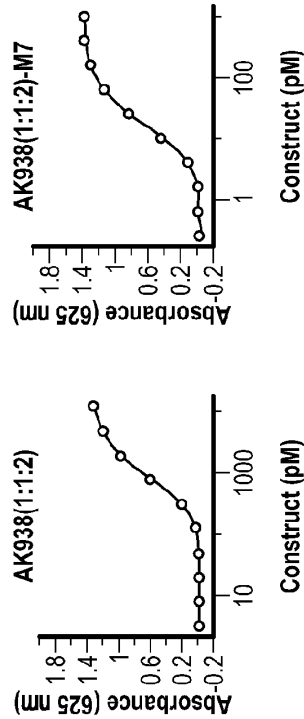
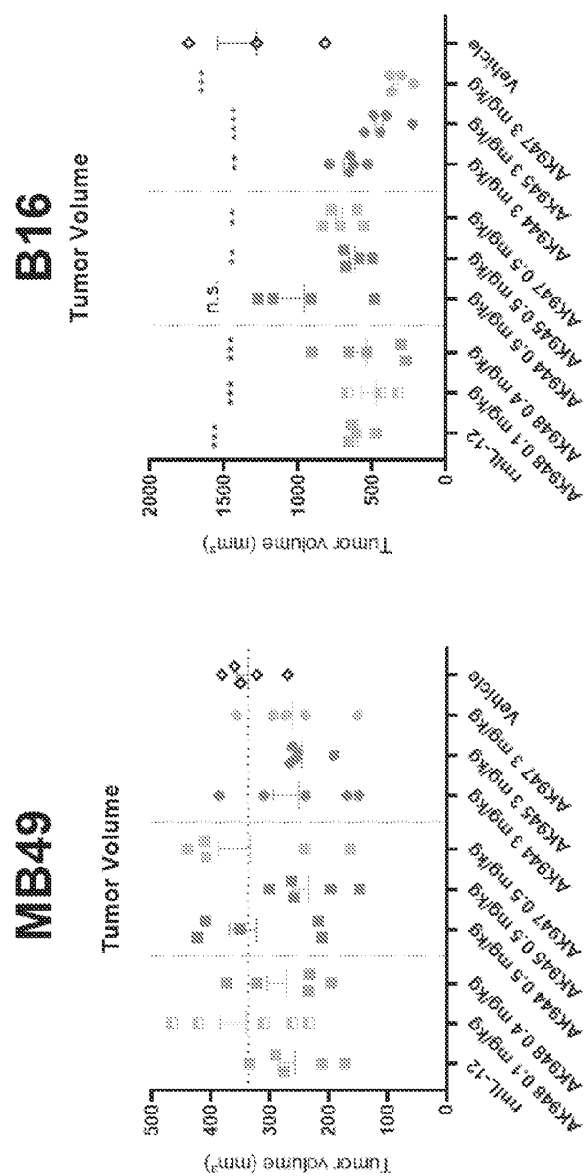


FIG. 54E (AK938)



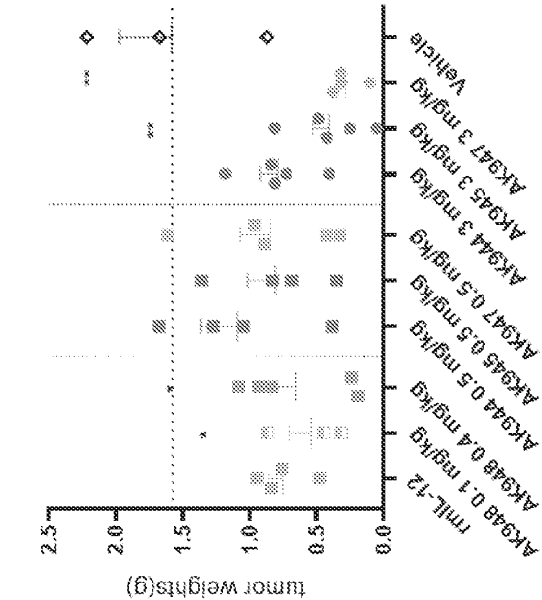
%TGI mg/kg to vehicle	nm-IL12	AK948 0.1 mpk	AK948 0.4 mpk	AK944 0.5 mpk	AK945 0.5 mpk	AK947 0.5 mpk	AK944 3 mpk	AK945 3 mpk	AK947 3 mpk
MB49	23.6	-0.7	19.18	4.18	30.49	1.17	25.54	27.08	22
B16	62.76	77.53	58	40.04	61.71	45.51	49.19	66.86	80.1

56

B16

MB49

B 16 Tumor Weights



MB 49 Tumor Weights

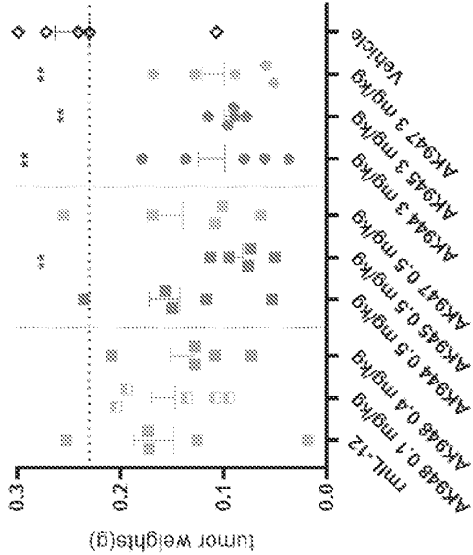
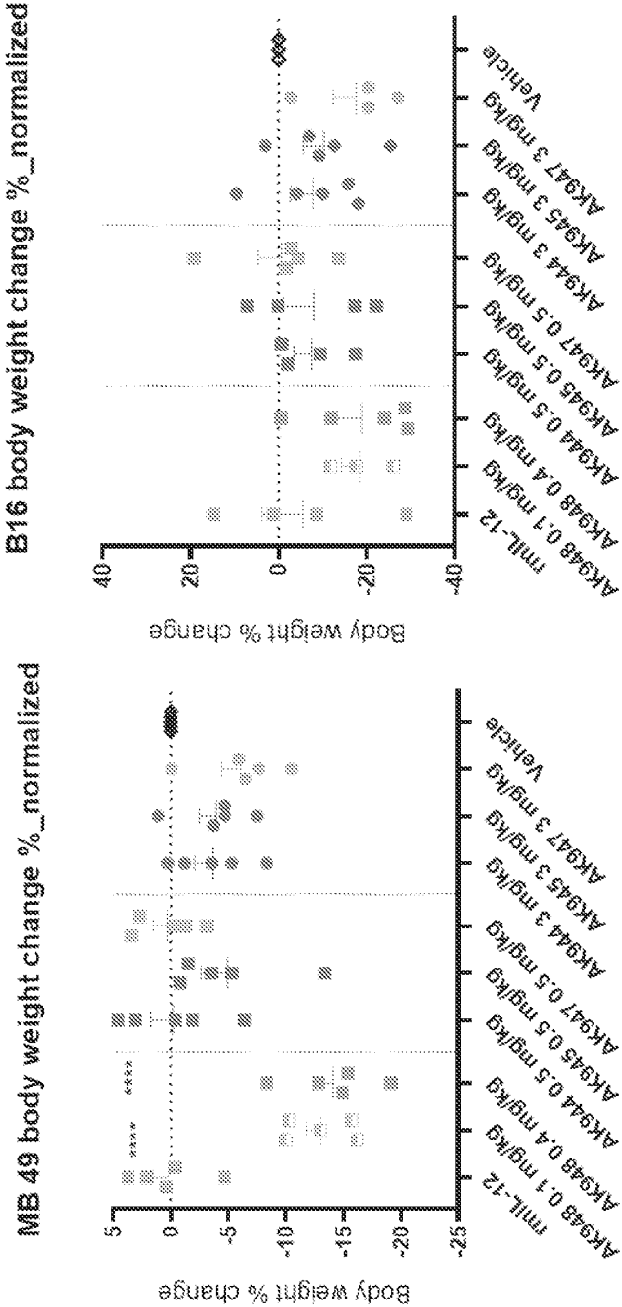


FIG 5



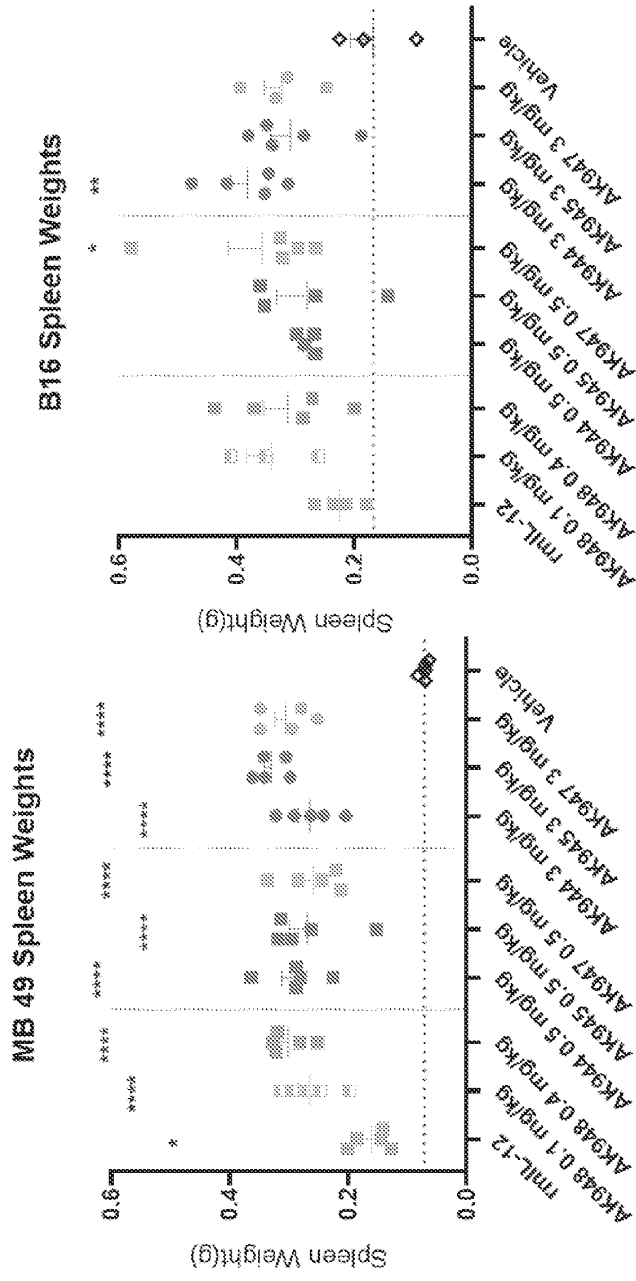
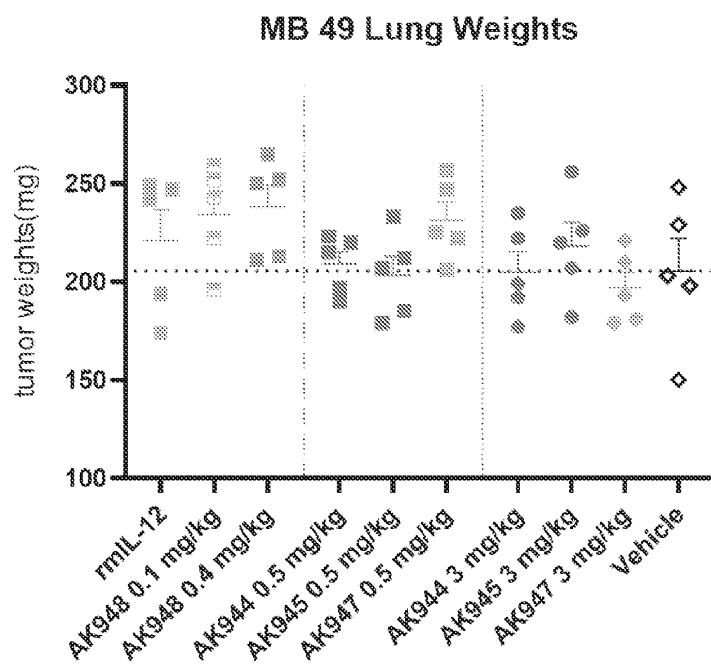


FIG 5E

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FIG 59



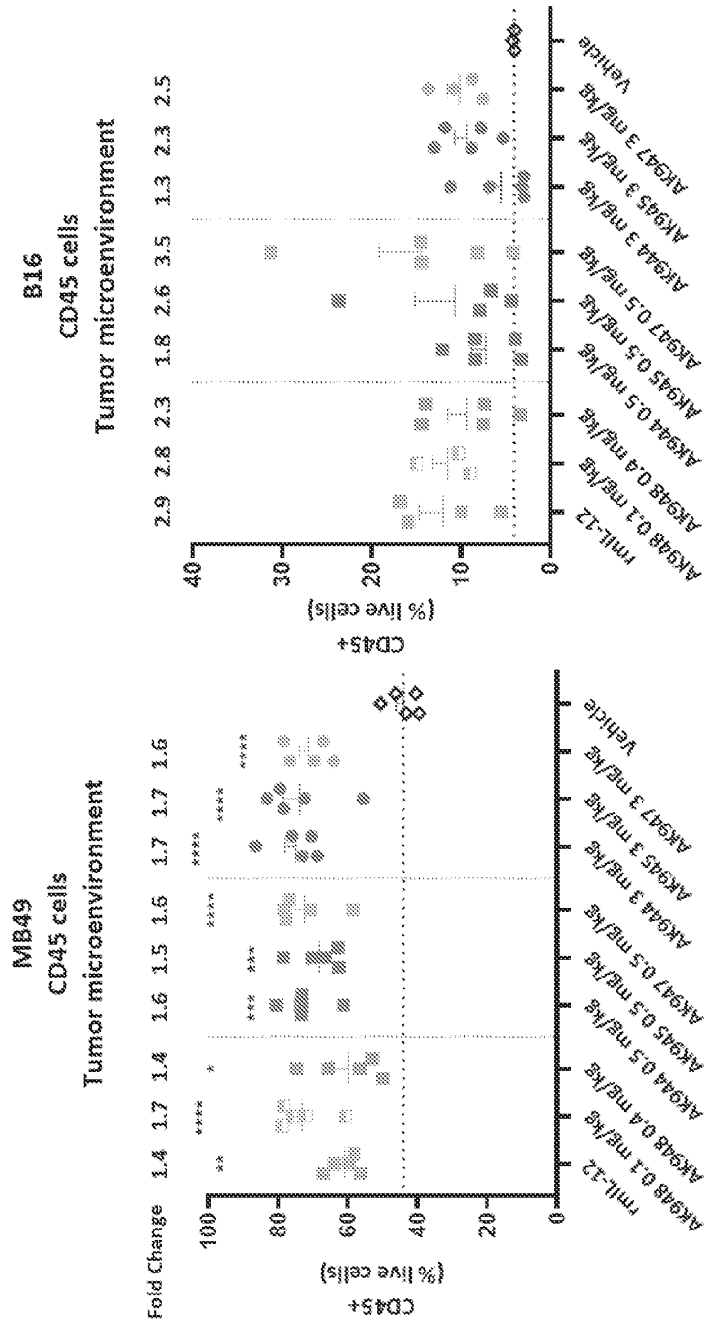


FIG 60

FIG 61A

MB49

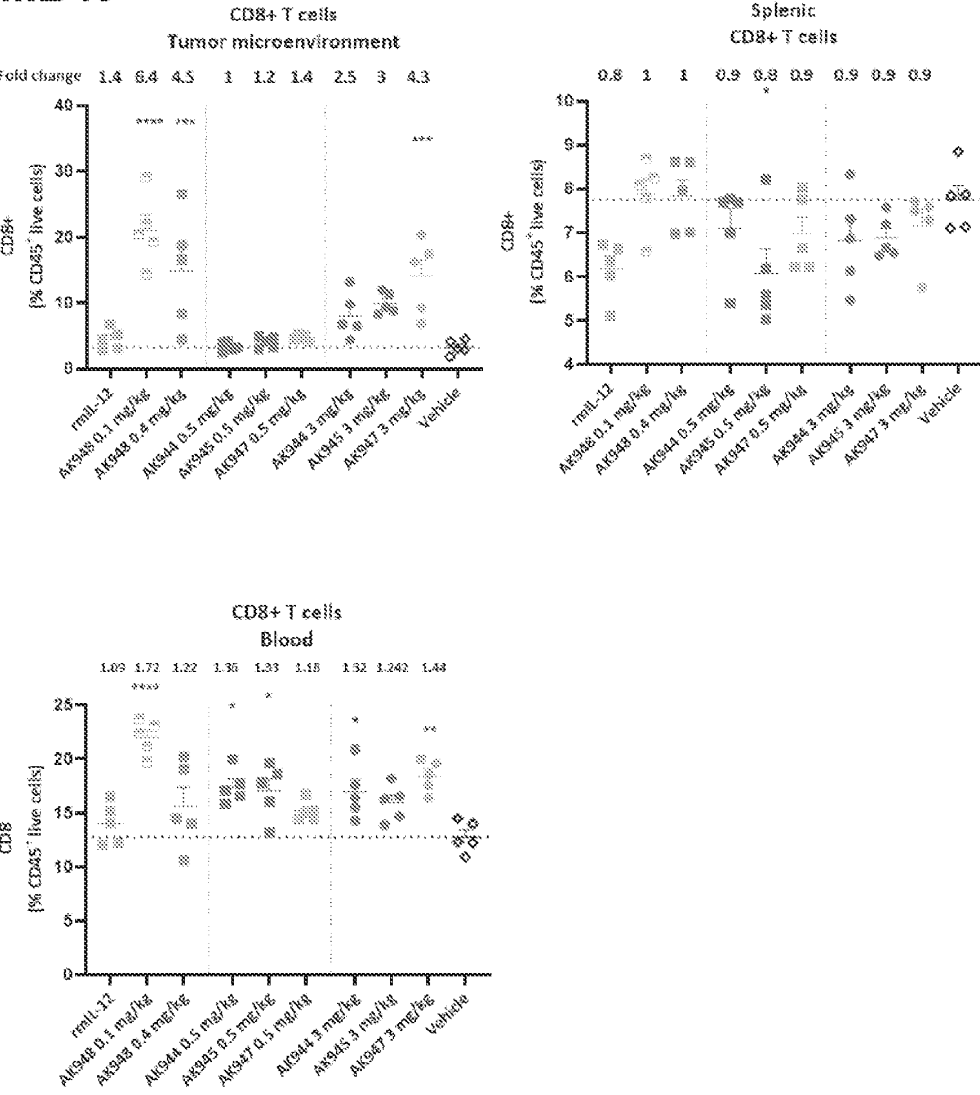
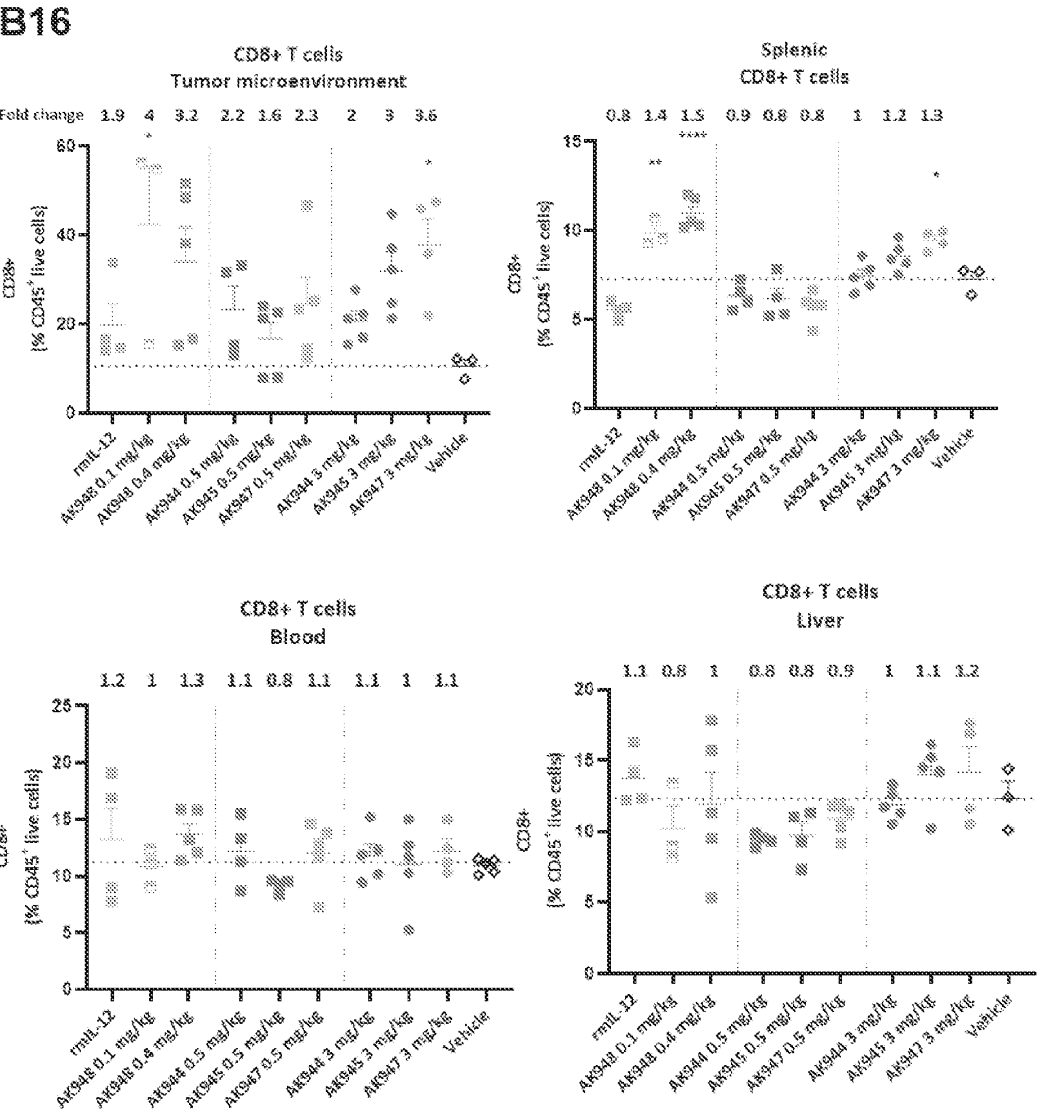


FIG 61B



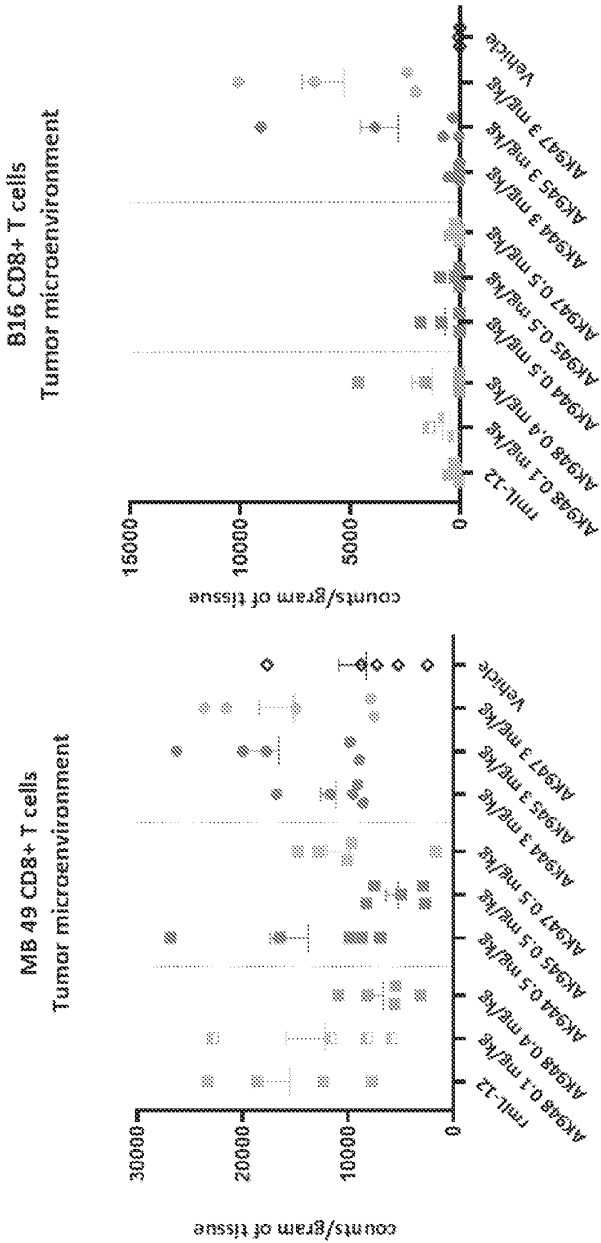


FIG 2

FIG 63A

MB49

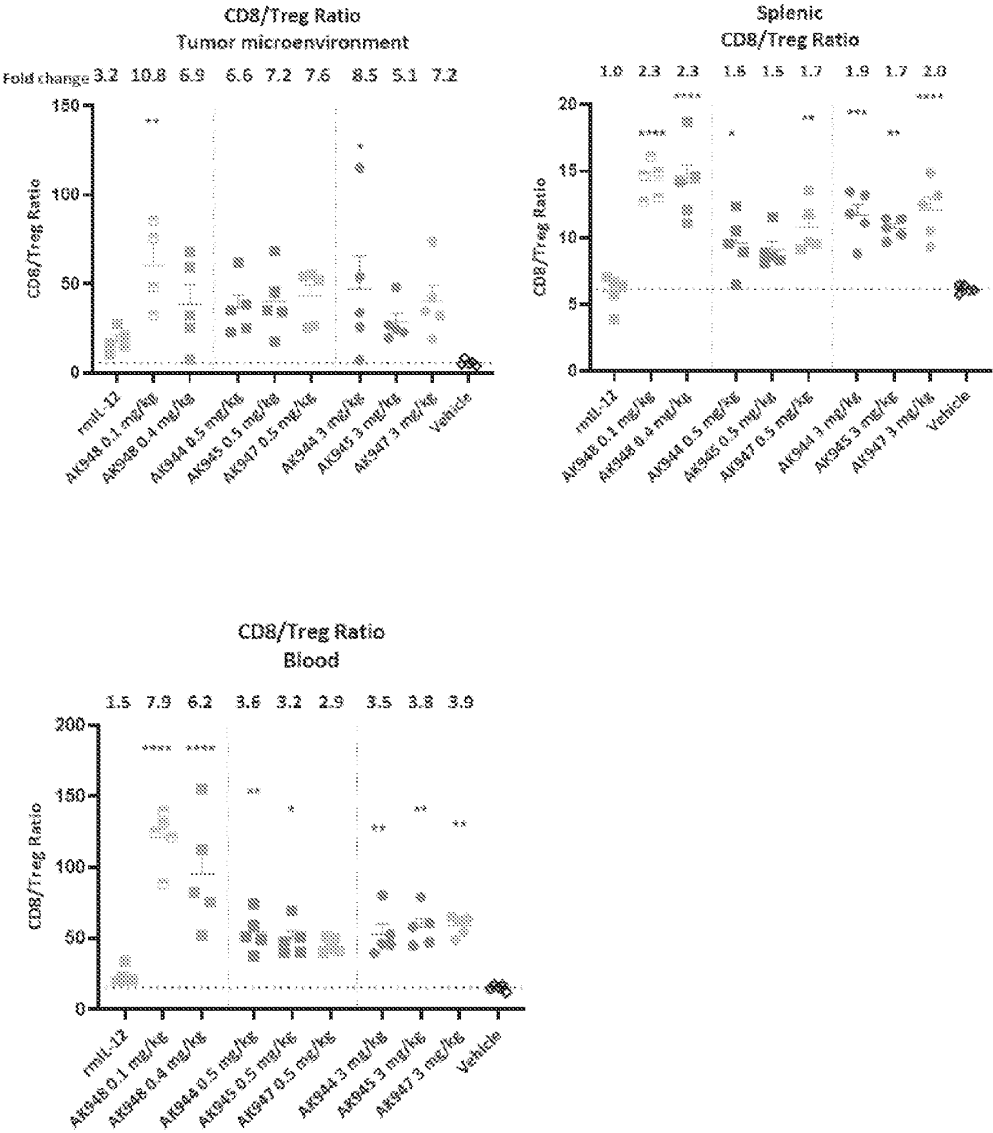


FIG 63B

B16

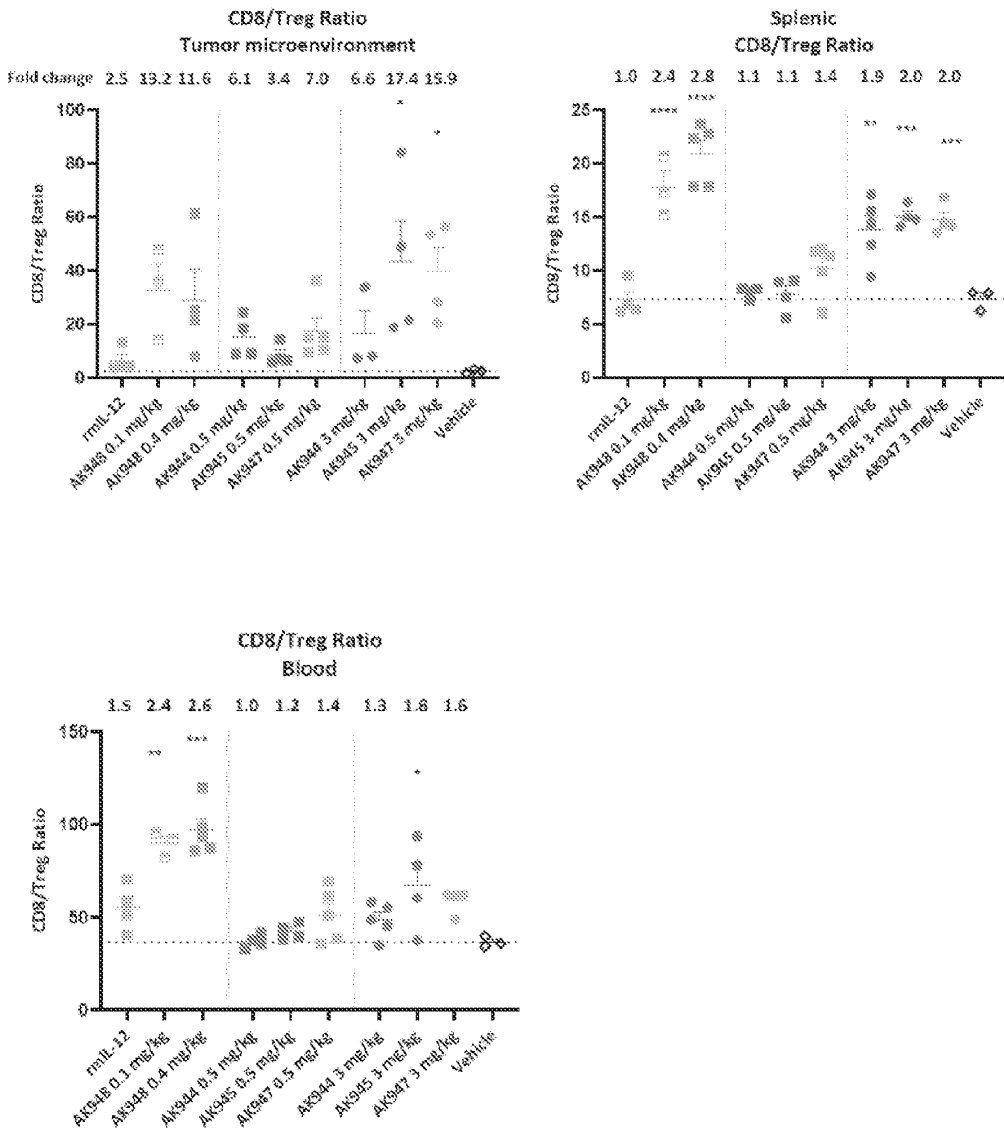


FIG 64A

MB49

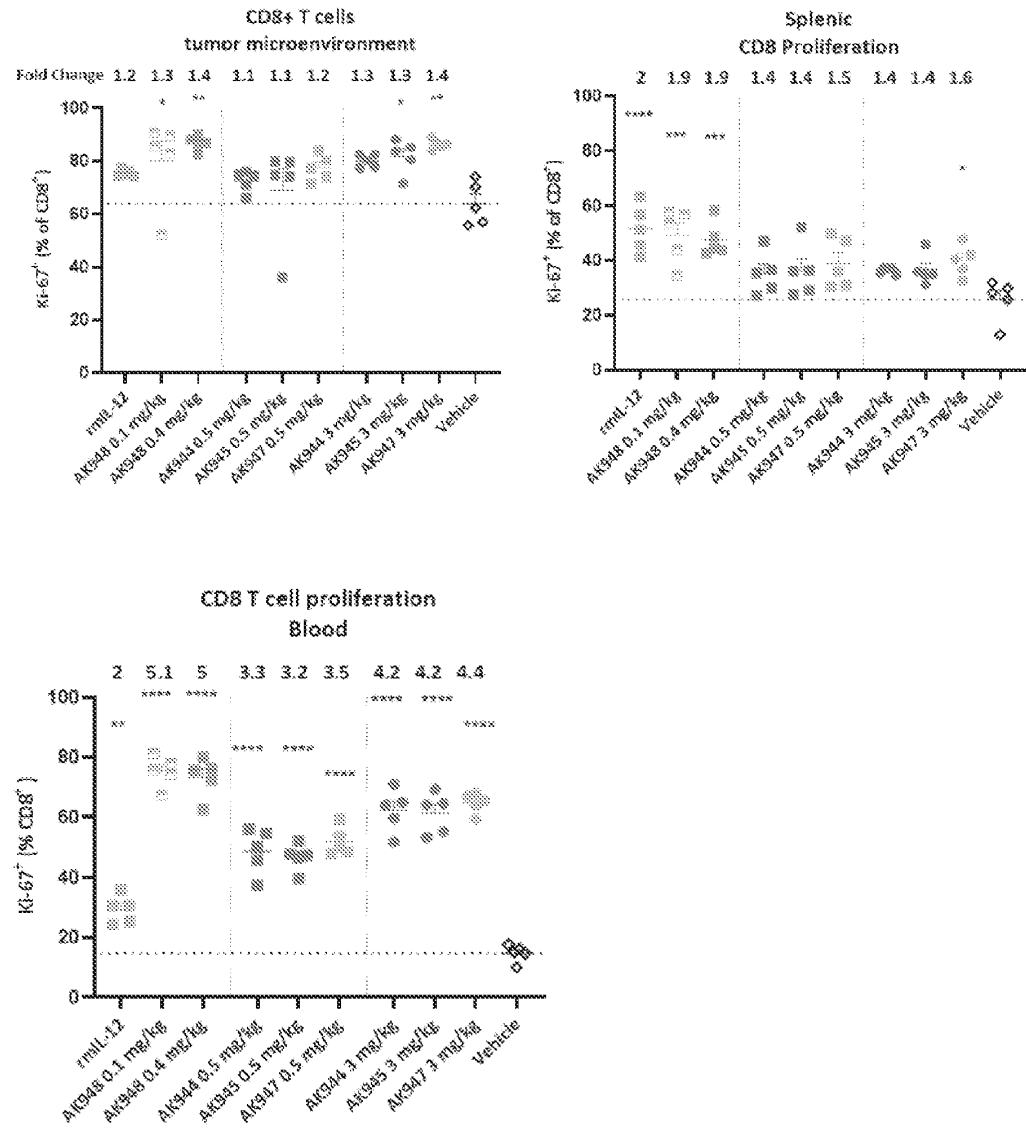


FIG 64B

B16

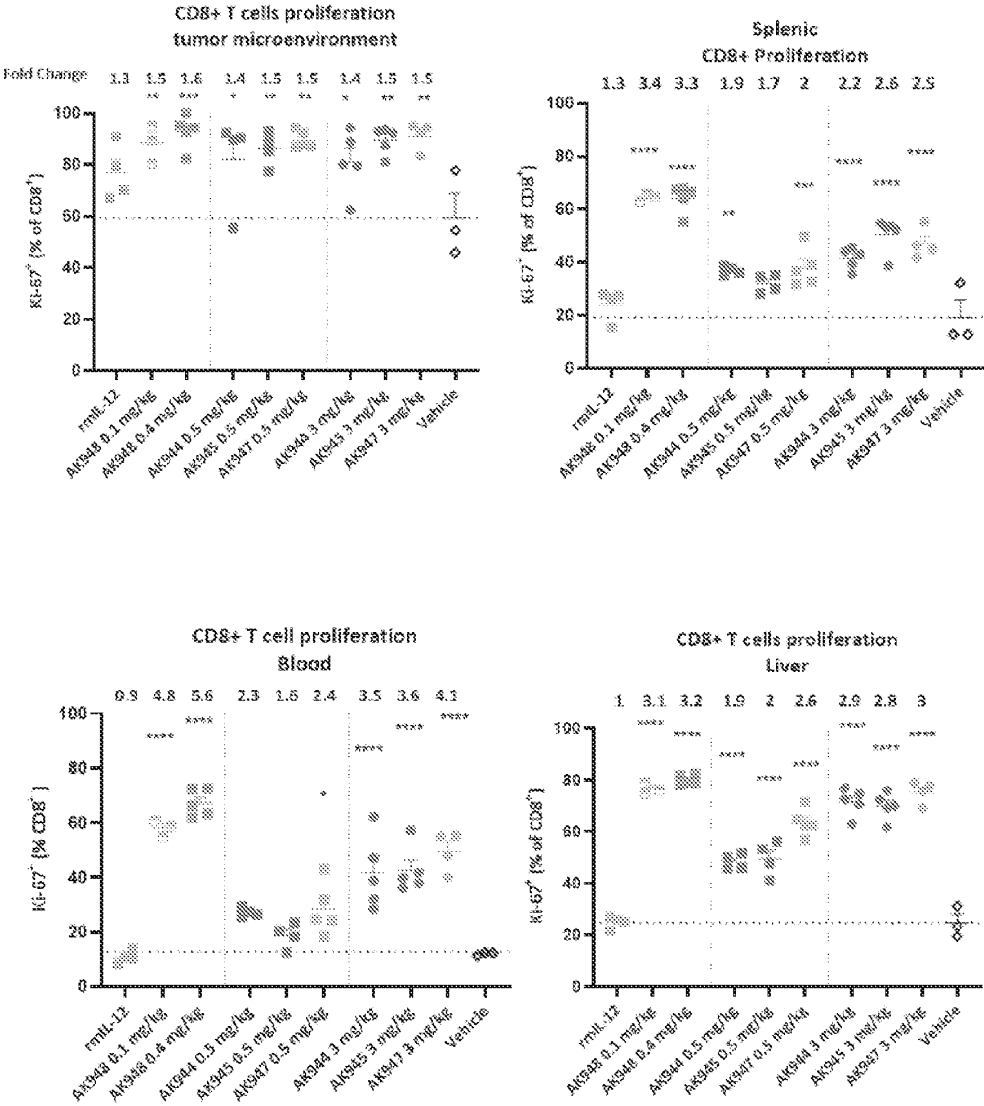


FIG 65A

MB49

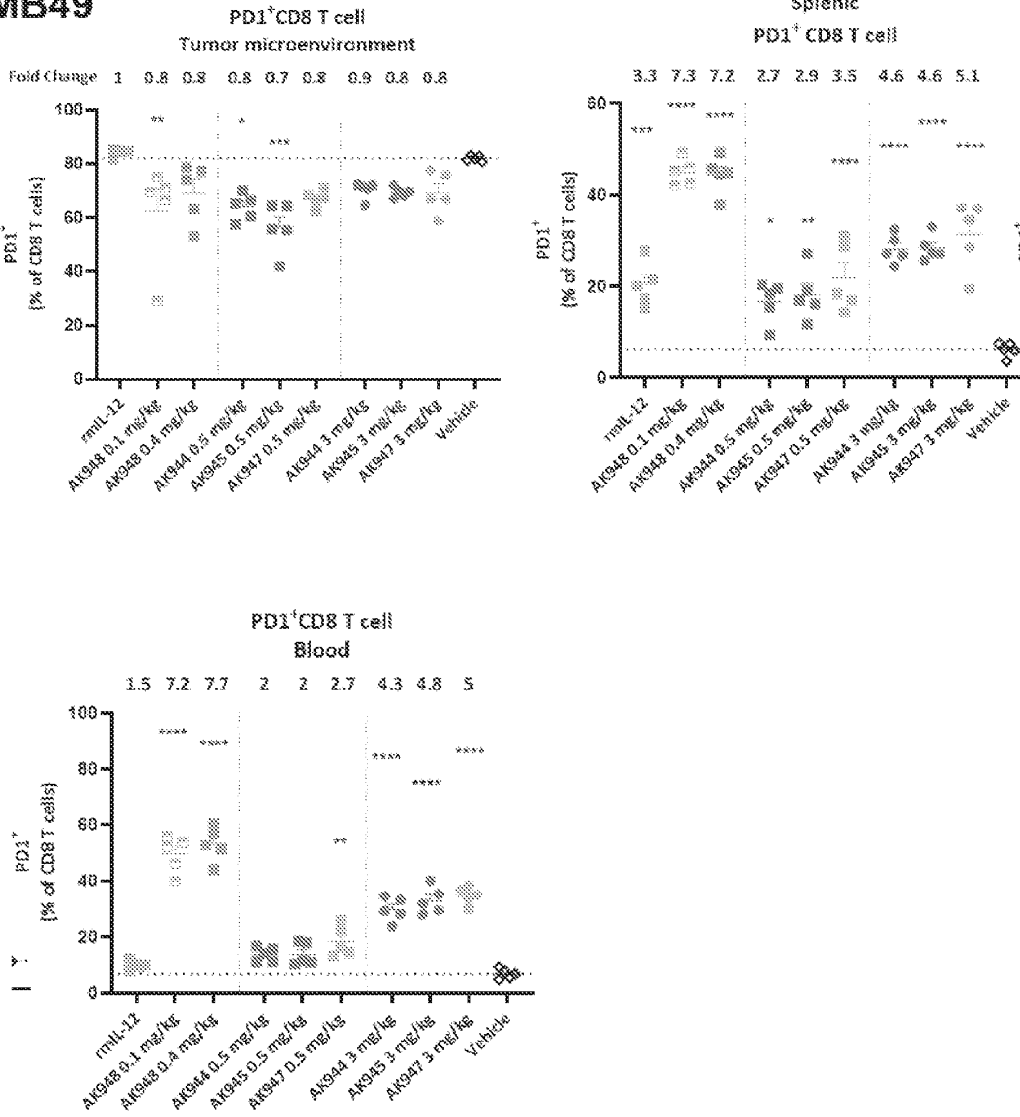


FIG 65B

B16

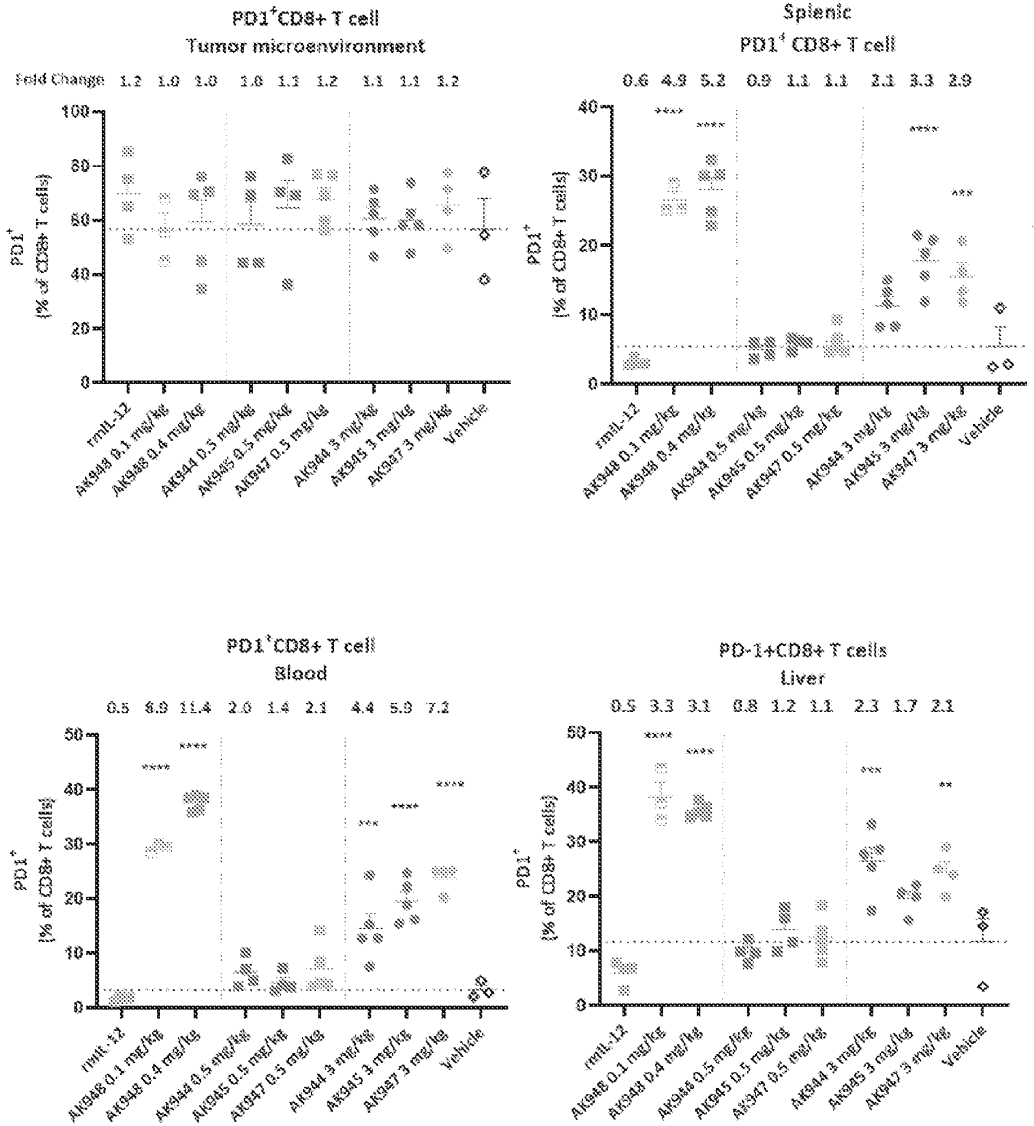
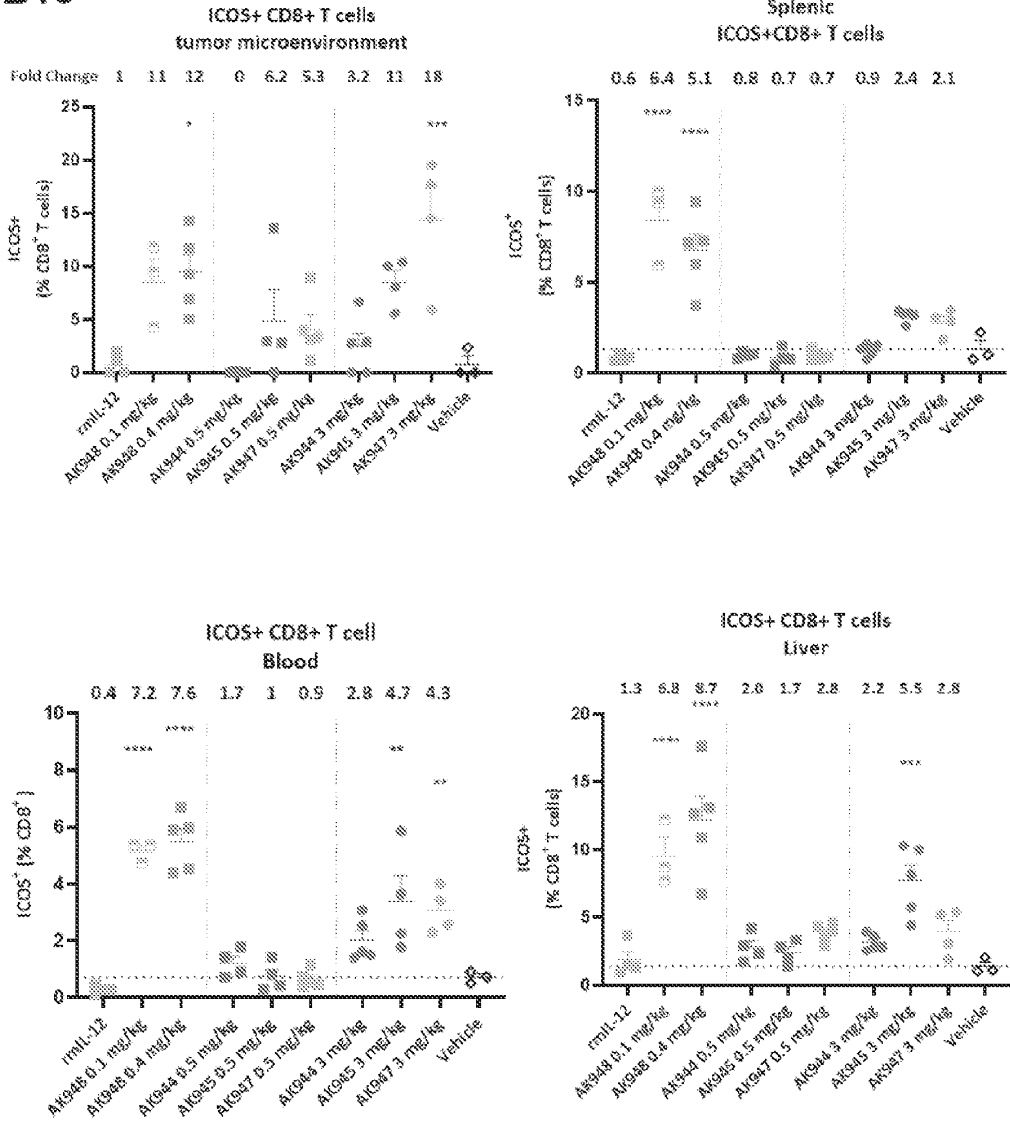


FIG 65C

B16



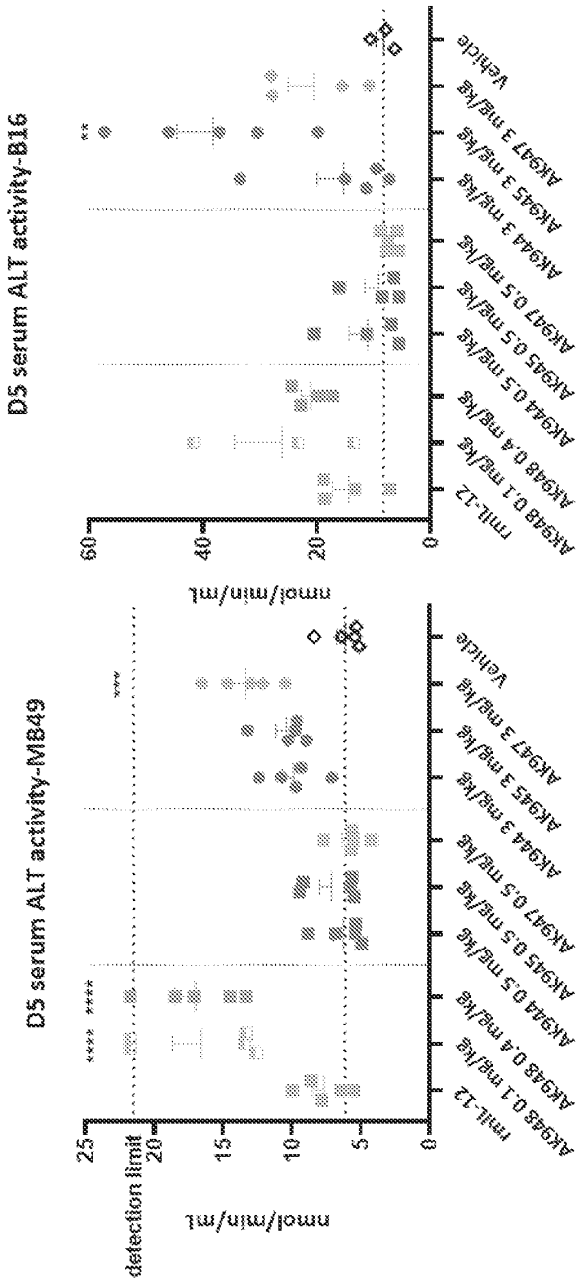


FIG. 66

B16

MB49

D3 serum IFN γ

D3 serum IFN γ

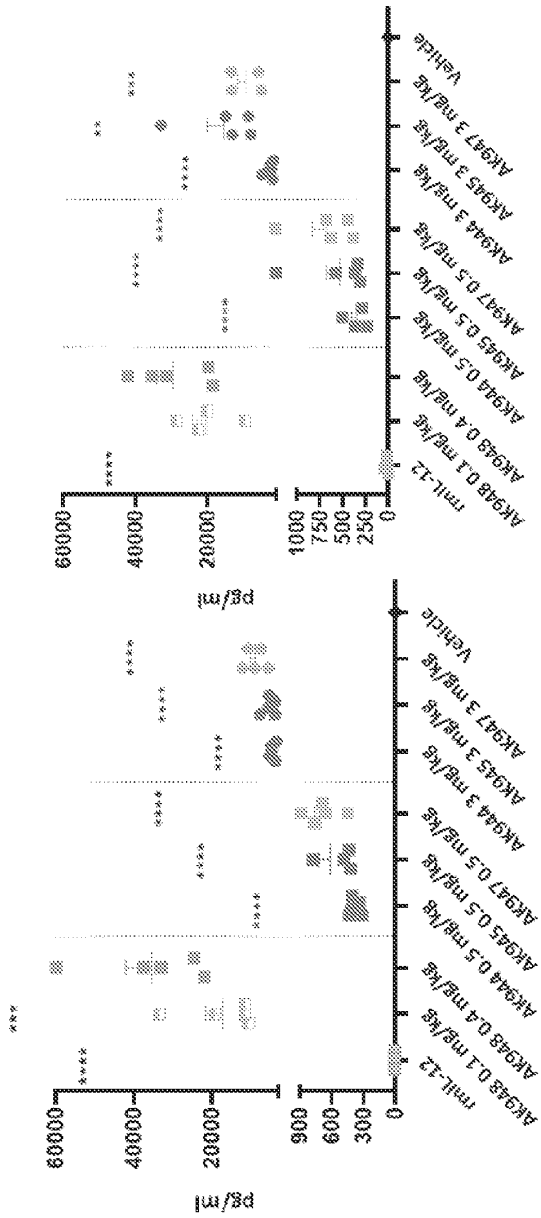
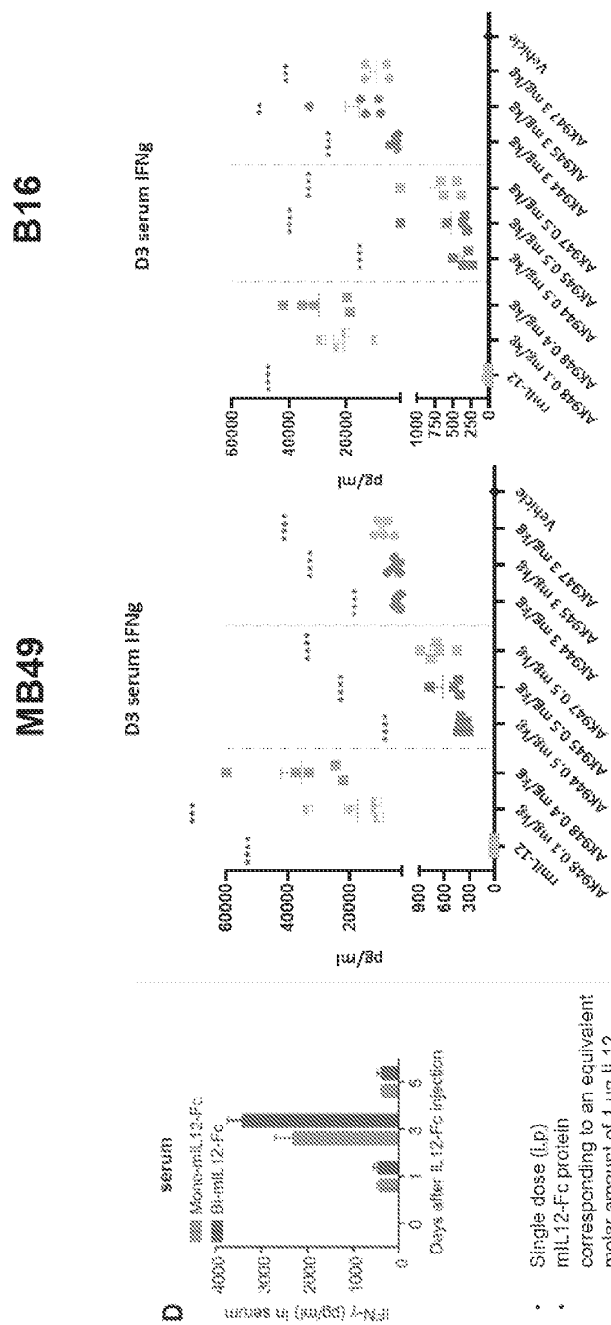


FIG 16

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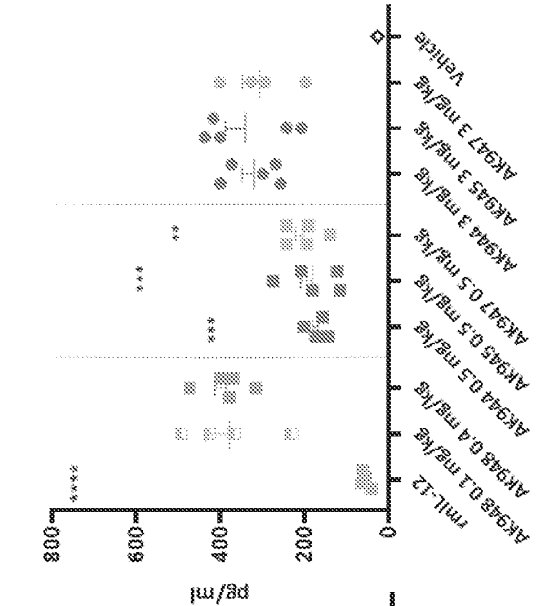


→ Dosing 10 times higher (0.5mpk), without induce significant increase of serum IFN γ

FIG 67B

B16

D3 serum TNFa



MB49

D3 serum TNFa

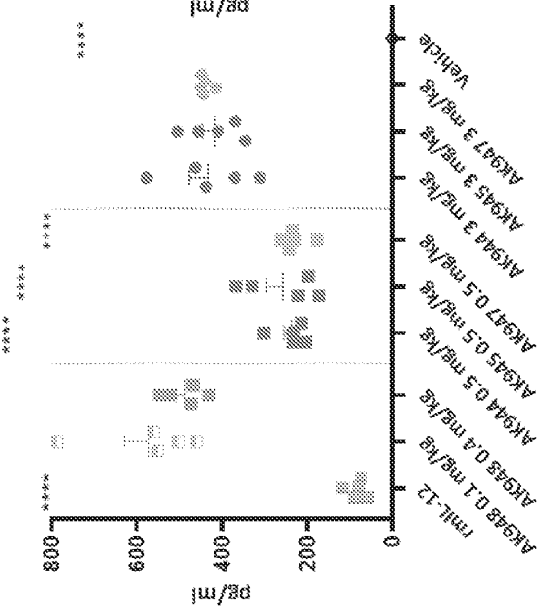
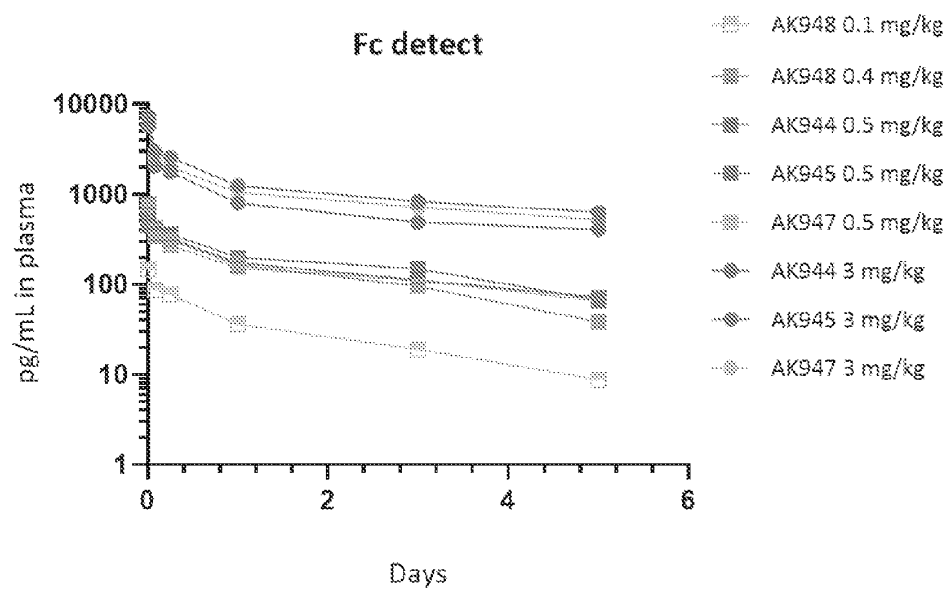


FIG 67C

FIG 68



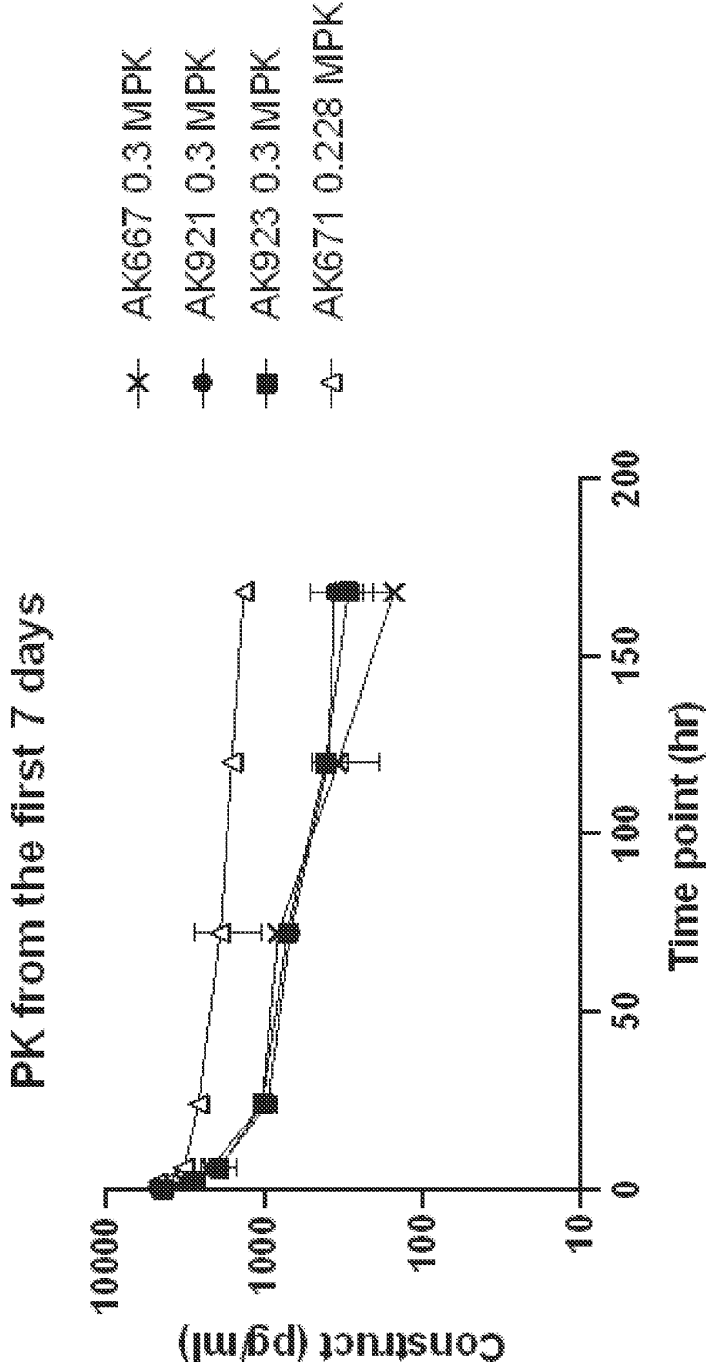


FIG 69

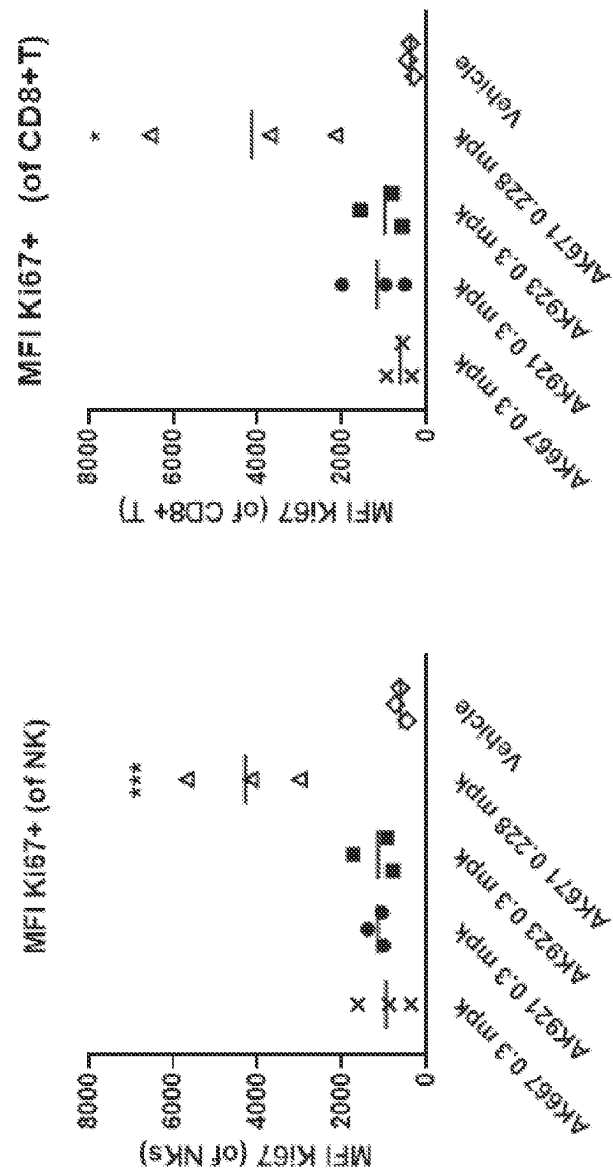
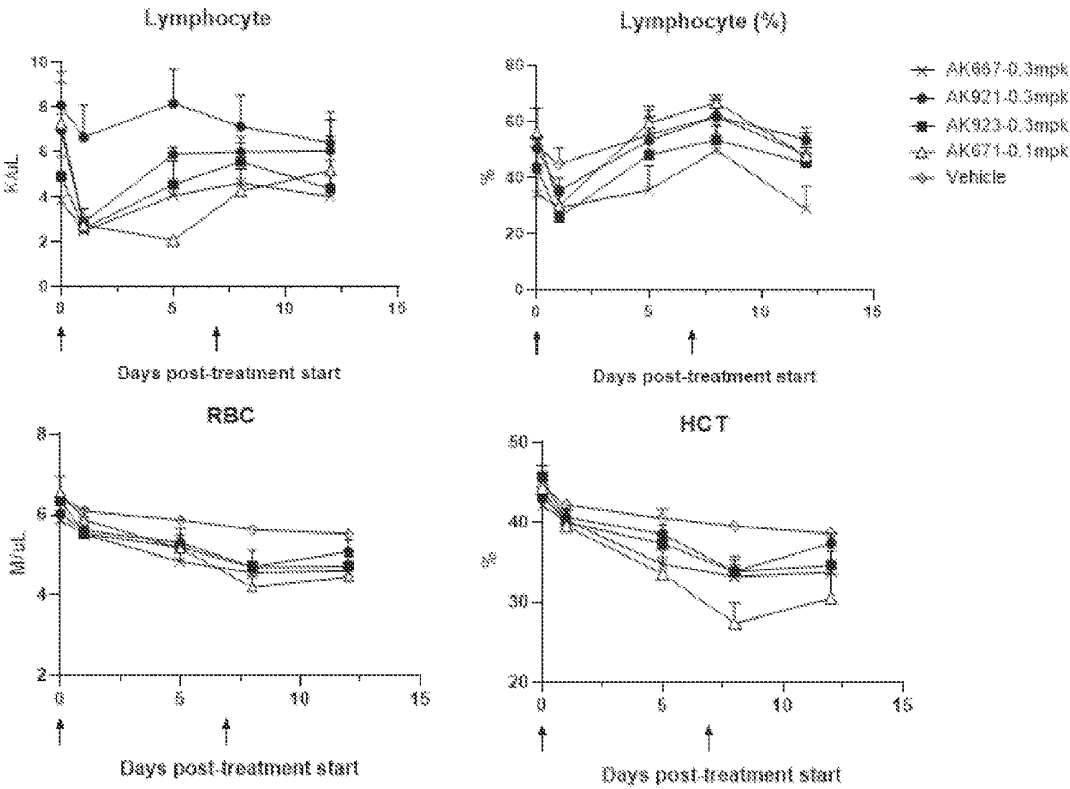


FIG 70

FIG 71A



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FIG 71B

