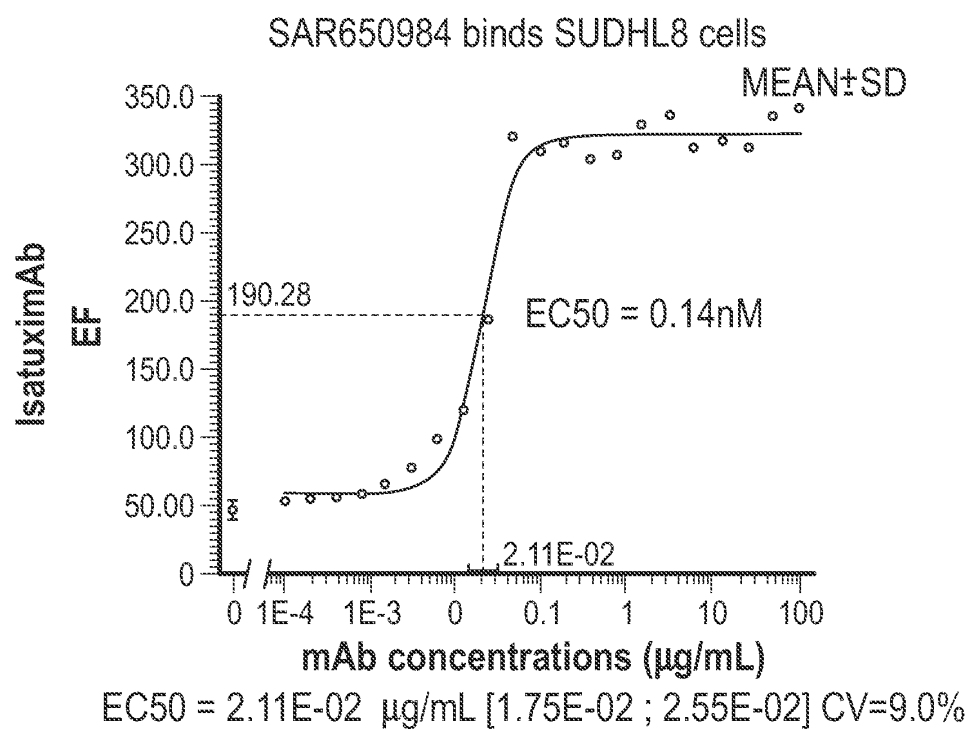
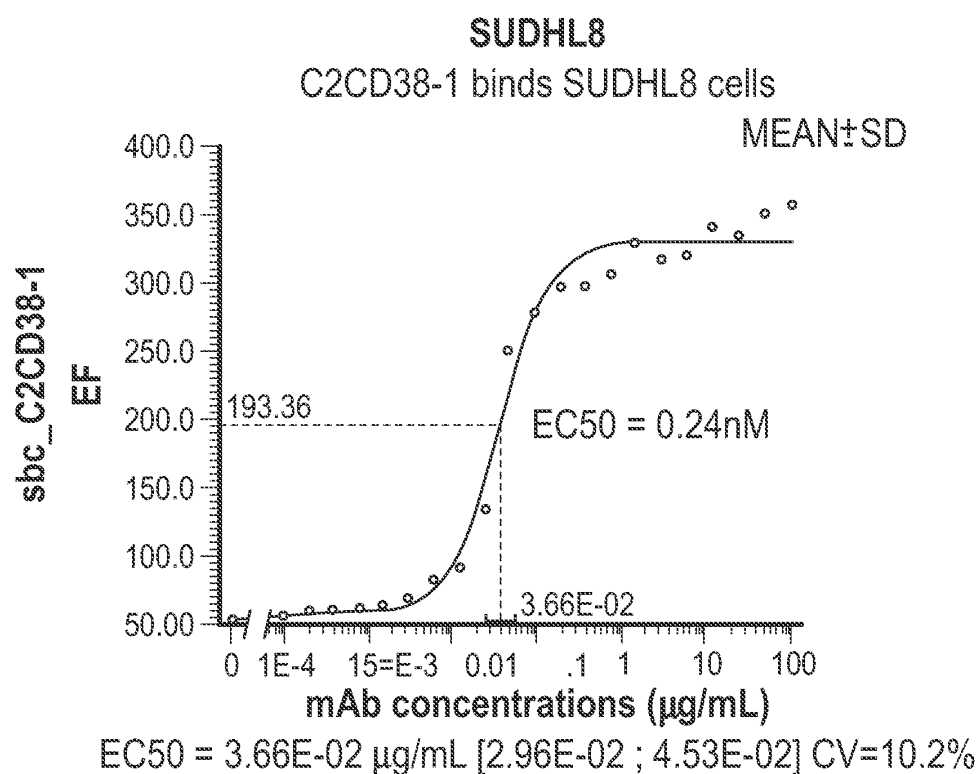
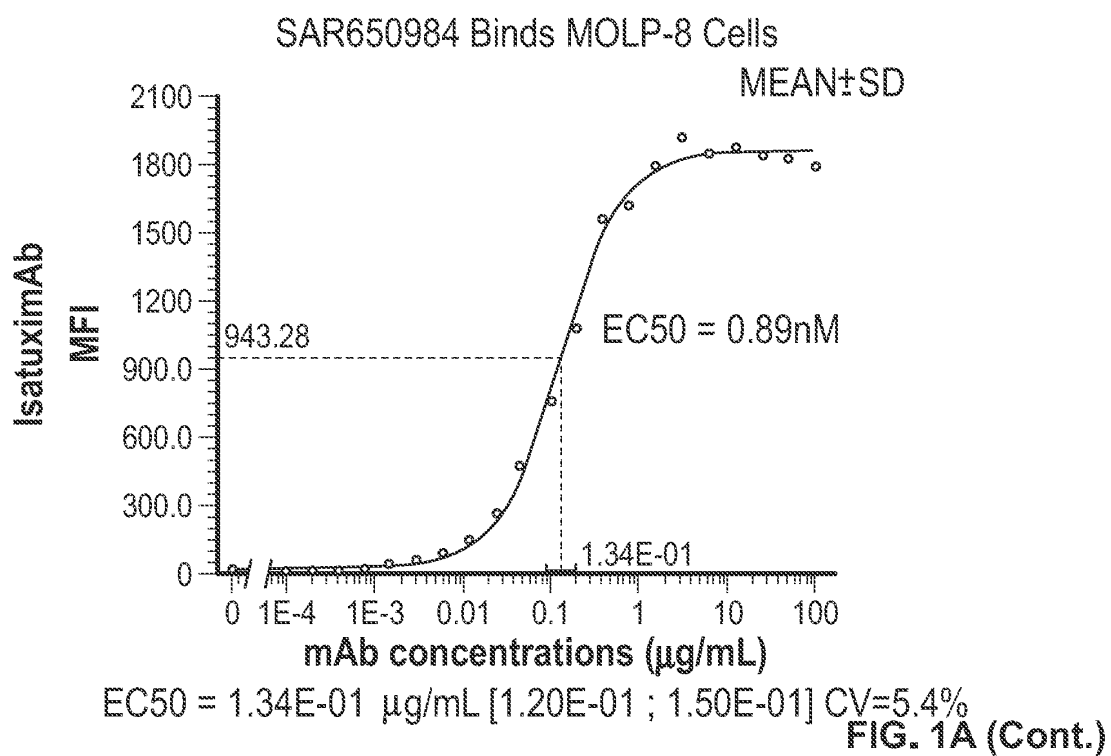
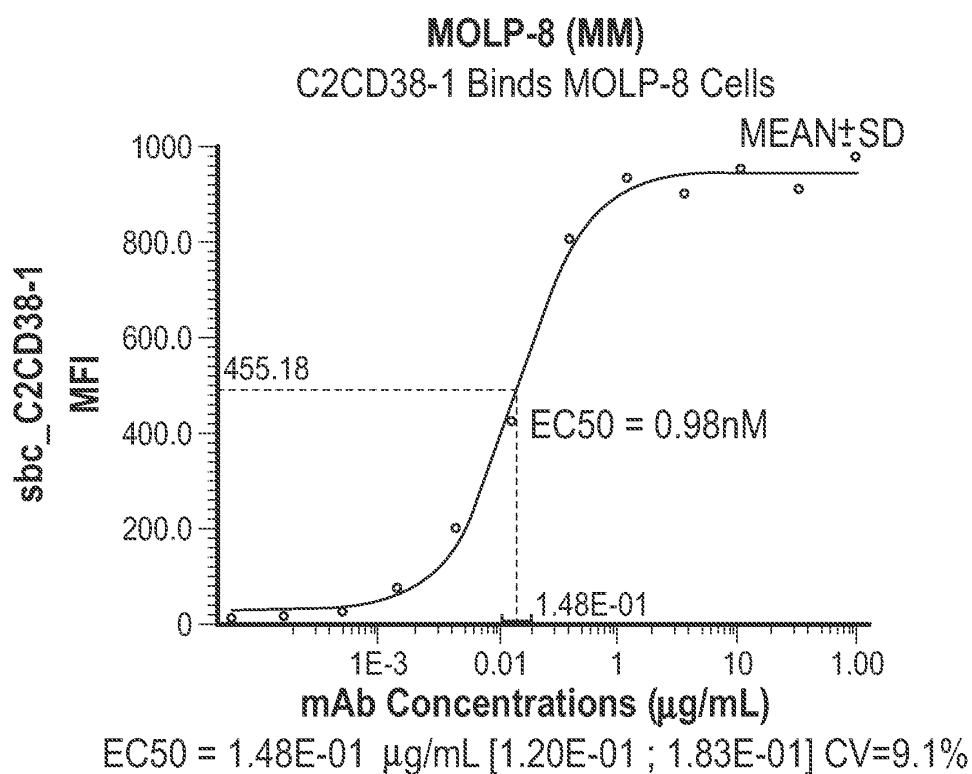
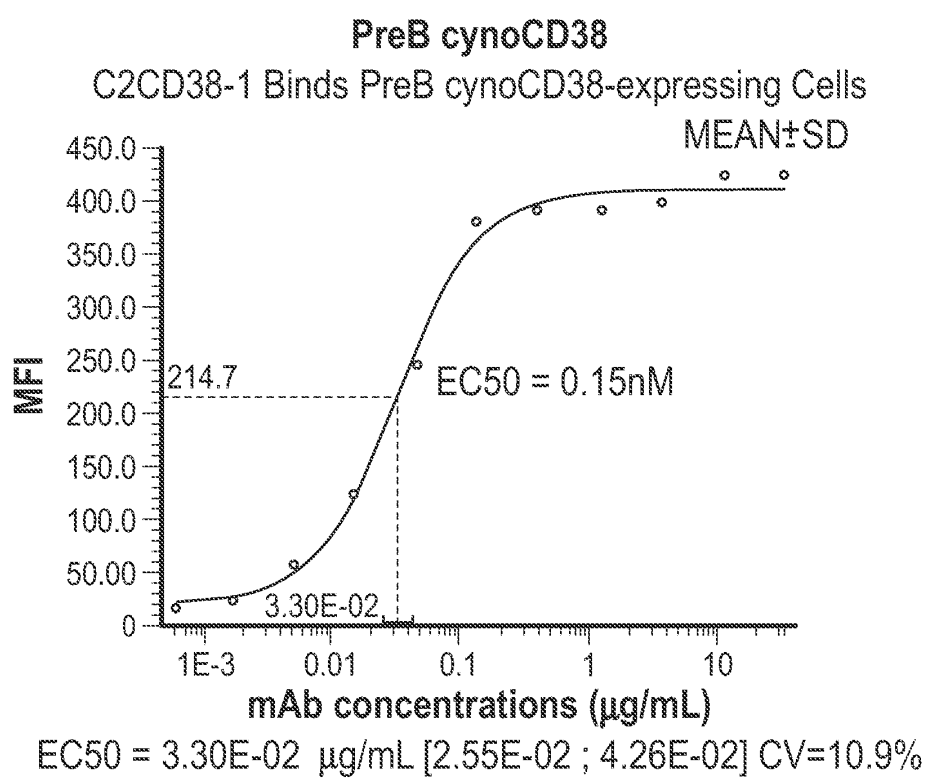


**FIG. 1A**



**FIG. 1B**

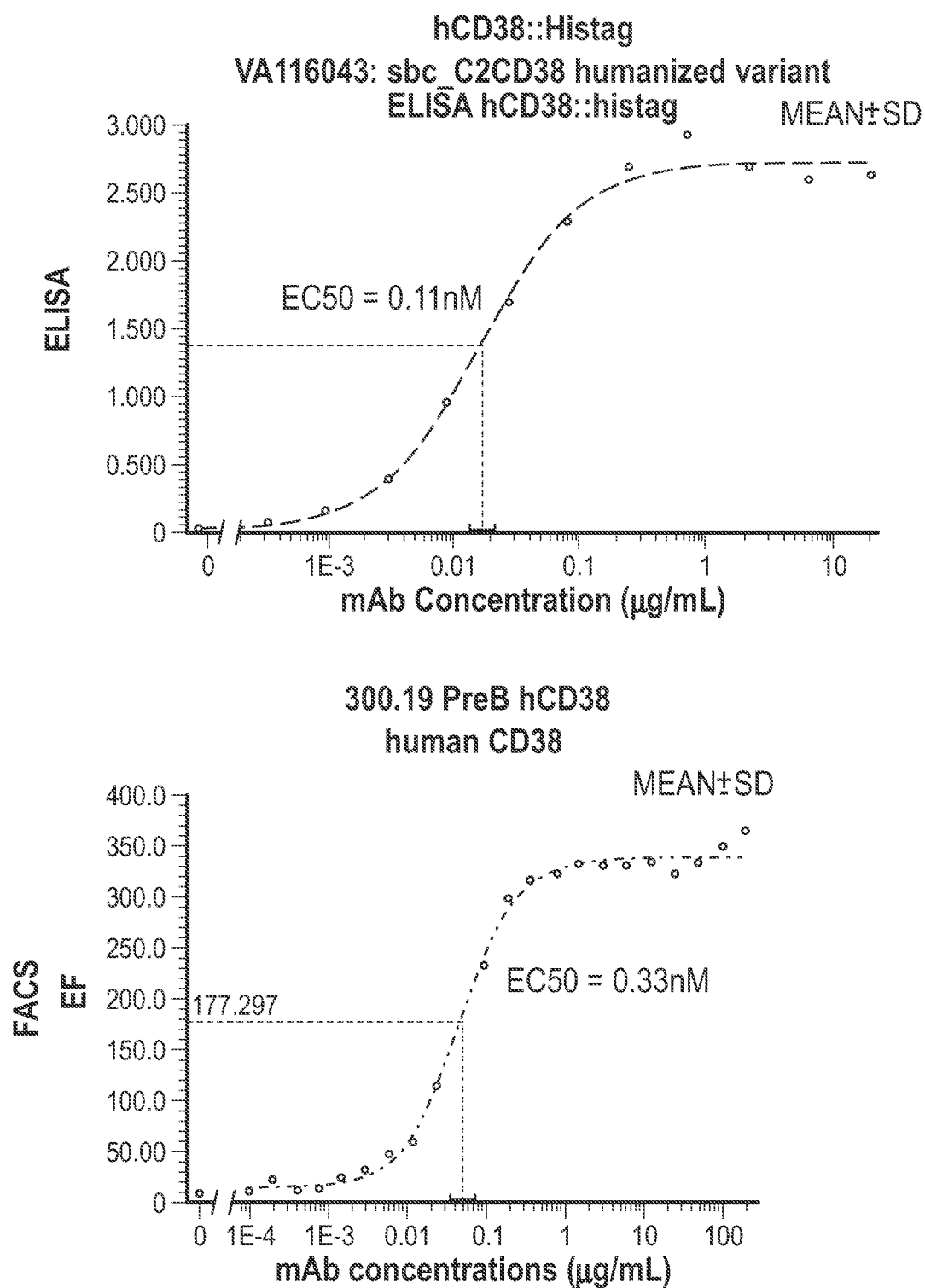


FIG. 2A

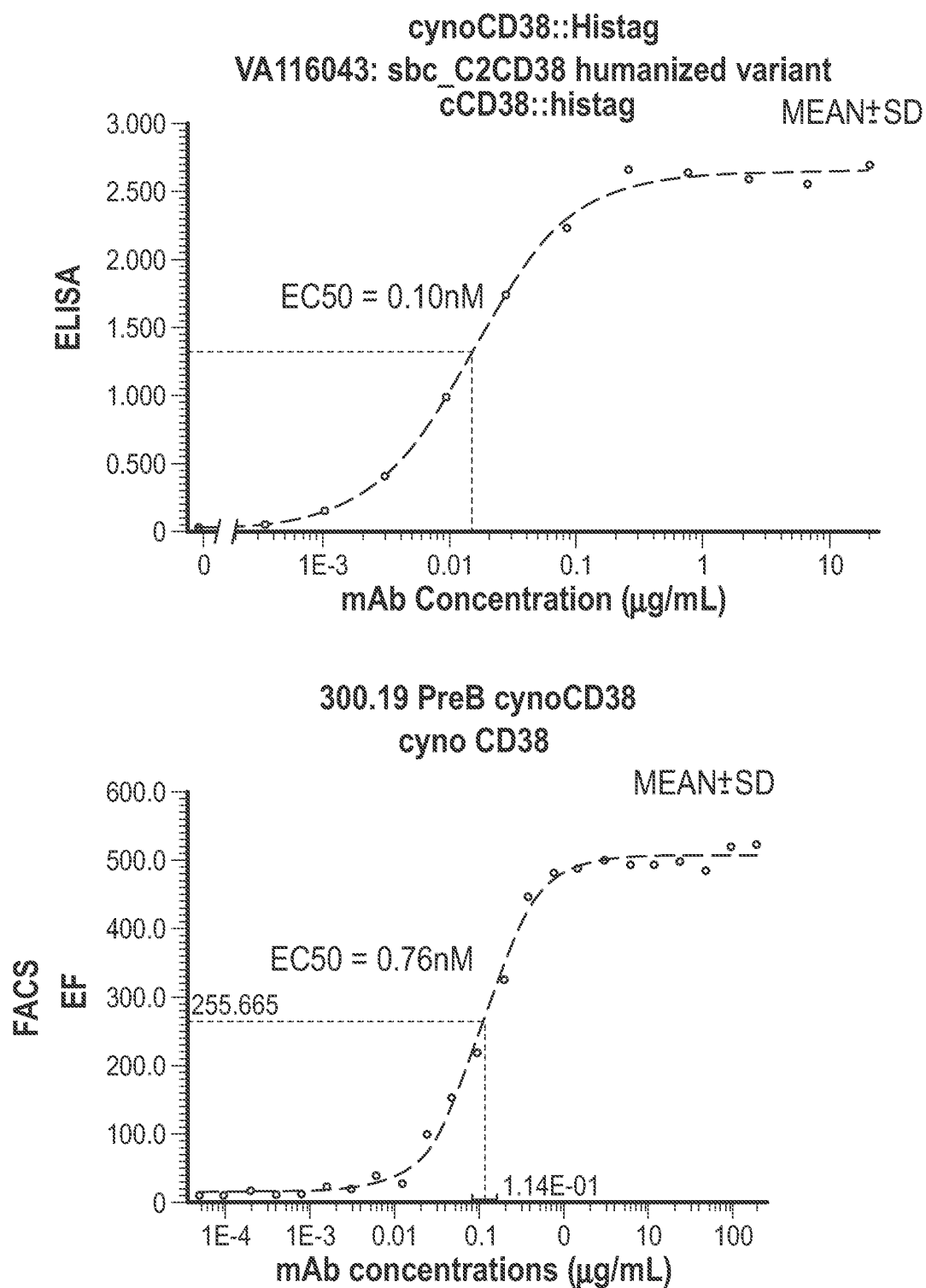


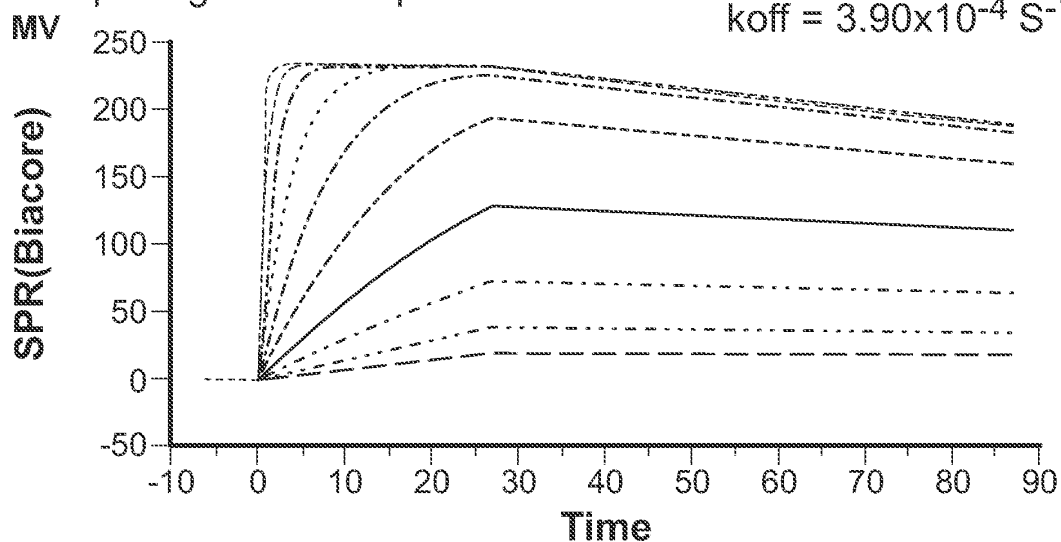
FIG. 2A (Cont.)

hCD38::Histag

Kinetics:VA116048-hCD38::His
2-1 T4,fit:'1. 1:1 Binding'

Curve: Fc*3-1 Ligand Target
4 Sample Ligand 1 Temp 25°C

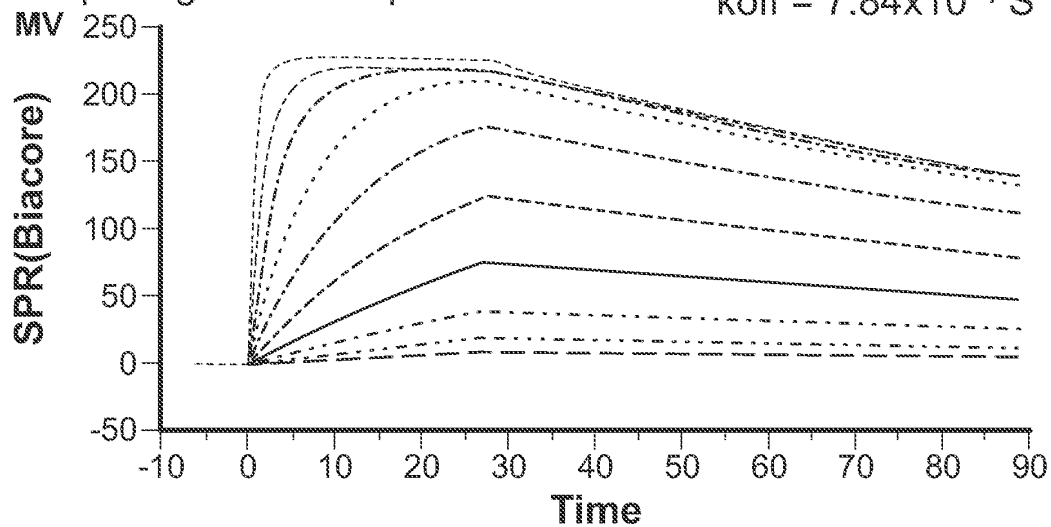
$K_D = 3.32 \times 10^{-10} \text{ M}$
 $k_{off} = 3.90 \times 10^{-4} \text{ S}^{-1}$

**cynoCD38::Histag**

Kinetics:VA116048-cCD38::His
2-1 T4,fit:'1. 1:1 Binding'

Curve: Fc*3-1 Ligand Target
4 Sample Ligand 1 Temp 25°C

$K_D = 3.44 \times 10^{-9} \text{ M}$
 $k_{off} = 7.84 \times 10^{-4} \text{ S}^{-1}$

**FIG. 2B**

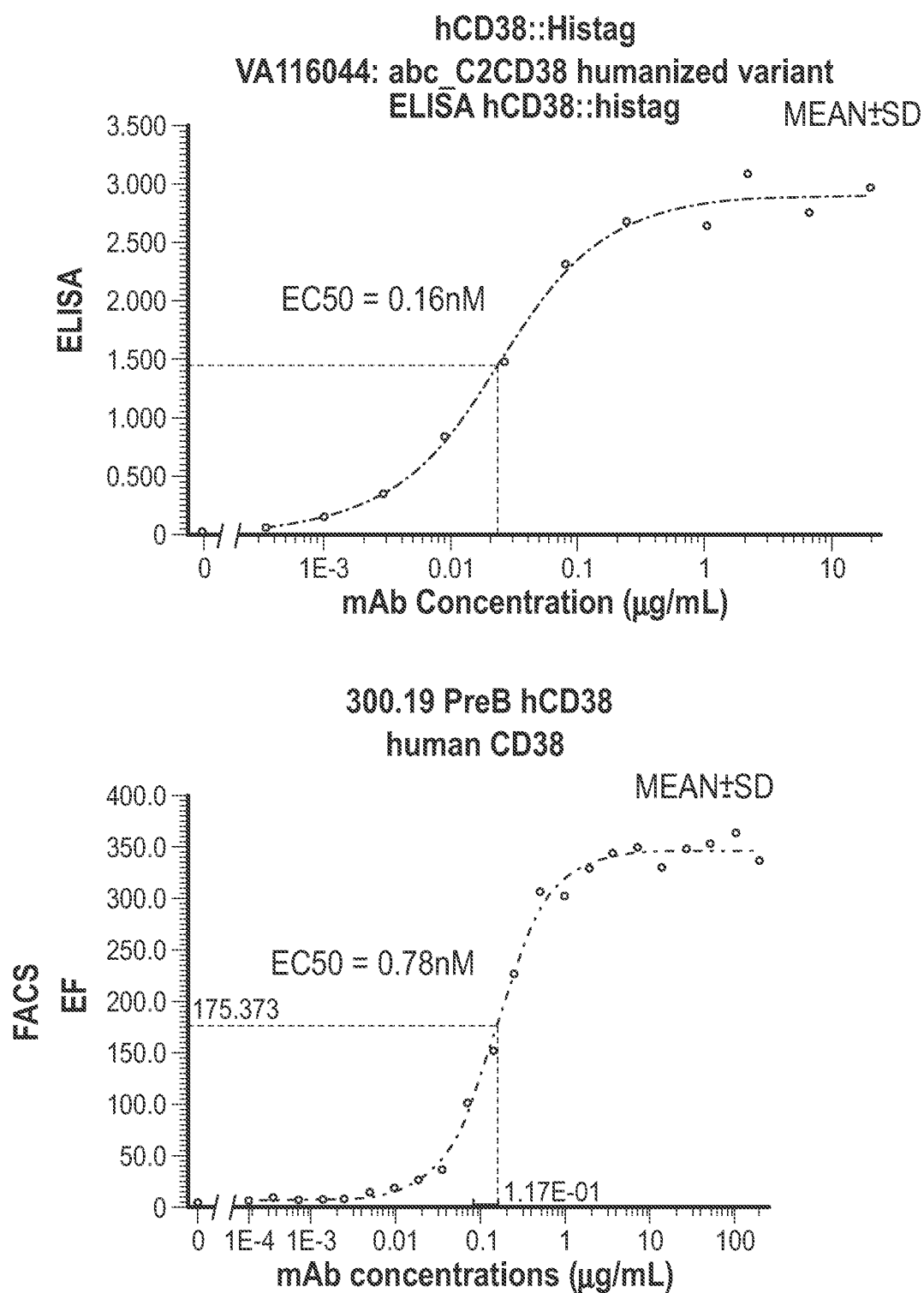


FIG. 2C

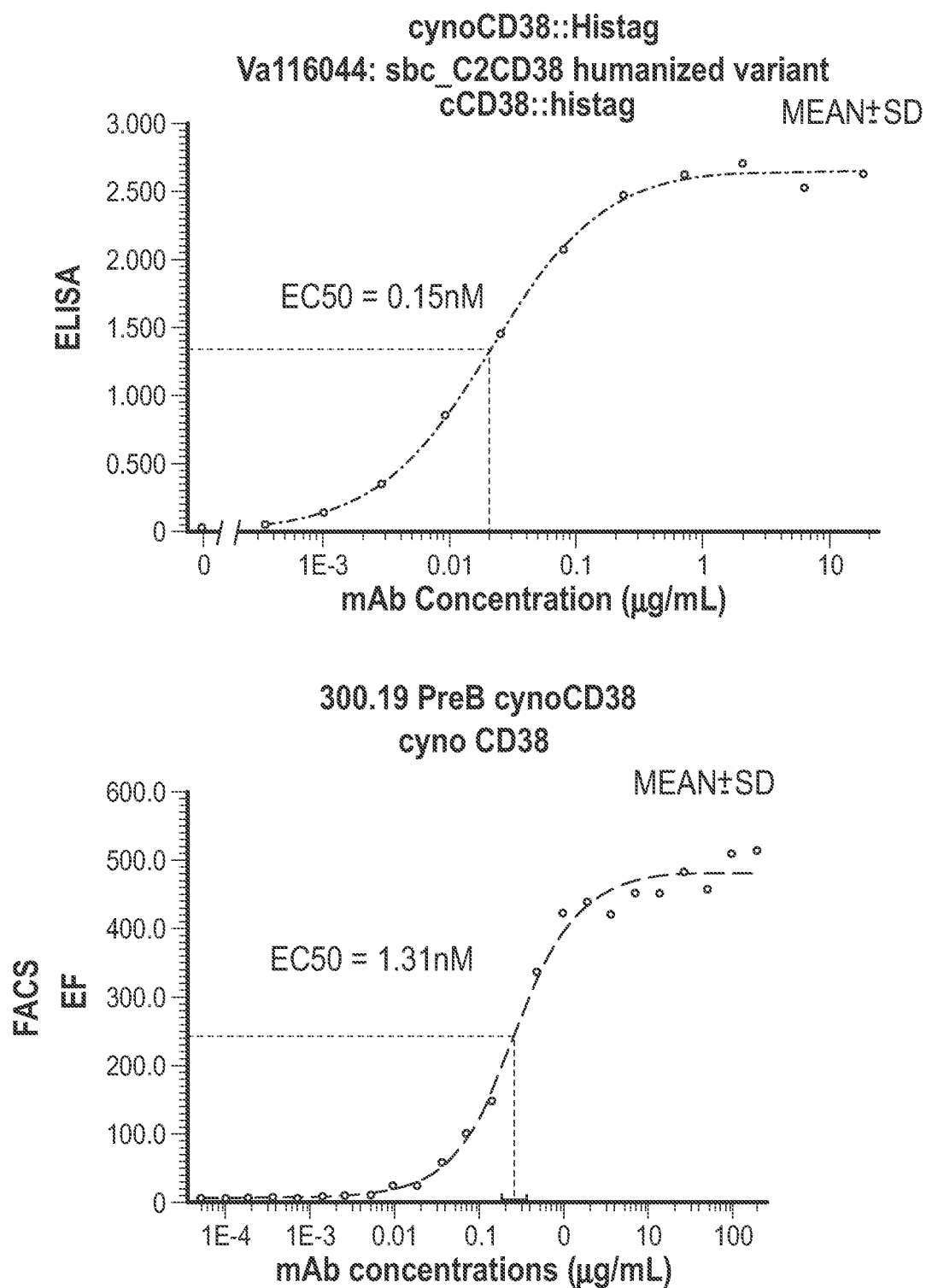


FIG. 2C (Cont.)

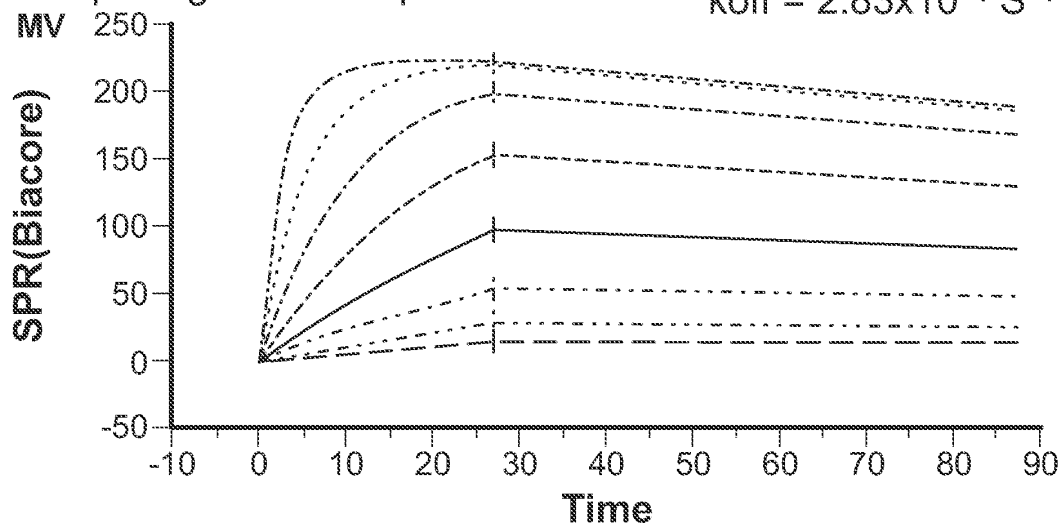
hCD38::Histag

Kinetics:VA116044-hCD38::His

3-1 T5 2',fit:'1. 1:1 Binding'

Curve: Fc*3-1 Ligand Target

5 Sample Ligand 1 Temp 25°C

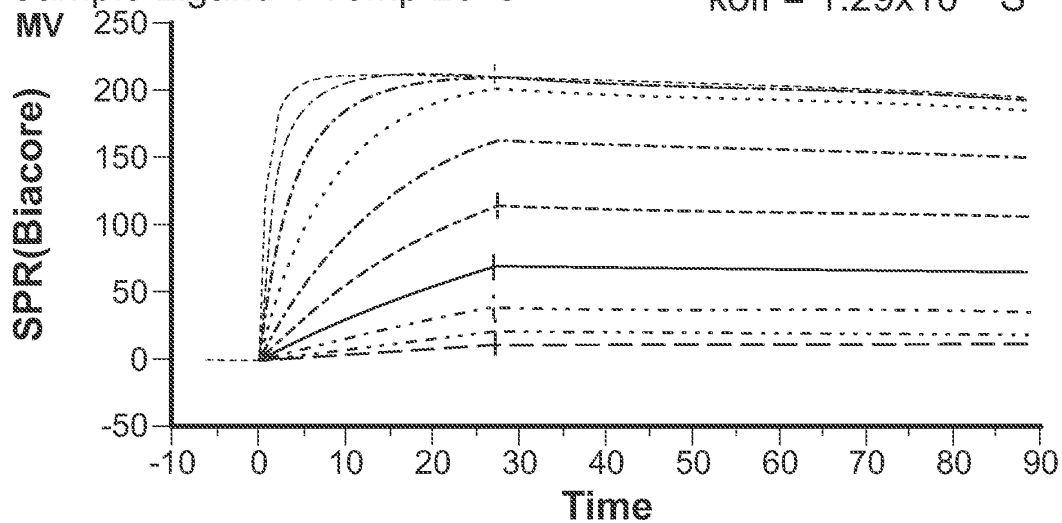
 $K_D = 4.83 \times 10^{-10} \text{ M}$ $k_{off} = 2.83 \times 10^{-4} \text{ S}^{-1}$ **cynoCD38::Histag**

Kinetics:VA116044-cCD38::His

3-1 T5,fit:'1. 1:1 Binding'

Curve: Fc*3-1 Ligand Target

5 Sample Ligand 1 Temp 25°C

 $K_D = 7.10 \times 10^{-10} \text{ M}$ $k_{off} = 1.29 \times 10^{-4} \text{ S}^{-1}$ **FIG. 2D**

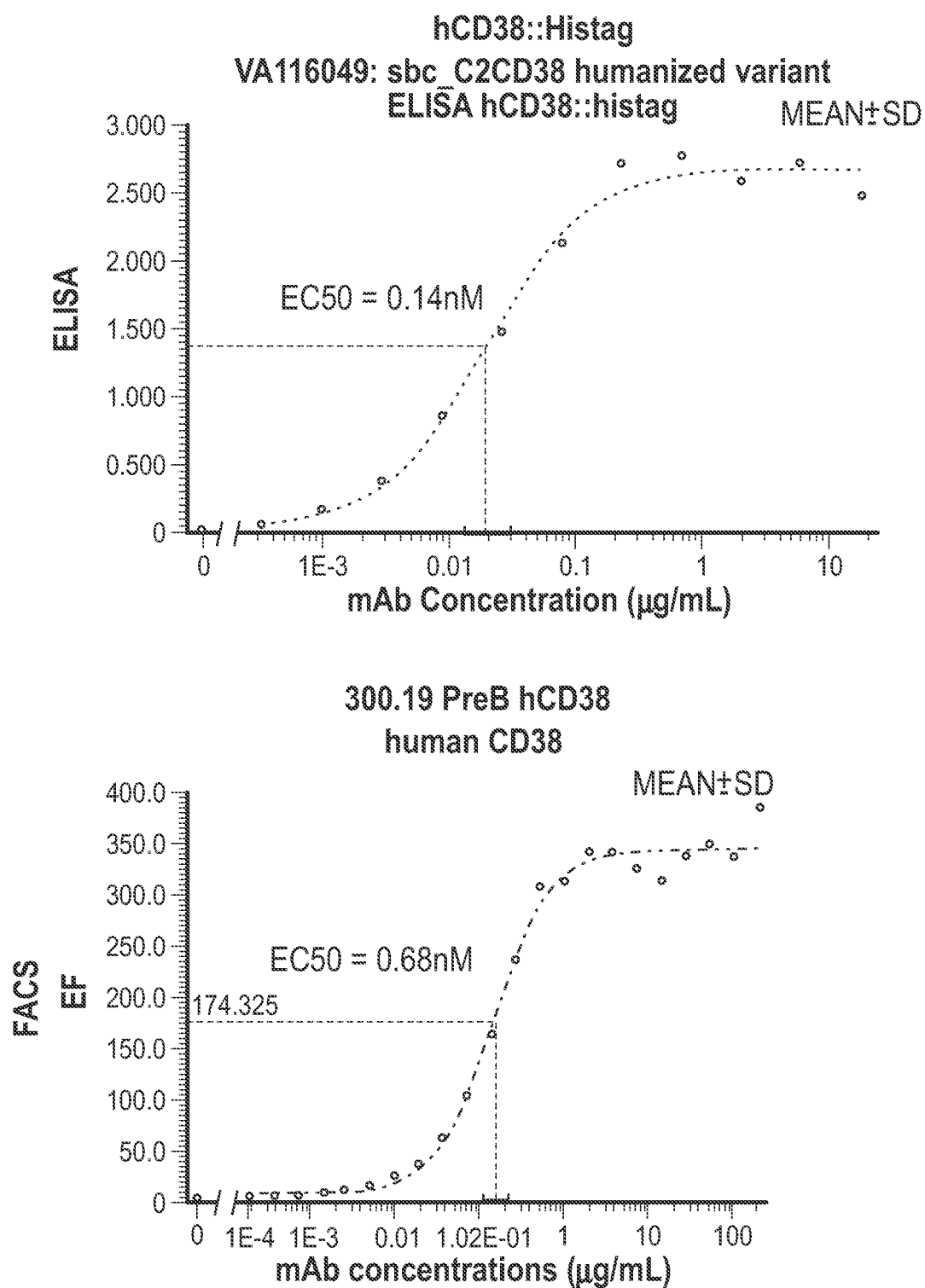


FIG. 2E

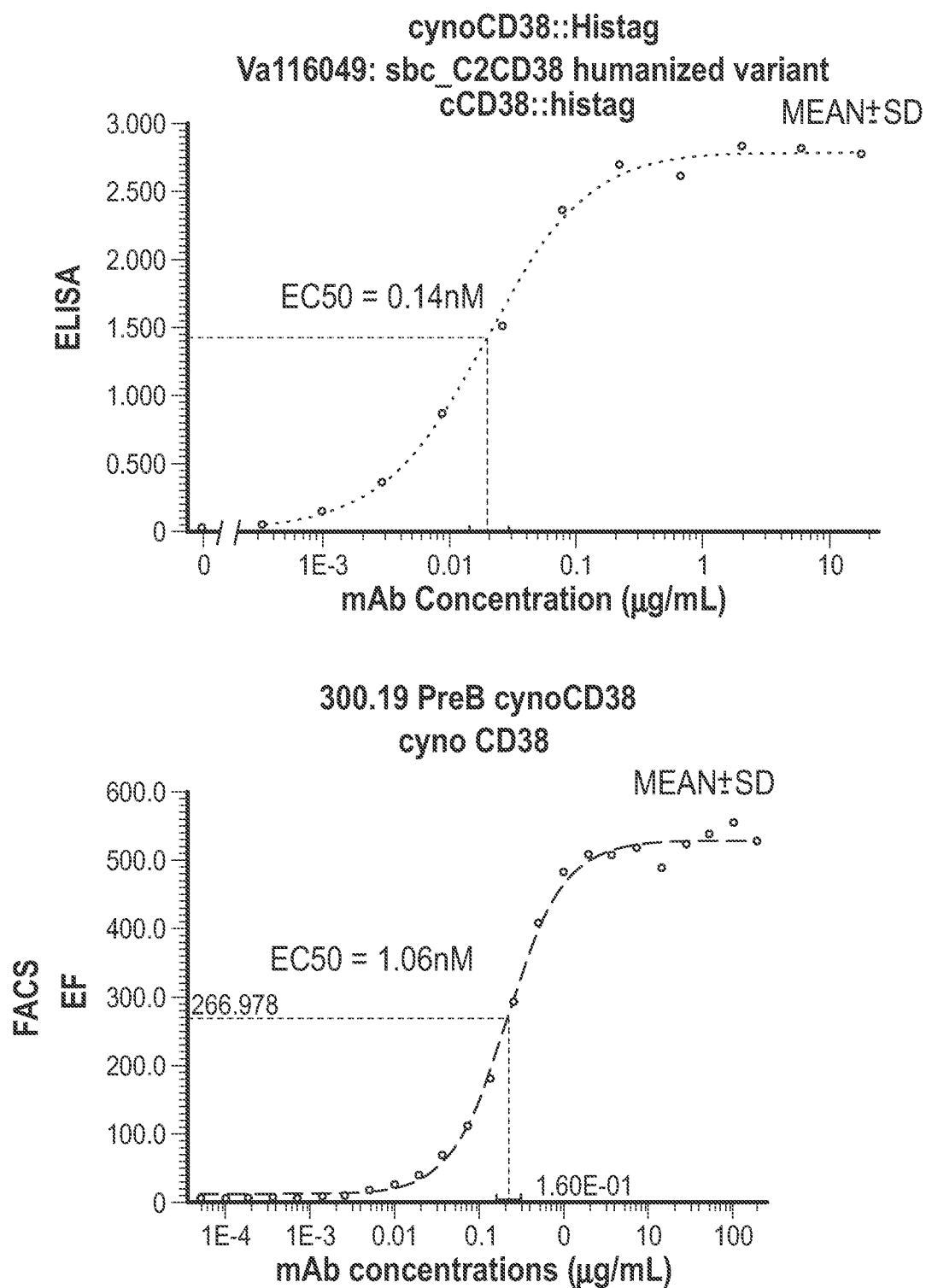


FIG. 2E (Cont.)

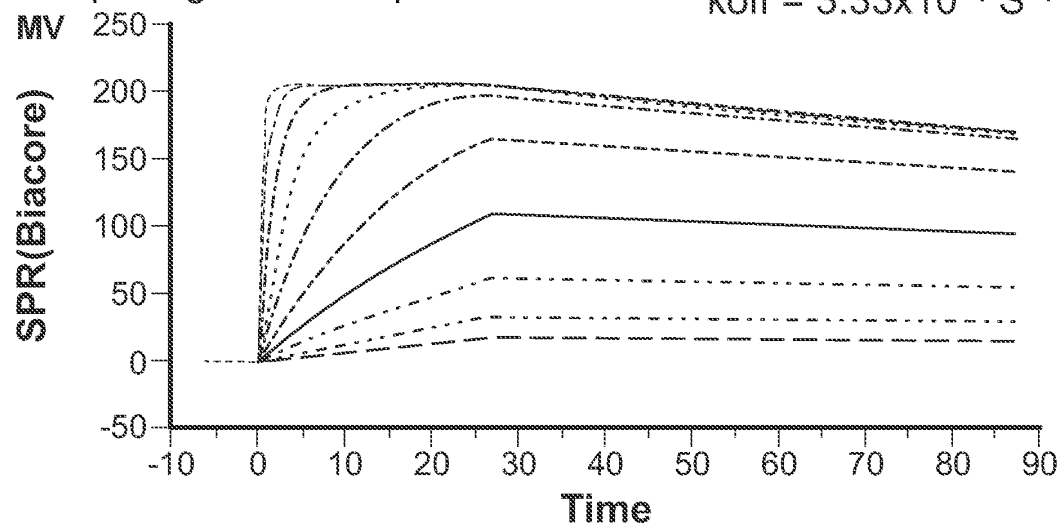
hCD38::Histag

Kinetics:VA116049-hCD38::His

2-1 T4',fit:'1. 1:1 Binding'

Curve: Fc*2-1 Ligand Target

4 Sample Ligand 1 Temp 25°C

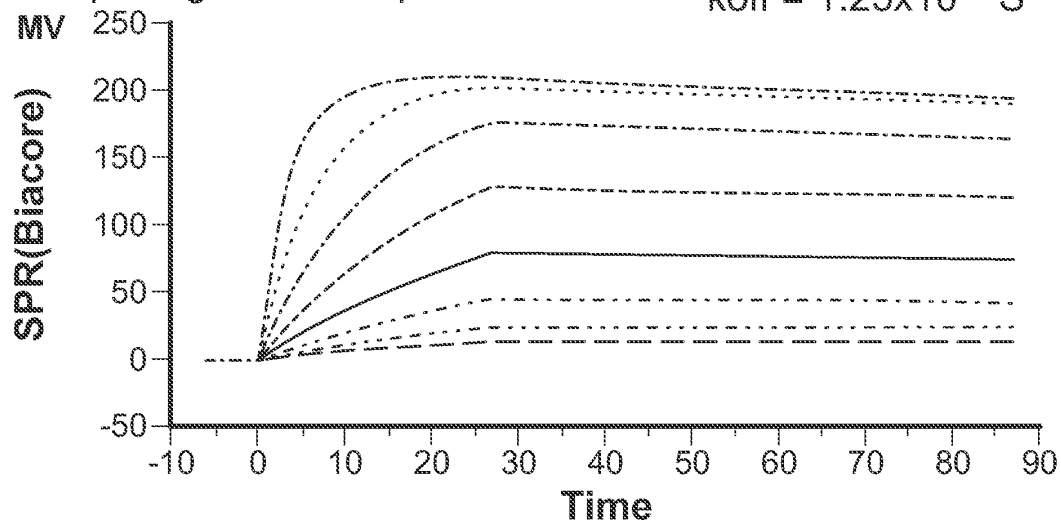
 $K_D = 3.12 \times 10^{-10} \text{ M}$ $k_{off} = 3.33 \times 10^{-4} \text{ S}^{-1}$ **cynoCD38::Histag**

Kinetics:VA116049-cCD38::His

2-1 T4 2',fit:'1. 1:1 Binding'

Curve: Fc*2-1 Ligand Target

4 Sample Ligand 1 Temp 25°C

 $K_D = 5.63 \times 10^{-10} \text{ M}$ $k_{off} = 1.25 \times 10^{-4} \text{ S}^{-1}$ **FIG. 2F**

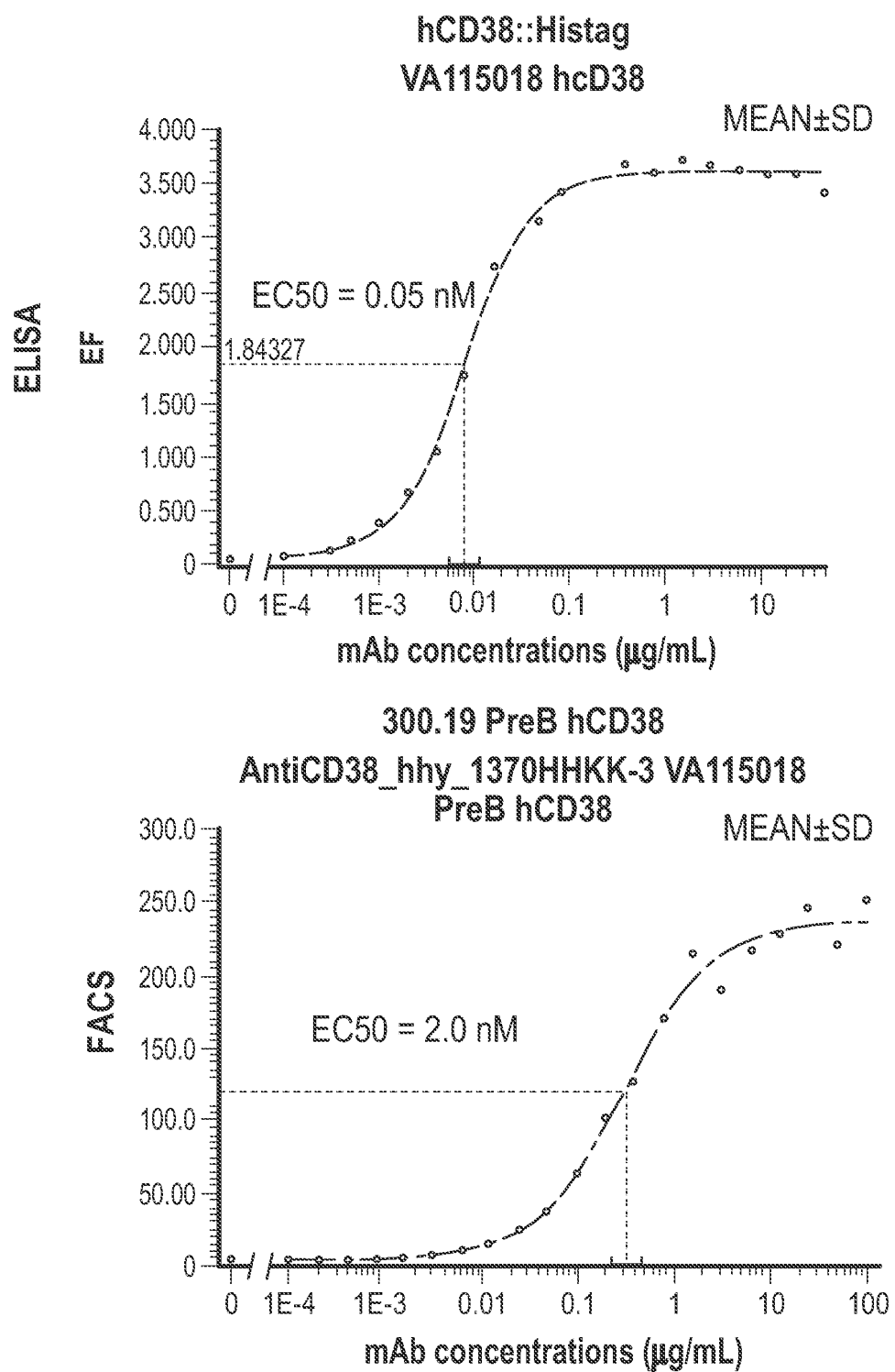


FIG. 2G

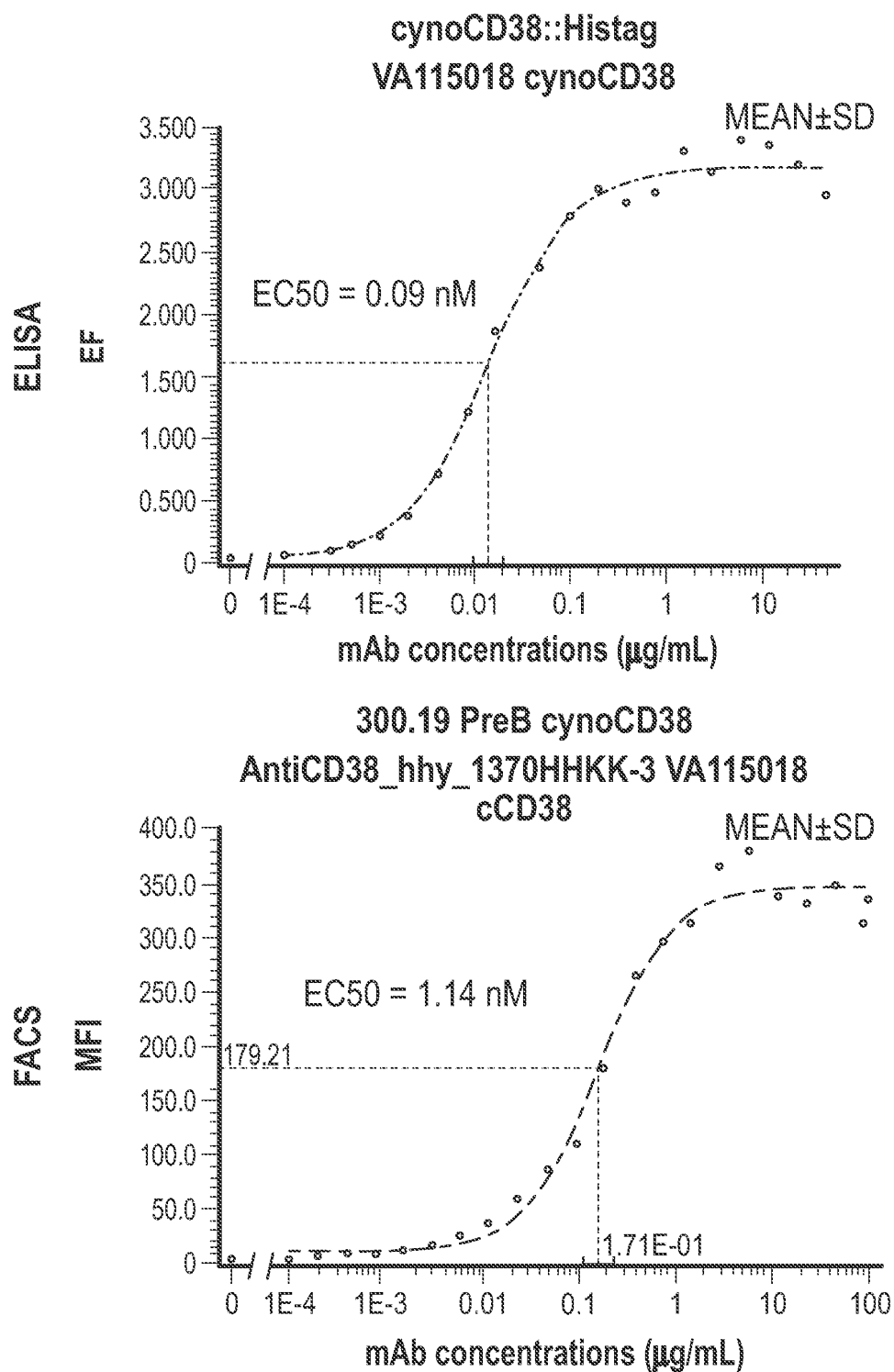


FIG. 2G (Cont.)

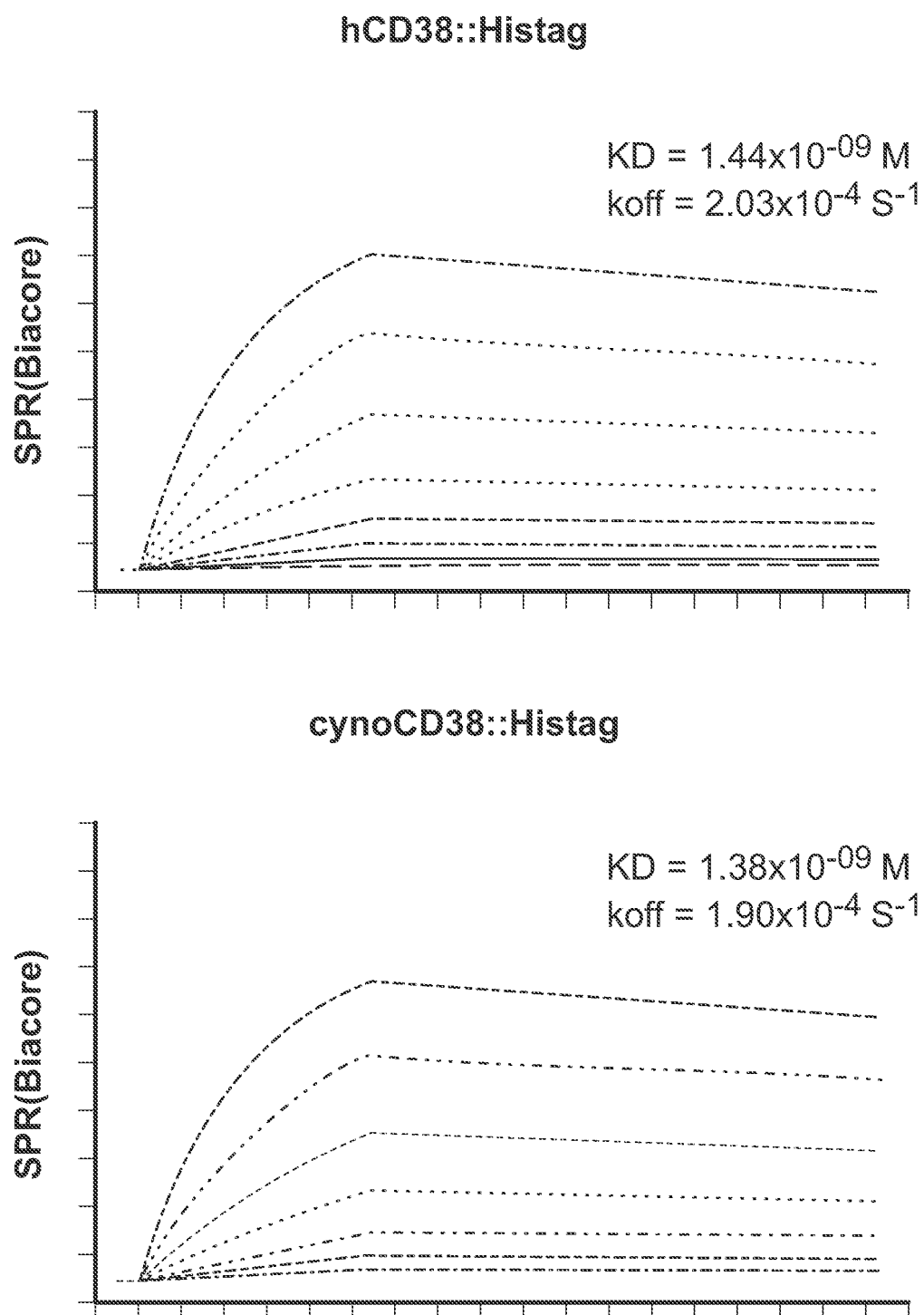


FIG. 2H

	INN nomenclature	ELISA EC50 nM		SPR KD nM		FACS EC50 nM		Human V region Identity	
		hu	cyno	hu	cyno	hu	cyno	H	L
AntiCD38_sbc_C2CD38-1_VL1-VH1	-zumAb	0.11	0.10	0.33	3.44	0.33	0.76	84.7%	87.1%
AntiCD38_sbc_C2CD38-1_VL3-VH3	-zumAb	0.16	0.15	0.48	0.71	0.78	1.31	83.7%	83.9%
AntiCD38_sbc_C2CD38-1_VL3-VH5	-zumAb	0.16	0.17	0.82	1.14	0.55	1.15	80.6%	83.9%
AntiCD38_sbc_C2CD38-1_VL3-VH6	-zumAb	0.14	0.14	0.31	0.56	0.68	1.06	81.6%	83.9%
AntiCD38_hhy_1370HHKK-3	-umAb	0.05	0.09	1.44	1.38	2.00	1.14	99.0%	95.8%

FIG. 2I

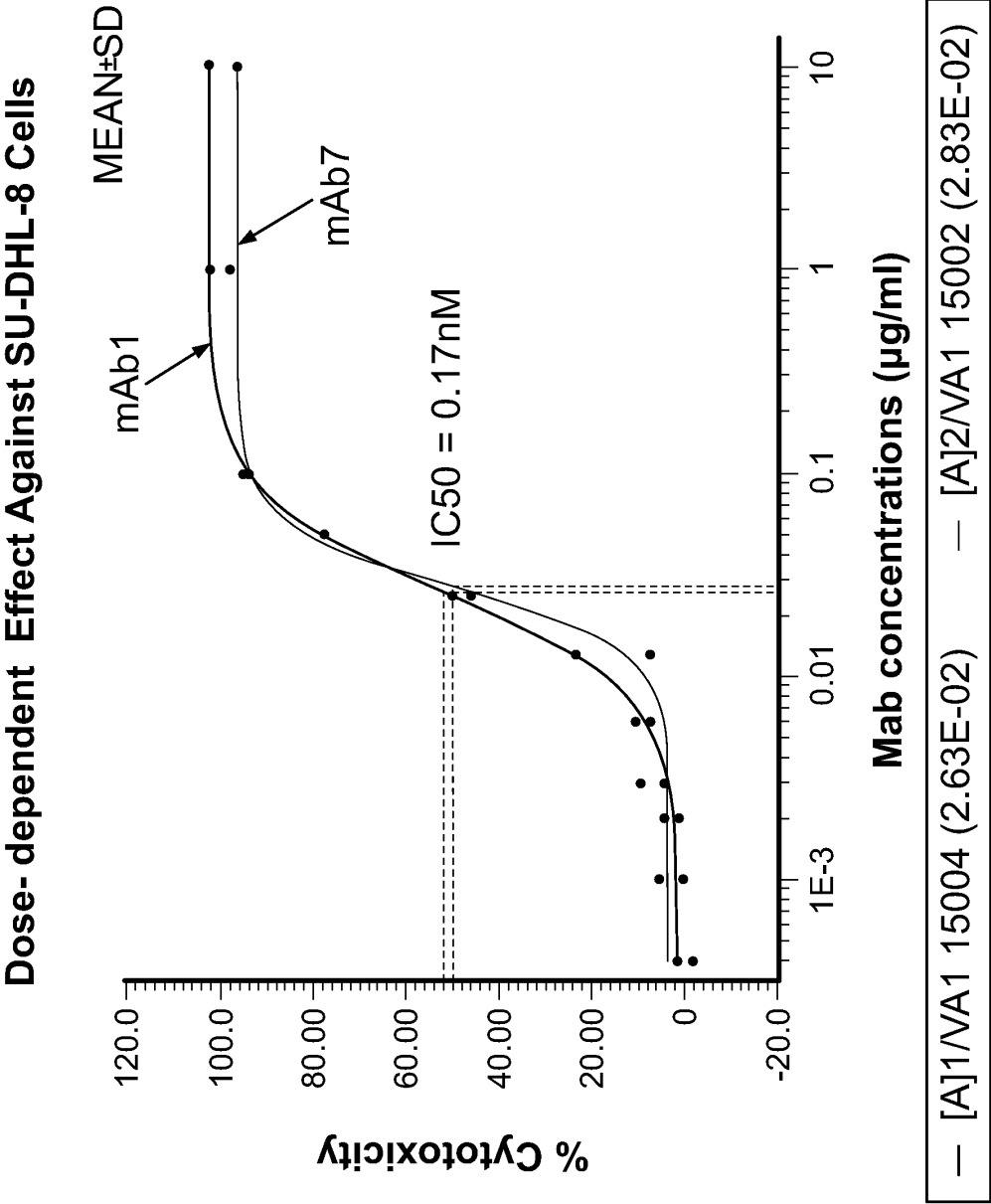


FIG. 2J

ADCC Activity Against SU-DHL-8 Cells

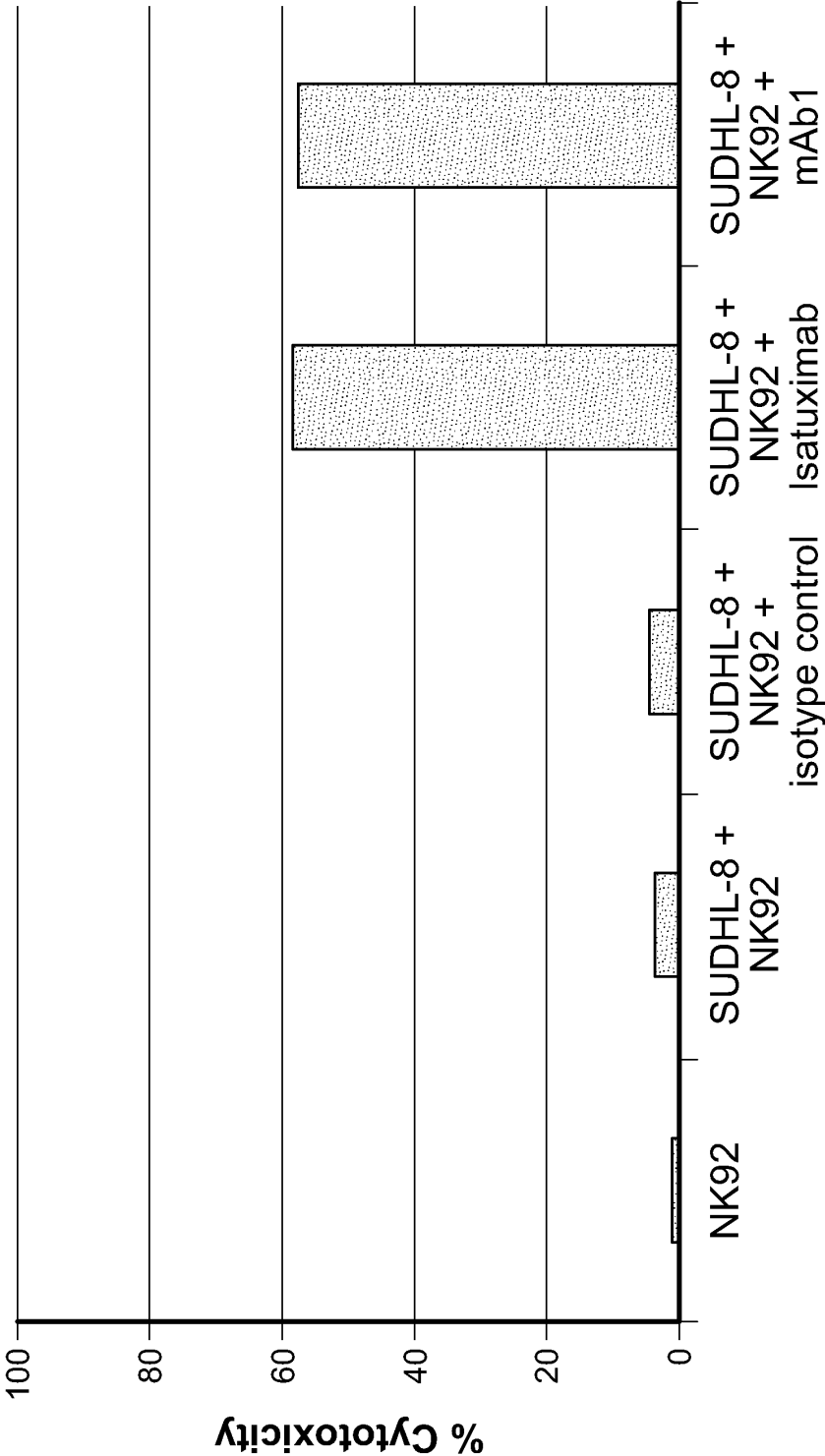
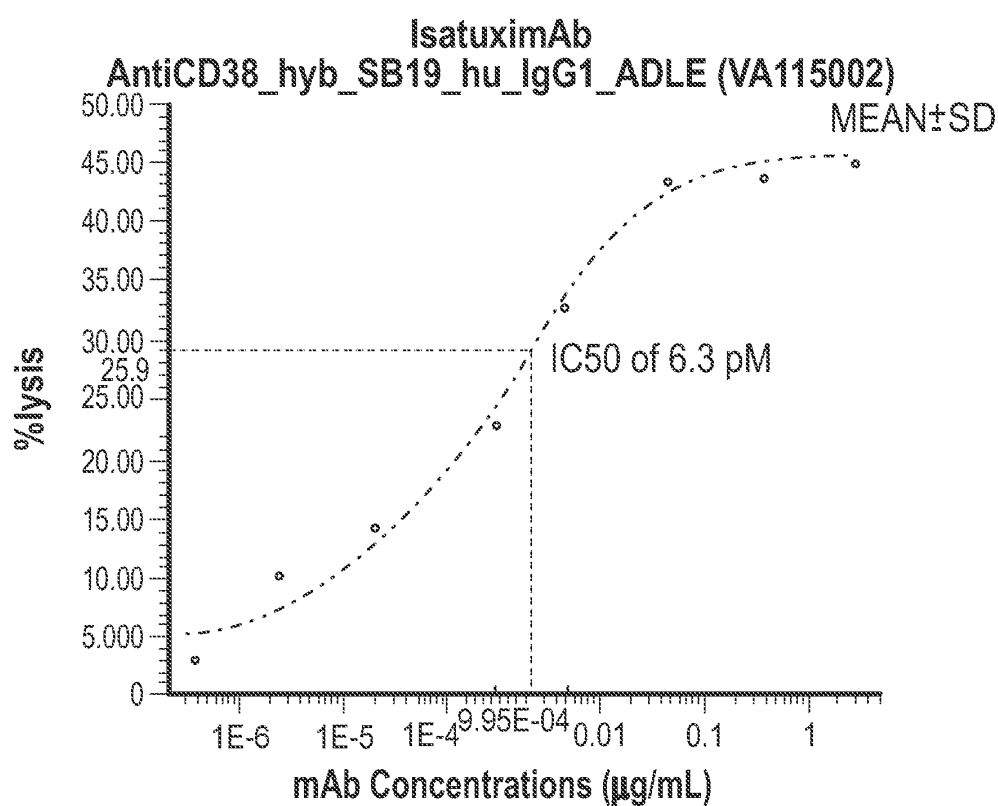
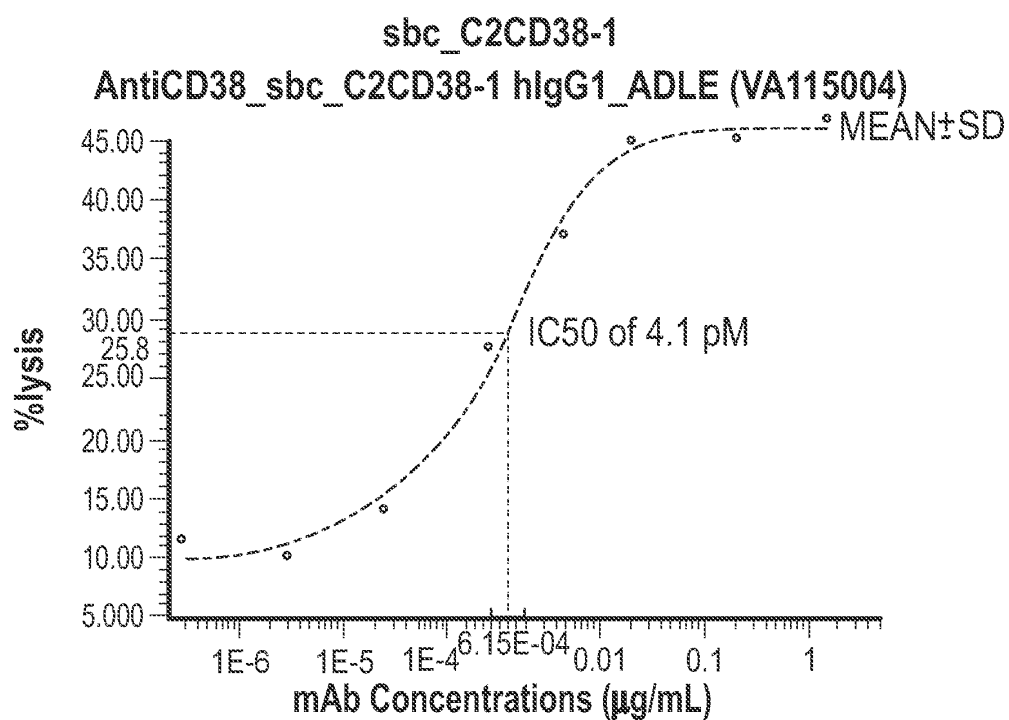


FIG. 2K

**FIG. 2L**

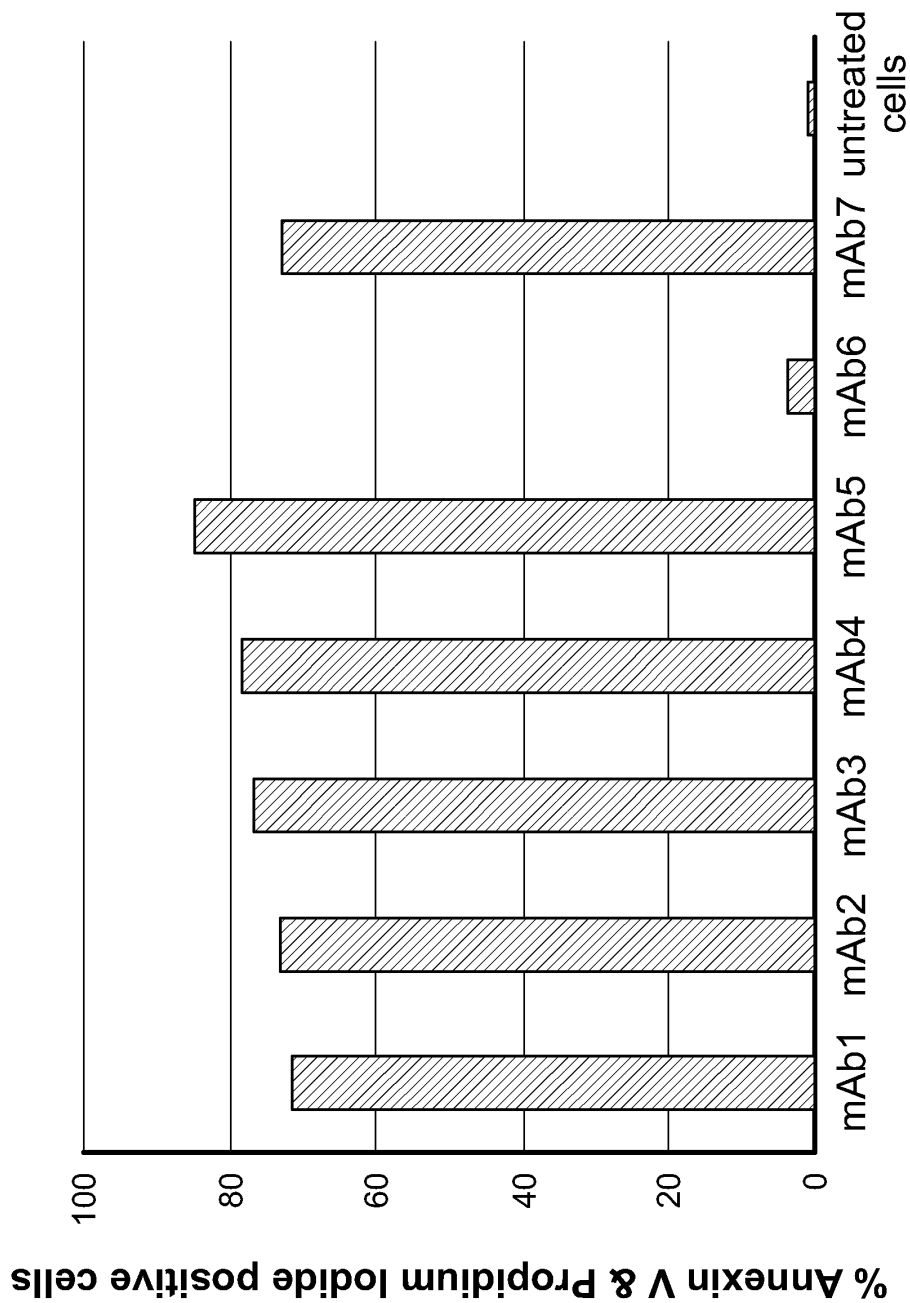
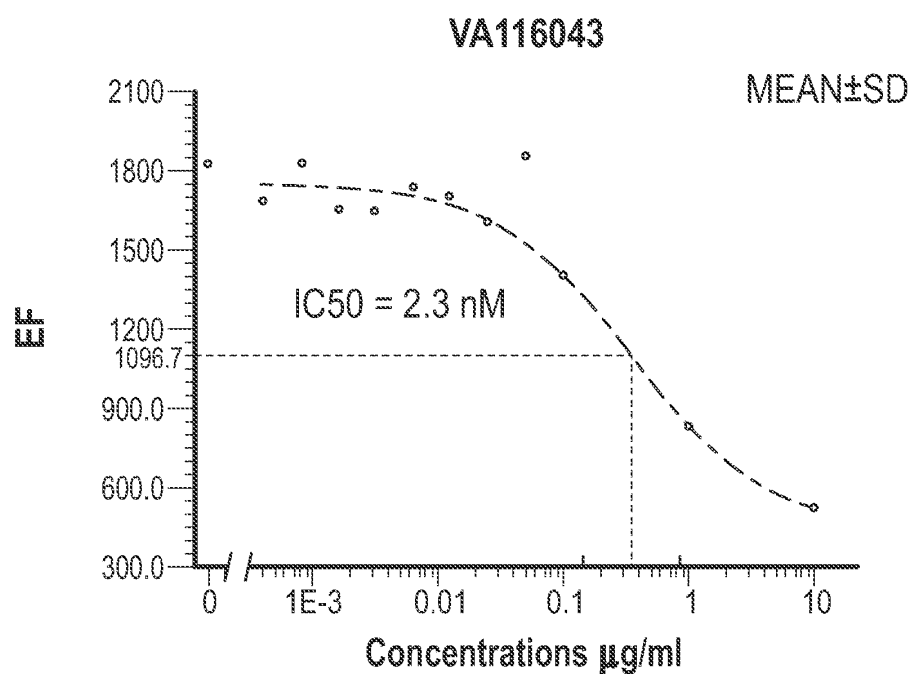
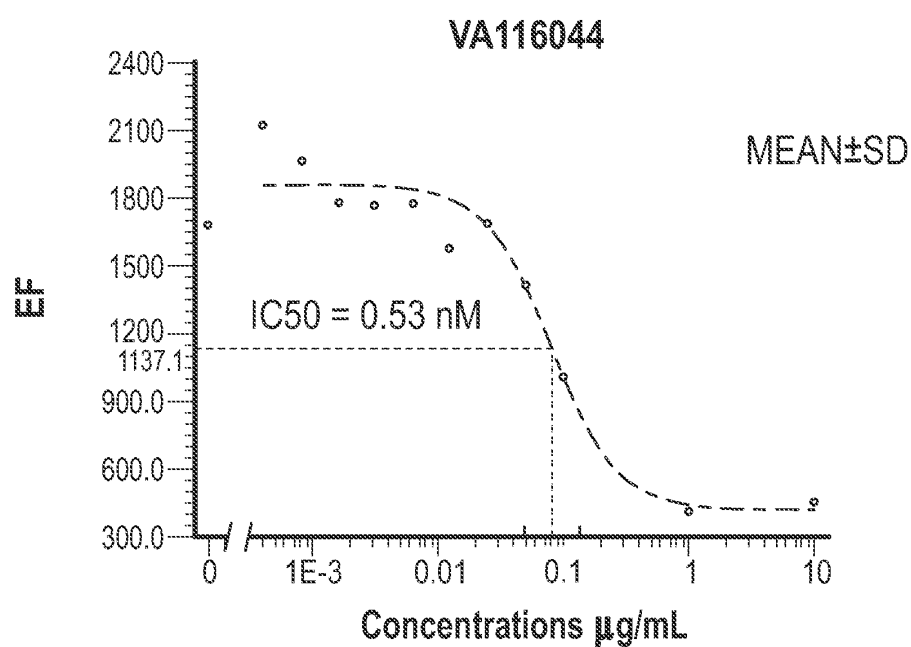
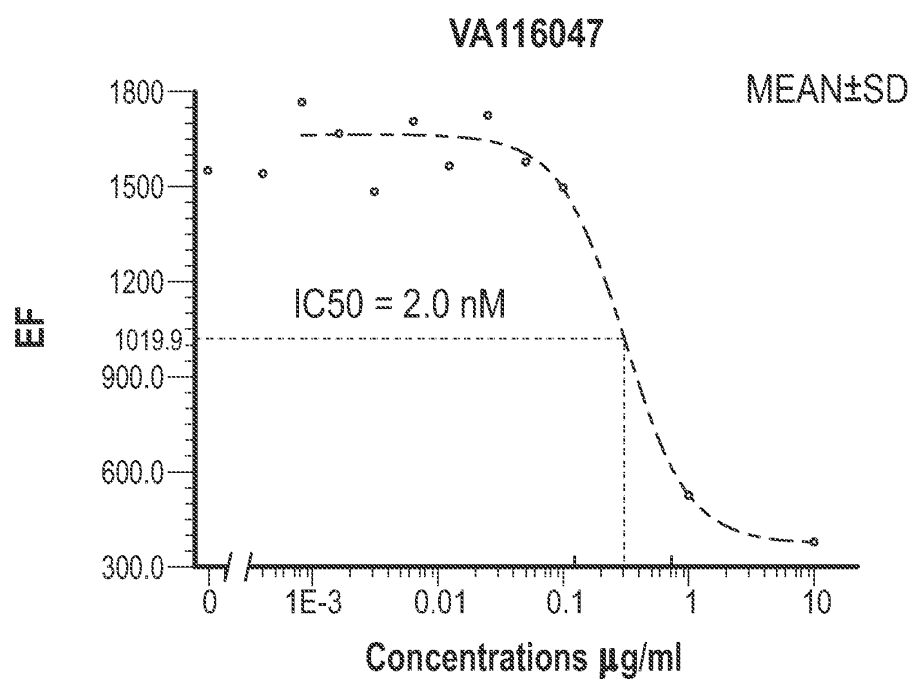
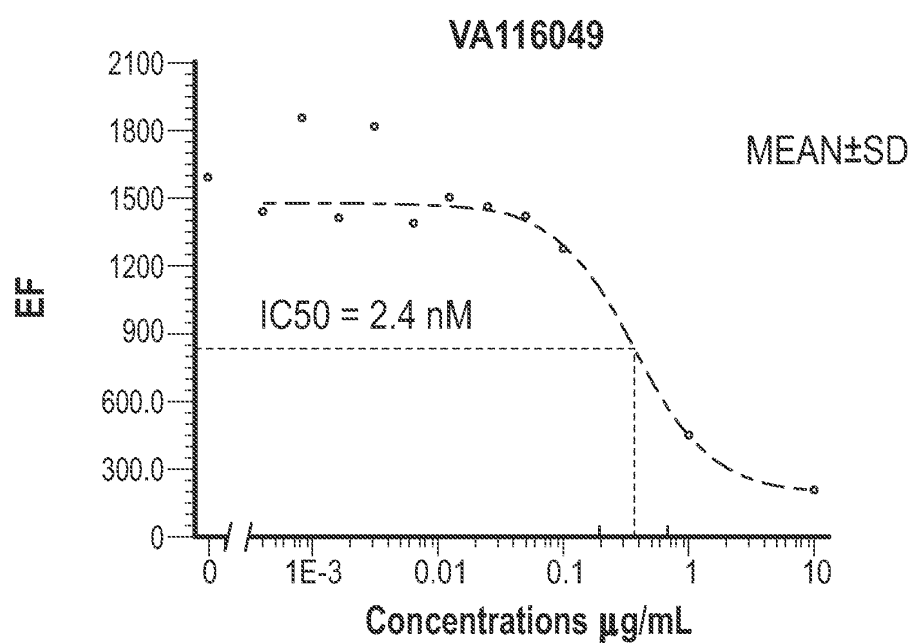


FIG. 2M

**FIG. 2N****FIG. 2O**

**FIG. 2P****FIG. 2Q**

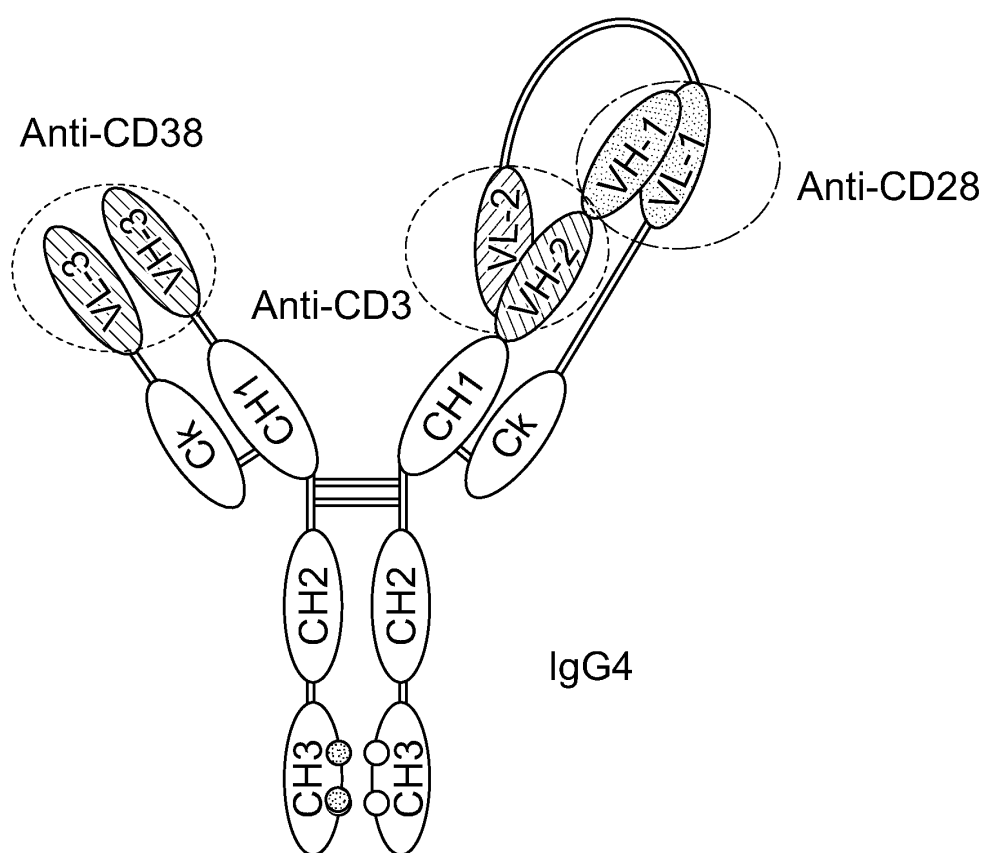


FIG. 3A

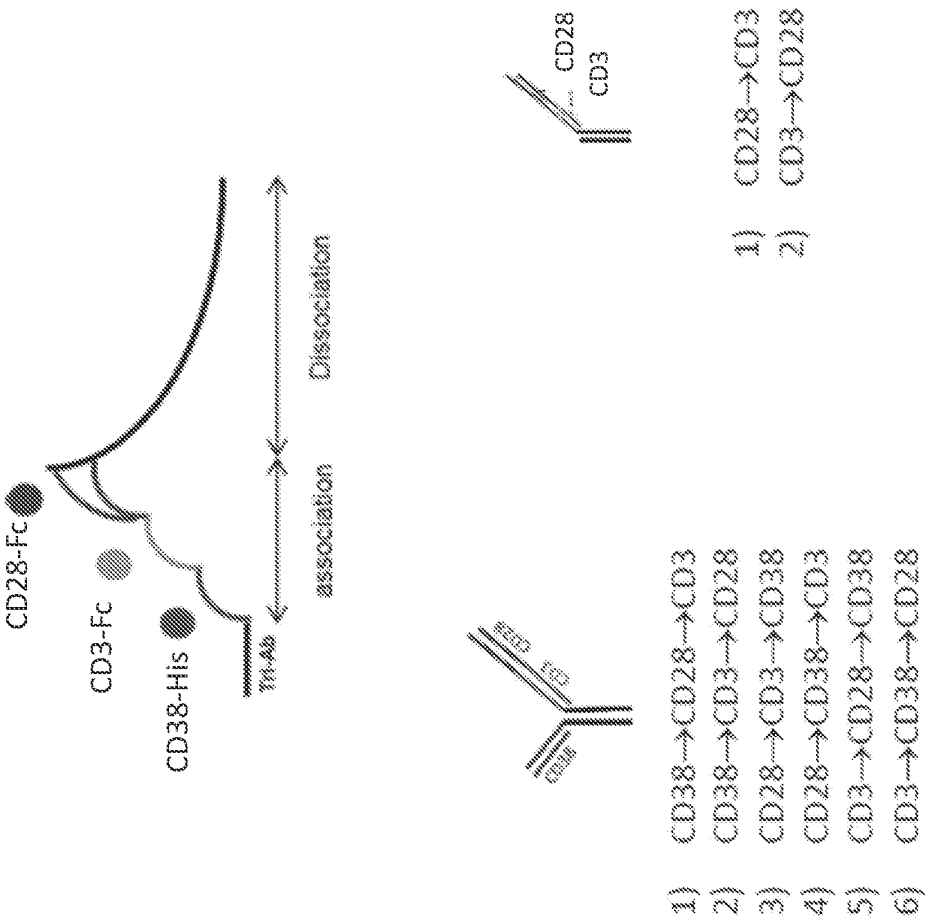


FIG. 3B

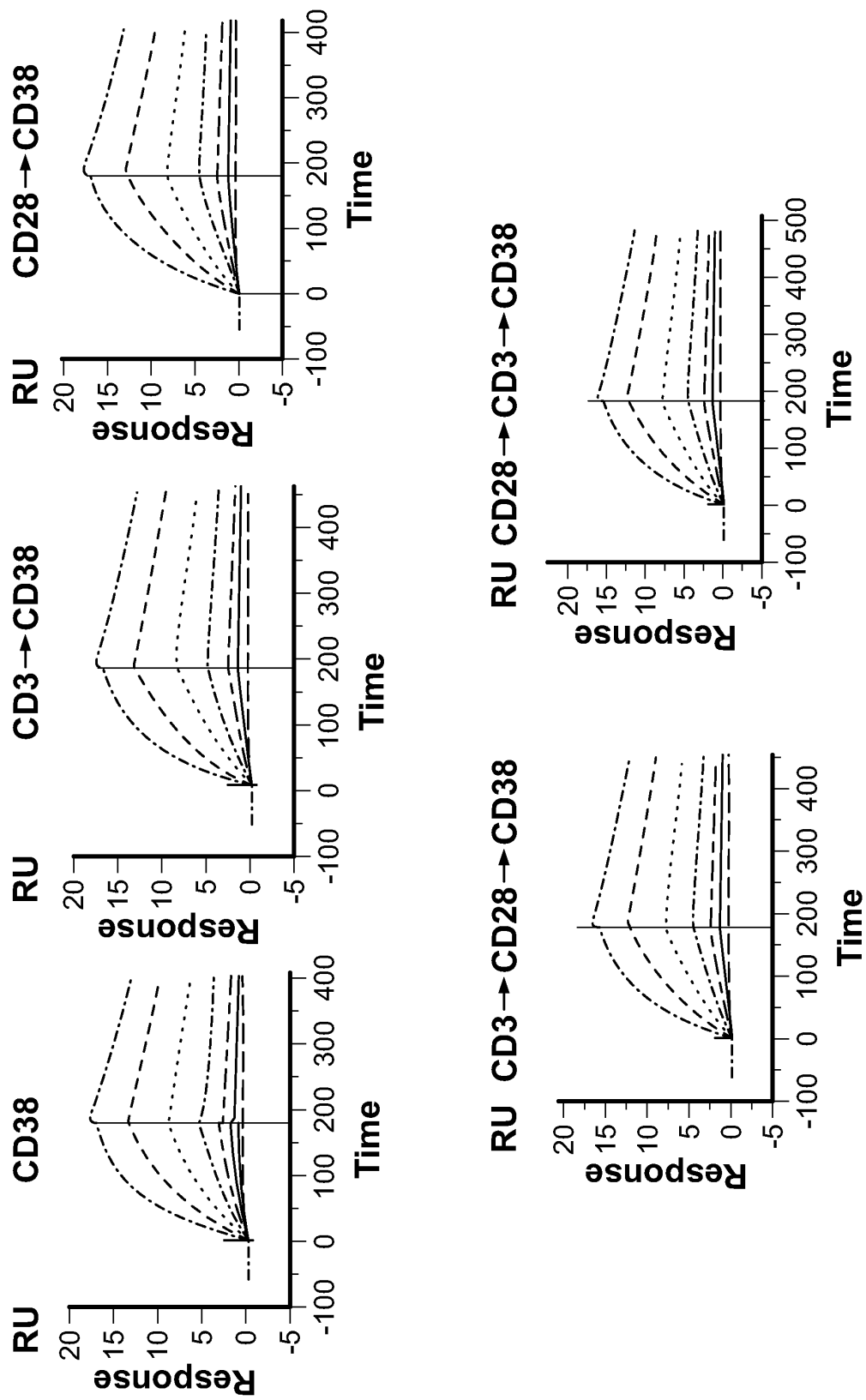


FIG. 3C

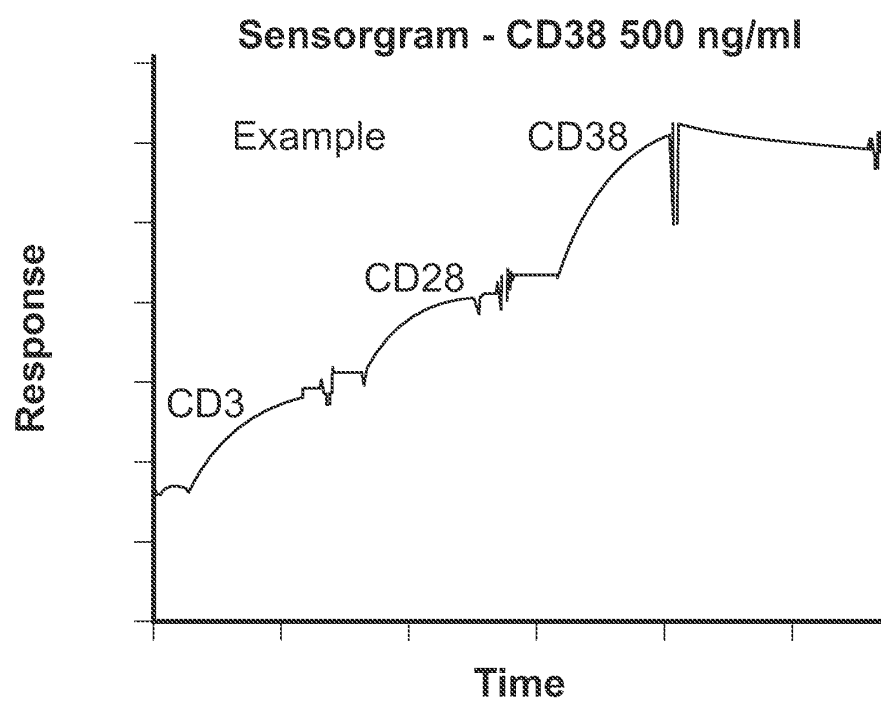


FIG. 4

Affinity of WT TsAbs for individual targets (K_D round up to integer)

TsAbs	CD38	CD28	CD3	Affinity order ranking
CD38 _{SB19} CD28 _{sup} CD3 _{mid}	2 nM	3 nM	23 nM	• CD38 binding: MsAb $\approx$ TsAbs • CD28 binding: MsAb > TsAb $\geq$ BsAbs • CD3 binding: MsAb $\approx$ BsAb $\approx$ TsAb
CD38 _{SB19} CD28 _{cvn} CD3 _{mid}	2 nM	17 nM	19 nM	
CD38 _{VH1} CD28 _{sup} CD3 _{mid/low}	4/6 nM	2/4 nM	21/76 nM	
CD38 _{VH1} CD28 _{cvn} CD3 _{mid/low}	4/6 nM	18/34 nM	23/59 nM	
CD38 _{HHY1370} CD28 _{sup} CD3 _{mid}	1 nM	5 nM	48 nM	
CD38 _{HHY1370} CD28 _{cvn} CD3 _{mid}	1 nM	19 nM	44 nM	

Impact of multi-target binding to CD38_{SB19} CD28_{sup} CD3_{mid}

State of TsAb	CD38	CD28	CD3	Comments
Single target	2 nM	3 nM	23 nM	Fast kinetics of CD3 binding when all targets are present
All targets	2 nM	4 nM	19 nM	

FIG. 5

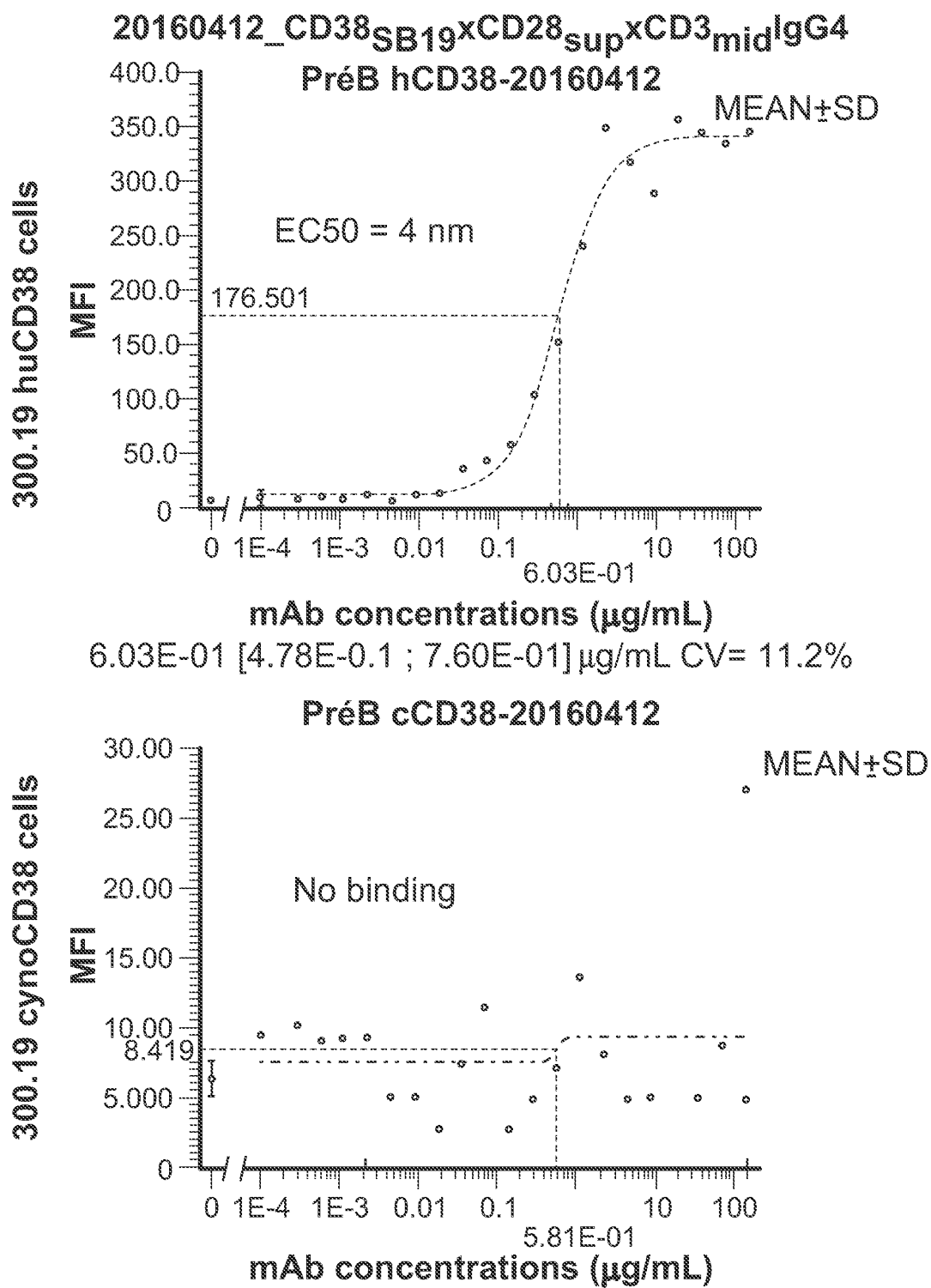


FIG. 6A

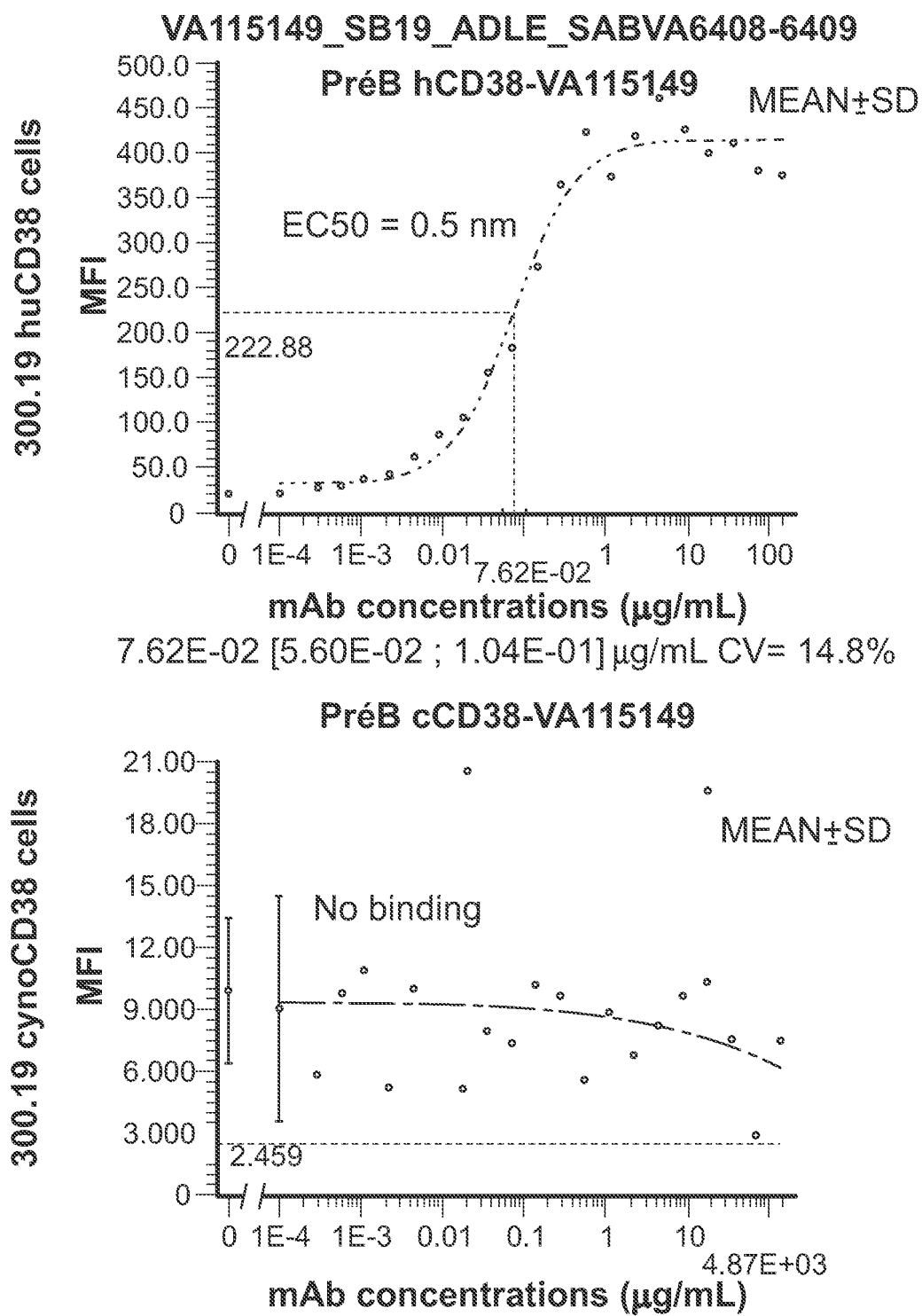


FIG. 6A (Cont.)

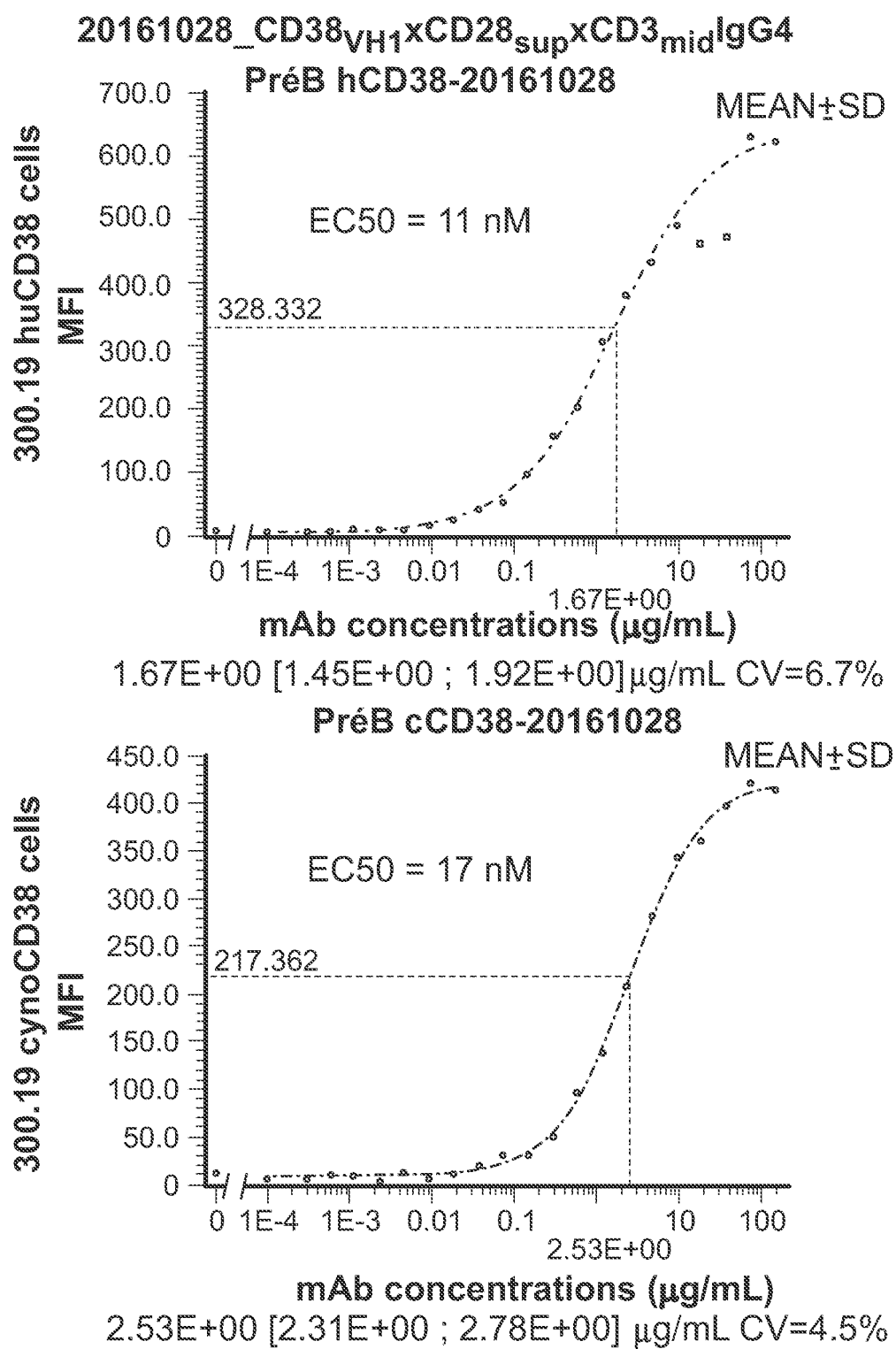


FIG. 6B

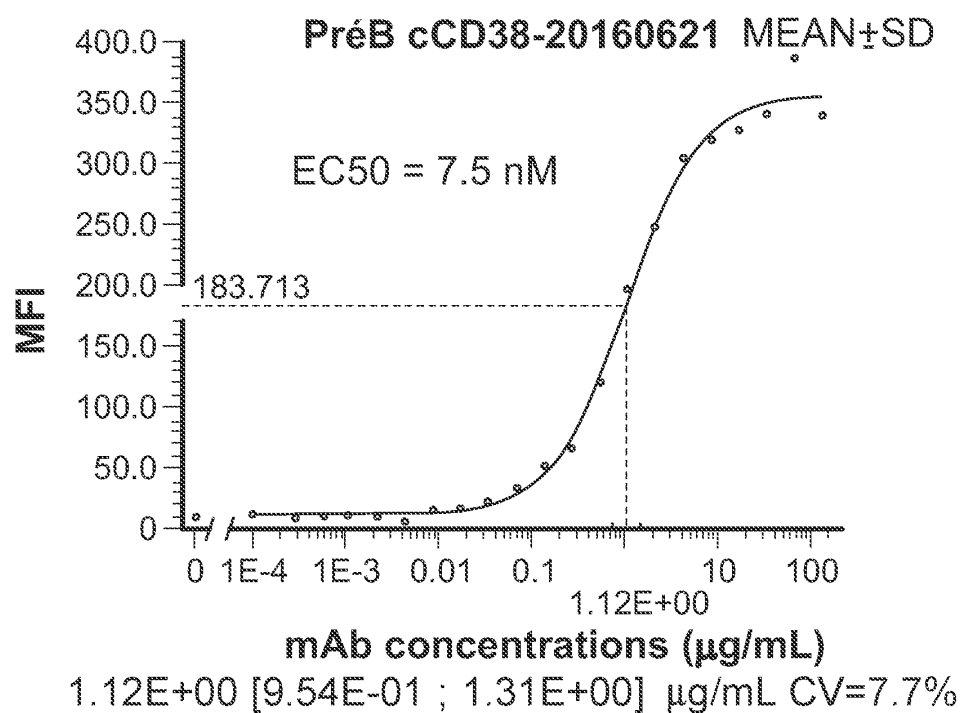
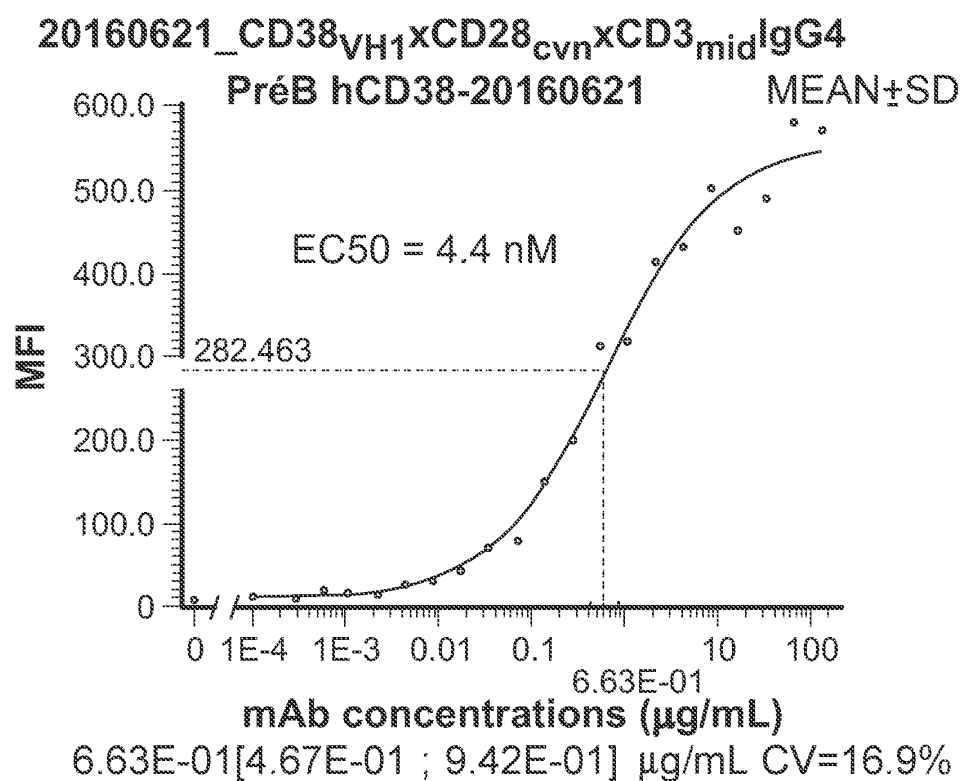


FIG. 6C

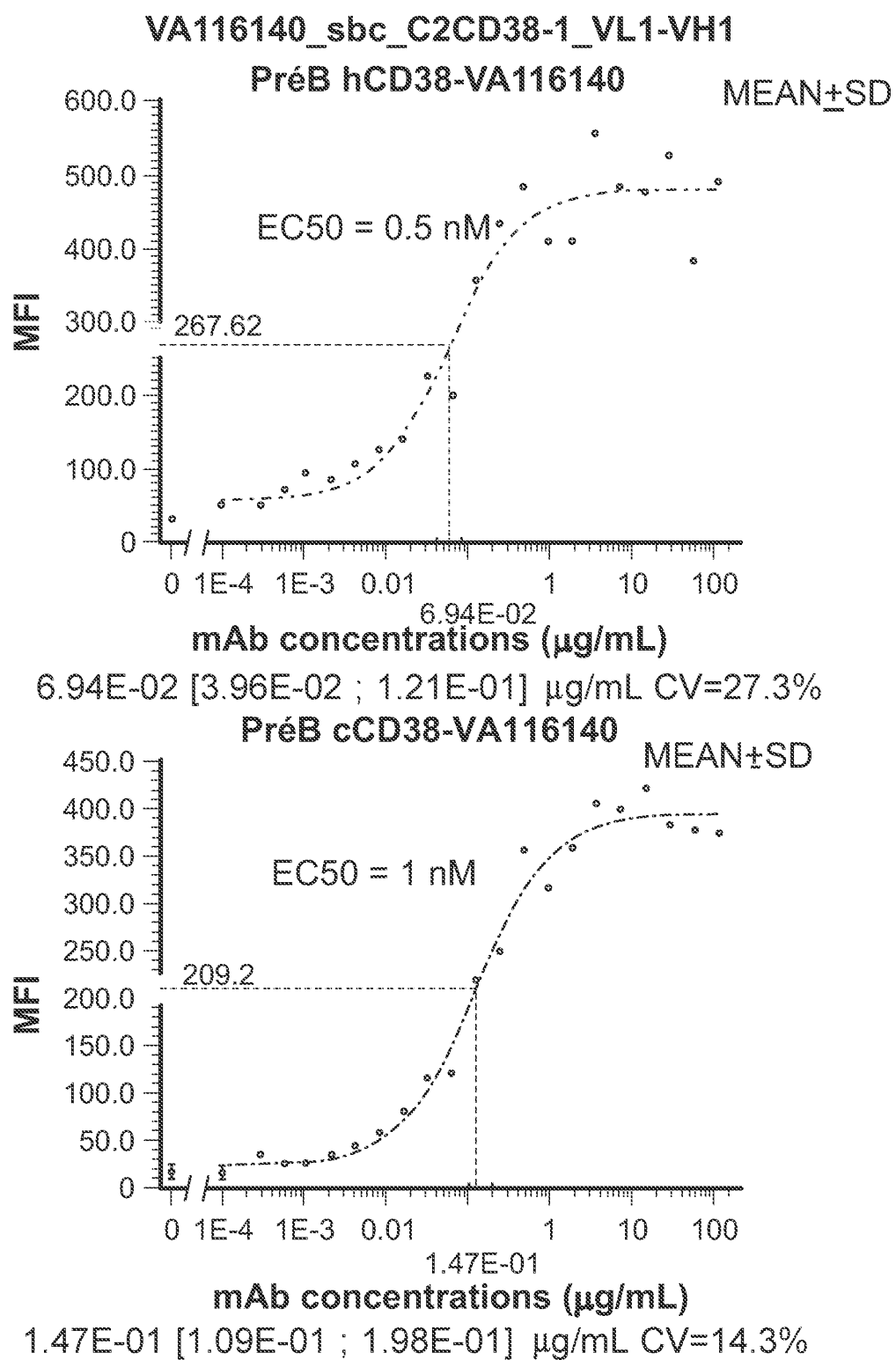


FIG. 6D

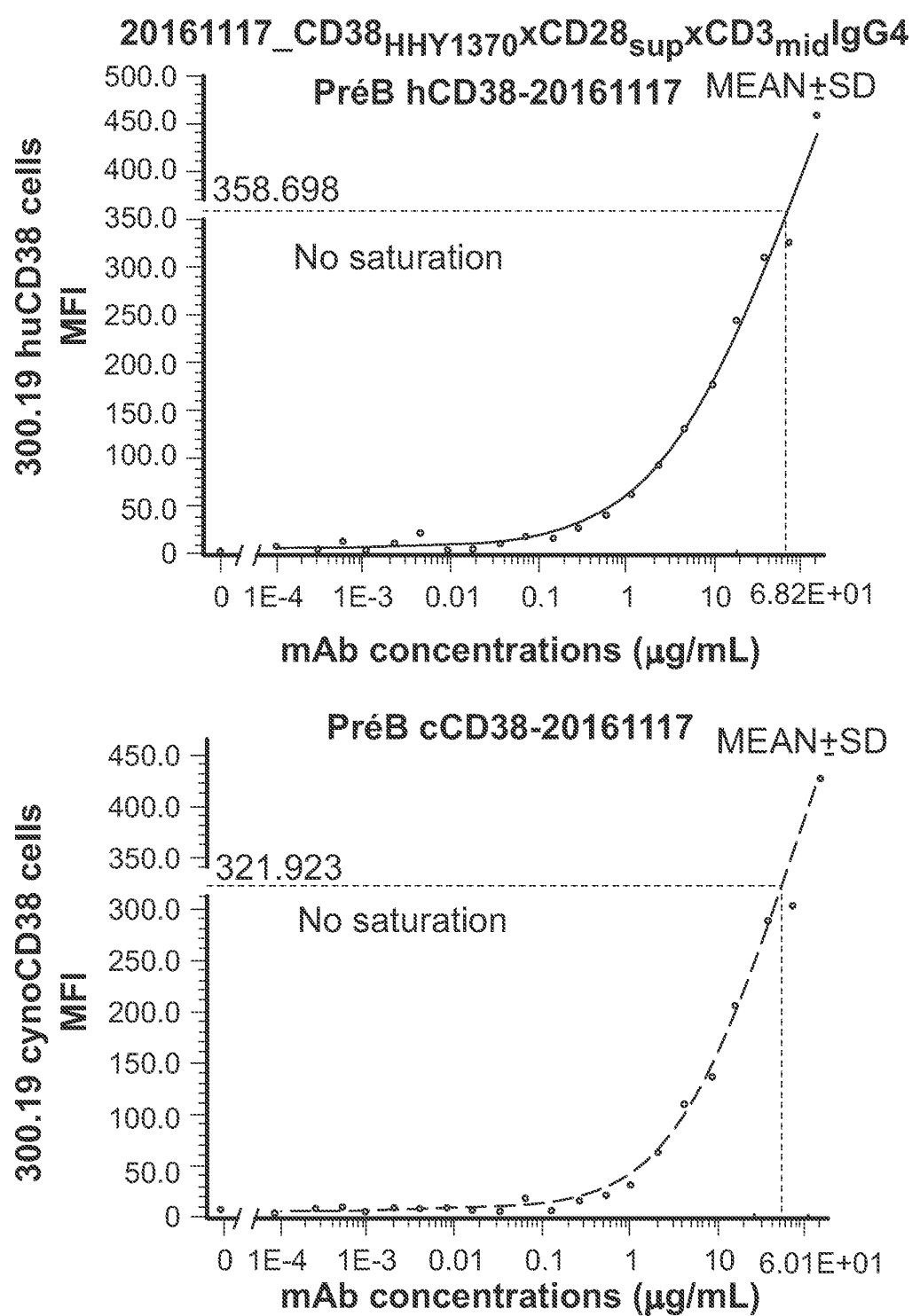


FIG. 6E

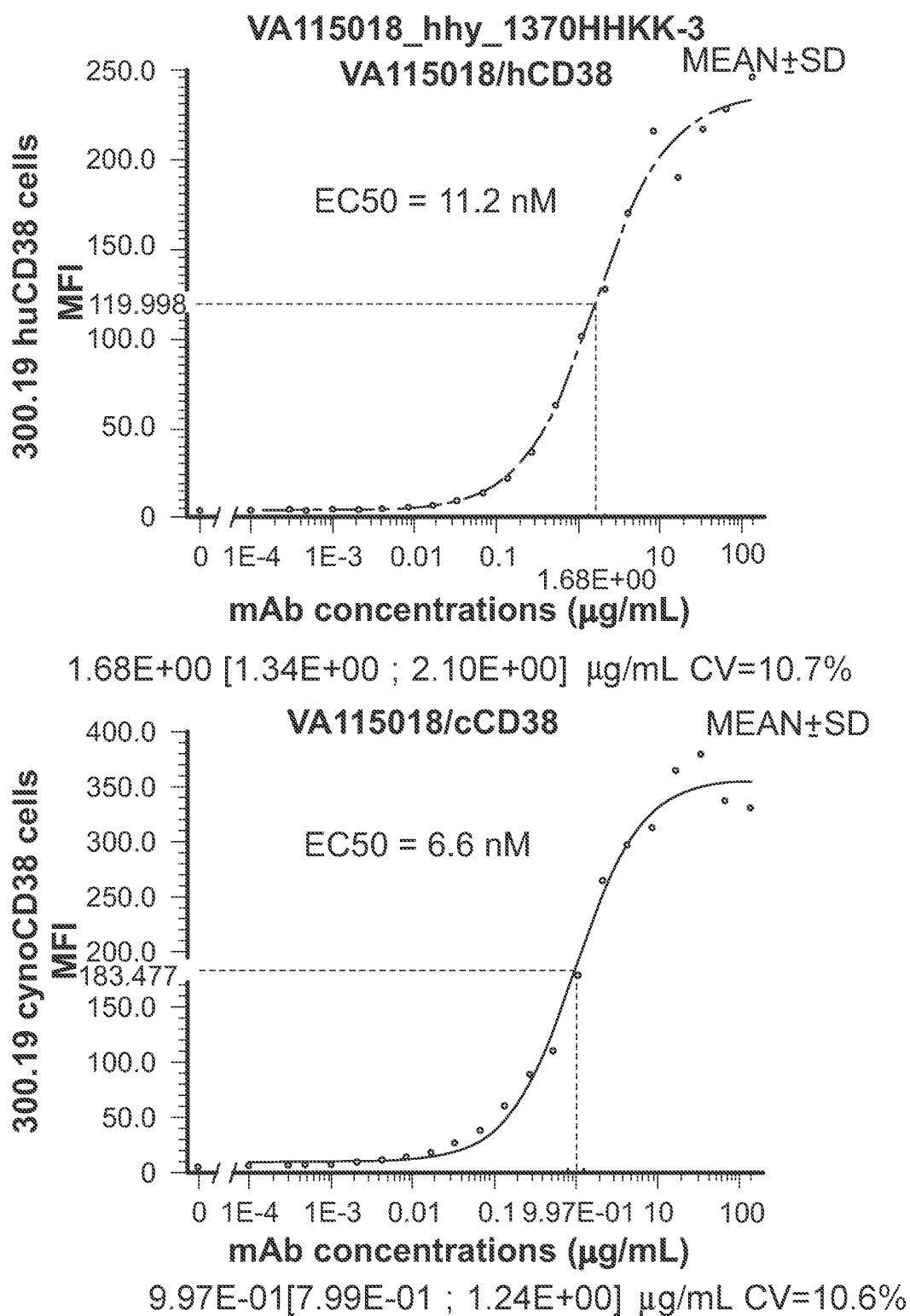


FIG. 6E (Cont.)

TsAbs	¹ KD value against rec. protein by SPR (nM)	² Apparent KD value against rec. cells by FACS (nM)
CD38 _{SB19} CD28 _{sup} CD3 _{mid}	2	4
CD38 _{VH1} CD28 _{sup} CD3 _{mid/low}	4/6	1.1
CD38 _{VH1} CD28 _{con} CD3 _{mid/low}	4/6	4.4
CD38 _{HHY1370} CD28 _{sup} CD3 _{mid}	1	no accurate EC50 value could be estimated (no saturation)

FIG. 6F

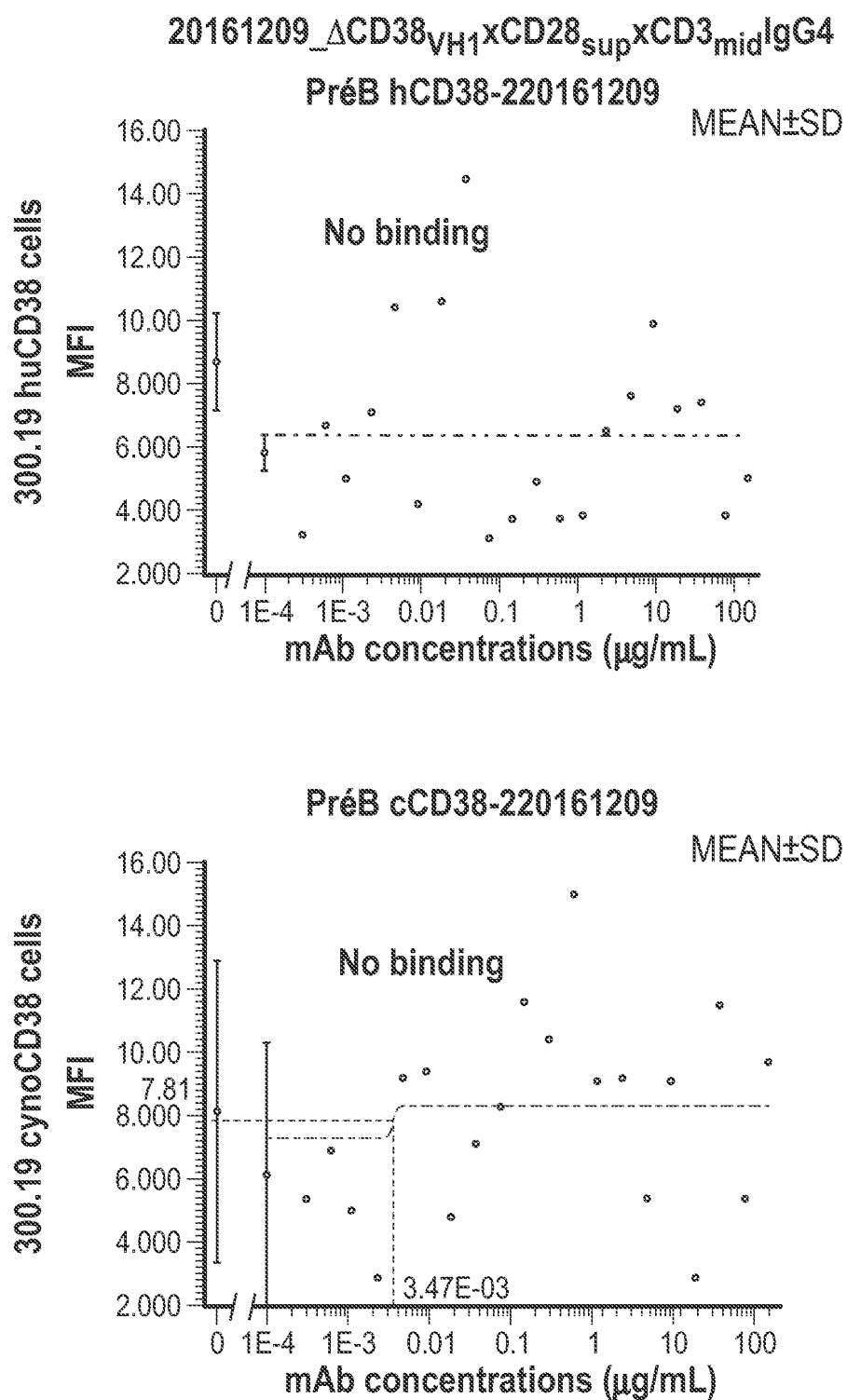


FIG. 6G

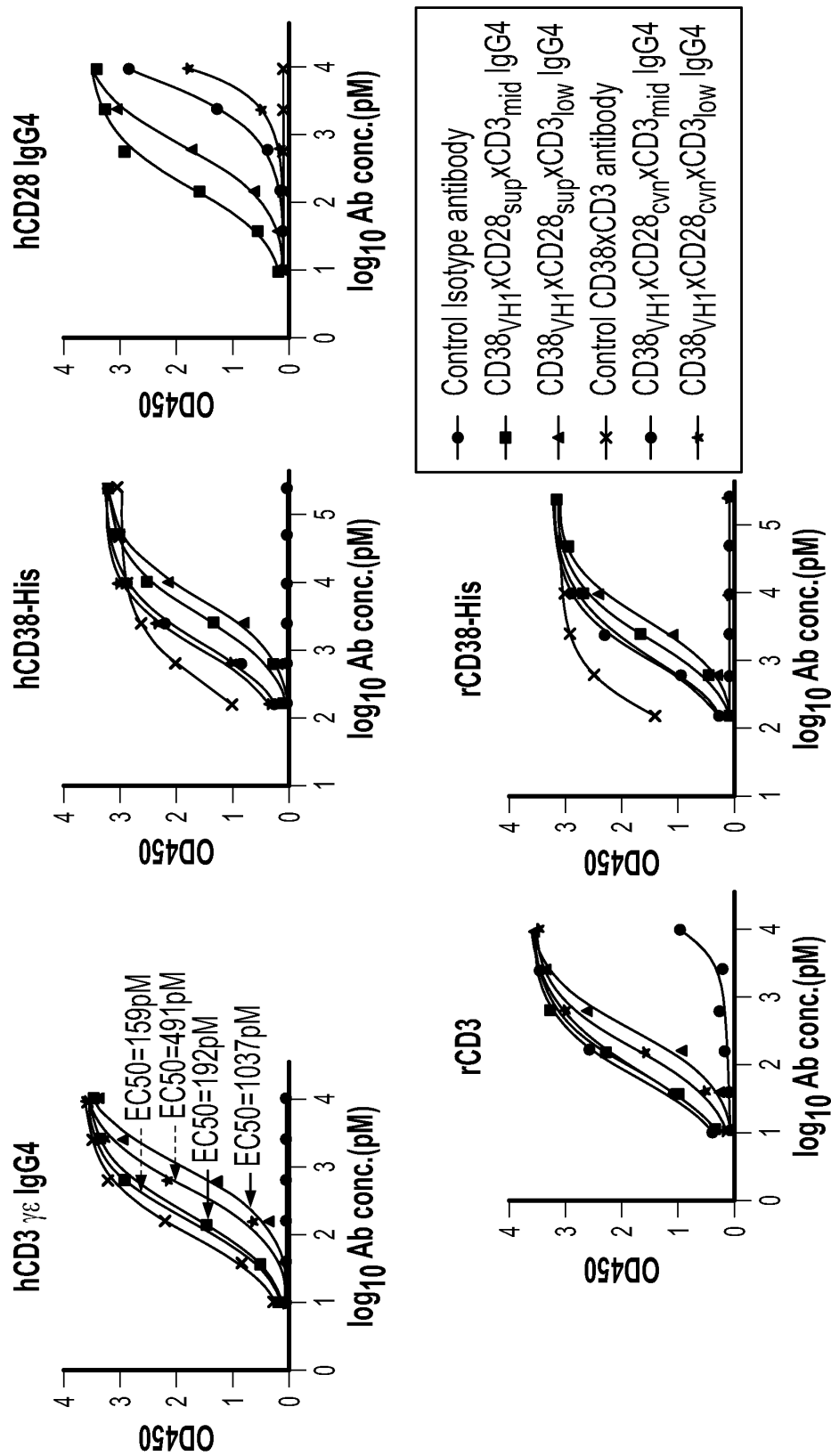


FIG. 7A

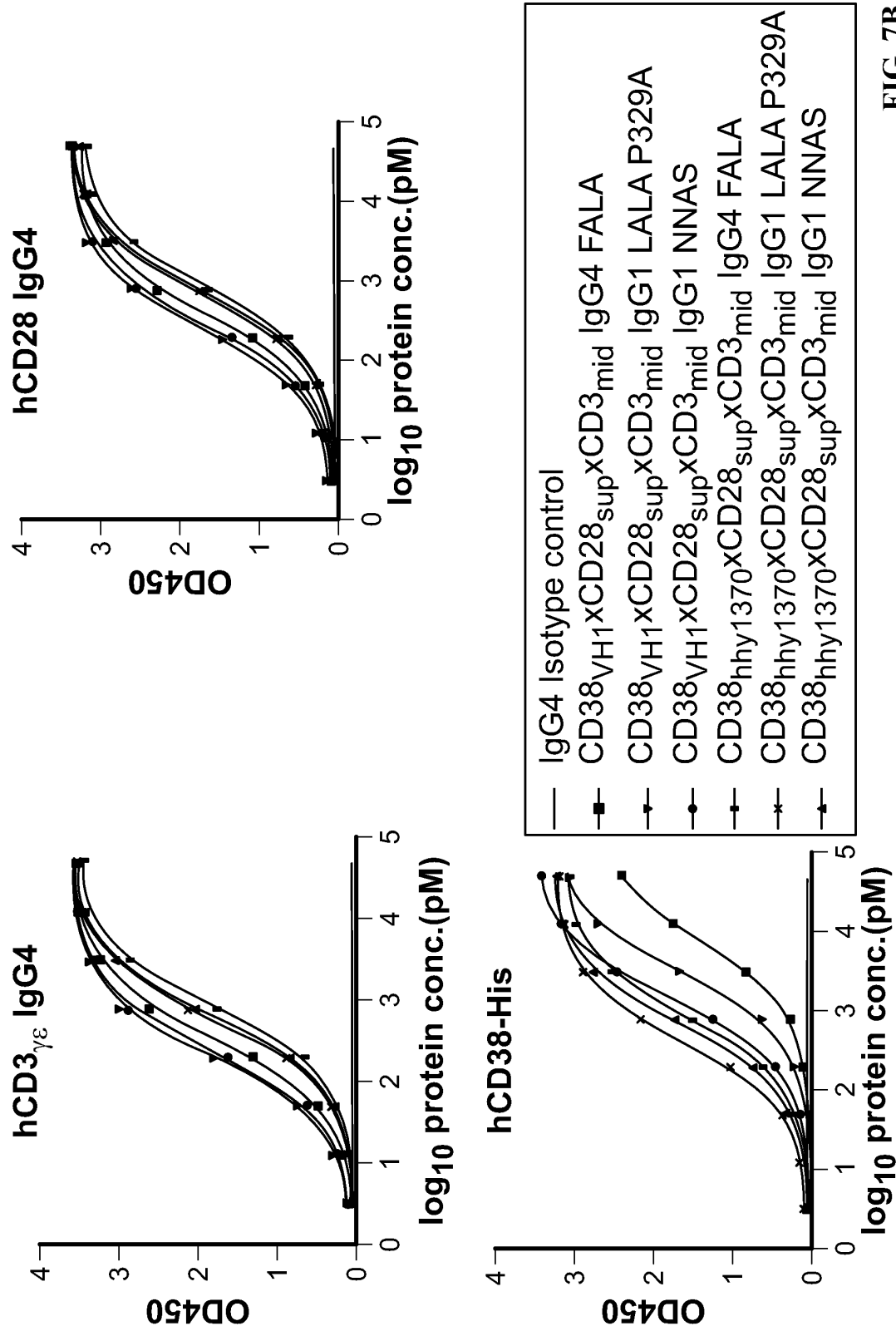


FIG. 7B

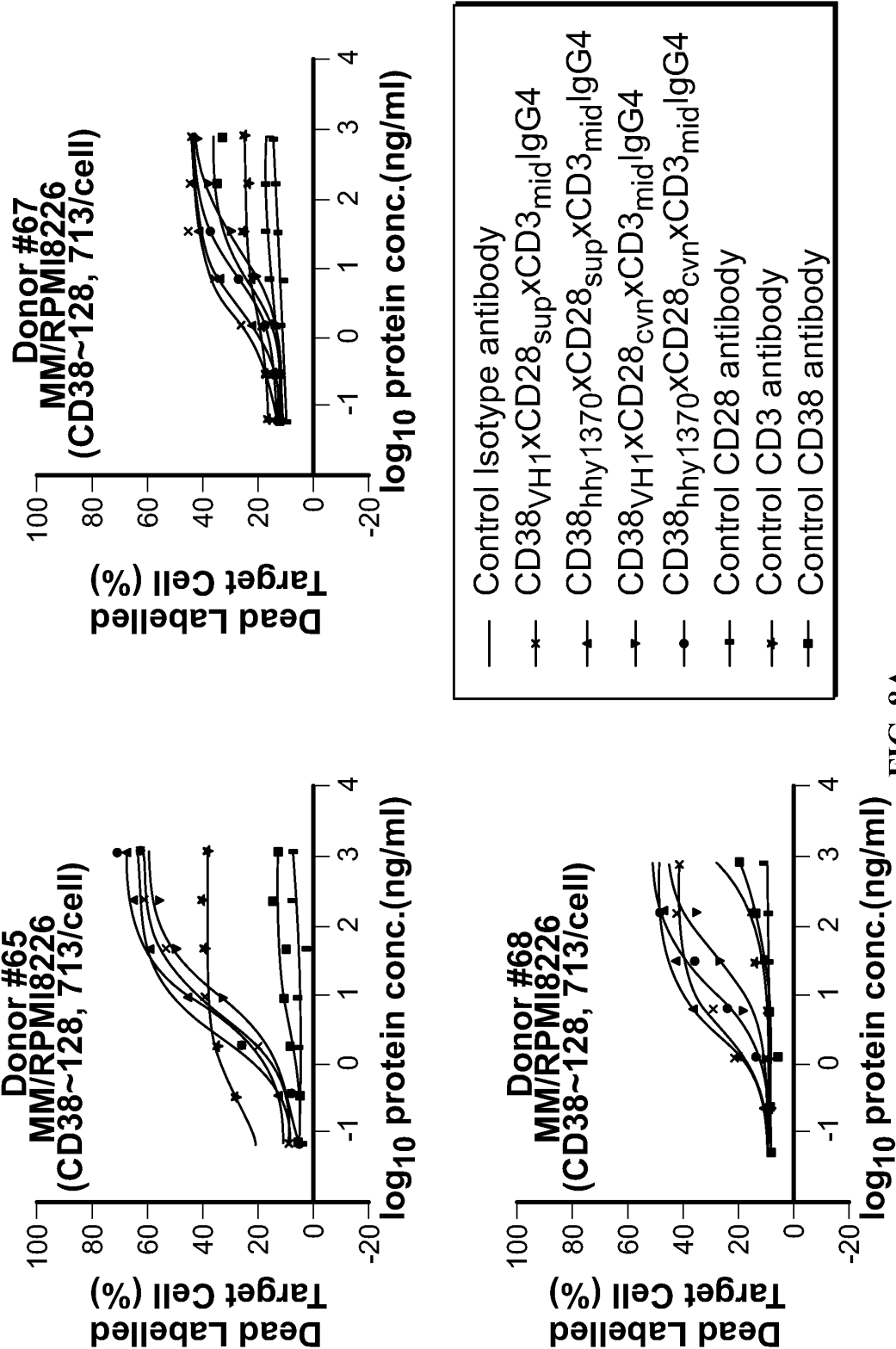


FIG. 8A

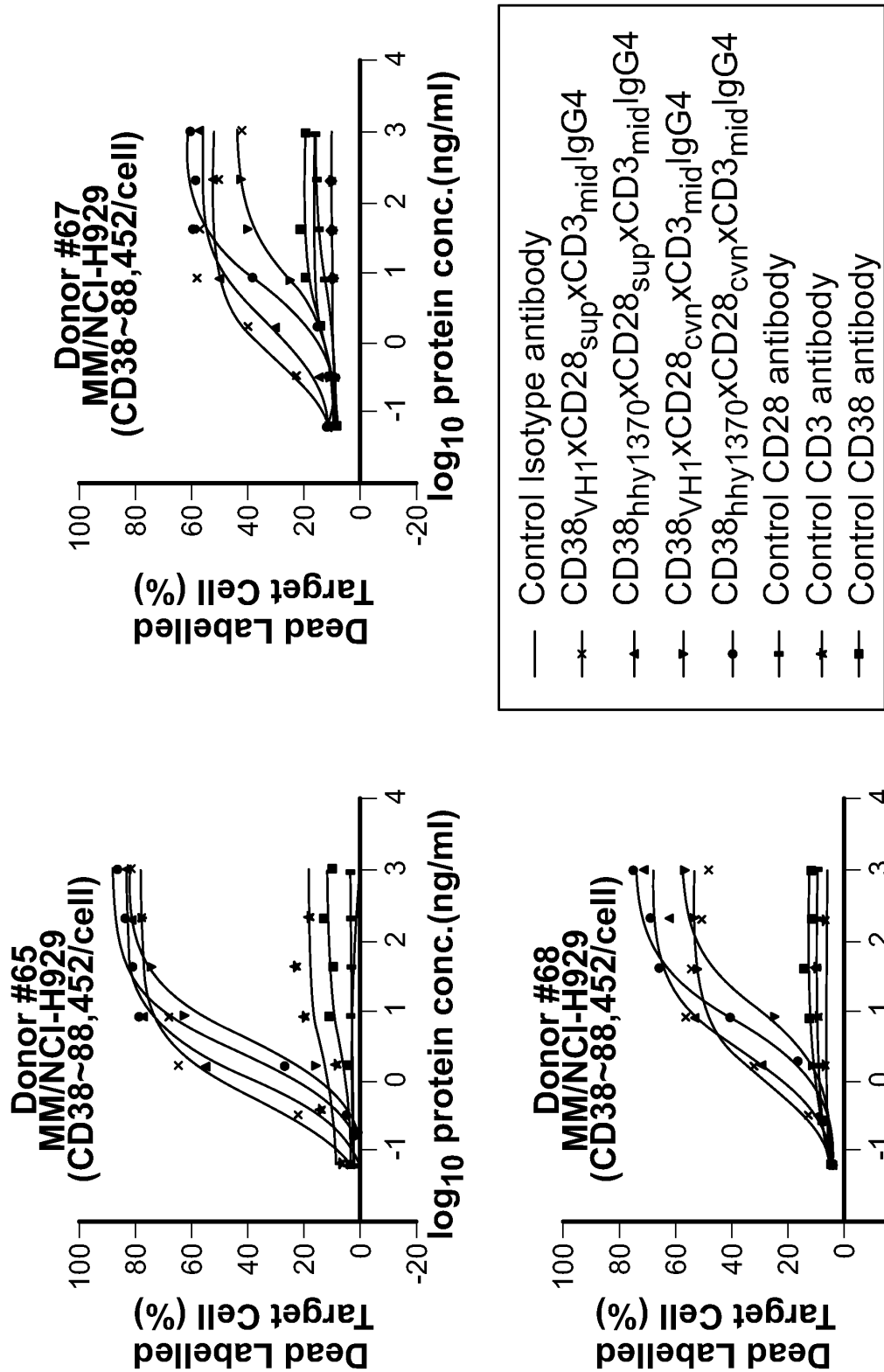


FIG. 8B

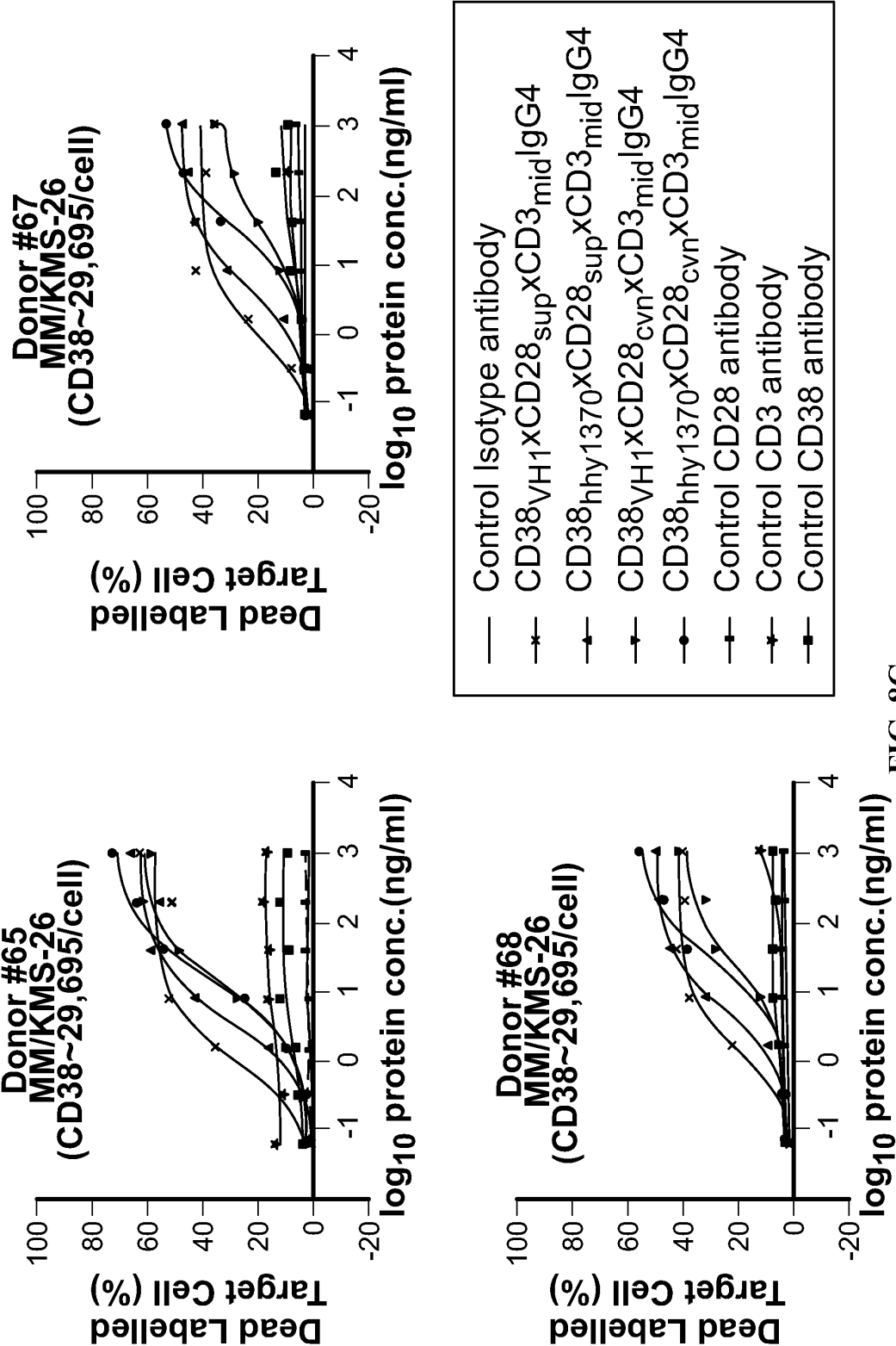


FIG. 8C

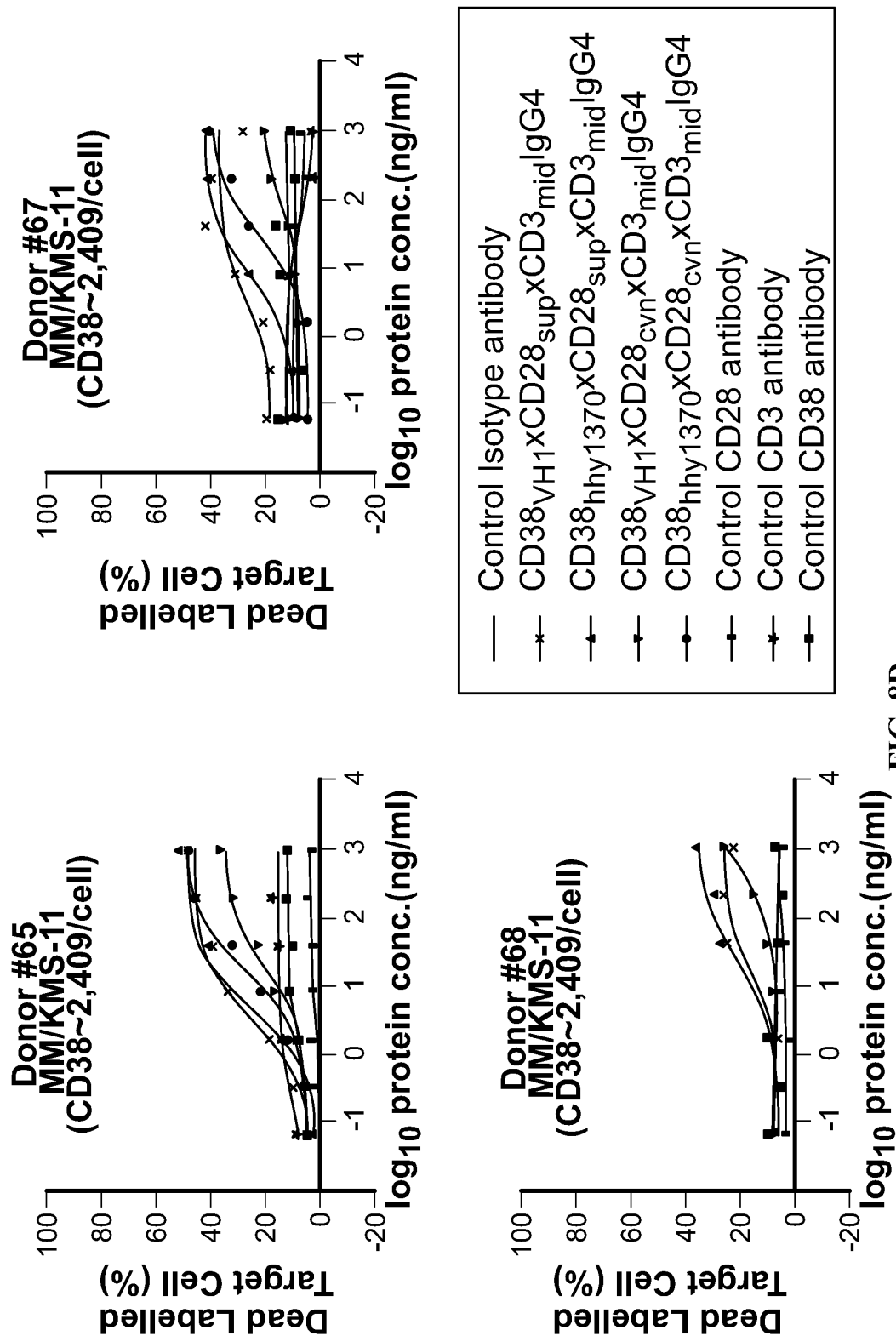
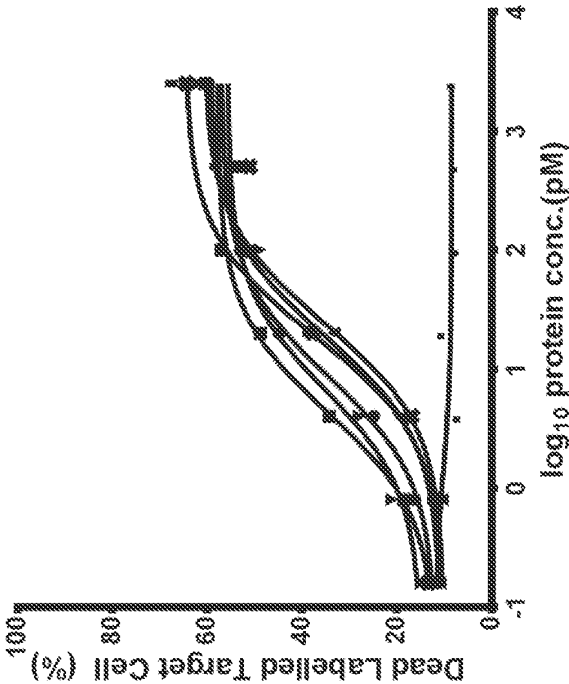
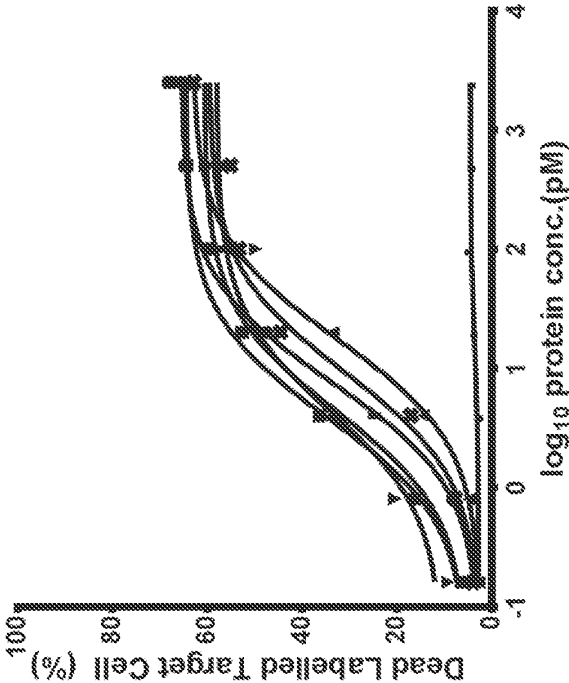


FIG. 8D

Donor2: KP50904



Donor1: KP50901



- lgG4 Isotype control
- CD38_{VH1}xCD28_{sup}xCD3_{mid} lgG4 FALA
- CD38_{VH1}xCD28_{sup}xCD3_{mid} lgG1 LALA P329A
- CD38_{VH1}xCD28_{sup}xCD3_{mid} lgG1 NNAS
- CD38_{hhy1370}xCD28_{sup}xCD3_{mid} lgG4 FALA
- CD38_{hhy1370}xCD28_{sup}xCD3_{mid} lgG1 LALA P329A
- CD38_{hhy1370}xCD28_{sup}xCD3_{mid} lgG1 NNAS

FIG. 8E

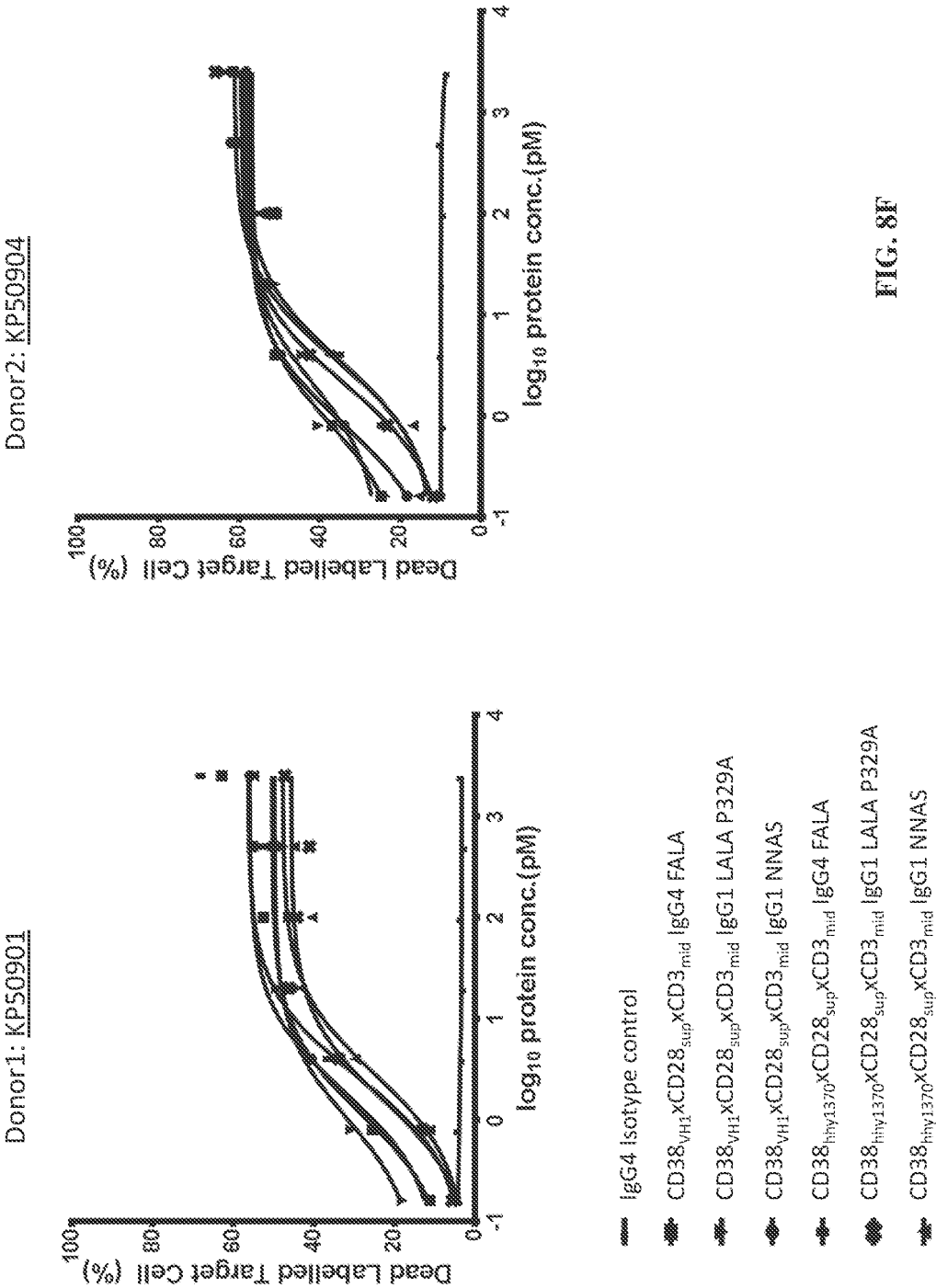


FIG. 8F

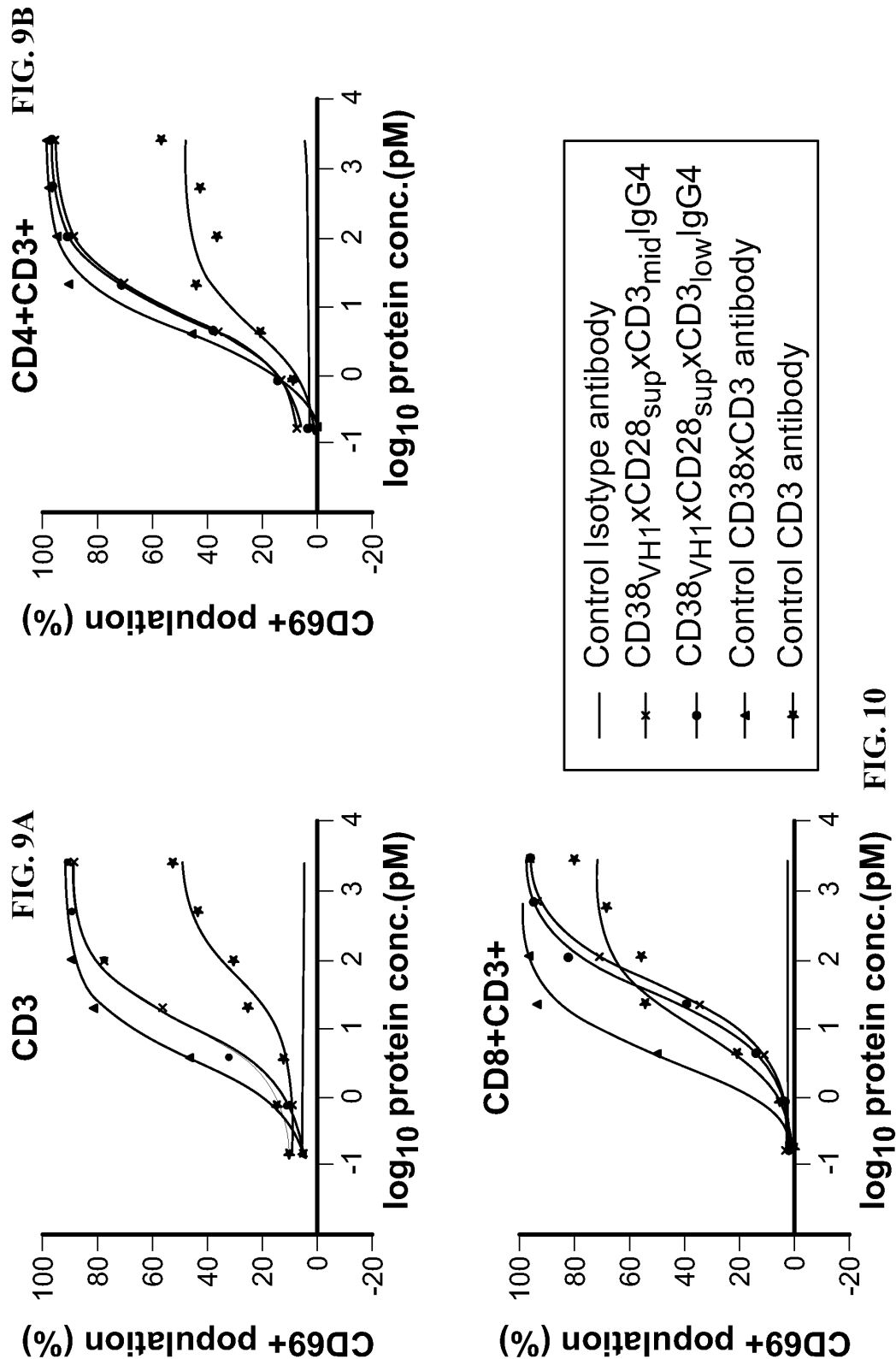


FIG. 10

CD8+CD3+

CD69+ population (%)

log₁₀ protein conc.(pM)

FIG. 10

CD4+CD3+

CD69+ population (%)

log₁₀ protein conc.(pM)

FIG. 11A

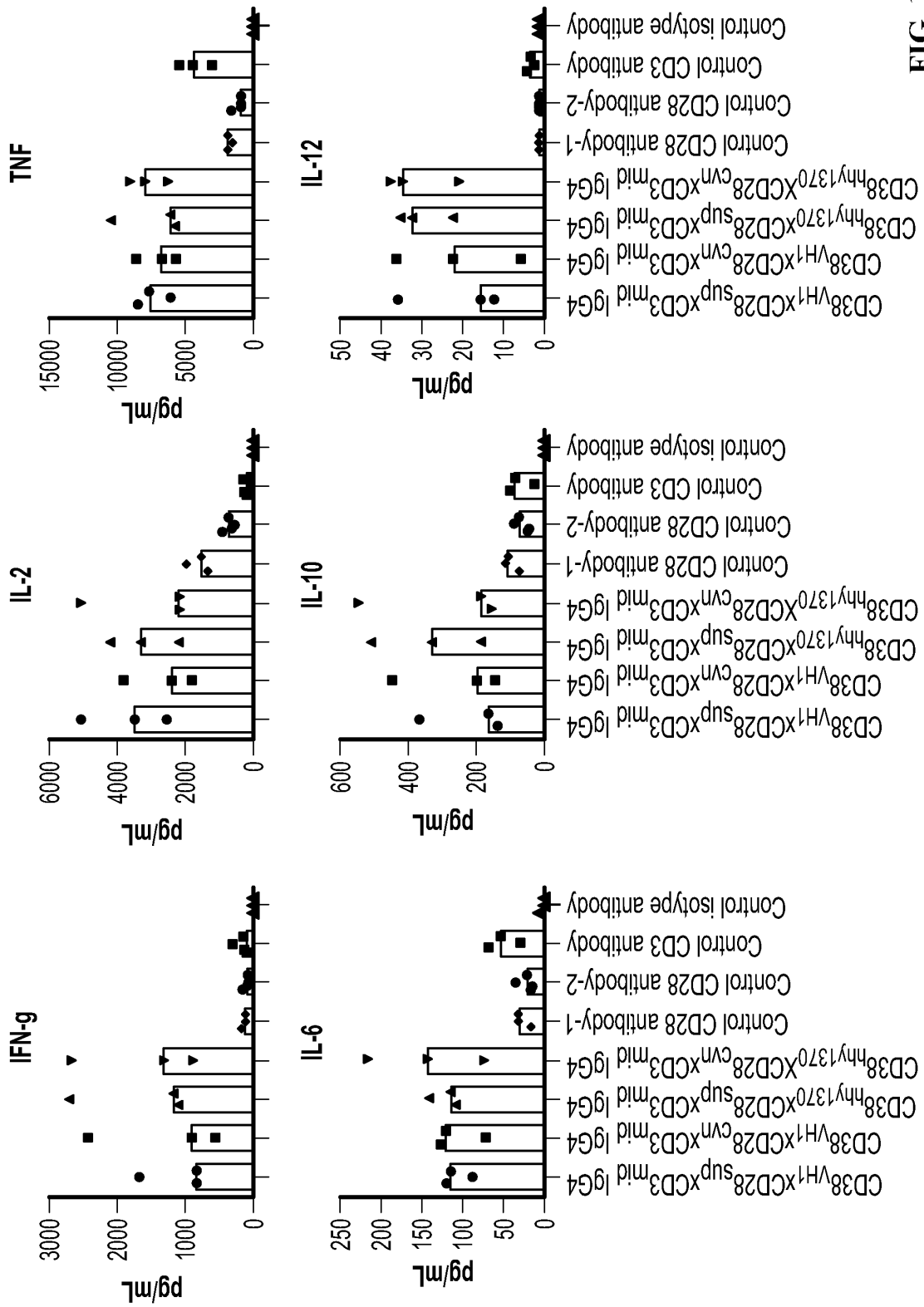
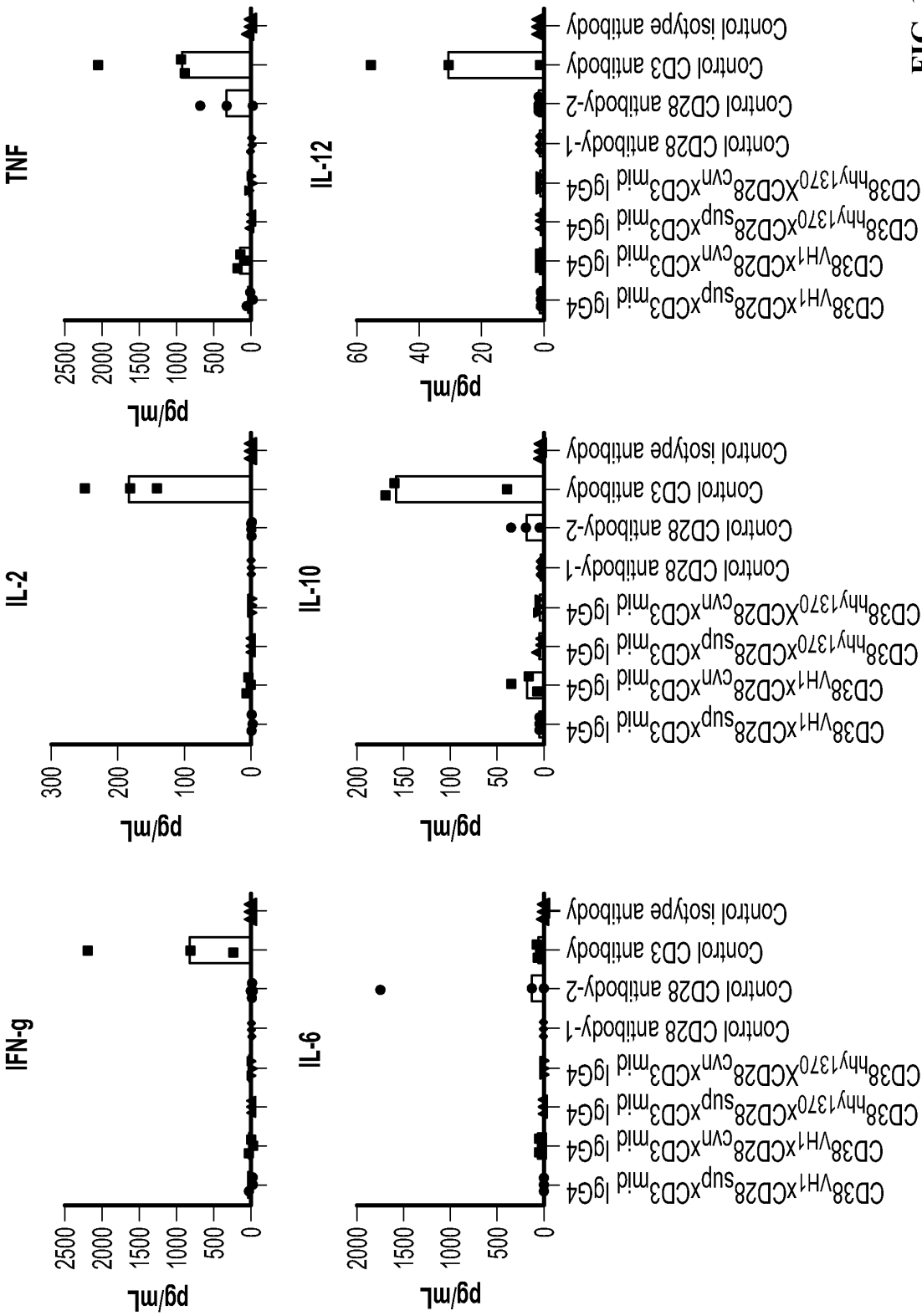


FIG. 11B



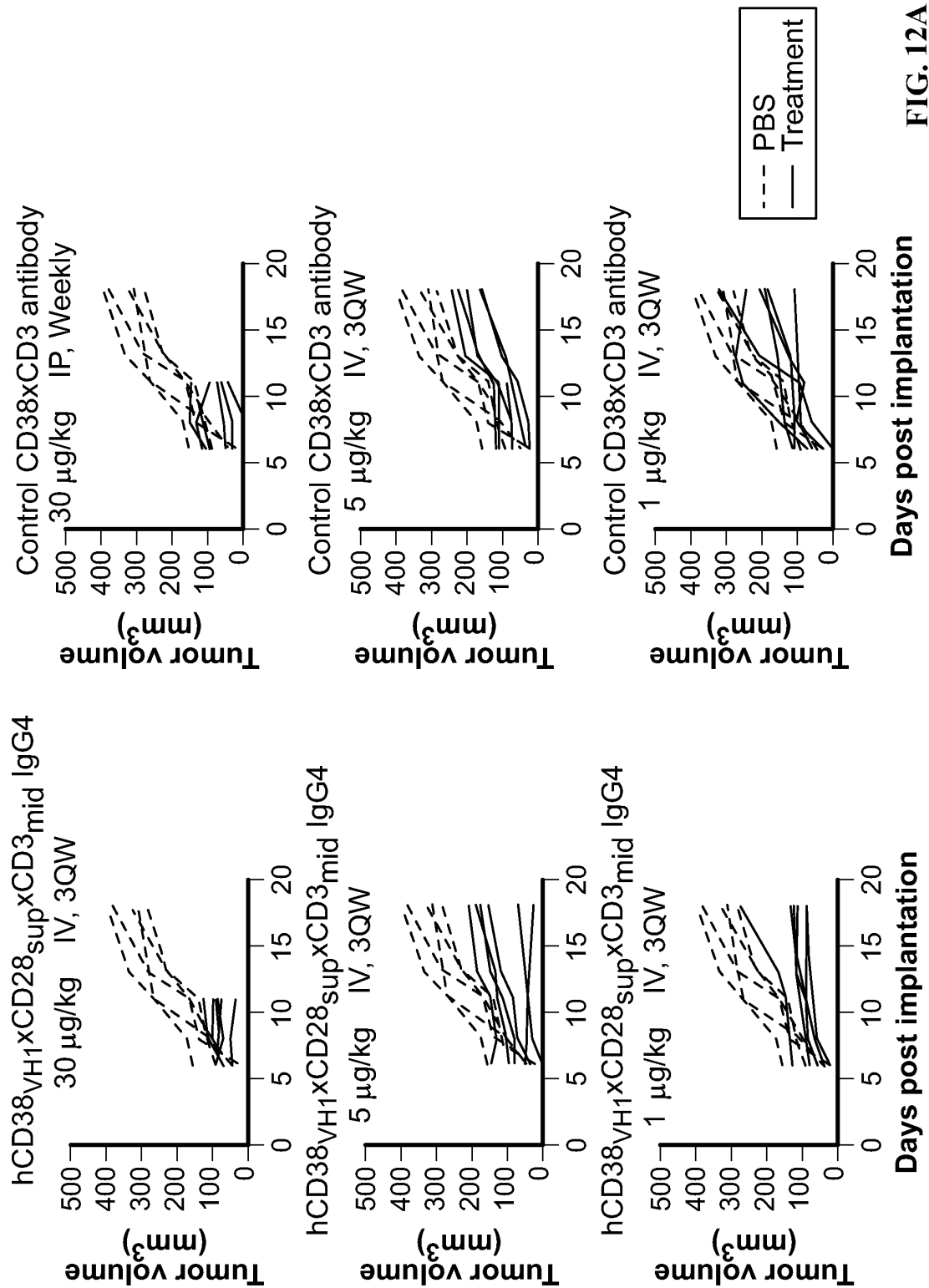


FIG. 12A

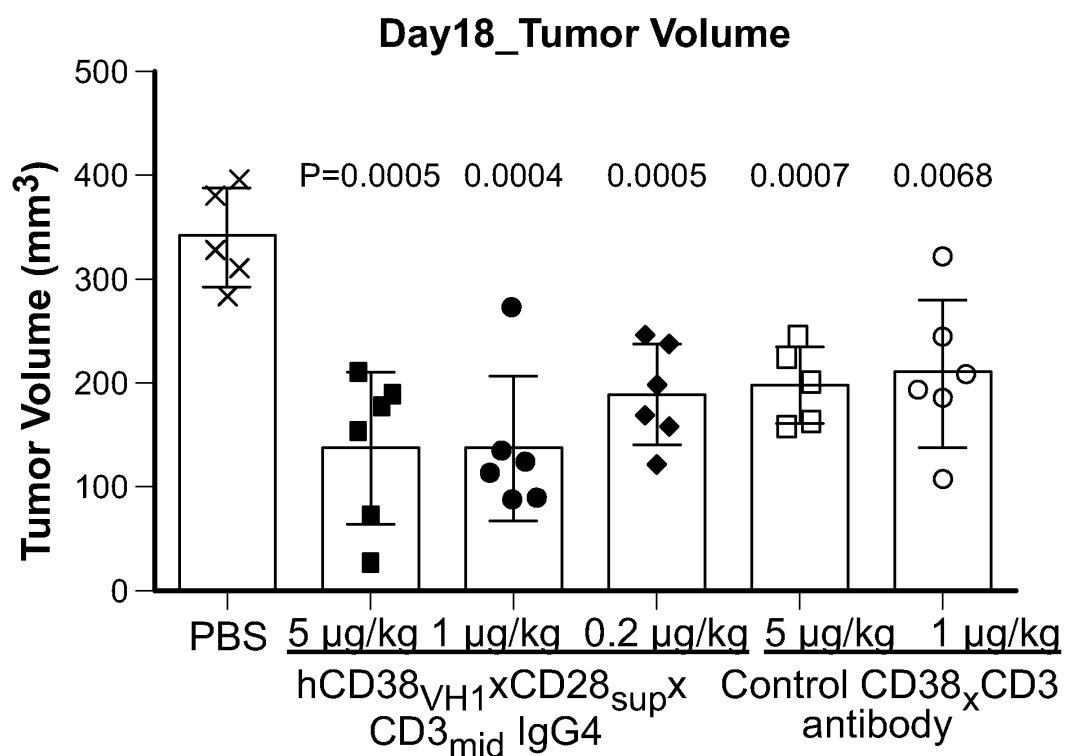


FIG. 12B

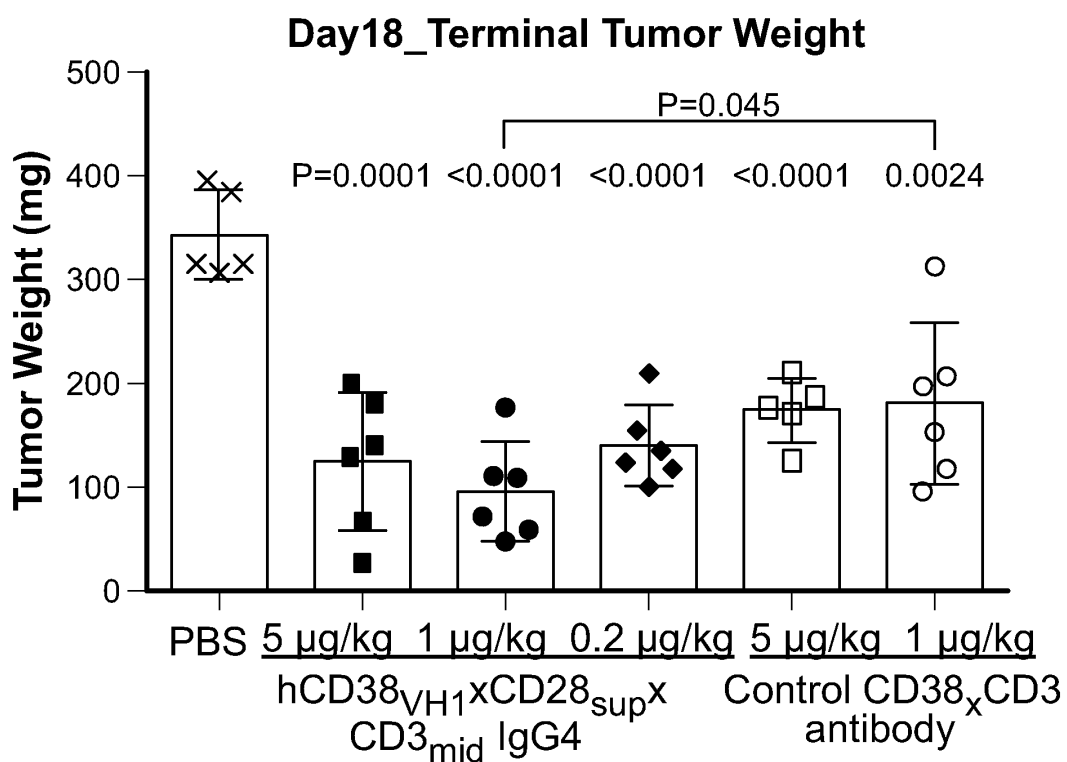


FIG. 12C

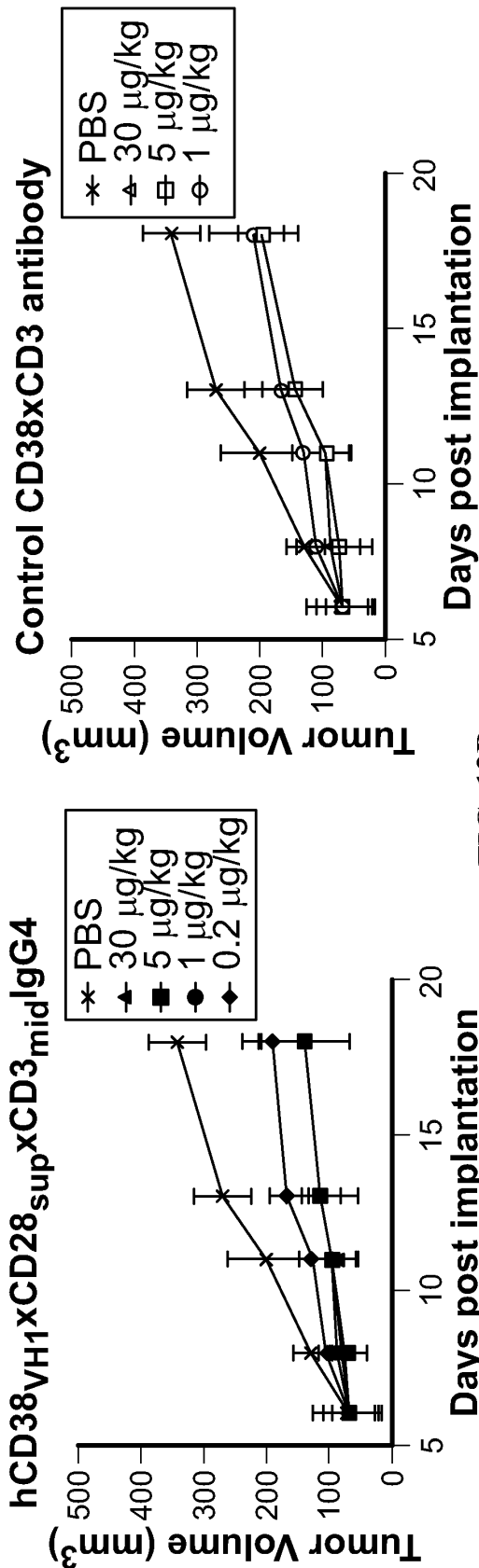


FIG. 12D

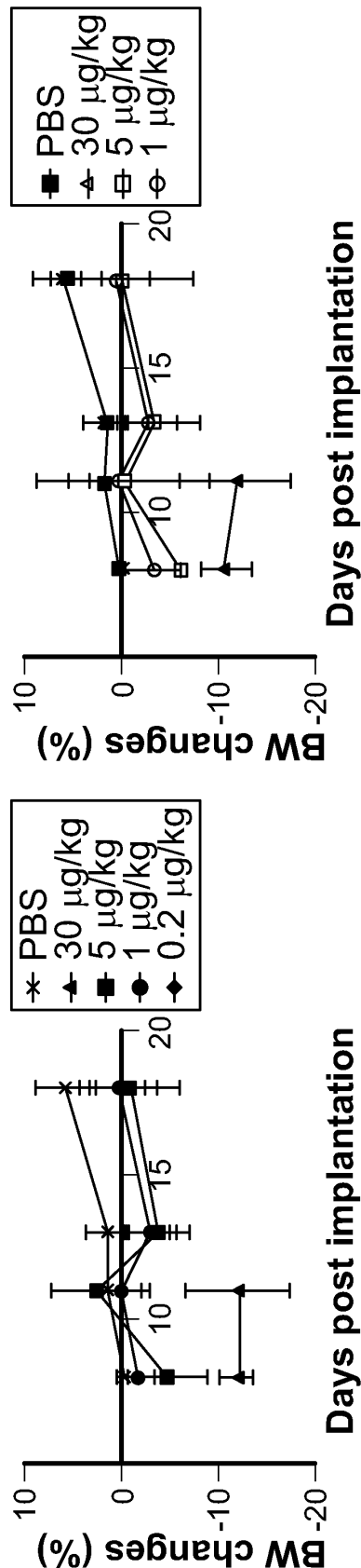


FIG. 12E

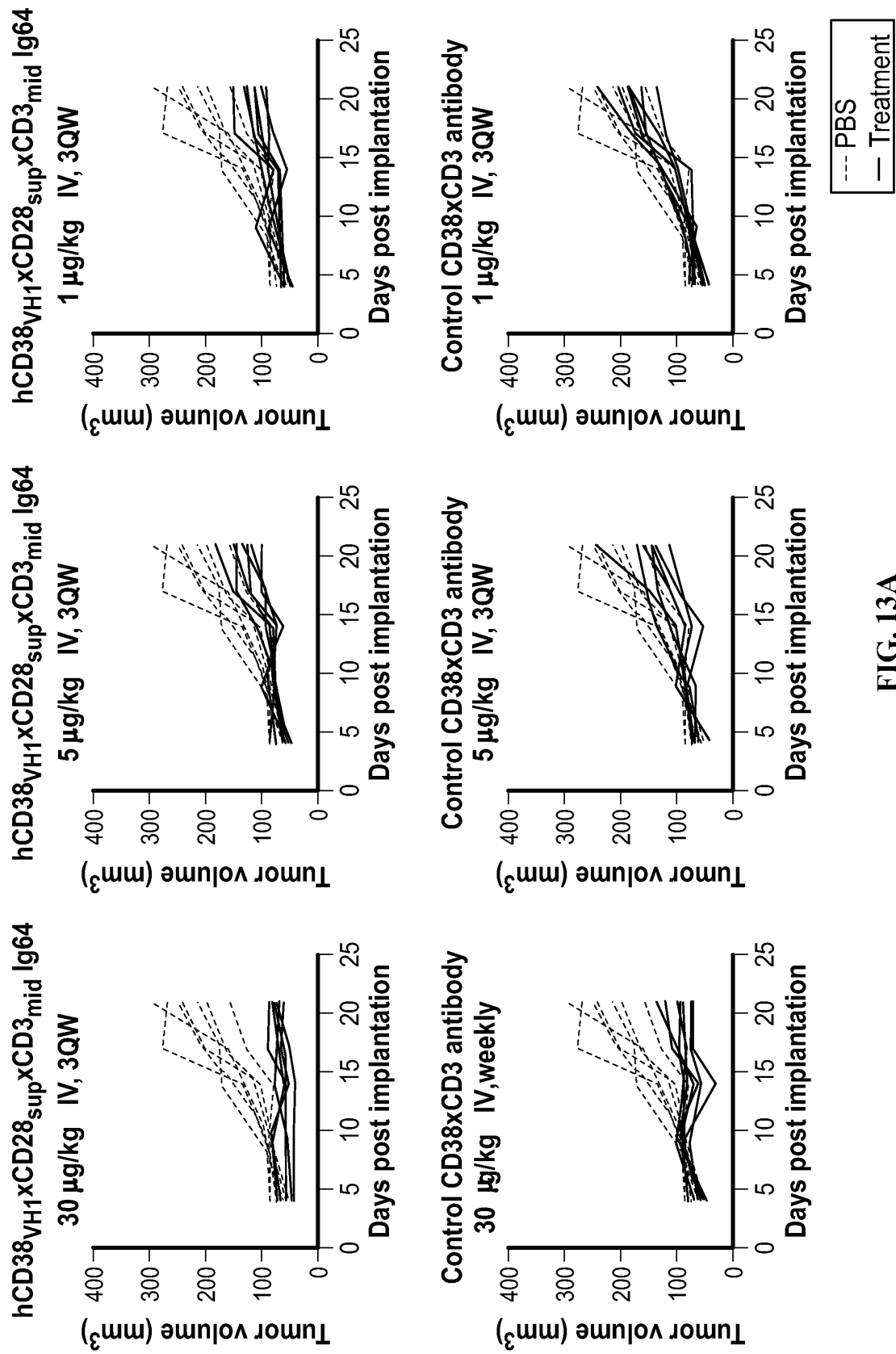


FIG. 13A

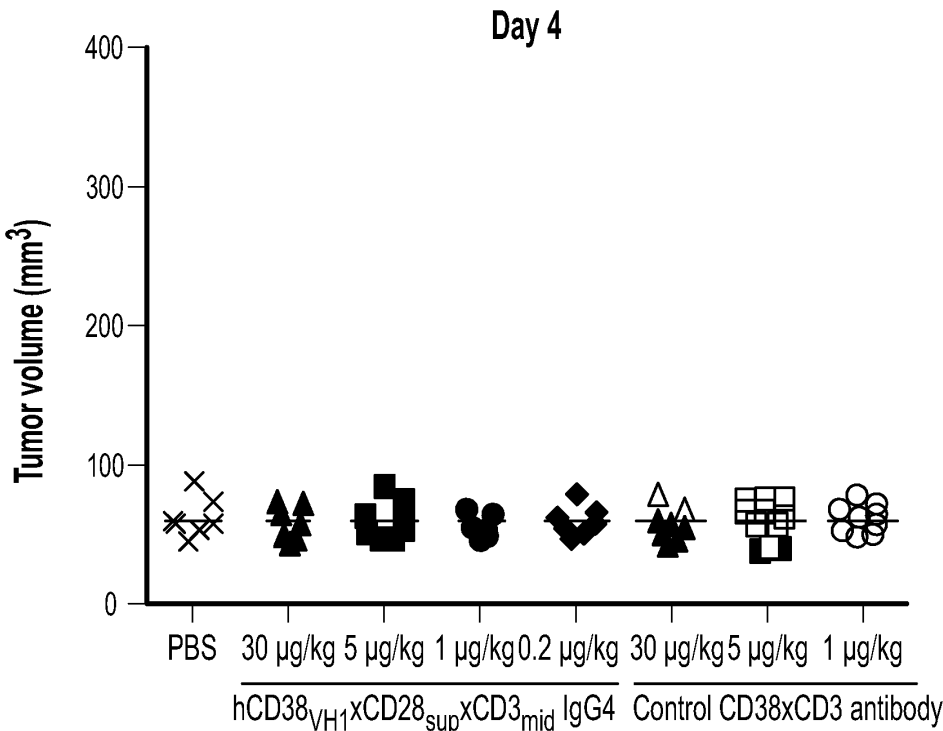


FIG. 13B

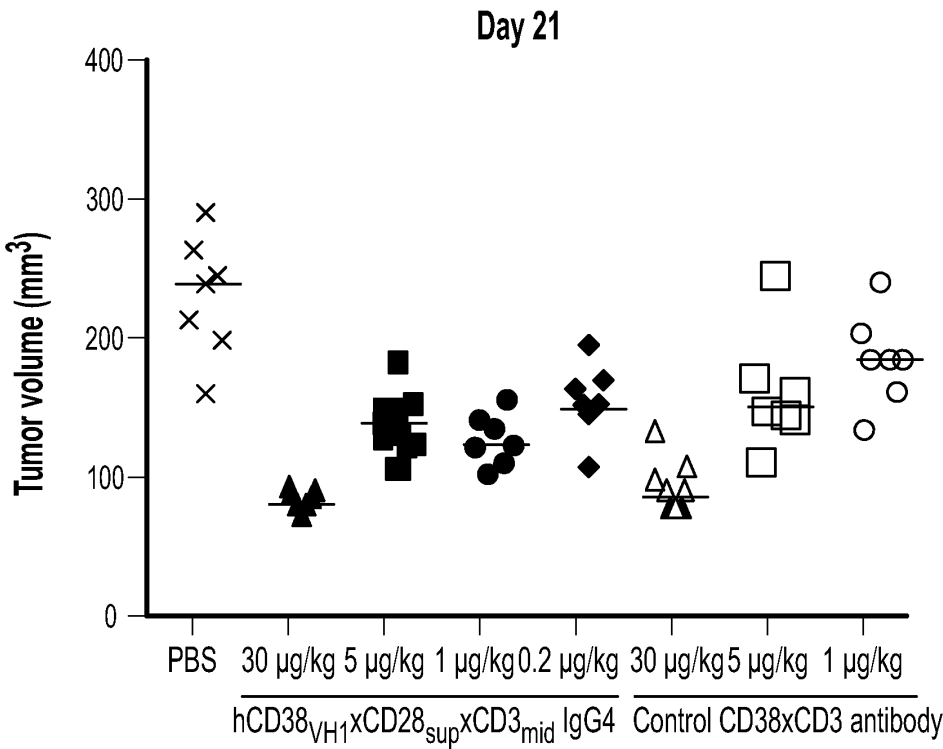
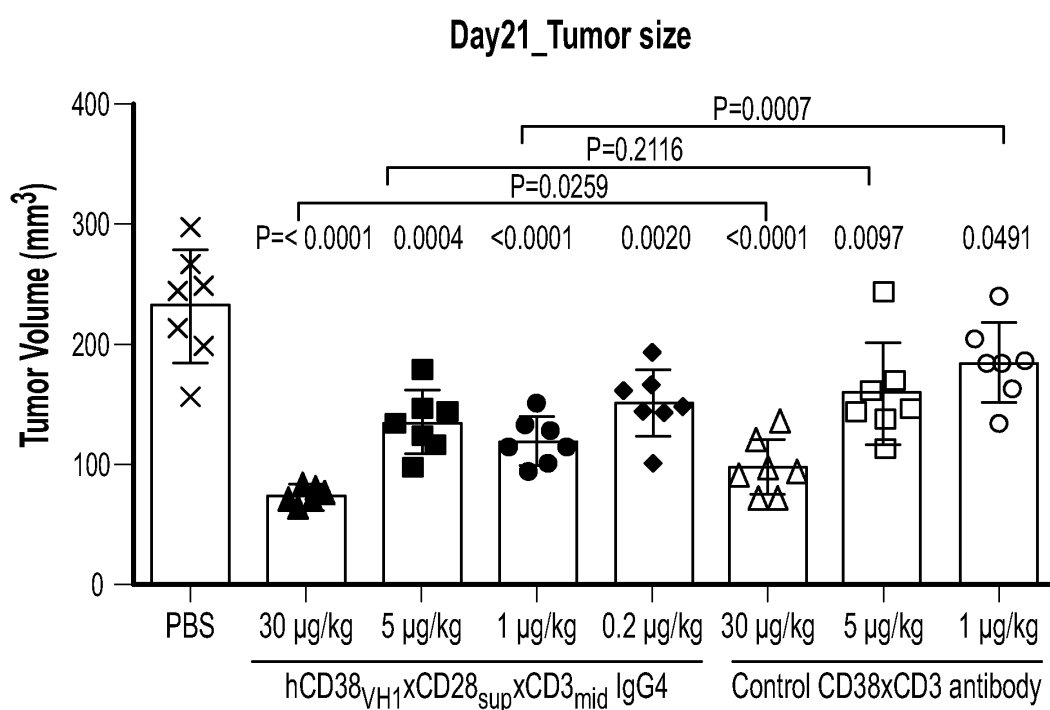
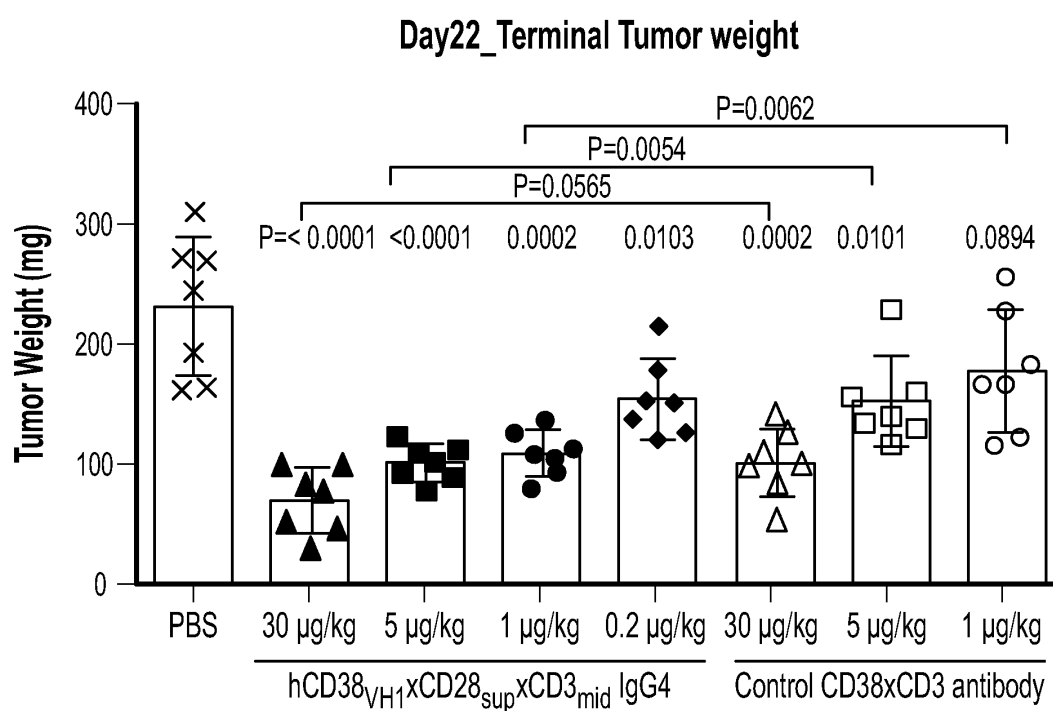


FIG. 13C

**FIG. 13D****FIG. 13E**

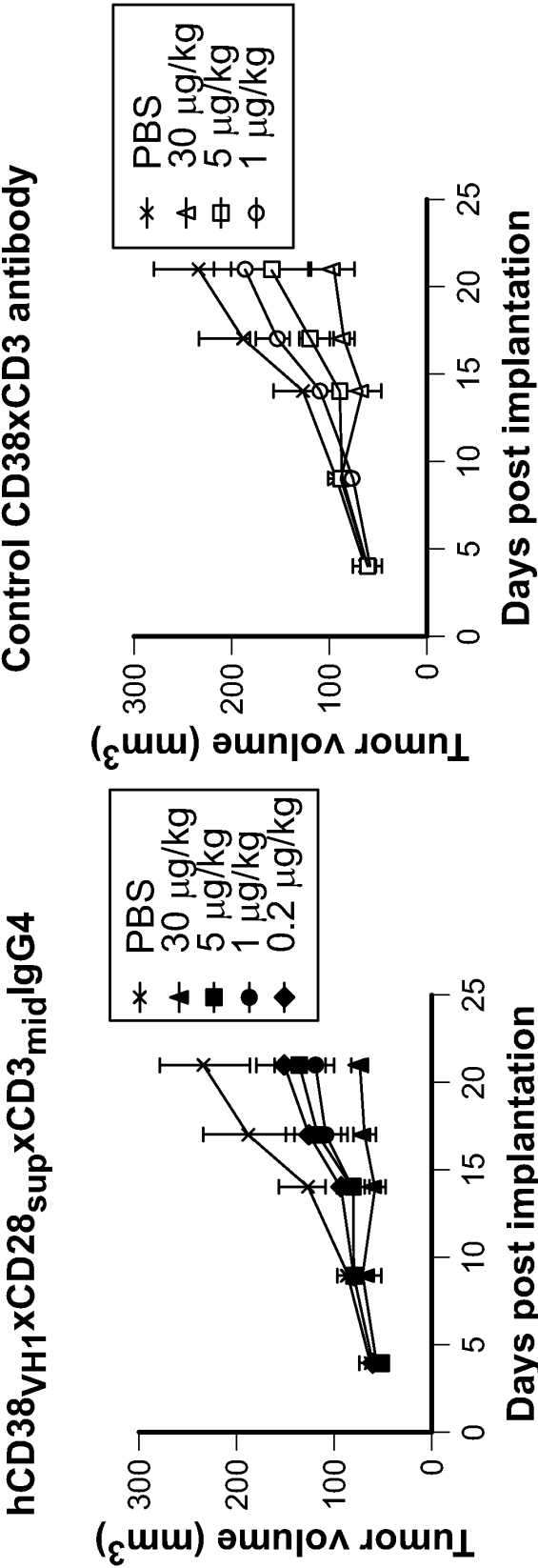
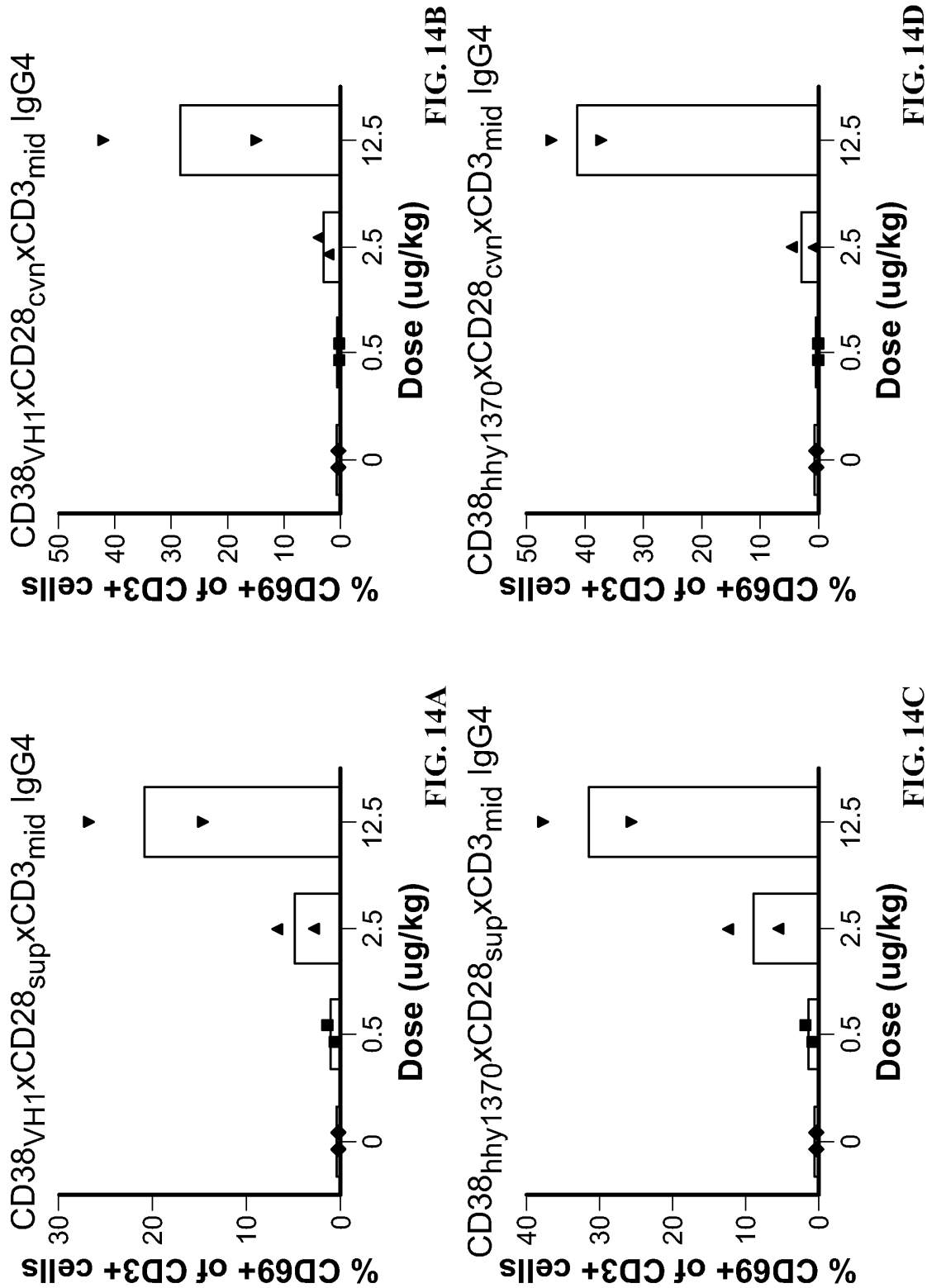
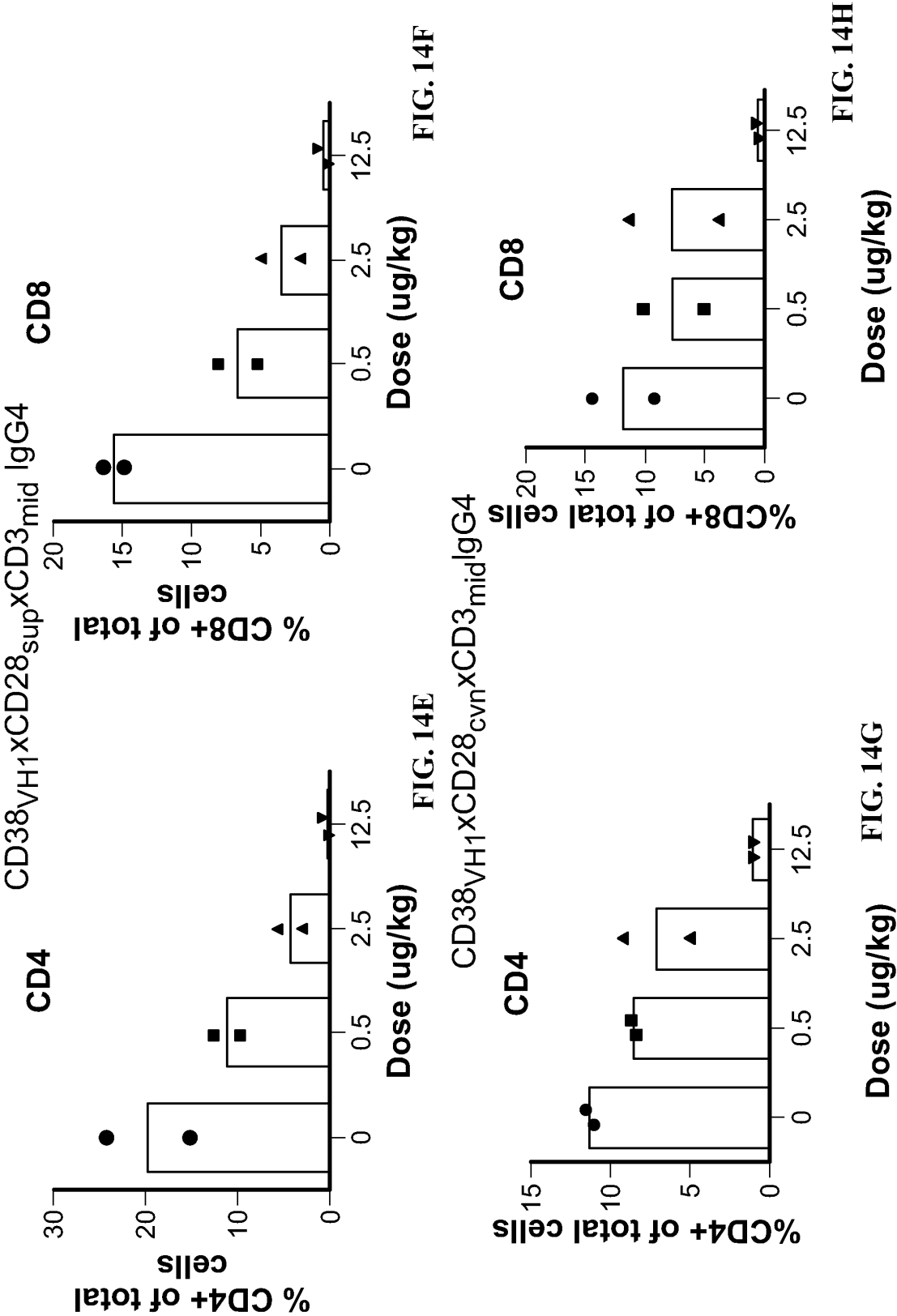
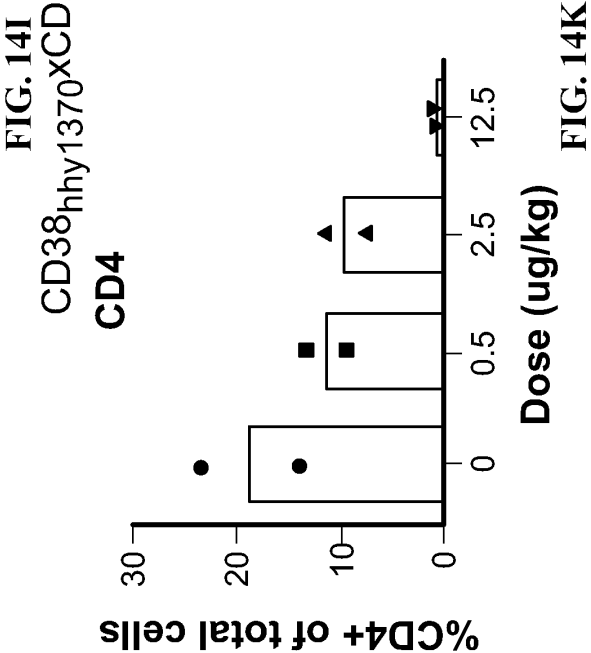
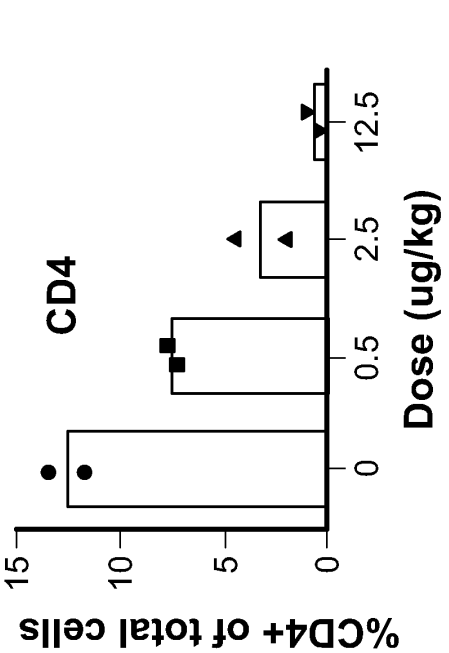
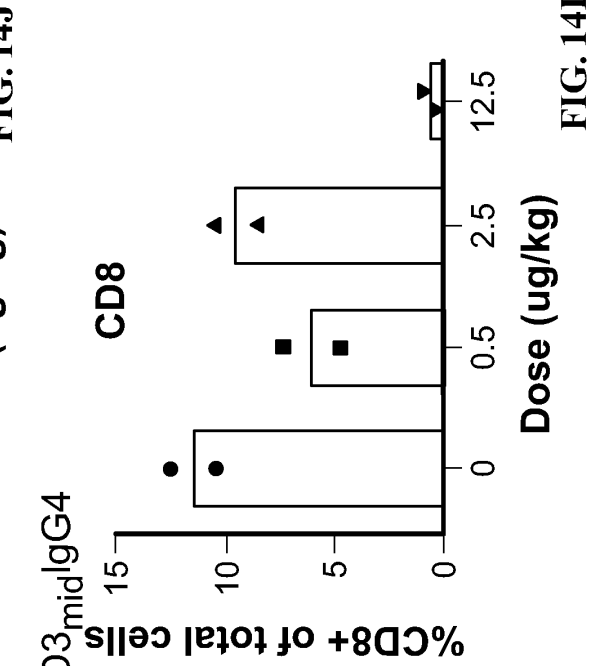
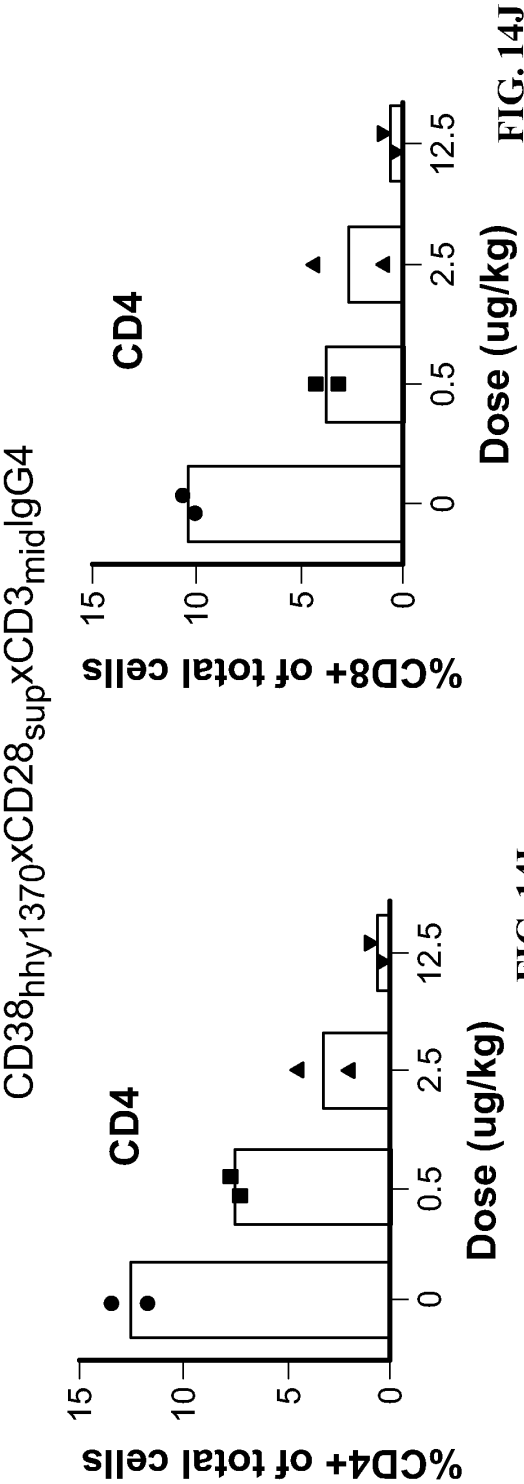
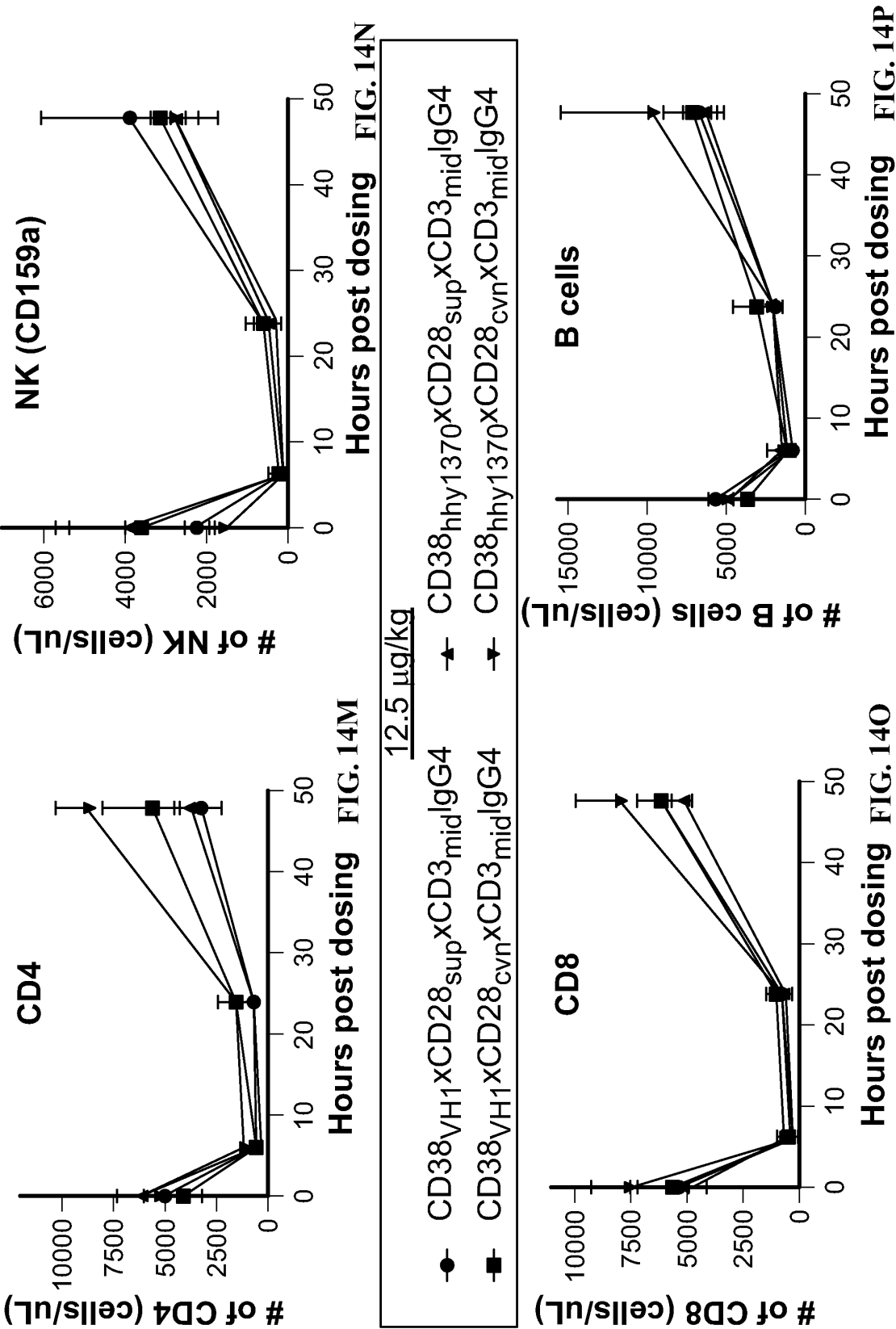


FIG. 13F









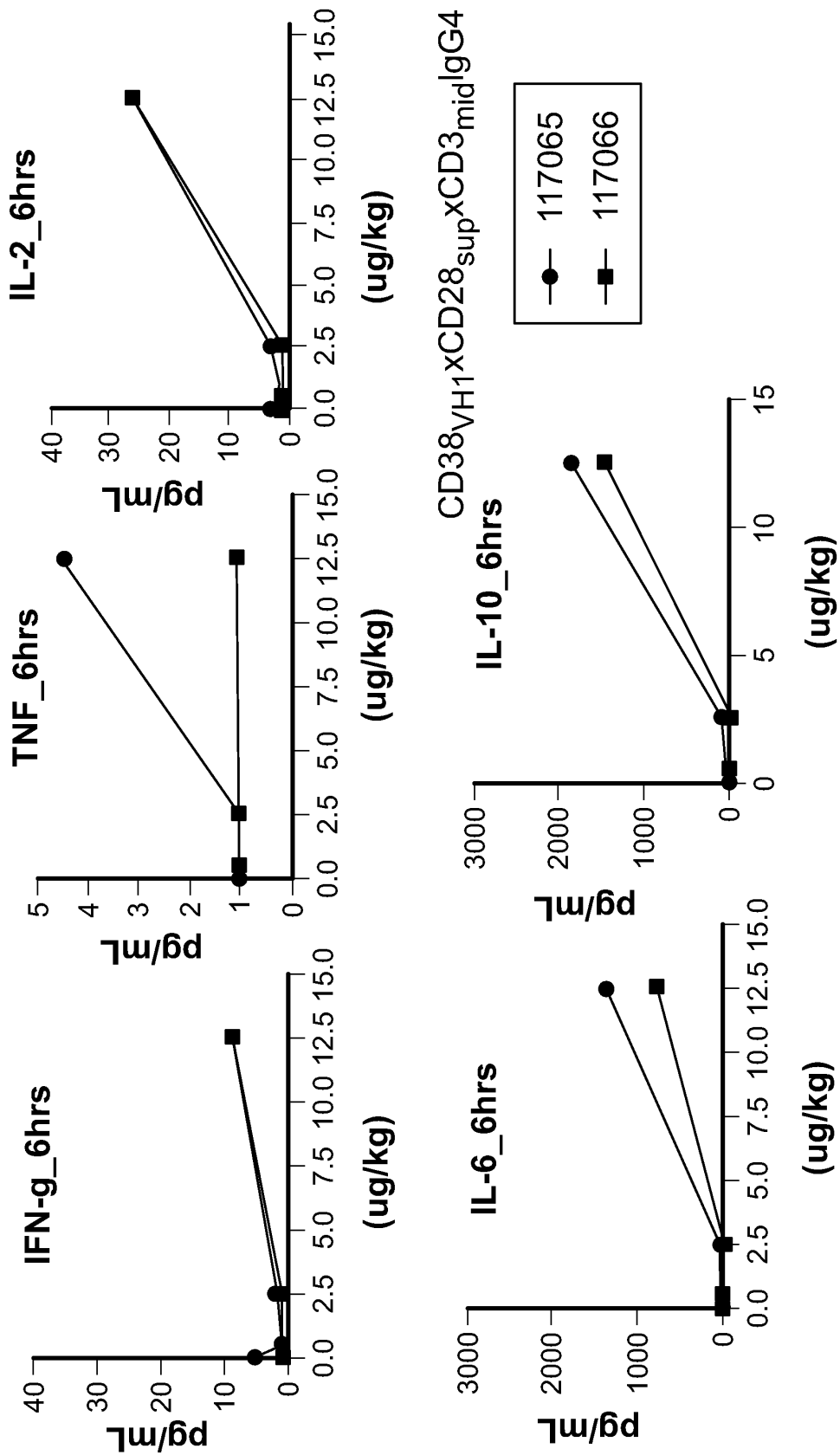


FIG. 14Q

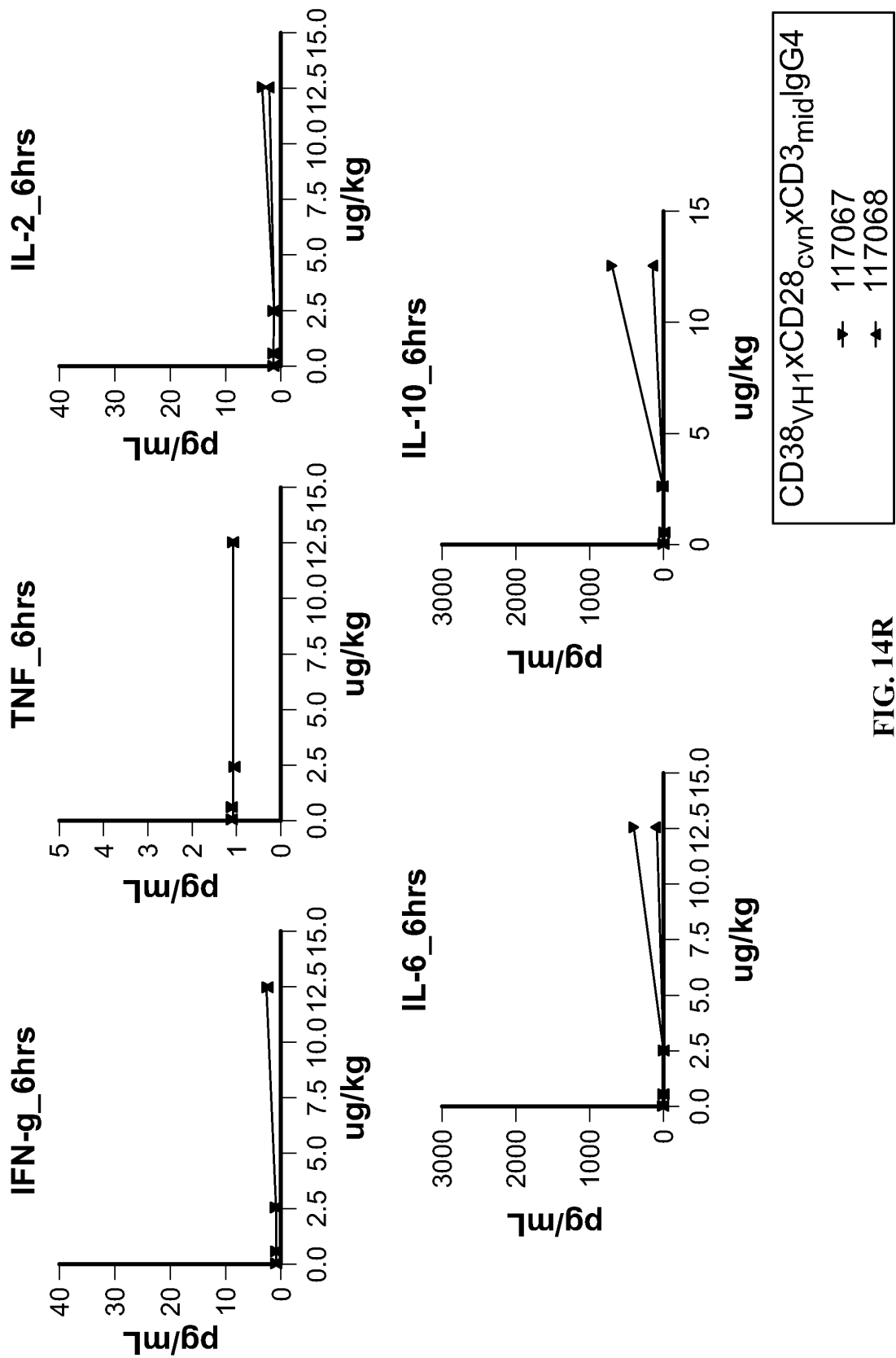


FIG. 14R

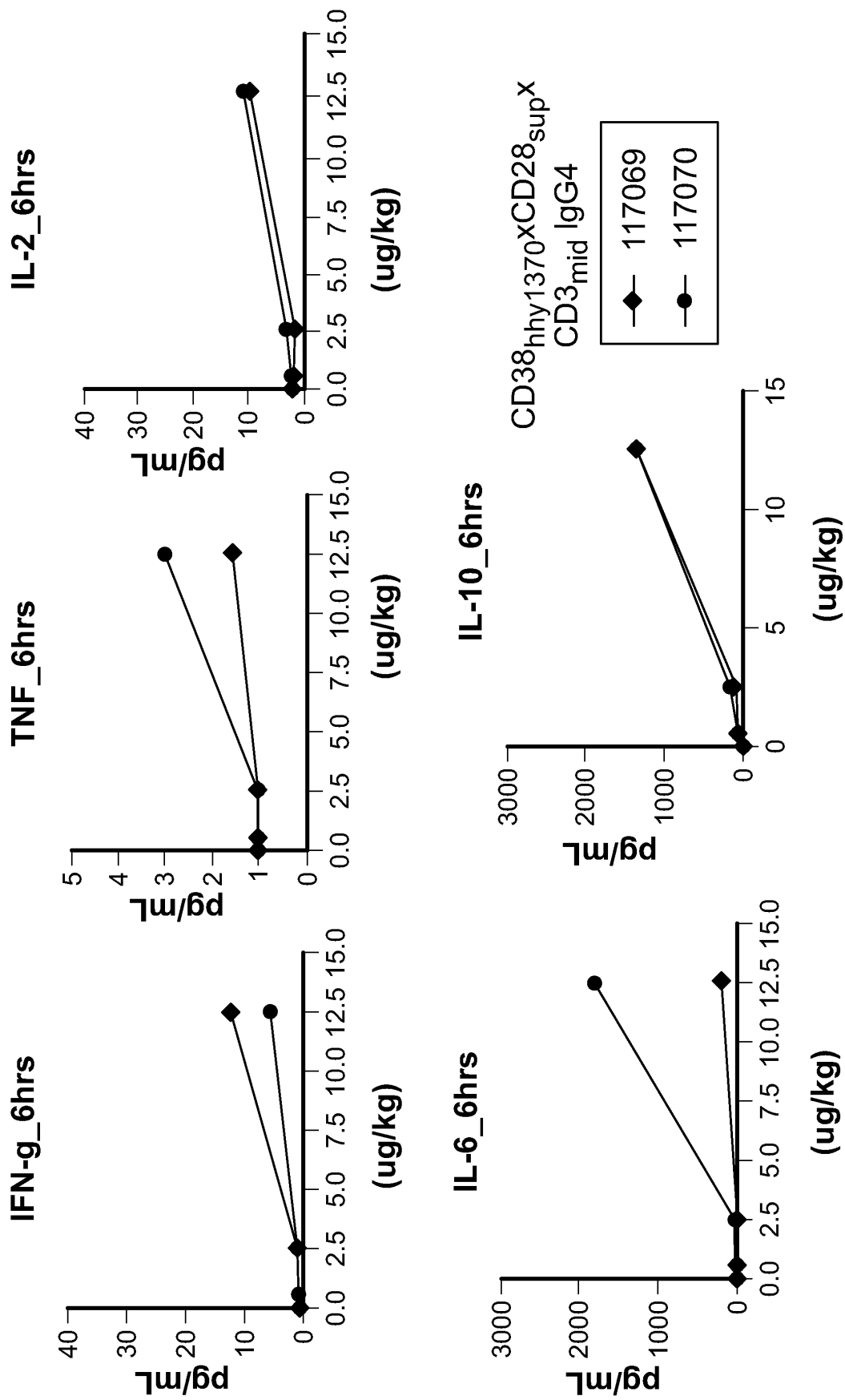


FIG. 14S

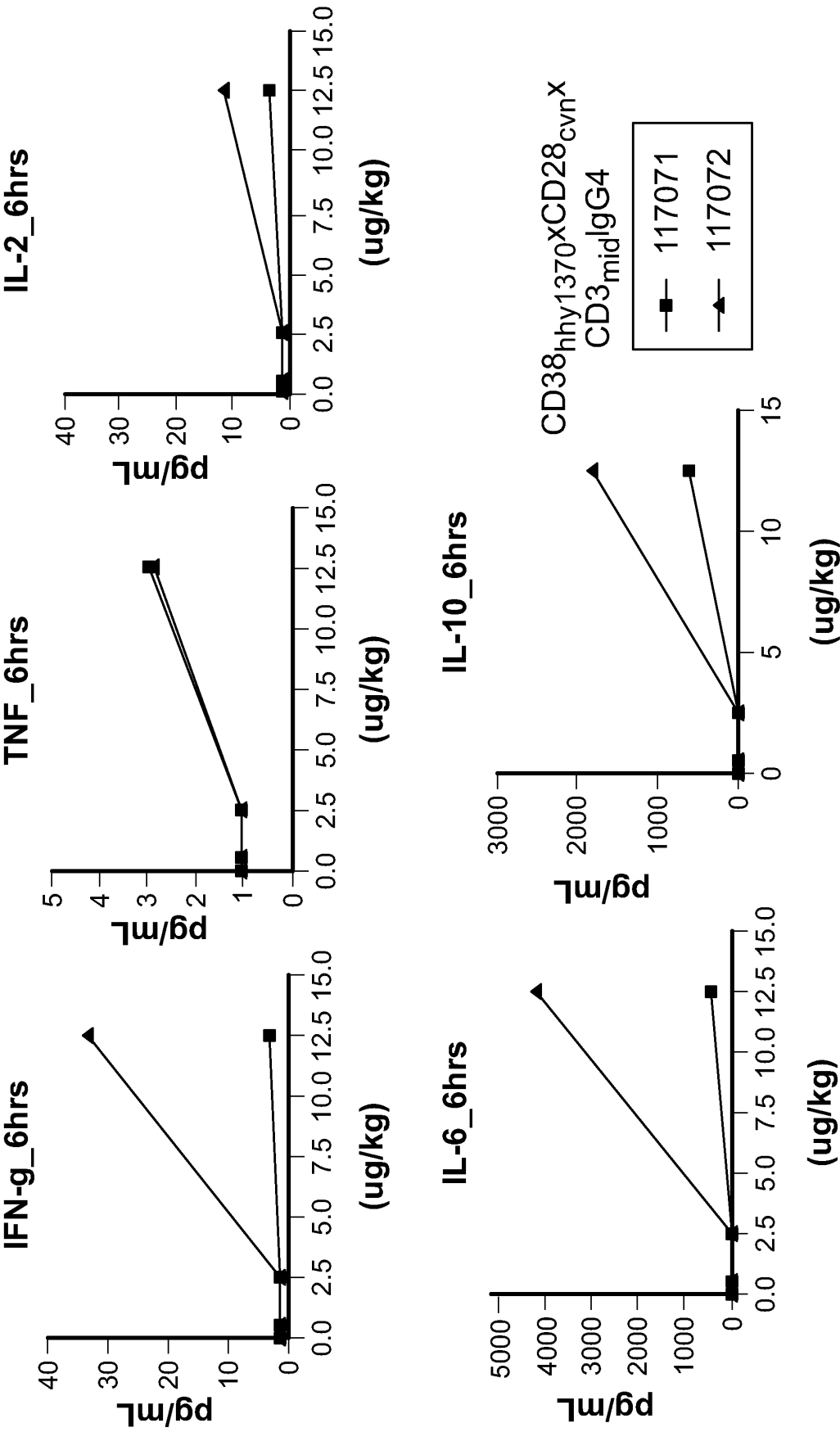


FIG. 14T

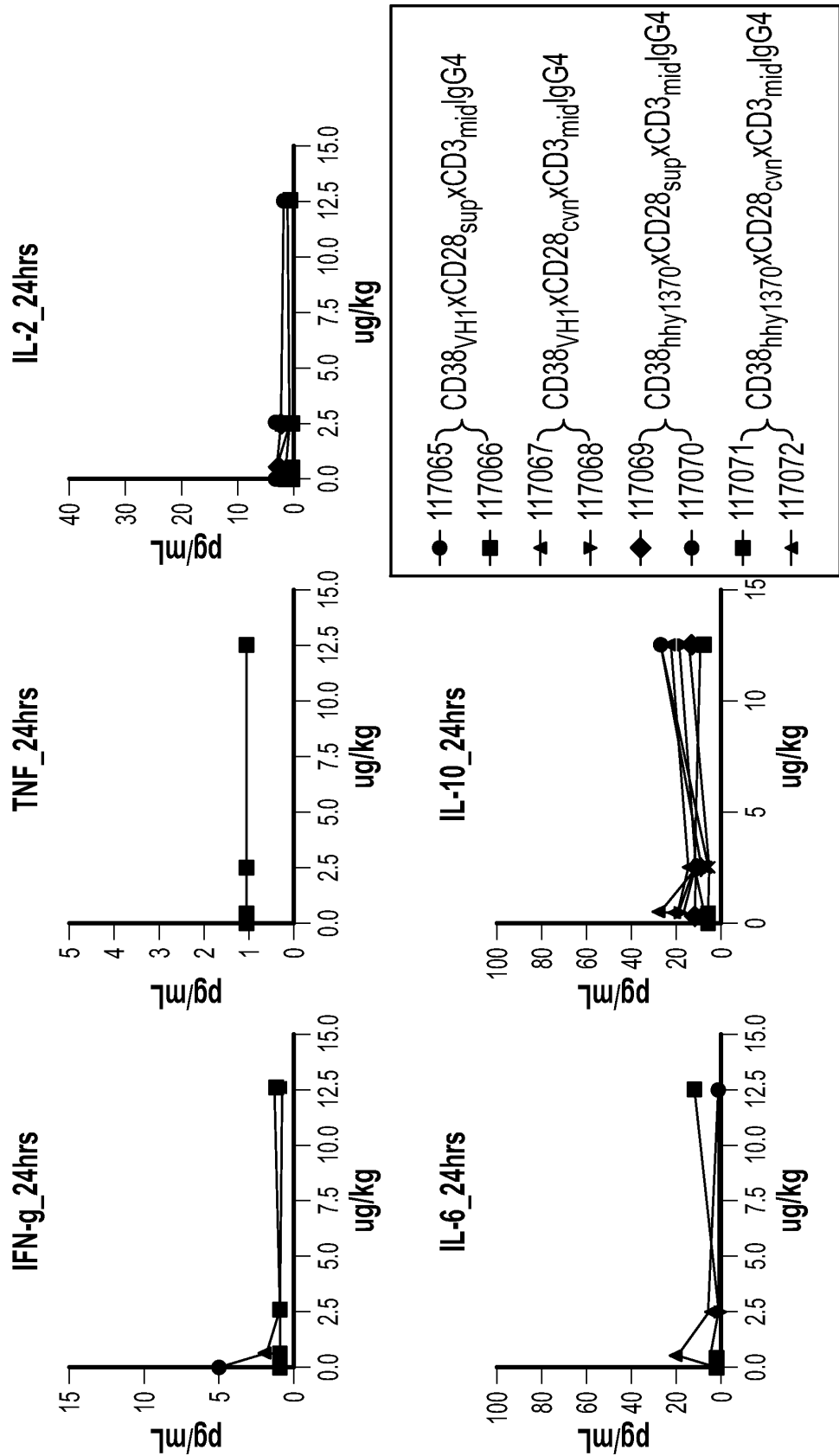


FIG. 14U

CD38^{VH1} / CD28^{cvn}xCD3^{mid} IgG4

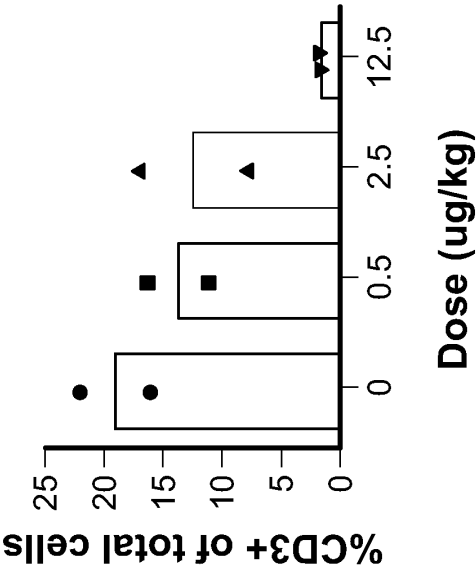


FIG. 14W

CD38^{VH1} / CD28^{sup}xCD3^{mid} IgG4

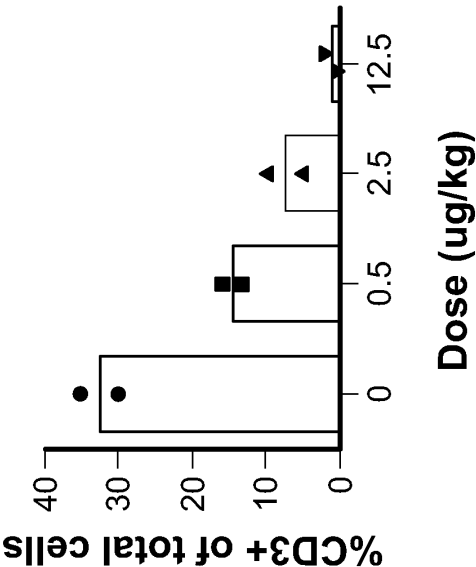


FIG. 14V

CD38_{hhy1370}/ CD28_{cvn}xCD3_{mid} IgG4

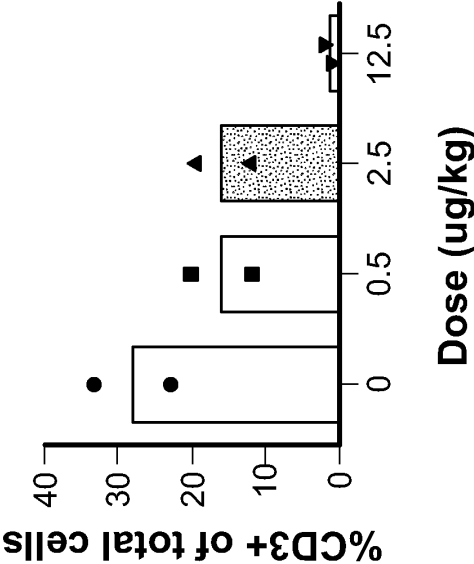


FIG. 14Y

CD38_{hhy1370}/ CD28_{sup}xCD3_{mid} IgG4

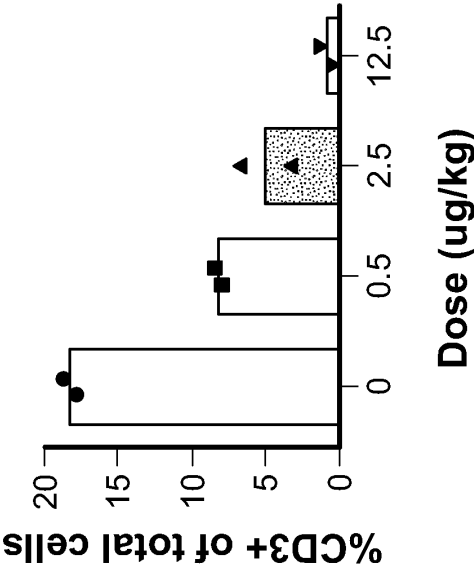


FIG. 14X

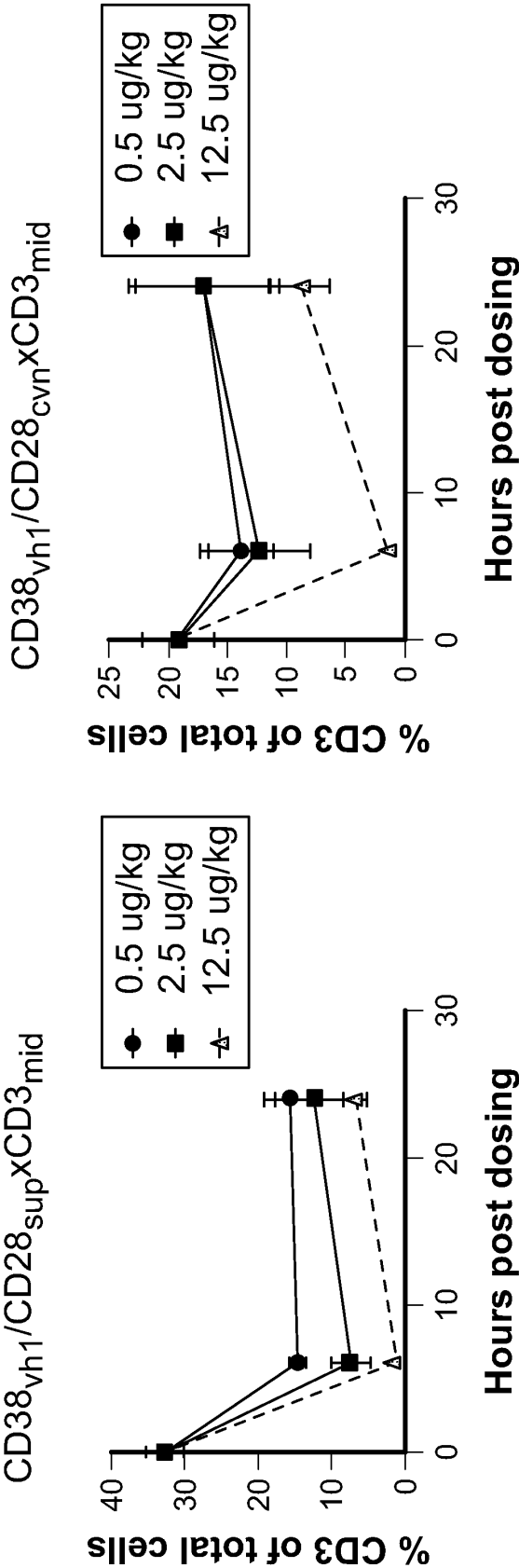


FIG. 14Z

FIG. 14AA

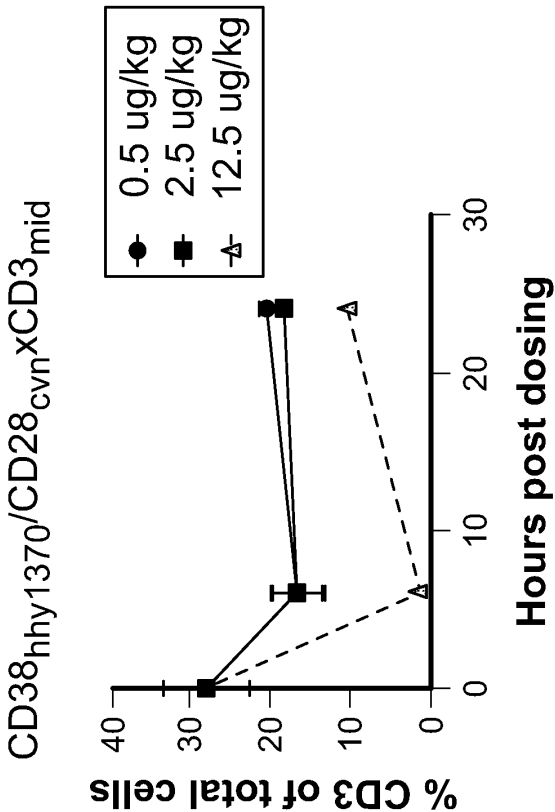


FIG. 14AC

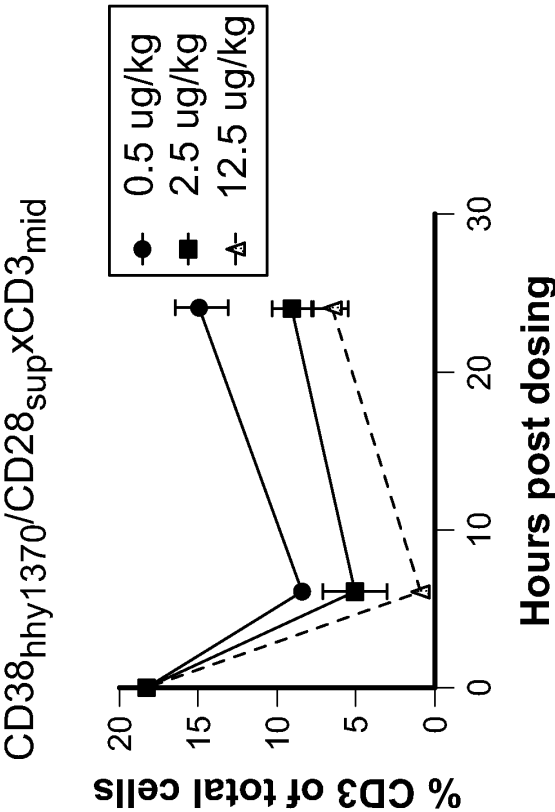


FIG. 14AB

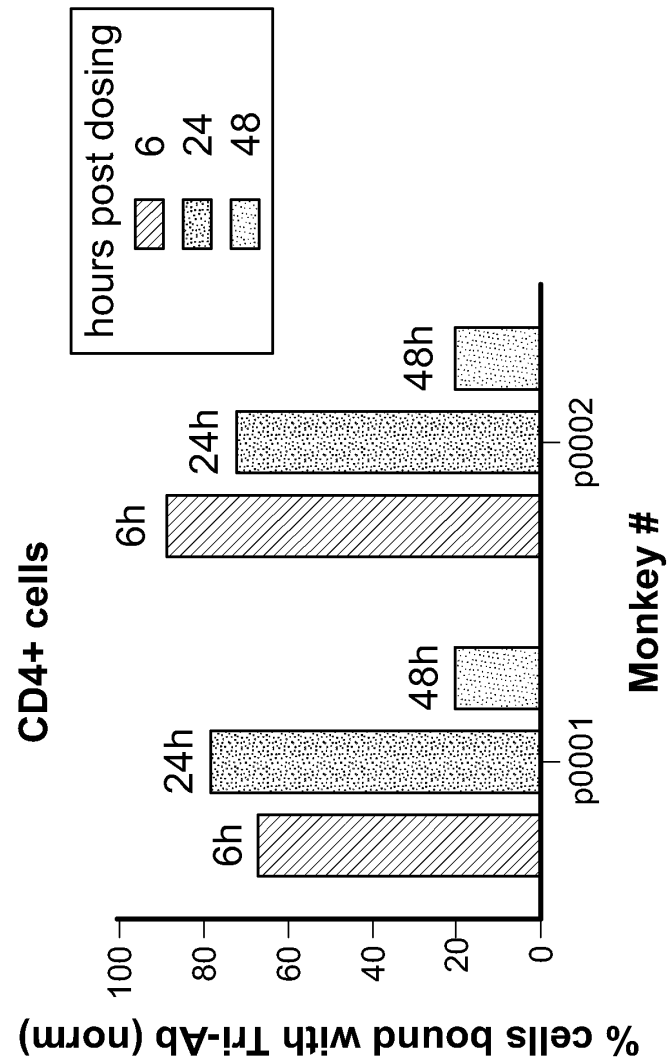


FIG. 14AD

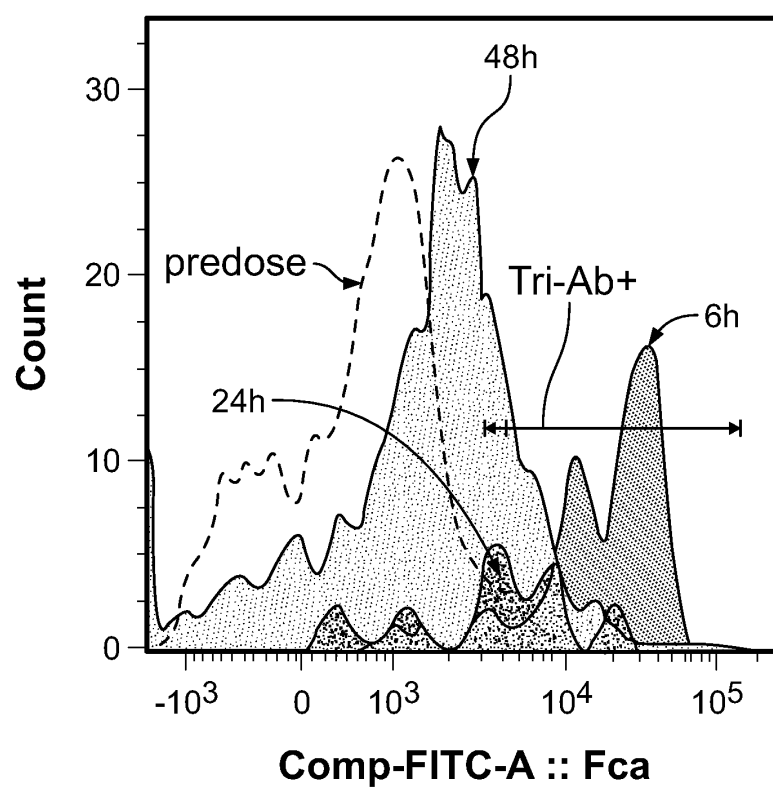
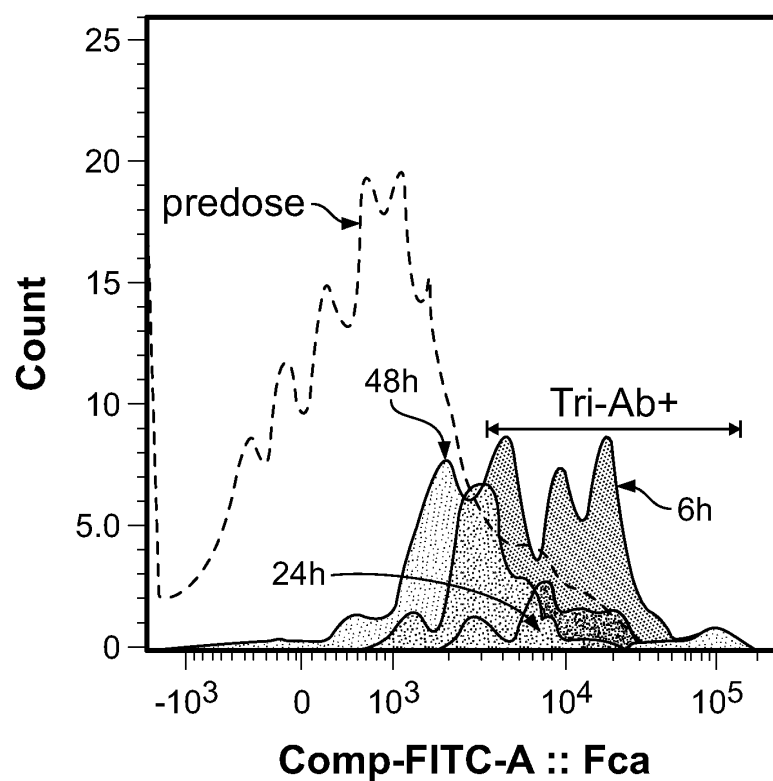


FIG. 14AE

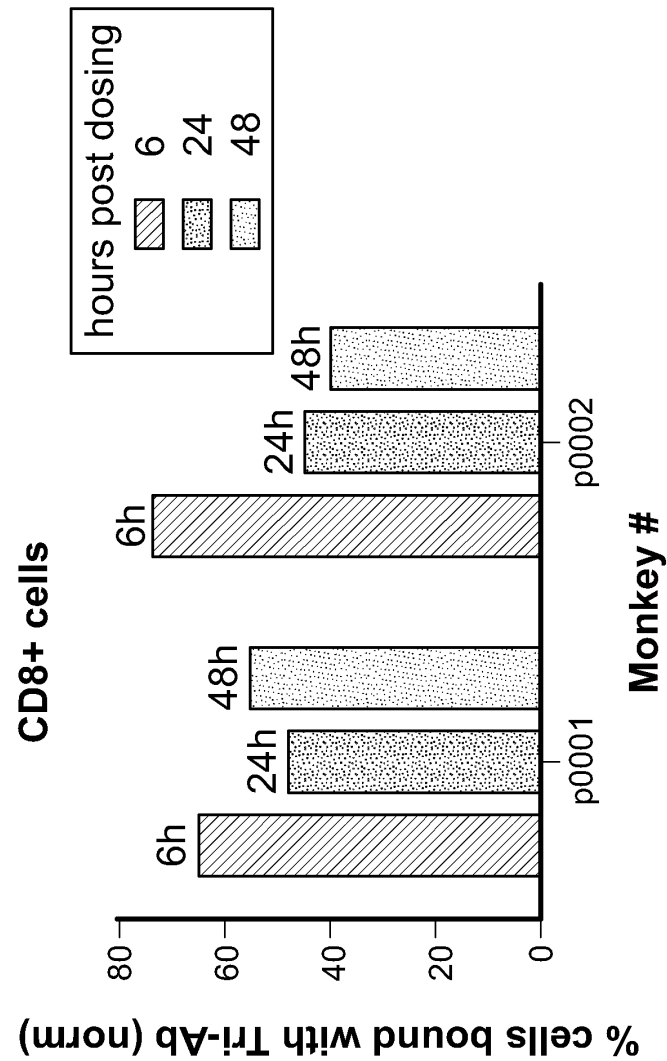


FIG. 14AF

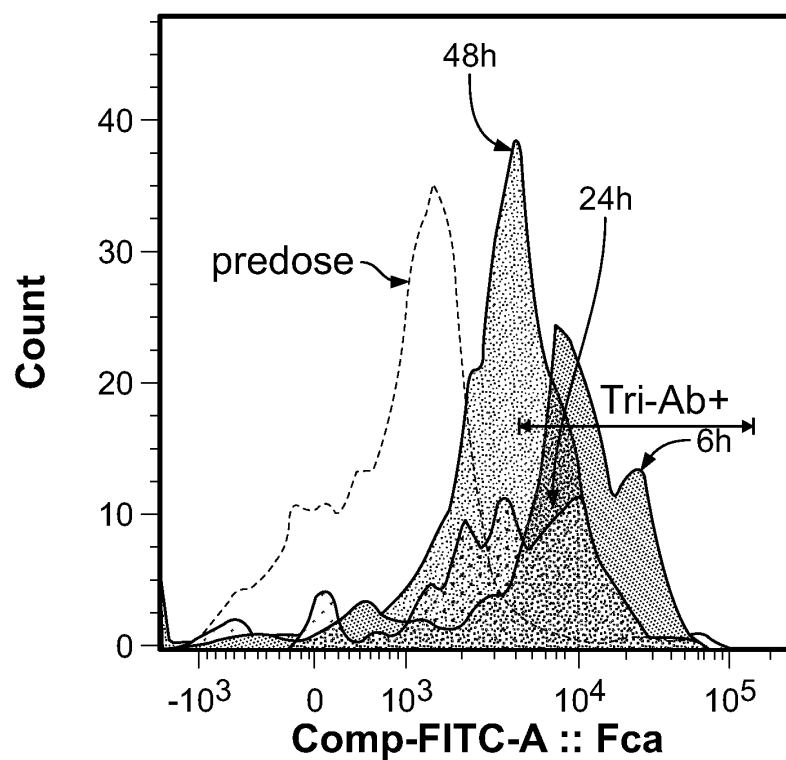
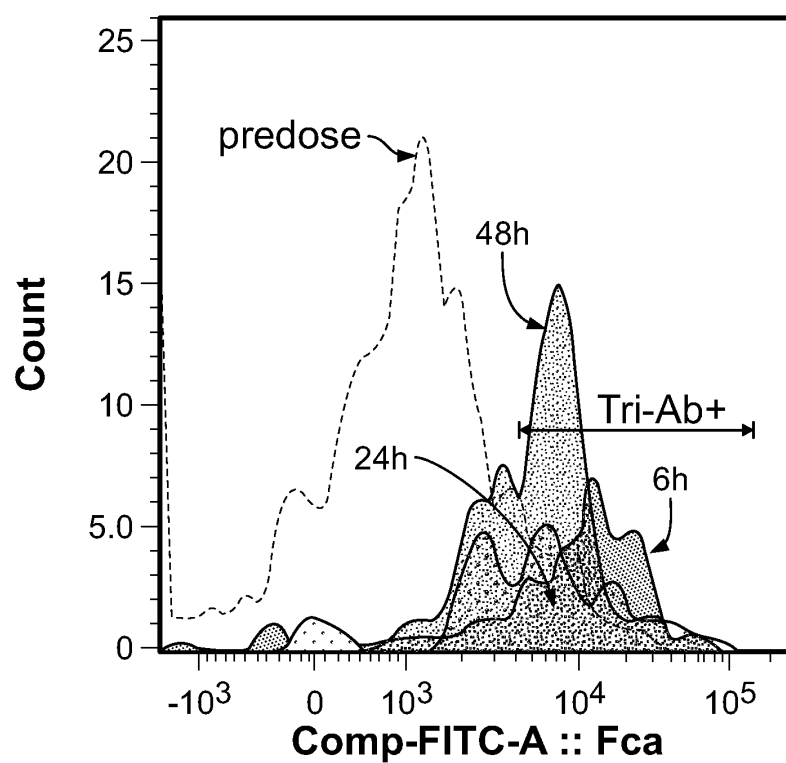


FIG. 14AG

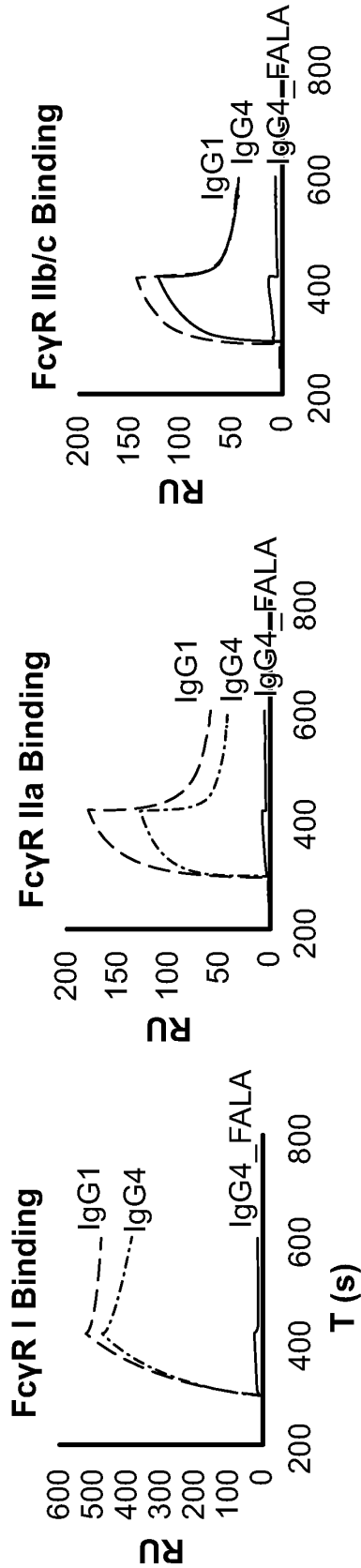


FIG. 15A

FIG. 15B

FIG. 15C

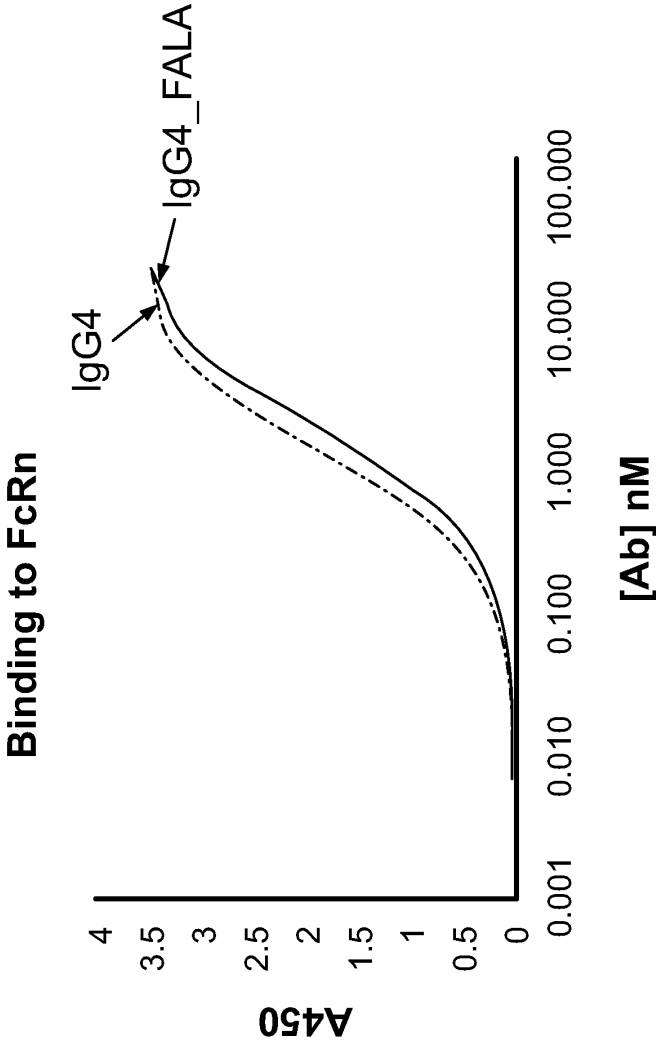


FIG. 16

Antibody	Tmax (hr)	Cmax (ng/ml)	Tlast (hr)	Clast (ng/ml)	T 1/2 (hr)	AUCall (hr* ng/ml)
anti- hCD38 _{VHH} /CD28 _{sup} X CD3 _{mid} IgG4	0.083	460	72	16.6	24	4850
anti- hCD38 _{VHH} /CD28 _{sup} X CD3 _{mid} IgG4 FALA	0.083	495	336	117.1	234	61200
anti- hCD38 _{VHH} /CD28 _{sup} X CD3 _{mid} IgG1 LALA P329A	0.083	621	336	93.2	277	49400
anti- hCD38 _{hhv137n} /CD28 _{su} pXCD3 _{mid} IgG4 FALA	0.083	645	336	112.9	255	64500

FIG. 17

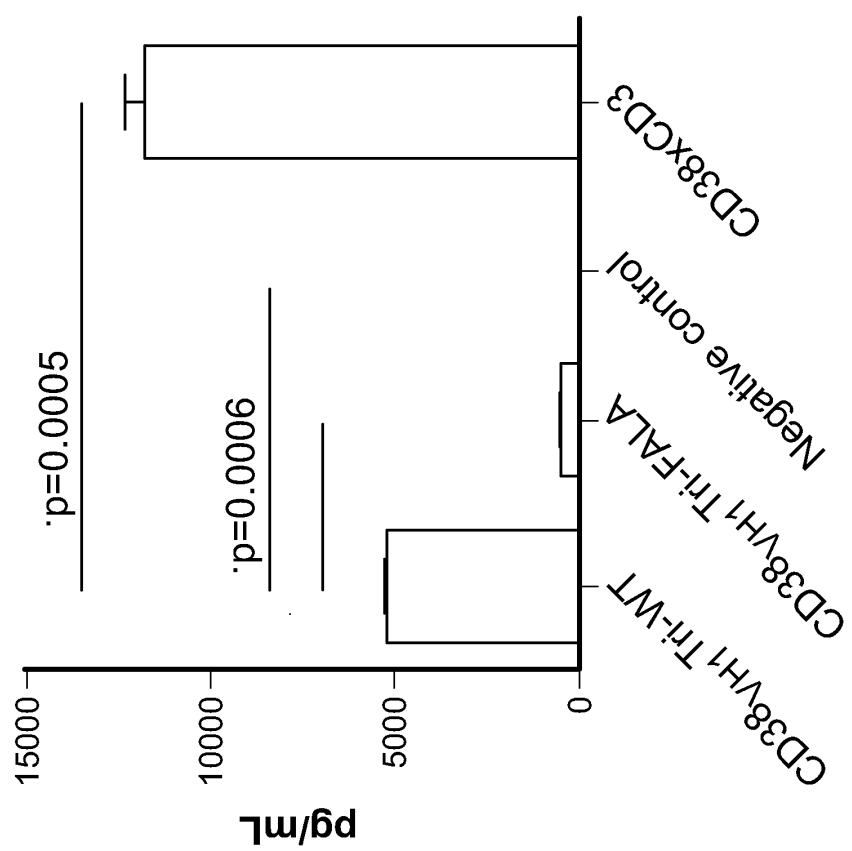


FIG. 18A

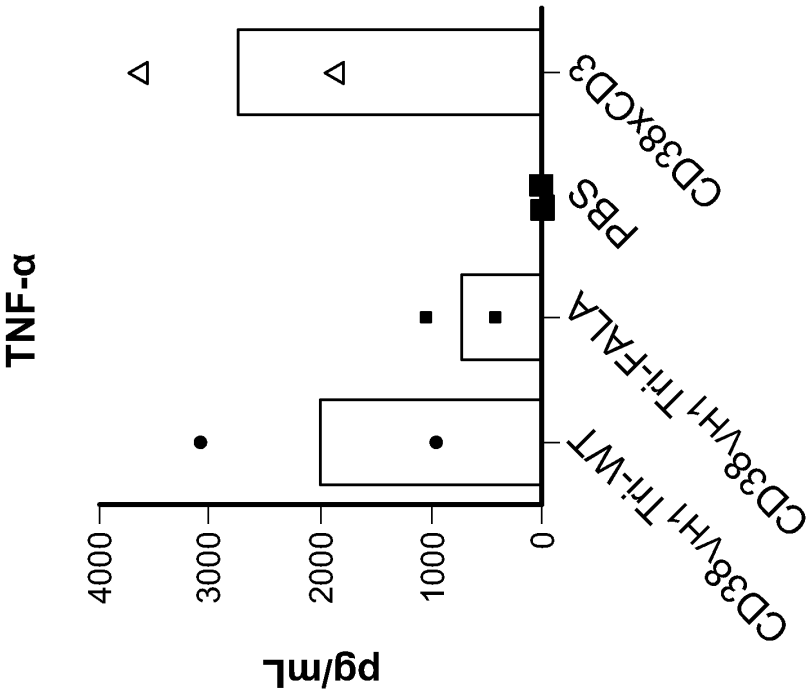


FIG. 18C

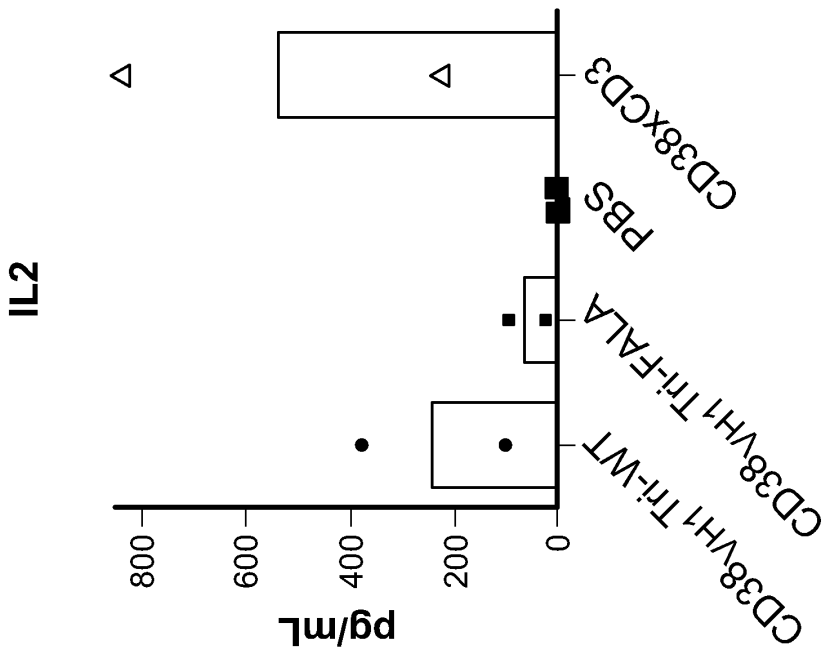


FIG. 18B

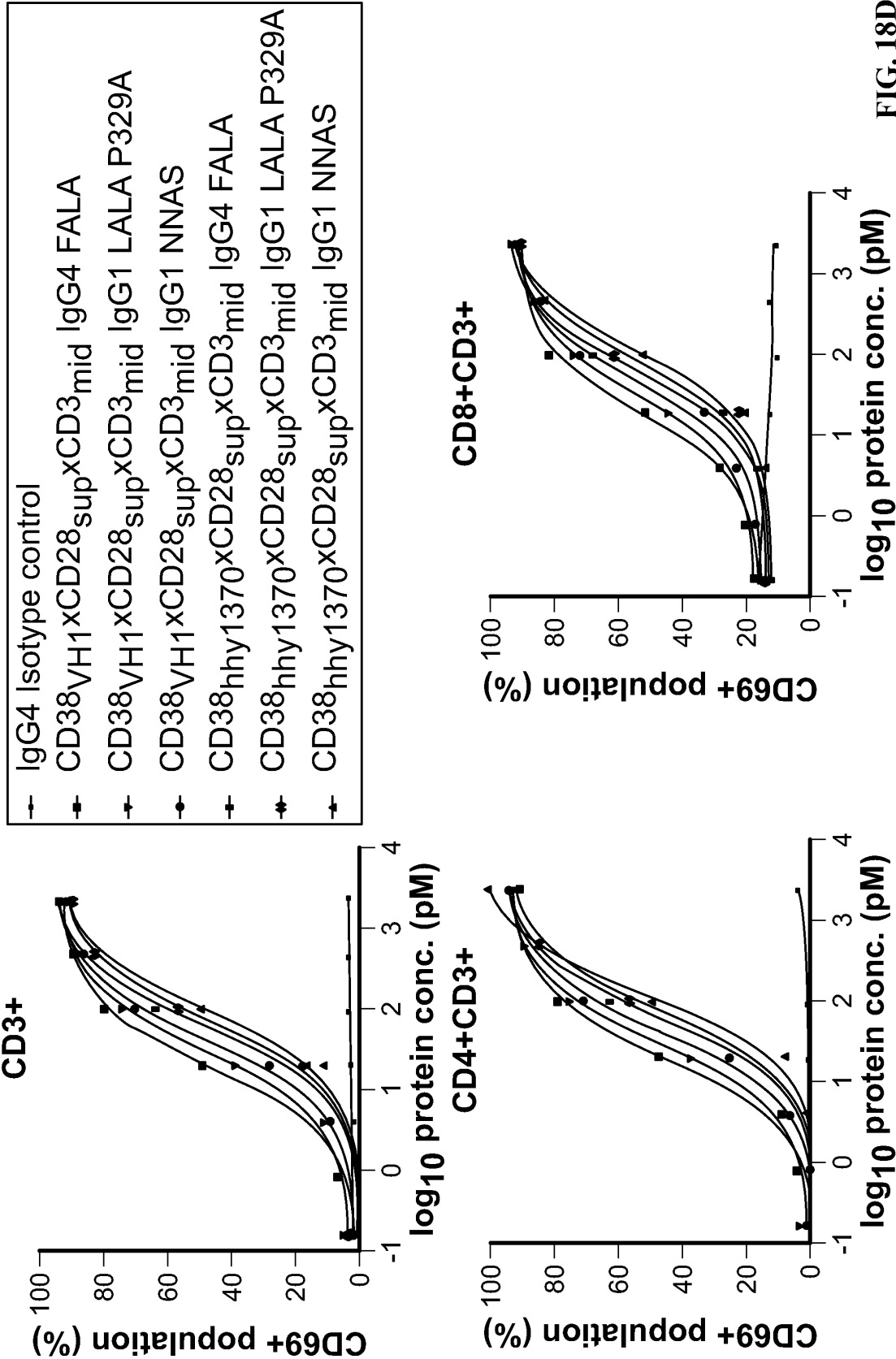


FIG. 18D

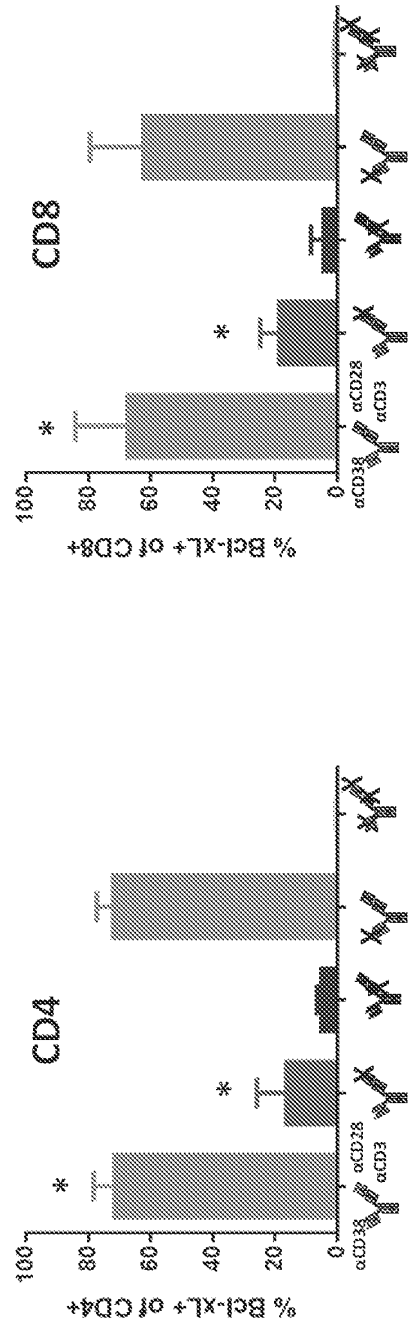
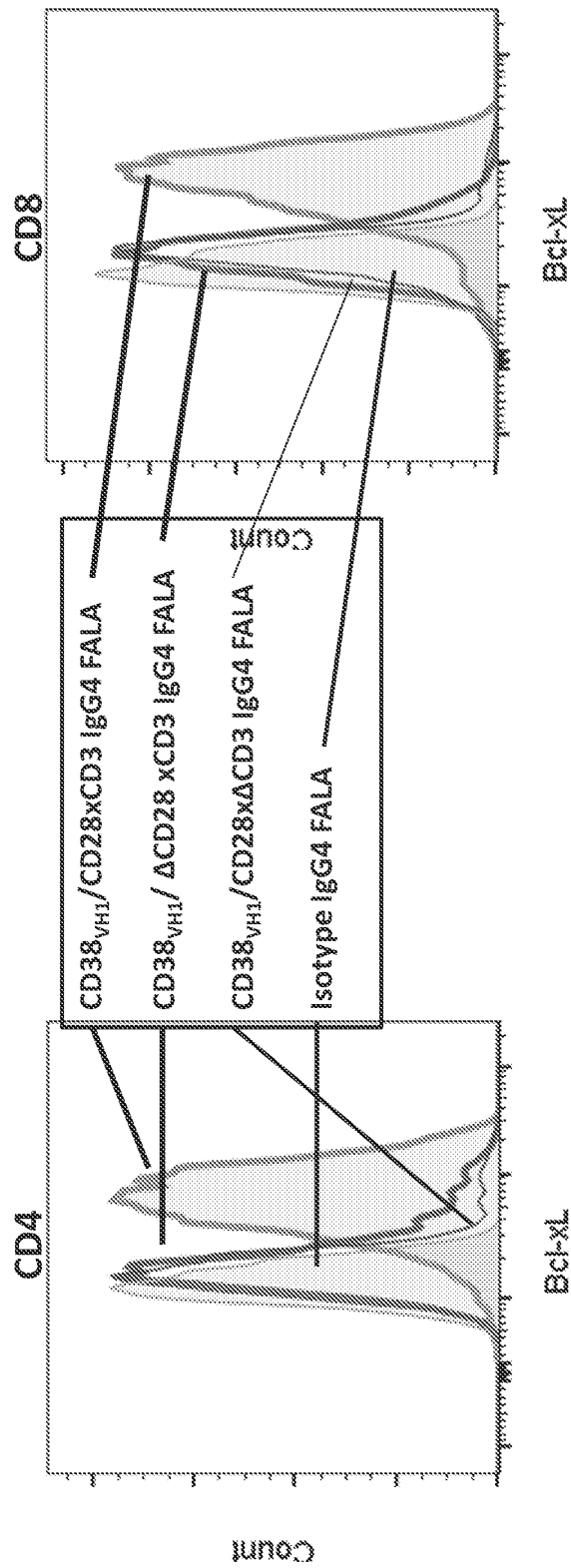


FIG. 19A

FIG. 19B

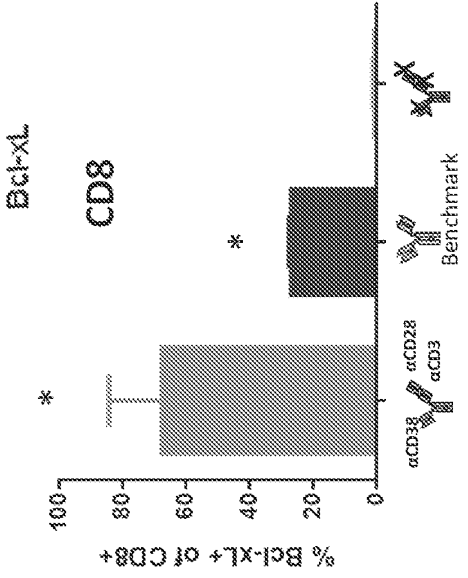
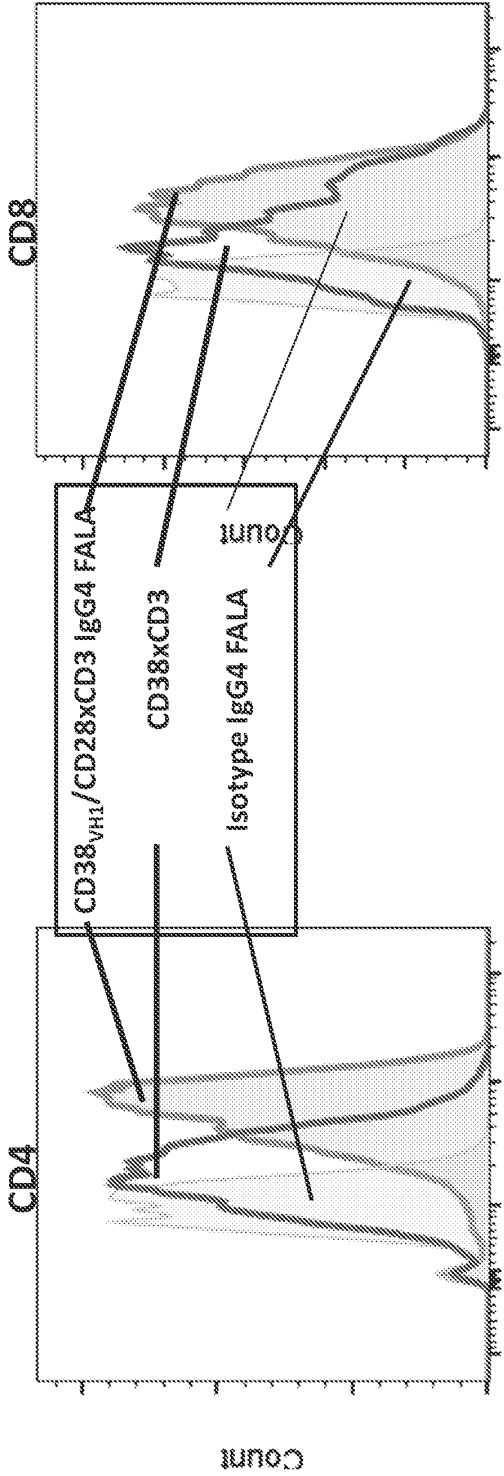


FIG. 19D

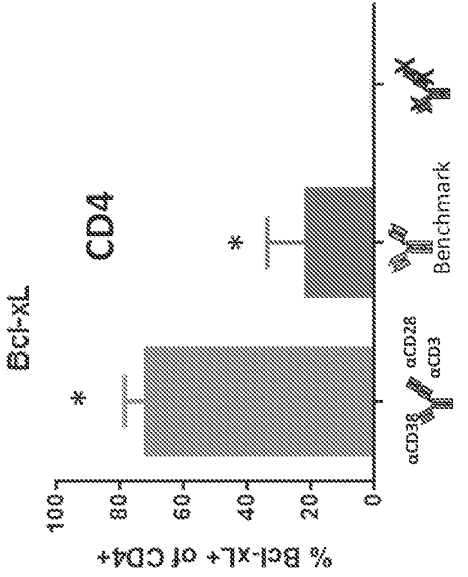


FIG. 19C

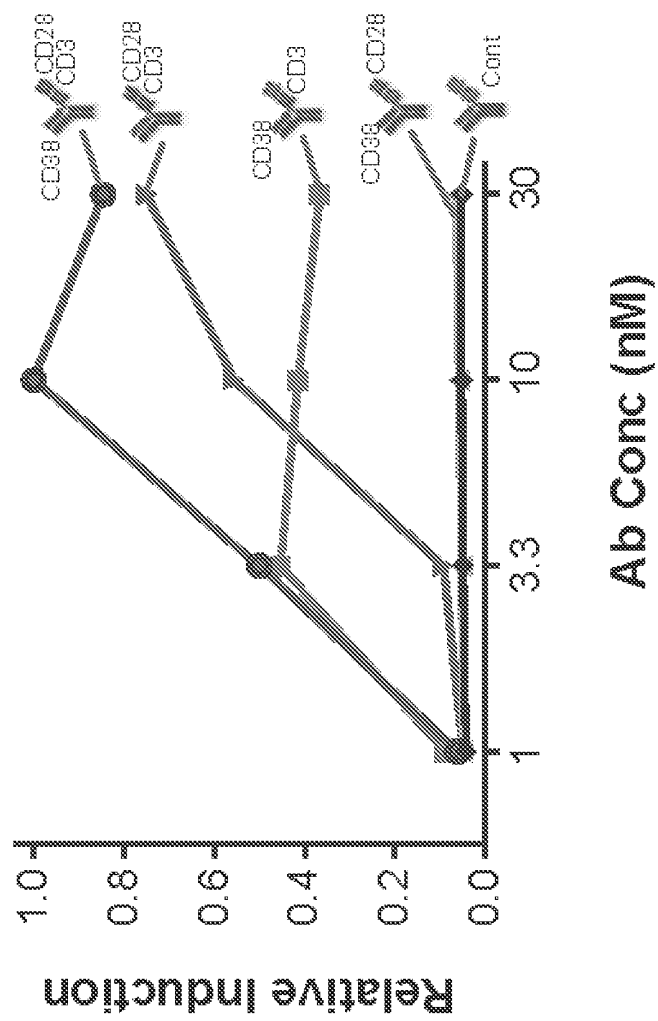


FIG. 19E

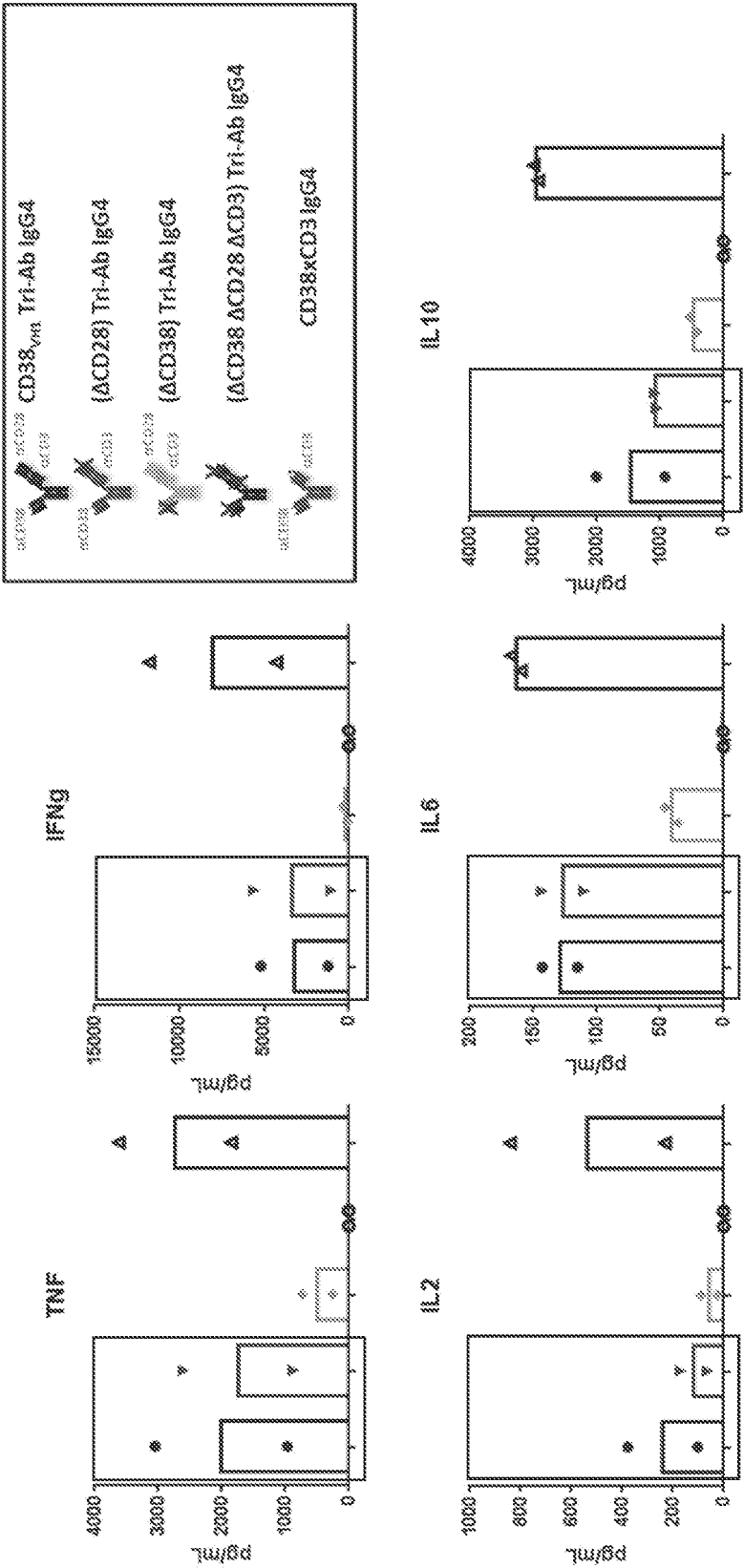


FIG. 19F

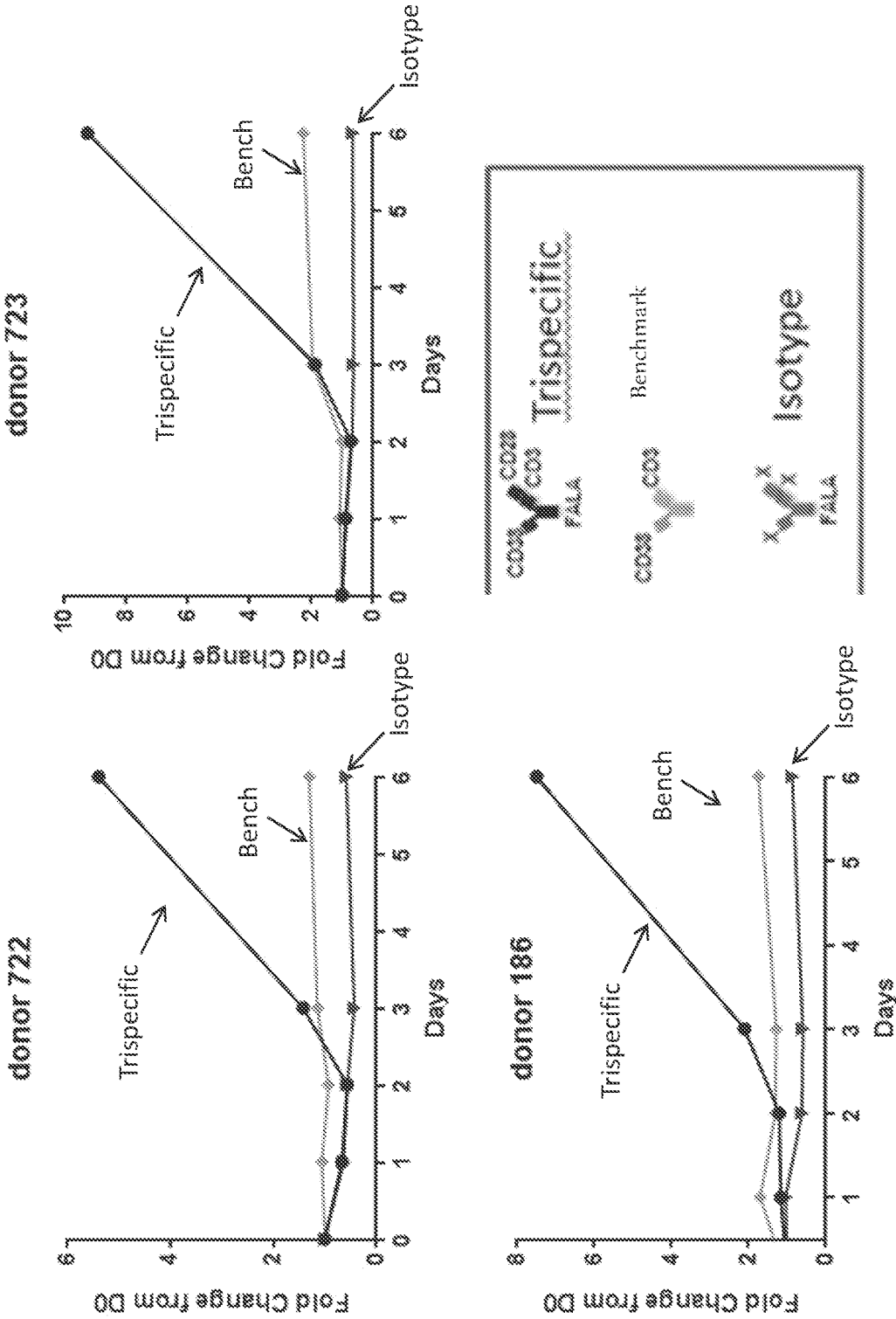


FIG. 19G

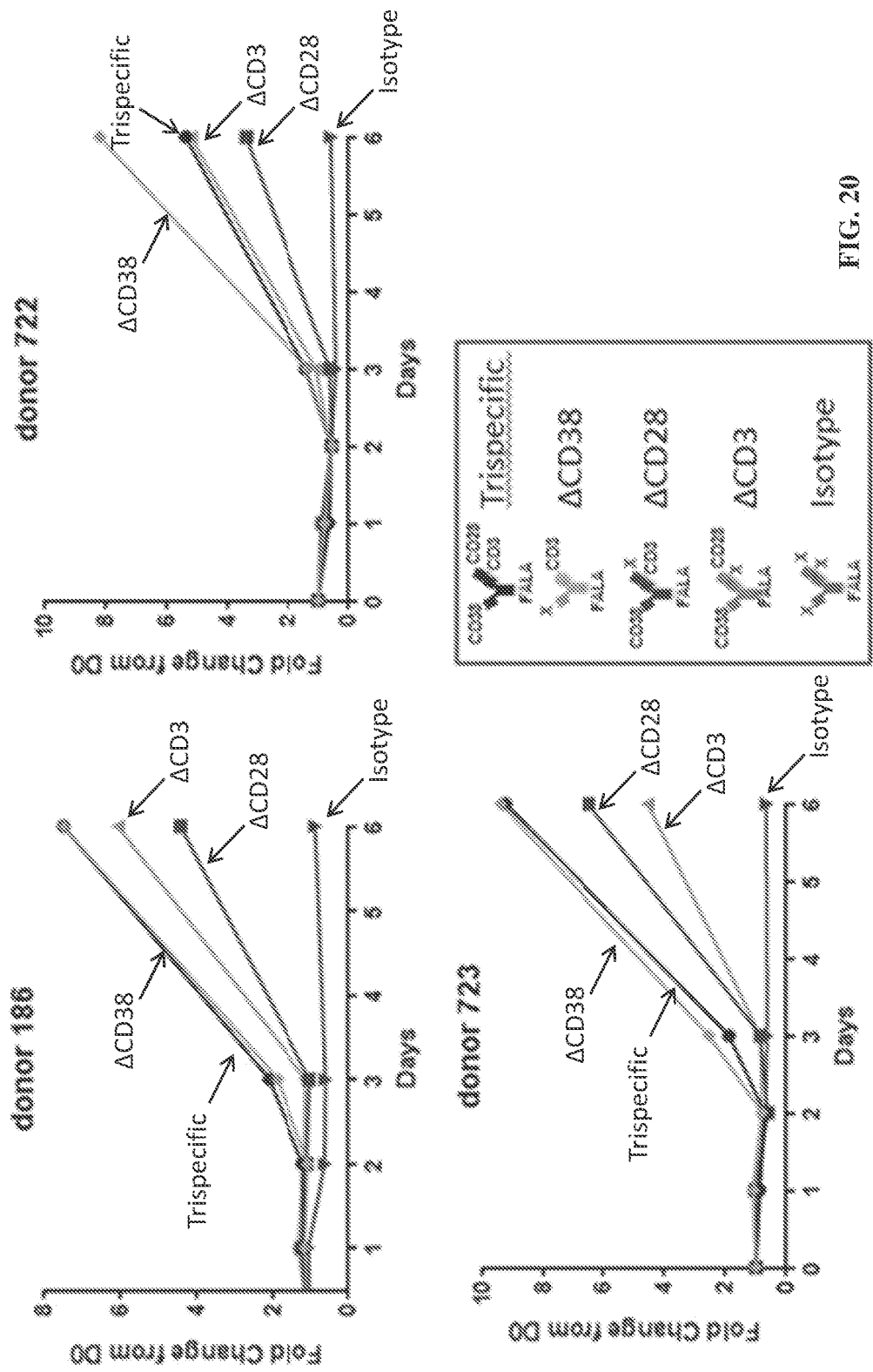


FIG. 20

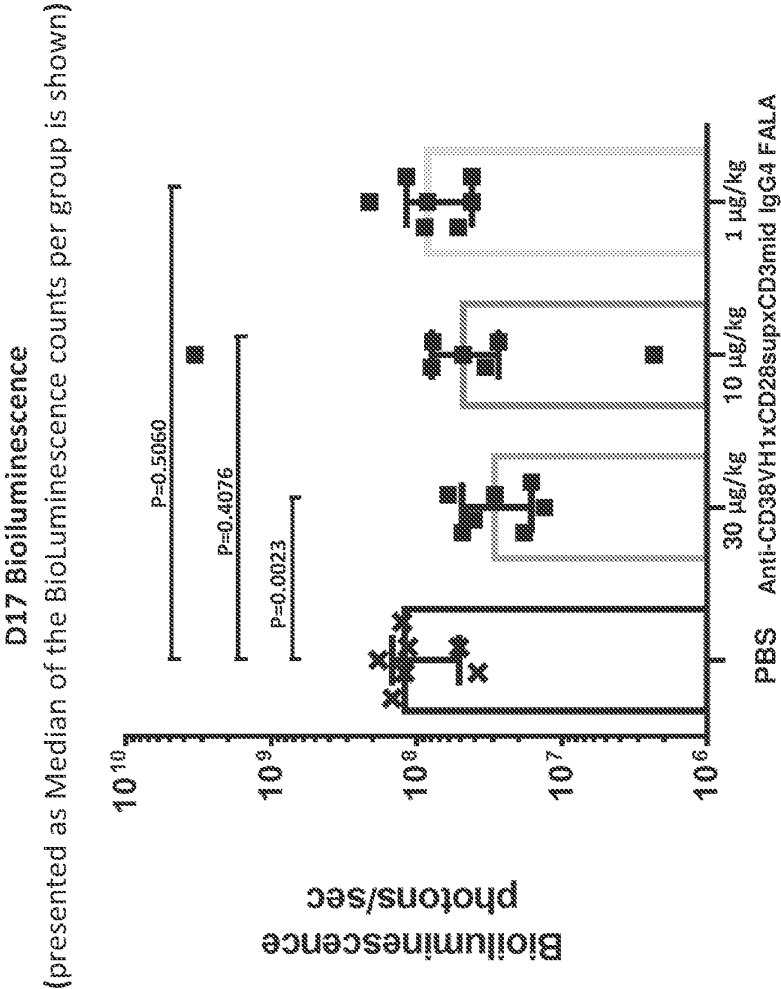


FIG. 21

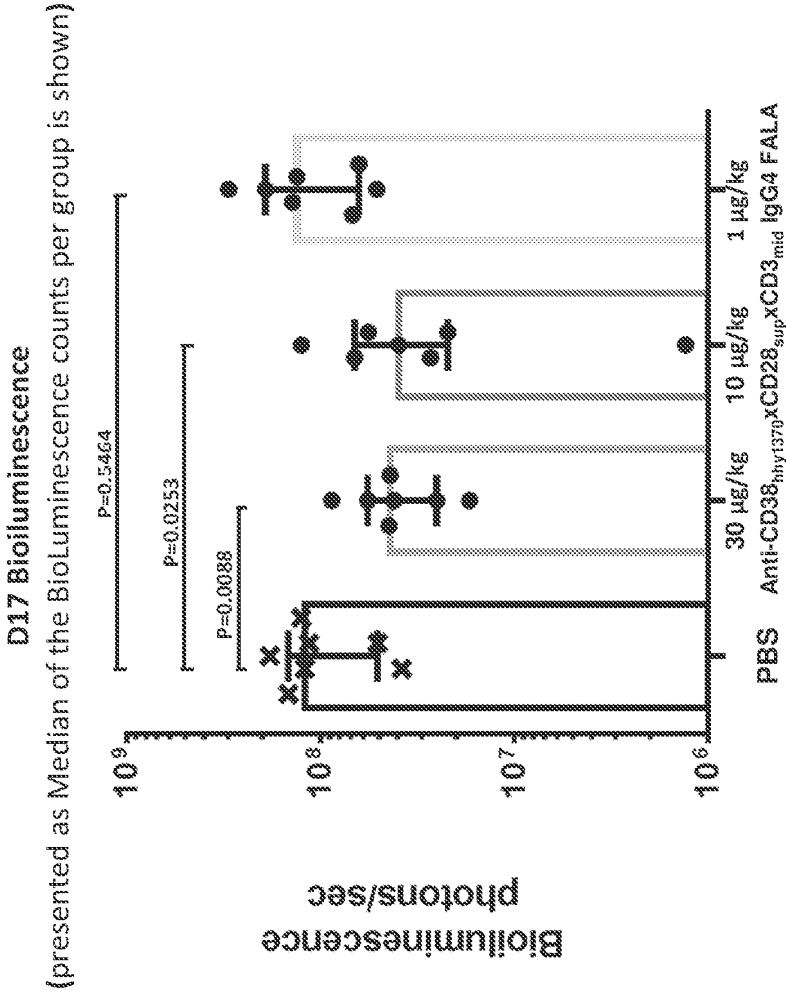
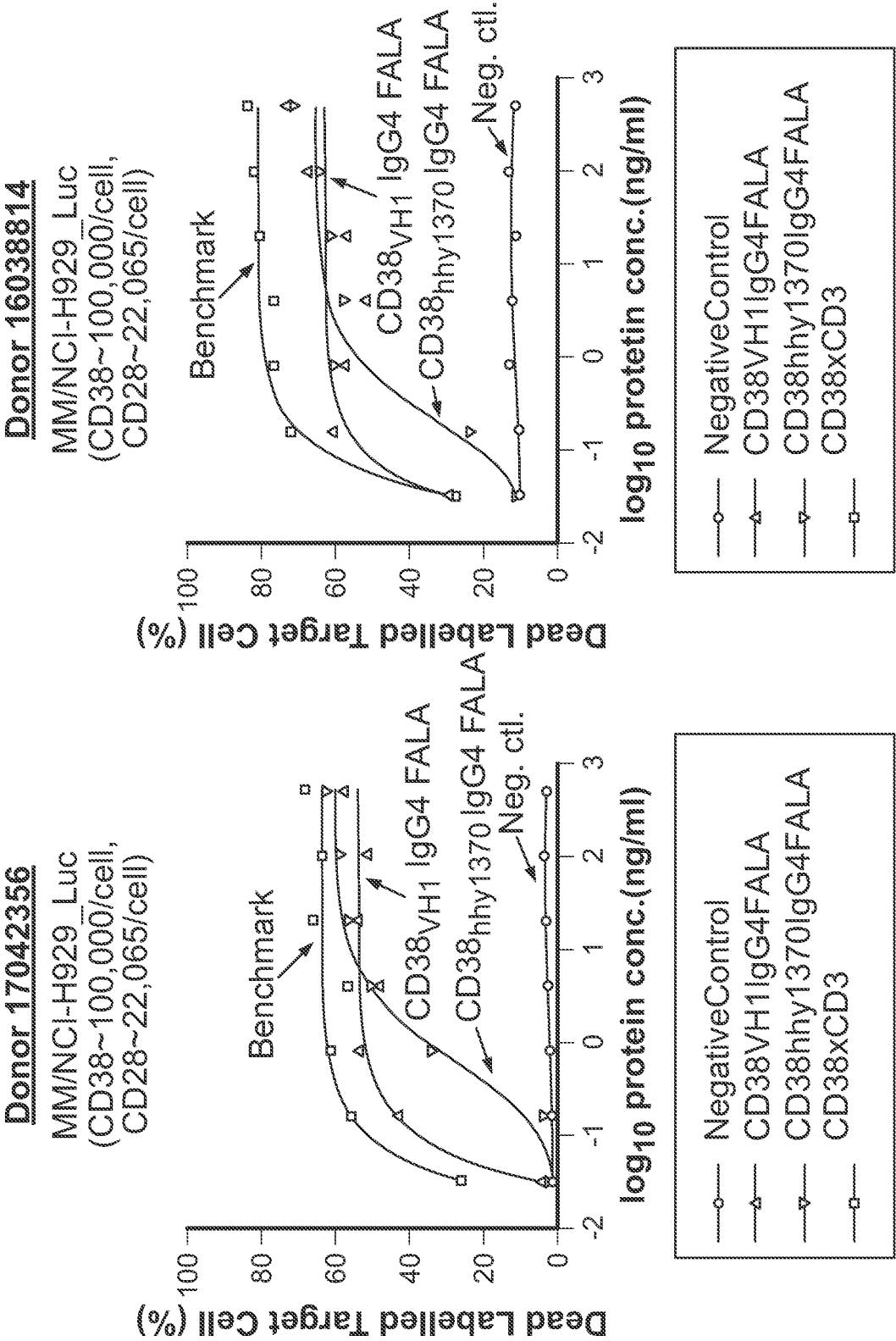


FIG. 22



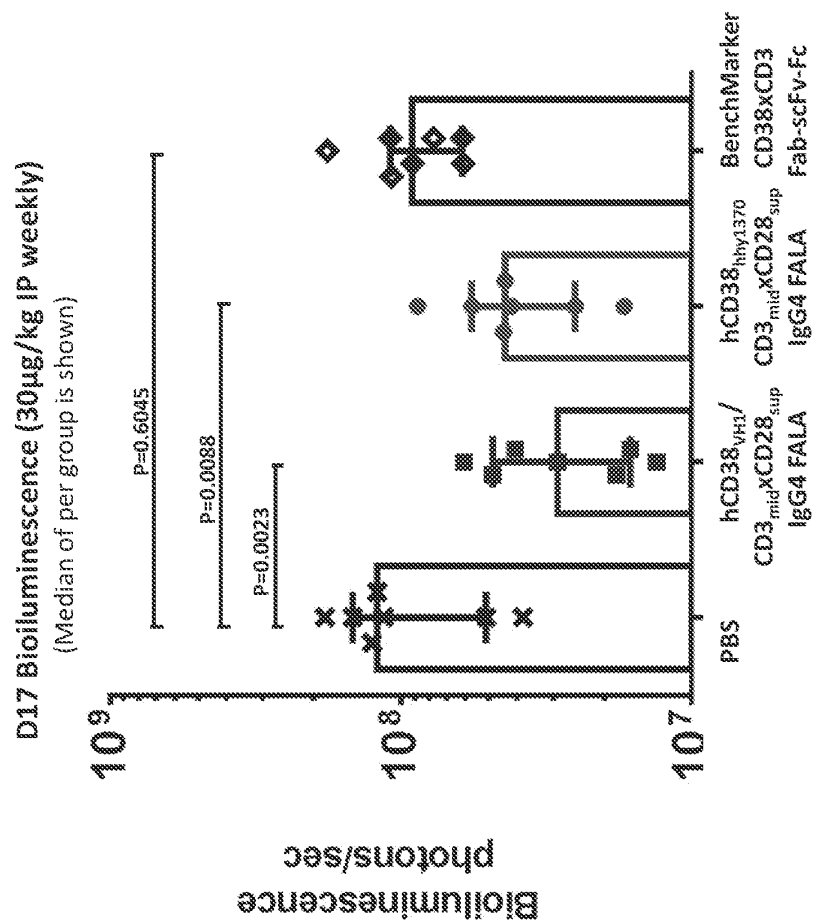


FIG. 23C

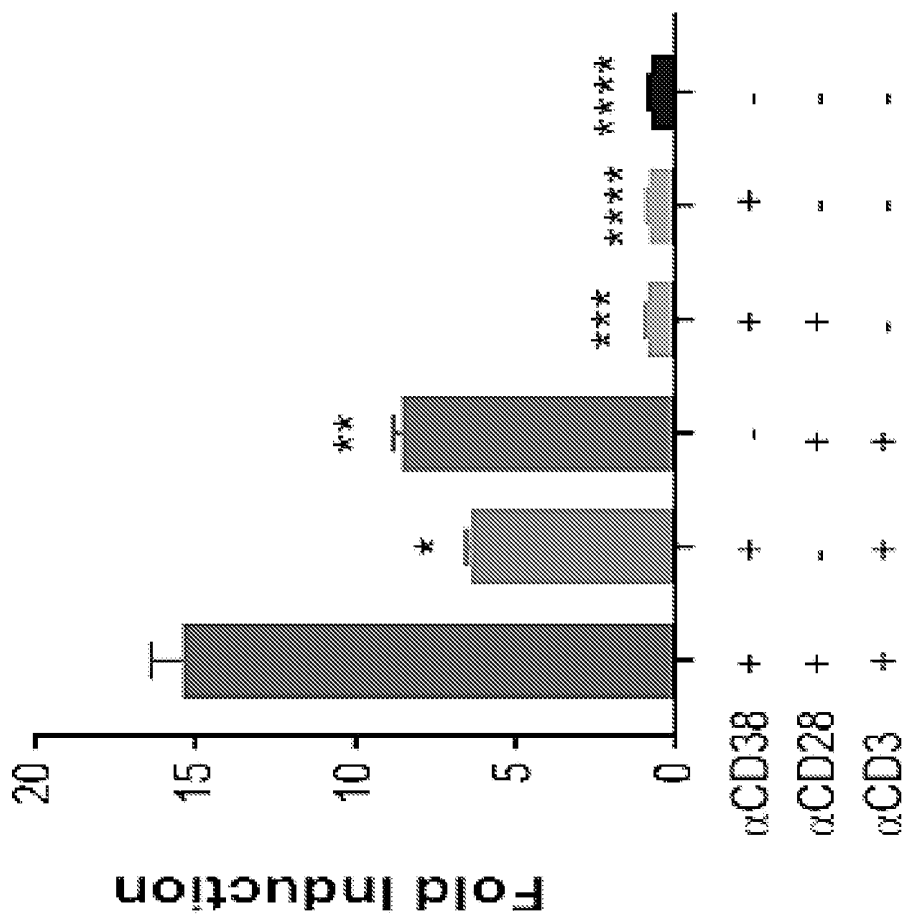


FIG. 24A

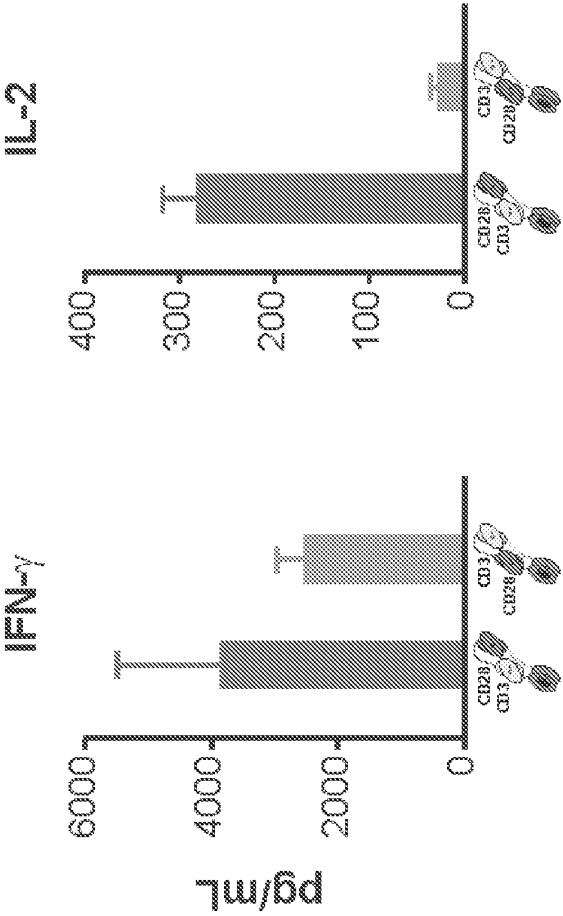


FIG. 24B

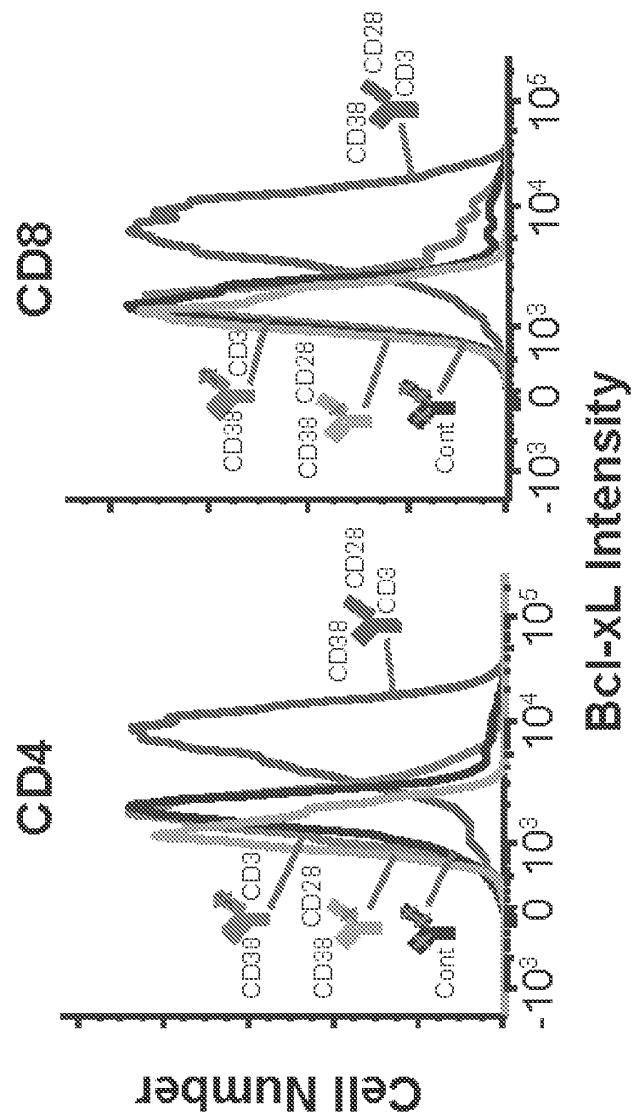


FIG. 25

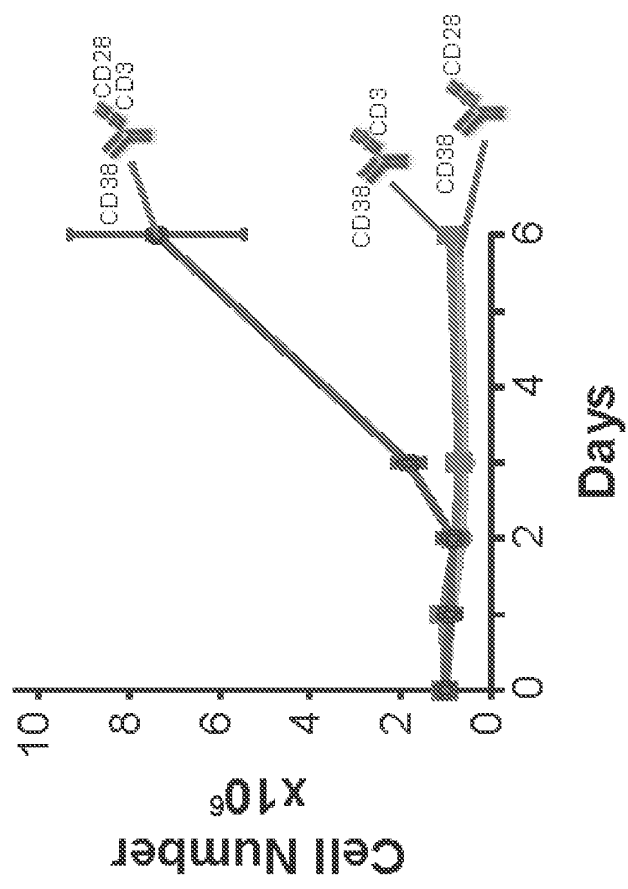


FIG. 26

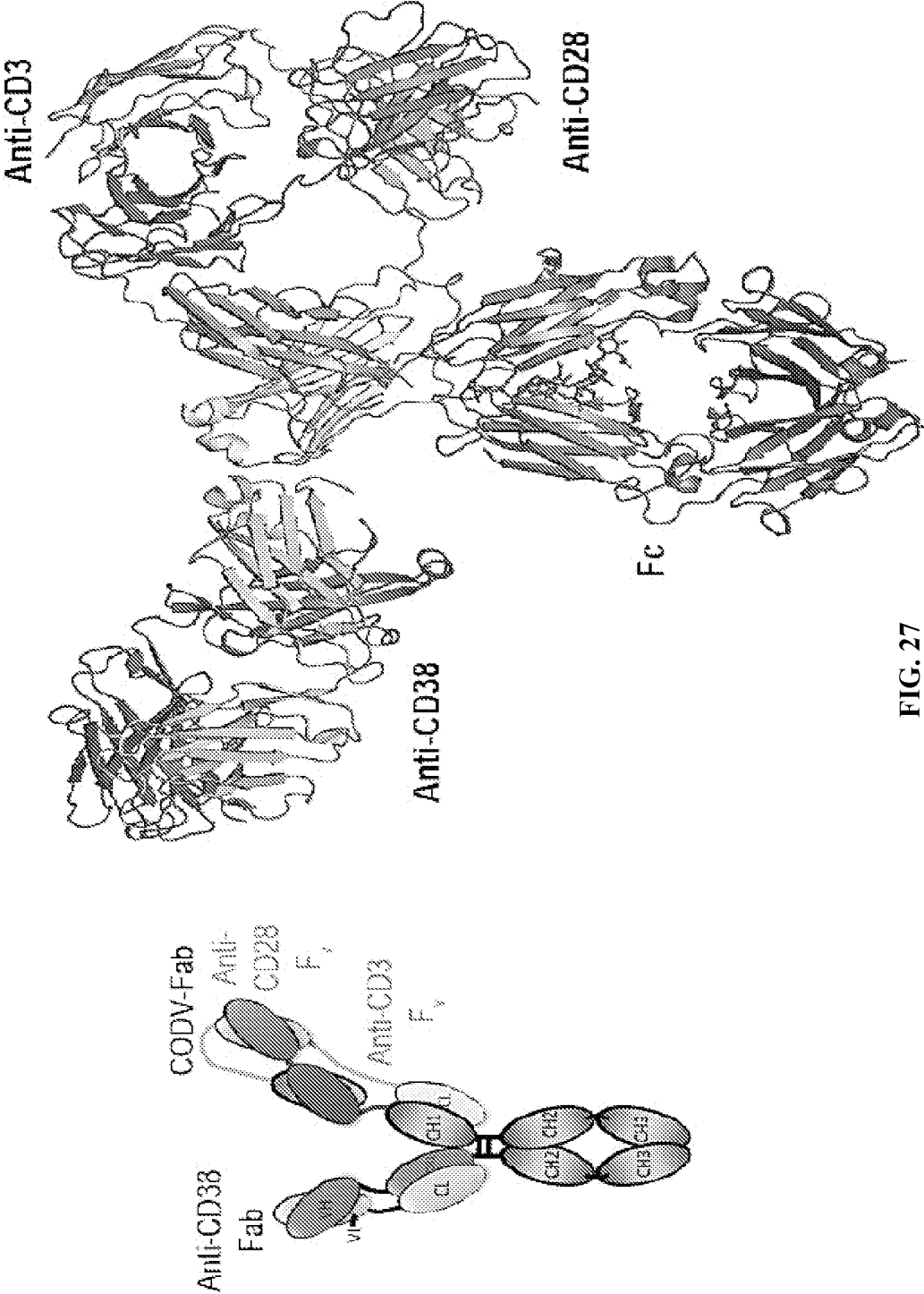


FIG. 27

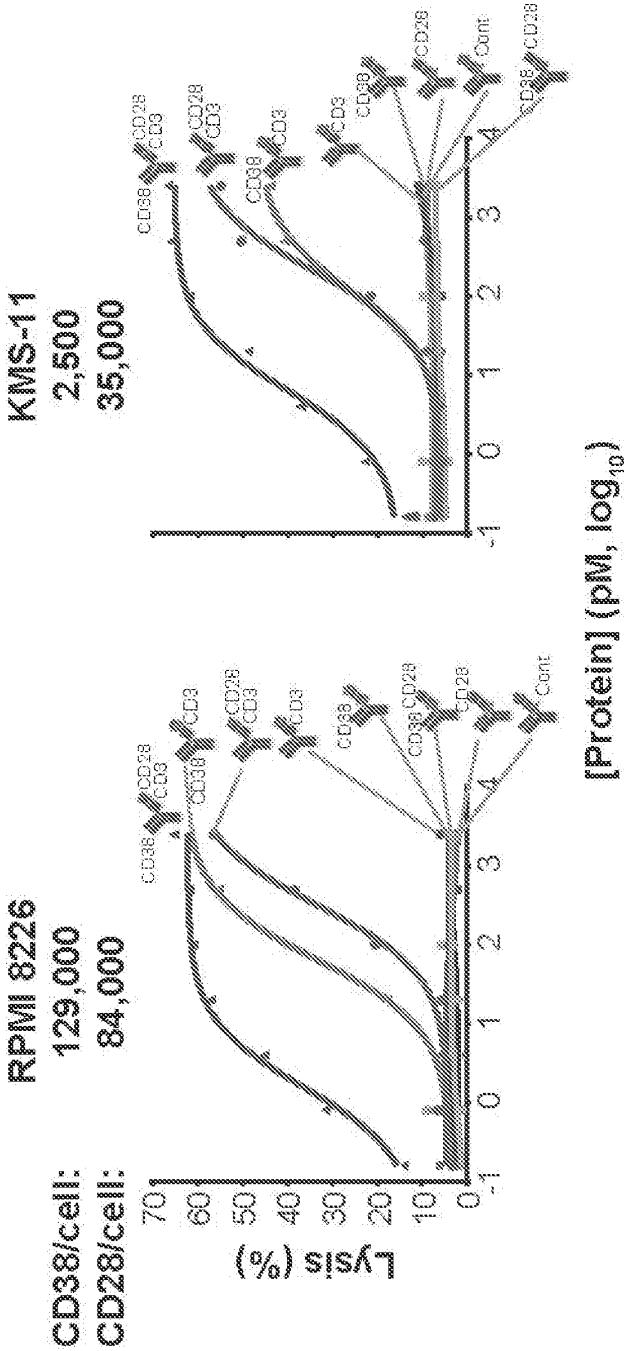


FIG. 28B

FIG. 28A

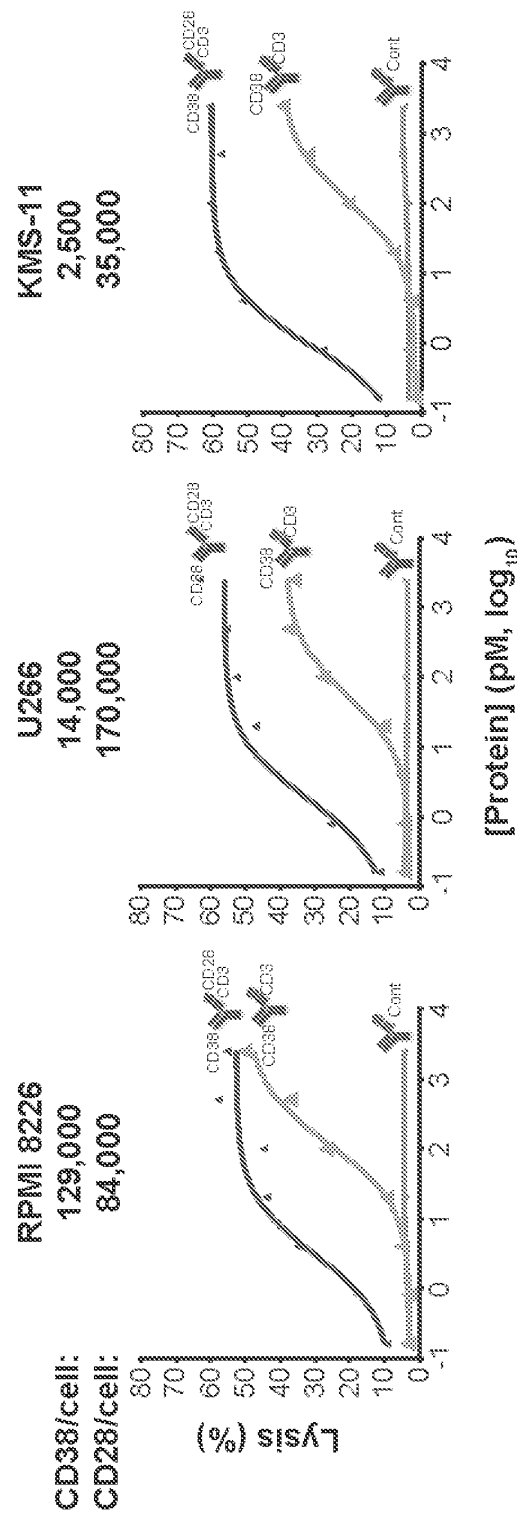


FIG. 29C

FIG. 29B

FIG. 29A

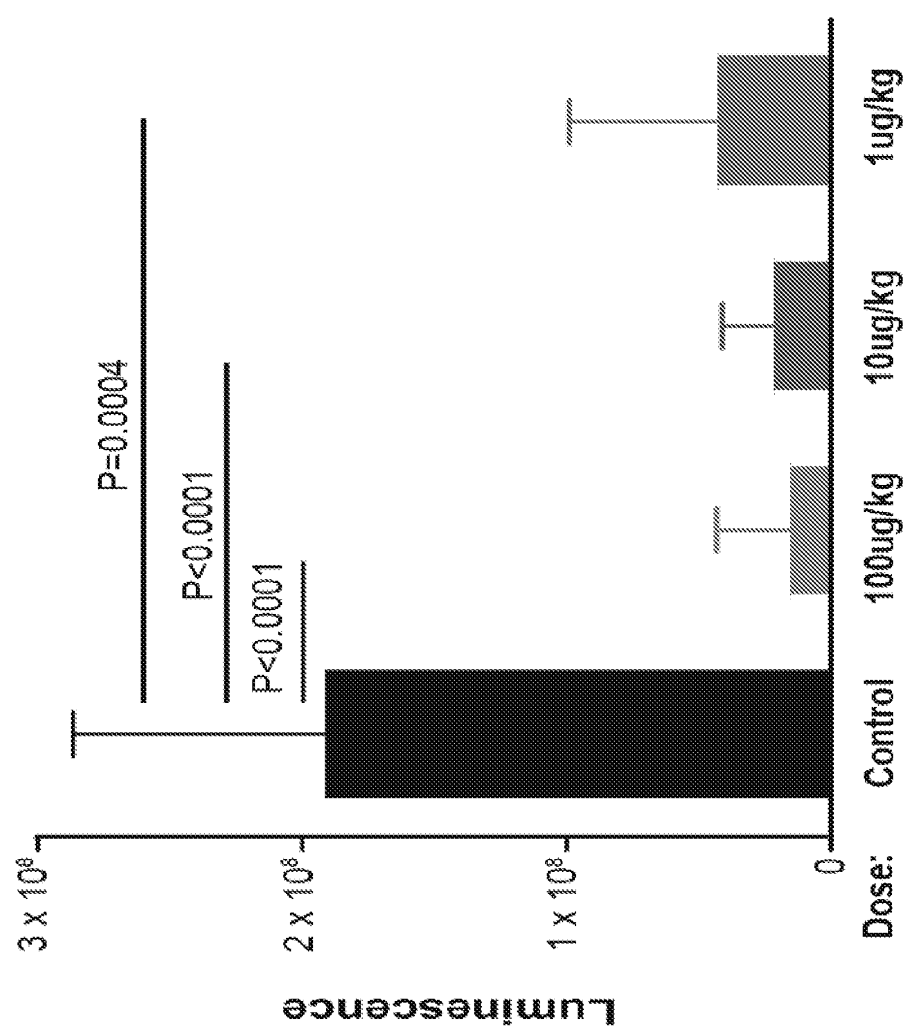


FIG. 30

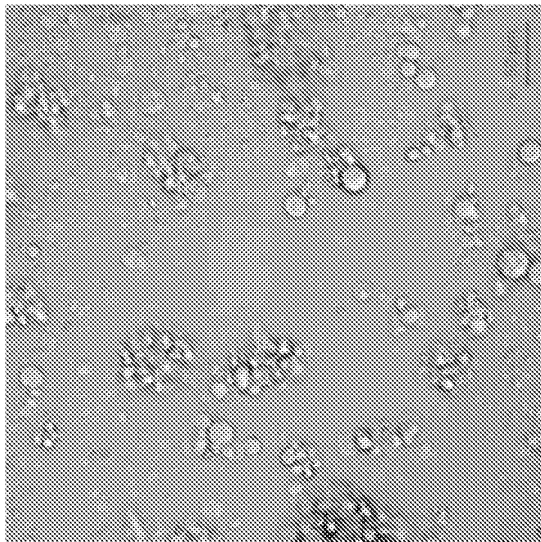


FIG. 31B

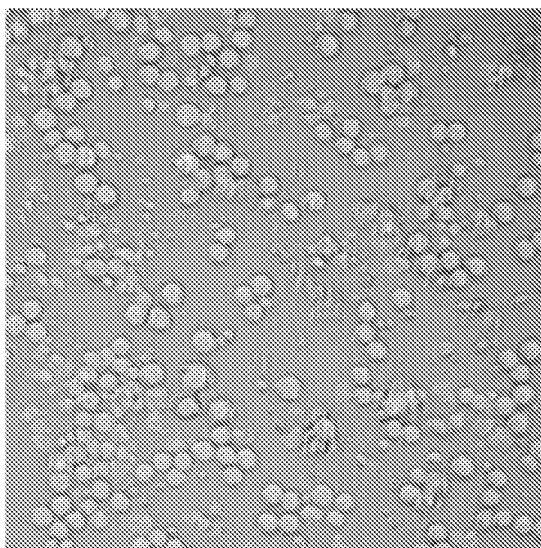


FIG. 31A

Wild type	
IgG1	CPPCPAPELLGGPS
IgG2	CPPCPAPPVAG-PS
IgG4	CPPCPAPEFLGGPS
Mutant	
IgG1 LALA/P239A	CPPCPAPEAAGGPS
IgG4 PVA	CPPCPAPPVAG-PS
IgG4 FALA	CPPCPAPEAAGGPS

FIG. 32

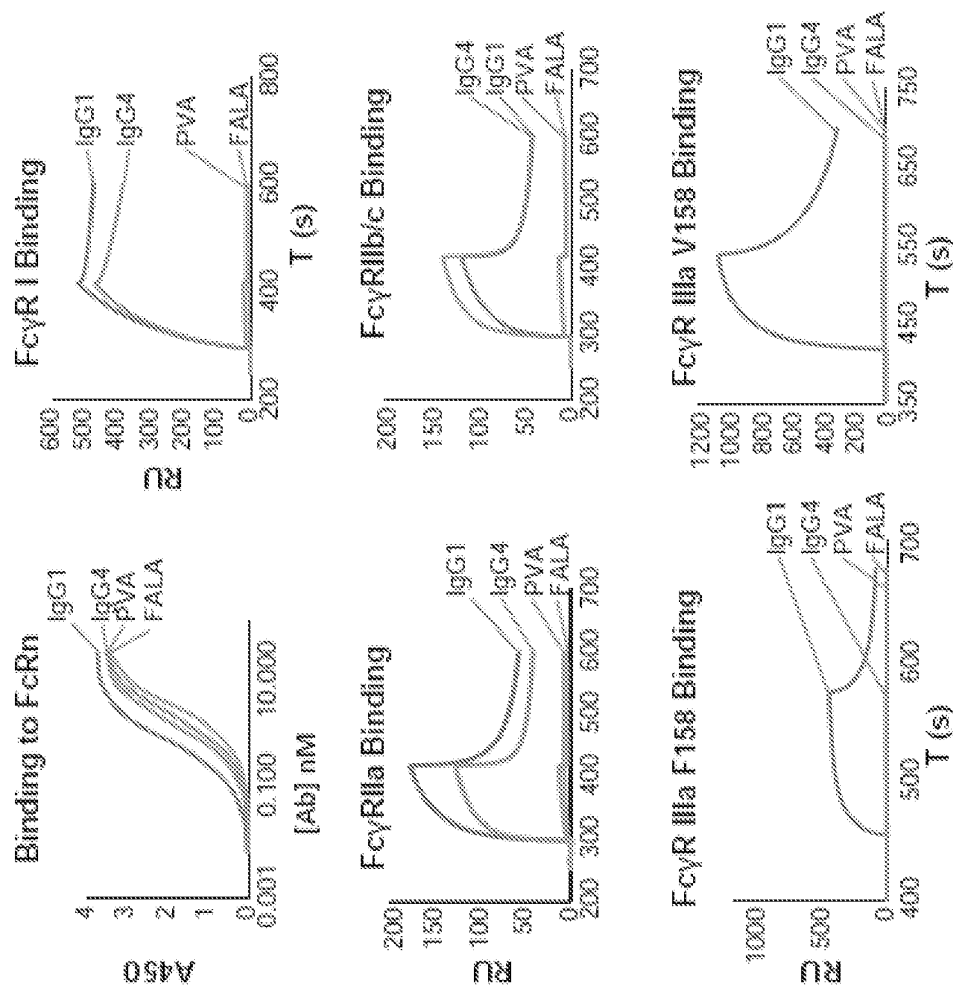


FIG. 33

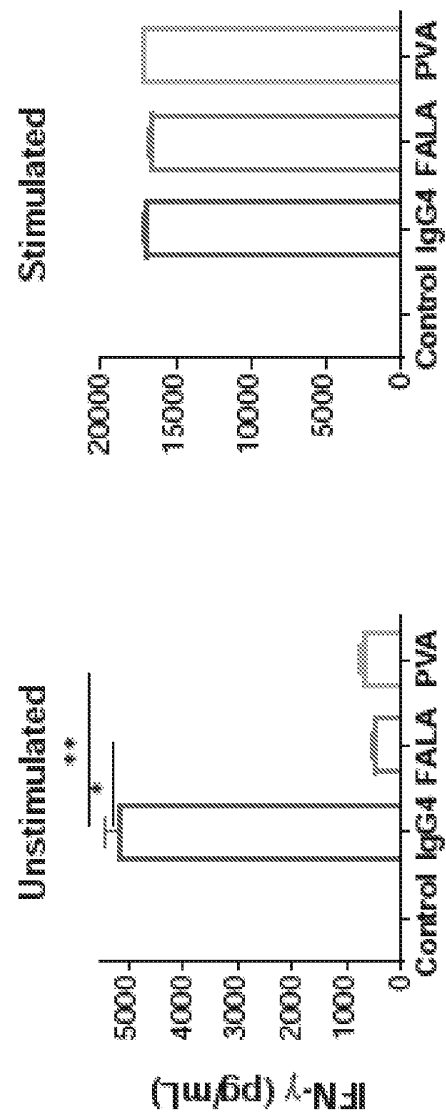


FIG. 34

		KMS-11
CD38/cell:	RPMI 8226	2,500
CD28/cell:	129,000	35,000
	84,000	

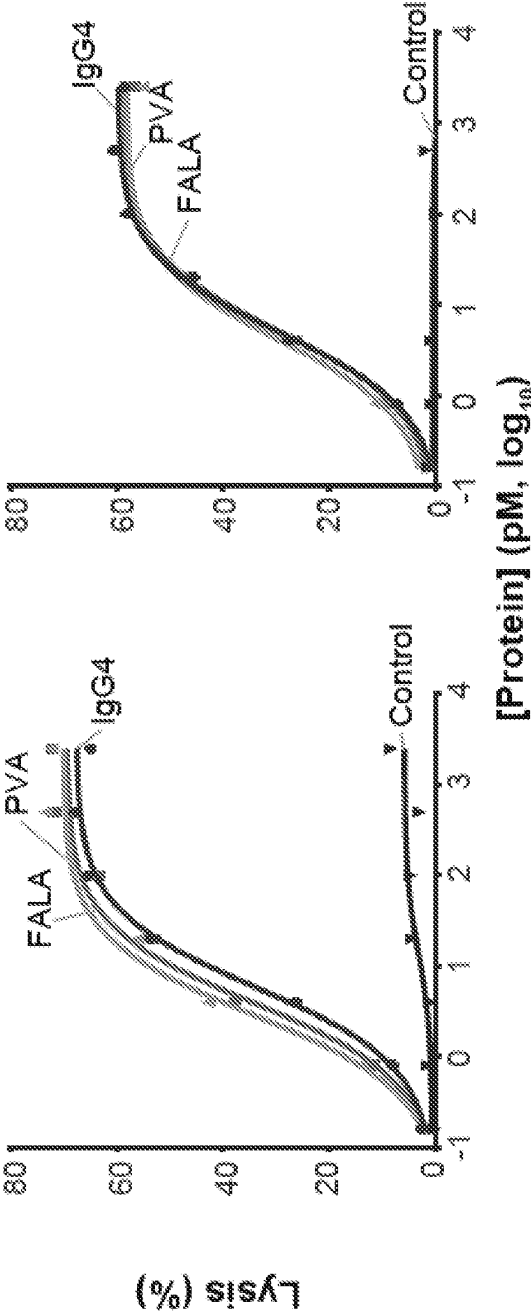


FIG. 35

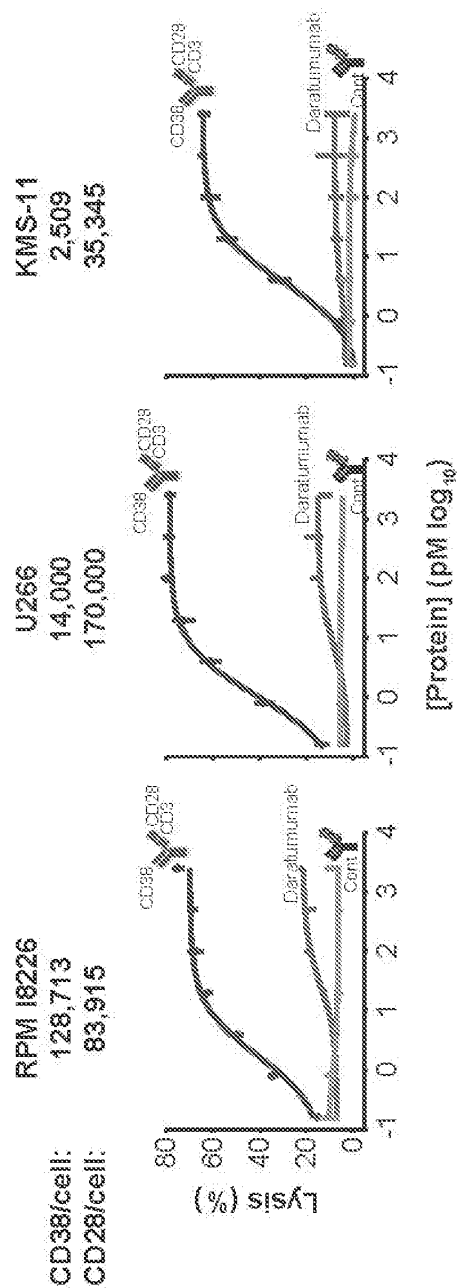


FIG. 36

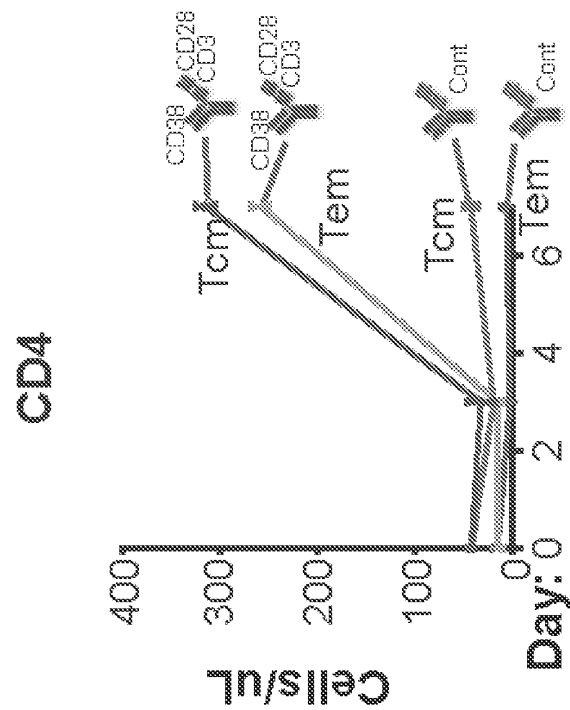


FIG. 37A

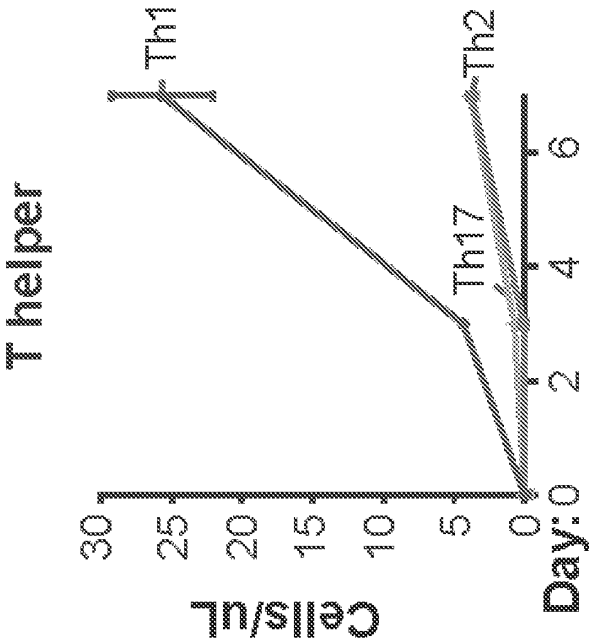


FIG. 37B

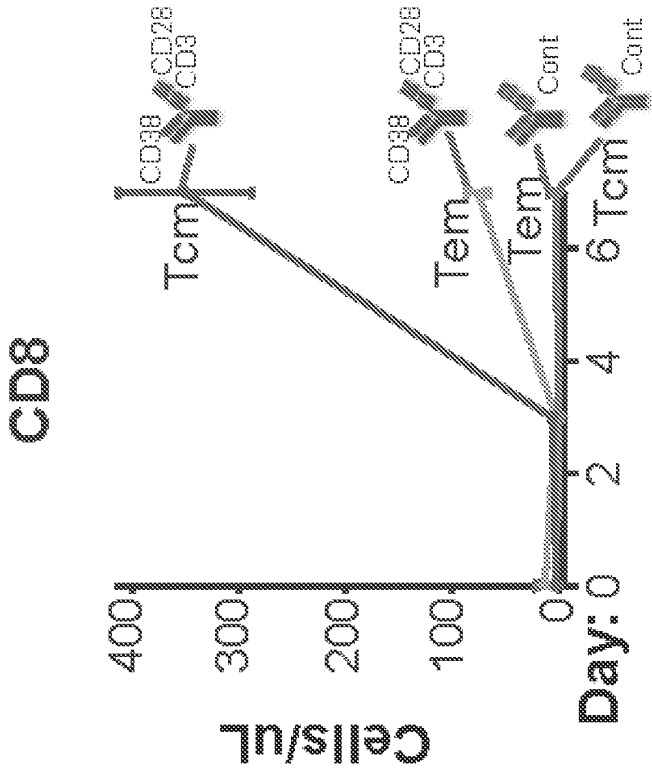


FIG. 37C

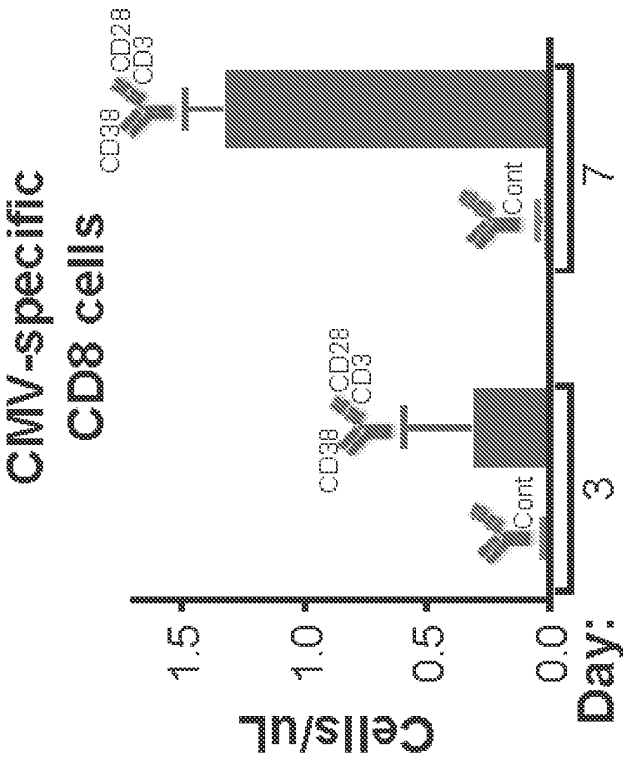


FIG. 37D

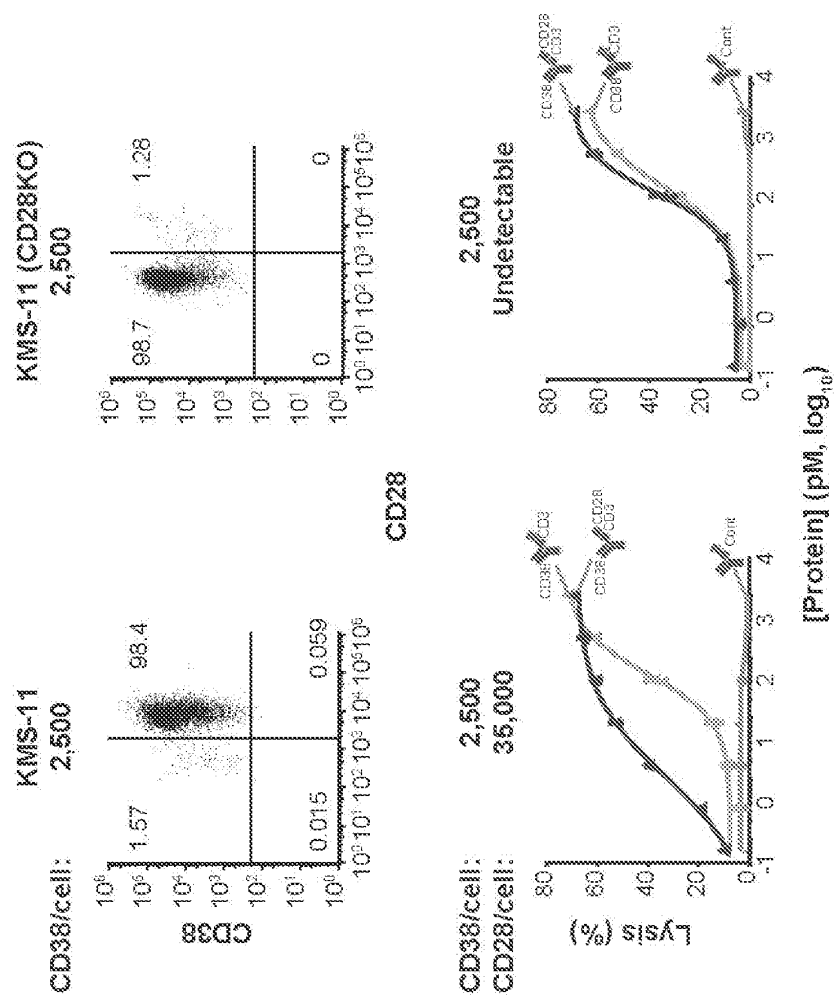


FIG. 38

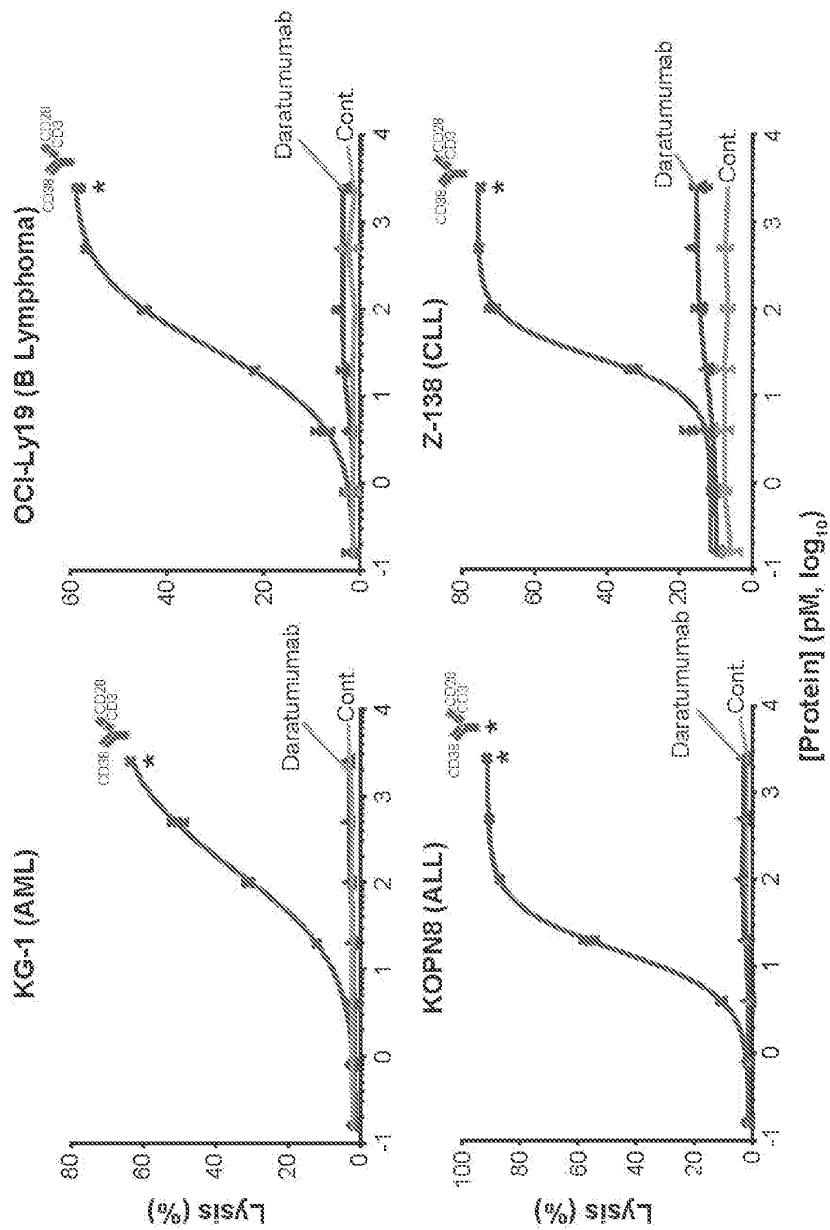


FIG. 39

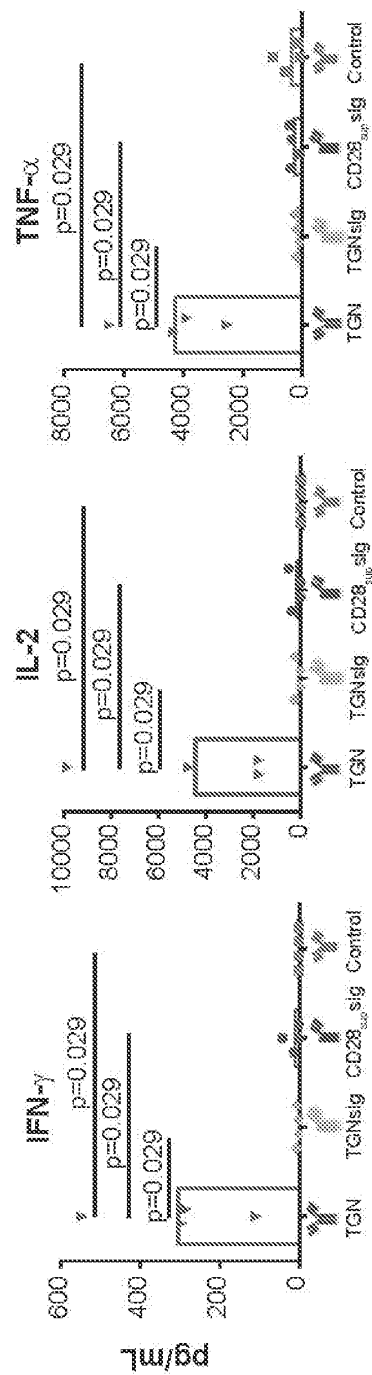


FIG. 40