

ANTICUERPO	RETRO-MUTACIONES VH / VL	SEQ ID NO CADENAS P/L	EXPRESIÓN TRANSITORIA (mg/L)	FAB T _m (°C)	TINCIÓN DE HPB- ALL CON RELACIÓN A QUIMERA OKT3
OKT3 QUIMÉRICO	N.A.	25/26	20	80.7	+++
VH/VL	-/-	27/39	50	88.1	-
VH/VL2	-/ M4L	27/41	47	90.6	-
VH/VL3	-/ M4L- F71Y	27/42	43	89.8	+
VH1/VL1	A49G/ F71Y	28/40	22	90.1	-
VH1/VL2	A49G/ M4L	28/41	42	90.5	-
VH1/VL3	A49G/ M4L-F71Y	28/42	40	90.7	+
VH2/VL1	I34M-A49G/ F71Y	29/40	51	89.5	-
VH2/VL2	I34M-A49G/ M4L	29/41	43	90.1	-
VH2/VL3	I34M-A49G/ M4L- F71Y	29/42	42.5	89.5	+
VH3/VL1	A49G-A71T/ F71Y	30/40	33.5	89.7	-
VH3/VL2	A49G-A71T/ M4L	30/41	42	90.4	-
VH3/VL3	A49G-A71T/ M4L- F71Y	30/42	56.5	89.8	+

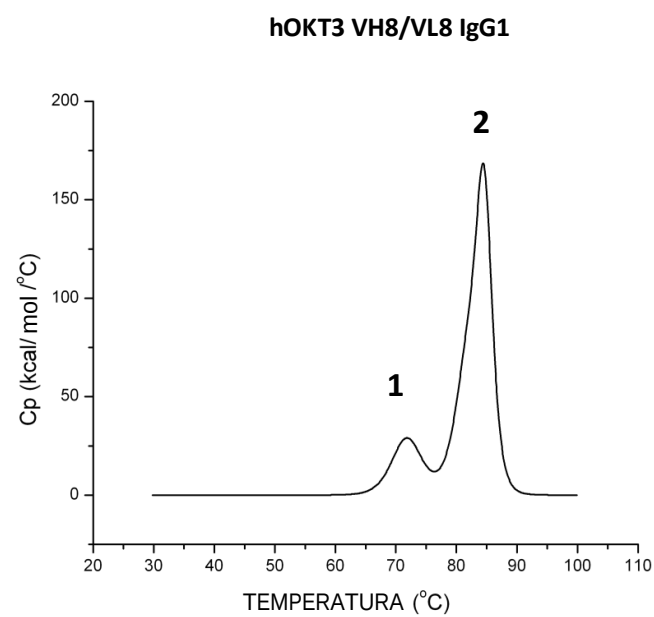
FIG. 1A

ANTICUERPO	RETRO-MUTACIONES	SEQ ID NO CADENAS P/L	EXPRESIÓN TRANSITORIA (mg/l)	FAB T _m (°C)	TINCIÓN DE HPB-ALL CON RELACIÓN A QUIMERA OKT3
VH4/VL2	I34M-A49G-A71T/ M4L	31/41	20	88.4	++
VH4/VL3	I34M-A49G-A71T/ M4L-F71Y	31/42	34	88.7	++
VH5/VL2	I34M-A49G-I69L-A71T-T73K/ M4L	32/41	40	87	++
VH5/VL3	I34M-A49G-I69L-A71T-T73K/ M4L-F71Y	32/42	36	87.2	++
VH5/VL4	I34M-A49G-I69L-A71T-T73K/ M4L-L46R-L47W-F71Y	32/43	12	80.3	+++
VH5/VL6	I34M-A49G-I69L-A71T-T73K / M4L-L46R-L47W-F71Y-P96F	32/45	15.6	78.6	+++
VH5/VL7	I34M-A49G-I69L-A71T-T73K / M4L-V33M-A34N-F71Y-P96F	32/46	35.4	84.1	++
VH6/VL3	I34M-V48I-A49G-I69L-A71T-T73K/ M4L-F71Y	33/42	23	88.3	++
VH6/VL4	I34M-V48I-A49G-I69L-A71T-T73K/ M4L-L46R-L47W-F71Y	33/43	14	80.8	+++
VH6/VL5	I34M-V48I-A49G-I69L-A71T-T73K/ M4L-V33M-A34N-F71Y	33/44	26	86.1	++
VH6/VL6	I34M-V48I-A49G-I69L-A71T-T73K / M4L-L46R-L47W-F71Y-P96F	33/45	14.8	79.1	+++
VH6/VL7	I34M-V48I-A49G-I69L-A71T-T73K / M4L-V33M-A34N-F71Y-P96F	33/46	32	85.3	++

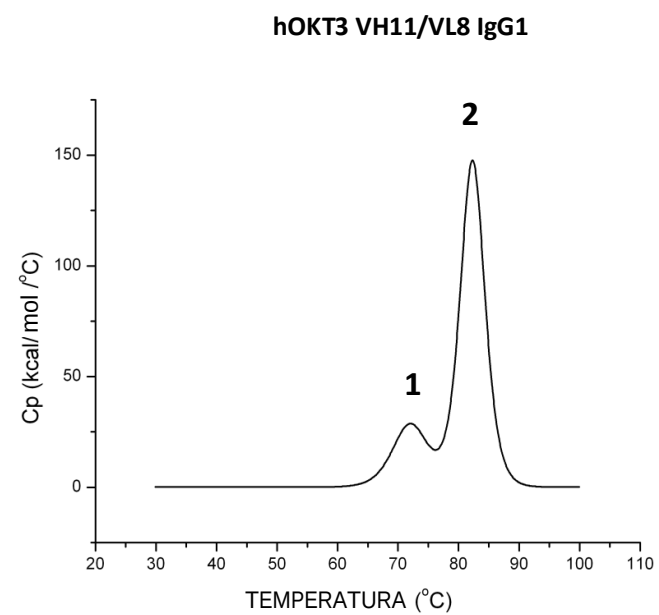
FIG. 1B

ANTICUERPO	RETRO-MUTACIONES	SEQ ID NO CADENAS P/L	EXPRESIÓN TRANSITORIA (mg/l)	FAB T _m (°C)	TINCIÓN DE HPB-ALL CON RELACIÓN A QUIMERA OKT3
VH6/VL8	I34M-V48I-A49G-I69L-A71T-T73K /M4L-L46R-L47W-R66G-F71Y	33/47	7	80.6	+++
VH7/VL3	I34M-A49G-R58N-I69L-A71T-T73K/ M4L-F71Y	34/42	21	86.1	++
VH7/VL4	I34M-A49G-R58N-I69L-A71T-T73K/ M4L-L46R-L47W-F71Y	34/43	25	80.5	+++
VH7/VL5	I34M-A49G-R58N-I69L-A71T-T73K/ M4L-V33M-A34N-F71Y	34/44	26	84.12	++
VH8/VL4	I34M-V48I-A49G-R58Y-I69L-A71T-T73K / M4L-L46R-L47W-F71Y	35/43	7	80.9	+++
VH8/VL8	I34M-V48I-A49G-R58Y-I69L-A71T-T73K / M4L-L46R-L47W-R66G-F71Y	35/47	23	83.5	+++
VH9/VL8	I34M-V48I-A49G-R58Y-G65S-I69L-A71T-T73K / M4L-L46R-L47W-R66G-F71Y	36/47	13	82	+++
VH10/VL4	I34M-V48I-A49G-R58Y-G65S-F67A-I69L-A71T-T73K / M4L-L46R-L47W-F71Y	37/43	7	78.6	+++
VH10/VL8	I34M-V48I-A49G-R58Y-G65S-F67A-I69L-A71T-T73K / M4L-L46R-L47W-R66G-F71Y	37/47	10	80.4	+++
VH11/VL4	I34M-V48I-A49G-R58Y-I69L-A71T-T73K-N82aS/ M4L-L46R-L47W-F71Y	38/43	8	80.3	+++
VH11/VL8	I34M-V48I-A49G-R58Y-I69L-A71T-T73K-N82aS / M4L-L46R-L47W-R66G-F71Y	38/47	15	82.3	+++

FIG. 1C



Tm(1): 71.8; Tm(2): 83.5 (FAB)

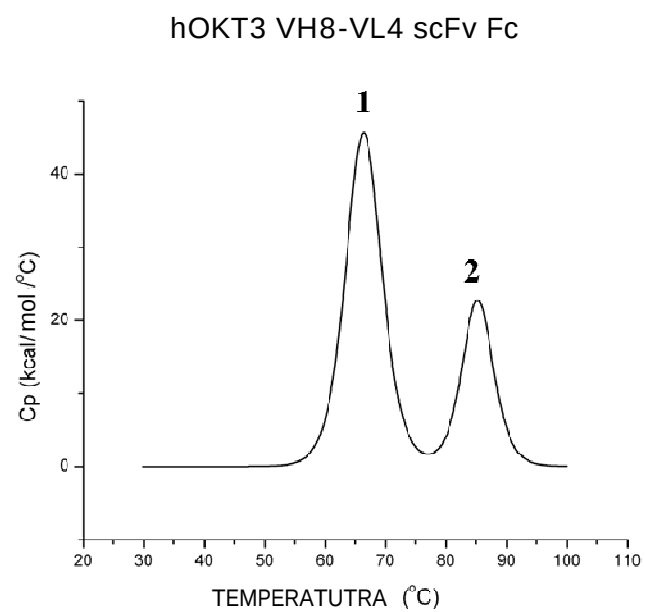


Tm(1): 72.1; Tm(2): 82.3 (FAB)

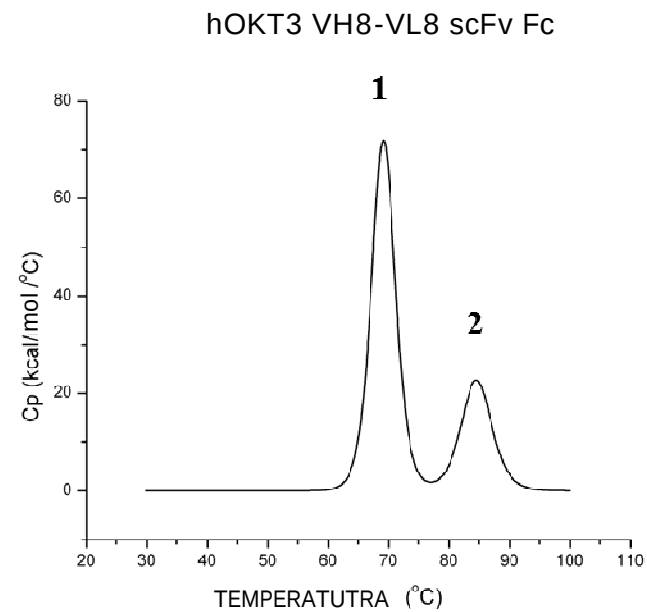
FIG. 1D

FUSIÓN DE scFv-Fc	SEQ ID NO	EXPRESIÓN TRANSITORIA (mg/L)	scFv T_m (°C)	TINCIÓN DE HPB-ALL CON RELACIÓN A QUIMERA OKT3
OKT3 DE RATÓN	52	0.35	-	++
VH5-VL3	53	21	71.2	+
VH6-VL4	54	29	65.3	++
VH6-VL5	55	27	71.2	++
VH8-VL4	56	28	66.4	+++
VH8-VL8	57	28	69.2	+++

FIG. 1E



Tm(1): 66.4 (scFv); Tm(2): 85.3 (CH3)



Tm(1) : 69.2 (scFv); Tm(2) : 84.6 (CH3)

FIG. 1F

ANTICUERPO	RETRO-MUTACIONES VH/VL	SEQ ID NO CADENAS P/L	FORMATO	EXPRESIÓN TRANSITORIA (mg/L)	SPR-UNIÓN A PROTEÍNAS 1- 26_Fc ÉPSILON CD3 DE HUMANO/ MONO CYNOMOLGUS
SP34 QUIMÉRICO	N.A.	62/63	IgG1	7	++++
VH1/VL1	-/-	64/69	IgG1	8	+
VH1/VL2	-/Q89A	64/70	IgG1	1	++++
VH1/VL3	-/8P DELETADO	64/71	IgG1	0.5	-
VH1/VL4	-/8P-Q89A DELETADO	64/72	IgG1	0.5	++++
VH1/VL5	-/A2I-Q89A	64/73	IgG1	2.6	++++
VH1/VL6	-/F44P-Q89A	64/74	IgG1	0.9	++++
VH1/VL7	-/A2I-F44P-Q89A	64/75	IgG1	SIN EXPRESIÓN	NO PROBADO
VH1/VL8	-/L66G-Q89A	64/76	IgG1	0.8	+
VH1/VL9	-/A2I-L66G-Q89A	64/77	IgG1	SIN EXPRESIÓN	NO PROBADO
VH1/VL10	-/F87Y-Q89A	64/78	IgG1	6	++++
VH1/VL11	-/L66G-D69T-Q89A	64/79	IgG1	0.8	+
VH1/VL12	-/D69T-Q89A	64/80	IgG1	1.5	++
VH1/VL13	-/S25A/Q89A	64/81	IgG1	1	+++
VH1/VL14	-/G46L-Q89A	64/82	IgG1	3	-
VH1/VL15	-/E38Q-Q89A	64/83	IgG1	3	++++
VH1/VL16	-/A2I-D69T-Q89A	64/84	IgG1	0.5	+
VH1/VL17	-/A2I-S25A-Q89A	64/85	IgG1	1	++
VH1/VL18	-/A2I-Q89A-Q100G	64/86	IgG1	1	++
VH1/VL19	-/A2I-D69T-F87Y-Q89A	64/87	IgG1	0.2	+
VH1/VL20	-/A2I-E38Q-D69T-F87Y-Q89A	64/88	IgG1	SIN EXPRESIÓN	NO PROBADO
VH1/VL21	-/A2I-F87Y-Q89A	64/89	IgG1	8	++++
VH1/VL22	-/A2I-E38Q-F87Y-Q89A	64/90	IgG1	2	+++

FIG. 2A

FUSIÓN DE ScFv-Fc	RETRO-MUTACIONES VH/VL	SEQ ID NO CADENAS P/L	FORMATO	EXPRESIÓN TRANSITORIA (mg/L)	SPR-UNIÓN A PROTEÍNAS 1-26_Fc ÉPSILON CD3 DE HUMANO/MONO CYNOMOLGUS
VH2/VL21	G65S /A2I -F87Y-Q89A	91	scFv-Fc	5	+++
VH3/VL23	G65S-W100eY /A2I-F87Y-Q89A-W91F	92	scFv-Fc	10	++
VH4/VL23	G65S-W100eF /A2I-F87Y-Q89A-W91F	93	scFv-Fc	5.5	++++
VH5/VL23	W100eY/A2I-F87Y-Q89A-W91F	94	scFv-Fc	15	++++
VH1/VL24	-/A2I-T27A-G27aA- F87Y-Q89A	349	scFvFc	SIN EXPRESIÓN	NO PROBADO
VH1/VL25	-/A2I-V27cA-T28A- F87Y-Q89A	350	scFvFc	4	-
VH1/VL26	-/A2I-T29A-S30A- F87Y-Q89A	351	scFvFc	12	++++
VH1/VL27	-/A2I-N31A-Y32A- F87Y-Q89A	95	scFv-Fc	2	-
VH1/VL28	-/A2I-N52A-K53A- F87Y-Q89A	96	scFv-Fc	SIN EXPRESIÓN	NO PROBADO
VH1/VL29	-/A2I-R54A-P56A- F87Y-Q89A	97	scFv-Fc	4	-
VH1/VL30	-/A2I-Y92A-S93A- F87Y-Q89A	98	scFv-Fc	2	+
VH1/VL31	-/A2I-N94A -F87Y-Q89A	99	scFv-Fc	2	++
VH5/VL32	W100eY/A2I-T29A-S30A-T51A-F87Y-Q89A- W91F	100	scFv-Fc	25	++++

FIG. 2B

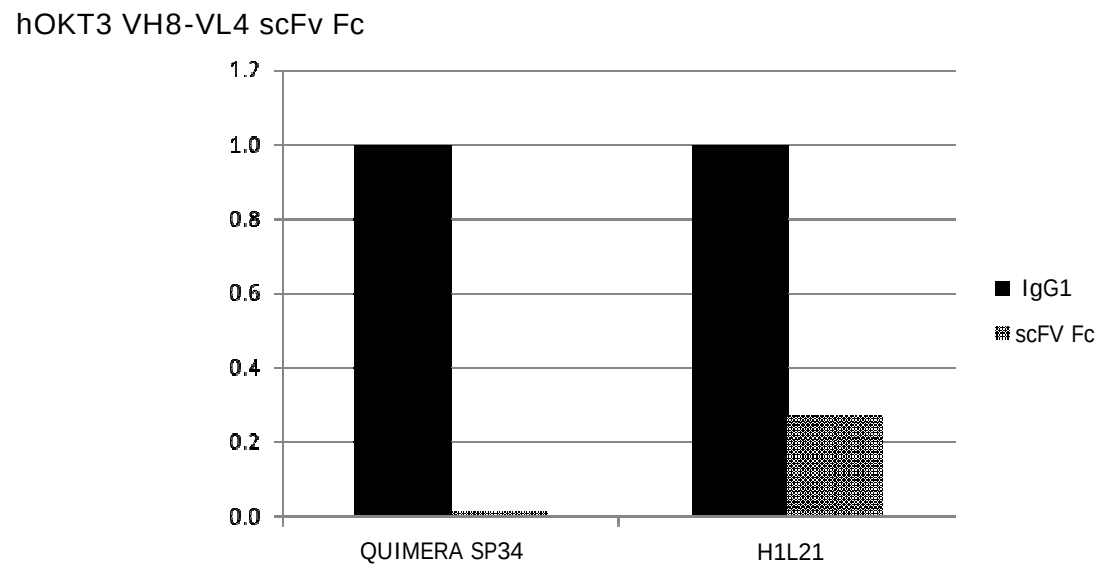


FIG. 3

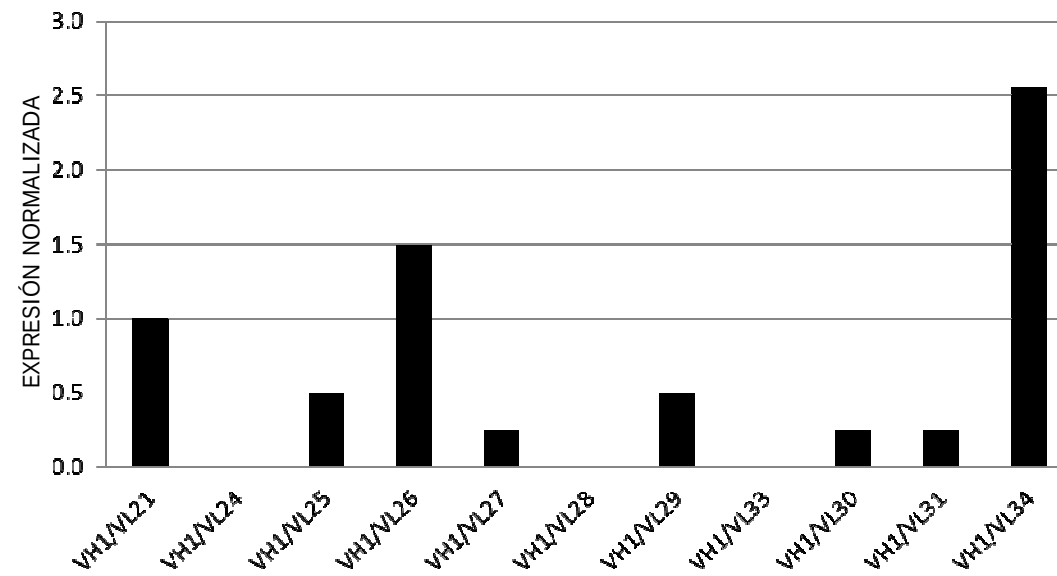
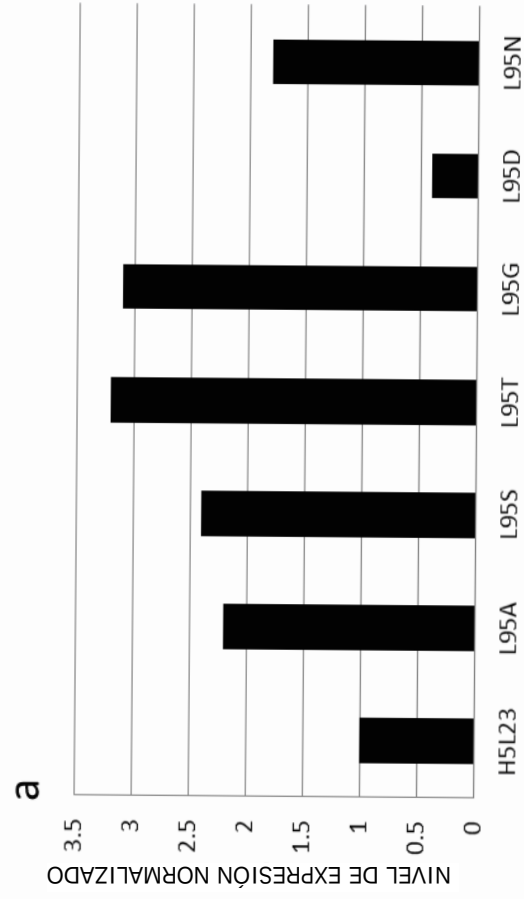
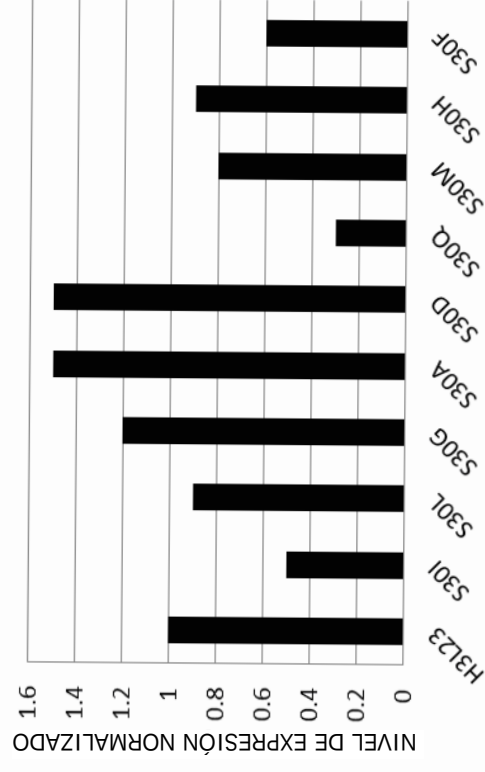
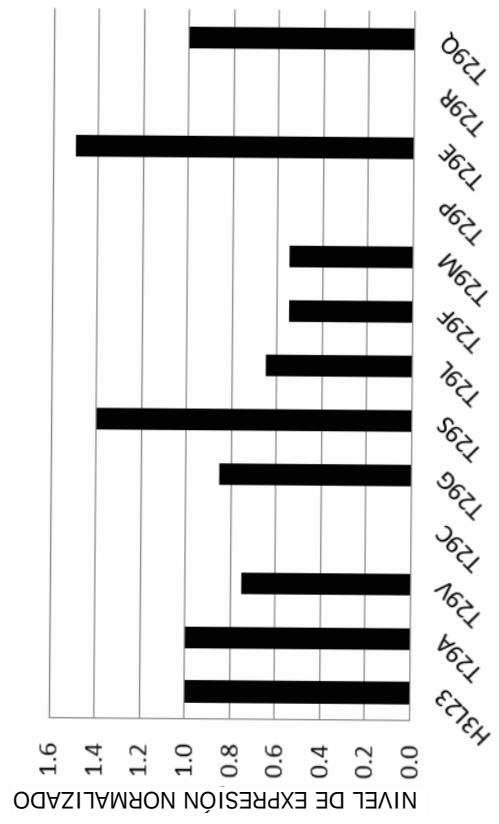


FIG. 4

FIG. 5

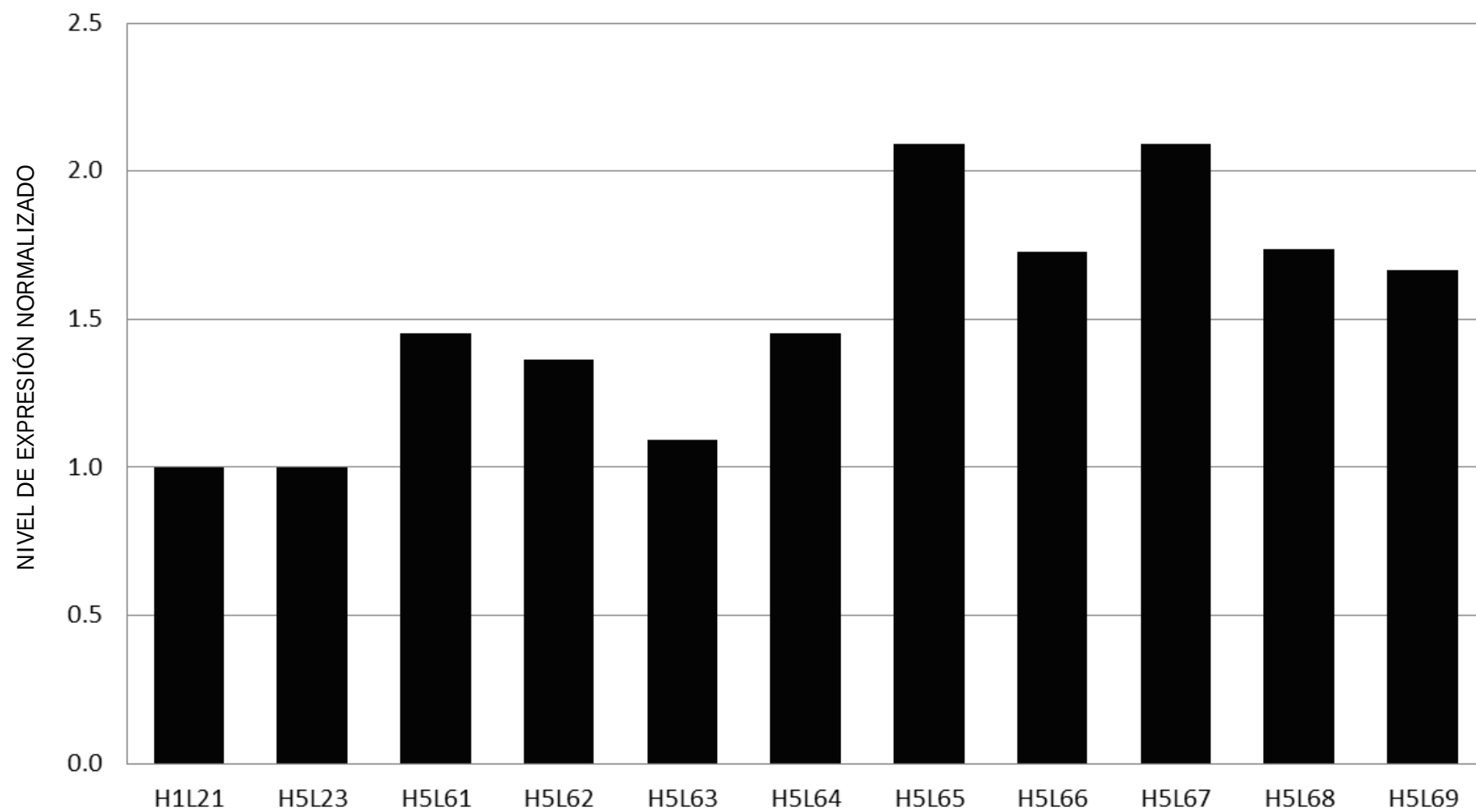


a

b

c

FIG. 6



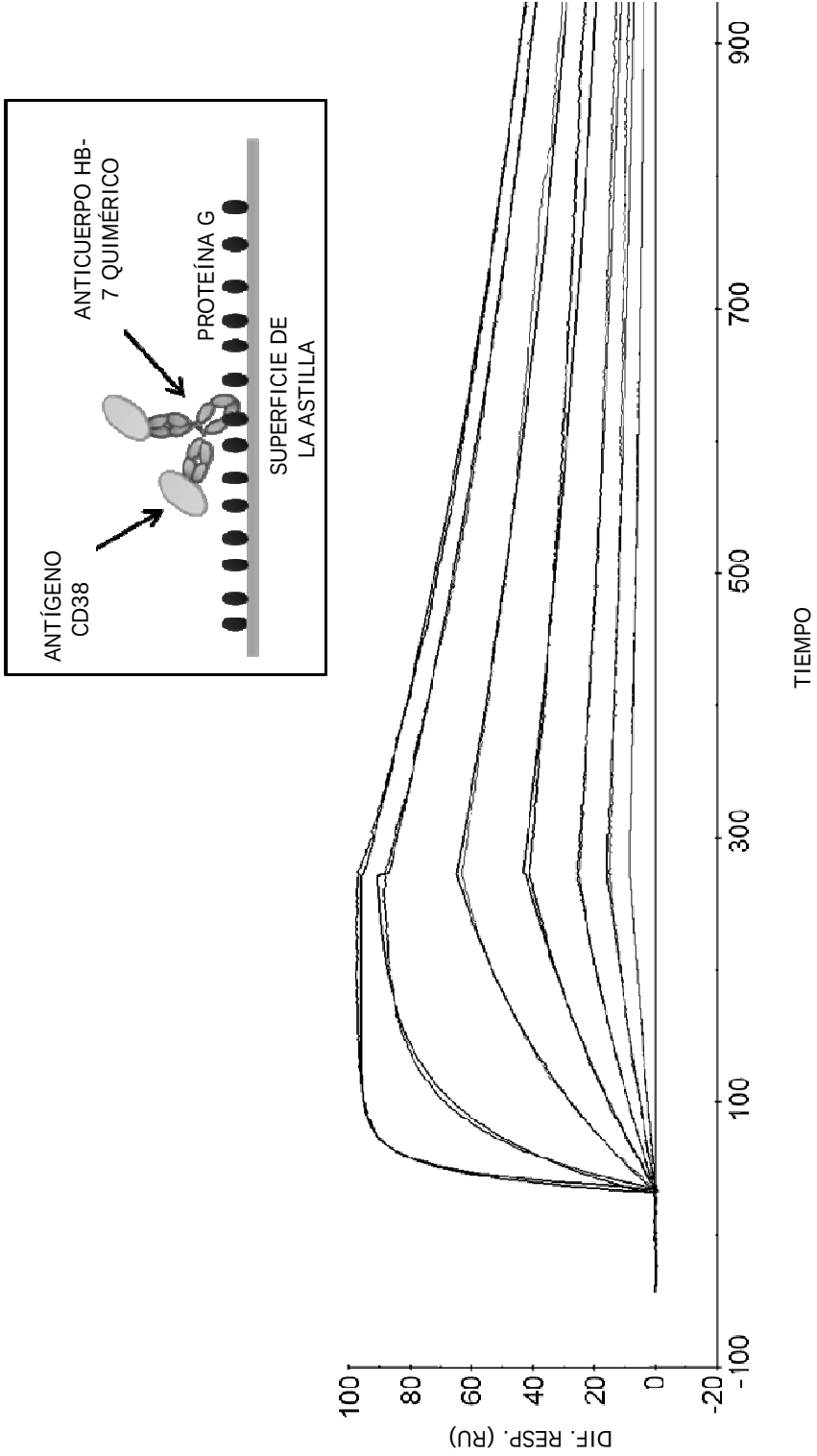
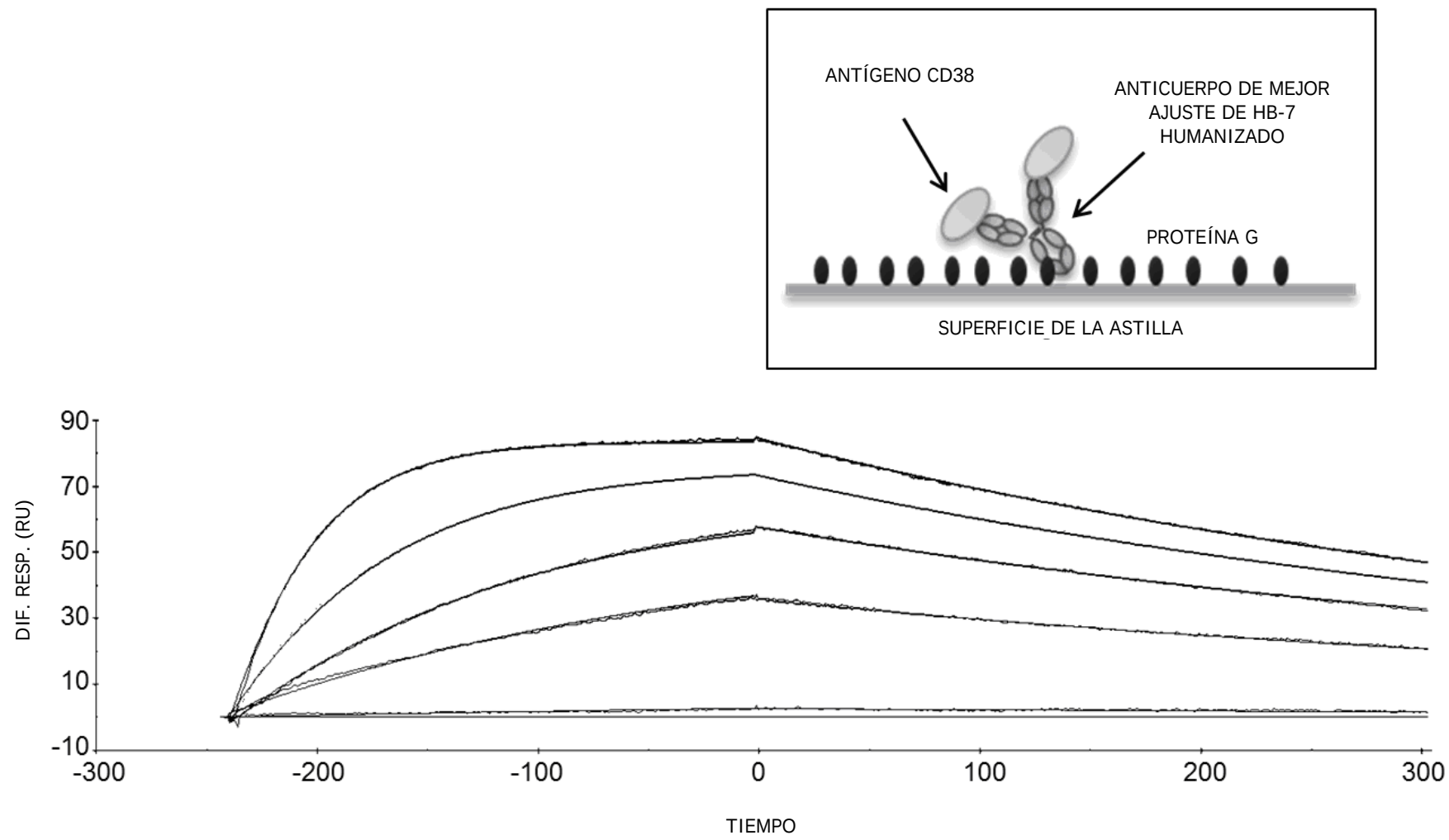


FIG. 7A

FIG. 7B



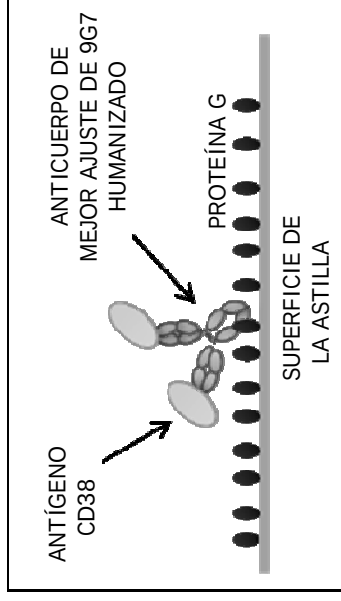
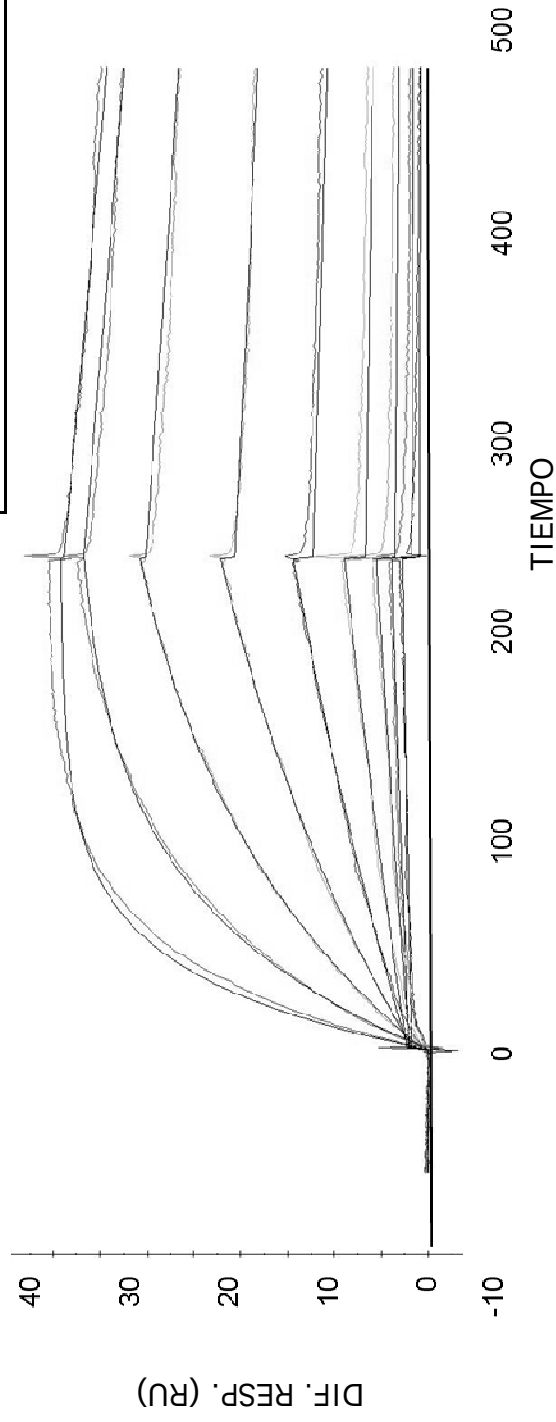


FIG. 7C

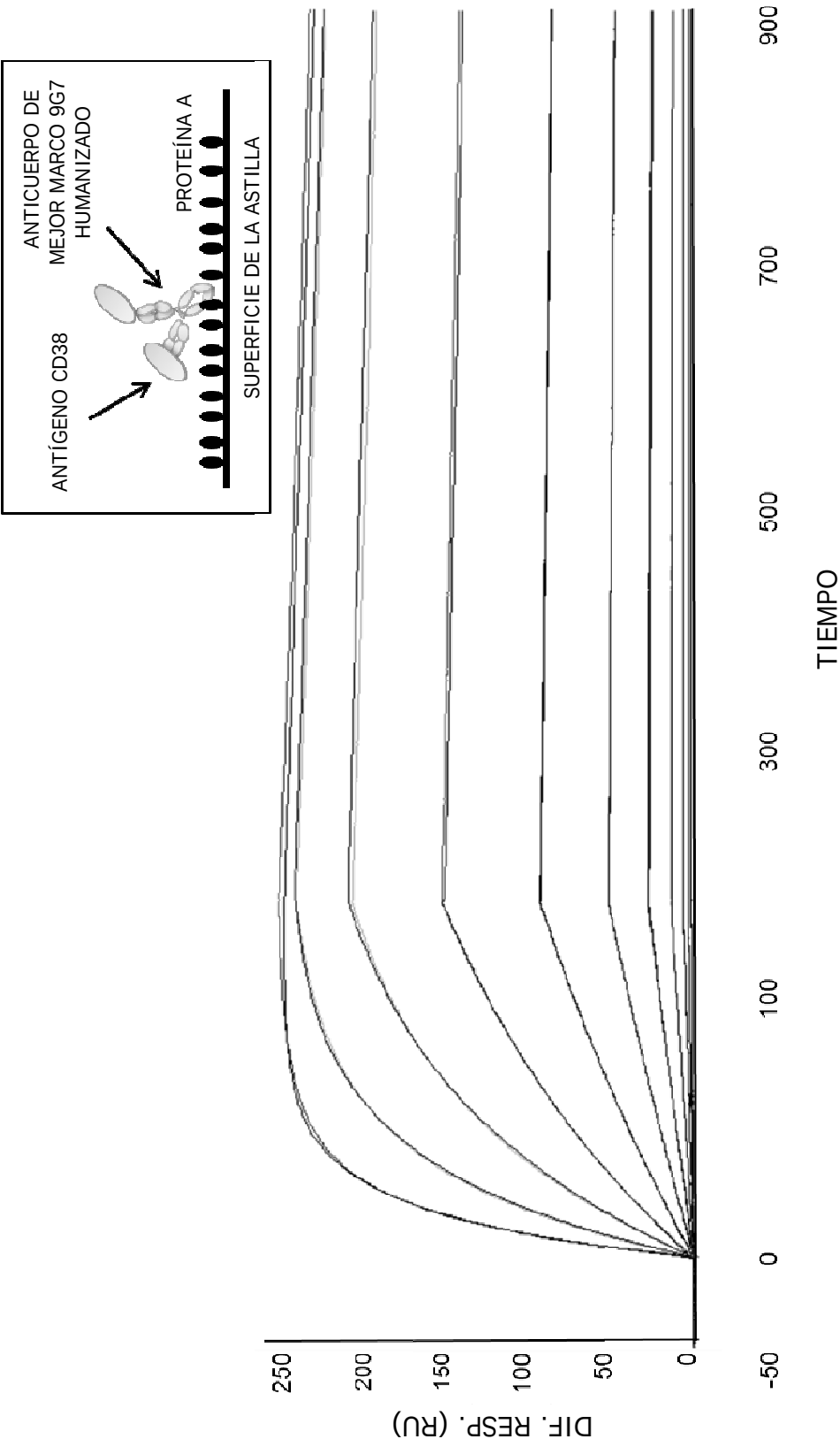


FIG. 7D

FIG. 7E

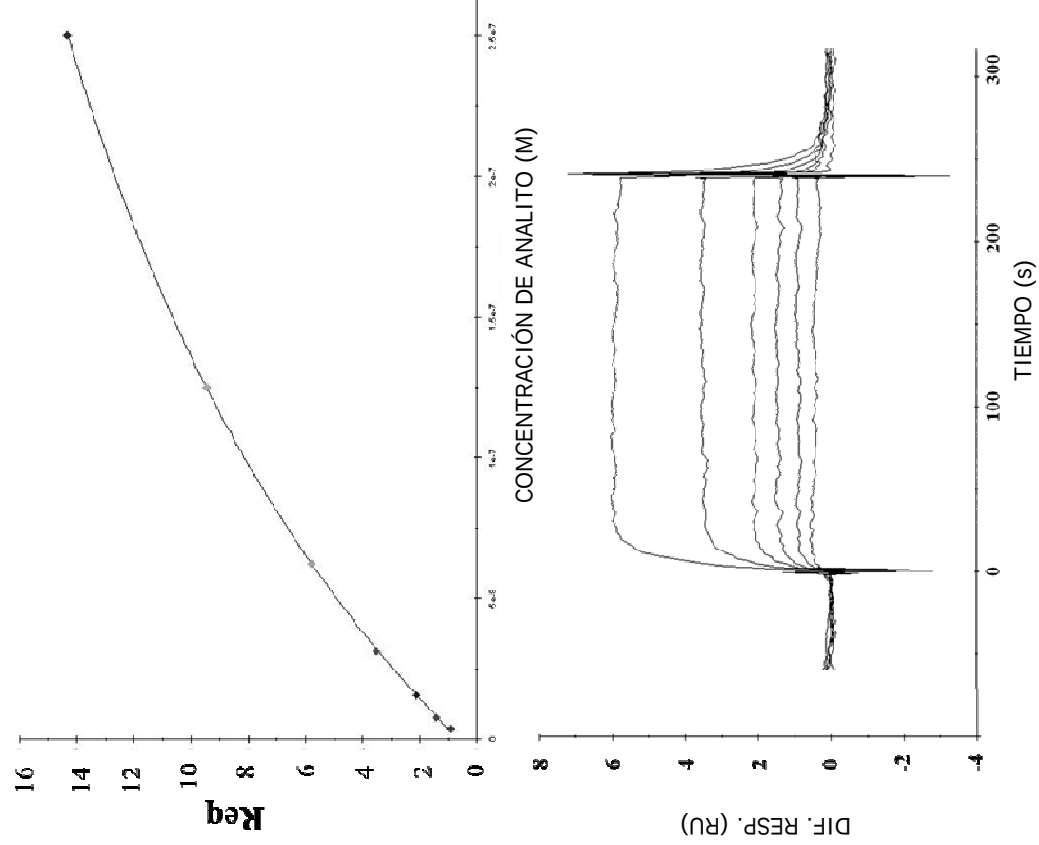
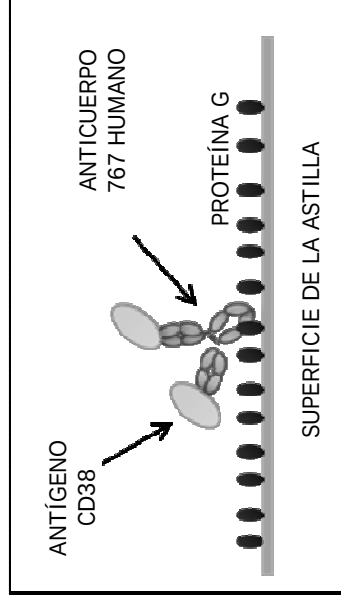
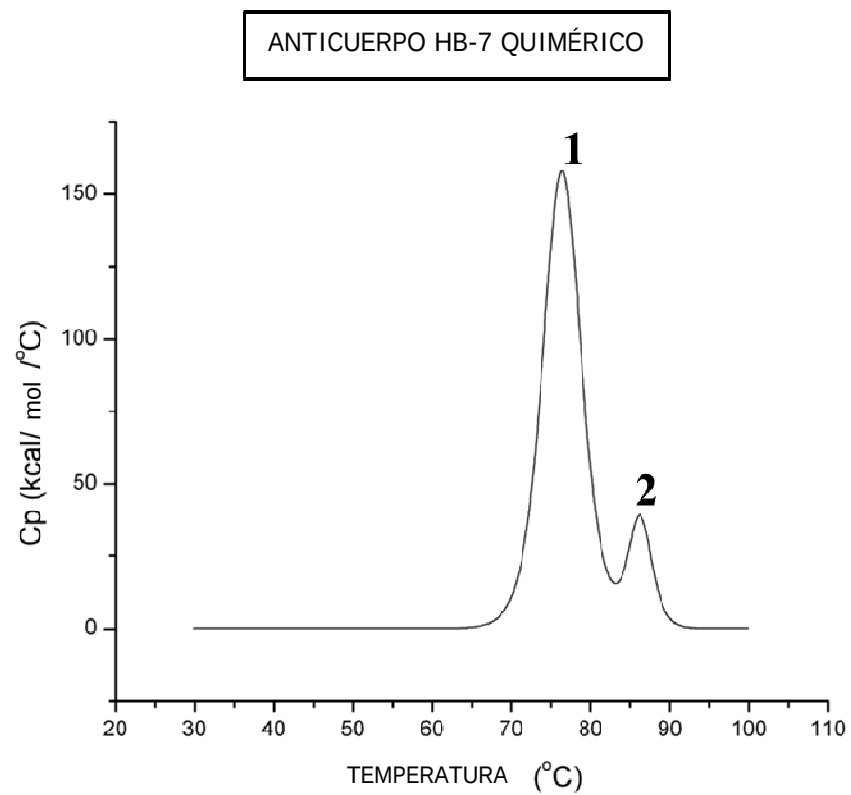
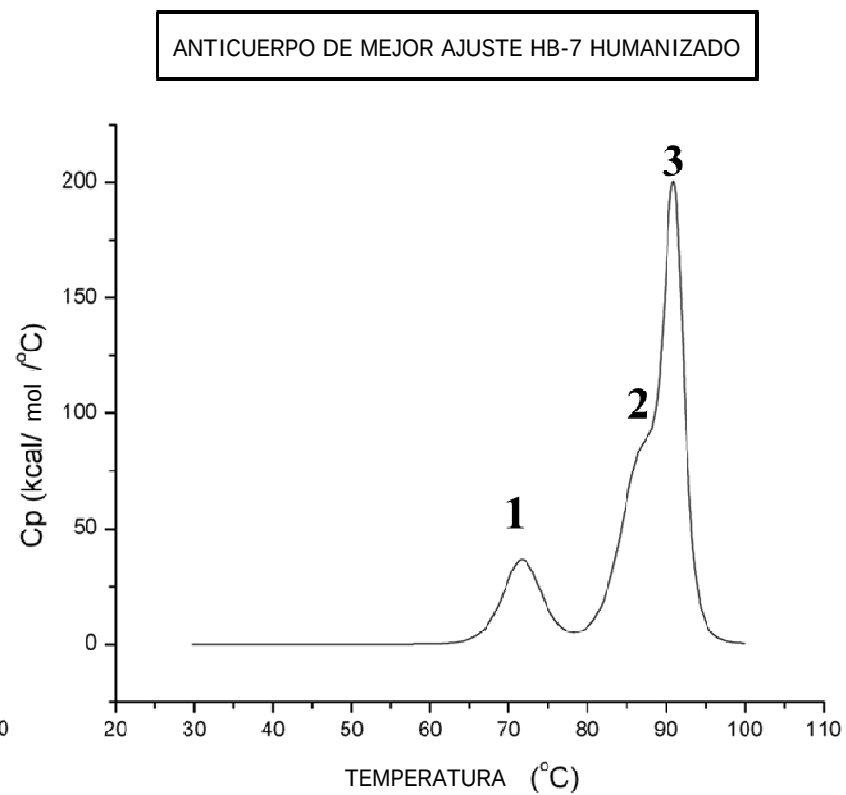


FIG. 7F

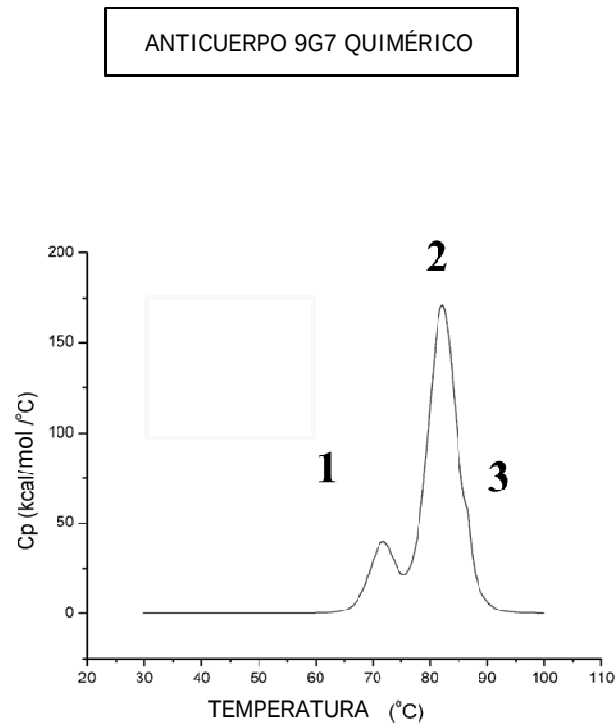


Tm(1): 76.40°C (FAB); Tm(2): 86.25°C

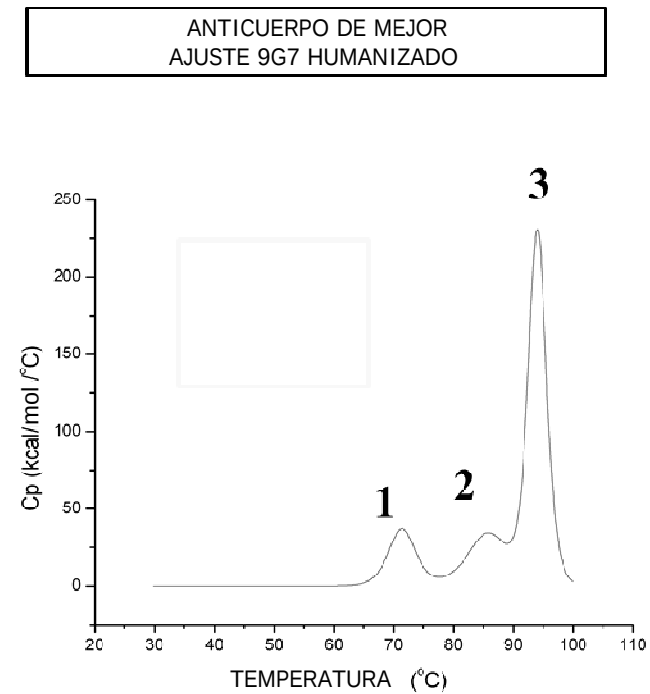


Tm(1): 71.70°C; Tm(2): 87.00°C; Tm(3): 91.00°C (FAB)

FIG. 7G



Tm(1): 71.70°C; Tm(2): 82.20°C (FAB); Tm(3): 86.6 °C



Tm(1): 71.4°C; Tm(2): 85.8 °C; Tm(3): 94.0°C (FAB)

FIG. 7H

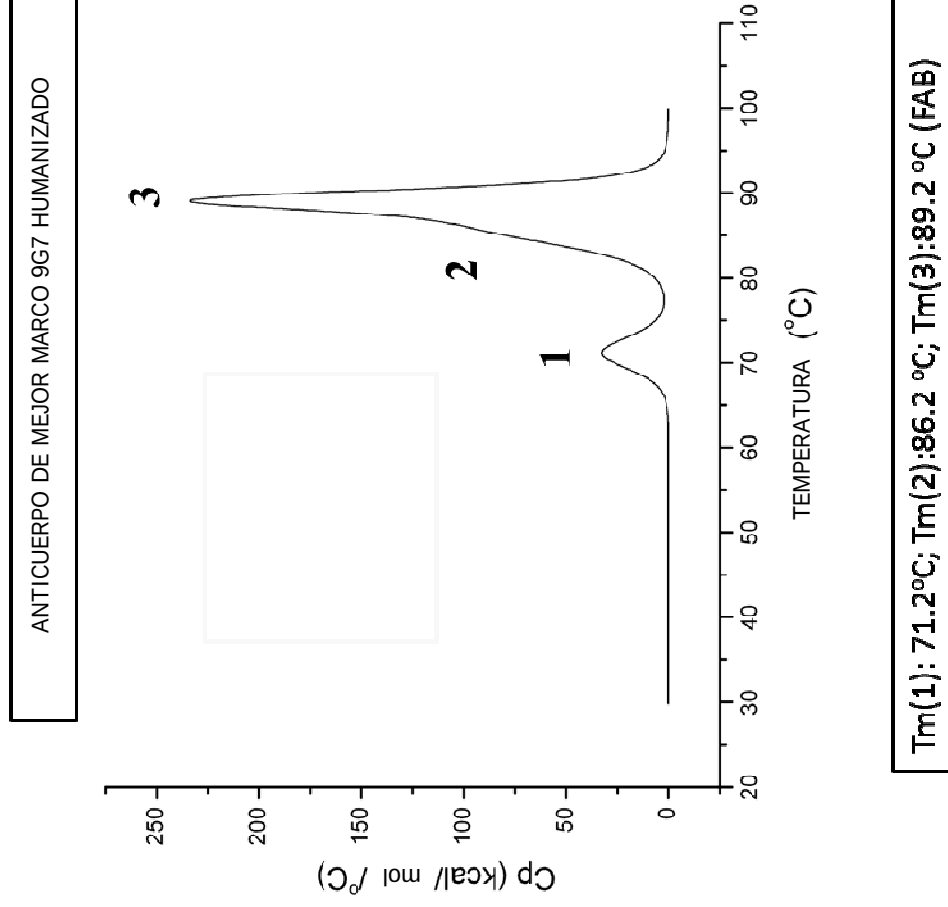
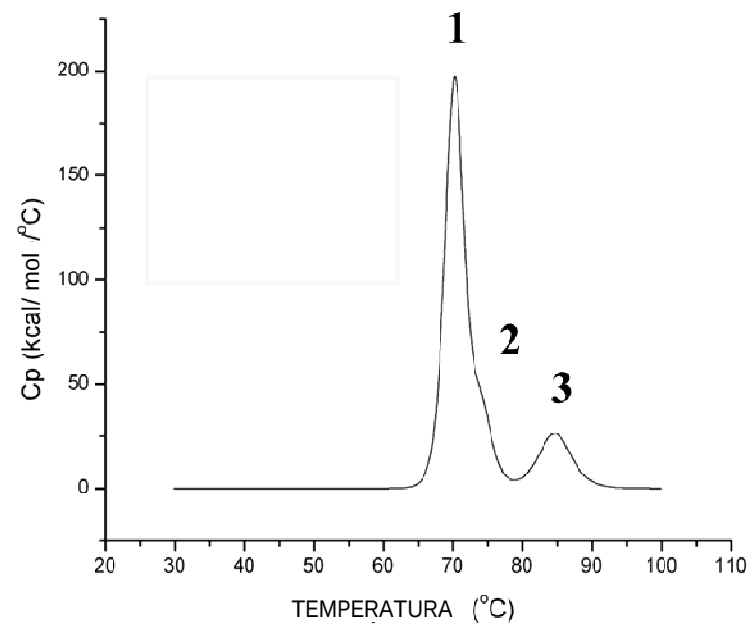


FIG. 7I

ANTICUERPO 767 HUMANO



Tm(1): 70.2°C (FAB); Tm(2):74.1 °C; Tm(3):84.7 °C

FIG. 7J

	ANTICUERPO 9G7 HUMANO	ANTICUERPO DE MEJOR AJUSTE 9G7 HUMANIZADO	ANTICUERPO DE MEJOR MARCO 9G7 HUMANIZADO
HC/LC SEQ ID NO	126/127	124/128	131/132
NIVELES DE EXPRESIÓN TRANSITORIA (mg/l)	20	11	17
CD38 HUMANO KD (nM)	0.4	0.5	0.4
MONO CYNOMOLGUS KD CD38 (nM)	1	3.2	1
FAB Tm (°C)	82.2	94	89.2

FIG. 8

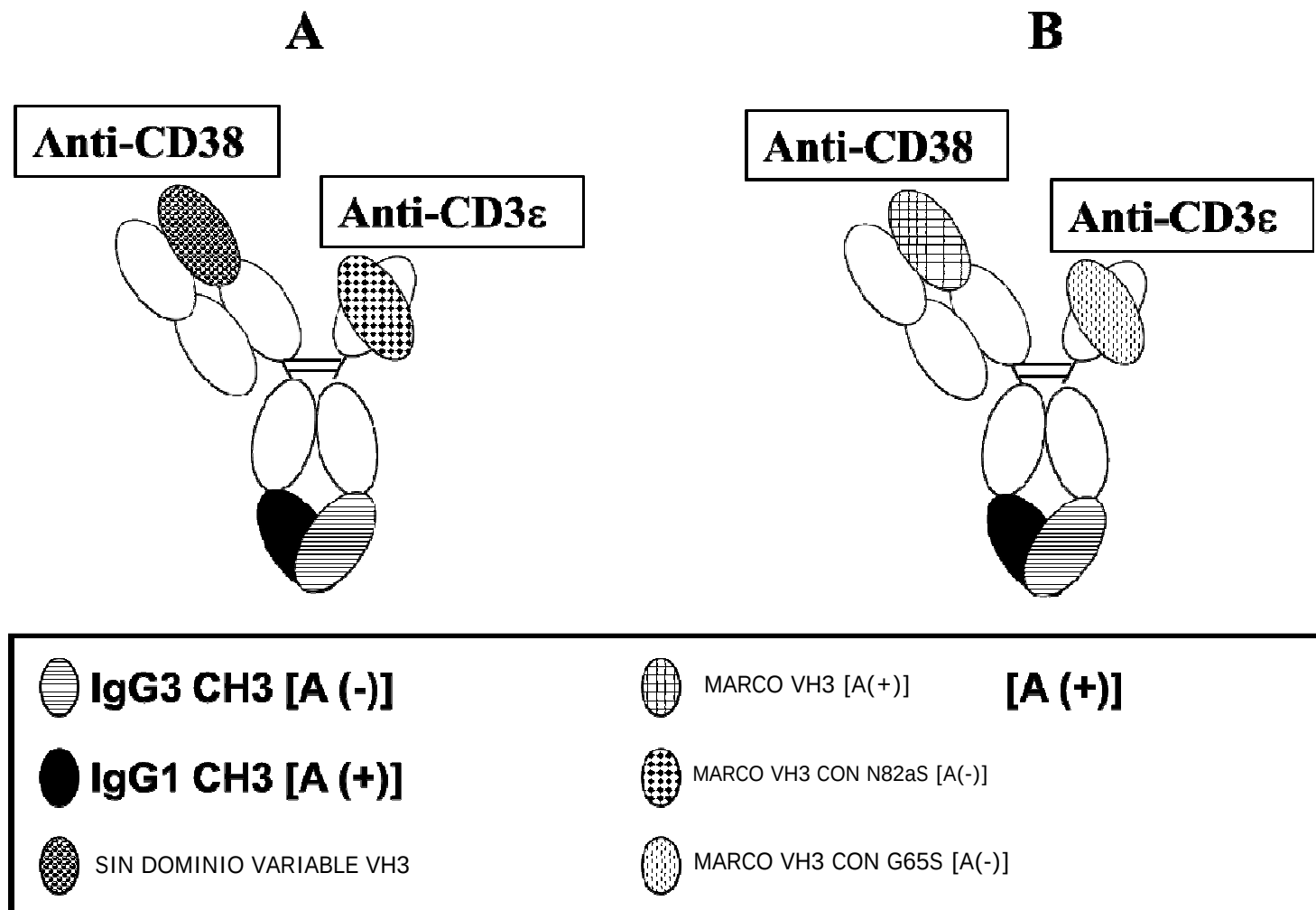


FIG. 9A

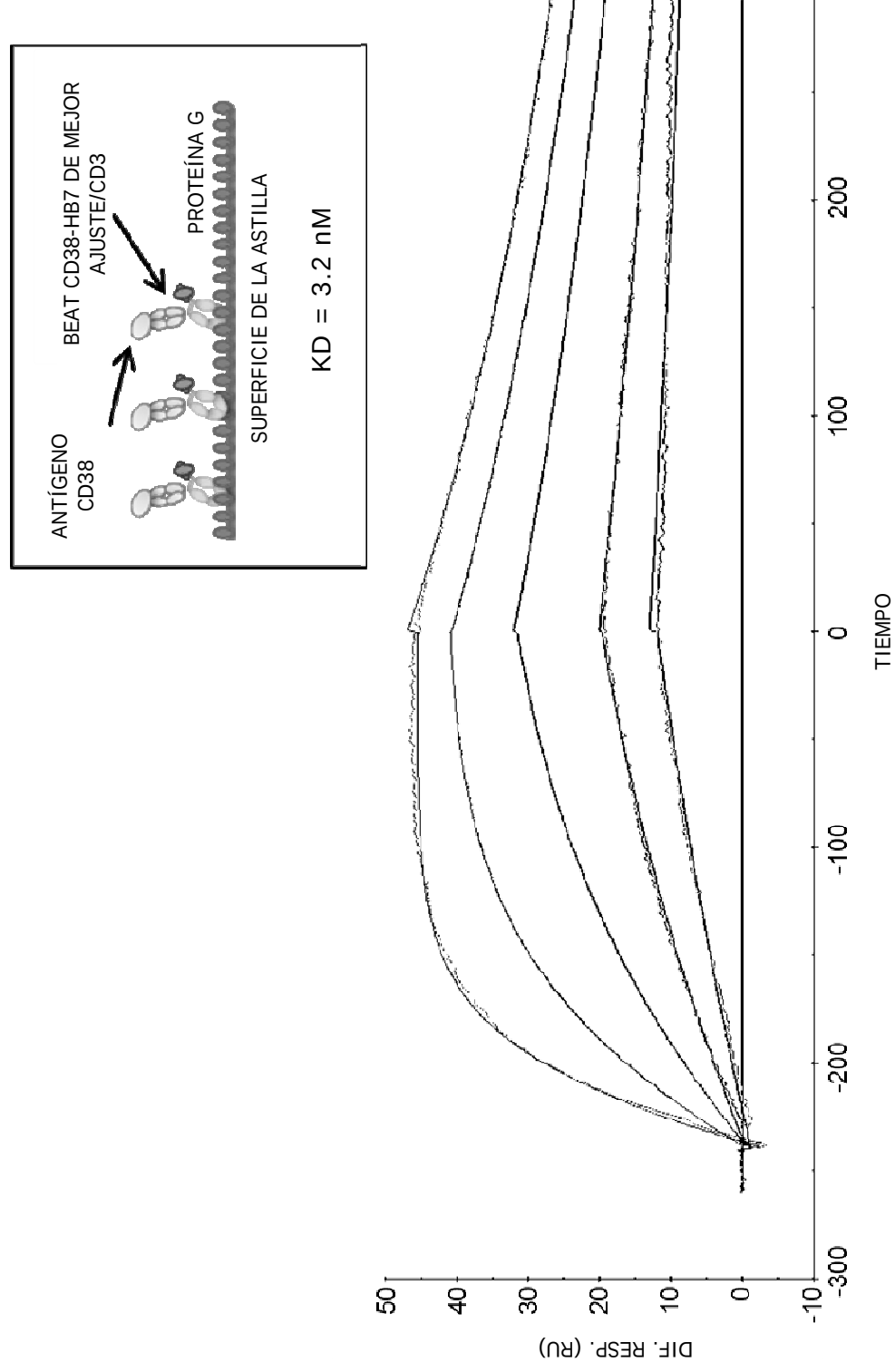
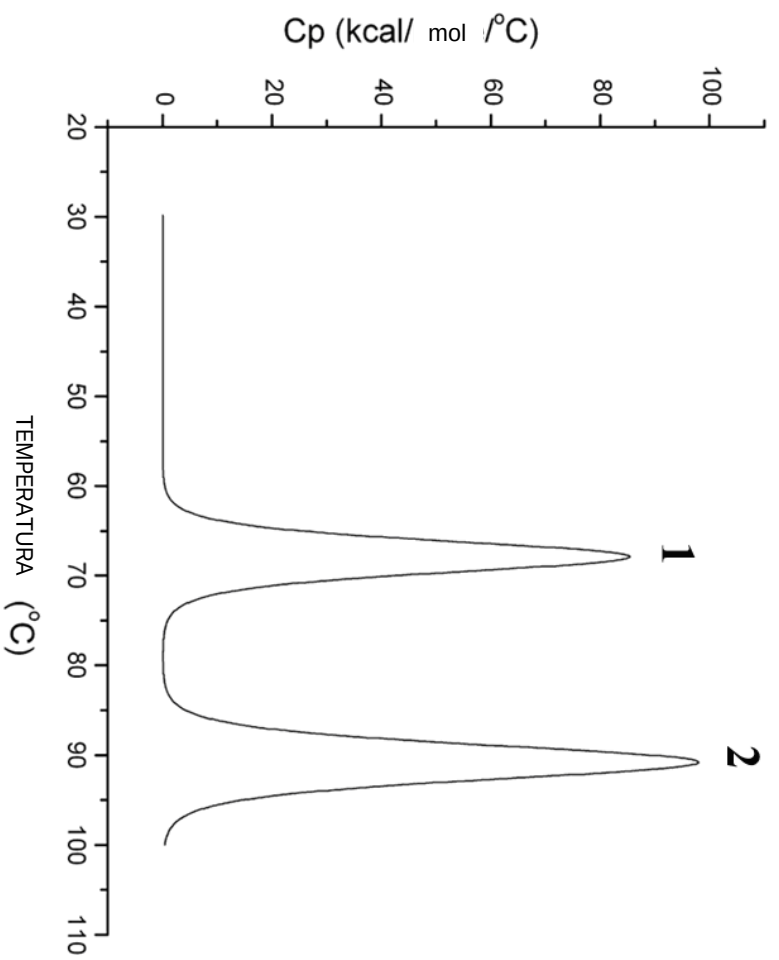


FIG. 9B



Tm(1): 67.9 $^{\circ}\text{C}$ (scFv); Tm(2): 90.8 $^{\circ}\text{C}$ (FAB)

FIG. 10

RPMI 8226

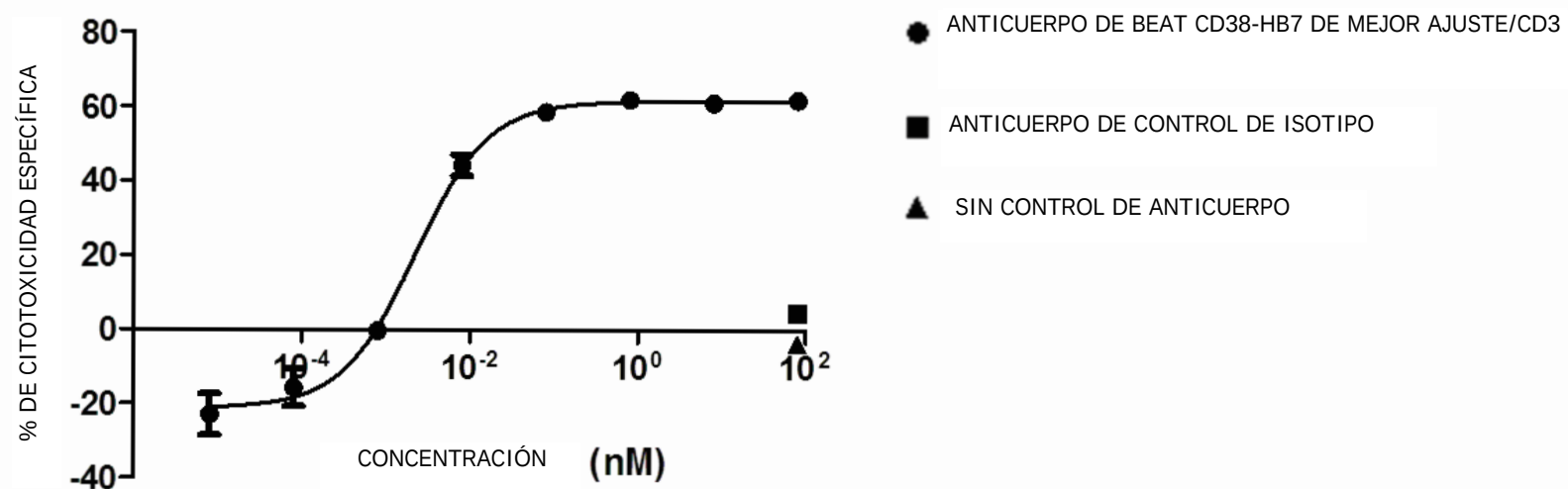


FIG. 11

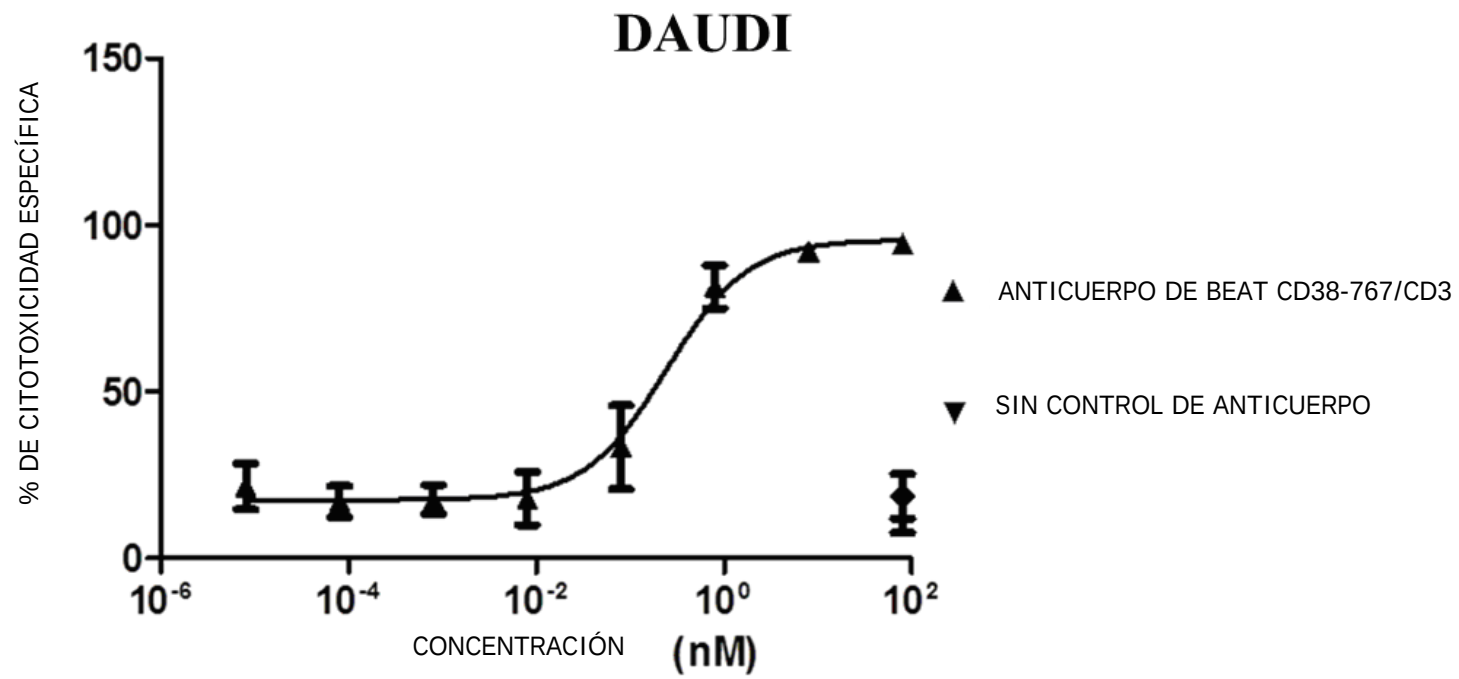


FIG. 12

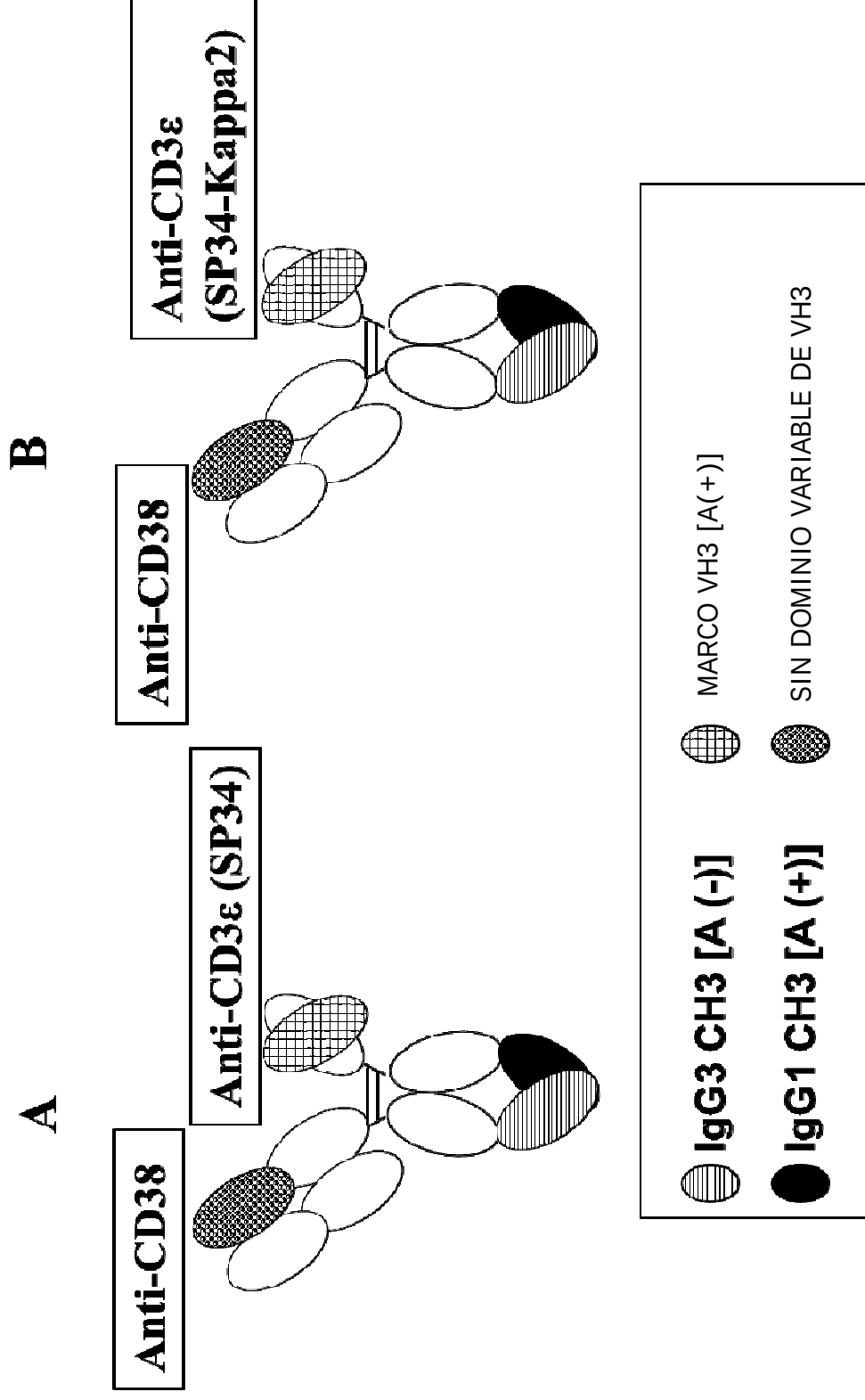


FIG. 13

DAUDI

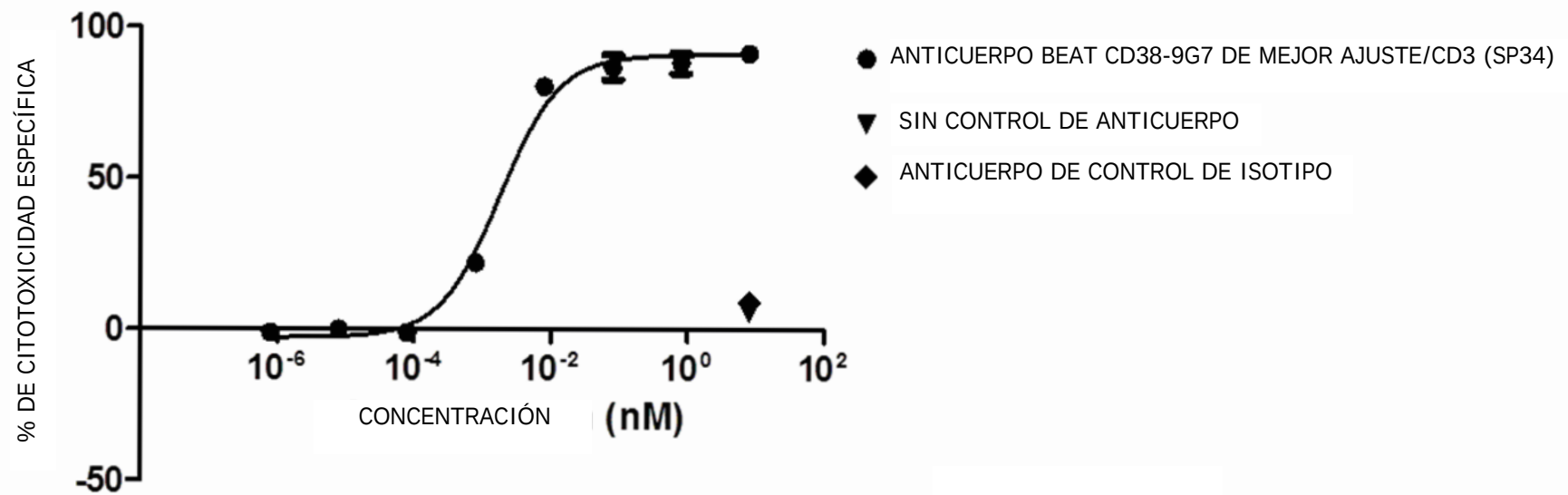


FIG. 13

DAUDI

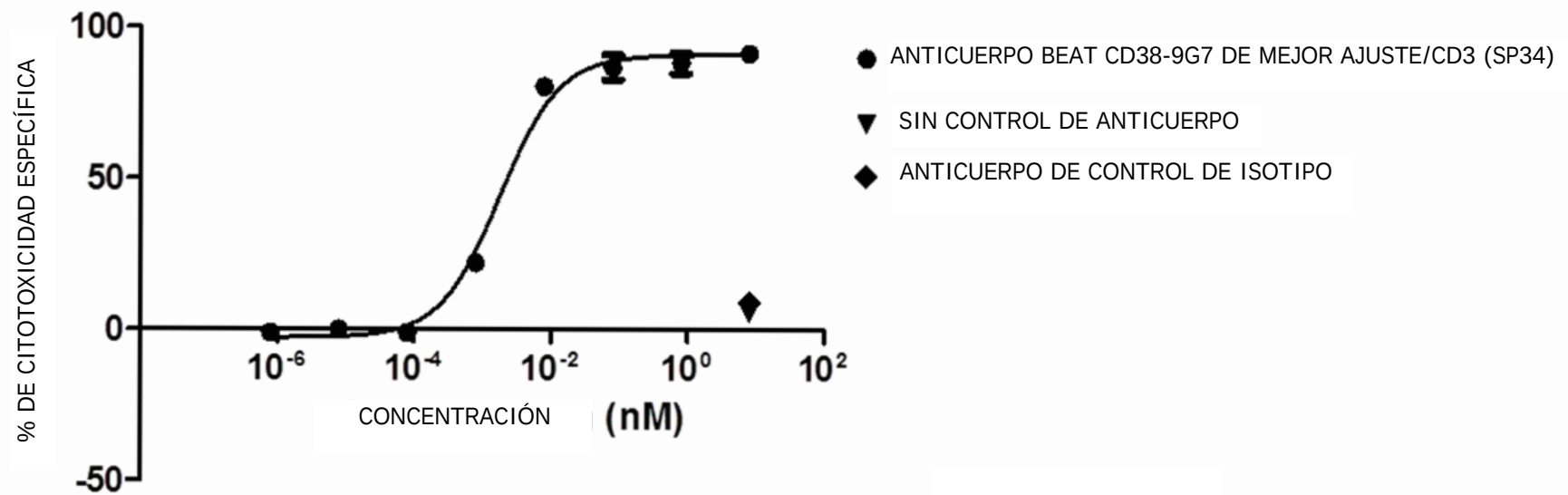


FIG. 14

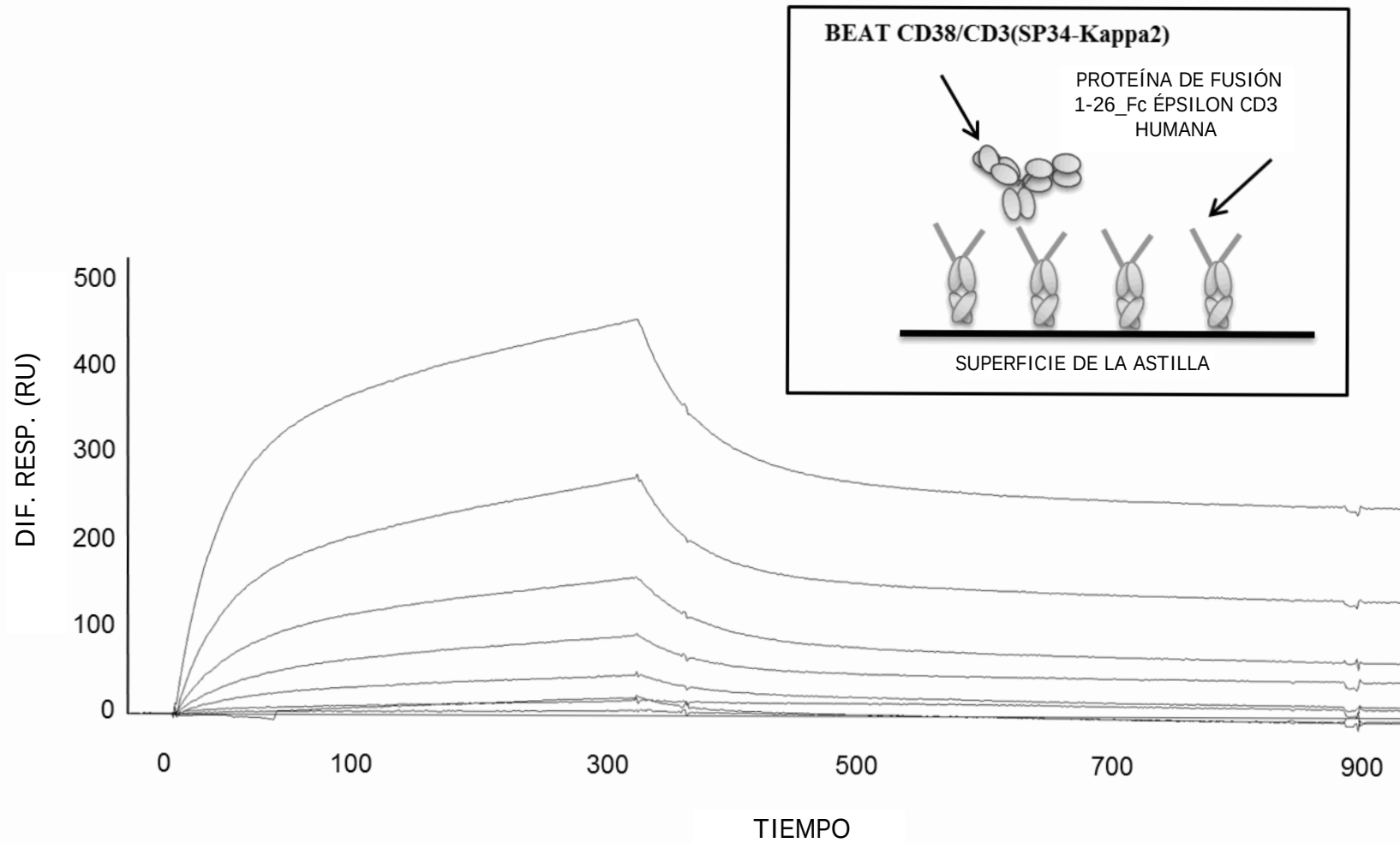


FIG. 15

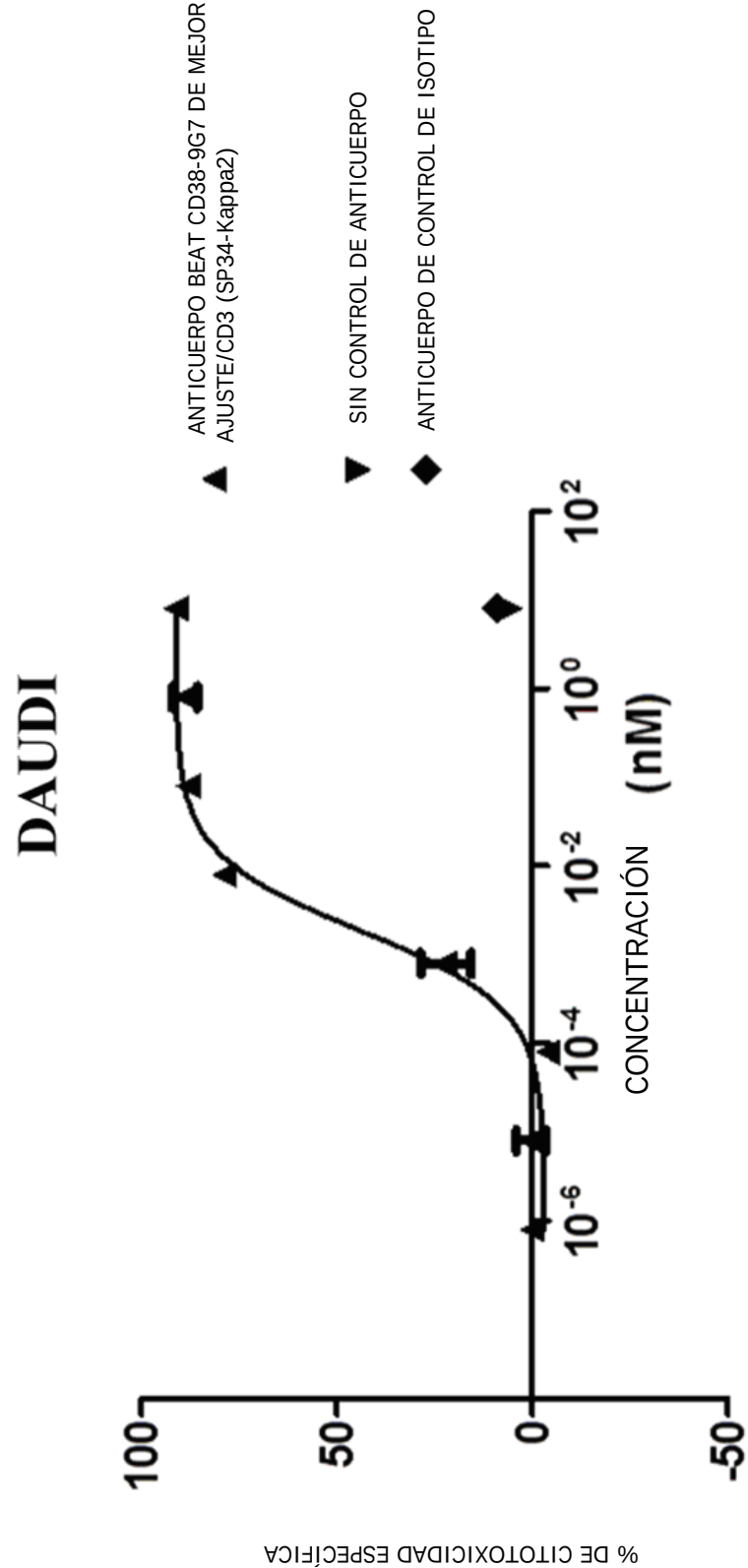
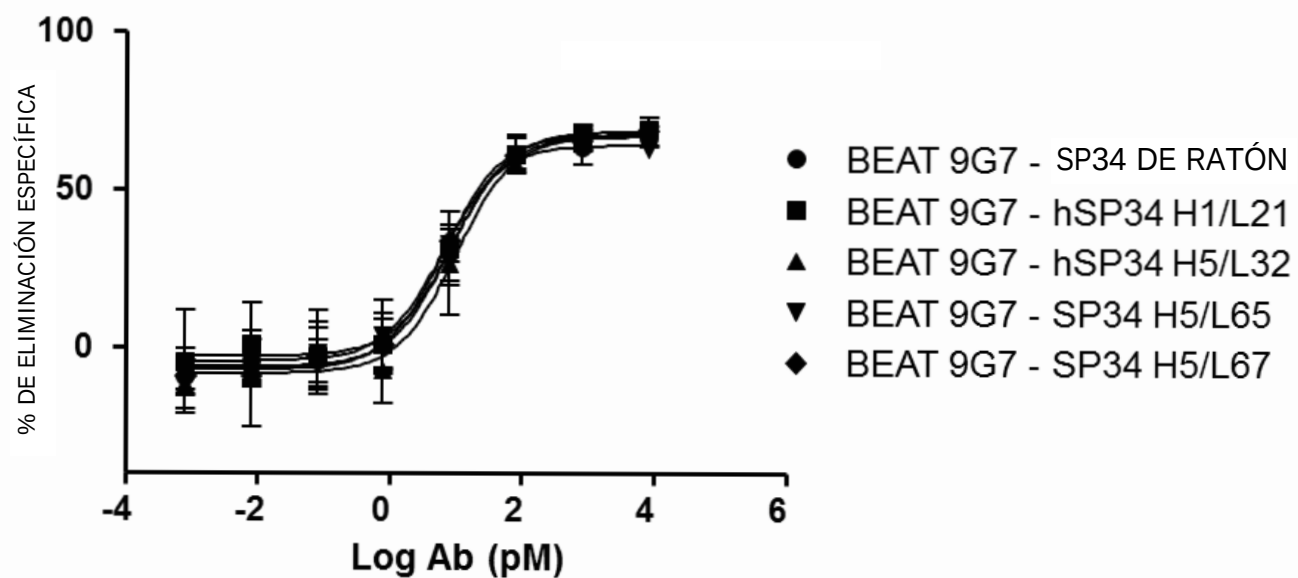


FIG. 16

RDL EN CÉLULAS RAJI - MEDIA DE 2 DONADORES



	EC50 BEAT 9G7 - SP34 DE RATÓN	EC50 BEAT 9G7 - hSP34 H1/L21	EC50 BEAT 9G7 - hSP34 H5/L32	EC50 BEAT 9G7 - hSP34 H5/L65	EC50 BEAT 9G7 - hSP34 H5/L67
MEDIA	7.883	8.807	10.09	6.170	6.493
DESVIACIÓN ESTÁNDAR	2.879	2.070	5.098	1.185	1.526

FIG. 17

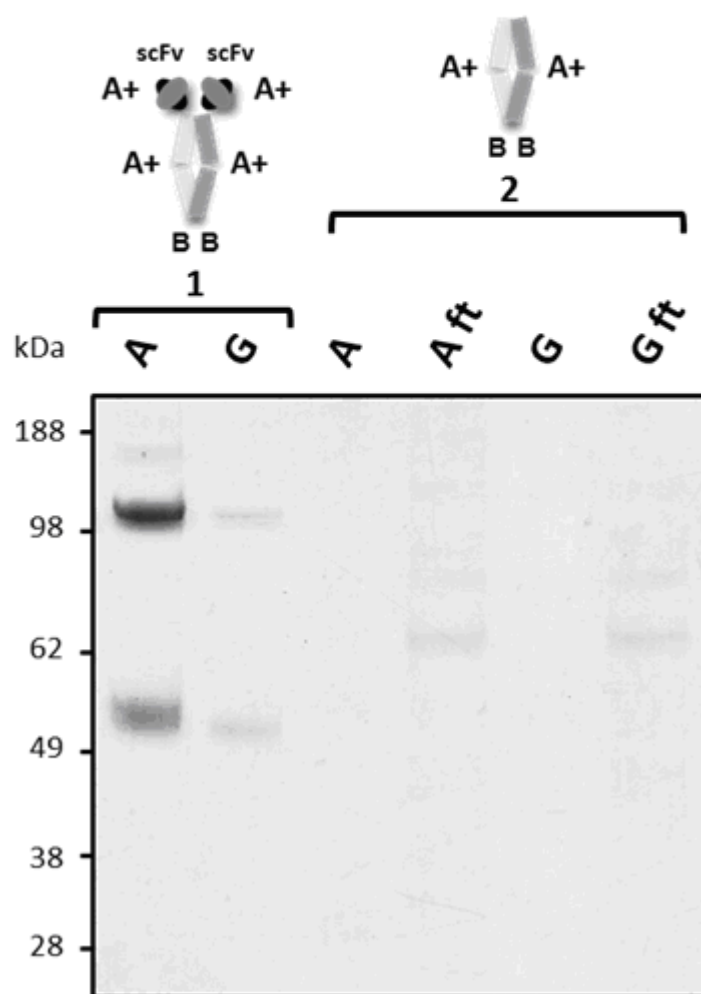


FIG. 18

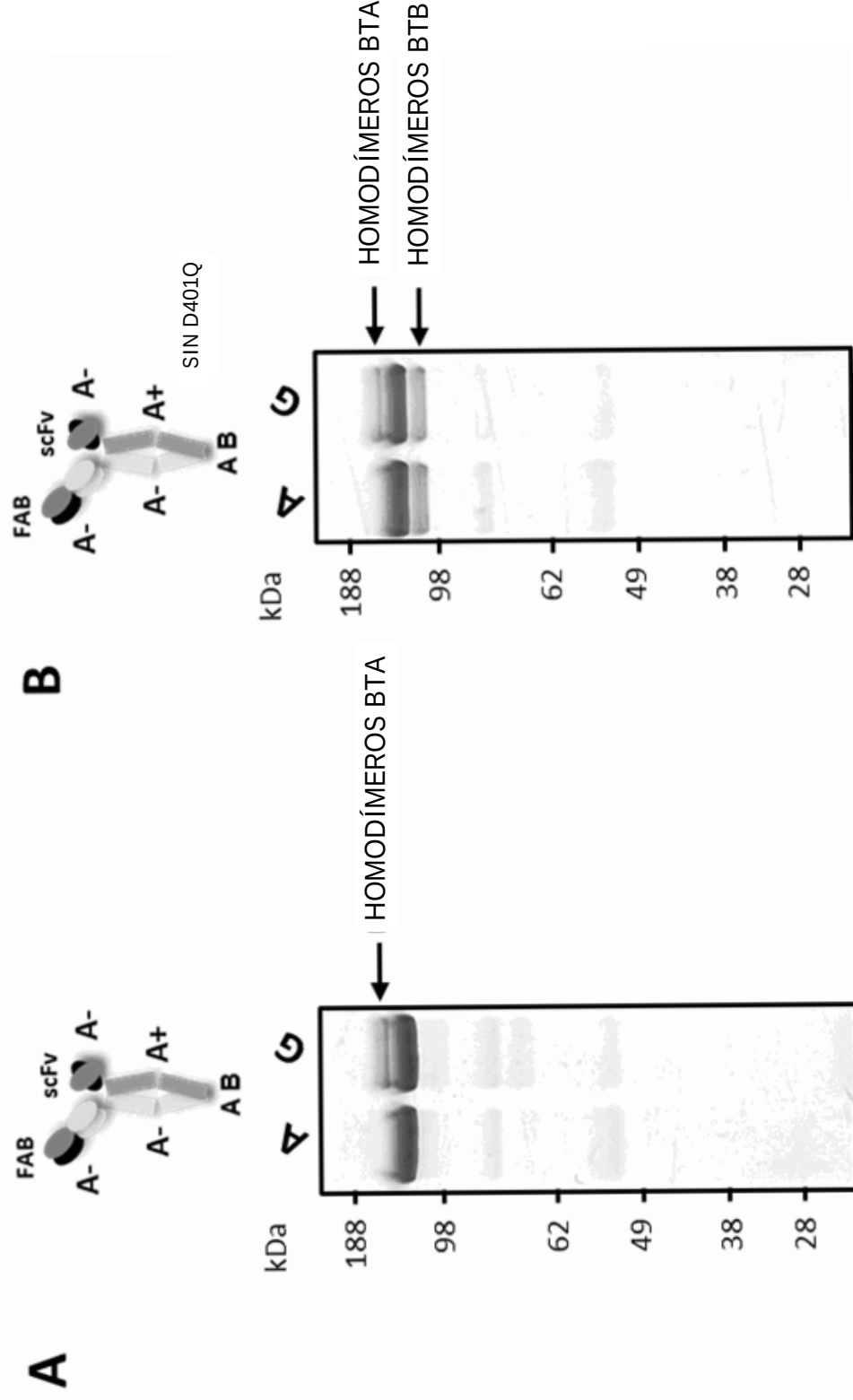
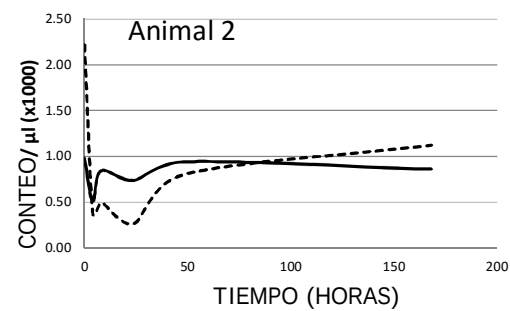
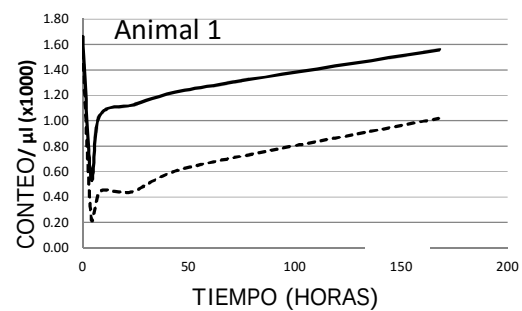


FIG. 19

DOSIS 1ug/kg



DOSIS 10 ug/kg

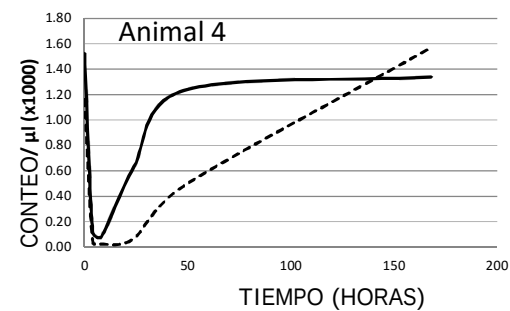
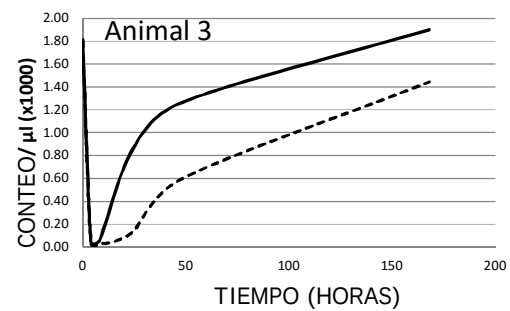


FIG. 20

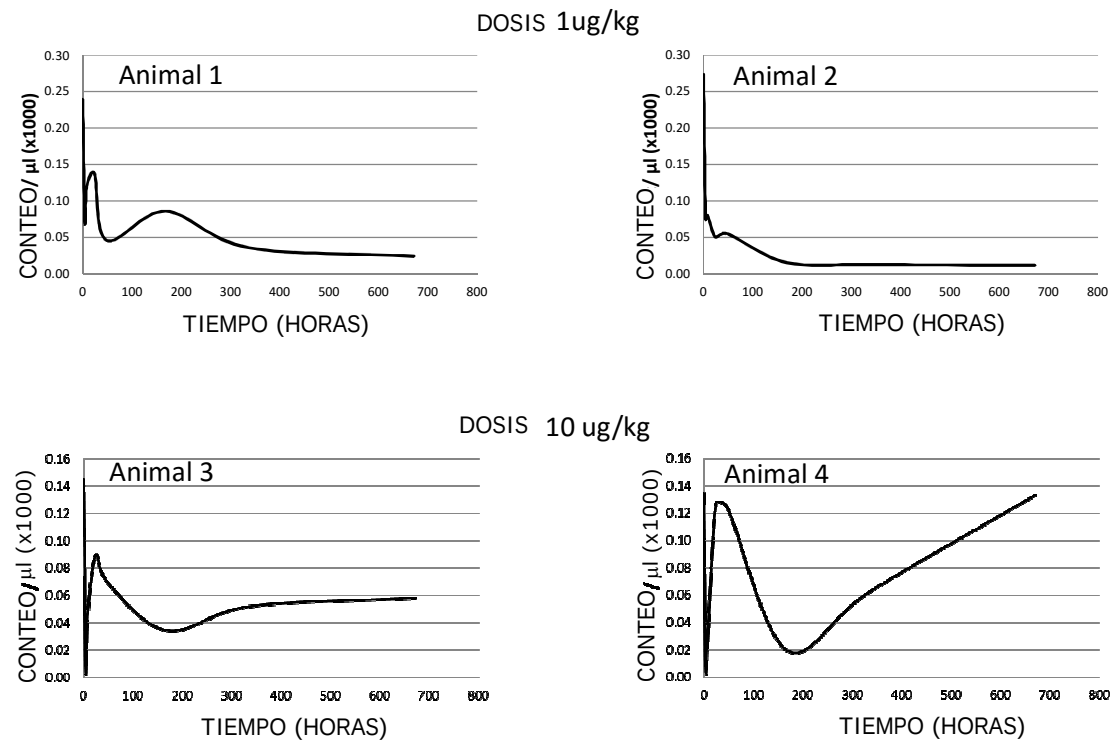


FIG. 21

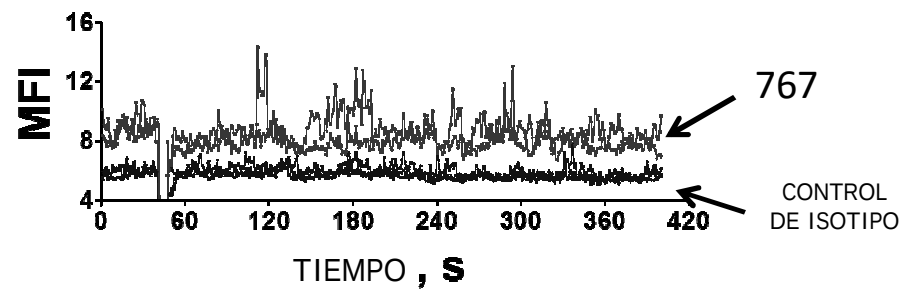
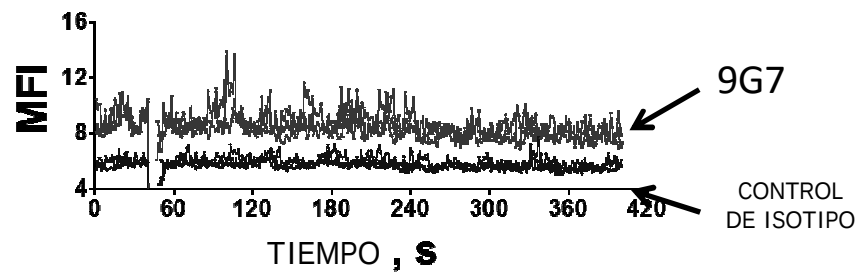
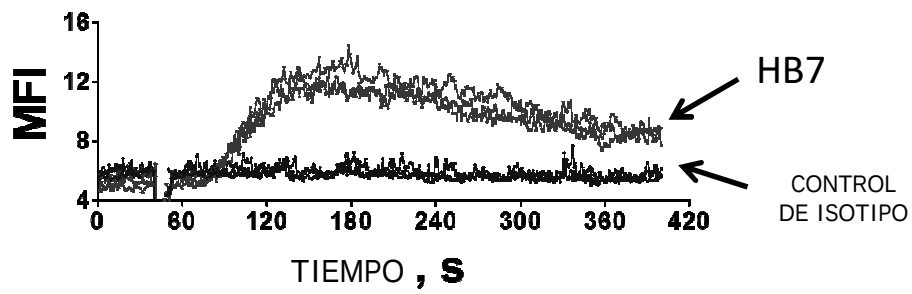


FIG. 22

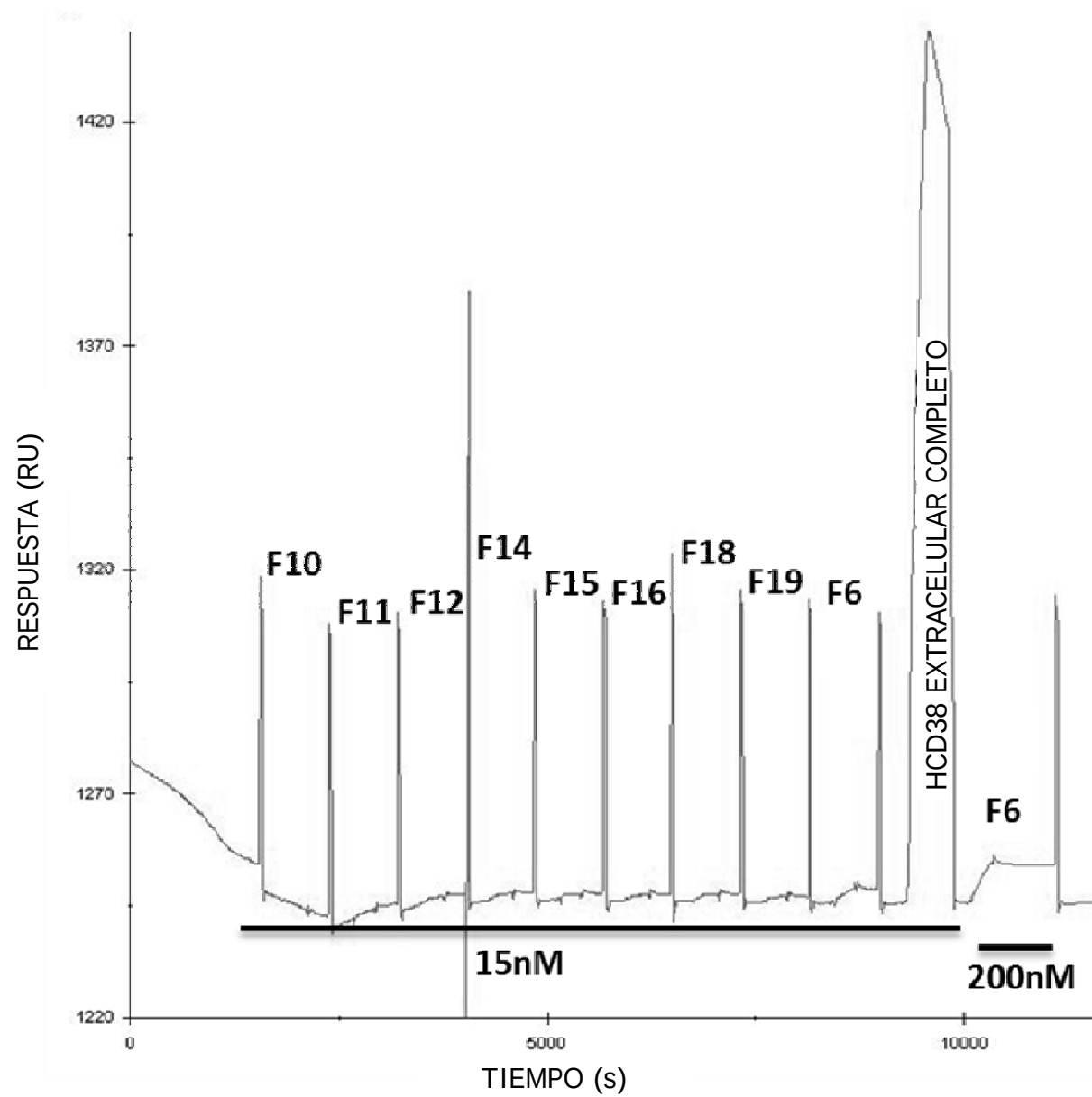


FIG. 23

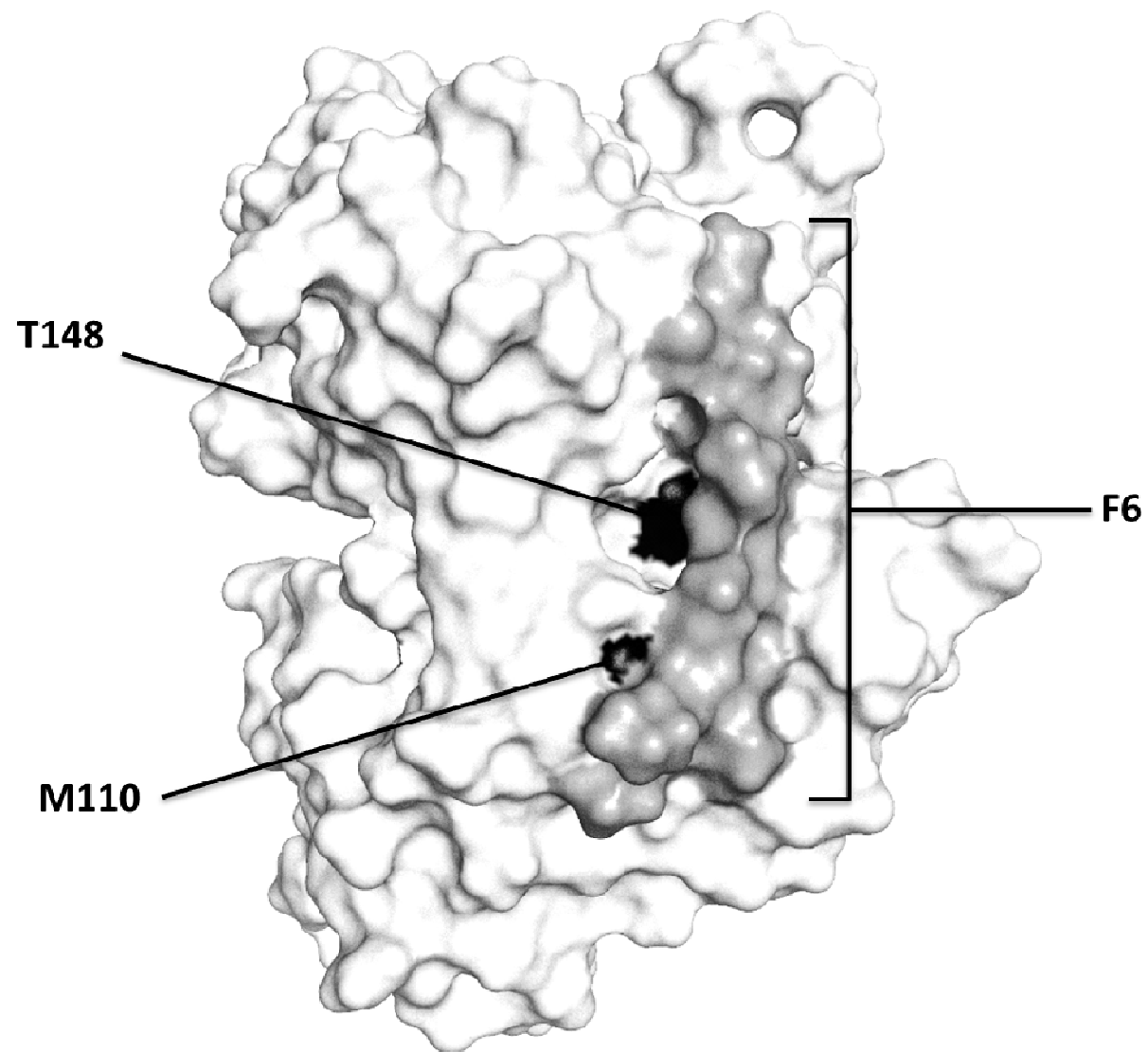


FIG. 24

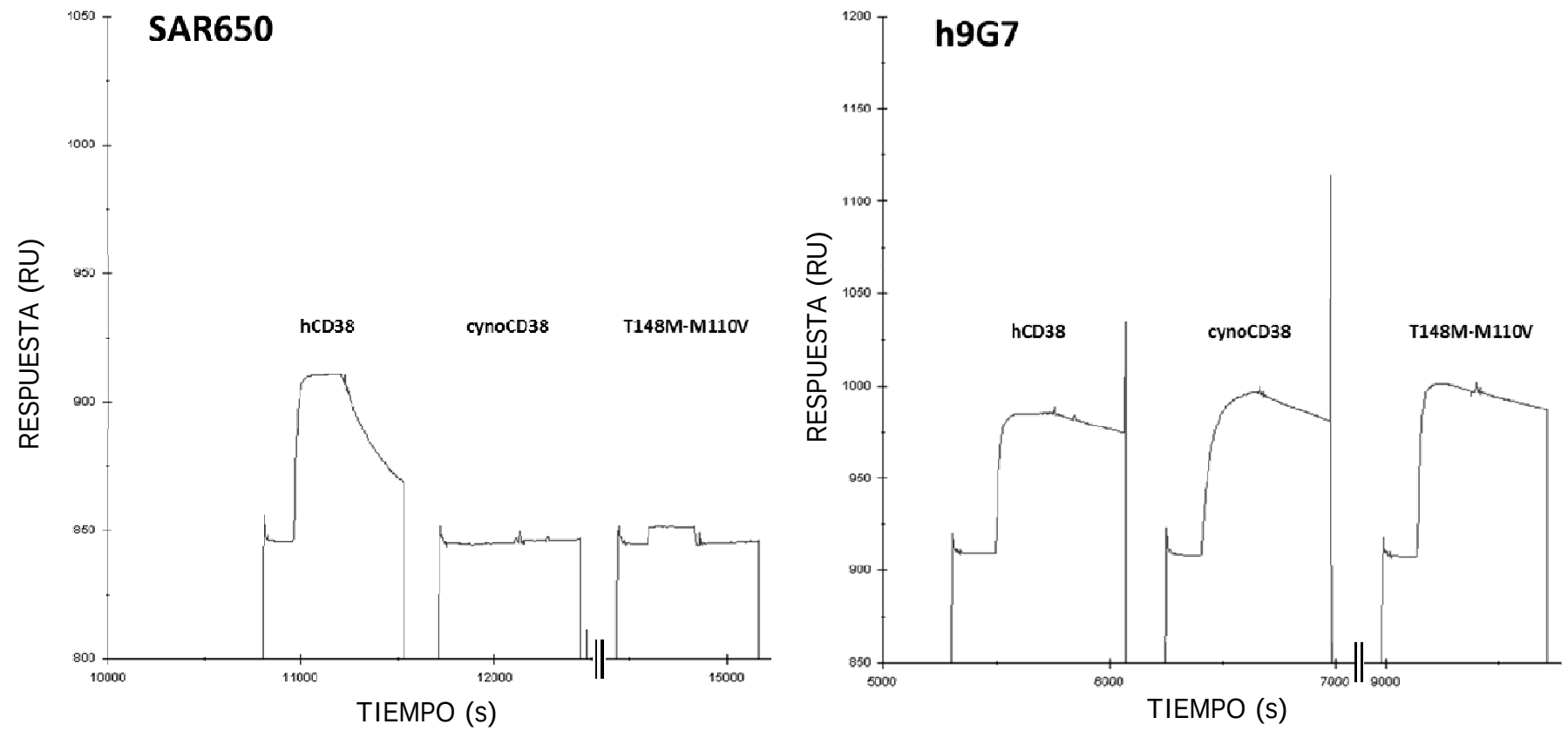


FIG. 25

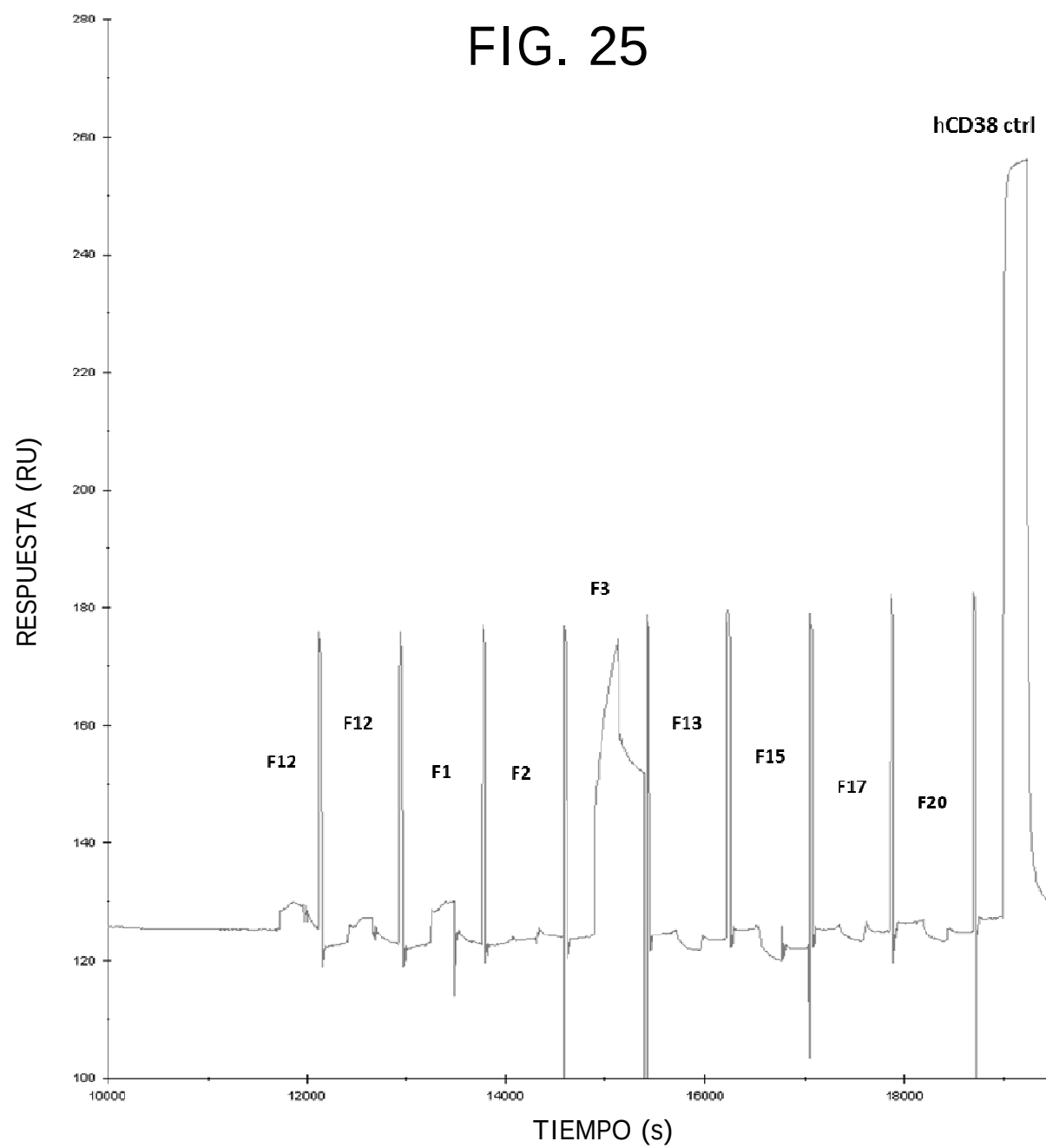


FIG. 26

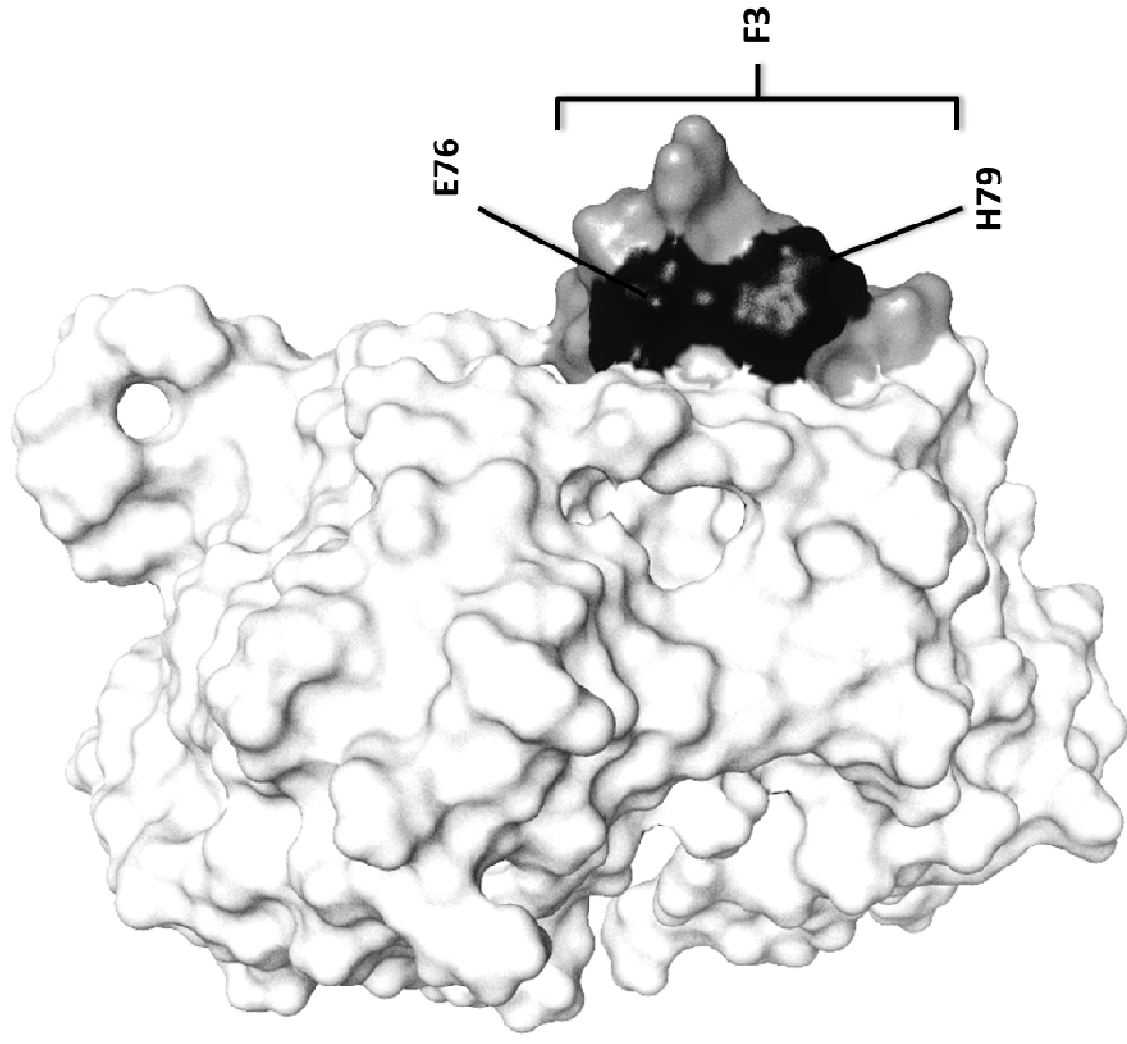


FIG. 27

