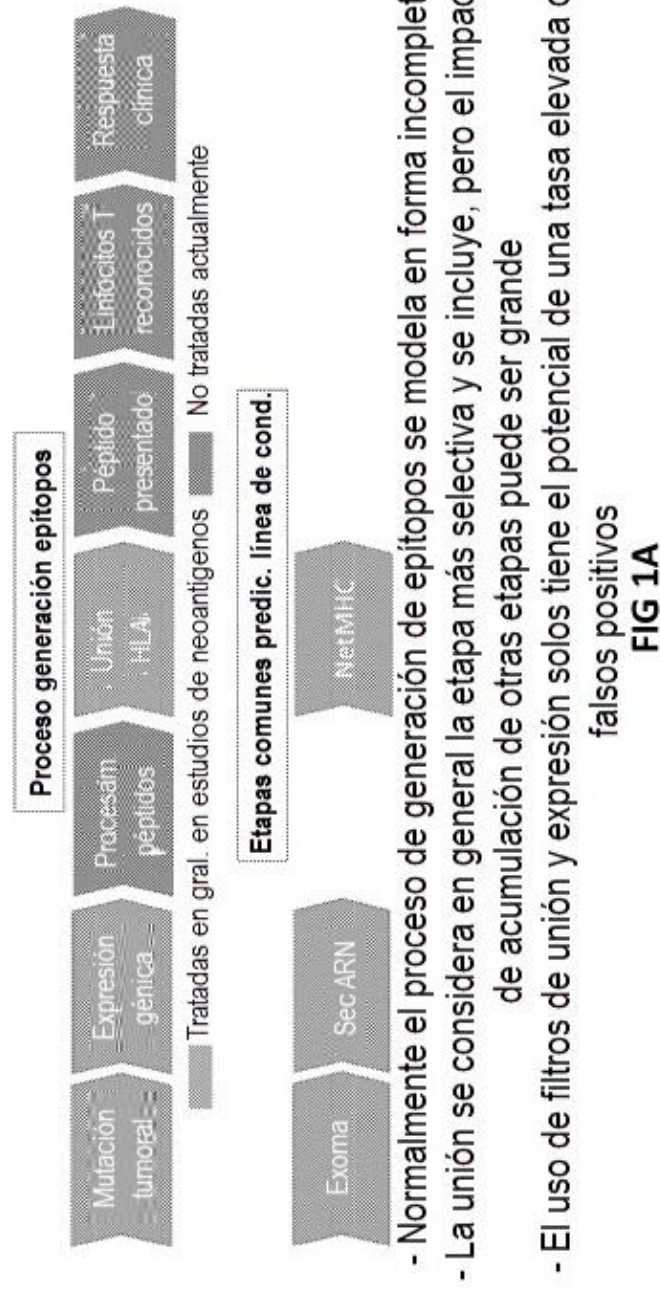
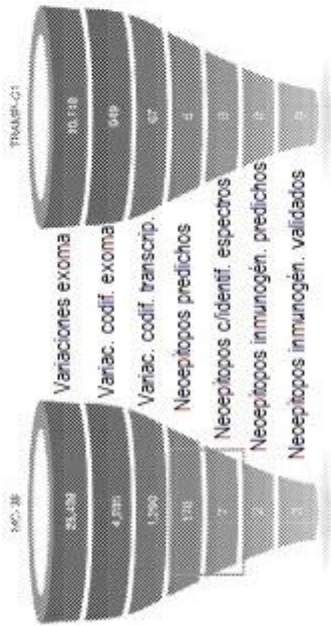


Enfoques clínicos actuales para la identificación de neoantígenos



La bibliografía más reciente indica que <5 % de péptidos unidos predichos pueden encontrarse presentadosen células tumorales



- Solo 7/170 (4 %) de neoepitopos predichos eluyeron y se detectaron mediante espec. de masas
- Posiblemente debido a limites de sensibilidad del enfoque de detección por espec. de masas particular

Predicción	Identificación según MS	
	HLAp	No detectado
Aglutinantes	1,579	47,777
No aglutin.	153	1,140,967

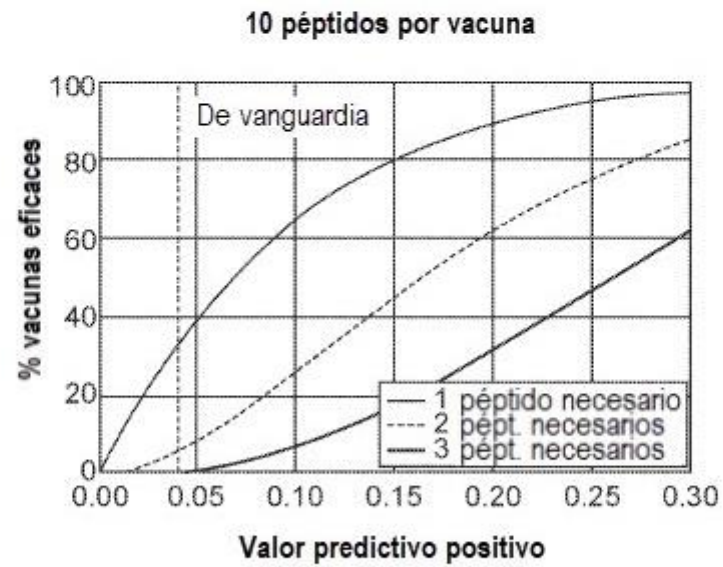
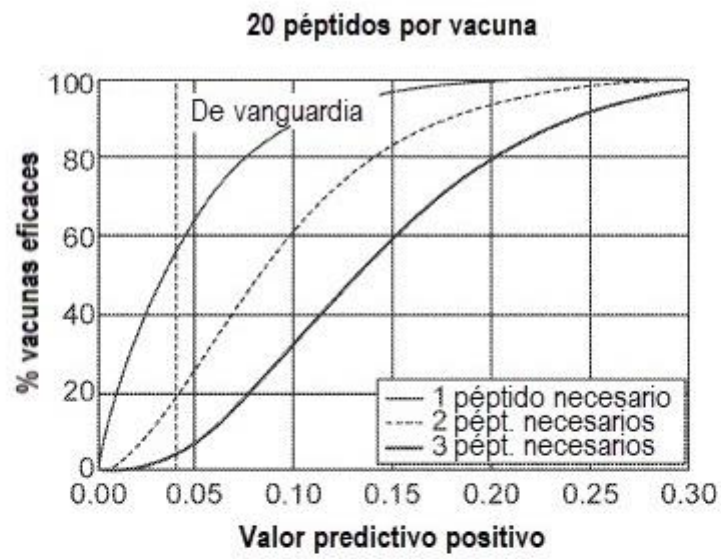
3%

Predicción	Identificación según MS	
	HLAp	No detectado
Aglutinantes	1,133	14,059
No aglutin.	599	1,174,685

Yadav, Nature Tomo 515 17 noviembre 2014

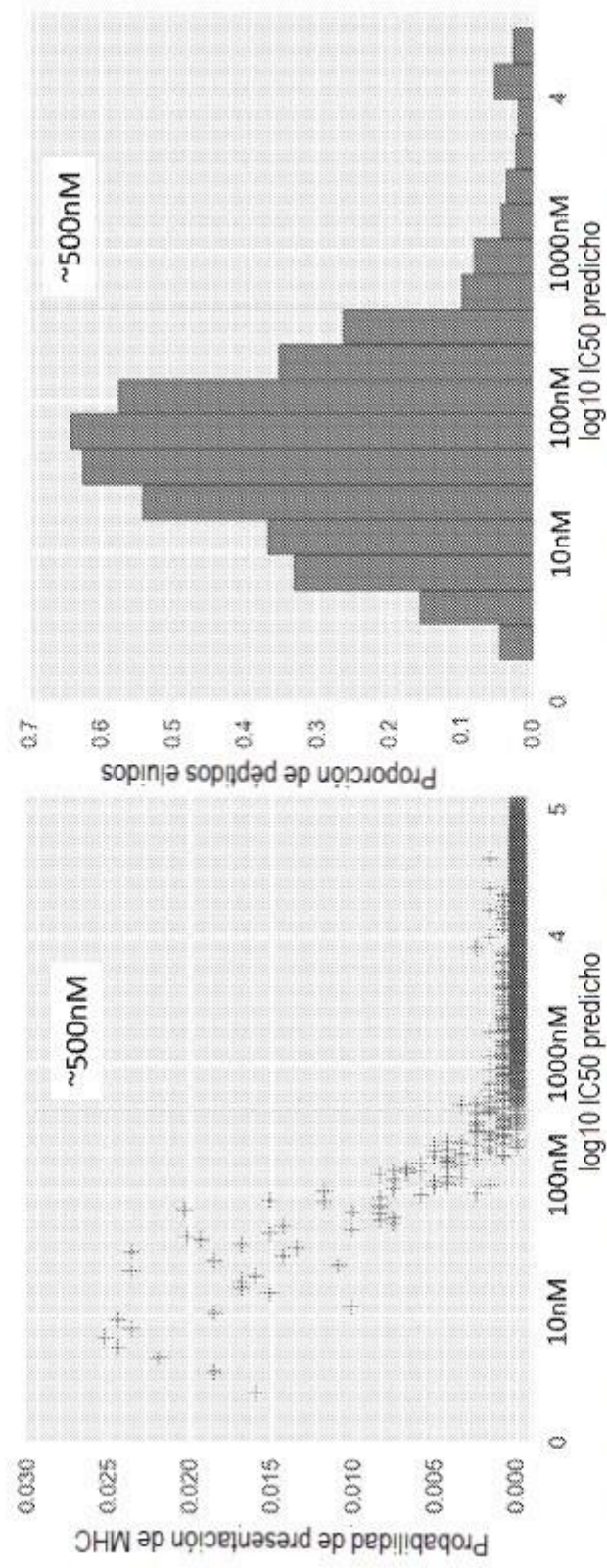
Bassani-Sternberg M, Mol Cell Proteomics. 2015;14(3):658-73

FIG 1B

**FIG 1C**

Predicción de unión necesaria pero no suficiente

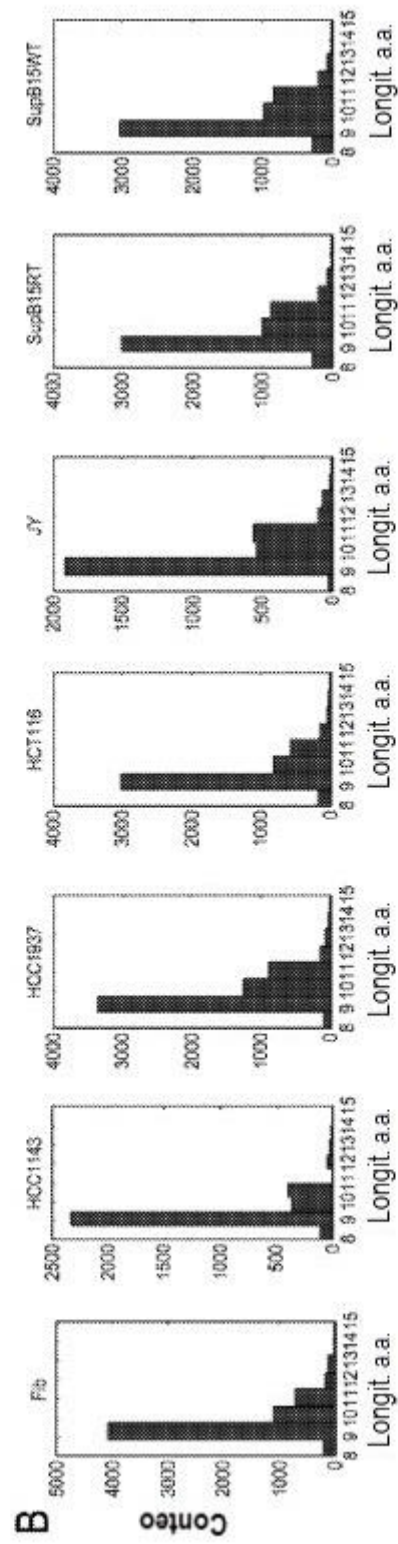
Predicción de afinidad de unión en opos. a detec. de péptidos por espec. de masas en LCL inmortaliz. c/JY (EBV)

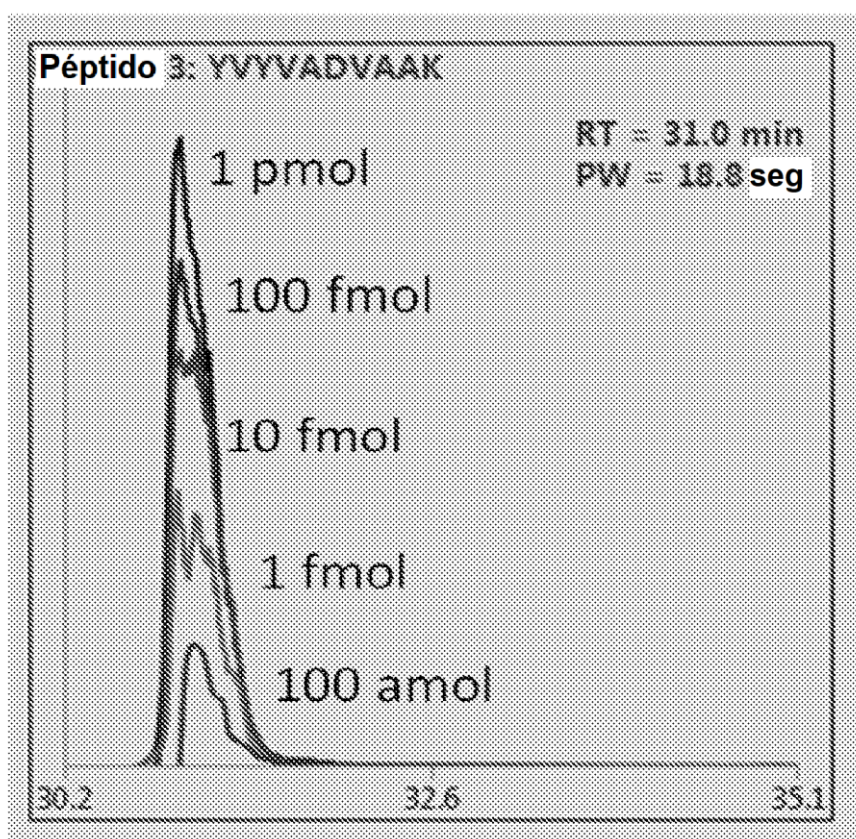


Máx. de predic. de afinidad para HLA-A-0201 y HLA-B-0702,
limitadas a genes en proteoma total

Datos de Bassani-Sternberg M, Mol Cell Proteomics. 2015;
Análisis de Gritstone

FIG 1D

**FIG 1E**

**FIG 1F**

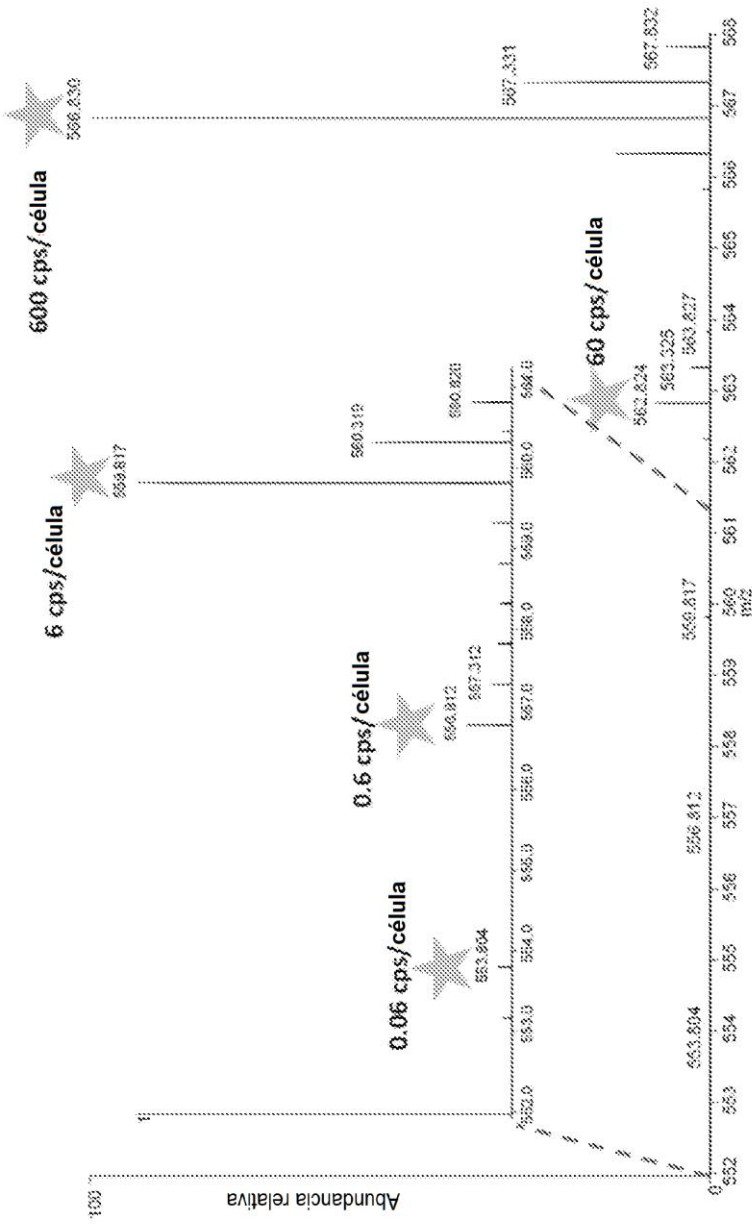
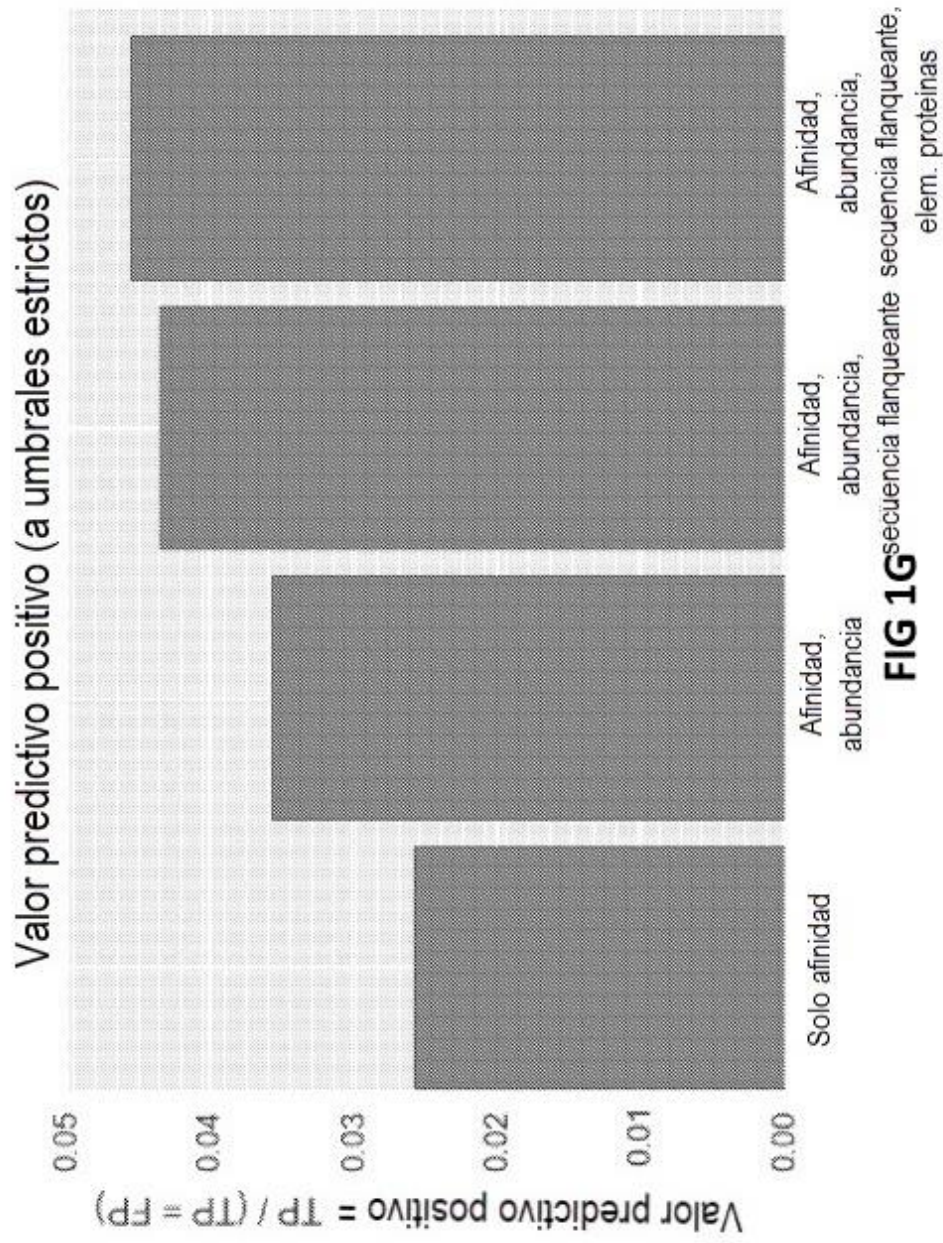


FIG 1F (Cont)



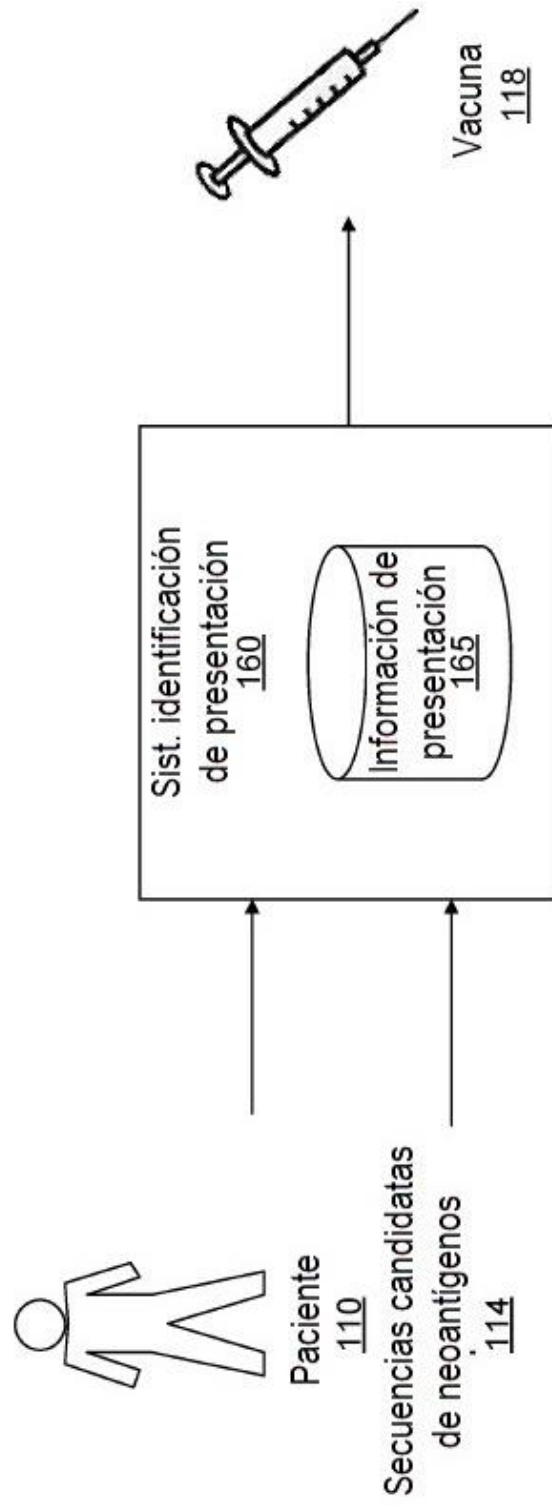
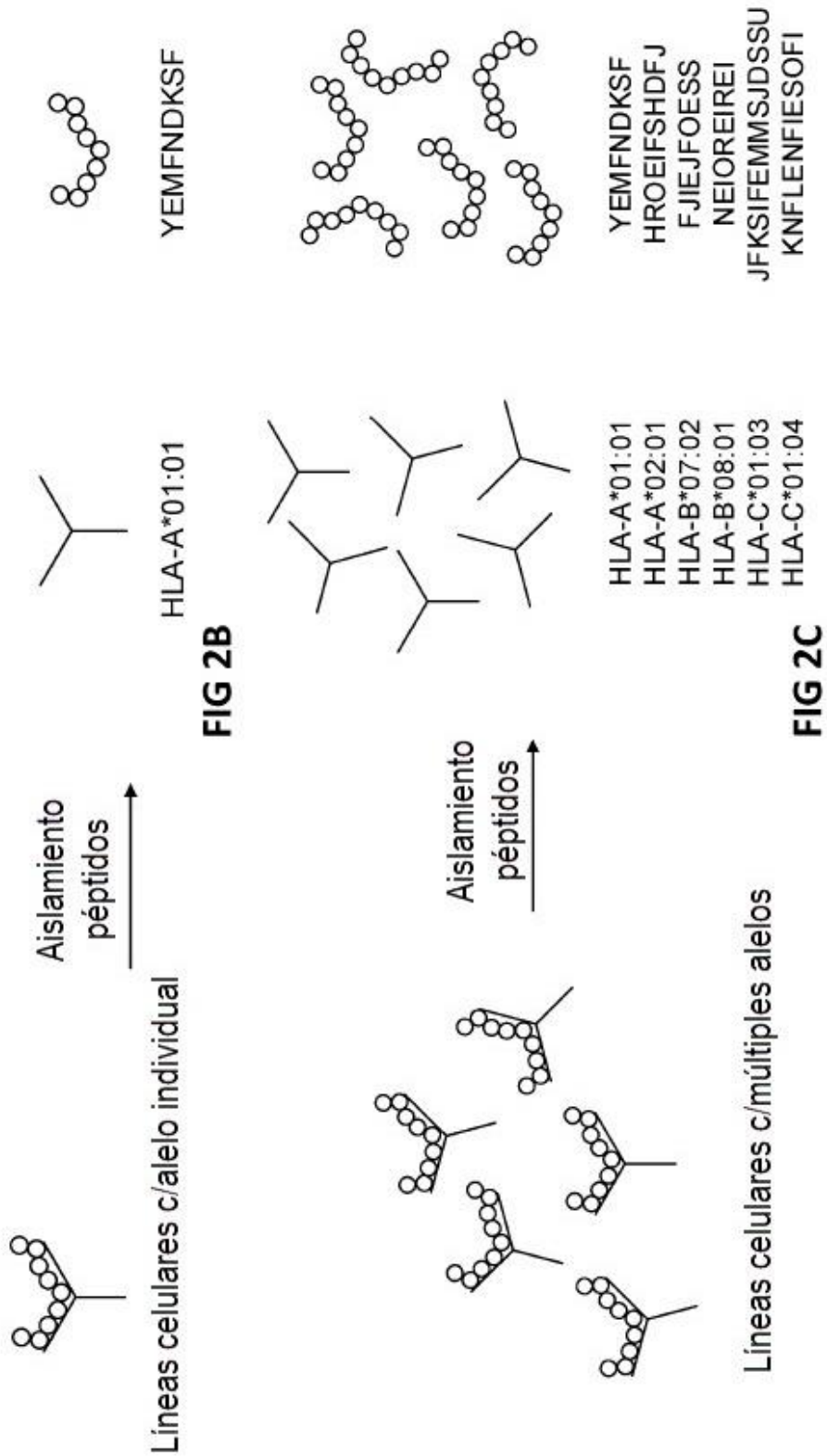


FIG 2A



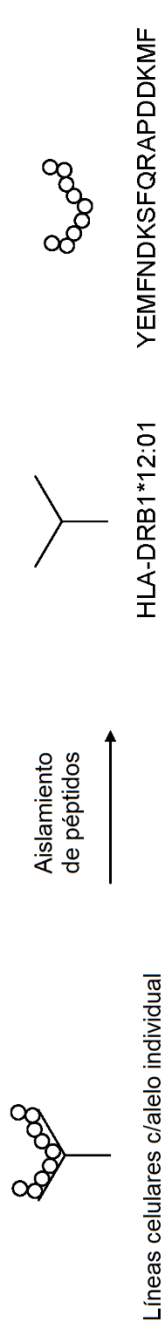


FIG. 2D

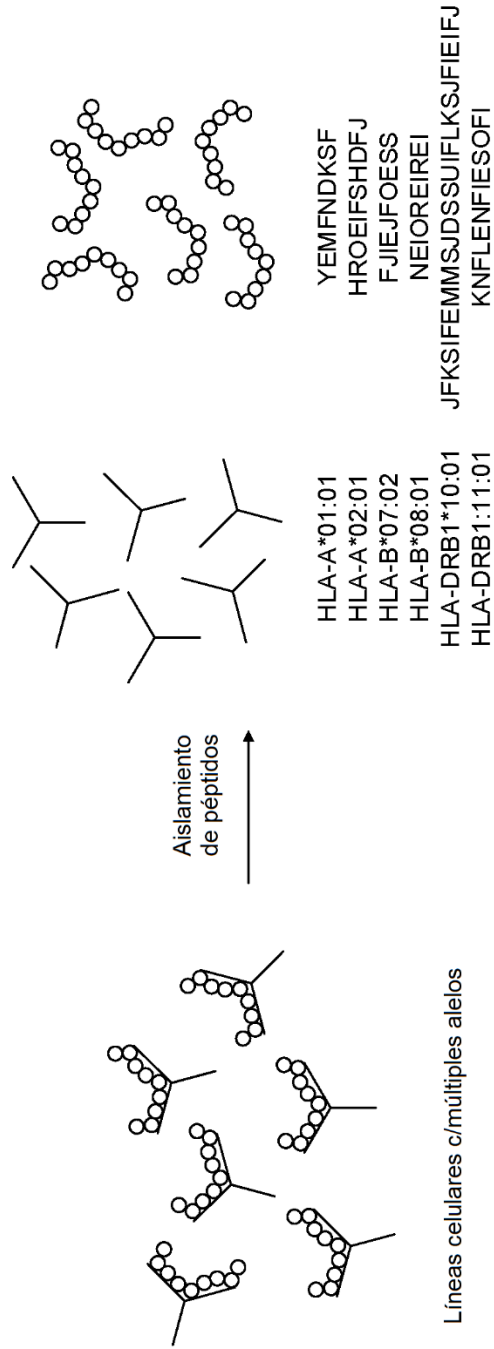


FIG. 2E

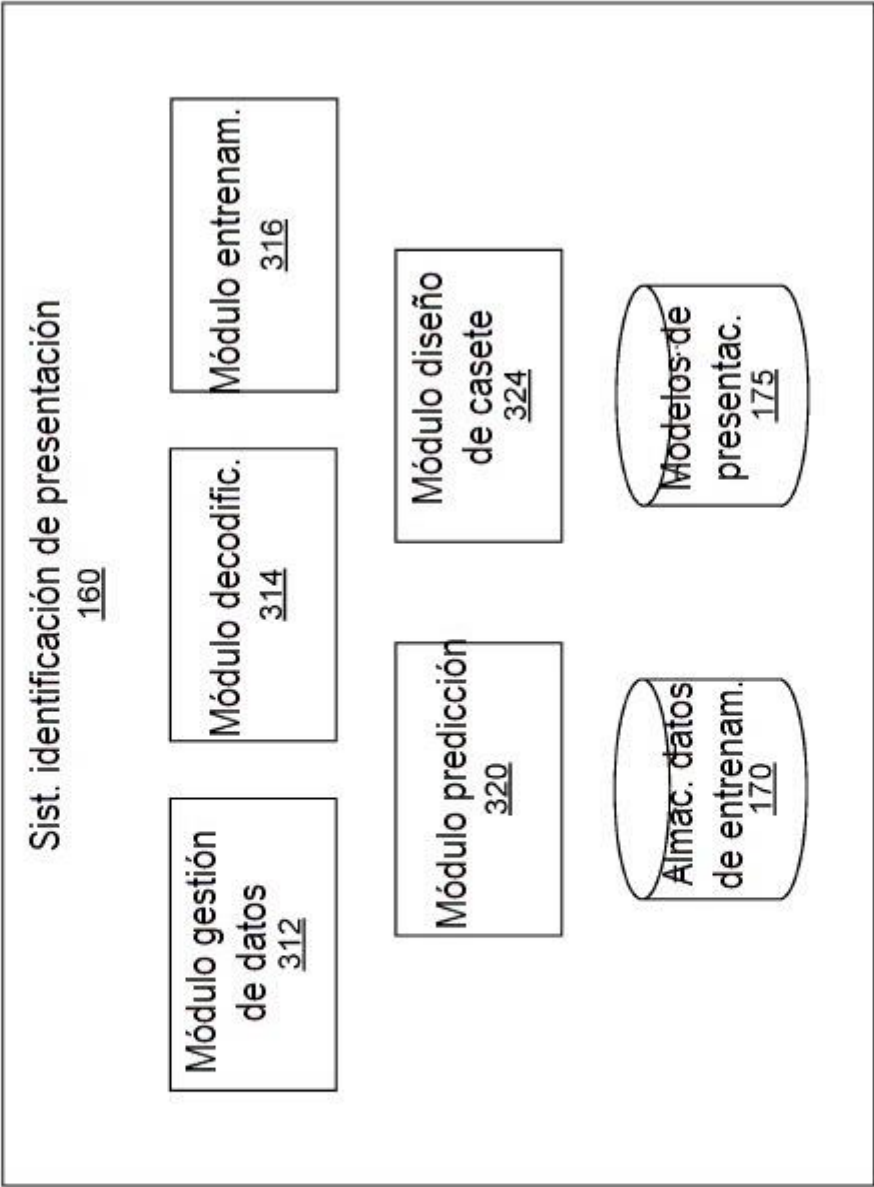


FIG 3

Datos de entrenamiento
170A

Dependiente de alelo (x')			Independiente de alelo (w')			
Secuencia pept. (p')	Afinidad (b' -nM)	Estabilidad (s' -h)	Alelo (a')	Sec. flanqueante C (c')	ARNm Q. (m' -FPKM)	Etiqueta(y')
QCEIOWARE	1000	1	HLA-C*01:03	FJELFISBOSJFIE	10^2	No presentada
FIEUHFWI	1500	15	HLA-C*01:03	FEGRKUOOI	10^{-3}	Presentada
FEWRHRJTRUJR	650	20	HLA-C*01:03	PJFIOEJOIJGEIO	10^1	Presentada
QIEJOEIJIE	500	1	HLA-B*07:02	PJFIOEJOIJGEIO	1	Presentada
	600	14	HLA-C*01:03			
	1200	7	HLA-A*01:01			

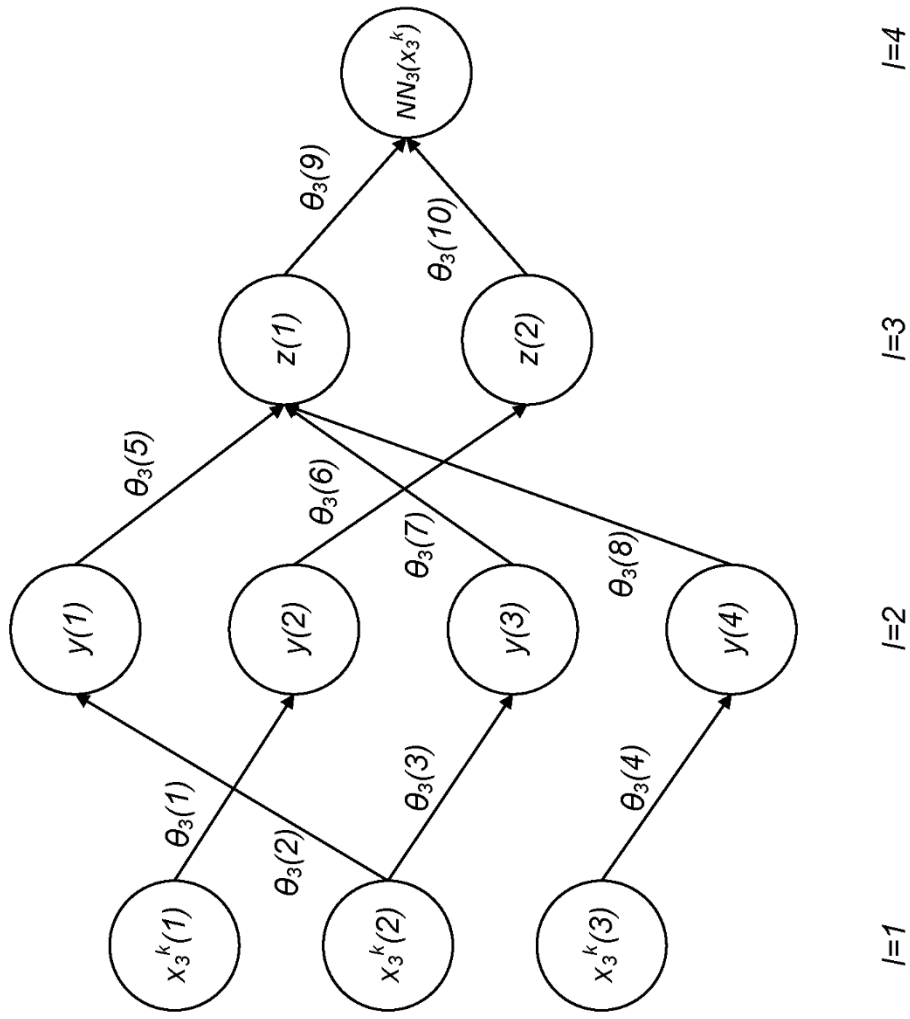
FIG 4A

Datos de entrenamiento
170A

Dependiente de alelo (x^j)

Secuencia peptídica (p^j)	Afinidad (b^j -nM)	Estabilidad (s^j -h)	Alelo (a^j)
QCEIOWAREFLKEIGJ	1000	1	HLA-DRB3:01:01

FIG 4B

**FIG 5**

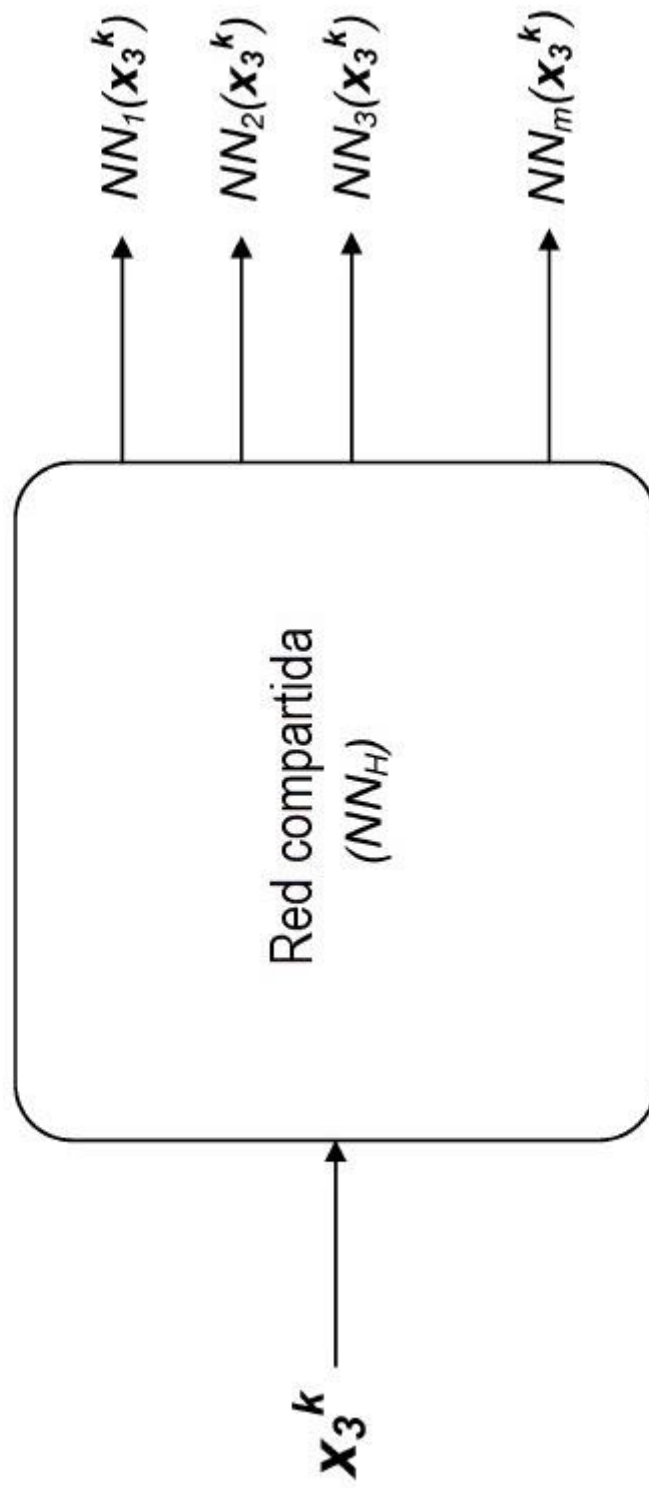


FIG 6A

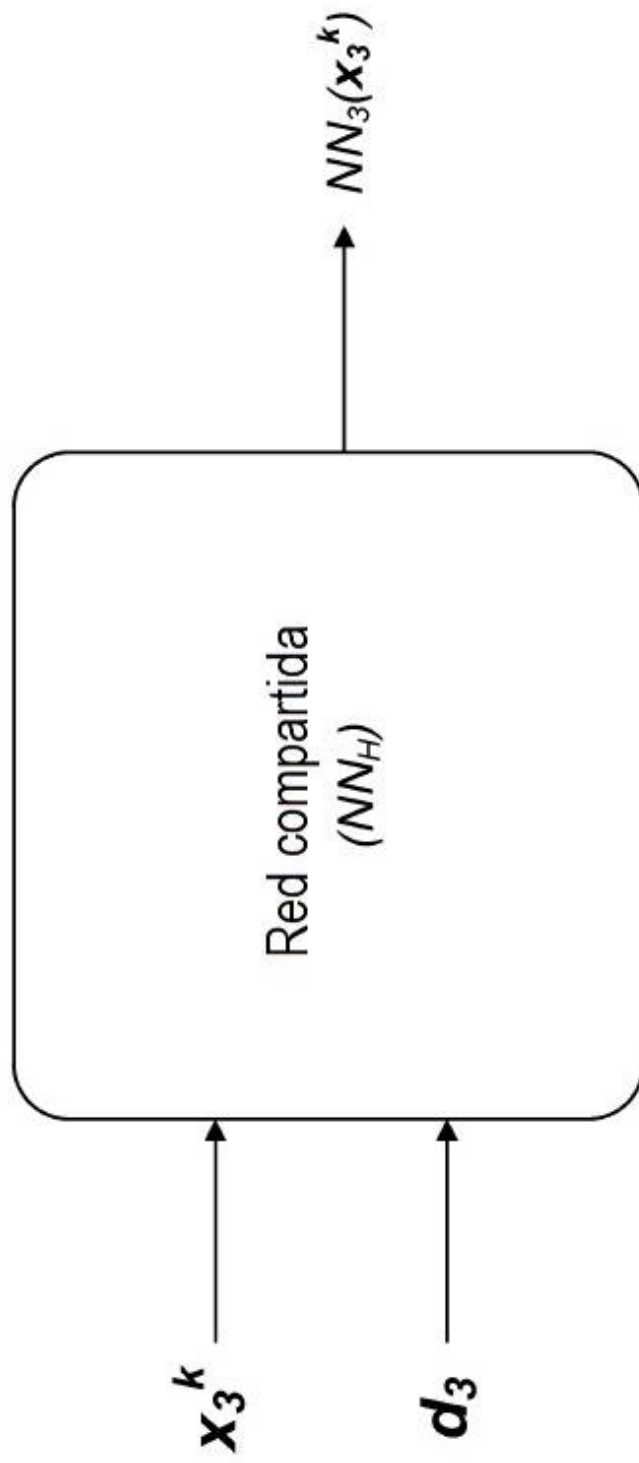


FIG 6B



FIG 7

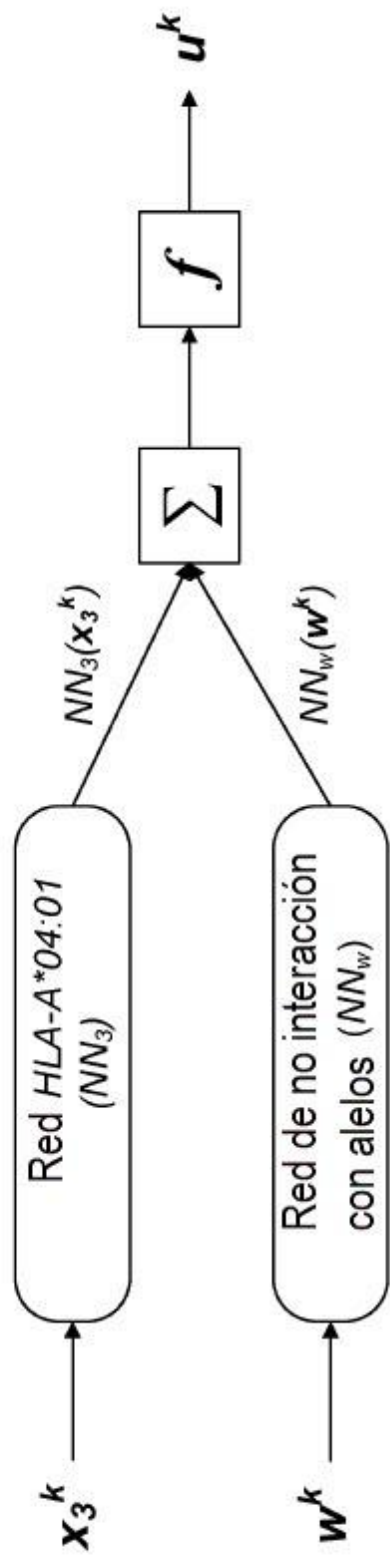


FIG 8

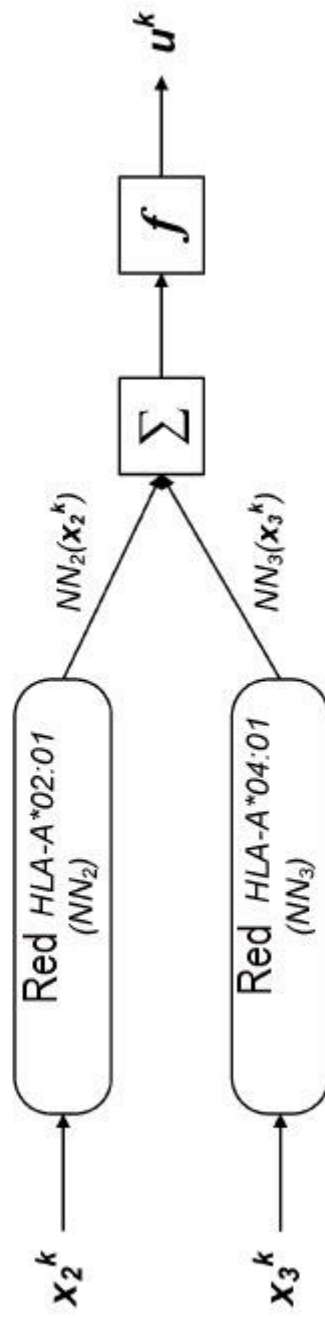


FIG 9

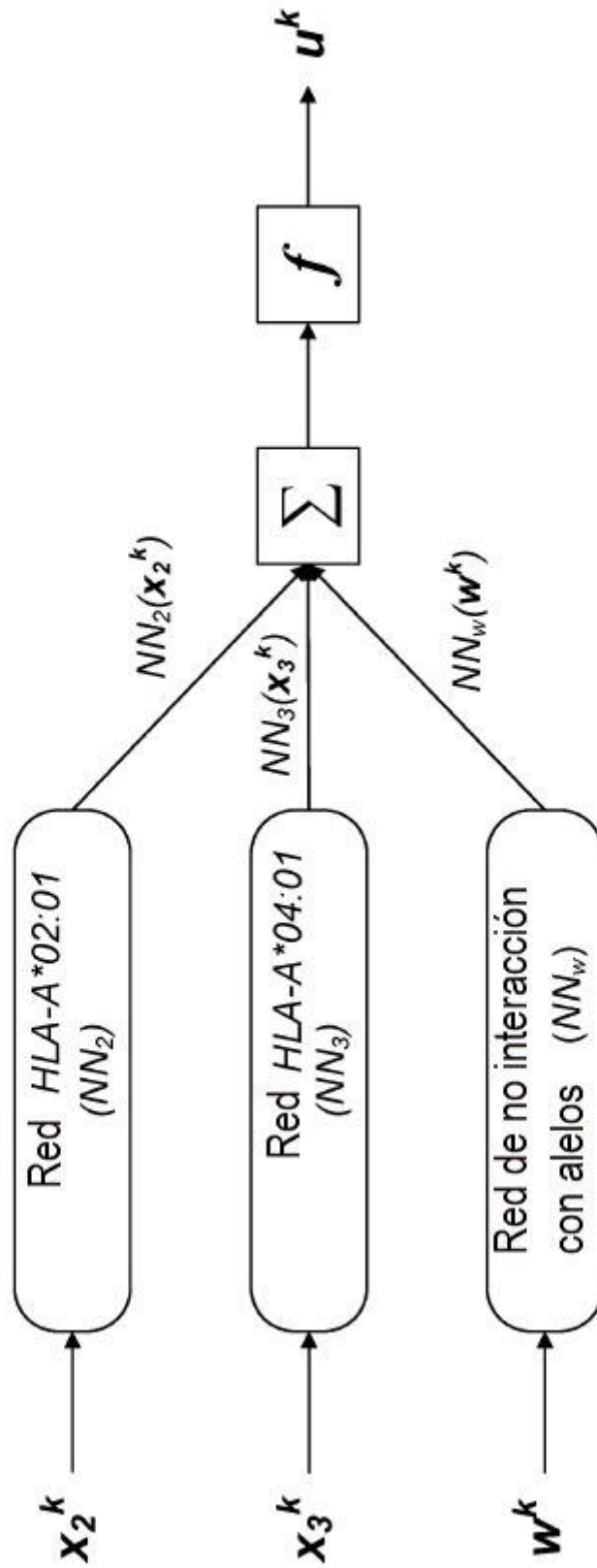


FIG 10

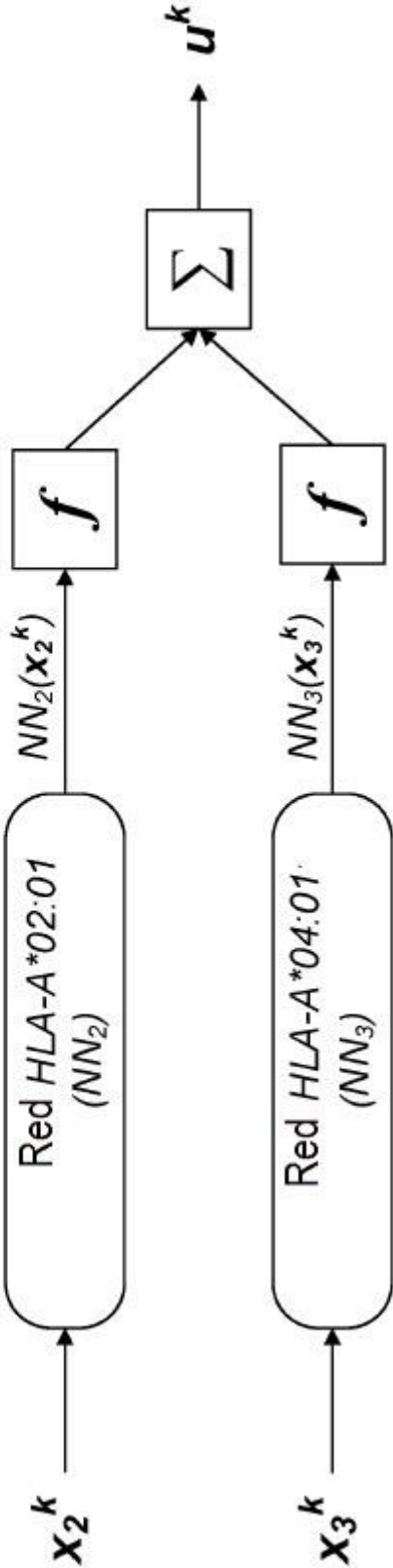


FIG 11

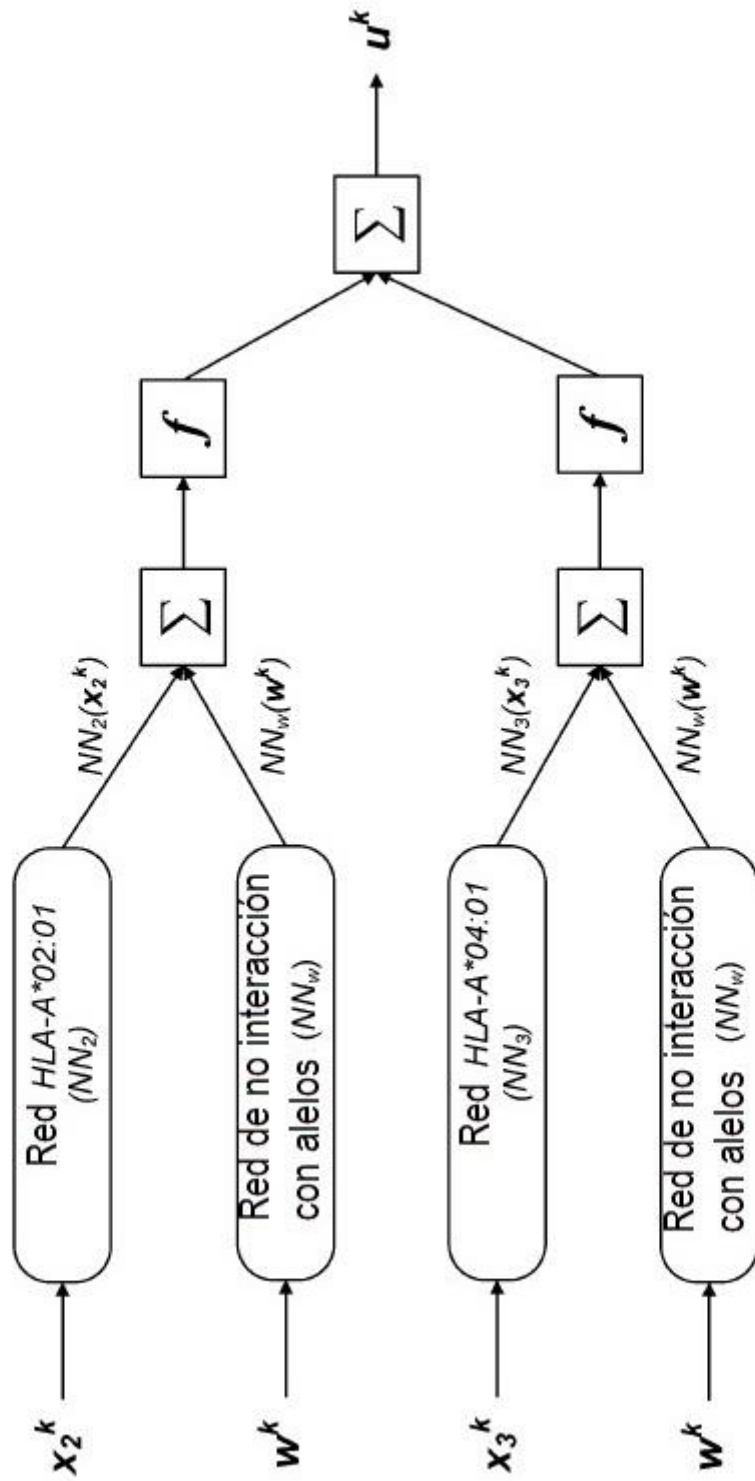
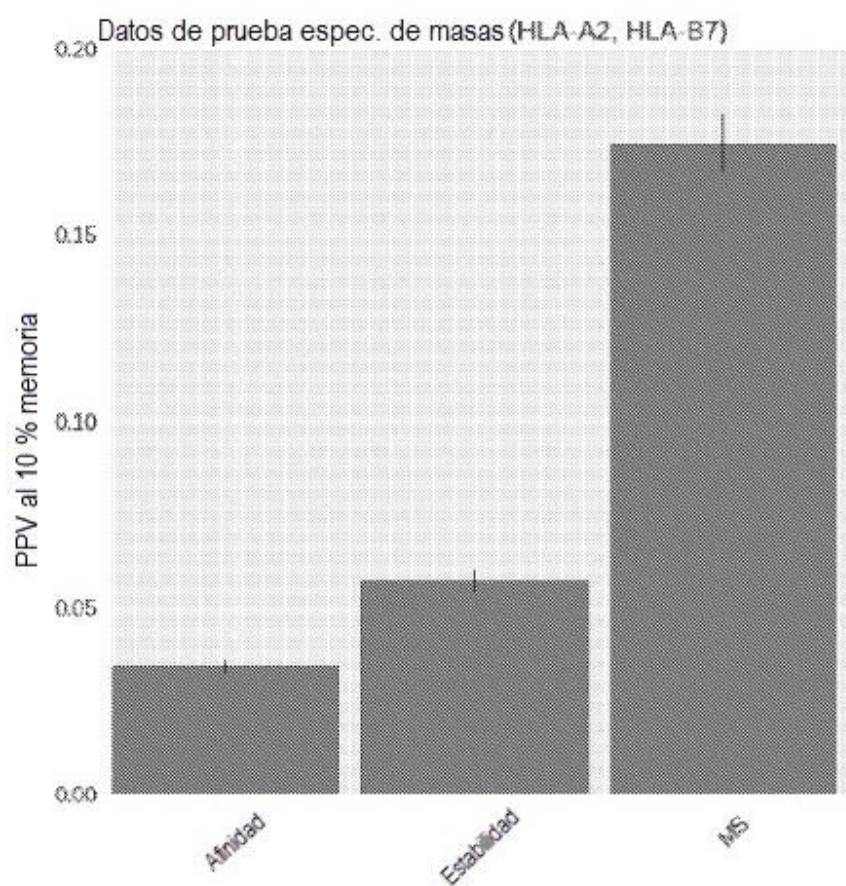
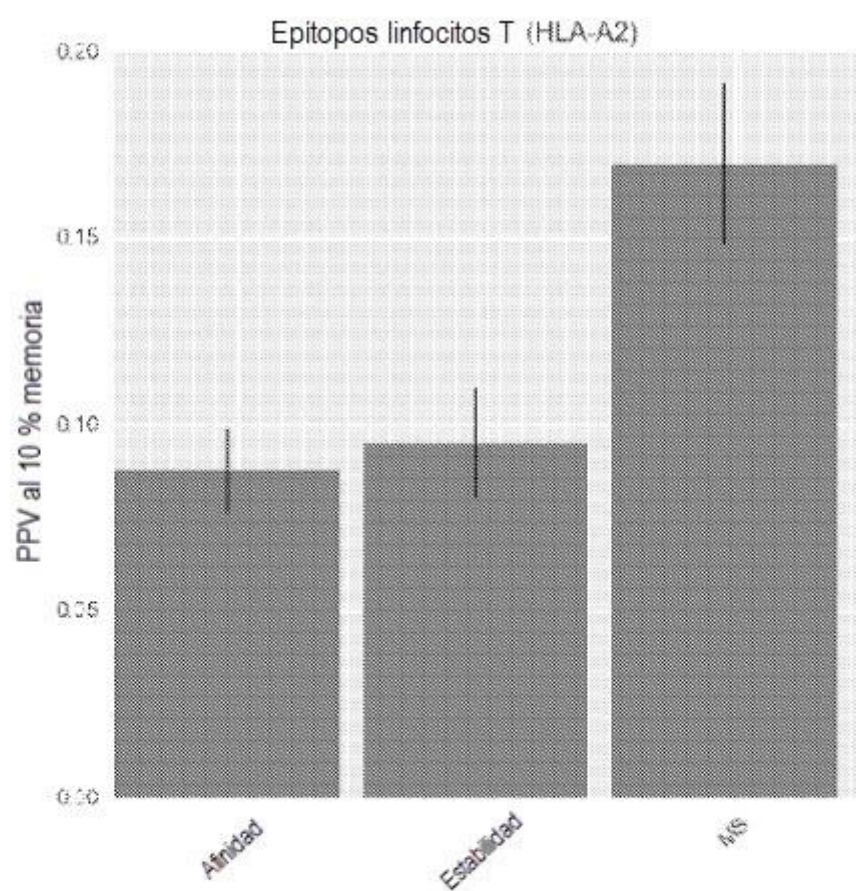


FIG 12

**FIG 13A**

**FIG 13B**

Modelo	AUC	Pérdida log.	PPV al 10 % memoria
Sigmoide de sumas	0.9278	$12.2 \cdot 10^{-4}$	0.114
Suma de sigmoides	0.9723	$5.78 \cdot 10^{-4}$	0.152
Tangente hiperbólica	0.9734	$5.72 \cdot 10^{-4}$	0.156
Segundo orden	0.9727	$5.74 \cdot 10^{-4}$	0.160

FIG 13C

Modelo	AUC	Pérdida log.	PPV al 10 % memoria
Con datos alelos individuales A2/B7	0.9818	$5.40 \cdot 10^{-4}$	0.215
Sin datos alelos individuales A2/B7	0.9803	$5.31 \cdot 10^{-4}$	0.211

FIG 13D

Configuración	Correlación	Alelo	P2	P9
Modelo A2 predictivo de B7	0.004	A2	L 89%	V 58%
Modelo A2 predictivo de A2	0.294		M 5%	L 32%
Modelo B7 predictivo de B7	0.366	B7	P 98%	L 76 %
Modelo B7 predictivo de A2	0.002			V 8%

FIG 13E

FIG 13F

Modelo	AUC	Pérdida log.	PPV al 10 % memoria
interacción con alelos	0.9723	$5.78 \cdot 10^{-4}$	0.152
no interacción con alelos	0.9732	$5.53 \cdot 10^{-4}$	0.188

FIG 13G

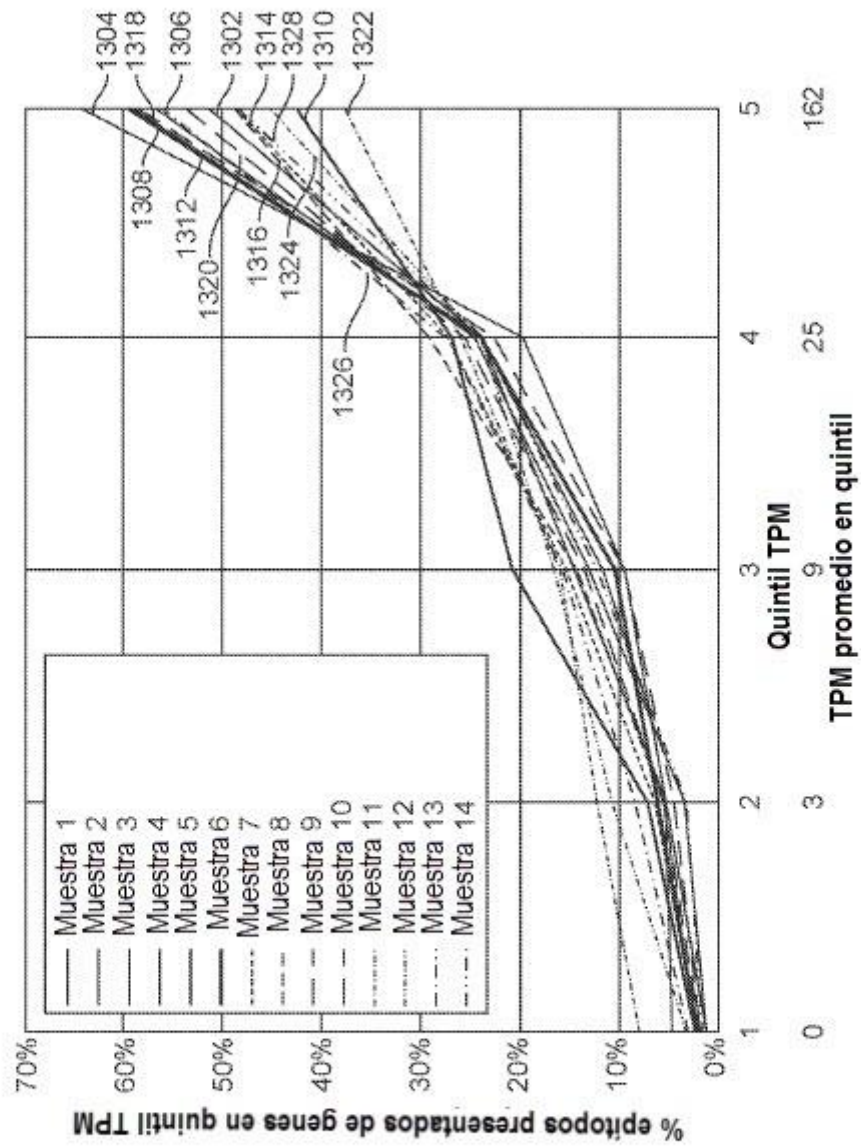
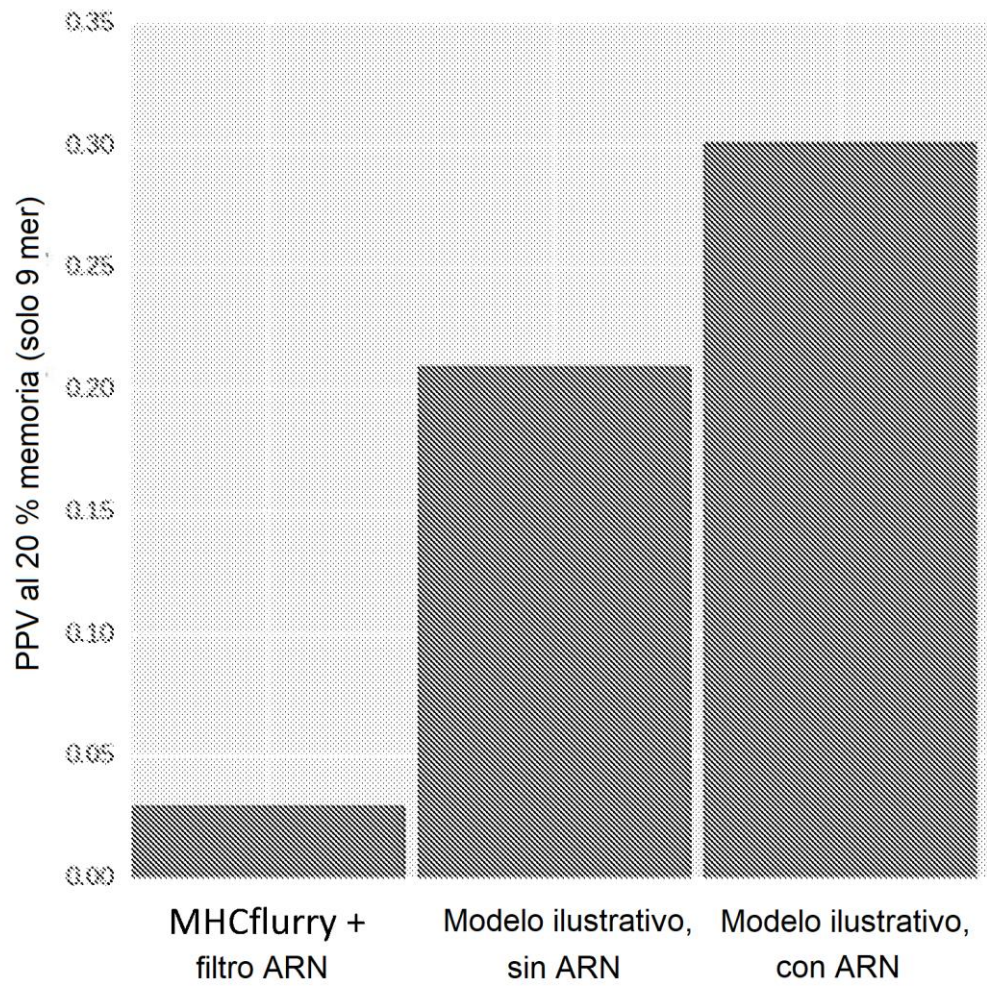
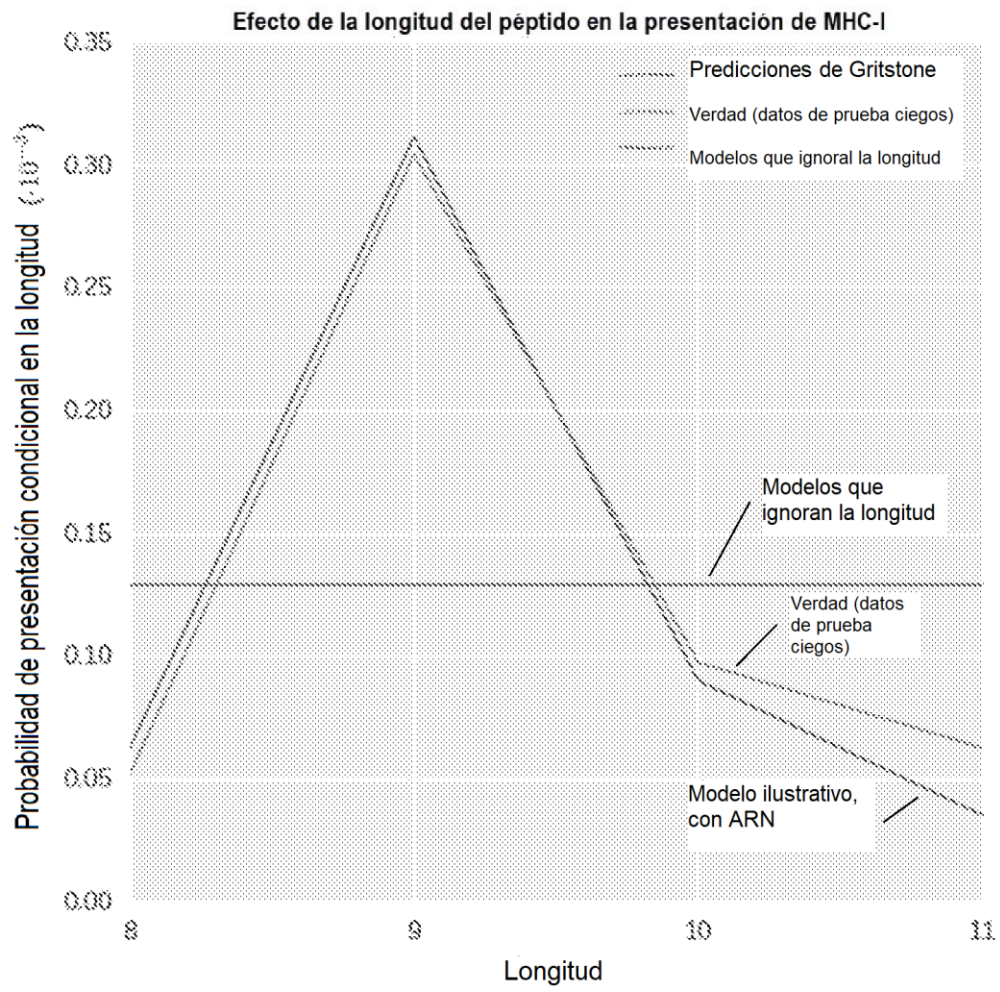
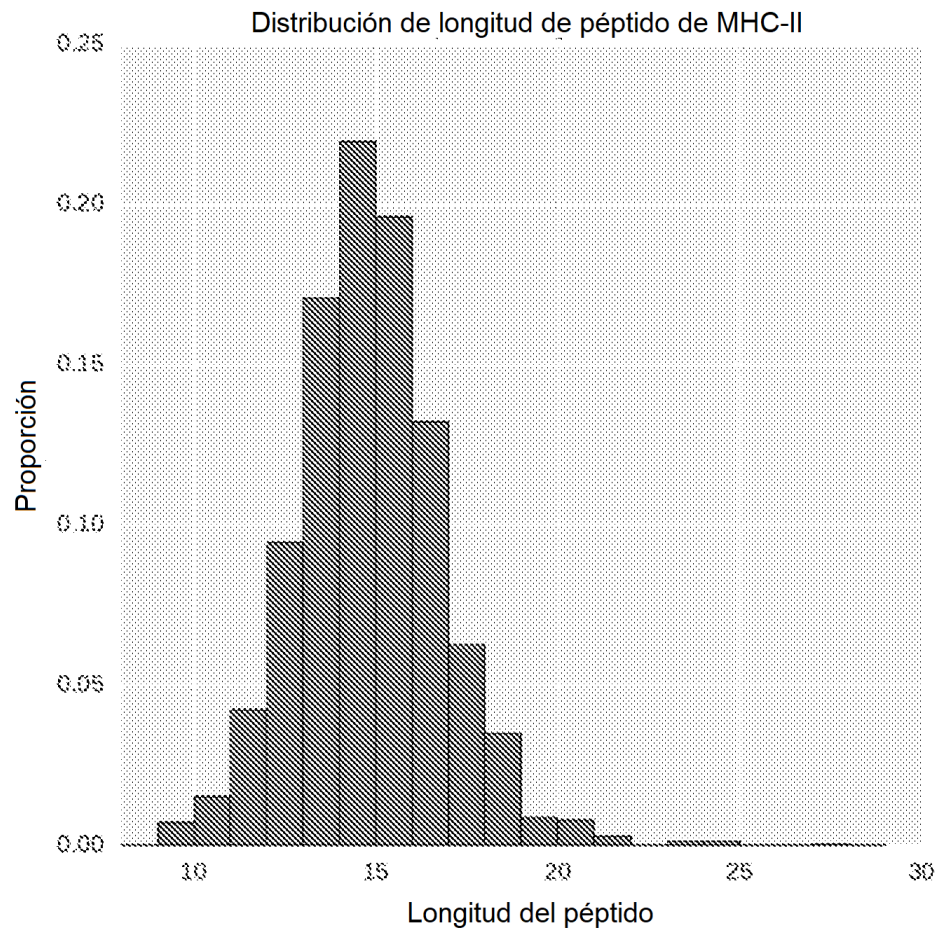


FIG 13H

**FIG 13I**

**FIG 13J**

**FIG 13K**

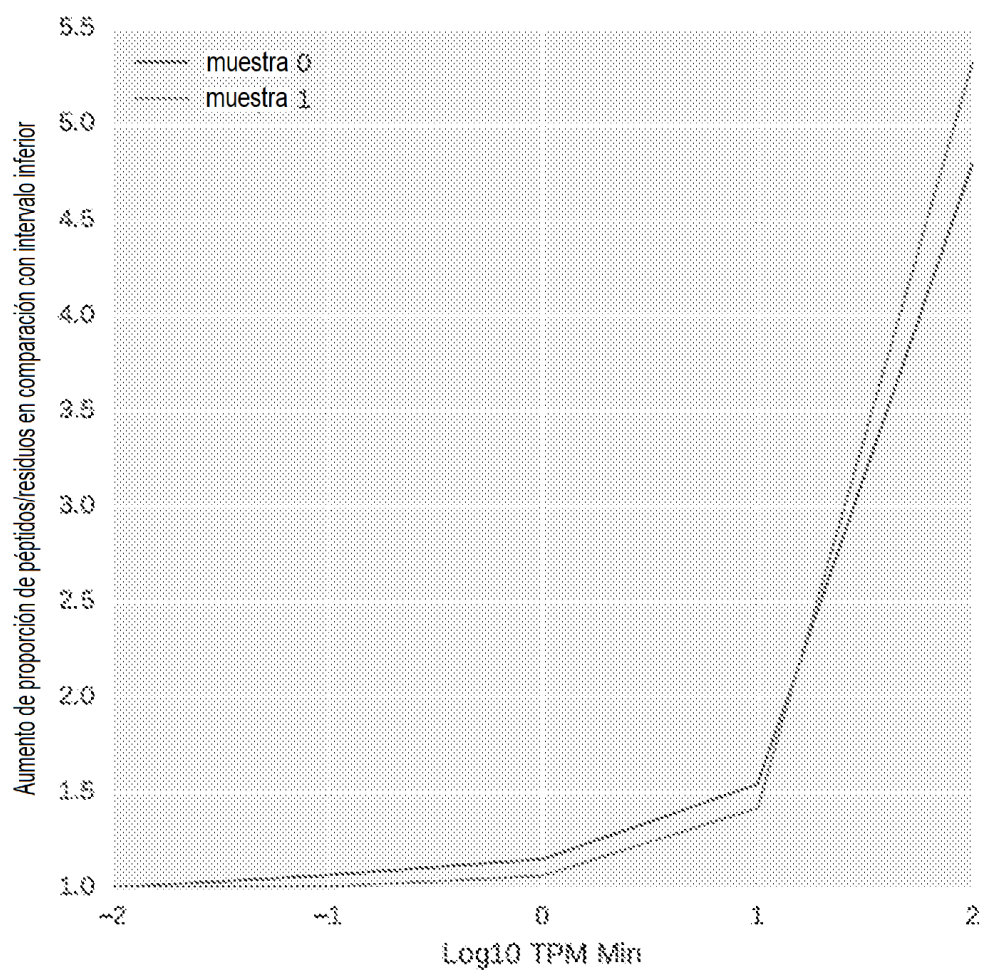
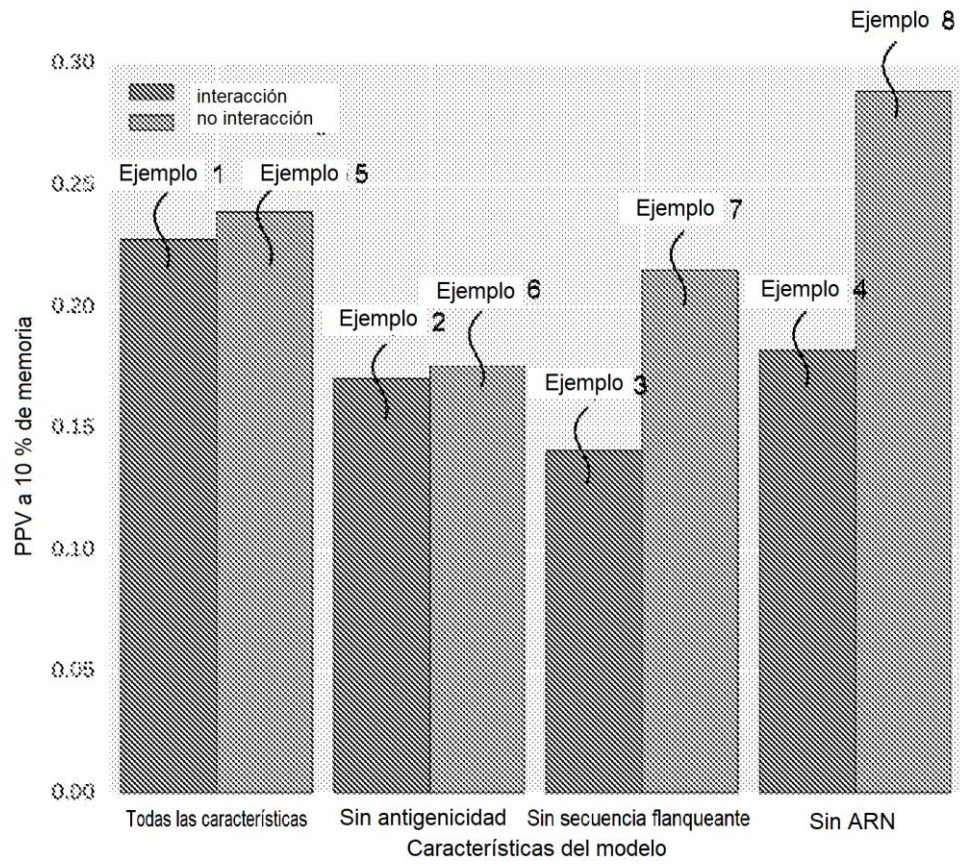
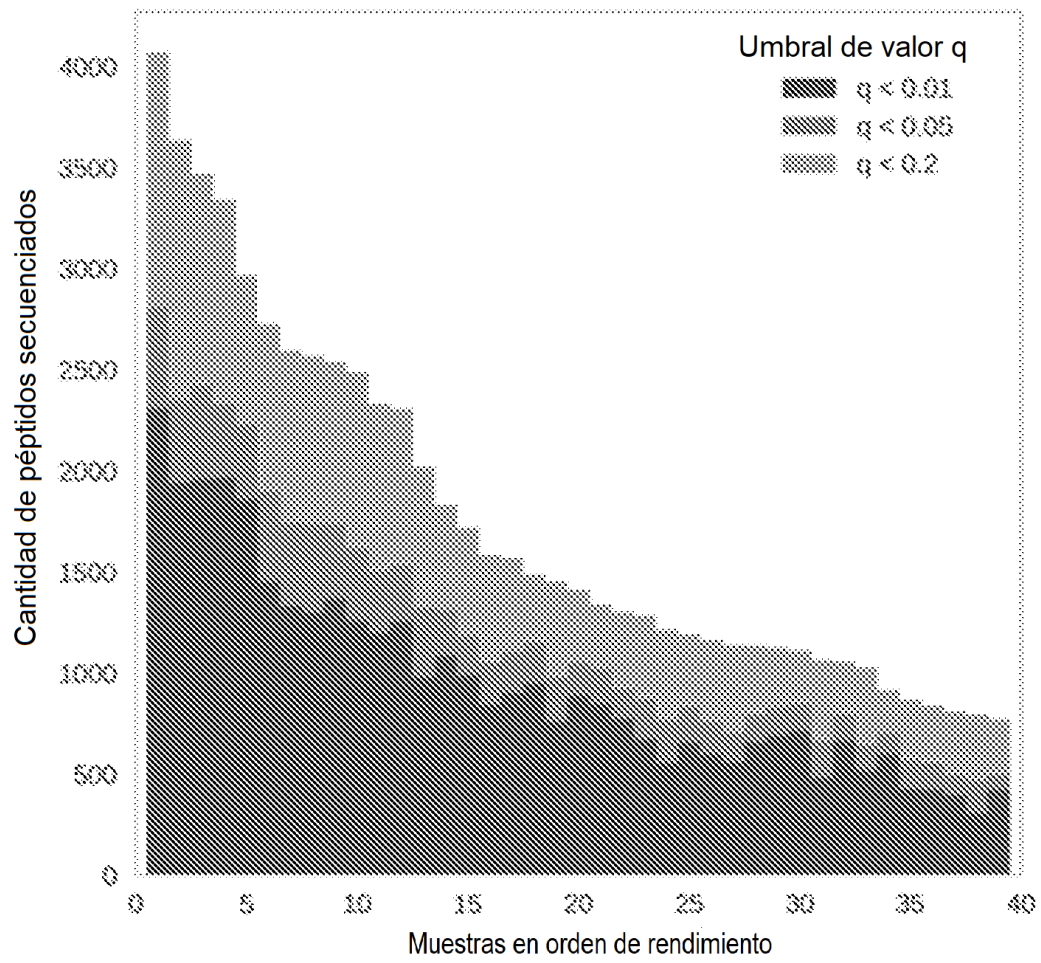


FIG 13L

**FIG 13M**

**FIG 13N**

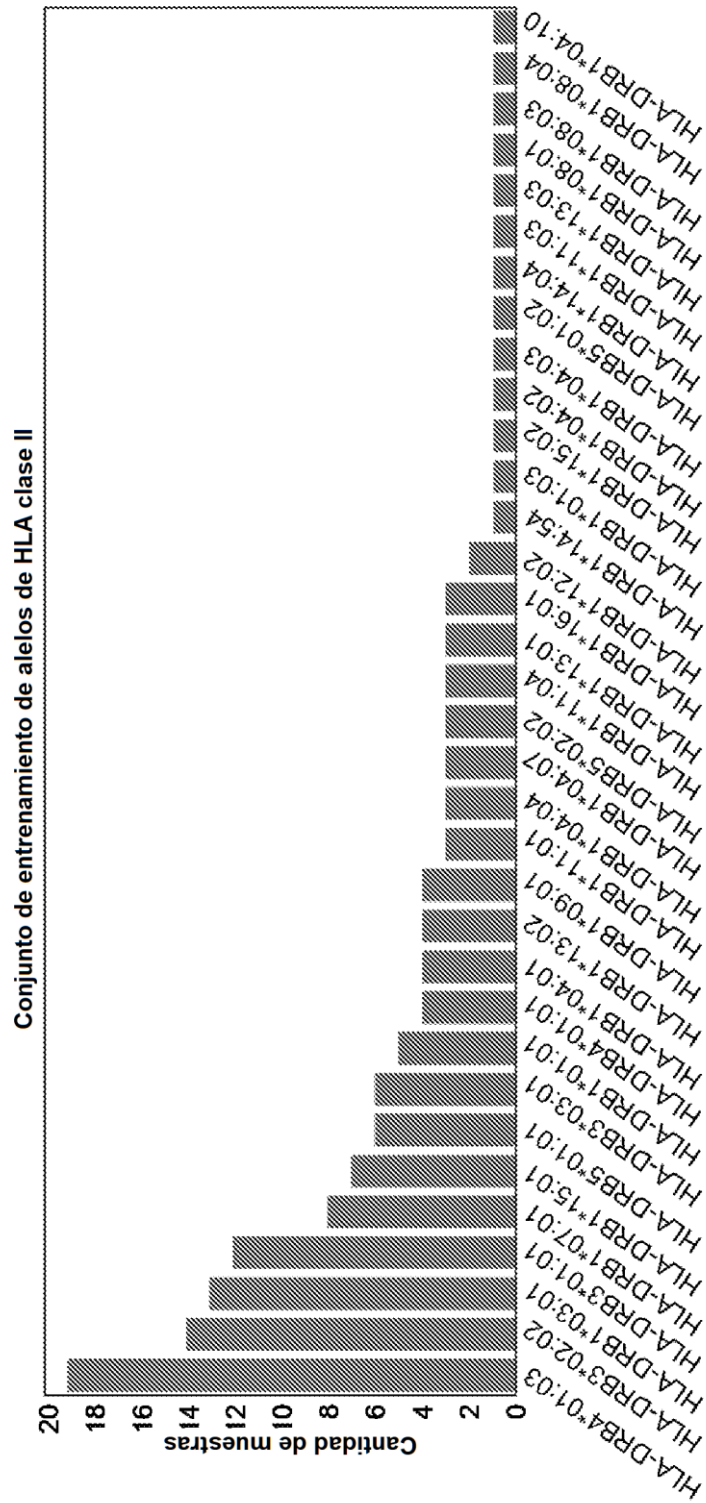
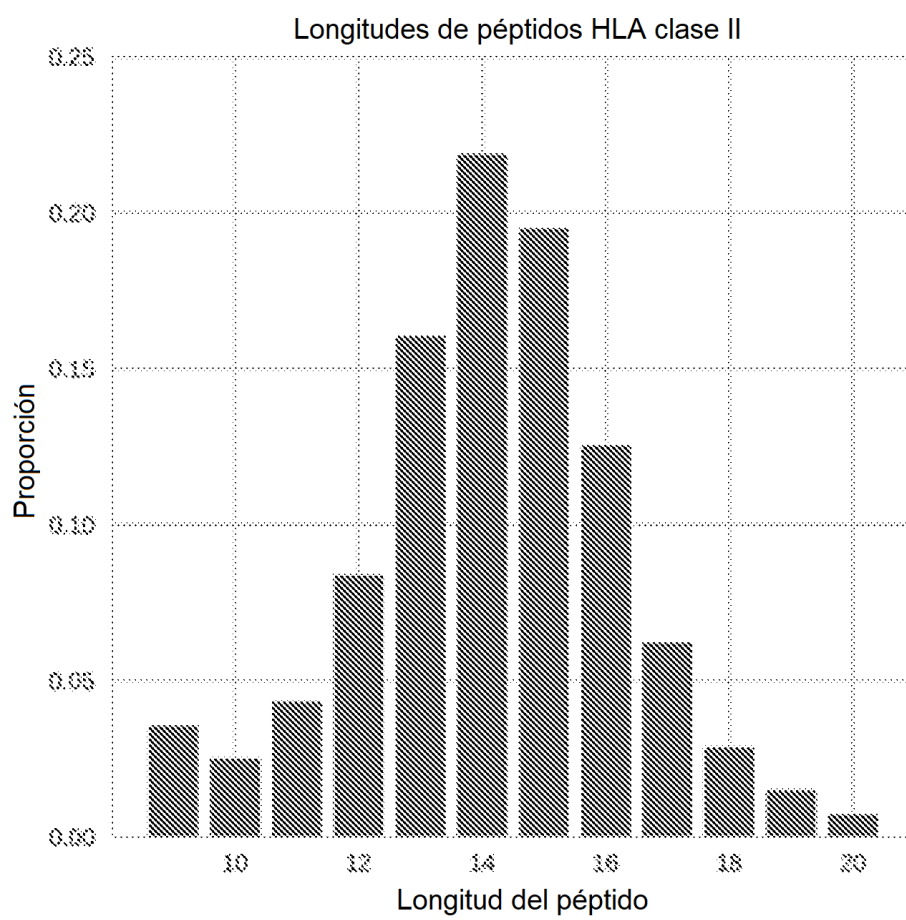
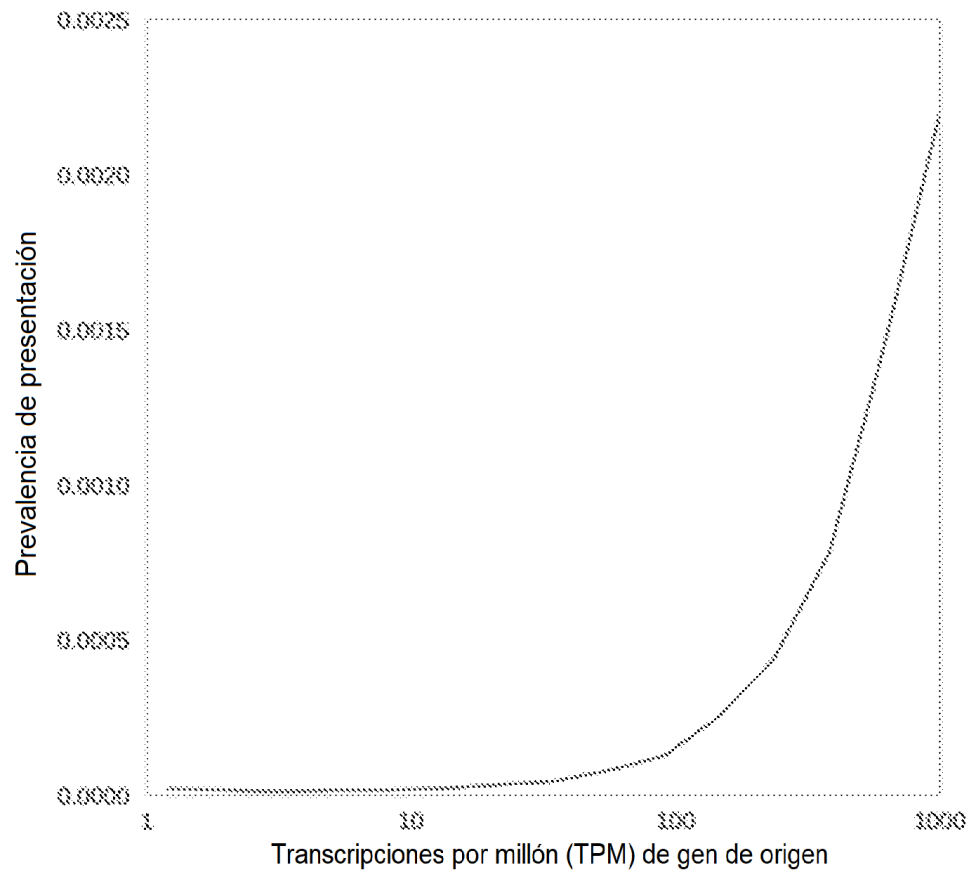
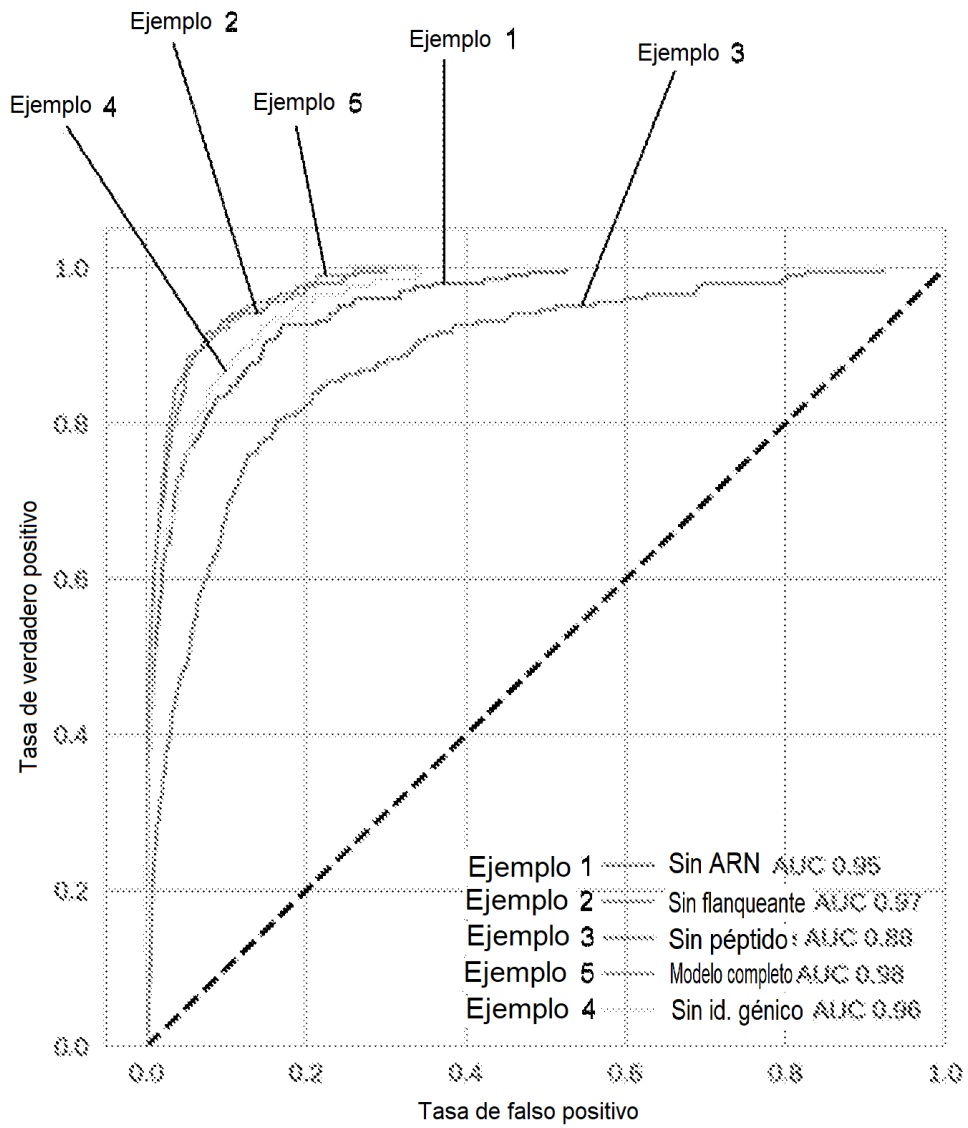
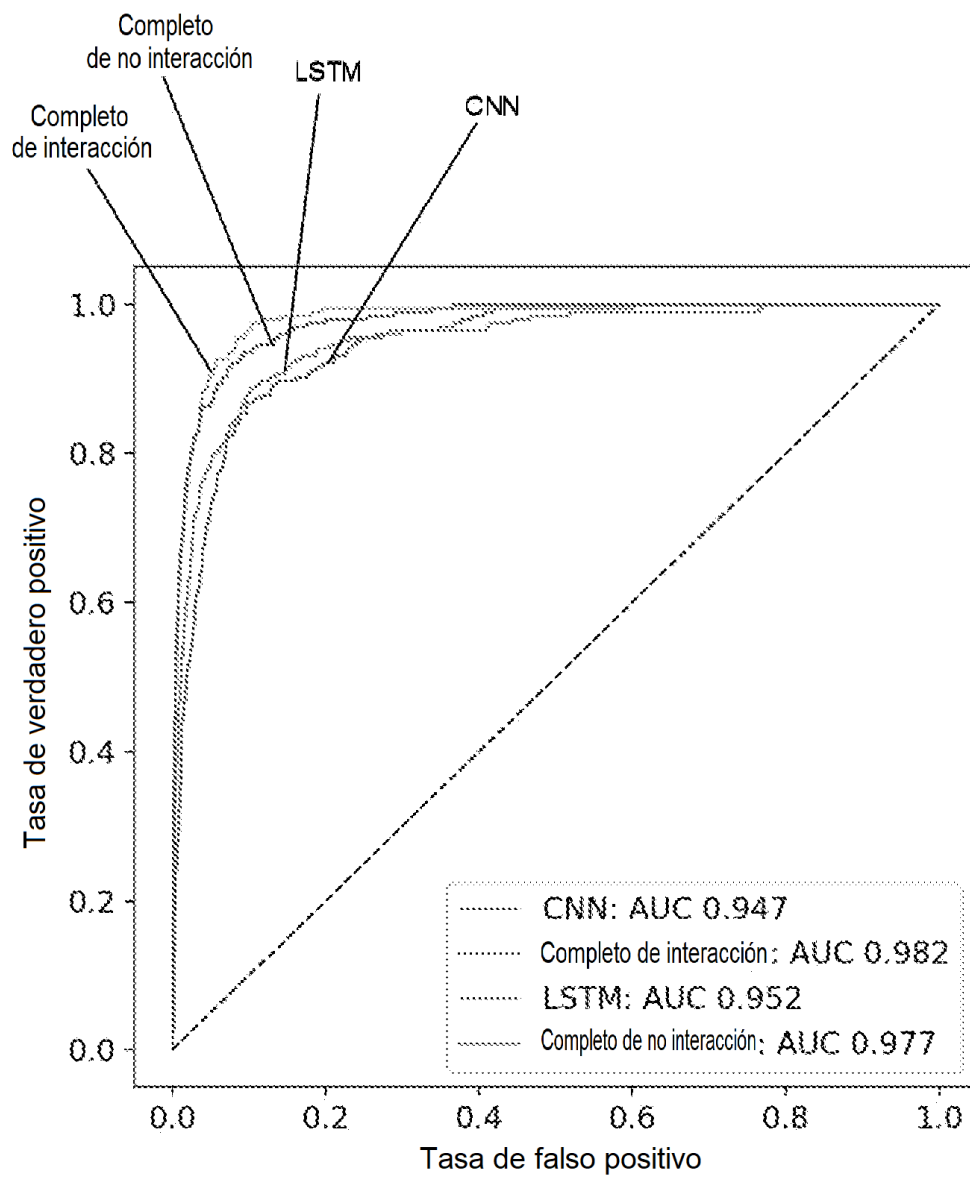


FIG 13-O

**FIG 13P**

**FIG 13Q**

**FIG 13H**

**FIG 13S**

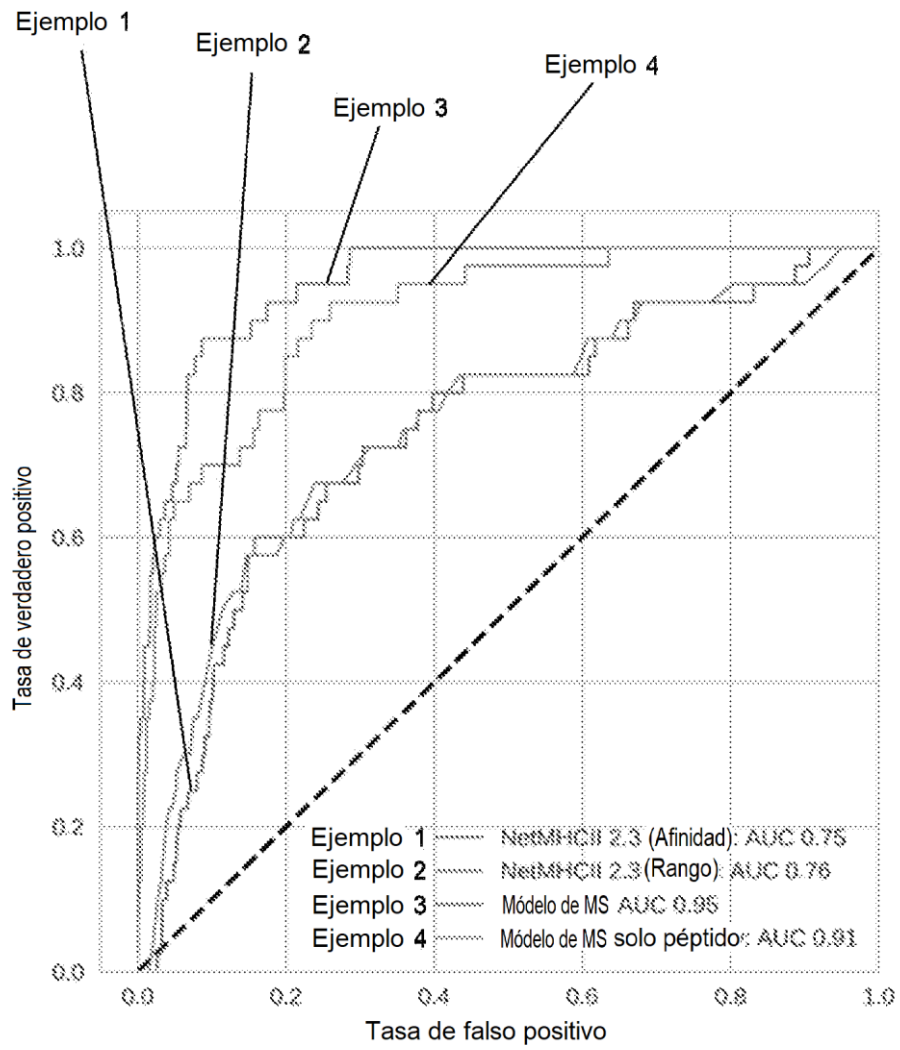
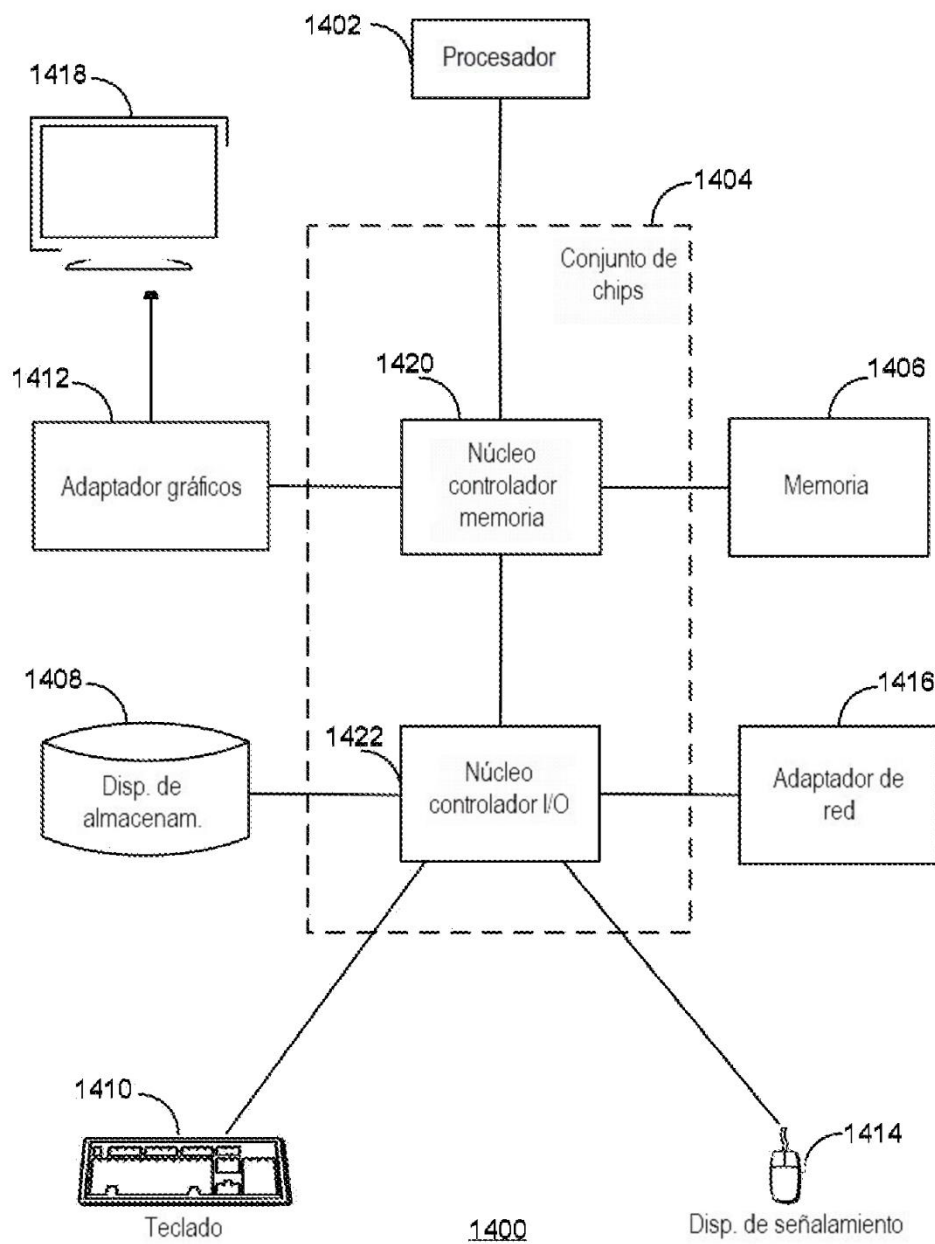


FIG 13T

**FIG 14**

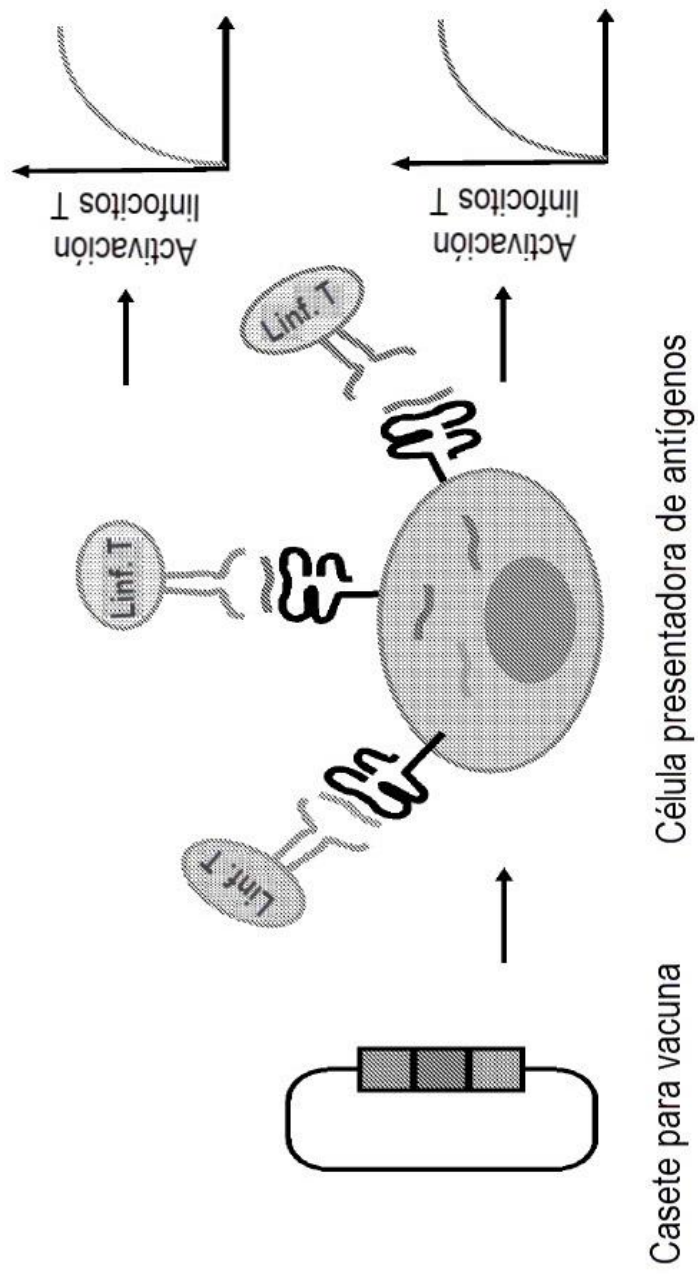


FIG 15

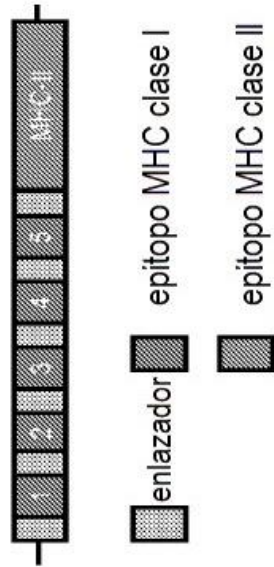


FIG 16A

#	HLA	Secuencia	Origen
1	A*0201	NLVPMVATV	HCMV pp65 (495–503)
2	A*0201	CLGGLTMV	EBV LMP2A(426-434)
3	A*0201	GLCTLVAML	EBV BMLF1 (280–288)
4	A*0201	LLFGYPVVV	HTLV-1 Tax (11–19)
5	A*0201	GILGFVFTL	Influenza A matriz 1 (58–66)
	MHC-II	AKFVAAWTLKAAA	PADRE (Sec. artificial)
	MHC-II	QYIKANSKFIGITE	Toxide tetánico (830–844)

FIG 16B

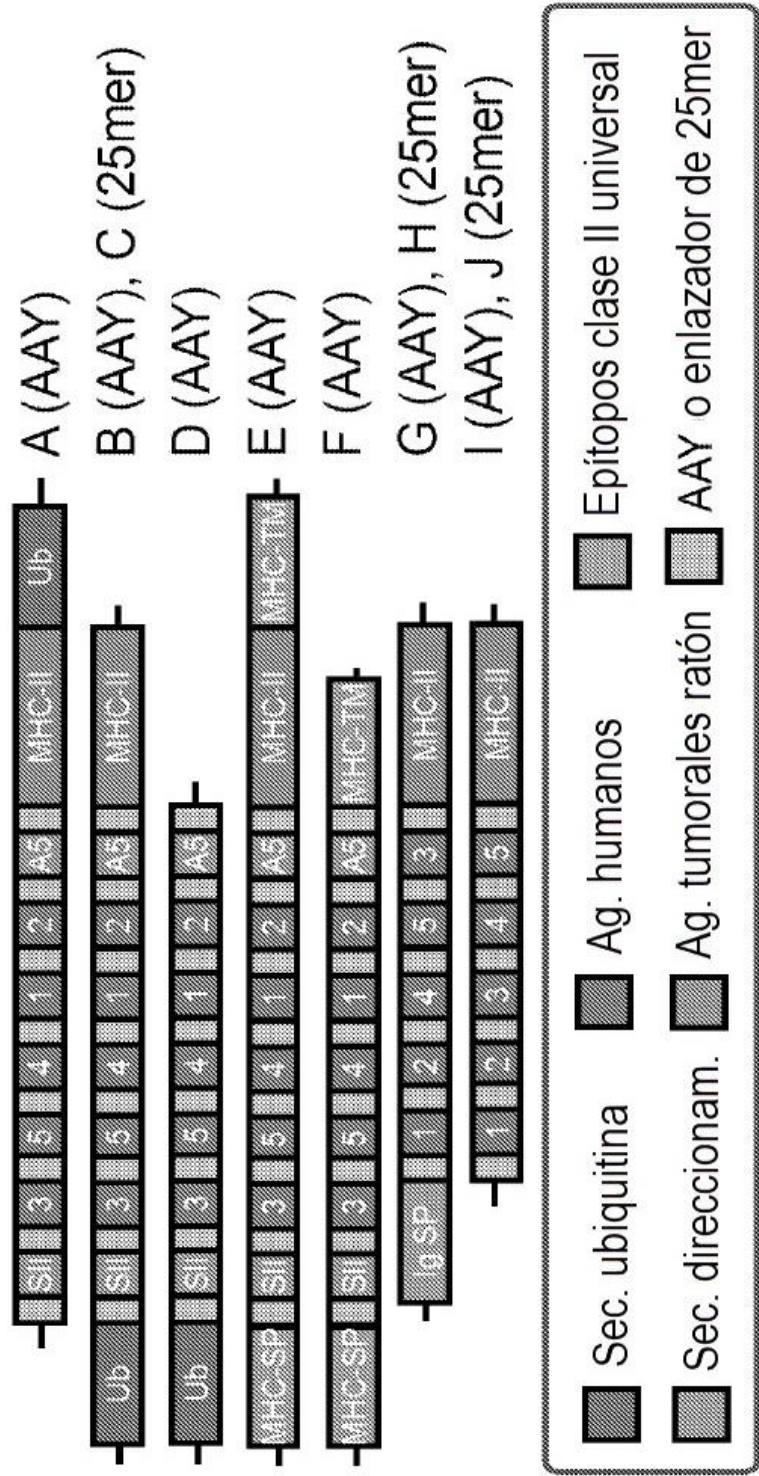


FIG 17

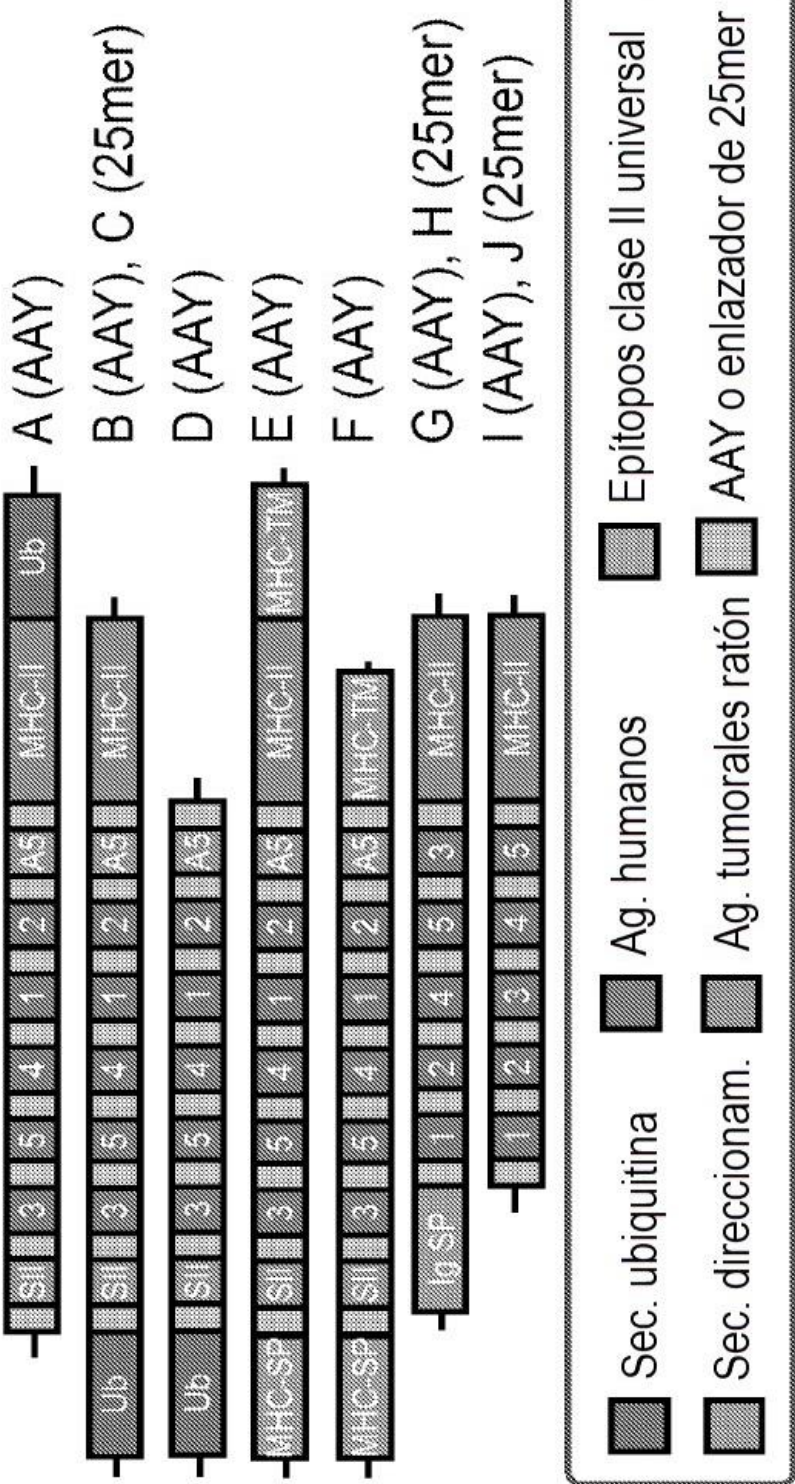


FIG 18

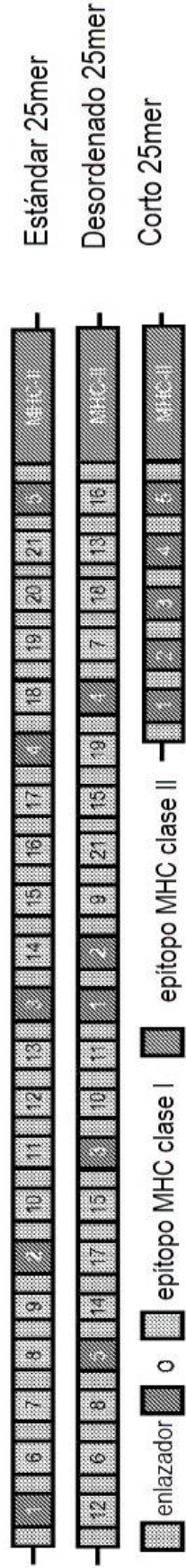


FIG 19A

#	HLA	Secuencia	Origen
1	A*02:01	NLVPMVATV	HCMV pp65 495-504
2	A*02:01	CLGGLTMV	EBV LMP-2 426-434
3	A*02:01	GLCTLVAML	EBV BMLF-1 259-267
4	A*02:01	LLFGYPVYV	HTLV1 Tax 11-19
5	A*02:01	GILGFVFTL	Influenza A MP 58-66
6	A*02:01	DLMGYIPAV	HCV nucl. 132-140
7	A*02:01	FLPSDFFPSV	HBV antígeno nucl.18-27
8	A*02:01	FLLTRILT	HBV cubierta 183-191
9	A*02:01	VL SLLVPFV	HBV antígeno superf.172-181
10	A*02:01	FLLSLGIHL	HBV polimerasa 573-581
11	A*02:01	ILKEPVHGV	HIV-1 RT 476-484
12	A*02:01	YMLDLQPETT	HPV 16 E7 11-20
13	A*02:01	CINGVCWTV	HCV NS3 1073-1081
14	A*02:01	YLLPRRGPR	HCV nucl. 35-44
15	A*02:01	FLYALALL	EBV LMP-2 356-364
16	A*02:01	AAGIGILTV	MELAN-A/MART-1 (27-35)
17	A*02:01	SLLMWITQV	NY-ESO-1(157-165) C9V
18	A*03:01	KLGGALQAK	CVM-IE1
19	A*03:01	RLRAEAQVK	EBV-EBNA-3a
20	B*44:05	EENLLDFVRF	EBV EBNA3C (281-290)
21	B*44:05	EEYLQAFTY	Proteína ABCD3 propia

FIG 19B

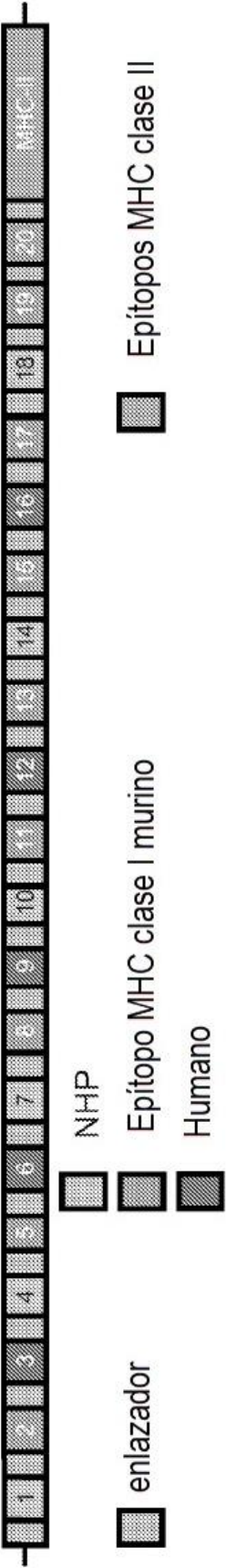


FIG 20A

Epítomos NHP		
MHC	Secuencia	
1 Mamu*01	CTPYDINQM	
4 Mamu*01	TTPESANL	
7 Mamu*01	CAPPGYALL	
10 Mamu*01	SGPKTNIV	
14 Mamu*01	LSPRTLNAW	
18 Mamu*01	TVPWPNASL	

Epítomos humanos		
HLA	Secuencia	
3 A*02:01	GILGFVFTL	
6 A*02:01	LLFGYPVYV	
9 A*02:01	GLCTLVAML	
12 A*02:01	NLVPMVATV	
16 A*02:01	CLGGLTMV	

Epítomos MHC-I murinos		
MHC	Secuencia	
2 H-2Kb	SIINFEKL	
5 H-2Ld	SPSYAYHQF	
8 H-2Db	EGPRNQDWL	
11 H-2Kb	DWENVSPKL	
13 H-2Kb	SIIVFNLL	
15 H-2Db	ASMTNMELM	
17 H-2Db	AQLANDVVL	
19 H-2Kb	SVYDFFVWL	
20 H-2Ld	MNKYAYHML	

Epítomos MHC-II universales		
HLA	Secuencia	
1 MHC-II	AKFVAAWTLKAAA	
2 MHC-II	QYIKANSKFIGITEL	

FIG 20B

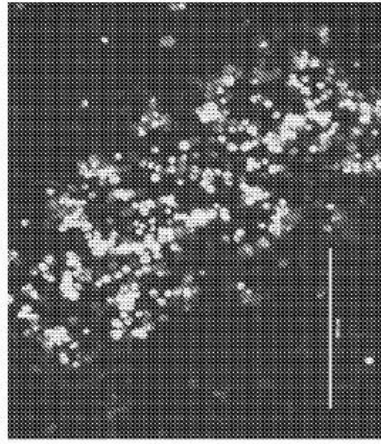


FIG 21C

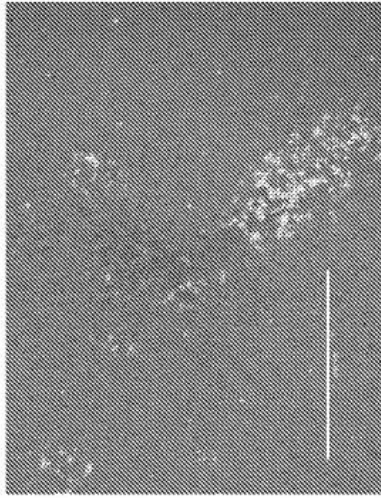


FIG 21B

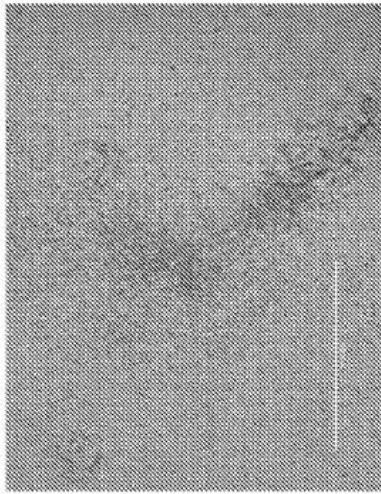


FIG 21A

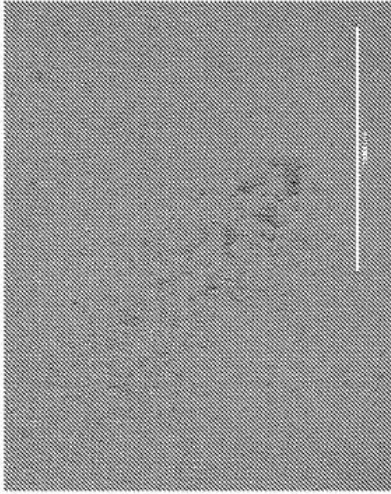


FIG 22A

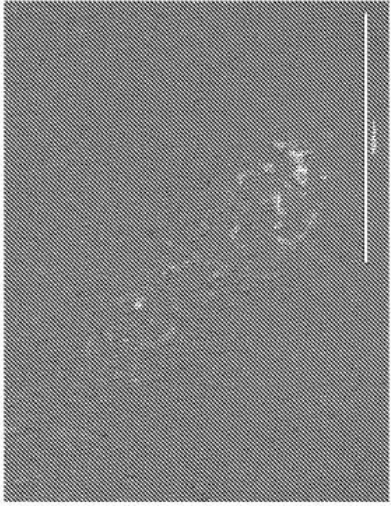


FIG 22B

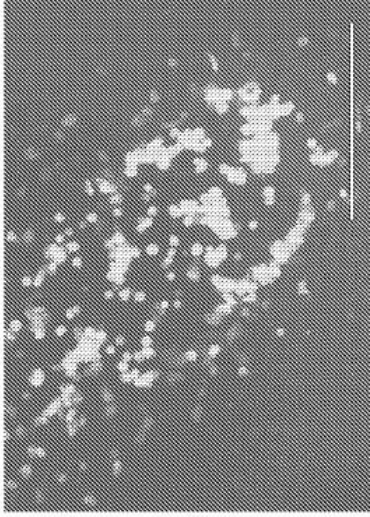


FIG 22C

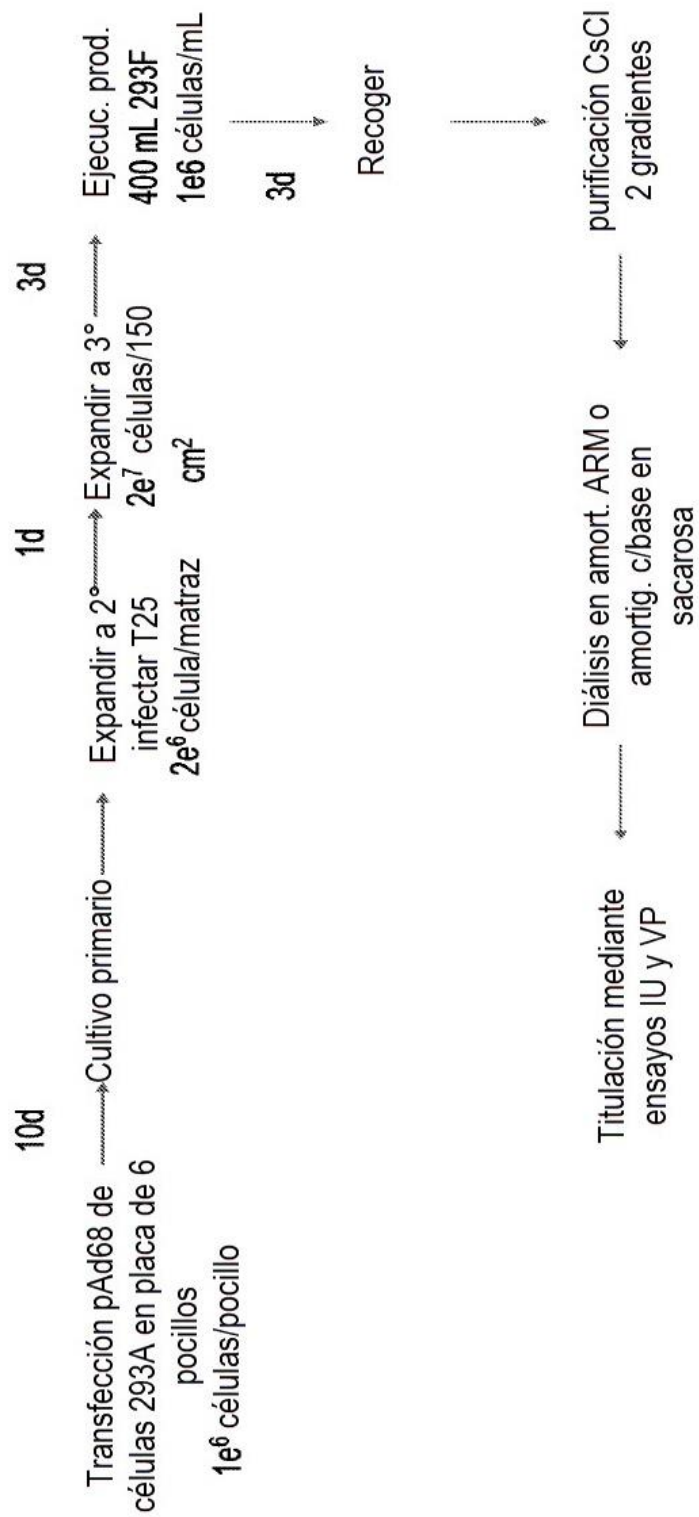


FIG 23

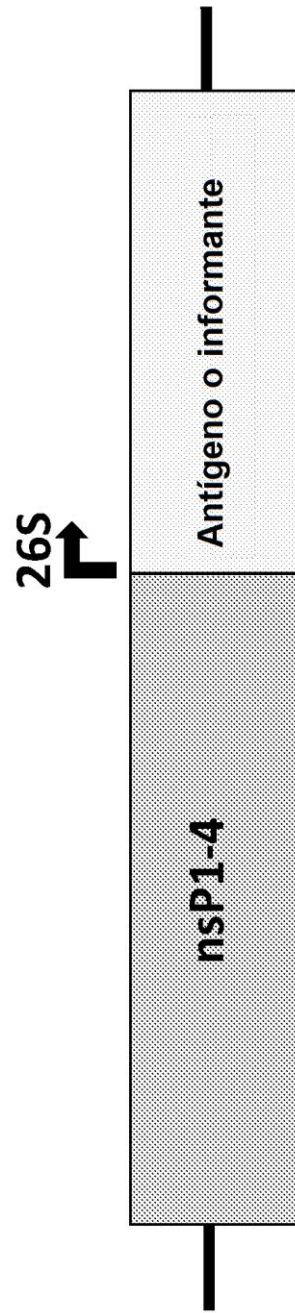
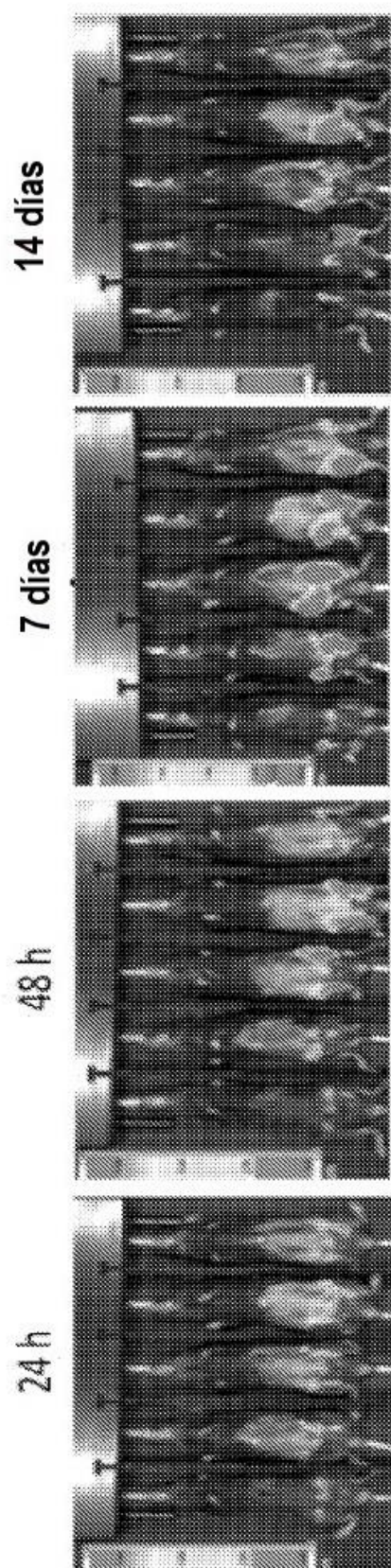
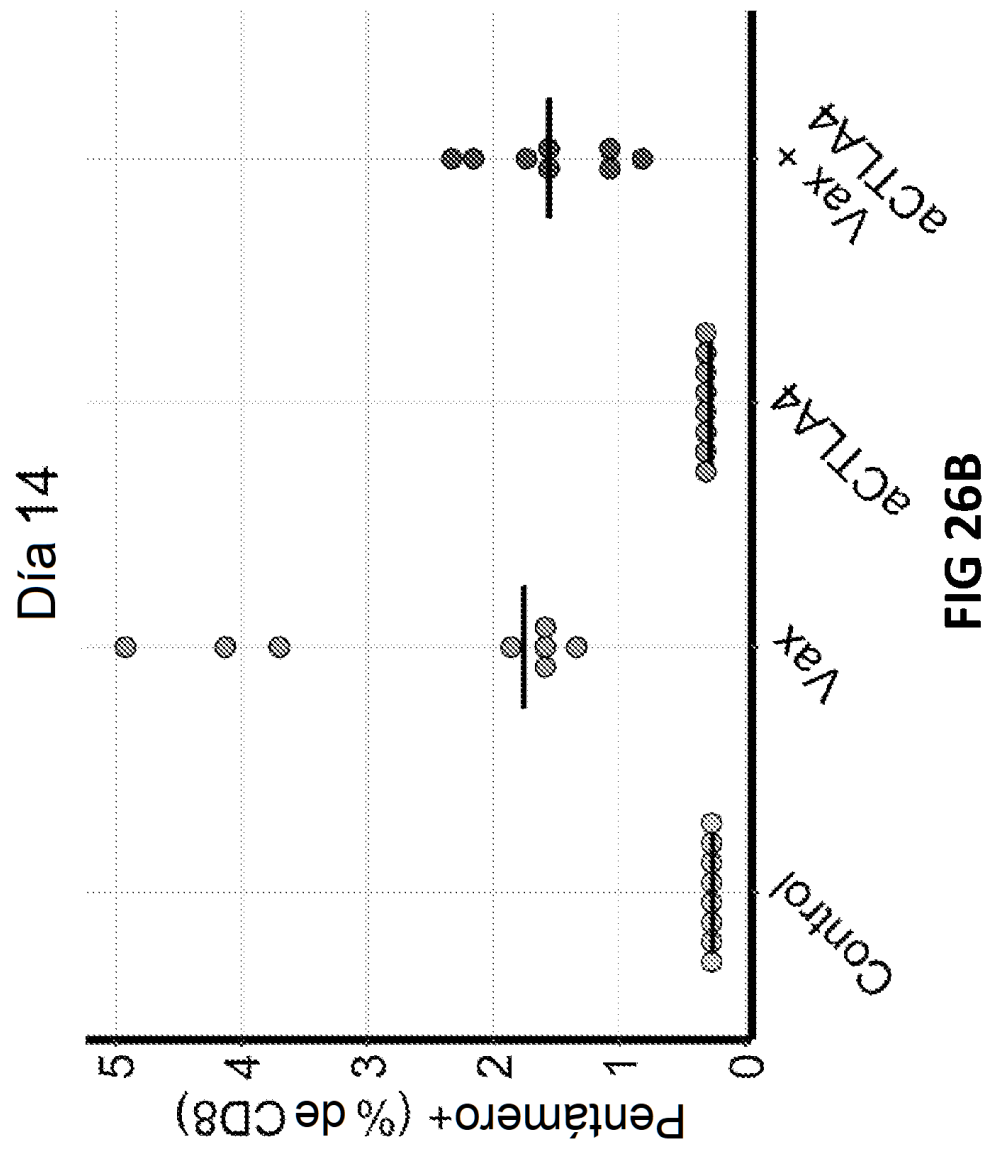
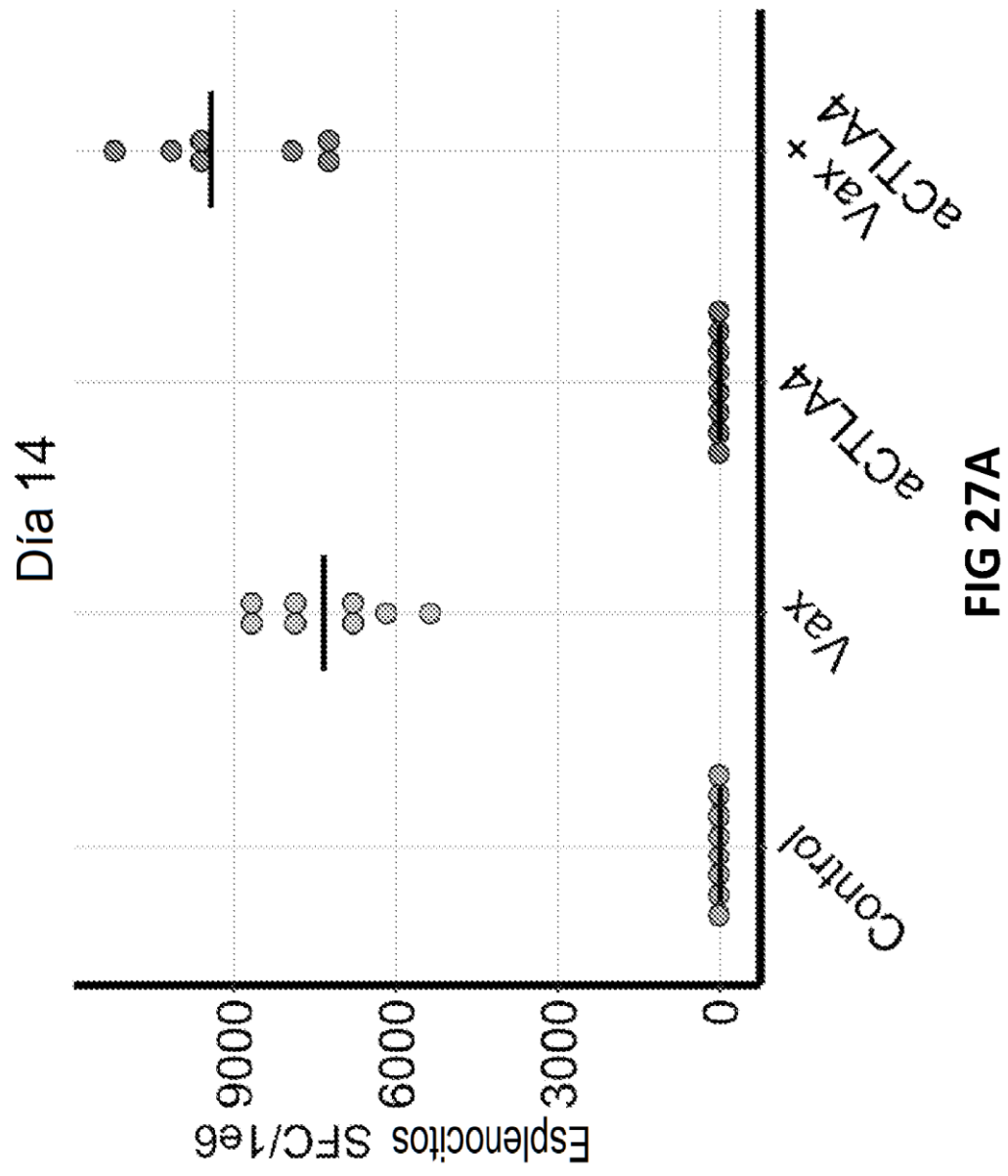


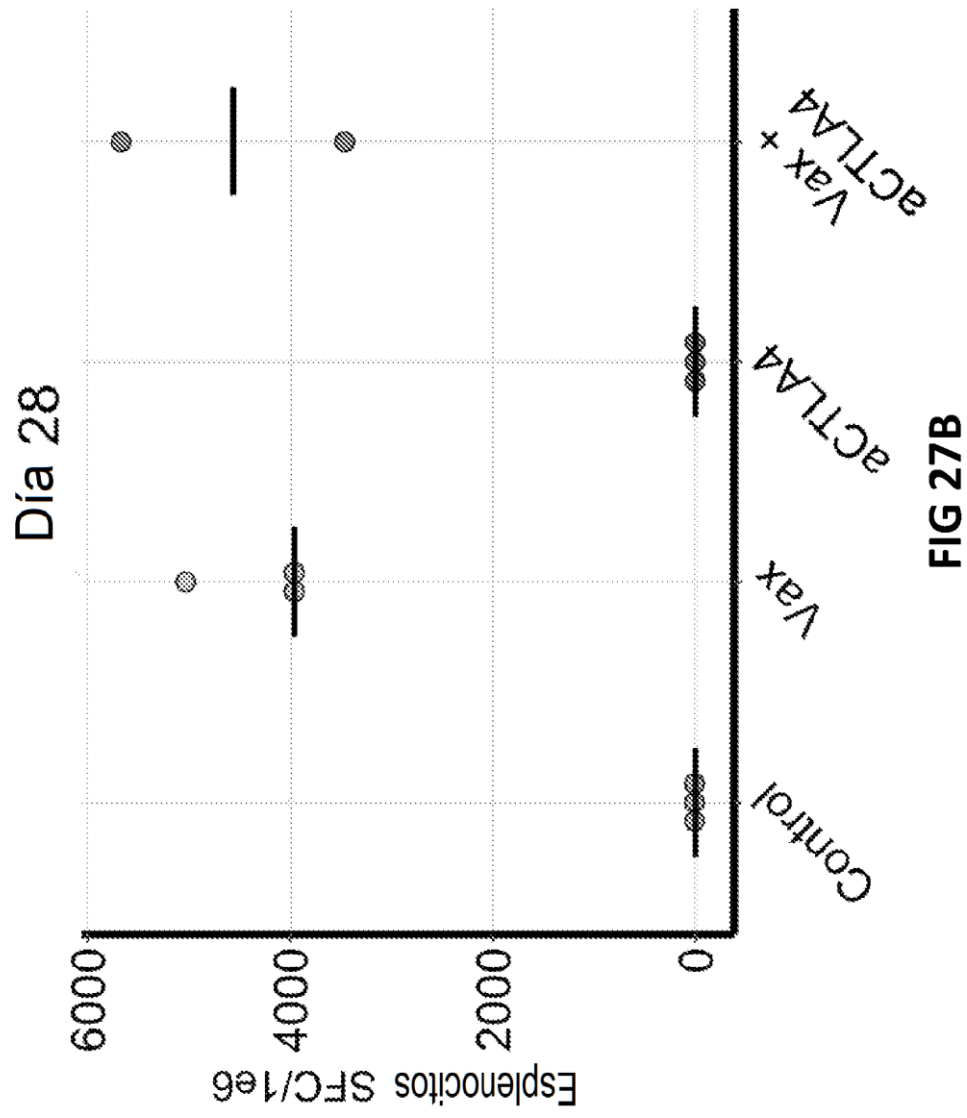
FIG 24

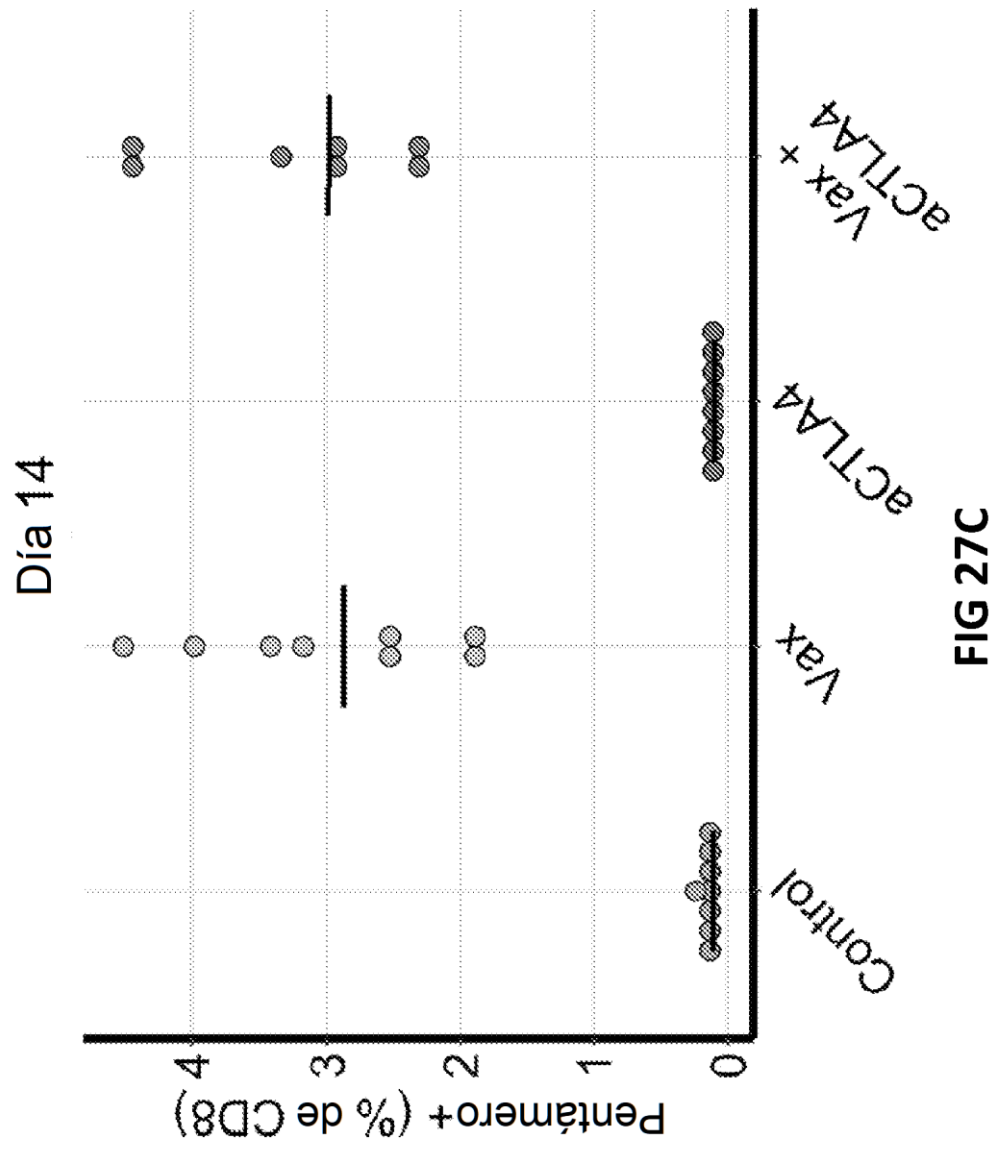
**FIG 25**

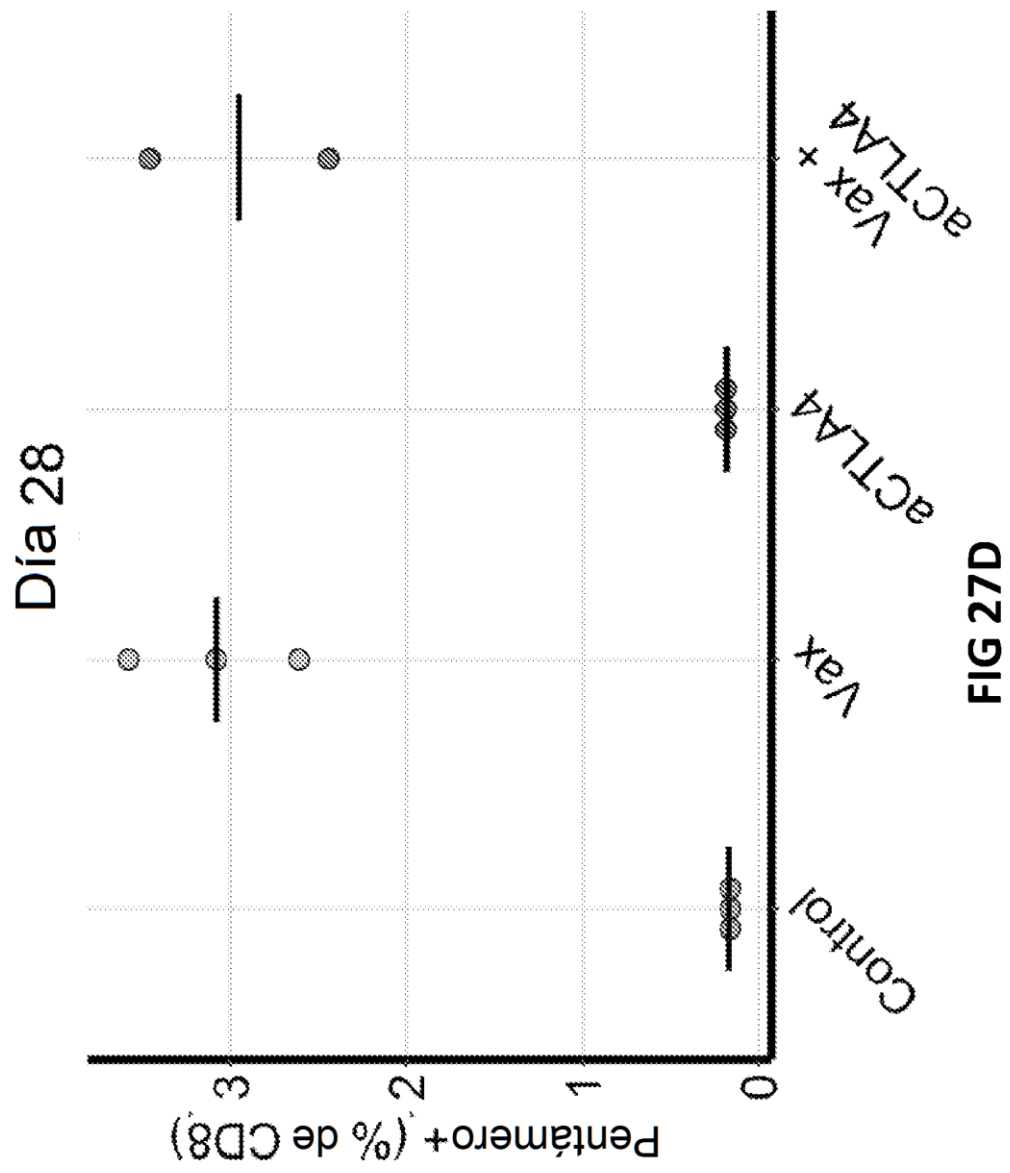


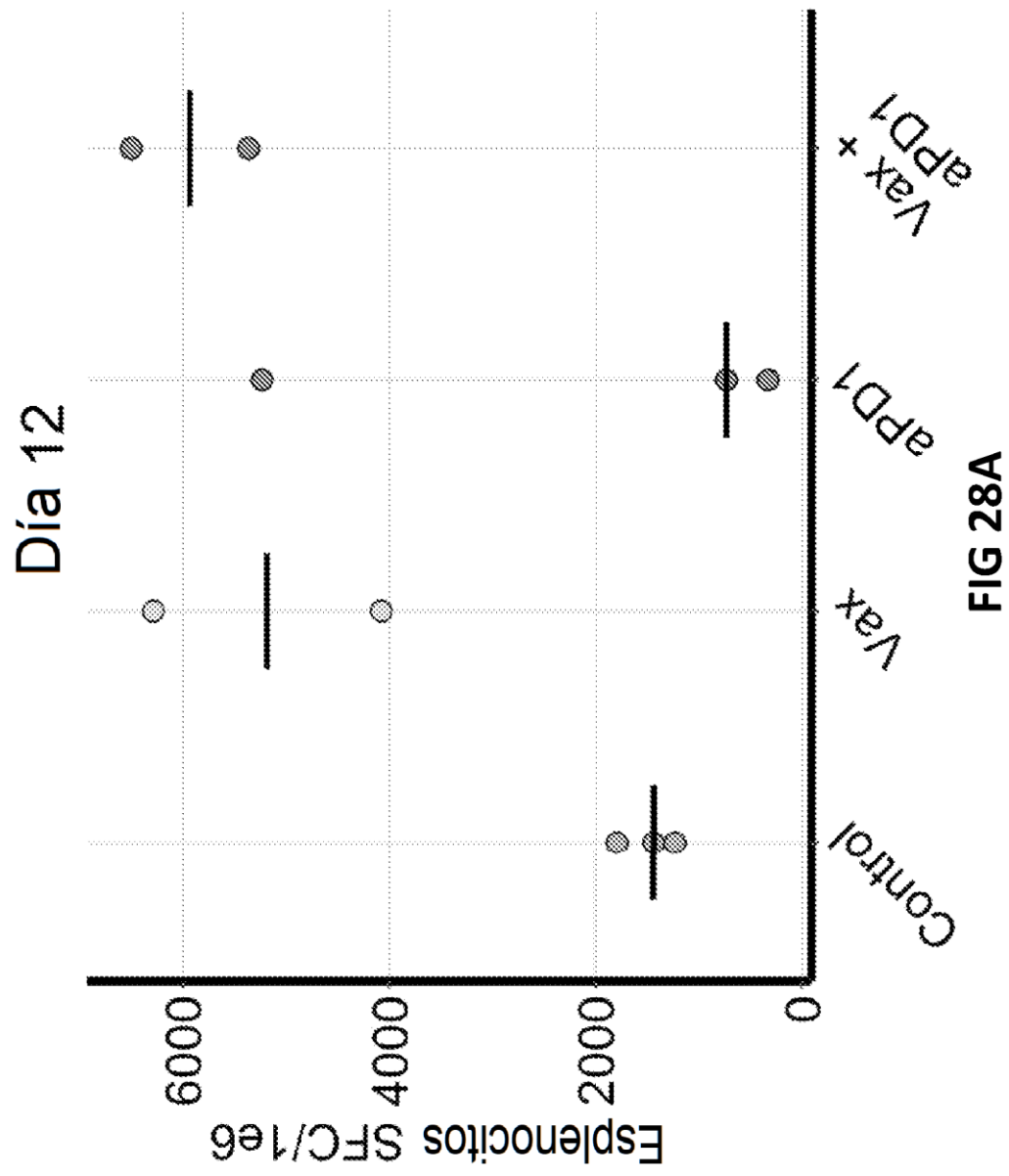


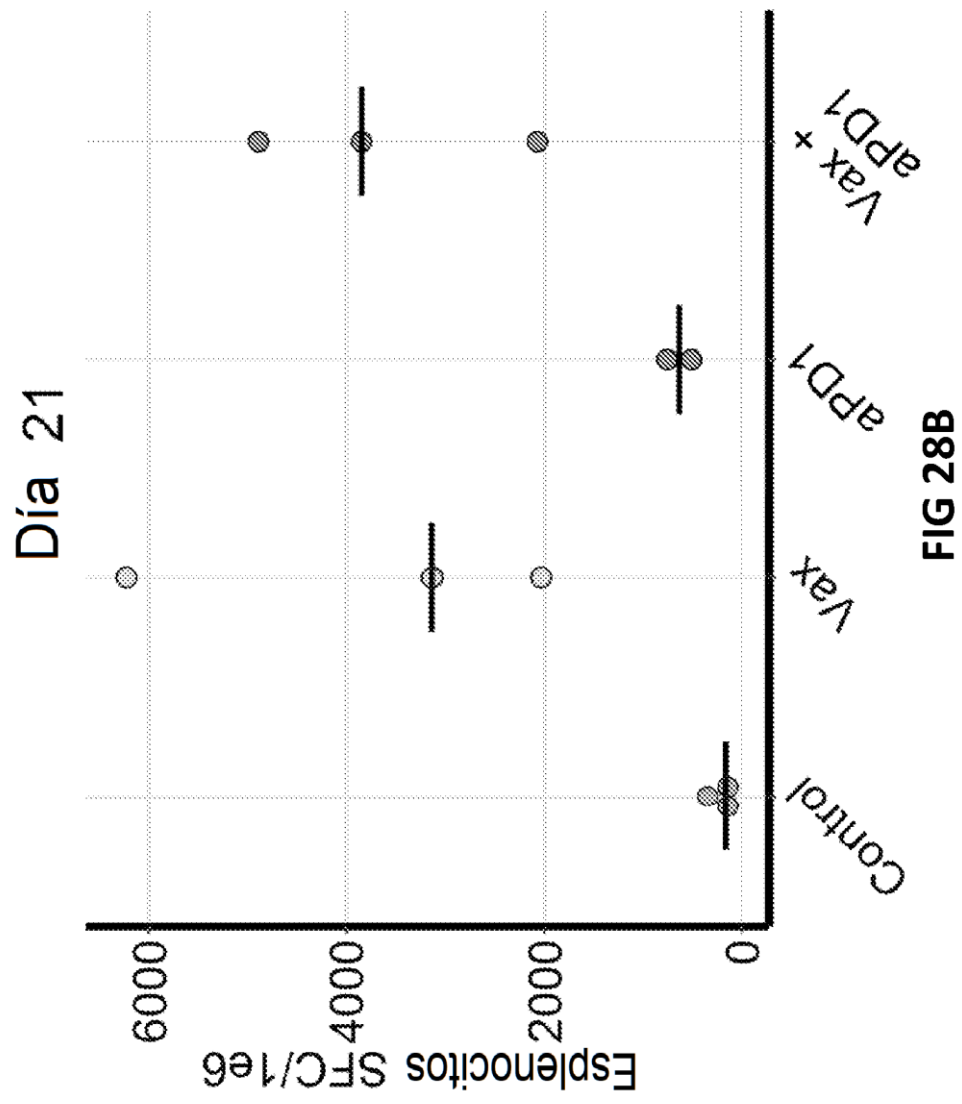


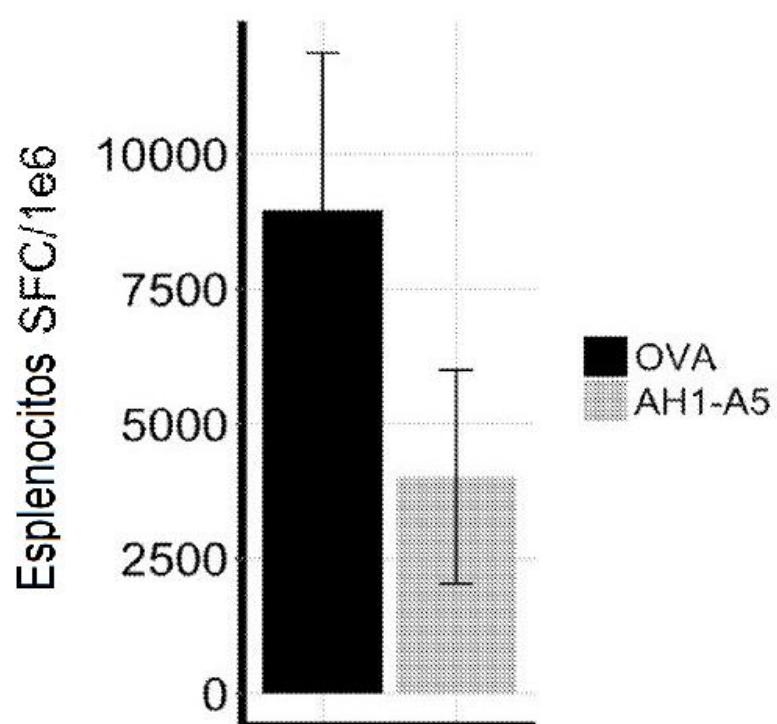


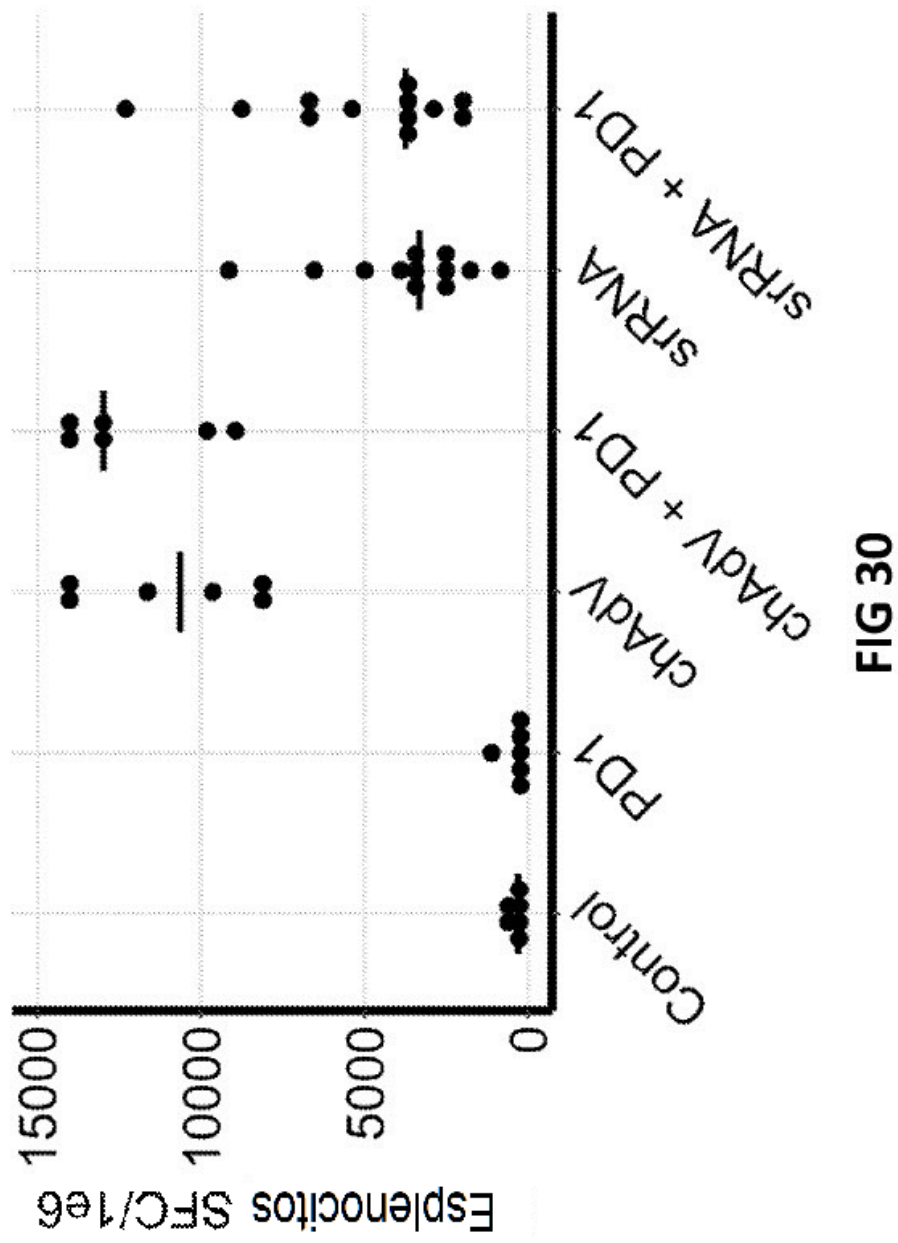


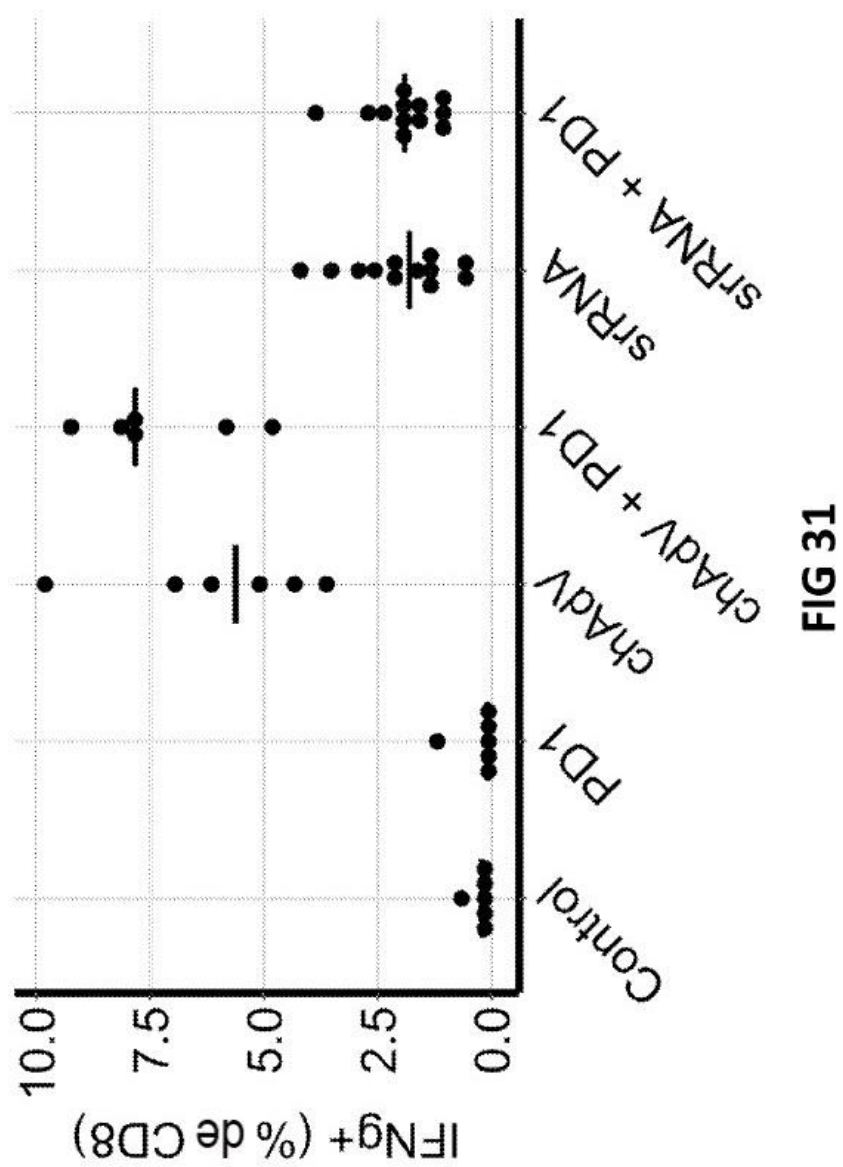






**FIG 29**





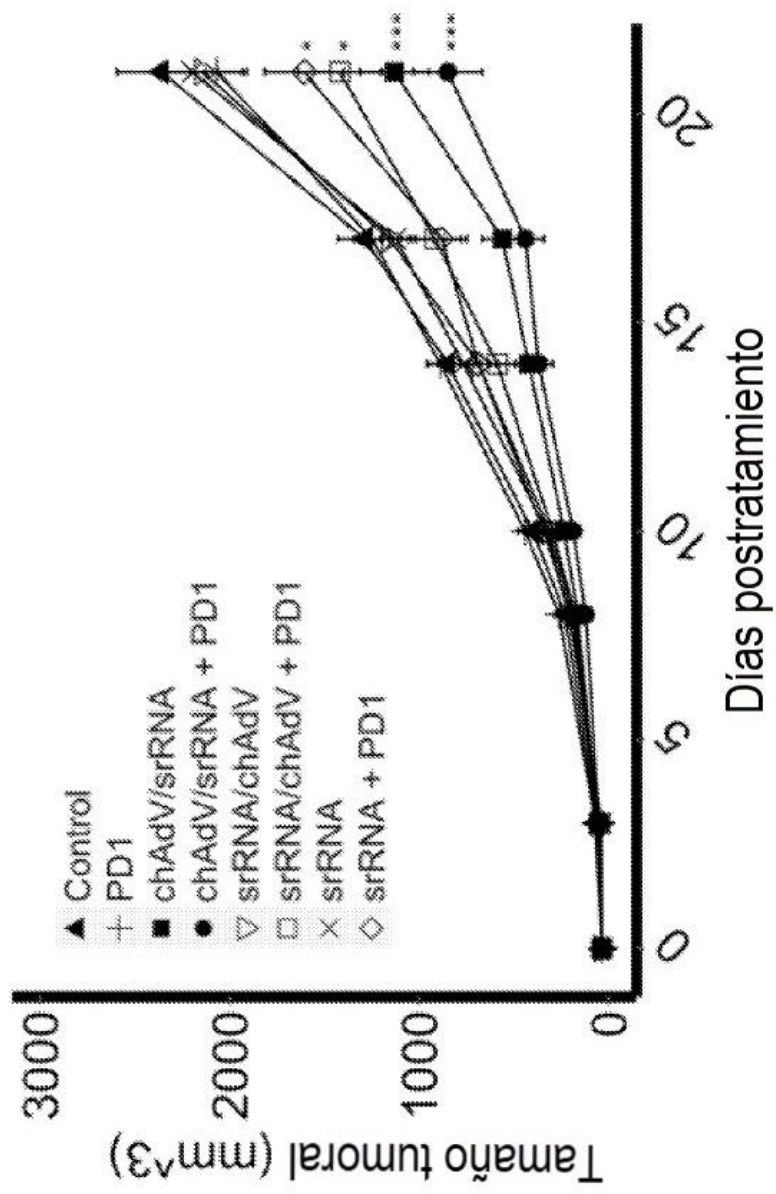


FIG 32

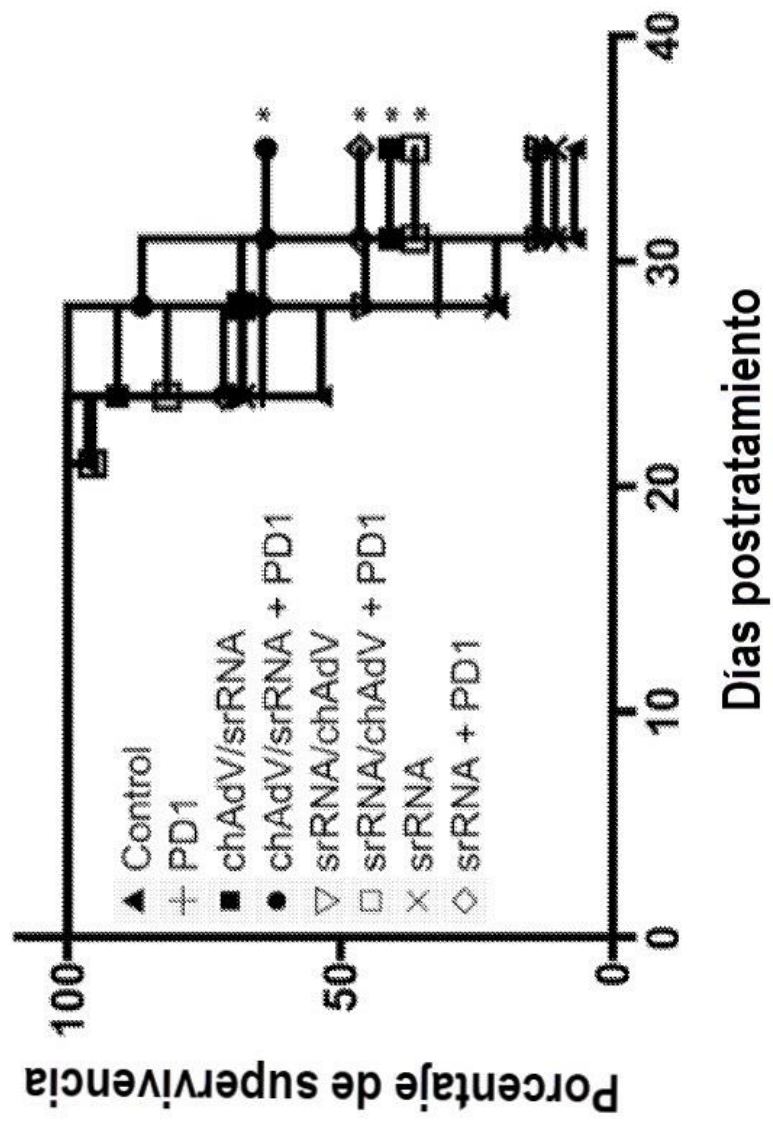


FIG 33

srRNA de VEE-MAG25mer -LNP1(30 µg)

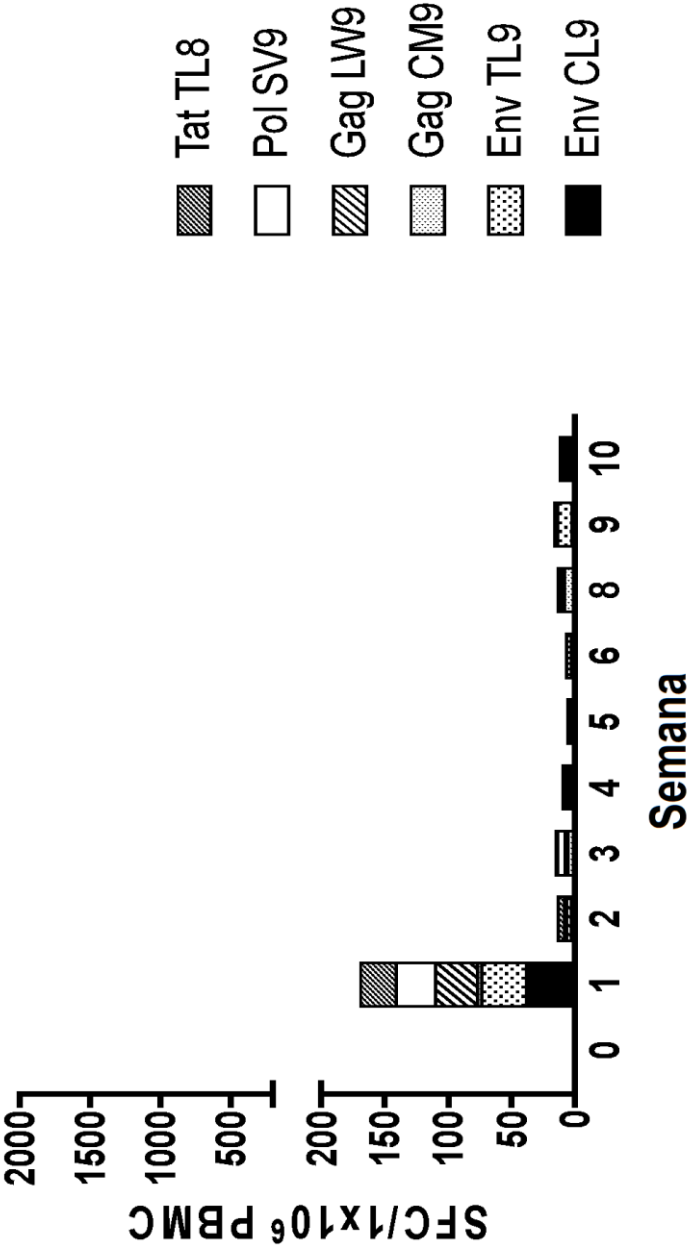


FIG 34A

srRNA de VEE-MAG25mer -LNP1(100 µg)



FIG 34B

srRNA de VEE-MAG25mer-LNP2(100 µg)

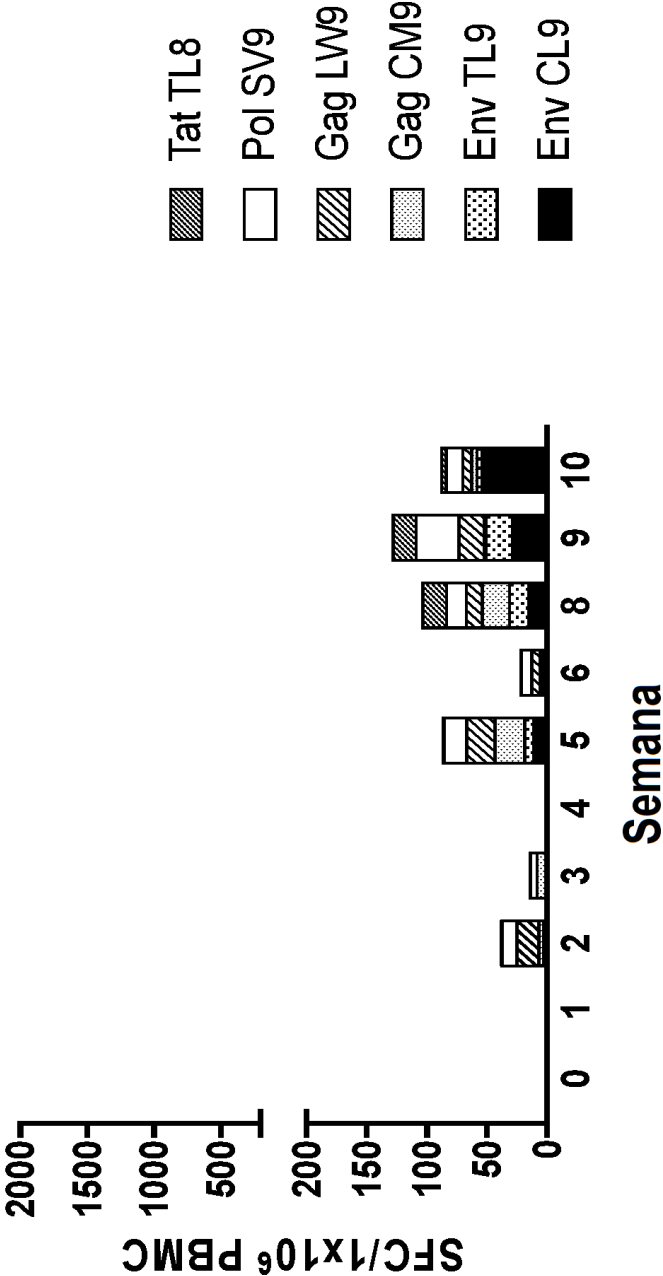


FIG 34C

ChAdV68.5WTnt.MAG25mer

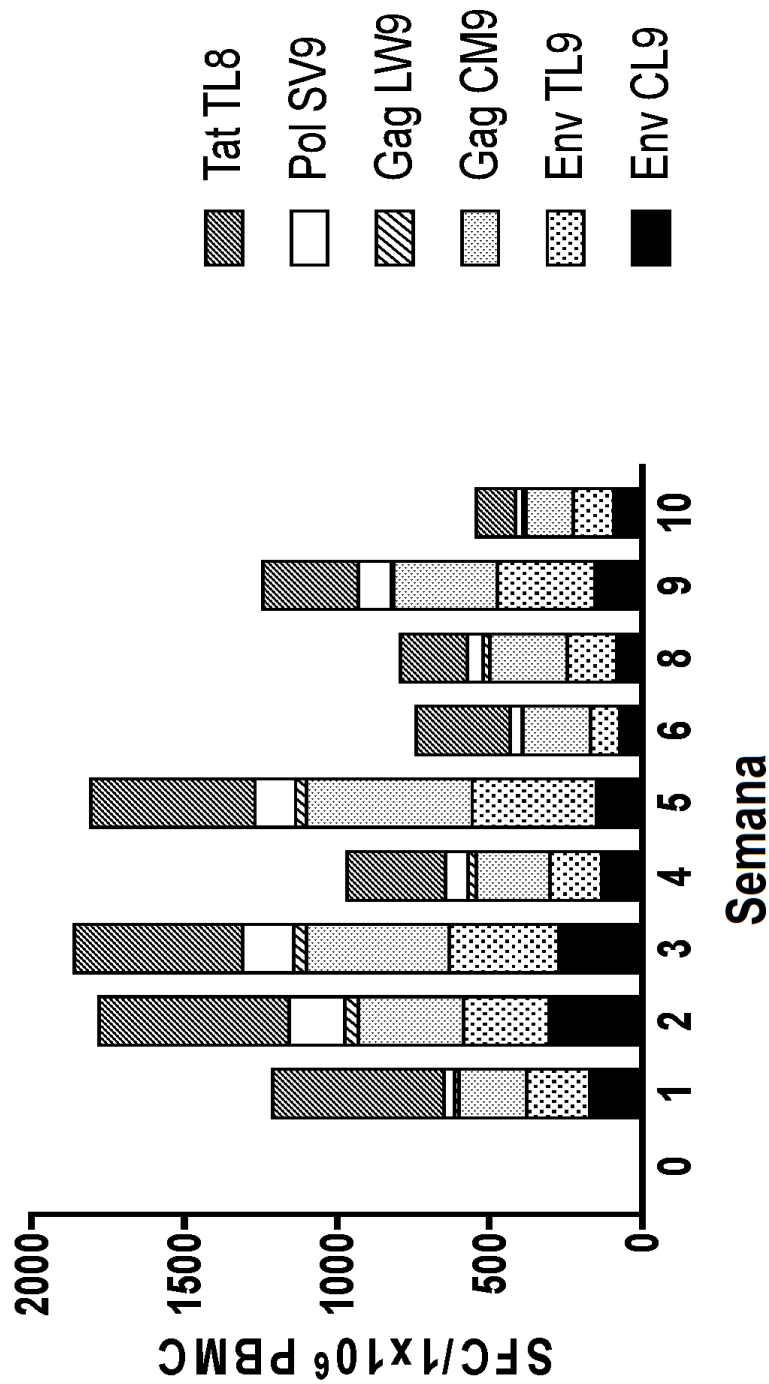


FIG 34D

ChAdV

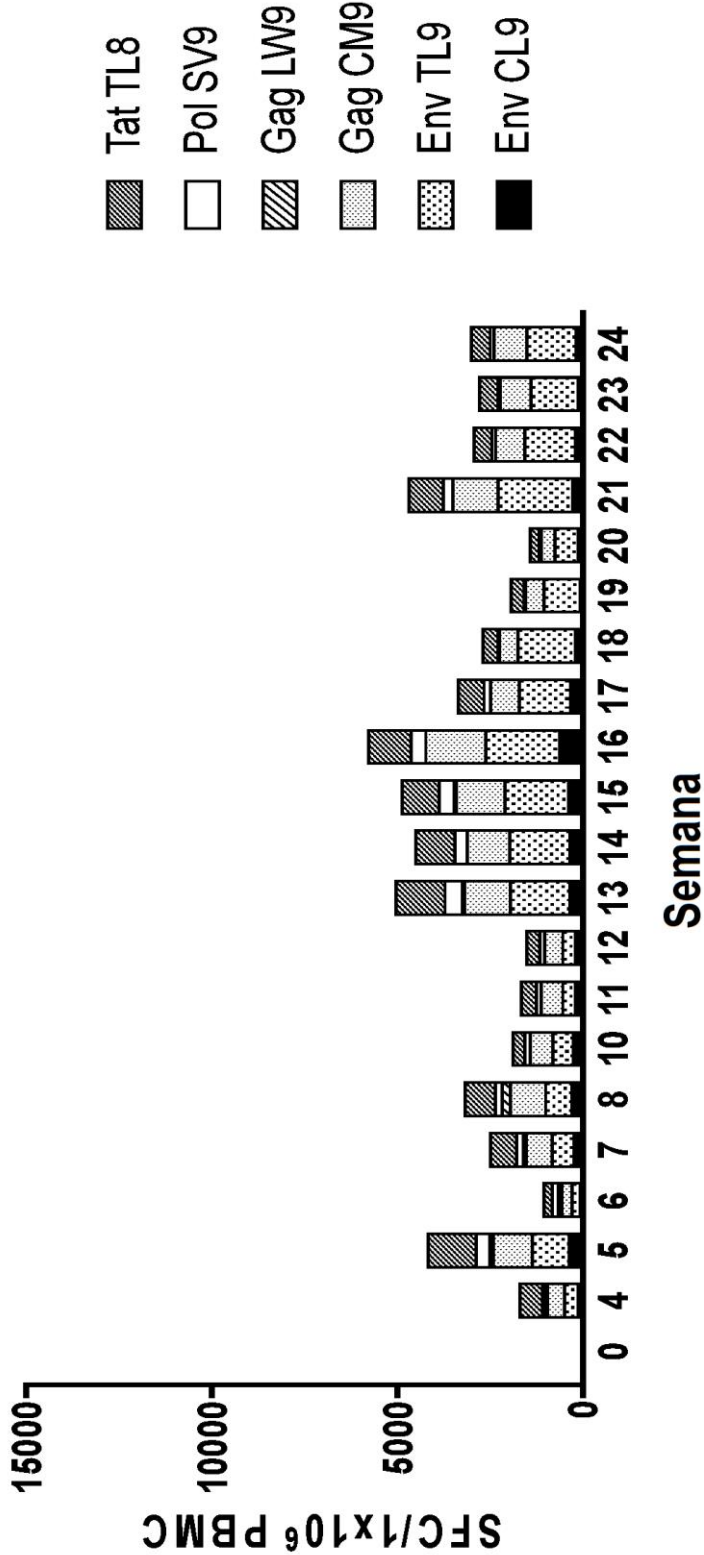


FIG 35

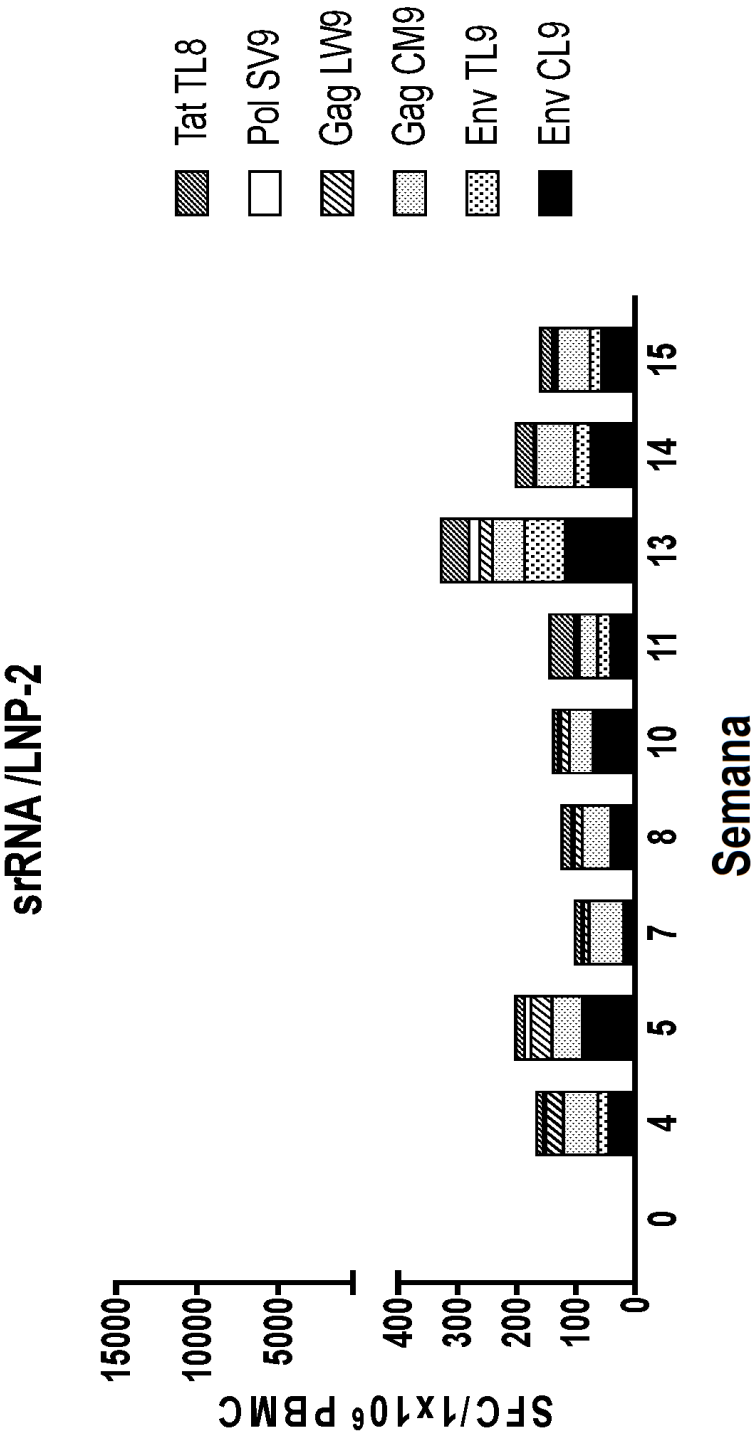


FIG 36

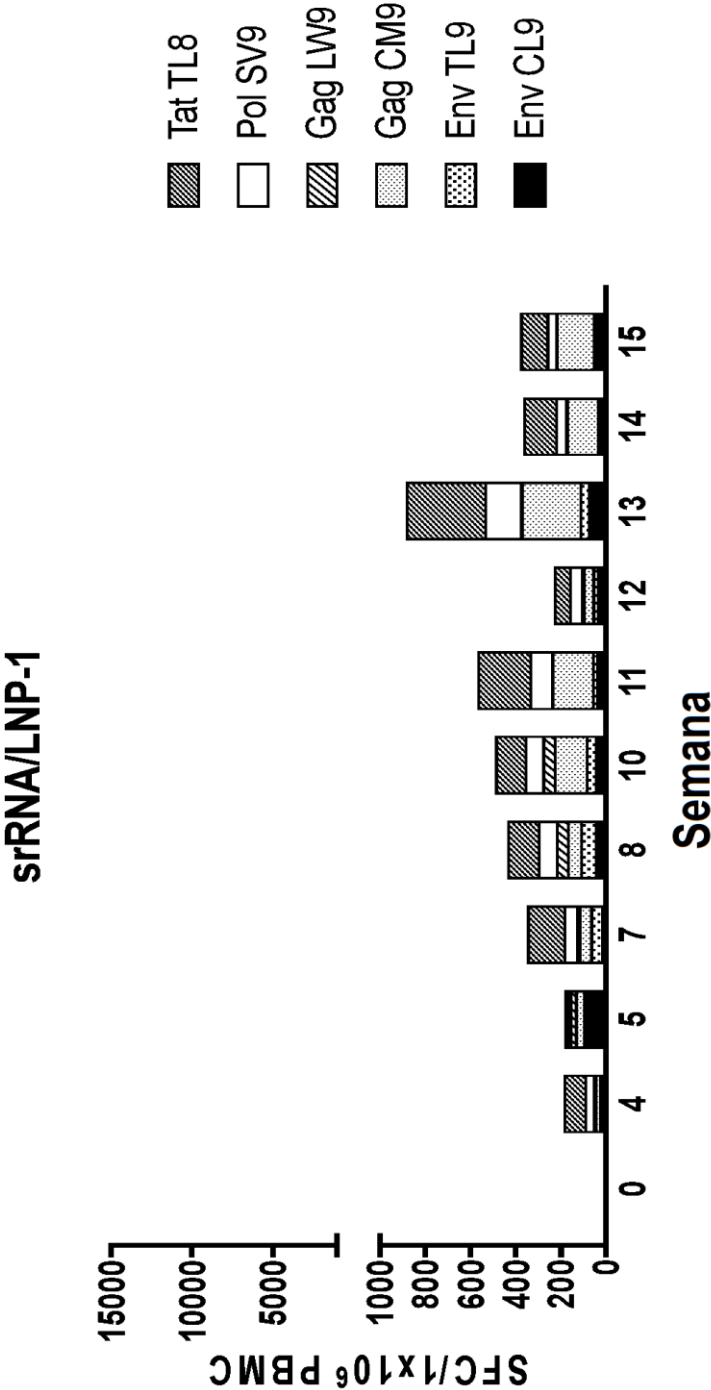


FIG 37

Casete 1

Epítomos de unión



Casete 2

Epítomos de unión



FIG 38