Figure 1
pAkt S473 on B cells

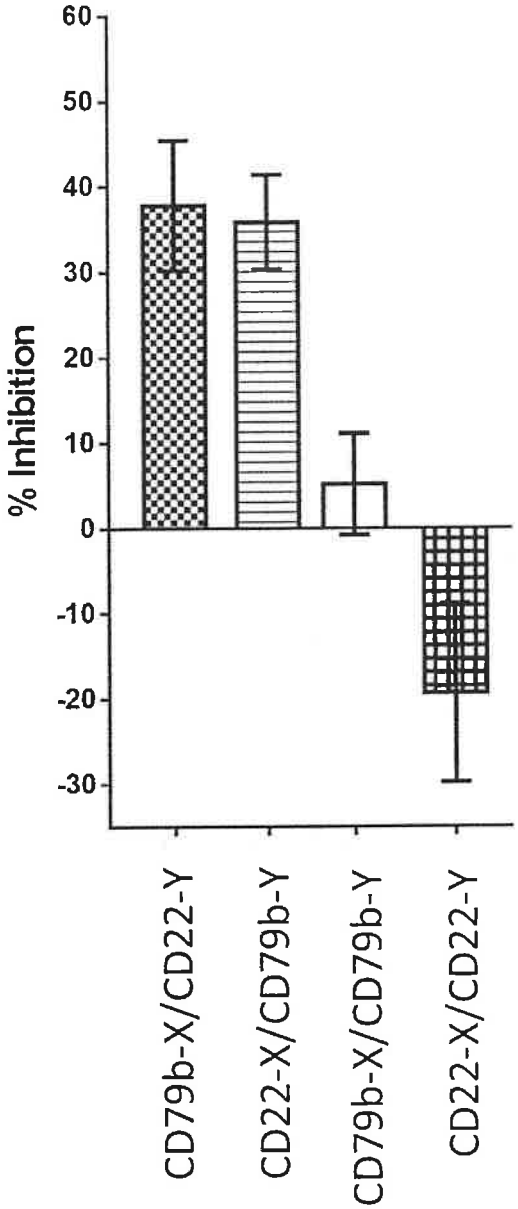


Figure 2
pPLCγ2 Y759 on B cells

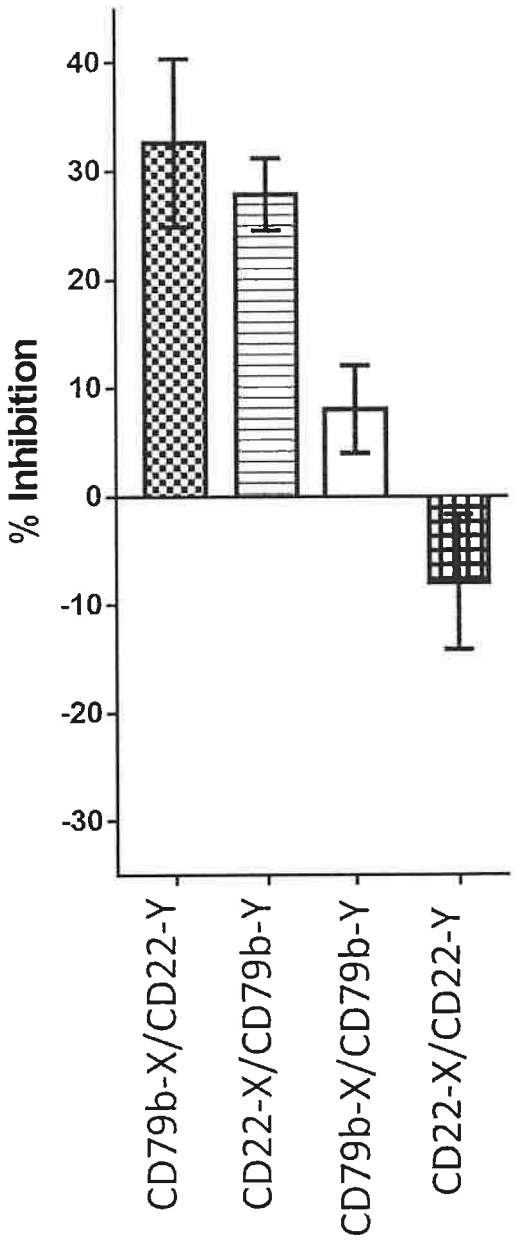


Figure 3

CD86 on B cells

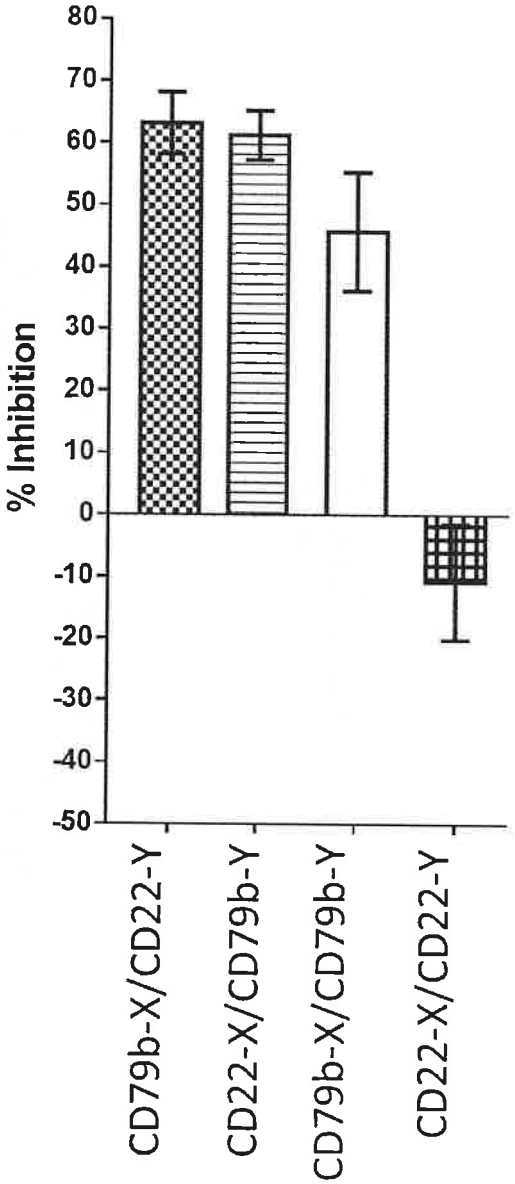


Figure 4

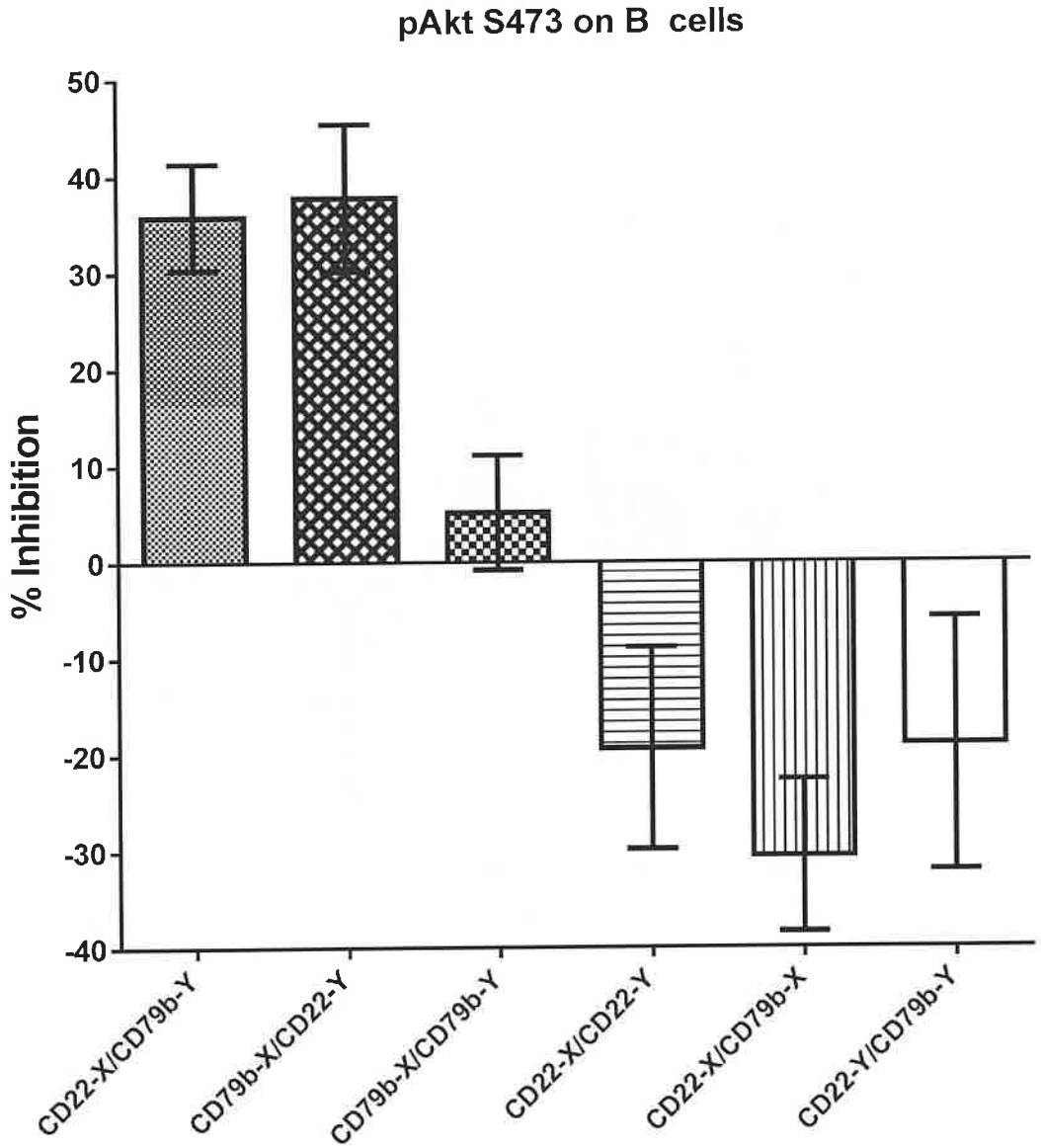

pAkt S473 on B cells
% Inhibition
50
40
30
20
10
0
-10
-20
-30
-40
CD22-X/CD79b-Y
CD79b-X/CD22-Y
CD79b-X/CD79b-Y
CD22-X/CD22-Y
CD22-X/CD79b-X
CD22-Y/CD79b-Y

Figure 5

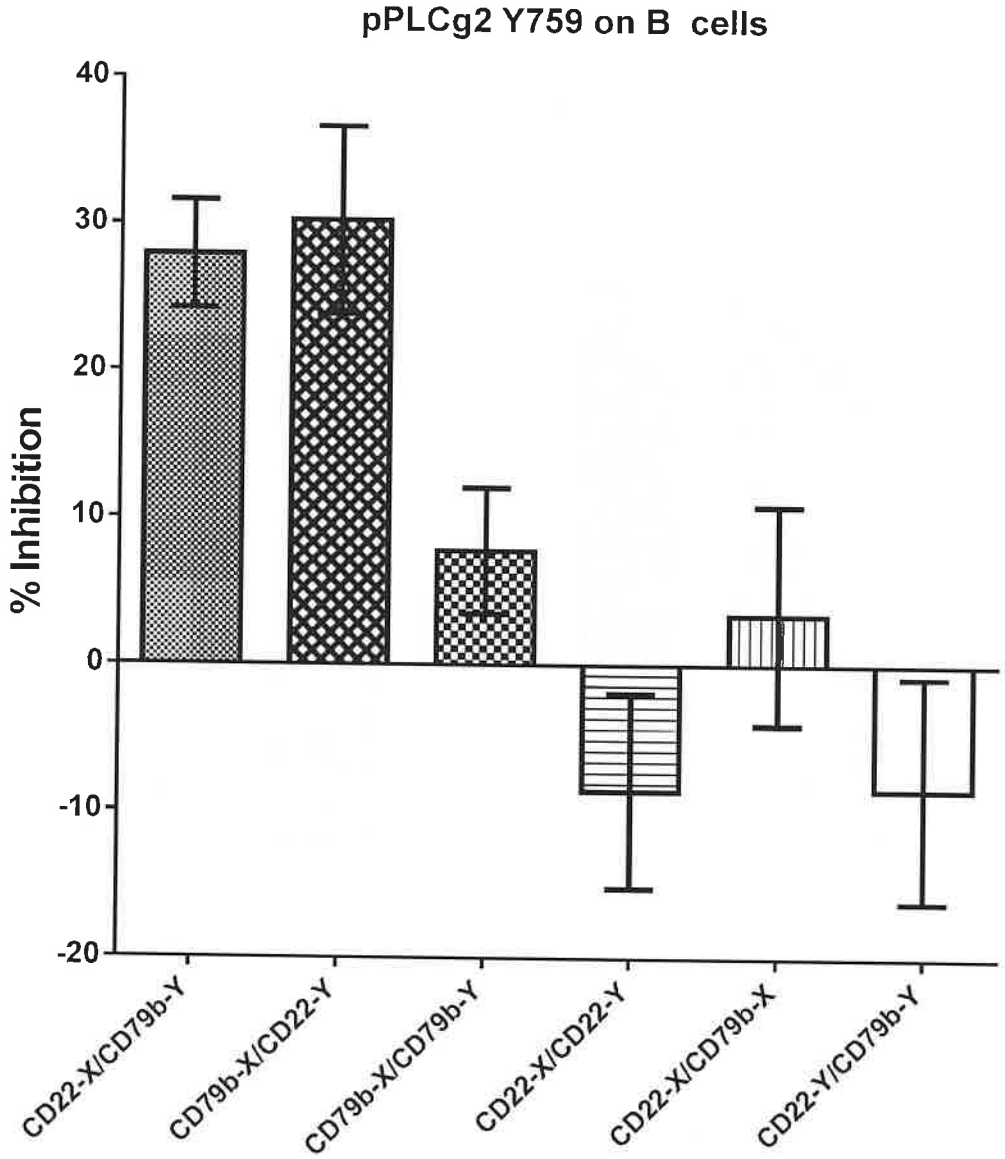

pPLCg2 Y759 on B cells
% Inhibition
40
30
20
10
0
-10
-20
CD22-X/CD79b-Y
CD79b-X/CD22-Y
CD79b-X/CD79b-Y
CD22-X/CD22-Y
CD22-X/CD79b-X
CD22-Y/CD79b-Y

Figure 6

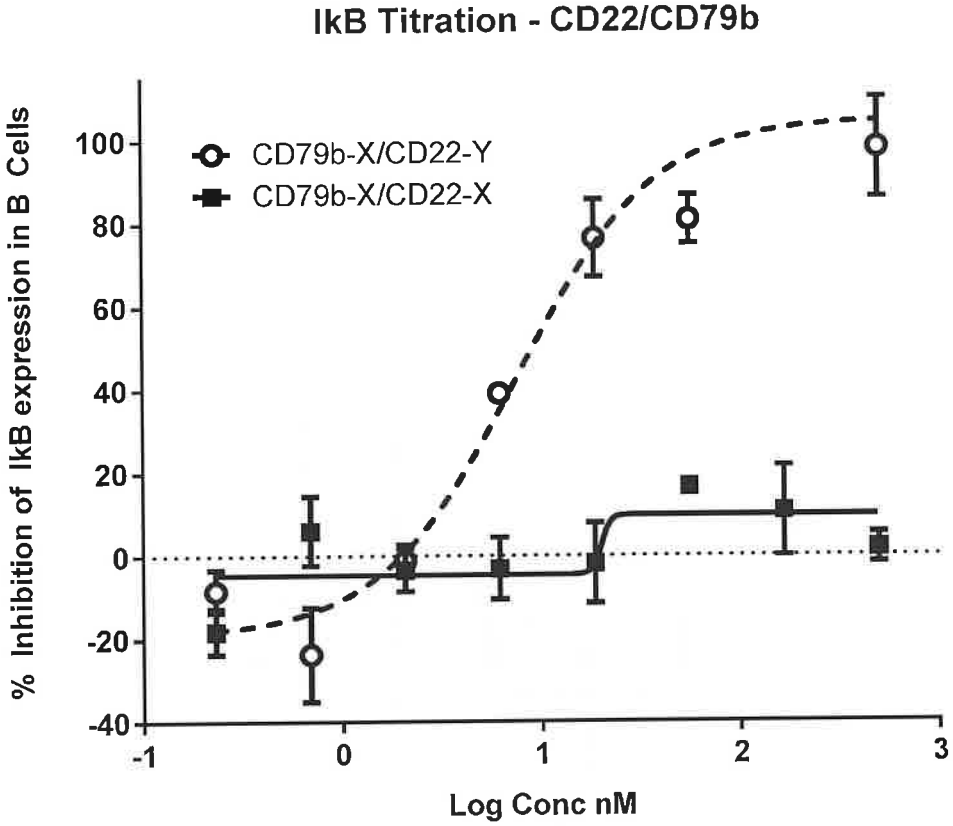

IkB Titration - CD22/CD79b
% Inhibition of IkB expression in B Cells
CD79b-X/CD22-Y
CD79b-X/CD22-X
100
80
60
40
20
0
-20
-40
-1
0
1
2
3
Log Conc nM

Figure 7

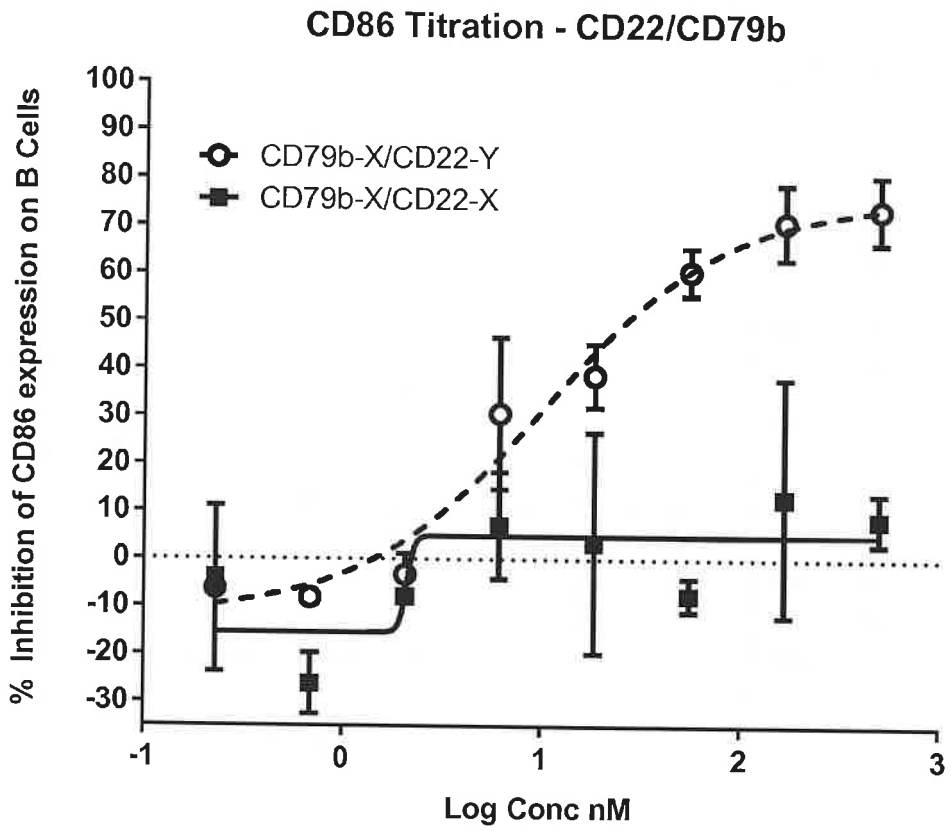

CD86 Titration - CD22/CD79b
% Inhibition of CD86 expression on B Cells
CD79b-X/CD22-Y
CD79b-X/CD22-X
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
-1
0
1
2
3
Log Conc nM

Figure 8

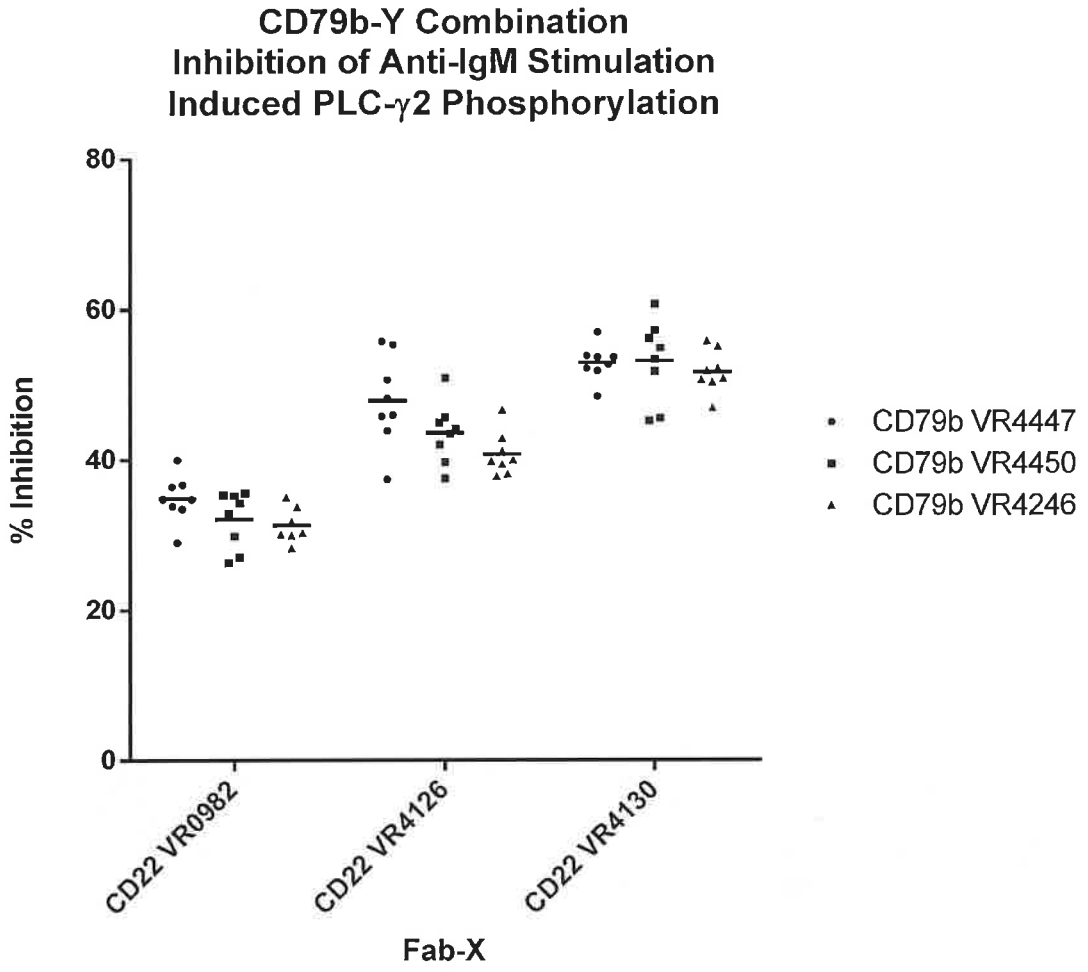

CD79b-Y Combination
Inhibition of Anti-IgM Stimulation
Induced PLC-γ2 Phosphorylation
% Inhibition
80
60
40
20
0
CD22 VR0982
CD22 VR4126
CD22 VR4130
Fab-X
CD79b VR4447
CD79b VR4450
CD79b VR4246

Figure 9

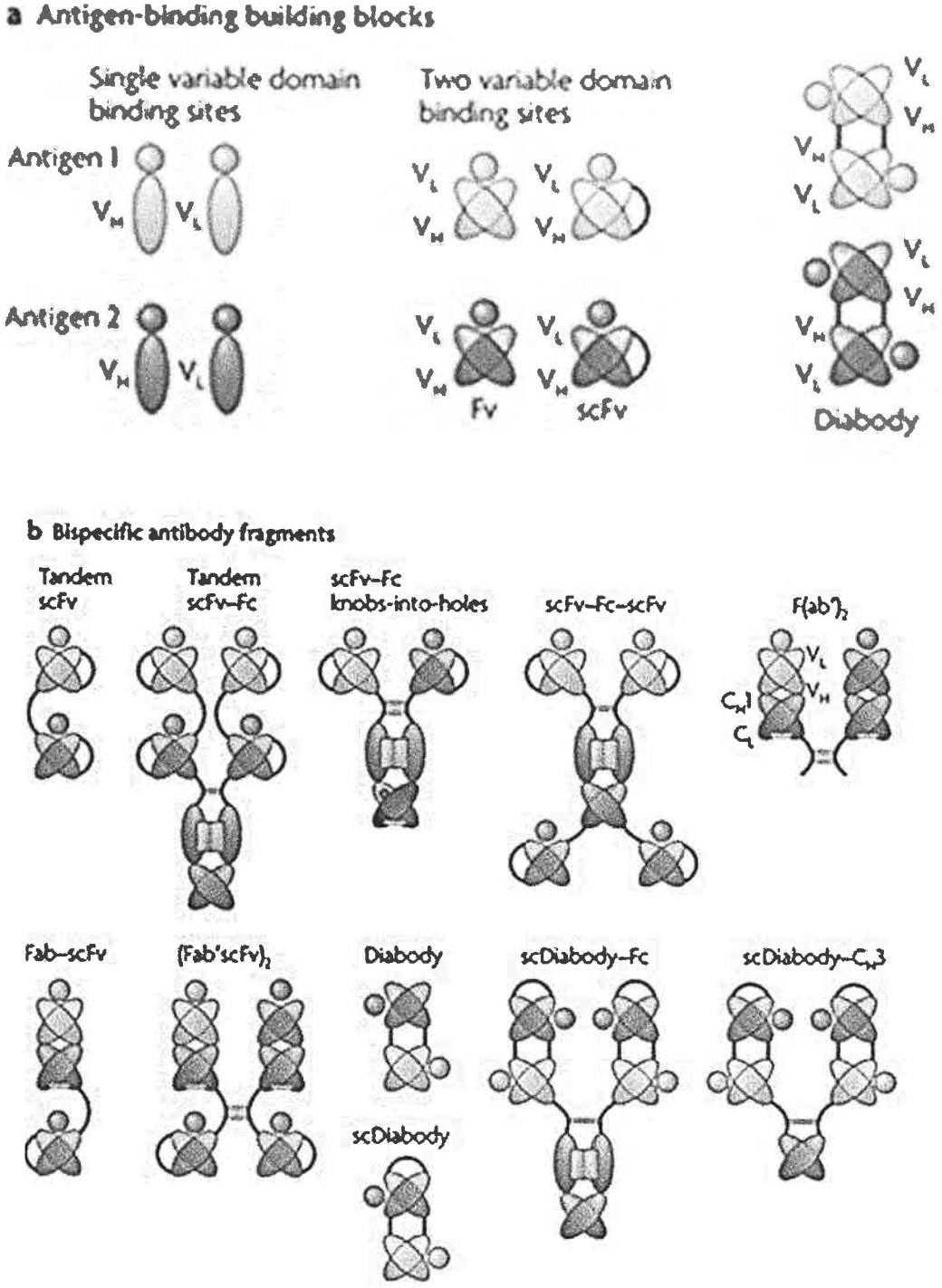
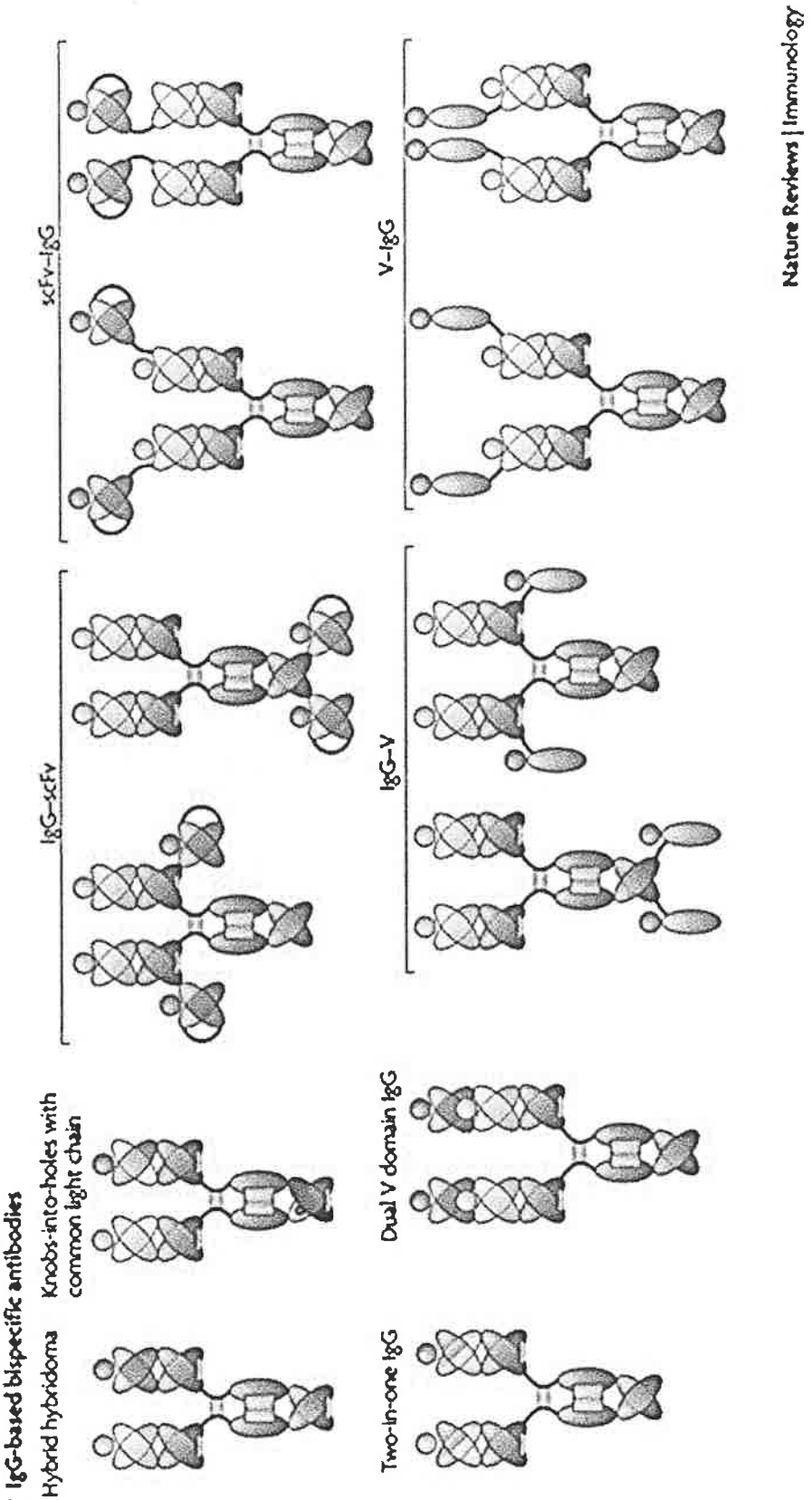

a Antigen-binding building blocks
Single variable domain binding sites
Two variable domain binding sites
Antigen 1
Antigen 2
Fv
scFv
Diabody
b Bispecific antibody fragments
Tandem scFv
Tandem scFv–Fc
scFv–Fc knobs-into-holes
scFv–Fc–scFv
F(ab')2
Fab–scFv
(Fab'scFv)2
Diabody
scDiabody
scDiabody–Fc
scDiabody–CH3

Figure 9 Continued



Figure

Fab-X specificity antigen 1 -15

SP_Y...	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	-4.37	33.57	10.45	13.99	3.81	4.26	8.34	21.07	4.10	13.98	6.07	16.03	7.39	9.00	23.01
2	27.22	25.26	52.32	63.81	30.98	19.94	26.90	29.48	20.58	30.61	9.05	4.18	14.73	36.56	33.04
3	17.62	69.66	3.88	16.35	7.81	-5.45	6.94	12.43	6.90	7.41	15.55	18.23	8.31	7.13	15.98
4	13.81	70.47	-9.21	11.98	2.91	-0.27	7.92	9.85	0.93	4.02	8.95	40.06	10.33	6.02	15.96
5	5.05	36.09	-1.78	-0.25	10.55	-14.55	11.68	6.91	-0.32	-2.82	9.14	12.00	3.48	7.99	9.03
6	---	21.62	7.24	15.78	16.88	2.69	2.50	14.67	9.48	4.44	11.14	20.93	12.37	---	---
7	10.54	35.72	2.40	16.16	14.92	1.39	2.23	14.14	5.64	10.62	8.02	17.58	9.49	10.65	10.80
8	6.03	26.05	-7.89	3.46	7.85	-18.33	0.26	-5.98	-2.08	0.09	7.83	5.13	2.60	9.59	9.47
9	13.56	32.14	-4.74	2.87	9.63	-7.13	5.17	10.72	0.79	1.69	9.22	13.53	2.49	15.70	10.52
10	15.35	54.98	13.21	17.70	-2.07	6.11	21.65	23.25	9.94	10.33	16.30	41.50	13.23	6.52	16.72
11	---	-0.28	-50.76	-5.43	-0.23	-118.10	-4.78	-9.59	0.08	-4.95	6.09	2.91	-9.06	---	---
12	5.85	8.47	19.70	42.01	20.13	12.42	15.14	26.89	20.69	24.69	18.86	36.32	18.07	20.28	38.97
13	---	31.56	22.19	28.34	15.50	13.12	14.23	27.59	22.46	14.25	16.00	26.84	16.21	---	---
14	9.13	40.70	10.80	14.56	5.88	8.89	7.52	22.68	6.27	9.04	7.34	33.39	11.20	7.01	14.84
15	9.38	33.18	7.13	11.20	15.92	11.35	9.90	19.61	9.90	10.62	13.98	28.99	15.26	13.77	25.64
16	---	26.46	-7.59	19.38	15.65	-24.93	12.05	14.00	15.27	11.98	13.29	20.57	11.99	---	---
17	---	22.79	-4.70	19.07	17.98	-37.56	10.99	11.71	15.83	8.61	10.98	21.28	9.71	---	---
18	---	28.91	29.09	33.25	23.16	10.61	13.85	26.28	21.37	18.39	18.45	32.78	18.27	---	---
19	---	33.63	-15.93	2.00	15.54	-24.55	11.73	10.55	7.32	4.45	15.19	20.98	10.61	---	---
20	---	24.94	-13.88	20.88	10.53	-21.56	8.43	6.69	8.81	7.57	10.73	17.52	13.55	---	---
21	---	23.94	6.69	22.70	22.45	-3.18	13.33	21.28	15.88	10.81	15.92	25.96	17.22	---	---
22	13.93	20.55	-18.75	-4.96	6.90	-17.32	4.12	-3.15	-4.19	-6.48	11.71	2.48	-0.84	9.14	11.68
23	---	24.25	-9.45	22.83	24.63	-26.70	9.65	13.79	10.74	7.96	13.02	24.43	18.33	---	---

Fab-Y specificity antigen 1 -23

% Inhibition Syk

Figure 11

Fab-X specificity antigen 1 -15

SP_Y...	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	0.81	22.29	11.45	10.78	5.39	1.60	7.43	5.90	2.24	3.29	-2.71	10.80	0.99	6.90	-4.08
2	19.70	18.61	44.00	50.83	23.17	19.01	24.57	21.47	25.89	39.80	12.35	0.52	18.91	28.55	25.89
3	17.93	61.18	3.00	15.38	5.38	-0.12	4.05	3.77	6.84	12.78	11.01	16.71	2.97	9.17	4.69
4	13.34	55.83	-3.82	7.24	1.41	-1.39	6.75	0.89	3.12	3.12	4.16	40.49	1.71	5.13	1.10
5	0.34	25.16	0.51	-0.63	7.36	-1.41	11.49	4.08	5.59	2.99	5.76	11.67	2.84	5.90	-2.06
6	---	20.71	-0.85	6.04	0.40	3.49	-2.60	-0.87	3.41	0.22	1.34	12.34	3.36	---	---
7	10.95	27.95	1.38	15.66	11.27	2.40	2.48	4.45	6.13	16.07	3.18	12.77	3.92	5.85	0.37
8	7.73	24.86	4.02	5.23	3.56	0.49	2.68	-1.16	2.39	1.45	4.10	8.50	-0.64	3.01	0.97
9	7.37	28.27	-0.02	3.22	6.39	1.35	4.75	4.06	4.92	4.09	3.10	10.50	0.62	5.62	1.50
10	17.08	47.69	7.72	5.65	-5.55	1.40	21.89	6.66	5.90	5.11	7.61	35.77	1.50	4.32	-0.06
11	---	11.76	-10.93	1.38	-0.56	-24.94	-1.36	0.83	3.58	3.88	5.92	11.18	-4.57	---	---
12	6.05	-3.88	9.02	29.48	4.92	1.15	1.89	5.75	7.23	20.95	5.44	17.92	3.37	16.34	8.67
13	---	23.78	-0.99	7.30	0.43	-1.40	1.83	6.41	8.91	3.25	2.76	11.64	5.41	---	---
14	4.40	28.11	1.77	5.61	4.01	1.73	5.95	2.45	4.05	6.85	-0.60	20.60	5.45	4.11	0.05
15	4.96	25.60	0.87	3.43	5.41	1.77	1.89	1.80	3.72	1.96	2.29	14.57	5.26	2.36	0.11
16	---	22.39	-5.77	4.50	2.41	-6.86	4.89	2.52	5.19	3.07	3.38	9.47	1.17	---	---
17	---	19.53	-6.98	6.73	2.99	-10.27	2.35	2.13	6.02	2.08	3.10	10.86	2.03	---	---
18	---	19.90	2.43	12.38	2.08	-1.05	1.09	4.25	6.70	4.90	4.40	12.49	4.34	---	---
19	---	35.50	-12.22	-2.38	-1.61	-9.05	5.97	1.78	5.27	4.63	5.92	15.60	3.16	---	---
20	---	21.53	-9.67	2.95	-0.16	-6.71	-3.46	-4.81	4.13	2.31	6.52	10.96	4.25	---	---
21	---	19.03	-6.66	2.36	1.10	-6.49	-0.95	5.09	4.96	3.55	3.97	10.89	3.63	---	---
22	14.73	26.47	-5.00	0.58	3.97	-0.08	3.70	-1.25	1.72	0.99	11.40	7.99	2.80	8.39	4.58
23	---	19.72	-16.22	0.75	-1.16	-11.03	-3.57	3.30	3.57	1.23	4.90	8.22	4.20	---	---

Fab-Y specificity antigen 1 -23

% Inhibition PLCg2

Figure 12

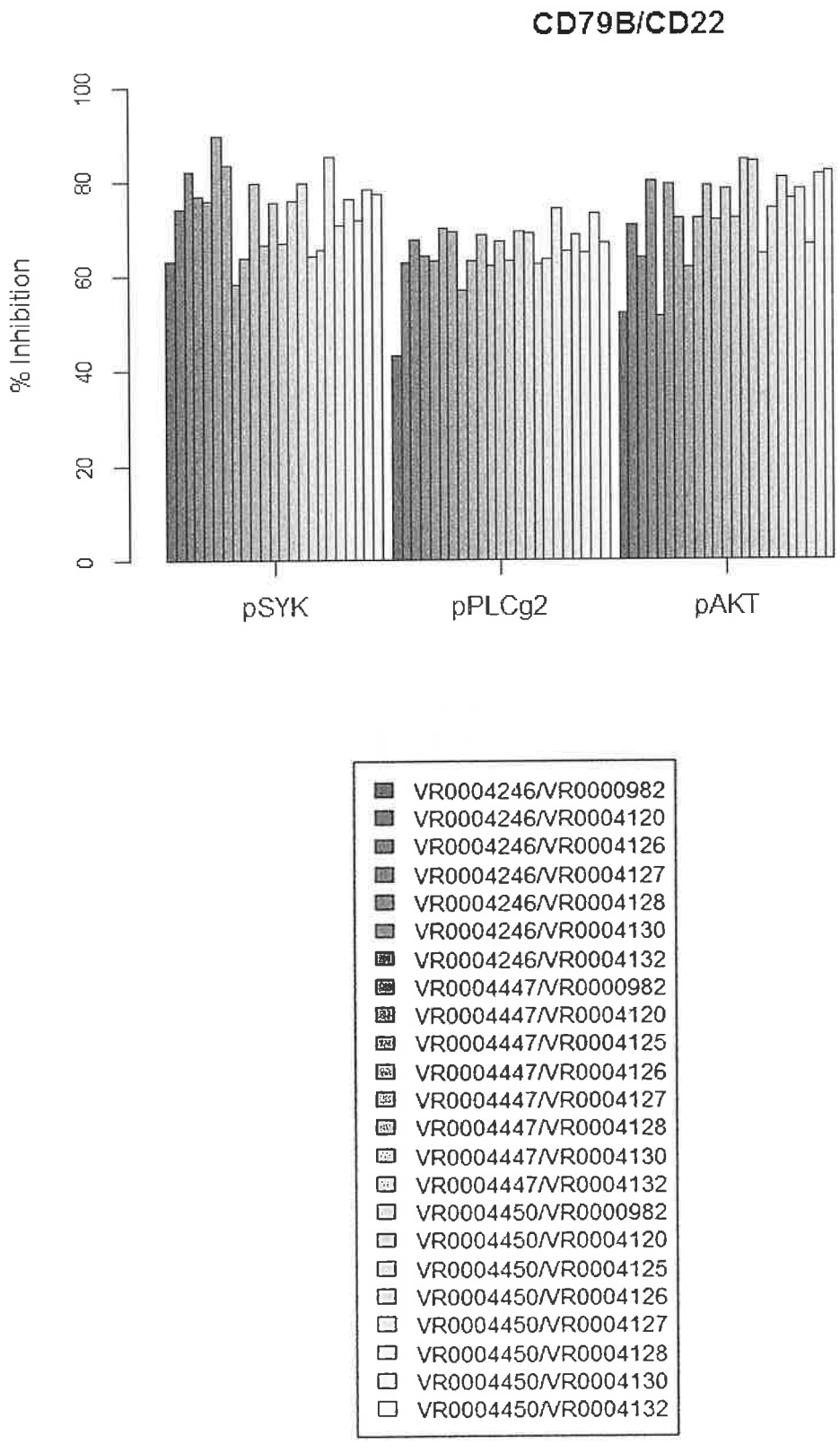
Fab-X specificity antigen 1 -15

SP_Y...	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1	-11.06	53.06	-1.56	6.02	-8.08	-12.41	3.84	-12.93	-8.22	-8.88	-11.49	-3.34	-17.29	-4.43	-6.28
2	40.41	37.15	48.29	48.35	39.50	30.66	40.36	25.61	42.23	42.64	32.59	37.11	26.58	35.70	38.11
3	13.19	70.81	2.37	15.53	8.68	7.93	12.32	3.78	10.56	14.18	8.76	-1.58	6.61	10.75	10.83
4	8.35	55.50	-6.07	17.80	7.97	7.14	8.49	6.54	6.98	9.67	12.96	41.04	5.99	9.28	7.89
5	-3.80	40.21	-0.85	13.54	2.05	-2.13	3.01	-6.86	0.91	2.02	0.76	4.48	-3.42	4.06	0.15
6	---	40.39	6.67	19.26	-4.86	12.95	3.52	2.59	6.73	5.65	5.28	4.77	-1.03	---	---
7	0.53	45.36	4.87	18.76	4.08	0.72	-1.43	5.07	4.69	11.49	6.48	5.72	4.78	0.73	-3.71
8	6.61	37.54	5.72	16.25	-1.45	2.38	0.64	0.17	1.10	2.08	6.50	7.58	2.18	-4.37	-4.53
9	0.51	42.34	0.95	9.41	-0.30	1.07	2.86	-2.56	0.51	-0.55	2.07	2.49	-2.84	4.54	0.16
10	11.13	52.32	3.75	12.67	-4.41	3.82	15.78	-3.15	5.70	4.26	1.77	22.73	-4.68	7.65	8.05
11	---	33.40	-3.95	18.04	7.48	6.00	3.13	4.24	5.66	13.11	9.85	11.24	2.04	---	---
12	0.69	29.50	-7.93	38.94	2.68	4.95	-0.13	-2.53	2.52	15.03	-0.82	3.63	-5.61	25.99	12.57
13	---	35.33	-4.80	10.35	-4.98	-7.45	-7.91	-6.47	3.78	-0.83	-4.68	-3.84	-9.54	---	---
14	1.62	44.02	0.91	16.05	1.80	-2.56	1.09	-4.49	3.94	5.30	-0.19	8.15	-5.85	5.21	0.66
15	2.25	36.02	-2.44	10.00	-0.22	0.37	-2.20	-2.11	2.41	1.84	3.23	2.78	2.51	-2.19	-4.62
16	---	33.56	-3.12	15.33	0.19	-5.46	-0.71	-5.67	1.83	1.35	-0.24	-1.99	-8.53	---	---
17	---	35.02	-4.92	16.87	1.78	-2.20	0.34	-2.12	3.07	1.17	0.98	0.80	-2.14	---	---
18	---	31.31	-1.77	19.71	-6.19	-4.39	-3.72	-3.91	2.70	3.44	-0.42	-1.65	-5.72	---	---
19	---	50.00	-2.93	9.92	2.01	9.54	10.19	2.60	11.44	9.84	7.96	9.17	3.37	---	---
20	---	38.56	-1.83	18.96	1.40	5.57	0.37	1.23	4.23	6.85	10.48	6.54	2.60	---	---
21	---	36.74	1.67	11.59	-5.60	6.23	0.59	6.00	6.99	5.11	3.12	3.73	3.44	---	---
22	-2.71	40.50	-2.45	12.91	-1.39	6.77	1.56	4.97	1.68	2.93	18.10	8.41	8.06	-2.35	-4.93
23	---	33.54	-1.68	5.45	-2.46	7.13	0.05	-3.14	2.99	3.34	6.02	4.97	-4.12	---	---

Fab-Y specificity antigen 1 -23

% Inhibition AKT

Figure 13


CD79B/CD22
% Inhibition
0
20
40
60
80
100
pSYK
pPLCg2
pAKT
VR0004246/VR0000982
VR0004246/VR0004120
VR0004246/VR0004126
VR0004246/VR0004127
VR0004246/VR0004128
VR0004246/VR0004130
VR0004246/VR0004132
VR0004447/VR0000982
VR0004447/VR0004120
VR0004447/VR0004125
VR0004447/VR0004126
VR0004447/VR0004127
VR0004447/VR0004128
VR0004447/VR0004130
VR0004447/VR0004132
VR0004450/VR0000982
VR0004450/VR0004120
VR0004450/VR0004125
VR0004450/VR0004126
VR0004450/VR0004127
VR0004450/VR0004128
VR0004450/VR0004130
VR0004450/VR0004132

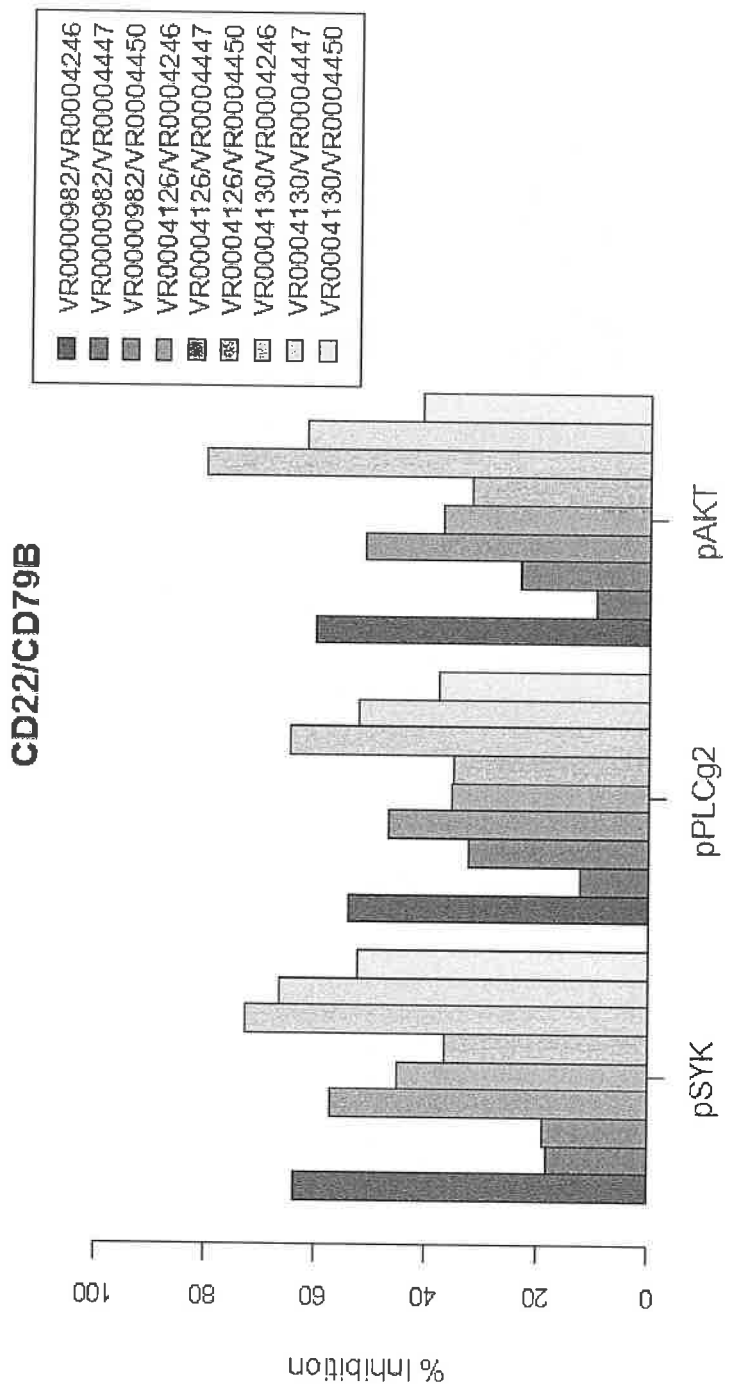

CD22/CD79B
VR0000982/VR0004246
VR0000982/VR0004447
VR0000982/VR0004450
VR0004126/VR0004246
VR0004126/VR0004447
VR0004126/VR0004450
VR0004130/VR0004246
VR0004130/VR0004447
VR0004130/VR0004450
pSYK
pPLCg2
pAKT
% Inhibition
0
20
40
60
80
100

Figure 14

Figure 15

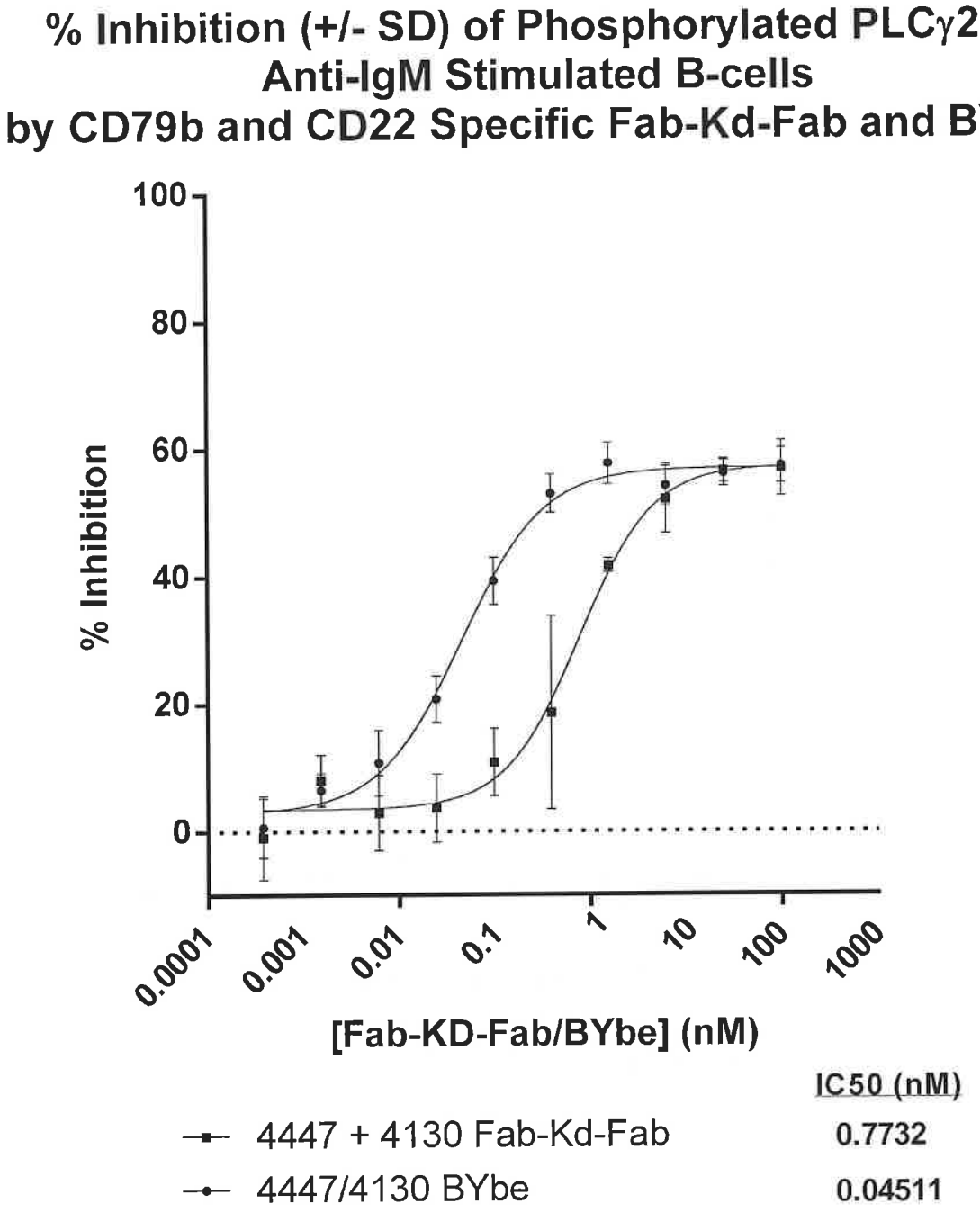
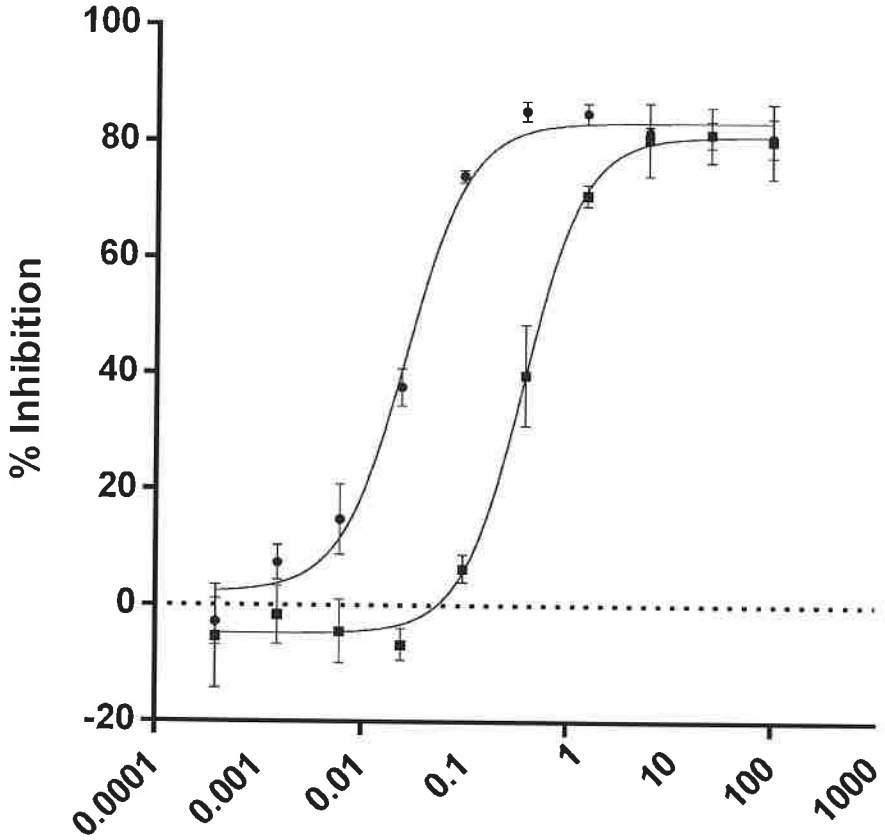

% Inhibition (+/- SD) of Phosphorylated PLCγ2 in Anti-IgM Stimulated B-cells by CD79b and CD22 Specific Fab-Kd-Fab and BYbe.
100
80
60
40
20
0
% Inhibition
0.0001
0.001
0.01
0.1
1
10
100
1000
[Fab-KD-Fab/BYbe] (nM)
IC50 (nM)
4447 + 4130 Fab-Kd-Fab
0.7732
4447/4130 BYbe
0.04511

Figure 16

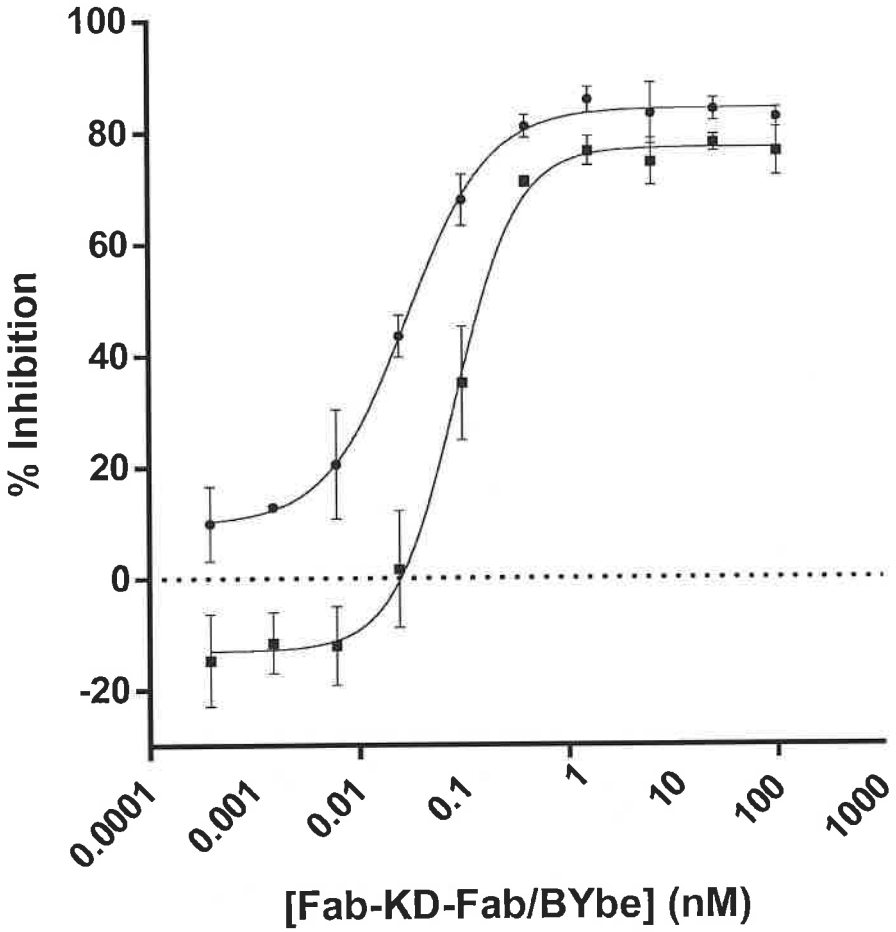
% Inhibition (+/- SD) of Phosphorylated P38 in Anti-IgM Stimulated B-cells, by CD79b and CD22 Specific Fab-Kd-Fab and BYbe.



	IC50 (nM)
4447 + 4130 Fab-Kd-Fab	0.3730
4447/4130 BYbe	0.02648

Figure 17

% Inhibition (+/- SD) of Phosphorylated Akt in Anti-IgM Stimulated B-cells, by CD79b and CD22 Specific Fab-Kd-Fab and BYbe.



	IC50 (nM)
4447 + 4130 Fab-Kd-Fab	0.08421
4447/4130 BYbe	0.02942

Figure 18

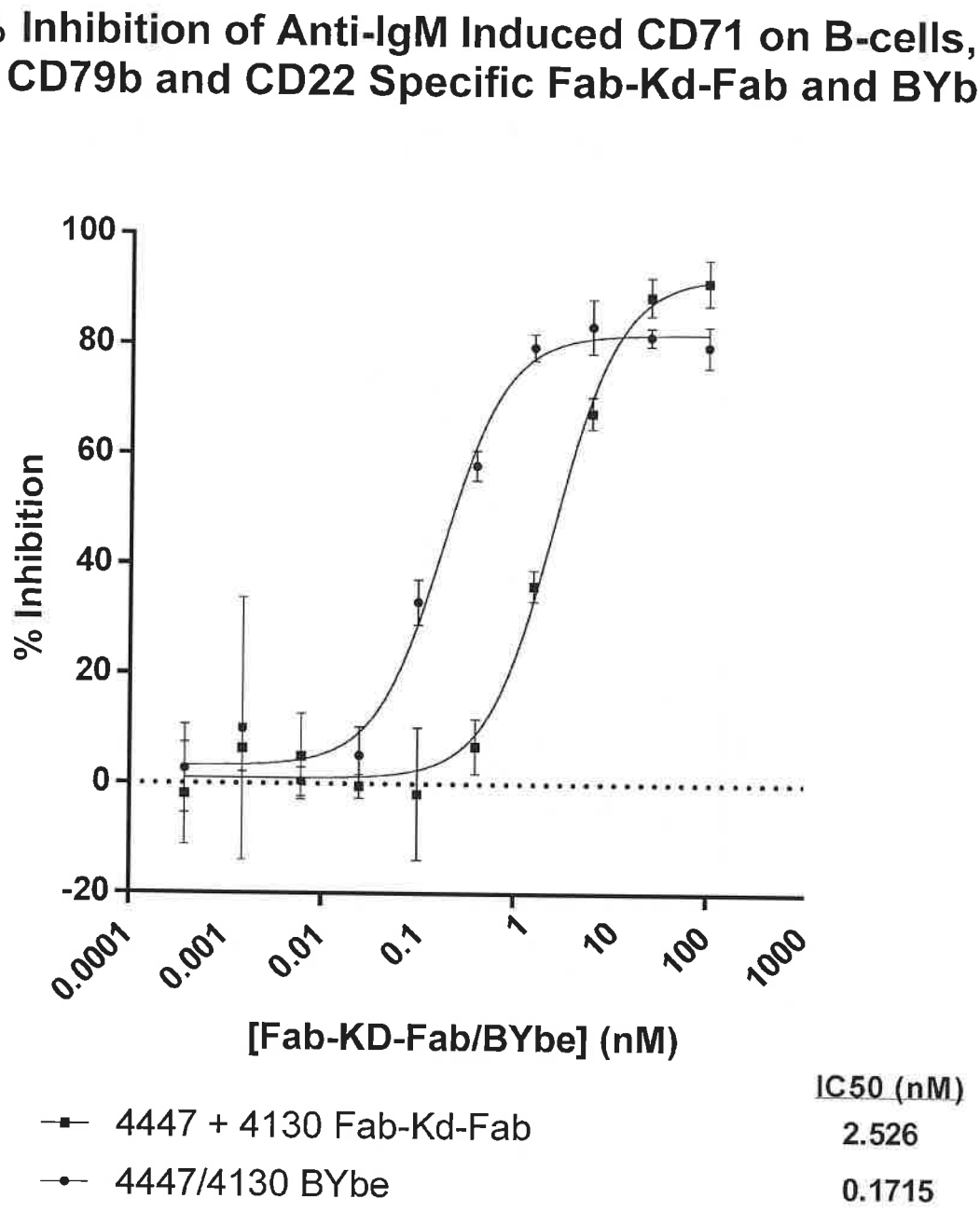

% Inhibition of Anti-IgM Induced CD71 on B-cells, by CD79b and CD22 Specific Fab-Kd-Fab and BYbe
100
80
60
40
20
0
-20
% Inhibition
0.0001
0.001
0.01
0.1
1
10
100
1000
[Fab-KD-Fab/BYbe] (nM)
IC50 (nM)
4447 + 4130 Fab-Kd-Fab
2.526
4447/4130 BYbe
0.1715

Figure 19

% Inhibition of Anti-IgM Induced CD40 on B-cells, by CD79b and CD22 Specific Fab-Kd-Fab and BYbe

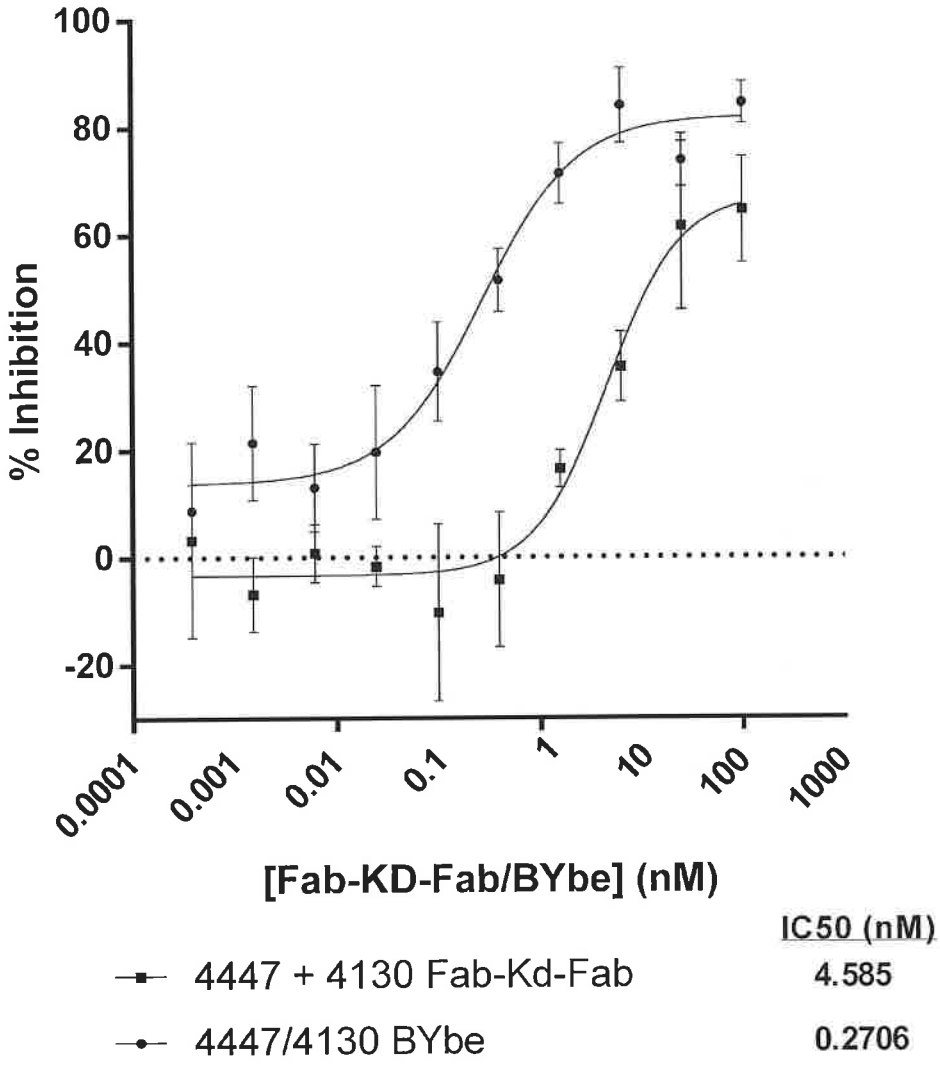


Figure 20

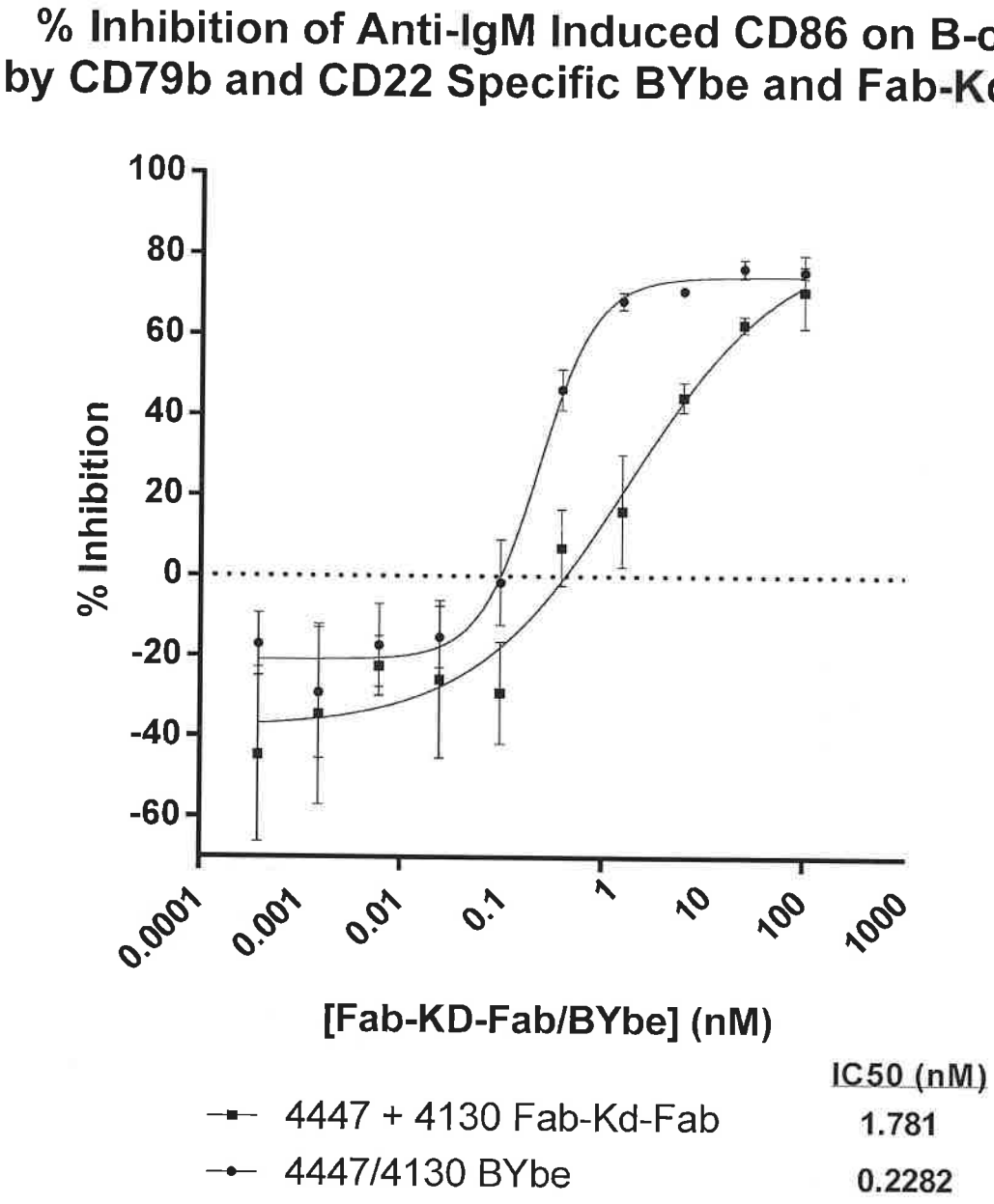

% Inhibition of Anti-IgM Induced CD86 on B-cells by CD79b and CD22 Specific BYbe and Fab-Kd-Fab
100
80
60
40
20
0
-20
-40
-60
% Inhibition
0.0001
0.001
0.01
0.1
1
10
100
1000
[Fab-KD-Fab/BYbe] (nM)
IC50 (nM)
4447 + 4130 Fab-Kd-Fab
1.781
4447/4130 BYbe
0.2282

Figure 21

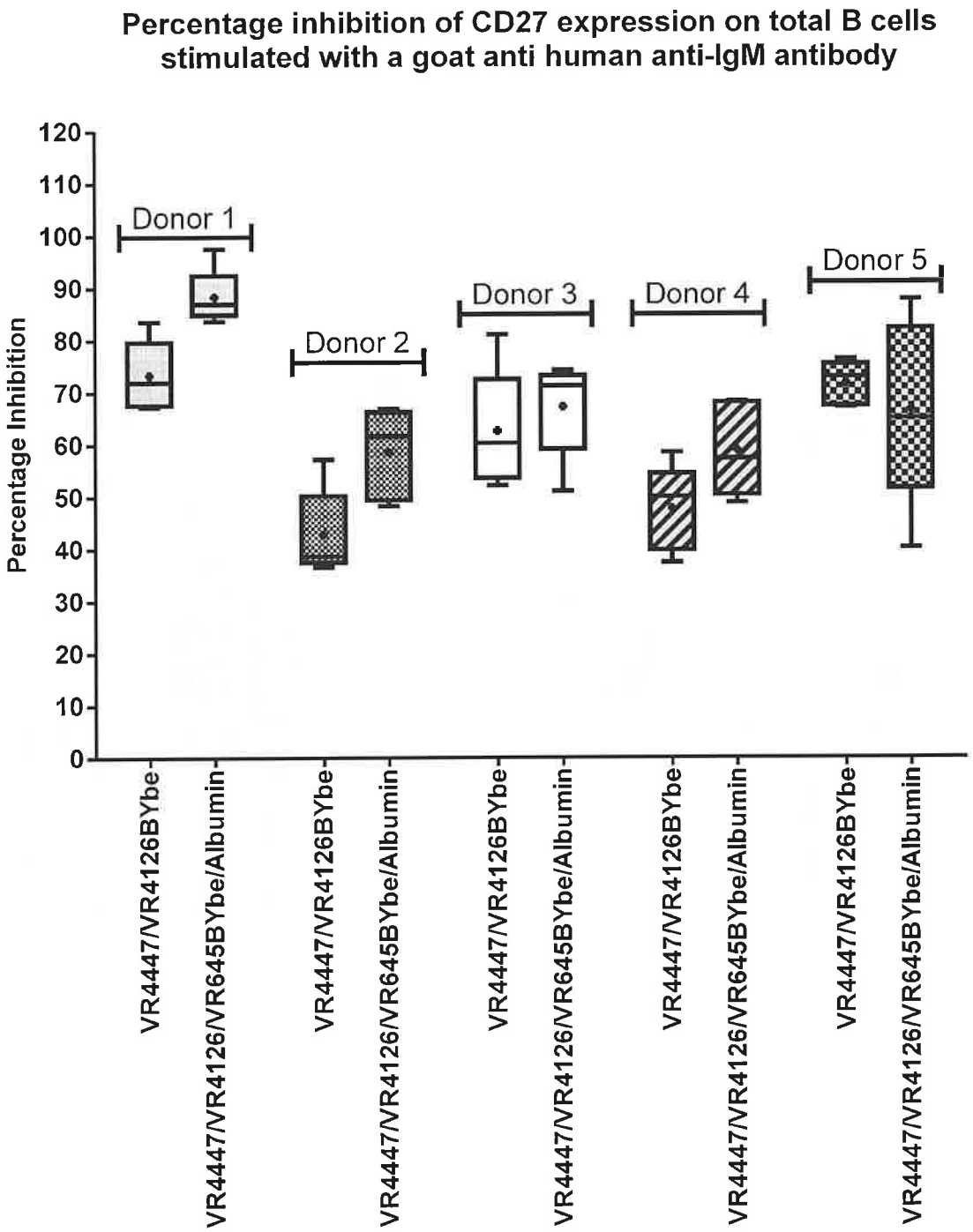

Percentage inhibition of CD27 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin

Figure 22

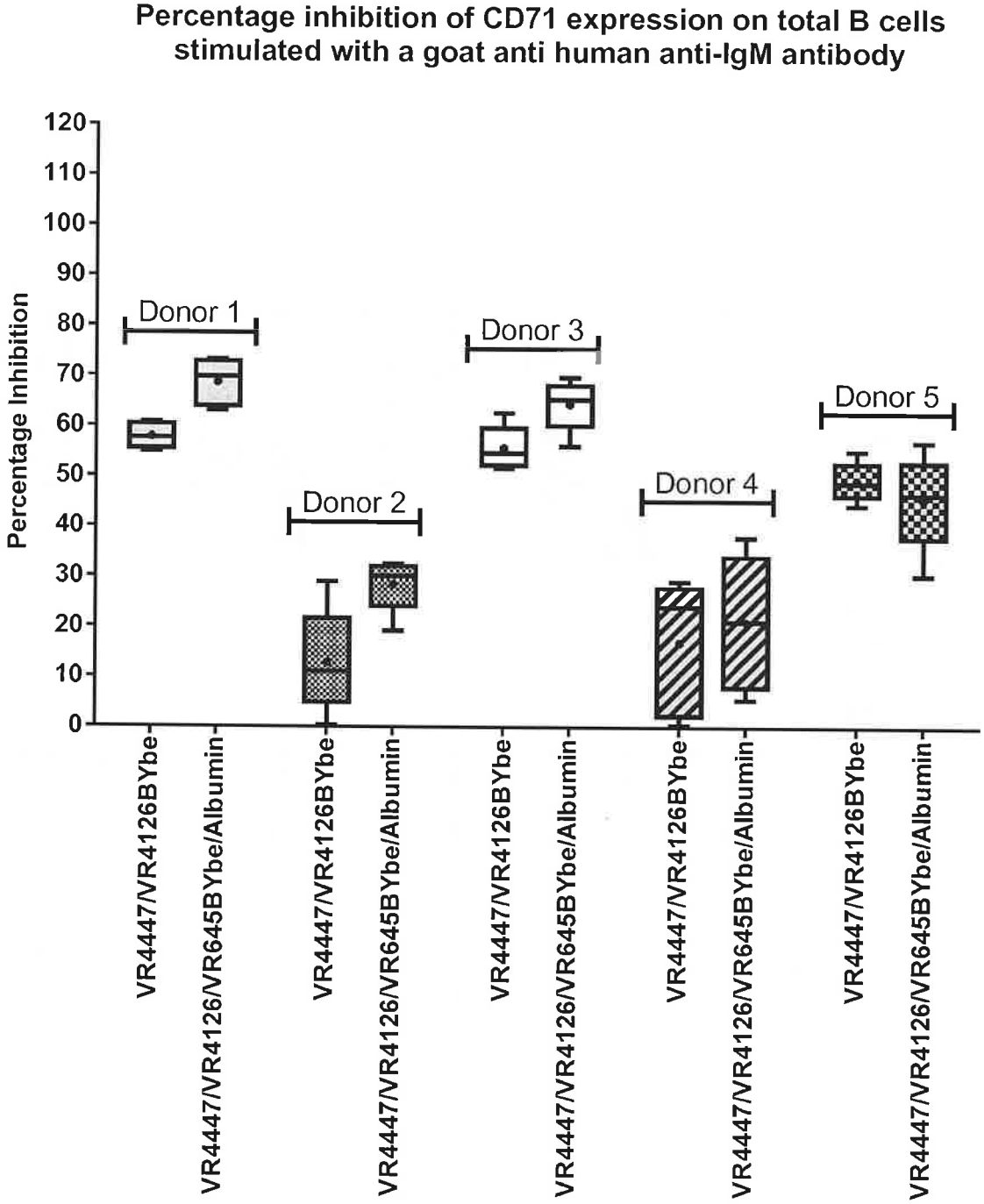

Percentage inhibition of CD71 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin

Figure 23

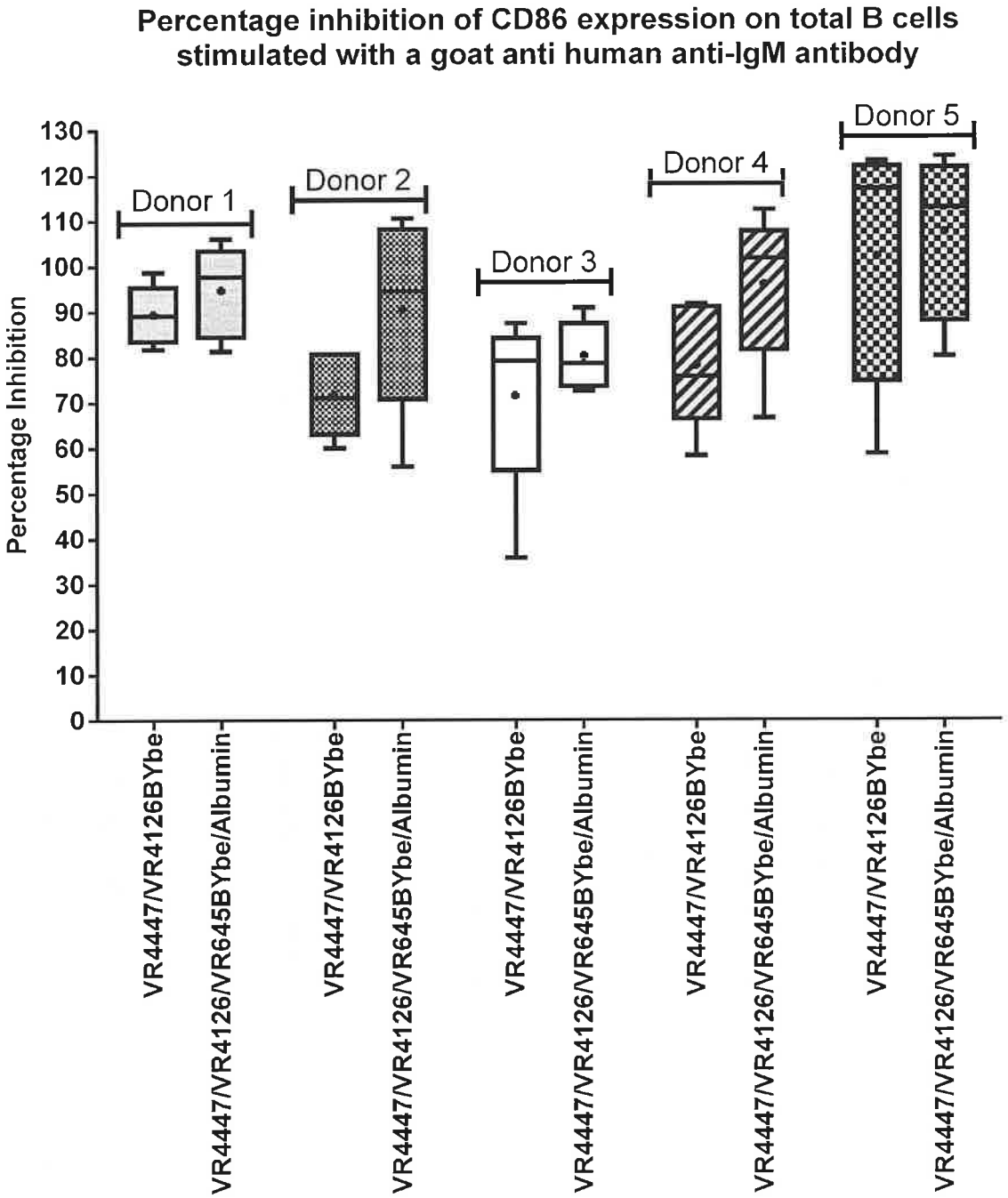

Percentage inhibition of CD86 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
130
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4126BYbe
VR4447/VR4126/VR645BYbe/Albumin

Figure 24

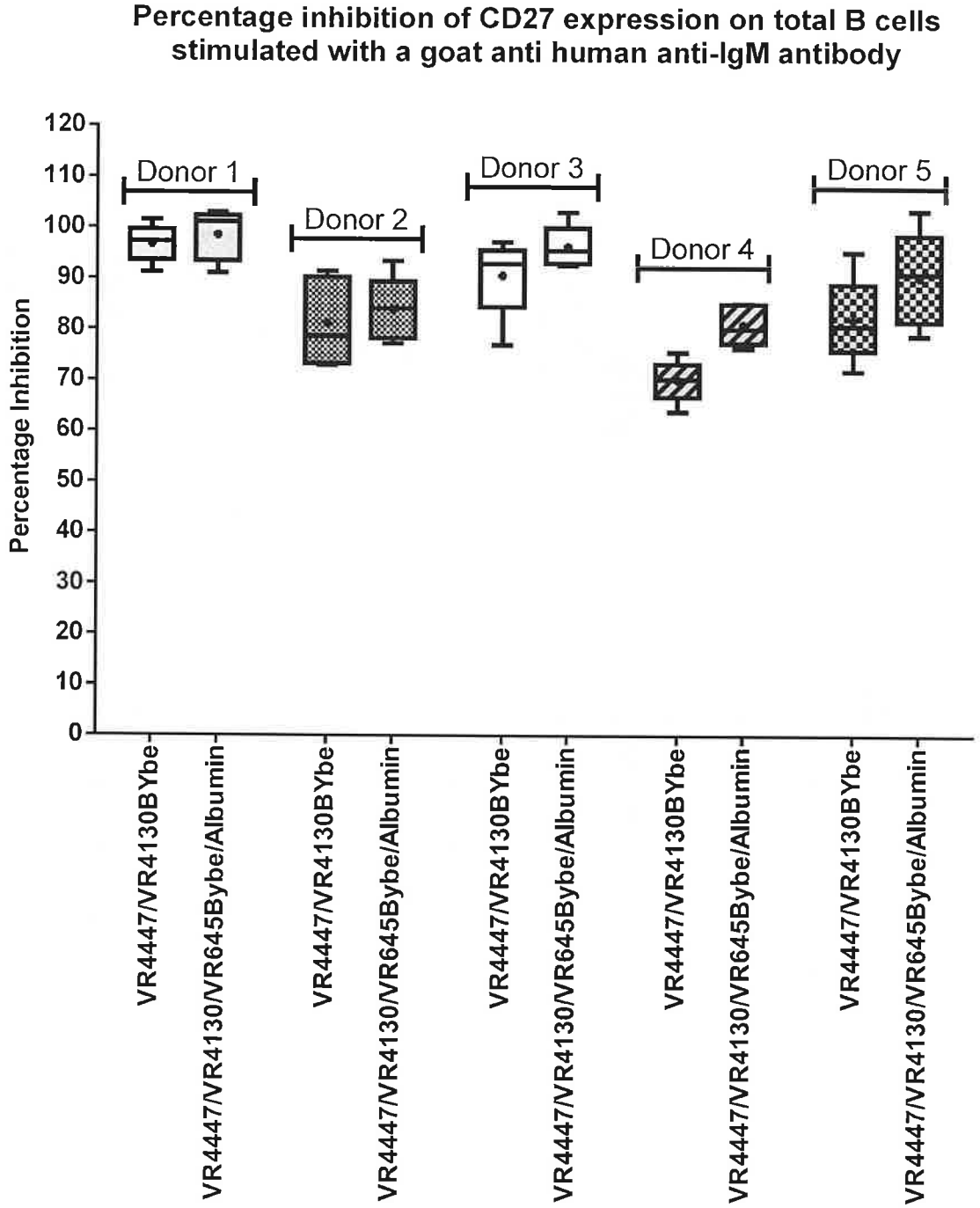

Percentage inhibition of CD27 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin

Figure 25

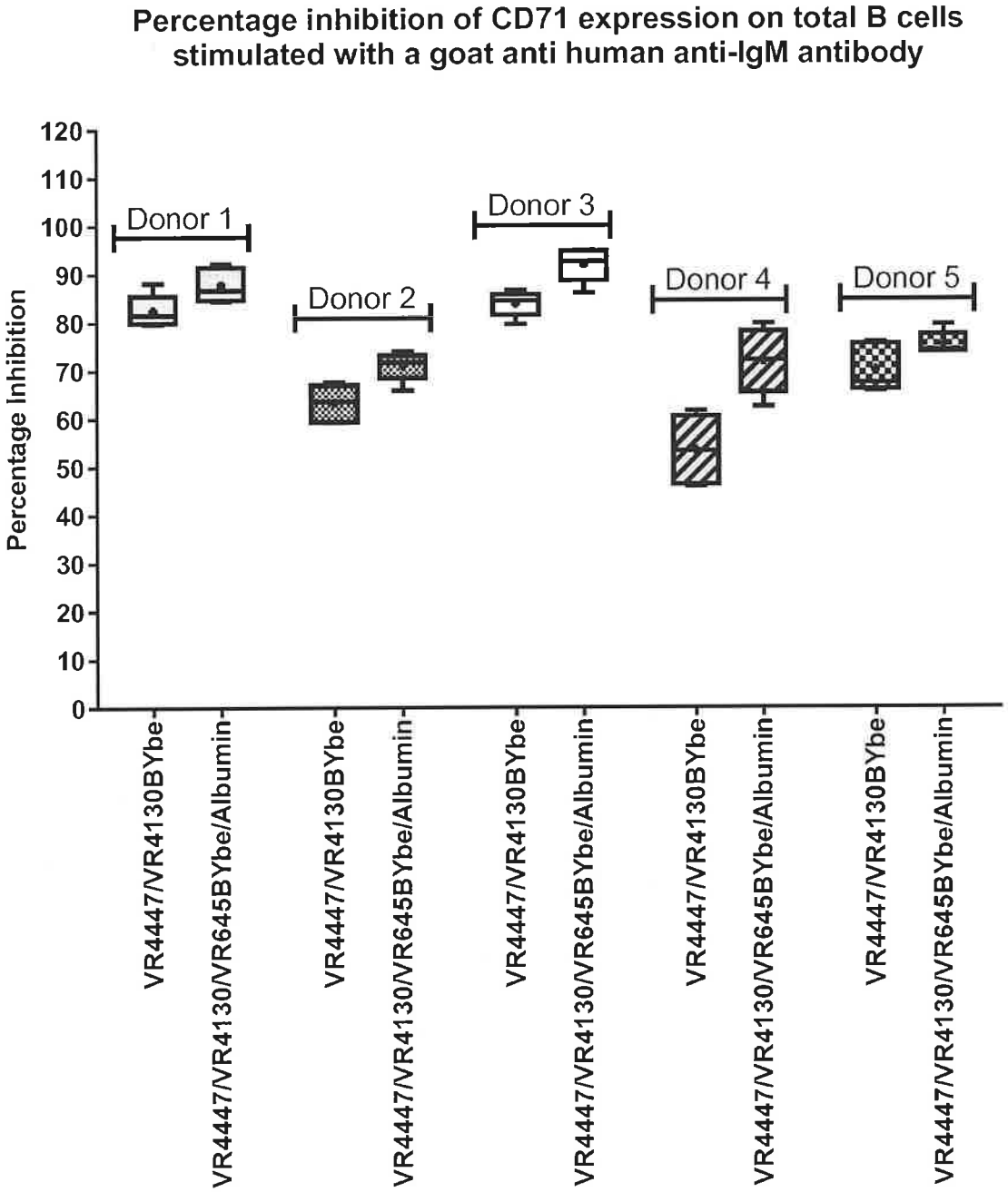

Percentage inhibition of CD71 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4130BYbe
VR4447/VR4130/VR645BYbe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645BYbe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645BYbe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645BYbe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645BYbe/Albumin

Figure 26

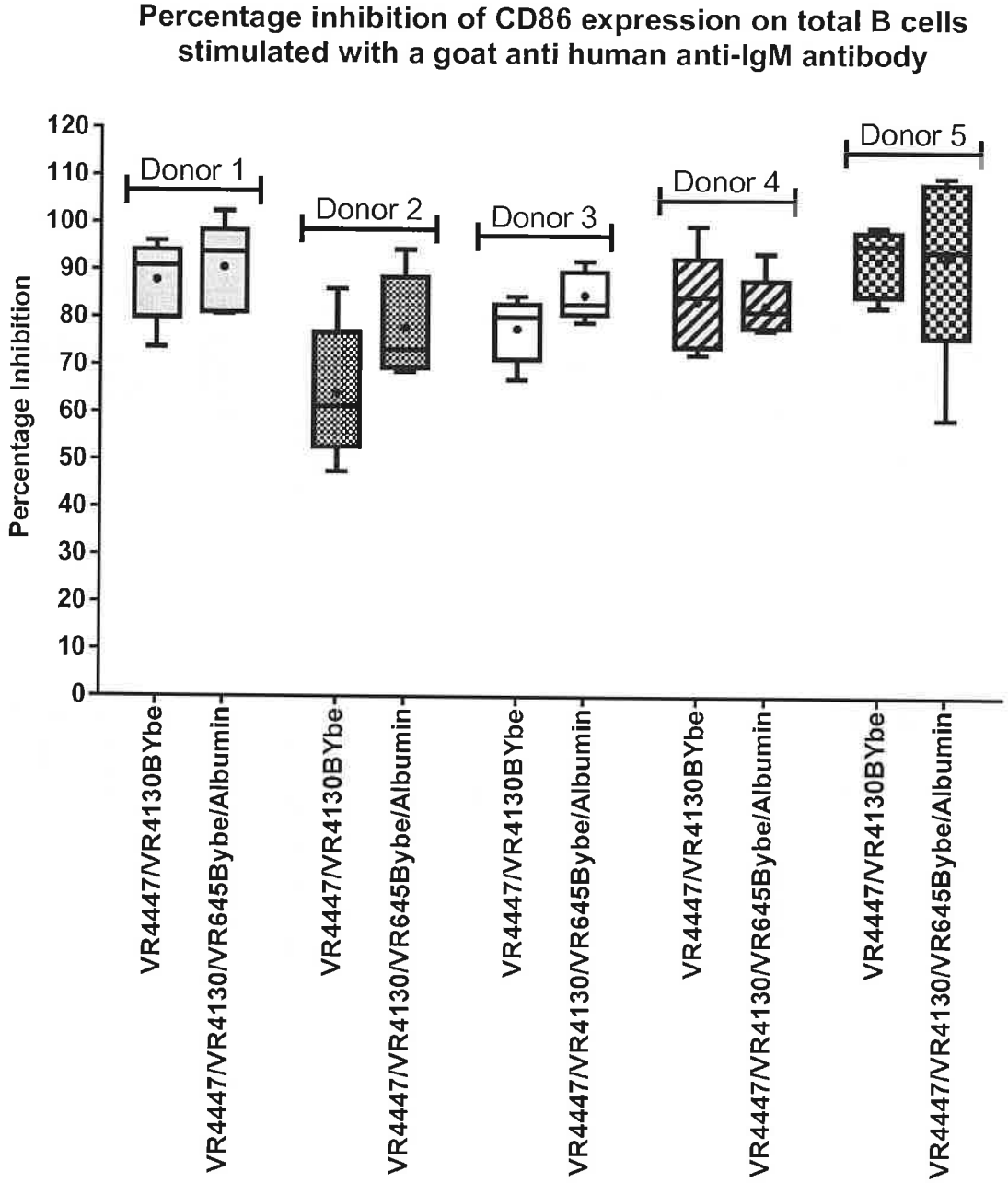

Percentage inhibition of CD86 expression on total B cells stimulated with a goat anti human anti-IgM antibody
Percentage Inhibition
120
110
100
90
80
70
60
50
40
30
20
10
0
Donor 1
Donor 2
Donor 3
Donor 4
Donor 5
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin
VR4447/VR4130BYbe
VR4447/VR4130/VR645Bybe/Albumin

Figure 27 Percentage inhibition of tetanus toxoid specific IgG production from human PBMCs

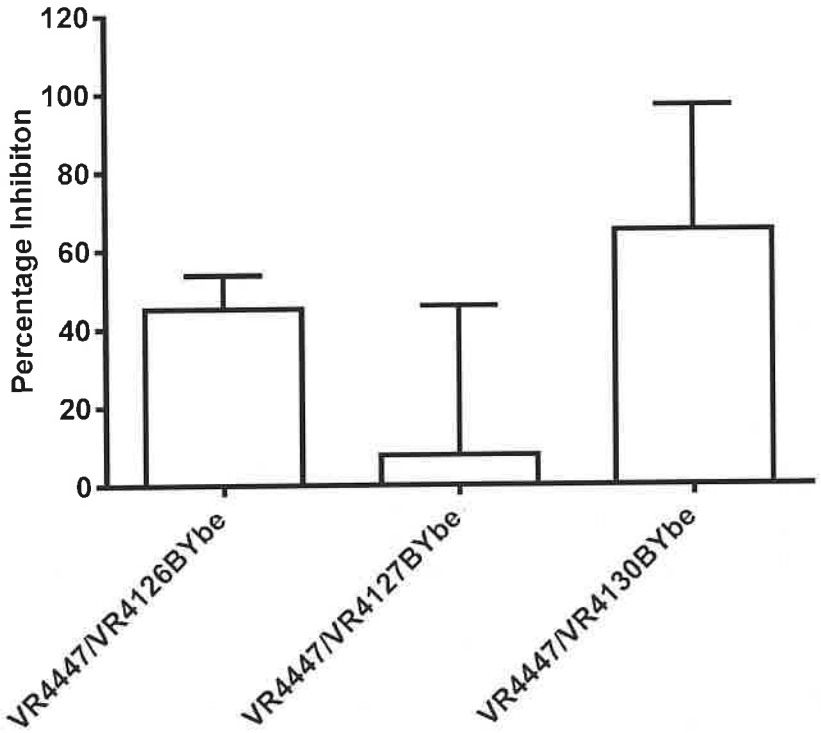


Figure 28 Percentage inhibition of tetanus toxoid specific IgG production from human B cells

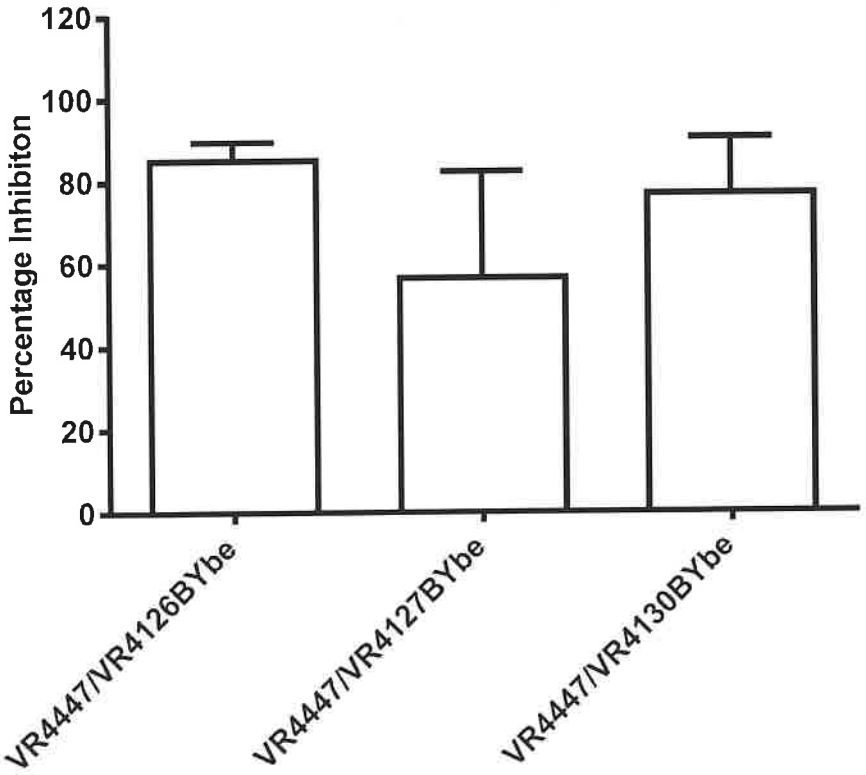


FIGURE 29

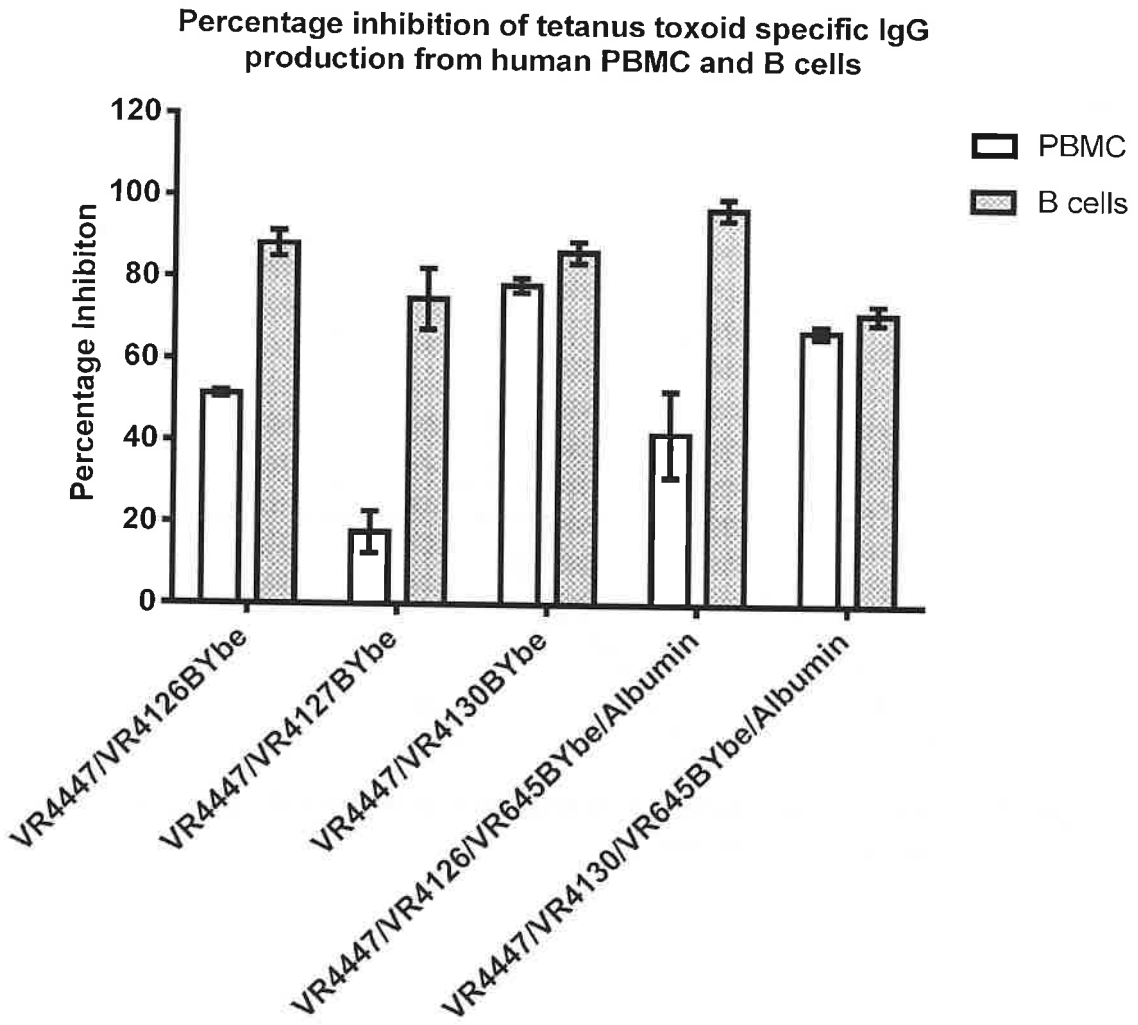

Percentage inhibition of tetanus toxoid specific IgG production from human PBMC and B cells
Percentage Inhibiton
120
100
80
60
40
20
0
PBMC
B cells
VR4447/VR4126BYbe
VR4447/VR4127BYbe
VR4447/VR4130BYbe
VR4447/VR4126/VR645BYbe/Albumin
VR4447/VR4130/VR645BYbe/Albumin

Figure 30 Baseline Levels of Phosphorylation in Unstimulated B-cells from 12 Healthy and 12 SLE Patient Samples

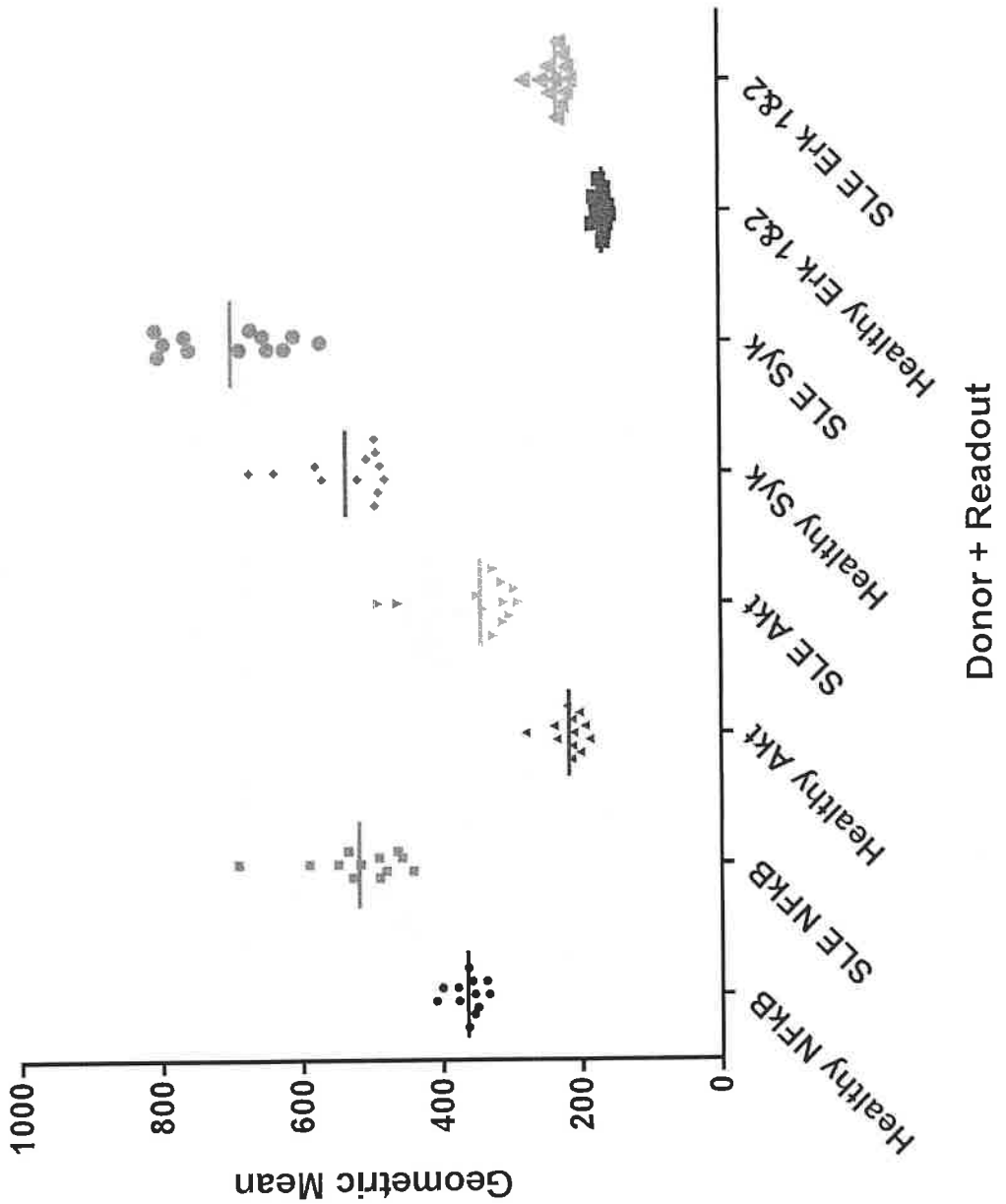


Figure 31 Effect of CD79b & CD22 Specific VR4447/4130 BYbe on Anti-IgM Induced B cell NFκB Phosphorylation from 12 Healthy and 12 SLE Patient Samples

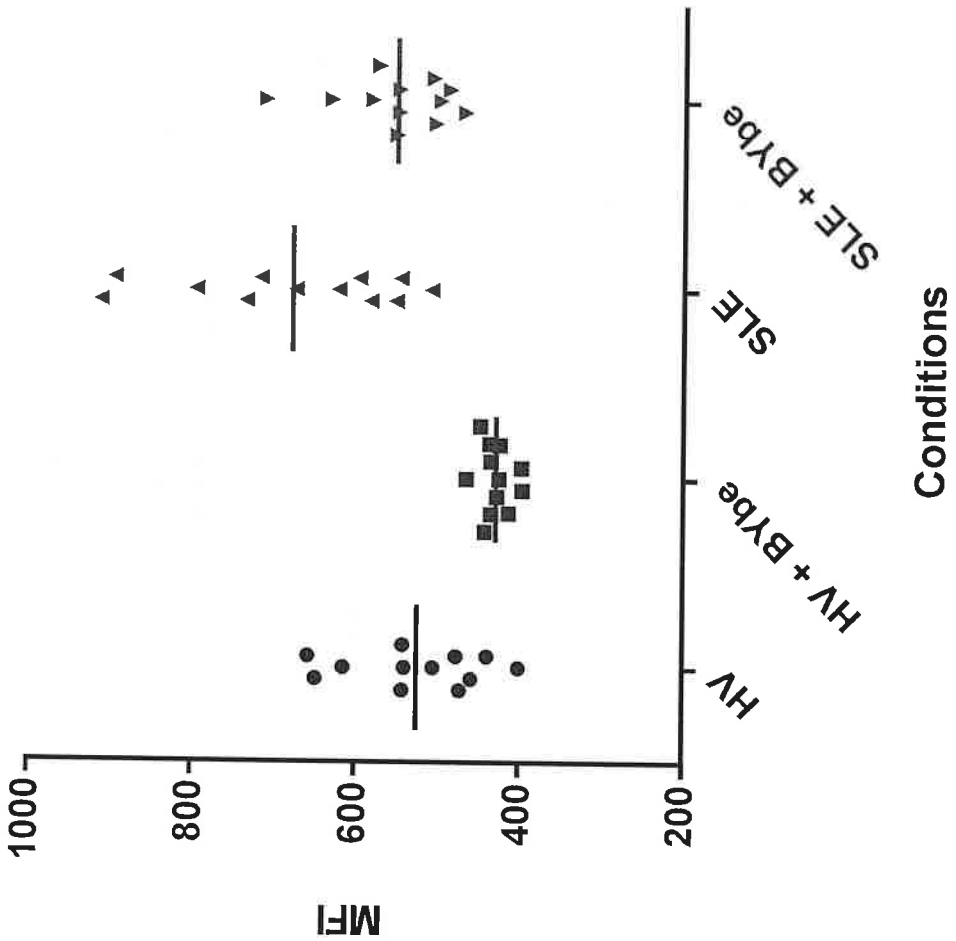


Figure 32 Effect of CD79b & CD22 Specific VR4447/4130 BYbe on Anti-IgM Induced B cell Akt Phosphorylation from 12 Healthy and 12 SLE Patient Samples

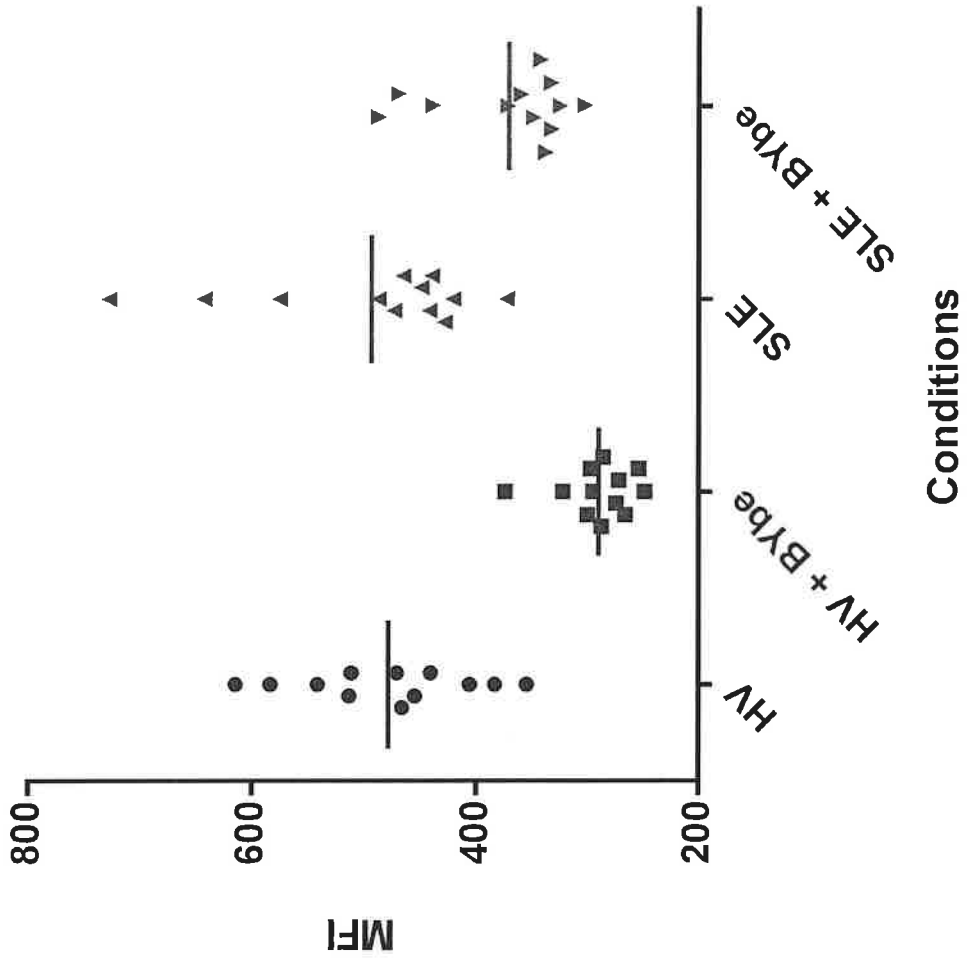


Figure 33 Effect of CD79b & CD22 Specific VR4447/4130 BYbe on Anti-IgM Induced B cell Syk Phosphorylation from 12 Healthy and 12 SLE Patient Samples

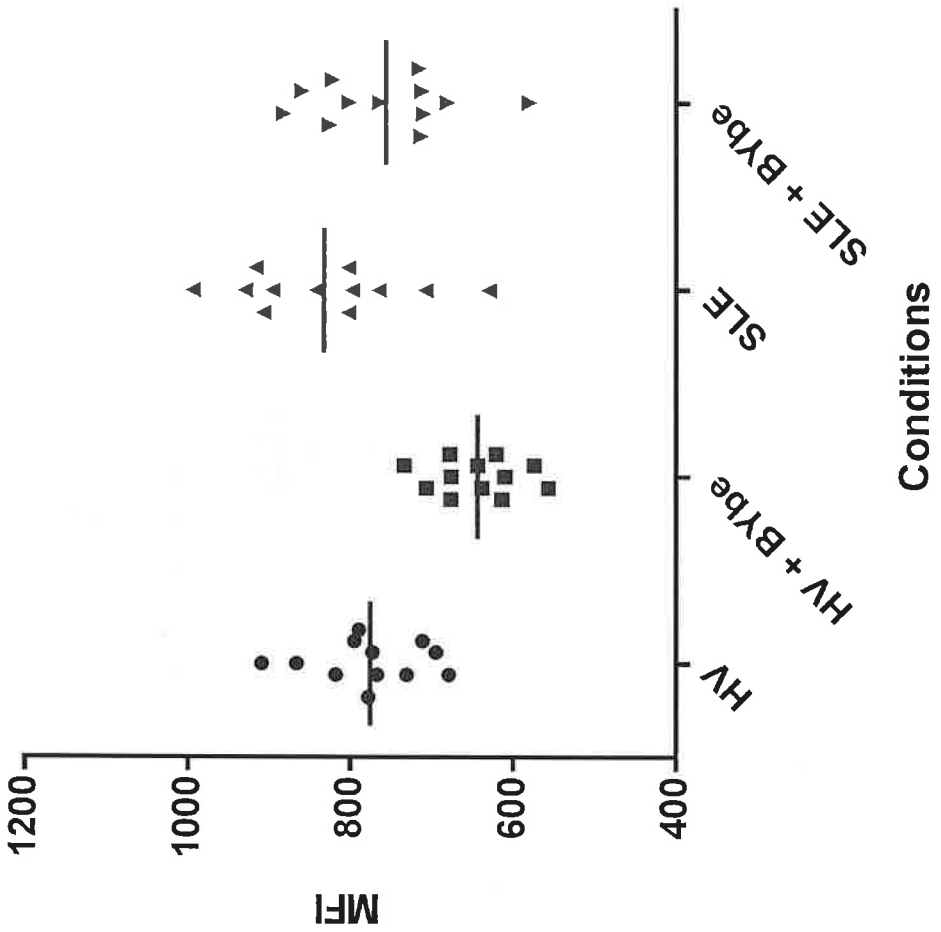


Figure 34 Effect of CD79b & CD22 Specific VR4447/4130 BYbe on Anti-IgM Induced B cell ERK1 & 2 Phosphorylation from 12 Healthy and 12 SLE Patient Samples

