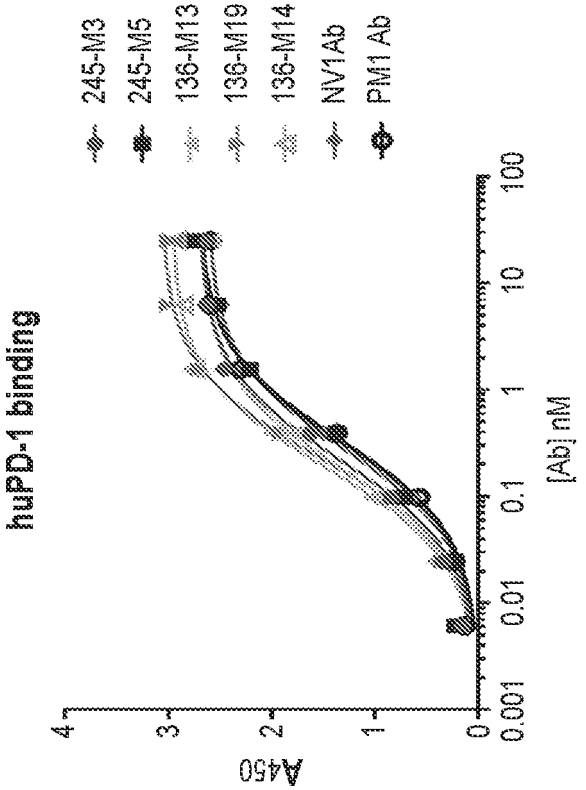


FIGURE 1

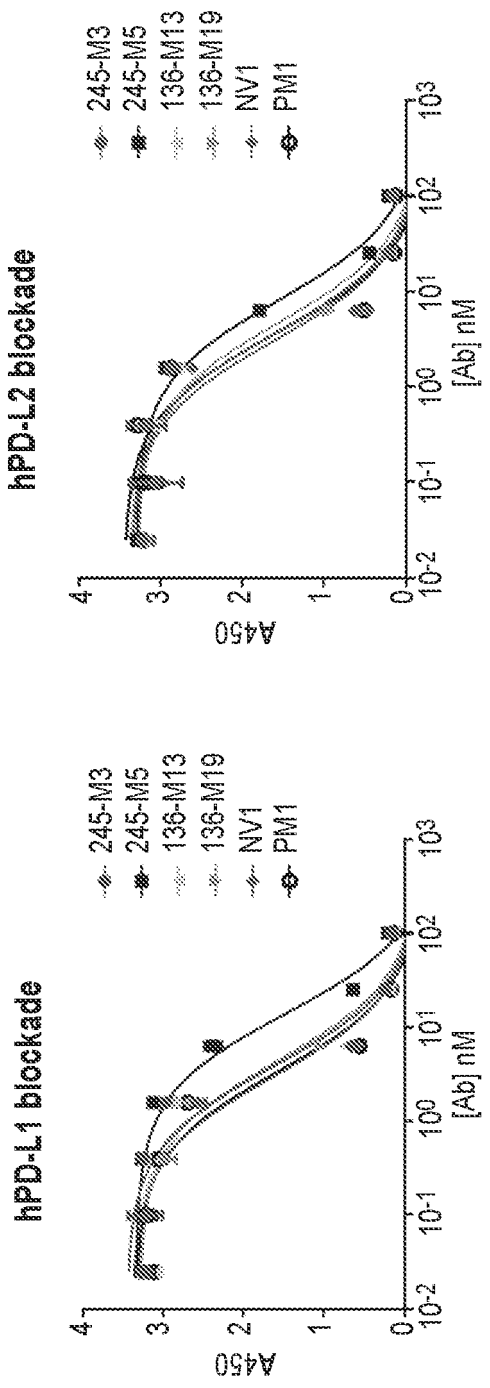


FIGURE 2

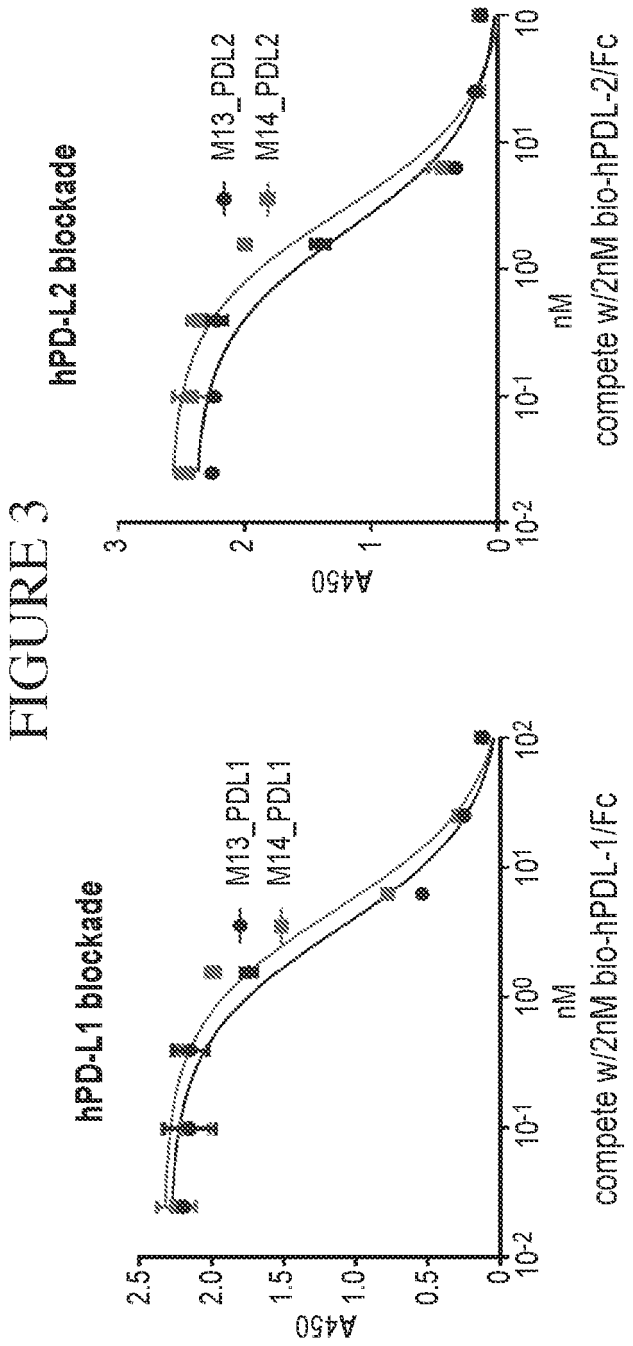


FIGURE 3

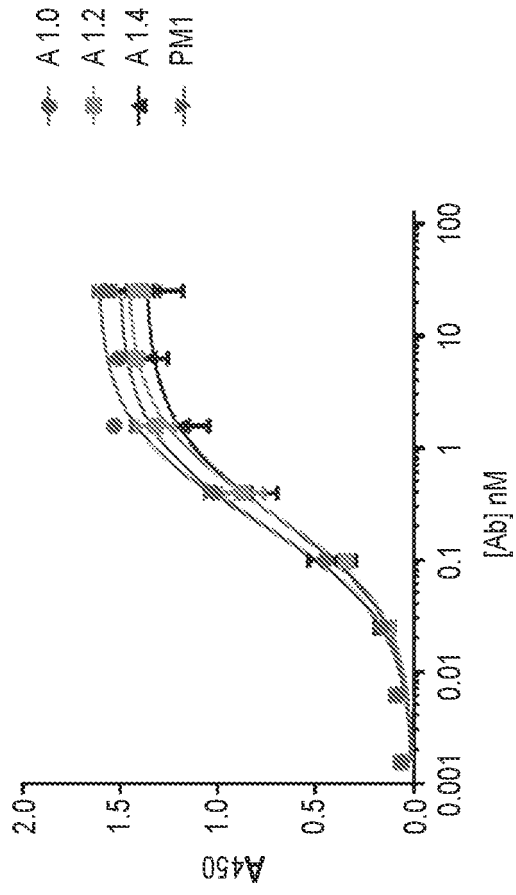


FIGURE 4

FIGURE 5

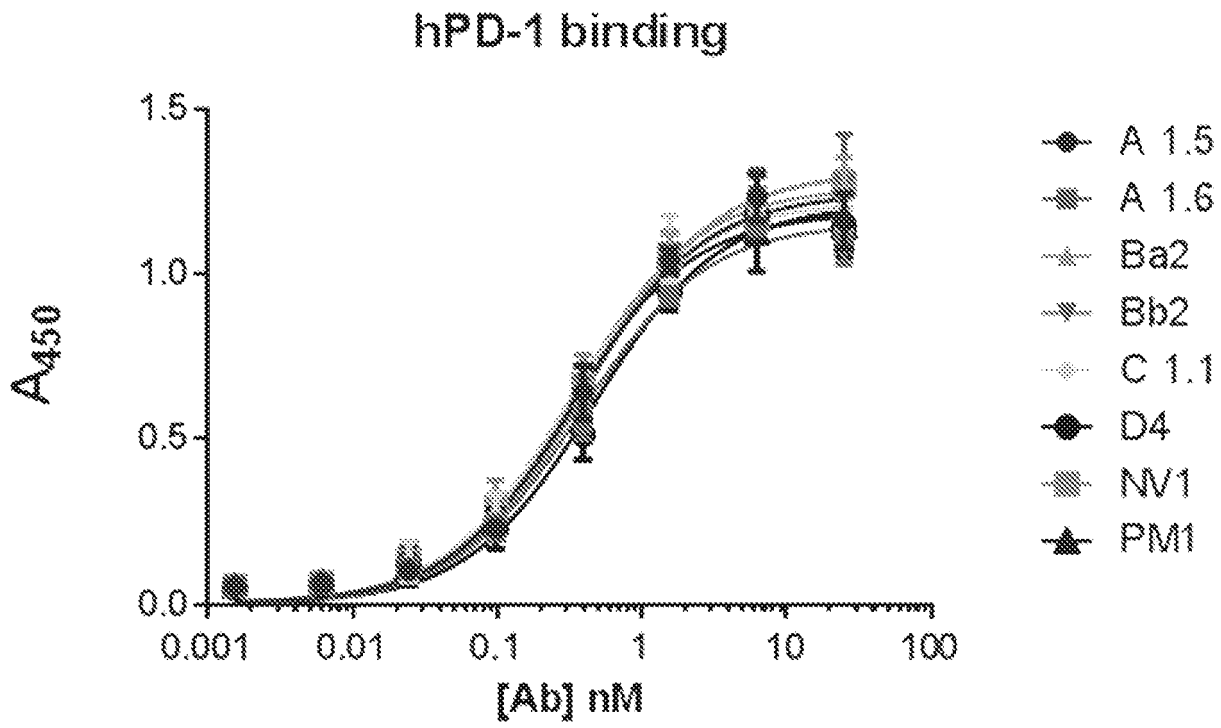
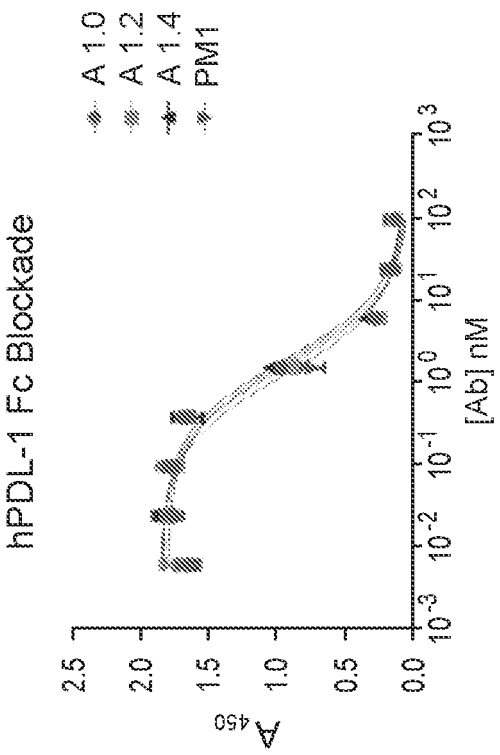
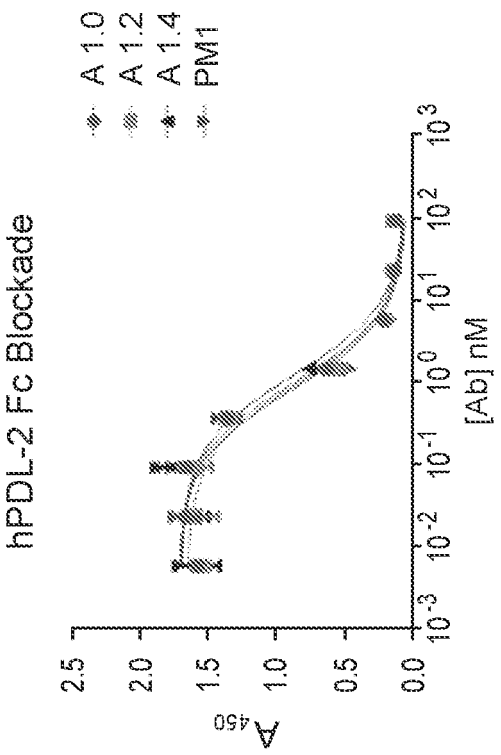

hPD-1 binding
1.5
1.0
0.5
0.0
A450
0.001
0.01
0.1
1
10
100
[Ab] nM
A 1.5
A 1.6
Ba2
Bb2
C 1.1
D4
NV1
PM1

FIGURE 6

	A 1.0	A 1.2	A 1.4	PM1
log(inhibitor) vs. response (three parameters)				
Best-fit values				
Bottom	0.02473	0.03867	0.06139	0.07407
Top	1.824	1.869	1.862	1.876
LogIC50	0.2671	0.1900	0.2838	0.08867
IC50	1.850	1.549	1.922	1.227
Span	1.800	1.830	1.800	1.802

	A 1.0	A 1.2	A 1.4	PM1
log(inhibitor) vs. response (three parameters)				
Best-fit values				
Bottom	0.05839	0.06423	0.06416	0.05329
Top	1.742	1.687	1.734	1.750
LogIC50	0.01826	0.002967	0.1109	-0.05539
IC50	1.043	1.007	1.291	0.8803
Span	1.683	1.622	1.670	1.696

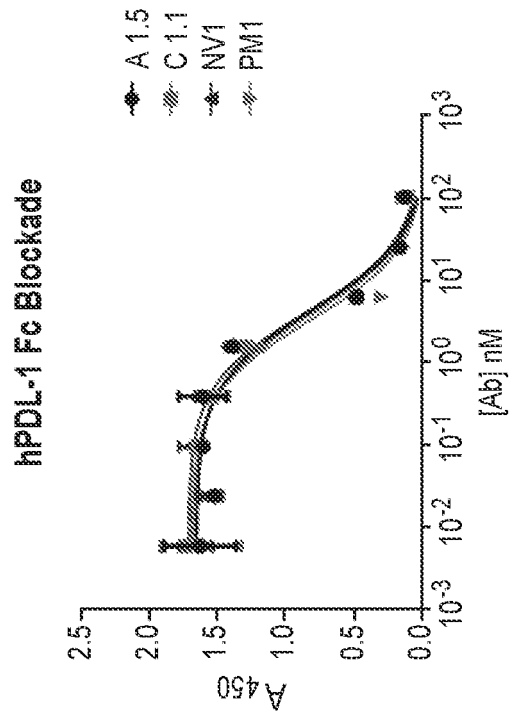




2nM of hPDL-1 Fc/hPDL-2Fc as blockade

FIGURE 7

	A 1.5	C 1.1	NV1	PM1
log(inhibitor) vs. response (three parameters)				
Best-fit values				
Bottom	-0.01122	-0.002852	0.01597	-0.01207
Top	1.672	1.691	1.735	1.710
LogIC50	0.6289	0.5712	0.6045	0.5045
IC50	4.255	3.726	4.023	3.196



	A 1.5	C 1.1	NV1	PM1
log(inhibitor) vs. response (three parameters)				
Best-fit values				
Bottom	0.01162	0.002368	0.02642	0.003166
Top	1.733	1.784	1.804	1.779
LogIC50	0.4676	0.4875	0.5231	0.4797
IC50	2.935	3.073	3.335	3.018

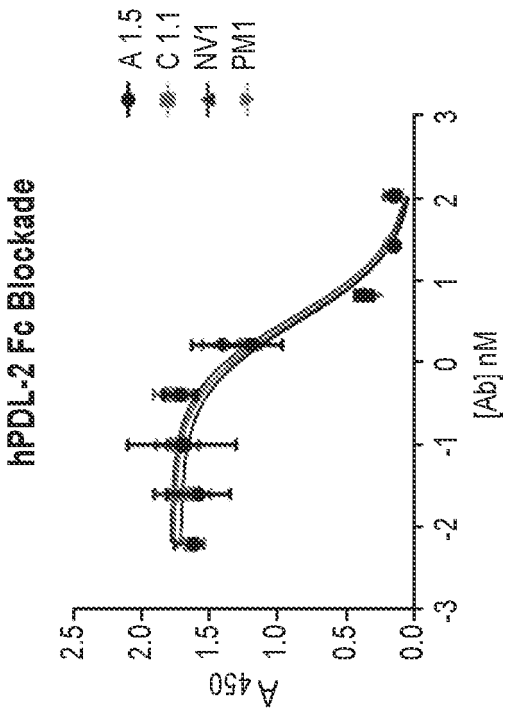
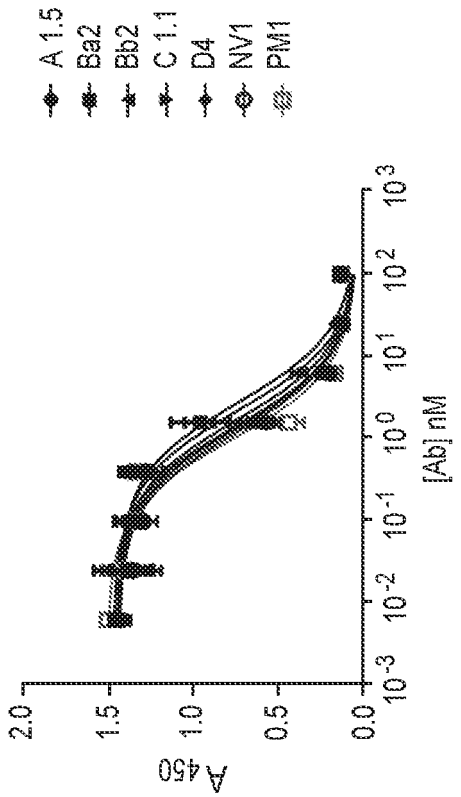


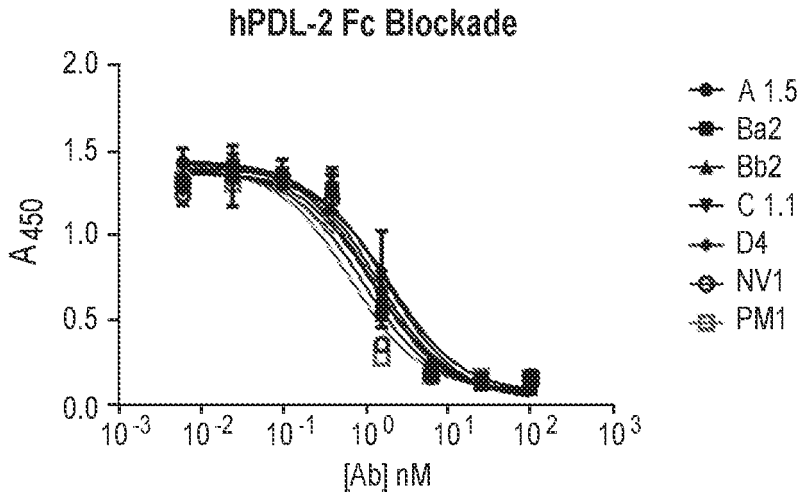
FIGURE 8



	A 1.5	Ba2	Bb2	C 1.1	D4	NV1	PM1
log(inhibitor) vs. response (three parameters)							
Best-fit values							
Bottom	0.03776	0.03156	0.04762	0.05233	0.04490	0.05720	0.04908
Top	1.494	1.469	1.471	1.472	1.460	1.461	1.529
LogIC50	0.1465	0.3417	0.2221	0.1209	0.4346	0.07608	-0.01427
IC50	1.401	2.196	1.668	1.321	2.720	1.191	0.9677
Span	1.457	1.437	1.423	1.420	1.415	1.404	1.480

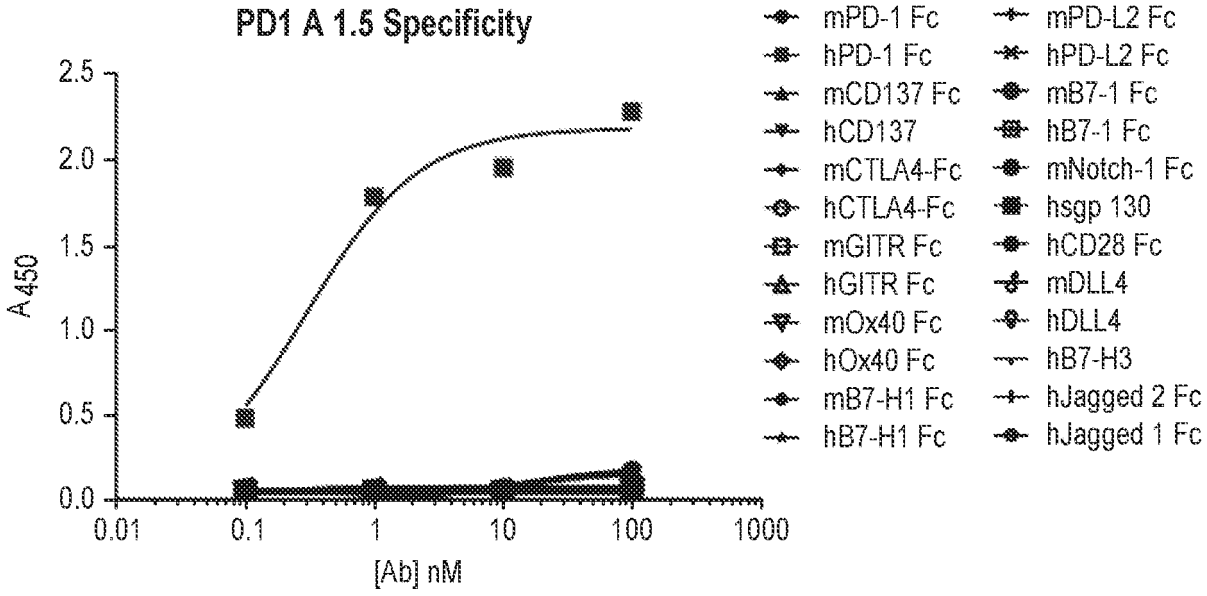
1.4571.4371.4231.4201.4151.4041.480

FIGURE 9



	A 1.5	Ba2	Bb2	C 1.1	D4	NV1	PM1
log(inhibitor) vs. response (three parameters)							
Best-fit values							
Bottom	0.05123	0.04694	0.02765	0.06529	0.06849	0.06895	0.08572
Top	1.445	1.430	1.404	1.385	1.370	1.391	1.404
LogIC50	0.1290	0.08061	0.2635	0.07807	0.2893	-0.03908	-0.1851
IC50	1.346	1.204	1.834	1.197	1.947	0.9140	0.6529
Span	1.344	1.383	1.376	1.320	1.302	1.322	1.318

FIGURE 10



Kd of A1.5 = 0.2948

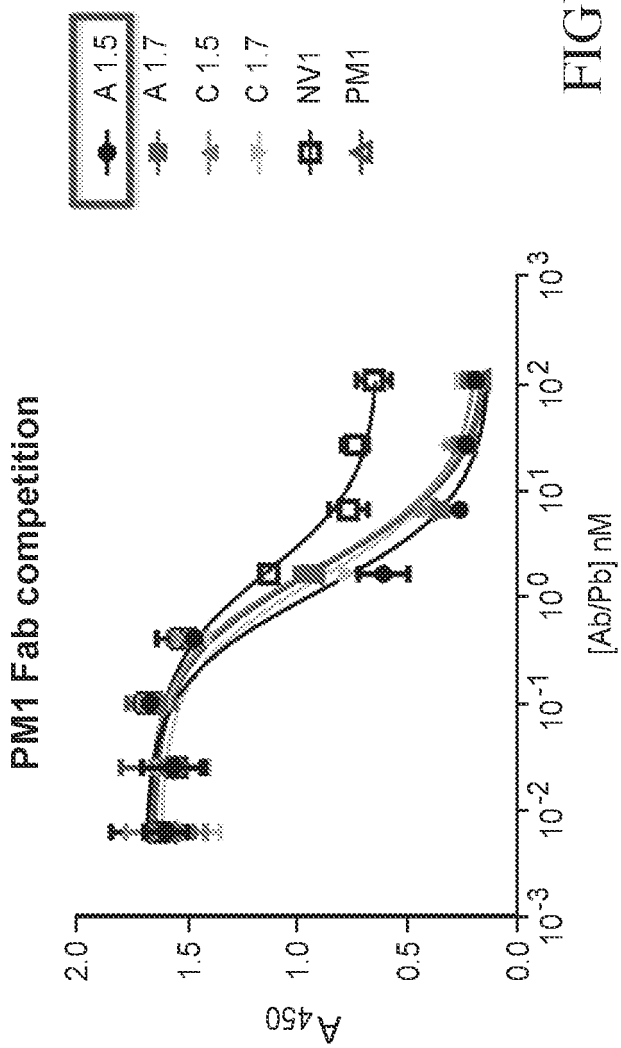


FIGURE 11a

	A 1.5	A 1.7	C 1.5	C 1.7		
log(inhibitor) vs. res ponse (three parameters)						
Best-fit values					NV1	PM1
Bottom	0.1248	0.1450	0.1778	0.1928	0.6340	0.1206
Top	1.694	1.653	1.678	1.626	1.660	1.676
LogIC50	0.03121	0.2458	0.2429	0.1508	0.2042	0.2741
IC50	1.075	1.761	1.749	1.415	1.600	1.880

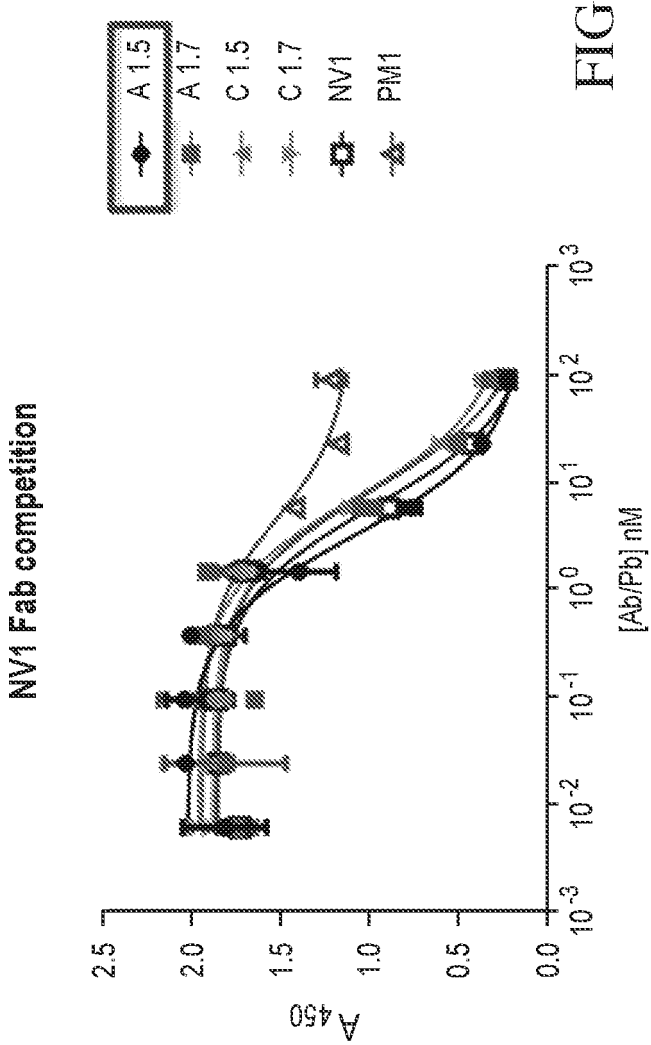
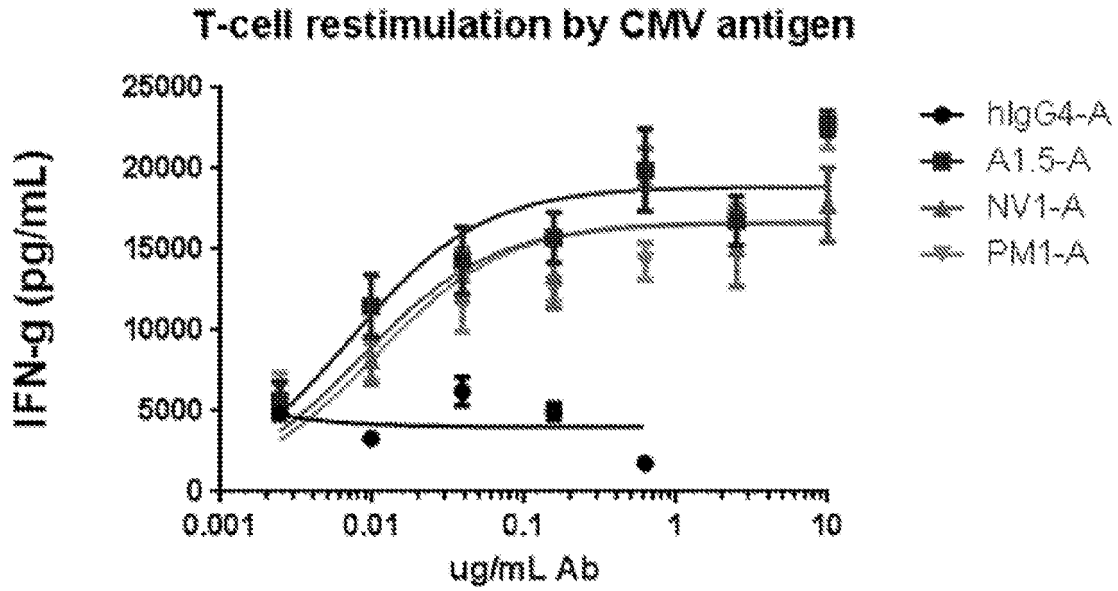


FIGURE 11b

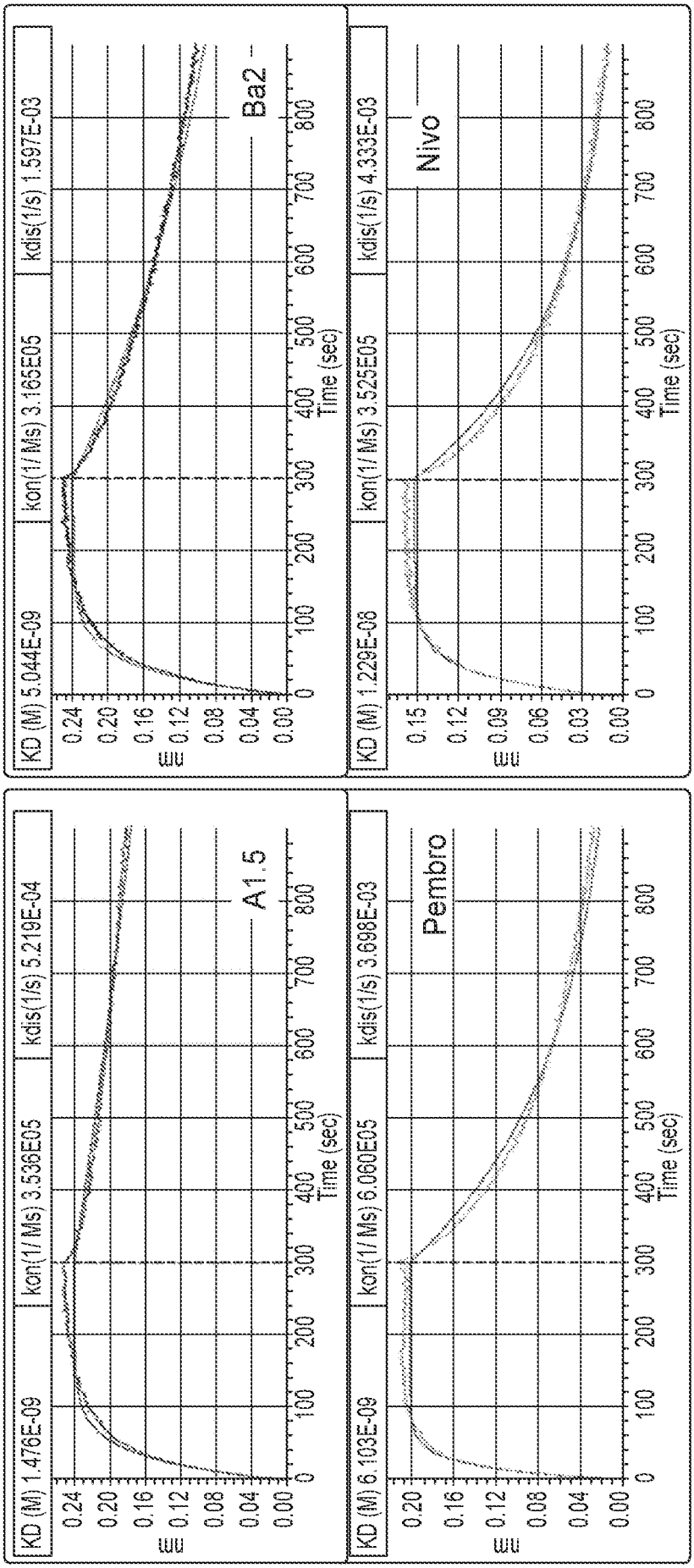
	A 1.5	A 1.7	C 1.5	C 1.7			
log(inhibitor) vs. response (three parameters)							
Best-fit values						NV1	PM1
Bottom	0.1491	0.1158	0.2335	0.2426		0.09043	1.140
Top	2.065	1.891	2.000	1.924		1.902	1.985
LogIC50	0.5390	0.9690	0.8798	0.8837		0.8130	0.6772
IC50	3.459	9.310	7.582	7.651		6.501	4.756

FIGURE 12


T-cell restimulation by CMV antigen
IFN-g (pg/mL)
25000
20000
15000
10000
5000
0
0.001
0.01
0.1
1
10
ug/mL Ab
hIgG4-A
A1.5-A
NV1-A
PM1-A

11/37

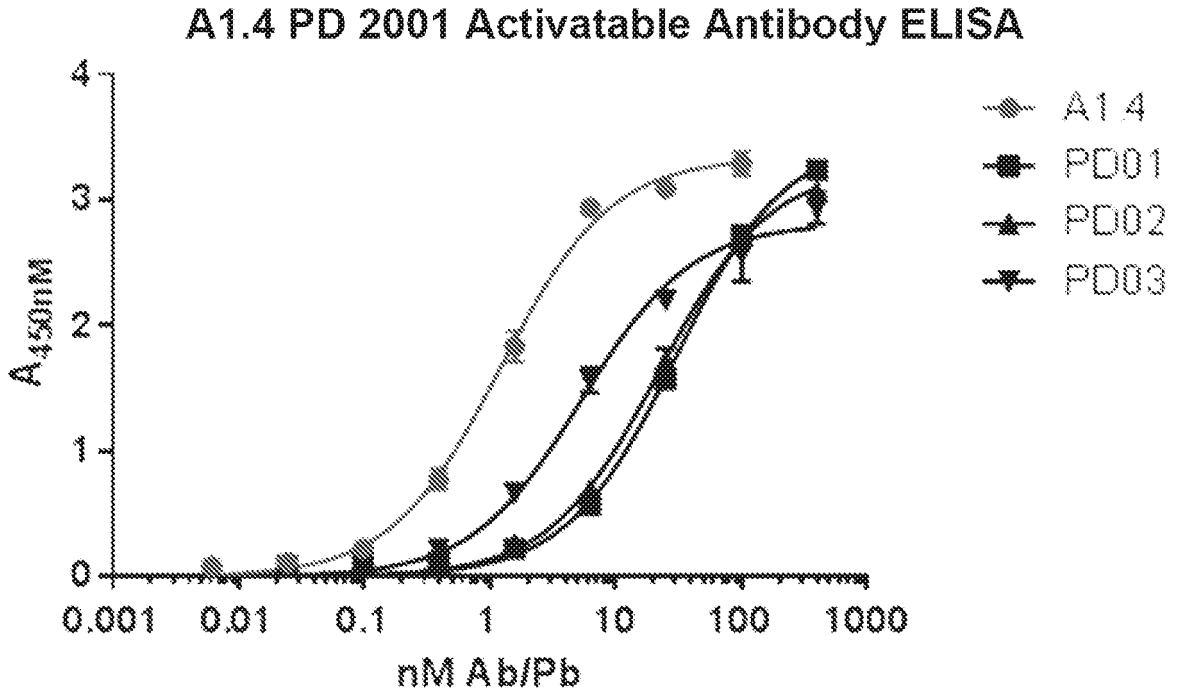
FIGURE 13



Sample ID	Conc. (nM)	Response	KD (M)	kon(1/Ms)	kon Error	kdis(1/s)	kdis Error	Full R^2	Loading Sample ID
hPD1-His	90	0.2526	1.48E-09	3.54E+05	1.82E+03	5.22E-04	2.75E-06	0.996503	A1.5 hIgG4
hPD1-His	90	0.1904	6.37E-09	2.96E+05	1.52E+03	1.89E-03	3.84E-06	0.997158	Ba2 hIgG4
hPD1-His	90	0.1981	1.24E-08	3.33E+05	2.08E+03	4.11E-03	7.81E-06	0.996902	C1.1 hIgG4
hPD1-His	90	0.2069	6.10E-09	6.06E+05	4.99E+03	3.70E-03	8.84E-06	0.994474	PM1 hIgG4

Sample ID	Conc. (nM)	Response	KD (M)	kon(1/Ms)	kon Error	kdis(1/s)	kdis Error	Full R^2	Loading Sample ID
hPD1-His	90	0.2487	5.04E-09	3.17E+05	2.16E+03	1.60E-03	4.65E-06	0.994442	B62 hIgG4
hPD1-His	90	0.1956	5.52E-09	1.62E+05	8.22E+02	8.95E-04	3.09E-06	0.997361	D4 hIgG4
hPD1-His	90	0.1577	1.23E-08	3.53E+05	3.27E+03	4.33E-03	1.19E-05	0.993183	NV1 hIgG4

FIGURE 14


A1.4 PD 2001 Activatable Antibody ELISA
A450nM
nM Ab/Pb
0.001
0.01
0.1
1
10
100
1000
0
1
2
3
4
A1.4
PD01
PD02
PD03

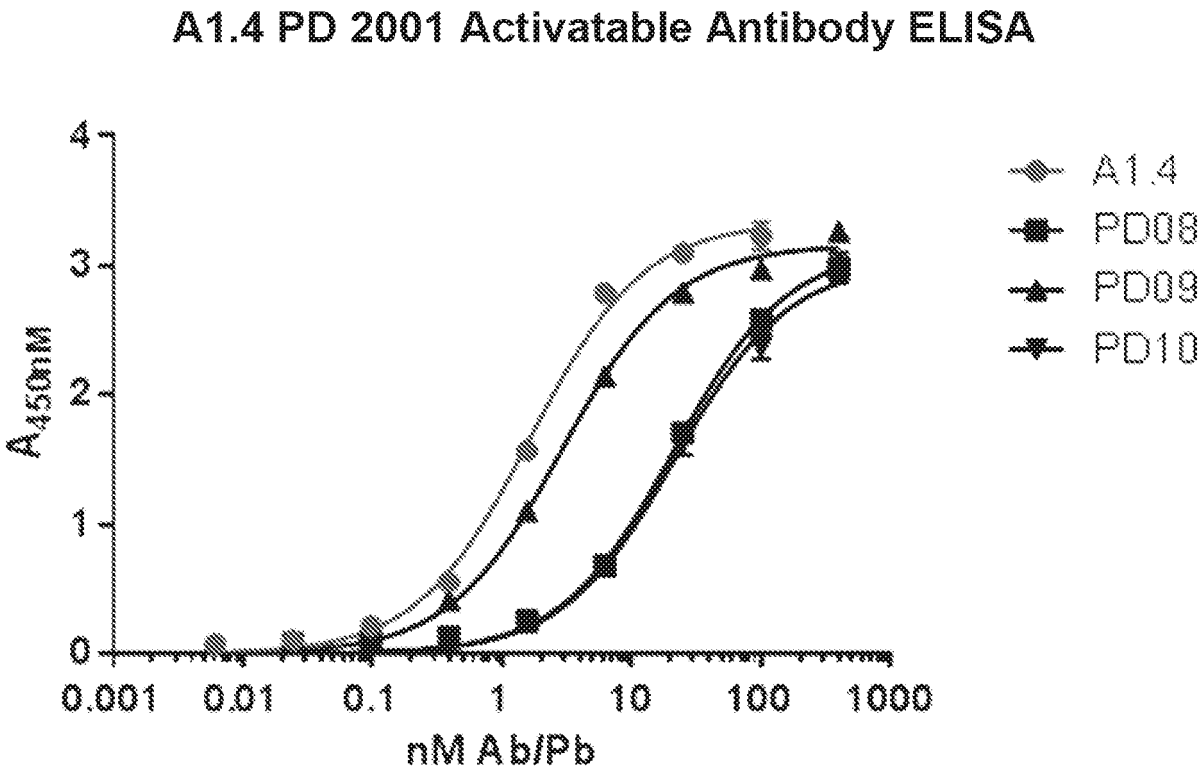
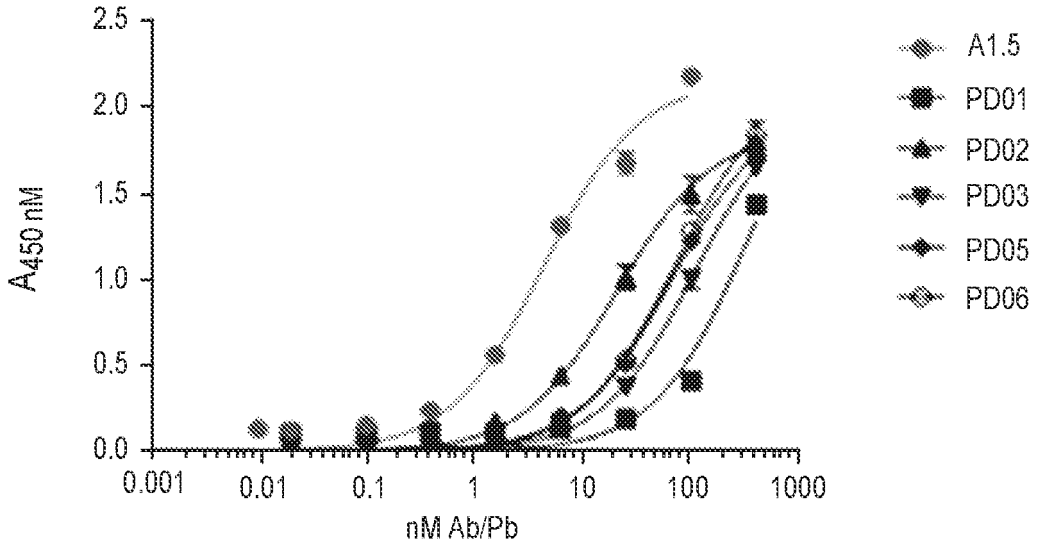

A1.4 PD 2001 Activatable Antibody ELISA
A450nM
nM Ab/Pb
0.001
0.01
0.1
1
10
100
1000
0
1
2
3
4
A1.4
PD08
PD09
PD10

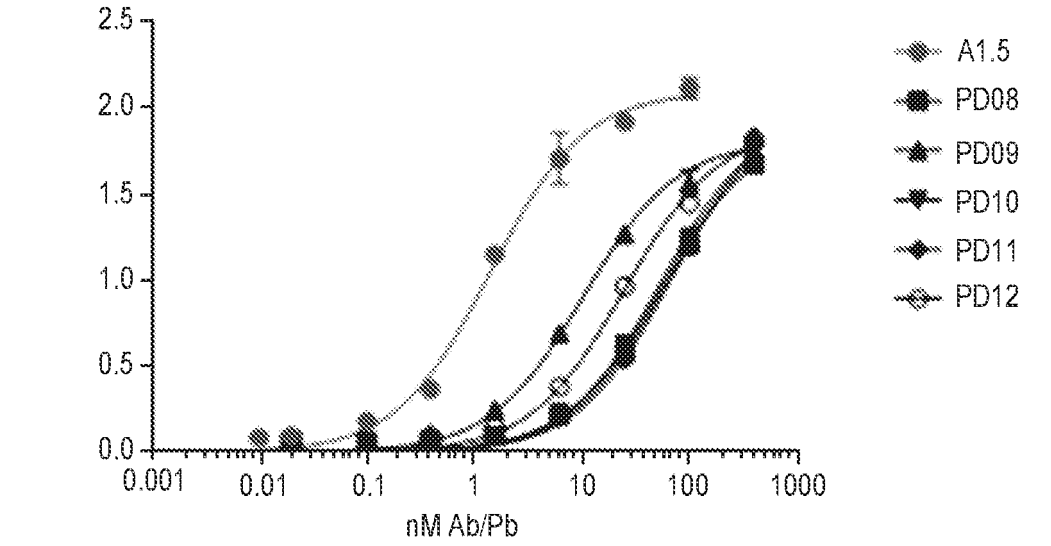
FIGURE 15

Plate 1



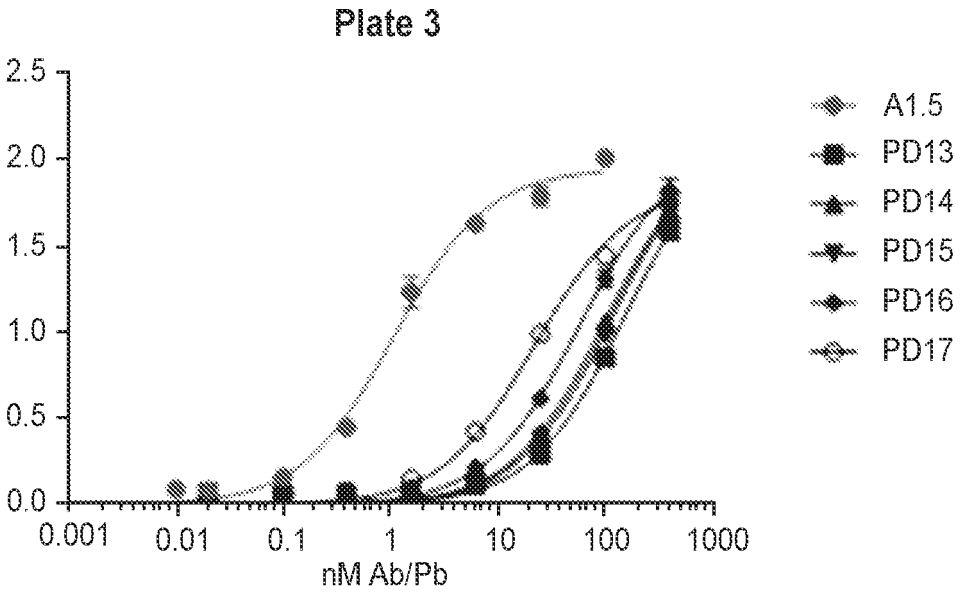
	A1.5	PD01	PD02	PD03	PD05	PD06
One site -- Specific binding		Hit constraint				
Best-fit values						
Bmax	2.145	-2.500	1.852	2.091	2.009	2.158
Kd	4.259	347.8	20.64	109.3	67.61	T1.01

Plate 2

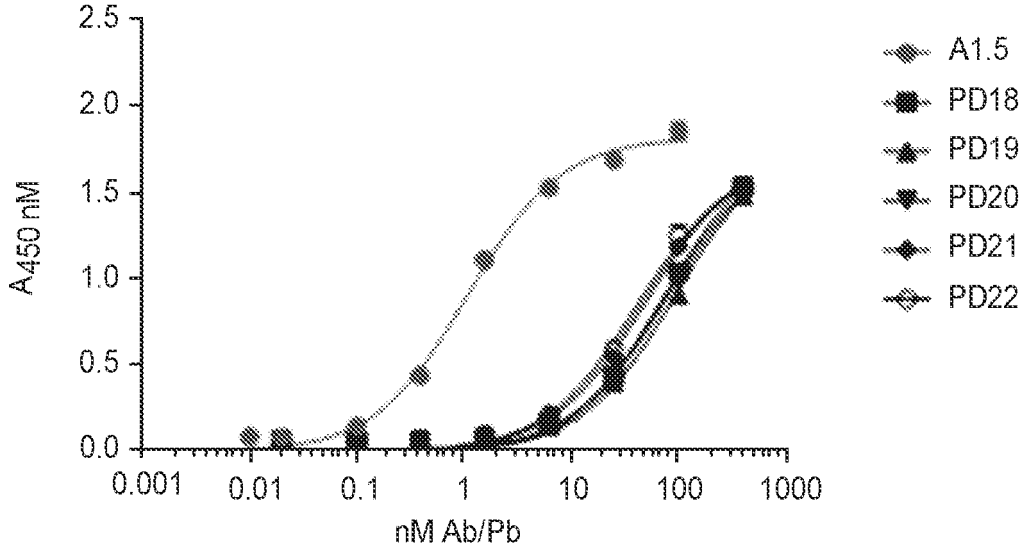


	A1.5	PD08	PD09	PD10	PD11	PD12
One site -- Specific binding						
Best-fit values						
Bmax	2.100	1.899	1.815	1.910	2.017	1.859
Kd	1.417	55.20	10.25	52.97	67.47	24.69

FIGURE 15, cont'd

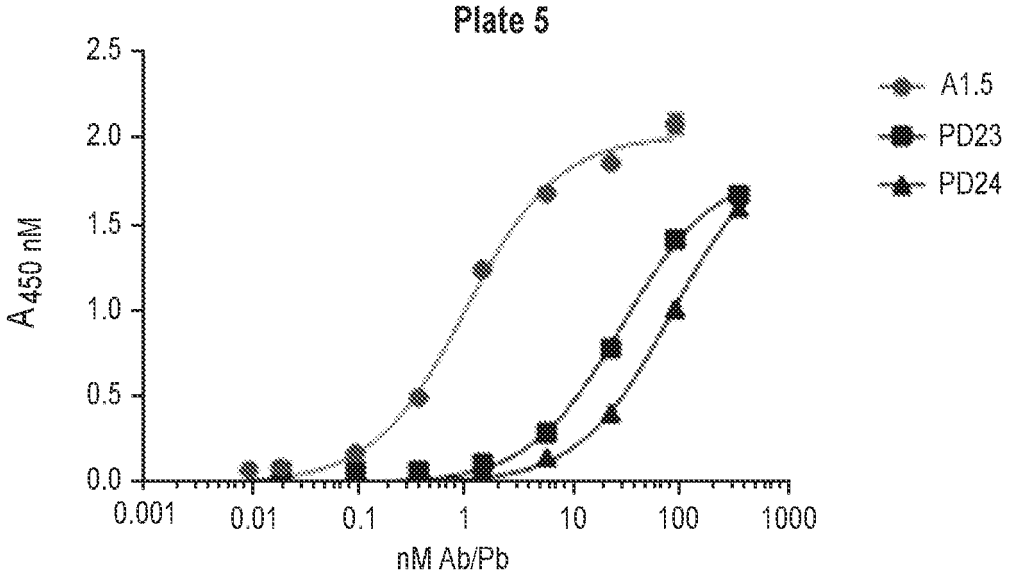


	A1.5	PD13	PD14	PD15	PD16	PD17
One site -- Specific binding		Hit constraint		Hit constraint		
Best-fit values						
Bmax	1.987	-2.200	2.162	-2.200	2.084	1.885
Kd	1.073	151.2	100.3	117.0	58.81	21.95



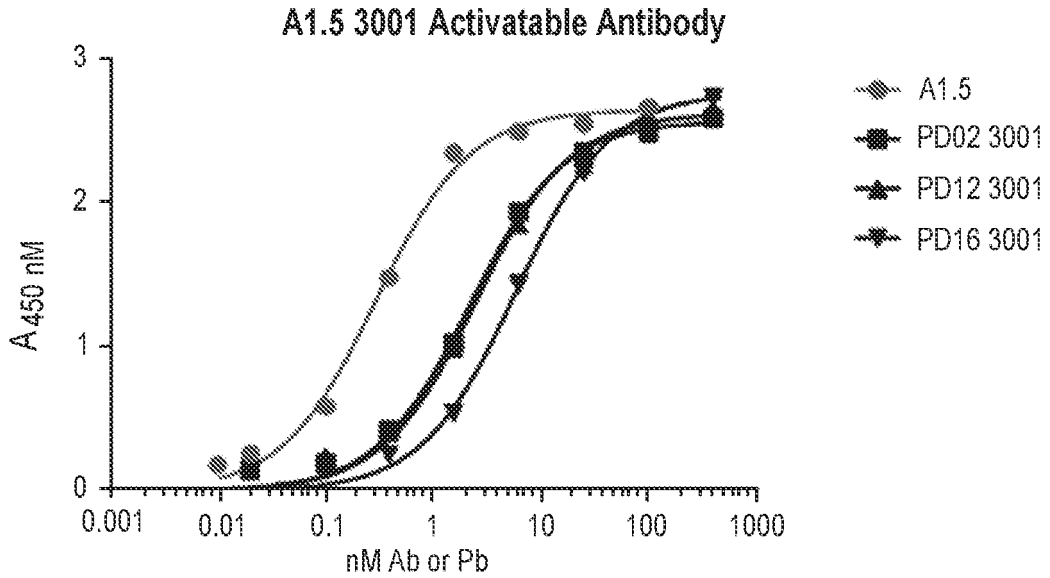
	A1.5	PD18	PD19	PD20	PD21	PD22
One site -- Specific binding						
Best-fit values						
Bmax	1.839	1.844	1.837	1.802	1.750	1.720
Kd	1.087	75.12	93.27	77.46	48.96	41.33

FIGURE 15, cont'd



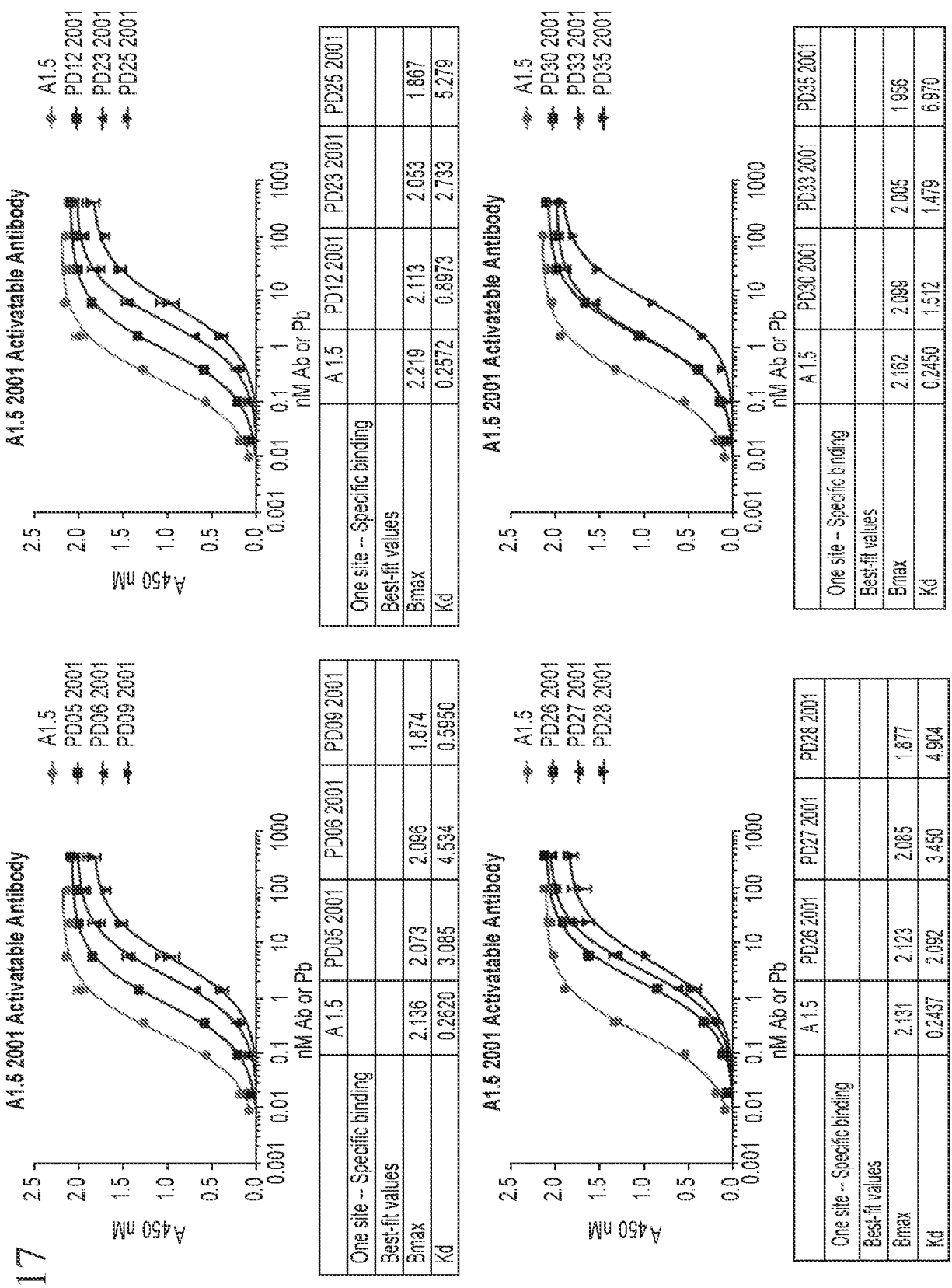
	A 1.5	PD23	PD24
One site -- Specific binding			
Best-fit values			
Bmax	2.049	1.847	1.993
Kd	1.086	31.37	92.42

FIGURE 16



	A 1.5	PD02 3001	PD12 3001	PD16 3001
One site -- Specific binding				
Best-fit values				
Bmax	2.660	2.580	2.632	2.777
Kd	0.2938	2.160	2.483	5.874

FIGURE 17



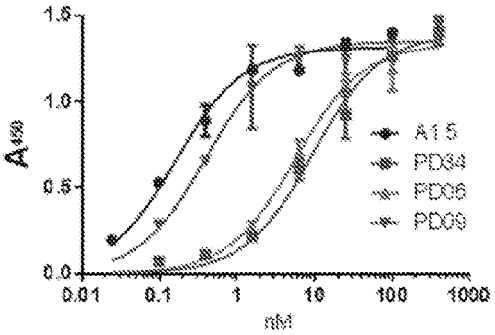
	A1.5	PD05 2001	PD06 2001	PD09 2001
One site -- Specific binding				
Best-fit values				
Bmax	2.136	2.073	2.096	1.874
Kd	0.2620	3.085	4.534	0.5950

	A1.5	PD12 2001	PD23 2001	PD25 2001
One site -- Specific binding				
Best-fit values				
Bmax	2.219	2.113	2.053	1.867
Kd	0.2572	0.8973	2.733	5.279

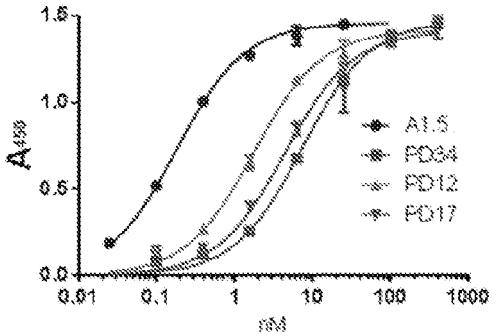
	A1.5	PD26 2001	PD27 2001	PD28 2001
One site -- Specific binding				
Best-fit values				
Bmax	2.131	2.123	2.085	1.877
Kd	0.2437	2.092	3.450	4.904

	A1.5	PD30 2001	PD33 2001	PD35 2001
One site -- Specific binding				
Best-fit values				
Bmax	2.162	2.089	2.005	1.956
Kd	0.2450	1.512	1.479	6.970

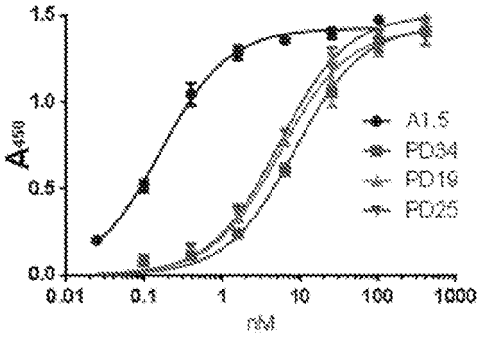
FIGURE 18



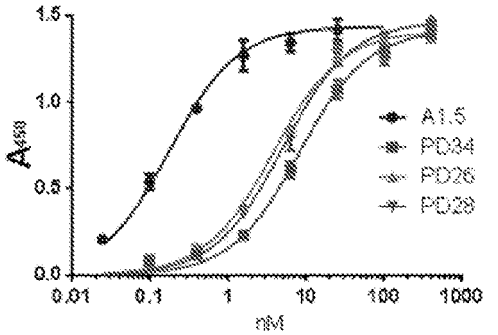
	A1.5	PD34	PD06	PD09
Kd	0.1620	9.372	5.663	0.3990



	A1.5	PD34	PD12	PD17
Kd	0.1803	7.297	1.738	4.364



	A1.5	PD34	PD19	PD25
Kd	0.1595	8.401	5.449	5.224



	A1.5	PD34	PD26	PD29
Kd	0.1762	8.123	3.754	4.970

FIGURE 19

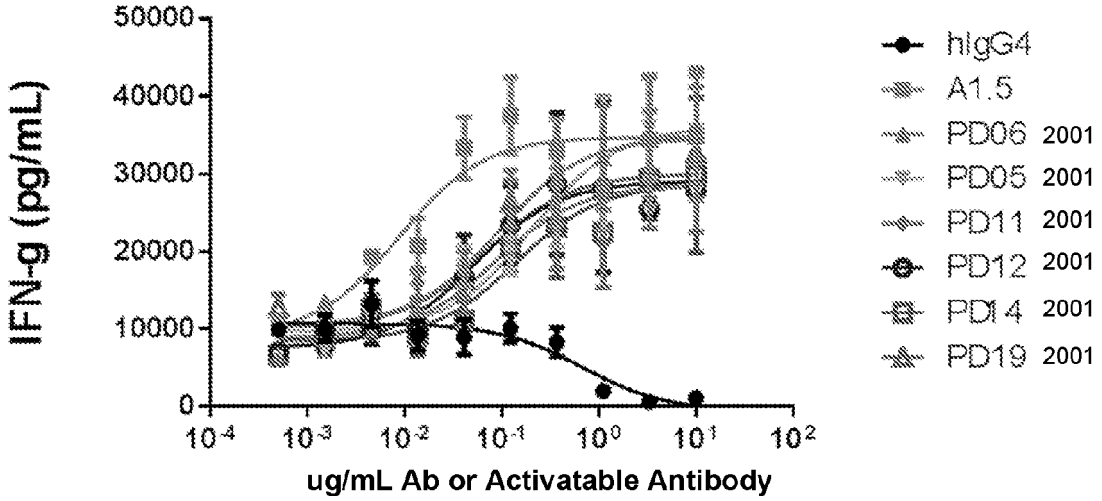
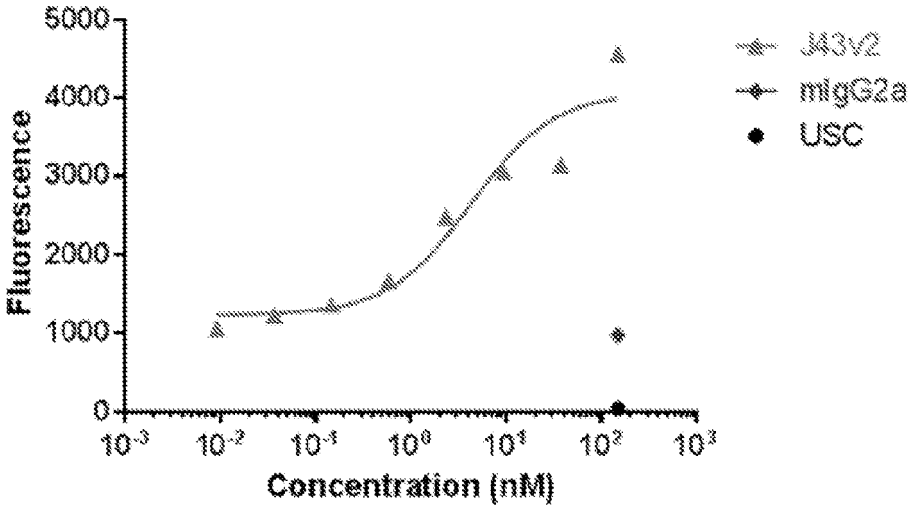


FIGURE 20A

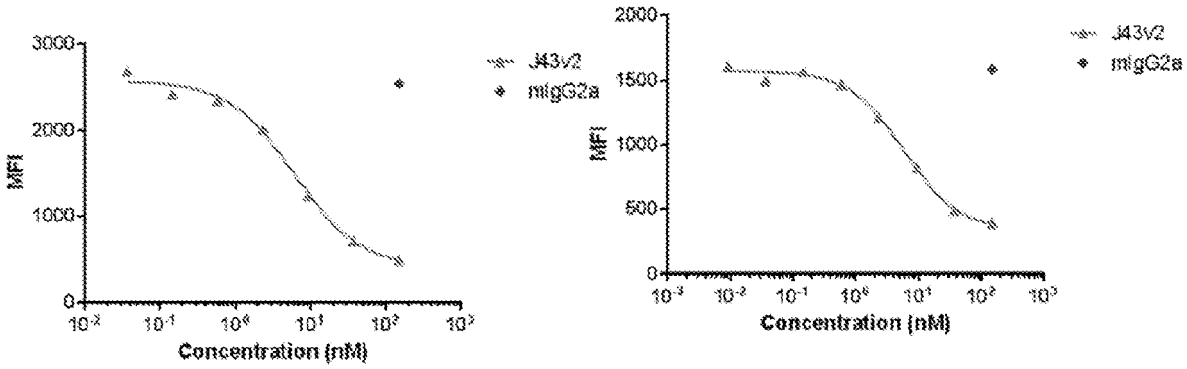
Binding:



Binding EC50 (nM)
J43v2
4.308

FIGURE 20B

Blocking:



	Blocking EC50 (nM)
	J43v2
biotin-mPD-L1	6.057
biotin-mPD-L2	5.899

FIGURE 21

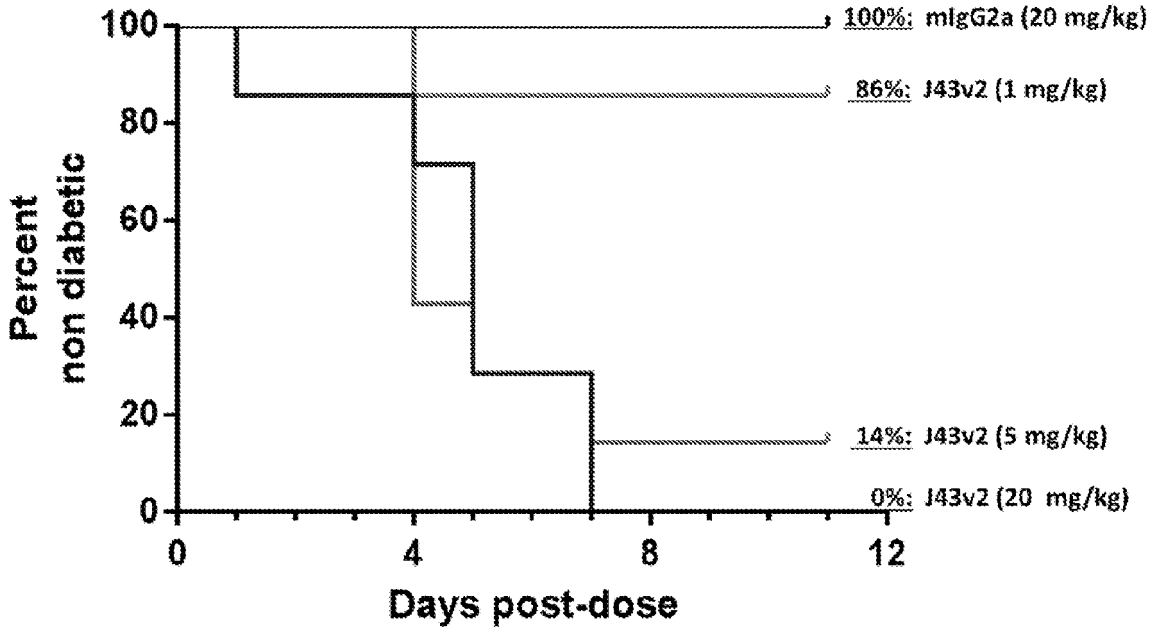


FIGURE 22

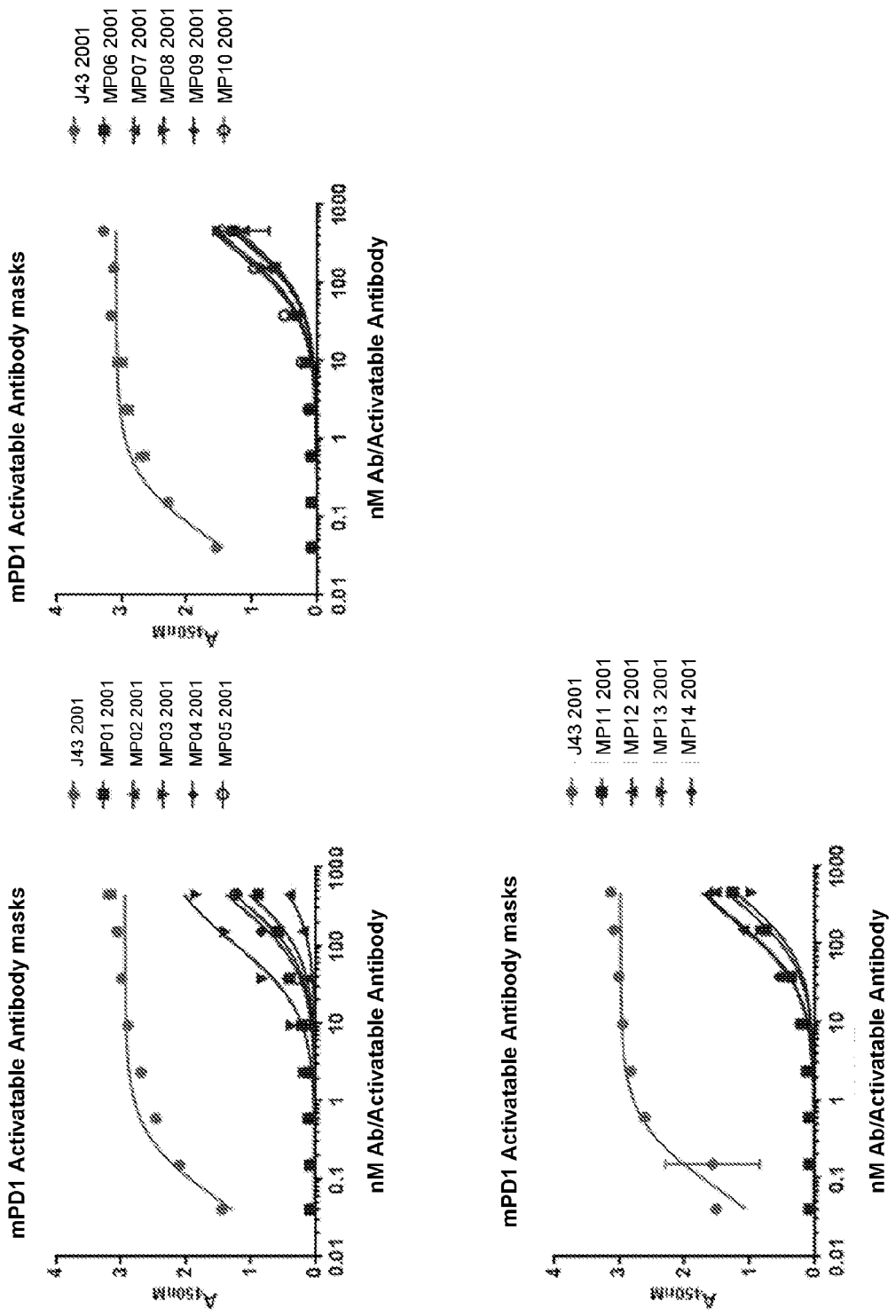
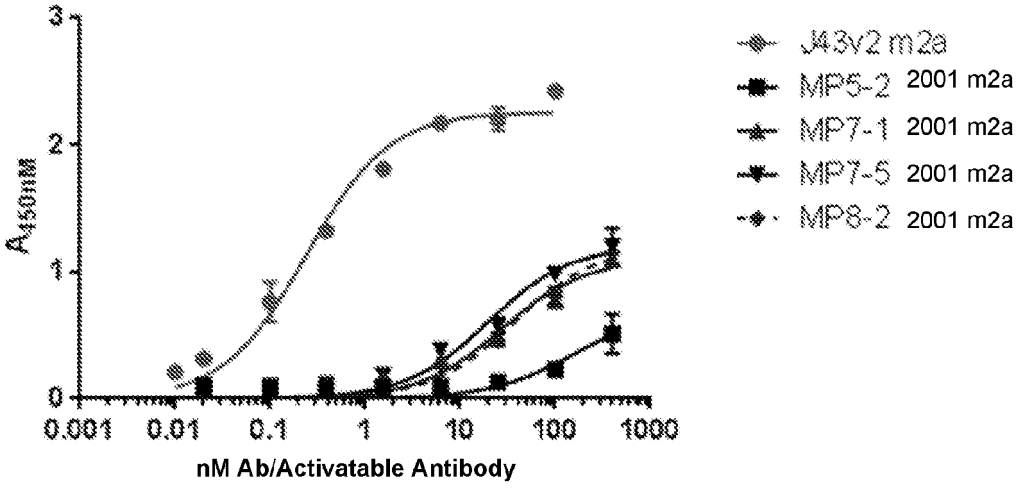

mPD1 Activatable Antibody masks
J43 2001
MP01 2001
MP02 2001
MP03 2001
MP04 2001
MP05 2001
nM Ab/Activatable Antibody
mPD1 Activatable Antibody masks
J43 2001
MP06 2001
MP07 2001
MP08 2001
MP09 2001
MP10 2001
nM Ab/Activatable Antibody
mPD1 Activatable Antibody masks
J43 2001
MP11 2001
MP12 2001
MP13 2001
MP14 2001
nM Ab/Activatable Antibody

FIGURE 23



J43 MP 2001 Activatable Antibody ELISA

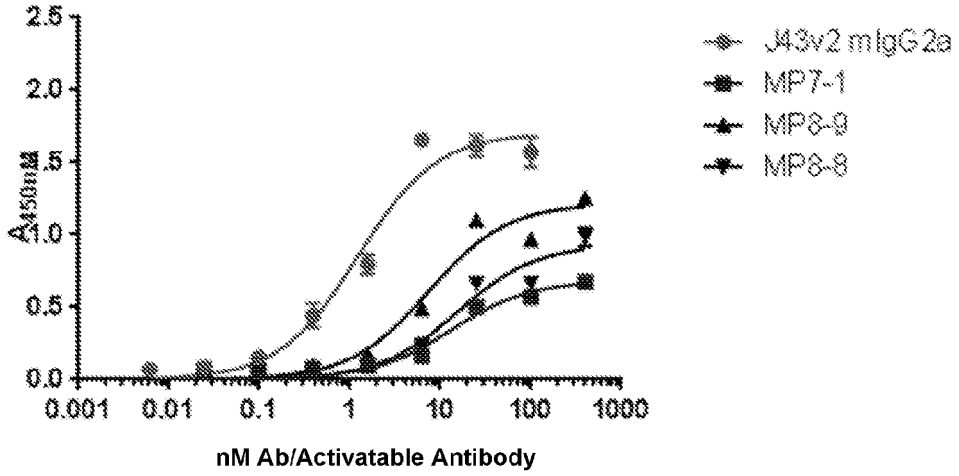


FIGURE 24

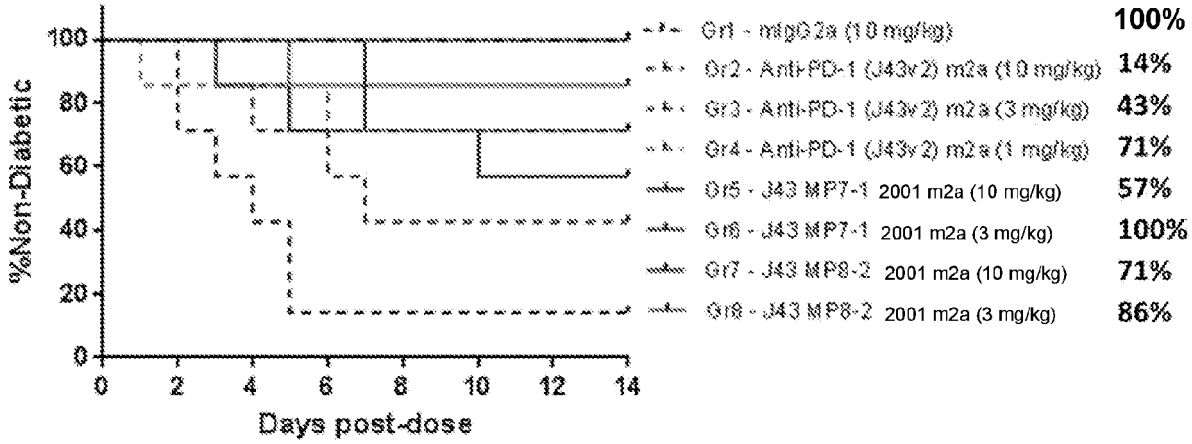


FIGURE 25A

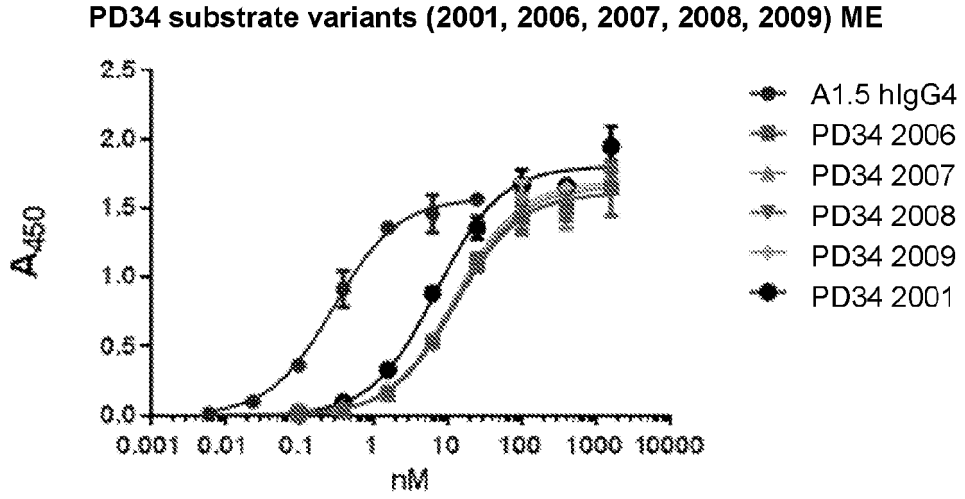


FIGURE 25B

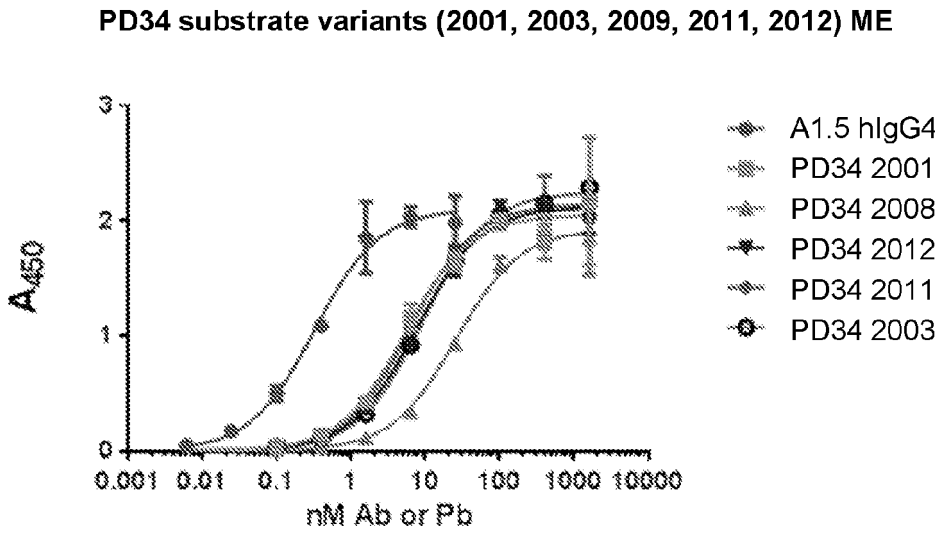

PD34 substrate variants (2001, 2003, 2009, 2011, 2012) ME
A450
0
1
2
3
0.001
0.01
0.1
1
10
100
1000
10000
nM Ab or Pb
A1.5 hIgG4
PD34 2001
PD34 2008
PD34 2012
PD34 2011
PD34 2003

FIGURE 26A

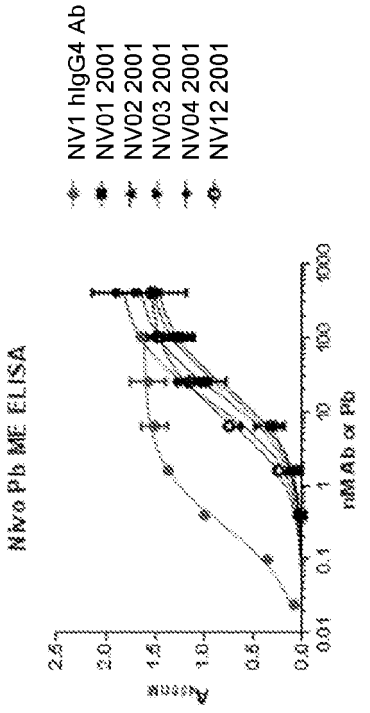


FIGURE 26B

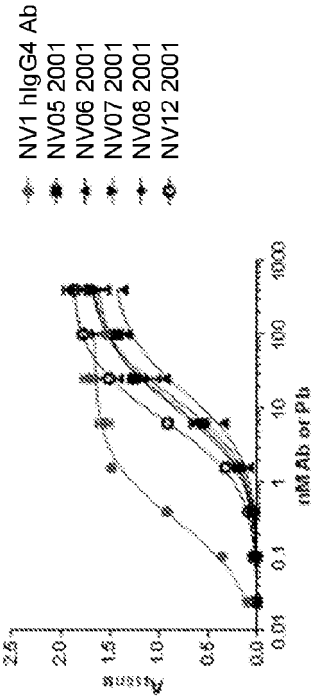


FIGURE 26C

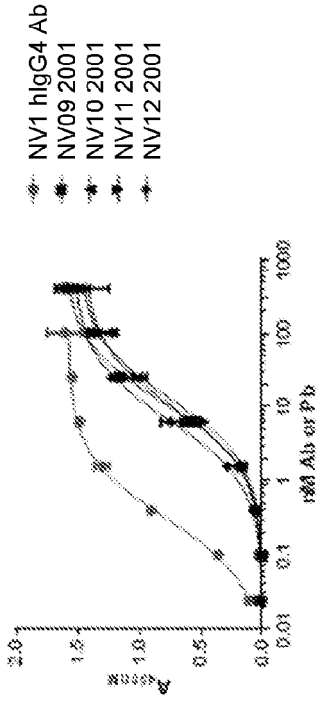


FIGURE 27A

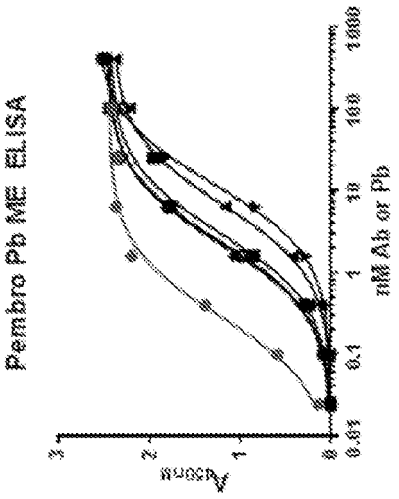


FIGURE 27B

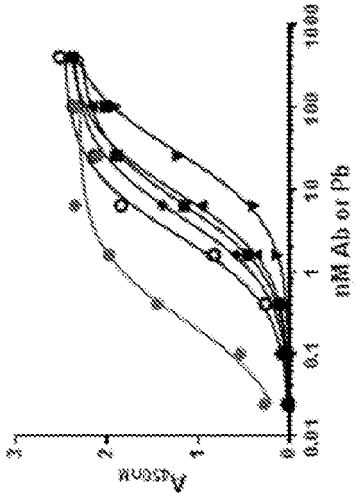


FIGURE 27C

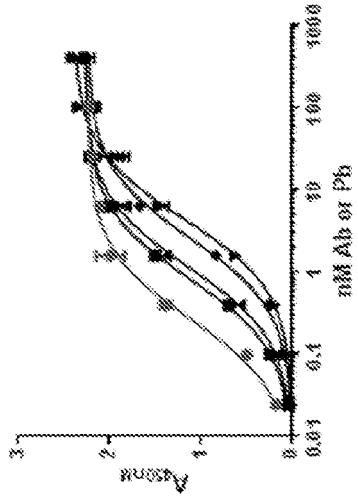


FIGURE 28

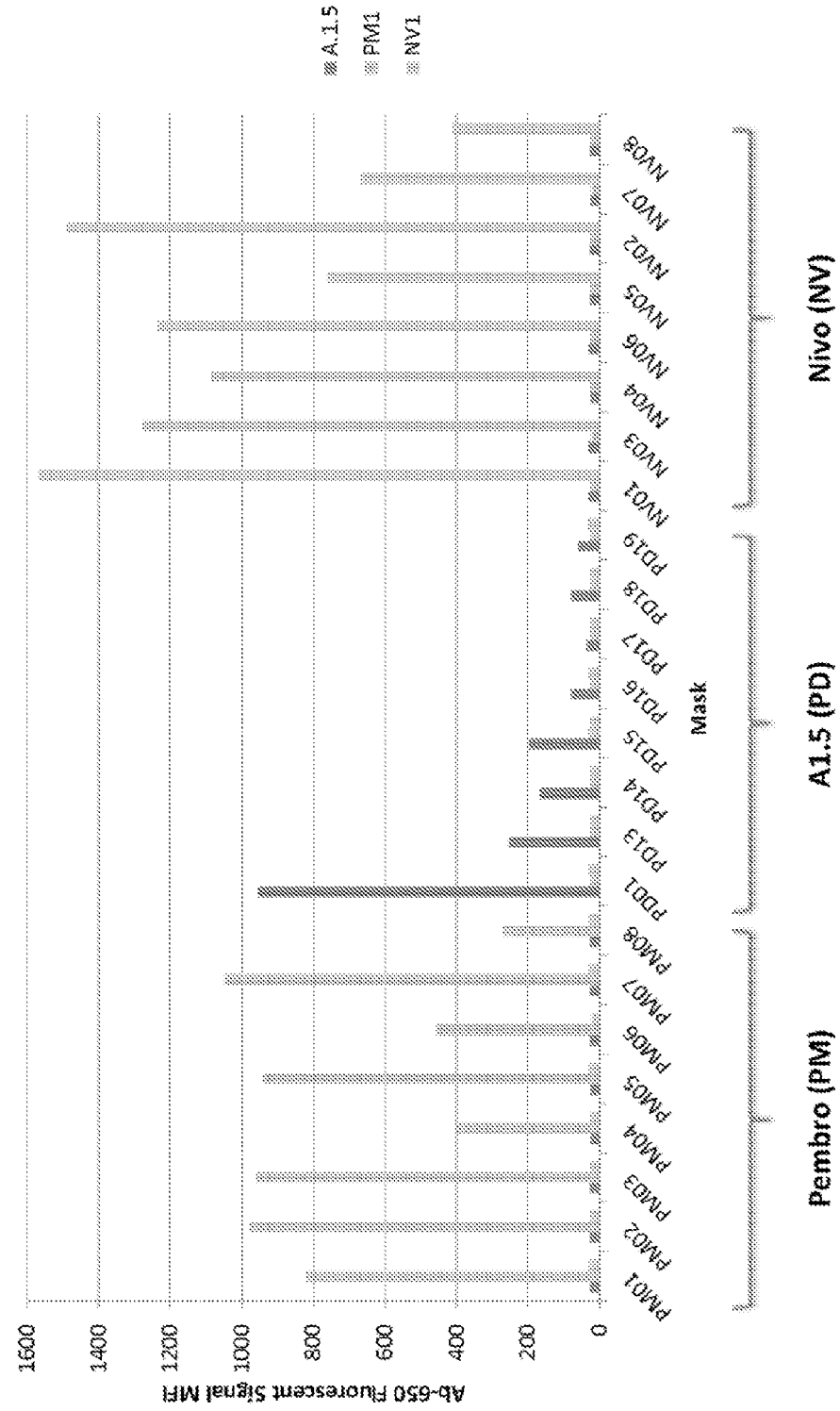

A.1.5
PM1
NV1
Ab-650 Fluorescent Signal MFI
1600
1400
1200
1000
800
600
400
200
0
Mask
PM01
PM02
PM03
PM04
PM05
PM06
PM07
PM08
PD01
PD13
PD14
PD15
PD16
PD17
PD18
PD19
NV01
NV03
NV04
NV06
NV05
NV02
NV07
NV08
Pembro (PM)
A1.5 (PD)
Nivo (NV)

FIGURE 29A

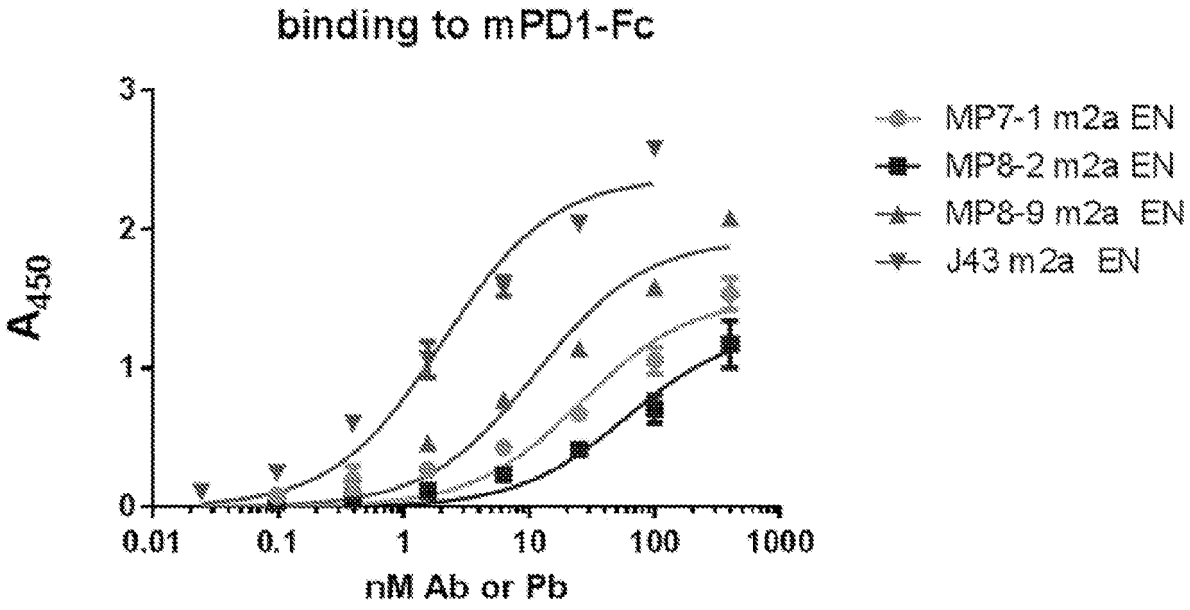


FIGURE 29B

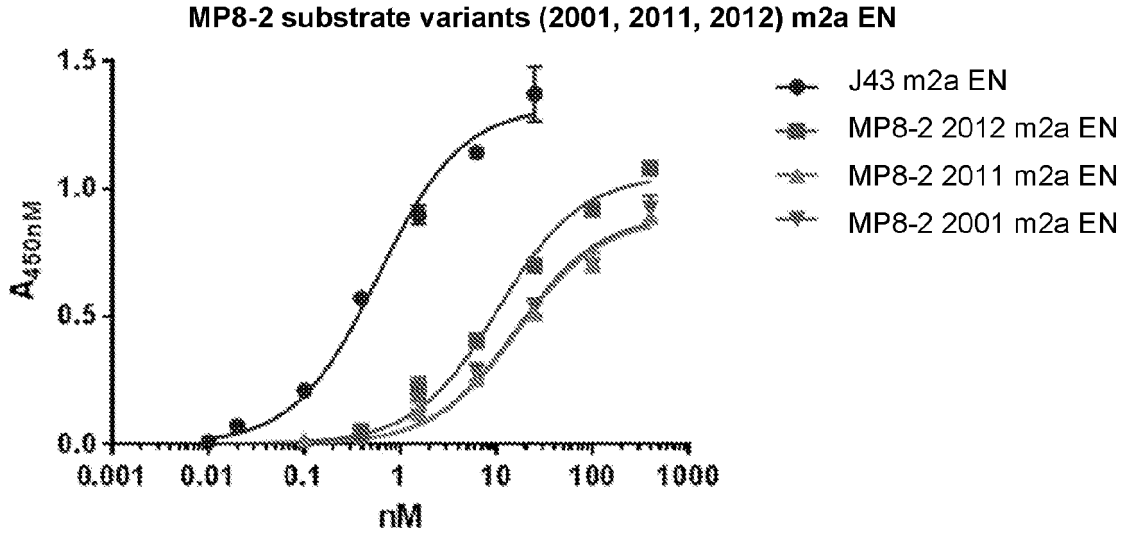


FIGURE 30

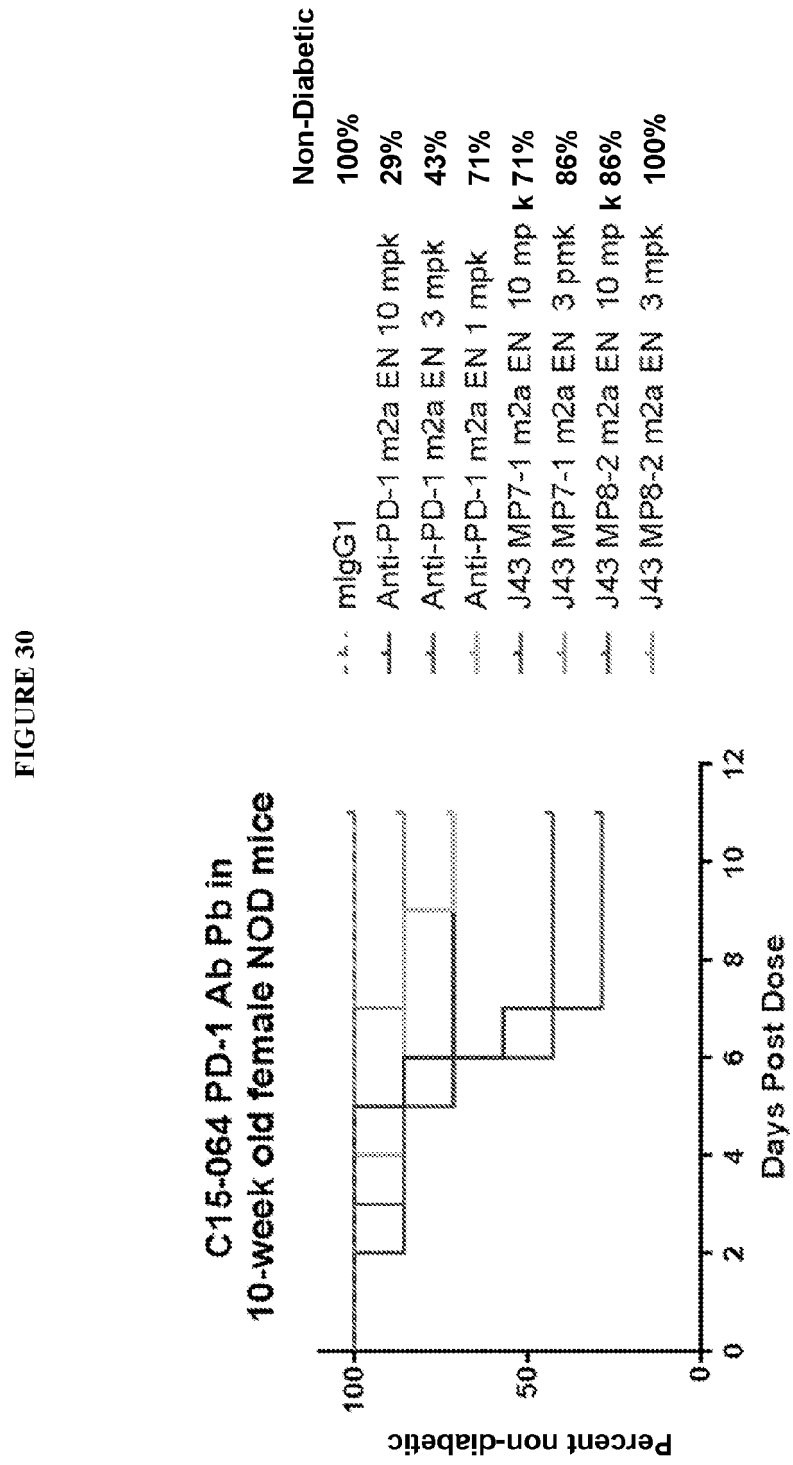

C15-064 PD-1 Ab Pb in
10-week old female NOD mice
Non-Diabetic
mIgG1 100%
Anti-PD-1 m2a EN 10 mpk 29%
Anti-PD-1 m2a EN 3 mpk 43%
Anti-PD-1 m2a EN 1 mpk 71%
J43 MP7-1 m2a EN 10 mpk 71%
J43 MP7-1 m2a EN 3 pmk 86%
J43 MP8-2 m2a EN 10 mpk 86%
J43 MP8-2 m2a EN 3 mpk 100%
Percent non-diabetic
100
50
0
0
2
4
6
8
10
12
Days Post Dose

FIGURE 31A

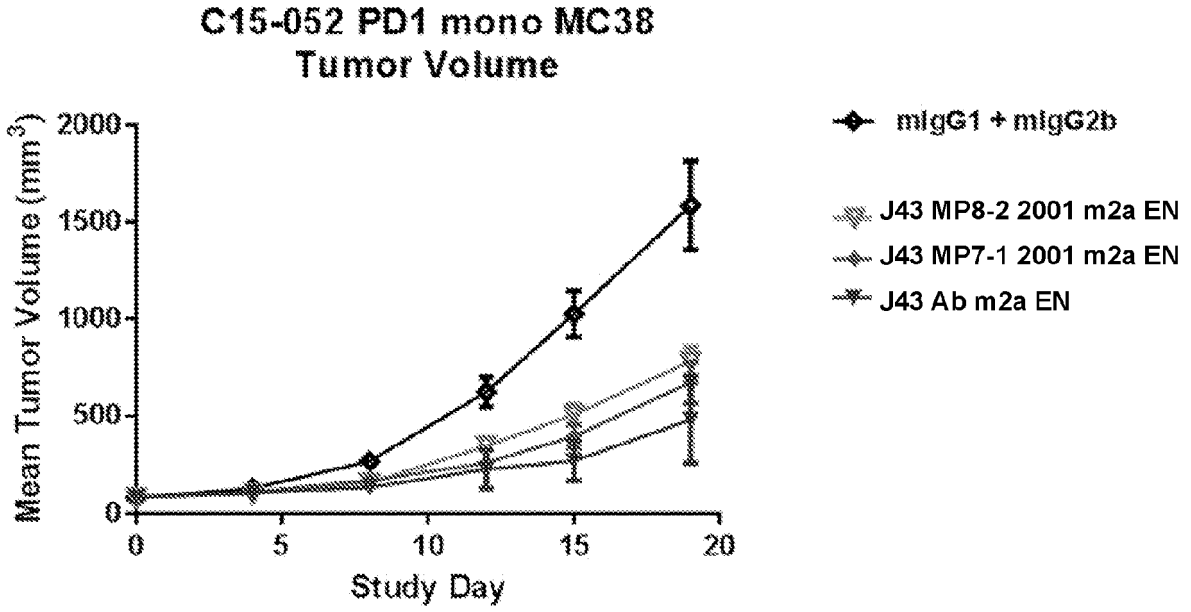


FIGURE 31B

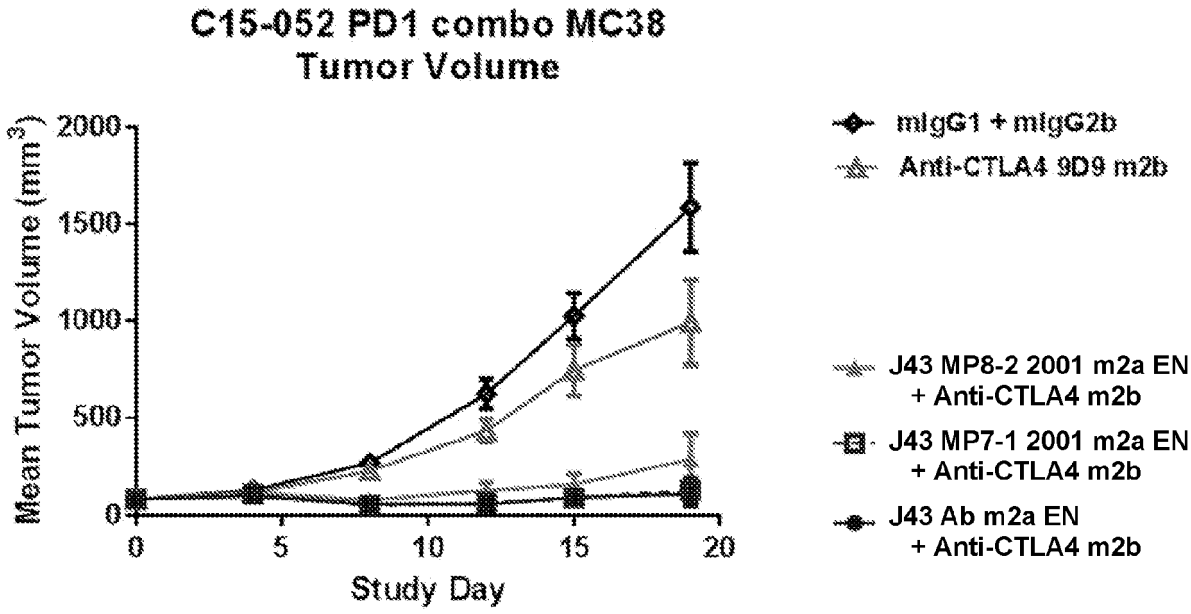


FIGURE 32A

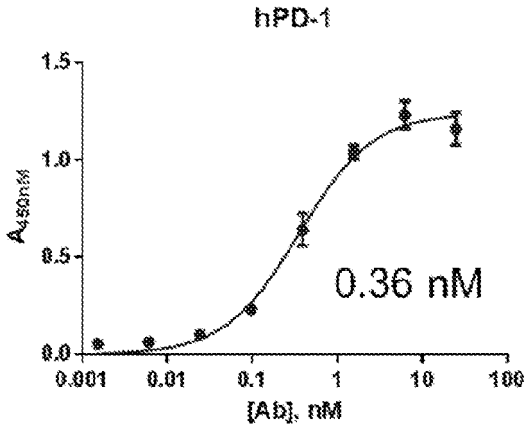


FIGURE 32B

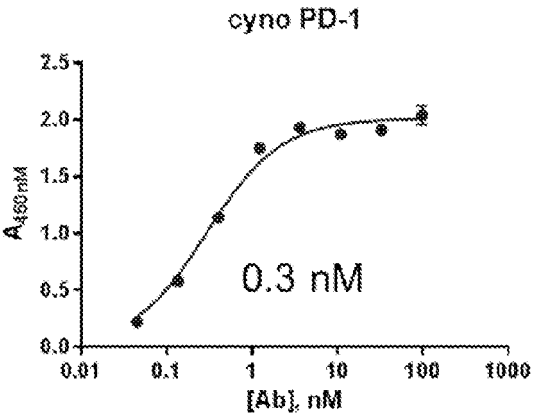


FIGURE 32C

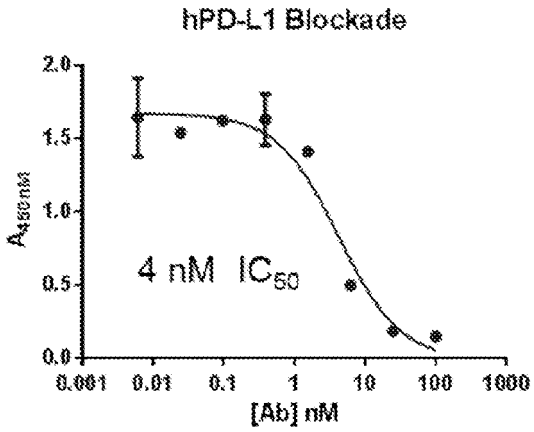


FIGURE 32D

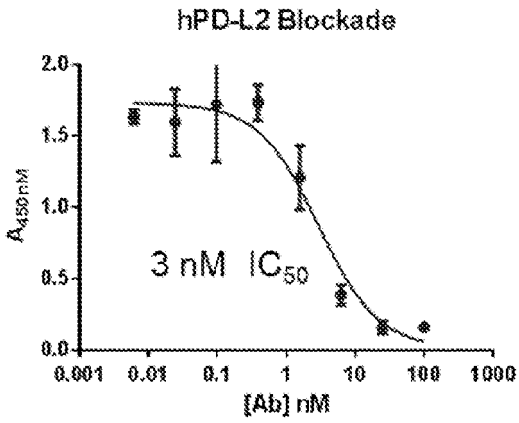


FIGURE 32E

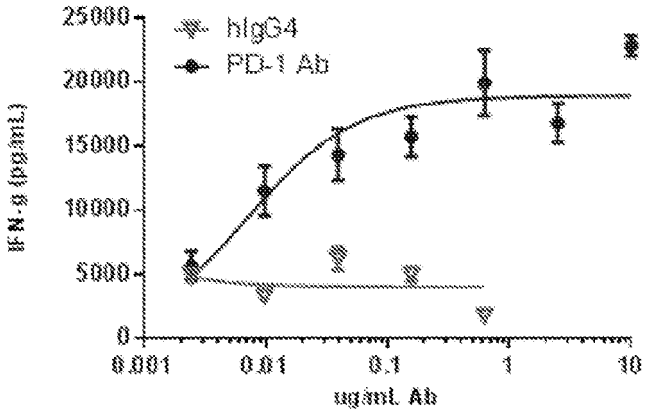


FIGURE 33A

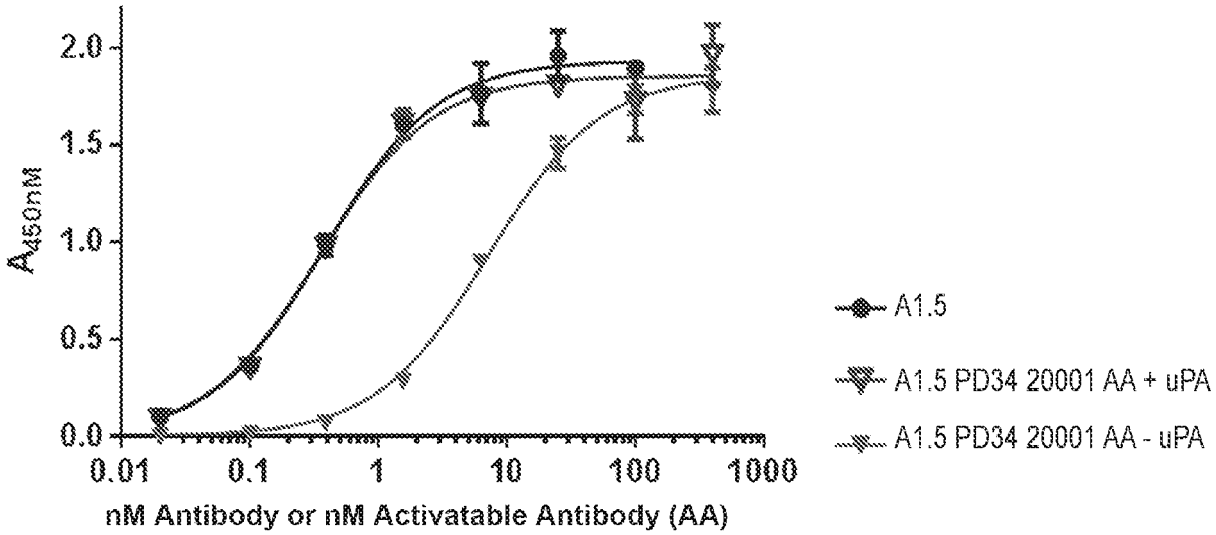


FIGURE 33B

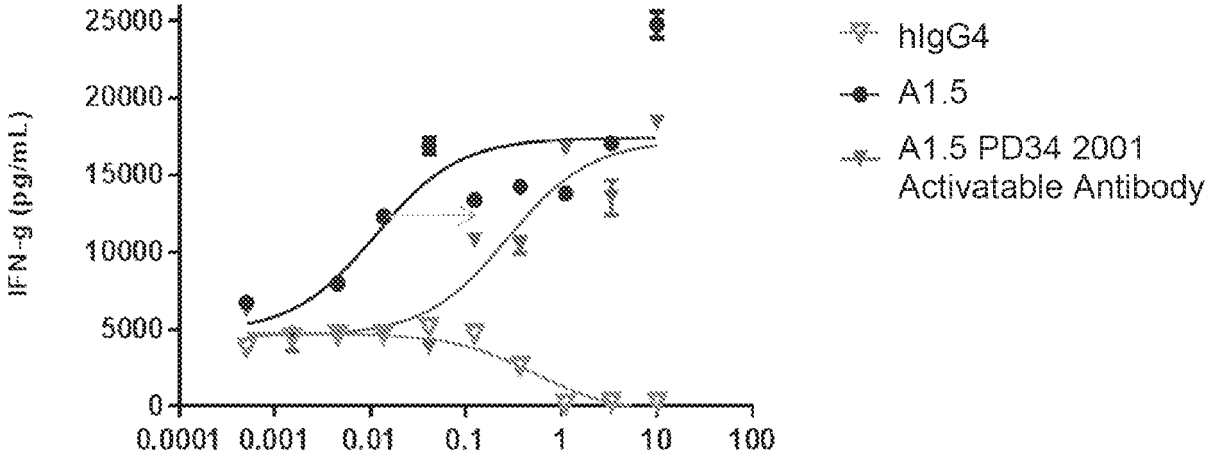
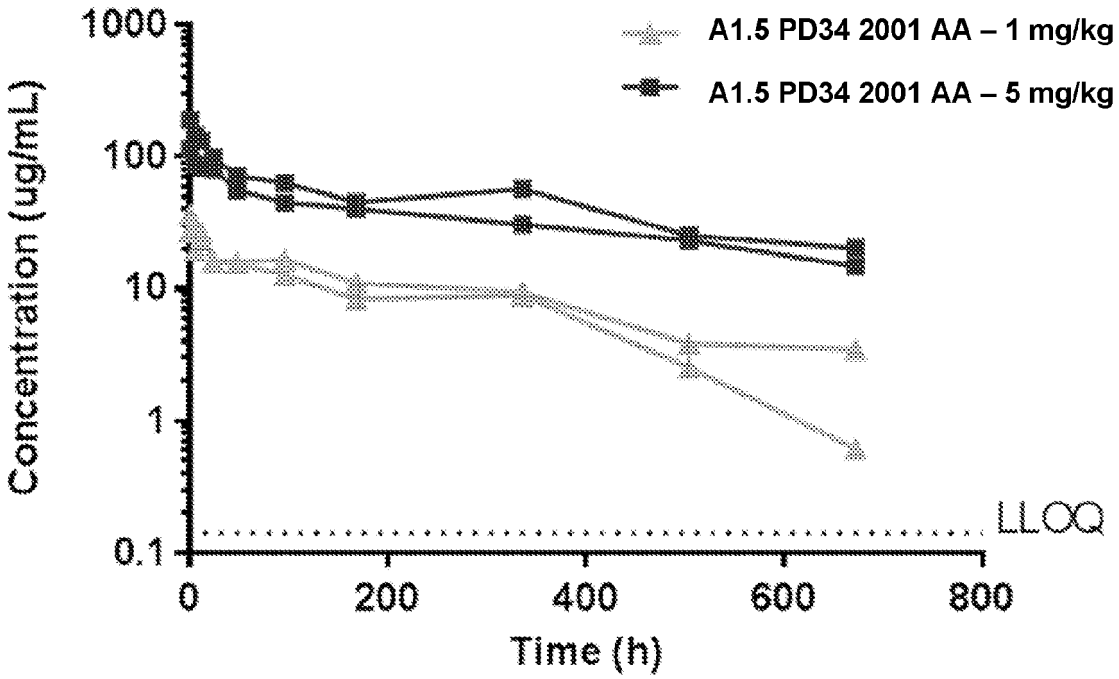


FIGURE 34



Test Article	Dose (mg/kg)	$t_{1/2}$ (days)	C_{max} (ug/mL)	AUC_{last} (day*ug/mL)
A1.5 PD34 2001 Activatable Antibody	1	8.5	32.1	228.8
	5	14.1	153.1	1132.2
A1.5 Antibody	1	8.3	34.1	184.1
	5	8.7	150.8	544.0

FIGURE 35

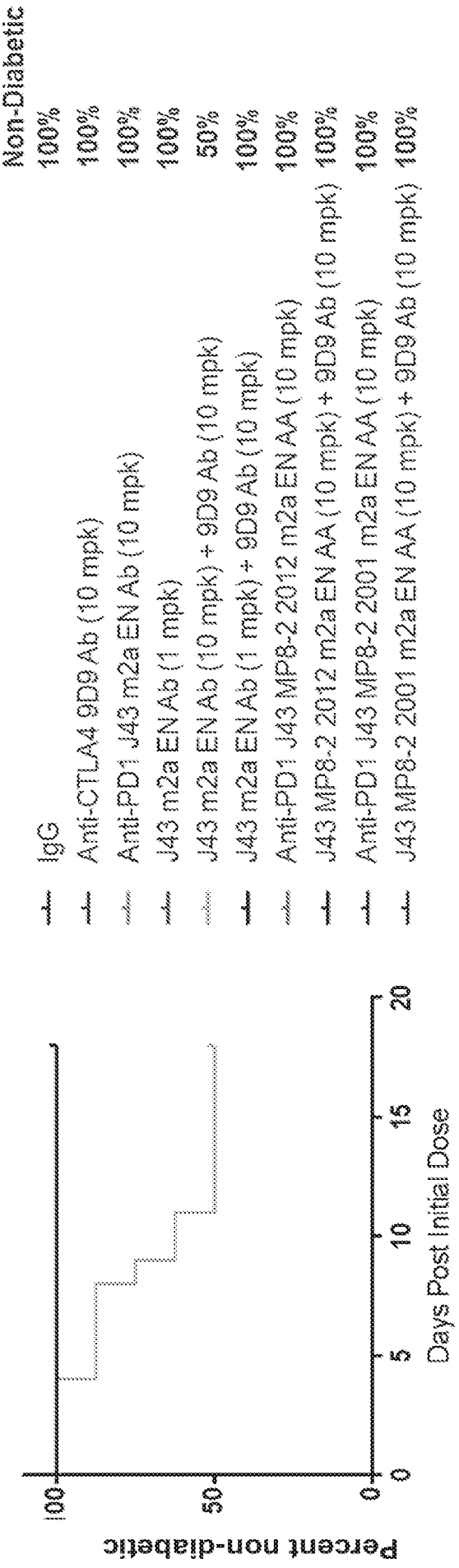

Non-Diabetic
IgG 100%
Anti-CTLA4 9D9 Ab (10 mpk) 100%
Anti-PD1 J43 m2a EN Ab (10 mpk) 100%
J43 m2a EN Ab (1 mpk) 100%
J43 m2a EN Ab (10 mpk) + 9D9 Ab (10 mpk) 50%
J43 m2a EN Ab (1 mpk) + 9D9 Ab (10 mpk) 100%
Anti-PD1 J43 MP8-2 2012 m2a EN AA (10 mpk) 100%
J43 MP8-2 2012 m2a EN AA (10 mpk) + 9D9 Ab (10 mpk) 100%
Anti-PD1 J43 MP8-2 2001 m2a EN AA (10 mpk) 100%
J43 MP8-2 2001 m2a EN AA (10 mpk) + 9D9 Ab (10 mpk) 100%
Percent non-diabetic
100
50
0
0
5
10
15
20
Days Post Initial Dose

FIGURE 36

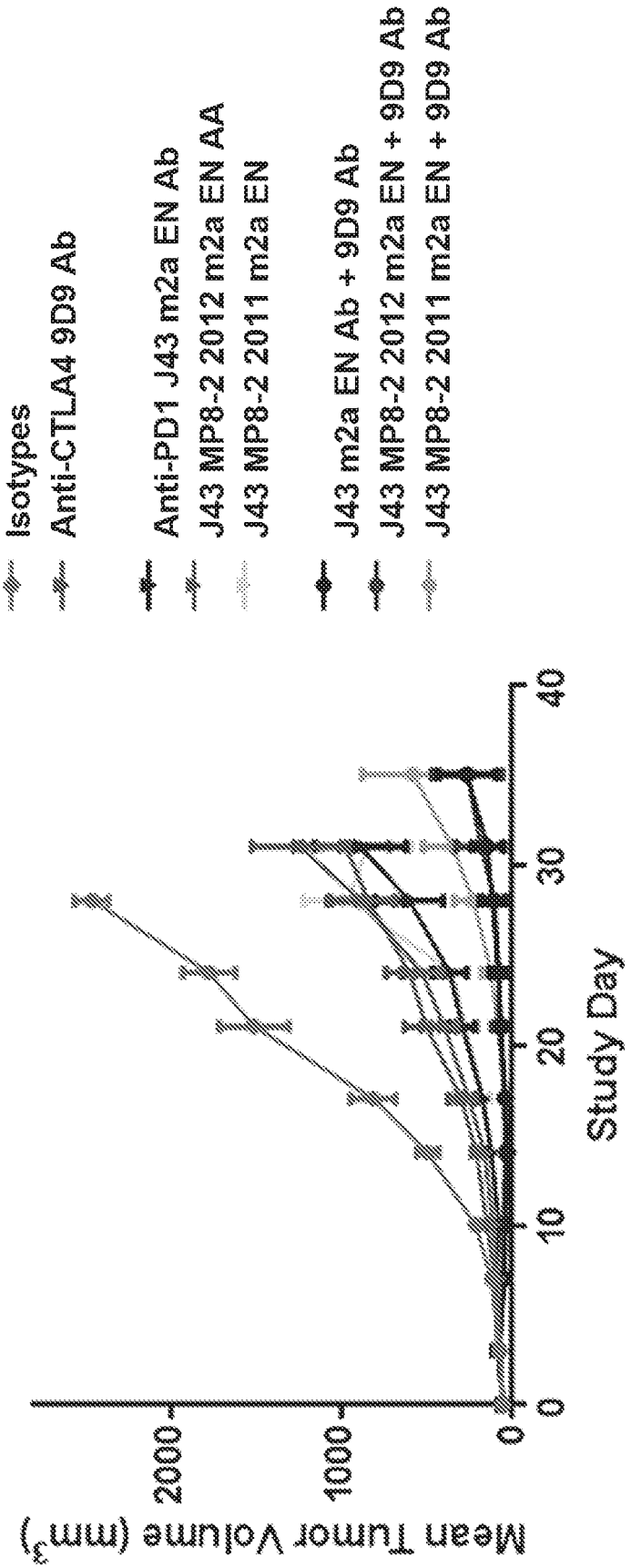

Isotypes
Anti-CTLA4 9D9 Ab
Anti-PD1 J43 m2a EN Ab
J43 MP8-2 2012 m2a EN AA
J43 MP8-2 2011 m2a EN
J43 m2a EN Ab + 9D9 Ab
J43 MP8-2 2012 m2a EN + 9D9 Ab
J43 MP8-2 2011 m2a EN + 9D9 Ab
Mean Tumor Volume (mm3)
2000
1000
0
0
10
20
30
40
Study Day

FIGURE 37

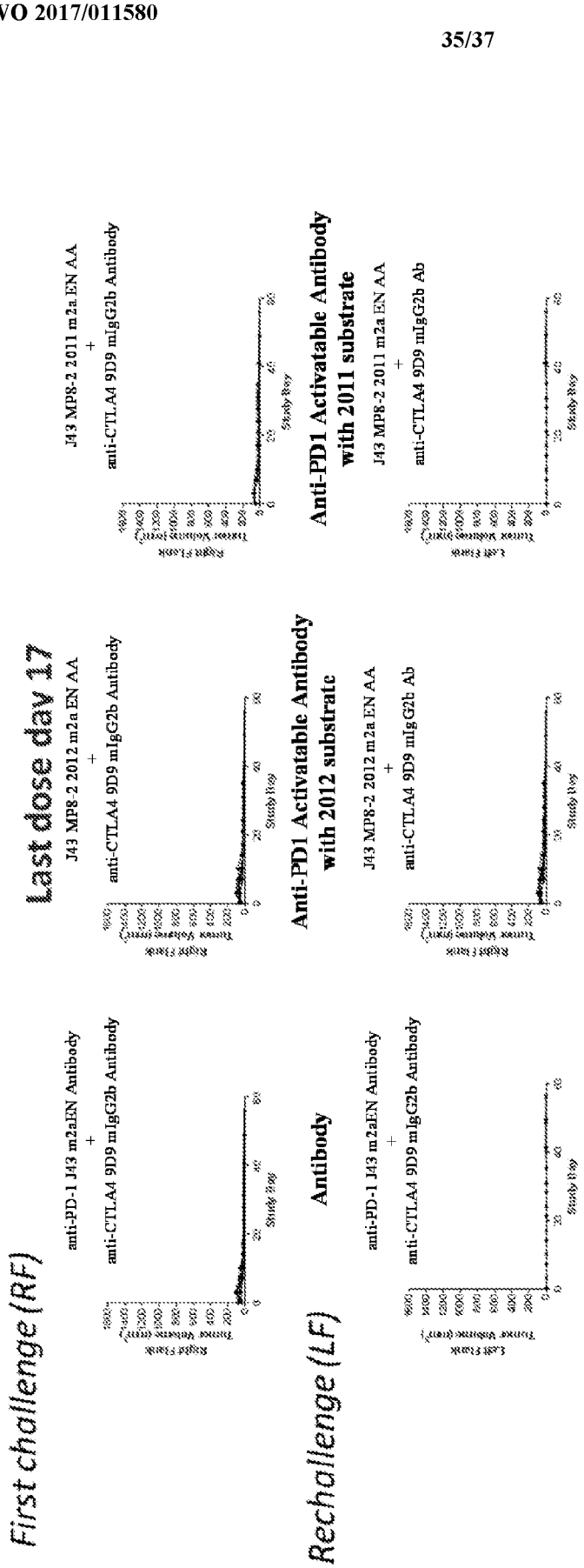

First challenge (RF)
Last dose day 17
J43 MP8-2 2012 m2a EN AA
+
anti-CTLA4 9D9 mIgG2b Antibody
J43 MP8-2 2011 m2a EN AA
+
anti-CTLA4 9D9 mIgG2b Antibody
anti-PD-1 J43 m2aEN Antibody
+
anti-CTLA4 9D9 mIgG2b Antibody
Rechallenge (LF)
Antibody
Anti-PD1 Activatable Antibody with 2012 substrate
Anti-PD1 Activatable Antibody with 2011 substrate
J43 MP8-2 2012 m2a EN AA
+
anti-CTLA4 9D9 mIgG2b Ab
J43 MP8-2 2011 m2a EN AA
+
anti-CTLA4 9D9 mIgG2b Ab
Rechallenge MC38 activity control
Control - Untreated
Study Day

FIGURE 38

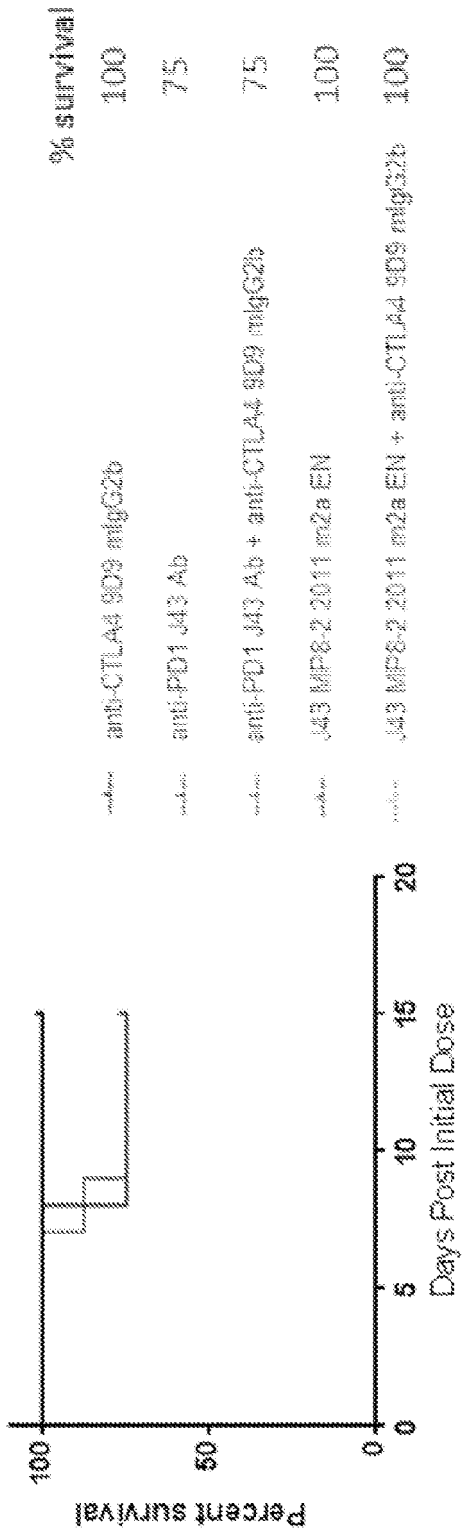

% survival
anti-CTLA4 9D9 mIgG2b 100
anti-PD1 J43 Ab 75
anti-PD1 J43 Ab + anti-CTLA4 9D9 mIgG2b 75
J43 MP8-2 2011 m2a EN 100
J43 MP8-2 2011 m2a EN + anti-CTLA4 9D9 mIgG2b 100
Percent survival
100
50
0
0
5
10
15
20
Days Post Initial Dose

FIGURE 39

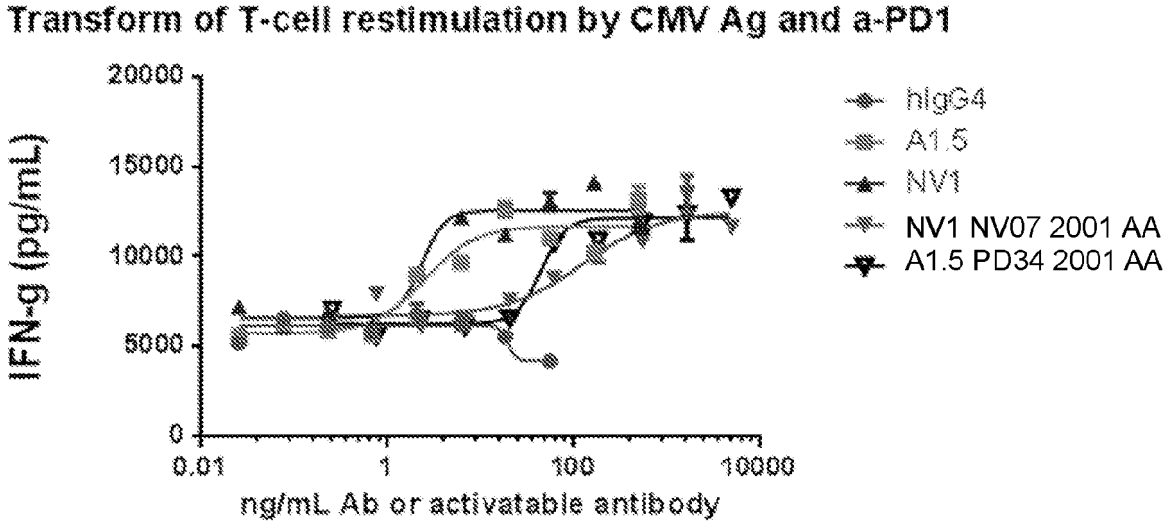
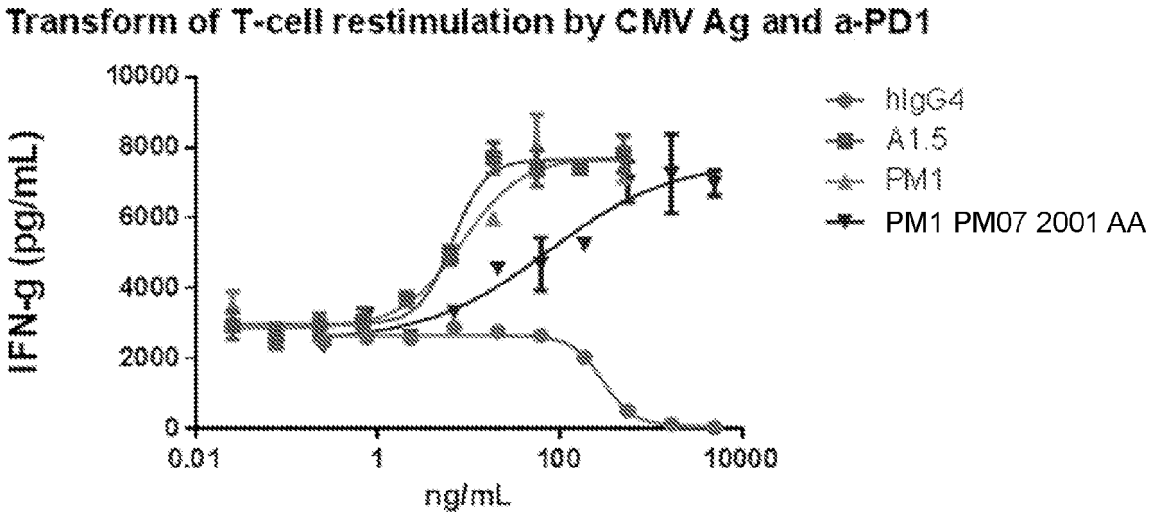



FIGURE 40