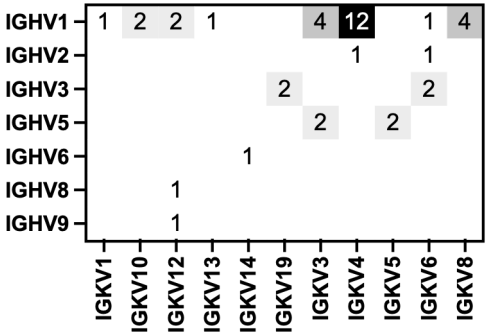
Figure S1

a


IGHV1
IGHV2
IGHV3
IGHV5
IGHV6
IGHV8
IGHV9
1 2 2 1 4 12 1 4
1 1
2 2
2 2
1
1
1
IGKV1
IGKV10
IGKV12
IGKV13
IGKV14
IGKV19
IGKV3
IGKV4
IGKV5
IGKV6
IGKV8

b

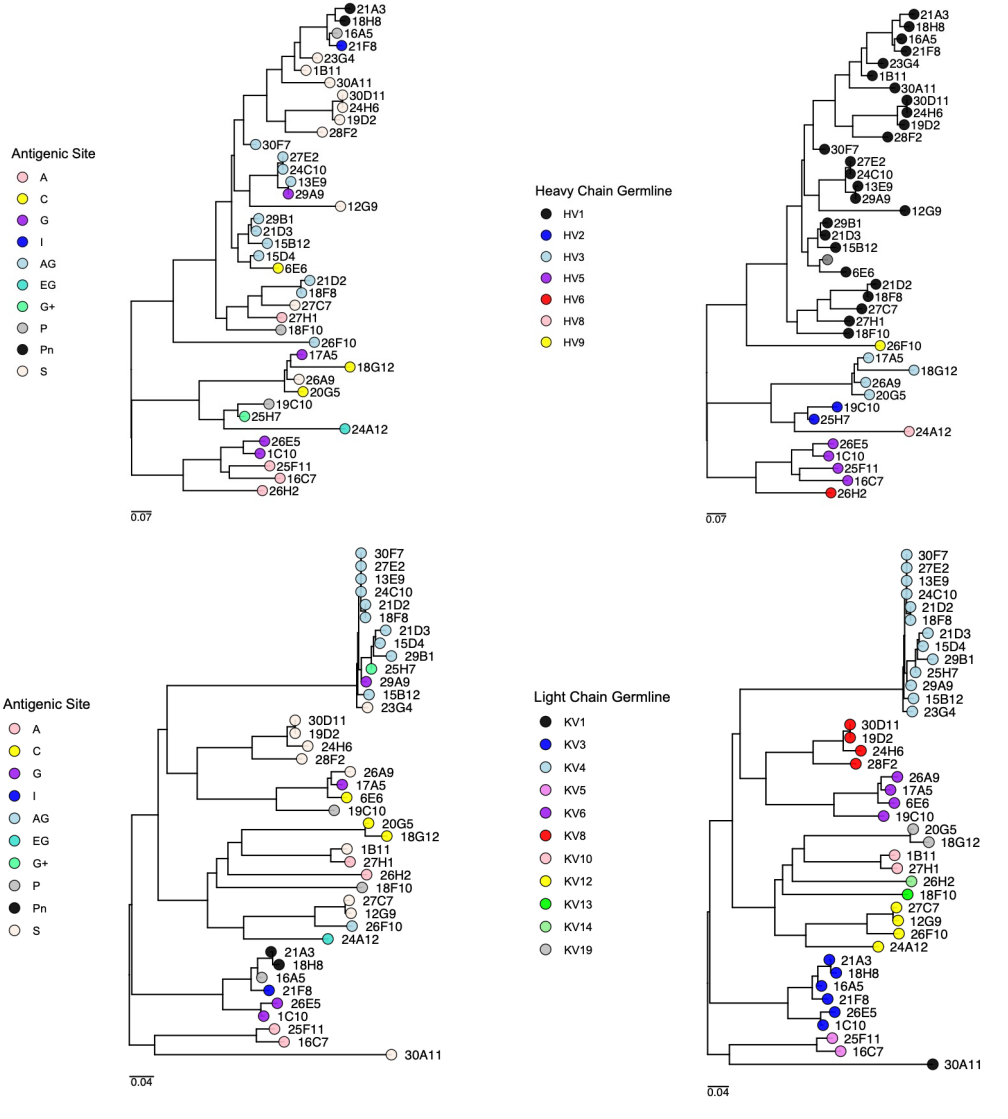

Antigenic Site
A
C
G
I
AG
EG
G+
P
Pn
S
21A3 18H8 16A5 21F8 23G4 1B11 30A11 30D11 24H6 19D2 28F2 30F7 27E2 24C10 13E9 29A9 12G9 29B1 21D3 15B12 15D4 6E6 21D2 18F8 27C7 27H1 18F10 26F10 17A5 18G12 26A9 20G5 19C10 25H7 24A12 26E5 1C10 25F11 16C7 26H2
0.07
Heavy Chain Germline
HV1
HV2
HV3
HV5
HV6
HV8
HV9
21A3 18H8 16A5 21F8 23G4 1B11 30A11 30D11 24H6 19D2 28F2 30F7 27E2 24C10 13E9 29A9 12G9 29B1 21D3 15B12 6E6 21D2 18F8 27C7 27H1 18F10 26F10 17A5 18G12 26A9 20G5 19C10 25H7 24A12 26E5 1C10 25F11 16C7 26H2
0.07
Antigenic Site
A
C
G
I
AG
EG
G+
P
Pn
S
30F7 27E2 13E9 24C10 21D2 18F8 21D3 15D4 29B1 25H7 29A9 15B12 23G4 30D11 19D2 24H6 28F2 26A9 17A5 6E6 19C10 20G5 18G12 1B11 27H1 26H2 18F10 27C7 12G9 26F10 24A12 21A3 18H8 16A5 21F8 26E5 1C10 25F11 16C7 30A11
0.04
Light Chain Germline
KV1
KV3
KV4
KV5
KV6
KV8
KV10
KV12
KV13
KV14
KV19
30F7 27E2 13E9 24C10 21D2 18F8 21D3 15D4 29B1 25H7 29A9 15B12 23G4 30D11 19D2 24H6 28F2 26A9 17A5 6E6 19C10 20G5 18G12 1B11 27H1 26H2 18F10 27C7 12G9 26F10 24A12 21A3 18H8 16A5 21F8 26E5 1C10 25F11 16C7 30A11
0.04

Figure S2

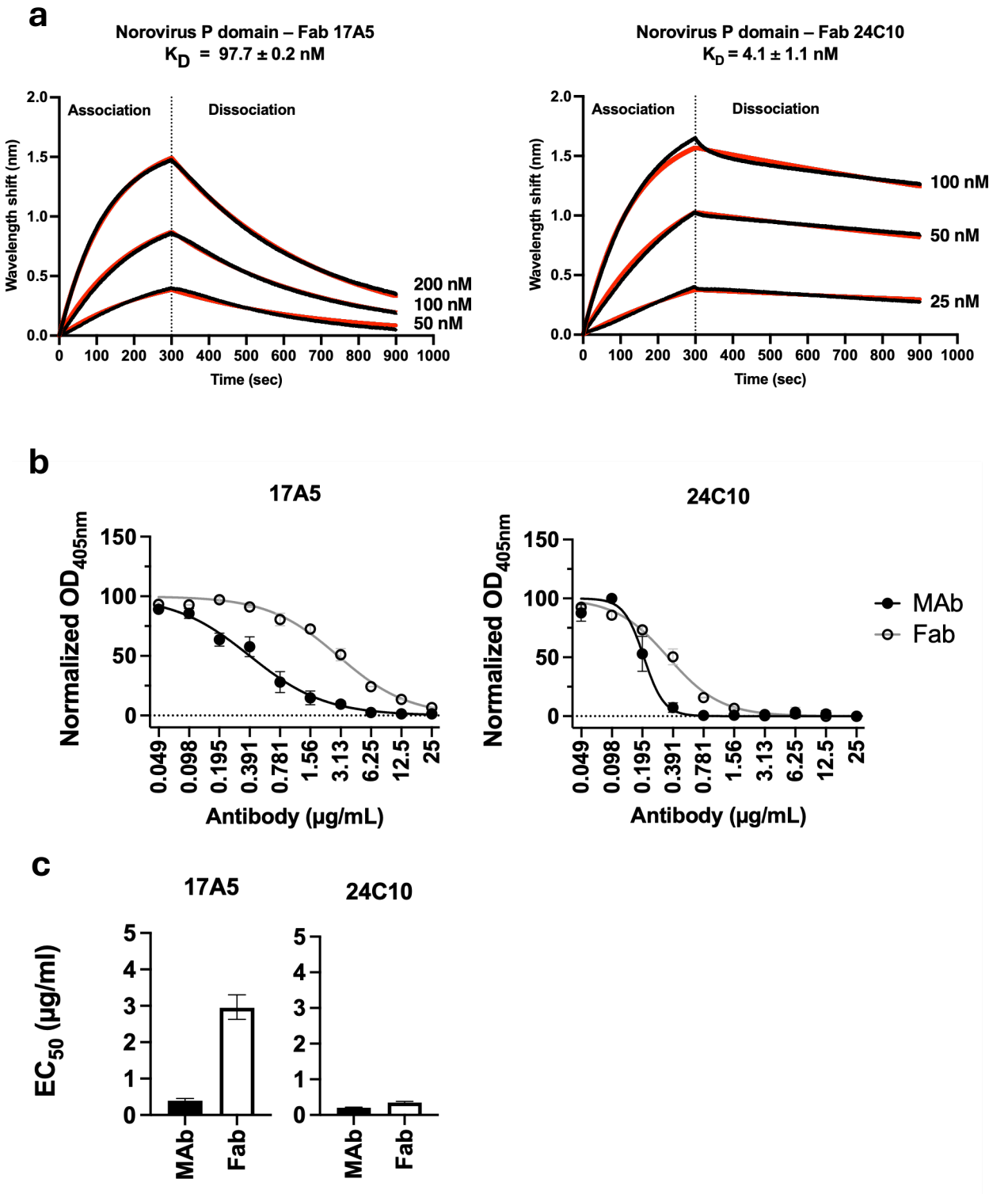

a
Norovirus P domain – Fab 17A5
K_D = 97.7 ± 0.2 nM
Association
Dissociation
Wavelength shift (nm)
Time (sec)
200 nM
100 nM
50 nM
Norovirus P domain – Fab 24C10
K_D = 4.1 ± 1.1 nM
100 nM
50 nM
25 nM
b
17A5
24C10
Normalized OD_{405nm}
Antibody (µg/mL)
MAb
Fab
c
17A5
24C10
EC_{50} (µg/ml)
MAb
Fab

Figure S3

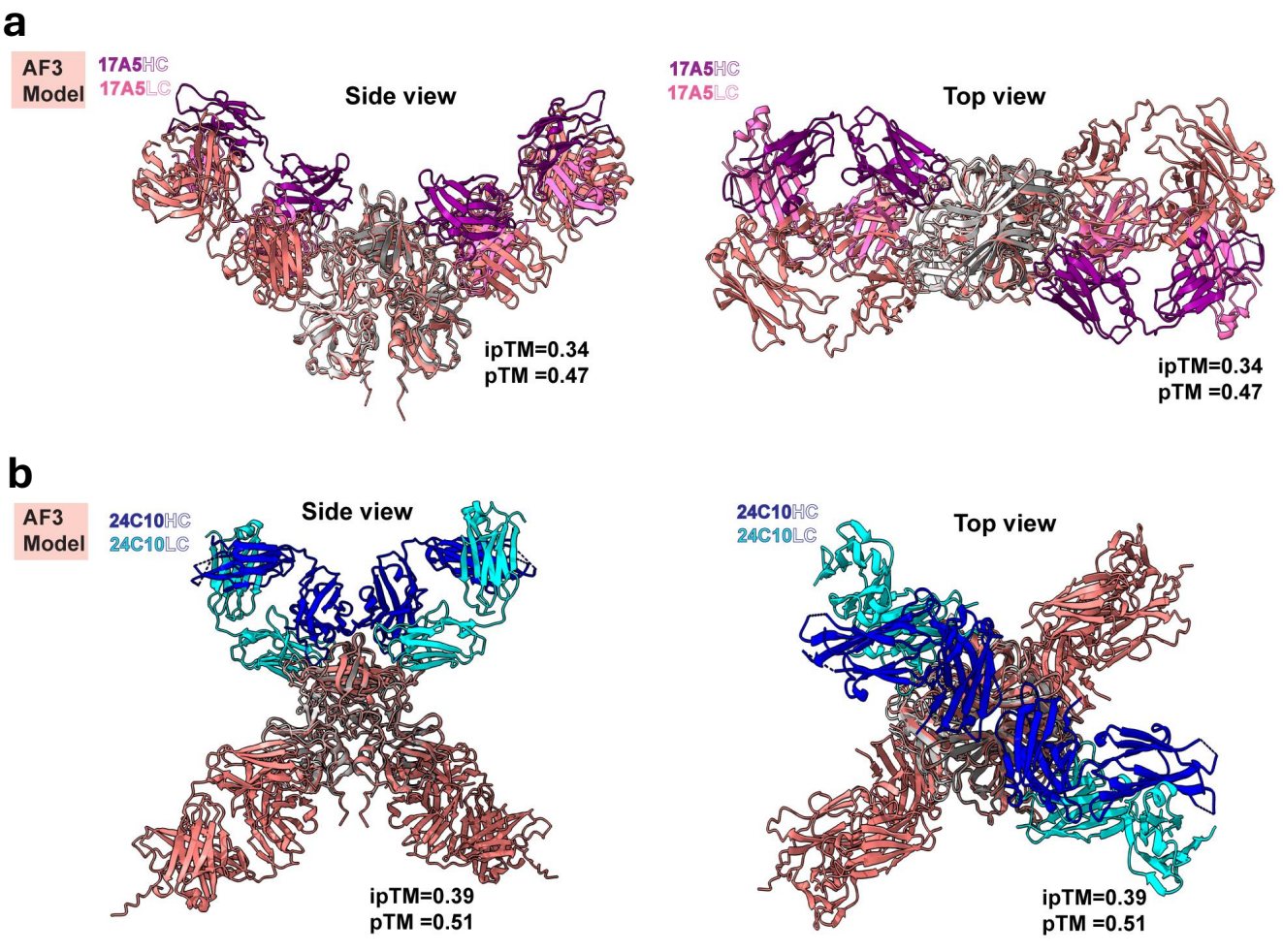

a
AF3 Model
17A5HC
17A5LC
Side view
ipTM=0.34
pTM =0.47
17A5HC
17A5LC
Top view
ipTM=0.34
pTM =0.47
b
AF3 Model
24C10HC
24C10LC
Side view
ipTM=0.39
pTM =0.51
24C10HC
24C10LC
Top view
ipTM=0.39
pTM =0.51

Figure S4

	Antigenic Site A								Antigenic Site G						ELISA Results	
Viruses (GenBank Acc/Strain/Year/Var)	294	295	296	297	298	368	372	373	352	355	356	357	359	364	17A5	24C10
KY424328/RockvilleD1/2012/SY	**T**	**G**	**S**	**R**	**N**	**E**	**D**	**H**	**Y**	**S**	**A**	**D**	**A**	**R**	+	+
JX023286/CHDC5191/1974	G	I	.	H	D	T	N	N	S	.	V	H	T	S		
AY032605/MD145/1987/CA	V	.	.	H	D	T	N	N	S	.	V	H	T	S		
AJ004864/Grimsby/1995/GR	A	.	.	H	D	T	N	N	S	.	V	H	I	S		
AF080556/Arizona/1996/GR	A	.	.	H	D	T	N	N	S	.	V	H	T	S		
DQ658413/MD3/2004/FH	A	D	T	H	.	N	N	N	S	D	V	H	T	S		
AB294781/Awa/2004/FH	A	.	T	H	.	N	N	N	S	D	V	H	T	S		
AY588022/Oxford/2003/FH	A	.	T	H	.	N	N	N	S	D	V	H	T	S		
EU078414/Cumberland/2004/HT	A	.	T	Q	.	S	S	N	S	.	V	H	T	S		
AB303941/Nijmegen/2004/HT	A	.	T	Q	.	S	S	N	S	.	I	H	T	S		
JX459599/SG4091/2007/HT	A	.	.	Q	T	S	S	T	S	.	.	Y	T	S		
EF126963/Yerseke/2006/YE	A	.	T	Q	E	S	S	N	S	.	V	H	T	.		
EU921348/Pune/2006/YE	A	.	T	Q	E	S	S	N	S	.	V	N	T	.		
AB294789/Kashiwa/2006/YE	A	.	T	Q	E	S	S	N	S	.	V	H	T	.		
AB220922/Sakai/2005/SA	P	.	T	.	T	A	.	N	S	.	V	.	T	S		+
EF126965/DenHaag/2006/DH	A	.	.	.	.	S	E	N	.	.	.	P	T	S		+
AB541218/Aomori/2007/DH	A	.	.	.	.	S	E	N	.	.	.	P	T	S		+
KX354081/Oregon/2012/DH	A	.	.	.	.	G	E	N	.	.	.	.	T	S	+	+
AB434770/Osaka/2007/OS	A	.	.	.	.	A	.	N	L	.	.	.	.	.	+	
AB541274/Iwate/2008/AP	.	.	.	.	.	A	.	N	.	.	.	.	.	.	+	+
KX353958/Virginia/2010/NO	P	.	.	.	.	A	.	N	.	.	.	.	S	.	+	+
KF060086/NSW675N/2012/NO	S	.	.	.	.	A	.	N	.	.	.	.	S	.	+	+
AB933752/Ehime/2009/NO	A	.	.	.	.	A	.	N	.	.	.	.	S	.	+	+
JX459908/NSW0514/2012/SY	.	.	.	.	.	.	.	R	.	.	.	.	.	.	+	+
MW305623/Arg12866/2014/SY	.	.	.	.	.	.	.	.	.	.	.	.	.	.	+	+
MW506849/Gabon561/2018/SF	A	.	T	H	.	A	T	N	.	.	N	.	.	.	+	
MN400355/HongKong/2019/HK	A	.	T	.	Q	G	E	D	S	A	.	.	.	N	+	

Figure S5

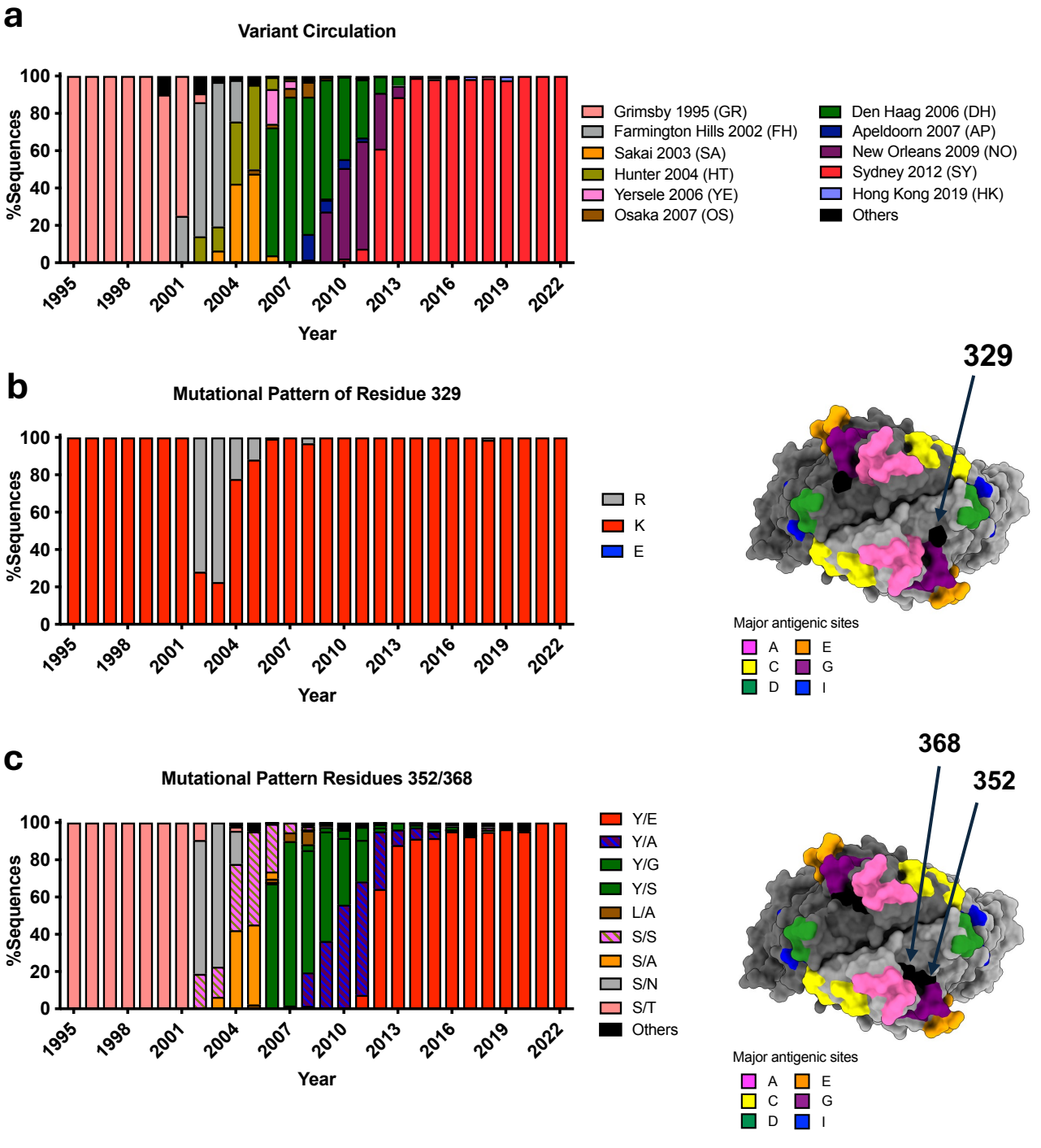

a
Variant Circulation
%Sequences
Year
Grimsby 1995 (GR)
Farmington Hills 2002 (FH)
Sakai 2003 (SA)
Hunter 2004 (HT)
Yersele 2006 (YE)
Osaka 2007 (OS)
Den Haag 2006 (DH)
Apeldoorn 2007 (AP)
New Orleans 2009 (NO)
Sydney 2012 (SY)
Hong Kong 2019 (HK)
Others
b
Mutational Pattern of Residue 329
R
K
E
329
Major antigenic sites
A
C
D
E
G
I
c
Mutational Pattern Residues 352/368
Y/E
Y/A
Y/G
Y/S
L/A
S/S
S/A
S/N
S/T
Others
368
352

Figure S6

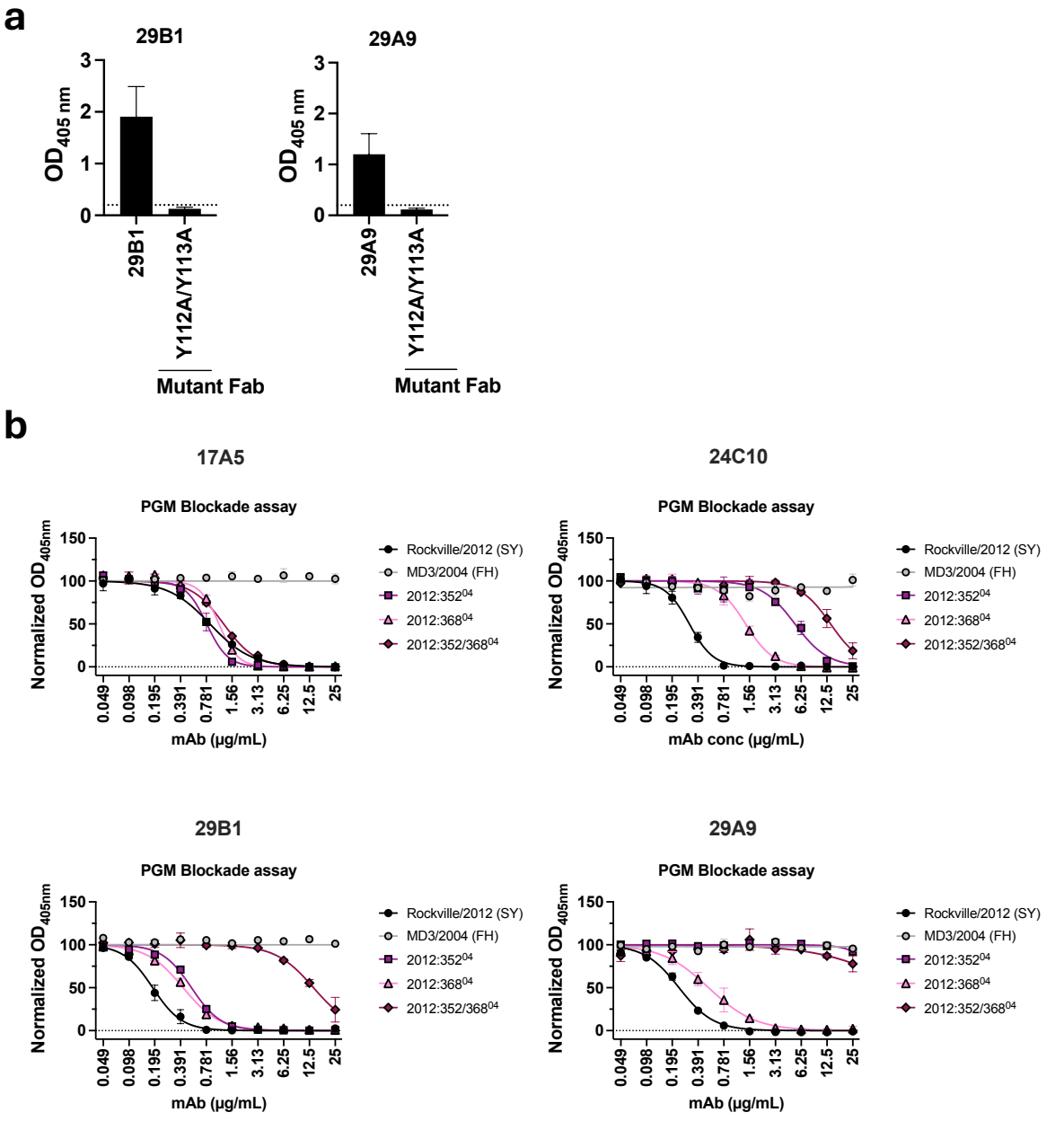

a
29B1
29A9
OD405 nm
3
2
1
0
29B1
Y112A/Y113A
29A9
Y112A/Y113A
Mutant Fab
Mutant Fab
b
17A5
24C10
29B1
29A9
PGM Blockade assay
Normalized OD405nm
150
100
50
0
0.049
0.098
0.195
0.391
0.781
1.56
3.13
6.25
12.5
25
mAb (µg/mL)
mAb conc (µg/mL)
Rockville/2012 (SY)
MD3/2004 (FH)
2012:352^04
2012:368^04
2012:352/368^04

Figure S7

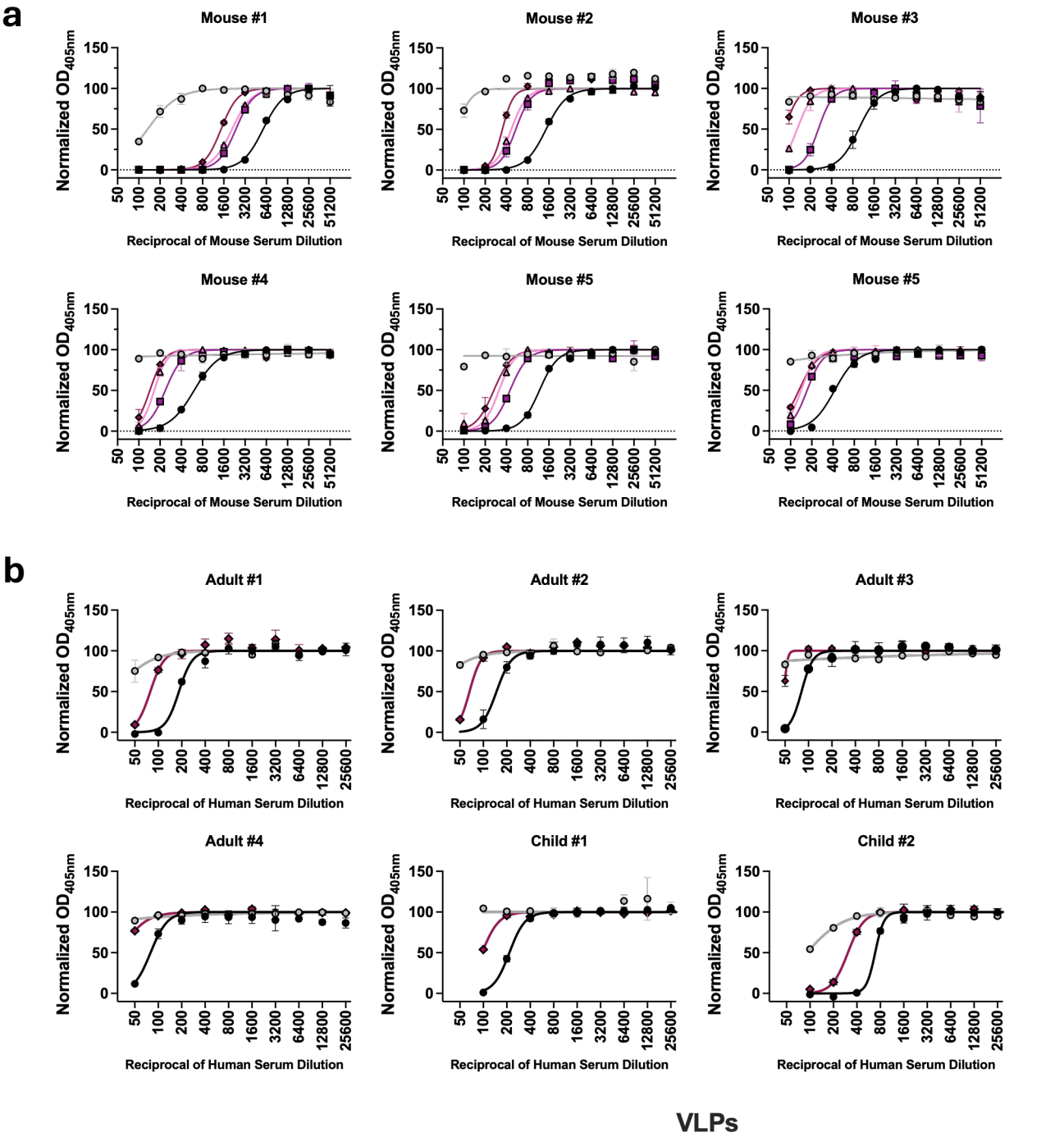

a
Mouse #1
Mouse #2
Mouse #3
Mouse #4
Mouse #5
Mouse #5
Normalized OD405nm
Reciprocal of Mouse Serum Dilution
b
Adult #1
Adult #2
Adult #3
Adult #4
Child #1
Child #2
Reciprocal of Human Serum Dilution
VLPs
Rockville/2012 (SY)
2012:352/04
2012:352/368/04
MD3/2004 (FH)
2012:368/04

Figure S8

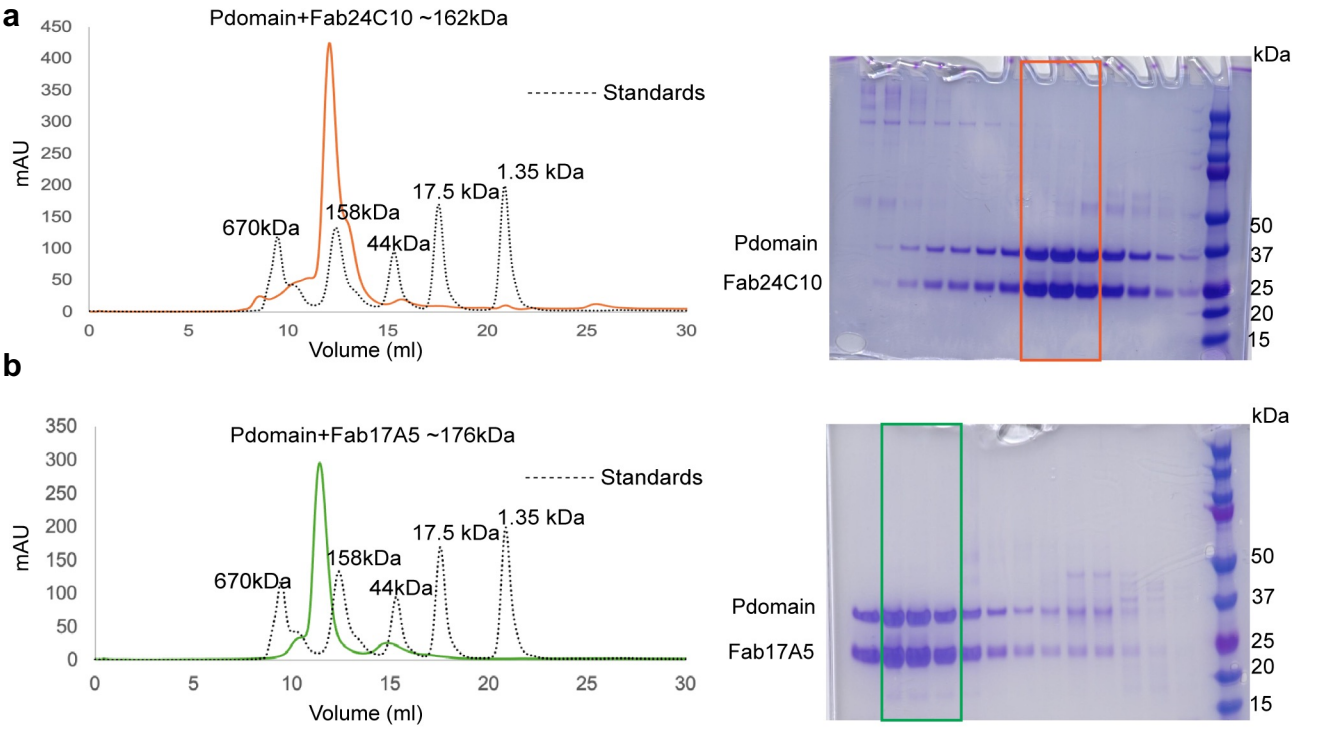

a
Pdomain+Fab24C10 ~162kDa
Standards
mAU
Volume (ml)
670kDa
158kDa
44kDa
17.5 kDa
1.35 kDa
kDa
Pdomain
Fab24C10
50
37
25
20
15
b
Pdomain+Fab17A5 ~176kDa
Standards
mAU
Volume (ml)
670kDa
158kDa
44kDa
17.5 kDa
1.35 kDa
kDa
Pdomain
Fab17A5
50
37
25
20
15

Table S1. Antibody germlines and CDRH3 sequence

Antibody _Antigenic Site	Germline Heavy	Germline Light	CDRH3
16C7_A	IGHV5-6-2*01 F	IGKV5-48*01 F	CVRHG-----DDALDYW
25F11_A	IGHV5-6-3*01 F	IGKV5-48*01 F	CARAT-----TVVGDYW
26H2_A	IGHV6-7-4*01 F	IGKV14-111*01 F	CCAYY--------RYLL
27H1_A	IGHV1-18*04 F	IGKV10-96*01 F	CARPDYD-GAWFA--YW
6E6_C	IGHV1-47-14*01 F	IGKV6-23*01 F	CTR-FGN---WYYFDYW
18G12_C	IGHV3-8*02 F	IGKV19-93*01 F	CARR--KGR--SLFDYW
20G5_C	IGHV3-1*02 F	IGKV19-93*01 F	CARS-REYV--NLFAYW
1C10_G	IGHV5-6-5*01 F	IGKV3-5*01 F	CARDANYGNYRDAMDYW
17A5_G	IGHV3-1*02 F	IGKV6-23*01 F	CAR----EV--TVFEYW
26E5_G	IGHV5-6-5*01 F	IGKV3-5*01 F	CAREGYYGSSPYYFDYW
29A9_G	IGHV1-9*02 F	IGKV4-59*01 F	CARAYYGN--YYAMDYW
21F8_I	IGHV1-4*02 F	IGKV3-4*01 F	CARRGAFG---NSFTYW
15B12_AG	IGHV1-69-5*01 F	IGKV4-59*01 F	CARSYSSGLPYYAMDQW
15D4_AG	IGHV1-47-14*01 F	IGKV4-59*01 F	CTR-VYEGYPYYAMDYW
18F8_AG	IGHV1-42*04 F	IGKV4-59*01 F	CA-TSWGGGDYYAMNYW
21D2_AG	IGHV1-42*04 F	IGKV4-59*01 F	CA-TSWGGGDYYAMNYW
21D3_AG	IGHV1-69-5*01 F	IGKV4-59*01 F	CARSFD-GYPYYAMDYW
24A12_EG	IGHV8-13-3*01 F	IGKV12-98*01 F	CARMGGNSN-YYAMDSW
24C10_AG	IGHV1-9*02 F	IGKV4-59*01 F	CARSWGFP--YYAIDYW
25H7_G+others	IGHV2-6-4*01 F	IGKV4-59*01 F	CARSIYDGYPYYAMDYW
26F10_AG	IGHV9-2-1*01 F	IGKV12-41*01 F	CARSRGYG--SSYPAYW
29B1_AG	IGHV1-69-5*01 F	IGKV4-59*01 F	CARSFD-GYPYYGLDYW
13E9_AG	IGHV1-9*02 F	IGKV4-59*01 F	CARIYYGN--YYAMDYW
27E2_AG	IGHV1-9*02 F	IGKV4-59*01 F	CARSWGFP--YYAIDYW
30F7_AG	IGHV1-69*02 F	IGKV4-59*01 F	CARTLGLP--YYAMDYW
16A5_P	IGHV1-4*02 F	IGKV3-4*01 F	CARRGAFG---NSFAYW
18F10_P	IGHV1-18-23*01 F	IGKV13-84*01 F	CTRSFTTATYYYAMDYW
19C10_P	IGHV2-9*02 F	IGKV6-17*01 F	CARG--DG---YDFTYW
18H8_Pn	IGHV1-4*02 F	IGKV3-4*01 F	CARRG-YG---NYLTYW
21A3_Pn	IGHV1-4*02 F	IGKV3-4*01 F	CARRG-YG---NYLTYW
12G9_S	IGHV1-18-17*01 F	IGKV12-44*01 F	CARHDGYG----YFDVW
26A9_S	IGHV3-1*02 F	IGKV6-23*01 F	CARPIYDAP--NYFDYW
28F2_S	IGHV1-47-2*01 F	IGKV8-27*01 F	CTRDGN----QAWFAYW
30A11_S	IGHV1-87*02 F	IGKV1-117*01 F	CVRRDYYG---DTFDYW
1B11_S	IGHV1-18-13*01 F	IGKV10-96*01 F, or IGKV10-96*07 F	CATIY--S---DYFDYW
19D2_S	IGHV1-71-11*01 F	IGKV8-30*01 F	CARTYGYDAEAVPFAYW
23G4_S	IGHV1-18-13*01 F	IGKV4-59*01 F	CASLI--G---TAFDHW
27C7_S	IGHV1-18*01 F	IGKV12-44*01 F	CARAPYDYGFYFD--YW
24H6_S	IGHV1-71-11*01 F	IGKV8-30*01 F	CARTYGYDDETVPFAYW
30D11_S	IGHV1-71-11*01 F	IGKV8-30*01 F	CARTYGYDDETVPFAYW

Table S2. Crystallography data collection and refinement

	P domain – Fab 17A5	P domain – Fab 24C10
Data Collection[a]		
PDB Code	11HB	11HA
Space group	C121	P21
α, β, γ (°)	90 91.75 90	90, 99.5,7 90
Resolution (Å)	48.43 - 3.36 (3.4 - 3.36)	47.78 - 2.70 (2.77 - 2.70)
R_{merge}	0.334 (2.594)	0.1463 (1.097)
I/sI	7.4 (1.0)	12.22 (1.24)
Completeness (%)	98.39 (96.65)	99.80 (100.00)
Multiplicity	6.9 (6.9)	13.6 (12.6)
$CC_{1/2}$	0.982 (0.415)	0.998 (0.723)
Refinement		
No. of reflections	68516 (2231)	49114 (3474)
Resolution (Å)	48.43 - 3.36	47.78 - 2.70
R_{work}/R_{free}[b]	0.2577 / 0.2996	0.2084 / 0.2455
Atoms	16393	11192
Protein	2112	1451
Water	0	0
Mean B factor (Å^2)	104.89	59.52
Protein (Å^2)	104.89	59.52
Water (Å^2)	N/A	N/A
RMSD		
Bond lengths (Å)	0.002	0.004
Bond angles (°)	0.5	0.68
Ramachandran statistics		
Favored (%)	92.26	96.58
Allowed (%)	7.74	3.42
Outliers (%)	0	0

[a] The values in parentheses are for the outermost shell.

[b] R_{free} is the R_{work} based on 10% of the data excluded from the refinement.

Table S3. GII.4 noroviruses used to make VLPs.

Names	Accession	Year	Location
CHDC5191/1974	JX023286	1974	United States
MD145/1987 (CA)[a]	AY032605	1987	United States
Grimsby/1995 (GR)	AJ004864	1995	United Kingdom
Arizona/1996 (GR)	AF080556	1996	United States
MD3/2004 (FH)	DQ658413	2004	United States
Awa/2004 (FH)	AB294781	2004	Japan
Oxford/2003 (FH)	AY588022	2003	United Kingdom
Cumberland/2004 (HT)	EU078414	2004	United States
Nijmegen/2004 (HT)	AB303941	2004	Netherlands
SG4091/2006 (HT)	JX459599	2006	Singapore
Sakai/2005 (SA)	AB220922	2005	Japan
Yerseke/2006 (YE)	EF126963	2006	Netherlands
Kashiwa/2006 (YE)	AB294789	2006	Japan
Pune/2006 (YE)	EU921348	2006	India
DenHaag/2006 (DH)	EF126965	2006	Netherlands
Oregon/2012 (DH)	KX354081	2012	United States
Aomori/2007 (DH)	AB541218	2007	Japan
Osaka/2007 (OS)	AB434770	2007	Japan
Iwate/2008 (AP)	AB541274	2008	Japan
Virginia/2010 (NO)	KX353958	2010	United States
NSW675N/2012 (NO)	KF060086	2012	Australia
Ehime/2009 (NO)	AB933752	2009	Japan
Rockville/2012 (SY)	KY424328	2012	United States
Arg12866/2014 (SY)	MW305623	2014	Argentina
NSW0514/2012 (SY)	JX459908	2012	Australia
Gabon561/2018 (SF)	MW506849	2018	Gabon
HongKong/2019 (HK)	MN400355	2019	Hong Kong

[a] Names of the GII.4 variants are abbreviated and indicated within parentheses as follows: Camberwell 1987 (CA), Grimsby 1995 (GR), Farmington Hills 2002 (FH), Sakai 2003 (SA), Hunter 2004 (HT), Yerseke 2006 (YE), Den Haag 2006 (DH), Osaka 2007 (OS), Apeldoorn 2008 (AP), New Orleans 2009 (NO), Sydney 2012 (SY), San Francisco 2017 (SF), Hong Kong 2019 (HK).