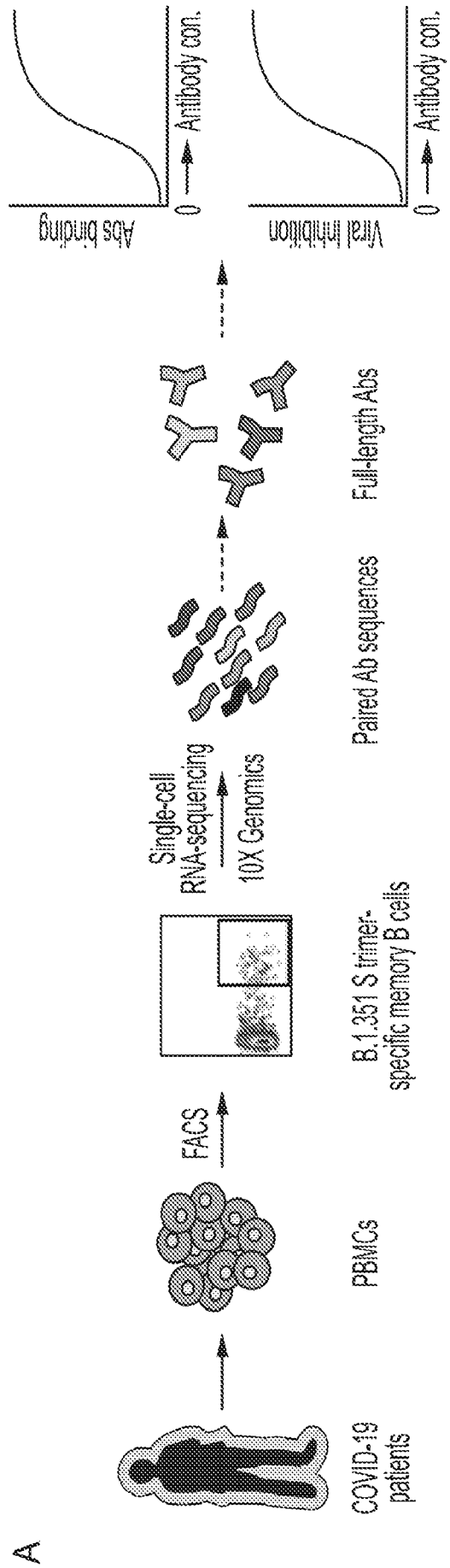

A
COVID-19 patients
PBMCs
FACS
B.1.351 S trimer-specific memory B cells
Single-cell RNA-sequencing
10X Genomics
Paired Ab sequences
Full-length Abs
Abs binding
0
Antibody con.
Viral inhibition
0
Antibody con.

FIG. 1A

B

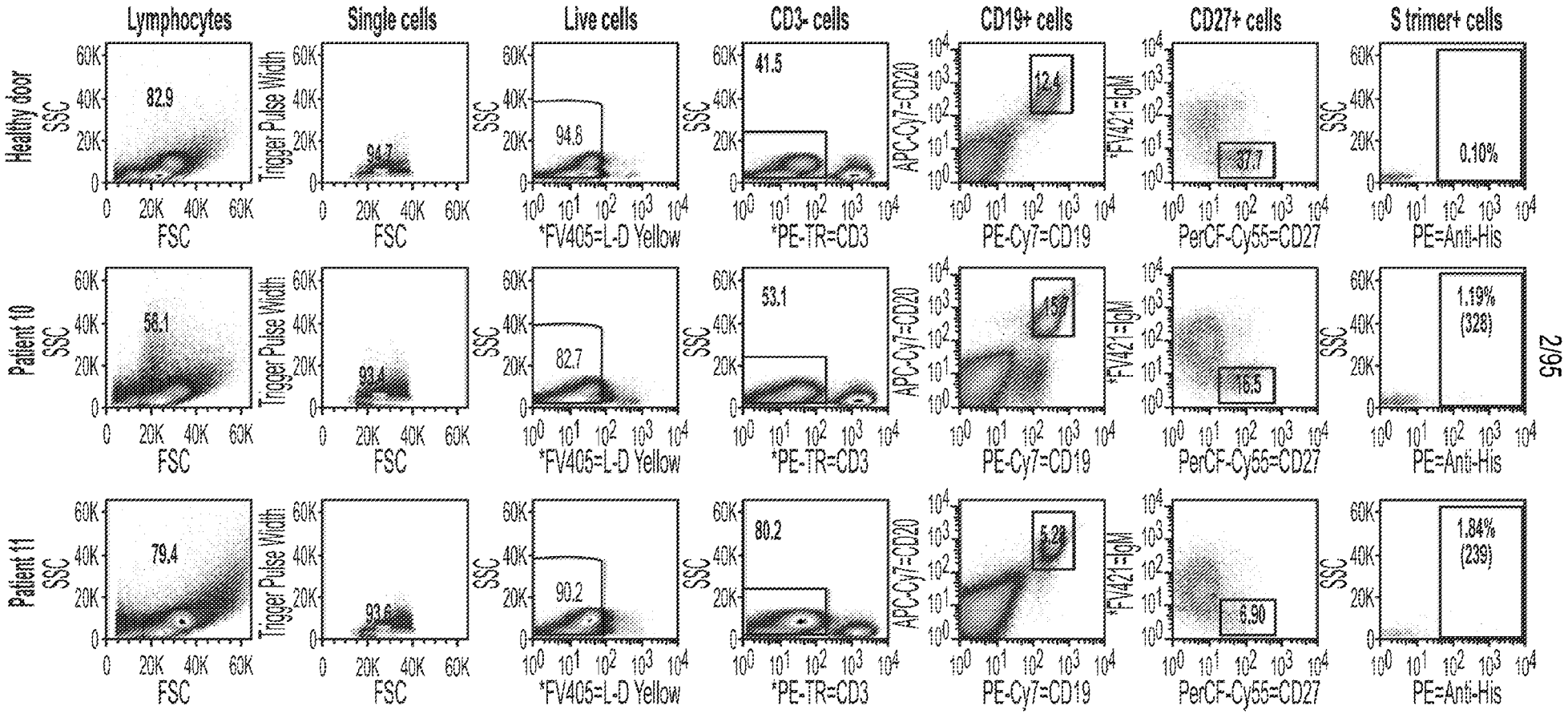

Lymphocytes
Single cells
Live cells
CD3- cells
CD19+ cells
CD27+ cells
S trimer+ cells
Healthy donor
Patient 10
Patient 11
SSC
FSC
Trigger Pulse Width
*FV405=L-D Yellow
*PE-TR=CD3
APC-Cy7=CD20
PE-Cy7=CD19
*FV421=IgM
PerCF-Cy55=CD27
PE=Anti-His
82.9
94.8
41.5
12.4
37.7
0.10%
58.1
82.7
53.1
15.7
16.5
1.19%
(329)
79.4
90.2
80.2
5.29
6.90
1.84%
(239)

FIG. 1B

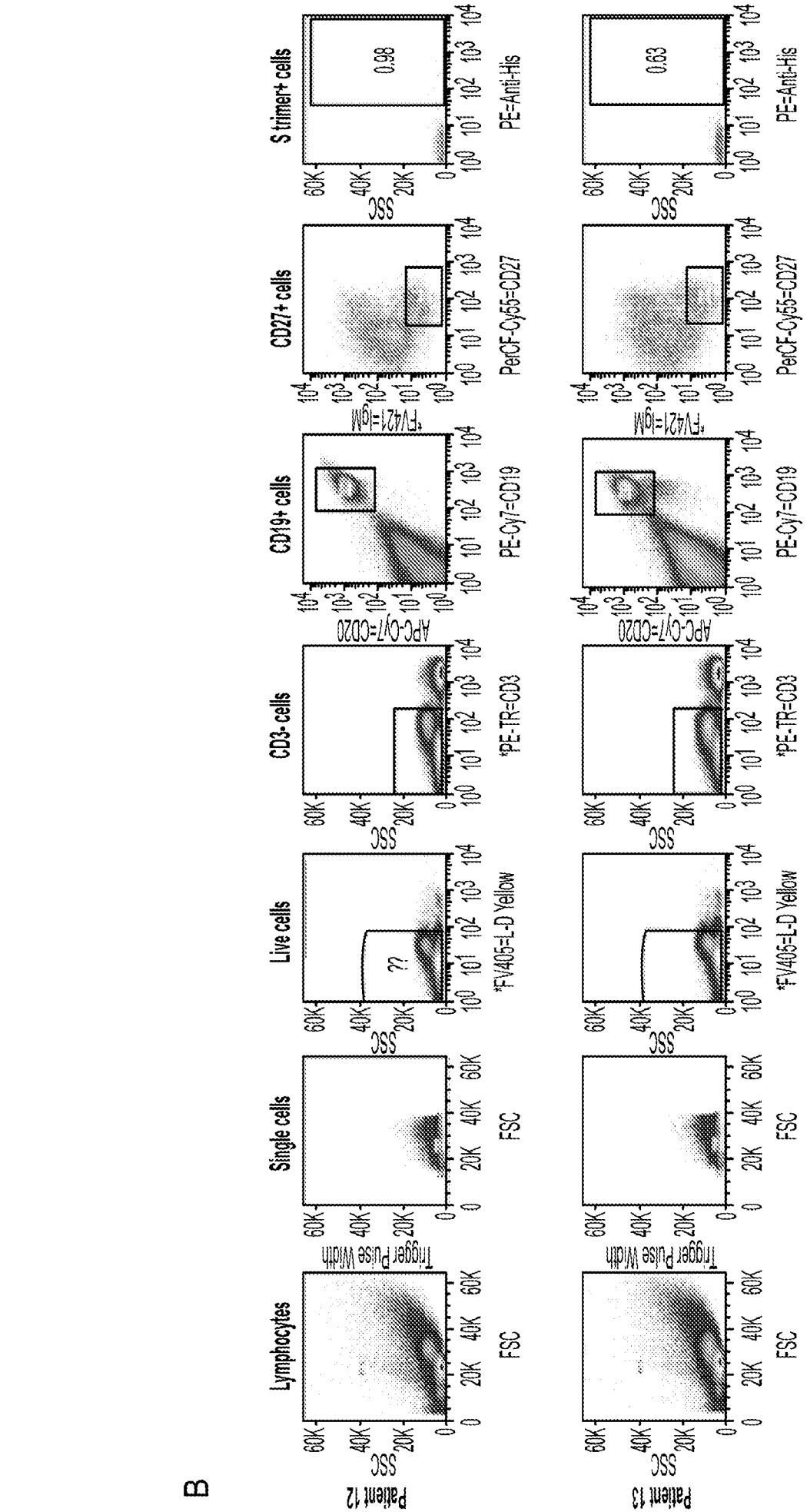


FIG. 1B
CONTINUED

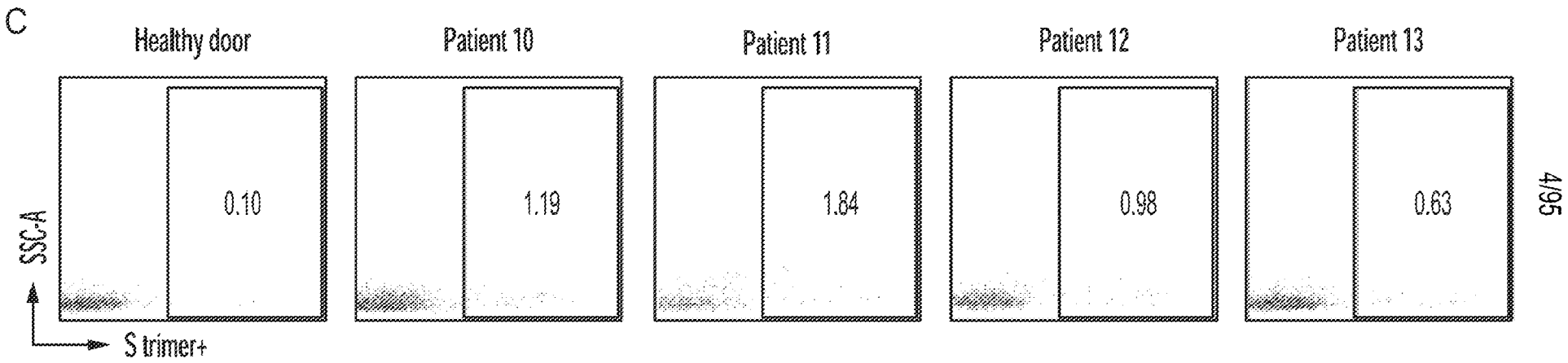
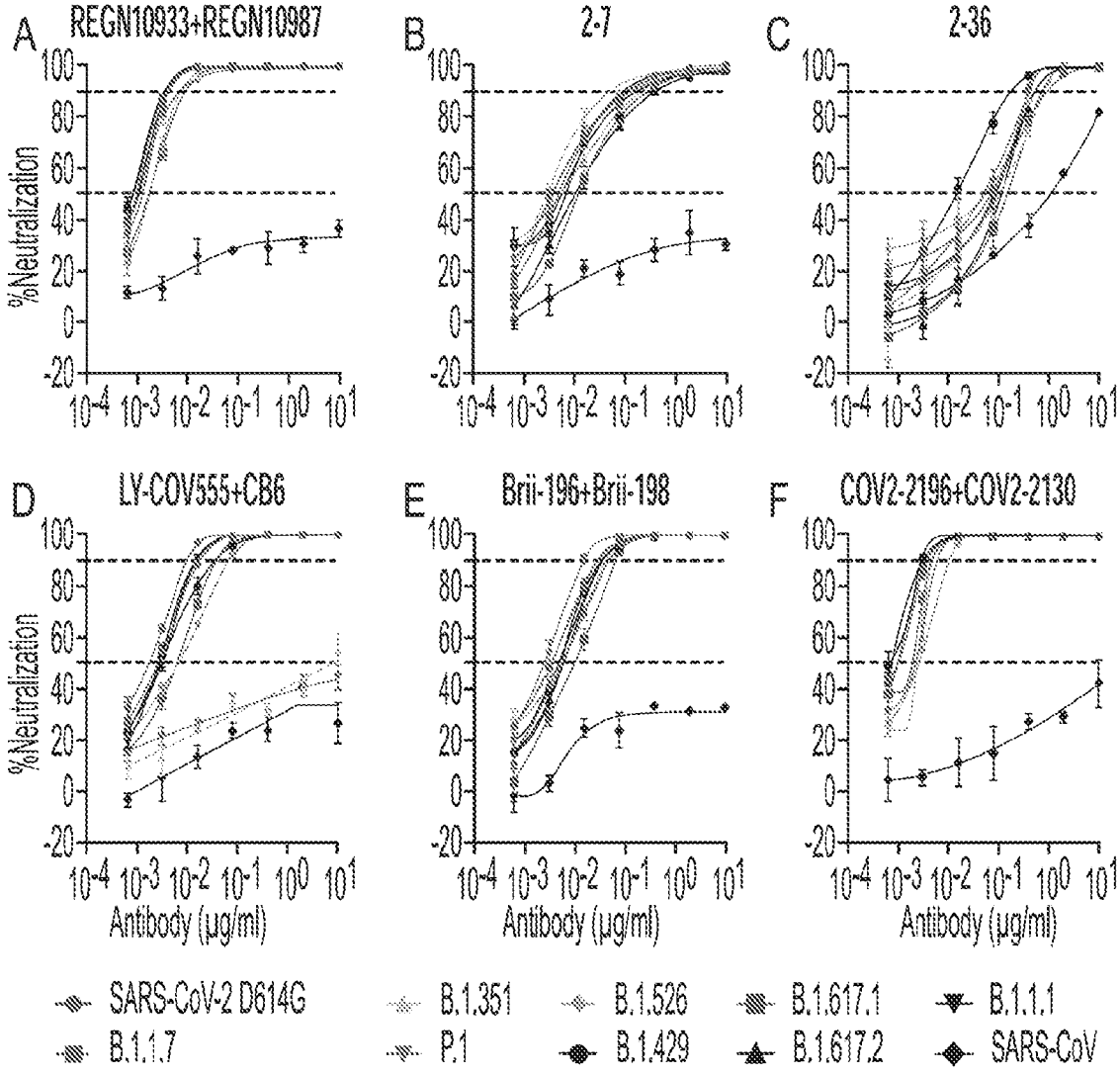
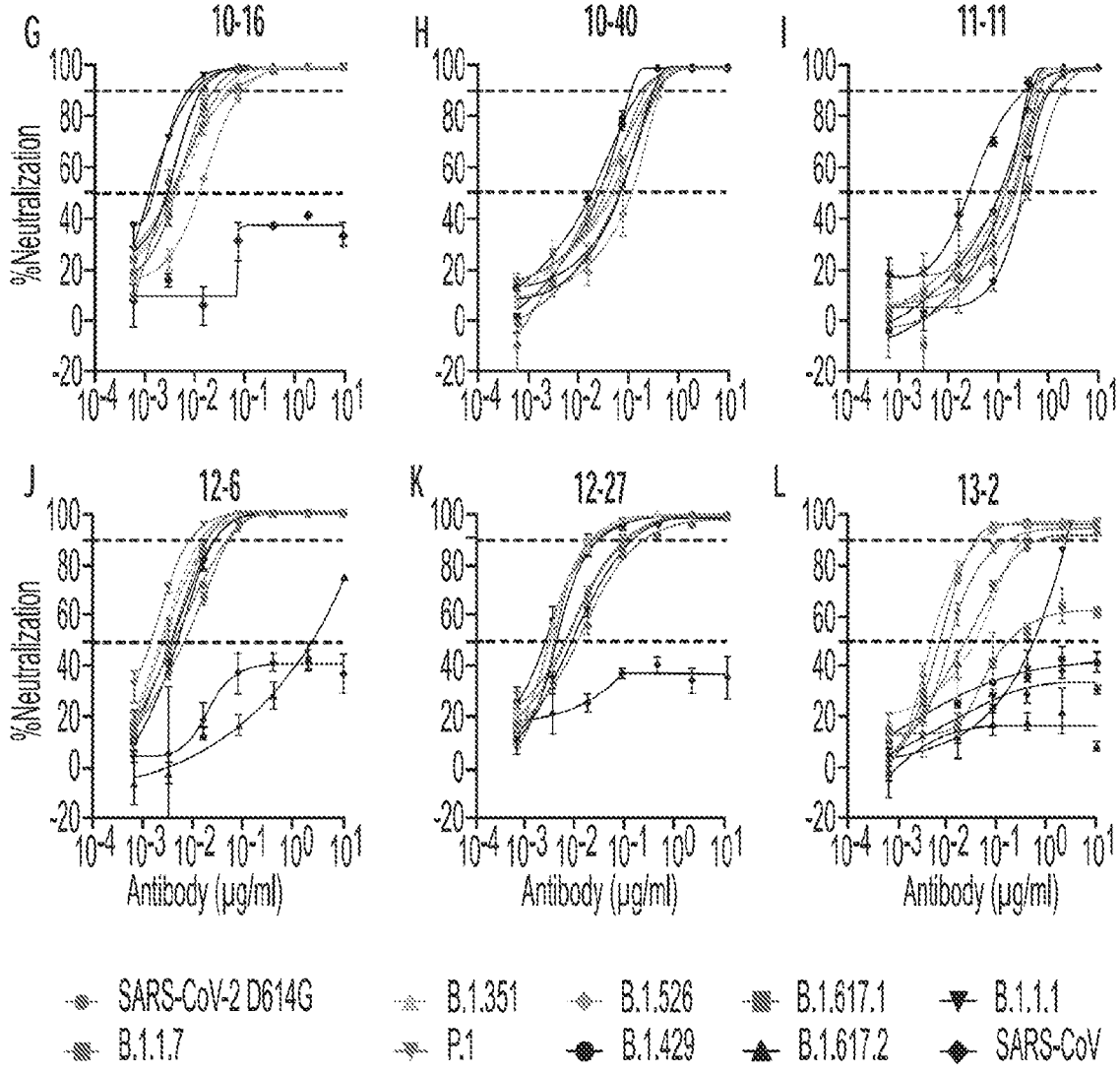

C
Healthy door
Patient 10
Patient 11
Patient 12
Patient 13
0.10
1.19
1.84
0.98
0.63
SSC-A
S trimer+

FIG. 1C


A
REGN10933+REGN10987
B
2-7
C
2-36
D
LY-COV555+CB6
E
Brii-196+Brii-198
F
COV2-2196+COV2-2130
%Neutralization
Antibody (µg/ml)
SARS-CoV-2 D614G
B.1.1.7
B.1.351
P.1
B.1.526
B.1.429
B.1.617.1
B.1.617.2
B.1.1.1
SARS-CoV

FIGS. 2A-F


G
10-16
H
10-40
I
11-11
J
12-6
K
12-27
L
13-2
%Neutralization
Antibody (µg/ml)
SARS-CoV-2 D614G
B.1.1.7
B.1.351
P.1
B.1.526
B.1.429
B.1.617.1
B.1.617.2
B.1.1.1
SARS-CoV

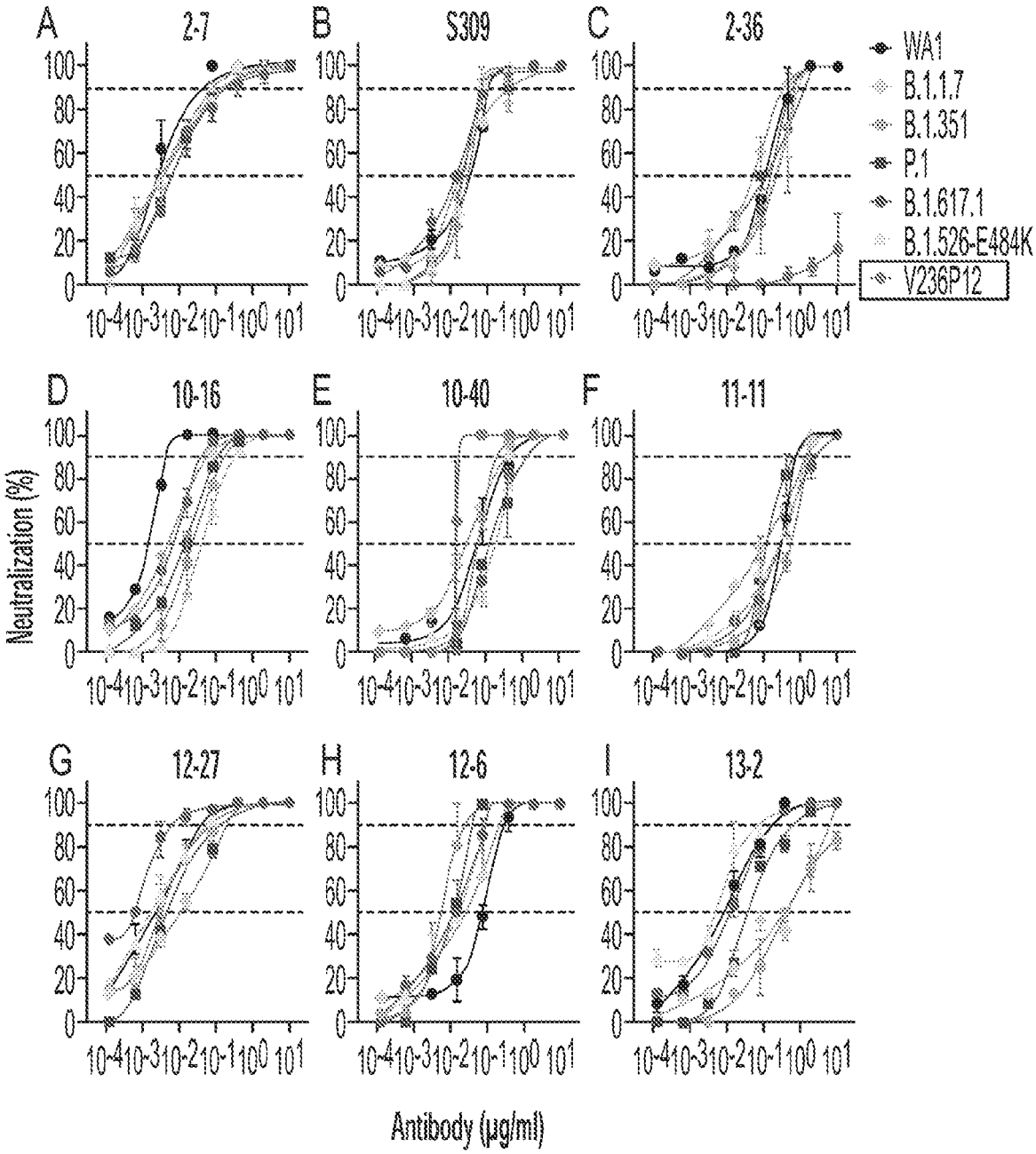
FIGS. 2G-L

IC50(μg/ml)	WT	B.1.1.7	B.1.351	P.1	B.1.526	B.1.429	B.1.617.1	B.1.617.2	B.1.1.1	SARS-CoV
2-7	0.003	0.005	0.003	0.004	0.005	0.006	0.012	0.011	0.007	>10
2-36	0.070	0.084	0.106	0.050	0.055	0.015	0.149	0.117	0.091	1.106
REGN10933+REGN10987	0.001	0.001	0.001	0.001	0.002	0.001	0.002	0.001	0.001	>10
COV2-2196+COV2-2130	0.001	0.001	0.002	0.002	0.002	0.001	0.002	0.001	0.001	>10
LY-COV555+CB6	0.002	0.003	7.024	>10	0.006	0.003	0.006	0.003	0.003	>10
Brii196+Brii198	0.005	0.003	0.004	0.003	0.006	0.005	0.010	0.006	0.005	>10
10-16	0.003	0.004	0.004	0.003	0.013	0.001	0.004	0.003	0.002	>10
10-40	0.028	0.035	0.053	0.045	0.117	0.027	0.069	0.053	0.069	0.018
11-11	0.207	0.372	0.170	0.111	0.140	0.106	0.176	0.128	0.284	0.025
12-6	0.007	0.004	0.002	0.001	0.002	0.004	0.003	2.476	0.005	>10
12-27	0.006	0.011	0.003	0.006	0.003	0.002	0.003	0.004	0.008	>10
13-2	0.022	0.172	0.036	0.011	0.005	>10	0.007	>10	0.539	>10

IC_{50} (μg/mL)

- <0.01
- 0.01-0.1
- 0.1-1
- 1-10
- >10

FIG. 3


A
2-7
B
S309
C
2-36
D
10-16
E
10-40
F
11-11
G
12-27
H
12-6
I
13-2
WA1
B.1.1.7
B.1.351
P.1
B.1.617.1
B.1.526-E484K
V236P12
Neutralization (%)
Antibody (µg/ml)

FIGS. 4A-I

J

mAb	Potency (IC50) µg/mL						
	WA1	B.1.1.7	B.1.351	P.1	B.1.617.1	B.1.526-E484K	V236P12 **
2-7	0.003	0.003	0.004	0.006	0.006	0.003	
S309	0.007	0.019	0.012	0.024	0.013	0.024	
2-36	0.114	0.052	0.215	0.109	0.149	0.21	50
10-16	0.002	0.005	0.024	0.016	0.007	0.042	
10-40	0.06	0.031	0.064	0.134	0.156	0.198	0.015
11-11	0.309	0.111	0.55	0.126	0.283	0.289	
12-6	0.035	0.027	0.006	0.013	0.014	0.018	
12-27	0.003	0.012	0.003	0.005	0.001	0.002	
13-2	0.008	6.399	59.316	0.038	0.012	0.005	

0.000
0.010
1.000
50.000
>50

** V236P12 tested for 10-40 and 10-28 only

FIG. 4J

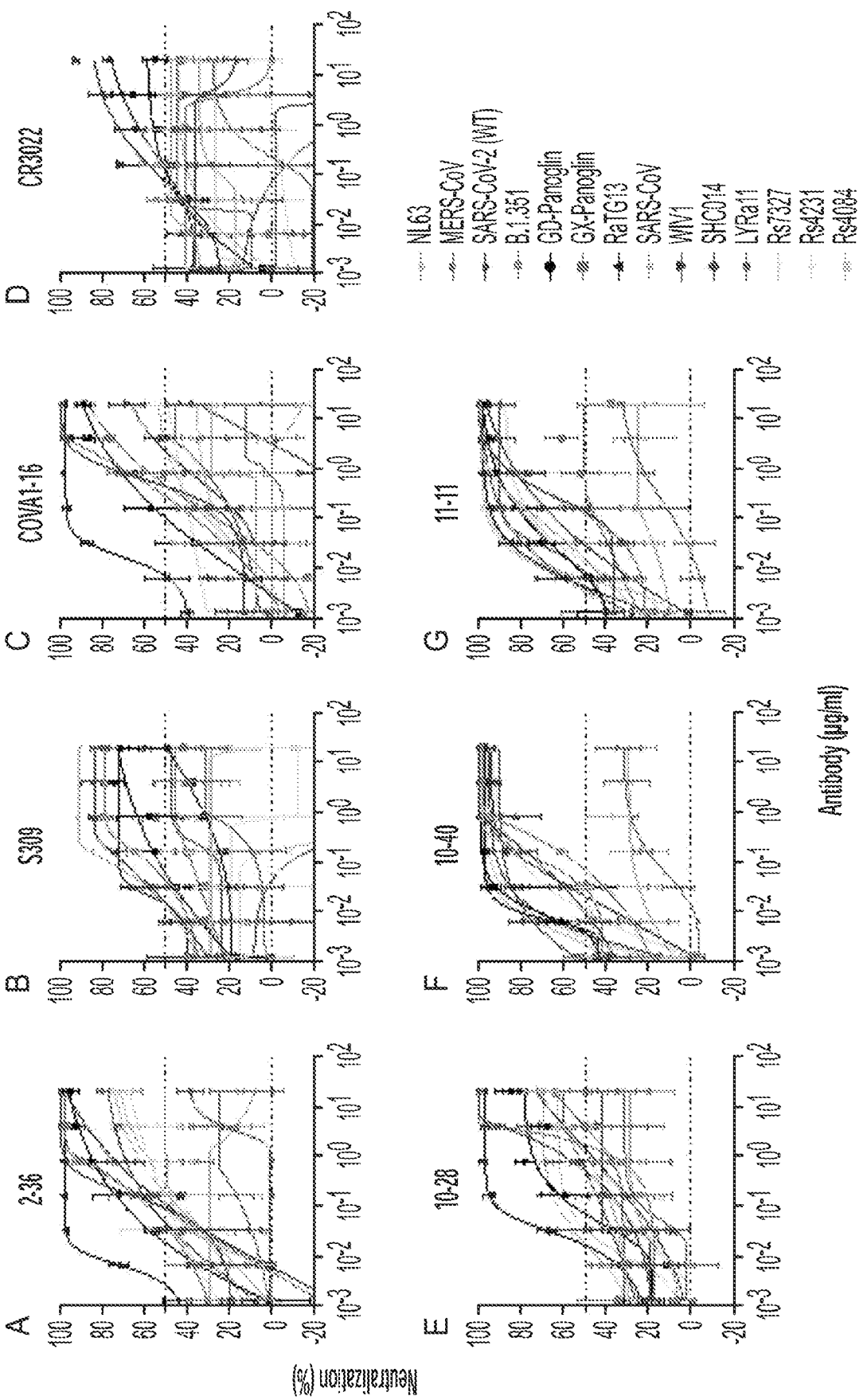

A
2-36
B
S309
C
COVA1-16
D
CR3022
E
10-28
F
10-40
G
11-11
Neutralization (%)
Antibody (μg/ml)
NL63
MERS-CoV
SARS-CoV-2 (WT)
B.1.351
GD-Pangolin
GX-Pangolin
RaTG13
SARS-CoV
WIV1
SHC014
LYRa11
Rs7327
Rs4231
Rs4084

FIG. 5A-G

H

IC50 (μg/ml)	SARS-CoV-2 (WT)	SARS-CoV-2 (B.1.351)	SARS-CoV	MERS-CoV	NL63	GD-Pangolin	GX-Pangolin	RaTG 13	WIV1	SHC 014	LYRa11	Rs 7327	Rs 4231	Rs 4084
2-36	0.091	0.041	>20	>20	>20	0.018	0.081	0.003	0.107	>20	0.046	0.278	0.097	>20
S309	0.015	0.043	0.013	>20	>20	0.057	>20	21.893	0.014	>20	>20	>20	>20	>20
COVA1-16	0.438	0.276	>20	>20	>20	0.102	0.475	0.007	2.184	>20	>20	>20	>20	2.743
CR3022	>20	>20	>20	>20	>20	0.102	>20	0.117	0.070	>20	>20	>20	>20	>20
10-28	0.520	1.660	1.078	>20	>20	0.069	3.778	0.016	1.422	0.521	>20	0.034	>20	0.018
10-40	0.010	0.070	0.020	>20	>20	0.004	0.030	0.004	0.021	0.001	0.004	0.003	0.010	0.002
11-11	0.137	0.125	0.015	>20	>20	0.007	0.396	0.004	0.029	0.008	0.004	0.006	0.013	0.003

IC_{50} (μg/mL)
- <0.01
- 0.01-0.1
- 0.1-1
- 1-20
- >20

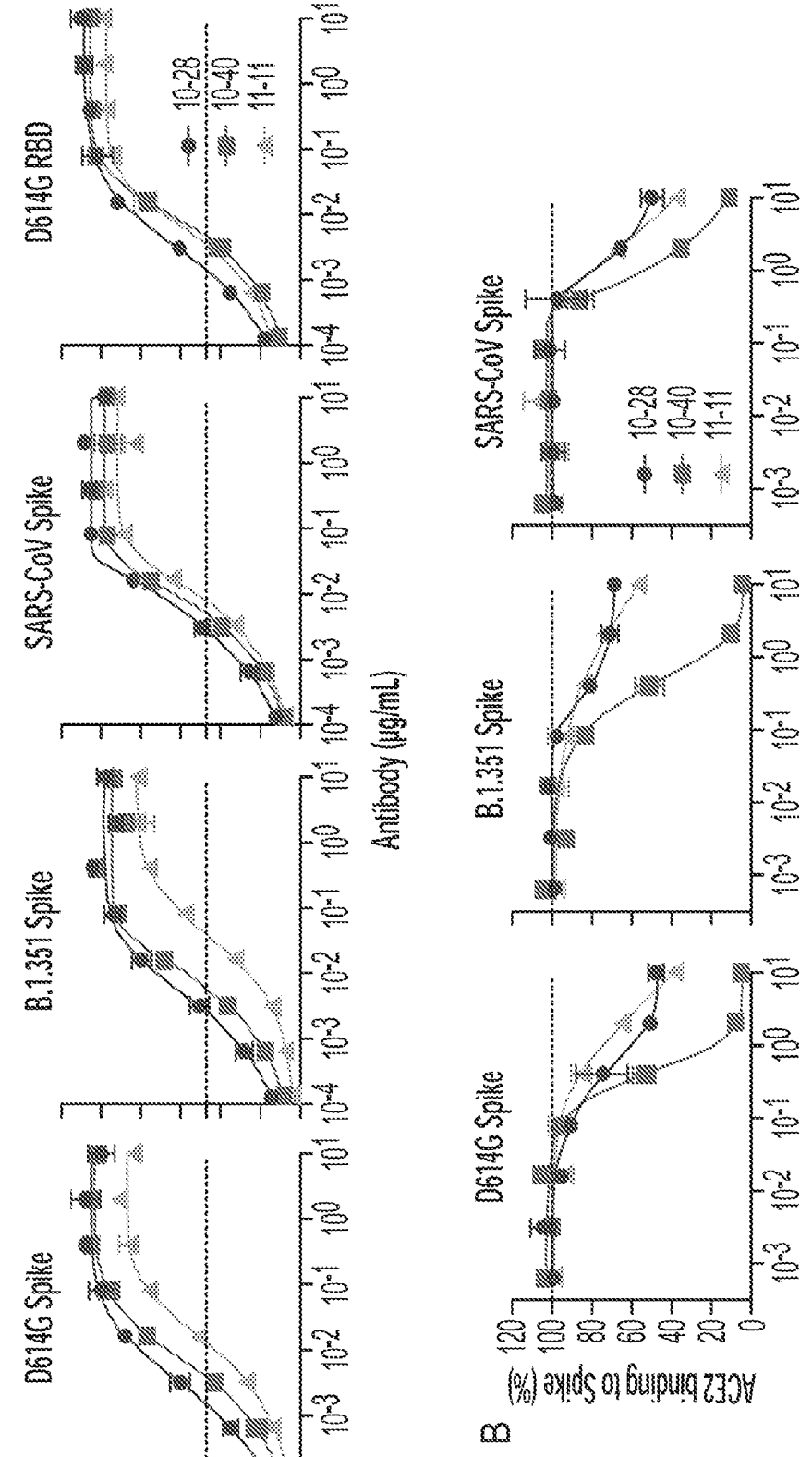
FIG. 5H

H

IC90 (μg/ml)	SARS-CoV-2 (WT)	SARS-CoV-2 (B.1.351)	SARS-CoV	MERS-CoV	NL63	GD-Pangolin	GX-Pangolin	RaTG 13	WIV1	SHC 014	LYRa11	Rs 7327	Rs 4231	Rs 4084
2-36	0.435	0.920	>20	>20	>20	2.788	0.803	0.012	5.744	>20	>20	>20	>20	0.175
S309	>20	>20	0.213	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
COVA1-16	1.852	2.804	>20	>20	>20	>20	>20	0.038	>20	>20	>20	>20	>20	>20
CR3022	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20	>20
10-28	4.017	3.876	>20	>20	>20	>20	>20	0.084	161.991	>20	>20	>20	>20	>20
10-40	0.413	0.663	0.254	>20	>20	0.027	0.299	0.015	0.309	0.780	0.073	0.034	0.855	0.021
11-11	1.343	1.394	0.466	>20	>20	0.620	>20	0.054	3.387	0.200	0.163	0.046	>20	0.038

IC_{50} (μg/mL)
- <0.01
- 0.01-0.1
- 0.1-1
- 1-20
- >20

FIG. 5H
CONTINUED


A
OD (450 nm)
D614G Spike
B.1.351 Spike
SARS-CoV Spike
D614G RBD
10-28
10-40
11-11
Antibody (µg/mL)
B
ACE2 binding to Spike (%)
D614G Spike
B.1.351 Spike
SARS-CoV Spike
10-28
10-40
11-11
Competitor antibody (µg/mL)

FIGS. 6A-B

C

AUC		Competitor Antibody											
		10-40	10-28	DH1047	S2X259	REGN 10985	ADG-2	11-11	2-36	COVA 1-16	CR3022	S2H97	S309
Biotinylated antibody	10-40	92	147	157	98	251	486	772	745	849	938	855	933
	10-28	107	107	174	128	325	1157	820	809	842	906	918	793
	DH1047	91	152	137	87	194	347	776	684	781	879	948	978
	S2X259	89	142	143	89	230	347	796	768	774	834	959	876
	REGN10985	108	189	160	95	153	119	437	361	613	713	749	766
	ADG-2	114	1064	110	69	193	179	732	643	740	1077	969	976
	11-11	124	129	140	113	184	145	199	165	279	512	917	959
	2-36	119	173	159	144	221	185	320	206	284	539	1015	850
	COVA1-16	144	158	165	147	247	160	268	167	240	569	153	782
	CR3022	189	160	192	191	377	940	244	270	293	302	536	726
	S2H97	952	1044	960	1045	965	1016	1021	962	1005	1035	111	946
	S309	1020	985	1014	1032	964	1073	1017	959	1052	937	1024	100

No competition — Competition

FIG. 6C

A

Pseudoviruses IC_{50} (μg/mL)	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
D614G	0.038	0.741	0.603	0.125	0.075	0.050	0.034	0.006	0.084	>10	0.504	0.020
B. 1.1.7	0.050	0.631	1.074	0.115	0.085	0.040	0.039	0.006	0.251	>10	0.281	0.062
B.1.351	0.092	0.456	0.258	0.197	0.024	0.040	0.021	0.007	0.161	>10	0.355	0.026
P.1	0.084	0.398	0.285	0.148	0.022	0.030	0.019	0.007	0.046	>10	0.100	0.024
B.1.526	0.126	0.762	0.271	0.205	0.045	0.053	0.026	0.007	0.175	>10	0.708	0.022
B.1.429	0.048	0.503	0.229	0.036	0.027	0.025	0.013	0.003	0.070	>10	0.216	0.032
B.1.617.1	0.098	0.983	0.256	0.219	0.035	0.041	0.027	0.004	0.166	>10	0.414	0.027
B.1.617.2	0.068	0.500	0.154	0.179	0.045	0.045	0.025	0.005	0.139	>10	0.244	0.032
B.1.1.1	0.095	1.024	0.425	0.161	0.076	0.071	0.037	0.003	0.188	>10	0.440	0.037
R.1	0.094	0.855	0.263	0.117	0.030	0.054	0.018	0.005	0.126	>10	0.283	0.030

<0.01	0.01-0.1	0.1-1	1-10	>10

FIG. 7A

B

Live viruses IC_{50} (μg/mL)	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
WA1	0.087	1.484	0.583	0.117	0.091	0.049	0.072	0.001	0.410	>50	0.101	0.039
B. 1.1.7	0.045	0.874	0.629	0.053	0.058	0.039	0.026	0.001	0.391	>50	0.075	0.017
B.1.351	0.104	1.907	0.776	0.204	0.042	0.064	0.019	0.003	0.509	>50	0.237	0.027
P.1	0.079	1.141	0.336	0.069	0.058	0.152	0.052	0.002	0.621	>50	0.176	0.021
B.1.617.2	0.298	0.921	1.017	0.171	0.092	0.033	0.054	0.009	0.456	>50	0.314	0.021
SARS-CoV	0.151	NA	NA	13.790	0.221	0.170	3.801	0.008	NA	NA	NA	NA

<0.01	0.01-0.1	0.1-1	1-10	>10

FIG. 7B

C

Pseudoviruses IC_{50} (μg/mL)	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
GD-Pangolin	0.011	0.493	0.056	0.076	0.035	0.010	0.006	0.004	0.388	>10	>10	0.140
GX-Pangolin	0.090	5.359	>10	0.197	0.082	4.043	>10	0.029	0.763	>10	5.684	3.526
RaTG13	0.006	0.014	0.006	0.005	0.013	0.009	0.003	>10	0.009	1.401	>10	>10
SARS-CoV	0.046	1.023	0.063	1.597	0.037	0.042	1.259	0.003	6.330	1.561	0.698	0.026
WIV1	0.013	1.175	0.078	0.667	0.107	0.039	0.647	0.005	7.058	1.659	0.956	1.117
SHC014	0.008	0.225	0.024	0.142	0.021	0.022	1.947	0.006	>10	>10	>10	>10
LYRa11	0.005	5.074	0.008	0.832	0.009	0.008	1.092	0.002	2.888	>10	>10	>10
Rs7327	0.004	4.669	0.011	>10	0.011	0.003	0.484	0.002	>10	>10	>10	>10
RS4231	0.236	>10	0.016	>10	0.215	0.248	0.408	0.009	>10	>10	>10	>10
Rs4084	0.006	>10	0.014	3.195	0.017	0.007	0.133	0.005	>10	>10	>10	>10
MERS	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10	>10

<0.01	0.01-0.1	0.1-1	1-10	>10

FIG. 7C

D

RBD ELISA EC_{50} (μg/mL)	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
BM-4831	0.003	0.002	1.503	>10	0.002	0.005	0.720	0.711	>10	>10	0.009	0.286
BtKY72	0.004	0.004	0.007	1.035	0.003	0.004	0.001	0.005	>10	0.005	0.006	>10
SHC014	0.005	0.002	0.006	0.002	0.003	0.007	0.003	0.003	0.049	0.006	>10	0.018
WIV1	0.004	0.003	0.006	0.026	0.003	0.005	0.003	0.005	>10	0.004	0.540	0.023
SARS-CoV	0.008	0.005	0.019	>10	0.009	0.015	>10	0.002	>10	0.009	0.015	0.011
GX-Pangolin	0.004	0.004	>10	0.008	0.006	0.035	3.296	0.089	0.043	0.030	0.026	0.052
RaTG13	0.003	0.002	>10	0.009	0.003	>10	>10	>10	0.614	0.262	0.008	>10
SARS-CoV-2	0.005	0.003	0.006	0.003	0.004	0.003	0.001	0.003	0.004	0.004	0.003	0.007
B.1.351	0.007	0.004	0.030	0.007	0.009	0.006	0.002	0.007	0.014	0.008	0.005	0.021
Rf1	0.004	0.004	>10	2.455	>10	>10	>10	>10	7.072	>10	0.005	>10
RmYN02	0.010	0.005	>10	1.071	0.010	>10	>10	>10	>10	>10	0.011	>10
Rs4081	0.009	0.007	>10	5.449	0.013	2.287	>10	>10	>10	0.826	0.009	>10
Yunnan2011	0.037	0.009	>10	>10	0.011	>10	>10	>10	>10	0.307	0.124	>10

<0.01	0.01-0.1	0.1-1	1-10	>10

FIG. 7D

E

Cell surface staining Positive %	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
GX-Pangolin	100	99	60	94	99	62	84	73	62	36	61	100
RaTG13	97	96	91	85	97	11	92	1	28	2	9	99
GD-Pangolin	99	99	98	99	99	65	99	61	35	68	61	100
RmYN02	96	96	4	90	96	20	0	1	1	1	12	1
ZC45	25	17	1	4	21	0	1	0	0	0	0	4
Yunnan2011	40	42	22	30	44	1	25	1	1	0	1	61
As6526	74	76	1	40	79	1	1	0	1	0	0	2
Rs4237	76	77	1	33	80	1	1	1	1	0	1	3
Rs4081	76	79	1	53	81	12	1	0	0	0	9	2

0% 100%

FIG. 7E

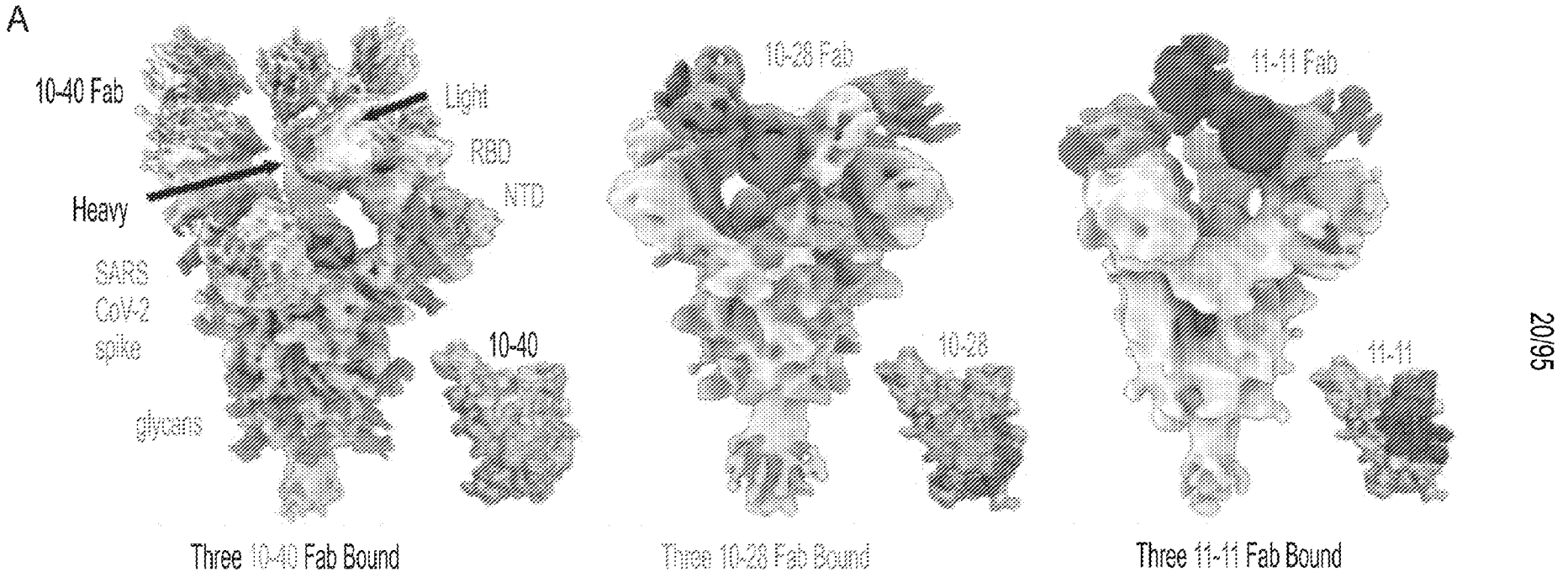
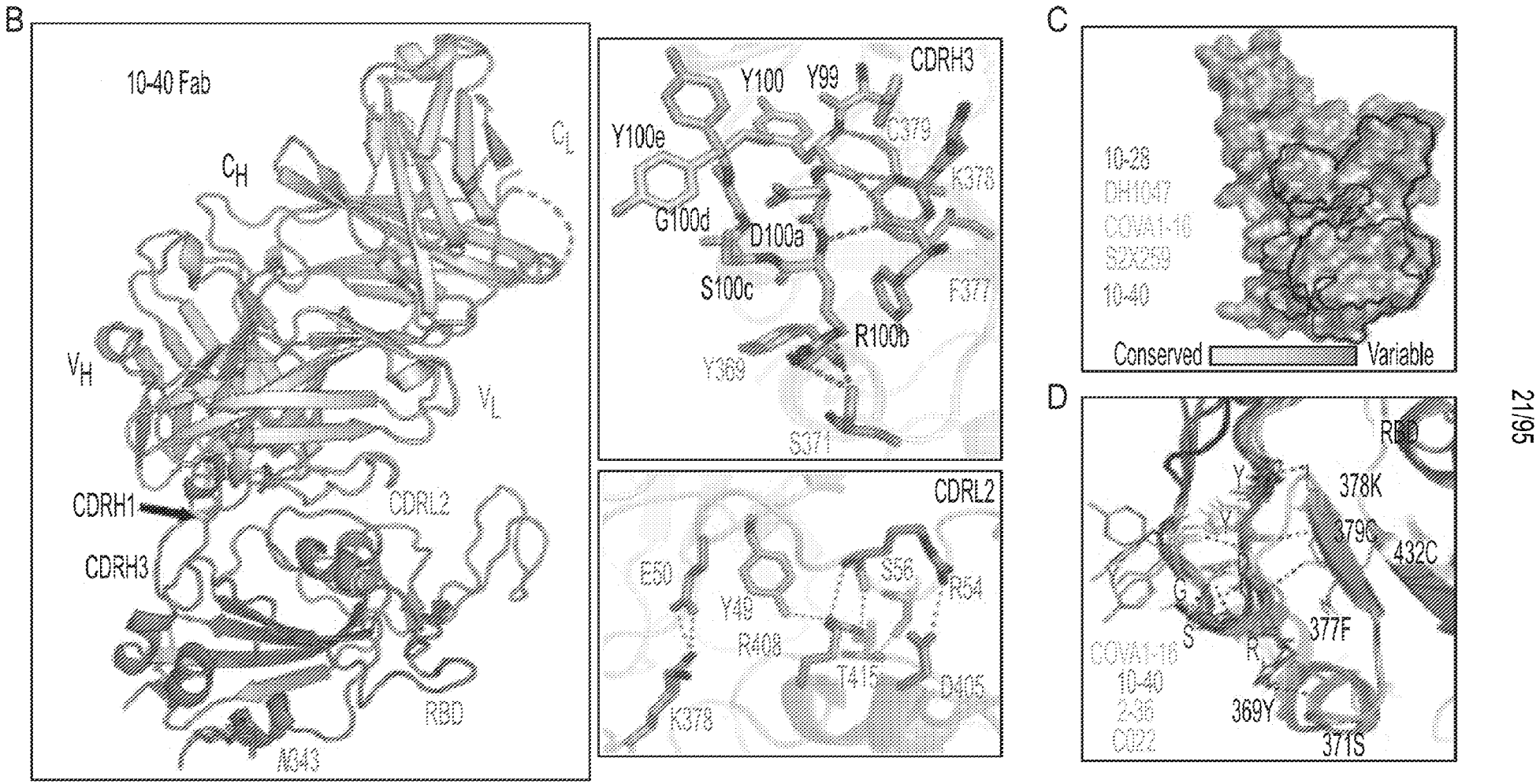
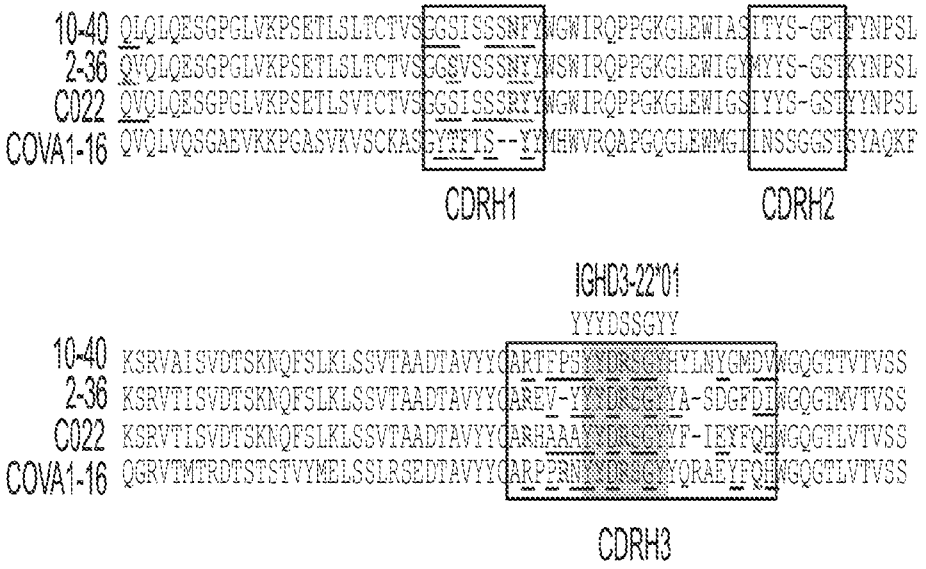

A
10-40 Fab
Light
RBD
NTD
Heavy
SARS
CoV-2
spike
glycans
10-40
Three 10-40 Fab Bound
10-28 Fab
10-28
Three 10-28 Fab Bound
11-11 Fab
11-11
Three 11-11 Fab Bound

FIG. 8A


B
10-40 Fab
C_H
C_L
V_H
V_L
CDRH1
CDRH3
CDRL2
RBD
N343
CDRH3
Y100
Y99
Y100e
C379
K378
G100d
D100a
S100c
F377
R100b
Y369
S371
CDRL2
E50
S56
R54
Y49
R408
T415
D405
K378
C
10-28
DH1047
COVA1-16
S2X259
10-40
Conserved
Variable
D
RBD
Y
378K
379C
432C
G
S
377F
R
COVA1-16
10-40
2-36
CD2
369Y
371S

FIGS. 8B-D

E


10-40
2-36
C022
COVA1-16
CDRH1
CDRH2
IGHD3-22*01
YYYDSSGYY
CDRH3

F

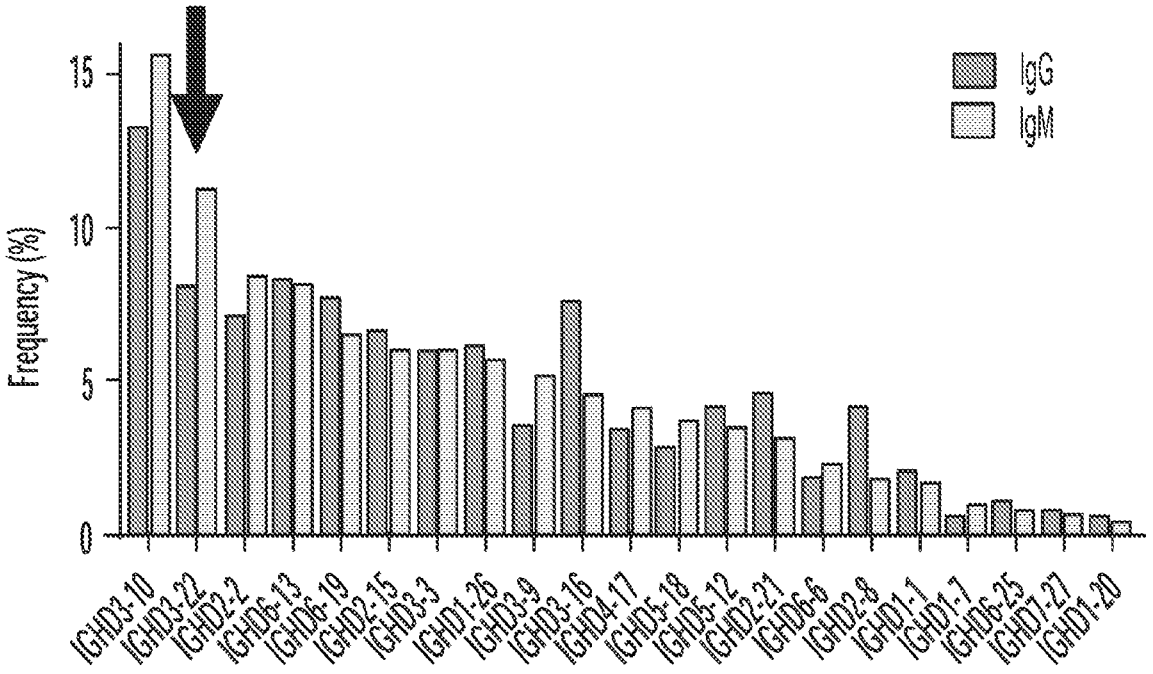
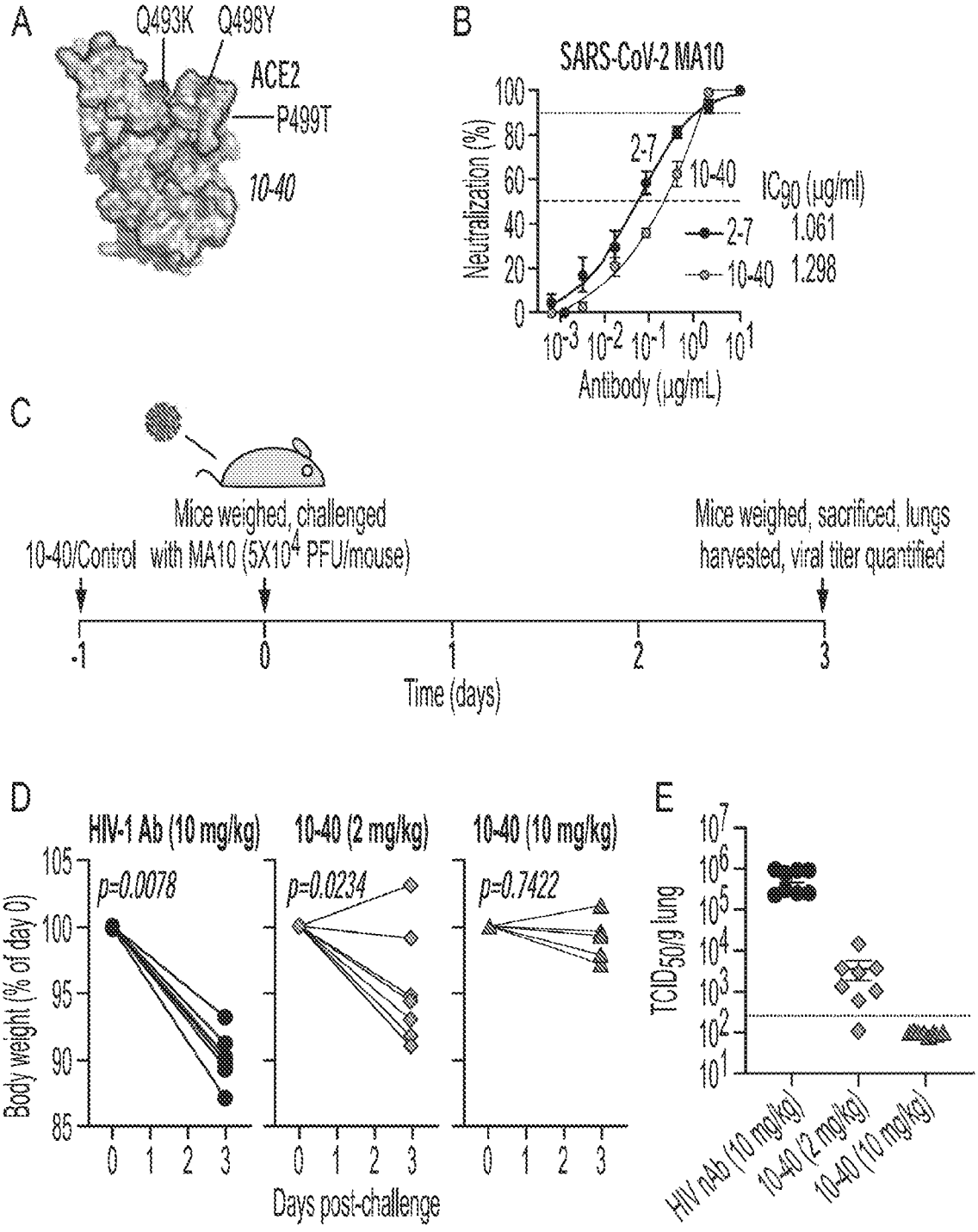
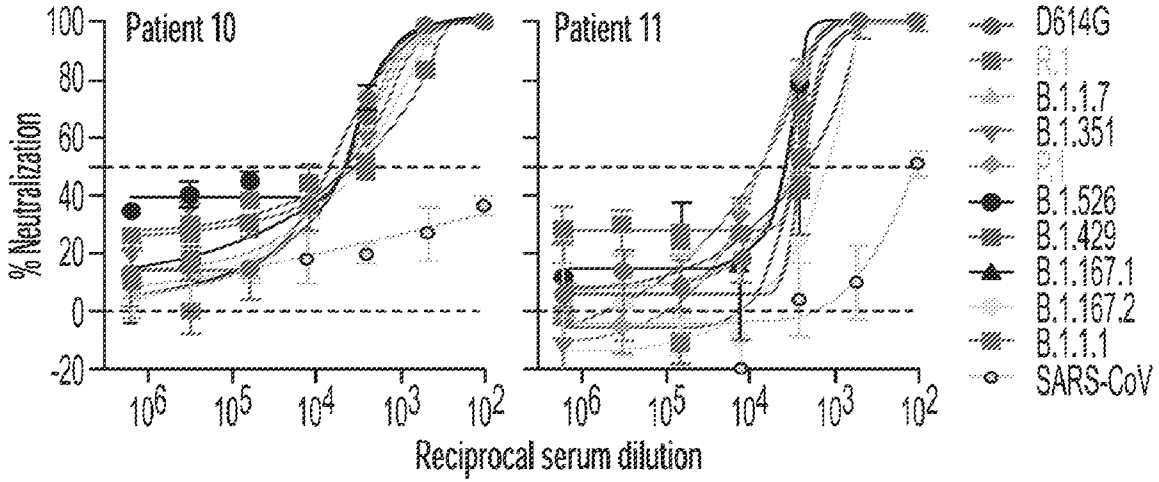

IgG
IgM
Frequency (%)
0
5
10
15
IGHD3-10
IGHD3-22
IGHD2-2
IGHD6-13
IGHD6-19
IGHD2-15
IGHD3-3
IGHD1-26
IGHD3-9
IGHD3-16
IGHD4-17
IGHD5-18
IGHD5-12
IGHD2-21
IGHD6-6
IGHD2-8
IGHD1-1
IGHD1-7
IGHD6-25
IGHD7-27
IGHD1-20

FIG. 8E-F


A
Q493K
Q498Y
ACE2
P499T
10-40
B
SARS-CoV-2 MA10
Neutralization (%)
2-7
10-40
IC90 (µg/ml)
2-7 1.061
10-40 1.298
Antibody (µg/mL)
C
Mice weighed, challenged
10-40/Control with MA10 (5X10^4 PFU/mouse)
Mice weighed, sacrificed, lungs
harvested, viral titer quantified
Time (days)
D
HIV-1 Ab (10 mg/kg)
10-40 (2 mg/kg)
10-40 (10 mg/kg)
p=0.0078
p=0.0234
p=0.7422
Body weight (% of day 0)
Days post-challenge
E
TCID50/g lung
HIV nAb (10 mg/kg)
10-40 (2 mg/kg)
10-40 (10 mg/kg)

FIGS. 9A-E

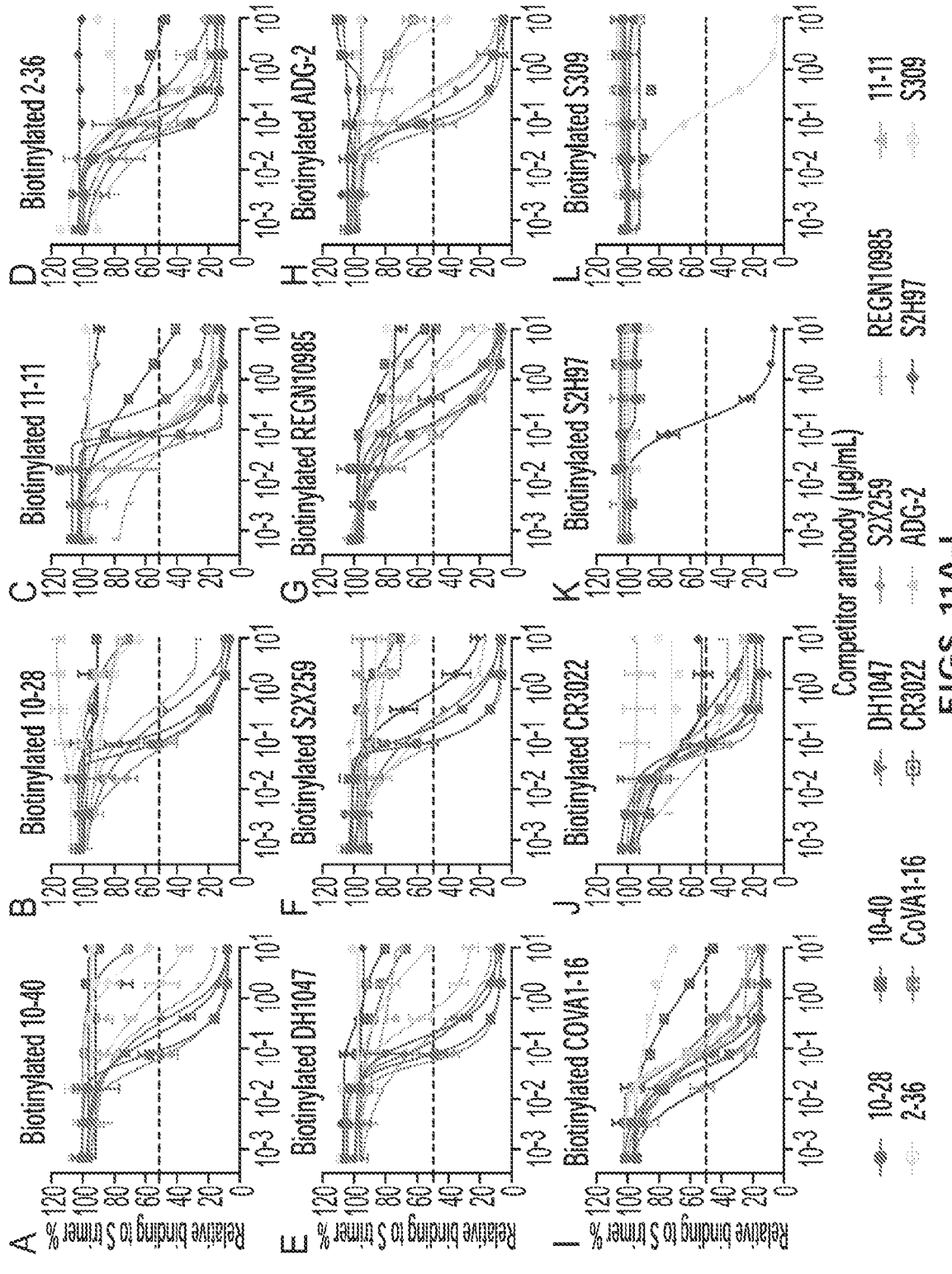
A



B

ID_{50}	Patient 10	Patient 11
D614G	6911	3635
R.1	3567	2641
B.1.1.7	4354	2967
B.1.1.351	4326	7147
P.1	4225	6625
B.1.526	4657	3562
B.1.429	7515	2112
B.1.617.1	4112	2238
B.1.617.2	3544	1126
B.1.1.1	4837	2781
SARS-CoV	>100	102

FIGS. 10A-B


A
Biotinylated 10-40
B
Biotinylated 10-28
C
Biotinylated 11-11
D
Biotinylated 2-36
E
Biotinylated DH1047
F
Biotinylated S2X259
G
Biotinylated REGN10985
H
Biotinylated ADG-2
I
Biotinylated COVA1-16
J
Biotinylated CR3022
K
Biotinylated S2H97
L
Biotinylated S309
Relative binding to S trimer %
Competitor antibody (µg/mL)
10-28
10-40
DH1047
S2X259
REGN10985
11-11
2-36
CoVA1-16
CR3022
ADG-2
S2H97
S309

FIGS. 11A-L

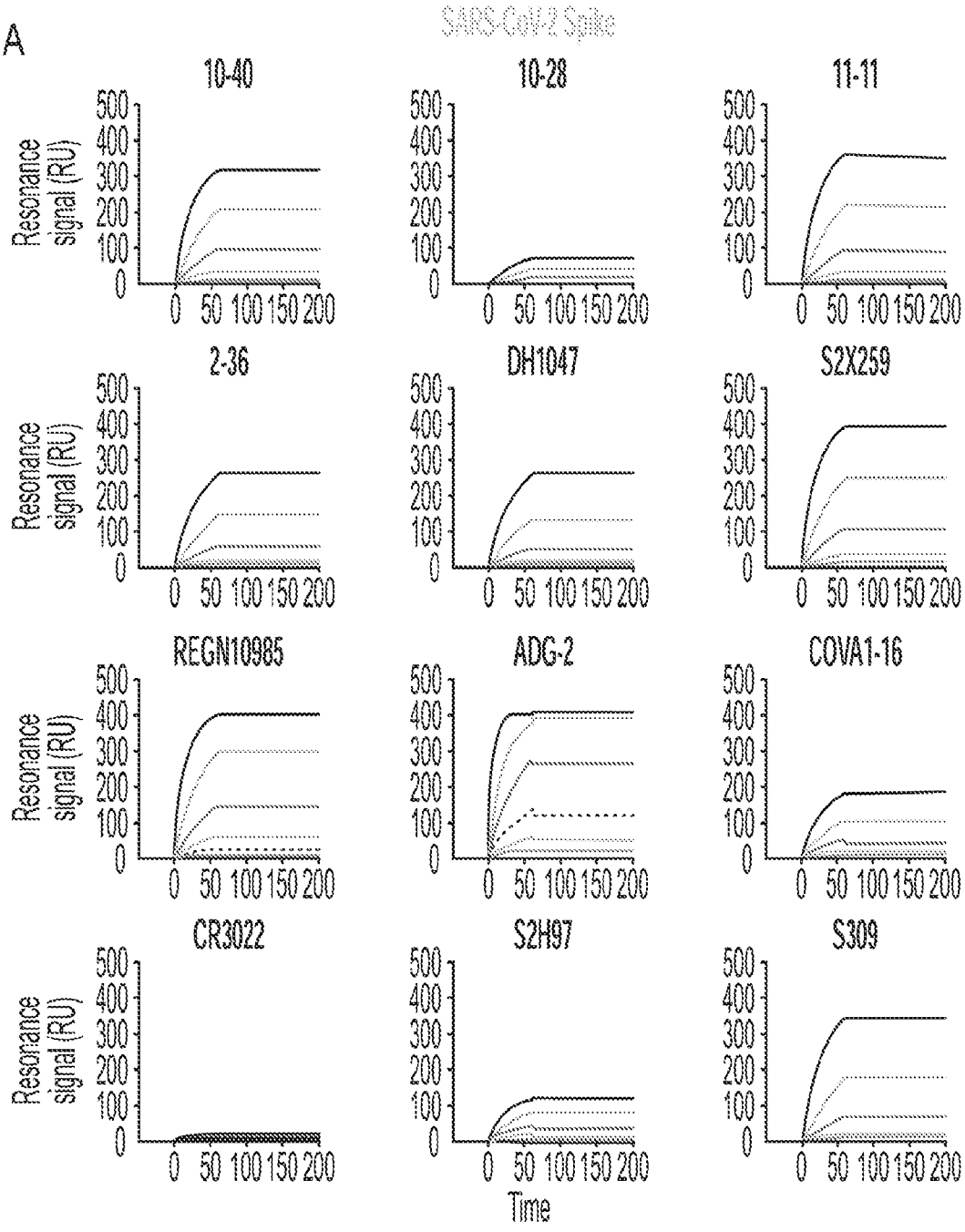

A
SARS-CoV-2 Spike
10-40
10-28
11-11
2-36
DH1047
S2X259
REGN10985
ADG-2
COVA1-16
CR3022
S2H97
S309
Resonance signal (RU)
0
100
200
300
400
500
0 50 100 150 200
Time

FIG. 12A

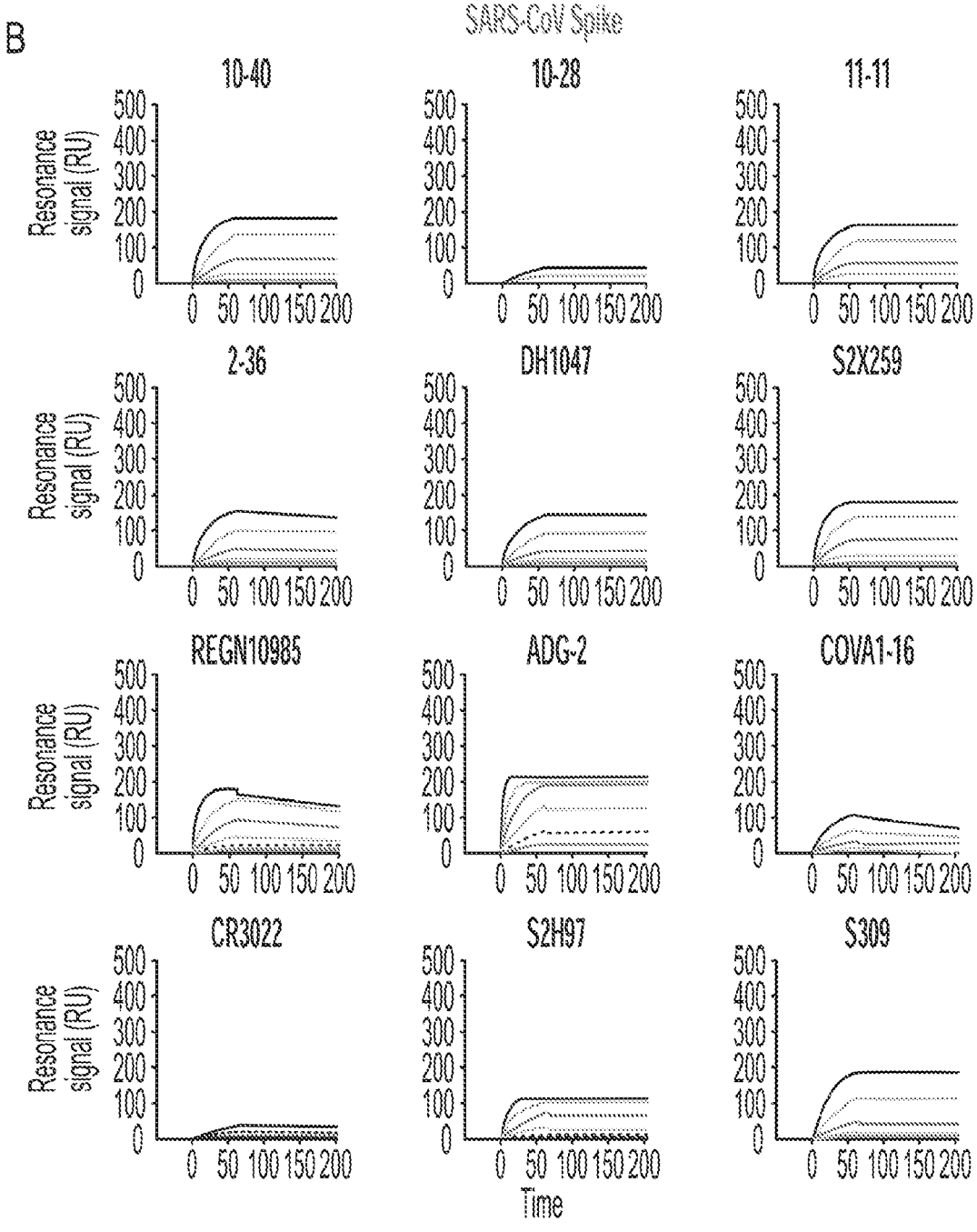

B
SARS-CoV Spike
10-40
10-28
11-11
2-36
DH1047
S2X259
REGN10985
ADG-2
COVA1-16
CR3022
S2H97
S309
Resonance signal (RU)
0
100
200
300
400
500
0 50 100 150 200
Time

FIG. 12B

C

mAb	SARS-CoV-2 Spike			SARS-CoV Spike		
	ka (1/Ms)	kd (1/s)	KD (M)	ka (1/Ms)	kd (1/s)	KD (M)
10-40	1.60E+05	7.22E-07	4.52E-12	2.05E+05	4.54E-07	2.21E-12
10-28	9.17E+04	7.17E-08	7.82E-13	5.44E+04	2.01E-07	3.69E-12
11-11	1.36E+05	2.09E-04	1.54E-09	1.85E+05	8.34E-07	4.51E-12
2-36	1.11E+05	1.68E-06	1.51E-11	1.69E+05	4.99E-04	2.96E-09
DH1047	8.59E+04	9.10E-08	1.06E-12	1.52E+05	1.69E-07	1.11E-12
S2X259	1.54E+05	1.38E-07	8.95E-13	2.41E+05	8.78E-07	3.65E-12
REGN10985	2.10E+05	1.83E-06	8.72E-12	4.08E+05	1.90E-03	4.65E-09
ADG-2	5.09E+05	5.00E-07	9.83E-13	1.23E+06	1.73E-06	1.41E-12
COVA1-16	1.03E+05	1.33E-07	1.29E-12	1.64E+05	3.20E-03	1.95E-08
CR3022	2.71E+05	4.85E-04	1.79E-09	8.59E+04	6.52E-08	7.59E-13
S2H97	1.64E+05	7.42E-07	4.53E-12	5.20E+05	3.67E-05	7.06E-11
S309	9.18E+04	1.78E-07	1.94E-12	1.35E+05	2.63E-07	1.95E-12

FIG. 12C

A

mAbs	HV	HD	HJ	Isotype	H_SHM(%)	H_CDR3_len	HCDR3
10-28	IGHV3-30*18	IGHD2-2*03	IGHJ4*02	IGHG1*04	2.4	13	CVKDGEQLVPLFDYW
10-40	IGHV4-39*01	IGHD3-22*01	IGHJ6*02	IGHG1*04	3	22	CARTFPSYYDRSGYHYLNYGMDVW
11-11	IGHV4-31*03	IGHD3-22*01	IGHJ6*02	IGHM*03	0.7	21	CASSNYYDGSGYNLLESYGMDVW

mAbs	LV	LJ	L_SHM(%)	L_CDR3_len	LCDR3
10-28	IGKV1-39*01	IGKJ3*01	0.4	10	CQQSYSTPGVTF
10-40	IGLV6-57*01	IGLJ3*02	0.3	9	CQSYDSSSWVF
11-11	IGLV1-40*01	IGLJ3*02	1	12	CQSYDSSLSGSWVF

FIG. 13A

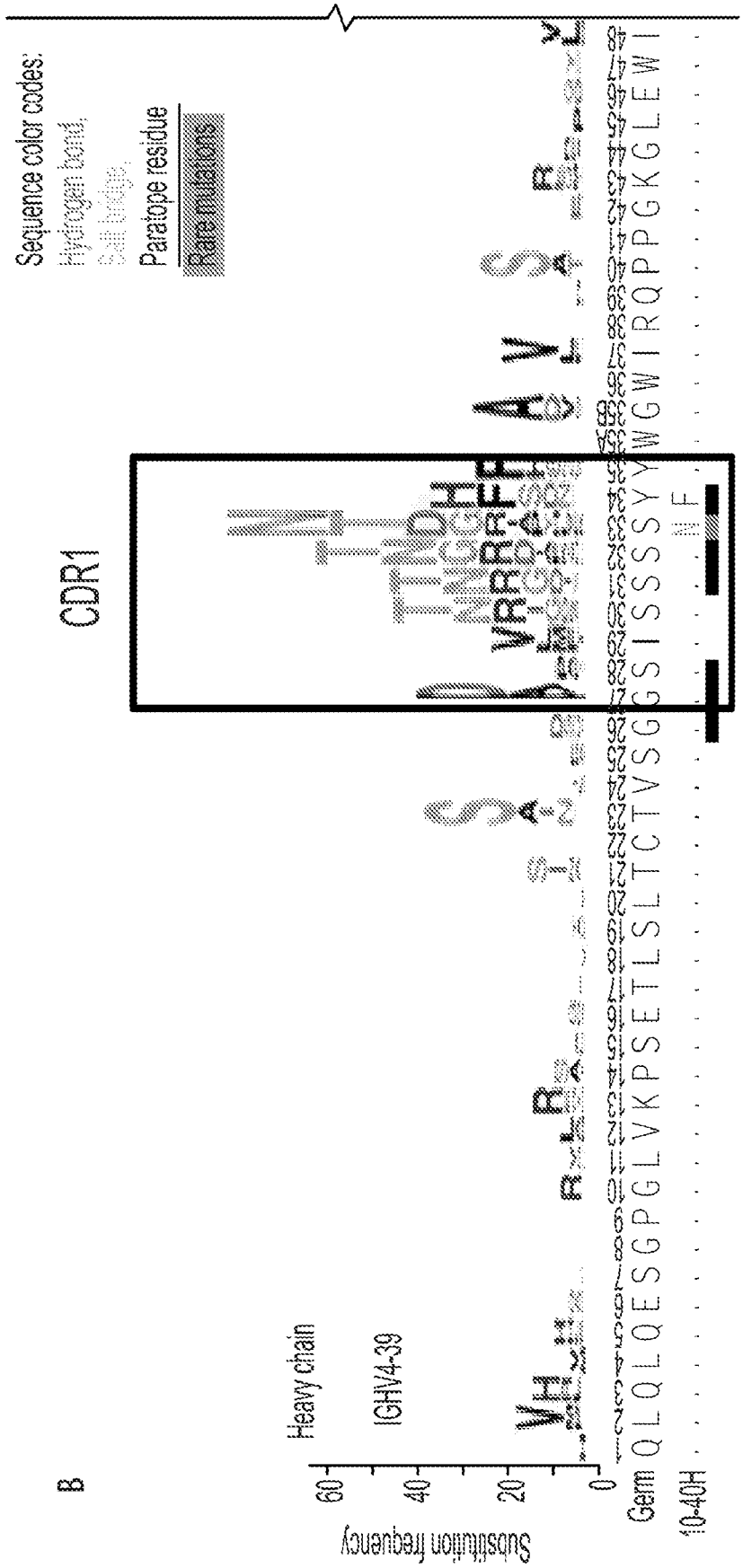

B
Heavy chain
IGHV4-39
Substitution frequency
60
40
20
0
Germ Q L Q L Q E S G P G L V K P S E T L S L T C T V S G G S I S S S S Y Y W G W I R Q P P G K G L E W I
10-40H
CDR1
Sequence color codes:
Hydrogen bond,
Salt bridge,
Paratope residue
Rare mutations

FIG. 13B

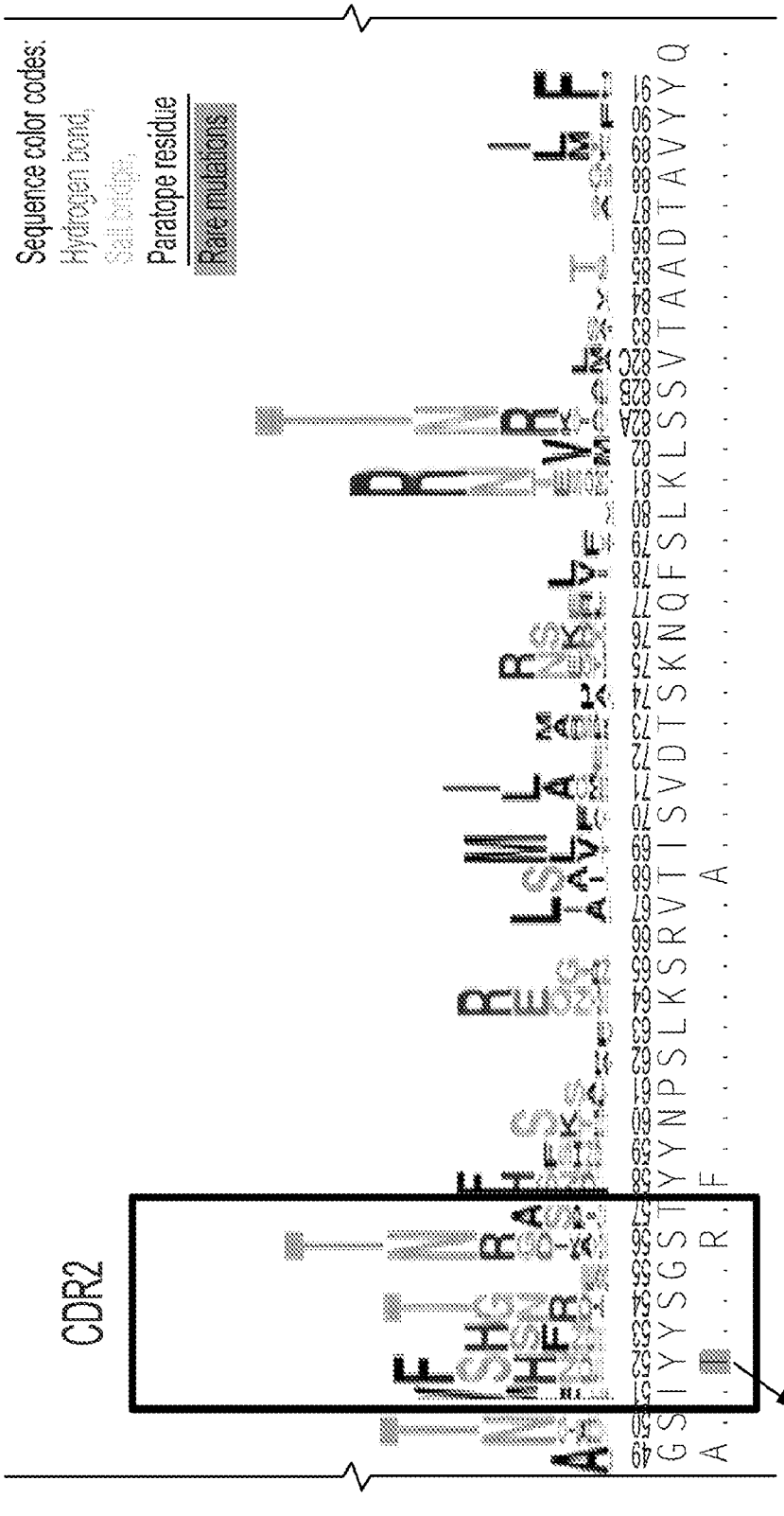


FIG. 13B
CONTINUED

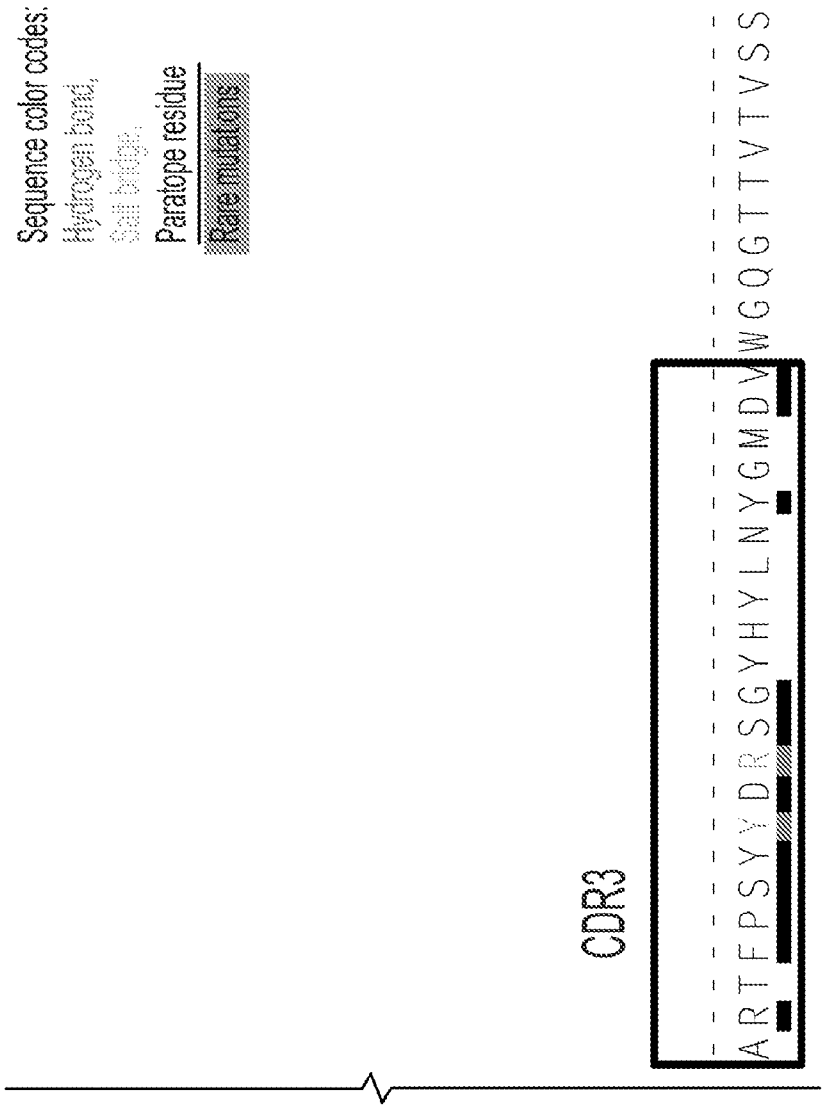
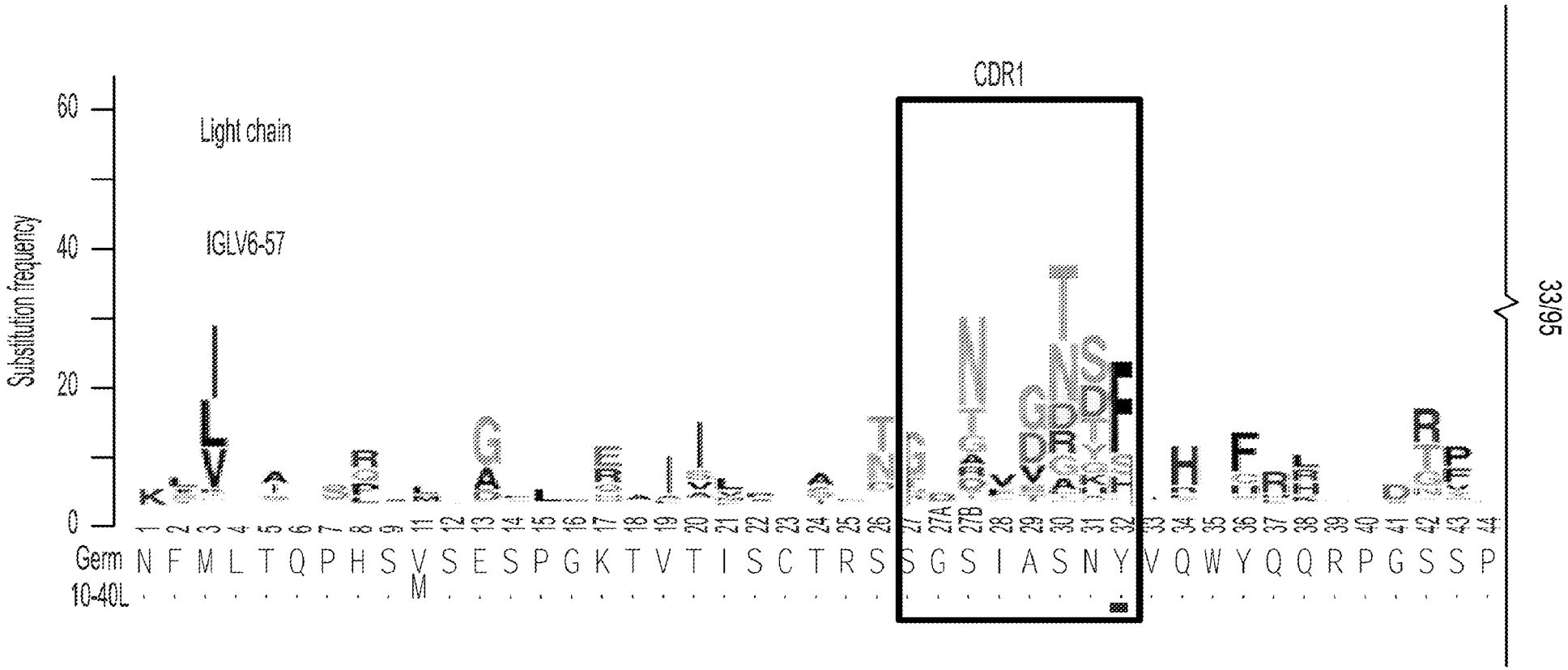


FIG. 13B
CONTINUED



33/95

FIG. 13B
CONTINUED

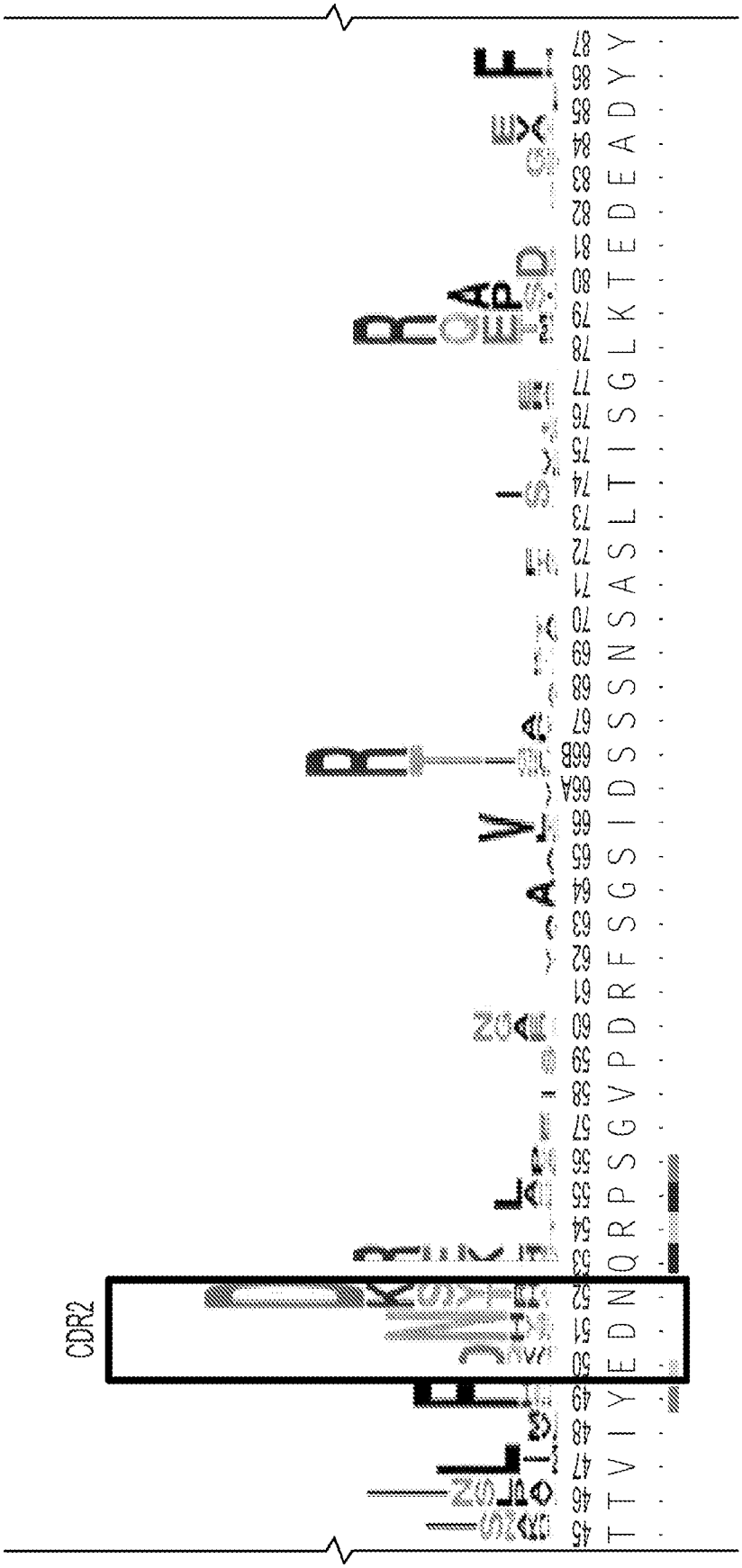


FIG. 13B
CONTINUED

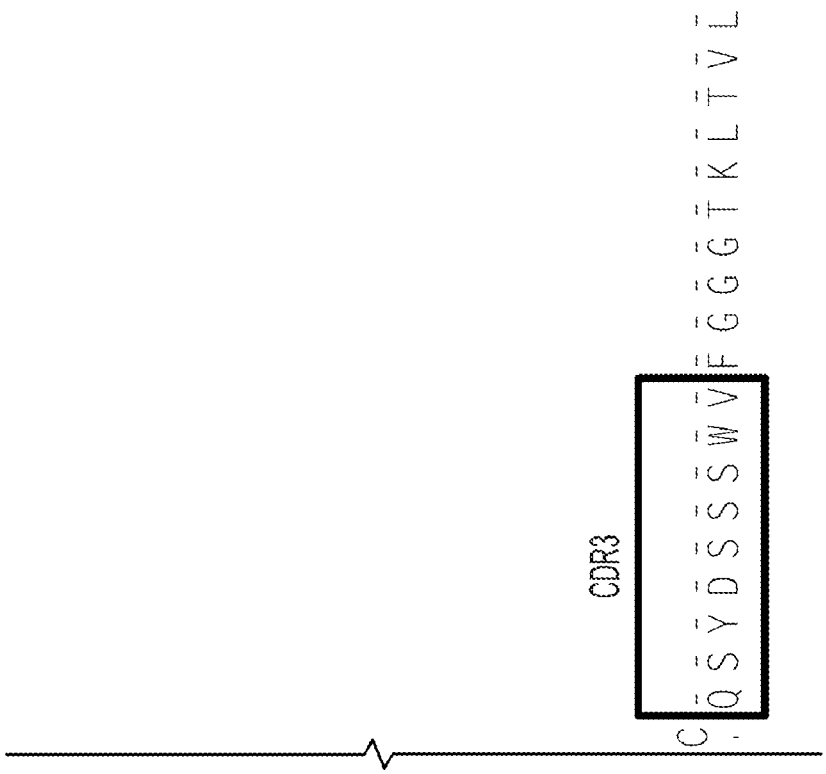
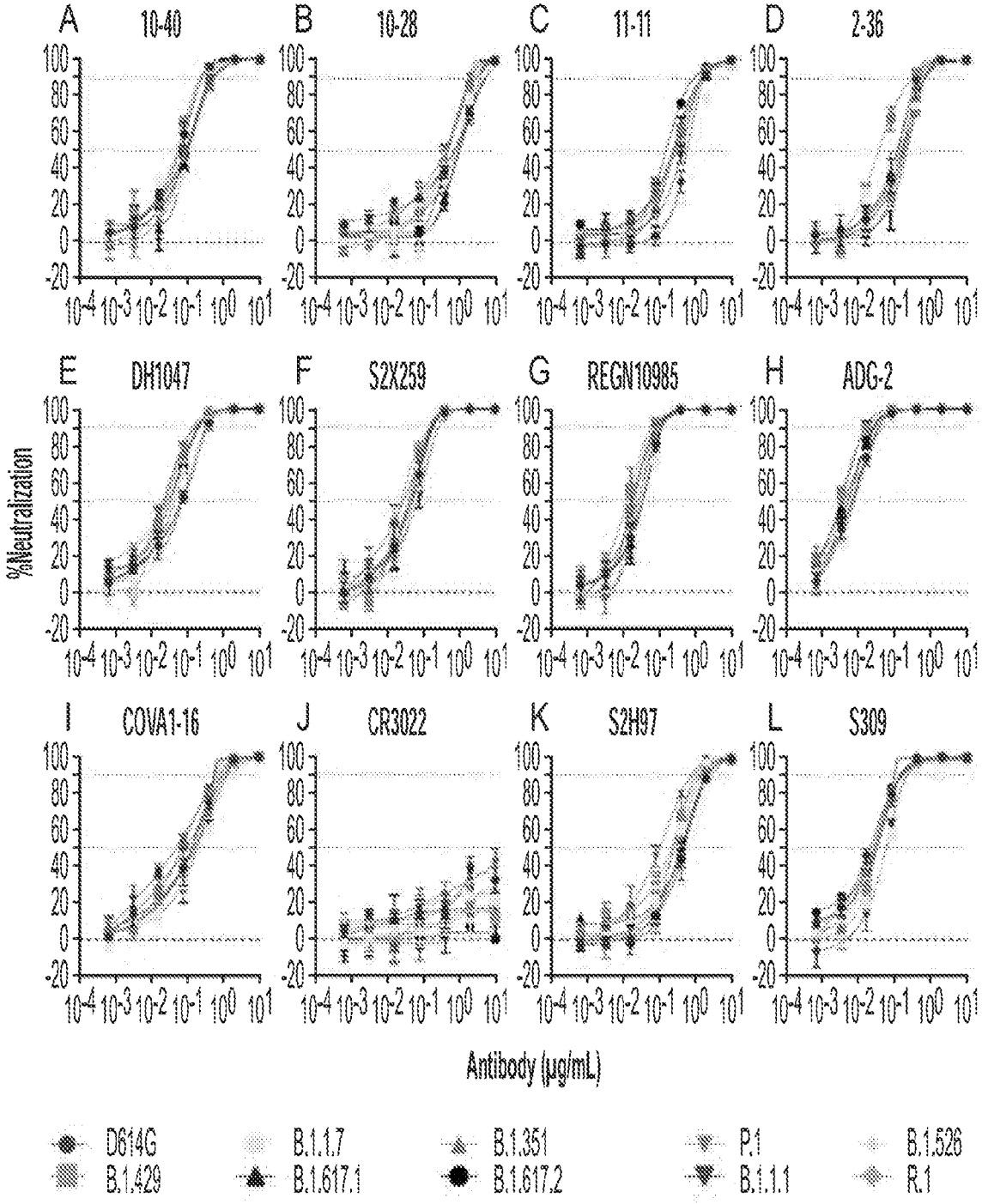


FIG. 13B
CONTINUED

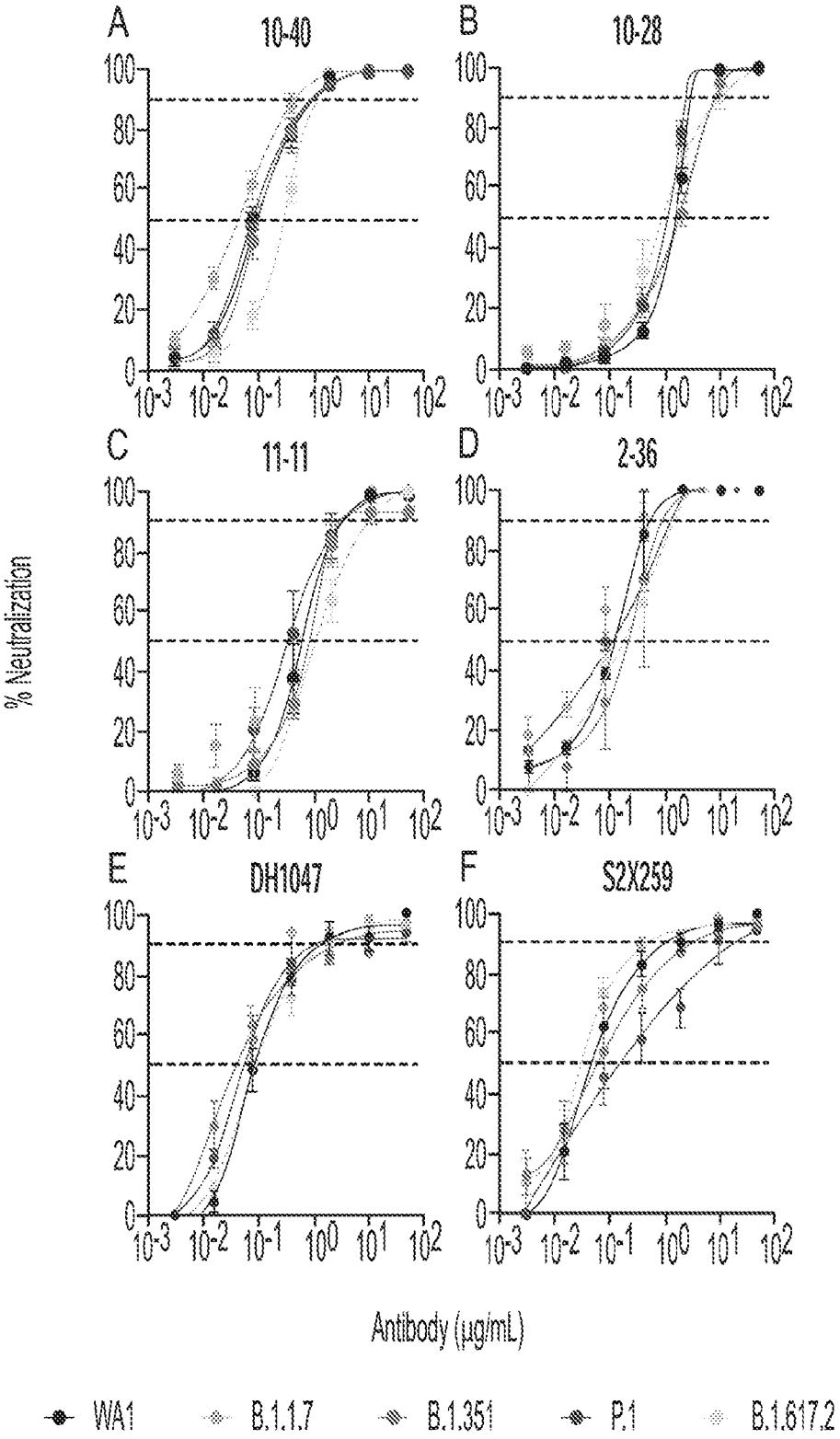
C

Region	Signature motifs	Compatible genes	Critical
CDRH1	GGS[IV]SSS[NR][FY]Y	IGHV4-39, IGHV4-61, IGHV4-31, IGHV4-30-2/4	No
	GYTFTSYY	IGHV1-46, IGHV1-2	No
CDRH3	ARx{4-5}YYDRSGYx{8-9}	IGHD3-22*01	Yes
Light Chain	NA	IGLV6-57, IGKV3-20, IGKV1-33, IGKV1-9	No

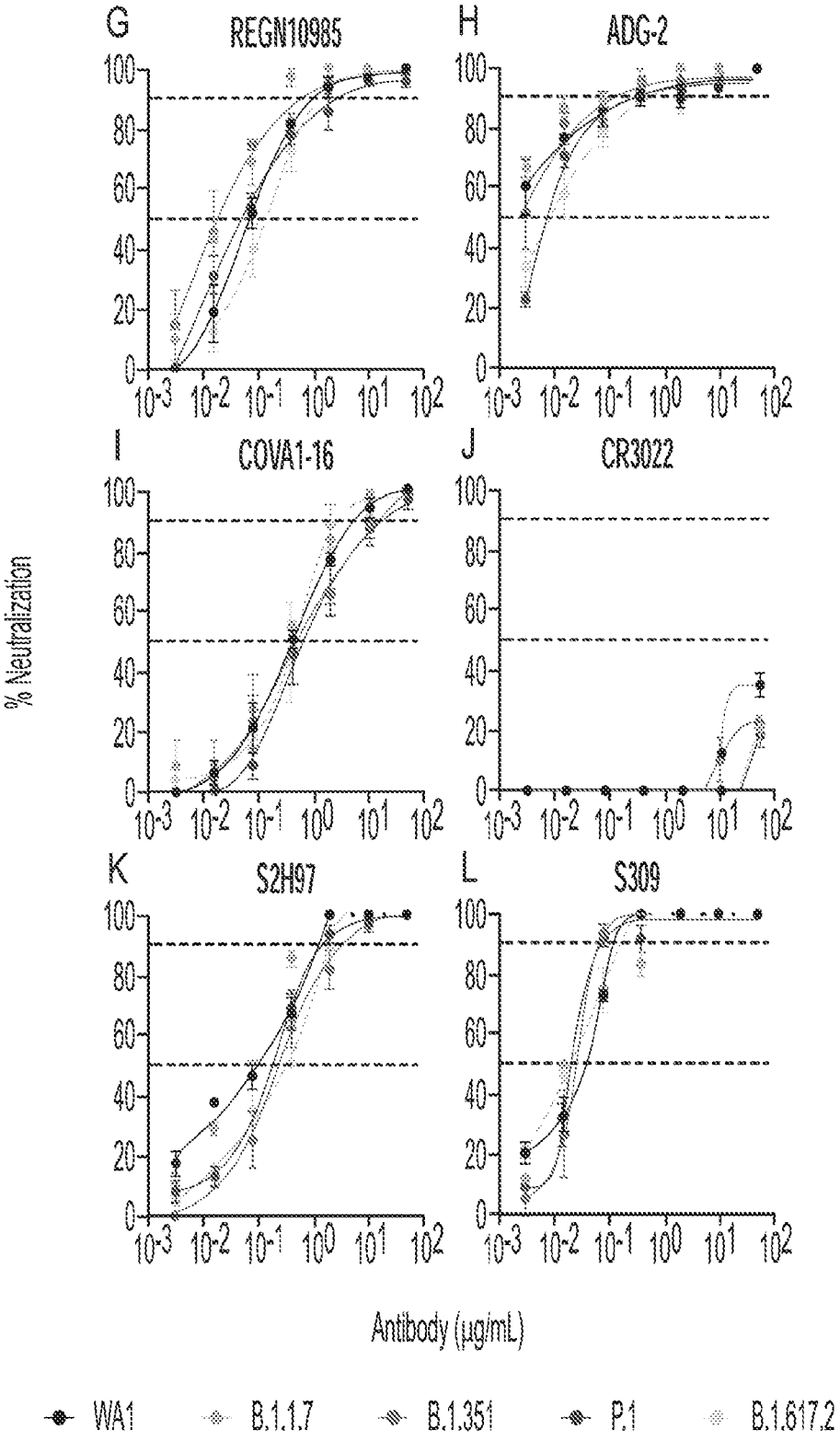
FIG. 13C


A
10-40
B
10-28
C
11-11
D
2-36
E
DH1047
F
S2X259
G
REGN10985
H
ADG-2
I
COVA1-16
J
CR3022
K
S2H97
L
S309
%Neutralization
Antibody (µg/mL)
D614G
B.1.429
B.1.1.7
B.1.617.1
B.1.351
B.1.617.2
P.1
B.1.1.1
B.1.526
R.1

FIGS. 14A-L


A
10-40
B
10-28
C
11-11
D
2-36
E
DH1047
F
S2X259
% Neutralization
Antibody (µg/mL)
WA1
B.1.1.7
B.1.351
P.1
B.1.617.2

FIGS. 15A-F


G
REGN10985
H
ADG-2
I
COVA1-16
J
CR3022
K
S2H97
L
S309
% Neutralization
Antibody (µg/mL)
WA1
B.1.1.7
B.1.351
P.1
B.1.617.2

FIGS. 15G-L

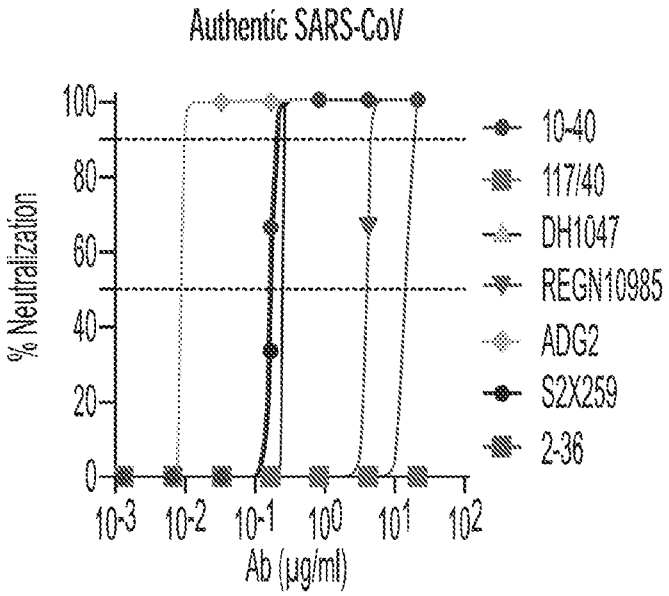
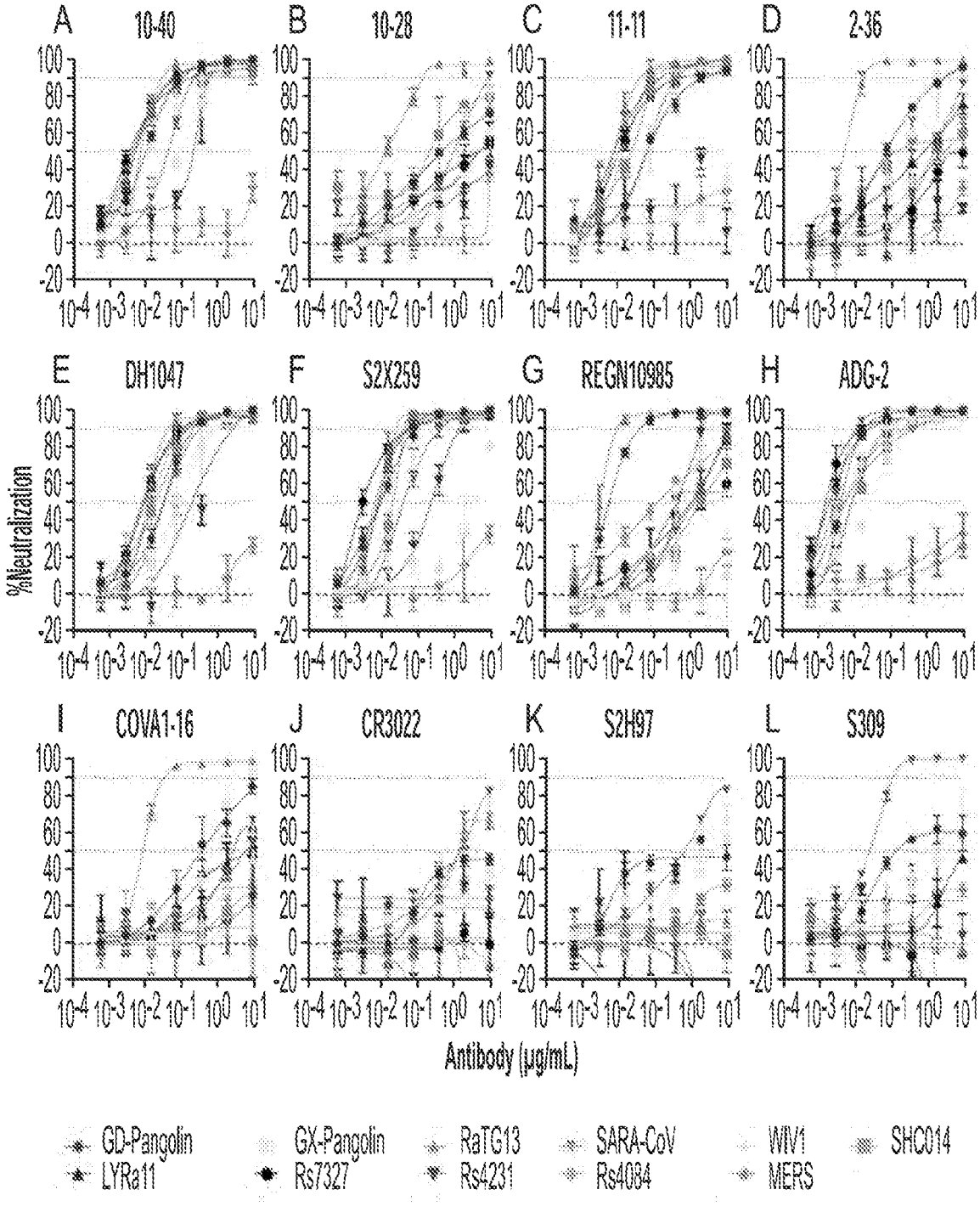
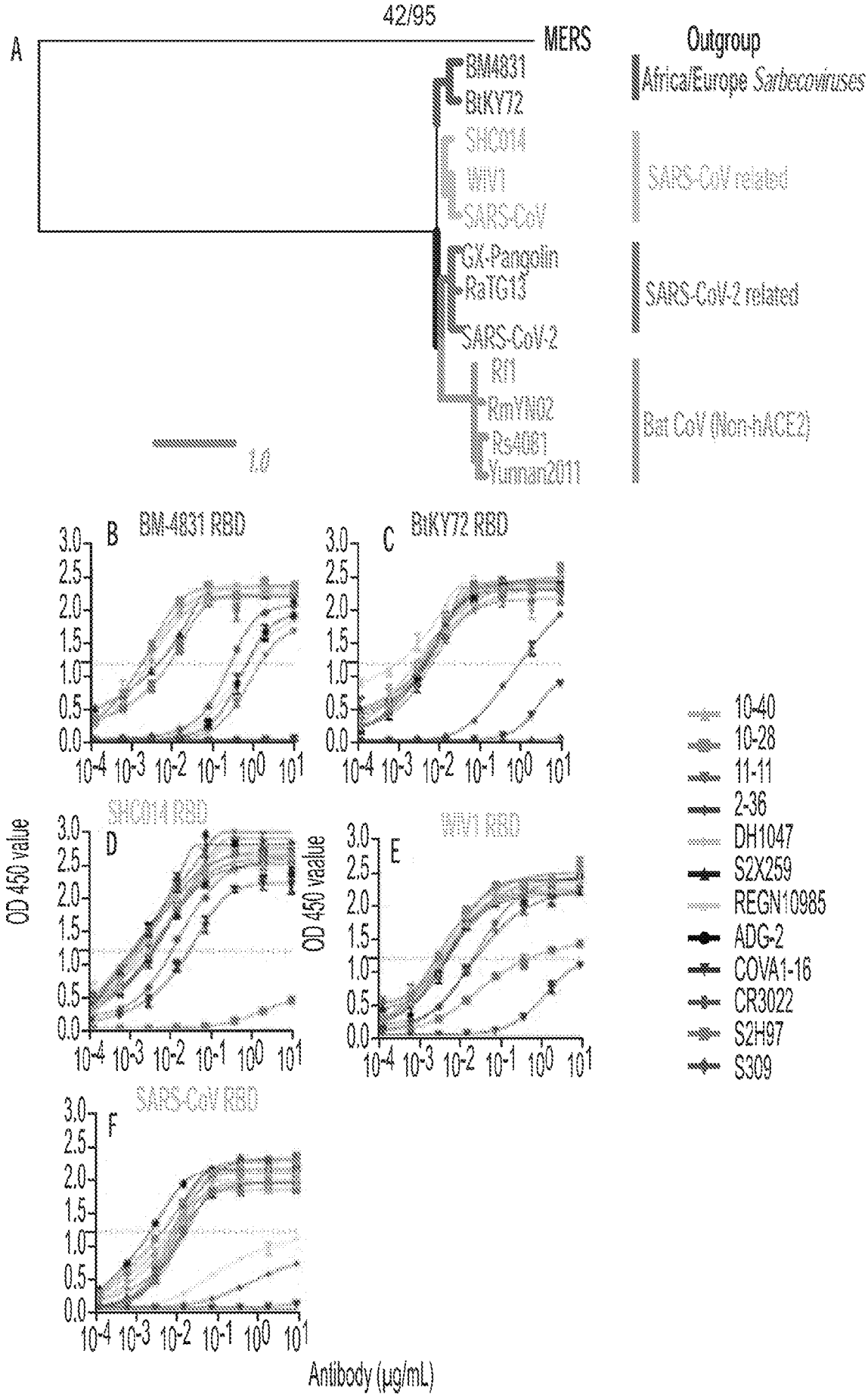

Authentic SARS-CoV
% Neutralization
100
80
60
40
20
0
10-3
10-2
10-1
100
101
102
Ab (µg/ml)
10-40
117/40
DH1047
REGN10985
ADG2
S2X259
2-36

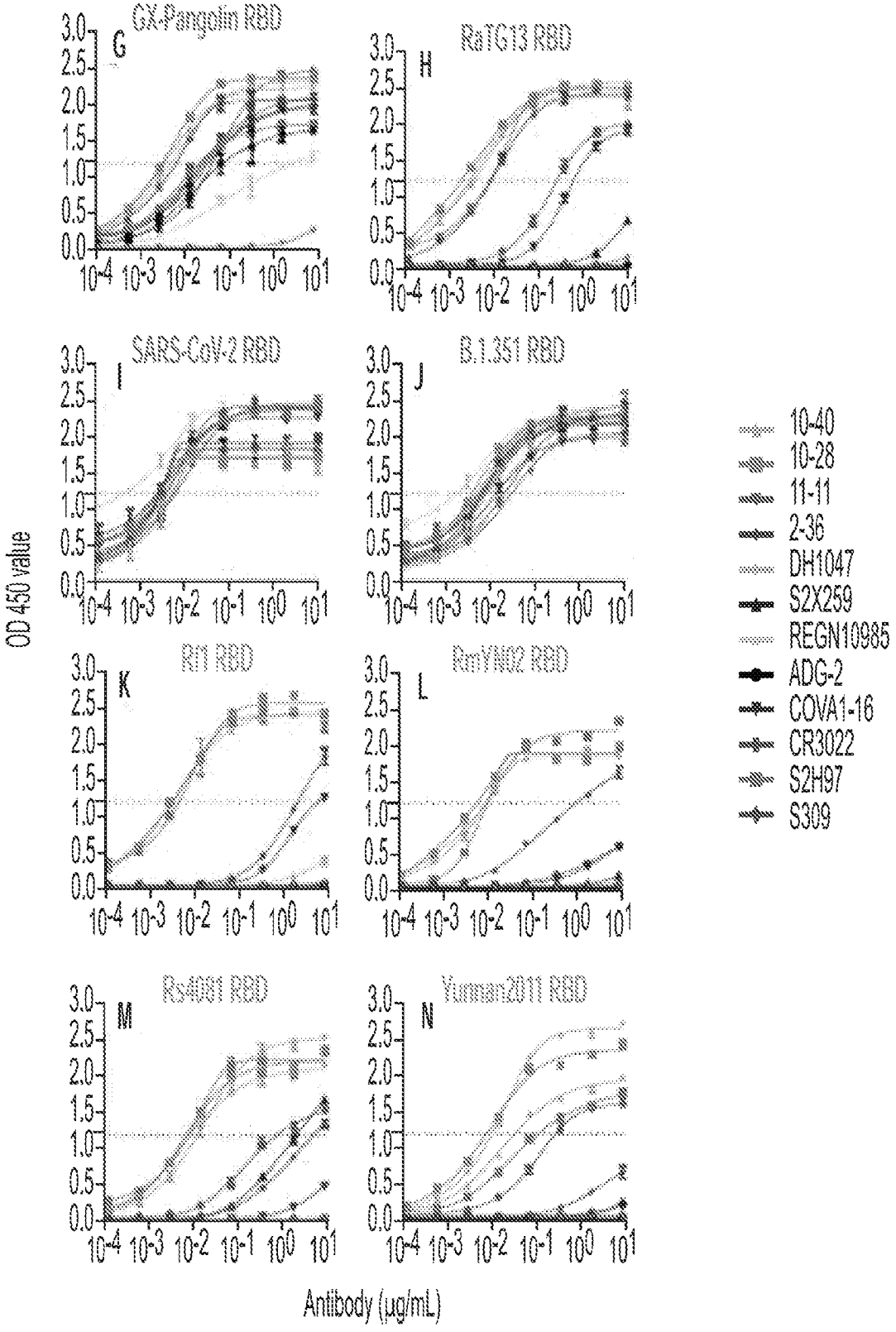
FIG. 15M


A
10-40
B
10-28
C
11-11
D
2-36
E
DH1047
F
S2X259
G
REGN10985
H
ADG-2
I
COVA1-16
J
CR3022
K
S2H97
L
S309
%Neutralization
Antibody (μg/mL)
GD-Pangolin
LYRa11
GX-Pangolin
Rs7327
RaTG13
Rs4231
SARA-CoV
Rs4084
WIV1
MERS
SHC014

FIGS. 16A-L


A
42/95
MERS
Outgroup
Africa/Europe Sarbecoviruses
BM4831
BtKY72
SHC014
WIV1
SARS-CoV
SARS-CoV related
GX-Pangolin
RaTG13
SARS-CoV-2
SARS-CoV-2 related
Rf1
RmYN02
Rs4081
Yunnan2011
Bat CoV (Non-hACE2)
1.0
B BM-4831 RBD
C BtKY72 RBD
D SHC014 RBD
E WIV1 RBD
F SARS-CoV RBD
OD 450 value
Antibody (μg/mL)
10-40
10-28
11-11
2-36
DH1047
S2X259
REGN10985
ADG-2
COVA1-16
CR3022
S2H97
S309

FIGS. 17A-F


GX-Pangolin RBD
RaTG13 RBD
SARS-CoV-2 RBD
B.1.351 RBD
R1 RBD
RmYN02 RBD
Rs4081 RBD
Yunnan2011 RBD
OD 450 value
Antibody (μg/mL)
10-40
10-28
11-11
2-36
DH1047
S2X259
REGN10985
ADG-2
COVA1-16
CR3022
S2H97
S309

FIGS. 17G-N

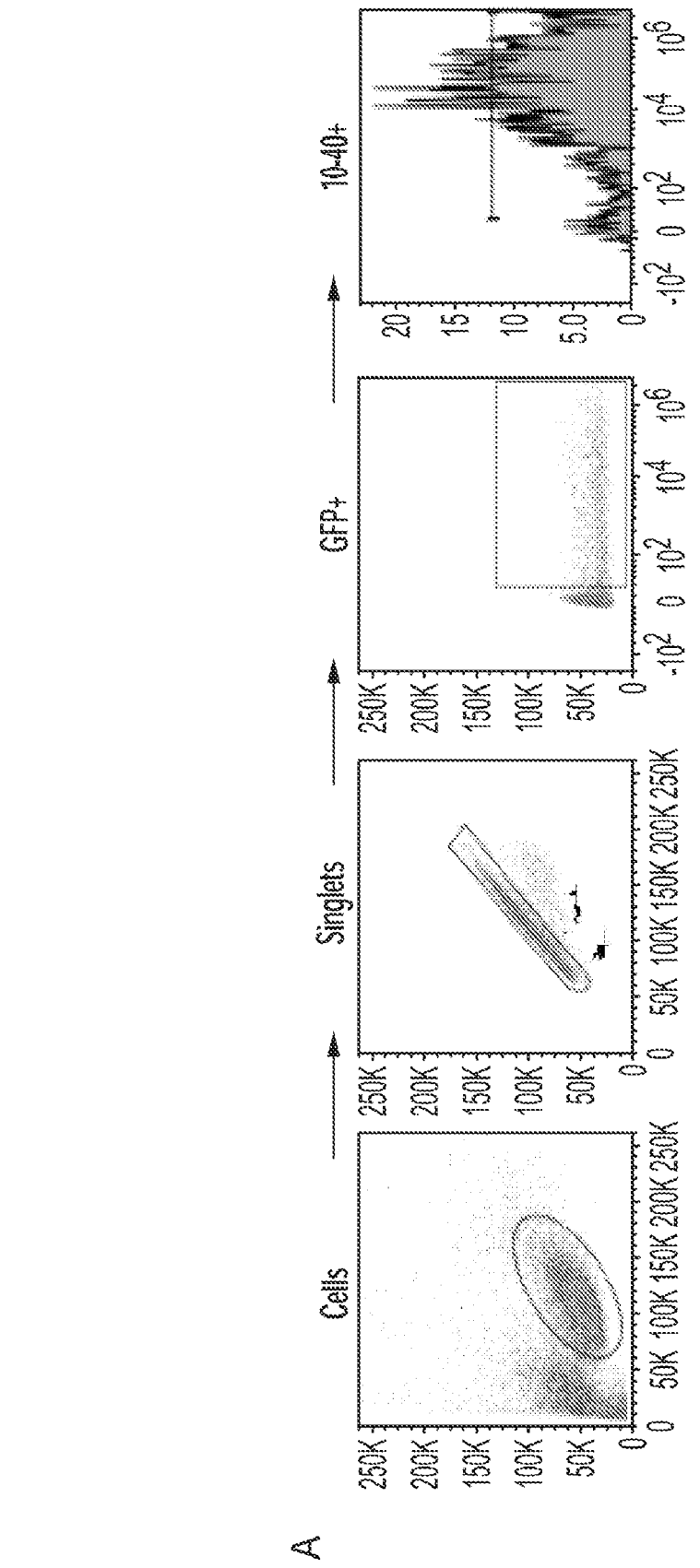

A
Cells
Singlets
GFP+
10-40+
250K
200K
150K
100K
50K
0
50K 100K 150K 200K 250K
-10^2
0
10^2
10^4
10^6
20
15
10
5.0

FIG. 18A

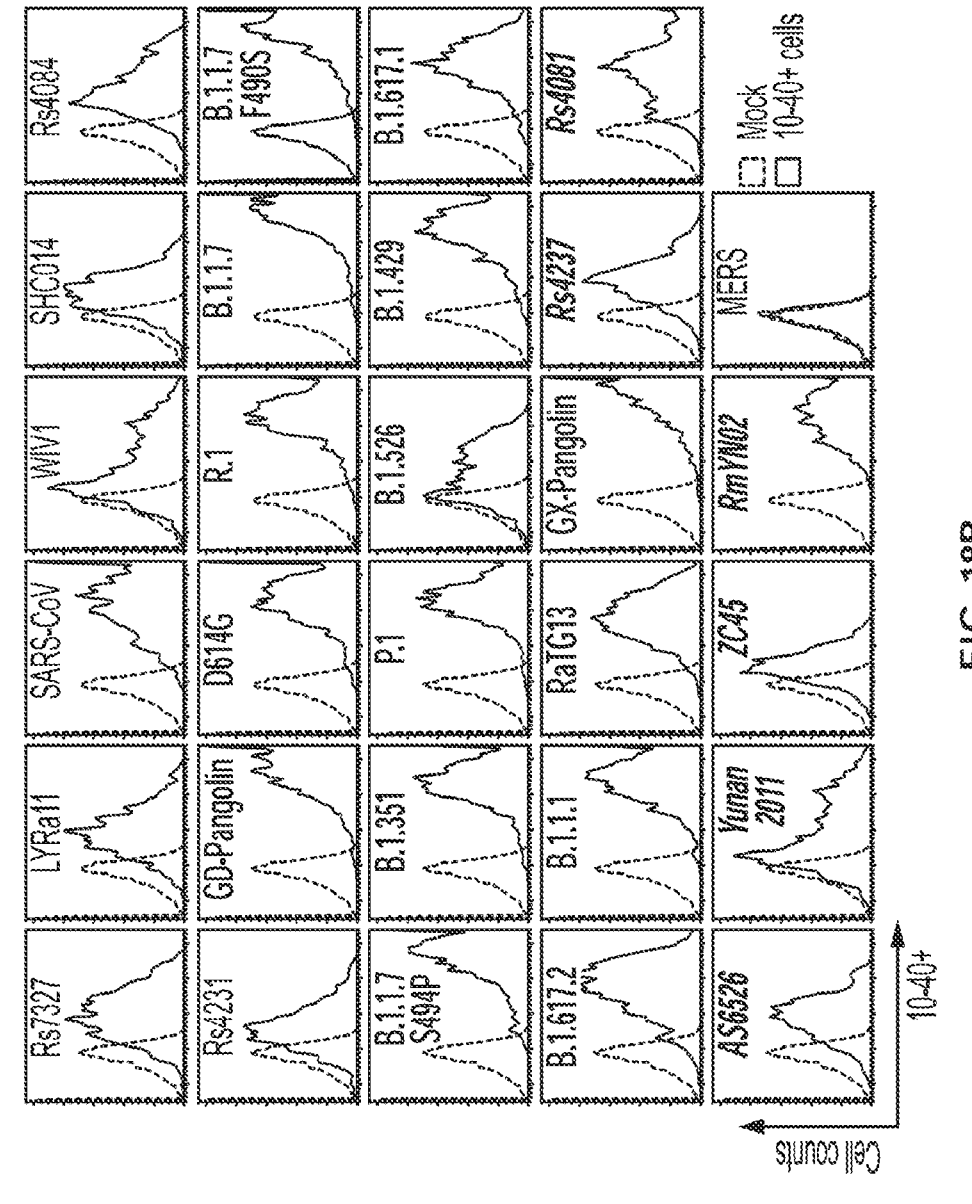
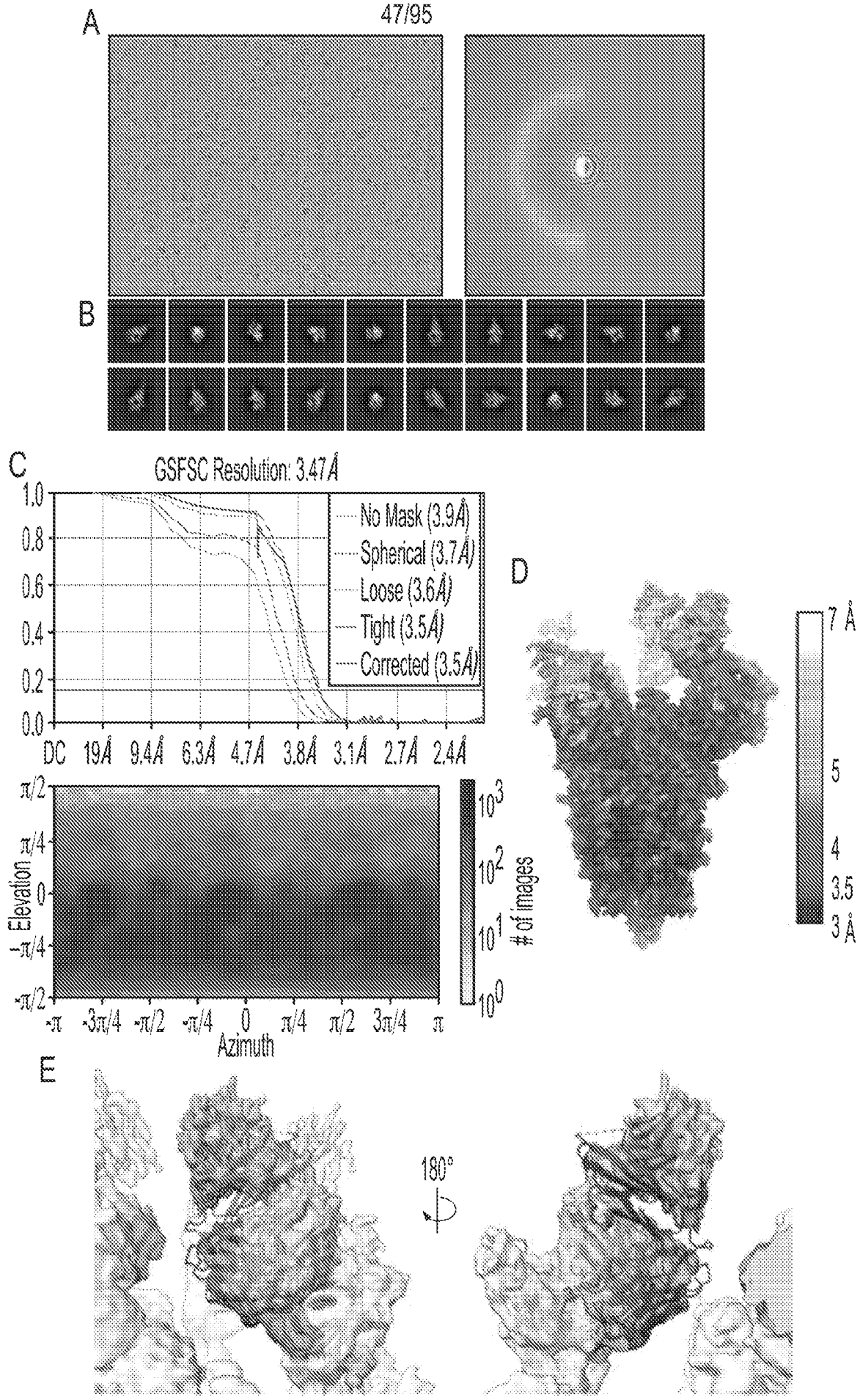

B
Rs7327
LYRa11
SARS-CoV
WIV1
SHC014
Rs4084
Rs4231
GD-Pangolin
D614G
R.1
B.1.1.7
B.1.1.7 F490S
B.1.1.7 S494P
B.1.351
P.1
B.1.526
B.1.429
B.1.617.1
B.1.617.2
B.1.1.1
RaTG13
GX-Pangolin
Rs4237
Rs4081
AS6526
Yunan 2011
ZC45
RmYN02
MERS
Mock
10-40+ cells
Cell counts
10-40+

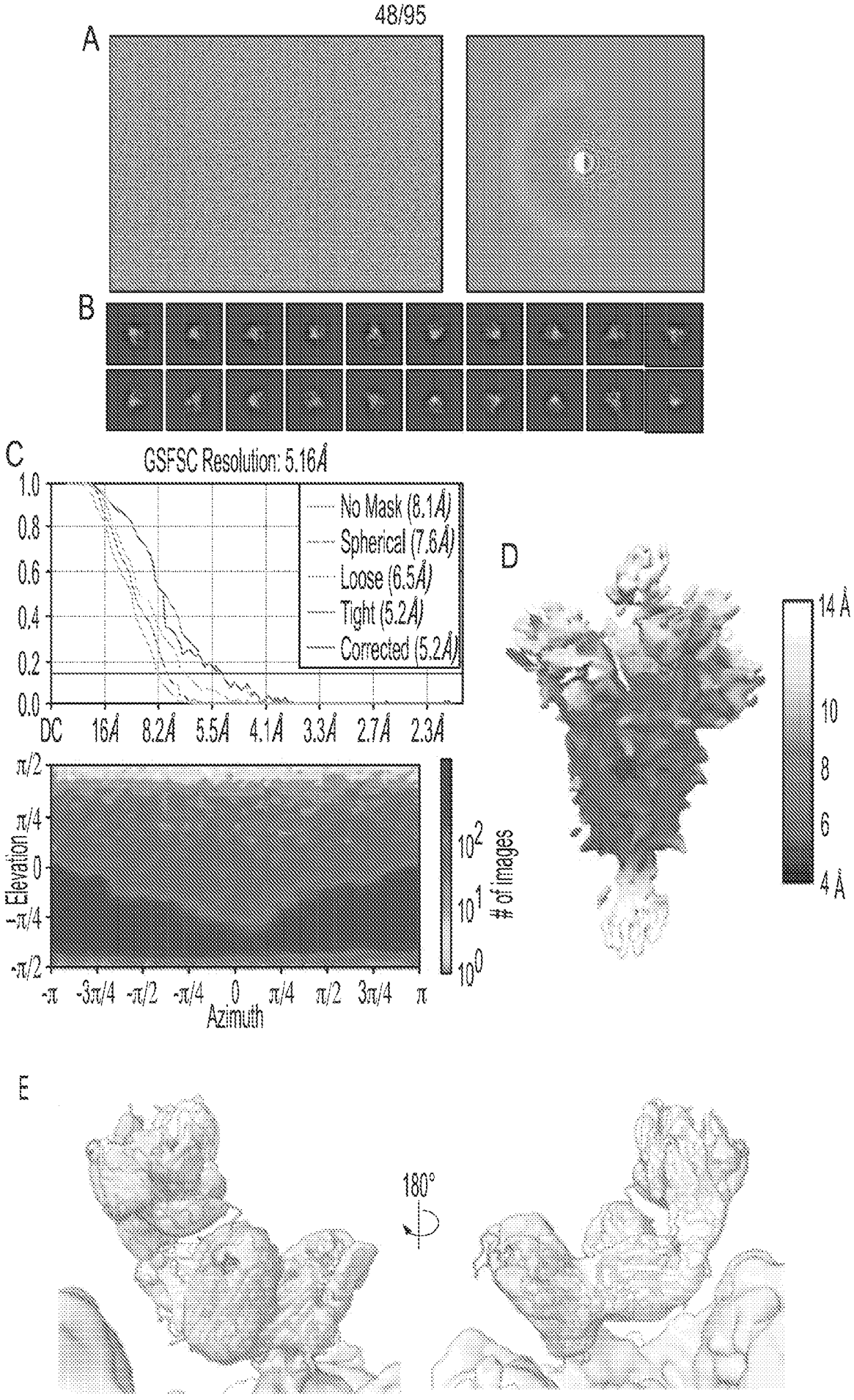
FIG. 18B

Cell surface staining MFI	10-40	10-28	11-11	2-36	DH1047	S2X259	REGN 10985	ADG-2	COVA 1-16	CR3022	S2H97	S309
GX-Pangolin	101476	58406	1518	91098	102843	5601	13651	5754	3138	664	6988	99701
RaTG13	9196	9209	5715	7972	10024	169	5296	208	238	52	63	101631
GD-Pangolin	91625	81502	86509	81271	87609	1856	34923	2810	558	2853	1989	114632
RmYN02	13124	14491	86	8349	11768	144	34	401	45	46	37	45
ZC45	244	176	71	108	233	31	47	31	32	30	31	221
Yunnan2011	1480	1498	830	1033	1518	34	630	46	34	31	47	8251
As6526	1633	1695	39	488	1786	41	33	38	31	29	32	105
Rs4237	1114	1131	93	415	1108	38	40	39	34	33	36	90
Rs4081	10903	11605	99	4113	11584	145	40	225	31	33	32	91

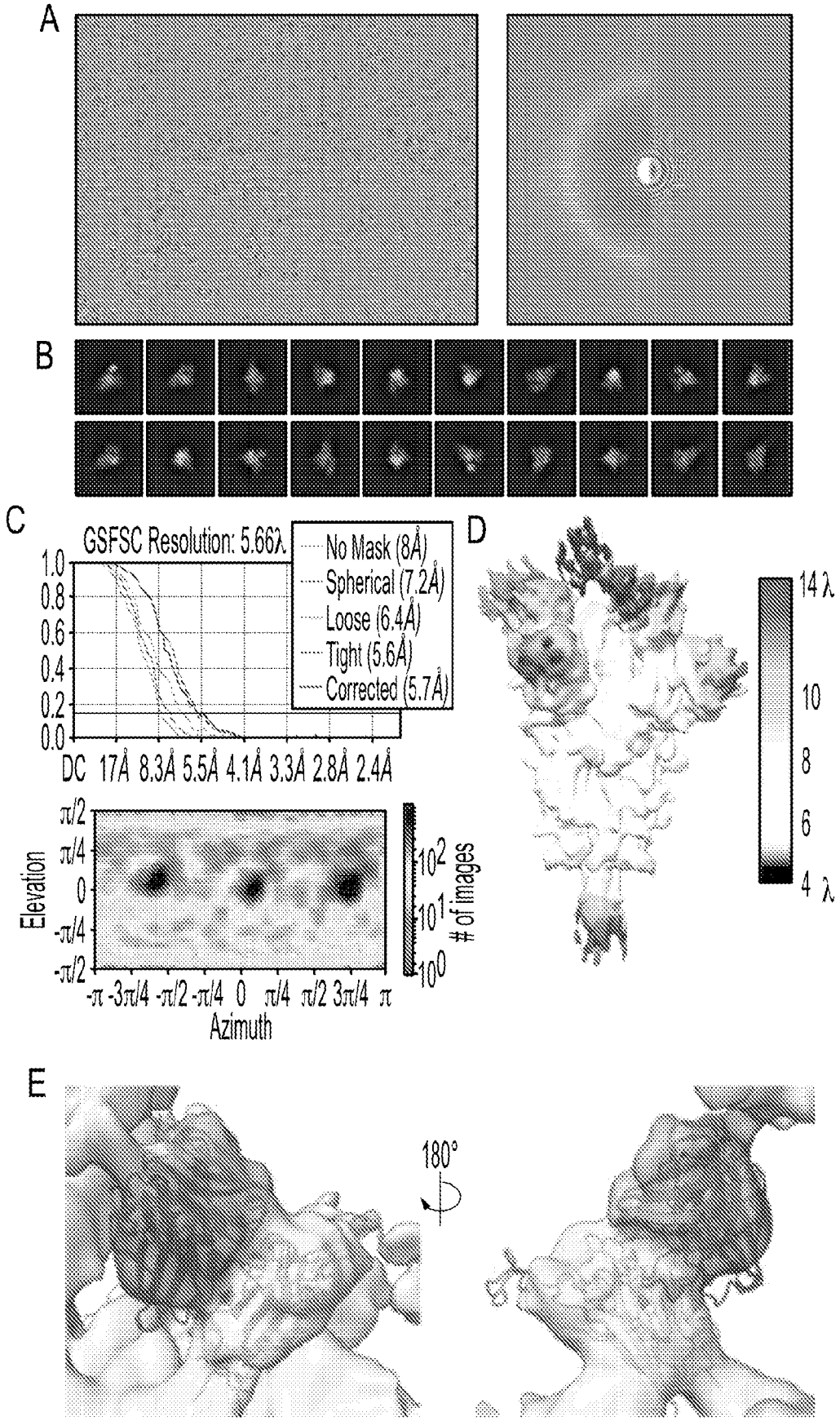
FIG. 19


A
B
C
GSFSC Resolution: 3.47Å
1.0
0.8
0.6
0.4
0.2
0.0
No Mask (3.9Å)
Spherical (3.7Å)
Loose (3.6Å)
Tight (3.5Å)
Corrected (3.5Å)
DC 19Å 9.4Å 6.3Å 4.7Å 3.8Å 3.1Å 2.7Å 2.4Å
π/2
π/4
0
-π/4
-π/2
Elevation
-π -3π/4 -π/2 -π/4 0 π/4 π/2 3π/4 π
Azimuth
10^3
10^2
10^1
10^0
# of images
D
7 Å
5
4
3.5
3 Å
E
180°

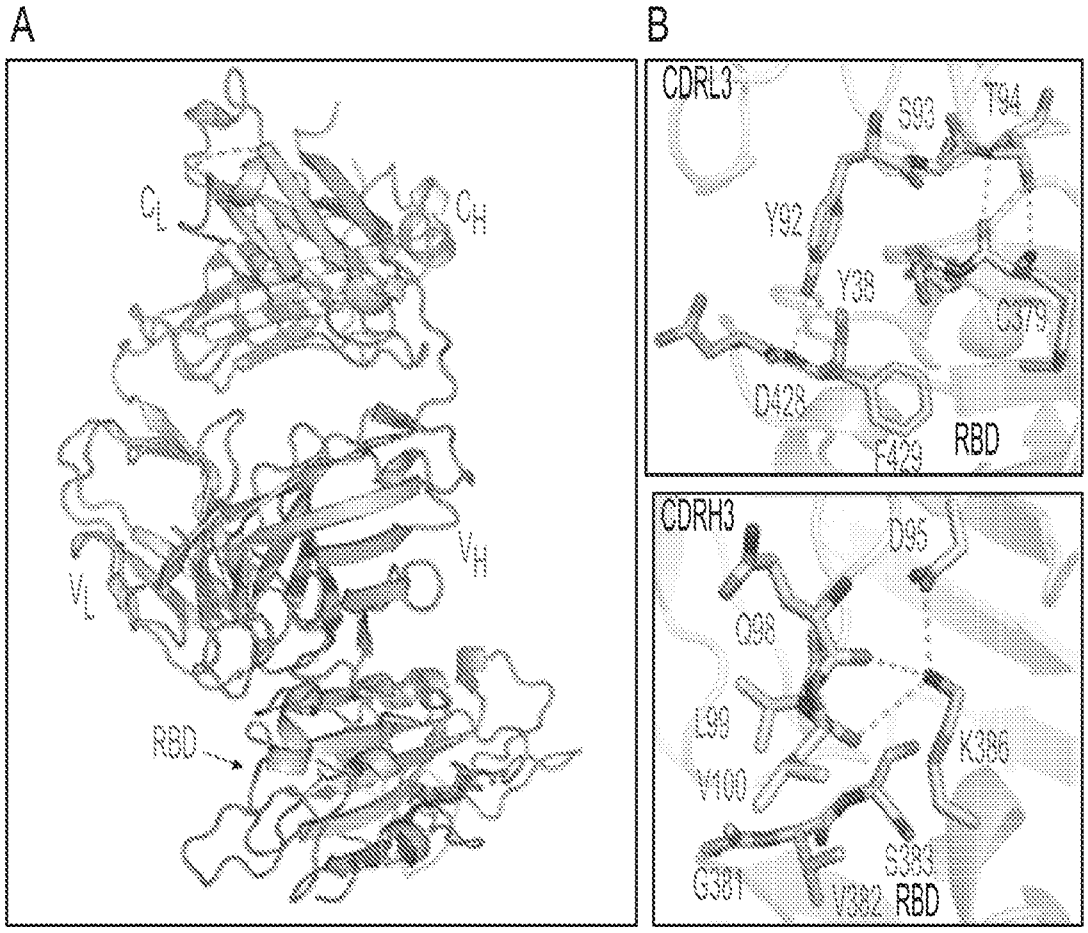
FIGS. 20A-E


A
B
C
GSFSC Resolution: 5.16Å
1.0
0.8
0.6
0.4
0.2
0.0
No Mask (8.1Å)
Spherical (7.6Å)
Loose (6.5Å)
Tight (5.2Å)
Corrected (5.2Å)
DC
16Å
8.2Å
5.5Å
4.1Å
3.3Å
2.7Å
2.3Å
π/2
π/4
0
-π/4
-π/2
Elevation
-π
-3π/4
-π/2
-π/4
0
π/4
π/2
3π/4
π
Azimuth
10^2
10^1
10^0
# of images
D
14 Å
10
8
6
4 Å
E
180°

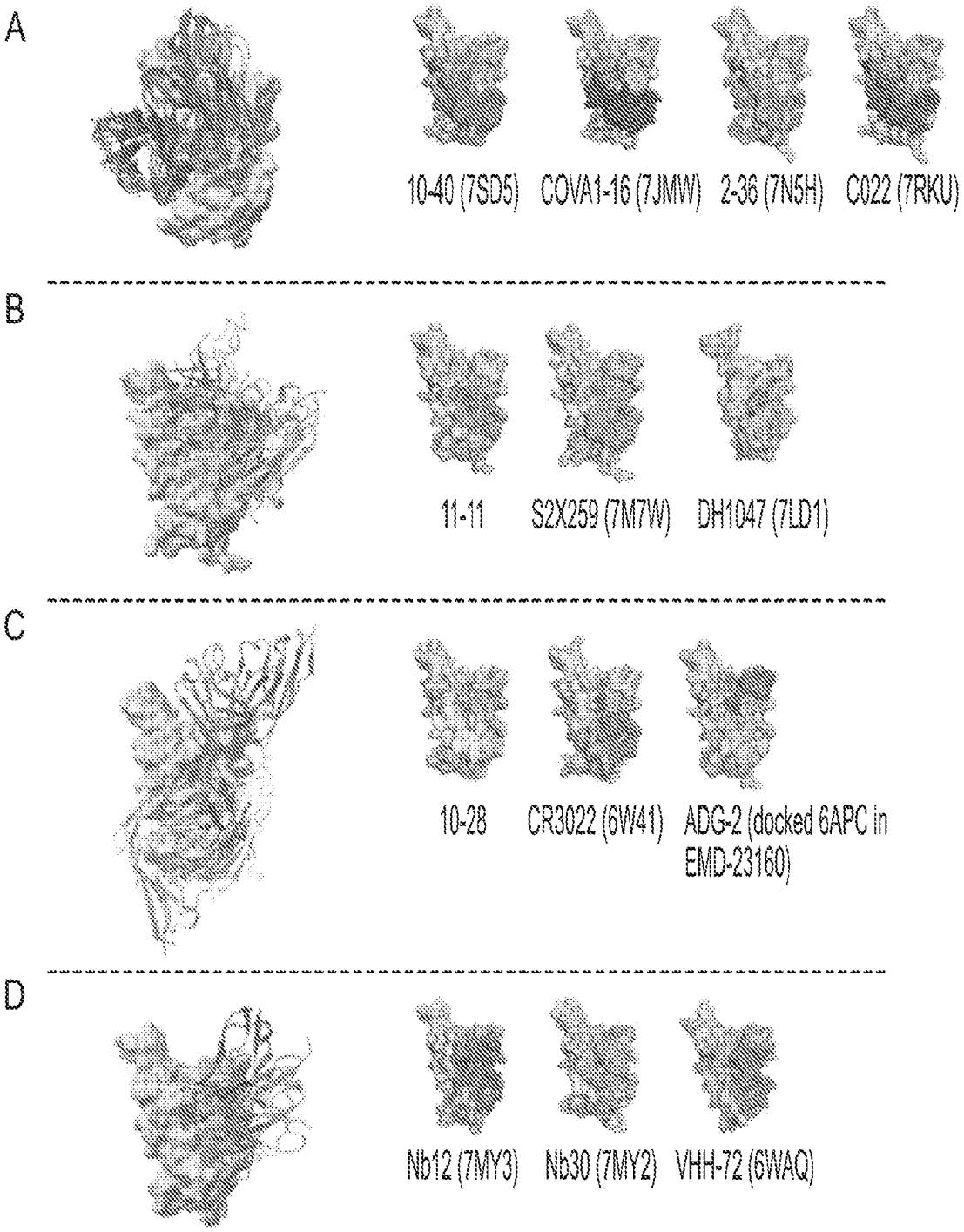
FIGS. 21A-E


A
B
C
GSFSC Resolution: 5.66λ
No Mask (8Å)
Spherical (7.2Å)
Loose (6.4Å)
Tight (5.6Å)
Corrected (5.7Å)
1.0
0.8
0.6
0.4
0.2
0.0
DC 17Å 8.3Å 5.5Å 4.1Å 3.3Å 2.8Å 2.4Å
Elevation
π/2
π/4
0
-π/4
-π/2
-π -3π/4 -π/2 -π/4 0 π/4 π/2 3π/4 π
Azimuth
10^2
10^1
10^0
# of images
D
14 λ
10
8
6
4 λ
E
180°

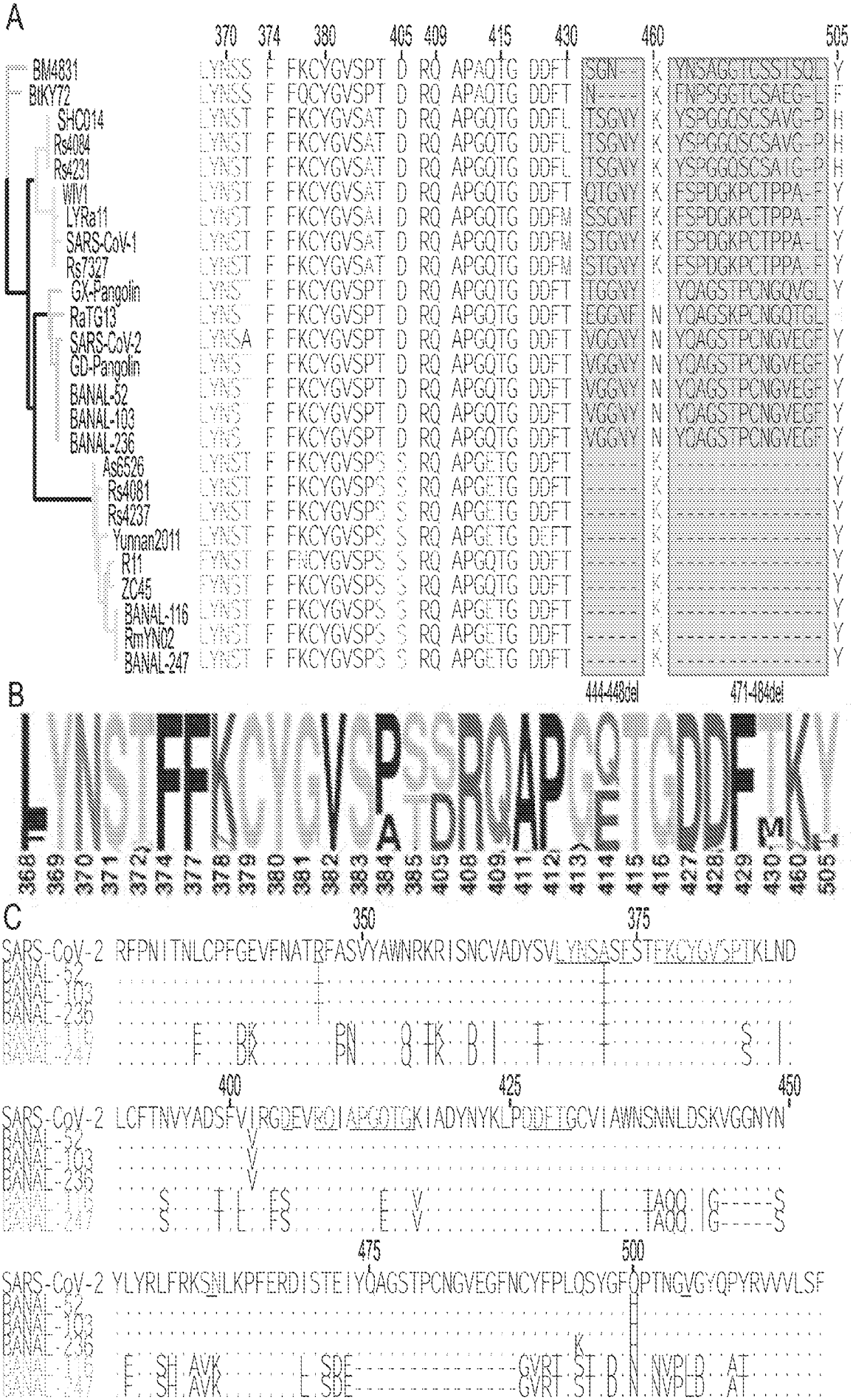
FIGS. 22A-E


A
B
C_L
C_H
V_H
V_L
RBD
CDRL3
S93
T94
Y92
Y36
S79
D28
F29
RBD
CDRH3
D95
Q96
L99
Y100
K386
S383
G381
V382
RBD

FIGS. 23A-B


A
10-40 (7SD5)
COVA1-16 (7JMW)
2-36 (7N5H)
C022 (7RKU)
B
11-11
S2X259 (7M7W)
DH1047 (7LD1)
C
10-28
CR3022 (6W41)
ADG-2 (docked 6APC in EMD-23160)
D
Nb12 (7MY3)
Nb30 (7MY2)
VHH-72 (6WAQ)

FIGS. 24A-D


A
B
C
444-448del
471-484del
SARS-CoV-2
BANAL-52
BANAL-103
BANAL-236
BANAL-247

FIGS. 25A-C

Region	Signature motifs	Compatible genes	Critical
CDRH1	GGS[IV]SSS[NR][FY]Y	IGHV4-39, IGHV4-61, IGHV4-31, IGHV4-30-2/4	No
	GYTFTSYY	IGHV1-46, IGHV1-2	No
CDRH3	ARx{4-5}YYDRSGYx{8-9}	IGHD3-22*01	Yes
Light Chain	NA	IGLV6-57, IGKV3-20, IGKV1-33, IGKV1-9	No

FIG. 26

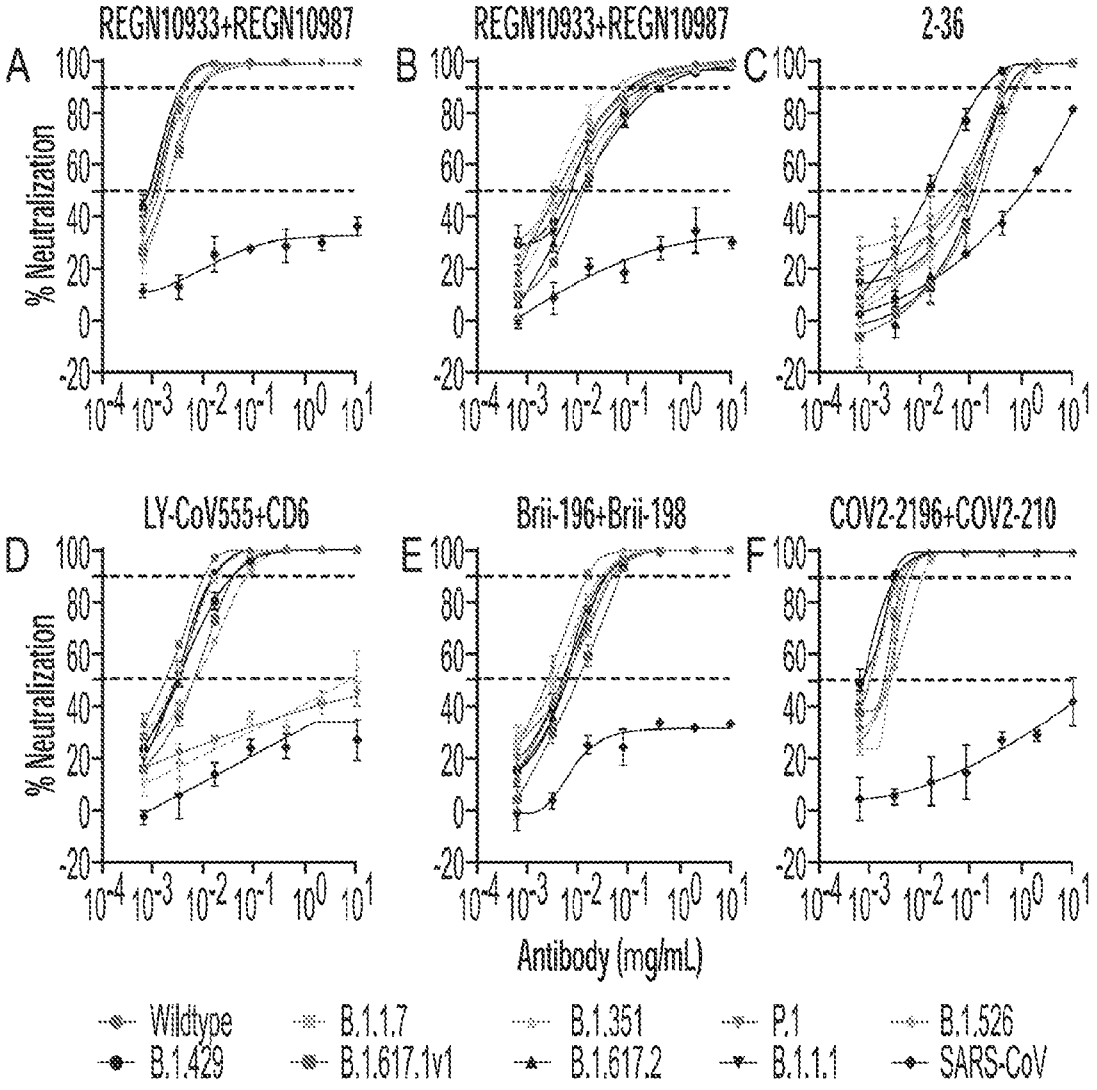
	SARS-CoV-2 B.1.351 S2P +10-40 Fab	SARS-CoV-2 B.1.351 S2P +10-28 Fab	SARS-CoV-2 B.1.351 S2P +11-11 Fab
EMDB ID	EMD-25146	EMD-25166	EMD-25167
Data Collection			
Microscope	FEI Titan Krios	FEI Titan Krios	FEI Titan Krios
Voltage (keV)	300	300	300
Magnification	81,000	81,000	81,000
Defocus Range (μm)	-0.8/-2.0	-0.8/-2.0	-0.8/-2.0
Camera	Gatan K3 BioQuantum	Gatan K3 BioQuantum	Gatan K3 BioQuantum
Pixel Size (Å/pix)	1.07	1.07	1.07
Recording Mode	counting	counting	counting
Total Dose (e-/Å^2)	42	42	42
Dose Rate (e-/pixel/s)	20	20	20
Exposure Time(s)	2.4	2.4	2.4
Frame Time(ms)	50	50	50
Software	SerialEM	SerialEM	SerialEM
Data Processing			
Software	cryoSPARC v3.2.0	cryoSPARC v3.2.0	cryoSPARC v3.2.0
Micrographs used	9,881	2,542	2,565
Number of Particles	799,933	251,871	281,235
Particles/Micrograph	81.0	99.1	109.6
Symmetry	C1	C1	C1
Box Size (pix)	440	384	384
Global Map FSC_{Q143} (Å)	3.5/3.6	5.2/6.5	5.6/6.4

FIG. 27

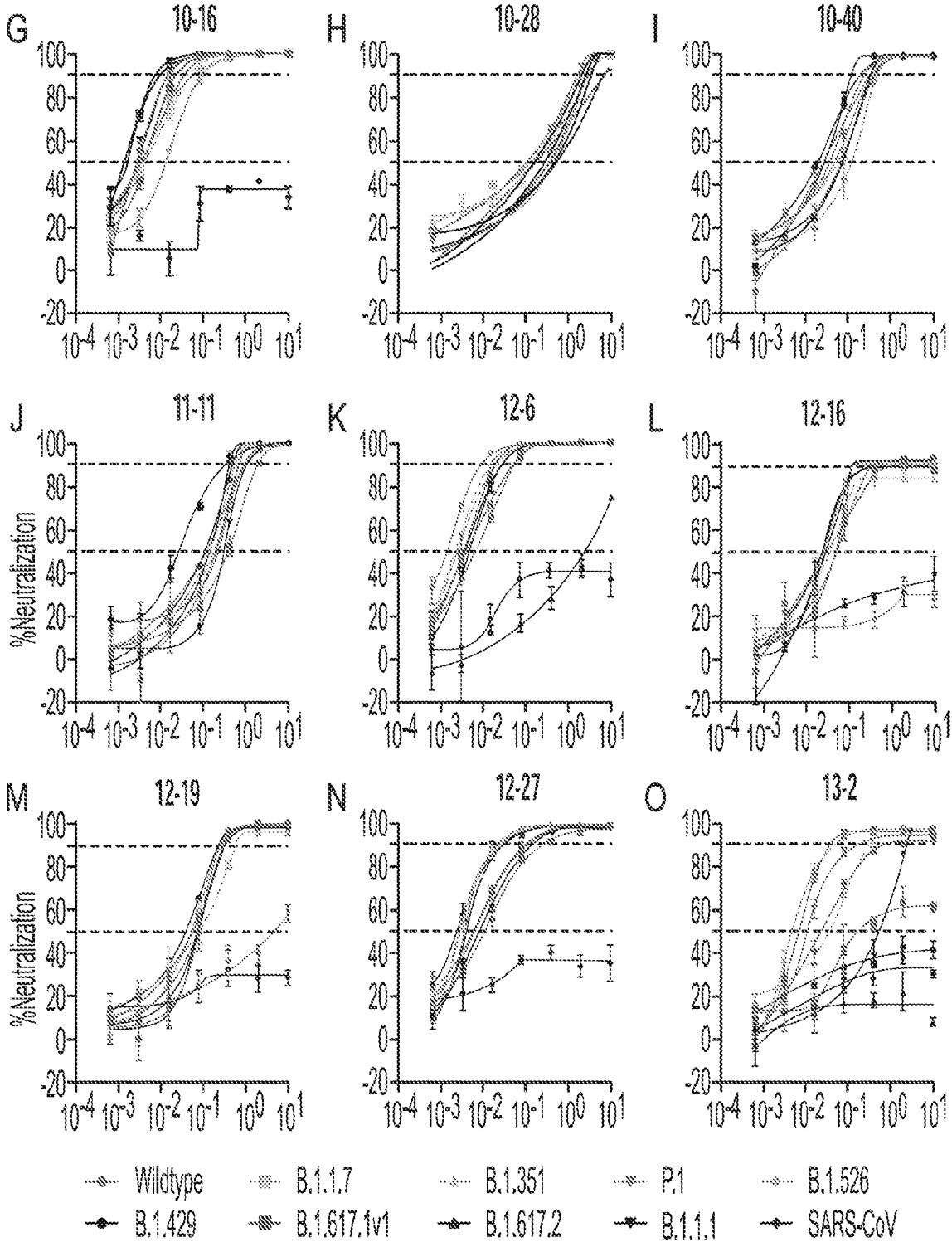
	SARS-CoV-2 RBD in complex with 10-40 Fab	SARS-CoV-2 RBD in complex with 10-28 Fab
PDB ID	7SD5	XXXX
Data Collection		
Space group	$P2_12_12_1$	$C222_1$
Unite cell dimensions		
a,b,c, (Å)	75.7, 79.8, 118.8	123.7, 226.6, 186.2
α,β,γ, (°)	90.0, 100.0, 90.0	90.0, 90.0, 90.0
Resolution range (Å)	47.67 - 1.50 (1.7-1.5)*	108.6 - 3.0 (3.12-3.00)*
Total reflections	221728 (17750)	86848 (8516)
Unique reflections	111815 (9153)	43474 (4062)
Completeness (%)	99.20 (98.96)	97.74 (94.91)
Redundancy	2.0 (1.9)	2.0 (2.0)
I/σ(I)	17.99 (0.89)	6.22 (1.29)
Rmerge	0.016 (0.83)	0.085 (0.67)
$CC_{1/2}$	1 (0.35)	0.690 (0.40)
Refinement		
Resolution range (Å)	47.67 - 1.50	88.03 - 3.20
Number of complexes per Asymmetric unit	1	3
Rwork/Rfree	0.17/0.19	0.23/0.28
Number of atoms		
Protein	4905	14340
Ligands	28	109
Water	627	0
B-factors ($Å^2$)		
Protein	30.7	81.4
Ligands	74.3	81.1
Water	38.3	
R.m.s. deviations		
Bond lengths (Å)	0.013	0.014
Bond angles (°)	1.33	1.97
Ramachandran statistics		
Favored (%)	97.60	96.24
Allowed (%)	2.40	3.76
Outliers (%)	0	0

Statistics for the highest-resolution shell are shown in the parentheses.

FIG. 28


A
REGN10933+REGN10987
B
REGN10933+REGN10987
C
2-36
D
LY-CoV555+CD6
E
Brii-196+Brii-198
F
COV2-2196+COV2-210
% Neutralization
Antibody (mg/mL)
Wildtype
B.1.1.7
B.1.351
P.1
B.1.526
B.1.429
B.1.617.1v1
B.1.617.2
B.1.1.1
SARS-CoV

FIGS. 29A-F


G
10-16
H
10-28
I
10-40
J
11-11
K
12-6
L
12-16
M
12-19
N
12-27
O
13-2
%Neutralization
Wildtype
B.1.1.7
B.1.351
P.1
B.1.526
B.1.429
B.1.617.1v1
B.1.617.2
B.1.1.1
SARS-CoV

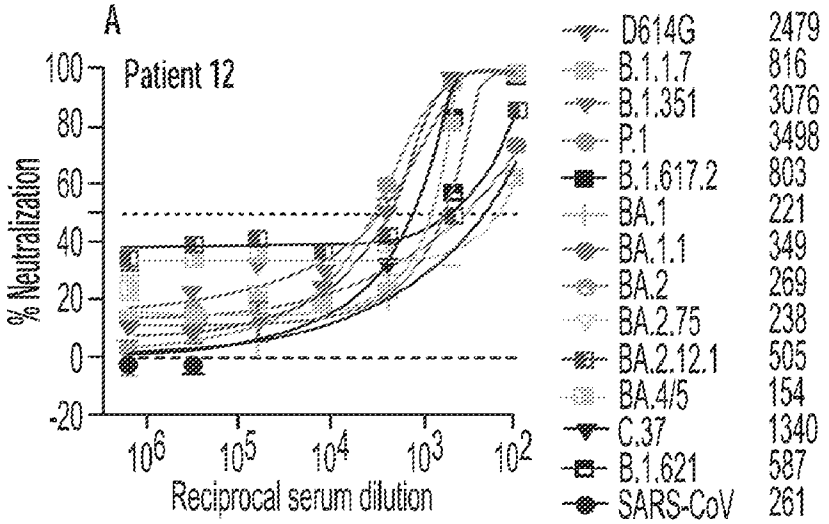
FIGS. 29G-O

IC50(μg/ml)	D614G	B.1.1.7	B.1.351	P.1	B.1.526	B.1.429	B.1.617.1	B.1.617.2	C.37	SARS-CoV
REGN10933+REGN10987	0.001	0.001	0.001	0.001	0.002	0.001	0.002	0.001	0.001	>10
2-7	0.003	0.005	0.003	0.004	0.005	0.006	0.012	0.011	0.007	>10
2-36	0.07	0.084	0.106	0.06	0.055	0.015	0.149	0.117	0.091	1.106
LY-CoV555+CB6	0.002	0.003	7.024	>10	0.006	0.003	0.006	0.003	0.003	>10
Brii196+Brii198	0.005	0.003	0.004	0.003	0.006	0.005	0.01	0.006	0.005	>10
COV2-2196+COV2-2130	0.001	0.001	0.002	0.002	0.002	0.001	0.002	0.001	0.001	>10
10-16	0.003	0.004	0.004	0.003	0.013	0.001	0.004	0.003	0.002	>10
10-28	0.161	0.132	0.167	0.103	0.447	0.166	0.336	0.271	0.432	0.534
10-40	0.028	0.035	0.053	0.045	0.117	0.027	0.069	0.053	0.059	0.049
11-11	0.207	0.372	0.17	0.111	0.14	0.106	0.176	0.128	0.264	0.025
12-6	0.007	0.004	0.002	0.001	0.002	0.004	0.003	2.476	0.005	>10
12-16	0.051	0.031	0.039	>10	0.025	0.023	0.05	0.03	0.023	>10
12-19	0.059	0.05	0.053	4.658	0.036	0.04	0.074	0.077	0.07	>10
12-27	0.006	0.011	0.003	0.006	0.003	0.002	0.003	0.004	0.008	>10
13-2	0.022	0.172	0.036	0.011	0.005	>10	0.007	>10	0.539	>10

IC_{50} (μg/mL)

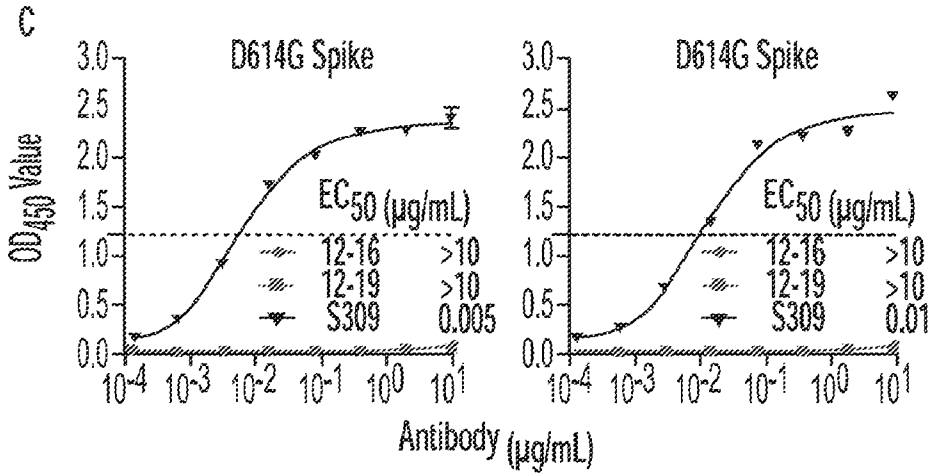
- <0.01
- 0.01-0.1
- 0.1-1
- 1-10
- >10

FIG. 30

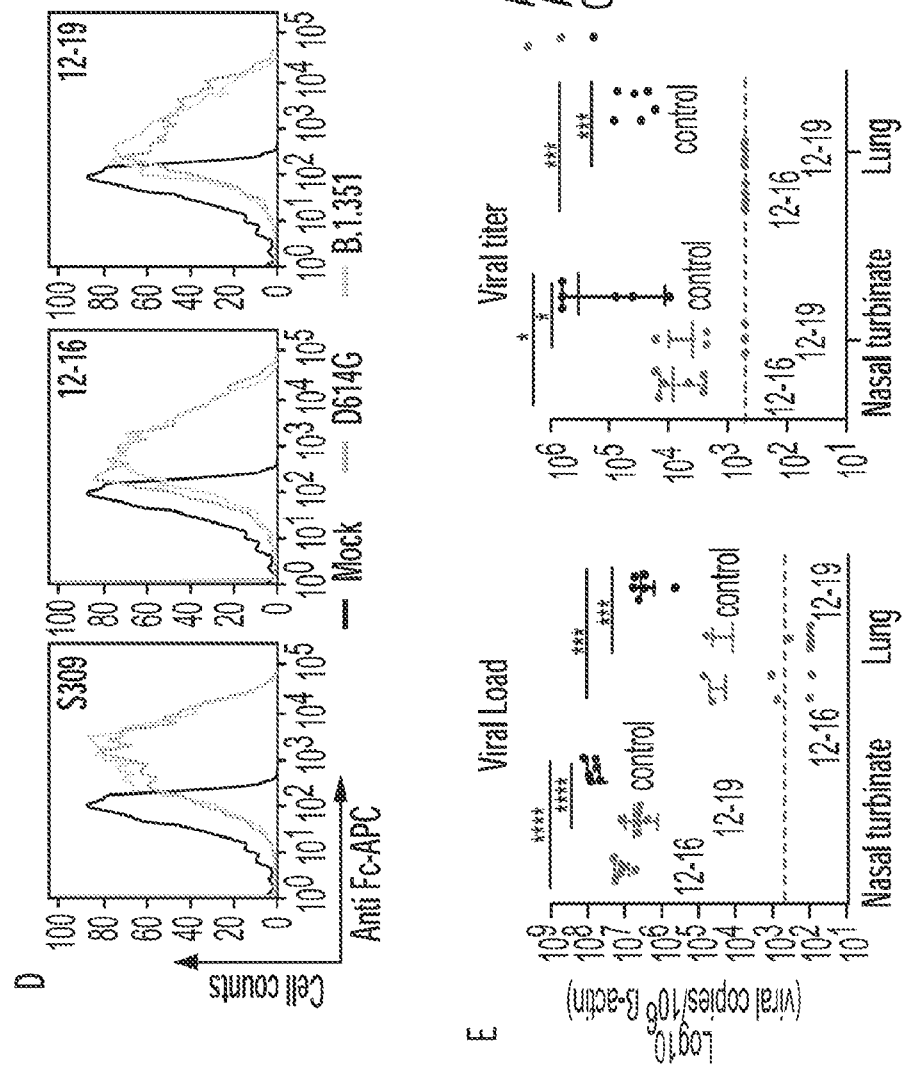


B

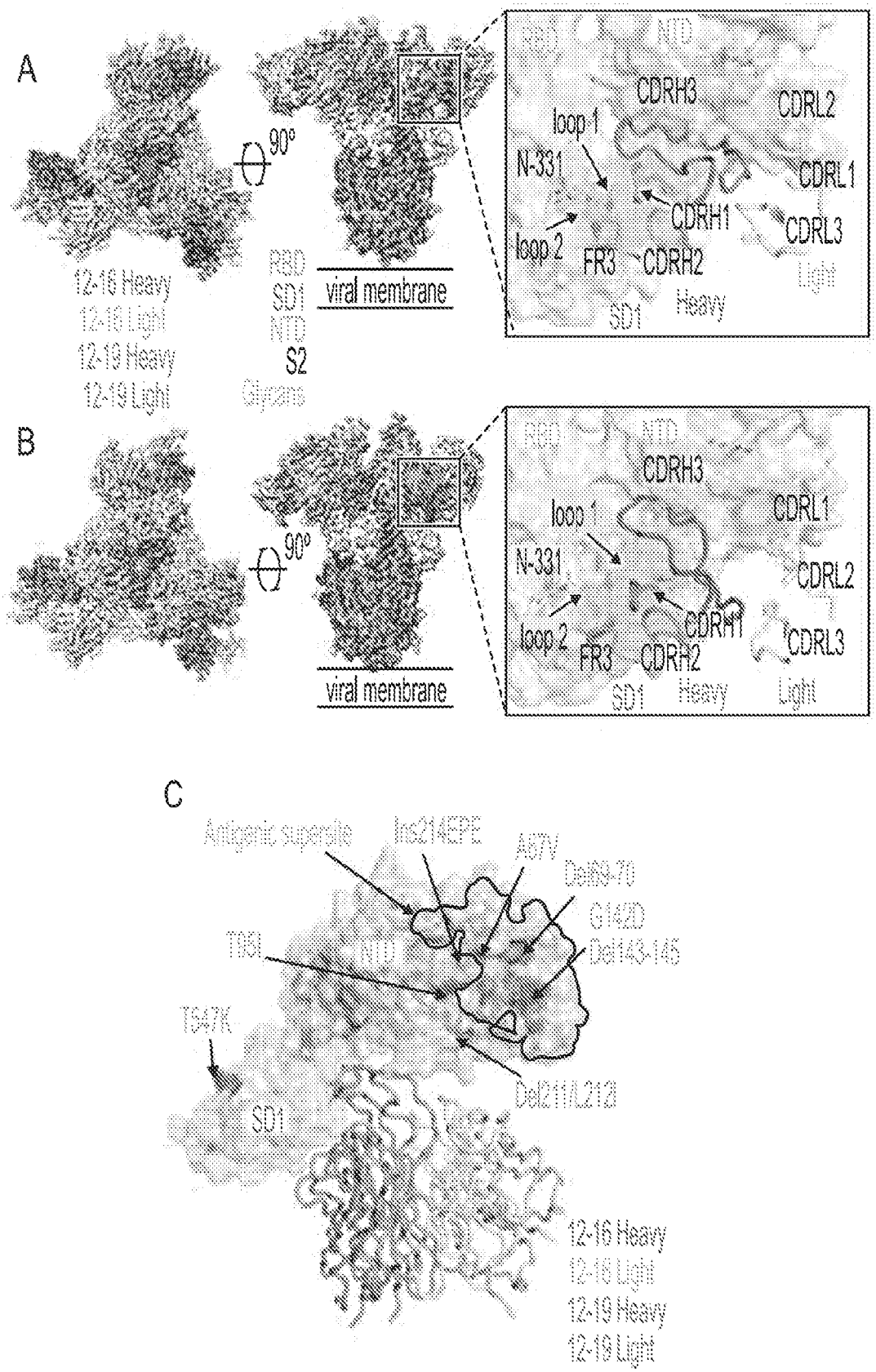
Viruses		IC_{50} (μg/mL) 12-16	12-19	S309
Pseudotyped	D614G	0.071	0.073	0.032
	B.1.1.7	0.064	0.083	0.061
	B.1.351	0.04	0.035	0.031
	P.1	>10	2.505	0.036
	B.1.617.2	0.05	0.099	0.042
	BA.1	0.031	0.057	0.138
	BA.1.1	0.079	0.086	0.13
	BA.2	0.074	0.043	1.24
	BA.2.75	0.036	0.058	1.035
	BA.2.12.1	0.036	0.095	0.98
	BA.4/5	0.031	0.098	1.12
	C.37	0.041	0.065	0.049
	B.1.621	0.123	0.182	0.03
Authentic	WA1	0.045	0.034	0.037
	BA.1	0.057	0.053	0.106



FIGS. 31A-C

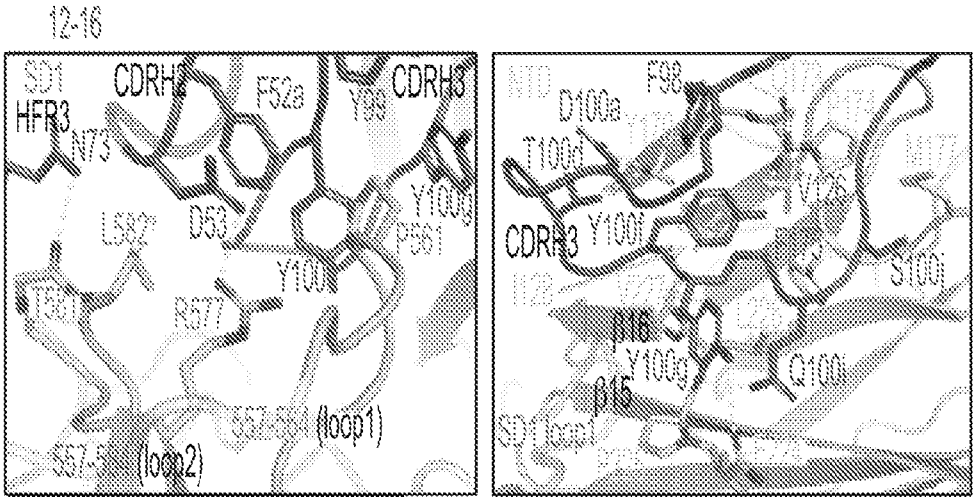

D
S309
12-16
12-19
Cell counts
Anti Fc-APC
Mock
D614G
B.1.351
E
Viral Load
Viral titer
Ab 12-16
Ab 12-19
Control Ab
Log10 (viral copies/10^6 β-actin)
control
12-16
12-19
Nasal turbinate
Lung

FIGS. 31D-E

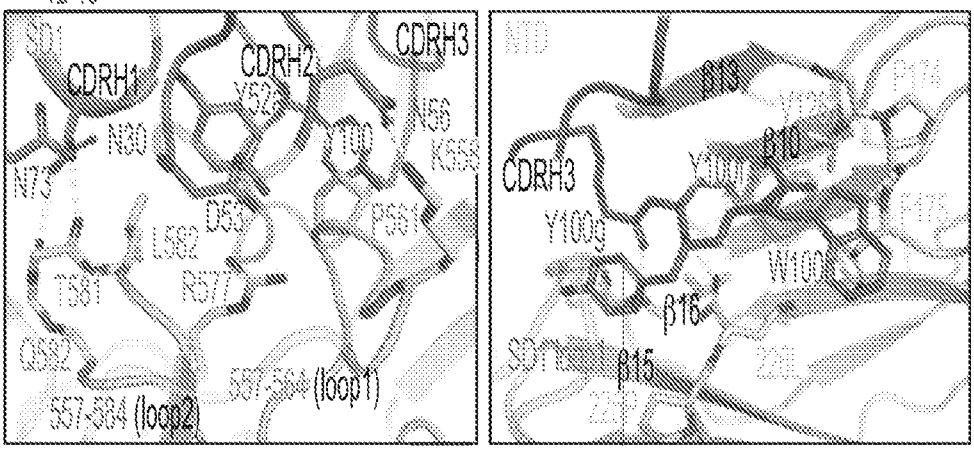

A
90°
12-16 Heavy
12-16 Light
12-19 Heavy
12-19 Light
RBD
SD1
NTD
S2
Glycans
viral membrane
RBD
NTD
CDRH3
loop 1
N-331
CDRL2
CDRL1
CDRH1
CDRL3
loop 2
FR3
CDRH2
Light
SD1
Heavy
B
90°
viral membrane
RBD
NTD
CDRH3
loop 1
CDRL1
N-331
CDRL2
CDRH1
loop 2
FR3
CDRH2
CDRL3
SD1
Heavy
Light
C
Antigenic supersite
Ins214EPE
A67V
Del69-70
G142D
T95I
NTD
Del143-145
T547K
SD1
Del211/L212I
12-16 Heavy
12-16 Light
12-19 Heavy
12-19 Light

FIGS. 32A-C

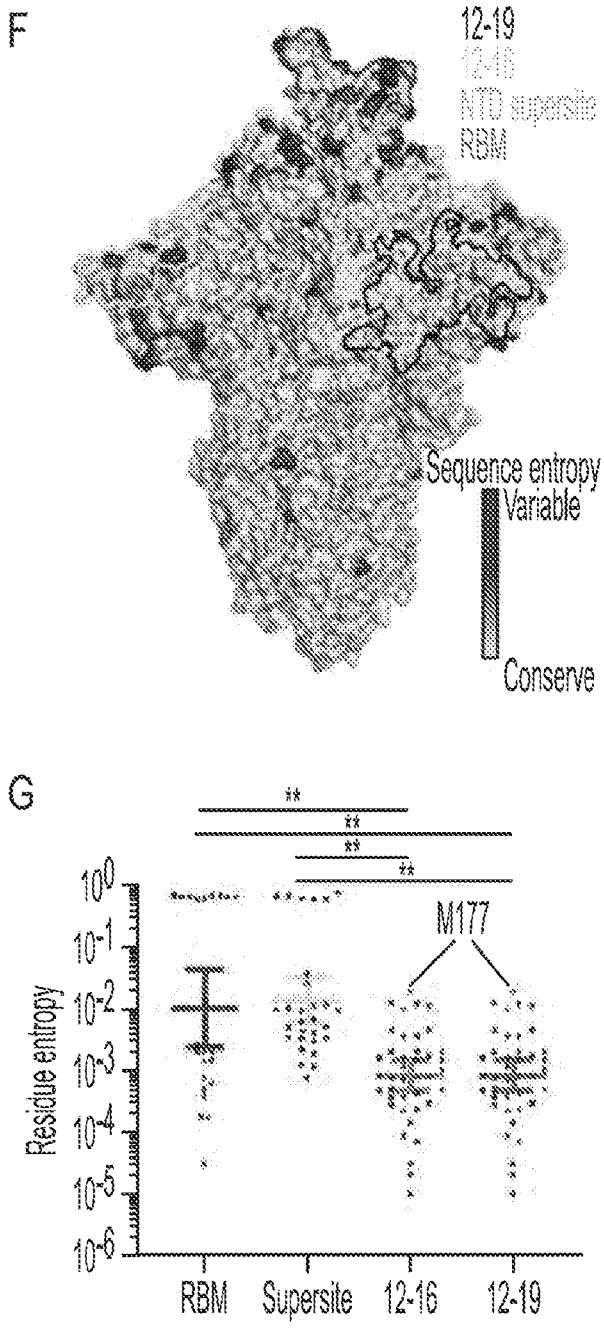
D


12-16
SD1
HFR3
CDRH2
F52a
Y58
CDRH3
N73
L582
D53
Y100g
P561
T581
Y100i
R577
557-564 (loop1)
557-5 (loop2)
HTD
D100a
T100d
F38
CDRH3
Y100i
V26
S100j
β16
Y100g
β15
Q100c
SD1 (loop1)

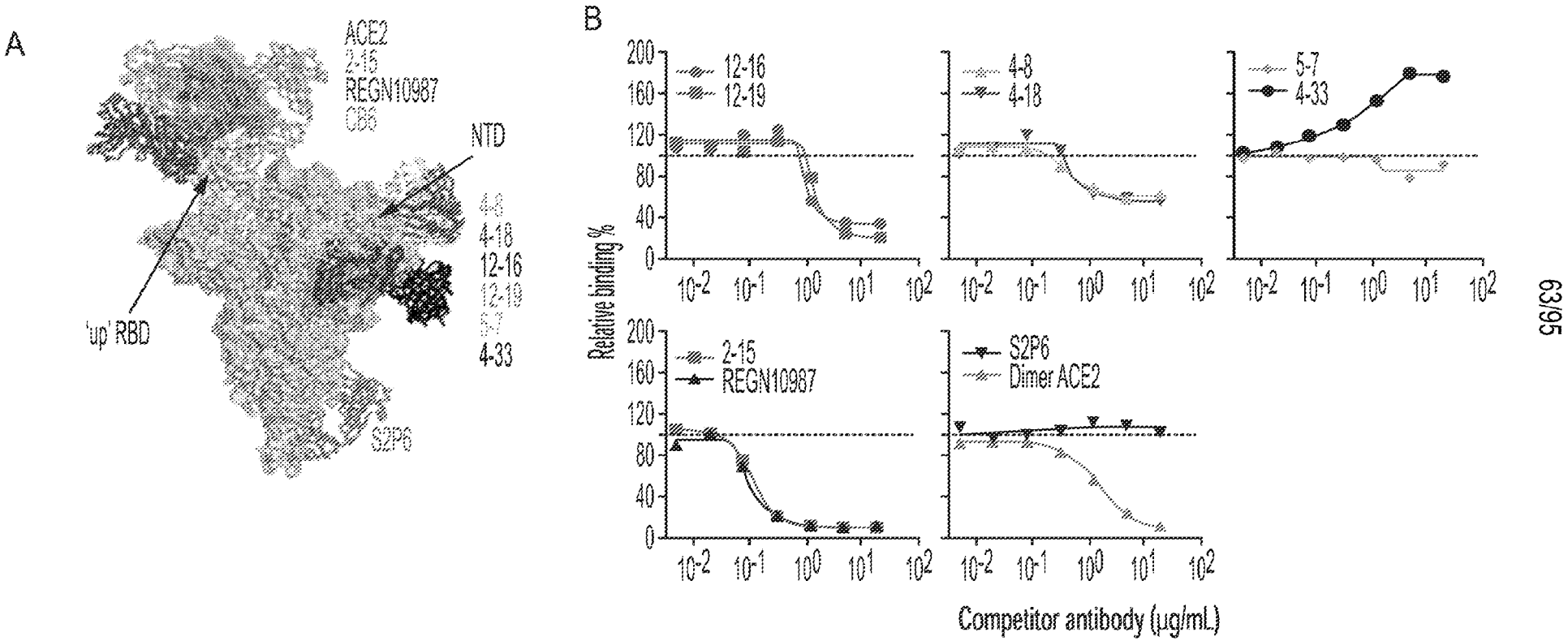
E


12-19
SD1
CDRH1
CDRH2
Y52a
CDRH3
N56
N30
Y100
K558
N73
D53
P561
L582
T581
R577
Q592
557-564 (loop1)
557-584 (loop2)
HTD
β13
β10
CDRH3
Y100i
Y100g
W100f
β16
β15
SD1 (loop1)

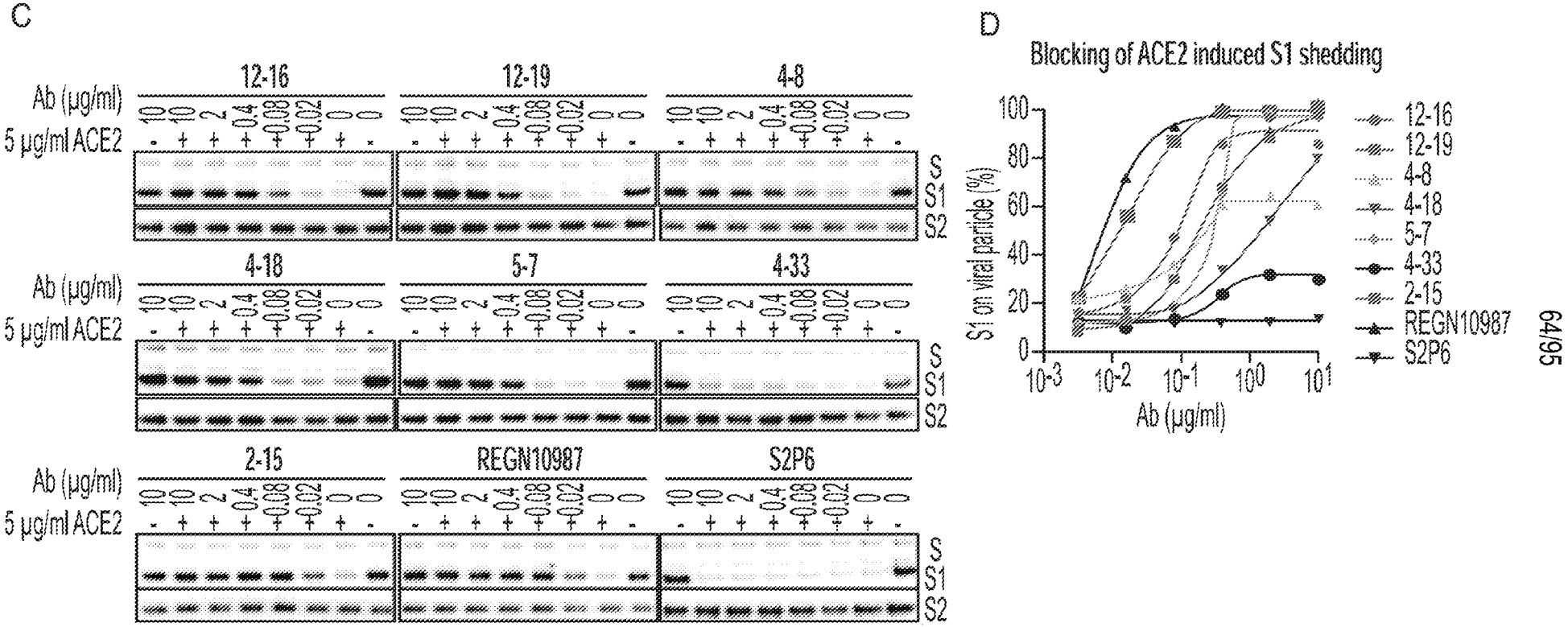
FIGS. 32D-E


F
12-19
12-16
NTD supersite
RBM
Sequence entropy
Variable
Conserve
G
**
**
**
**
M177
Residue entropy
10^{0}
10^{-1}
10^{-2}
10^{-3}
10^{-4}
10^{-5}
10^{-6}
RBM
Supersite
12-16
12-19

FIGS. 32F-G


A
ACE2
2-15
REGN10987
CB6
NTD
4-8
4-18
12-16
12-19
5-7
4-33
'up' RBD
S2P6
B
Relative binding %
12-16
12-19
4-8
4-18
5-7
4-33
2-15
REGN10987
S2P6
Dimer ACE2
Competitor antibody (µg/mL)

FIGS. 33A-33B


C
12-16
12-19
4-8
4-18
5-7
4-33
2-15
REGN10987
S2P6
Ab (μg/ml)
5 μg/ml ACE2
10
2
0.4
0.08
0.02
0
S
S1
S2
D
Blocking of ACE2 induced S1 shedding
S1 on viral particle (%)
Ab (μg/ml)
12-16
12-19
4-8
4-18
5-7
4-33
2-15
REGN10987
S2P6

FIGS. 33C-33D

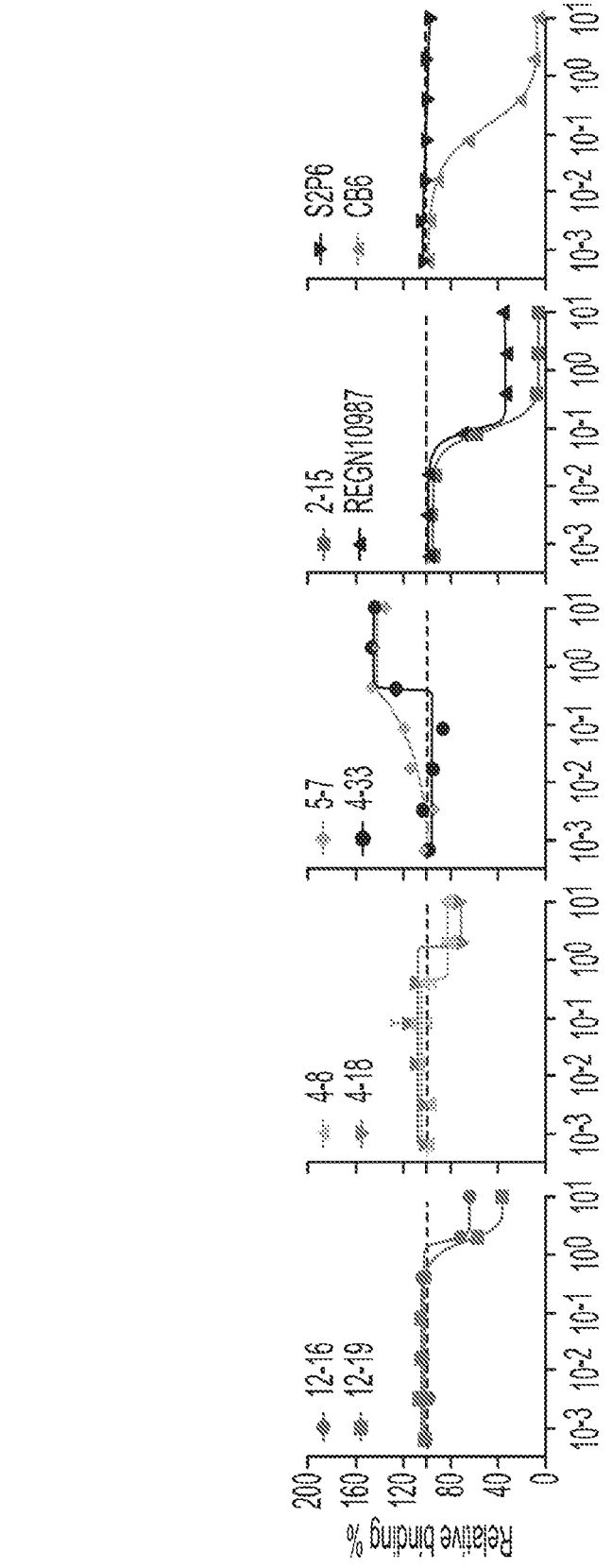

E
Relative binding %
200
160
120
80
40
0
12-16
12-19
4-8
4-18
5-7
4-33
2-15
REGN10987
S2P6
CB6
10-3 10-2 10-1 100 101
Competitor antibody (µg/mL)

FIG. 33E

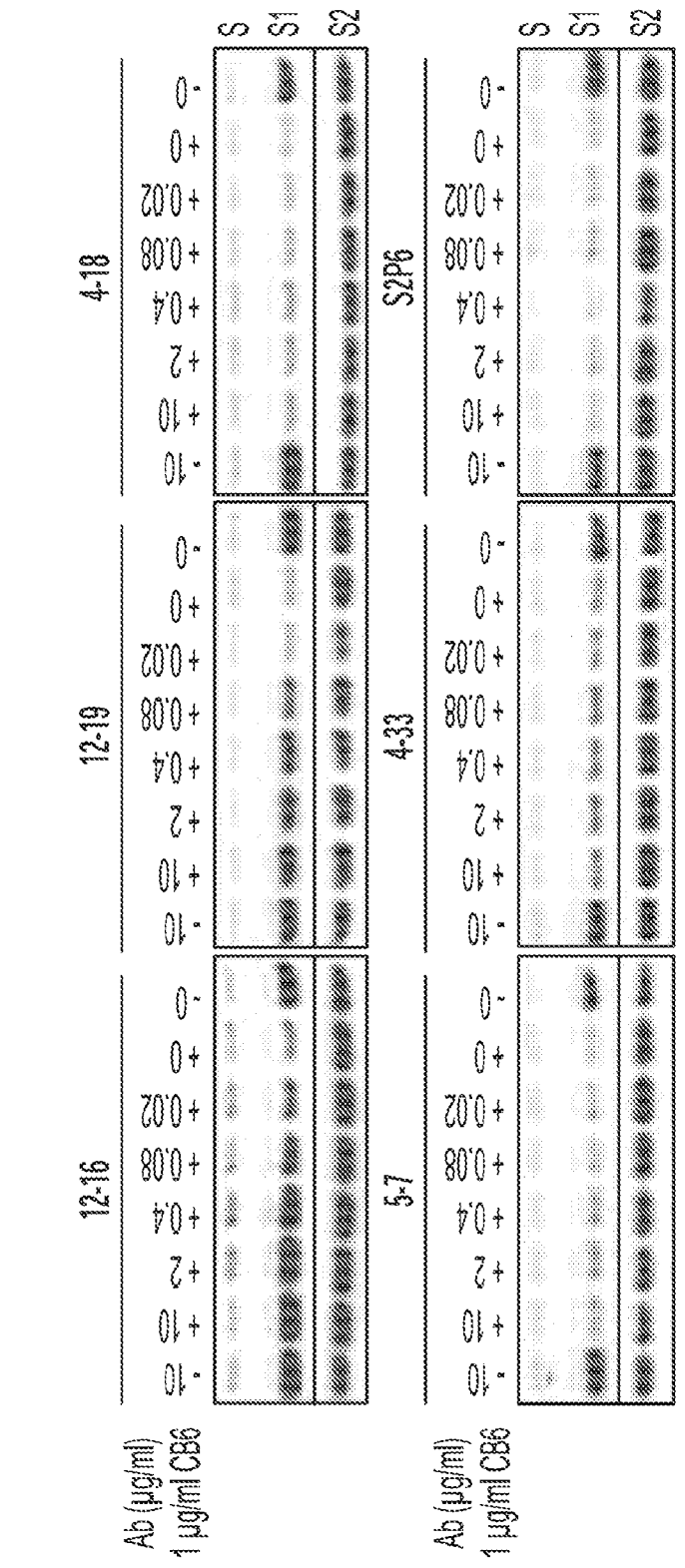

F
12-16
12-19
4-18
5-7
4-33
S2P6
Ab (µg/ml)
1 µg/ml CB6
-10
+10
+2
+0.4
+0.08
+0.02
+0
-0
S
S1
S2

FIG. 33F

G

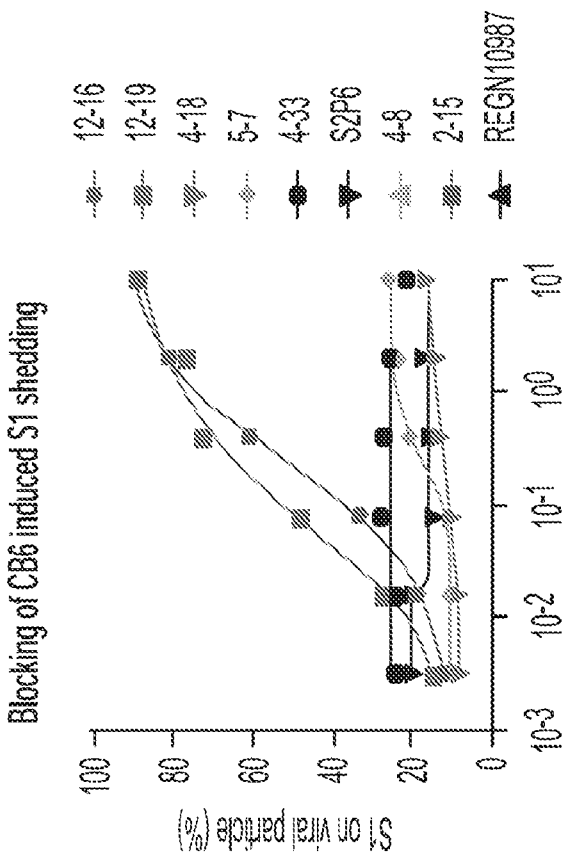
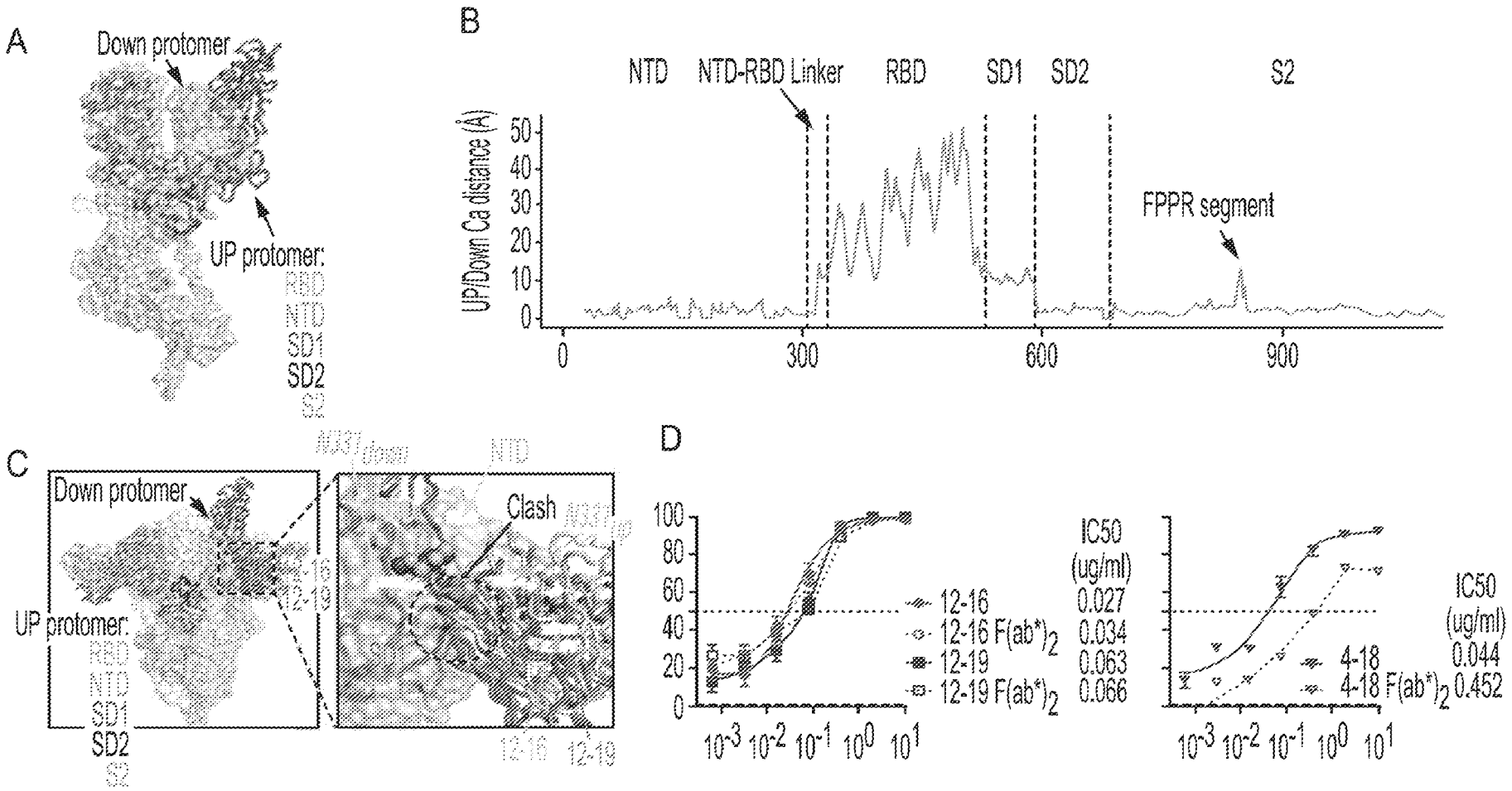

Blocking of CB6 induced S1 shedding
S1 on viral particle (%)
100
80
60
40
20
0
10-3
10-2
10-1
100
101
Ab (µg/ml)
12-16
12-19
4-18
5-7
4-33
S2P6
4-8
2-15
REGN10987

FIG. 33G


A
Down protomer
UP protomer:
RBD
NTD
SD1
SD2
S2
B
NTD
NTD-RBD Linker
RBD
SD1
SD2
S2
FPPR segment
UP/Down Cα distance (Å)
50
40
30
20
10
0
0
300
600
900
C
Down protomer
UP protomer:
RBD
NTD
SD1
SD2
S2
12-16
12-19
Clash
NTD
12-16
12-19
D
100
80
60
40
20
0
12-16
12-16 F(ab*)2
12-19
12-19 F(ab*)2
IC50 (ug/ml)
0.027
0.034
0.063
0.066
4-18
4-18 F(ab*)2
IC50 (ug/ml)
0.044
0.452
10-3 10-2 10-1 100 101

FIGS. 34A-D

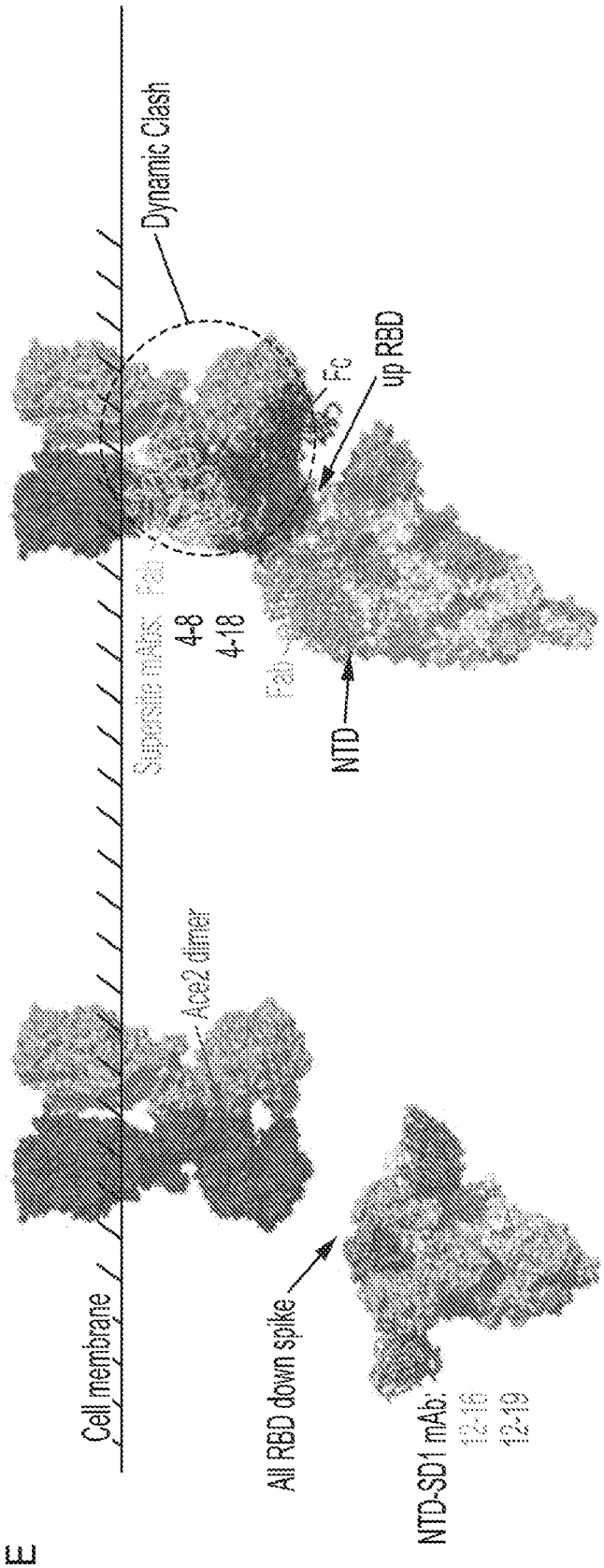

E
Cell membrane
Ace2 dimer
All RBD down spike
NTD-SD1 mAb:
12-16
12-19
Lock to RBD down
Dynamic Clash
Supersite mAbs
4-8
4-18
Fab
Fc
up RBD
NTD
Block hACE2

FIG. 34E

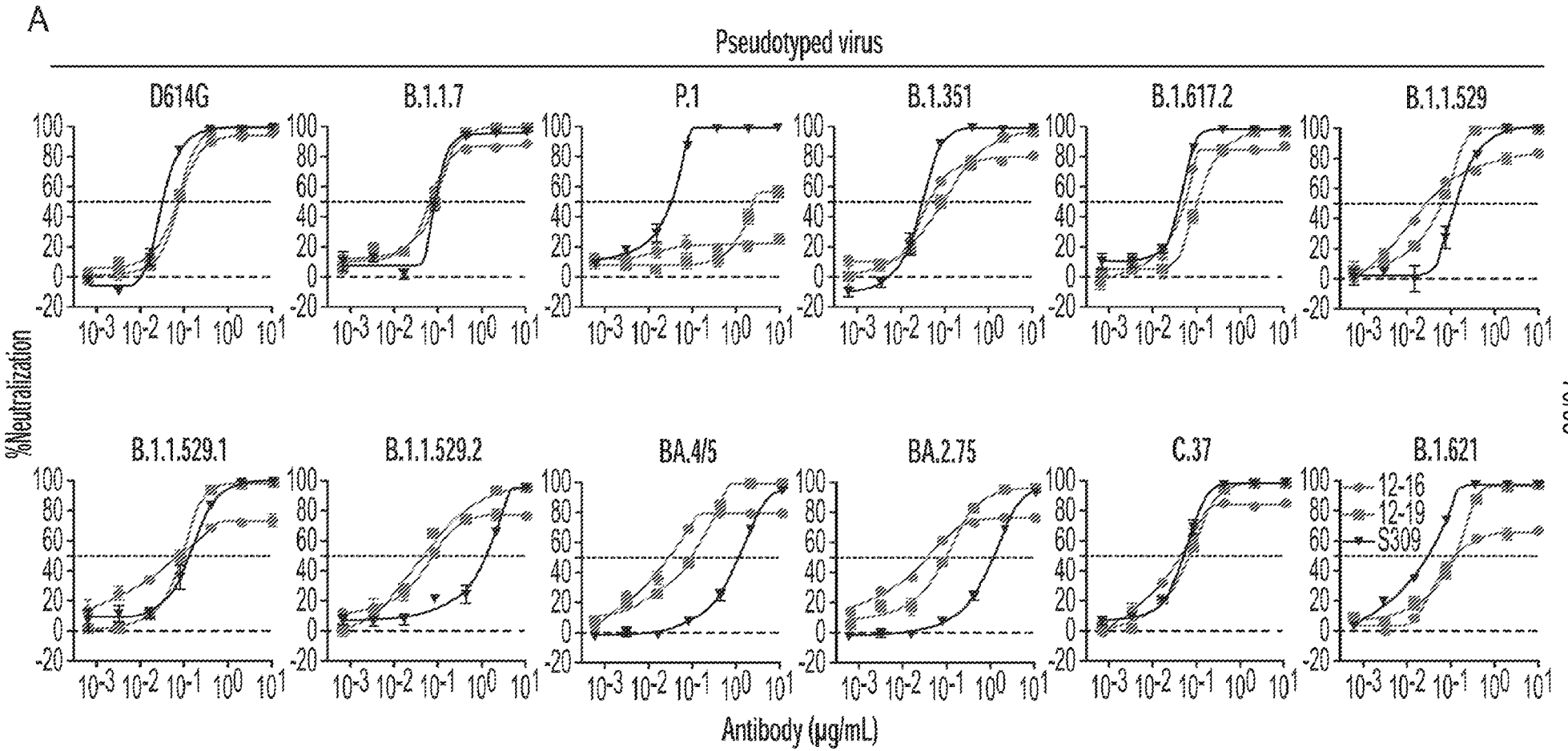

A
Pseudotyped virus
D614G
B.1.1.7
P.1
B.1.351
B.1.617.2
B.1.1.529
B.1.1.529.1
B.1.1.529.2
BA.4/5
BA.2.75
C.37
B.1.621
12-16
12-19
S309
%Neutralization
Antibody (μg/mL)

FIG. 35A

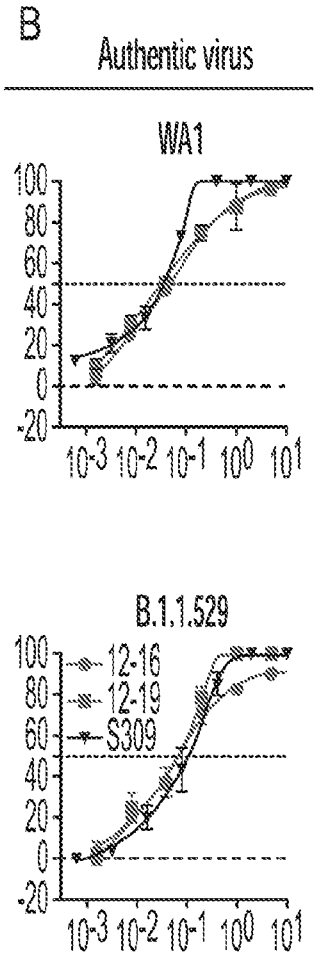

B
Authentic virus
WA1
100
80
60
40
20
0
-20
10-3 10-2 10-1 100 101
B.1.1.529
12-16
12-19
S309
100
80
60
40
20
0
-20
10-3 10-2 10-1 100 101

FIG. 35B

A

mAbs	HV	HD	HJ	Isotype	H_SHM	CDRH3_len	HCDR3	LV	LJ	L_SHM	CDRL3_len	LCDR3
12-16	IGHV3-30*18	IGHD3-9*01	IGHJ6*02	IGHG3*04	1.7%	25	AKDLSFYYDISTGYYPQSYNSGTDV	IGLV3-1*01	IGLJ1*01	1.4%	11	QGWDRSTGYYV
12-19	IGHV3-33*01	IGHD3-9*01	IGHJ6*02	IGHG1*04	2.7%	26	ARDRTPVYDILTGYYWPPPRVDGMDV	IGKV2-29*02	IGKJ2*02	2.3%	9	MQSIQLPFT

FIG. 36A

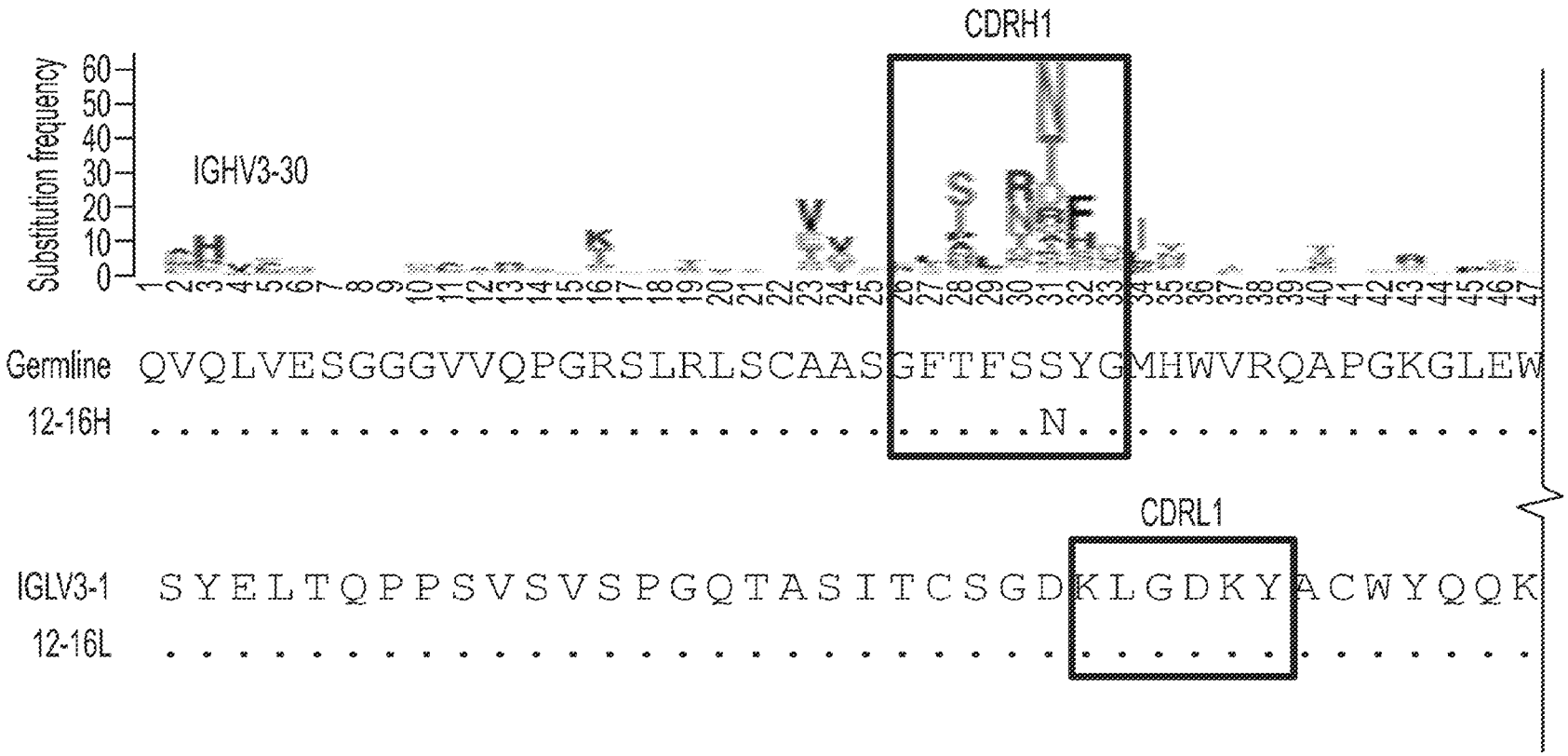

CDRH1
Substitution frequency
60
50
40
30
20
10
0
IGHV3-30
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47
Germline QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEW
12-16H . . . . . N . . . . . .
CDRL1
IGLV3-1 SYELTQPPSVSVSPGQTASITCSGDKLGDKYACWYQQK
12-16L . . . . . .

FIG. 36B

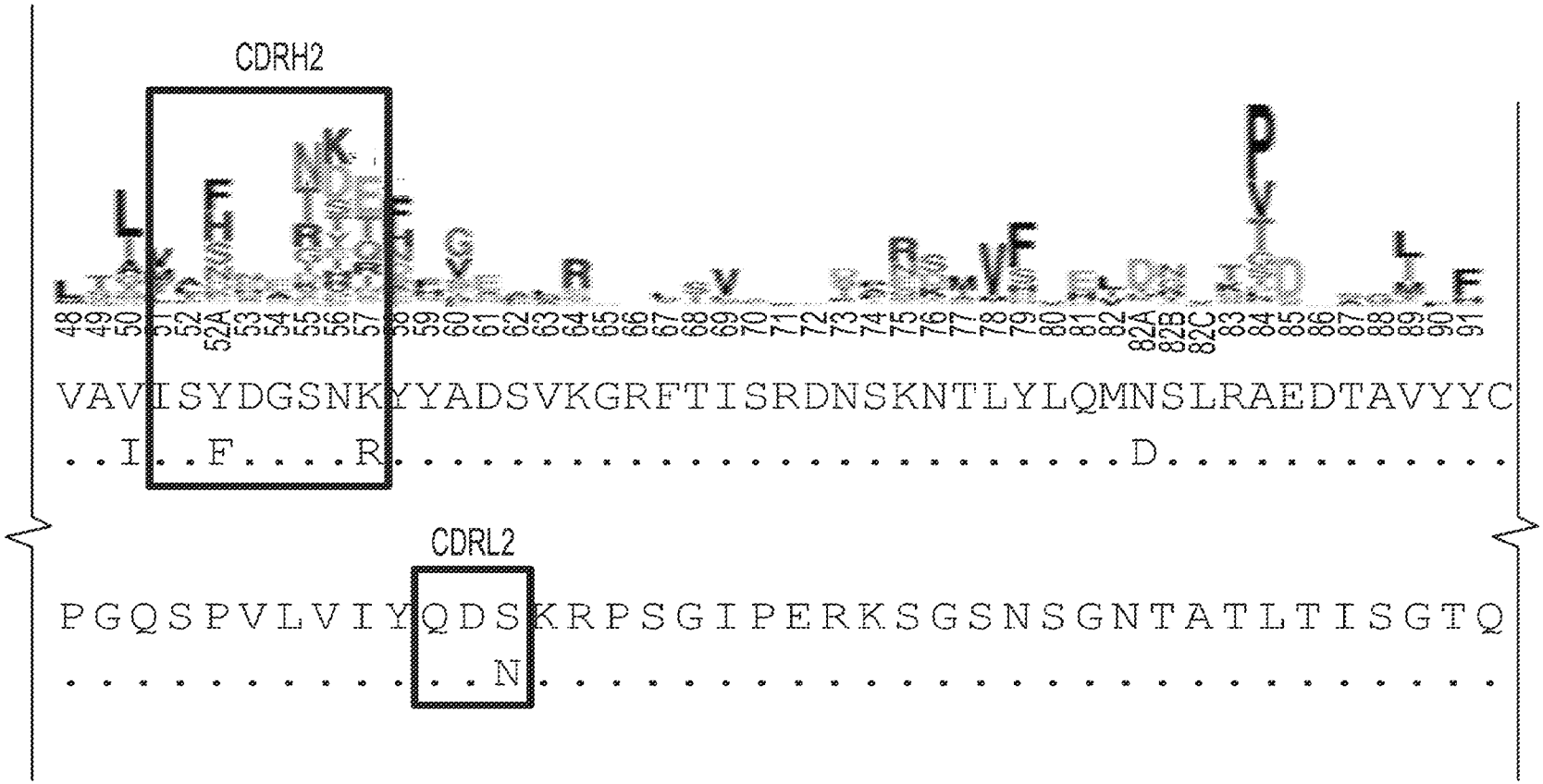


FIG. 36B
CONTINUED

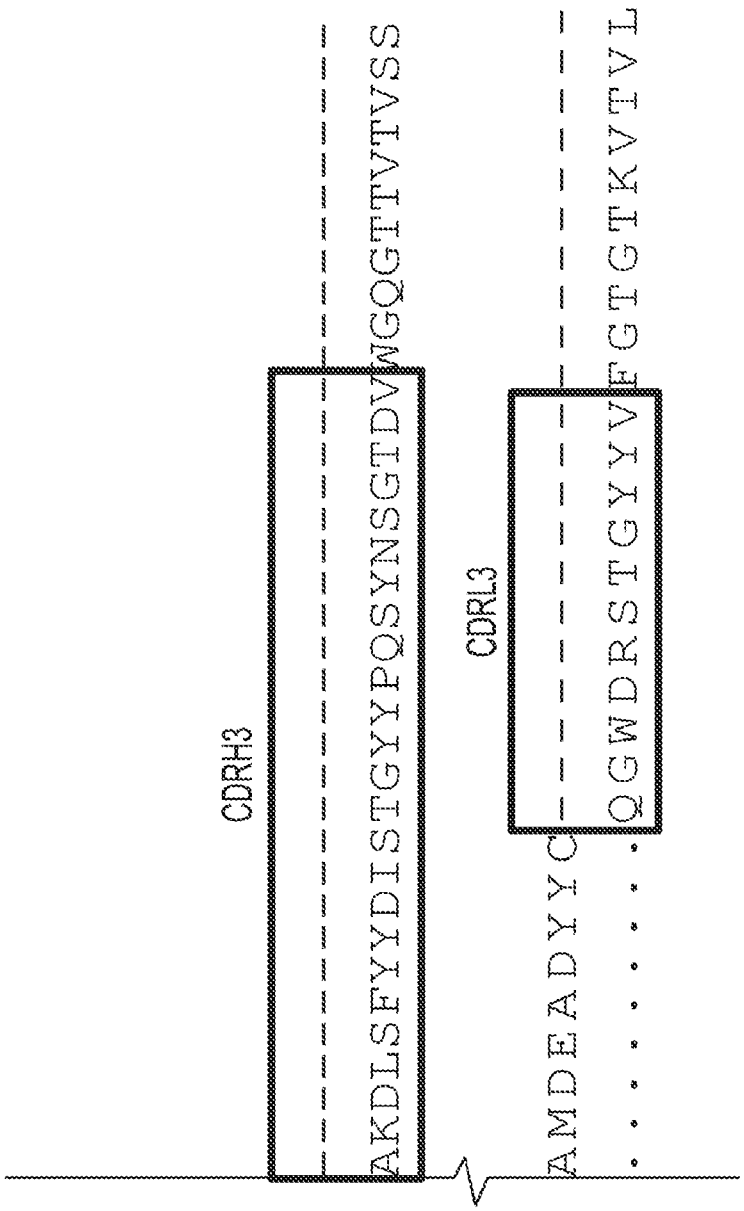


FIG. 36B
CONTINUED

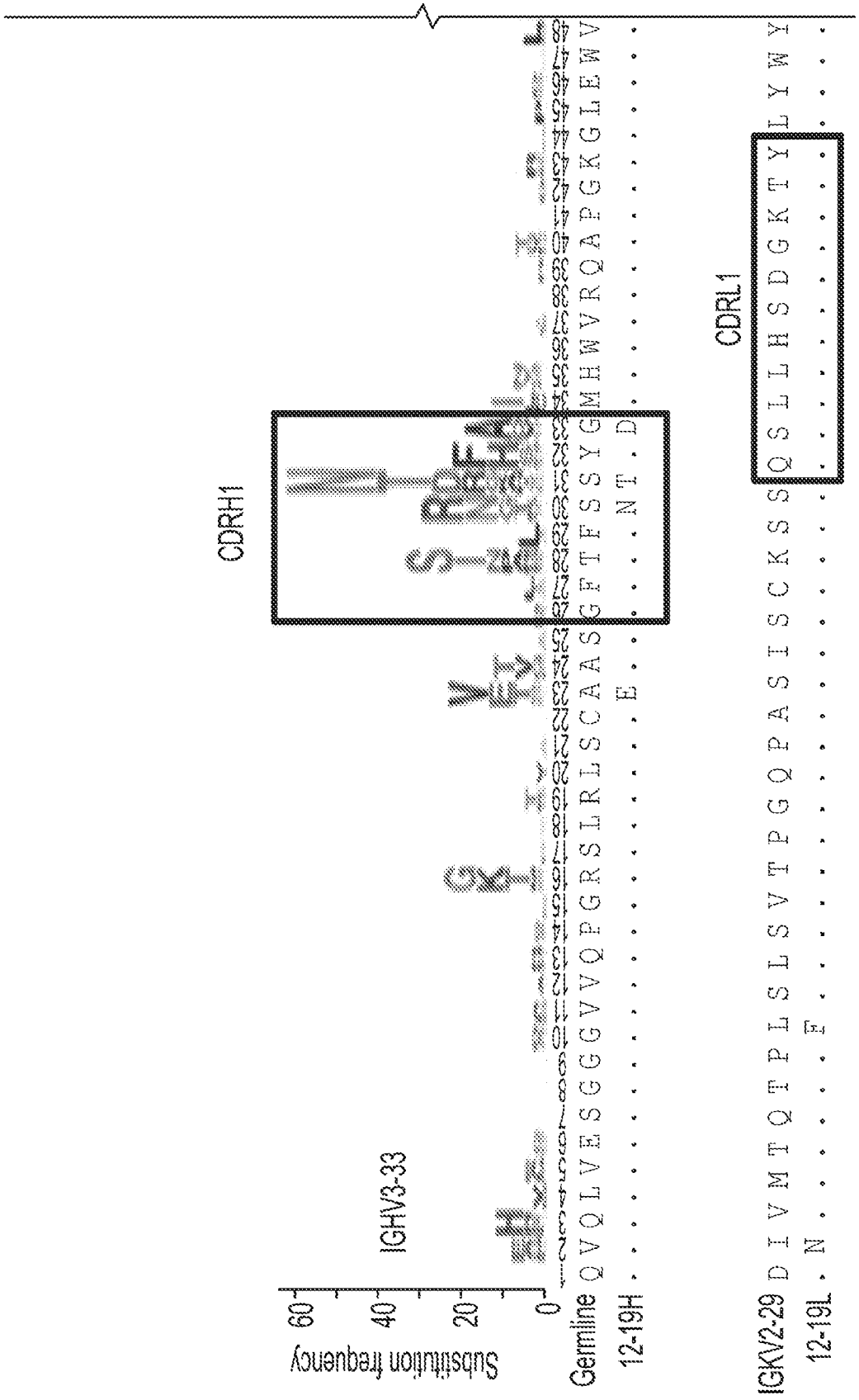

CDRH1
CDRL1
IGHV3-33
IGKV2-29
Substitution frequency
60
40
20
0
Germline Q V Q L V E S G G G V V Q P G R S L R L S C A A S G F T F S S Y G M H W V R Q A P G K G L E W V
12-19H . . . . . E . . . . . N T . D . . . . . .
IGKV2-29 D I V M T Q T P L S L S V T P G Q P A S I S C K S S Q S L L H S D G K T Y L Y W Y
12-19L . N . . . . . E . . . . . .

FIG. 36C

FIG. 36C
CONTINUED

CDRH3

```
- - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - -
A R D R T P V Y D I L T G Y Y W P P P R V D G M D V W G Q G T T V T V S S
```

CDRL3

```
R V E A E D V G V Y Y C - - - - - - - - - - - - - - - - - - -
. . . . . . . . . . . . M Q S I Q L P F T F G Q G T K L E I K
```

FIG. 36C
CONTINUED

D

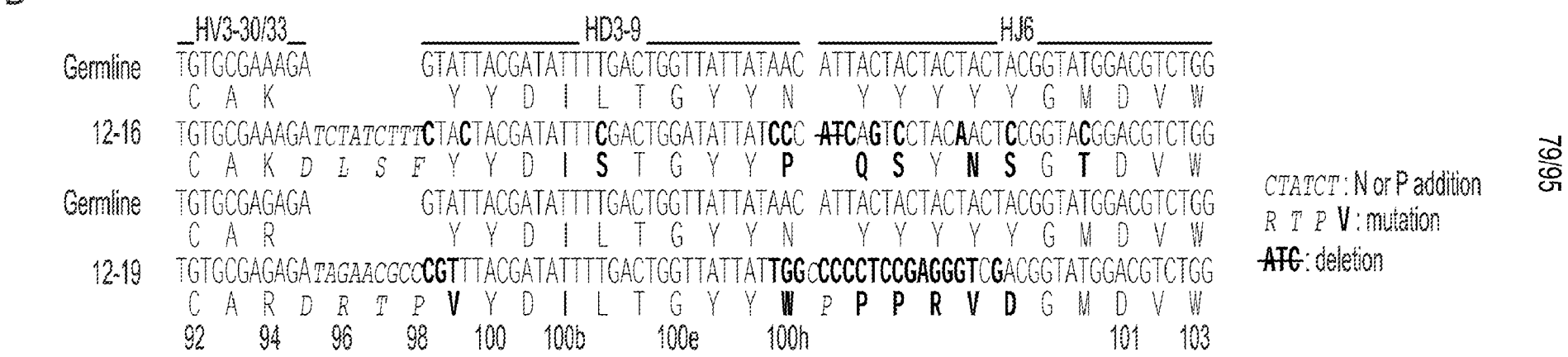
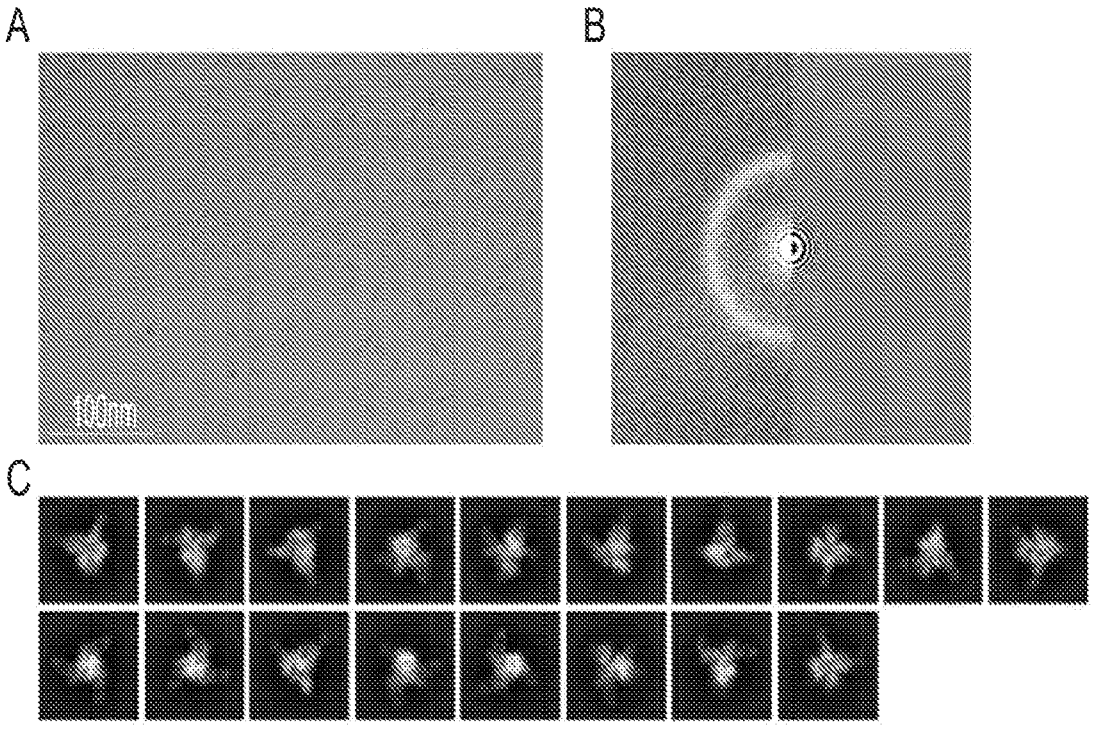
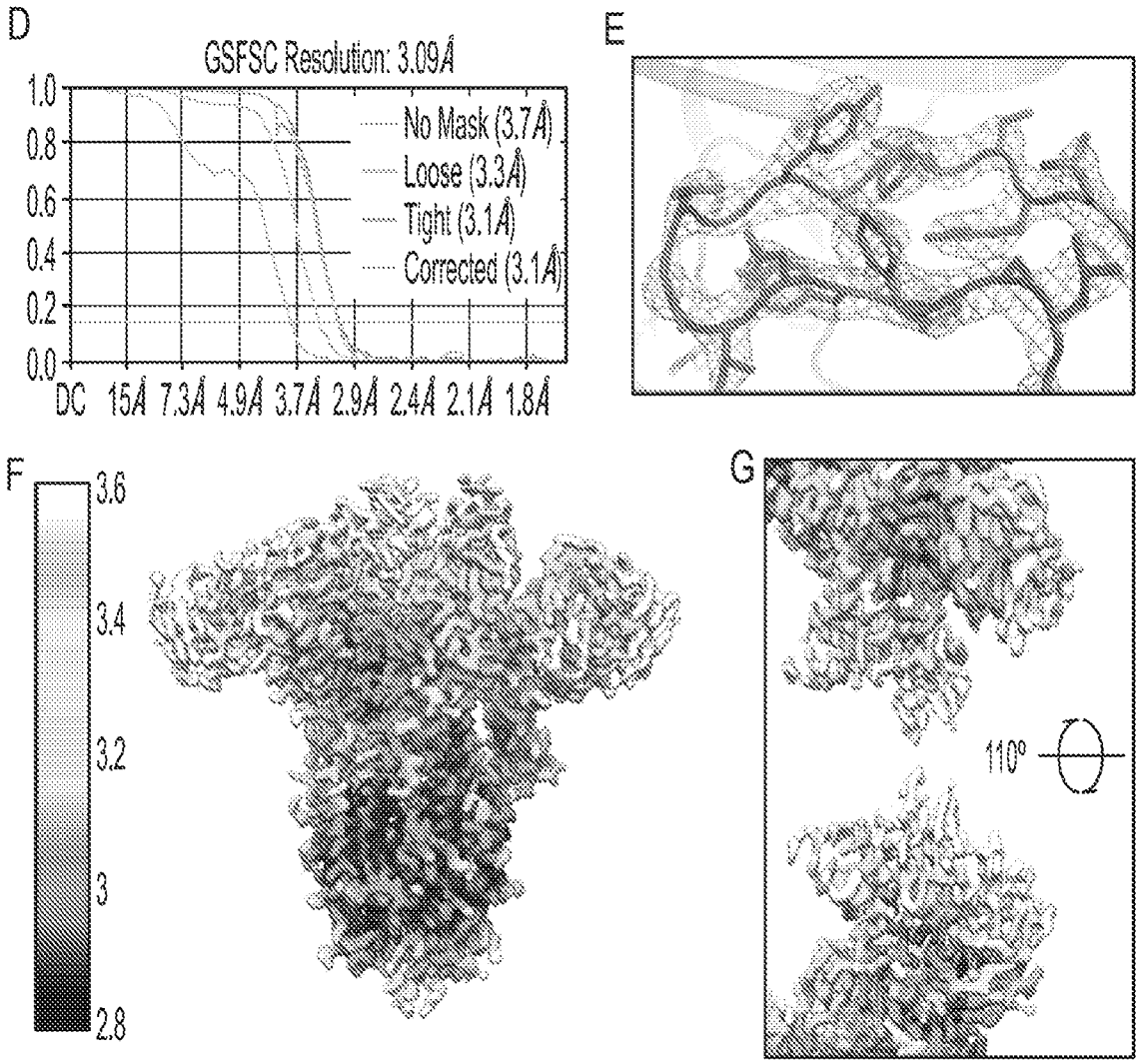

_HV3-30/33_
HD3-9
HJ6
Germline
TGTGCCGAAAGA GTATTACGATATTTTGACTGGTTATTATAAC ATTACTACTACTACTACGGTATGGACGTCTGG
C A K Y Y D I L T G Y Y N Y Y Y Y Y G M D V W
12-16
TGTGCCGAAAGATCTATCTTTCTACTACGATATTTCGACTGGATATTATCCC ATCAGTCCTACAACTCCGGTACGGACGTCTGG
C A K D L S F Y Y D I S T G Y Y P Q S Y N S G T D V W
Germline
TGTGCCGAGAGA GTATTACGATATTTTGACTGGTTATTATAAC ATTACTACTACTACTACGGTATGGACGTCTGG
C A R Y Y D I L T G Y Y N Y Y Y Y Y G M D V W
12-19
TGTGCGAGAGATAGAACGCCCGTTTACGATATTTTGACTGGTTATTATTGGCCCCCTCCGAGGGTCGACGGTATGGACGTCTGG
C A R D R T P V Y D I L T G Y Y W P P P R V D G M D V W
92 94 96 98 100 100b 100e 100h 101 103
CTATCT: N or P addition
R T P V: mutation
ATC: deletion

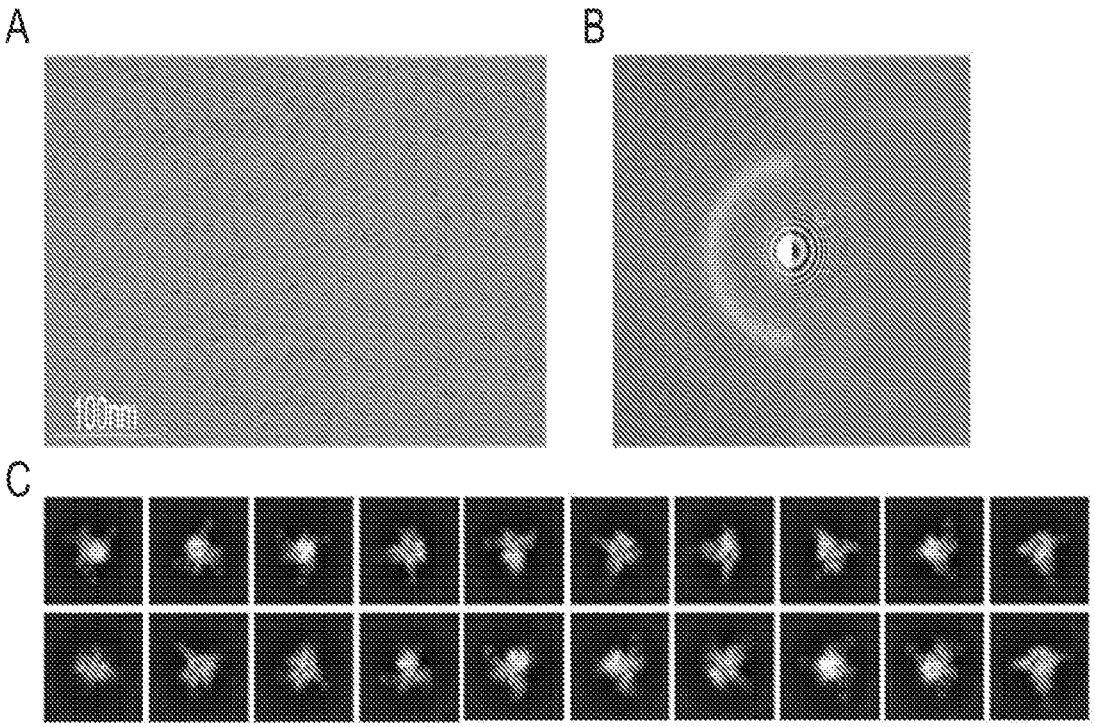
FIG. 36D



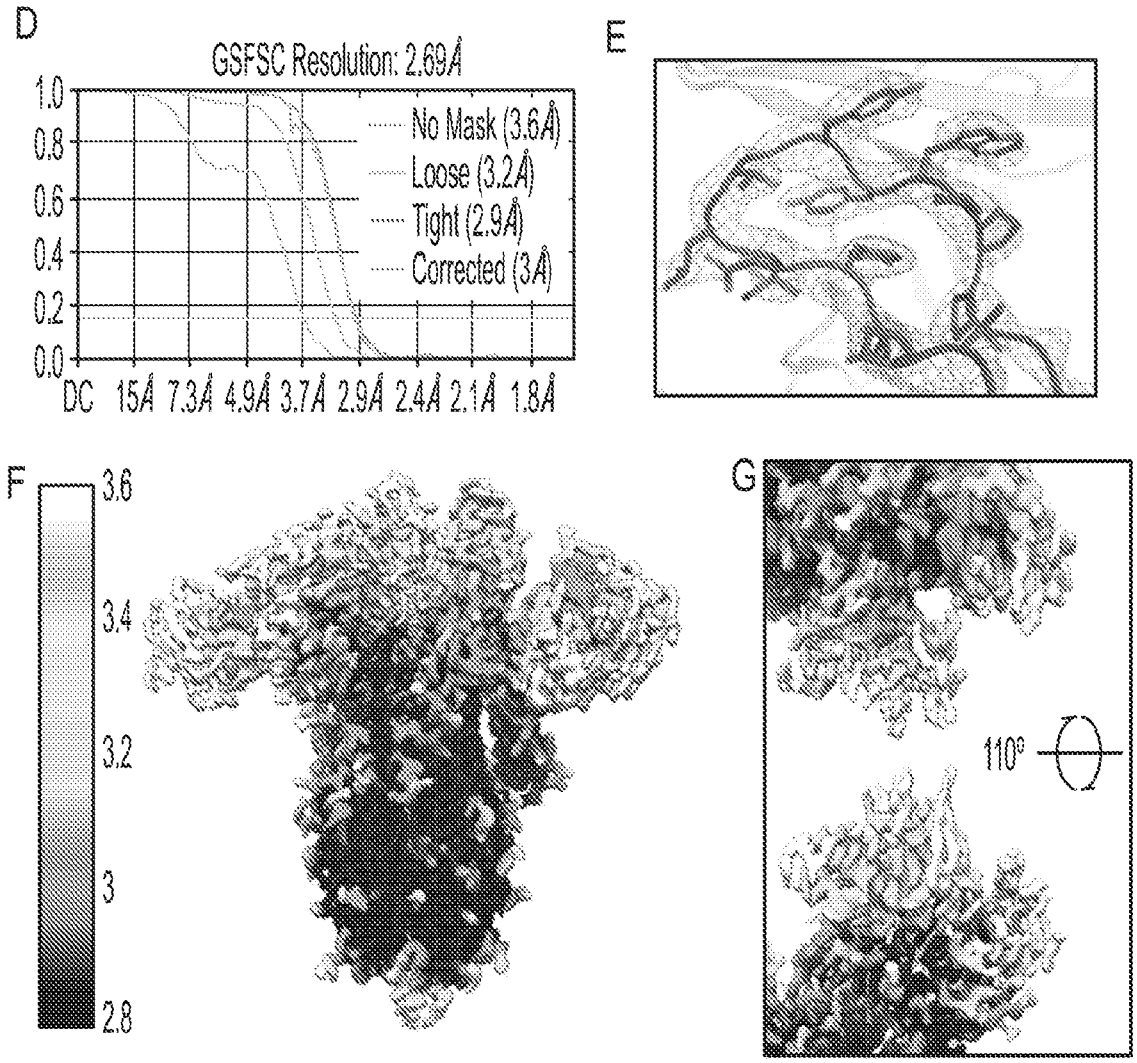
FIGS. 37A-C


D
GSFSC Resolution: 3.09Å
1.0
0.8
0.6
0.4
0.2
0.0
No Mask (3.7Å)
Loose (3.3Å)
Tight (3.1Å)
Corrected (3.1Å)
DC 15Å 7.3Å 4.9Å 3.7Å 2.9Å 2.4Å 2.1Å 1.8Å
E
F
3.6
3.4
3.2
3
2.8
G
110°

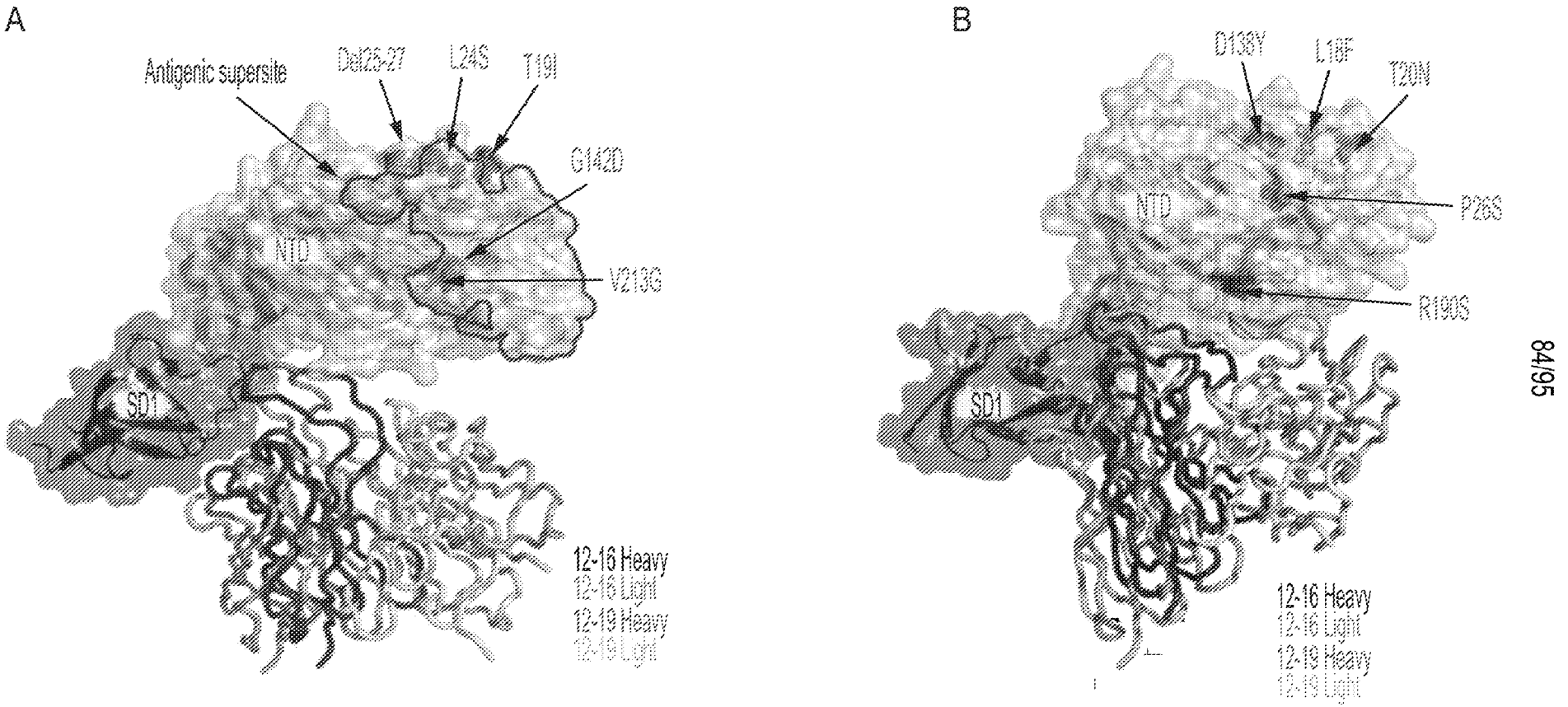
FIGS. 37D-G



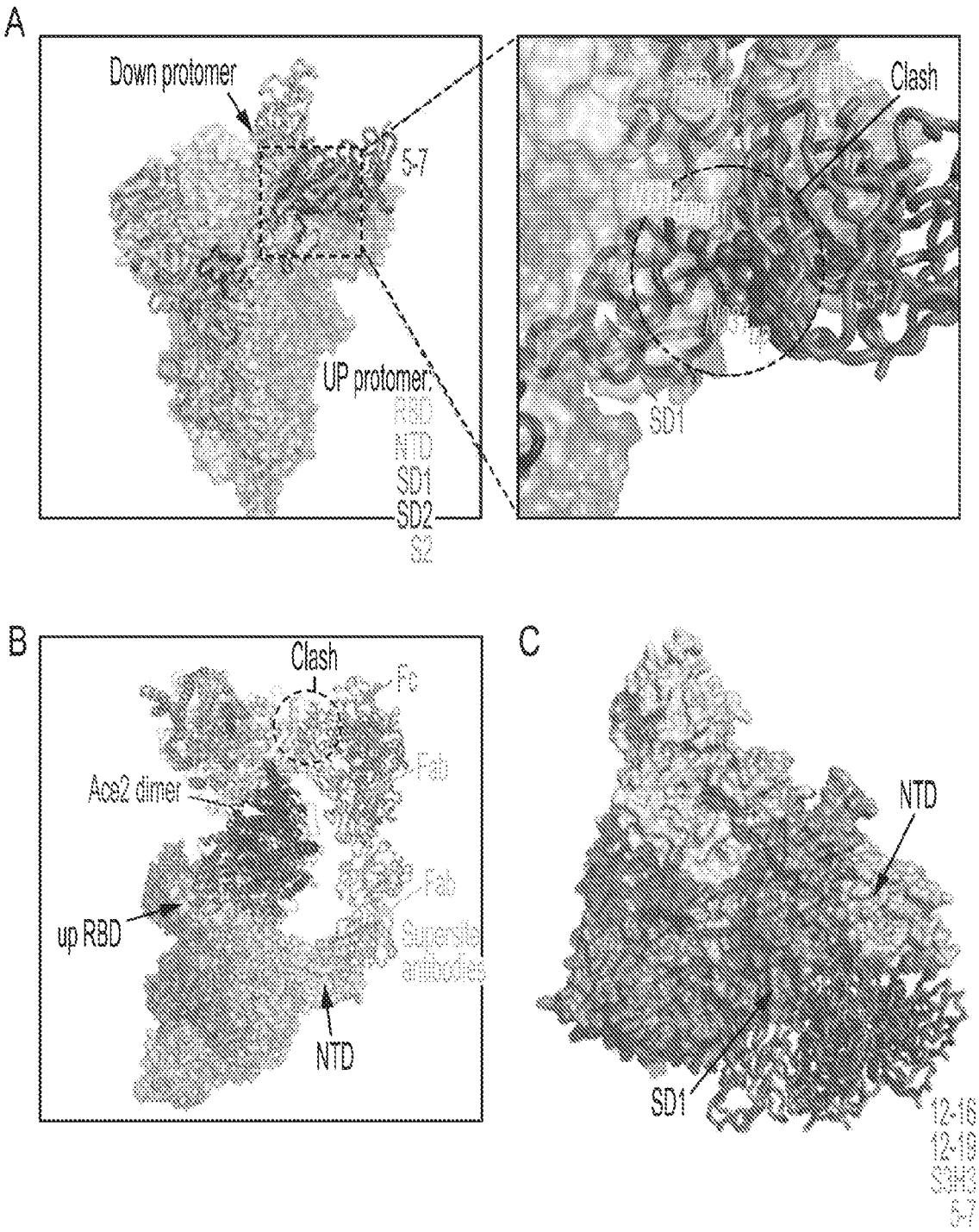
FIGS. 38A-C


D
GSFSC Resolution: 2.69Å
1.0
0.8
0.6
0.4
0.2
0.0
No Mask (3.6Å)
Loose (3.2Å)
Tight (2.9Å)
Corrected (3Å)
DC 15Å 7.3Å 4.9Å 3.7Å 2.9Å 2.4Å 2.1Å 1.8Å
E
F
3.6
3.4
3.2
3
2.8
G
110°

FIGS. 38D-G


A
Antigenic supersite
Del25-27
L24S
T19I
G142D
V213G
NTD
SD1
12-16 Heavy
12-16 Light
12-19 Heavy
12-19 Light
B
D138Y
L18F
T20N
P26S
NTD
R190S
SD1
12-16 Heavy
12-16 Light
12-19 Heavy
12-19 Light

FIGS. 39A-B


A
Down protomer
5-7
UP protomer
RBD
NTD
SD1
SD2
S2
Clash
SD1
B
Clash
Fc
Fab
Ace2 dimer
Fab
up RBD
Supersite antibodies
NTD
C
NTD
SD1
12-16
12-19
S2H3
5-7

FIGS. 40A-C

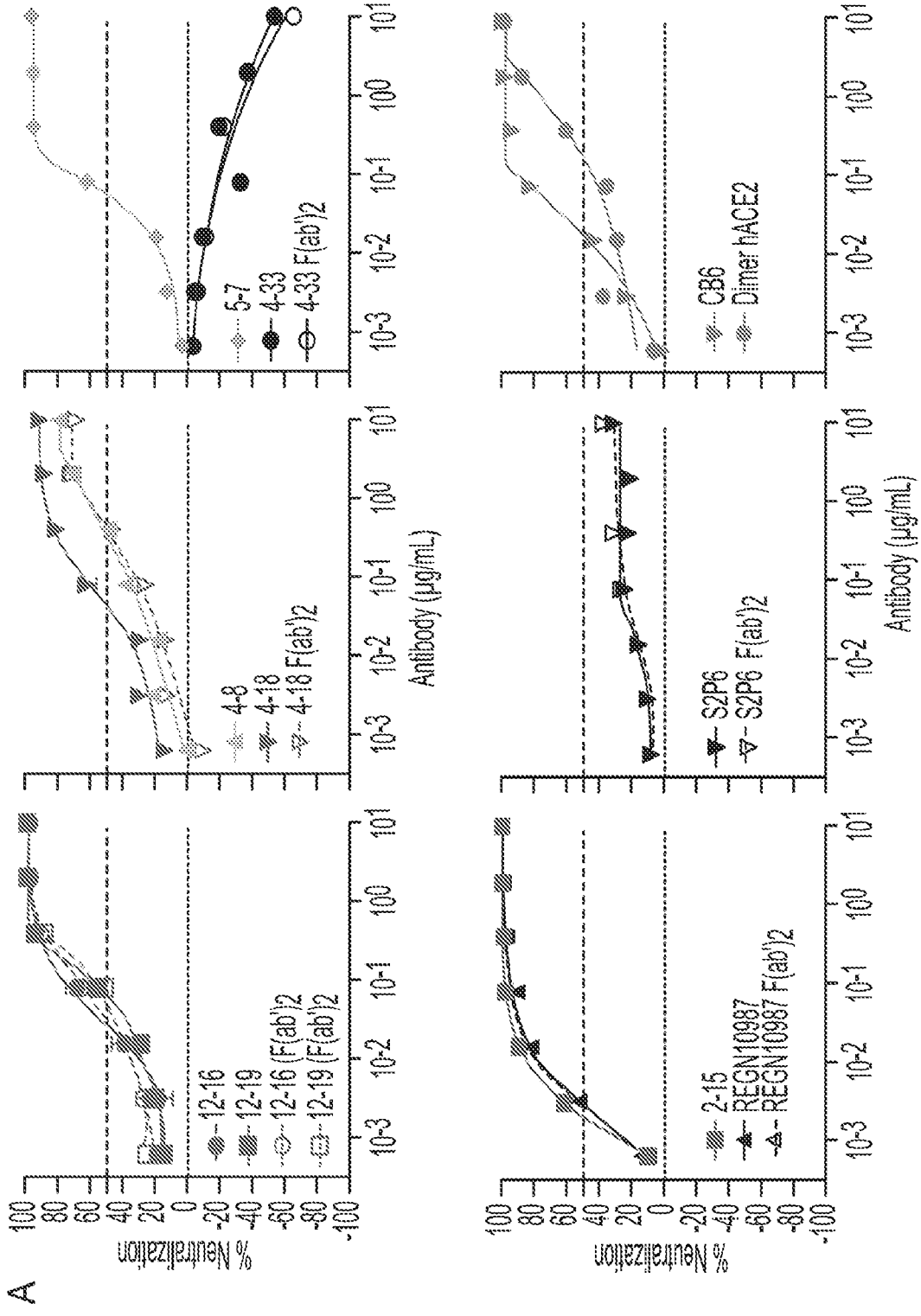

A
% Neutralization
Antibody (µg/mL)
12-16
12-19
12-16 (F(ab')2
12-19 (F(ab')2
4-8
4-18
4-18 F(ab')2
5-7
4-33
4-33 F(ab')2
2-15
REGN10987
REGN10987 F(ab')2
S2P6
S2P6 F(ab')2
CB6
Dimer hACE2

FIG. 41A

B

mAb	12-16		12-19		4-18		4-33		S2P6		REGN10987						
Format	WT	F(ab')2	WT	F(ab')2	WT	F(ab')2	WT	F(ab')2	WT	F(ab')2	WT	F(ab')2	4-8	5-7	2-16	CB6	hACE2-Fc
IC50 (µg/ml)	0.027	0.004	0.063	0.006	0.044	0.452	>10	>10	>10	>10	0.003	0.003	0.338	0.056	0.002	0.02	0.172

FIG. 41B

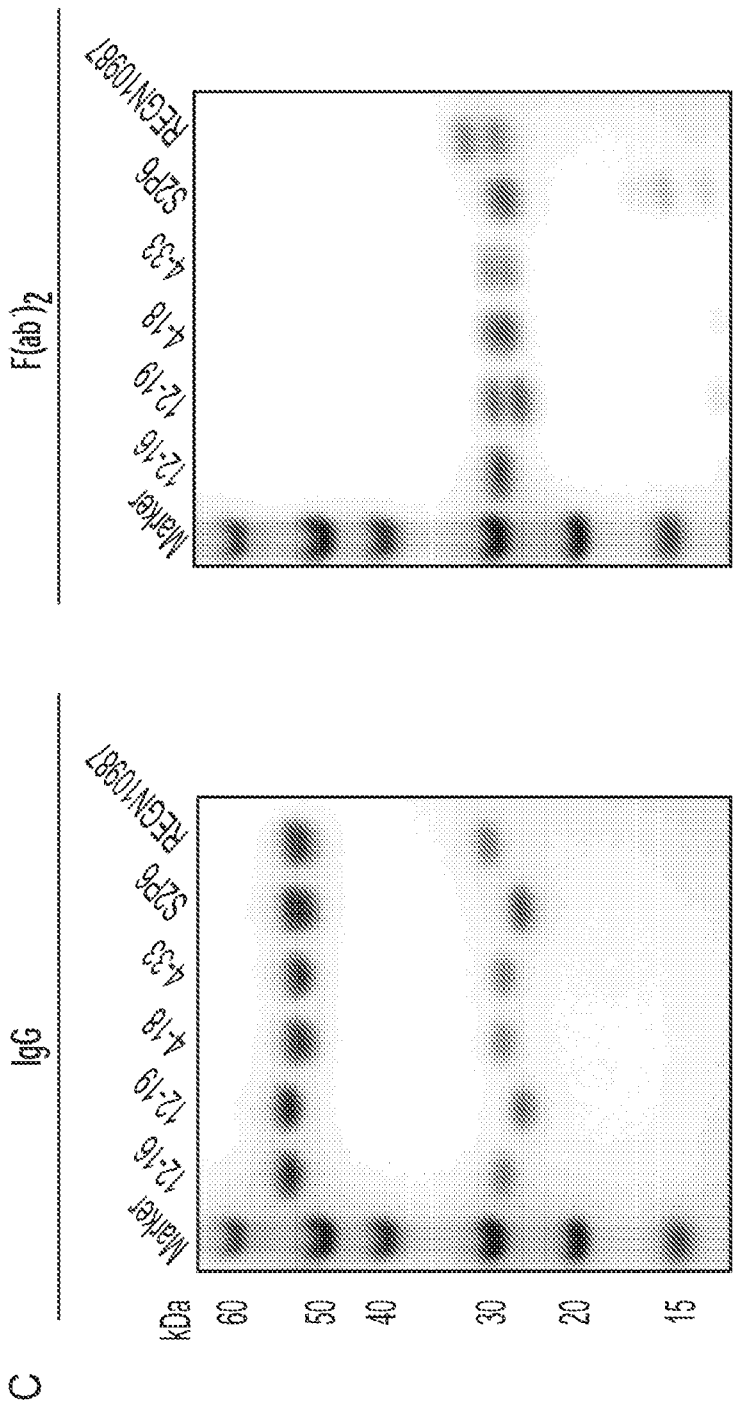
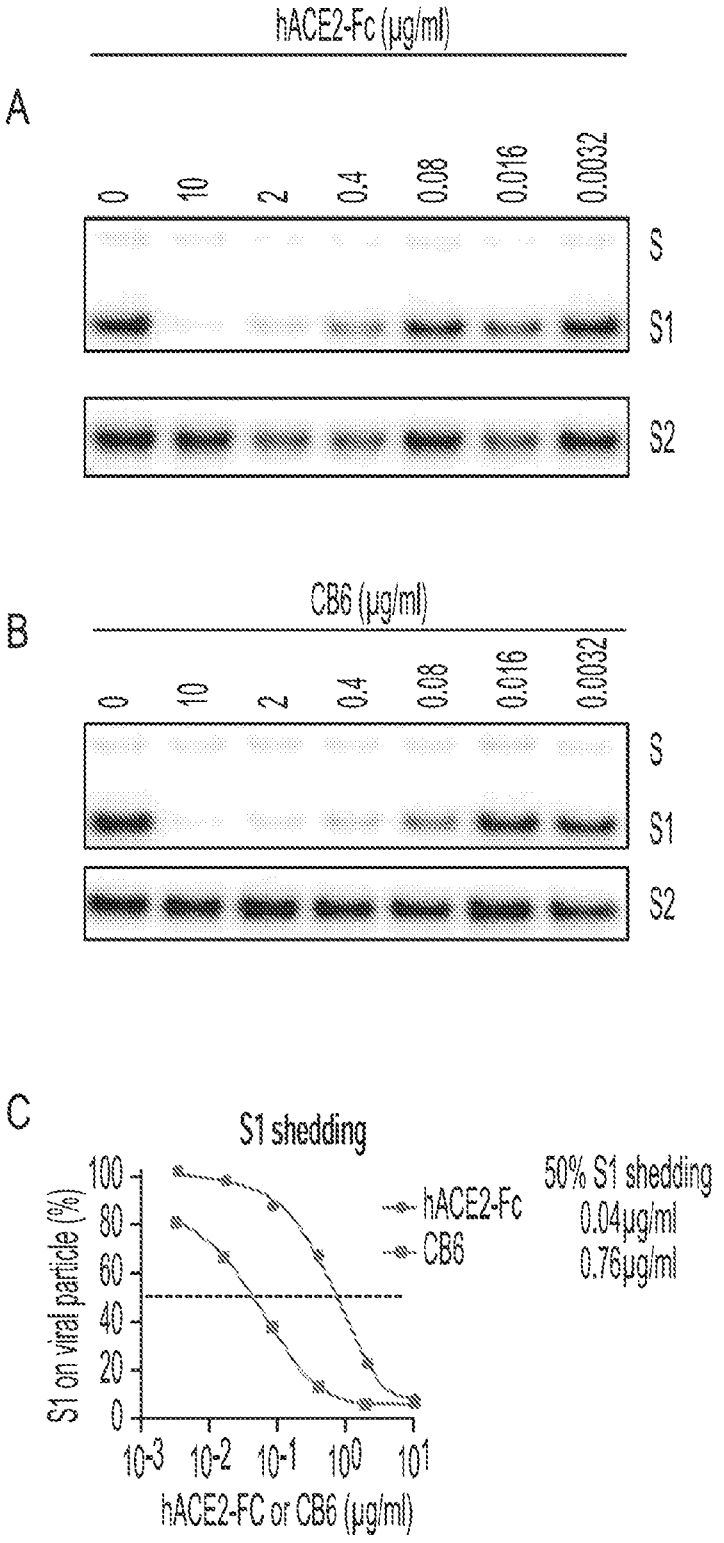
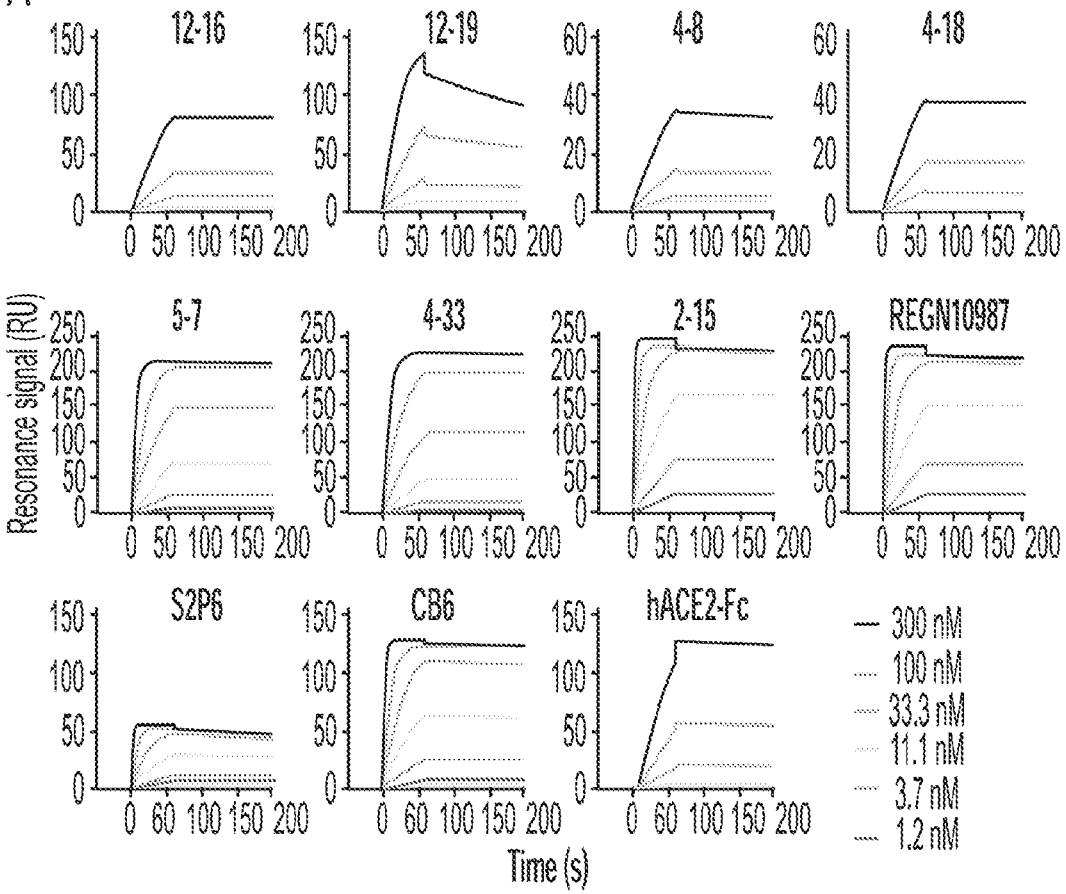

C
IgG
F(ab)2
kDa
60
50
40
30
20
15
Marker
12-16
12-19
4-18
4-33
S2P6
RECNI09987

FIG. 41C


hACE2-Fc (μg/ml)
A
0
10
2
0.4
0.08
0.016
0.0032
S
S1
S2
CB6 (μg/ml)
B
0
10
2
0.4
0.08
0.016
0.0032
S
S1
S2
C
S1 shedding
S1 on viral particle (%)
100
80
60
40
20
0
10-3
10-2
10-1
100
101
hACE2-FC or CB6 (μg/ml)
hACE2-Fc
CB6
50% S1 shedding
0.04μg/ml
0.76μg/ml

FIGS. 42A-C

A



B

	SARS-CoV-2 Spike		
mAb	ka (1/Ms)	kd (1/s)	KD (M)
12-16	4.14E+04	6.62E-05	1.60E-09
12-19	2.35E+05	2.20E-03	9.35E-09
4-8	3.90E+04	4.94E-04	1.26E-08
4-18	6.17E+04	6.24E-07	1.01E-11
5-7	6.16E+05	5.60E-05	9.09E-11
4-33	3.61E+05	3.45E-05	9.57E-11
2-15	2.03E+06	1.57E-04	7.74E-11
REGN10987	1.73E+06	1.75E-04	1.01E-10
S2P6	1.41E+06	8.89E-04	6.30E-10
CB6	1.05E+06	1.92E-04	1.83E-10
hACE2-Fc	5.69E+04	2.97E-04	5.21E-09

FIGS. 43A-B

	SARS-CoV-2 S2P + 12-16 Fab	SARS-CoV-2 S2P + 12-19 Fab
EMDB ID		
PDB ID		
Data Collection		
Microscope	FEI Titan Krios	FEI Titan Krios
Voltage (keV)	300	300
Magnification	105k	105k
Defocus Range (μm)	-0.8/-2.0	-0.8/-2.0
Camera	Gatan K3 BioQuantum	Gatan K3 BioQuantum
Pixel Size (Å/pix)	0.83	0.83
Recording Mode	counting	counting
Dose Rate (e-/pixel/s)	16	16
Electron Dose (e-/Å2)	58	58
Data Processing		
Software	cryoSPARC v3.3	cryoSPARC v3.3
Micrographs used	3,691	4,042
Number of Particles	463,850	475,759
Symmetry	C1	C1
Box Size (pix)	440	440
Global Map $FSC_{0.143}$ (Å)	3.09	2.96
Refinement and Validation		
Software	Phenix, ISOLDE, Rosetta	Phenix, ISOLDE, Rosetta
Initial Model Used	6XM5(Spike), Alphafold(Fab)	6XM5(Spike), Alphafold(Fab)
Number of Atoms	30,246	28,230
Protein Residues	3,795	3,526
Ligands	NAG: 48	NAG: 47
Model vs. Data CC (mask)	0.83	0.76
RMS deviations		
Bond lengths (Å) (# >4σ)	1	4
Bond angles (°) (# >4σ)	25	17
MolProbity Score	1.25	1.26
Clashscore (all atom)	2.52	2.57
Poor rotamers (%)	0	0
Ramachandran plot		
Favored (%)	96.63	96.59
Allowed (%)	3.37	3.41
Outliers (%)	0	0

FIG. 44

A

The multiple sequence alignment of the light chain variable domains

mAbs	10-16	10-28	10-40	11-11	12-6	12-27	13-2	*12-16*	*12-19*
10-16	100	71	48	55	70	61	53	50	61
10-28	71	100	48	53	94	81	50	49	56
10-40	50	50	100	66	50	46	59	58	43
11-11	55	53	64	100	54	52	62	60	48
12-6	70	94	48	54	100	80	51	47	56
12-27	61	81	44	52	80	100	46	43	52
13-2	53	50	57	62	51	46	100	76	54
12-16	50	49	55	60	47	43	76	100	48
12-19	61	56	41	48	56	52	54	48	100

B

The multiple sequence alignment of the heavy chain variable domains

mAbs	10-16	10-28	10-40	11-11	12-6	12-27	13-2	*12-16*	*12-19*
10-16	100	49	42	41	68	50	50	49	47
10-28	49	100	47	50	52	52	84	75	75
10-40	42	47	100	81	41	47	54	52	52
11-11	41	50	81	100	44	47	54	54	50
12-6	68	52	46	47	100	59	56	55	51
12-27	50	52	47	47	59	100	52	47	47
13-2	50	84	54	54	53	52	100	83	81
12-16	49	75	52	54	52	47	83	100	82
12-19	47	75	52	49	48	47	81	82	100

The similarities among antibody sequences were calculated by blastp in BLAST+ 2.8.1

FIGS. 45A-B

A

The multiple amino acid sequence alignment of the complementarity determining regions (CDRs) in the light chain variable domains

mAbs	10-16	10-28	10-40	11-11	12-6	12-27	13-2	*12-16*	*12-19*
10-16	100	46	39	<10	60	40	<10	<10	<10
10-28	46	100	<10	<10	93	<10	<10	<10	<10
10-40	39	<10	100	57	33	<10	45	38	<10
11-11	<10	<10	57	100	<10	<10	75	<10	<10
12-6	60	93	33	<10	100	<10	<10	<10	<10
12-27	40	<10	<10	<10	<10	100	<10	<10	<10
13-2	<10	<10	45	75	<10	<10	100	42	<10
12-16	<10	<10	38	<10	<10	<10	42	100	<10
12-19	<10	<10	<10	<10	<10	<10	<10	<10	100

B

The multiple amino acid sequence alignment of the complementarity determining regions (CDRs) in the heavy chain variable domains

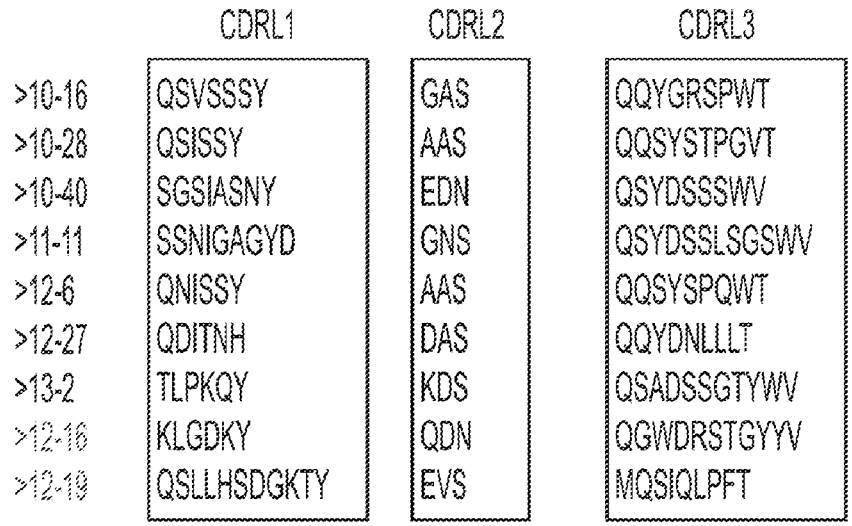
mAbs	10-16	10-28	10-40	11-11	12-6	12-27	13-2	*12-16*	*12-19*
10-16	100	<10	<10	47	<10	<10	<10	<10	<10
10-28	<10	100	<10	<10	<10	25	50	68	54
10-40	<10	<10	100	63	0	54	38	38	38
11-11	47	<10	63	100	0	<10	50	<10	<10
12-6	<10	<10	40	36	100	<10	39	45	46
12-27	<10	25	54	<10	<10	100	<10	<10	<10
13-2	<10	50	38	50	<10	<10	100	56	59
12-16	<10	68	38	<10	<10	<10	56	100	55
12-19	<10	54	38	<10	<10	<10	59	55	100

The similarities among antibody sequences were calculated by blastp in BLAST+ 2.8.1

FIGS. 46A-B

	CDRH1	CDRH2	CDRH3
>10-16	GFTFISSA	IVVGSGNT	AAPYCNSTNCYDAFNI
>10-28	GFTFSSYD	ISYDGSSK	VKDGEQLVPLFDY
>10-40	GGSISSSNFY	ITYSGRT	ARTFPSYYDRSGYHYLNYGMDV
>11-11	GGSISSGGYY	IYYSGST	ASSNYYDGSGYNLLESYGMDV
>12-6	GGTFSNYA	FIRIFDTA	ARSPYYYDKSGYYYFDH
>12-27	GYNFTFYW	IYPGDSE	TARLSGVQTALEYFDF
>13-2	GFIFSDFG	ISYDGSN	KARDYYDISGFYHPPNFDY
>12-16	GFTFSNYG	ISFDGSNR	AKDLSFYYDISTGYYPQSYNSGTDV
>12-19	GFTFNTYD	IWYDGSNK	ARDRTPVYDILTGYYWPPPRVDGMDV

FIG. 47



	CDRL1	CDRL2	CDRL3
>10-16	QSVSSSY	GAS	QQYGRSPWT
>10-28	QSISSY	AAS	QQSYSTPGVT
>10-40	SGSIASNY	EDN	QSYDSSSWV
>11-11	SSNIGAGYD	GNS	QSYDSSLSGSWV
>12-6	QNISSY	AAS	QQSYSPQWT
>12-27	QDITNH	DAS	QQYDNLLLT
>13-2	TLPKQY	KDS	QSADSSGTYWV
>12-16	KLGDKY	QDN	QGWDRSTGYYV
>12-19	QSLLHSDGKTY	EVS	MQSIQLPFT

FIG. 48