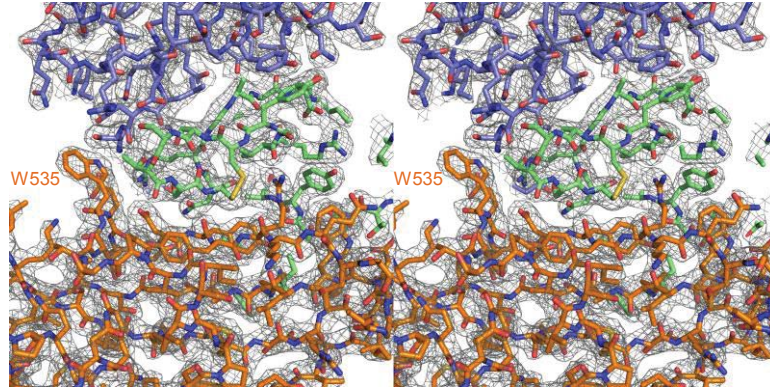
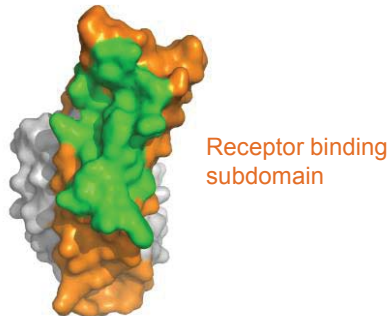
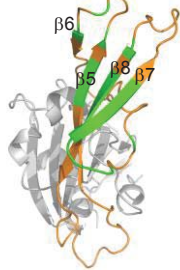


Supplementary Figure 1

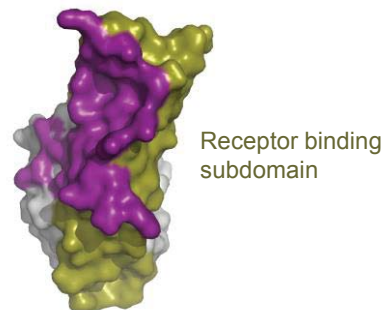
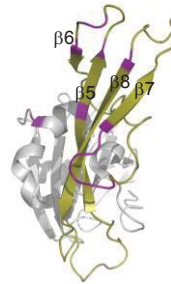
a Electron density at the interface of m336 and MERS-CoV RBD



b M336 epitope



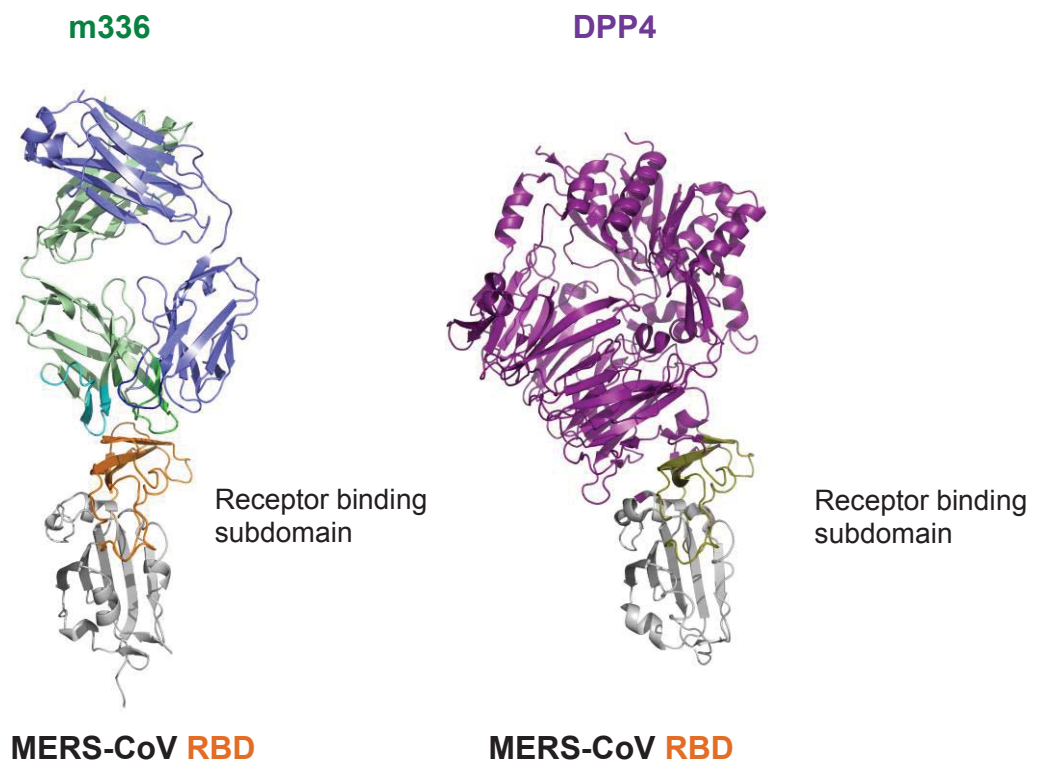
c DPP4 contacts



Supplementary Figure 1. Representative electron density map and comparison of m336 epitope and DPP4 binding site on MERS-CoV RBD

(a) Stereo view of $2F_o - F_c$ electron density at the interface of m336 and MERS-CoV RBD contoured at 1.0σ level. The MERS-CoV RBD, m336 heavy and light chains are shown with stick representation with C α atoms colored orange, light green and light blue, respectively. MERS-CoV RBD residue 535 is labeled for view orientation. (b and c) Side-by-side comparison of m336 epitope and DPP4 binding site on MERS-CoV RBD shown in both cartoon (top) and surface representation (bottom). The epitope of m336 (b) is colored in green and the binding site of DPP4 (c) is colored in purple on MERS-CoV RBD .

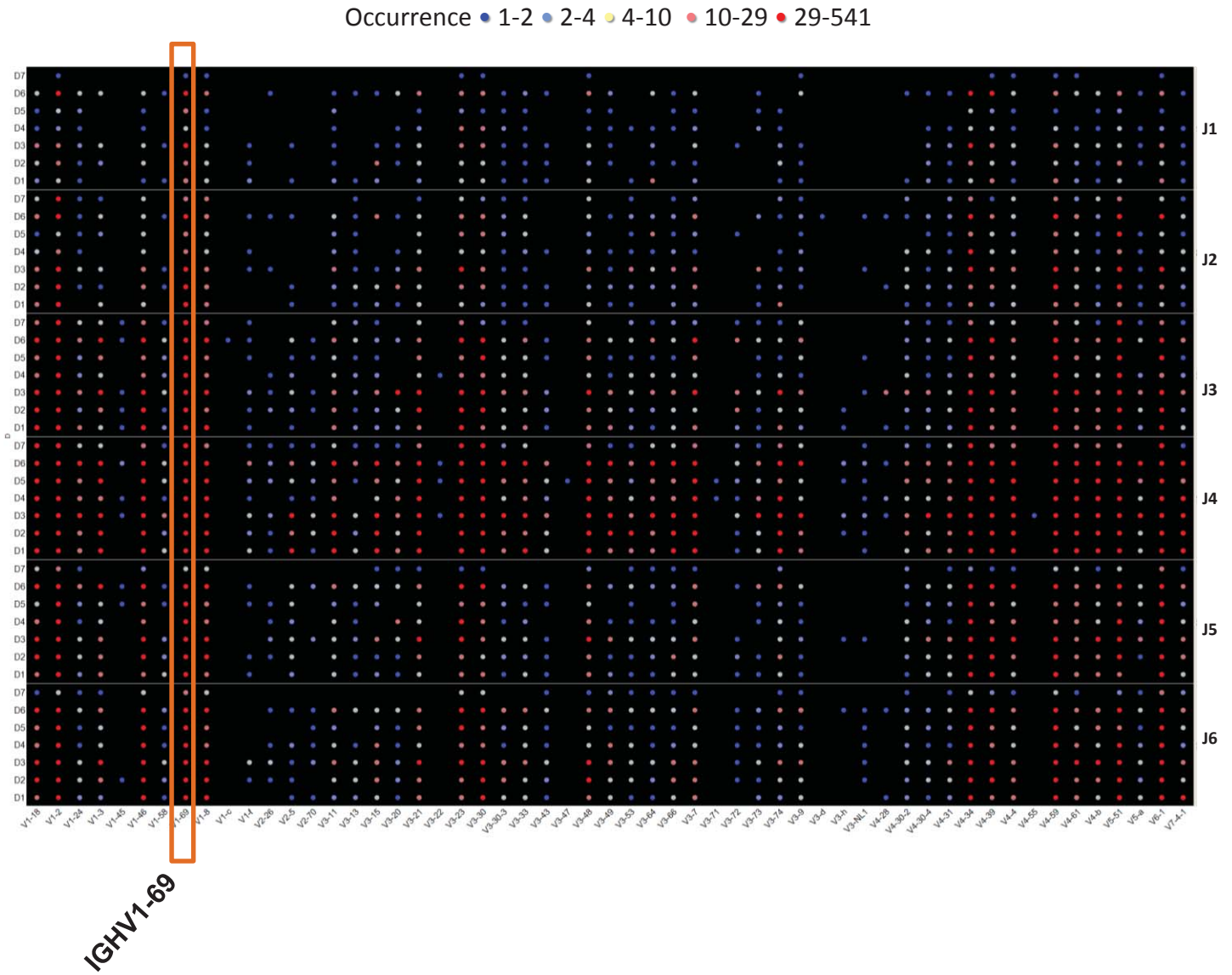
Supplementary Figure 2



Supplementary Figure 2. m336 mimics receptor DPP4 with similar angle of approach to engage MERS-CoV

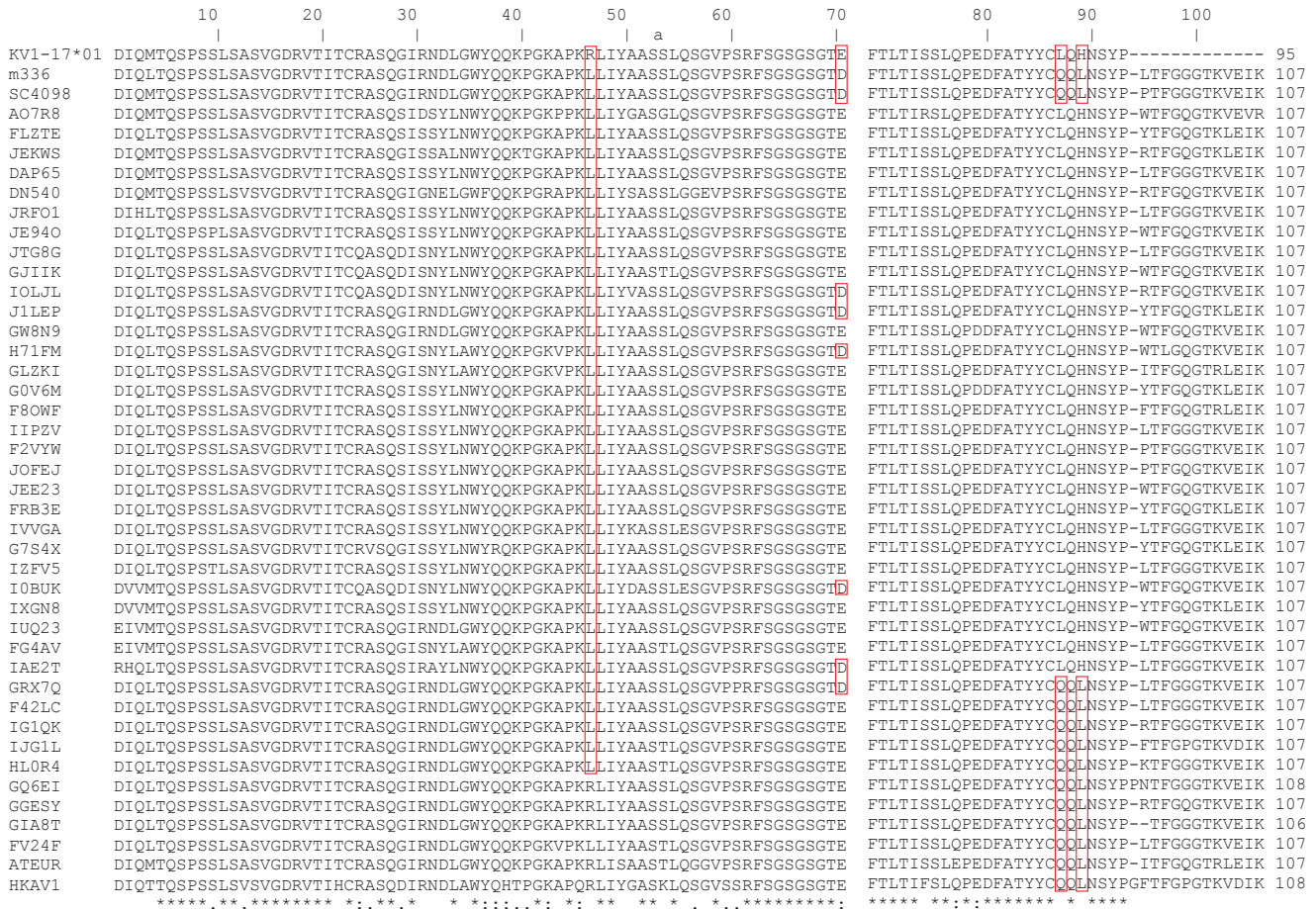
The MERS-CoV RBD, m336 heavy and light chains as well as the receptor DPP4 are shown in cartoon representation with the same color scheme as in Figures 1 and 2.

Supplementary Figure 3



Supplementary Figure 3. VDJ frequencies showing the productive VH rearrangements from different IGHV germline genes as quantified from the 454 sequencing analysis of IgM libraries derived from 69 healthy human subjects
The IGHV1-69 contributes significantly (12.7%) to the antibody repertoires, boxed in orange (out of the total of 74,393 VH sequences).

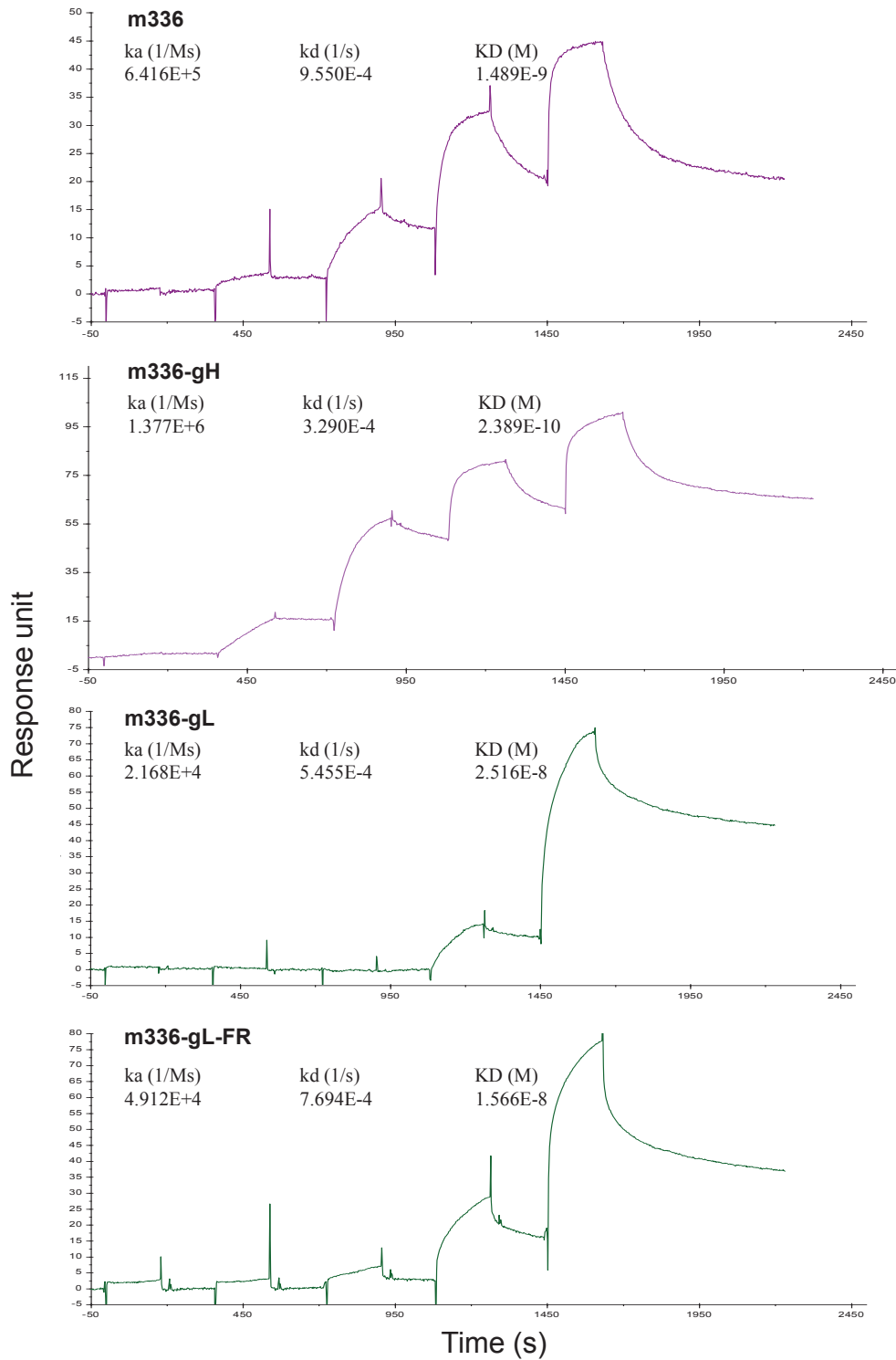
Supplementary Figure 4



Supplementary Figure 4. Multiple alignment of m336 V_L-like sequences from naïve IgM libraries derived from 69 healthy human subjects and 2 newborn babies and an anti-rabies virus V_L antibody sequence

Amino acid sequences of 40 V_L antibody domains (denoted by 5-letter codes) that were found similar to that of m336 from 454 sequencing analysis of IgM libraries derived 69 adults and 2 babies., and a VL antibody chain from anti-rabies virus antibody (SC4098) from the report by Kramer *et al* Eur. J. Immunol. 2005. Red boxes show the pre-existing mutations in the IgM naïve repertoire as identical to that found in m336 V_L suggesting a naturally germline-related m336 V_L.

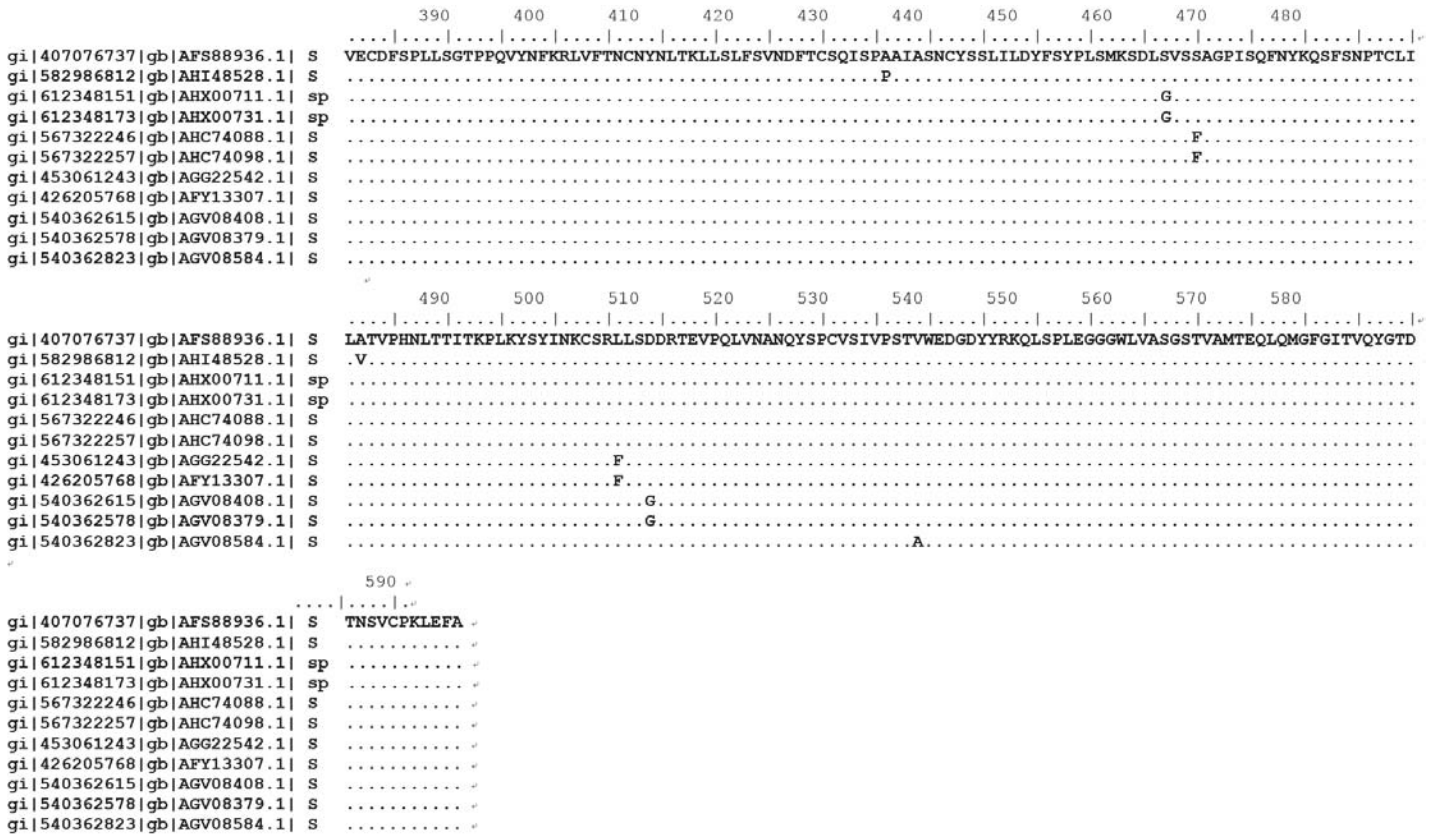
Supplementary Figure 5



Supplementary Figure 5. The binding kinetics of m336, m336-gH, m336-gL and m336-gL-FR to MERS-CoV S1

Single-cycle surface plasmon resonance analyses were carried out to assess binding of m336 variants to MERS-CoV S1. Antibody at five concentrations were injected incrementally in a single cycle onto a CM5 sensor chip immobilized with MERS-CoV S1 protein. The kinetic profiles are shown in each panel.

Supplementary Figure 6



Supplementary Figure 6. Multiple sequence alignment of known MERS-CoV RBD sequences with point mutations from clinical isolates was shown with the prototype EMC/2012 sequence (top)

Isolates harboring the identified A431P, S457G, S460F, A482V, L506F, D509G, and V534A substitution are shown with conserved residues marked as dots.

Supplementary Table 1. Contribution of different m336 regions to its MERS-CoV RBD binding interface

	Heavy chain (Å²)	Light chain (Å²)
Framework 1	0	0
CDR1*	203 (23.6%)	0
Framework 2	0	0
CDR2	280 (32.6%)	0
Framework 3	14 (1.7%)	0
CDR3	250 (29.1%)	111 (12.9%)
Total	747 (87.1)	111 (12.9%)

*: all complementarity determining regions (CDRs) were defined according to Kabat nomenclature.

Supplementary Table 2. Hydrogen bonds and salt bridges between m336 and MERS-CoV RBD

Hydrogen bonds				
	m336	Distance (Å)	MERS-CoV RBD	Conserved DPP4 interaction
1	H:SER30[OG]	3.08	A:ASP510[OD2]	Arg317
2	H:ASN100d[ND2]	3.43	A:GLY538[O]	Gln286
3	H:ARG100e[NH1]	2.75	A:ASP539[OD1]	Lys267
4	H:ARG100e[NH2]	2.98	A:ASP539[OD2]	
5	H:CYS100c[N]	2.70	A:TYR540[O]	
6	H:ASN100d[OD1]	2.96	A:TYR540[N]	
7	H:SER31[O]	2.64	A:TYR540[OH]	
8	H:CYS100c[SG]	3.66	A:ARG542[N]	
9	H:SER31[O]	3.52	A:ARG542[NE]	
10	H:VAL99[O]	3.25	A:ARG542[NH2]	
11	H:SER30[OG]	3.74	A:TRP553[NE1]	
12	L:TYR94[N]	3.14	A:GLU536[OE2]	
13	L:SER93[OG]	2.80	A:TRP535[NE1]	

Salt bridges				
	m336	Distance (Å)	MERS-CoV RBD	Conserved DPP4 interaction
1	H:ARG100e[NH1]	2.75	A:ASP539[OD1]	Lys267
2	H:ARG100e[NH2]	2.98	A:ASP539[OD2]	Lys267

Supplementary Table 3. Analysis of the junction showing the mapping of IGHD with a high identity with possible N1/N2 addition along with 3'V- region and 5'J-region.

Analysis of the JUNCTION

D-REGION is in reading frame 2.

Click on mutated (underlined) nucleotide to see the original one:

Input	V name	3'V-REGION	N1	D-REGION	N2	5'J-REGION	J name	D name	Vmut	Dmut	Jmut	Ngc
m336VH	Homsap IGHV1-69*06	tgtgcgagag.	t	tgga <u>tattgtagtagtaccagctgc</u>	aaccgag	...tgcttttgatatctgg	Homsap IGHJ3*02	Homsap IGHD2-2*03	0	0	0	5/9

Translation of the JUNCTION

Click on mutated (underlined) amino acid to see the original one:

	104	105	106	107	108	109	110	111	111.1	111.2	112.3	112.2	112.1	112	113	114	115	116	117	118	Frame	CDR3-IMGT length	Molecular mass	pI	PhysicoChemical Descriptor (by BRFAA)
	C	A	<u>R</u>	V	E	Y	C	S	S	T	S	C	<u>N</u>	<u>R</u>	G	A	F	D	I	W	+	18	2,196.48	7.87	CARVGYCSSTSCNRGAFDIW
m336VH	tgt	gcg	aga	ggt	gga	tat	tgt	agt	agt	acc	agc	tgc	aac	cga	ggt	gct	ttt	gat	atc	tgg	+	18	2,196.48	7.87	CARVGYCSSTSCNRGAFDIW

Be aware that some allele reference sequences may be incomplete or from cDNAs. In those cases, IMGT/JunctionAnalysis uses automatically the allele *01 for the analysis of the JUNCTION.

Closest D-REGIONS

	Score	Identity
M35648 Homsap IGHD2-2*03 F	118	89.66% (26/29 nt)
J00232 Homsap IGHD2-2*01 F	109	86.21% (25/29 nt)
X97051 Homsap IGHD2-2*02 F	109	86.21% (25/29 nt)

Alignment

m336VH	ttggatattgtagtagtaccagctgcaacc
M35648 Homsap IGHD2-2*03 F	.-----t-tgcc
J00232 Homsap IGHD2-2*01 F	.a-----t-tgcc
X97051 Homsap IGHD2-2*02 F	.a-----t-tacc
IGHD2-2*03	GYCSSTSC YA

Supplementary Table 4. Analysis of the nucleotide divergence of m336 heavy chain and light chain from its germline counterpart

Heavy chain:

```

<----- FR1 - IMGT -----
1           5           10           15
  Q   V   Q   L   V   Q   S   G   A           E   V   K   K   P
m336VH     cag gtg cag ctg gtg cag tct ggg gct ... gag gtg aag aag cct

L22583 Homsap IGHV1-69*06 F     --- --- --- --- --- --- --- --- --- --- --- --- --- ---

----->
           20           25           30
  G   S   S   V   K   V   S   C   K   A   S   G   G   T   F
m336VH     ggg tcc tcg gtg aag gtc tcc tgc aag gct tct gga ggc acc ttc

L22583 Homsap IGHV1-69*06 F     --- --- --- --- --- --- --- --- --- --- --- --- --- ---

___ CDR1 - IMGT _____ <-----
           35           40           45
           S   S   Y   A   I   S   W   V   R   Q   A
m336VH     ... .. agc agc tat gct atc agc tgg gtg cga cag gcc

L22583 Homsap IGHV1-69*06 F     ... .. --- --- --- --- --- --- --- --- --- ---

FR2 - IMGT -----> _____ CDR2
           50           55           60
  P   G   Q   G   L   E   W   M   G   G   I   I   P   I
m336VH     cct gga caa ggg ctt gag tgg atg gga ggg atc atc cct atc ...

L22583 Homsap IGHV1-69*06 F     --- --- --- --- --- --- --- --- --- --- ...

- IMGT _____ <-----
           65           70           75
           F   G   T   A   S   Y   A   Q   K   F   Q           G   R
m336VH     ... ttt ggt aca gca agc tac gca cag aag ttc cag ... ggc aga
           N
L22583 Homsap IGHV1-69*06 F     ... --- --- --- --- -a- --- --- --- --- --- ---

----- FR3 - IMGT -----
           80           85           90
  V   T   I   T   A   D   K   S   T   S   T   A   Y   M   E
m336VH     gtc acg att acc gcg gac aaa tcc acg agc aca gcc tac atg gag

L22583 Homsap IGHV1-69*06 F     --- --- --- --- --- --- --- --- --- --- --- ---

-----> _____
           95           100           104
  L   S   S   L   R   S   E   D   T   A   V   Y   Y   C   A
m336VH     ctg agc agc ctg aga tct gag gac acg gcc gtg tat tac tgt gcg

L22583 Homsap IGHV1-69*06 F     --- --- --- --- --- --- --- --- --- --- --- ---

_____ CDR3 - IMGT _____
  R   V   G   Y   C   S   S   T   S   C   N   R   G   A   F
m336VH     aga gtt gga tat tgt agt agt acc agc tgc aac cga ggt gct ttt

```

L22583 Homsap IGHV1-69*06 F

--- -a

m336VH

D I W G Q G T M V T V S S
 gat atc tgg ggc caa ggg aca atg gtc acc gtc tct tca

L22583 Homsap IGHV1-69*06 F

Nucleotide (nt) mutations

IMGT labels		V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT
Nb of positions including IMGT gaps (nt)		319 (320)	78	36	51	30	117	7 (8)
Nb of nucleotides		295 (296)	75	24	51	24	114	7 (8)
Nb of identical nucleotides		294	75	24	51	24	113	7
Nb of mutations		1 (2)	0	0	0	0	1	0 (1)
Mutations	Silent	0 (1)	0	0	0	0	0	0 (1)
	Nonsilent	1	0	0	0	0	1	0
Transitions	a>g	1	0	0	0	0	1	0
	g>a	0	0	0	0	0	0	0
	c>t	0	0	0	0	0	0	0
	t>c	0	0	0	0	0	0	0
Transversions	a>c	0	0	0	0	0	0	0
	c>a	0	0	0	0	0	0	0
	a>t	0 (1)	0	0	0	0	0	0 (1)
	t>a	0	0	0	0	0	0	0
	g>c	0	0	0	0	0	0	0
	c>g	0	0	0	0	0	0	0
	g>t	0	0	0	0	0	0	0
t>g	0	0	0	0	0	0	0	

Amino acid (AA) changes

IMGT labels		V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT
Nb of positions including IMGT gaps (AA)		106	26	12	17	10	39	2
Nb of AA		98	25	8	17	8	38	2
Nb of identical AA		97	25	8	17	8	37	2
Nb of AA changes		1	0	0	0	0	1	0
AA changes	Very similar	(+++)	0	0	0	0	0	0
	Similar	(++-)	0	0	0	0	0	0
		(+-+)	0	0	0	0	0	0
	Dissimilar	(+--)	0	0	0	0	0	0
		(-+-)	0	0	0	0	0	0
		(--+)	0	0	0	0	0	0
Very dissimilar	(---)	1	0	0	0	0	1	

Light chain:

```

<----- FR1 - IMGT -----
1             5             10             15
m336VL       gac atc cag ttg acc cag tct cca tcc tcc ctg tct gca tct gta
X72808 Homsap IGKV1-17*01 F   --- --- --- a-- --- --- --- --- --- --- --- ---
D88255 Homsap IGKV1-17*02 F   --- --- --- a-- --- --- --- --- --- --- --- ---
M64858 Homsap IGKV1-6*01 F   -c- --- --- a-- --- --- --- --- --- --- --- ---
KM455558 Homsap IGKV1-6*02 F  -c- --- --- a-- --- --- --- --- --- --- --- -t
Z00006 Homsap IGKV1-13*02 F  -c- --- --- --- --- --- --- --- --- --- ---

```

```

----->
                20             25             30
m336VL       gga gac aga gtc acc atc act tgc cgg gca agt cag ggc att ...
X72808 Homsap IGKV1-17*01 F   --- --- --- --- --- --- --- --- --- ---
D88255 Homsap IGKV1-17*02 F   --- --- --- --- --- --- --- --- --- ---
M64858 Homsap IGKV1-6*01 F   --- --- --- --- --- --- --- --- --- ---
KM455558 Homsap IGKV1-6*02 F  --- --- --- --- --- --- --- --- --- ---
Z00006 Homsap IGKV1-13*02 F  --- --- --- --- --- --- --- --- --- ---

```

```

___ CDR1 - IMGT _____ <-----
                35             40             45
m336VL       ... .. . . . . . . . . . . . . . . . . . . . . . . . .
X72808 Homsap IGKV1-17*01 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
D88255 Homsap IGKV1-17*02 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
M64858 Homsap IGKV1-6*01 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
KM455558 Homsap IGKV1-6*02 F  ... .. . . . . . . . . . . . . . . . . . . . . . . . .
Z00006 Homsap IGKV1-13*02 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .

```

```

FR2 - IMGT -----> _____ CDR2
                50             55             60
m336VL       cca ggg aaa gcc cct aag ctc ctg atc tat gct gca ... .. .
X72808 Homsap IGKV1-17*01 F   --- --- --- --- -g- --- --- --- --- --- ... .. .
D88255 Homsap IGKV1-17*02 F   --- --- --- --- -g- --- --- --- --- --- ... .. .
M64858 Homsap IGKV1-6*01 F   --- --- --- --- --- --- --- --- --- --- --- ... .. .
KM455558 Homsap IGKV1-6*02 F  --- --- --- --- --- --- --- --- --- --- --- ... .. .
Z00006 Homsap IGKV1-13*02 F   --- --- --- -t --- --- --- --- --- -a- -c ... .. .

```

```

- IMGT _____ <-----
                65             70             75
m336VL       ... .. . . . . . . . . . . . . . . . . . . . . . . . .
X72808 Homsap IGKV1-17*01 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
D88255 Homsap IGKV1-17*02 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
M64858 Homsap IGKV1-6*01 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .
KM455558 Homsap IGKV1-6*02 F  ... .. . . . . . . . . . . . . . . . . . . . . . . . .
Z00006 Homsap IGKV1-13*02 F   ... .. . . . . . . . . . . . . . . . . . . . . . . . .

```

```

----- FR3 - IMGT -----
                80             85             90
m336VL       ttc agc ggc agt gga ... .. . . . . . . . . . . . . . . . . .
X72808 Homsap IGKV1-17*01 F   --- --- --- --- --- --- --- -g- --- -a- --- --- --- -a
D88255 Homsap IGKV1-17*02 F   --- --- --- --- --- --- --- -g- --- -a- --- --- --- -a
M64858 Homsap IGKV1-6*01 F   --- --- --- --- --- --- --- --- --- --- --- --- --- ---
KM455558 Homsap IGKV1-6*02 F  --- --- --- --- --- --- --- --- --- --- --- --- --- ---
Z00006 Homsap IGKV1-13*02 F   --- --- --- --- --- --- --- -g- --- --- --- --- --- ---

```

```

-----> _____
                95             100             104
m336VL       atc agc agc ctg cag cct gaa gat ttt gca act tat tac tgt caa
X72808 Homsap IGKV1-17*01 F   --- --- --- --- --- --- --- --- --- --- --- --- --- -t-

```

D88255 Homsap IGKV1-17*02 F --- -a- --- --- --- --- --- --- --- -t-
M64858 Homsap IGKV1-6*01 F --- --- --- --- --- --- --- --- --- -t-
KM455558 Homsap IGKV1-6*02 F --- --- --- --- --- --- --- --- --- -t-
Z00006 Homsap IGKV1-13*02 F --- --- --- --- --- --- --- --- ---

_____ CDR3 - IMGT _____

m336VL cag ctt aat agt tac ccg ctc act ttc ggc gga ggg acc aaa gtg
X72808 Homsap IGKV1-17*01 F --- -a- --- --- --- -t -c
D88255 Homsap IGKV1-17*02 F --- -a- --- --- --- -t -c
M64858 Homsap IGKV1-6*01 F --a ga- t-c -a- --- -t -c
KM455558 Homsap IGKV1-6*02 F --a ga- t-c -a- --- -t -c
Z00006 Homsap IGKV1-13*02 F --- t-- --- --- --- -t -a

Nucleotide (nt) mutations

IMGT labels		V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT
Nb of positions including IMGT gaps (nt)		332 (335)	78	36	51	30	117	20 (23)
Nb of nucleotides		284 (287)	78	18	51	9	108	20 (23)
Nb of identical nucleotides		276 (277)	77	18	50	9	104	18 (19)
Nb of mutations		8 (10)	1	0	1	0	4	2 (4)
Mutations	Silent	3 (5)	0	0	0	0	3	0 (2)
	Nonsilent	5	1	0	1	0	1	2
Transitions	a>g	0	0	0	0	0	0	0
	g>a	1	0	0	0	0	1	0
	c>t	0 (1)	0	0	0	0	0	0 (1)
	t>c	0	0	0	0	0	0	0
Transversions	a>c	1	0	0	0	0	1	0
	c>a	0	0	0	0	0	0	0
	a>t	3	1	0	0	0	1	1
	t>a	1	0	0	0	0	0	1
	g>c	1	0	0	0	0	1	0
	c>g	0	0	0	0	0	0	0
	g>t	1	0	0	1	0	0	0
	t>g	0 (1)	0	0	0	0	0	0 (1)

Amino acid (AA) changes

IMGT labels		V-REGION	FR1-IMGT	CDR1-IMGT	FR2-IMGT	CDR2-IMGT	FR3-IMGT	CDR3-IMGT
Nb of positions including IMGT gaps (AA)		110 (111)	26	12	17	10	39	6 (7)
Nb of AA		94 (95)	26	6	17	3	36	6 (7)
Nb of identical AA		89 (90)	25	6	16	3	35	4 (5)
Nb of AA changes		5	1	0	1	0	1	2
AA changes	Very similar	(+++)	0	0	0	0	0	0
	Similar	(++-)	1	1	0	0	0	0
		(+-+)	1	0	0	0	0	1
	Dissimilar	(+--)	0	0	0	0	0	0
		(-+-)	1	0	0	1	0	0
		(--+)	0	0	0	0	0	0
	Very dissimilar	(---)	2	0	0	0	0	2