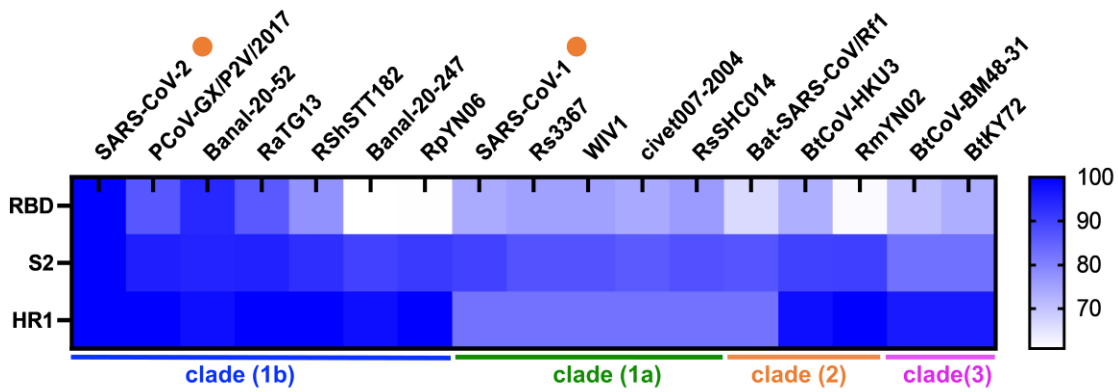
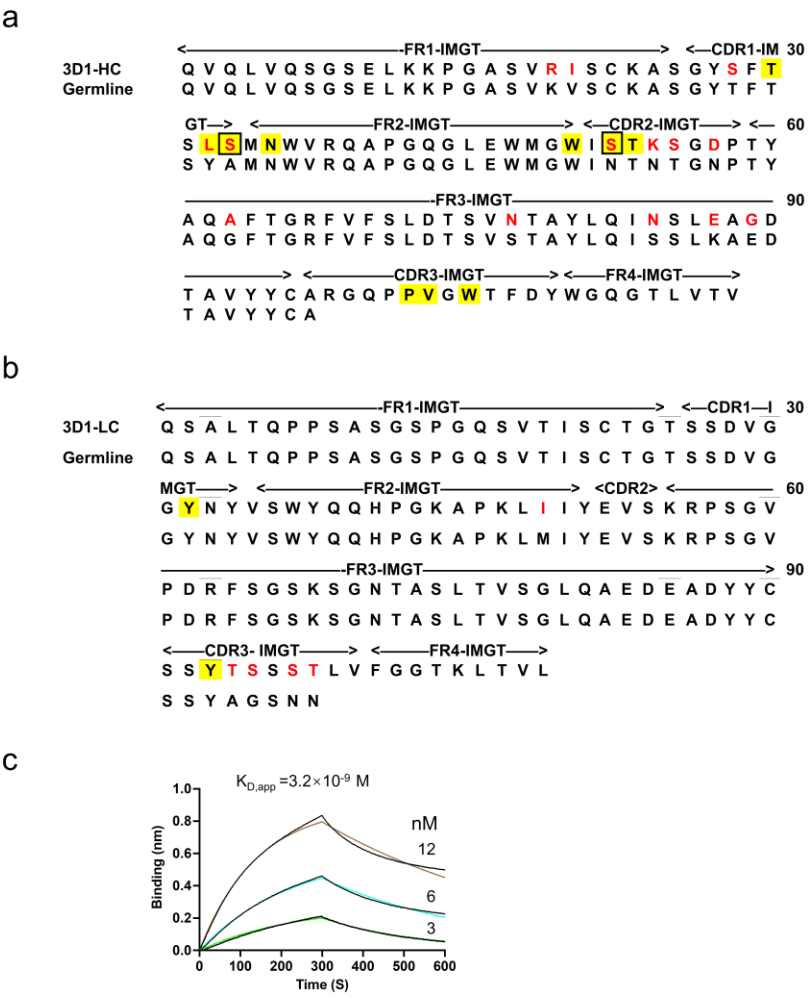
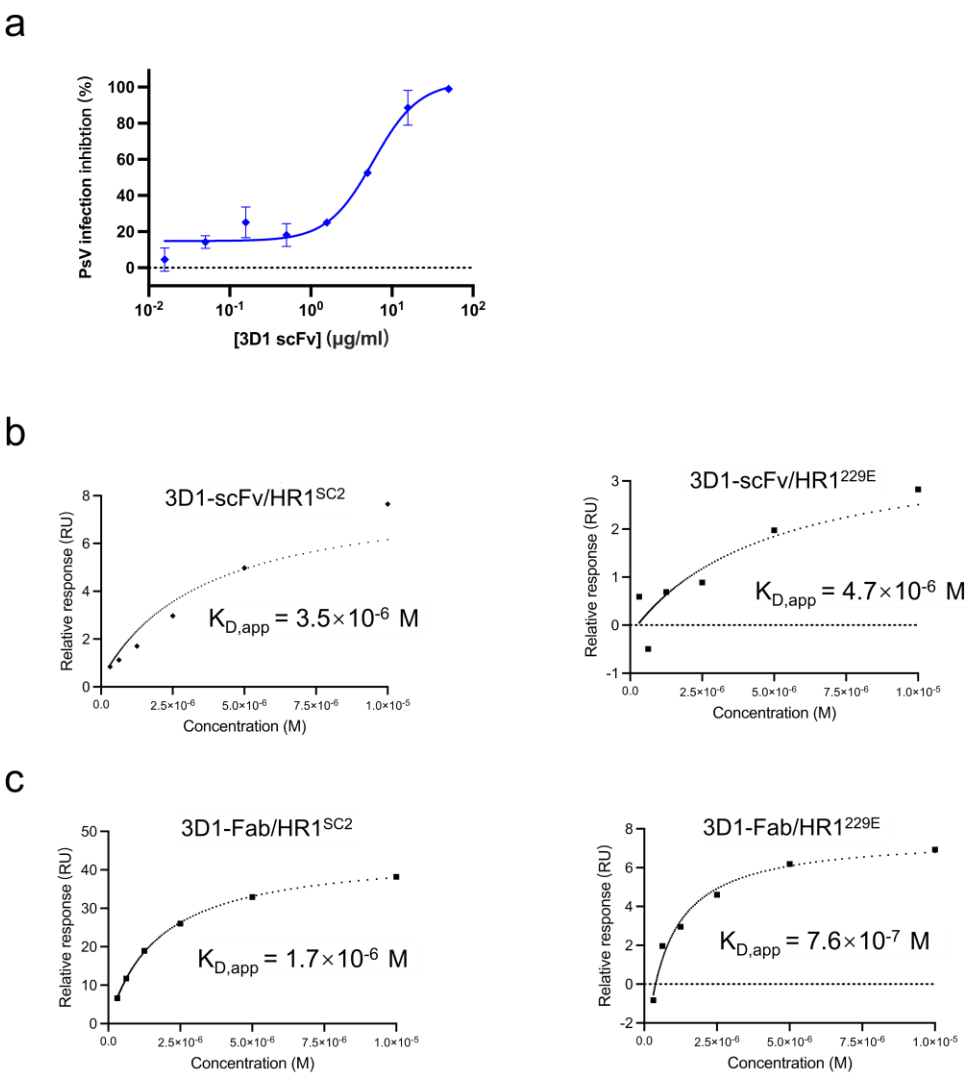
Extended Figures and Legends



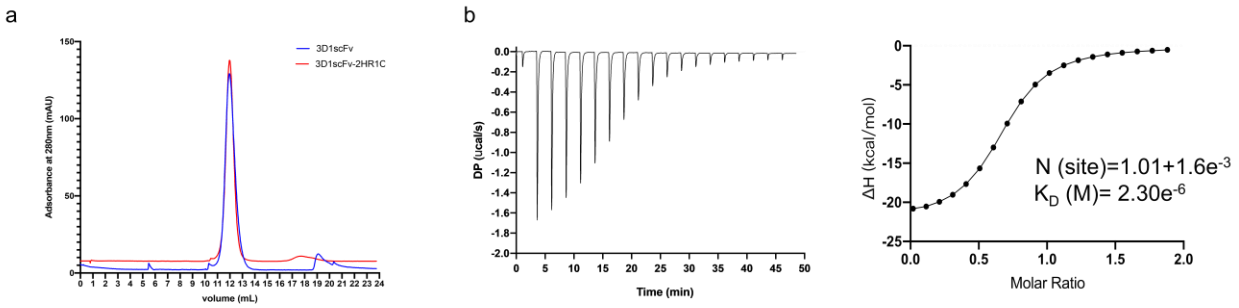
Extended Fig. 1 Heat map depicting sequence homology and identity of the RBD domains, S2 subunits, and HR1 domains between SARS-CoV-2 and related sarbecoviruses from clades (1a), (1b), (2), and (3).



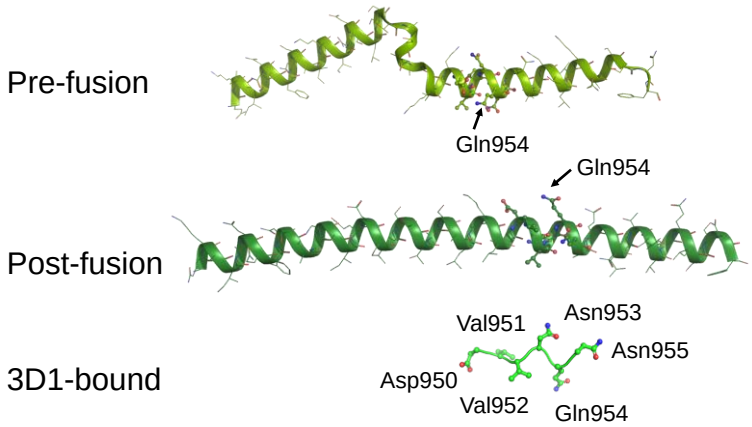
Extended Fig. 2 Germline analysis of 3D1. The putative germline sequence and SHM germline sequences are aligned to the heavy (3D1-HC) (a) and light 3D1-LC (b) chain sequences. Residues from SHM are colored in red, and paratopes are highlighted with a yellow background. Residues in SHMs that are involved in interactions between side chains and their epitope are boxed. c, BLI results of 3D1-Germline against SARS-CoV-2 HR1C.



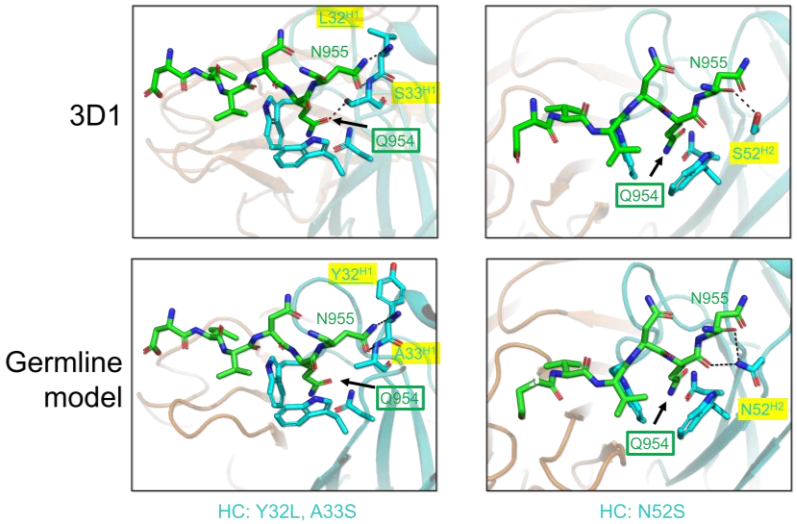
Extended Fig. 3 a, Dose-dependent inhibition of PsV of SARS-CoV-2 Dleta VOC by 3D1-scFv. **b-c,** SPR-based affinity measurement of 3D1-scFv (**b**) or 3D1-Fab (**c**) to $HR1^{SC2}$ (left panel) and $HR1^{229E}$ (right panel).



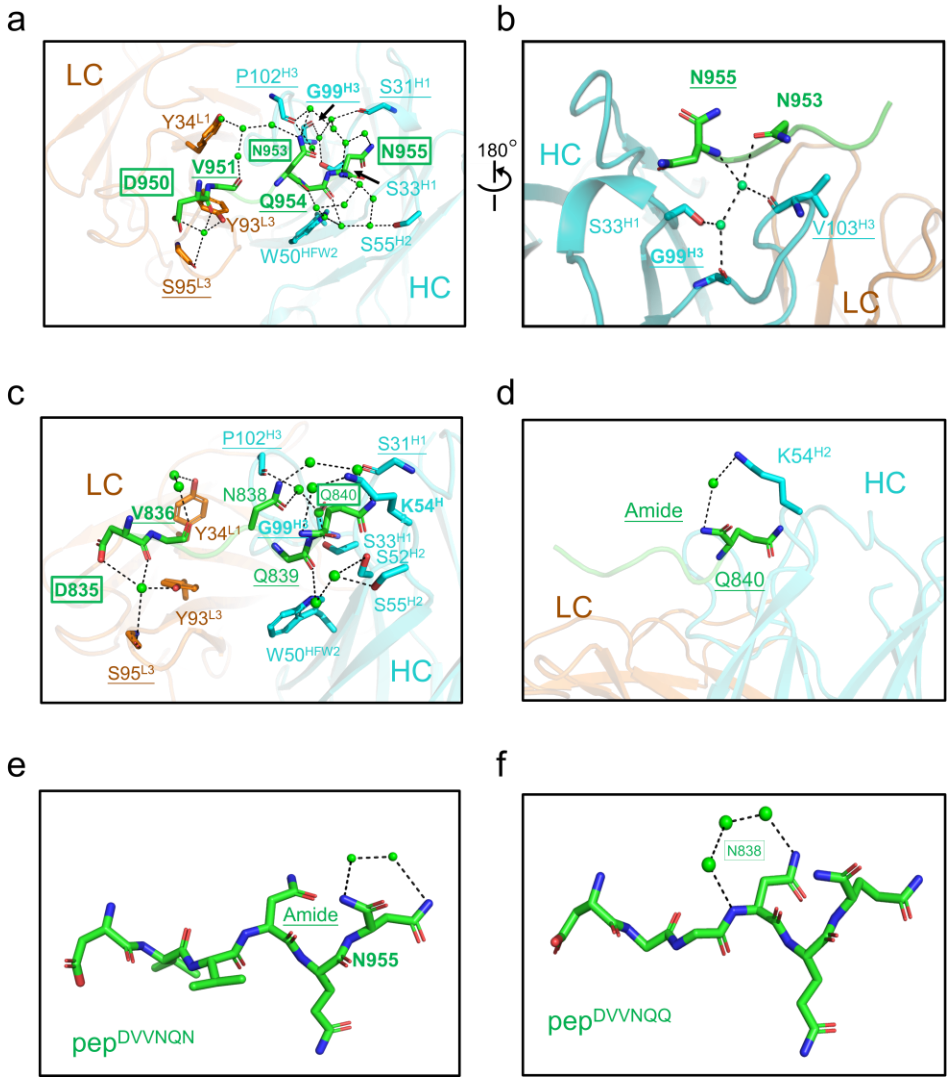
Extended Fig. 4 Biophysical and stoichiometric analyses of 3D1 binding to HR1. **a,** SEC profile of 3D1-scFv incubated with $HR1^{SC2}$ on a Superdex^{TM} 75pg column. **b,** ITC results of the titration of $HR1^{SC2}$ into 3D1-scFv.



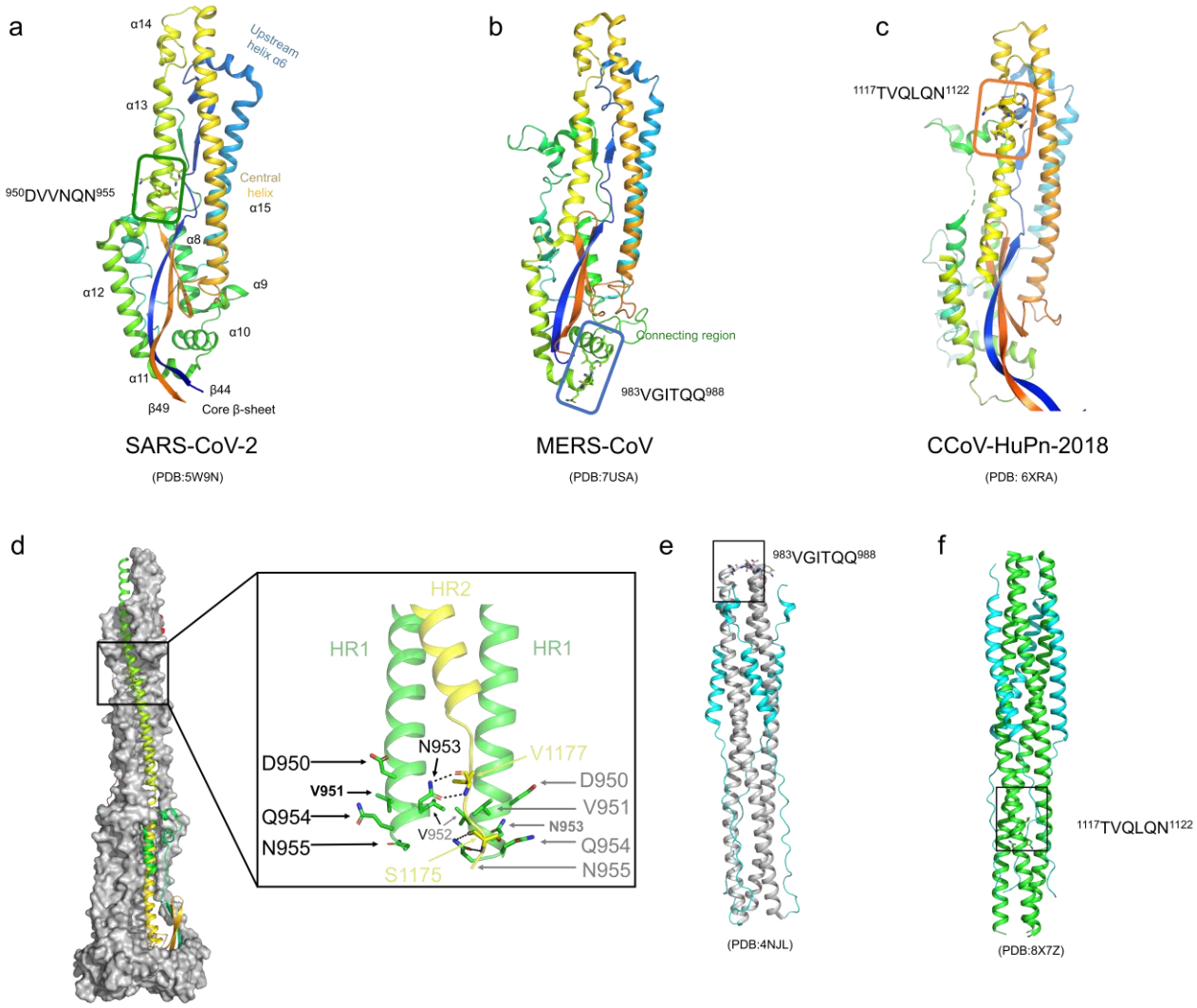
Extended Fig. 5 Comparison of the HR1 conformation of 3D1-bound with those of HR1 in different fusion states. The signature-fold of ^{950}DVVNQN^{955} is displayed as sticks, while other residues in the helical structures of HR1 in the prefusion and post-fusion states are shown as lines.



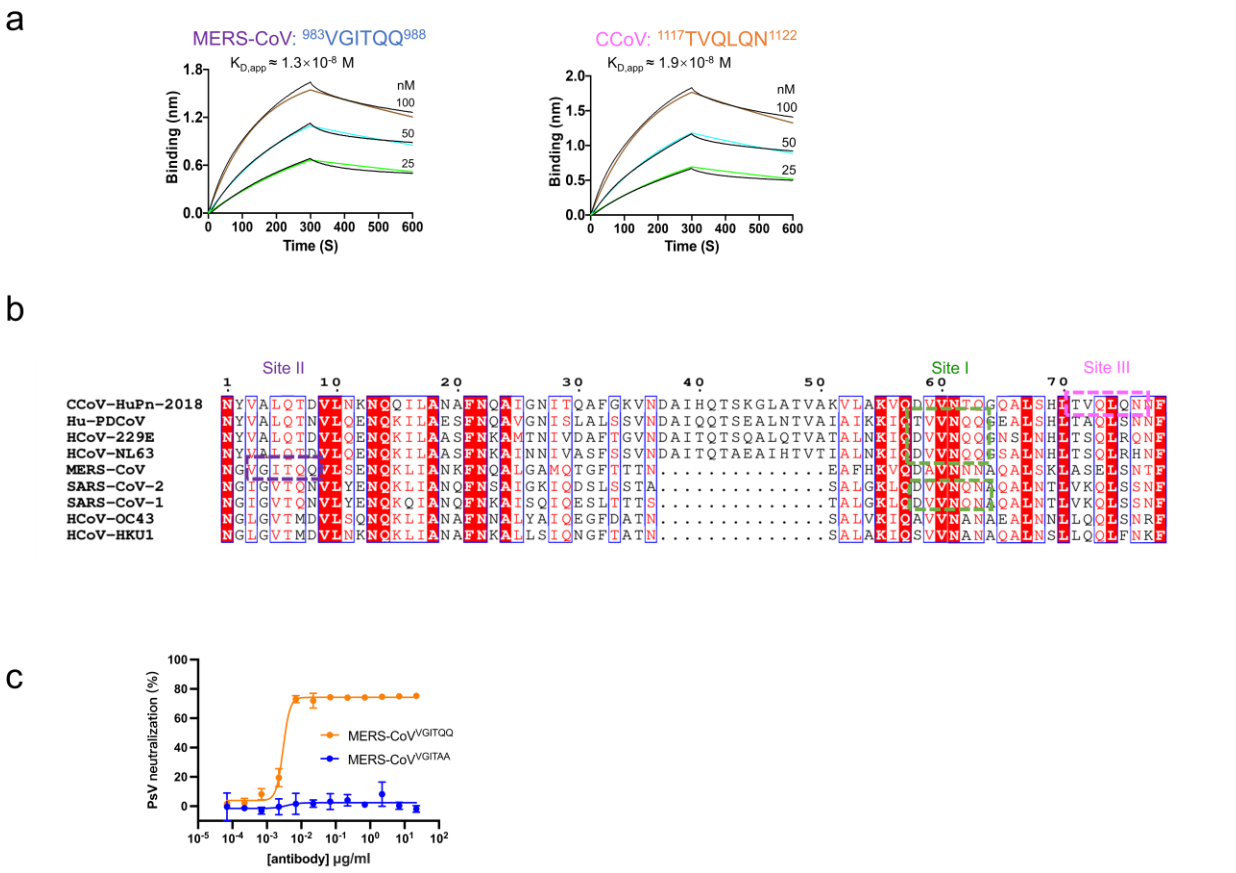
Extended Fig. 6 Back-to-back comparison between Germline-HR1C^{SC2} (model) and 3D1-HR1C^{SC2}. SHM residues are shaded in yellow, and residues that participate in main-chain-to-side-chain interactions are underlined.



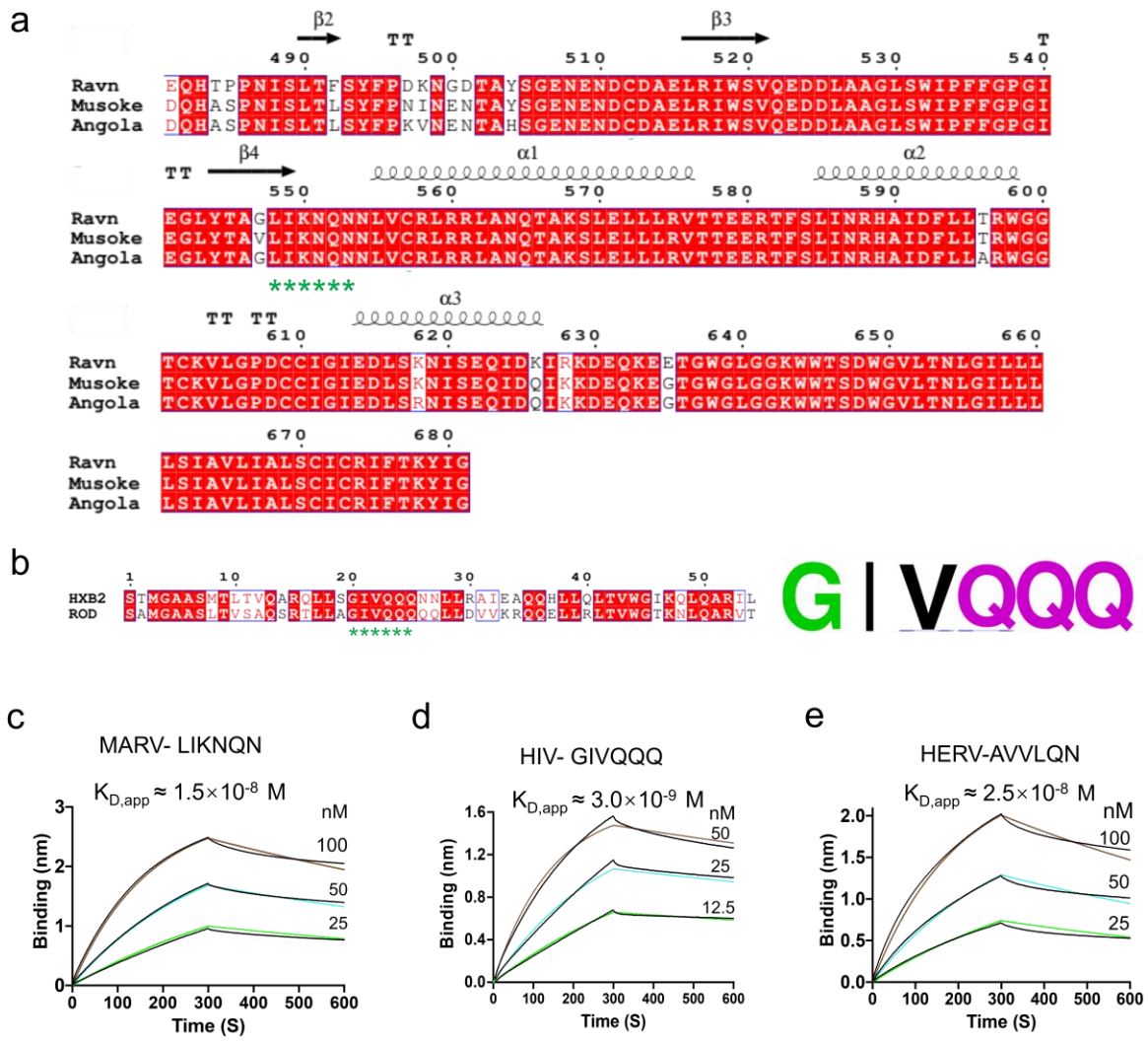
Extended Fig. 7 Extensive hydrogen networks mediated by water molecules between 3D1 and HR1C^{SC2} (**a-d**) and intrapeptide hydrogen bonds mediated by water (**e-f**), respectively. Water molecules are displayed as green spheres.



Extended Fig. 8 Ribbon diagrams showing the structure of monomeric S2 of SARS-CoV-2 (starting at residue 755, PDB: 6VXX) (**a**), MERS-CoV (PDB: 5W9N) (**b**), and CCoV-HuPn-2018 (PDB: 7USA) (**c**) in the prefusion state. The epitopes of 3D1 on each S2 protomer are boxed. **d**, Trimeric S2 in the post-fusion state, along with a close-up view of the residues of the 'DVVNQN' motif, which is critical for the registration of HR2 into the groove formed by two neighboring HR1. (**e-f**) The post-fusion states of the spikes of MERS-CoV (**e**) and CCoV-HuPn-2018 (**f**), with their epitopes also indicated.



Extended Fig. 9 Discovery and validation of alternative epitopes of 3D1**. a,** BLI results of 3D1 against peptides from MERS-CoV ^{VGITQQ} (left panel) and CCoV-HuPn-2018^{TVQLQN} (right panel). **b**, Sequence alignments of extended HR1 domains from HCoVs. Epitopes of 3D1 at different sites are indicated. **c**, Mutations occurring in Site II of MERS-CoV spike that escape neutralization of 3D1.



Extended Fig. 10 **a,** Sequence alignment of GP2 from Marburgvirus RAVV (Ravn virus) and MARV (Musoke and Angola strains). The "LIKNQN" motif is indicated with green asterisks. **b,** Sequence alignment of NHR domains from HIV-1 (HXB2 strain) and HIV-2 (ROD strain). A WebLogo plot displaying NHR sequences of HIV-1 spanning the "GIVQQQ" region shared by 7,936 out of 8,070 strains deposited in the HIV sequence database up to 2019 is shown alongside (https://www.hiv.lanl.gov/content/sequence/NEWALIGN/align.html). BLI binding profiles of 3D1 towards peptides from MARV (**c**), HIV (**d**), and HERV (**e**).

Supplementary Tables

Table S1. Hydrogen bonds identified at the antibody-peptide interface calculated by the PISA program (*1*).

Chain	Residue	Ato	Distance (Å)	Chain	Residue	Atom
Peptide				3D1		
A	Asp 950	OD2	2.70	L	Tyr 32	OH
A	Asp 950	O	3.75	L	Tyr 93	OH
A	Val 952	N	3.02	L	Tyr 93	OH
A	Val 952	O	2.83	H	Trp 105	NE1
A	Asn 953	ND2	3.08	H	Pro 102	O
A	Gln 954	OE1	2.64	H	Ser 33	OG
A	Gln 954	OE1	2.93*	H	Asn 35	ND2
A	Gln 954	NE2	3.00*	H	Asn 35	OD1
A	Gln 954	O	2.88*	H	Trp 50	NE1
A	Gln 954	N	2.93*	H	Val 103	O
A	Asn 955	ND2	3.03	H	Thr 30	O
A	Asn 955	OD1	3.52*	H	Ser 52	OG
A	Asn 955	O	2.73	H	Ser 52	OG
A	Asn 955	OD1	2.84	H	Thr 53	N
A	Asn 955	OD1	3.27*	H	Thr 53	OG1
A	Asn 955	ND2	3.16 *	H	Thr 53	OG1

Note: Hydrogen bonds are defined as interactions exhibiting the necessary geometry with contact distances of 3.8 Å or less.

Table S2. Hydrogen bonds identified at antibody-peptide interface calculated by the PISA program (*1*).

Chain	Residue	Ato	Distance (Å)	Chain	Residue	Atom
Peptide				3D1		
A	Asp 835	O	3.69	L	Tyr 93	OH
A	Val 837	N	3.11	L	Tyr 93	OH
A	Val 837	O	2.92	H	Trp 105	NE1
A	Gln 839	OE1	2.81	H	Ser 33	OG
A	Gln 839	NE2	2.90*	H	Asn 35	OD1
A	Gln 839	OE1	2.75*	H	Asn 35	ND2
A	Gln 839	O	2.80*	H	Trp 50	NE1
A	Gln 839	N	2.87*	H	Val 103	O
A	Gln 840	NE2	3.07	H	Thr 30	O
A	Gln 840	O	2.87*	H	Ser 52	OG
A	Gln 840	OE1	3.60	H	Ser 52	OG
A	Gln 840	OE1	2.96	H	Thr 53	N
A	Gln 840	OE1	3.25*	H	Thr 53	OG1
A	Gln 840	NE2	3.14*	H	Thr 53	OG1

Note: Hydrogen bonds are defined as interactions exhibiting the necessary geometry with contact distances of 3.8 Å or less.