

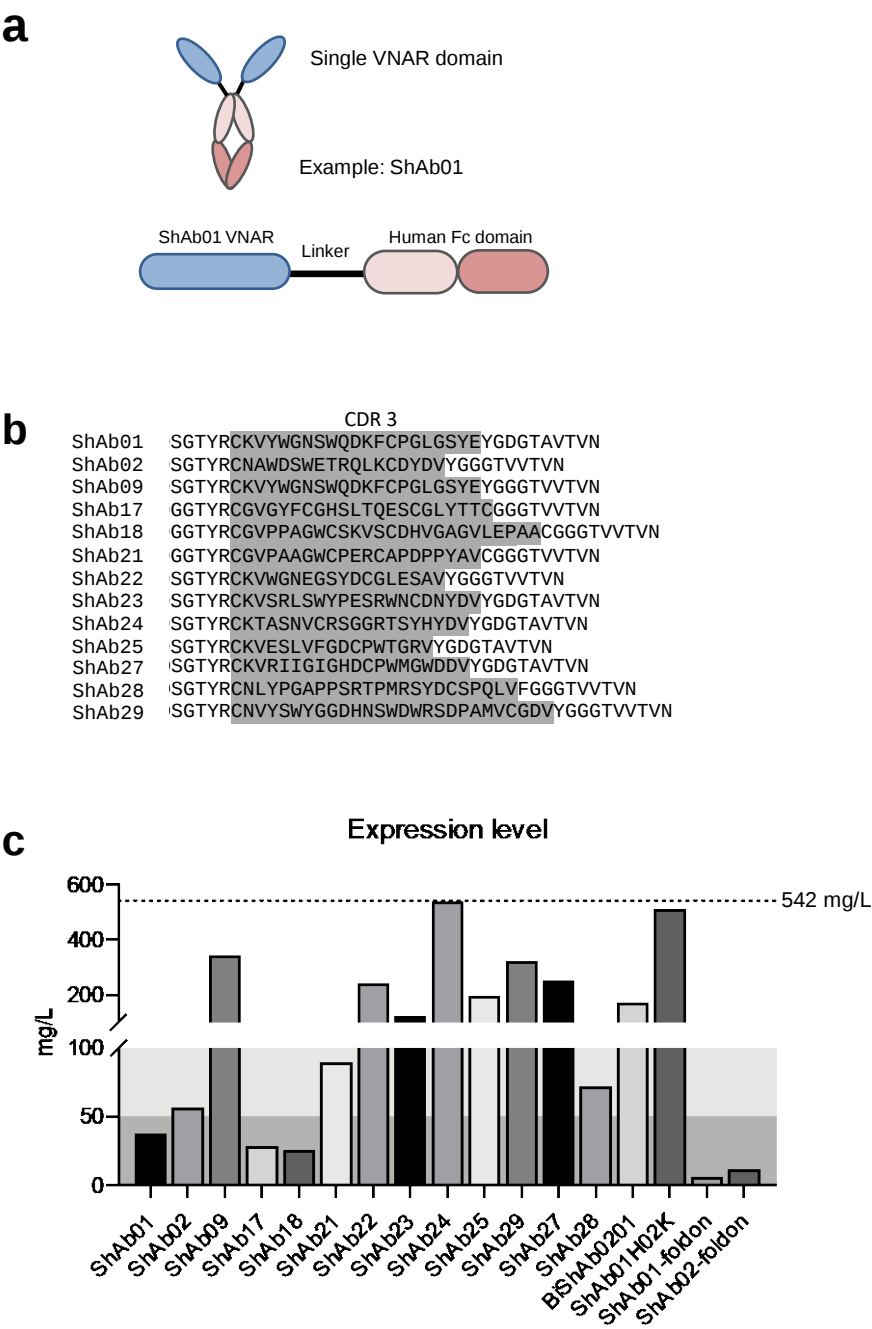
Supplementary Information

Shark nanobodies with potent SARS-CoV-2 neutralizing activity and broad sarbecovirus reactivity

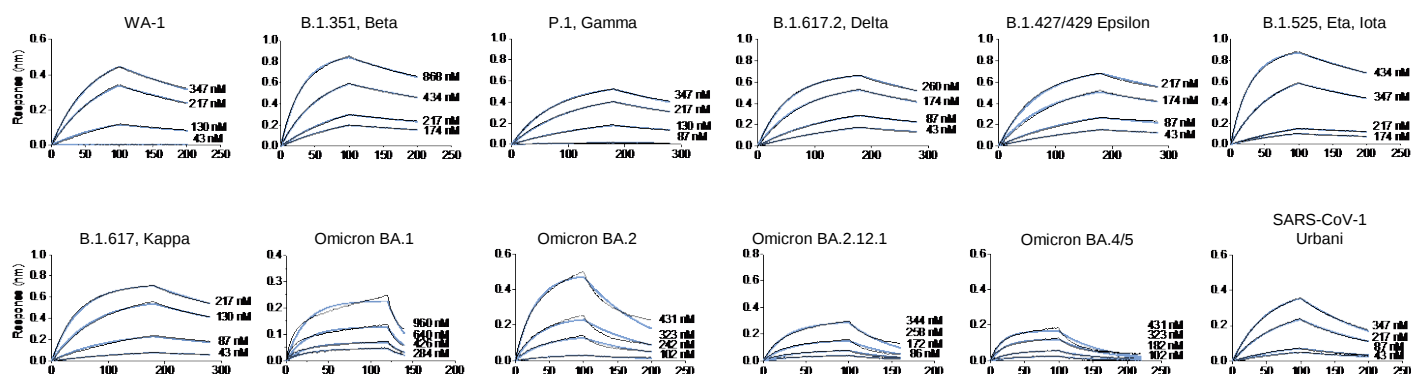
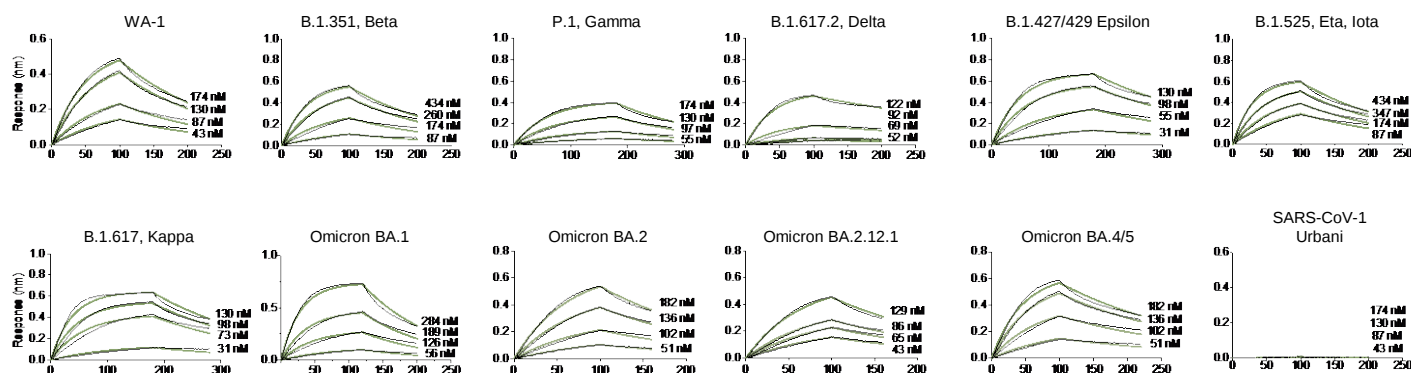
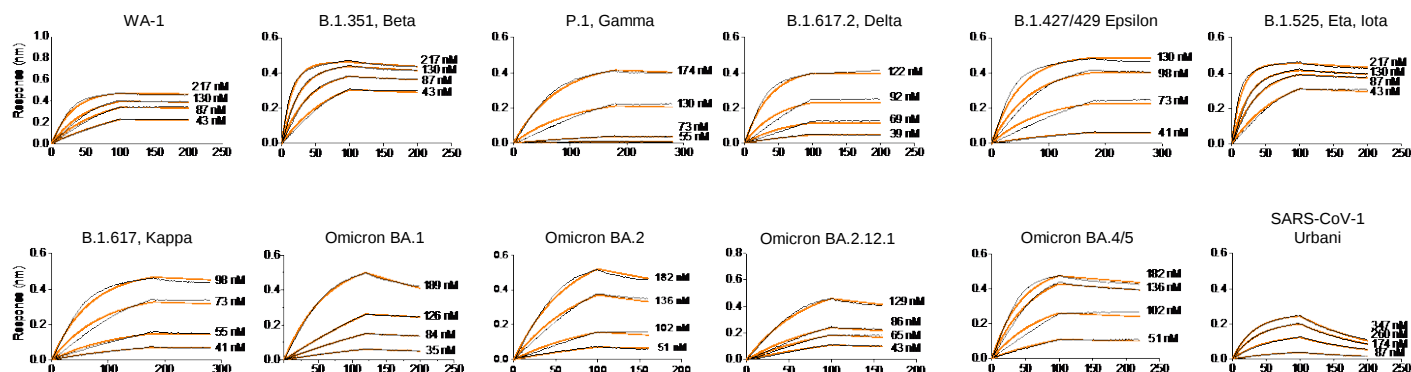
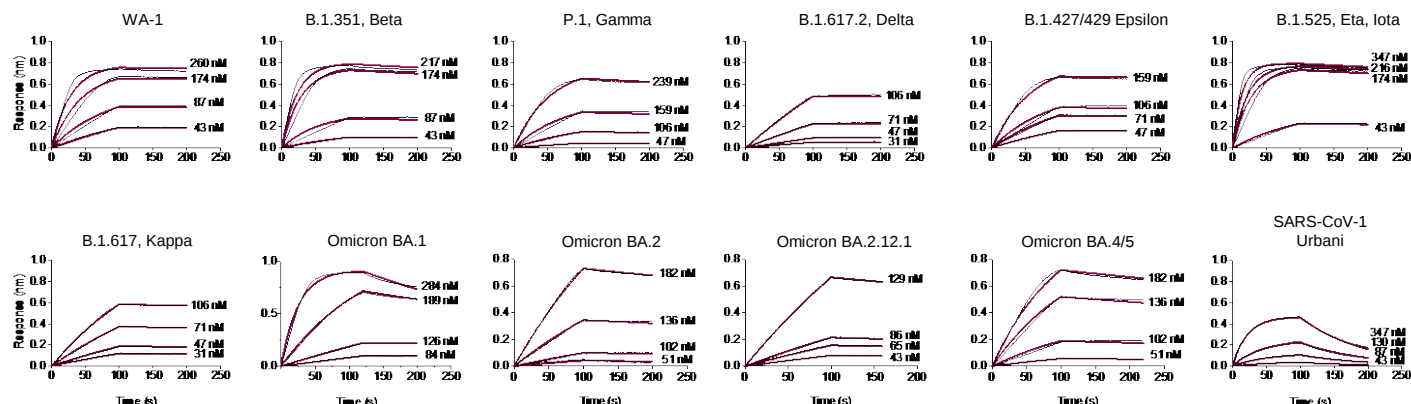
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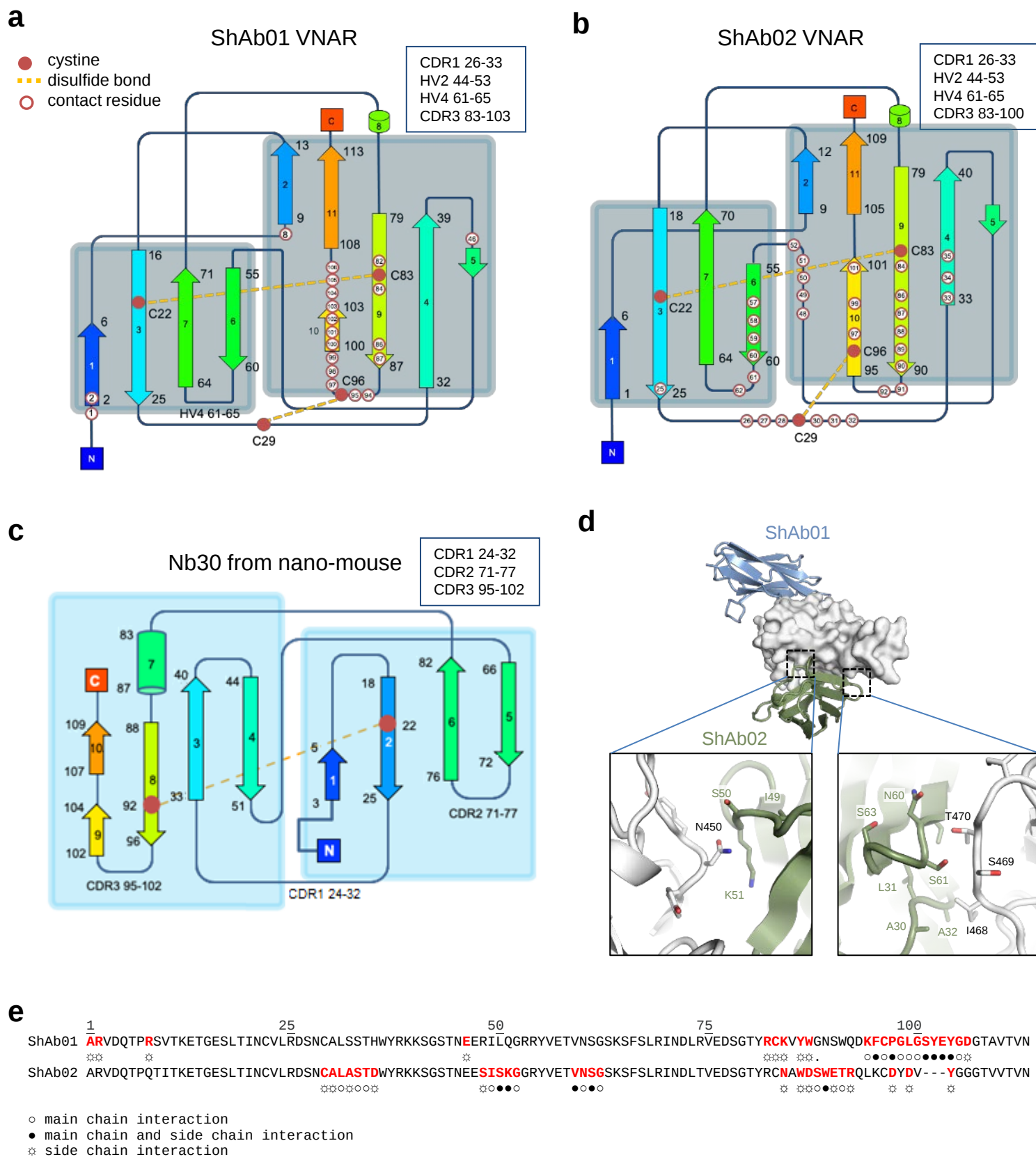
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Supplementary Fig. 1. Fc chimera schematic, VNAR ShAb CDR3 sequences and expression level of ShAb molecules.
a, Schematic of the VNAR-Fc nanobody design.
b, Sequence alignment of the CDR3 regions of the ShAb VNARs.
c, ShAb protein expression levels in mammalian Expi293F cells by transient transfection.
Source data are provided as a Source Data file.

a ShAb01**b** ShAb02**c** ShAb01H02K**d** BiShAb0201

Supplementary Fig. 2. ShAb affinity to SARS-CoV-2 VoC and SARS-CoV-1 RBDs. BLI binding kinetic measurements were carried out using immobilized ShAb molecules, and the RBD molecules in solution. Representative binding curves (black lines) are fitted to a 1:1 binding model (colored lines). Source data are provided as a Source Data file.

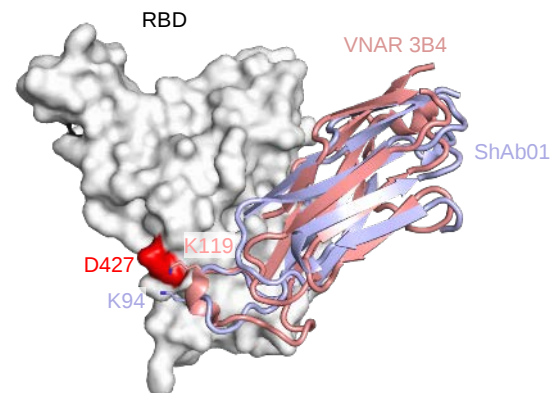


Supplementary Fig. 3. Structural analysis of ShAb01 and ShAb02 VNARs.

a, b, c, Topology diagram of ShAb01, ShAb02, and Nb30 with β -strands (arrows) and α -helices (tube) drawn and labeled. Cysteines forming disulfide bonds are shown as solid red circles, disulfide bonds are shown as yellow dashed lines. SARS-CoV-2 RBD contacting residues are shown as open circles with numbers.

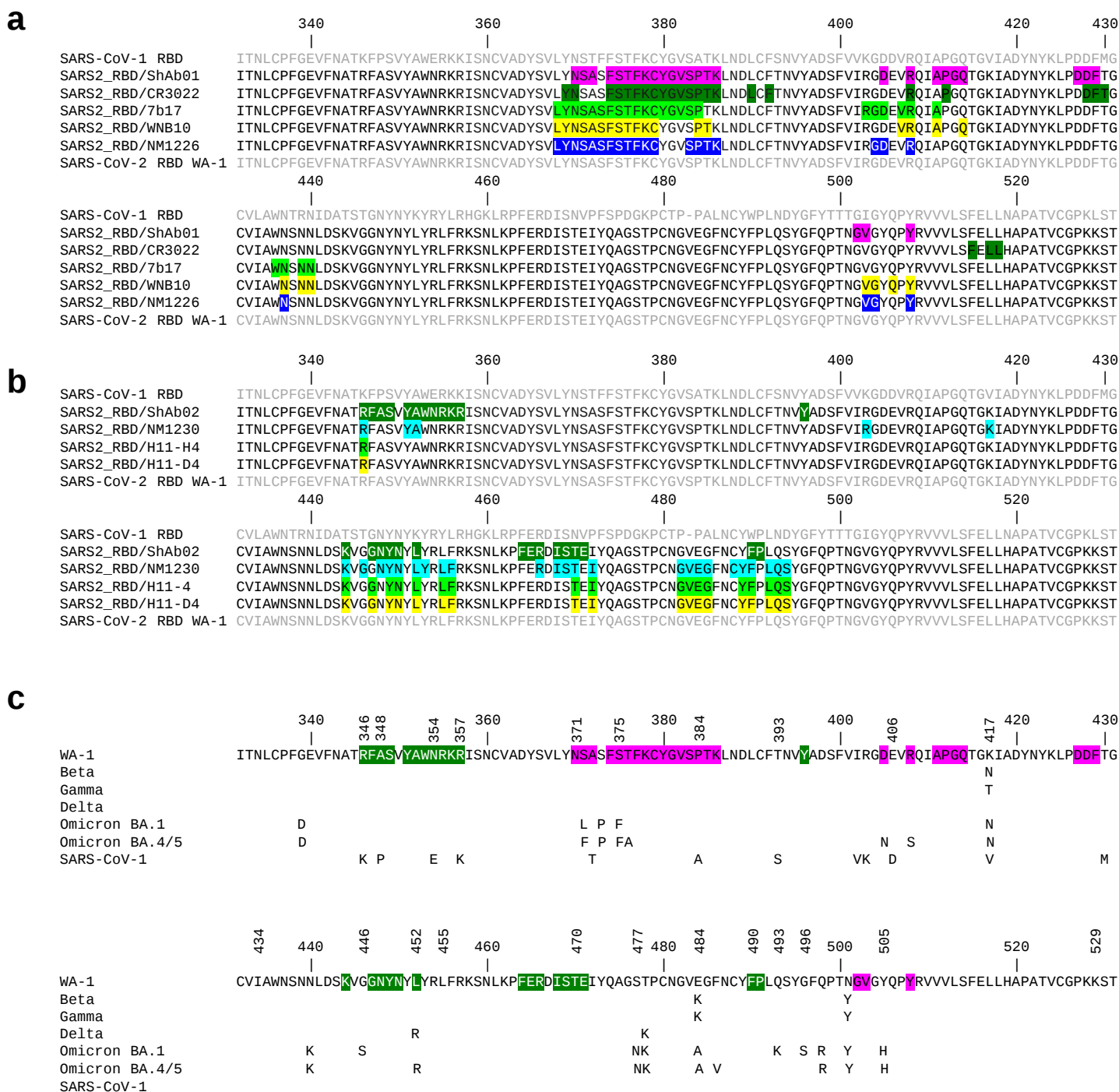
d, Contact residues of ShAb02 in complex with SARS-CoV-2 RBD.

e, ShAb01, and ShAb02 VNAR sequence with paratope contact residues indicated (open sphere: main chain-only contact; closed sphere: main- and side-chain contacts; sun sphere: side-chain-only contacts).



e

e, Sequence alignment of VNAR 3B4 and ShAb01 VNAR domain sequences.

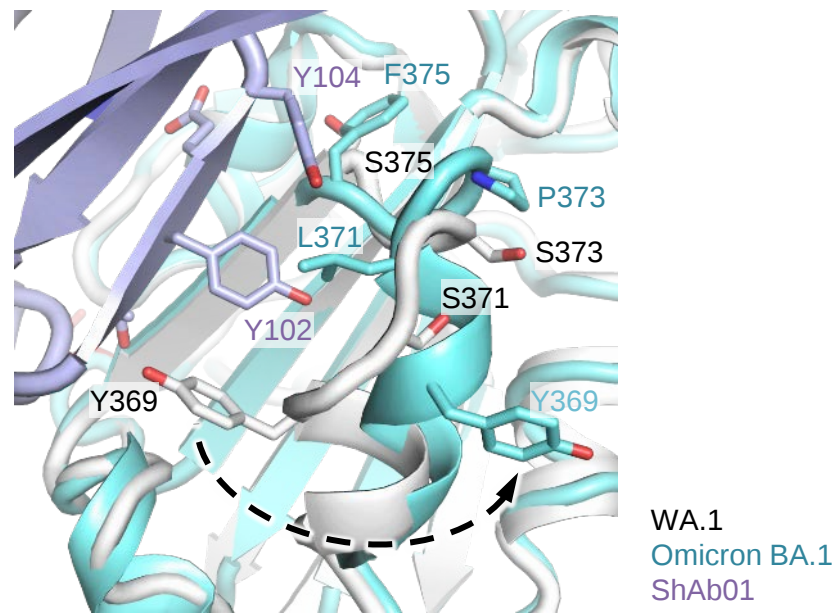


Supplementary Fig. 5. Sequence alignment of RBD antibody and nanobody epitopes.

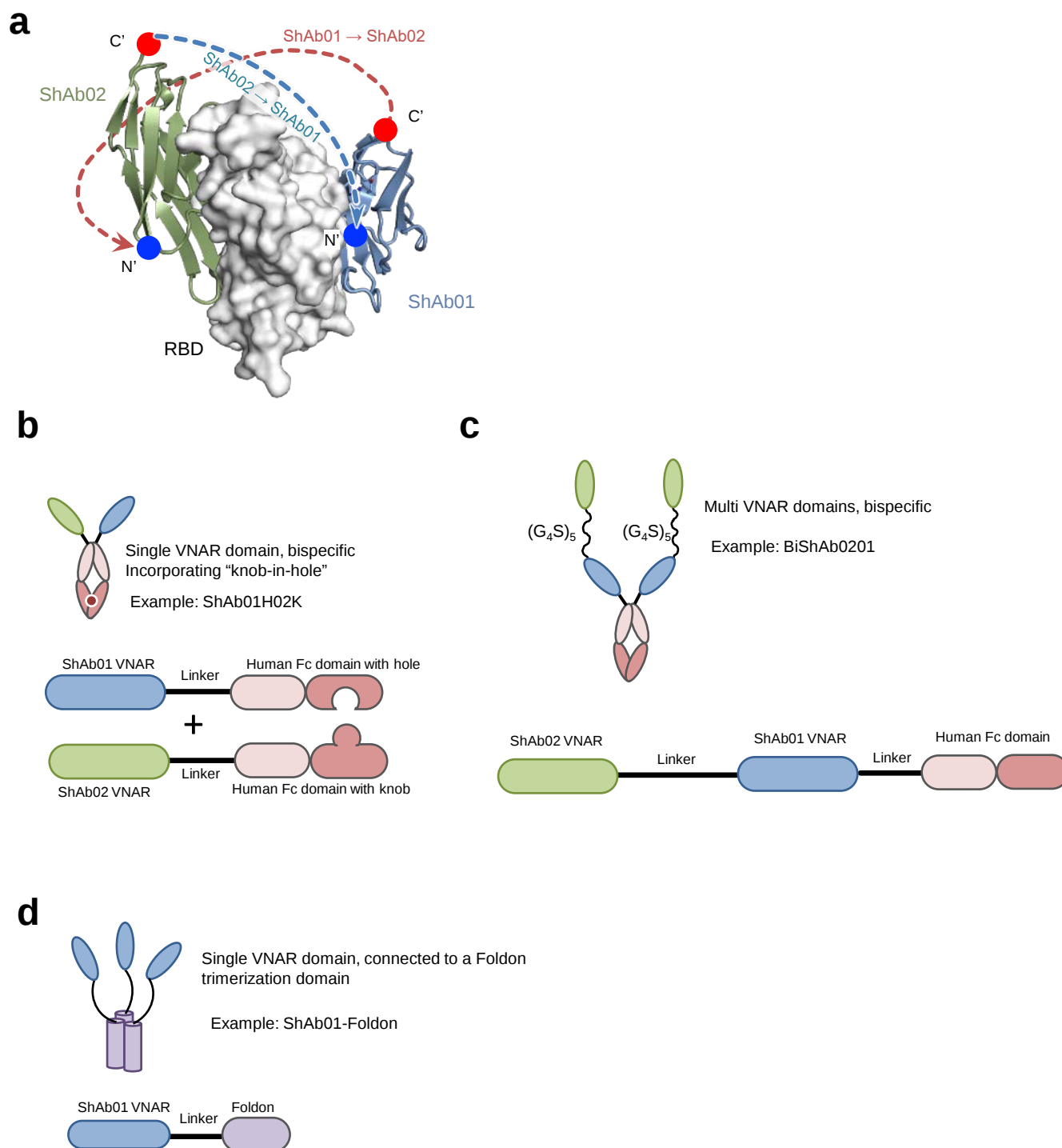
a, Sequence alignment of RBD molecules with epitope residues highlighted for ShAb01 (colored green), CR3022 and other nanobodies with overlapping epitopes.

b, Sequence alignment of RBD molecules with epitope residues highlighted for ShAb02 (colored purple), and nanobodies with overlapping epitopes.

c, Sequences alignment of RBD molecule (residues N331 - S530) of VoCs. Mutations are indicated using the 1-letter amino acid convention.



Supplementary Fig. 6. Comparison of the ShAb01 (purple) recognition in the context of the WA-1 RBD (white) and Omicron BA.1 (cyan). The Omicron BA.1 RBD model is taken from PDB:7WPB with all molecules shown in ribbon representation.



Supplementary Fig. 7. Construction of multi-domain ShAb nanobodies.

a, SARS-CoV-2 RBD is shown in surface representation with ShAb01 and ShAb02 VNARs in ribbon representation. The linkage of ShAb02 to ShAb01, or ShAb01 to ShAb02 are indicated by dashed lines.

b, Single VNAR domain, bispecific nanobody Incorporating "knob-in-hole" e.g., ShAb01H02K. c, multi-VNAR on a single chain, bi-specific, e.g., BiShAb0201.

d, single VNAR connected to a Foldon trimerization domain, e.g., ShAb01-Foldon.

a

RBD K_D value decrease

	Over ShAb01		Over ShAb02	
WA-1	102.4	62.0	186.3	112.8
Alpha	29.9	35.9	40.2	48.3
Beta	33.7	39.3	34.1	39.8
Delta	389000.0	389000.0	149000.0	149000.0
Omicron BA.1	494.0	304.5	7.2	4.4
Omicron BA.5	10.2	27.1	3.3	8.9
SARS-CoV-1	1.9	1.6	N/A	N/A
	BiShAb0201	ShAb01H02K	BiShAb0201	ShAb01H02K

b

Neutralization potency changes

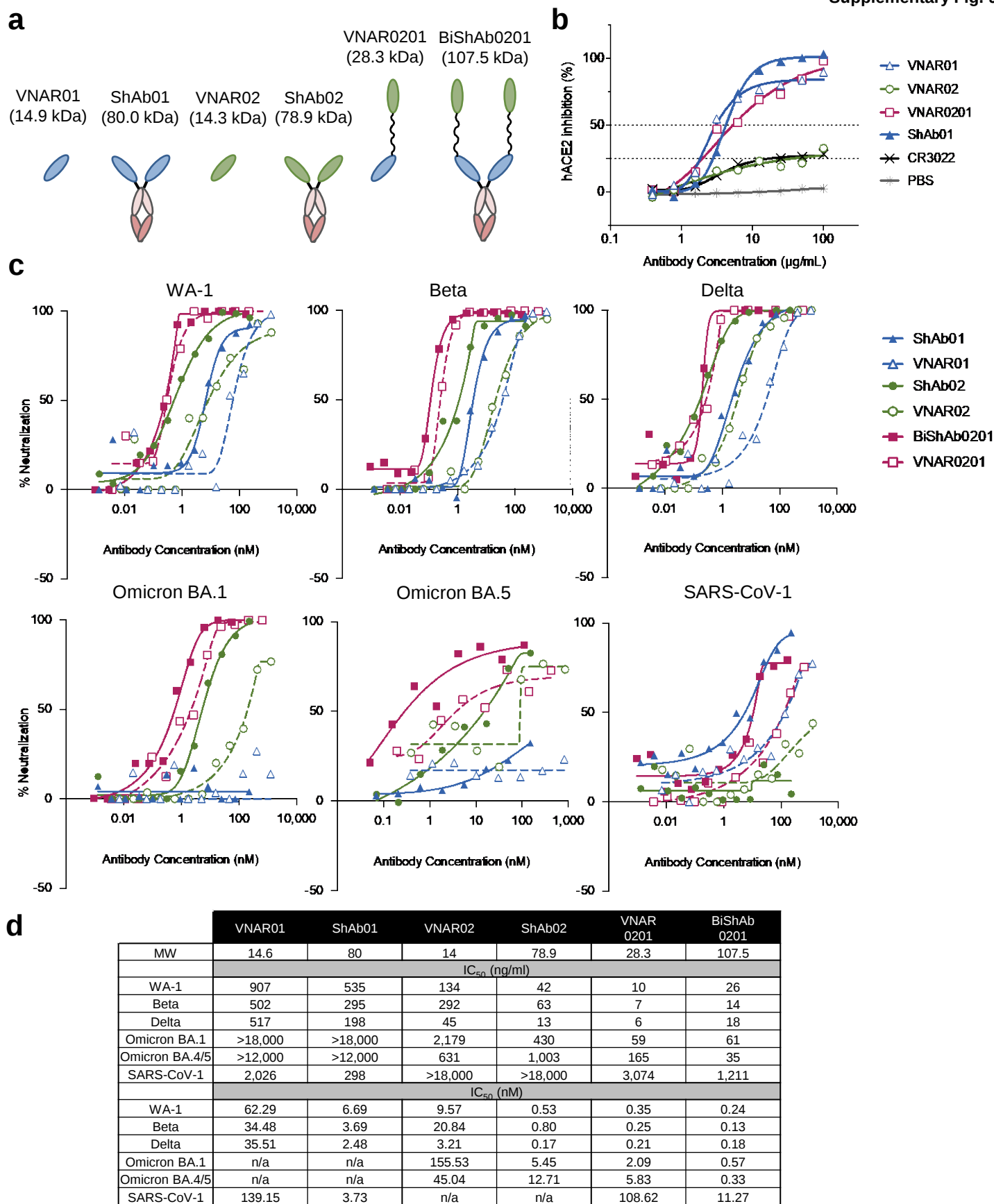
	Over ShAb01			Over ShAb02		
WA-1	25.4	26.5	2.0	2.2	2.3	0.2
Alpha	19.1	18.3	3.5	1.1	1.0	0.7
Beta	23.8	56.3	8.3	0.9	2.1	0.1
Delta	37.6	94.0	1.5	3.0	7.5	2.1
Omicron BA.1	>666.7	>46.0	N/A	6.6	0.5	2.5
Omicron BA.5	>342.9	>22.9	N/A	28.7	1.9	21.3
SARS-CoV-1	0.4	0.5	2.2	4.8	6.4	N/A
	BiShAb0201	ShAb01H02K	ShAb01-Foldon	BiShAb0201	ShAb01H02K	ShAb02-Foldon

Supplementary Fig. 8. Change in binding and pseudovirus neutralization levels for multi-specific nanobodies relative to parental ShAb molecules.

a, Fold increase in RBD binding affinity of multi-specific ShAbs compared to ShAb01 and ShAb02.

b, Fold change in pseudovirus neutralization IC₅₀ potency of multi-domain ShAbs compared to ShAb01 and ShAb02.

Source data are provided as a Source Data file.



Supplementary Fig. 9. Evaluation of ShAbs compared to their VNAR-only counterparts.

a, Schematic representation of ShAbs and VNARs.

b, BLI measurement of ACE2-inhibition to SARS-CoV-2 WA-1 RBD. The measurements are performed with immobilized SARS-CoV-1 RBD, with ShAb molecules and hACE2 in solution.

c, Neutralization of SARS-CoV-2 WA-1, Beta, Delta, Omicron BA.1, Omicron BA.4/5, and SARS-CoV-1 Urbani pseudoviruses.

d, Neutralization table to compare the IC₅₀ of VNAR0201 and BiShAb0201. ShAb and VNAR IC₅₀ values for neutralization of each pseudovirus, are shown in ng ml⁻¹ and nanomolar (nM).

Source data are provided as a Source Data file.

Supplementary Table 1. Immunization schedule and ShAb identification

Immunogen	Shark	Gender	Week of collection for library construction	Panning target	ShAb
RBD protein (RBD)	'Pink'	female	15	RBD	01
RBD protein (RBD)	'Red'	female	10	RBD	02
RBD-Ferritin (RFN)	'Green'	male	38+40	SpFN	17-18
RBD-Ferritin (RFN)	'Yellow'	female	38+40	SpFN	21
Spike-Ferritin (SpFN)	'Purple'	female	10	SpFN	09
Spike-Ferritin (SpFN)	'Purple'	female	10	RFN	28-29
Spike-Ferritin (SpFN)	'Blue'	male	10	RFN	22-27

Supplementary Table 2. Binding kinetics of ShAb01 and ShAb02 to RBD molecules
Source data are provided as a Source Data file.

	ShAb01			ShAb02		
	K _D (nM)	k _{on} (M*s) ⁻¹	k _{off} (s) ⁻¹	K _D (nM)	k _{on} (M*s) ⁻¹	k _{off} (s) ⁻¹
WA-1	47.1 ± 0.713	4.16 × 10 ⁴	1.96 × 10 ⁻³	85.7 ± 2.29	8.12 × 10 ⁴	6.96 × 10 ⁻³
K417N	55.0 ± 0.299	4.51 × 10 ⁴	2.48 × 10 ⁻³	53.9 ± 0.818	1.51 × 10 ⁵	8.15 × 10 ⁻³
E484K, N501Y	73.0 ± 39.6	3.47 × 10 ⁴	2.53 × 10 ⁻³	49.0 ± 0.865	1.14 × 10 ⁵	5.57 × 10 ⁻³
B.1.427/429, Epsilon (L452R)	35.1 ± 0.585	5.74 × 10 ⁴	2.01 × 10 ⁻³	29.8 ± 0.574	1.31 × 10 ⁵	3.91 × 10 ⁻³
B.1.1.7, Alpha (N501Y)	53.9 ± 0.408	4.12 × 10 ⁴	2.22 × 10 ⁻³	72.4 ± 1.03	1.16 × 10 ⁵	8.36 × 10 ⁻³
B.1.351, Beta (K417N, E484K, N501Y)	70.8 ± 0.392	3.73 × 10 ⁴	2.61 × 10 ⁻³	71.6 ± 1.25	9.68 × 10 ⁴	6.93 × 10 ⁻³
B.1.617.2, Delta (L452R, T478K)	38.9 ± 0.303	6.28 × 10 ⁴	2.45 × 10 ⁻³	14.9 ± 0.592	1.88 × 10 ⁵	2.80 × 10 ⁻³
P.1, Gamma (K417T, E484K, N501Y)	86.3 ± 0.661	3.11 × 10 ⁴	2.68 × 10 ⁻³	90.4 ± 2.26	6.50 × 10 ⁴	5.88 × 10 ⁻³
B.1.525, Eta, Iota (E484K)	70.0 ± 0.466	3.73 × 10 ⁴	2.61 × 10 ⁻³	49.6 ± 0.730	1.31 × 10 ⁵	6.50 × 10 ⁻³
B.1.617, Kappa (L452R, E484Q)	31.4 ± 0.385	8.63 × 10 ⁴	2.71 × 10 ⁻³	29.3 ± 0.712	1.68 × 10 ⁵	4.93 × 10 ⁻³
B.1.1.529, Omicron BA.1 (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H)	7463.1 ± 2230	5.25 × 10 ³	3.92 × 10 ⁻²	108.2 ± 2.98	9.16 × 10 ⁴	9.86 × 10 ⁻²
B.1.1.529.2, Omicron BA.2 (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H)	161.0 ± 4.14	5.99 × 10 ⁴	9.64 × 10 ⁻³	125 ± 5.69	5.30 × 10 ⁴	6.60 × 10 ⁻³
B.1.1.529.2.12.1, Omicron BA.2.12.1 (G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452Q, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H.)	307.0 ± 12.2	5.83 × 10 ⁴	1.79 × 10 ⁻²	86.5 ± 3.97	7.44 × 10 ⁴	6.43 × 10 ⁻³
Omicron BA.4/5 (G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, L452R, S477N, T478K, E484A, F486V, G496S, Q498R, N501Y, Y505H)	152.9 ± 5.36	1.02 × 10 ⁵	1.56 × 10 ⁻²	50.1 ± 1.41	9.63 × 10 ⁴	4.82 × 10 ⁻³
SARS-CoV-1 Urbani	198.1 ± 2.81	3.77 × 10 ⁴	7.47 × 10 ⁻³	n/d	n/d	n/d

n/d: not determined

Supplementary Table 3. Crystallography data collection and refinement statistics

	SARS-CoV-2 RBD + ShAb01 VNAR + ShAb02 VNAR
Crystallization condition	14.5% PEG20000, 0.1M HEPES pH7.0
<u>Data collection</u>	
Space group	P2 ₁ 2 ₁ 2 ₁
Cell dimensions	
a, b, c (Å)	51.1, 62.8, 147.9
α, β, γ (°)	90, 90, 90
Resolution (Å)	57.8-2.5 (2.6-2.5)
R _{sym}	0.303 (1.598)
I / σI	5.5 (0.94)
Reflections (total/unique)	216,995/ 16,633
Completeness (%)	99.49 (95.51)
Redundancy	13.0 (13.2)
CC _(1/2)	0.996 (0.375)
R _{pim}	0.0808 (0.8802)
<u>Refinement</u>	
Resolution (Å)	57.8-2.5 (2.6-2.5)
No. reflections	16,573 (1,554)
R _{work} / R _{free} *	23.1/27.9
Ramachandran	
favored/allowed/outliers	95.7 / 4.1 / 0.2
<u>B-Factor</u>	
Protein/water	82.3/58.8
R.m.s deviations	
Bond lengths (Å)	0.002
Bond angles (°)	0.579
PDB ID	7S83

Supplementary Table 4. ShAb01 interface with RBD

	ShAb01a	RBD	Distance (Å)
HYDROGEN BONDS	A:ALA 1[O]	C:LYS 378[NZ]	2.90
	A:LEU 99[O]	C:SER 383[OG]	2.31
	A:GLY 100[O]	C:TYR 369[OH]	2.68
	A:SER 101[OG]	C:CYS 379[N]	2.81
	A:TYR 102[O]	C:PHE 377[N]	3.13
	A:GLY 98[N]	C:CYS 379[O]	2.51
	A:SER 101[OG]	C:CYS 379[O]	3.51
	A:TYR 102[N]	C:PHE 377[O]	3.20
	A:TYR 102[OH]	C:TYR 369[O]	3.07
	A:TYR 102[OH]	C:SER 371[O]	3.57
	A:TYR 104[N]	C:SER 375[O]	2.97
SALT BRIDGE	A:GLU 103[OE1]	C:LYS 378[NZ]	2.99

Supplementary Table 5. ShAb02 interface with RBD

	ShAb02a	RBD	Distance (Å)
HYDROGEN BONDS	B:GLU 90[N]	C:ARG 355[O]	3.67
	B:LYS 51[N]	C:ASN 450[OD1]	2.80
	B:SER 61[N]	C:THR 470[OG1]	3.10
	B:SER 61[OG]	C:THR 470[OG1]	3.57
	B:ASP 99[OD1]	C:ARG 346[NH1]	2.94
	B:TYR 37[OH]	C:ARG 346[NH2]	2.34
	B:TYR 101[OH]	C:ARG 346[NH2]	3.71
	B:ASP 87[OD1]	C:ASN 354[ND2]	3.65
	B:SER 88[O]	C:ASN 354[ND2]	3.81
	B:SER 88[O]	C:ARG 355[N]	2.66
	B:GLU 90[OE1]	C:ARG 357[NE]	2.90
	B:GLU 90[OE2]	C:TYR 396[OH]	3.70
	B:ILE 49[O]	C:ASN 450[ND2]	3.21
	B:ASP 87[OD1]	C:ARG 466[NH1]	3.03
	B:ASP 87[OD2]	C:ARG 466[NH2]	3.13
	B:SER 61[OG]	C:THR 470[N]	3.09
	B:VAL 59[O]	C:THR 470[OG1]	2.82
SALT BRIDGE	B:ASP 99[OD1]	C:ARG 346[NH1]	2.94
	B:GLU 90[OE1]	C:ARG 357[NE]	2.90
	B:ASP 87[OD2]	C:ARG 466[NH1]	3.90
	B:ASP 87[OD1]	C:ARG 466[NH1]	3.03
	B:ASP 87[OD2]	C:ARG 466[NH2]	3.13
	B:ASP 87[OD1]	C:ARG 466[NH2]	3.63

Supplementary Table 6. Buried surface Area (BSA in Å²) of ShAb01-RBD

ShAb01	BOND TYPE	BSA	RBD	BOND TYPE	BSA
A:ALA 1	H	57.94	C:TYR 369	H	59.70
A:ARG 2		49.47	C:SER 371	H	17.89
A:ARG 8		34.89	C:ALA 372		45.55
A:GLU 46		13.42	C:PHE 374		25.75
A:ARG 82		21.77	C:SER 375	H	54.01
A:LYS 84		6.98	C:THR 376		18.27
A:TYR 86		8.65	C:PHE 377	H	40.84
A:TRP 87		9.26	C:LYS 378	HS	101.24
A:LYS 94		56.43	C:CYS 379	H	24.81
A:PHE 95		99.50	C:TYR 380		57.16
A:CYS 96		11.50	C:GLY 381		6.06
A:PRO 97		40.89	C:VAL 382		5.17
A:GLY 98	H	32.18	C:SER 383	H	31.24
A:LEU 99	H	56.41	C:PRO 384		23.69
A:GLY 100	H	30.01	C:THR 385		20.22
A:SER 101	H	46.05	C:LYS 386		4.35
A:TYR 102	H	123.28	C:ASP 405		0.16
A:GLU 103	S	35.43	C:ARG 408		78.80
A:TYR 104	H	56.78	C:ALA 411		3.00
A:ASP 106		27.30	C:PRO 412		28.51
H: HYDROGEN BOND, S: SALT BRIDGE			C:GLY 413		19.10
			C:GLN 414		13.48
			C:ASP 427		39.68
			C:ASP 428		20.09
			C:PHE 429		3.32
			C:GLY 502		3.25
			C:VAL 503		64.74
			C:TYR 508		2.31
			H: HYDROGEN BOND, S: SALT BRIDGE		

Supplementary Table 7. Buried surface Area (BSA in Å²) of ShAb02-RBD

ShAb02	BOND TYPE	BSA	RBD	BOND TYPE	BSA
B:CYS 29		0.83	C:ARG 346	HS	130.75
B:ALA 30		22.72	C:PHE 347		6.65
B:LEU 31		11.08	C:ALA 348		18.24
B:ALA 32		49.27	C:SER 349		1.30
B:SER 33		19.18	C:TYR 351		18.81
B:ASP 35		12.50	C:ALA 352		20.45
B:TYR 37	H	17.97	C:TRP 353		8.38
B:SER 48		5.03	C:ASN 354	H	53.78
B:ILE 49	H	5.40	C:ARG 355	H	69.81
B:SER 50		51.02	C:LYS 356		36.80
B:LYS 51	H	63.08	C:ARG 357	HS	30.20
B:GLY 52		4.50	C:TYR 396	H	20.98
B:GLU 57		2.58	C:LYS 444		25.74
B:THR 58		7.71	C:GLY 447		3.30
B:VAL 59	H	48.38	C:ASN 448		1.42
B:ASN 60		4.19	C:TYR 449		26.31
B:SER 61	H	57.84	C:ASN 450	H	91.28
B:GLY 62		2.90	C:LEU 452		6.69
B:ASN 84		2.56	C:PHE 464		5.28
B:TRP 86		86.90	C:GLU 465		0.33
B:ASP 87	HS	22.80	C:ARG 466	HS	75.71
B:SER 88	H	55.16	C:ILE 468		68.27
B:TRP 89		100.62	C:SER 469		11.18
B:GLU 90	HS	95.15	C:THR 470	H	64.23
B:THR 91		7.02	C:GLU 471		5.71
B:ARG 92		1.24	C:PHE 490		21.28
B:CYS 96		0.16	C:LEU 492		0.34
B:ASP 97		20.70	H: HYDROGEN BOND, S: SALT BRIDGE		
B:ASP 99	HS	11.66			
B:TYR 101	H	6.92			
H: HYDROGEN BOND, S: SALT BRIDGE					

Supplementary Table 8. Binding kinetics table for multi-specific ShAb molecules to CoV RBDs
Source data are provided as a Source Data file.

	ShAb01H02K			BiShAb0201		
	K _D (nM)	k _{on} (M*s) ⁻¹	k _{off} (s) ⁻¹	K _D (nM)	k _{on} (M*s) ⁻¹	k _{off} (s) ⁻¹
WA-1	0.57 ± 0.007	1.22 × 10 ⁵	6.98 × 10 ⁻⁵	1.07 ± 0.026	2.63 × 10 ⁴	2.82 × 10 ⁻⁵
K417N	1.3 ± 0.065	3.53 × 10 ⁵	4.57 × 10 ⁻⁴	1.7 ± 0.358	2.11 × 10 ⁵	3.52 × 10 ⁻⁴
E484K, N501Y	1.9 ± 0.107	2.77 × 10 ⁵	5.12 × 10 ⁻⁴	2.3 ± 0.415	1.77 × 10 ⁵	4.12 × 10 ⁻⁴
B.1.427/429, Epsilon (L452R)	0.08 ± 0.431	1.56 × 10 ⁵	1.21 × 10 ⁻⁵	1.2 ± 0.532	1.09 × 10 ⁵	1.33 × 10 ⁻⁴
B.1.1.7, Alpha (N501Y)	1.5 ± 0.091	3.41 × 10 ⁵	5.13 × 10 ⁻⁴	1.8 ± 0.331	2.07 × 10 ⁵	3.70 × 10 ⁻⁴
B.1.351, Beta (K417N, E484K, N501Y)	1.8 ± 0.083	2.94 × 10 ⁵	5.38 × 10 ⁻⁴	2.1 ± 0.380	2.06 × 10 ⁵	4.36 × 10 ⁻⁴
B.1.617.2, Delta (L452R, T478K)	<0.001 ± 0.004	9.00 × 10 ⁴	<1 × 10 ⁻⁷	0.72 ± 0.008	5.7 × 10 ⁴	4.10 × 10 ⁻⁵
P.1, Gamma (K417T, E484K, N501Y)	4.2 ± 0.806	7.35 × 10 ⁴	3.05 × 10 ⁻⁴	6.5 ± 0.752	7.80 × 10 ⁴	5.08 × 10 ⁻⁴
B.1.525, Eta, Iota (E484K)	1.6 ± 0.098	3.10 × 10 ⁵	5.11 × 10 ⁻⁴	2.0 ± 0.255	2.10 × 10 ⁵	4.15 × 10 ⁻⁴
B.1.617, Kappa (L452R, E484Q)	2.2 ± 0.430	1.51 × 10 ⁵	3.26 × 10 ⁻⁴	4.4 ± 0.328	5.36 × 10 ⁴	2.38 × 10 ⁻⁴
B.1.1.529, Omicron BA.1 (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H)	24.5 ± 24.5	7.13 × 10 ⁴	1.75 × 10 ⁻³	15.1 ± 1.47	1.02 × 10 ⁵	1.54 × 10 ⁻³
B.1.1.529.2, Omicron BA.2 (G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493K, G496S, Q498R, N501Y, Y505H)	24.1 ± 1.63	7.70 × 10 ⁴	1.86 × 10 ⁻³	33.2 ± 1.89	2.26 × 10 ⁴	7.49 × 10 ⁻⁴
B.1.1.529.2.12.1, Omicron BA.2.12.1 (G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, L452Q, S477N, T478K, E484A, Q493R, Q498R, N501Y, Y505H)	17.4 ± 1.24	9.85 × 10 ⁴	1.71 × 10 ⁻³	46.9 ± 2.70	1.97 × 10 ⁴	9.22 × 10 ⁻⁴
Omicron BA.4/5 (G339D, S371F, S373P, S375F, T376A, D405N, R408S, K417N, N440K, G446S, L452R, S477N, T478K, E484A, F486V, G496S, Q498R, N501Y, Y505H)	5.6 ± 0.43	1.23 × 10 ⁵	6.92 × 10 ⁻⁴	14.9 ± 0.91	5.15 × 10 ⁴	7.67 × 10 ⁻⁴
SARS-CoV-1 Urbani	122.9 ± 1.10	6.95 × 10 ⁴	8.54 × 10 ⁻³	102.3 ± 0.971	1.03 × 10 ⁵	1.06 × 10 ⁻²