SUPPLEMENTARY FIGURES AND LEGENDS

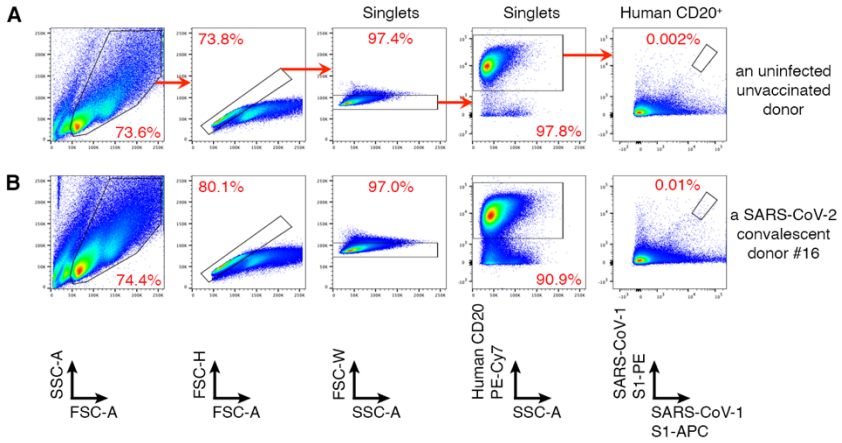


Figure S1. Gating strategy for B cell sorting.

(A and B) Human memory B cells recognizing SARS-CoV-1 S1 protein were single-cell sorted for antibody cloning. From left to right, each figure corresponds to the sequential gating strategy. Frequencies of double positive (S1-PE^{+} S1-APC^{+}) memory B cells are shown in the right most panel. FSC, forward scatter; SSC, side scatter (-A, area; -H, height; -W, width). Compared with the uninfected unvaccinated donor (A), the percentage of memory B cells recognizing SARS-CoV-1 S1 antigen significantly increased.

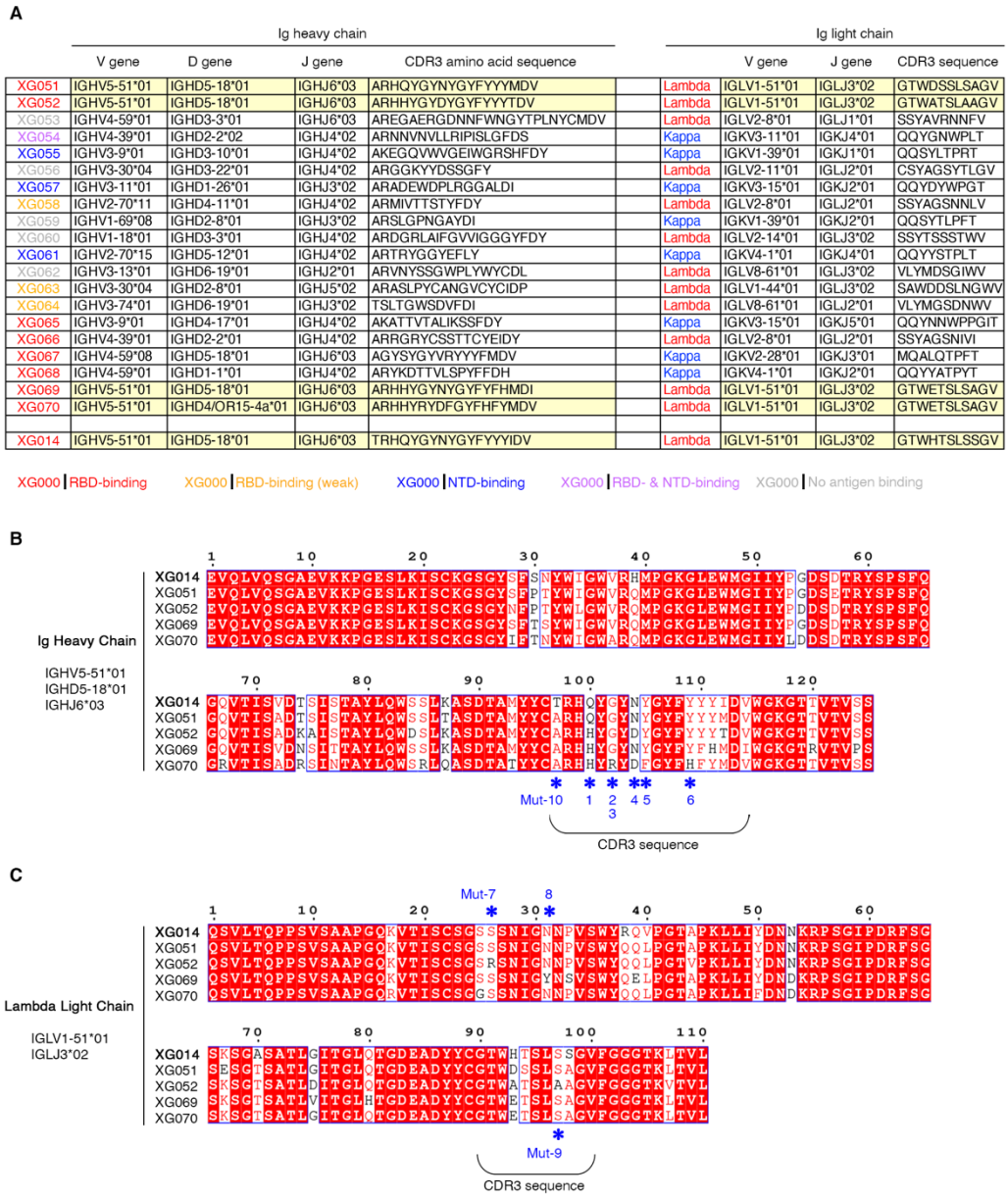


Figure S2. Sequence information of our cloned SARS-CoV-1-cross-reactive mAbs. (A) Detailed information of the 20 cloned mAbs. These mAbs have naturally paired heavy and light chains. Variable (V), diversity (D) and joining (J) genes, and CDR3 amino acid sequences of both heavy and light chains are listed. Based on the ELISA results, antibody names are color-coded: red, RBD-binding antibodies; orange, weak RBD-binding antibodies; blue, NTD-binding antibodies; purple, antibodies binding both RBD and NTD; and gray, no binding on the tested antigens. XG014 was isolated

previously from the same donor by using SARS-CoV-2 S-ECD as the bait protein [17,20]. (B) Amino acid sequence alignment of five antibody family members, including XG051, XG052, XG069, XG070, and XG014. These mAbs were originally from the same expanded B cell clone, since they are encoded by the same Ig variable gene segments with closely related CDR3 sequences. Ten amino acid residues for generating antibody variants are marked by asterisks.

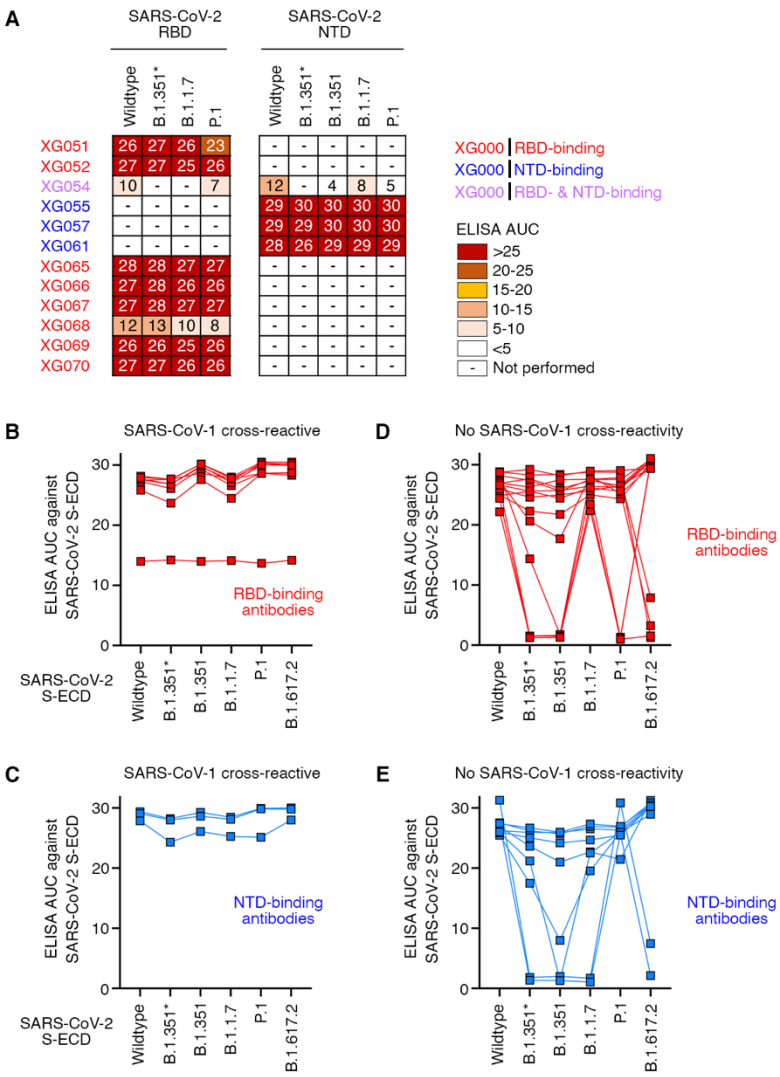


Figure S3. ELISA assays for our cloned cross-reactive mAbs.

(A) ELISA results against various recombinant RBD or NTD proteins. The area under the curve (AUC) values were calculated by PRISM.

(B) ELISA results for SARS-CoV-1-cross-reactive RBD-binding mAbs.

(C) ELISA results for SARS-CoV-1-cross-reactive NTD-binding mAbs.

(D) ELISA results for RBD-binding mAbs with no SARS-CoV-1 cross-reactivity.

(E) ELISA results for NTD-binding mAbs with no SARS-CoV-1 cross-reactivity. The antigen proteins used in (B-E) were recombinant S-ECD proteins of wildtype SARS-CoV-2 or its variants.

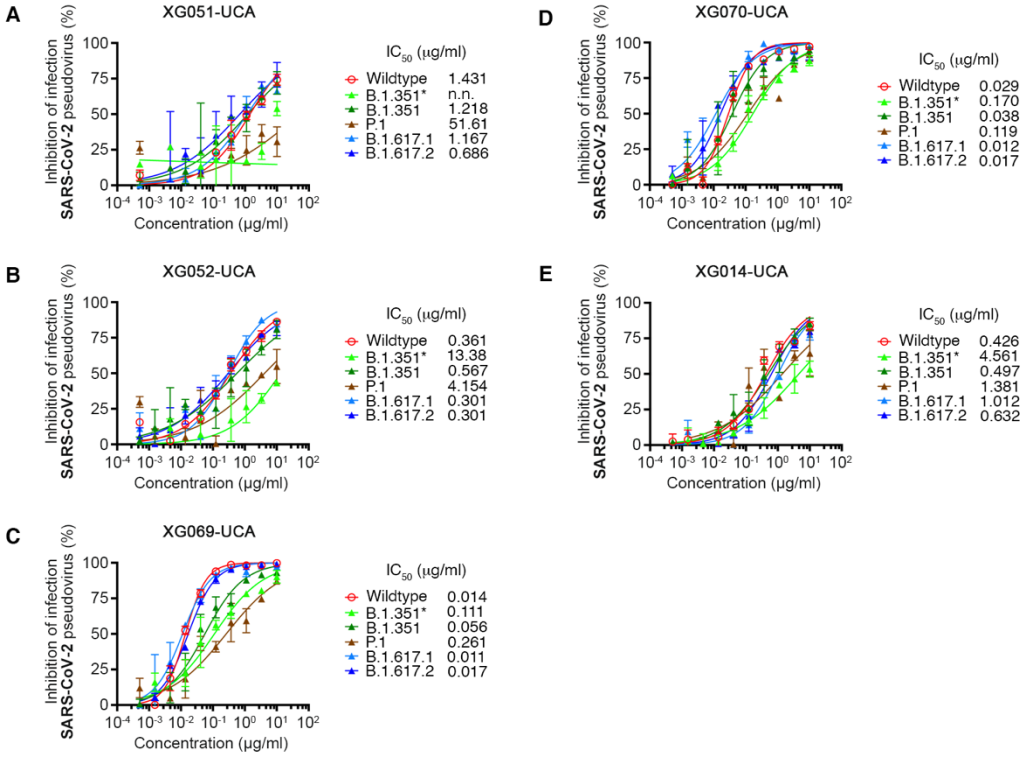


Figure S4. In vitro neutralization assays of five unmutated common ancestor (UCA) antibodies.

(A-E) XG051-UCA (A), XG052-UCA (B), XG069-UCA (C), XG070-UCA (D), and XG014-UCA (E) antibodies showed neutralizing activity against wildtype SARS-CoV-2 and several variants. Percent inhibition of infection was normalized to the luciferase signals in the control samples, which had no antibody added. The data are shown as mean ± SEM. The IC_{50} values were calculated by nonlinear regression analysis in PRISM software.

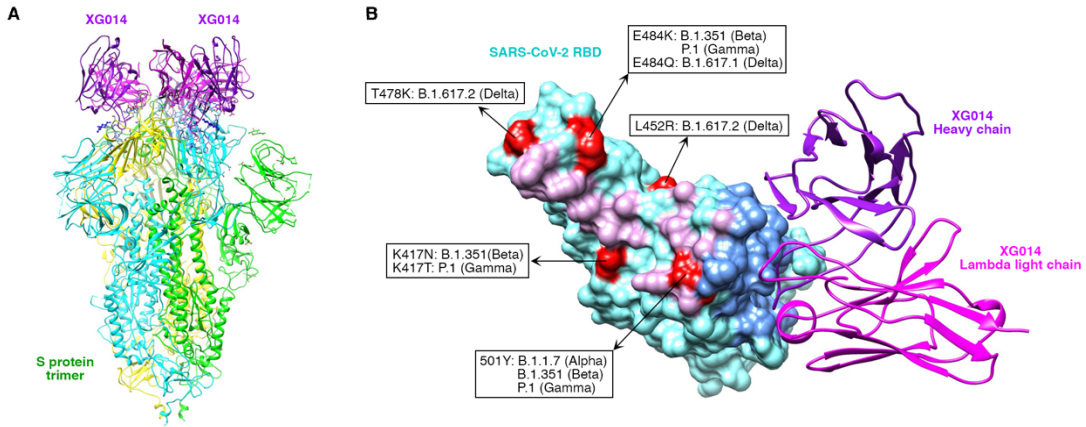


Figure S5. Structural analysis of XG014-S trimer complex.

(A) Cryo-EM structure of the XG014-S trimer complex (PDB ID 7V2A). XG014 recognizes RBD epitope and locks three RBDs in "down" (closed) conformation [20]. The immunoglobulin heavy/light chains of XG014 are colored in dark/light purple, while the three subunits of SARS-CoV-2 S trimer are colored as green, yellow, and cyan, respectively.

(B) Structural basis for the XG014 neutralization breadth against SARS-CoV-2 VOCs, except Omicron. The molecular surface of SARS CoV-2 RBD (cyan), together with XG014 heavy/light chains (dark/light purple), showed that the popular escape mutation sites (red) are located outside of the interaction surface of XG014-RBD (blue).

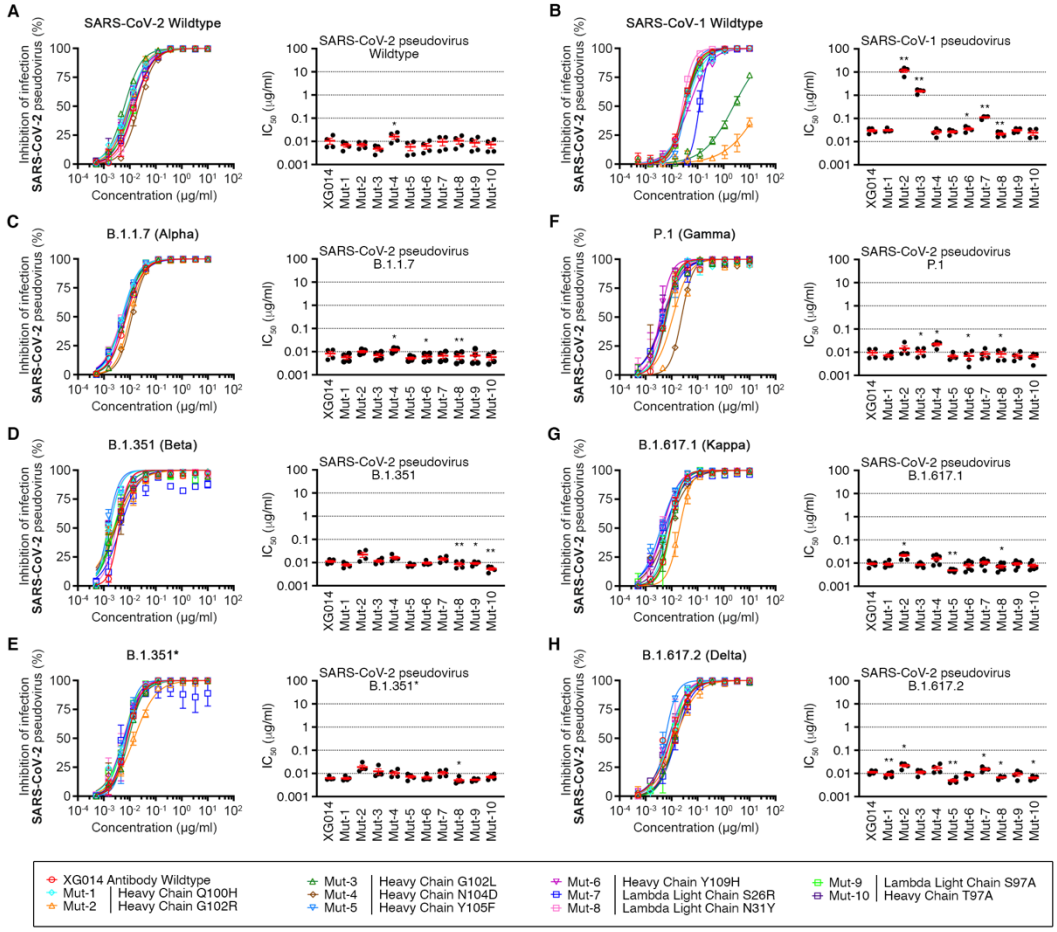


Figure S6. In vitro neutralization assays to identify the key amino acid residues for XG014 neutralization potency and breadth.

(A-H) Neutralizing activities of XG014 and its 10 antibody variants, Mut-1~10, against wildtype SARS-CoV-2 (A), wildtype SARS-CoV-1 (B), B.1.1.7 (Alpha) (C), B.1.351 (Beta) (D), B.1.351* (E), P.1 (Gamma) (F), B.1.617.1 (Kappa) (G), and B.1.617.2 (Delta) (H). The data are shown as mean ± SEM. The IC_{50} values were calculated by nonlinear regression analysis in PRISM software. Statistical analysis was performed using the Wilcoxon rank-sum test, and the p values are indicated by stars, * $p < 0.05$; ** $p < 0.01$.

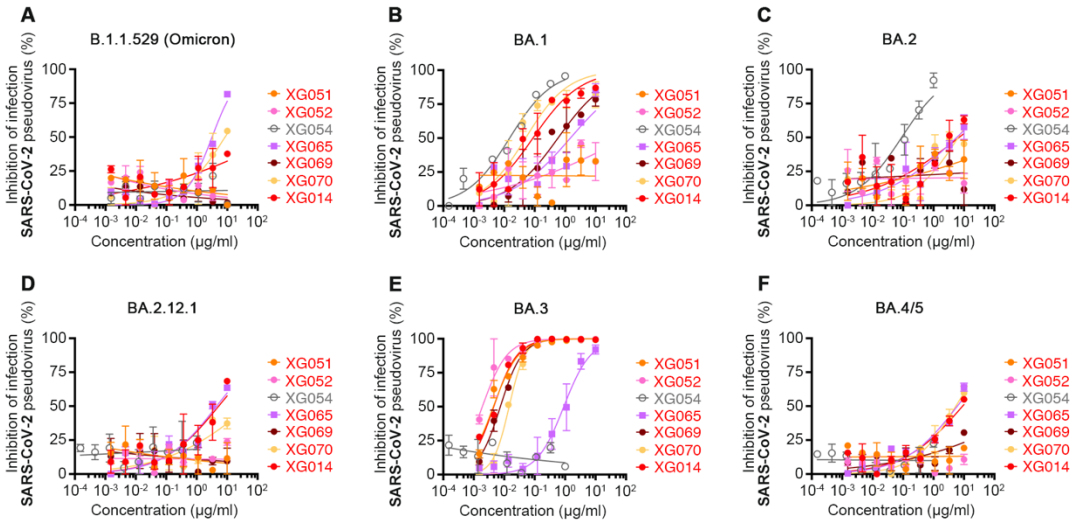
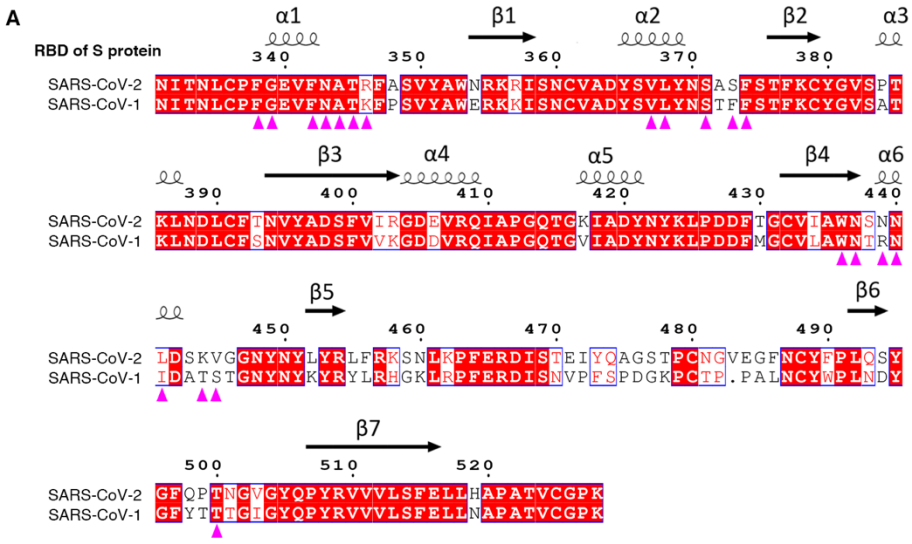


Figure S7. In vitro neutralization assays against pseudoviruses of Omicron sublineages using the seven SARS-CoV-1-cross-reactive mAbs.

(A-F) The neutralizing activities of the seven cloned cross-reactive mAbs, XG051, XG052, XG054, XG065, XG069, XG070, and XG014, varied considerably against SARS-CoV-2 Omicron sublineages. Percent inhibition of infection was normalized to the luciferase signals in the control samples, which had no antibody added. The data are shown as mean ± SEM.



B

B.1.1.529	BA.1	BA.2	BA.2.12.1	BA.3	BA.4/5
		T19I	T19I		T19I
		L24S	L24S		L24S
		del25/27	del25/27		del25/27
A67V	A67V				
del69/70	del69/70				del69/70
T95I	T95I				
G142D	G142D	G142D	G142D		G142D
del143/145	del143/145				
del211	N211I				
L212I	del212/212				
		V213G	V213G		V213G
ins214EPE					
G339D	G339D	G339D	G339D		G339D
S371L	S371L	S371F	S371F		S371F
S373P	S373P	S373P	S373P		S373P
S375F	S375F	S375F	S375F		S375F
		T376A	T376A		T376A
		D405N	D405N		D405N
		R408S	R408S		R408S
K417N		K417N	K417N		K417N
N440K		N440K	N440K		N440K
G446S					
			L452Q		L452R
S477N	S477N	S477N	S477N		S477N
T478K	T478K	T478K	T478K		T478K
E484A	E484A	E484A	E484A		E484A
					F486V
Q493R	Q493R	Q493R	Q493R		
G496S	G496S				
Q498R	Q498R	Q498R	Q498R		Q498R
N501Y	N501Y	N501Y	N501Y		N501Y
Y505H	Y505H	Y505H	Y505H		Y505H
T547K	T547K				
D614G	D614G	D614G	D614G	D614G	D614G
H655Y	H655Y	H655Y	H655Y	H655Y	H655Y
N679K	N679K	N679K	N679K	N679K	N679K
P681H	P681H	P681H	P681H	P681H	P681H
			S704L		
N764K	N764K	N764K	N764K	N764K	N764K
D796Y	D796Y	D796Y	D796Y	D796Y	D796Y
N856K	N856K				
Q954H	Q954H	Q954H	Q954H	Q954H	Q954H
N969K	N969K	N969K	N969K	N969K	N969K
L981F	L981F				

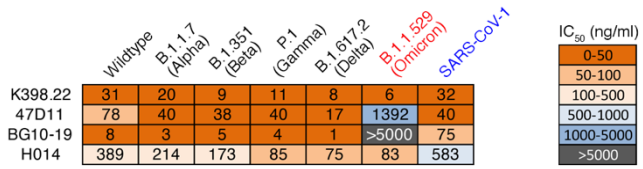
Receptor-binding domain (RBD)

Figure S8. Comparison of S protein sequences.

(A) Amino acid sequence alignment of RBD regions from SARS-CoV-1 and SARS-CoV-2. The highly conserved amino acid residues between these two different viruses are marked in red. The amino acid residues involved in XG014-RBD interaction are

indicated by purple triangles.

(B) Amino acid mutations in the S protein of B.1.1.529 (Omicron) and its sublineages, BA.1, BA.2, BA.2.12.1, BA.3, BA.4, and BA.5, compared with wildtype SARS-CoV-2. The amino acid sequences of BA.4 and BA.5 S proteins are exactly the same.



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91 **Figure S9. IC_{50} values for several mAbs cross-neutralizing SARS-CoV-1.**

92 Calculated IC_{50} values based on our in vitro neutralization assays. Four reported anti-

93 SARS-CoV-2 bNAbs with cross-neutralizing activity against SARS-CoV-1 include

94 K398.22 [34], 47D11 [30], BG10-19 [31], and H014 [53].

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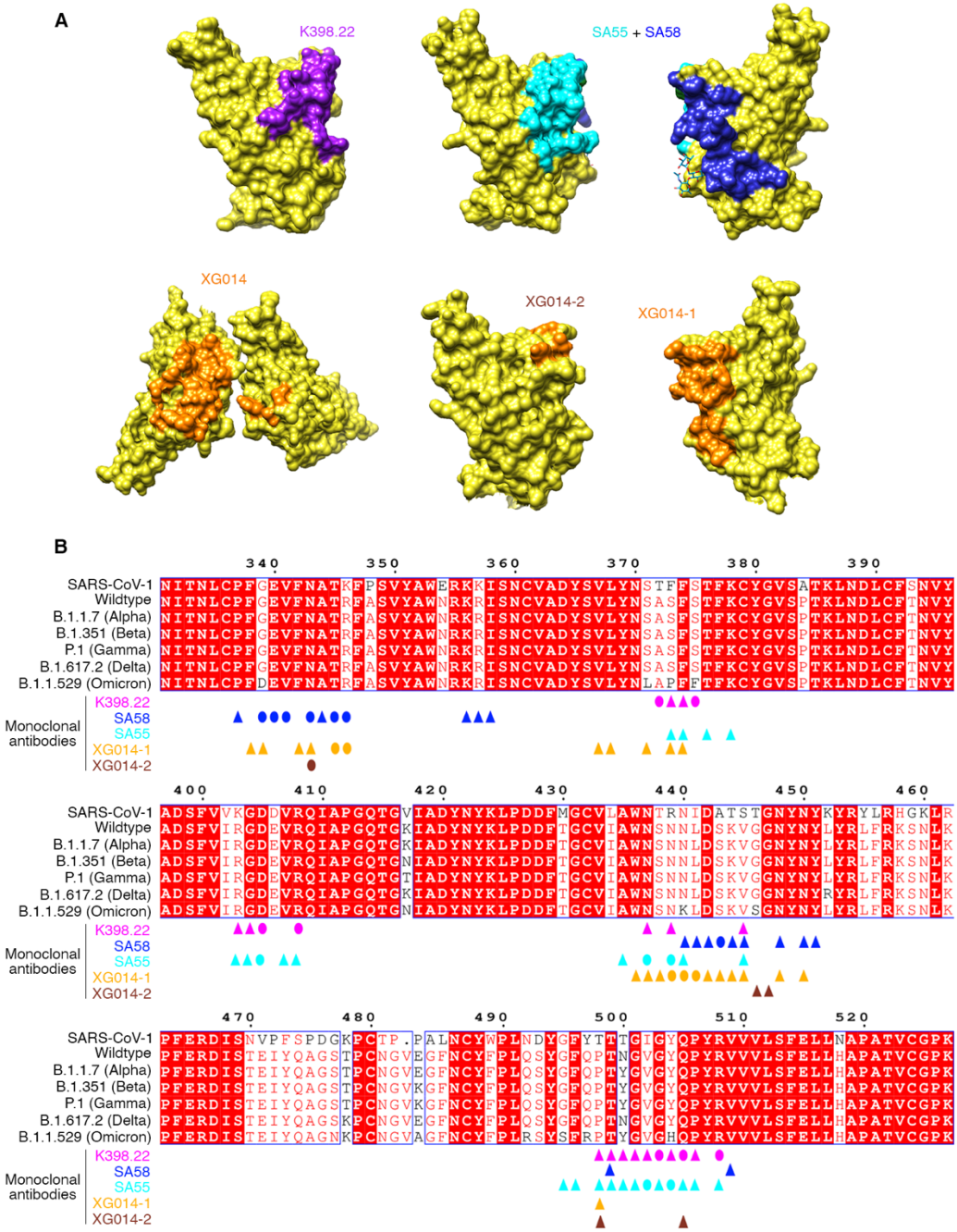

Figure S10. Comparison of K398.22, SA58, SA55, and XG014 epitopes.

(A) RBD model shown in surface mode with the epitope of K398.22 shown in purple (PDB ID 7TP4).

(B) RBD surface with SA58 and SA55 epitopes shown in cyan and blue, respectively (PDB ID 7Y0W).

(C) RBD surface with XG014 epitopes shown in orange (PDB ID 7V2A).

(D) Sequence alignment of RBDs from SARS-CoV-1, SARS-CoV-2 wildtype and five SARS-CoV-2 VOCs. Conserved amino acids are highlighted as red. Residues involved in K398.22, SA58, SA55, and XG014 interactions are marked with triangles in purple, cyan, blue, and orange, respectively. Residues involved in strong interactions (hydrogen bonds and salt bridges) are marked with circles.