

1

2 **Structural basis of a public antibody response to SARS-CoV-2**

3

4 Meng Yuan^{1,*}, Hejun Liu^{1,*}, Nicholas C. Wu^{1,*}, Chang-Chun D. Lee¹, Xueyong Zhu¹,

5 Fangzhu Zhao^{2,3,4}, Deli Huang², Wenli Yu¹, Yuanzi Hua¹, Henry Tien¹,

6 Thomas F. Rogers^{2,5}, Elise Landais^{2,3,6}, Devin Sok^{3,4,6}, Joseph G. Jardine^{3,6}, Dennis R.

7 Burton^{2,3,4,7}, Ian A. Wilson^{1,3,4,8,§}

8

9 ¹ Department of Integrative Structural and Computational Biology, The Scripps Research
10 Institute, La Jolla, CA 92037, USA

11 ² Department of Immunology and Microbiology, The Scripps Research Institute, La Jolla,
12 CA 92037, USA

13 ³ IAVI Neutralizing Antibody Center, The Scripps Research Institute, La Jolla, CA 92037,
14 USA

15 ⁴ Consortium for HIV/AIDS Vaccine Development (CHAVID), The Scripps Research
16 Institute, La Jolla, CA 92037, USA

17 ⁵ Division of Infectious Diseases, Department of Medicine, University of California, San
18 Diego, La Jolla, CA 92037, USA

19 ⁶ IAVI, New York, NY10004, USA

20 ⁷ Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of
21 Technology, and Harvard University, Cambridge, MA 02139, USA

22 ⁸ The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla,
23 CA, 92037, USA

24 * These authors contributed equally to this work

25 [§] Correspondence: wilson@scripps.edu (I.A.W.)

26 **ABSTRACT**

27 Molecular-level understanding of human neutralizing antibody responses to SARS-CoV-
28 2 could accelerate vaccine design and facilitate drug discovery. We analyzed 294
29 SARS-CoV-2 antibodies and found that IGHV3-53 is the most frequently used IGHV
30 gene for targeting the receptor binding domain (RBD) of the spike (S) protein. We
31 determined crystal structures of two IGHV3-53 neutralizing antibodies +/- Fab CR3022
32 ranging from 2.33 to 3.11 Å resolution. The germline-encoded residues of IGHV3-53
33 dominate binding to the ACE2 binding site epitope with no overlap with the CR3022
34 epitope. Moreover, IGHV3-53 is used in combination with a very short CDR H3 and
35 different light chains. Overall, IGHV3-53 represents a versatile public VH in neutralizing
36 SARS-CoV-2 antibodies, where their specific germline features and minimal affinity
37 maturation provide important insights for vaccine design and assessing outcomes.

38 **MAIN**

39 The ongoing COVID-19 pandemic, which is caused by severe acute respiratory
40 syndrome coronavirus 2 (SARS-CoV-2), is far from an end (1). The increasing global
41 health and socioeconomic damage require urgent development of an effective COVID-
42 19 vaccine. While multiple vaccine candidates have entered clinical trials (2), the
43 molecular features that contribute to an effective antibody response are not clear. Over
44 the past decade, the concept of a public antibody response (also known as multidonor
45 class antibodies) to specified microbial pathogens has emerged. A public antibody
46 response describes antibodies that have shared genetic elements and modes of
47 recognition, and can be observed in multiple individuals against a given antigen. Such
48 responses to microbial pathogens have been observed against influenza (3), dengue (4),
49 malaria (5), and HIV (6). Identification of public antibody responses and characterization
50 of the molecular interactions with cognate antigen can provide insight into the
51 fundamental understanding of the immune repertoire and its ability to quickly respond to
52 novel microbial pathogens, as well as facilitate rational vaccine design against these
53 pathogens (7, 8).

54

55 The spike (S) protein is the major surface antigen of SARS-CoV-2. The S protein utilizes
56 its receptor-binding domain (RBD) to engage the host receptor ACE2 for viral entry (9-
57 12). Therefore, RBD-targeting antibodies could neutralize SARS-CoV-2 by blocking
58 ACE2 binding. A number of antibodies that target the RBD of SARS-CoV-2 have now
59 been discovered in very recent studies (13-28). We compiled a list of 294 SARS-CoV-2
60 RBD-targeting antibodies where information on IGHV gene usage is available (17-28)
61 (Table S2), and found that IGHV3-53 is the most frequently used IGHV gene among
62 such antibodies (Fig. 1A). Of 294 RBD-targeting antibodies, 10% are encoded by
63 IGHV3-53, as compared to only 0.5% to 2.6% in the repertoire of naïve healthy

64 individuals (29) with a mean of 1.8% (30). The prevalence of IGHV3-53 in the antibody
65 response in SARS-CoV-2 patients has also been recognized in some recent antibody
66 studies (20, 22, 27). These observations indicate that IGHV3-53 represents a frequent
67 and public antibody response to the SARS-CoV-2 RBD.

68

69 To understand the molecular features that endow IGHV3-53 with the ability to act as a
70 public antibody, we determined crystal structures of two IGHV3-53 neutralizing
71 antibodies, namely CC12.1 and CC12.3, in complex with the SARS CoV-2 RBD and also
72 in the presence of the SARS-CoV1/2 cross-reactive Fab CR3022 (17). CC12.1 and
73 CC12.3 were previously isolated from a SARS-CoV-2-infected patient and shown to be
74 SARS-CoV-2 RBD-specific (27). Although CC12.1 and CC12.3 are both encoded by
75 IGHV3-53, CC12.1 utilizes IGHJ6, IGKV1-9, and IGKJ3, whereas CC12.3 utilizes IGHJ4,
76 IGKV3-20, and IGKJ1. This variation in IGHJ, IGKV, and IGKJ usage indicates that
77 CC12.1 and CC12.3 belong to different clonotypes, but are encoded by a common
78 IGHV3-53 germline gene. IgBlast analysis (31) shows that IGHV and IGKV of CC12.1
79 are only 1% somatically mutated at the nucleotide sequence level (two amino-acid
80 changes each). Similarly, the IGHV and IGKV of CC12.3 are also minimally somatically
81 mutated at 1.4% in both IGHV (four amino-acid changes) and IGKV (a single amino-acid
82 deletion). The binding affinities (K_d) of Fabs CC12.1 and CC12.3 to SARS-CoV-2 RBD
83 are 17 nM and 14 nM, respectively (Fig. S2). Moreover, competition experiments
84 suggest that CC12.1 and CC12.3 bind to a similar epitope, which overlaps with the
85 ACE2 binding site, but not the CR3022 epitope (Fig. S3).

86

87 We determined four complex crystal structures, CC12.1/RBD, CC12.3/RBD,
88 CC12.1/RBD/CR3022, and CC12.3/RBD/CR3022 at resolutions of 3.11 Å, 2.33 Å, 2.90
89 Å, and 2.70 Å, respectively (Table S1). CC12.1 and CC12.3 bind to the ACE2 binding

90 site on SARS-CoV-2 RBD with an identical angle of approach (Fig. 1B-F). Interestingly,
91 another IGHV3-53 antibody B38, whose structure was determined recently (23), also
92 binds to the ACE2 binding site on SARS-CoV-2 RBD in a similar manner (Fig. S4).
93 Similar to the ACE2 binding site (11), the epitopes of these antibodies can only be
94 accessed when the RBD is in the “up” conformation (Fig. S5). Among 16 ACE2 binding
95 residues on RBD, 10 are within the epitopes of CC12.1 and B38, and 6 are in the
96 epitope of CC12.3 (Fig. 2A-D). Many of the epitope residues are not conserved between
97 SARS-CoV-2 and SARS-CoV (Fig. 2E), explaining their lack of cross-reactivity (27). The
98 buried surface area (BSA) from the heavy-chain interaction is quite similar in CC12.1
99 (723 \AA^2), CC12.3 (698 \AA^2), and B38 (713 \AA^2). In contrast, the light-chain interaction is
100 much smaller for CC12.3 (176 \AA^2) compared to CC12.1 (566 \AA^2) and B38 (495 \AA^2),
101 consistent with different light-chain gene usage. While both CC12.1 and B38 utilize
102 IGKV1-9, CC12.3 utilizes IGKV3-20. This observation suggests that IGHV3-53 can pair
103 with different light chains to target the ACE2 binding site of the SARS-CoV-2 RBD.
104 Given that CC12.3 (80% BSA from the heavy chain) binds the RBD with similar affinity to
105 CC12.1 (56% BSA from heavy chain) (Fig. S2), the light-chain identity seems not to be
106 as critical as the heavy chain. In fact, among the RBD-targeting IGHV3-53 antibodies,
107 nine different light chains are observed, although IGKV1-9 and IGKV3-20 are the most
108 frequently found to date (Fig. S6).

109

110 To understand why IGHV3-53 is elicited as a public antibody response, the molecular
111 interactions between the RBD and the heavy chains of CC12.1, CC12.3, and B38 were
112 analyzed. The complementarity-determining regions (CDR) H1 and H2 of these
113 antibodies interact extensively with the RBD mainly through specific hydrogen bonds
114 (Fig. 3A-B). Interestingly, all residues on CDR H1 and H2 that hydrogen bond with the
115 RBD are encoded by the germline IGHV3-53 (Fig. S1 and S7, Table S3). These

116 interactions are almost identical among CC12.1, CC12.3, and B38 with the only
117 difference at V_H residue 58. A somatic mutation V_H Y58F is present in both CC12.1 and
118 CC12.3, but not in B38 (Fig. 3A-C, boxed residues). Nevertheless, this somatic mutation
119 is unlikely to be essential for IGHV3-53 to engage the RBD, since V_H residue 58 in B38
120 still interacts with the RBD through an additional hydrogen bond (Fig. 3C). Of note, none
121 of these antibody interactions mimic ACE2 binding (Fig. 3D).

122

123 Our structural analysis reveals two key motifs in the IGHV3-53 germline sequence that
124 are important for RBD binding, namely an NY motif at V_H residues 32 and 33 in the CDR
125 H1, and an SGGS motif at V_H residues 53 to 56 in the CDR H2 (Fig. S8). The side chain
126 of V_H N32 in the NY motif forms a hydrogen bond with the backbone carbonyl of A475 on
127 the RBD, and this interaction is stabilized by an extensive network of hydrogen bonds
128 with other antibody residues as well as a bound water molecule (Fig. 4A). V_H N32 also
129 hydrogen bonds with V_H R94, which in turn hydrogen bonds with N487 and Y489 on the
130 RBD (Fig. 4A). These interactions enhance not only RBD-Fab interaction, but also
131 stabilize CDR and framework residues and conformations. V_H Y33 in the NY motif
132 inserts into a hydrophobic cage formed by RBD residues Y421, F456, L455 and the
133 aliphatic component of K417 (Fig. 4B). A hydrogen bond between V_H Y33 and the
134 carbonyl oxygen of L455 on RBD further strengthens the interaction. The second key
135 motif SGGS in CDR H2 forms extensive hydrogen bond network with the RBD (Fig. 4C),
136 including four hydrogen bonds that involve the hydroxyl side chains of V_H S53 and V_H
137 S56, and four water-mediated hydrogen bonds to the backbone carbonyl of V_H G54, the
138 backbone amide of V_H S56, and the side chain of V_H S56. Along with V_H Y52, the SGGS
139 motif takes part in a type I beta turn, with a positive Φ -angle for V_H G55 at the end of the
140 turn. In addition, the C α of V_H G54 is only 4 Å away from the RBD, indicating that side
141 chains of other amino acids would clash with the RBD if they were present at this

142 position. As a result, the SGGS motif is a perfect fit for interacting with the RBD at this
143 location.

144

145 Overall, these observations demonstrate the importance of the NY and SGGS motifs,
146 which are both encoded in the IGHV3-53 germline, for engaging the RBD. In fact,
147 besides IGHV3-53, the only other IGHV gene that contains an NY motif in CDR H1 and
148 an SGGS motif in CDR H2 is IGHV3-66, which is a closely-related IGHV gene to IGHV3-
149 53 (32). As compared to IGHV3-53, IGHV3-66 has a lower occurrence frequency in the
150 repertoire of healthy individuals (0.3% to 1.7%) (29), which may explain why IGHV3-66
151 is less prevalent than IGHV3-53, but yet is still quite commonly observed (19-22, 24, 26)
152 in antibodies in SARS-CoV-2 patients (Fig. 1A). Overall, our structural analysis has
153 identified two germline-encoded binding motifs that enable IGHV3-53 to act as a public
154 antibody and target the SARS CoV-2 RBD with no mutations required from affinity
155 maturation.

156

157 While the binding mode of CDR H1 and H2 to RBD is highly similar among CC12.1,
158 CC12.3, and B38, CDR H3 interaction with the RBD is different (Fig. 3A-C) due to
159 differences in the CDR H3 sequences and conformations (Fig. 5A-B). For example,
160 while CDR H3 of CC12.1 can interact with RBD Y453 through a hydrogen bond, CDR
161 H3s of CC12.3 and B38 do not form such a hydrogen bond (Fig. 3A-C). Similarly, due to
162 the difference in light-chain gene usage, the light-chain interactions with the RBD can
163 vary substantially in IGHV3-53 antibodies (Fig. S9). Overall, our structural analysis
164 demonstrates that IGHV3-53 provides a highly versatile framework for antibodies to
165 target the ACE2 binding site in SARS-CoV-2 RBD.

166

167 An interesting feature of CC12.1 and CC12.3 is their relatively short CDR H3. While the
168 CDR H3 sequences of CC12.1 and CC12.3 are very different, both have a length of nine
169 amino acids (Kabat numbering), whereas the average CDR H3 length for human
170 antibodies is around 13 (33), as compared to for example very long CDR H3s (up to 30
171 residues) on average that seem to be required for many broadly neutralizing antibodies
172 to HIV-1 (34). Similarly, antibody B38 has a very short CDR H3 length of seven residues
173 (23). It is unlikely that longer CDR H3's can be accommodated in these antibodies since
174 their epitopes are relatively flat with no large pocket to insert a protruding CDR (Fig. 2A-
175 C). This conclusion was also arrived in a recent study that also reported SARS-CoV-2
176 RBD-targeting antibodies that are encoded by either IGHV3-53 or IGHV3-66 tend to
177 have a short CDR H3 (28). In fact, IGHV3-53 and IGHV3-66 antibodies in general have
178 slightly shorter than average CDR H3's (by around one residue), but do appear to have
179 a few much shorter CDR H3's (<10 amino acids) than average in the baseline antibody
180 repertoire (30). In CC12.1 and CC12.3, the space for CDR H3 to fit in the interface within
181 the RBD is limited (Fig. 5A-B), which thus constrains its length. Consistently, among
182 RBD-targeting antibodies currently reported (17-28), those encoded by IGHV3-53 have a
183 significantly shorter CDR H3 compared to those encoded by other IGHV genes (p-value
184 = 6e-8, Mann-Whitney U test) (Fig. 5C). These observations provide structural and
185 statistical evidence that a short CDR H3 length is a molecular feature of the IGHV3-53-
186 encoded public antibody response to the SARS-CoV-2 RBD, reminiscent of a short 5-
187 residue CDR L3 in IGHV1-2 antibodies to the CD4 receptor binding site in gp120 of HIV-
188 1 Env (35).

189

190 Besides IGHV3-53, several other IGHV genes such as IGHV1-2, IGHV3-9, and IGHV3-
191 30 are also more frequently observed than other germlines in SARS-CoV-2 RBD-
192 targeting antibodies (Fig. 1A). The molecular mechanisms of these antibody responses

193 to SARS-CoV-2 will need to be characterized in the future. In addition, whether other
194 antibody germline gene segments, including the IGHD and the light chain, contribute to
195 public antibody responses to SARS-CoV-2 will also need to be further addressed.
196 Notwithstanding, the detailed characterization of this public antibody response to SARS
197 CoV-2 is already be a promising starting point for rational vaccine design (36), especially
198 given limited to no affinity maturation is required from the germline to achieve a high
199 affinity neutralizing antibody response to the RBD. In addition, IGHV3-53 exists at a
200 reasonable frequency in healthy individuals (29, 30), indicating that this public antibody
201 could be commonly elicited during vaccination (37), and aid in design of both antibody
202 and small molecule therapeutics (7, 38).

203

204 REFERENCES

- 205 1. S. M. Kissler, C. Tedijanto, E. Goldstein, Y. H. Grad, M. Lipsitch, Projecting the
206 transmission dynamics of SARS-CoV-2 through the postpandemic period.
207 *Science* 10.1126/science.abb5793 (2020).
- 208 2. N. Lurie, M. Saville, R. Hatchett, J. Halton, Developing COVID-19 vaccines at
209 pandemic speed. *N Engl J Med* **382**, 1969-1973 (2020).
- 210 3. S. F. Andrews, A. B. McDermott, Shaping a universally broad antibody response
211 to influenza amidst a variable immunoglobulin landscape. *Curr Opin Immunol* **53**,
212 96-101 (2018).
- 213 4. P. Parameswaran *et al.*, Convergent antibody signatures in human dengue. *Cell*
214 *Host Microbe* **13**, 691-700 (2013).
- 215 5. K. Pieper *et al.*, Public antibodies to malaria antigens generated by two LAIR1
216 insertion modalities. *Nature* **548**, 597-601 (2017).
- 217 6. I. Setliff *et al.*, Multi-donor longitudinal antibody repertoire sequencing reveals the
218 existence of public antibody clonotypes in HIV-1 infection. *Cell Host Microbe* **23**,
219 845-854 e846 (2018).
- 220 7. N. C. Wu, I. A. Wilson, Structural insights into the design of novel anti-influenza
221 therapies. *Nat Struct Mol Biol* **25**, 115-121 (2018).
- 222 8. A. Lanzavecchia, A. Fruhwirth, L. Perez, D. Corti, Antibody-guided vaccine
223 design: identification of protective epitopes. *Curr Opin Immunol* **41**, 62-67 (2016).

- 224 9. P. Zhou *et al.*, A pneumonia outbreak associated with a new coronavirus of
225 probable bat origin. *Nature* **579**, 270-273 (2020).
- 226 10. M. Letko, A. Marzi, V. Munster, Functional assessment of cell entry and receptor
227 usage for SARS-CoV-2 and other lineage B betacoronaviruses. *Nat Microbiol* **5**,
228 562-569 (2020).
- 229 11. R. Yan *et al.*, Structural basis for the recognition of the SARS-CoV-2 by full-
230 length human ACE2. *Science* **367**, 1444-1448 (2020).
- 231 12. J. Lan *et al.*, Structure of the SARS-CoV-2 spike receptor-binding domain bound
232 to the ACE2 receptor. *Nature* **581**, 215-220 (2020).
- 233 13. W. Li *et al.*, Potent neutralization of SARS-CoV-2 in vitro and in an animal model
234 by a human monoclonal antibody. *bioRxiv* 10.1101/2020.05.13.093088 (2020).
- 235 14. E. Andreano *et al.*, Identification of neutralizing human monoclonal antibodies
236 from Italian Covid-19 convalescent patients. *bioRxiv* 10.1101/2020.05.05.078154
237 (2020).
- 238 15. S. J. Zost *et al.*, Rapid isolation and profiling of a diverse panel of human
239 monoclonal antibodies targeting the SARS-CoV-2 spike protein. *bioRxiv*
240 10.1101/2020.05.12.091462 (2020).
- 241 16. A. Z. Wec *et al.*, Broad sarbecovirus neutralizing antibodies define a key site of
242 vulnerability on the SARSCoV-2 spike protein. *bioRxiv*
243 10.1101/2020.05.15.096511 (2020).
- 244 17. M. Yuan *et al.*, A highly conserved cryptic epitope in the receptor-binding
245 domains of SARS-CoV-2 and SARS-CoV. *Science* **368**, 630-633 (2020).
- 246 18. D. Pinto *et al.*, Cross-neutralization of SARS-CoV-2 by a human monoclonal
247 SARS-CoV antibody. *Nature* 10.1038/s41586-020-2349-y (2020).
- 248 19. B. Ju *et al.*, Human neutralizing antibodies elicited by SARS-CoV-2 infection.
249 *Nature* 10.1038/s41586-020-2380-z (2020).
- 250 20. Y. Cao *et al.*, Potent neutralizing antibodies against SARS-CoV-2 identified by
251 high-throughput single-cell sequencing of convalescent patients' B cells. *Cell*
252 10.1016/j.cell.2020.05.025 (2020).
- 253 21. P. J. M. Brouwer *et al.*, Potent neutralizing antibodies from COVID-19 patients
254 define multiple targets of vulnerability. *bioRxiv* 10.1101/2020.05.12.088716
255 (2020).
- 256 22. D. F. Robbiani *et al.*, Convergent antibody responses to SARS-CoV-2 infection in
257 convalescent individuals. *bioRxiv* 10.1101/2020.05.13.092619 (2020).
- 258 23. Y. Wu *et al.*, A noncompeting pair of human neutralizing antibodies block COVID-
259 19 virus binding to its receptor ACE2. *Science* 10.1126/science.abc2241 (2020).

- 260 24. X. Chi *et al.*, A potent neutralizing human antibody reveals the N-terminal domain
261 of the Spike protein of SARS-CoV-2 as a site of vulnerability. *bioRxiv*
262 10.1101/2020.05.08.083964 (2020).
- 263 25. E. Seydoux *et al.*, Characterization of neutralizing antibodies from a SARS-CoV-
264 2 infected individual. *bioRxiv* 10.1101/2020.05.12.091298 (2020).
- 265 26. R. Shi *et al.*, A human neutralizing antibody targets the receptor binding site of
266 SARS-CoV-2. *Nature* 10.1038/s41586-020-2381-y (2020).
- 267 27. T. F. Rogers *et al.*, Rapid isolation of potent SARS-CoV-2 neutralizing antibodies
268 and protection in a small animal model. *bioRxiv* 10.1101/2020.05.11.088674
269 (2020).
- 270 28. C. O. Barnes *et al.*, Structures of human antibodies bound to SARS-CoV-2 spike
271 reveal common epitopes and recurrent features of antibodies. *bioRxiv*
272 10.1101/2020.05.28.121533 (2020).
- 273 29. S. D. Boyd *et al.*, Individual variation in the germline Ig gene repertoire inferred
274 from variable region gene rearrangements. *J Immunol* **184**, 6986-6992 (2010).
- 275 30. B. Briney, A. Inderbitzin, C. Joyce, D. R. Burton, Commonality despite
276 exceptional diversity in the baseline human antibody repertoire. *Nature* **566**, 393-
277 397 (2019).
- 278 31. J. Ye, N. Ma, T. L. Madden, J. M. Ostell, IgBLAST: an immunoglobulin variable
279 domain sequence analysis tool. *Nucleic Acids Res* **41**, W34-40 (2013).
- 280 32. The amino-acid sequences of IGHV3-53 and IGHV3-66 germline genes only
281 differ by one amino acid at residue 12. Specifically, IGHV3-53 contains Ile12,
282 whereas IGHV3-66 contains Val12.
- 283 33. M. Zemlin *et al.*, Expressed murine and human CDR-H3 intervals of equal length
284 exhibit distinct repertoires that differ in their amino acid composition and
285 predicted range of structures. *J Mol Biol* **334**, 733-749 (2003).
- 286 34. L. Yu, Y. Guan, Immunologic basis for long HCDR3s in broadly neutralizing
287 antibodies against HIV-1. *Front Immunol* **5**, 250 (2014).
- 288 35. J. G. Jardine *et al.*, Priming a broadly neutralizing antibody response to HIV-1
289 using a germline-targeting immunogen. *Science* **349**, 156-161 (2015).
- 290 36. D. R. Burton, L. M. Walker, Rational vaccine design in the time of COVID-19. *Cell*
291 *Host Microbe* **27**, 695-698 (2020).
- 292 37. R. K. Abbott, S. Crotty, Factors in B cell competition and immunodominance.
293 *Immunol Rev* 10.1111/imr.12861 (2020).
- 294 38. M. J. P. van Dongen *et al.*, A small-molecule fusion inhibitor of influenza virus is
295 orally active in mice. *Science* **363**, eaar6221 (2019).

296 39. E. Krissinel, K. Henrick, Inference of macromolecular assemblies from crystalline
297 state. *J Mol Biol* **372**, 774-797 (2007).
298

299 **ACKNOWLEDGEMENTS**

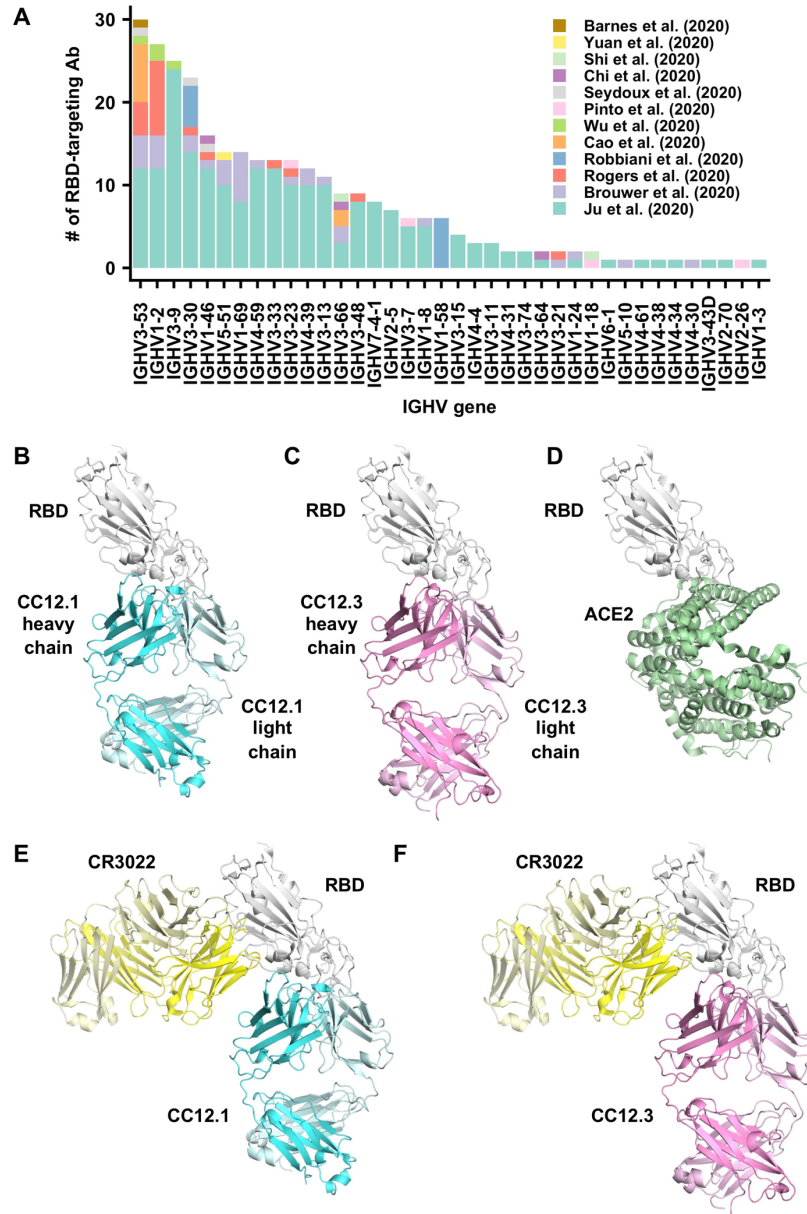
300 We thank Robyn Stanfield for assistance in data collection and Bryan Briney for naïve
301 antibody germline analysis. We are grateful to the staff of Stanford Synchrotron
302 Radiation Laboratory (SSRL) Beamline 12-1 for assistance. This work was supported by
303 NIH K99 AI139445 (N.C.W.), the Bill and Melinda Gates Foundation OPP1170236
304 (I.A.W. and D.R.B.), NIH CHAVD (UM1 AI44462 to I.A.W., D.S. and D.R.B.), and the
305 IAVI Neutralizing Antibody Center. Use of the SSRL, SLAC National Accelerator
306 Laboratory, is supported by the U.S. Department of Energy, Office of Science, Office of
307 Basic Energy Sciences under Contract No. DE-AC02-76SF00515. The SSRL Structural
308 Molecular Biology Program is supported by the DOE Office of Biological and
309 Environmental Research, and by the National Institutes of Health, National Institute of
310 General Medical Sciences (including P41GM103393).

311

312 **AUTHOR CONTRIBUTIONS**

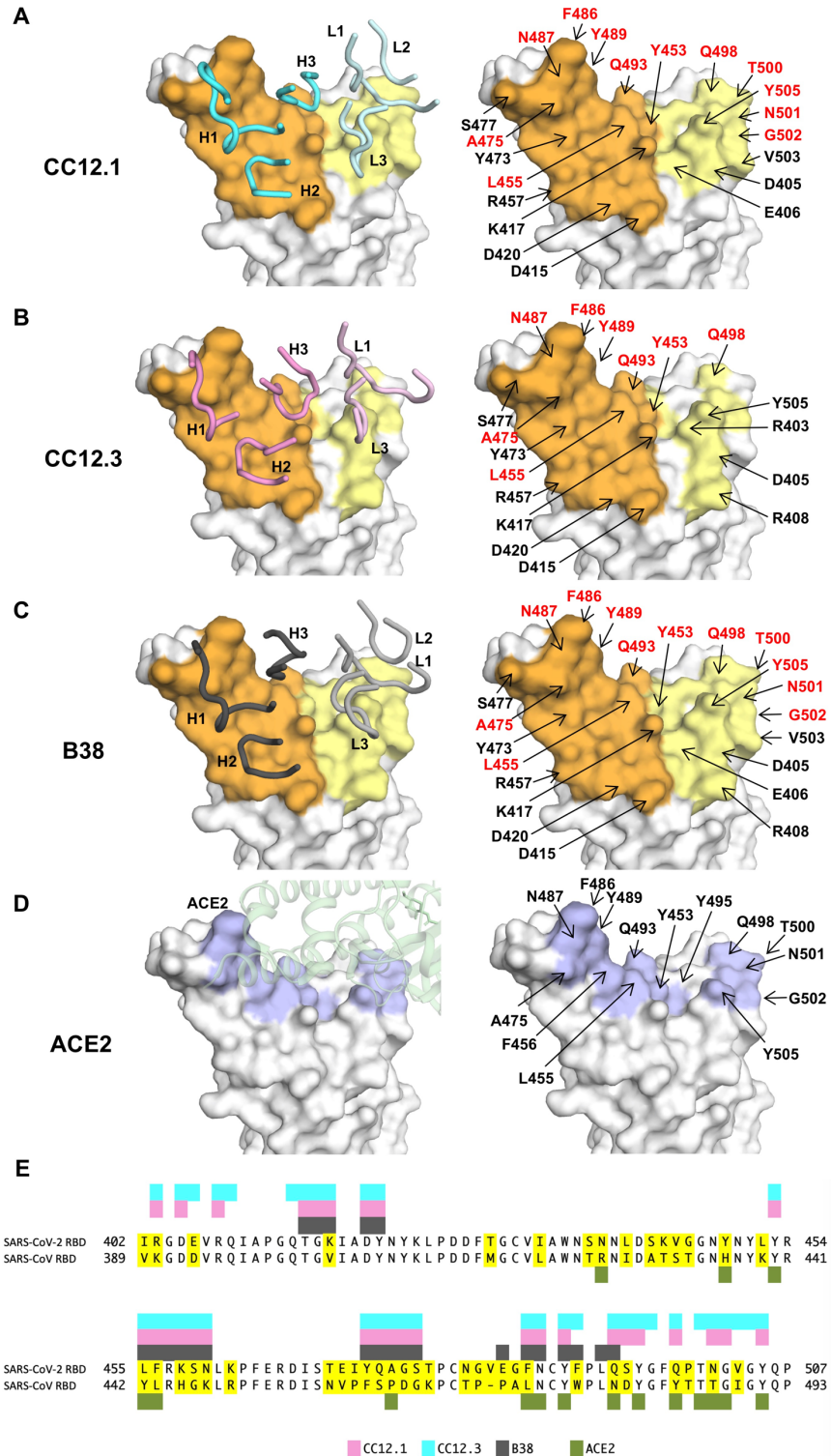
313 M.Y., H.L., N.C.W., F.Z., D.H., T.F.R., E.L., D.S, J.G.J., D.R.B. and I.A.W. conceived
314 and designed the study. M.Y., H.L., N.C.W., C.C.D.L., W.Y. and Y.H. expressed and
315 purified the proteins. M.Y. and C.C.D.L. performed biolayer interferometry binding
316 assays. M.Y., H.L., N.C.W., X.Z. and H.T. performed the crystallization and X-ray data
317 collection. M.Y. and X.Z. determined and refined the X-ray structures. M.Y., H.L.,
318 N.C.W., C.C.D.L. and X.Z. analyzed the data. M.Y., H.L., N.C.W. and I.A.W. wrote the
319 paper and all authors reviewed and/or edited the paper.

320



321

322 **Figure 1. Structures of two IGHV3-53 antibodies. (A)** The distribution of IGHV gene
 323 usage is shown for a total of 294 RBD-targeting antibodies (17-28). **(B-F)** Crystal
 324 structures of **(B)** CC12.1 in complex with SARS-CoV-2 RBD, **(C)** CC12.3 with SARS-
 325 CoV-2 RBD, **(D)** human ACE2 with SARS-CoV-2 RBD (PDB 6M0J) (12), **(E)** SARS-
 326 CoV-2 RBD with CC12.1 and CR3022, and **(F)** SARS-CoV-2 RBD with CC12.3 and
 327 CR3022.

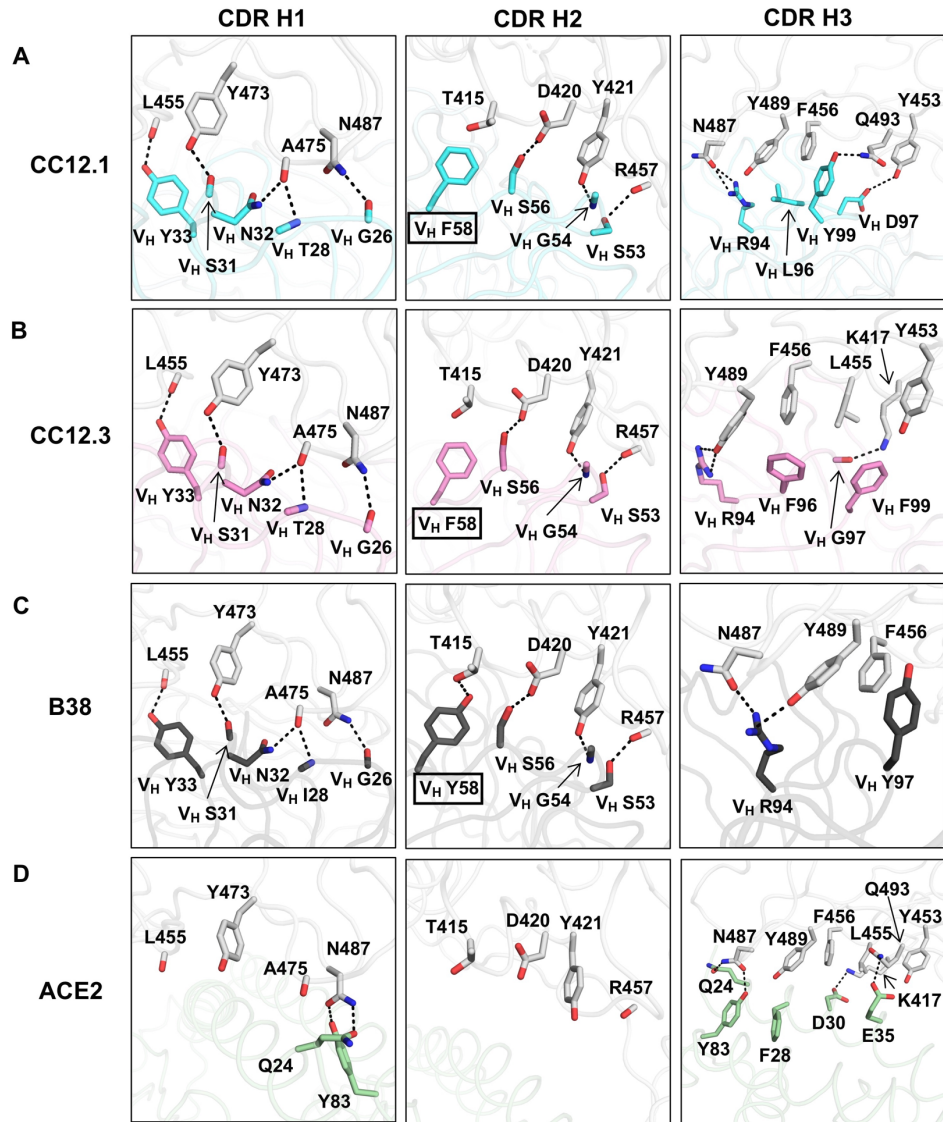


328

329 **Figure 2. Epitopes of IGHV35-3 antibodies. (A-C) Epitopes of (A) CC12.1, (B)**

330 **CC12.3, and (C) B38 (PDB 7BZ5) (23). Epitope residues contacting the heavy chain are**

331 in orange and the light chain are in yellow. On the left panels, CDR loops are labeled. On
332 the right panels, epitope residues are labeled. For clarity, only representative epitope
333 residues are labeled. Epitope residues that are also involved in ACE2 binding are in red.
334 **(D)** ACE2-binding residues are shown in blue. On the left panel, ACE2 is shown in green
335 with in semi-transparent representation. On the right panel, ACE2-binding residues are
336 labeled. A total of 16 residues are used for ACE2 binding (12), but only 13 are labeled
337 here since the other three are at the back of the structure in this view and do not interact
338 with the antibodies of interest. **(E)** Epitope residues for CC12.1, CC12.3, and B38 were
339 identified by PISA (39) and annotated on the SARS-CoV-2 RBD sequence, which is
340 aligned to the SARS-CoV RBD sequence with non-conserved residues highlighted. The
341 16 ACE2-binding residues were as described previously (12).
342



343

344 **Figure 3. Interactions between the RBD and the heavy chain CDR loops. (A-C)**

345 Highly similar interaction modes between SARS-CoV-2 RBD and the antibody CDR H1

346 and H2 loops, but not the H3 loop are observed for in **(A)** CC12.1, **(B)** CC12.3, and **(C)**

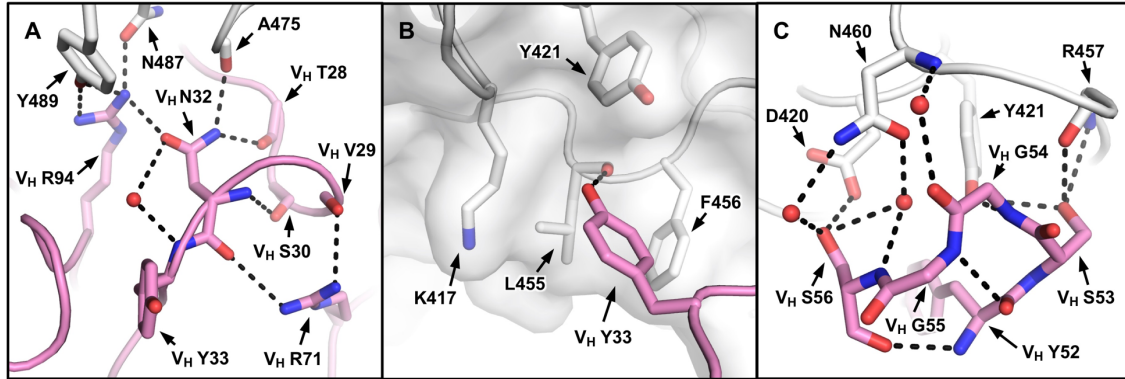
347 B38 (PDB 7BZ5) (23). The RBD is in white and antibody residues are in cyan, pink, and

348 dark gray, respectively. Oxygen atoms are in red, and nitrogen atoms in blue. Hydrogen

349 bonds are represented by dashed lines. **(D)** The interaction between ACE2 (green) and

350 residues of the RBD (PDB 6M0J) (12) that are shown in **(A-C)**.

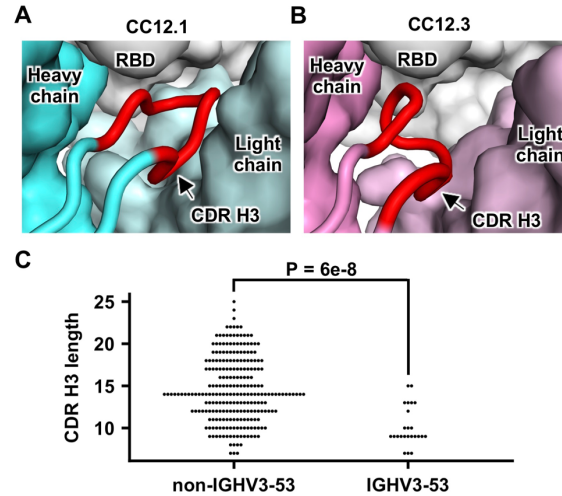
351



352

353 **Figure 4. Two IGHV3-53 germline-encoded motifs. (A)** The extensive hydrogen bond
354 network that involves V_H N32 of the NY motif in CDR H1 is illustrated. **(B)** The
355 hydrophobic cage interaction between the RBD and V_H Y33 of the NY motif in CDR H1 is
356 shown. **(C)** The hydrogen bond network that involves the SGGS motif in CDR H2 is
357 highlighted. CC12.3 is shown because its structure is at higher resolution than CC12.1.

358



359

360 **Figure 5. Constraints on CDR H3 length.** (A) The heavy and light chains of CC12.1
361 (cyan), as well as the RBD (white) are shown in surface representation, with CDR H3
362 (red) highlighted in cartoon representation. (B) Same as panel A, except that CC12.3
363 (pink) is shown. (C) The lengths of CDR H3 in RBD-targeting antibodies that were
364 previously isolated (17-28) are analyzed. The distribution of CDR H3 lengths in RBD-
365 targeting IGHV3-53 antibodies and those in non-IGHV3-53-encoded antibodies are
366 compared. A Mann-Whitney U test was performed to compute the p-value.

367

368 **MATERIALS AND METHODS**

369 **Expression and purification of SARS-CoV-2 RBD**

370 The receptor-binding domain (RBD) (residues 319-541) of the SARS-CoV-2 spike (S)
371 protein (GenBank: QHD43416.1) was cloned into a customized pFastBac vector (40),
372 and fused with an N-terminal gp67 signal peptide and C-terminal His₆ tag (17). A
373 recombinant bacmid DNA was generated using the Bac-to-Bac system (Life
374 Technologies). Baculovirus was generated by transfecting purified bacmid DNA into Sf9
375 cells using FuGENE HD (Promega), and subsequently used to infect suspension
376 cultures of High Five cells (Life Technologies) at an MOI of 5 to 10. Infected High Five
377 cells were incubated at 28 °C with shaking at 110 r.p.m. for 72 h for protein expression.
378 The supernatant was then concentrated using a 10 kDa MW cutoff Centrimate cassette
379 (Pall Corporation). The RBD protein was purified by Ni-NTA, followed by size exclusion
380 chromatography, and buffer exchanged into 20 mM Tris-HCl pH 7.4 and 150 mM NaCl.

381

382 **Expression and purification of Fabs**

383 For CC12.1 and CC12.3, the heavy and light chains were cloned into pHCMV3. The
384 plasmids were transiently co-transfected into ExpiCHO cells at a ratio of 2:1 (HC:LC)
385 using ExpiFectamine™ CHO Reagent (Thermo Fisher Scientific) according to the
386 manufacturer's instructions. The supernatant was collected at 10 days post-transfection.
387 The Fabs were purified with a CaptureSelect™ CH1-XL Affinity Matrix (Thermo Fisher
388 Scientific) followed by size exclusion chromatography. CR3022 was expressed and
389 purified as described previously (17).

390

391 **Expression and purification of ACE2**

392 The N-terminal peptidase domain of human ACE2 (residues 19 to 615, GenBank:
393 BAB40370.1) was cloned into pHCMV3 vector, and fused with a C-terminal Fc tag. The

394 plasmids were transiently transfected into Expi293F cells using ExpiFectamine™ 293
395 Reagent (Thermo Fisher Scientific) according to the manufacturer's instructions. The
396 supernatant was collected at 7 days post-transfection. Fc-tagged ACE2 protein was then
397 purified with a Protein A column (GE Healthcare) followed by size exclusion
398 chromatography.

399

400 **Crystallization and structural determination**

401 CC12.1/RBD, CC12.3/RBD, CC12.1/CR3022/RBD, and CC12.3/CR3022/RBD
402 complexes were formed by mixing each of the protein components at an equimolar ratio
403 and incubated overnight at 4°C. Each complex was adjusted to 13 mg/ml and screened
404 for crystallization using the 384 conditions of the JCSG Core Suite (Qiagen) and ProPlex
405 screen (Molecular Dimensions) on either our custom-designed robotic CrystalMation
406 system (Rigaku) or an Oryx8 (Douglas Instruments) at Scripps Research. Crystallization
407 trials were set-up by the vapor diffusion method in sitting drops containing 0.1 µl of
408 protein and 0.1 µl of reservoir solution. Diffraction-quality crystals were obtained in the
409 following conditions:

410

411 CC12.1/RBD complex (13 mg/ml): 0.1M sodium citrate pH 5.5 and 15% (w/v)
412 polyethylene glycol 6000 at 20°C

413 CC12.3/RBD complex (13 mg/mL): 0.1 M sodium phosphate pH 6.5 and 12% (w/v)
414 polyethylene glycol 8000 at 20°C

415 CC12.1/RBD/CR3022 complex (13 mg/mL): 20% PEG-3000, 0.2 M sodium chloride, 0.1
416 M HEPES pH 7.5 at 20°C

417 CC12.3/RBD/CR3022 complex (13 mg/mL): 0.1M Tris pH 8, 15% ethylene glycol, 1M
418 lithium chloride, 10% PEG 6000 at 20°C

419

420 Of note, these four complexes crystallized in a broad range of pHs. All crystals appeared
421 on day 3 and were harvested on day 7. Before flash cooling in liquid nitrogen for X-ray
422 diffraction studies, crystals were equilibrated in reservoir solution supplemented the
423 following cryoprotectants:

424

425 CC12.1/RBD complex: 20% glycerol

426 CC12.3/RBD complex: 20% glycerol

427 CC12.1/RBD/CR3022 complex: 10% ethylene glycol

428 CC12.3/RBD/CR3022 complex: none were required

429

430 Diffraction data were collected at cryogenic temperature (100 K) at Stanford Synchrotron
431 Radiation Lightsource (SSRL) on the new Scripps/Stanford beamline 12-1 with a beam
432 wavelength of 0.97946 Å, and processed with HKL2000 (41). Structures were solved by
433 molecular replacement using PHASER (42) with PDB 6YLA (43), 4TSA, and 4ZD3 (44).
434 Iterative model building and refinement were carried out in COOT (45) and PHENIX (46),
435 respectively. Epitope and paratope residues, as well as their interactions, were identified
436 by accessing PISA at the European Bioinformatics Institute
437 (http://www.ebi.ac.uk/pdbe/prot_int/pistart.html) (39).

438

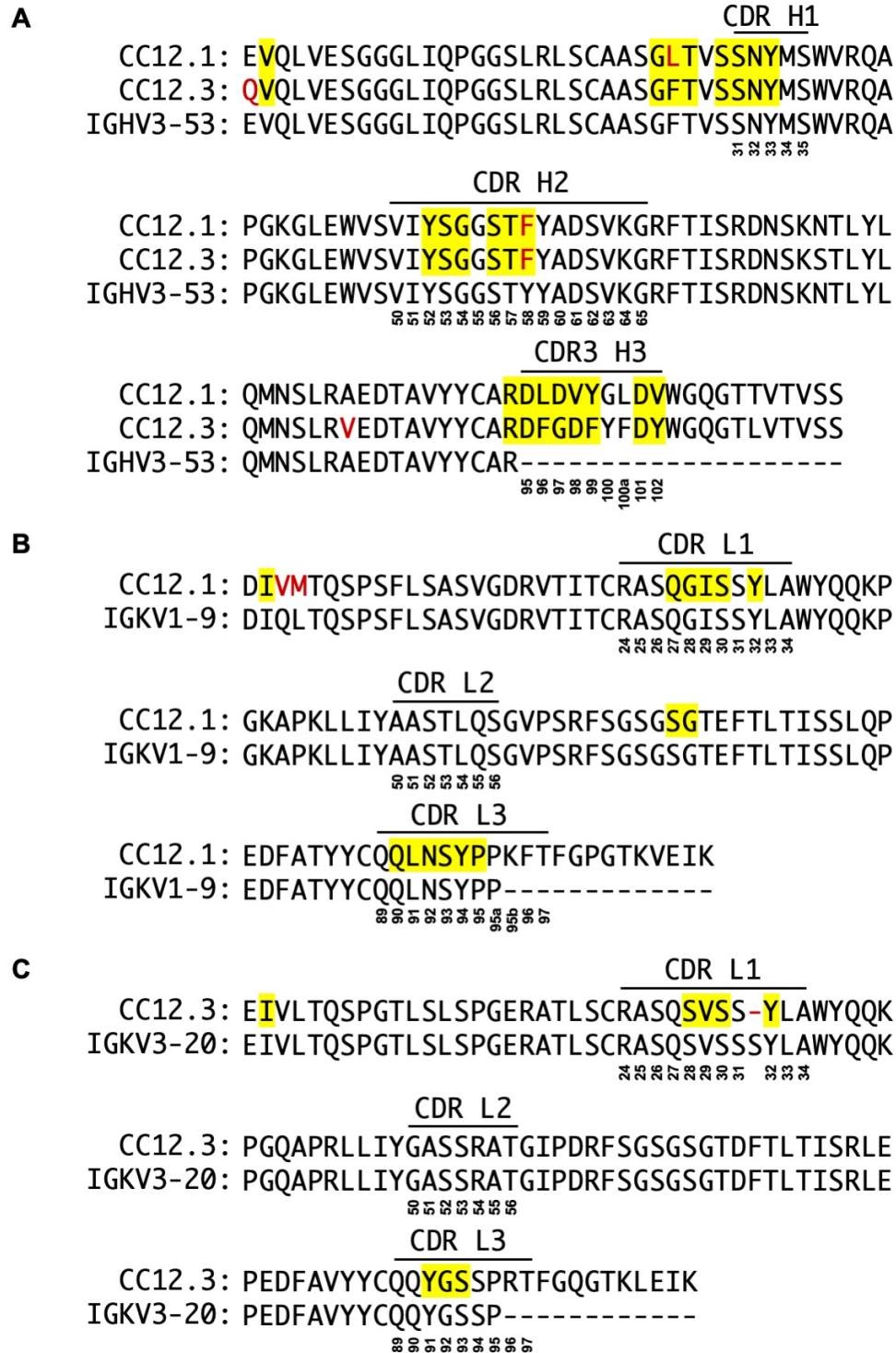
439 **Biolayer interferometry binding assay**

440 Antibody binding and competition assays were performed by biolayer interferometry
441 (BLI) using an Octet Red instrument (FortéBio) as described previously (47), with Ni-
442 NTA biosensors. There were five steps in the assay: 1) baseline: 60 s with 1x kinetics
443 buffer; 2) loading: 180 s with 20 µg/mL of 6x His-tagged SARS-CoV-2 RBD proteins; 3)
444 baseline: 135 s with 1x kinetics buffer; 4) association: 240 s with serial diluted
445 concentrations of CC12.1 Fab or CC12.3 Fab; and 5) dissociation: 240 s with 1x kinetics

446 buffer. For K_d estimation, a 1:1 binding model was used.

447

448 For competition assays, CC12.1 Fab, CC12.3 Fab, CR3022 Fab, and human ACE2-Fc
449 were all diluted to 250 nM. Ni-NTA biosensors were used. In brief, the assay has five
450 steps: 1) baseline: 60 s with 1x kinetics buffer; 2) loading: 120 s with 20 $\mu\text{g/mL}$, 6x His-
451 tagged SARS-CoV-2 RBD proteins; 3) baseline: 120 s with 1x kinetics buffer; 4) first
452 association: 180 s with CC12.1 Fab, CC12.3 Fab or CR3022 Fab; and 5) second
453 association: 180 s with CC12.1 Fab, CC12.3 Fab, CR3022 Fab, or human ACE2-Fc or
454 disassociation with 1x kinetics buffer for each first association.

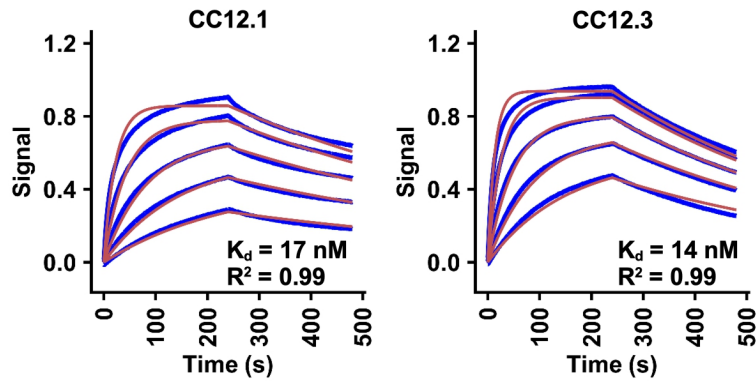


455

456 **Fig. S1. Comparison of CC12.1 and CC12.3 sequence to the IGHV3-53 germline**

457 **sequence. (A)** Alignment of the heavy chain variable domain sequences of CC12.1 and

458 CC12.3 with the germline IGHV3-53 sequence **(B)** Alignment of the light-chain variable
459 domain sequence of CC12.1 with the germline IGKV1-9 sequence. **(C)** Alignment of the
460 light-chain variable domain sequence of CC12.3 with the germline IGKV3-20 sequence.
461 The regions that correspond to CDR H1, H2, H3, L1, L2, and L3 are indicated. Residues
462 that differ from the germline are highlighted in red. Residue positions in the CDRs are
463 labeled according to the Kabat numbering scheme. Residues that interact with the RBD
464 are highlighted in yellow.
465



466

467 **Fig. S2. Sensorgrams for binding of CC12.1 and CC12.3 Fabs to SARS-CoV-2 RBD.**

468 Binding kinetics of CC12.1 and CC12.3 Fab against SARS-CoV-2 RBD were measured

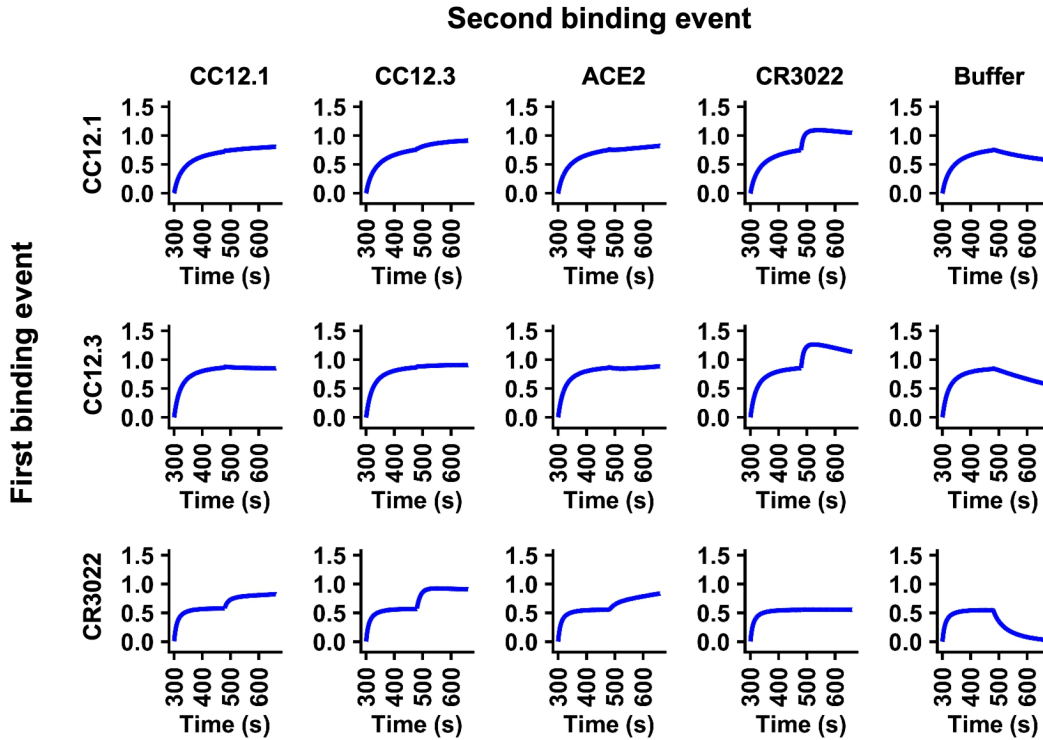
469 by biolayer interferometry (BLI). Y-axis represents the response. Blue lines represent the

470 response curves and red lines represent the 1:1 binding model. Binding kinetics were

471 measured for five concentrations of Fab at 2-fold dilution ranging from 500 nM to 31.25

472 nM. The K_d and R^2 of the fitting are indicated.

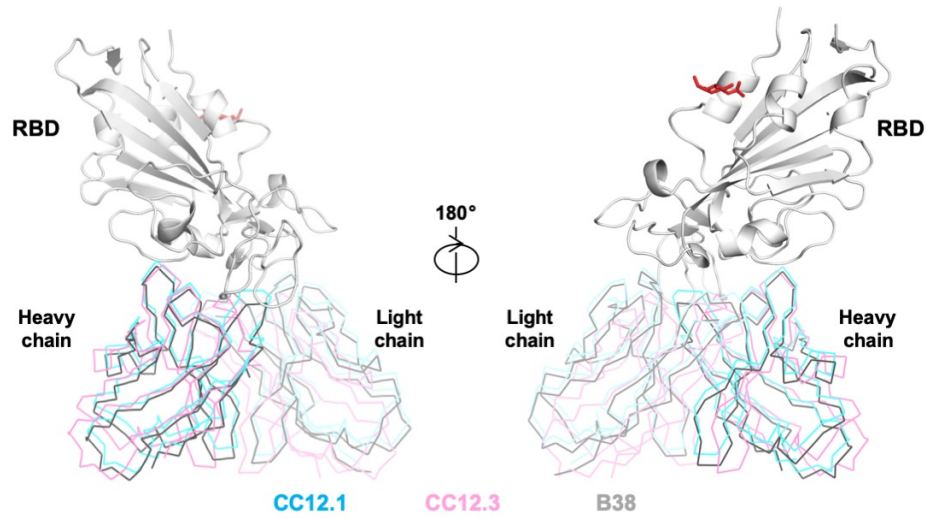
473



474

475 **Fig. S3. Competition assay between different Fabs and ACE2.** Competition between
476 CC12.1, CC12.3, CR3022, and ACE2 was measured by biolayer interferometry (BLI). Y-
477 axis represents the response. The biosensor was first loaded with SARS-CoV-2 RBD,
478 followed by two binding events: 1) CC12.1, CC12.3, or CR3022, and 2) CC12.1,
479 CC12.3, or CR3022, ACE2, and buffer (negative control). A period of 180 s was used for
480 each of the binding events. A further increase in signal during the second binding event
481 (starting at 480 s time point) indicates lack of competition with the first ligand.

482



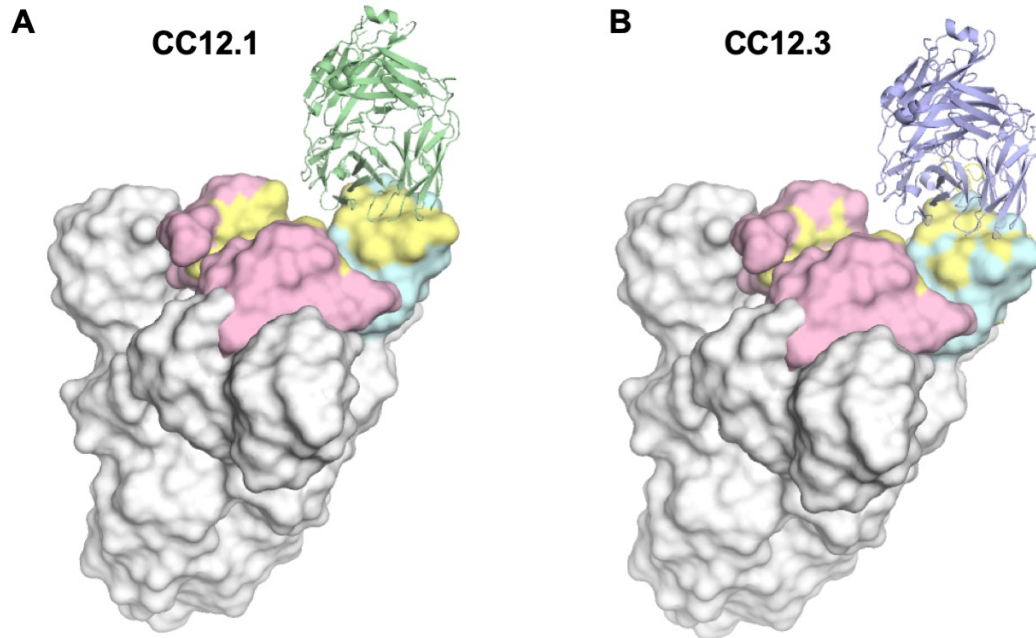
483

484 **Fig. S4. Structural comparison of the binding modes among IGHV3-53 antibodies.**

485 The binding modes of CC12.1 (cyan), CC12.3 (pink), and B38 (gray) to SARS-CoV-2

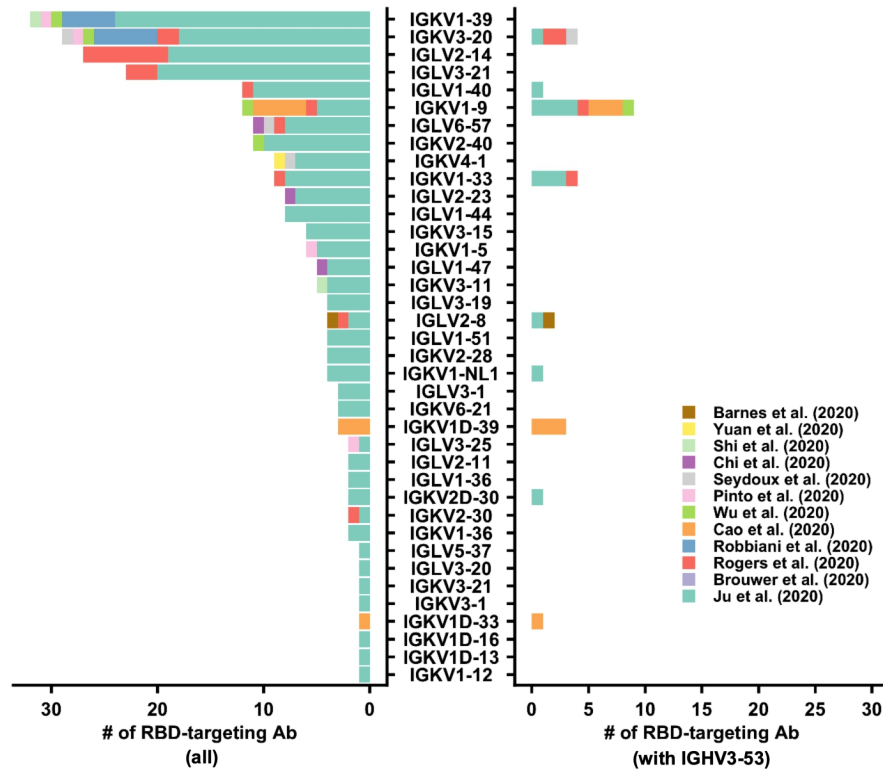
486 (white) are compared. B38 in complex with SARS-CoV-2 RBD was from PDB 7BZ5 (23).

487 The N-glycan observed at SARS-CoV-2 RBD N343 is shown in red.



488

489 **Fig. S5. Modelling the binding of CC12.1 and CC12.3 on the homotrimeric spike (S)**
490 **protein.** The S trimer is shown with one RBD in the up conformation (cyan) and two
491 RBDs in the down conformation (pink). The CC12.1 and CC12.3 epitopes are shown in
492 yellow. **(A)** Model of the binding of CC12.1 (green) to the RBD up conformation. **(B)**
493 Model of the binding of CC12.3 (blue). PDB 6VSB is used in the modeling (48). The
494 complete epitopes of CC12.1 and CC12.3 are accessible only when the RBD is in the
495 up, but not the down, conformation.



496

497 **Fig. S6. Light-chain germline gene use in SARS-CoV-2 RBD-targeting antibodies.**

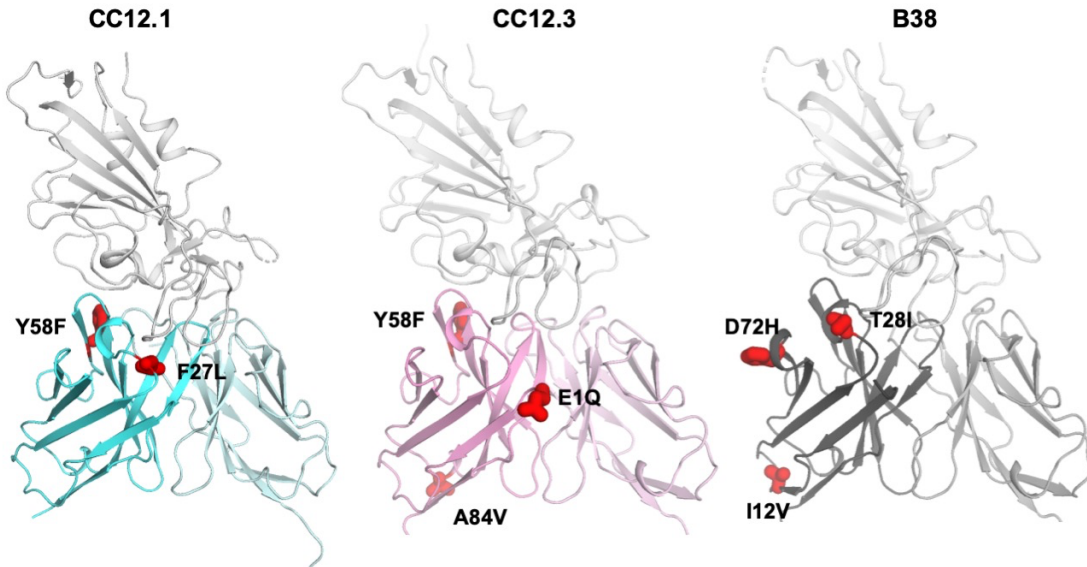
498 The distribution of light-chain germline gene use of SARS-CoV-2 RBD-targeting

499 antibodies that have been recently isolated (17-28) is shown on the left. The distribution

500 of light-chain germline gene use in antibodies that target SARS-CoV-2 RBD to the

501 subset of antibodies that pair with IGHV3-53 is shown on the right.

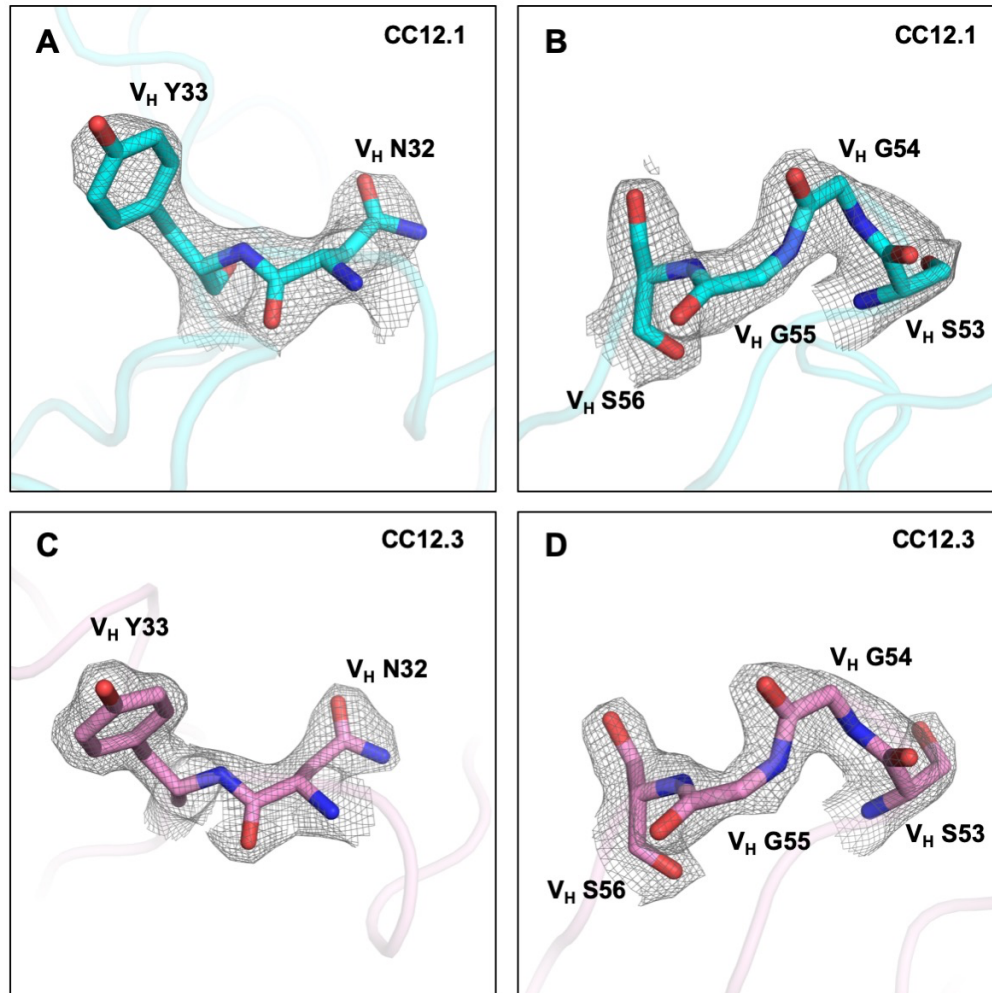
502



503

504 **Fig. S7. Locations of heavy chain somatic mutations.** Somatic mutations on the
505 heavy chains of CC12.1, CC12.3, and B38 are labeled and shown in red on the
506 structure. Somatic mutations contribute minimally to the antibody binding interactions.

507



508

509 **Fig. S8. Electron density maps for IGHV3-53-encoded paratope regions of CC12.1**

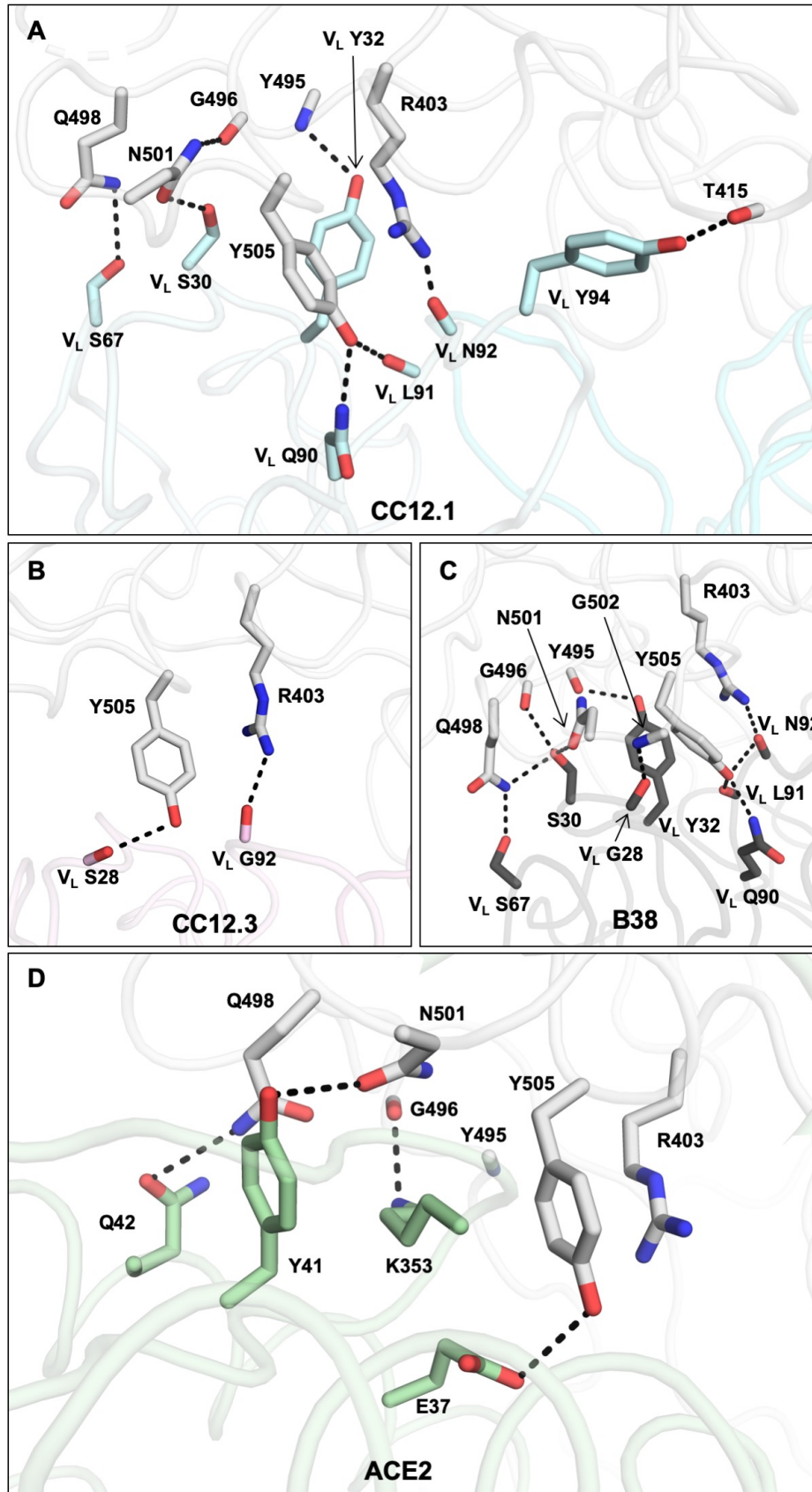
510 **and CC12.3. (A-B) Final 2Fo-Fc electron density maps for the IGHV3-53-encoded**

511 **paratope regions around V_H N32 and Y33 (CDR H1) and V_H S53 to S56 (CDR H2) of**

512 **CC12.1, both contoured at 1.2 σ . (C-D) Final 2Fo-Fc electron density maps for IGHV3-**

513 **53-encoded paratope regions around V_H N32 and Y33 and V_H S53 to S56 of CC12.3,**

514 **both contoured at 1.8 σ .**



516 **Fig. S9. Interactions between the light chain and the RBD. (A-C)** Representative
517 interactions between SARS-CoV-2 RBD and the light chain in **(A)** CC12.1, **(B)** CC12.3,
518 and **(C)** B38 (PDB 7BZ5) (23) are shown. RBD is in white. Oxygen atoms are in red.
519 Nitrogen atoms are in blue. Hydrogen bonds are represented by dashed lines. The light
520 chains from both CC12.1 and B38 form an extensive hydrogen bond network with the
521 RBD, whereas the interaction between the light chain of CC12.3 and the RBD is
522 minimal. **(D)** The interaction between ACE2 and RBD residues (PDB 6M0J) (12) that are
523 shown in **(A-C)**. None of the interactions between the light chain and RBD mimic those
524 between ACE2 and RBD.
525

526

Table S1. X-ray data collection and refinement statistics

Data collection				
	CC12.1 + RBD	CC12.3 + RBD	CC12.1 + RBD + CR3022	CC12.3 + RBD + CR3022
Beamline	SSRL 12-1	SSRL 12-1	SSRL 12-1	SSRL 12-1
Wavelength (Å)	0.97946	0.97946	0.97946	0.97946
Space group	P 1 2 ₁ 1	P 1 2 ₁ 1	P 4 ₁ 2 ₁ 2	P 4 ₁ 2 ₁ 2
Unit cell parameters				
a, b, c (Å)	80.7, 143.5, 81.5	56.1, 105.6, 165.9	109.8, 109.8, 235.7	110.9, 110.9, 228.5
α, β, γ (°)	90, 118.7, 90	90, 92.8, 90	90, 90, 90	90, 90, 90
Resolution (Å) ^a	50.0-3.20 (3.27-3.20)	50.0-2.33 (2.38-2.33)	50.0-2.70 (2.76-2.70)	50-2.90 (2.97-2.90)
Unique reflections ^a	25,802 (1,234)	78,783 (7,298)	40,463 (3,945)	32,870 (3,160)
Redundancy ^a	1.5 (1.3)	2.4 (2.1)	5.7 (3.7)	13.6 (12.6)
Completeness (%) ^a	88.3 (42.5)	97.6 (98.8)	99.9 (100.0)	99.9 (100.0)
<I/σ _I > ^a	7.4 (1.1)	10.2 (1.0)	16.2 (1.2)	20.1 (1.1)
R _{sym} ^b (%) ^a	16.3 (57.4)	14.3 (95.4)	16.7 (>100)	12.9 (>100)
R _{pim} ^b (%) ^a	11.6 (45.0)	7.0 (50.8)	5.3 (41.6)	3.6 (46.7)
CC _{1/2} ^c (%) ^a	96.6 (61.7)	98.7 (50.8)	100.6 (60.3)	99.6 (65.2)
Refinement statistics				
Resolution (Å)	39.7-3.11	41.7-2.34	41.6-2.70	42.3-2.88
Reflections (work)	25,776	78,774	40,462	32,868
Reflections (test)	1,289	3,800	1,963	1,654
R _{cryst} ^d / R _{free} ^e (%)	21.3/26.7	18.4/21.9	17.7/22.4	21.9 (25.9)
No. of atoms				
Macromolecules	9,580	9,632	8,148	8,152
Glycans	28	28	28	39
Solvent	0	649	170	0
Average B-value (Å ²)				
Macromolecules	70	39	49	76
Glycans	98	65	72	94
Solvent	-	41	43	-
Wilson B-value (Å ²)	70	35	53	80
RMSD from ideal geometry				
Bond length (Å)	0.003	0.004	0.003	0.003
Bond angle (°)	0.68	0.78	0.70	0.78
Ramachandran statistics (%)				
Favored	94.7	96.5	96.8	95.9
Outliers	0.16	0.24	0.10	0.19
PDB code				
	6XC2	6XC4	6XC3	6XC7

527
528
529
530
531
532
533

^a Numbers in parentheses refer to the highest resolution shell.

^b $R_{sym} = \sum_{hkl} \sum_i |I_{hkl,i} - \langle I_{hkl} \rangle| / \sum_{hkl} \sum_i I_{hkl,i}$ and $R_{pim} = \sum_{hkl} (1/(n-1))^{1/2} \sum_i |I_{hkl,i} - \langle I_{hkl} \rangle| / \sum_{hkl} \sum_i I_{hkl,i}$, where $I_{hkl,i}$ is the scaled intensity of the i^{th} measurement of reflection h, k, l , $\langle I_{hkl} \rangle$ is the average intensity for that reflection, and n is the redundancy.

^c $CC_{1/2}$ = Pearson correlation coefficient between two random half datasets.

^d $R_{cryst} = \sum_{hkl} |F_o - F_c| / \sum_{hkl} |F_o| \times 100$, where F_o and F_c are the observed and calculated structure factors, respectively.

^e R_{free} was calculated as for R_{cryst} , but on a test set comprising 5% of the data excluded from refinement.

534

Table S2. A list of previously reported SARS-CoV-2 RBD-targeting antibodies.

Antibody name	Heavy chain	Light chain	CDR H3 length	Reference
S124	IGHV2-26	IGKV1-39	15	Pinto et al. (2020)
S309	IGHV1-18	IGKV3-20	18	Pinto et al. (2020)
S315	IGHV3-7	IGLV3-25	15	Pinto et al. (2020)
S303	IGHV3-23	IGKV1-5	15	Pinto et al. (2020)
P1A-1C7	IGHV1-46	IGKV1-39	13	Ju et al. (2020)
P1A-1C10	IGHV1-69	IGKV1-5	14	Ju et al. (2020)
P1A-1C11	IGHV1-69	IGKV1-5	14	Ju et al. (2020)
P1A-1C6	IGHV3-13	IGKV1-39	17	Ju et al. (2020)
P1A-1D3	IGHV3-13	IGKV1-39	16	Ju et al. (2020)
P1A-1C2	IGHV3-23	IGKV1-36	8	Ju et al. (2020)
P1A-1B2	IGHV3-30	IGLV2-14	10	Ju et al. (2020)
P1A-1C1	IGHV3-33	IGKV1D-13	15	Ju et al. (2020)
P1A-1D1	IGHV3-53	IGLV2-8	10	Ju et al. (2020)
P1A-1D5	IGHV3-53	IGKV1-33	13	Ju et al. (2020)
P1A-1D6	IGHV3-53	IGKV1-33	13	Ju et al. (2020)
P2A-1A10	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2B-1A4	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2B-1B2	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2B-2G1	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2B-2G12	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2C-1A10	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2C-1B10	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2C-1D6	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2C-1D12	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2C-1F10	IGHV1-2	IGKV2-40	17	Ju et al. (2020)
P2B-1F8	IGHV1-2	IGKV3-20	12	Ju et al. (2020)
P2B-2G9	IGHV1-2	IGKV3-20	12	Ju et al. (2020)
P2B-1C3	IGHV1-46	IGKV1-5	13	Ju et al. (2020)
P2C-1C10	IGHV1-69	IGKV3-11	9	Ju et al. (2020)
P2B-2G10	IGHV1-69	IGKV1-39	9	Ju et al. (2020)
P2B-1F11	IGHV1-69	IGLV1-40	15	Ju et al. (2020)
P2B-1D9	IGHV2-5	IGLV1-47	14	Ju et al. (2020)
P2B-1E2	IGHV2-5	IGKV1-5	10	Ju et al. (2020)
P2B-1E4	IGHV2-5	IGLV2-14	9	Ju et al. (2020)
P2B-1F4	IGHV2-70	IGLV1-44	12	Ju et al. (2020)
P2C-1A3	IGHV3-11	IGKV1-9	10	Ju et al. (2020)
P2B-1D6	IGHV3-15	IGLV1-44	22	Ju et al. (2020)
P2C-1B12	IGHV3-15	IGLV6-57	11	Ju et al. (2020)
P2B-1F9	IGHV3-15	IGKV1-NL1	14	Ju et al. (2020)
P2C-1D5	IGHV3-23	IGLV3-21	12	Ju et al. (2020)
P2B-1B4	IGHV3-30	IGKV1-39	20	Ju et al. (2020)
P2B-1F2	IGHV3-33	IGLV2-11	9	Ju et al. (2020)
P2B-2G4	IGHV3-33	IGLV2-11	9	Ju et al. (2020)
P2C-1C8	IGHV3-33	IGKV2D-30	11	Ju et al. (2020)
P2A-1B3	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-1B11	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-1B12	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-1C4	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-1E11	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-2H7	IGHV3-48	IGKV3-20	14	Ju et al. (2020)

P2B-1G12	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2C-1E5	IGHV3-48	IGKV3-20	14	Ju et al. (2020)
P2B-1A10	IGHV3-53	IGKV1-33	13	Ju et al. (2020)
P2B-1F5	IGHV3-53	IGKV1-NL1	12	Ju et al. (2020)
P2C-1D7	IGHV3-53	IGKV2D-30	10	Ju et al. (2020)
P2B-1G1	IGHV3-66	IGKV3-20	9	Ju et al. (2020)
P2C-1E1	IGHV3-66	IGKV3-11	7	Ju et al. (2020)
P2C-1F11	IGHV3-66	IGKV3-20	9	Ju et al. (2020)
P2A-1A8	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2B-1B10	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2B-1C10	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2B-1D3	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2B-2H4	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2C-1A5	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2C-1A8	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2C-1B1	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2C-1C12	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2C-1A6	IGHV3-9	IGLV2-14	21	Ju et al. (2020)
P2A-1A9	IGHV3-9	IGLV1-40	15	Ju et al. (2020)
P2C-1A1	IGHV3-9	IGLV1-40	15	Ju et al. (2020)
P2B-2G11	IGHV3-9	IGLV1-40	15	Ju et al. (2020)
P2B-1E12	IGHV3-9	IGLV3-20	15	Ju et al. (2020)
P2B-2F6	IGHV4-38	IGLV2-8	18	Ju et al. (2020)
P2A-1B10	IGHV4-39	IGLV1-47	18	Ju et al. (2020)
P2B-1B9	IGHV4-39	IGKV1-NL1	7	Ju et al. (2020)
P2B-2F11	IGHV4-39	IGKV1-NL1	7	Ju et al. (2020)
P2B-1G8	IGHV4-39	IGKV1-5	9	Ju et al. (2020)
P2B-1A1	IGHV4-59	IGLV2-14	12	Ju et al. (2020)
P2B-1D11	IGHV4-59	IGLV3-25	20	Ju et al. (2020)
P2B-1F11	IGHV4-59	IGKV1-39	13	Ju et al. (2020)
P2C-1A7	IGHV5-51	IGLV3-1	15	Ju et al. (2020)
P2B-1A12	IGHV7-4-1	IGKV1-39	14	Ju et al. (2020)
P2B-1G5	IGHV7-4-1	IGLV3-21	10	Ju et al. (2020)
P3A-1F1	IGHV3-13	IGKV1-39	15	Ju et al. (2020)
P3A-1G8	IGHV3-64	IGLV1-44	17	Ju et al. (2020)
P4A-2A10	IGHV1-46	IGLV1-40	24	Ju et al. (2020)
P4B-1F6	IGHV1-69	IGLV2-23	13	Ju et al. (2020)
P4B-1E11	IGHV2-5	IGLV1-36	16	Ju et al. (2020)
P4A-2A2	IGHV3-23	IGLV1-51	12	Ju et al. (2020)
P4A-2A8	IGHV3-23	IGLV3-21	9	Ju et al. (2020)
P4A-2C1	IGHV3-23	IGKV2-28	14	Ju et al. (2020)
P4A-1H5	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4B-1G2	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4A-2B3	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4A-1H6	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4B-1G5	IGHV3-30	IGLV3-21	20	Ju et al. (2020)
P4A-2E10	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4B-1E3	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4A-2D9	IGHV3-30	IGKV1-39	19	Ju et al. (2020)
P4B-1F4	IGHV3-30	IGKV2-30	20	Ju et al. (2020)
P4B-1E7	IGHV3-43D	IGKV3-1	18	Ju et al. (2020)
P4B-1F10	IGHV3-7	IGKV3-21	11	Ju et al. (2020)
P4A-2D1	IGHV3-9	IGKV1-12	11	Ju et al. (2020)

P4A-2D2	IGHV4-39	IGKV3-20	14	Ju et al. (2020)
P4B-1E12	IGHV4-59	IGLV1-44	9	Ju et al. (2020)
P4A-2C12	IGHV5-51	IGLV1-44	13	Ju et al. (2020)
P8A-1A8	IGHV3-23	IGLV3-21	9	Ju et al. (2020)
P8A-1C6	IGHV3-30	IGKV1-33	18	Ju et al. (2020)
P8A-1A5	IGHV5-51	IGLV1-47	16	Ju et al. (2020)
P8A-1D5	IGHV6-1	IGKV3-20	14	Ju et al. (2020)
P5A-1A1	IGHV1-24	IGKV2-28	13	Ju et al. (2020)
P5A-1C8	IGHV1-46	IGKV1-33	20	Ju et al. (2020)
P5A-2D5	IGHV1-46	IGLV1-40	22	Ju et al. (2020)
P5A-2C8	IGHV1-46	IGLV2-23	13	Ju et al. (2020)
P5A-2E9	IGHV1-46	IGLV2-14	20	Ju et al. (2020)
P5A-3B8	IGHV1-46	IGLV2-23	14	Ju et al. (2020)
P5A-3A11	IGHV1-69	IGKV1-39	12	Ju et al. (2020)
P5A-3C10	IGHV1-69	IGLV6-57	20	Ju et al. (2020)
P5A-1A2	IGHV1-8	IGLV1-40	19	Ju et al. (2020)
P5A-1C11	IGHV1-8	IGLV3-21	15	Ju et al. (2020)
P5A-2F11	IGHV1-8	IGKV4-1	13	Ju et al. (2020)
P5A-3B9	IGHV1-8	IGKV1-36	13	Ju et al. (2020)
P5A-2C12	IGHV2-5	IGKV3-11	14	Ju et al. (2020)
P5A-3C12	IGHV2-5	IGKV4-1	17	Ju et al. (2020)
P5A-3C3	IGHV2-5	IGLV6-57	10	Ju et al. (2020)
P5A-3C1	IGHV3-11	IGLV3-21	11	Ju et al. (2020)
P5A-1C4	IGHV3-13	IGKV1-39	18	Ju et al. (2020)
P5A-2G8	IGHV3-13	IGKV1-39	11	Ju et al. (2020)
P5A-2D3	IGHV3-13	IGKV1-39	14	Ju et al. (2020)
P5A-3B10	IGHV3-13	IGKV1-39	14	Ju et al. (2020)
P5A-1D8	IGHV3-13	IGLV3-19	16	Ju et al. (2020)
P5A-2G10	IGHV3-13	IGLV3-19	16	Ju et al. (2020)
P5A-2H6	IGHV3-15	IGLV3-19	16	Ju et al. (2020)
P5A-1D6	IGHV3-23	IGLV3-21	11	Ju et al. (2020)
P5A-2E12	IGHV3-23	IGLV3-21	12	Ju et al. (2020)
P5A-3D12	IGHV3-23	IGLV1-47	22	Ju et al. (2020)
P5A-1B6	IGHV3-30	IGKV1-33	18	Ju et al. (2020)
P5A-2E6	IGHV3-30	IGKV1-33	18	Ju et al. (2020)
P5A-1B1	IGHV3-33	IGKV3-15	12	Ju et al. (2020)
P5A-1C5	IGHV3-33	IGKV3-15	12	Ju et al. (2020)
P5A-2H7	IGHV3-33	IGKV3-15	12	Ju et al. (2020)
P5A-2G9	IGHV3-33	IGLV5-37	10	Ju et al. (2020)
P5A-2G11	IGHV3-33	IGLV2-14	15	Ju et al. (2020)
P5A-1B8	IGHV3-53	IGKV1-9	7	Ju et al. (2020)
P5A-1D2	IGHV3-53	IGLV1-40	13	Ju et al. (2020)
P5A-1D1	IGHV3-53	IGKV1-9	9	Ju et al. (2020)
P5A-2C9	IGHV3-7	IGKV3-20	12	Ju et al. (2020)
P5A-2E4	IGHV3-7	IGKV3-20	12	Ju et al. (2020)
P5A-2G12	IGHV3-7	IGLV6-57	10	Ju et al. (2020)
P5A-2D12	IGHV3-7	IGKV2-28	16	Ju et al. (2020)
P5A-2F1	IGHV3-74	IGLV6-57	10	Ju et al. (2020)
P5A-1C10	IGHV3-9	IGLV3-21	12	Ju et al. (2020)
P5A-2E8	IGHV3-9	IGLV3-21	11	Ju et al. (2020)
P5A-3A2	IGHV3-9	IGLV3-21	12	Ju et al. (2020)
P5A-2D6	IGHV3-9	IGLV1-40	12	Ju et al. (2020)
P5A-1B12	IGHV3-9	IGLV1-51	15	Ju et al. (2020)

P5A-3A6	IGHV3-9	IGLV2-14	25	Ju et al. (2020)
P5A-3D9	IGHV3-9	IGKV3-15	14	Ju et al. (2020)
P5A-1D10	IGHV3-11	IGLV2-14	19	Ju et al. (2020)
P5A-3A1	IGHV3-53	IGKV3-20	9	Ju et al. (2020)
P5A-3C8	IGHV3-53	IGKV1-9	9	Ju et al. (2020)
P5A-2D10	IGHV4-31	IGLV6-57	10	Ju et al. (2020)
P5A-2G5	IGHV4-31	IGLV3-21	12	Ju et al. (2020)
P5A-1A12	IGHV4-39	IGKV4-1	15	Ju et al. (2020)
P5A-2C7	IGHV4-39	IGLV2-23	14	Ju et al. (2020)
P5A-2F7	IGHV4-39	IGLV2-23	16	Ju et al. (2020)
P5A-2F9	IGHV4-39	IGLV2-23	12	Ju et al. (2020)
P5A-1A5	IGHV4-4	IGLV2-14	12	Ju et al. (2020)
P5A-1C6	IGHV4-4	IGLV1-40	20	Ju et al. (2020)
P5A-3A10	IGHV4-4	IGKV1-39	19	Ju et al. (2020)
P5A-1B9	IGHV4-59	IGKV4-1	20	Ju et al. (2020)
P5A-3A7	IGHV4-59	IGKV4-1	20	Ju et al. (2020)
P5A-3B1	IGHV4-59	IGKV4-1	20	Ju et al. (2020)
P5A-3B6	IGHV4-59	IGKV4-1	20	Ju et al. (2020)
P5A-2C10	IGHV4-59	IGLV3-21	15	Ju et al. (2020)
P5A-2E5	IGHV4-59	IGLV6-57	10	Ju et al. (2020)
P5A-2G4	IGHV4-59	IGKV1D-16	10	Ju et al. (2020)
P5A-2G7	IGHV4-61	IGLV2-14	18	Ju et al. (2020)
P5A-1B10	IGHV5-51	IGKV2-28	10	Ju et al. (2020)
P5A-1C9	IGHV5-51	IGLV3-19	9	Ju et al. (2020)
P5A-2D11	IGHV5-51	IGLV1-44	11	Ju et al. (2020)
P5A-3B4	IGHV5-51	IGLV1-44	11	Ju et al. (2020)
P5A-2H3	IGHV5-51	IGLV1-44	11	Ju et al. (2020)
P5A-2E1	IGHV5-51	IGLV3-21	10	Ju et al. (2020)
P5A-1B11	IGHV7-4-1	IGKV1-39	18	Ju et al. (2020)
P5A-2D7	IGHV7-4-1	IGKV6-21	8	Ju et al. (2020)
P5A-3C9	IGHV7-4-1	IGKV6-21	8	Ju et al. (2020)
P5A-3D11	IGHV7-4-1	IGKV6-21	8	Ju et al. (2020)
P16A-1A3	IGHV1-3	IGLV6-57	9	Ju et al. (2020)
P16A-1A8	IGHV1-46	IGLV3-21	18	Ju et al. (2020)
P16A-1B5	IGHV1-46	IGLV3-21	11	Ju et al. (2020)
P16A-1C6	IGHV1-46	IGLV3-21	14	Ju et al. (2020)
P16A-1C1	IGHV3-13	IGKV1-39	19	Ju et al. (2020)
P16A-1A5	IGHV3-33	IGKV1-33	13	Ju et al. (2020)
P16A-1A12	IGHV3-33	IGLV1-51	17	Ju et al. (2020)
P16A-1B1	IGHV3-74	IGLV1-36	13	Ju et al. (2020)
P16A-1B3	IGHV3-9	IGLV3-1	22	Ju et al. (2020)
P16A-1B12	IGHV4-34	IGLV1-51	14	Ju et al. (2020)
P16A-1B8	IGHV5-51	IGLV3-1	17	Ju et al. (2020)
P16A-1A7	IGHV7-4-1	IGLV3-21	12	Ju et al. (2020)
P16A-1A10	IGHV7-4-1	IGLV3-21	13	Ju et al. (2020)
P22A-1E10	IGHV1-46	IGKV3-11	13	Ju et al. (2020)
P22A-1D2	IGHV1-8	IGLV1-40	19	Ju et al. (2020)
P22A-1D8	IGHV3-23	IGKV3-15	18	Ju et al. (2020)
P22A-1D7	IGHV3-33	IGKV1-39	11	Ju et al. (2020)
P22A-1D1	IGHV3-53	IGKV1-9	9	Ju et al. (2020)
P22A-1E8	IGHV3-9	IGKV3-15	14	Ju et al. (2020)
P22A-1D5	IGHV4-39	IGLV2-23	12	Ju et al. (2020)
P22A-1E6	IGHV4-59	IGKV3-20	14	Ju et al. (2020)

BD-494	IGHV3-53	IGKV1-9	9	Cao et al. (2020)
BD-498	IGHV3-66	IGKV1-9	9	Cao et al. (2020)
BD-500	IGHV3-53	IGKV1D-39	9	Cao et al. (2020)
BD-503	IGHV3-53	IGKV1D-39	9	Cao et al. (2020)
BD-504	IGHV3-66	IGKV1-9	9	Cao et al. (2020)
BD-505	IGHV3-53	IGKV1D-33	9	Cao et al. (2020)
BD-506	IGHV3-53	IGKV1-9	9	Cao et al. (2020)
BD-507	IGHV3-53	IGKV1-9	9	Cao et al. (2020)
BD-508	IGHV3-53	IGKV1D-39	9	Cao et al. (2020)
CR3022	IGHV5-51	IGKV4-1	10	Yuan et al. (2020)
CC12.1	IGHV3-53	IGKV1-9	-	Rogers et al. (2020)
CC12.2	IGHV3-53	IGKV3-20	-	Rogers et al. (2020)
CC12.3	IGHV3-53	IGKV3-20	-	Rogers et al. (2020)
CC12.4	IGHV1-2	IGLV2-8	-	Rogers et al. (2020)
CC12.5	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.6	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.7	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.8	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.9	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.10	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.11	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.12	IGHV1-2	IGLV2-14	-	Rogers et al. (2020)
CC12.13	IGHV3-53	IGKV1-33	-	Rogers et al. (2020)
CC12.14	IGHV3-21	IGKV2-30	-	Rogers et al. (2020)
CC12.15	IGHV3-48	IGLV1-40	-	Rogers et al. (2020)
CC12.16	IGHV3-33	IGLV3-21	-	Rogers et al. (2020)
CC12.17	IGHV3-30	IGLV3-21	-	Rogers et al. (2020)
CC12.18	IGHV1-46	IGLV6-57	-	Rogers et al. (2020)
CC12.19	IGHV3-23	IGLV3-21	-	Rogers et al. (2020)
COVA1-07	IGHV1-69	-	13	Brouwer et al. (2020)
COVA1-08	IGHV3-30	-	12	Brouwer et al. (2020)
COVA1-10	IGHV3-66	-	19	Brouwer et al. (2020)
COVA1-12	IGHV1-2	-	13	Brouwer et al. (2020)
COVA1-16	IGHV1-46	-	20	Brouwer et al. (2020)
COVA1-18	IGHV3-66	-	10	Brouwer et al. (2020)
COVA2-01	IGHV3-13	-	12	Brouwer et al. (2020)
COVA2-02	IGHV4-39	-	13	Brouwer et al. (2020)
COVA2-04	IGHV3-53	-	10	Brouwer et al. (2020)
COVA2-05	IGHV5-51	-	18	Brouwer et al. (2020)
COVA2-07	IGHV3-53	-	7	Brouwer et al. (2020)
COVA2-11	IGHV3-21	-	17	Brouwer et al. (2020)
COVA2-13	IGHV1-69	-	10	Brouwer et al. (2020)
COVA2-15	IGHV3-23	-	20	Brouwer et al. (2020)
COVA2-16	IGHV1-69	-	14	Brouwer et al. (2020)
COVA2-17	IGHV1-69	-	11	Brouwer et al. (2020)
COVA2-20	IGHV3-53	-	15	Brouwer et al. (2020)
COVA2-23	IGHV1-2	-	18	Brouwer et al. (2020)
COVA2-24	IGHV5-10	-	18	Brouwer et al. (2020)
COVA2-27	IGHV1-8	-	14	Brouwer et al. (2020)
COVA2-29	IGHV4-30	-	18	Brouwer et al. (2020)
COVA2-31	IGHV1-2	-	16	Brouwer et al. (2020)
COVA2-32	IGHV1-69	-	13	Brouwer et al. (2020)
COVA2-36	IGHV5-51	-	14	Brouwer et al. (2020)

COVA2-39	IGHV3-53	-	15	Brouwer et al. (2020)
COVA2-44	IGHV3-30	-	13	Brouwer et al. (2020)
COVA2-45	IGHV1-2	-	22	Brouwer et al. (2020)
COVA2-46	IGHV4-39	-	10	Brouwer et al. (2020)
COVA3-05	IGHV1-24	-	14	Brouwer et al. (2020)
COVA3-06	IGHV1-69	-	16	Brouwer et al. (2020)
COVA3-09	IGHV4-59	-	12	Brouwer et al. (2020)
COVA3-10	IGHV5-51	-	14	Brouwer et al. (2020)
B5	IGHV1-2	IGKV3-20	-	Wu et al. (2020)
B38	IGHV3-53	IGKV1-9	7	Wu et al. (2020)
H2	IGHV3-9	IGKV1-39	-	Wu et al. (2020)
H4	IGHV1-2	IGKV2-40	17	Wu et al. (2020)
COV21.1	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV21.2	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV57.1	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV57.2	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV107.1	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV107.2	IGHV1-58	IGKV3-20	14	Robbiani et al. (2020)
COV21.3	IGHV3-30	IGKV1-39	14	Robbiani et al. (2020)
COV21.4	IGHV3-30	IGKV1-39	12	Robbiani et al. (2020)
COV72.1	IGHV3-30	IGKV1-39	14	Robbiani et al. (2020)
COV72.2	IGHV3-30	IGKV1-39	14	Robbiani et al. (2020)
COV72.3	IGHV3-30	IGKV1-39	14	Robbiani et al. (2020)
1M-1D2	IGHV3-64	IGLV1-47	18	Chi et al. (2020)
2M-10B11	IGHV3-66	IGLV6-57	10	Chi et al. (2020)
2M-4G4	IGHV1-46	IGLV2-23	23	Chi et al. (2020)
CV5	IGHV1-46	IGKV4-1	-	Seydoux et al. (2020)
CV30	IGHV3-53	IGKV3-20	-	Seydoux et al. (2020)
CV43	IGHV3-30	IGLV6-57	-	Seydoux et al. (2020)
CA1	IGHV1-18	IGKV3-11	21	Shi et al. (2020)
CB6	IGHV3-66	IGKV1-39	11	Shi et al. (2020)
C105	IGHV3-53	IGLV2-8	-	Barnes et al. (2020)

535
536

537
538
539

Table S3. Hydrogen bonds and salt bridges identified at the antibody-RBD interface using the PISA program.

SARS-CoV-2 RBD	Distance [Å]	CC12.1
Hydrogen bonds		
TYR 473[OH]	3.63	VH SER 53[OG]
TYR 473[OH]	2.77	VH SER 31[O]
ASP 420[OD2]	2.51	VH SER 56[OG]
TYR 421[O]	3.39	VH SER 53[N]
LEU 455[O]	2.59	VH TYR 33[OH]
ALA 475[O]	3.02	VH ASN 32[ND2]
ALA 475[O]	3.16	VH THR 28[N]
ASN 487[OD1]	3.13	VH ARG 94[NH1]
ASN 487[OD1]	3.16	VH ARG 94[NH2]
TYR 489[OH]	3.26	VH ARG 94[NH2]
GLN 493[OE1]	2.85	VH TYR 99[OH]
TYR 505[OH]	2.95	VL LEU 91[O]
ARG 403[NH2]	2.08	VL ASN 92[O]
TYR 505[OH]	3.11	VL ASN 92[O]
SER 494[O]	3.55	VL TYR 32[OH]
GLN 498[OE1]	3.61	VL SER 67[OG]
TYR 505[OH]	2.94	VL GLN 90[NE2]
TYR 453[OH]	3.29	VL ASN 92[ND2]
THR 415[O]	2.69	VL TYR 94[OH]
Salt bridges		
LYS 417[NZ]	3.17	VH ASP 97[OD1]

540

SARS-CoV-2 RBD	Distance [Å]	CC12.3
Hydrogen bonds		
ASP 420[OD2]	2.60	VH SER 56[OG]
TYR 421[OH]	3.36	VH SER 53[OG]
TYR 421[OH]	3.72	VH SER 53[N]
LEU 455[O]	2.65	VH TYR 33[OH]
ARG 457[O]	2.81	VH SER 53[OG]
ALA 475[O]	2.97	VH ASN 32[ND2]
ALA 475[O]	3.13	VH THR 28[N]
ASN 487[OD1]	2.67	VH ARG 94[NH2]
TYR 489[OH]	2.88	VH ARG 94[NH1]
TYR 489[OH]	2.71	VH ARG 94[NH2]
SER 477[N]	3.88	VH THR 28[OG1]
TYR 473[OH]	2.74	VH SER 31[O]
ARG 457[N]	3.64	VL SER 53[OG]
TYR 495[O]	3.87	VL TYR 32[OH]
TYR 505[OH]	3.88	VL SER 93[N]
TYR 505[OH]	3.21	VL SER 28[O]

541

542 **SUPPLEMENTARY REFERENCES**

- 543 40. D. C. Ekiert *et al.*, A highly conserved neutralizing epitope on group 2 influenza A
544 viruses. *Science* **333**, 843-850 (2011).
- 545 41. Z. Otwinowski, W. Minor, Processing of X-ray diffraction data collected in
546 oscillation mode. *Methods Enzymol* **276**, 307-326 (1997).
- 547 42. A. J. McCoy *et al.*, Phaser crystallographic software. *J Appl Crystallogr* **40**, 658-
548 674 (2007).
- 549 43. J. Huo *et al.*, Neutralization of SARS-CoV-2 by destruction of the prefusion
550 Spike. *bioRxiv* 10.1101/2020.05.05.079202 (2020).
- 551 44. X. Chen *et al.*, Structural basis for antigen recognition by transglutaminase 2-
552 specific autoantibodies in celiac disease. *J Biol Chem* **290**, 21365-21375 (2015).
- 553 45. P. Emsley, B. Lohkamp, W. G. Scott, K. Cowtan, Features and development of
554 Coot. *Acta Crystallogr D Biol Crystallogr* **66**, 486-501 (2010).
- 555 46. P. D. Adams *et al.*, PHENIX: a comprehensive Python-based system for
556 macromolecular structure solution. *Acta Crystallogr D Biol Crystallogr* **66**, 213-
557 221 (2010).
- 558 47. N. C. Wu *et al.*, In vitro evolution of an influenza broadly neutralizing antibody is
559 modulated by hemagglutinin receptor specificity. *Nat Commun* **8**, 15371 (2017).
- 560 48. D. Wrapp *et al.*, Cryo-EM structure of the 2019-nCoV spike in the prefusion
561 conformation. *Science* **367**, 1260-1263 (2020).
562