Painting a Landscape: Defining nuanced epitope communities targeted by antibodies against SARS-CoV-2 spike protein

CoVIC: Coronavirus Immunotherapeutics Consortium

SHARON SCHENDEL

Carterra Symposium Series: Unlocking High-Throughput Biology and Drug Discovery

Zürich

June 13, 2023

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January 30, 2020

Novel 2019 coronavirus genome

SARS-CoV-2 coronavirus

edward_holmes 7 Jan '20

> 10th January 2020
>
> [illegible]ated by Edward C. Holmes, University of Sydney on behalf of the consortium led by Professor Yong-Zhen Zhang, Fudan University, Shanghai

The Shanghai Public Health Clinical Center & School of Public Health, in collaboration with the Central Hospital of Wuhan, Huazhong University of Science and Technology, the Wuhan Center for Disease Control and Prevention, the National Institute for Communicable Disease Control and Prevention, Chinese Center for Disease Control, and the University of Sydney, Sydney, Australia is releasing a coronavirus genome from a case of a respiratory disease from the Wuhan outbreak. The sequence has also been deposited on GenBank (accession MN908947 33.4k) and will be released as soon as possible.

Update: This genome is now available on GenBank and an updated version has been posted 33.4k.

Disclaimer:
Please feel free to download, share, use, and analyze this data[1]. We ask that you communicate with us if you wish to publish results that use these data in a journal. If you have any other questions –then please also contact us directly.

Professor Yong-Zhen Zhang,
Shanghai Public Health Clinical Center & School of Public Health,
Fudan University,
Shanghai, China.

email: zhangyongzhen@shphc.org.cn

[1] We know that “data” is plural but we were in a hurry.

La Jolla Institute of Immunology: COVID-19: mAb Clearing House

GRANT ORIENTATION

March 2020

La Jolla Institute of Immunology: COVID-19: mAb Clearing House

GRANT ORIENTATION

GATES DISCUSSION 3.23.20
Karen Makar:
Need standardized assay performance set up key performance sites.

Georgia Tomaras Duke University (GLP lab- qualified binding, affinity, avidity) Carterra system for epitope binning will support; doing malaria mAb already
Asked that she pivot resources to develop similar assays for screen and clone of mAbs against CV
Full-length S and RBD. What other antigens we need?
Is ACE2 binding inhibition assay useful?

Carterra offered some capacity such that if Duke capacity insufficient or not right approach, Carterra could take over or take the overflow

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Antibody therapy

Quintillion possible antibodies in human sera
Companies racing to find the best
Each different strategy, different candidates
Which are best?

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Antibody therapy

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Which are best?

Are they best in combination?

How to make them affordable?
More potent, more durable: more people
Global access?

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Coronavirus Immunotherapeutic Consortium

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Coronavirus Immunotherapeutic Consortium

CoVIC

Global Collaboration

Side-by-side analysis

Which are best? What makes them best?

Best in combination?

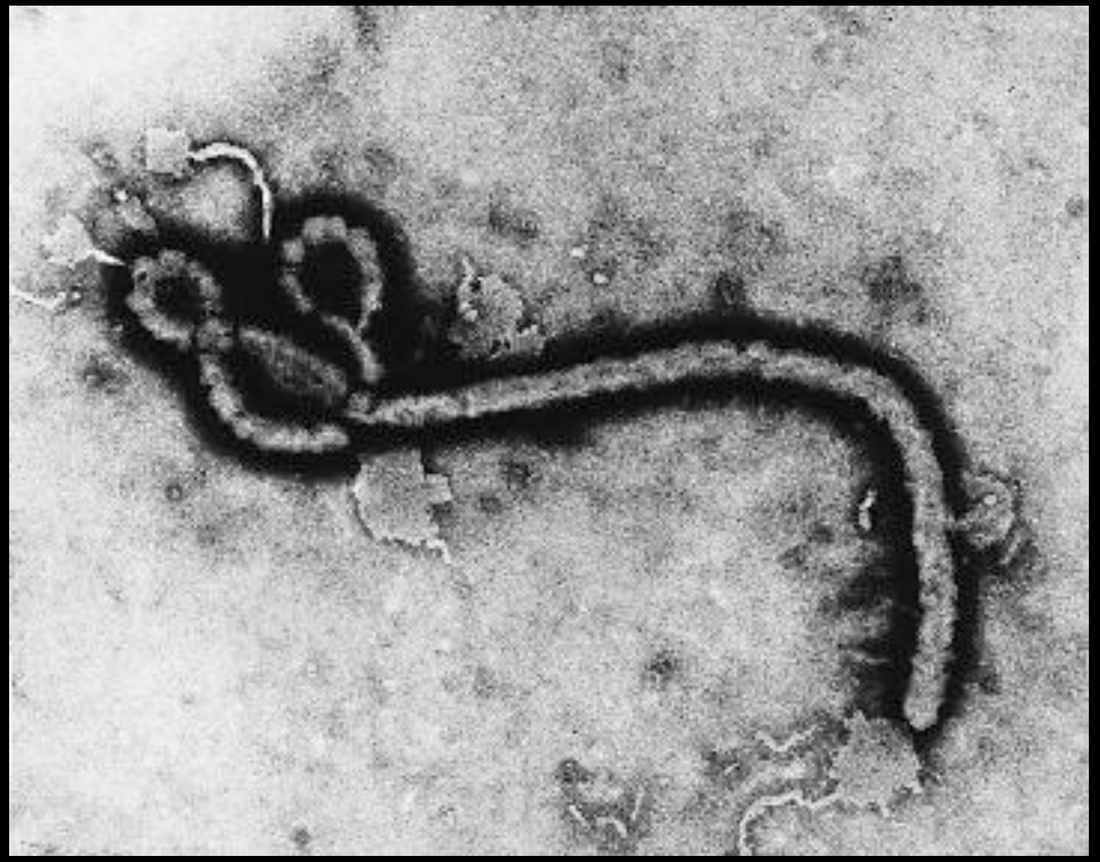
Make available to everyone

La Jolla Institute FOR IMMUNOLOGY

this idea came from…..


ATTENTION !
EBOLA !
Beaufort
UN
UN

Ebola virus



When we started:
No vaccine
No drugs
No treatments

2013, Ebola virus:
Antibodies that worked in vitro, but not in vivo
Antibodies that protected in vivo, but didn’t work in vitro

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Missing information.
Need better tools, more samples.
Everyone is working in a silo.
Escalating epidemic….

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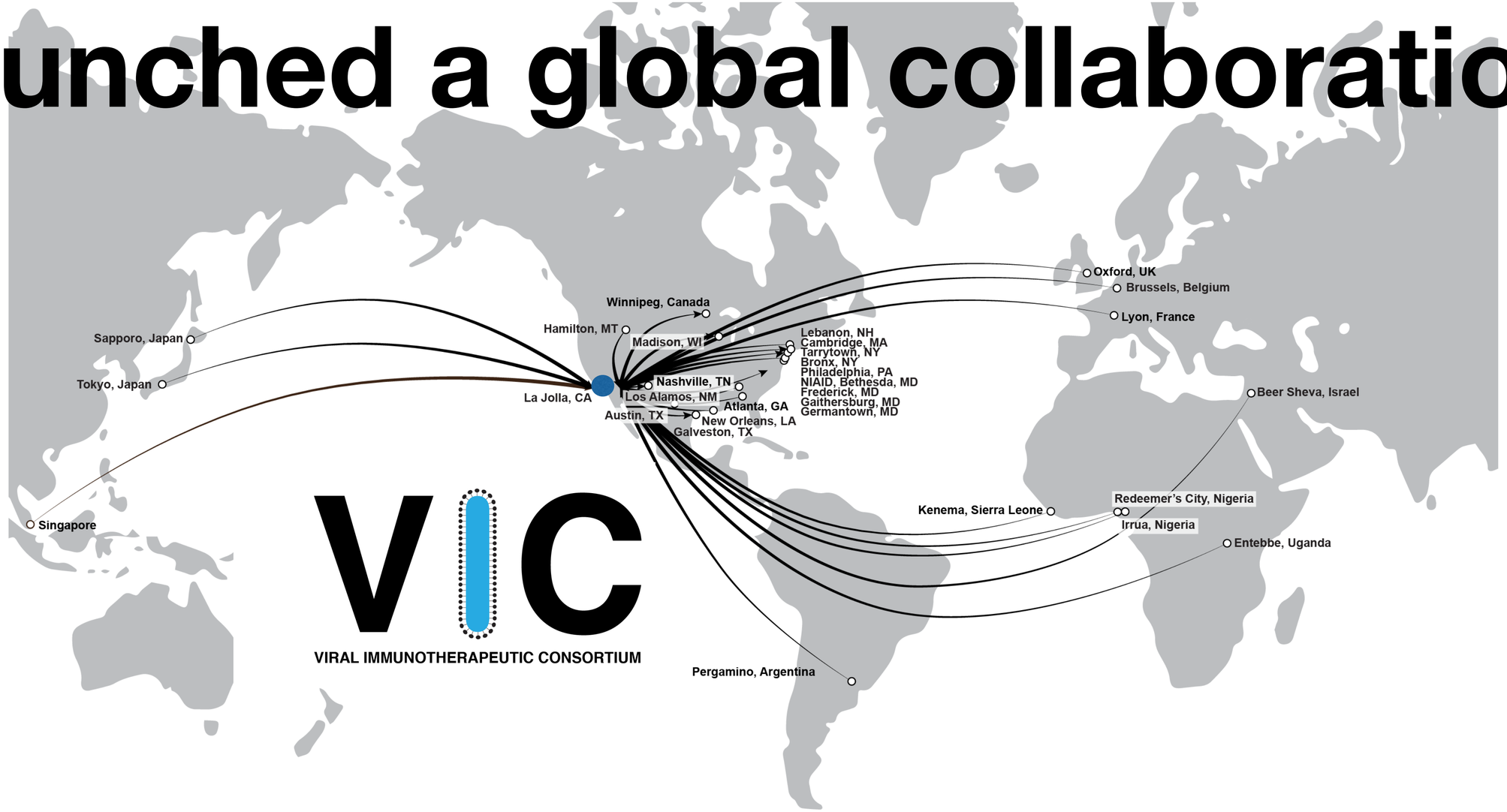
Escalating epidemic….

Need to work smarter.
Need to work faster.
Need to work together.

Launched a global collaboration



Launched a global collaboration

VIC

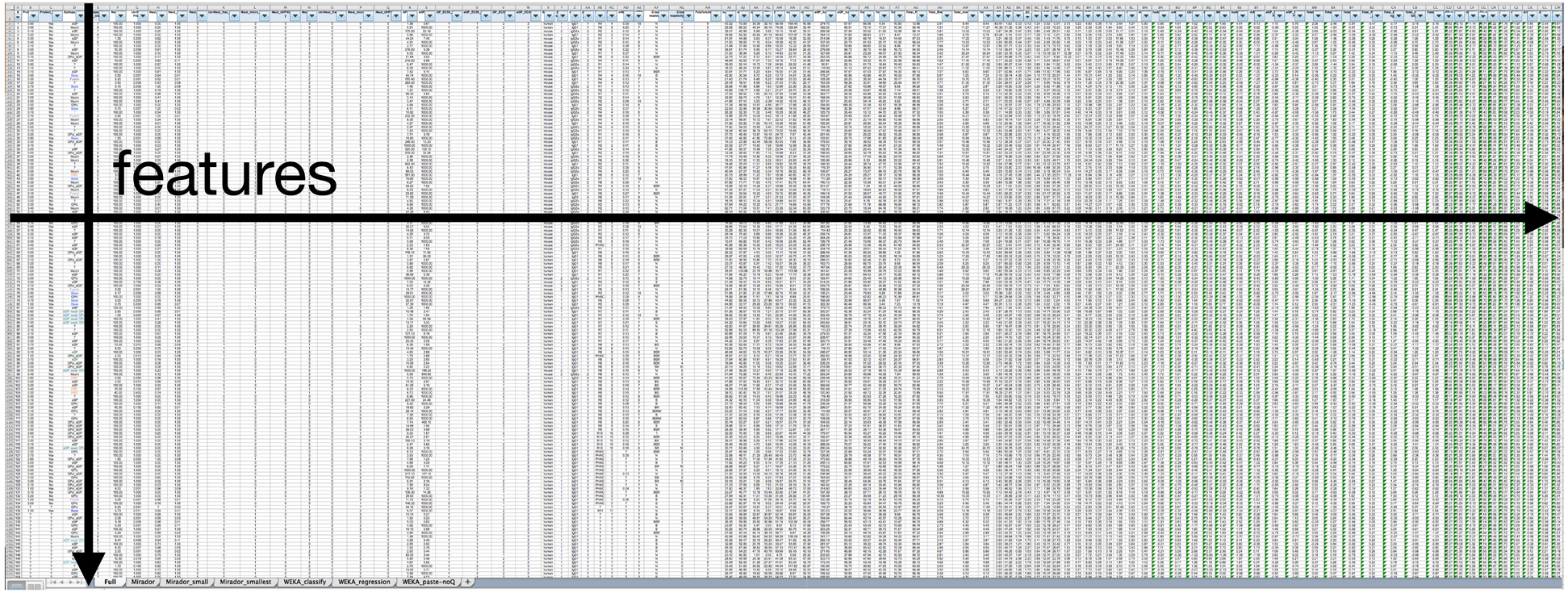
VIRAL IMMUNOTHERAPEUTIC CONSORTIUM

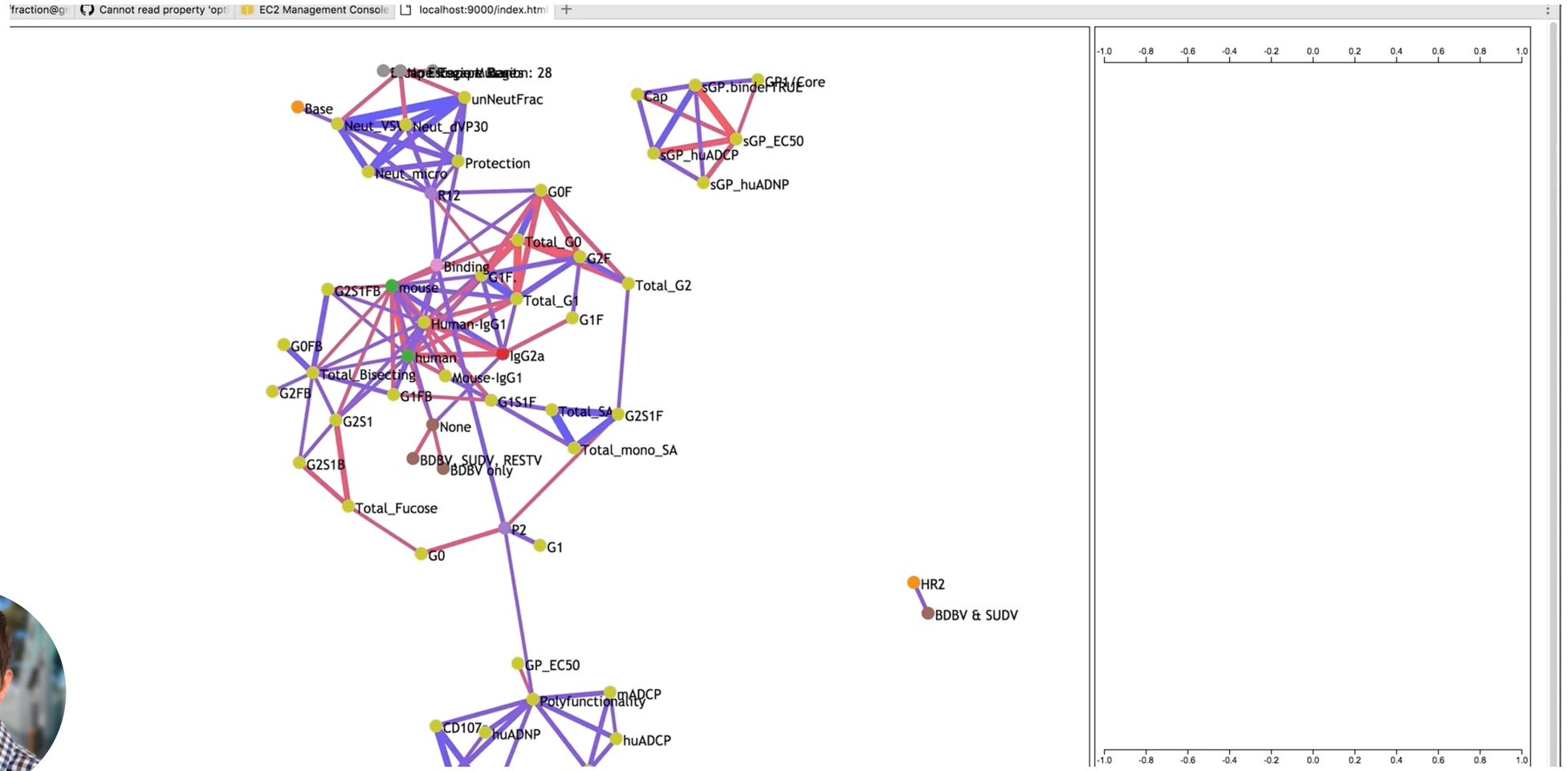
44 labs, 5 continents
academic-industry-government
single comprehensive effort
What antibodies are best? How do we find them?

200 people:

antibodies

features

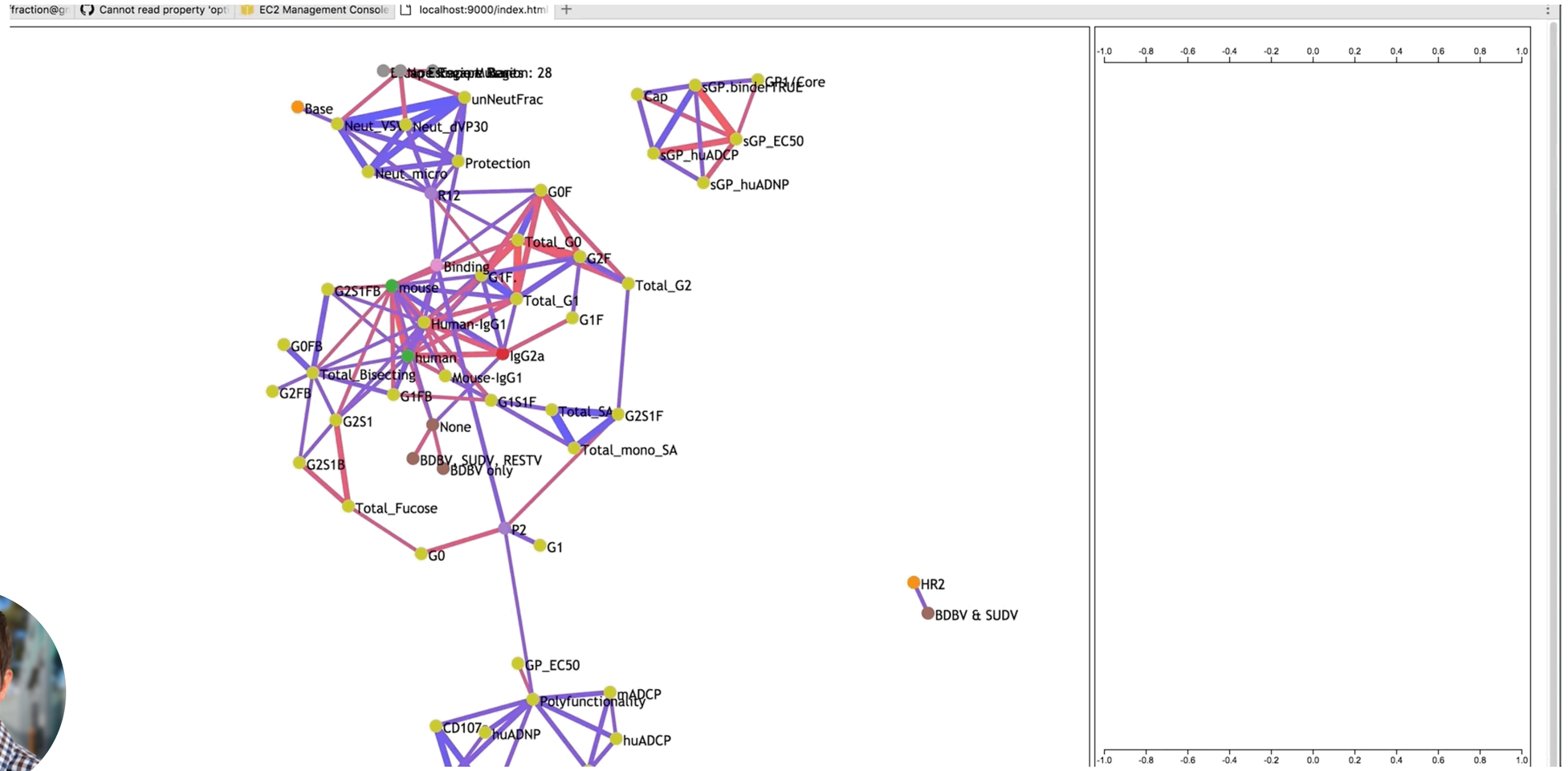




Kristian Andersen

Scripps Research

http://apps.vhfimmunotherapy.org/corrnetwork/



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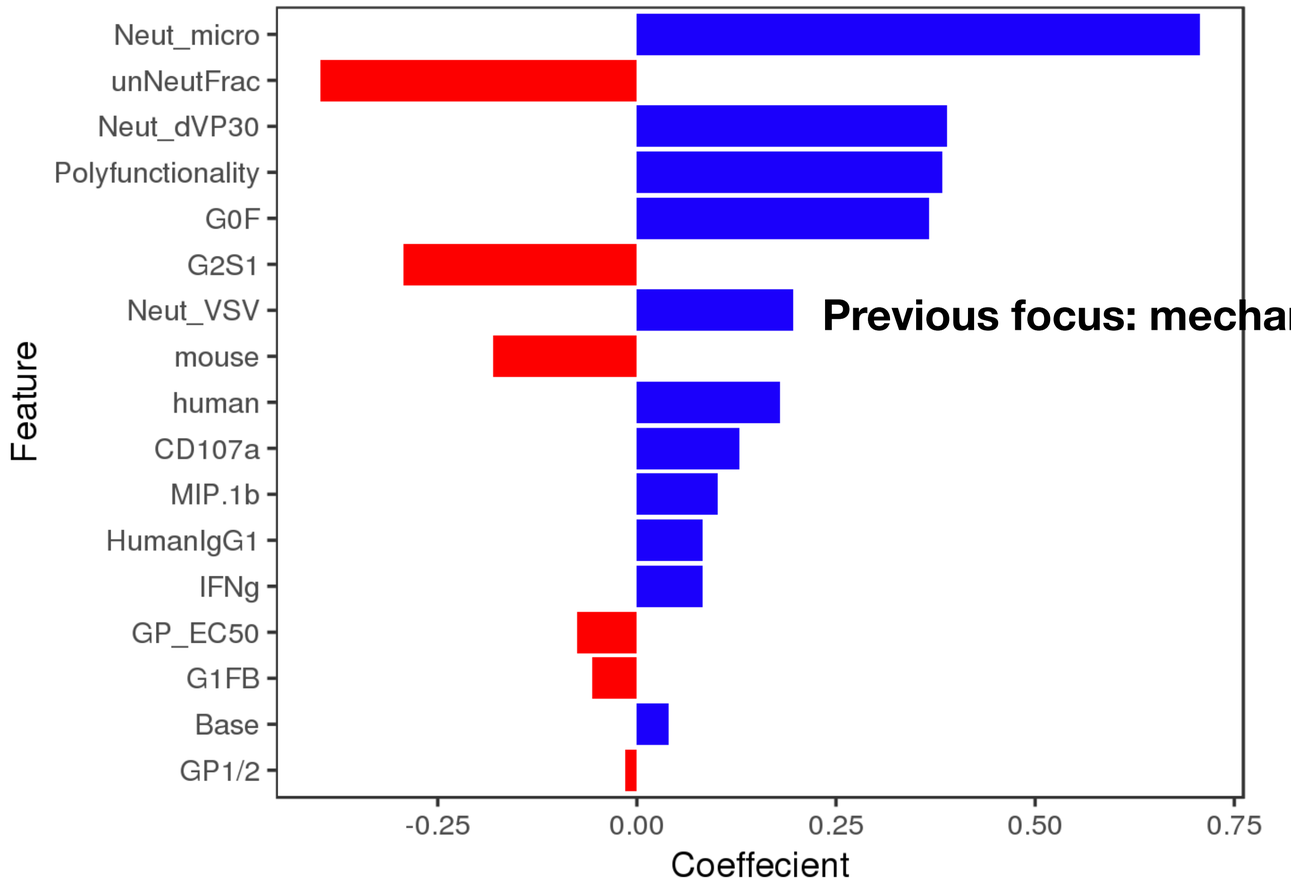
Logistic regression: 17 features predictive of protection (AUC 0.958)



Previous focus: mechanics

Coefficients that weight individual features in the equation that predicts protection

$$P = 1/1 + e^{-(\beta_0+\beta_1 X_1+\beta_2 X_2+\beta_3 X_3+\beta_4 X_4 \ldots)}$$

Galit Alter, John Dye, Kartik Chandran, Yoshihiro Kawaoka, Kristian Andersen

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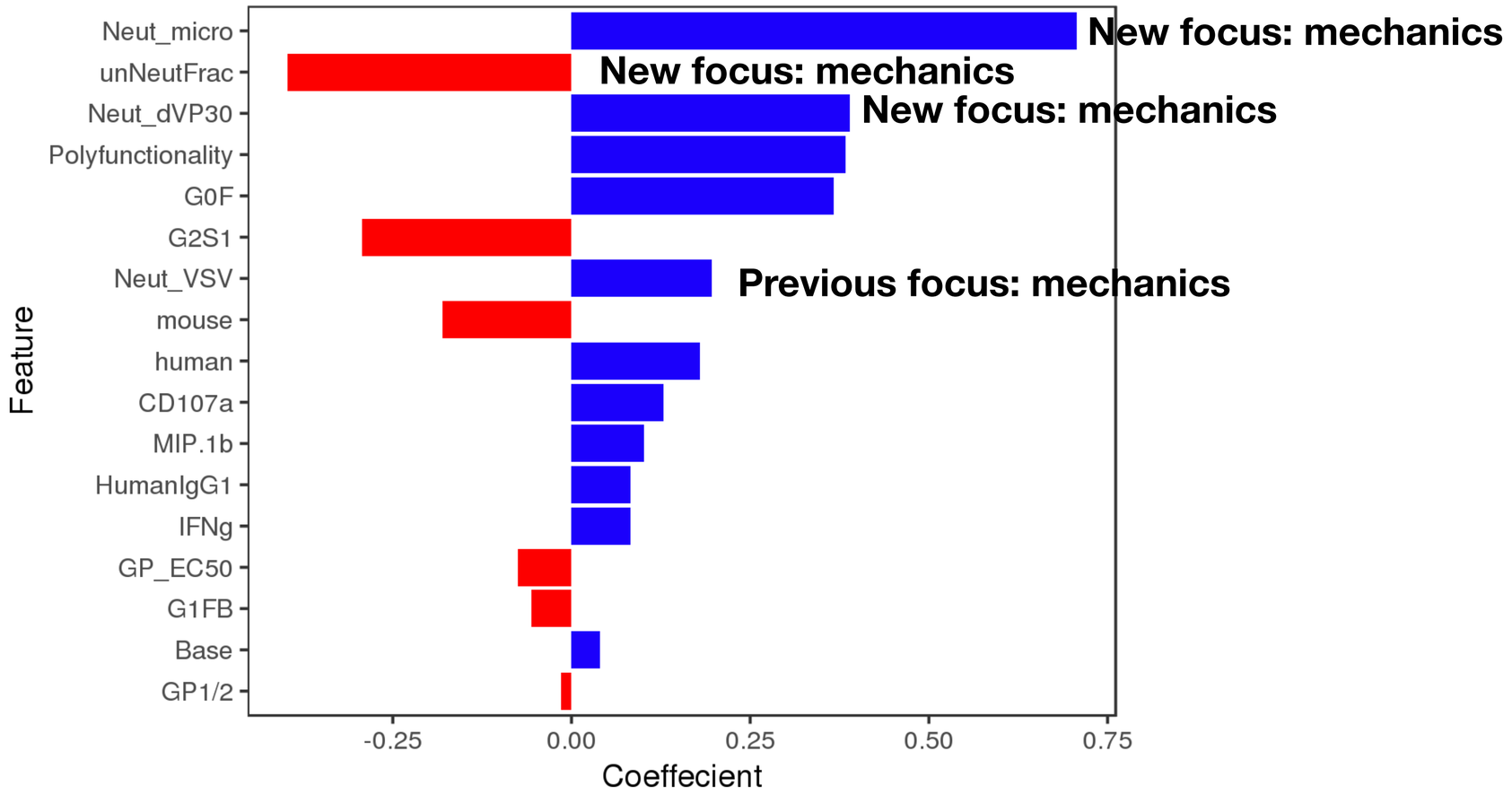

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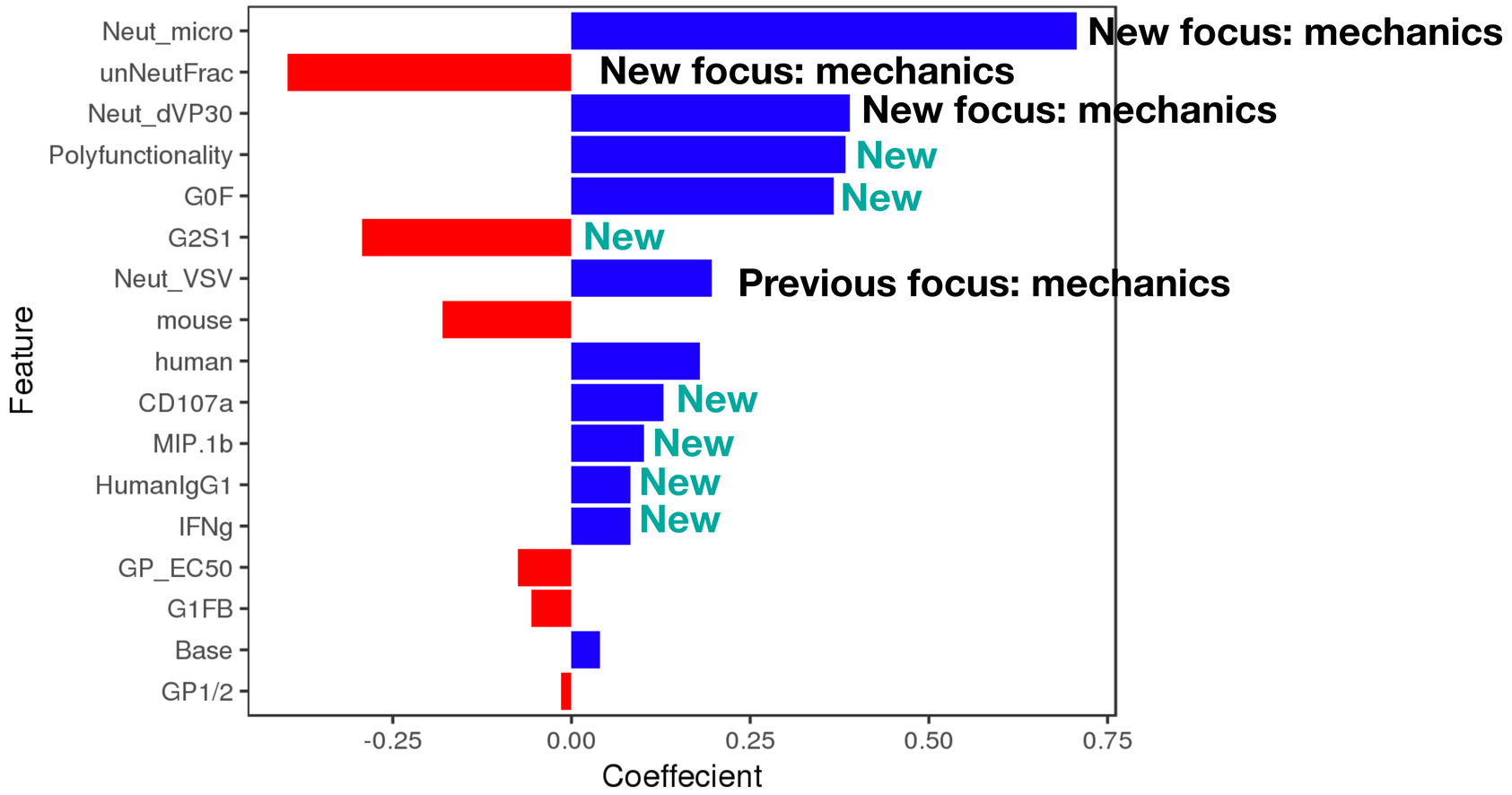

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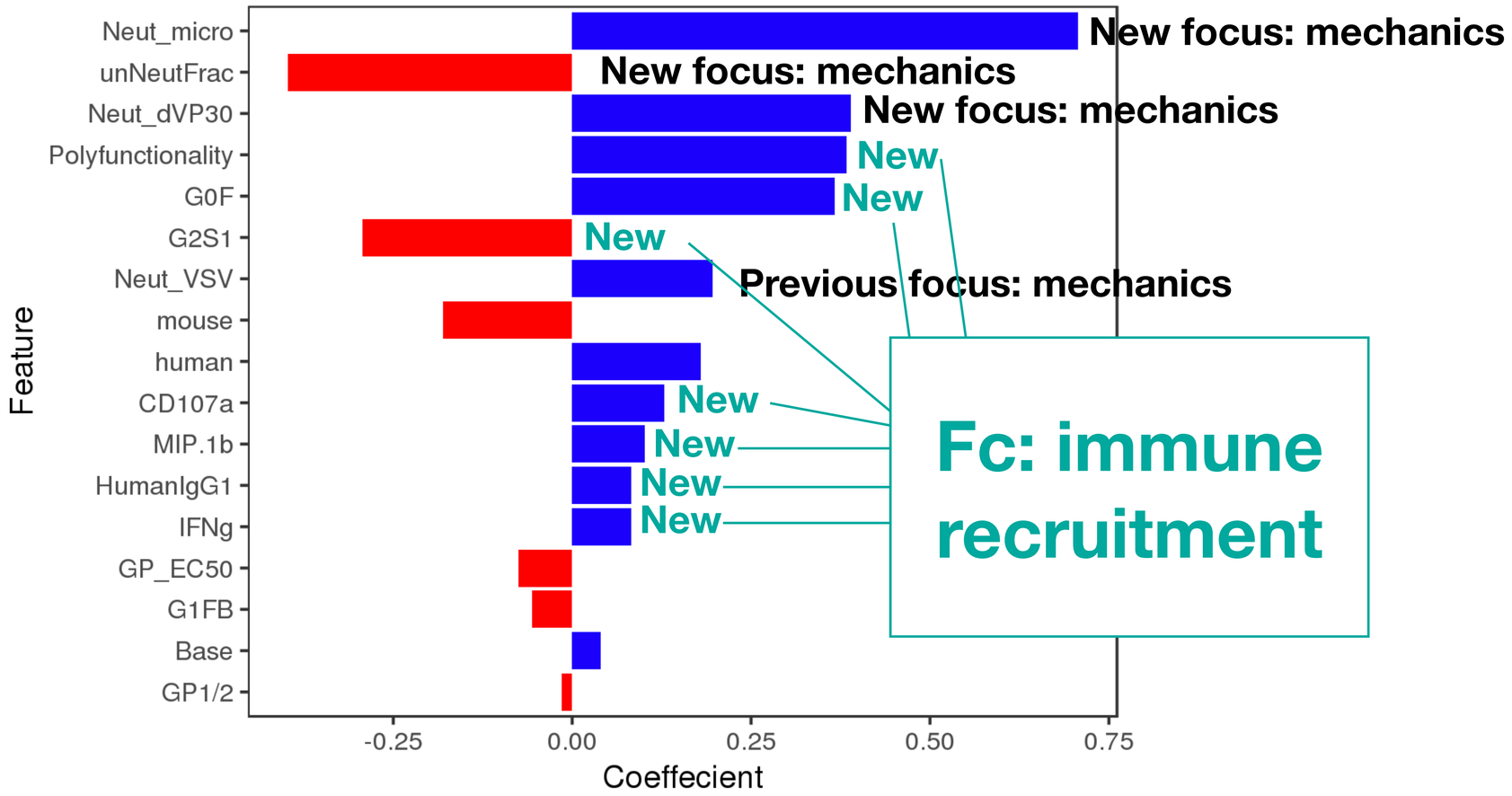

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The New York Times

A Cure for Ebola? Two New Treatments Prove Highly Effective in Congo

The therapies saved roughly 90 percent of the patients who were newly infected, a turning point in the decades-long fight against the virus.

August 2019

Coronavirus Immunotherapeutic Consortium

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Side-by-side analysis

Which are best? What makes them best?

Best in combination?

Make available to everyone

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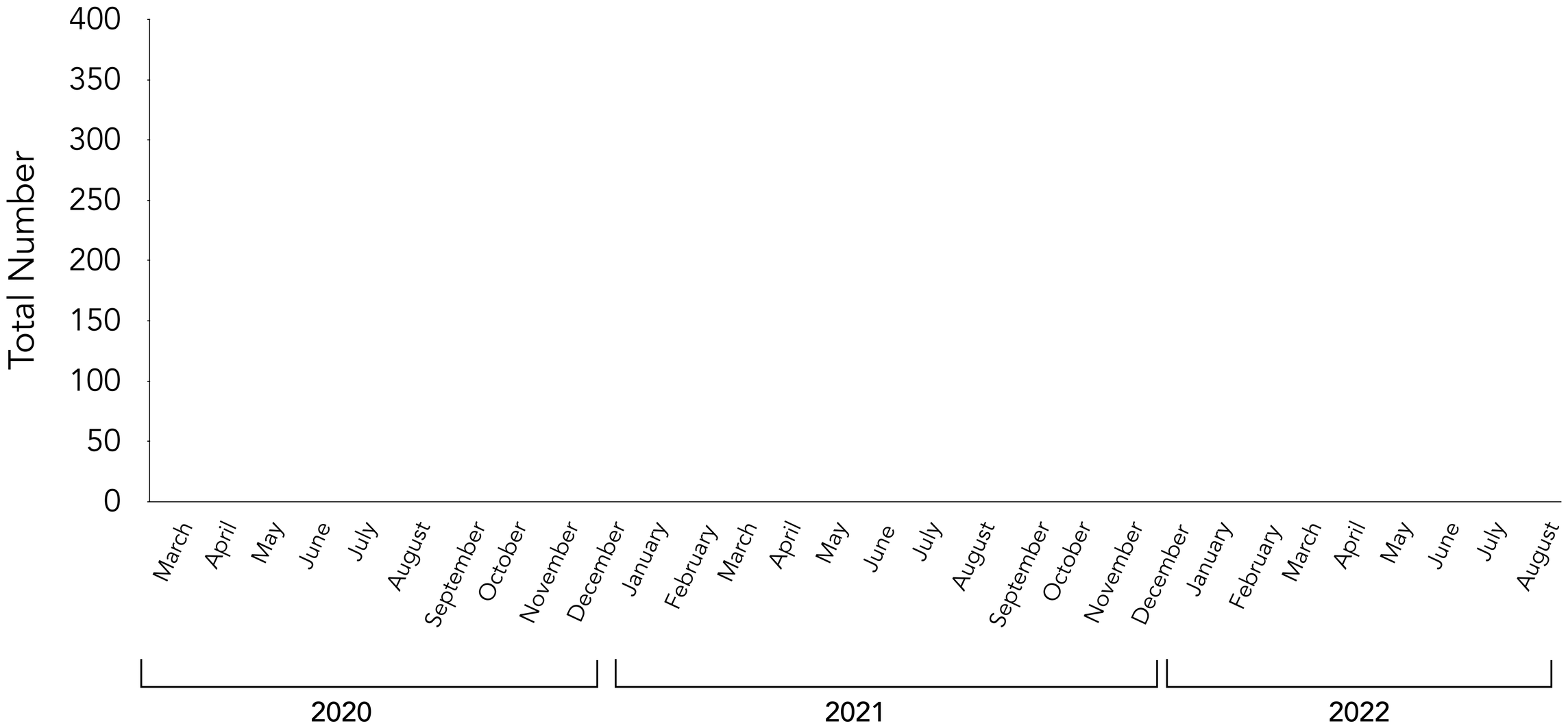
CoVIC Antibody Panel



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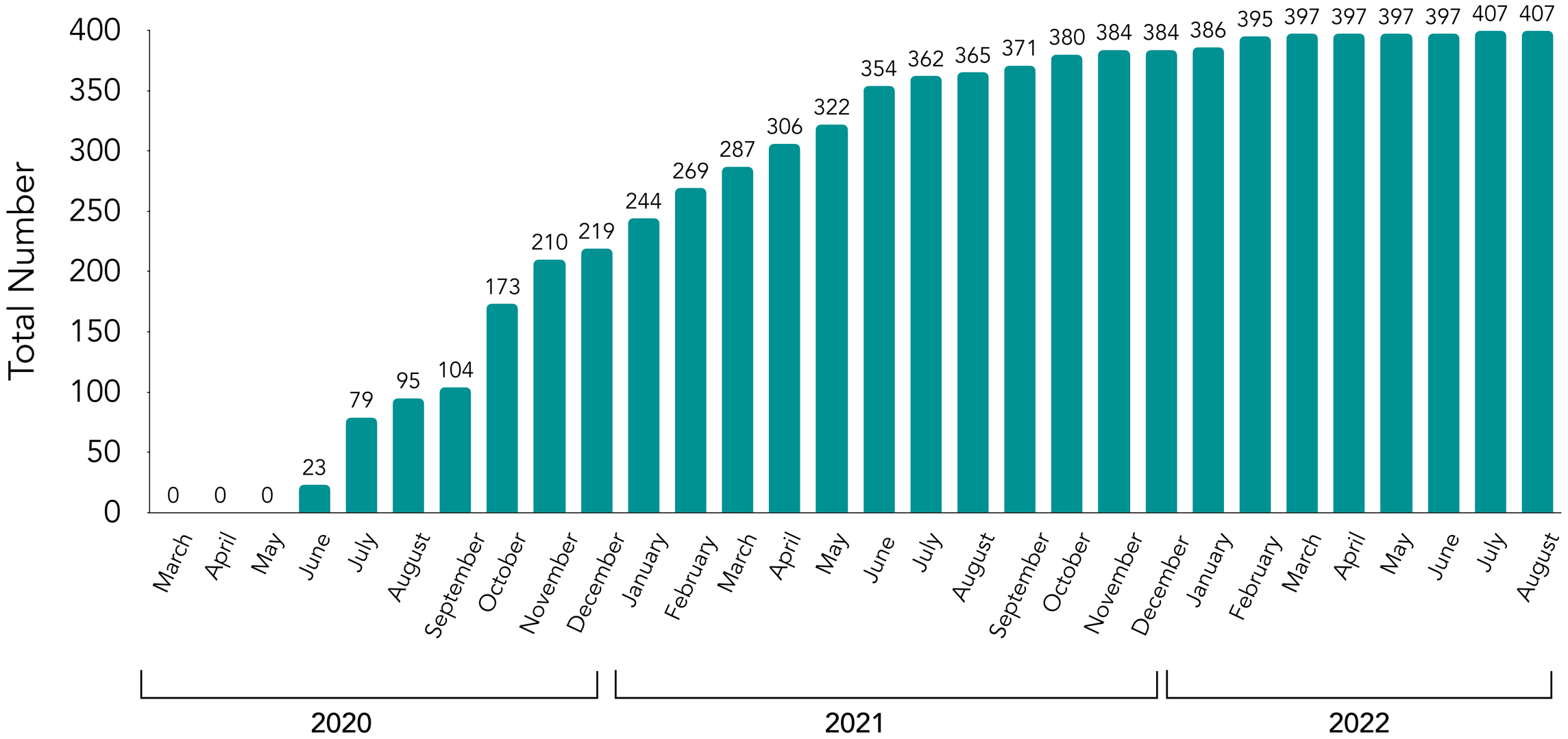

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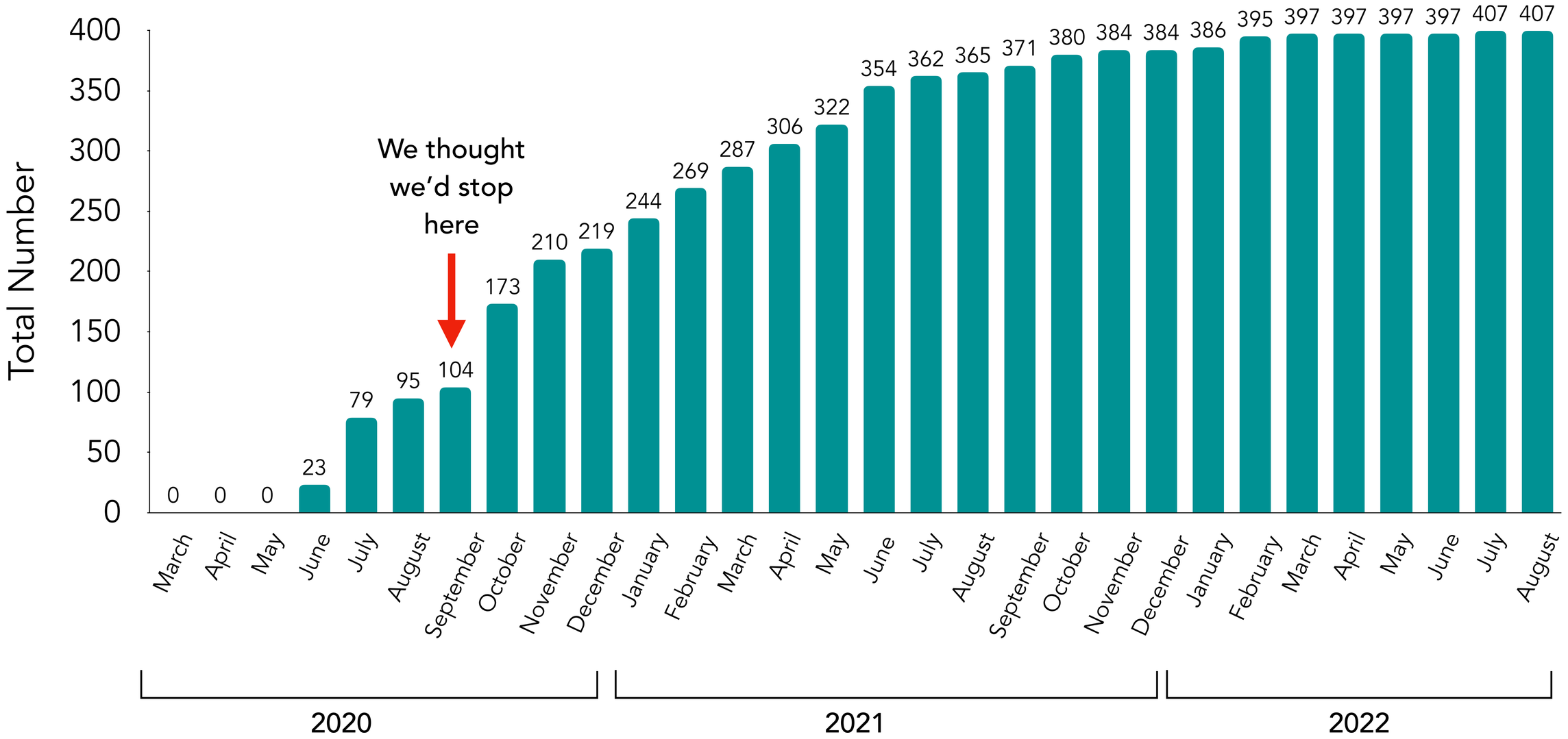

CoVIC Contributor Profile

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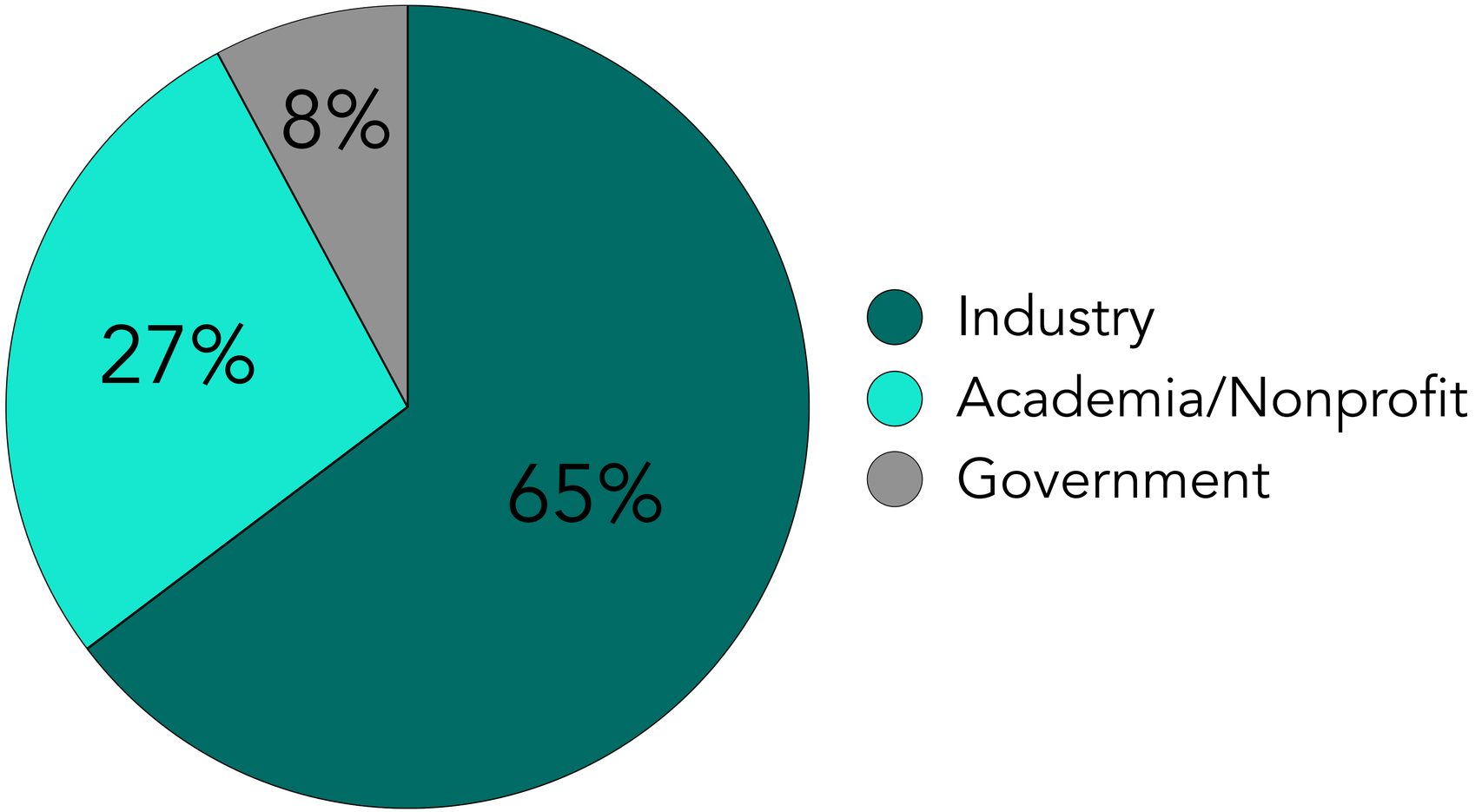

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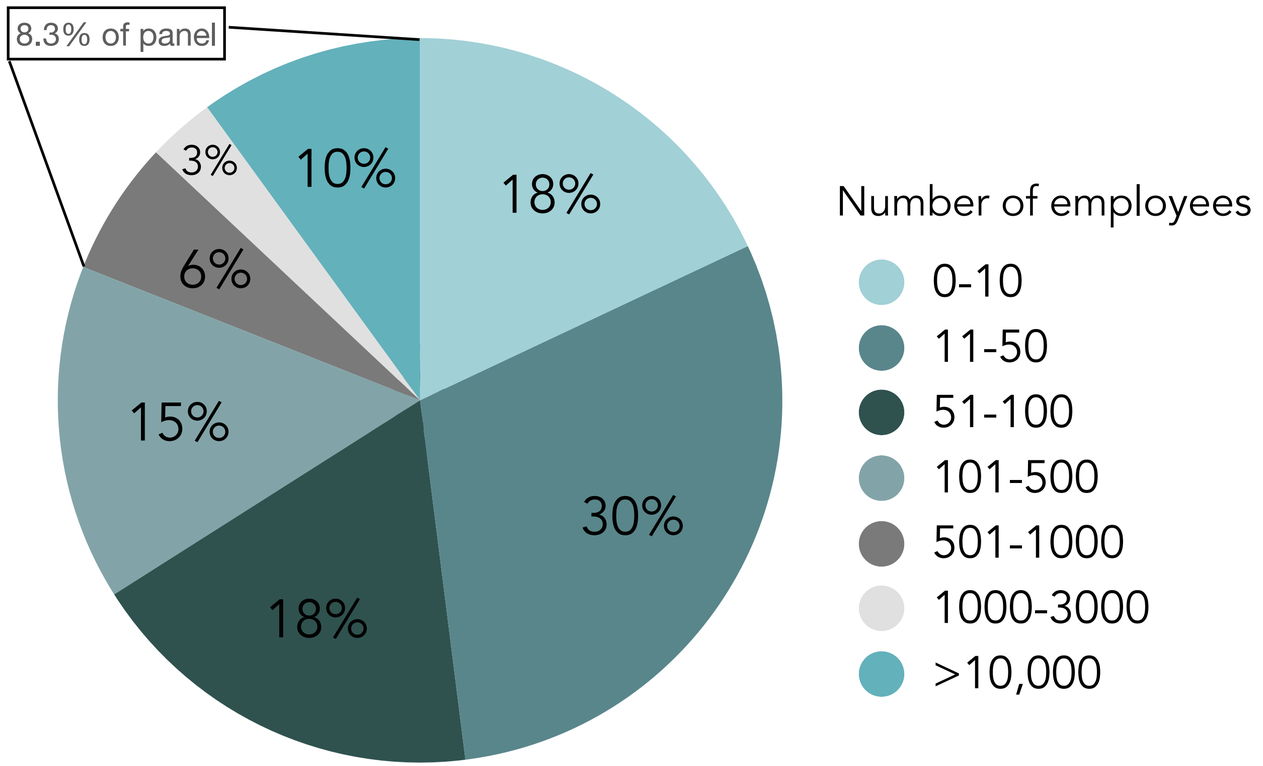
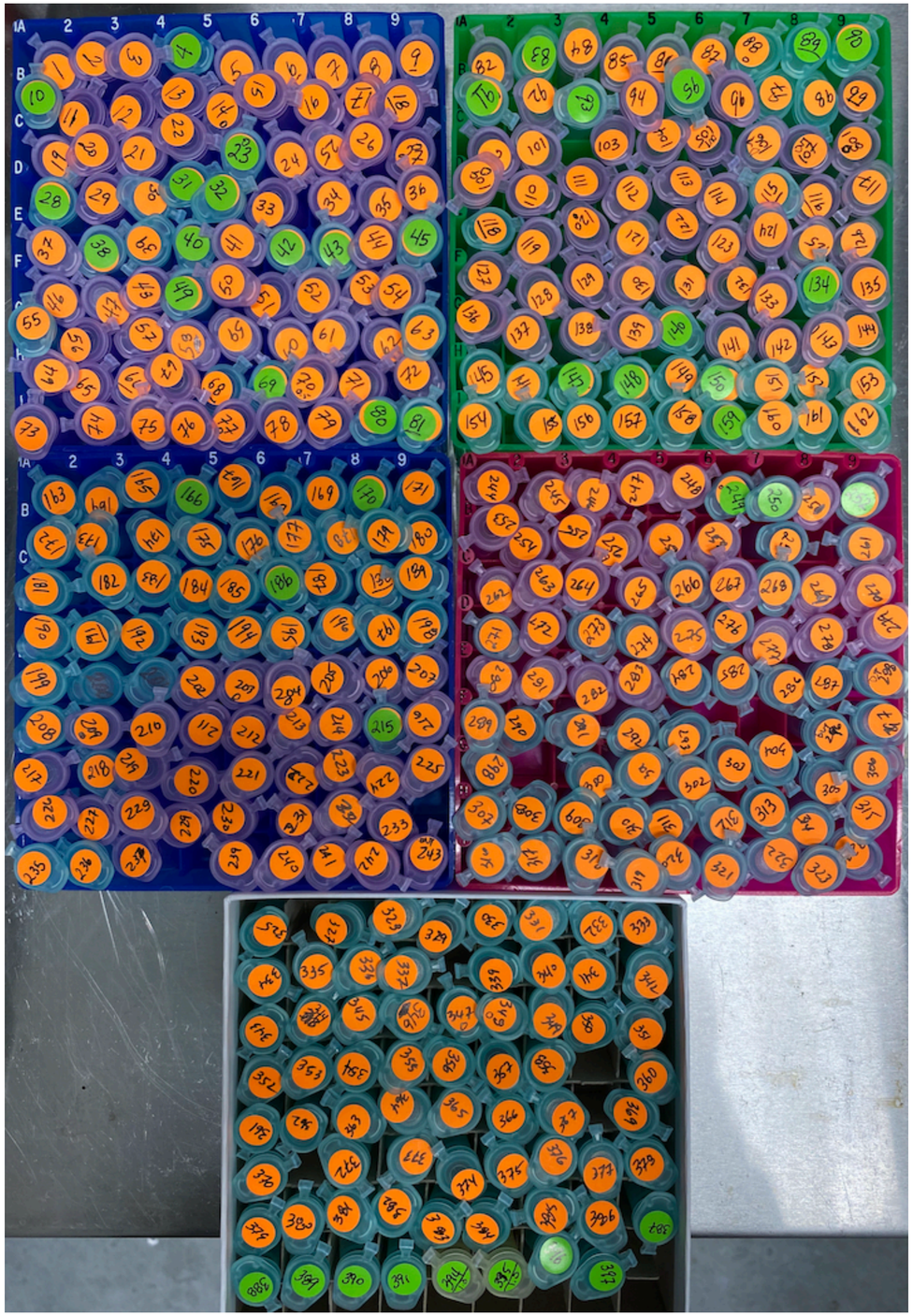
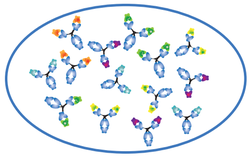




CoVIC workflow



downselect (affinity, block ACE2 binding, neutralize)

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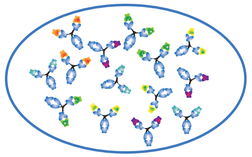

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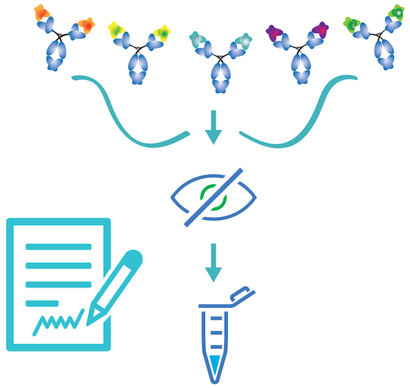

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aliquot & distribute

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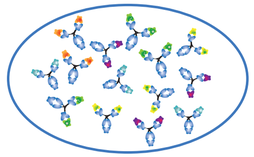

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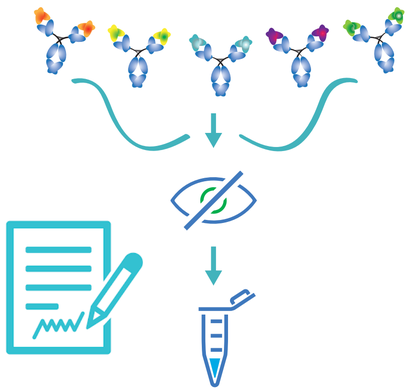

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assay	affinity avidity isotype	epitope binning	neutralization pseudotyped virus	neutralization authentic virus	in vivo protection	structural[a] analyses	FcRN model	Fc activities	escape resistance
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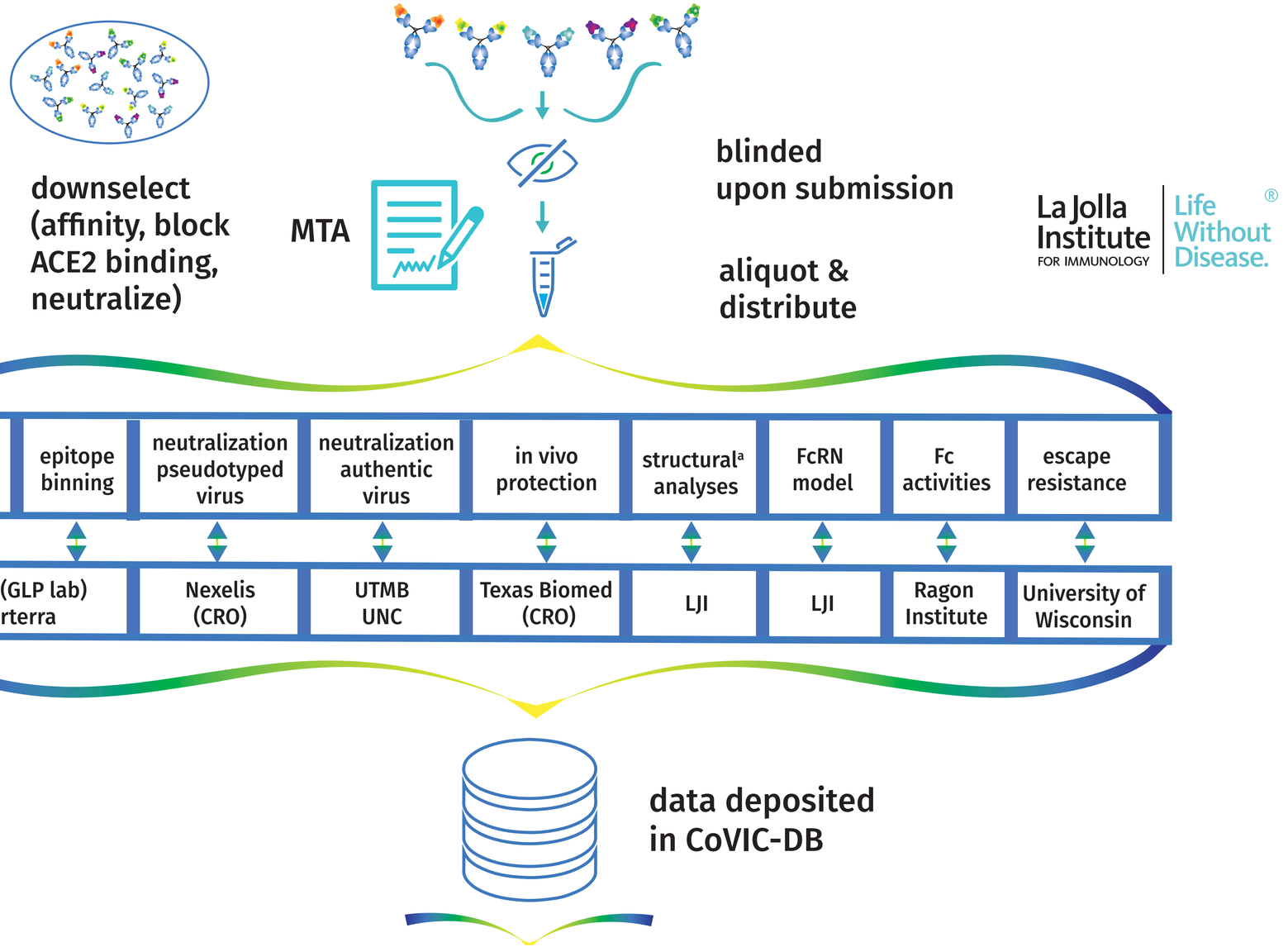
CoVIC workflow



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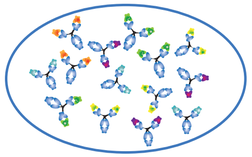

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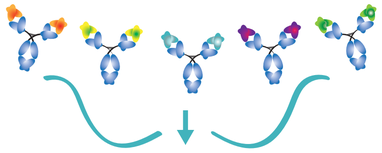

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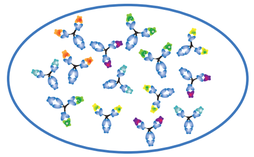
data deposited in CoVIC-DB

analyze and downselect

CoVIC workflow



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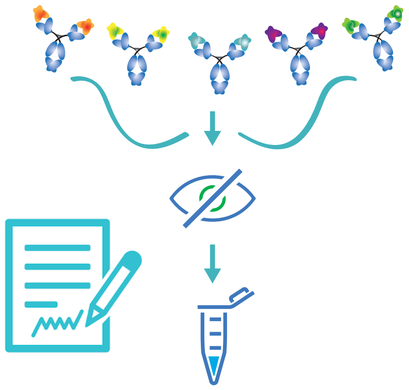

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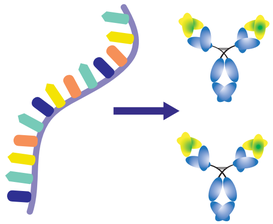
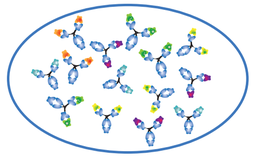


sequence optimization

CoVIC workflow



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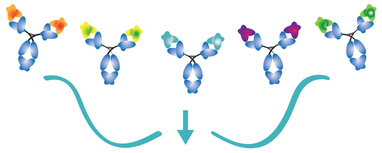

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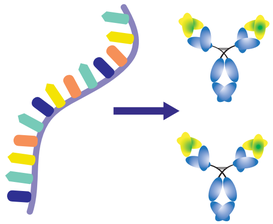

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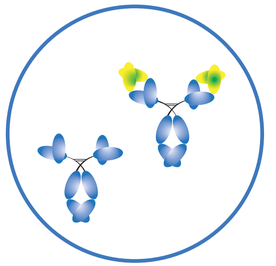
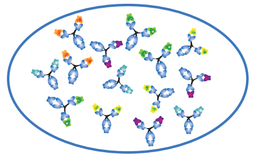


therapeutic antibody cocktails

CoVIC workflow



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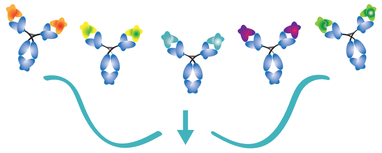

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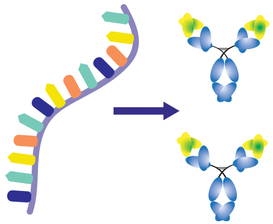

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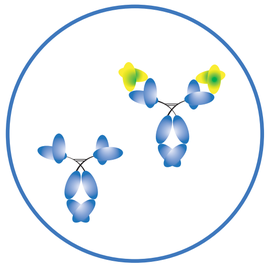

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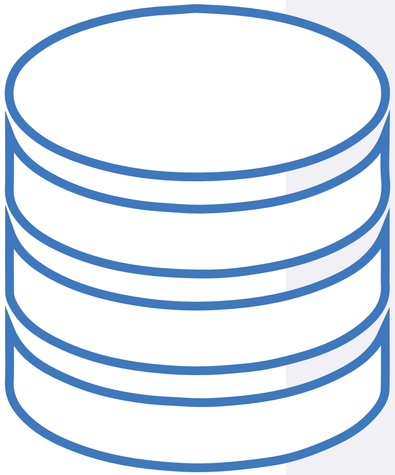
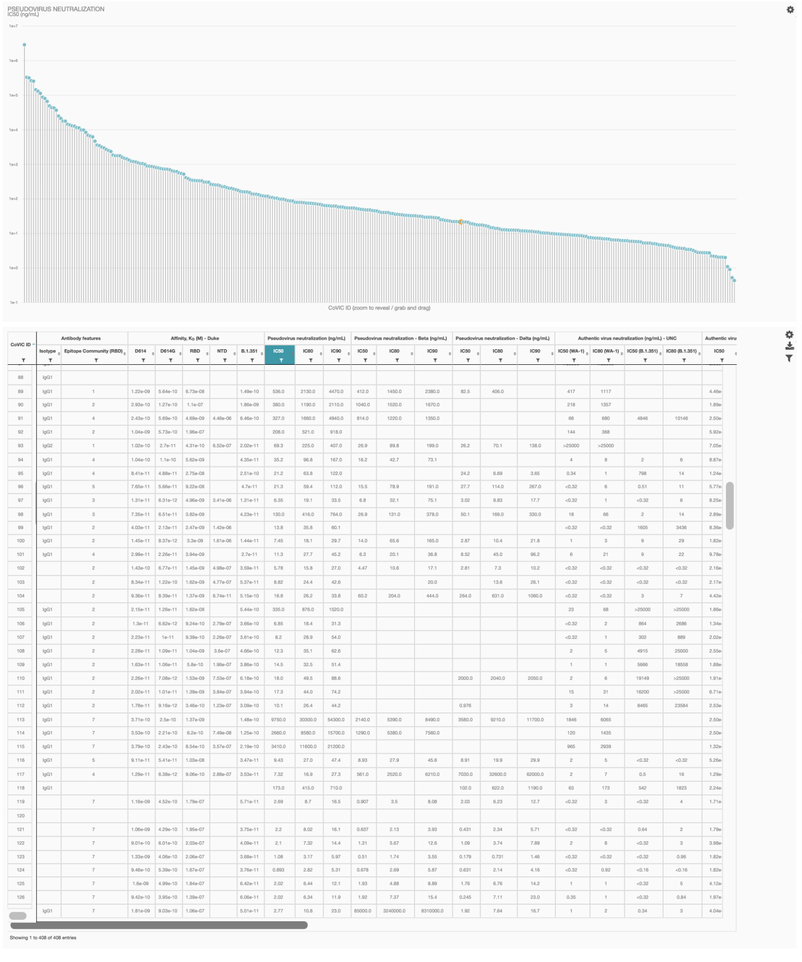
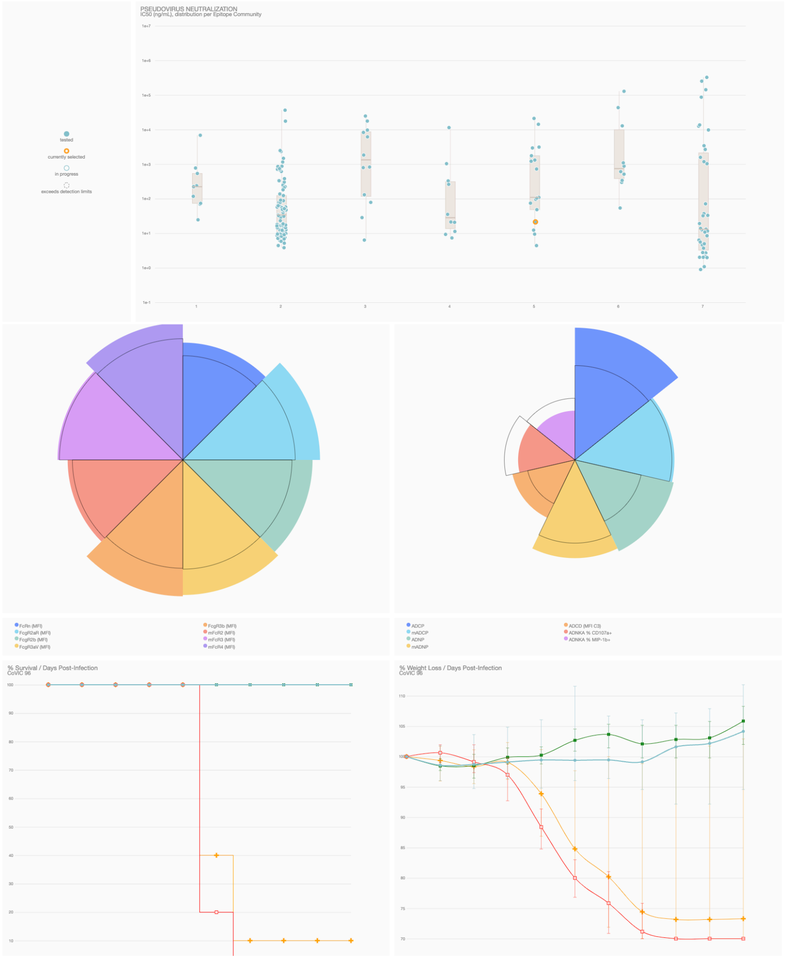
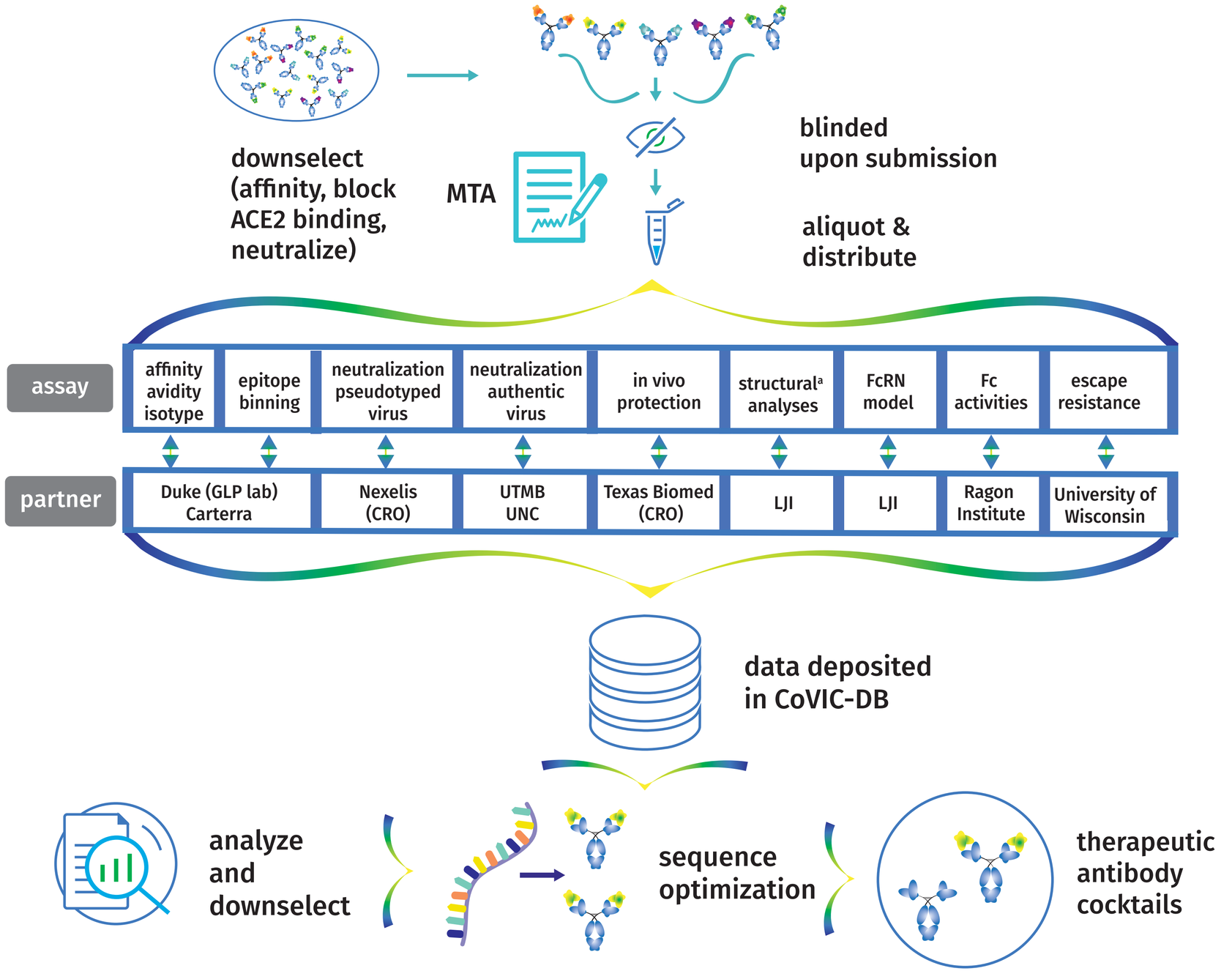






COVIC-DB: https://covicdb-submission.lji.org/dashboard

Brendan Ha, Mari Kojima, Randi Vita, Mahita Jarjapu, James Overton, Anais Gambiez, Jason Greenbaum, Bjoern Peters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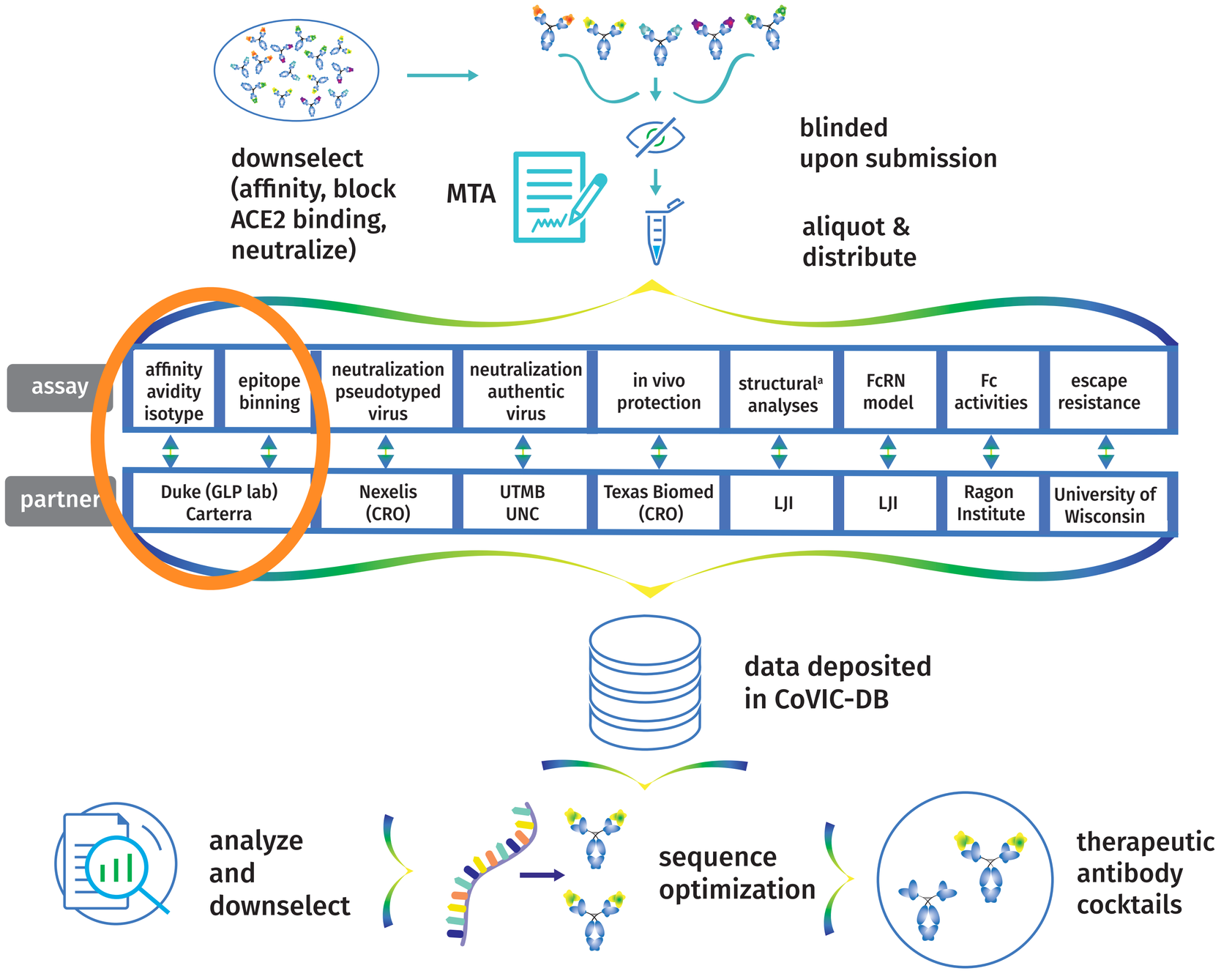
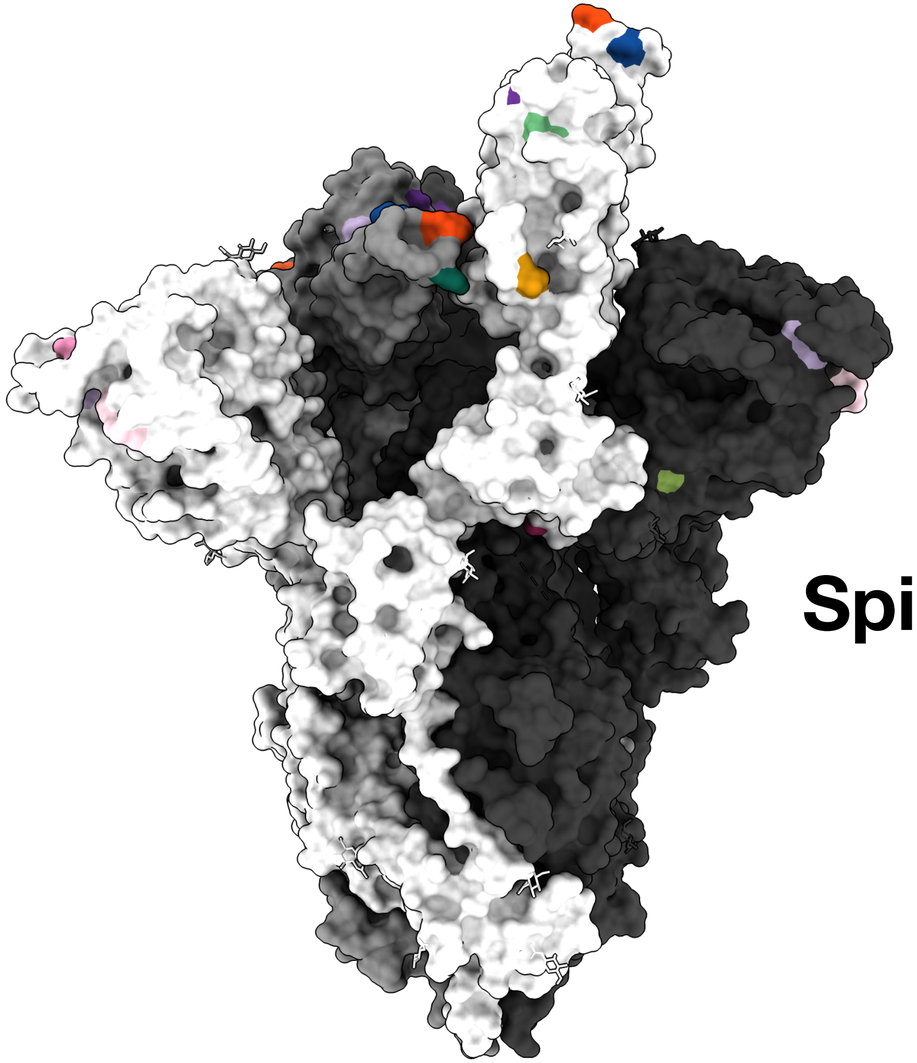
sequence optimization
therapeutic antibody cocktails


downselect
(affinity, block
ACE2 binding,
neutralize)
MTA
blinded
upon submission
aliquot &
distribute
assay
affinity
avidity
isotype
epitope
binning
neutralization
pseudotyped
virus
neutralization
authentic
virus
in vivo
protection
structural[a]
analyses
FcRN
model
Fc
activities
escape
resistance
partner
Duke (GLP lab)
Carterra
Nexelis
(CRO)
UTMB
UNC
Texas Biomed
(CRO)
LJI
LJI
Ragon
Institute
University of
Wisconsin
data deposited
in CoVIC-DB
analyze
and
downselect
sequence
optimization
therapeutic
antibody
cocktails

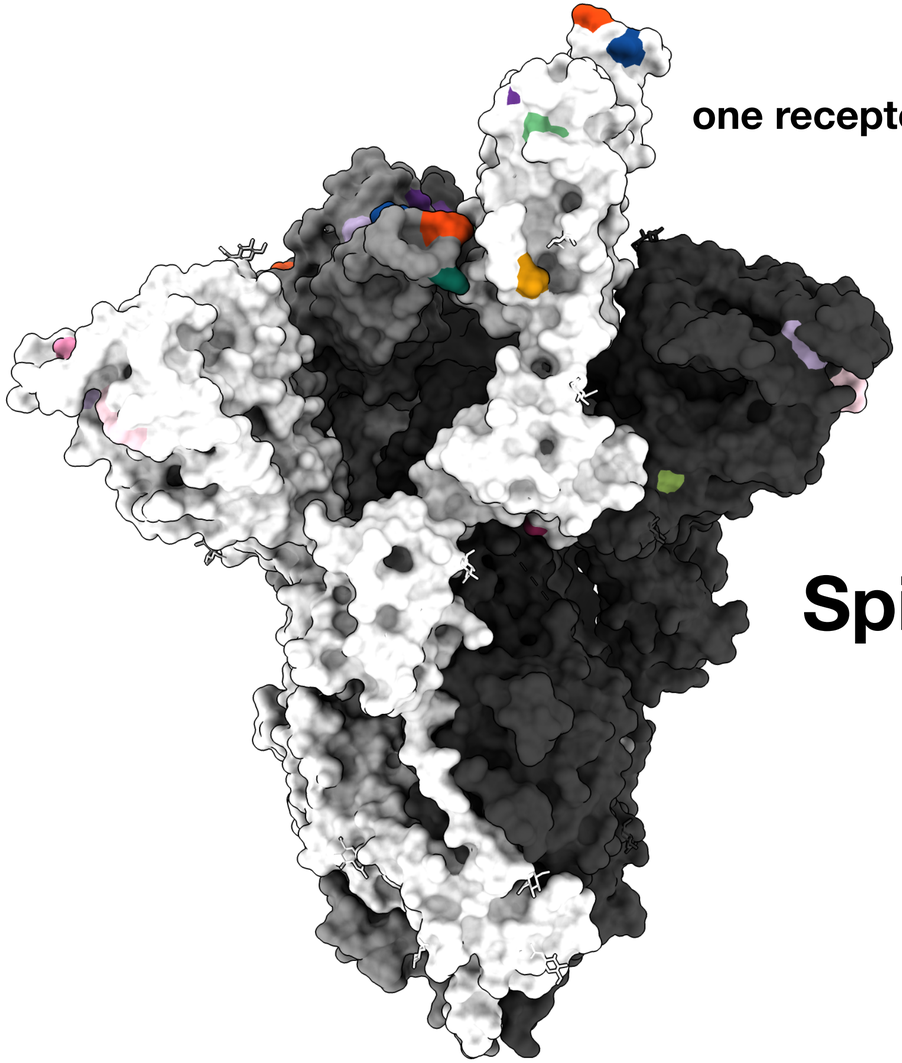
target cell



Spike

viral membrane

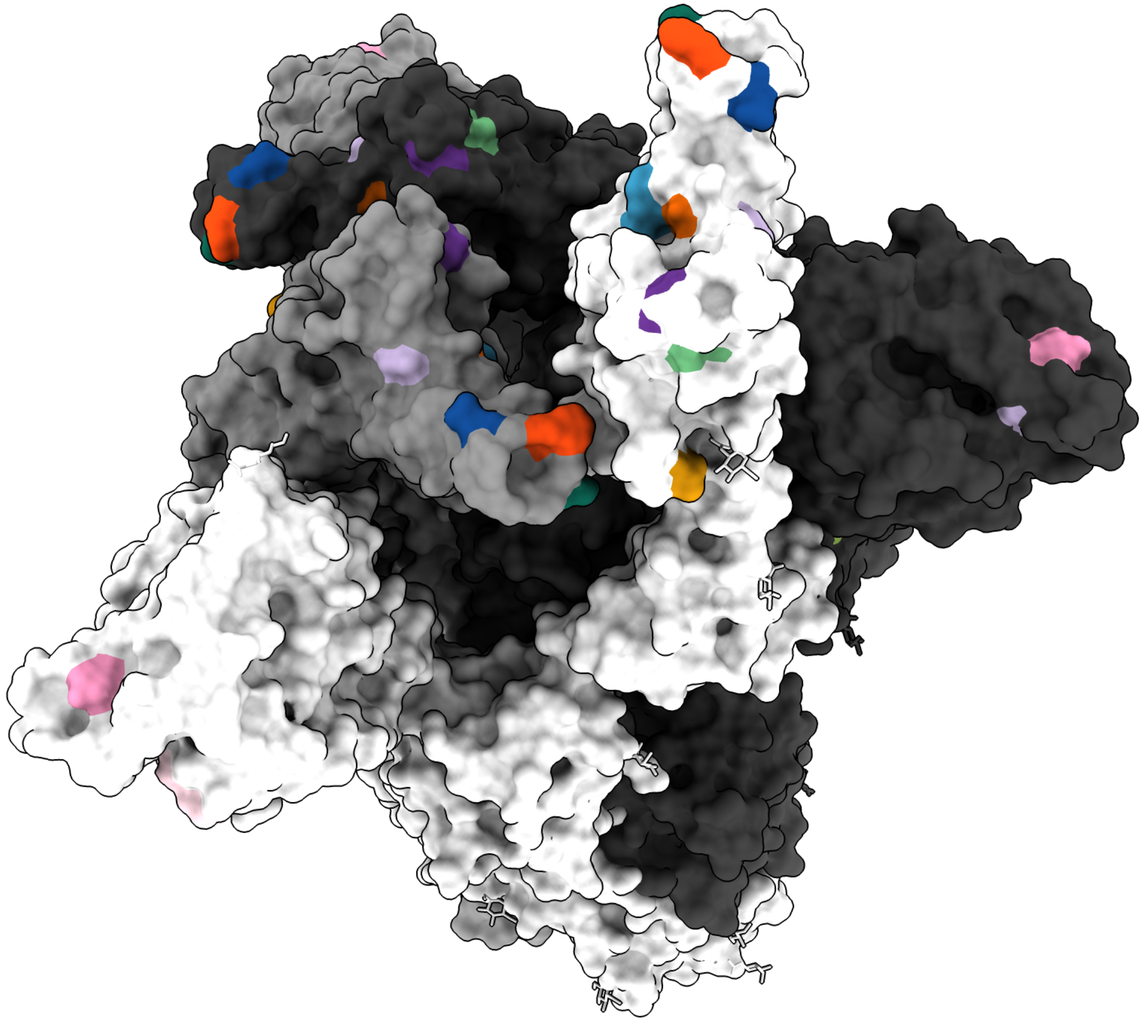
target cell

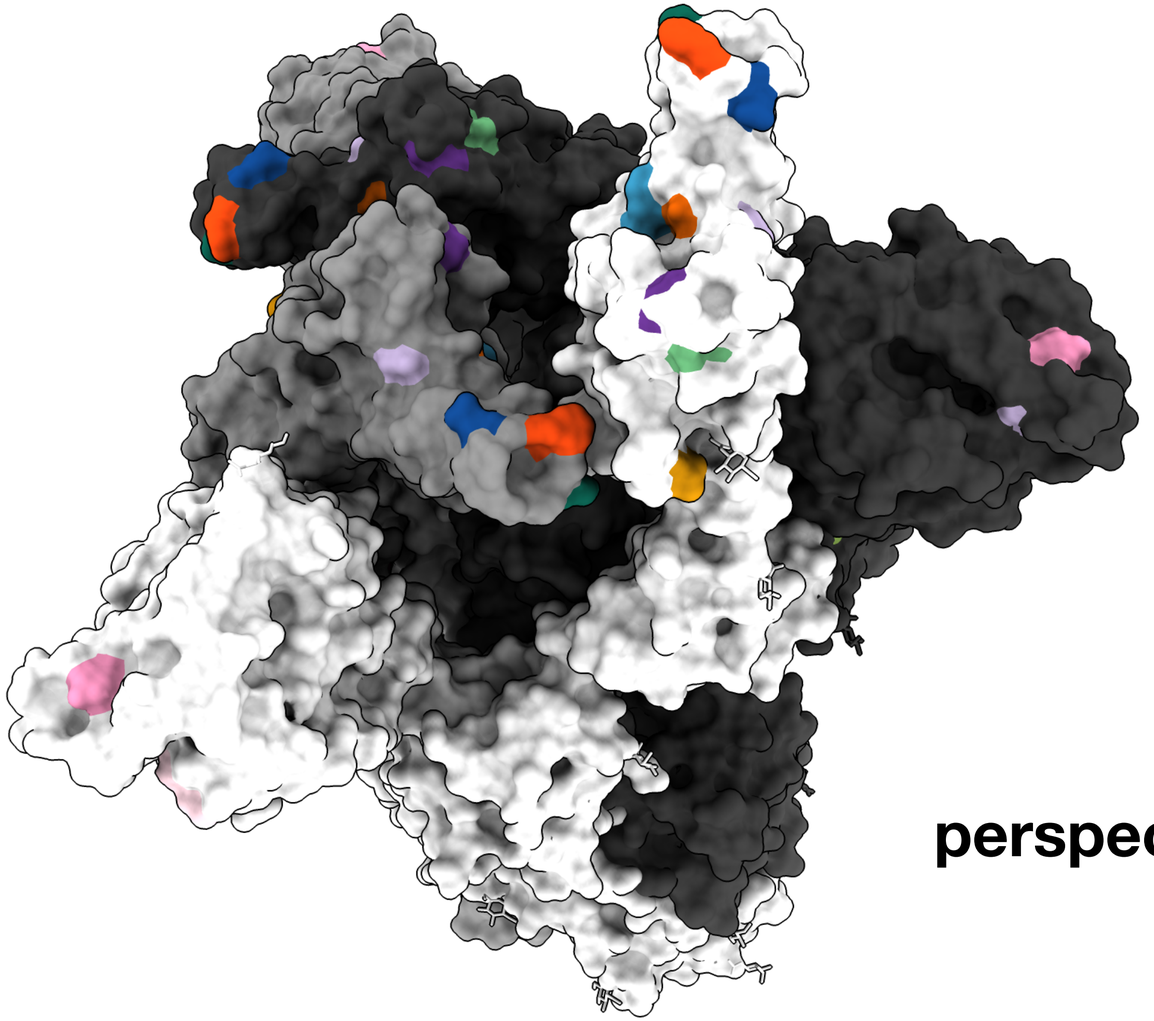


one receptor binding domain is “up”

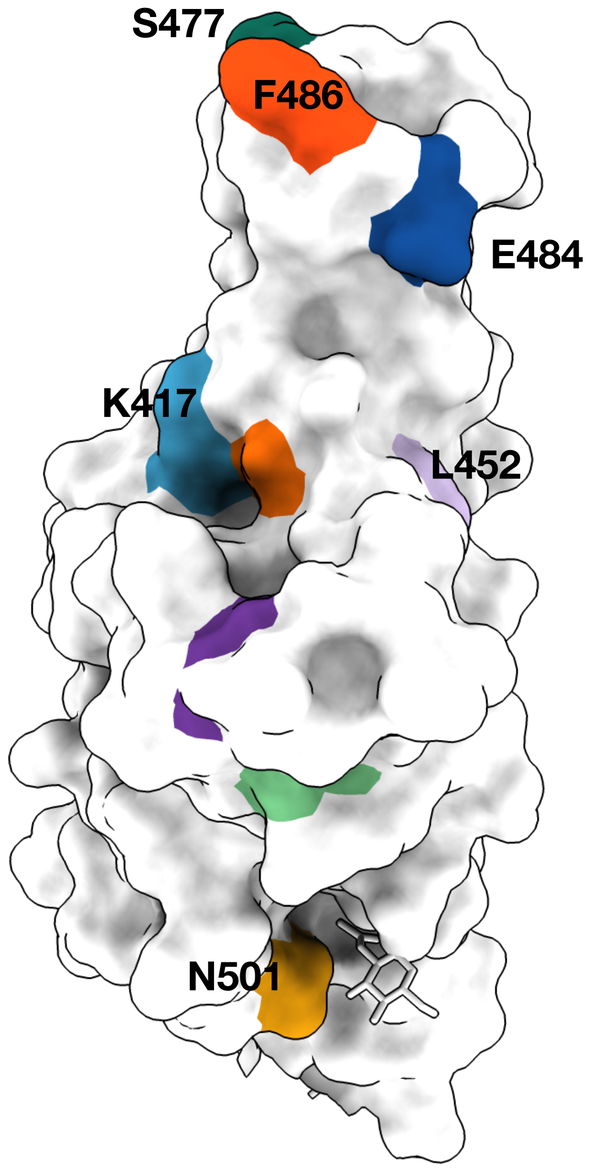
Spike

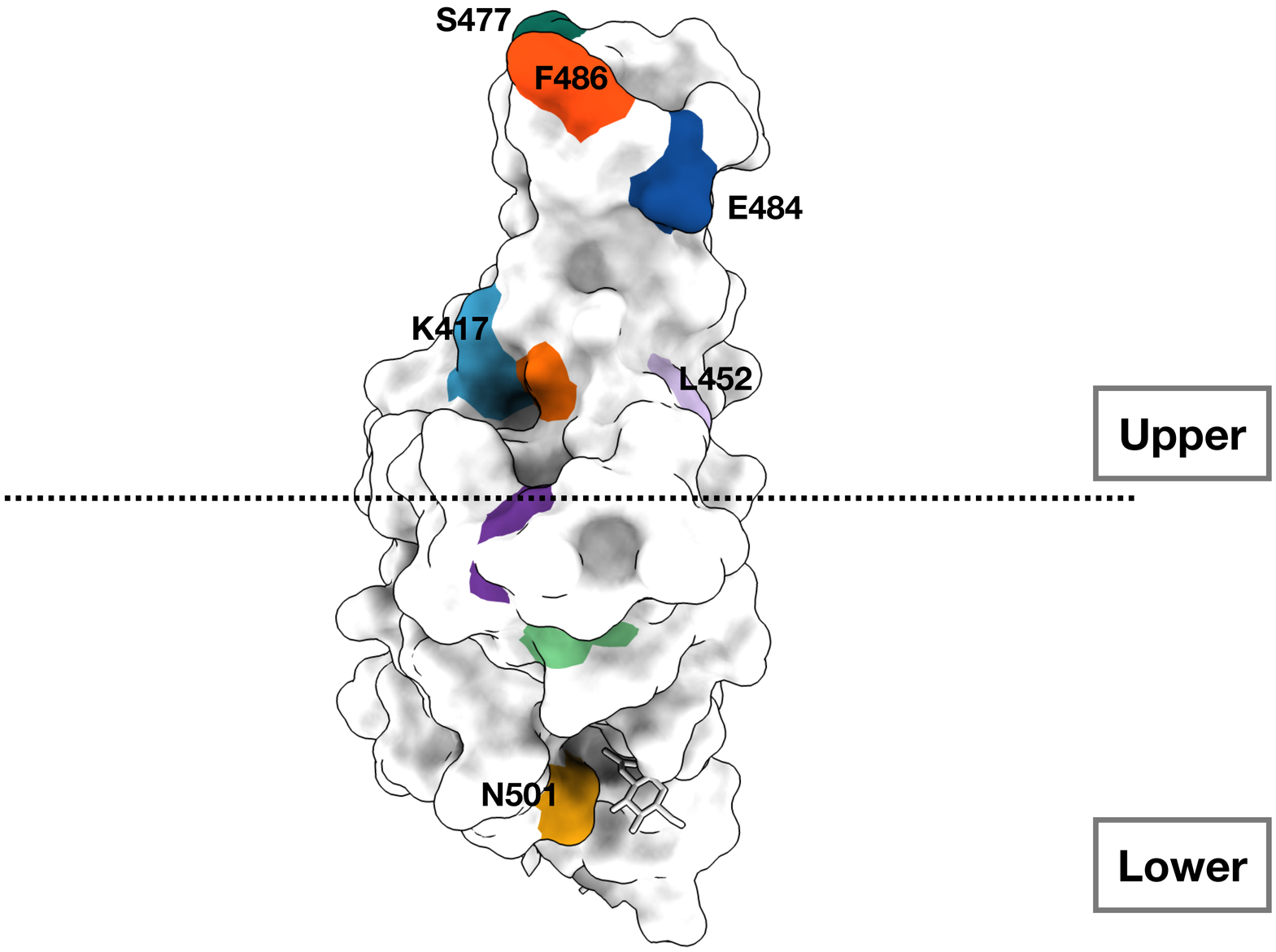
viral membrane

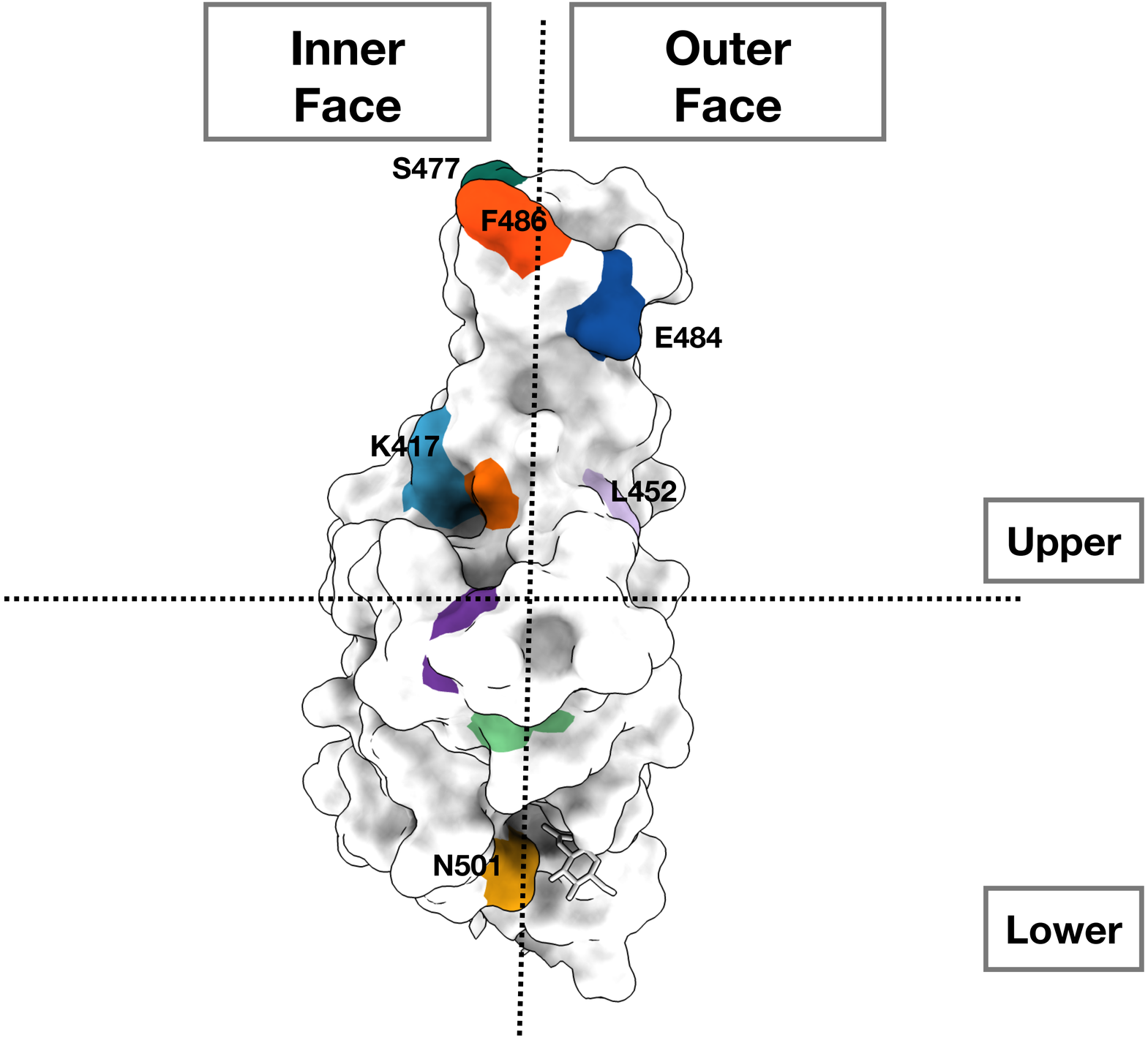


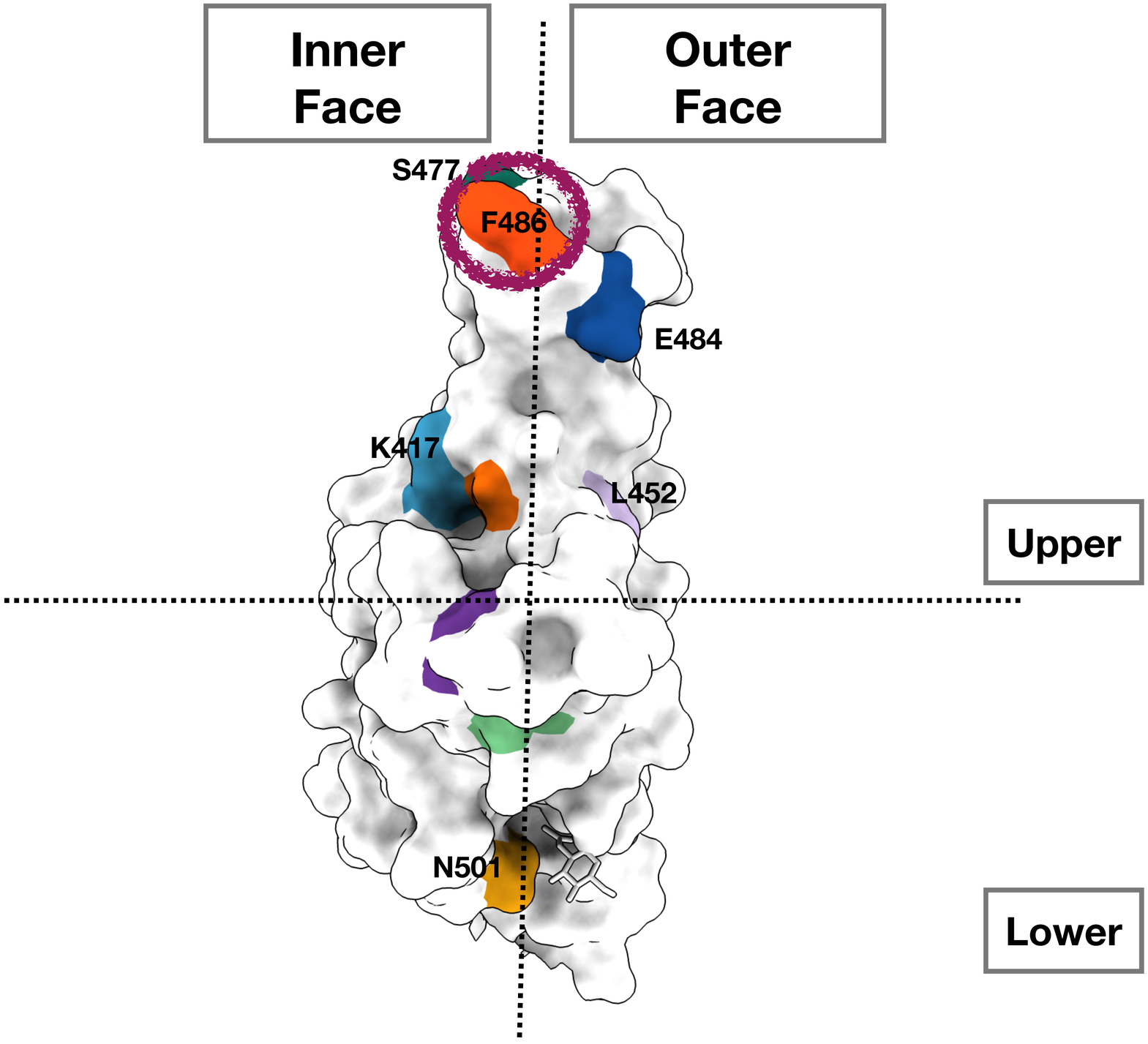


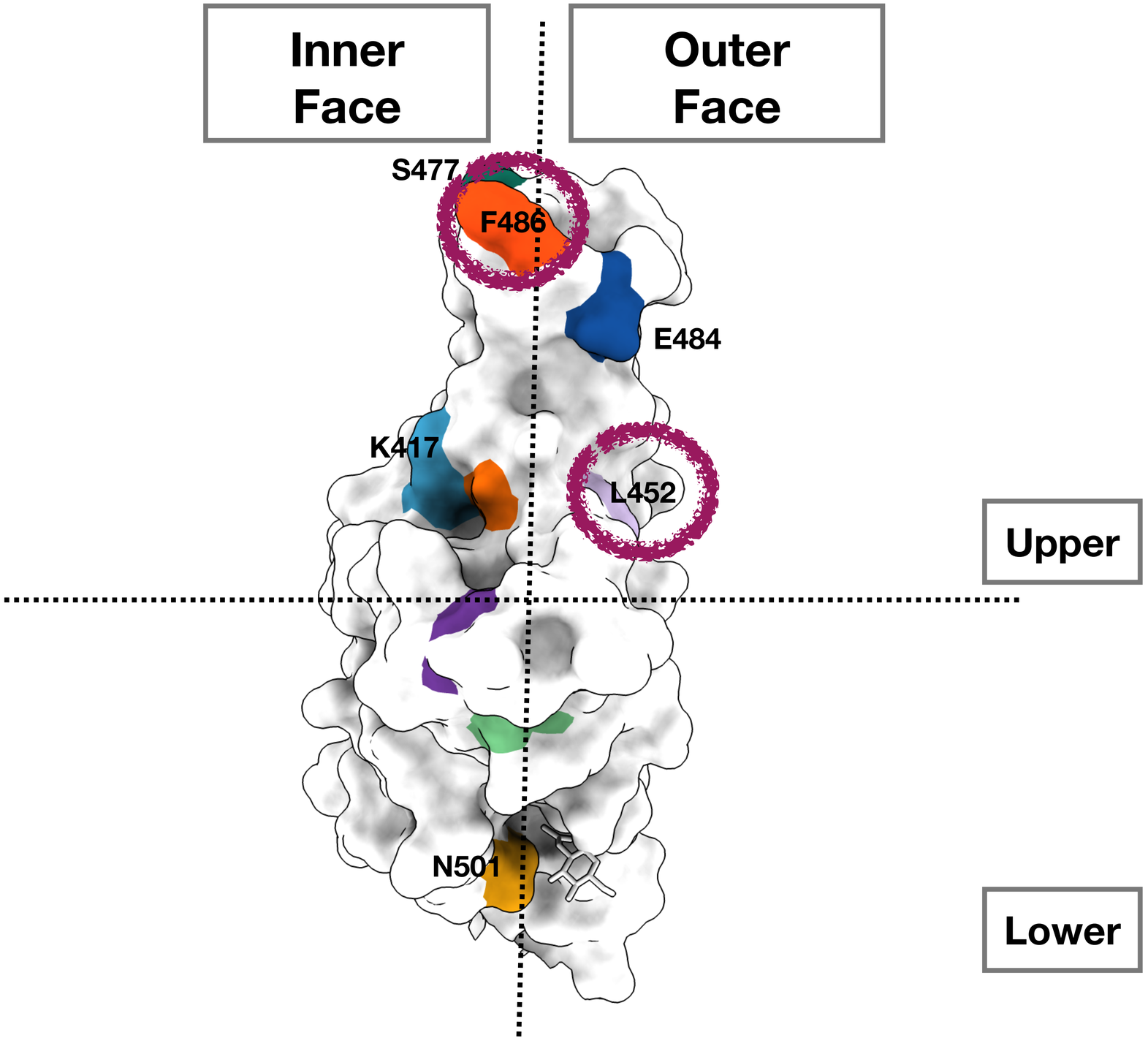
View is from perspective of the target cell

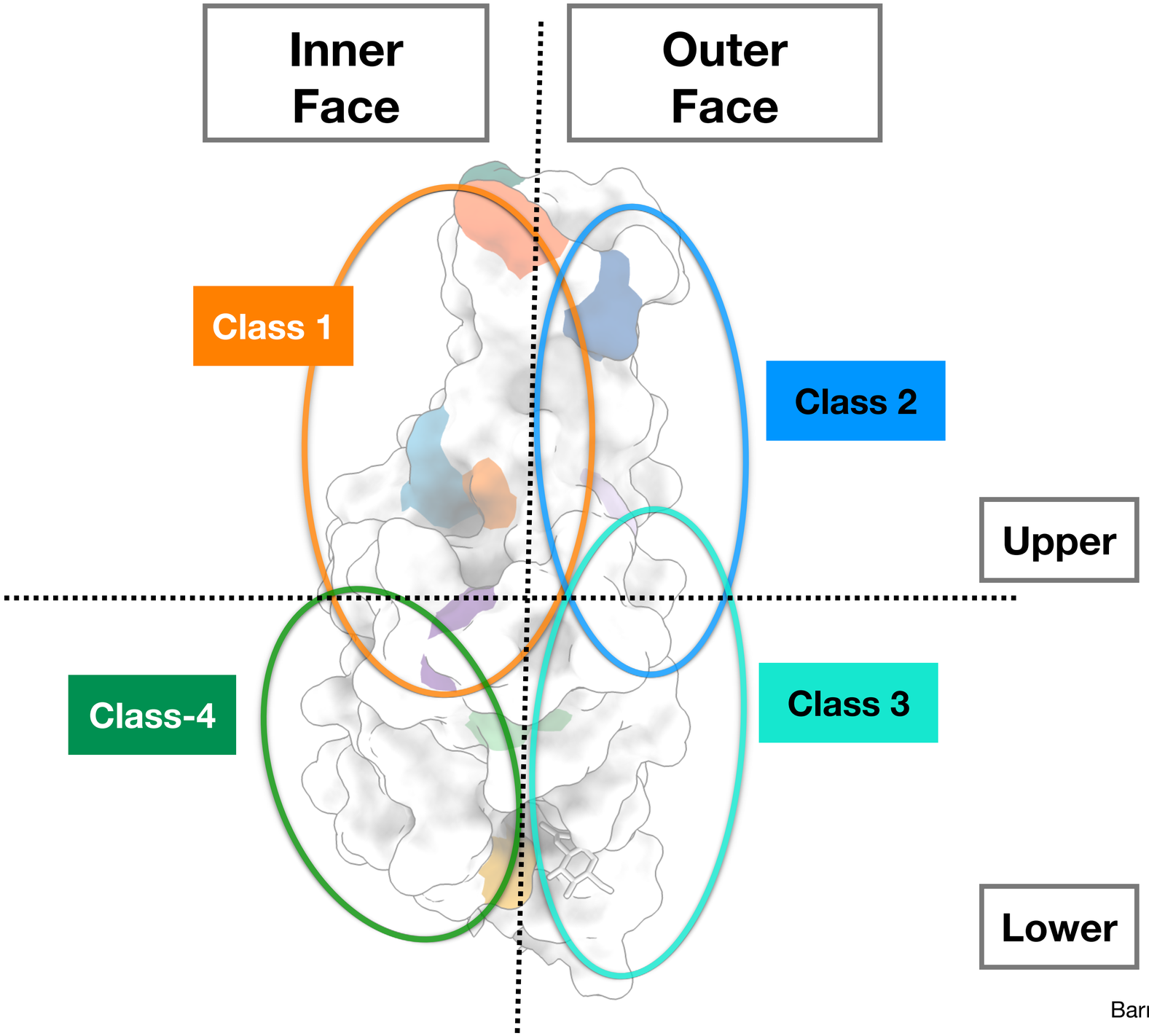

S477
F486
E484
K417
L452
N501


S477
F486
E484
K417
L452
N501
Upper
Lower


Inner Face
Outer Face
S477
F486
E484
K417
L452
N501
Upper
Lower

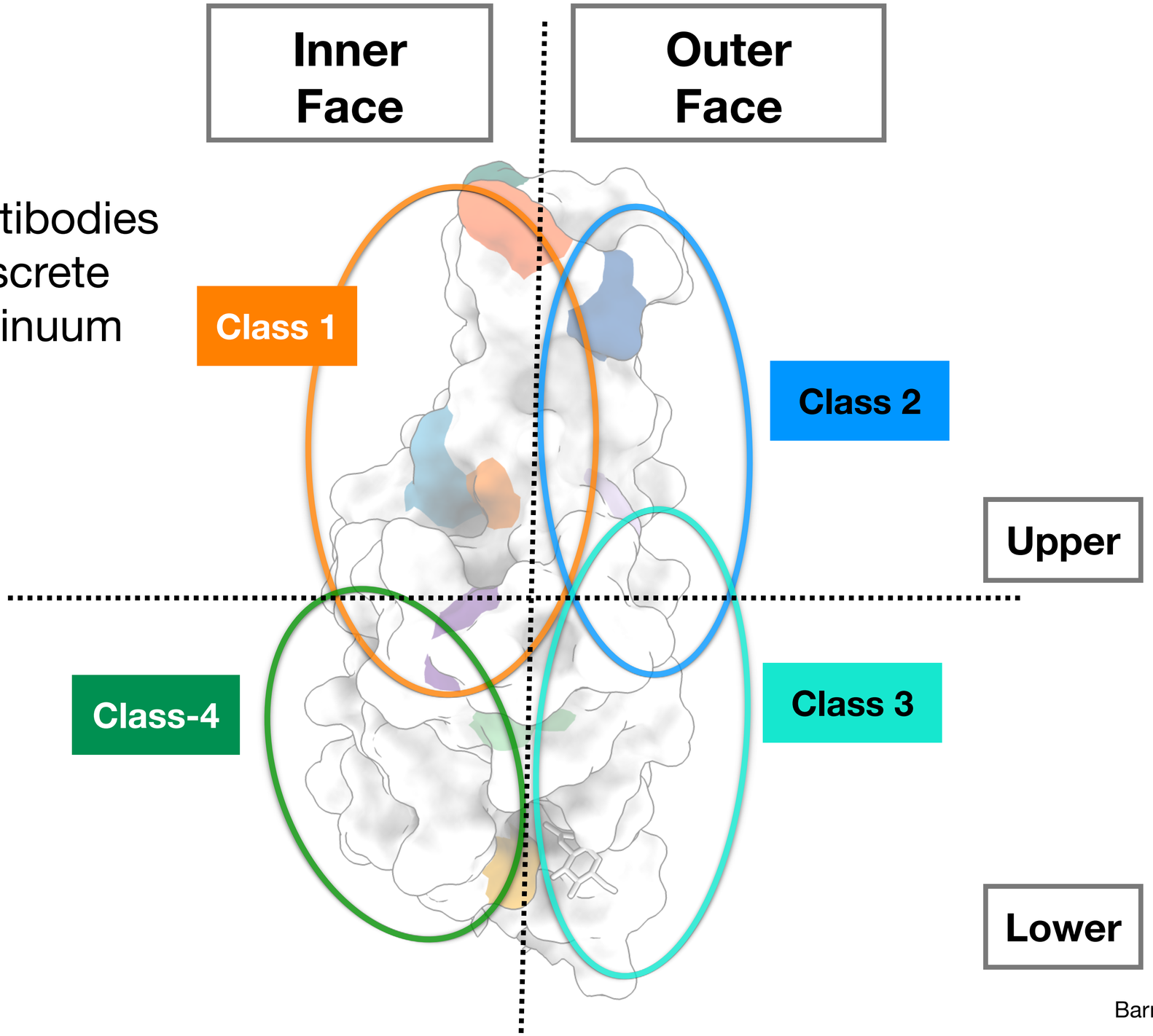

Inner Face
Outer Face
S477
F486
E484
K417
L452
N501
Upper
Lower


Inner Face
Outer Face
S477
F486
E484
K417
L452
N501
Upper
Lower



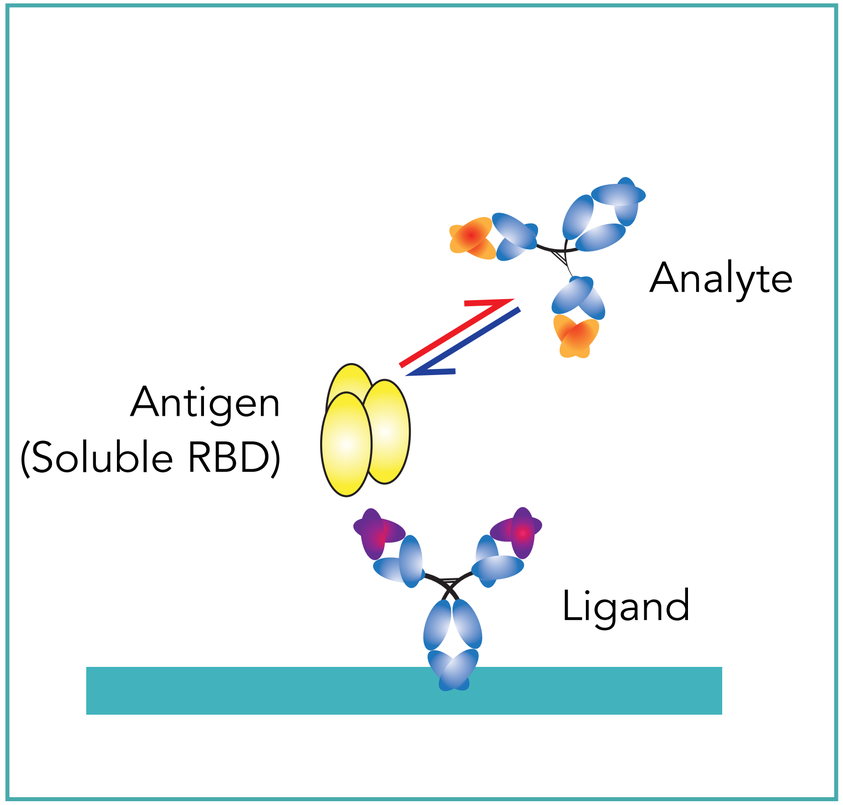
Barnes, et al, Nature, 2020

Quintillion possible antibodies
Epitopes are not discrete
Landscape is a continuum

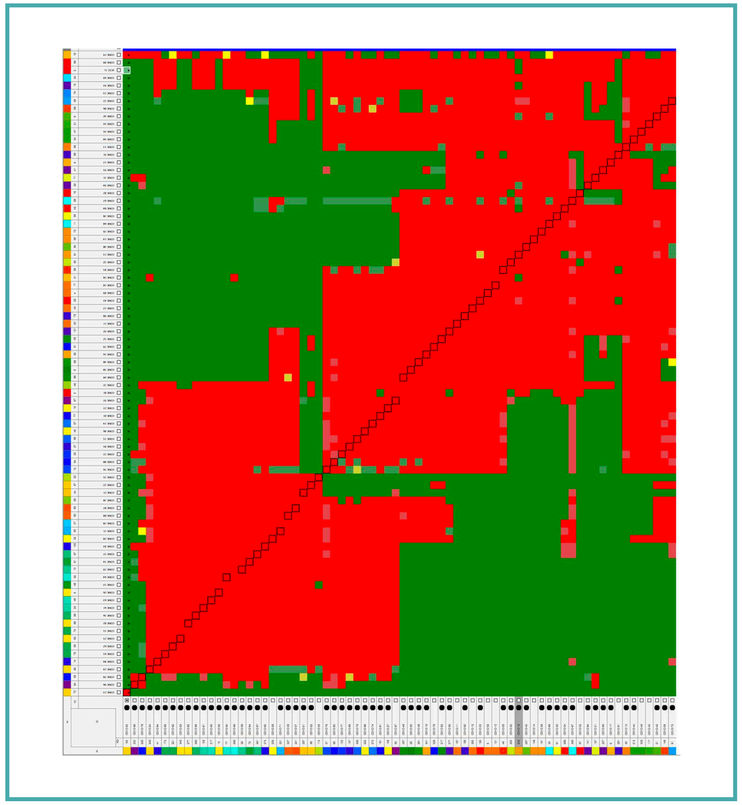


Barnes, et al, Nature, 2020

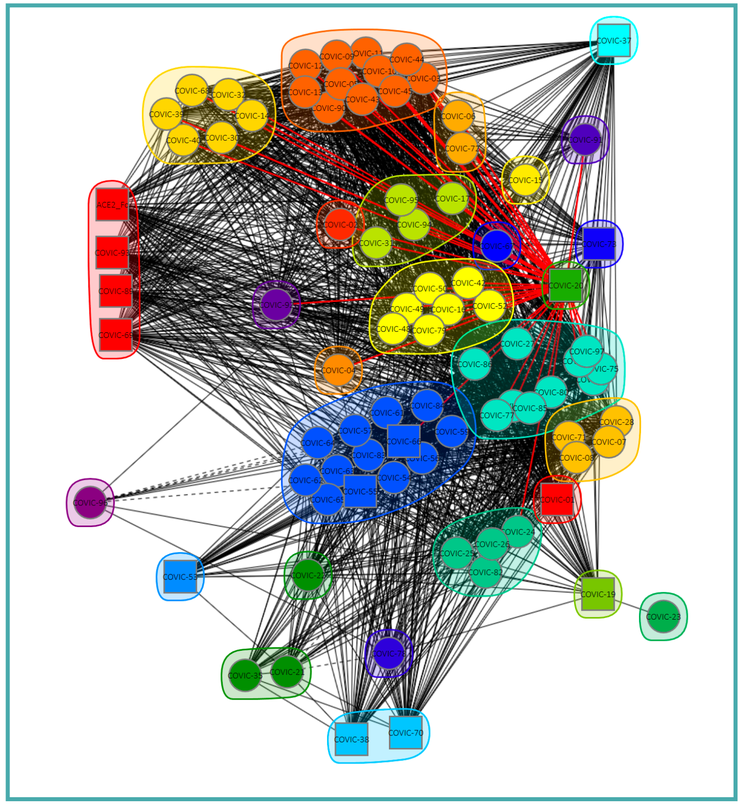
Epitope binning



Antibodies arrayed on chip and a second set of antibodies is flowed across the chip



Interaction matrix of antibodies in ligand (rows) vs. analyte (columns) format
Red: blocking pairs; Green: sandwiching pairs; black outline (self)

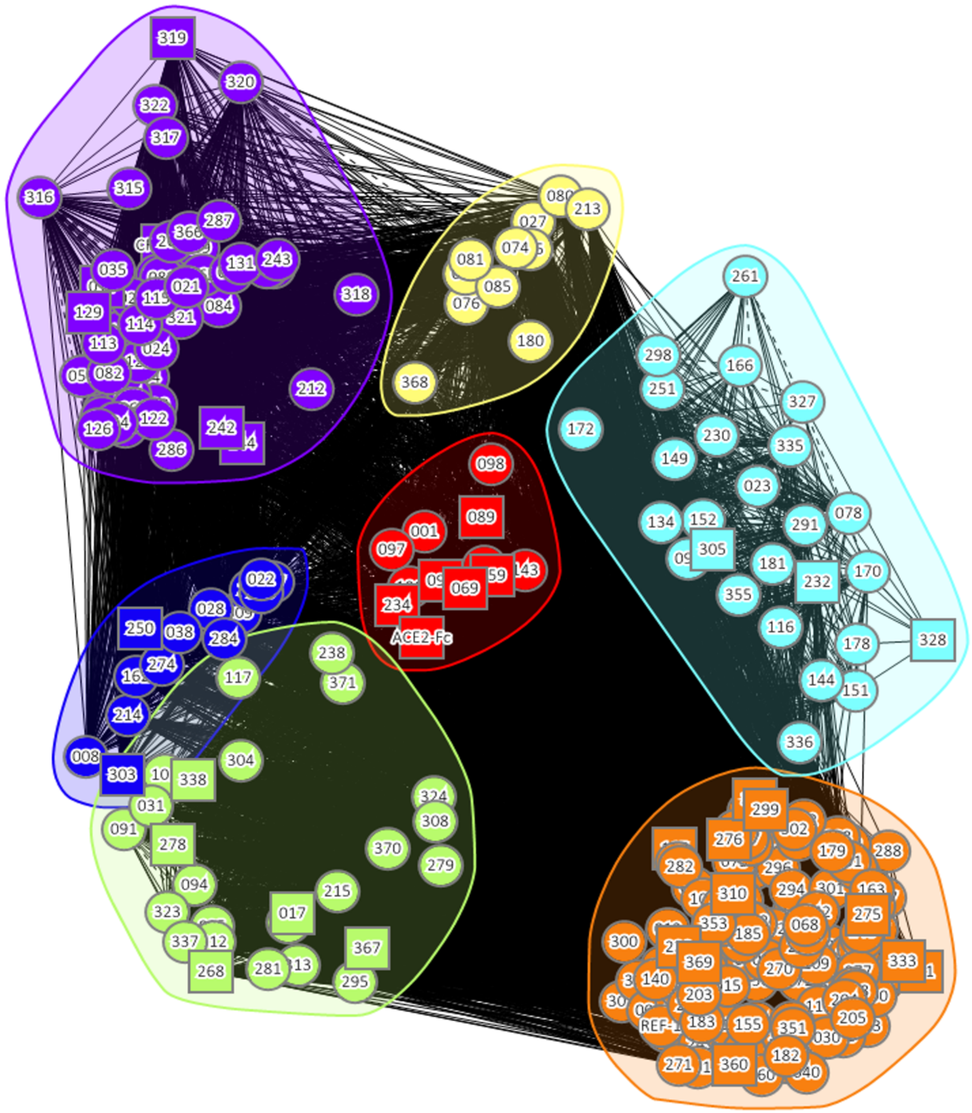


Network plot; epitope bins are colored and correspond to heat map plot

Dan Bedinger
carterra

First, competition analysis:

~370 mAbs analyzed in HTP SPR (Carterra LSA)



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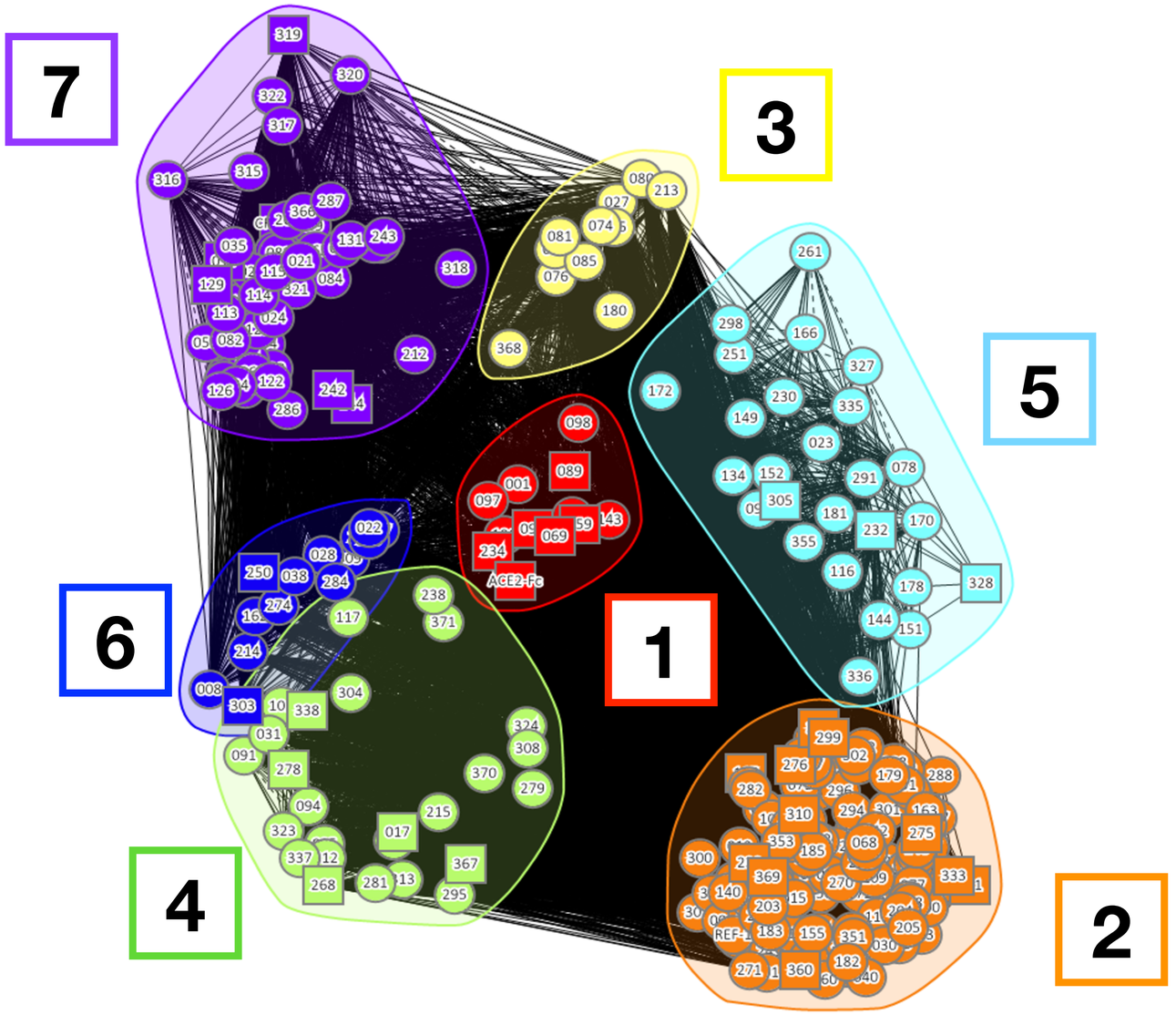
Carterra

7 core RBD-directed communities



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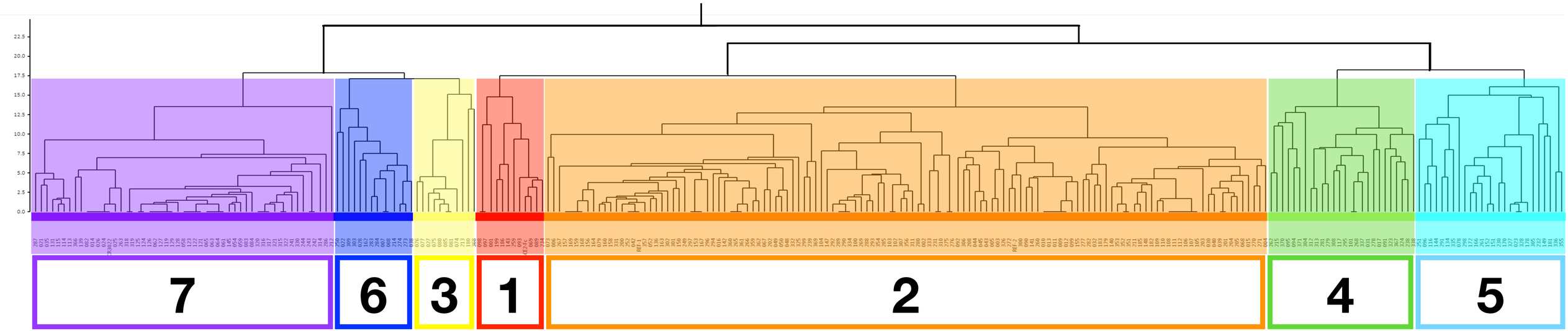
7 core RBD-directed communities



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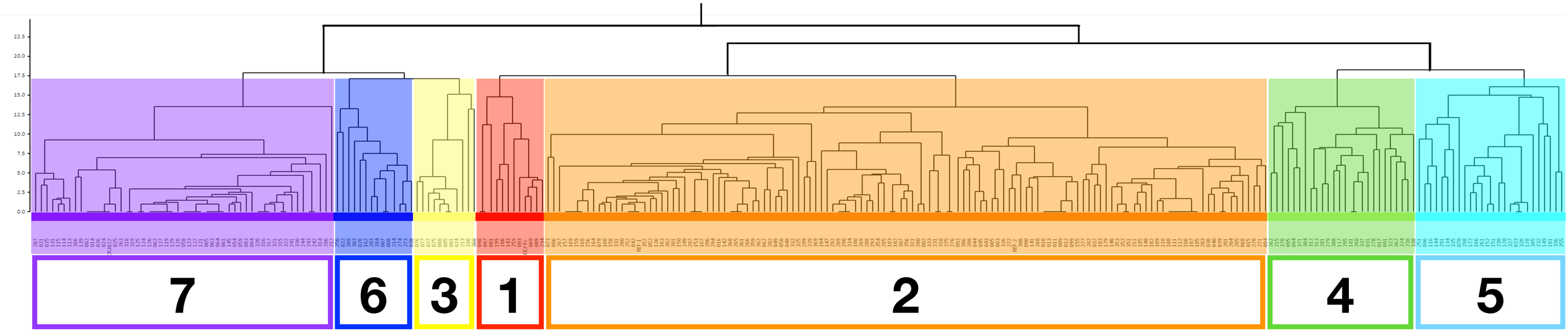
7 core RBD-directed communities

Separation is by degree of competition



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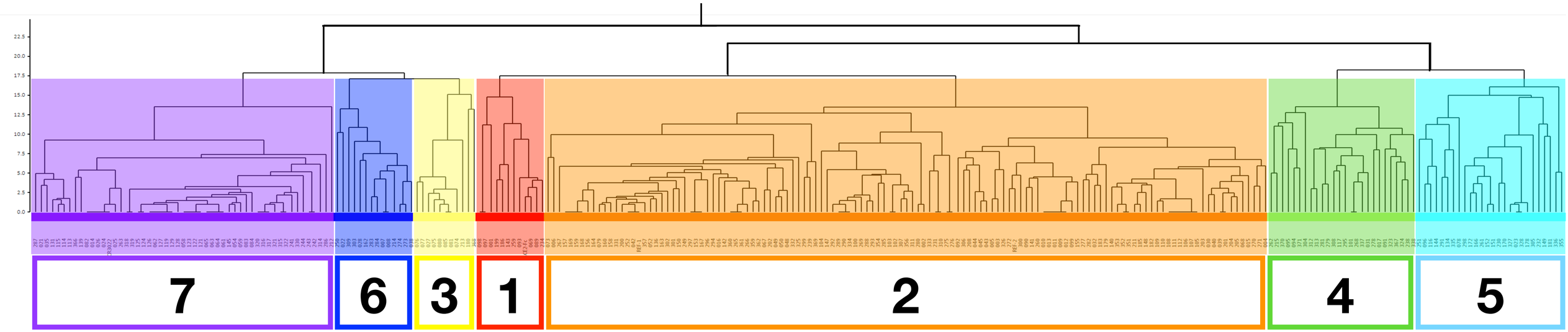
7 core RBD-directed communities

Separation is by degree of competition

first major division



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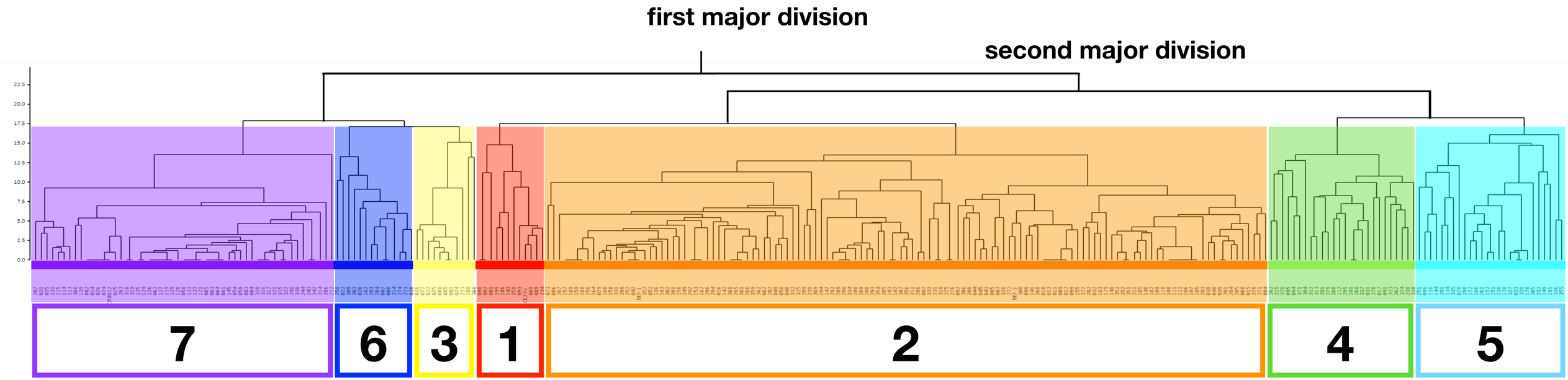
7 core RBD-directed communities

Separation is by degree of competition



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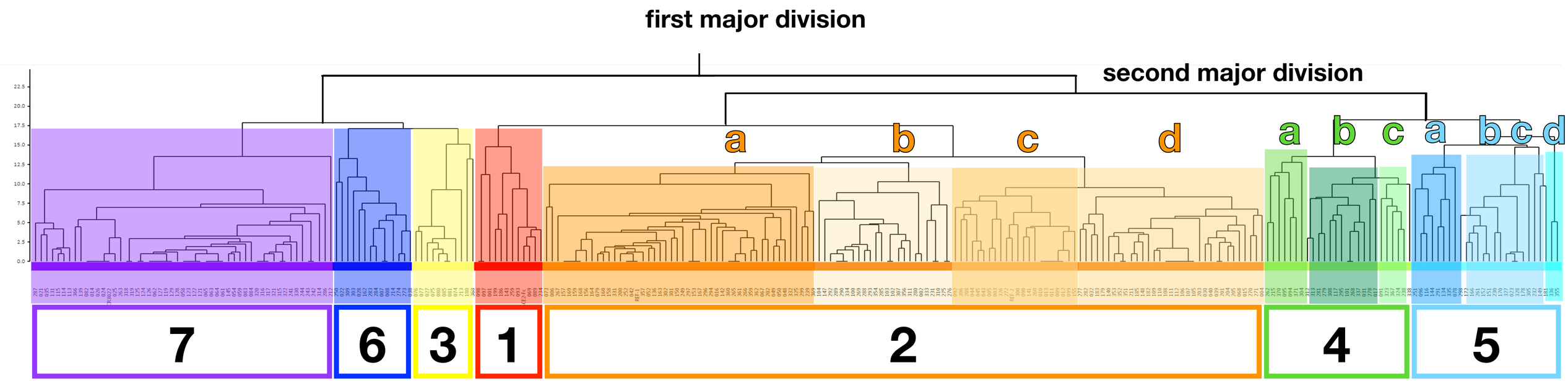
7 core RBD-directed communities

Separation is by degree of competition



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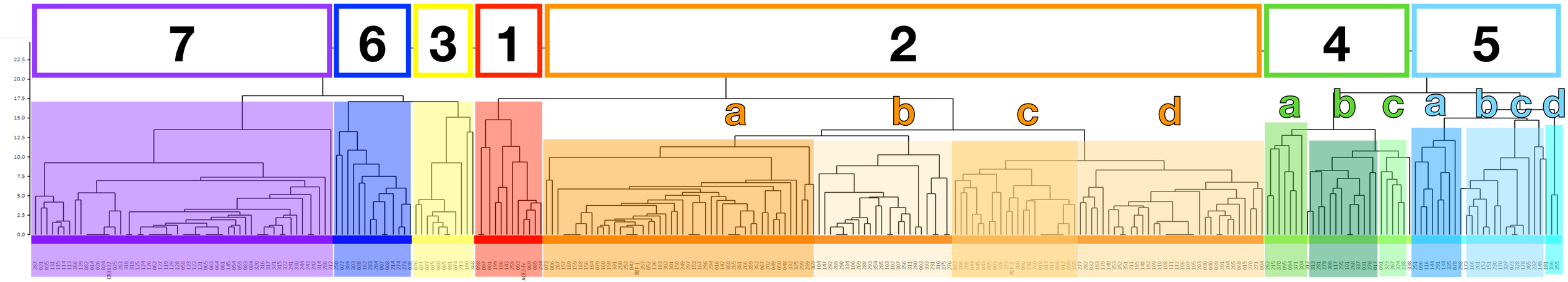
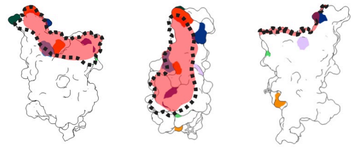
7 core RBD-directed communities

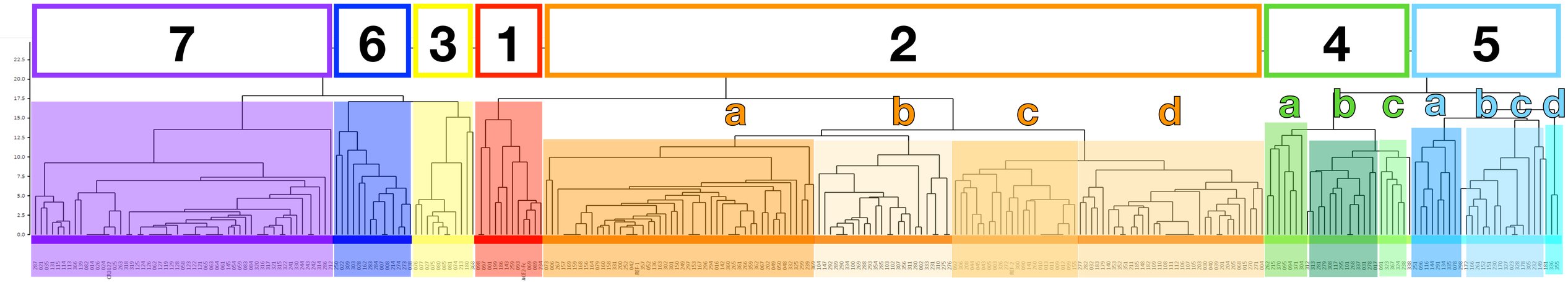


RBD-1



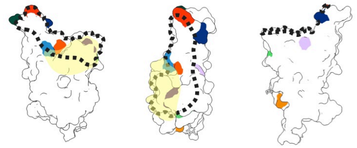
Haoyang Li + Saphire Lab

7 core RBD-directed communities

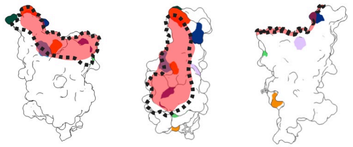


RBD-7

RBD-3

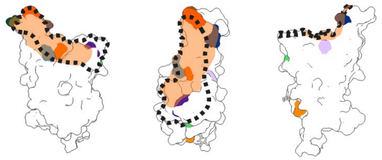


RBD-1



Inner Top Outer

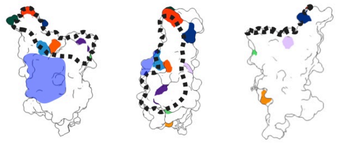
RBD-2



RBD-4

RBD-5

RBD-6



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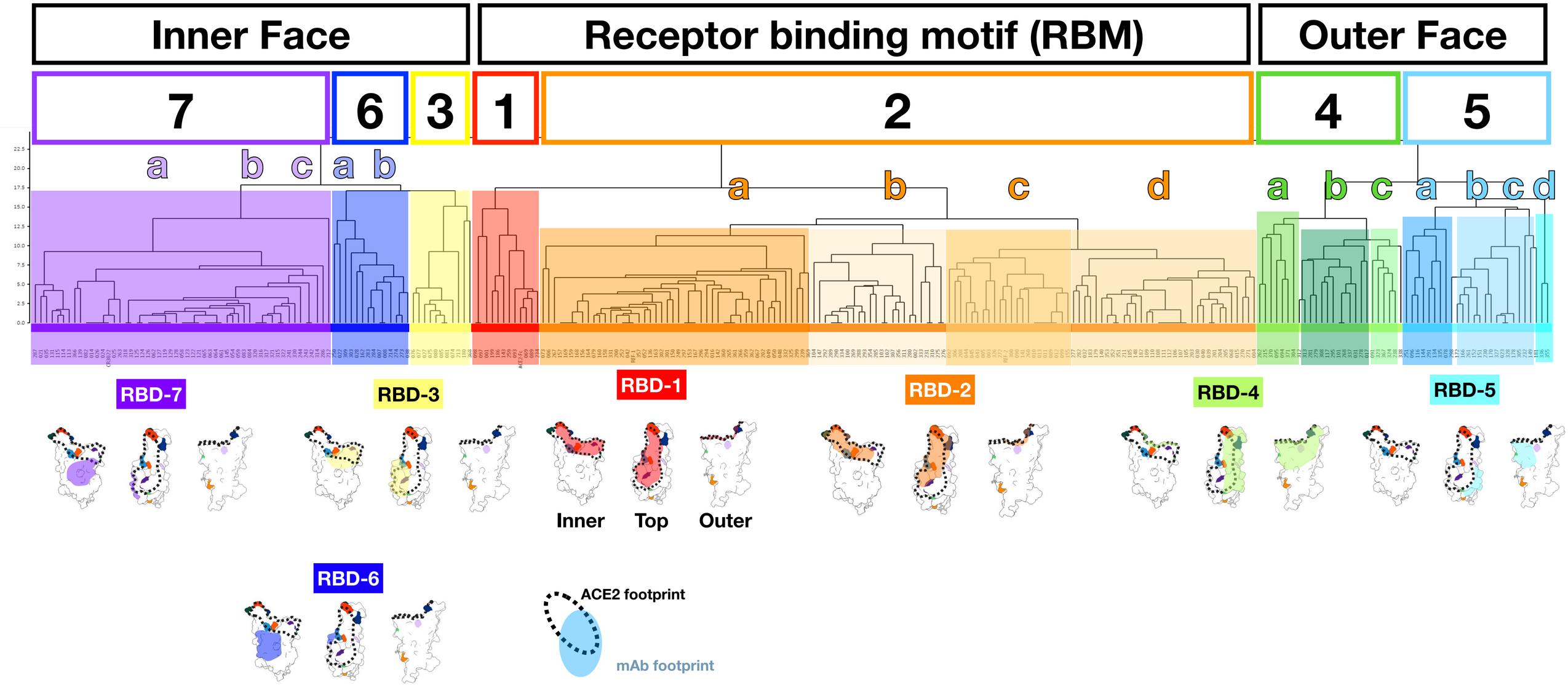
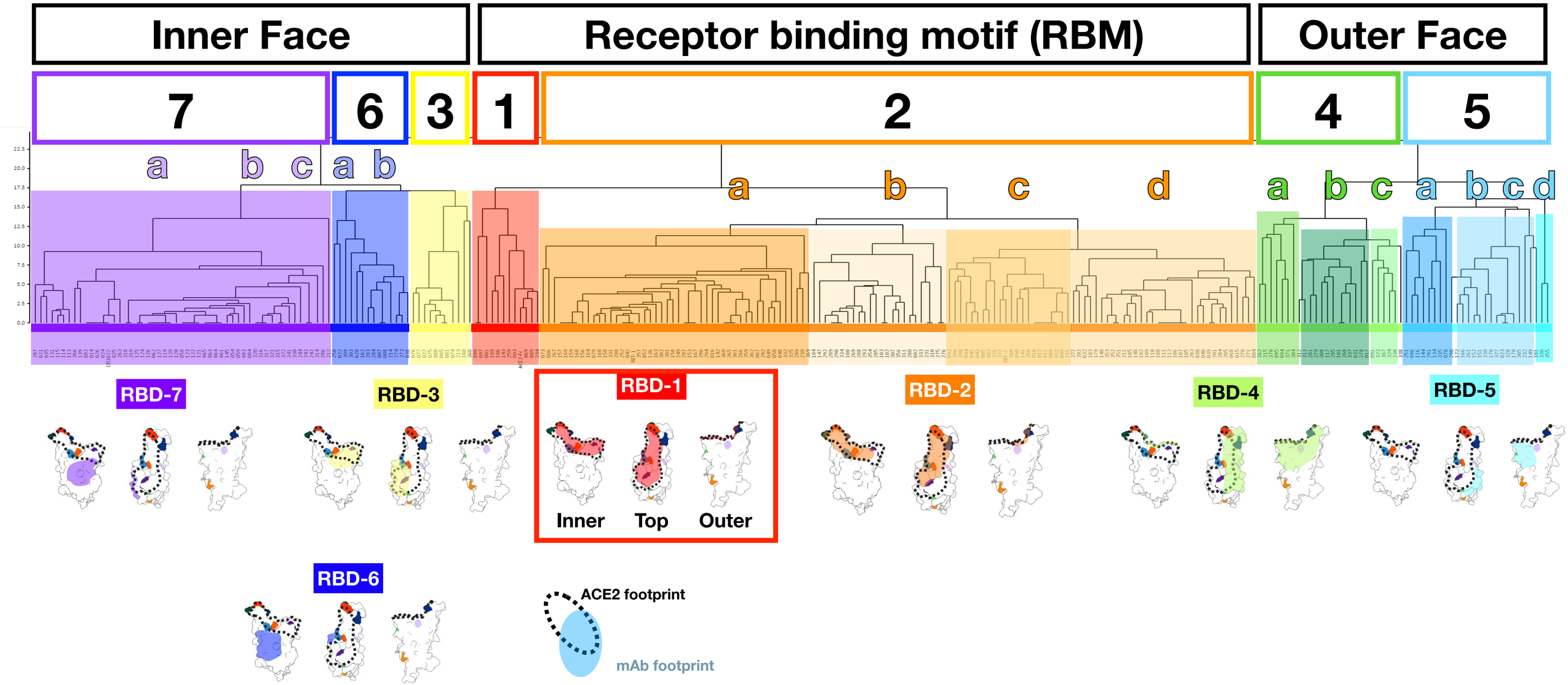
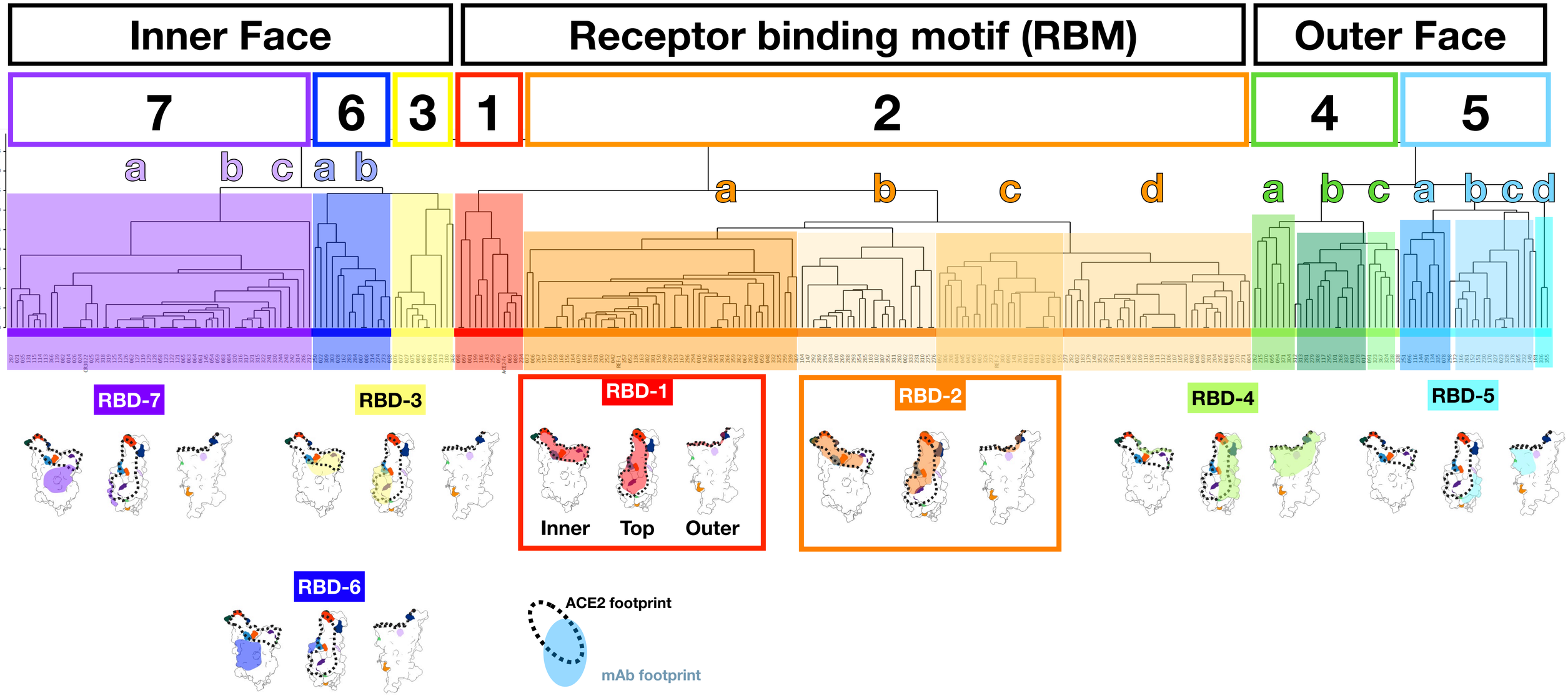
7 core RBD-directed communities



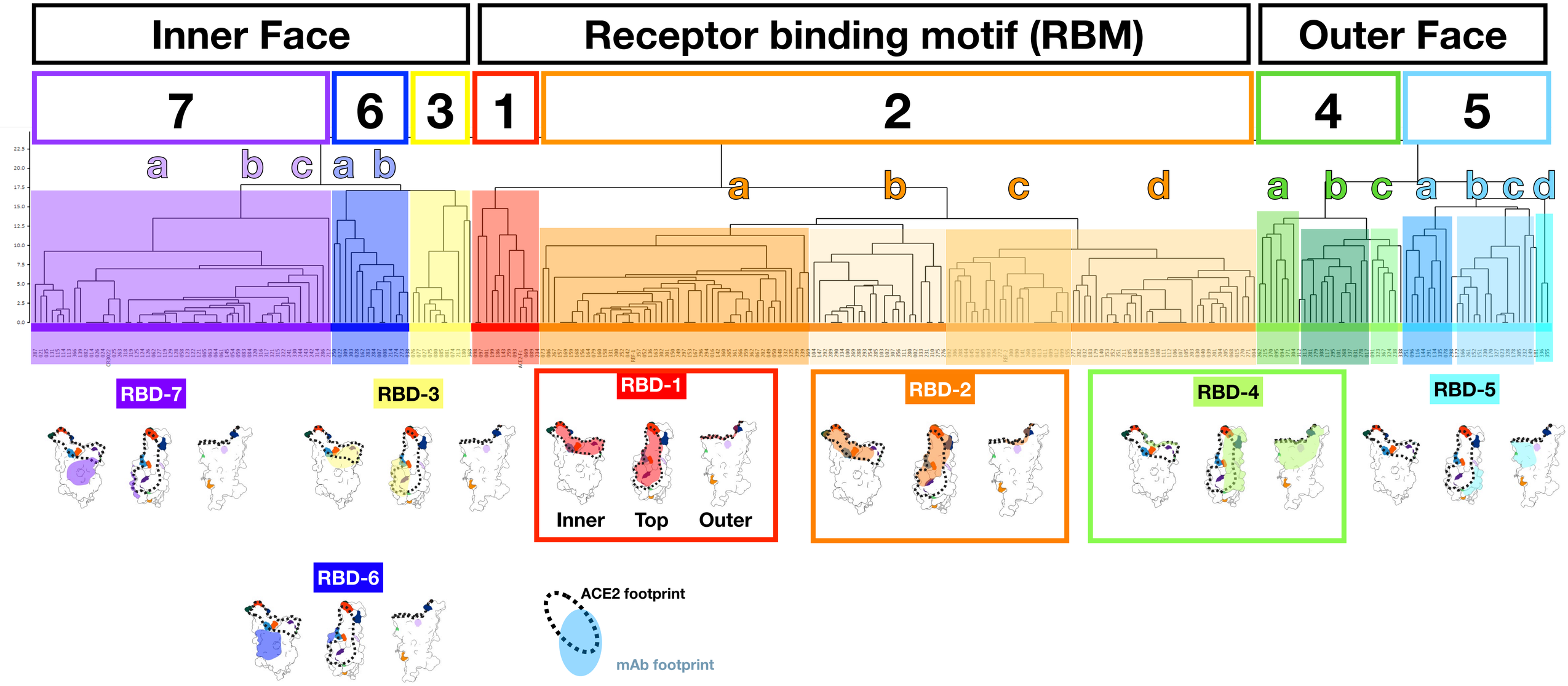
7 core RBD-directed communities



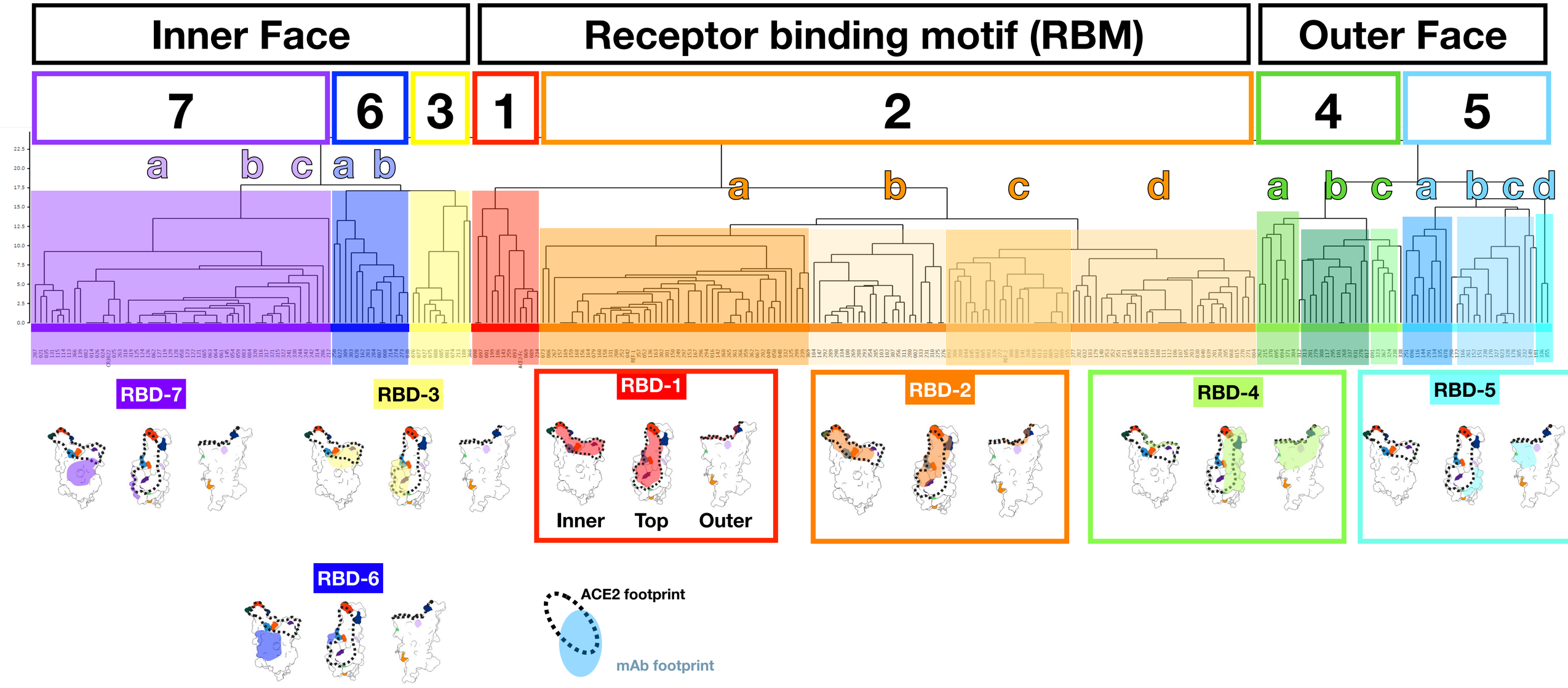
7 core RBD-directed communities



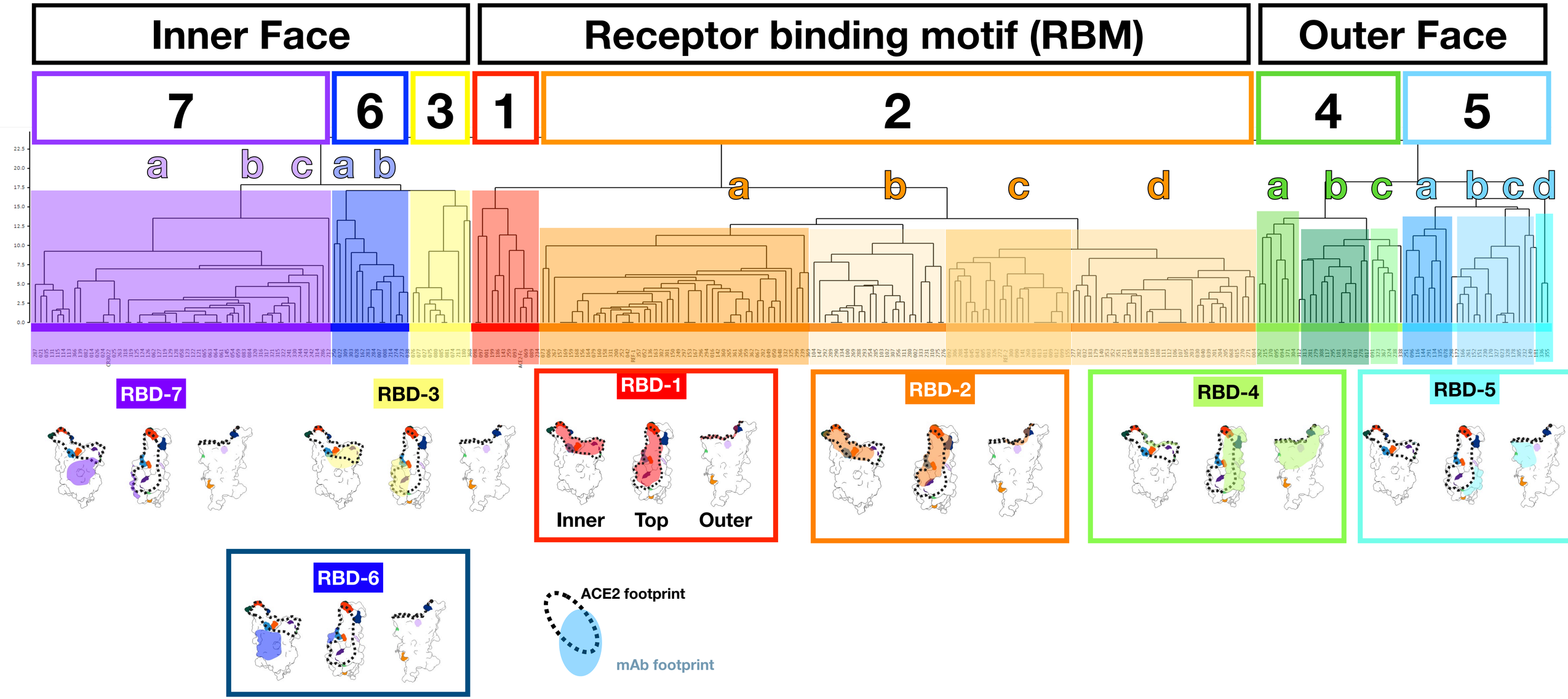
7 core RBD-directed communities



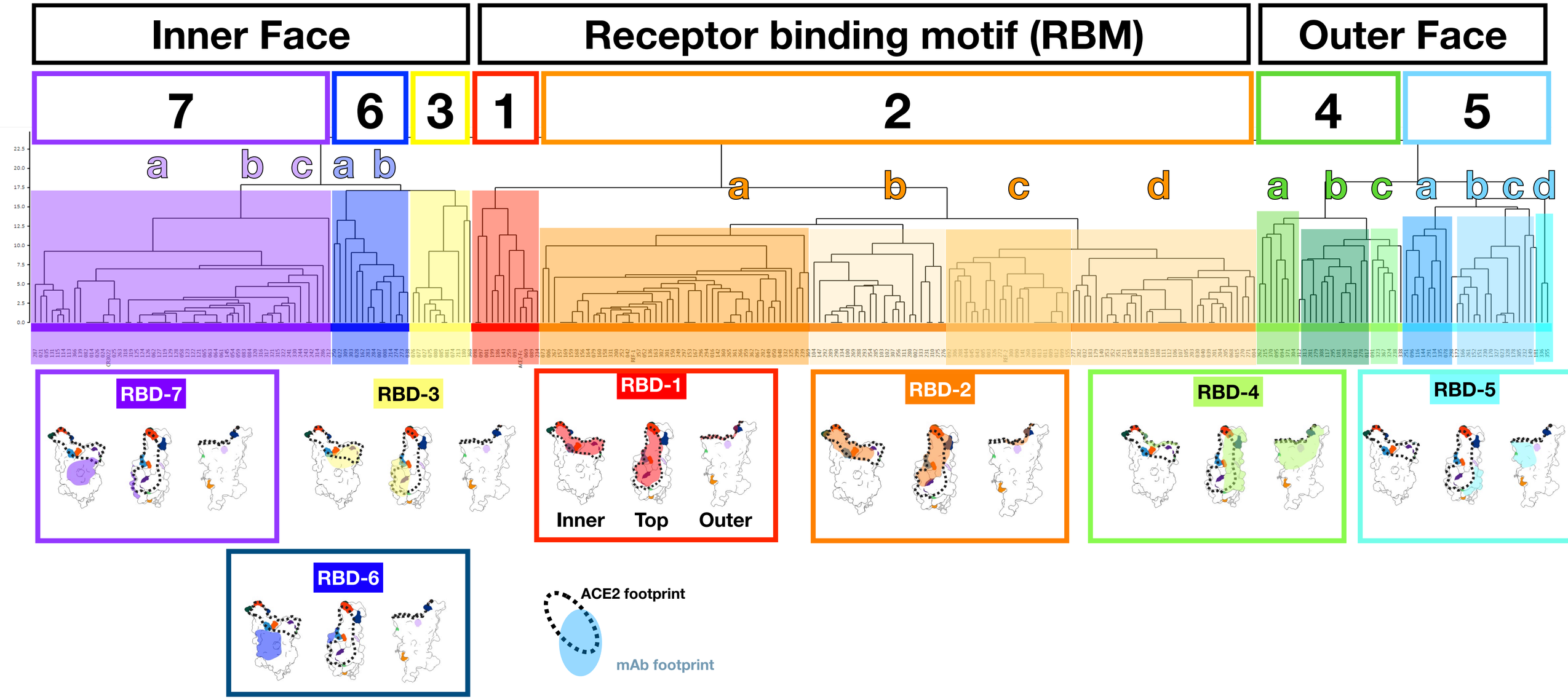
7 core RBD-directed communities



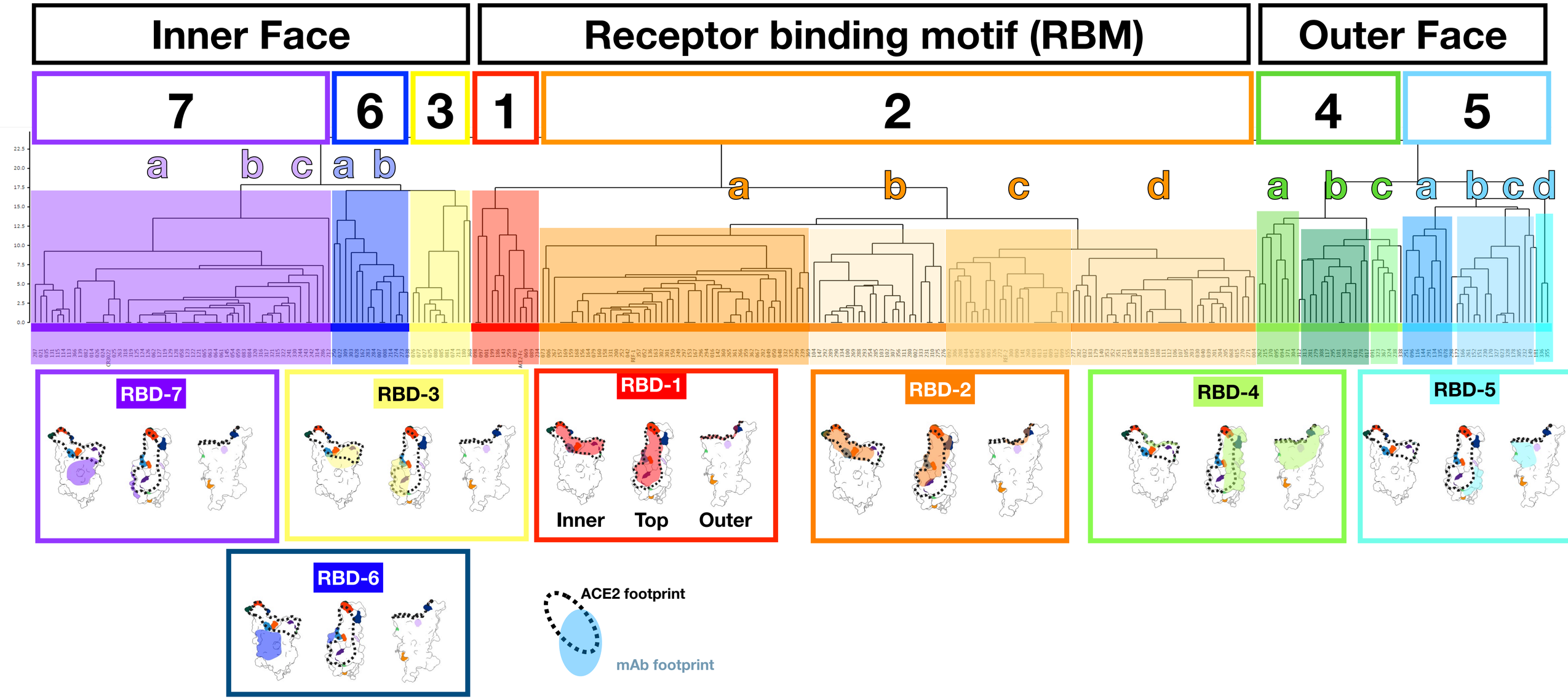
7 core RBD-directed communities



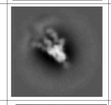
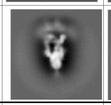
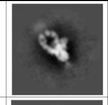
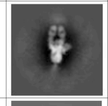
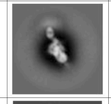
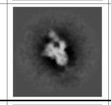
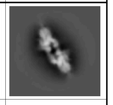
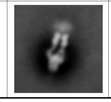
7 core RBD-directed communities

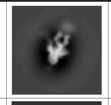
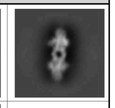
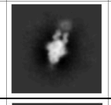


7 core RBD-directed communities



IgG binding behavior by community

Community	CoVIC NO.	Antibody version used for NS-EM	EMD Access NO.	EM-map Side view	EM-map Top view	Typical populations (EM 2D classes)	
RBD-1	CoVIC-69	Soluble human ACE2					
	CoVIC-186	IgG					
	CoVIC-259	IgG					
RBD-2a	CoVIC-249	IgG					
	CoVIC-252	IgG					
	CoVIC-49	IgG					
	CoVIC-73	scFv					
RBD-2c	CoVIC-43	IgG					
	CoVIC-10	IgG					
	CoVIC-90	IgG					

Community	CoVIC NO.	Antibody version used for NS-EM	EMD Access NO.	EM-map Side view	EM-map Top view	Typical populations (EM 2D classes)	
RBD-2d	CoVIC-140	IgG					
	CoVIC-148	IgG					
RBD-2b	CoVIC-2	Fab					
	CoVIC-147	IgG					
RBD-3	CoVIC-80	IgG					
	CoVIC-81	Fab					
RBD-4a	CoVIC-94	VHH-Fc					
	CoVIC-31	IgG	N/A	N/A	N/A		
RBD-4b	CoVIC-91	IgG					

Community	CoVIC NO.	Antibody version used for NS-EM	EMD Access NO.	EM-map Side view	EM-map Top view	Typical populations (EM 2D classes)	
RBD-5a	CoVIC-134	IgG					
RBD-5b	CoVIC-96	IgG					
RBD-5c	CoVIC-166	IgG	N/A	N/A	N/A		
RBD-6a	CoVIC-250	IgG					
RBD-6b	CoVIC-38	IgG					
RBD-7a	CoVIC-63	scFv					
	CoVIC-83	IgG	N/A	N/A	N/A		
RBD-7b	CR3022	PDB: 7LOP (PMID: 34016740)					
RBD-7c	CoVIC-21	Fab					

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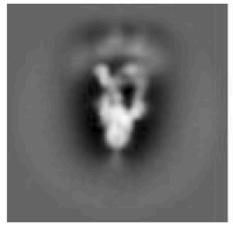
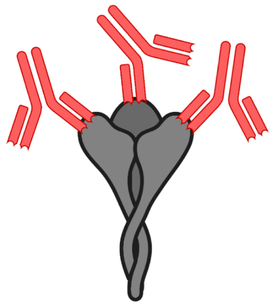
RBD-1
(CoVIC-259)



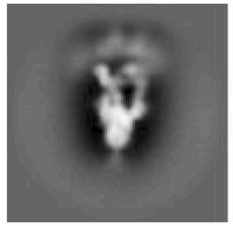
Fully occupied Spike

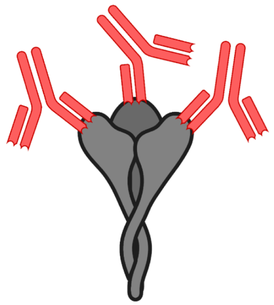


IgG binding behavior by community

IgG binding behavior by community

RBD-1
(CoVIC-259)



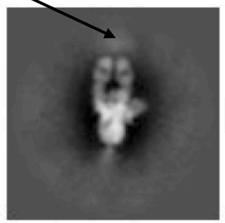


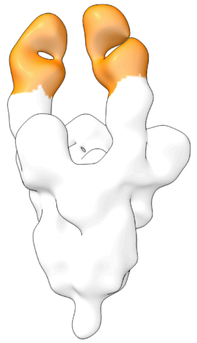
Fully occupied Spike

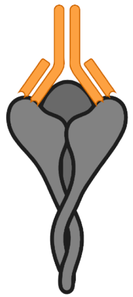
Bivalent, intra-spike binding

Fc

RBD-2
(CoVIC-252)

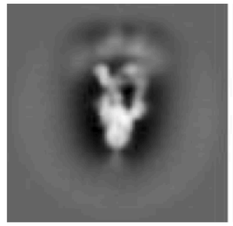


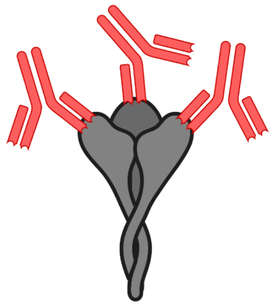




IgG binding behavior by community

RBD-1 (CoVIC-259)

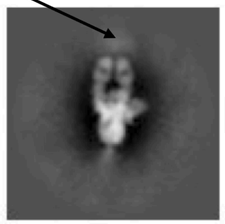


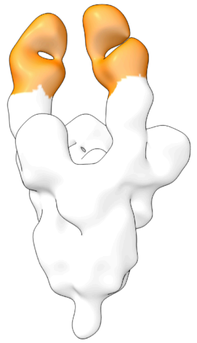


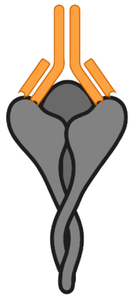
Fully occupied Spike

Bivalent, intra-spike binding

RBD-2 (CoVIC-252)

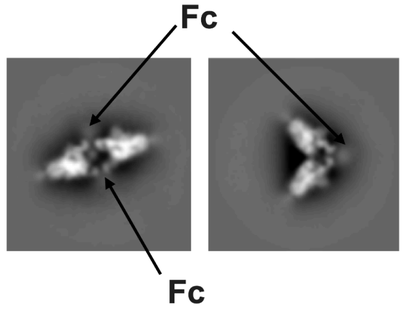


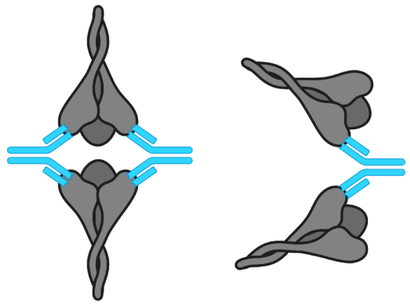




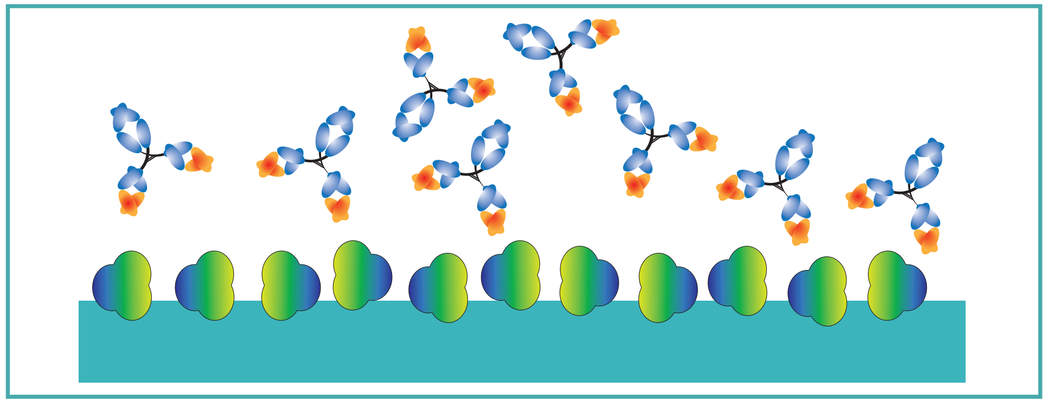
Inter-spike cross-linking

RBD-5 (CoVIC-96)

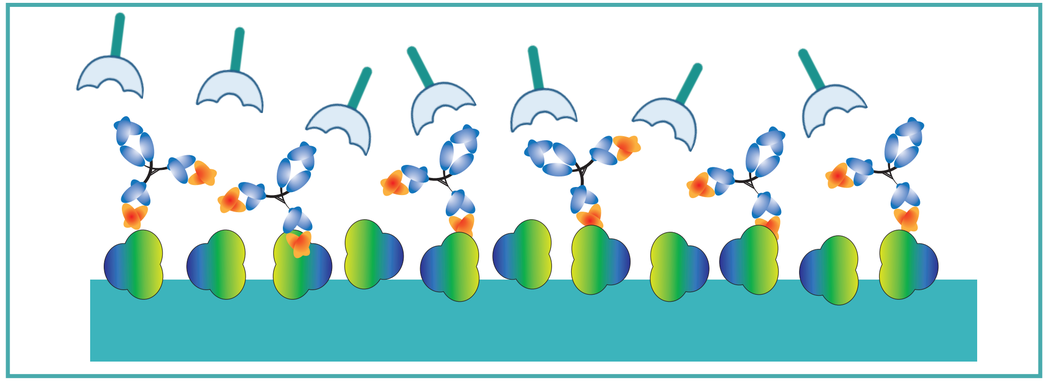




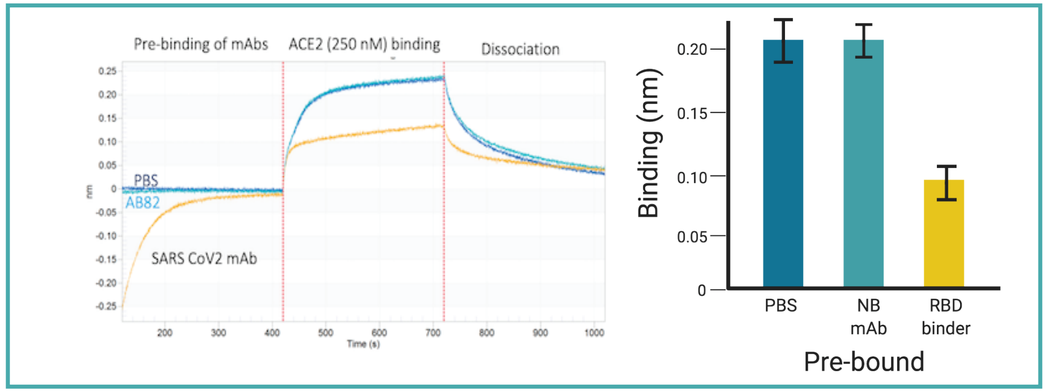
Antibody inhibition of Spike-ACE-2 interaction



RBD immobilized on BLI biosensors is dipped into wells containing saturating amount of antibody (20µg/mL)

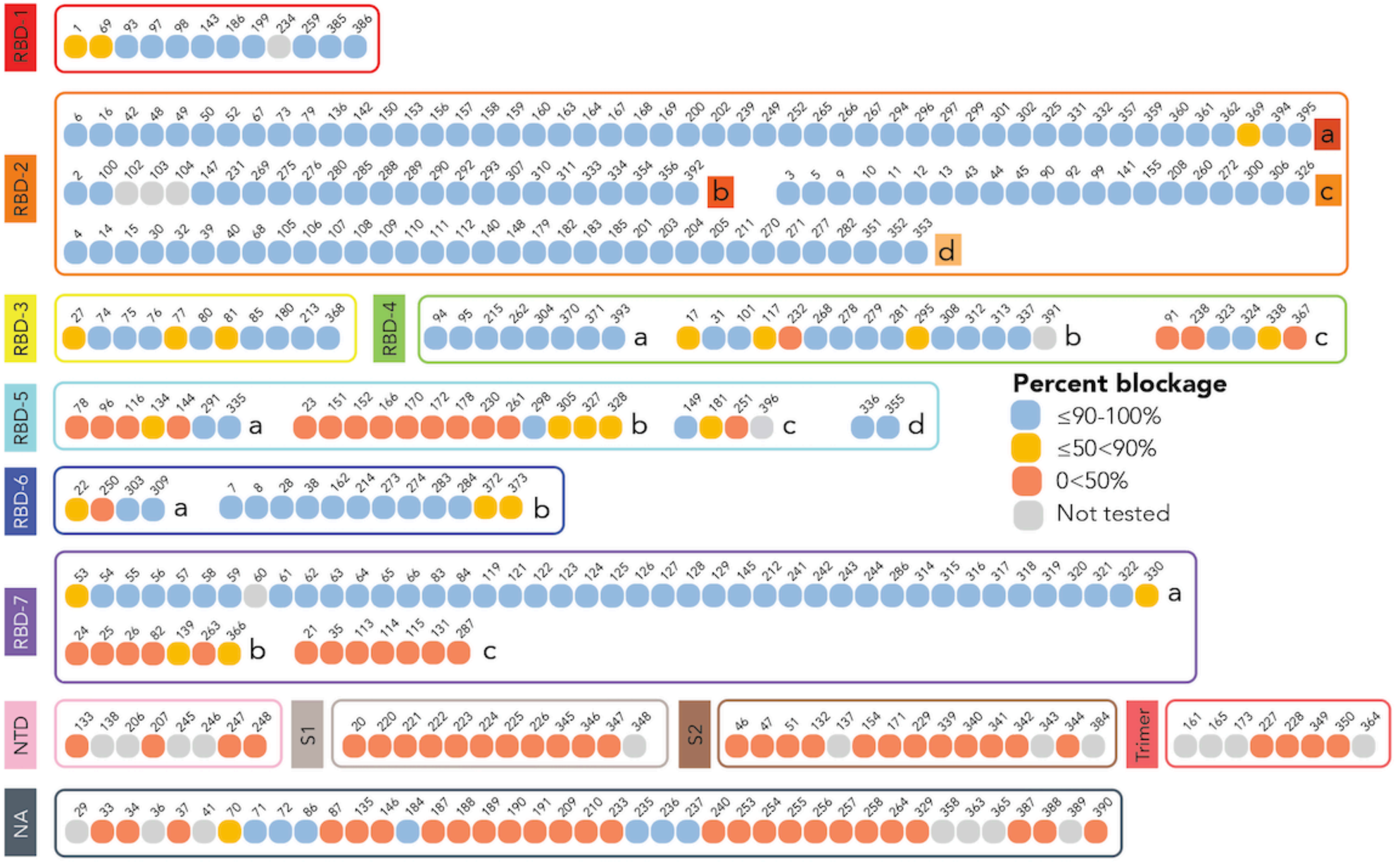


Antibody-bound RBD sensors are dipped into soluble ACE2 (250nM) for 300 s and dissociation is followed for 300 s

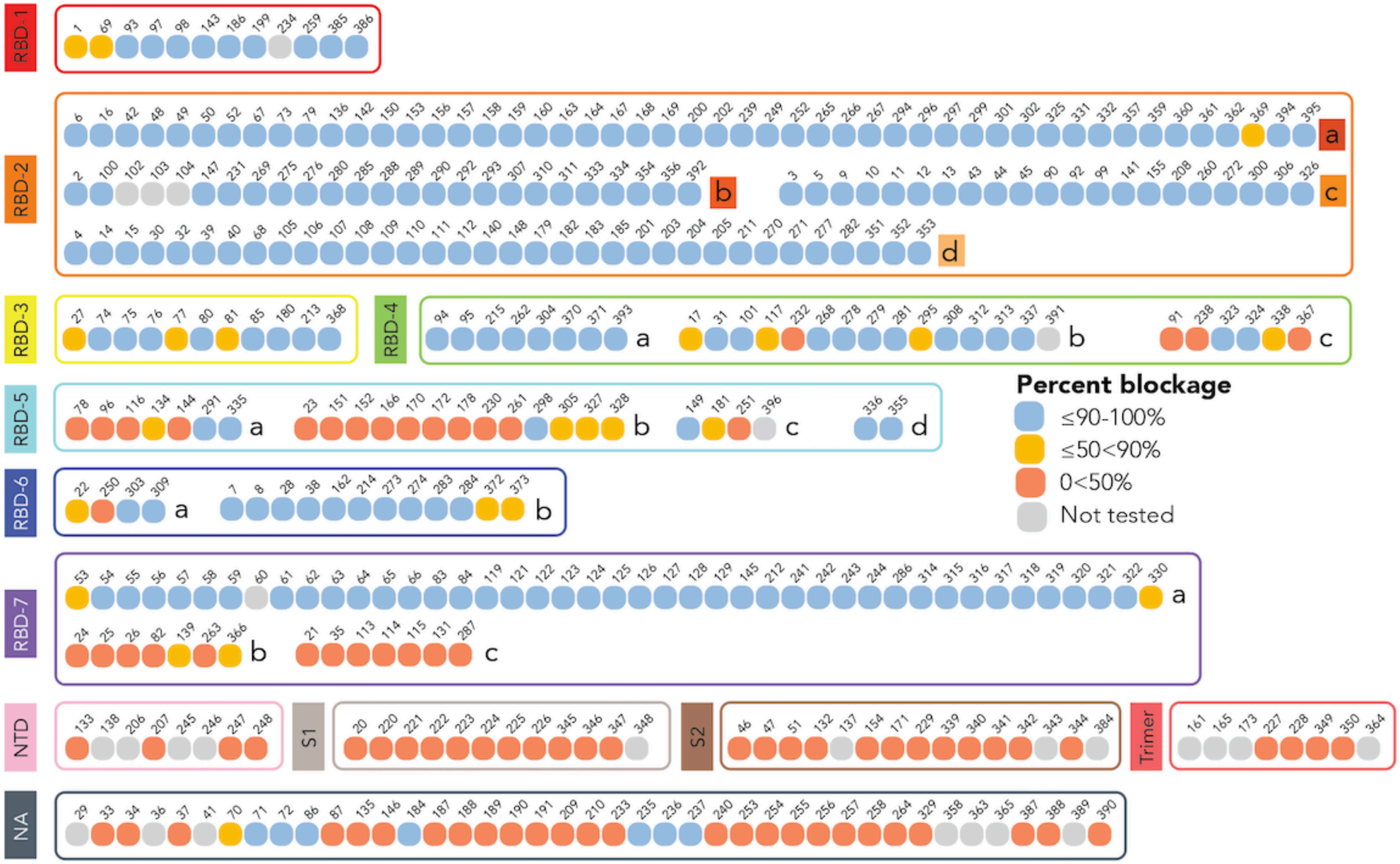


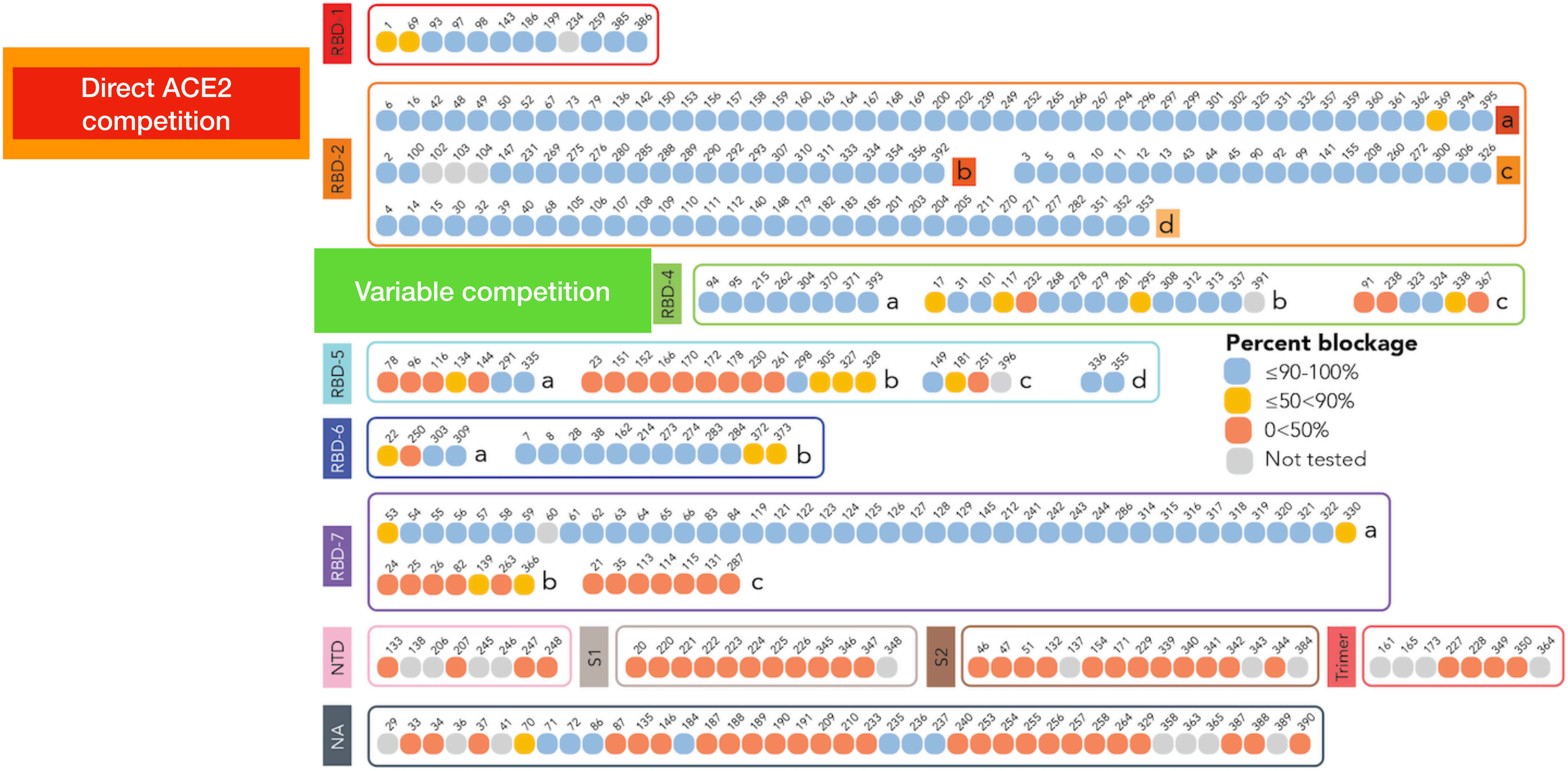
The percentage inhibition is determined relative to buffer only and non-RBD-binding control mAb

Georgia Tomaras
Duke Human Vaccine Institute
Duke University School of Medicine


RBD-1
1 69 93 97 98 143 186 199 234 259 385 386
RBD-2
6 16 42 48 49 50 52 67 73 79 136 142 150 153 156 157 158 159 160 163 164 167 168 169 200 202 239 249 252 265 266 267 294 296 297 299 301 302 325 331 332 357 359 360 361 362 369 394 395 a
2 100 102 103 104 147 231 269 275 276 280 285 288 289 290 292 293 307 310 311 333 334 354 356 392 b
3 5 9 10 11 12 13 43 44 45 90 92 99 141 155 208 260 272 300 306 326 c
4 14 15 30 32 39 40 68 105 106 107 108 109 110 111 112 140 148 179 182 183 185 201 203 204 205 211 270 271 277 282 351 352 353 d
RBD-3
27 74 75 76 77 80 81 85 180 213 368
RBD-4
94 95 215 262 304 370 371 393 a
17 31 101 117 232 268 278 279 281 295 308 312 313 337 391 b
91 238 323 324 338 367 c
RBD-5
78 96 116 134 144 291 335 a
23 151 152 166 170 172 178 230 261 298 305 327 328 b
149 181 251 396 c
336 355 d
RBD-6
22 250 303 309 a
7 8 28 38 162 214 273 274 283 284 372 373 b
Percent blockage
≤90-100%
≤50<90%
0<50%
Not tested
RBD-7
53 54 55 56 57 58 59 60 61 62 63 64 65 66 83 84 119 121 122 123 124 125 126 127 128 129 145 212 241 242 243 244 286 314 315 316 317 318 319 320 321 322 330 a
24 25 26 82 139 263 366 b
21 35 113 114 115 131 287 c
NTD
133 138 206 207 245 246 247 248
S1
20 220 221 222 223 224 225 226 345 346 347 348
S2
46 47 51 132 137 154 171 229 339 340 341 342 343 344 384
Trimer
161 165 173 227 228 349 350 364
NA
29 33 34 36 37 41 70 71 72 86 87 135 146 184 187 188 189 190 191 209 210 233 235 236 237 240 253 254 255 256 257 258 264 329 358 363 365 387 388 389 390

Direct ACE2 competition

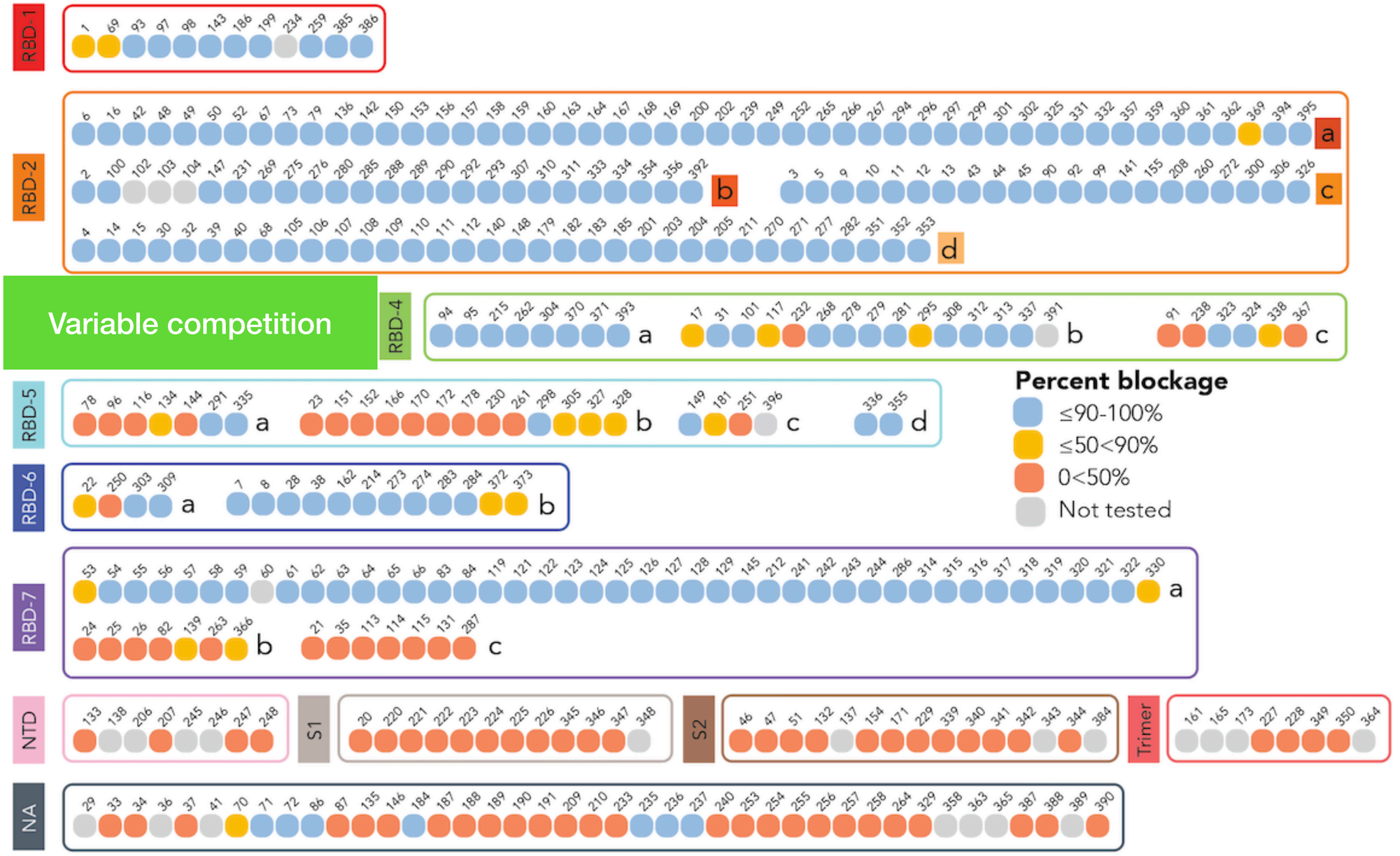


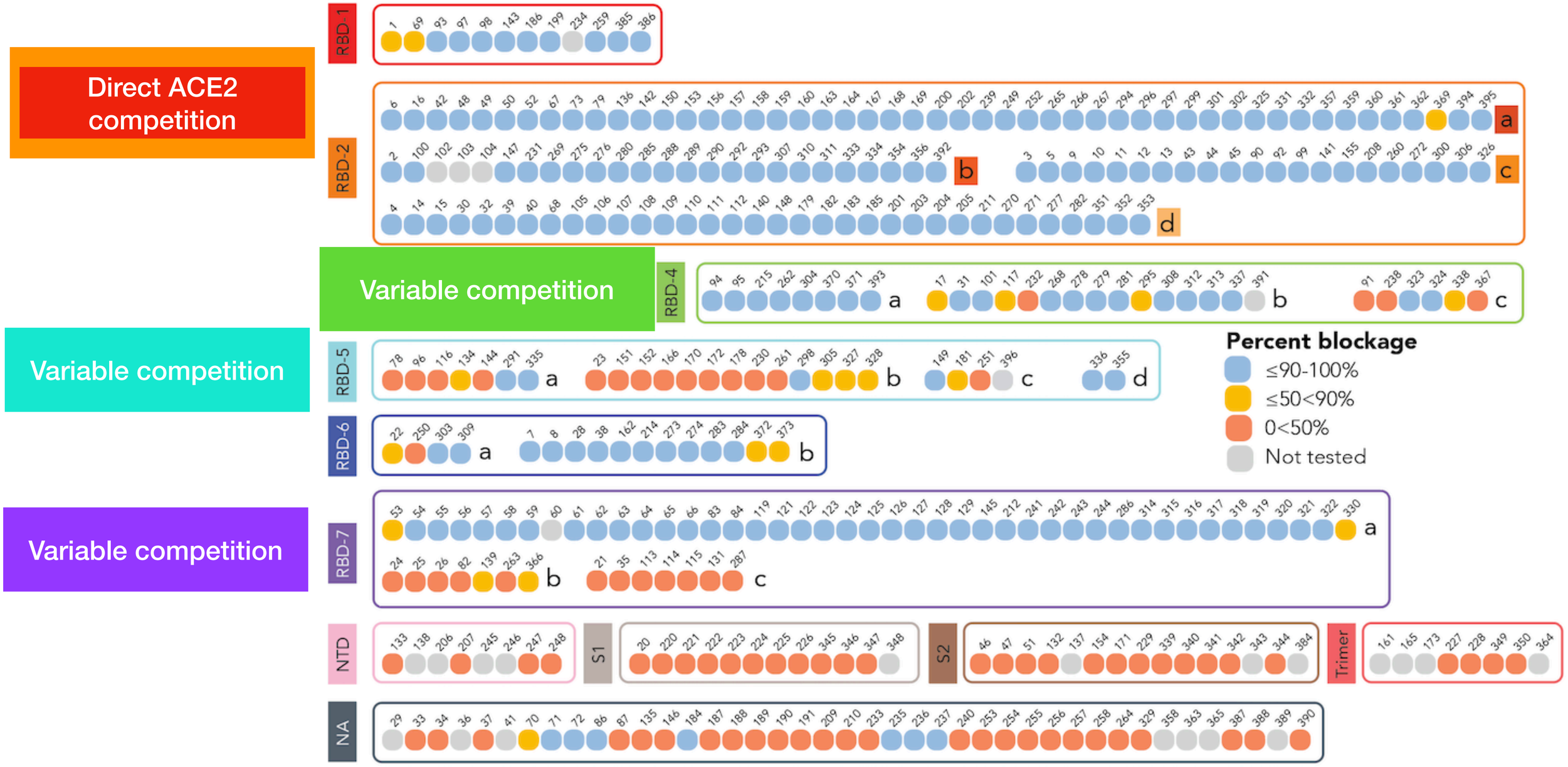

Direct ACE2 competition
Variable competition
RBD-1
RBD-2
RBD-4
RBD-5
RBD-6
RBD-7
NTD
S1
S2
Trimer
NA
Percent blockage
≤90-100%
≤50<90%
0<50%
Not tested

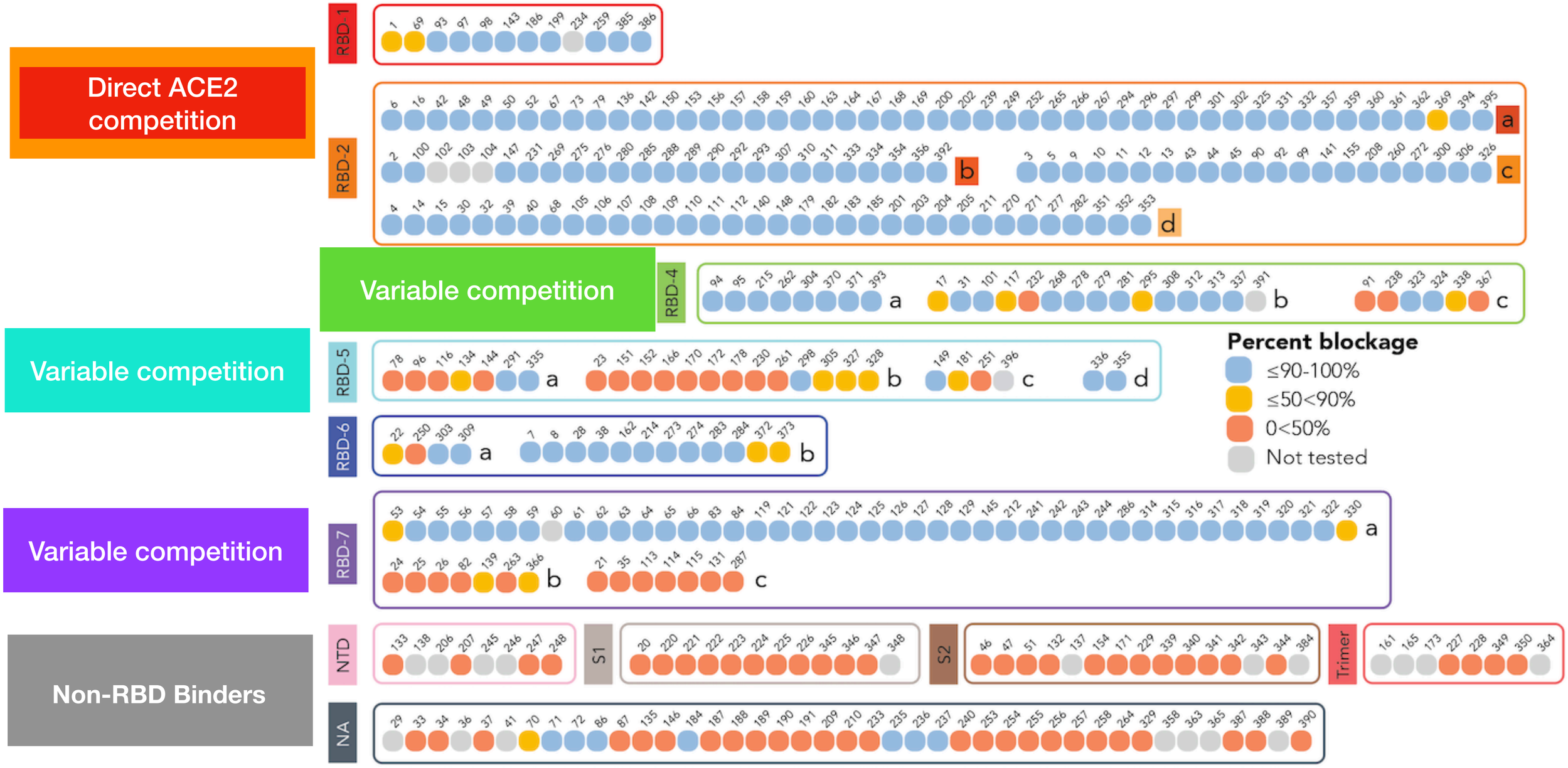
Direct ACE2 competition

Variable competition

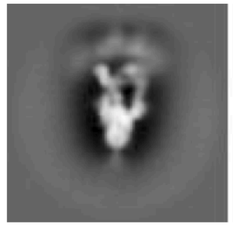
Variable competition



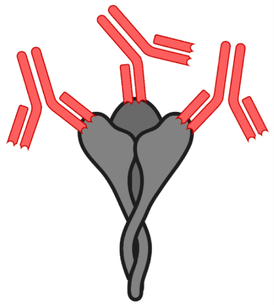

Direct ACE2 competition
Variable competition
Variable competition
Variable competition
RBD-1
1 69 93 97 98 143 186 199 234 259 385 386
RBD-2
6 16 42 48 49 50 52 67 73 79 136 142 150 153 156 157 158 159 160 163 164 167 168 169 200 202 239 249 252 265 266 267 294 296 297 299 301 302 325 331 332 357 359 360 361 362 369 394 395 a
2 100 102 103 104 147 231 269 275 276 280 285 288 289 290 292 293 307 310 311 333 334 354 356 392 b
3 5 9 10 11 12 13 43 44 45 90 92 99 141 155 208 260 272 300 306 326 c
4 14 15 30 32 39 40 68 105 106 107 108 109 110 111 112 140 148 179 182 183 185 201 203 204 205 211 270 271 277 282 351 352 353 d
RBD-4
94 95 215 262 304 370 371 393 a
17 31 101 117 232 268 278 279 281 295 308 312 313 337 391 b
91 238 323 324 338 367 c
RBD-5
78 96 116 134 144 291 335 a
23 151 152 166 170 172 178 230 261 298 305 327 328 b
149 181 251 396 c
336 355 d
RBD-6
22 250 303 309 a
7 8 28 38 162 214 273 274 283 284 372 373 b
Percent blockage
≤90-100%
≤50<90%
0<50%
Not tested
RBD-7
53 54 55 56 57 58 59 60 61 62 63 64 65 66 83 84 119 121 122 123 124 125 126 127 128 129 145 212 241 242 243 244 286 314 315 316 317 318 319 320 321 322 330 a
24 25 26 82 139 263 366 b
21 35 113 114 115 131 287 c
NTD
133 138 206 207 245 246 247 248
S1
20 220 221 222 223 224 225 226 345 346 347 348
S2
46 47 51 132 137 154 171 229 339 340 341 342 343 344 384
Trimer
161 165 173 227 228 349 350 364
NA
29 33 34 36 37 41 70 71 72 86 87 135 146 184 187 188 189 190 191 209 210 233 235 236 237 240 253 254 255 256 257 258 264 329 358 363 365 387 388 389 390


Direct ACE2 competition
Variable competition
Variable competition
Variable competition
Non-RBD Binders
RBD-1
1 69 93 97 98 143 186 199 234 259 385 386
RBD-2
6 16 42 48 49 50 52 67 73 79 136 142 150 153 156 157 158 159 160 163 164 167 168 169 200 202 239 249 252 265 266 267 294 296 297 299 301 302 325 331 332 357 359 360 361 362 369 394 395 a
2 100 102 103 104 147 231 269 275 276 280 285 288 289 290 292 293 307 310 311 333 334 354 356 392 b
3 5 9 10 11 12 13 43 44 45 90 92 99 141 155 208 260 272 300 306 326 c
4 14 15 30 32 39 40 68 105 106 107 108 109 110 111 112 140 148 179 182 183 185 201 203 204 205 211 270 271 277 282 351 352 353 d
RBD-4
94 95 215 262 304 370 371 393 a
17 31 101 117 232 268 278 279 281 295 308 312 313 337 391 b
91 238 323 324 338 367 c
RBD-5
78 96 116 134 144 291 335 a
23 151 152 166 170 172 178 230 261 298 305 327 328 b
149 181 251 396 c
336 355 d
RBD-6
22 250 303 309 a
7 8 28 38 162 214 273 274 283 284 372 373 b
RBD-7
53 54 55 56 57 58 59 60 61 62 63 64 65 66 83 84 119 121 122 123 124 125 126 127 128 129 145 212 241 242 243 244 286 314 315 316 317 318 319 320 321 322 330 a
24 25 26 82 139 263 366 b
21 35 113 114 115 131 287 c
NTD
133 138 206 207 245 246 247 248
S1
20 220 221 222 223 224 225 226 345 346 347 348
S2
46 47 51 132 137 154 171 229 339 340 341 342 343 344 384
Trimer
161 165 173 227 228 349 350 364
NA
29 33 34 36 37 41 70 71 72 86 87 135 146 184 187 188 189 190 191 209 210 233 235 236 237 240 253 254 255 256 257 258 264 329 358 363 365 387 388 389 390
Percent blockage
≤90-100%
≤50<90%
0<50%
Not tested

RBD-1
(CoVIC-259)



Fully occupied Spike

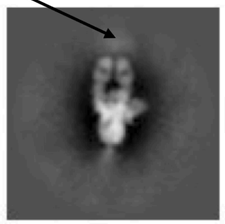


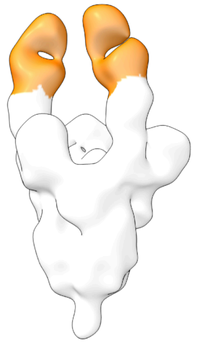
Direct ACE2 competition

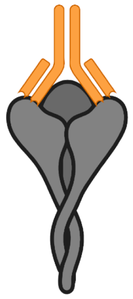
Bivalent, intra-spike binding

Fc

RBD-2
(CoVIC-252)



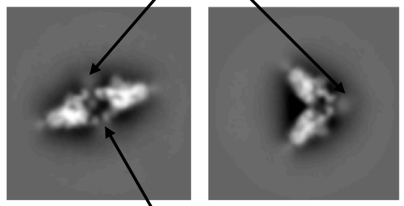




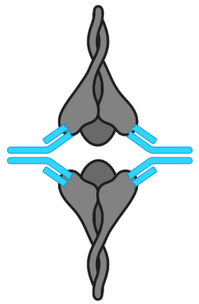
Inter-spike cross-linking

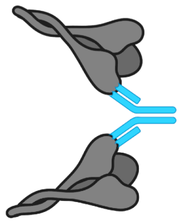
Fc

RBD-5
(CoVIC-96)



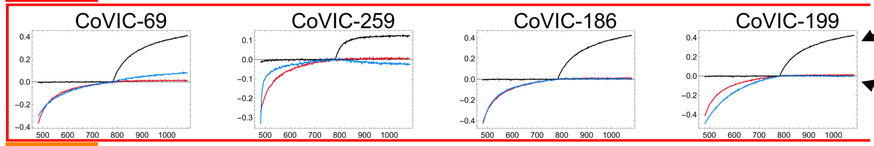
Fc



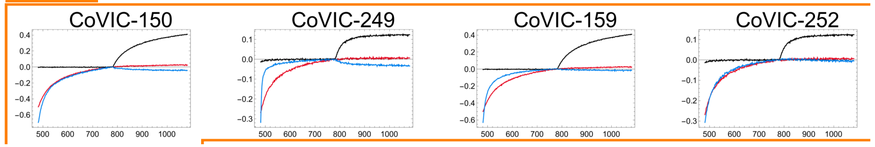


IgG binding behavior by community

RBD-1



RBD-2a



ACE2 bound

ACE2 blocked

CoVIC mAb
Buffer
Pos ctrl

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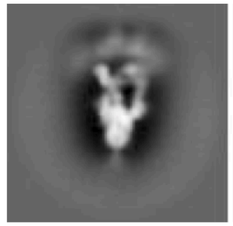
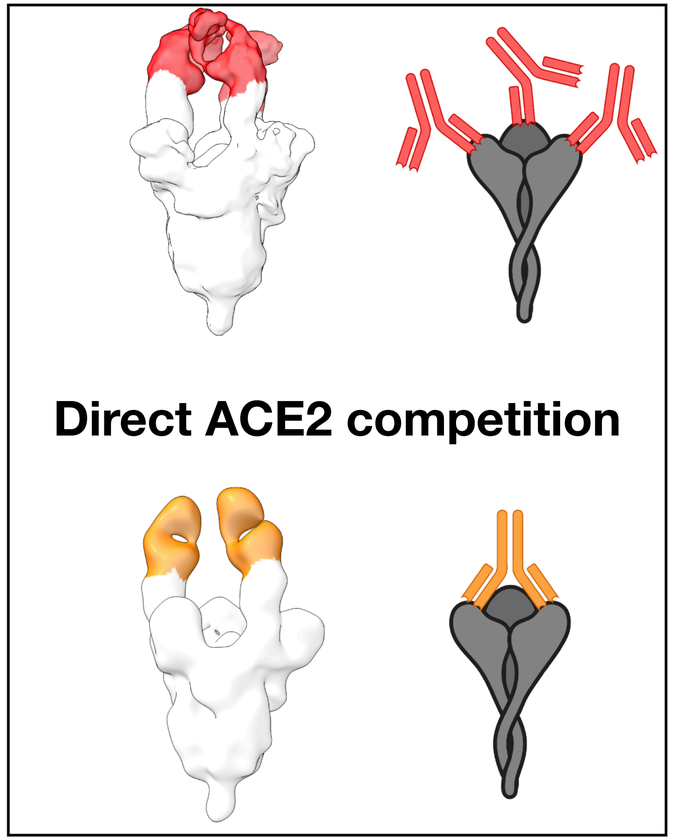
RBD-1
(CoVIC-259)



Fully occupied Spike

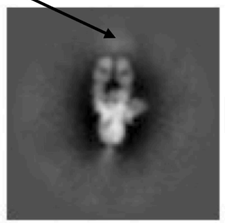


Direct ACE2 competition

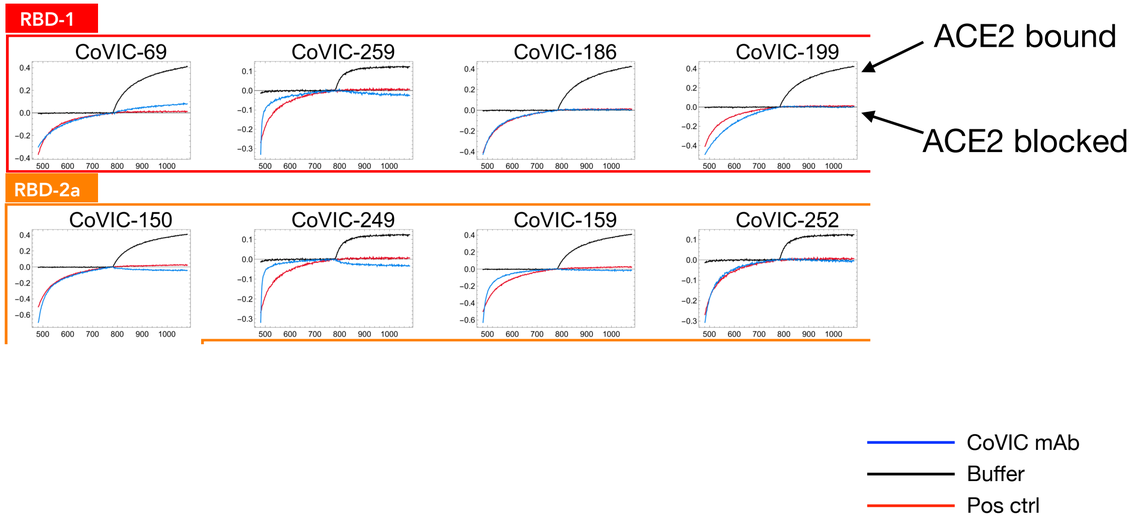
Bivalent, intra-spike binding

Fc

RBD-2
(CoVIC-252)



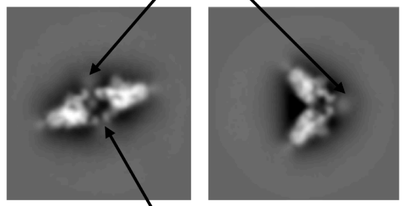
IgG binding behavior by community



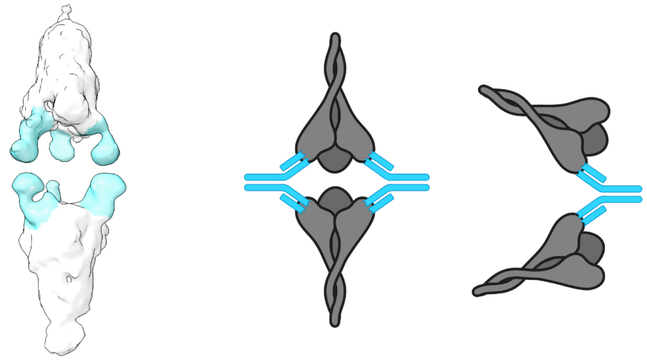
Inter-spike cross-linking

RBD-5
(CoVIC-96)

Fc



Fc



neutralization, protection

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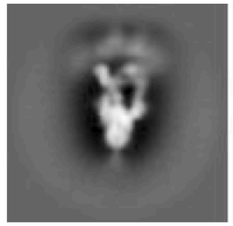
Tomaras Lab, Duke

RBD-1
(CoVIC-259)

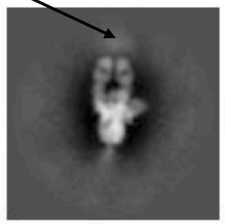


Fully occupied Spike

Bivalent, intra-spike binding

Fc

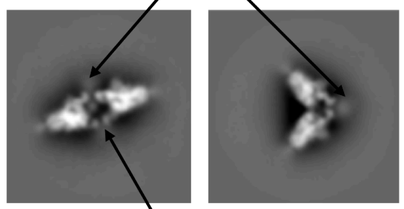
RBD-2
(CoVIC-252)



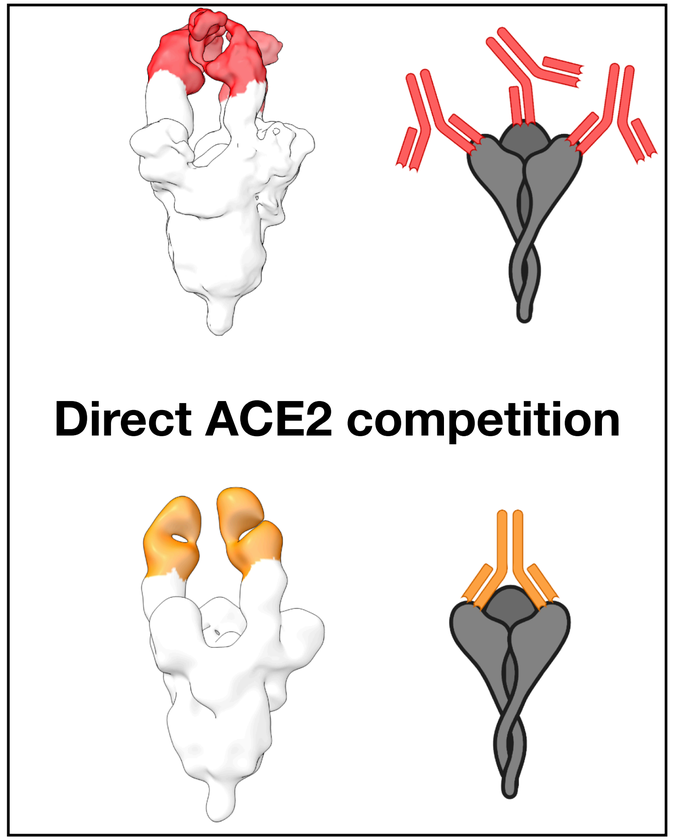
Inter-spike cross-linking

Fc

RBD-5
(CoVIC-96)

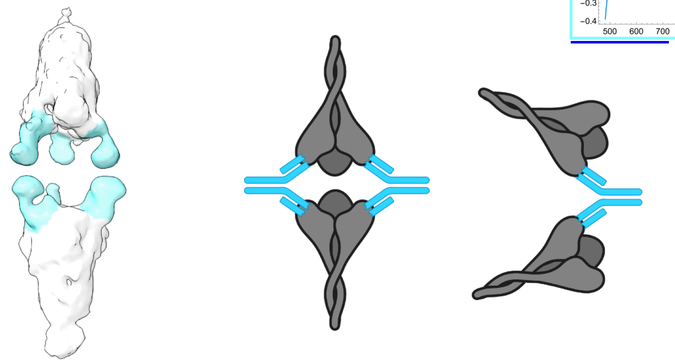


Fc

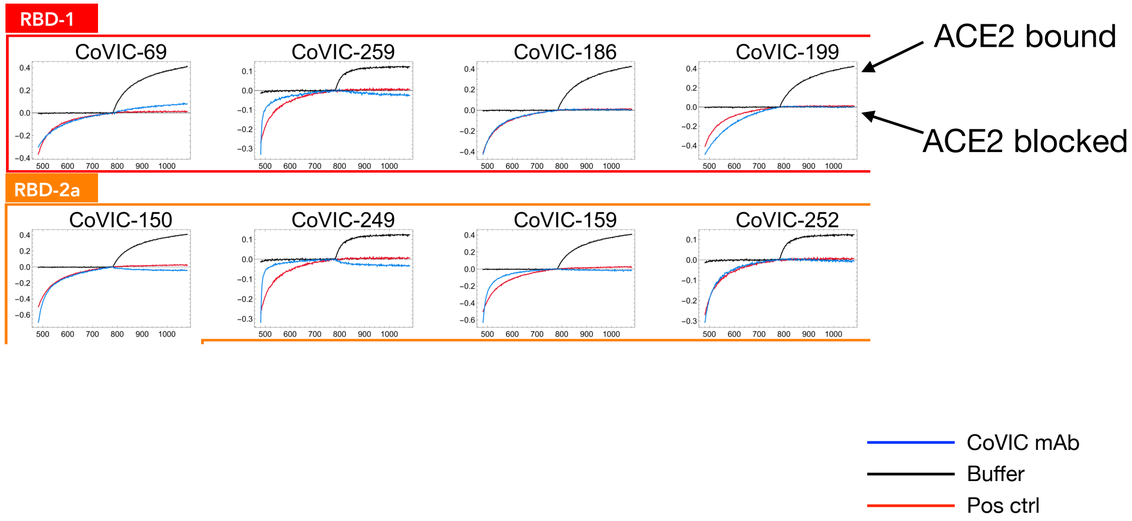


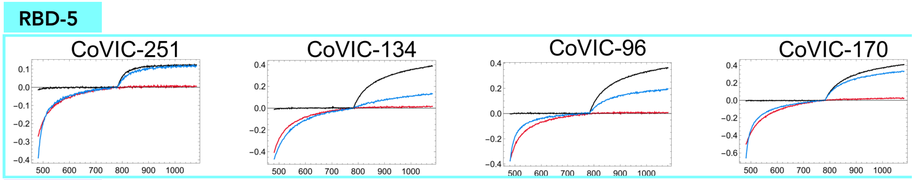
Direct ACE2 competition

Variable ACE2 competition



IgG binding behavior by community





neutralization, protection

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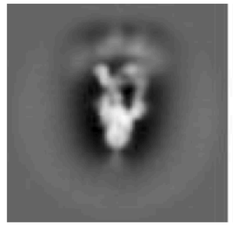
Tomaras Lab, Duke

RBD-1
(CoVIC-259)

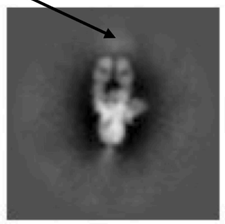


Fully occupied Spike

Bivalent, intra-spike binding

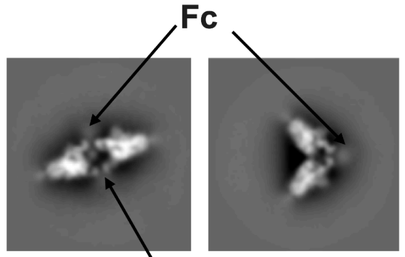
Fc

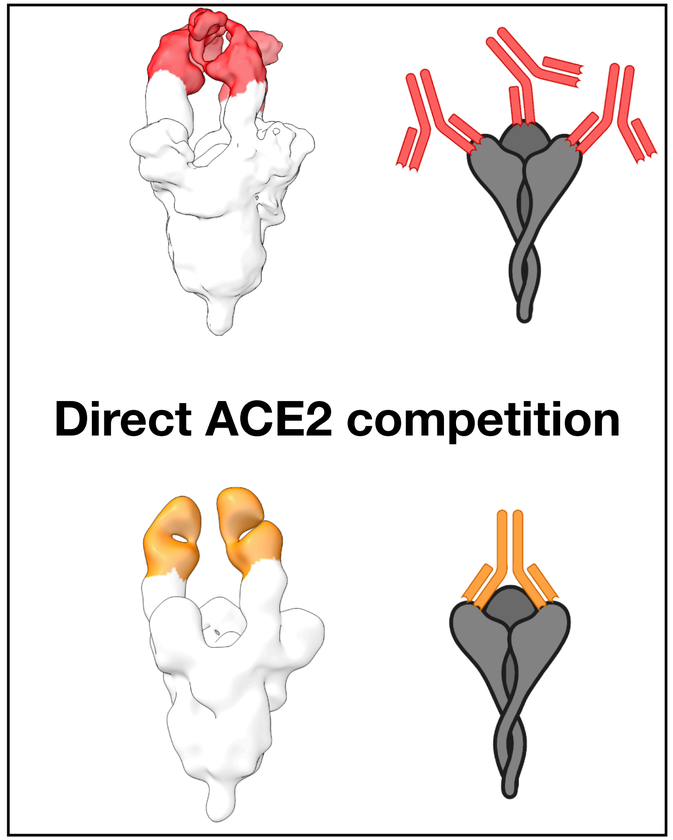
RBD-2
(CoVIC-252)



Inter-spike cross-linking

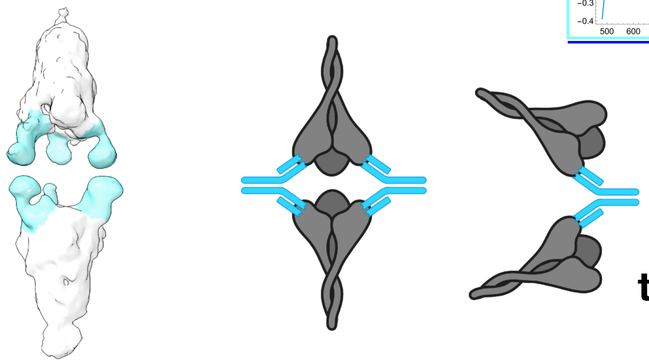
RBD-5
(CoVIC-96)



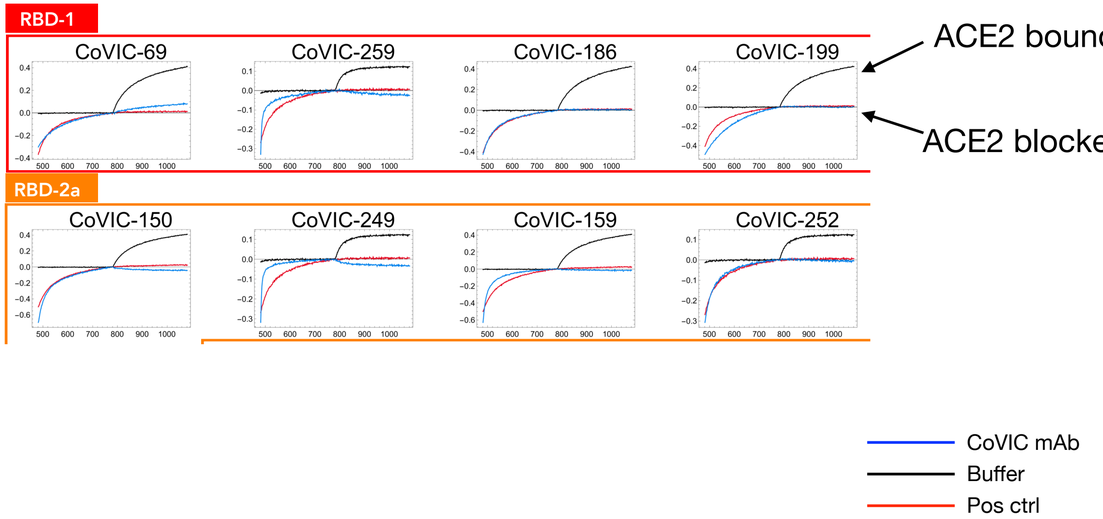


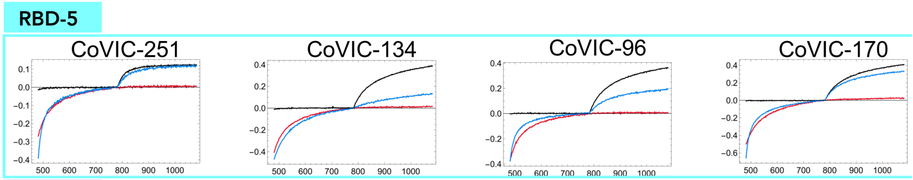
Direct ACE2 competition

Variable ACE2 competition



IgG binding behavior by community



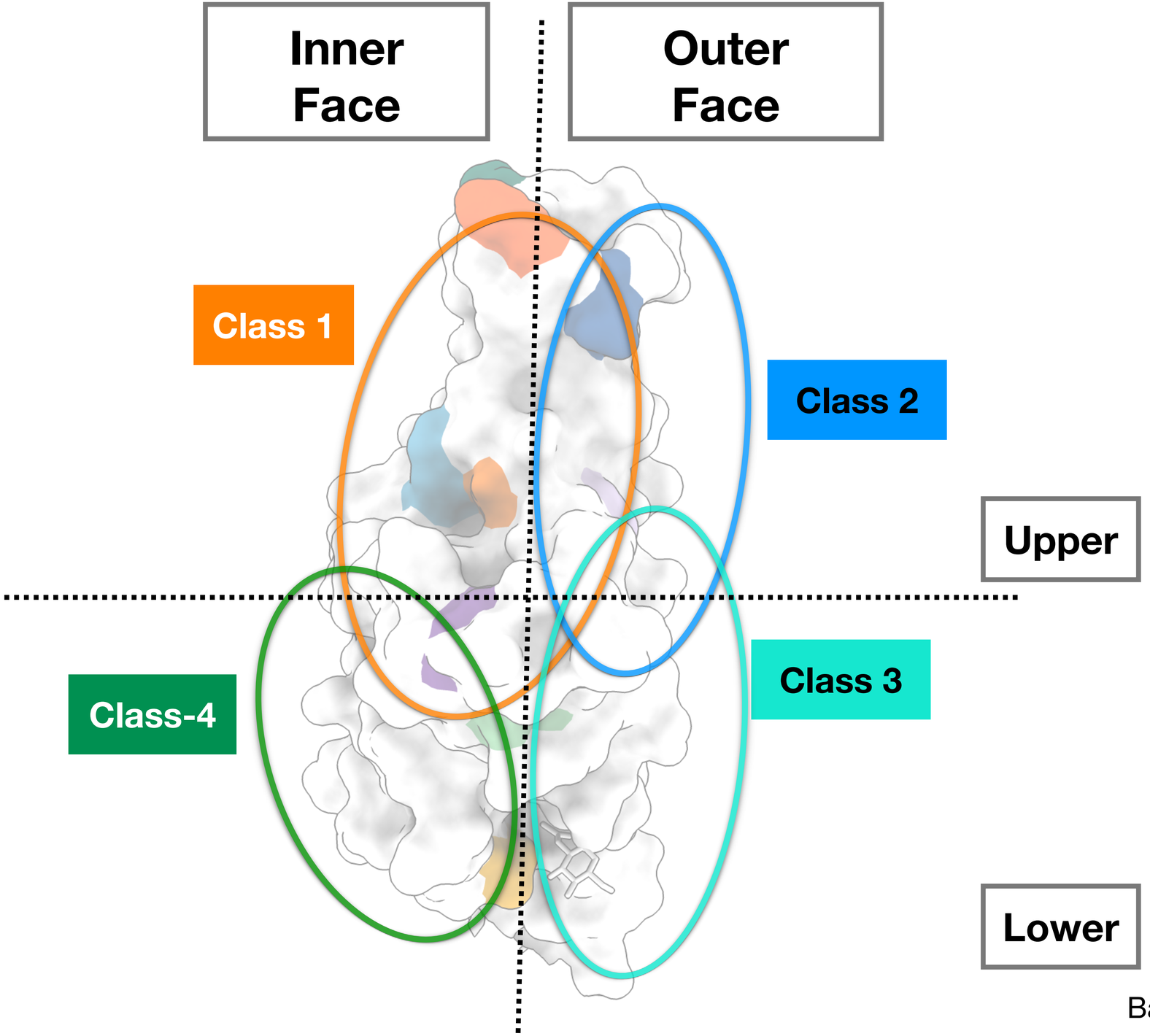


neutralization, protection

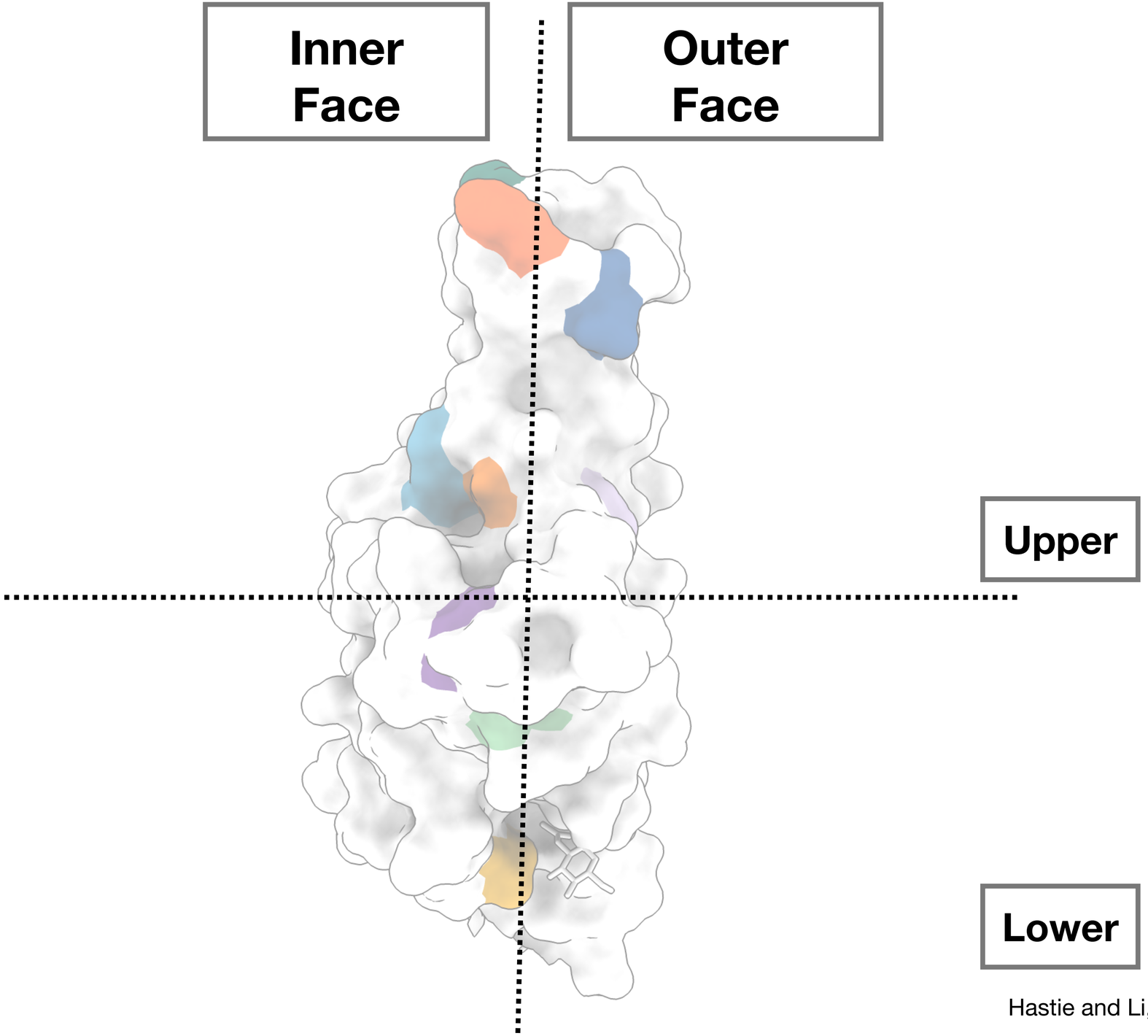
Possible ACE2 steric hindrance through cross-linking on virion surface

La Jolla Institute FOR IMMUNOLOGY | Life Without Disease.®

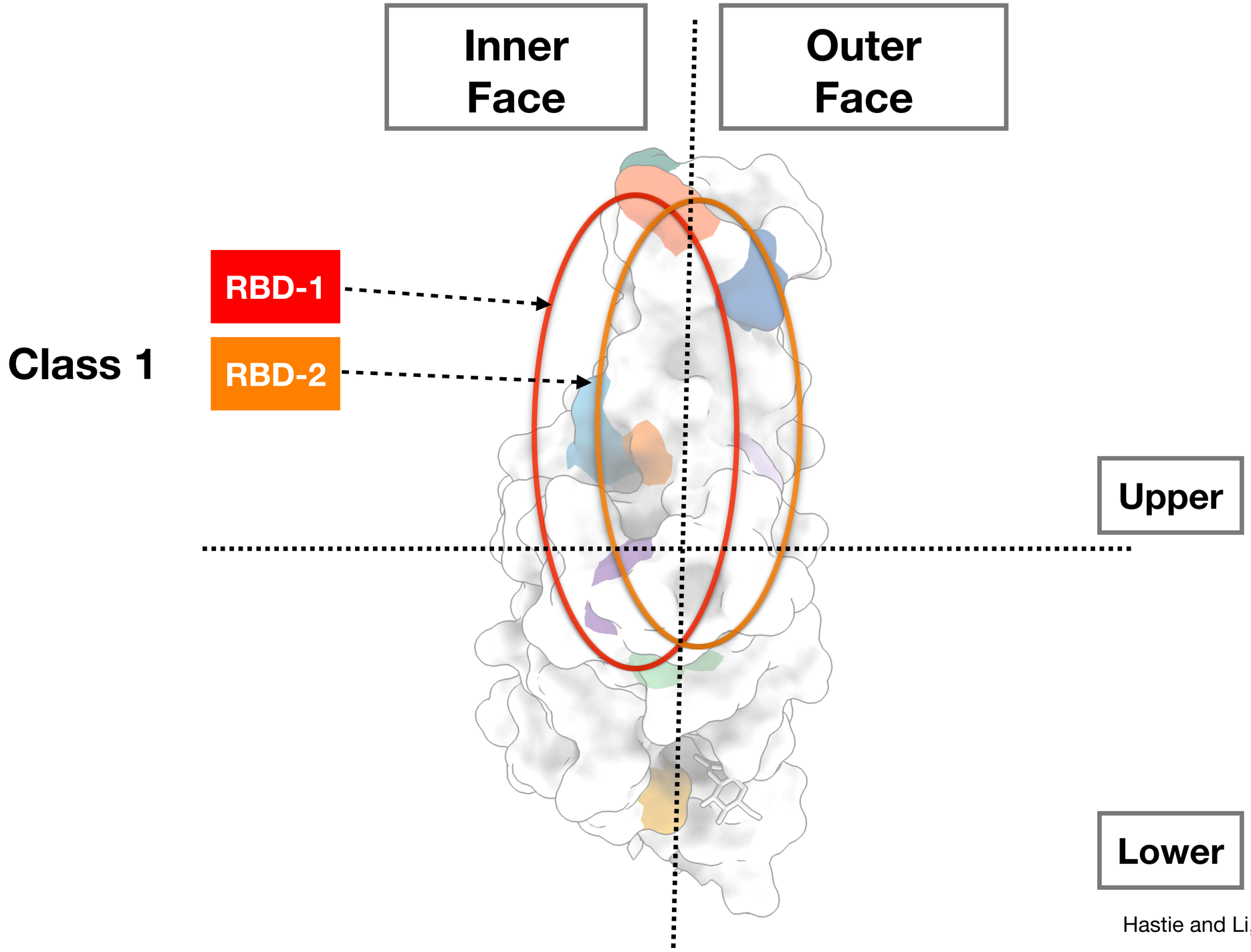
Tomaras Lab, Duke



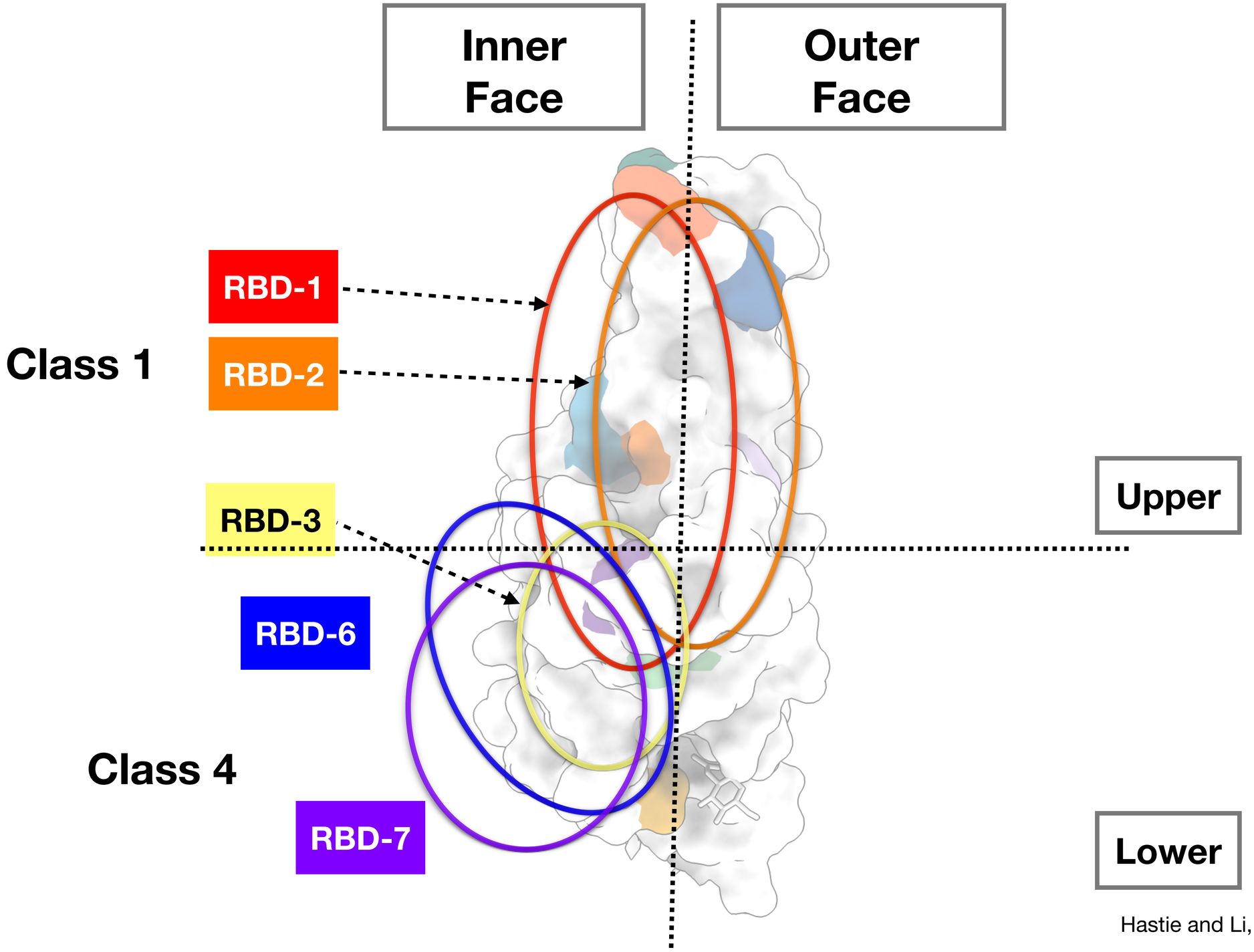
Barnes, et al. 2020



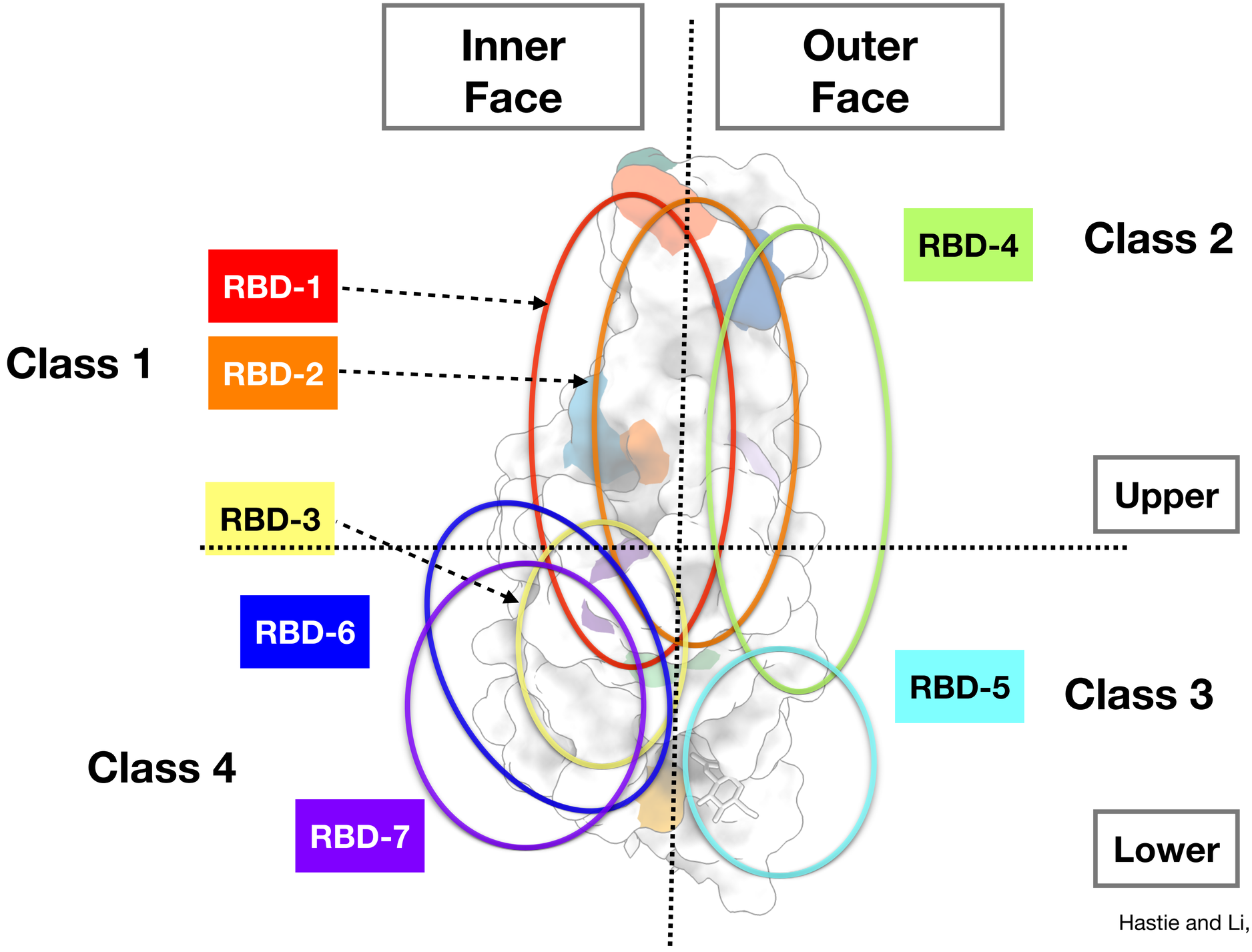
Hastie and Li, et al., Science 2021



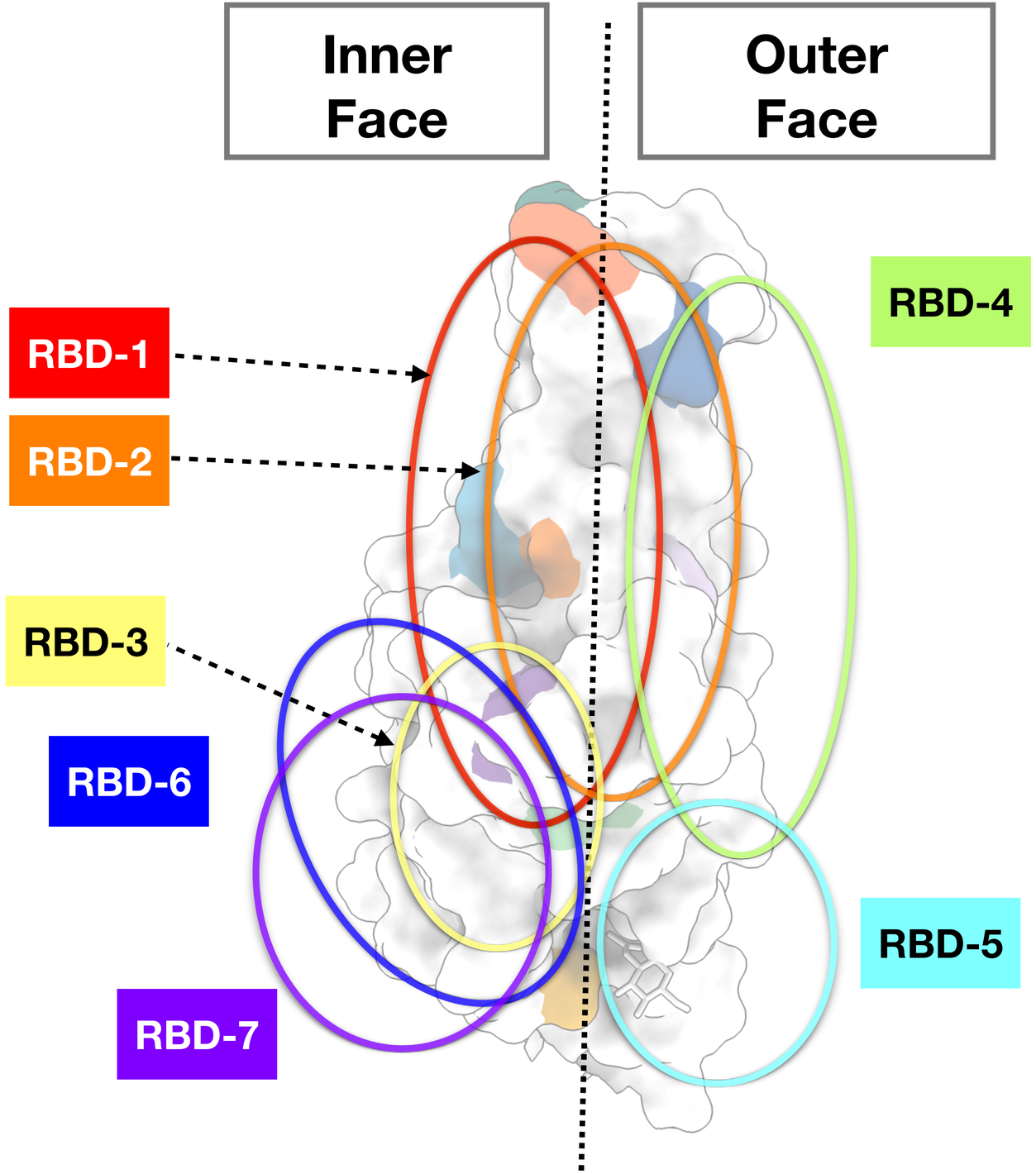
Hastie and Li, et al., Science 2021



Hastie and Li, et al., Science 2021

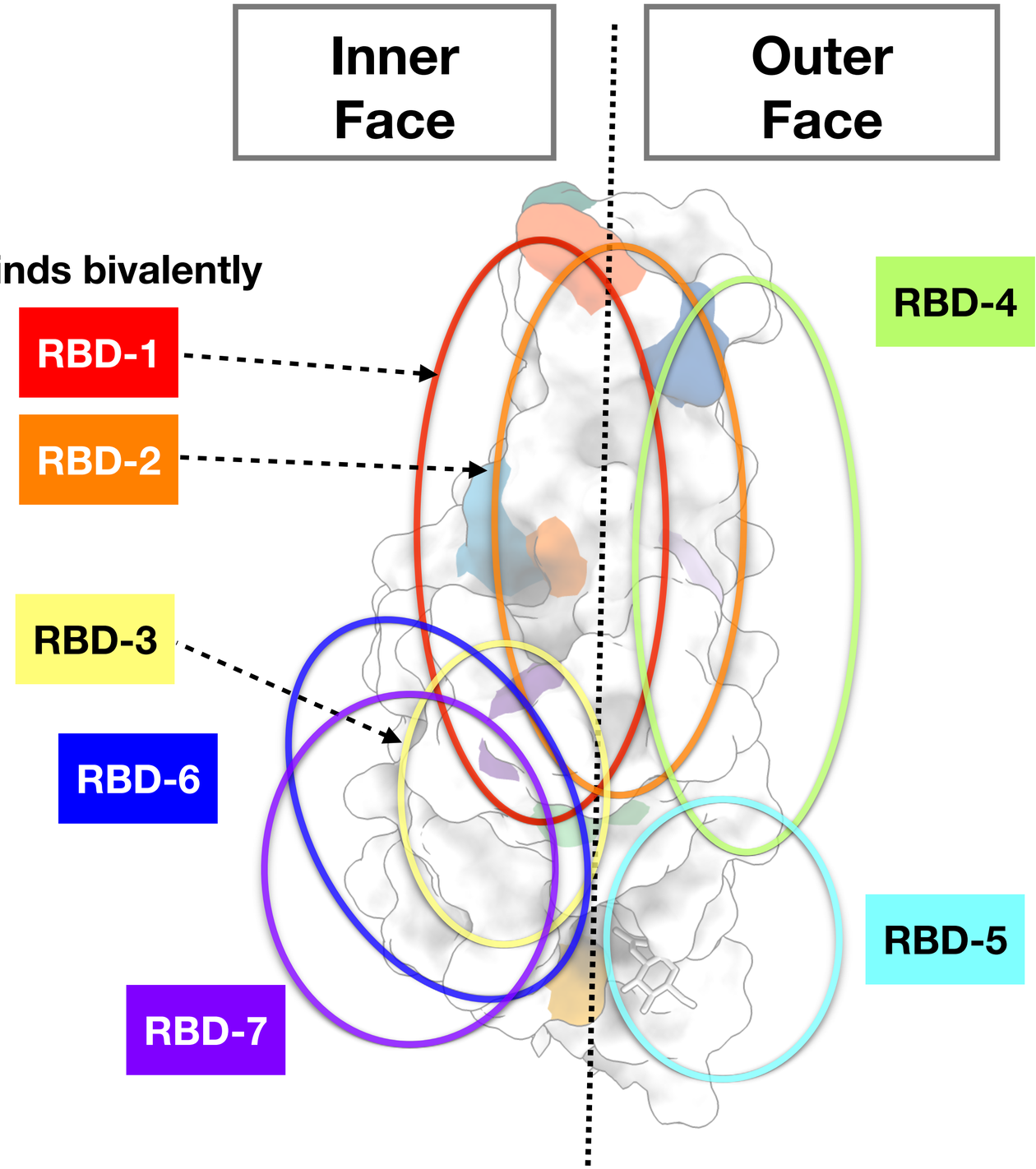


Hastie and Li, et al., Science 2021



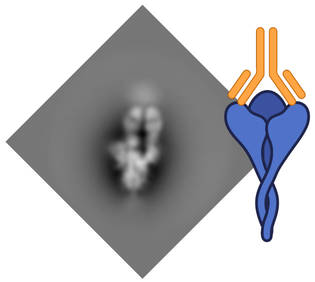
Hastie and Li, et al., Science 2021

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Hastie and Li, et al., Science 2021

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Inner Face

Outer Face

RBD-1

RBD-2

RBD-3

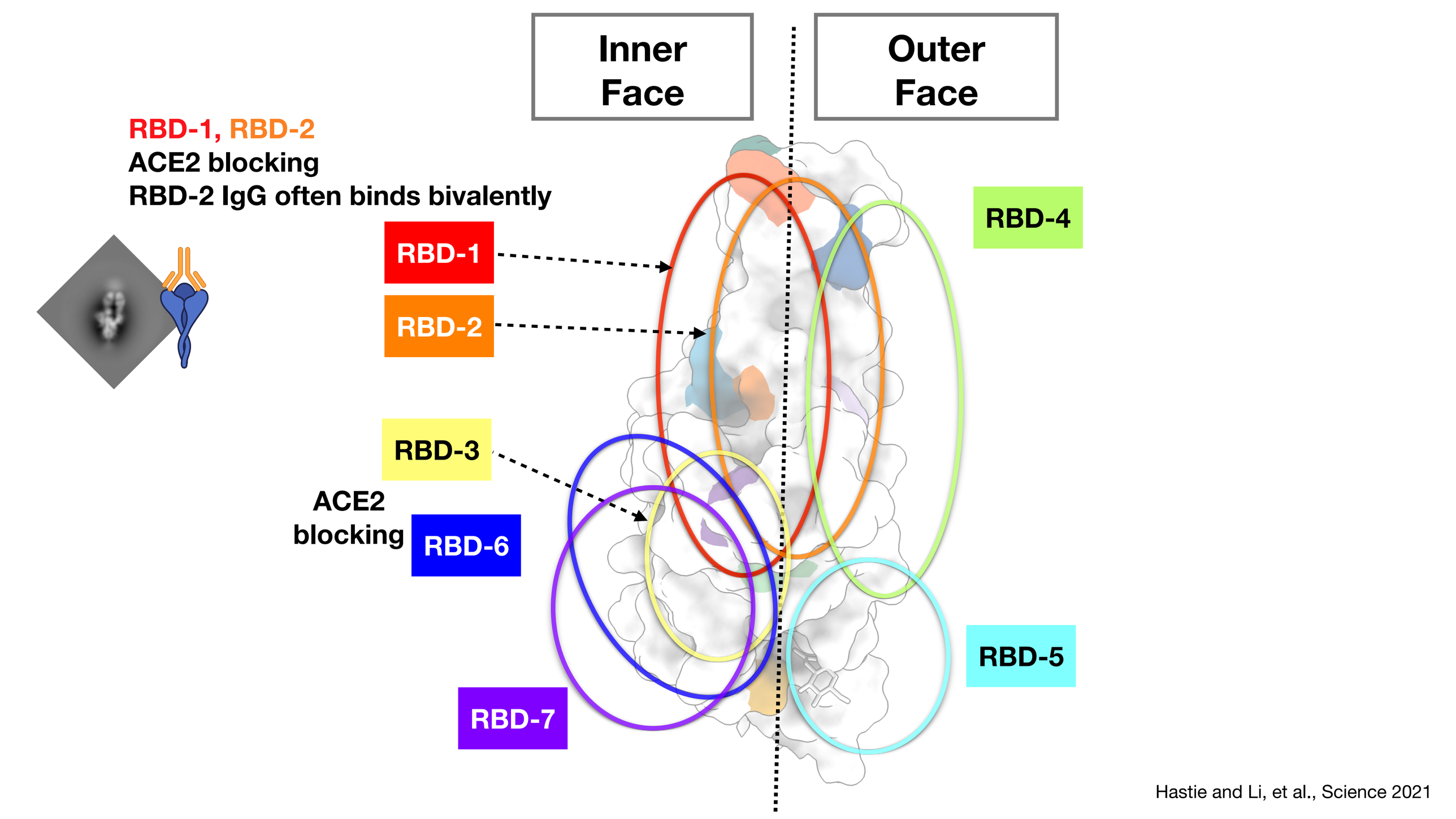
RBD-6

RBD-7

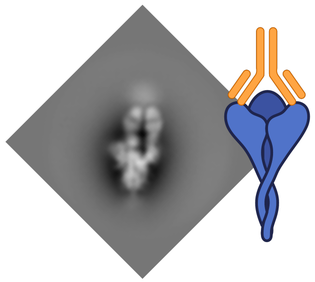
RBD-4

RBD-5

Hastie and Li, et al., Science 2021



Hastie and Li, et al., Science 2021



RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently

Inner Face

Outer Face

RBD-1

RBD-2

RBD-3

ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD-4

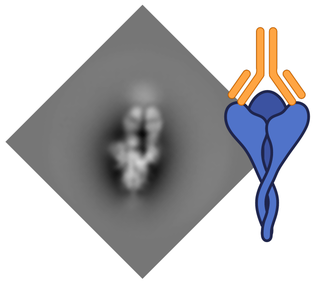
RBD-5

Hastie and Li, et al., Science 2021

Inner Face

Outer Face

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Require up-RBD

RBD-1

RBD-2

RBD-3

ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD-4

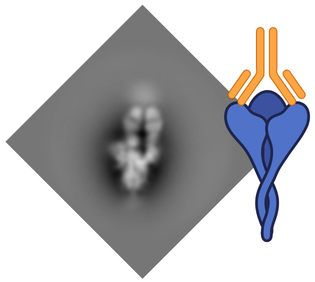
RBD-5

Hastie and Li, et al., Science 2021

Inner Face

Outer Face

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Require up-RBD

RBD-1

RBD-2

RBD-3

ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD-4

ACE2 blocking

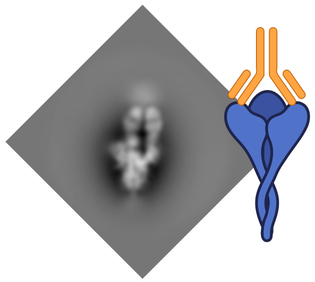
RBD-5

Hastie and Li, et al., Science 2021

Inner Face

Outer Face

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Require up-RBD

RBD-1

RBD-2

RBD-3

ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD-4 **ACE2 blocking**

RBD-5

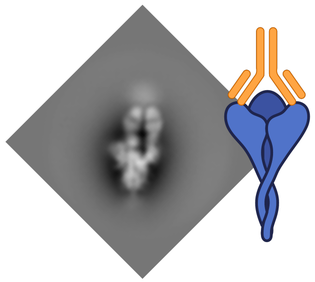
Variable ACE2 blocking
IgG bridges trimers

Hastie and Li, et al., Science 2021

Inner Face

Outer Face

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



Require up-RBD

RBD-1

RBD-2

RBD-3

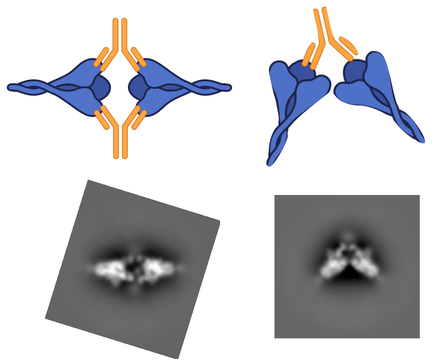
ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD-4 ACE2 blocking



RBD-5

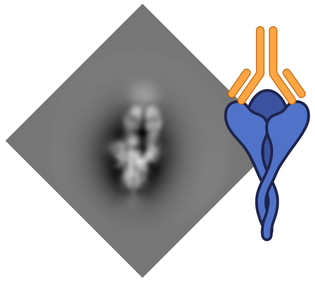
Variable ACE2 blocking
IgG bridges trimers

Hastie and Li, et al., Science 2021

Inner Face

Outer Face

RBD-1, RBD-2
ACE2 blocking
RBD-2 IgG often binds bivalently



RBD-1

RBD-2

RBD-4 ACE2 blocking

Require up-RBD

RBD-3

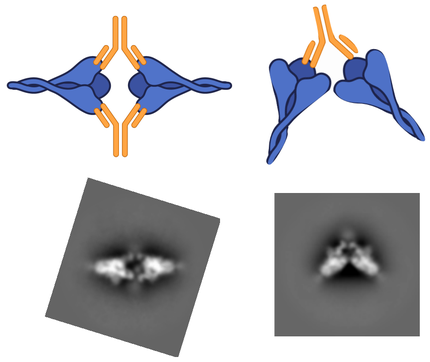
ACE2 blocking

RBD-6

Variable ACE2 blocking

RBD-7

RBD up *or* down



RBD-5

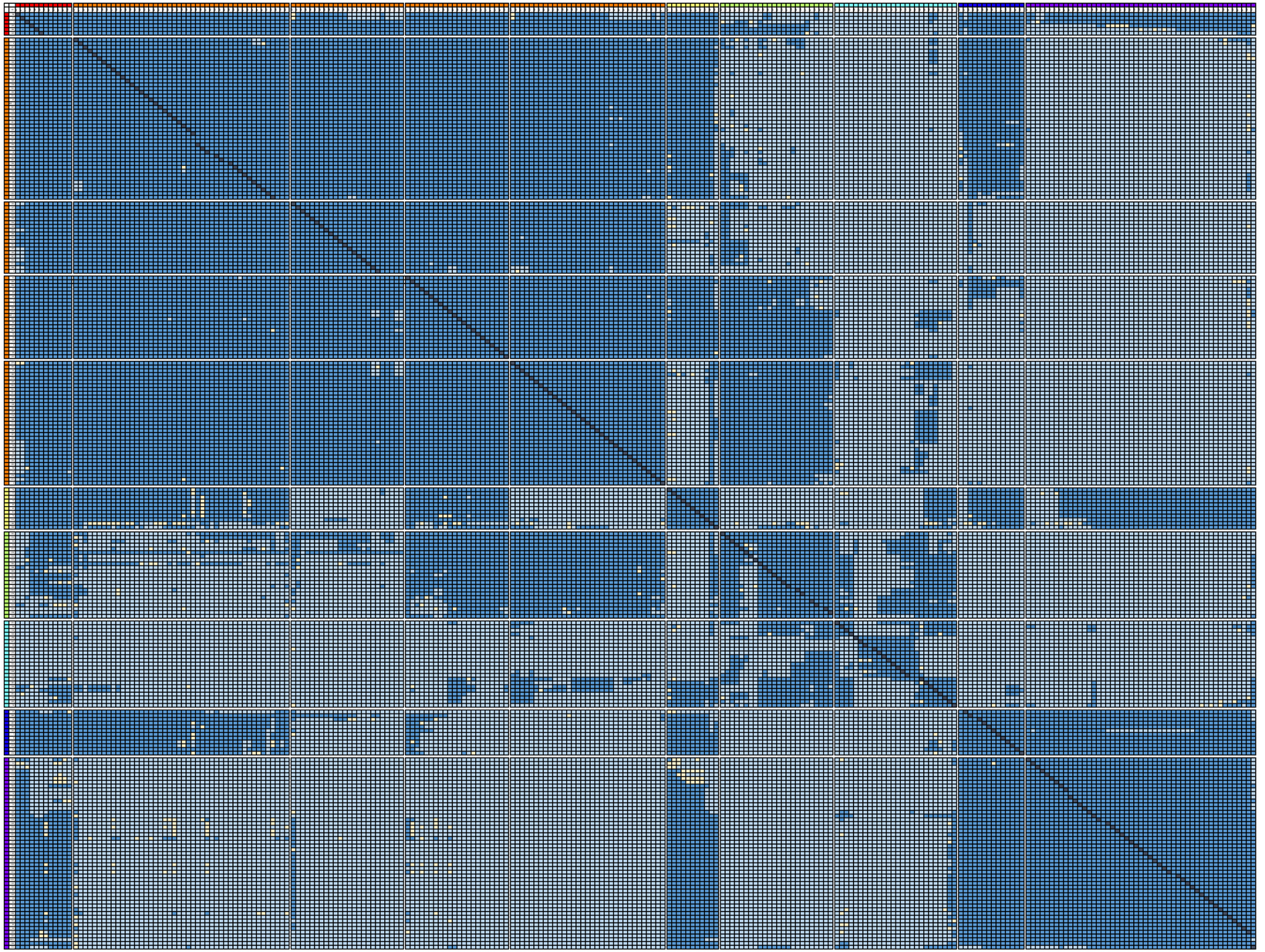
Variable ACE2 blocking
IgG bridges trimers

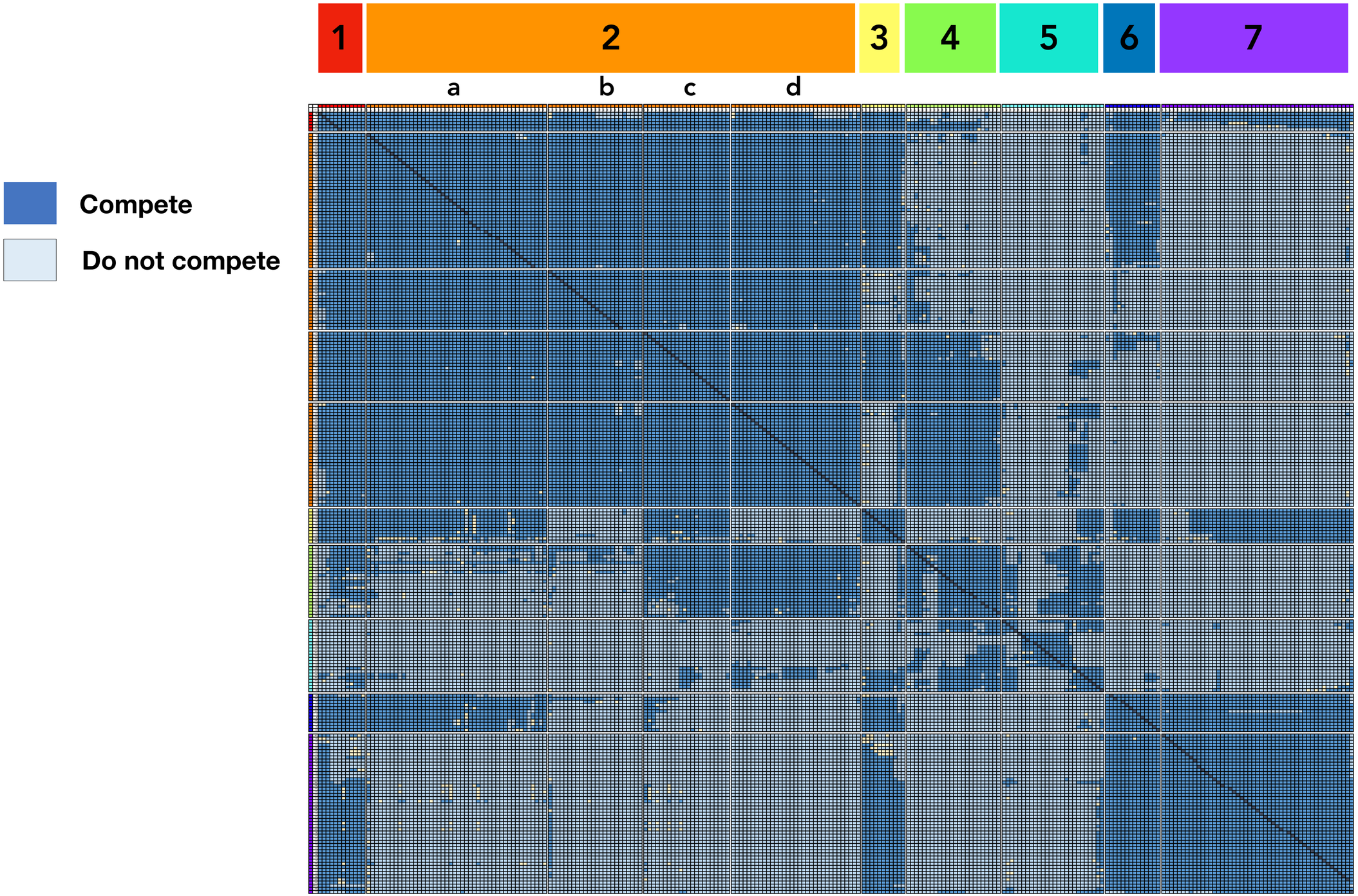
Hastie and Li, et al., Science 2021

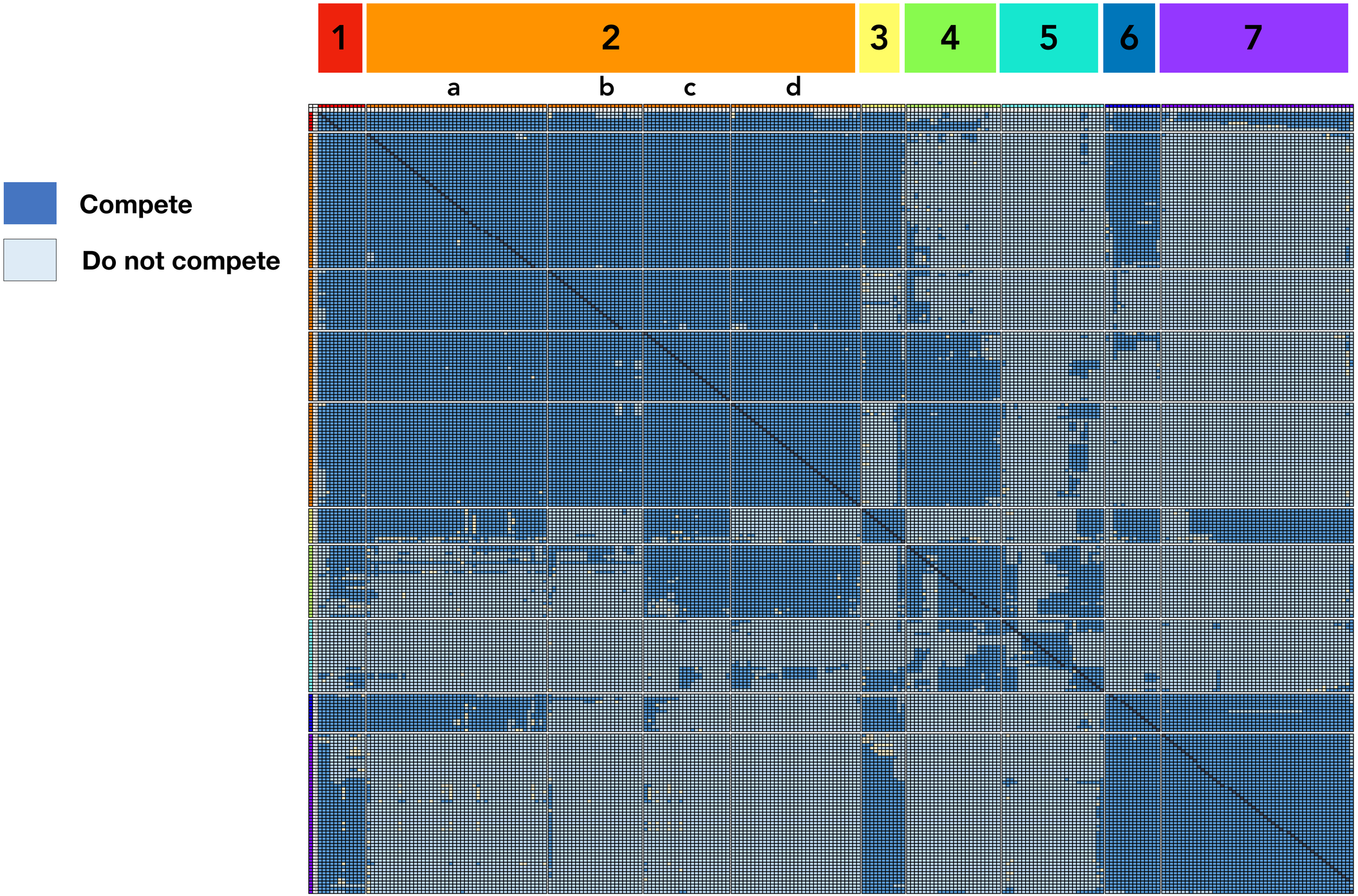
Competition grid across ~370 CoVIC mAbs

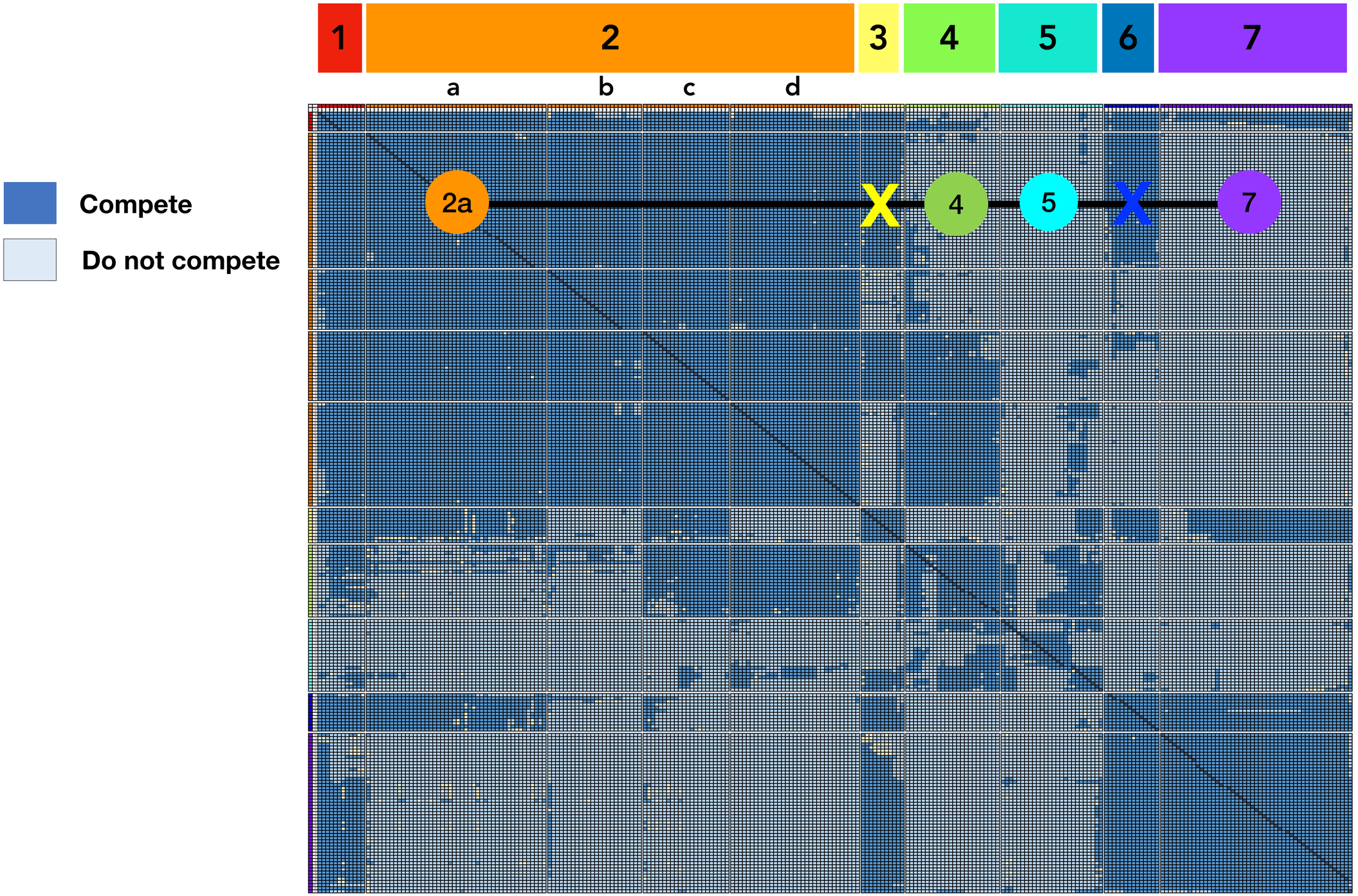
Compete

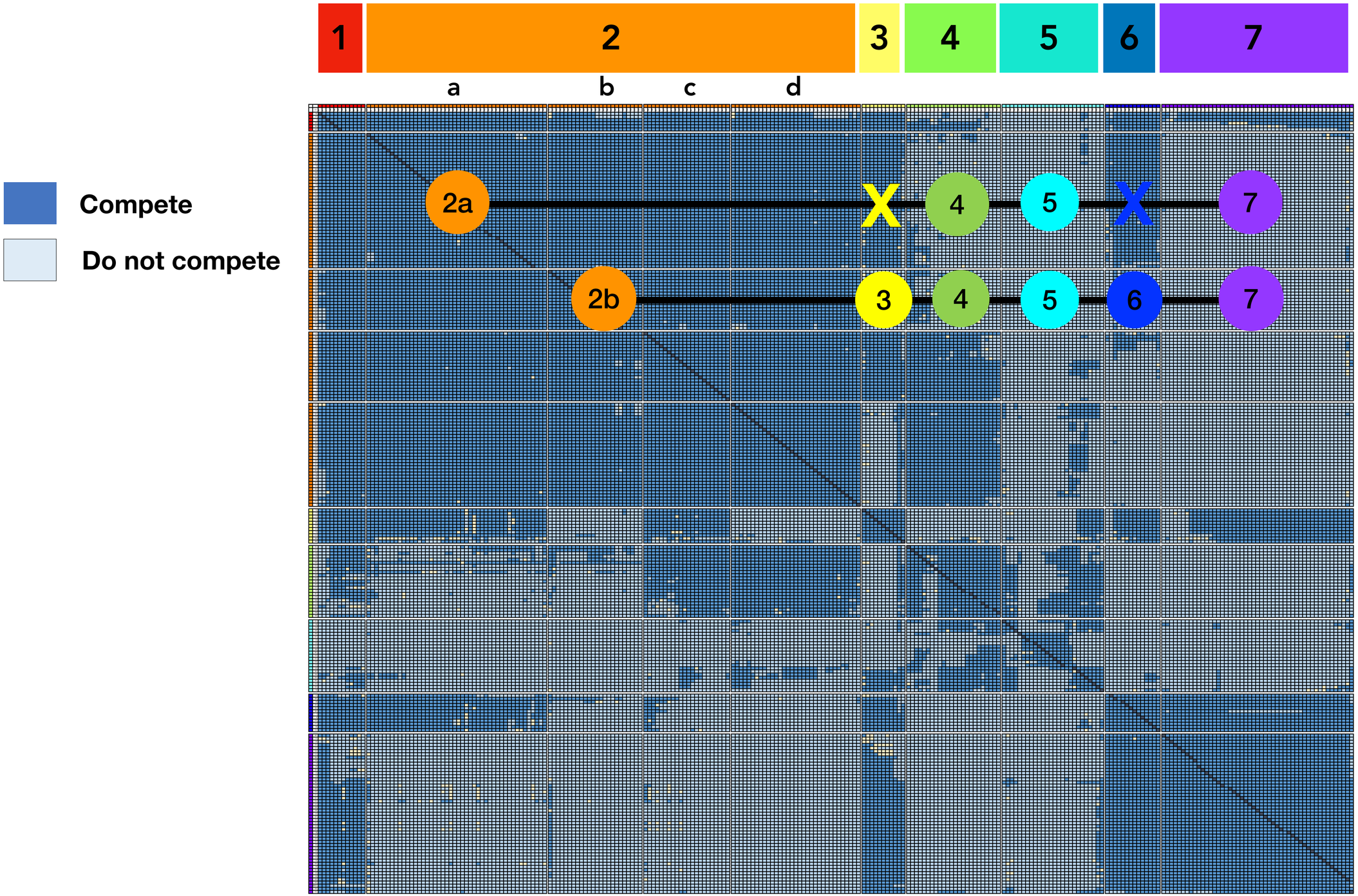
Do not compete

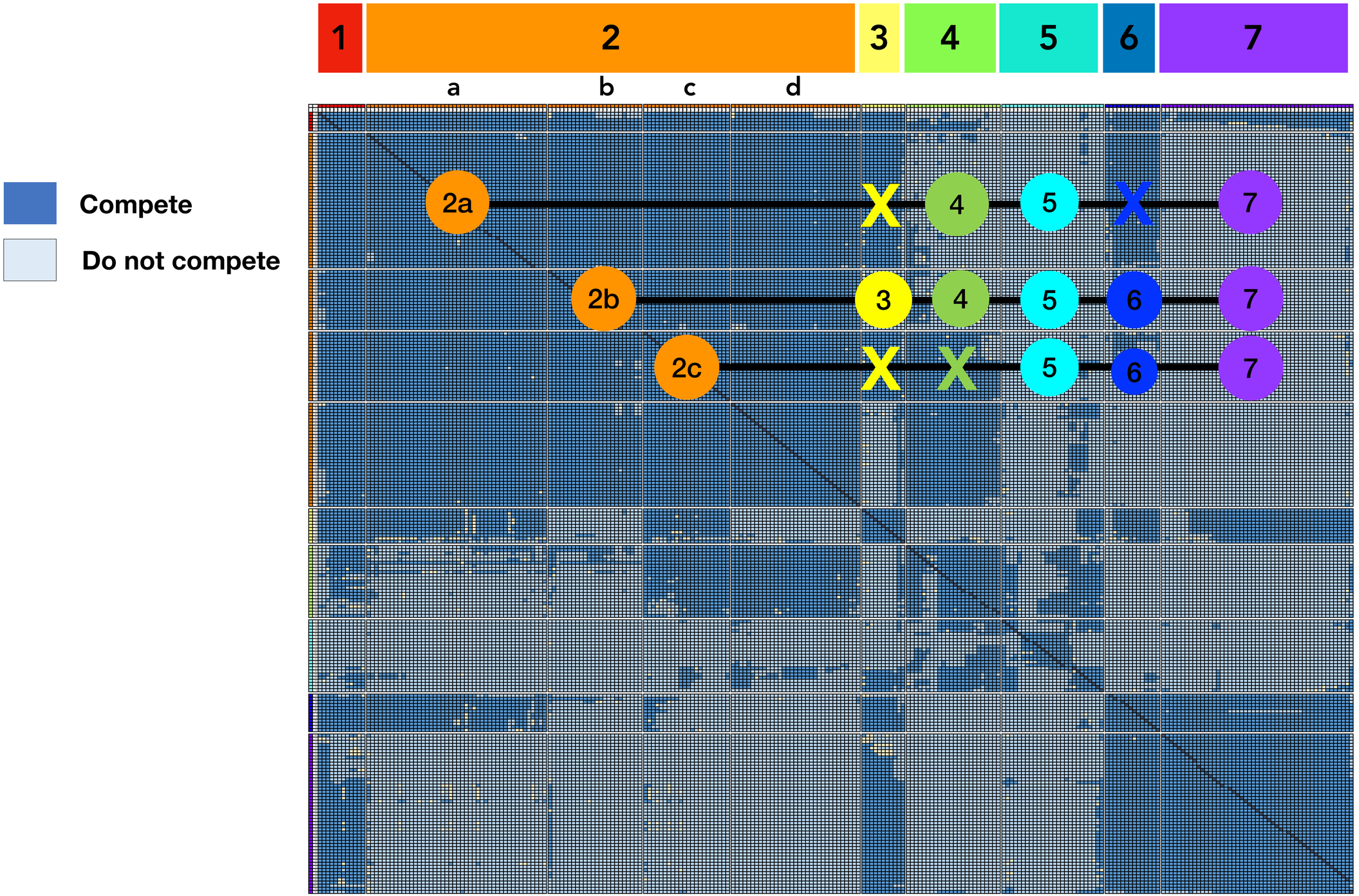


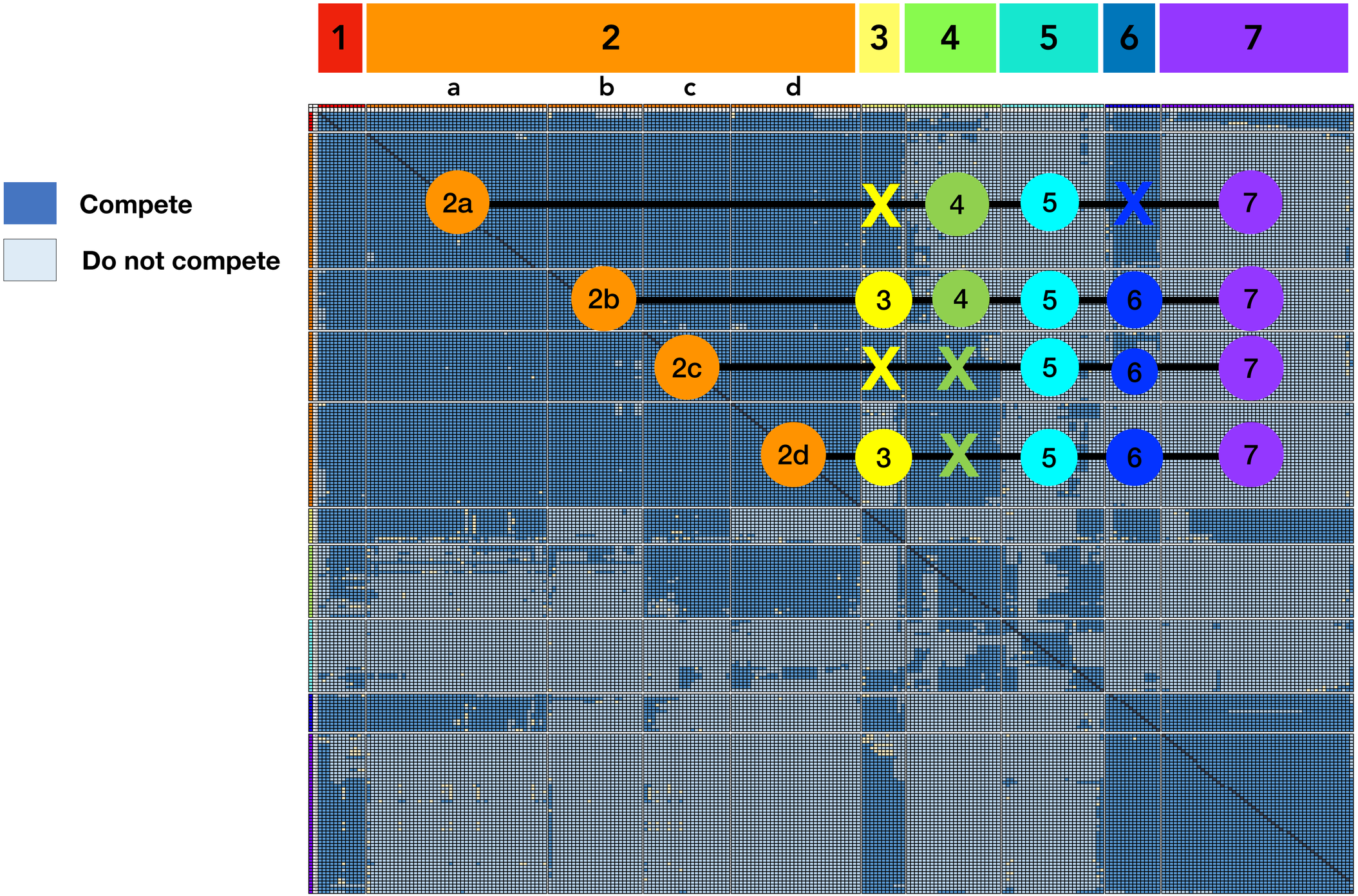

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete

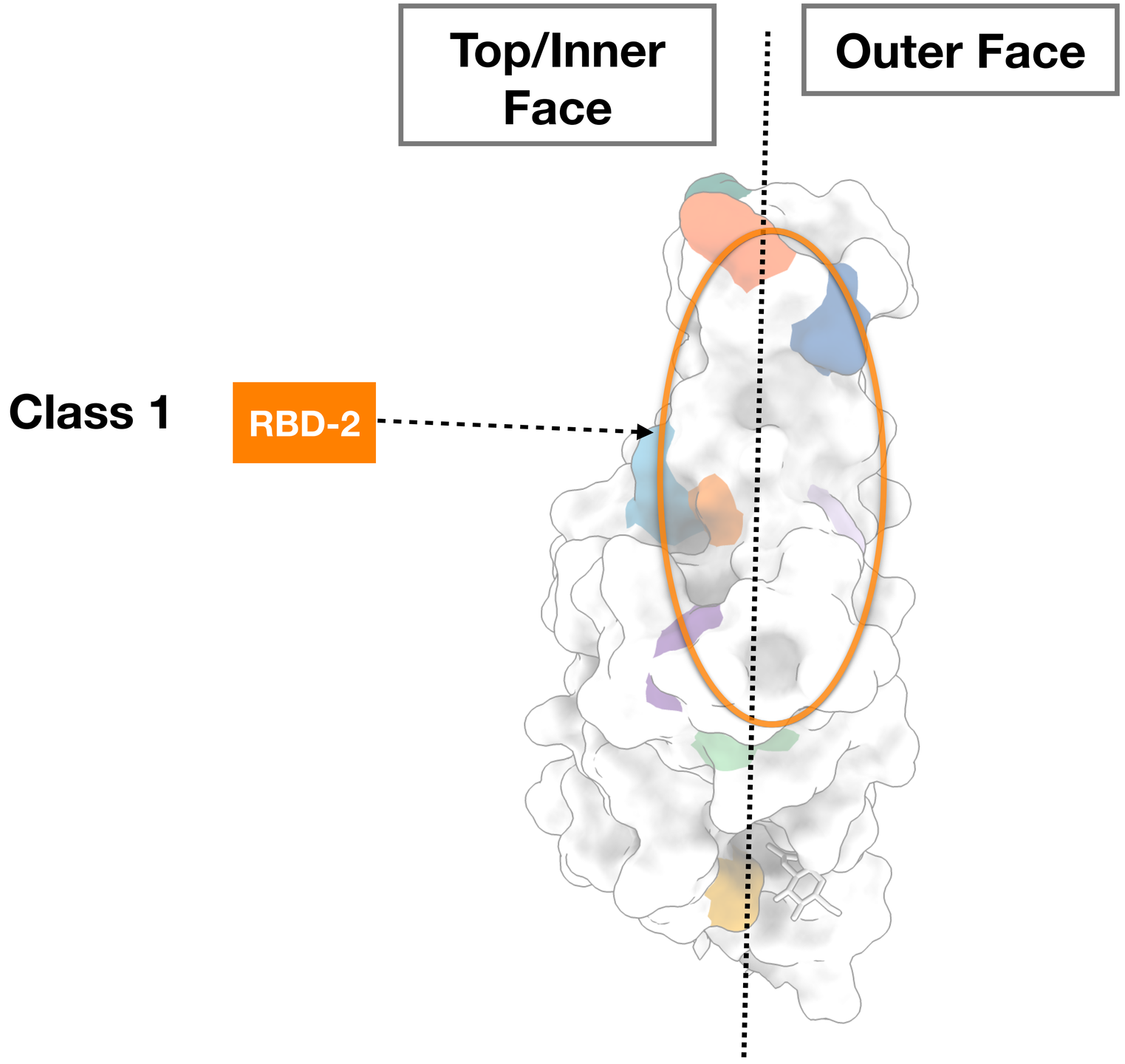

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete

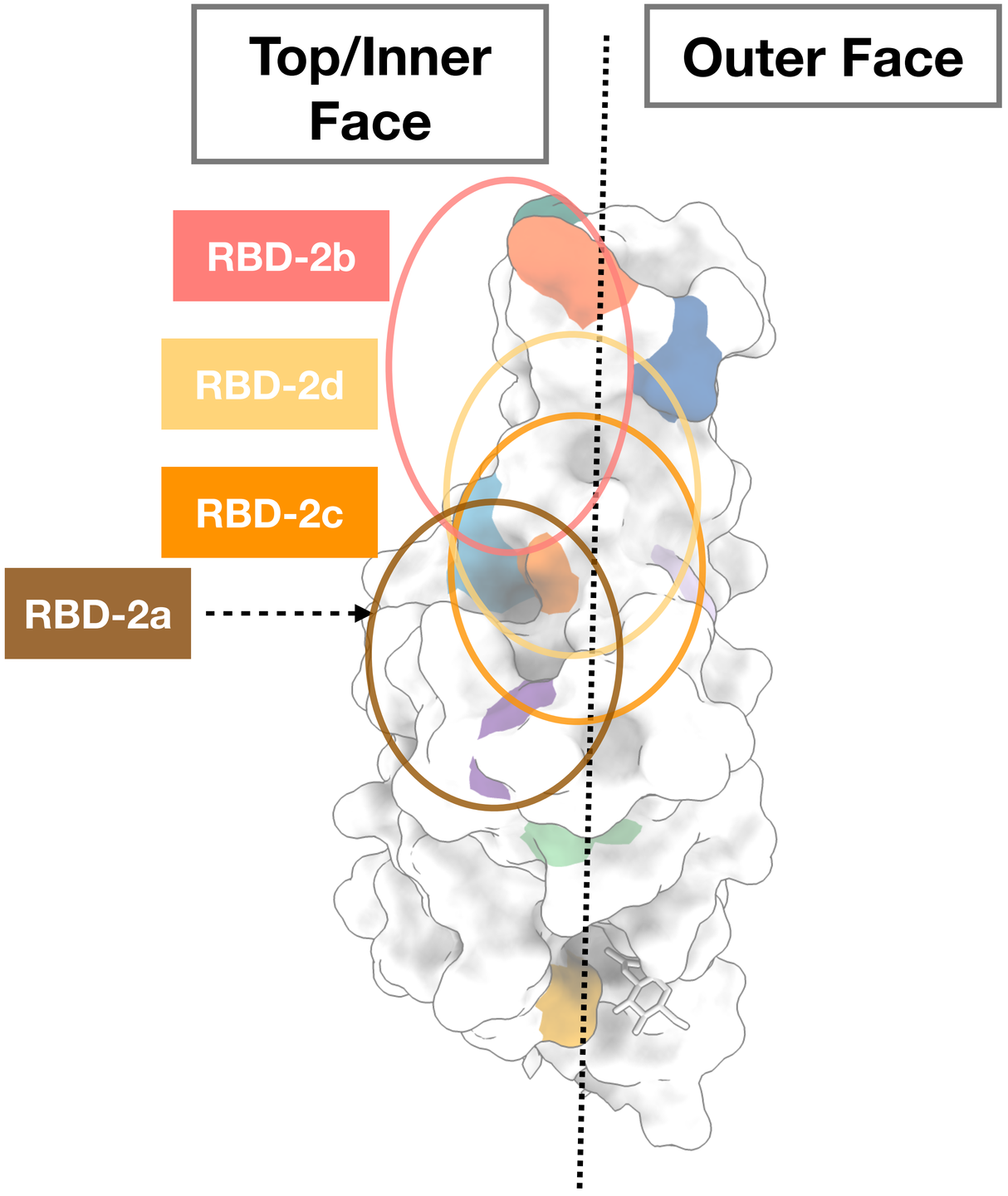

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete
2a
X
4
5
X
7

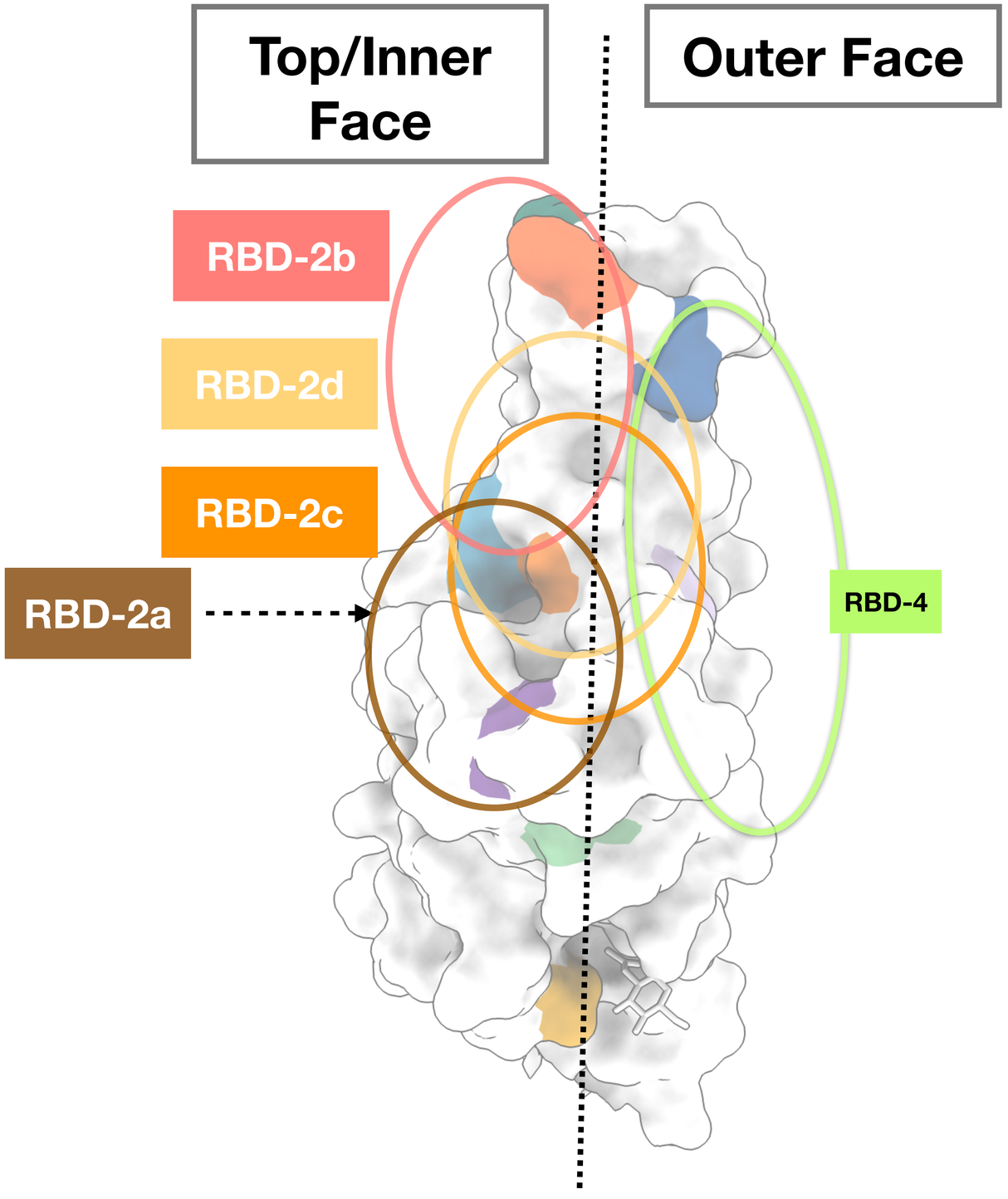

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete
2a
2b
3
4
5
6
7

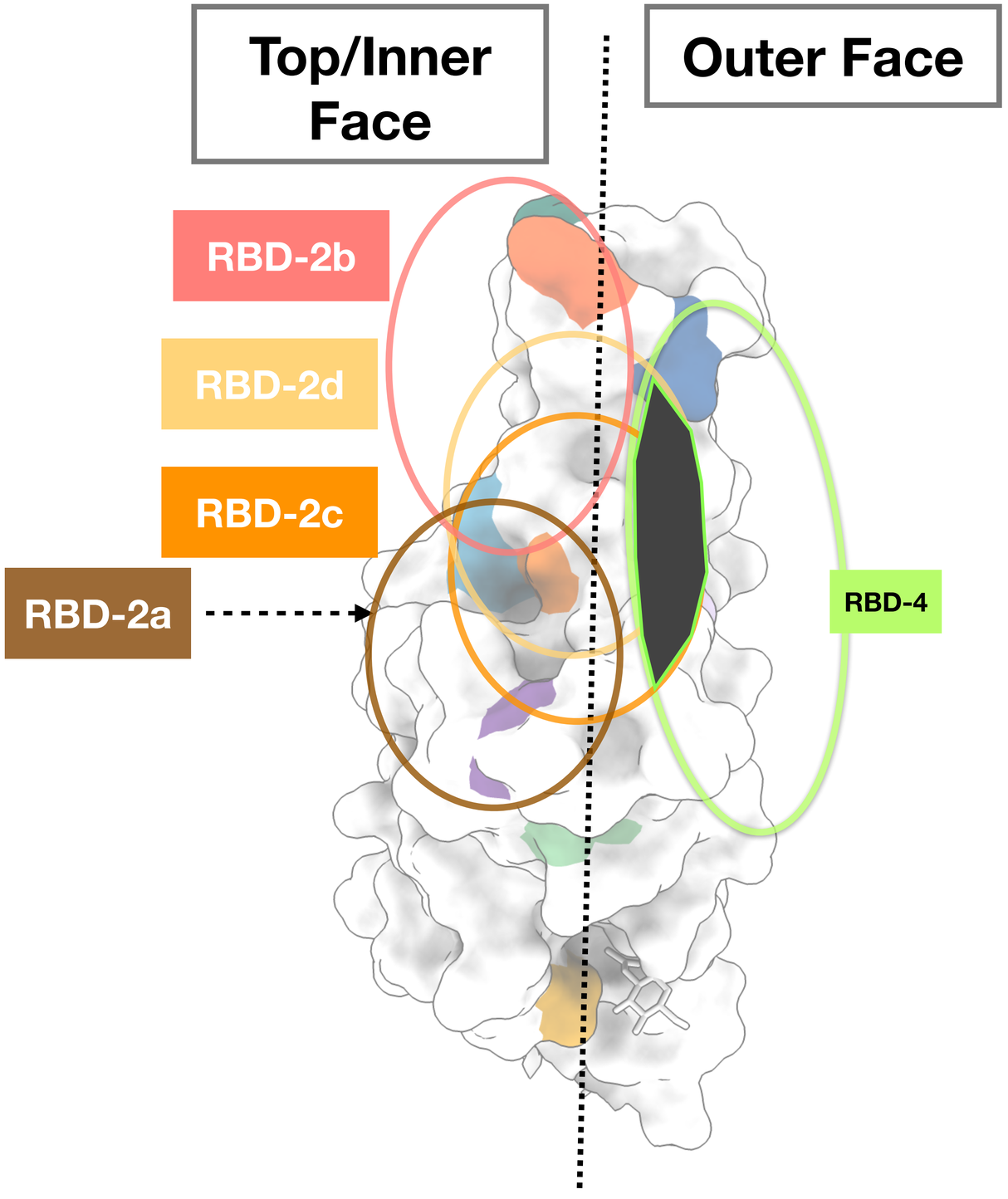

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete
2a
2b
2c

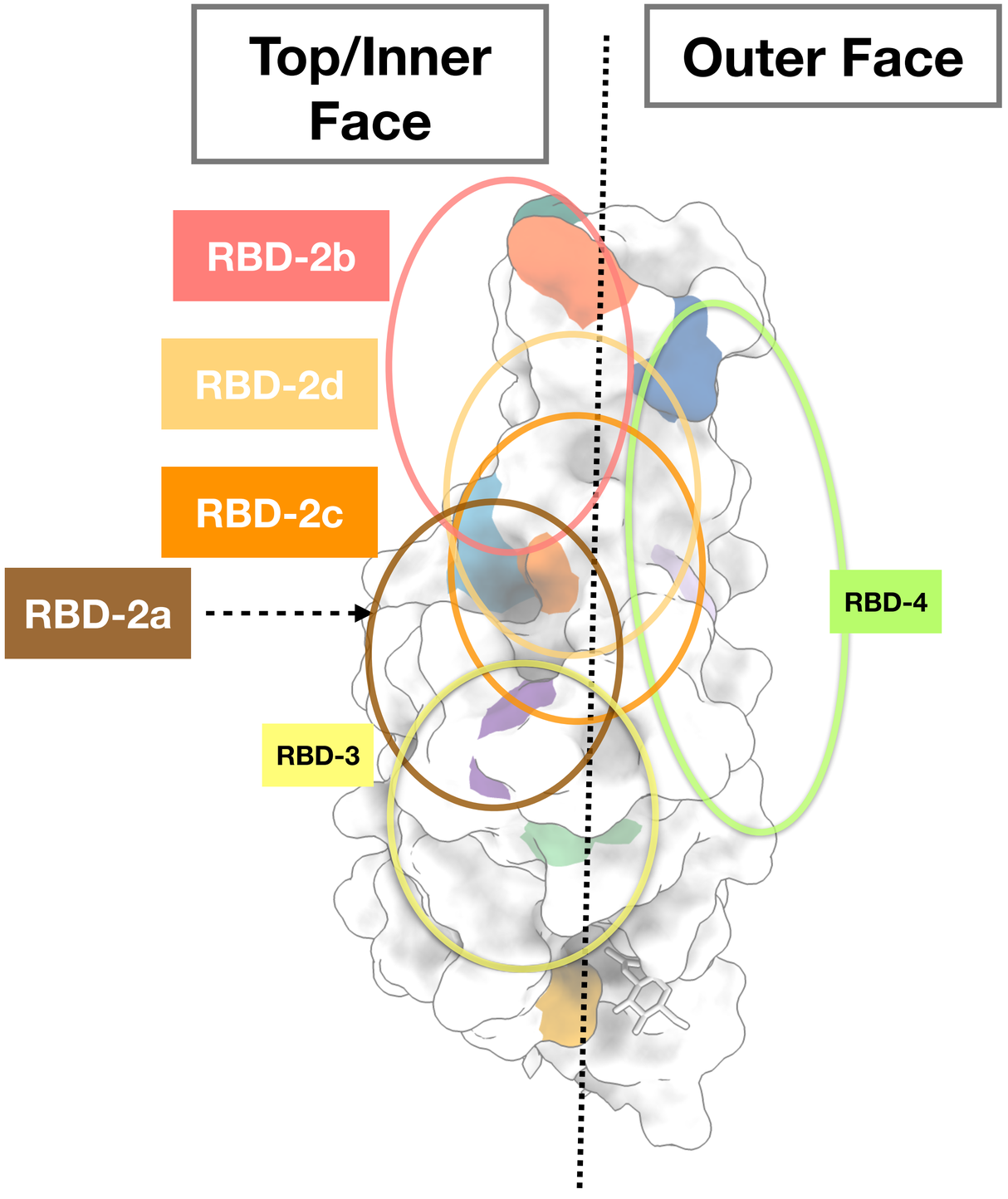

1
2
3
4
5
6
7
a
b
c
d
Compete
Do not compete
2a
2b
2c
2d

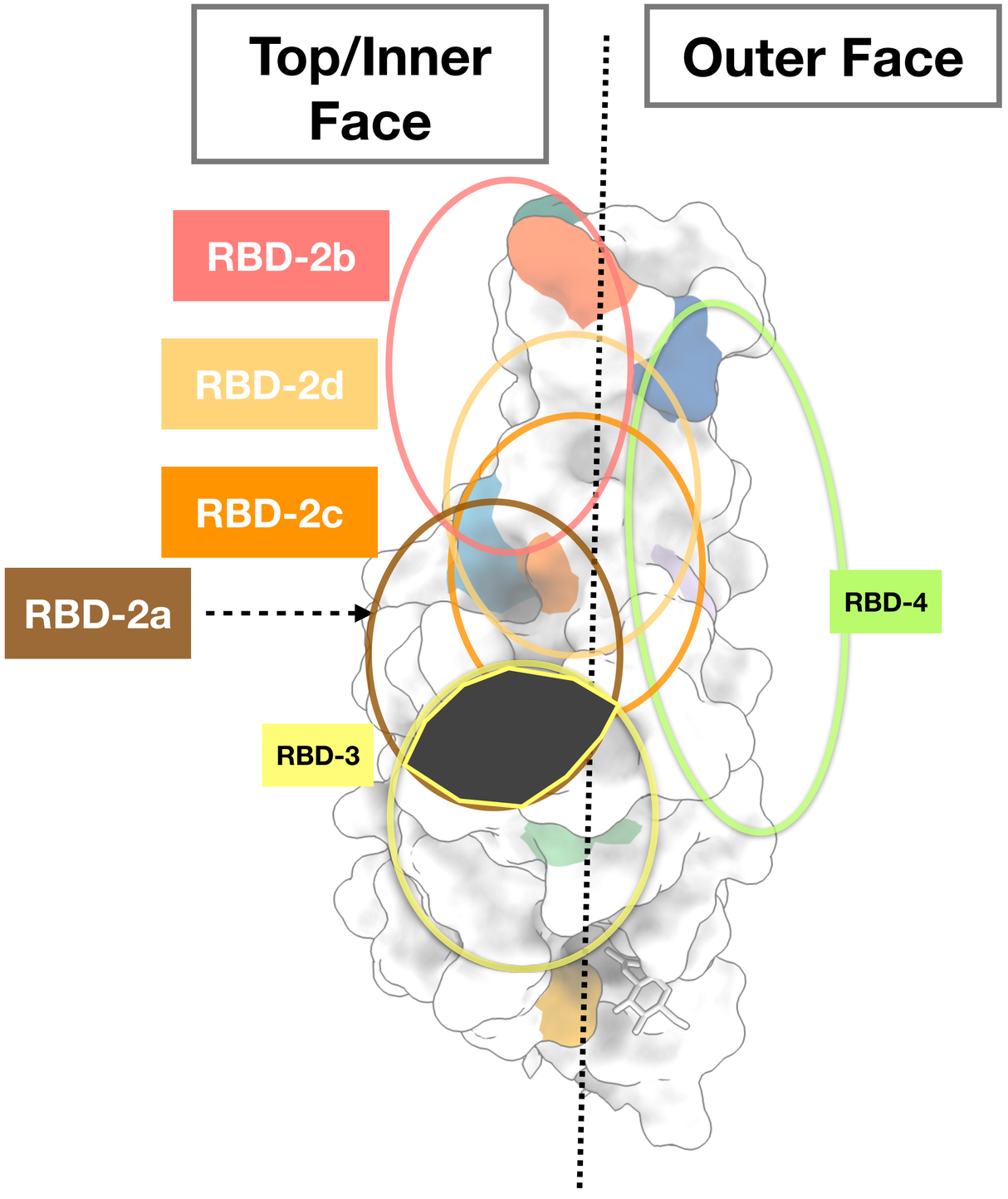

Top/Inner Face
Outer Face
Class 1
RBD-2

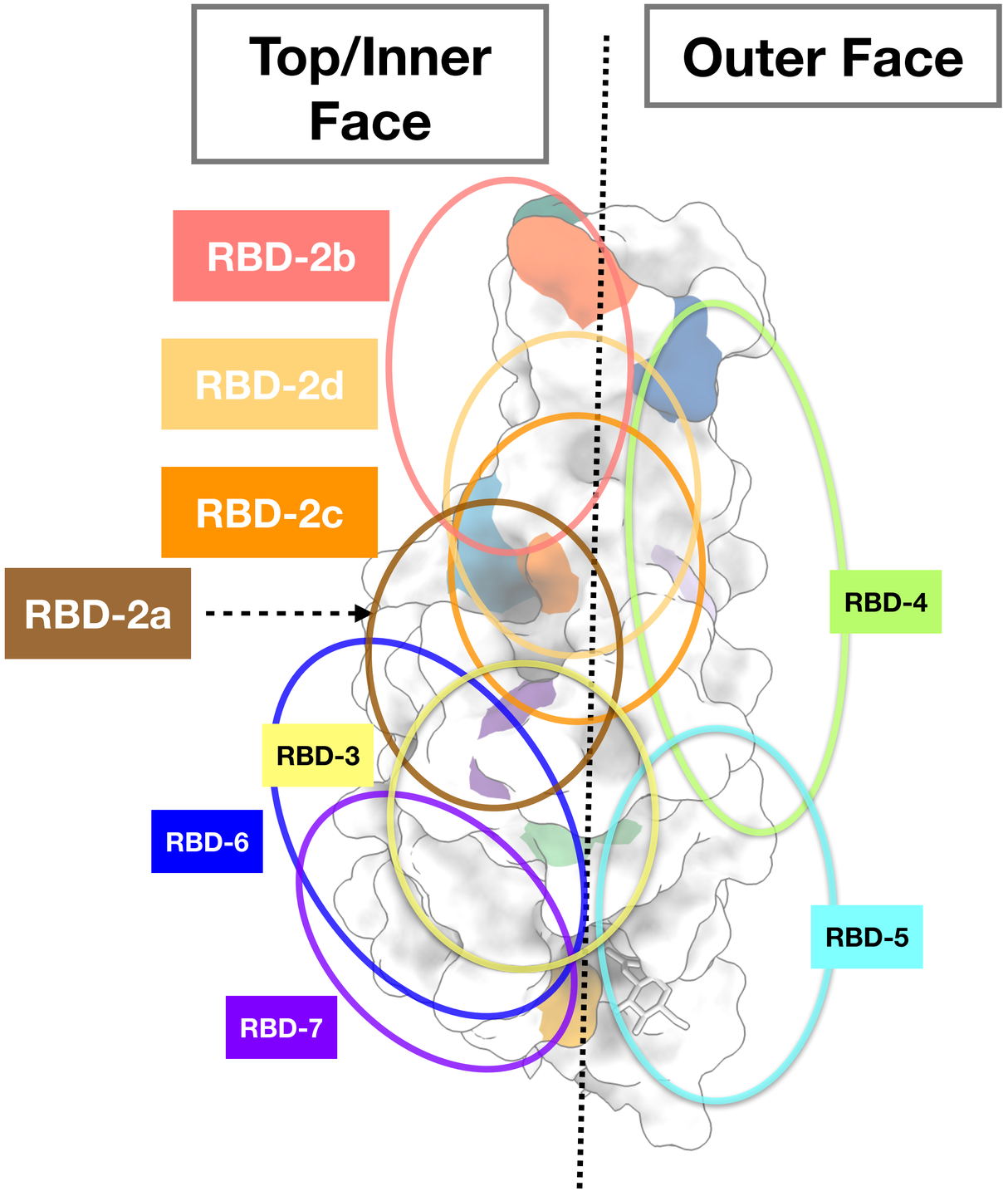

Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a

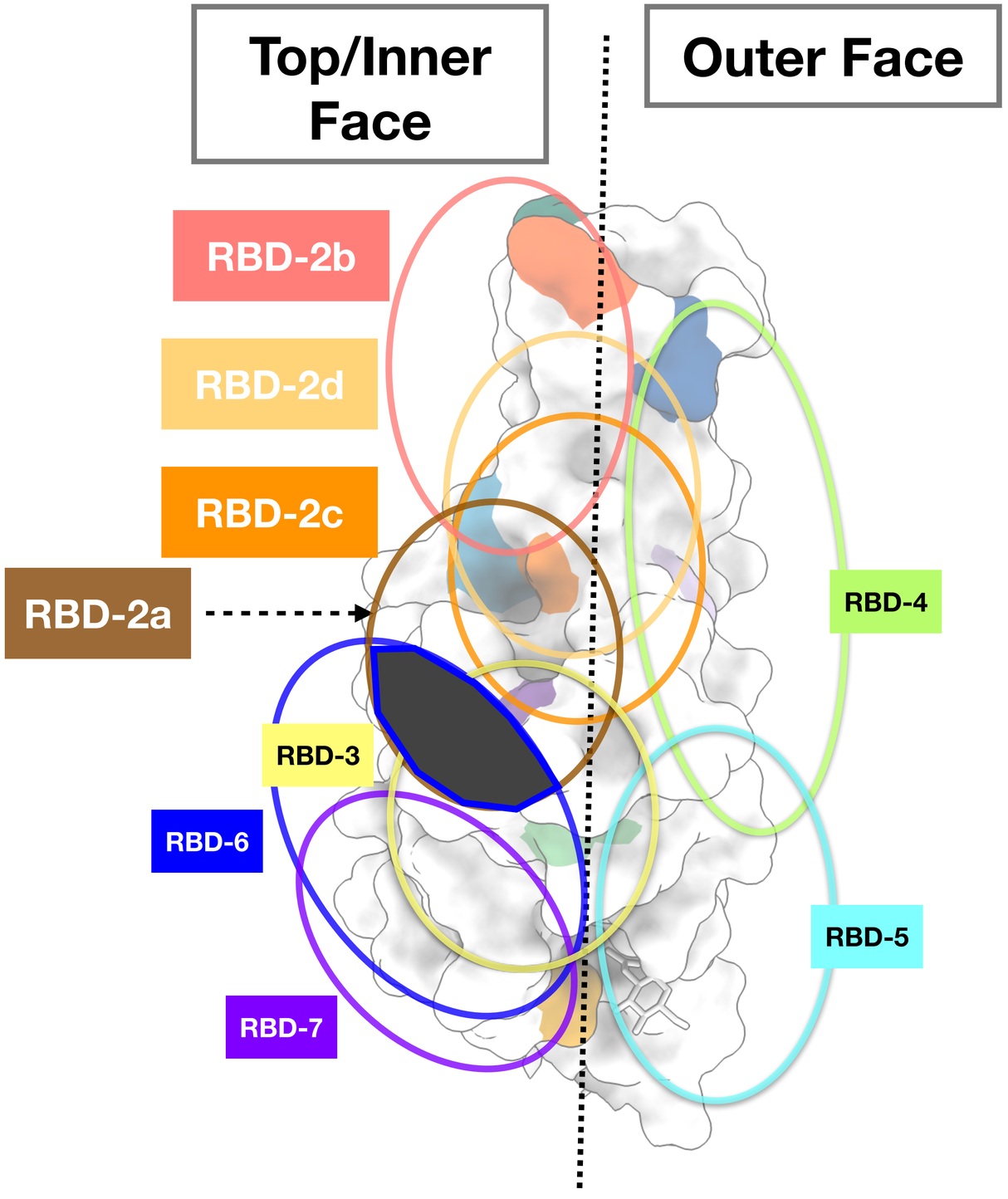

Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-4


Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-4


Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-3
RBD-4

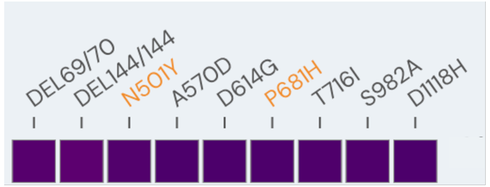

Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-3
RBD-4


Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-4
RBD-3
RBD-6
RBD-5
RBD-7

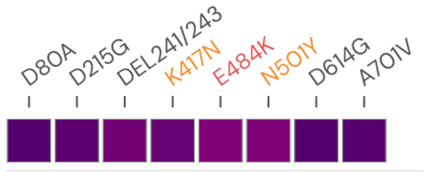

Top/Inner Face
Outer Face
RBD-2b
RBD-2d
RBD-2c
RBD-2a
RBD-4
RBD-3
RBD-6
RBD-5
RBD-7

October 2020: Variants Of Concern

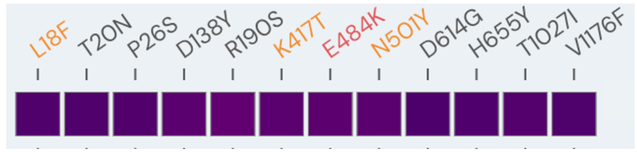
October 2020 : Alpha



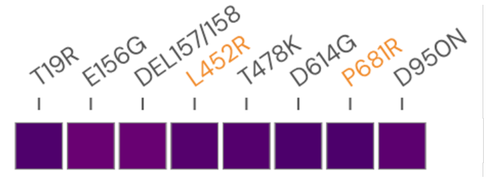
December 2020 : Beta



January 2021 : Gamma



May 2021 : Delta

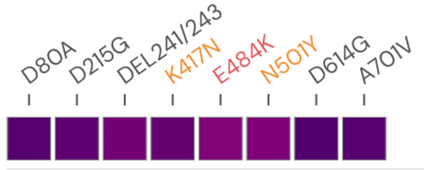


From outbreak.info

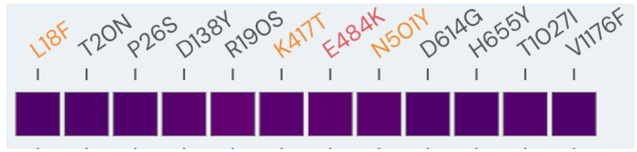
October 2020 : Alpha

N501Y

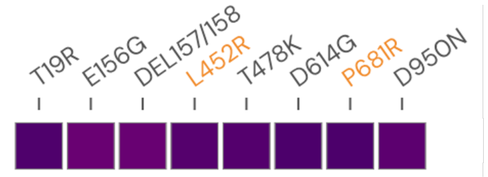
December 2020 : Beta



January 2021 : Gamma



May 2021 : Delta

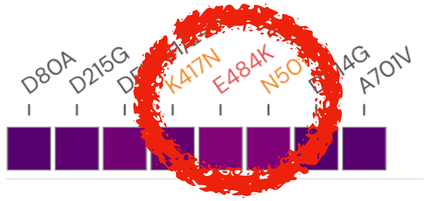


From outbreak.info

October 2020 : Alpha

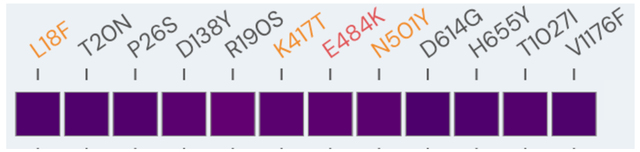
N501Y

December 2020 : Beta

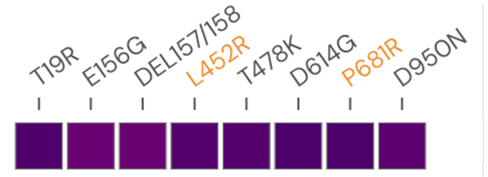


K417N, E484K, N501Y

January 2021 : Gamma



May 2021 : Delta

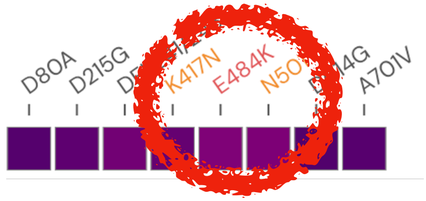


From outbreak.info

October 2020 : Alpha

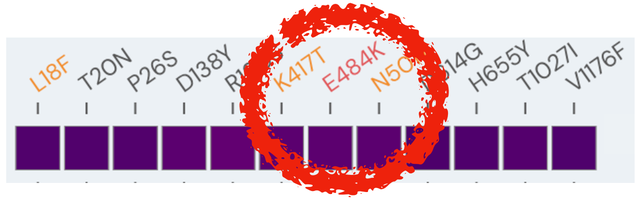
N501Y

December 2020 : Beta



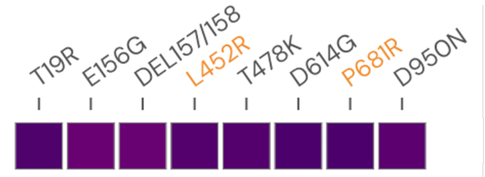
K417N, E484K, N501Y

January 2021 : Gamma



K417N, E484K, N501Y

May 2021 : Delta

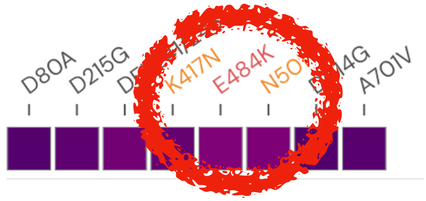


From outbreak.info

October 2020 : Alpha

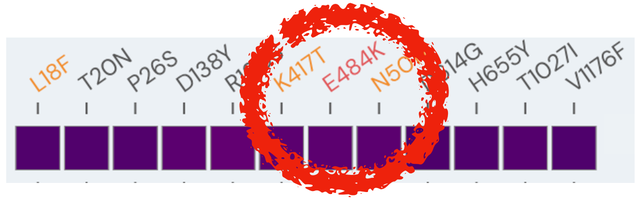
N501Y

December 2020 : Beta



K417N, E484K, N501Y

January 2021 : Gamma

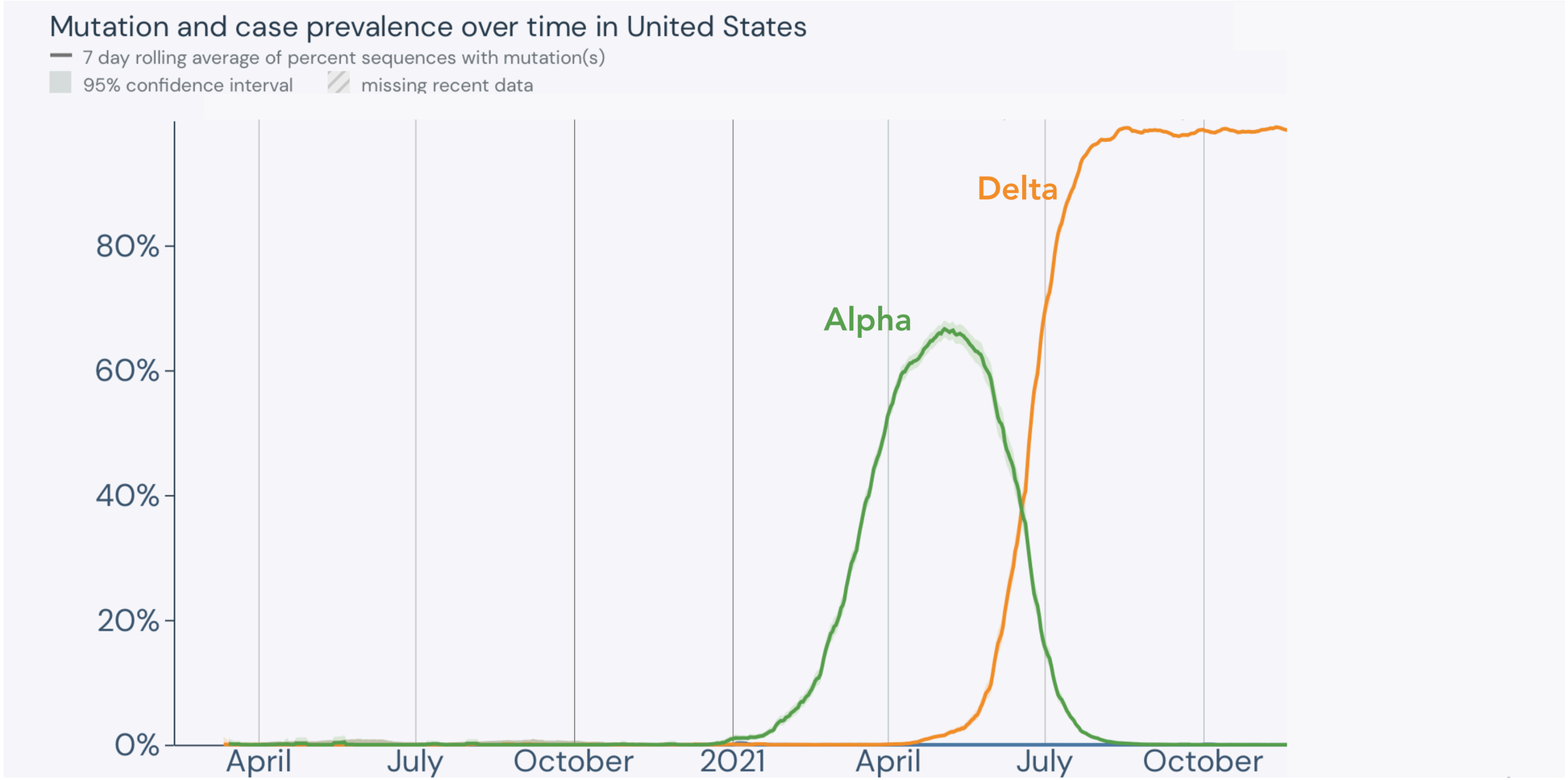


K417N, E484K, N501Y

May 2021 : Delta

L452R

From outbreak.info



From outbreak.info

October 2020: Variants Of Concern

Which CoVIC mAbs are resistant to VOC?
What epitope group are they in?
What combinations good for cocktails?

Select 40 representative mAbs to map resistance

RESEARCH

CORONAVIRUS

Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies: A global consortium study

Kathryn M. Hastie[1]†, Haoyang Li[1]†, Daniel Bedinger[2], Sharon L. Schendel[1], S. Moses Dennison[3], Kan Li[3], Vamseedhar Rayaprolu[1], Xiaoying Yu[1], Colin Mann[1], Michelle Zandonatti[1], Ruben Diaz Avalos[1], Dawid Zyla[1], Tierra Buck[1], Sean Hui[1], Kelly Shaffer[1], Chitra Hariharan[1], Jieyun Yin[1], Eduardo Olmedillas[1], Adrian Enriquez[1], Diptiben Parekh[1], Milite Abraha[3], Elizabeth Feeney[3], Gillian Q. Horn[3], CoVIC-DB team[1], Yoann Aldon[4], Hanif Ali[5], Sanja Aracic[6], Ronald R. Cobb[7], Ross S. Federman[8], Joseph M. Fernandez[9], Jacob Glanville[10], Robin Green[8], Gevorg Grigoryan[8], Ana G. Lujan Hernandez[11], David D. Ho[12], Kuan-Ying A. Huang[13], John Ingraham[8], Weidong Jiang[14], Paul Kellam[15,16], Cheolmin Kim[17], Minsoo Kim[17], Hyeong Mi Kim[17], Chao Kong[18], Shelly J. Krebs[19], Fei Lan[9,20], Guojun Lang[18], Sooyoung Lee[17], Cheuk Lun Leung[8], Junli Liu[14], Yanan Lu[9,21], Anna MacCamy[22], Andrew T. McGuire[22], Anne L. Palser[15], Terence H. Rabbitts[5,23], Zahra Rikhtegaran Tehrani[24], Mohammad M. Sajadi[24], Rogier W. Sanders[4], Aaron K. Sato[11], Liang Schweizer[25], Jimin Seo[17], Bingqing Shen[25], Jonne L. Snitselaar[4], Leonidas Stamatatos[22], Yongcong Tan[18], Milan T. Tomic[26], Marit J. van Gils[4], Sawsan Youssef[10], Jian Yu[12], Tom Z. Yuan[11], Qian Zhang[25], Bjoern Peters[1,27], Georgia D. Tomaras[3], Timothy Germann[2], Erica Ollmann Saphire[1,27]*

Antibody-based therapeutics and vaccines are essential to combat COVID-19 morbidity and mortality after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Multiple mutations in SARS-CoV-2 that could impair antibody defenses propagated in human-to-human transmission and spillover or spillback events between humans and animals. To develop prevention and therapeutic strategies, we formed an international consortium to map the epitope landscape on the SARS-CoV-2 spike protein, defining and structurally illustrating seven receptor binding domain (RBD)–directed antibody communities with distinct footprints and competition profiles. Pseudovirion-based neutralization assays reveal spike mutations, individually and clustered together in variants, that affect antibody function among the communities. Key classes of RBD-targeted antibodies maintain neutralization activity against these emerging SARS-CoV-2 variants. These results provide a framework for selecting antibody treatment cocktails and understanding how viral variants might affect antibody therapeutic efficacy.

Hastie and Li, et al., Science, July 2021

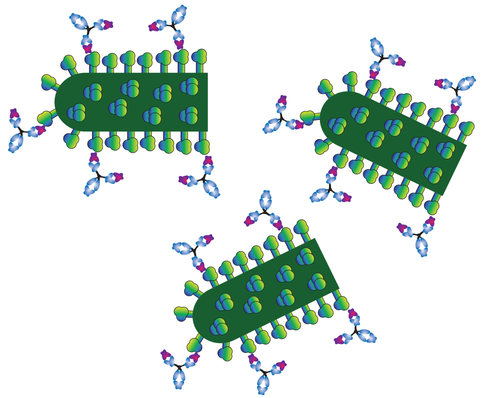
Pseudovirus neutralization

SARS-CoV-2 Spike source: Wuhan Hu-1 strain or VOC

Base pseudovirus: VSVΔG

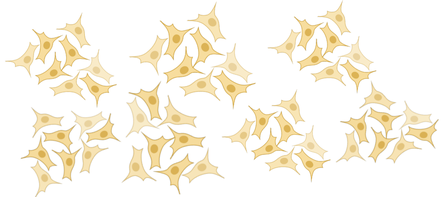
Pseudovirus transduction: HEK293K cells transfected with SARS-CoV-2ΔCT (C-term 19 aa deleted)

Pseudovirus: VSVΔG-SpikeΔCT



Pre-incubate pseudovirus with CoVIC mAbs at indicated concentration for 1 hr at 37 ˚C

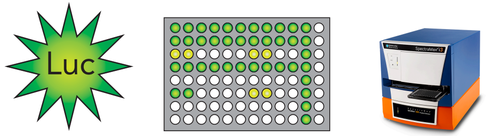
Target cells: Vero



Incubate antibody-pseudovirus complexes with target cells

Reporter: GFP

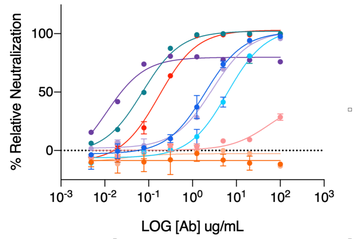
Plate reader: CX5 CellInsight



Stain cells, autoenumeration of infected cells

Calculation method: 4-PL curves

Software: Prism



Generate neutralization curves from average of triplicate measurements; calculate IC_{50}, IC_{80}

Kate Hastie
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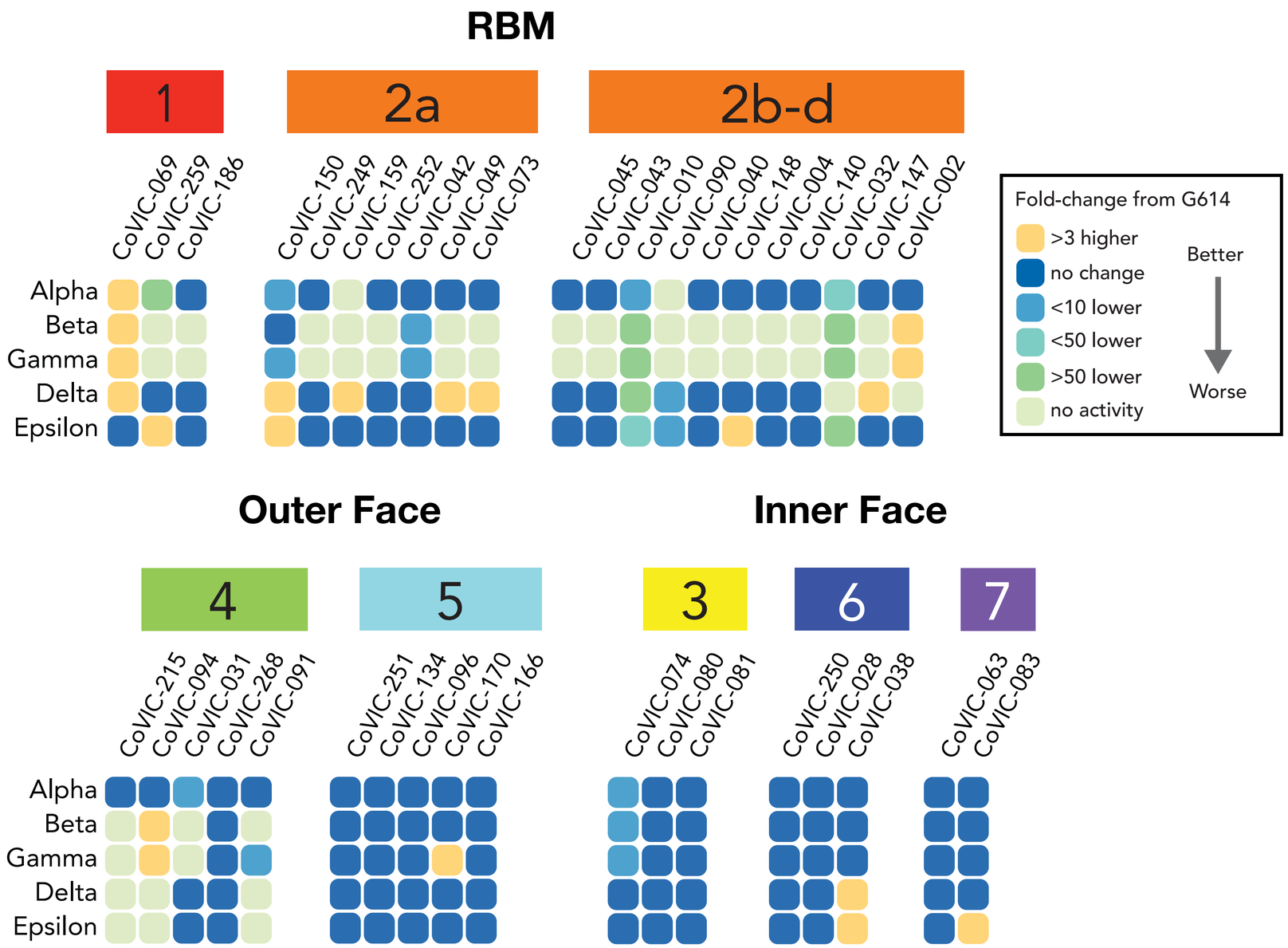
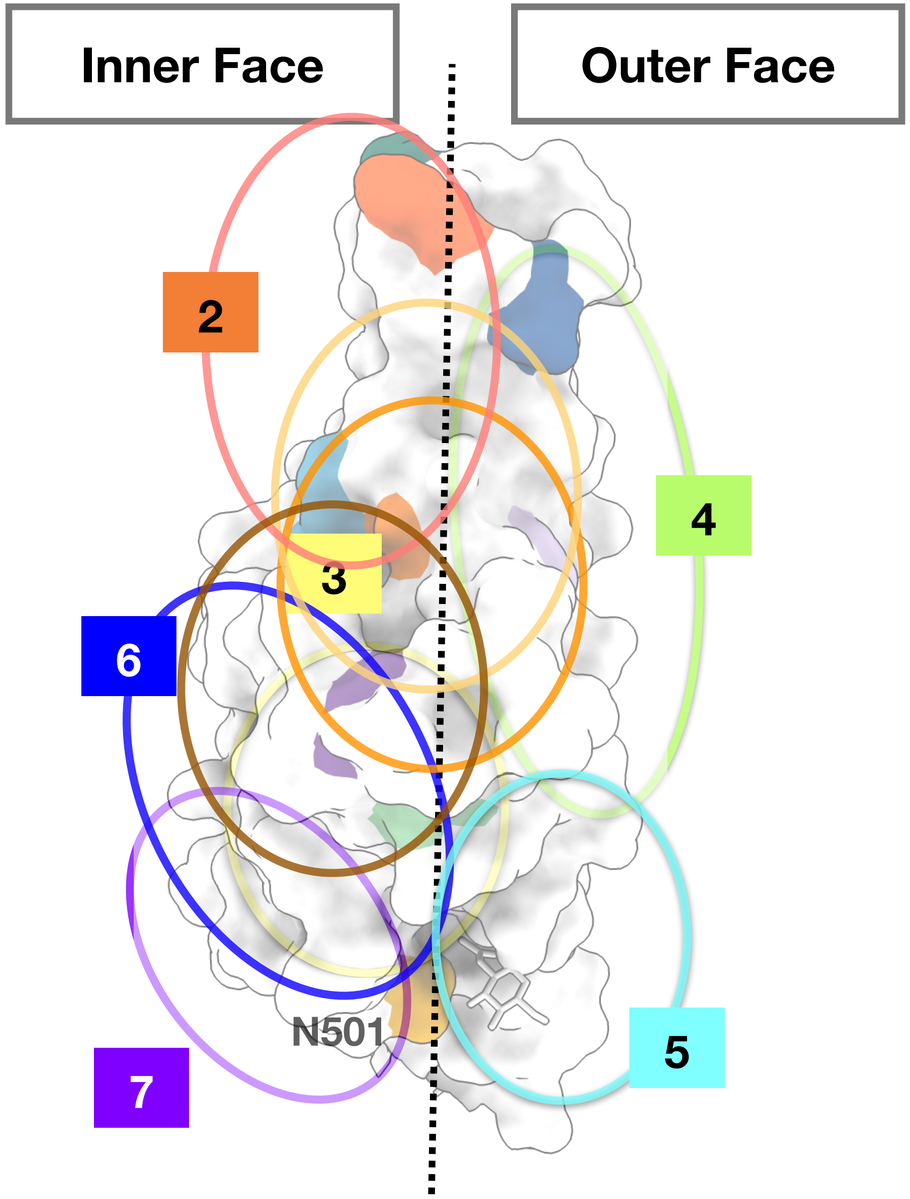
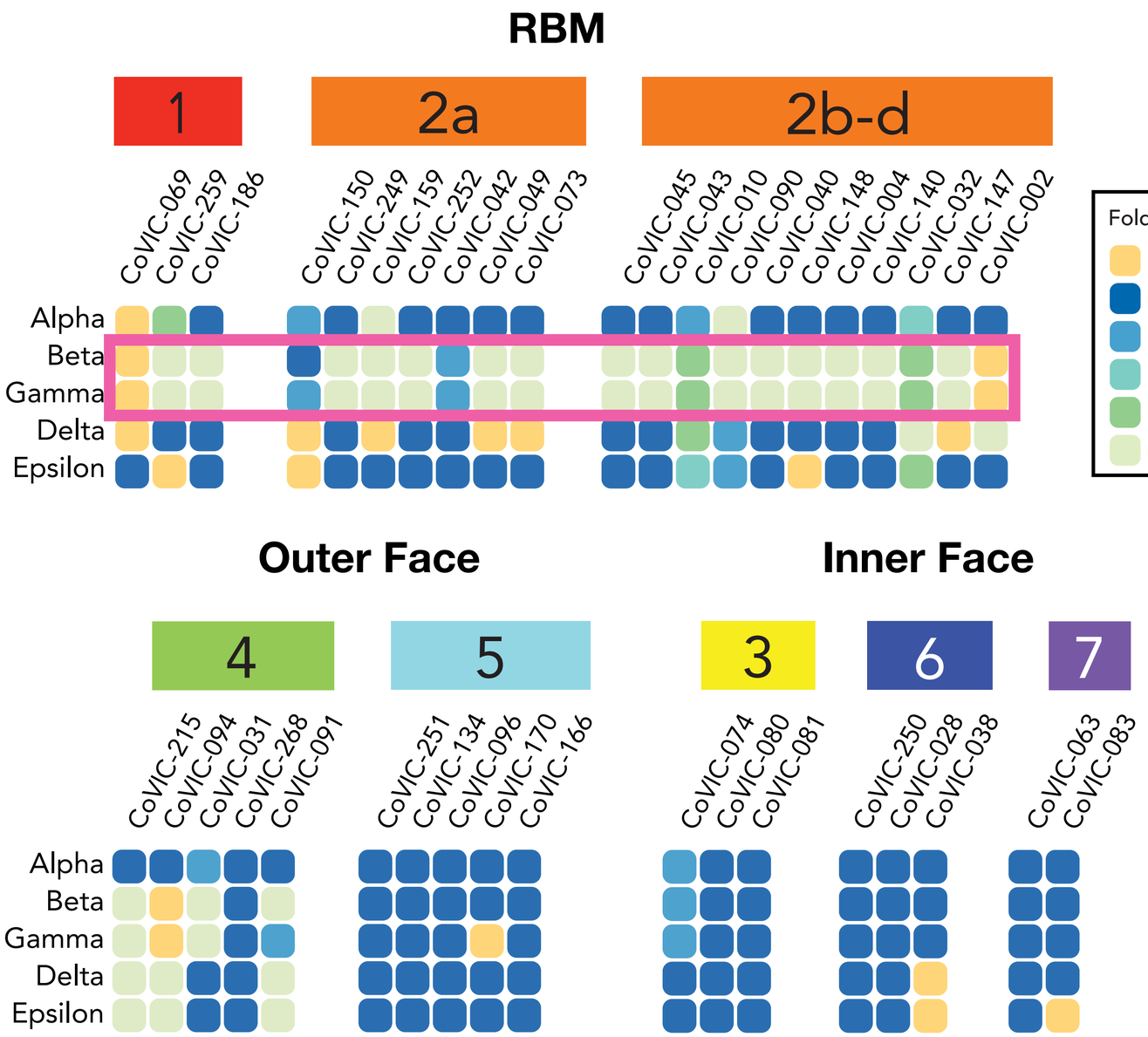
Select 40 representative mAbs to map resistance

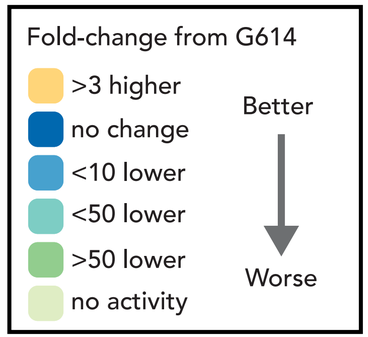


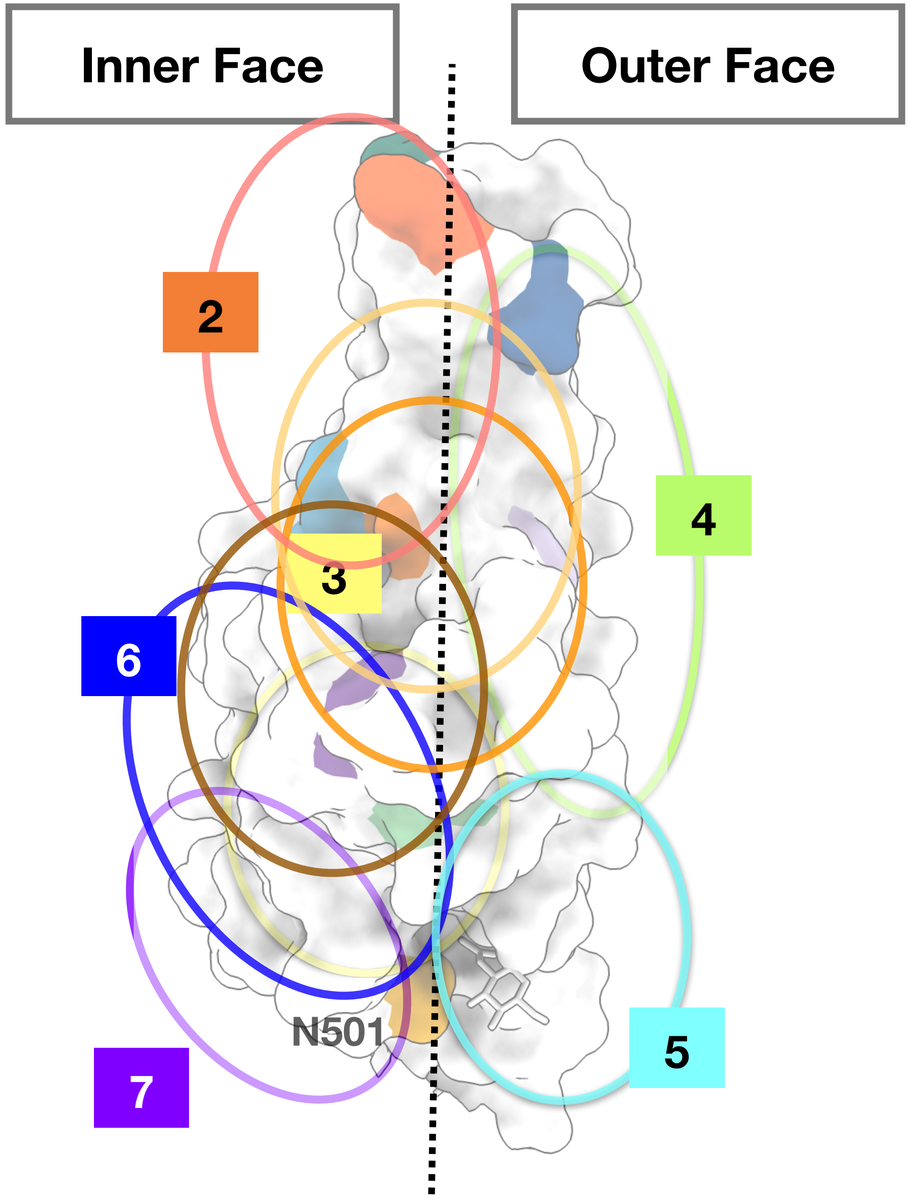


Hastie and Li, et al., Science, July 2021

Select 40 representative mAbs to map resistance

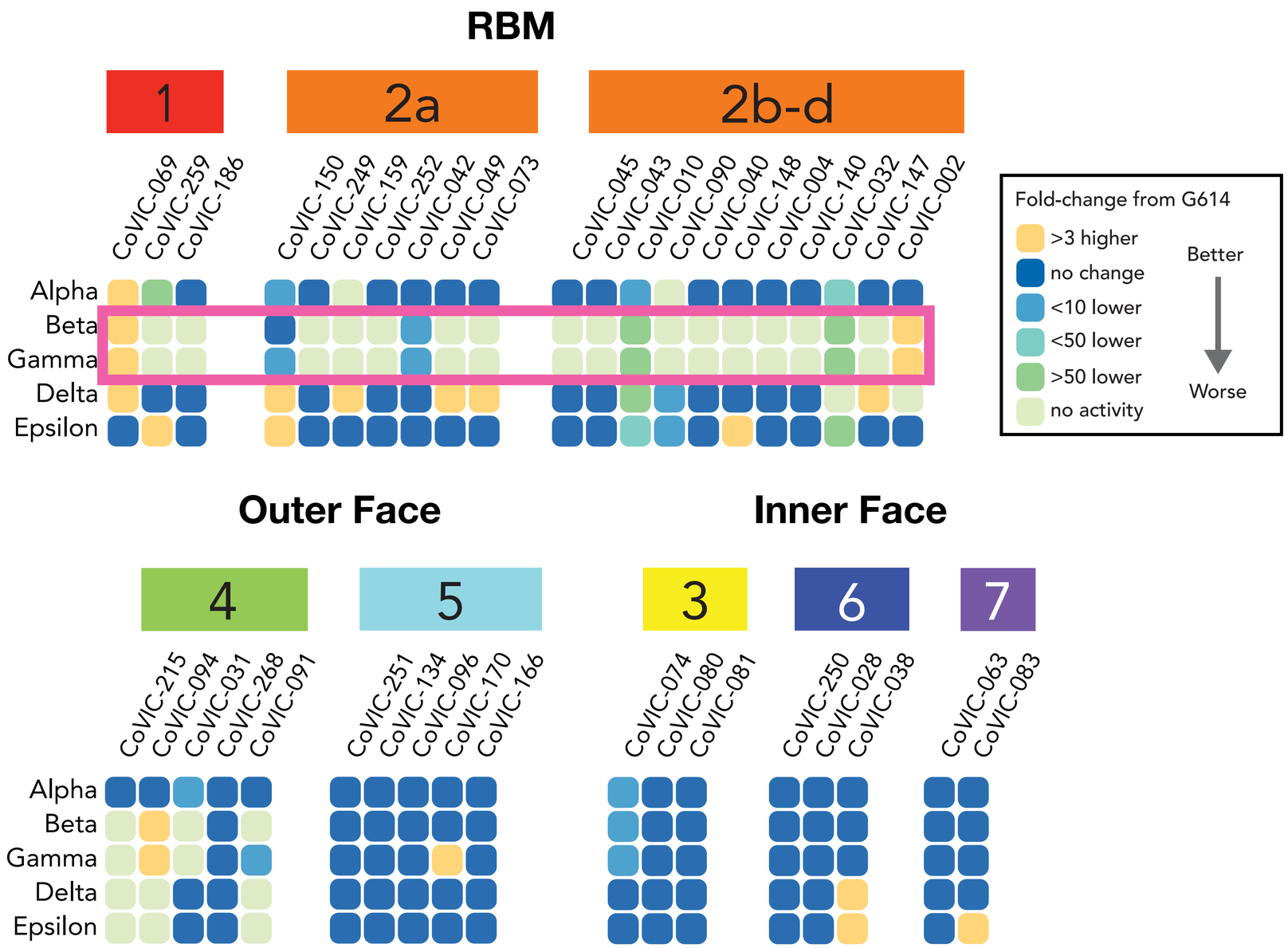


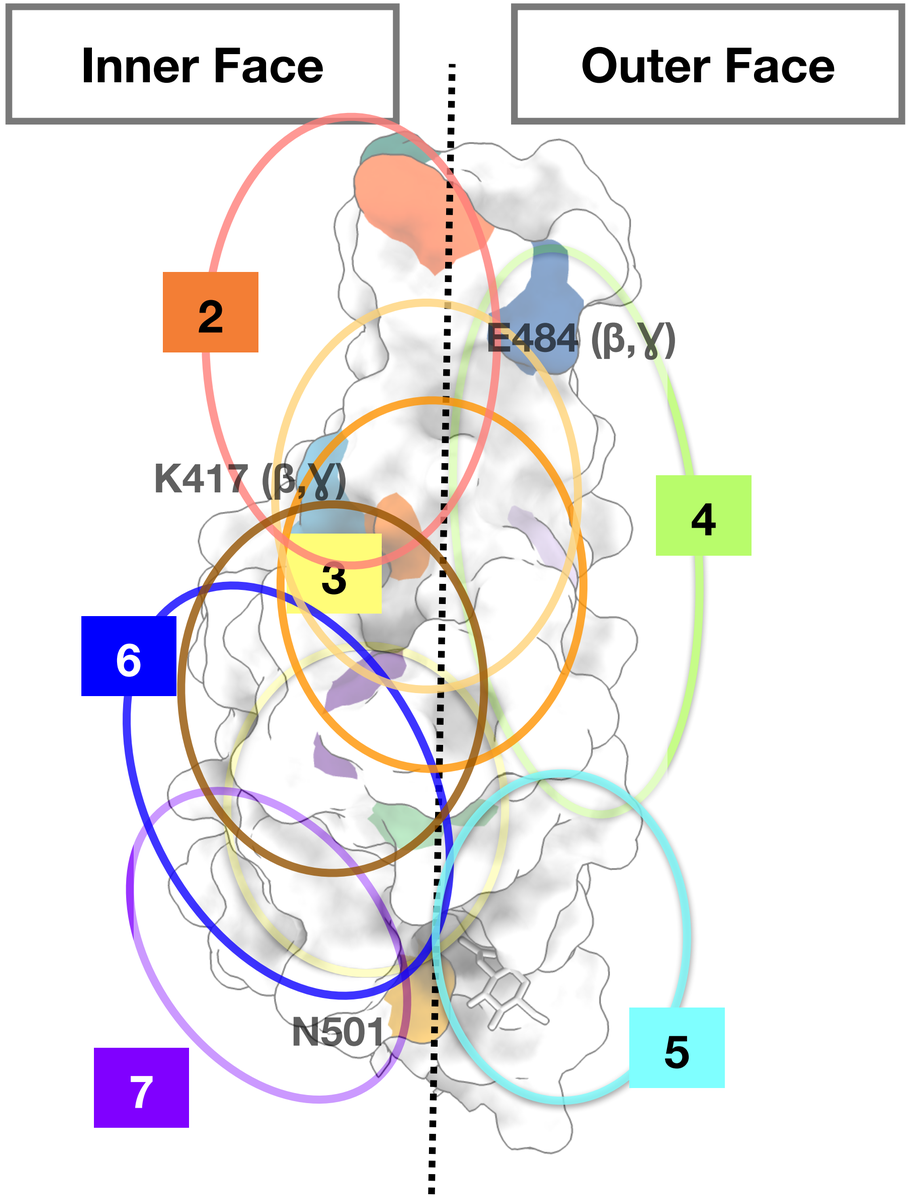




Hastie and Li, et al., Science, July 2021

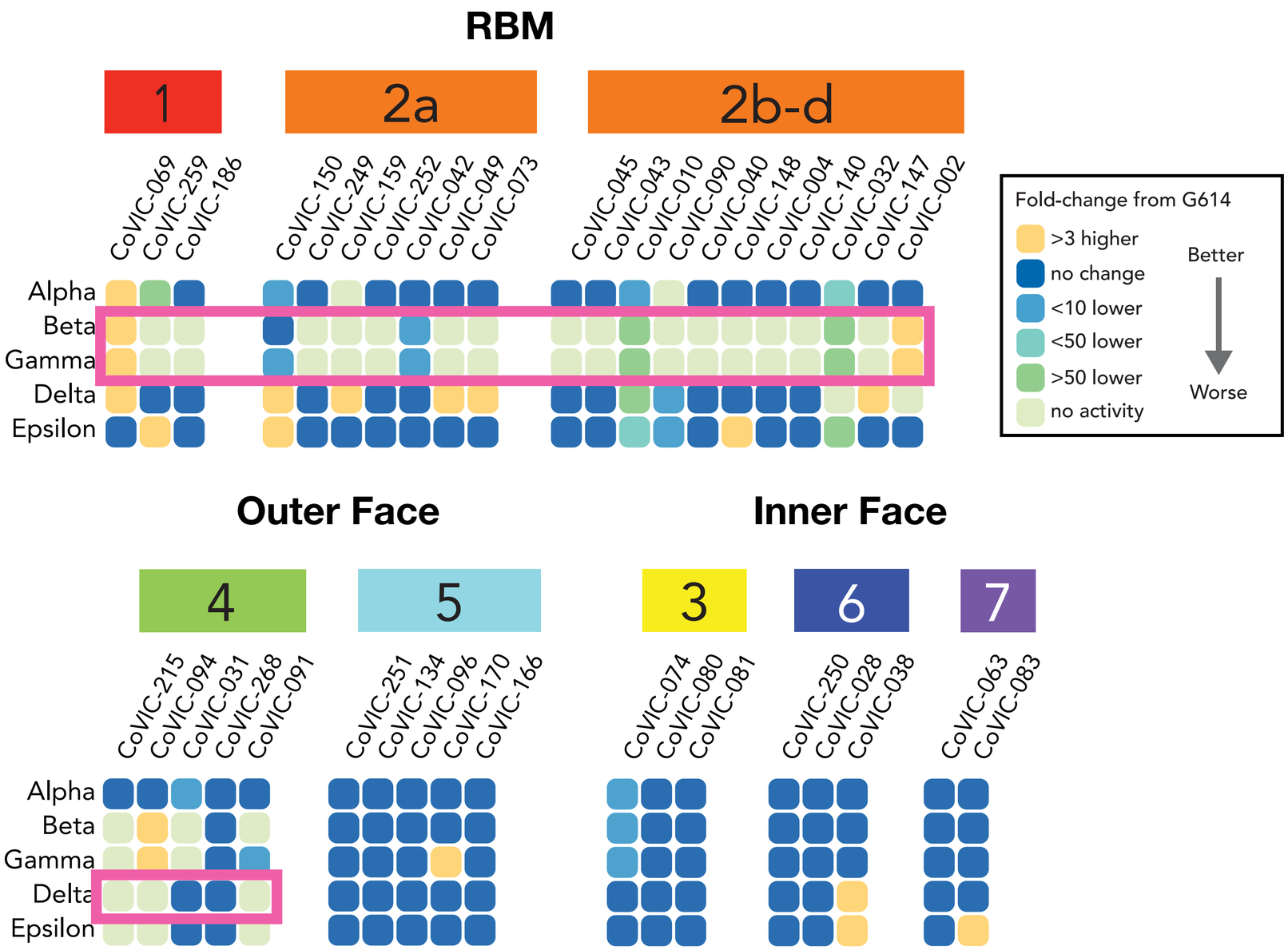
Select 40 representative mAbs to map resistance

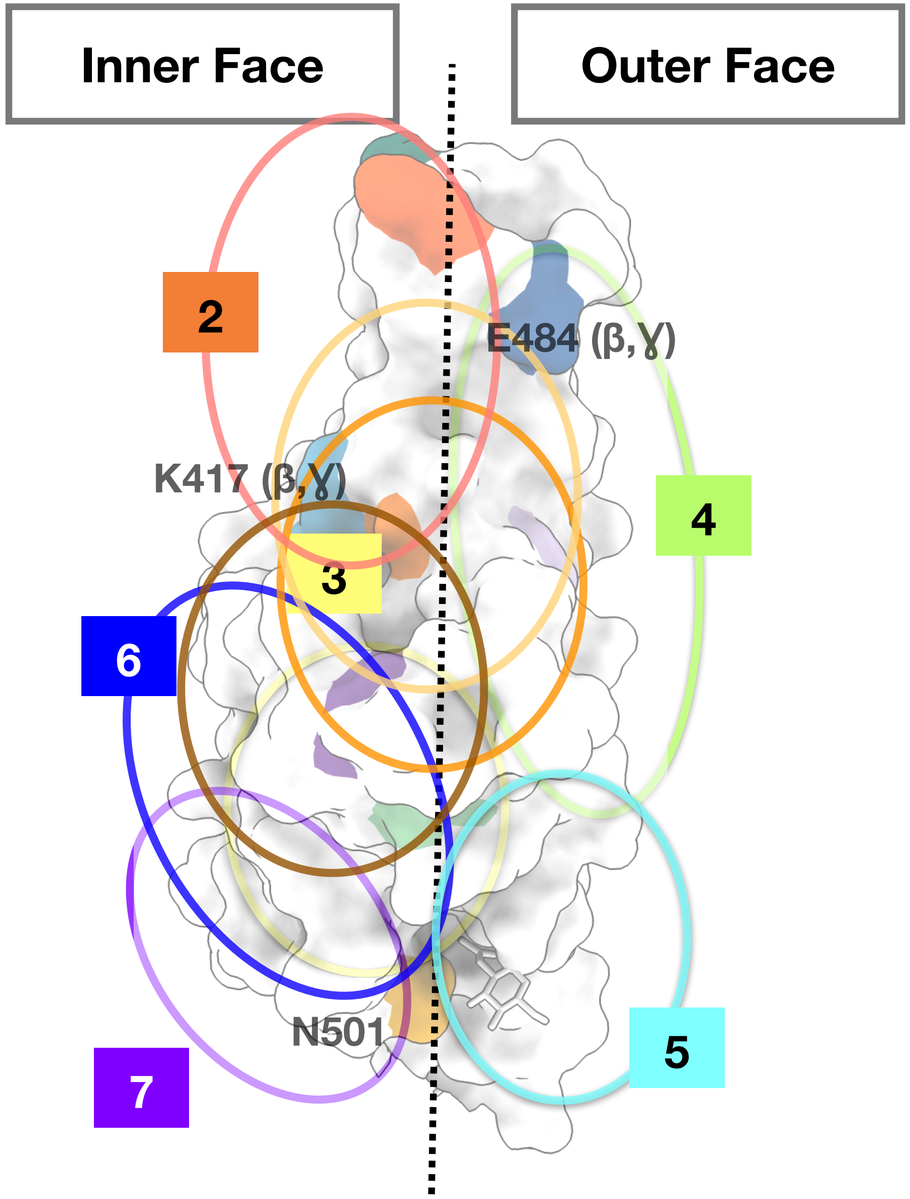




Hastie and Li, et al., Science, July 2021

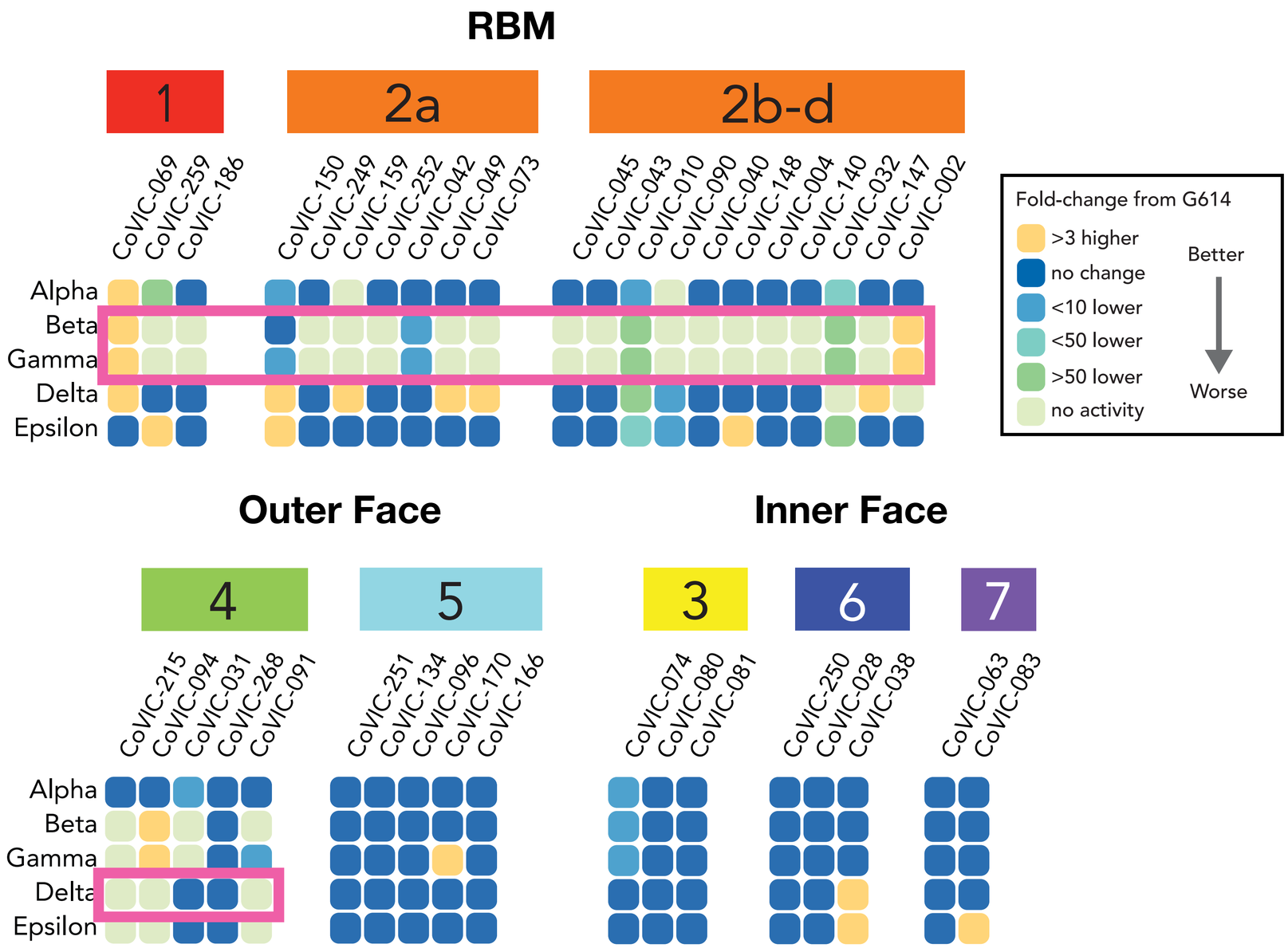
Select 40 representative mAbs to map resistance

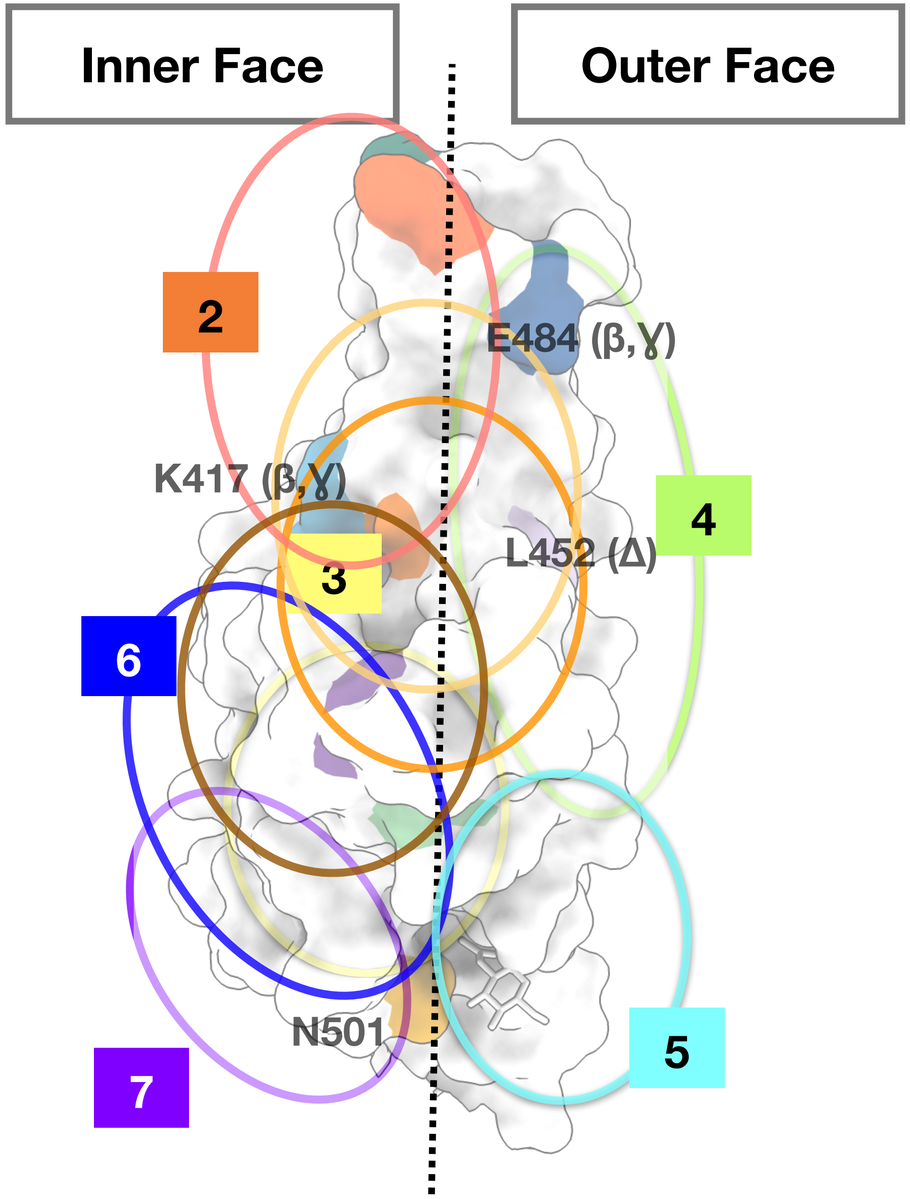




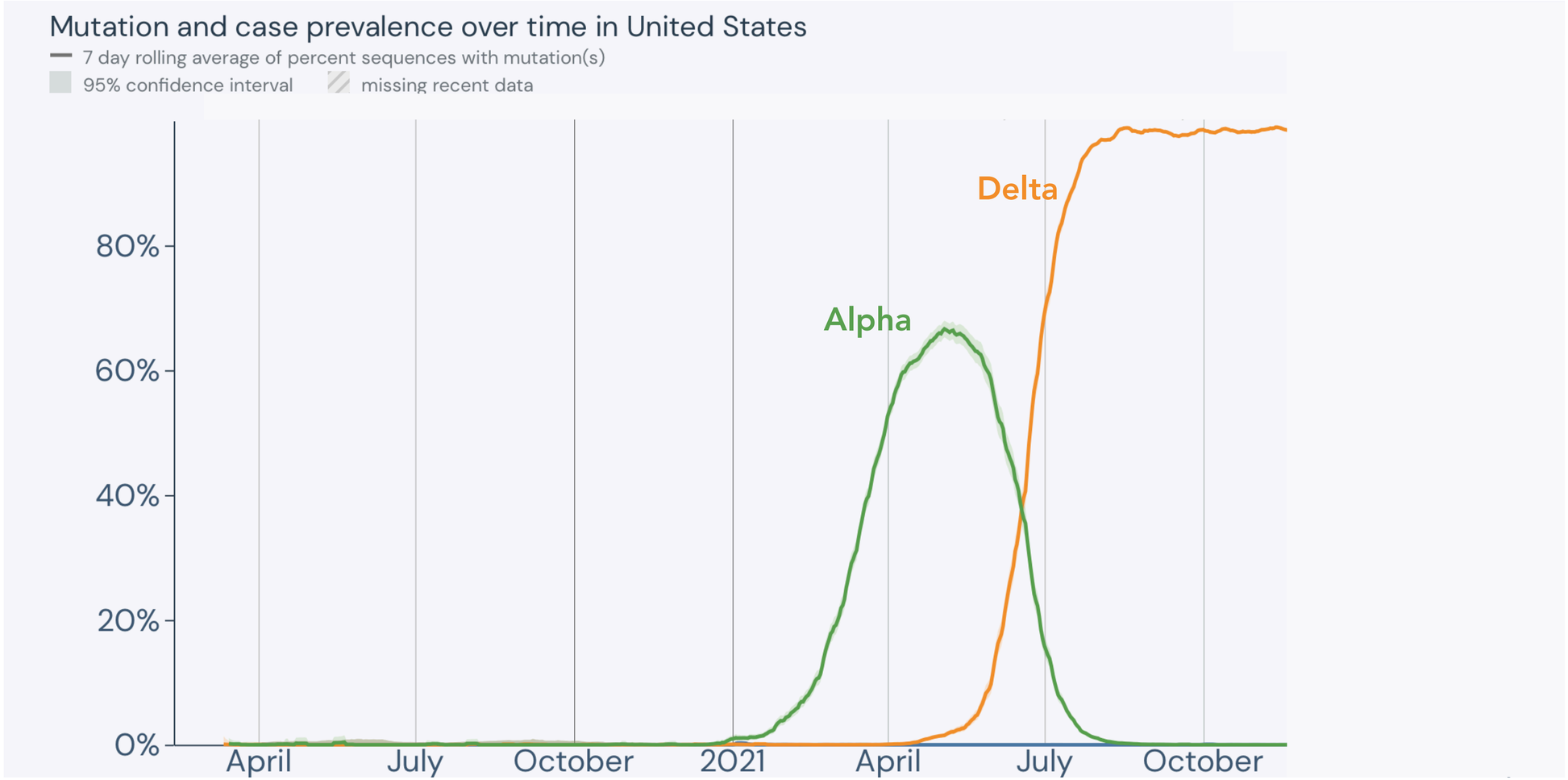
Hastie and Li, et al., Science, July 2021

Select 40 representative mAbs to map resistance





Hastie and Li, et al., Science, July 2021



From outbreak.info

Fwd: New very divergent Spikes in GISAID

CoVIC/Reagents/S protein/Variants ×

Erica Saphire <erica@lji.org>
to Saphire

Wed, Nov 24, 2021, 8:31 PM

Unusual variants have emerged in Africa. Sequences in the attached.
Erica

Fwd: New very divergent Spikes in GISAID

CoVIC/Reagents/S protein/Variants ×

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to Saphire

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Unusual variants have emerged in Africa. Sequences in the attached.
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Fwd: New very divergent Spikes in GISAID CoVIC/Reagents/S protein/Variants ×

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to Saphire

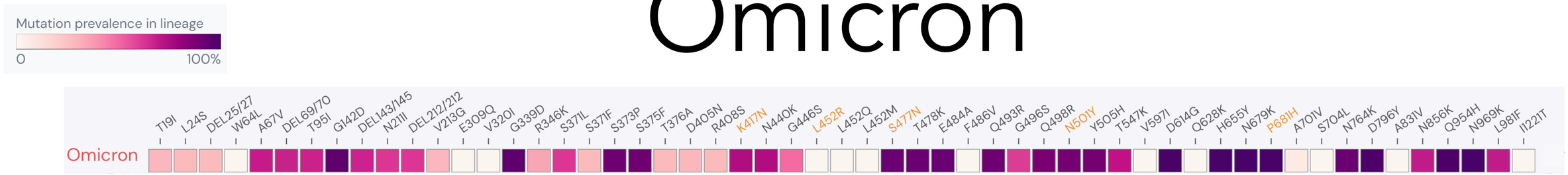
Wed, Nov 24, 2021, 8:31 PM

Unusual variants have emerged in Africa. Sequences in the attached.
Erica

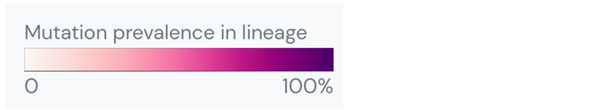
Los Alamos NATIONAL LABORATORY

Bette Korber

Omicron


Mutation prevalence in lineage
0
100%
Omicron
T19I
L24S
DEL25/27
W64L
A67V
DEL69/70
T95I
G142D
DEL143/145
N211I
DEL212/212
V213G
E309Q
V320I
G339D
R346K
S371L
S371F
S373P
S375F
T376A
D405N
R408S
K417N
N440K
G446S
L452R
L452Q
L452M
S477N
T478K
E484A
F486V
Q493R
G496S
Q498R
N501Y
Y505H
T547K
V597I
D614G
Q628K
H655Y
N679K
P681H
A701V
S704L
N764K
D796Y
A831V
N856K
Q954H
N969K
L981F
I1221T

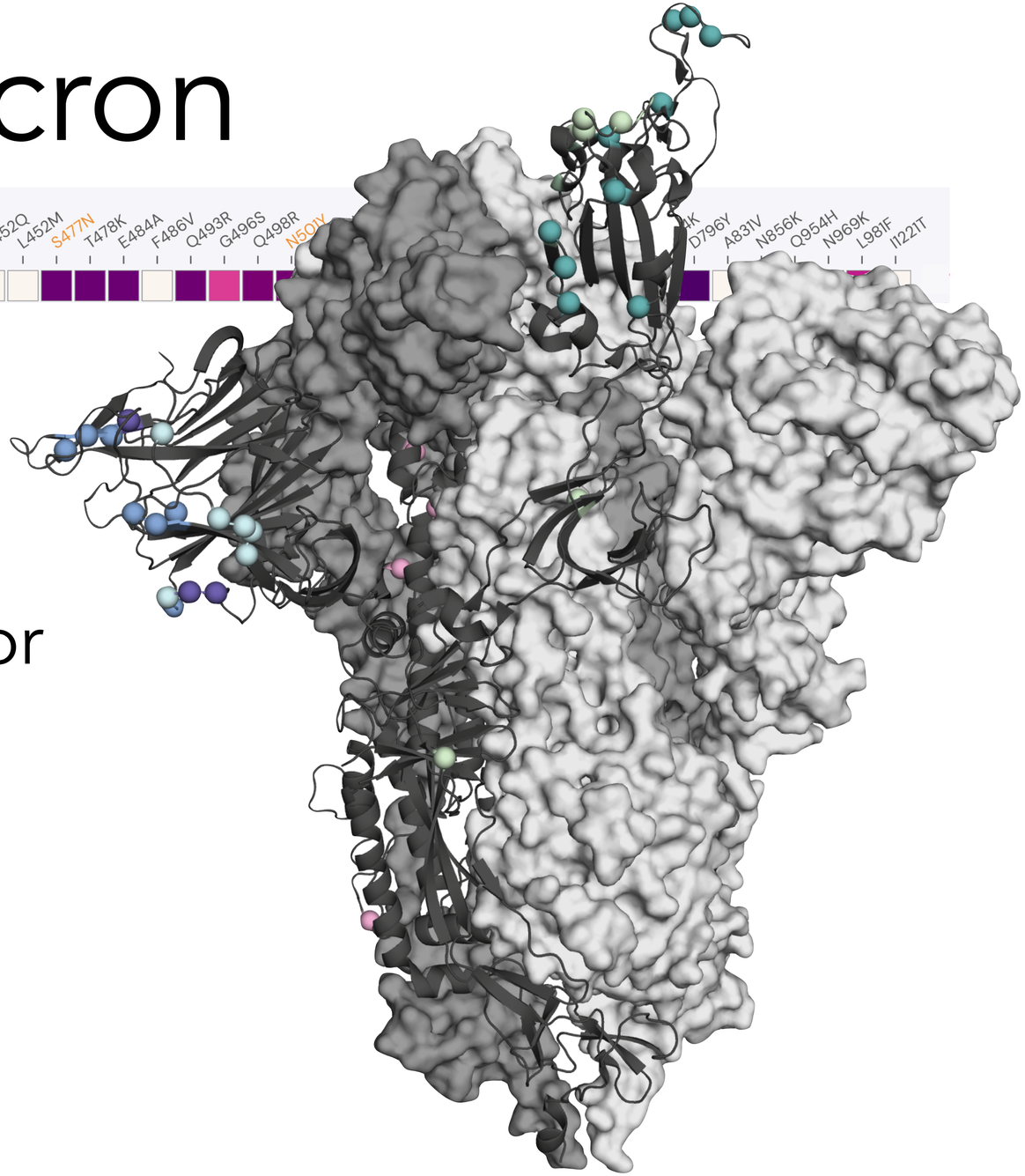
Omicron

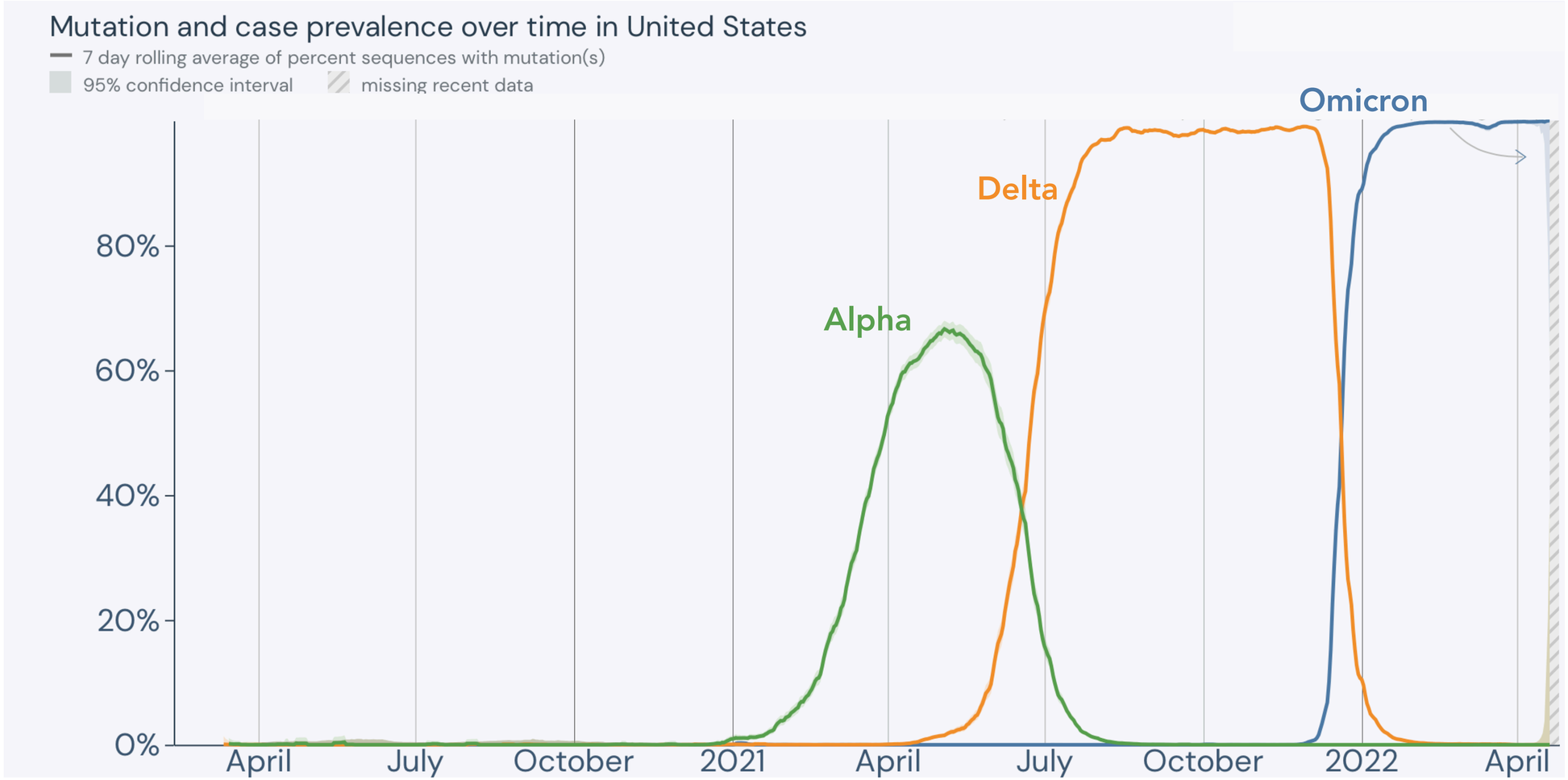


34 mutations - 15 in the receptor binding domain alone

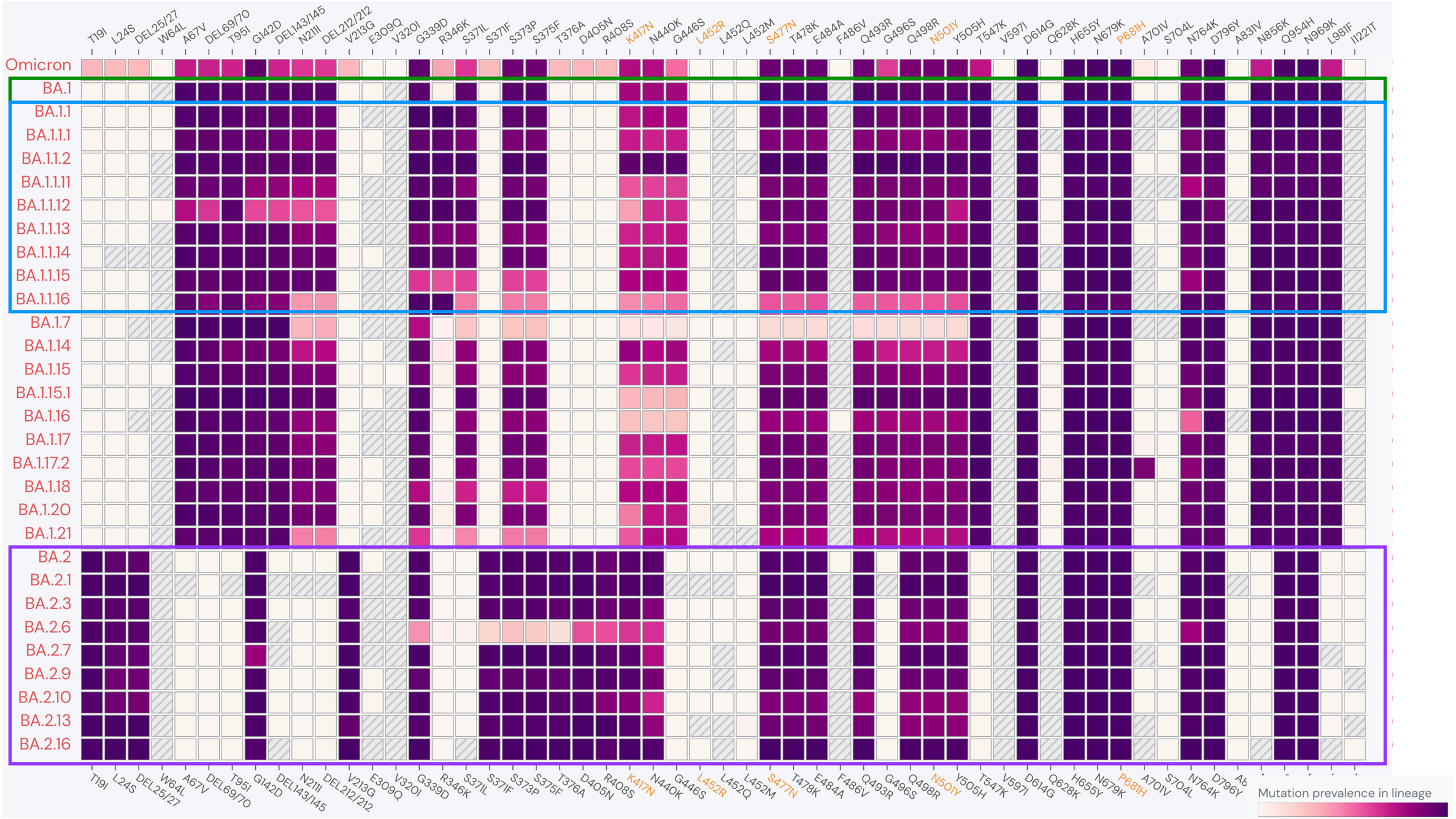
Omicron

34 mutations - 15 in the receptor binding domain alone

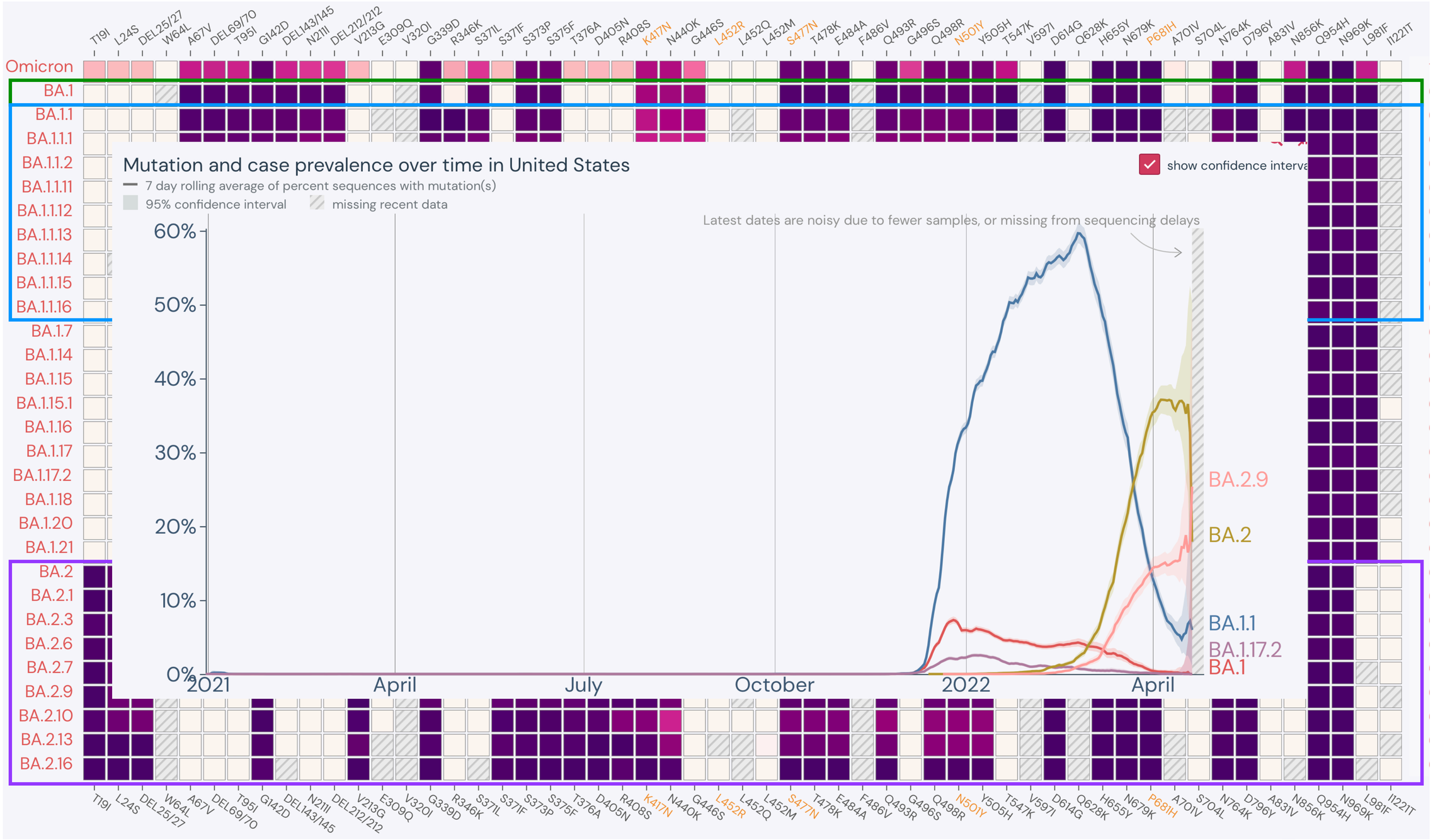




From outbreak.info



From outbreak.info



From outbreak.info

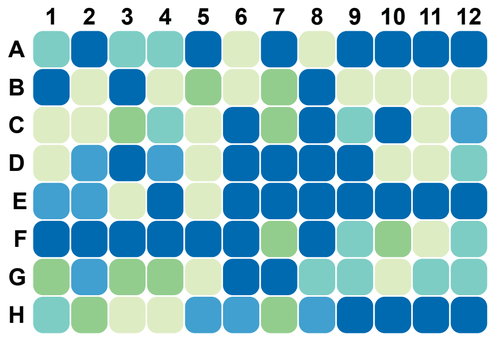
We’re gonna need a bigger data set.

Neutralization of VOC pseudovirus

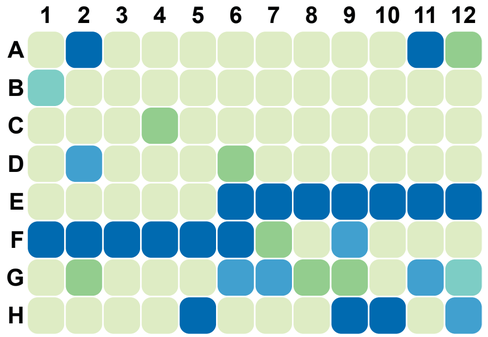
Rapid screening of entire CoVIC panel : thumbs up or down
High (25ug/mL) and Low (250ng/mL) neutralization of VOC pseudovirus

CoVIC 1-96, 250ng/mL

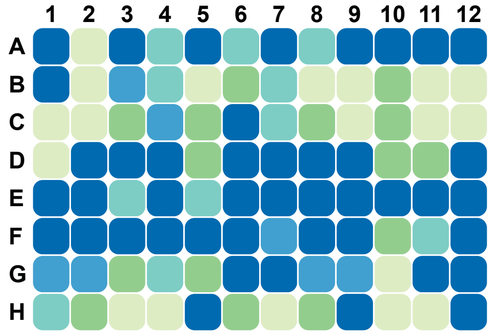
G614



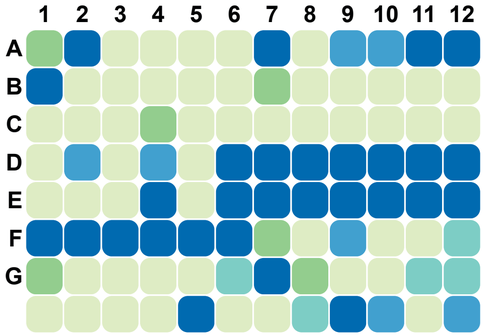
Beta



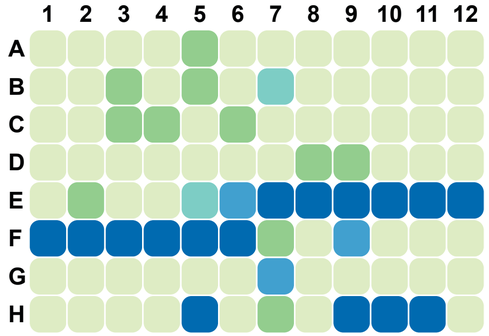
Delta



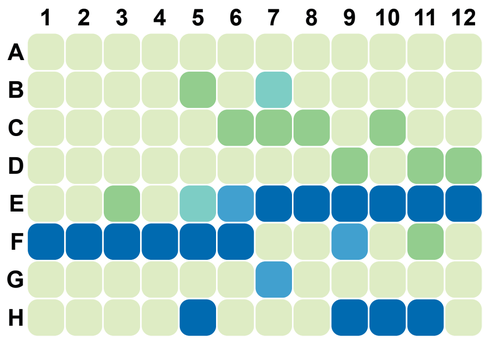
Mu



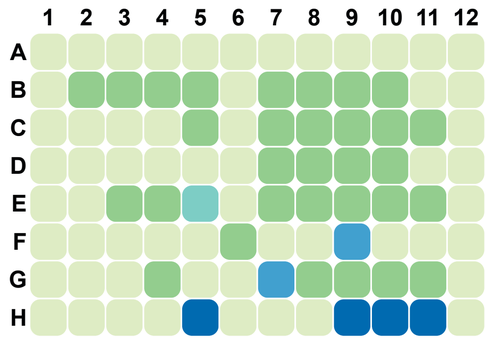
BA.1

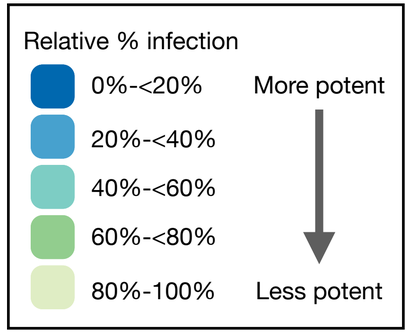


BA.1.1



BA.2





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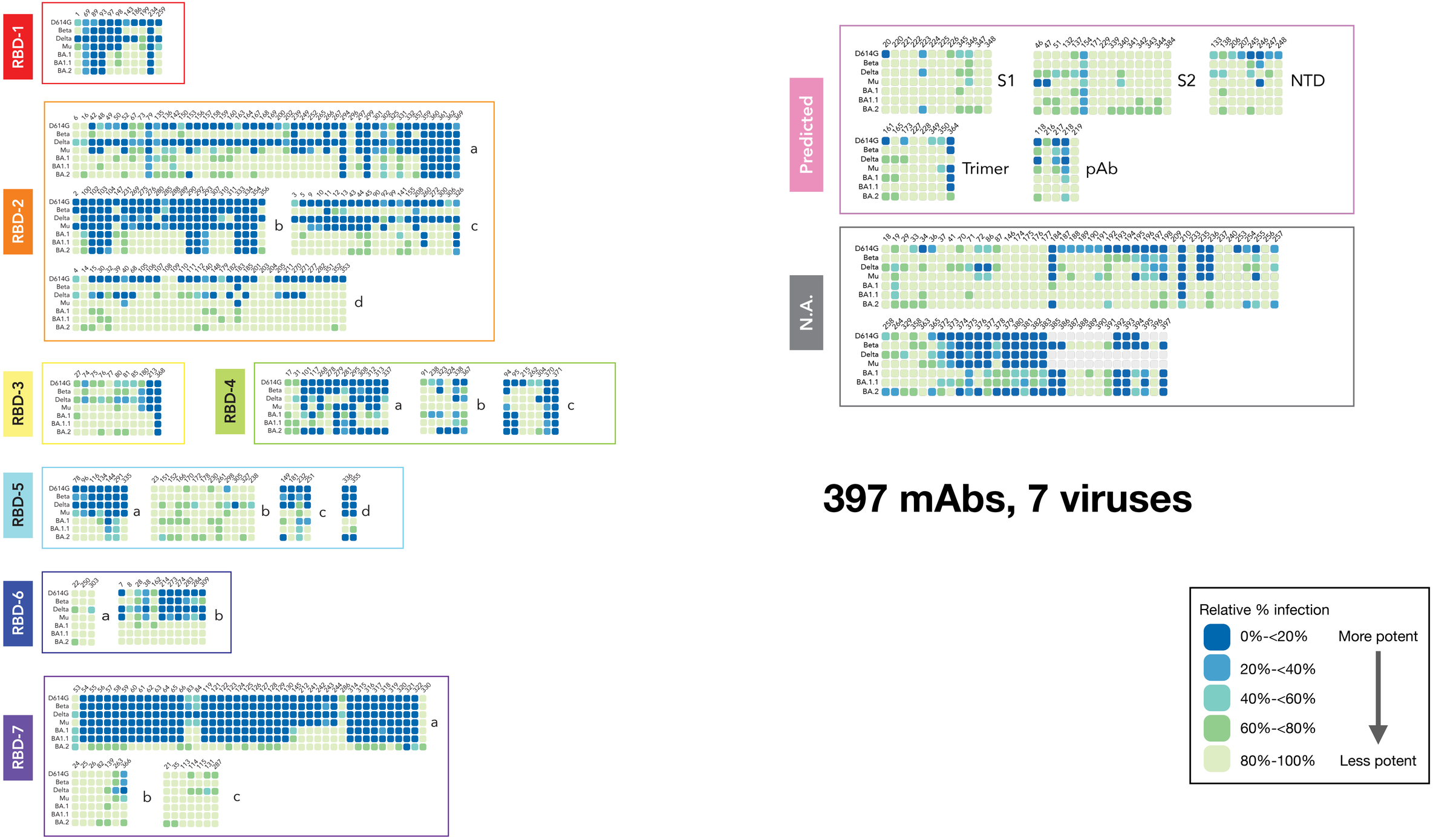
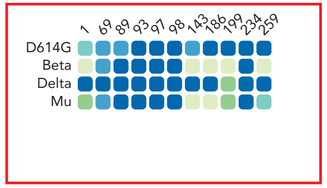

RBD-1
RBD-2
RBD-3
RBD-4
RBD-5
RBD-6
RBD-7
Predicted
N.A.
S1
S2
NTD
Trimer
pAb
D614G
Beta
Delta
Mu
BA.1
BA.1.1
BA.2
a
b
c
d
397 mAbs, 7 viruses
Relative % infection
0%-<20%
20%-<40%
40%-<60%
60%-<80%
80%-100%
More potent
Less potent

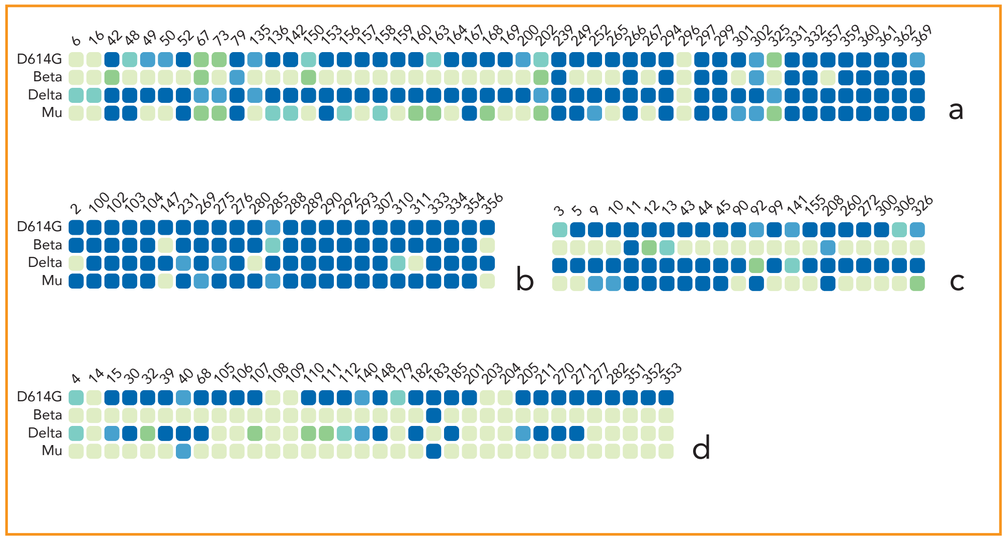
Pre-Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



RBD-2



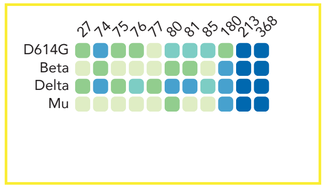
Outer face

RBD-4

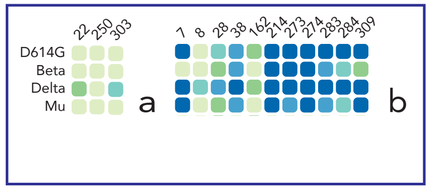
RBD-5

Inner face

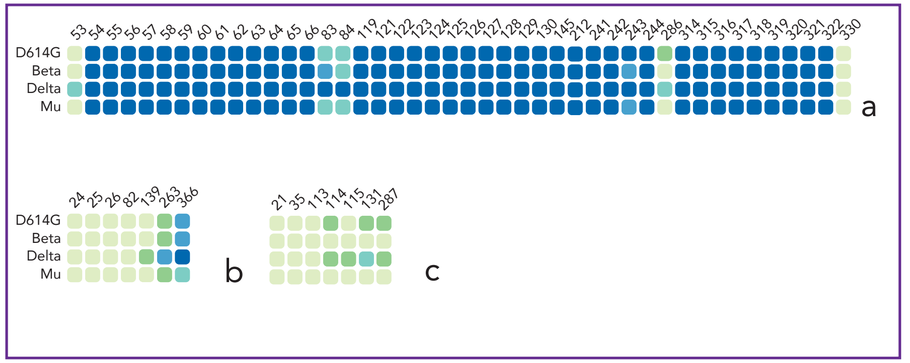
RBD-3

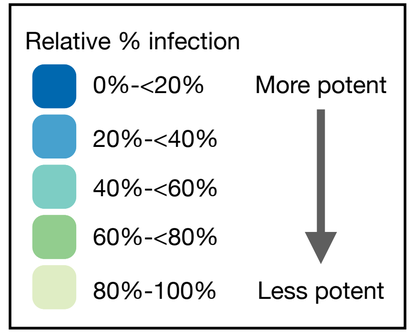


RBD-6



RBD-7

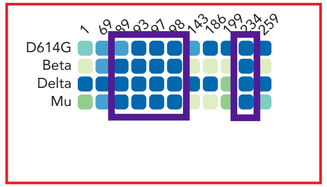




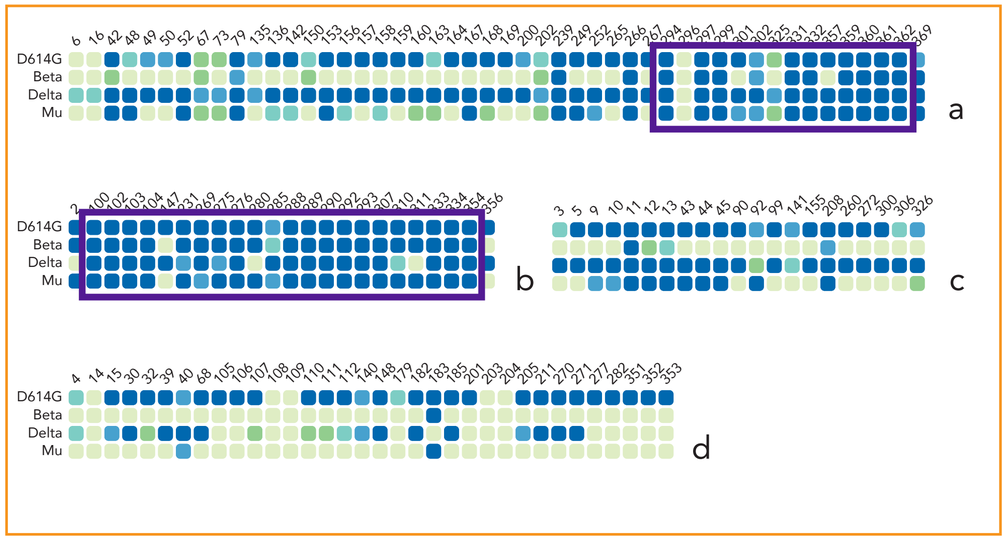
Pre-Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



RBD-2



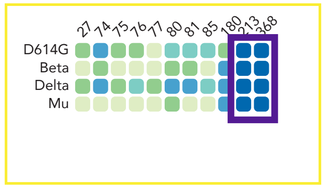
Outer face

RBD-4

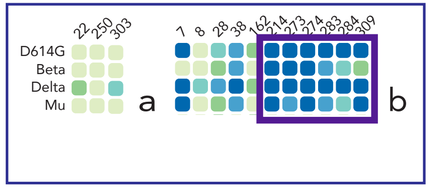
RBD-5

Inner face

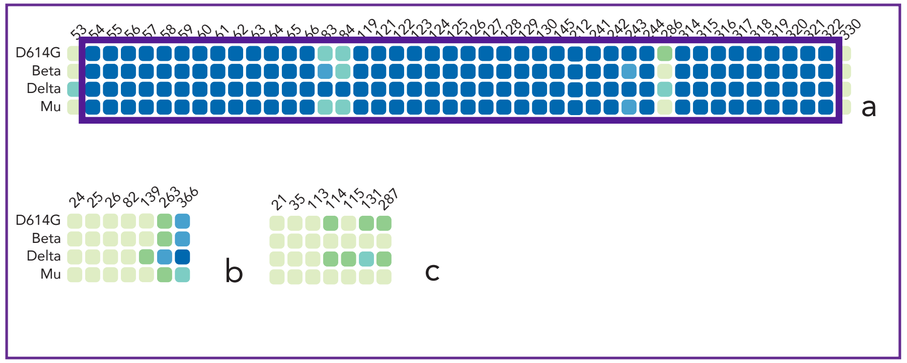
RBD-3

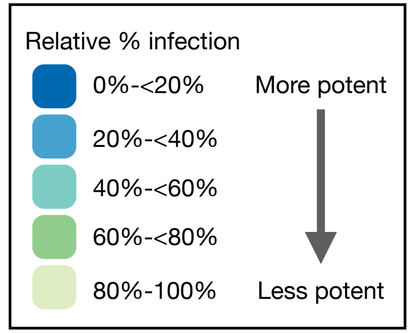


RBD-6



RBD-7





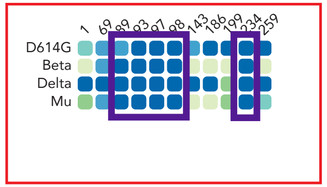
Pre-Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

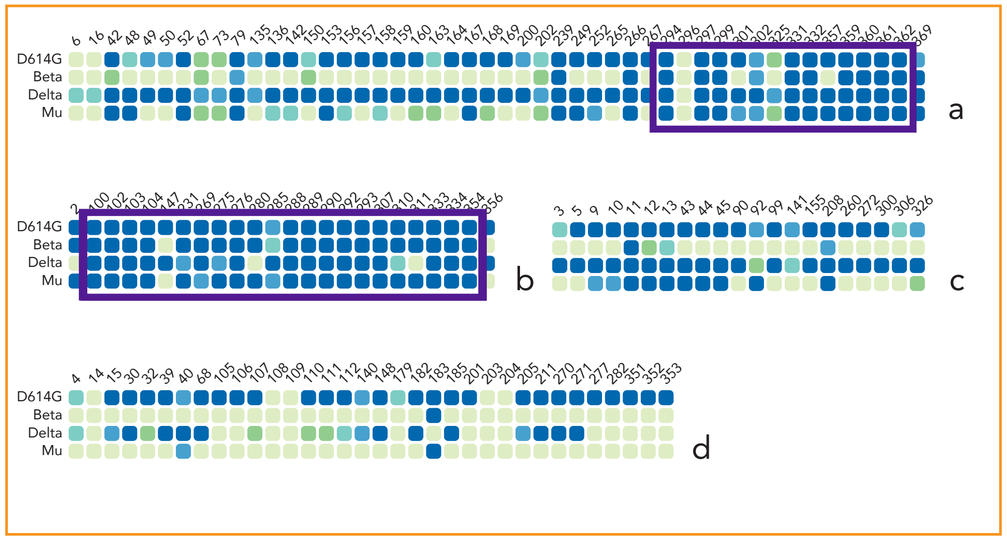
G614, Beta, Delta, Mu

90/397
23%

RBD-1



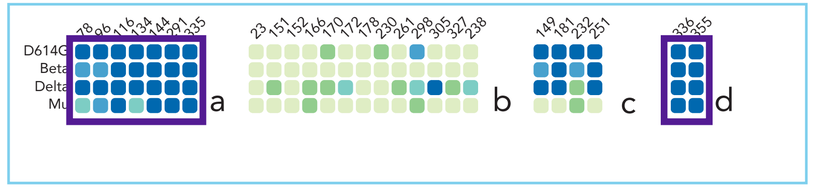
RBD-2



Outer face

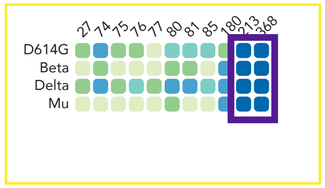
RBD-4

RBD-5

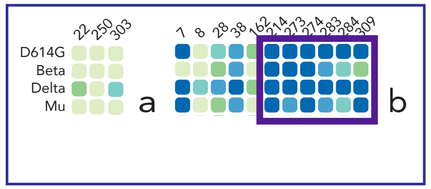


Inner face

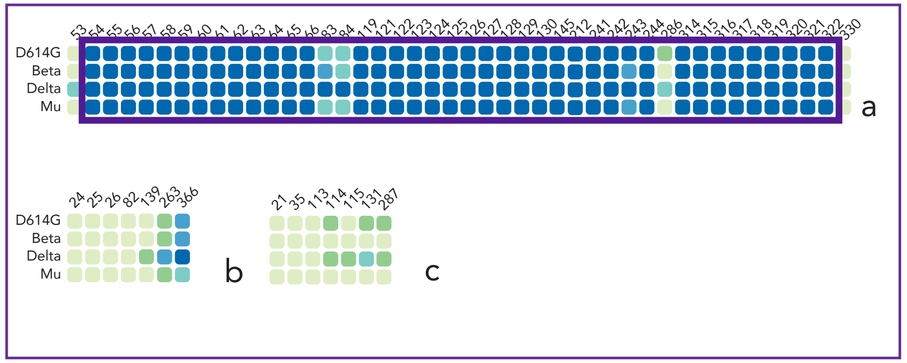
RBD-3

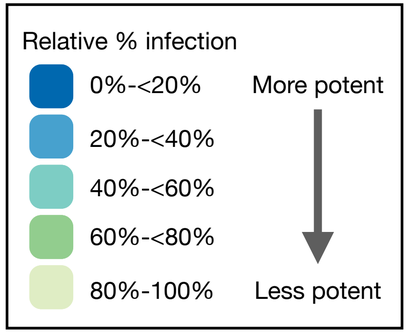


RBD-6



RBD-7

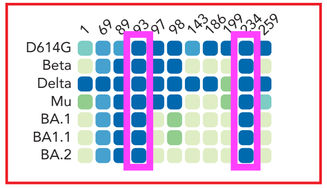




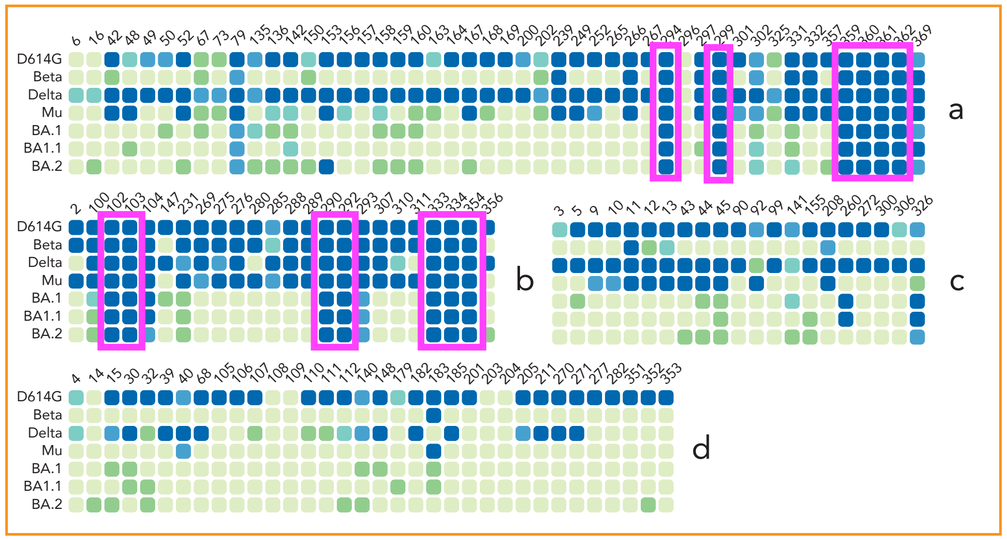
+ Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



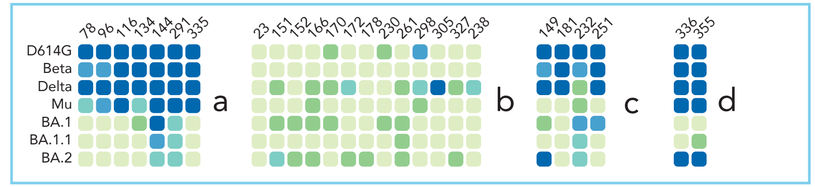
RBD-2



Outer face

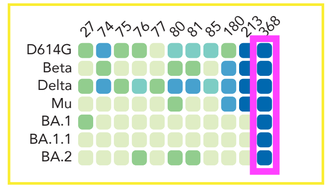
RBD-4

RBD-5

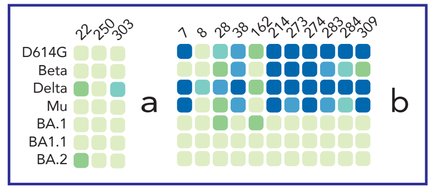


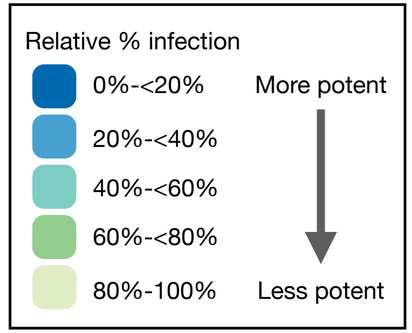
Inner face

RBD-3

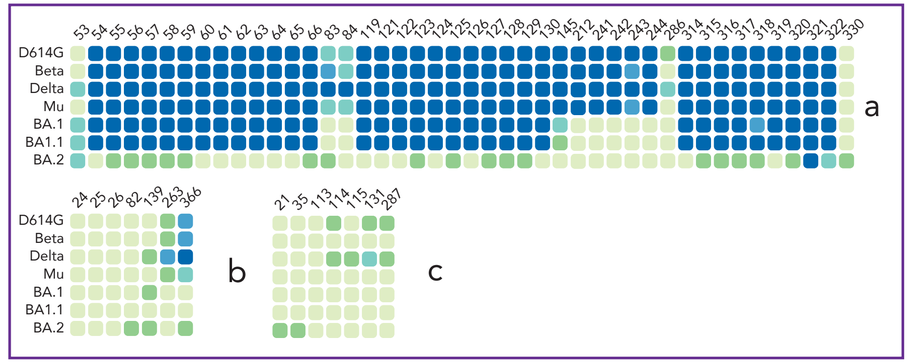


RBD-6





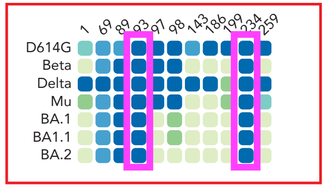
RBD-7



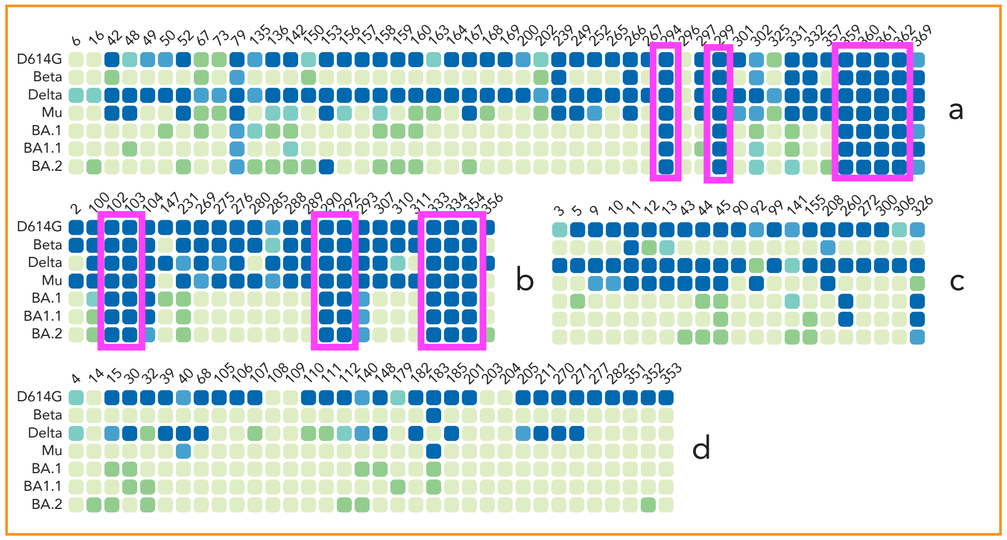
+ Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



RBD-2



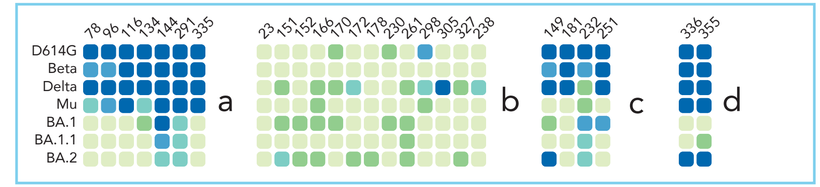
G614, Beta, Delta, Mu + Omicron

18/397 ~5%

Outer face

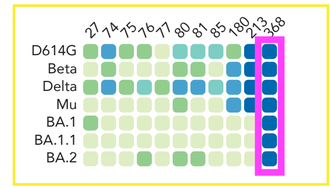
RBD-4

RBD-5

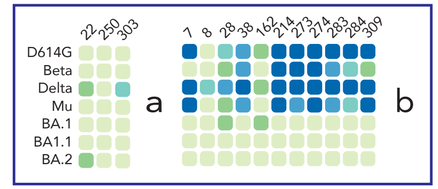


Inner face

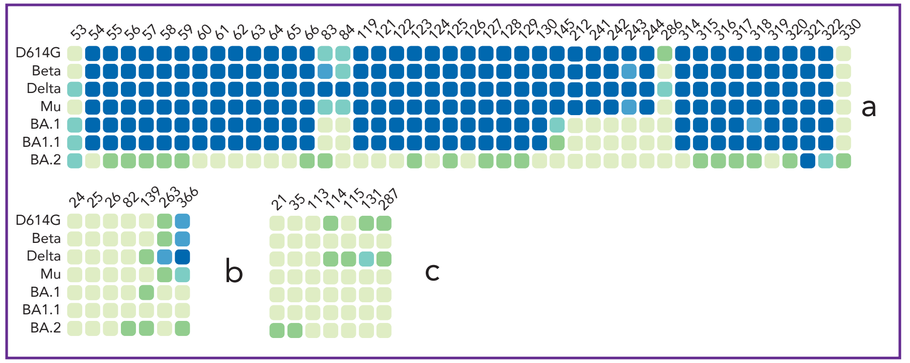
RBD-3

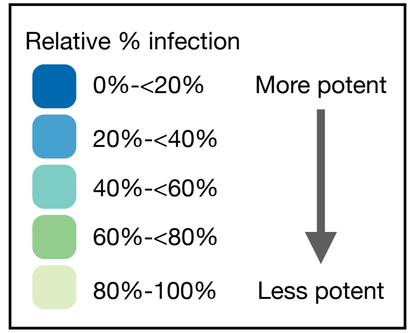


RBD-6



RBD-7

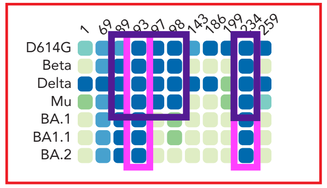




+ Omicron
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



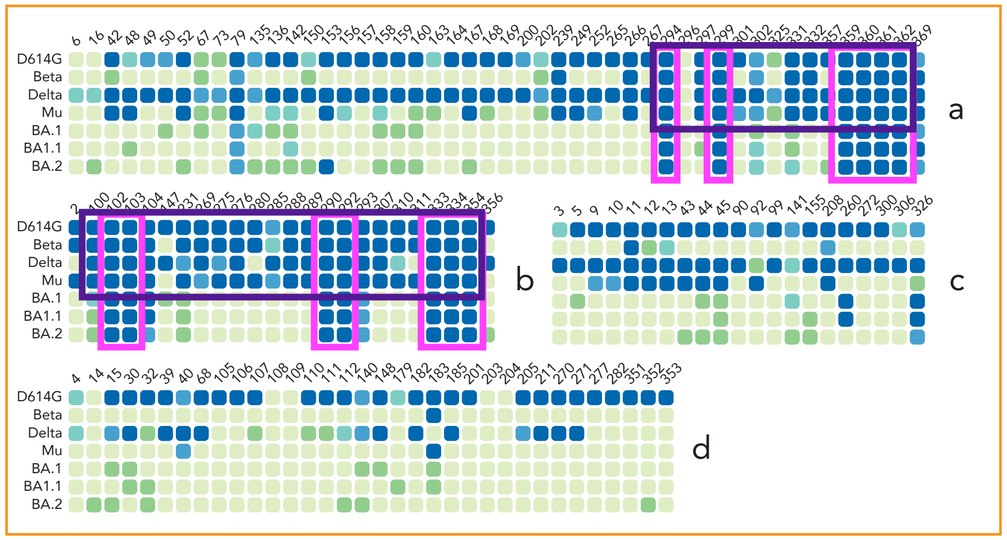
G614, Beta, Delta, Mu

90/397
23%

G614, Beta, Delta, Mu + Omicron

18/397
~5%

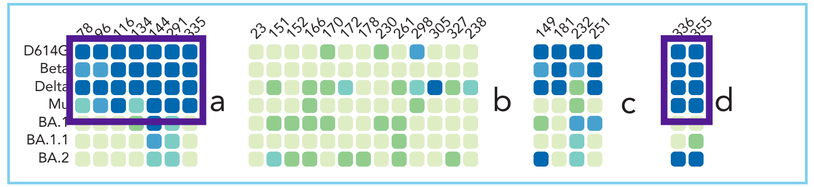
RBD-2



Outer face

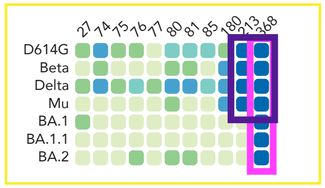
RBD-4

RBD-5

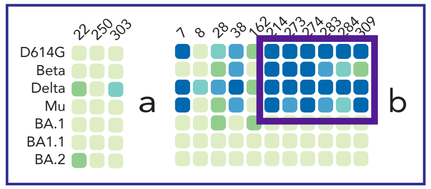


Inner face

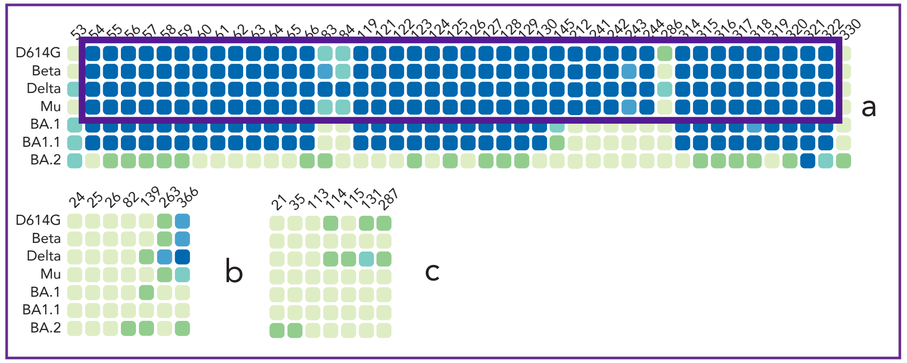
RBD-3



RBD-6



RBD-7



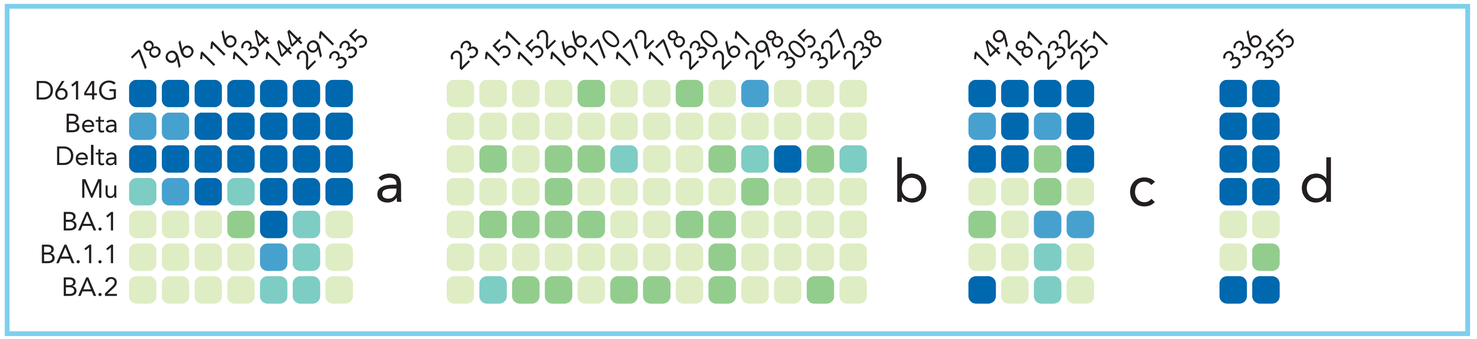
Relative % infection

- 0%-<20%
- 20%-<40%
- 40%-<60%
- 60%-<80%
- 80%-100%

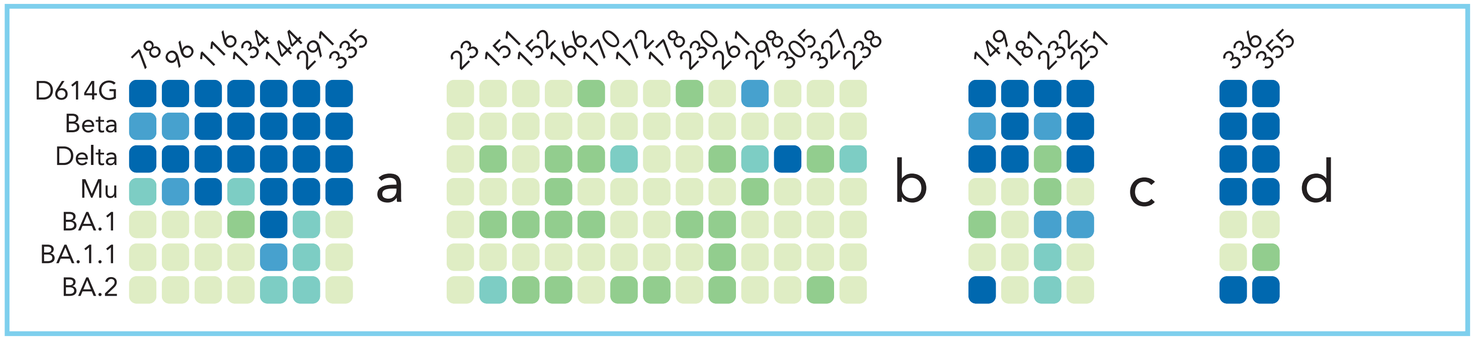
More potent

Less potent

RBD-5


78 96 116 134 144 291 335
D614G
Beta
Delta
Mu
BA.1
BA.1.1
BA.2
a
23 151 152 166 170 172 178 230 261 298 305 327 238
b
149 181 232 251
c
336 355
d

RBD-5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D614G
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78
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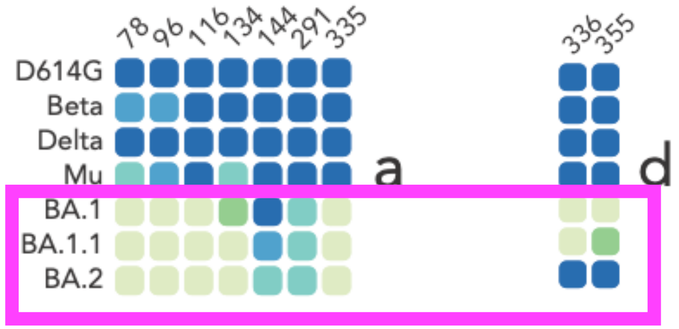
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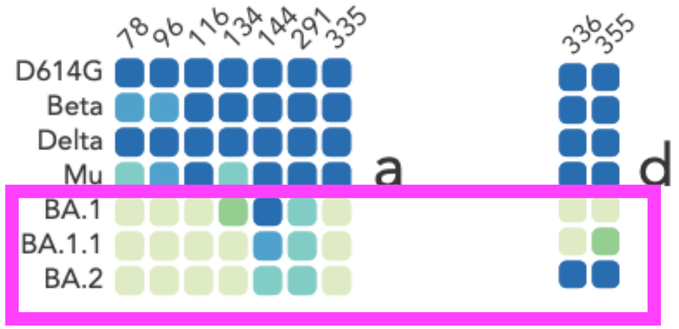
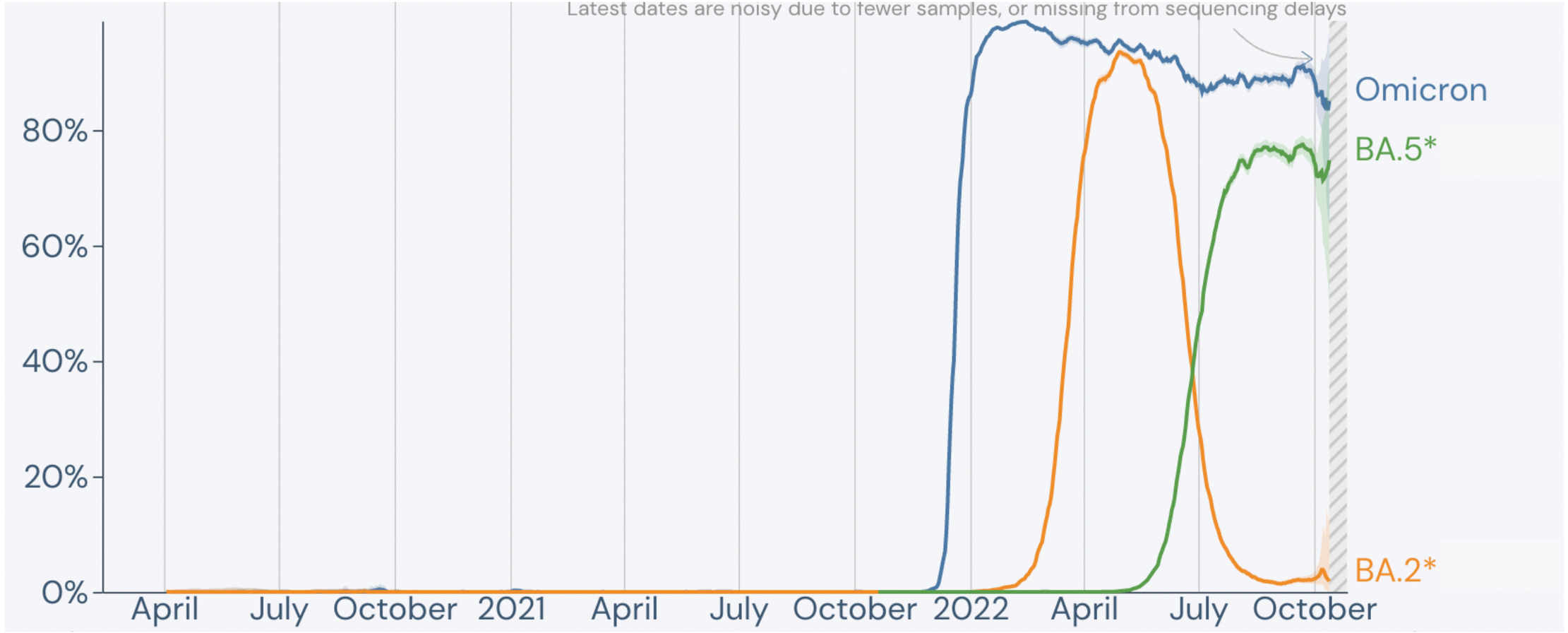


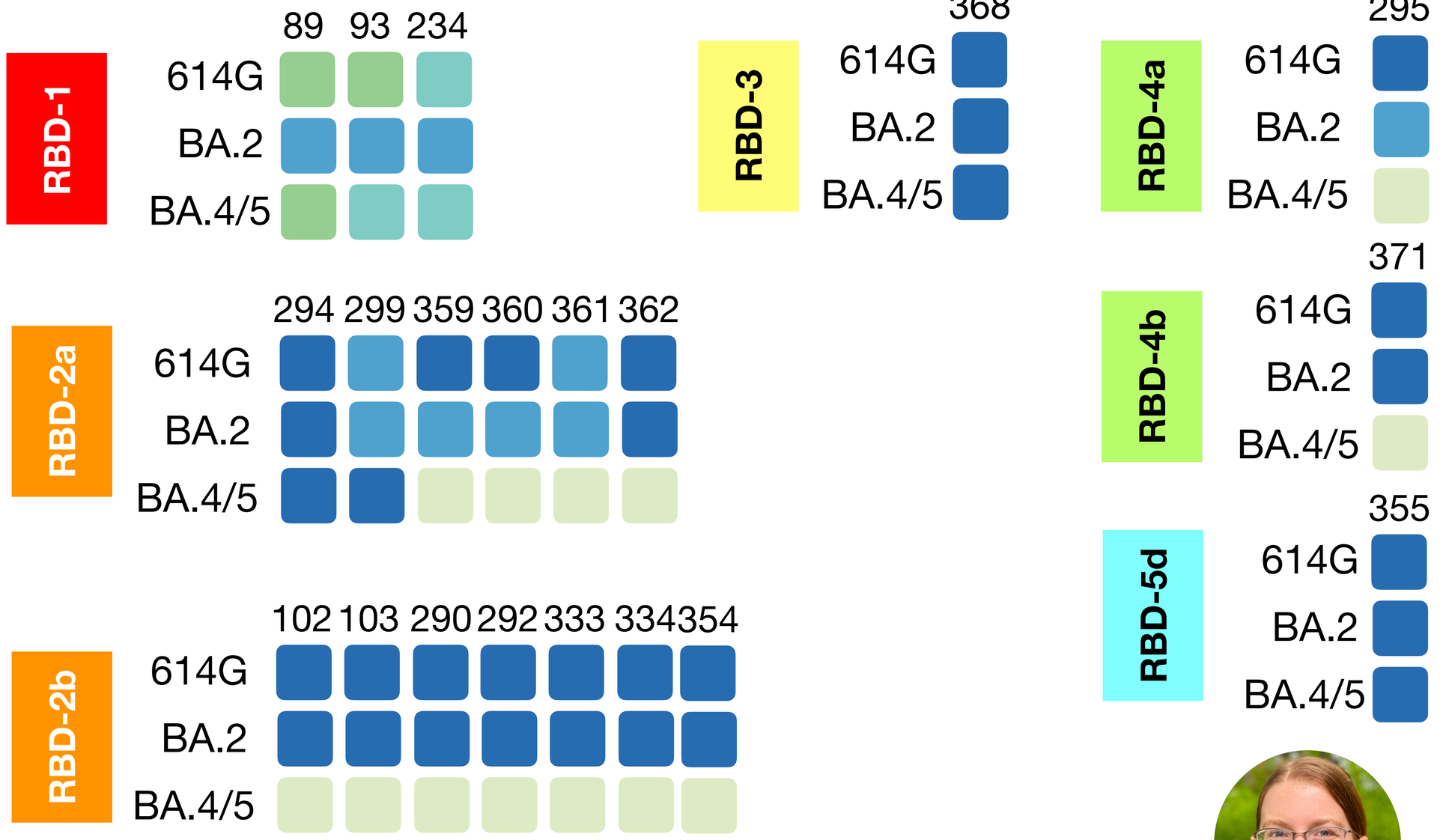
Within an epitope community, the LSA could separate antibodies that had different activity against Omicron sublineages



From outbreak.info

G614, Beta, Delta, Mu + Omicron

18/397
~5%



Heather Callaway, LJI

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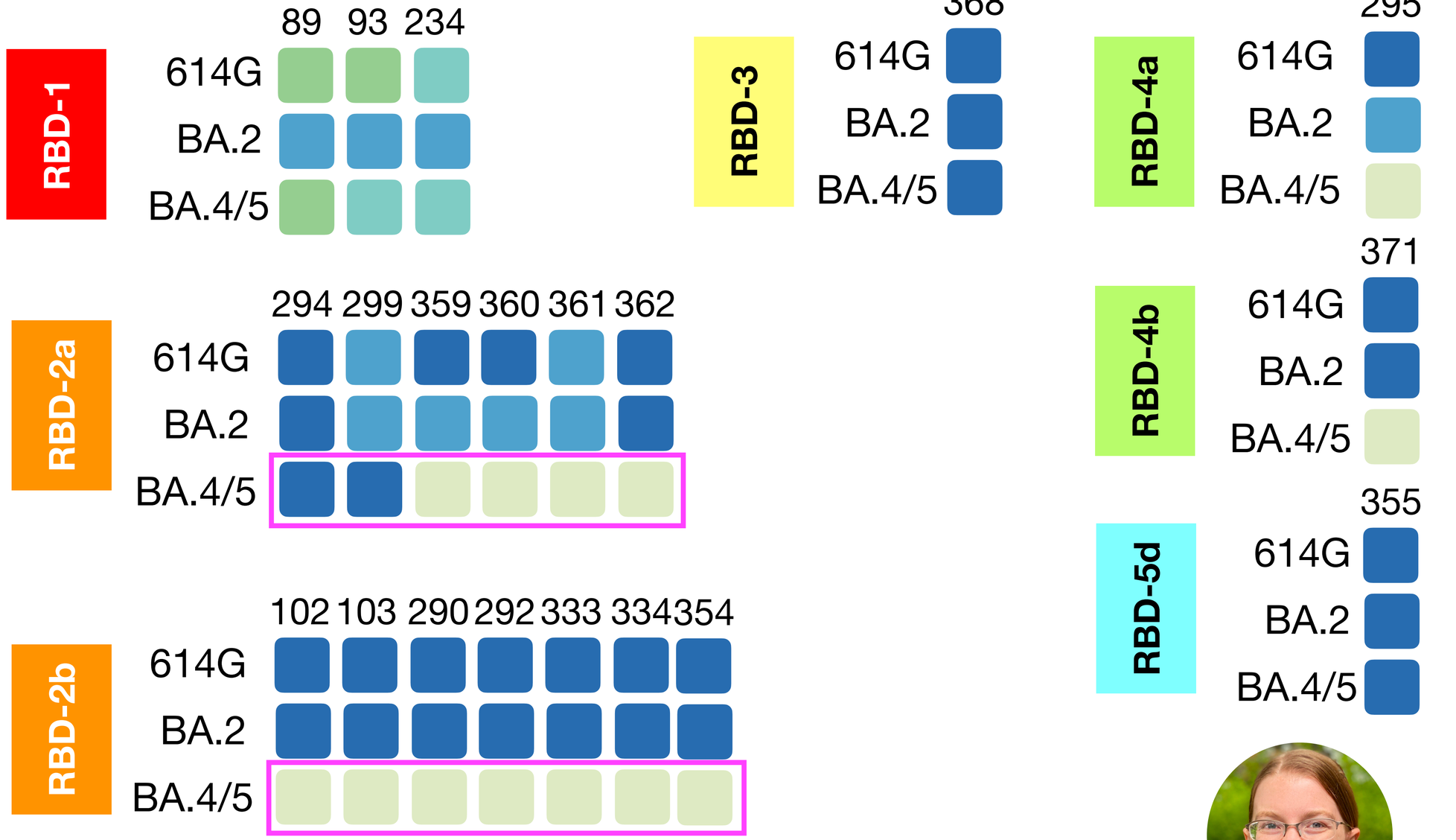

IC_{50} (ng/mL)

- ≤20
- 20-50
- >50-100
- >100-500
- >500

Heather Callaway, LJI

G614, Beta, Delta, Mu + Omicron

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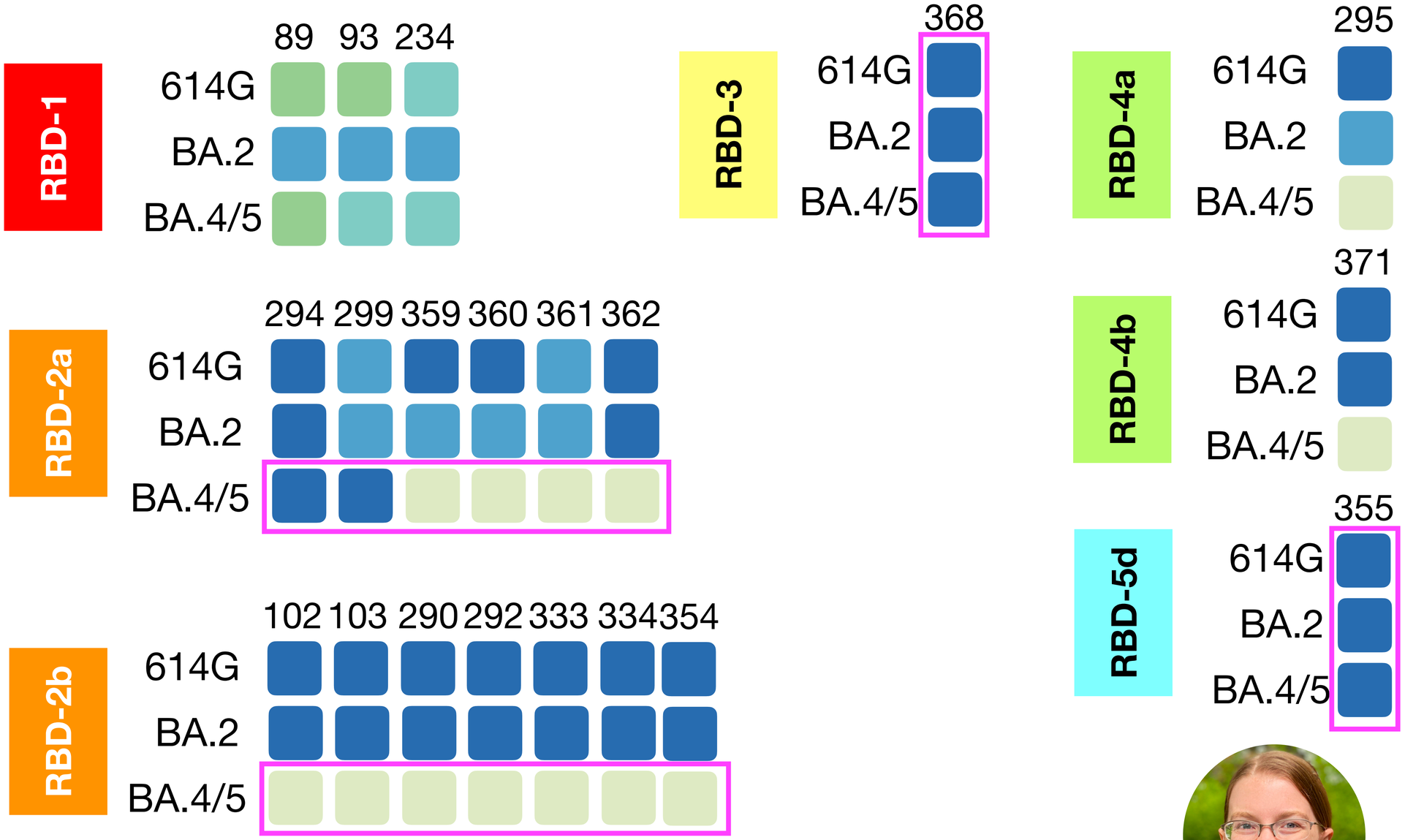

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Heather Callaway, LJI

23% of the 400 mAbs neutralize original through mu.

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Only 5% of the 400 mAb panel neutralizes through early Omicron

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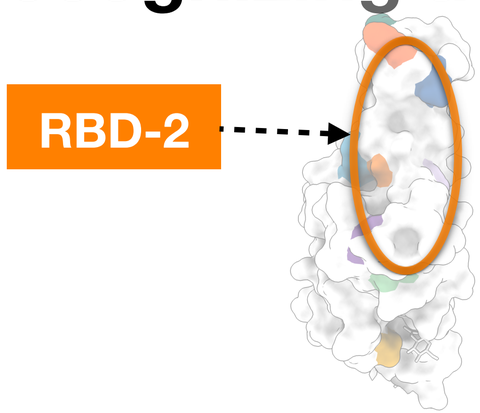

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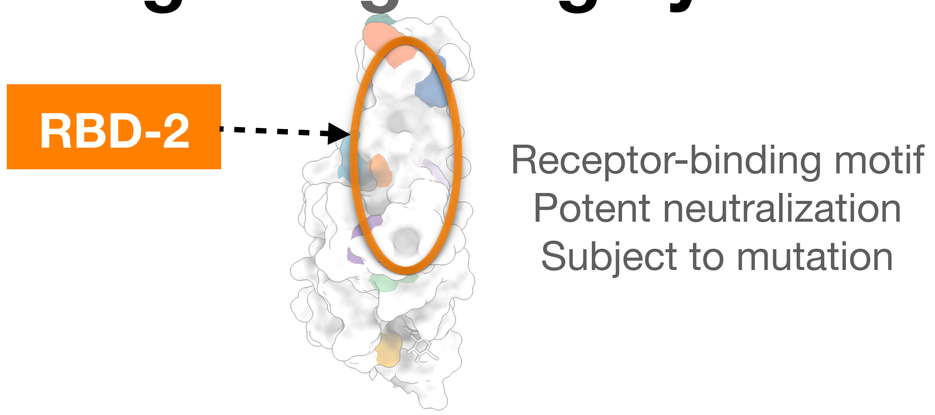
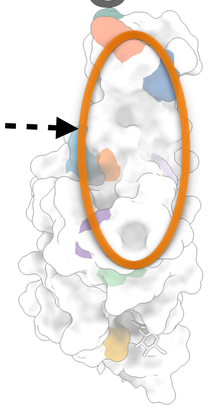


Others persist in neutralization despite recognizing a highly mutated site.

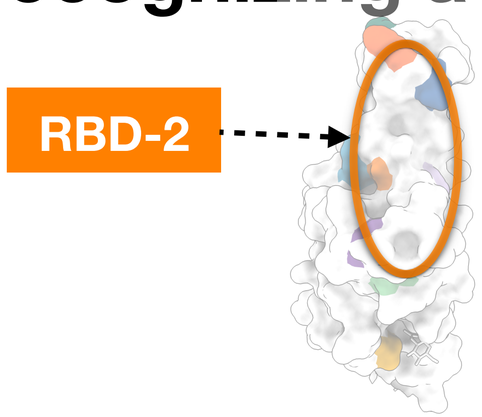
RBD-2



Receptor-binding motif
Potent neutralization
Subject to mutation

Callaway et al Cell Reports 2023

Others persist in neutralization despite recognizing a highly mutated site.



Receptor-binding motif
Potent neutralization
Subject to mutation

The RBD-2s recognize a similar footprint
Yet some still neutralize omicron and others do not.
Why? What's the difference?

Callaway et al Cell Reports 2023

Others persist in neutralization despite recognizing a highly mutated site.

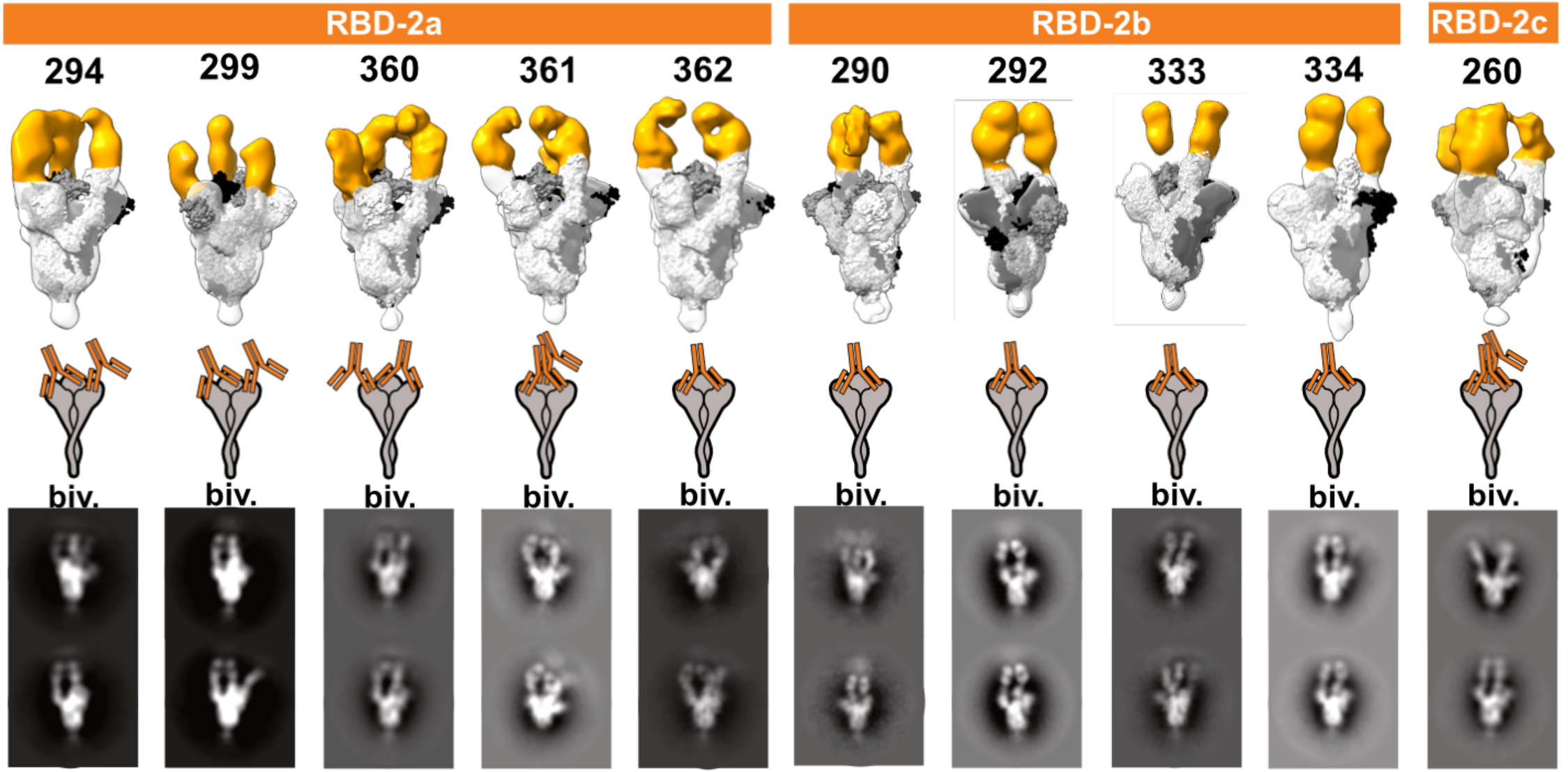
Receptor-binding motif
Potent neutralization
Subject to mutation

The RBD-2s recognize a similar footprint
Yet some still neutralize omicron and others do not.
Why? What's the difference?

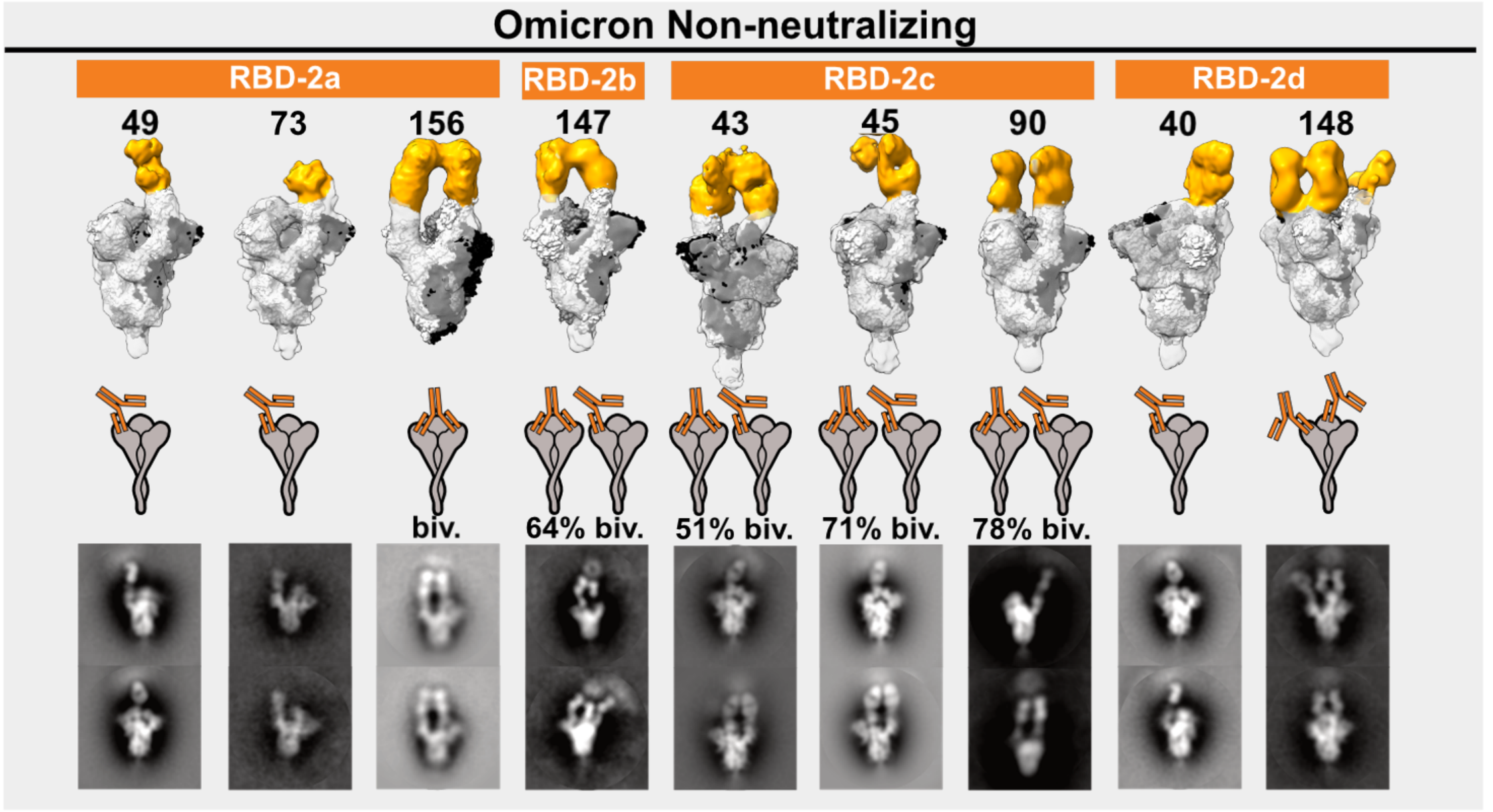
Look at the IgG-spike complexes by electron microscopy

Callaway et al Cell Reports 2023

These RBD-2 antibodies can neutralize Omicron

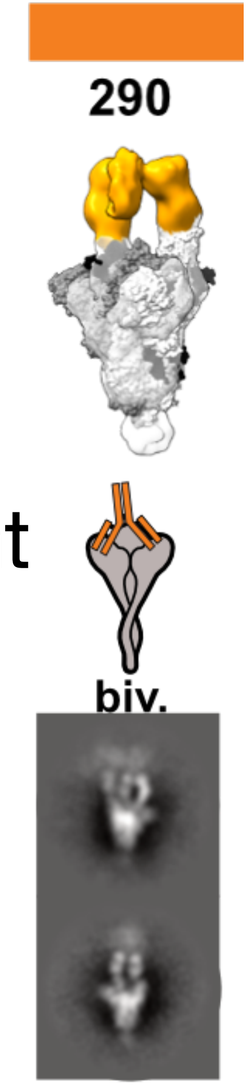


These RBD-2 antibodies can NOT neutralize Omicron



Neutralize Omicron

One Bivalent



Neutralize Omicron

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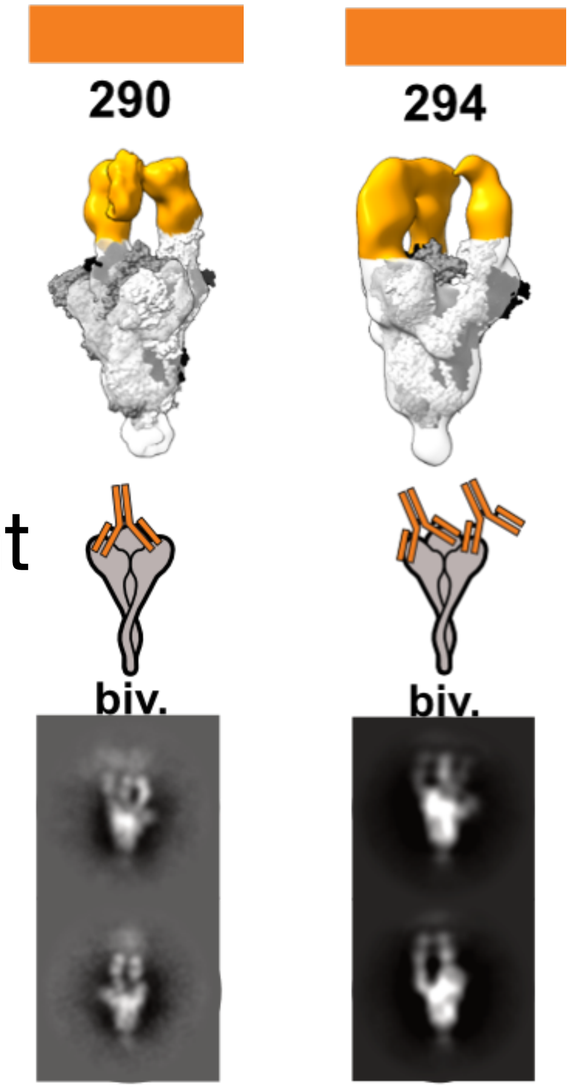
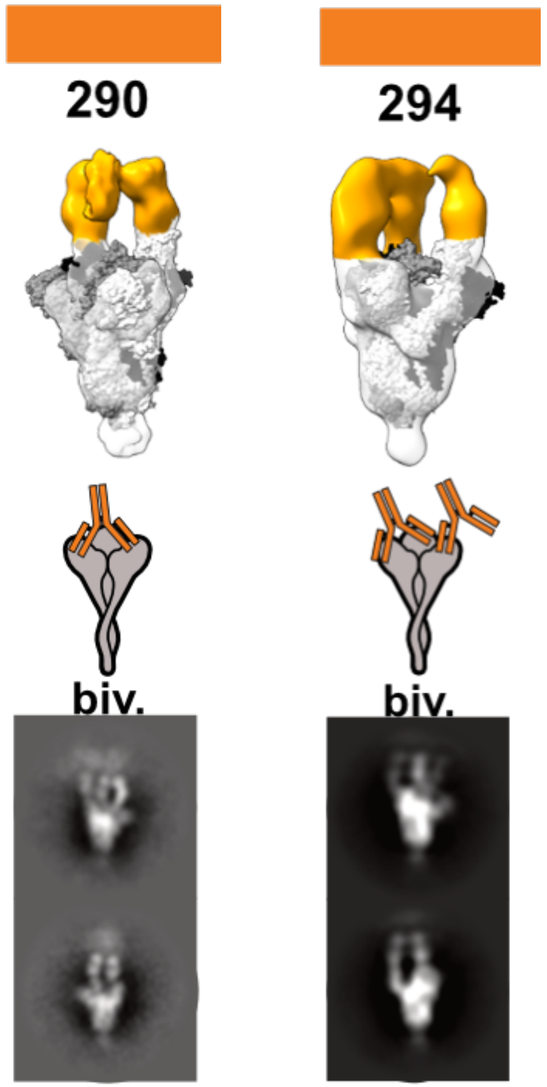


One Bivalent
One extra

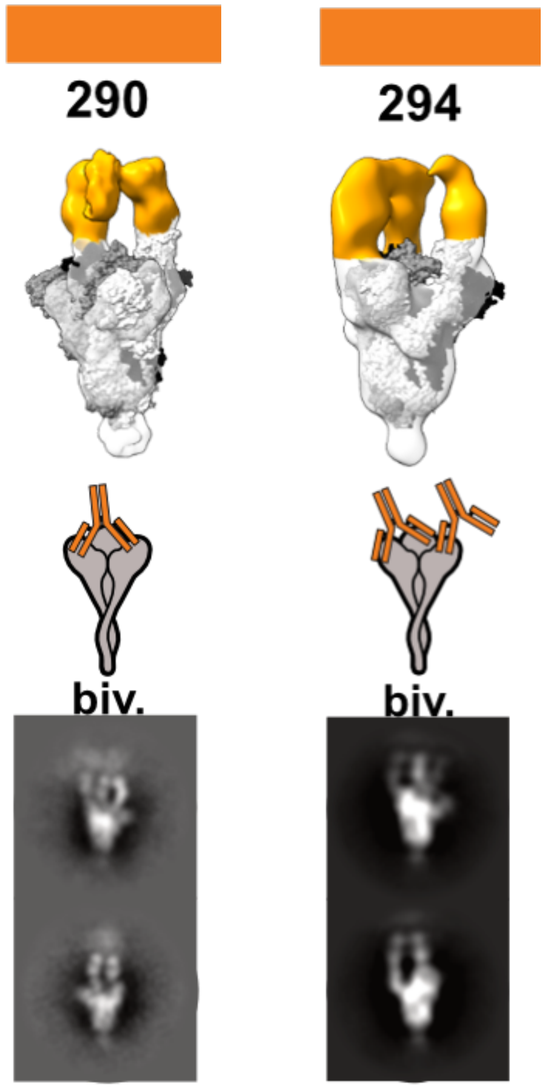
Neutralize Omicron



Callaway et al Cell Reports 2023

Neutralize Omicron

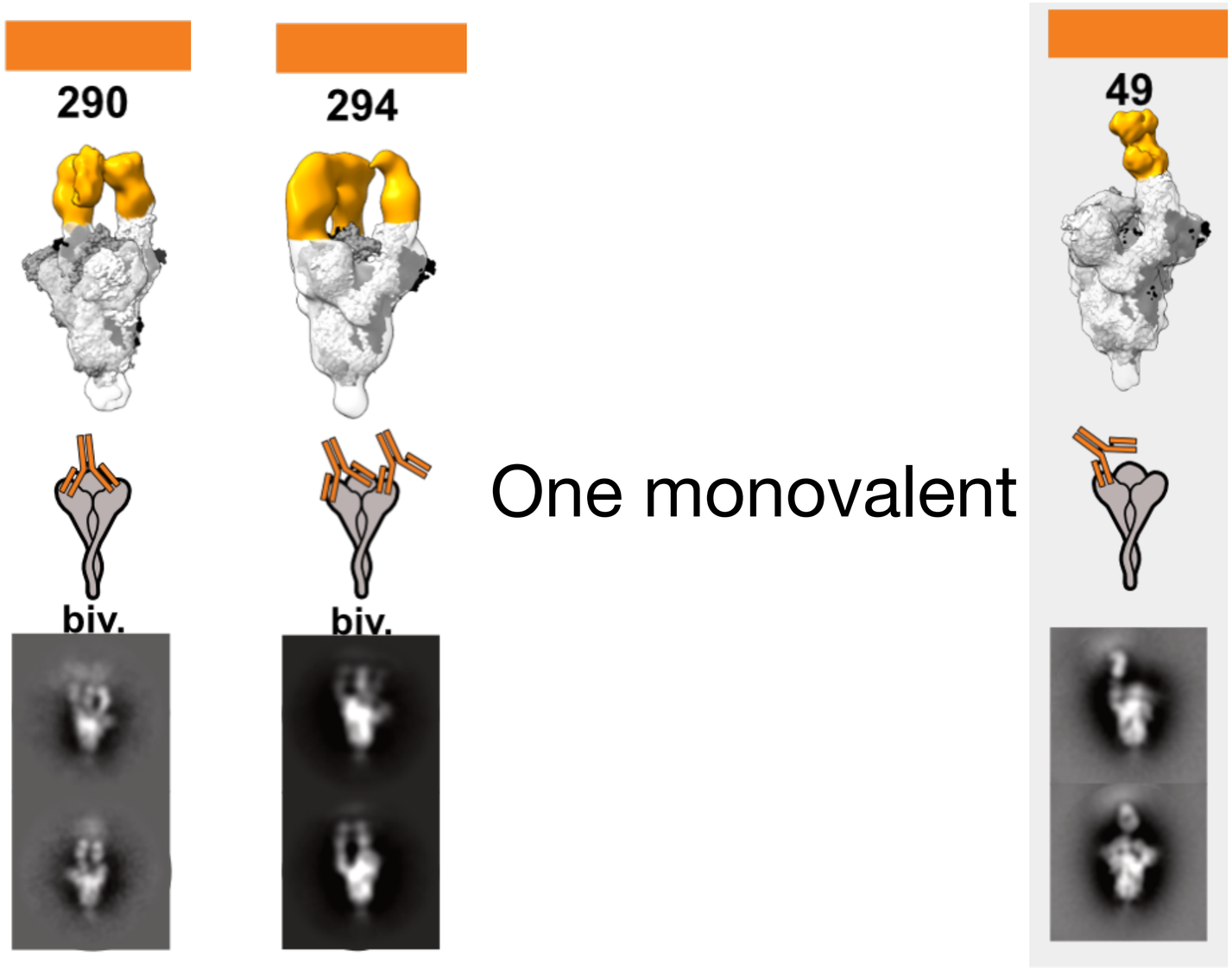
Do NOT Neutralize Omicron



Callaway et al Cell Reports 2023

Neutralize Omicron

Do NOT Neutralize Omicron

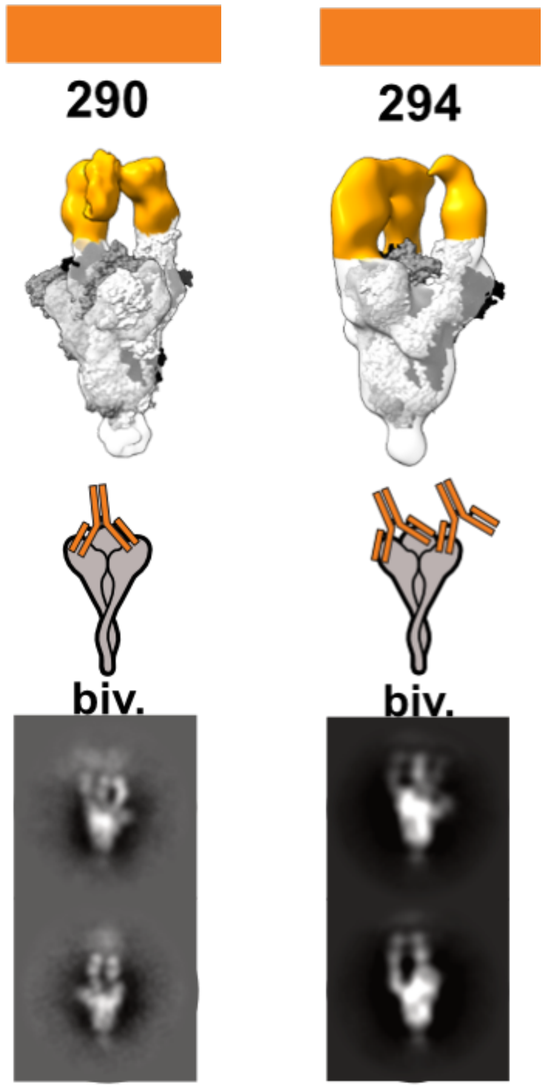


One monovalent

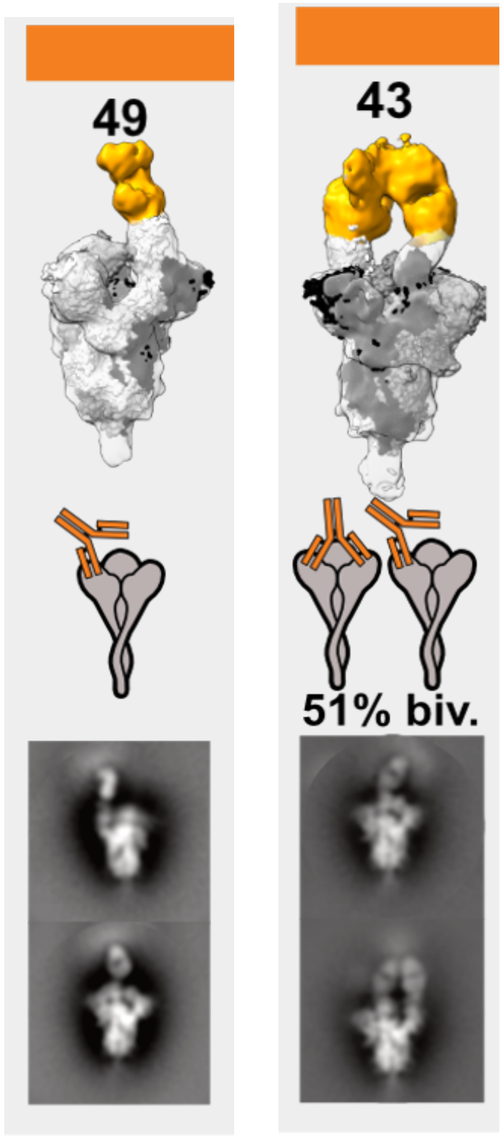
Callaway et al Cell Reports 2023

Neutralize Omicron

Do NOT Neutralize Omicron



One monovalent



Half bivalent
Half monovalent

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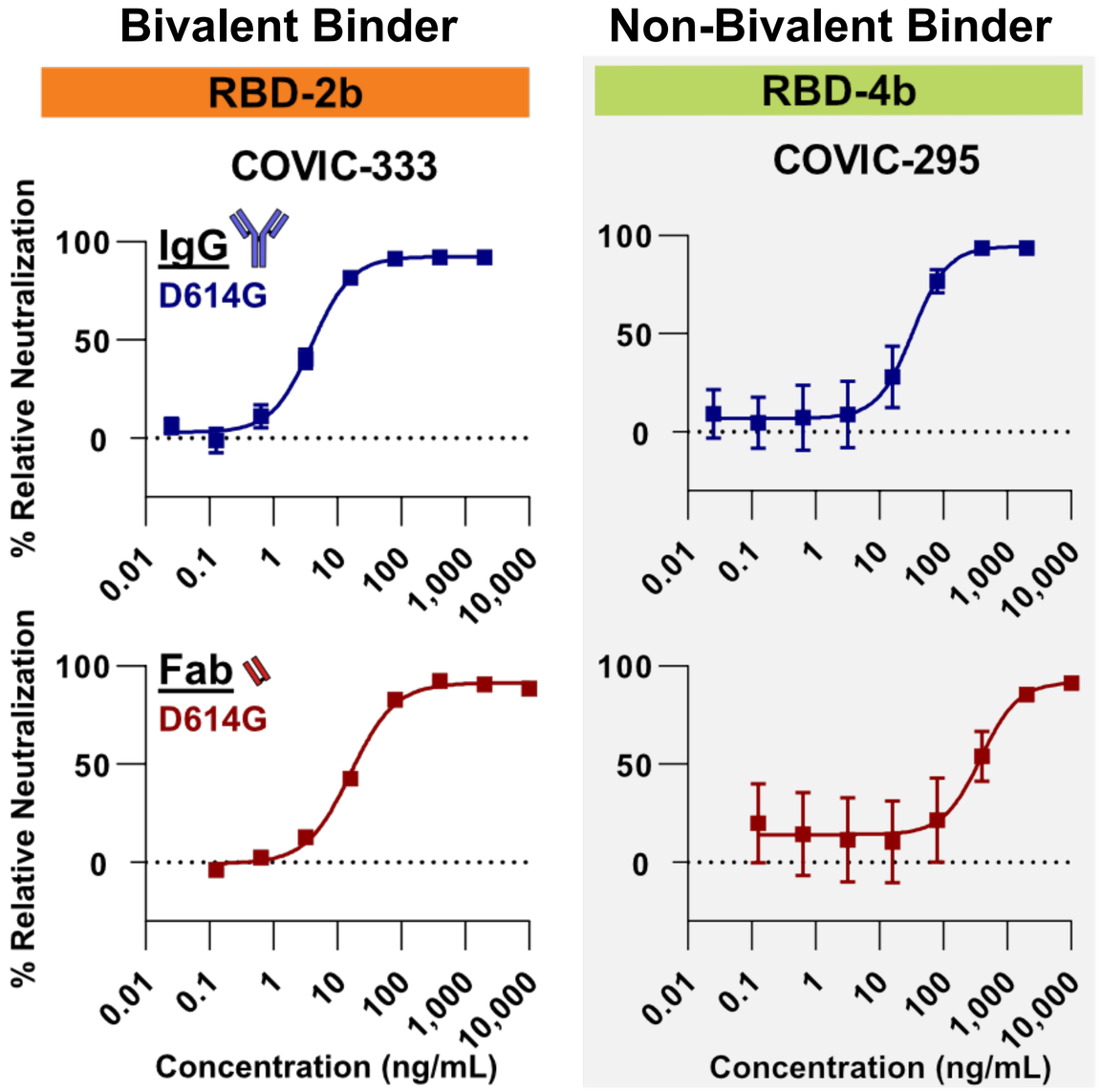
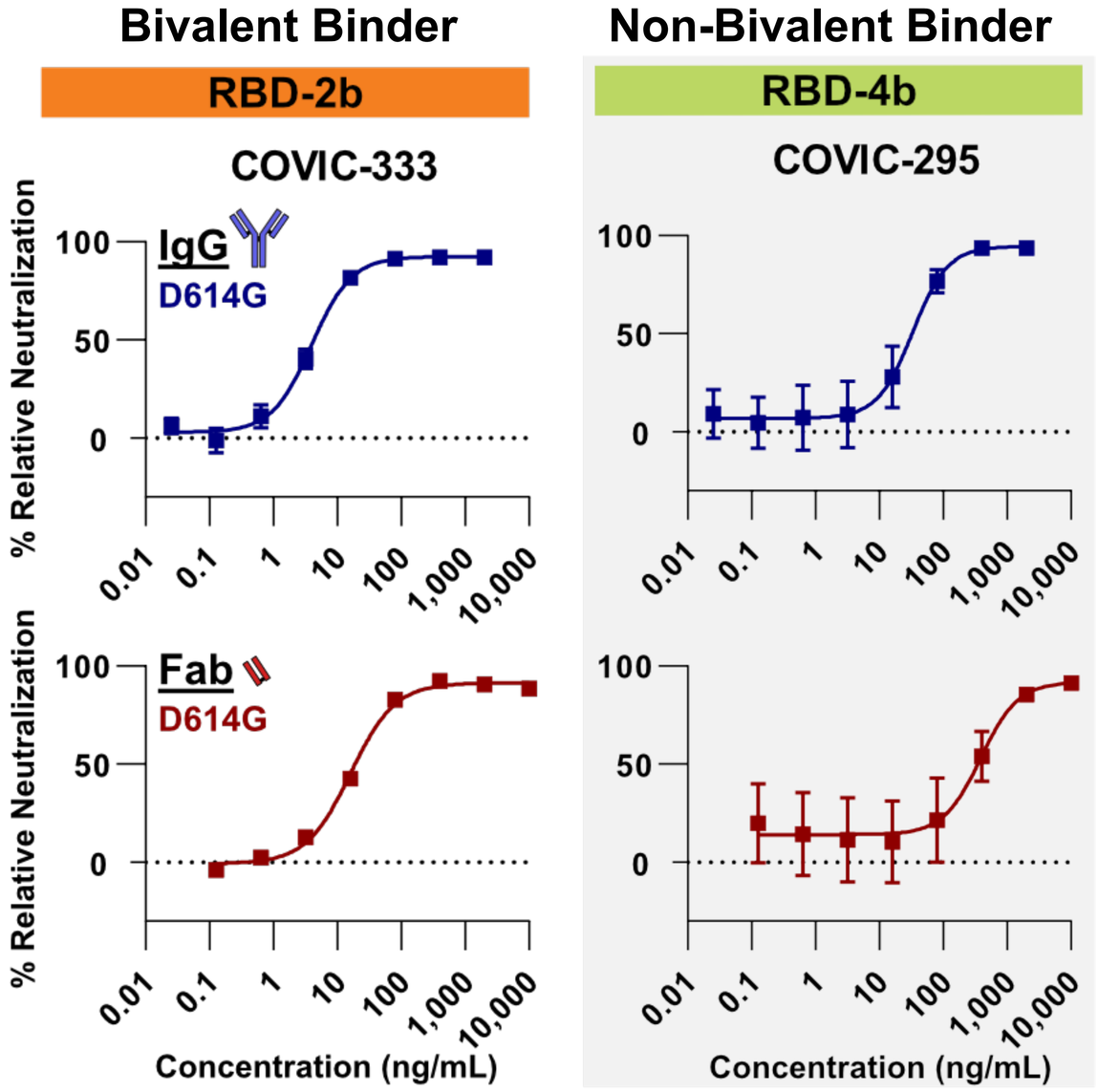
Bivalent binders use avidity to compensate for lower affinity

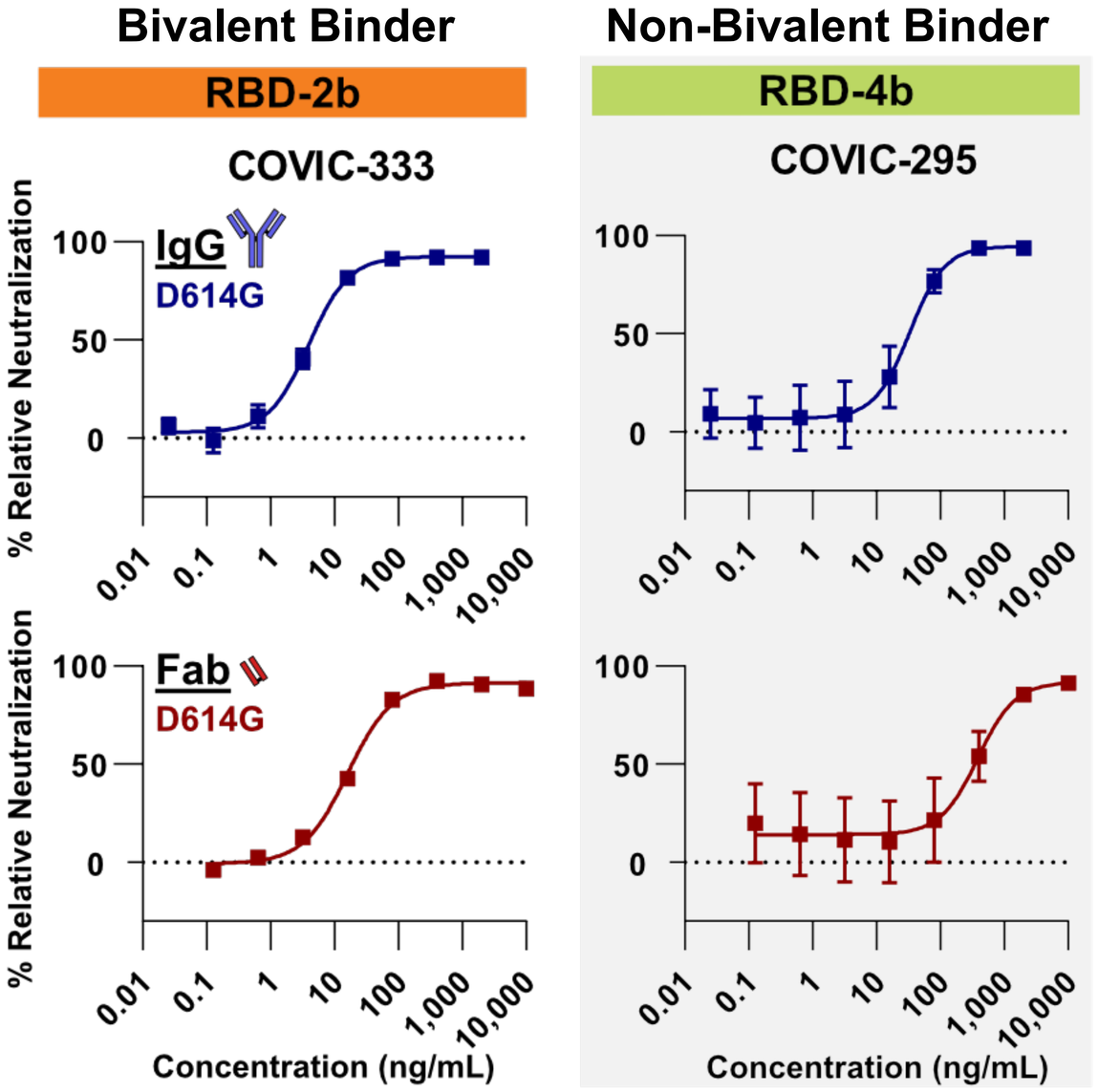


Bivalent binders use avidity to compensate for lower affinity



With D614G:

Bivalent binders use avidity to compensate for lower affinity

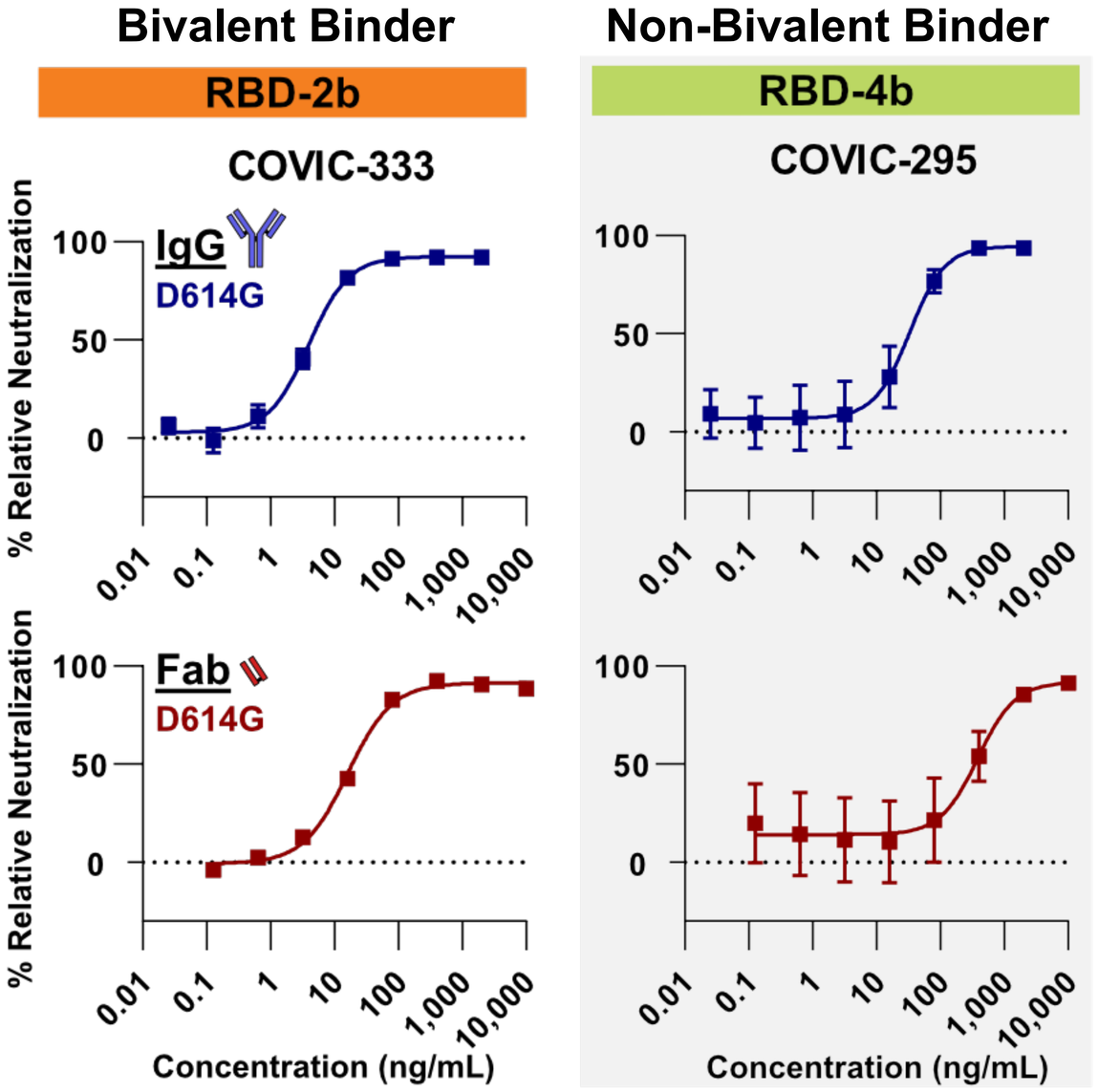


With D614G:

IgGs neutralize

Fabs neutralize

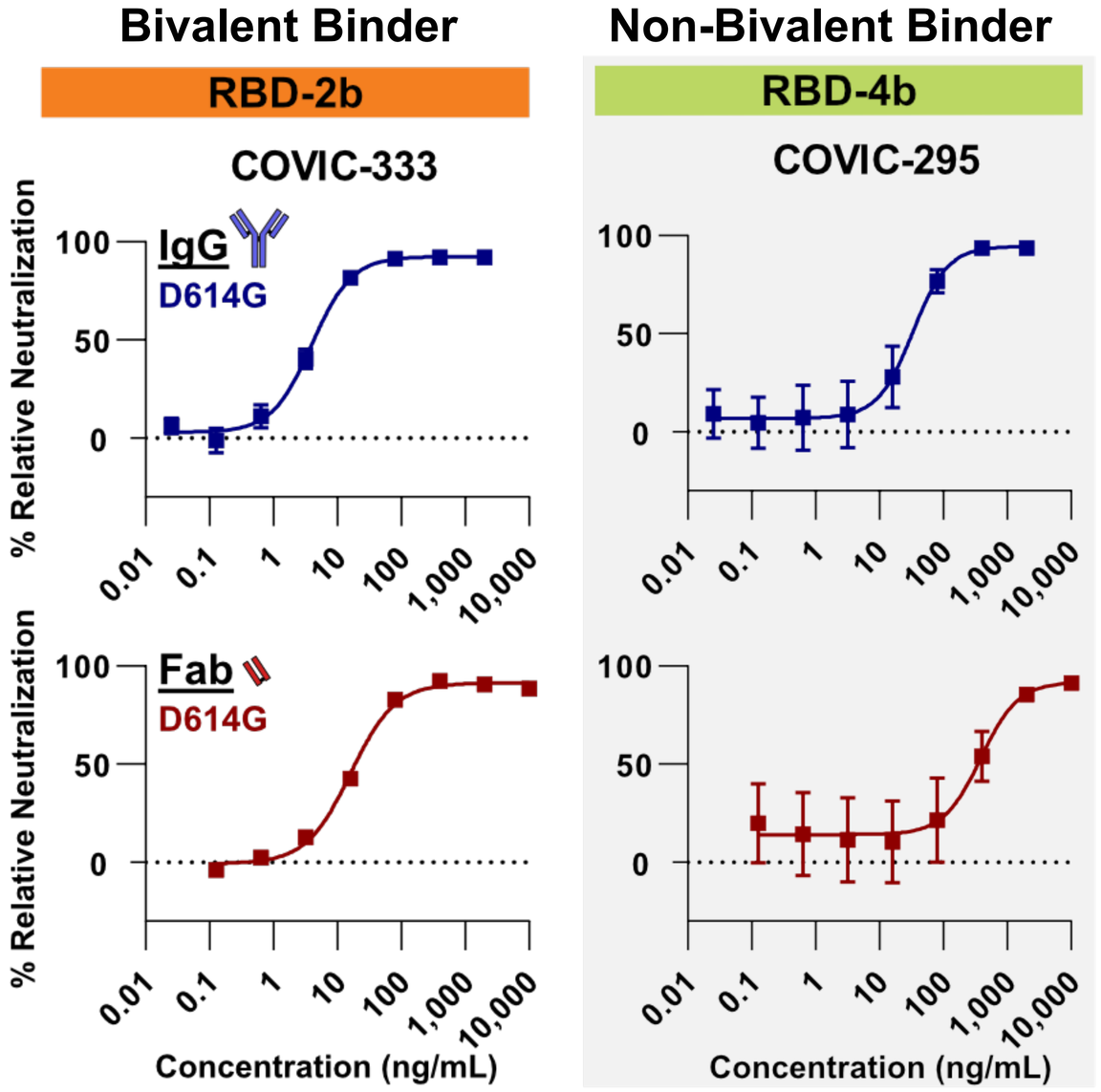
Bivalent binders use avidity to compensate for lower affinity



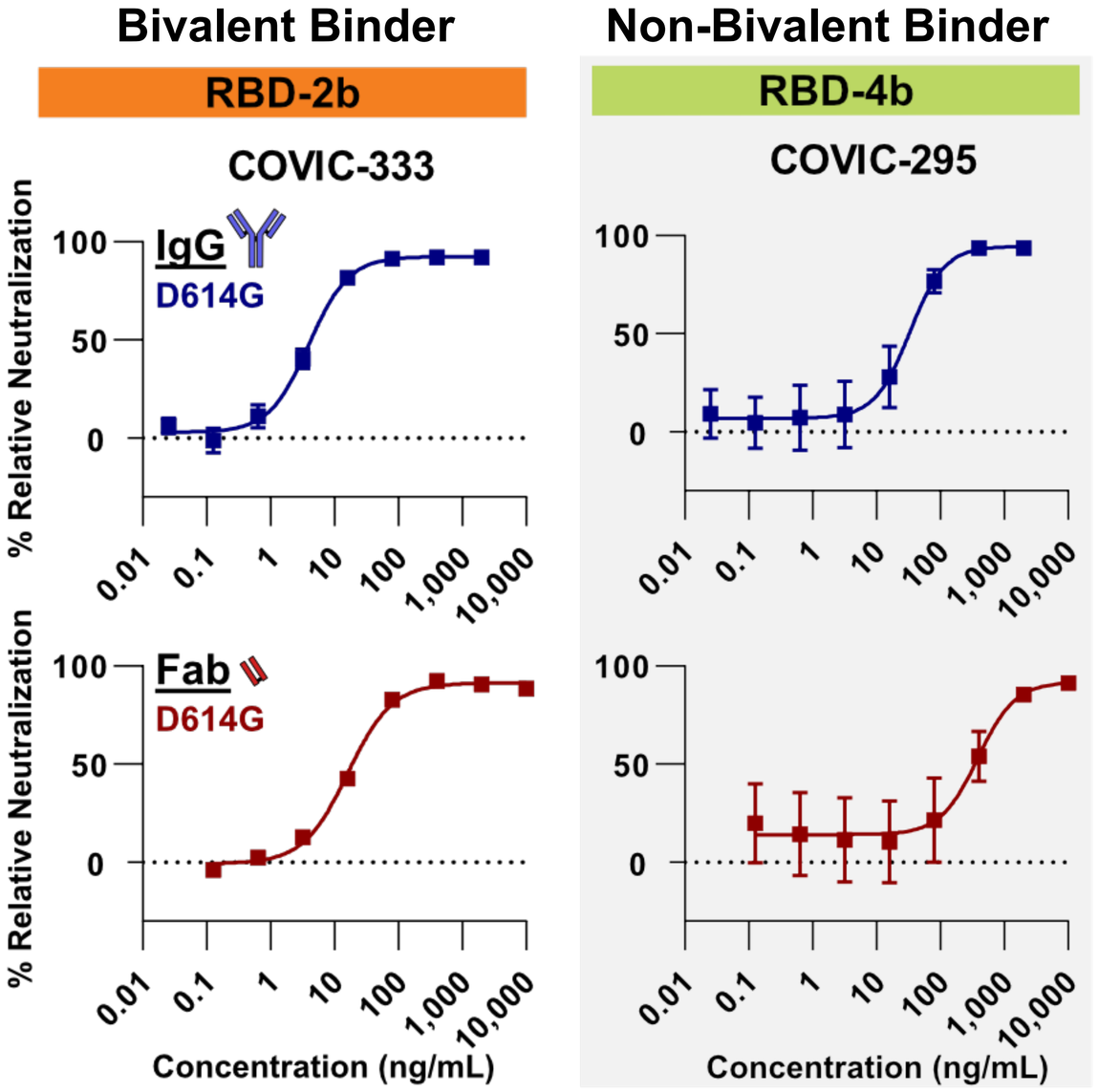
IgGs neutralize

Fabs neutralize

Bivalent binders use avidity to compensate for lower affinity

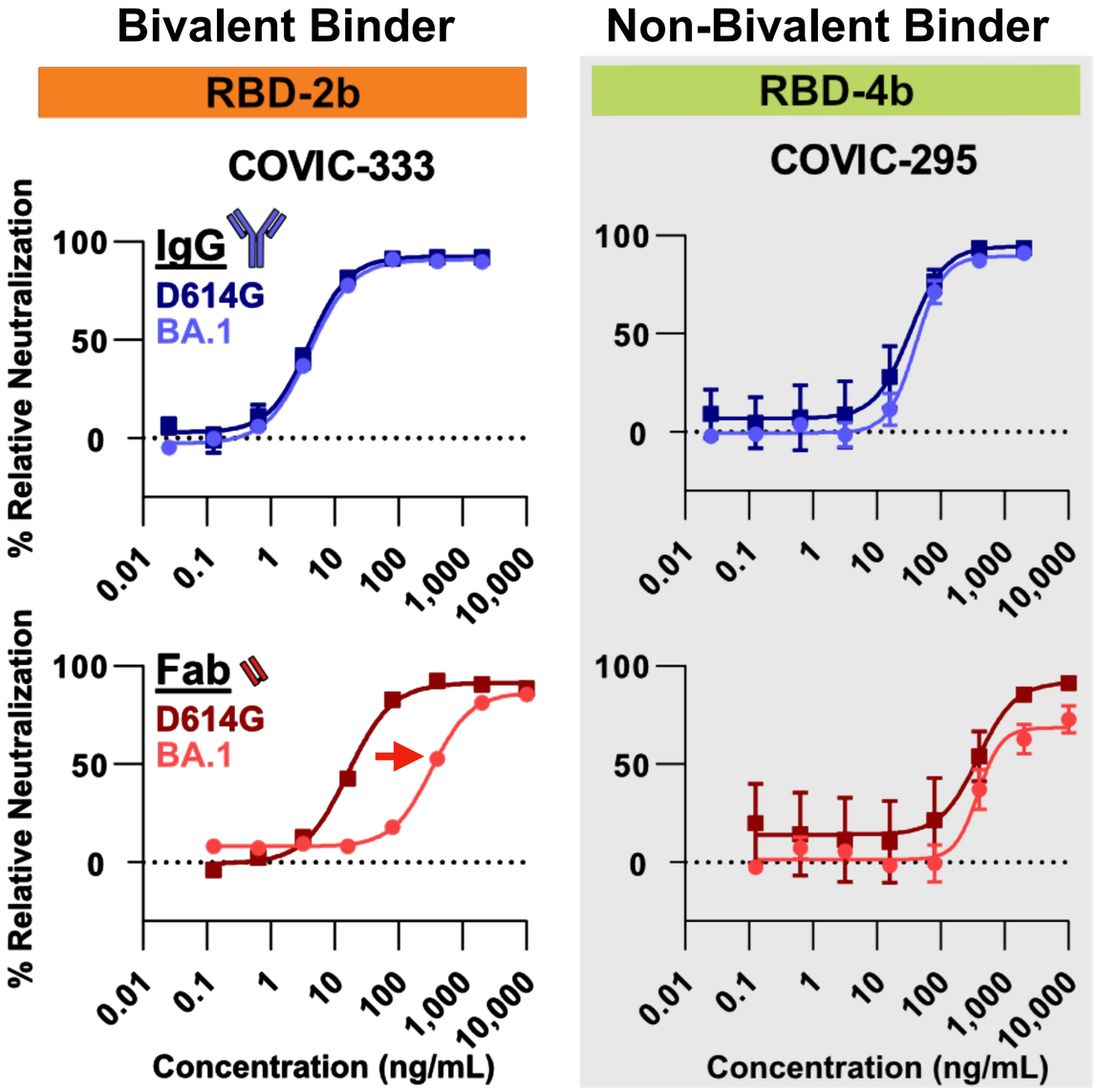


Bivalent binders use avidity to compensate for lower affinity



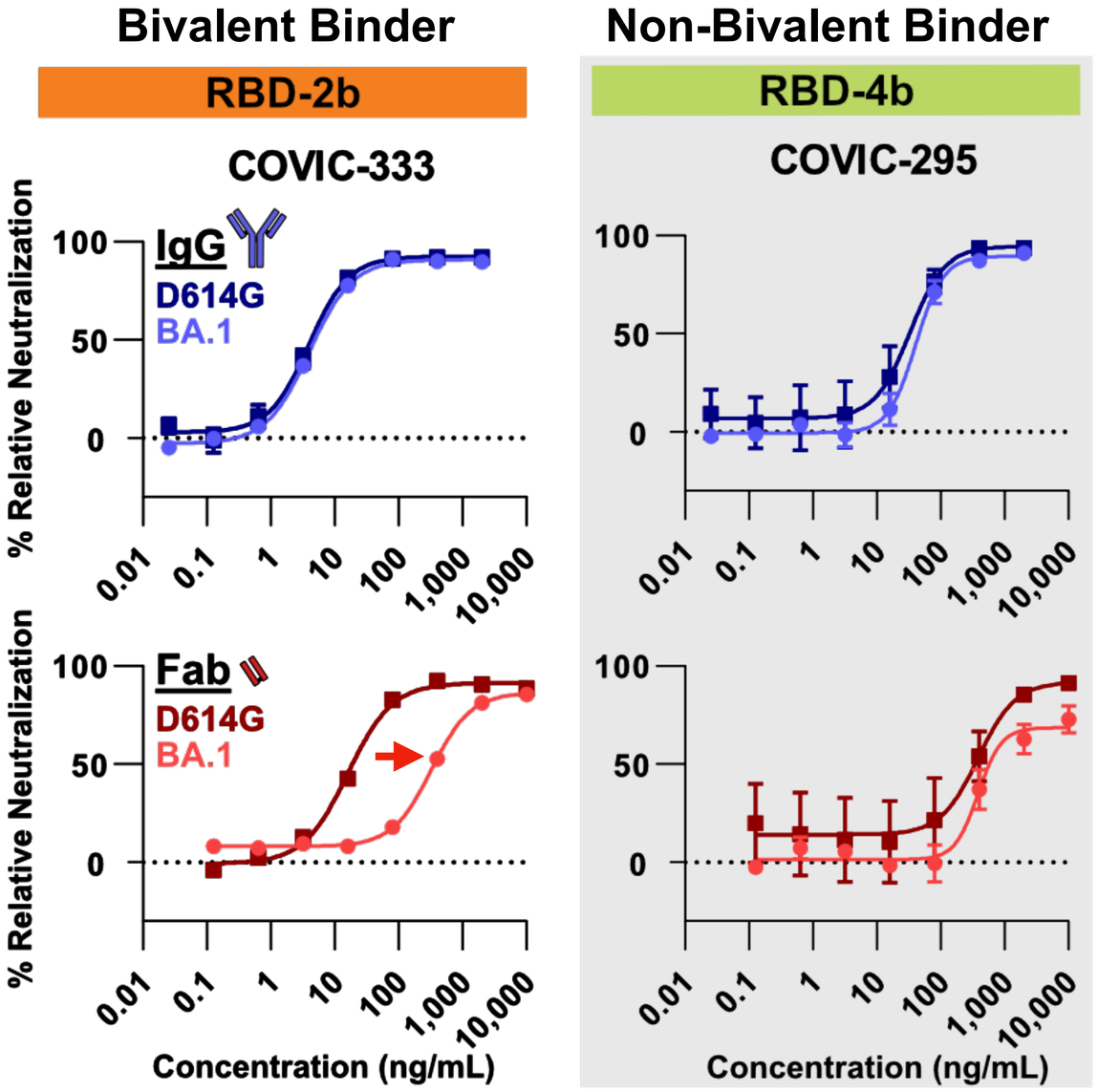
With BA.1:

Bivalent binders use avidity to compensate for lower affinity



With BA.1:

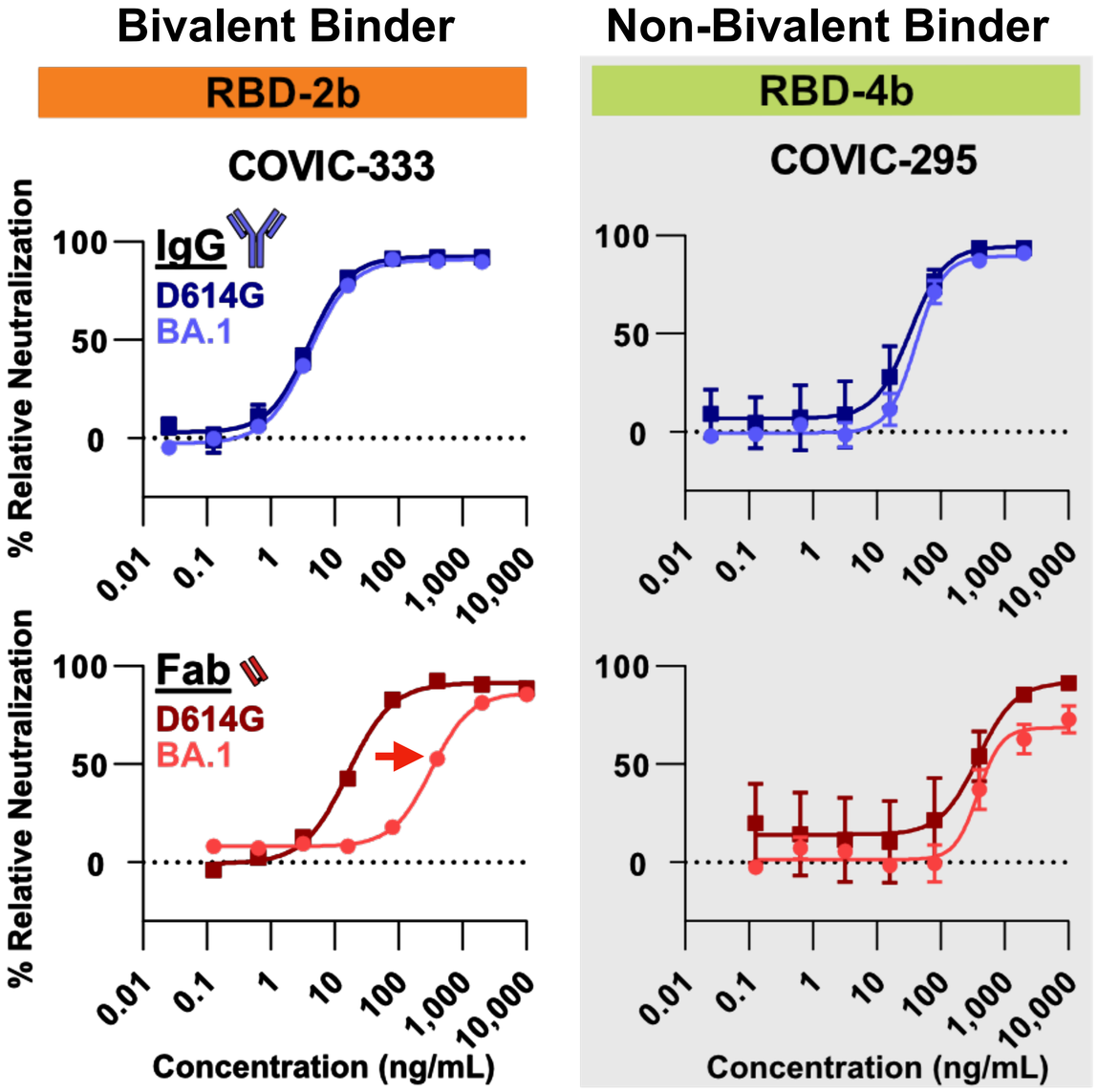
Bivalent binders use avidity to compensate for lower affinity



With BA.1:

IgGs still neutralize

Bivalent binders use avidity to compensate for lower affinity



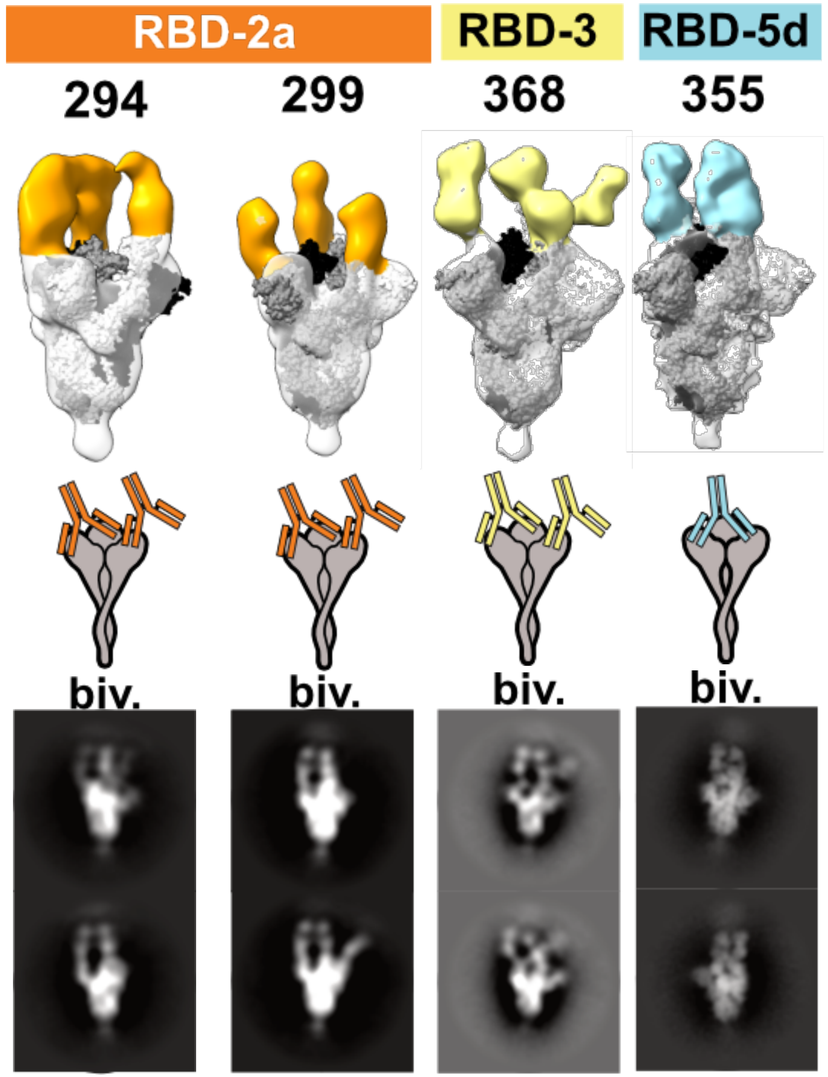
Fab from bivalent IgG struggles to neutralize, even though its IgG does just fine

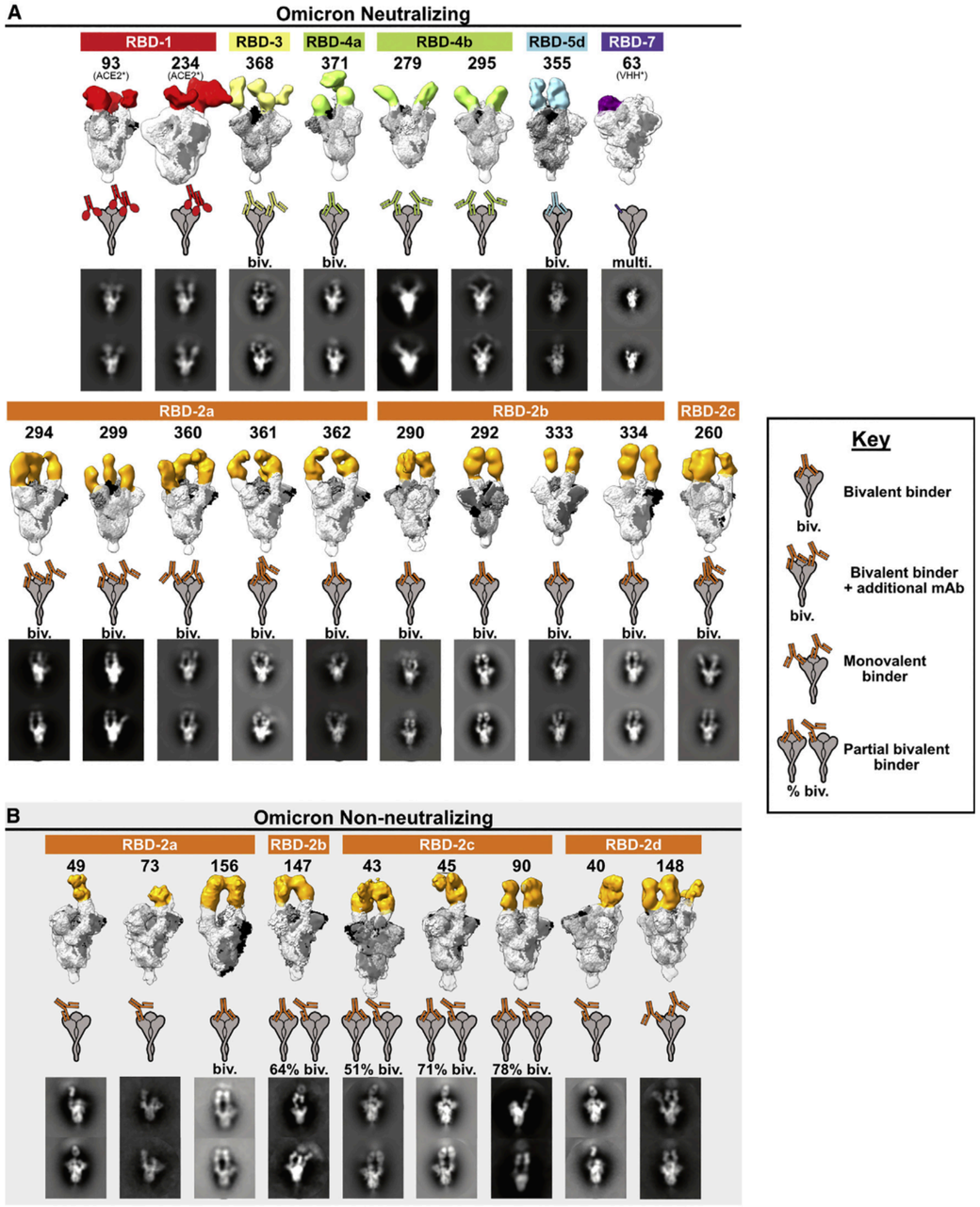
With BA.1:

IgGs still neutralize

BA.4/5 survivors:

IgG that bind bivalently

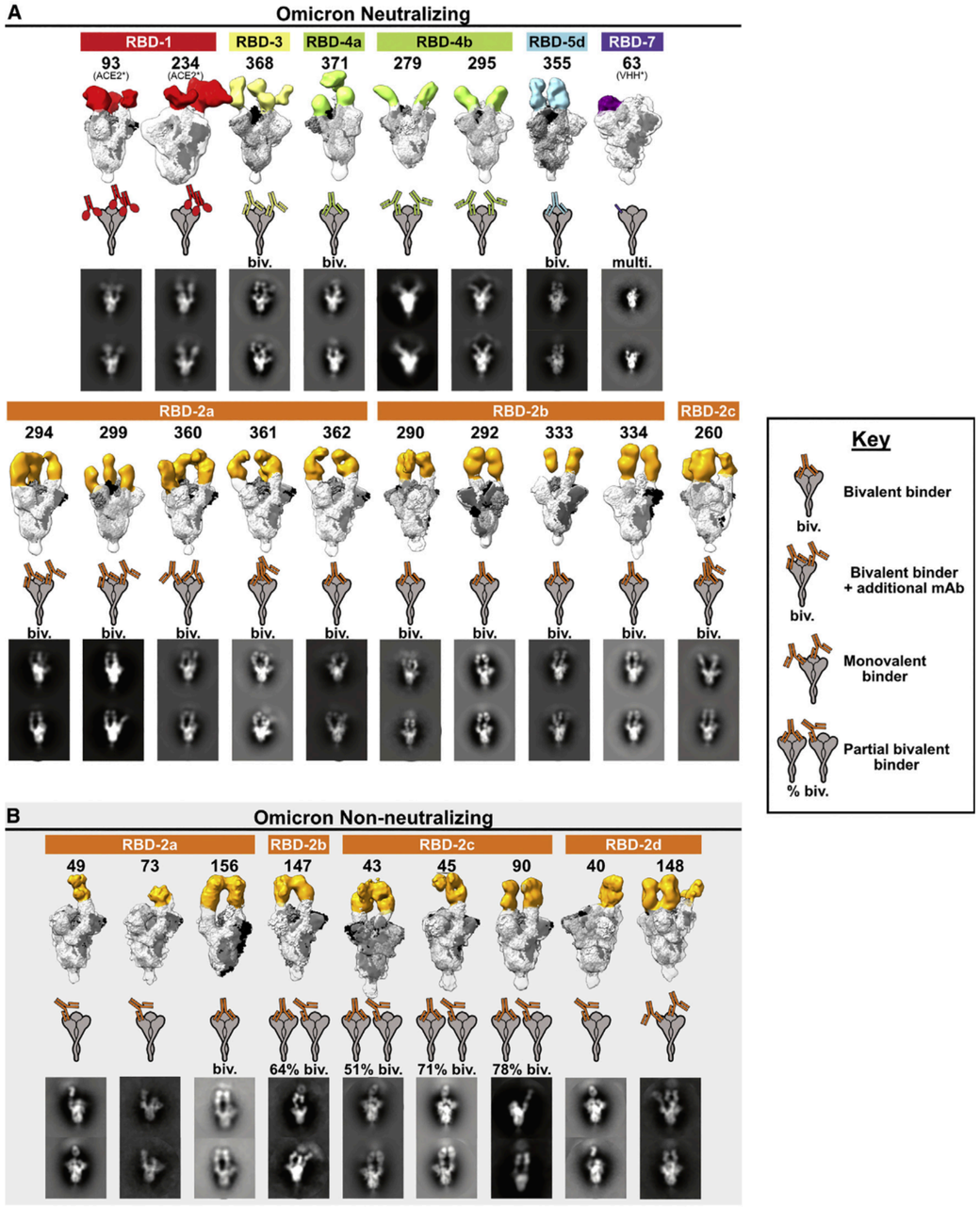



A
Omicron Neutralizing
RBD-1
RBD-3
RBD-4a
RBD-4b
RBD-5d
RBD-7
93 (ACE2*)
234 (ACE2*)
368
371
279
295
355
63 (VHH*)
biv.
biv.
biv.
multi.
RBD-2a
RBD-2b
RBD-2c
294
299
360
361
362
290
292
333
334
260
biv.
B
Omicron Non-neutralizing
RBD-2a
RBD-2b
RBD-2c
RBD-2d
49
73
156
147
43
45
90
40
148
biv.
64% biv.
51% biv.
71% biv.
78% biv.
Key
Bivalent binder
biv.
Bivalent binder + additional mAb
biv.
Monovalent binder
Partial bivalent binder
% biv.

LESSONS LEARNED:
Bivalent binding maintained neutralization vs. Omicron

Classical approach with Fab only would NOT have been revealed this binding mechanism

Considerations for different constructs, e.g., bispecifis

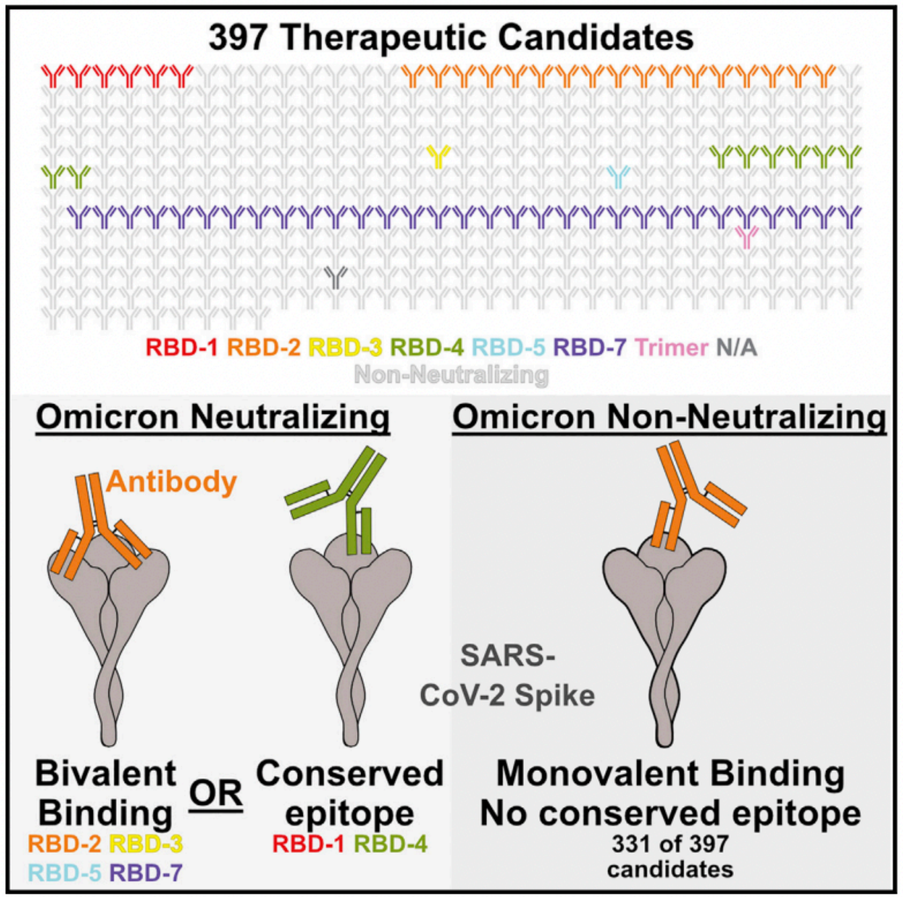


Cell Reports

Article

Bivalent intra-spike binding provides durability against emergent Omicron lineages: Results from a global consortium

Graphical abstract



Authors

Heather M. Callaway, Kathryn M. Hastie, Sharon L. Schendel, ..., Bjoern Peters, Georgia Tomaras, Erica Ollmann Saphire

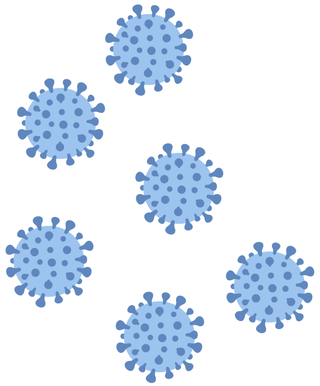
Correspondence

erica@lji.org

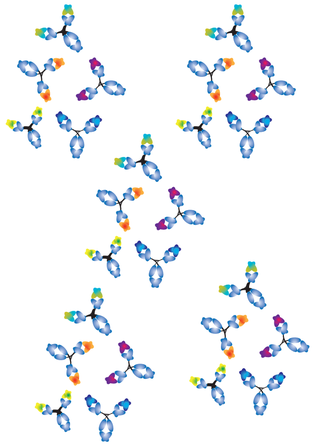
In brief

Callaway et al. examine a panel of 397 SARS-CoV-2 antibodies to understand how some antibodies, generated early during the COVID-19 pandemic, maintain the ability to neutralize Omicron variants despite extensive mutation in their epitopes. Antibodies against highly mutated epitopes retain neutralization by binding bivalently: cleavage to Fab eliminates neutralization.

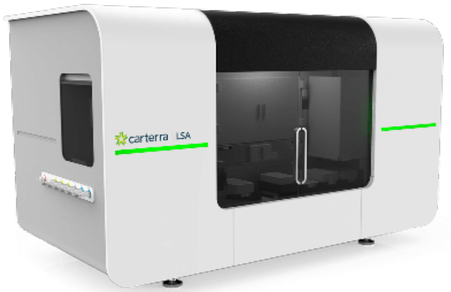
CoVIC guidance for the future…

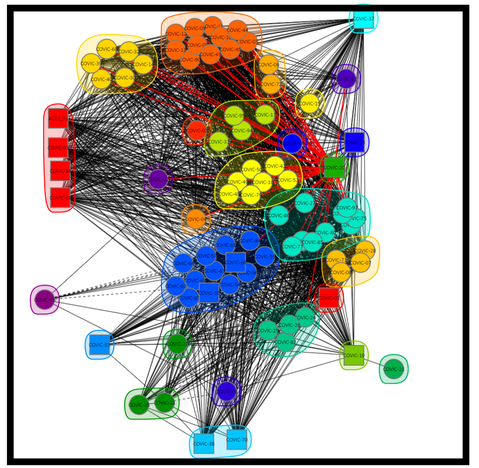


Next pandemic

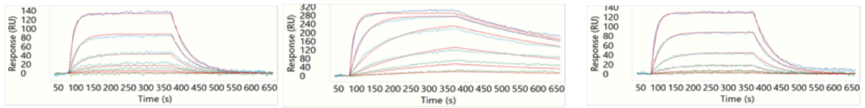


Isolate antibodies



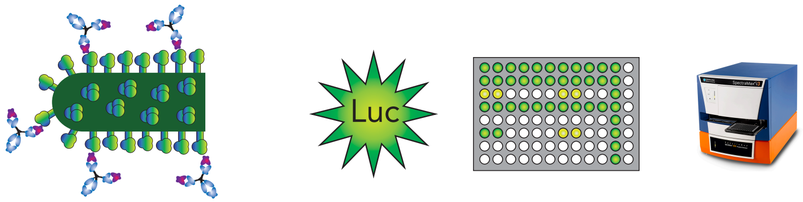


Bin them



Affinity

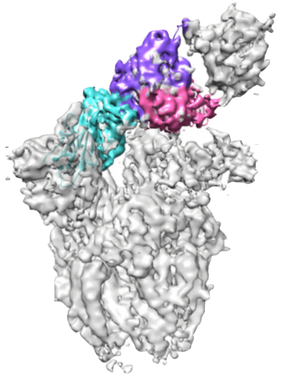
or



Neut

(Pseudo- or authentic OK for SARS-CoV-2)

Measure



For each bin, choose representative for in vivo and structure

CoVIC

COVID-19 Therapeutics Accelerator

A partnership of
The Bill & Melinda Gates Foundation
Mastercard, The Wellcome Trust and
others

NIH/NIAID supplement to
The Consortium for Immunotherapeutics
Against Emerging Viral Threats (VIC)
CETR U19 AI142790

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Overton Family

Jacqueline Kirchner, BMGF
Ann Eakin, NIAID
Tina Parker, NIAID
Laura Powell, Latham

Ralph Baric, UNC
Alex Bukreyev, UTMB
Galit Alter, Ragon Institute
Caroline Atyeo, Ragon
Sujan Shresta, LJI

Paula Pino Tamayo, Texas Biomed.
Jordi Torrelles, Texas Biomed.
Luis Martinez, Texas Biomed.

Erica Ollmann Saphire, LJI
Kathryn M. Hastie, LJI
Haoyang Li, LJI
Heather Callaway, LJI
Xiaoying Yu, LJI
Dawid Zyla, LJI
Jieyun Yin, LJI
Chitra Hariharan, LJI
Ruben Diaz, LJI
Eduardo Olmedillas, LJI
Colin Mann, LJI
Hal Wasserman, LJI

Bjoern Peters, LJI
Brendan Ha, LJI
Mari Kojima, LJI
Mahita Jarjapu, LJI
Randi Vita, LJI
James Overton, LJI

Dan Bedinger, Carterra
Tim Germann, Carterra
Georgia Tomaras, Duke
Moses Sekaran, Duke
Jonathan Li, Duke
Luc Gagnon, Nexelis
Mary Osei-Twum, Nexelis

All the CoVIC participants