Complete antibody escape mapping of the SARS-CoV-2 spike RBD

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Alissa Eckert, Dan Higgins, https://phil.cdc.gov/Details.aspx?pid=23312

Disclosures

James Crowe, a co-author on this study, has served as a consultant for Sanofi; is on the Scientific Advisory Boards of CompuVax and Meissa Vaccines; is a recipient of previous unrelated research grants from Moderna and Sanofi; and is a founder of IDBiologics.

Vanderbilt University has applied for patents concerning SARS-CoV-2 antibodies analyzed in this work.



Jesse Bloom



Tyler Starr



The RBD binds ACE2 on target cells to mediate viral entry

Receptor Binding Domain (RBD)

ACE2

target cell

spike

The RBD is a target of neutralizing antibodies

Antibody therapeutics are being designed to target the RBD







Understanding how RBD mutations affect antibody recognition is important for therapeutics and vaccines



How can we measure the effects of all these mutations?



(201 sites) X (19 amino-acid mutations per site) = **3,819** mutations

Starr*, Greaney*, ..., Bloom. Cell. (2020)

Yeast display enables high-throughput binding experiments



Starr*, Greaney*, ..., Bloom. Cell. (2020)

How do mutations affect antibody binding?



We can hake high-resolution antibody escape maps



Growing virus in the presence of a single antibody selects escape mutants

antibody	escape / replicates	mutations
COV2-2050	4 / 30	E484K (4)
COV2-2499	5 / 16	G446D (3), Q498R (2)



Greaney*, Starr*, Glichuk*, Zost*, ..., Crowe, Bloom. *bioRxiv*. (2020) Case, Rothlauf, ..., Whelan. *Cell Host & Microbe*. (2020) Gilchuk, ..., Crowe. *Immunity*. (2020)

Why are these mutations selected?

antibody	escape / replicates	mutations
COV2-2050	4 / 30	E484K (4)
COV2-2499	5 / 16	G446D (3), Q498R (2)



Viral escape mutants are accessible by a single nucleotide change

antibody	escape / replicates	mutations
COV2-2050	4 / 30	E484K (4)
COV2-2499	5 / 16	G446D (3), Q498R (2)



Viral escape mutants are minimally deleterious for ACE2 binding



antibody	escape / replicates	mutations
COV2-2050	4 / 30	E484K (4)
COV2-2499	5 / 16	G446D (3) Q498R (2)

COV2-2165 does not select viral escape mutants

antibody	escape / replicates	mutations
COV2-2050	4 / 30	E484K (4)
COV2-2499	5 / 16	G446D (3), Q498R (2)
COV2-2165	0 / 56	NA



1-nt mutations

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A475

site

= -

N487

Greaney*, Starr*, Glichuk*, Zost*, ..., Crowe, Bloom. bioRxiv. (2020)

All 1-nucleotide mutants that reduce COV2-2165 binding have functional deficits



mutation type

× multi-nucleotide • single-nucleotide

A cocktail of 2 antibodies that compete for binding but have distinct escape mutations prevents escape



Conclusions

We can make high-resolution antibody escape maps

and integrate with functional data

to predict which mutations will arise in viral growth.

This can inform the selection of escape-resistant antibodies and cocktails.

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