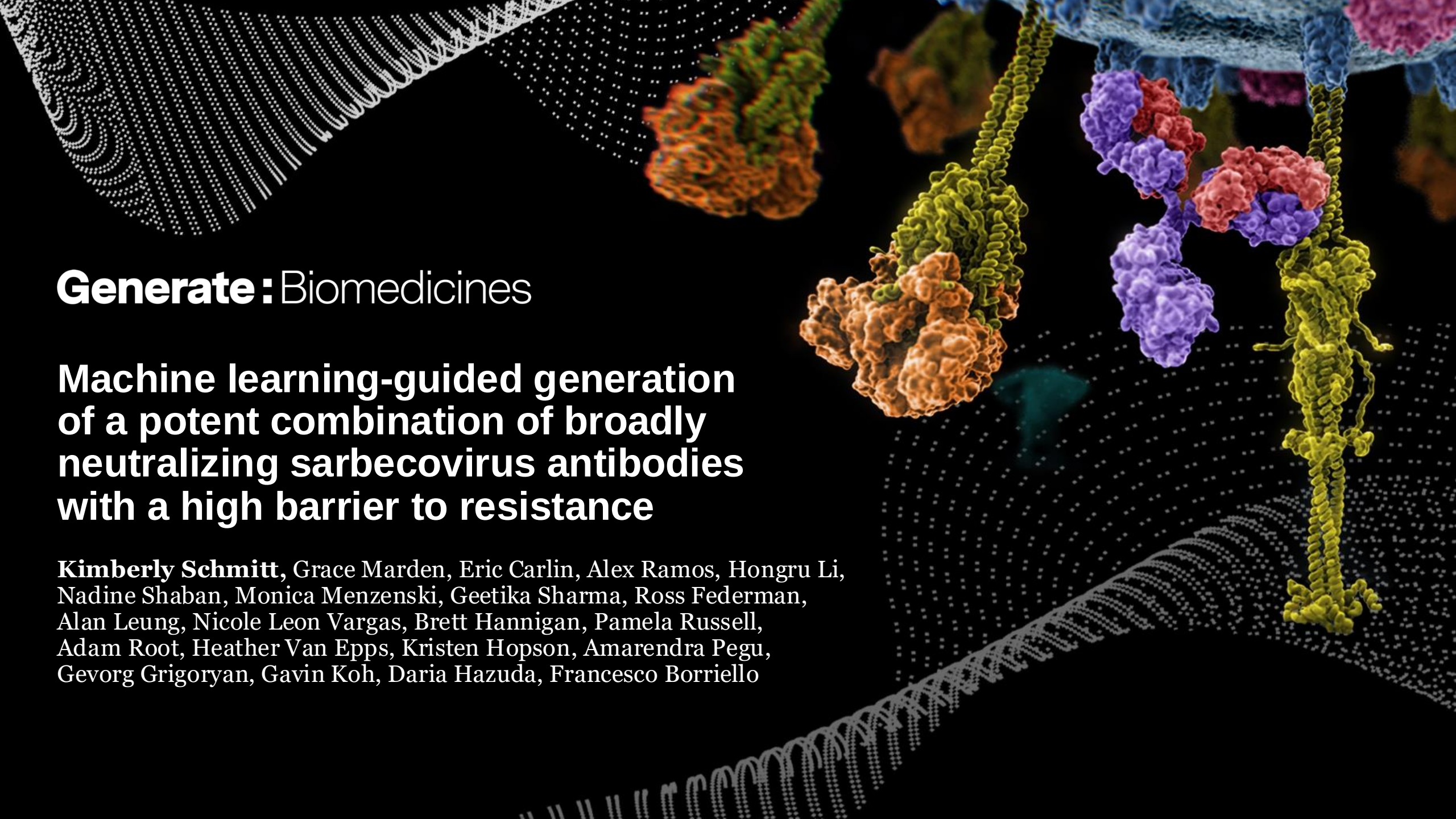

Generate : Biomedicines

Machine learning-guided generation of a potent combination of broadly neutralizing sarbecovirus antibodies with a high barrier to resistance

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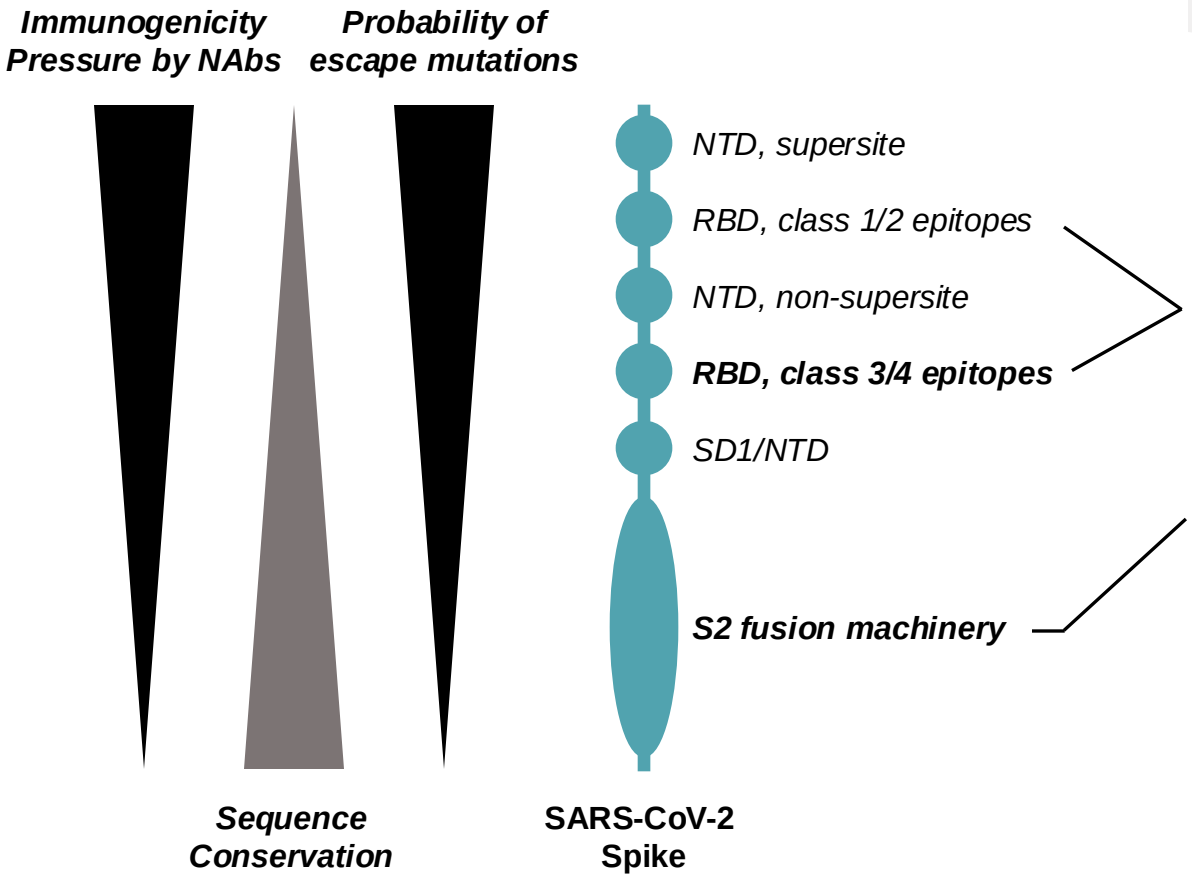
Disclosures

Dr. Schmitt is a current employee of Generate:Biomedicines.

All relevant financial disclosures have been mitigated.

Tackling SARS CoV-2 viral evolution through an understanding of the antigenic landscape of the Spike protein and immune escape



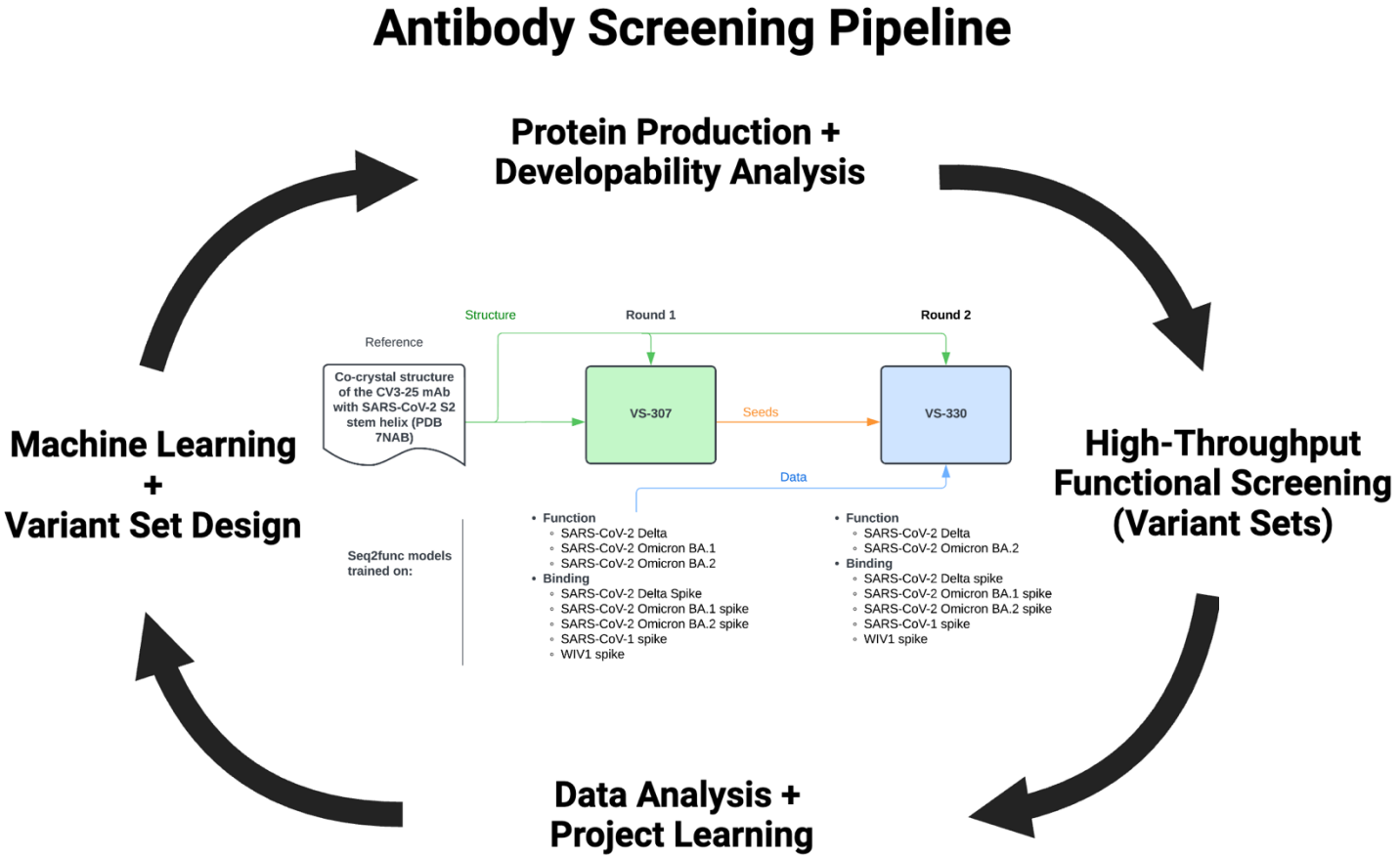
Escape mutations develop under evolutionary pressure exerted by neutralizing antibodies (NAbs) during natural infection and/or as a consequence of vaccination

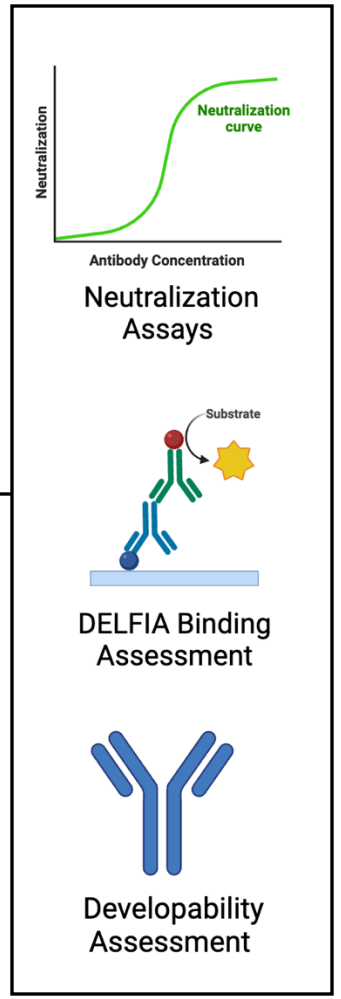
Most NAbs target immunodominant, generally non-conserved epitopes (RBD and NTD)

- Within the RBD, the class 1 and 2 epitopes (receptor binding motif, RBM) are under even more evolutionary pressure compared to class 3 and 4 epitopes (RBD core)
- The fusion machinery of the S2 domain (fusion peptide, stem helix, heptad repeats) is highly conserved and under less evolutionary pressure – with few mutations

Targeting less immunogenic conserved domains (class 3/4 RBD, SD1/NTD and S2 epitopes) provides rationale for developing broadly NAbs with decreased potential for immune escape

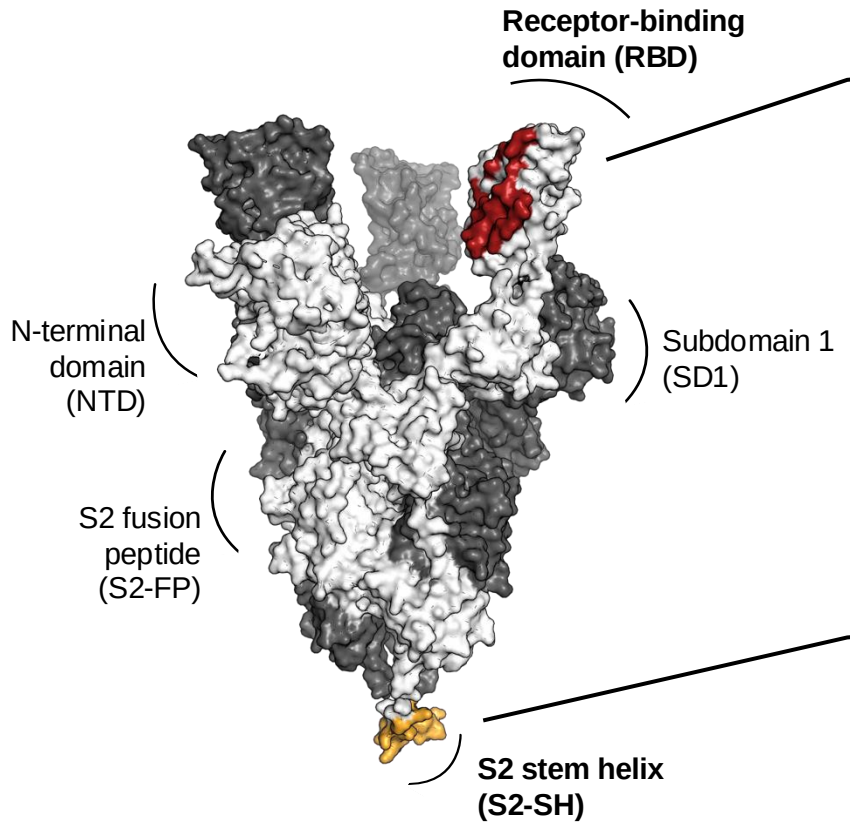
Screening and identification of anti-S2 stem helix and Class 4 anti-RBD antibodies with improved neutralization potency and breadth





Combination of Generative and Sequence-to-Function ML models enables efficient sequence co-optimization of developability, binding, and function.

The identification of potent, half-life extended therapeutics targeting two distinct epitopes on SARS-CoV-2 Spike



***Anti-RBD Class 4 mAb (PRO-37587)**:*

Recovery and improvement of neutralization potency against escape variants of antibodies targeting conserved epitopes within sarbecovirus subgenus

+

***Anti-S2-SH mAb (GB-0669)**:*

The epitope of GB-0669 is >99% conserved and subject to limited immune pressure

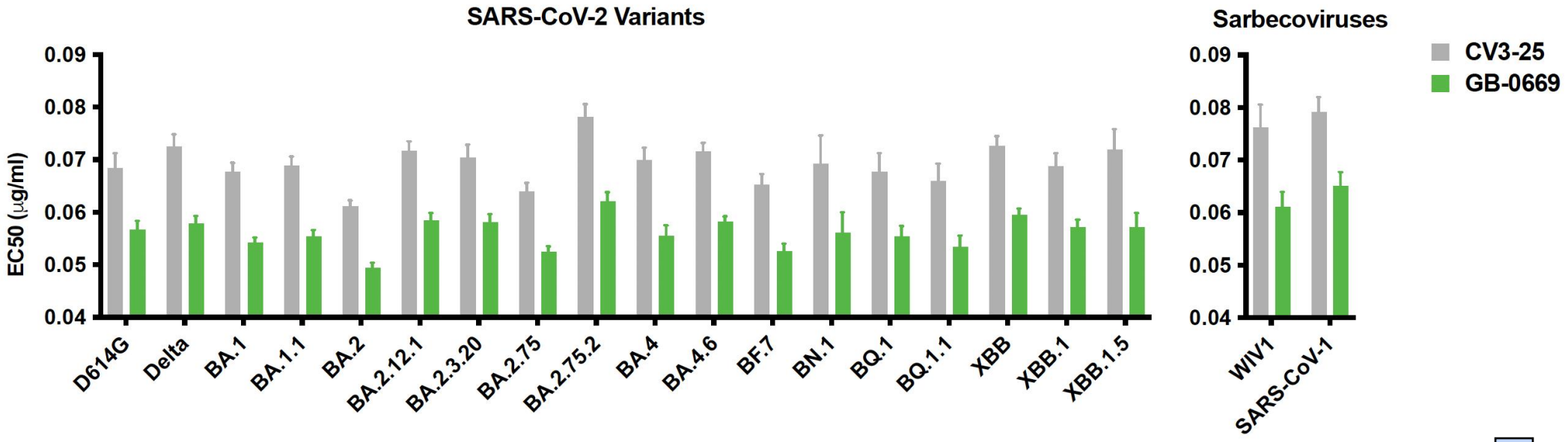
Highly conserved epitopes, less prone to immune escape

Broadly neutralizing combination targeting non-overlapping epitopes

Generated and tested with mutations to **extend half-life** and promote **mucosal translocation** while preserving Fc effector functions

The anti-S2 mAb, GB-0669, shows improved neutralization potency and binding as compared to reference mAb, CV3-25

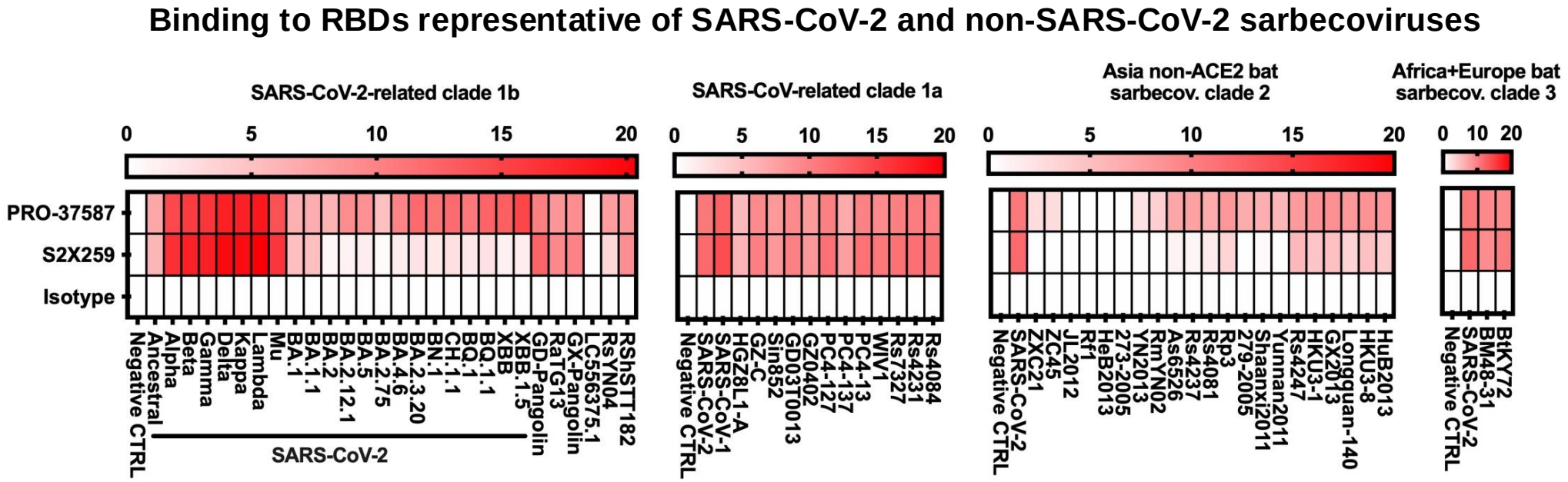
Binding to Spike trimers representative of SARS-CoV-2 variants and non-SARS-CoV-2 sarbecoviruses



Pseudovirus Neutralization, EC50 [ng/ml]													
	SARS-CoV-1	WIV1	SARS-CoV-2 D614G	SARS-CoV-2 Delta	SARS-CoV-2 BA.1	SARS-CoV-2 BA.2	SARS-CoV-2 BA.2.3.20	SARS-CoV-2 BA.2.75.2	SARS-CoV-2 BA.4.6	SARS-CoV-2 CH.1.1	SARS-CoV-2 BF.7	SARS-CoV-2 BQ.1	SARS-CoV-2 XBB.1.5
GB-0669	12	63	19	39	6.4	9.6	12	4.9	9.4	3.8	8.9	8.5	8.8
CV3-25	220	1100	180	800	64	160	100	62	170	28	78	94	93

≤ 50 ng/ml
51-200 ng/ml
201-1000 ng/ml
>1000 ng/ml

The Class 4 anti-RBD mAb, PRO-37587, shows improved neutralization potency and increased breadth across SARS-CoV-2 Omicron variants compared to reference mAb, S2X259



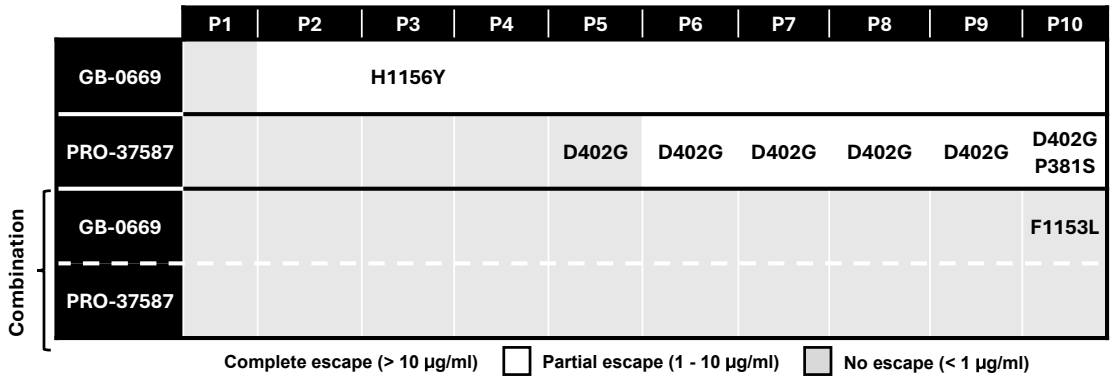
Pseudovirus Neutralization, EC50 [ng/ml]									
	SARS-CoV-1	WIV1	SARS-CoV-2 D614G	SARS-CoV-2 Delta	SARS-CoV-2 BA.2	SARS-CoV-2 BA.4/5	SARS-CoV-2 BQ.1.1	SARS-CoV-2 XB.1.5	SARS-CoV-2 EG.5.1
PRO-37587	0.77	0.38	22	12	27	15	38	12	12
S2X259	2.2	1.7	21	25	ND*	ND*	ND*	ND*	ND*

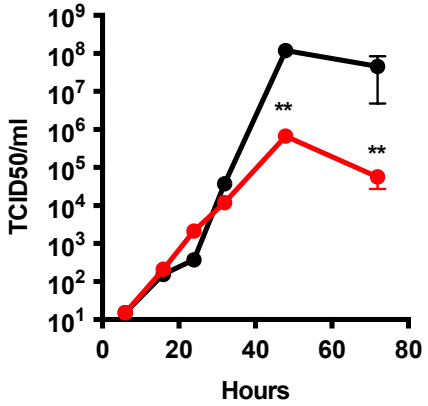
≤ 50 ng/ml
51-200 ng/ml
201-1000 ng/ml
>1000 ng/ml

ND (Not determined), poor or incomplete best fit value, unable to determine the confidence interval*

The combination of GB-0669 and PRO-37587 exhibits a high resistance barrier to in vitro live SARS-CoV-2 BA.1 escape; escape-associated mutations are highly infrequent across SARS-CoV-2 variants and non-SARS-CoV-2 sarbecoviruses

Escape of SARS-CoV-2 BA.1 live virus from monoclonal and combination therapies in vitro





** Mutations associated with GB-0669 and GB-0669 + PRO-37587 combination treatment did not confer an impact on viral fitness*

Frequency of escape mutations across circulating SARS-CoV-2 variants and non-SARS-CoV-2 sarbecoviruses

Mutation	Region	Relative Frequency SARS-CoV-2 Variants (Mar 2023 - Mar 2024)	Relative Frequency SARS-CoV-2 Variants (Jan 2020 - Mar 2024)	Relative Frequency non-SAR-CoV-2 Sarbecoviruses
381S	Class 4 RBD (PRO-37587)	0.00010	0.00016	0.0175
402G	Class 4 RBD (PRO-37587)	0	0.0000095	0
381S + 402G	Class 4 RBD (PRO-37587)	0	0	0
1153L	S2 stem helix (GB-0669)	0.0000074	0.000026	0
1156Y	S2 stem helix (GB-0669)	0.00012	0.000055	0

- The GB-0669 + PRO-37587 combination shows no evidence of complete or partial escape through 10 passages
- All escape mutations identified are present at a very low frequency in SARS-CoV-2 genomic sequences deposited over the past year or since the beginning of the pandemic
- With the exception of P381S, these mutations were also not observed across a range of non-SARS-CoV-2 sarbecoviruses
- Mutations in the RBD that leads to escape from PRO-37587 are unlikely to occur due to a cost in viral fitness

Conclusions

Using our platform and by focusing on epitopes less prone to immune escape, we generated two half-life extended antibodies which target the SARS-CoV-2 Spike S2 stem helix and Class 4 site on the RBD, both of which retain broad activity across SARS-CoV-2 variants and non-SARS-CoV-2 sarbecoviruses

- This unique combination of antibodies has the potential for pandemic response/preparedness
- Contact residues identified in the epitopes of both GB-0669 and PRO-37587 are highly conserved across SARS-CoV-2 variants and related sarbecoviruses
- Mutations selected in vitro that confer escape from GB-0669 are unlikely to arise because of limited population-level immune pressure
- Mutations in the RBD selected in vitro that confer escape to PRO-37587 are unlikely to occur due the associated cost to viral fitness
- This approach used for SARS-CoV-2 validates a framework for identifying broadly neutralizing mAbs against other genetically diverse pathogens

GB-0669 is currently undergoing Phase I evaluation in healthy volunteers: #89 “First-in-human study of a novel half-life extended monoclonal antibody (GB-0669) against SARS-CoV-2 and related sarbecoviruses”, presented by Dr. Dinesh De Alwis

Acknowledgements

Pre-clinical
Grace Marden
Eric Carlin
Hongru Li
Geetika Sharma
Leslee Morrow
Giovanni Tosi
Ross Federman
Nicole Leon Vargas
Alan Leung
Jon Fallon
Amarendra Pegu
Heather Van Epps
Kristen Hopson
Daria Hazuda

DNA Team
Robin Green
Brian Patuto
Babu Ram
Prasad Saravanan

Protein Sciences
Nadine Shaban
Monica Menzenski
Yanyan Lu
Avery Farnham
Darren Ferguson
Brett Blakely
Ben Manning
Sandra Sipsey
Adi Ravipati
Lucy Xu
Alexandra Gurney
Atreyi Bhattacharya
Lyle McPherson
Ramsey Fadlalla
Nathan Wong
Alex Ayoub
Patrick Brophy
Mark Benhaim
Nate Joh
Adam Root

Clinical
Francesco Borriello
Dinesh De Alwis
Gavin Koh
Nicholas Robertson
Anna Allen
Lovely Goyal
Loona Borgohain
Syam Chandrala
Pam Farmer
Stephanie Straley
Rounak Nassirpour
Smita Clements
Alex Synder

Tech Ops
Lisa Wyman
Tyson Fetzer
Vikram Sadineni
Guy DelloRusso
Farrah Chaudhary

Regulatory
Andrew Robertson
Irene Figari

Compliance
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Sarah Hurley

Project Management
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Novel Therapeutics
Anne Jecrois
Joe Garlick
Claudio Perez
Max Zimmerman
Eugene Palovcak
Dana Lord

Comp Sci.
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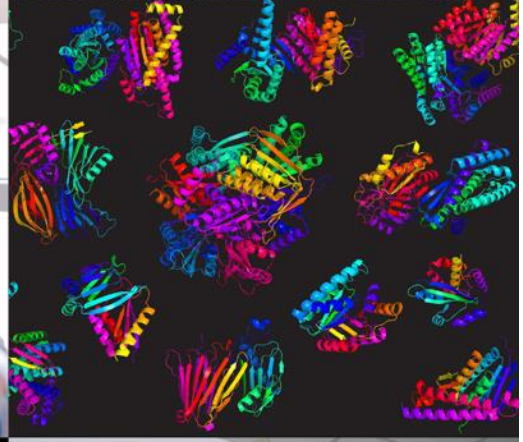
Jenhan Tao
Pam Russell
Brett Hannigan
Gevorg Grigoryan



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