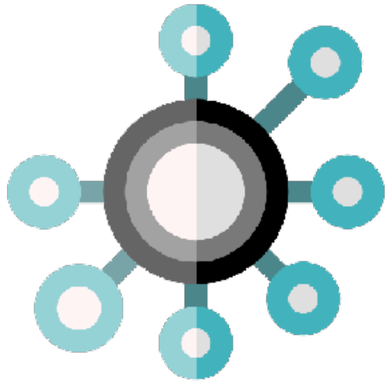
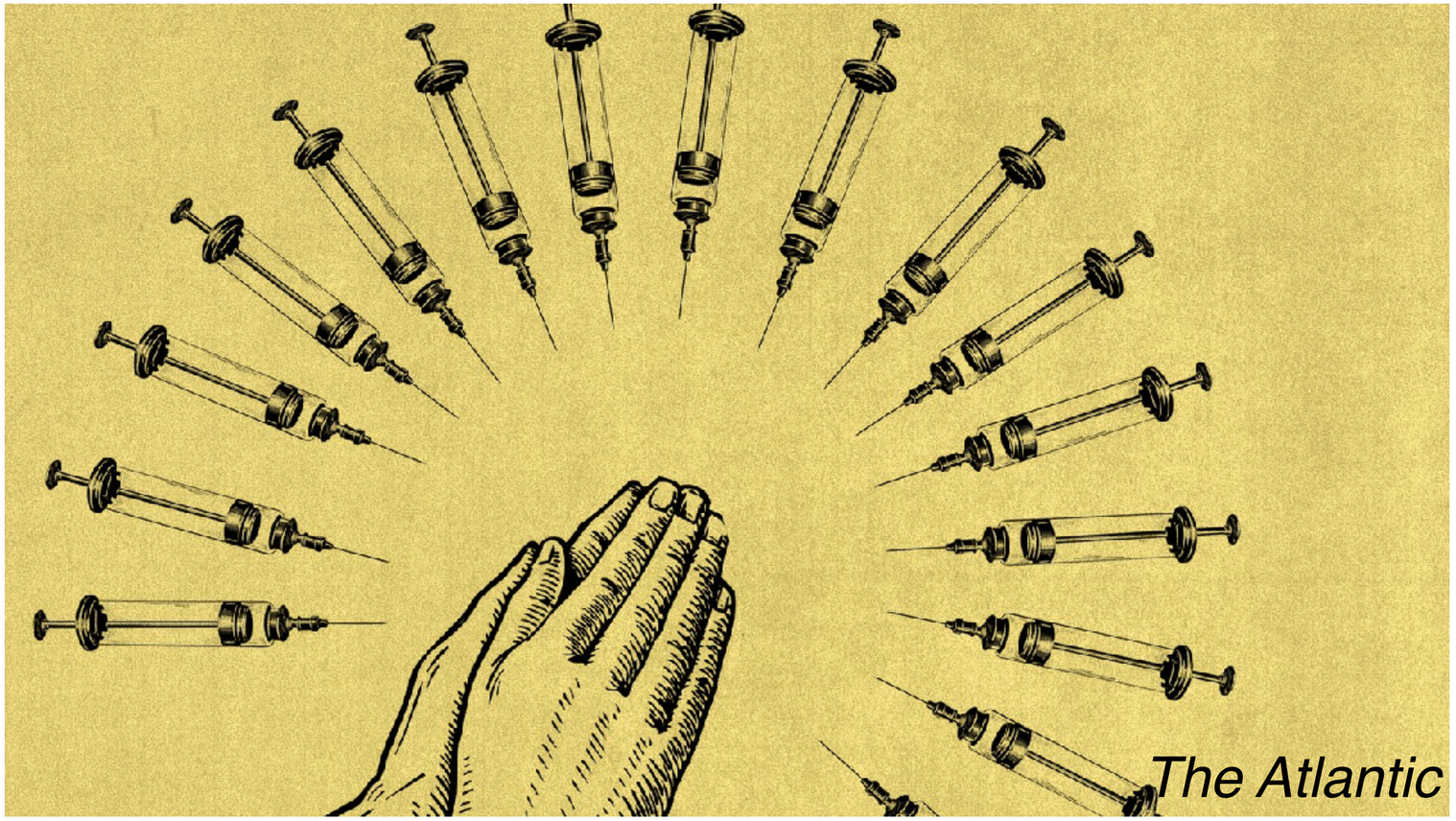
Coronavirus Immunotherapeutics Consortium



CoVIC

COVIC-19 Therapeutics Accelerator:
The Bill & Melinda Gates Foundation, Mastercard,
The Wellcome Trust and others

NIAID U19 AI142790-02S1
and the GHR Foundation



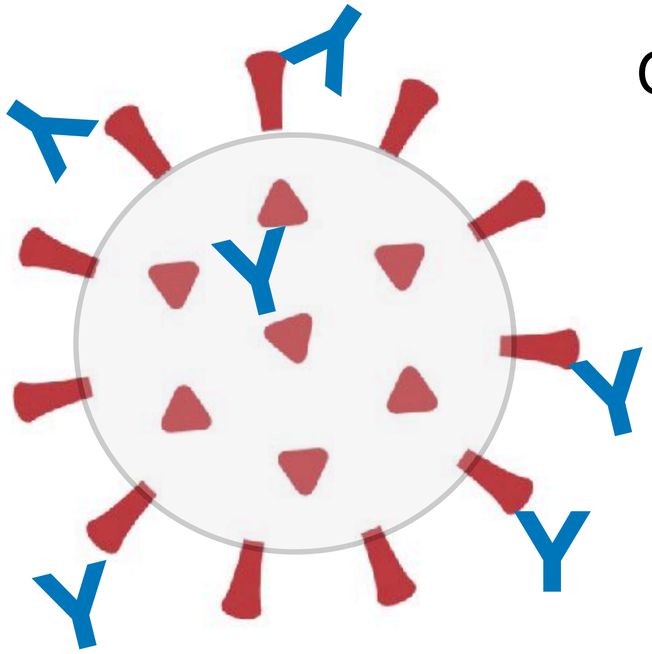
We are praying for vaccines.

But, there will be those who are not vaccinated,

not vaccinated *yet*,

who can’t be vaccinated,

or in whom vaccines didn’t take or didn’t last



One goal of a vaccine is production of antibody.

You can deliver antibody
right away, as a drug
“Antibody therapy or Immunotherapy”

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Use cases of antibody therapy

Treatment

Mild to moderate COVID-19

Treatment for individuals who are at high risk for severe disease

Prophylaxis

Health Care Workers and First Responders

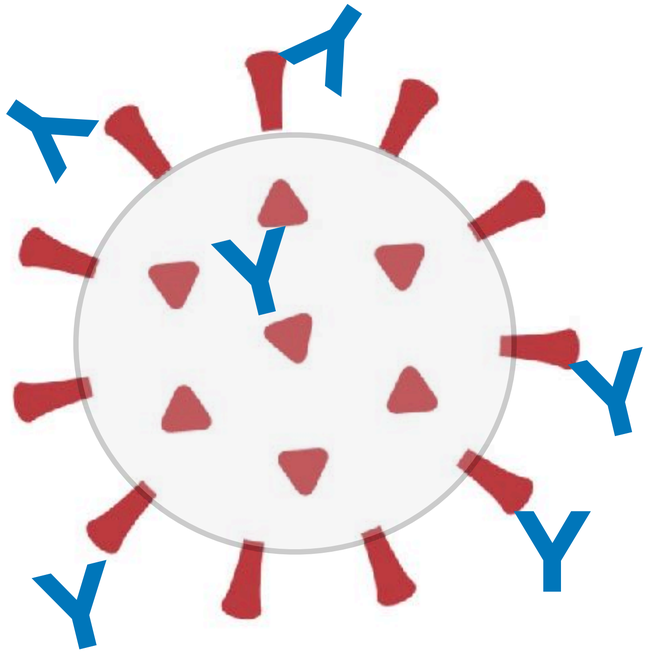
High risk Groups

Disease Outbreaks

Immediate protection for:

- Health care workers and first responders
- High risk groups (e.g., pregnant women)
- Ring vaccination-type response to disease outbreaks

CoVIC



Millions of possible antibodies,
which 1 or 2 are best?
What makes them the best?
How do we know? (Which assays/features)
Cocktail: what's the best pairing?
Different labs' assays, different results?

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Goals of CoVIC

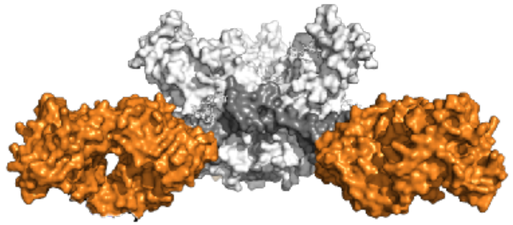
- **Primary - Translational**
  - Evaluate promising therapeutic candidates against SARS-CoV-2 in independent, standardized platforms
  - Identify cocktail of human neutralizing monoclonal antibodies against Spike to prevent severe COVID-19 in low and middle income countries
- **Secondary - Basic**
  - How do anti-SARS-CoV-2 antibodies work? Landscape of activities: CoVIC-DB database
  - Which features at which epitopes? which features correlate with protection?
  - Evaluate current assays for future use (i.e. do in vitro assays and animal models adequately correlate with success in humans? If not, why not?)

Why do a broad study?


ATTENTION !
EBOLA !
Beaufort
UN
UN

2013:

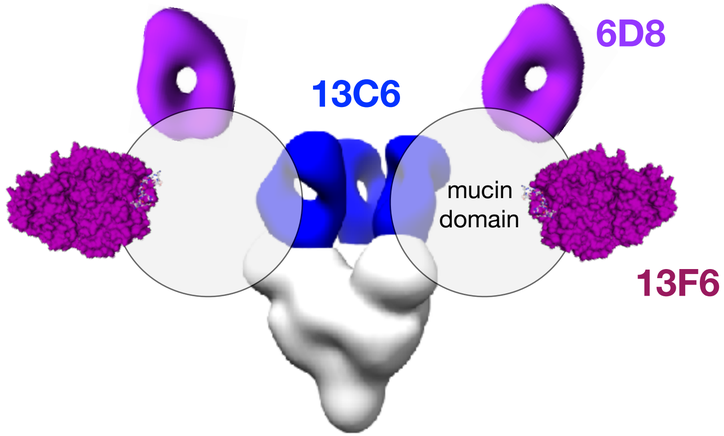
Neutralizes, Didn't protect



KZ52

KZ52 monotherapy
CHO cell production
50 mg/kg days -1, 4
0% survival
(Oswald et al)

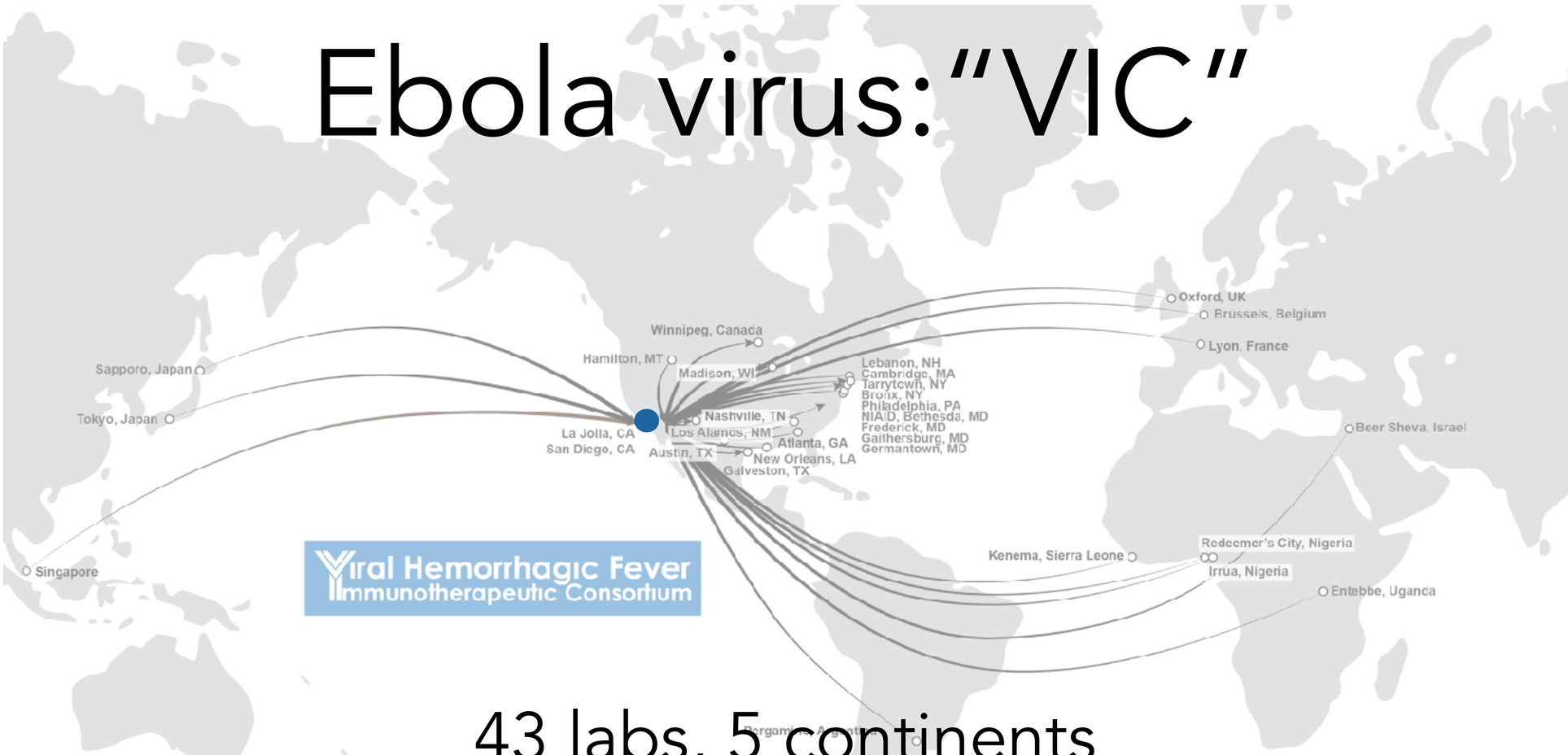
Protected, Don't neutralize



MB-003 cocktail
CHO or *Nicotiana*
50 mg/kg (CHO) or
16.7 mg/kg (*Nicotiana*) days 0,4,7
50% (CHO) or 100% (*Nicotiana)* survival
(Pettitt, Olinger et al)

Need a combination? Something about Fc?
Neutralization not enough?
Not measuring neutralization properly?
Found the exceptions so far, and not the rule?

Ebola virus: "VIC"



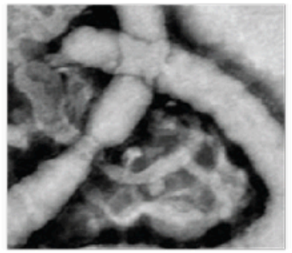
43 labs, 5 continents

academic-industry-government

168 mAbs - 32 features measured side-by-side

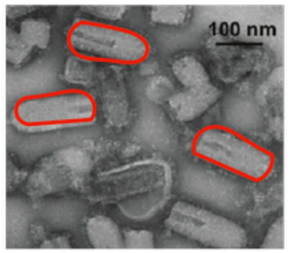
Three different neut. assays & un-neut. %

Incubate virus with mAb
Infect Vero cells



Authentic EBOV

Ebola-ΔVP-Luc



rVSV-EBOV GP

Detect	KZ52 2° Alexa-Fluor	LUC	EGFP
sGP	✔	✔	✘
	BSL-4	BSL-2/3	BSL-2+
Group	Dye USAMRIID	Kawaoka U Wisc.	Chandran Einstein

(Micrographs: EBOV: Golding et al. *Sci Rep.* PMID: 27212232; DVP30: Halfmann et al. *PNAS*, PMID: 18212124; VSV: Ivanov et al. *Virus Res.* PMID: 21963663; images are scaled relative to rVSV)

Saphire et al. *Cell* 2018 PMID: 30096313

Relationship between Ebola virus neutralization and protection

(1) Bin by epitope

Cap

GP1/Head

Mucin

Base

Fusion

GP1/Core

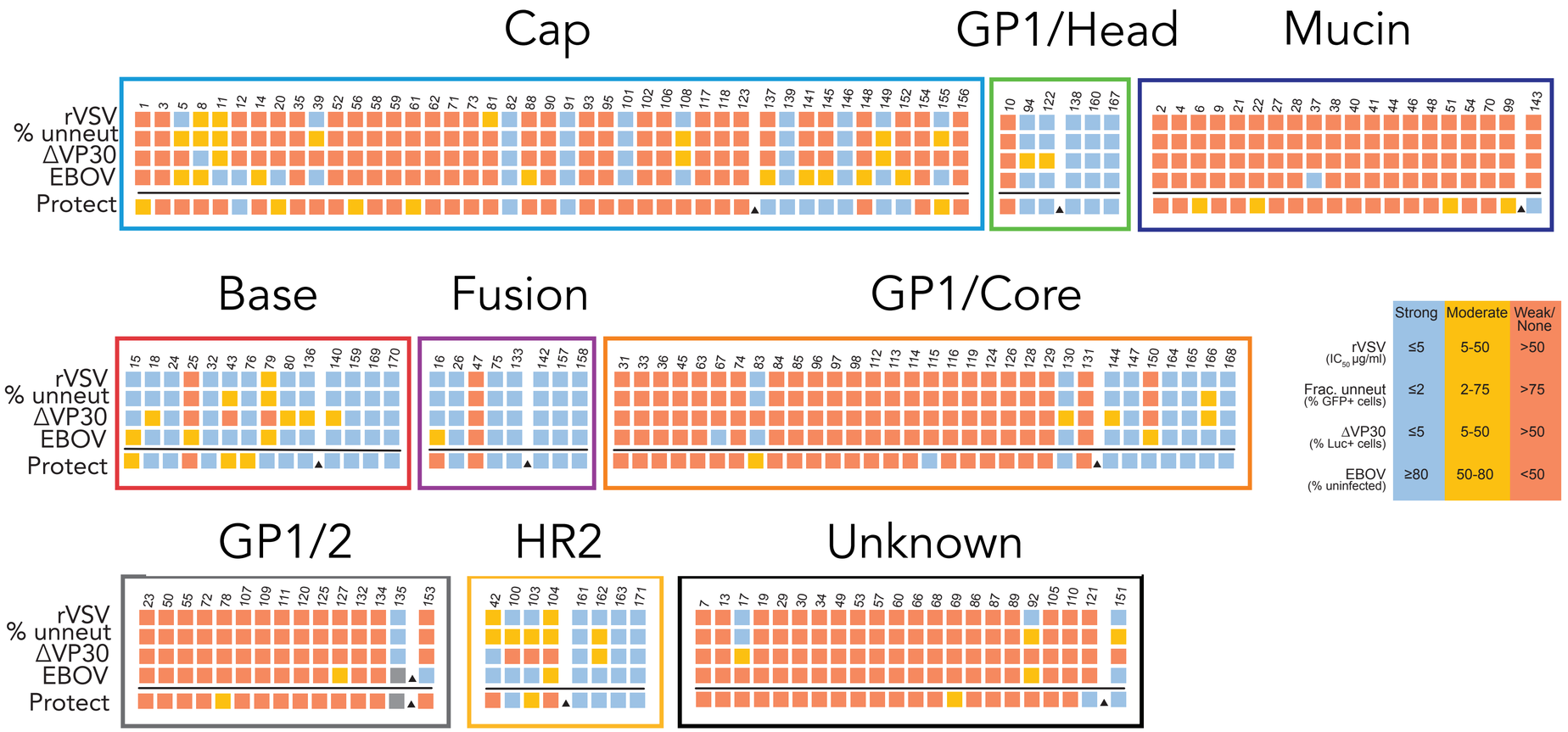
GP1/2

HR2

Unknown

Saphire et al. *Cell* 2018 PMID: 30096313

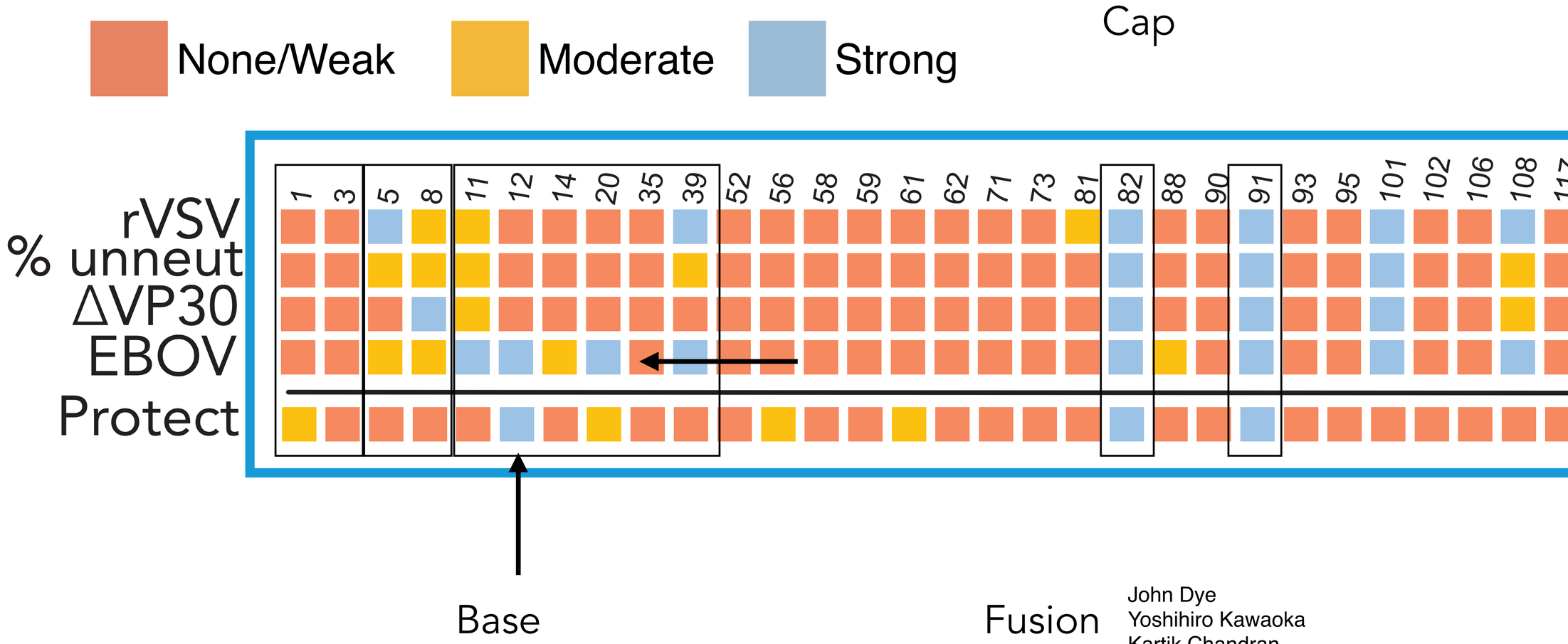
Binned by epitope, compared by assay



Saphire et al. *Cell* 2018 PMID: 30096313

John Dye, USAMRIID
Yoshihiro Kawaoka, Wisc.
Kartik Chandran, Einstein

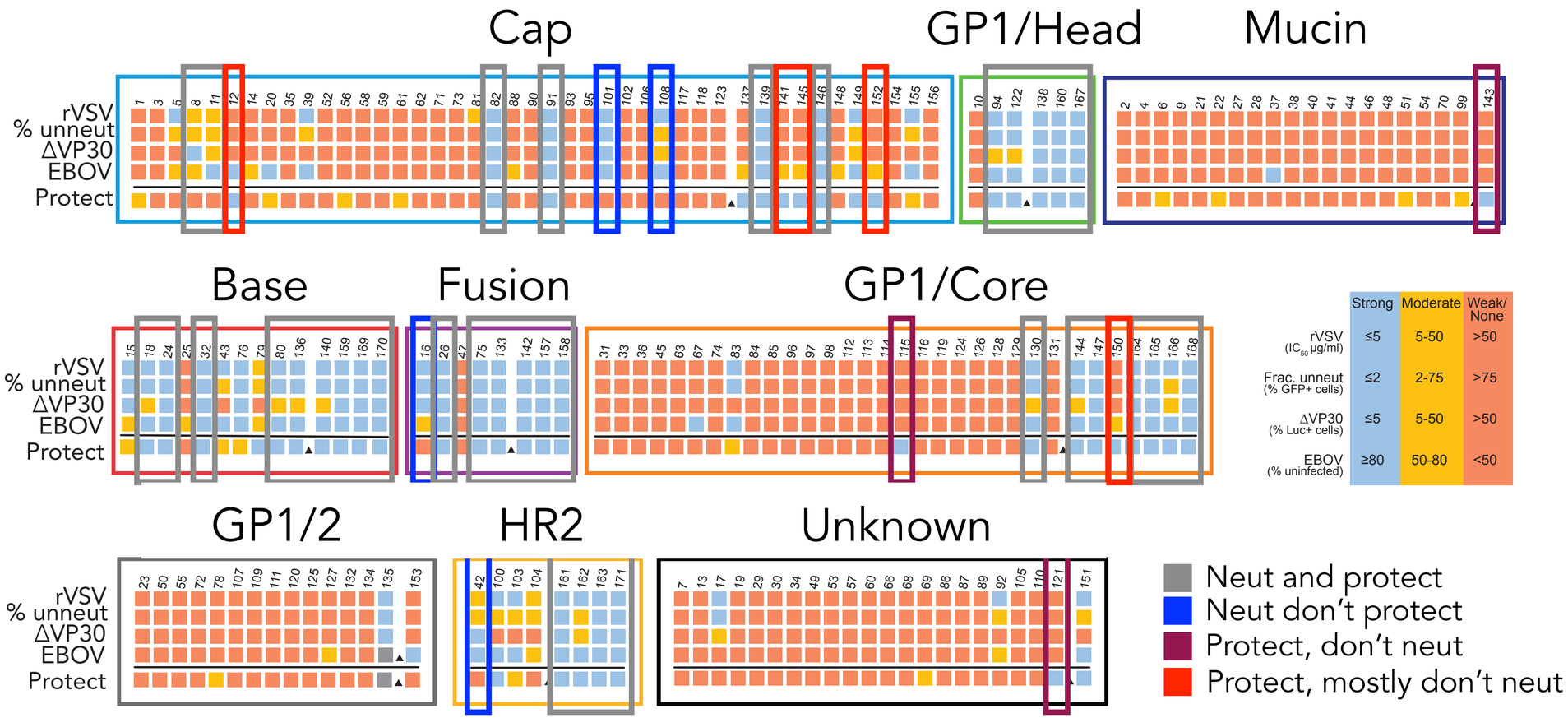
Relationship between Ebola virus neutralization and protection



John Dye
Yoshihiro Kawaoka
Kartik Chandran

Saphire et al. *Cell* 2018 PMID: 30096313

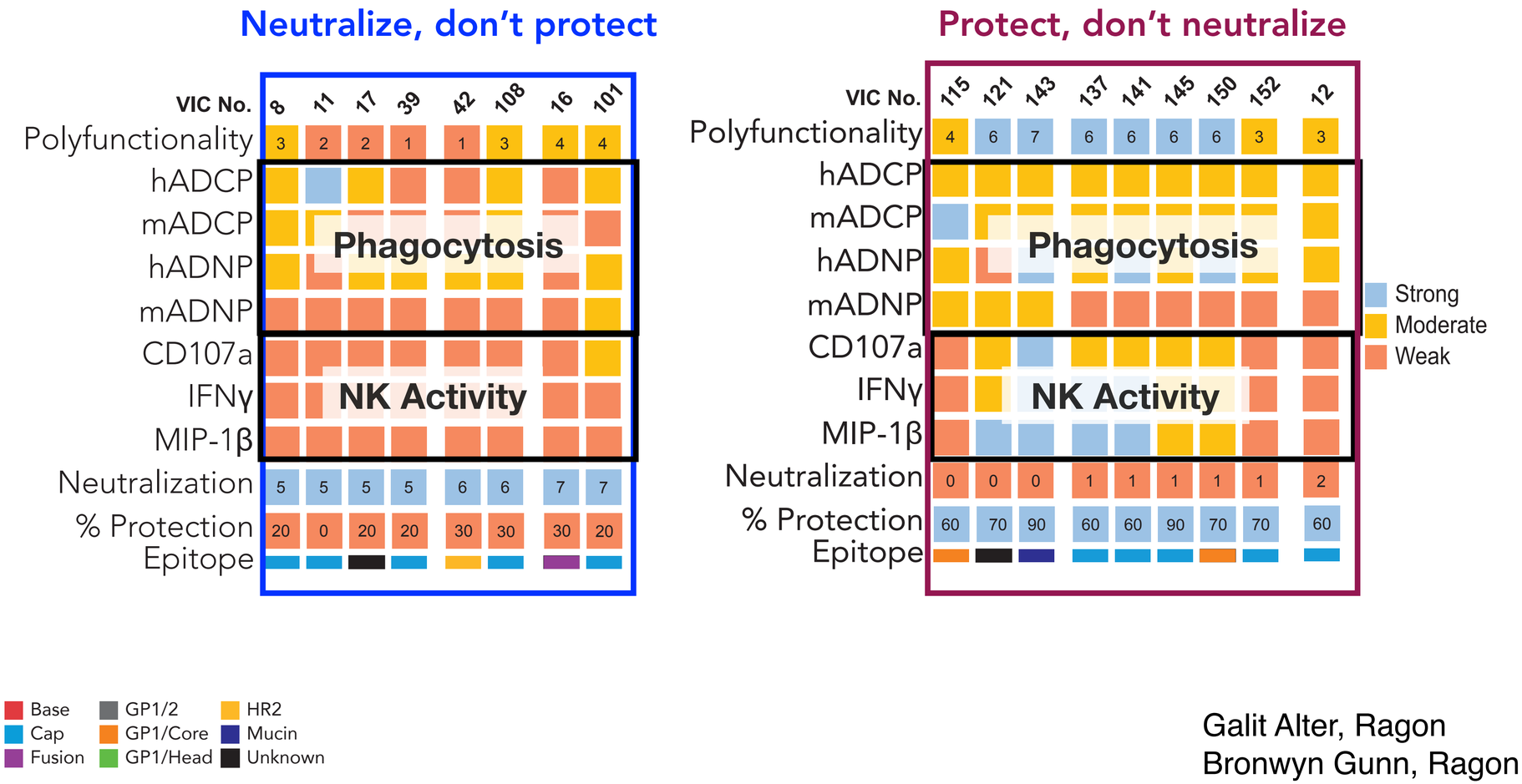
Relationship between neutralization and protection



Saphire et al. *Cell* 2018 PMID: 30096313

John Dye, USAMRIID
Yoshihiro Kawaoka, Wisc.
Kartik Chandran, Einstein

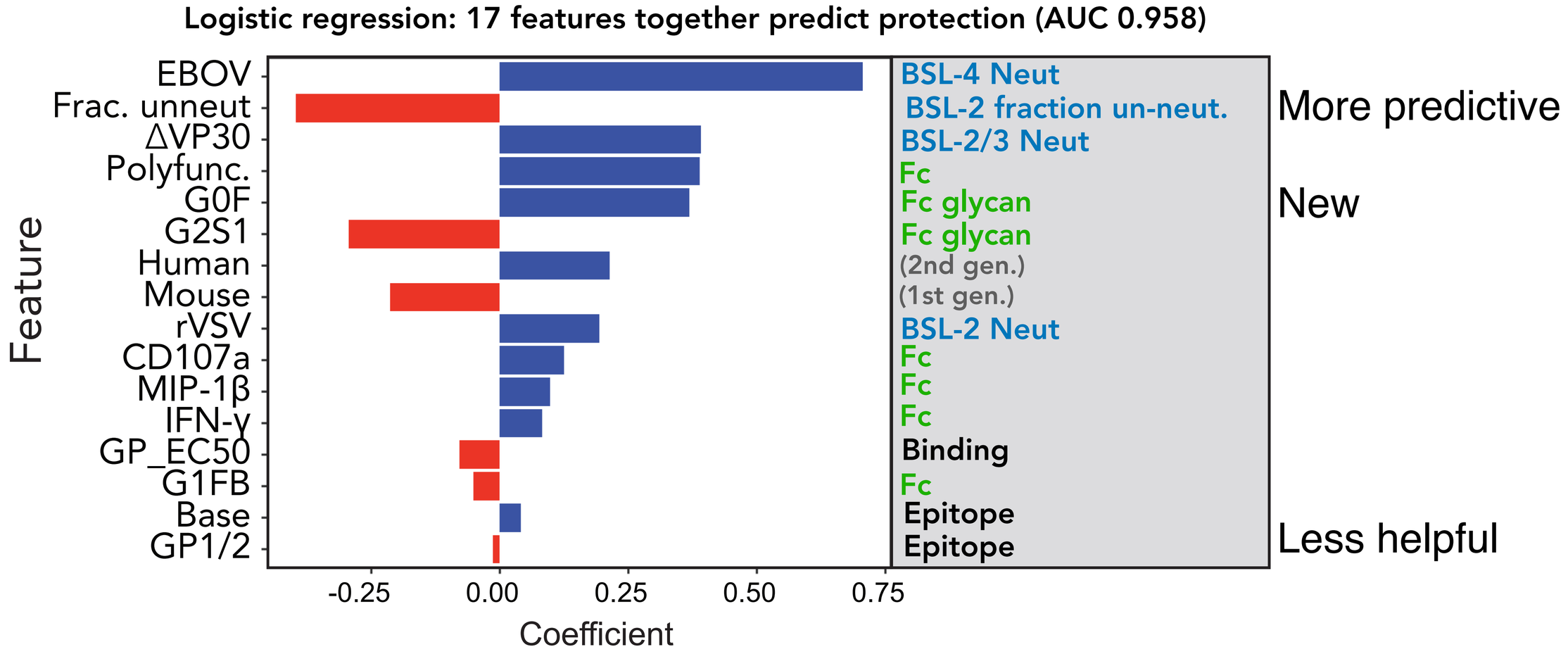
Fc function contributes to *in vivo* protection



Saphire et al. *Nature Immunology* 2018 PMID: 30333617

Galit Alter, Ragon
Bronwyn Gunn, Ragon
Sharon Schendel, LJI

Antibody features that predict protection



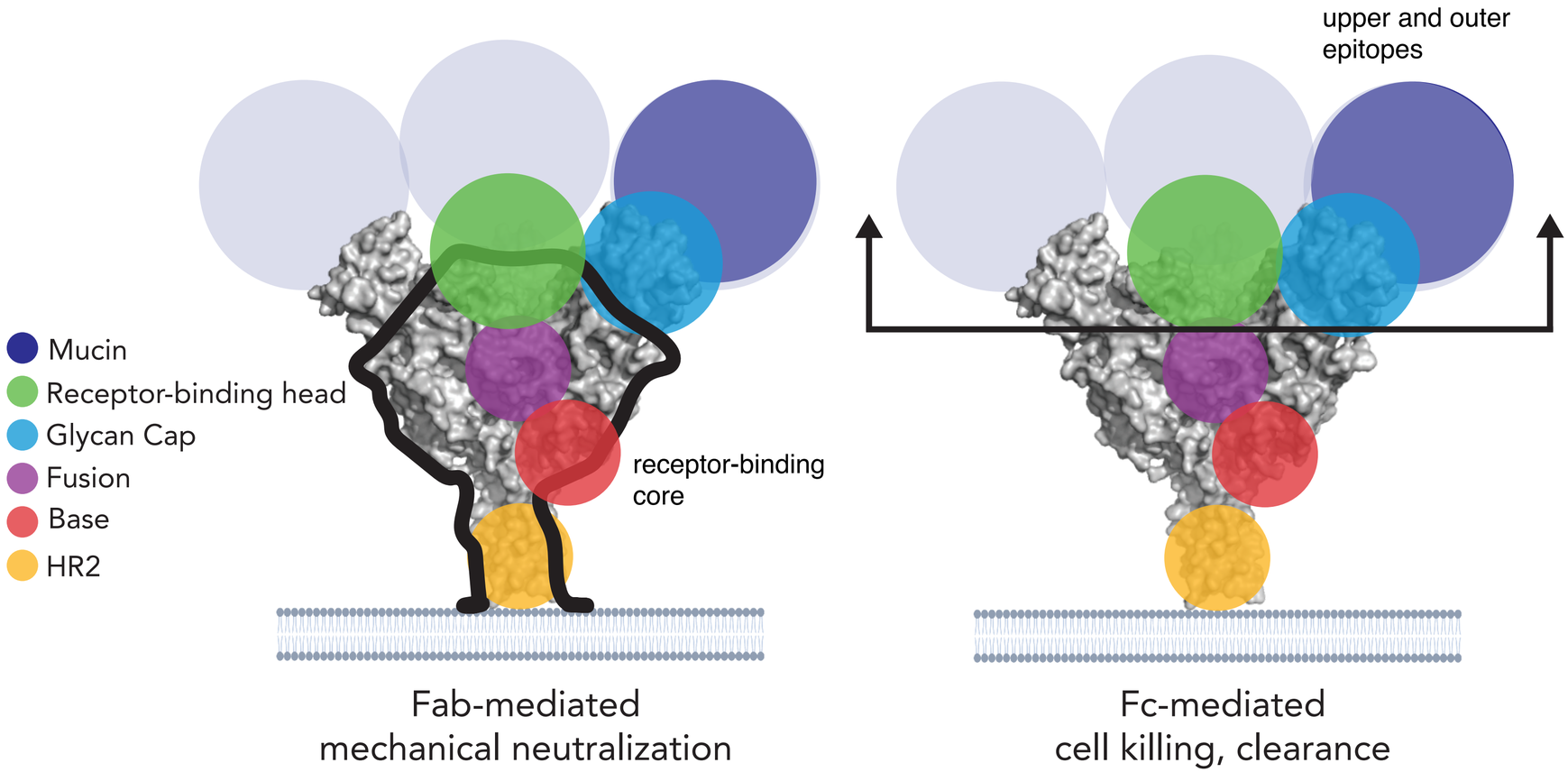
Coefficients that weight individual features in the equation that predicts protection

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

Kristian Andersen, TSRI
Bette Korber, LANL

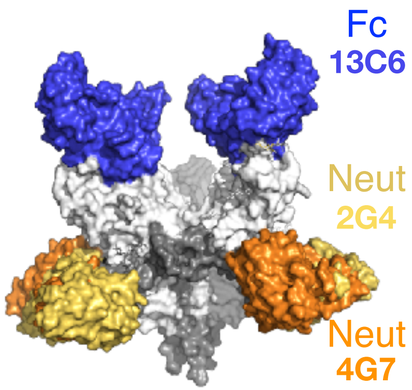
Saphire et al. *Cell* 2018 PMID: 30096313

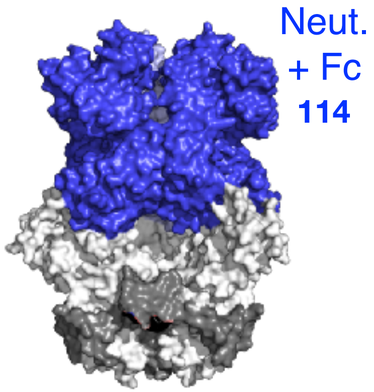
We want both features in cocktails

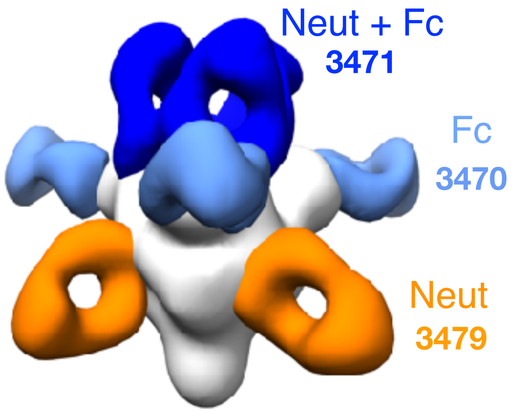


SARS-CoV2? Complementary resistance patterns, synergistic binding and neutralization…

Clinical testing: PALM trial

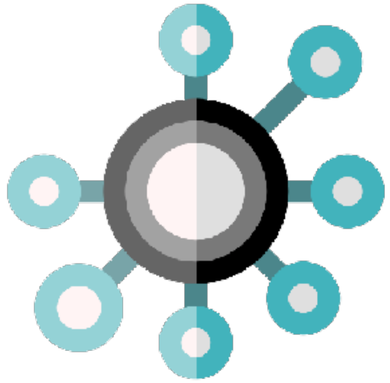






	ZMapp cocktail	**mAb 114 monotherapy**	**REGN-EB3 cocktail**
survival	50% (85/169)	65% (113/174)	66% (103/155)

Mulangu et al. *N. Engl. J. Med.* 2019 PMID: 31774950



CoVIC

- Evaluate therapeutics heading to clinical trials
- Find therapeutics we can mobilize to low- and middle-income countries

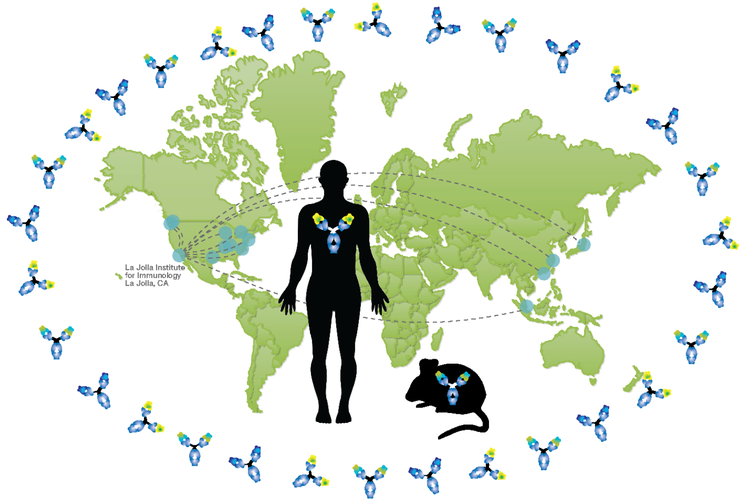
Launch:

COVIC-19 Therapeutics Accelerator:
The Bill & Melinda Gates Foundation, Mastercard, The Wellcome Trust and others

Expansion:

NIH/NIAID U19 AI142790-02S1 and the GHR Foundation

CoVIC workflow



donated antibodies

intellectual property protected
Can use data for IND

sample blinding

aliquot & distribute

potency, efficacy, structural analyses

catalog in CoVIC-DB database

analyze & downselect

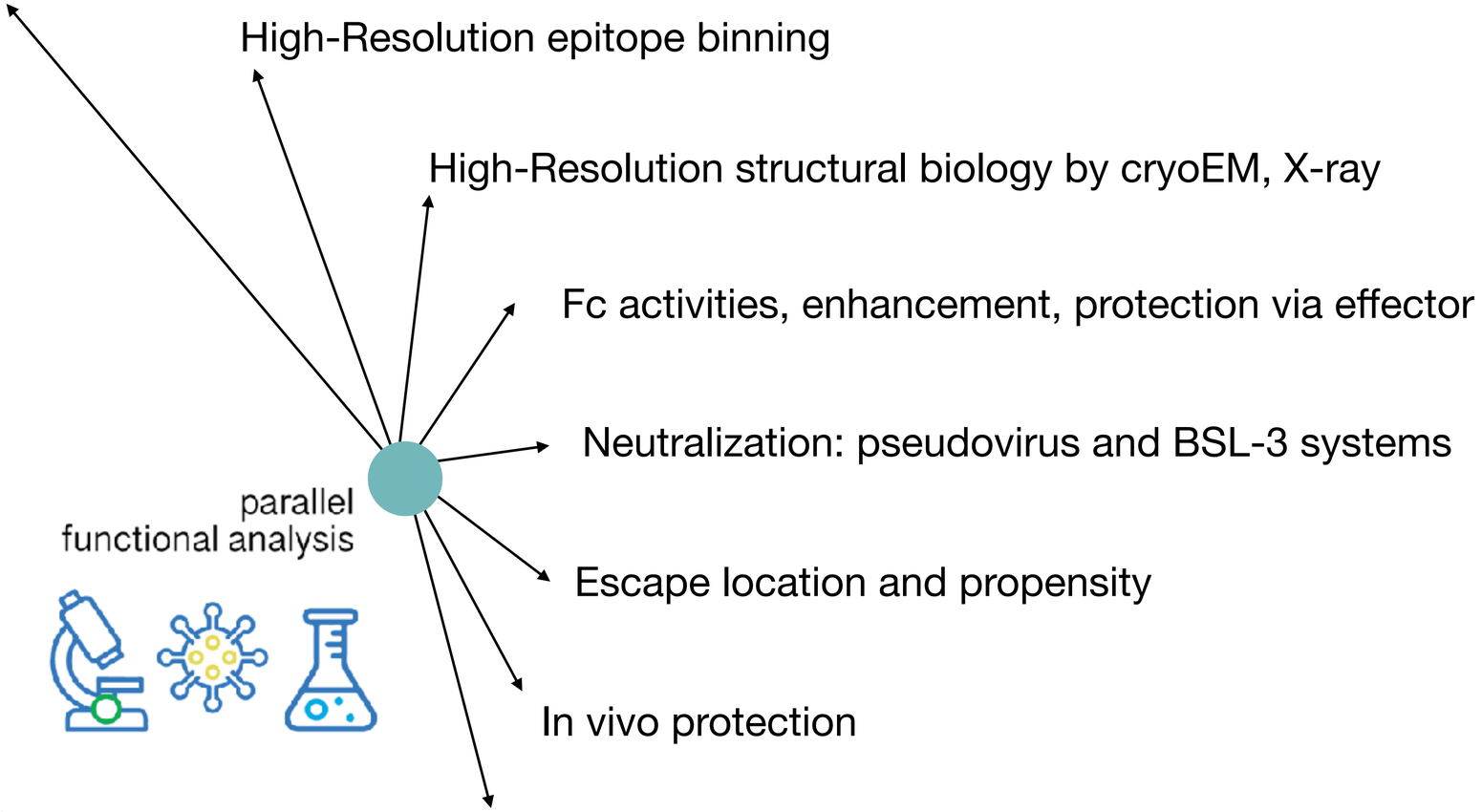
sequence optimization

therapeutic antibody cocktails

CoVIC

CoVIC

Binding (on/off rates) to forms, regions and variants of spike



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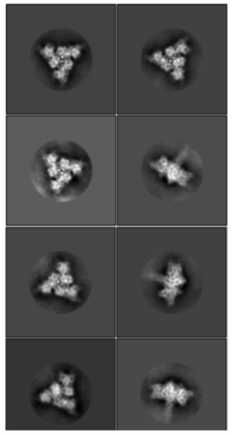
High-resolution structural analyses

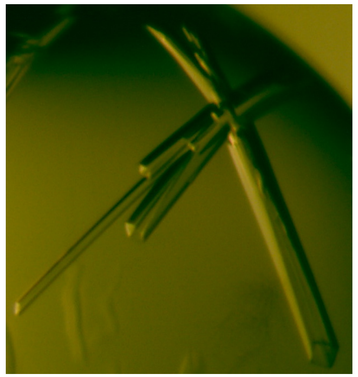


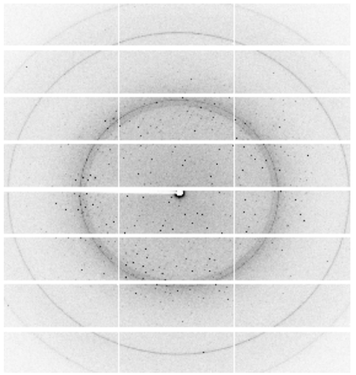
Cryo-electron Microscopy

mAb Fab domains in complex with:

- Full-length S
- RBD or NTD
- transmembrane surface spike

Intact mAbs in complex with FcR and Spike





X-ray Crystallography

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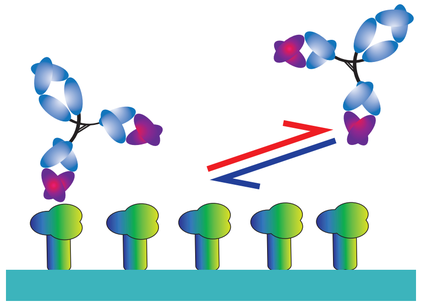
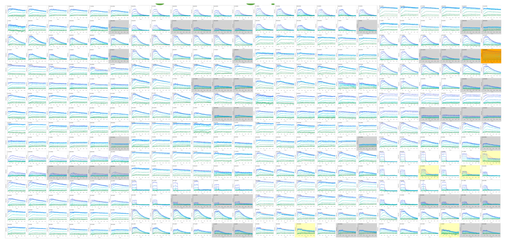
Erica Ollmann Saphire

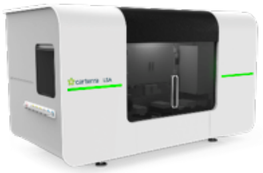
CoVIC

Binding analyses

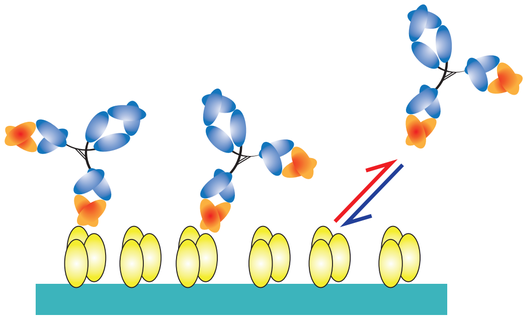


S protein binding kinetics
Block ACE2 binding
Avidity
FcγR binding

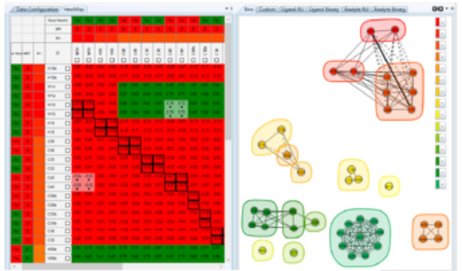




LSA Platform



Epitope binning



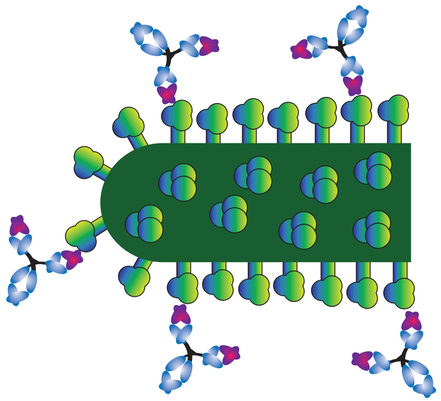
- Binding kinetics analyses and epitope binning using standardized, structural biology-grade antigens (**reference strain**, **D614G and other variants of S**) in a **GLP setting** (Tomaras lab, Duke)

Georgia Tomaras
Duke Human Vaccine Institute
Duke University School of Medicine

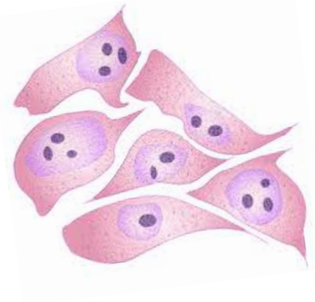
Daniel Bedinger
carterra

CoVIC

Pseudovirus neutralization

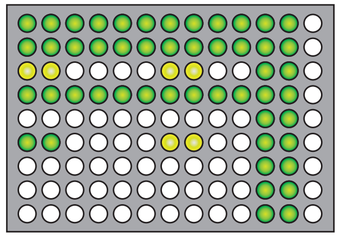


VSVΔG expressing SARS-CoV-2 S (reference strain or D614G) and GFP



Vero cells

Measure fluorescence



Calculate IC_{50}, IC_{90}, fraction neutralized

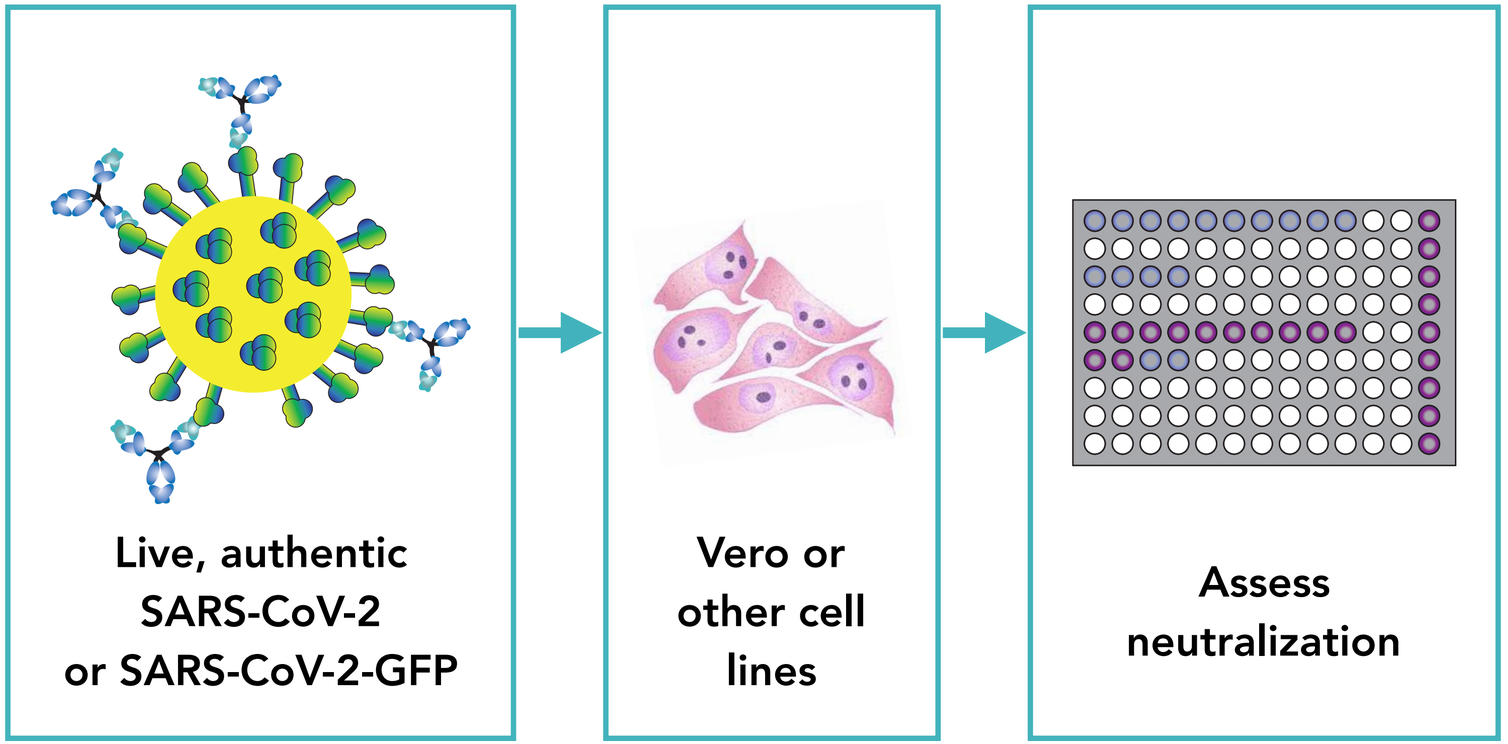
- Lentivirus platform is licensed to Nexelis by NIAID Vaccine Research Center

Luc Gagnon

nexelis

CoVIC

Authentic virus neutralization



- Neutralization assays at BSL-3 with authentic virus
- Data will be compared against neutralization of pseudovirus systems

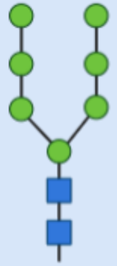
utmb Health
Galveston National Laboratory

(pending)

CoVIC

Immune profiling of mAbs against SARS-CoV-2 Spike

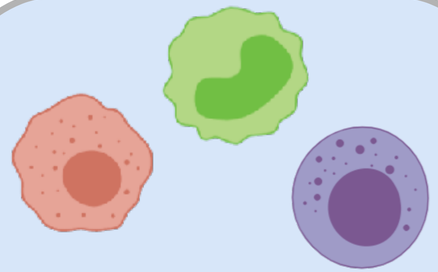
mAb-FcR binding profiles



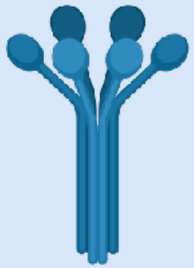
mAb glycosylation

mAb-dependent phagocytosis

NK cell degranulation



Innate immune effector cell activation



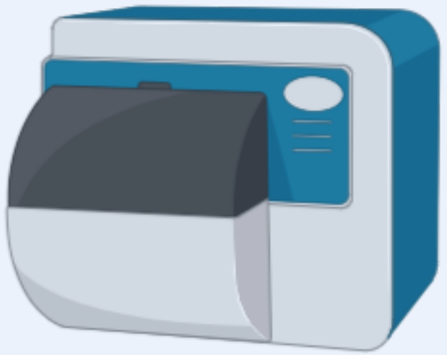
complement deposition

Ragon Institute of MGH, MIT and Harvard

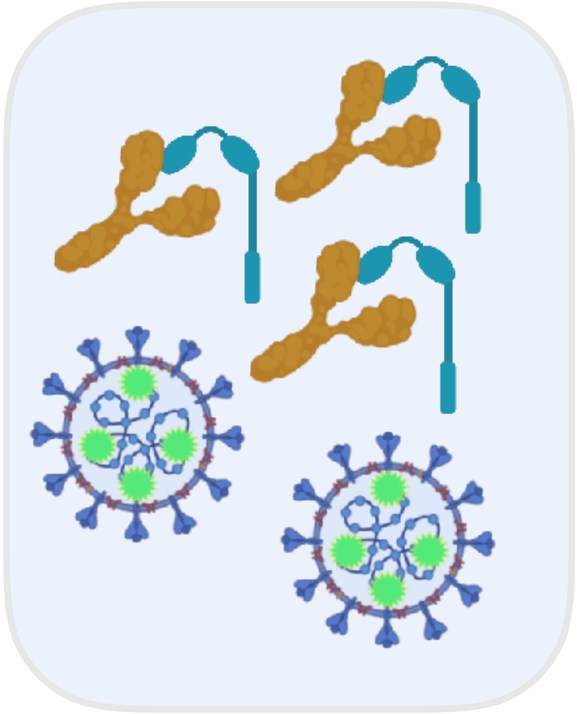
Galit Alter

High-throughput systems serology to profile Fc-driven activities of anonymized mAbs.

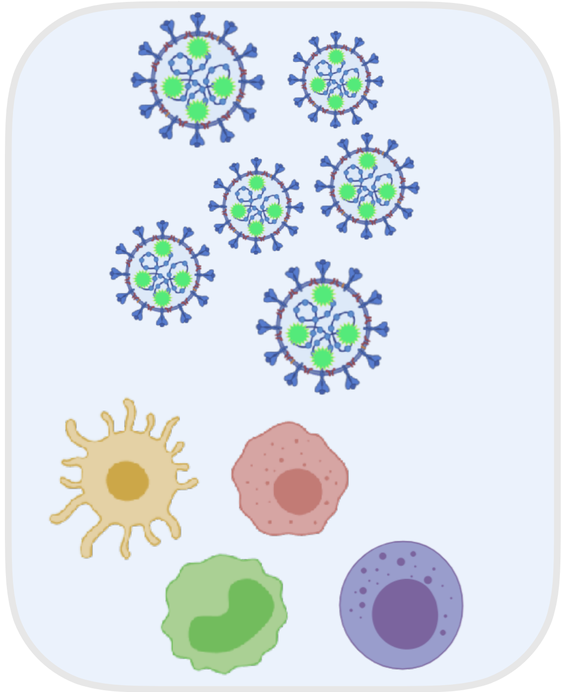
Cellular studies: Fc function and resistance of to ADE



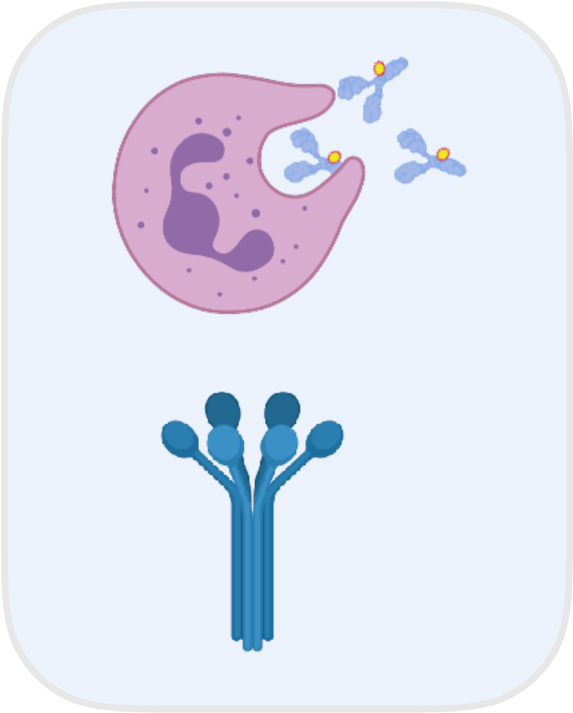
Bio-layer interferometry (BLI) to determine binding kinetics and affinity of mAbs for FcRs



Effect of blocking FcɣR on mAb inhibition of infection by SARS-CoV-2



Propensity to infect primary human myeloid cell types



Determine phagocytic score and complement deposition

Alexander Bukreyev

utmb Health
Galveston National Laboratory

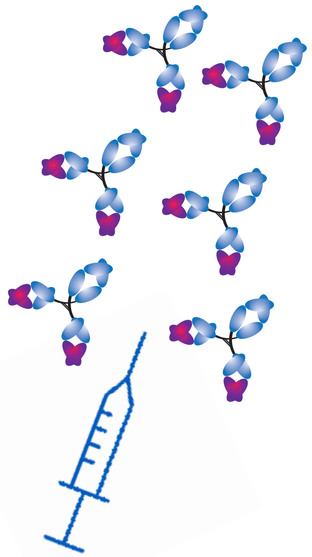
*Xie et al. *Cell Host Microbe* 2020 PMID 32289263

In vivo efficacy

Syrian golden hamster

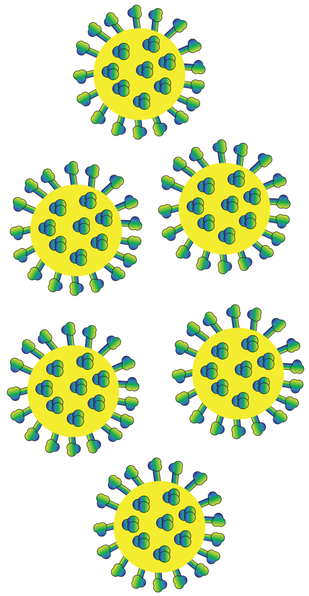
hACE2 tg

NHPs



Treat with mAbs

mAb delivery Pre- or Post-Exposure



Infect with SARS-CoV-2

Survival

Weight loss

Lung titer (at peak replication)

Histopathology

Serum PK

- mAbs will be delivered either pre- or post-SARS-CoV-2 infection
- Initial testing in hamsters and mice transgenic for hACE2
- A subset of mAb combinations will be tested in NHPs

In vivo analyses of antibody half-life and ADE resistance in human Fc-FcRn binding setting*

Triple knock-in mice expressing human ACE2, FcRN and TMPRSS2

- Evaluate novel mouse model for predictive efficacy
- Viral load, kinetics and histopathology
- Half-life, efficacy without ADE

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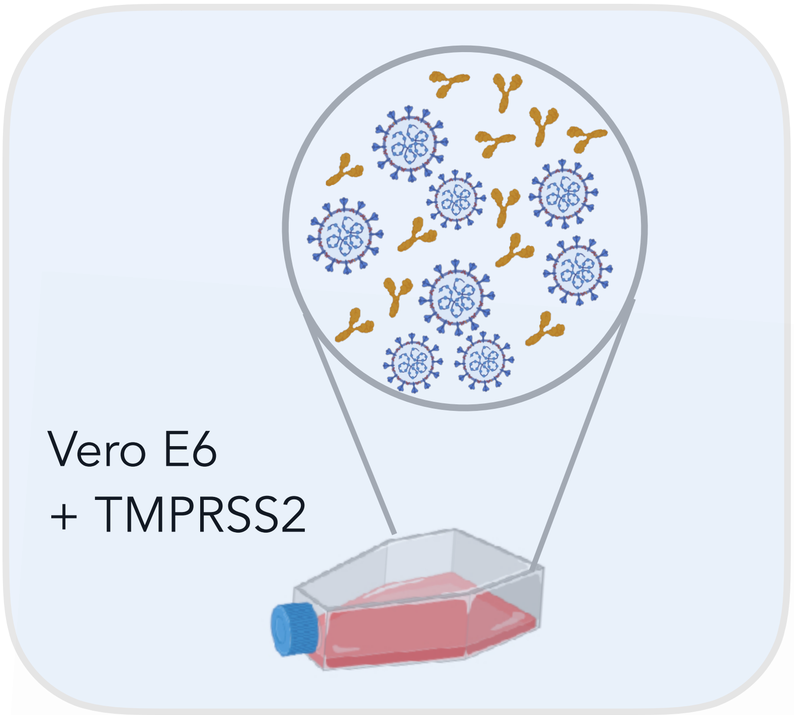
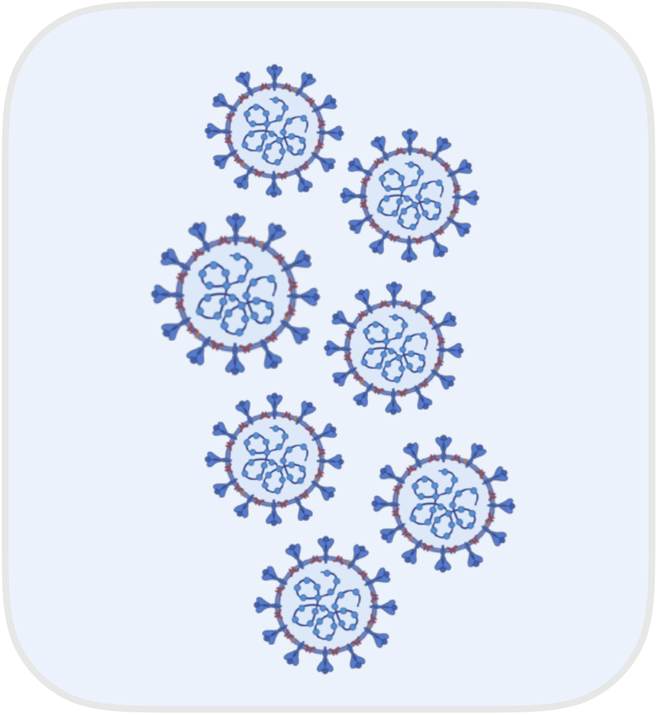
Sujan Shresta

*Antibody owners may opt-in to this study

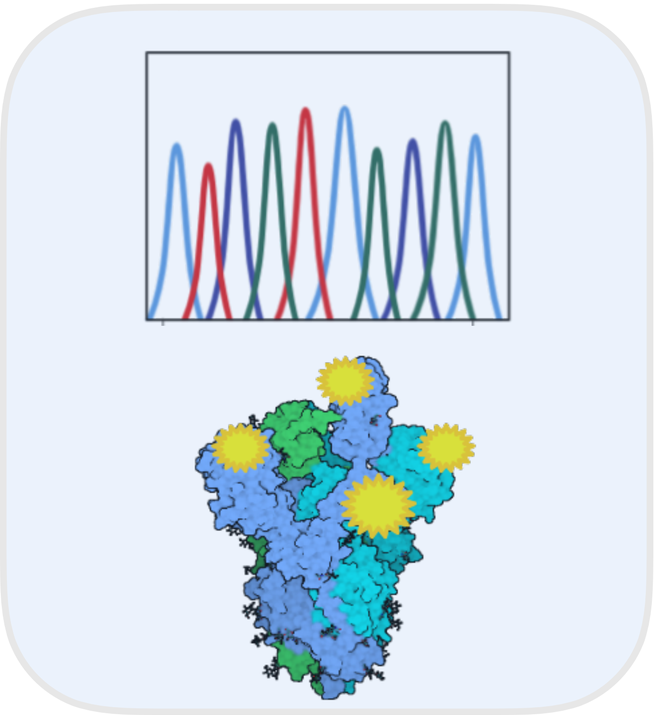
Mapping escape site, resistance in vitro



Incubate cells with 10^2-10^5 virus particles and 0.1-10 µg/mL mAbs



Harvest virus particles



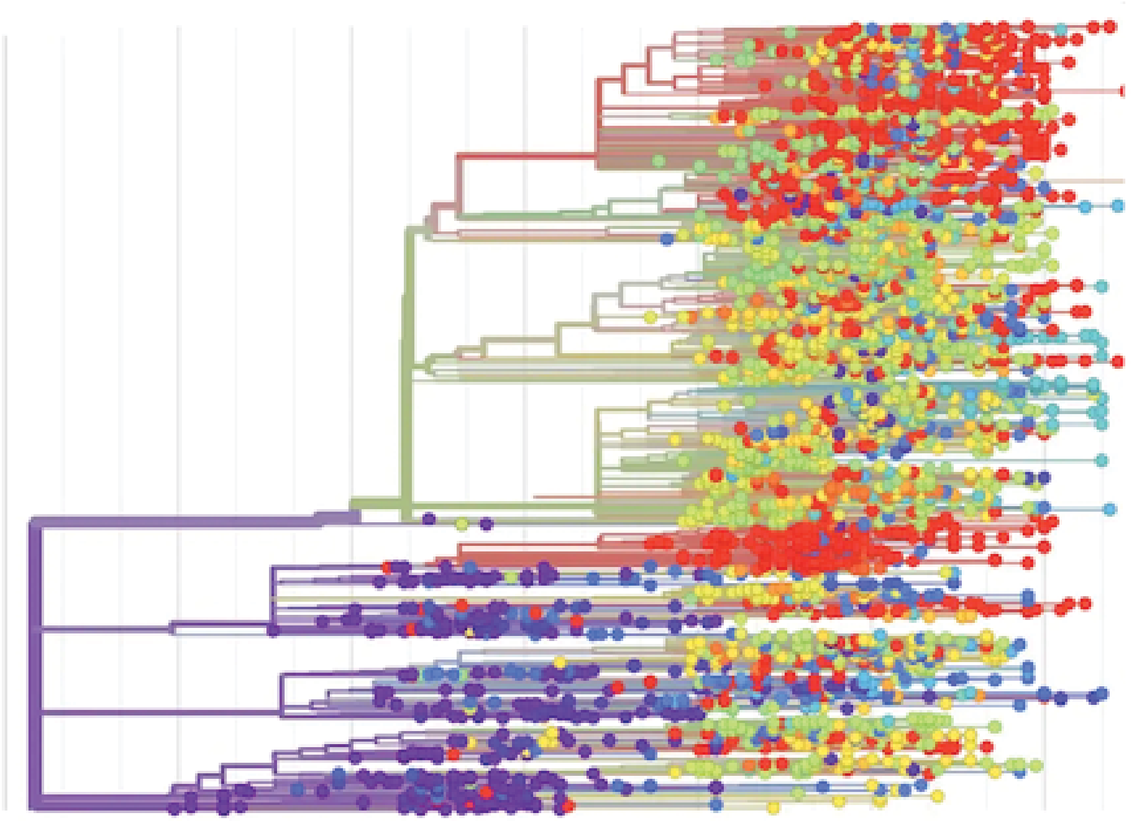
Sequence S protein

to identify mutations

Yoshihiro Kawaoka

WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

Tracking Spike mutations in global human-to-human transmission

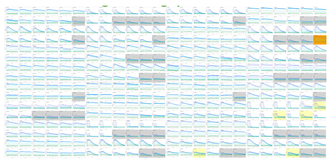


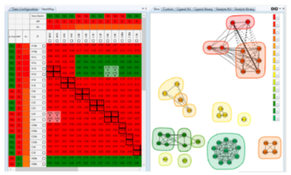
- GISAID: recurrent spatial, regional changes
- New tools for mutational tracking
- Keep researchers abreast of emerging mutations
- Suggest therapeutic candidates that remain responsive to emergent mutations

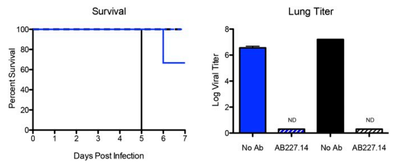
Los Alamos NATIONAL LABORATORY

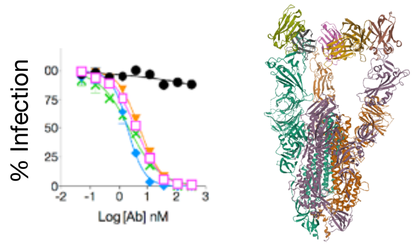
Bette Korber

CoVIC database: a profile of therapeutic antibodies against SARS-CoV-2 Spike protein



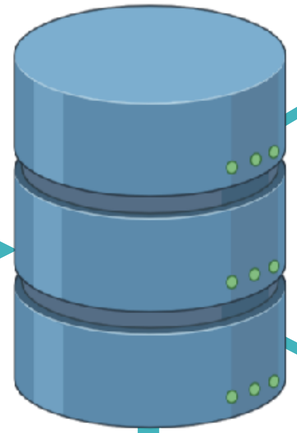






Data generated by partner reference labs

CoVIC Database
CoVIC-DB



Data analysis
Landscape of activities of anonymized mAbs

Contributors can view

- Unblinded data for their mAbs
- How their mAbs compare with other blinded mAbs in the panel

Contributors will receive

- Email confirmation of mAb submission
- Email alerts when new data are available
- Data that can be used for IND filings

Bjoern Peters, LJI

CoVIC

And we’re off!

Thank you Contributors!

Academics

Non-profits

Small biotechs

Large biotechs

Major corporations

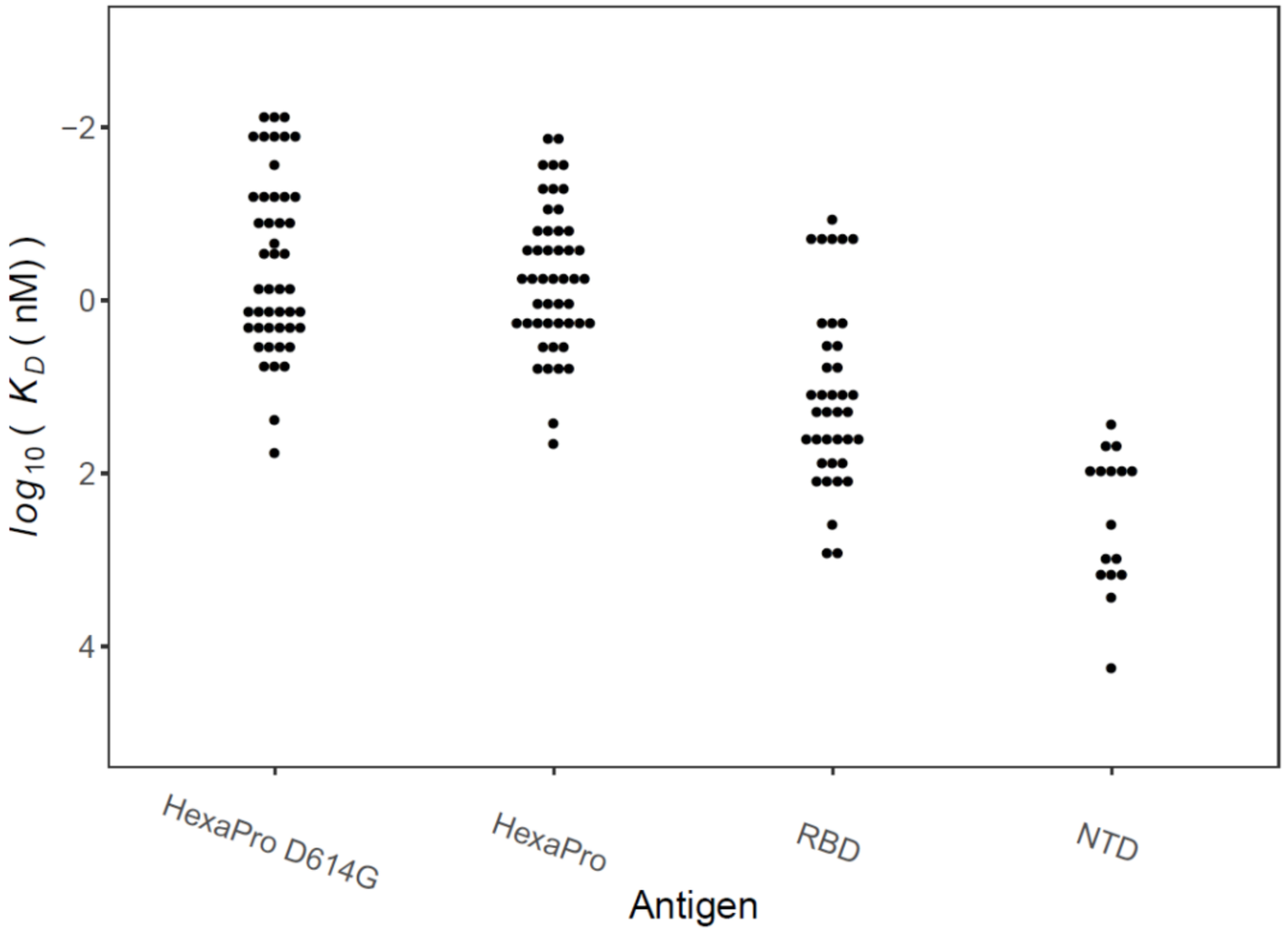
on four continents

Preliminary SARS-CoV-2 neutralization data for VSV pseudovirus

Some mAbs have clear matches across pseudoneut backbones (VSV and HIV) and with authentic virus

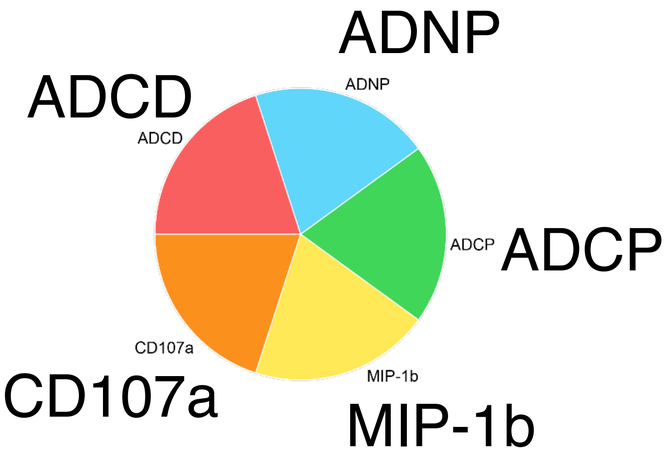
	IC 50 (µg/mL)		
COVID ID	**VSV backbone Nexelis**	**HIV backbone (reported)**	**Authentic virus (reported)**
COVIC-30	0.009	0.008	0.007
COVIC-32	0.009	0.008	0.009

Affinity landscape of CoVIC antibodies (1-47)



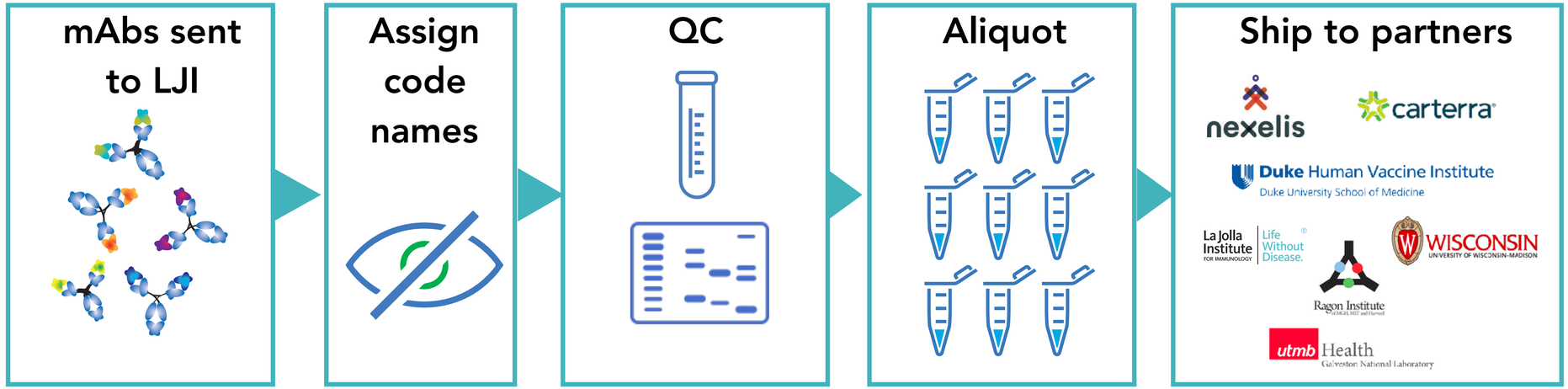
Georgia Tomaras Lab

Spread of functional ability among CoVIC mAbs



Galit Alter, Caroline Atyeo

Antibody contribution



- CoVIC PI and all reference labs are blinded to mAb name and source.
- OWS and BMGF Program Officers and CoVIC Program Manager are unblinded (but keep data confidential)
- Contributors know code names of their own mAbs, can view data as it is collected, can request re-analysis if data not as expected
- Contributors retain all IP and may publish and develop as they wish

CoVIC

Experiments in progress. More data to come!

Georgia Tomaras

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