Pandemic Defense Enabled by Synchrotron Radiation

SSRL 50th Anniversary Celebration

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Professor, President and CEO
La Jolla Institute for Immunology
April 20, 2023

Our Wits vs. Their Genes

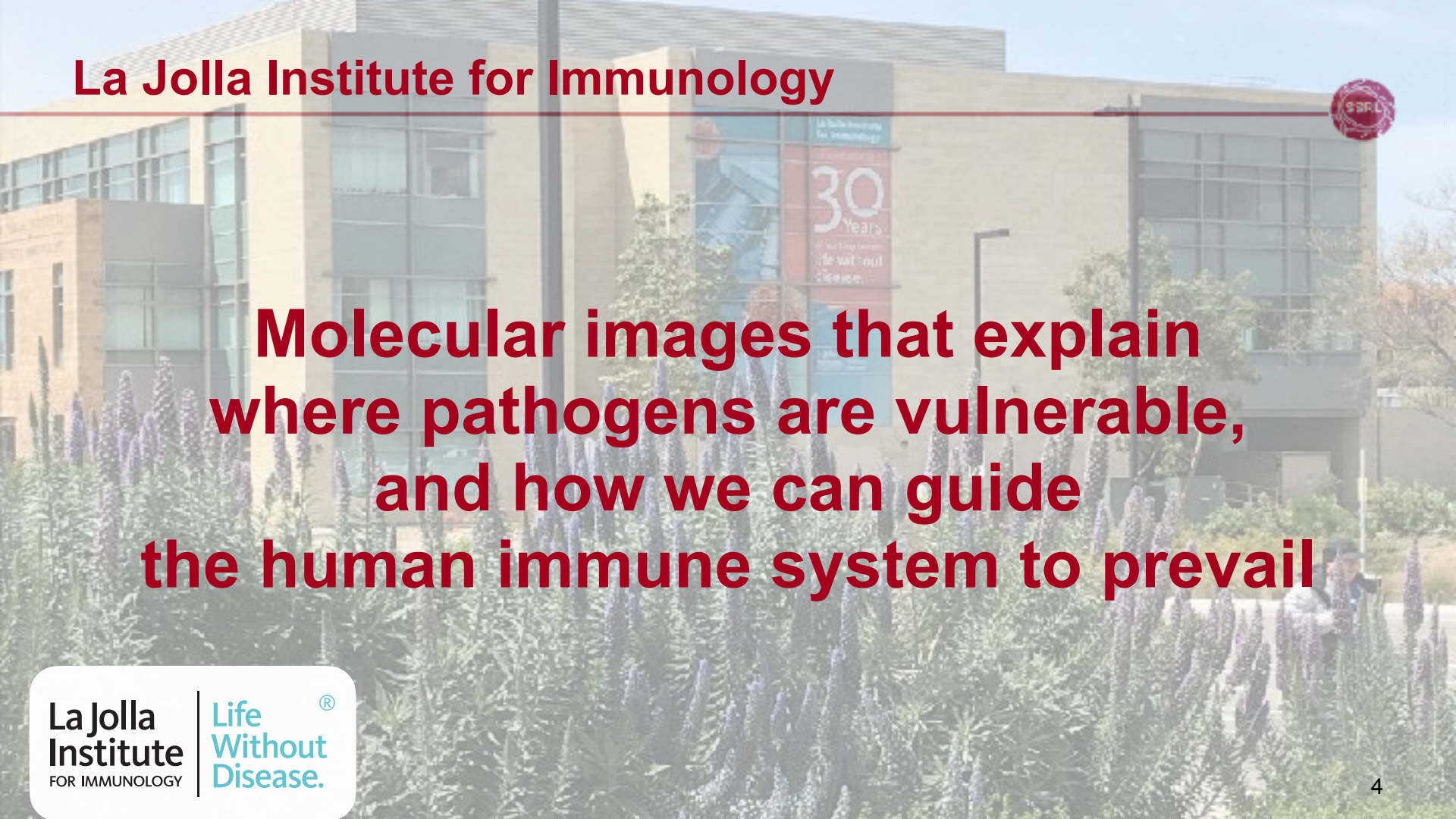
"The future of humanity and microbes likely will unfold as episodes of a suspense thriller that could be titled "Our Wits Versus Their Genes" - *Joshua Lederberg*

- > 1400 known human pathogens so far

- COVID-19, global: $16 Trillion ($16,000,000,000,000)
- Ebola virus, West Africa: $53 billion ($53,000,000,000)
- Measles, Clark County, Washington State ($3,400,000 $47,000 per case and $800 per contact)

Our Wits vs. Their Genes

- Rapid evolution
- Simple machines
- Nucleic acid and proteins.
  - SARS-CoV-2 - 12 proteins.
  - Ebola - 8 proteins.
  - Measles - 6 proteins.



Molecular images that explain where pathogens are vulnerable, and how we can guide the human immune system to prevail

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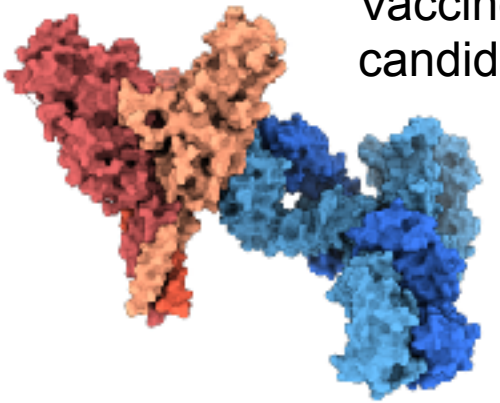
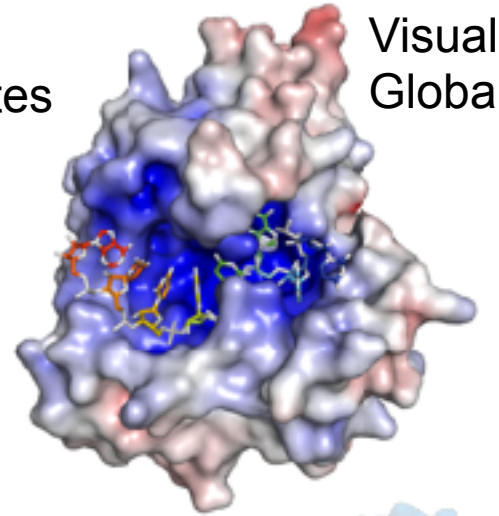
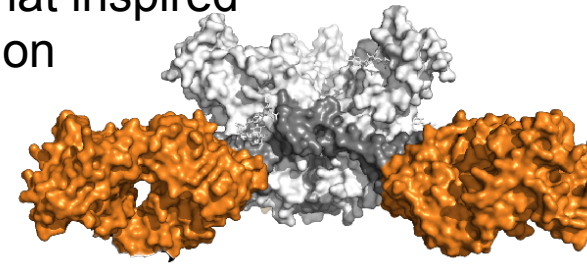
Synchrotron Radiation has given us…



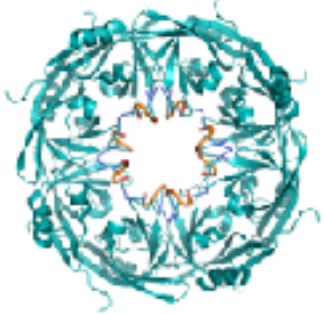
Vaccine candidates



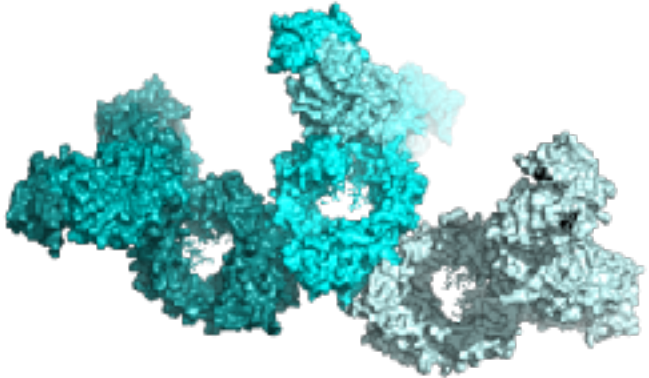
Visual roadmap that inspired Global collaboration

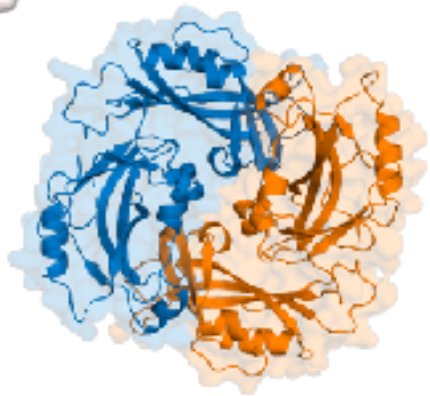


Fundamental Knowledge



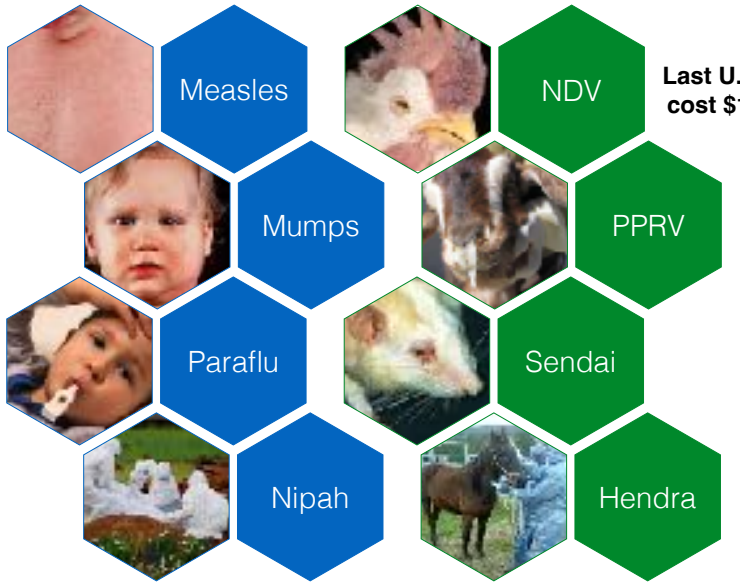
Antibody Therapeutics





Drug Targets

Paramyxoviruses



Last U.S. outbreak cost $121 million)

$2.1 billion globally per year

>$200 million in annual hospitalizations (croup)

Highly infectious, respiratory spread

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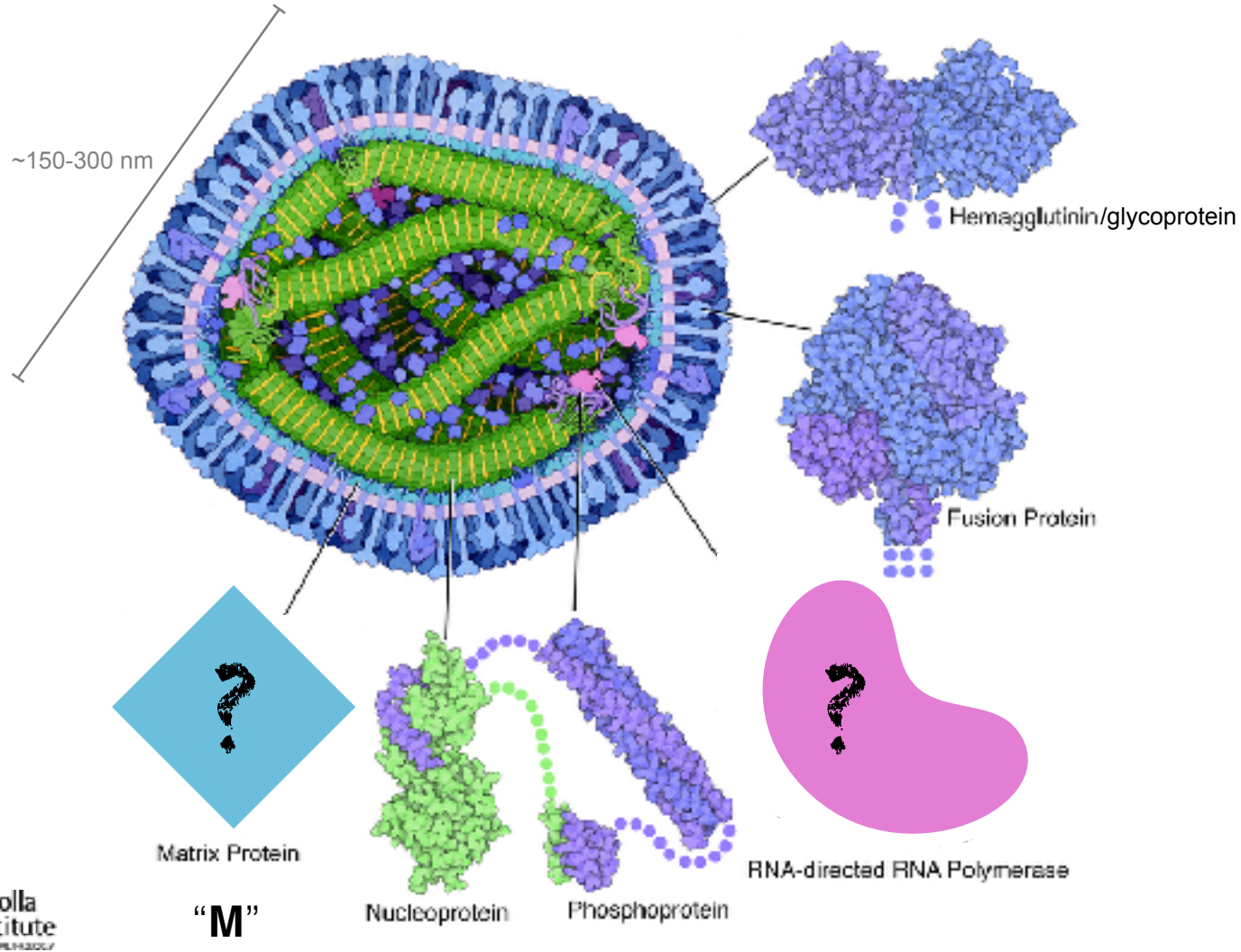
R_0 16-18

2019:
USA: 1,200 cases
DRC: 300,000 cases
(6,000 deaths)

40-75% lethality

annual outbreaks
in Bangladesh
and India



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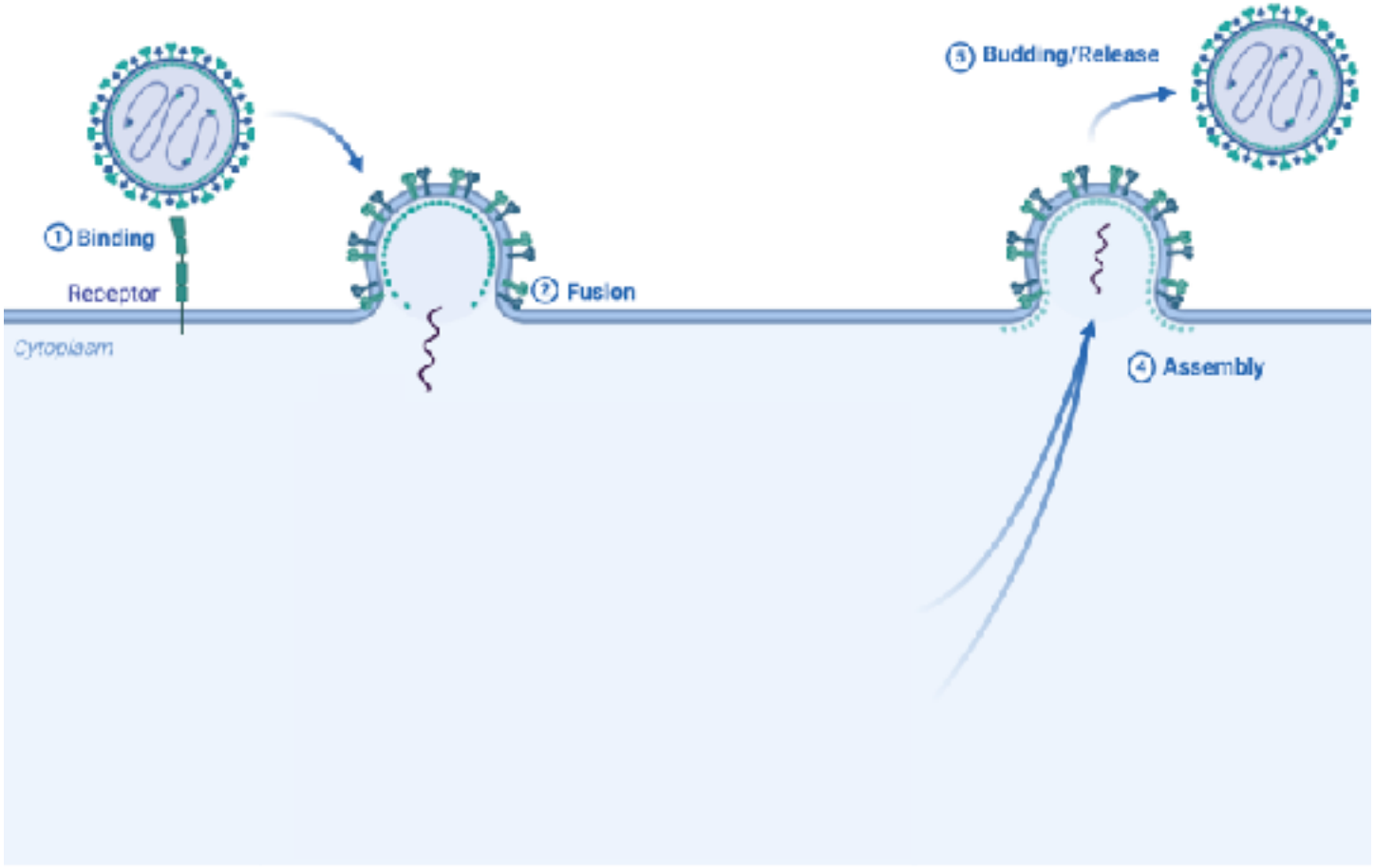
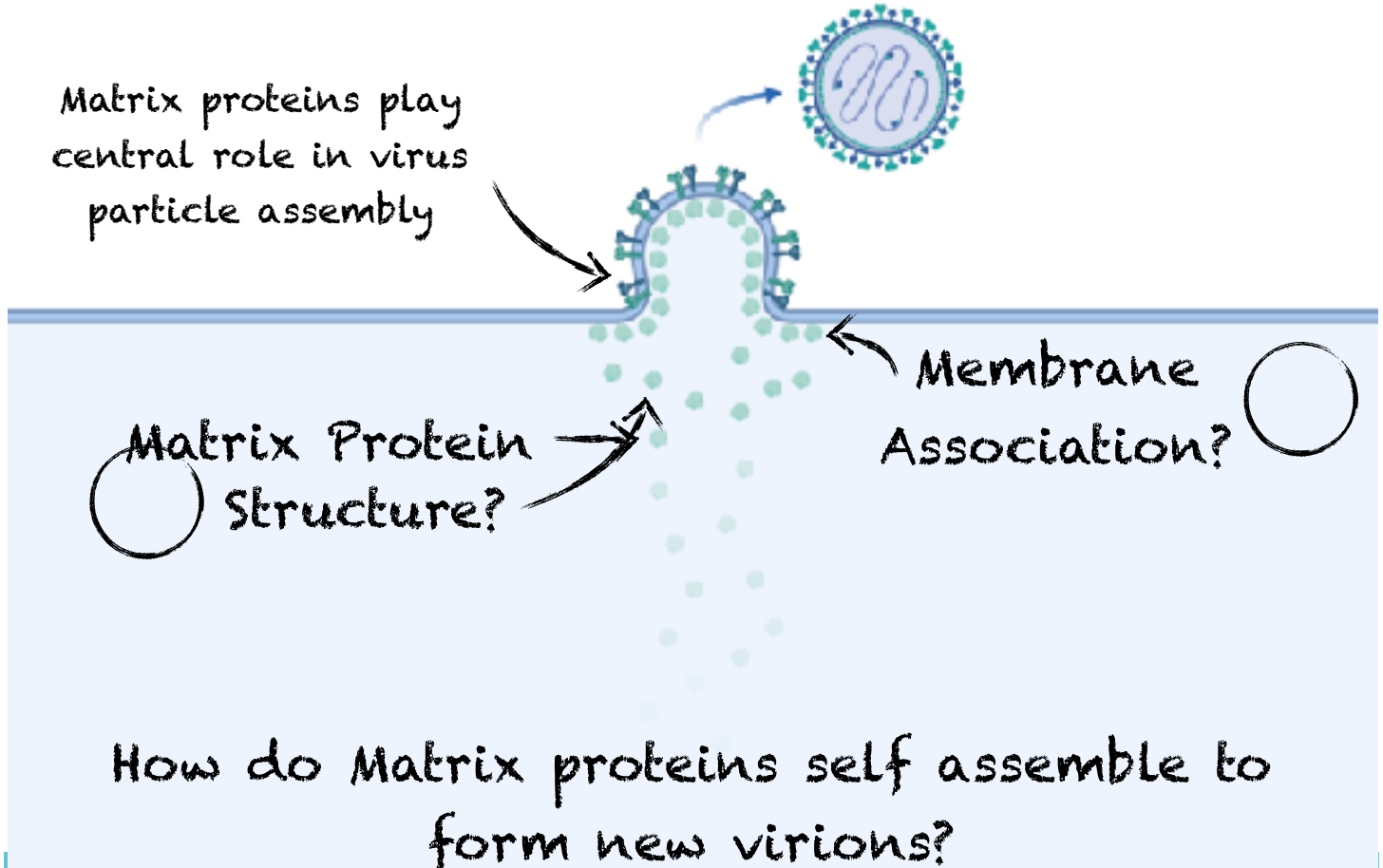
Paramyxovirus Replication

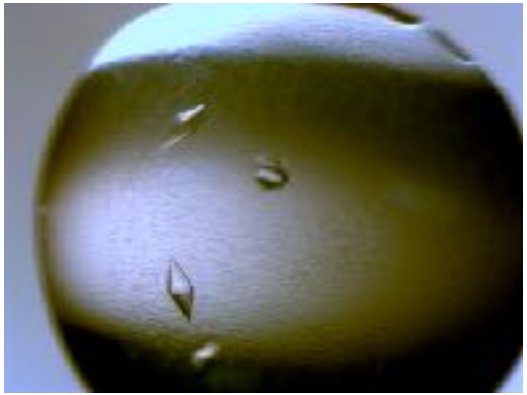


Paramyxovirus Assembly



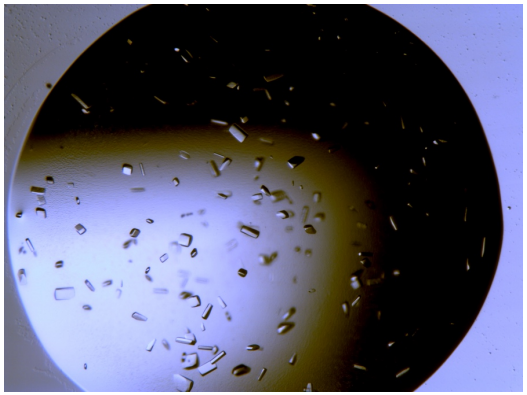
Crystallization of Paramyxovirus M Proteins

Measles-M



19% (v/v) Isopropanol, 19% (w/v) PEG 4000, 5% (v/v) Glycerol, 0.095 M Sodium Citrate pH 5.6

Nipah-M



0.1 M Tris pH 7.5, 20% PEG400

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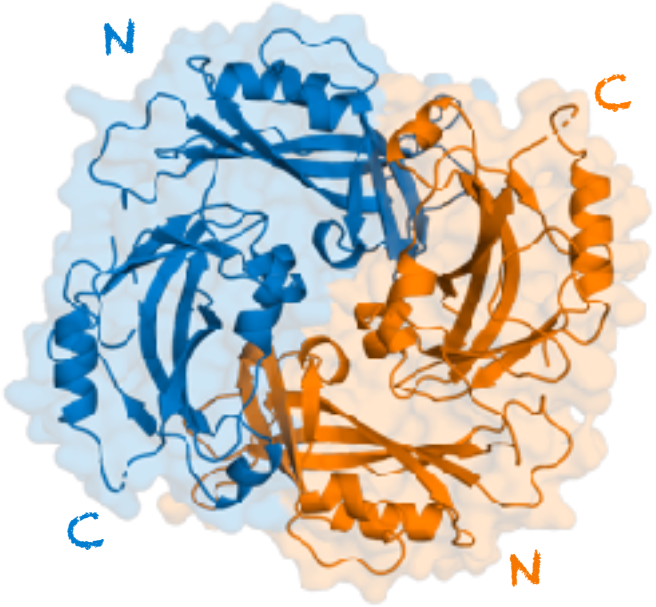
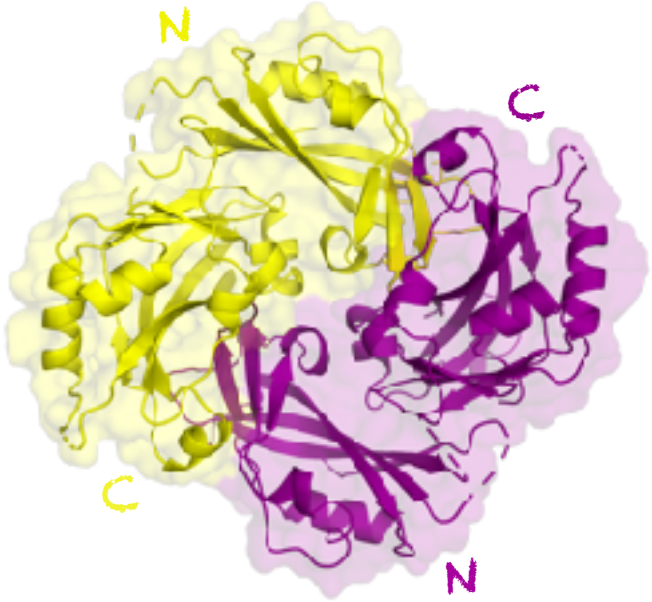
Measles-M



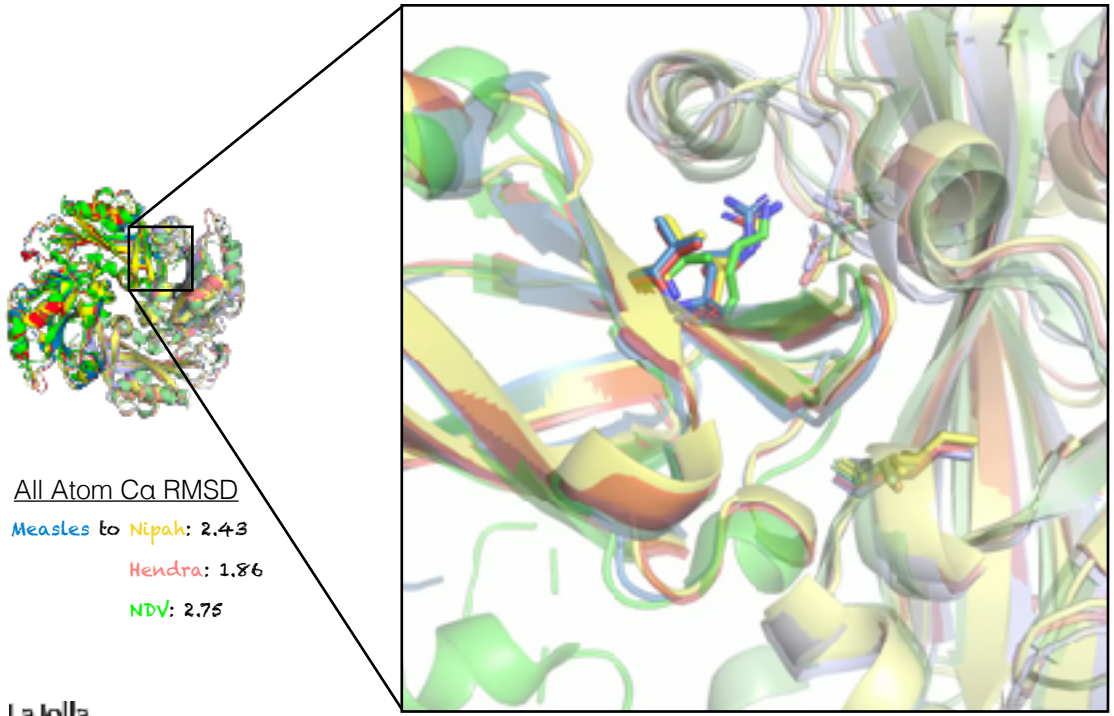
2.4 Å Resolution

Nipah-M



1.6 Å Resolution

Interface conserved across the Paramyxovirus family (broad-spectrum inhibitors?)



Measles

Nipah

Hendra

NDV

All Atom Cα RMSD

Measles to Nipah: 2.43

Hendra: 1.86

NDV: 2.75

All Atom RMSD of Interface

Measles to Nipah: 1.75

Hendra: 1.36

NDV: 1.98

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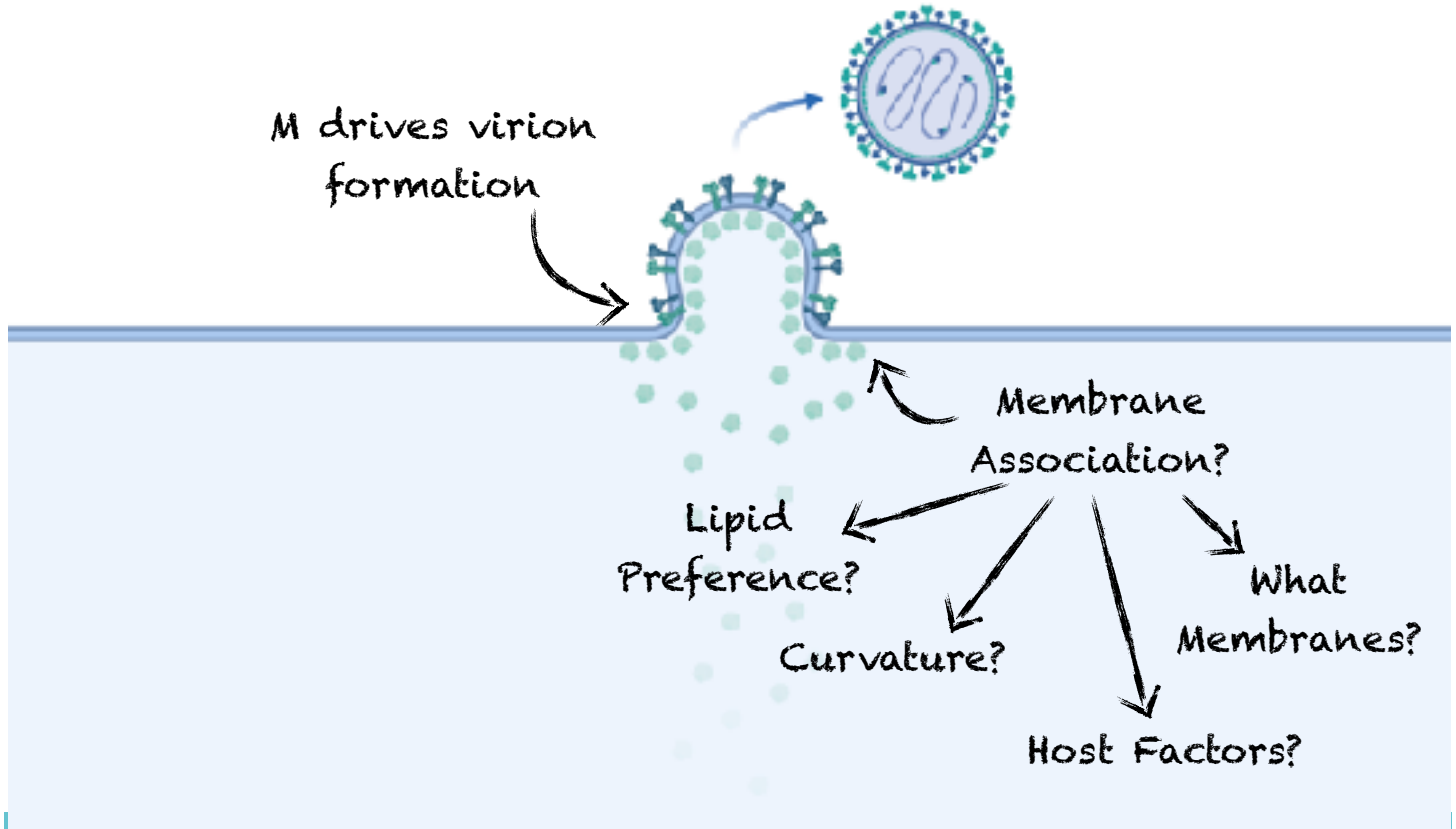
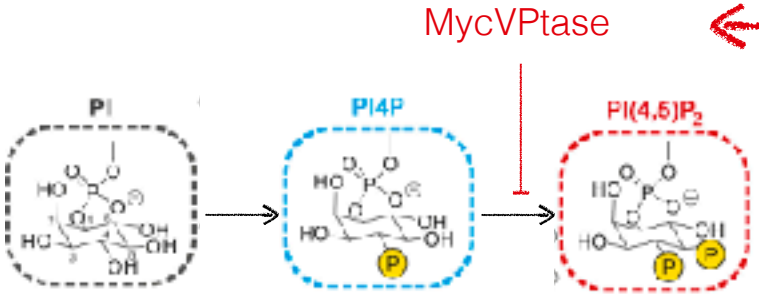
How does Matrix interact with membrane?

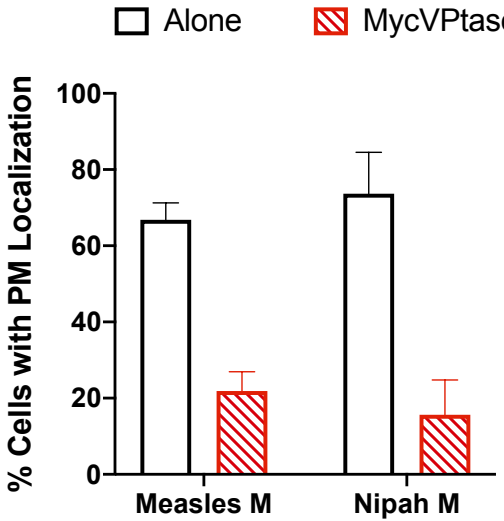


And without PI(4,5)P2, Measles and Nipah viruses can't grow.



Enzyme removes phosphate at D5

Phosphate @ position 5 of 4,5 important for matrix-membrane binding

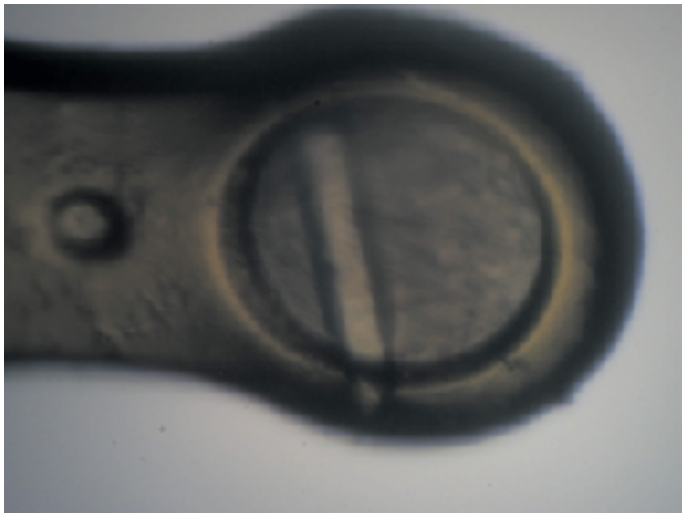


PURDUE UNIVERSITY

How do these viruses bind $PI(4,5)P_2$?

Co-crystallization with $PI(4,5)P_2$

Nipah-M + $PI(4,5)P_2$



0.1 M HEPES pH 7.5,
2.0 M Ammonium
sulfate + Seeds

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Michael Norris

Structure of Nipah Matrix in Complex with $PI(4,5)P_2$

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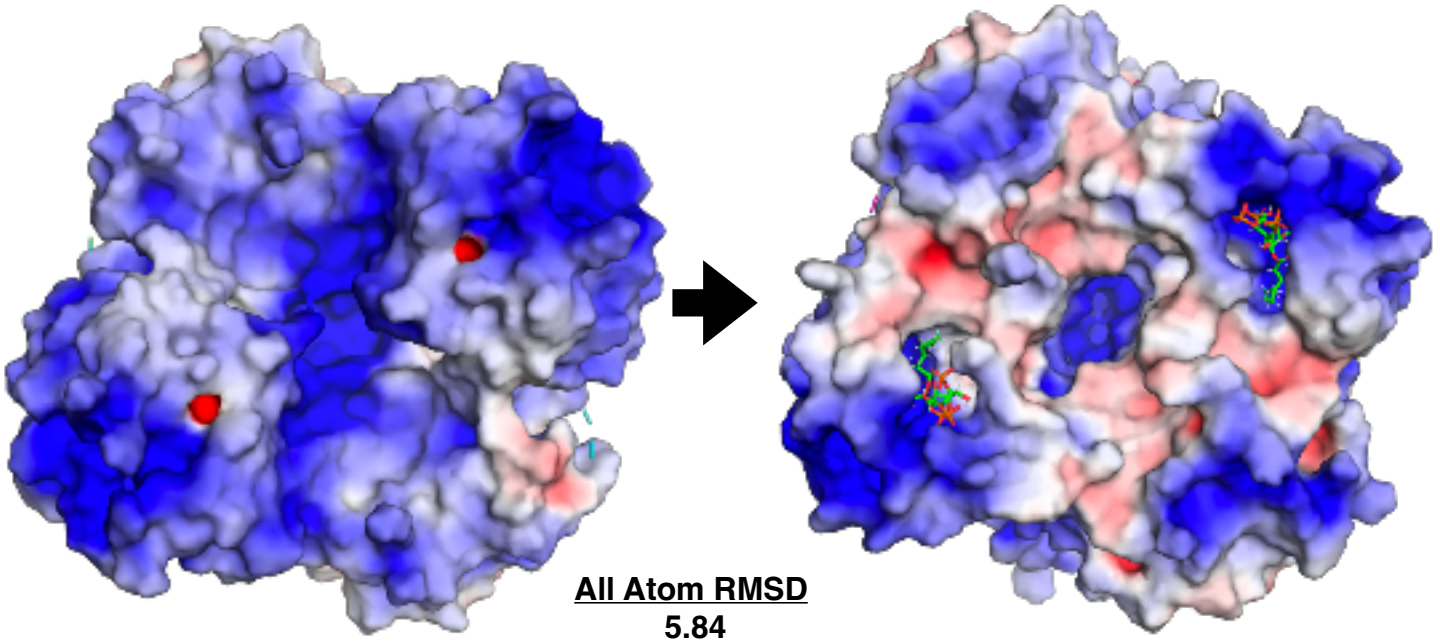
2.0 Å Resolution

Michael Norris

Surface changes with PIP2 binding

Unbound Dimer

$PI(4,5)P_2$ Bound Dimer



All Atom RMSD
5.84

Negative −5.000 5.000 Positive

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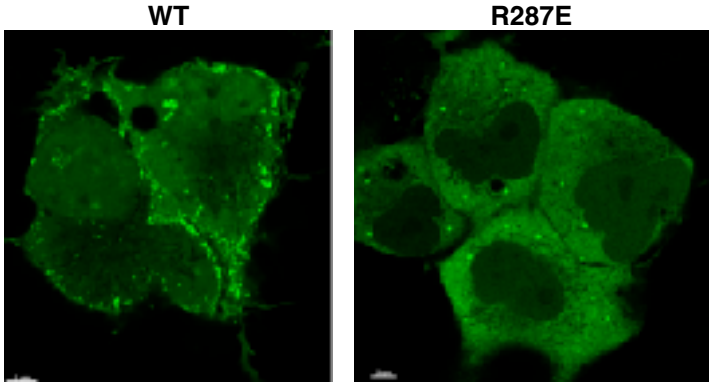
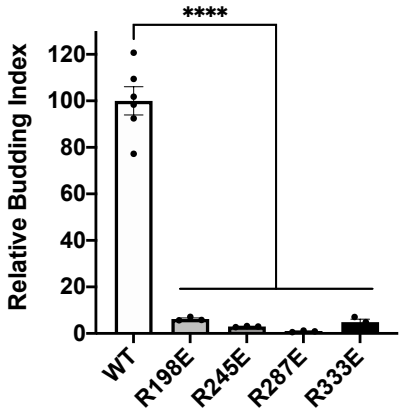
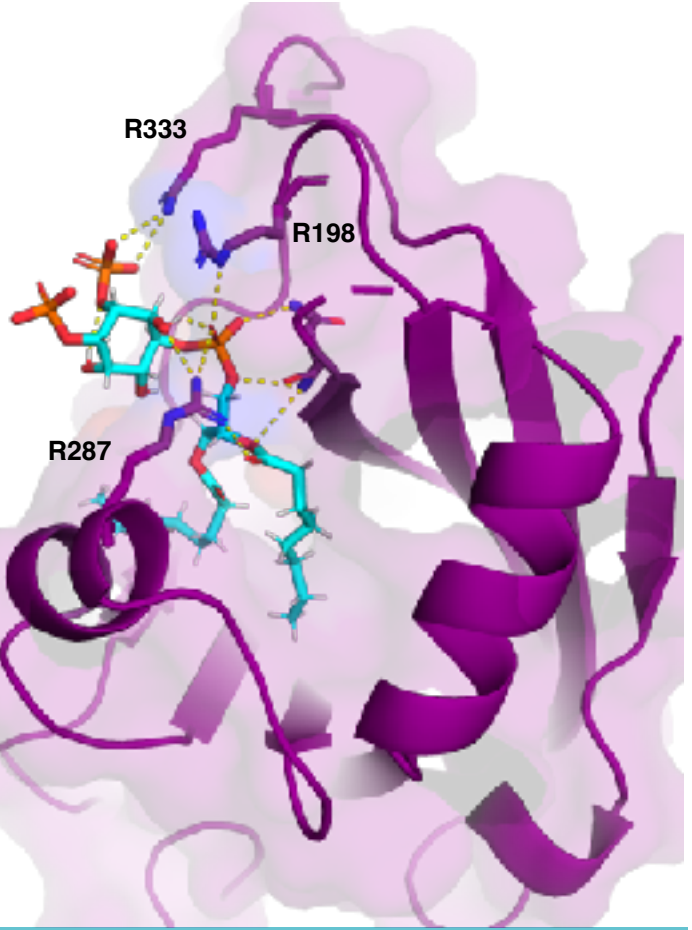
Structure of $PI(4,5)P_2$ Pocket







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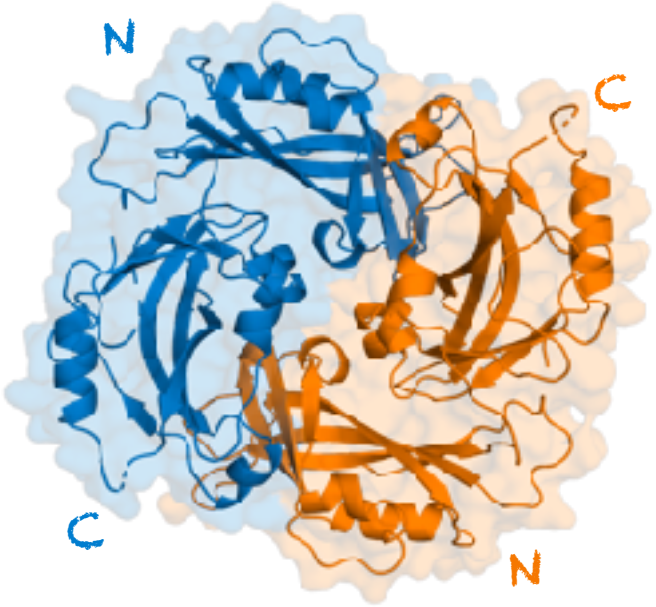
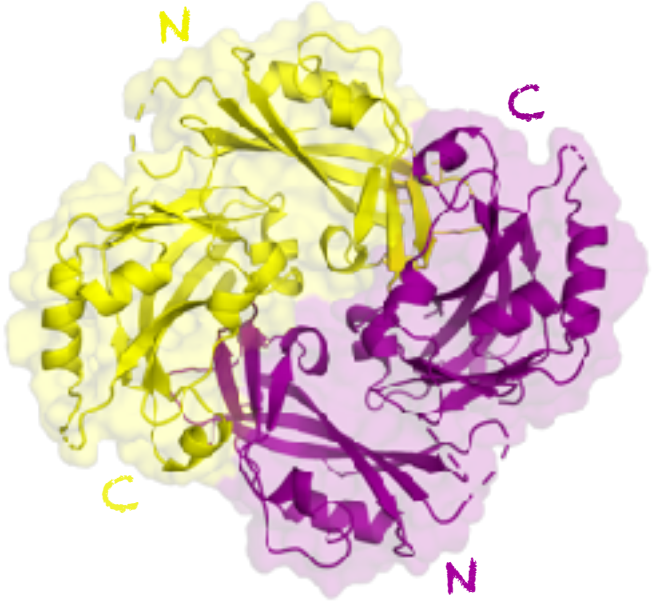
Measles-M



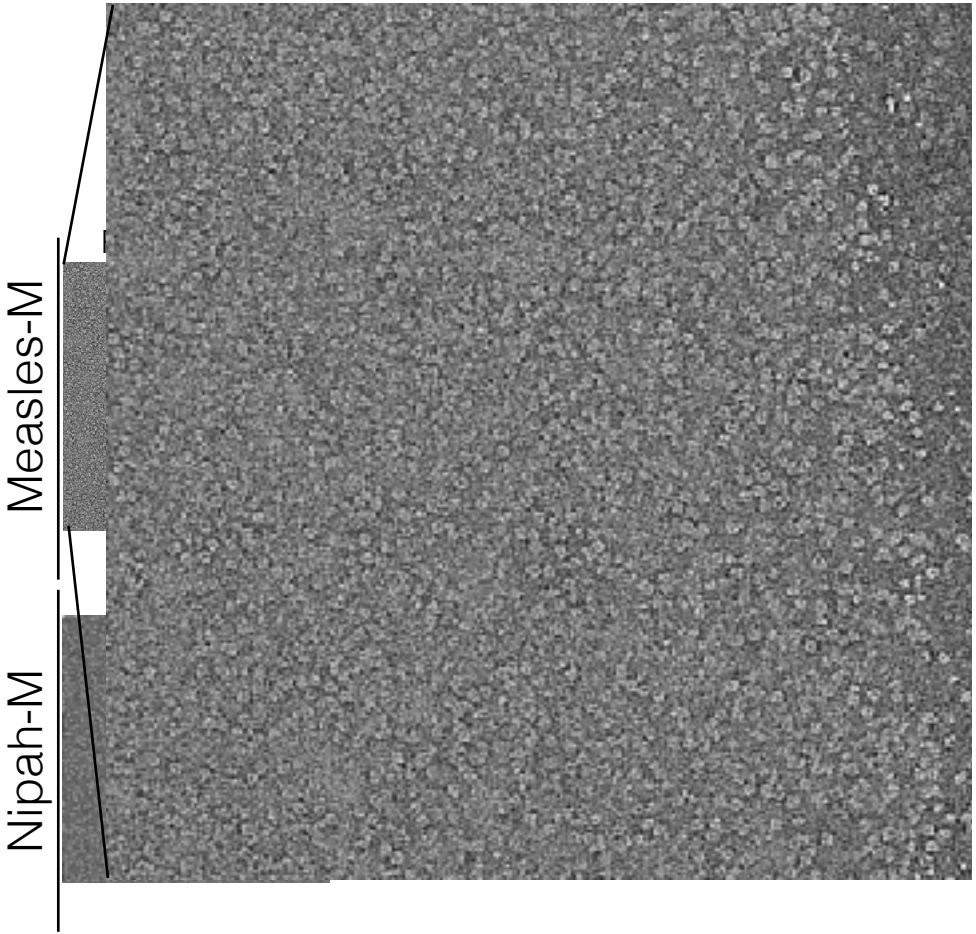
2.4 Å Resolution

Nipah-M

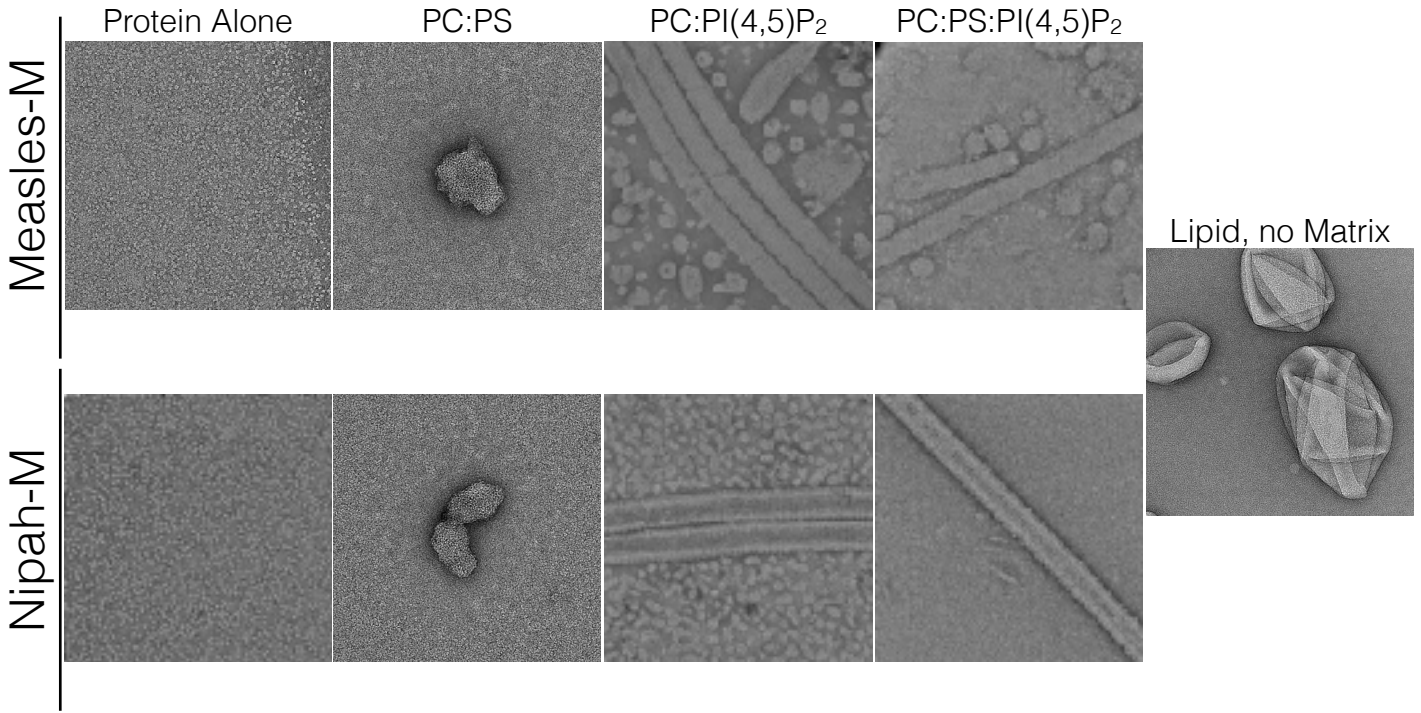


1.6 Å Resolution

Matrix Self Assembly with

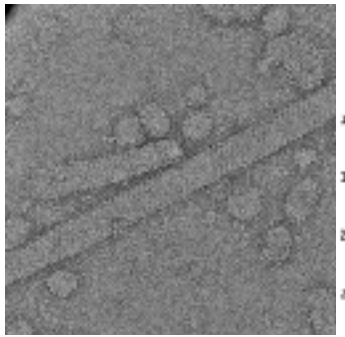


Matrix Self Assembly with $PI(4,5)P_2$

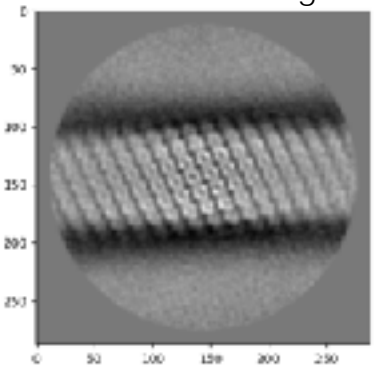


Measles-M

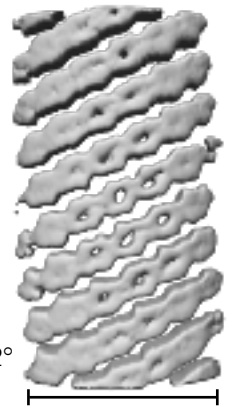
96,000x



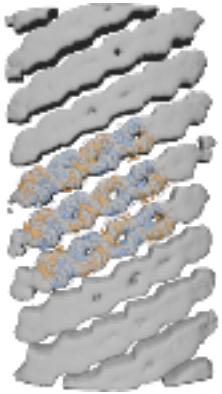
2D Class Average



3D Projection



Xtal Docked



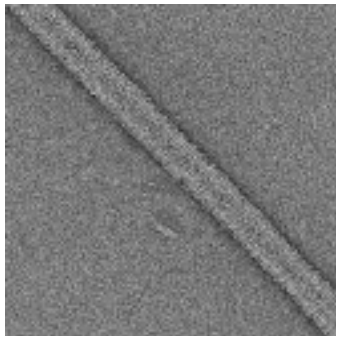
27.2°

450Å

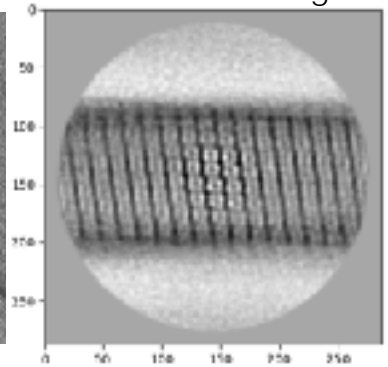
Measles

Nipah-M

96,000x



2D Class Average



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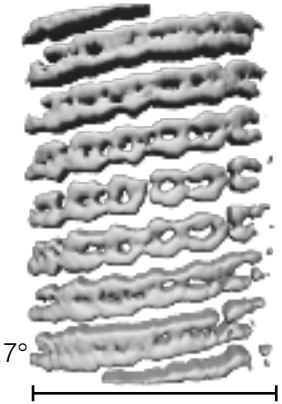

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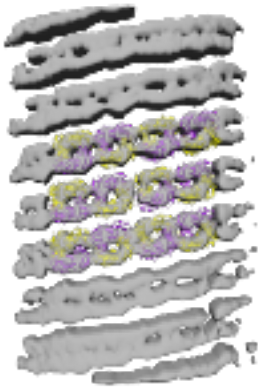

7.7°

537Å

Nipah

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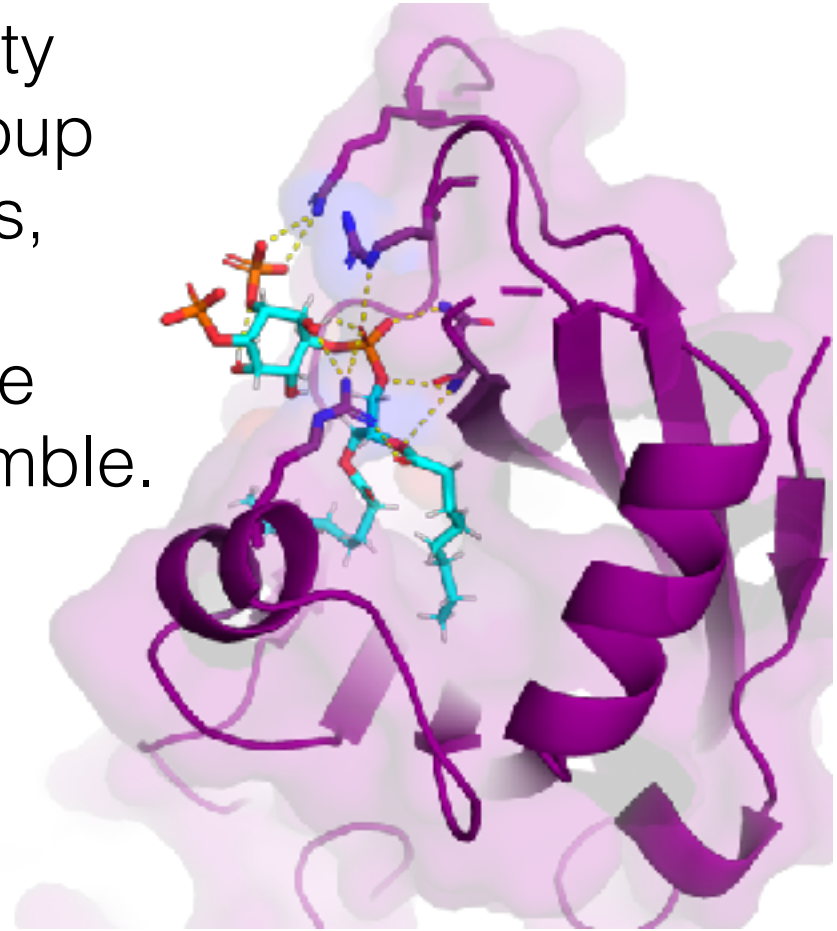
Synchrotron radiation
showed us a new vulnerability
conserved across a major group
of human and animal viruses,

And fundamental knowledge
about how theses viruses assemble.



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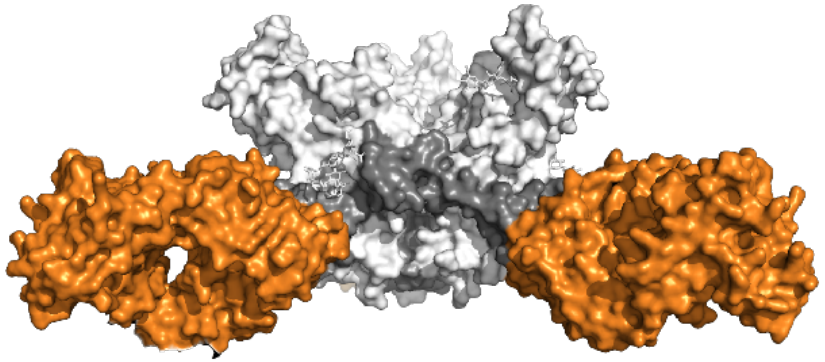
Institute

Synchrotron radiation also drew the roadmap for two global consortia.



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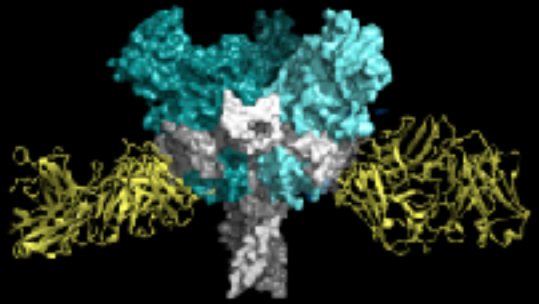
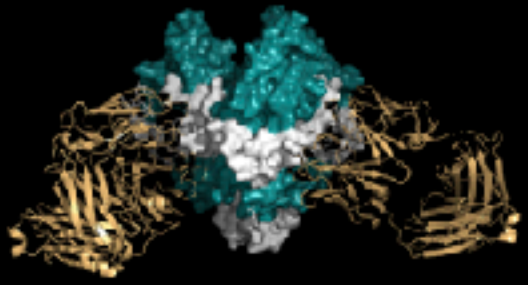
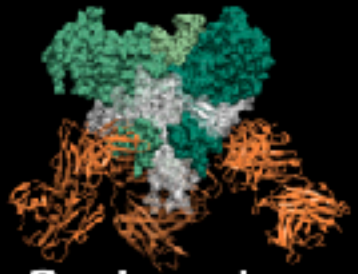
ATTENTION !
EBOLA !
Beaufort
UN
UN



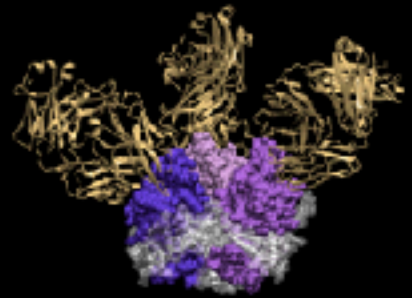
Ebola virus



Bundibugyo virus



Sudan virus



Marburg virus

Synchrotron radiation solved the structures of the surface proteins of a class of viruses like Ebola, and showed where human antibodies target them.

Problem in antibody therapeutics for Ebola:

In vitro success
≠ in vivo success

Problem in antibody therapeutics for Ebola:

Some molecules:
Neutralized virus in vitro
Failed in vivo

Other molecules:
Protected in vivo
But didn’t work in vitro

Need to understand what leads to in vivo protection.
Need a statistically significant pool of antibodies to do so.

Need to understand what leads to in vivo protection.
Need a statistically significant pool of antibodies to do so.

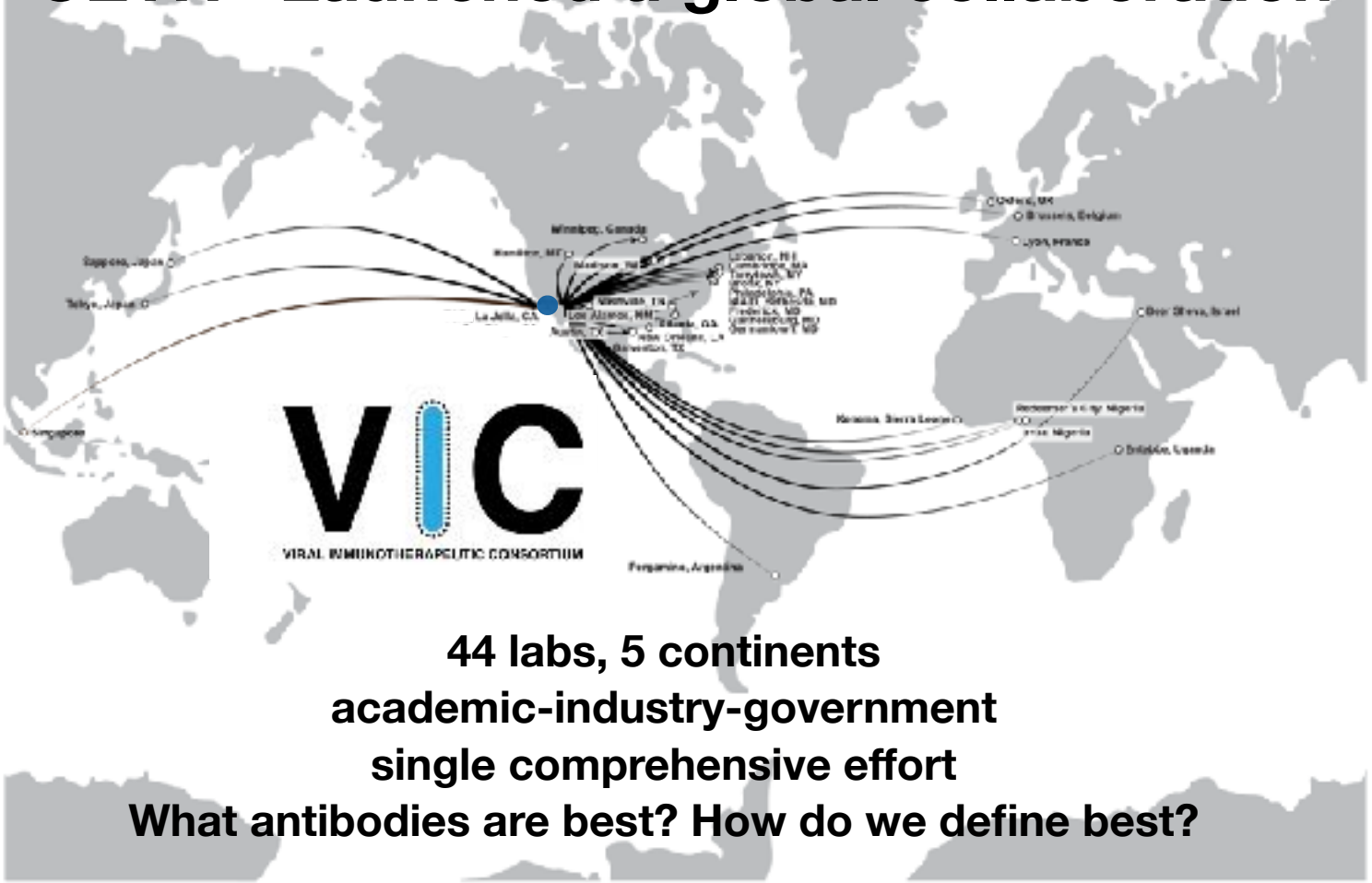
Need better tools, more samples.
Everyone is working in a silo.
Escalating pandemic….

Need a research framework
that enables collaboration, sample/data sharing
within an environment built on competition

Blinding samples
Protecting intellectual Property
Parallel experimental tracks:
Fast track and comprehensive track
All guided by the framework of structural biology, from synchrotron radiation

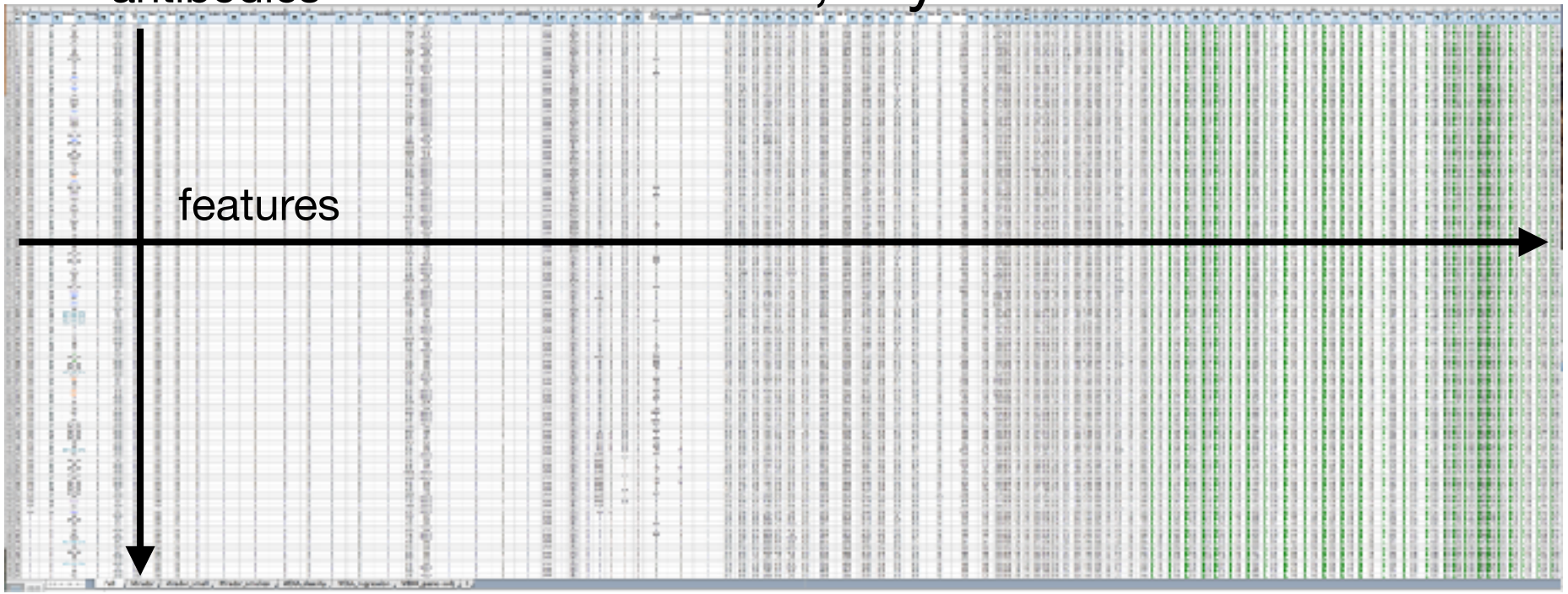
NIAID CETR

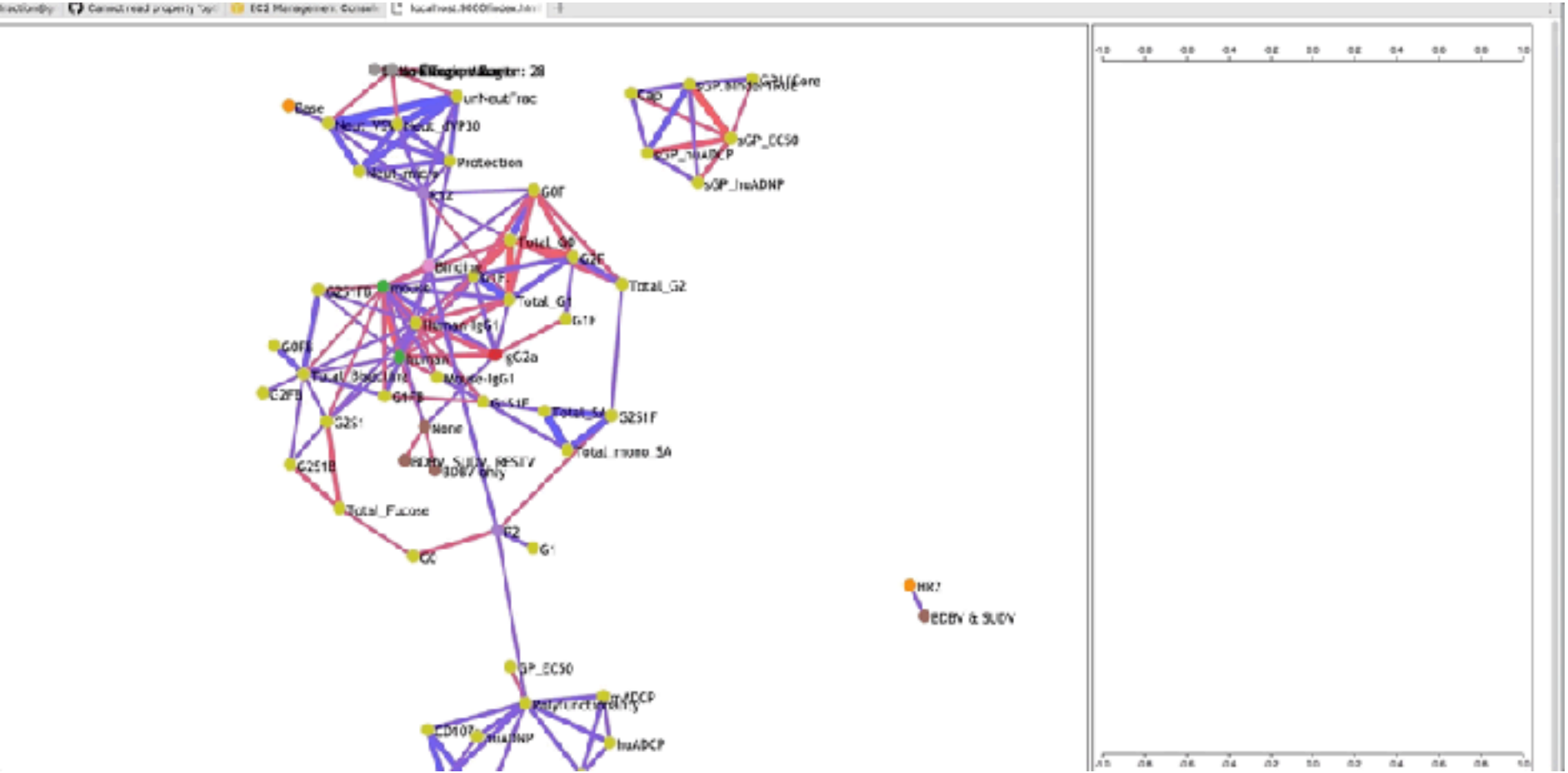
NIAID CETR Launched a global collaboration



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

200 mAbs, 3 years:

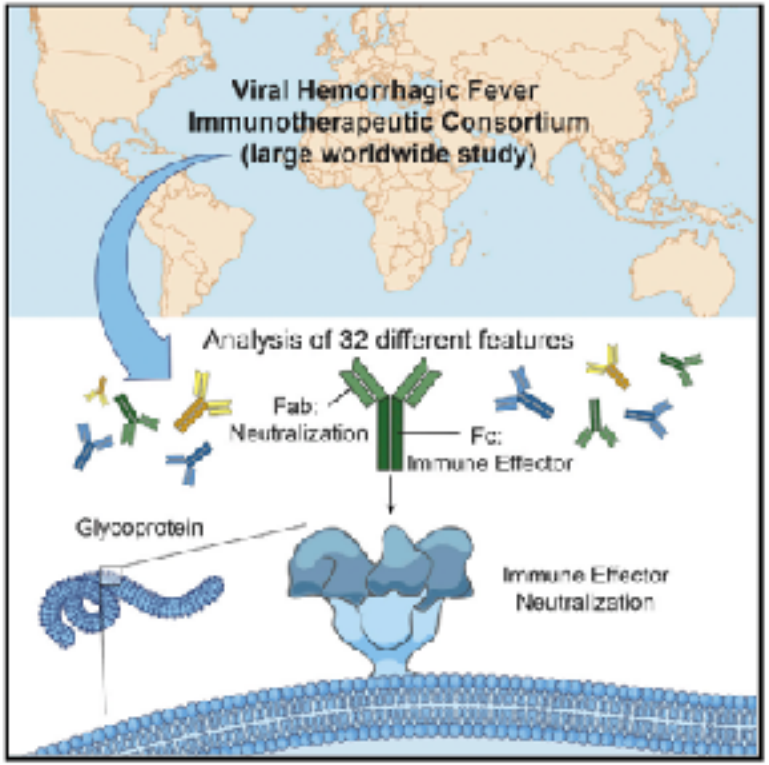




Kristian Andersen for the VIC study

Systematic Analysis of Monoclonal Antibodies against Ebola Virus GP Defines Features that Contribute to Protection

Graphical Abstract



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GLOBAL HEALTH

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.

Systematic Analysis of Monoclonal Antibodies against Ebola Virus GP Defines Features that Contribute to Protection

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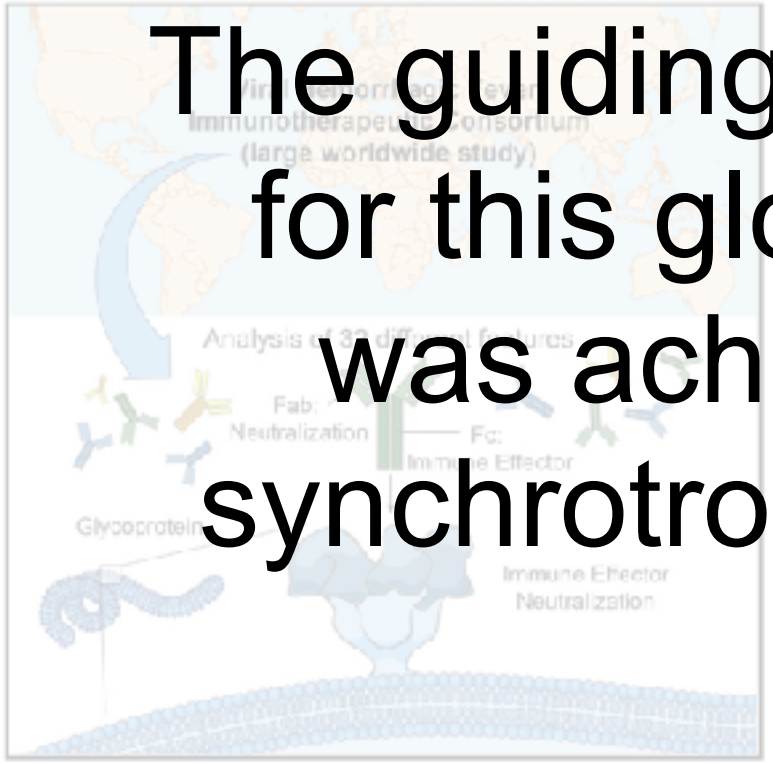

A Cure for Ebola? Two New Treatments Are Highly Effective in Congo

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

The guiding framework for this global effort was achieved by synchrotron radiation

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>400 Candidate mAbs from >65 companies/labs

Goals:

- Compare therapeutic candidates side-by-side
- Independent evaluation of Abs for NIAID clinical trials
- Learn what features lead to protection

BILL & MELINDA GATES foundation

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

GRANT ORIENTATION

March 2020

From Alpha to Omicron: Defining variant-resistant epitopes targeted by SARS-CoV-2 antibodies

CoVIC: Coronavirus Immunotherapeutics Consortium

ERICA OLLMANN SAPHIRE, Ph.D.

@EOSaphire

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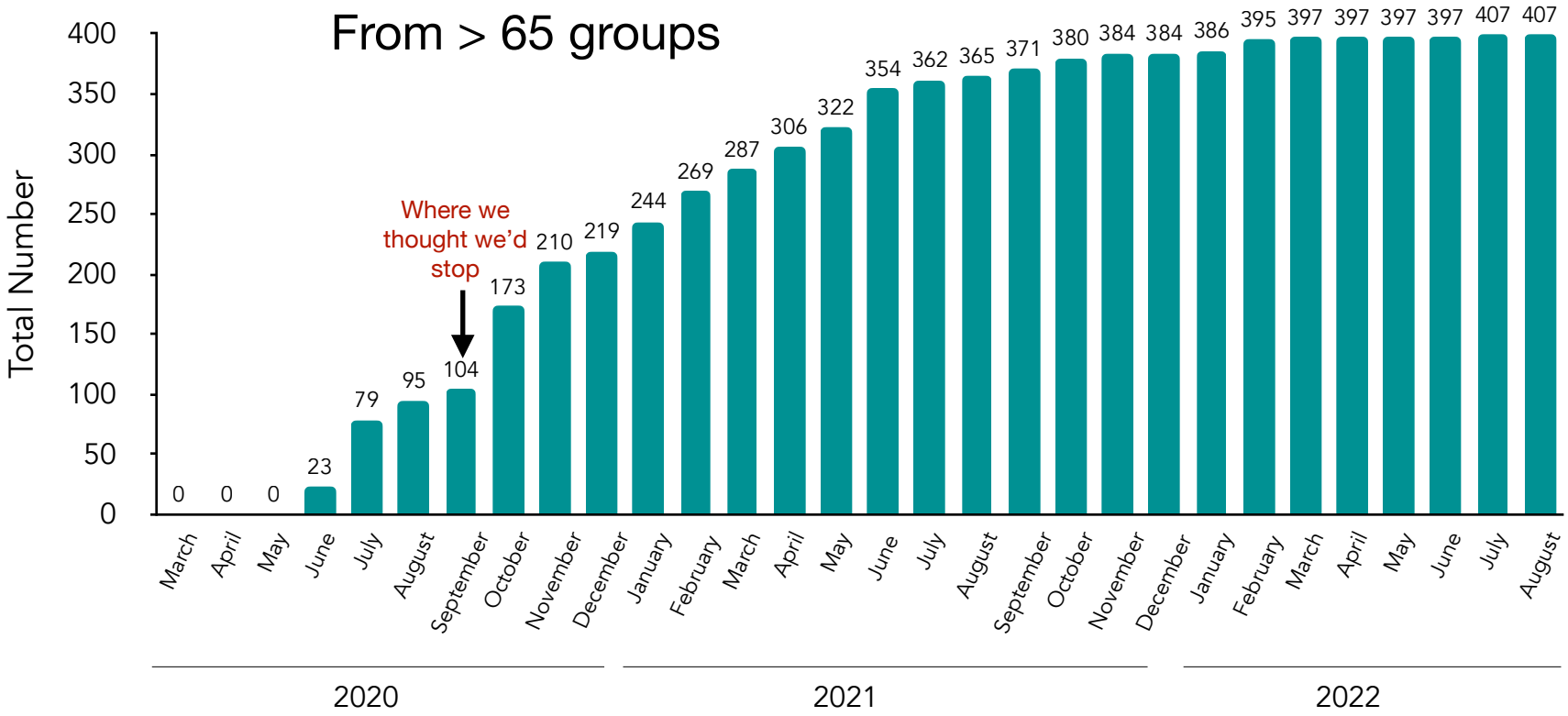
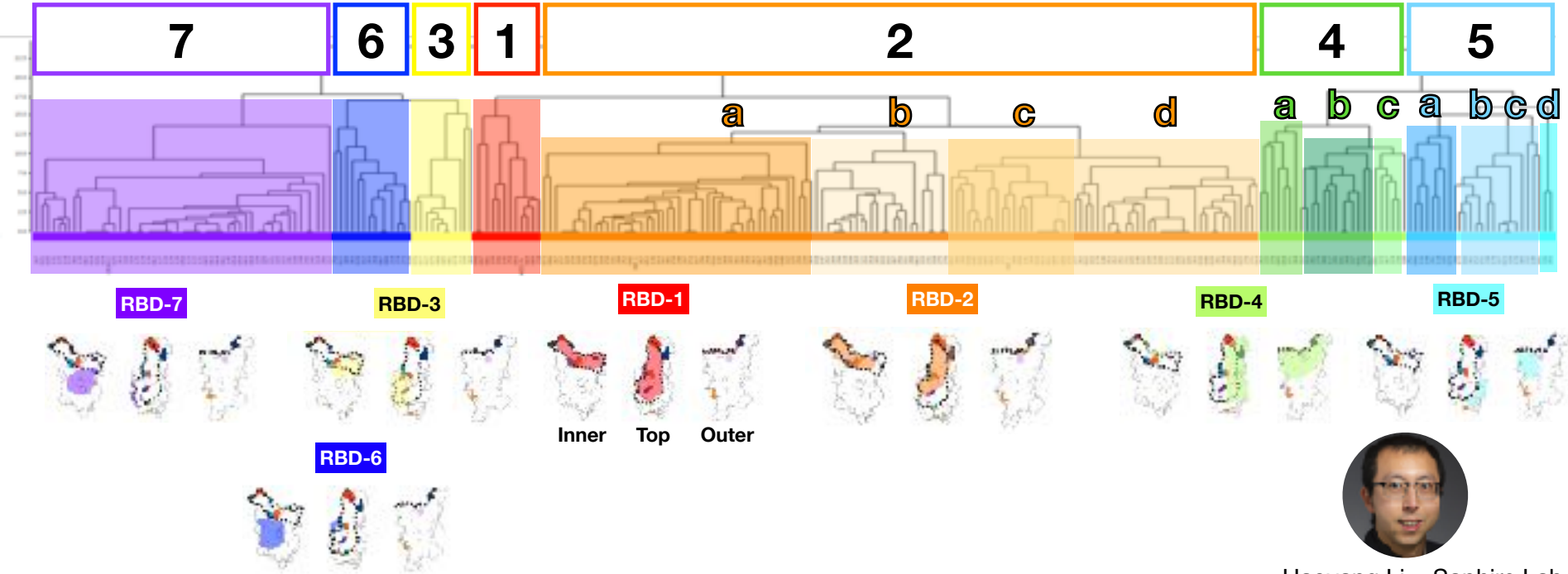
CoVIC Antibody Panel



Using structural biology as the framework, we finely sorted the antibodies by their footprint on SARS-CoV-2 spike

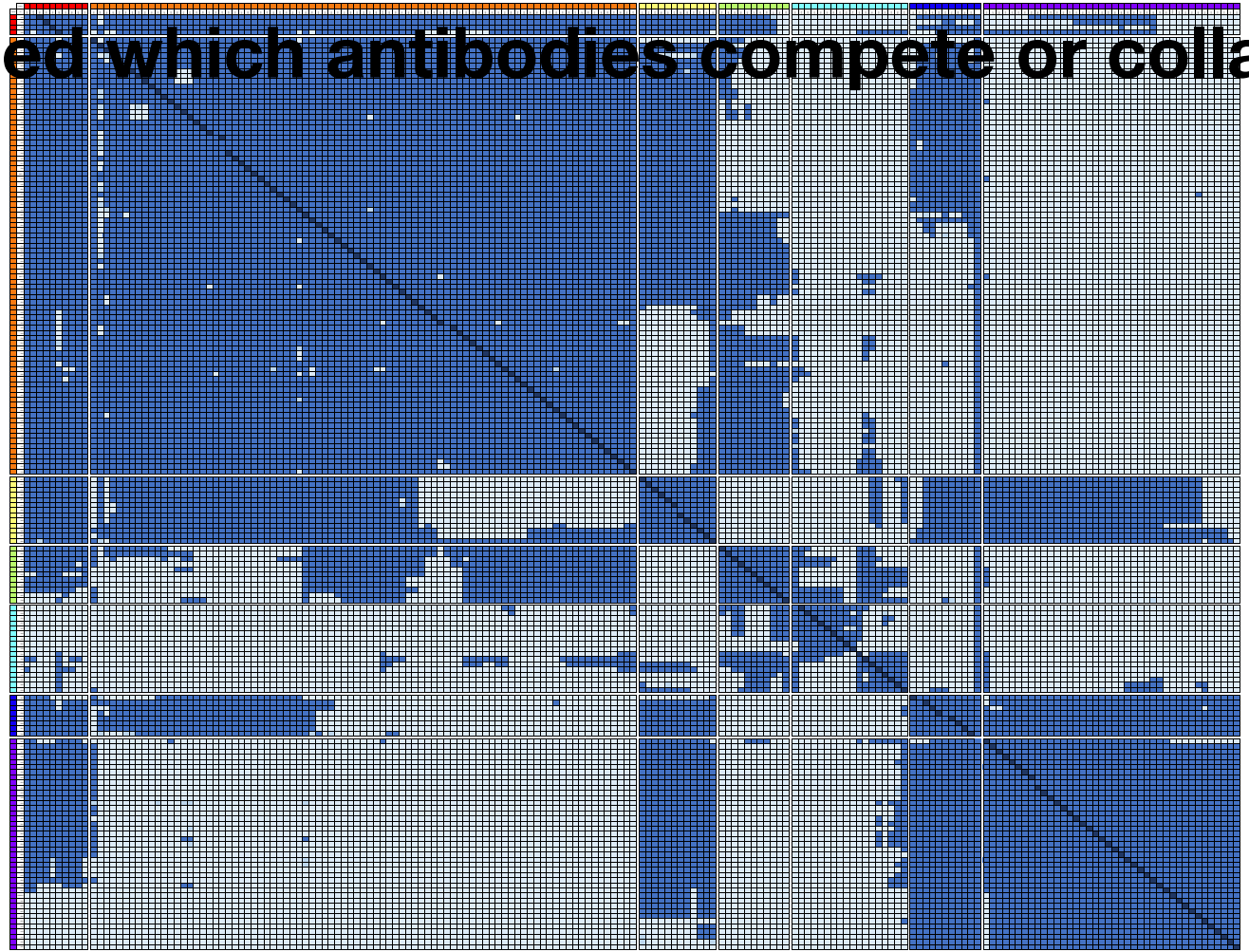


Haoyang Li + Saphire Lab

Mapped which antibodies compete or collaborate

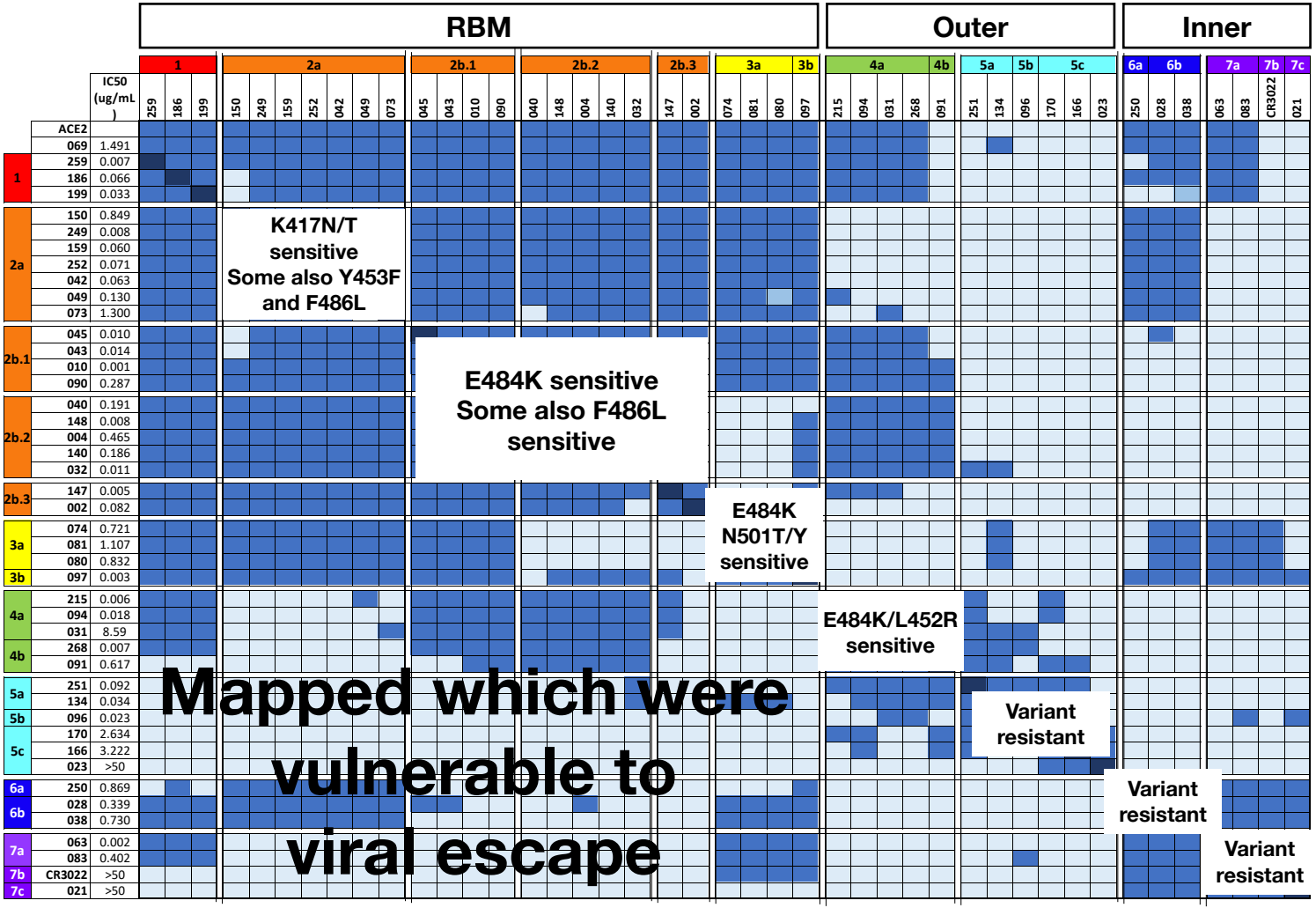
Compete

Do not compete



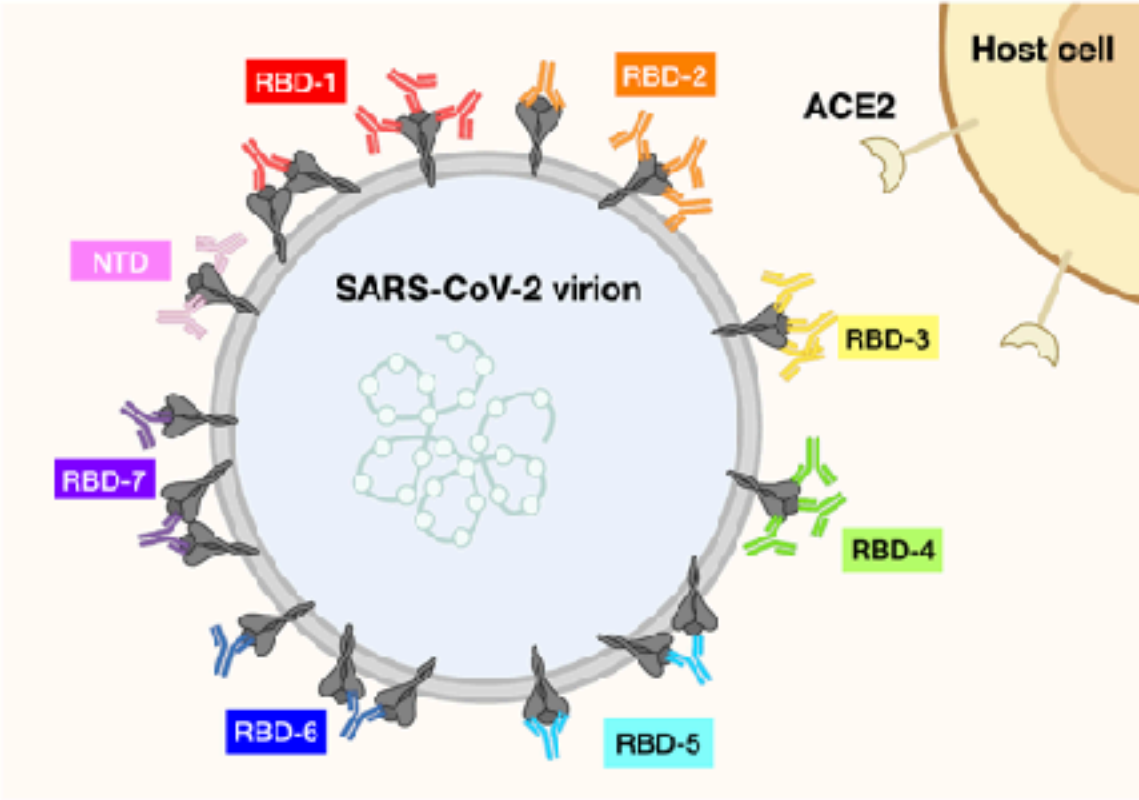
Dan Bedinger and Tim Germann, Carterra

Epitope communities



La Jolla Institute FOR IMMUNOLOGY | Life Without Disease.®

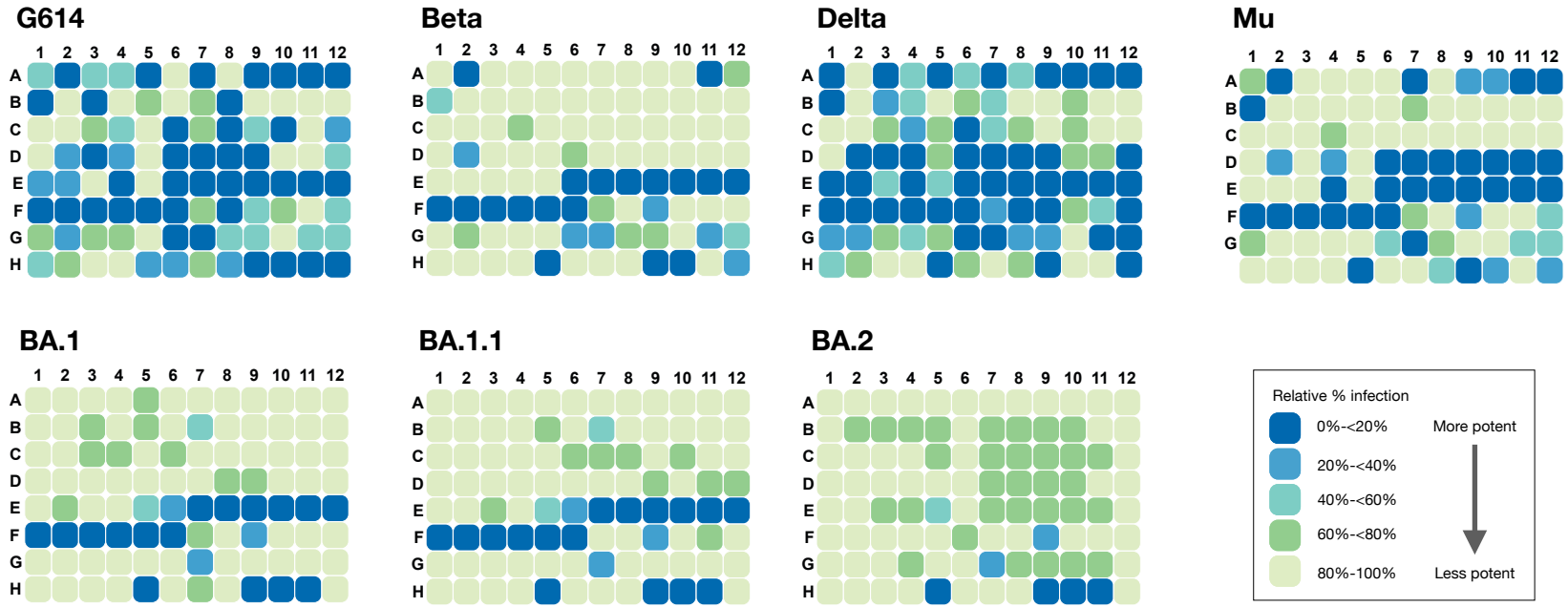
Offered us the visual framework to interpret how activity changed as variants of concern emerged.

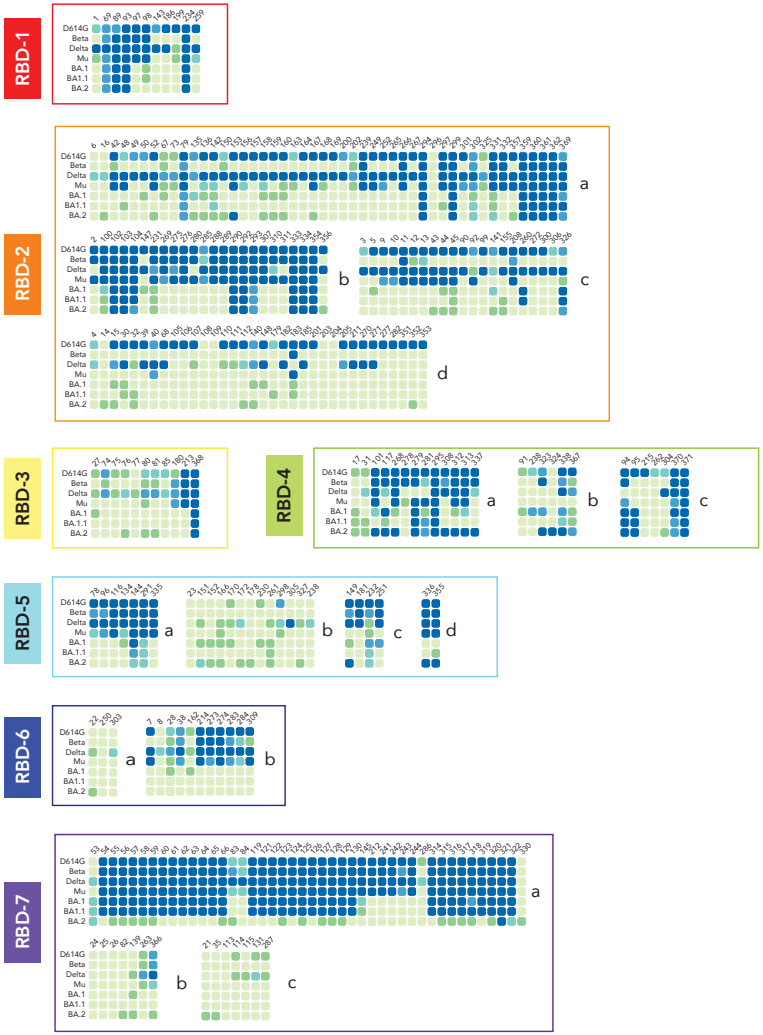


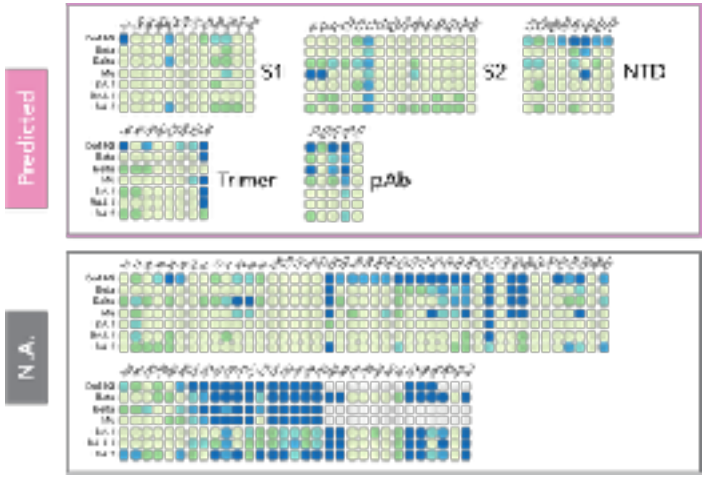
5600 neut expts: 397 mAbs x 7 viruses x 2 conc.

Entire CoVIC panel : High (25ug/mL) and Low (250ng/mL) neutralization of VOC pseudoviruses

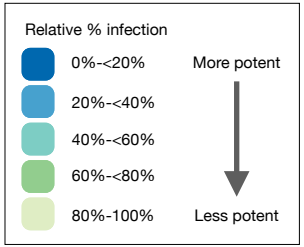
Example results: CoVIC 1-96, 250ng/mL







397 mAbs, 7 viruses

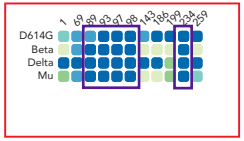


Pre-Omicron

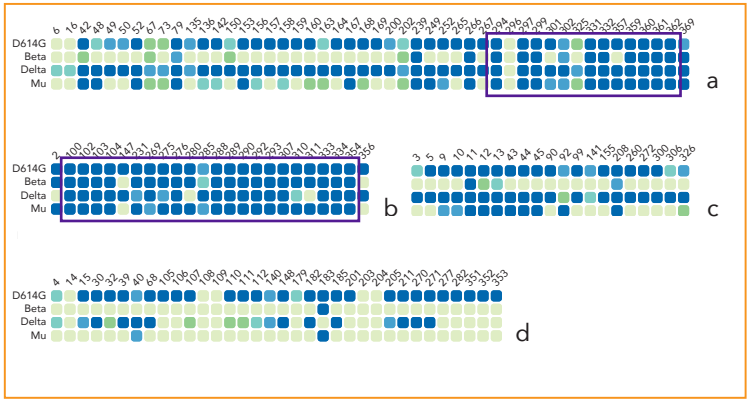
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



RBD-2



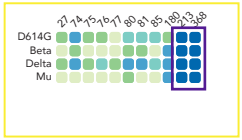
Outer face

RBD-4

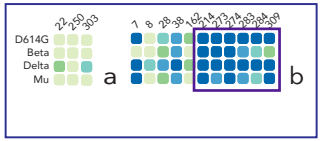
RBD-5

Inner face

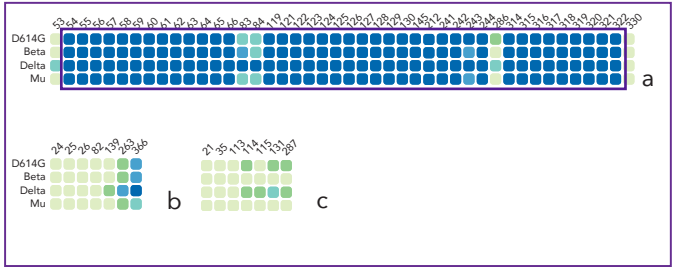
RBD-3

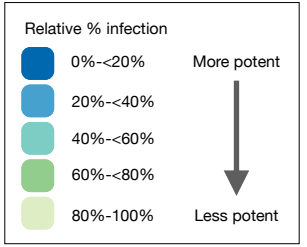


RBD-6



RBD-7





Pre-Omicron

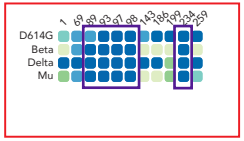
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

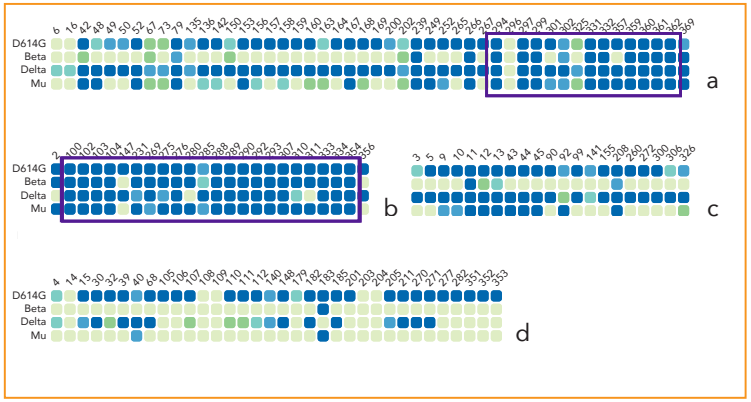
G614, Beta, Delta, Mu

90/397
23%

RBD-1



RBD-2



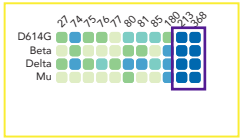
Outer face

RBD-4

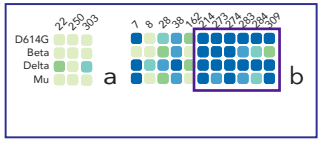
RBD-5

Inner face

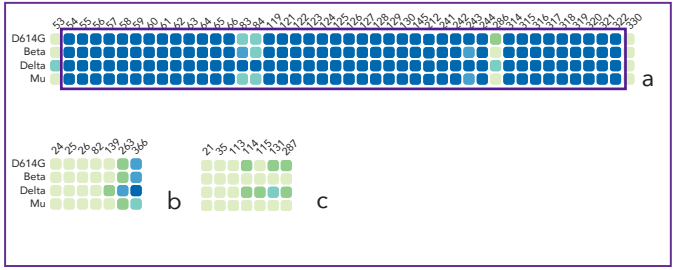
RBD-3

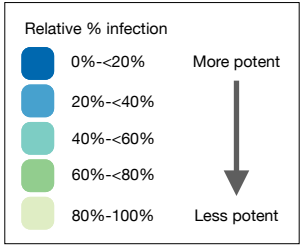


RBD-6



RBD-7



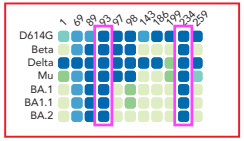


After Omicron

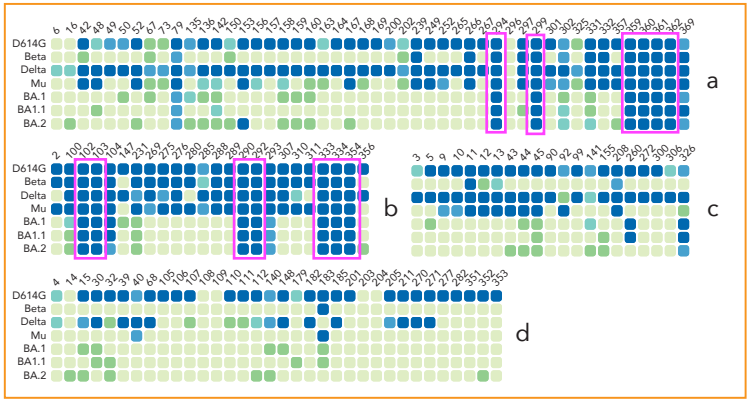
IC80 ~ 250ng/mL

Receptor binding motif (RBM)

RBD-1



RBD-2



G614, Beta, Delta, Mu + Omicron

18/397 ~5%

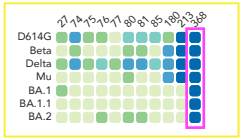
Outer face

RBD-4

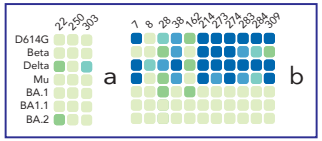
RBD-5

Inner face

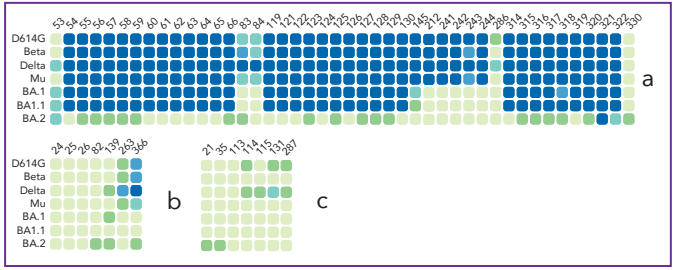
RBD-3

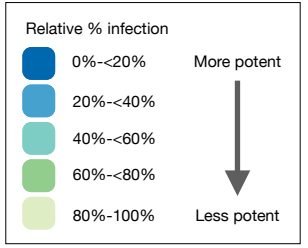


RBD-6



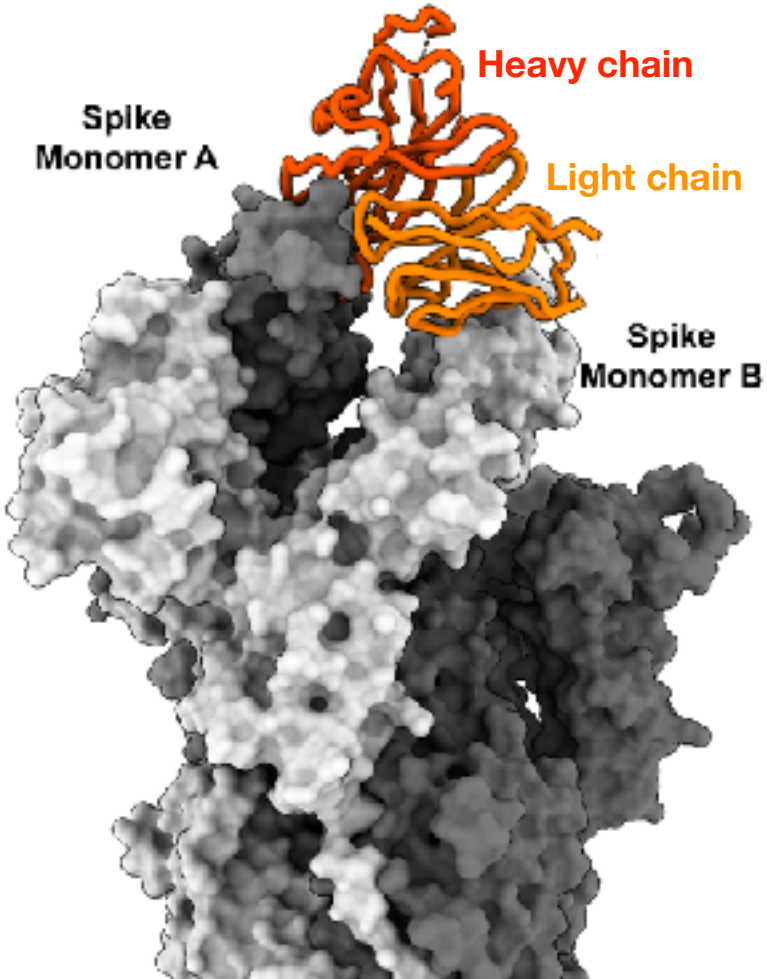
RBD-7





Moderna-vaccinated
San Diegan
made this
Omicron-neutralizing
antibody

Hastie, et al. 2023 in press.



Our Wits vs. viral genes

SARS-CoV-2:

Kathryn Hastie, LJI
Haoyang Li, LJI
Mahita Jarjapu, LJI
Bjoern Peters, LJI
Sharon Schendel, LJI
Heather Callaway, LJI
Xiaoying Yu, now Arcturus

Measles and Nipah virus:

Mike Norris, now Univ. Toronto
Rob Stahelin, Purdue
Paul Duprex, Pittsburgh

Ebola virus:

Jeff Lee, now Univ of Toronto
Joao Dias, now Lilly
Takao Hashiguchi, now Kyoto
Marnie Fusco, now Wyoming
Sharon Schendel, LJI

NIH NIAID
Bill and Melinda Gates Foundation
SSRL and other synchrotrons
Beamline Operators
DOE support

100+ academic, industry, gov't labs who contributed to VIC, CoVIC