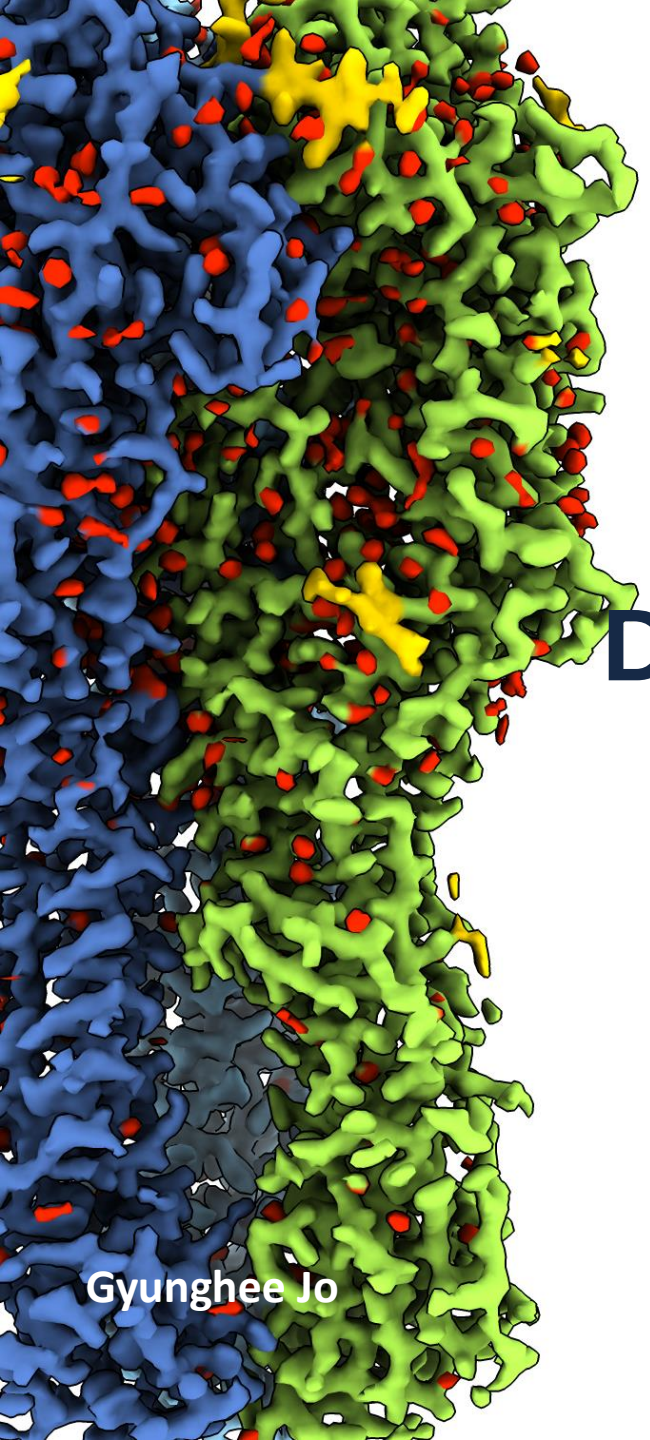


Gyunghee Jo

Decoding viruses for vaccine innovation

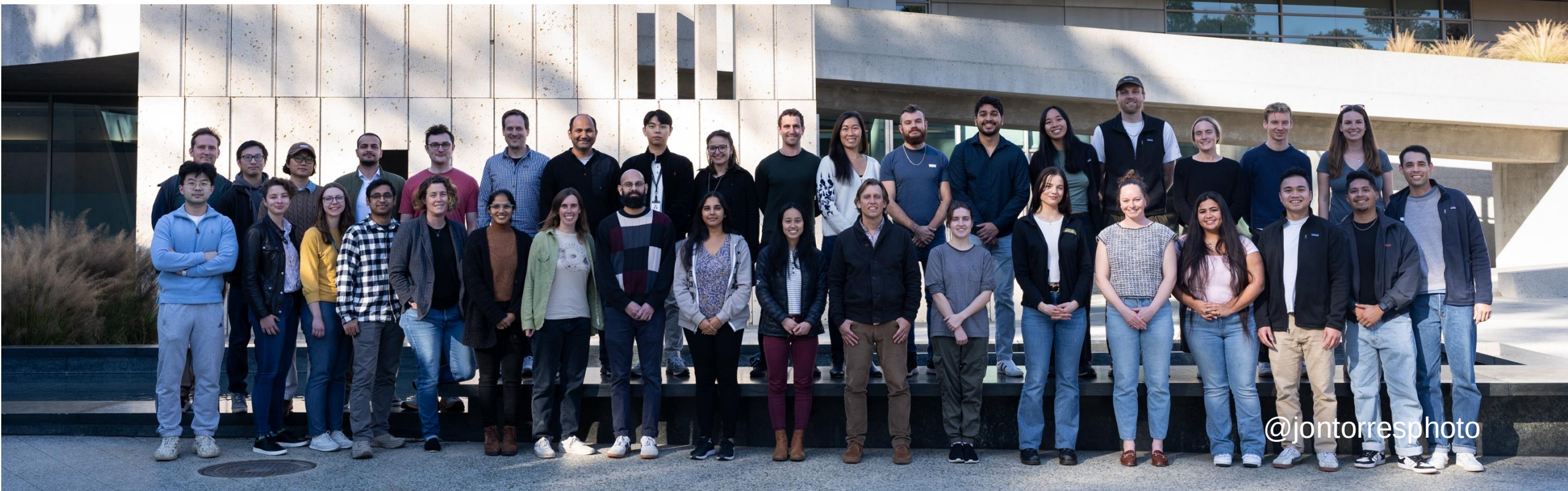
How mentorship, state-of-the-art technology, talented trainees, collaborators, and the Scripps ecosystem shaped my career

Andrew B. Ward, PhD

March 19, 2025

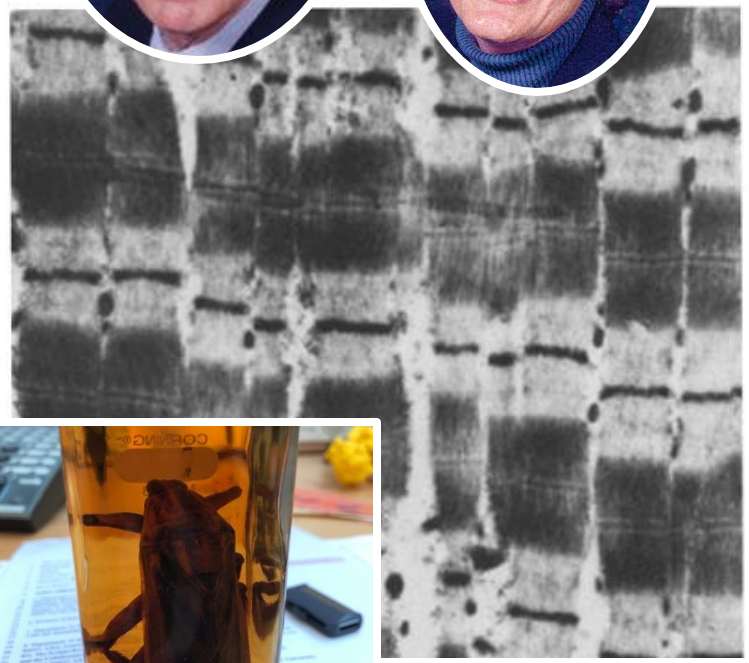
Scripps Research

Ward Lab 2025

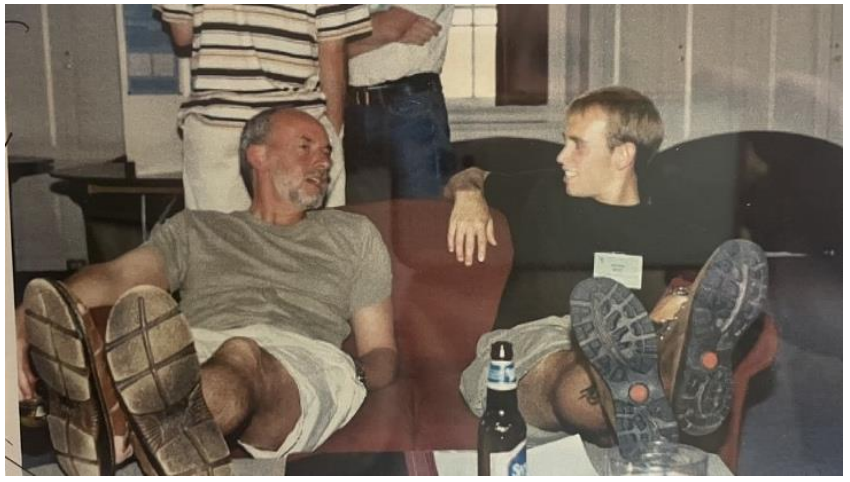


Mentorship

Michael and Mary Reedy



Lethocerus indicus



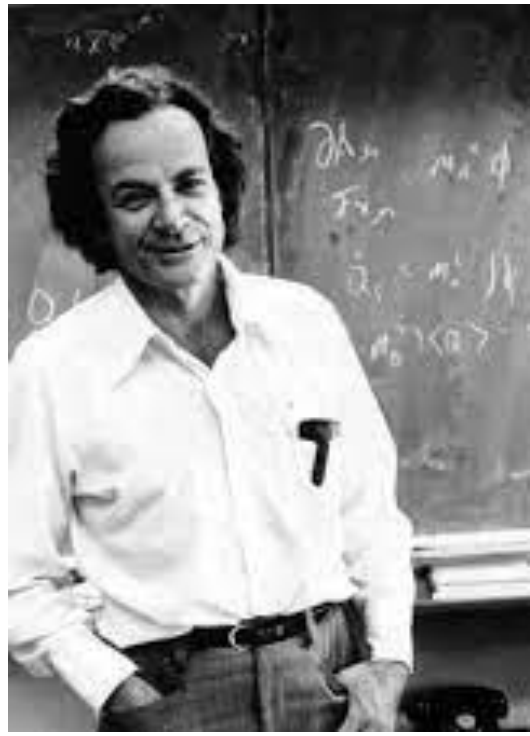
Ron Milligan

Ian Wilson

Dennis Burton

Jamie Williamson

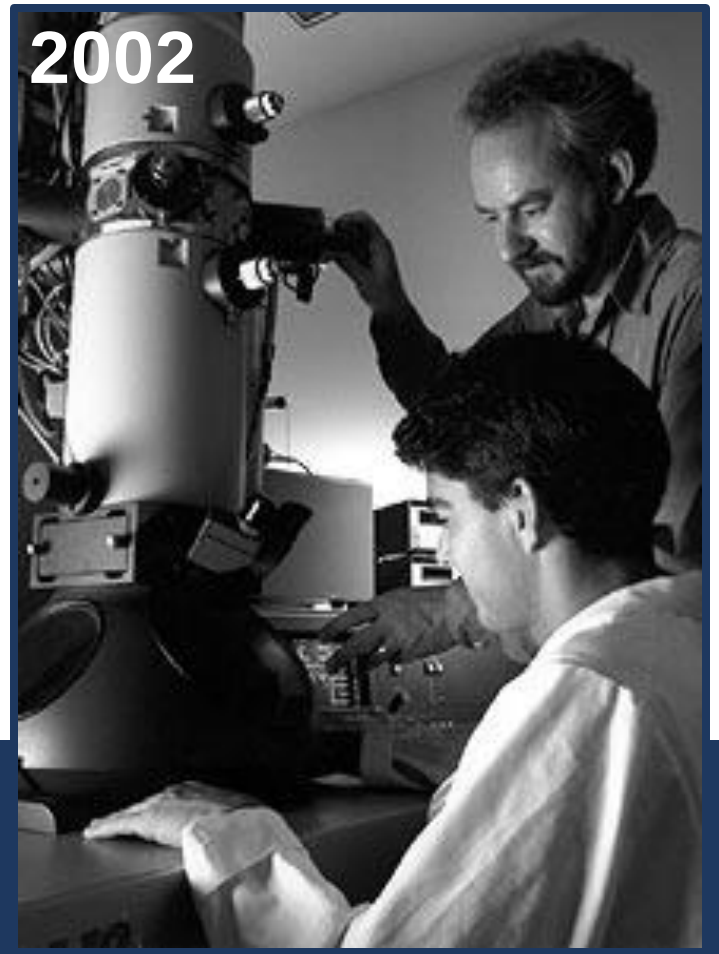
“**It is very easy to answer many of these fundamental biological questions; you just look at the thing!** You will see the order of bases in the chain; you will see the structure of the microsome. Unfortunately, the present microscope sees at a scale which is just a bit too crude. ***Make the microscope one hundred times more powerful, and many problems of biology would be made very much easier*.** I exaggerate, of course, but the biologists would surely be very thankful to you – and they would prefer that to the criticism that they should use more mathematics. ”



Richard Feynman, *There’s Plenty of Room at the Bottom* Dec. 29, 1959.

CryoEM before it was CryoEM

Cutting-Edge Molecular Microscopy Center Prepares to Open, 2002

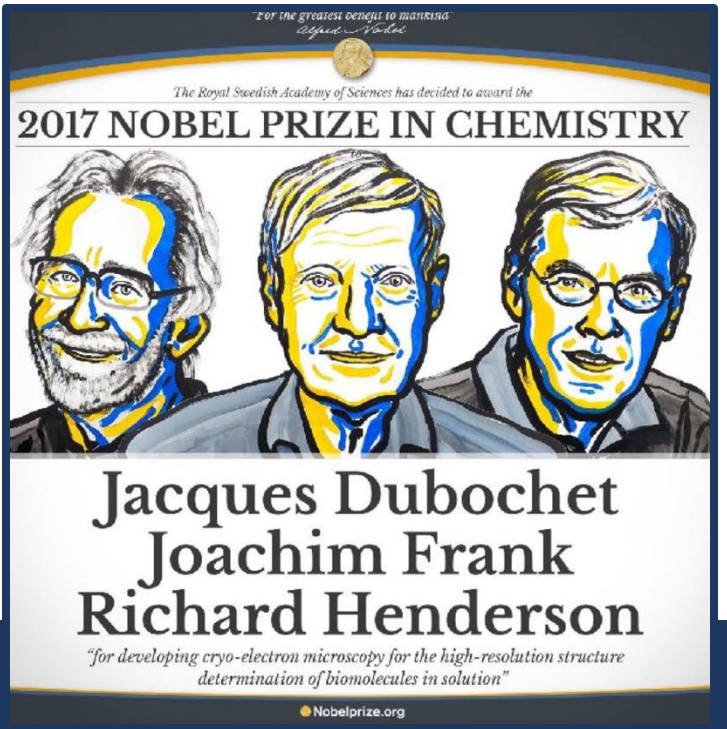


"…after they sat down with Professor Ron Milligan over drinks one night and drew up plans"

Bridget Carragher

Clint Potter

Ron Milligan

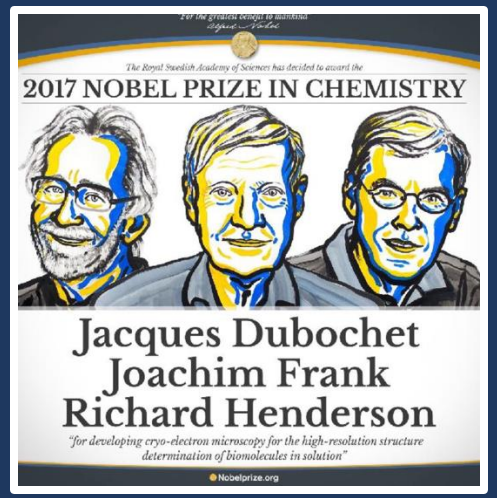


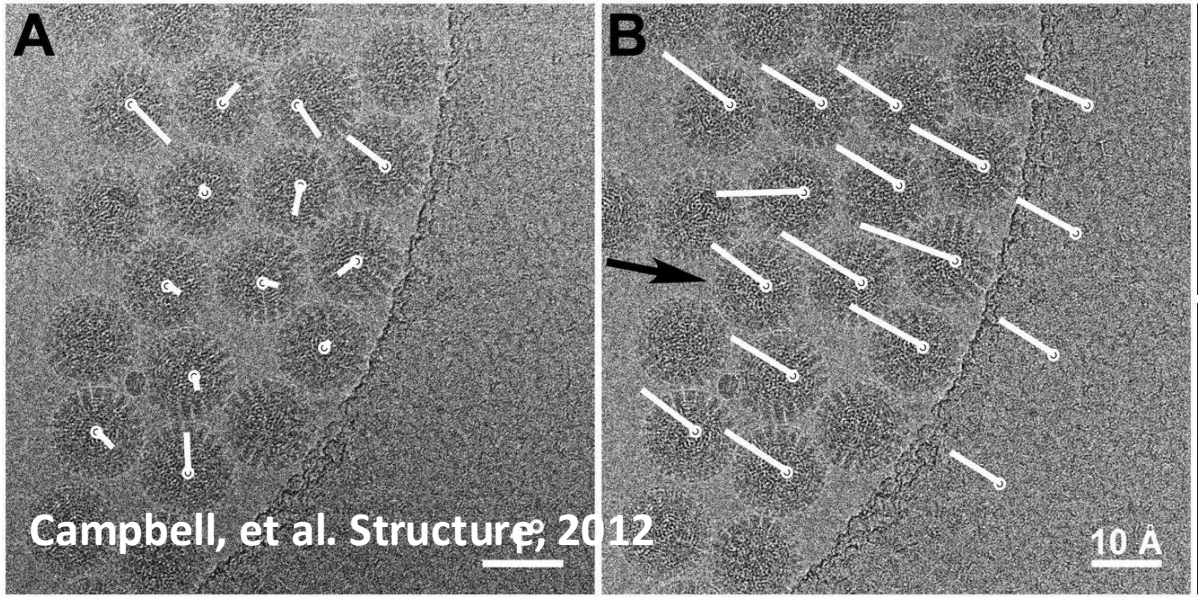
"EM is not a routine technique. Calculating an EM structure manually takes weeks or even months. It can be tedious." -RM

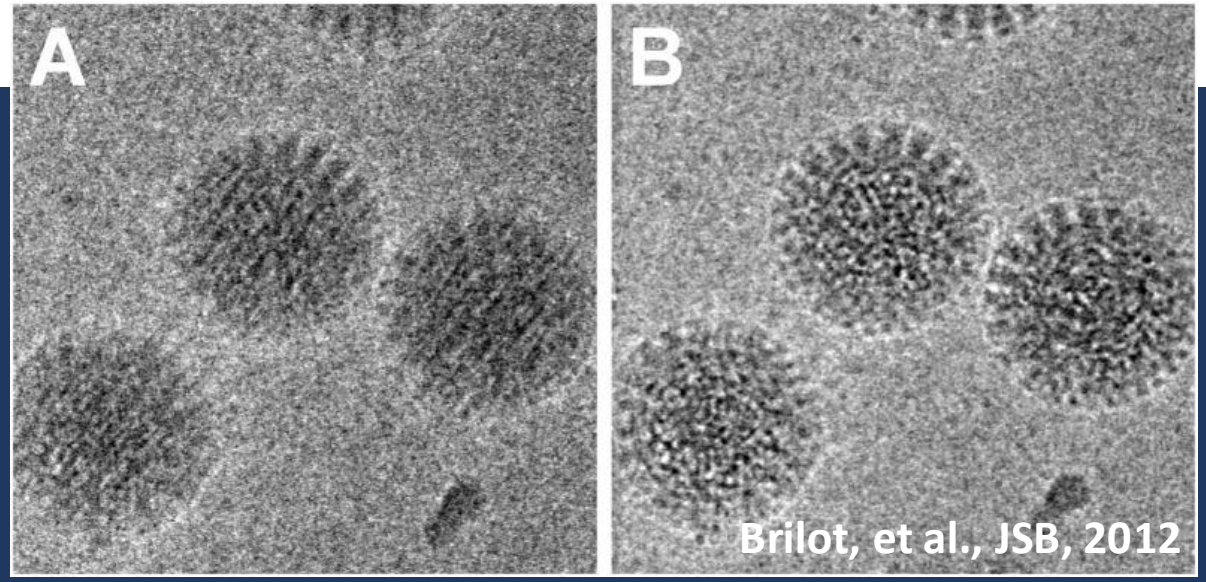
Electron Microscope

+

Direct detector



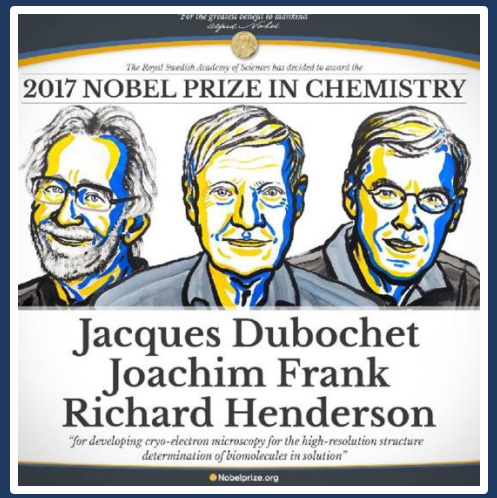




Electron Microscope

+

Direct detector



iPhone 11

CryoEM @ Scripps

Bill Anderson

Hannah Turner

Will Lessin

Tecnai Spirit

Talos

Talos Fortuna

Apr. 2024

Talos Arctica

Falcon 4i

Titan Krios

K3

+

+ Phase plates

Aquilos Cryo-FIB

Jan. 2022 Sep. 2023 Oct. 2024

Glacios

Falcon 4

Glacios 2

Falcon 4i

Glacios 2

Falcon 4i

CryoEM @ Scripps

Bill Anderson

Hannah Turner

Will Lessin

Jan. 2022 | Sep. 2023 | Oct. 2024

Tecnai Spirit | Talos | Talos Fortuna

Apr. 2024

Talos Arctica

Falcon 4i

Titan Krios

K3

+

+ Phase plates

Aquilos Cryo-FIB

Glacios

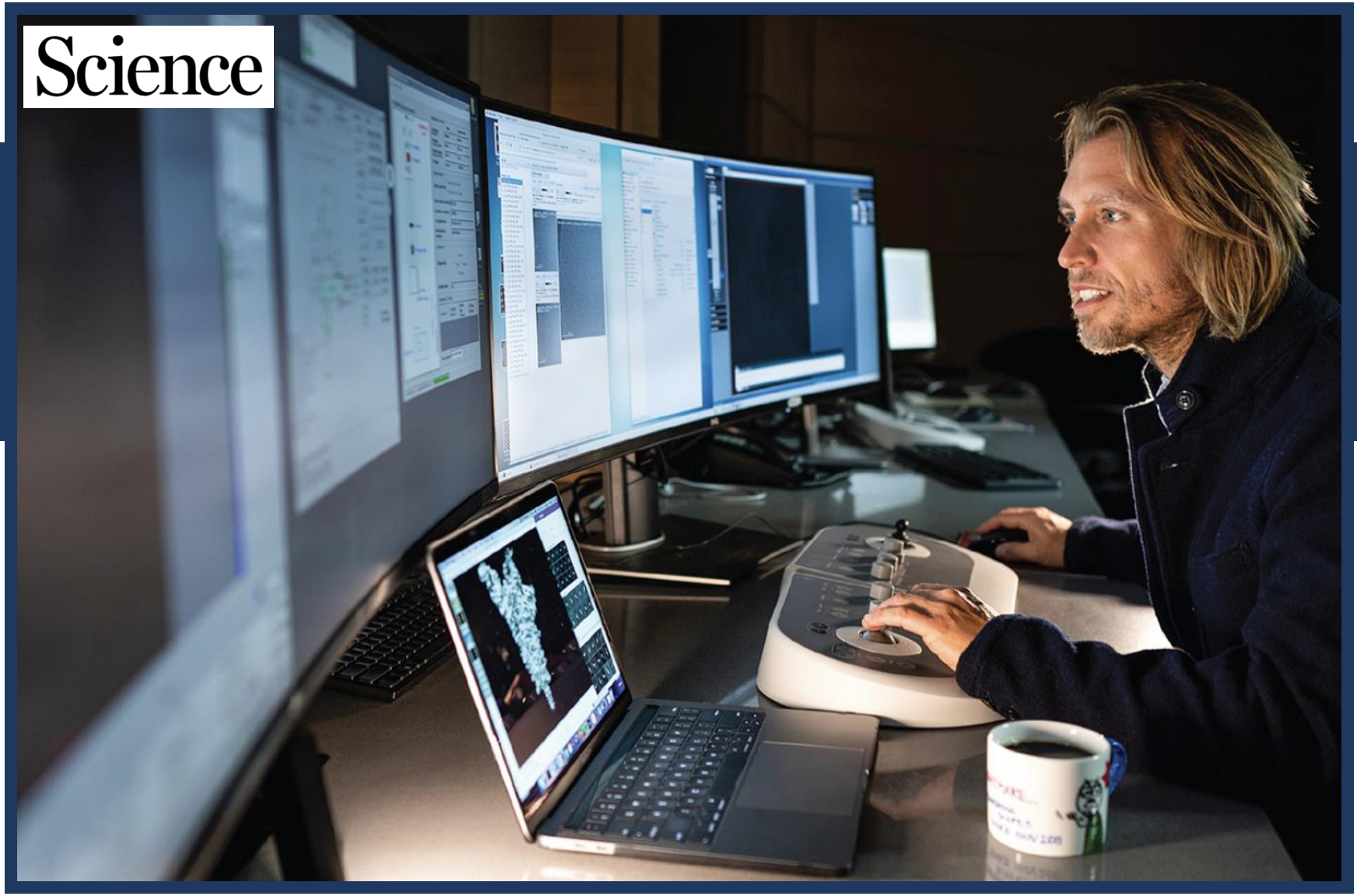
Falcon 4

Glacios 2

Falcon 4i

Glacios 2

Falcon 4i



Structural biologist Andrew Ward studies the nooks and crannies of a coronavirus spike protein for features common to spikes in other members of the virus family.

PHOTO: JONATHAN L. TORRES

@jontorresphoto

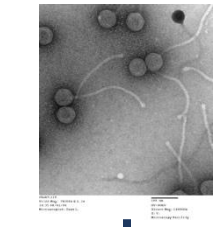
"The dream vaccine"
Jon Cohen
Science, 2021

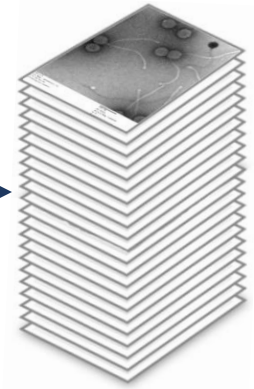
High performance computing

Data Collection

Data Processing

Data Storage





1.25 ft / s

1500 fps

Terabytes of data every day

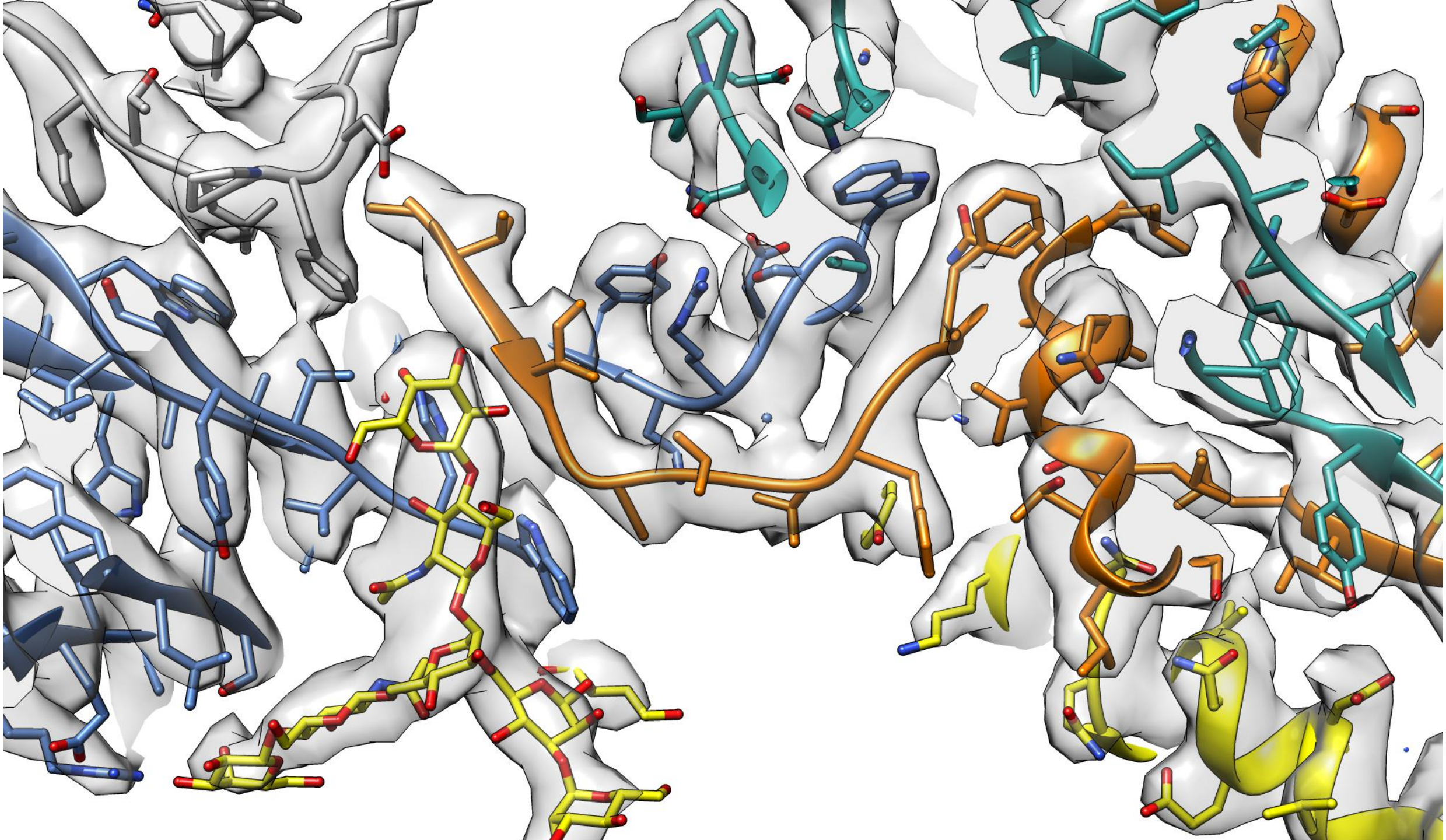
in 6.45 Hours

OR

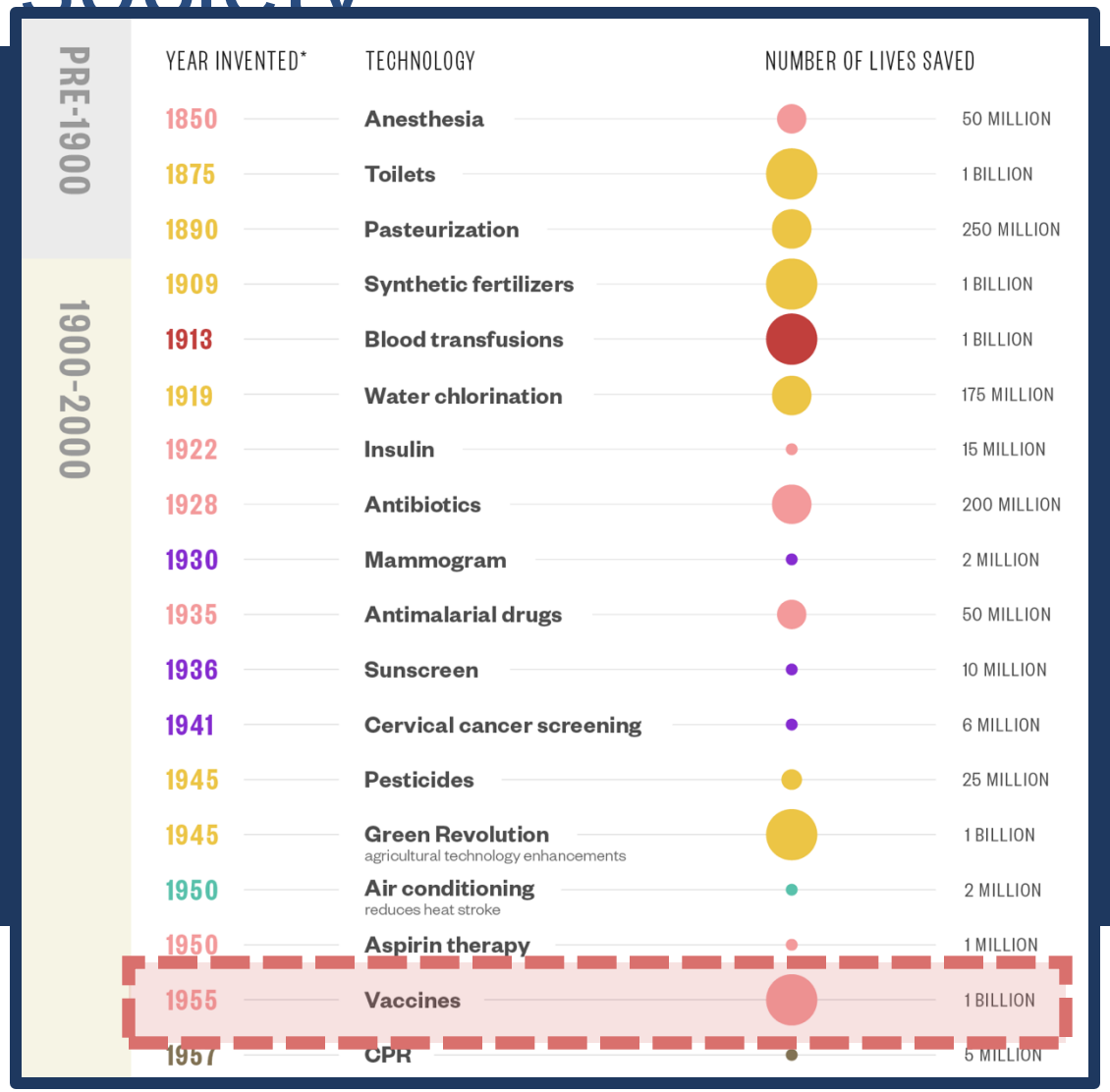
7 inches

JC Ducom
TSRI HPC Manager

Charlie Bowman
Ward Lab Staff Scientist



Vaccines have had an extraordinary impact on society



COVID vaccines saved **~2-20 million lives** in the first year *Lancet 2022*

"Without vaccination the U.S. would have experienced 1.5 times more infections, 3.8 times more hospitalizations, and **4.1 times more deaths**," the authors wrote. "These losses would have been accompanied by more than **$1 trillion** in additional medical costs that were averted because of fewer infections, hospitalizations, and deaths." *Commonwealth Fund, 2022*

Viruses cause 15-20% of cancers. HPV vaccines (Gardasil, Cervarix) have resulted in a >90% reduction in cervical and other related cancers. Vaccines can induce a butterfly effect beyond those vaccinated due to herd immunity.

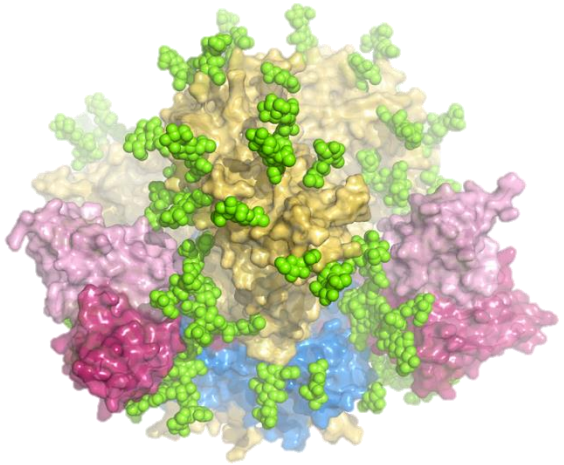
1 Billion

World Economic Forum, 2018

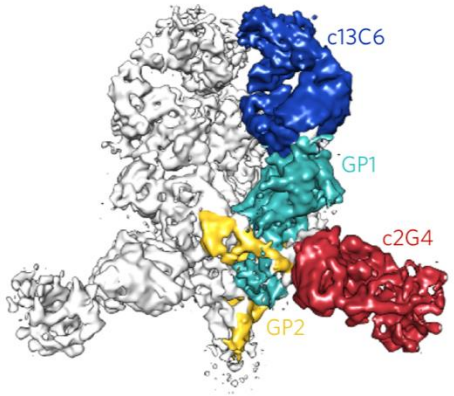
*Mathematical modeling requires robust, publicly available databases

A rogue’s gallery of pathogen weak spots

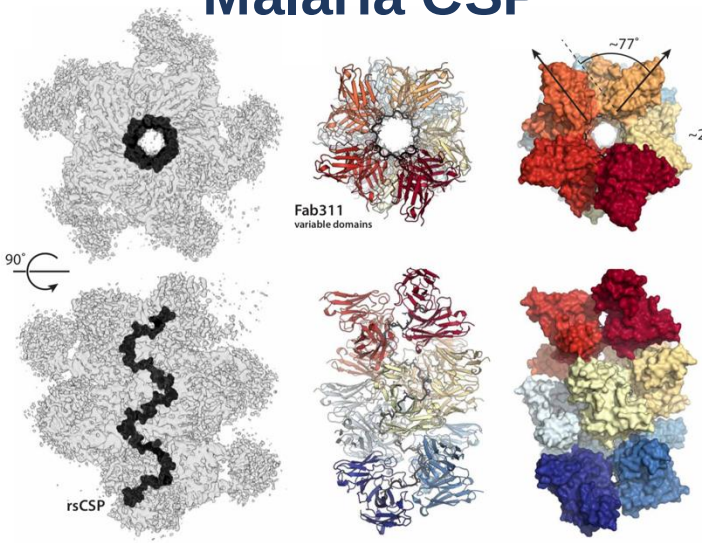
HIV Env



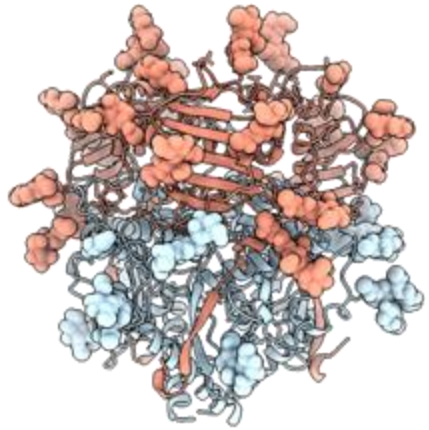
Ebola GP



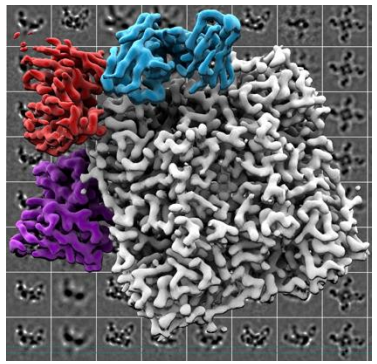
Malaria CSP



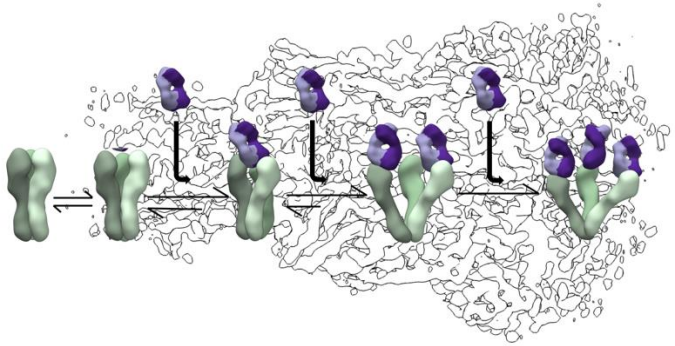
Lassa GPC



Influenza NA/HA

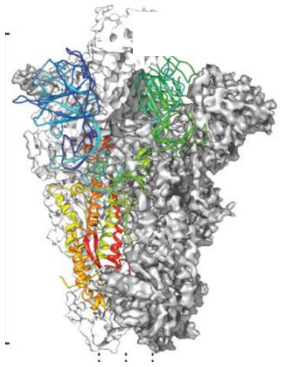


Neuraminidase

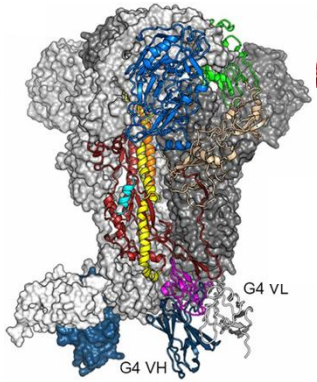


Hemagglutinin

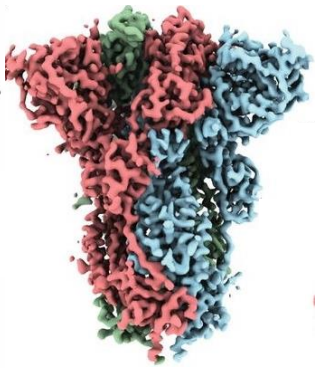
Coronavirus S



HKU1

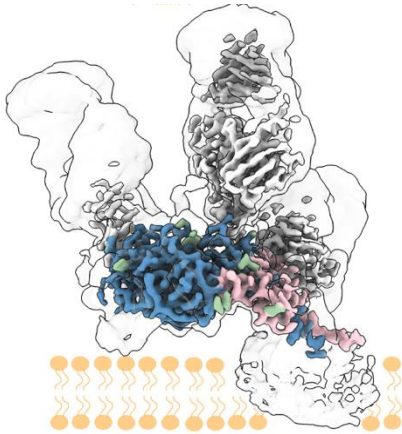


MERS

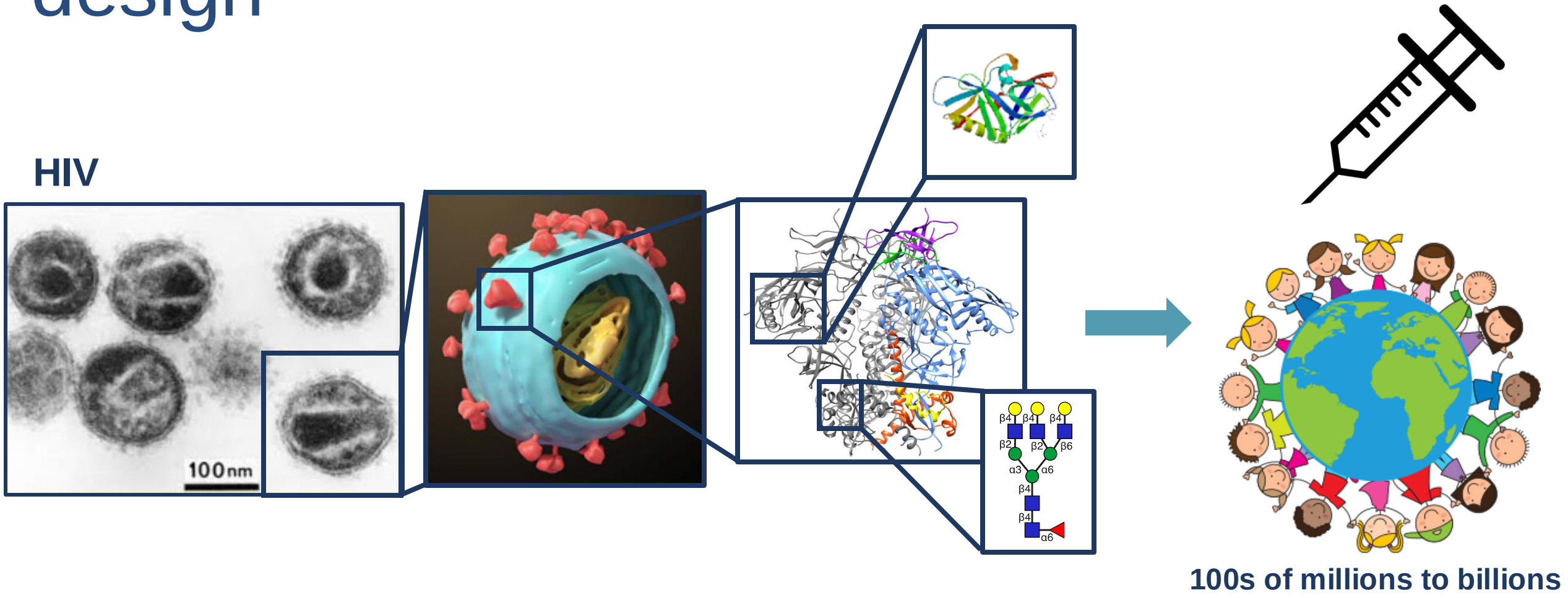


SARS

HCV E1E2

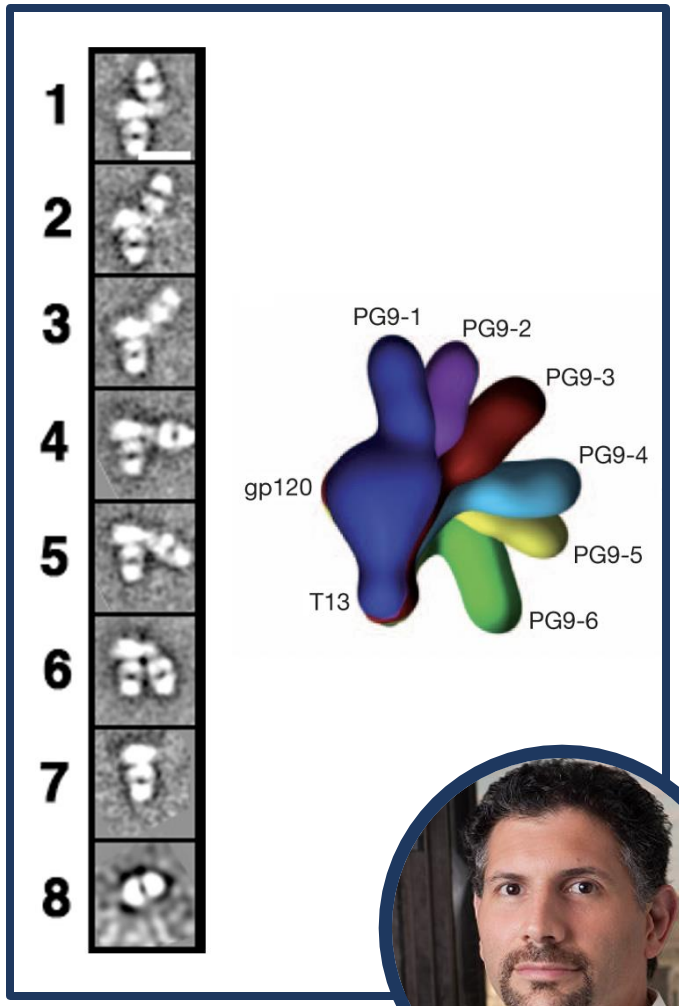


Programming immunity through protein design



Extrapolating atomic level details to vaccines effective on a global scale

Seeing is believing



Reza Khayat

Faculty, City College New York

Why won't these crystallize?
-Ian Wilson (2011)

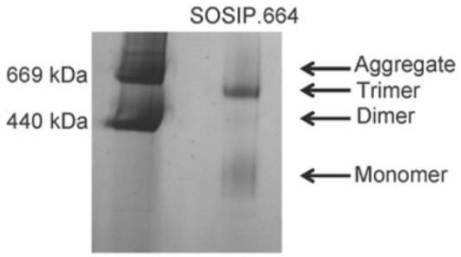
"It is very easy to answer many of these fundamental biological questions; you just look at the thing!" Richard Feynman

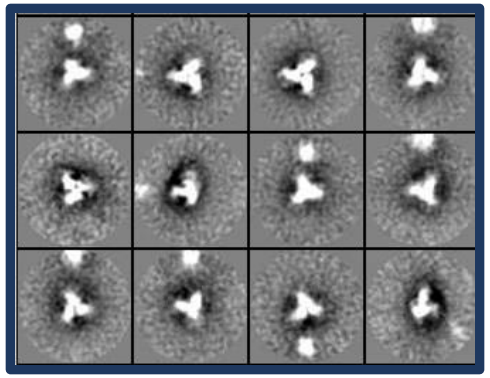
Over a decade of development by:J Moore, J Binley, R Sanders, I Wilson, and others

From bench to bedside

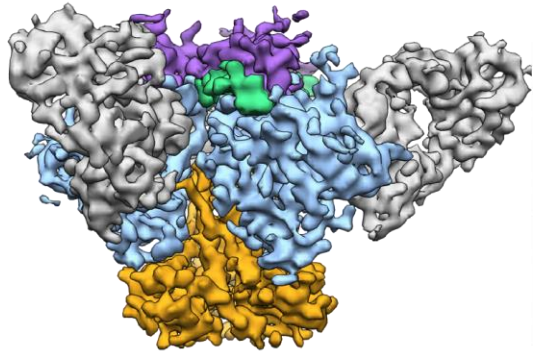
2011-2012 → **2013** → **2019** → **Present**

Research begins



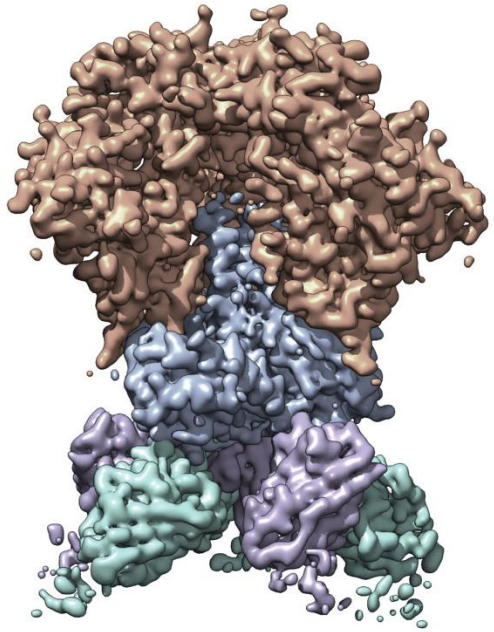


First structure of HIV Env trimer

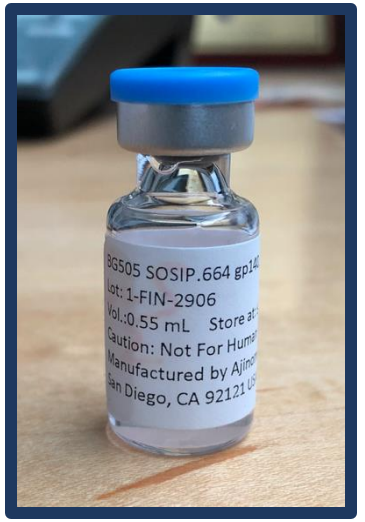


Direct detector

First structure of GMP clinical material



Ongoing clinical trials



Lyumkis, et al., Science 2013

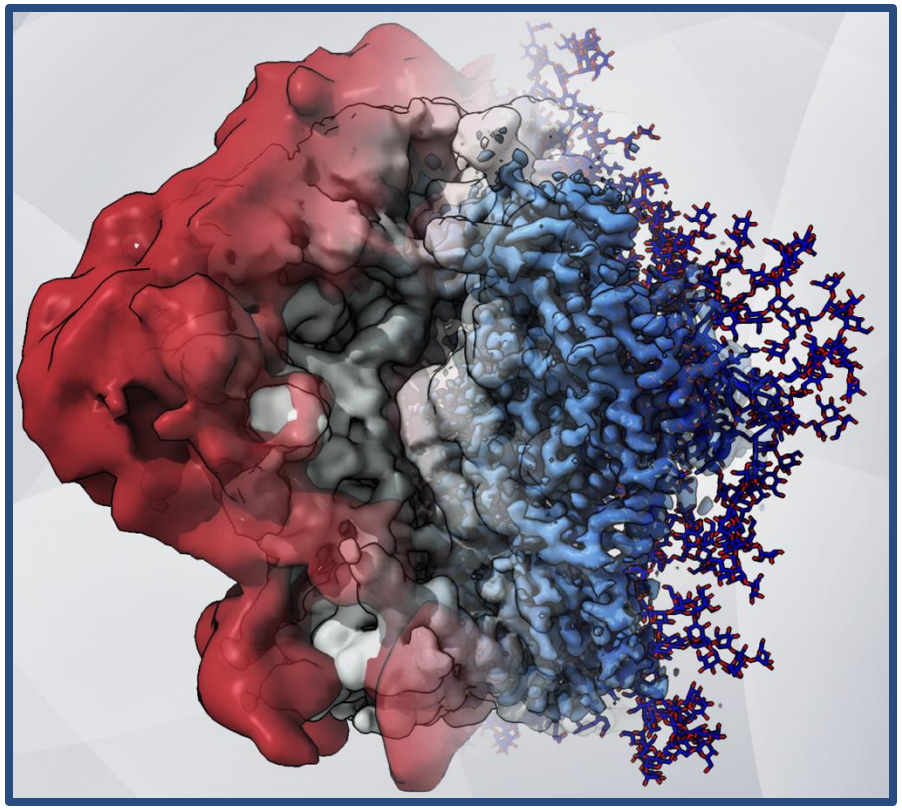
Research Arc: Zack Berndsen

Leveraging structure and computational biology to study diverse human disease

Zack Berndsen

Assistant Professor, University of Missouri

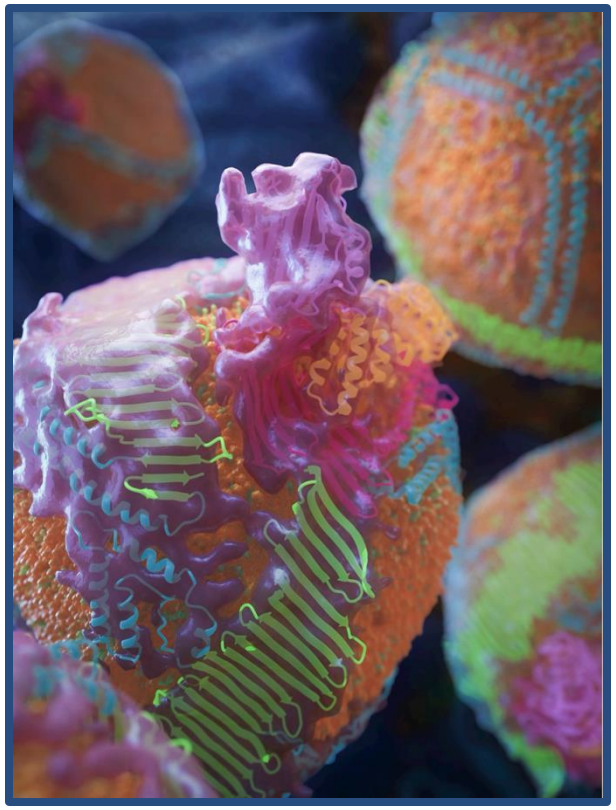
HIV envelope glycoprotein



Berndsen, et al., *PNAS,* 2020

Scripps Research postdoc

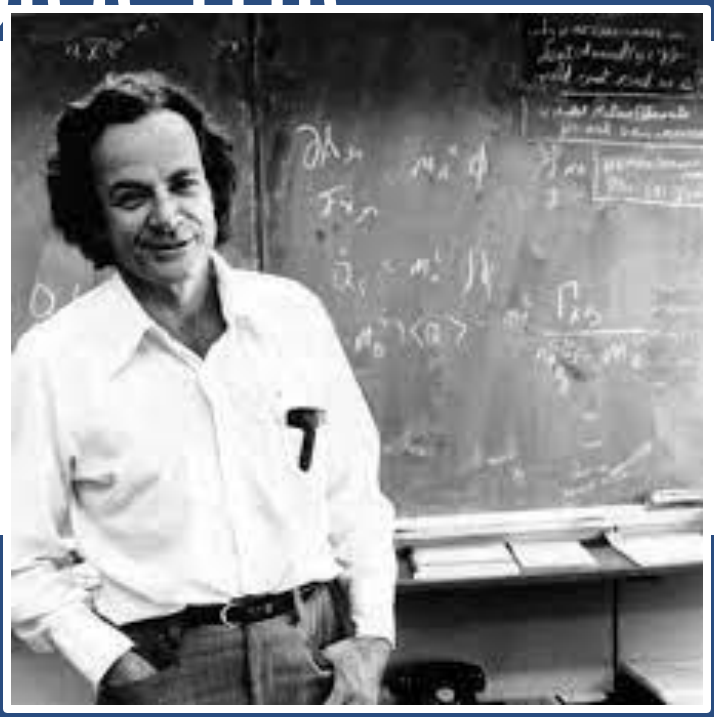
Human LDL particle



Berndsen and Cassidy, *Nature,* 2025

U Missouri faculty

We are not ready for the next epidemic



Prepare for the worst case:
~$10 Trillion was spent on the cold war despite invasion by Russia having a relatively low probability of happening.

Why doesn't the same logic apply to climate change [and pandemic preparedness]?
-Richard Feynman, 1990

"If anything kills over 10 million people in the next few decades, it's most likely to be a highly infectious virus rather than a way—not missiles but microbes," he said at the time. "We have invested a huge amount in nuclear deterrents, but we've actually invested very little in a system to stop an epidemic. ***We're not ready for the next epidemic."***

-Bill Gates, 2015

2015: Long before COVID

SARS outbreak: 2003
MERS outbreak: 2012

Jason McLellan

From: Andrew Ward [mailto:abward@scripps.edu]
Sent: Friday, May 01, 2015 5:50 PM
To: Jason S. McLellan
Cc: Robert Kirchdoerfer
Subject: Corona Virus

Hi Jason,
Great talking to you the other day. I would like to introduce you to Rob Kirchdoerfer, the postdoc I mentioned on the phone. He is very interested to get some EM projects going in my lab as part of his K99 application, and will primarily be focusing on Corona Virus RNP complexes. He would be happy to also work on your spike proteins, which will help you get up and running on EM and him with his application. The points below summarize how I see that we can proceed:

1. You send us spike protein/Fab complexes and Rob evaluates them by negative stain, and if they look good we move into cryo. If you have anything ready to go it would be great because he could include some preliminary data in his application due early June (I believe).
2. We have you out for a seminar and to see our workflow, instrumentation, etc. You could spend a few days and see how we do things.
3. We can then divide up the screening of samples and/or you could get that up and running at Dartmouth, while we push cryoEM efforts.
4. We are hugely successful, publish lots of high impact papers, Rob gets a faculty position, and we figure out how to keep collaborating based on our strengths and occasionally run into each other at meetings and have a beer.

Let me know what you think.
Best,
Andrew

“Just look at the thing”

VS.

In collaboration with Jason McLellan and Barney Graham

All downhill from there

Email to Jason
May 1, 2015

First samples arrive
May 7, 2015

Aug. 16, 2015
First cryoEM maps

Model building
& refinement

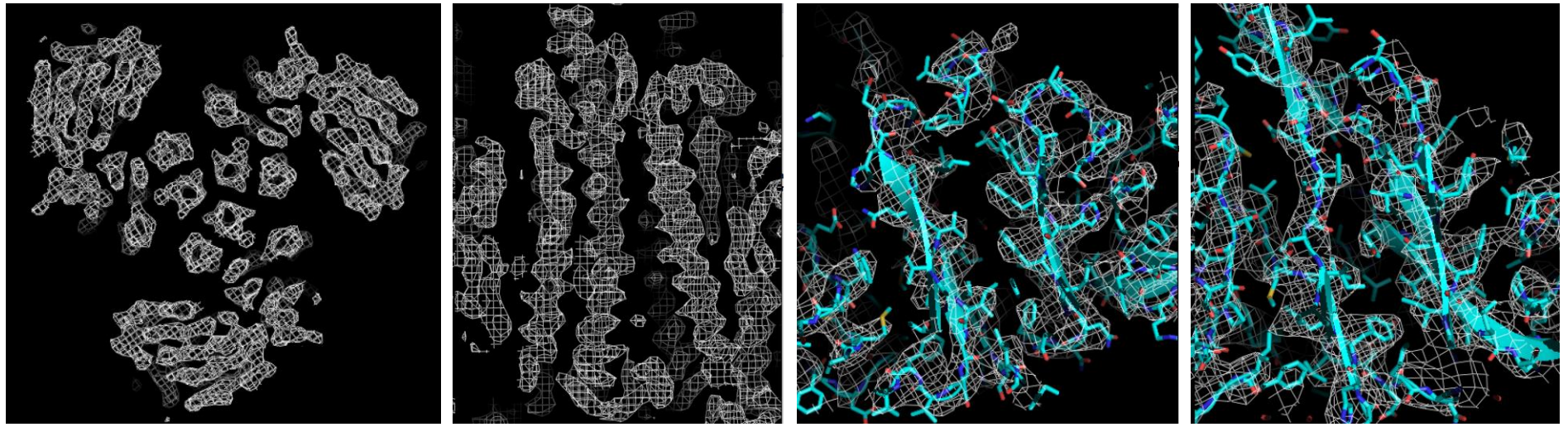
Manuscript submitted
Jan. 18, 2016

Feb. 4, 2016
R01 grant submitted

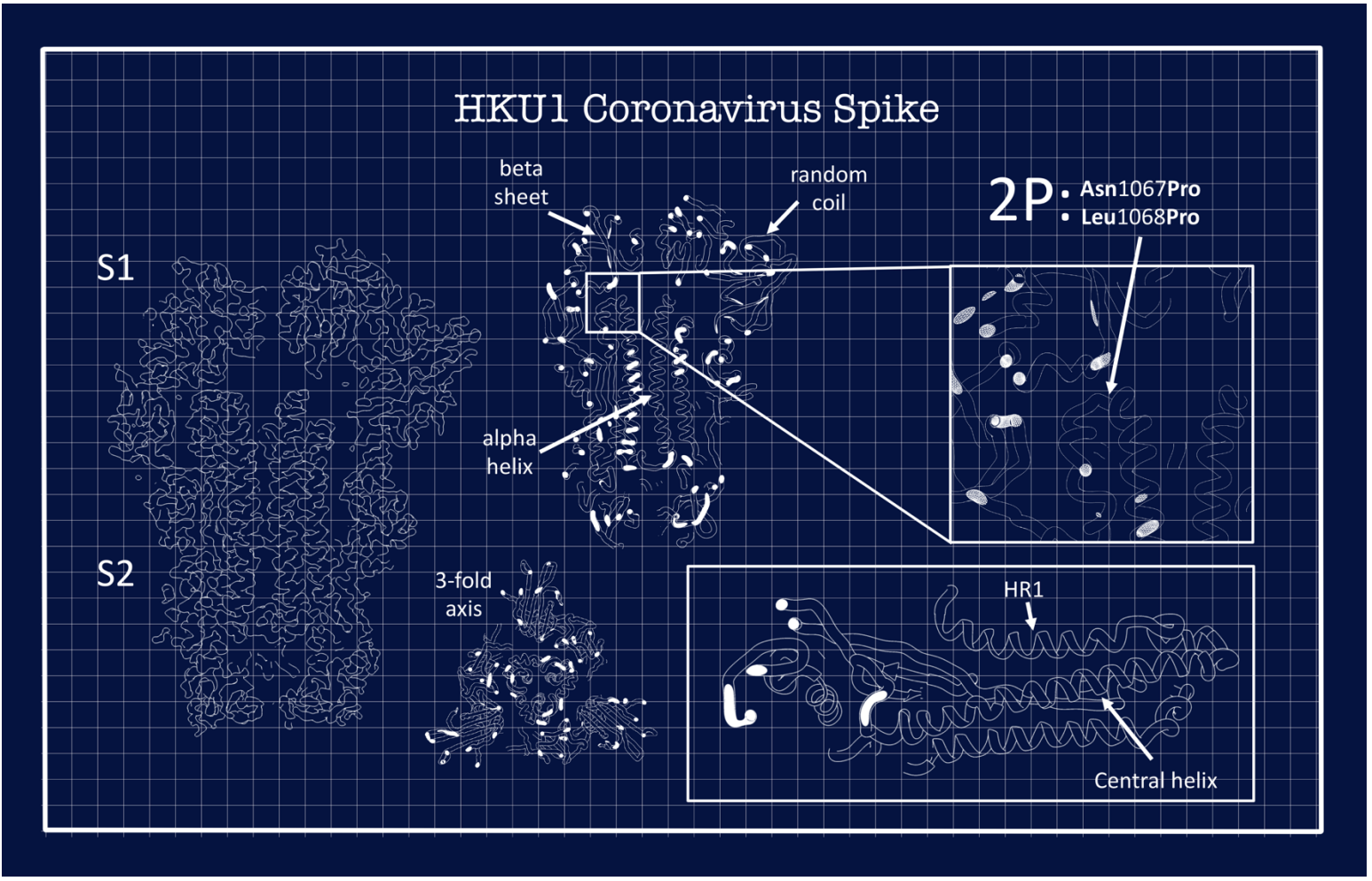
Manuscript accepted
Feb. 5, 2016

Manuscript online
Mar. 3, 2016

MERS, SARS…



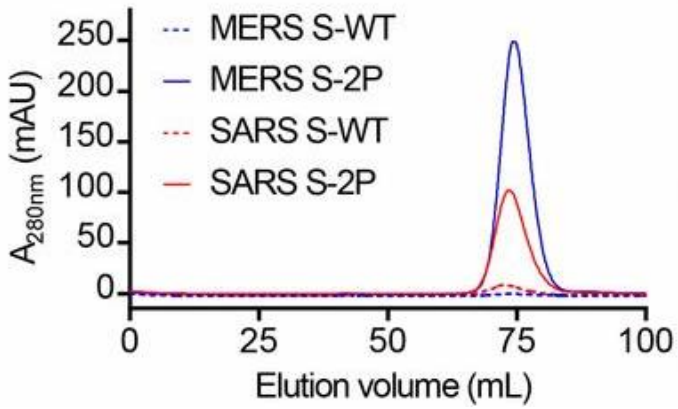
HKU1 spike structure unlocks ability to engineer SARS spike



The structural blueprints enabled rational design of stabilized prefusion spikes from MERS, SARS, other CoVs.

Over 25,000 possibilities to screen if each amino acid was mutated to each of the 20 possible amino acids.

2P mutations stabilize Spike in the pre-fusion conformation and increase its expression.



Kirchdoerfer, Cottrell, et al., *Nature*, 2016

Pallesen, Wang, et al., *PNAS*, 2017

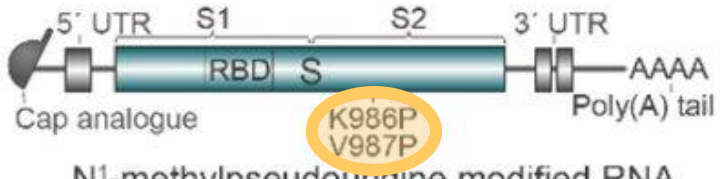
“2P”

Moderna

In early January 2020, a novel CoV (nCoV) was identified as the cause of a respiratory virus outbreak occurring in Wuhan, China. Within 24 hours of the release of the SARS-CoV-2 isolate sequences (then known as “2019-nCoV”) on January 10th, the 2P mutations were substituted into S positions aa986 and 987 to produce prefusion-stabilized SARS-CoV-2 S (S-2P) protein for structural analysis[23] and serological assay development[24,25] *in silico* without additional experimental validation. Within 5 days of sequence release, current Good Manufacturing Practice (cGMP) production of mRNA/LNP expressing the SARS-CoV-2 S-2P as a transmembrane-anchored protein with the native furin cleavage site (mRNA-1273) was initiated in parallel with preclinical evaluation.

Corbett et al, *Nature* 2020

Pfizer/BioNTech

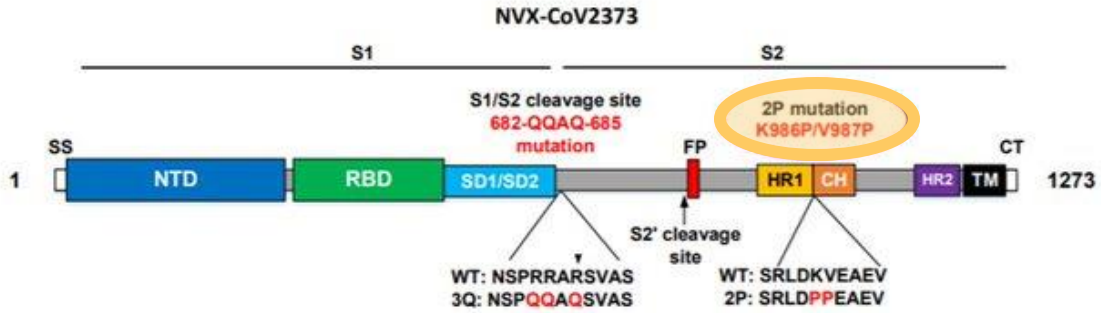


BNT162b2

N¹-methylpseudouridine modified RNA

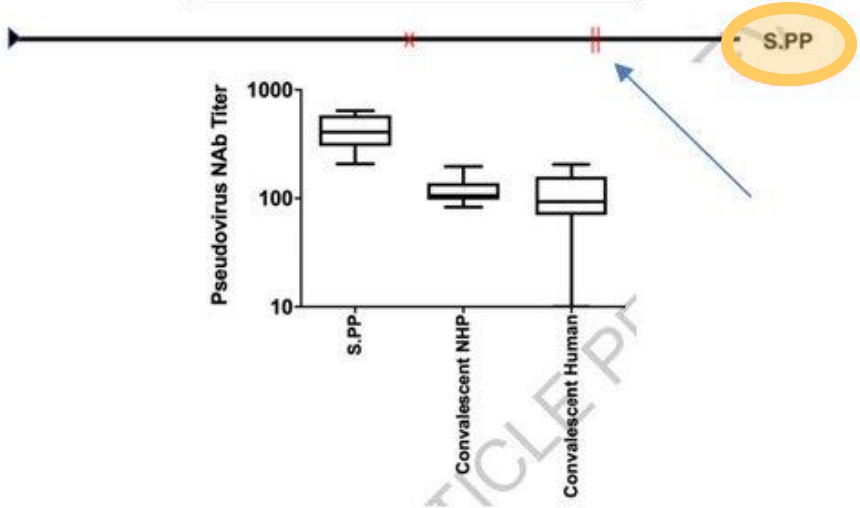
https://www.biorxiv.org/content/10.1101/2020.09.08.280818v1

Novavax



https://www.biorxiv.org/content/10.1101/2020.06.29.178509v1

Johnson & Johnson



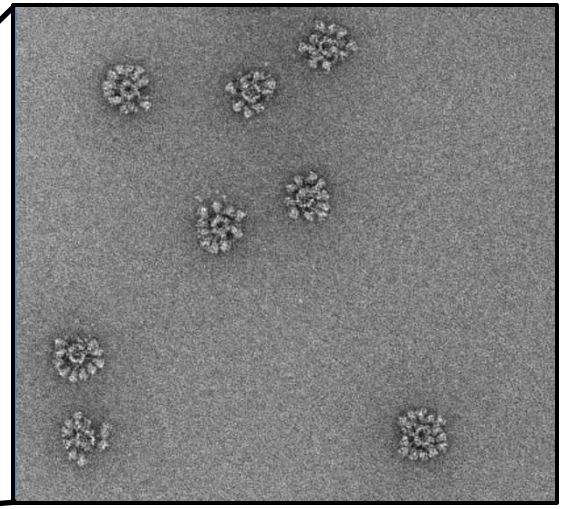
Mercado et al, *Nature* 2020

(US10960070B2, WO2018081318A1)

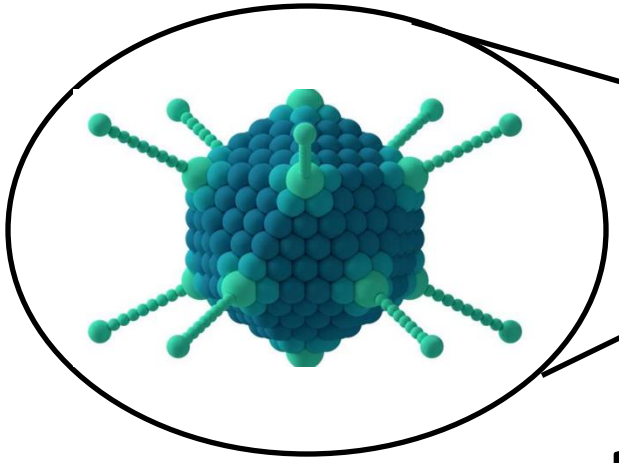
Vaccine Platforms

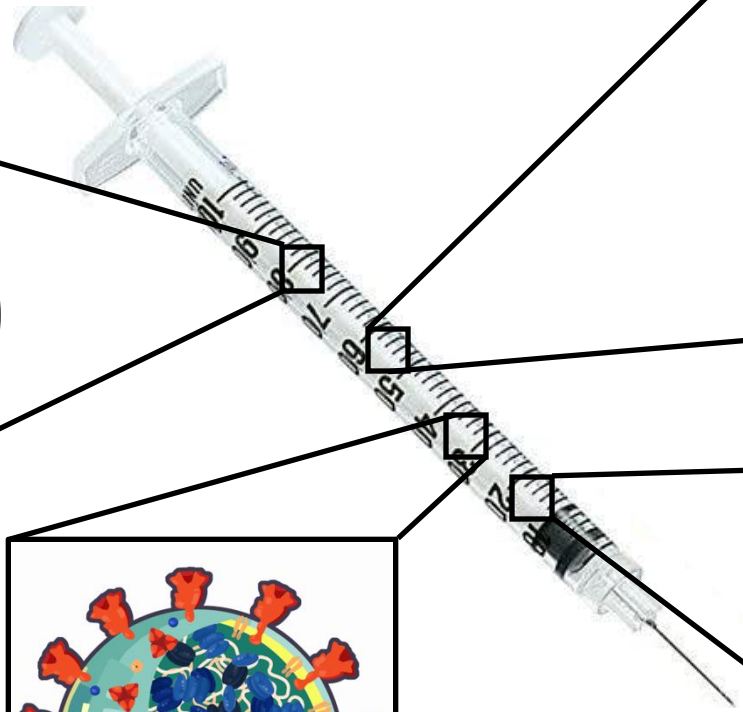
Lots of different ways to deliver antigen (spike)

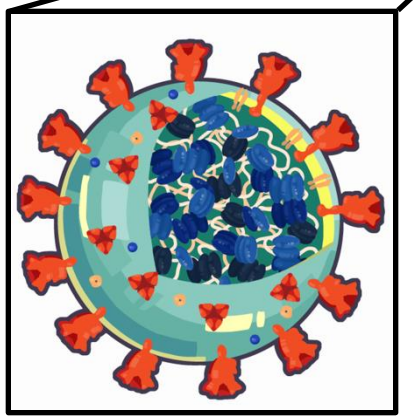
Protein subunit



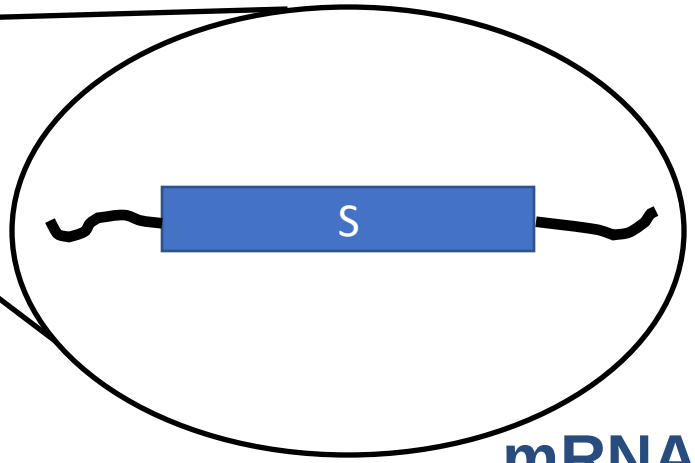
Vectored





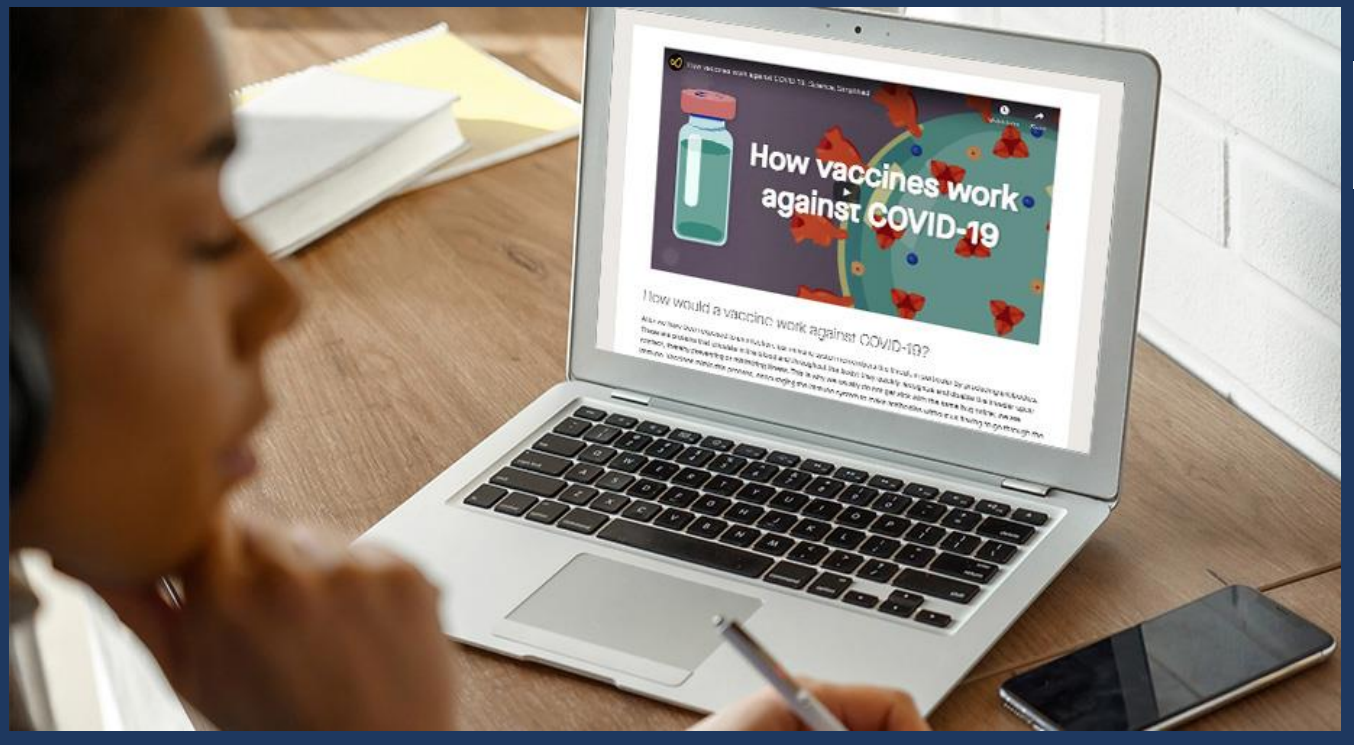


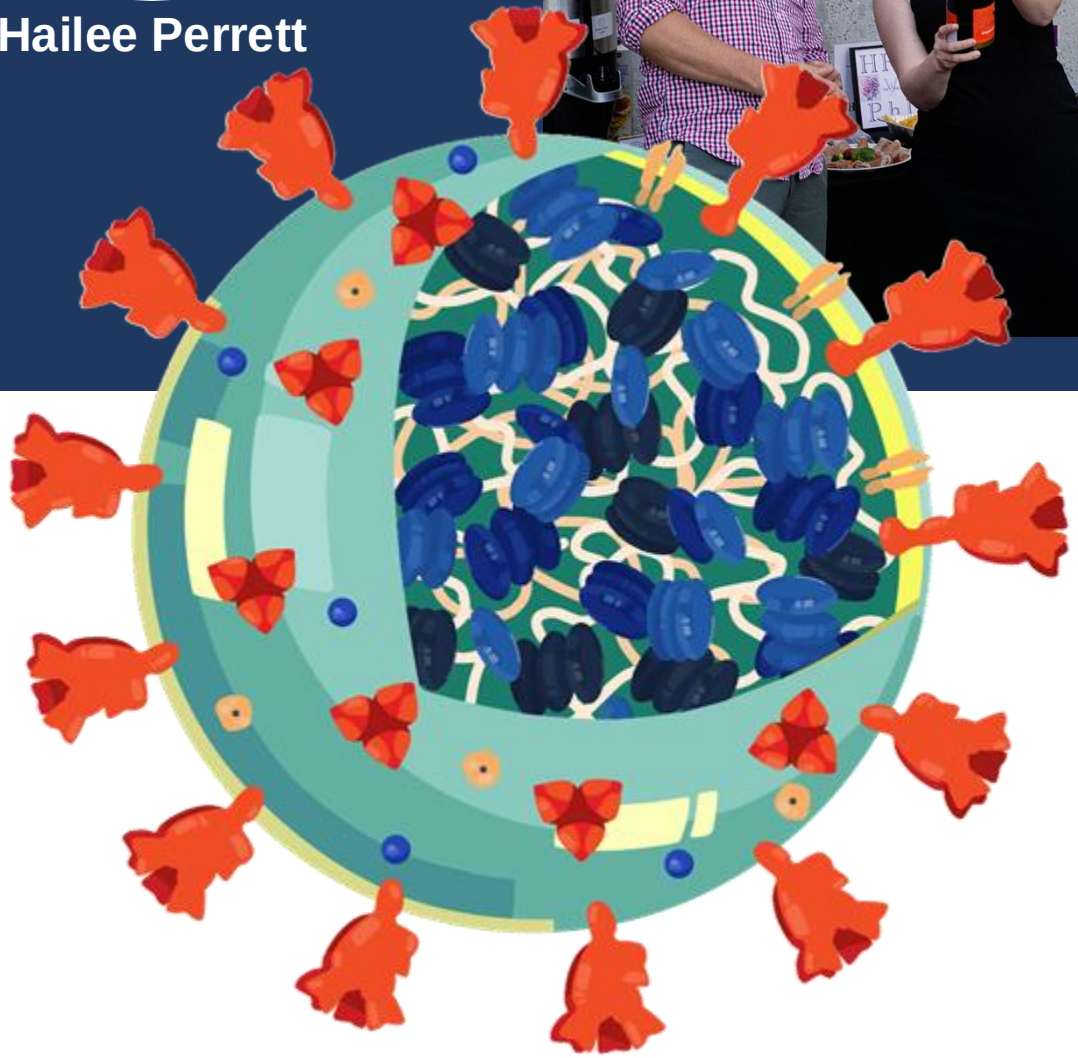
Inactivated



mRNA

Hailee Perrett





Answering the Big Questions with Science, Simplified

How a graduate student's scientific illustrations have gone viral, leading to an award-winning video series.

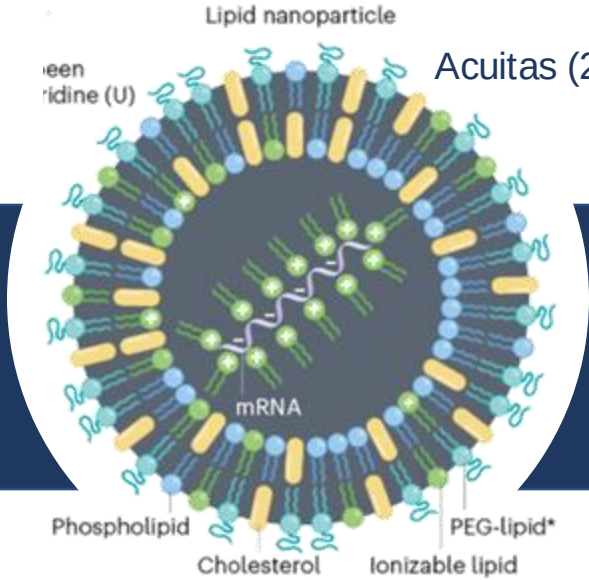
January 20, 2021

LA JOLLA, CA—A picture is worth a thousand words. When those words are dense scientific terms for the nature of viruses, that picture is invaluable. This is the thought process behind Science, Simplified, an animated video series focused on COVID-19 from Scripps Research that aims to take complex topics and break them down into short, easily digestible bites.

Basic research enabled vaccine development

Modified mRNA

Developed 1978-2010



Acuitas (2014)

WIRED

JOÃO MEDEIROS SCIENCE MAR 13, 2025 4:00 AM

Covid Vaccines Have Paved the Way for Cancer Vaccines

The mRNA technology behind coronavirus vaccines is now being used to create bespoke vaccines for cancer patients.

Modified RNA to prevent immune recognition and degradation

Basic research enabled vaccine development

Public databases

Real time updates

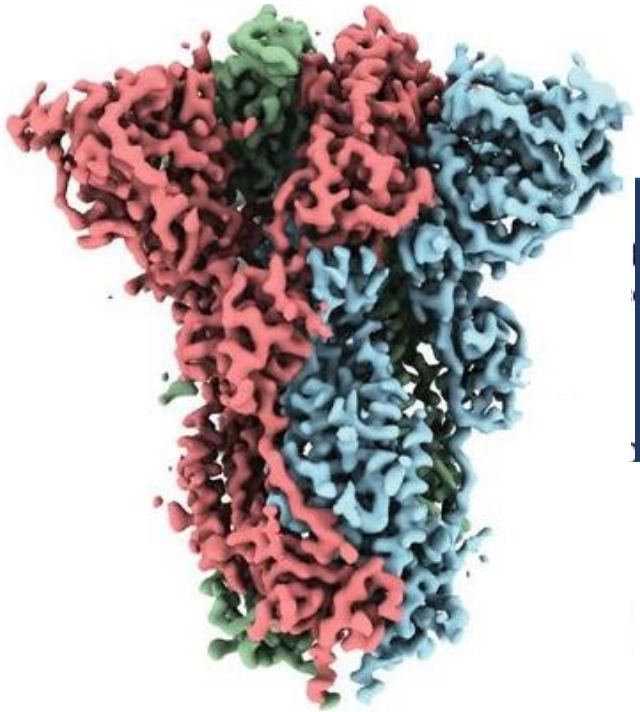
GISAID

Nextstrain

Real-time tracking of pathogen evolution

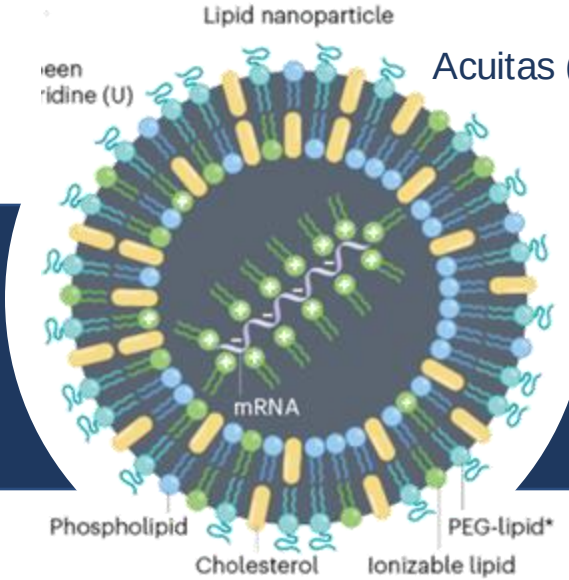
2P Spike Stabilization

Developed 2015-2016



Modified mRNA

Developed 1978-2010



Acuitas (2014)

Modified RNA to prevent immune recognition and degradation

Exhibit at the Smithsonian

Portrait of the research team collaborating on vaccine development.
Photos: National Institutes of Health

Rob Kirchdoerfer

Hannah Turner

Chris Cottrell

Jesper Pallesen

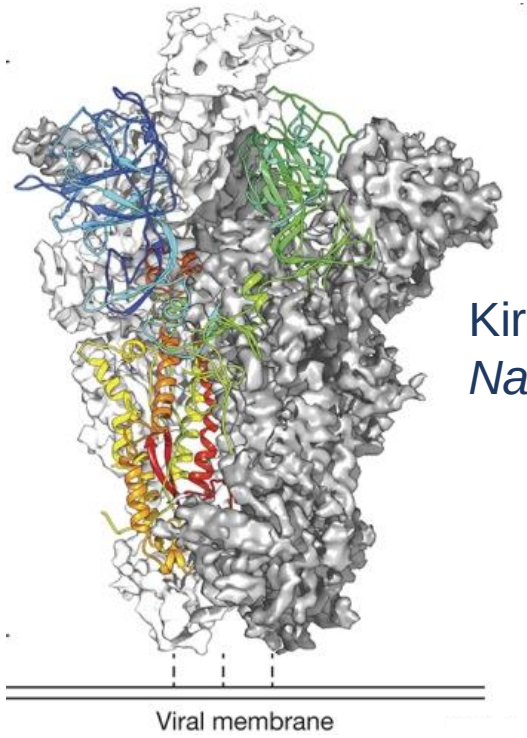
Research Arc: Rob Kirchdoerfer

Multi-pronged attack on Coronaviruses

Robert Kirchdoerfer

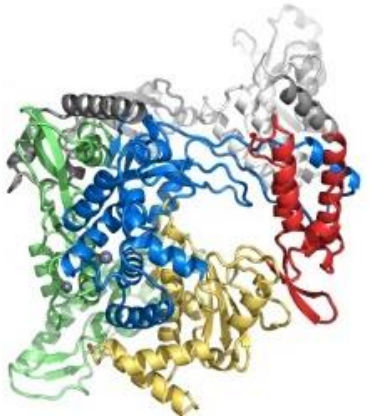
Assistant Professor,
University of Wisconsin–Madison

CoV Spike

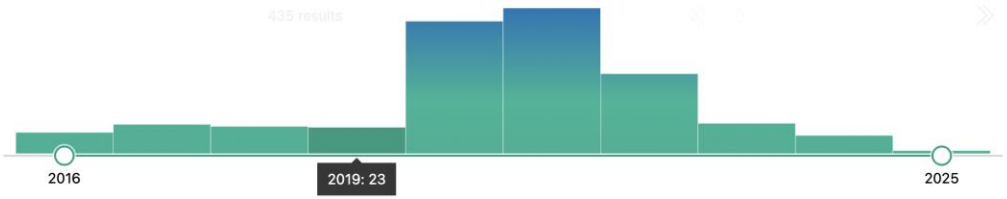


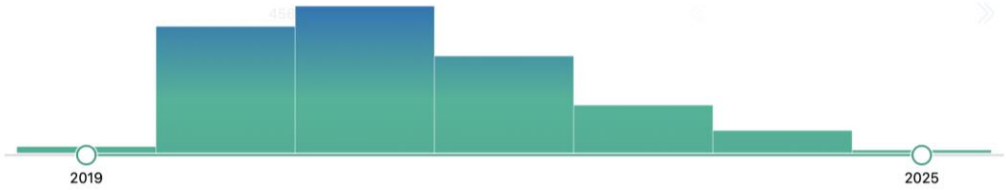
Kirchdoerfer, et al., *Nature*, 2016

SARS polymerase

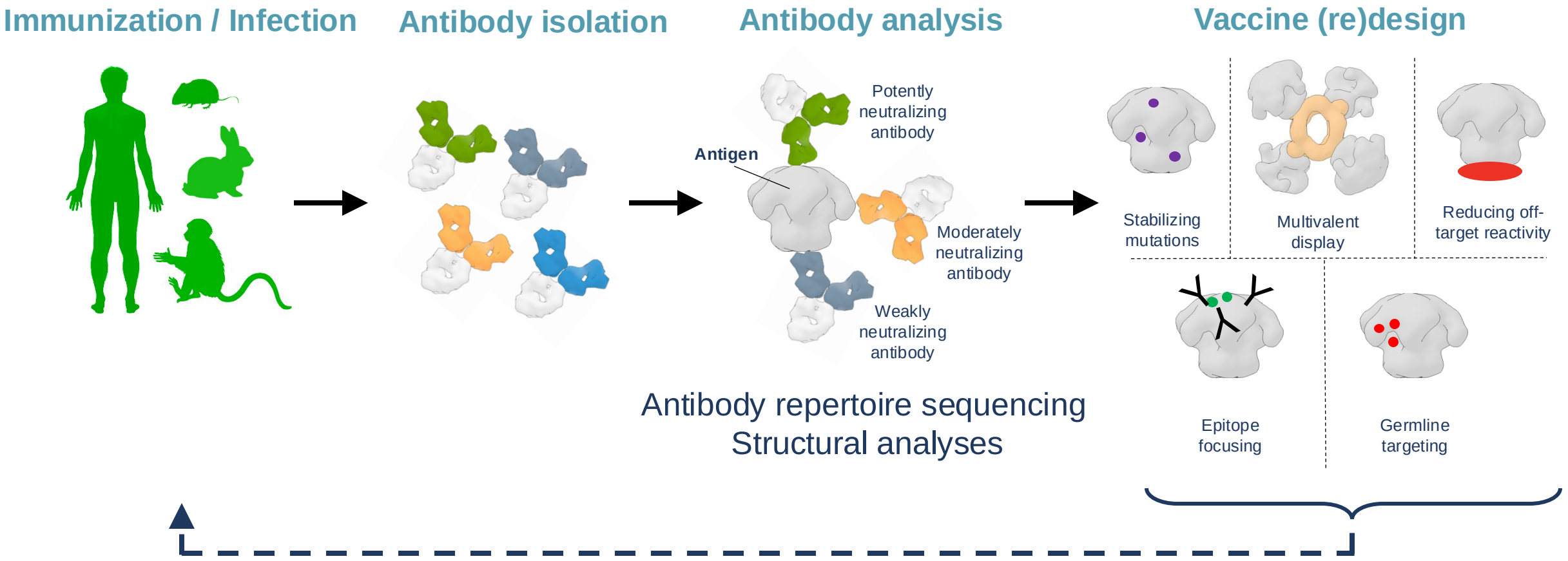


Kirchdoerfer and Ward, *Nat Comm*, 2019





How do we make better vaccines?



Rational vaccine design process requires iteration

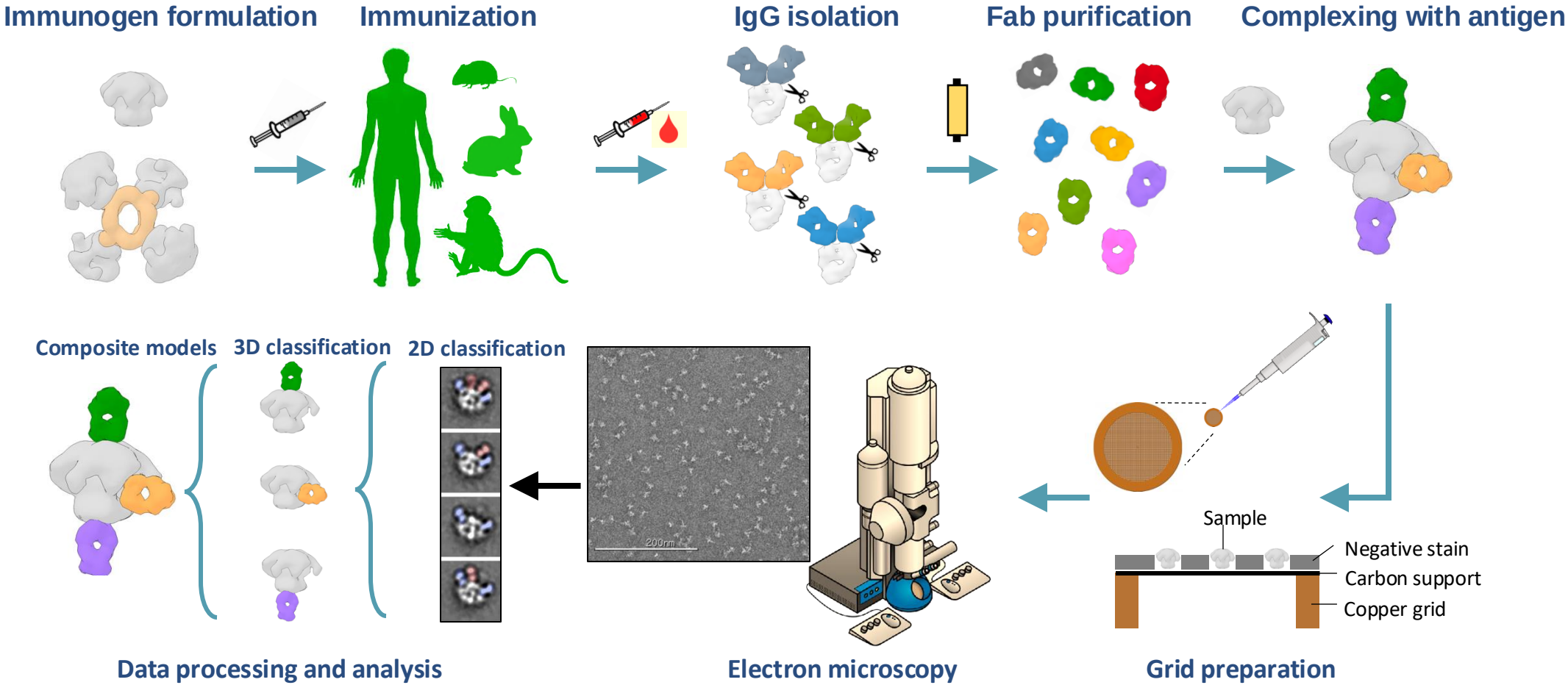
EM-based polyclonal epitope mapping (EMPEM)

Hannah Turner

Lars Hangartner

Matteo Bianchi

Comprehensive epitope mapping in days



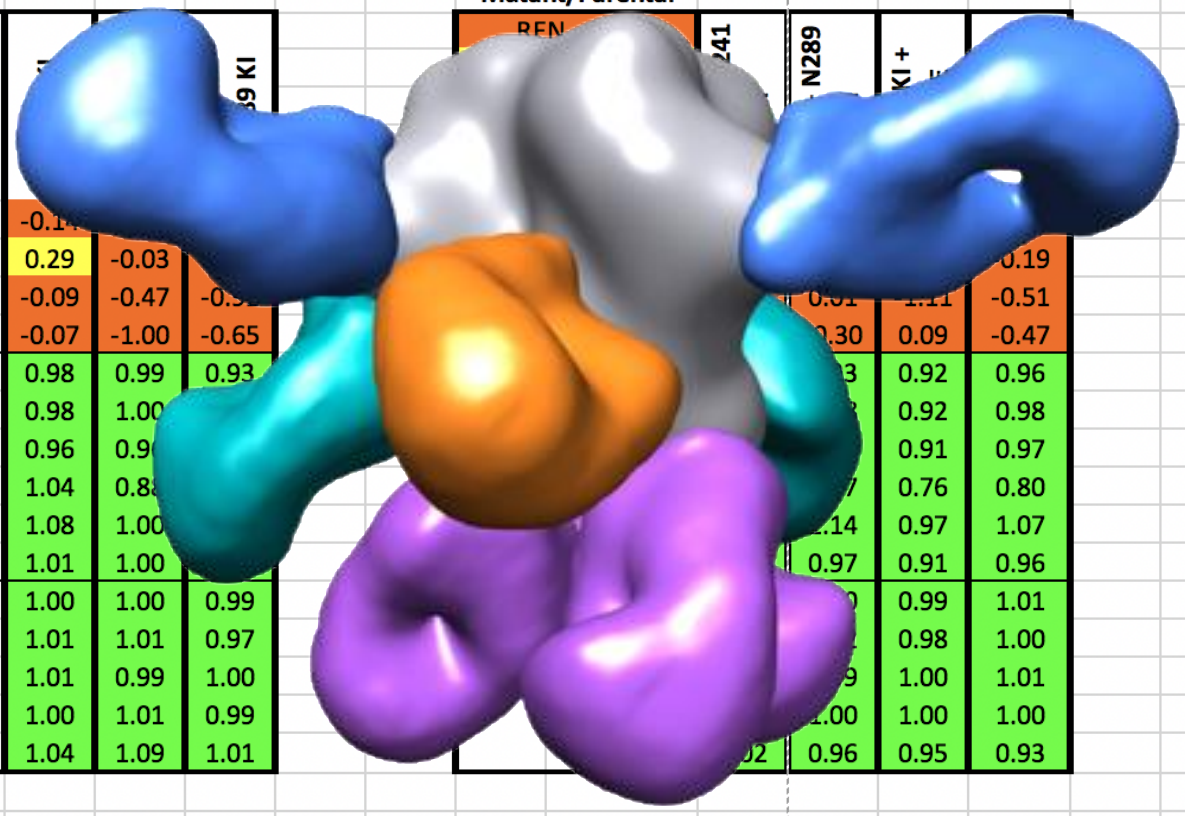
Bianchi, Turner, et al., *Immunity*, 2018

A picture is worth a thousand assays…

Klasse, et al., *PLoS Path*, 2018

SI Figure 3A

Mutant/Parental						Mutant/Parental					
REN <0.25		EN			89 KI		241	N289	KI +		
REN ≥0.25, ≤0.75											
REN >0.75, ≤1.25											
REN >1.25											
	Animal										
Group 1	r5726	74	-0.1								
	r5747	76	0.29	-0.03						0.19	
	r5749	79	-0.09	-0.47	-0.5			0.01	1.11	-0.51	
	r5725	78	-0.07	-1.00	-0.65			0.30	0.09	-0.47	
Group 2	r5739	87	0.98	0.99	0.93			3	0.92	0.96	
	r5743	98	0.98	1.00					0.92	0.98	
	r5744	97	0.96	0.9					0.91	0.97	
	r5723	89	1.04	0.8				7	0.76	0.80	
	r5727	84	1.08	1.00				1.14	0.97	1.07	
	r5738	94	1.01	1.00				0.97	0.91	0.96	
Group 3	r5724	99	1.00	1.00	0.99			0	0.99	1.01	
	r5742	98	1.01	1.01	0.97			1	0.98	1.00	
	r5741	96	1.01	0.99	1.00			9	1.00	1.01	
	r5740	99	1.00	1.01	0.99			1.00	1.00	1.00	
	r5751	94	1.04	1.09	1.01			02	0.96	0.95	0.93
MAbs	11A	80	0.17	-0.20	0.08	MAbs	11A	0.25	-0.18	-0.15	-0.17
	11B	82	0.42	0.15	0.41		11B	0.36	0.11	0.30	0.08

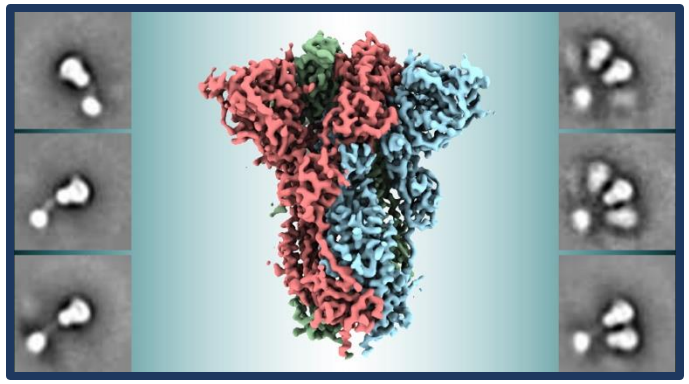


Research Arc: Sandhya Bangaru

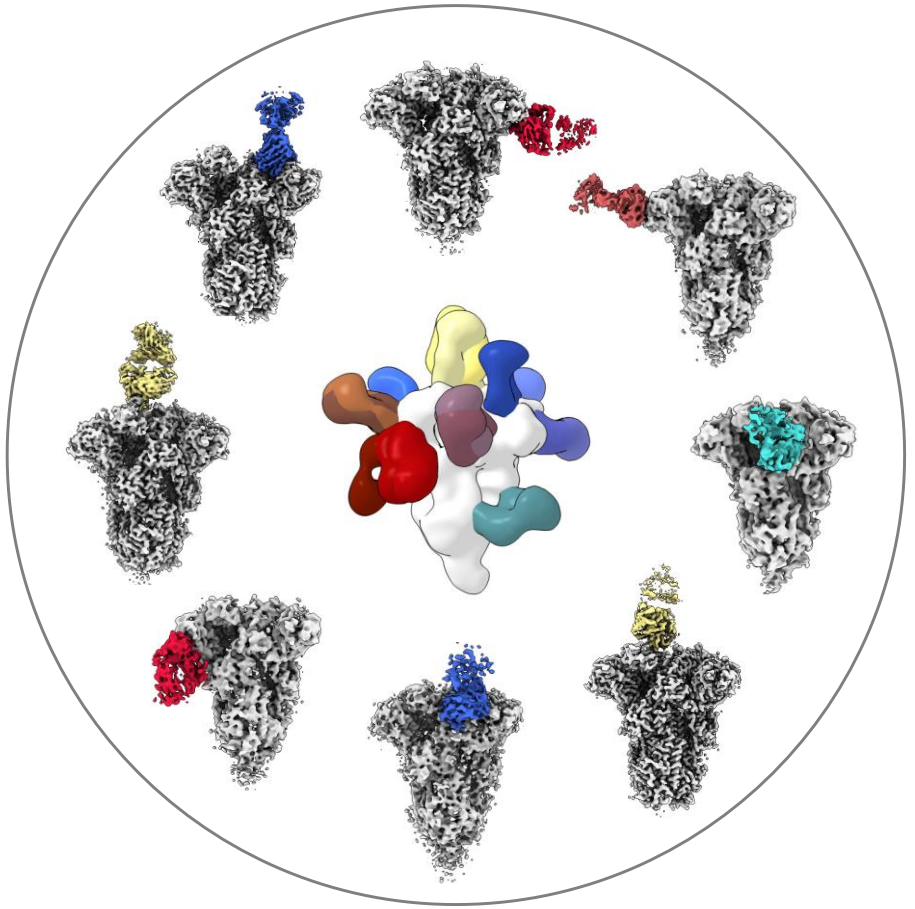
Monitoring immune responses at high resolution

Sandhya Bangaru
Staff Scientist,
Scripps Research

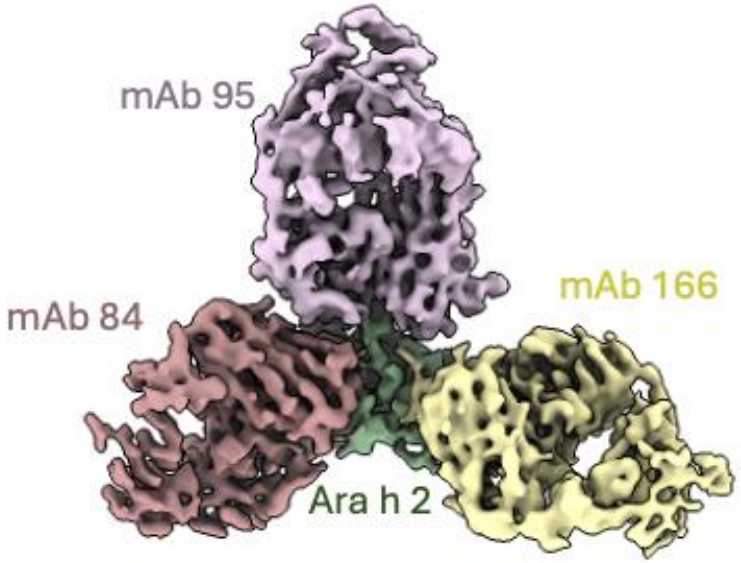
"I want to work on something that isn't as popular and crowded as flu."
-SB, 2018



Bangaru, et al., *Science*, 2021

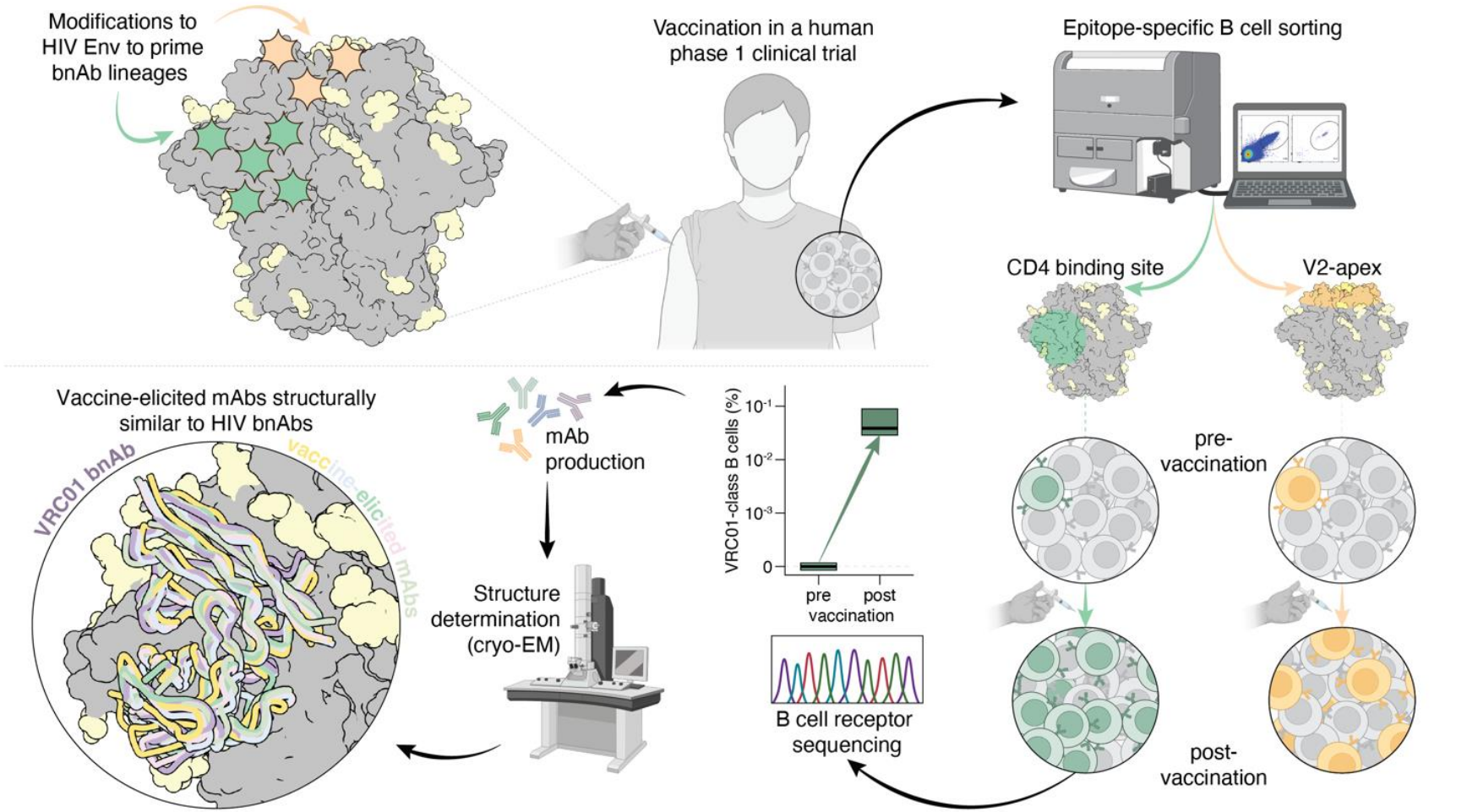


Bangaru et al.,*Science Advances*, 2021



Molecular basis of peanut allergy

Molecular serology now in the clinic



Caniels, et al., *Science*, 2025

Gabe Ozorowski

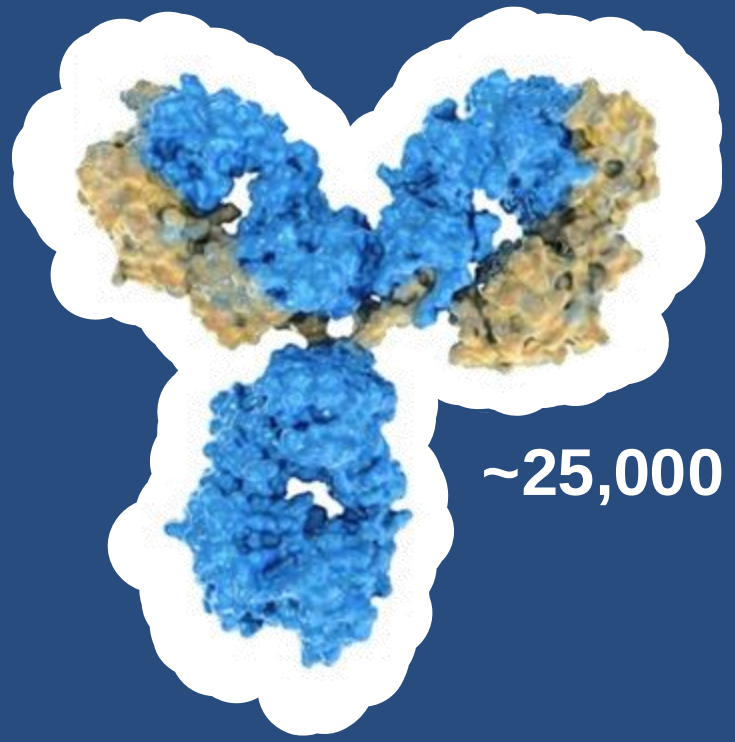
Institute Investigator, Scripps Research

Complementary approaches

Vaccine

Elicits diverse antibody responses and ideally long-term immunity

Antibody Therapy

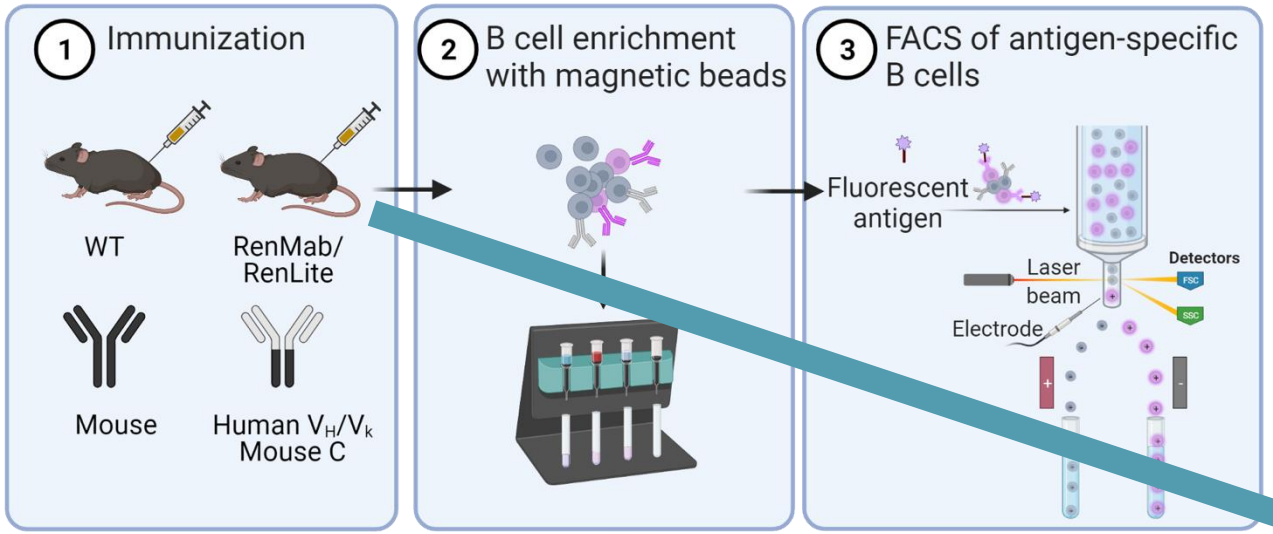


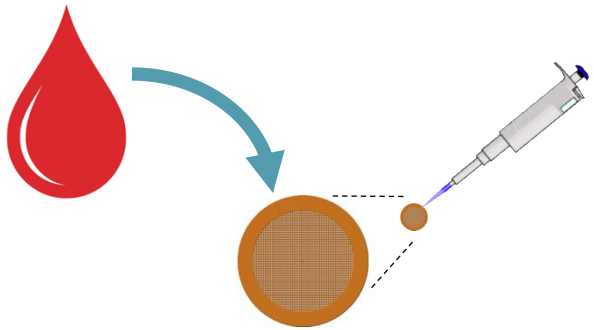
~25,000 atoms

- Can be given in place of a vaccine for immunocompromised, elderly.
~20% of new drugs being developed are antibodies

cryoEMPEM redefines antibody discovery

Case study: Making antibodies directly from sera/plasma

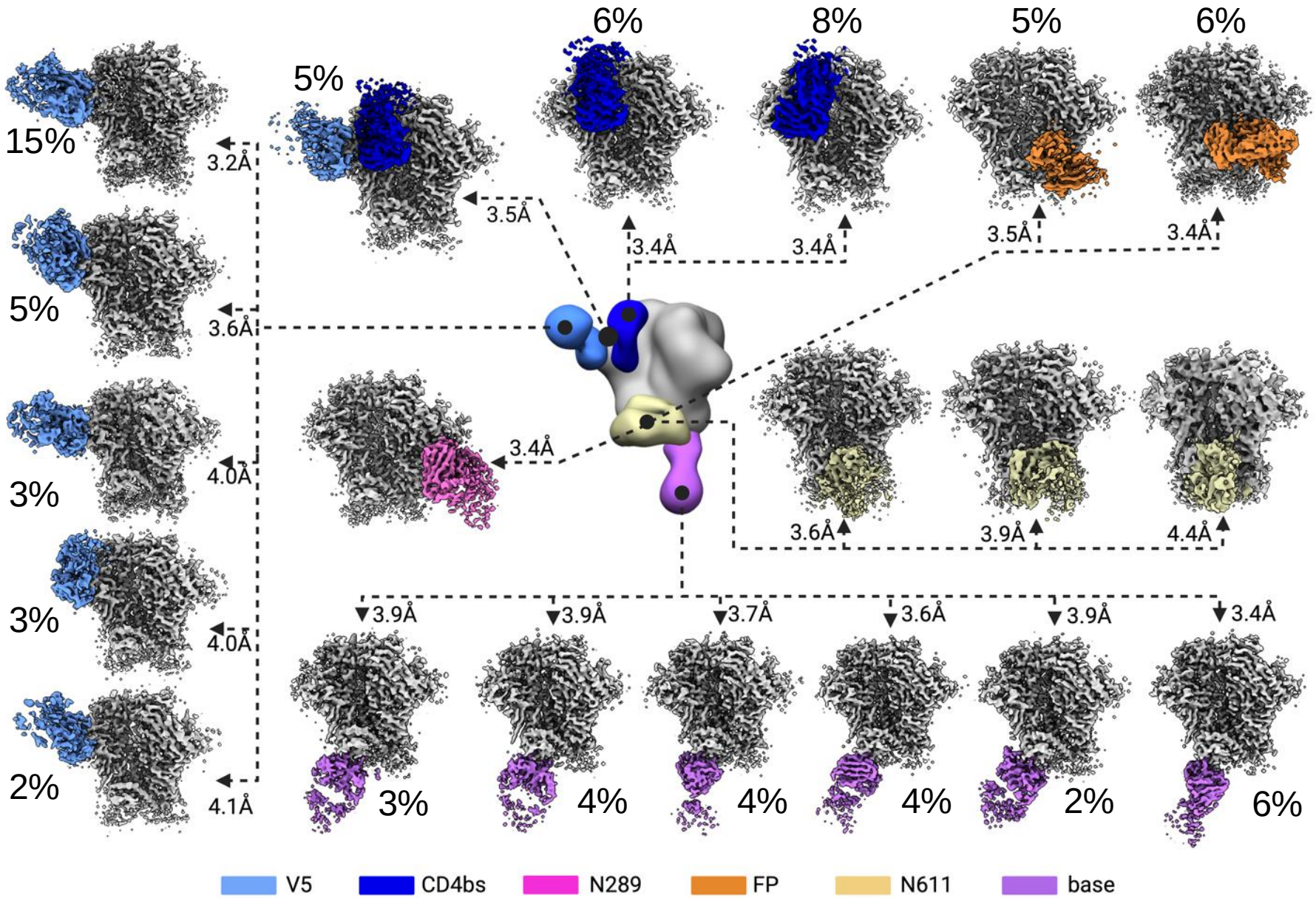




characterization → **structure**

Rational design and improvement

So many structures from a single blood draw



Shiyu Zhang (Moderna)

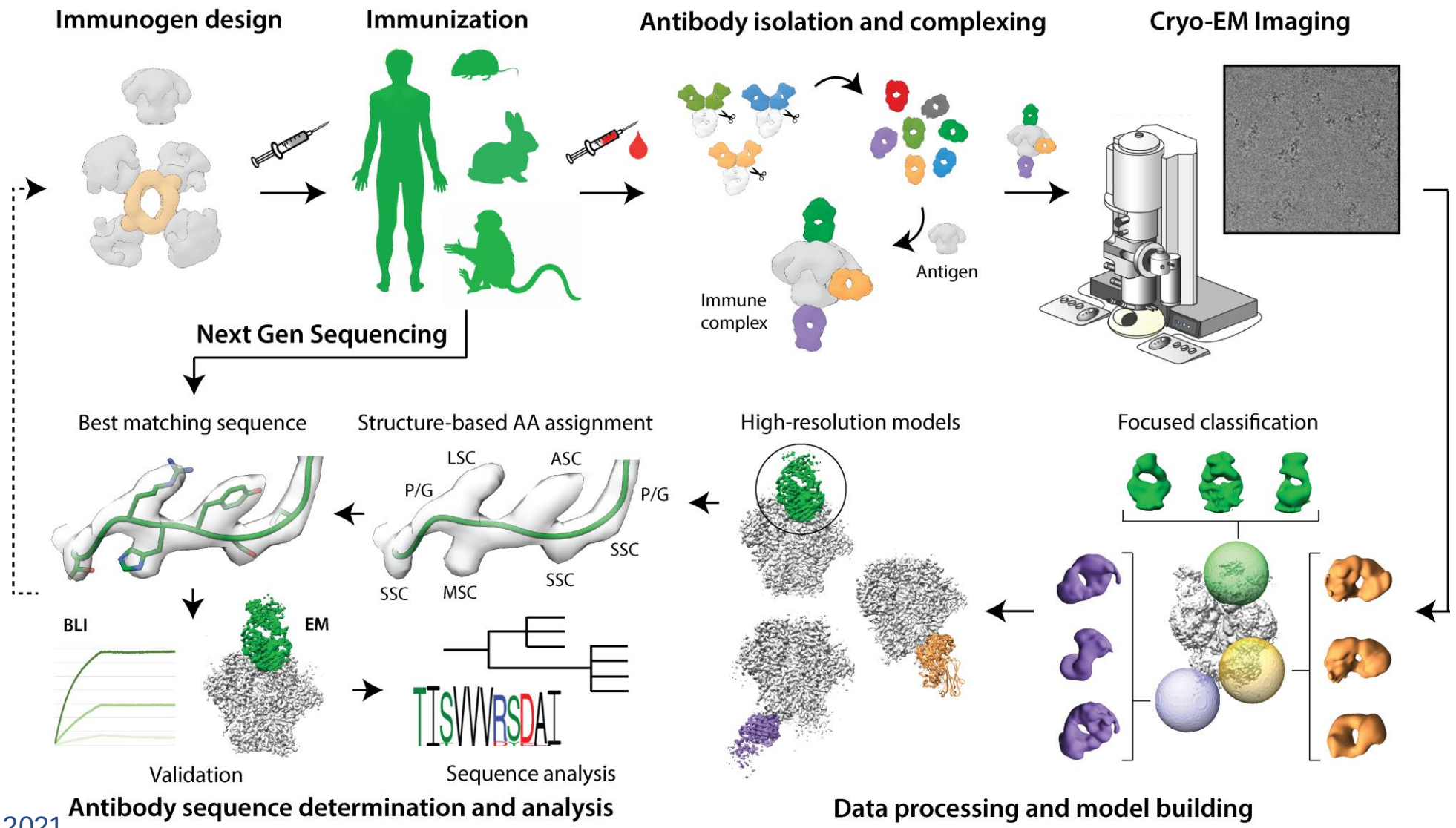
Gabe Ozorowski

CryoEMPEM: From structure to sequence

Aleks Antanasijević

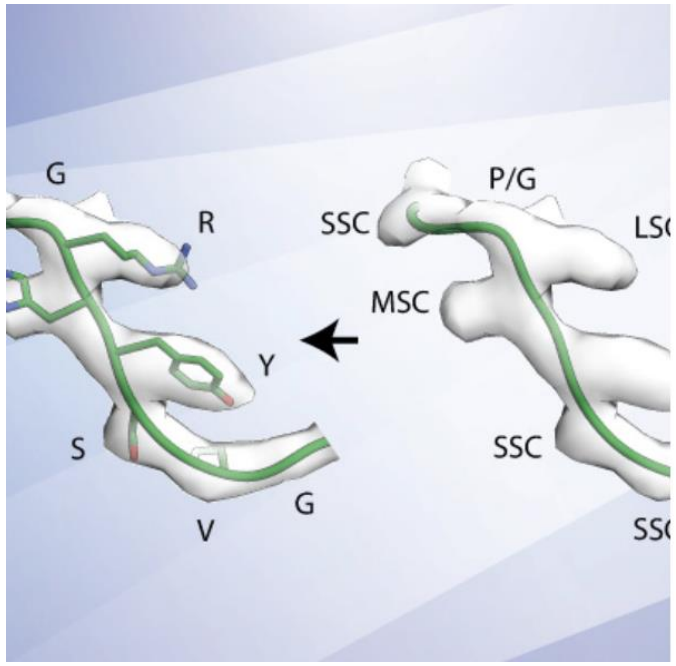
Scripps postdoc

Assistant Professor,
Ecole Polytechnique
Fédérale de Lausanne



Antanasijevic, et al., *Nat Comm*, 2021
Antanasijevic, et al., *Sci Adv*, 2022

Sequencing from structure



New electron microscopy technique could shortcut the development of vaccines and monoclonal antibody therapies

The new method by scientists at Scripps Research identifies specific antibodies in immune responses to vaccination or infection in fraction of time needed for traditional approach.

READ MORE »

News

Aleks Antanasijević

Rob Kirchdoerfer

Chris Cottrell

Charlie Bowman

Gabe Ozorowski

Recruiting, mentoring, and enabling the next generation of scientists

Julianne Han Alesandra Rodriguez

SCRIPPSRESEARCH MAGAZINE

Education Outreach Fund: How one scientist is seeding the future

2023/2024

Newly Awarded Endowed Fellowships

in the Skaggs Graduate School of Chemical and Biological Sciences

Presented to Professor Andrew Ward

Jordan Barrett
Professor Ronald A. Milligan Endowed Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Joseph Cruz
Francis Colón, PhD, Endowed Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Kehinde Ezekiel
Jairo H. Arévalo, PhD, Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Anthony Gurunian
Professor Ian A. Wilson Endowed Fellowship for Structural Biology in the Skaggs Graduate School of Chemical and Biological Sciences

Joseph Harmon
Professor Daniel R. Salomon Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Ian Levitan
Mary and Michael Reedy Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Daniella Marinelli
César Milstein, PhD, Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Heewon Seo
Professor Kerri Anne Mowen Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Shiqi (Charlotte) Wang
Mary Maynard Daly, PhD, Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Drason Zhang
Dr. Charles R. Drew Memorial Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Scripps Research
Science Changing Life

2023 Award Notification

Professor Ronald A. Milligan Endowed Fellowship

in the Skaggs Graduate School of Chemical and Biological Sciences

Jordan Barrett

2023-2024 recipient of the Professor Ronald A. Milligan Endowed Fellowship in the Skaggs Graduate School of Chemical and Biological Sciences

Thanks!