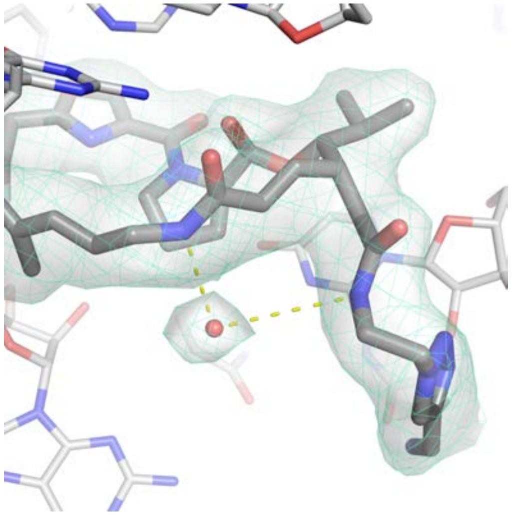
Targeting COVID-19 Viral Enzymes in an Evolving Landscape of Publishing and Peer Review

Osher Mini-Med School

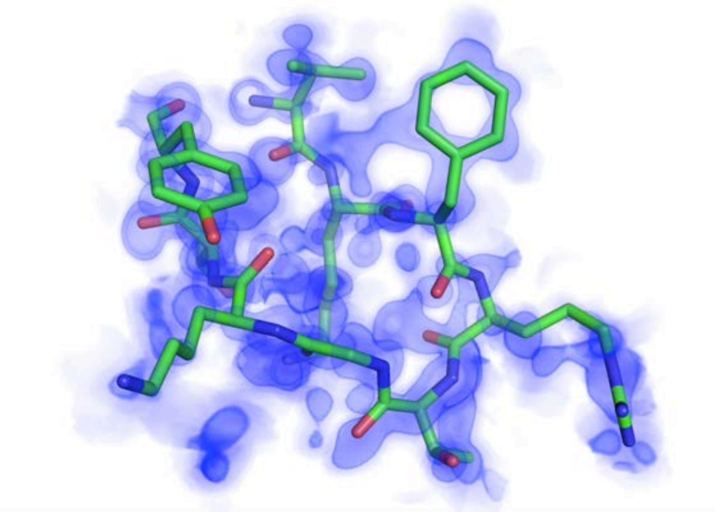
JAMES FRASER
(he/him)
@FRASER_LAB

What we were up to in **March**…



Antibiotic resistance and evolution
(with Ian Seiple)

Li*, Pellegrino*…Fraser, Seiple, Nature, 2020



Temperature response, conformational heterogeneity,
and small molecule design

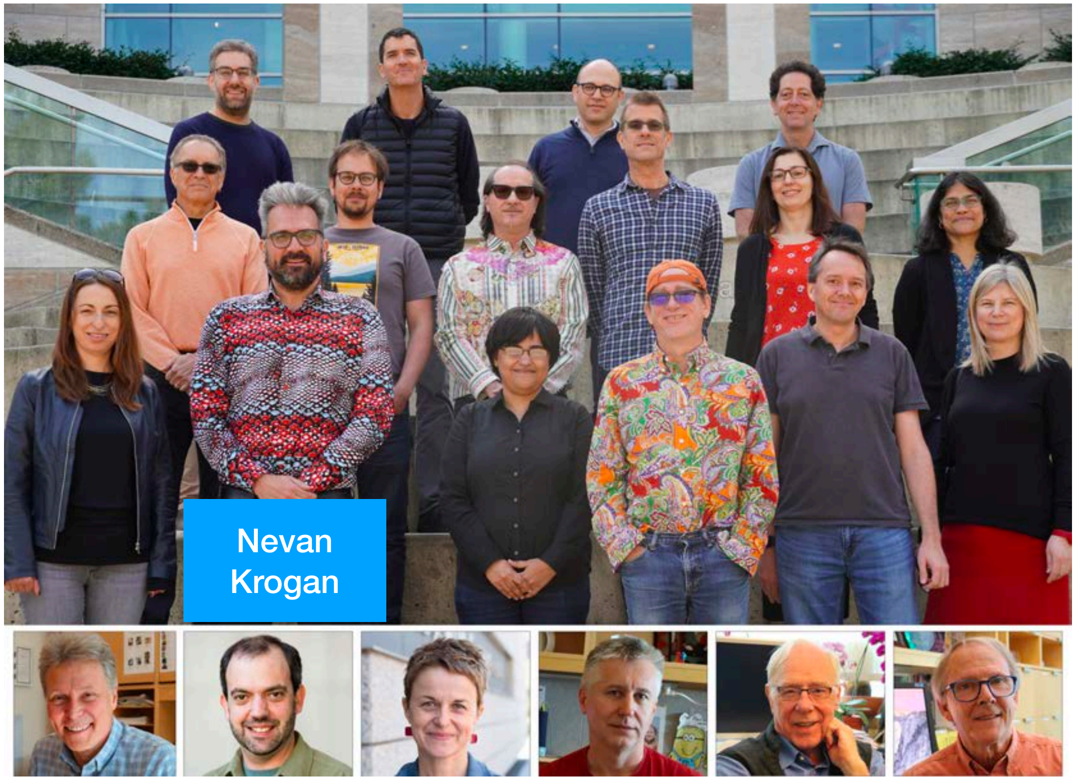
qFit: Riley…Keedy, van den Bedem, BioRxiv, 2020
T-jumps: Thompson…Fraser, Nature Chemistry, 2019
Ensemble protein design: Broom, Rakotoharisoa…
Fraser, Chica, Nature Communications, 2020

ASAPbio

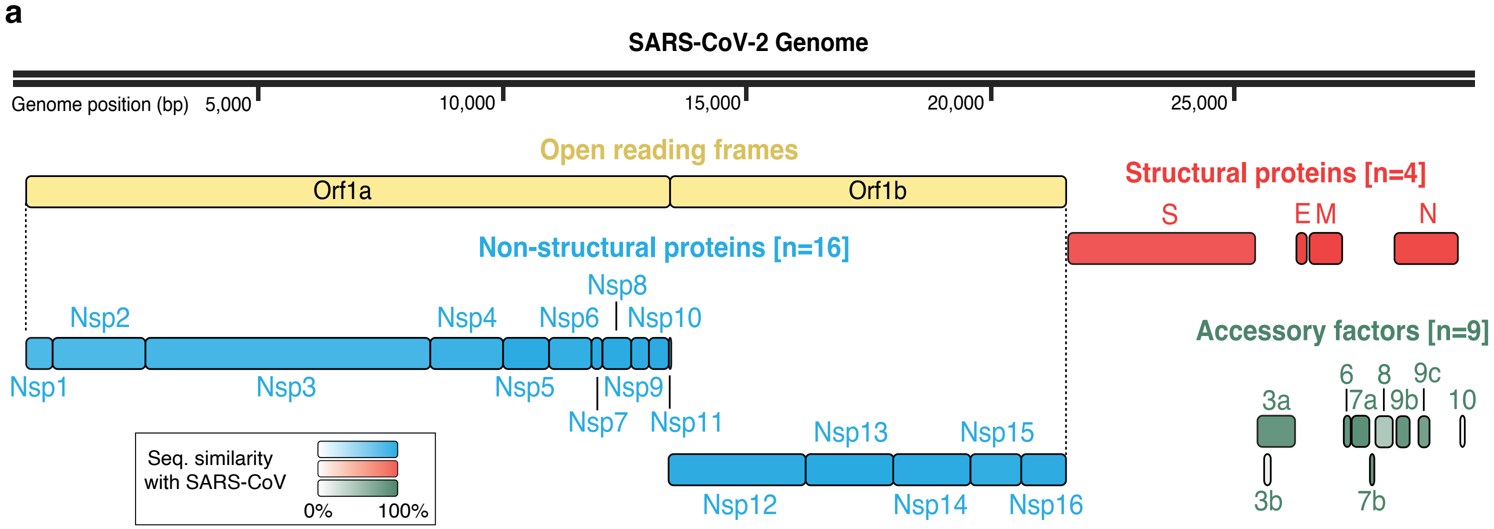
Advocacy around preprints

And what March (**and April, and May, and June…**) became…

UCSF Quantitative Biosciences Institute
Coronavirus Research Group
QCRG



How does a virus with only **14 genes** take over a human cell?



Some are processed into multiple proteins, but that’s still only 27-30 proteins total!

AP-MS on SARS CoV 2 proteins identifies **human interacting proteins**

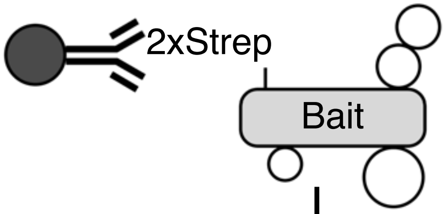
27 baits (26 proteins, 1 mutant), 2xStrep-tagged

↓

Expression in HEK293T cells in biological triplicate

↓

Affinity purification



↓

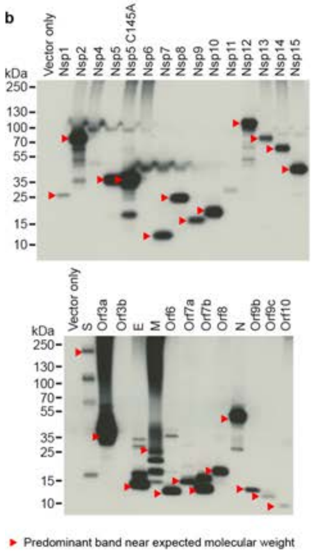
Mass spectrometry analysis

↓

PPI scoring

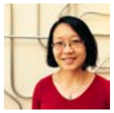
↓

SARS-CoV-2 - Human PPI map



David E. Gordon

Gwendolyn M. Jang



Jiewei Xu

Mehdi Bouhaddou

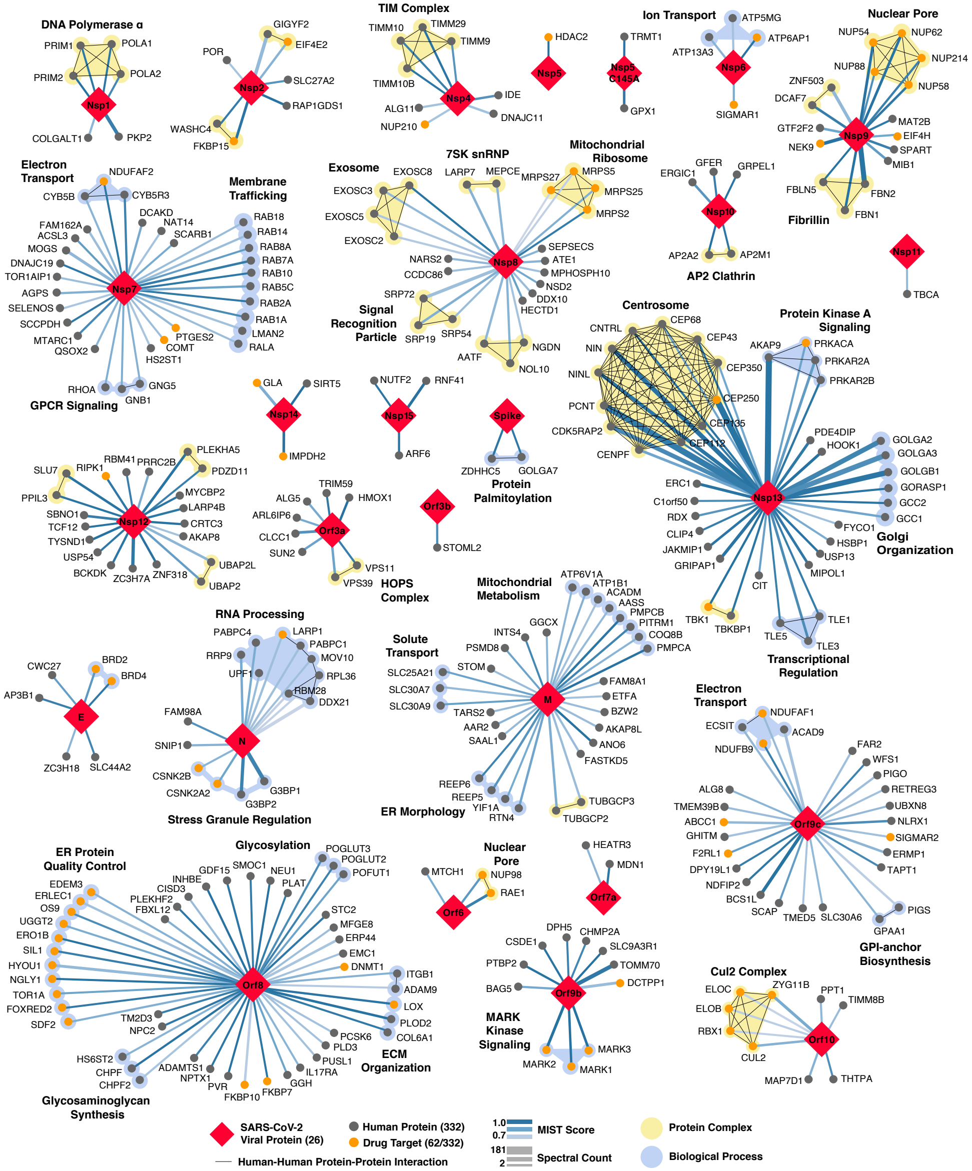
Kirsten Obernier

Nevan Krogan

26 SARS CoV 2 Proteins

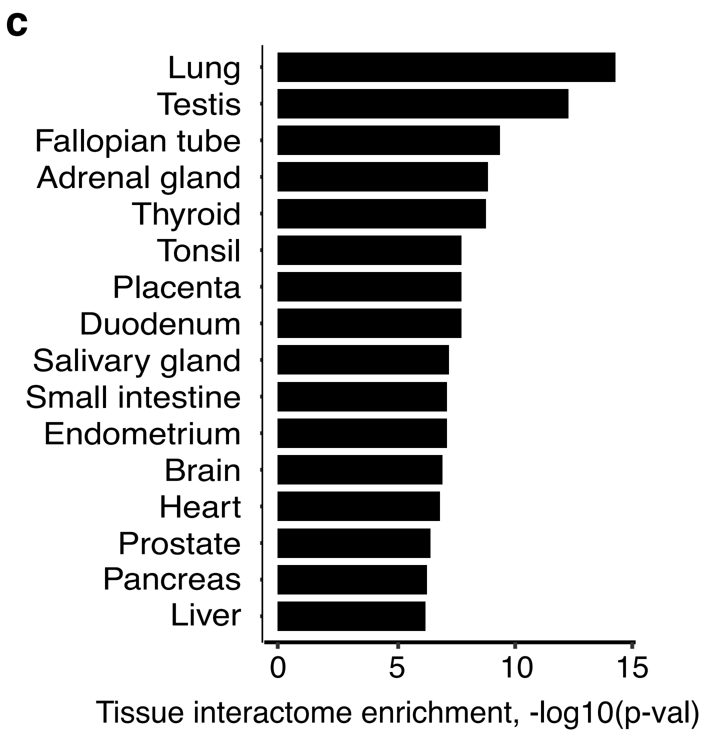
332 interactions with Human proteins

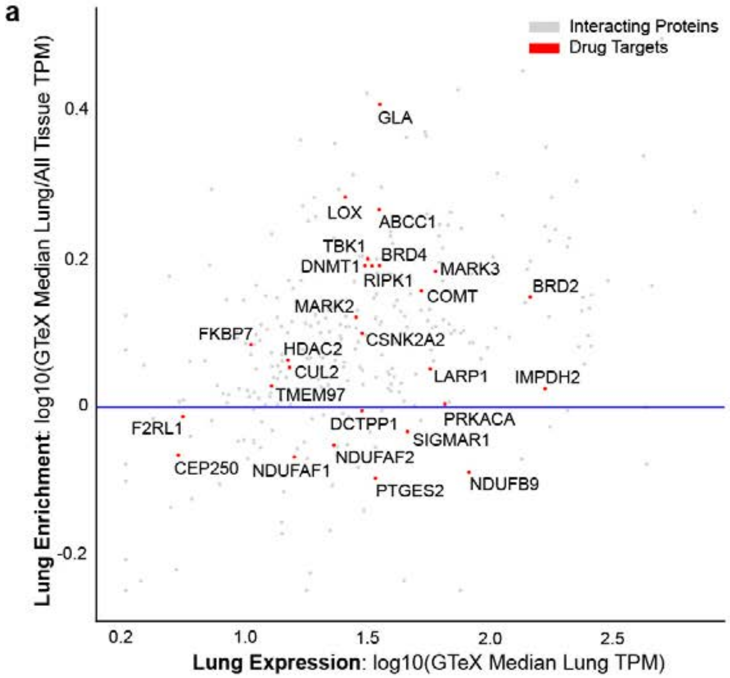
-plasmids requested by >300 labs (35 countries)

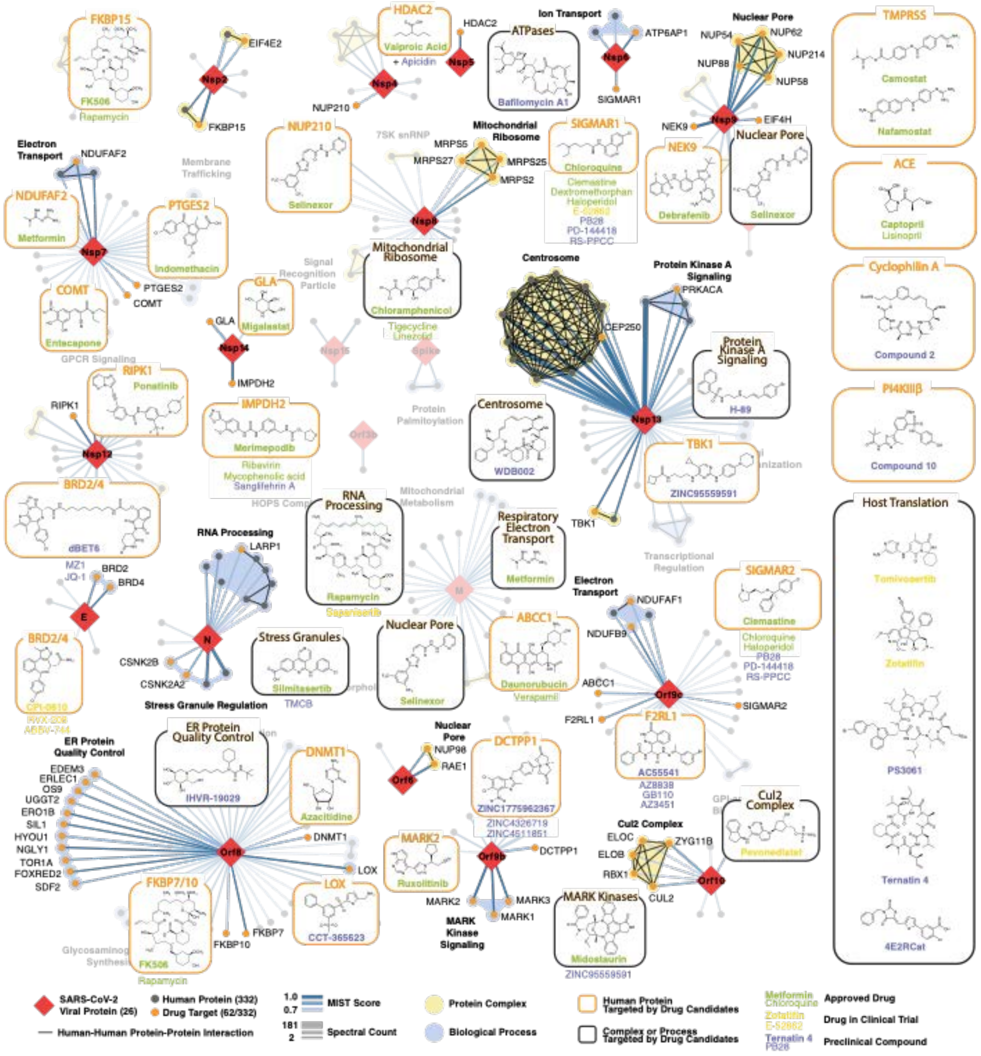


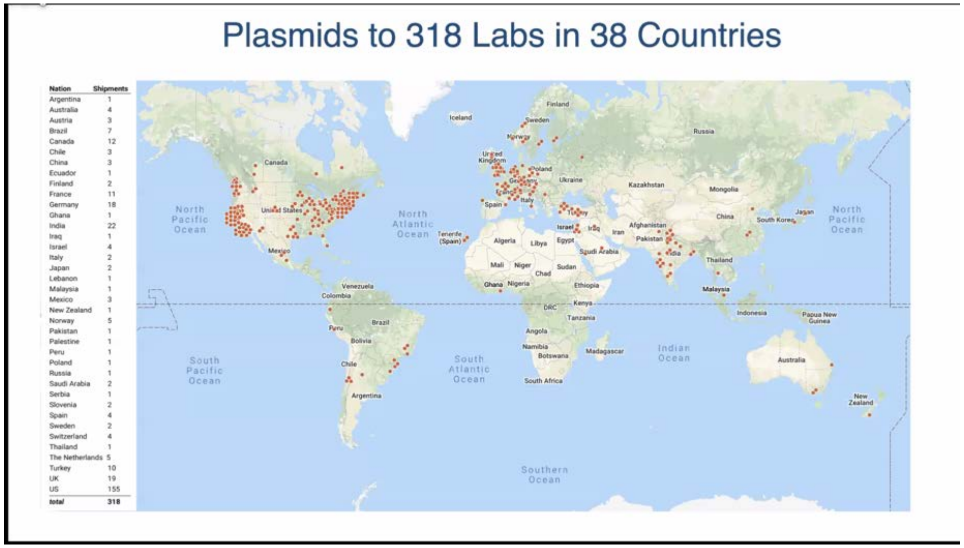
Gordon…Krogan, *Nature*, 2020

Interacting proteins are **enriched** in the **lung**
(even though the experiment used kidney cells)









Plasmids to 318 Labs in 38 Countries

Nation	Shipments
Argentina	1
Australia	4
Austria	3
Brazil	7
Canada	12
Chile	3
China	3
Ecuador	1
Finland	2
France	11
Germany	18
Ghana	1
India	22
Iraq	1
Israel	4
Italy	2
Japan	2
Lebanon	1
Malaysia	1
Mexico	3
New Zealand	1
Norway	5
Pakistan	1
Palestine	1
Peru	1
Poland	1
Russia	1
Saudi Arabia	2
Serbia	1
Slovenia	2
Spain	4
Sweden	2
Switzerland	4
Thailand	1
The Netherlands	5
Turkey	10
UK	19
US	155
total	318

From Protein-Protein interactions to drug repositioning

Coverage BEFORE peer-review

MATTER

Hundreds of Scientists Scramble to Find a Coronavirus Treatment

In an ambitious international collaboration, researchers have "mapped" proteins in the coronavirus and identified 50 drugs to test against it.

Lisa Miorin, an assistant professor of microbiology at the Icahn School of Medicine at Mount Sinai in New York, carrying sterilized trays into a high-security lab to use in a coronavirus study. Victor J. Blue for The New York Times

By Carl Zimmer

March 17, 2020

MATTER

Scientists Identify 69 Drugs to Test Against the Coronavirus

Two dozen of the medicines are already under investigation. Also on the list: chloroquine, a drug used to treat malaria.

A worker checking the production of chloroquine phosphate in China last month. There has been "anecdotal evidence" that chloroquine, a drug used to treat malaria, might work against the coronavirus. FeatureChina, via Associated Press

By Carl Zimmer

Published March 22, 2020 Updated April 9, 2020

Preprint to paper - Timeline

Version 1 (March 22, 2020 - 20:07).

bioRxiv
THE PREPRINT SERVER FOR BIOLOGY

New Results

Comments (29)

A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing

David E. Gordon, Gwendolyn M. Jang, Mehdi Bouhaddou, Jiewei Xu, Kirsten Obernier, Matthew J. O'Meara, Jeffrey Z. Guo, Danielle L. Swaney, Tia A. Tummino, Ruth Huettenhain, Robyn M. Kaake, Alicia L. Richards, Beril Tutuncuoglu, Helene Foussard, Jyoti Batra, Kelsey Haas, Maya Modak, Minkyu Kim, Paige Haas, Benjamin J. Polacco, Hannes Braberg, Jacqueline M. Fabius, Manon Eckhardt, Margaret Soucheray, Melanie J. Bennett, Merve Cakir, Michael J. McGregor, Qiongyu Li, Zun Zar Chi Naing, Yuan Zhou, Shiming Peng, Ilsa T. Kirby, James E. Melnyk, John S. Chorba, Kevin Lou, Shizhong A. Dai, Wenqi Shen, Ying Shi, Ziyang Zhang, Inigo Barrio-Hernandez, Danish Memon, Claudia Hernandez-Armenta, Christopher J.P. Mathy, Tina Perica, Kala B. Pilla, Sai J. Ganesan, Daniel J. Saltzberg, Rakesh Ramachandran, Xi Liu, Sara B. Rosenthal, Lorenzo Calviello, Srivats Venkataramanan, Jose Liboy-Lugo, Yizhu Lin, Stephanie A. Wankowicz, Markus Bohn, Phillip P. Sharp, Raphael Trenker, Janet M. Young, Devin A. Cavero, Joseph Hiatt, Theodore L. Roth, Ujjwal Rathore, Advait Subramanian, Julia Noack, Mathieu Hubert, Ferdinand Roesch, Thomas Vallet, Björn Meyer, Kris M. White, Lisa Miorin, Oren S. Rosenberg, Kliment A Verba, David Agard, Melanie Ott, Michael Emerman, Davide Ruggero, Adolfo García-Sastre, Natalia Jura, Mark von Zastrow, Jack Taunton, Alan Ashworth, Olivier Schwartz, Marco Vignuzzi, Christophe d'Enfert, Shaeri Mukherjee, Matt Jacobson, Harmit S. Malik, Danica G. Fujimori, Trey Ideker, Charles S. Craik, Stephen Floor, James S. Fraser, John Gross, Andrej Sali, Tanja Kortemme, Pedro Beltrao, Kevan Shokat, Brian K. Shoichet, Nevan J. Krogan

doi: https://doi.org/10.1101/2020.03.22.002386

Received	Accepted	Published
23 March 2020	22 April 2020	30 April 2020

Issue Date
16 July 2020

nature

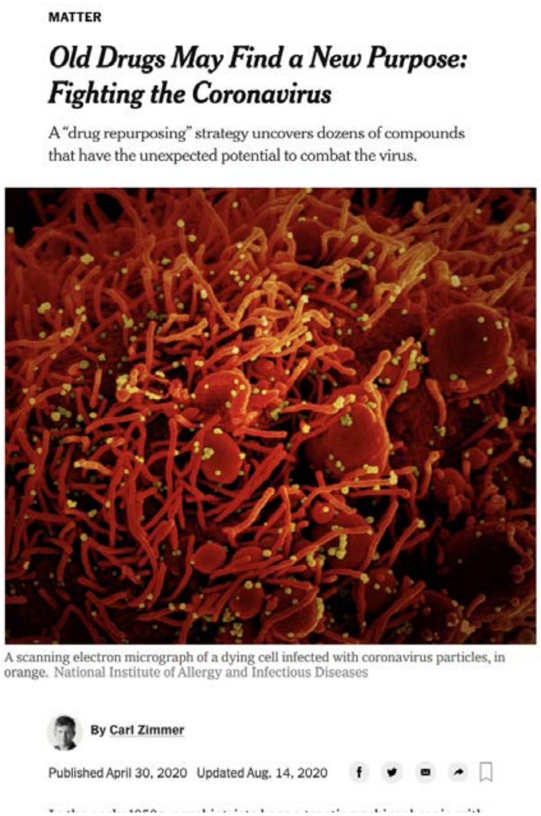
A SARS-CoV-2 protein interaction map reveals targets for drug repurposing

David E. Gordon, Gwendolyn M. Jang, Mehdi Bouhaddou, Jiewei Xu, Kirsten Obernier, Kris M. White, Matthew J. O'Meara, Veronica V. Rezelj, Jeffrey Z. Guo, Danielle L. Swaney, Tia A. Tummino, Ruth Hüttenhain, Robyn M. Kaake, Alicia L. Richards, Beril Tutuncuoglu, Helene Foussard, Jyoti Batra, Kelsey Haas, Maya Modak, Minkyu Kim, Paige Haas, Benjamin J. Polacco, Hannes Braberg, Jacqueline M. Fabius, Manon Eckhardt, Margaret Soucheray, Melanie J. Bennett, Merve Cakir, Michael J. McGregor, Qiongyu Li, Bjoern Meyer, Ferdinand Roesch, Thomas Vallet, Alice Mac Kain, Lisa Miorin, Elena Moreno, Zun Zar Chi Naing, Yuan Zhou, Shiming Peng, Ying Shi, Ziyang Zhang, Wenqi Shen, Ilsa T. Kirby, James E. Melnyk, John S. Chorba, Kevin Lou, Shizhong A. Dai, Inigo Barrio-Hernandez, Danish Memon, Claudia Hernandez-Armenta, Jiankun Lyu, Christopher J. P. Mathy, Tina Perica, Kala Bharath Pilla, Sai J. Ganesan, Daniel J. Saltzberg, Ramachandran Rakesh, Xi Liu, Sara B. Rosenthal, Lorenzo Calviello, Srivats Venkataramanan, Jose Liboy-Lugo, Yizhu Lin, Xi-Ping Huang, YongFeng Liu, Stephanie A. Wankowicz, Markus Bohn, Maliheh Safari, Fatima S. Ugur, Cassandra Koh, Nastaran Sadat Savar, Quang Dinh Tran, Djoshkun Shengjuler, Sabrina J. Fletcher, Michael C. O'Neal, Yiming Cai, Jason C. J. Chang, David J. Broadhurst, Saker Klippsten, Phillip P. Sharp, Nicole A. Wenzell, Duygu Kuzuoglu-Ozturk, Hao-Yuan Wang, Raphael Trenker, Janet M. Young, Devin A. Cavero, Joseph Hiatt, Theodore L. Roth, Ujjwal Rathore, Advait Subramanian, Julia Noack, Mathieu Hubert, Robert M. Stroud, Alan D. Frankel, Oren S. Rosenberg, Kliment A. Verba, David A. Agard, Melanie Ott, Michael Emerman, Natalia Jura, Mark von Zastrow, Eric Verdin, Alan Ashworth, Olivier Schwartz, Christophe d'Enfert, Shaeri Mukherjee, Matt Jacobson, Harmit S. Malik, Danica G. Fujimori, Trey Ideker, Charles S. Craik, Stephen N. Floor, James S. Fraser, John D. Gross, Andrej Sali, Bryan L. Roth, Davide Ruggero, Jack Taunton, Tanja Kortemme, Pedro Beltrao, Marco Vignuzzi ✉, Adolfo García-Sastre ✉, Kevan M. Shokat ✉, Brian K. Shoichet ✉ & Nevan J. Krogan ✉ -Show fewer authors

Nature **583**, 459–468(2020) | Cite this article

What is a preprint?

Coverage AFTER peer-review



MATTER

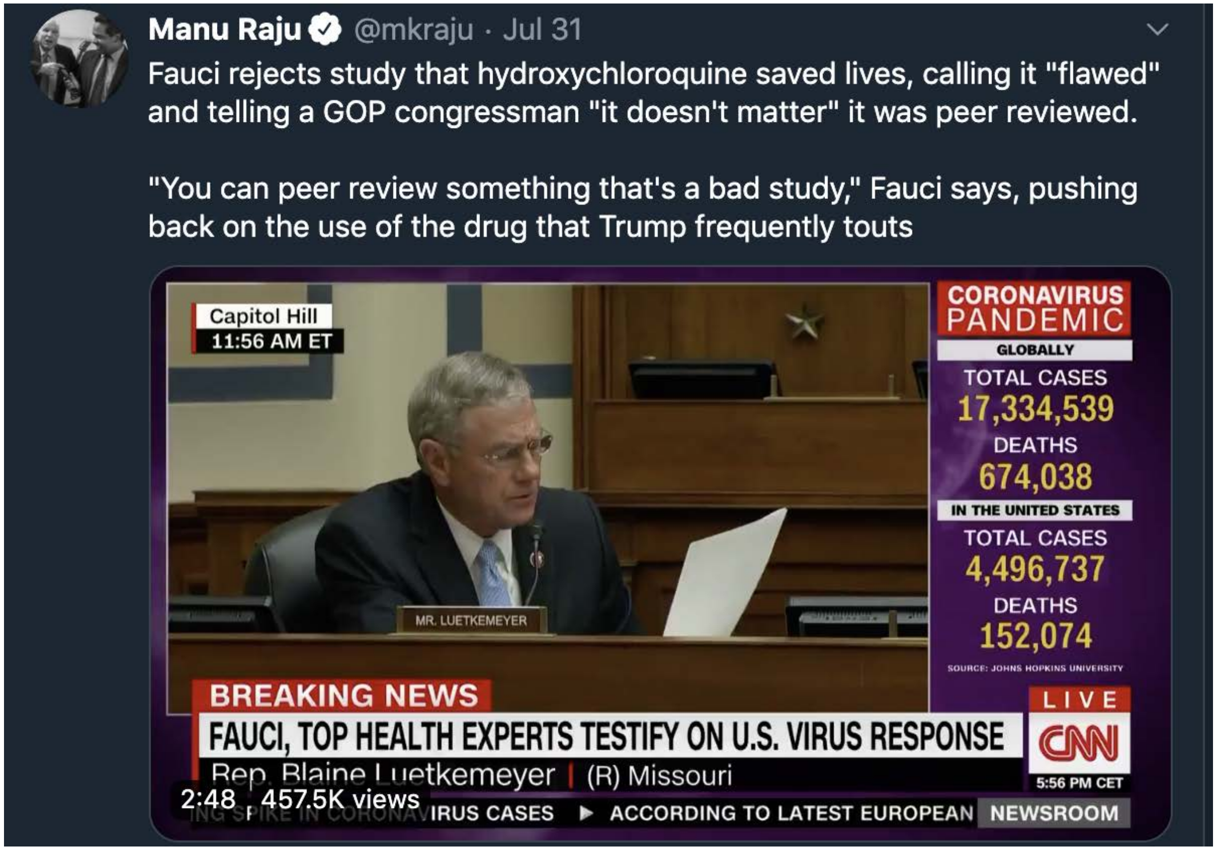
Old Drugs May Find a New Purpose: Fighting the Coronavirus

A "drug repurposing" strategy uncovers dozens of compounds that have the unexpected potential to combat the virus.

A scanning electron micrograph of a dying cell infected with coronavirus particles, in orange. National Institute of Allergy and Infectious Diseases

By Carl Zimmer

Published April 30, 2020 Updated Aug. 14, 2020

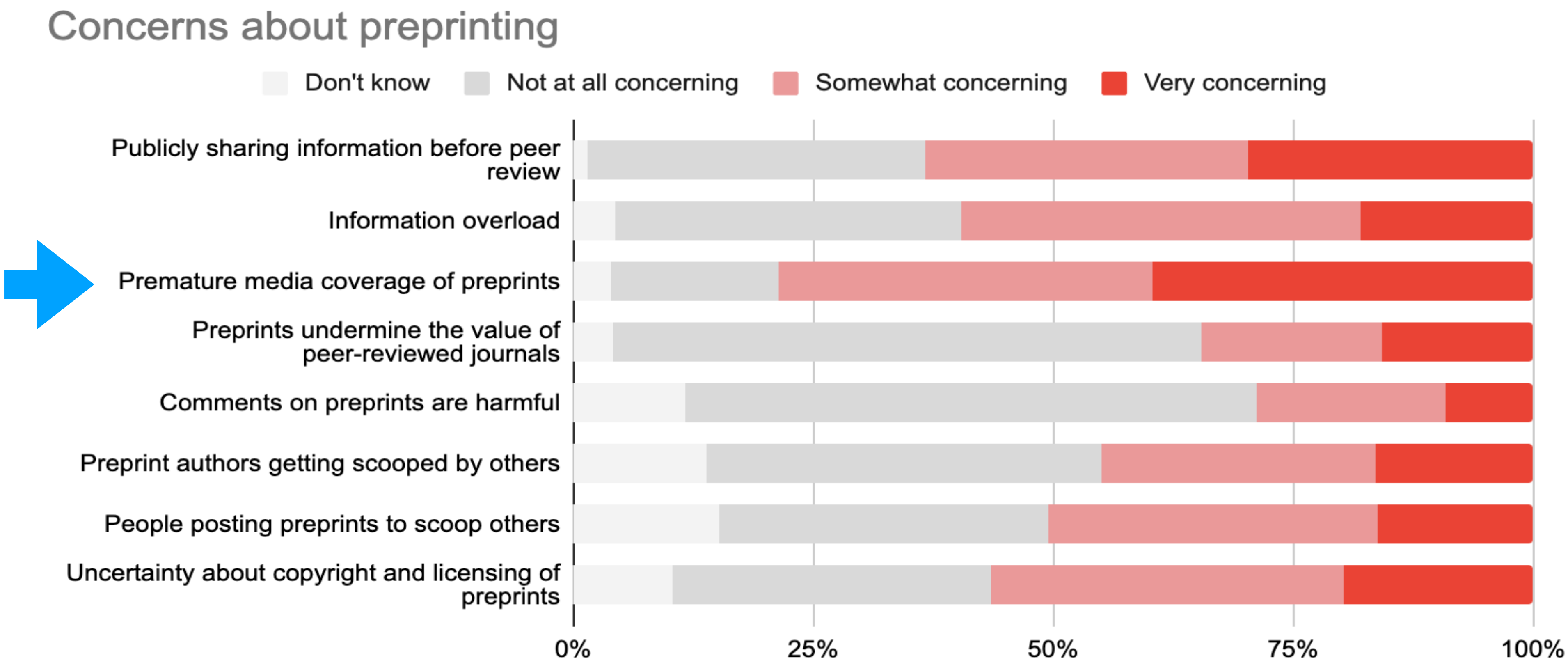


Manu Raju @mkraju · Jul 31

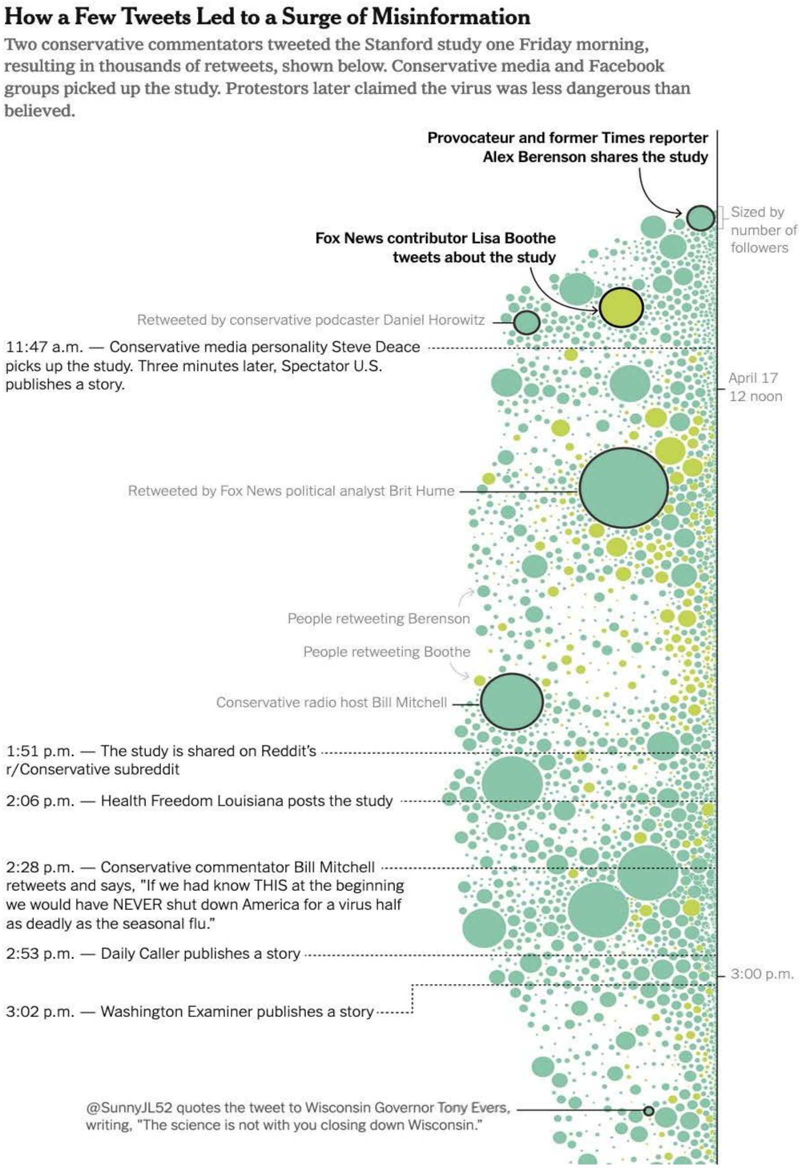
Fauci rejects study that hydroxychloroquine saved lives, calling it "flawed" and telling a GOP congressman "it doesn't matter" it was peer reviewed.

"You can peer review something that's a bad study," Fauci says, pushing back on the use of the drug that Trump frequently touts

Premature media coverage mentioned as main concern about preprints in ASAPbio & #biopreprints2020 survey



ASAPbio & #biopreprints2020 survey
N = 512



How a Few Tweets Led to a Surge of Misinformation

Two conservative commentators tweeted the Stanford study one Friday morning, resulting in thousands of retweets, shown below. Conservative media and Facebook groups picked up the study. Protestors later claimed the virus was less dangerous than believed.

Response to medRxiv preprint '[COVID-19 Antibody Seroprevalence in Santa Clara County, California](#)'

The New York Times

Opinion

A Study Said Covid Wasn't That Deadly. The Right Seized It.

How coronavirus research is being weaponized.

By Aleszu Bajak and Jeff Howe

Mr. Bajak and Mr. Howe teach journalism at Northeastern University.

Image By Aleszu Bajak and Stuart A. Thompson

The New York Times

Opinion

How to Identify Flawed Research Before It Becomes Dangerous

Scientists and journalists need to establish a service to review research that's publicized before it is peer reviewed.

By Michael B. Eisen and Robert Tibshirani

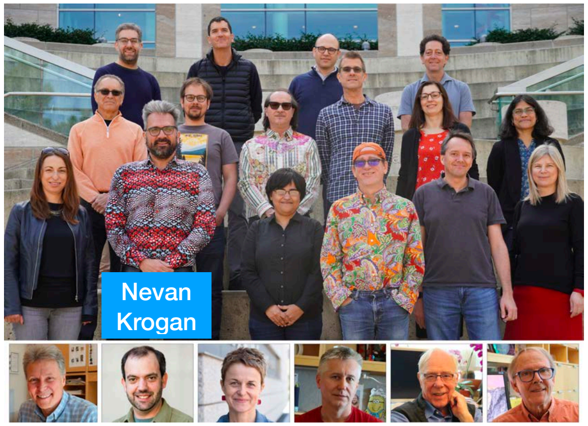
Mr. Eisen is a biologist at the University of California, Berkeley. Mr. Tibshirani is a statistician at Stanford University.

July 20, 2020

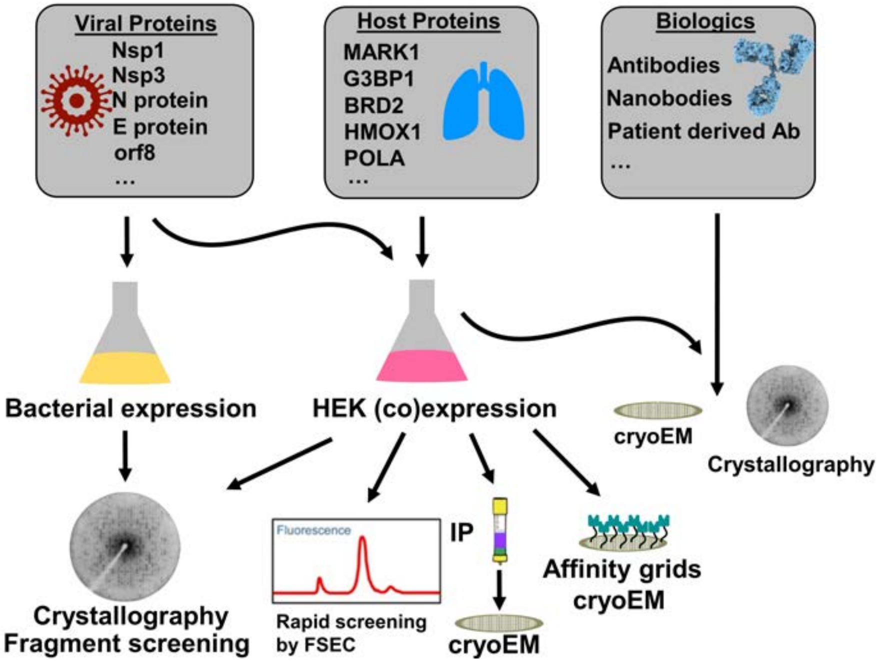
How can journalists balance coverage of research that is promptly shared but has not yet undergone peer review?

What technology, oversight and practice would support transparent and reliable media coverage of preprints?

QCRG Structural Biology Consortium



+5 other screens of zoom…



Viral Proteins
Nsp1
Nsp3
N protein
E protein
orf8
…

Host Proteins
MARK1
G3BP1
BRD2
HMOX1
POLA
…

Biologics
Antibodies
Nanobodies
Patient derived Ab
…

Bacterial expression

HEK (co)expression

cryoEM

Crystallography

Crystallography
Fragment screening

Rapid screening
by FSEC

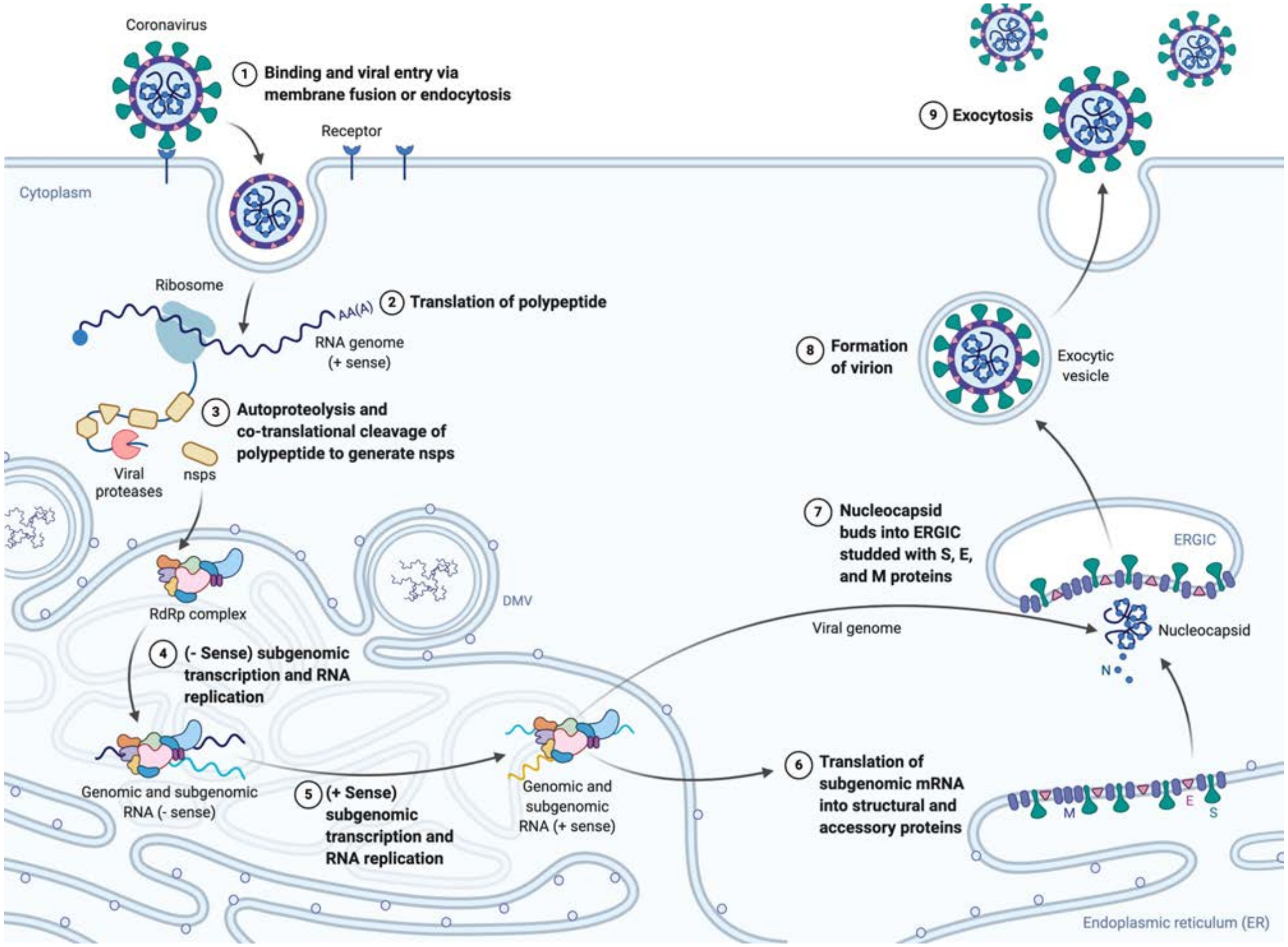
IP

cryoEM

Affinity grids
cryoEM

3 spots to stop SARS:

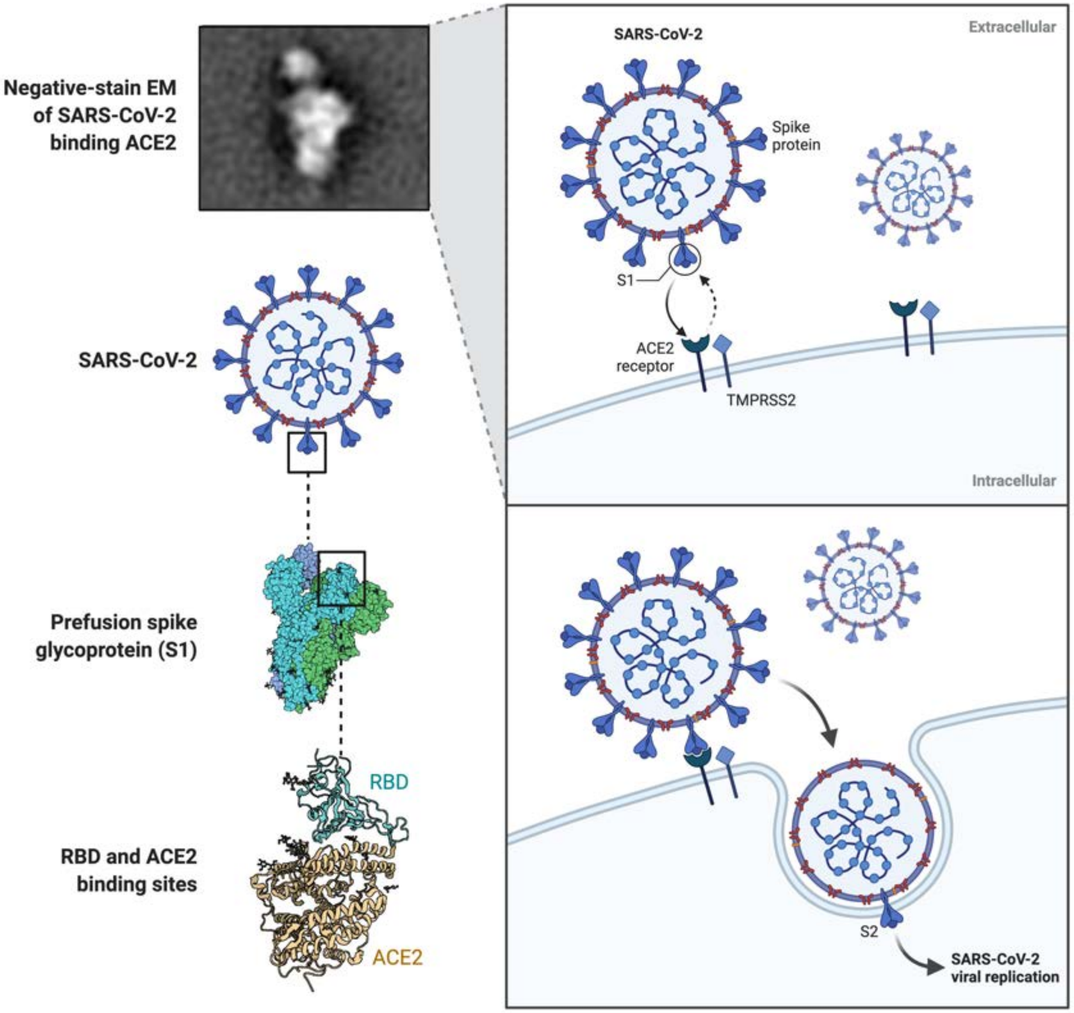
Entry, Protein Processing, Signaling



3 spots to stop SARS:

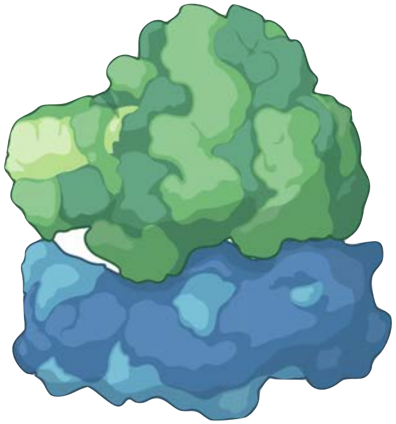
<u>Entry</u>

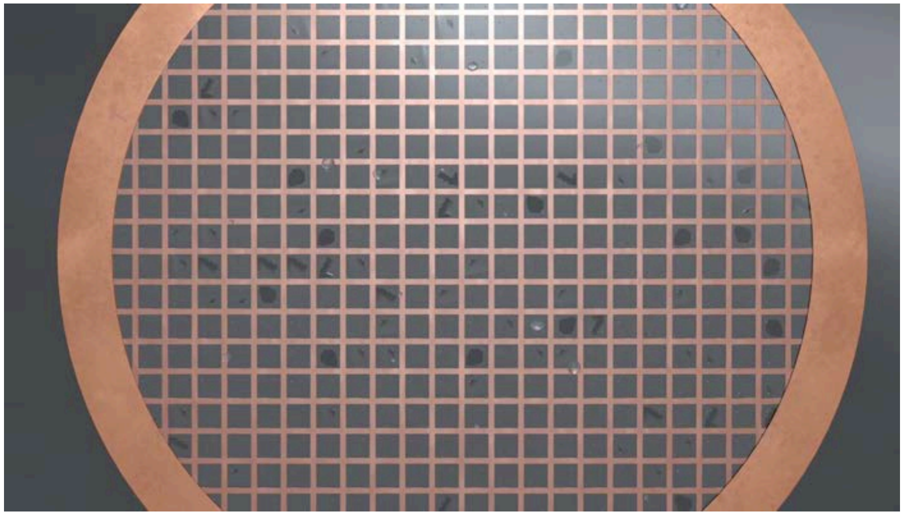
Using biologics (antibodies, nanobodies)



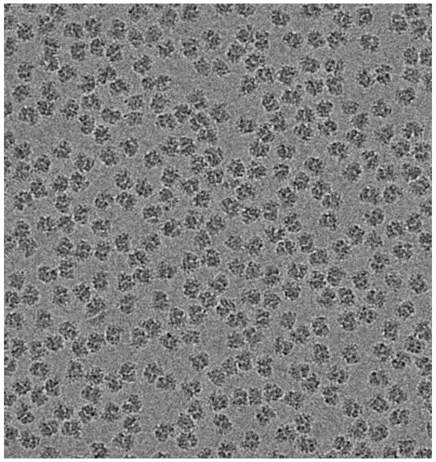
SARS-CoV-2 Entry through Host ACE2

We use powerful **electron microscopes** (cryoEM) to visualize Spike protein and biologics





cryoem101.org



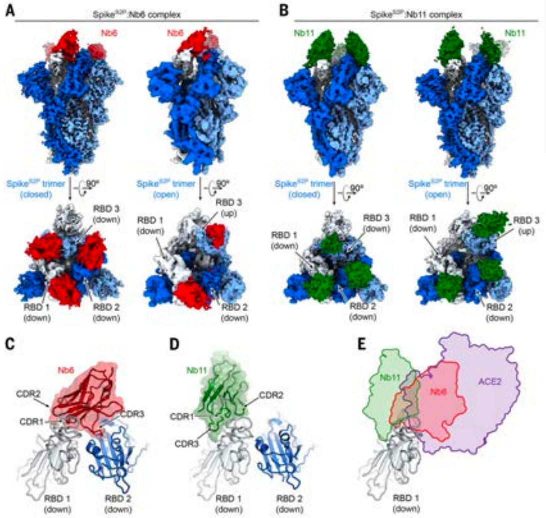
Prof. Yifan Cheng

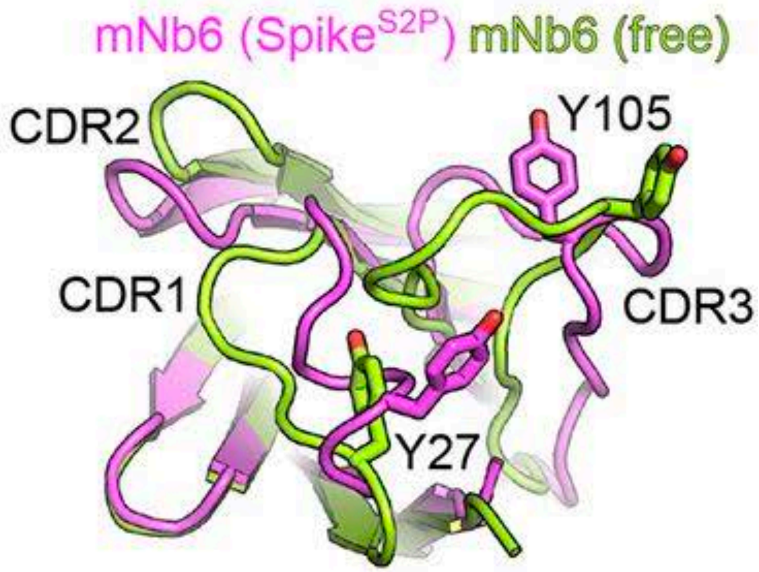
Prof. David Agard

Research · August 11, 2020

‘AeroNabs’ Promise Powerful, Inhalable Protection Against COVID-19

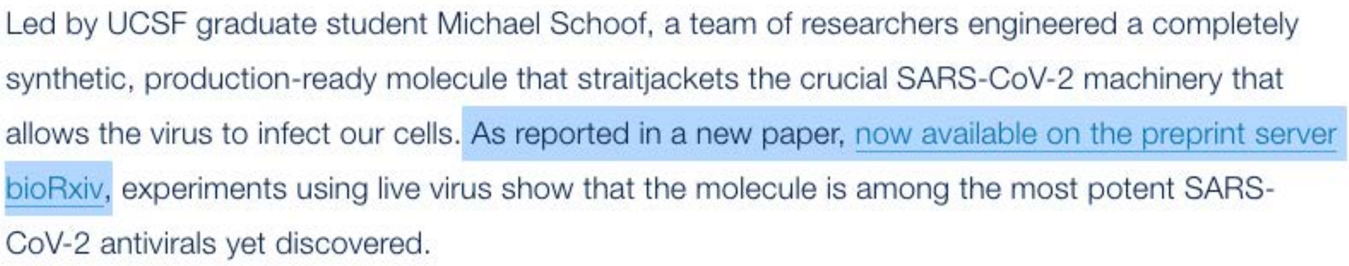
By Jason Alvarez





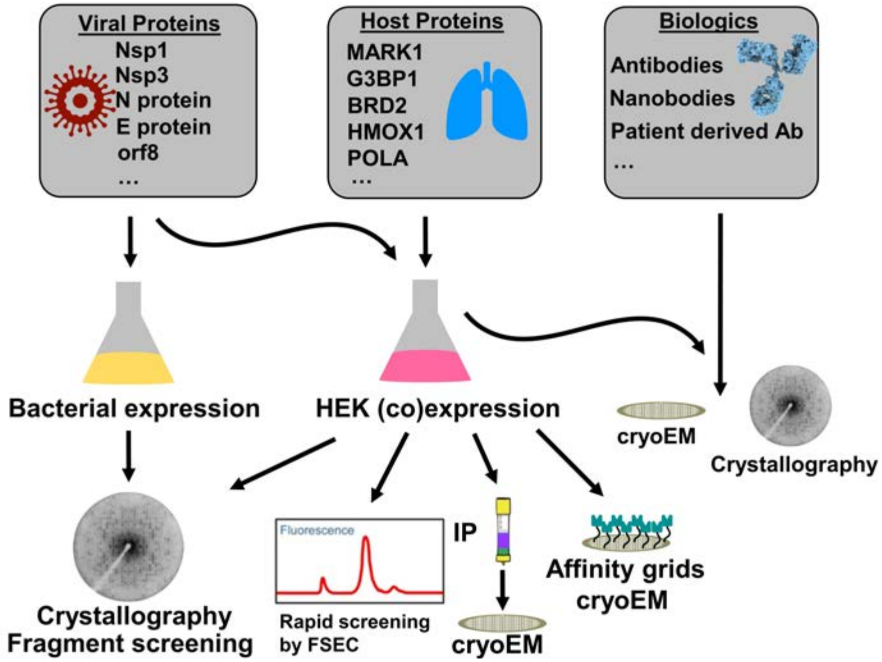
History: Received for publication August 15, 2020
Accepted for publication October 30, 2020

Schoof, Faust… Walter, Manglik
Science, 2020



Led by UCSF graduate student Michael Schoof, a team of researchers engineered a completely synthetic, production-ready molecule that straitjackets the crucial SARS-CoV-2 machinery that allows the virus to infect our cells. As reported in a new paper, now available on the preprint server bioRxiv, experiments using live virus show that the molecule is among the most potent SARS-CoV-2 antivirals yet discovered.

We currently have no effective small molecule therapies to stop the spread of SARS CoV 2



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- Nsp1
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- …

Bacterial expression

HEK (co)expression

cryoEM

Crystallography

Crystallography
Fragment screening

Rapid screening
by FSEC

IP

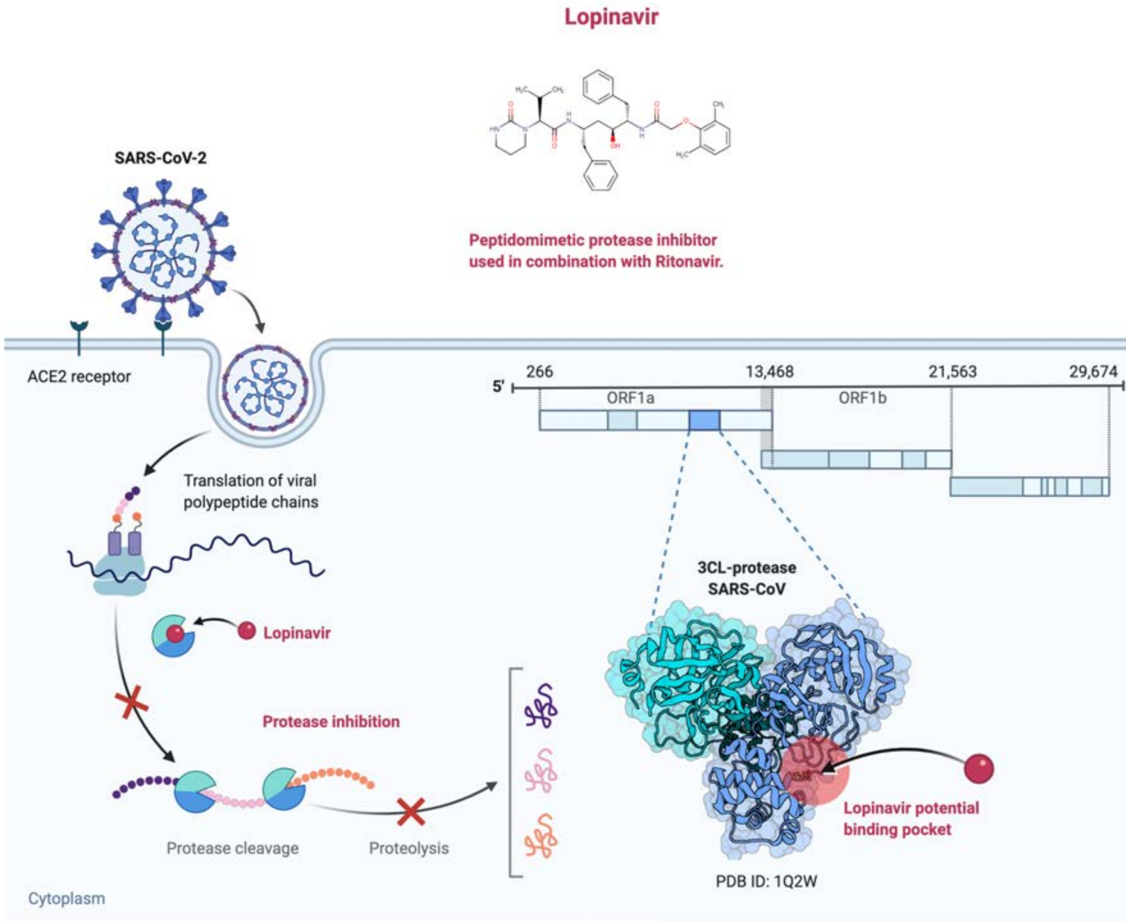
cryoEM

Affinity grids
cryoEM

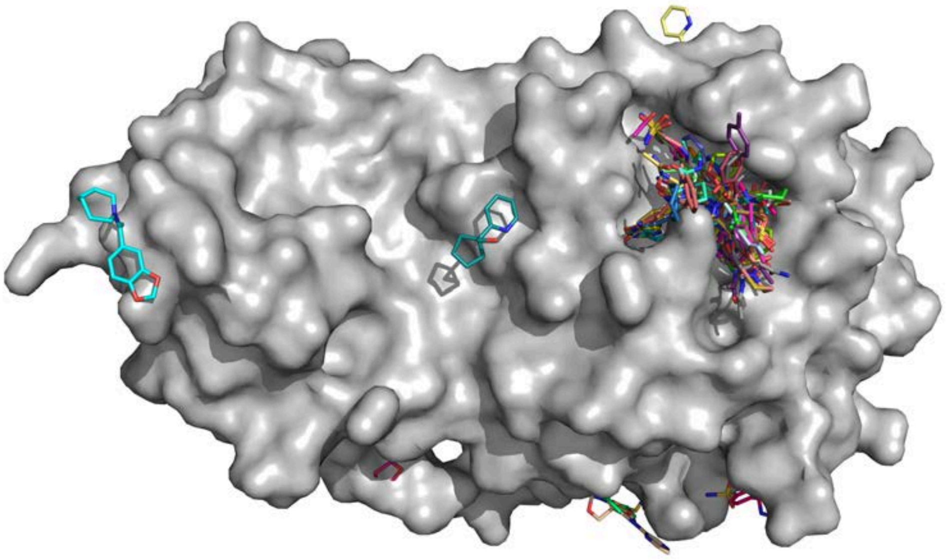
3 spots to stop SARS:

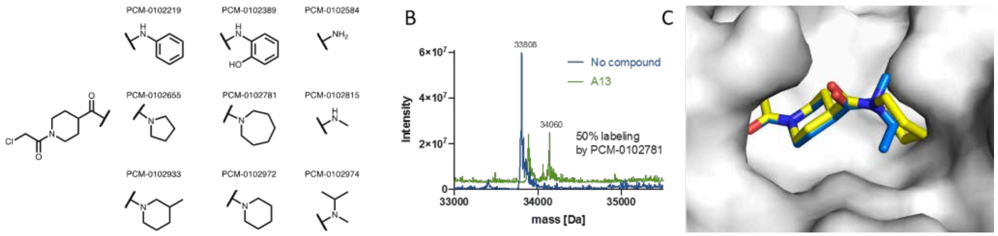
Protein Processing

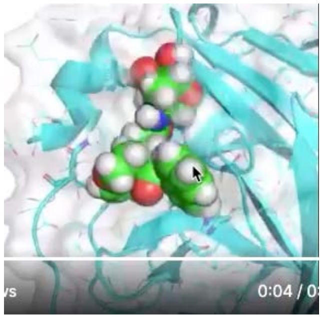
Using small molecules



We gained inspiration from Oxford
(Martin Walsh, Frank von Delft…and Nir London of the Weizmann)
attacking the Main Protease (MPro) with fragments and electrophiles



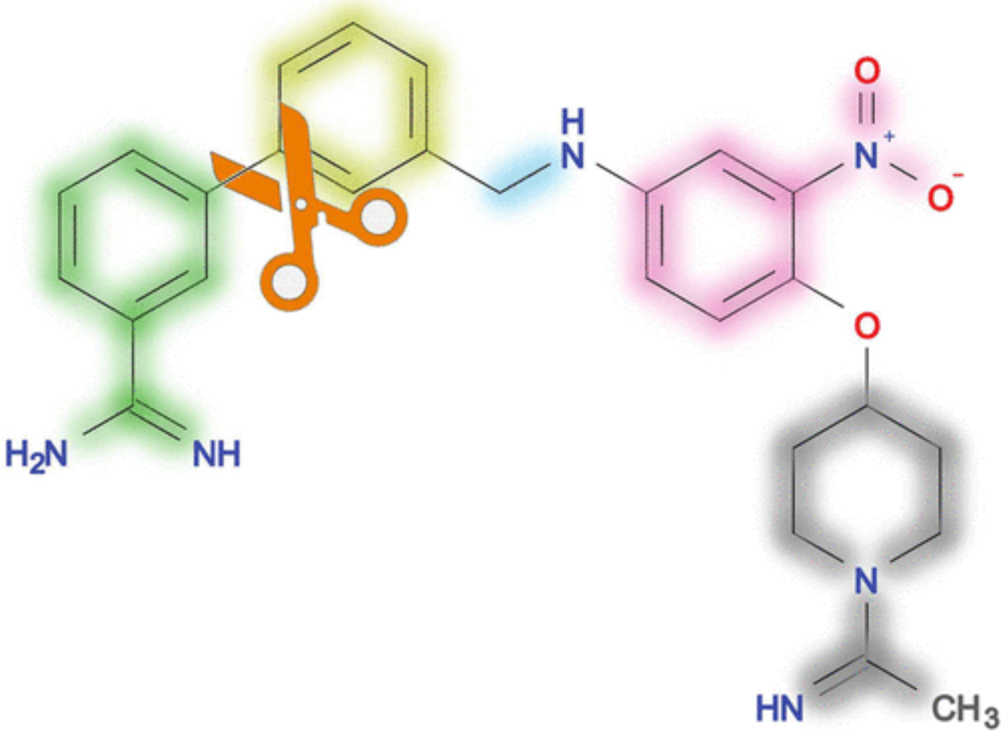




John Chodera (MSKCC) and COVID Moonshot

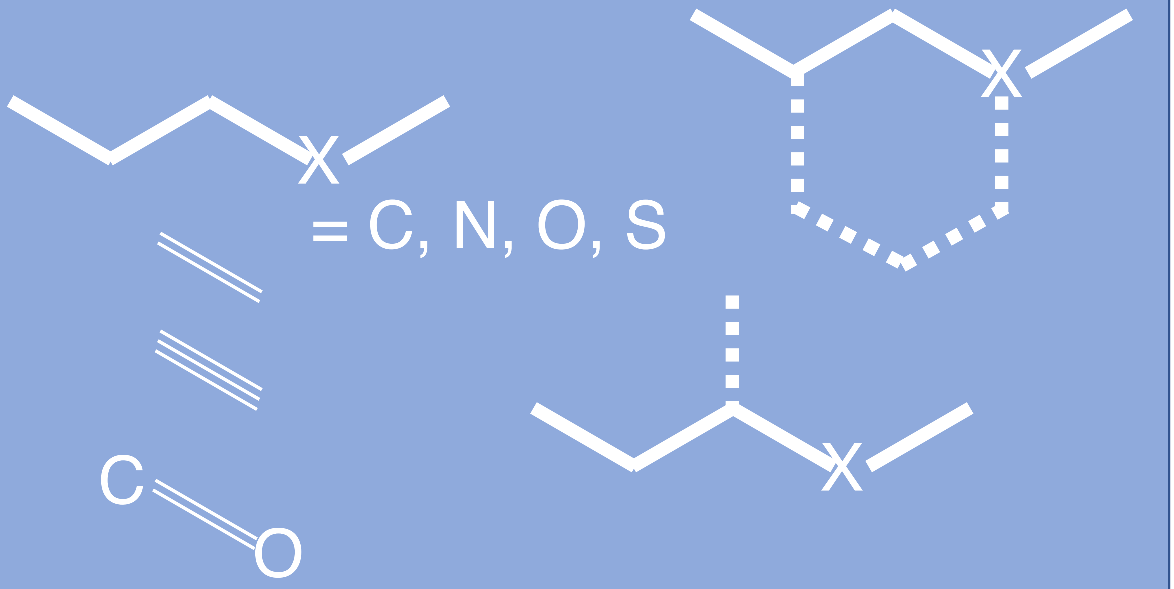
https://www.diamond.ac.uk/covid-19/for-scientists/Main-protease-structure-and-XChem.html

What is a **fragment**?



Chemical space

Possible compounds with <600 Da



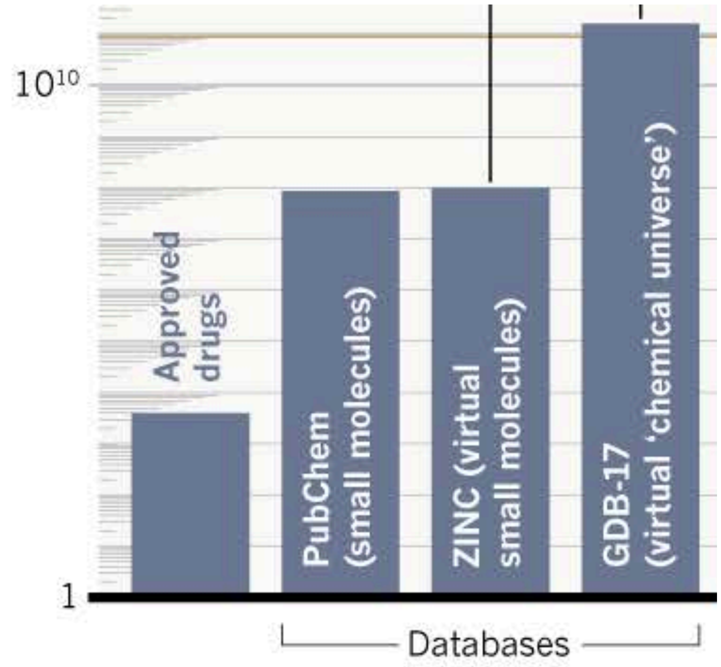
$\sim 10^{63}$

Bohacek RS *et al Molecular Research Reviews* 1,3-50 (1996)

Chemical space is huge!

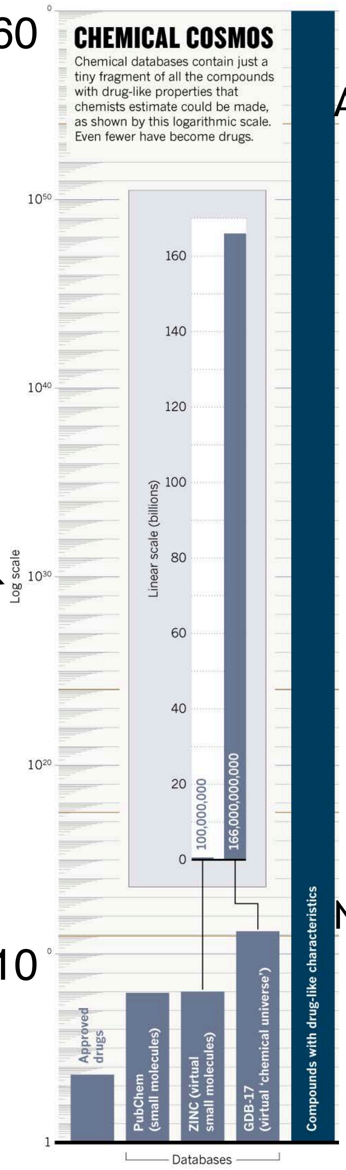
Mullard A *Nature* 549,445 (2017)

Chemical space is huge!



Mullard A *Nature* 549,445 (2017)

10^{60}


CHEMICAL COSMOS

Chemical databases contain just a tiny fragment of all the compounds with drug-like properties that chemists estimate could be made, as shown by this logarithmic scale. Even fewer have become drugs.

Atoms in the solar system

Log scale!

Stars in the universe

Neurons in the human brain

10^{10}

Mullard A *Nature* 549,445 (2017)

Needles in enormous haystacks

Finding that rare needle…

High throughput screening

Library
30 heavy atoms
$\sim 10^6$

Hit

Lead

Candidate

High throughput screening

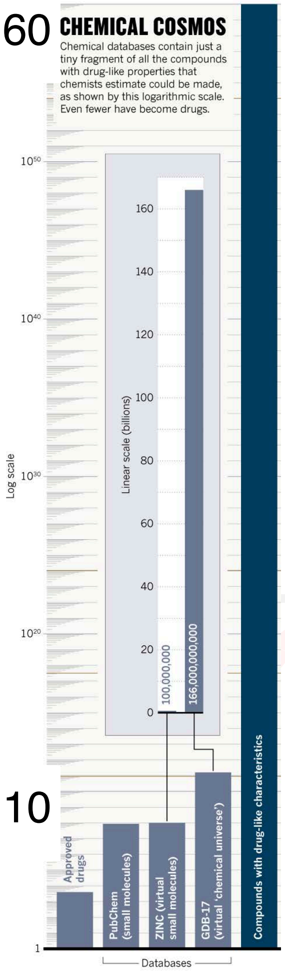
Library

30 heavy atoms

~10^6

Vast undersampling!

10^{60}



CHEMICAL COSMOS

Chemical databases contain just a tiny fragment of all the compounds with drug-like properties that chemists estimate could be made, as shown by this logarithmic scale. Even fewer have become drugs.

10^{10}

Candidate

Lead

Fragment based drug discovery

Library

15 heavy atoms

~10^5

Less undersampling

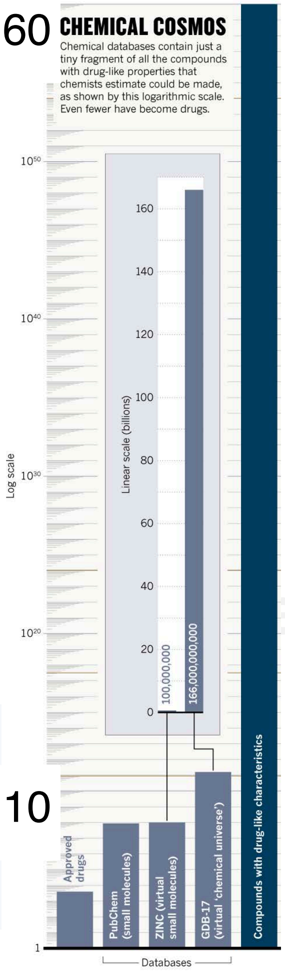
Evaluate WEAK binding

Rational optimize

ead

Candidate

10^{60}



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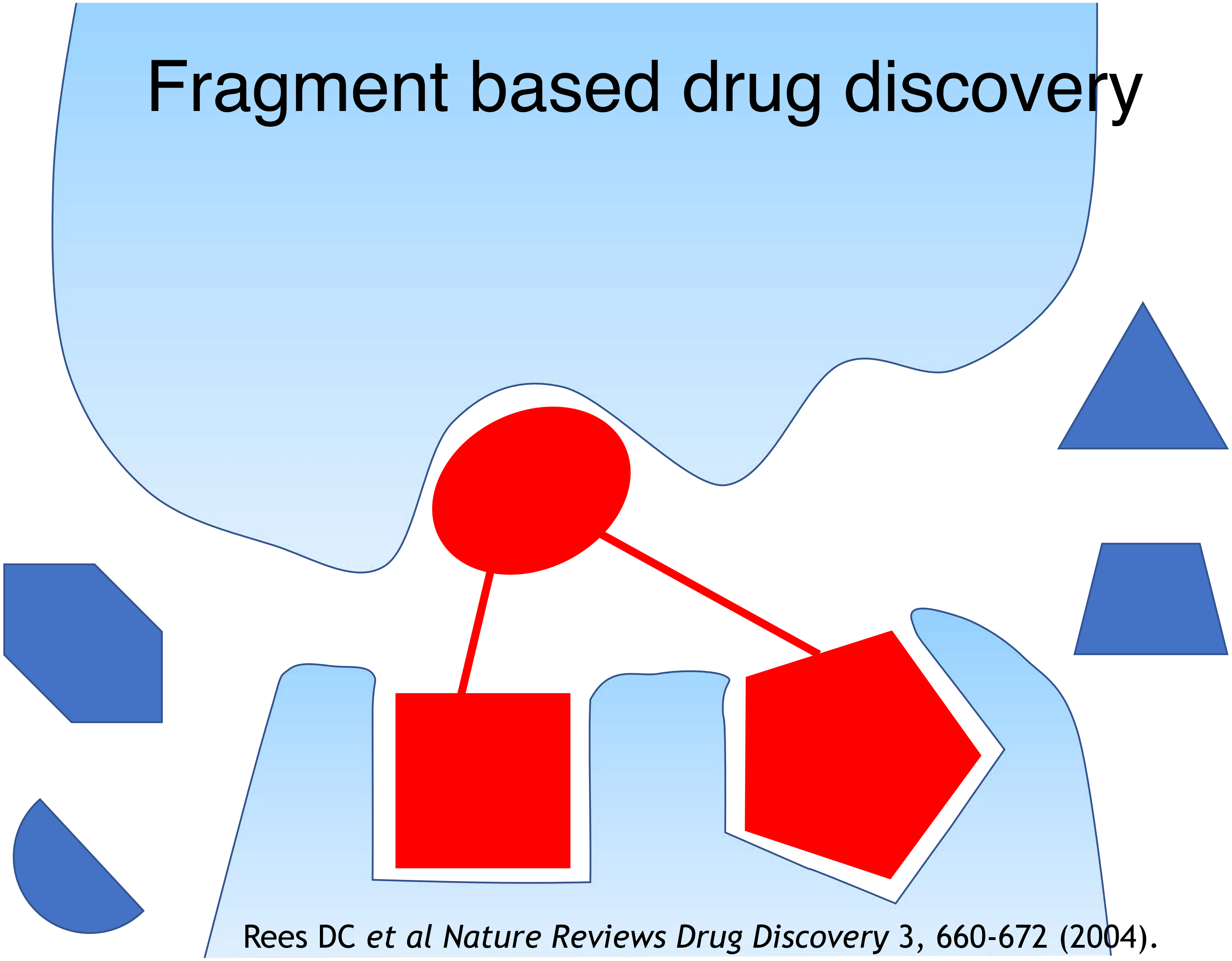
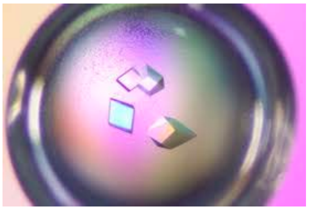
10^{10}

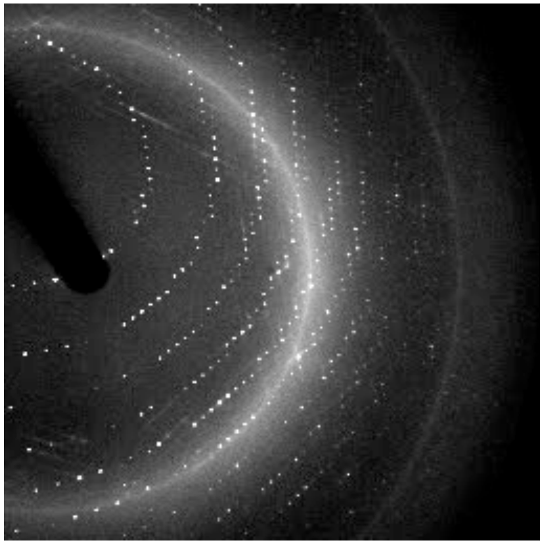
Fragment based drug discovery



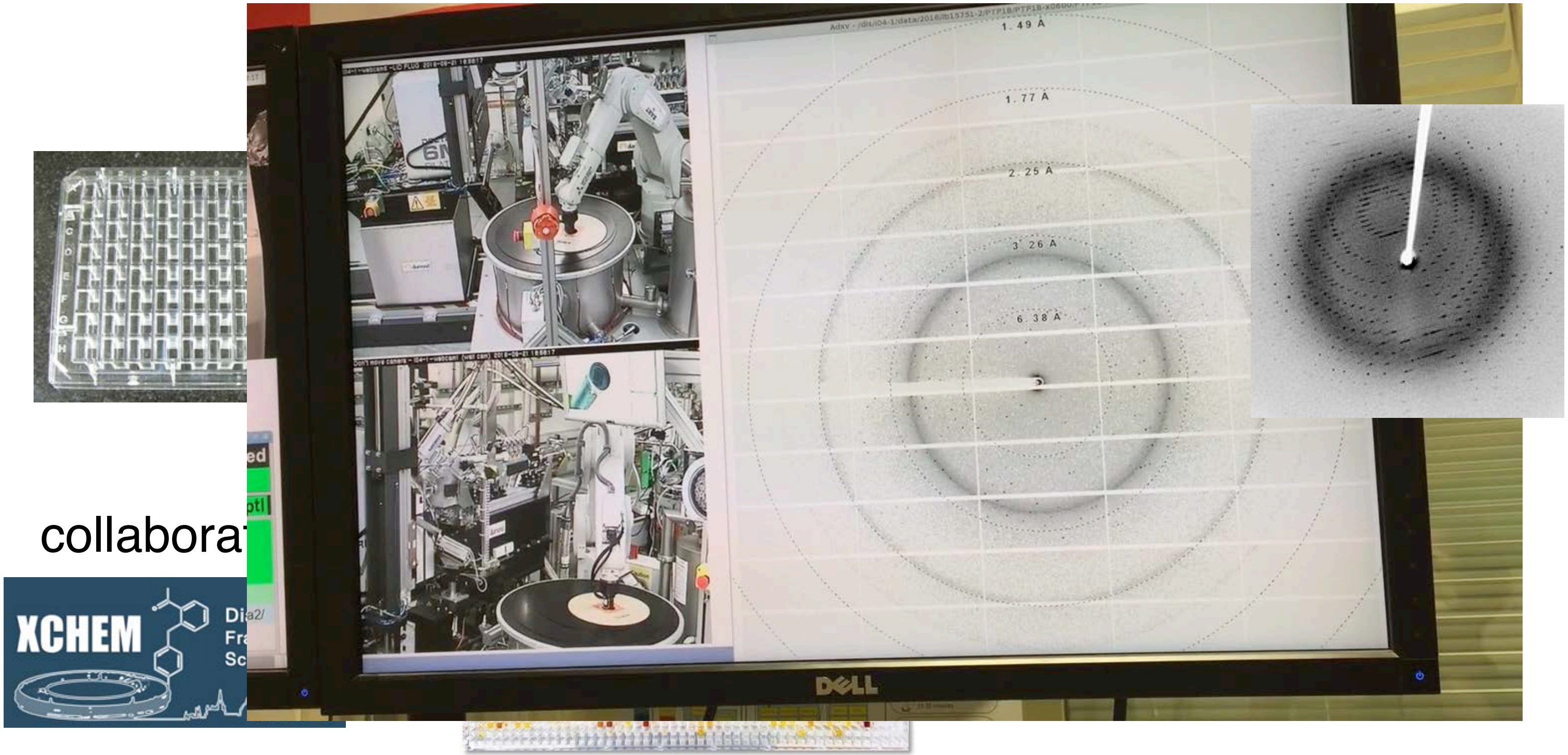
Rees DC *et al Nature Reviews Drug Discovery* 3, 660-672 (2004).

Protein Crystallography





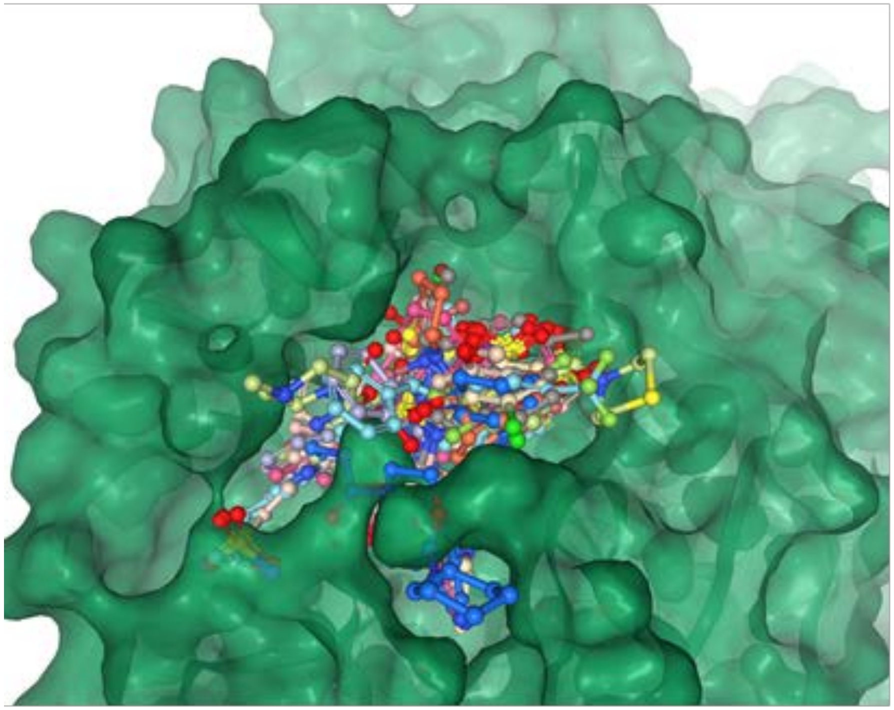
We have been building a new
fragment-soaking pipeline here at UCSF

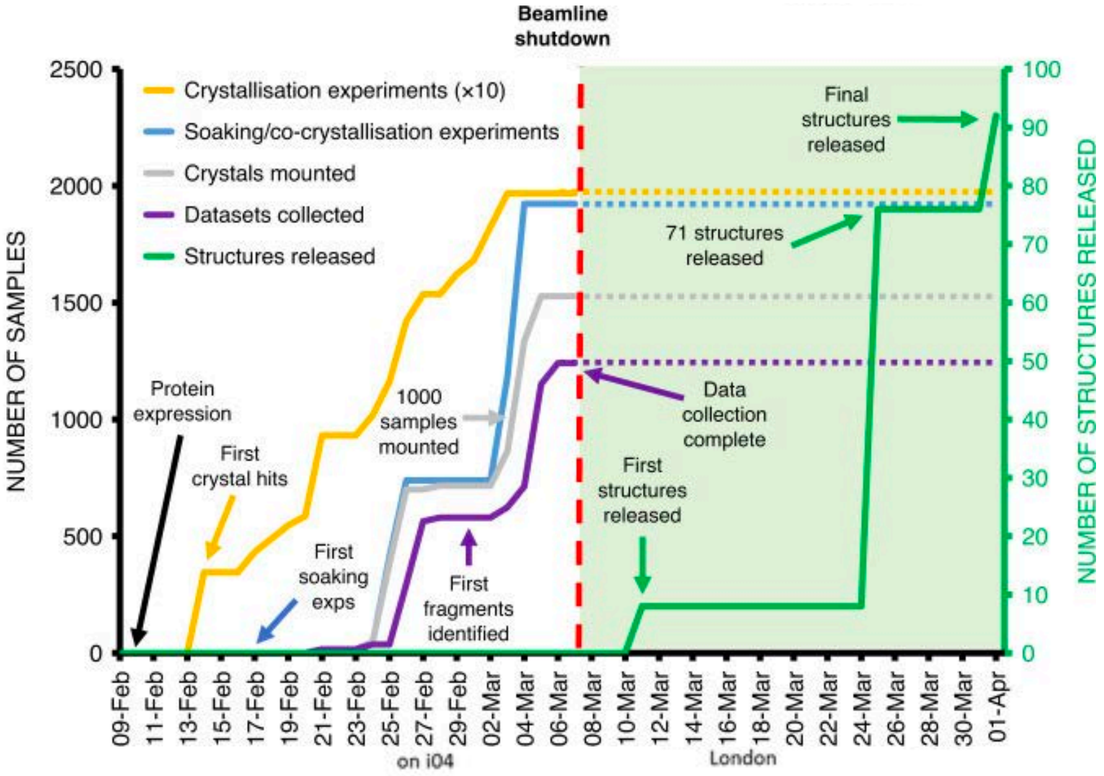


collabora

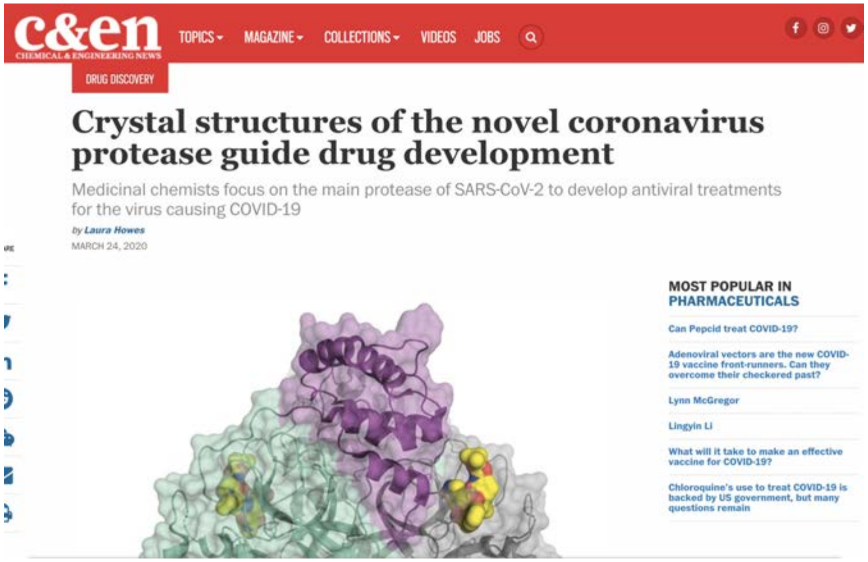
Frank von Delft

Work on COVID Protease by Diamond Light Source has been inspirational





Publishing and media in the time of COVID - data released in March! Even BioRxiv is too slow



DRUG DISCOVERY

Crystal structures of the novel coronavirus protease guide drug development

Medicinal chemists focus on the main protease of SARS-CoV-2 to develop antiviral treatments for the virus causing COVID-19

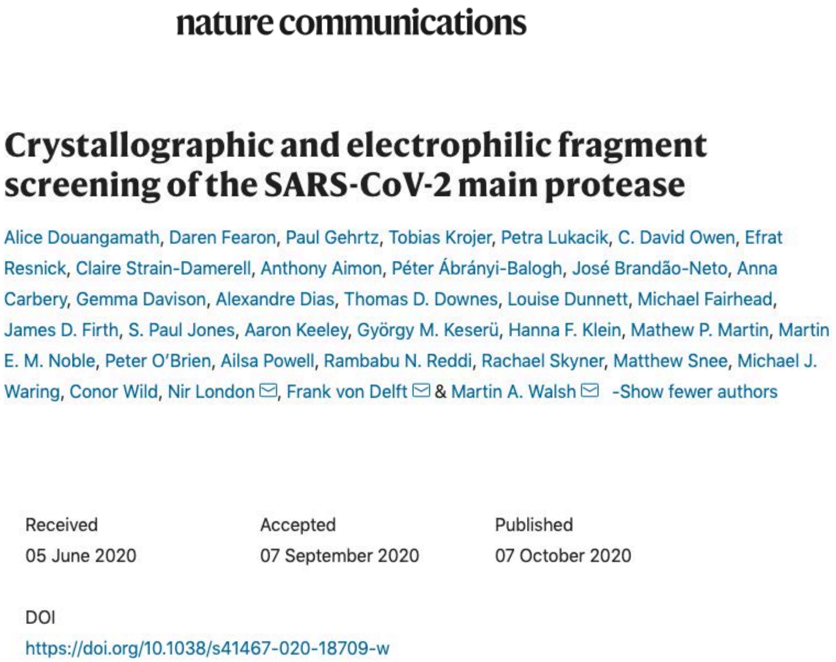
by *Laura Howes*

MARCH 24, 2020

MOST POPULAR IN PHARMACEUTICALS

- Can Pepcid treat COVID-19?
- Adenoviral vectors are the new COVID-19 vaccine front-runners. Can they overcome their checkered past?
- Lynn McGregor
- Lingyin Li
- What will it take to make an effective vaccine for COVID-19?
- Chloroquine's use to treat COVID-19 is backed by US government, but many questions remain

https://www.diamond.ac.uk/covid-19/for-scientists/Main-protease-structure-and-XChem.html



nature communications

Crystallographic and electrophilic fragment screening of the SARS-CoV-2 main protease

Alice Douangamath, Daren Fearon, Paul Gehrtz, Tobias Krojer, Petra Lukacik, C. David Owen, Efrat Resnick, Claire Strain-Damerell, Anthony Aimon, Péter Ábrányi-Balogh, José Brandão-Neto, Anna Carbery, Gemma Davison, Alexandre Dias, Thomas D. Downes, Louise Dunnett, Michael Fairhead, James D. Firth, S. Paul Jones, Aaron Keeley, György M. Keserü, Hanna F. Klein, Mathew P. Martin, Martin E. M. Noble, Peter O'Brien, Ailsa Powell, Rambabu N. Reddi, Rachael Skyner, Matthew Snee, Michael J. Waring, Conor Wild, Nir London ✉, Frank von Delft ✉ & Martin A. Walsh ✉ -Show fewer authors

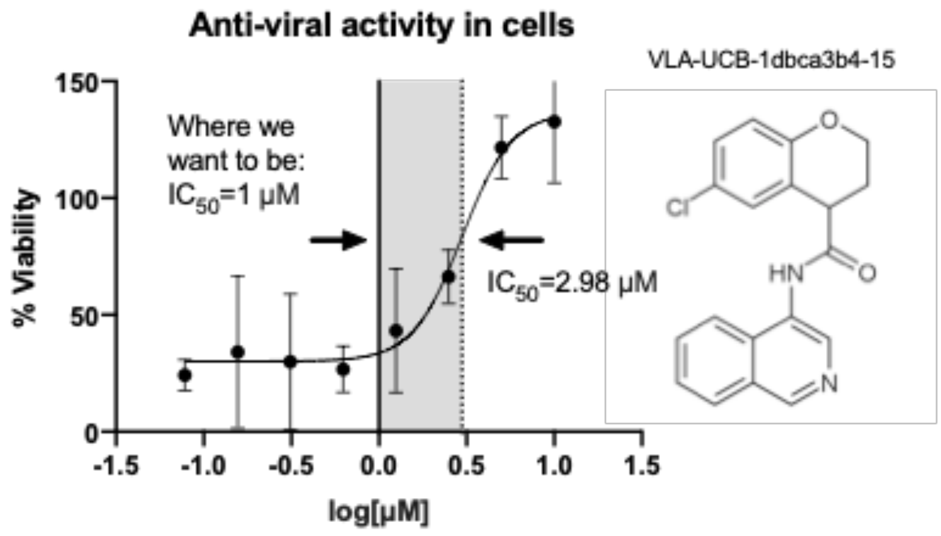
Received	Accepted	Published
05 June 2020	07 September 2020	07 October 2020

DOI
https://doi.org/10.1038/s41467-020-18709-w

data March, preprint June, paper October

Where are they now?

https://covid.postera.ai/covid



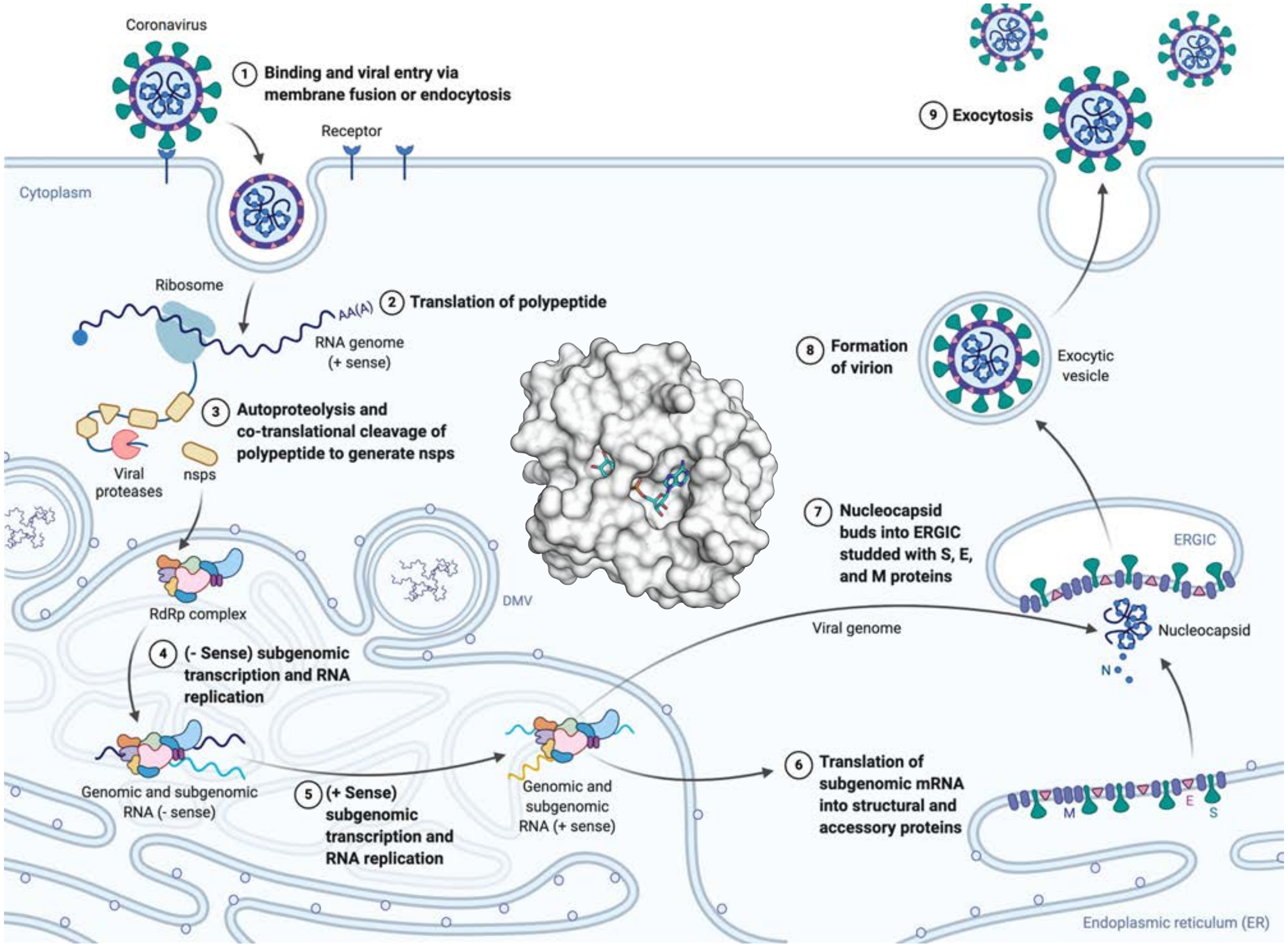
COVID Moonshot: Open Science Discovery of SARS-CoV-2 Main Protease Inhibitors by Combining Crowdsourcing, High-Throughput Experiments, Computational Simulations, and Machine Learning

The COVID Moonshot Consortium, Hagit Achdout, Anthony Aimon, Elad Bar-David, Haim Barr, Amir Ben-Shmuel, James Bennett, Melissa L Bobby, Juliane Brun, BVNBS Sarma, Mark Calmiano, Anna Carbery, Emma Cattermole, John D. Chodera, Austin Clyde, Joseph E. Coffland, Galit Cohen, Jason Cole, Alessandro Contini, Lisa Cox, Milan Cvitkovic, Alex Dias, Alice Douangamath, Shirly Duberstein, Tim Dudgeon, Louise Dunnett, Peter K. Eastman, Noam Erez, Michael Fairhead, Daren Fearon, Oleg Fedorov, Matteo Ferla, Holly Foster, Richard Foster, Ronen Gabizon, Paul Gehrtz, Carina Gileadi, Charline Giroud, William G. Glass, Robert Glen, Itai Glinert, Marian Gorichko, Tyler Gorrie-Stone, Edward J Griffen, Jag Heer, Michelle Hill, Sam Horrell, Matthew F.D. Hurley, Tomer Israely, Andrew Jajack, Eric Jnoff, Tobias John, Anastassia L. Kantsadi, Peter W. Kenny, John L. Kiappes, Lizbe Koekemoer, Boris Kovar, Tobias Krojer, Alpha Albert Lee, Bruce A. Lefker, Haim Levy, Nir London, Petra Lukacik, Hannah Bruce Macdonald, Beth MacLean, Tika R. Malla, Tatiana Matviiuk, Willam McCorkindale, Sharon Melamed, Oleg Michurin, Halina Mikolajek, Aaron Morris, Garrett M. Morris, Melody Jane Morwitzer, Demetri Moustakas, Jose Brandao Neto, Vladas Oleinikovas, Gijs J. Overheul, David Owen, Ruby Pai, Jin Pan, Nir Paran, Benjamin Perry, Maneesh Pingle, Jakir Pinjari, Boaz Politi, Ailsa Powell, Vladimir Psenak, Reut Puni, Victor L. Rangel, Rambabu N. Reddi, St Patrick Reid, Efrat Resnick, Matthew C. Robinson, Ralph P. Robinson, Dominic Rufa, Christopher Schofield, Aarif Shaikh, Jiye Shi, Khriesto Shurrush, Assa Sittner, Rachael Skyner, Adam Smalley, Mihaela D. Smilova, John Spencer, Claire Strain-Damerell, Vishwanath Swamy, Hadas Tamir, Rachael Tennant, Andrew Thompson, Warren Thompson, Susana Tomasio, Anthony Tumber, Ioannis Vakonakis, Ronald P. van Rij, Finny S. Varghese, Mariana Vaschetto, Einat B. Vitner, Vincent Voelz, Annette von Delft, Frank von Delft, Martin Walsh, Walter Ward, Charlie Weatherall, Shay Weiss, Conor Francis Wild, Matthew Wittmann, Nathan Wright, Yfat Yahalom-Ronen, Daniel Zaidmann, Hadeer Zidane, Nicole Zitzmann

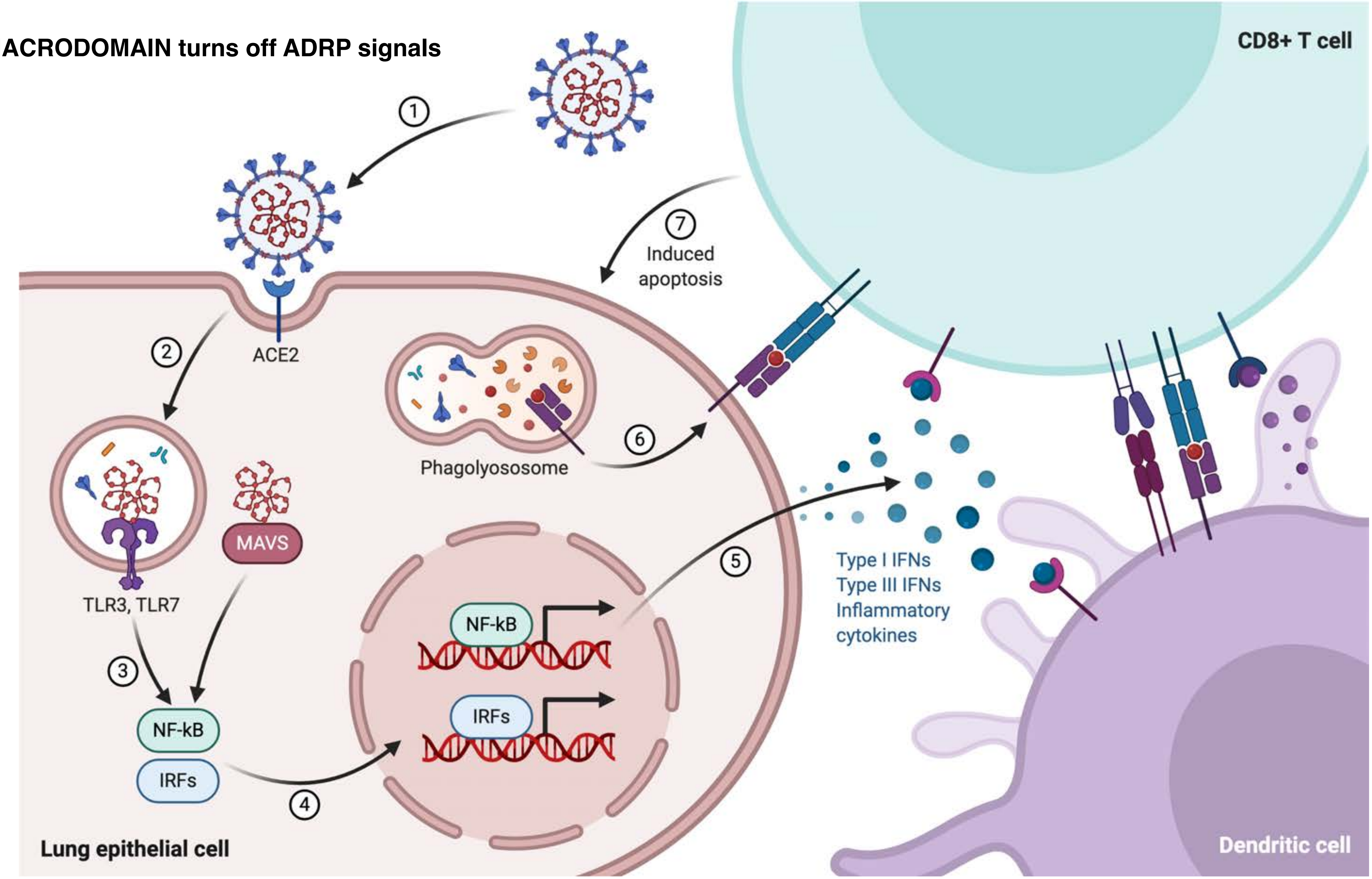
Posted October 30, 2020.

3 spots to stop SARS:

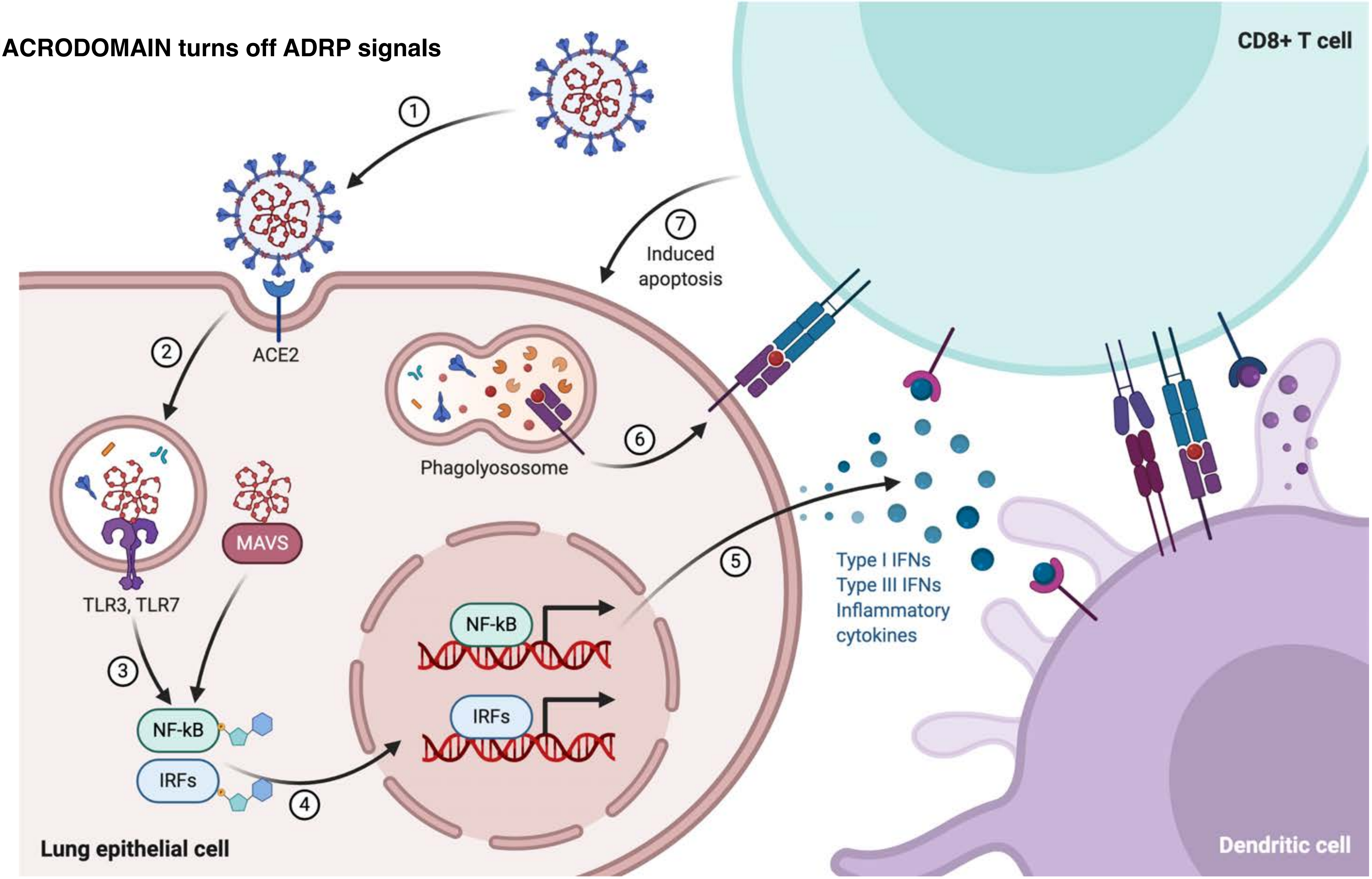
Signaling



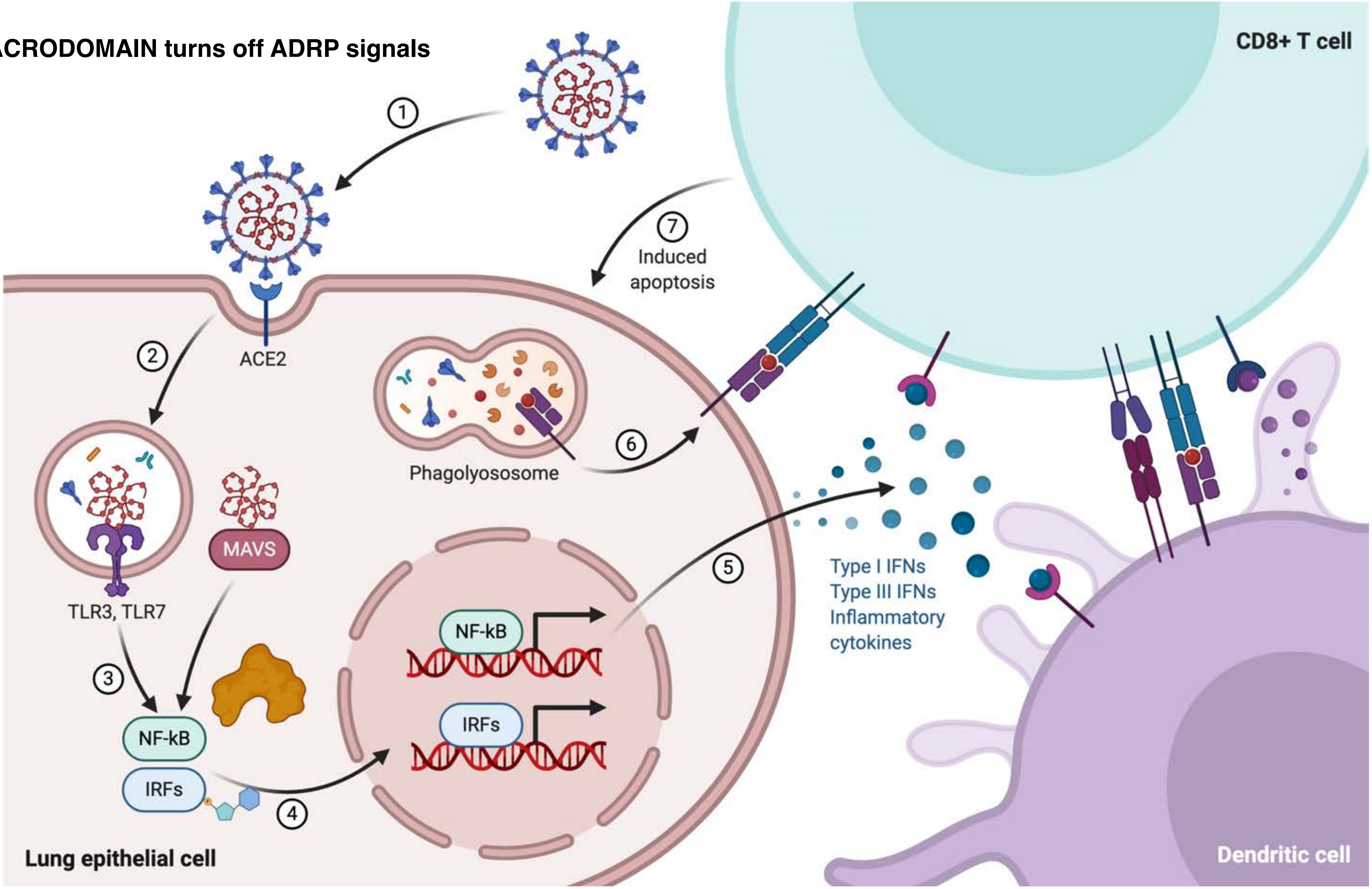
MACRODOMAIN turns off ADRP signals



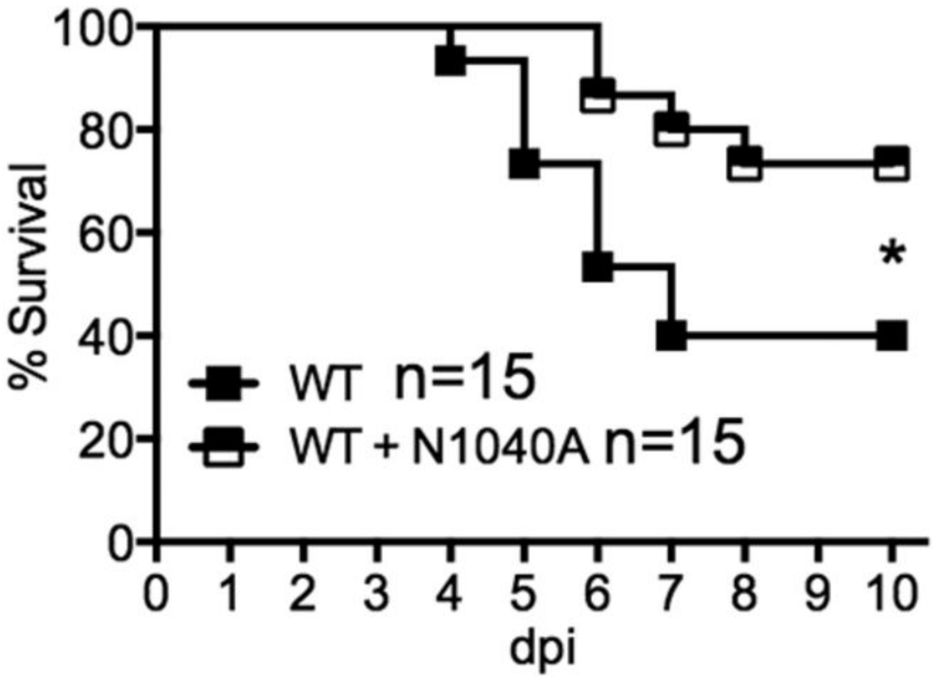
MACRODOMAIN turns off ADRP signals



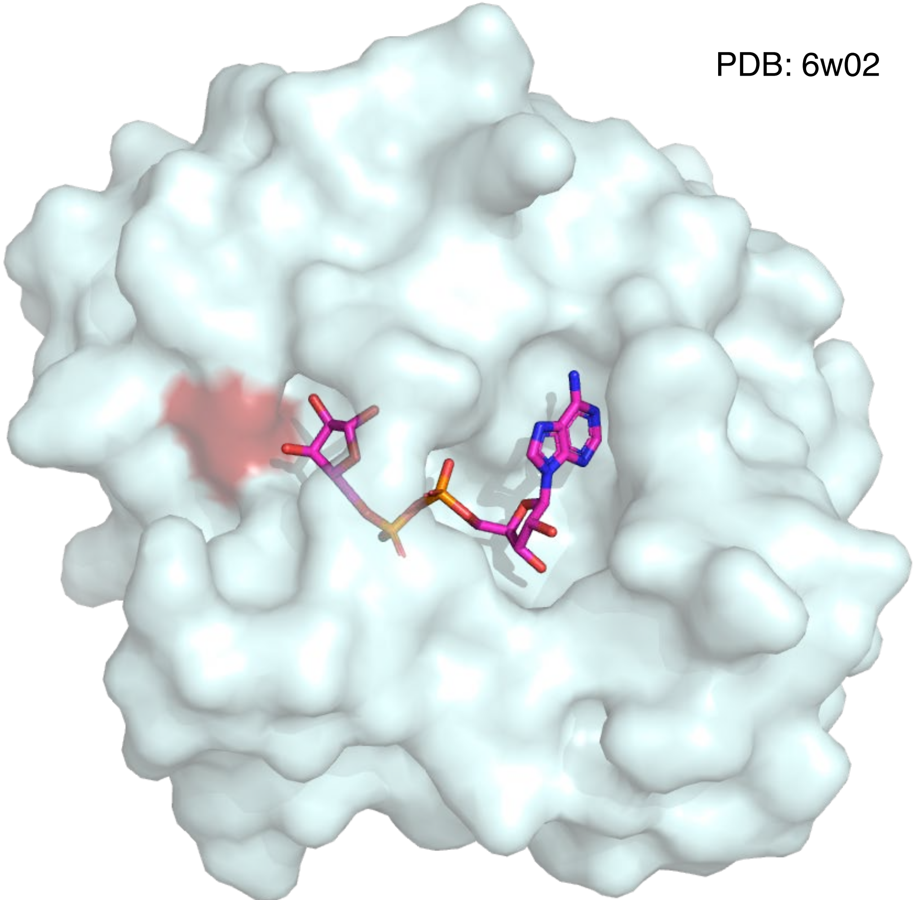
MACRODOMAIN turns off ADRP signals



Macrodomain catalytic mutations **reduce virulence** of SARS-1



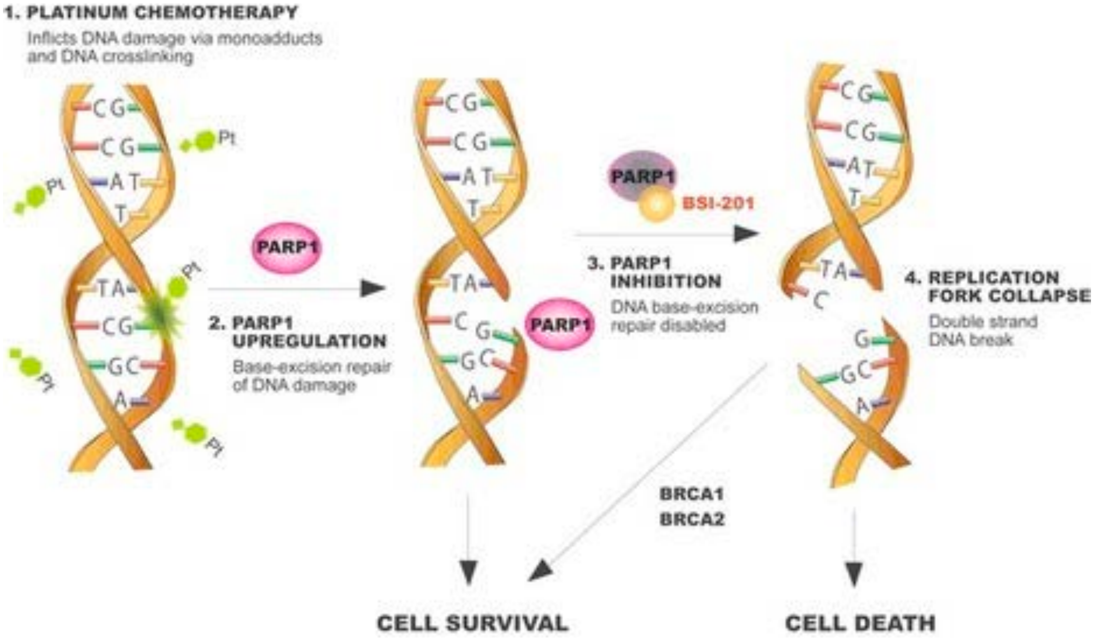
Fehr…Ahel, Perlman. mBio. 2016



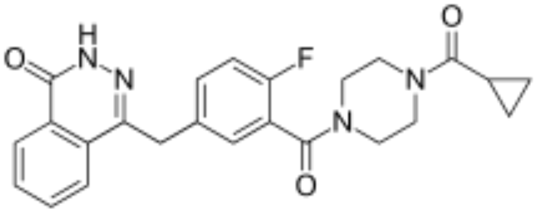
PDB: 6w02

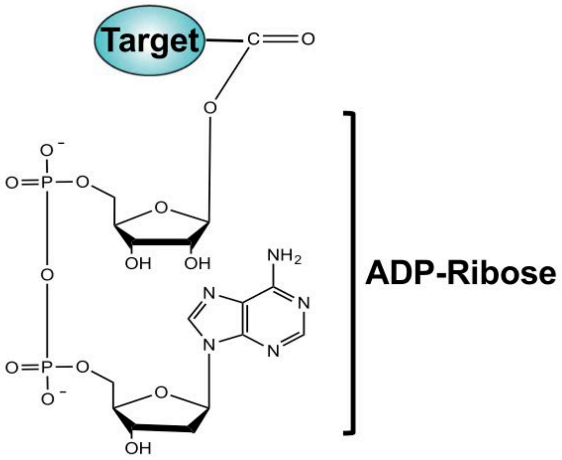
….but ADPr is the only chemical matter known to bind…

ADRP signaling is also prevalent in cancer!



Olaparib



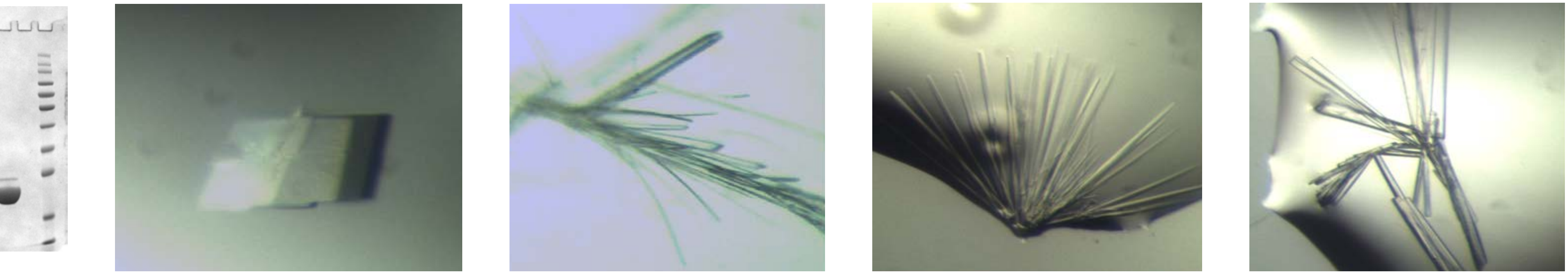


Prof. Alan Ashworth

We currently have no effective small molecule therapies to stop the spread of SARS CoV 2

We currently have no validated small molecule binders to macrodomain

QCRG proceeded from **clone to crystals** very rapidly!



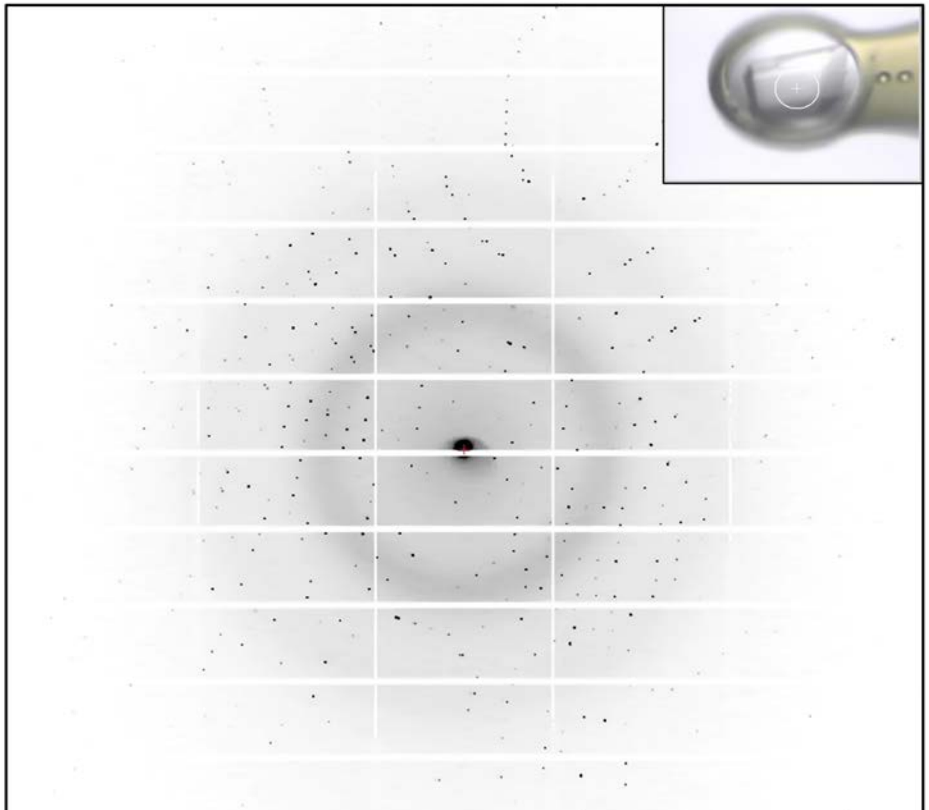
Ursula
Schulze-Gahmen

Tristan
Owens

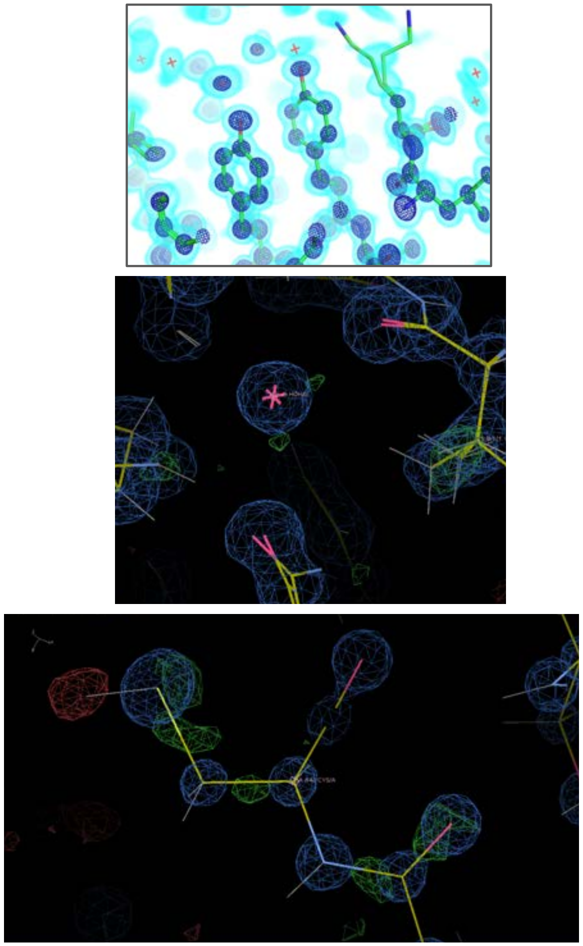
Robbie
Díaz

Ultra-high resolution diffraction means we can visualize hydrogens and bond features!

Prof. Michael Thompson (UC Merced)



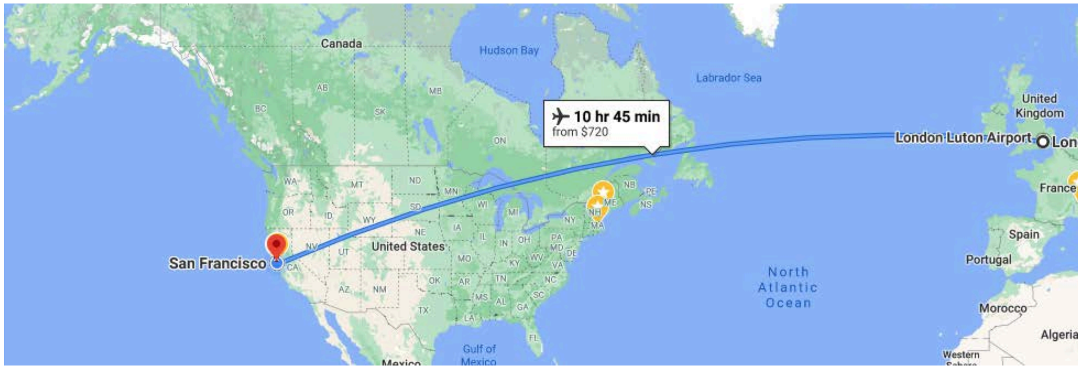
SARS-CoV2 nsp3 Macrodomain, Resolution ~0.8Å

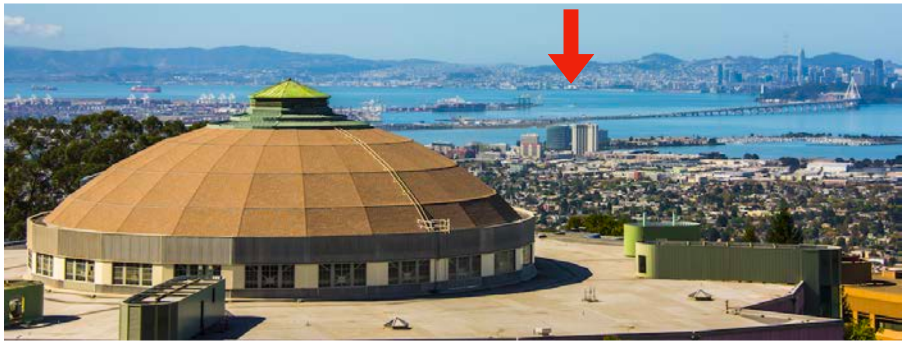


Prof. Frank von Delft (SGC, Diamond)

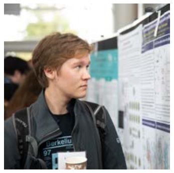
Prof. Ivan Ahel (Oxford)

Dr. Marion Schuller (OXford)





Prof. Michael Thompson (UC Merced)



Dr. Iris Young

Dr. Galen Correy

(and the QCRG Structural Biology team!)

ALS: James Holton, George Meigs
SSRL: Aina Cohen, Silvia Russi, Clyde Smith, Lisa Dunn, Jeney Wierman

We collected ~1000 datasets from the UCSF effort!

Crystallization

Soaking

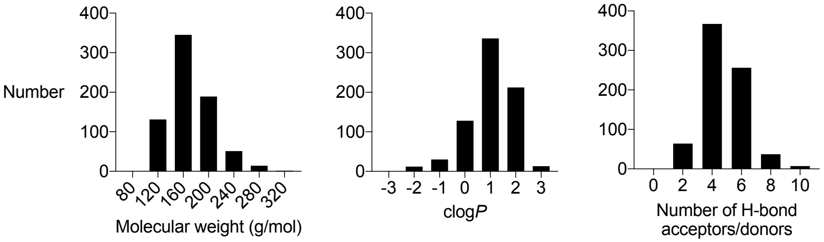
Vitrification

X-ray diffraction

Data analysis

Enamine library
320 compounds

UCSF custom
92 compounds



Justin Biel (Fraser lab)
Liam McKay, Loren Jiang (UCSF MSG facility)
James Holton, George Meigs (ALS/LBL/UCSF)

PBBR grant - Jason Gestwicki, John Irwin, Michelle Arkin

Our team worked around the clock to get this done!

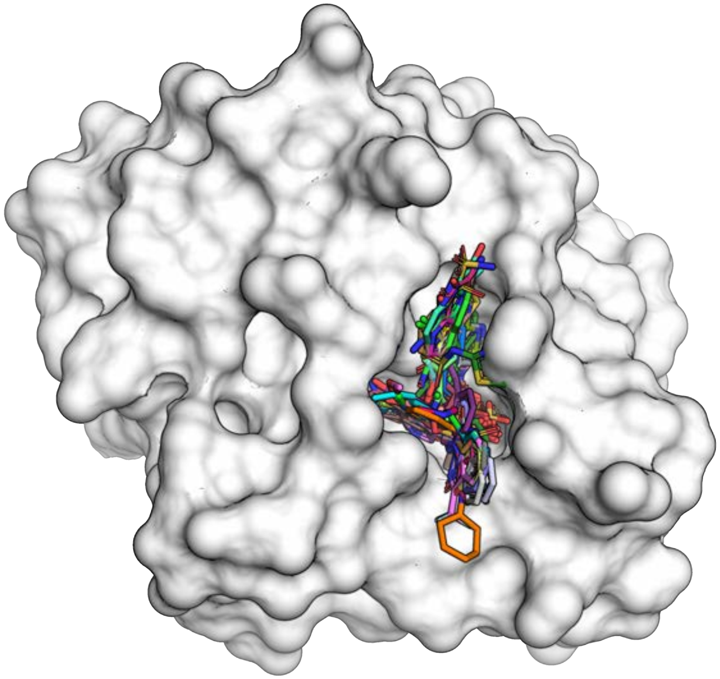
Galen 4:09 AM

Ok - there were a

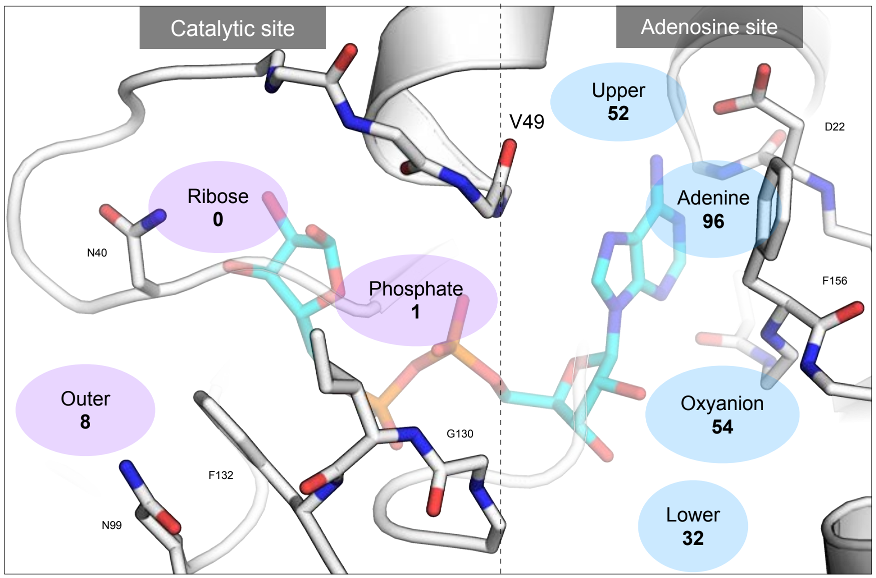
UCSF fragment libraries

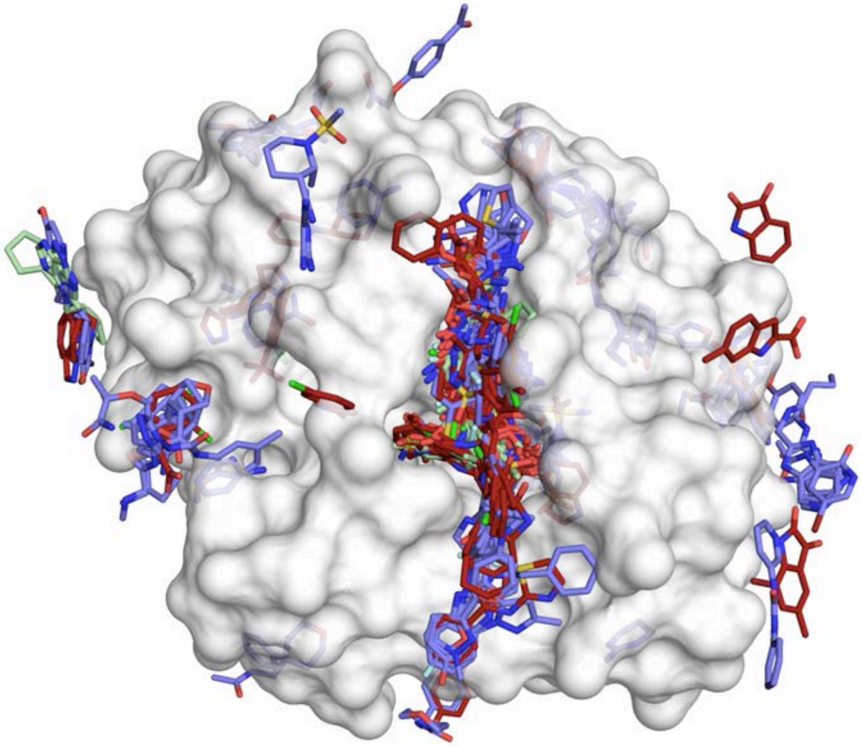
69 hits, 58 in adenine binding site

411 screened

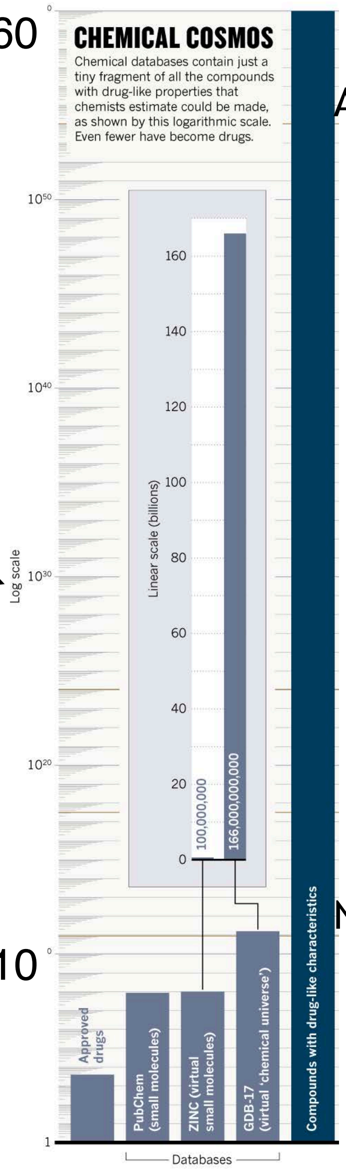


We were surprised by the **location of hits** (north-south rather than east-west)





10^{60}



Atoms in the solar system

Log scale!

Stars in the universe

Neurons in the human brain

10^{10}

Mullard A *Nature* 549,445 (2017)

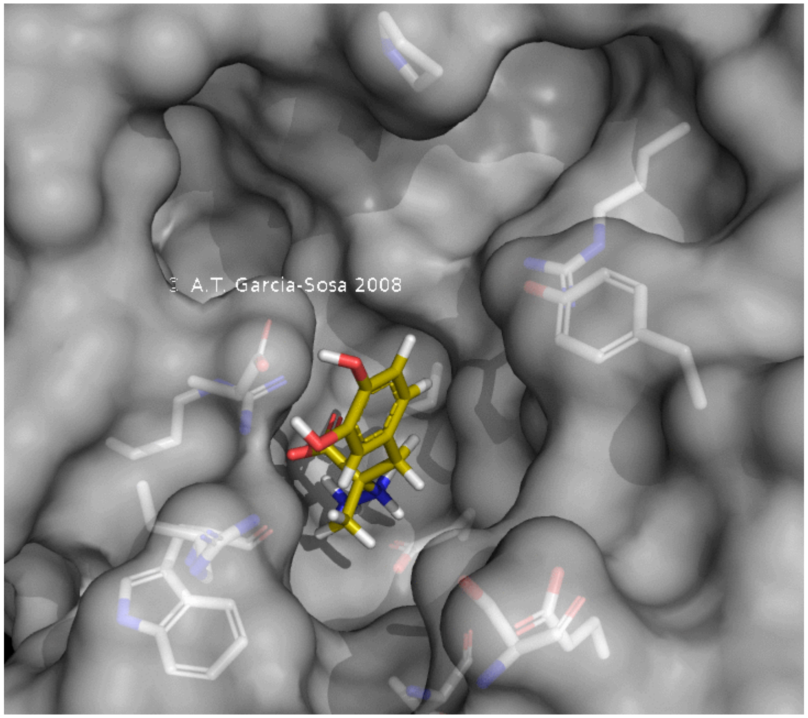
Computational docking screens against macrodomain

- Experimental fragment libraries for soaking

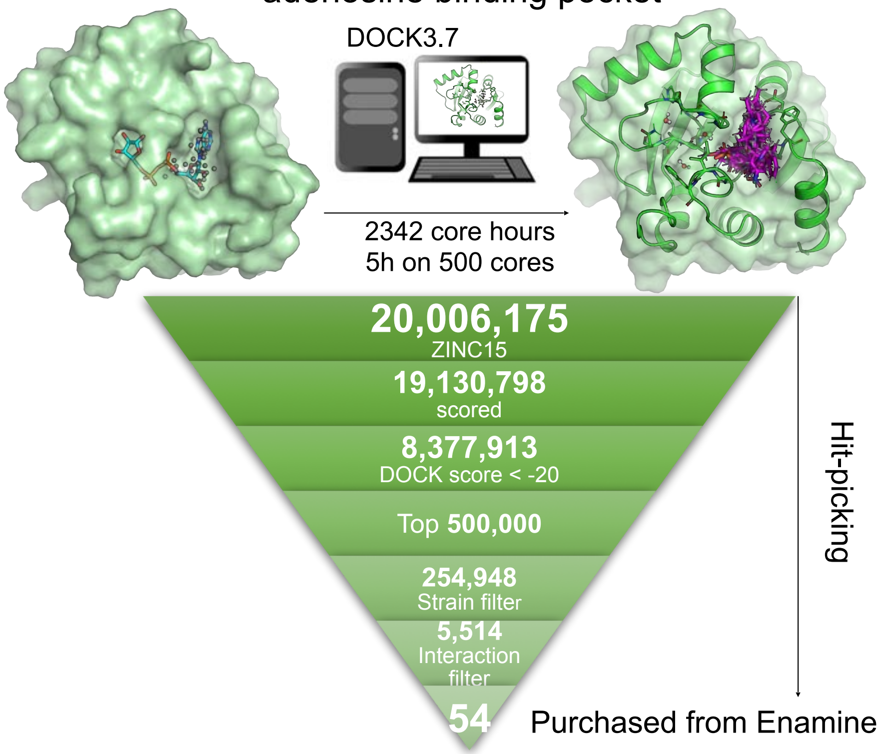
  (UCSF):
  411 fragments
  (XChem):
  2,126 fragments

- Computer-aided drug discovery: Fragment docking

  Shoichet lab (UCSF):
  20,006,175 fragments (ZINC15.org)



Fragment docking campaign against adenosine binding pocket



2342 core hours
5h on 500 cores

20,006,175
ZINC15

19,130,798
scored

8,377,913
DOCK score < -20

Top **500,000**

254,948
Strain filter

5,514
Interaction filter

54 Purchased from Enamine

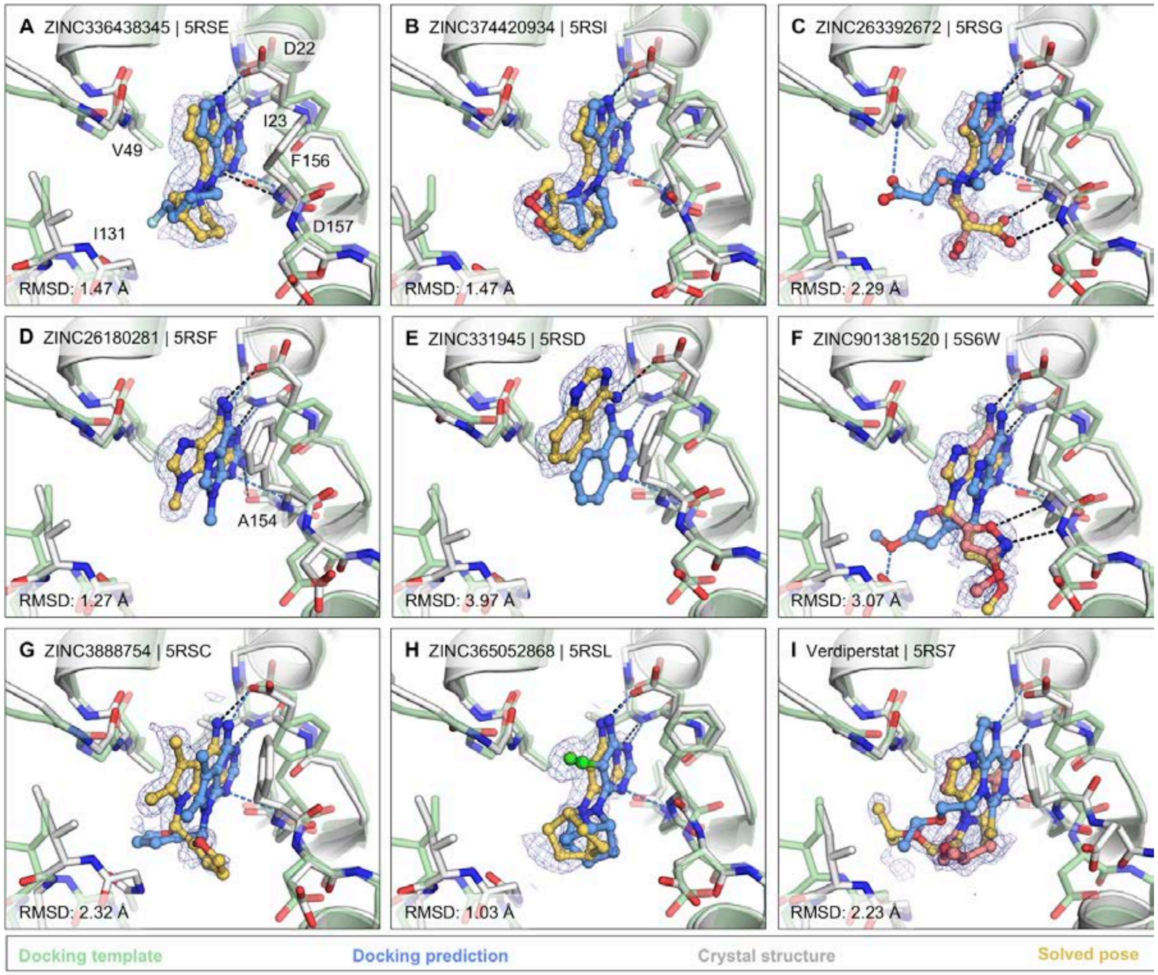
9 in-stock
33/45 **make-on-demand**

+ 722,963 ZINC15 in-stock 8

+ 21,000 “in-human” library 10

60 molecules from docking

Experimental confirmation of **docking poses**

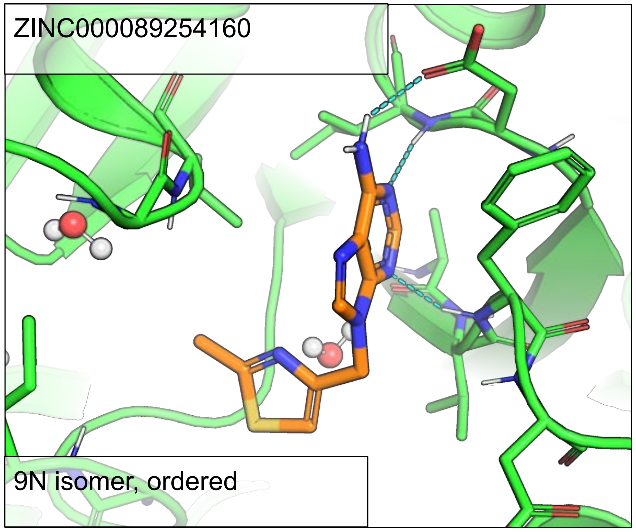


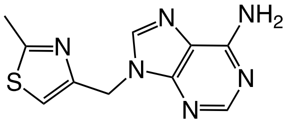
Prof. Brian Shoichet

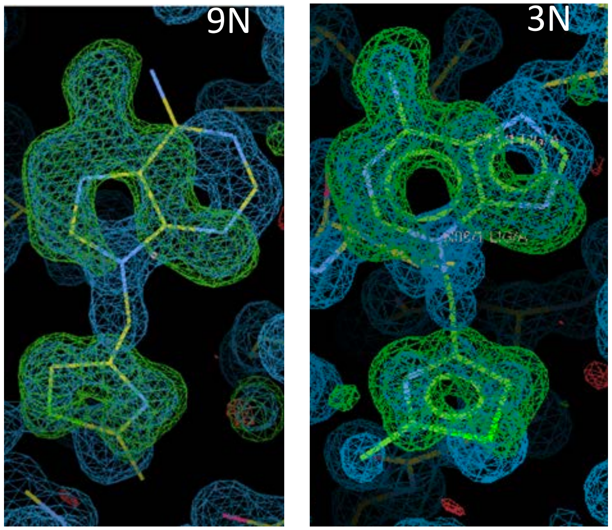
Dr. Stefan Gahbauer

Electron density reveals **different isomers** of “make on demand” compounds!

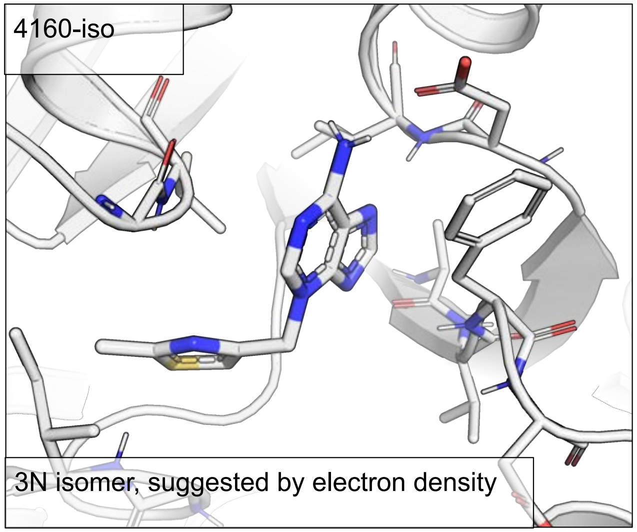
- Electron density suggests 3N-alkyl adenine instead of 9N-alkyl adenine isomer

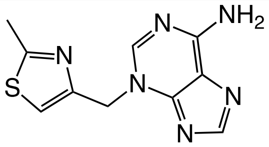




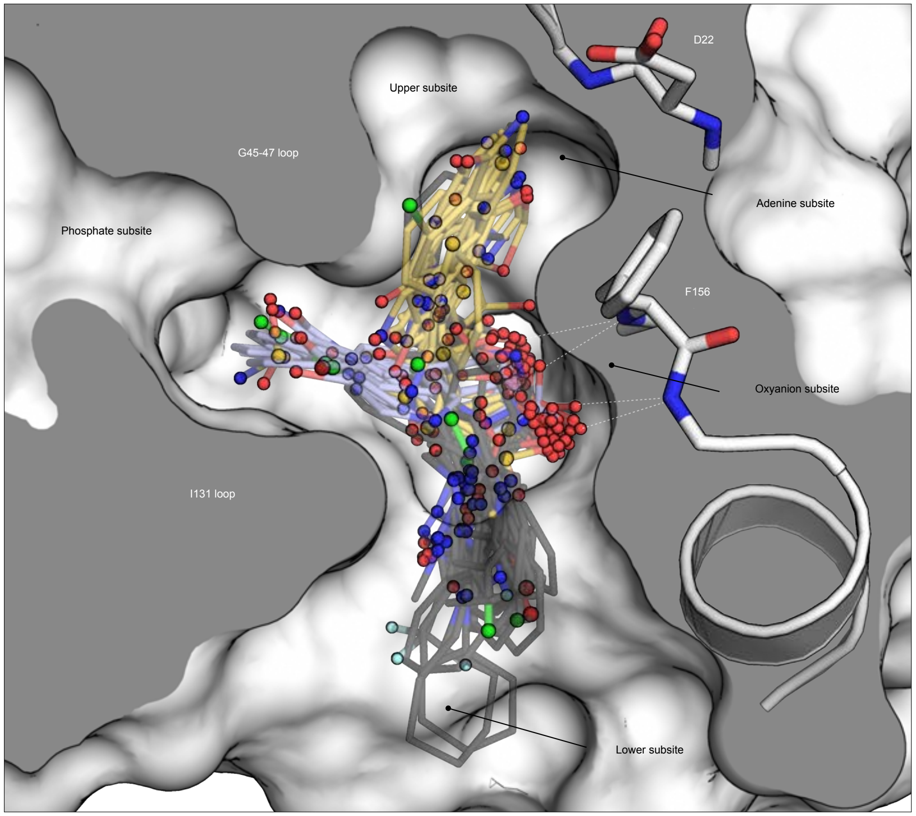


Isomeric species are analyzed by
Michael Johnson (ChemPartner)

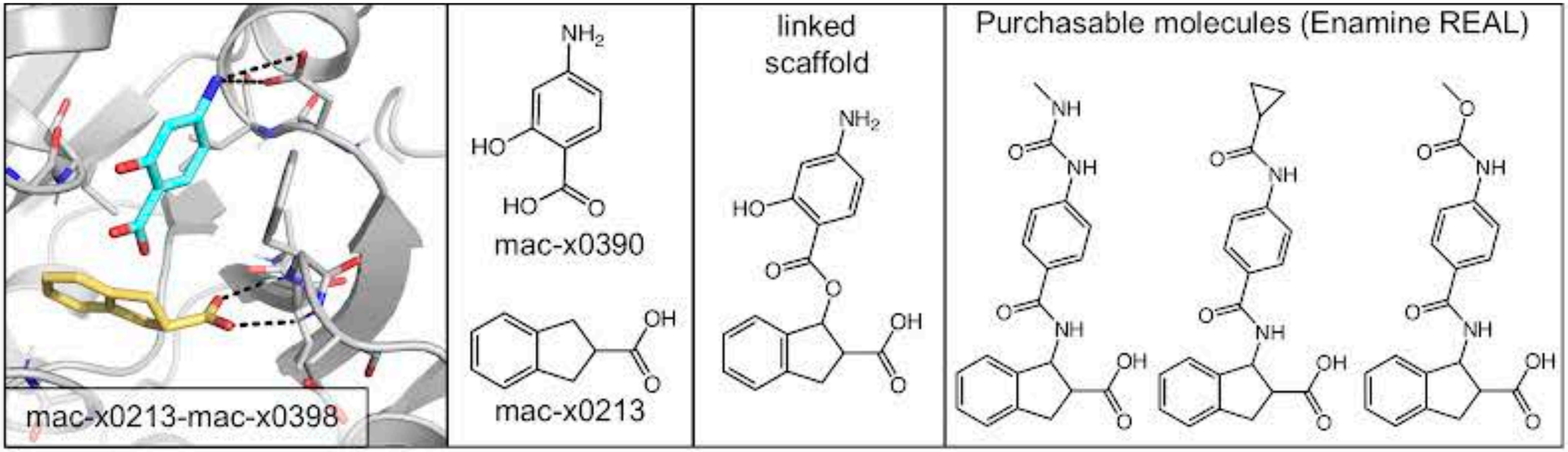




Fragment linking/merging opportunities are revealed by structures

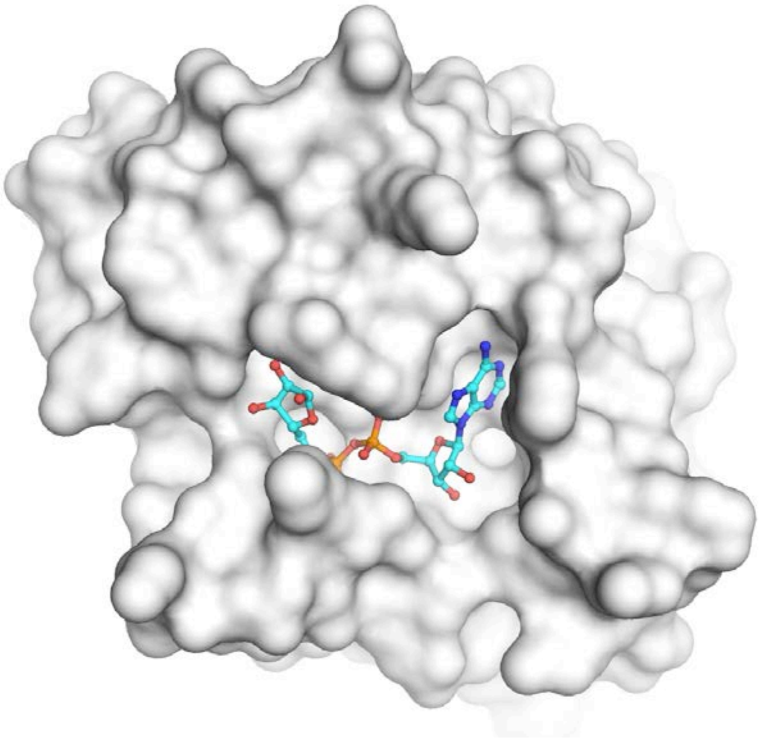


Fragment linking proposes new molecules

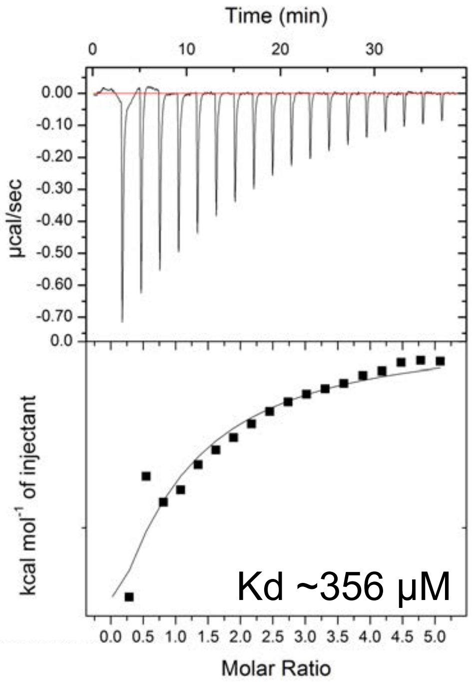


Matteo Ferla, Frank von Delft

Merging molecules together creates reasonable, purchasable compounds

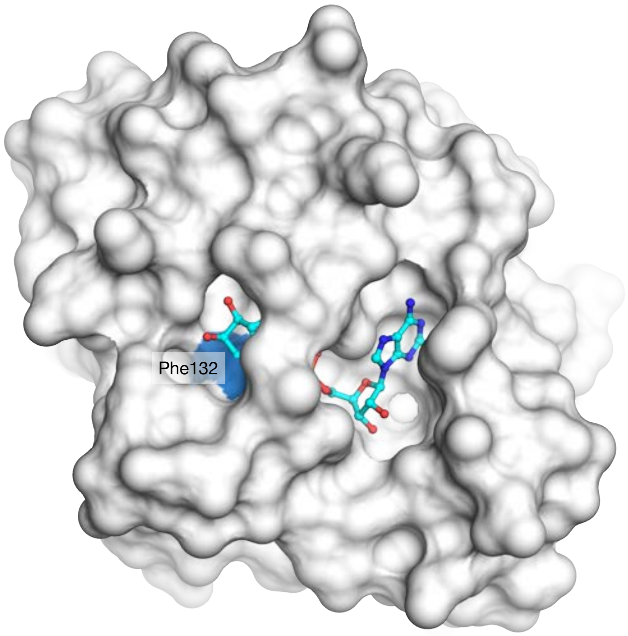


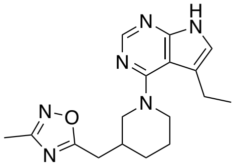
Multiple lead-like docking hits dramatically remodel active site



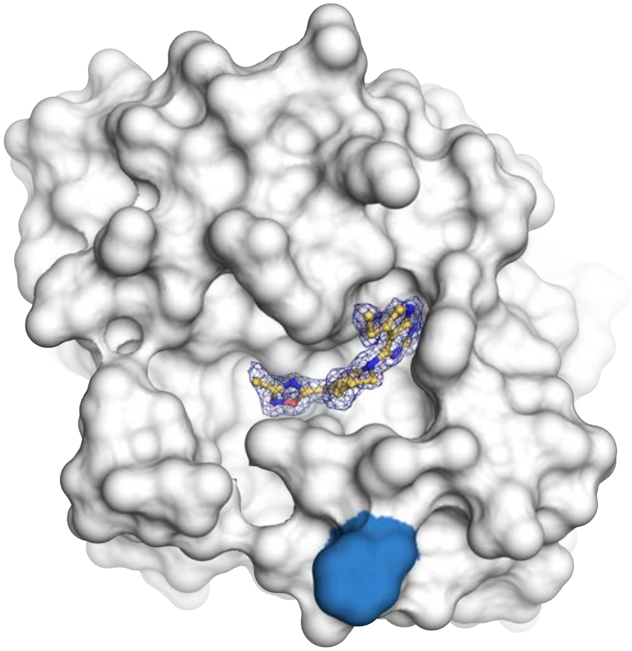
Kd ~356 µM

ADP-ribose co-crystal structure

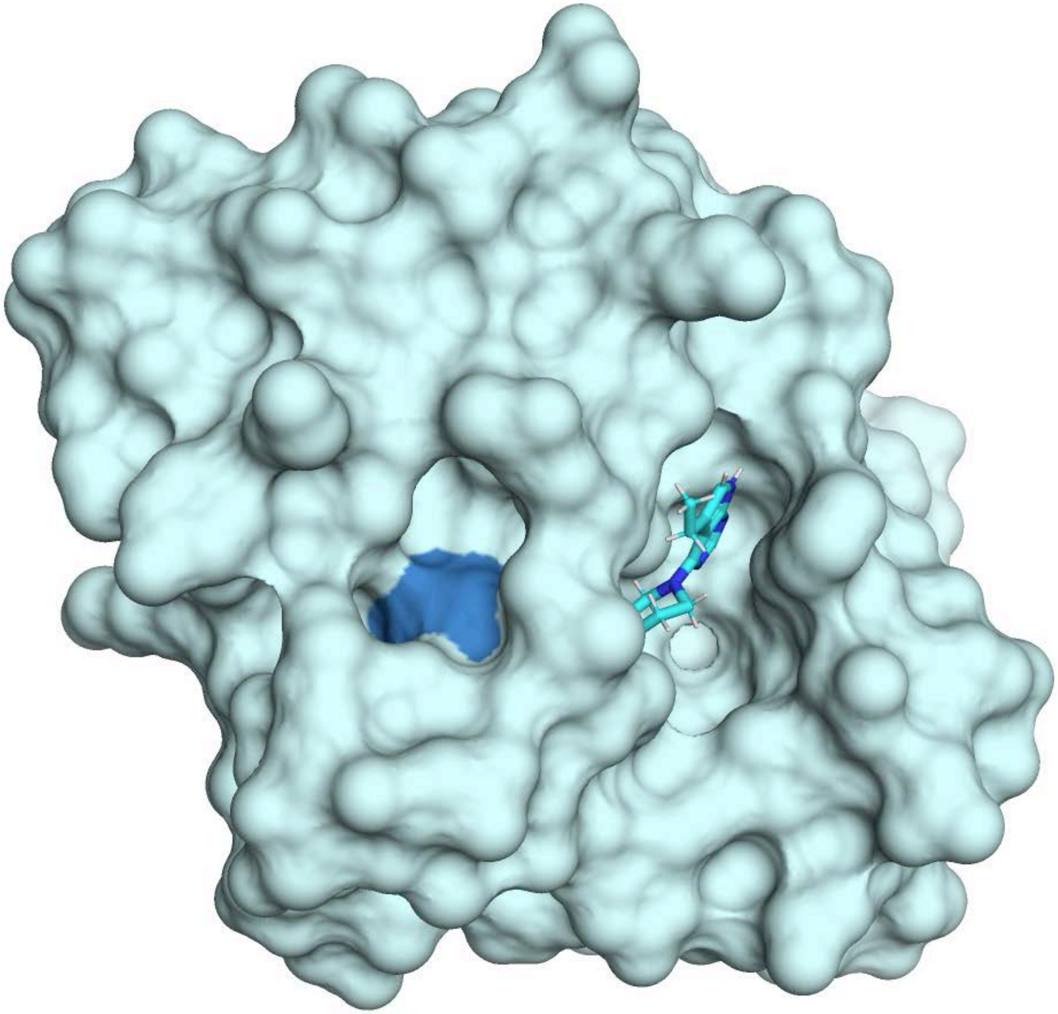




ZINC000896845531



Robbie Diaz



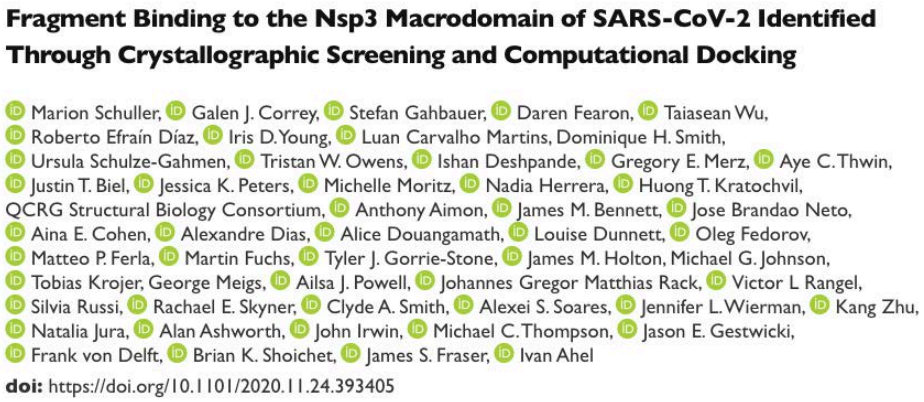
While the “**publication**” process is going, we are getting advice from chemists around the world…

Research • July 9, 2020

Building Blocks for COVID-19 Antiviral Drugs Identified in Rapid Study

Data Posted Online as an Open Resource for Scientists Developing Coronavirus Treatments

https://fraserlab.com/macrodomain/



Fragment Binding to the Nsp3 Macrodomain of SARS-CoV-2 Identified Through Crystallographic Screening and Computational Docking

Marion Schuller, Galen J. Correy, Stefan Gahbauer, Daren Fearon, Taiasean Wu,
Roberto Efraín Díaz, Iris D. Young, Luan Carvalho Martins, Dominique H. Smith,
Ursula Schulze-Gahmen, Tristan W. Owens, Ishan Deshpande, Gregory E. Merz, Aye C. Thwin,
Justin T. Biel, Jessica K. Peters, Michelle Moritz, Nadia Herrera, Huong T. Kratochvil,
QCRG Structural Biology Consortium, Anthony Aimon, James M. Bennett, Jose Brandao Neto,
Aina E. Cohen, Alexandre Dias, Alice Douangamath, Louise Dunnett, Oleg Fedorov,
Matteo P. Ferla, Martin Fuchs, Tyler J. Gorrie-Stone, James M. Holton, Michael G. Johnson,
Tobias Krojer, George Meigs, Ailsa J. Powell, Johannes Gregor Matthias Rack, Victor L Rangel,
Silvia Russi, Rachael E. Skyner, Clyde A. Smith, Alexei S. Soares, Jennifer L. Wierman, Kang Zhu,
Natalia Jura, Alan Ashworth, John Irwin, Michael C. Thompson, Jason E. Gestwicki,
Frank von Delft, Brian K. Shoichet, James S. Fraser, Ivan Ahel

doi: https://doi.org/10.1101/2020.11.24.393405

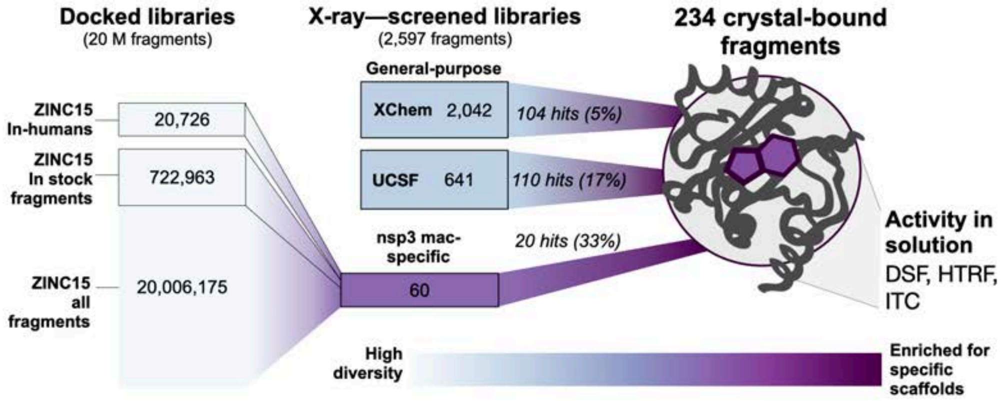
bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

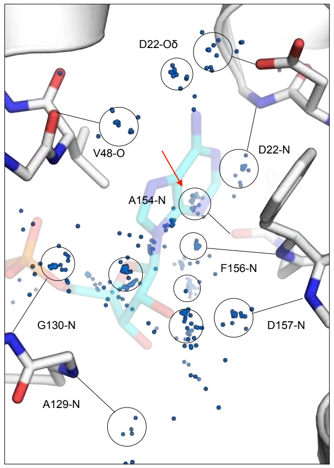
Posted November 24, 2020.

…and ordering more molecules to test!

The **macrodomain** can be targeted by small molecules - but strong inhibition is a ways off…

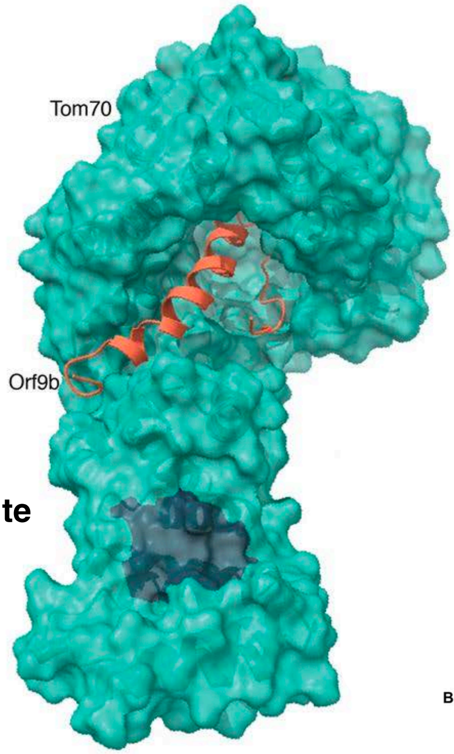
- High fragment soaking hit rate, providing many starting points
- Docking works! Solution binding experiments highly correlated with soaking success in crystallography
- Recurrent binding motifs (hinge, oxyanion) - can be linked, retaining high chemical diversity, by Fragmenstein



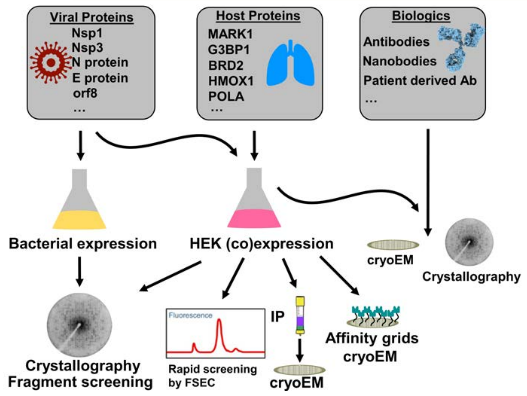


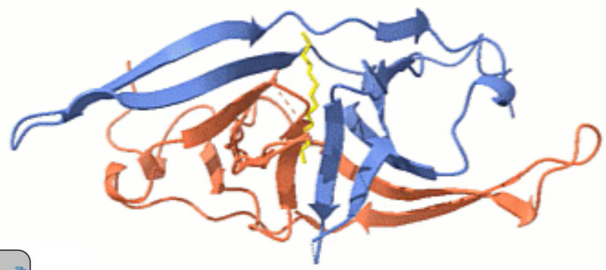
What’s next?

CryoEM platform reveals the structural basis of Orf9b hijack of Tom70 (mitochondrial chaperone)



Hsp90 interaction site





Klim Verba, Oren Rosenberg

Gordon…Krogan, *Science*, 2020

PERSPECTIVE

The COVID-19 response illustrates that traditional academic reward structures and metrics do not reflect crucial contributions to modern science

Adam J. Kucharski*, Sebastian Funk, Rosalind M. Eggo

Centre for Mathematical Modelling of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom

* adam.kucharski@lshtm.ac.uk

Abstract

The COVID-19 pandemic has motivated many open and collaborative analytical research projects with real-world impact. However, despite their value, such activities are generally overlooked by traditional academic metrics. Science is ultimately improved by analytical work, whether ensuring reproducible and well-documented code to accompany papers, developing and maintaining flexible tools, sharing and curating data, or disseminating analysis to wider audiences. To increase the impact and sustainability of modern science, it will be crucial to ensure these analytical activities—and the people who do them—are valued in academia.

Natalie E. Dean, PhD @nataliexdean · Nov 25

With respect to the AstraZeneca vaccine, I am guessing people think my objection is to science by press release, and that I want a peer-reviewed publication. But no, not really. What I want is reliable and definitive evidence to inform policies impacting millions. 1/4

Natalie E. Dean, PhD @nataliexdean · Nov 25

If the answer is that AstraZeneca needs to go back and add a new half-dose arm to their trials so that they can prospectively evaluate its efficacy in diverse subgroups, then we have to carefully consider the value of a peer-reviewed publication at this moment. 2/4

Natalie E. Dean, PhD @nataliexdean · Nov 25

We've written about this in @NEJM. Basically, there are risks to publishing results that are "promising but inconclusive." Though it seems slower at the time, in the long run it is better to generate the conclusive evidence while we still can. 3/4

Creating a Framework for Conducting Randomized ...
Sounding Board from The New England Journal of Medicine — Creating a Framework for Conducting ...
nejm.org

Natalie E. Dean, PhD @nataliexdean · Nov 25

I am very encouraged by the prospect of multiple safe and effective vaccines, particularly cheaper and easier to store vaccines, but these results have major policy implications. And implications for the public's trust! We have to make sure we get it right. 4/4

ALS: James Holton, George Meigs
SSRL: Aina Cohen, Silvia Russi,
Clyde Smith, Lisa Dunn,
Jeney Wierman

Dr. Iris
Young

Robbie
Diaz

Dr. Galen
Correy


Prof. Michael
Thompson
(UC Merced)


Prof. Frank
von Delft
(SGC, Diamond)


Prof. Ivan
Ahel (Oxford)


Dr. Marion
Schuller (OXford)

Alan Ashworth, Jason Gestwicki, Taia Wu
Brian Shoichet, **Stefan Gahbauer**

Funding:

Q B I

NSF RAPID

NIGMS

Sangvhi-Agarwal
Innovation Award,
Byers Award,
Bowes Biomedical
Investigator Program

RELAY

Conflict of Interest:
Equity, Consulting,
Funding

QCRG Structural Biology Consortium
Klim Verba, Oren Rosenberg
Natalia Jura
Team Leads, including:
Ursula Schulze-Gahmen, Tristan Owens

Dr. Iris Young

Robbie Diaz

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Funding:

QBI

NSF RAPID

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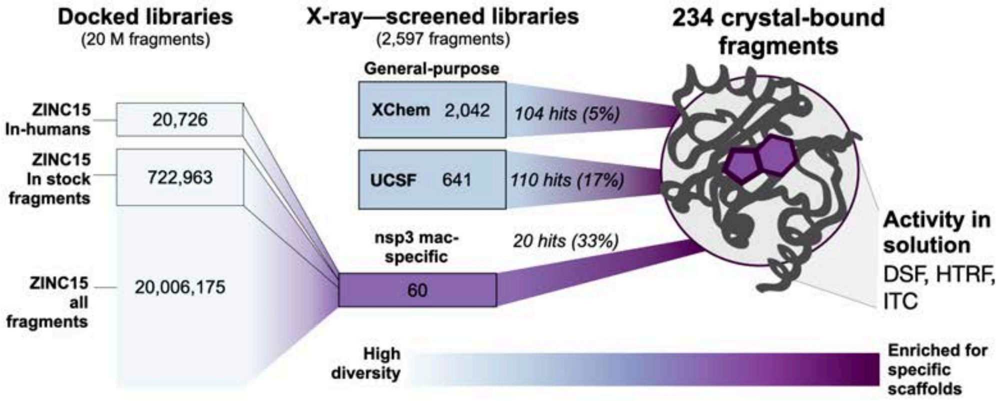
RELAY THERAPEUTICS

Conflict of Interest:
Equity, Consulting,
Funding

The **macrodomain** can be targeted by small molecules - but strong inhibition is a ways off…

- High hit rate, but variability across crystal forms
- Docking works! Solution binding experiments highly correlated with soaking success in crystallography
- Recurrent binding motifs (hinge, oxyanion) - can be linked, retaining high chemical diversity, by Fragmenstein



Docked libraries
(20 M fragments)

ZINC15 In-humans 20,726

ZINC15 In stock fragments 722,963

ZINC15 all fragments 20,006,175

X-ray—screened libraries
(2,597 fragments)

General-purpose

XChem 2,042 *104 hits (5%)*

UCSF 641 *110 hits (17%)*

nsp3 mac-specific 60 *20 hits (33%)*

234 crystal-bound fragments

Activity in solution
DSF, HTRF, ITC

High diversity

Enriched for specific scaffolds