slides and materials will be posted to: https://www.choderalab.org/news

A MOONSHOT ON THEORY AND PRACTICE

John D. Chodera
MSKCC Computational and Systems Biology Program
http://choderalab.org

DISCLOSURES:
Scientific Advisory Board, OpenEye Scientific, Ventus Therapeutics, Redesign Science*, Interline Therapeutics*
All funding sources: http://choderalab.org/funding
* Denotes equity interests

CUP XX : MAR 10-12, 2020

THE LAST SCIENTIFIC MEETING OF 2020

C.D.C. Officials Warn of Coronavirus Outbreaks in the U.S.

Clusters of infection are likely in American communities, health officials said. Some lawmakers questioned whether the nation is prepared.

"This is an unprecedented, potentially severe health challenge globally," Alex M. Azar II, the health and human services secretary, told a Senate subcommittee on Tuesday.
T.J. Kirkpatrick for The New York Times


By Pam Belluck and Noah Weiland

Published Feb. 25, 2020 Updated March 9, 2020


This is not just a cute poster
KEEP
CALM
AND
CARRY
ON

The U.S. Now Leads the World in Confirmed Coronavirus Cases

Following a series of missteps, the nation is now the epicenter of the pandemic.

A line for coronavirus testing outside of Elmhurst Hospital Center in Queens on Wednesday. Dave Sanders for The New York Times

By Donald G. McNeil Jr.

Published March 26, 2020 Updated May 28, 2020

https://www.nytimes.com/2020/03/26/health/usa-coronavirus-cases.html

DON'T WORRY: REPURPOSING WILL SAVE US!

Science

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HOME > SCIENCE > VOL. 368, NO. 6493 > RAPID REPURPOSING OF DRUGS FOR COVID-19

PERSPECTIVE | VIEWPOINT: COVID-19

Rapid repurposing of drugs for COVID-19

R. KIPLIN GUY, ROBERT S. DIPAOLA, FRANK ROMANELLI, AND , REBECCA E. DUTCH Authors Info & Affiliations

SCIENCE • 8 May 2020 • Vol 368, Issue 6493 • pp. 829-830 • DOI: 10.1126/science.abb9332

1,093 123

HOME » BLOG

BROADMINDED BLOG

BLOG / 05.12.20

Combing through old drugs to find new ones for COVID-19

By Namrata Sengupta

The Broad Institute's Drug Repurposing Hub has opened its repository of nearly 7,000 drug compounds to help scientists discover COVID-19 treatments.

Credit : Erik Jacob
Florence Wagner, who spoke about drug repurposing at a public talk at the Broad in November 2019, is collaborating with scientists involved in COVID-19 therapeutics research.

COVID-19 Public health information from CDC | Research information from NIH | Español | NIH staff guidance on coronavirus (NIH Only)

Home » News & Events » News Releases

NEWS RELEASES

Monday, April 19, 2021

Large clinical trial to study repurposed drugs to treat COVID-19 symptoms

Using an ACTIV master protocol, the trial will focus on potential interventions for mild-to-moderate illness.

The National Institutes of Health will fund a large, randomized, placebo-controlled Phase 3 clinical trial to test several existing prescription and over-the-counter medications for people to self-administer to treat symptoms of COVID-19. Part of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) public–private partnership, the ACTIV-6 trial aims to provide evidence-based treatment options for the majority of adult patients with COVID-19 who have mild-to-moderate symptoms and are not sick enough to

Institute/Center

National Center for Advancing Translational Sciences (NCATS)

Contact

NCATS Communications Branch
301-435-0888

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SMALL MOLECULE DRUG REPURPOSING IS AN APPEALING IDEA. TOO BAD IT HAS NEVER WORKED.

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

ACS AUTHORCHOICE

pubs.acs.org/jcim

Viewpoint

What Are the Odds of Finding a COVID-19 Drug from a Lab Repurposing Screen?

Aled Edwards*

Cite This: *J. Chem. Inf. Model.* 2020, 60, 5727–5729

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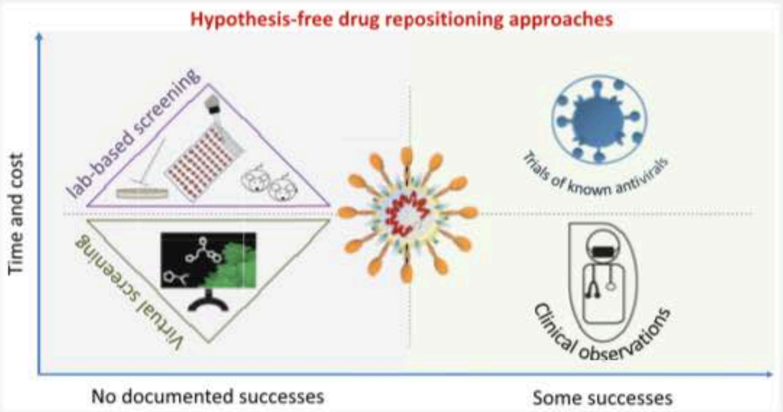
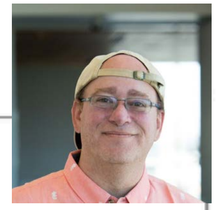
ABSTRACT: Massive drug repurposing (or repositioning) campaigns are trying to find potential antiviral treatments for COVID-19. Many involve experimental or virtual screening of libraries of compounds previously proven safe in humans—"old drugs". In 20 years of these efforts in many other diseases, never has a new therapeutic hypothesis derived from screening of old drugs in a lab led to the drug being approved for the new indication.



Aled Edwards
SGC Toronto

https://pubs.acs.org/doi/abs/10.1021/acs.jcim.0c00861



CORONAVIRUS

Drug-induced phospholipidosis confounds drug repurposing for SARS-CoV-2

Tia A. Tummino[1,2,3,4]†, Veronica V. Rezelj[5]†, Benoit Fischer[6]†, Audrey Fischer[6]†, Matthew J. O'Meara[7], Blandine Monel[8], Thomas Vallet[5], Kris M. White[9,10], Ziyang Zhang[3,4,11,12], Assaf Alon[13], Heiko Schadt[6], Henry R. O'Donnell[1], Jiankun Lyu[1,3,4], Romel Rosales[9,10], Briana L. McGovern[9,10], Raveen Rathnasinghe[9,10,14], Sonia Jangra[9,10], Michael Schotsaert[9,10], Jean-René Galarneau[15], Nevan J. Krogan[3,4,11,16], Laszlo Urban[15], Kevan M. Shokat[3,4,11,12], Andrew C. Kruse[13], Adolfo García-Sastre[9,10,17,18], Olivier Schwartz[8], Francesca Moretti[6]*, Marco Vignuzzi[5]*, Francois Pognan[6]*, Brian K. Shoichet[1,3,4]*

Repurposing drugs as treatments for COVID-19, the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has drawn much attention. Beginning with sigma receptor ligands and expanding to other drugs from screening in the field, we became concerned that phospholipidosis was a shared mechanism underlying the antiviral activity of many repurposed drugs. For all of the 23 cationic amphiphilic drugs we tested, including hydroxychloroquine, azithromycin, amiodarone, and four others already in clinical trials, phospholipidosis was monotonically correlated with antiviral efficacy. Conversely, drugs active against the same targets that did not induce phospholipidosis were not antiviral. Phospholipidosis depends on the physicochemical properties of drugs and does not reflect specific target-based activities—rather, it may be considered a toxic confound in early drug discovery. Early detection of phospholipidosis could eliminate these artifacts, enabling a focus on molecules with therapeutic potential.

Screening for drugs that don't work

In the battle against COVID-19, drugs discovered in repurposing screens are of particular interest because these could be rapidly implemented as treatments. However, Tummino *et al*. deliver a cautionary tale, finding that many leads from such screens have an antiviral effect in cells through phospholipidosis, a phospholipid storage disorder that can be induced by cationic amphiphilic drugs (see the Perspective by Edwards and Hartung). There is a strong correlation between drug-induced phospholipidosis and inhibition of severe acute respiratory syndrome coronavirus 2 replication in cells. Unfortunately, drugs that have an antiviral effect in cells through phospholipidosis are unlikely to be effective in vivo. Screening out such drugs may allow a focus on drugs with better clinical potential. —VV

do not induce phospholipidosis (e.g., melperone and DTG), are not antiviral. Unfortunately, CAD induction of phospholipidosis—at least at the potencies observed in this work—does not translate in vivo (Fig. 5). More encouragingly, this study illuminates a method to rapidly identify confounds in cellular antiviral screens, allowing us to eliminate them from further study and to focus on molecules with true potential.

Although the molecular mechanisms for the antiviral effects of phospholipidosis remain unclear, certain associations may be tentatively advanced. SARS-CoV-2, like many viruses, subverts the cell to produce double membrane vesicles in which it replicates (*41*–*43*). Disruption of lipid homeostasis by the induction of phospholipidosis may disrupt these vesicles, reducing viral replication. The disruption of lysosomal (*44*) and endosomal (*45*) compartments and CAD-induced shifts in compartmental pH (*46*) may further affect viral entry and propagation (*47*). Accordingly, targeting the endosomal-lysosomal pathway has been suggested as a viable strategy against SARS-CoV-2 infection (*48*), but developing potent and targeted inhibitors remains challenging.

The cost to the community of investments in what appears to be a confound merits consideration for future pandemics. According to the DrugBank COVID-19 dashboard (*49*), which draws from US and international clinical trials, putatively antiviral CADs have been promoted into an astonishing 316 phase 1 to phase 3 clinical trials against COVID-19. Although 57% of these trials study the phospholipidosis-inducing CADs hydroxychloroquine (Fig. 3A, top row) or chloroquine, that still leaves 136 trials across 33 other predicted or known phospholipidosis inducers. Using conservative estimates (*50*, *51*), the expense of the clinical trials component alone over the last year for phospholipidosis-inducing CADs may be over $6 billion US dollars (table S9).

Certain caveats merit mentioning. First, the correlation between antiviral activity and phospholipidosis, as strong as it is, does not illuminate the mechanism by which phospholipidosis is antiviral. Phospholipidosis is itself only partly understood, and there are no good genetic or chemical ways to either inhibit its induction by drugs nor to promote it by target-selective reagents. Second, predicting whether a molecule will induce phospholipidosis remains

$6B and countless lives wasted through just <u>one</u> of these intellectually bankrupt hypotheses

https://www.science.org/doi/full/10.1126/science.abi4708

WELL, CRAP.

WHAT DO WE DO NOW?

SARS-CoV-2 genome published 24 Jan 2020

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

SUMMARY

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)

From the NHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, Chinese Center for Disease Control and Prevention (N.Z., W.W., J.S., X.Z., B.H., R.L., P.N., X.M., D.W., W.X., G.W., G.F.G., W.T.), and the Department of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University (X.L.) — both in Beijing; Wuhan Jinyintan Hospital (D.Z.), the Division for Viral Disease Detection, Hubei Provincial Center for Disease Control and Prevention (B.Y., F.Z.), and the Center for Biosafety Mega-Science, Chinese Academy of Sciences (W.T.) — all in Wuhan; and the Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China (W.S.). Address reprint requests to Dr. Tan at the NHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, China CDC, 155 Changbai Road, Changping District, Beijing 102206, China; or at tanwj@ivdc.chinacdc.cn, Dr. Gao at the National Institute for Viral Disease Control and Prevention, China CDC, Beijing 102206, China, or at gaof@im.ac.cn, or Dr. Wu at the NHC Key Laboratory of Biosafety, National Institute for Viral Disease Control and Prevention, China CDC, Beijing 102206, China, or at wugz@ivdc.chinacdc.cn.

Drs. Zhu, Zhang, W. Wang, Li, and Yang contributed equally to this article.

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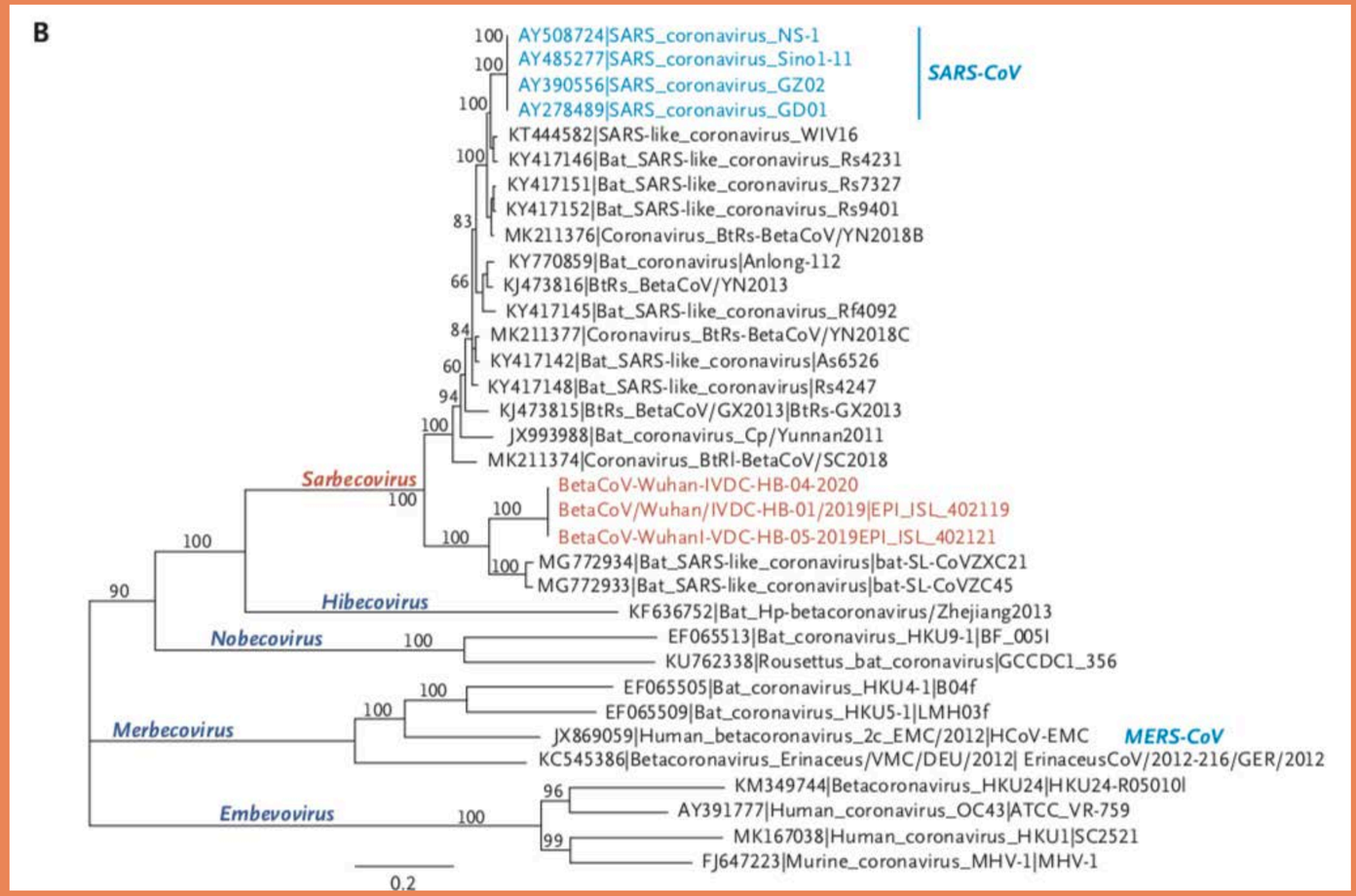
N Engl J Med 2020;382:727-33.
DOI: 10.1056/NEJMoa2001017

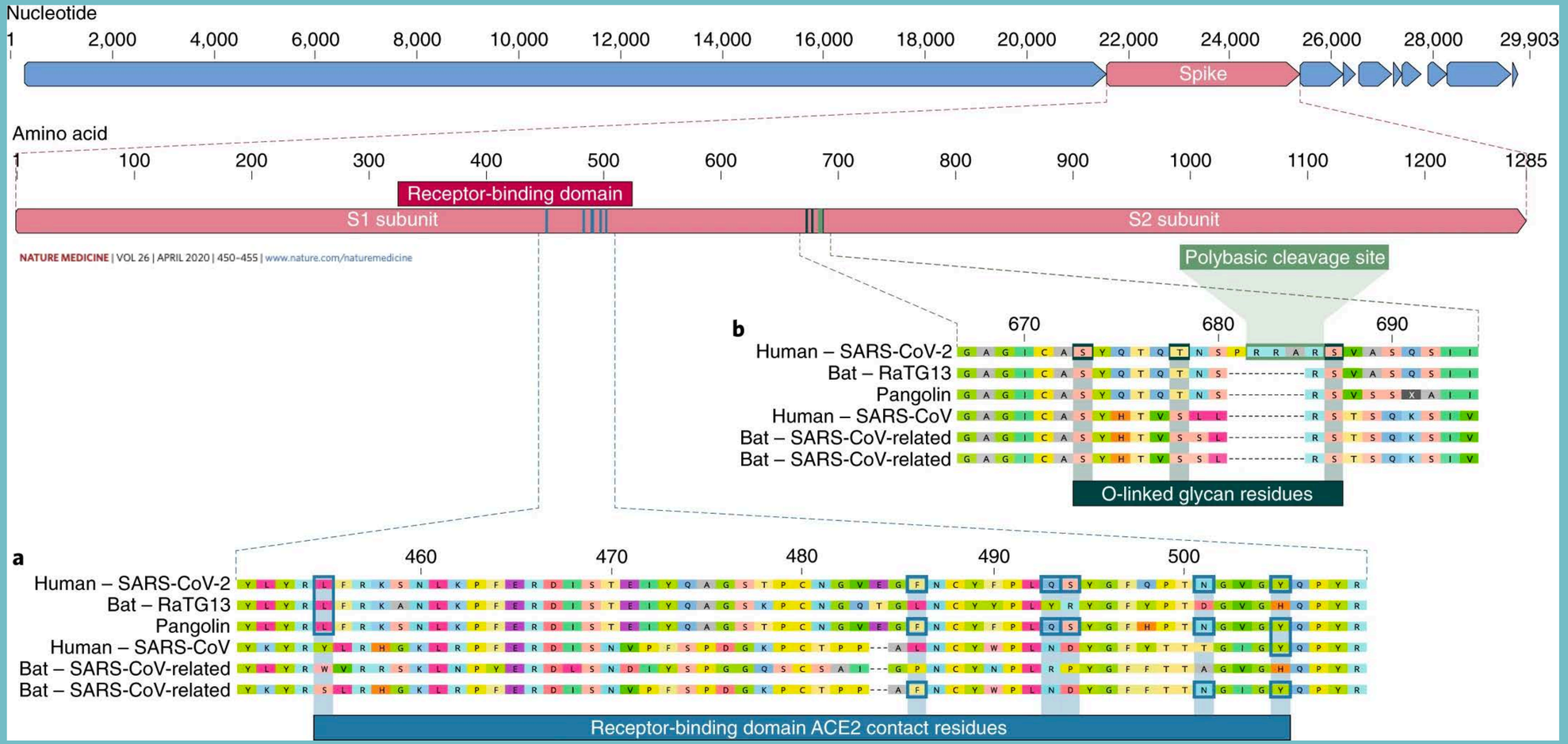
EMERGING AND REEMERGING PATHOGENS ARE GLOBAL CHALLENGES FOR public health.[1] Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases.[2,3] Six coronavirus species are known to cause human disease.[4] Four viruses — 229E, OC43, NL63, and HKU1 — are prevalent and typically cause common cold symptoms in immunocompetent individuals.[4] The two other strains — severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) — are zoonotic in origin and have been linked to sometimes fatal illness.[5] SARS-CoV was the causal agent of the severe acute respiratory syndrome outbreaks in 2002 and 2003 in Guangdong Province, China.[6-8] MERS-CoV was the pathogen responsible for severe respiratory disease outbreaks in 2012 in the Middle East.[9] Given the high prevalence and wide distribution of coronaviruses, the large genetic diversity and frequent recombination of their genomes, and increasing human–animal interface activities, novel coronaviruses are likely to emerge periodically in humans owing to frequent cross-species infections and occasional spillover events.[5,10]

In late December 2019, several local health facilities reported clusters of patients with pneumonia of unknown cause that were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China.[11] On December 31, 2019, the Chinese Center for Disease Control and Prevention (China CDC) dispatched a rapid response team to accompany Hubei provincial and Wuhan city health authorities and to conduct an epidemiologic and etiologic investigation. We report the results of this investigation, identifying the source of the pneumonia



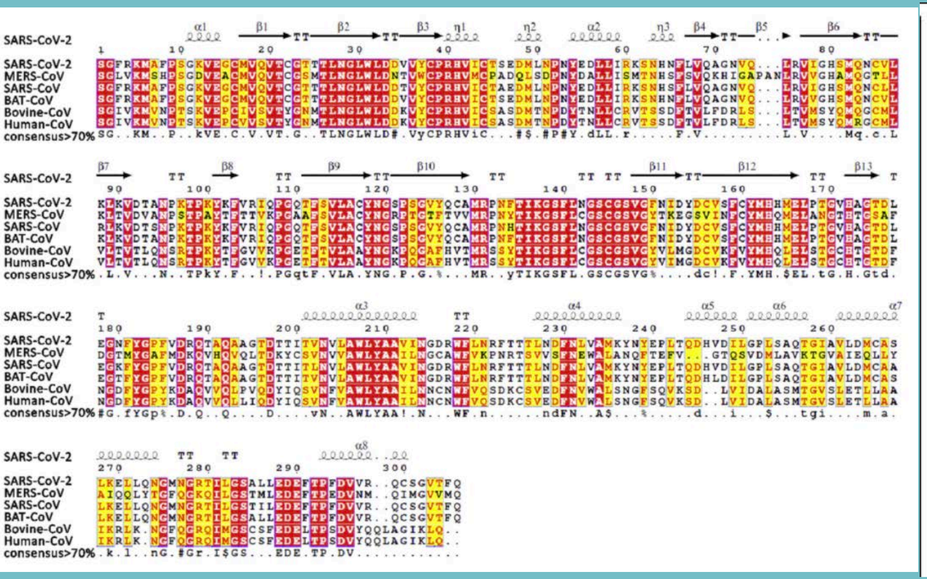
Striking similarity to SARS-CoV and MERS-CoV

SARS-CoV-2 showed significant sequence conservation with SARS-CoV-1



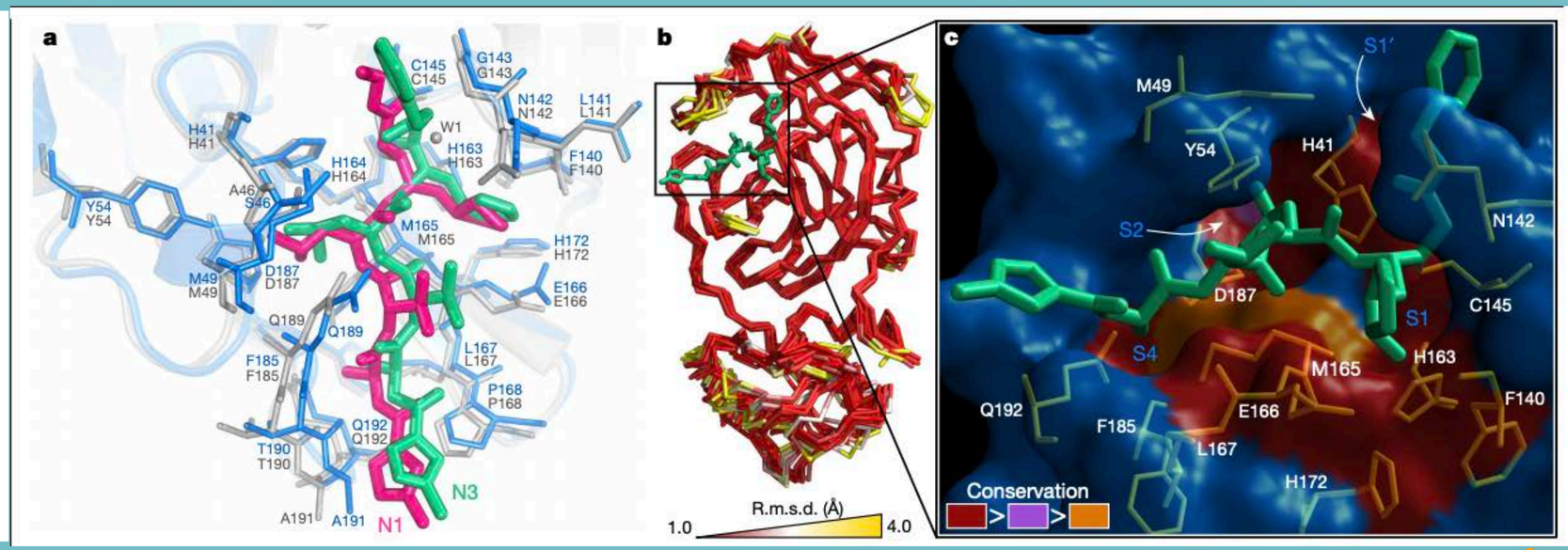
The main viral protease (Mpro) is highly conserved among SARS-CoV, MERS-CoV, and SARS-CoV-2

sequence (24 Jan 2020)



Tahir ul Qamal et al. J Pharm Anal, in press
doi:10.1016/j.jpha.2020.03.009

structure (PDB structure released 5 Feb 2020)

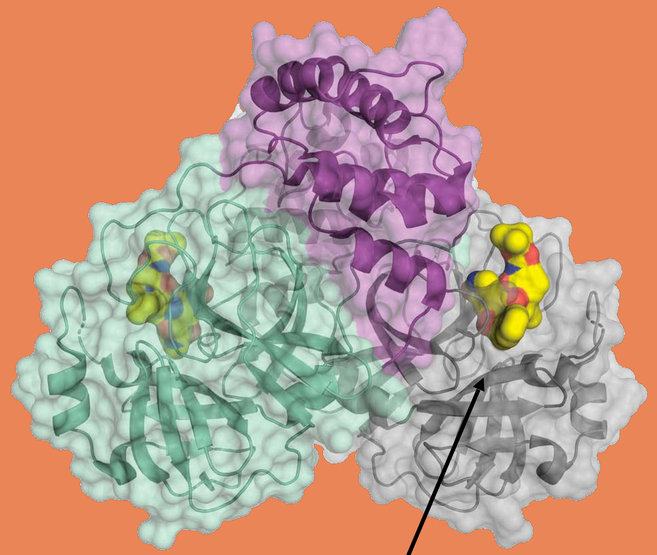


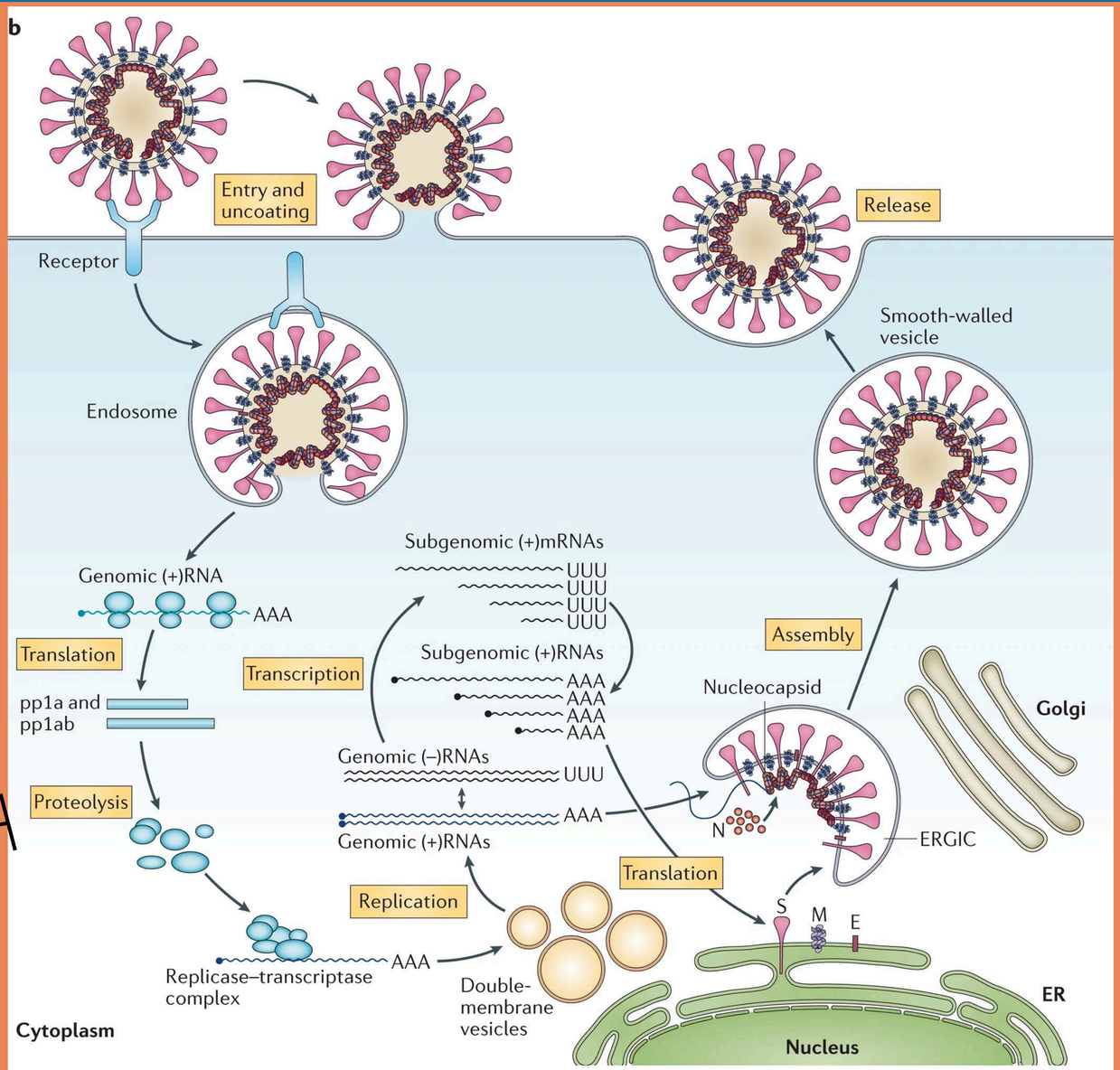
Jin et al. Nature 582:289, 2020
doi:10.1038/s41586-020-2223-y

Could this be a viable drug target for COVID-19?

Mpro is essential for viral replication

3CL^{Pro}
or: M^{pro}





de Wit et al. Nat. Rev. Microbiology (2016)

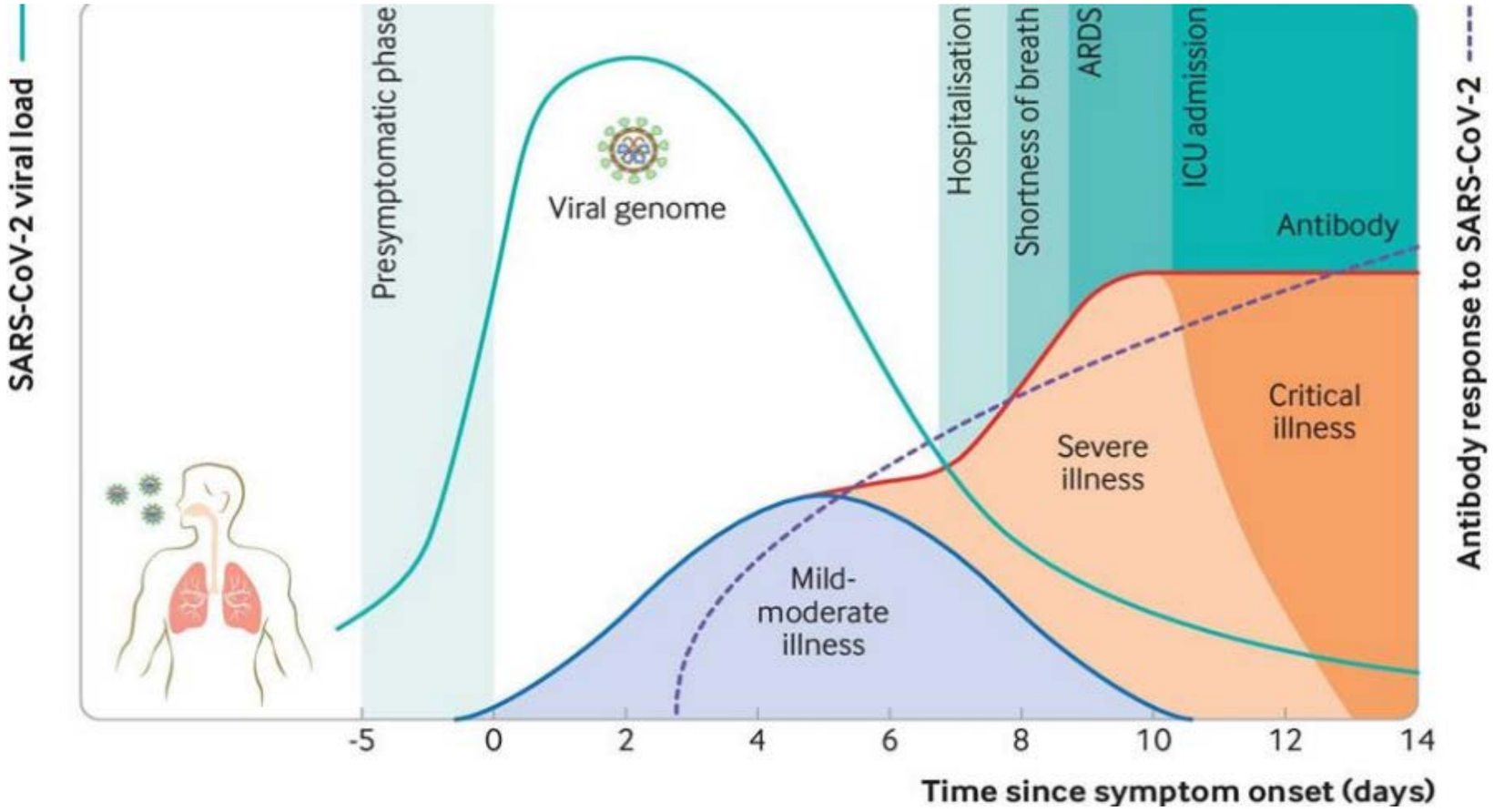
DIRECT-ACTING ANTIVIRALS HAVE A NARROW WINDOW OF OPPORTUNITY FOR EFFECTIVE TREATMENT

Vaccines effective only if administered weeks prior to exposure

Window of opportunity for oral antivirals (prophylaxis or early treatment)
May need coupling to frequent testing
Antivirals could reduce transmission

Virus no longer drives disease; primarily inflammation-mediated injury
Antivirals less effective
Hospitalized: access to IV drugs

IV antibodies potentially useful if delivered sufficiently early



Muge Cevik et al. BMJ 2020;371:bmj.m3862
https://doi.org/10.1136/bmj.m3862

There has never been a human coronavirus Mpro inhibitor approved as a drug…

Antiviral Research 97 (2013) 161–168

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Potent inhibition of feline coronaviruses with peptidyl compounds targeting coronavirus 3C-like protease

Yunjeong Kim [a,*], Sivakoteswara Rao Mandadapu [b], William C. Groutas [b], Kyeong-Ok Chang [a]

[a] Department of Diagnostic Medicine and Pathobiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506, USA
[b] Department of Chemistry, Wichita State University, Wichita, KS 67260, USA

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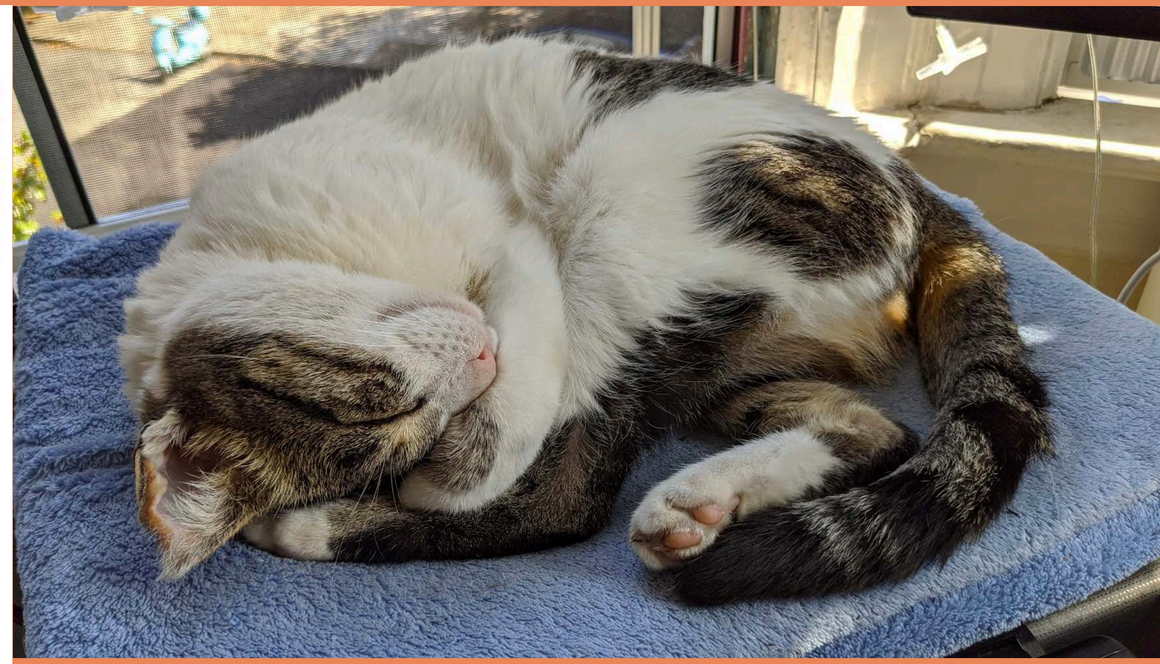
Protease inhibitor
Cathepsin B
Synergy
3CL protease

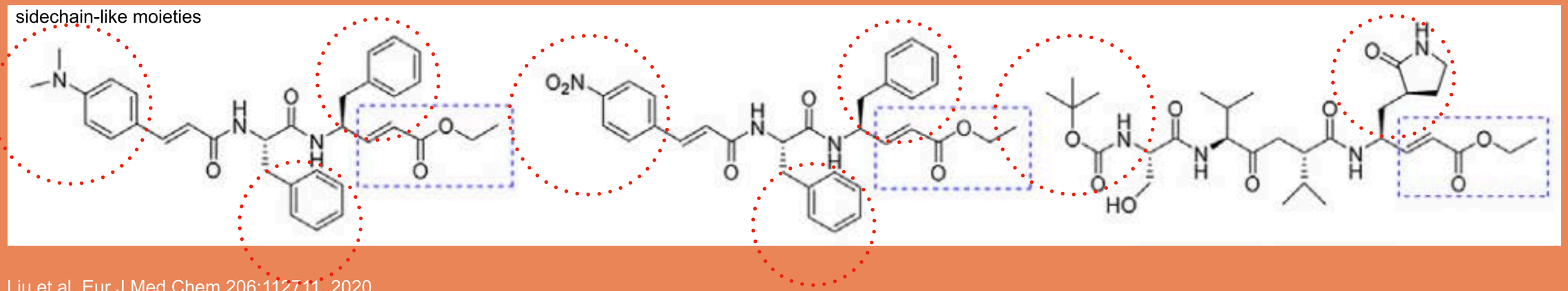
ABSTRACT

Feline coronavirus infection is common among domestic and exotic felid species and usually associated with mild or asymptomatic enteritis; however, feline infectious peritonitis (FIP) is a fatal disease of cats that is caused by systemic infection with a feline infectious peritonitis virus (FIPV), a variant of feline enteric coronavirus (FECV). Currently, there is no specific treatment approved for FIP despite the importance of FIP as the leading infectious cause of death in young cats. During the replication process, coronavirus produces viral polyproteins that are processed into mature proteins by viral proteases, the main protease (3C-like [3CL] protease) and the papain-like protease. Since the cleavages of viral polyproteins are an essential step for virus replication, blockage of viral protease is an attractive target for therapeutic intervention. Previously, we reported the generation of broad-spectrum peptidyl inhibitors against viruses that possess a 3C or 3CL protease. In this study, we further evaluated the antiviral effects of the peptidyl inhibitors against feline coronaviruses, and investigated the interaction between our protease inhibitor and a cathepsin B inhibitor, an entry blocker, against a feline coronavirus in cell culture. Herein we report that our compounds behave as reversible, competitive inhibitors of 3CL protease, potently inhibited the replication of feline coronaviruses (EC_{50} in a nanomolar range) and, furthermore, combination of cathepsin B and 3CL protease inhibitors led to a strong synergistic interaction against feline coronaviruses in a cell culture system.



But coronavirus Mpro inhibitors HAVE demonstrated success in cats

Previously known Mpro inhibitors were peptidomimetics, which are difficult to develop into useful oral drugs*

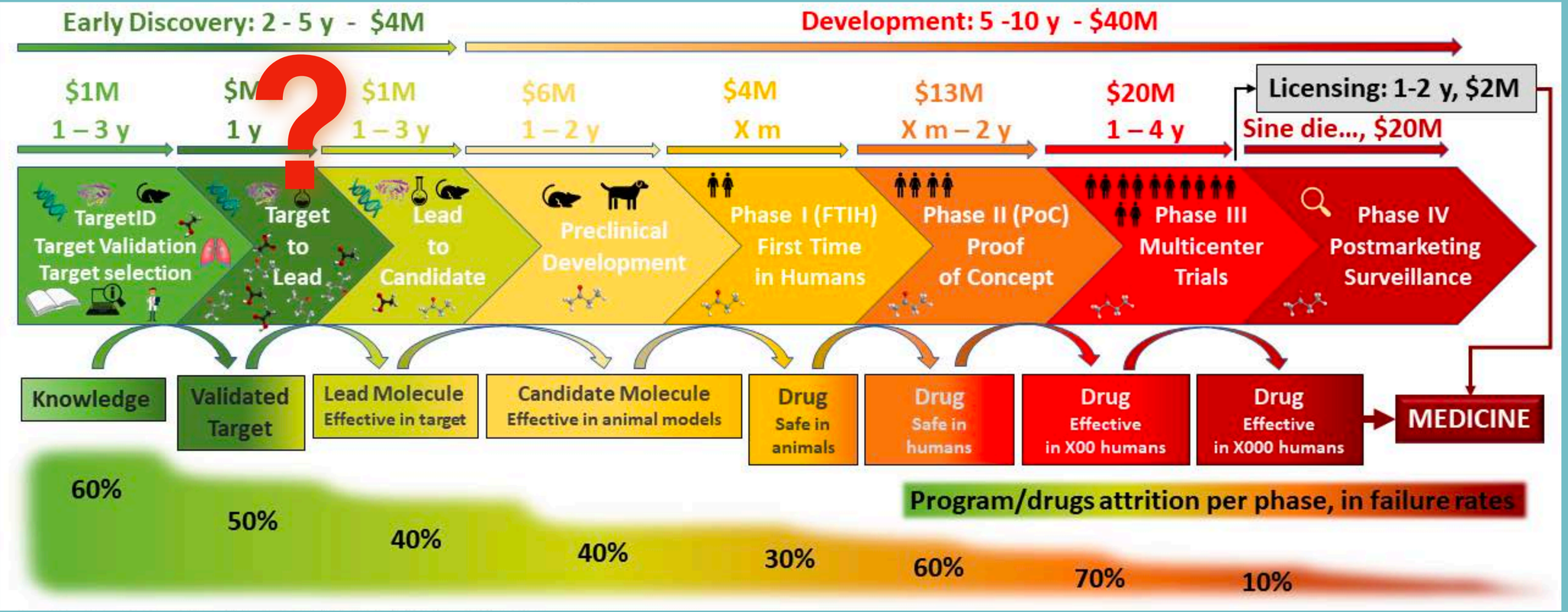


Liu et al. Eur J Med Chem 206:112711, 2020

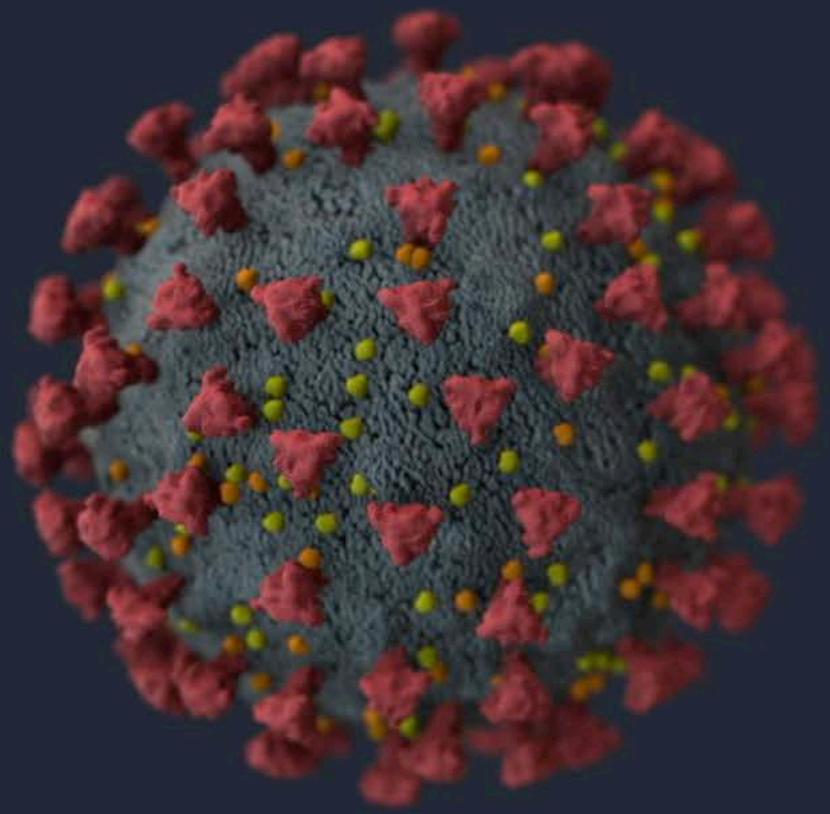
Known inhibitors were also covalent inhibitors, which can be difficult to optimize to prevent off-target issues*

* unless you're Pfizer med chem wizards, who seemingly bent the laws of space and time to give us Paxlovid!

Drug discovery is usually a long and expensive process



https://doctortarget.com/machine-learning-applied-drug-discovery/



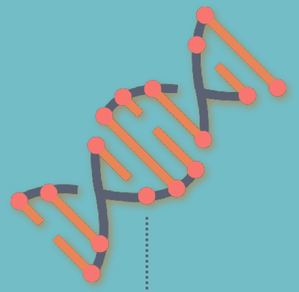
foolish and naïve!

OUR GOAL

14 Feb 2020 - Frank von Delft

Diamond Light Source prosecuted a high-throughput X-ray fragment screen in a matter of weeks

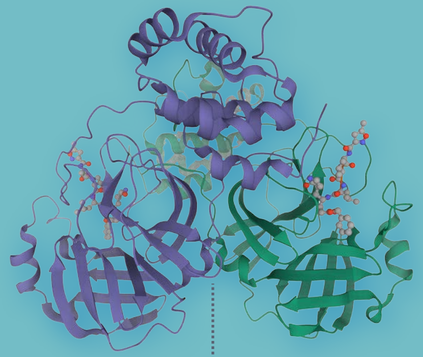
Frank von Delft
Diamond Light Source / XChem / SGC



February 14

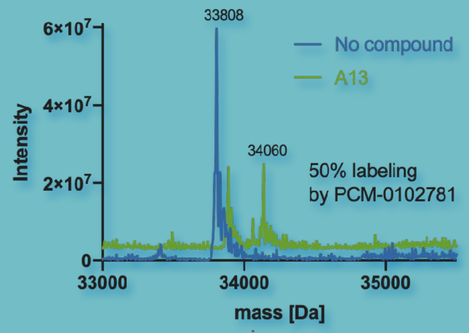
Main protease cloned and produced at Diamond after COVID shutdown of Haitao Yang lab in Shanghai

Martin Walsh



February 20

Atomic resolution structure of the protease determined

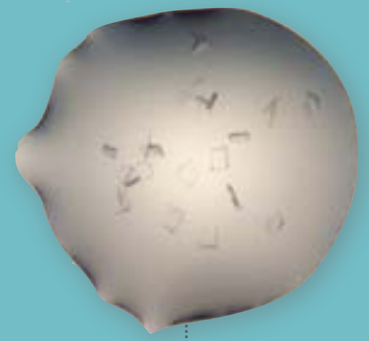


February 25

Covalent screen finds 150 active site hits

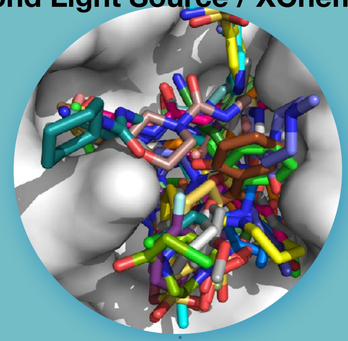
>40 hits validated

Nir London



March 5

1,500 crystals collected in one day (!)

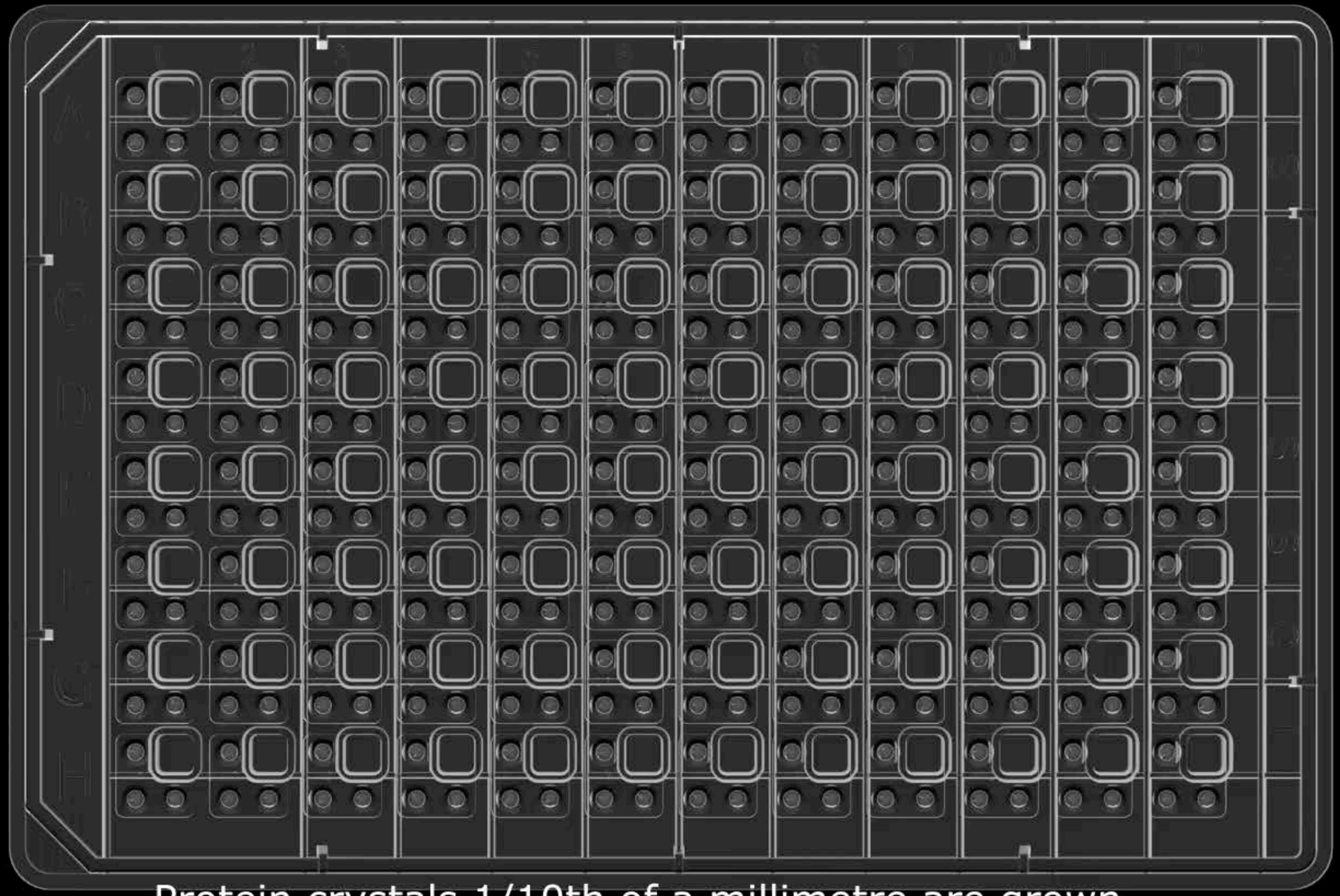


March 18

78 fragment-bound structures solved and released to the web

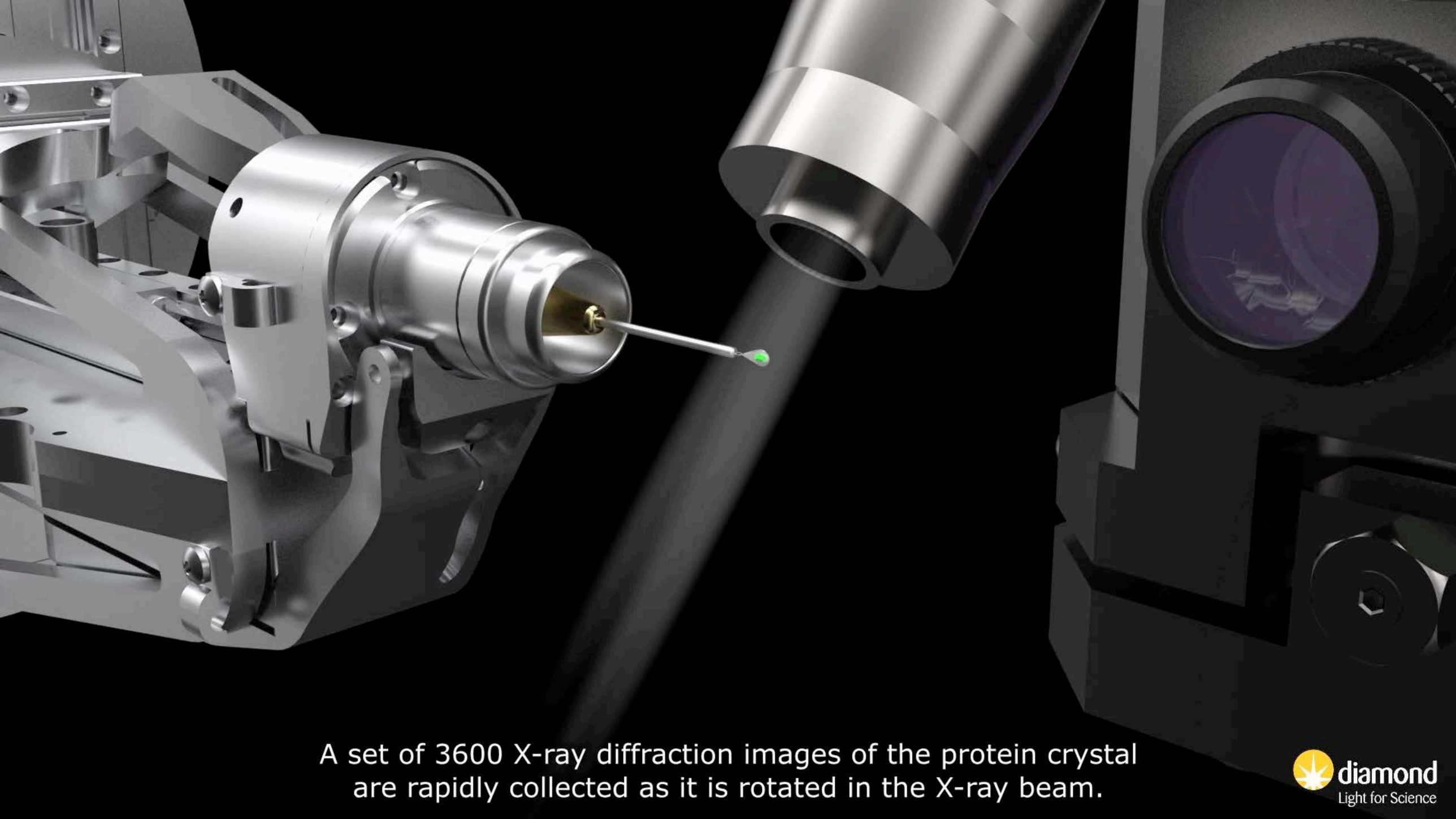
48 covalent fragments
71 active site fragments

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



Protein crystals 1/10th of a millimetre are grown
in microscopic drops no larger than 1 mm.

diamond
Light for Science



A set of 3600 X-ray diffraction images of the protein crystal are rapidly collected as it is rotated in the X-ray beam.

diamond
Light for Science

All data was immediately released online

diamond | Coronavirus Science

Home | For Scientists | For Journalists | For the Public | For Staff | Diamond Website

In This Section

- Main protease structure and XChem fragment screen
  - COVID MoonShot - Taking fragments to impact
  - Electron density evidence
  - Downloads
  - Highlights on progress
  - Credits
  - FAQ
- Nsp3 macrodomain ADP-ribosyl hydrolase and XChem fragment screen
- New scientific animations
- Rapid Access
- Research Areas
- Our collaborators

Main protease structure and XChem fragment screen

Summary

To contribute to the global effort to combat COVID-19, Diamond has been able to solve a new structure of the SARS-CoV-2 main protease (M^{Pro}) at high resolution (PDB ID: 6YB7), and complete a large XChem crystallographic fragment screen against it (detailed below). Data have been deposited with the PDB, but we are making the results available immediately to the world on this page; additional work is ongoing, and updates will be continually posted here in coming days and weeks.

This work builds on the sensationally fast crystal structure of M^{Pro} at 2.16 Å in complex with a covalent inhibitor, released in January this year by Prof Zihe Rao (6LU7, published here, described here). We thus ordered the synthetic gene and cloned the full length protein as previously described for the SARS main protease (Xue et al 2007). This yielded crystals of the unliganded enzyme that diffracted to high resolution (1.25 Å) on beamline I04-1, in a different space group to the inhibitor complex, and the structure was determined and refined rapidly. ***Critically, this showed it had the active site empty and solvent accessible - perfect for fragment screening.***

So it proved: the first 600-crystal experiment could be completed in 72 hours, through growing large numbers of crystals, optimising the soaking conditions, soaking and harvesting all 600 crystals and completing the data collection run on beamline I04-1. The hits from this initial run and other details were pre-released on March 6th.

By the 24th of March, the initial 1500-crystal experiment was complete, and the results made publicly available. Screening additional libraries throughout April brought the total number of active site fragments to 71, with 48 fragments binding covalently (full timeline here and download page here). This was an exceptionally large screen which yielded a remarkably rich readout, with vast opportunities for fragment growing and merging.

We have already triggered computationally-driven follow-up work internally, and externally joined forces to launch a fully-open crowdsourcing and crowdfunding initiative – the COVID Moonshot - to establish urgently the shortest route possible to clinical impact by maximally exploiting the readout - you can help, read more here.

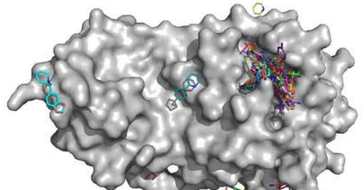
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

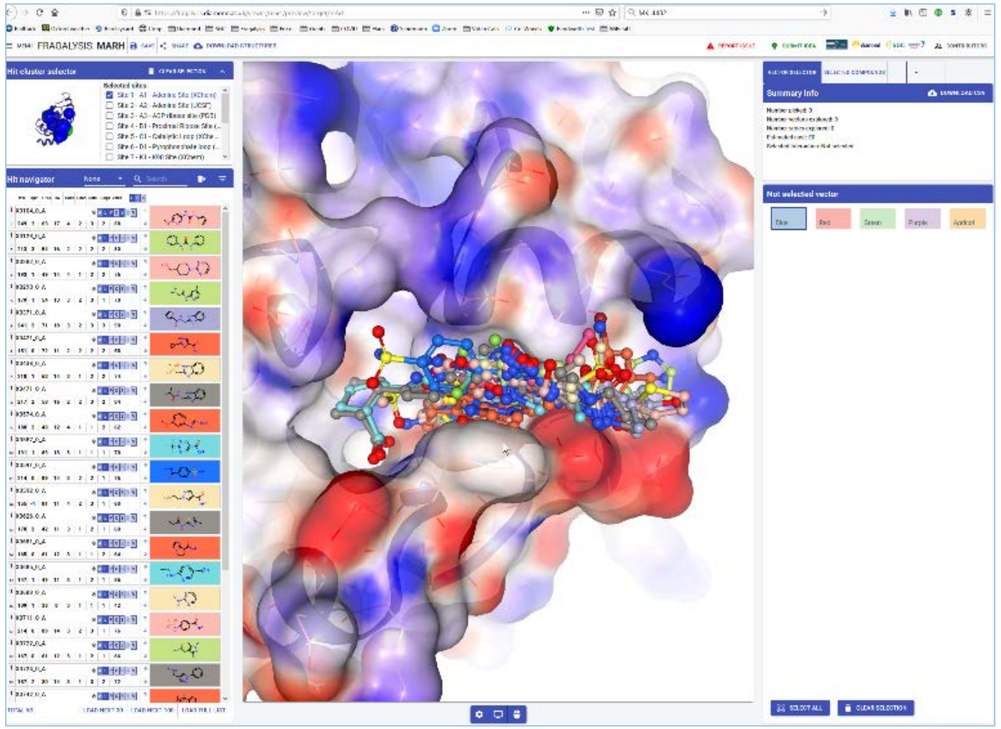
XChem fragment screen

The initial screen encompassed multiple fragment libraries: the DSI-poised library, MiniFrags (Astex) FragLites & Peplites (CRUK Newcastle Drug Discovery Unit (Newcastle University)), York3D (University of York), SpotFinder and heterocyclic electrophilic fragment library (Hungarian Academy of Sciences) and an electrophilic fragment library designed and pre-screened by mass spec at the Weizmann Institute (see below).

There were 74 hits of high interest - data and extensive details are here, and some interactive views here:

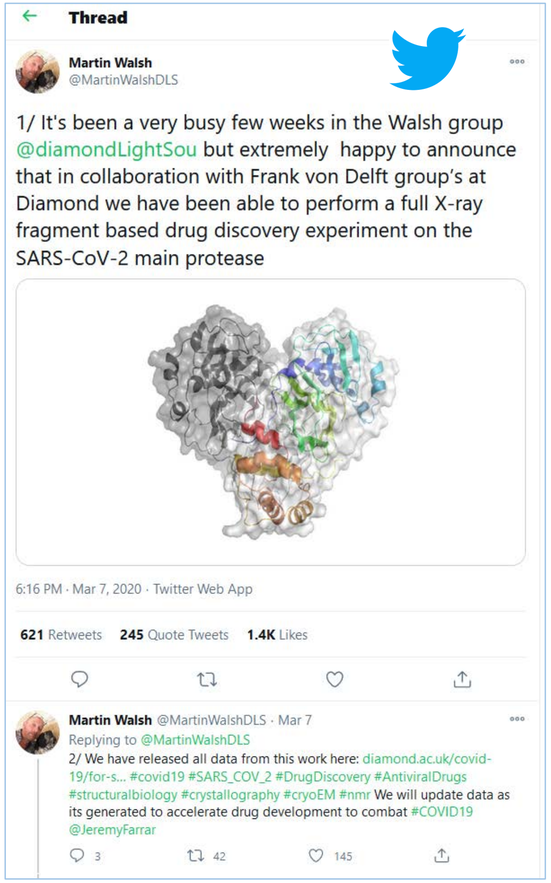
- 23 non-covalent hits in the active site
- 48 covalent hits in the active site
- 3 hits in the dimer interface, one in a calculated hotspot





https://fragalysis.diamond.ac.uk

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

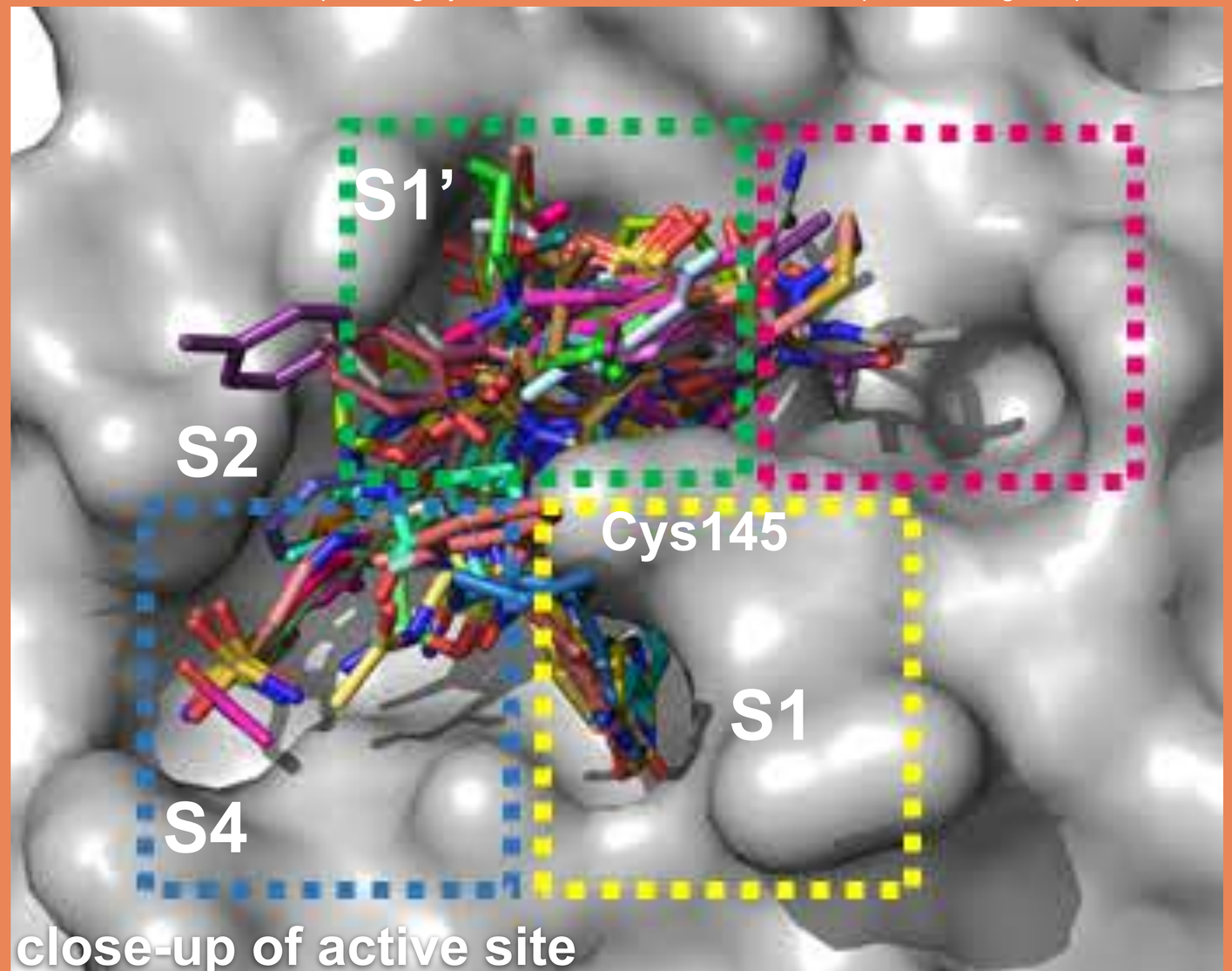


COVID Moonshot

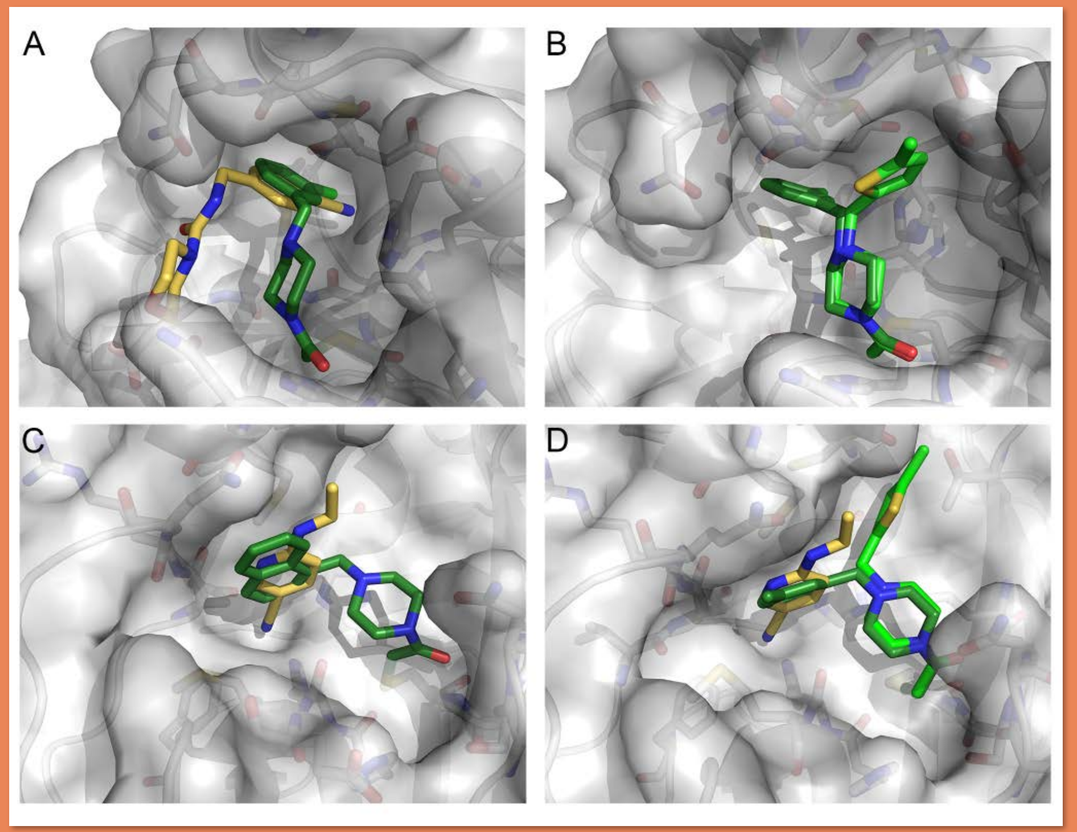
Centre for Medicines Discovery
University of Oxford
XCHEM Diamond Fragment Screening
diamond

Fragment hits completely cover the active site, and suggest fragment mergers could be potent inhibitors

interactive view: https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro



close-up of active site



Could we merge our way to potent lead compounds directly?

Douangamath et al., Nature Communications 11:5047, 2020
https://www.nature.com/articles/s41467-020-18709-w

Which strategies would most quickly get us from fragment structures all the way to a useful drug?

Nir London
Weizmann Institute

What if we tried ALL OF THEM?

First, we needed a cool name to motivate people

COVID Moonshot

An international effort to

DISCOVER A COVID ANTIVIRAL

The COVID Moonshot adopted a global open science, patent-free, collaborative approach to drug discovery

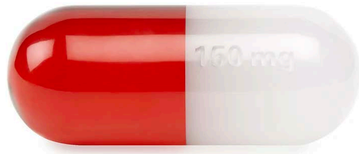
Open science

COVID Moonshot

Open data

http://postera.ai/covid

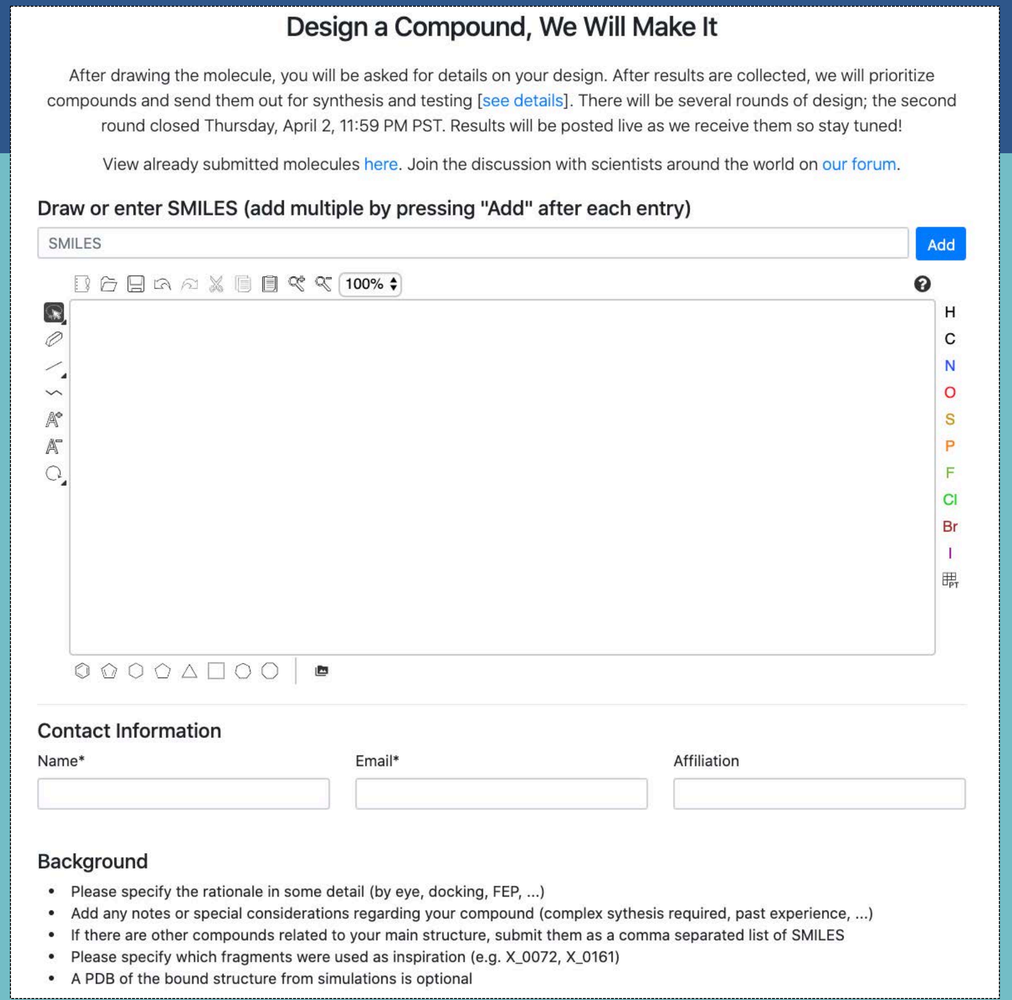
Patent-free



Alpha Lee (PostEra/Cambridge) tapped PostEra to create an open drug discovery commons website

Alpha Lee
Cambridge/PostEra

COVID Moonshot



Design a Compound, We Will Make It

After drawing the molecule, you will be asked for details on your design. After results are collected, we will prioritize compounds and send them out for synthesis and testing [see details]. There will be several rounds of design; the second round closed Thursday, April 2, 11:59 PM PST. Results will be posted live as we receive them so stay tuned!

View already submitted molecules here. Join the discussion with scientists around the world on our forum.

Draw or enter SMILES (add multiple by pressing "Add" after each entry)

SMILES | Add

100% | H C N O S P F Cl Br I

Contact Information

Name* | Email* | Affiliation

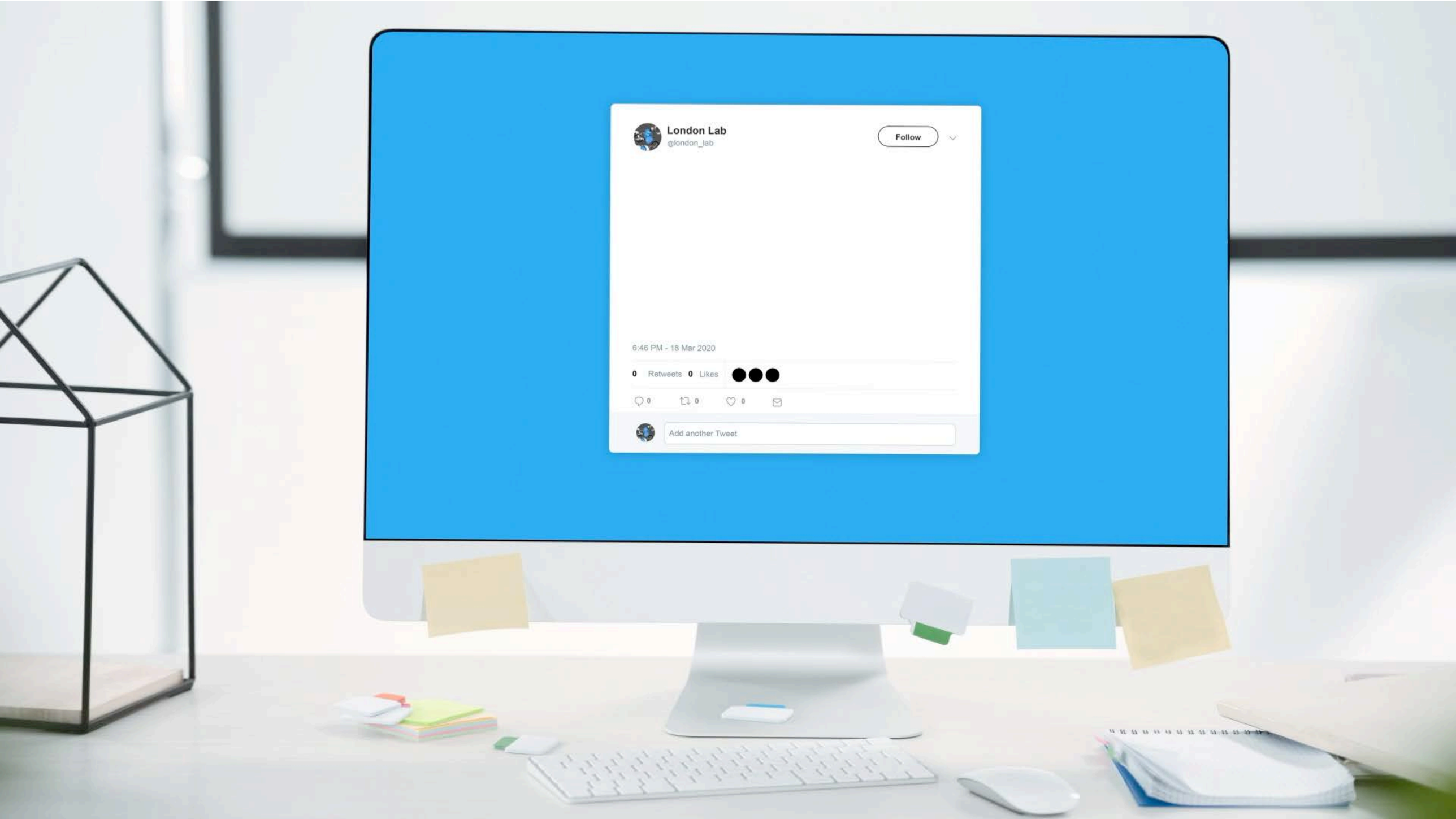
Background

- Please specify the rationale in some detail (by eye, docking, FEP, ...)
- Add any notes or special considerations regarding your compound (complex sythesis required, past experience, ...)
- If there are other compounds related to your main structure, submit them as a comma separated list of SMILES
- Please specify which fragments were used as inspiration (e.g. X_0072, X_0161)
- A PDB of the bound structure from simulations is optional

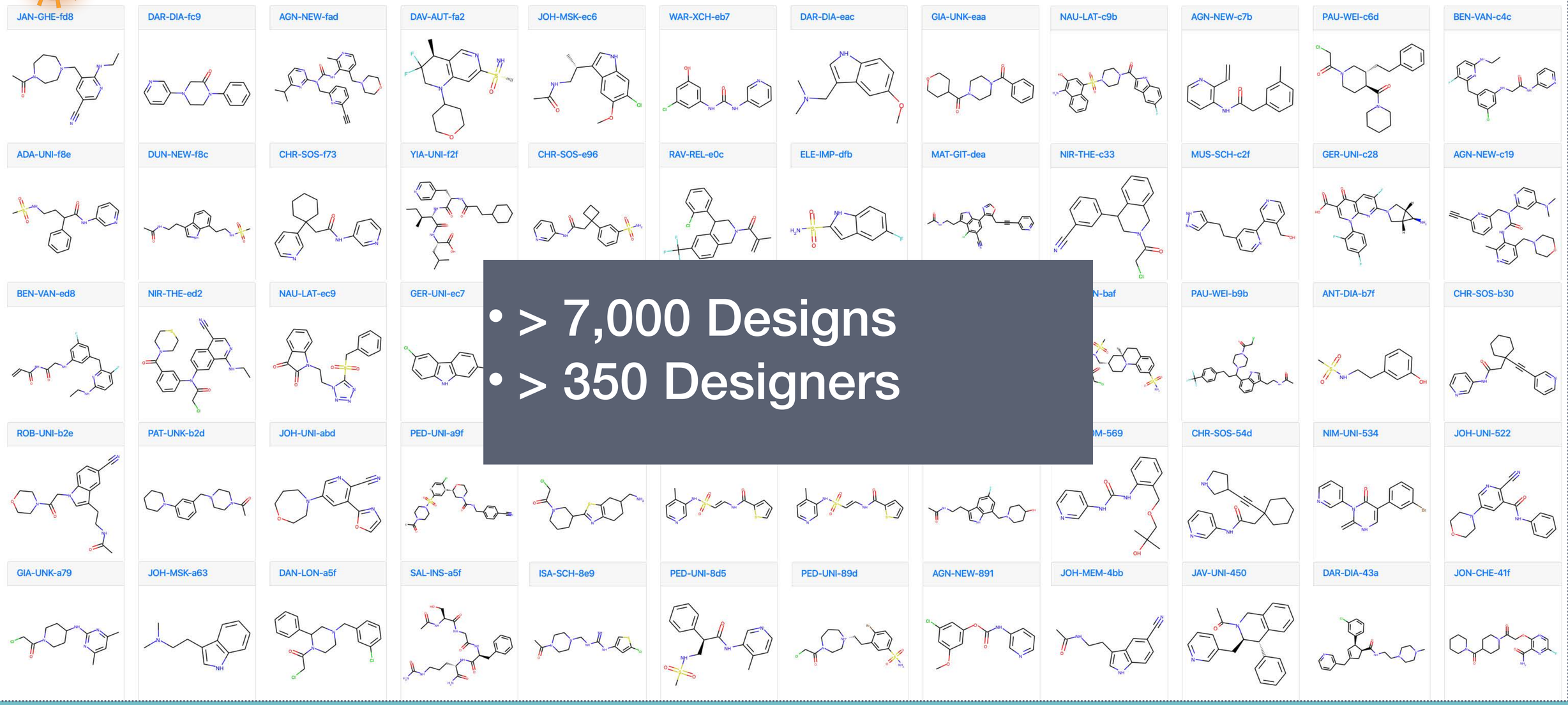
Molecule sketcher!
2D compound design viewer!
Discussion boards!

http://postera.ai/covid

+ Matthew Robinson (PostEra)


London Lab
@london_lab
Follow
6:46 PM - 18 Mar 2020
0 Retweets 0 Likes
Add another Tweet

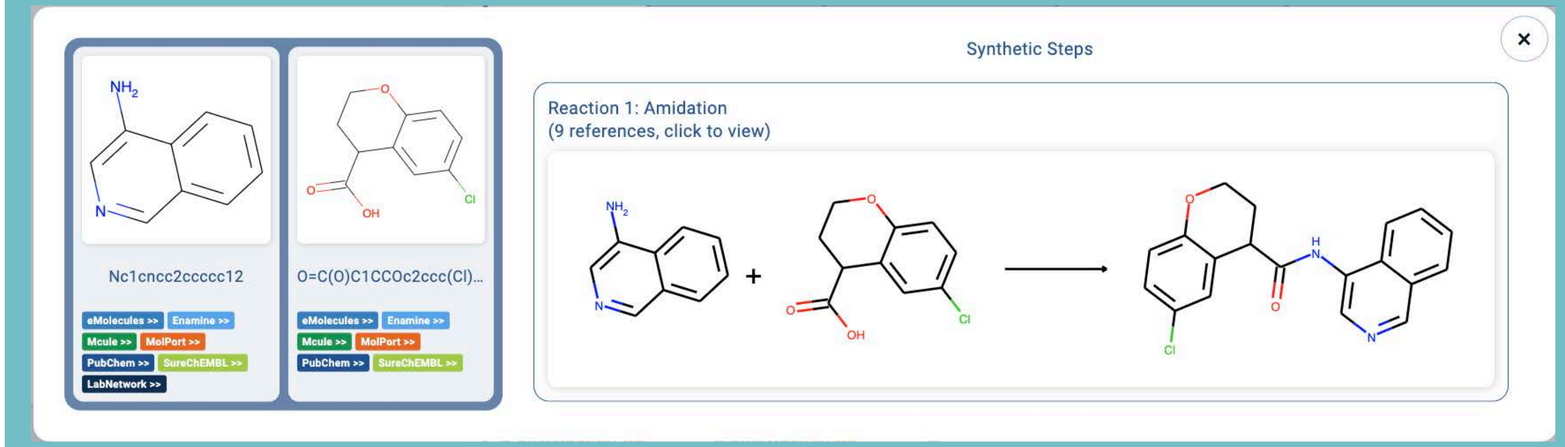
…and there was overwhelming response



- > 7,000 Designs
- > 350 Designers

PostEra's synthetic route prediction models identified which designs could be synthesized by CROs in a matter of hours

CRO catalogue-aware optimal synthetic route



CROs donating effort

- **Enamine**
- WuXi
- Sai

http://postera.ai/manifold

MANIFOLD

Synthesis and Search
across every available molecule

* free for academics!

Quickly made 850 compounds in a matter of weeks!

http://postera.ai/covid

Schwaller et al. ACS Central Science 5:9, 2019
https://pubs.acs.org/doi/10.1021/acscentsci.9b00576

THERE WERE SOME ... INTERESTING ... IDEAS TOO

MAK-UNK-e05327b2-1

MAK-UNK-e05327b2-2

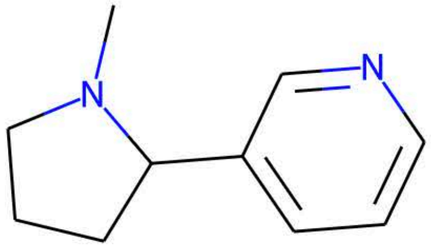
MAK-UNK-e05327b2-3

MAK-UNK-e05327b2-5

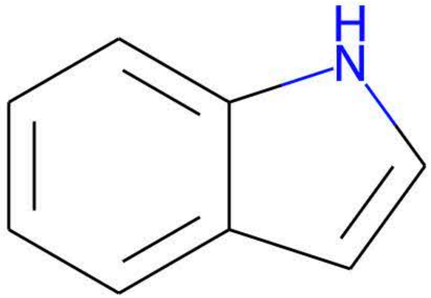
Design Rationale:

using https://molmatinf.com/covid19/ as a score reference

THERE WERE SOME … INTERESTING … IDEAS TOO



KTA-UNK-dac325de-1



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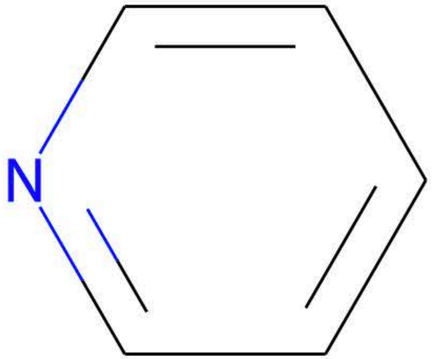
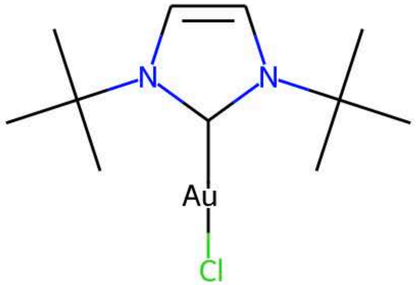


KTA-UNK-dac325de-3

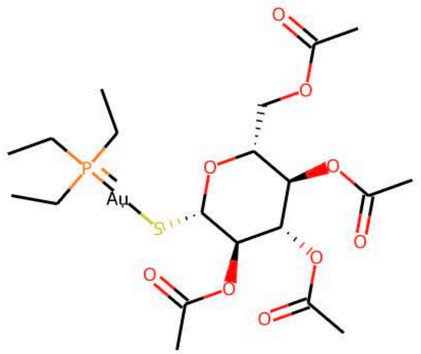
Design Rationale:

these compounds has similar Hansen Solubility Parameter values with other protease inhibitors

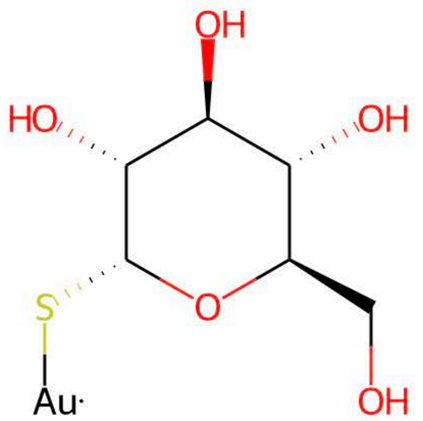
THERE WERE SOME ... INTERESTING ... IDEAS TOO



JOH-UNI-44664832-1



JOH-UNI-44664832-2

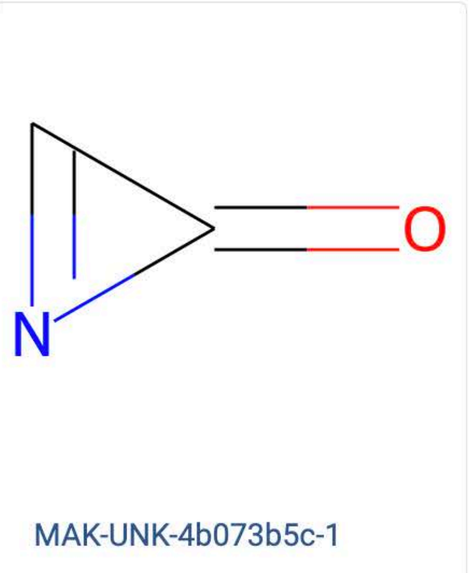


JOH-UNI-44664832-3

Design Rationale:

gold is thiophilic. These can be sourced from eMolecules and tested vs MPro especially as auronofin acts on covid-19 cells "Georgia State Researchers Find Rheumatoid Arthritis Drug Is Effective Against Coronavirus". News Hub. 15 April 2020. Retrieved 15 April 2020.

THERE WERE SOME ... INTERESTING ... IDEAS TOO



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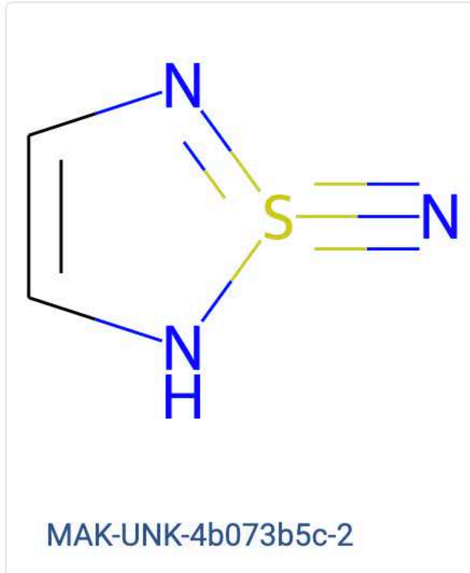
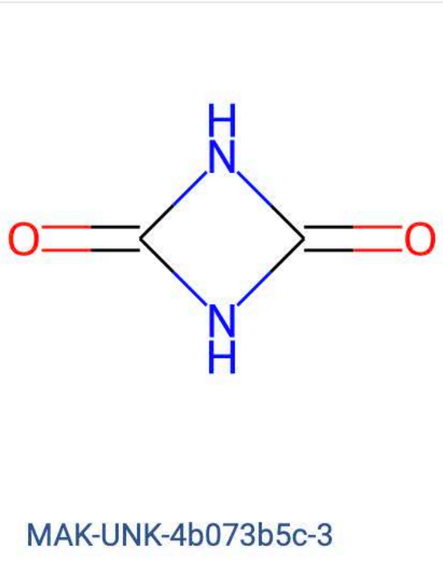
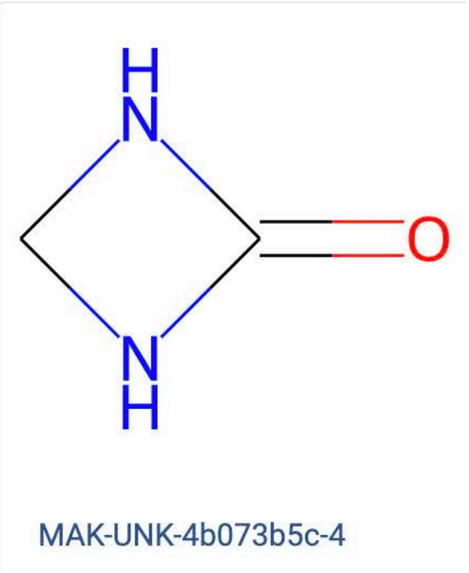


MAK-UNK-4b073b5c-2



MAK-UNK-4b073b5c-3



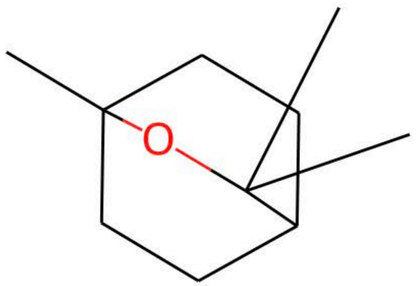
MAK-UNK-4b073b5c-4

Design Rationale:

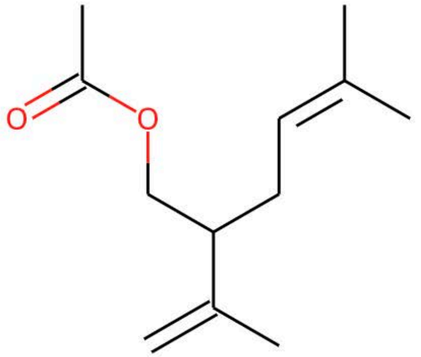
by eye, tiny molecules

THERE WERE SOME ... INTERESTING ... IDEAS TOO

Molecule(s):



BET-COM-8a5969bb-1

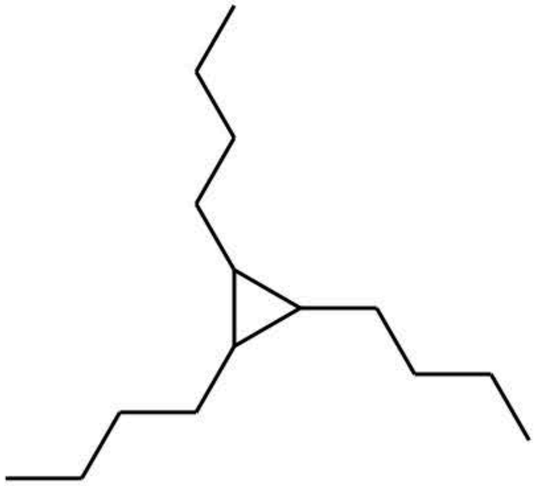


BET-COM-8a5969bb-2

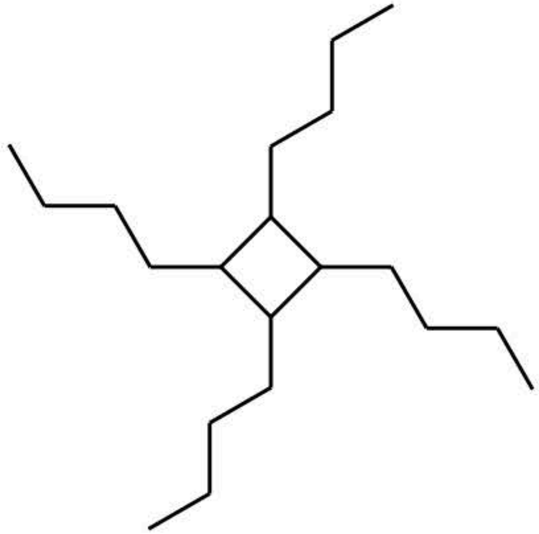
Design Rationale:

I'm looking for common, inexpensive, widely available compounds, preferably volatile, that humans already safely inhale, and, if possible, enjoy inhaling, that might also be harmful to the virus. I have quite a list of possibilities. These two are components of lavender and eucalyptus. They definitely fit into

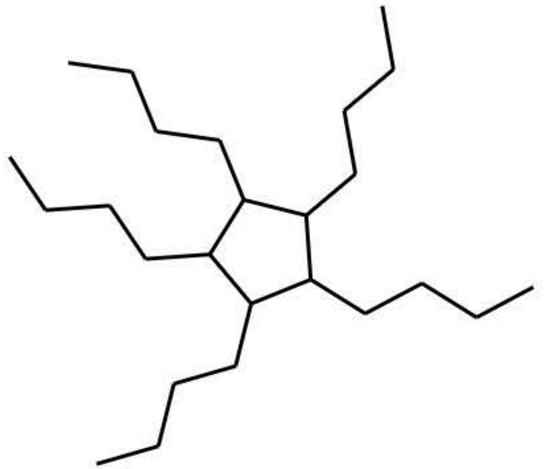
THERE WERE SOME ... INTERESTING ... IDEAS TOO



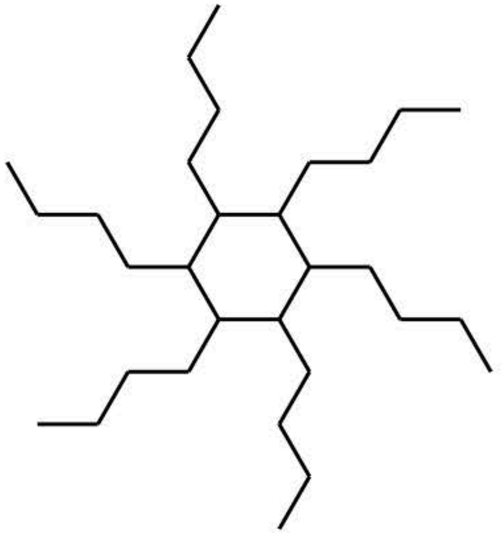
THE-UNK-833274f3-1



THE-UNK-833274f3-2



THE-UNK-833274f3-3



THE-UNK-833274f3-4

Design Rationale:

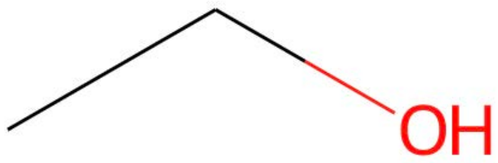
These substances are only carbon, and they have no alarm.

THERE WERE SOME ... INTERESTING ... IDEAS TOO

Design Rationale:

I used random numbers to find this compound.

THERE WERE SOME ... INTERESTING ... IDEAS TOO



JAM-UNK-fcc74568-1

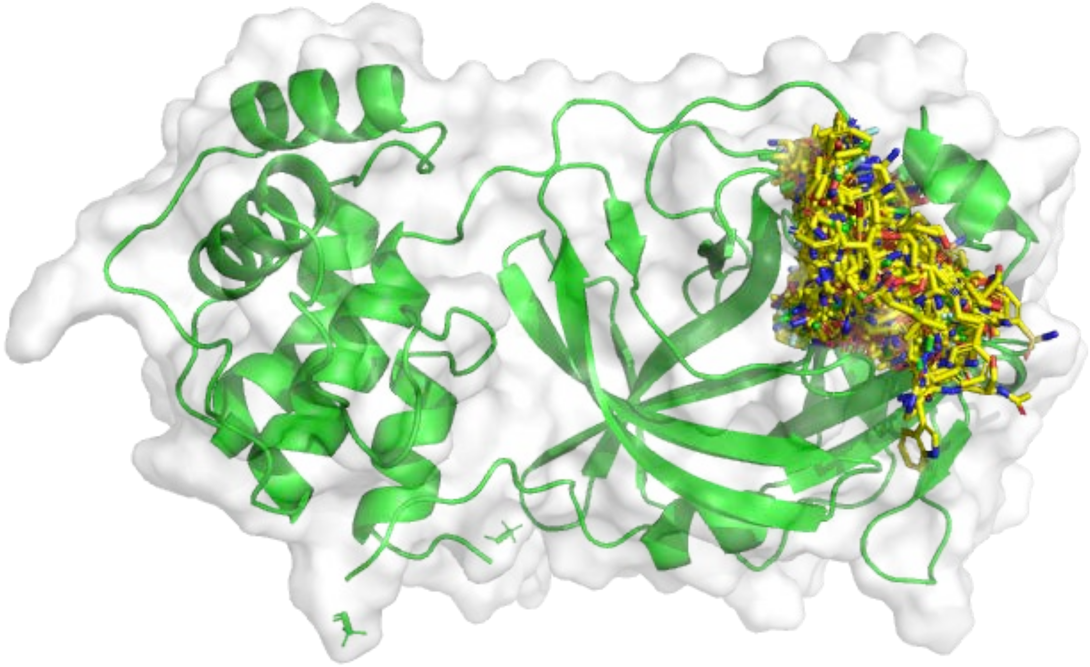
Design Rationale:

Common sense

Other Notes:

I'm sure it works, on a dish at least.

FRED DID A PRETTY GOOD JOB WITH HYBRID DOCKING TO INSPIRATION FRAGMENT TO WEED OUT TERRIBLE IDEAS

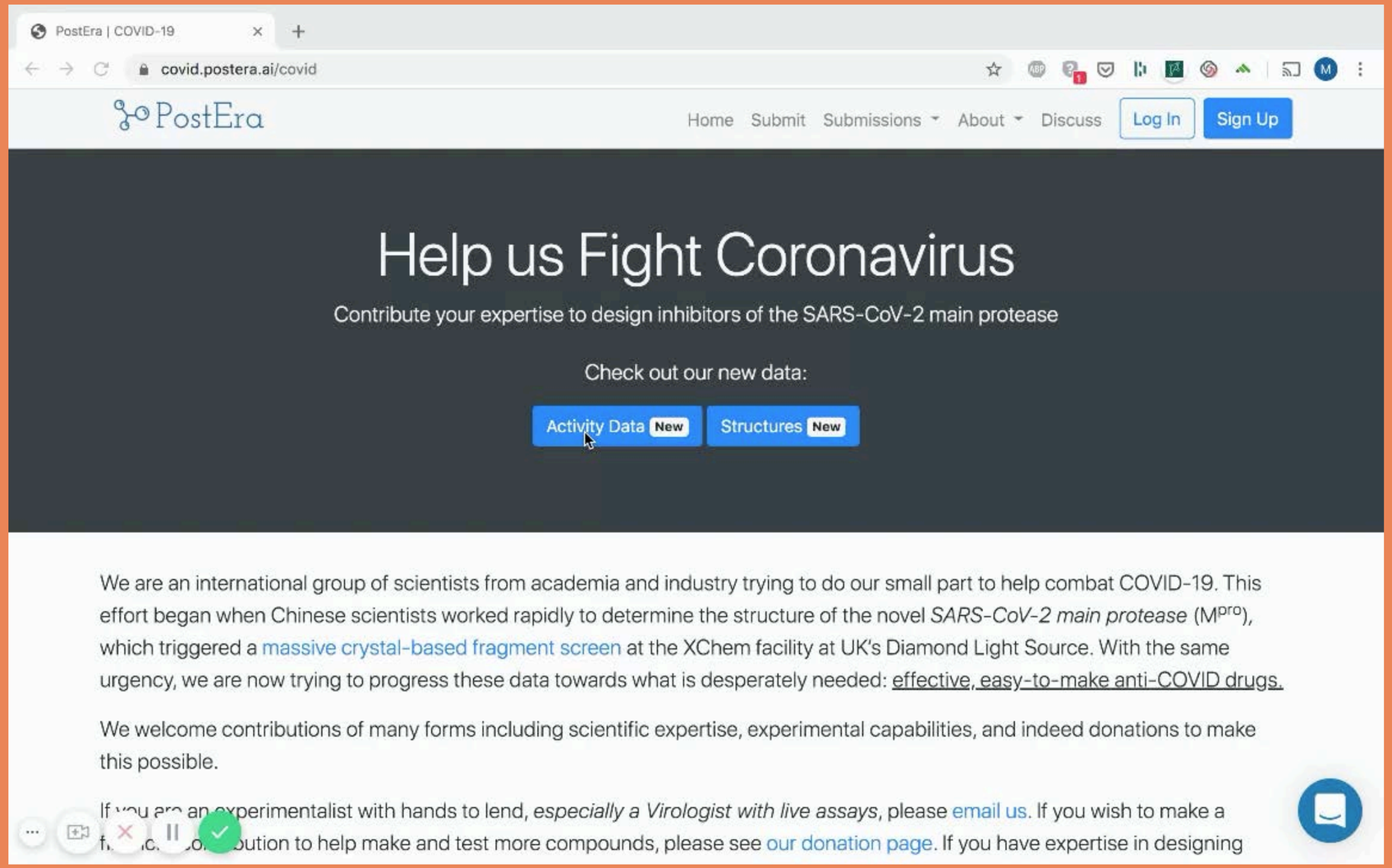


code and docking results: https://github.com/FoldingAtHome/covid-moonshot/tree/master/moonshot-submissions

The London lab and Oxford set up biochemical assays to measure SARS-CoV-2 Mpro inhibition

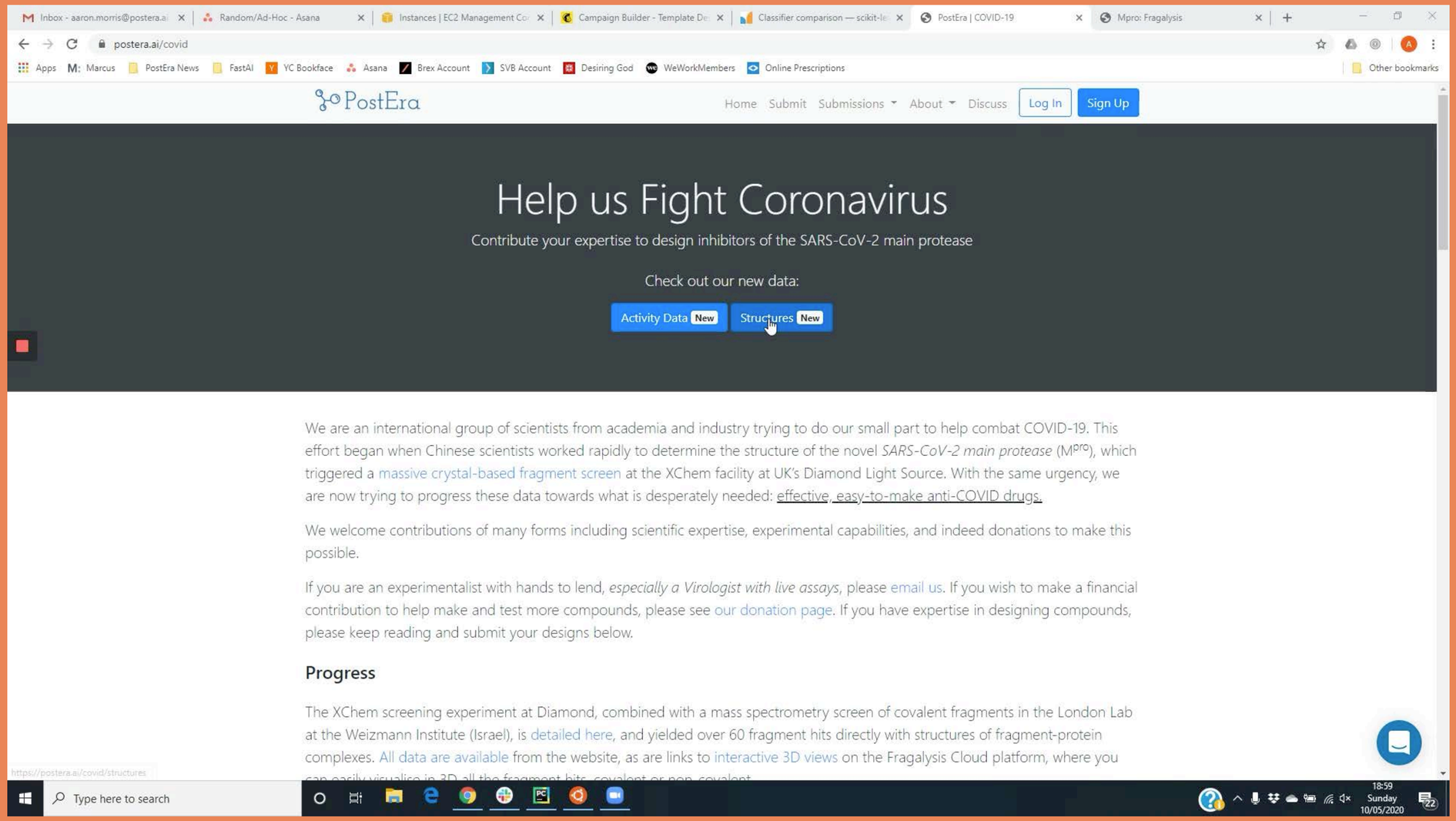
Nir London
Weizmann Institute

In a first for a drug discovery project, all data was immediately reported back to the community



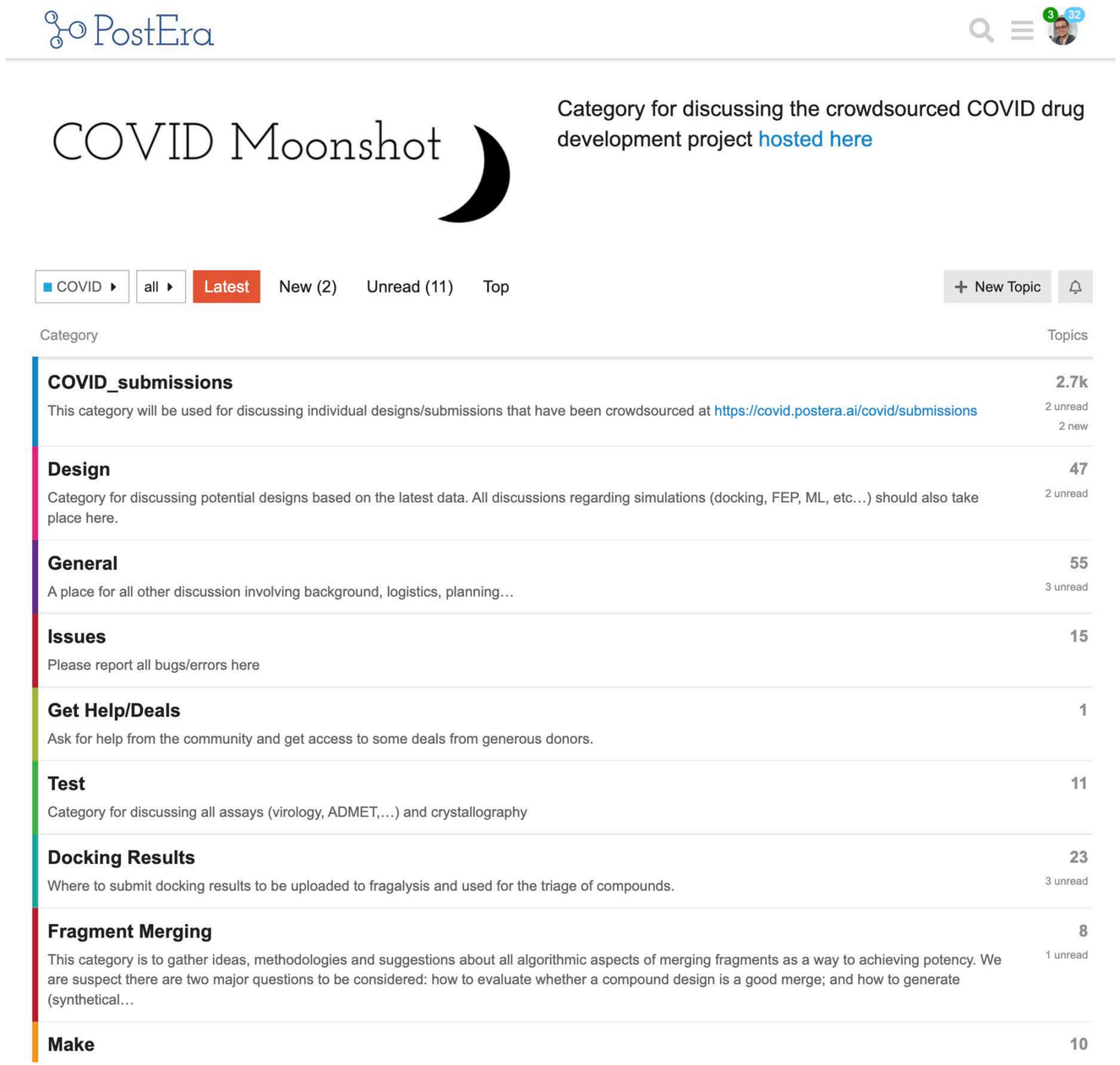
http://postera.ai/covid

Diamond XChem's automated beamline enabled us to turn structures around in days



http://postera.ai/covid

WE EVEN SET UP A DISCUSSION BOARD



https://discuss.postera.ai/c/covid/5

THOUGH IT QUICKLY TURNED INTO PETER KENNY'S ONLINE MED CHEM BLOG

pwkenny

Peter Kenny

Joined Apr 1, '20 Last Post Mar 1 Seen 1 day Views 283 Trust Level regular

Summary Activity Notifications Invites Badges Preferences

STATS

642 days visited **1d** read time **1h** recent read time **790** topics viewed **1.5k** posts read

259 posts created

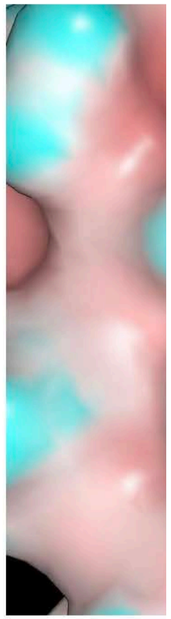
https://discuss.postera.ai/c/covid/5

Design implications of P1090 crystal structure (MAT-POS-4223bc15-23)

COVID Design

pwkenny Aug '21

The P1090 crystal structure 3 for the MPro complex with MAT-POS-4223bc15-23 5 is very interesting and I'll mention @mc-robinson @edgriffen @Ben_DNDi @JSPEN @RGlen @frankvondelft @Daren_Fearon 5 does not appe P1 isoquinoline. stabilization of th (colored by curva isoquinoline).



The NH of the pe what one would NH of the penda

Jorgensen et al MPro inhibitors

COVID General

pwkenny

The recent article 14 by Jorgensen et al may be of interest to members of the COVID N community ar @londonir

Jorgensen et analogous ma c9c1e0d8-3 preference of MAT-POS-bb not attemptin PET-UNK-ab would presen dihydrouracil The successf e8933450-1 center.

Jorgensen et against auton pyridine. For 02c6a514-44

SAR analysis for 3-aminopyridine-like inhibito

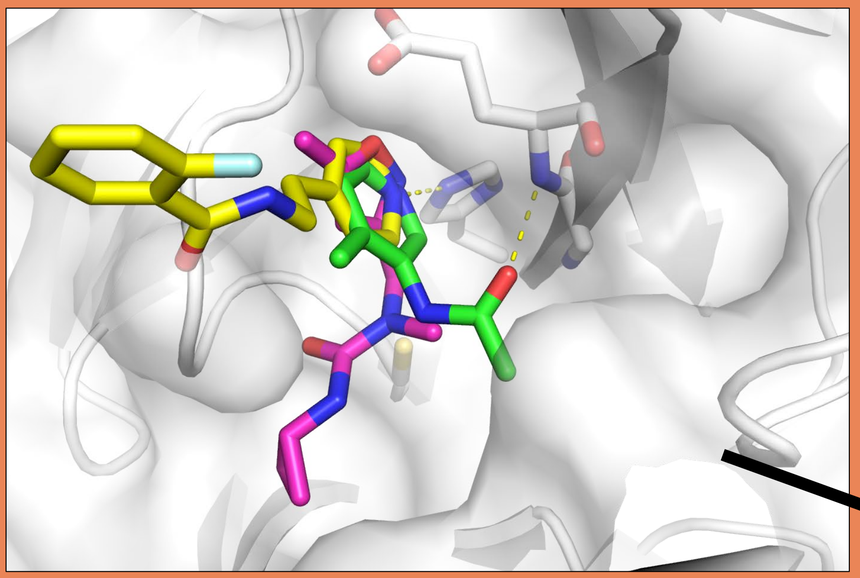
COVID Design

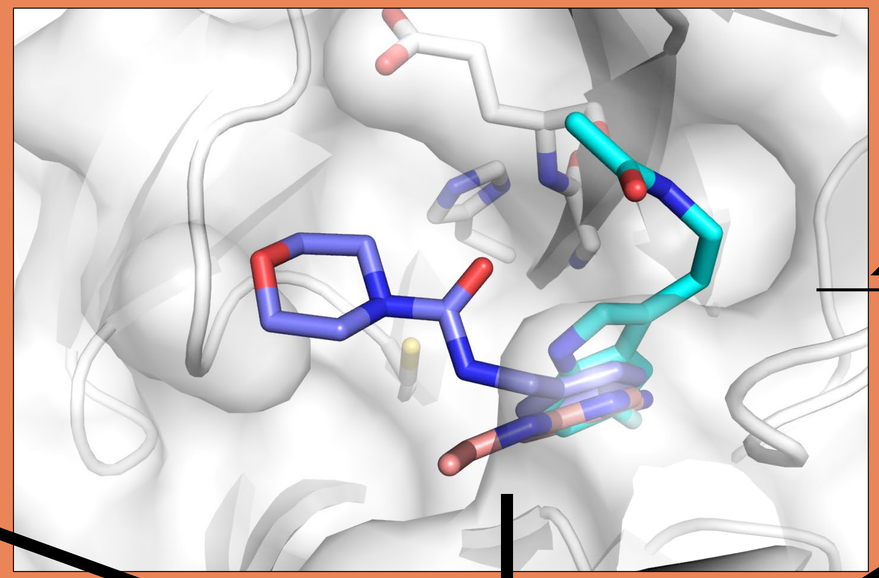
pwkenny

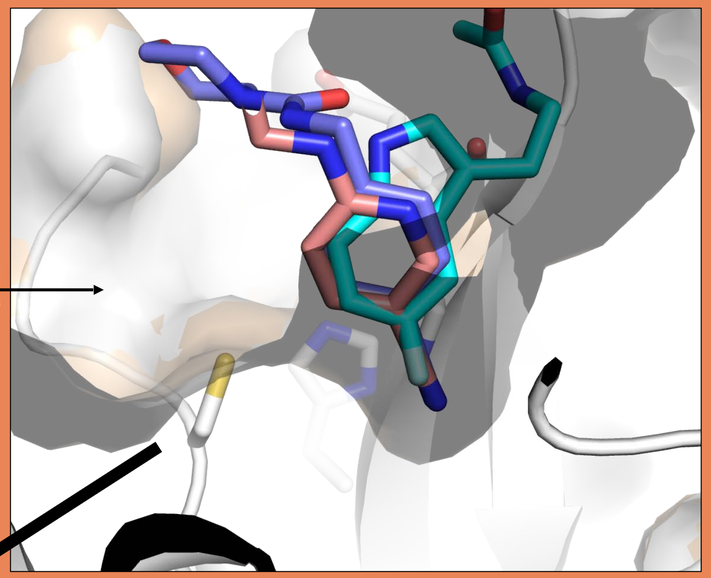
One question of potential interest to COVID Moonshot designers is whether th isoquinoline at P1 relative to pyridine are maintained when the P1 heterocycle opposed to NH). In terms of potency, an isoquinoline at P1 needs to 'pay its w (naphthalene is less aromatic than benzene and therefore more reactive) as w more lipophilic than pyridine. Here is some SAR analysis which suggests that less beneficial (relative to pyridine) when linked to carbonyl by CH2. Let me kn and/or if you spot any errors. This analysis has implications for lipophilicity ma the 'benzotriazole series' (isoquinoline has been substituted for benzotriazole mention @mc-robinson @edgriffen @alphalee.

The starting point for the analysis is to note that 'reversing' the acetamide link potency (f: fluorescence; RF: RapidFire) for methylpyridine at P1.

Crowdsourcing generated a number of novel chemical series by fragment merging





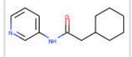


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

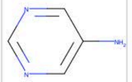
Design Rationale:

The design of the molecules was done by superimposing the different fragments from the crystal structures (by eye). The reactions should be fairly easy urea formation or amide coupling all from readily available starting materials. Fragments used for the conception of the ideas are the following x0107, x0434, x0678, x0748, x0995, x1382

Inspired By:



ALE-HEI-f28a35b5-9



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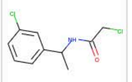
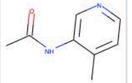
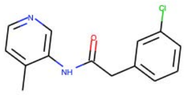


AAR-POS-0daf6b7e-10



MAK-UNK-6435e6c2-8

AAR-POS-d2a4d1df-11



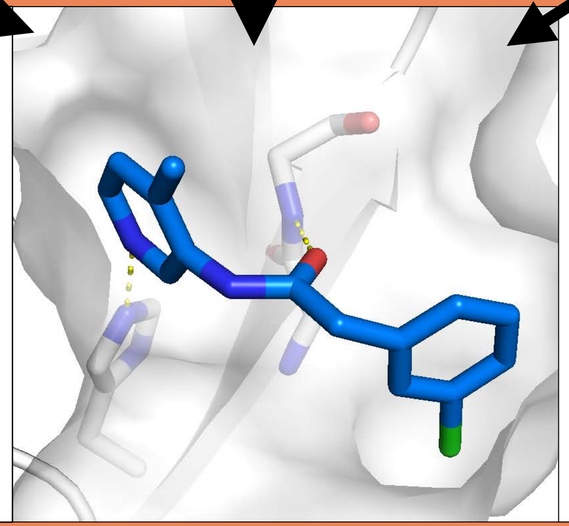
TRY-UNI-714a760b-6

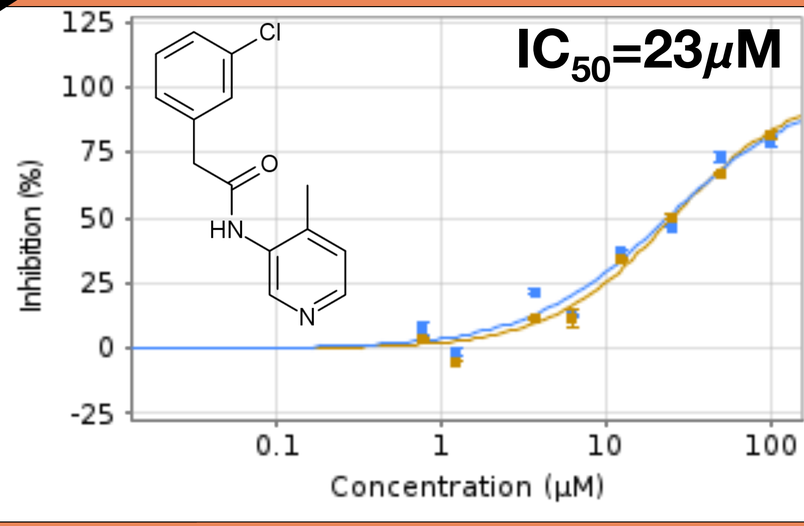
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

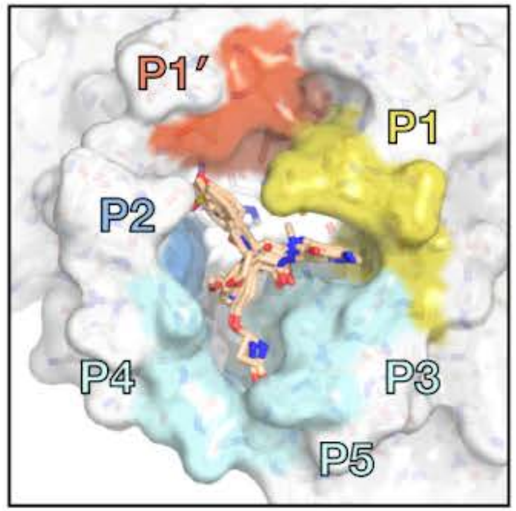
Enamine Mcule MolPort Assayed

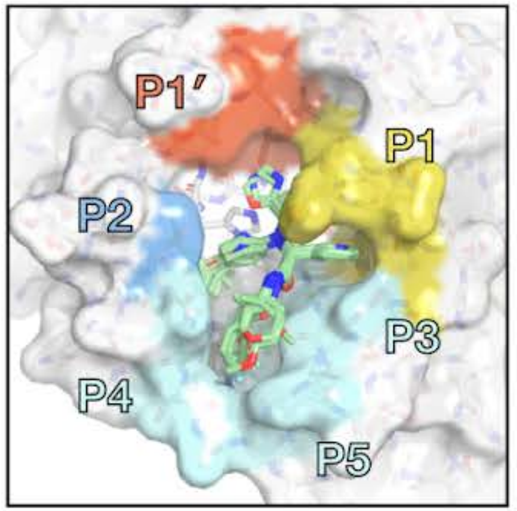
View

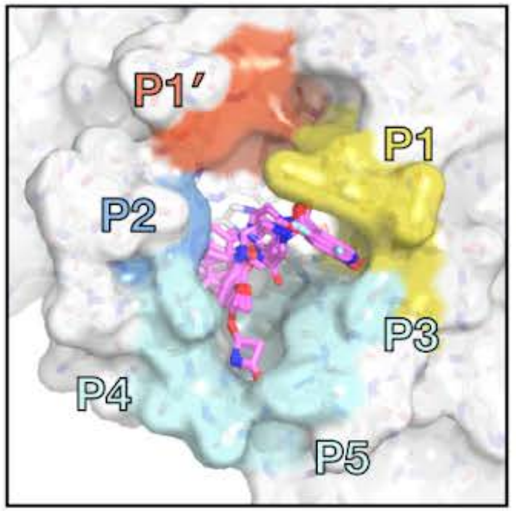


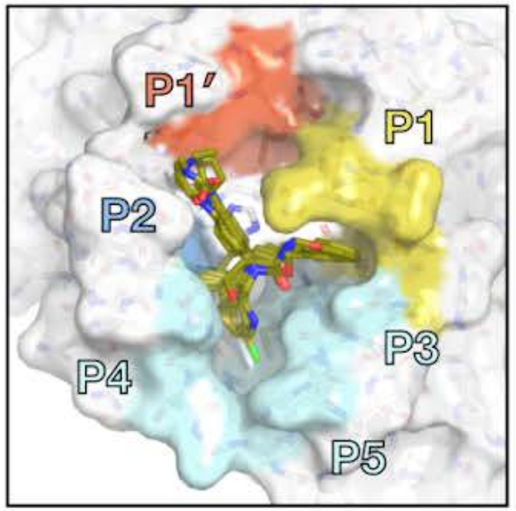


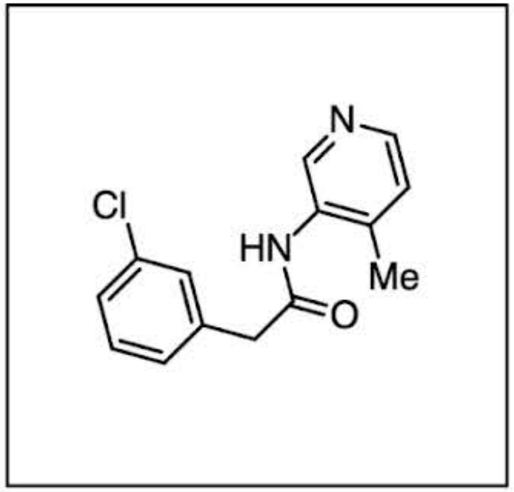
Crowdsourcing generated multiple novel, noncovalent chemotypes via fragment mergers



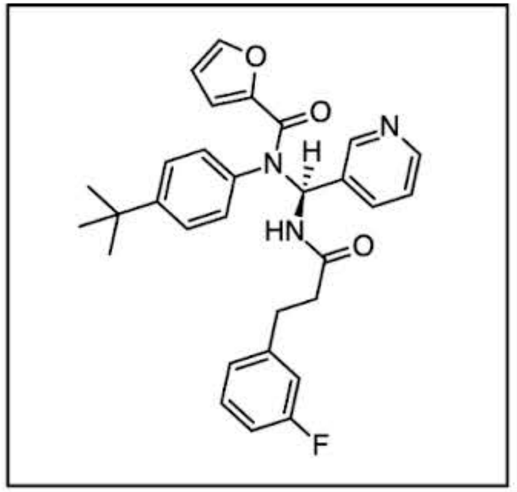




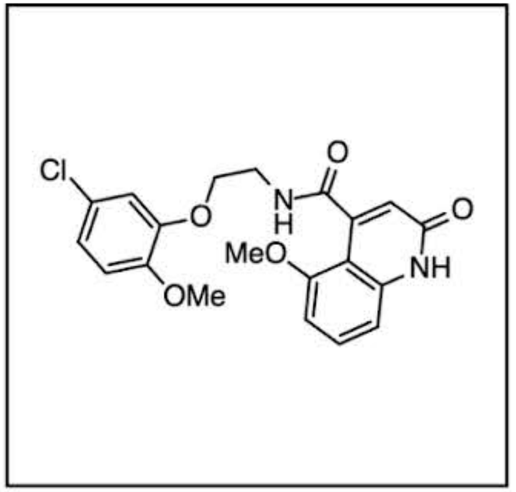




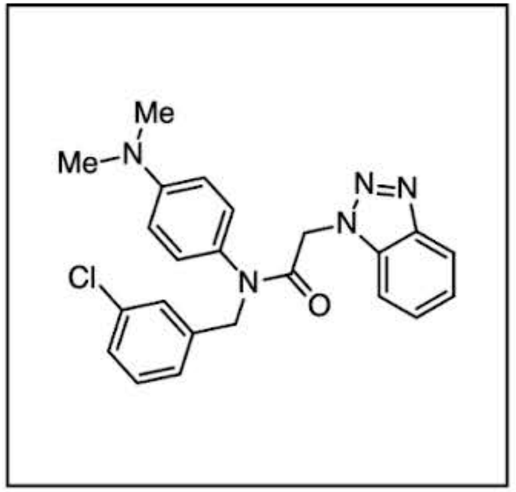
Aminopyridines



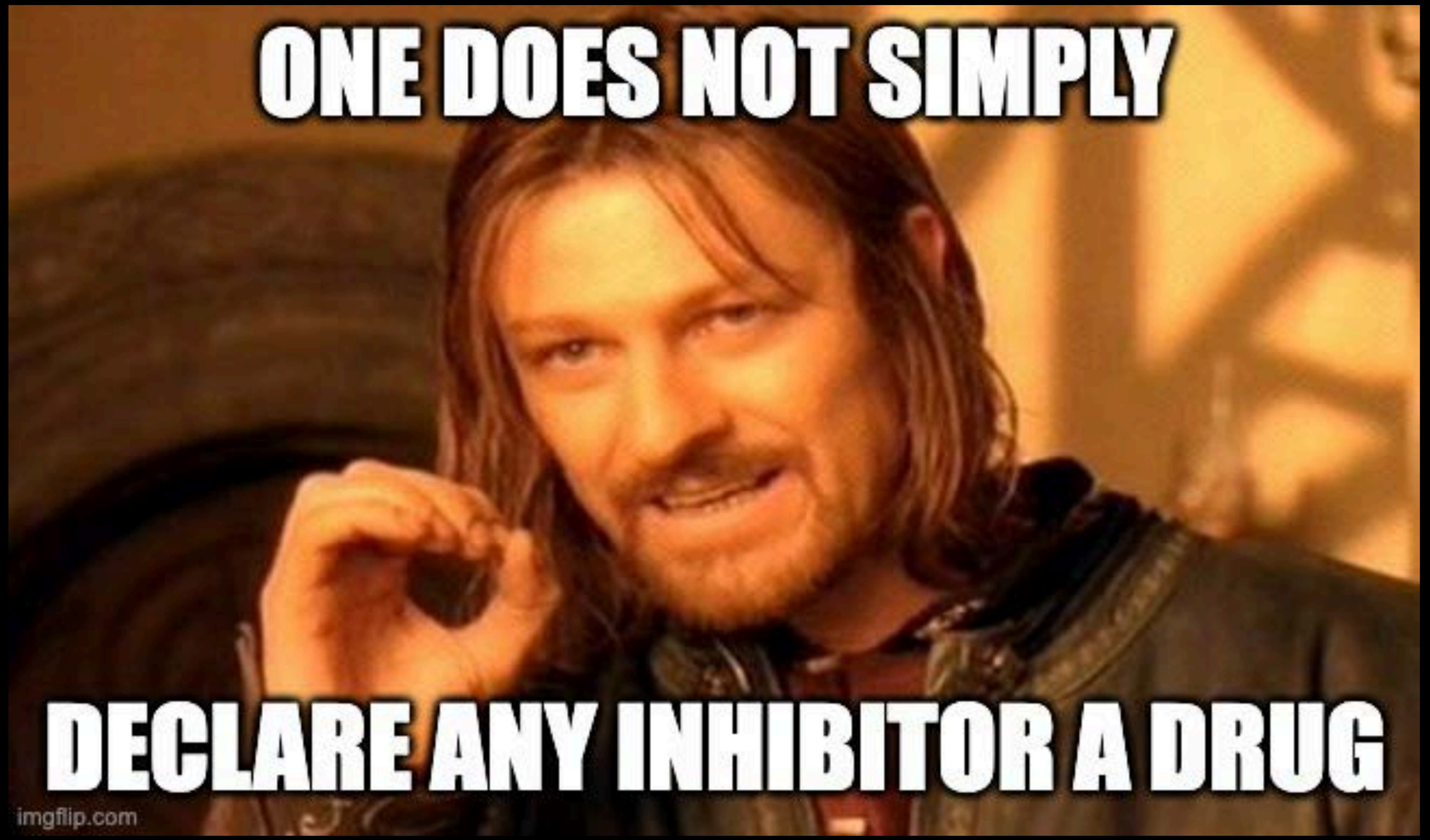
Ugis



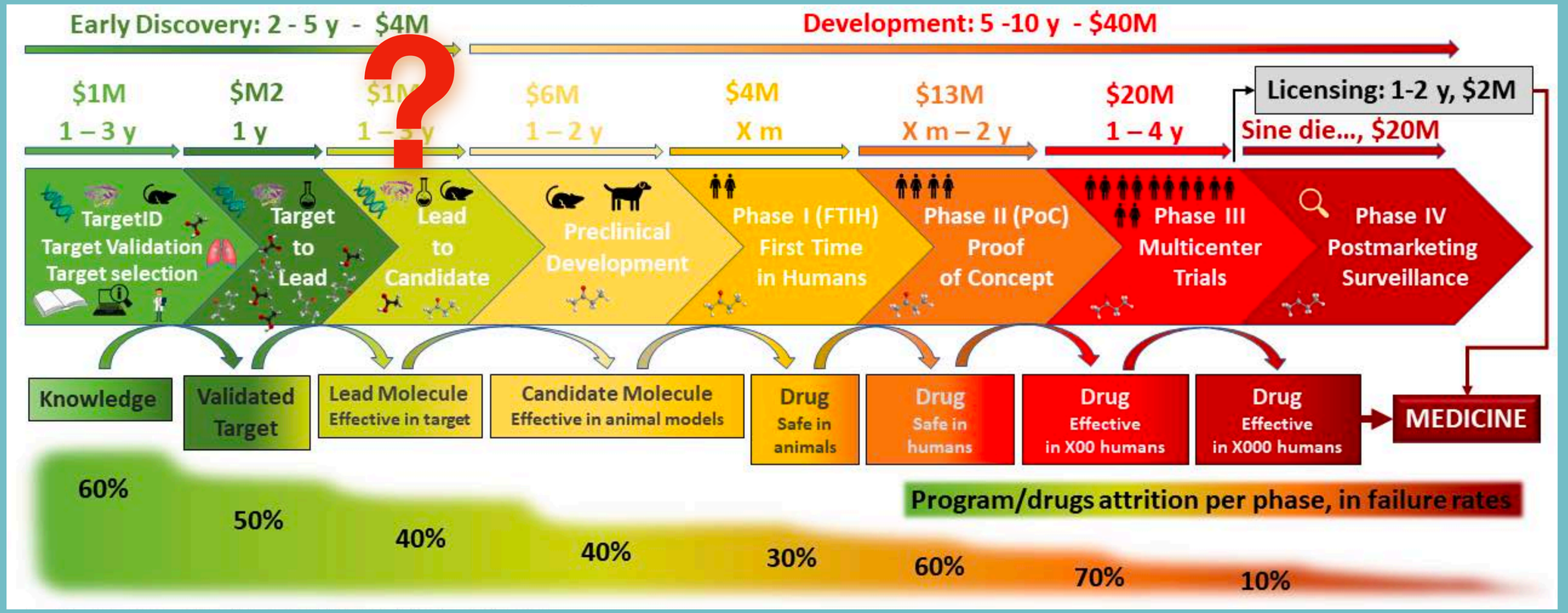
Quinolones



Benzotriazoles


ONE DOES NOT SIMPLY
DECLARE ANY INHIBITOR A DRUG
imgflip.com

So, uh, what the hell do we do now?

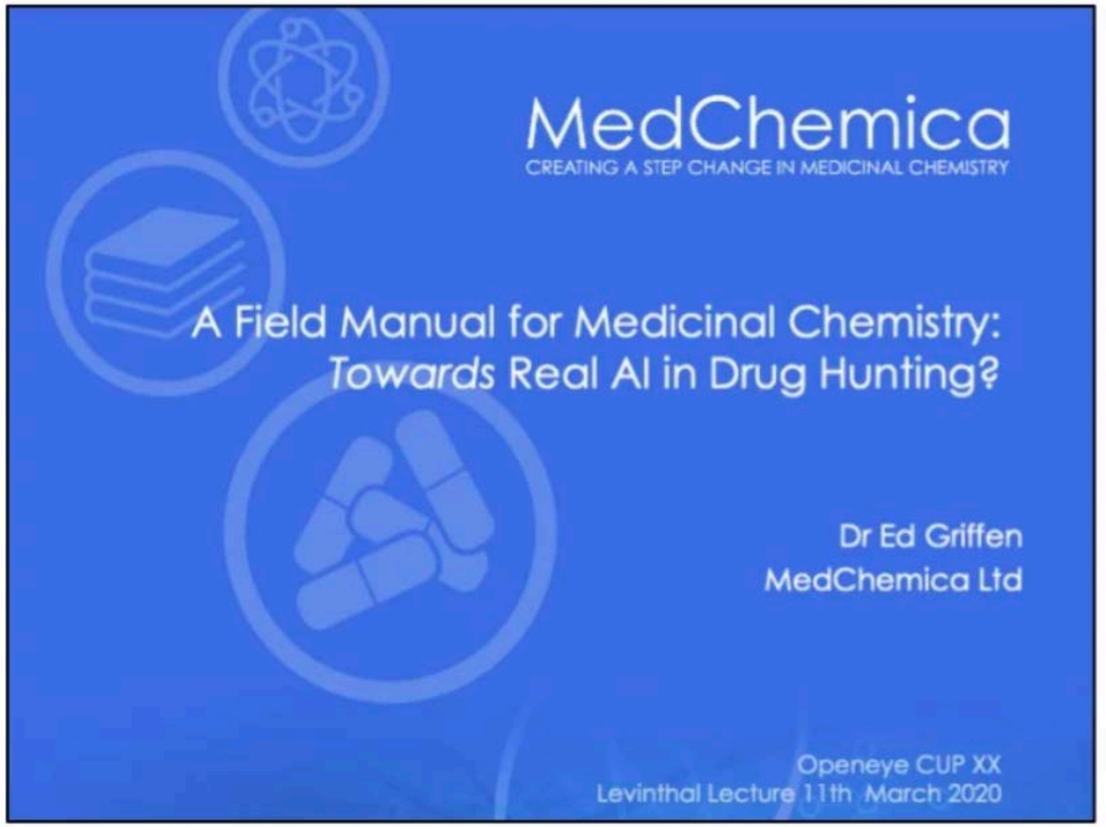


https://doctortarget.com/machine-learning-applied-drug-discovery/

- 4:45 – **Levinthal Lecture:**

  Ed Griffen, Technical Director and Founder, *MedChemica*

  "A Field Manual for Medicinal Chemistry: Towards Real AI in Drug Hunting?" –



Hi John, Just got off a call with Matt and Aaron at Postera, he said you were doing some of the coordinating of the COVID FBLG campaign. Do you have TPPs yet, or a medchem plan strategy yet? Happy to help in any way. Ed

Mar 23, 2020, 2:13 PM

We could use the help! Where can I email you?

Mar 23, 2020, 2:31 PM ✓

ed.griffen@medchemica.com, we're up for it.

Mar 23, 2020, 2:42 PM

Ed gave us some guiding principles

- **Aim for small, efficient molecules**
  - Less opportunity for off target effects
  - Reduce permeability and metabolic risks
  - Keep within the substrate envelope to minimize resistance risks
  - Simplicity of compounds – reduce cost of development and cost of goods
    = speed of development and equitable access

- **Avoid peptidomimetics**
  - Present a different development and toxicity risk profile

- **Potency first, covalency later (if needed)**
  - Make the compounds potent and selective first add covalent warhead if needed
    - Efficient selective ligand rather than “hot” warhead

- **Speed over breadth**
  - Broader spectrum pan-coronaviral activity is not a primary goal of this first-generation program

The target product profile was *almost identical* to what Ed presented in his Levinthal Lecture

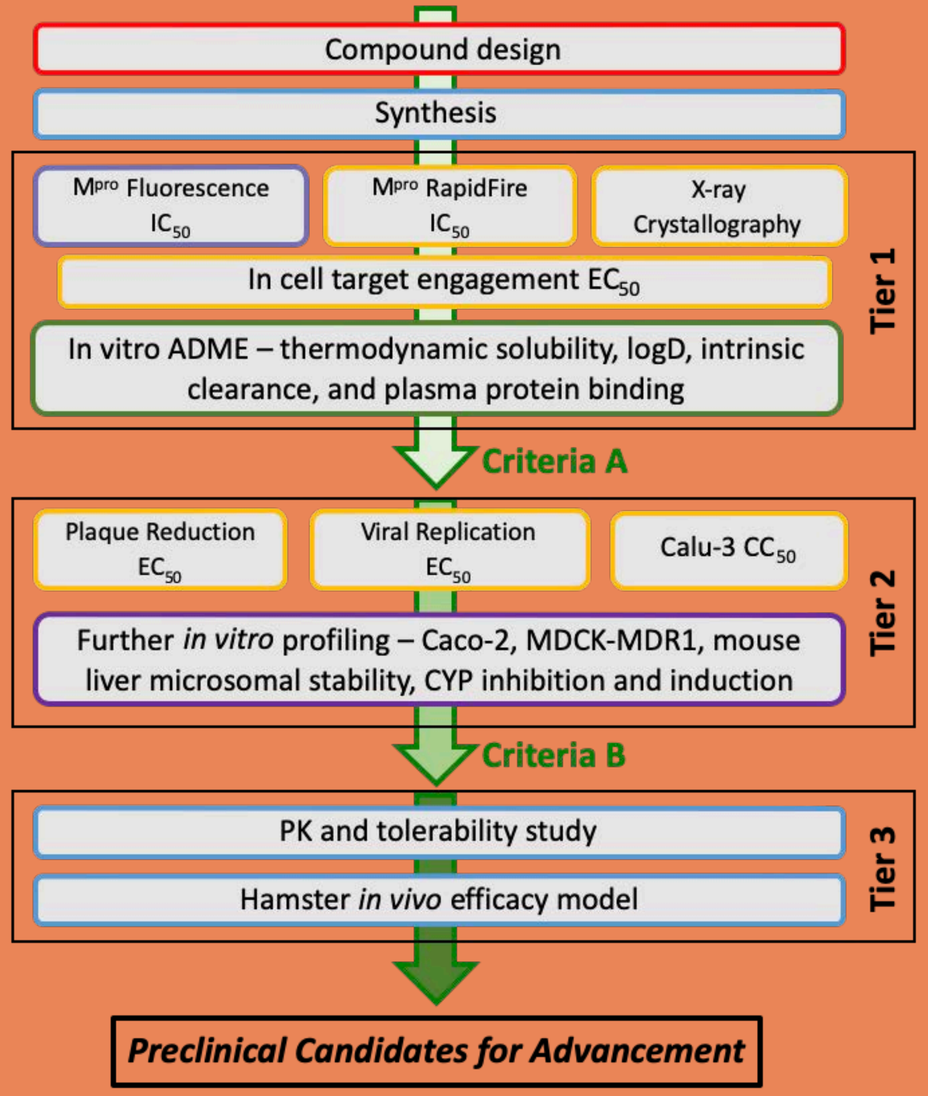
Ed Griffen
Medchemica

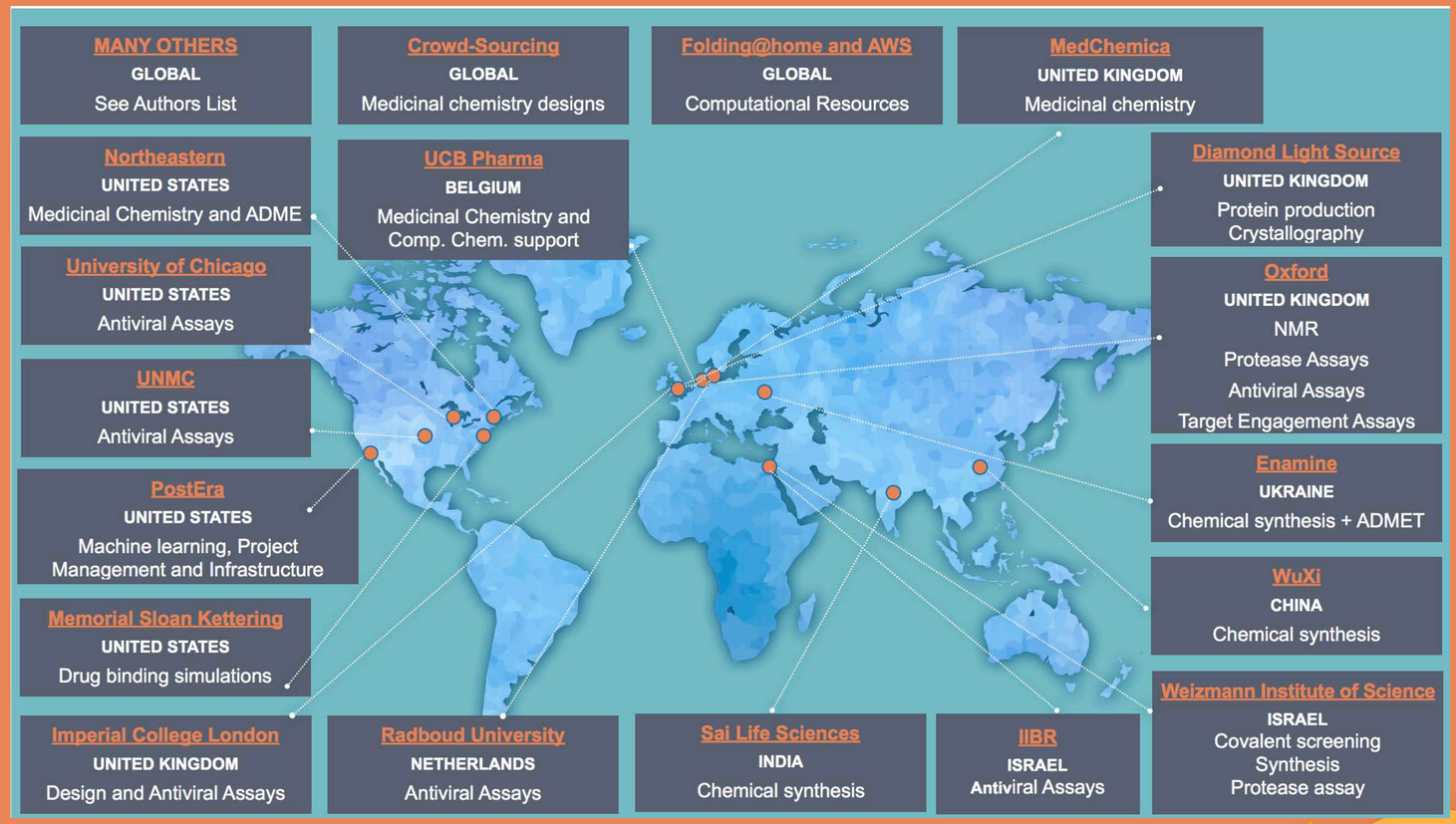
TPP for 5-day oral antiviral course following exposure, SARS-CoV-2 PCR+, or onset of symptoms

Property	Target range	Rationale
protease assay	IC_{50} < 50 nM	Extrapolation from other anti-viral programs
viral replication	EC_{50} < 0.2µM	Suppression of virus at achievable blood levels
plaque reduction	EC_{50} < 0.2µM	Suppression of virus at achievable blood levels
Coronavirus spectrum	SARS-CoV2 B1.1.7 , 501.V2, B.1.1.248 variants essential, SARS-CoV1 & MERS desirable	Treat vaccine resistant variants and future pandemic preparation.
route of administration	oral	bid/tid(qid)- compromise PK for potency if pharmacodynamic effect achieved
solubility	> 5 mg/mL, >100µM tolerable	Aim for biopharmaceutical class 1 assuming <= 750 mg dose
half-life	Ideally>= 8 h (human) est from rat and dog	Assume PK/PD requires continuous cover over plaque inhibition for 24 h
safety	Only reversible and monitorable toxicities No significant DDI - clean in 5 CYP450 isoforms hERG and NaV1.5 IC_{50} > 50 µM No significant change in QTc Ames negative No mutagenicity or teratogenicity risk	No significant toxicological delays to development DDI aims to deal with co-morbidities / combination therapy, cardiac safety for COVID-19 risk profile Low carcinogenicity risk reduces delays in manufacturing Patient group will include significant proportion of women of childbearing age

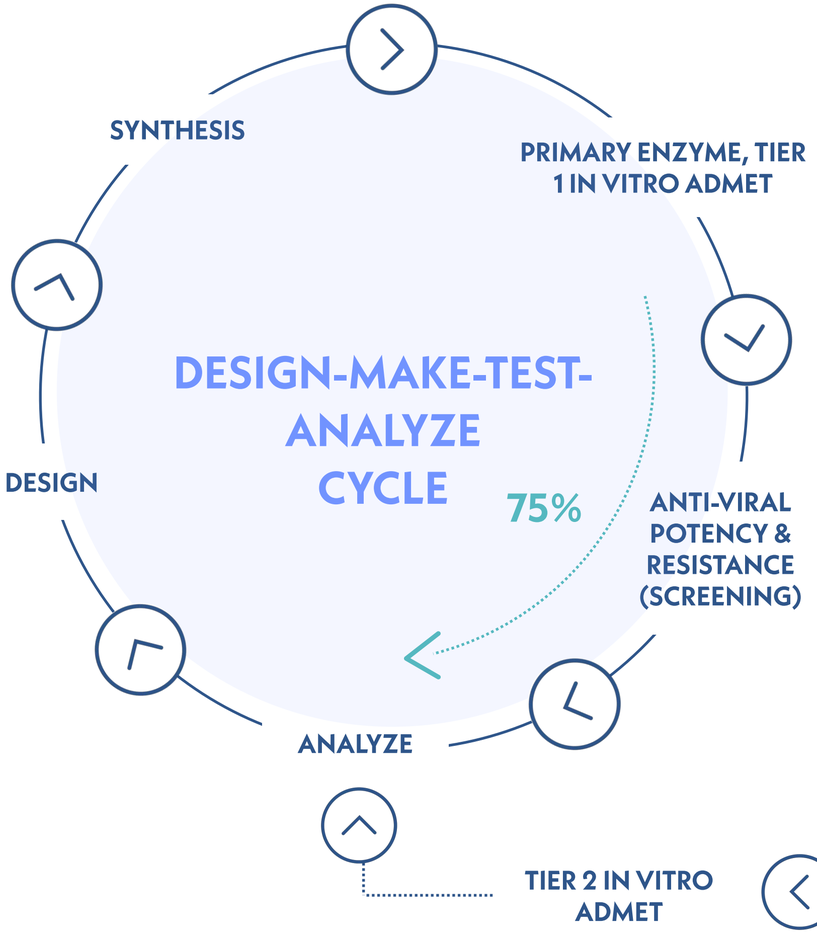
We quickly assembled an assay cascade to help us meet the TPP using labs and CROs around the world

Ed Griffen
Medchemica





WE LAUNCHED INTO DESIGN-MAKE-TEST-ANALYZE CYCLES



20% (~ 500 compounds)

6% of total (120 compounds)

PRIMARY IN VIVO ADMET

45 compounds → In vivo tool compounds

TIER 2 IN VITRO ADMET

Anti-viral Animal (profiling)

Anti-viral Cellular (profiling)

10 compounds

TIER 3 IN VITRO ADMET

SECONDARY IN VIVO ADMET

DOSE TO HUMAN PREDICTION

LEAD OPTIMIZATION ASSAY CASCADE

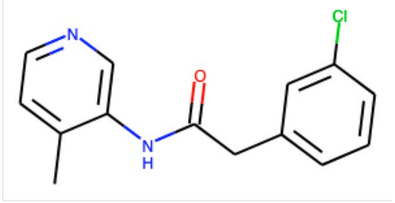
WE HAVE STRUCTURES. A LOT OF THEM.

I BUILD TOOLS FOR FREE ENERGY CALCULATIONS.

HOW CAN WE ACTUALLY HAVE IMPACT?

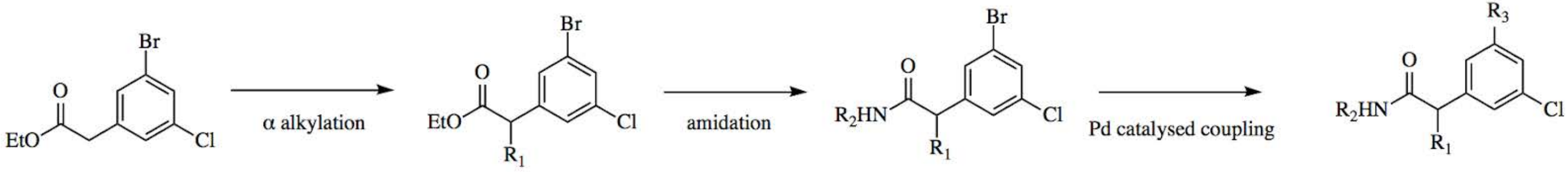
MANY DMTA CYCLES SHARED A COMMON OPERATION:

1. Select a current good design

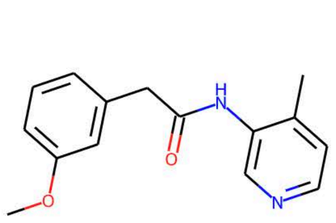


IC_{50} = 25 µM
TRY-UNI-714a760b-6

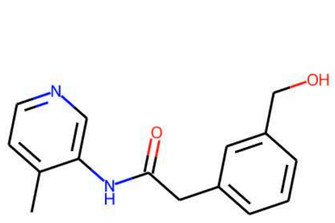
2. Select one of many possible retrosynthetic pathways (aided by Manifold) capable of installing Enamine building blocks to replace part of the molecule that engages a pocket



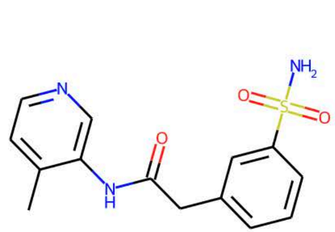
3. Pick compounds we think might work well from the (often very) large enumerated synthetic space



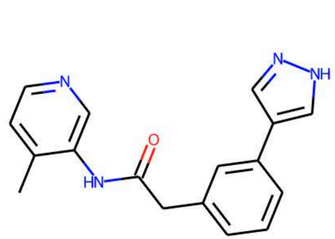
EDJ-MED-e58735b6-1



EDJ-MED-e58735b6-2

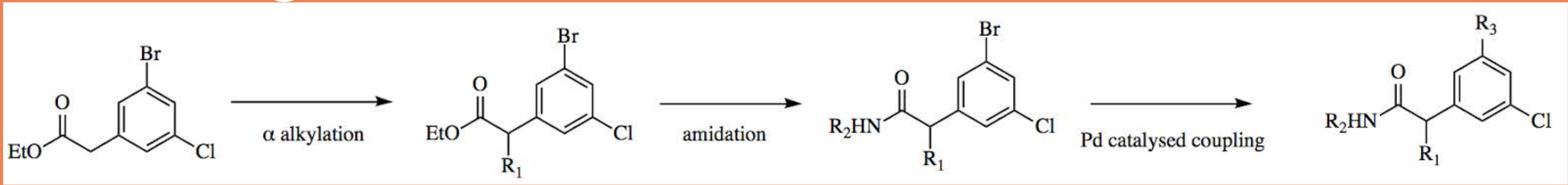


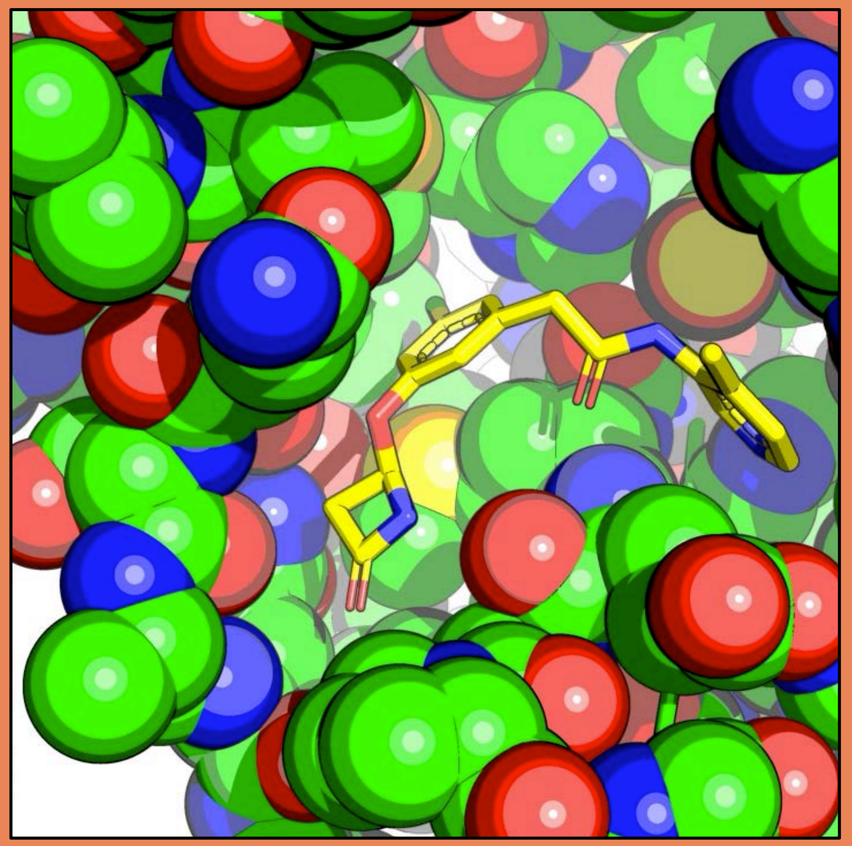
EDJ-MED-e58735b6-3



EDJ-MED-e58735b6-4

Surely we can use free energy calculations to assess these designs and find ideas the chemists overlooked!

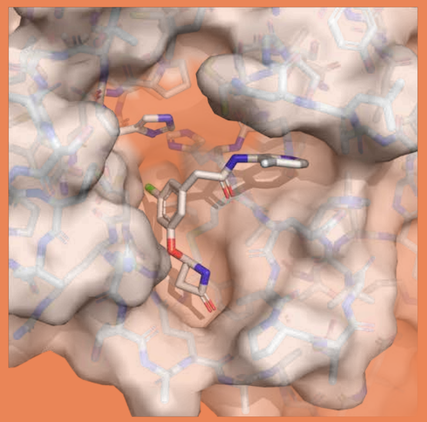




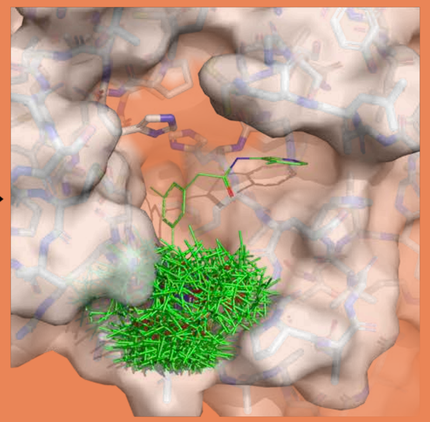
Our OpenMM-based perses relative free energy code appeared to work well on some retrospective transformations

Dominic Rufa
Tri-I TPCB PhD student

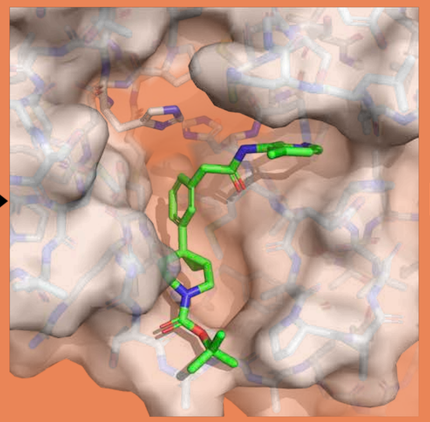
X-ray structure as reference



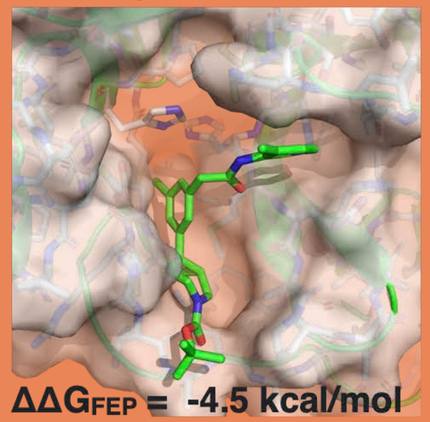
constrained enumeration of poses for proposed molecule



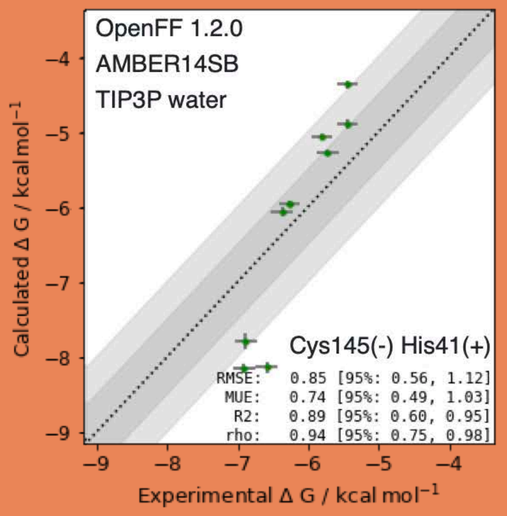
selection of pose with best docking score



nonequilibrium alchemical free energy calculation final posed structure



retrospective performance on 3-aminopyridine lead series



perses: open source relative alchemical free energy calculations
http://github.com/choderalab/perses
Open Force Field Initiative OpenFF (“Parsley”) small molecule force field
http://openforcefield.org
Simple star maps

+ Hannah Bruce Macdonald
William Glass
Matt Wittman
David Dotson

open forcefield

An open and collaborative approach to better force fields

OPEN SOURCE

Software permissively licensed under the MIT License and developed openly on GitHub.

OPEN SCIENCE

Scientific reports as blog posts, webinars and preprints

OPEN DATA

Curated quantum chemical and experimental datasets used to parameterize and benchmark Open Force Fields.

NEWS TUTORIALS ROADMAP

http://openforcefield.org

The Open Force Field 1.0 small molecule force field, our first optimized force field (codename "Parsley")

At the end of our first year, the Open Force Field Consortium releases its first optimized force field: the Open Force Field 1.0 (codename "Parsley") small molecule force field

35 minute read, Published: 10 Oct, 2019

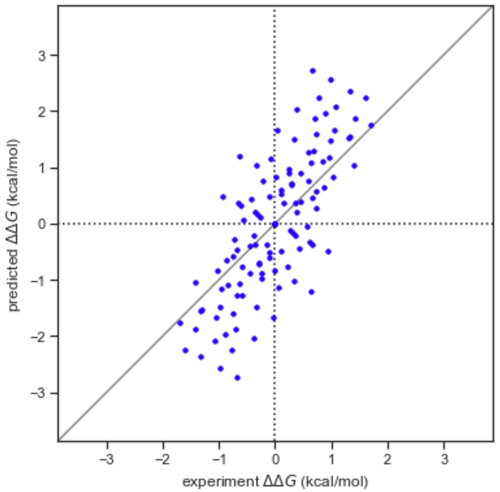
We're delighted to announce the release of "Parsley", the Open Force Field 1.0 small molecule force field---the first in a series of iteratively-improved small molecule force fields for biomolecular simulation funded in part by the Open Force Field Consortium. This is the first optimized force field to use the SMIRNOFF force field specification for atom type-free direct chemical perception, and provides substantially improved valence (bond, angle, and torsion) parameters relative to its predecessor, the AMBER-lineage SMIRNOFF99Frosst. This force field was optimized to improve agreement with quantum chemical geometries, energetics, and vibrational frequencies, and will likely provide improved accuracy (relative to its predecessor) for a wide variety of properties, especially energetics and geometries relative to gas phase quantum chemical calculations

https://openforcefield.org/news/introducing-openforcefield-1.0/

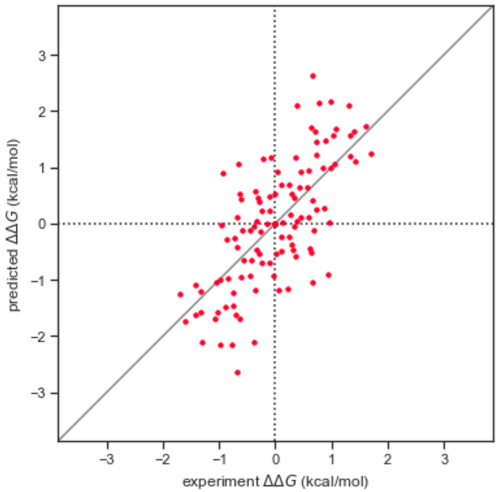
OPENFF HAD MADE SIGNIFICANT PROGRESS: LET'S JUST USE THE LATEST FORCE FIELD FOR EACH SPRINT

Open Force Field Initiative →

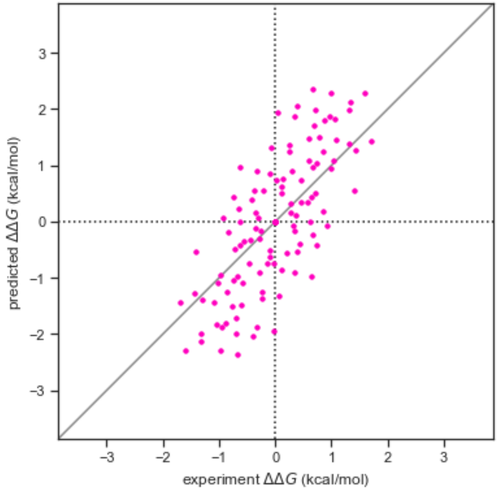
GAFF 1 (1999)



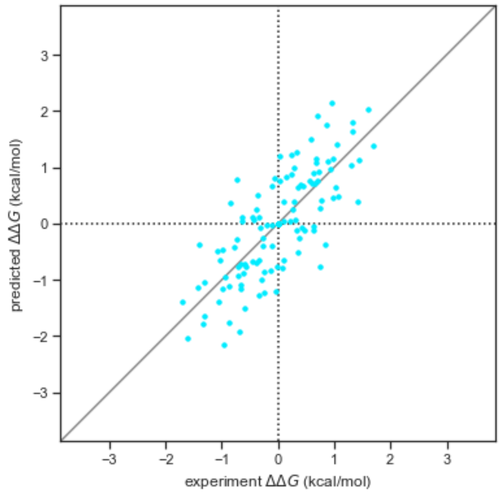
OPLS2.1 (2015)



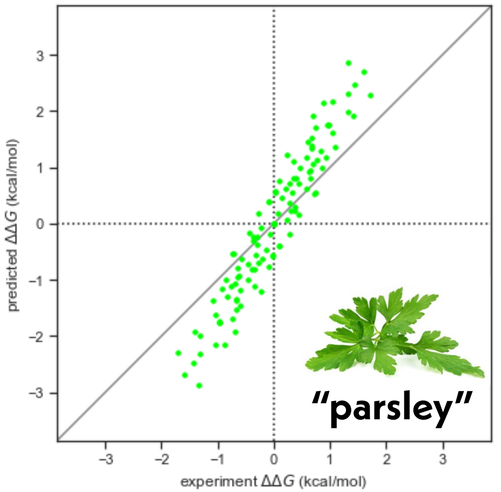
GAFF 2 (2016)



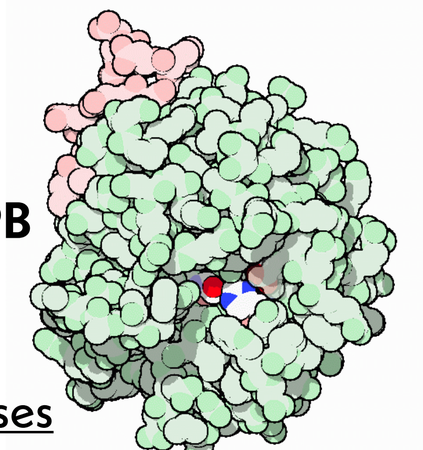
smirnoff99Frosst (2018)



openff 1.0 (2019)



thrombin
PDB101: 1PPB

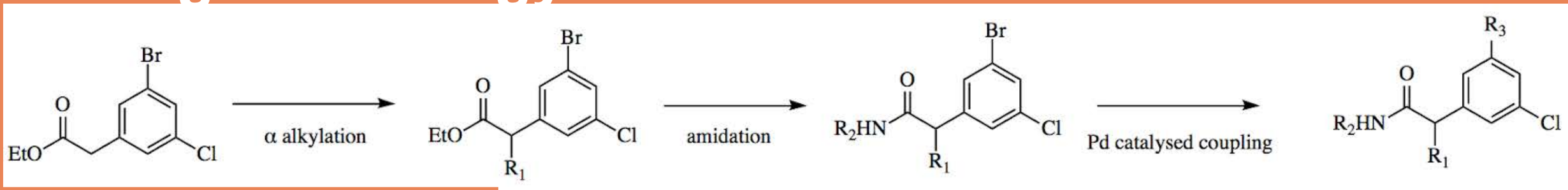


HANNAH BRUCE MACDONALD
MSKCC

http://github.com/choderalab/perses

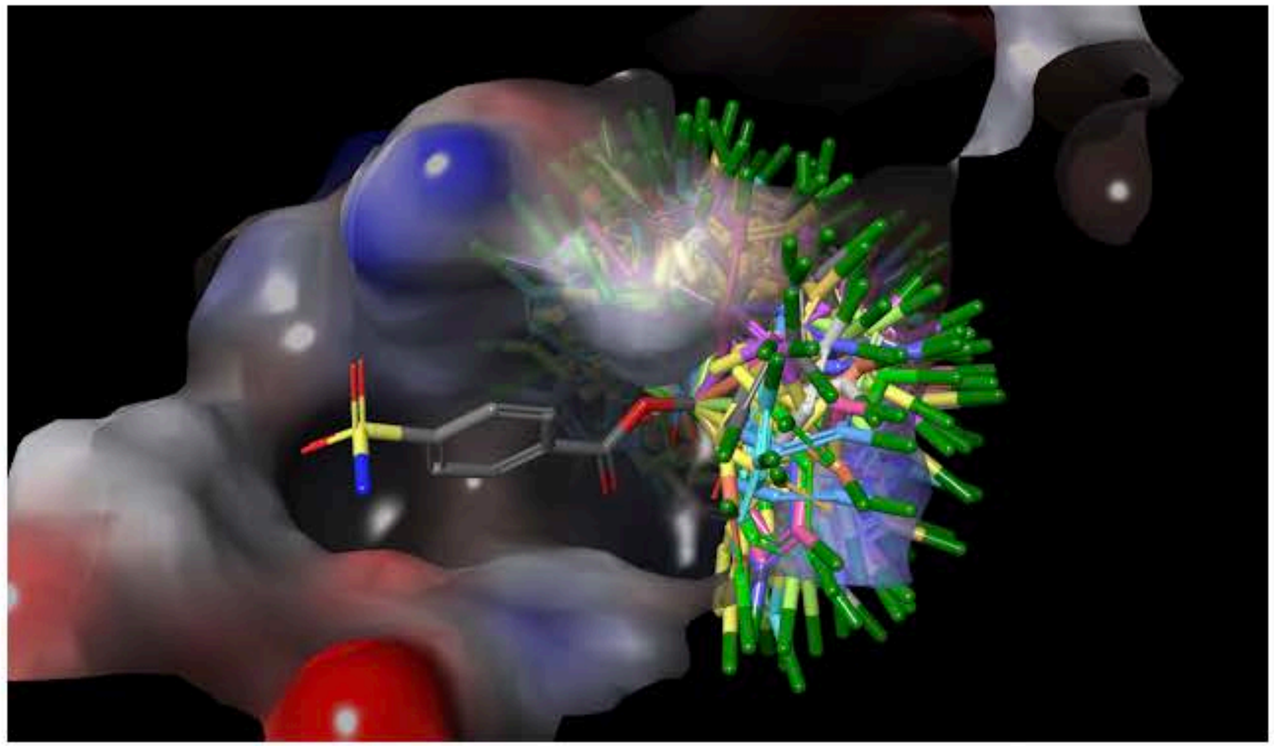
DOMINIC RUFA

How do we generate appropriate poses for relative binding free energy calculations?



PAT WALTERS

The cool part of this is that, since we kept **BF** fixed, the conformers are already aligned in the binding site.



HOW DO WE RUN AT SCALE?

Our lab had started to use Folding@home to aid experimental collaborators in pursuing COVID-19 drug discovery projects

FOLDING @HOME

Client statistics by OS

OS Type	Native TFLOPS*	x86 TFLOPS*	Active CPUs	Active Cores	Total CPUs
Windows	857	857	67,467	187,104	5,857,235
Mac OS X	91	91	8,083	85,382	217,033
Linux	87	87	6,383	26,457	882,200
NVIDIA GPU	1	2	4	4	348,371
ATI GPU	10,243	21,613	7,178	7,178	426,335
NVIDAI Fermi GPU	36,065	76,097	21,570	21,587	624,822
Total	47,344	98,747	110,685	327,712	8,355,996

1924085 people have non-anonymously contributed to Folding@home.

Table last updated at Sat, 19 Oct 2019 18:23:11

~100 pflop/s!

We built the first exaFLOP/s computing platform as the public joined in our effort

FOLDING@HOME TAKES UP THE FIGHT AGAINST COVID-19 / 2019-NCOV

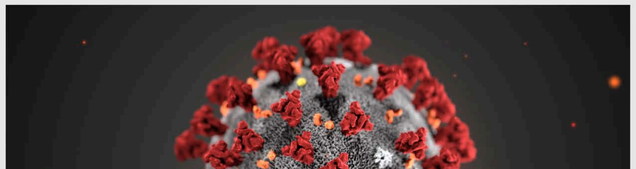
February 27, 2020
by Greg Bowman

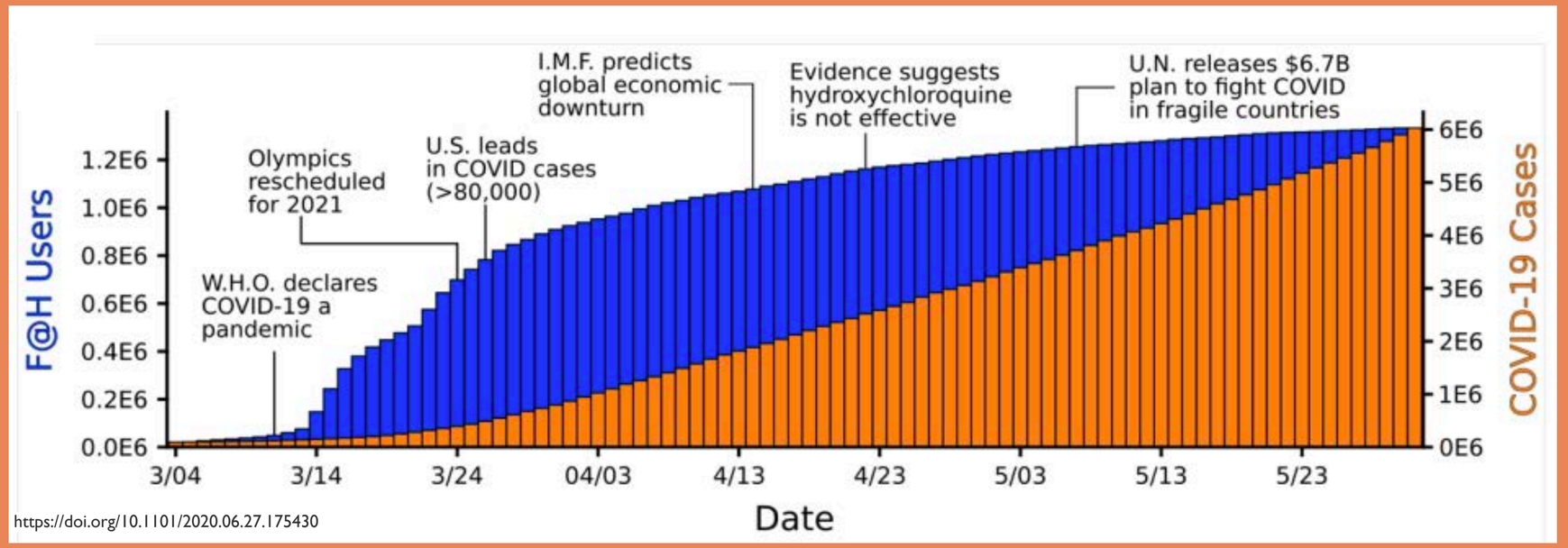
We need your help! Folding@home is joining researchers around the world working to better understand the 2019 Coronavirus (2019-nCoV) to accelerate the open science effort to develop new life-saving therapies. By downloading Folding@Home, you can donate your unused computational resources to the Folding@home Consortium, where researchers working to advance our understanding of the structures of potential drug targets for 2019-nCoV that could aid in the design of new therapies. The data you help us generate will be quickly and openly disseminated as part of an open science collaboration of multiple laboratories around the world, giving researchers new tools that may unlock new opportunities for developing lifesaving drugs.

2019-nCoV is a close cousin to SARS coronavirus (SARS-CoV), and acts in a similar way. For both coronaviruses, the first step of infection occurs in the lungs, when a protein on the surface of the virus binds to a receptor protein on a lung cell. This viral protein is called the spike protein, depicted in red in the image below, and the receptor is known as ACE2. A therapeutic antibody is a type of protein that can block the viral protein from binding to its receptor, therefore preventing the virus from infecting the lung cell. A therapeutic antibody has already been developed for SARS-CoV, but to develop therapeutic antibodies or small molecules for 2019-nCoV, scientists need to better understand the structure of the viral spike protein and how it binds to the human ACE2 receptor required for viral entry into human cells.

Proteins are not stagnant—they wiggle and fold and unfold to take on numerous shapes. We need to study not only one shape of the viral spike protein, but all the ways the protein wiggles and folds into alternative shapes in order to best understand how it interacts with the ACE2 receptor, so that an antibody can be designed. Low-resolution structures of the SARS-CoV spike protein exist and we know the mutations that differ between SARS-CoV and 2019-nCoV. Given this information, we are uniquely positioned to help model the structure of the 2019-nCoV spike protein and identify sites that can be targeted by a therapeutic antibody. We can build computational models that accomplish this goal, but it takes a lot of computing power.

This is where you come in! With many computers working towards the same goal, we aim to help develop a therapeutic remedy as quickly as possible. By downloading Folding@home here [LINK] and selecting to contribute to "Any Disease", you can help provide us with the computational power required to tackle this problem. One protein from 2019-nCoV, a protease encoded by the viral RNA, has already been crystallized. Although the 2019-nCoV spike protein of interest has not yet been resolved bound to ACE2, our objective is to use the homologous structure of the SARS-CoV spike protein to identify therapeutic antibody targets.



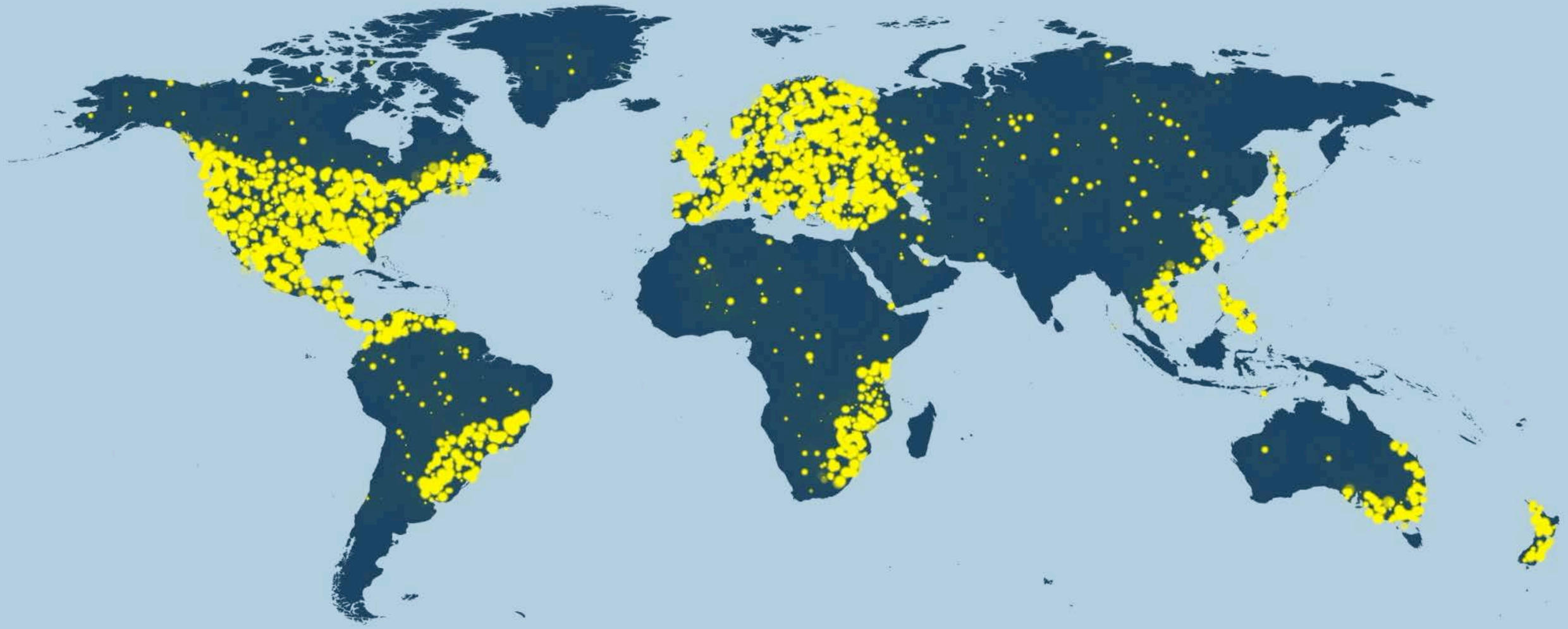


https://doi.org/10.1101/2020.06.27.175430

Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

Ivy Zhang (CBM)



This honestly came as a bit of a surprise

Folding@home

Team Monthly | Team | Donor | OS Stats

Active CPUs & GPUs by OS

OS	AMD GPUs	NVidia GPUs	CPUs	CPU cores	TFLOPS	x86 TFLOPS
Windows	75,823	314,952	474,277	3,588,315	680,371	1,384,998
Linux	3,675	41,113	78,124	811,997	85,028	167,152
macOSX	0	0	41,582	230,198	2,578	2,578
Totals	79,498	356,065	593,983	4,630,510	767,977	1,554,728

CPUs and GPUs which have returned Work Units within the last 50 days are listed by OS. FLOPS per core is estimated.

TFLOPS is Tera Floating-point OPerations per Second or trillions of math operations per second. Please see our FLOPS FAQ for more information.

Reported on Wed, 25 Mar 2020 23:42:36 GMT

~1.5 exaflops

> sum of top-10 supercomputers

This would cost $6.8B/year on AWS.

Use Your Computer To Help Folding@Home Solve The COVID-19 Virus Pandemic

Longmont Observer · Yesterday

- 400,000 new people have joined Folding@Home's fight against COVID-19

  Engadget · 2 days ago

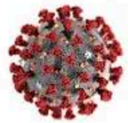
View Full Coverage

Folding@home software diverts users' excess processing power to finding coronavirus cure

Dezeen · 22 hours ago

Folding@Home Network Breaks the ExaFLOP Barrier In Fight Against Coronavirus

Tom's Hardware · 5 hours ago



How to Fight Coronavirus With Folding@home and a Gaming PC

How-To Geek · 5 days ago

Join Team Hackaday To Crunch COVID-19 Through Folding@Home

Hackaday · 7 days ago

Coronavirus And Folding@Home; More On How Your Computer Helps Medical Research

THE ONLY PROBLEM WAS THAT WE HAD NEVER RUN FREE ENERGY CALCULATIONS ON FOLDING@HOME WITH OPENMM

ALCHEMICAL FREE ENERGY CALCULATIONS CAN USE A VARIETY OF DIFFERENT SCHEMES TO SAMPLE FROM ALCHEMICAL STATES

Independent simulations

Easy to parallelize, but sampling problems at any λ can make calculations unreliable

simple but dangerous

Hamiltonian replica exchange ★

Good sampling at any λ can rescue problems at other λ if good λ overlap

reliable but complex and costly

Single-replica methods

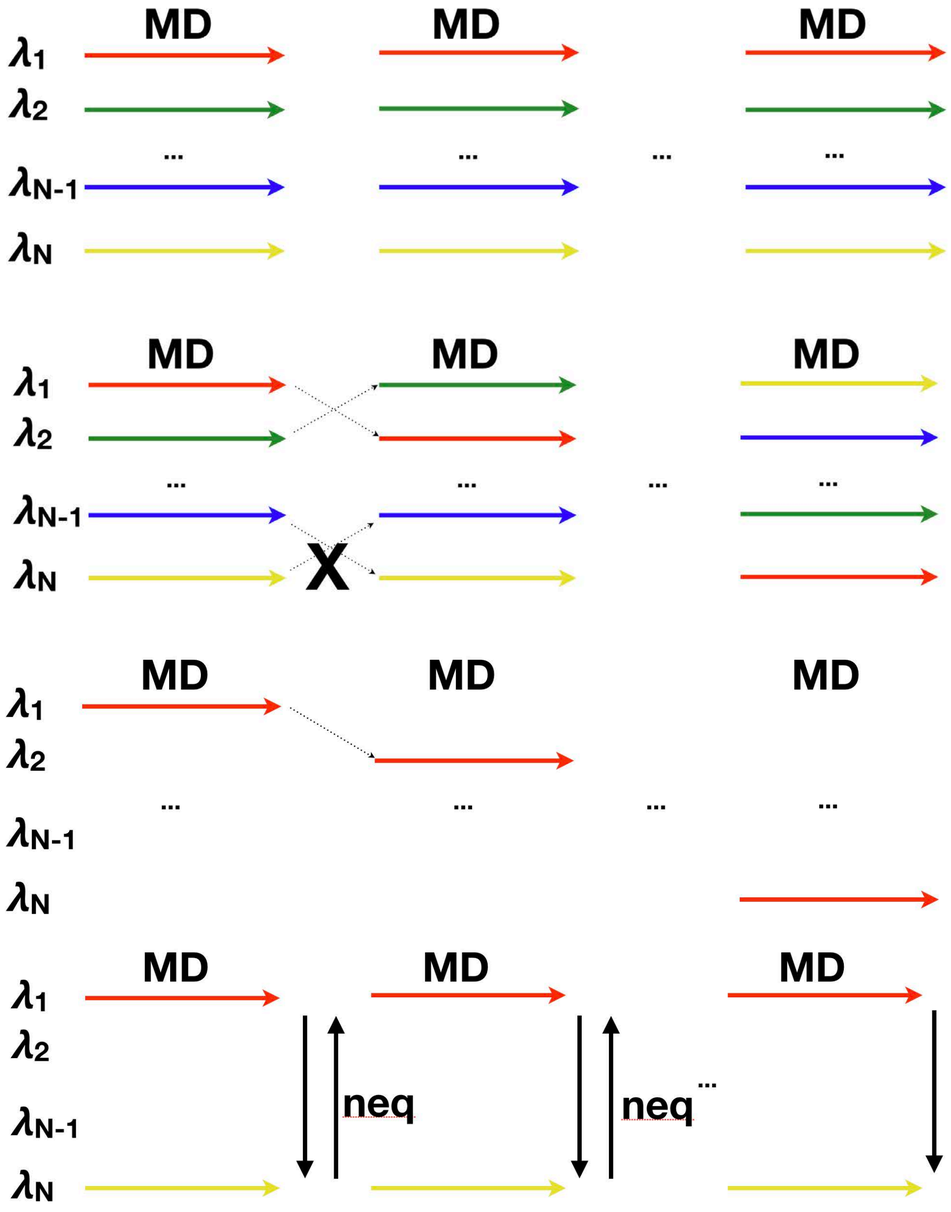
For certainly problems, can converge extremely quickly in a fraction of computer effort; tricky to make reliable

promising but relatively immature

Nonequilibrium methods

Less efficient than equilibrium calculations, but can work robustly and scalably if properly tuned

promising and cloud-friendly



★ current best practice

AMBER18 TI
Song, Lee, Zhu, York, Merz 2019
https://doi.org/10.1021/acs.jcim.9b00105

Schrödinger FEP+
Wang, Wu, Deng, Kim, ... Abel 2015
https://doi.org/10.1021/ja512751q

NAMD
Jiang, Thirman, Jo, Roux 2018
http://doi.org/10.1021/acs.jpcb.8b03277

also **OpenMM** (via **openmmtools**)

Hongzhi, Fayer, Wang 2006
https://doi.org/10.1063/1.2424700
Tan 2017
https://doi.org/10.1080/10618600.2015.1113

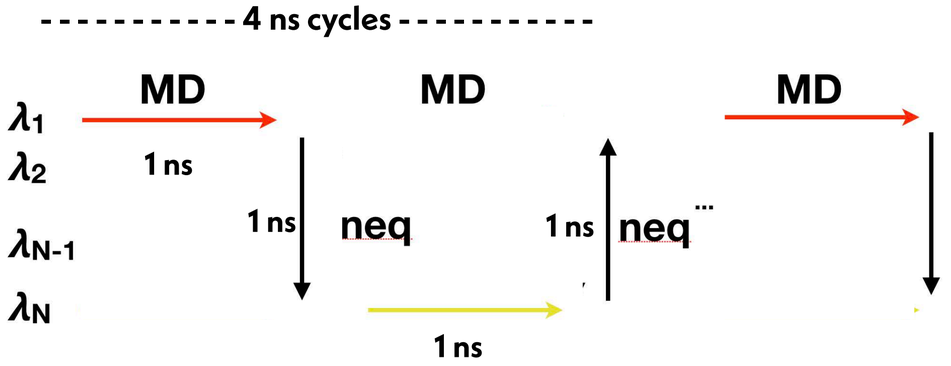
pmx / gromacs
Aldeghi, Gapsys, de Groot 2018
https://doi.org/10.1021/acscentsci.8b00717

A TERRIBLE HACK INSPIRED BY BEAUTIFUL WORK: NONEQUILIBRIUM CYCLING

Nonequilibrium cycling

Can approximate nonequilibrium switching if relaxation is fast (or restraints are used to limit motion)

a terrible hack, but it just might work



pmx / gromacs

Aldeghi, Gapsys, de Groot 2018

https://doi.org/10.1021/acscentsci.8b00717

TOGETHER, WE ARE POWERFUL

Together, we have created the most powerful supercomputer on the planet, and are using it to help understand SARS-CoV-2/COVID-19 and develop new therapies. We need your help pushing toward a potent, patent-free drug.

Use your PC to help fight COVID-19.

DOWNLOAD FOLDINGATHOME

[Available for Windows, Mac, Linux]

Progress on the current Sprint 2 to evaluate a batch of potential drugs Started Sun Aug 16 01:00:00 UTC 2020

25.996%

The **progress bar** measures the fraction of compounds we could synthesize that we've evaluated for each sprint

You can also see the progress bar on the COVID Moonshot page, where all experimental data is open and freely available.

HOW YOU CAN HELP

Fund Us

Funds go toward making and testing the most promising antiviral candidates.

$56,987 raised of $1,500,000

GoFundMe

Share Your Compute Power

Run molecular simulations on your computer when idle to help us find new molecules to test.

96.5% of sprint completed

Sprint 5½ : Started Sun Jan 24 00:00:00 UTC 20...

Folding@home

Contribute Your Expertise

Submit drug design ideas using the form below.

16,638 molecules submitted

1,851 synthesized and tested

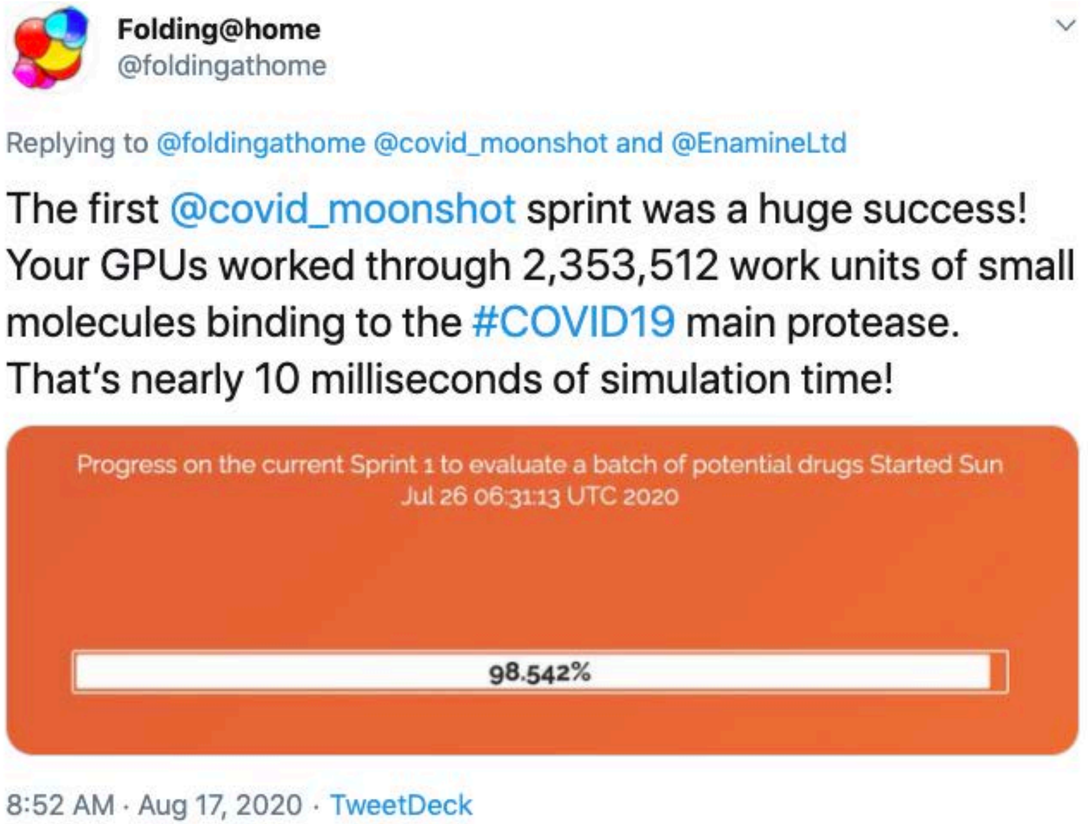
258 structures

Submit Molecule(s)

Please feel free to email us if you think you can be of additional help.

http://postera.ai/covid

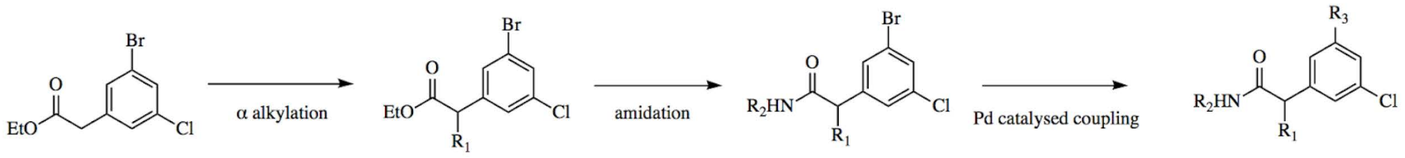
We generated a *lot* of data, which we have shared online via AWS



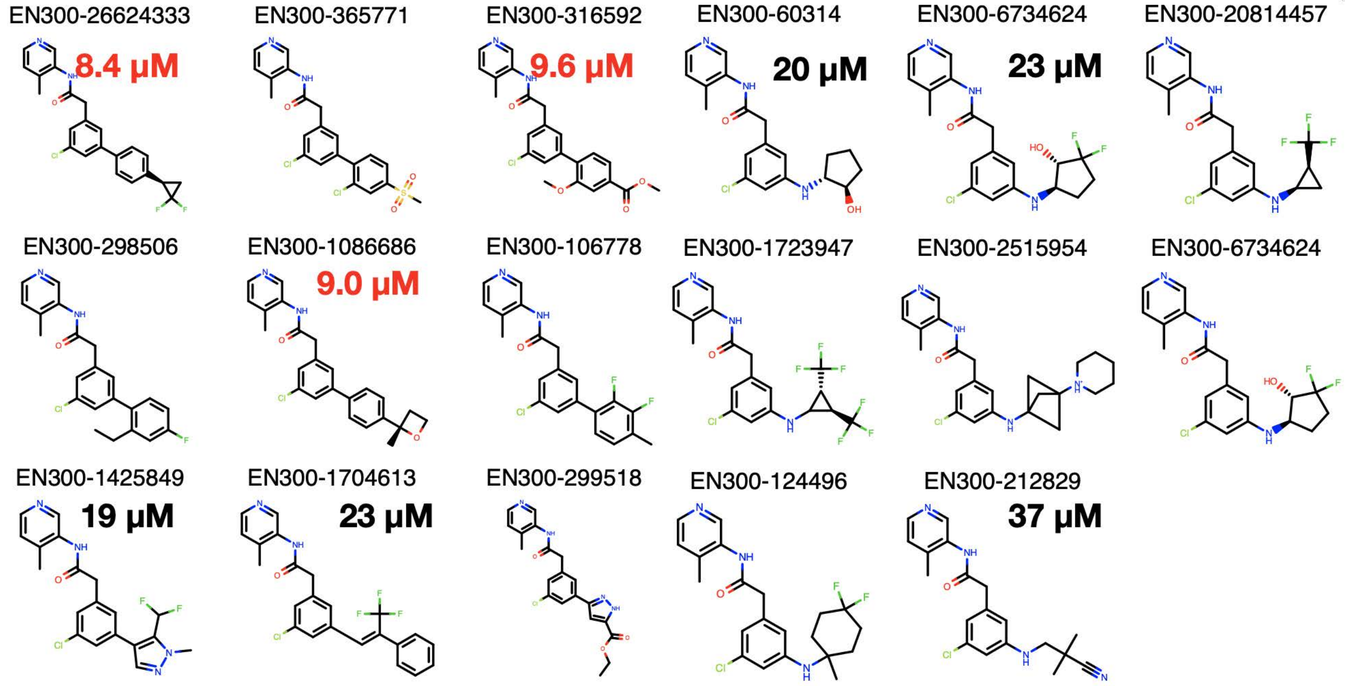
https://registry.opendata.aws/foldingathome-covid19/
https://covid.molssi.org//org-contributions/#folding--home

EVEN LARGE TRANSFORMATIONS WERE SUCCESSFUL IN IDENTIFYING MORE POTENT COMPOUNDS

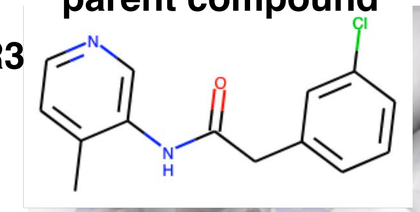
Can we engage S4 from this 5,000-compound virtual synthetic library varying R3



Top free energy calculation compounds and experimental affinity measurements:

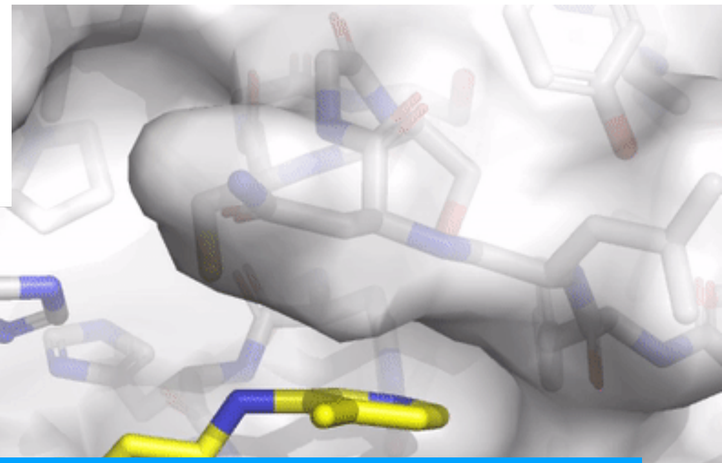


parent compound



IC_{50} = 25 μM

TRY-UNI-714a760b-6



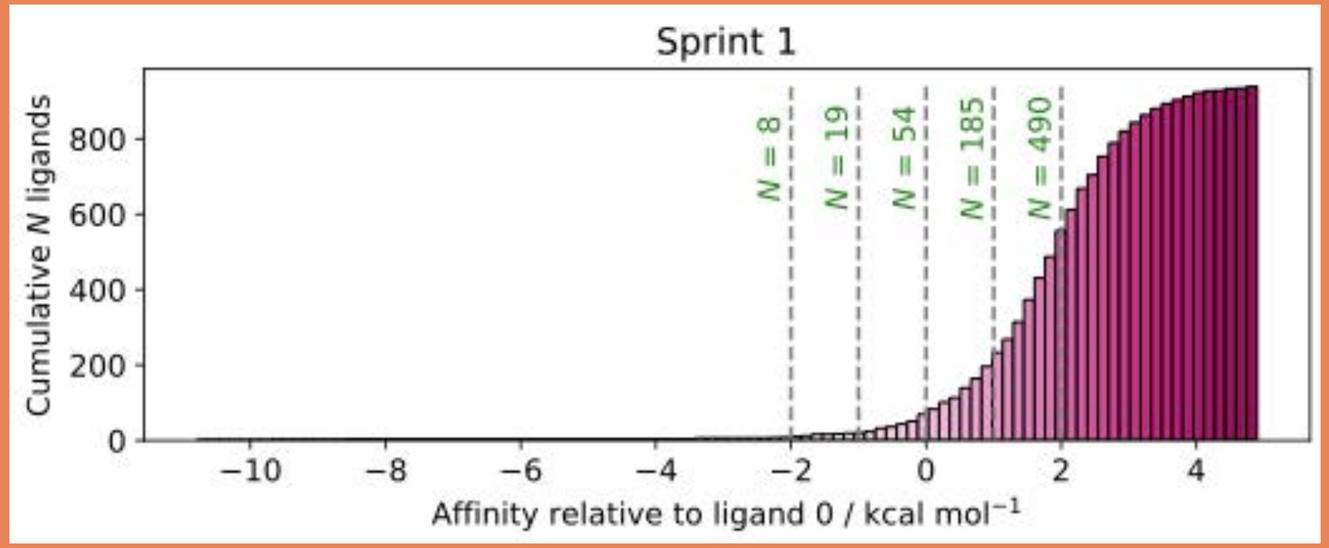
Important lesson from the first sprint:

It's useful to filter out designs that your chemists would not want to progress! There's no point to making more potent compounds that aren't going to advance the project.

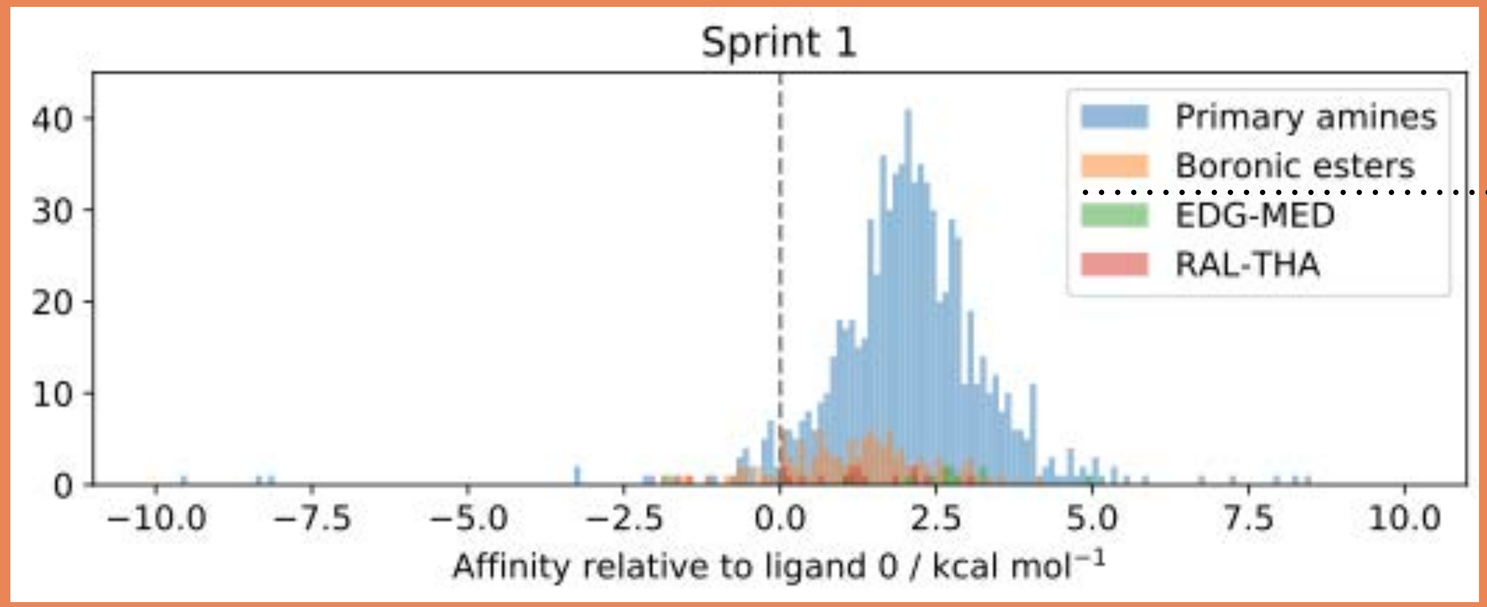
COVID Moonshot: [Moonshot] [Fragalysis] [Dashboard]

Most ideas were bad ideas

better **worse**



Human chemists are better, but limited in the number of designs they can evaluate



computer

humans

There is a clear advantage to combining human design with automated assessment of everything else we can make from the same common synthetic intermediates.

This would make a great Orion floe!

WE SET UP A DASHBOARD TO PROVIDE A REAL-TIME LEADERBOARD

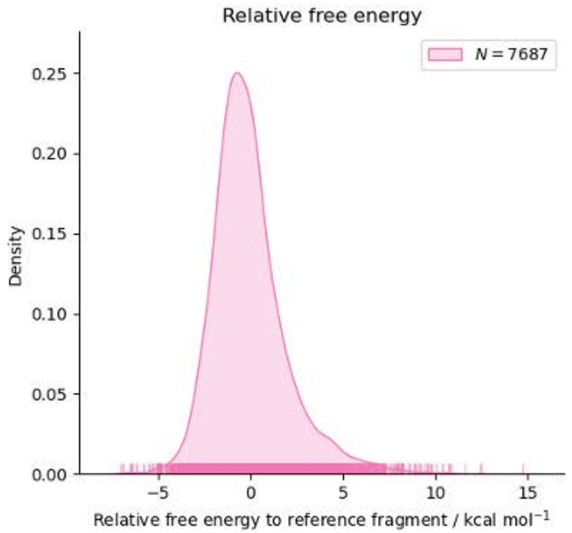
Description

COVID Moonshot Sprint 5 for benzopyran-isoquinoline series retrospective based on x11498 (MAT-POS-b3e365b9-1) to optimize substituents in the P1' pocket with Mpro dimer and neutral Cys145:His41 catalytic dyad

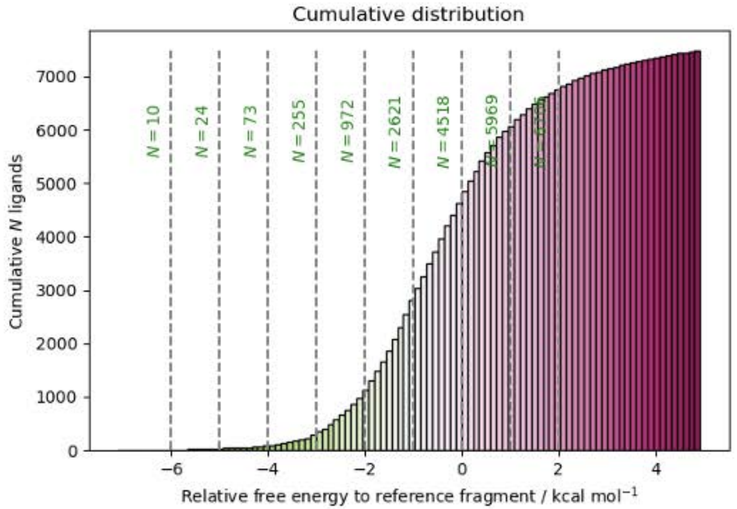
Progress

98.25%

Distributions



Updated 2021-02-21T21:35:59.343106+00:00



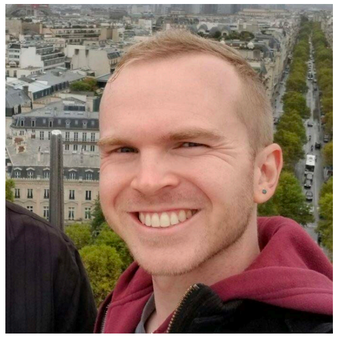
Updated 2021-02-21T21:35:59.343106+00:00

Leaderboard

Rank	Compound		SMILES	ΔG / kcal mol⁻¹	pIC50
1	VLA-UNK-83c3754c-1		c1ccc2c(c1)cncc2N3C(=O)[C@@]4(COc5c4cc(cc5)Cl)NC3=O	−15.9 ± 0.2	11.6 ± 0.2
2	ADA-UCB-dc2b944c-1		c1ccc2c(c1)cncc2N3C(=O)CN([C@@]4(C3=O)CCOc5c4cc(cc5)Cl)CC6CCCCC6	−15.5 ± 0.3	11.3 ± 0.2

Matthew Wittmann

David Dotson



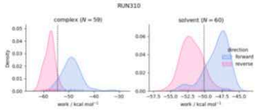
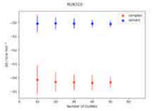
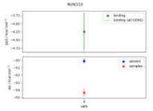
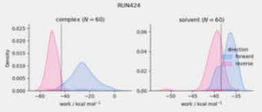
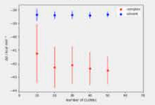
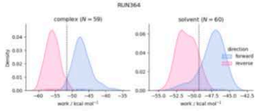
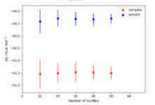
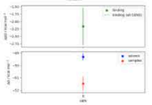
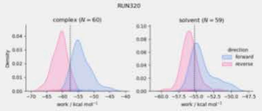
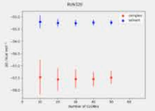
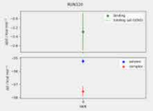
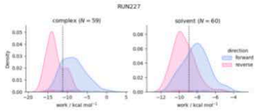
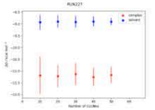
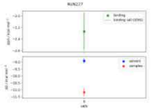
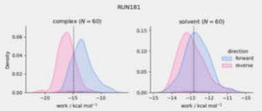
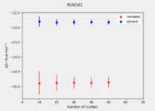
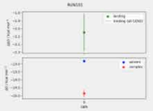
dashboard: https://fah-public-data-covid19-moonshot-sprints.s3.us-east-2.amazonaws.com/dashboards/sprint-5-dimer/sprint-5-dimer-x11498-dimer-neutral/index.html

WE CAN ALSO INSPECT INDIVIDUAL TRANSFORMATIONS AND MAPS

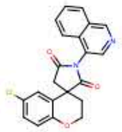
COVID Moonshot Sprint 11 | Summary | Compounds | Microstates | Transformations | **Reliable Transformations** | Retrospective Transformations | Retrospective Compounds

Reliable Transformations

Showing 1 through 100 of 100

RUN	Atom map	Initial microstate		Final microstate		ΔΔG / kcal M^{-1}	Work distribution	Bootstrapping	Convergence
RUN310	map	VLA-UCB-50c39ae8-2_1	pdb	MAT-POS-c2d406ed-1_2	pdb	−4.0 ± 0.3			
RUN424	map	VLA-UCB-50c39ae8-2_1	pdb	LUO-POS-b5068a05-1_2	pdb	−3.4 ± 0.5			
RUN364	map	VLA-UCB-50c39ae8-2_1	pdb	MAT-POS-c2d406ed-2_2	pdb	−2.5 ± 0.3			
RUN320	map	VLA-UCB-50c39ae8-2_1	pdb	MAT-POS-c2d406ed-1_1	pdb	−2.5 ± 0.2			
RUN227	map	VLA-UCB-50c39ae8-2_1	pdb	VLA-UNK-f702bf1c-5_1	pdb	−2.3 ± 0.2			
RUN181	map	VLA-UCB-50c39ae8-2_1	pdb	VLA-UNK-f702bf1c-6_1	pdb	−2.2 ± 0.1			

POTENT HUMAN CHEMIST DESIGNS SOMETIMES UNEXPECTEDLY FLOAT TO THE TOP

7	BEN-BAS-c2bc0d80-6		c1ccc2c(c1)cncc2N3C(=0)CC4(C3=0)CC0c5c4cc(cc5)Cl

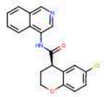
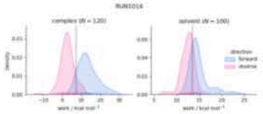
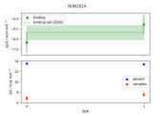
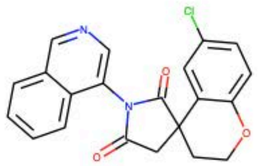
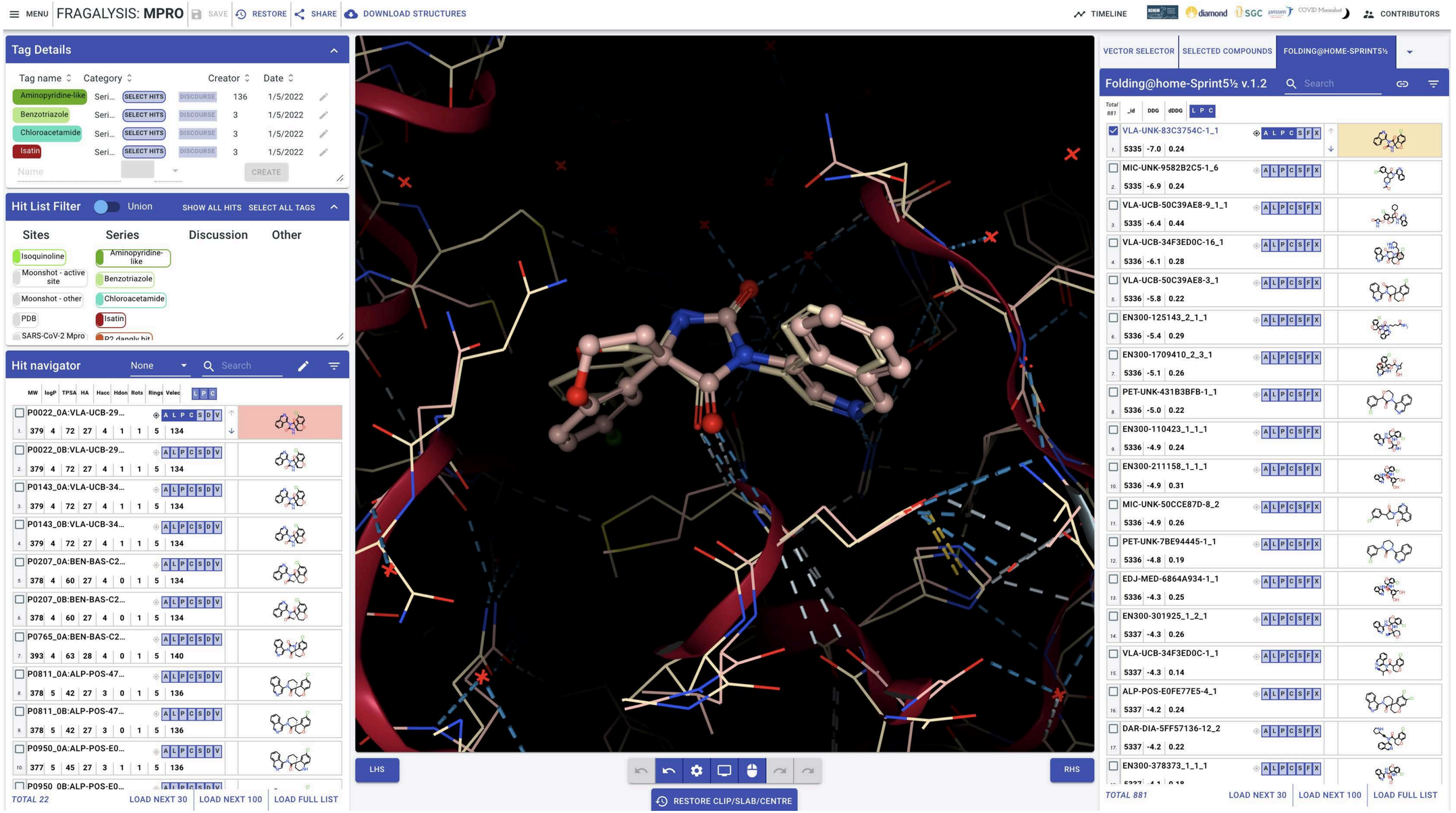
RUN1014	MAT-POS-b3e365b9-1_1		sdf	pdb	BEN-BAS-c2bc0d80-6_1		sdf	pdb	−6.2 ± 0.2	 

Image	Molecule	IC50 Curves	IC50 (µM) - Fluorescence
	BEN-BAS-c2bc0d80-6 O=C1CC2(CC0c3ccc(Cl)cc32)C(=O)N1c1cncc2ccccc12 3-aminopyridine-like Assayed Check Availability on Manifold	Fluorescence RapidFire	0.49

dashboard: https://tinyurl.com/fah-sprint-5-dimer
Fragalysis viewer: https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro

IT'S SURPRISING HOW WELL POSES CAN BE PREDICTED



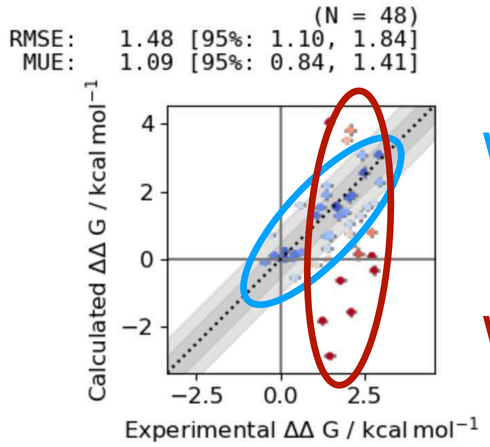
dashboard: https://tinyurl.com/fah-sprint-5-dimer

Fragalysis viewer: https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro

https://fragalysis.diamond.ac.uk/viewer/react/projects/1264/924

RAPID CYCLES OF PREDICTION AND POSTMORTEM GENERATES ACTIONABLE INSIGHTS AT AN INCREDIBLE PACE

Retrospective Transformations



Well-predicted transformations

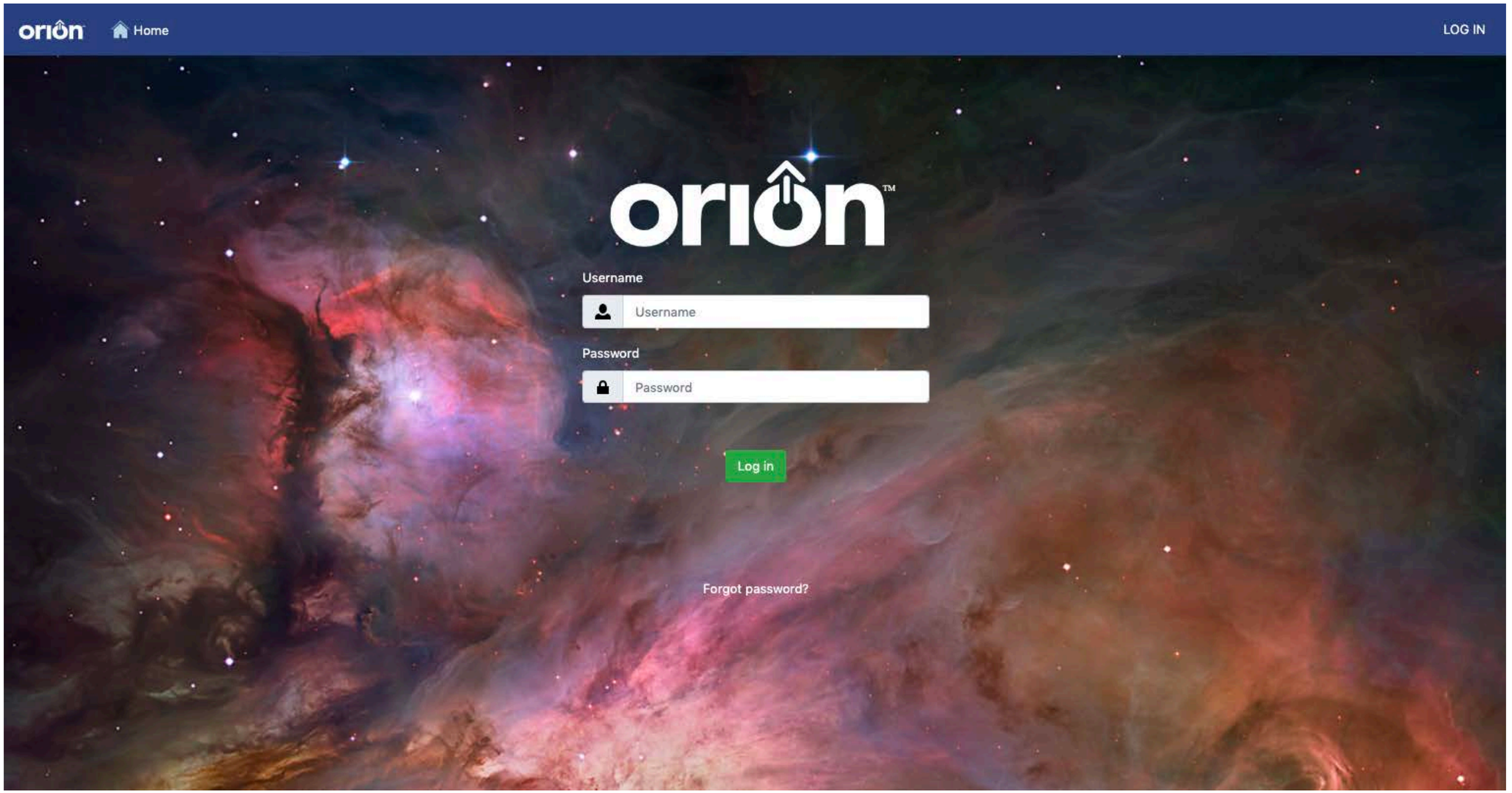
WTF? All modifications of P1 substituent pKa => **His163 is accepting H-bond, not donating!**

Fuck, now we need constant-pH free energy calculations.

Showing 1 through 48 of 48

RUN	Initial microstate			Final microstate			ΔΔG / kcal M^{-1}	ΔΔG$_{exp}$ / kcal M^{-1}	|ΔΔG-ΔΔG$_{exp}$| / kcal M^{-1}	Work distribution	Convergence
RUN52	ADA-UCB-6c2cb422-1_1	sdf	pdb	JAN-GHE-5a013bed-2_1	sdf	pdb	−2.9 ± 0.1	1.5 ± 0.2	4.3 ± 0.2		
RUN711	ADA-UCB-6c2cb422-1_1	sdf	pdb	PET-UNK-b1ef24dc-1_1	sdf	pdb	−1.6 ± 0.1	2.1 ± 0.2	3.6 ± 0.2		
RUN300	ADA-UCB-6c2cb422-1_1	sdf	pdb	EDJ-MED-c8e7a002-4_1	sdf	pdb	−0.3 ± 0.2	2.8 ± 0.2	3.1 ± 0.2		

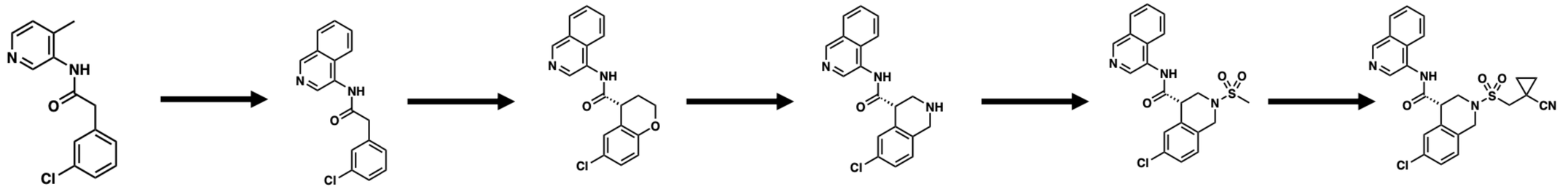
WE'RE WORKING TO MAKE THESE TOOLS AVAILABLE IN ORION



SUCCESSIVE ROUNDS OF MEDICINAL CHEMISTRY PRODUCED POTENT MPRO INHIBITORS WITH ANTIVIRAL ACTIVITY

P1

P2

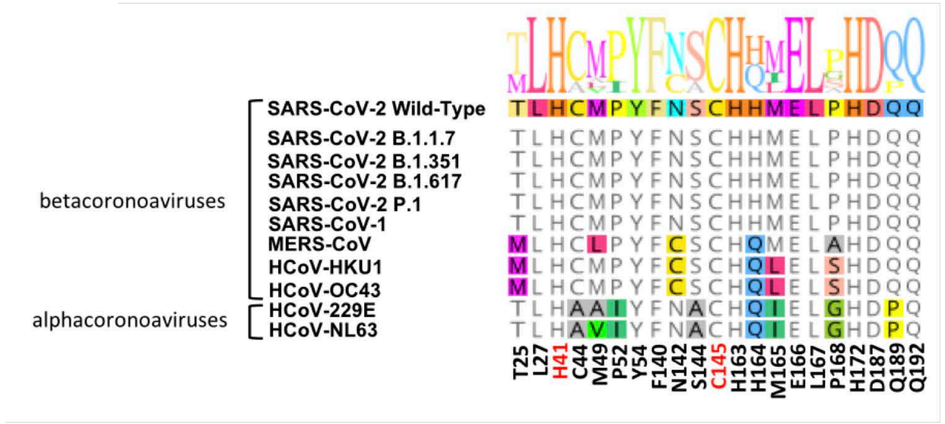


	TRY-UNI-714a760b-6	ADA-UCB-6c2cb422-1	MAT-POS-b3e365b9-1	MAT-POS-3ccb8ef6-1	MAT-POS-e194df51-1	MAT-POS-e194df51-1
IC_{50}(Mpro)/uM	25	0.73	0.21	0.28	0.141	0.037
EC_{50}(SARS-CoV-2, A549)/uM	n.d.	4.5	7.0	1.9	1.65	0.064

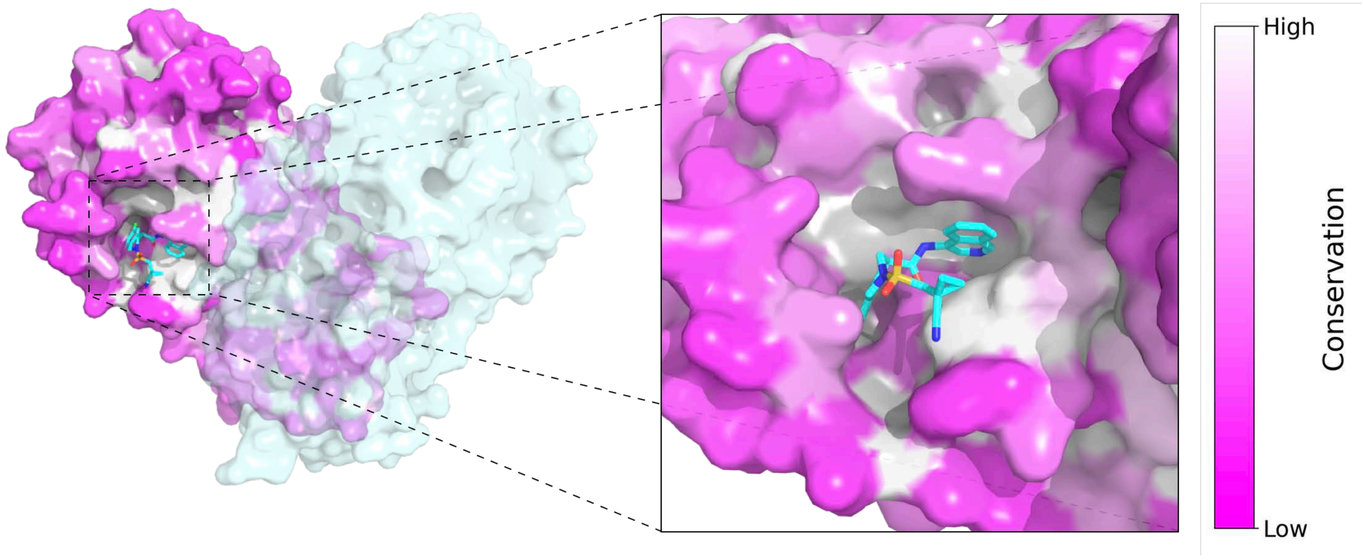
crowdsourced
merged fragment hit

OUR INHIBITORS ARE SMALL, NONCOVALENT, AND ENGAGE HIGHLY CONSERVED RESIDUES

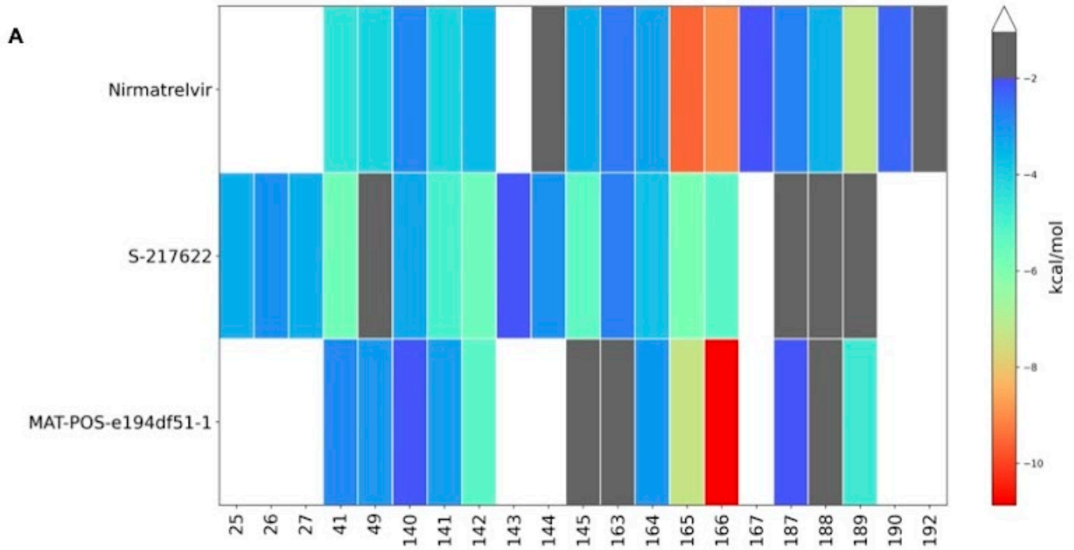
active-site residue conservation
of pathogenic coronaviruses

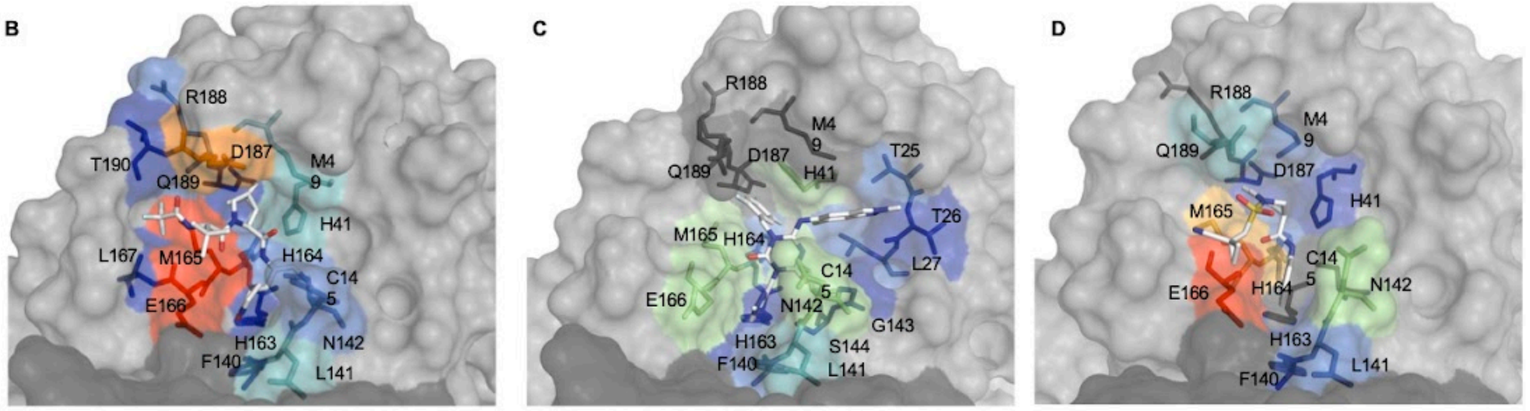


residue conservation
mapped onto Mpro structure



OUR INHIBITOR IS SMALL, NONCOVALENT, AND ENGAGE HIGHLY CONSERVED RESIDUES, PRESENTING A DIFFERENTIATED RESISTANCE PROFILE TO PAXLOVID AND THE SHIONOGI MPRO INHIBITOR



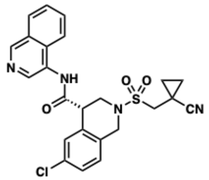


nirmatrelvir (Paxlovid)
Pfizer

S-217622
Shionogi
(modeled from figure)

MAT-POS-e194df51-1
COVID Moonshot

THE FIRST COMPOUND TO MEET OUR MEDICINAL CHEMISTRY TARGET PRODUCT PROFILE HAS ACHIEVABLE HUMAN DOSE PREDICTIONS



MAT-POS-e194df51-1

Antiviral efficacy				
Mpro IC50 /uM		0.037		
A549 IC50 /uM		0.064		
In vitro ADME				
LogD [measured]		2.5		
MDCK-LE FA (%)		92.9		
	Rat	**Dog**	**Minipig**	**Human**
Liver microsomes Cl ul/min/kg	604	164	542	152
Liver microsomes t ½ (min)	2.4	8.5	2.6	9.1
Heps Cl ul/min/kg	67.6	61.4	65.9	10.3
Heps t ½ (min)	10.3	11.3	10.5	67.5
PPB free fraction (%)	5.4			10.1
Safety / Drug-drug interactions				
Cyp450 (uM) 2C9/2D6/3A4		25/9.4/10.3		
PXR risk		Low		
Herg (uM)		>30		
In vivo pharmacokinetics				
Rat IV Vd (l/kg)	1.05			
Rat IV CL	34.8			
Rat t ½ IV/PO (h)	0.448 / 1.4			
Rat Bioavailability (%)	18			

human dose projections of 100-350 mg t.i.d.

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

bioRxiv posts many COVID19-related papers. A reminder: they have not been formally peer-reviewed and should not guide health-related behavior or be reported in the press as conclusive.

New Results

Follow this preprint

Open Science Discovery of Oral Non-Covalent SARS-CoV-2 Main Protease Inhibitor Therapeutics

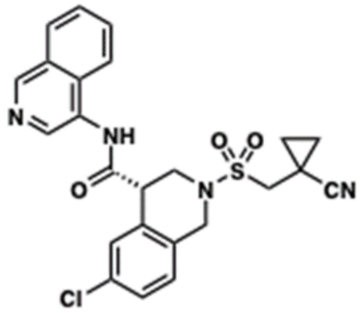
https://doi.org/10.1101/2020.10.29.339317

(updated Mon 31 Jan)

Over 180 contributors/authors:
https://tinyurl.com/covid-moonshot-authors

We're still actively pursuing multiple backups to enter an accelerated preclinical program

THIS COMPOUND HAS EXCELLENT ANTIVIRAL ACTIVITY AGAINST ALL VARIANTS



MAT-POS-e194df51-1

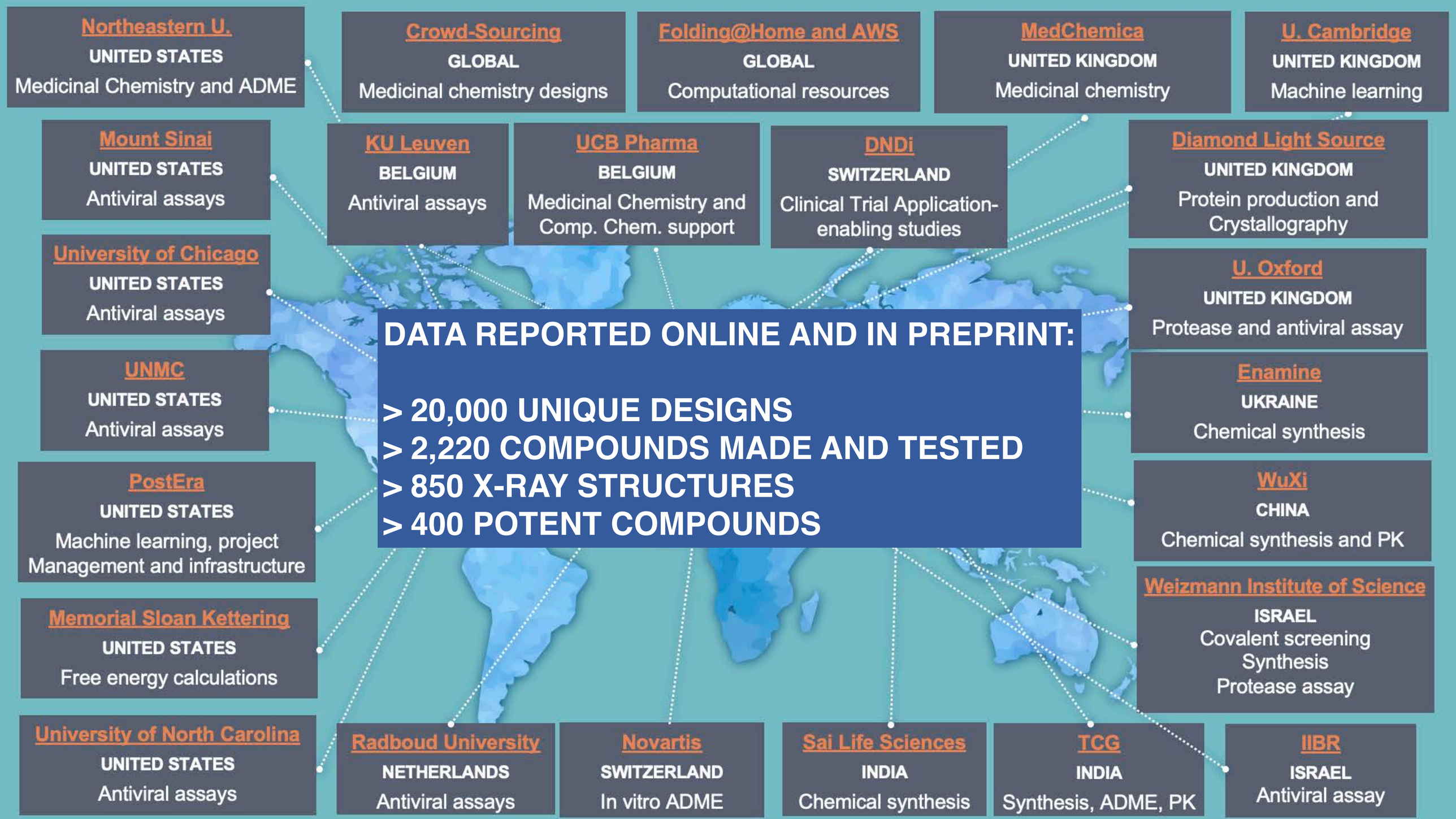
37 nM SARS-CoV-2 Mpro IC_{50} (enzymatic)
64 nM SARS-CoV-2 antiviral EC_{50} (A549 cells)

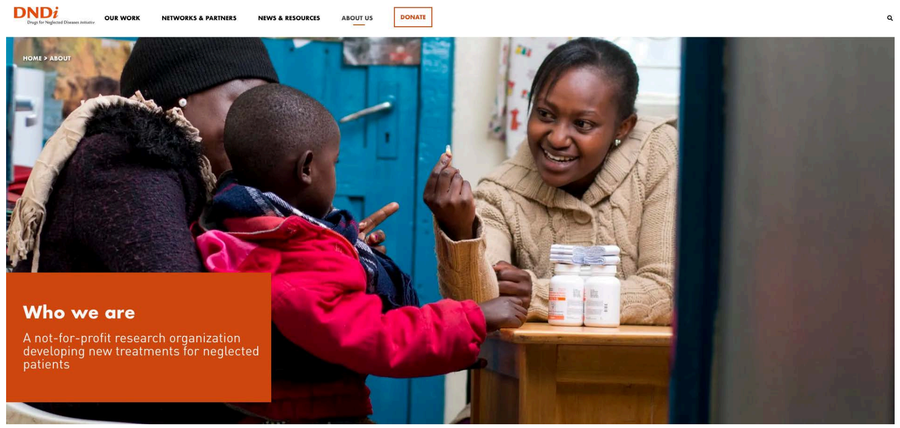
	MAT-POS-e194df51-1		Nirmatrelvir	
	IC50	CC50	IC50	CC50
Alpha variant (B.1.1.7.	0.38	>20	0.12	>10
Beta variant (B.1.351)	1.48	>20	0.21	>10
Delta variant (B.1.617.2)	1.52	>20	0.21	>10
Omicron variant (B.1.529)	0.29	>20	0.07	>10
MA-SARS-CoV-2/WA1	0.43	>20	0.14	>10

(micromolar)

CPE assay in HelaACE2 cells

https://doi.org/10.1101/2020.10.29.339317


Northeastern U.
UNITED STATES
Medicinal Chemistry and ADME
Crowd-Sourcing
GLOBAL
Medicinal chemistry designs
Folding@Home and AWS
GLOBAL
Computational resources
MedChemica
UNITED KINGDOM
Medicinal chemistry
U. Cambridge
UNITED KINGDOM
Machine learning
Mount Sinai
UNITED STATES
Antiviral assays
KU Leuven
BELGIUM
Antiviral assays
UCB Pharma
BELGIUM
Medicinal Chemistry and Comp. Chem. support
DNDi
SWITZERLAND
Clinical Trial Application-enabling studies
Diamond Light Source
UNITED KINGDOM
Protein production and Crystallography
University of Chicago
UNITED STATES
Antiviral assays
U. Oxford
UNITED KINGDOM
Protease and antiviral assay
UNMC
UNITED STATES
Antiviral assays
Enamine
UKRAINE
Chemical synthesis
DATA REPORTED ONLINE AND IN PREPRINT:
> 20,000 UNIQUE DESIGNS
> 2,220 COMPOUNDS MADE AND TESTED
> 850 X-RAY STRUCTURES
> 400 POTENT COMPOUNDS
PostEra
UNITED STATES
Machine learning, project Management and infrastructure
WuXi
CHINA
Chemical synthesis and PK
Weizmann Institute of Science
ISRAEL
Covalent screening
Synthesis
Protease assay
Memorial Sloan Kettering
UNITED STATES
Free energy calculations
University of North Carolina
UNITED STATES
Antiviral assays
Radboud University
NETHERLANDS
Antiviral assays
Novartis
SWITZERLAND
In vitro ADME
Sai Life Sciences
INDIA
Chemical synthesis
TCG
INDIA
Synthesis, ADME, PK
IIBR
ISRAEL
Antiviral assay



COVID Moonshot funded by COVID-19 Therapeutics Accelerator to rapidly develop a safe, globally accessible and affordable antiviral pill

GENEVA / OXFORD / NEW YORK / TEL AVIV — 27 SEP 2021

The COVID Moonshot, a non-profit, open-science consortium of scientists from around the world dedicated to the discovery of globally affordable and easily-manufactured antiviral drugs against COVID-19 and future viral pandemics has received key funding of £8 million from Wellcome, on behalf of the Covid-19 Therapeutics Accelerator.

'*Faced with global vaccine inequality and the rapid spread of variants of concern, the need for easily-accessible antiviral therapeutics to treat people with COVID-19 is as pressing as ever, especially in low- and middle-income countries*,' said Annette von Delft, Translational Scientist at the University of Oxford and NIHR Oxford Biomedical Research Centre.

'*Most of the research and funding efforts early in the pandemic focused predominantly on repurposing of existing small molecule drugs and the more rapid development of novel monoclonal antibodies. Now, with the realization that COVID-19 will be a global issue for the foreseeable future we urgently need to develop novel antiviral therapeutics. We are therefore thrilled to receive this critical funding from Wellcome and hope it can lead to more support*,' said Alpha Lee, Chief Scientific Officer at PostEra and Faculty Member at the University of Cambridge.

The Moonshot started as a spontaneous virtual collaboration in March 2020. As countries locked down, a group of scientists, academics, pharmaceutical research teams and students began a worldwide, twitter-fuelled race against the clock to identify new molecules that could block SARS-CoV-2 infection and develop pills that would be readily available to the most vulnerable communities.

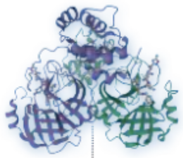
Ultimately more than 150 scientists – including dozens of students who put their own projects on hold – joined Moonshot to crowdsource ideas for molecular compounds, model them and evaluate them in-vitro against the virus. Their goal: a safe, globally affordable, not-for-profit oral treatment for COVID-19 and related viral pandemics.

https://dndi.org/press-releases/2021/covid-moonshot-funded-by-wellcome-to-rapidly-develop-safe-globally-accessible-affordable-antiviral-pill/

WE WENT FROM FRAGMENT SCREEN TO PRECLINICAL PHASE IN JUST 18 MONTHS, SPENDING LESS THAN $1M

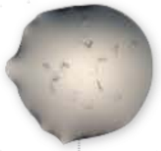
Feb 14 2020

Main protease cloned and produced at Diamond



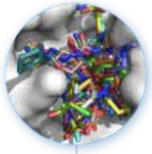
Feb 20 2020

Atomic resolution structure of the protease determined



Mar 5 2020

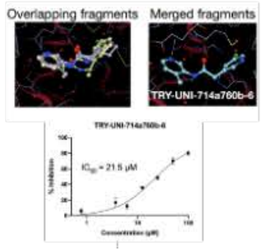
1,500 crystals collected in one day



Mar 7 2020

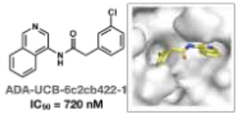
78 fragment-bound structures solved and released to the web

48 covalent fragments
71 active site fragments



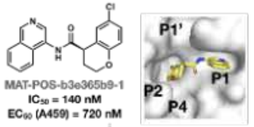
Mar 17 2020

Registration of the hit designed using a fragment merge strategy



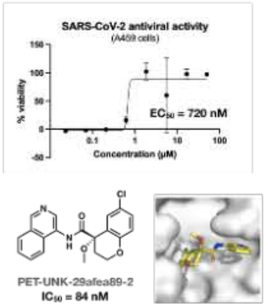
Jul 19 2020

First nM inhibitor in the series



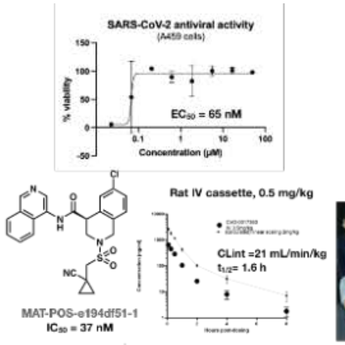
Aug 08 2020

First compound with measurable antiviral activity



Feb 02 2021

First compound with sub nM antiviral activity



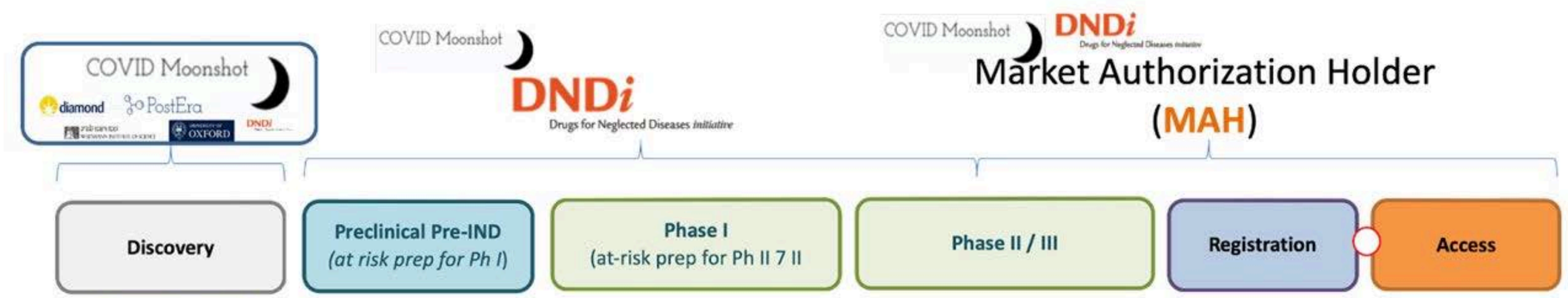
Jun 9 2021

First compound with sub nM antiviral activity and acceptable rodent PK

Jul 1 2021

Wellcome Trust/ ACTA announces $11m funding to The COVID Moonshot for IND-enabling studies

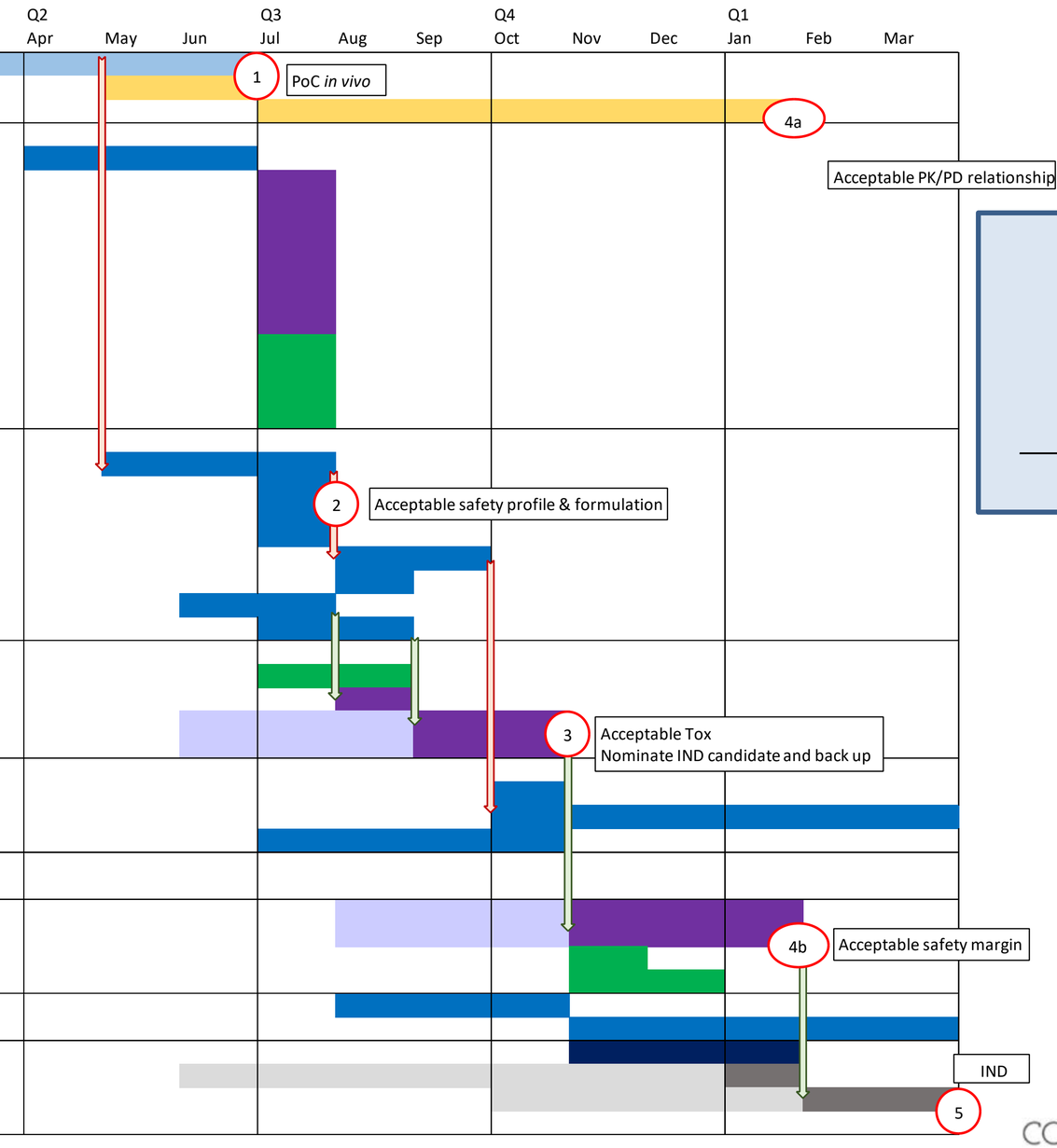
WE'RE AIMING TO BRING AN ANTIVIRAL TO MANUFACTURE WITH MINIMAL OR NO IP



We have a path to go "straight to generics" (potentially entirely free of patents)
to enable true, low-cost global access to meet the needs of underserved LMICs

Getting to Investigational New Drug (IND) approval in <1 year is complex and expensive

			No/cmpds
Preparation of regulatory phase			
WP 1	**Identify up to 5 optimized leads**	Medicinal Chemistry	
		Efficacy	
		Efficacy vs PK/PD	
WP2	**Build Optimized Lead profile package**	**5 compounds**	
		Compound synthesis at risk for WP2 (5-10g)	at risk
		In Silico DEREK / UCB D2P2	5
	pure sample compound	Safety pharmacology (Ames, Genotox)	5
		Hepatotoxicity cellular assay	5
		Patch clamp cardiomyocytes	5
		Safety 44 panel receptor binding panel	5
		Check CNS exposure - initial assessment (Irwin test)	5
		Acceptable drug interaction profile (CYP, TDI)	5
		ADME for human dose prediction	5
		Multi-dosing study (rat)	5
		Multi-dosing study (dog)	5
		Ascending dose study (rat)	5
WP3	**Optimized lead scale-up**	**5 compounds**	
		Process chemistry assessment of scale up feasibility	at risk 5
		Formulation assessment	5
		Formulation for PK	5
		2-3 compounds	
		Formulation Phase 1	3
		Forced degradation study	3
		Compound synthesis for 7 day tox	at risk 5
		Compound synthesis for DRF pilot toxicology	at risk 5
WP4	**Exploratory toxicology**	**2-3 compounds**	
		Bioanalysis validated (ICH), rat, dog, human	3
		7 d ascending dose (non GLP) tox rat	3
		Dose Range Finding (DRF) pilot toxicology - rat	3
		Dose Range Finding (DRF) pilot toxicology - dog	3
WP5	**Large-scale synthesis/stability**	**2-3 compounds**	
		Stability in capsule	at risk 3
		Stability (3 - 6 months)	at risk 3
		Large scale synthesis for GLP tox	at risk 5
Regulatory phase		**1 compound (and back-up)**	
WP6	GLP toxicology and safety	GLP tox - 1 month dog (assume 5 days dosing)	1
		GLP tox - 1 month rat (assume 5 days dosing)	1
		Acceptable PK (with a validated bioanalytical method) rat/dog GLP	1
		PK scaling and Dose to Human prediction	1
WP7	GMP manufacture	GMP manufacture feasibility	at risk 3
		GMP manufacture	1
WP8	Regulatory assessments	Develop clinical endpoints	1
		Regulatory assessments	1
		Clear IND regulatory path	1
		HPOC/CPOC plan is acceptable to regulatory agency	1



$/milestone	
1	570000
2	607500
3	995000
4	1085000
5	1710000
	4967500 Total

Efficacy
CMC
Pharmacokinetics
Regulatory
Clinical
Safety

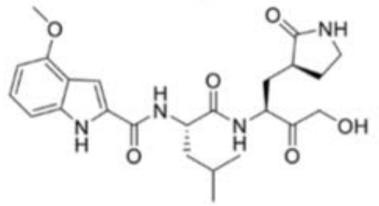
COVID Moonshot

PFIZER DEVELOPED THEIR IV MPRO INHIBITOR INTO AN ORAL ANTIVIRAL IN RECORD TIME

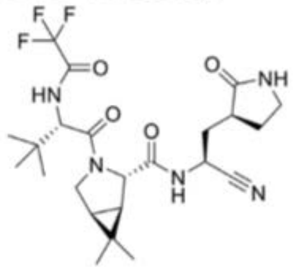
intravenous antiviral
(clinical trials paused)

paxlovid oral antiviral
(co-dosed with ritonavir as bait for CYPs)

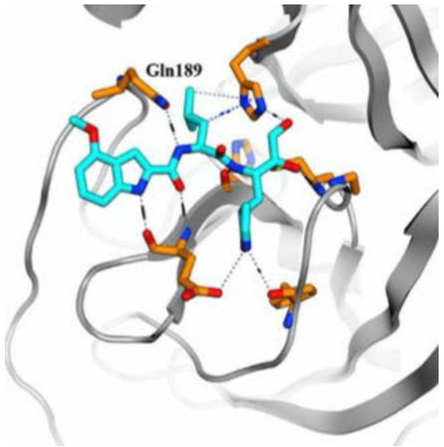
1 (PF-00835231)



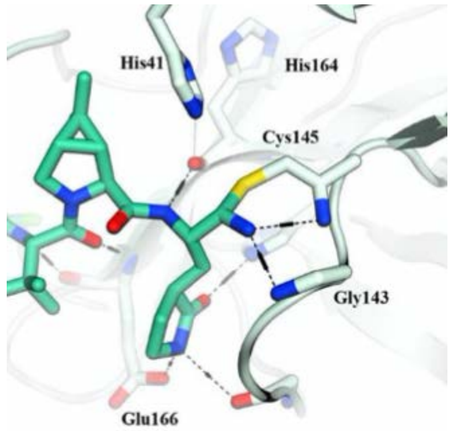
6 (PF-07321332)



350 people
roughly $1B
11 months from start to clinic
clinical trials Mar-Nov 2021



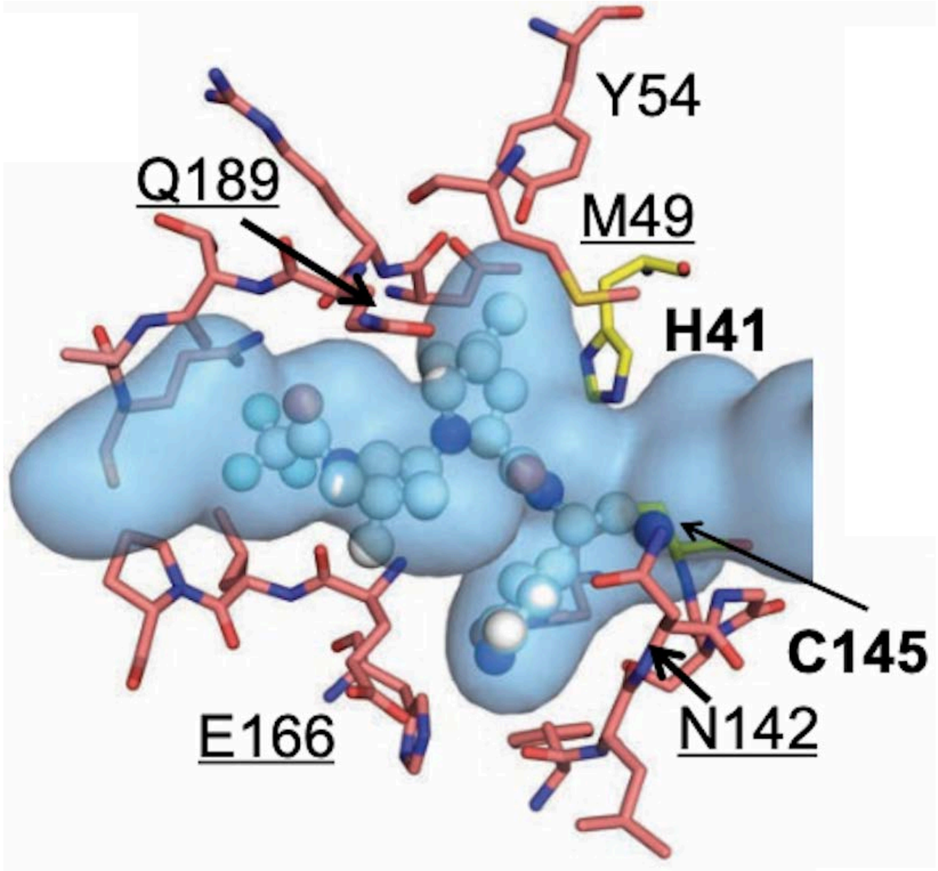
Ki 0.3 [0.2, 0.5] nM
EC50 230 [160, 340] nM (VeroE6)
1.4% oral bioavailability



Ki 3 [1,7] nM
EC50 75 [66,83] nM (VeroE6)
50% oral bioavailbility

https://www.science.org/doi/10.1126/science.abl4784

WE STILL NEED MORE THAN ONE ORAL ANTIVIRAL



Defining the Substrate Envelope of SARS-CoV-2 Main Protease to Predict and Avoid Drug Resistance

Ala M. Shaqra, Sarah Zvornicanin, Qiu Yu Huang, Gordon J. Lockbaum, Mark Knapp, Laura Tandeske, David T. Barkan, Julia Flynn, Daniel N.A. Bolon, Stephanie Moquin, Dustin Dovala, Nese Kurt Yilmaz, Celia A. Schiffer

doi: https://doi.org/10.1101/2022.01.25.477757

https://www.biorxiv.org/content/10.1101/2022.01.25.477757v1

4 CONTRAINDICATIONS

PAXLOVID is contraindicated in patients with a history of clinically significant hypersensitivity reactions [e.g., toxic epidermal necrolysis (TEN) or Stevens-Johnson syndrome] to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

PAXLOVID is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions *[see Drug Interactions (7.3)]*:

- Alpha$_1$-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, piroxicam, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

PAXLOVID is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. PAXLOVID cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer *[see Drug Interactions (7.3)]*:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

EUA contains **seven pages** of drug-drug interactions, leaving a significant vulnerable untreated population

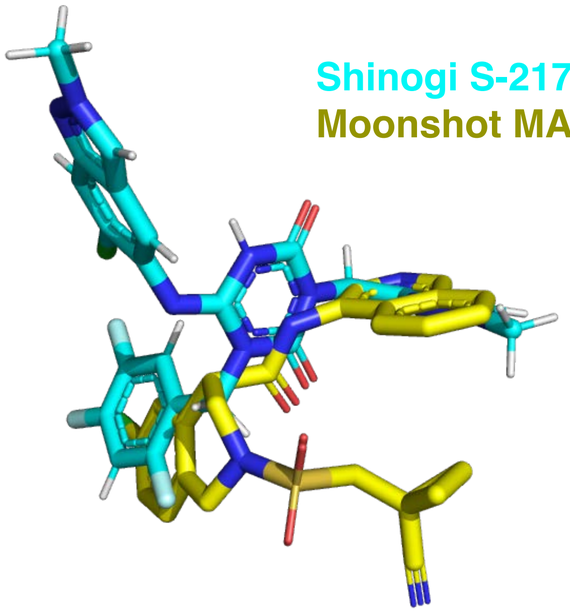
FDA Paxlovid Emergency Use Authorization
https://www.fda.gov/media/155050/download

SHINOGI RECENTLY REPORTED THE DISCOVERY OF S-217622, DISCOVERED WITH THE HELP OF MOONSHOT DATA

COVID Moonshot molecules and X-ray structures informed pharmacophore used to identify compound in internal collection for pain program

Rapidly developed into potent antiviral with extraordinary PK (one pill/day!)

Currently in Phase 3 trials with readout expected soon



Shinogi S-217622
Moonshot MAT-POS-e194df51-1

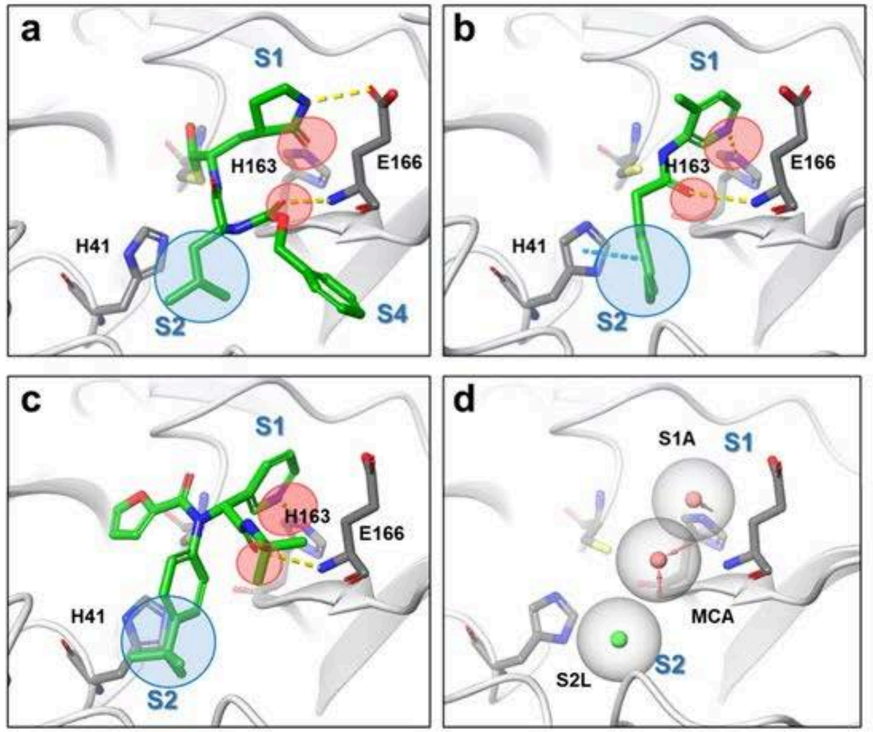


Figure 2. Binding modes of 3CL^{pro} inhibitors, their pharmacophores, and defined pharmacophore filters for virtual screening. (a) Crystal structures of GC376 (PDB: 6WTT), (b) 3-aminopyridine-like compound of the Postera COVID moonshot project (PDB: 5RH2) and (c) ML188 (PDB: 7L0D). The common H-bond acceptors are circled in red; the common hydrophobic pharmacophores are circled in blue. (d) Common pharmacophores shared with inhibitors A–C. Red and green spheres represent H-bond acceptors and lipophilic features, respectively.

https://www.biorxiv.org/content/10.1101/2022.01.26.477782v1

THE ONLY REASON WE DIDN'T HAVE ANTIVIRALS FOR SARS-COV-2 WAS DUE TO MARKET FAILURE

Comment

A white-knuckle ride of open COVID drug discovery

Frank von Delft, John Chodera, Ed Griffen, Alpha Lee, Nir London, Tatiana Matviuk, Ben Perry, Matt Robinson, Mark Calmiano & Annette von Delft

In early 2020, a spontaneous global collaboration came together to design a new, urgent antiviral treatment. There are lessons in what happened next.

Nearly 15 months ago, a large, fast-moving and unscheduled experiment began: probing a key protein of the coronavirus SARS-CoV-2 to find chemical starting points for drug discovery. The end point was to develop pills that people could take to treat COVID-19 and related diseases.

This experiment pulled together a spontaneous, open, global, Twitter-fuelled collaboration called the COVID Moonshot. Urgency and a commitment to working openly recruited more than 150 active participants, spanning a huge range of expertise and technology across academia, biotechnology, pharmaceuticals and more, all working without claiming intellectual property. Open drug-discovery efforts are invariably super slow — ours has been an express train on tracks we have laid down as we go. It is a way of working that none of us realized was possible.

The intention for the original experiment was simply to help jump-start large drug-discovery initiatives that could draw directly on our data. In those first weeks, before the pandemic had taken hold in the United Kingdom or Israel (where the experiment started), we expected that some international effort was already in the works for countries and companies to collaborate on finding COVID-19 treatments, as was happening with vaccines.

Disappointingly, from the start of the COVID-19 fight, international funders decided to support only the development of repurposed small-molecule drugs and monoclonal antibodies to deliver treatments quickly, neglecting other approaches. The world seemed to give up on new antivirals before they even started, agreeing on a self-fulfilling prophesy that such drugs would take years to develop. Few seemed willing to contemplate such a timescale for this pandemic. Our first grant proposal was rejected, so we had to find a different way to press on.

Amazing virtual collaborations sprang up around the pandemic in many fields: bioinformaticians and phylogeneticists worked out ways to track new variants. Epidemiologists and computer modellers ran simulations. The World Health Organization activated a network of experts to vet new publications and preprints. Military personnel transported medical equipment and vaccines, and set up community testing centres.

Our COVID Moonshot is different. Rather than engaging with patients while using personal protective equipment, we work in chemistry hoods and with spectrometers, X-rays, computer models and courier companies. It's driven by a conviction that conventional wisdom is wrong about *de novo* drug discovery being a job only for big pharma and peripheral to a fast-moving global outbreak: the pandemic is still here, and antiviral drugs against COVID-19 are not.

The screens

Drug-discovery efforts generally require a target, such as a protein that has an important role in disease. Promising drug compounds bind to the protein, affect its function and act safely in the body. Diamond Light Source near Oxford is the UK national synchrotron — a particle accelerator essential for modern X-ray crystallography, the go-to technique for determining 3D structures of proteins. There, one of us (F.v.D.) leads the XChem facility that uses the technique to screen for very small compounds called fragments that bind to drug targets. Although these 'fragment hits' bind weakly and the throughput is low compared with other techniques (screening fewer than 1,000 compounds per experiment), the 3D structures show exactly how each fragment binds. This provides powerful clues about how to create bigger, more potent molecules.

By late January 2020, scientists in China had solved the first 3D crystal structures of the SARS-CoV-2 main protease (M^{pro}), an essential viral enzyme, and made them public. With their guidance, a group at Diamond led by Martin Walsh generated new, high-quality crystals by mid-February — lightning fast for such work. The group also shipped M^{pro} protein to the Weizmann Institute of Science in Rehovot, Israel, where N.L.'s group uses mass spectrometry to quickly identify covalent fragments that attach to proteins irreversibly. This is another way to find useful starting points for drugs.

Racing to exploit the two weeks before scheduled shutdown of the synchrotron from 6 March last year, more than a dozen scientists from the Walsh, F.v.D. and N.L. groups dropped everything to complete an XChem experiment four times the normal size[1]. All the data were analysed within one month, and as soon as we had the first batch of results, we posted downloadable data and a short write-up on the Diamond web page, then tweeted the link on 7 March (see go.nature.com/3vju8vb).

The tweets

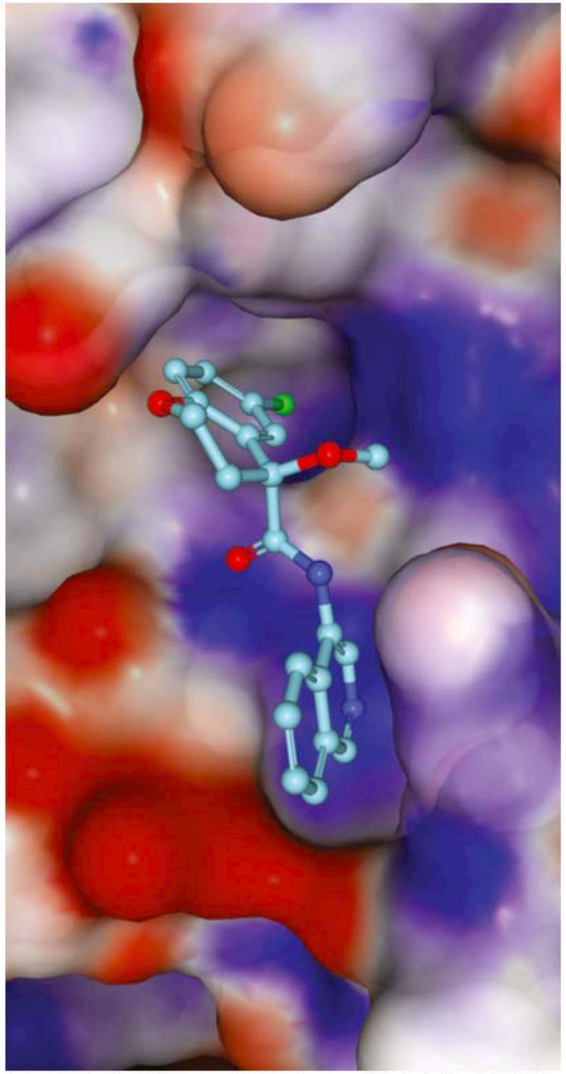
The response surprised us: almost 1,000 retweets in a week, and diverse offers for help. A.L. and M.R., two co-founders of the US–Israeli technology firm PostEra, got in touch to suggest that their machine-learning technology could propose synthetic routes to make new molecules inspired by the fragment hits. But first we needed drug-like molecules to be designed, and N.L. realized whom we could ask: medicinal chemists newly under lockdown restrictions but full of expertise and desperate to help.

The next step was a tweet to crowdsource ideas for such molecules, declaring that we would make and test the best ones. A web page built by M.R. and his team in 48 hours enabled participants to submit machine-readable suggestions for compounds. The site made clear that contributions would have no strings attached, no intellectual property and no remuneration. We expected a few hundred submissions at most — in two weeks, we had more than 4,000, and had to work out how to test them.

The experiments

From March to May last year, we were on Zoom calls almost daily, lining up collaborators, logistics, expertise, funding, institutional support and permissions. All around us, the world was shutting down. We were trying to work out how to keep ourselves, our colleagues and our families sane, and our laboratories open.

We tapped an inexhaustible wellspring of goodwill. At the Ukrainian company Enamine, T.M. convinced management to commit to doing synthesis at cost, and to handle compound logistics. Its 650 chemists made molecules to order and have a renowned collection of building blocks for quick synthesis. In early May, new compounds were being shipped weekly from Enamine to organizations in four countries, and that work continues. Two other contract research organizations, WuXi in China and Sai Life Sciences in India, pitched in with offers of chemists and discounts.



Crystal structure of a COVID Moonshot advanced compound (turquoise) in the active site of the SARS-CoV-2 main protease. The molecular surface colours show electrostatic charge.

Chris Schofield and his team at the University of Oxford, UK, together with Haim Barr and his colleagues at the Weizmann Institute, developed distinct biochemical assays that were key to cross-validating how well molecules inhibited the working M^{pro} enzyme. At the same time, for all compounds, the 3D mode of binding was assessed at Diamond in crystal structures. Half a dozen graduate students and postdocs suspended their own projects to coordinate, run and evaluate these assays, week after week. The work hasn't stopped since.

By mid-April 2020, a volunteer troop of industry-based medicinal chemists, chaired by E.G., were holding weekly meetings to scrutinize submissions, review results, discuss strategies, design molecules and coordinate with synthetic chemists at Enamine. This work continues, too.

Computational chemists assembled their own team through their own network, then met weekly to work out algorithms to rank submissions. J.C. developed new ways to use Folding@home, the world's largest crowdsourced supercomputer, which was already being used to generate models of viral proteins. It crunched 'free energy' calculations to predict the best binders for up to 10,000 compounds a week: 100 times more than had been attempted before.

Pharmaceutical companies develop elaborate information systems to track, store and analyse compounds and their associated data; our global effort urgently needed this, too. The informatics web platform CDD Vault donated us cloud space in its infrastructure just hours after a phone call, also arranging training and support. Many other vendors provided licences for free, and XChem's platform for sharing 3D data, the Fragalysis cloud, had fortunately just been released. M.R. built a back-end system that sent all data live on GitHub, which is more often used as a repository for programming code.

As the pandemic unfolded, on some calls, you could hear the ambulance sirens from half a world away. The first agenda item of every meeting was a list of participants' latest constraints — lockdowns, lab closures and home-schooling. Children made regular Zoom appearances, and at least two of us came down with COVID-19 ourselves. People pulled their weight not for glory or reward, but because there was a job that needed doing, and it was one that they could do.

To cells and live virus

By June 2020, the Zoom-based collaboration had identified sets of molecules that clearly inhibited a crucial viral protein. The next step was to test antiviral activity in living cells. These are complex experiments, requiring level-three biosafety labs certified for airborne pathogens. A.v.D., a translational clinician, coordinated a shifting coalition of groups. One virologist friend and colleague lived a 10-minute walk away, and they planned experiments on lockdown evening strolls. Other virology groups responded to our tweet for help, and offered a variety of assays. Compounds were shipped, early results trickled in and some compounds unambiguously stalled the virus. These initial successes were crucial, both scientifically and for morale.

Researchers at the Israel Institute for Biological Research near Rehovot agreed to run a single test plate once we had molecules that were sufficiently potent. When that test showed signs of drug-like activity, they worked out how to conduct regular measurements, filling a crucial gap in our testing cascade.

By September, we had reached a milestone with a chemical series that instilled confidence: the compounds inhibited enzymes at submicromolar concentrations, and blocked viral activity at single-digit micromolar concentrations.

The slog

Since then, for the past nine months, the project has entered familiar territory in medicinal chemistry: we have been tweaking and testing compound designs, and optimizing early lead molecules so that they behave like drugs — entering the blood and staying there without being toxic. Potency against the M^{pro} enzyme has improved 100-fold, as has antiviral activity, and we are honing compounds' solubility and rate of metabolism by the liver.

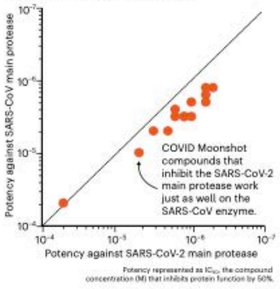
Above all, we can start predicting that these molecules will be straightforward to synthesize and will work as pills that are suitable for vaccine-hesitant or immunocompromised individuals, health-care workers and others in risky situations who could take them prophylactically. Furthermore, we expect them to work against vaccine-resistant variants: whereas vaccines target the spike protein on the virus capsule, our compounds target a conserved part of the virus machinery that works inside cells.

We've also had to deal with rejected grant proposals to advance antiviral drugs. Still, as vaccines have showed their dramatic successes, further variants have arrived and funders have begun calling urgently for antivirals and looking at how projects might be accelerated. In April this year, 16 months after the outbreak of SARS-CoV-2 in Wuhan, China, the United Kingdom finally launched a task force focusing on antivirals[2].

Pfizer's March announcement of early clinical trials for its antiviral pill is confirmation that an accelerated approach can work, and that we should persevere. Our molecules also inhibit proteins of the coronavirus that causes severe acute respiratory syndrome (SARS; see 'Missed opportunity'): had drug discovery persevered during the SARS epidemic in 2003, antiviral drugs would have been available when this pandemic hit. Above all, it has become much clearer how an antiviral would be most effective: the treatment must be readily available to everybody, long before they are hospitalized. Accordingly, we have been able to develop a clear plan for how to proceed, and the resources required.

MISSED OPPORTUNITY

Had direct-acting antivirals been developed for SARS, they would have worked for COVID-19.



Potency represented as IC_{50}, the compound concentration (M) that inhibits protein function by 50%.

We are approaching the capital-intensive, highly regulated phases of animal studies, producing kilograms of substance for clinical trials and, beyond that, worldwide manufacture and distribution of billions of pills. Our initial goal of delivering a drug straight from the discovery pipeline, free from patents and available for anyone to manufacture, cannot offer investors any conventional return on investment. Yet COVID-19 is not conventional, and vaccines have elevated the normally arcane question of intellectual property into a major political concern. Perhaps the COVID Moonshot can also shape how open drug discovery reaches patients.

> **"People pulled their weight not for glory or reward, but because there was a job that needed doing."**

The moral

So, what has made our approach work? Presumably, the fact that the mission was clear, even if distant, and the ethos was unambiguous and clearly signposted[3,4]. Initially, a few of us, fuelled by the urgency of the moment, acted on a conviction that our various combined technologies would accelerate drug discovery. We were soon joined by many people who did the hard work because they felt it was the right thing to do.

Also crucial was the existing large ecosystem of expertise and biopharma supply chains, coupled with new capabilities driven by long-term strategic investments in national infrastructure and research institutes. Tools for online collaboration have reached a critical mass, both general ones (such as Zoom or Google Docs) and those specific to drug discovery (in our case, CDD Vault). Serendipitously, for the segments of our project that had the most collaborators — such as submitting ideas for molecules — the requested contributions broke into discrete, doable tasks that easily accommodated each contributor's availability and know-how.

The project self-selected a team of reflexively collaborative people, with no big egos. So far, we have avoided bureaucracy — no one claims to be the head of the COVID Moonshot. We retained momentum with collective trust, combined with sufficiently diverse expertise and perspectives, which allowed us to rapidly reach and implement strategic decisions. Reassuringly, people seemed to leave the collaboration only once their part of the project had been completed.

Perhaps the most surprising asset was that we did not have time to plan much at all — if we had, we'd have been paralysed. It seems you just have to get started and set deadlines for when to move on. Even now, we are astonished at how quickly this infrastructure self-assembled, just by scientists unabashedly asking for help from colleagues, distant connections or vendors. With so clear a goal, so obvious a need and the complete absence of contracts, people across the world stepped up.

The authors

Frank von Delft is professor of structural chemical biology at the University of Oxford, UK, and principal beamline scientist at Diamond Light Source, Didcot, UK. **John Chodera** is associate member at the Memorial Sloan Kettering Cancer Center, New York, USA. **Ed Griffen** is technical director and co-founder of MedChemica, Ryecraft, UK. **Alpha Lee** is group leader in the Department of Physics, University of Cambridge, UK, and chief scientific officer at PostEra, Boston, Massachusetts, USA. **Nir London** is assistant professor in the Department of Organic Chemistry at the Weizmann Institute of Science, Rehovot, Israel. **Tatiana Matviuk** is principal scientist at Enamine, Kiev, Ukraine. **Ben Perry** is discovery open innovation leader at the Drugs for Neglected Diseases initiative, Geneva, Switzerland. **Matt Robinson** is chief technology officer of PostEra, Boston, Massachusetts, USA. **Mark Calmiano** is a computational chemist at UCB Biopharma, Brussels, Belgium. **Annette von Delft** is a translational scientist at the University of Oxford, UK
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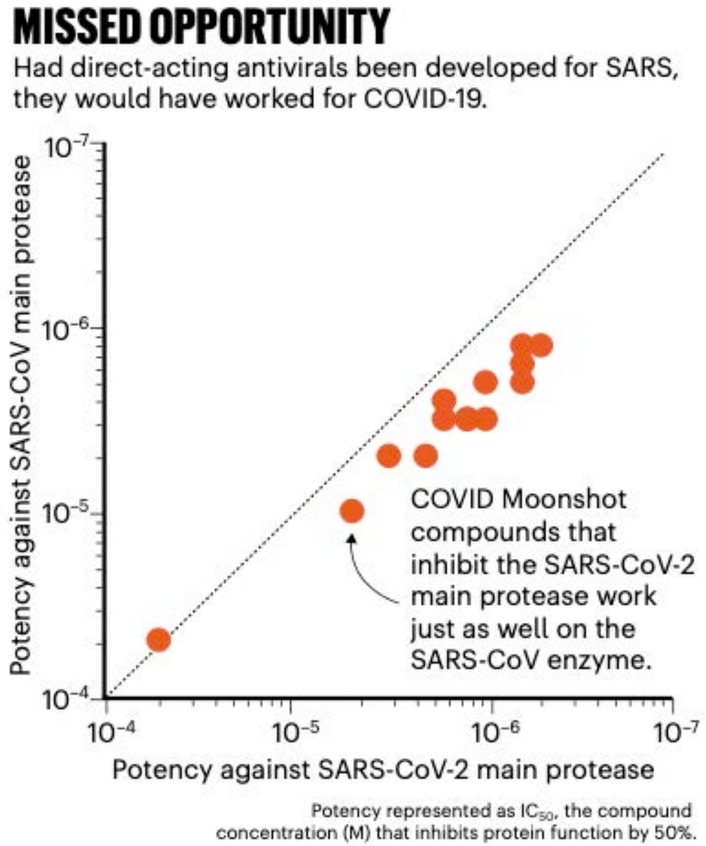
1. Douangamath, A. *et al. Nature Commun.* **11**, 5047 (2020).
2. Mahase, E. *Br. Med. J.* **373**, n1077 (2021).
3. The COVID Moonshot Consortium *et al.* Preprint at bioRxiv https://doi.org/10.1101/2020.10.29.339317 (2020).
4. Chodera, J., Lee, A. A., London, N. & von Delft, F. *Nature Chem.* **12**, 581 (2020).

J.C., E.G., A.L., N.L. & M.R. declare competing interests.

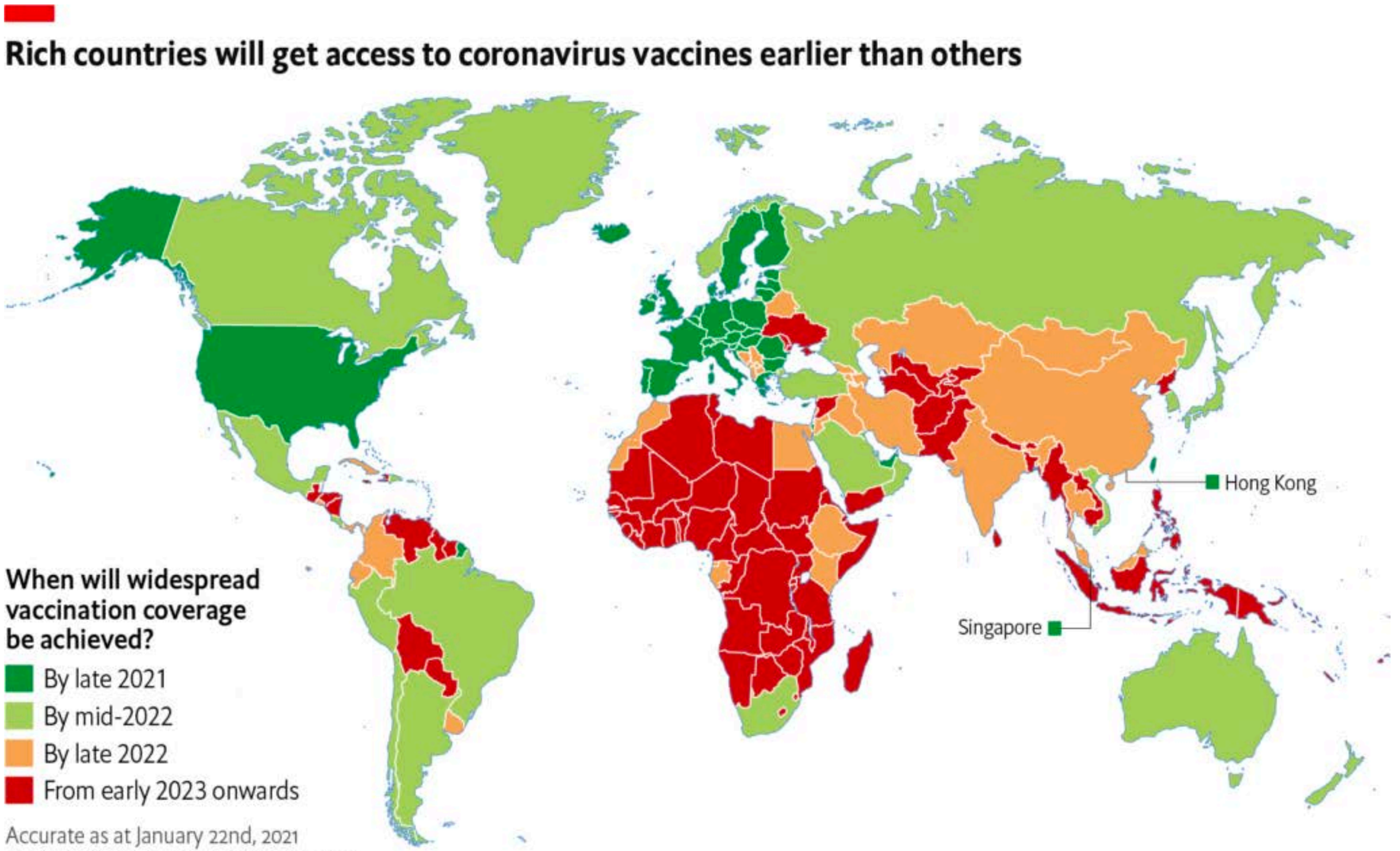
THE ONLY REASON WE DIDN'T HAVE ANTIVIRALS FOR SARS-COV-2 WAS DUE TO MARKET FAILURE



Our compounds are **equipotent** against SARS-CoV-1.

There's **no reason we couldn't have done this in 2004** after the 2003 SARS pandemic.

Much of the world will not receive vaccines until well into 2023, and variants are already a problem



https://www.eiu.com/n/85-poor-countries-will-not-have-access-to-coronavirus-vaccines/

GLOBAL, EQUITABLE ACCESS IS A HUGE PROBLEM

America And The TRIPS Waiver: You Can Talk The Talk, But Will You Walk The Walk?

Vineeta Gupta, Sreenath Namboodiri

JULY 13, 2021 10.1377/hblog20210712.248782

ADD TO FAVORITES SHARE

As nations grapple with the issues surrounding global COVID-19 vaccine manufacturing and distribution, the Trade-Related Aspects of Intellectual Property Rights (TRIPS) Agreement has found itself in mainstream conversation in the US more than ever before. A difficult concept to fully grasp, TRIPS refers to a World Trade Organization (WTO)-led international agreement about the protection of intellectual property rights and trade.

In October 2020, the governments of India and South Africa, with the support of 62 WTO member states, proposed a TRIPS Agreement waiver proposal that would temporarily waive intellectual property rights protections for technologies needed to prevent, contain, or treat COVID-19, including vaccines and vaccine-related technologies. More than 100 low-income countries support this proposal, but it is receiving much opposition from many high-income countries, including some European Union (EU) member states, the UK, Japan, Canada, and Australia. On May 5, 2021, the Biden administration announced support for negotiating this waiver, intensifying debate in the US and the EU—but so far the US has not gone further than its announcement of support.

The TRIPS waiver is critical to combating the COVID-19 pandemic around the world. Demand for the vaccine has already surpassed supply, with high-income countries taking a large share of reserved doses. Given that no single vaccine manufacturer could produce enough vaccines to meet the demand of the entire globe, supporters of the waiver ponder the ethics of multinational manufacturers holding exclusive rights to information and technology, preventing other companies from entering the markets that are not being served—primarily in low- and middle-income countries. Sharing vaccine-related information will not only help get the pandemic in check now, but it could also encourage firms to develop the next round of vaccines that will be necessary to address new variants.

The TRIPS waiver is critical to ensuring an equitable distribution of vaccines around the globe.

TRIPS patent waiver requests from India and 100 low-income countries to expand vaccine production have been pending since October 2020**, and nothing has happened**

Meanwhile….

Forbes

EDITORS' PICK | Jul 28, 2021, 01:48pm EDT | 40,696 views

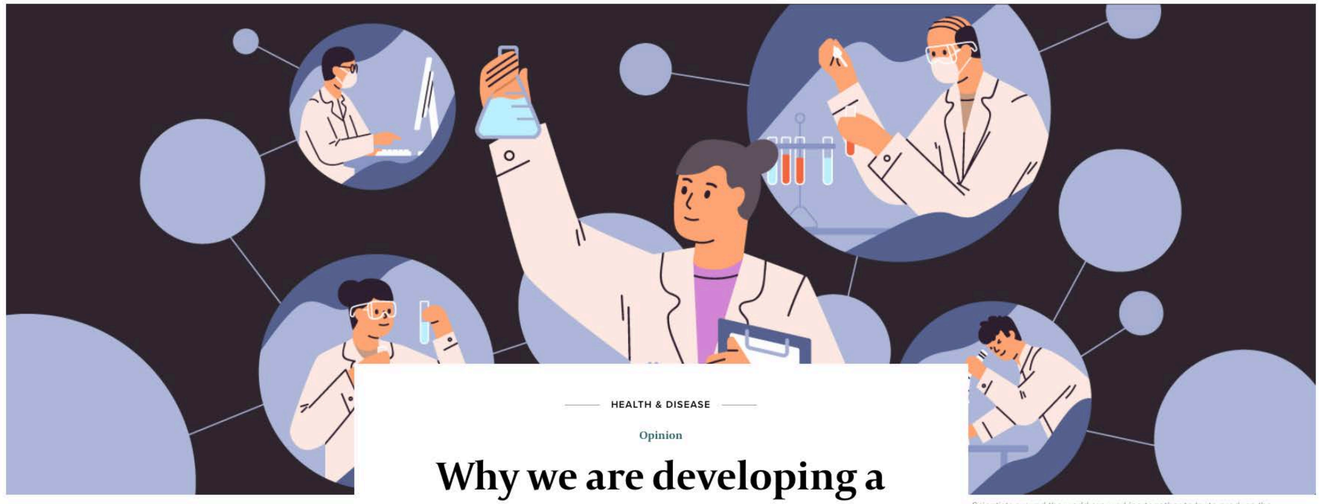
Pfizer Expects $33.5 Billion In Vaccine Revenue In 2021

Moderna, Racing for Profits, Keeps Covid Vaccine Out of Reach of Poor

Some poorer countries are paying more and waiting longer for the company's vaccine than the wealthy — if they have access at all.

Moderna and U.S. at Odds Over Vaccine Patent Rights

https://www.healthaffairs.org/do/10.1377/hblog20210712.248782/full/
https://www.forbes.com/sites/aayushipratap/2021/07/28/pfizer-expects-335-billion-in-vaccine-revenue-in-2021/?sh=f49a83c217d4
https://www.nytimes.com/2021/11/09/us/moderna-vaccine-patent.html
https://www.nytimes.com/2021/10/09/business/moderna-covid-vaccine.html



Scientists around the world are working together to try to produce the world's first patent-free antiviral therapy aimed at Covid-19. During a deadly pandemic, this is how drug development should proceed, the researchers argue.

CREDIT: GOODSTUDIO / SHUTTERSTOCK

HEALTH & DISEASE

Opinion

Why we are developing a patent-free Covid antiviral therapy

OPINION: During global health crises such as pandemics, drug discovery should be publicly funded and open, with no research secrets locked away

By Alpha Lee and John Chodera | By Frank von Delft | 09.27.2021

The rapid development of vaccines against Covid-19 is a scientific triumph. But the recipes for making these vaccines are the exclusive intellectual property of pharmaceutical companies, which means countries cannot manufacture an approved vaccine themselves, thus limiting distribution worldwide. For this and other reasons — such as problems with medical infrastructure and a lack of trained workers to administer the vaccine — most poor countries won't be widely vaccinated until at least 2024.

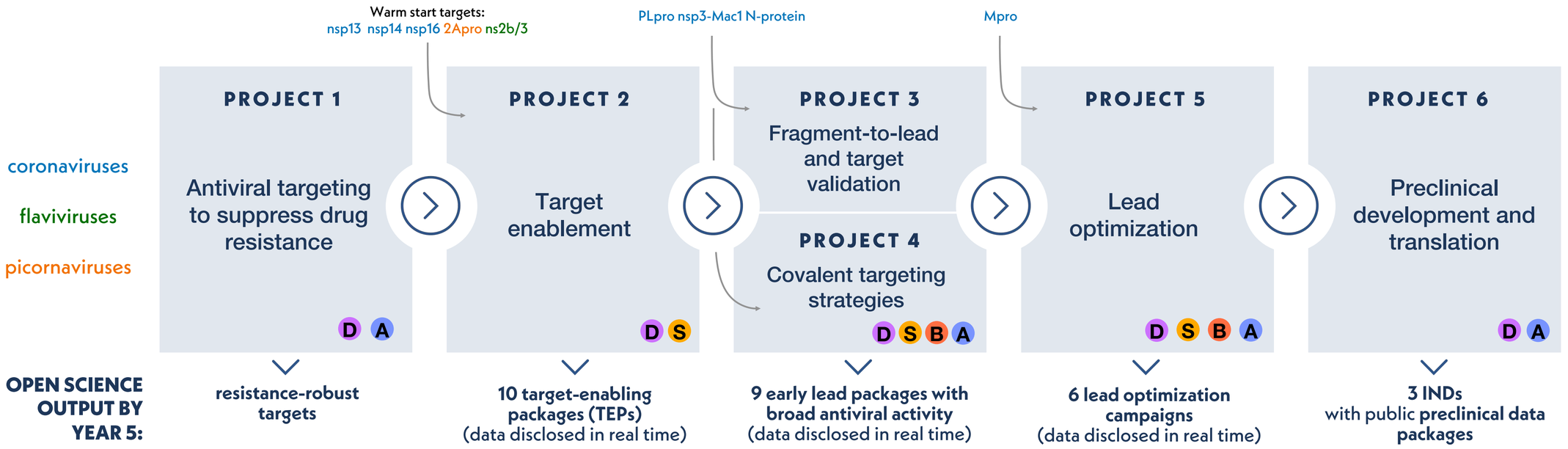
Much of the process of discovering a new drug or vaccine — as researchers hunt for new candidates, and companies develop those into safe, effective products — is typically conducted behind closed doors. Even once a product is approved, patent protections prevent other manufacturers from making and selling it. Eventually, patents expire; but some aspects of the lifesaving science behind the development of those patented products — such as which candidates don't work — often remain forever locked up in corporate silos, hindering research that may prevent future pandemics.

More from *Reset* — An ongoing series exploring how the world is navigating the coronavirus pandemic, its consequences and the way forward.

WE CAN TRANSFORM DRUG DISCOVERY FOR PANDEMICS

- **Build an accelerated platform for structure-based drug discovery** that uses machine learning and physical modeling to rapidly progress from fragment screen to chemical probes (to validate biology) to preclinical candidates
- **Exercise this platform** repeatedly during “peacetime” to generate a pool of **phase II ready drug candidates** for viruses of pandemic concern.
- **Focus on inexpensive oral therapeutics for accessible global access.**
- Use **open science** and **minimal IP** for diseases with no clear market incentive
- Pre-organize partnerships with pharma to **accelerate discovery during emergent pandemics**

AI-DRIVEN STRUCTURE-ENABLED ANTIVIRAL PLATFORM (ASAP)



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https://www.choderalab.org/news/2021/10/26/asap-avidd-proposal

THIS CAN BE A KNOWLEDGE-GENERATING ENGINE FOR OUR FIELD

- **We can generate open discovery data**
- **We can test different physical modeling and AI/ML models**
  - **continuous integration testing**
  - **automated blind predictive testing**
- **We can support the field with open source infrastructure**
- **We can use a common infrastructure for large-scale open data free energy calculations on Folding@home to help evaluate methods and advance chemistry for open molecules**
- **We can focus the field on important challenges that will deliver value**

“A rising tide lifts all boats”

- JFK (but really probably Wen Kang during the Qing dynasty)

The COVID Moonshot collaboration is worldwide

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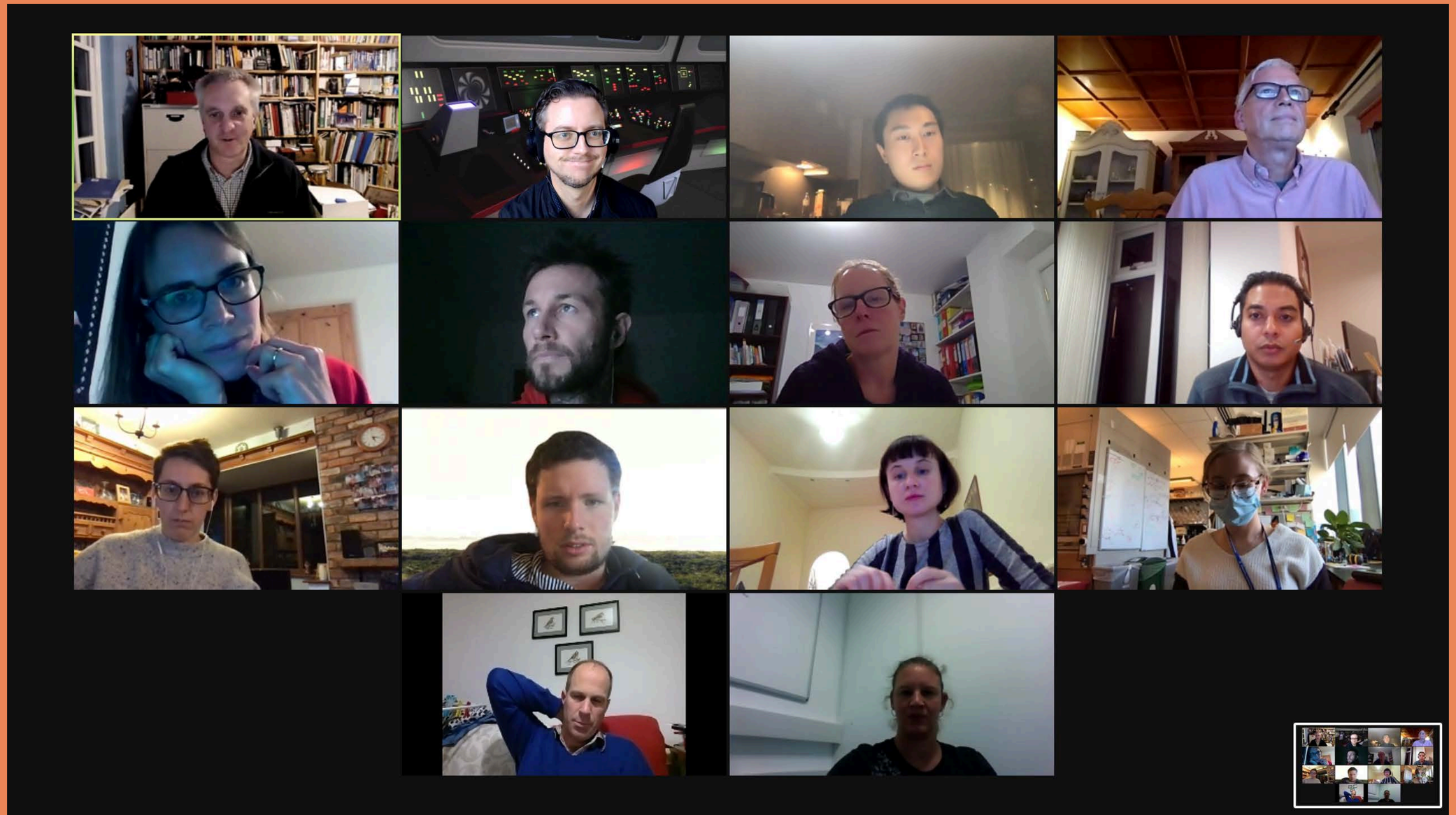

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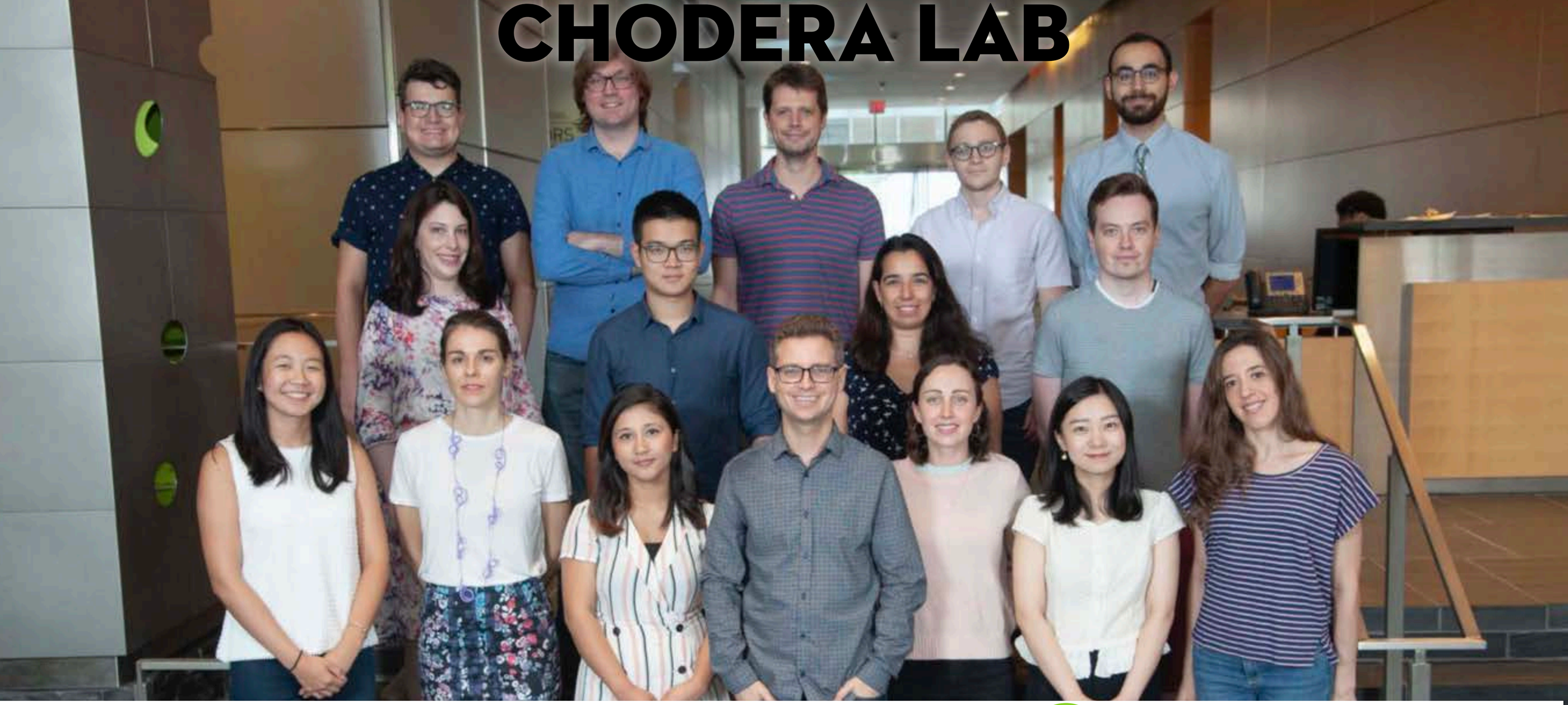

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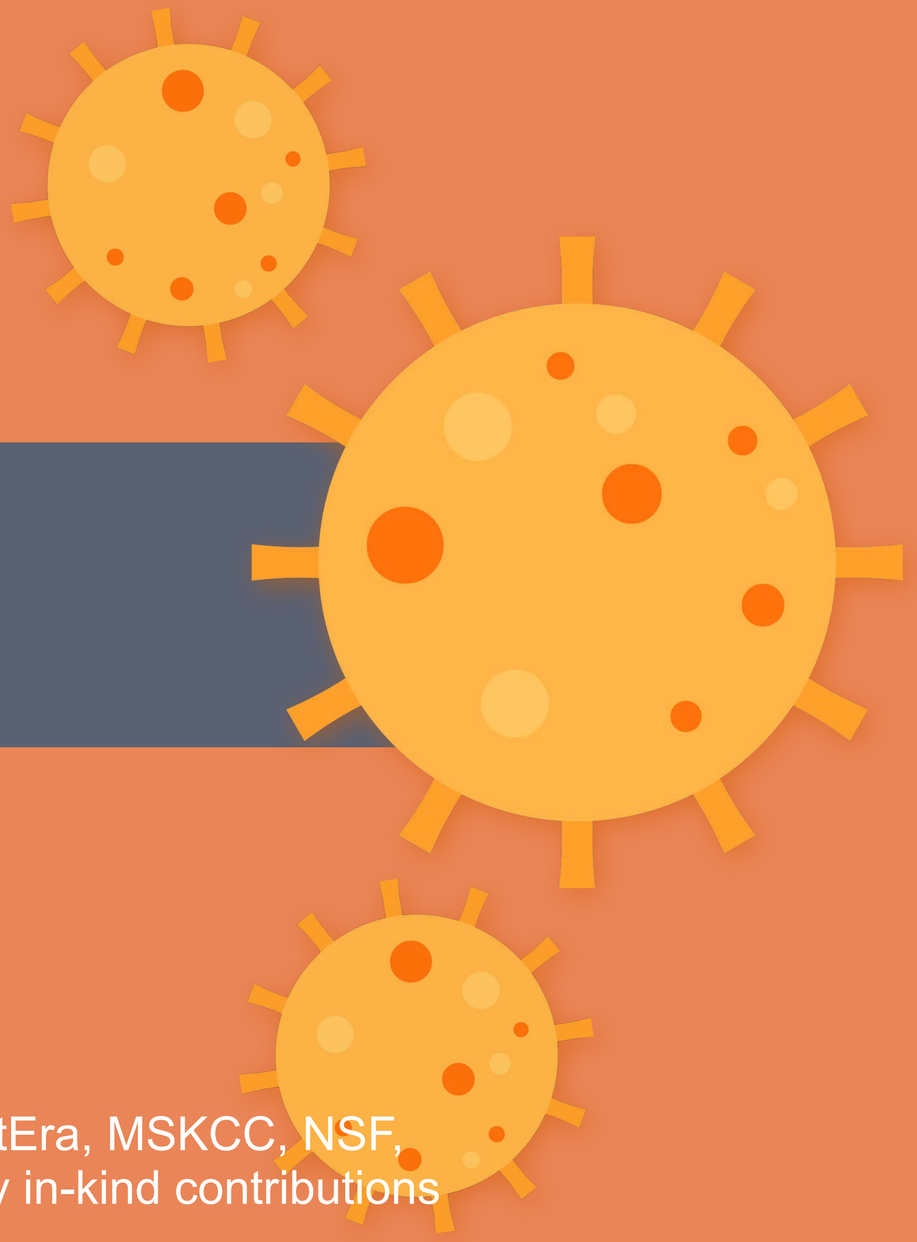

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