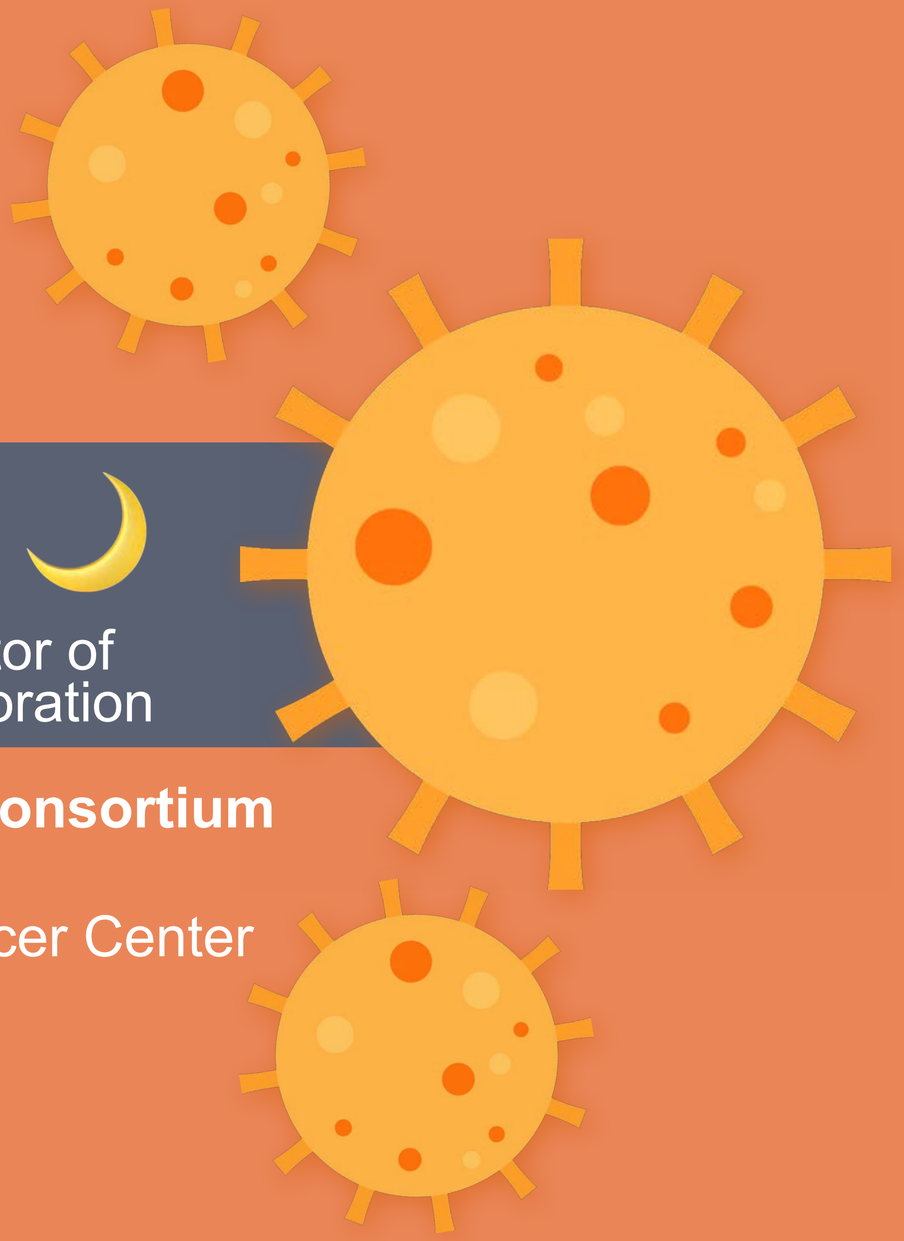
data: http://postera.ai/covid
slides: http://choderalab.org/news



THE COVID MOONSHOT 🌙

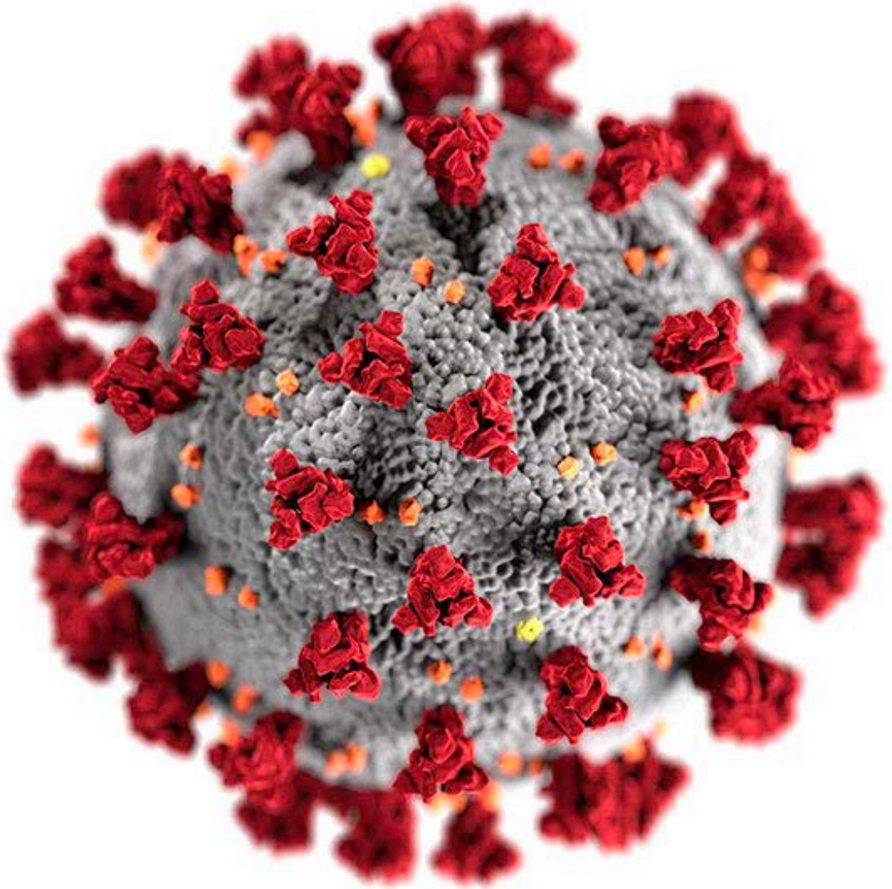
Closing in on an orally-bioavailable small molecule inhibitor of SARS-CoV-2 Mpro through a global open science collaboration

John D. Chodera on behalf of the **COVID Moonshot Consortium**
Computational and Systems Biology Program
Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center

DISCLOSURES:
- Scientific Advisory Board: OpenEye Scientific, Redesign Science, Foresite Labs
  All funding: http://choderalab.org/funding

Winter RosettaCon - 16 Mar 2021 - Cyberspace

10 Jan 2020



COVID-19 is caused by a novel coronavirus

Researchers uploaded the first draft genome of the novel coronavirus on 10 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.

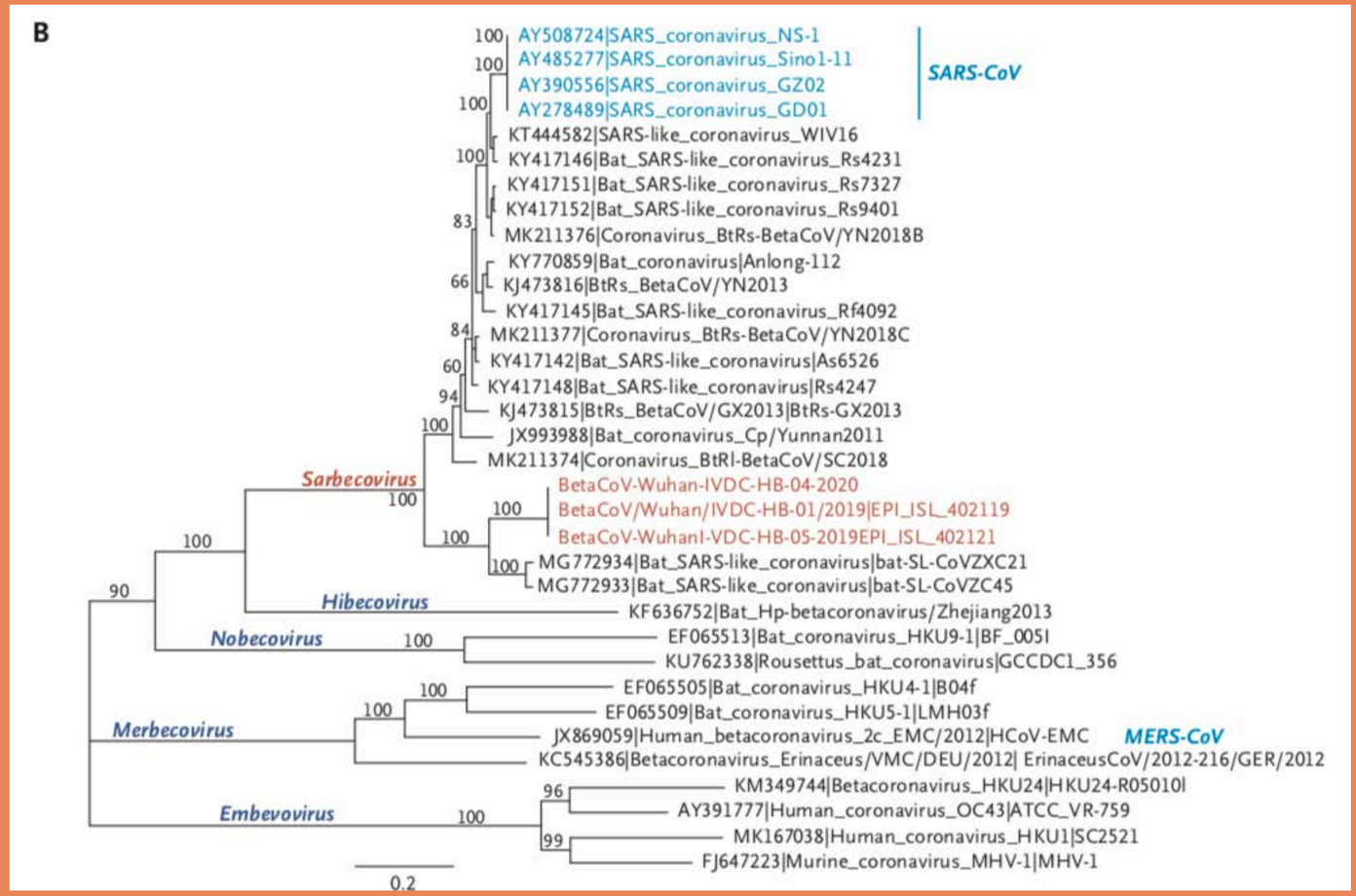
Drs. Zhu, Zhang, W. Wang, Li, and Yang contributed equally to this article.

This article was published on January 24, 2020, and updated on January 29, 2020, at NEJM.org.

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

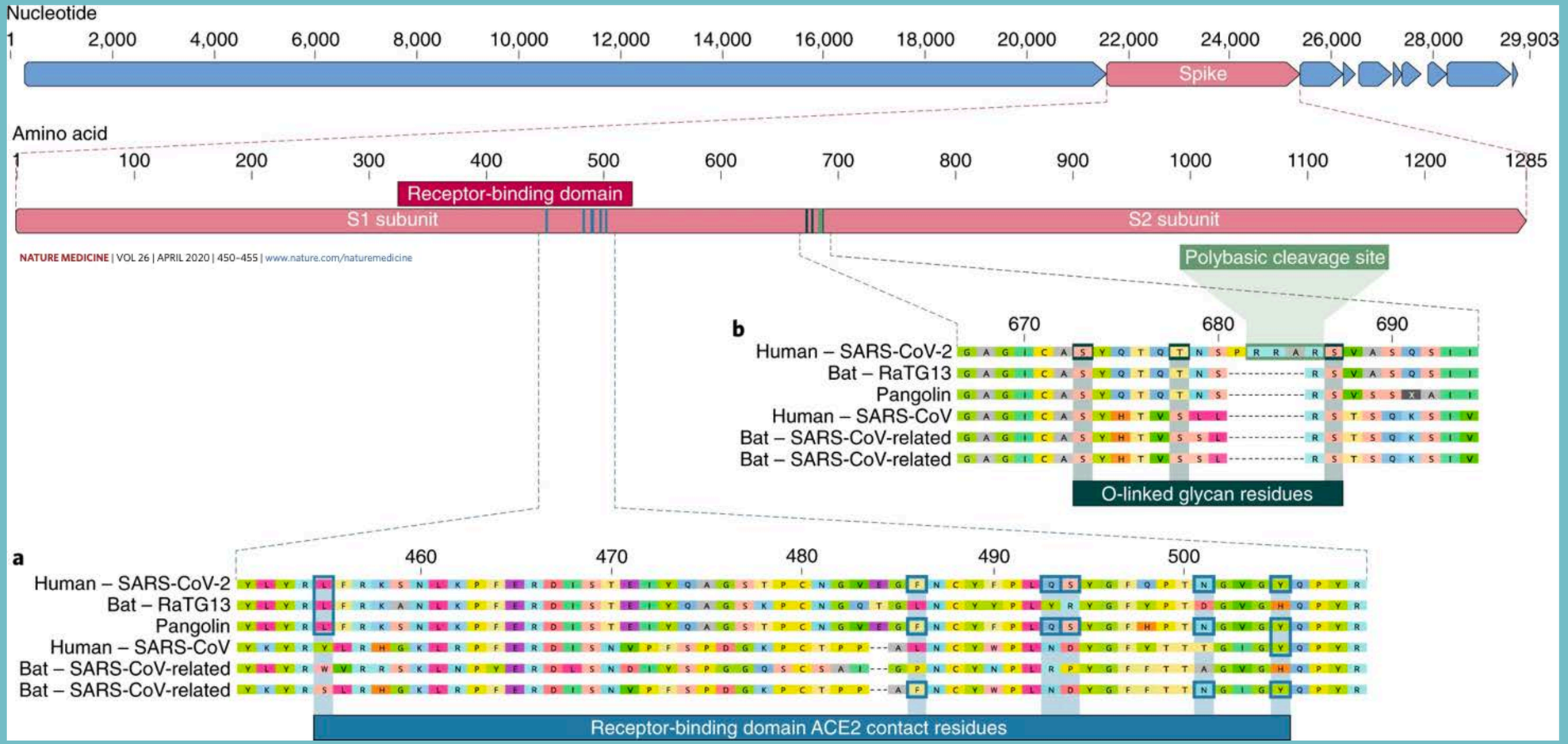
EMERGING AND REEMERGING PATHOGENS ARE GLOBAL CHALLENGES FOR public health.[1] Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases.[2,3] Six coronavirus species are known to cause 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

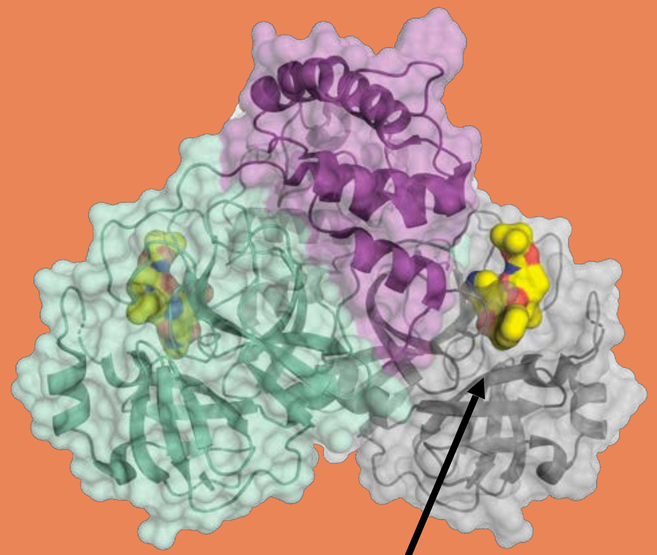
The viral genome sequence was surprisingly similar to SARS-CoV-1: It was ultimately designated SARS-CoV-2

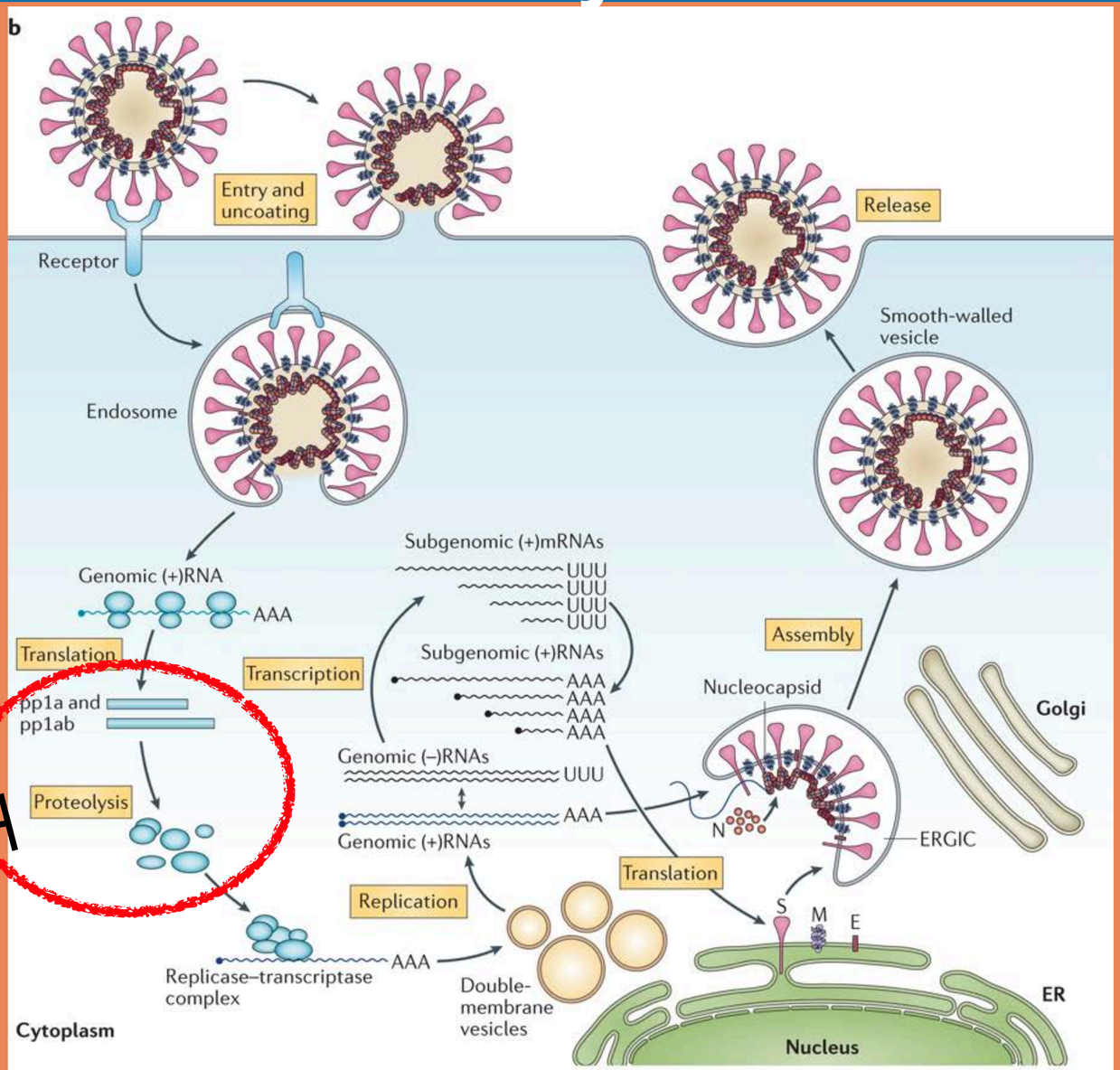


The SARS-CoV-2 main viral protease (Mpro) is essential for a key stage in the viral life cycle

M^{pro}

also: nsp5, 3CL^{Pro}





de Wit et al. Nature Reviews Microbiology 14:523, 2016
https://www.nature.com/articles/nrmicro.2016.81

Why would we need a new oral antiviral?

If vaccinating ~100% public (7.7 billion people), need complete safety, and some individuals will not be eligible for vaccination

A drug taken when needed doesn't require 100% compliance by public

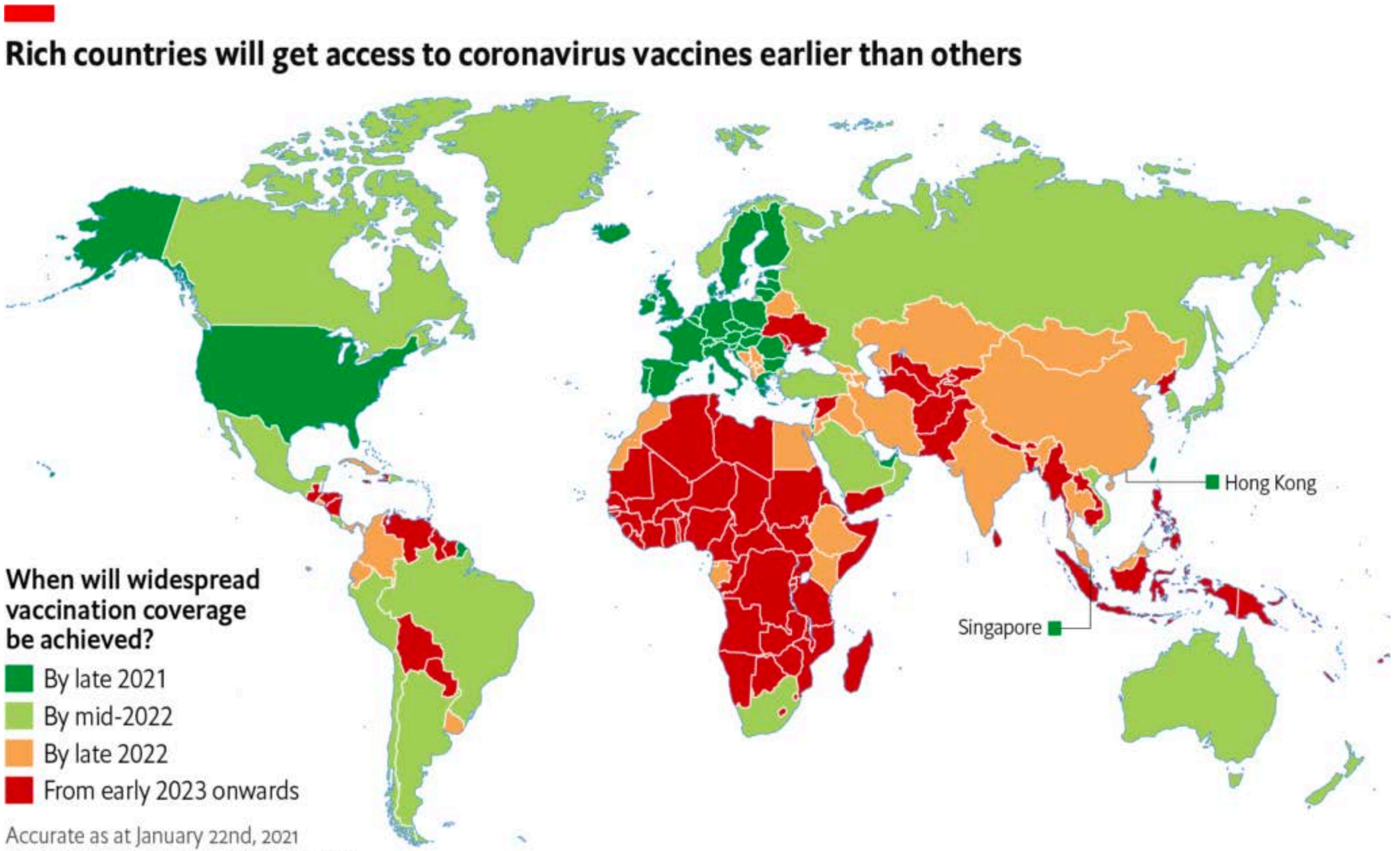
Oral antivirals could be taken early, as opposed to IV drugs

Mpro inhibitors remain effective against mutations that Spike-targeting vaccines may provide incomplete protection against

Shelf-stable oral inhibitor would enable practical global deployment without the complications of cold chain storage

A simple synthetic route could enable rapid production at low cost

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/

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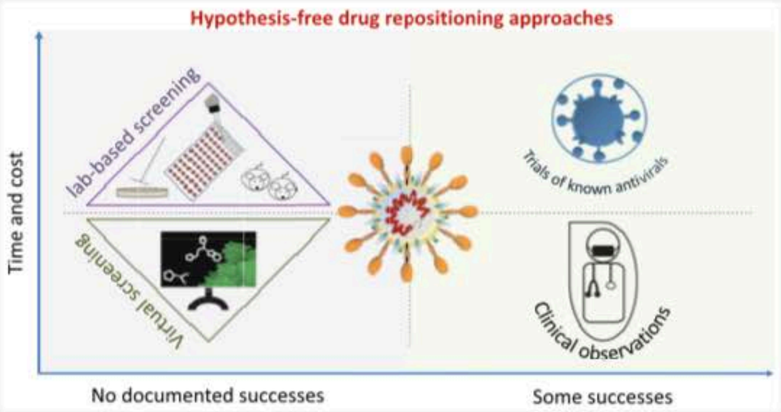
ABSTRACT: Massive drug repurposing (or repositioning) campaigns are trying to find potential antiviral treatments for COVID-19. Many involve experimental or virtual screening of libraries of compounds previously proven safe in humans—"old drugs". In 20 years of these efforts in many other diseases, never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

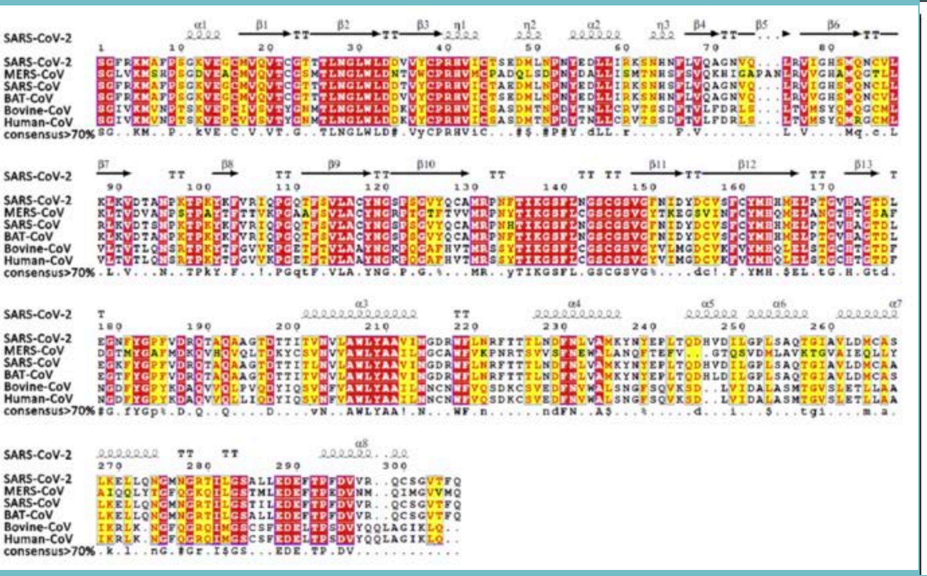


Aled Edwards
SGC Toronto

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

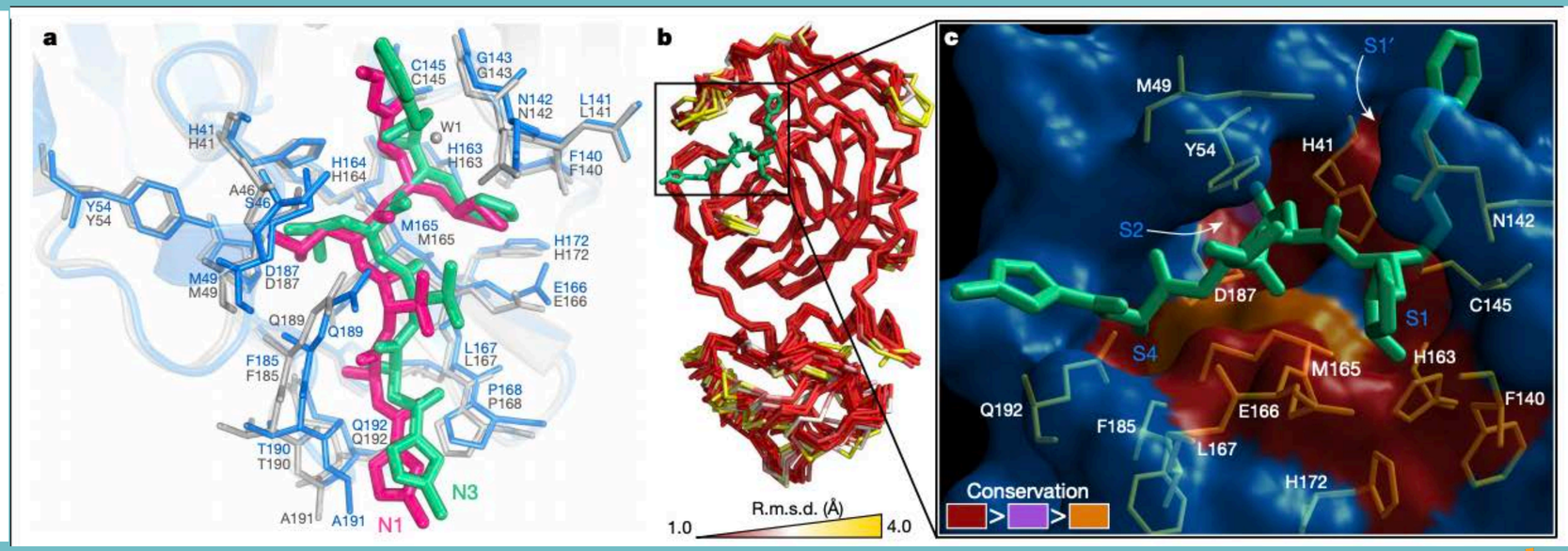
Mpro is an essential enzyme highly conserved among viruses that cause SARS, MERS, and COVID

sequence (24 Jan 2020)



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

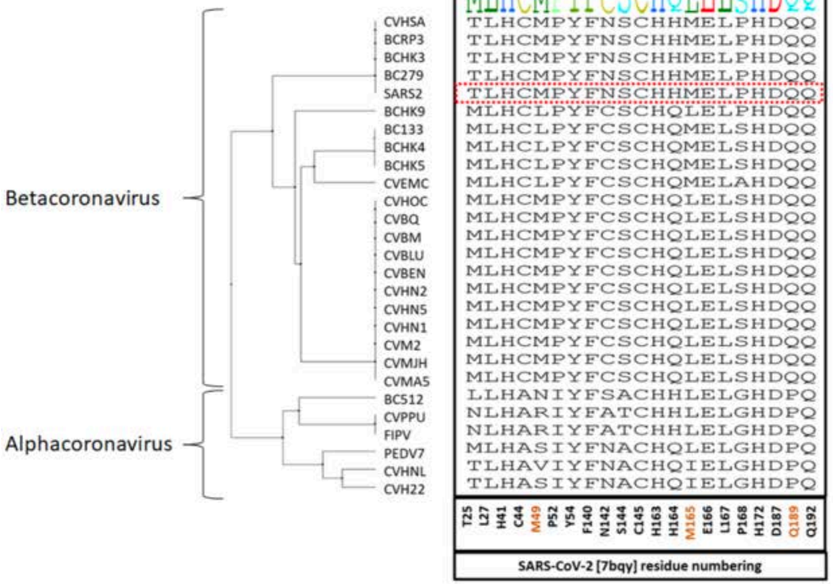
structure (PDB structure released 5 Feb 2020)



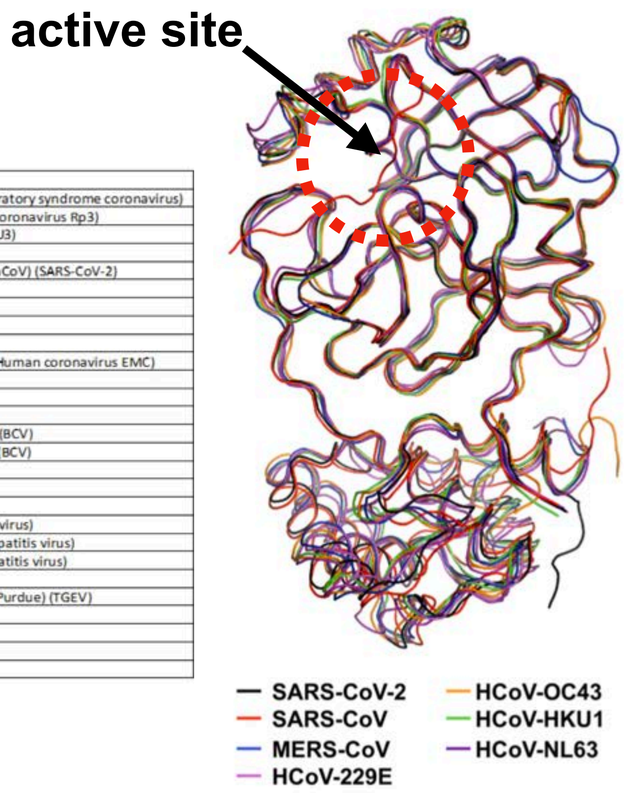
Jin et al. Nature 582:289, 2020
doi:10.1038/s41586-020-2223-y

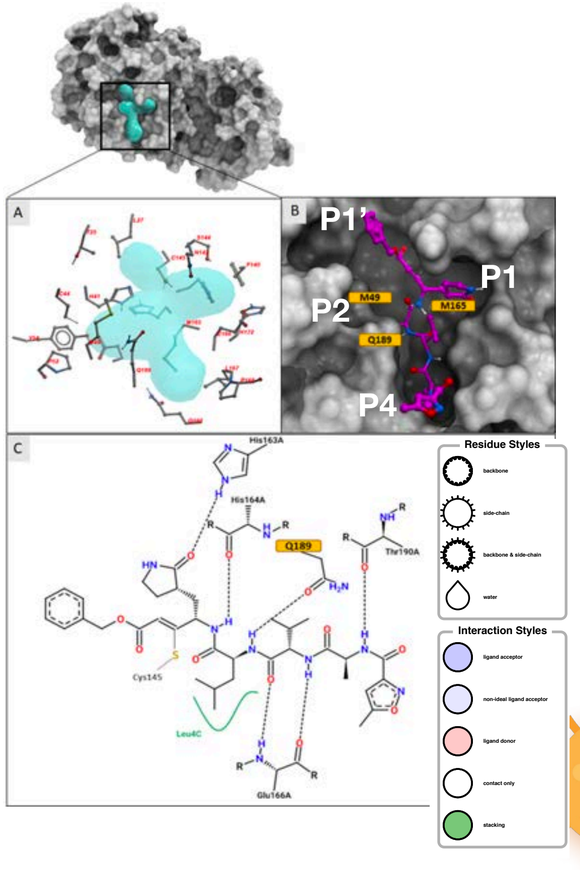
Mpro appears to be a viable target for developing a SARS-CoV-2 antiviral as well as pan-coronavirus antivirals

Mpro active site is so highly conserved, it makes for an appealing pan-coronavirus target



Entry	Organism
CVHSA	Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus)
BCRP3	Bat coronavirus Rp3/2004 (BtCoV/Rp3/2004) (SARS-like coronavirus Rp3)
BCHK3	Bat coronavirus HKU3 (BtCoV) (SARS-like coronavirus HKU3)
BC279	Bat coronavirus 279/2005 (BtCoV) (BtCoV/279/2005)
SARS2	Severe acute respiratory syndrome coronavirus 2 (2019-nCoV) (SARS-CoV-2)
BCHK9	Bat coronavirus HKU9 (BtCoV) (BtCoV/HKU9)
BC133	Bat coronavirus 133/2005 (BtCoV) (BtCoV/133/2005)
BCHK4	Bat coronavirus HKU4 (BtCoV) (BtCoV/HKU4/2004)
BCHK5	Bat coronavirus HKU5 (BtCoV) (BtCoV/HKU5/2004)
CVEMC	Middle East respiratory syndrome-related coronavirus (Human coronavirus EMC)
CVHOC	Human coronavirus OC43 (HCoV-OC43)
CVBQ	Bovine coronavirus (strain Quebec) (BCoV) (BCV)
CVBM	Bovine coronavirus (strain Mebus) (BCoV) (BCV)
CVBLU	Bovine coronavirus (strain 98TXSF-110-LUN) (BCoV-LUN) (BCV)
CVBEN	Bovine coronavirus (strain 98TXSF-110-ENT) (BCoV-ENT) (BCV)
CVHN2	Human coronavirus HKU1 (isolate N2) (HCoV-HKU1)
CVHN5	Human coronavirus HKU1 (isolate N5) (HCoV-HKU1)
CVHN1	Human coronavirus HKU1 (isolate N1) (HCoV-HKU1)
CVM2	Murine coronavirus (strain 2) (MHV-2) (Murine hepatitis virus)
CVMJH	Murine coronavirus (strain JHM) (MHV-JHM) (Murine hepatitis virus)
CVMA5	Murine coronavirus (strain A59) (MHV-A59) (Murine hepatitis virus)
BC512	Bat coronavirus 512/2005 (BtCoV) (BtCoV/512/2005)
CVPPU	Porcine transmissible gastroenteritis coronavirus (strain Purdue) (TGEV)
FIPV	Feline coronavirus (strain FIPV WSU-79/1146) (FCoV)
PEDV7	Porcine epidemic diarrhea virus (strain CV777) (PEDV)
CVHNL	Human coronavirus NL63 (HCoV-NL63)
CVH22	Human coronavirus 229E (HCoV-229E)





Yazdani et al. Methods of Mapping Genetic Variability onto SARS-CoV-2 Protein Crystal Structures. Zenodo; 2020. https://doi.org/10.5281/zenodo.3834875
Roe et al. Journal of General Virology. 2021; p. 001558. https://doi.org/10.1099/jgv.0.001558

While no human coronavirus Mpro inhibitors had been 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]

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[b] Department of Chemistry, Wichita State University, Wichita, KS 67260, USA

ARTICLE INFO

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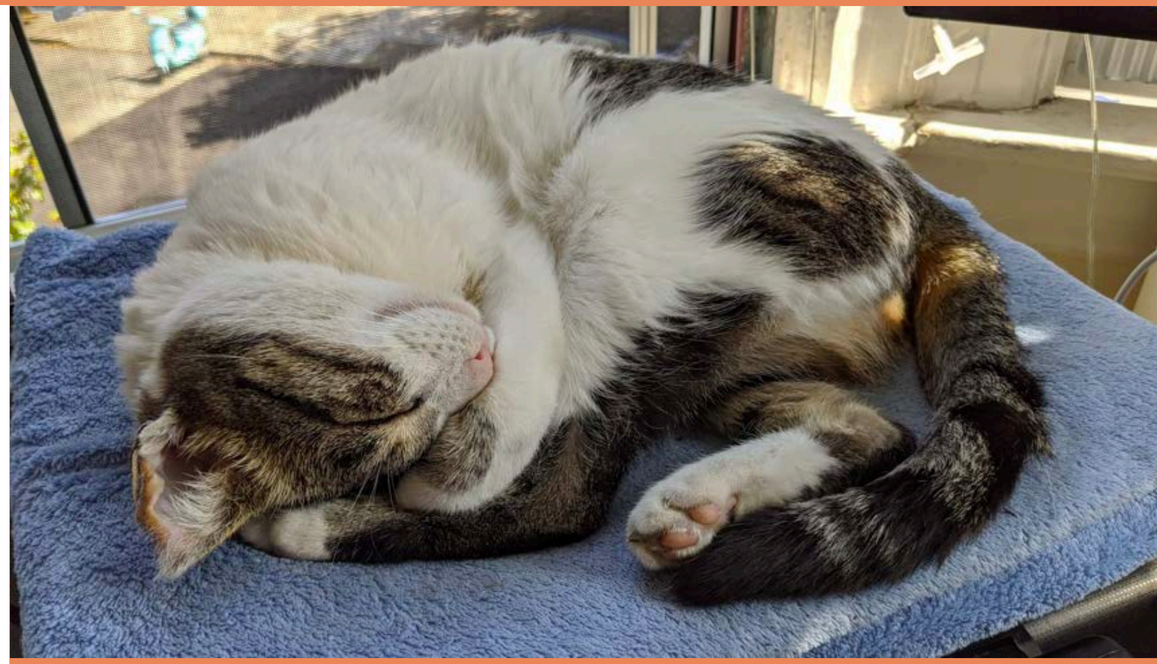
Cathepsin B
Synergy
3CL protease

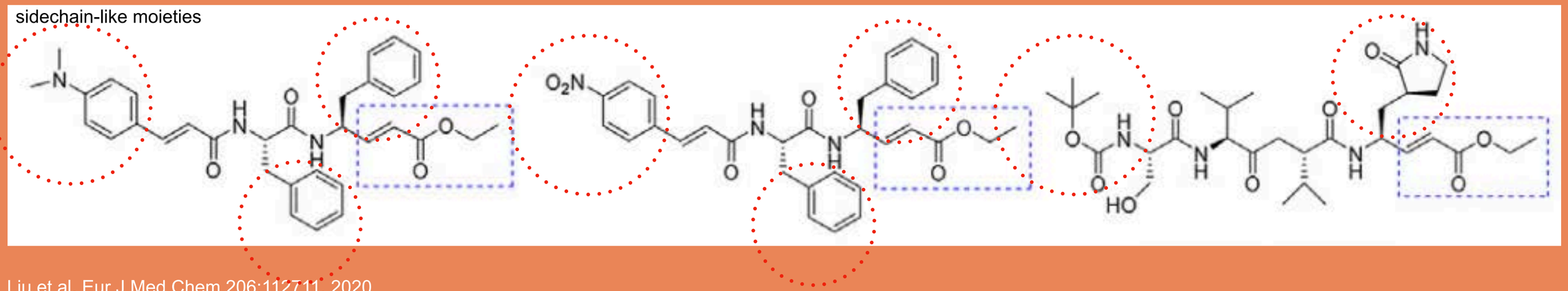
ABSTRACT

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.



an Mpro inhibitor had successfully treated cats

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



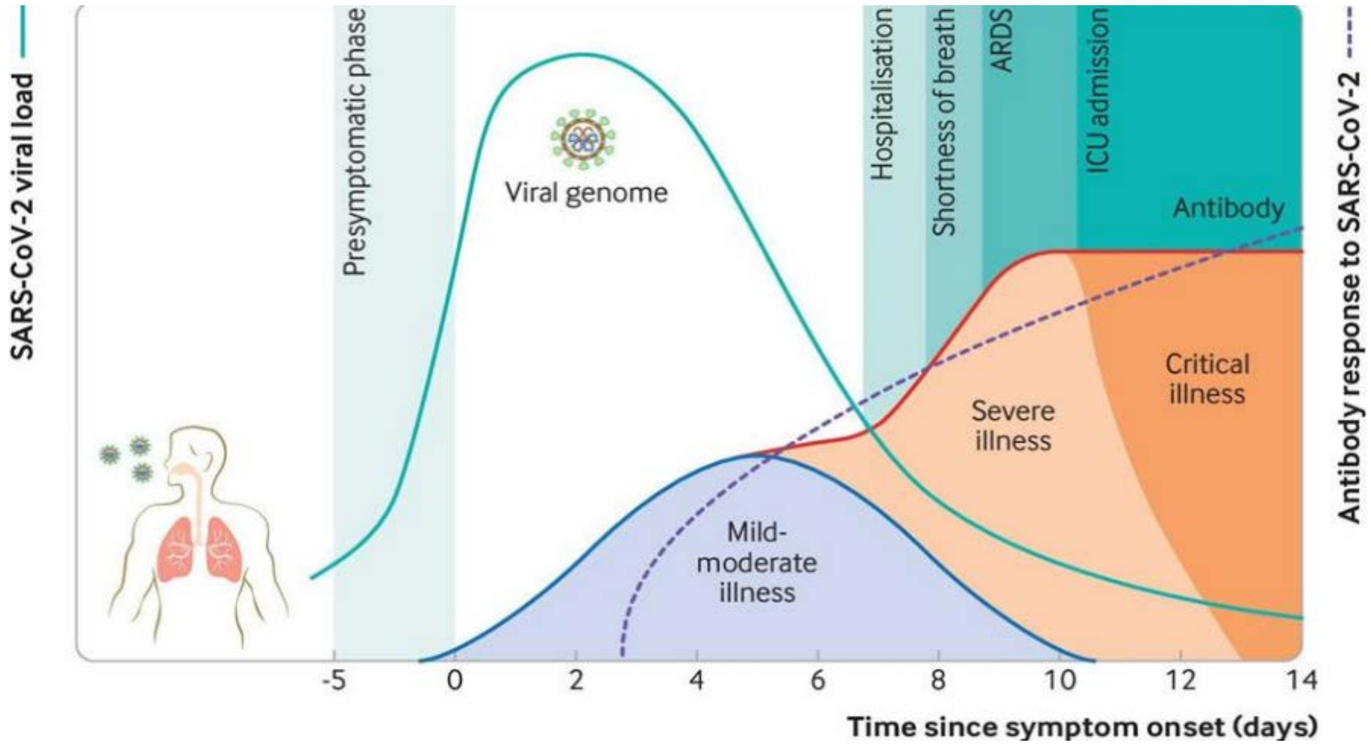
Liu et al. Eur J Med Chem 206:112711, 2020

Known inhibitors were also covalent inhibitors, which can run into selectivity problems against host proteases

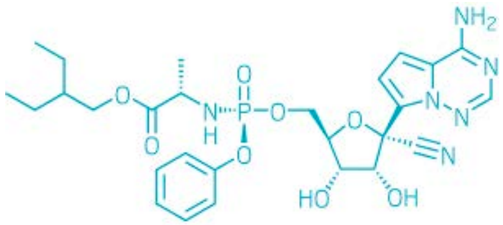
Oral drugs turn out to be much more useful than IV drugs in impacting the course of disease

Oral antiviral
Window of opportunity

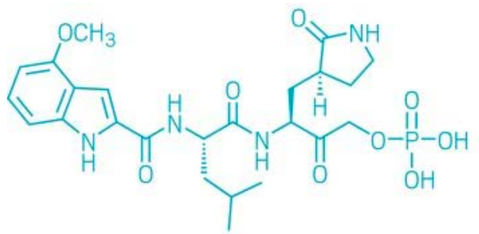
Virus no longer drives disease
Antivirals less effective
Hospitalized, so access to IV drugs



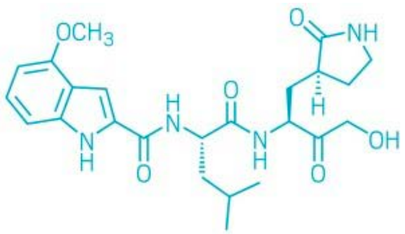
all IV dosing



Remdesivir



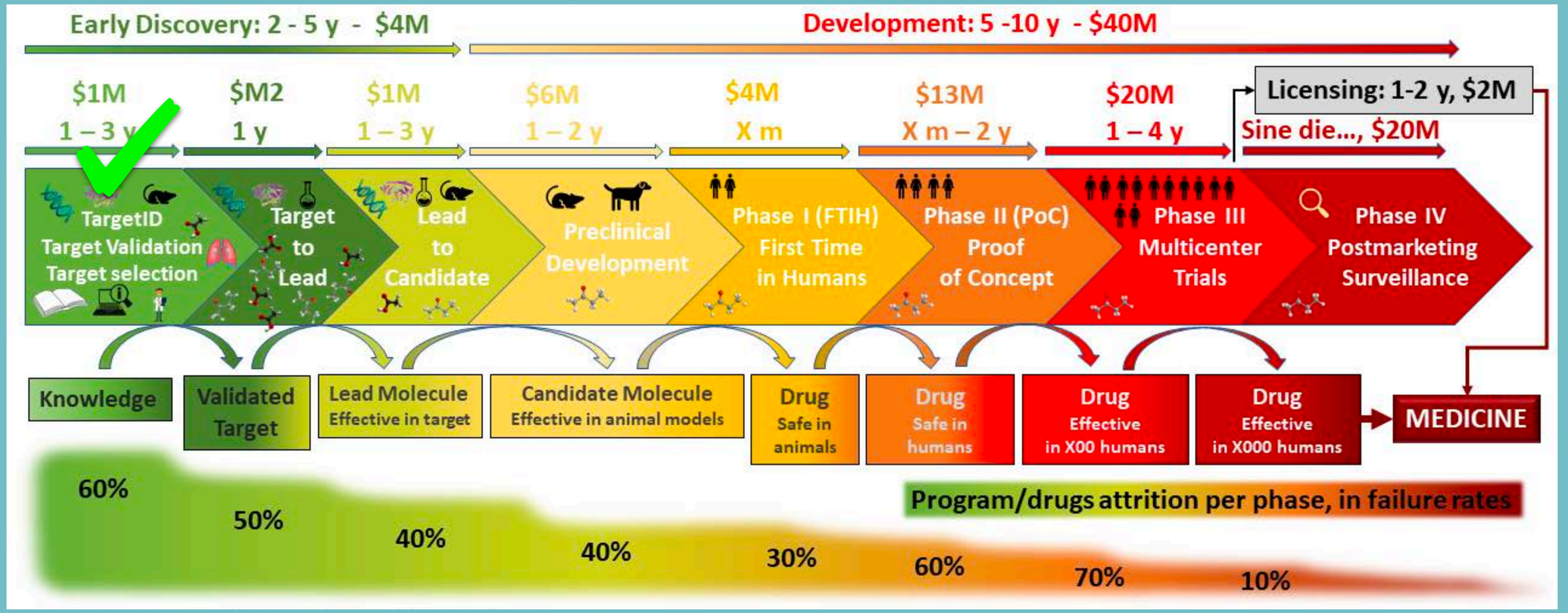
PF-07304814



PF-00835231

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

Drug discovery is usually a long and expensive process

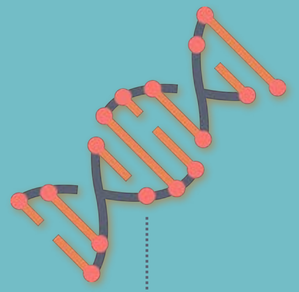


https://doctortarget.com/machine-learning-applied-drug-discovery/

How can we drastically cut down this timeline and ensure we will succeed?

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

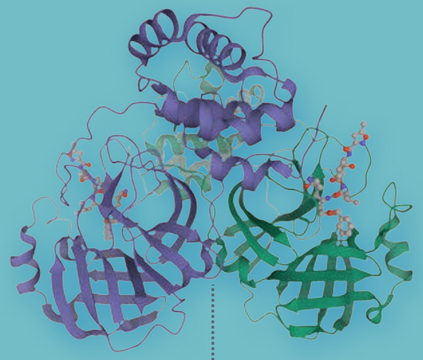
Frank von Delft
Diamond Light Source / XChem / SGC



February 14

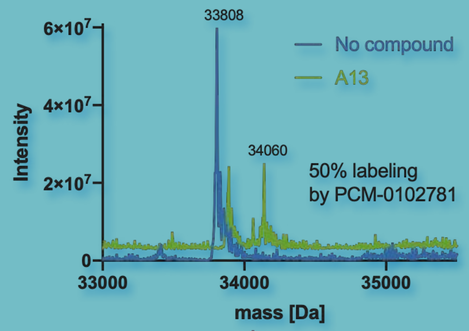
Main protease cloned and produced at Diamond after COVID shutdown of Haitao Yang lab in Shanghai

Martin Walsh



February 20

Atomic resolution structure of the protease determined

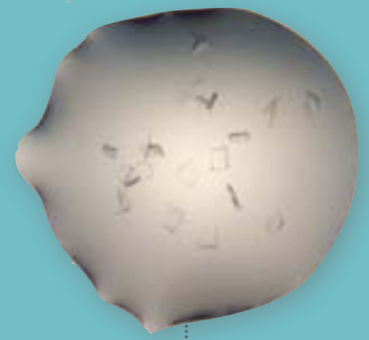


February 25

Covalent screen finds 150 active site hits

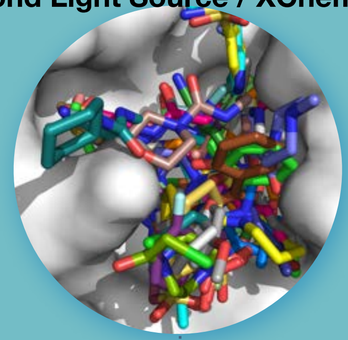
>40 hits validated

Nir London



March 5

1,500 crystals collected in one day (!)

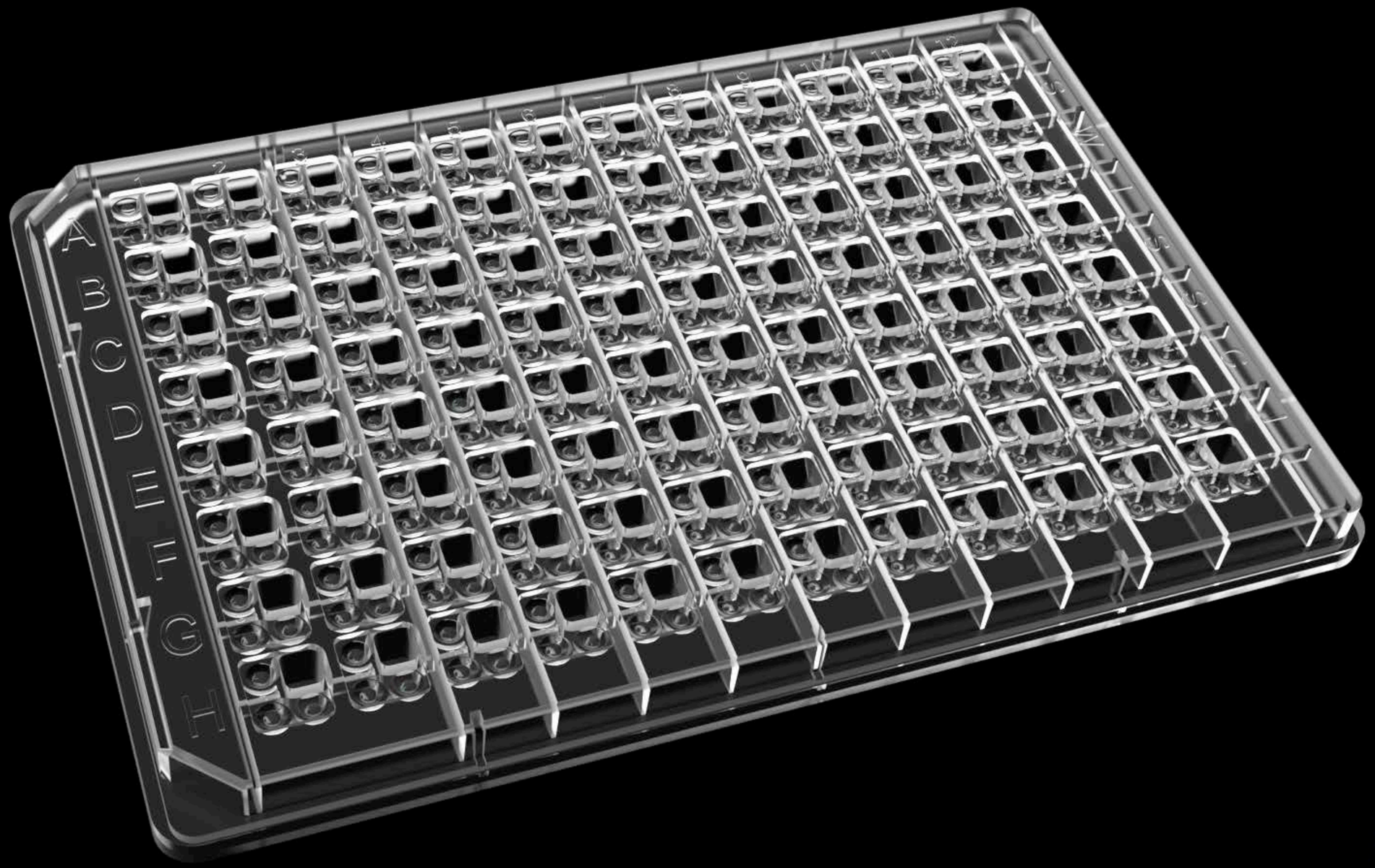


March 18

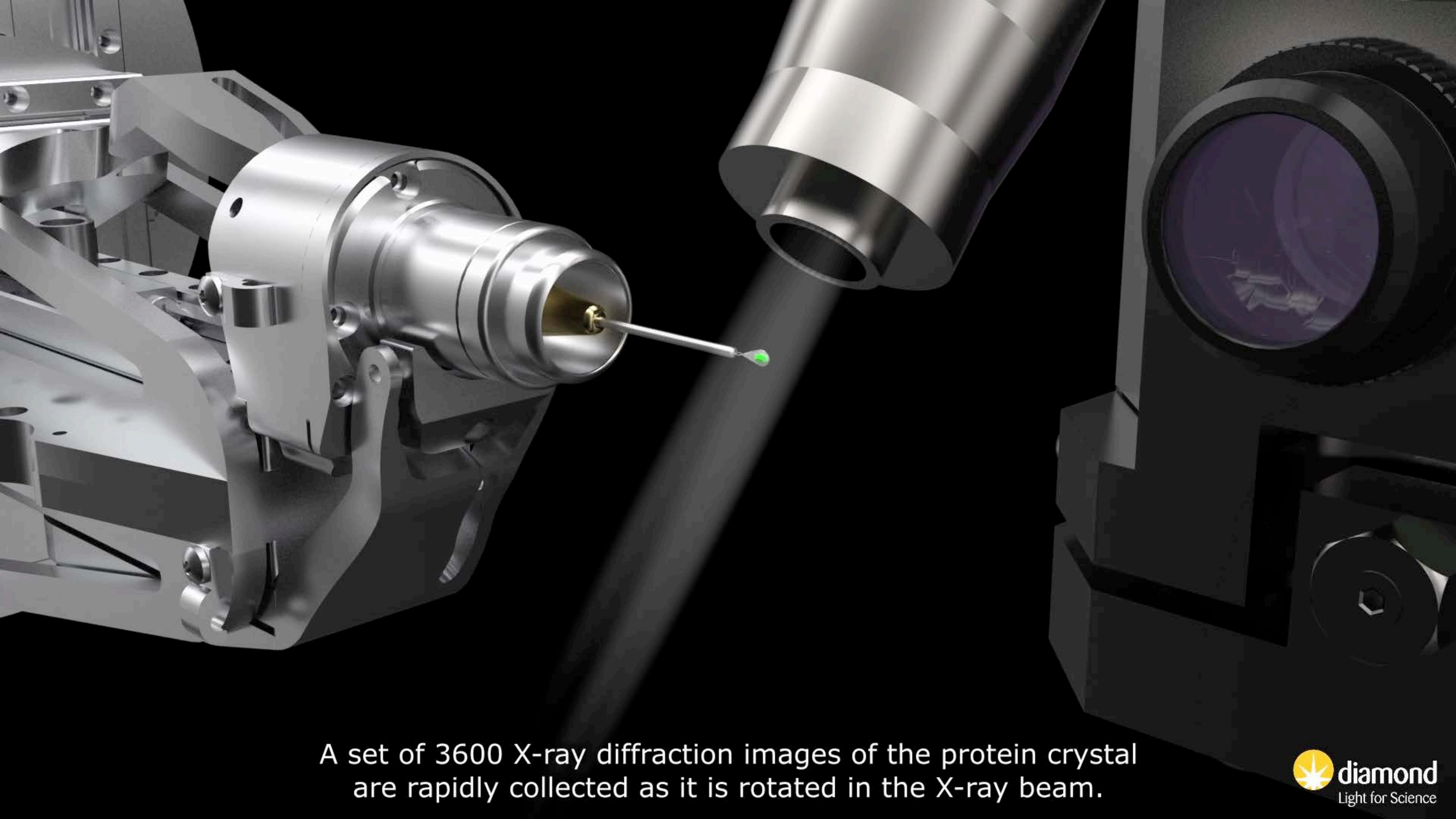
78 fragment-bound structures solved and released to the web

48 covalent fragments
71 active site fragments

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



diamond
Light for Science

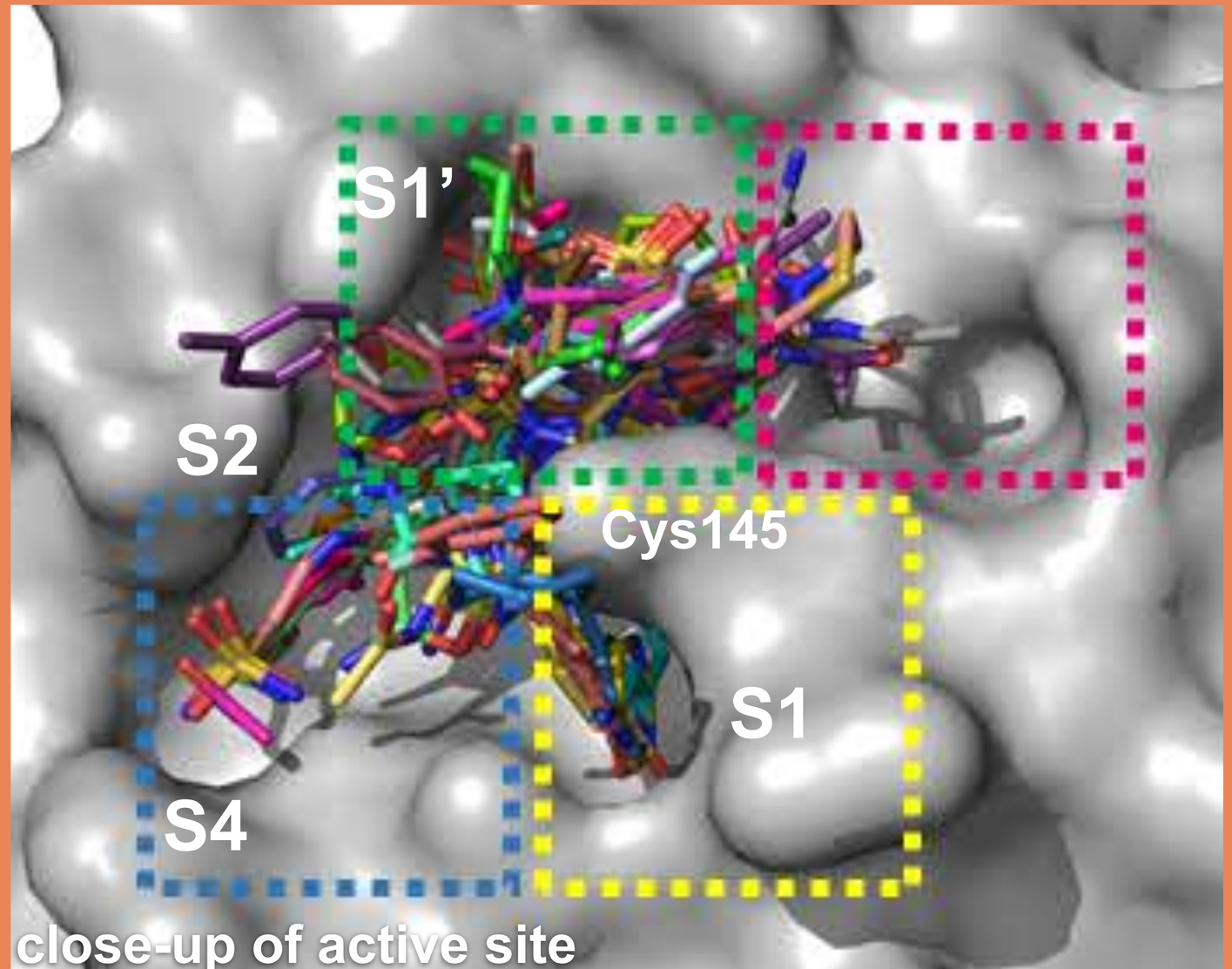


A set of 3600 X-ray diffraction images of the protein crystal are rapidly collected as it is rotated in the X-ray beam.

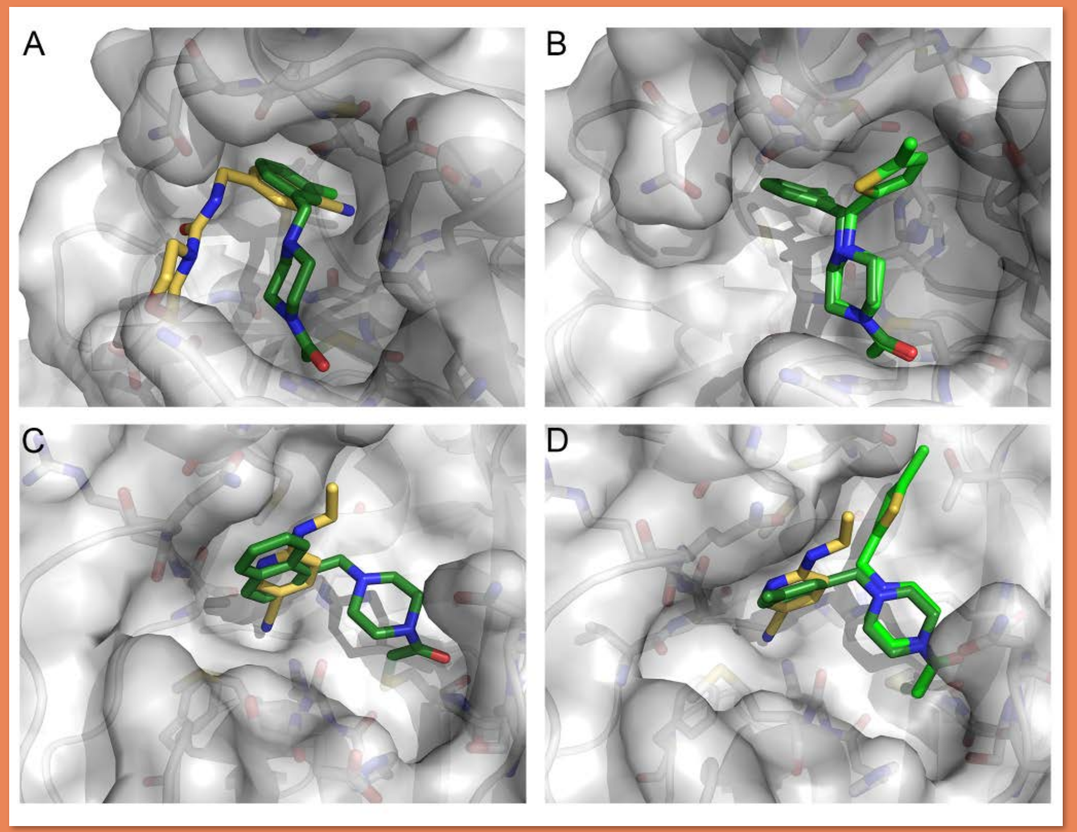
diamond
Light for Science

Fragment hits completely cover the active site

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

All data was immediately released online (we're pre-preprinting here!)

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.

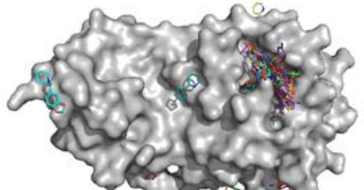
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

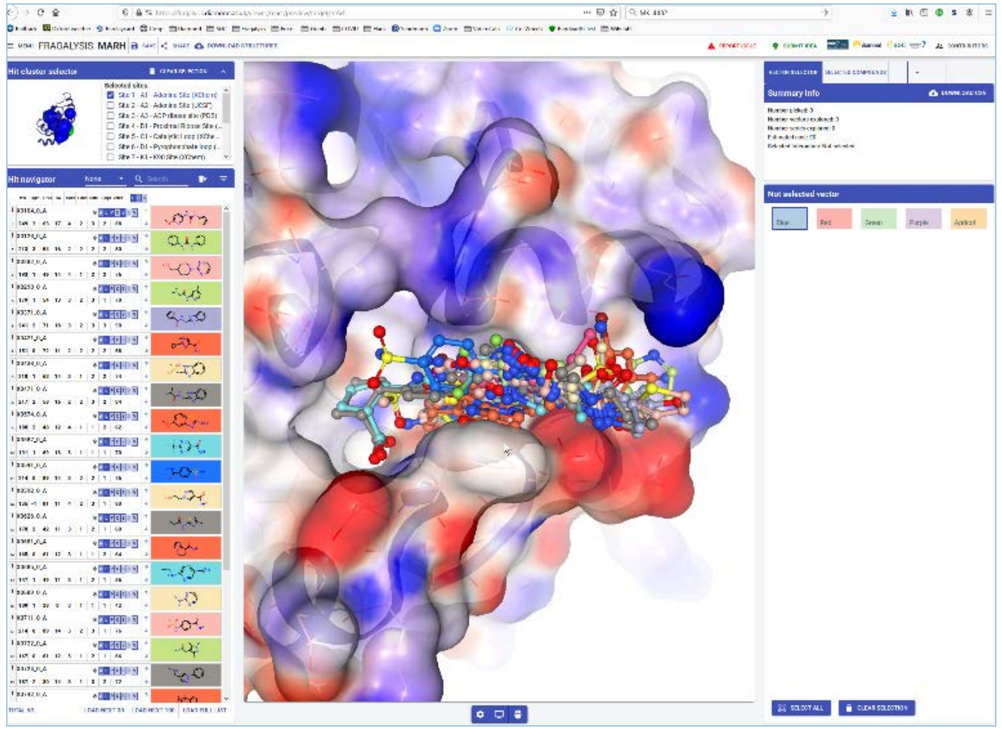
XChem fragment screen

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:

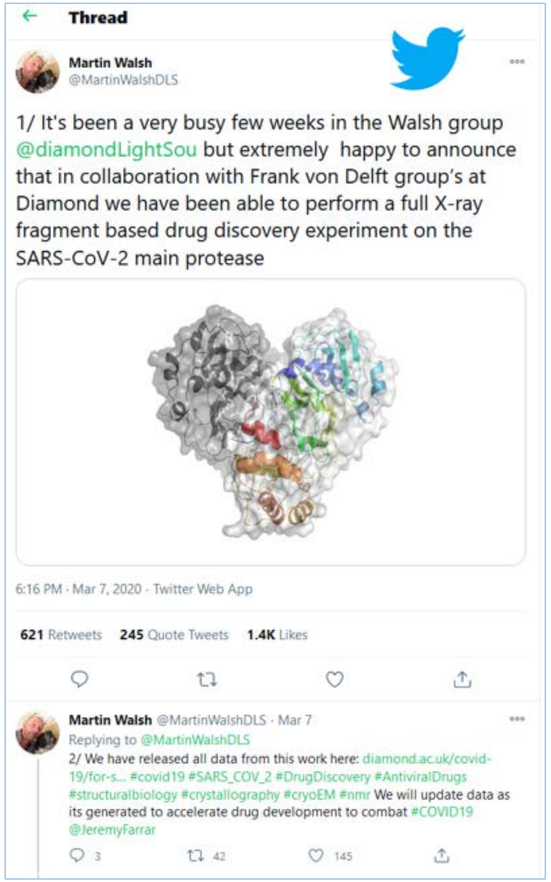
- 23 non-covalent hits in the active site
- 48 covalent hits in the active site
- 3 hits in the dimer interface, one in a calculated hotspot





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

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?

Alpha Lee (PostEra/Cambridge) quickly set up the COVID Moonshot 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

http://postera.ai/covid

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

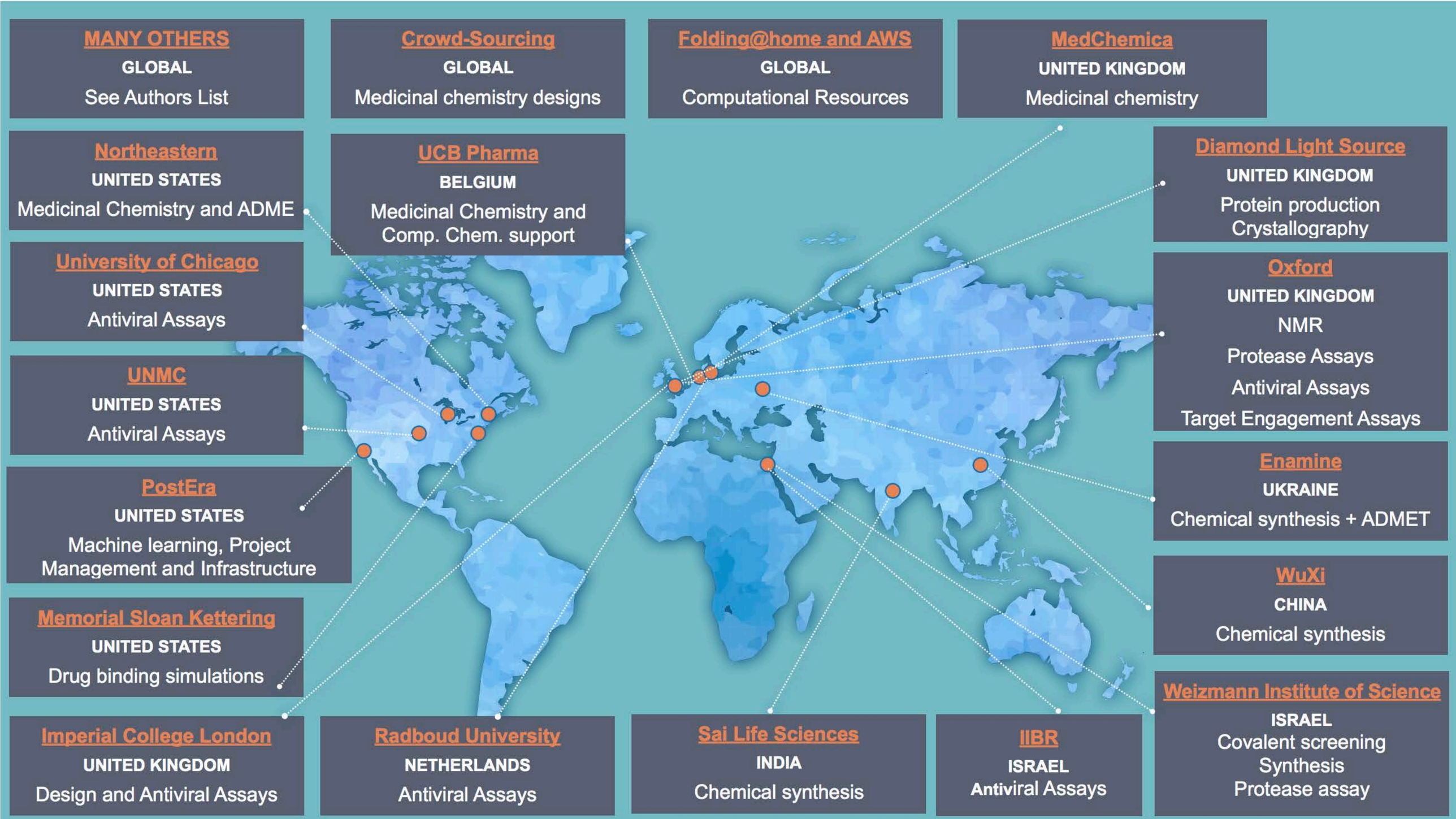
Open science

COVID Moonshot

Open data

http://postera.ai/covid

Patent-free


MANY OTHERS
GLOBAL
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Medicinal chemistry designs
Folding@home and AWS
GLOBAL
Computational Resources
MedChemica
UNITED KINGDOM
Medicinal chemistry
Northeastern
UNITED STATES
Medicinal Chemistry and ADME
UCB Pharma
BELGIUM
Medicinal Chemistry and Comp. Chem. support
Diamond Light Source
UNITED KINGDOM
Protein production
Crystallography
University of Chicago
UNITED STATES
Antiviral Assays
Oxford
UNITED KINGDOM
NMR
Protease Assays
Antiviral Assays
Target Engagement Assays
UNMC
UNITED STATES
Antiviral Assays
Enamine
UKRAINE
Chemical synthesis + ADMET
PostEra
UNITED STATES
Machine learning, Project Management and Infrastructure
WuXi
CHINA
Chemical synthesis
Memorial Sloan Kettering
UNITED STATES
Drug binding simulations
Weizmann Institute of Science
ISRAEL
Covalent screening
Synthesis
Protease assay
Imperial College London
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Design and Antiviral Assays
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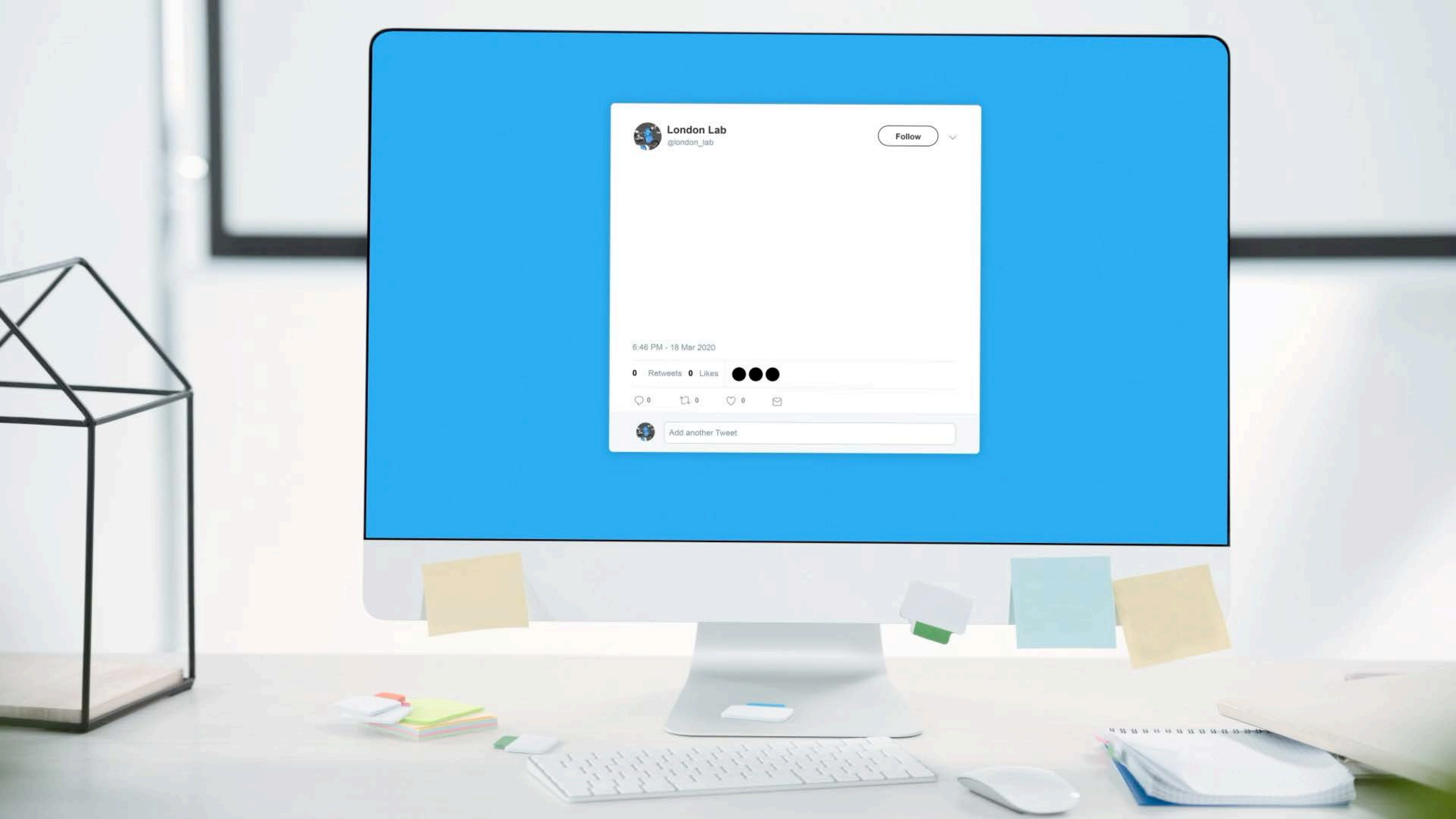
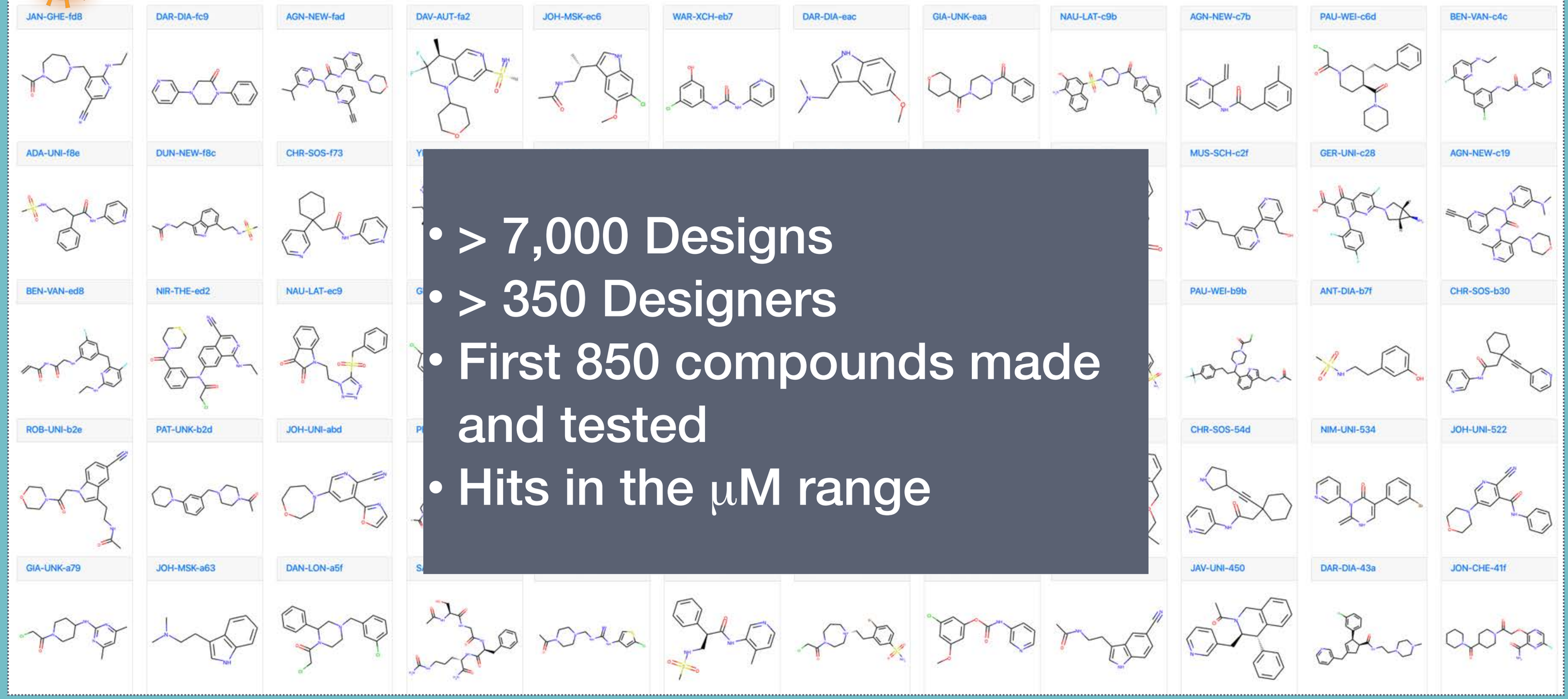
Antiviral Assays


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

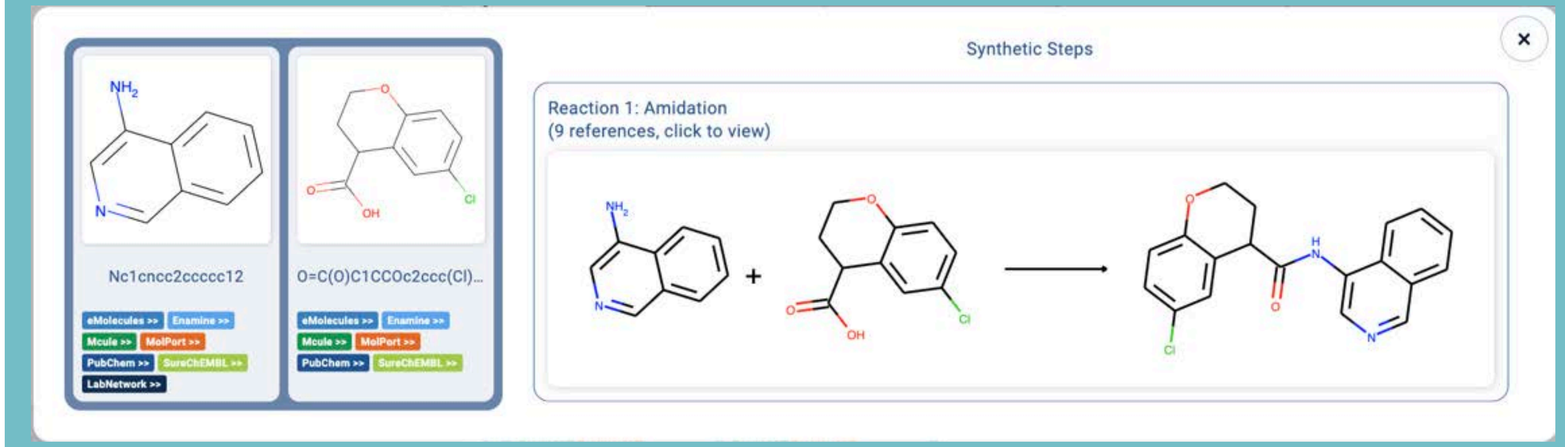
…and there was overwhelming response



- > 7,000 Designs
- > 350 Designers
- First 850 compounds made and tested
- Hits in the μM range

PostEra's synthetic route prediction AI 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!

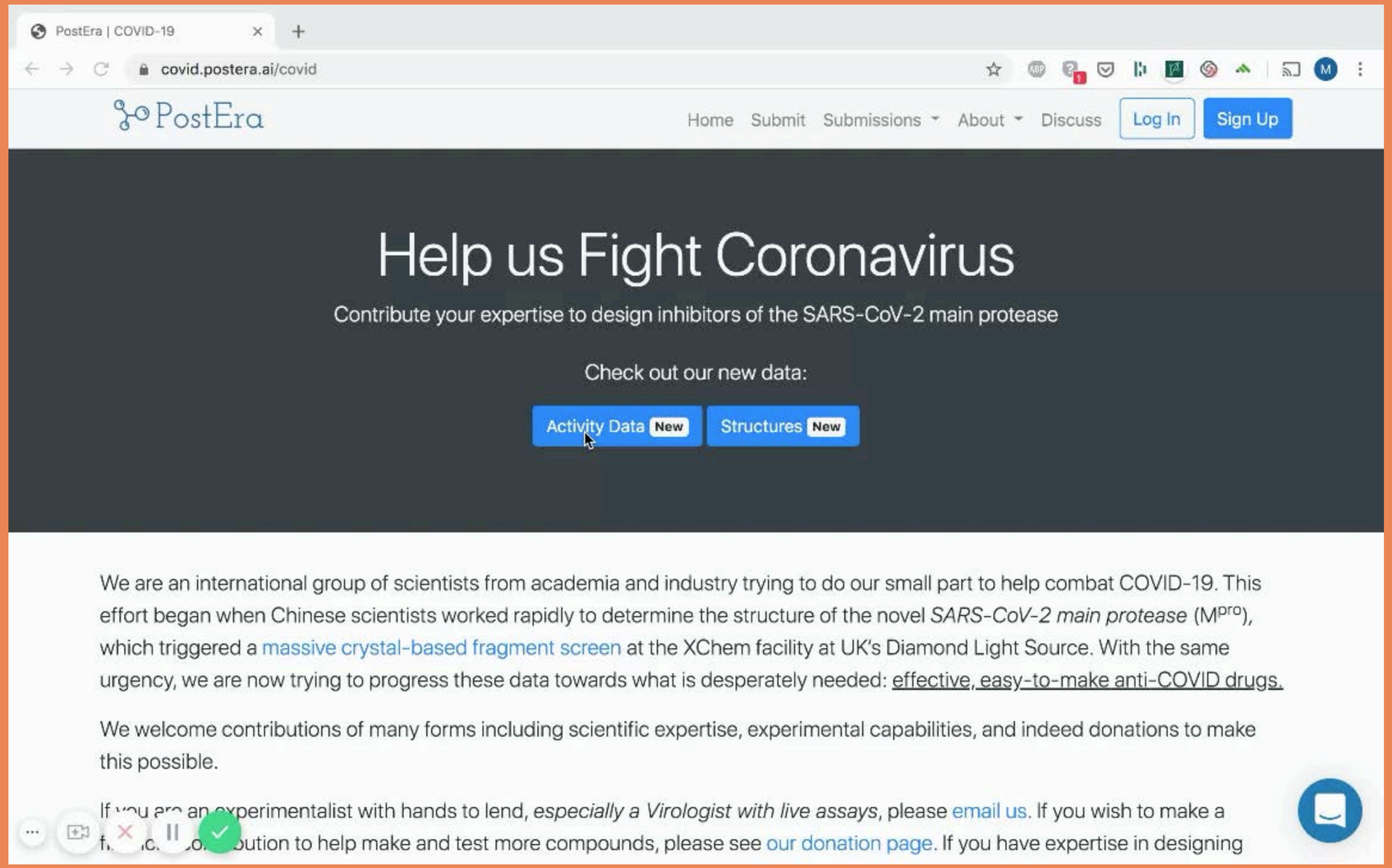
http://postera.ai/covid

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

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



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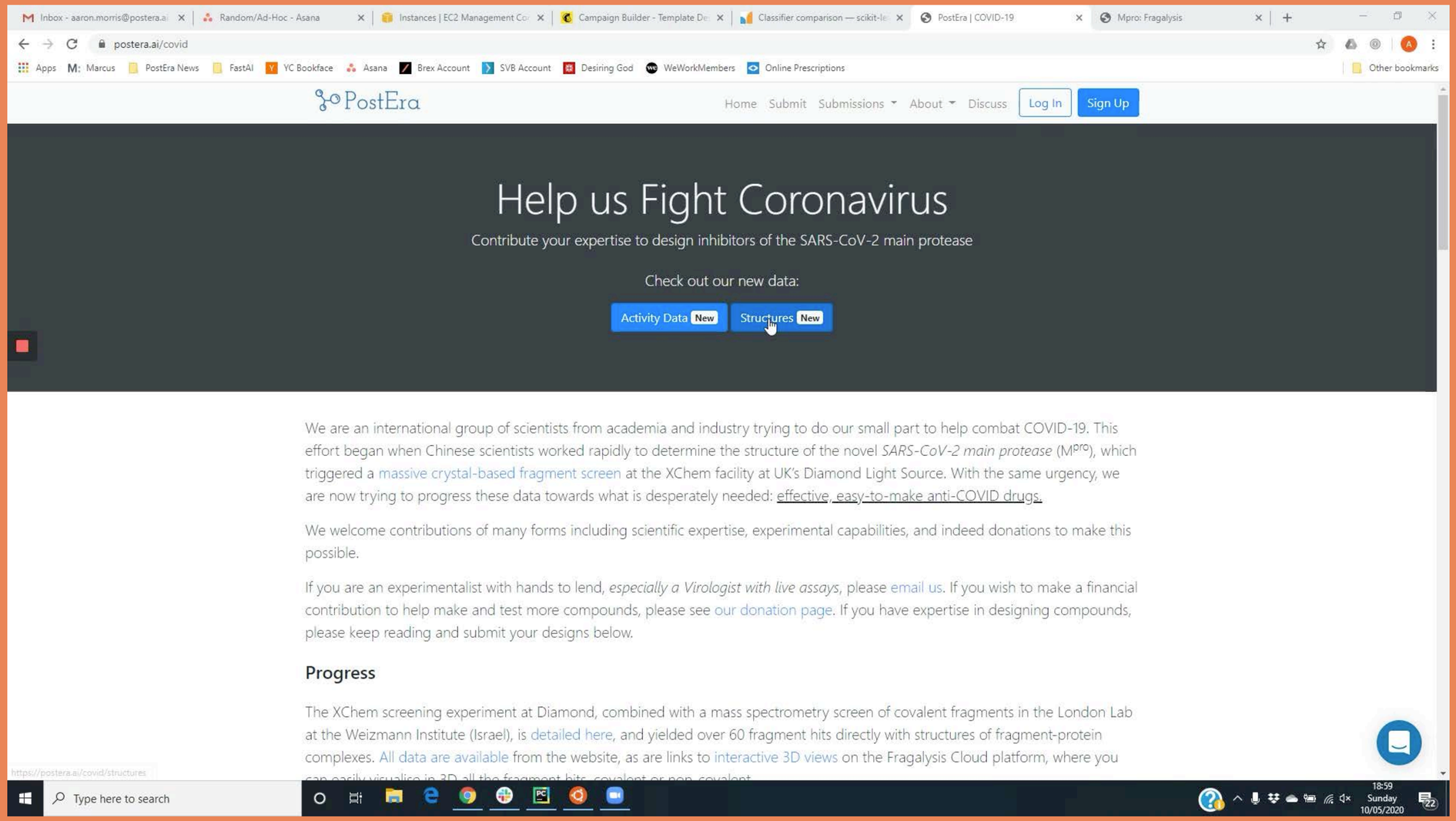
Diamond XChem's automated beamline enabled us to turn structures around in days



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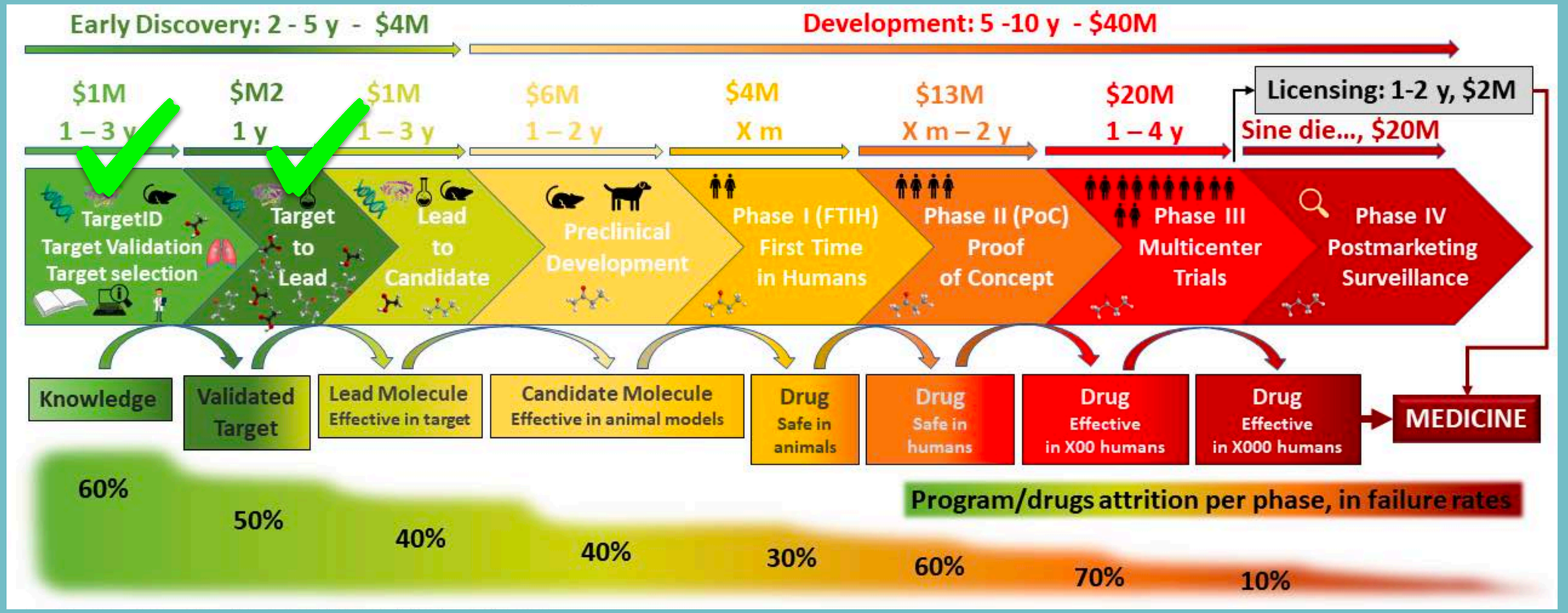
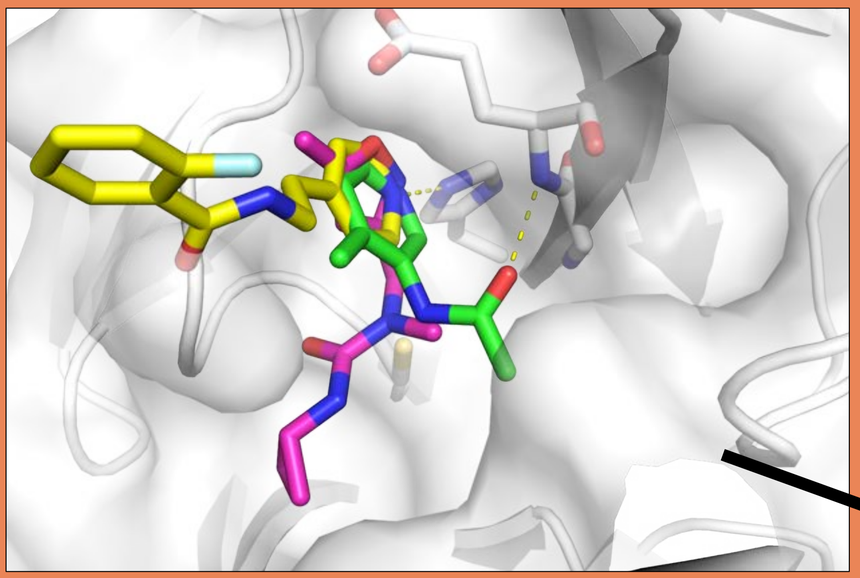
Drug discovery is usually a long and expensive process

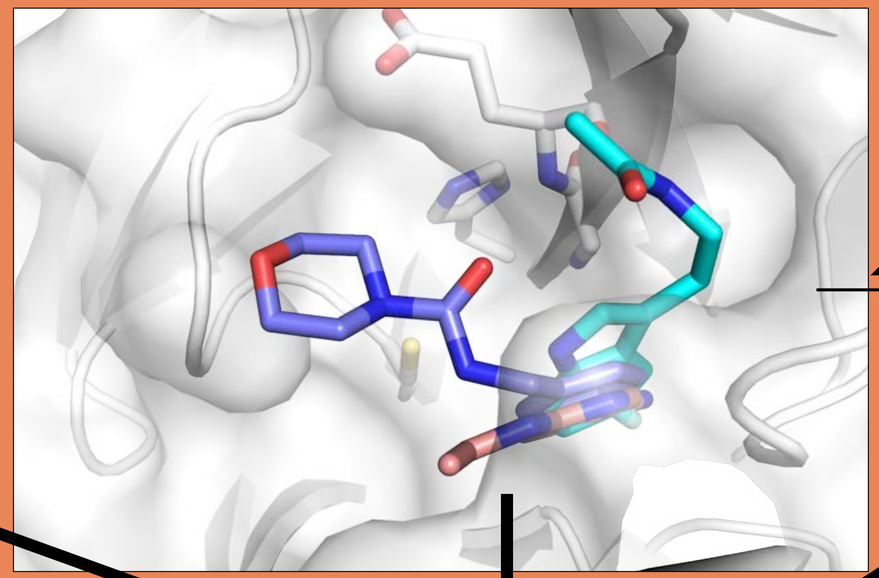


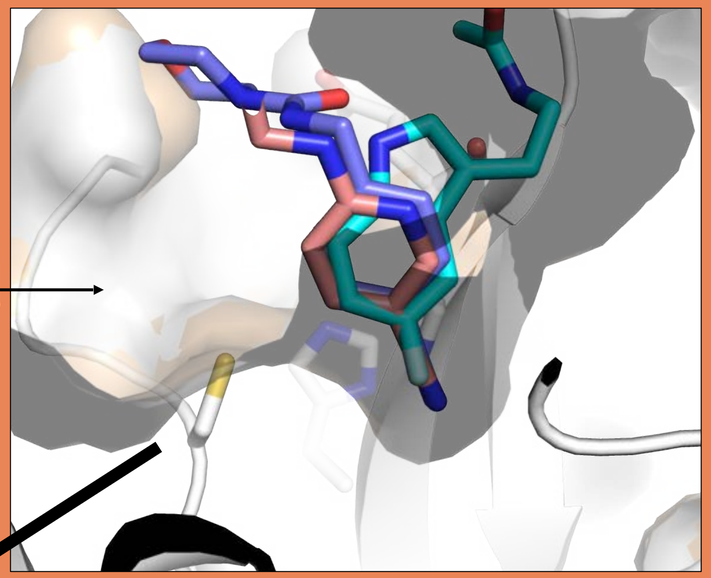
https://doctortarget.com/machine-learning-applied-drug-discovery/

How can we drastically cut down this timeline and ensure we will succeed?

Crowdsourcing generated a number of novel chemical series by fragment merging





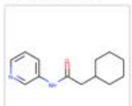


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

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:



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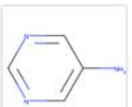

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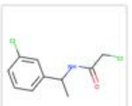

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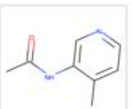

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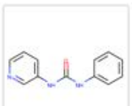

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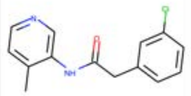


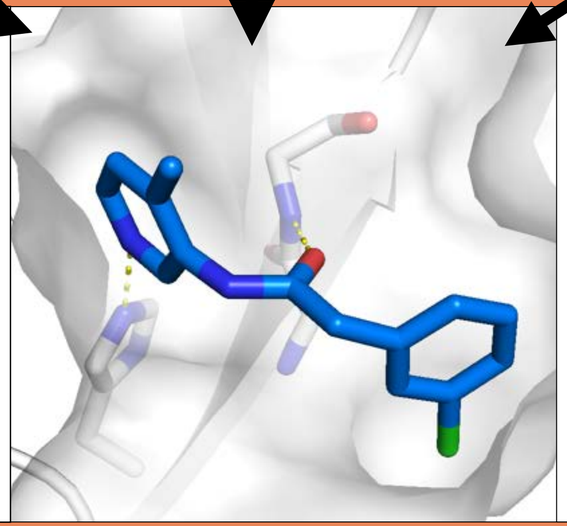
TRY-UNI-714a760b-6

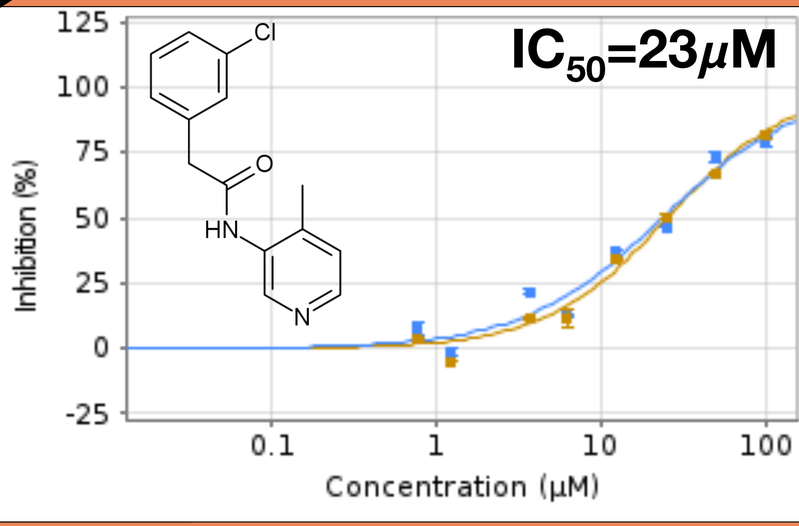
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

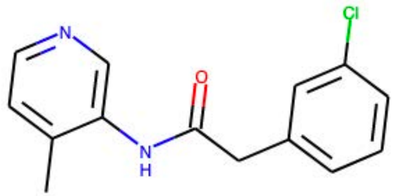
Enamine Mcule MolPort Assayed

View

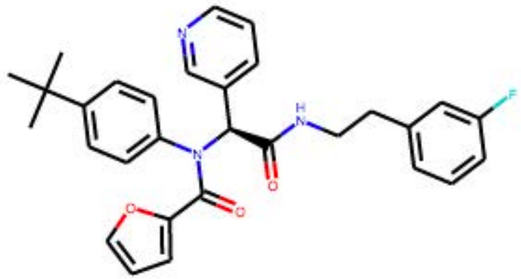




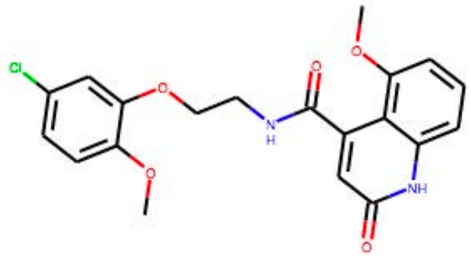
Crowdsourcing yielded multiple lead series



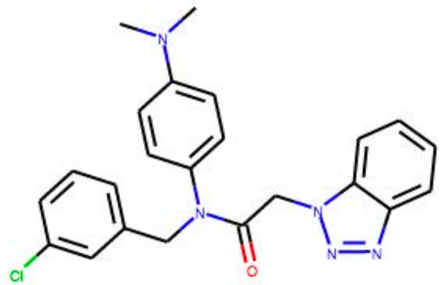
3-aminopyridines



Ugis



quinolones



benzotriazoles

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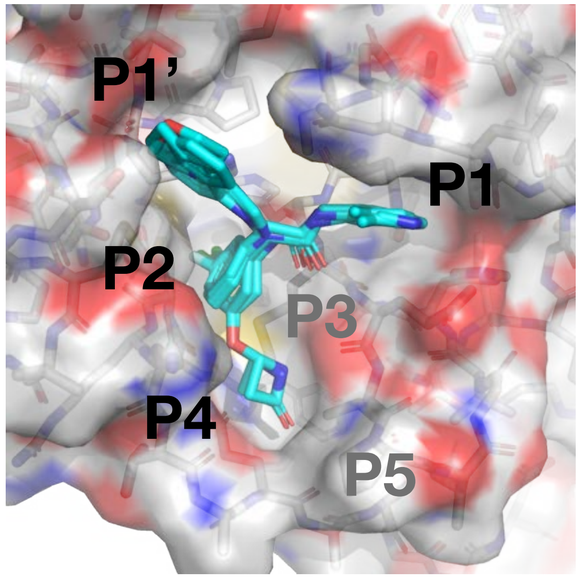
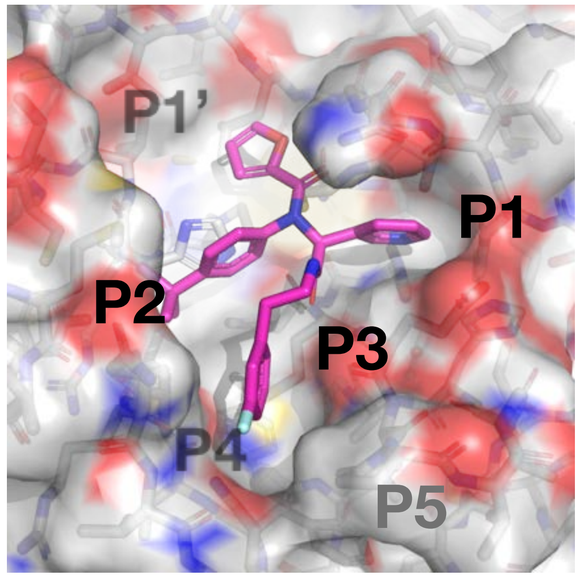
[As of 16 Mar 2021]

Crowdsourcing yielded multiple lead series



3-aminopyridines



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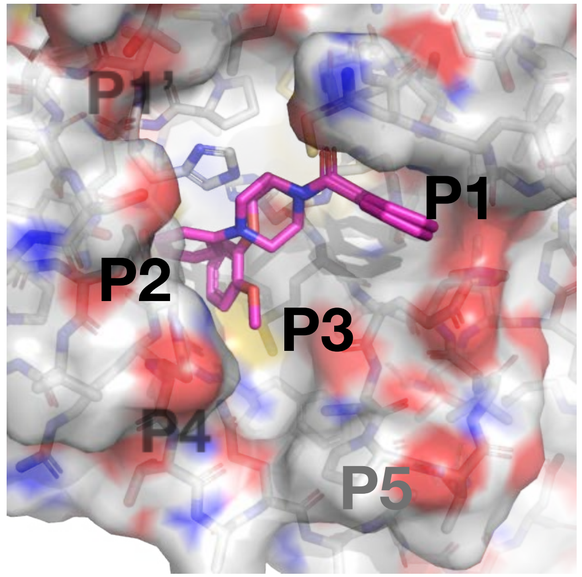
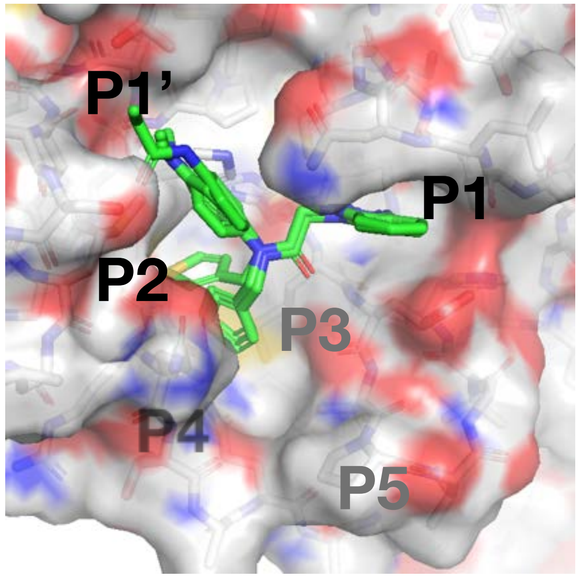


quinolones



benzotriazoles

http://postera.ai/covid

[As of 16 Mar 2021]

Every real drug discovery project needs a target product profile (TPP) to know what we are aiming to achieve

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

MedChemica
CREATING A STEP CHANGE IN MEDICINAL CHEMISTRY

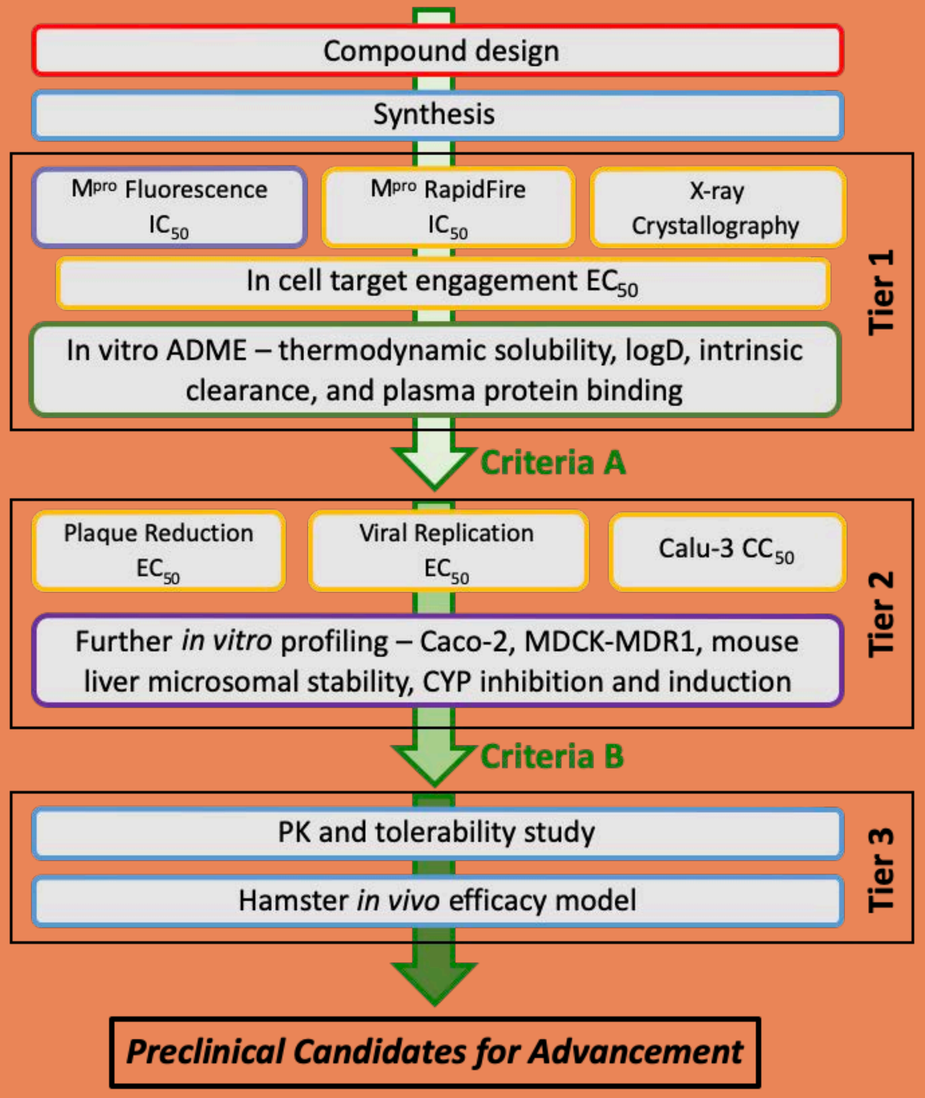
COVID Moonshot

Centre for Medicines Discovery
UNIVERSITY OF OXFORD

XCHEM Diamond Fragment Screening
diamond

Our assay cascade is designed to allow us to rapidly make progress against our TPP objectives

Ed Griffen
Medchemica



Does it inhibit Mpro? How does it bind?

Does it enter cells and inhibit Mpro?

Does it have a chance of working in humans?

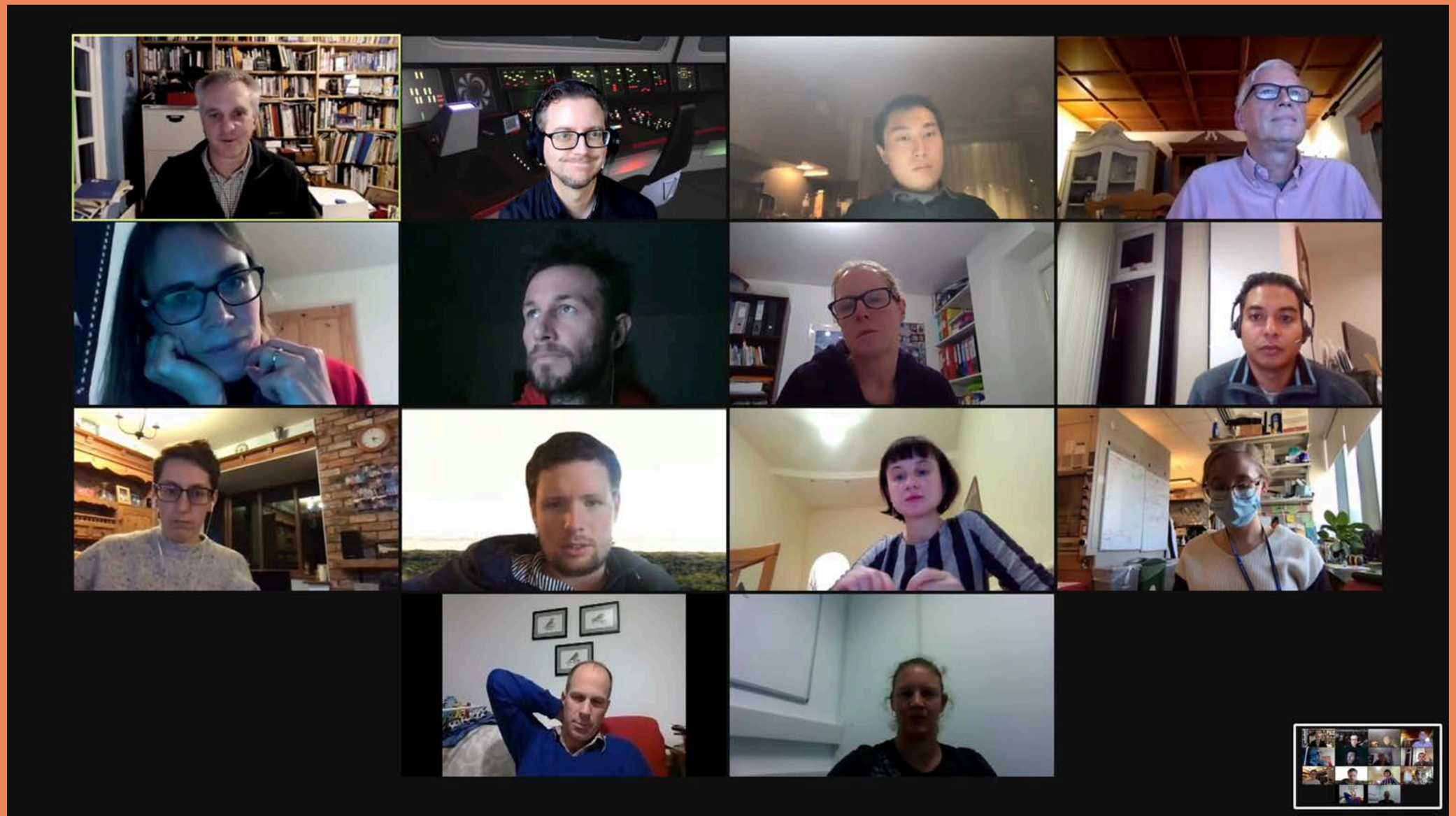
Does it kill virus in infected cells, sparing healthy cells?

Does it have a favorable safety profile?

Is it orally bioavailable at required concentrations?

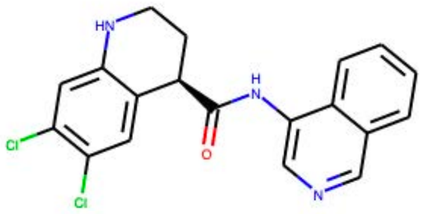
Assay components donated by groups and CROs around the world

Weekly project meetings look a little different from normal drug discovery projects

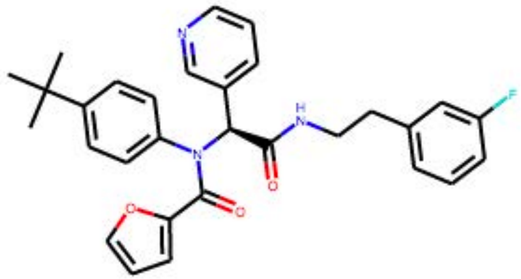


The med chem design team brought >100 years of industry med chem experience to bear

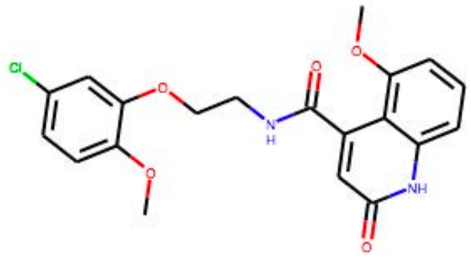
Ed Griffen
Medchemica



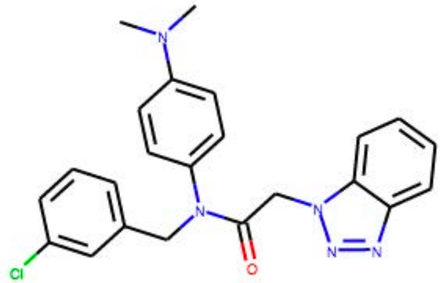
3-aminopyridines
948 compounds
(primary series)



Ugis
403 compounds
(backup series)



quinolones
86 compounds
(backup series)



benzotriazoles
42 compounds
(backup series)

258 X-ray structures (and rapidly growing)
>25% of all SARS-CoV-2 structures!

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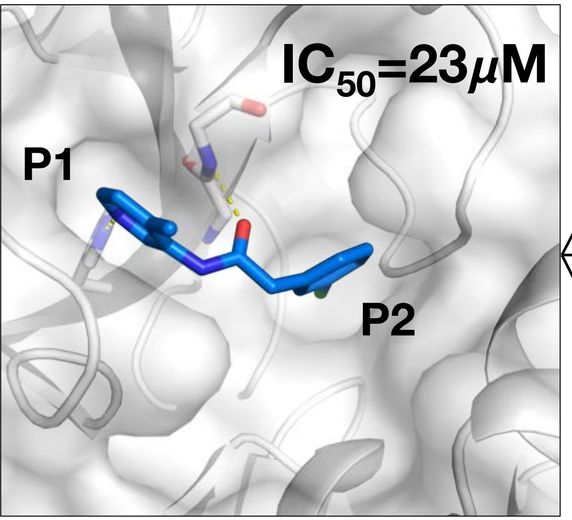
[As of 16 Mar 2021]

3-aminopyridines provide a potent P1-P2 scaffold capable of accessing P4 and P1' pockets

>300 aminopyridine compounds synthesized



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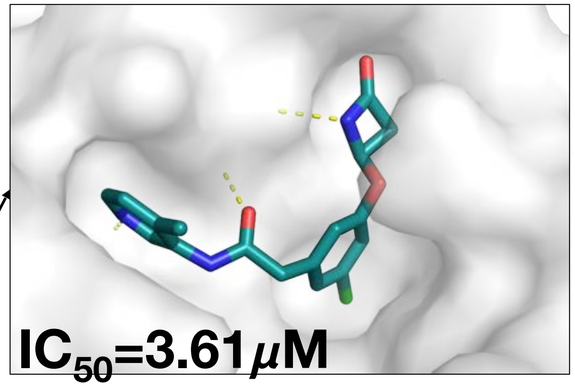

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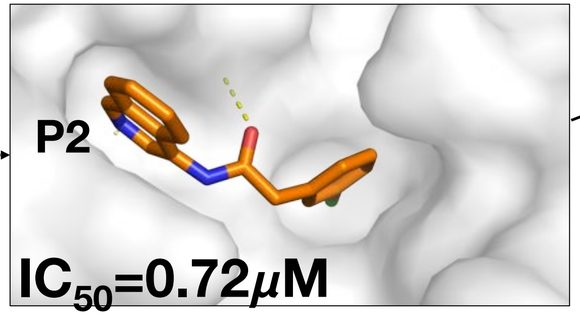
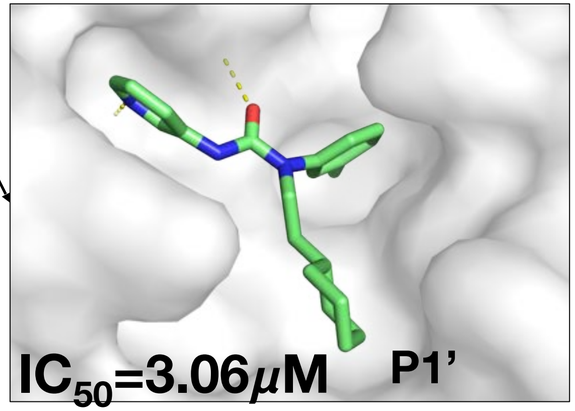
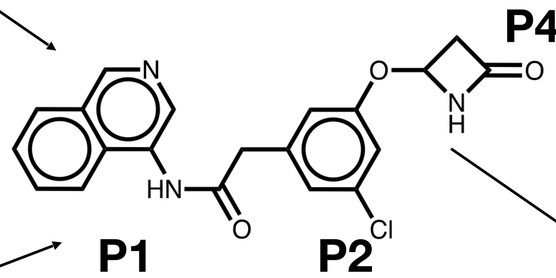
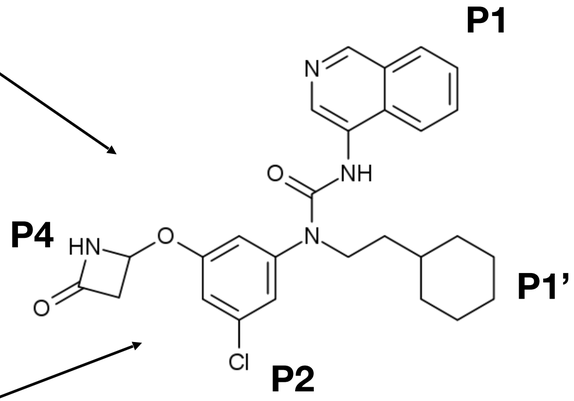


7.5x

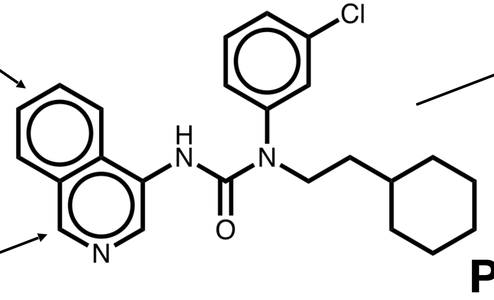


IC_{50}=260 nM





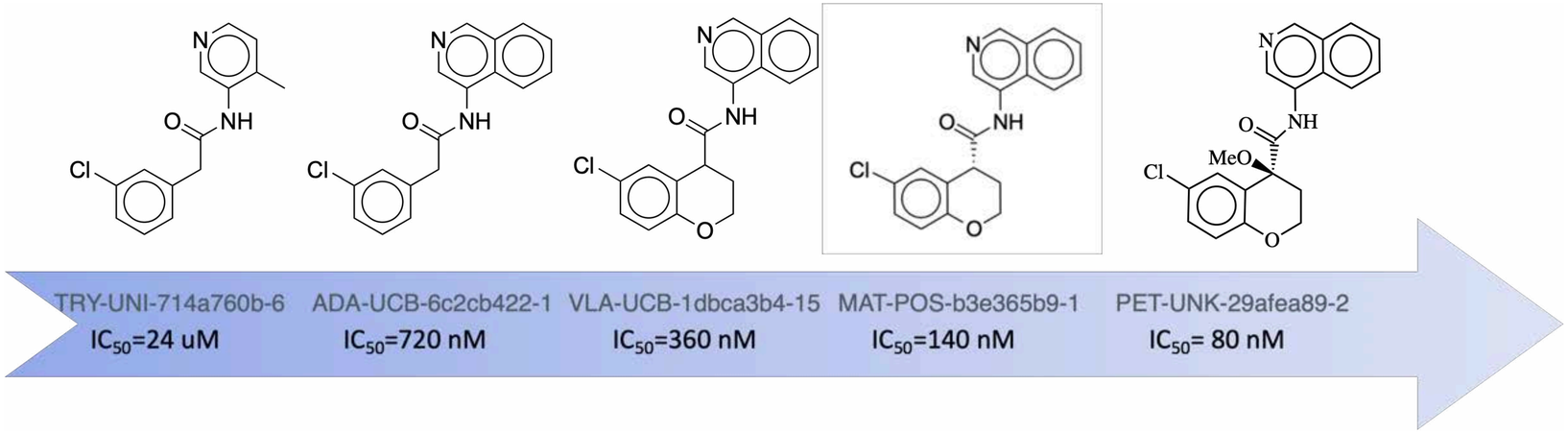
IC_{50}= 105 nM

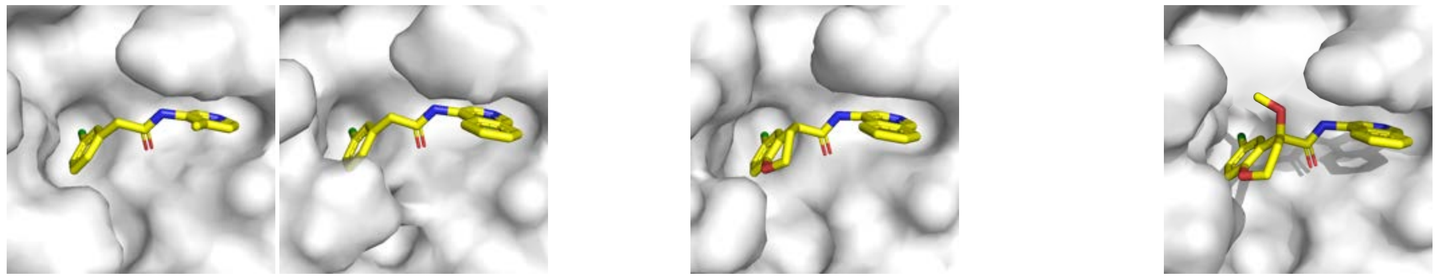


IC_{50}=270 nM

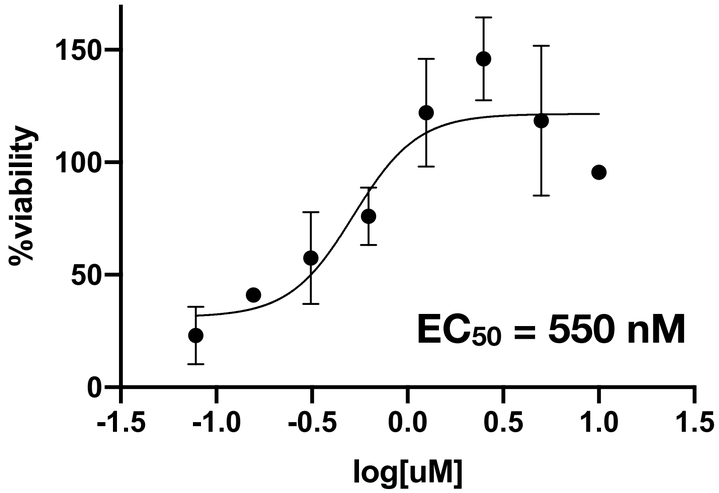
http://postera.ai/covid

Optimization of the P1-P2 scaffold resulted in incredibly potent compound with ~0.5 µM antiviral activity





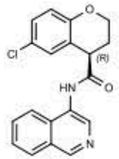
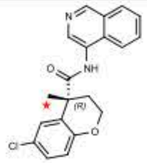
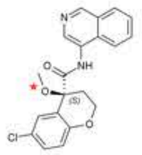
Lead compound active against live SARS-CoV-2



http://postera.ai/covid

With the Israel Institute of Biological Research

P1-P2 scaffold is close to meeting our target product profile (TPP) objectives even without P1'/P4 substituents

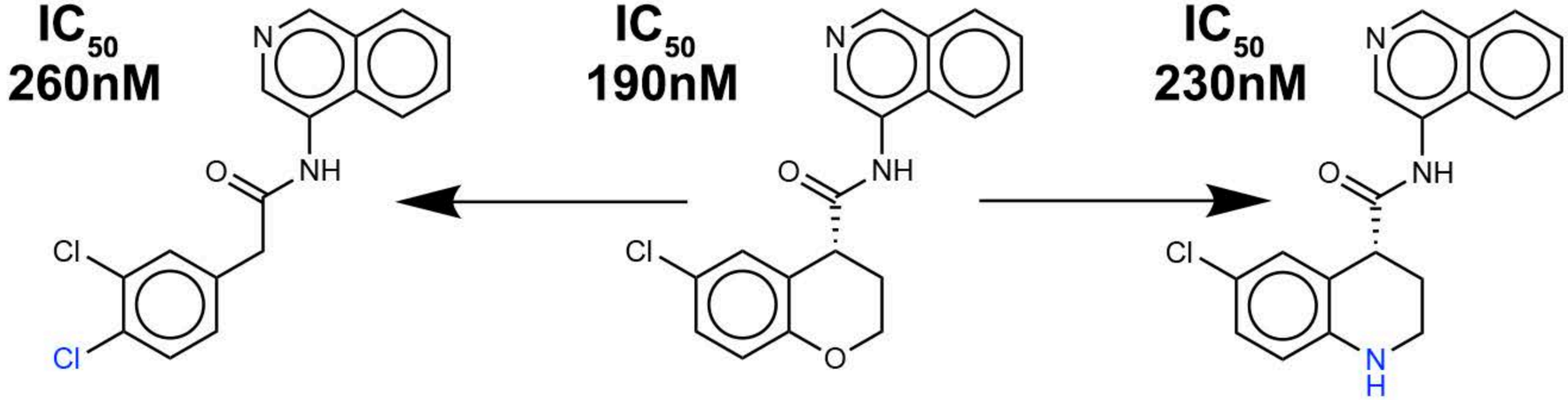
					Activity					ADME				Off-target				*in vivo* stability		*in vivo* PK							
Postera ID	**CDD ID**	**Structure**	**Mw** (g/mol)	**log P**	**Antiviral IC50** (µM) *Vero6 CPE (IIBR)* *<0.2*	**Antiviral IC50** (µM) *Calu3 FFU (Oxford)*	**Cytotox CC50** (µM) *Calu3 (Oxford)*	**Protease IC50** (µM) *Fluorescence (Weizmann)* *<0.05*	**Protease IC50** (µM) *MassSpec (Oxford)* *<0.05*	**Solubility (uM)** *>10uM (ideal >5mg/ml)*	**HLM $t_{1/2}$** (/min) *Human liver microsms*	**HLM CLint** (µg/min/mg prot) *Human liver microsms* *=<10*	**permeability Mean Papp** (10^{-6}/cms) *MDCK-MDR1 A2B* *>=3*	**CYP inhibition** *5 Cyp profile*	**Off-target most potent** *Eurofins Safety 44*	**hERG IC50** (mM) *>= 30*	**Protease most potent hit** *Nanosyn panel 40 proteases*	**Rat Heps $t_{1/2}$** (/min) *Rat hepatocytes*	**Rat Heps Clint** *Rat hepatocytes* *=< 10*	**Species in vivo**	**Oral $t_{1/2}$** (/min)	**IV $t_{1/2}$** (/min)	**Oral cpd conc. (2h)**	**Oral cpd conc. (4h)**	**Bio-avail.** *>= 10%*	**Free drug** (%) *>1%*	**Calc.dose 70kg hum** (mg) *=< 750*
MAT-POS-b3e365b9-1	CVD-0013192		**338.79**	3.33	2.51	1.06	>100	0.19	0.25	33 *(0.011mg/ml)*	14	98.3	**40.8**				**clean**	17.8	78.1	Rat	60	formulation issues	25	< LoD	-	**12 (rat)**	
EDJ-MED-92e193ae-1	CVD-0014805		**337.81**	2.96	0.9 (rac) (n=2)			0.23		94 (rac)	95 (rac)	18 (rac)		IC50 1.8uM 2C9, 10uM 3A4, >33uM 1A2, 2C19, 2D6	**clean**			11.8	117	Mouse	20	19.2	3.6	<LoD	3%		
EDJ-MED-e4b030d8-13	CVD-0013210		**352.82**	3.89	2.5			0.28	0.32	172	80	21						6.88	202								
PET-UNK-29afea89-2	CVD-0013943		**368**	3.16	0.5 (n=2)			0.08 (n=2)		130	97	17						Mouse NCATS		Mouse	11	31	1.7	ND	2%		

http://postera.ai/covid

Good SAR during lead optimization points the way toward meeting our goals for selecting a clinical candidate

Solubility

189 µM	33 µM	94 µM (racemate)
IC_{50} 260nM	IC_{50} 190nM	IC_{50} 230nM

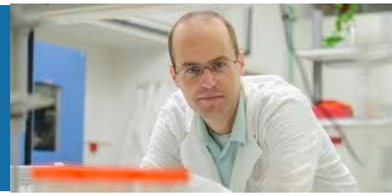


103.3 min	14.1 min.	94.8 min

Human Liver Microsomes ($t_{1/2}$)

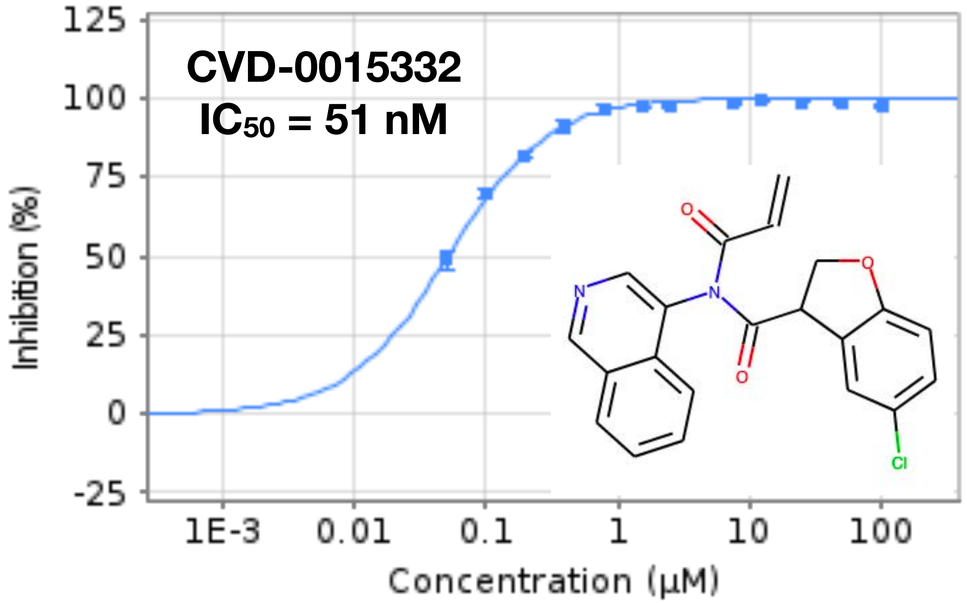
http://postera.ai/covid

Scaffold is well-poised for covalentization

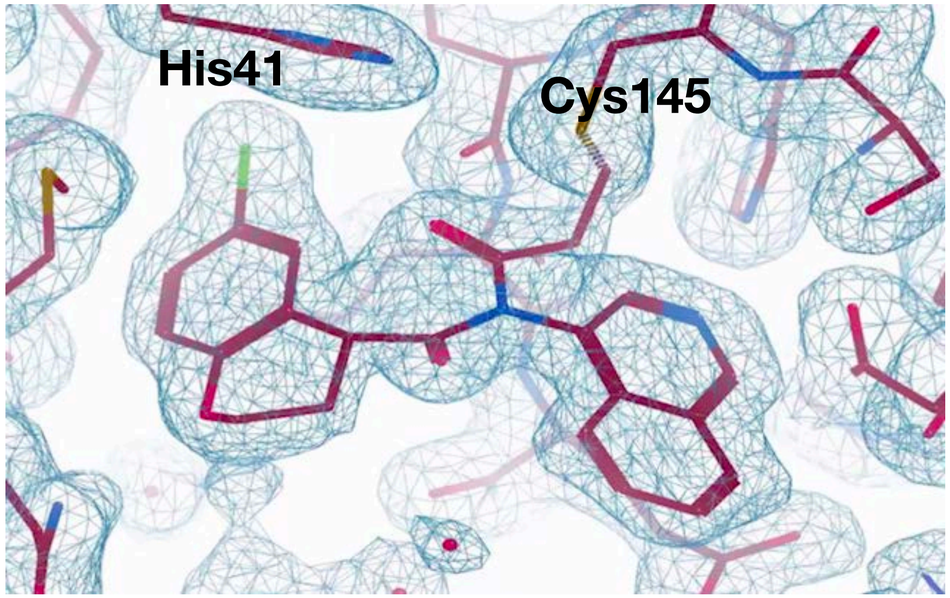


Nir London
Weizmann Institute

MAT-POS-e69ad64a-2



Matt Robinson, PostEra



Diamond Light Source / XChem
Daeron Fearon

http://postera.ai/covid

How can we design optimal P1’/P4 substituents?

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

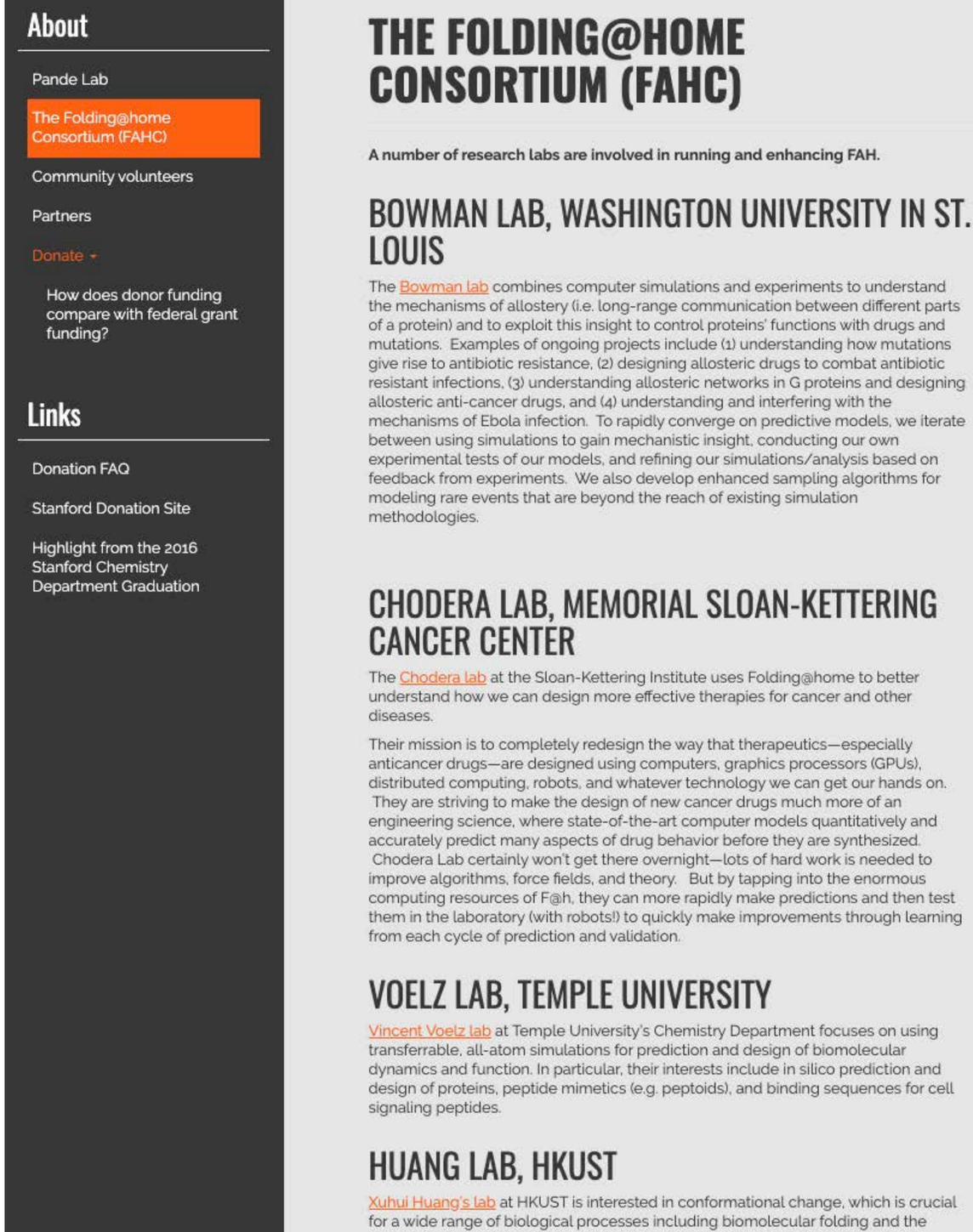
1924085 people have non-anonymously contributed to Folding@home.

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

~100 pflop/s!

WE MOBILIZED THE FOLDING@HOME CONSORTIUM TO FOCUS ON COVID-19

* **generating structural ensembles** to enable small molecule drug discovery
* **identifying cryptic pockets** for allosteric inhibition
* **free energy calculations** for prioritizing compounds tested by experimental collaborators
* **multiple targets:** spike protein, 3CL protease, ACE2, polymerase targets



About

Pande Lab

The Folding@home Consortium (FAHC)

Community volunteers

Partners

Donate

How does donor funding compare with federal grant funding?

Links

Donation FAQ

Stanford Donation Site

Highlight from the 2016 Stanford Chemistry Department Graduation

THE FOLDING@HOME CONSORTIUM (FAHC)

A number of research labs are involved in running and enhancing FAH.

BOWMAN LAB, WASHINGTON UNIVERSITY IN ST. LOUIS

The Bowman lab combines computer simulations and experiments to understand the mechanisms of allostery (i.e. long-range communication between different parts of a protein) and to exploit this insight to control proteins' functions with drugs and mutations. Examples of ongoing projects include (1) understanding how mutations give rise to antibiotic resistance, (2) designing allosteric drugs to combat antibiotic resistant infections, (3) understanding allosteric networks in G proteins and designing allosteric anti-cancer drugs, and (4) understanding and interfering with the mechanisms of Ebola infection. To rapidly converge on predictive models, we iterate between using simulations to gain mechanistic insight, conducting our own experimental tests of our models, and refining our simulations/analysis based on feedback from experiments. We also develop enhanced sampling algorithms for modeling rare events that are beyond the reach of existing simulation methodologies.

CHODERA LAB, MEMORIAL SLOAN-KETTERING CANCER CENTER

The Chodera lab at the Sloan-Kettering Institute uses Folding@home to better understand how we can design more effective therapies for cancer and other diseases.

Their mission is to completely redesign the way that therapeutics—especially anticancer drugs—are designed using computers, graphics processors (GPUs), distributed computing, robots, and whatever technology we can get our hands on. They are striving to make the design of new cancer drugs much more of an engineering science, where state-of-the-art computer models quantitatively and accurately predict many aspects of drug behavior before they are synthesized. Chodera Lab certainly won't get there overnight—lots of hard work is needed to improve algorithms, force fields, and theory. But by tapping into the enormous computing resources of F@h, they can more rapidly make predictions and then test them in the laboratory (with robots!) to quickly make improvements through learning from each cycle of prediction and validation.

VOELZ LAB, TEMPLE UNIVERSITY

Vincent Voelz lab at Temple University's Chemistry Department focuses on using transferrable, all-atom simulations for prediction and design of biomolecular dynamics and function. In particular, their interests include in silico prediction and design of proteins, peptide mimetics (e.g. peptoids), and binding sequences for cell signaling peptides.

HUANG LAB, HKUST

Xuhui Huang's lab at HKUST is interested in conformational change, which is crucial for a wide range of biological processes including biomolecular folding and the

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

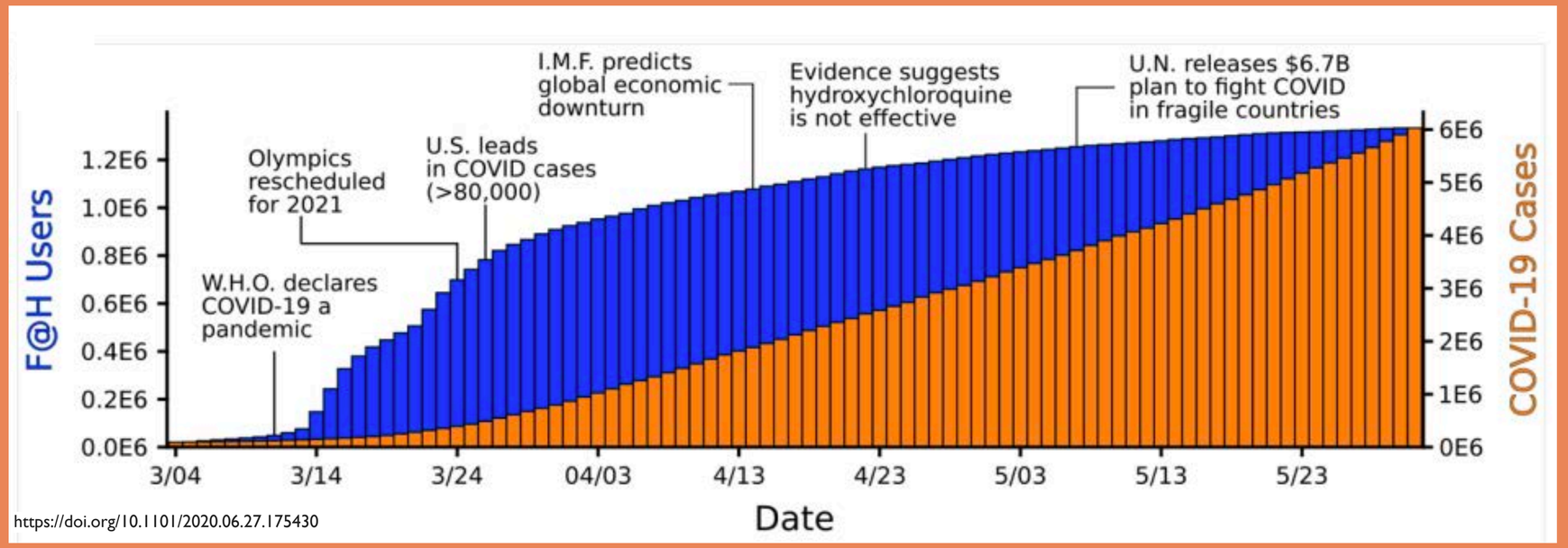
February 27, 2020
by Greg Bowman

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

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

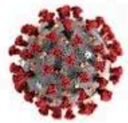
View Full Coverage

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

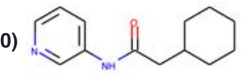
Hackaday · 7 days ago

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

There are multiple design vectors to explore

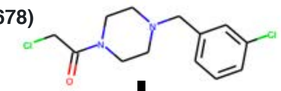
fragment merger produced initial lead compound

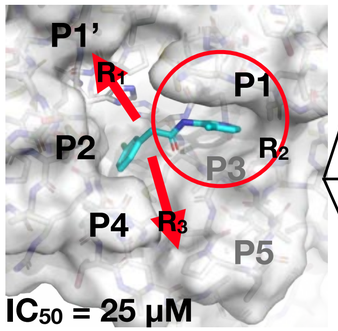
(x0770)



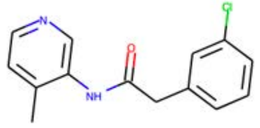
x

(x0678)





IC_{50} = 25 µM

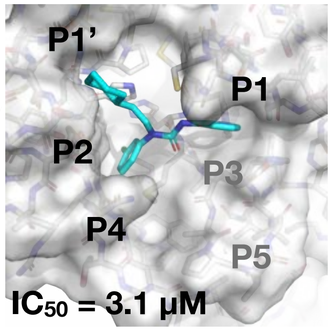


TRY-UNI-714a760b-6 (x2646)
current lead compound

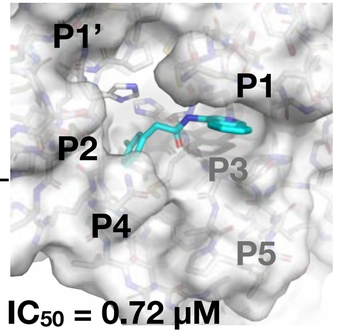
8x

35x

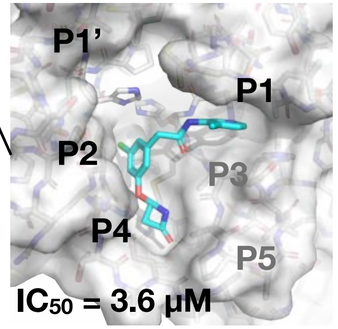
7x



IC_{50} = 3.1 µM

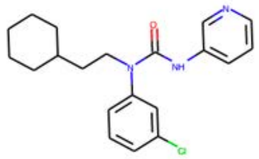


IC_{50} = 0.72 µM



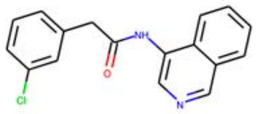
IC_{50} = 3.6 µM

P1' pocket engagement



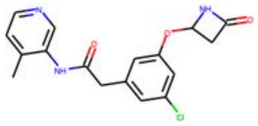
JOR-UNI-2fc98d0b-12 (x10201)

P1 substituent optimization



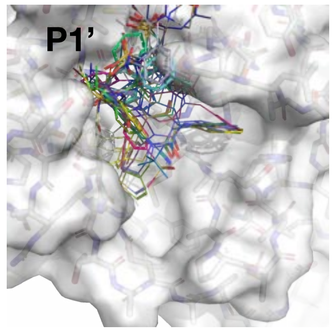
ADA-UCB-6c2cb422-1 (x10959)

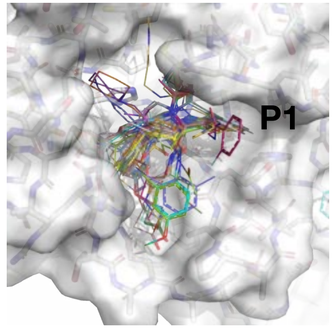
P4 pocket engagement

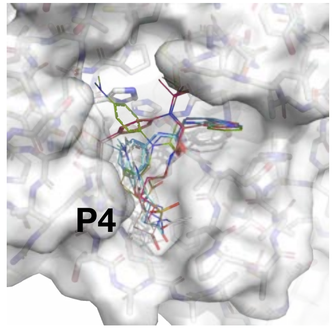


TRY-UNI-2eddb1ff-7 (x10789)

fragment-derived inspiration



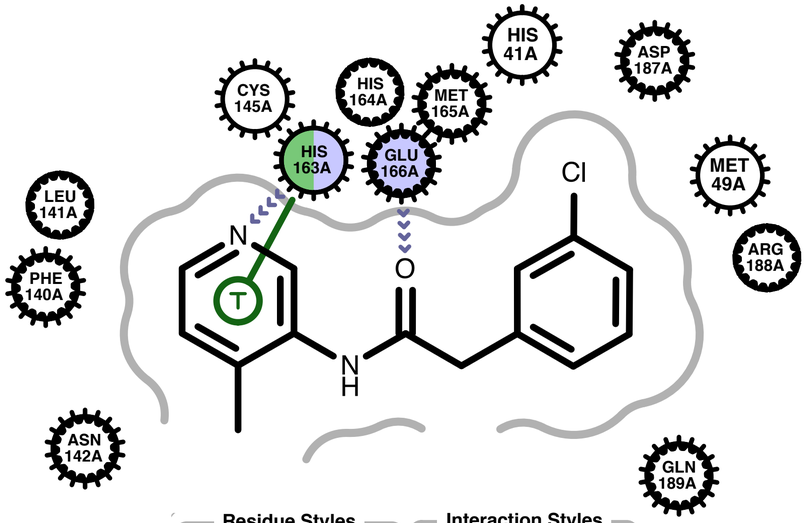




available fragment X-ray structures spanning pockets

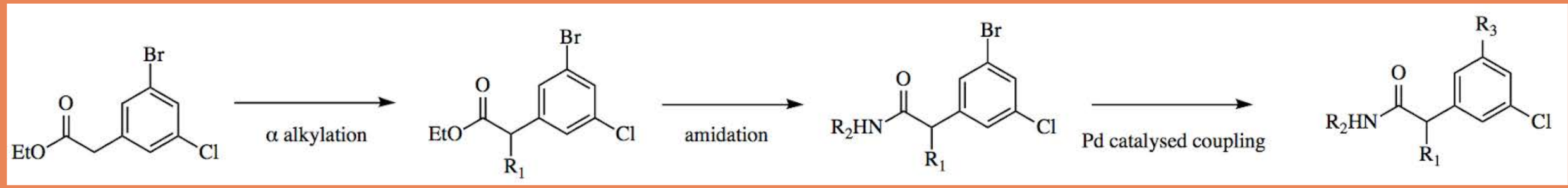
3-aminopyridine scaffold interactions

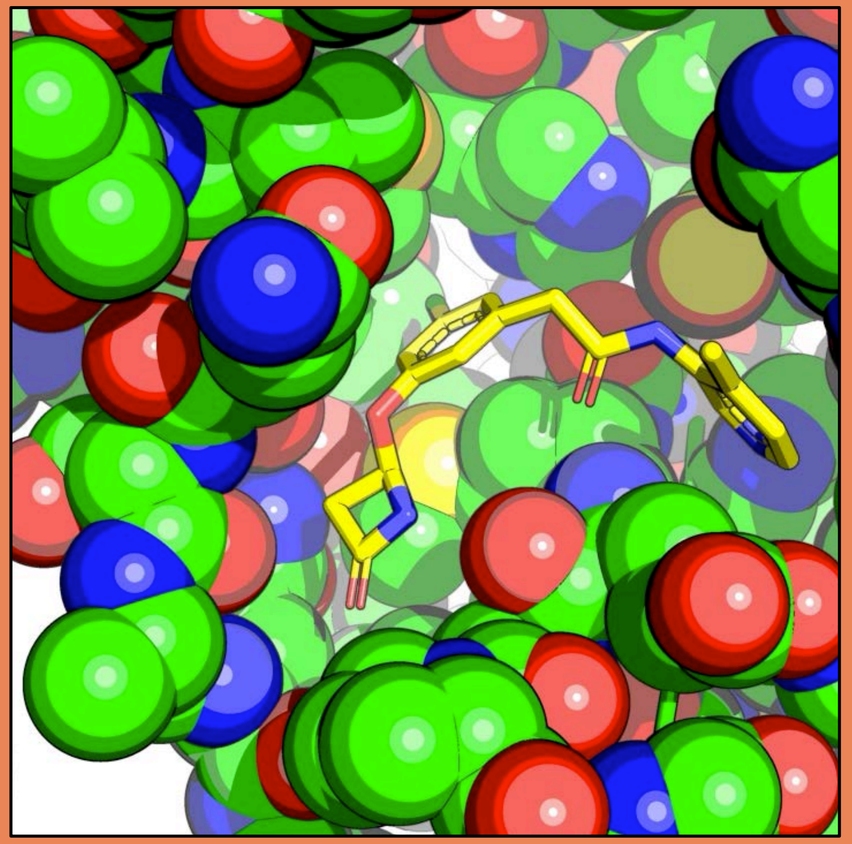
(264 assayed compounds in series)



TRY-UNI-714a760b-6 (x2646)
current lead compound

We can enumerate a huge variety of molecules that can be quickly synthesized by changing out the ingredients used in the final step

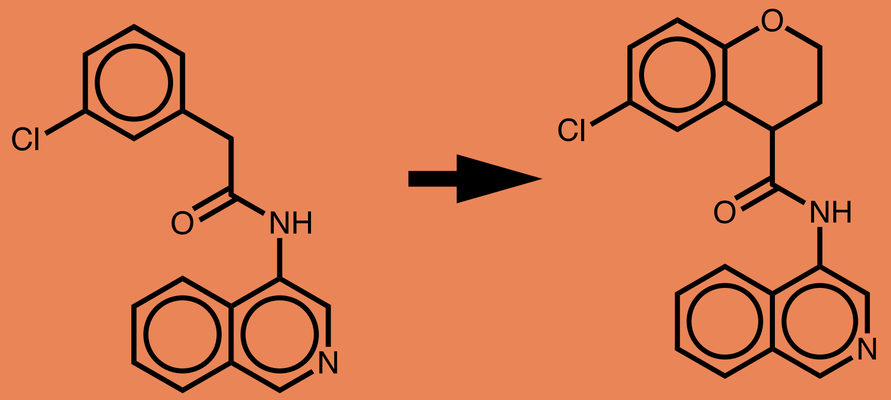




We can use Folding@home to run alchemical free energy calculations to evaluate which designs should bind better

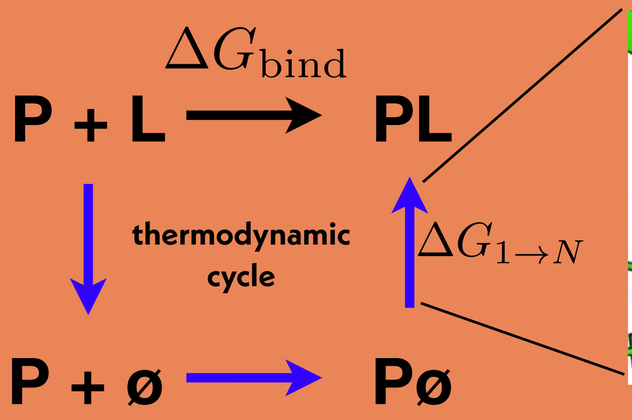
Instead of transmuting **lead** into **gold…**

…we change **one molecule** into **another!**

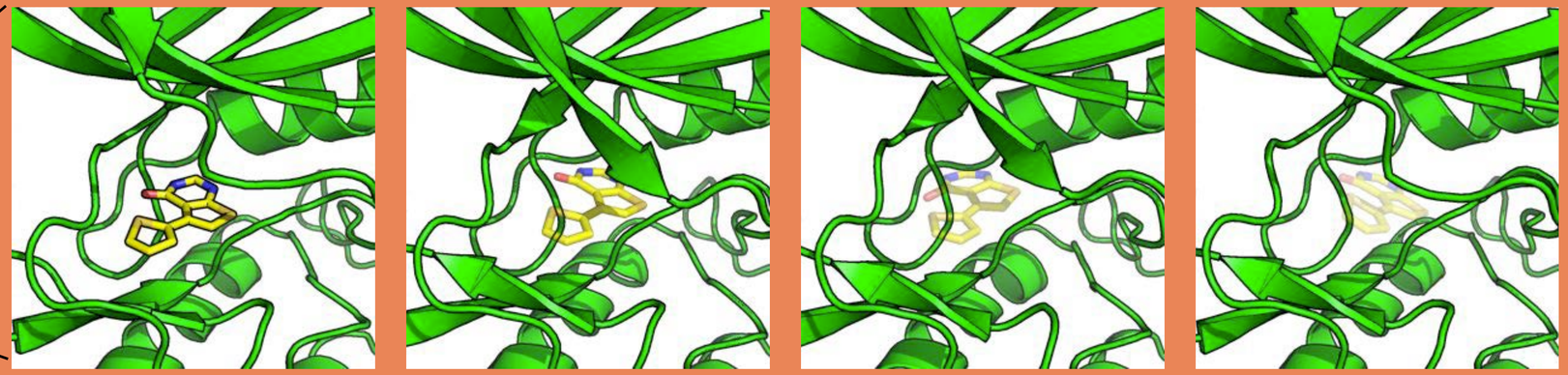


Neither process can be done with chemistry, but we can do it in a computer!

We can use Folding@home to run alchemical free energy calculations to evaluate which designs should bind better



multiple simulations of alchemical intermediates

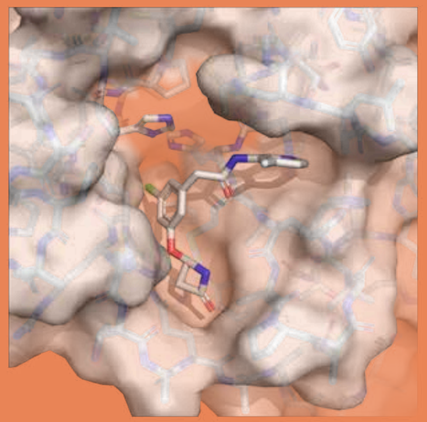


restraint imposition | discharging | steric decoupling | noninteracting

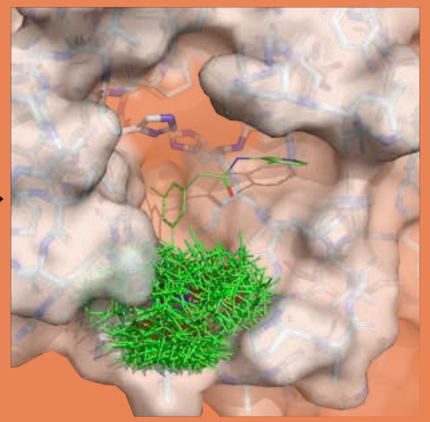
Folding@home can run relative alchemical free energy calculations at planetary scale, performing tens of thousands of transformations/week

Dominic Rufa
Tri-I TPCB PhD student

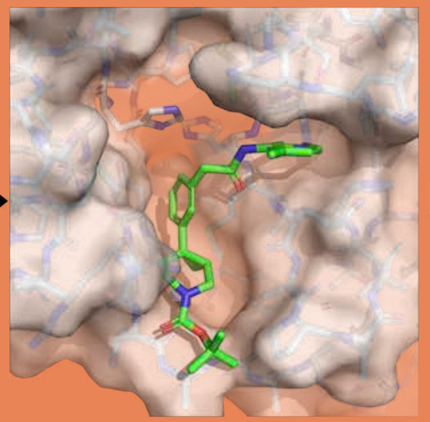
X-ray structure as reference



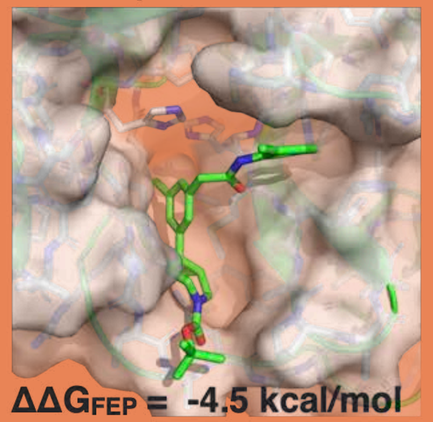
constrained enumeration of poses for proposed molecule



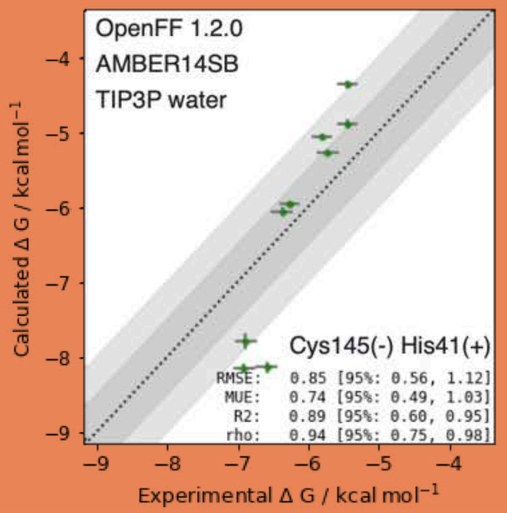
selection of pose with best docking score



nonequilibrium alchemical free energy calculation final posed structure



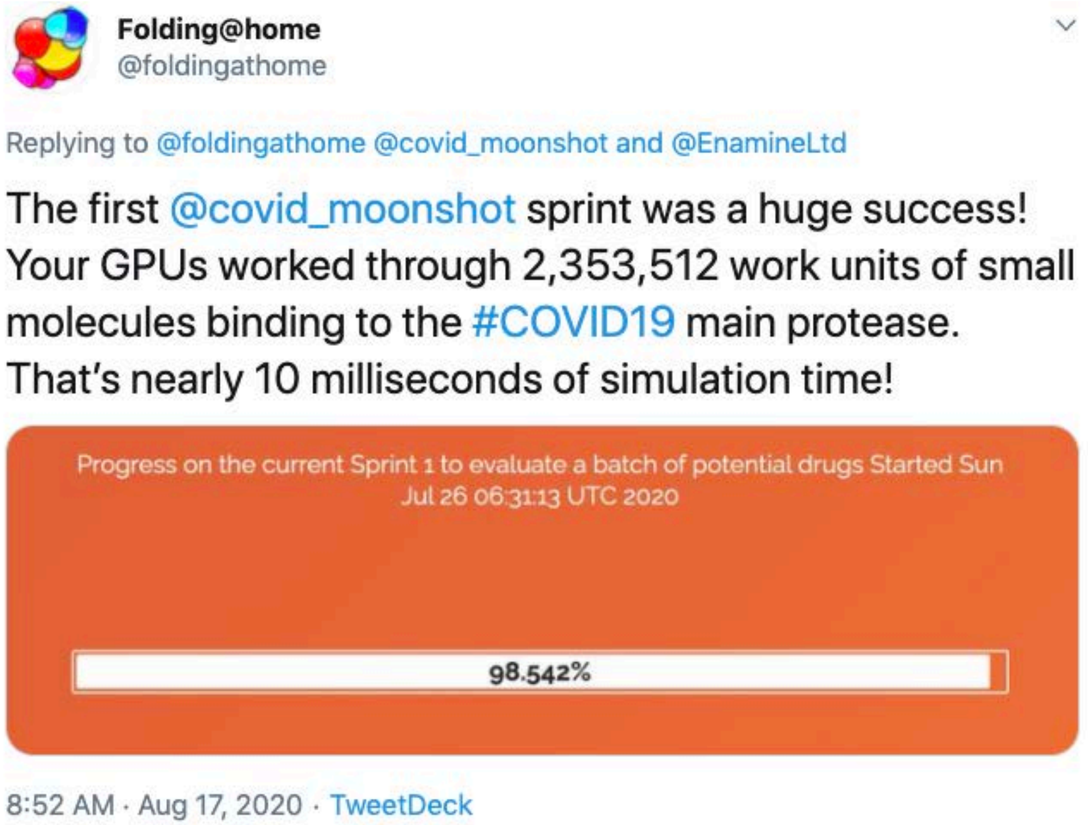
retrospective performance on 3-aminopyridine lead series



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

+ Hannah Bruce Macdonald
William Glass
Matt Wittman
David Dotson

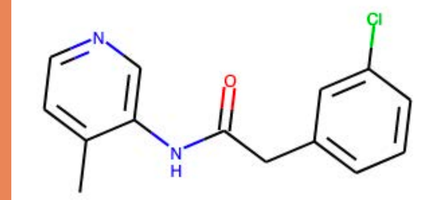
The Folding@home COVID Moonshot sprints represent an incredible amount of computational effort in service of a great cause



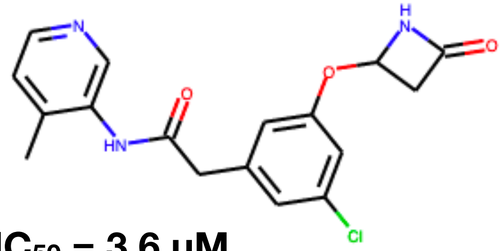
Our Folding@home free energy calculations aim to identify optimal P1’ and P4 substituents

Hannah Bruce Macdonald

MolSSI Investment Postroctoral Fellow, MSKCC
(now at Merck Research Labs, London)

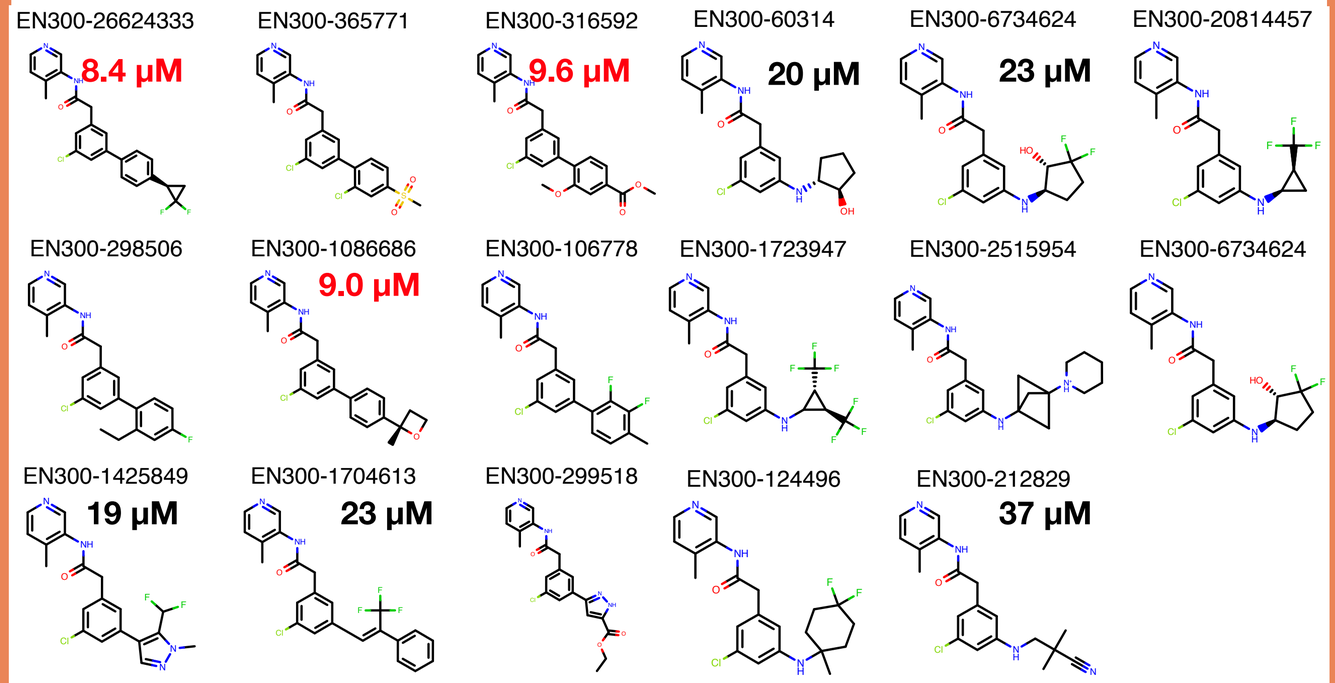


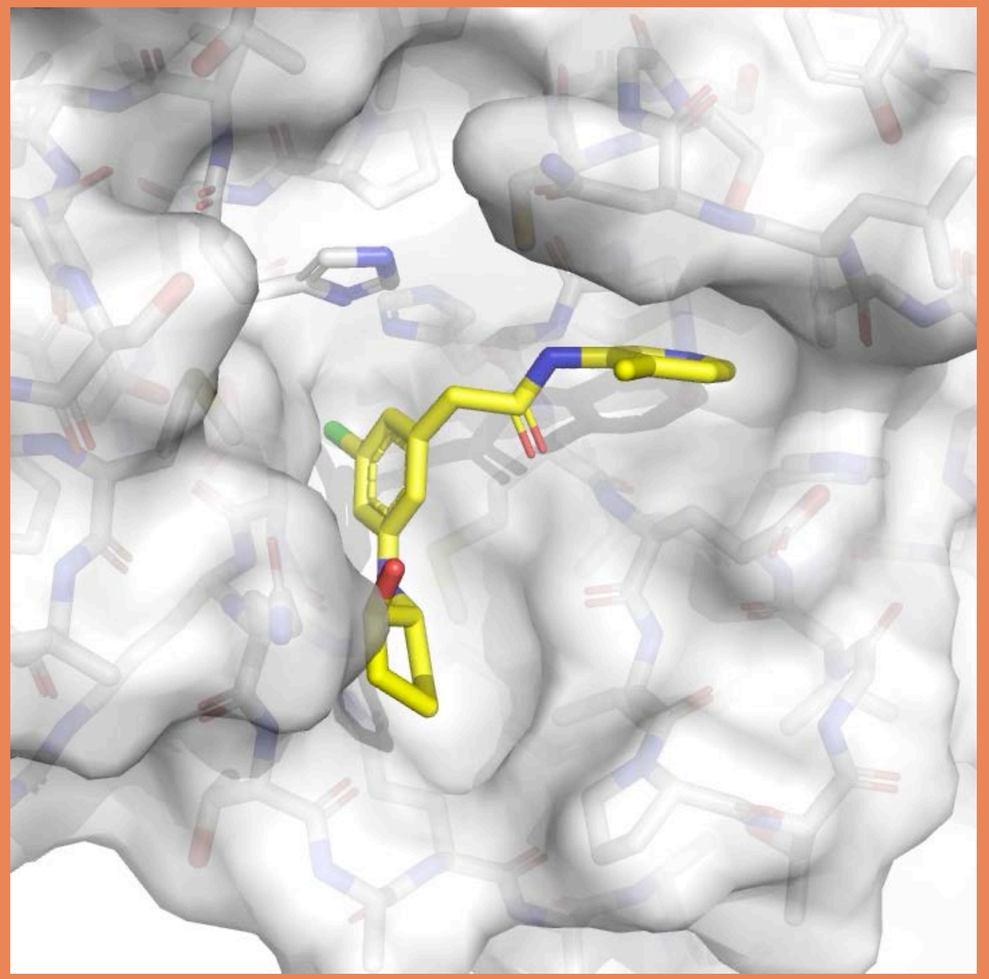
7x better



IC_{50} = 25 µM
TRY-UNI-714a760b-6

IC_{50} = 3.6 µM
TRY-UNI-2eddb1ff-7

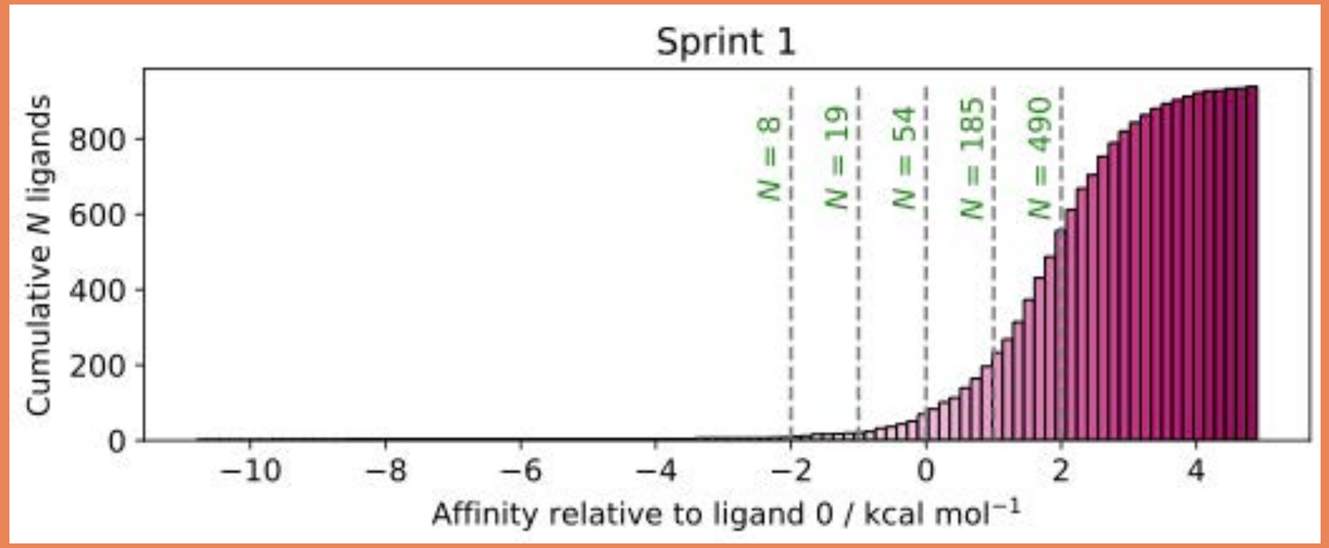




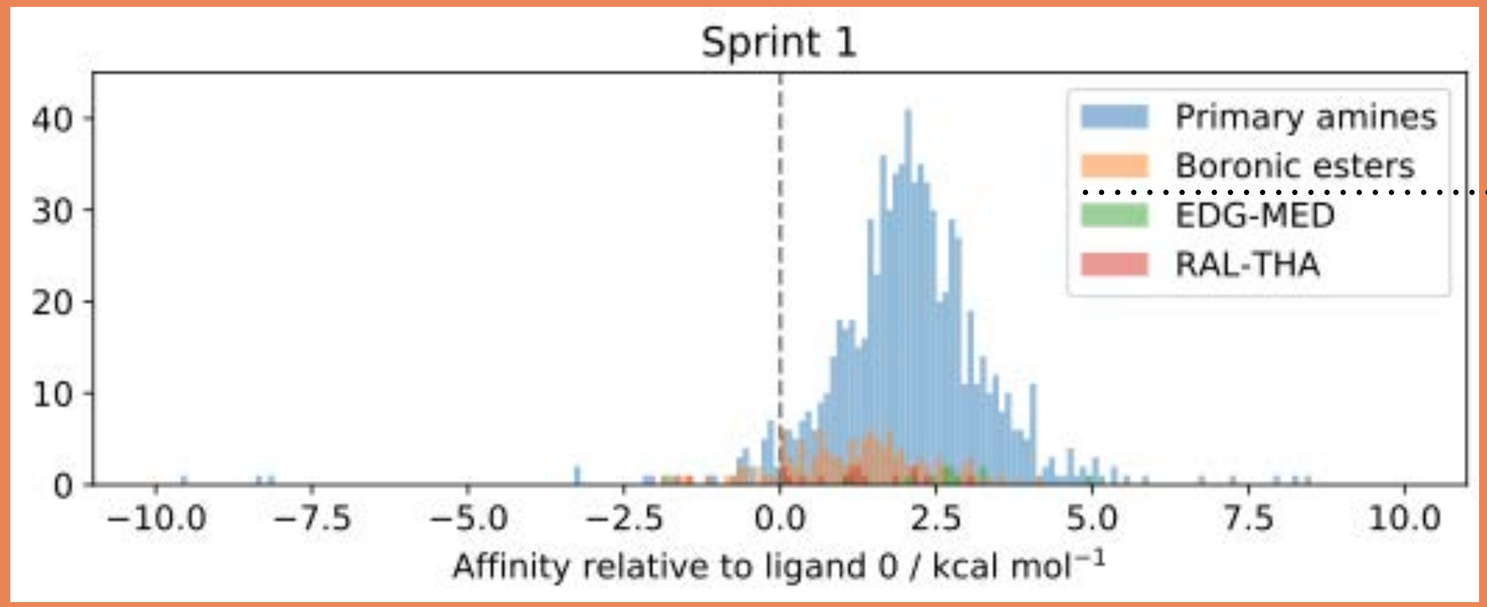
DATA: https://covid.postera.ai/covid/submissions/f42f3716-f86f-41d8-9906-c4fb7b6f5773

Most ideas were bad ideas

better **worse**



Human chemists seem better than random, but it's hard to get them to generate enough ideas

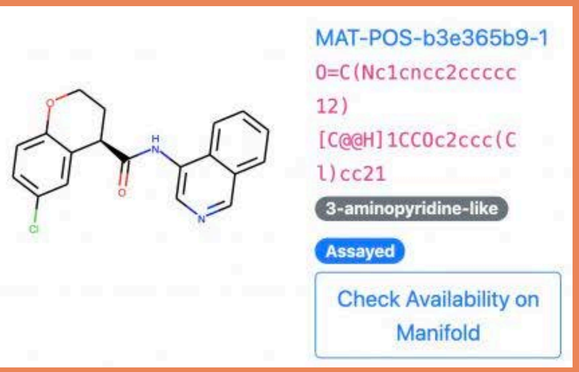


computer

humans

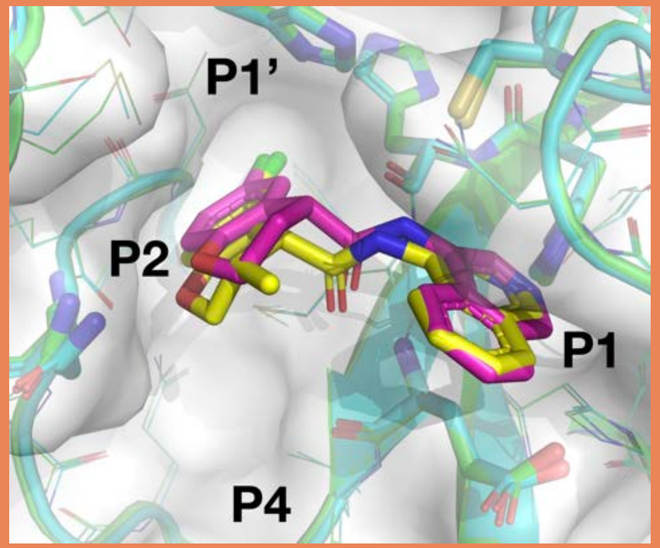
Sprint 5 builds on our current primary scaffold to explore the P1’ pocket to gain potency

benzopyran-isoquinoline series

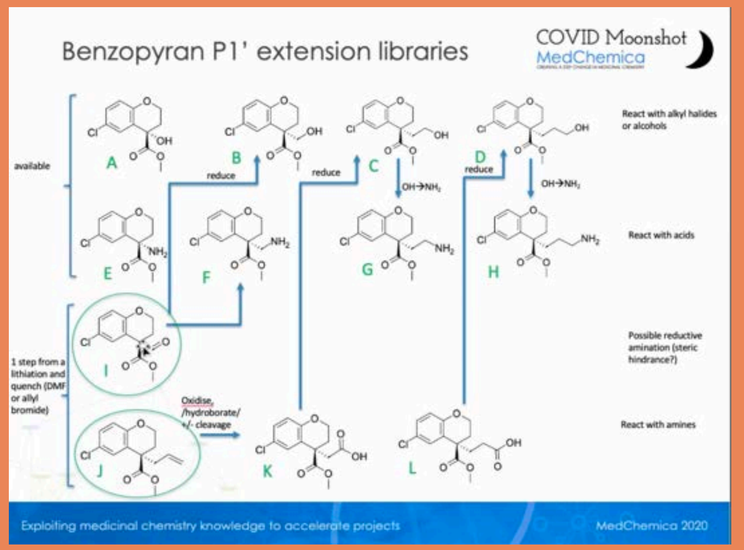


(evolved from 3-aminopyridine series from Sprints 1 + 2)

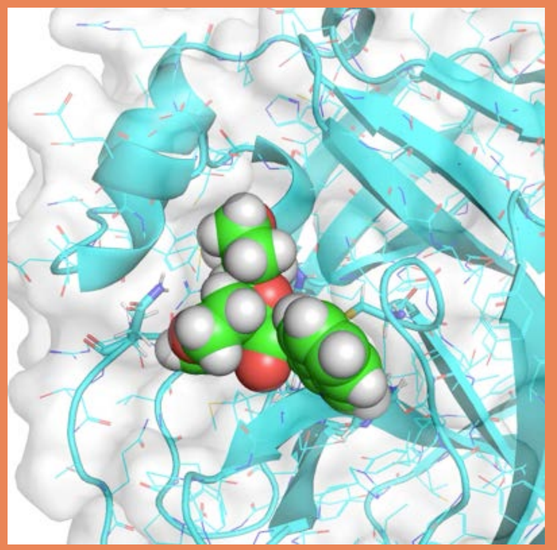
X-ray structures fof this series from Diamond



synthetic routes for ~15,000 compounds from MedChemica/PostEra



initial docked structures for Folding@home



Sprint 5
Science Dashboard

(compounds are currently being synthesized by Enamine)

COVID Moonshot Sprint 5 | Summary | Compounds | Microstates | Transformations | Reliable transformations | Retrospective transformations

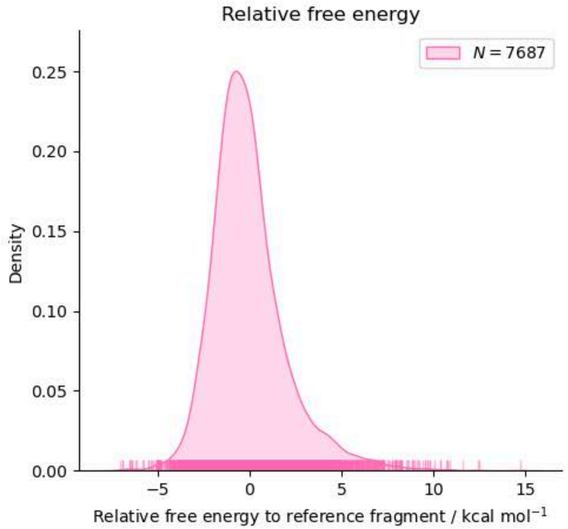
Description

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

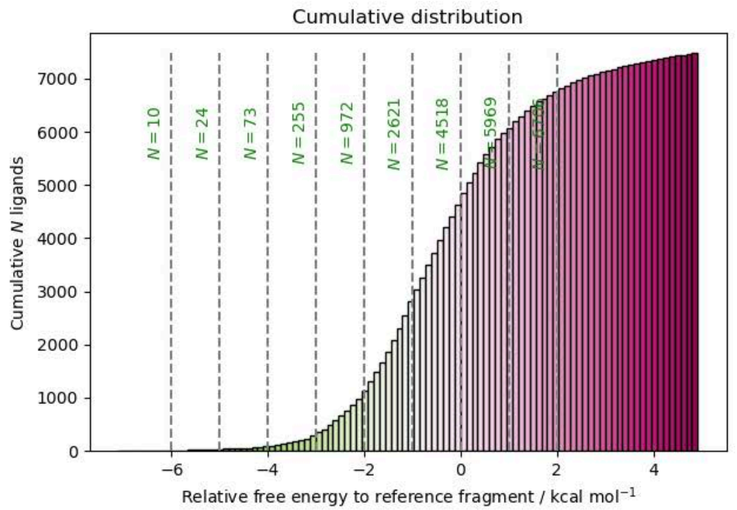
Progress

98.25%

Distributions



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

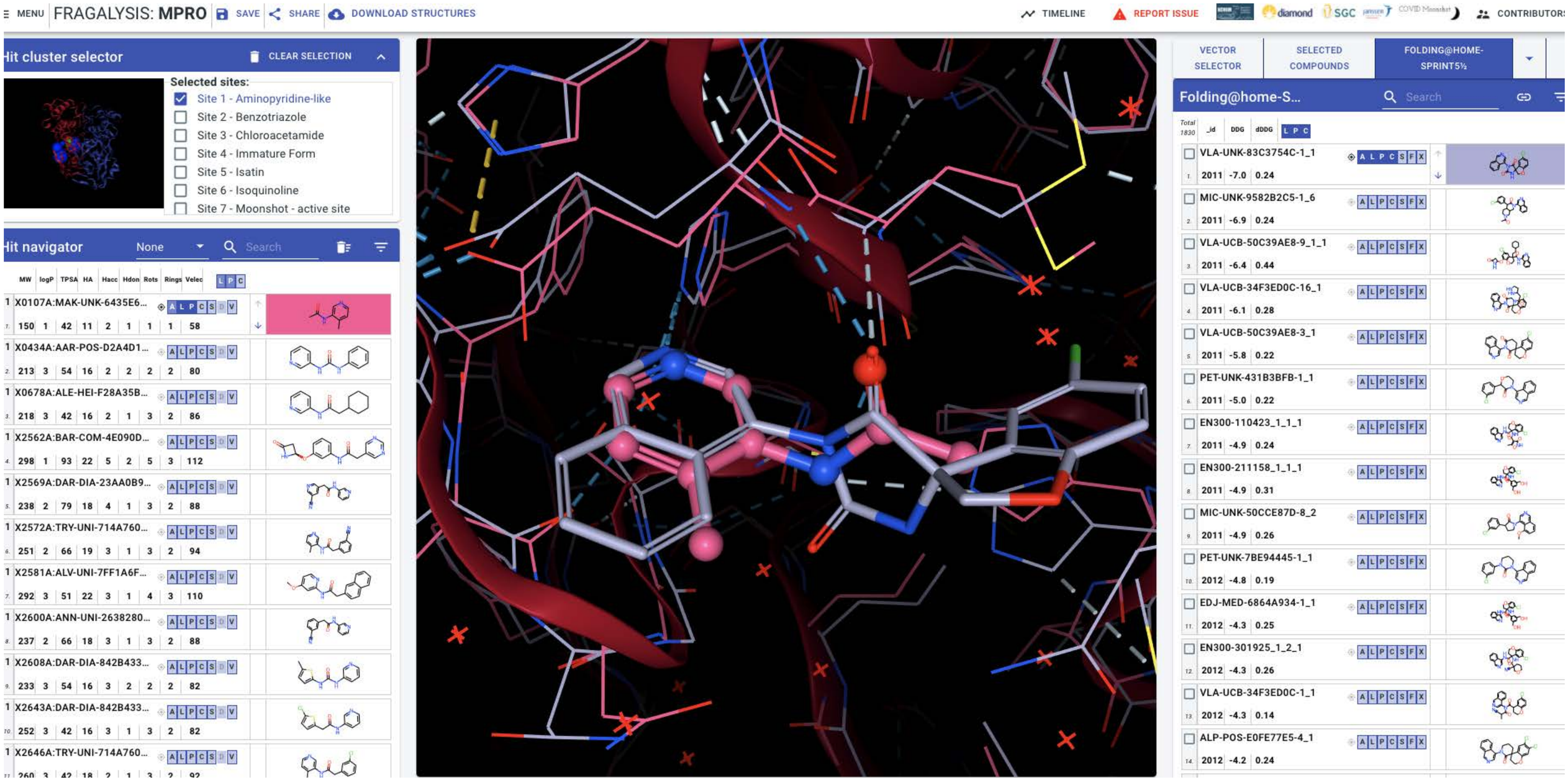


Updated 2021-02-21T21:35:59.343106+00:00

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
3	VLA-UCB-34f3ed0c-18	c1ccc2c(c1)cncc2N3C(=O)CN([C@@]4(C3=O)CCOc5c4cc(cc5)Cl)C(=O)N6CCNCC6	−15.4 ± 0.3	11.2 ± 0.2

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



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

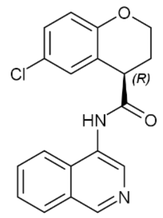
We are close to achieving our TPP objectives

Orally bioavailable inhibitor for therapeutic and prophylactic use

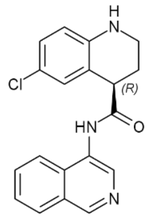
Property	Target range	Progress March 2021
protease assay	IC_{50} < 50 nM (compromise if clean and anti viral activity sufficient)	50nM (mean n=3)
viral replication (Vero-E6)	EC_{50} < 0.2µM	~0.5 µM VeroE6 CPE
plaque reduction (Vero-E6, Calu-3)	EC_{50} < 0.2µM	~0.25 µM Calu3
PK-PD	Cmin > EC90 (plaque reduction) for 24h	Studies in progress
Coronavirus spectrum	SARS-CoV2 B1.1.7 , 501.V2, B.1.1.248 variants essential SARS-CoV-1 & MERS desirable	Active against B1.1.7 , 501.V2 in cellular assays Compounds dispatched for panel testing (Takeda)
Route of administration	oral	Some oral exposure observed
solubility	> 5 mg/mL, >100µM tolerable	< 1mg/ml
half-life	Ideally>= 8 h (human) est from rat and dog	Rat 2h
safety	No significant protease activity >50% at 10µM (Nanosyn 61 protease panel) Only reversible and monitorable toxicities (NOAEL > 30x Cmax) No significant DDI - clean in 5 CYP450 isoforms Critical transporter check (*e.g.* OATP) hERG and NaV1.5 IC_{50} > 50 µM No significant change in QTc No mutagenicity or teratogenicity risk	Protease panel clean Eurofins / CEREP 44 target panel clean Cyp450: 1.8µM 2C9, 10µM 3A4 Cardiotoxicity in vivo testing planned Live phase planned Ames planned

We have demonstrated antiviral activity agaisnt variants

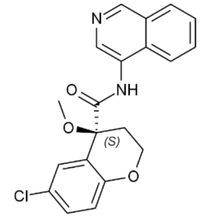
CVD-0013192



CVD-0014805

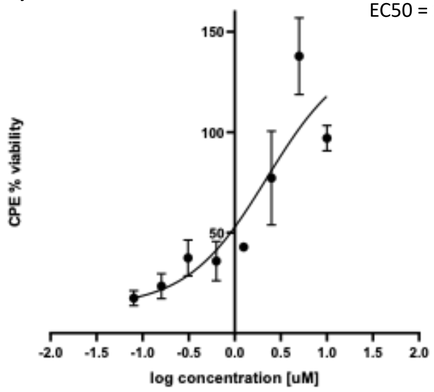


CVD-0013943

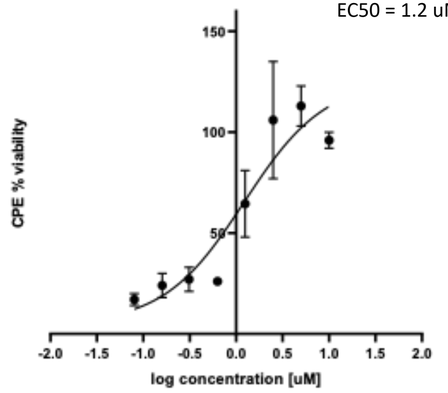


VeroE6
CPE assays

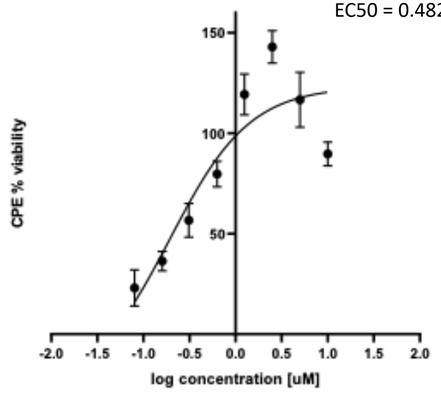
EC50 = 1.57 uM



EC50 = 1.2 uM

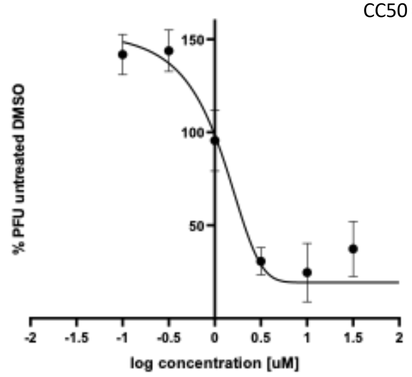


EC50 = 0.482 uM

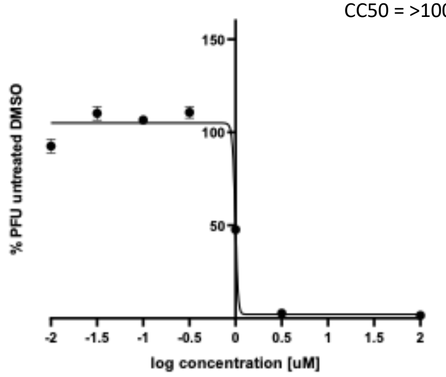


Calu-3
Plaque assay

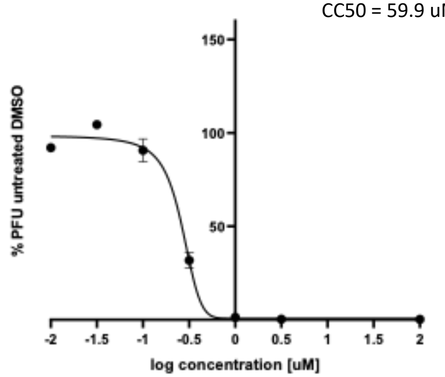
IC50 = 1.09 uM
CC50 = >100 uM



IC50 = 0.986 uM
CC50 = >100 uM



IC50 = 0.244 uM
CC50 = 59.9 uM



Activity of CVD-0013943

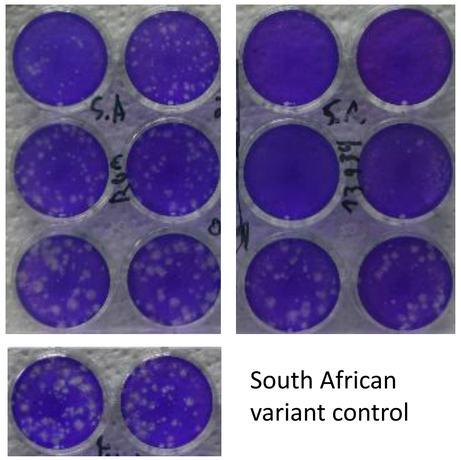
other viral strains:
B1.135 IC50 = 0.469 uM
B1.1.7 ongoing

other cell types
Hela ACE2 IC50 = 3.58 uM

other coronavirus strains
OC43 IC50 = 3.82 uM
MHV ongoing

Remdesivir CVD-0013943

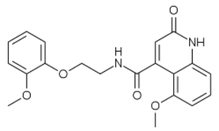
2 μM
1 μM
0.1 μM

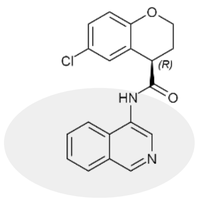


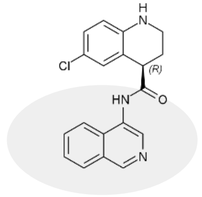
South African variant control

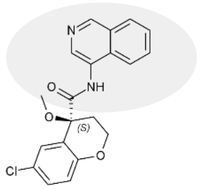
COVID Moonshot

We’re focusing into improving oral pharmacokinetics

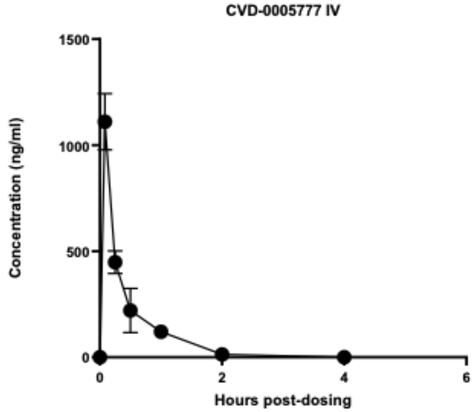




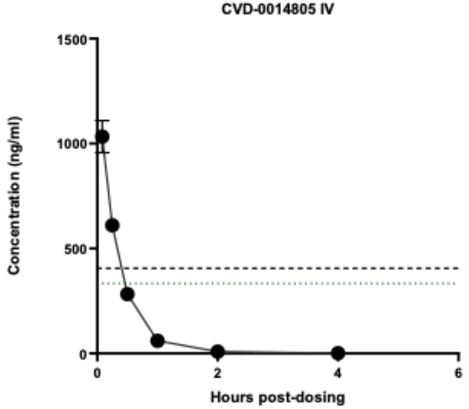


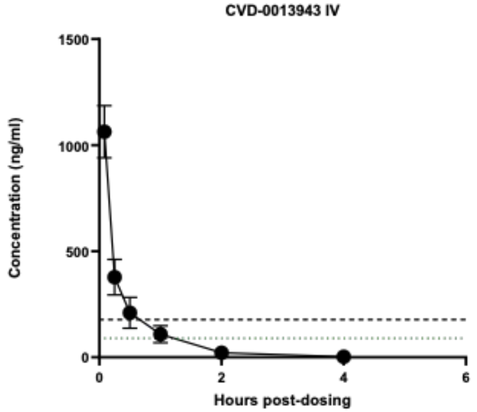


IV 2mg/kg



no IV formulation available for CVD-0013192

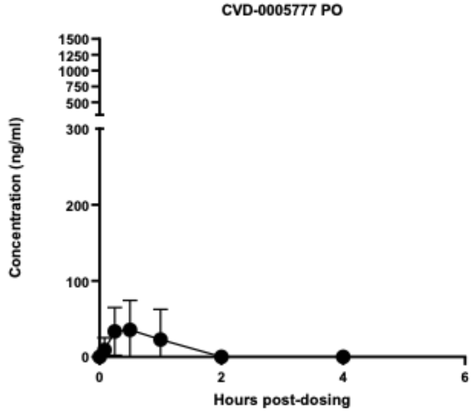


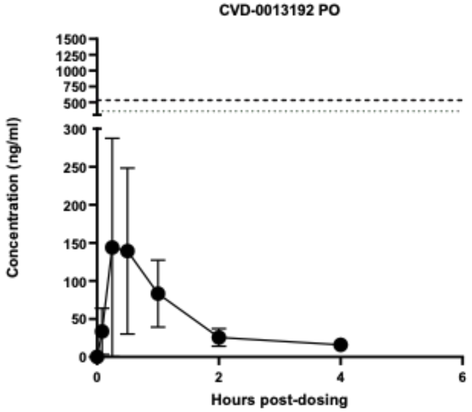


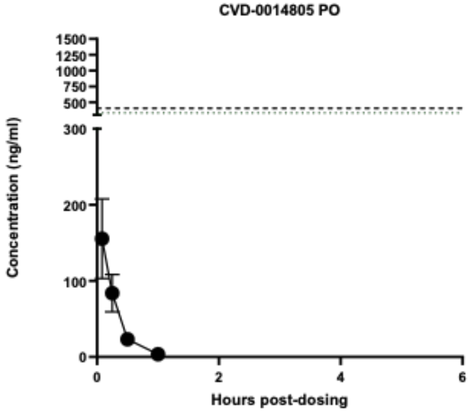
VeroE6 (CPE)

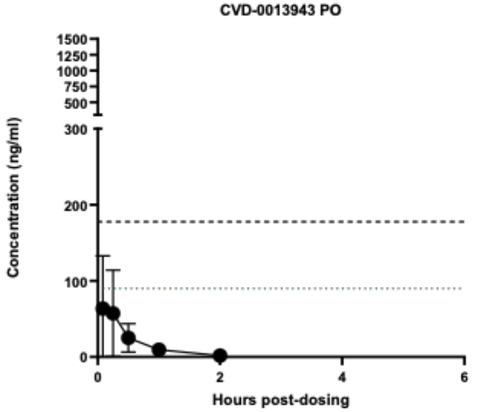
Calu-3 (PFU)

PO 10mg/kg









VeroE6 (CPE)

Calu-3 (PFU)

Wistar rat

Balb/c mouse

COVID Moonshot

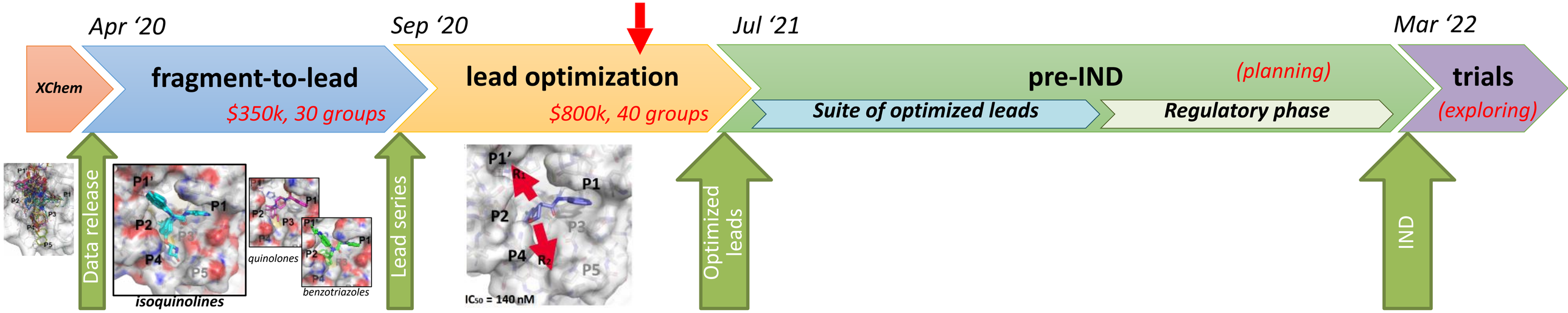
We're lining up IND-enabling studies now

Goal: new potent antiviral: therapeutic & prophylactic

- *simple synthesis*
- *orally available*
- *pharmacologically behaved*
- *pre-clinically safe*

Strategy: work fully open to enable rapid global availability

- *no IP encumbrance*
- *generic drug straight from pipeline*
- *assays/structures/discussions: http://postera.ai/covid*
- *protocols: https://doi.org/10.1101/2020.10.29.339317*
- *(unprecedented – no template available)*



6 months:
3 lead series
200nM enzyme inhibition
cellular antiviral activity
(philanthropic funding)

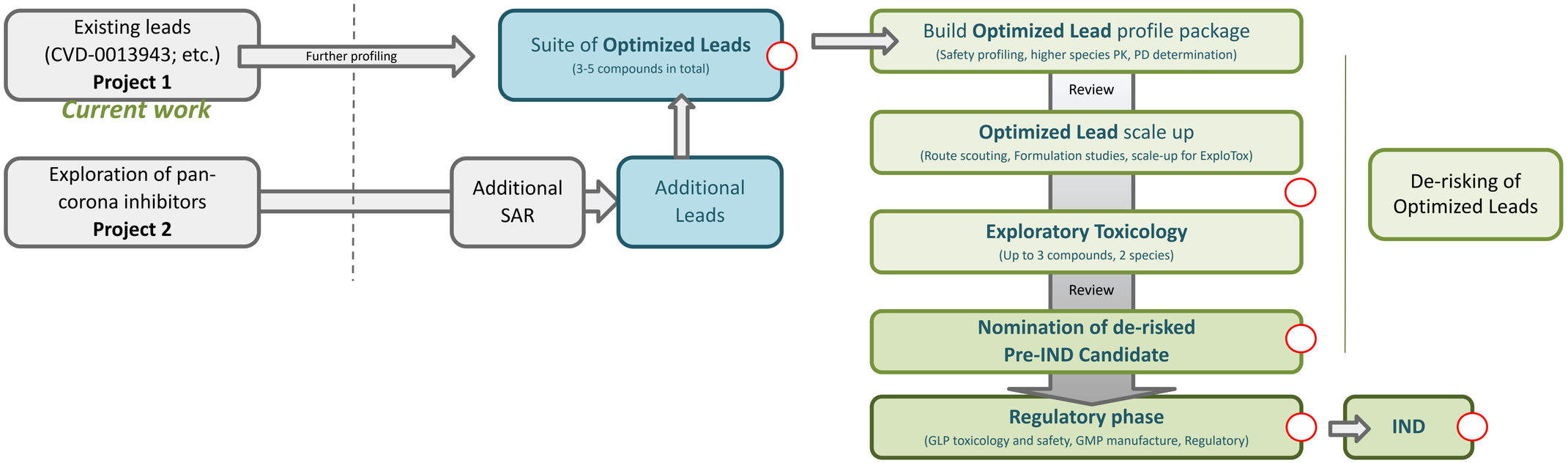
Current status:
50nM enzyme inhibition
(comprehensive SAR and crystal structures)
250nM antiviral inhibition
cross-reactive against SA strain
clean protease selectivity
encouraging safety prediction
solubility

Optimizing:
metabolic stability
PK/oral exposure

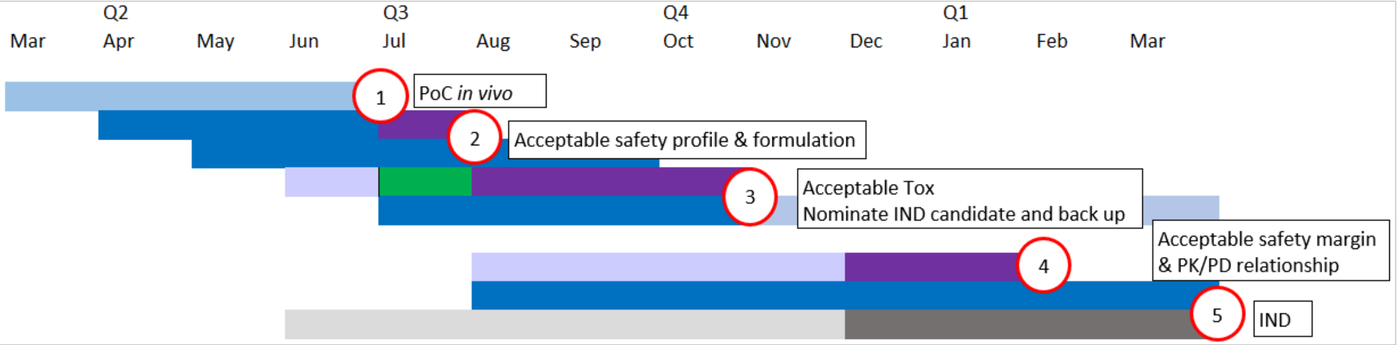
establishing:
pre-IND delivery
strategy to pharmacy
keystone partner
delivery partners
healthcare system
funding sources
ways to accelerate

COVID Moonshot

We aim to get a SARS-CoV-2 antiviral to the clinic



		Number of compounds
Preparation of regulatory phase		
WP 1	**Identify up to 5 optimized leads**	
WP2	**Build Optimized Lead profile package**	**5 compounds**
WP3	**Optimized lead scale-up**	**5 compounds**
WP4	**Exploratory toxicology**	**2-3 compounds**
WP5	**Large-scale synthesis/stability**	**2-3 compounds**
Regulatory phase		
WP6	**GLP toxicology and safety**	**1 compound (+ 1 back-up)**
WP7	**GMP manufacture**	**1 compound (+ 1 back-up)**
WP8	**Regulatory assessments**	**1 compound (+ 1 back-up)**



	£/milestone
1	645000
2	720000
3	1170000
4	1140000
5	1300000
	4975000

Activity 1: Identify up to 5 optimized leads

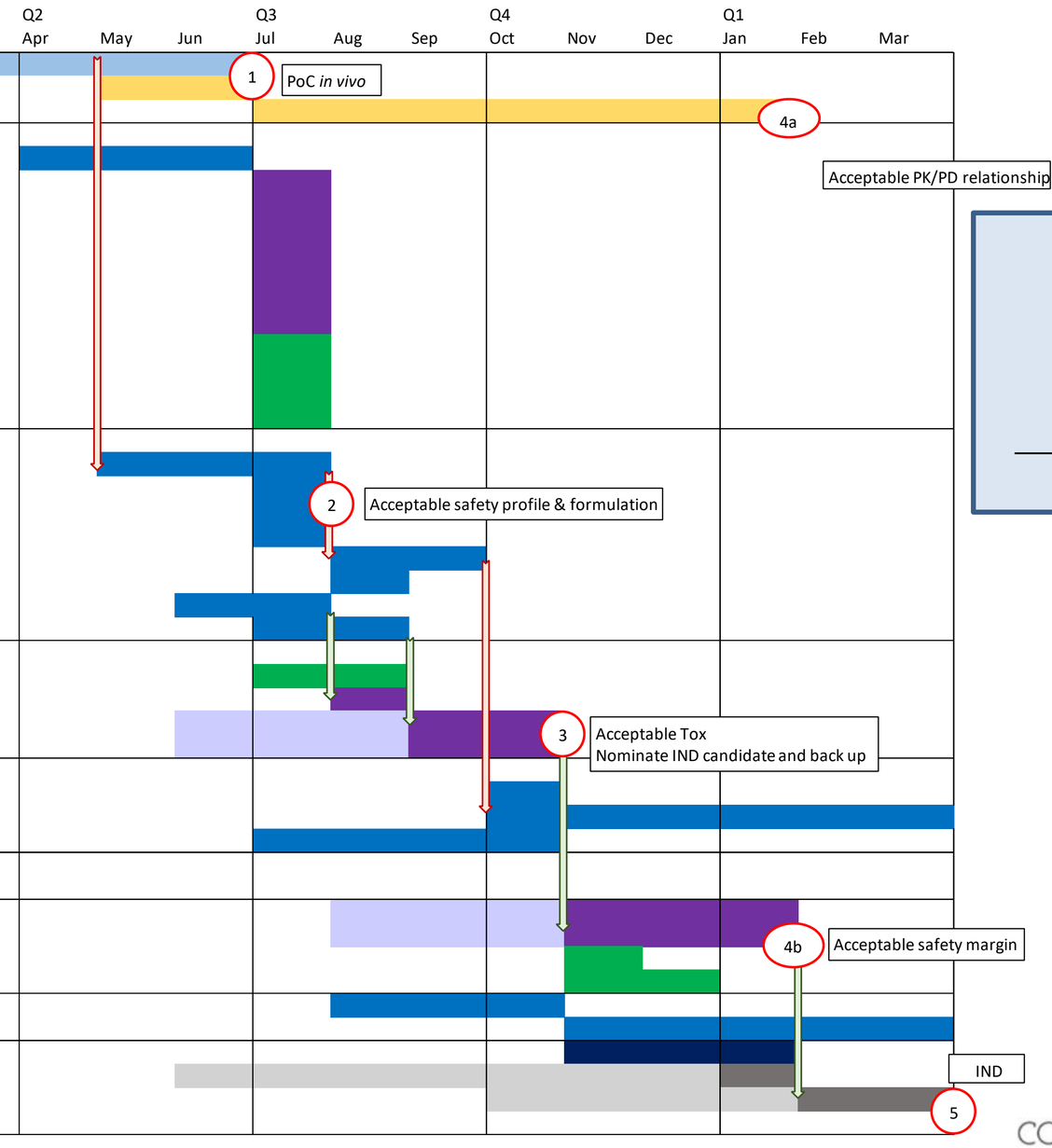
Activity 2: Preliminary work for exploratory toxicity studies

Activity 3: 14-day exploratory toxicity studies in rat and dog

Activity 4: Pre-IND including GLP toxicology, GMP manufacture and regulatory

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

			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

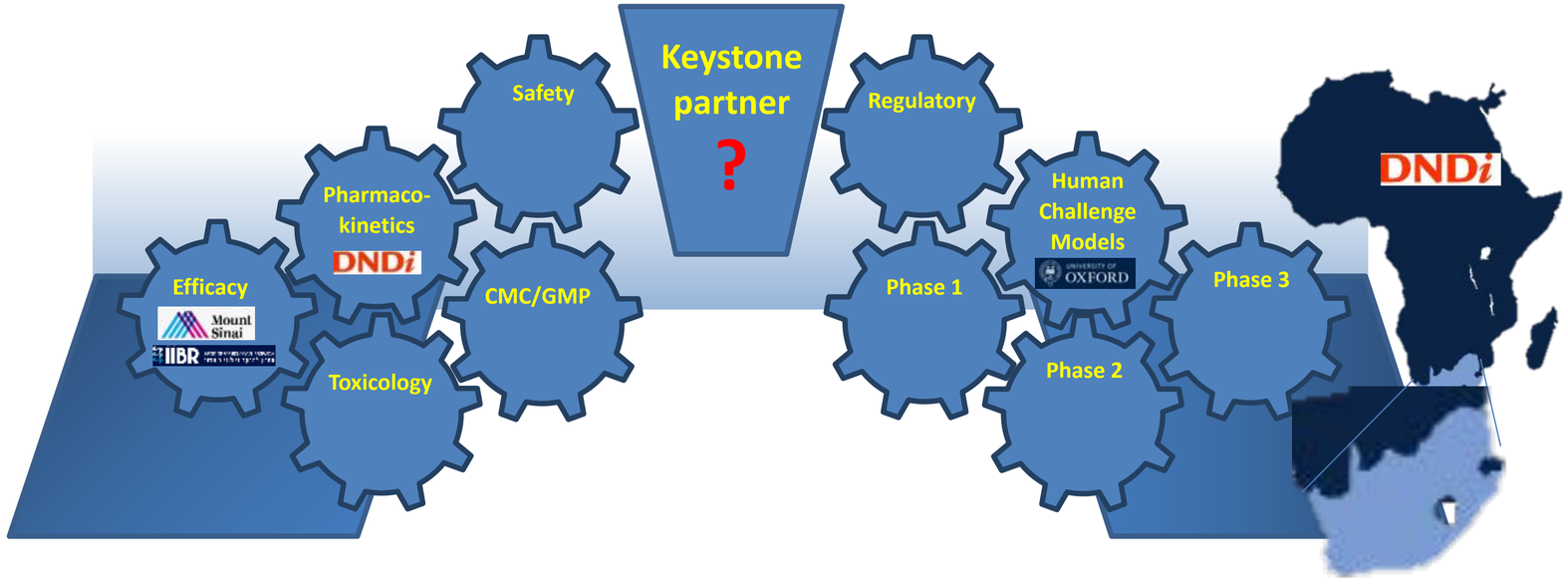


$/milestone	
1	570000
2	607500
3	995000
4	1085000
5	1710000
	4967500 Total

Efficacy
CMC
Pharmacokinetics
Regulatory
Clinical
Safety

COVID Moonshot

We're now searcing for a keystone partner to accelerate IND-enabling studies and initiation of clinical trials



- Ideally: one (or few) efficient CROs can be recruited on these terms
- More likely: multiple delivery partners must be coordinated by Consortium
  - Some of necessary expertise already recruited
  - Multiple conversations initiated
- Either way: Credibility of Keystone partner likely crucial for driving timelines

Ongoing conversations

DNDi
NOVARTIS
Takeda
CARE
City of Hope
FARMOVS
Integrated research solutions
UFS UV
evotec
APCONIX
janssen
LifeArc
NIH National Center for Advancing Translational Sciences

The COVID Moonshot collaboration is worldwide

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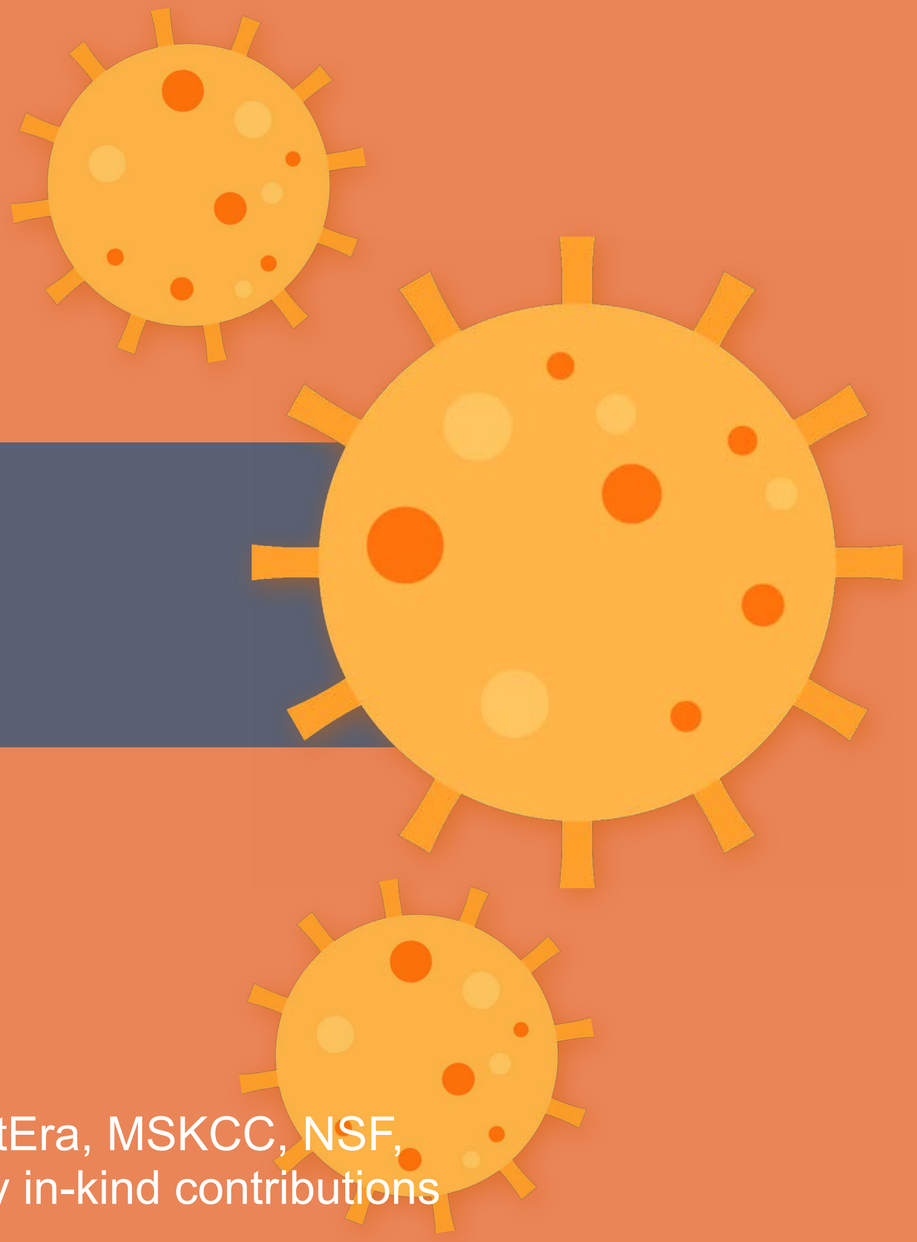
THANK YOU!



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