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

THE COVID MOONSHOT 🌙

An open science collaboration to develop an orally bioavailable inhibitor of SARS-CoV-2 main viral protease

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

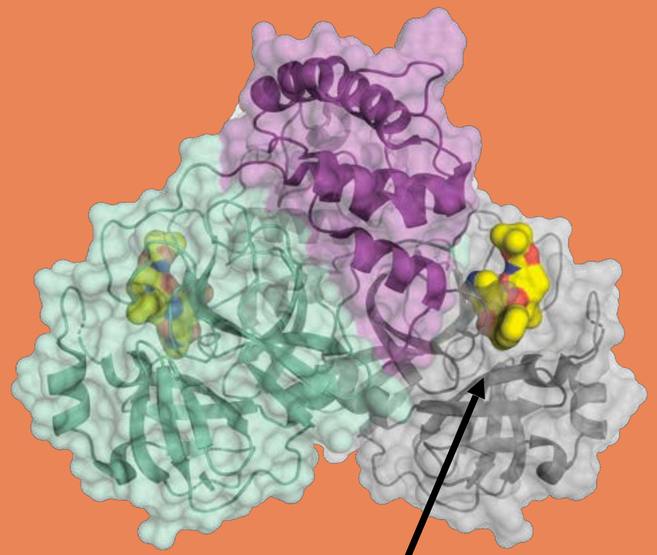
DISCLOSURES:
Scientific Advisory Board: OpenEye Scientific, Redesign Science*, Interline Therapeutics*
All funding: http://choderalab.org/funding
* denotes equity interests

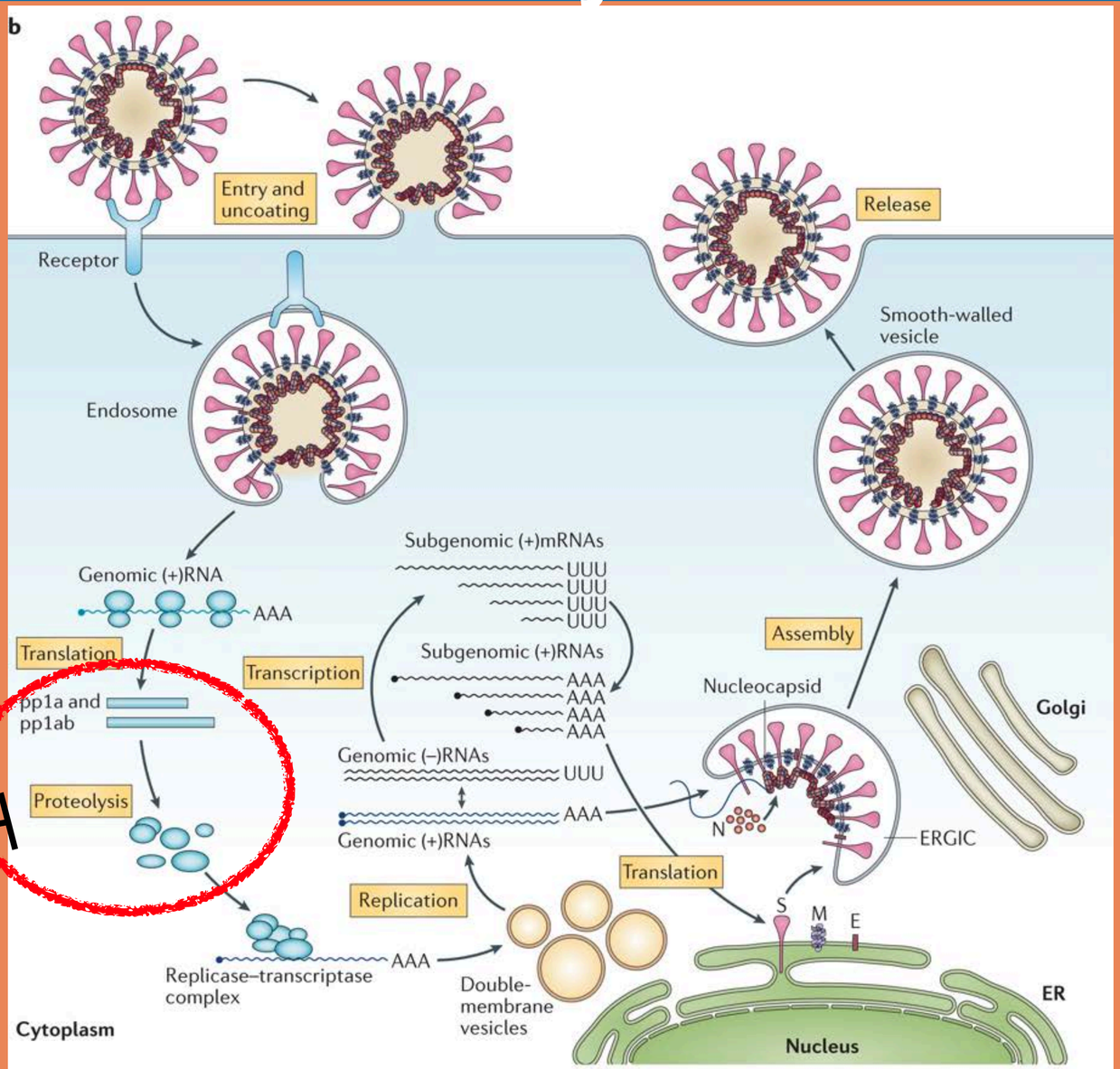
ACS Spring 2021 meeting - 5 Apr 2021

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

M^{pro}

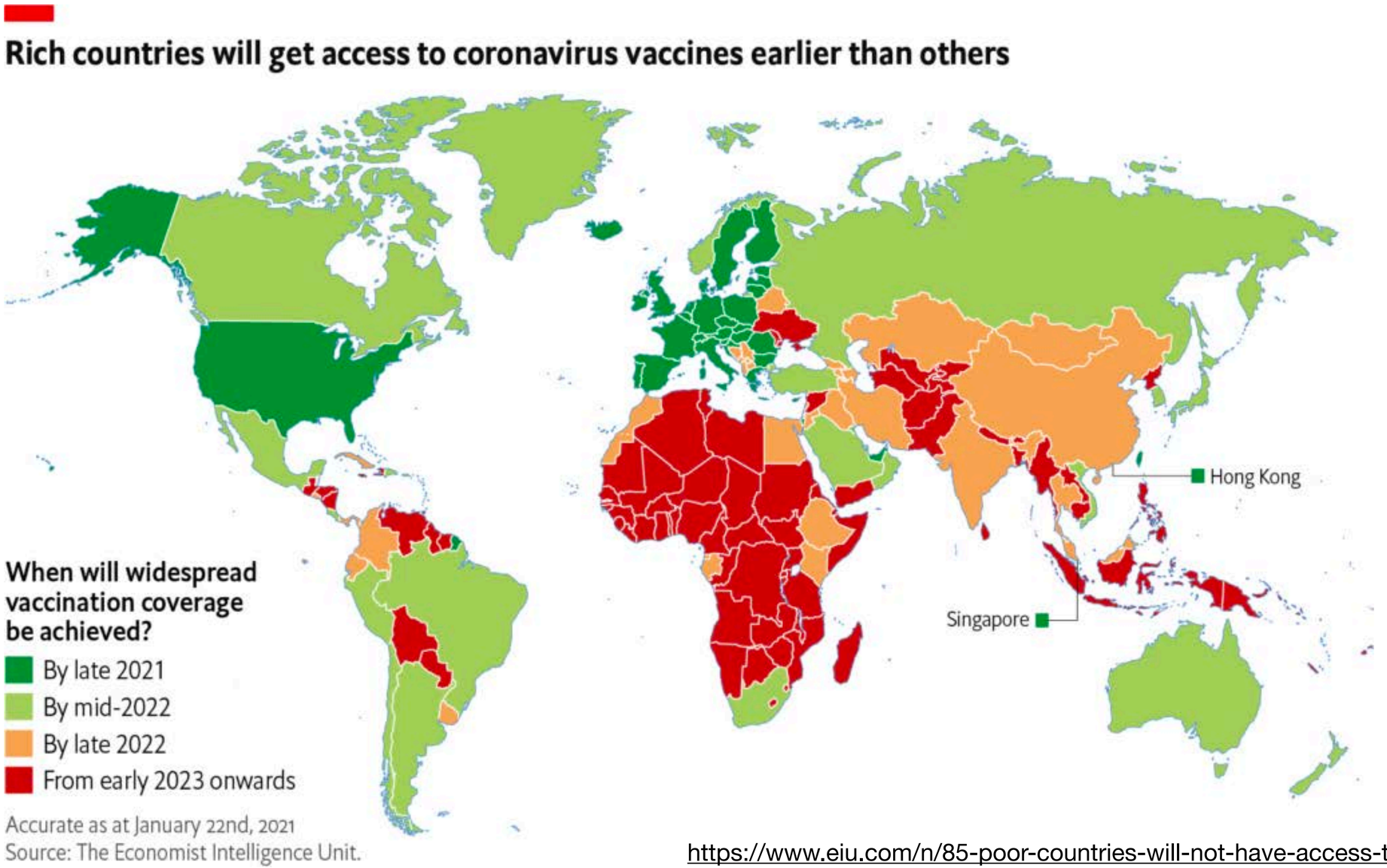
also: nsp5, 3CL^{Pro}





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

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, but 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?

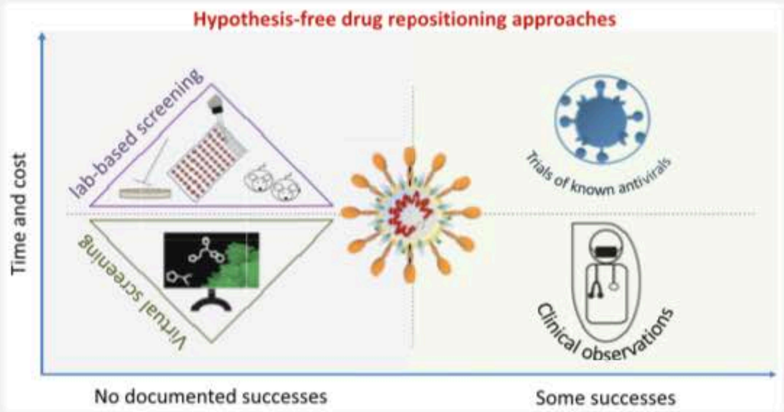
Aled Edwards*

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

Read Online

ACCESS | Metrics & More | Article Recommendations

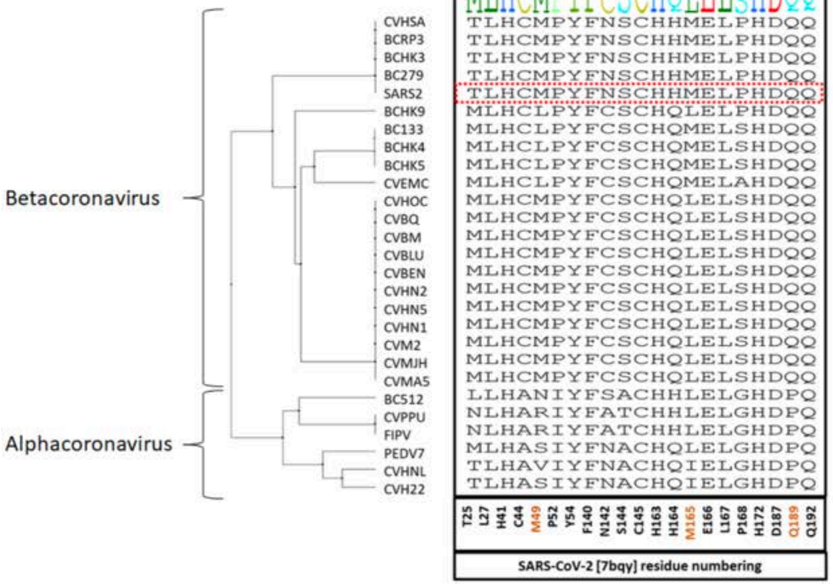
ABSTRACT: Massive drug repurposing (or repositioning) campaigns are trying to find potential antiviral treatments for COVID-19. Many involve experimental or virtual screening of libraries of compounds previously proven safe in humans—"old drugs". In 20 years of these efforts in many other diseases, never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



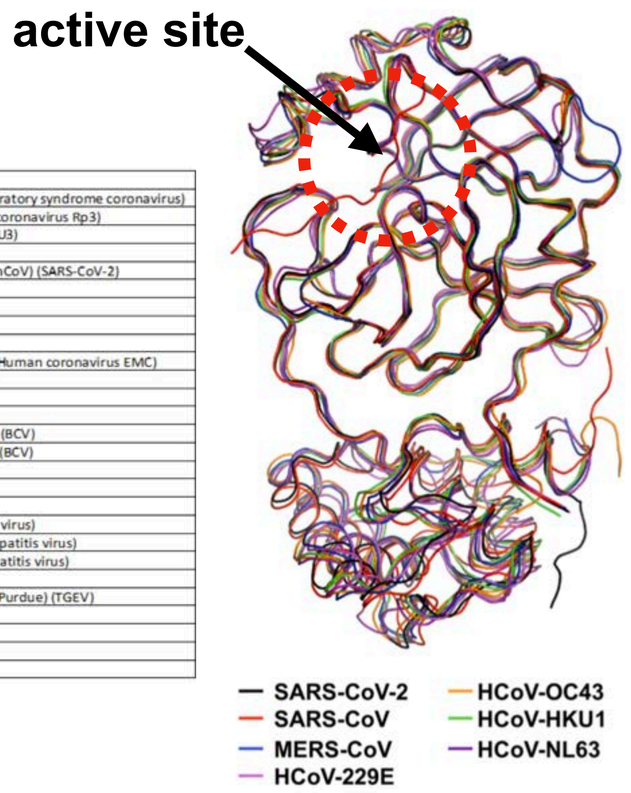
Aled Edwards
SGC Toronto

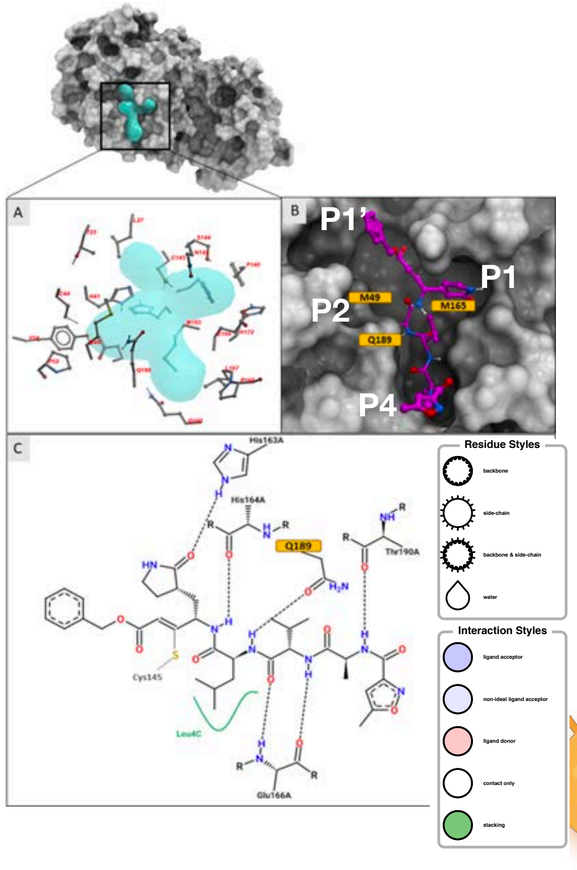
https://pubs.acs.org/doi/abs/10.1021/acs.jcim.0c00861

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



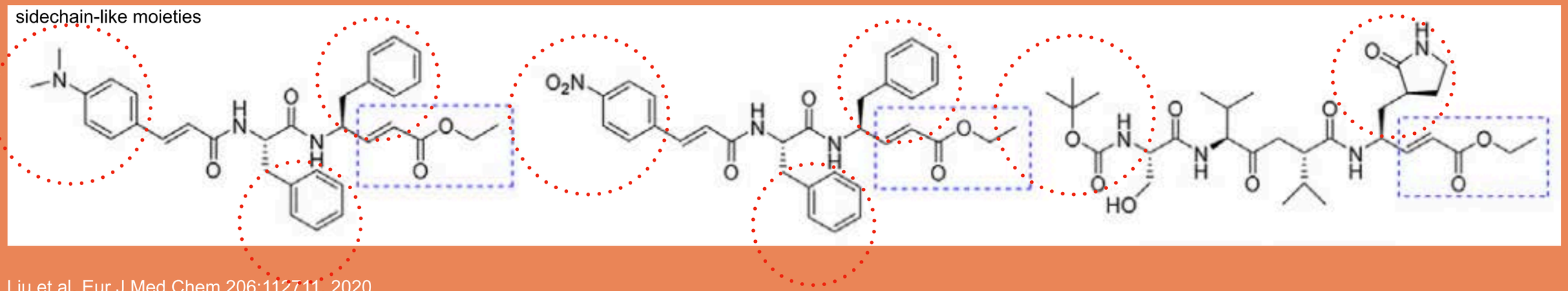
Entry	Organism
CVHSA	Human SARS coronavirus (SARS-CoV) (Severe acute respiratory syndrome coronavirus)
BCRP3	Bat coronavirus Rp3/2004 (BtCoV/Rp3/2004) (SARS-like coronavirus Rp3)
BCHK3	Bat coronavirus HKU3 (BtCoV) (SARS-like coronavirus HKU3)
BC279	Bat coronavirus 279/2005 (BtCoV) (BtCoV/279/2005)
SARS2	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

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



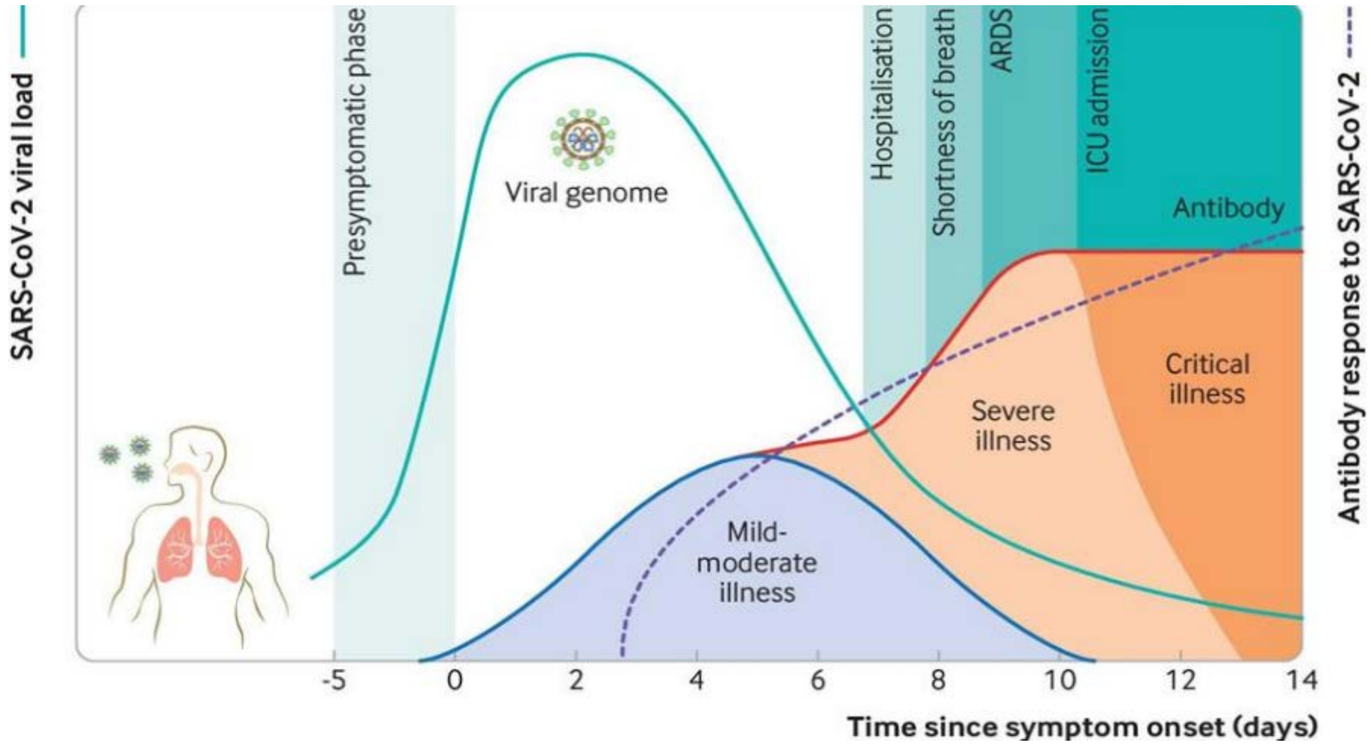
Liu et al. Eur J Med Chem 206:112711, 2020

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

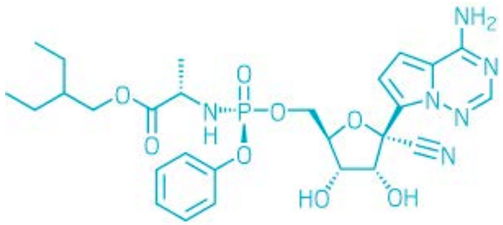
Oral (not intravenous) Mpro inhibitors are needed to impact the course of disease

Oral antiviral
Window of opportunity

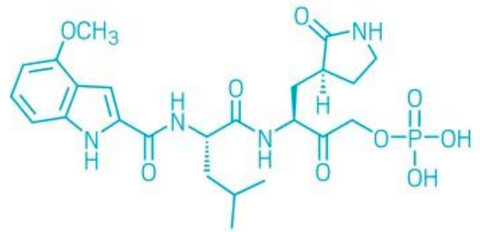
Virus no longer drives disease
Antivirals less effective
Hospitalized, so access to IV drugs



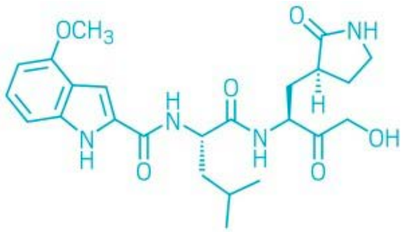
all IV dosing



Remdesivir



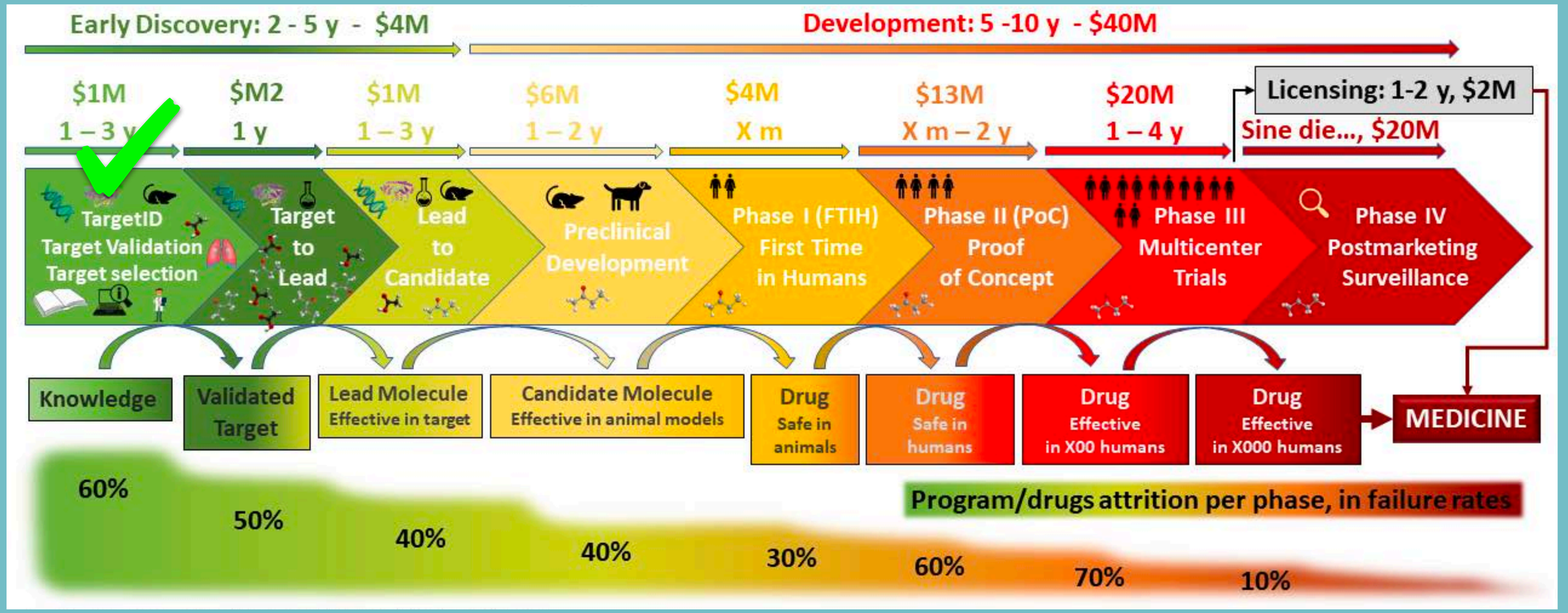
PF-07304814



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

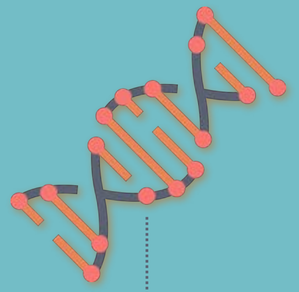


https://doctortarget.com/machine-learning-applied-drug-discovery/

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

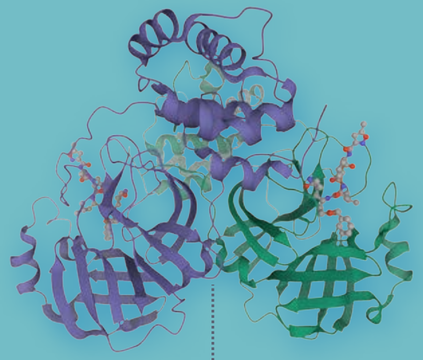
Frank von Delft
Diamond Light Source / XChem / SGC



February 14

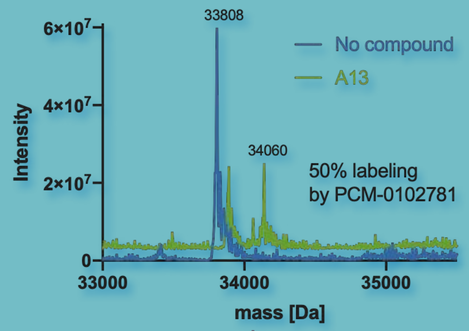
Main protease cloned and produced at Diamond after COVID shutdown of Haitao Yang lab in Shanghai

Martin Walsh



February 20

Atomic resolution structure of the protease determined

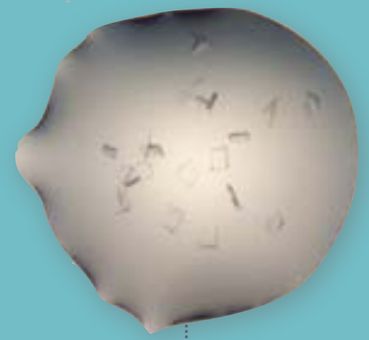


February 25

Covalent screen finds 150 active site hits

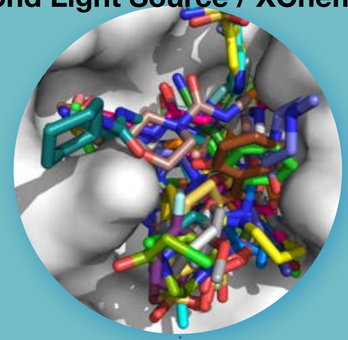
>40 hits validated

Nir London



March 5

1,500 crystals collected in one day (!)

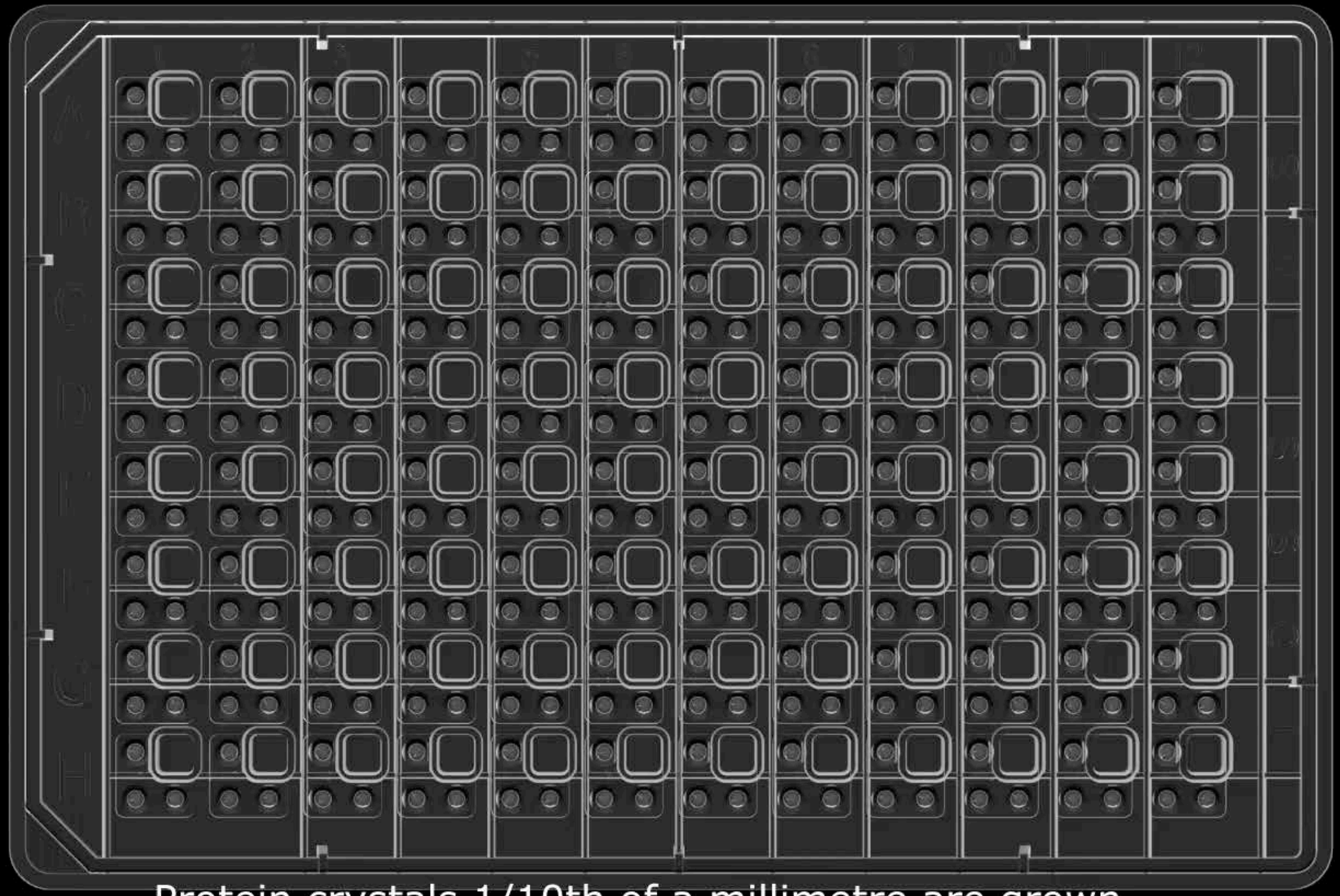


March 18

78 fragment-bound structures solved and released to the web

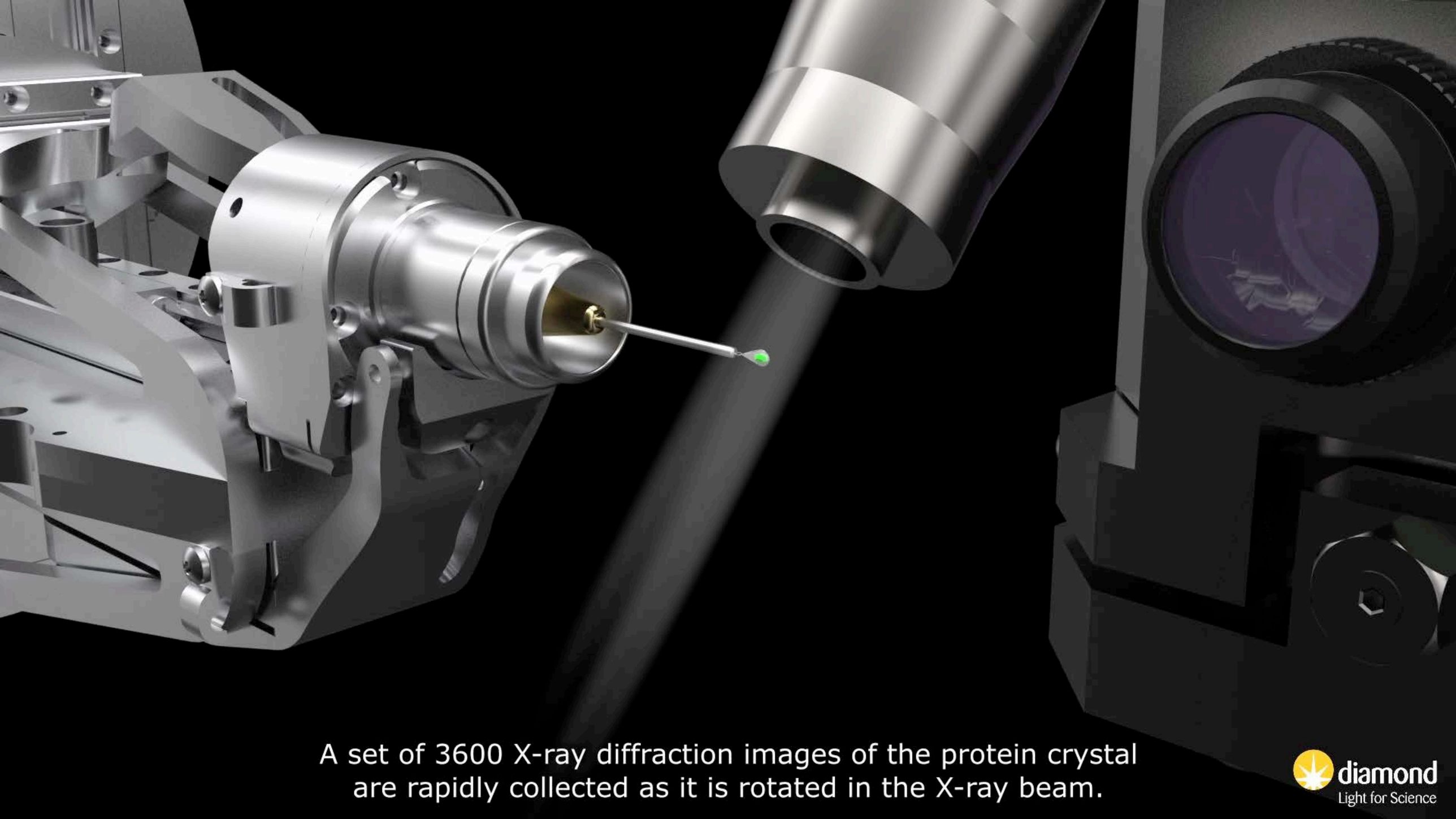
48 covalent fragments
71 active site fragments

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



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

diamond
Light for Science

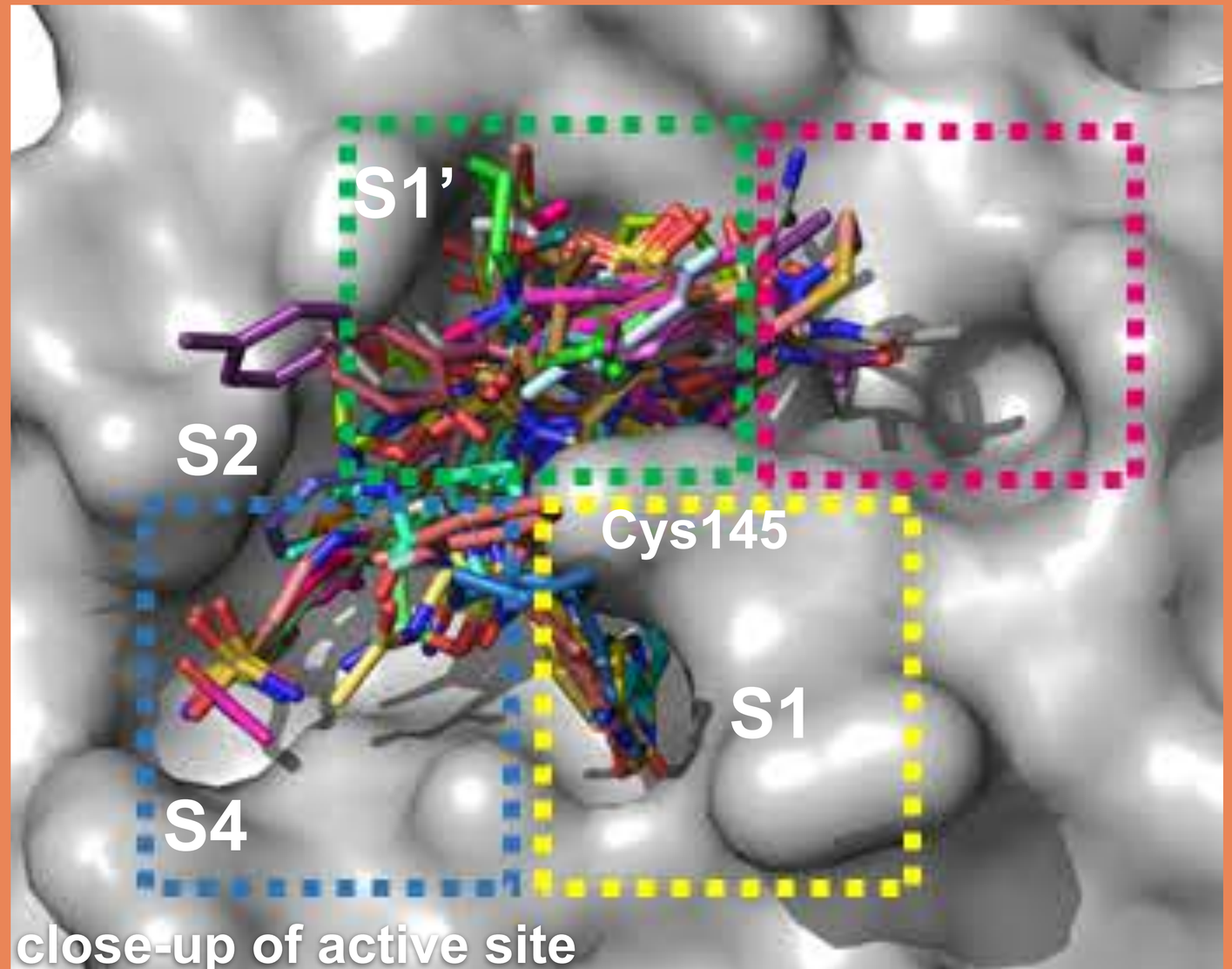


A set of 3600 X-ray diffraction images of the protein crystal are rapidly collected as it is rotated in the X-ray beam.

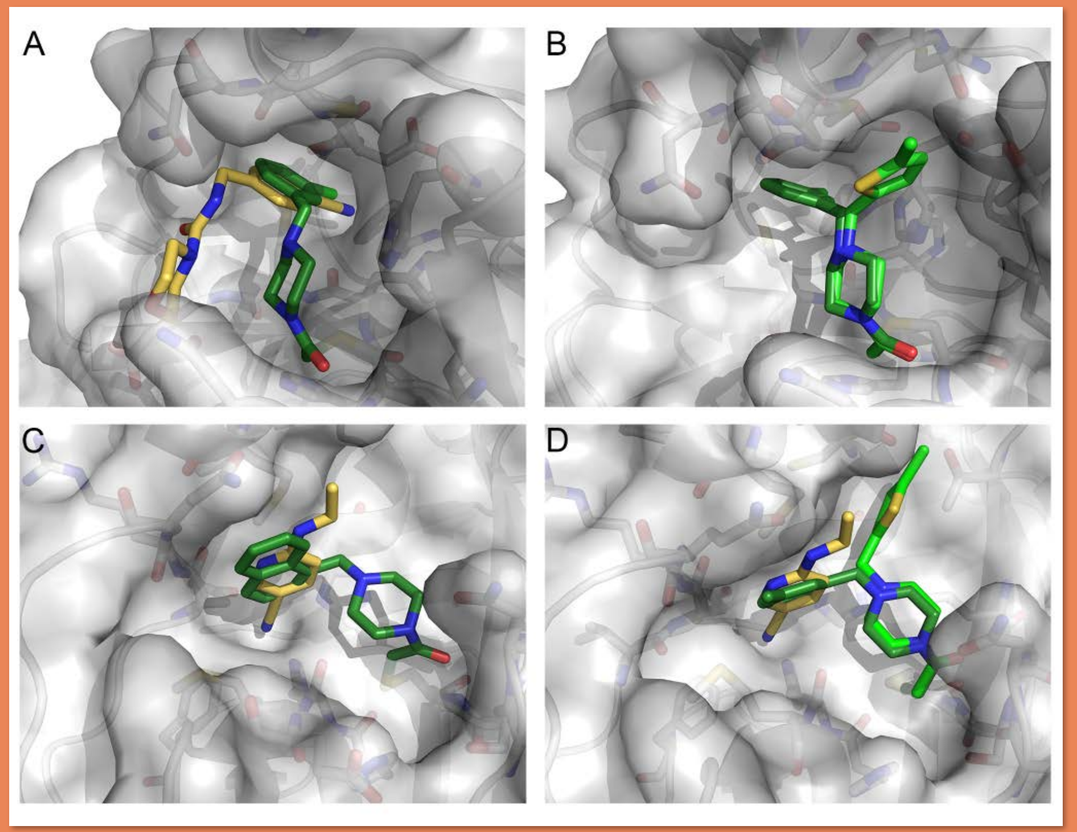
diamond
Light for Science

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

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

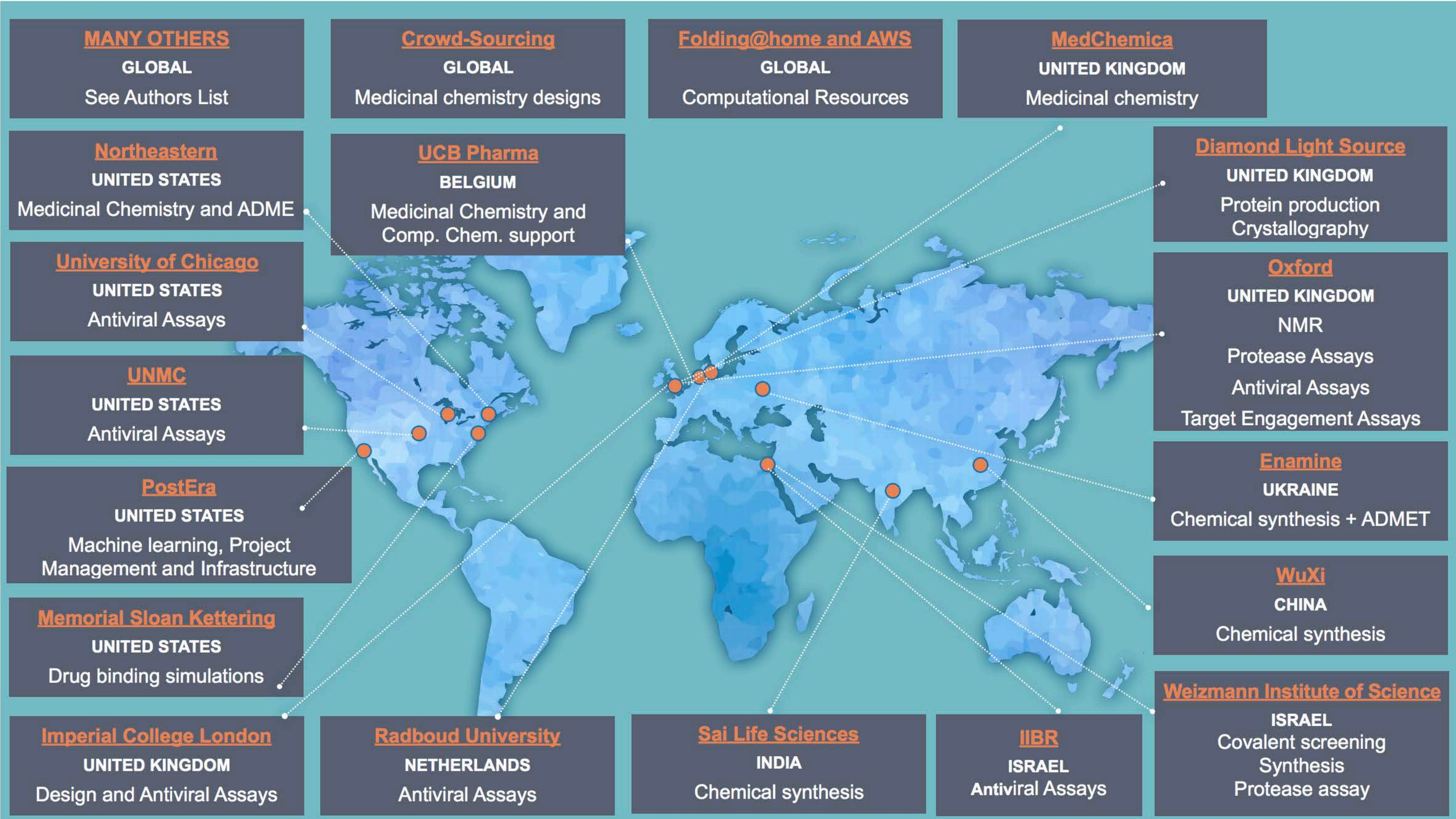
Open science

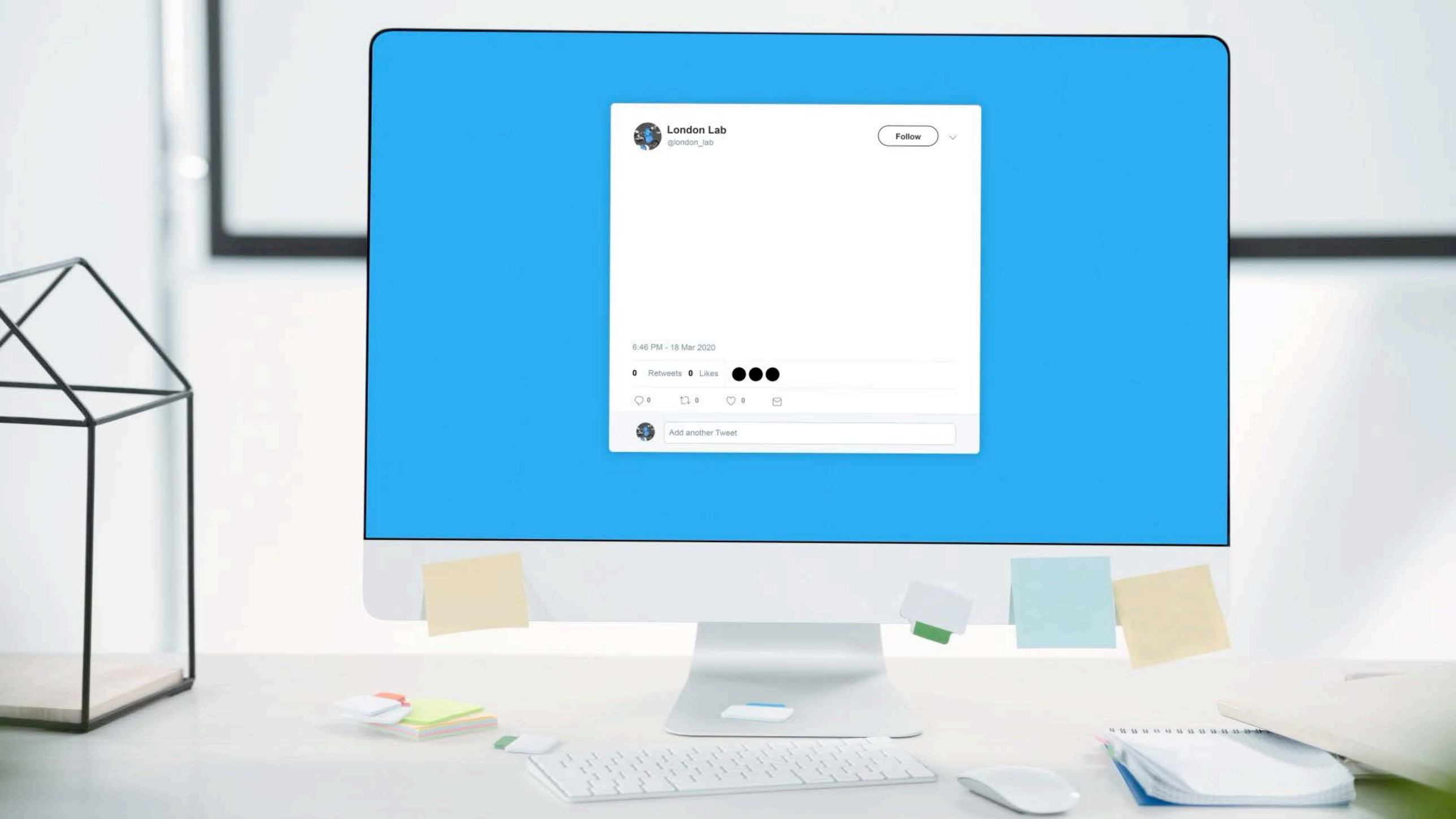
COVID Moonshot

Open data

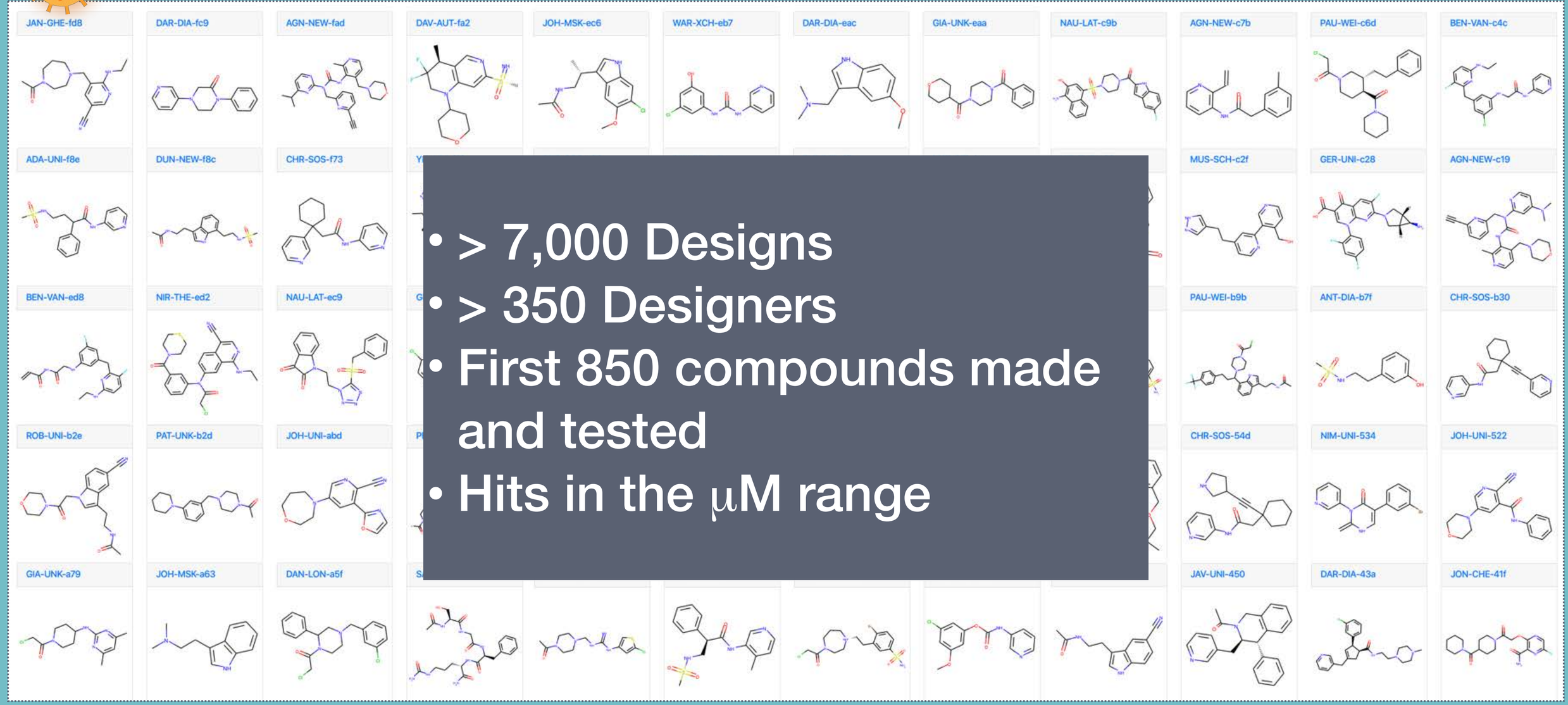
http://postera.ai/covid

Patent-free


MANY OTHERS
GLOBAL
See Authors List
Crowd-Sourcing
GLOBAL
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
UNITED KINGDOM
Design and Antiviral Assays
Radboud University
NETHERLANDS
Antiviral Assays
Sai Life Sciences
INDIA
Chemical synthesis
IIBR
ISRAEL
Antiviral Assays


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

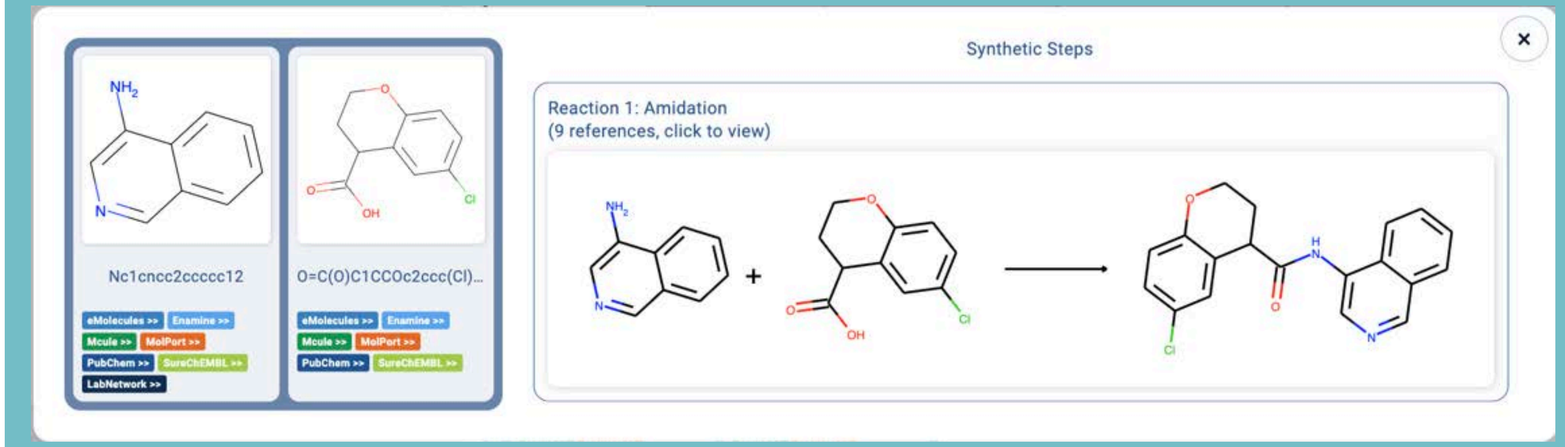
…and there was overwhelming response



- > 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

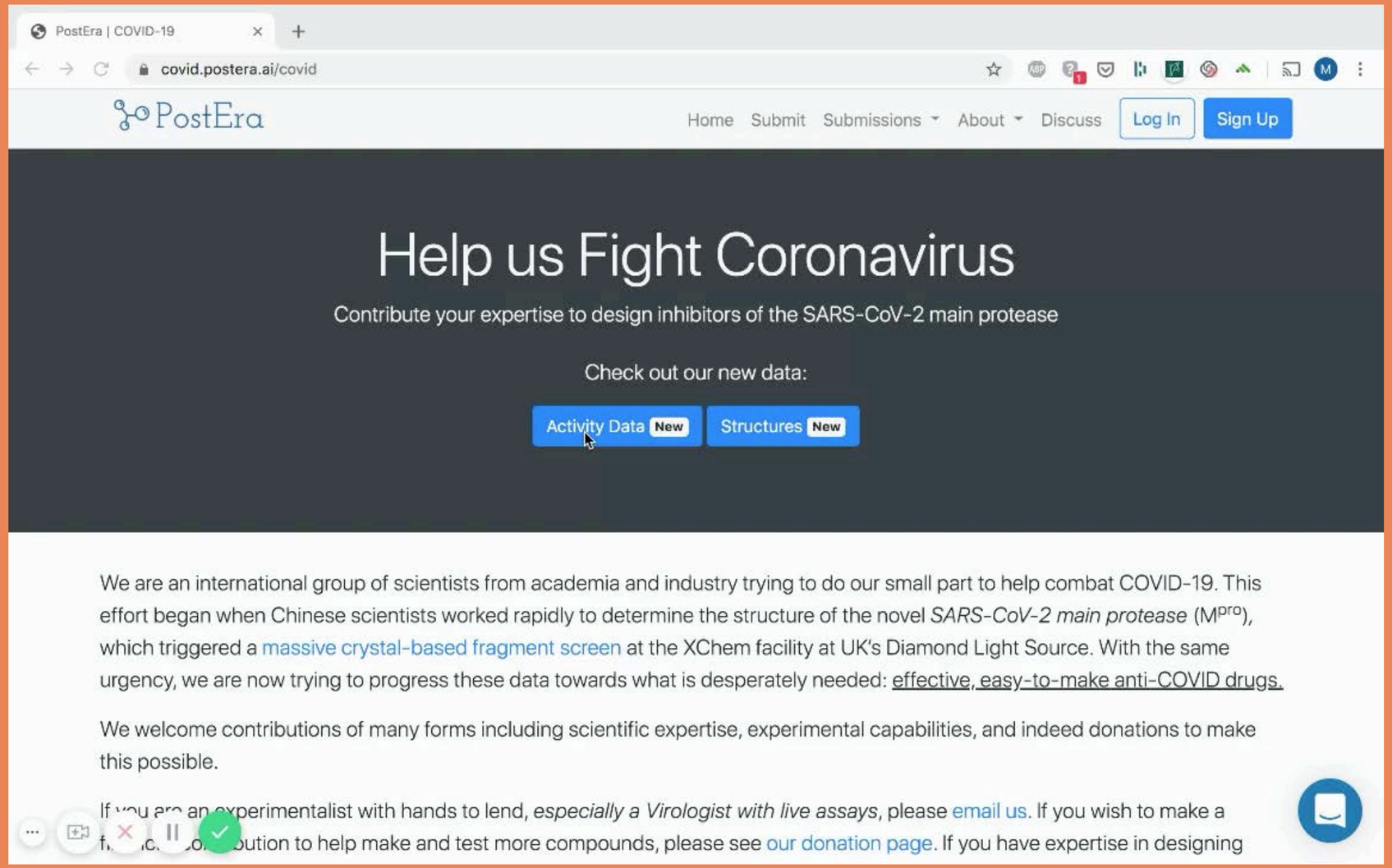
Synthesis and Search
across every available molecule

* free for academics!

http://postera.ai/covid

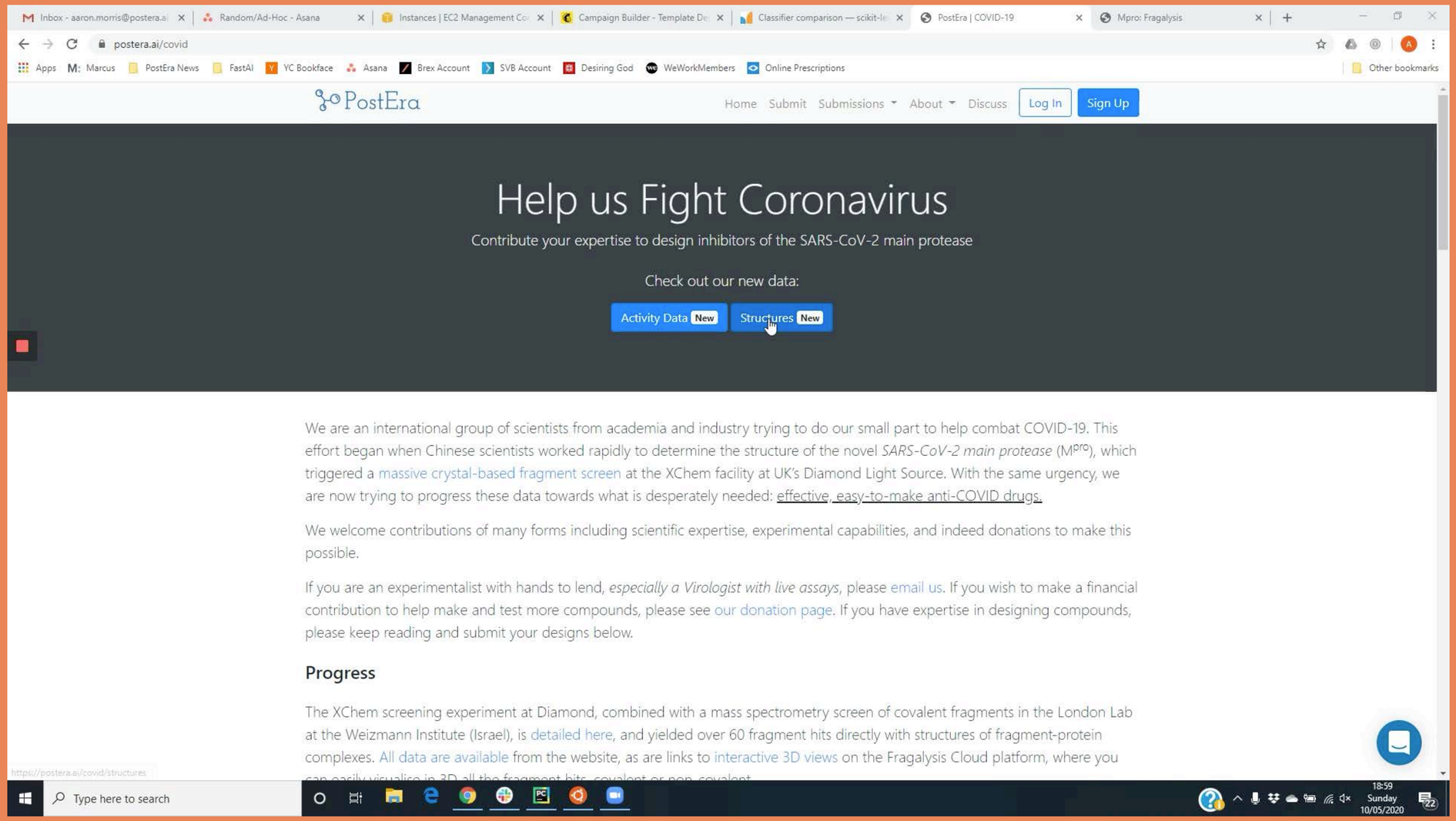
Schwaller et al. ACS Central Science 5:9, 2019
https://pubs.acs.org/doi/10.1021/acscentsci.9b00576

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



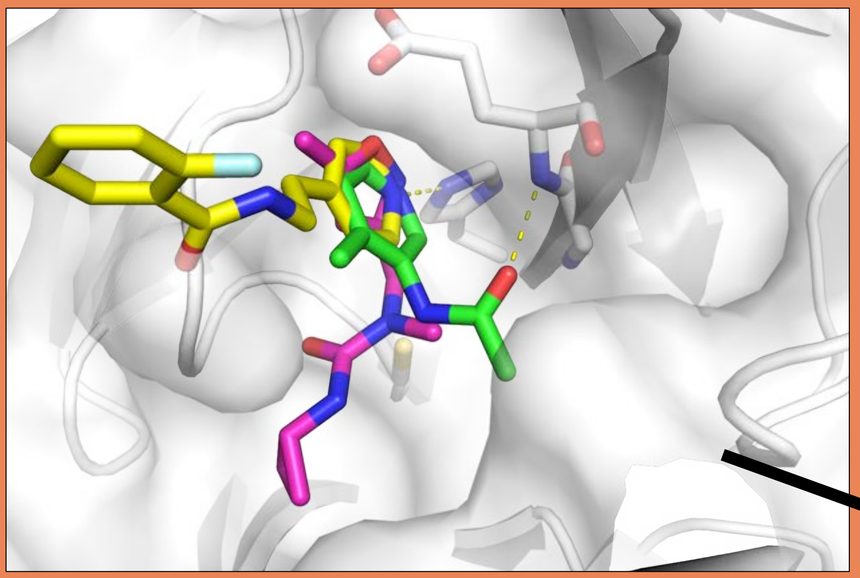
http://postera.ai/covid

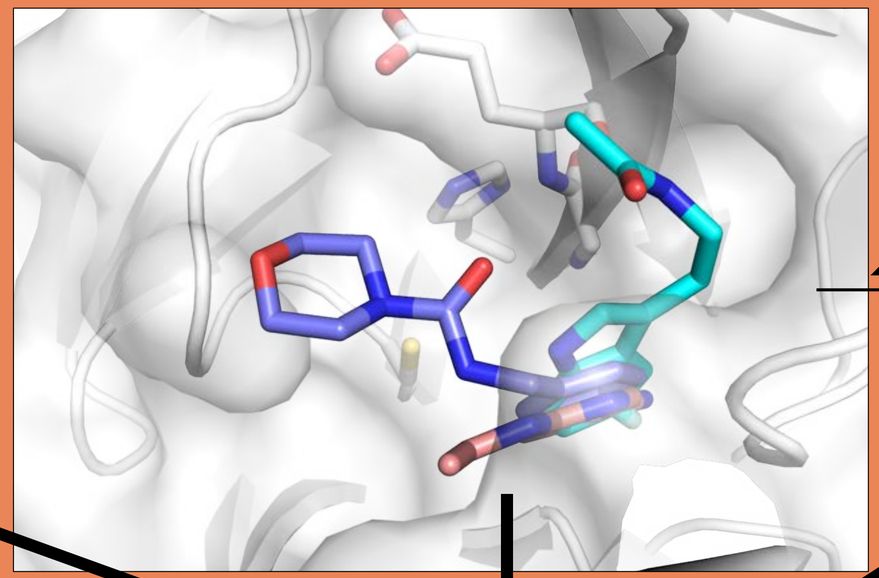
Diamond XChem's automated beamline enabled us to turn structures around in days

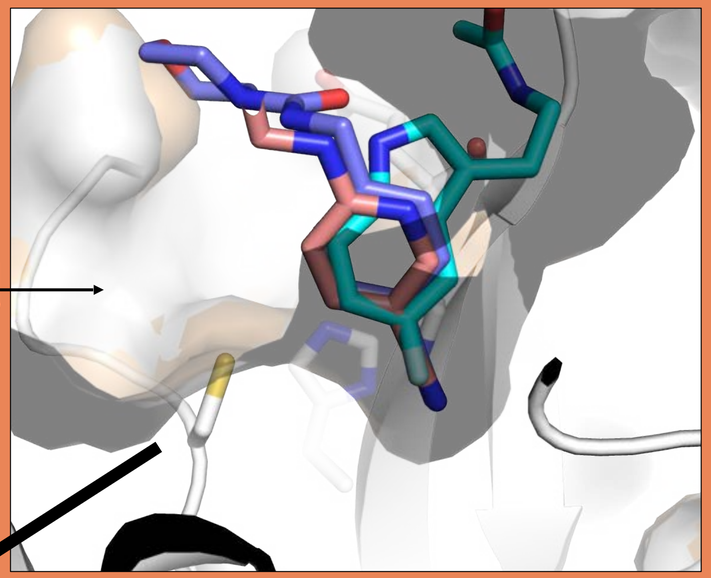


http://postera.ai/covid

Crowdsourcing generated a number of novel chemical series by fragment merging





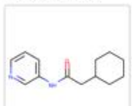


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

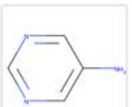
Design Rationale:

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

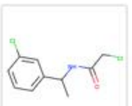
Inspired By:



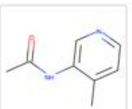
ALE-HEI-f28a35b5-9



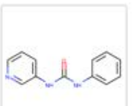
AAR-POS-d2a4d1df-18



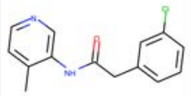
AAR-POS-0daf6b7e-10



MAK-UNK-6435e6c2-8



AAR-POS-d2a4d1df-11



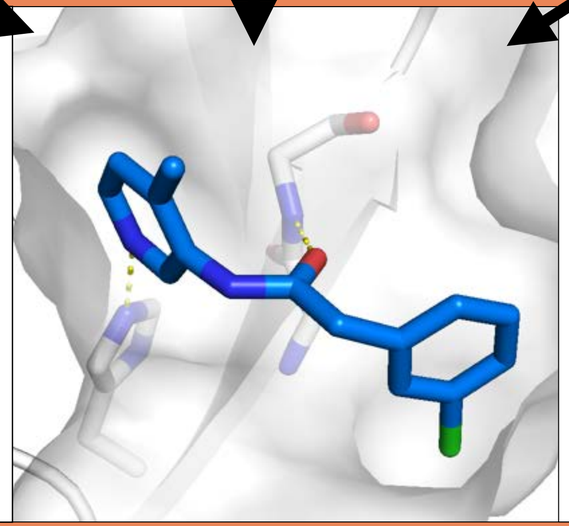
TRY-UNI-714a760b-6

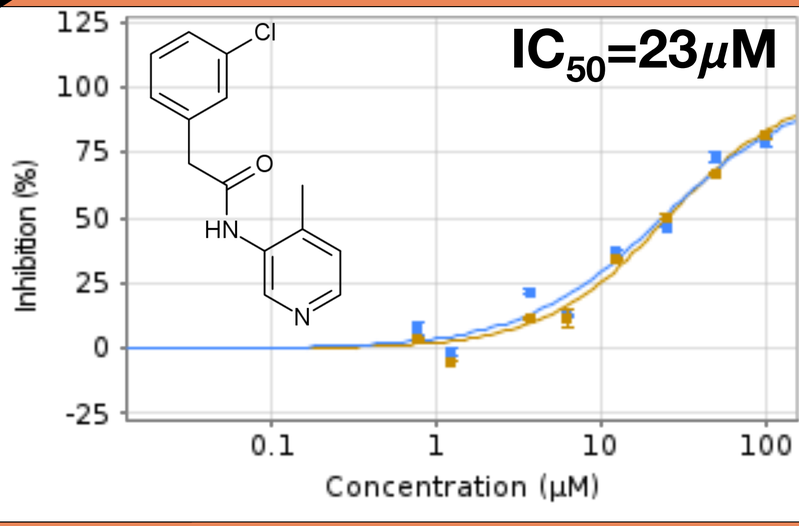
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

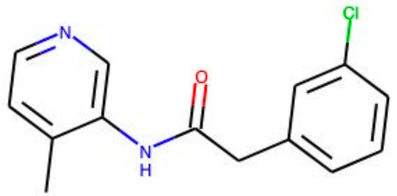
Enamine Mcule MolPort Assayed

View

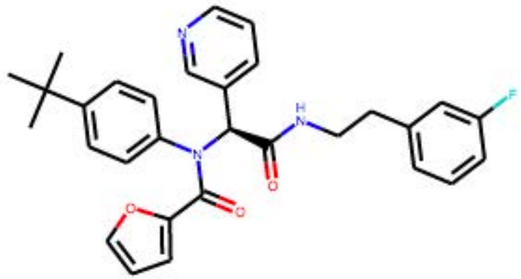




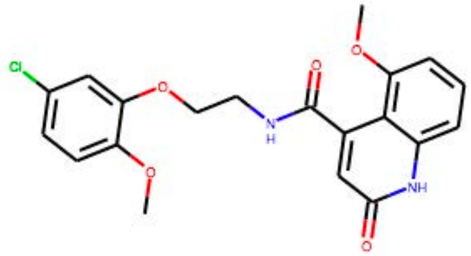
Crowdsourcing yielded multiple lead series



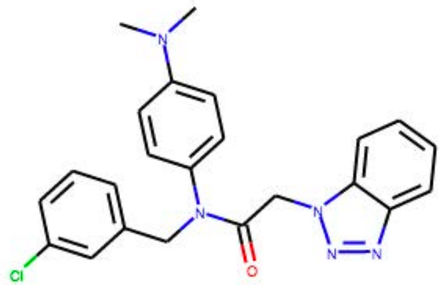
3-aminopyridines



Ugis



quinolones

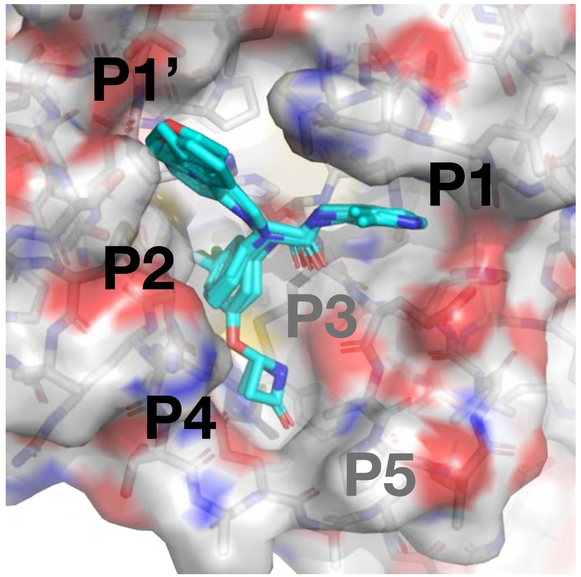


benzotriazoles

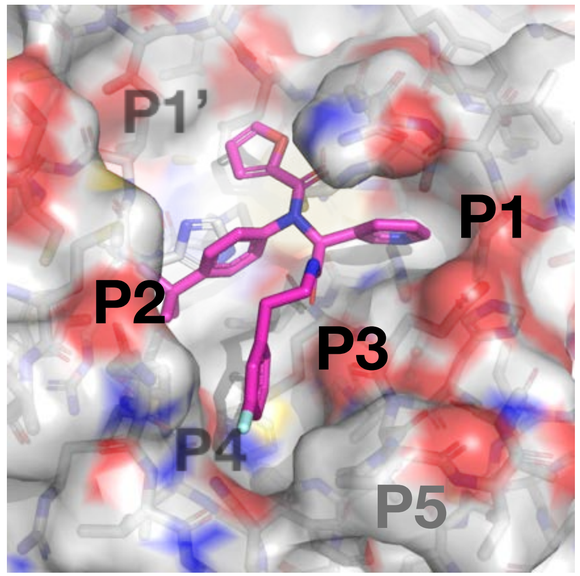
http://postera.ai/covid

[As of 16 Mar 2021]

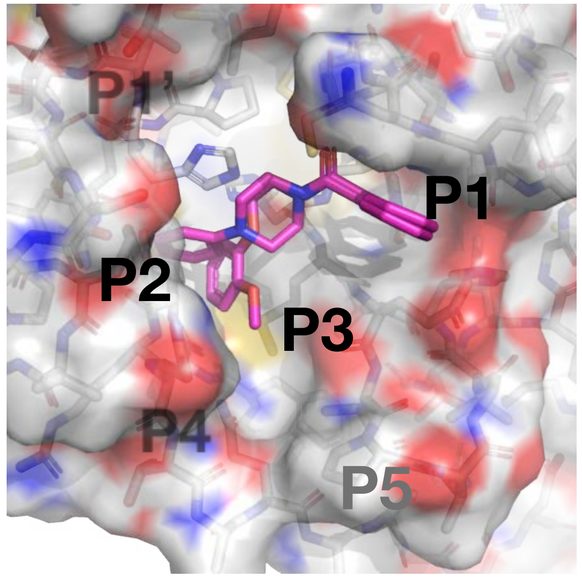
Crowdsourcing yielded multiple lead series



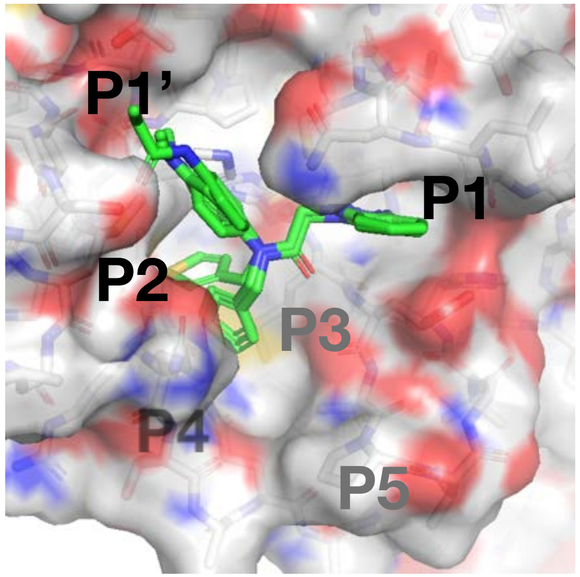
3-aminopyridines



Ugis



quinolones

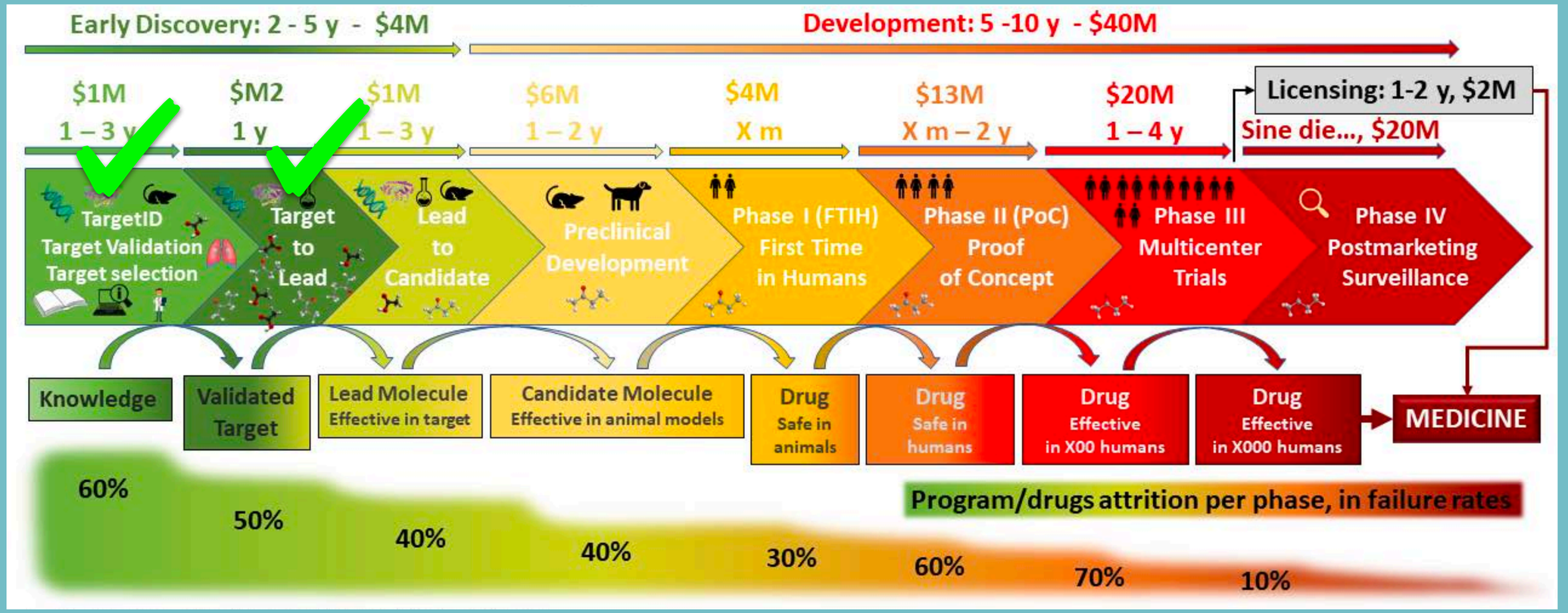


benzotriazoles

http://postera.ai/covid

[As of 16 Mar 2021]

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?

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

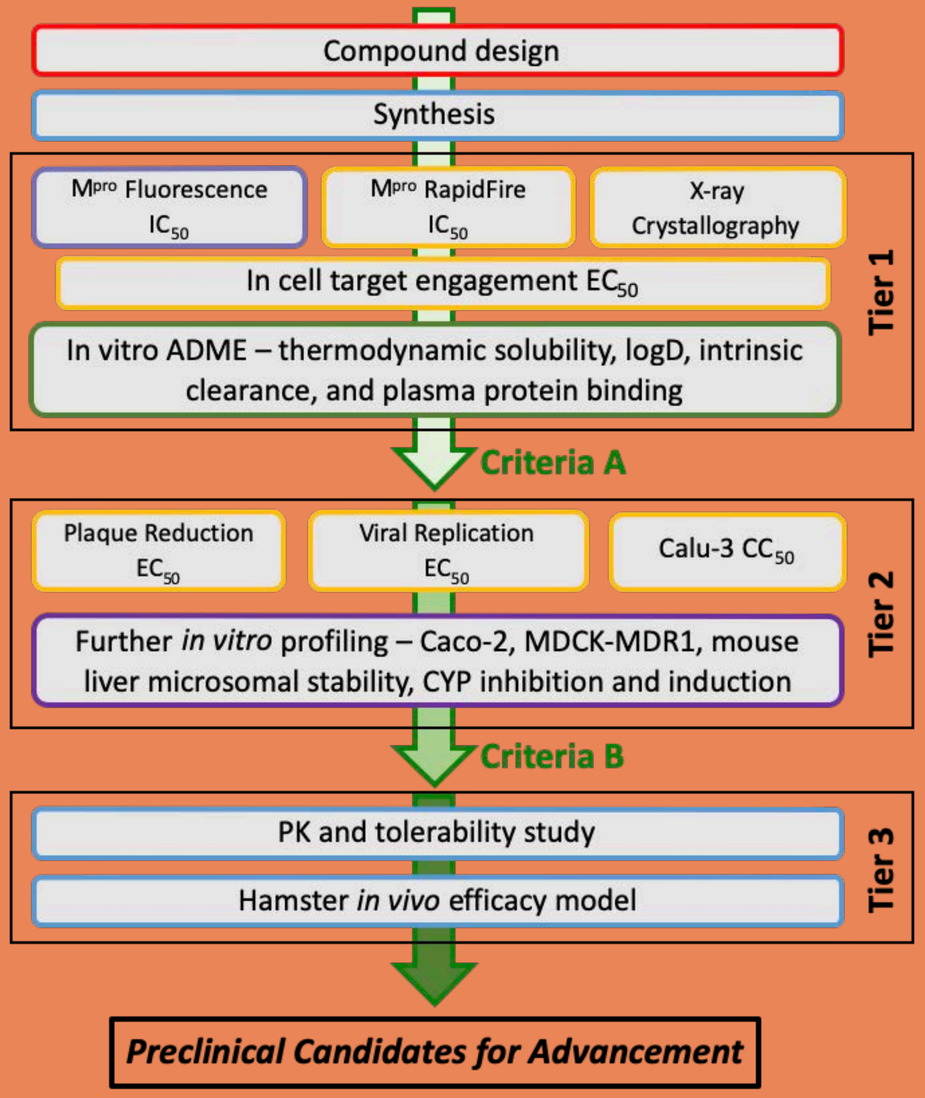
COVID Moonshot

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?

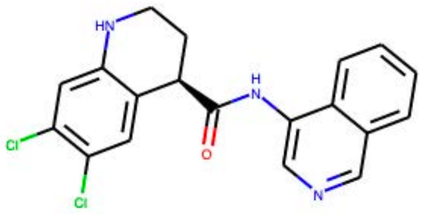
Does it have a favorable safety profile?

Is it orally bioavailable at required concentrations?

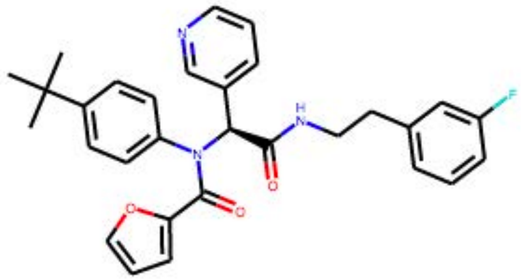
Assay components donated by groups and CROs around the world

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

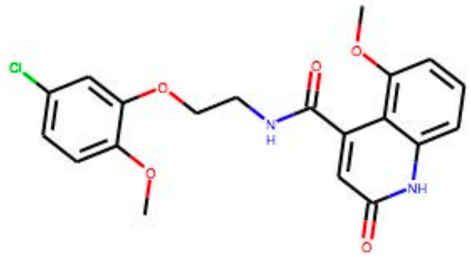
Ed Griffen
Medchemica



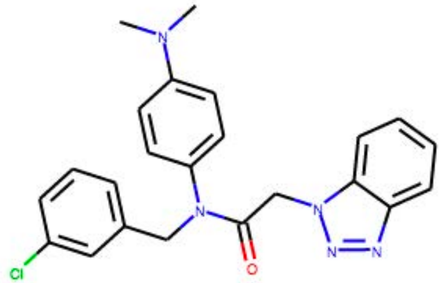
3-aminopyridines
948 compounds
(primary series)



Ugis
403 compounds
(backup series)



quinolones
86 compounds
(backup series)



benzotriazoles
42 compounds
(backup series)

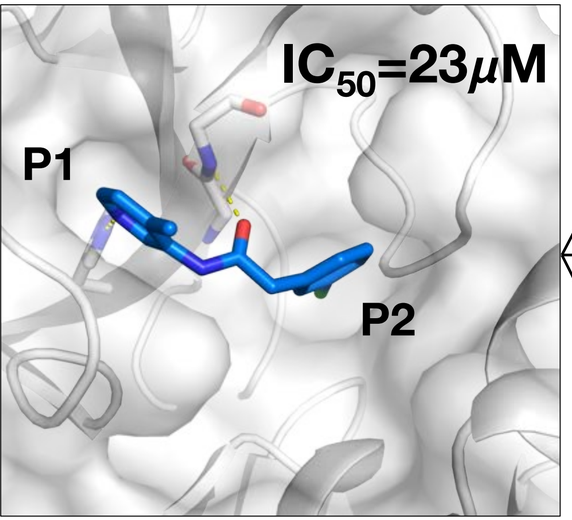
258 X-ray structures (and rapidly growing)
>25% of all SARS-CoV-2 structures!

http://postera.ai/covid

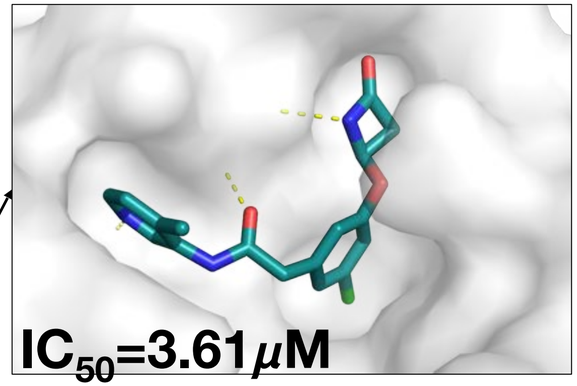
[As of 16 Mar 2021]

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

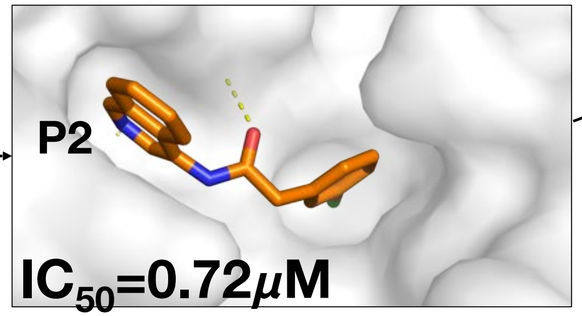
>300 aminopyridine compounds synthesized



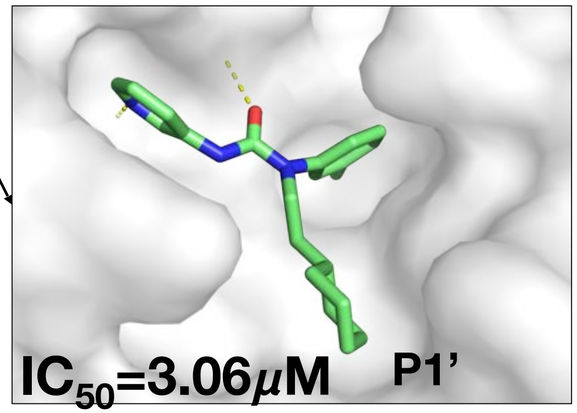
6.4x



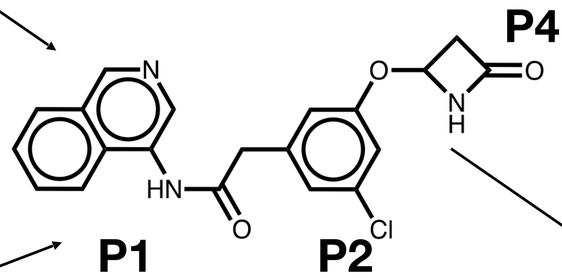
32x

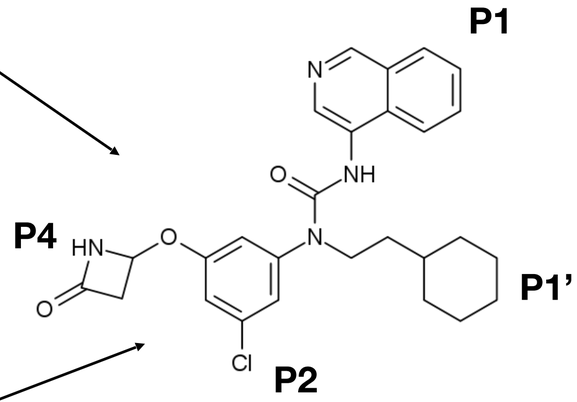


7.5x

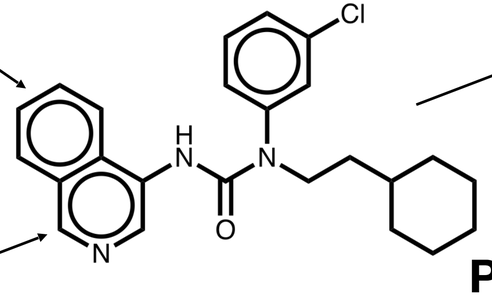


IC_{50}=260 nM





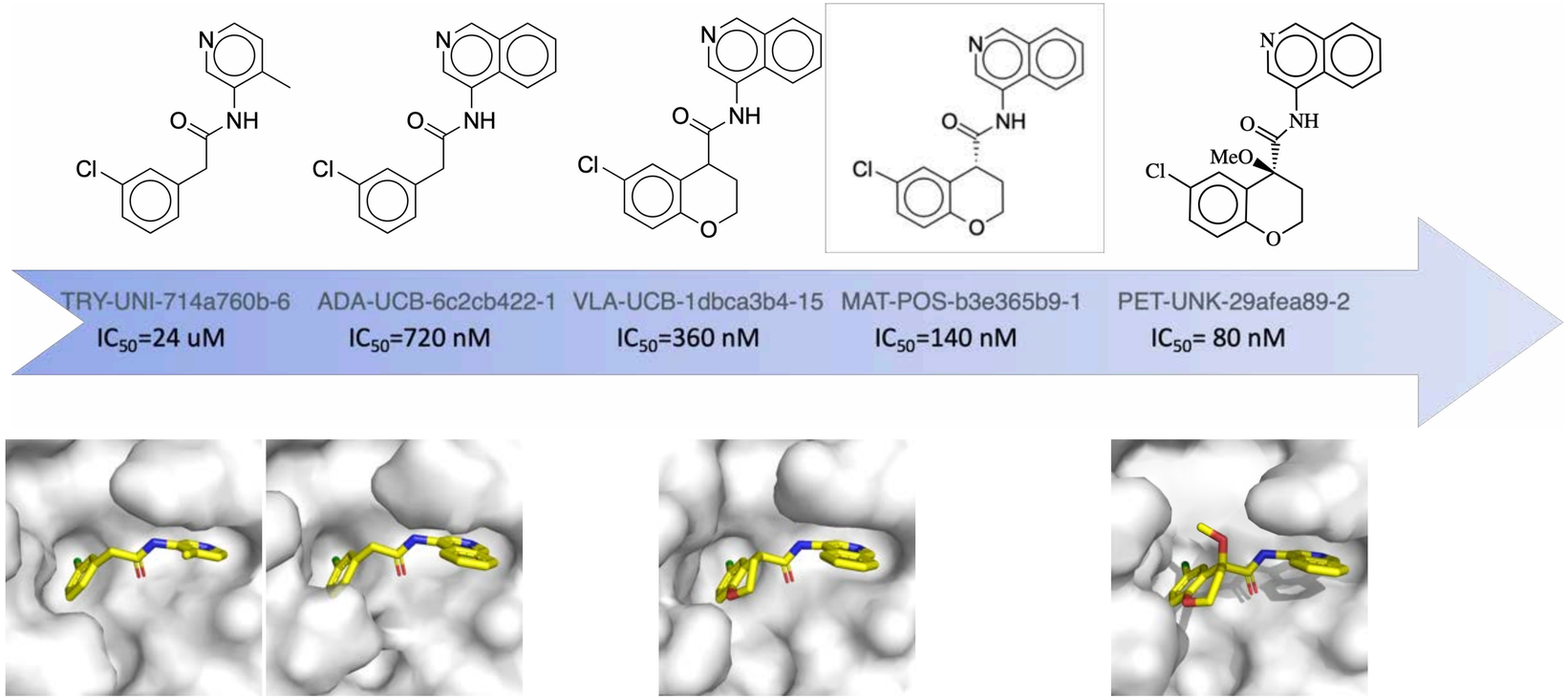
IC_{50}= 105 nM



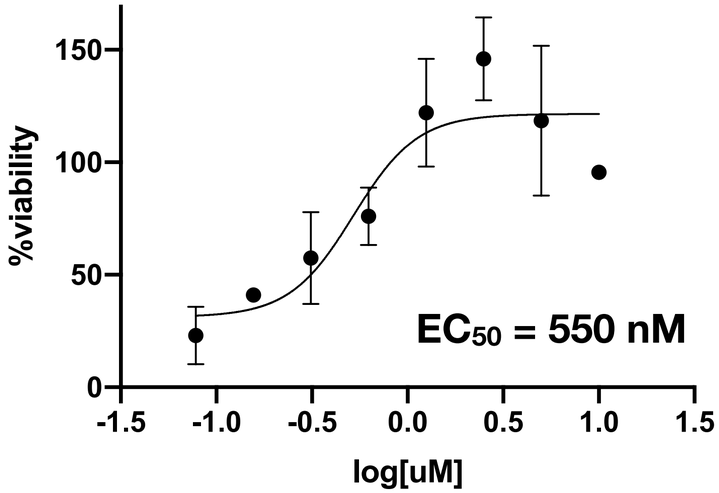
IC_{50}=270 nM

http://postera.ai/covid

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



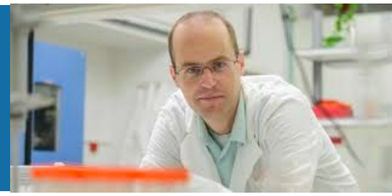
Lead compound active against live SARS-CoV-2



http://postera.ai/covid

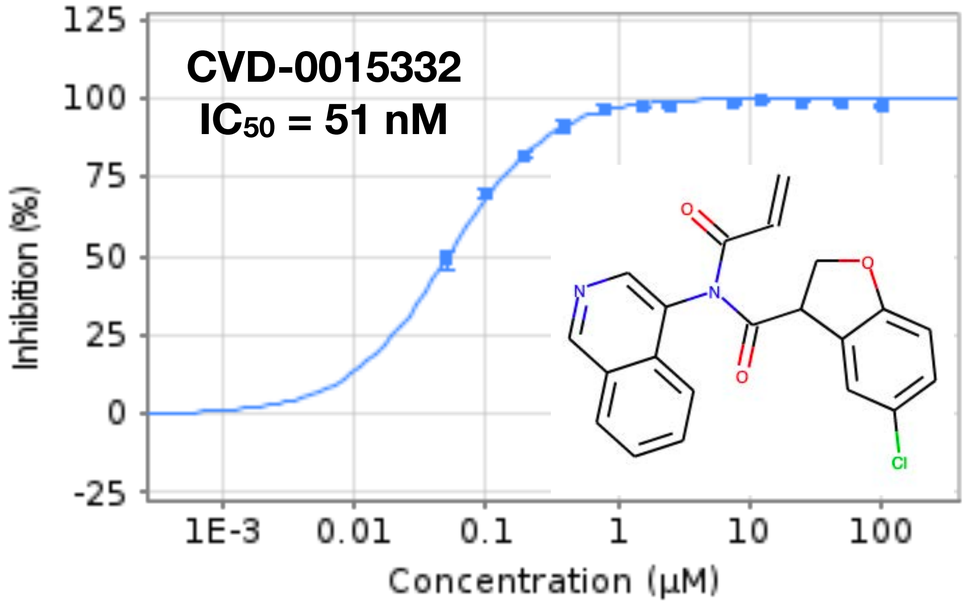
With the Israel Institute of Biological Research

Scaffold is well-poised for covalentization

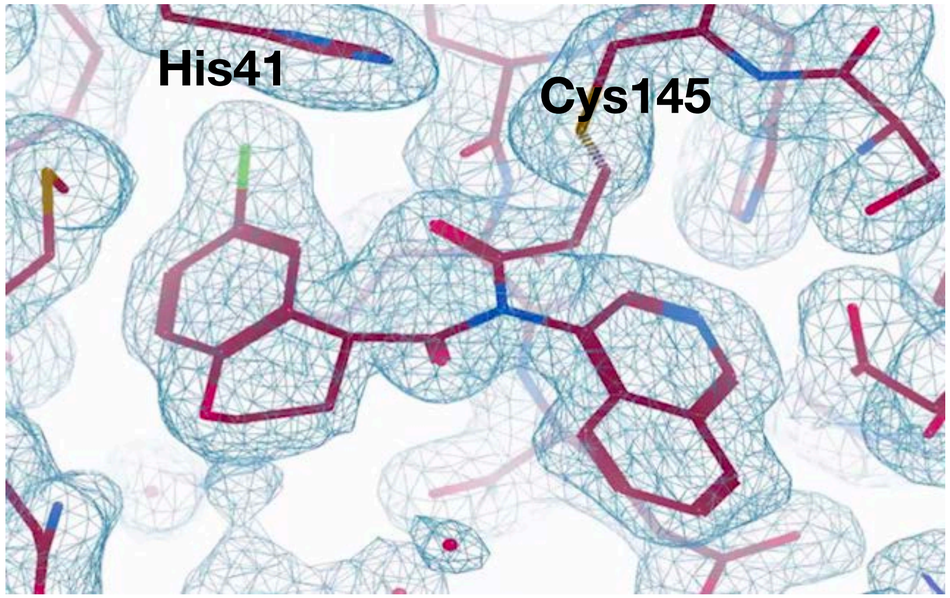


Nir London
Weizmann Institute

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?

http://postera.ai/covid

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

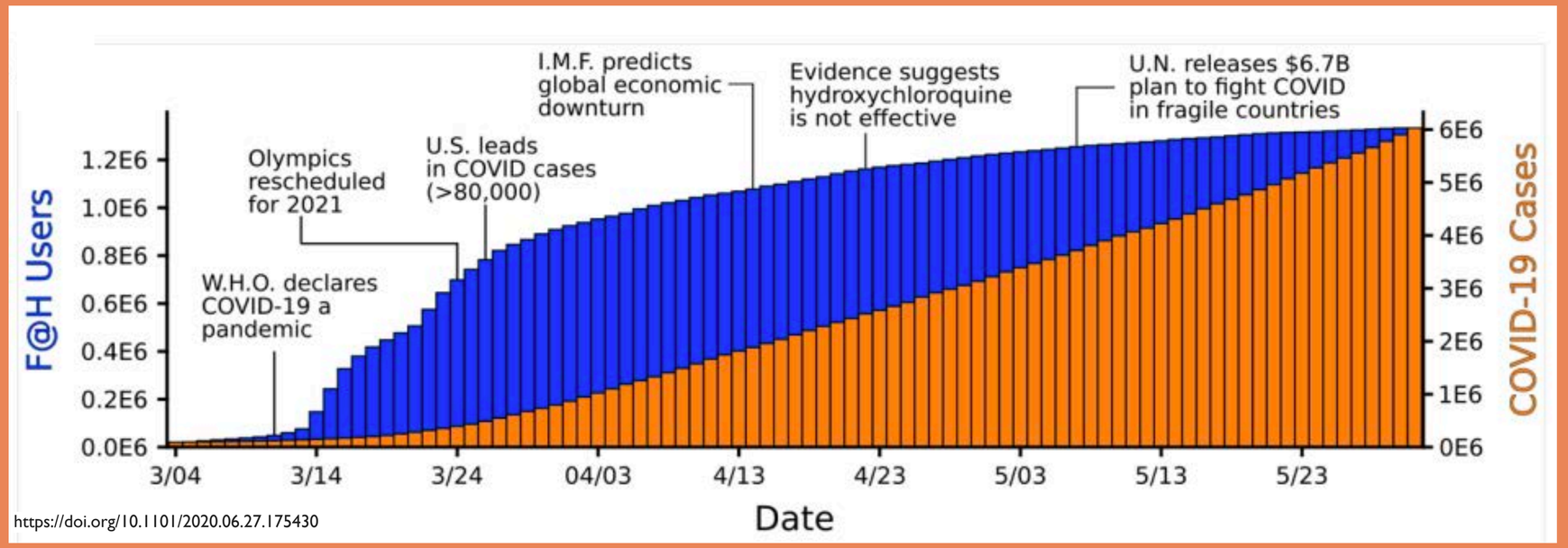
February 27, 2020
by Greg Bowman

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)

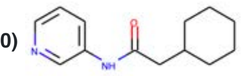
~1.5 exaflops

> sum of top-10 supercomputers

There are multiple design vectors to explore

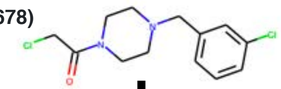
fragment merger produced initial lead compound

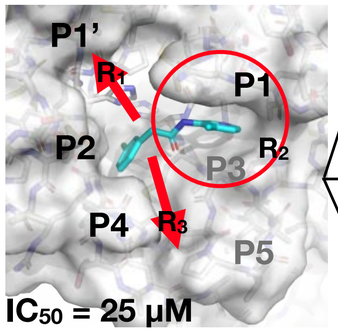
(x0770)



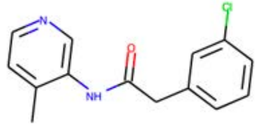
x

(x0678)





IC_{50} = 25 µM

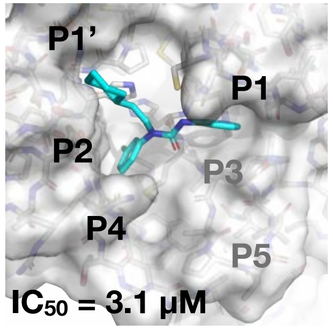


TRY-UNI-714a760b-6 (x2646)
current lead compound

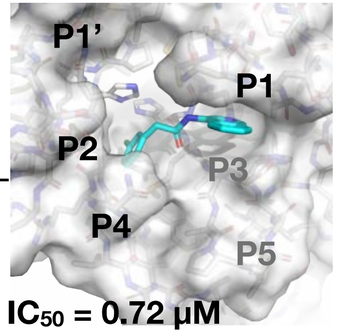
8x

35x

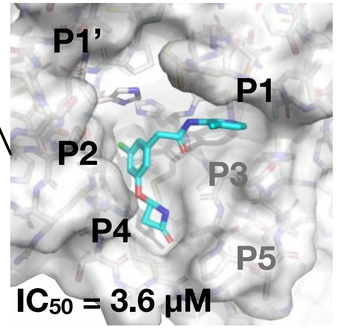
7x



IC_{50} = 3.1 µM

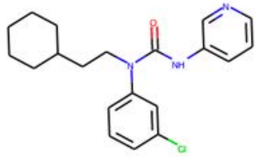


IC_{50} = 0.72 µM



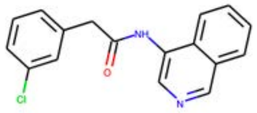
IC_{50} = 3.6 µM

P1' pocket engagement



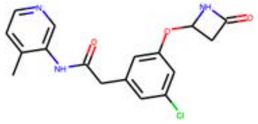
JOR-UNI-2fc98d0b-12 (x10201)

P1 substituent optimization



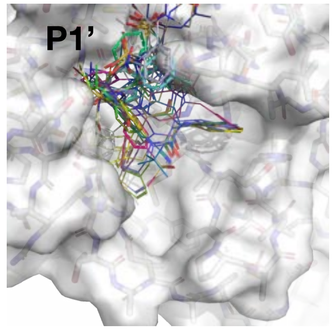
ADA-UCB-6c2cb422-1 (x10959)

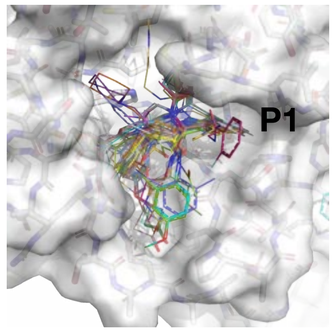
P4 pocket engagement

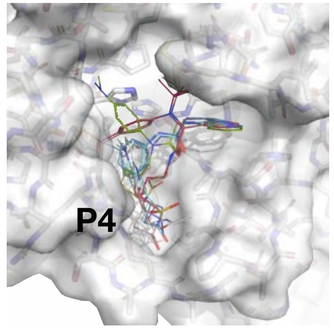


TRY-UNI-2eddb1ff-7 (x10789)

fragment-derived inspiration



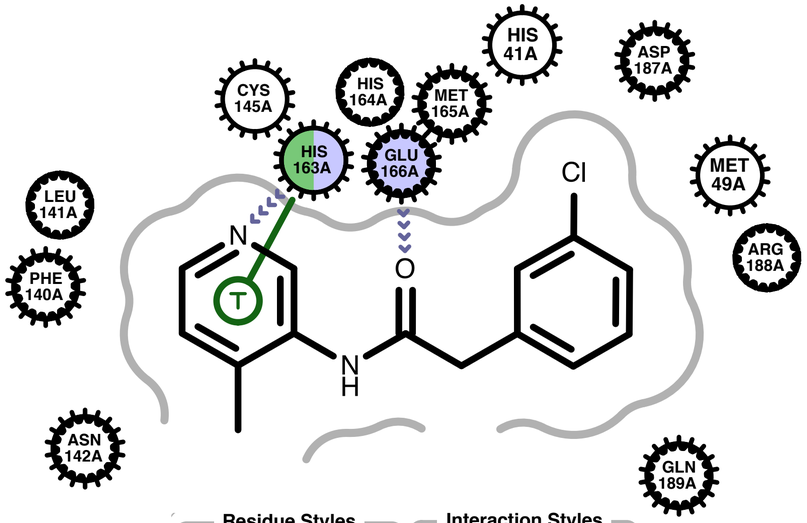




available fragment X-ray structures spanning pockets

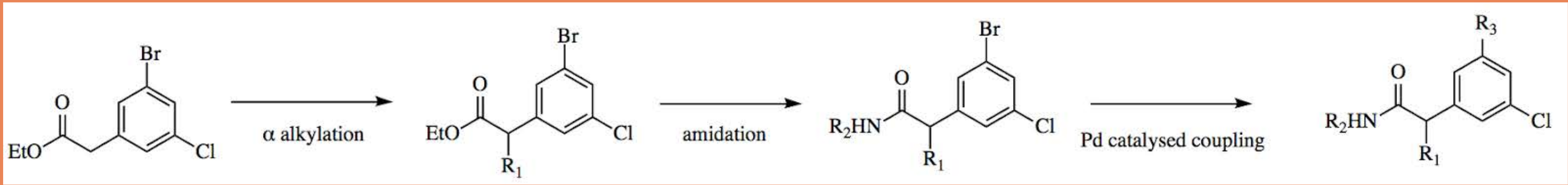
3-aminopyridine scaffold interactions

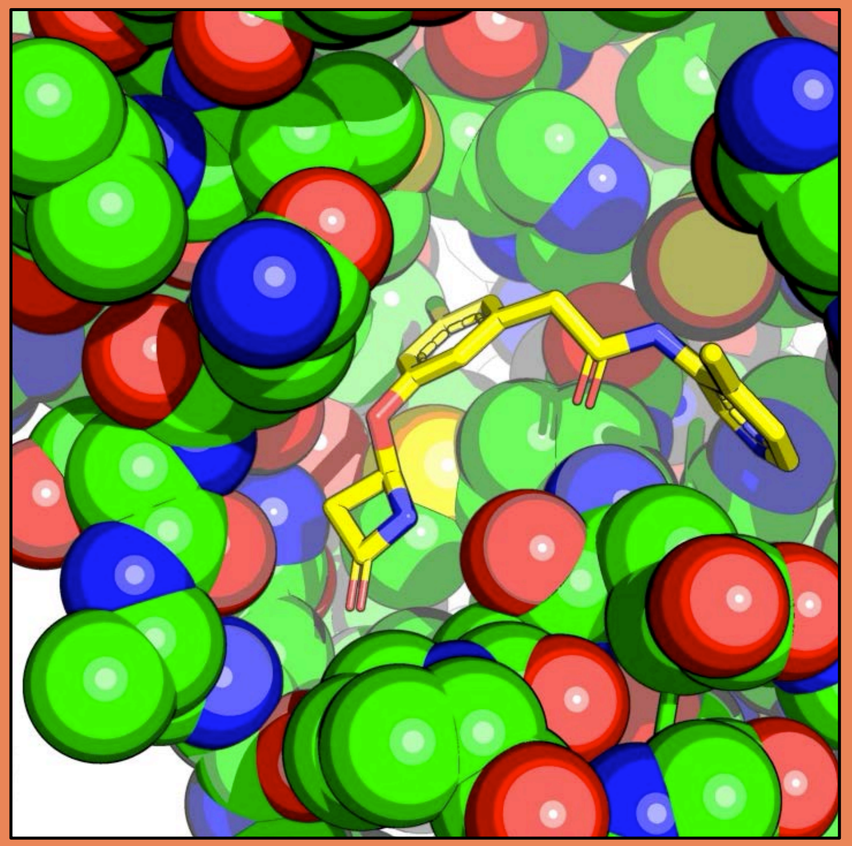
(264 assayed compounds in series)



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

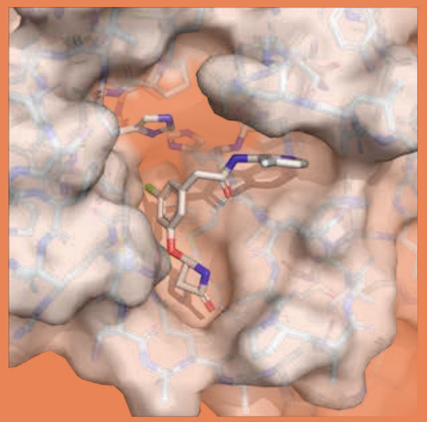




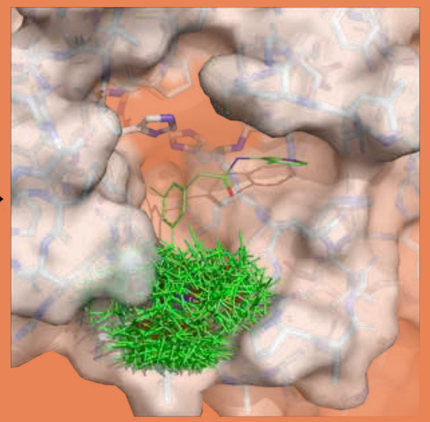
Folding@home can run relative alchemical free energy calculations at planetary scale, performing tens of thousands of transformations/week

Dominic Rufa
Tri-I TPCB PhD student

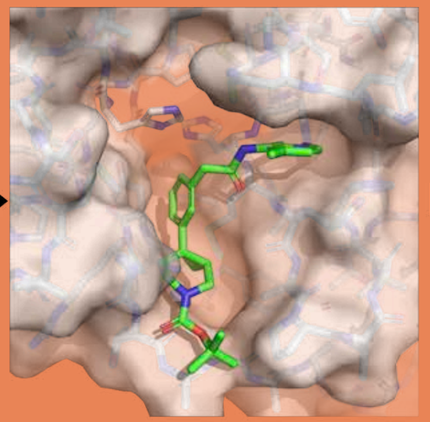
X-ray structure as reference



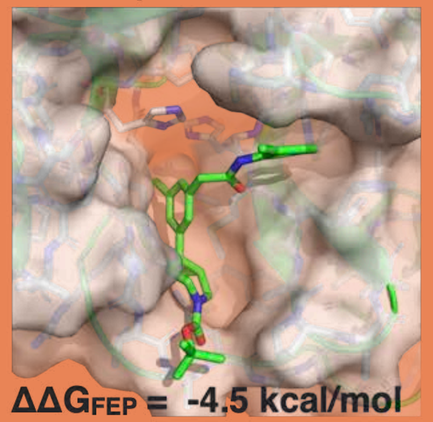
constrained enumeration of poses for proposed molecule



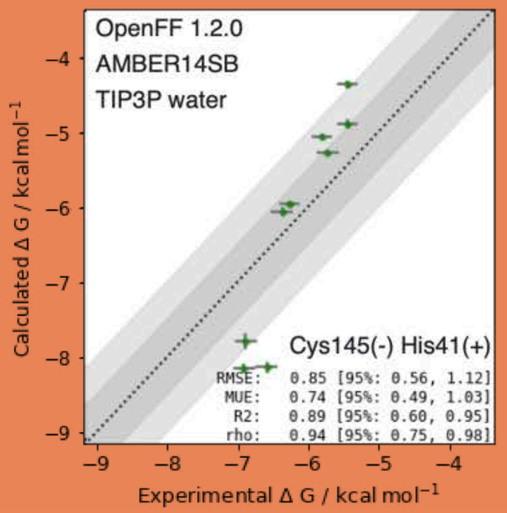
selection of pose with best docking score



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

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

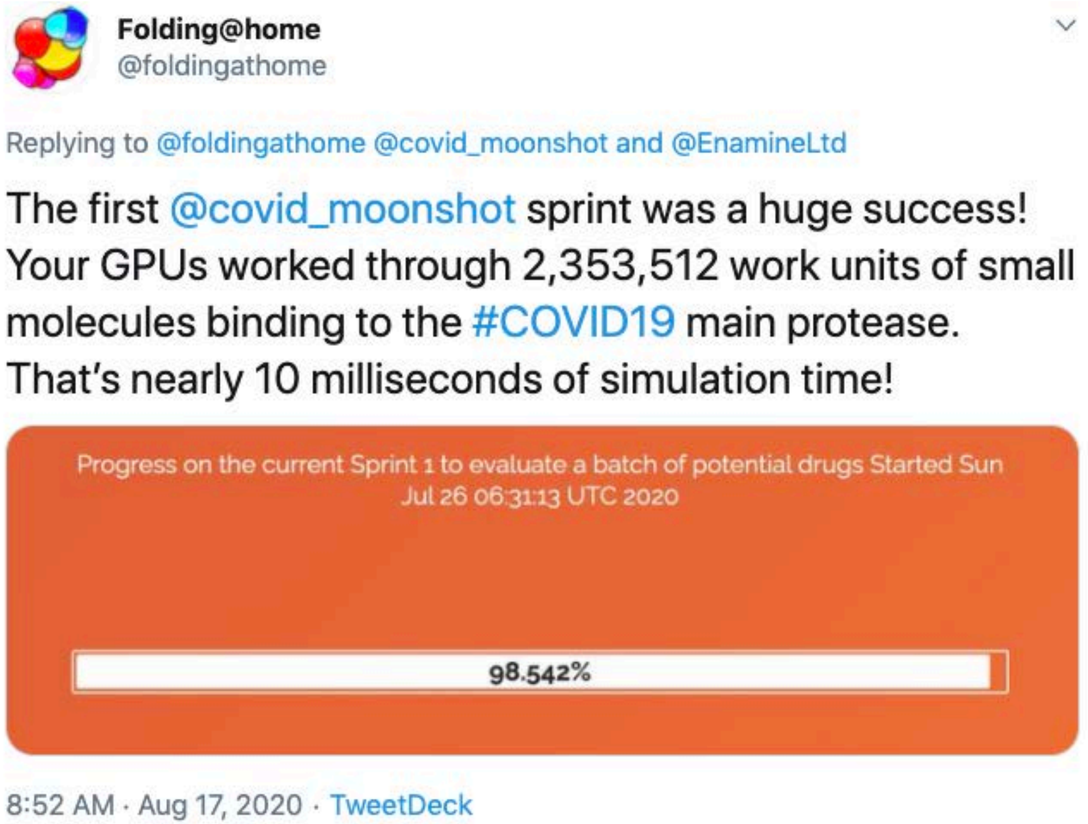
[Available for Windows, Mac, Linux]

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

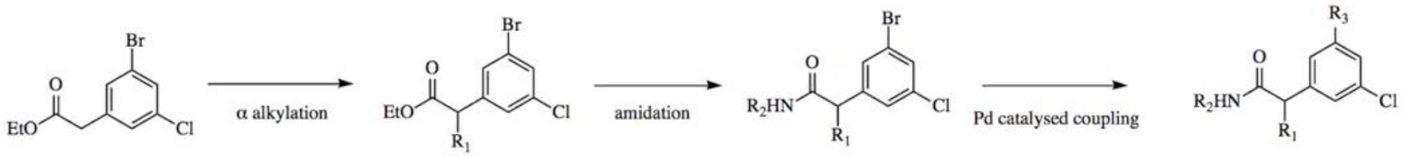
We generated a *lot* of data, which we have shared online via AWS



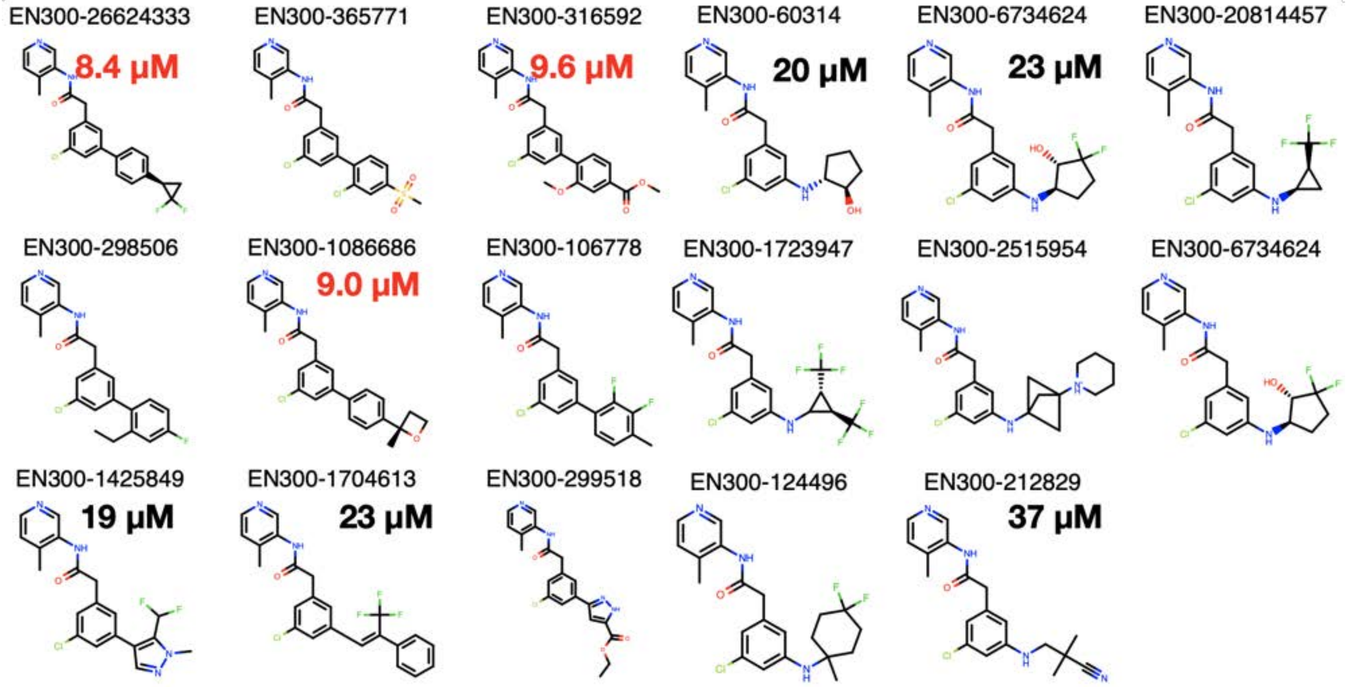
https://registry.opendata.aws/foldingathome-covid19/
https://covid.molssi.org//org-contributions/#folding--home

FREE ENERGY CALCULATIONS CAN RAPIDLY PRIORITIZE COMPOUNDS FROM LARGE VIRTUAL SYNTHETIC LIBRARIES

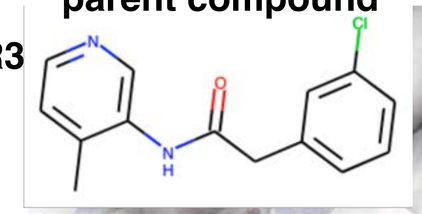
Can we engage S4 from this 5,000-compound virtual synthetic library varying R3



Top free energy calculation compounds and experimental affinity measurements:



parent compound



IC_{50} = 25 µM

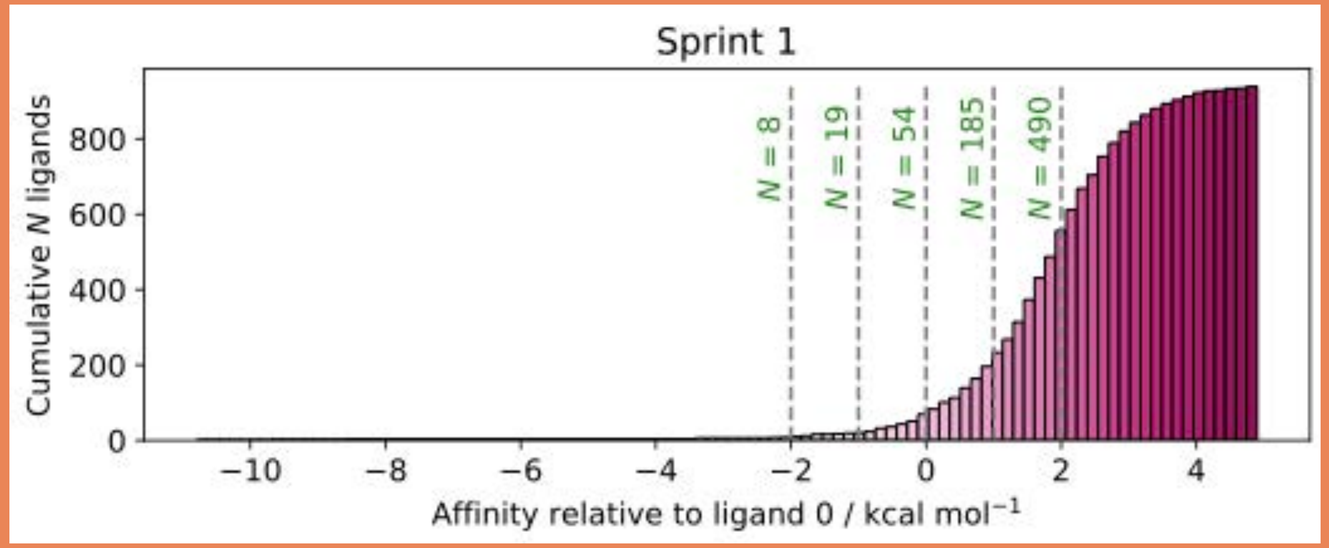
TRY-UNI-714a760b-6

top compounds from free energy calculations

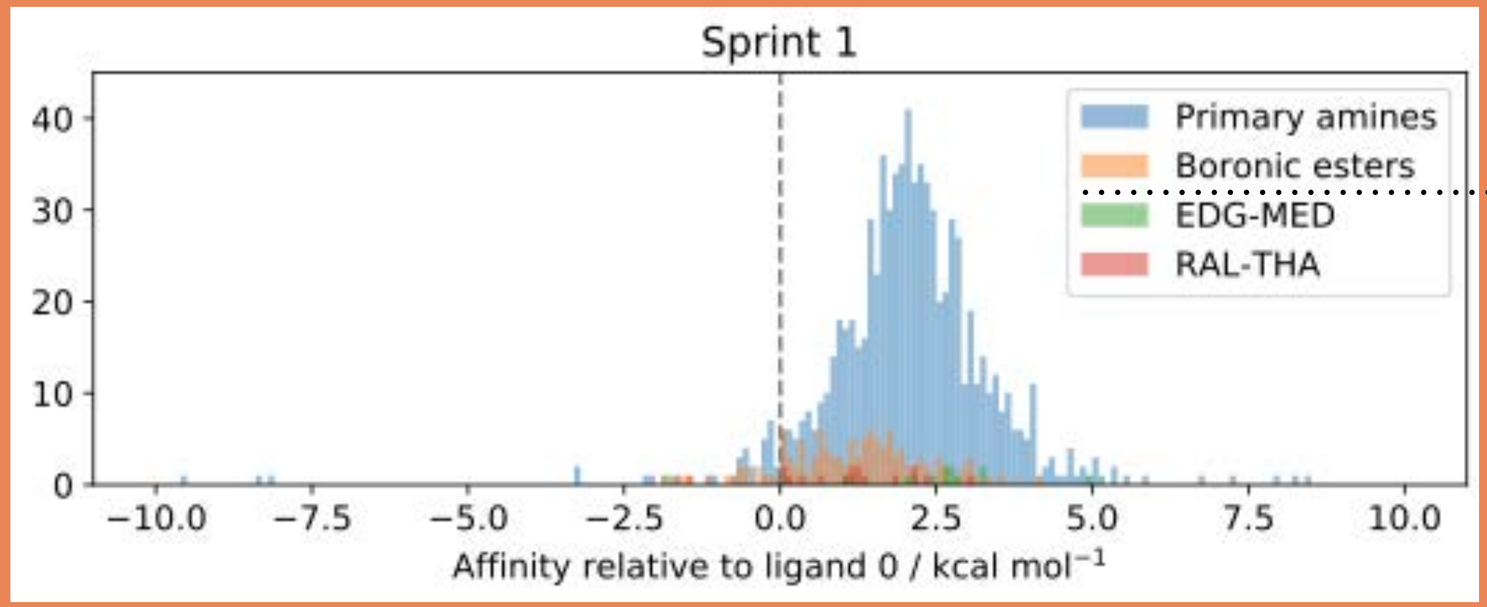
COVID Moonshot: [Moonshot] [Fragalysis] [Dashboard]

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
Science Dashboard

(compounds are currently being synthesized by Enamine)

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

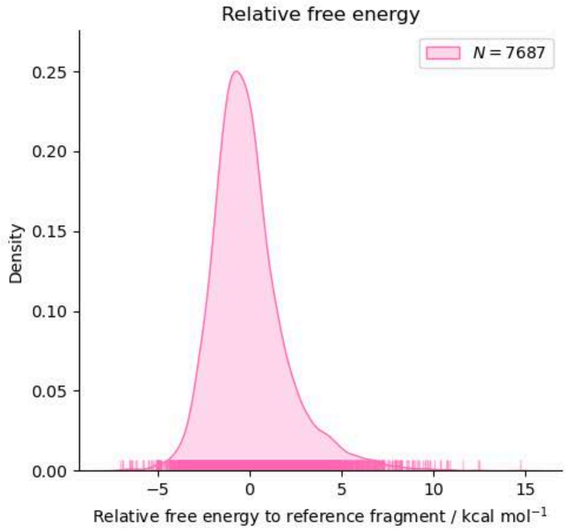
Description

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

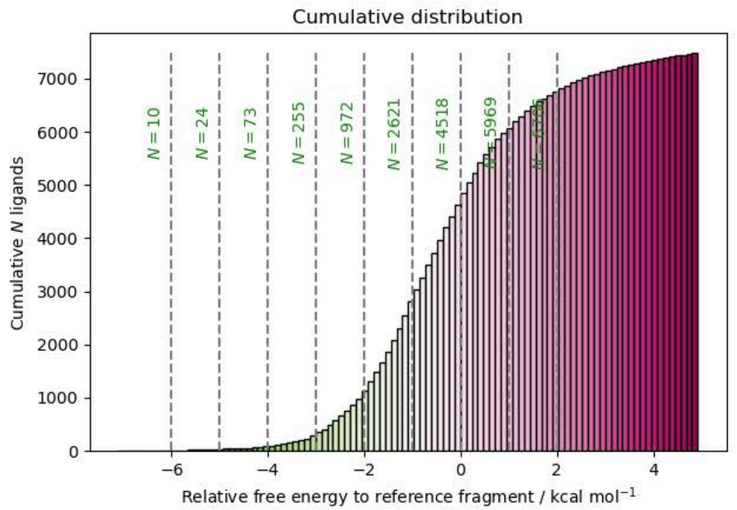
Progress

98.25%

Distributions



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

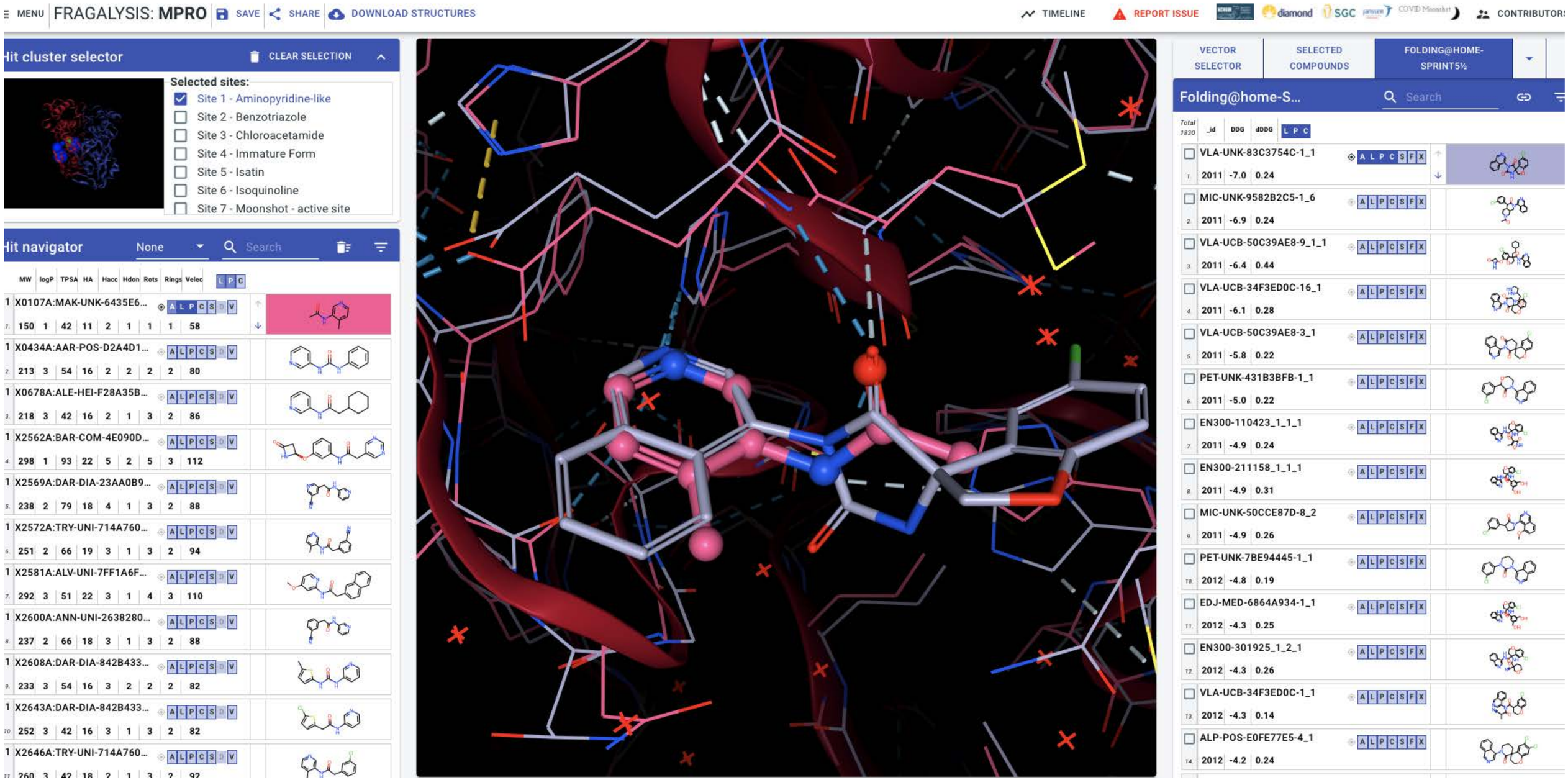


Updated 2021-02-21T21:35:59.343106+00:00

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



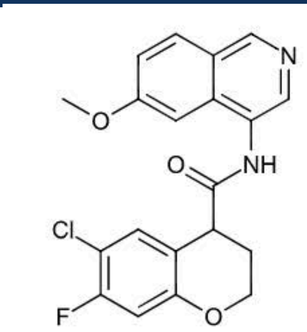
dashboard: https://tinyurl.com/fah-sprint-5-dimer
Fragalysis viewer: https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro

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

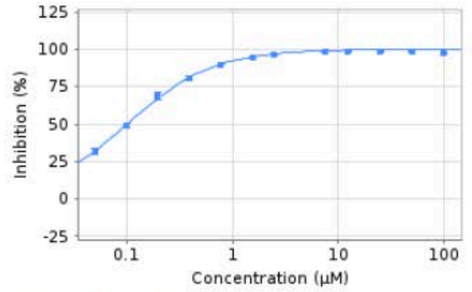
We're lining up IND-enabling studies now



CVD-0016872
COVID Moonshot

MAT-POS-96f51285-3

0.101



Flag outliers & Override

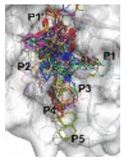
100 nM racemate (likely ~50 nM) predicted to be metabolically stable!

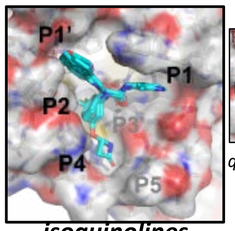
Apr '20 *Sep '20* *Jul '21* *Mar '22*

XChem | **fragment-to-lead** *$350k, 30 groups* | **lead optimization** *$800k, 40 groups* | **pre-IND** *(planning)* | **trials** *(exploring)*

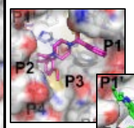
Suite of optimized leads | ***Regulatory phase***

Data release

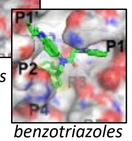




isoquinolines

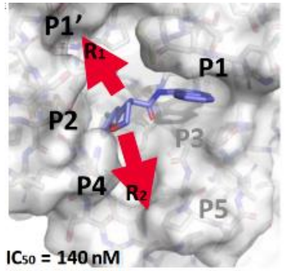


quinolones



benzotriazoles

Lead series



IC_{50} = 140 nM

Optimized leads

IND

COVID Moonshot

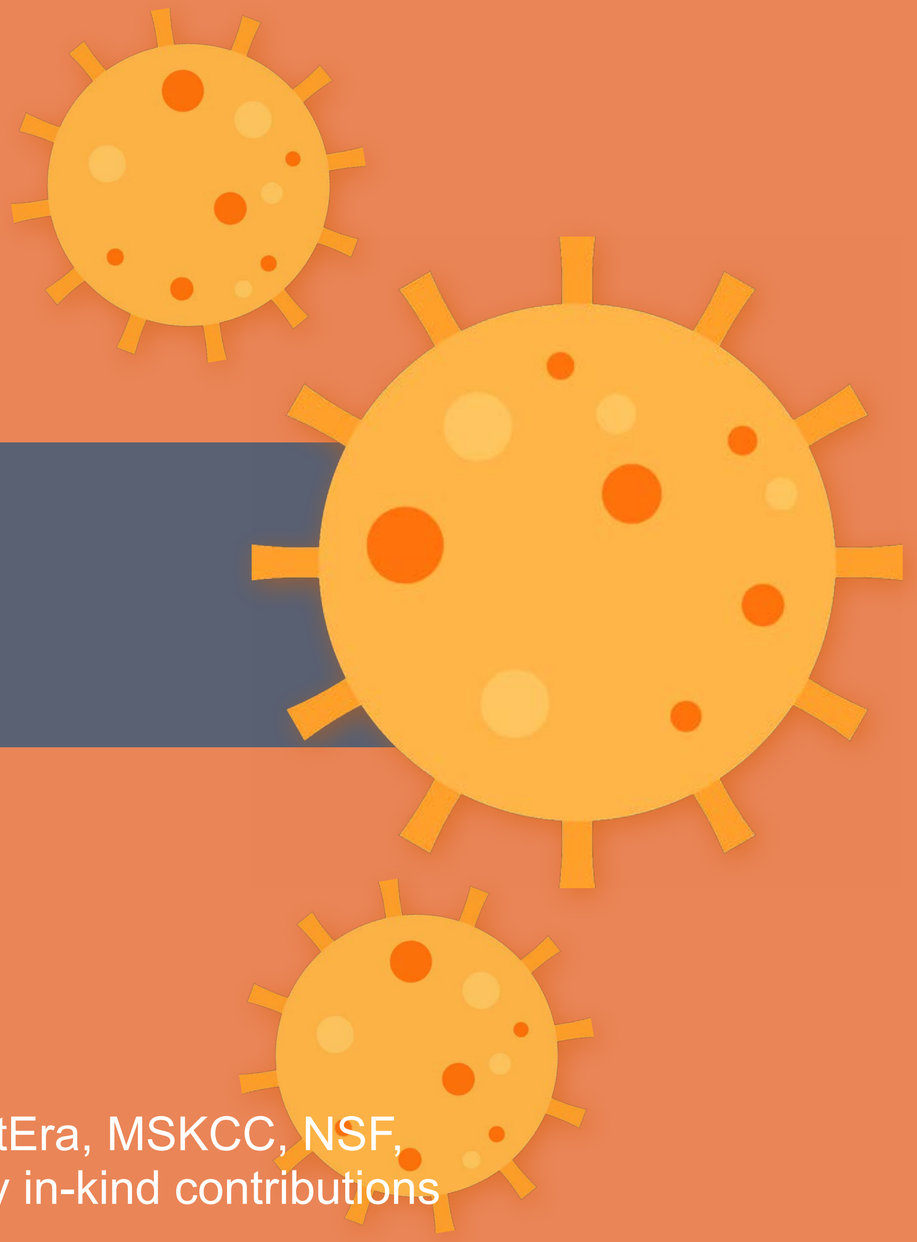
The COVID Moonshot collaboration is worldwide

all contributors: https://tinyurl.com/covid-moonshot-authors

Matthew C. Robinson	PostEra Inc.
Nir London	The Weizmann Institute of Science
Efrat Resnick	The Weizmann Institute of Science
Daniel Zaidmann	The Weizmann Institute of Science
Paul Gehrtz	The Weizmann Institute of Science
Rambabu N. Reddi	The Weizmann Institute of Science
Ronen Gabizon	The Weizmann Institute of Science
Haim Barr	The Weizmann Institute of Science
Shirly Duberstein	The Weizmann Institute of Science
Hadeer Zidane	The Weizmann Institute of Science
Khriesto Shurrush	The Weizmann Institute of Science
Galit Cohen	The Weizmann Institute of Science
Leonardo J. Solmesky	The Weizmann Institute of Science
Alpha Lee	PostEra Inc.; University of Cambridge
Andrew Jajack	PostEra Inc.
Milan Cvitkovic	PostEra Inc.
Jin Pan	PostEra Inc.
Ruby Pai	PostEra Inc.
Tatiana Matviiuk	Enamine Ltd
Oleg Michurin	Enamine Ltd
Marian Gorichko	Taras Shevchenko National University of Kyiv
Aarif Shaikh	Sai Life Sciences
Jakir Pinjari	Sai Life Sciences
Vishwanath Swamy	Sai Life Sciences
Maneesh Pingle	Sai Life Sciences
Sarma BVNBS	Sai Life Sciences
Anthony Aimon	Diamond Light Source Ltd; Research Complex at Harwell
Frank von Delft	Diamond Light Source Ltd; University of Oxford; Research Complex at Harwell;
Daren Fearon	Diamond Light Source Ltd; Research Complex at Harwell
Louise Dunnett	Diamond Light Source Ltd; Research Complex at Harwell
Alice Douangamath	Diamond Light Source Ltd; Research Complex at Harwell
Alex Dias	Diamond Light Source Ltd; Research Complex at Harwell
Ailsa Powell	Diamond Light Source Ltd; Research Complex at Harwell
Jose Brandao Neto	Diamond Light Source Ltd; Research Complex at Harwell
Rachael Skyner	Diamond Light Source Ltd; Research Complex at Harwell
Warren Thompson	Diamond Light Source Ltd; Research Complex at Harwell
Tyler Gorrie-Stone	Diamond Light Source Ltd; Research Complex at Harwell
Martin Walsh	Diamond Light Source Ltd; Research Complex at Harwell
David Owen	Diamond Light Source Ltd; Research Complex at Harwell
Petra Lukacik	Diamond Light Source Ltd; Research Complex at Harwell
Claire Strain-Damerell	Diamond Light Source Ltd; Research Complex at Harwell
Halina Mikolajek	Diamond Light Source Ltd; Research Complex at Harwell
Sam Horrell	Diamond Light Source Ltd; Research Complex at Harwell
Lizbé Koekemoer	University of Oxford
Tobias Krojer	University of Oxford
Mike Fairhead	University of Oxford
Beth MacLean	University of Oxford
Andrew Thompson	University of Oxford
Conor Francis Wild	University of Oxford
Mihaela D. Smilova	University of Oxford
Nathan Wright	University of Oxford
Annette von Delft	University of Oxford
Carina Gileadi	University of Oxford
Victor L. Rangel	School of Pharmaceutical Sciences of Ribeirao Preto
Chris Schofield	University of Oxford
Tika R. Malla	University of Oxford
Anthony Tumber	University of Oxford
Tobias John	University of Oxford
Ioannis Vakonakis	University of Oxford
Anastassia L. Kantsadi	University of Oxford
Nicole Zitzmann	University of Oxford
Juliane Brun	University of Oxford
J. L. Kiappes	University of Oxford
Michelle Hill	University of Oxford
Finny S. Varghese	Radboud University Medical Center
Ronald P. van Rij	Radboud University Medical Center
Gijs J. Overheul	Radboud University Medical Center
Susana Tomásio	Collaborative Drug Discovery
Charlie Weatherall	Collaborative Drug Discovery
Mariana Vaschetto	Collaborative Drug Discovery

Hannah Bruce Macdonald	Memorial Sloan Kettering Cancer Center
John D. Chodera	Memorial Sloan Kettering Cancer Center
Dominic Rufa	Memorial Sloan Kettering Cancer Center
Matthew Wittmann	Memorial Sloan Kettering Cancer Center
Melissa L. Boby	Memorial Sloan Kettering Cancer Center;Weil Cornell Medical College
William G. Glass	Memorial Sloan Kettering Cancer Center
Peter K. Eastman	Stanford University
Joseph E. Coffland	Cauldron Development
Ed J. Griffen	MedChemica Ltd
William McCorkindale	University of Cambridge
Aaron Morris	PostEra Inc
Robert Glen	University of Cambridge
Jason Cole	Cambridge Crystallographic Datacentre
Richard Foster	University of Leeds
Holly Foster	University of Leeds
Mark Calmiano	UCB
Rachael Tennant	Lhasa Ltd. UK
Jag Heer	UCB
Jive Shi	UCB
Eric Jnoff	UCB
Matthew F.D. Hurley	Temple University
Bruce A. Lefker	Thames Pharma Partners LLC
Ralph P. Robinson	Thames Pharma Partners LLC
Charline Giroud	University of Oxford
James Bennett	University of Oxford
Oleg Fedorov	University of Oxford
St Patrick Reid	Department of Pathology and Microbiology
Melody Jane Morwitzer	Department of Pathology and Microbiology
Lisa Cox	Life Compass Consulting Ltd
Garrett M. Morris	University of Oxford
Matteo Ferla	University of Oxford
Demetri Moustakas	Relay Therapeutics
Tim Dudgeon	Informatics Matters
Vladimír Pšenák	M2M solutions, s.r.o
Boris Kovar	M2M solutions, s.r.o
Vincent Voelz	Temple University
Warren Thompson	Diamond Light Source Ltd; Research Complex at Harwell
Anna Carbery	University of Oxford;Diamond Light Source
Alessandro Contini	University of Milan
Austin Clyde	Argonne National Laboratory
Amir Ben-Shmuel	Israel Institution of Biological Research
Assa Sittner	Israel Institution of Biological Research
Boaz Politi	Israel Institution of Biological Research
Einat B. Vitner	Israel Institution of Biological Research
Elad Bar-David	Israel Institution of Biological Research
Hadas Tamir	Israel Institution of Biological Research
Hagit Achdout	Israel Institution of Biological Research
Haim Levy	Israel Institution of Biological Research
Itai Glinert	Israel Institution of Biological Research
Nir Paran	Israel Institution of Biological Research
Noam Erez	Israel Institution of Biological Research
Reut Puni	Israel Institution of Biological Research
Sharon Melamed	Israel Institution of Biological Research
Shay Weiss	Israel Institution of Biological Research
Tomer Israely	Israel Institution of Biological Research
Yfat Yahalom-Ronen	Israel Institution of Biological Research
Adam Smalley	UCB
Vladas Oleinikovas	UCB
John Spencer	University of Sussex
Peter W. Kenny	
Beniamin Perry	DNDi
Walter Ward	Walter Ward Consultancy and Training
Emma Cattermole	University of Oxford
Lori Ferrins	Northeastern University
Charles J. Evermann	Northeastern University
Bruce F. Milne	University of Coimbra

THANK YOU!



preprint: https://doi.org/10.1101/2020.10.29.339317
contributors: https://tinyurl.com/covid-moonshot-authors
twitter: https://twitter.com/covid_moonshot
slides: http://choderalab.org/news
Moonshot data: http://postera.ai/covid
Folding@home data: http://covid.molssi.org
funding: Diamond, Oxford COVID Response Fund, Weizmann, PostEra, MSKCC, NSF, DNDi, LifeArc, Wellcome Trust TEP Strategic Award, and so many in-kind contributions