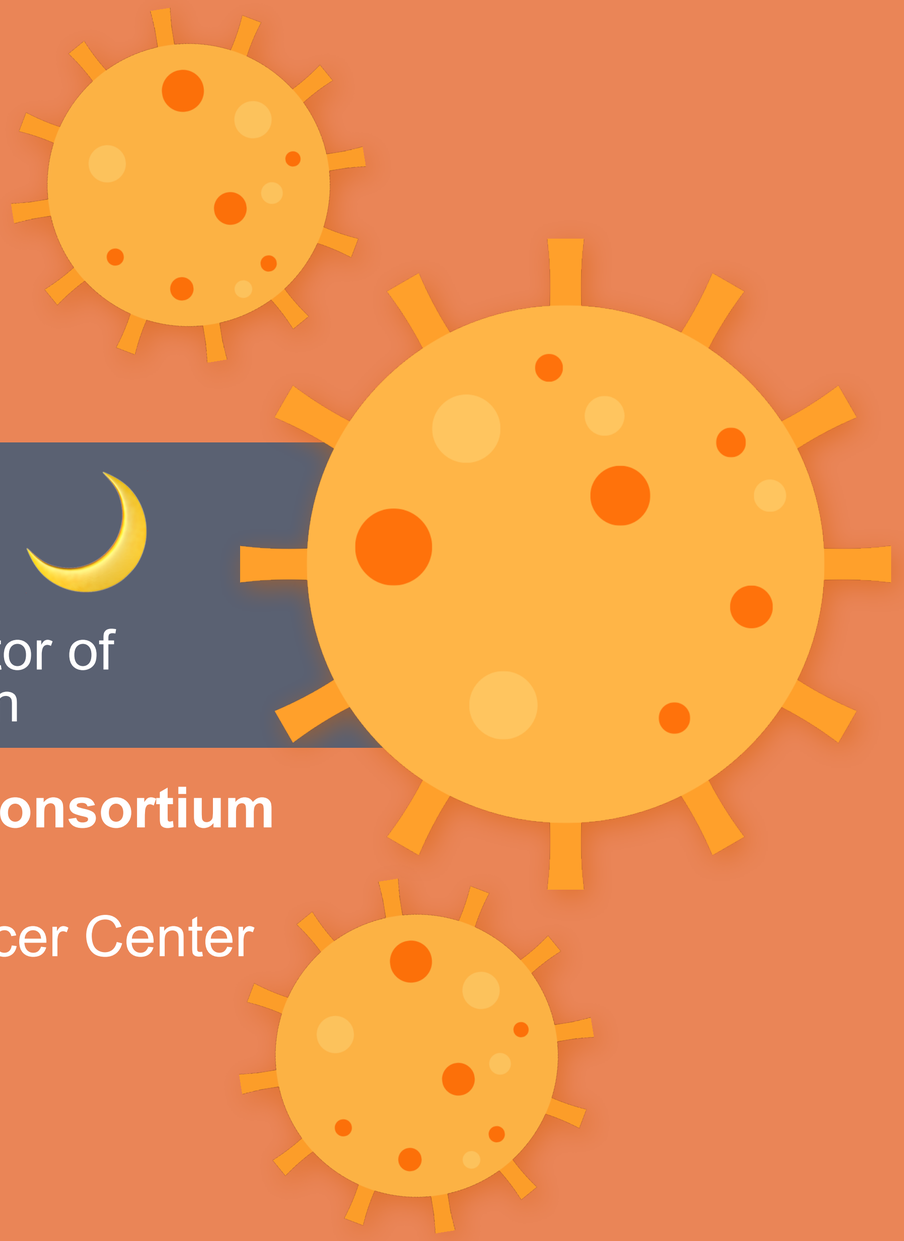
data: http://postera.ai/covid
slides: http://choderalab.org/news



THE COVID MOONSHOT 🌙

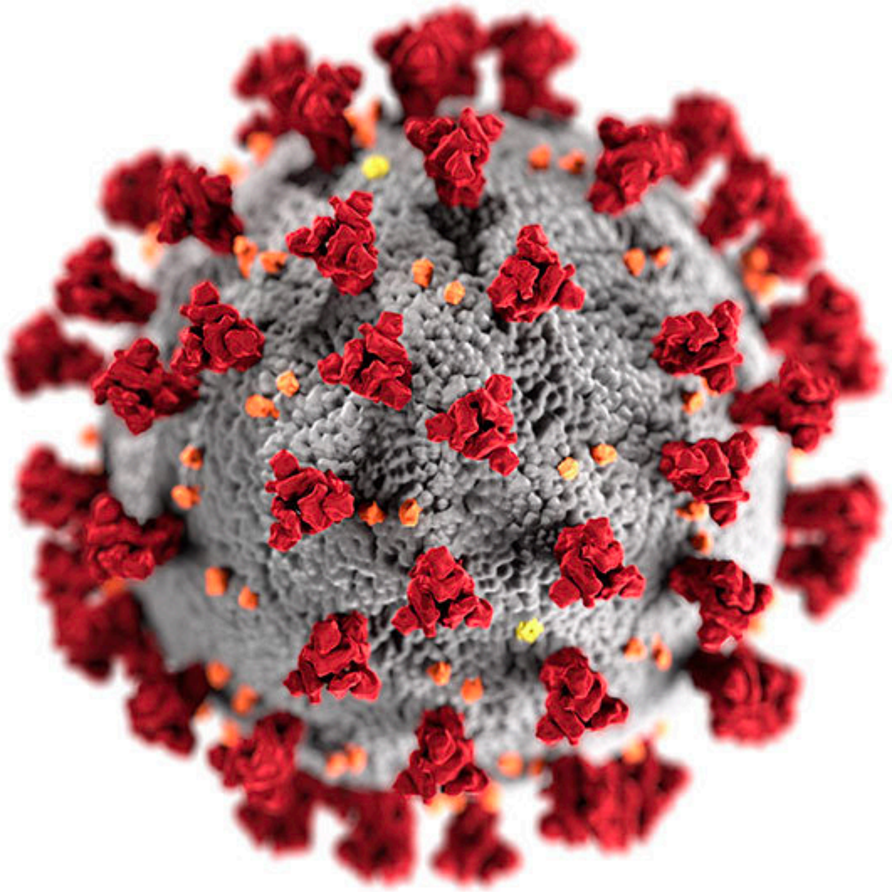
Closing in on an orally-bioavailable small molecule inhibitor of SARS-CoV-2 Mpro through an open science collaboration

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, Interline
  All funding: http://choderalab.org/funding

Biophysical Society Meeting - 26 Feb 2021 - Cyberspace

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.

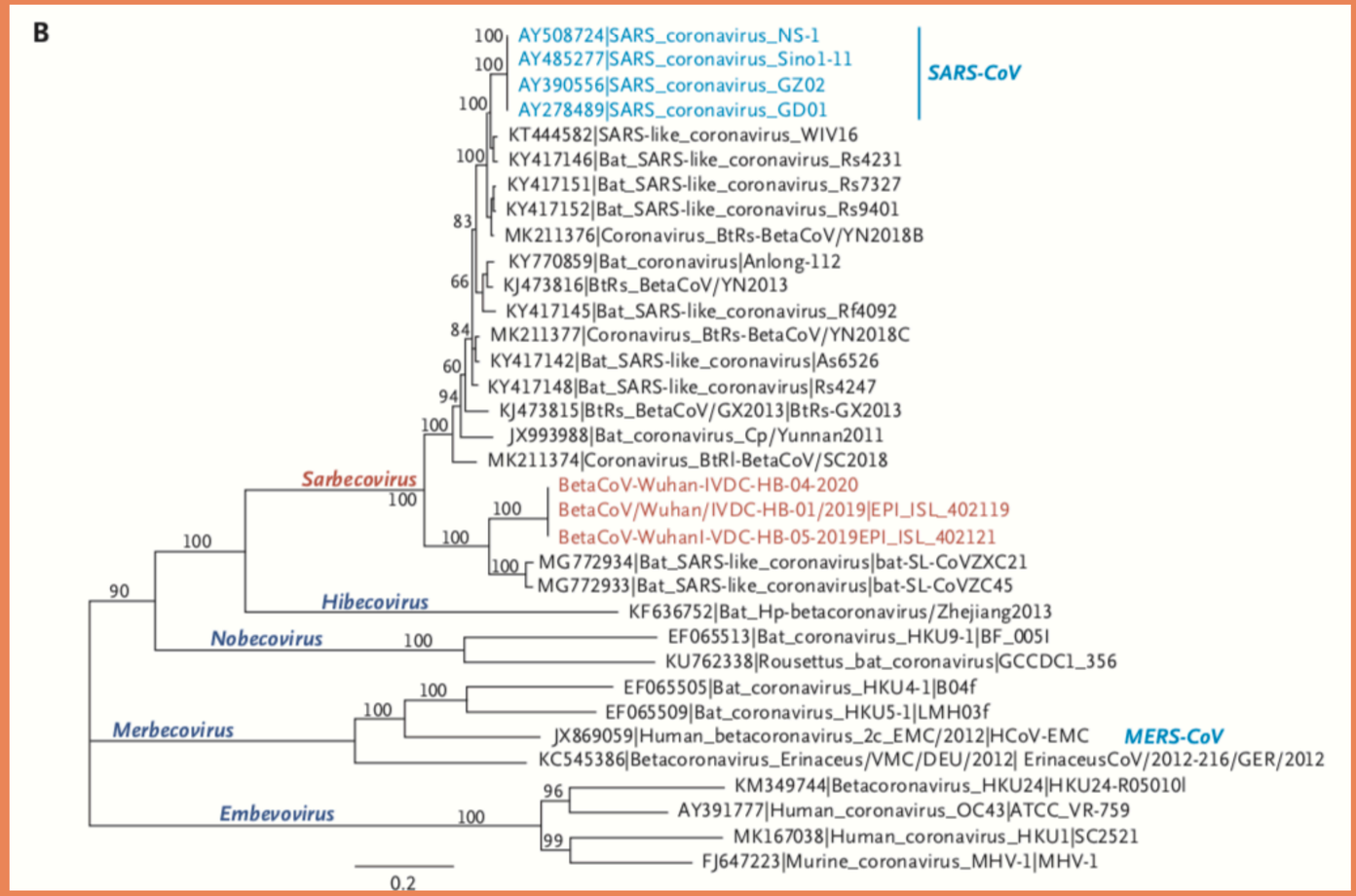
Drs. Zhu, Zhang, W. Wang, Li, and Yang contributed equally to this article.

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

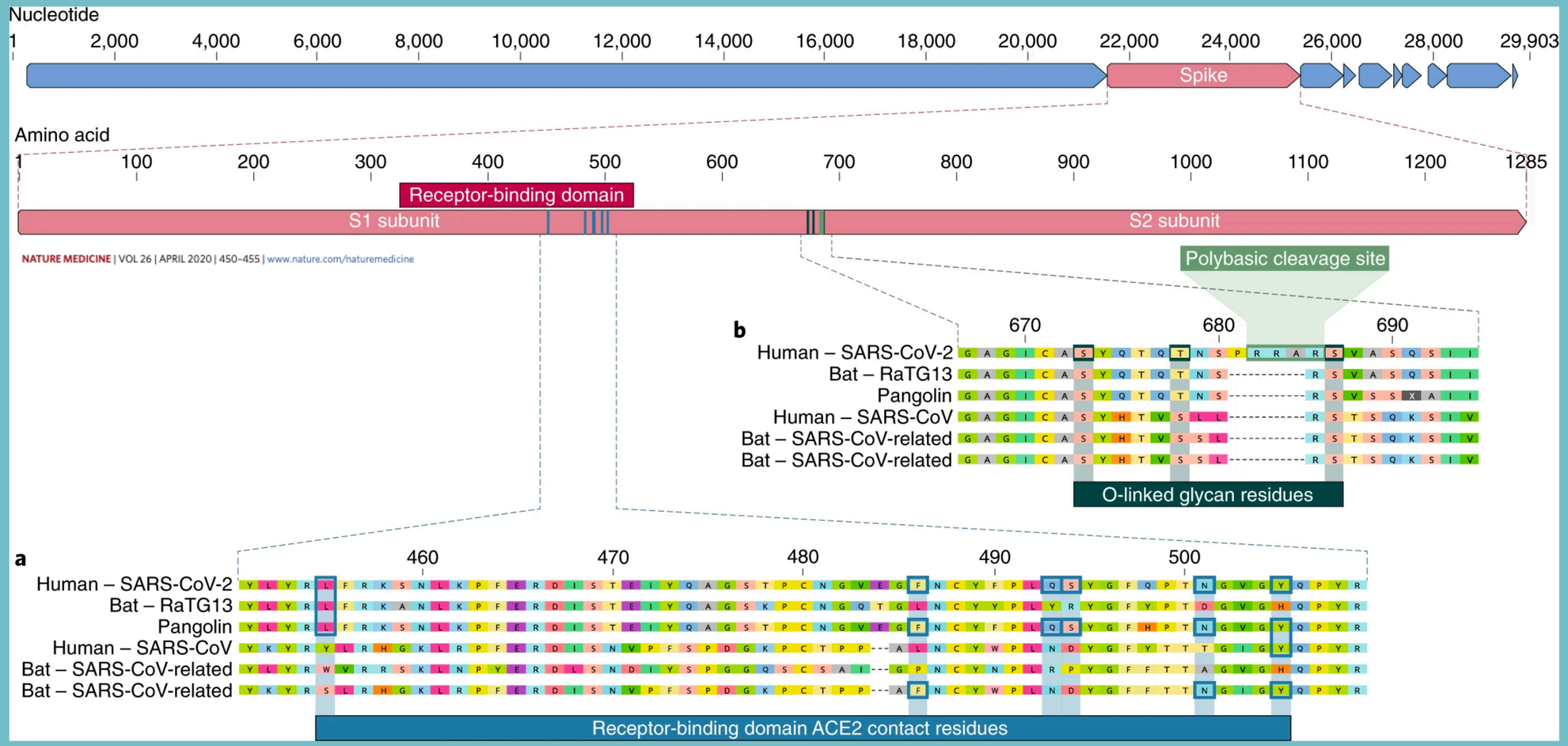
EMERGING AND REEMERGING PATHOGENS ARE GLOBAL CHALLENGES FOR public health.[1] Coronaviruses are enveloped RNA viruses that are distributed broadly among humans, other mammals, and birds and that cause respiratory, enteric, hepatic, and neurologic diseases.[2,3] Six coronavirus species are known to cause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

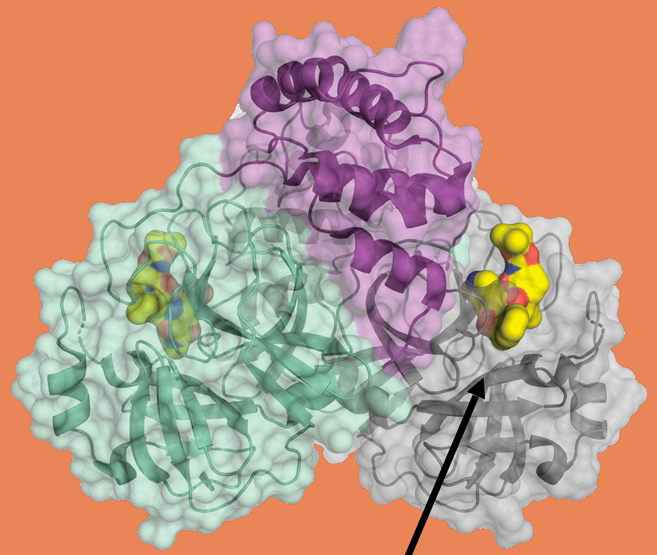
The viral genome sequence was surprisingly similar to SARS-CoV-1: Hence the name SARS-CoV-2!

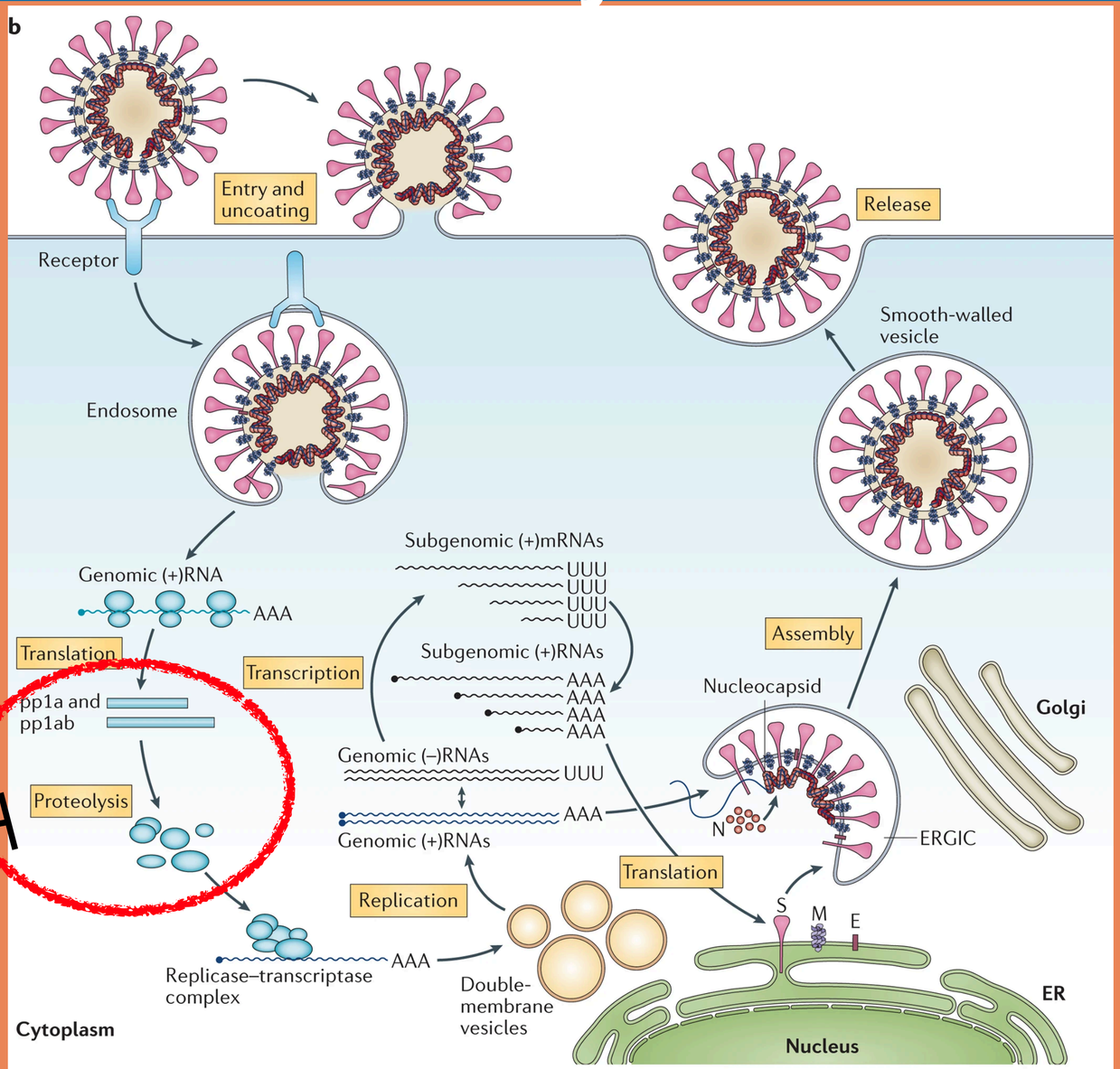


The SARS-CoV-2 main viral protease (Mpro) is essential for a key stage in the viral life cycle

M^{pro}

also: nsp5, 3CL^{Pro}

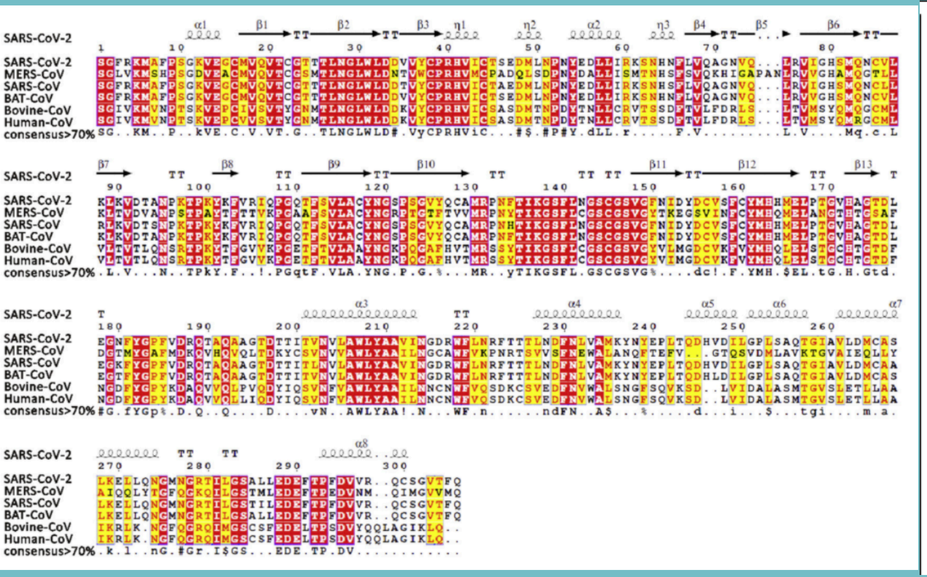




de Wit et al. Nat. Rev. Microbiology (2016)

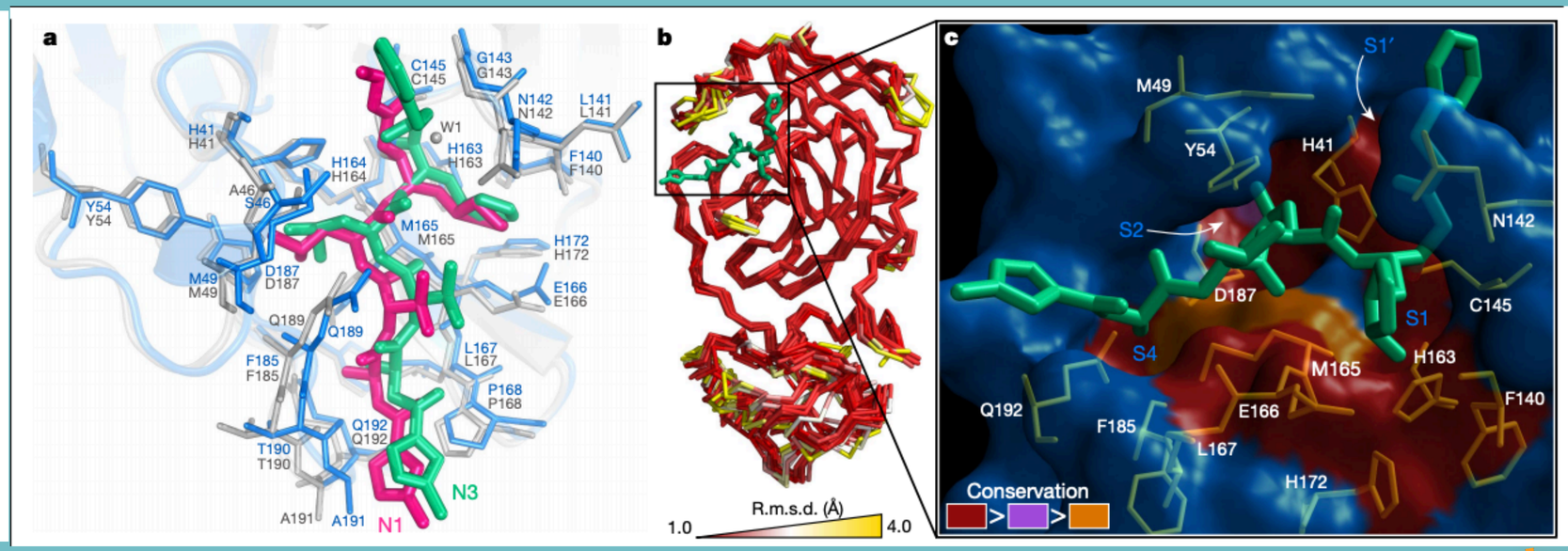
Mpro is highly conserved among viruses that cause SARS, MERS, and COVID

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 antiviral therapy and potentially pan-coronavirus therapy

While no human coronavirus Mpro inhibitors have 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

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Feline coronaviruses
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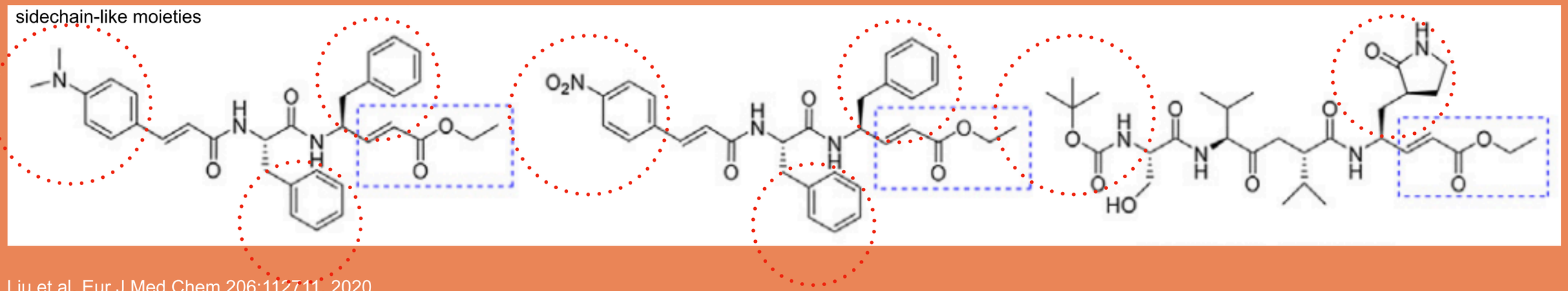
Protease inhibitor
Cathepsin B
Synergy
3CL protease

ABSTRACT

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

there IS a successful drug for cats

Previously known Mpro inhibitors mimic peptides, which are difficult to develop into useful oral drugs



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

We needed a new potent small molecule drug.
How do we get there *quickly*?

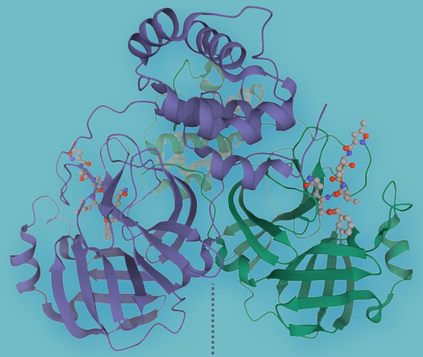
Diamond Light Source prosecuted a high-throughput X-ray fragment screen in a matter of weeks

Frank von Delft
Diamond Light Source / XChem / SGC

February 14

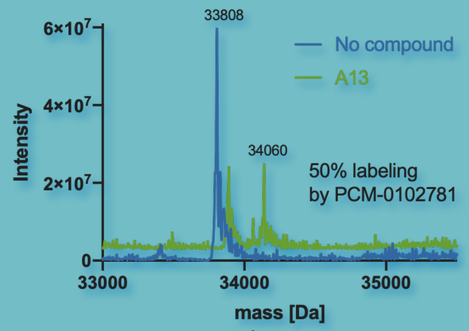
Main protease cloned and produced

Martin Walsh



February 20

Atomic resolution structure of the protease determined

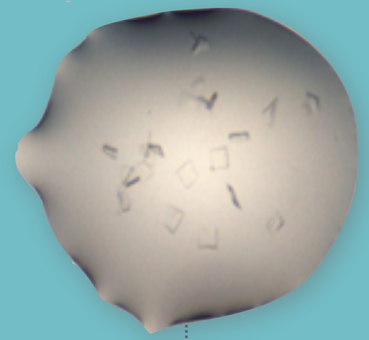


February 25

Covalent screen finds 150 active site hits

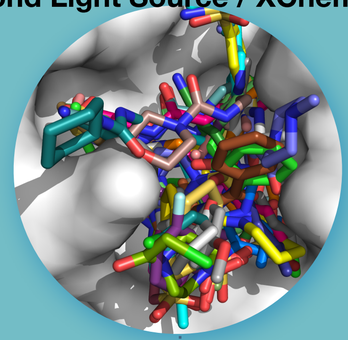
>40 hits validated

Nir London



March 5

1,500 crystals collected in one day (!)

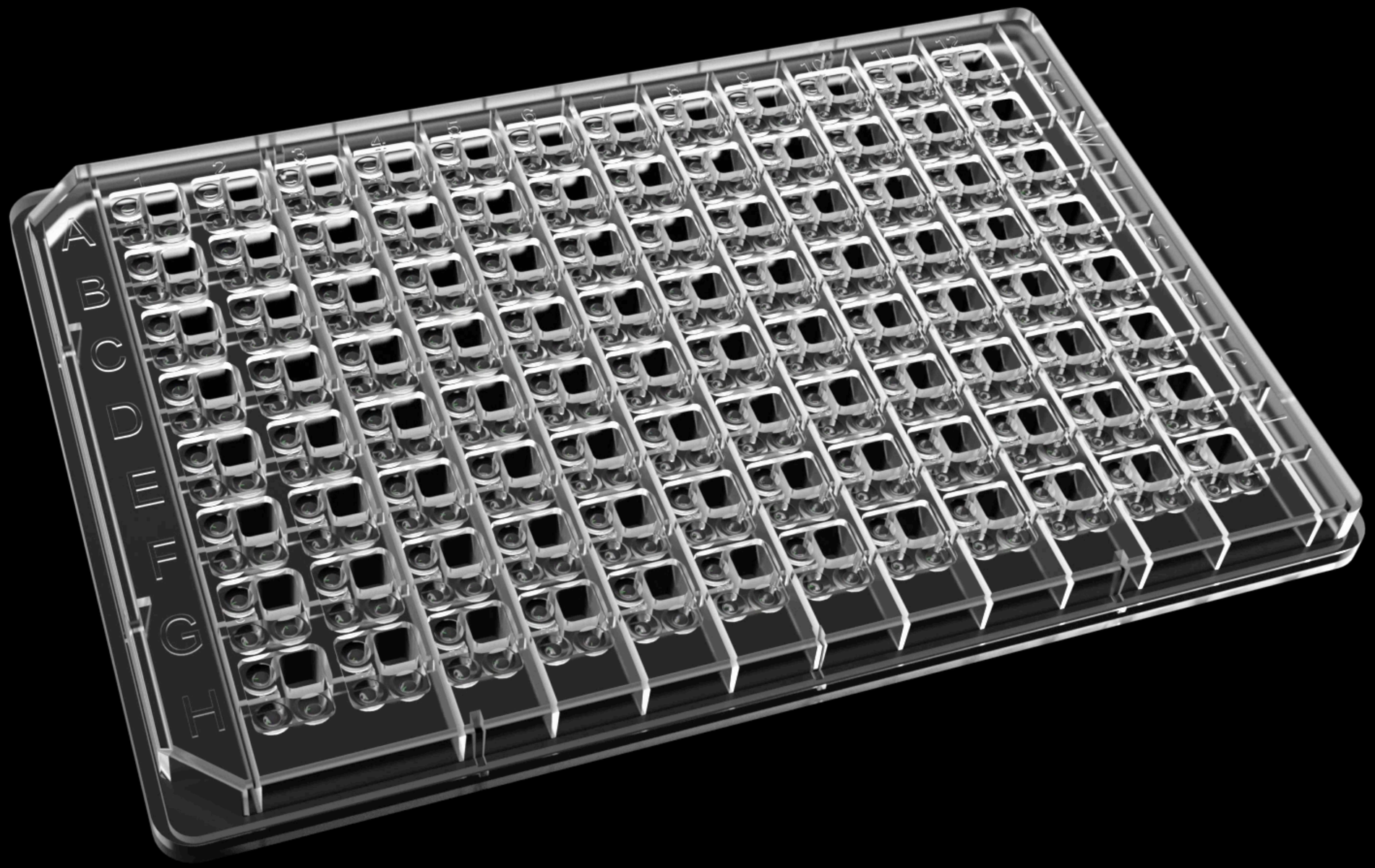


March 18

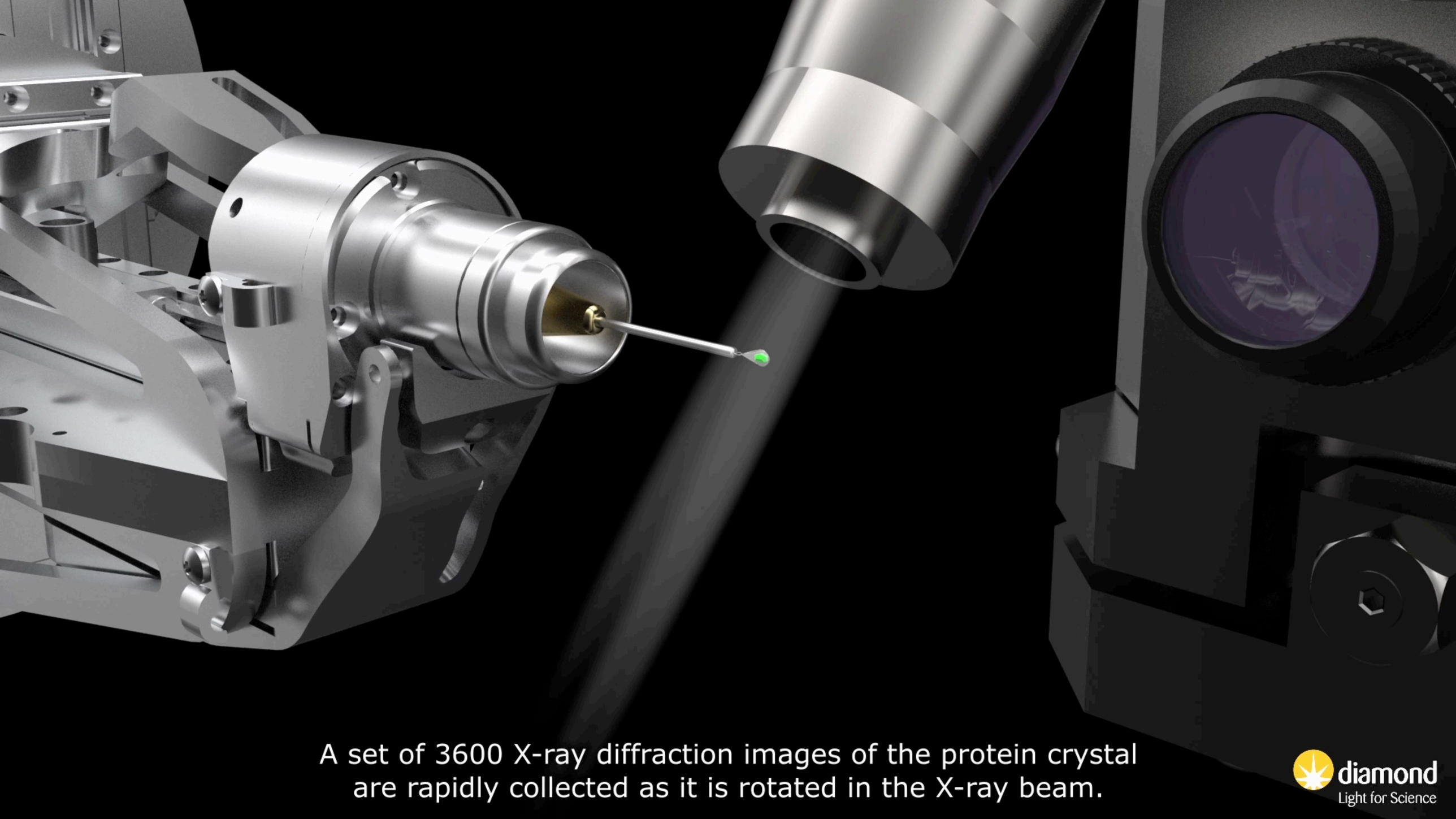
78 fragment-bound structures solved and released to the web

48 covalent fragments
71 active site fragments

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

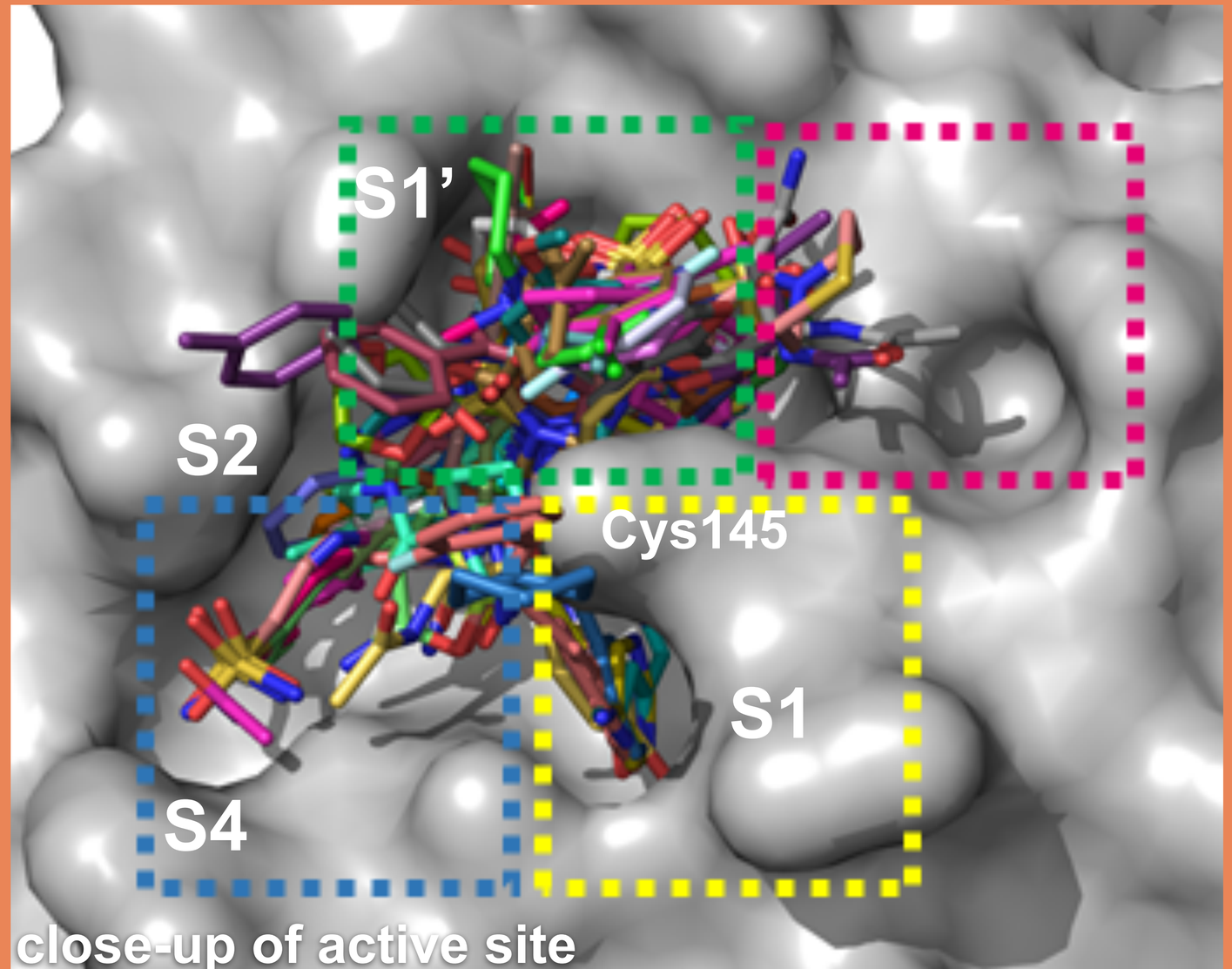


diamond
Light for Science

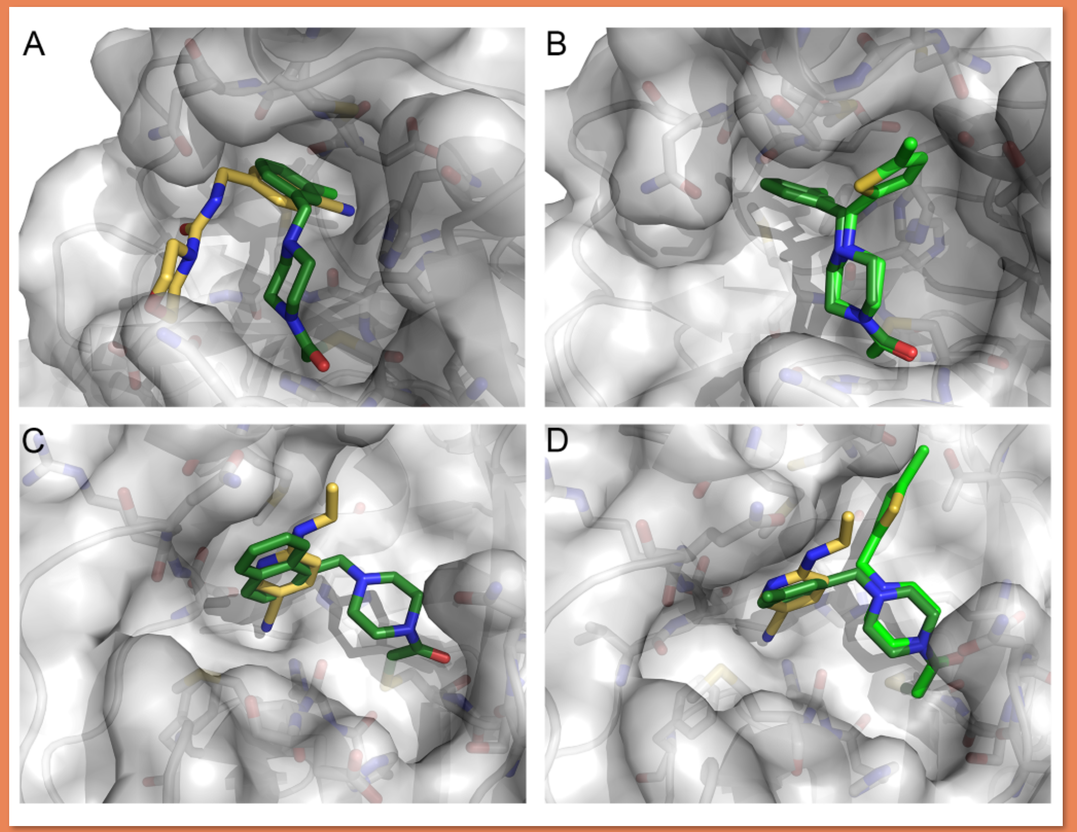

A set of 3600 X-ray diffraction images of the protein crystal
are rapidly collected as it is rotated in the X-ray beam.
diamond
Light for Science

The Diamond fragments completely cover the active site

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



close-up of active site



Could fragment merges reveal a path to potent inhibition?

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

All data was immediately released online (pre-preprinted!)

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.

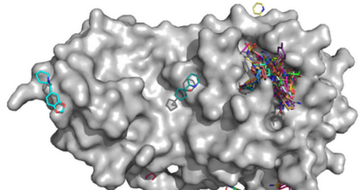
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

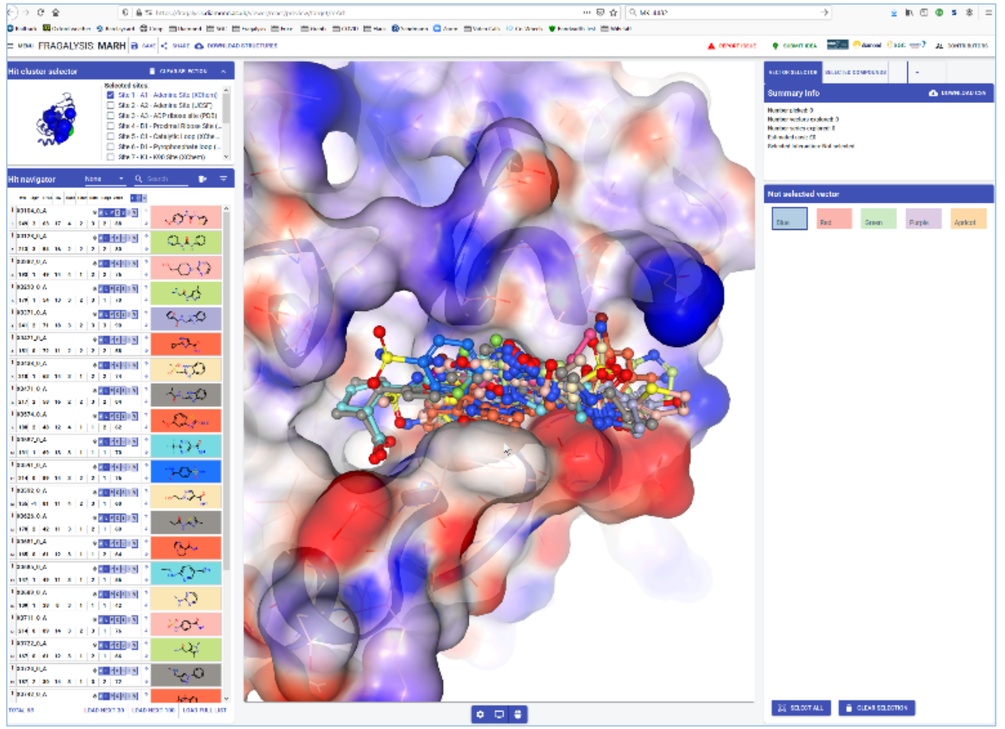
XChem fragment screen

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:

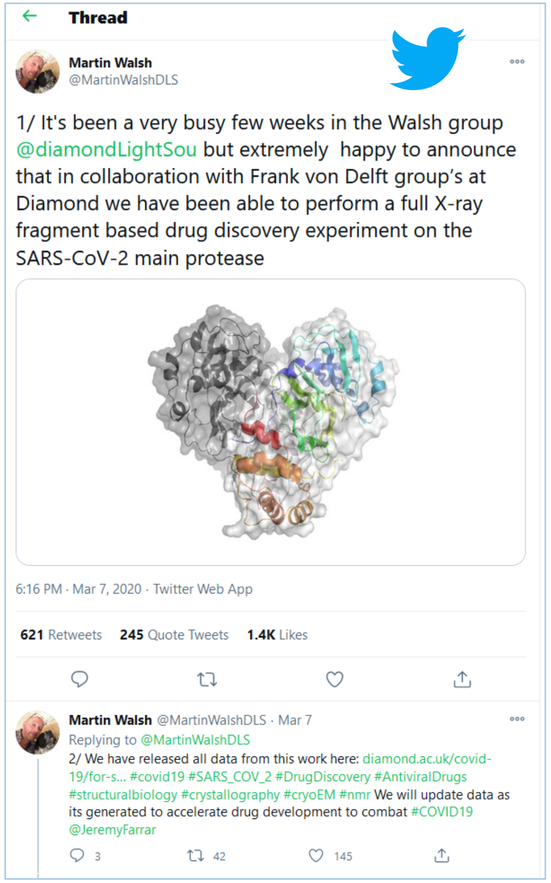
- 23 non-covalent hits in the active site
- 48 covalent hits in the active site
- 3 hits in the dimer interface, one in a calculated hotspot





https://fragalysis.diamond.ac.uk

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



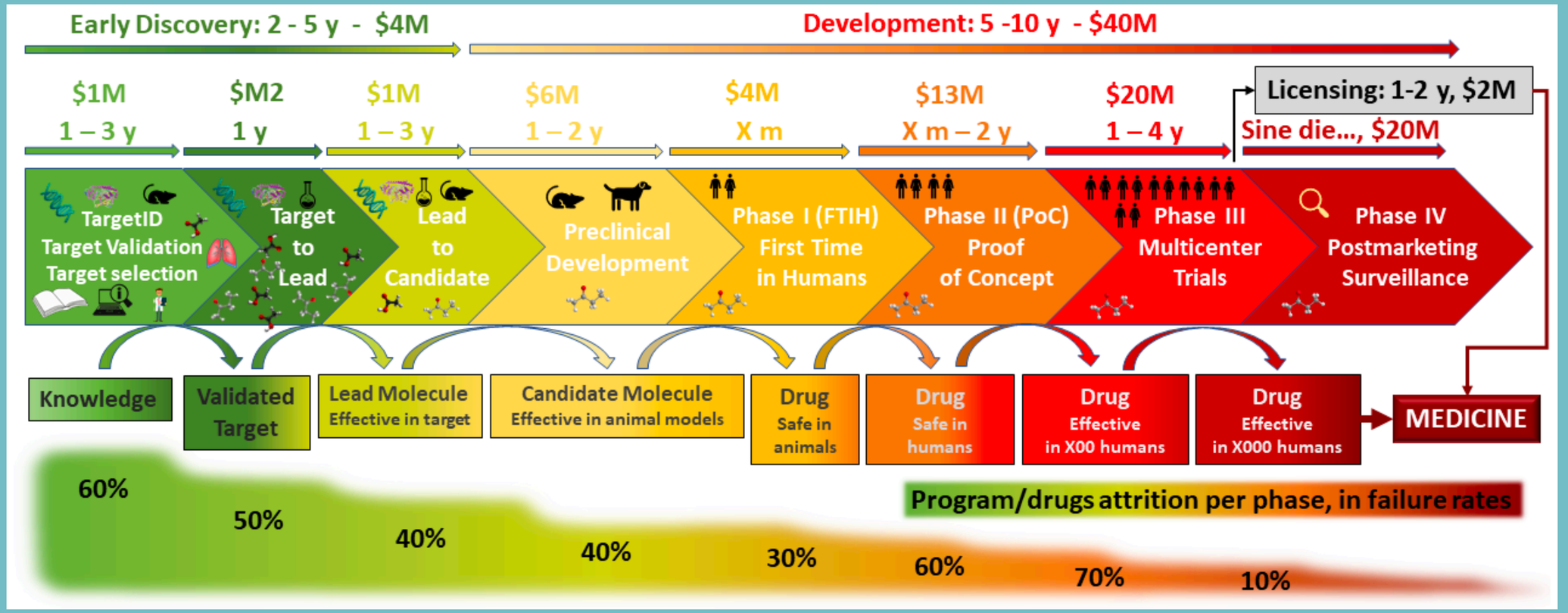
COVID Moonshot

Centre for Medicines Discovery, University of Oxford

XCHEM Diamond Fragment Screening

diamond

Drug discovery is usually a long and expensive process



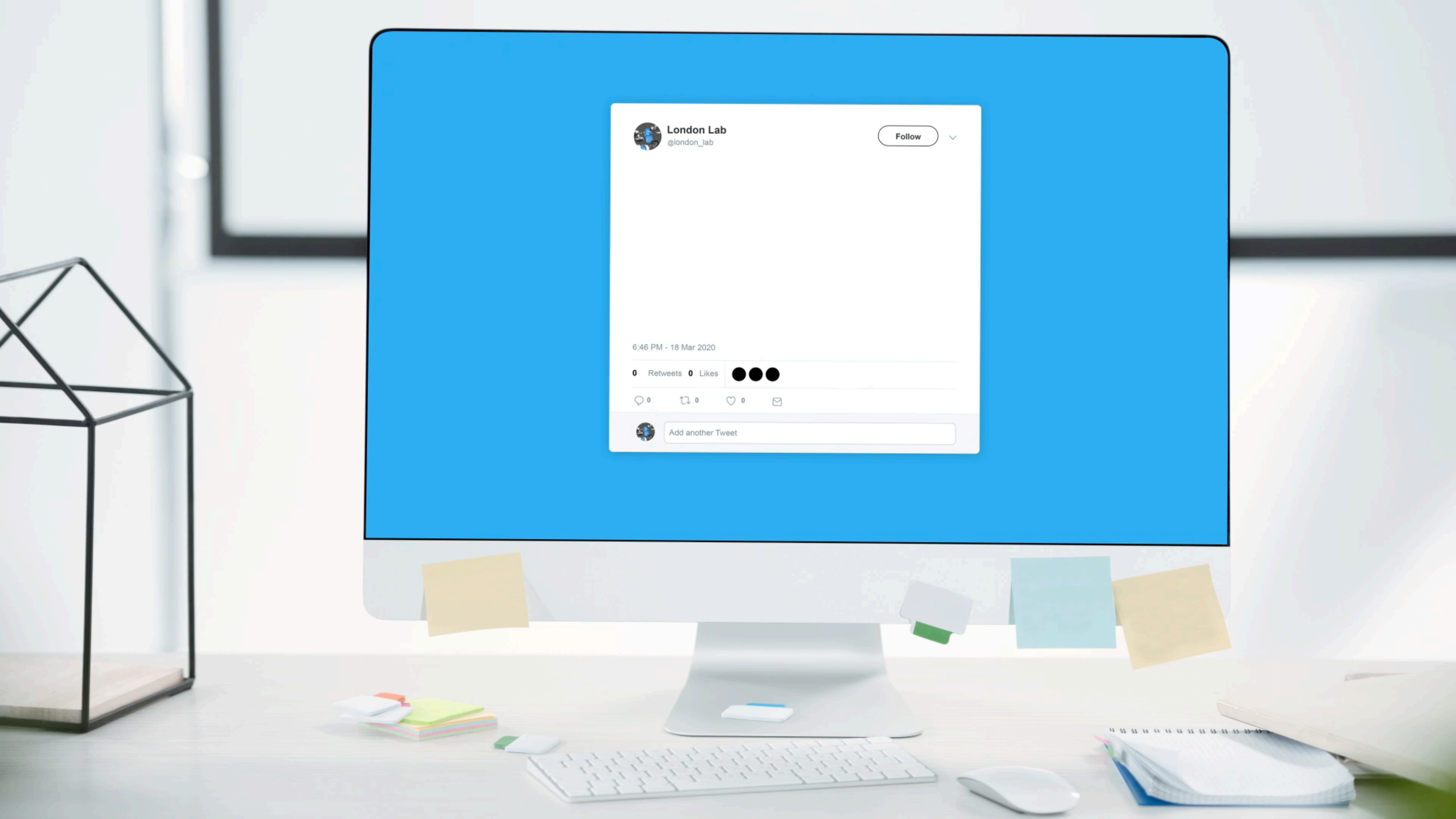
https://doctortarget.com/machine-learning-applied-drug-discovery/

How can we cut down this timeline?

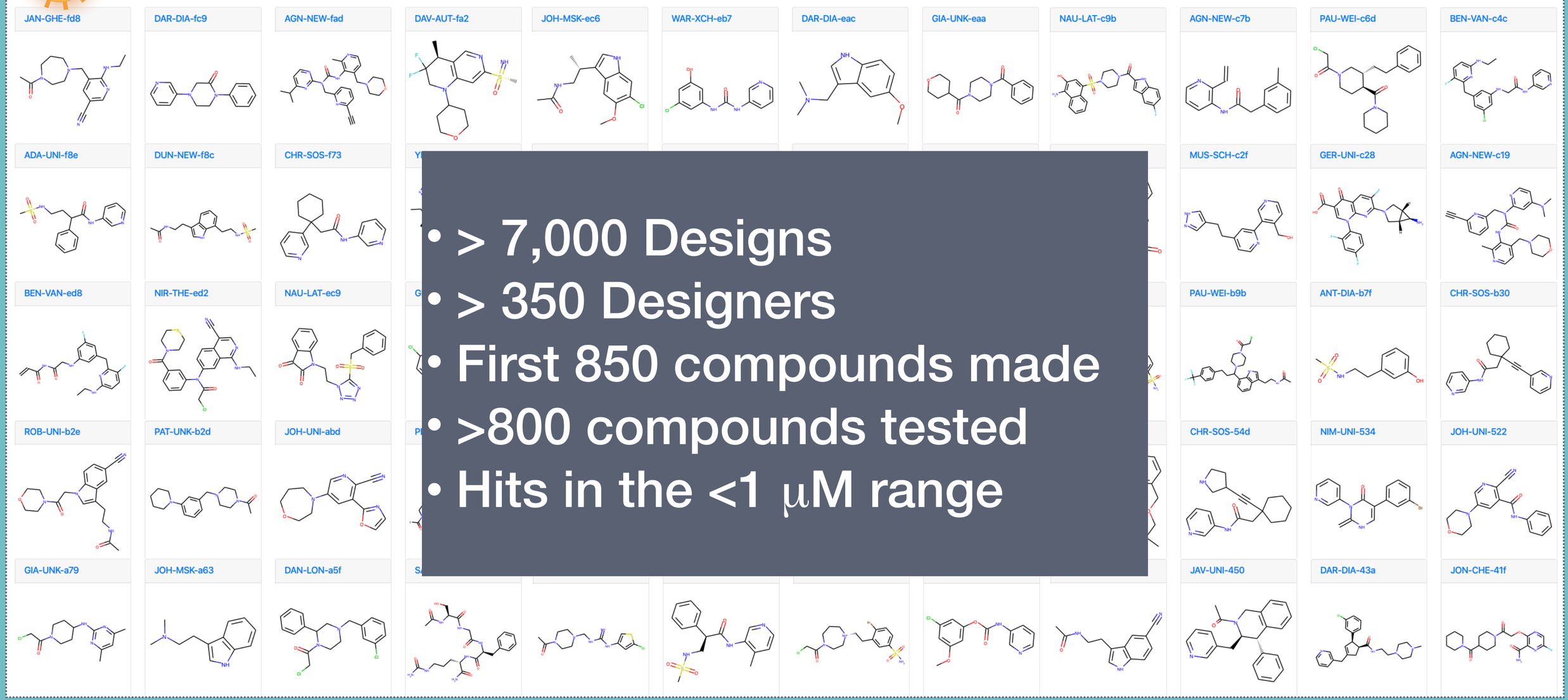
Which strategies would most quickly get us from fragment structures all the way to a useful drug?

Nir London
Weizmann Institute

What if we tried ALL OF THEM?


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

…and there was overwhelming response

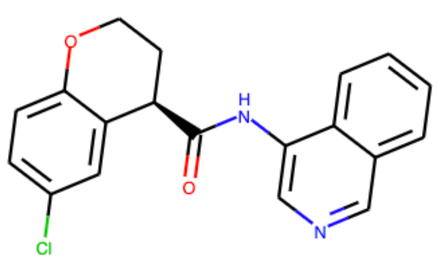


- > 7,000 Designs
- > 350 Designers
- First 850 compounds made
- >800 compounds tested
- Hits in the <1 μM range

PostEra used synthetic route prediction AI to quickly identify with designs could be rapidly synthesized

MOLECULE DETAILS

MAT-POS-b3e365b9-1 View Submission



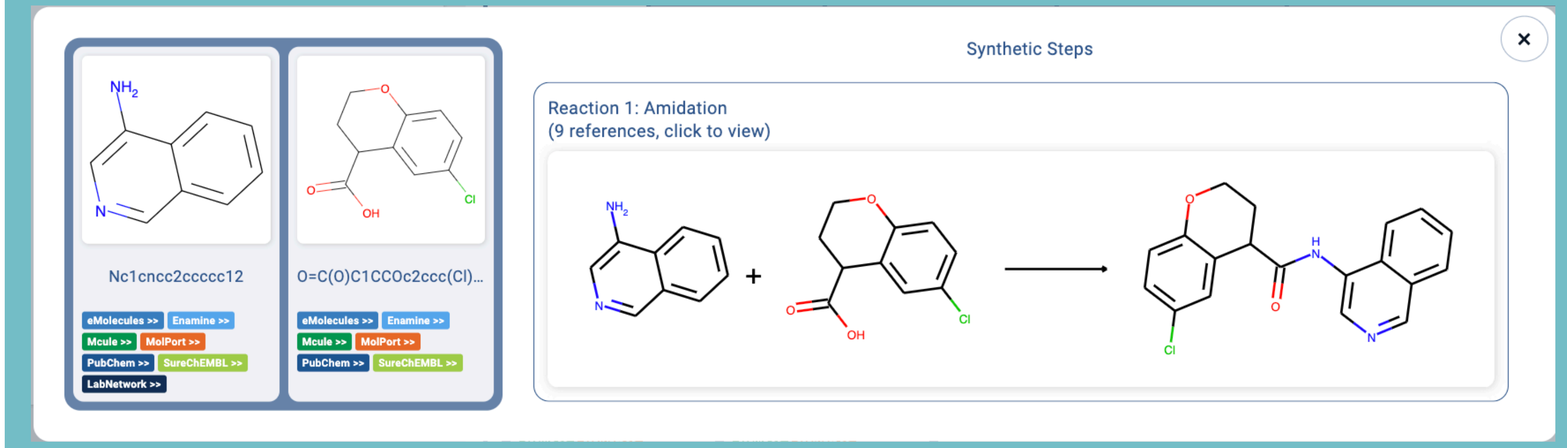
3-aminopyridine-like Assayed

Check Availability on Manifold

View on Fragalysis x11612

Fluorescence RapidFire

CRO catalogue-aware optimal synthetic route



http://postera.ai/manifold

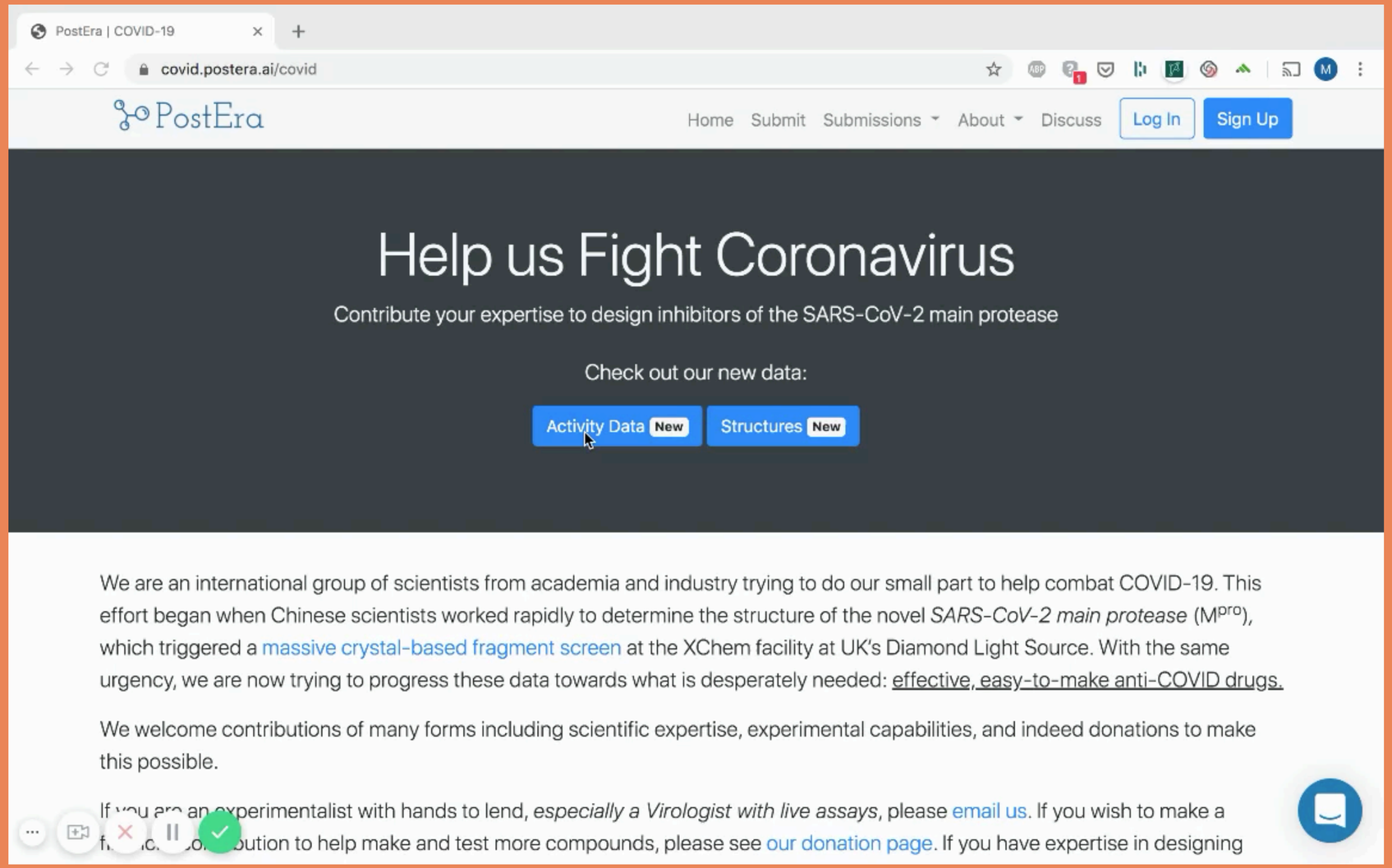
CROs donating effort

- Enamine
- WuXi
- Sai

http://postera.ai/covid

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

Data reported back to community



http://postera.ai/covid

The COVID Moonshot emerged as an global open science, patent-free, collaborative drug discovery project

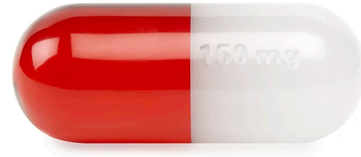
Open science

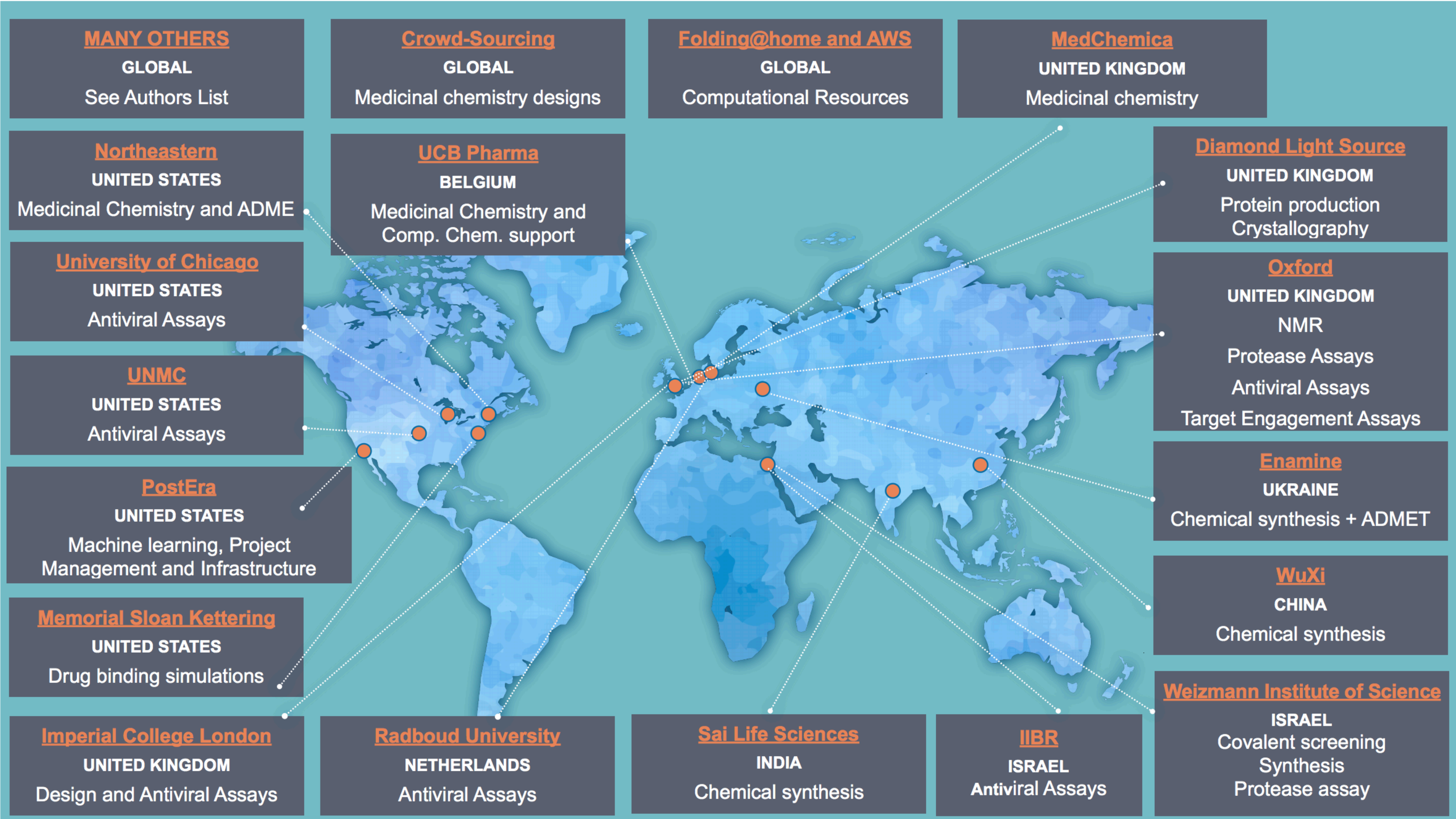
COVID Moonshot

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

Why do we need oral drugs if we have vaccines?

If vaccinating ~100% public (7.7 billion people), need complete safety

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

Oral drugs could be deployed early, unlike IV drugs

Could remain effective against mutations that vaccine may provide incomplete protection against

Oral inhibitor without cold chain storage requirements would be practical and inexpensive enough to deploy globally

Oral inhibitor could provide prophylaxis following exposure or treat acute illness at onset of symptoms, rather than require IV administration

Defined a target product profile (TPP) for oral Mpro inhibitor for use in early disease or prophylactic use following exposure

Ed Griffen
Medchemica

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

Assay cascade aims to help us reach target product profile goals as rapidly as possible

Ed Griffen
Medchemica

design team

Oxford/Diamond

Weizmann

AZ (via NEU)

CRL (via NEU)

CRO (via PostEra)

Compound design

Synthesis

Tier 1

- M^{pro} Fluorescence IC_{50}
- M^{pro} RapidFire IC_{50}
- X-ray Crystallography
- In cell target engagement EC_{50}
- In vitro ADME – thermodynamic solubility, logD, intrinsic clearance, and plasma protein binding

Criteria A

Tier 2

- Plaque Reduction EC_{50}
- Viral Replication EC_{50}
- Calu-3 CC_{50}
- Further *in vitro* profiling – Caco-2, MDCK-MDR1, mouse liver microsomal stability, CYP inhibition and induction

Criteria B

Tier 3

- PK and tolerability study
- Hamster *in vivo* efficacy model

Preclinical Candidates for Advancement

Does it inhibit Mpro? How does it bind?

Does it enter cells and inhibit Mpro?

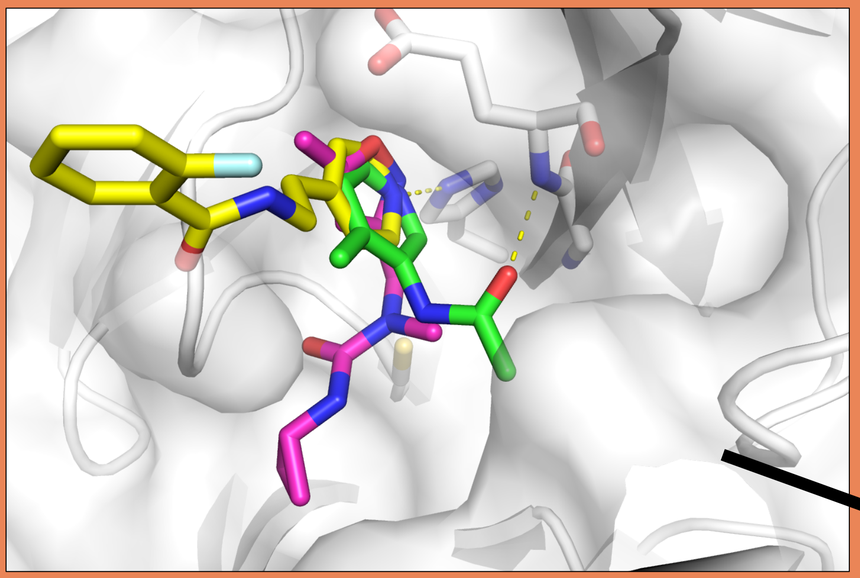
Does it have a chance of working in humans?

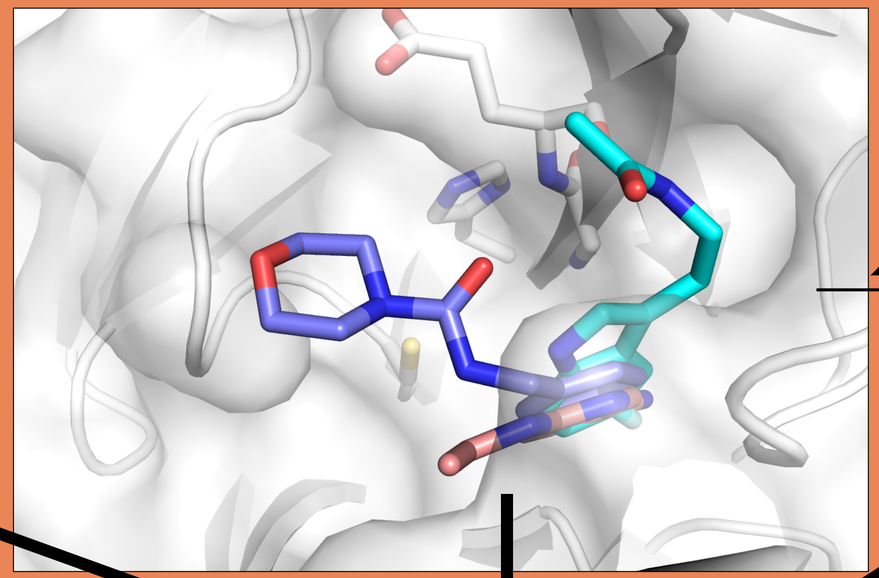
Does it kill virus in infected cells, sparing healthy cells?

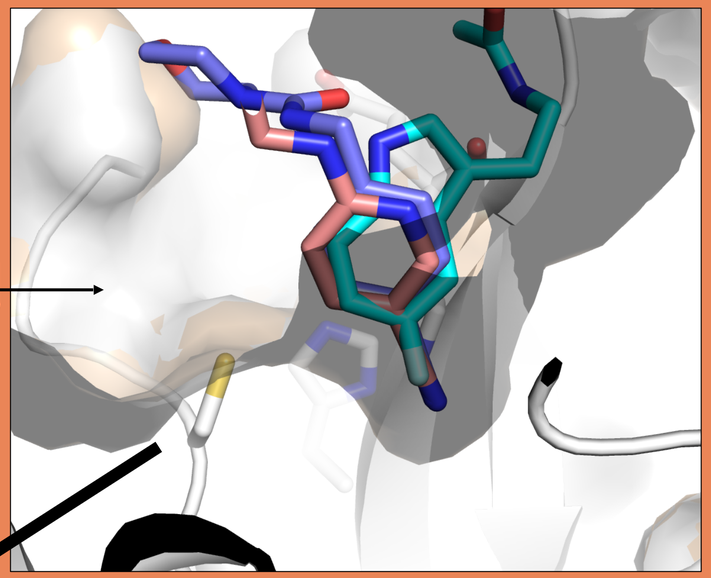
Does it have a favorable safety profile?

Is it orally bioavailable at required concentrations?

Crowdsourcing generated a number of novel chemical series by fragment merging





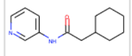


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

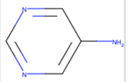
Design Rationale:

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

Inspired By:



ALE-HEI-f28a35b5-9



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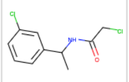

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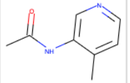

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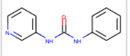

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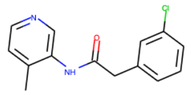


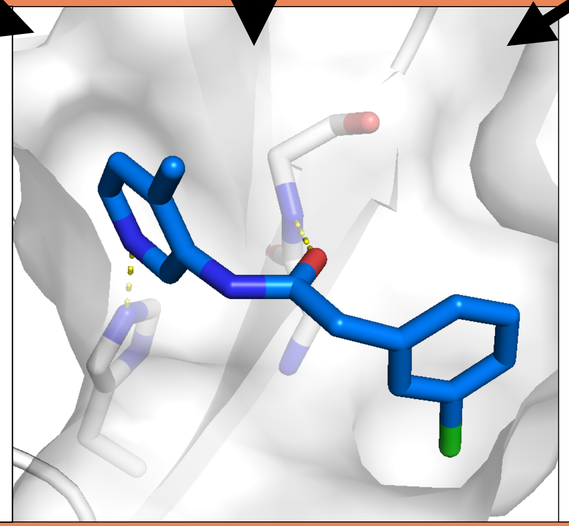
TRY-UNI-714a760b-6

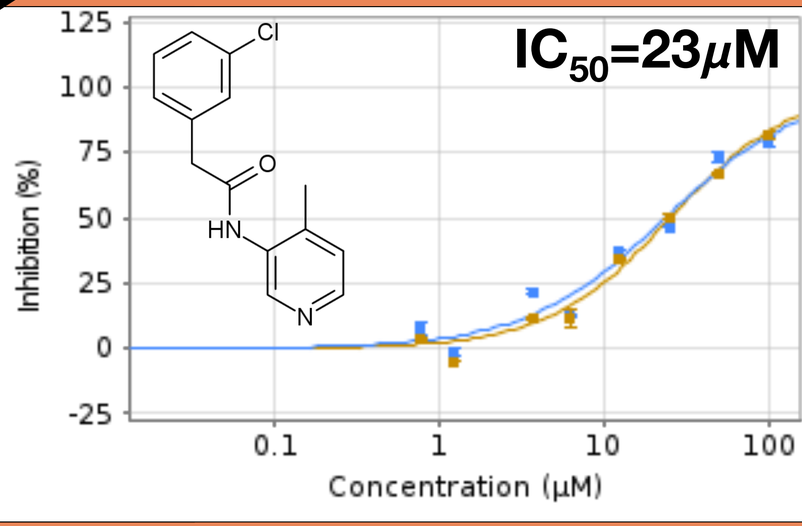
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

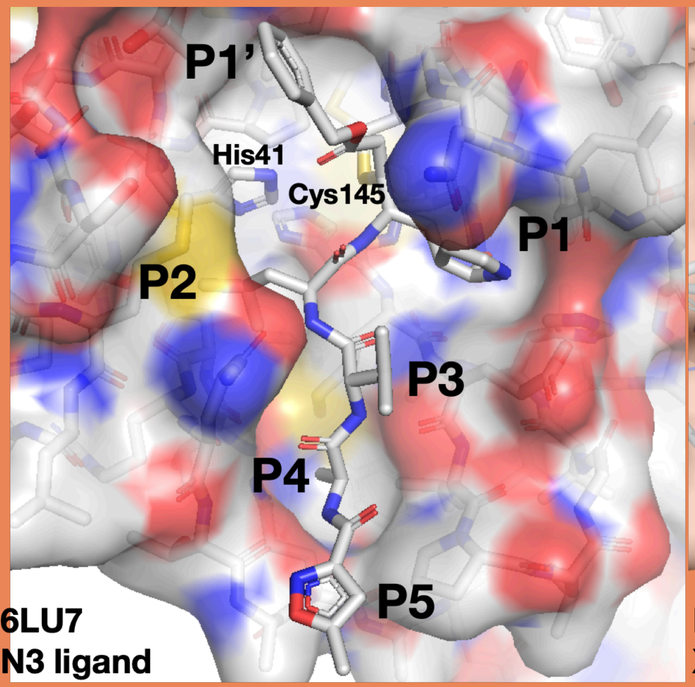
Enamine Mcule MolPort Assayed

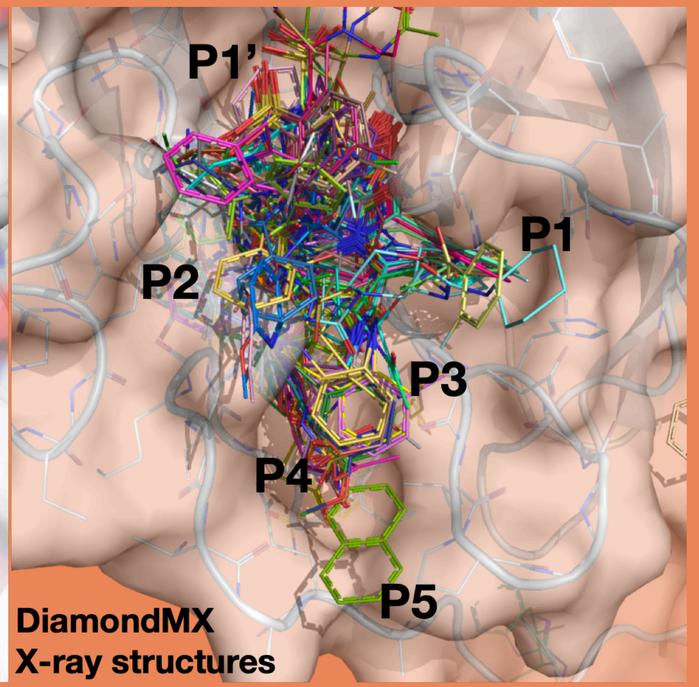
View

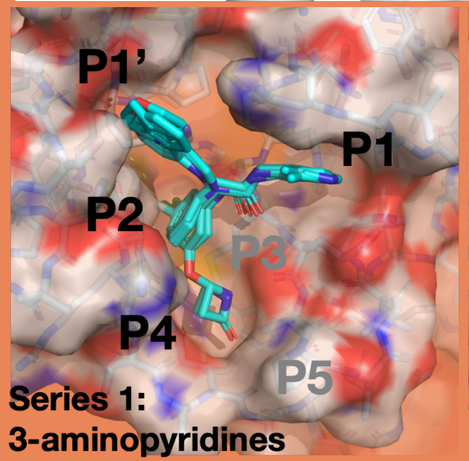


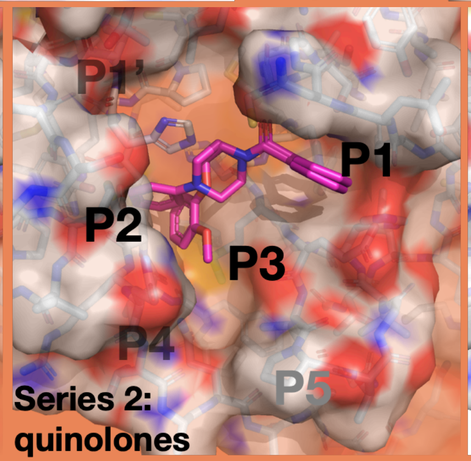


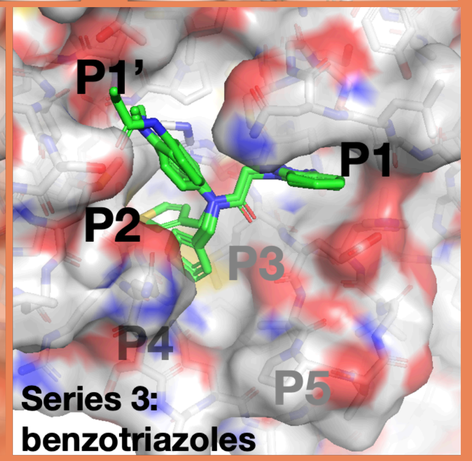
Crowdsourcing generated too many potent leads to follow up on, so we focused on three noncovalent series











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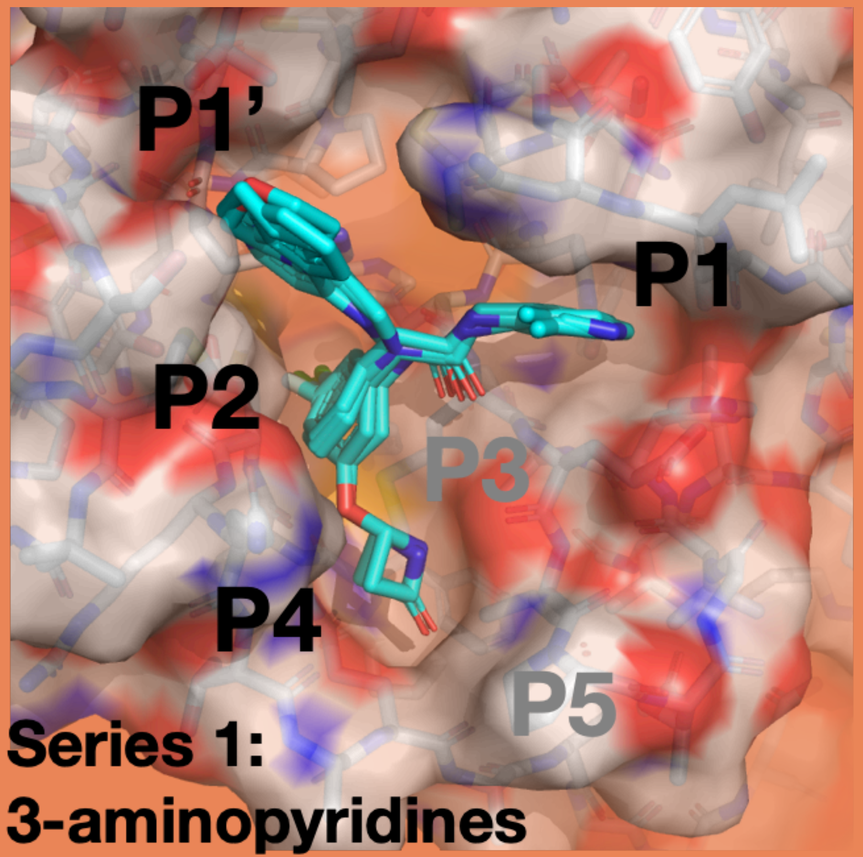
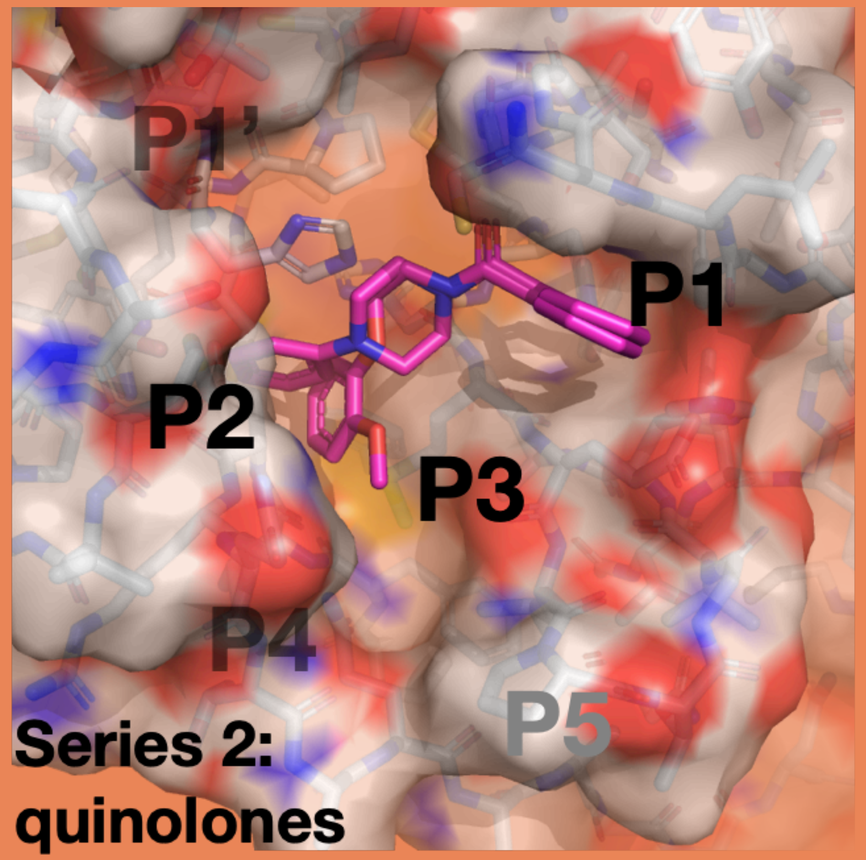
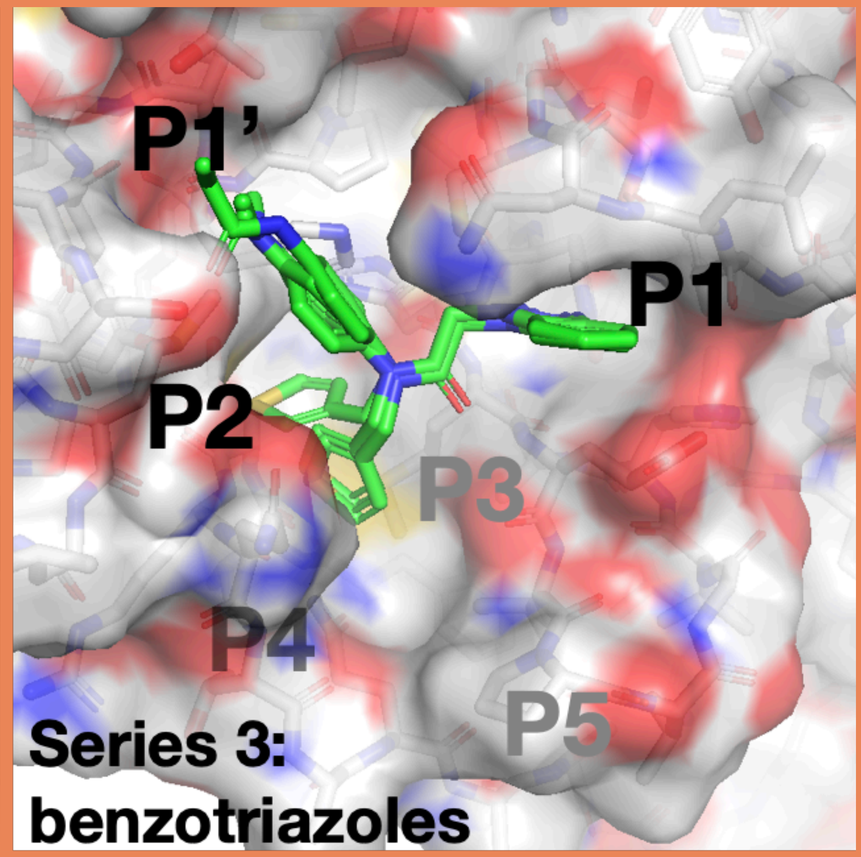
Crowdsourcing generated too many potent leads to follow up on, so we focused on three noncovalent series



564 compounds
(primary series)



74 compounds
(backup series)



35 compounds
(backup series)

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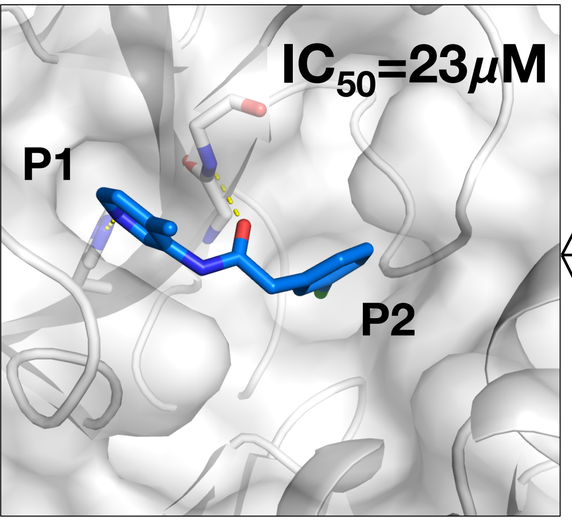
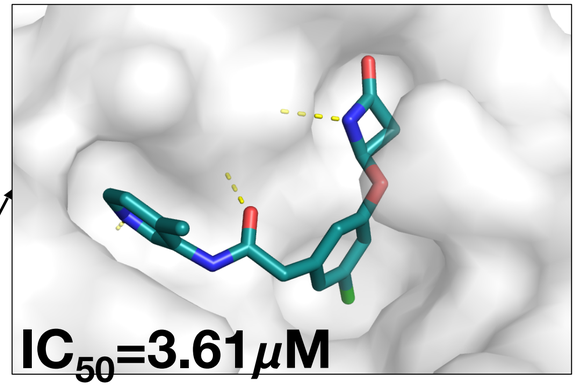
3-aminopyridines provide a potent P1-P2 scaffold capable of accessing P4 and P1’ pockets

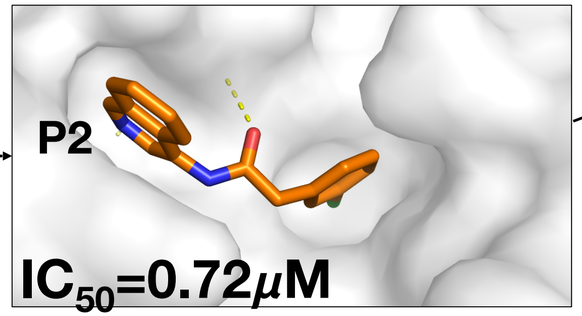
>300 aminopyridine compounds synthesized



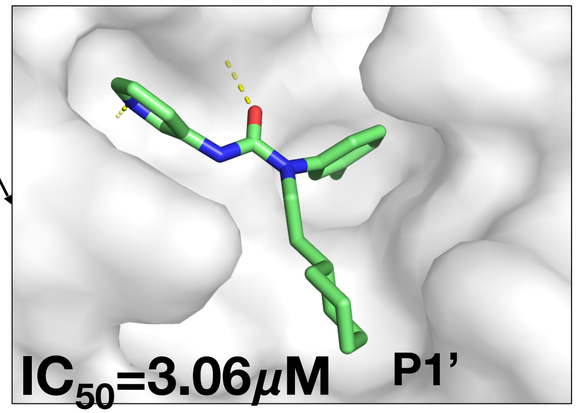
6.4x



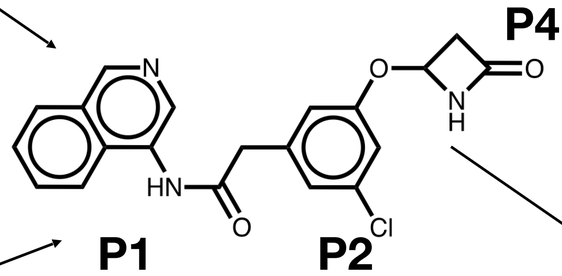
32x

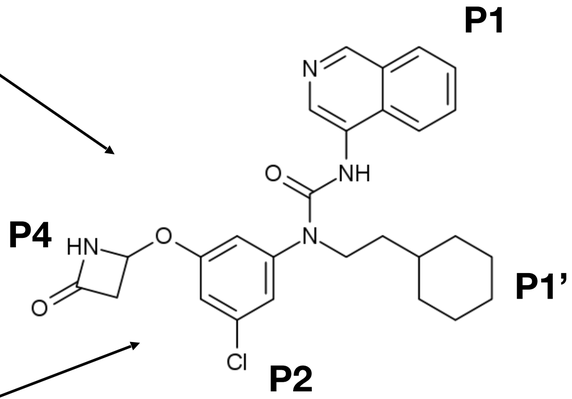


7.5x

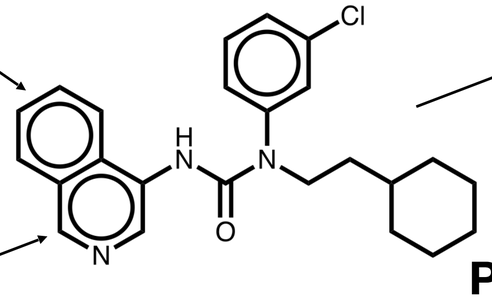


IC_{50}=260 nM





IC_{50}= 105 nM



IC_{50}=270 nM

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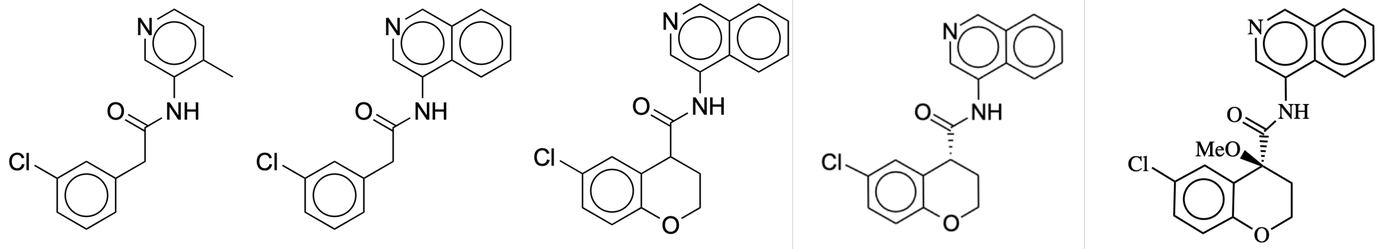
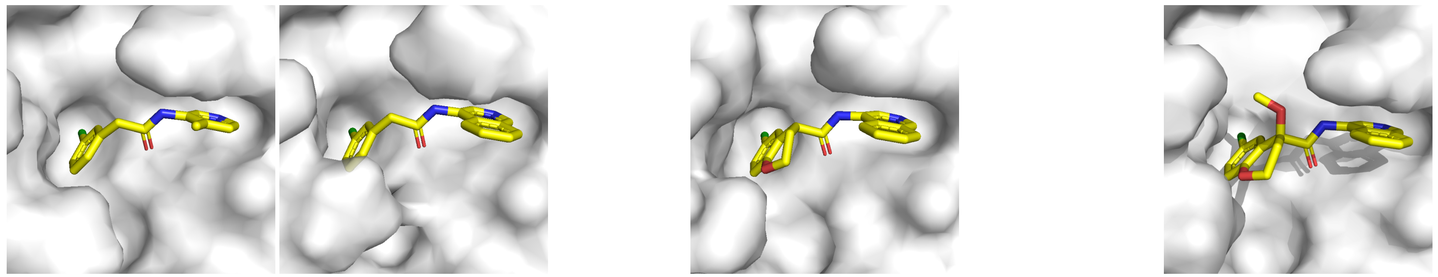
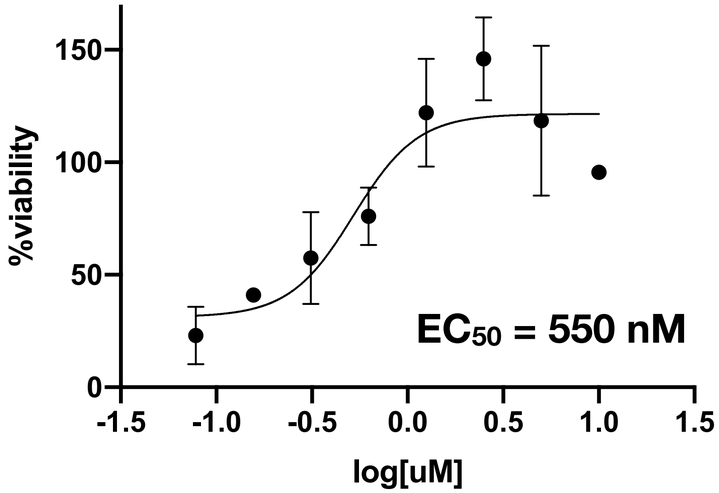
Optimization of the P1-P2 scaffold resulted in incredibly potent compound with ~0.5 µM antiviral activity



TRY-UNI-714a760b-6	ADA-UCB-6c2cb422-1	VLA-UCB-1dbca3b4-15	MAT-POS-b3e365b9-1	PET-UNK-29afea89-2
IC_{50}=24 uM	IC_{50}=720 nM	IC_{50}=360 nM	IC_{50}=140 nM	IC_{50}= 80 nM



Lead compound active against live SARS-CoV-2



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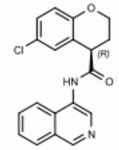
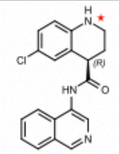
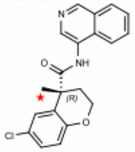
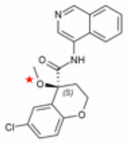
With the Israel Institute of Biological Research

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)*	Antiviral IC50 (μM) *Calu3 FFU (Oxford)*	Cytotox CC50 (μM) *Calu3 (Oxford)*	Protease IC50 (μM) *Fluorescence (Weizmann)*	Protease IC50 (μM) *MassSpec (Oxford)*	Solubility (uM)	HLM $t_{1/2}$ (/min) *Human liver microsms*	HLM CLint (μg/min/mg prot) *Human liver microsms*	permeability Mean Papp (10^{-6}/cms) *MDCK-MDR1 A2B*	CYP inhibition *5 Cyp profile*	Off-target most potent *Eurofins Safety 44*	hERG IC50 (mM)	Protease most potent hit *Nanosyn panel 40 proteases*	Rat Heps $t_{1/2}$ (/min) *Rat hepatocytes*	Rat Heps Clint *Rat hepatocytes*	Species in vivo	Oral $t_{1/2}$ (/min)	IV $t_{1/2}$ (/min)	Oral cpd conc. (4h)	Bio-avail.	Free drug (%)	Calc.dose 70kg hum (mg)
					<0.2			*<0.05*	*<0.05*	*>10uM (ideal >5mg/ml)*		*=<10*	*>=3*			*>= 30*			*=< 10*				*>= 10%*	*>1%*	*=< 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	< 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)		in progress	**clean**			11.8	117	Mouse	in progress					
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	in progress					

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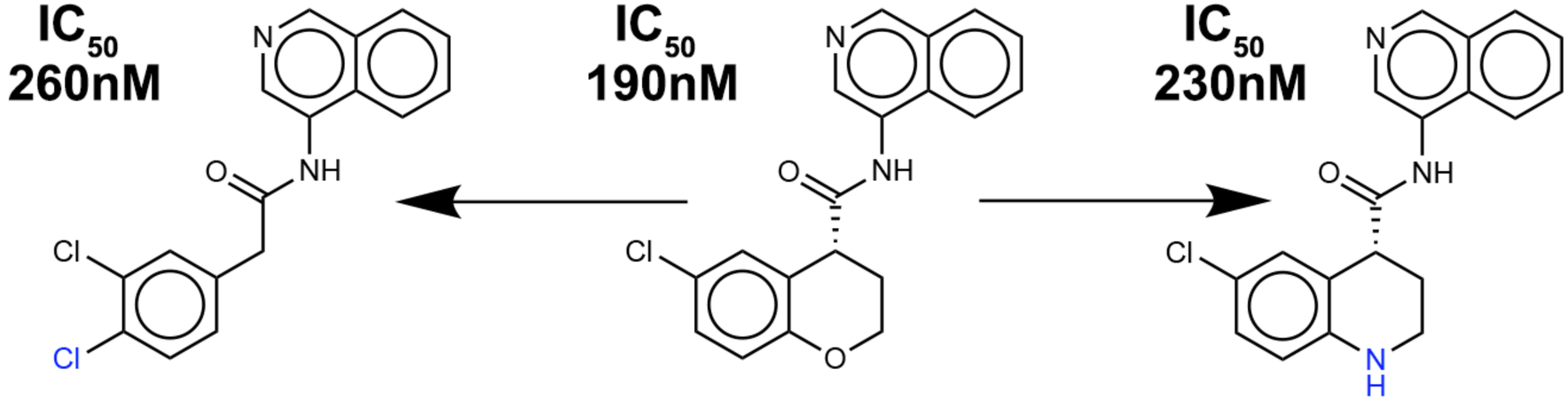
Good SAR during lead optimization points the way toward meeting our goals for selecting a clinical candidate

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 ($t_{1/2}$)

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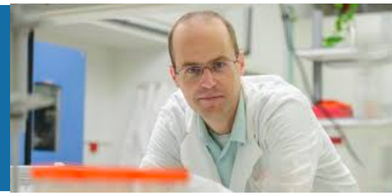
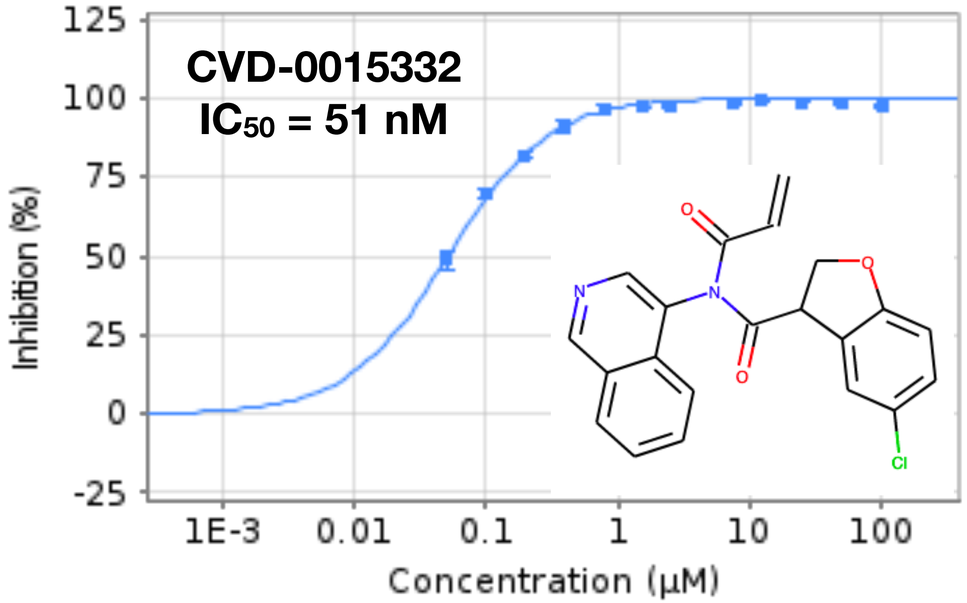
Scaffold is well-poised for covalentization

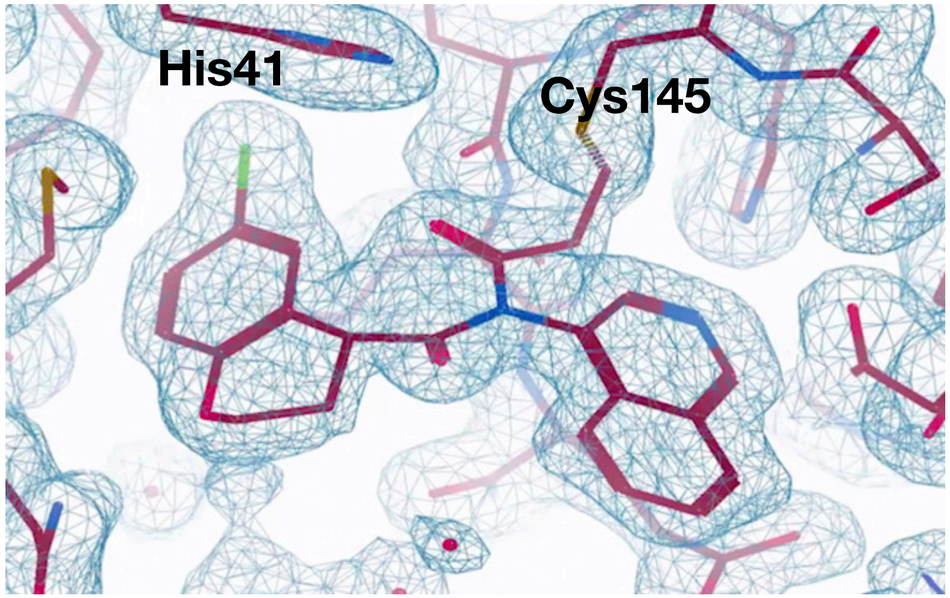


Nir London
Weizmann Institute

MAT-POS-e69ad64a-2



Matt Robinson, PostEra



Diamond Light Source / XChem
Daeron Fearon

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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

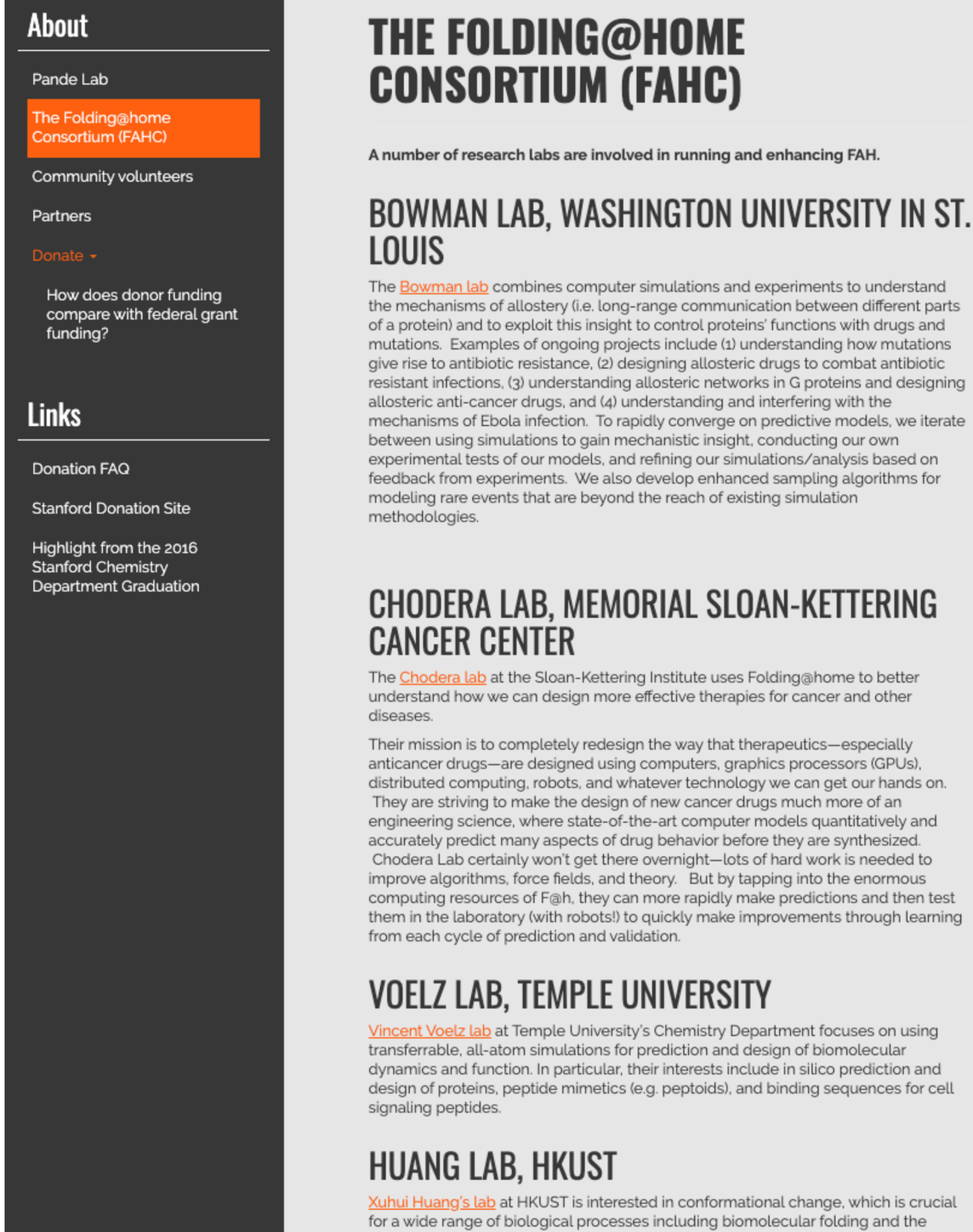
1924085 people have non-anonymously contributed to Folding@home.

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

~100 pflop/s!

WE 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

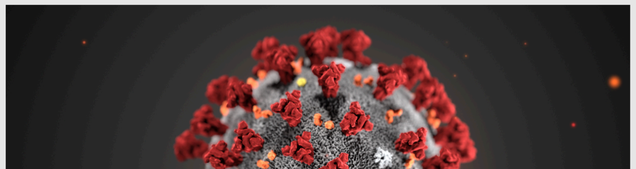
February 27, 2020
by Greg Bowman

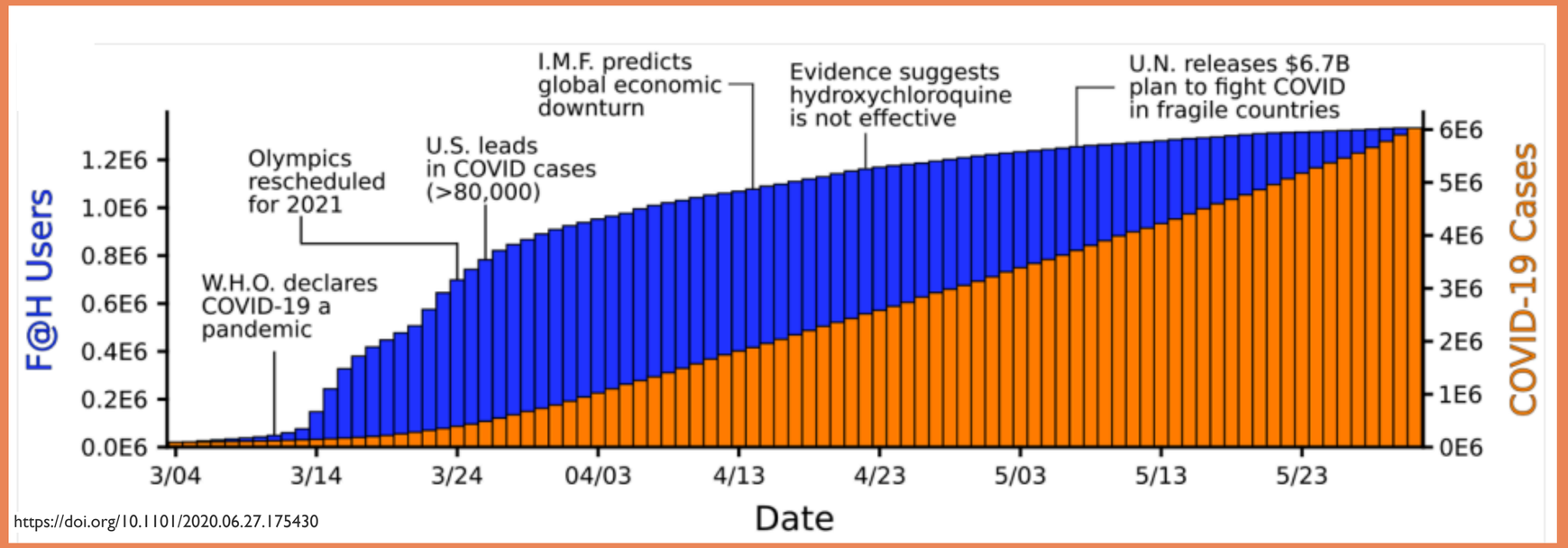
We need your help! Folding@home is joining researchers around the world working to better understand the 2019 Coronavirus (2019-nCoV) to accelerate the open science effort to develop new life-saving therapies. By downloading Folding@Home, you can donate your unused computational resources to the Folding@home 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.





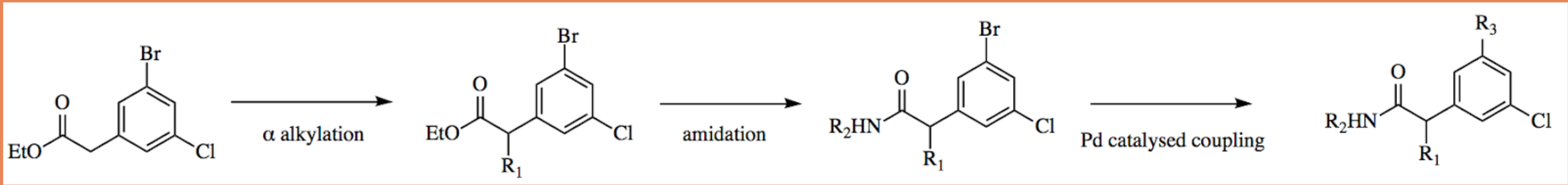
https://doi.org/10.1101/2020.06.27.175430

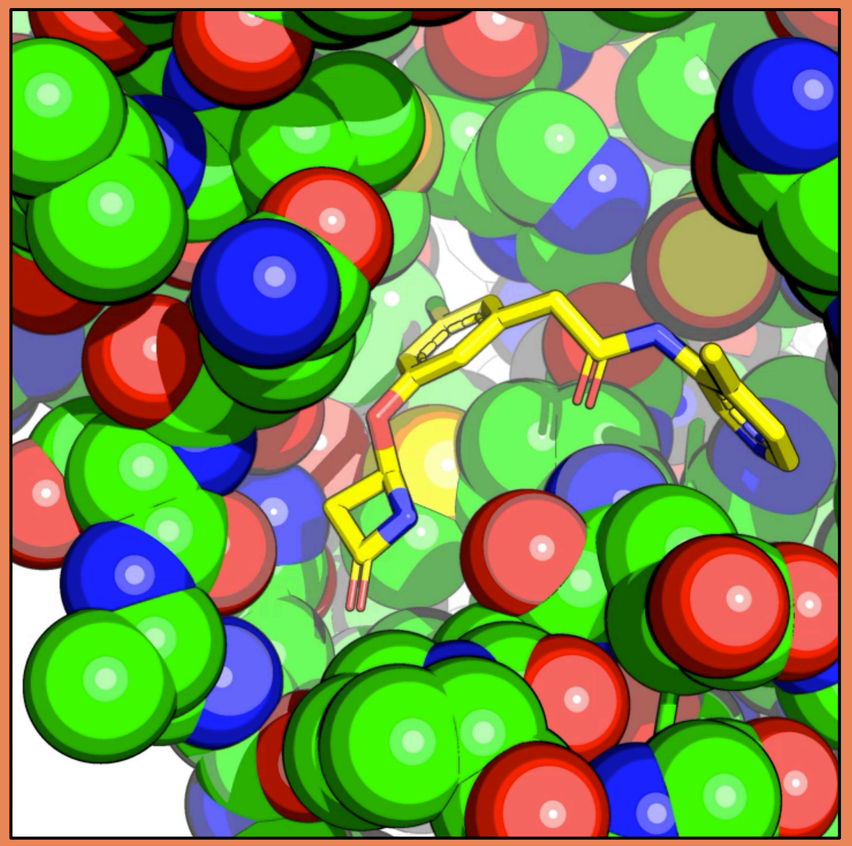
Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

Ivy Zhang (CBM)

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

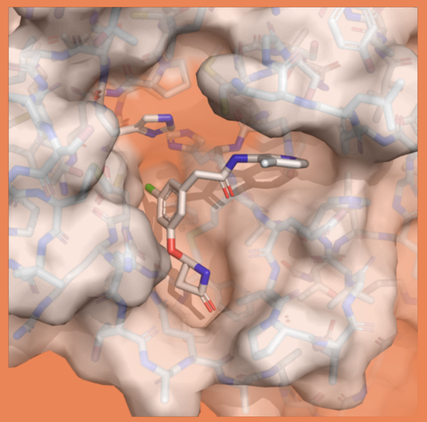




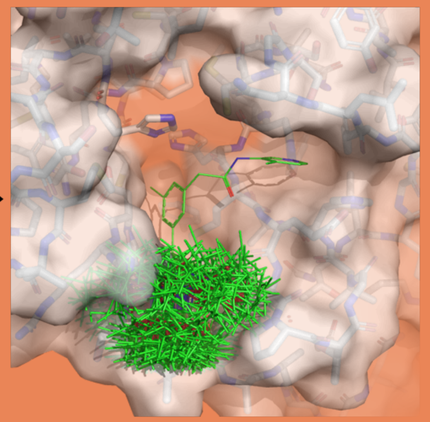
Folding@home can run relative alchemical free energy calculations at planetary scale, performing tens of thousands of transformations/week

Dominic Rufa
Tri-I TPCB PhD student

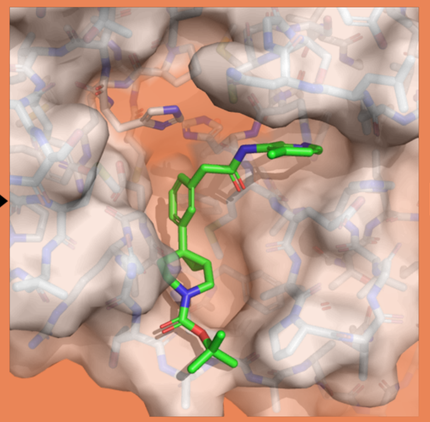
X-ray structure as reference



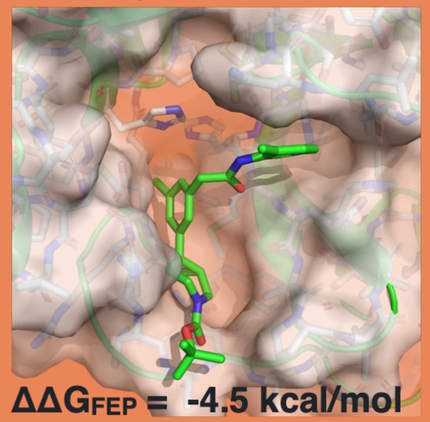
constrained enumeration of poses for proposed molecule



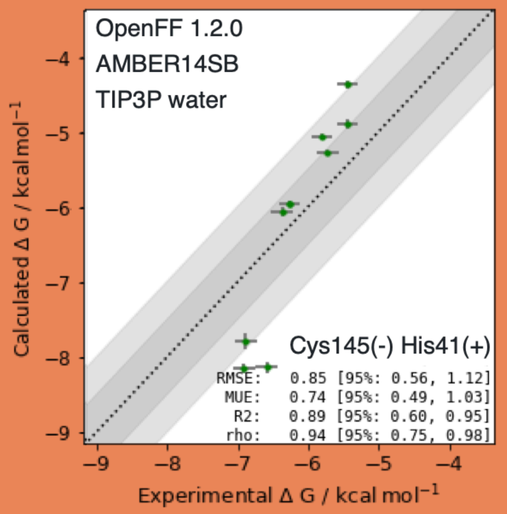
selection of pose with best docking score



nonequilibrium alchemical free energy calculation final posed structure



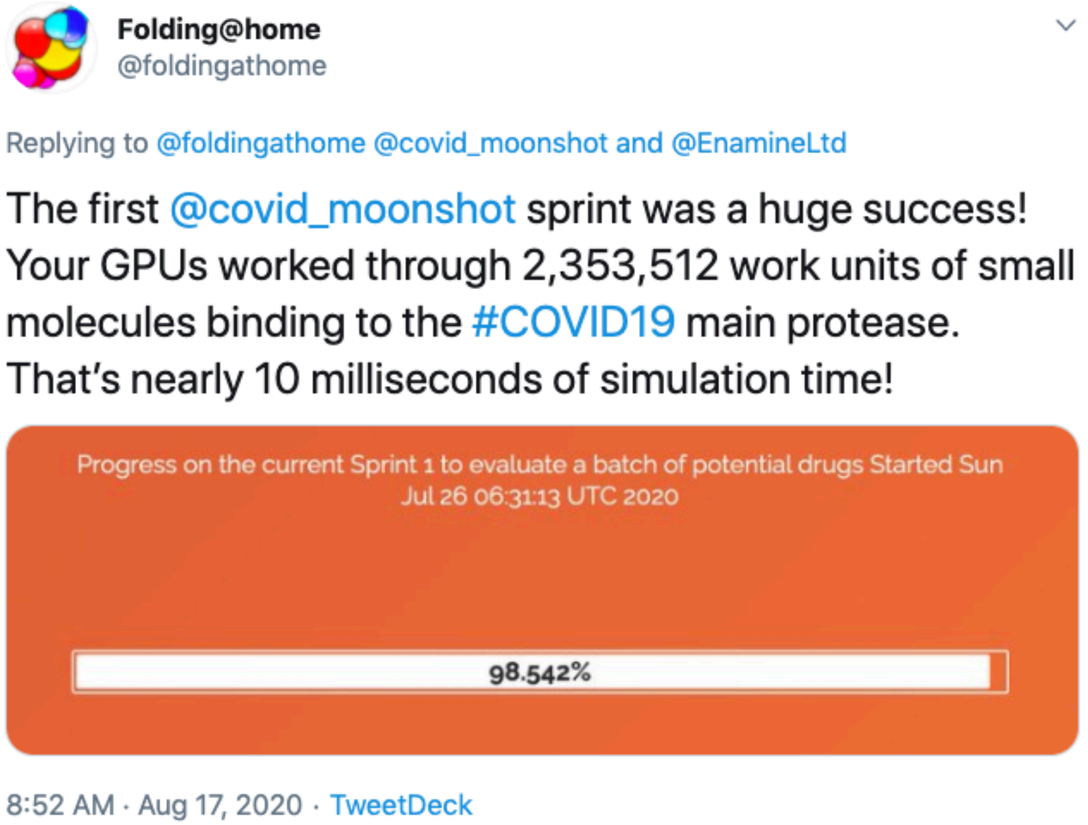
retrospective performance on 3-aminopyridine lead series



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

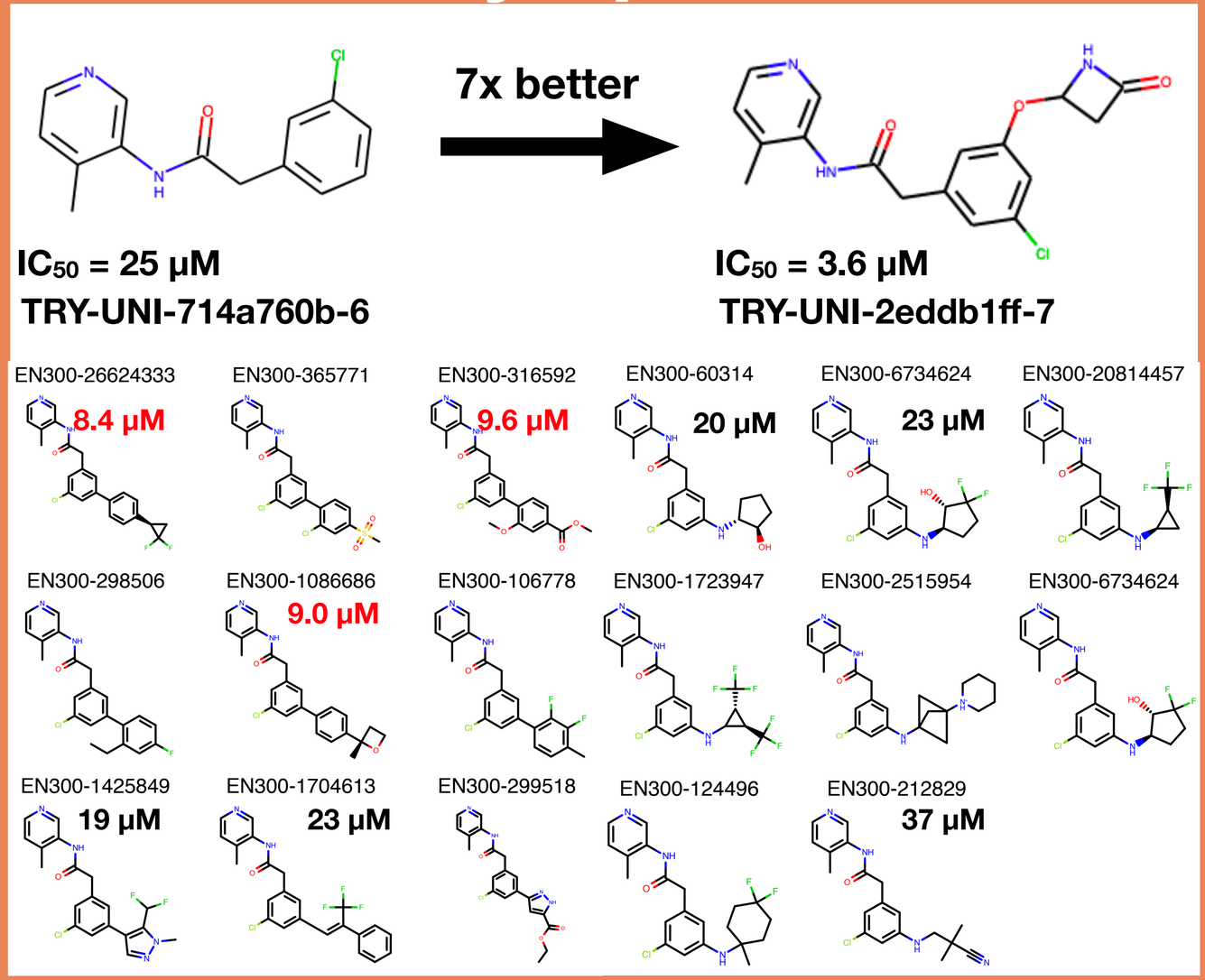
The Folding@home COVID Moonshot sprints represent an incredible amount of computational effort in service of a great cause

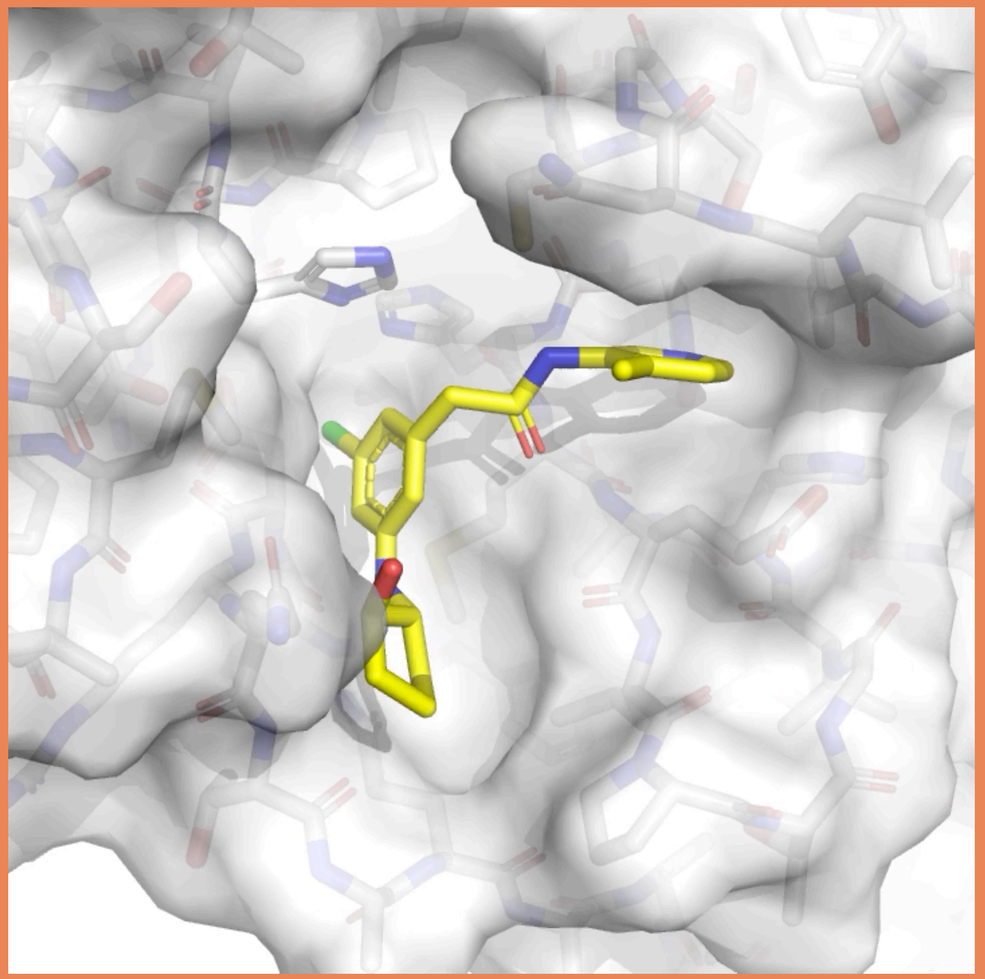


Our Folding@home free energy calculations aim to identify optimal P1’ and P4 substituents

Hannah Bruce Macdonald

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

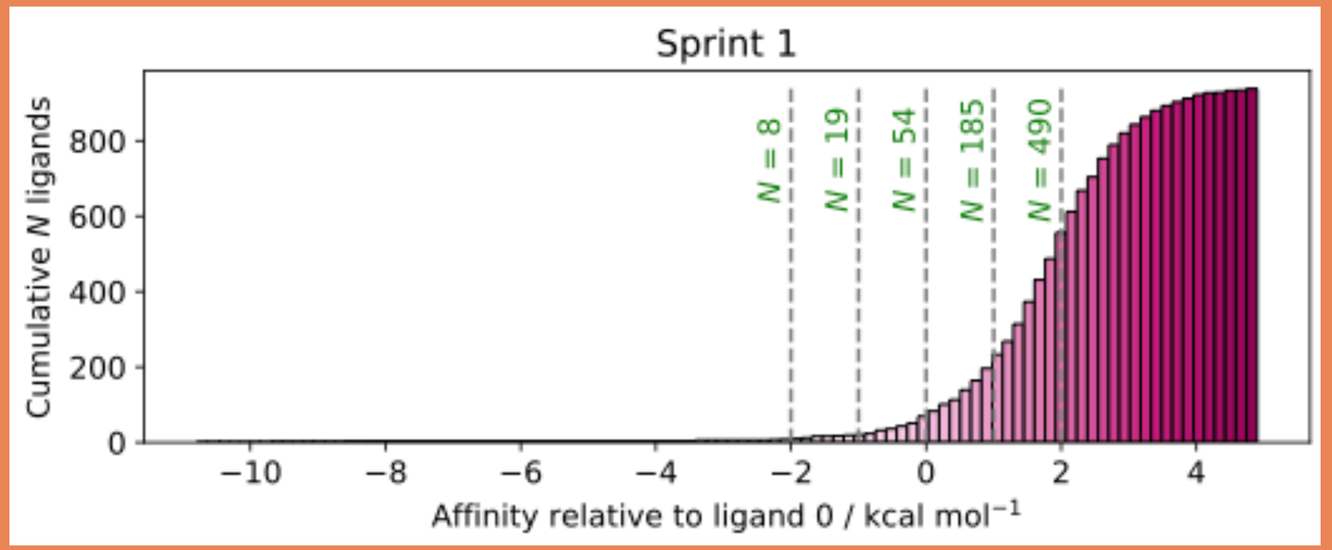




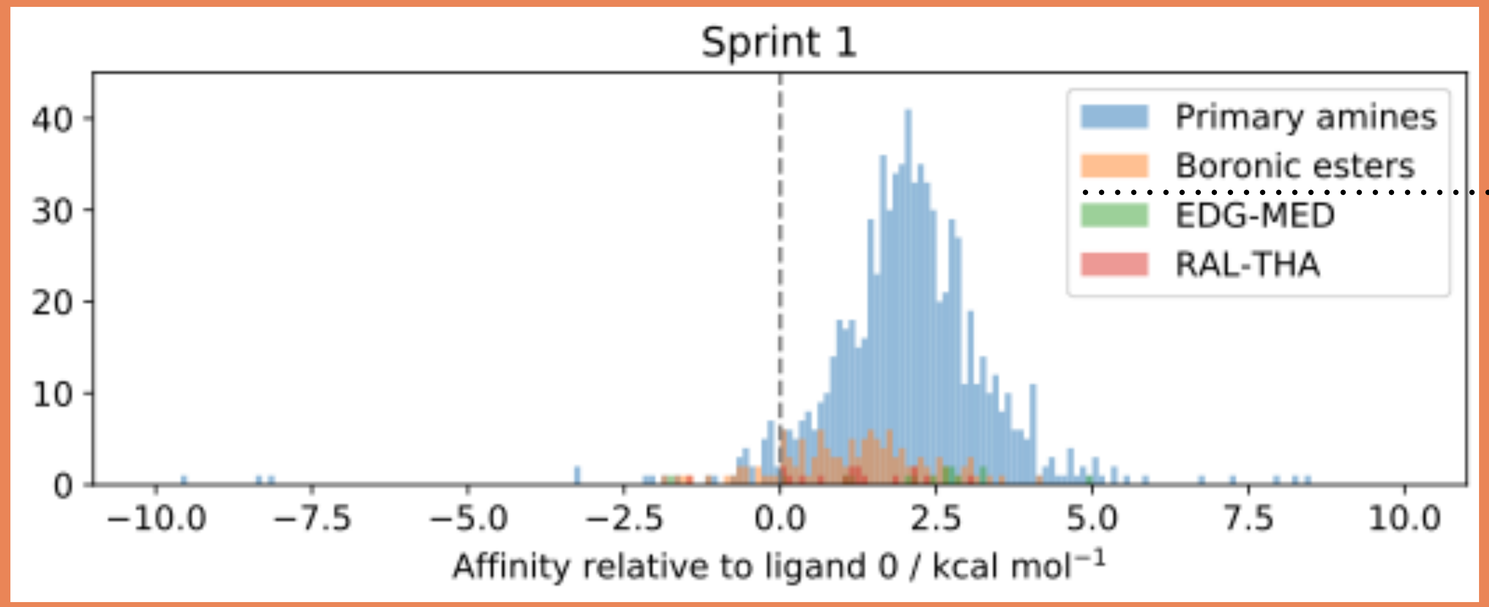
DATA: https://covid.postera.ai/covid/submissions/f42f3716-f86f-41d8-9906-c4fb7b6f5773

Most ideas were bad ideas

better **worse**



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

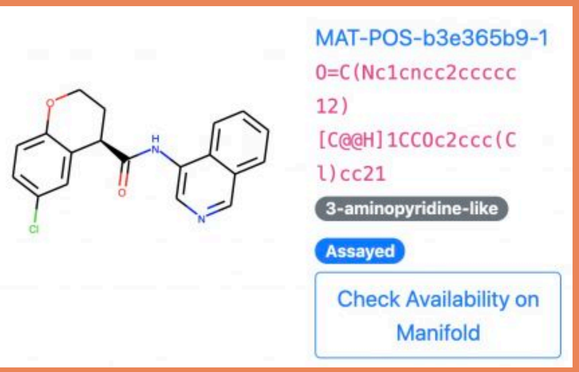


computer

humans

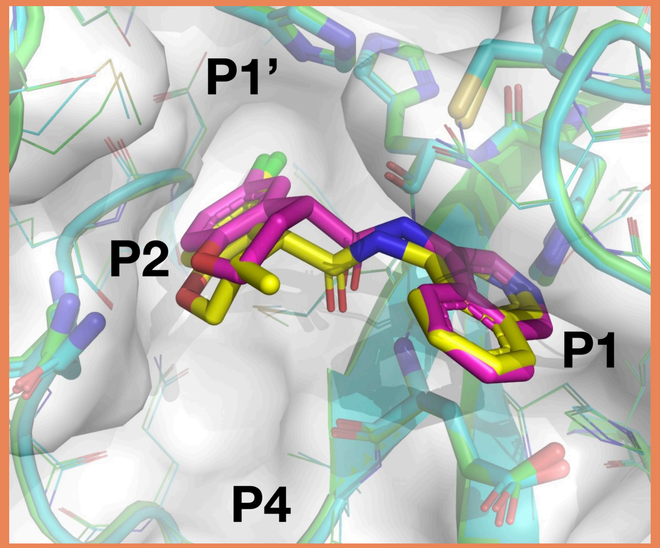
Sprint 5 builds on our current primary scaffold to explore the P1’ pocket to gain potency

benzopyran-isoquinoline series

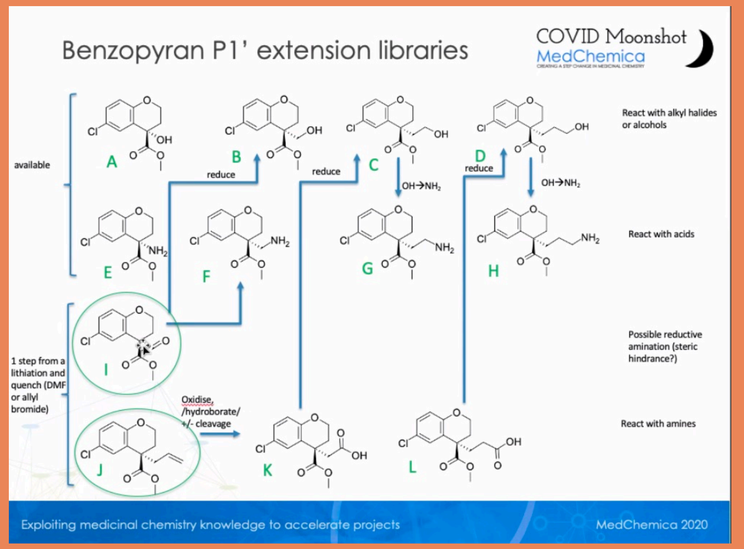


(evolved from 3-aminopyridine series from Sprints 1 + 2)

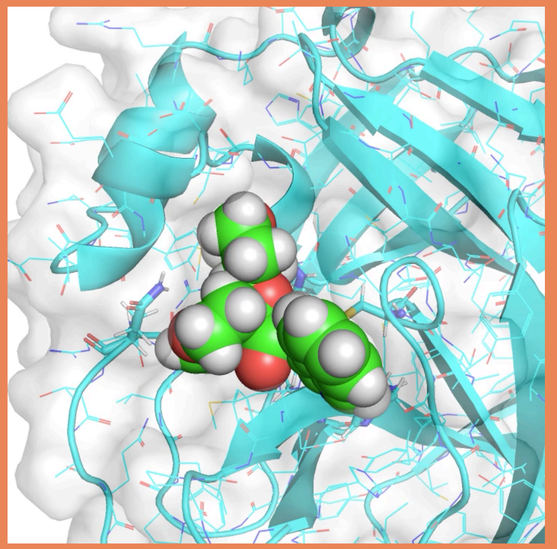
X-ray structures fof this series from Diamond



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

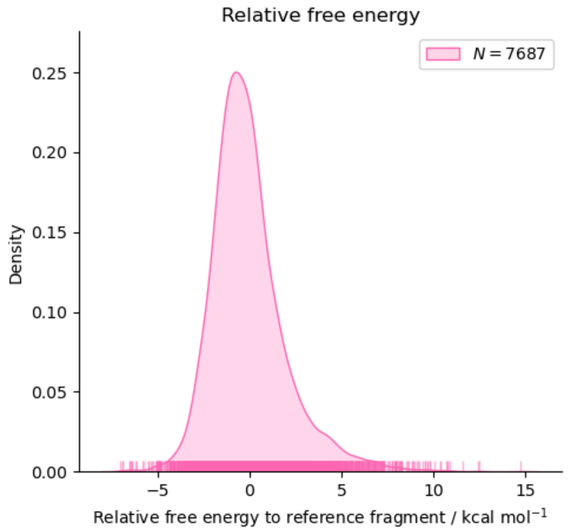
Description

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



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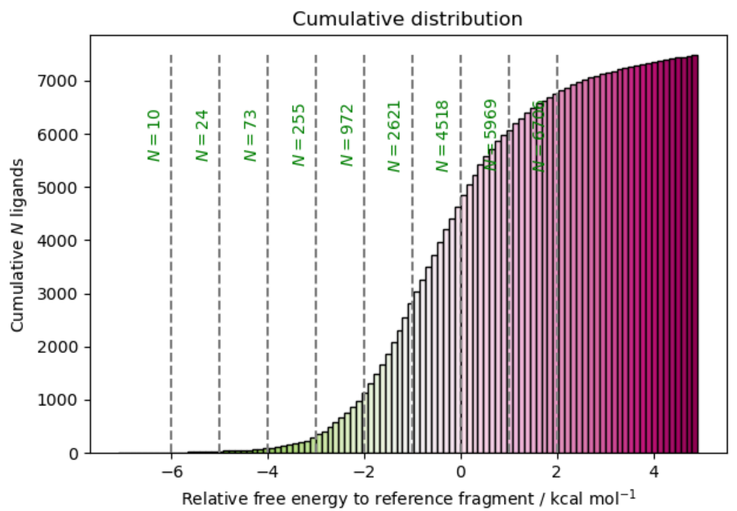
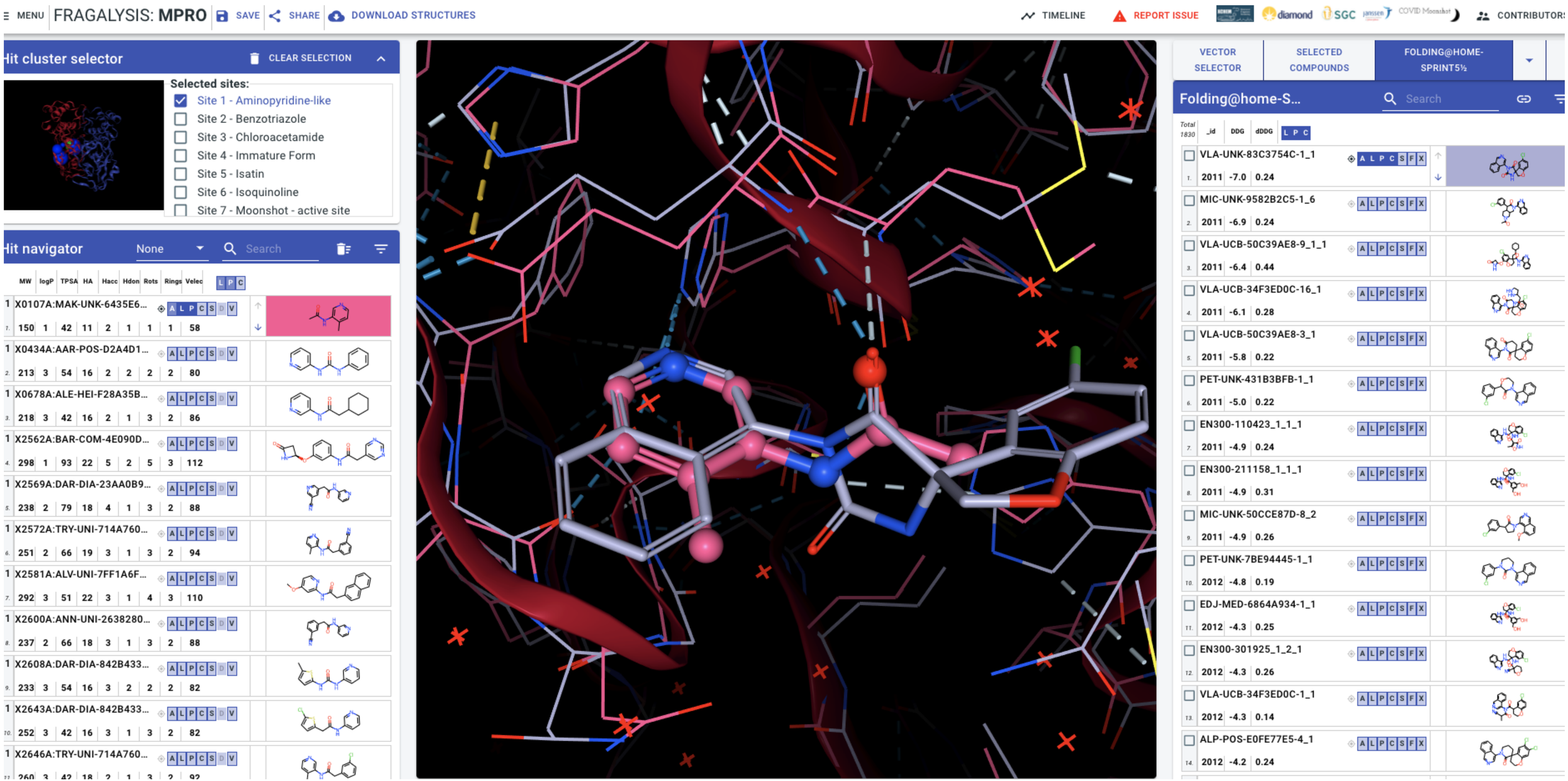


Updated 2021-02-21T21:35:59.343106+00:00

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 aim to nominate a clinical candidate in Mar 2021

Goal: new potent antiviral: therapeutic & prophylactic

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

Strategy: work fully open to ensure rapid global availability

- *no IP encumbrance*
- *generic drug*
- *assays/structures/discussions: http://postera.ai/covid*
- *protocols: https://doi.org/10.1101/2020.10.29.339317*

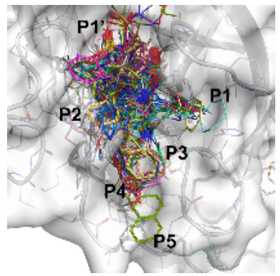
April — *Sept* — *Dec* — *Apr '21*

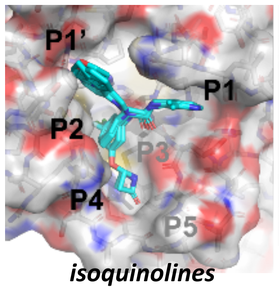
XChem & data release

fragment-to-lead
$350k, 30 groups

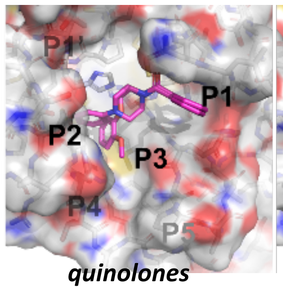
lead optimization
$400k, 40 groups

toxicity, pre-clinical
$1.5-2m, 50 groups

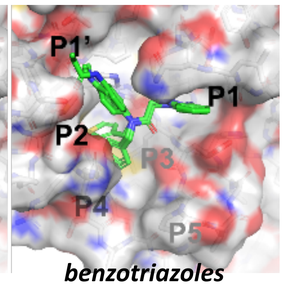




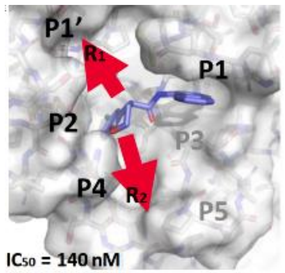
isoquinolines



quinolones



benzotriazoles



6 months:
- *3 lead series*
- *100nM enzyme inhibition*
- *cellular antiviral activity*
- *(some philanthropic funding)*

achieved:
- *oral availability*
- *antiviral IC_{50} <1μM*
- *protease selectivity*

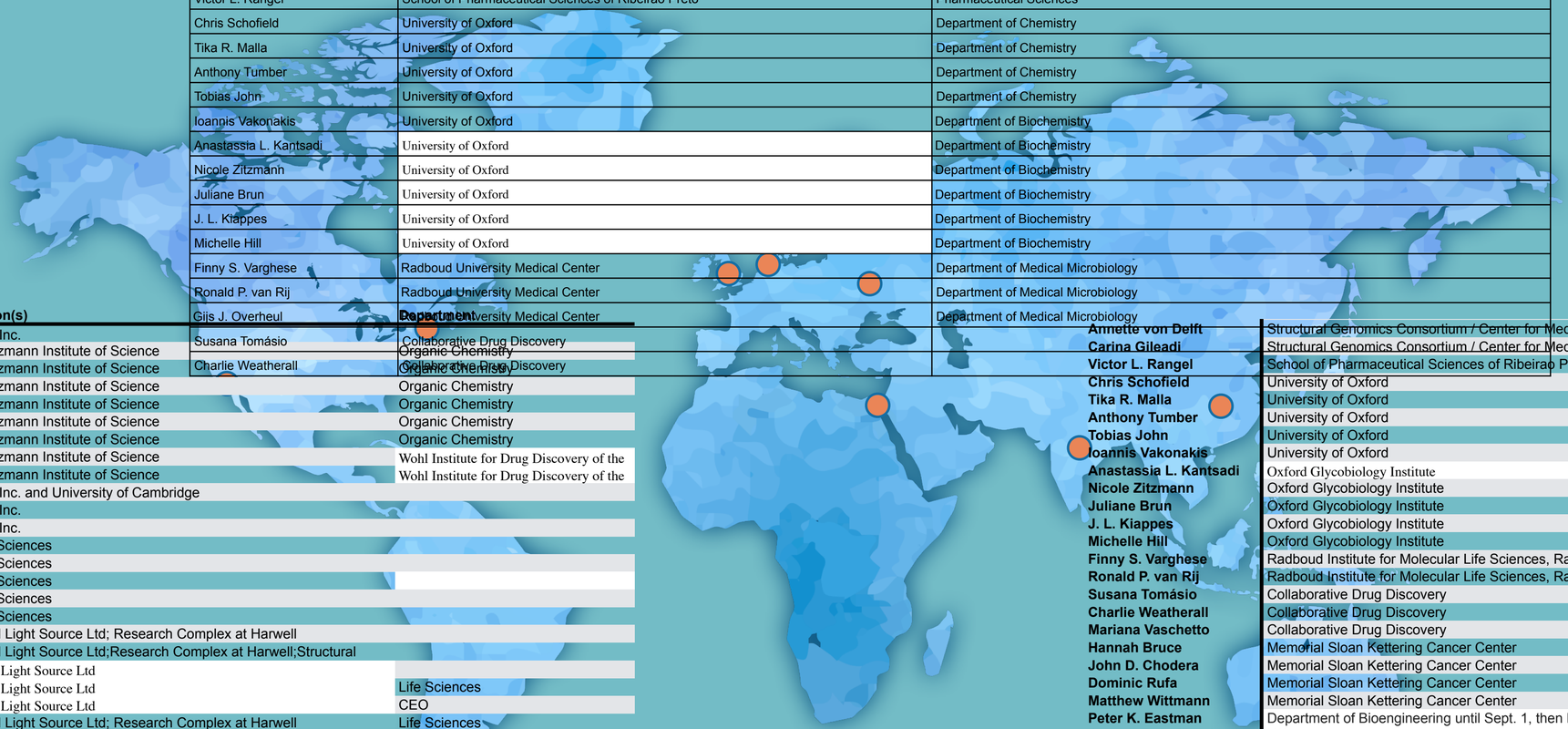
improving:
- *potency*
- *solubility*
- *metabolic stability*

seeking:
- ***critical mass funding***
- *partners (curr: charity, gov)*
- *formulation & manufacturing*
- *clinical trials*

http://postera.ai/covid

The COVID Moonshot collaboration is worldwide

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



Name	Institution(s)	Department
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	Organic Chemistry
Paul Gehrtz	The Weizmann Institute of Science	Organic Chemistry
Rambabu N. Reddi	The Weizmann Institute of Science	Organic Chemistry
Ronen Gabizon	The Weizmann Institute of Science	Organic Chemistry
Haim Barr	The Weizmann Institute of Science	Wohl Institute for Drug Discovery of the
Shirly Valter	The Weizmann Institute of Science	Wohl Institute for Drug Discovery of the
Alpha Lee	PostEra Inc. and University of Cambridge	
Andrew Jajack	PostEra Inc.	
Milan Cvitkovic	PostEra Inc.	
Aarif Shaikh	Sai Life Sciences	
Iakir Piniari	Sai Life Sciences	
Vishwanath Swamy	Sai Life Sciences	
Maneesh Pingle	Sai Life Sciences	
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Frank von Delft	Diamond Light Source Ltd;Research Complex at Harwell;Structural	
Daren Fearon	Diamond Light Source Ltd	
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Jose Brandao Neto	Diamond Light Source Ltd; Research Complex at Harwell	Life Sciences
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Warren Thompson	Diamond Light Source Ltd	
Tyler Gorrie-Stone	Diamond Light Source Ltd; Research Complex at Harwell	Life Sciences
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Tika R. Malla	University of Oxford	Department of Chemistry
Anthony Tumber	University of Oxford	Department of Chemistry
Tobias John	University of Oxford	Department of Chemistry
Ioannis Vakonakis	University of Oxford	Department of Biochemistry
Anastassia L. Kantsadi	University of Oxford	Department of Biochemistry
Nicole Zitzmann	University of Oxford	Department of Biochemistry
Juliane Brun	University of Oxford	Department of Biochemistry
J. L. Kiappes	University of Oxford	Department of Biochemistry
Michelle Hill	University of Oxford	Department of Biochemistry
Finny S. Varghese	Radboud University Medical Center	Department of Medical Microbiology
Ronald P. van Rij	Radboud University Medical Center	Department of Medical Microbiology
Gijs J. Overheul	Radboud University Medical Center	Department of Medical Microbiology
Susana Tomásio	Collaborative Drug Discovery	
Charlie Weatherall	Collaborative Drug Discovery	

Annette von Delft	Structural Genomics Consortium / Center for Medicines Discovery	Nuffield Department of Medicine
Carina Gileadi	Structural Genomics Consortium / Center for Medicines Discovery	Nuffield Department of Medicine
Victor L. Rangel	School of Pharmaceutical Sciences of Ribeirao Preto	Pharmaceutical Sciences
Chris Schofield	University of Oxford	Department of Chemistry
Tika R. Malla	University of Oxford	Department of Chemistry
Anthony Tumber	University of Oxford	Department of Chemistry
Tobias John	University of Oxford	Department of Chemistry
Ioannis Vakonakis	University of Oxford	Department of Biochemistry
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The COVID Moonshot collaboration is worldwide

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The next steps

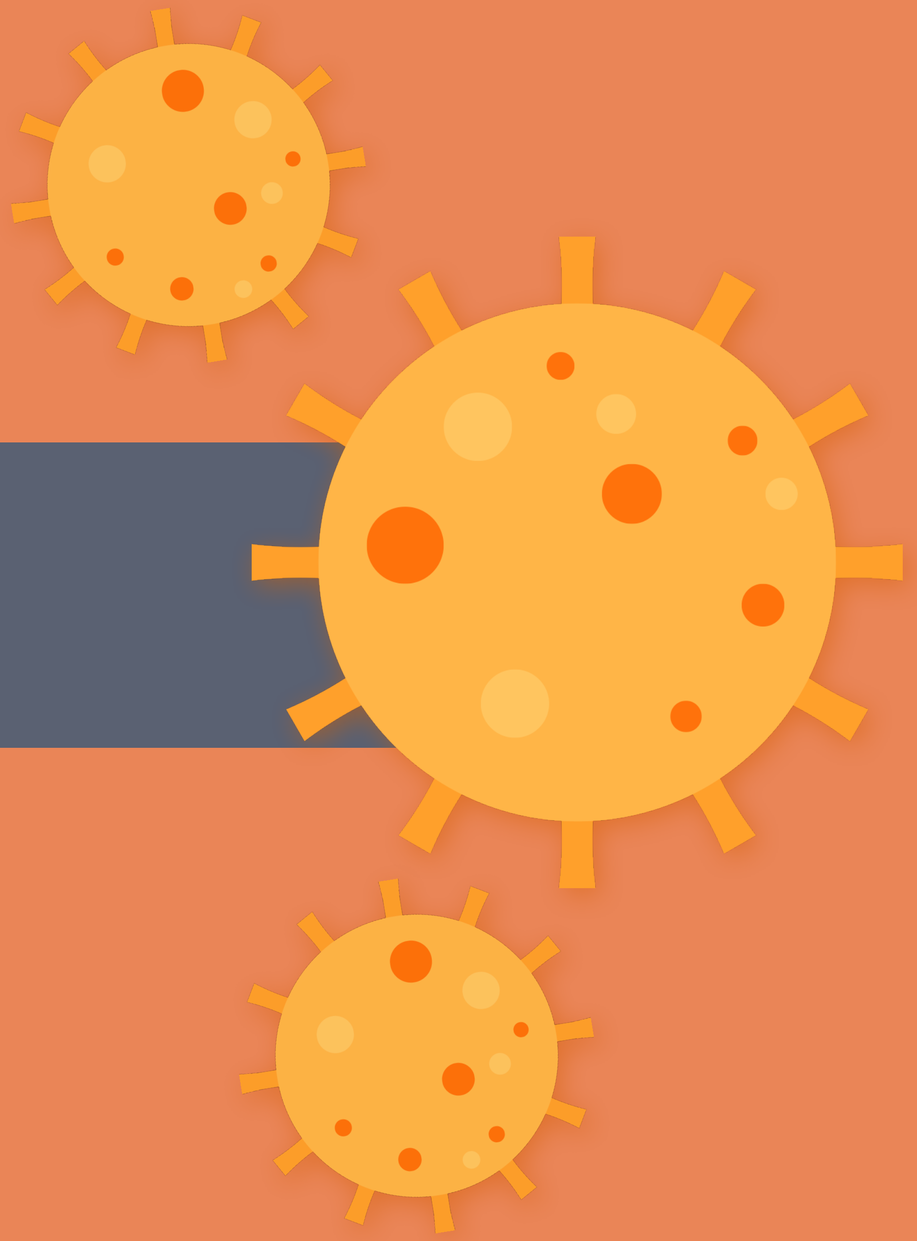
We are currently working to identify a partner for IND-enabling studies of a clinical candidate nominated Apr 2021

Still need funding: NIAID COVID-19 R01 was **Not Discussed**
We've resorted to a GoFundMe to pay for final chemistry:
https://www.gofundme.com/f/covidmoonshot

Immediately planning follow-on development of a pan-coronavirus inhibitor to prevent future pandemics

helpcurecovid.org

THANK YOU!



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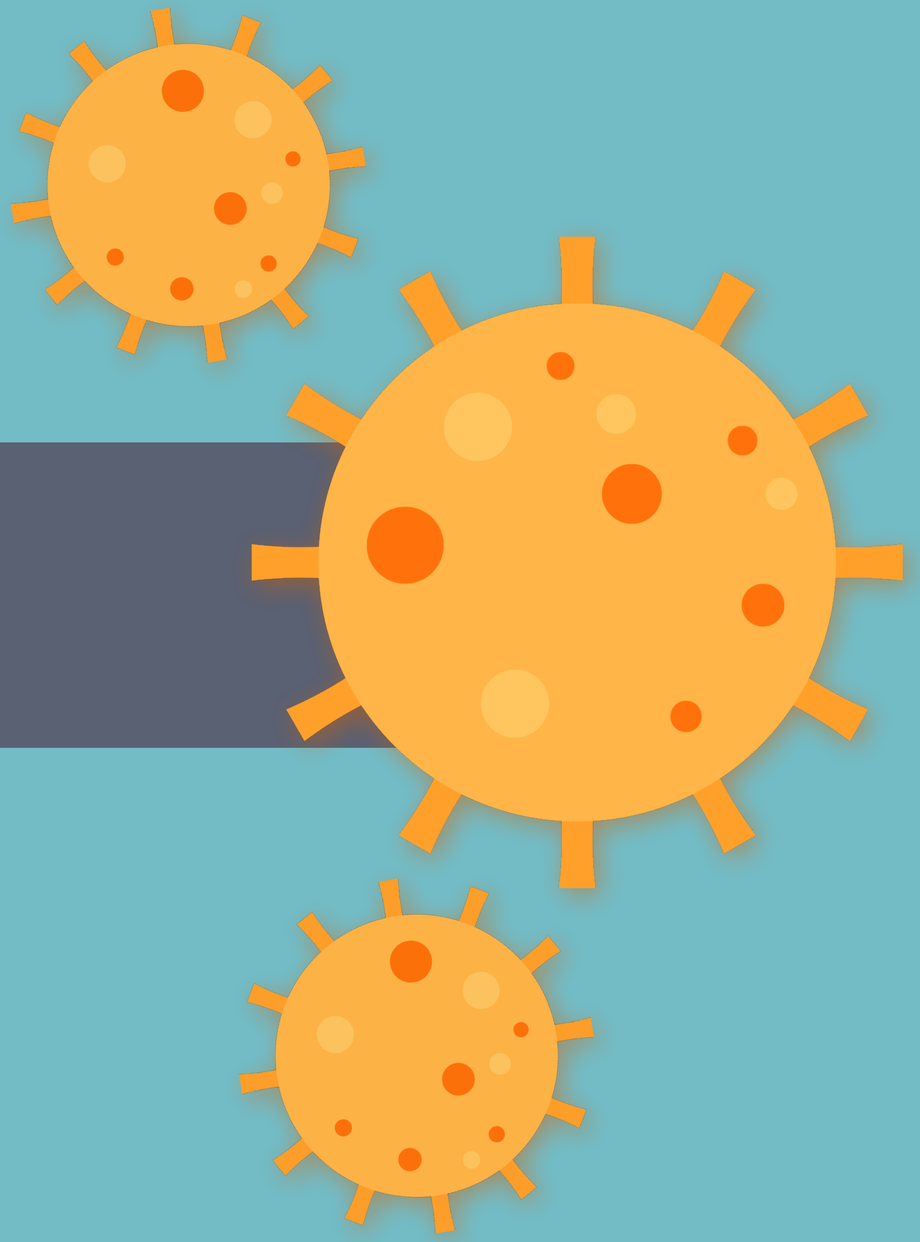
Folding@home data: http://covid.molssi.org

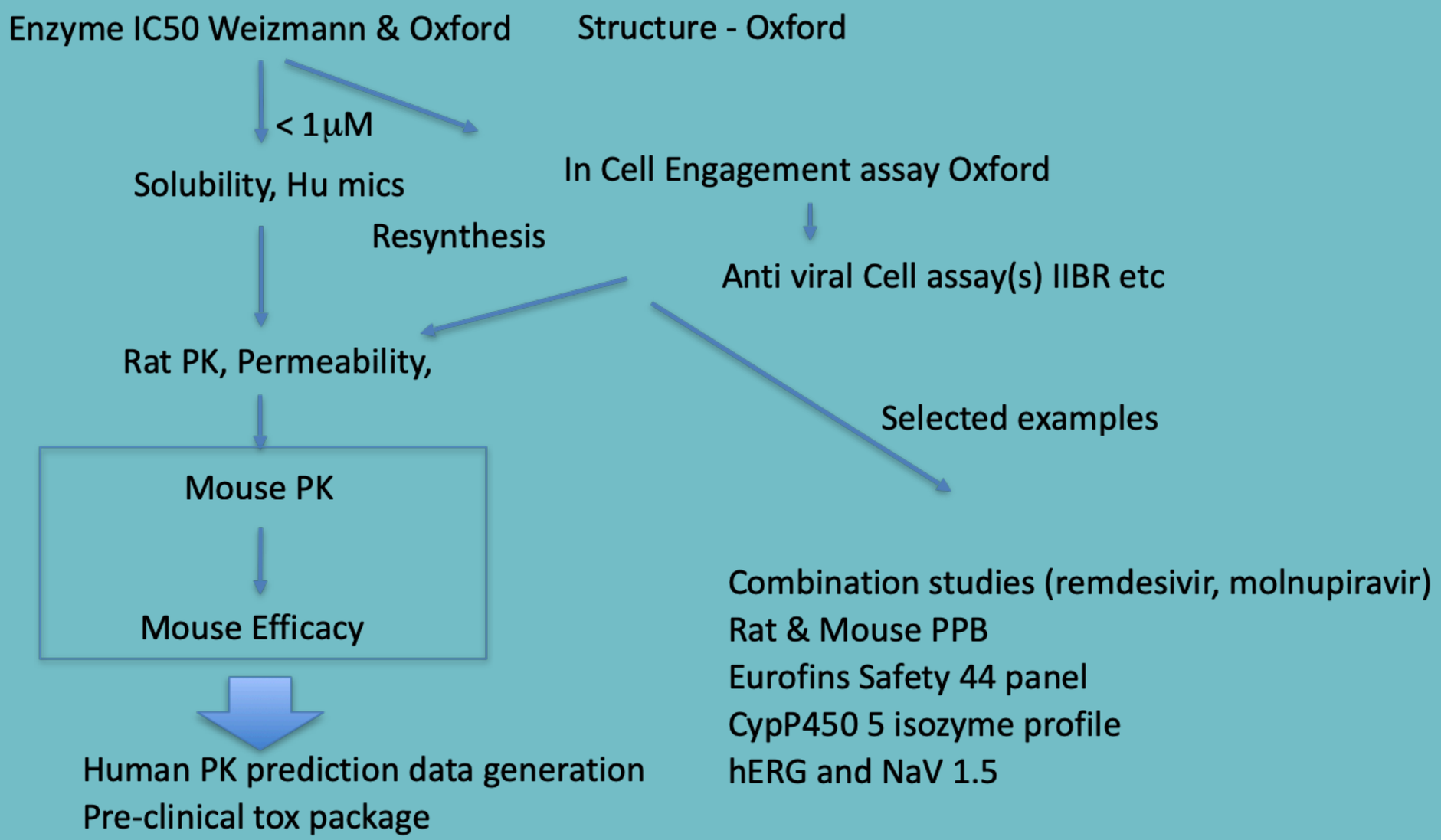
BACKUP SLIDES



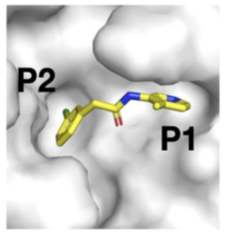
Current TPP for oral Mpro inhibitor

Property	Target range	Rationale	
Protease assay	IC_{50} < 50 nM (compromise if clean and anti viral activity sufficient)	Extrapolation from other anti-viral programs	105 nM
Viral replication	EC_{50} < 0.2µM (Vero-E6, and Calu-3)	Suppression of virus at achievable blood levels	0.4-1 µM
Plaque reduction	EC_{50} < 0.2µM (Vero-E6, and Calu-3)	Suppression of virus at achievable blood levels	in progress
PK-PD	Cmin > EC90(plaque reduction) for 24h	Assume constant suppression of viral replication	
Coronavirus spectrum	SARS-CoV2 B1.1.7 , B.1.1.248 variants essential, SARS-CoV1 & MERS desirable	Treat vaccine resistant variants and future pandemic preparation.	oral exposure observed
Route of administration	oral	bid/tid(qid)- compromise PK for potency if pharmacodynamic effect achieved	
Solubility	> 5 mg/mL	Aim for biopharmaceutical class 1 assuming <= 750 mg dose	< 1 mg/mL
Half-life	Ideally>= 8 h (human) estimated from rat and dog PK	Assume PK/PD requires continuous cover over viral replication for 24 h	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 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 Avoid DDI to support co-morbidities & combination therapy, Critical 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	clean protease panel live phase planned CYP450s in progress cardiotoxicity in vivo testing planned Ames planned

Critical path for assay cascade



Primary series: Aminopyridines



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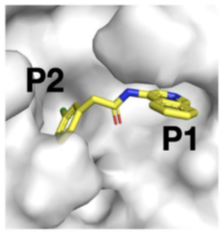

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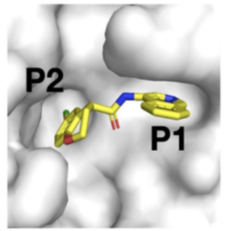

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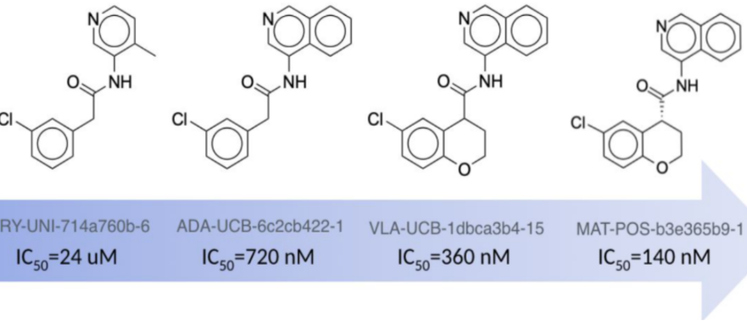

Assay	Type	August	December	December	TPP goal
Tier 1		**JOR-UNI-2fc98d0b-12**	**MAT-POS-b3e365b9-1**	**MAT-POS-53907a1c-3**	
Mpro inhibition (Fluorescence)	IC50	3.1 µM	141 nM	58 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	3.3 µM	257 nM		<50 nM
thermodynamic solubility	solubility		34 µM		>10 µM
plasma protein binding	fraction unbound		12±2% unbound		>1% unbound
Tier 2					
VeroE6 antiviral activity (CPE)	IC50		1.57 µM		<5 µM
VeroE6 antiviral activity (qPCR)	IC50	7.31 µM	2.63 µM		<5 µM
VeroE6 cytotoxicity	CC50	25.5 µM	>500 µM		>100 µM
A549 cytotoxicity	CC50	14.1 µM	>100 µM		>100 µM
Calu-3 cytotoxicity	CC50	18.2 µM	>100 µM		>100 µM
protease selectivity at 100 µM	40 human protease panel		<12%		<40%
MDCK-MDR1	Papp		41±1 x10^-6 cm/s		>10 x10^-6 cm/s
human liver	CLint		98.3 µg/min/mg protein		<10 µg/min/mg protein
microsomal stability	t 1/2		14.1 min		>120 min
Tier 3					
rat oral bioavailability	t 1/2		1 h		>8 h

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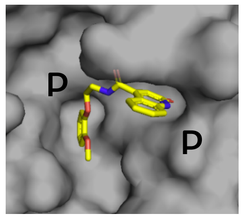
Backup series 1: Quinolones



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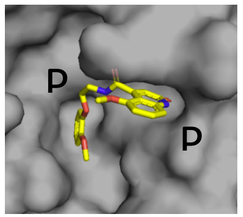
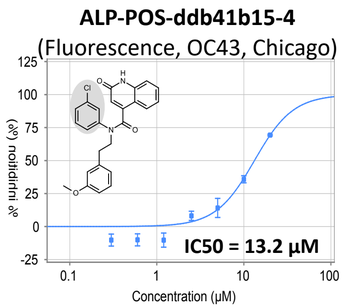
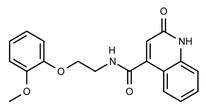
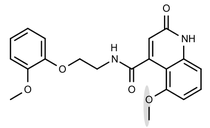


DiamondMX/XChem x11294

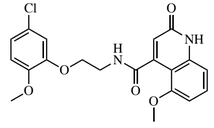




MAT-POS-916a2c5a-2
IC_{50} = 7 µM



EDJ-MED-6af13d92-3
IC_{50} = 2 µM



MAT-POS-3b536971-1
IC_{50} = 870 nM

Assay	Type	August	December	December	TPP goal
Tier 1		**MAT-POS-916a2c5a-2**	**EDJ-MED-6af13d92-3**	**MAT-POS-3b536971-1**	
Mpro inhibition (Fluorescence)	IC50	7.5 µM	2.03 µM	870 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	3.5 µM	2.08 µM		<50 nM
thermodynamic solubility	solubility		84 µM		>10 µM
plasma protein binding	fraction unbound		29.5±0.7% unbound		>1% unbound
Tier 2					
VeroE6 antiviral activity (fluorescence, OC43)	IC50		>20 µM		<5 µM
VeroE6 antiviral activity (CPE)	IC50		not active		<5 µM
VeroE6 cytotoxicity	CC50		>20 µM		>100 µM
A549 cytotoxicity	CC50		>10 µM		>100 µM
Calu-3 cytotoxicity	CC50		>100 µM		>100 µM
protease selectivity at 100 µM	40 human protease panel		<10%		<40%
MDCK-MDR1	Papp		2.0±0.1 x 10^-6 cm/s		>10 x 10^-6 cm/s
human liver	CLint		19.3 µg/min/mg protein		<10 µg/min/mg protein
microsomal stability	t 1/2		71.9 min		>120 min
Tier 3					
rat oral bioavailability	t 1/2		43 min		>8 h

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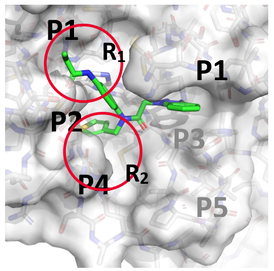
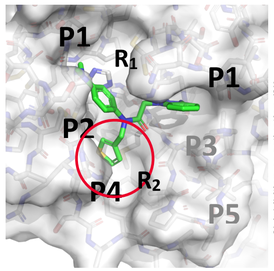
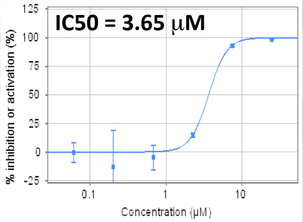
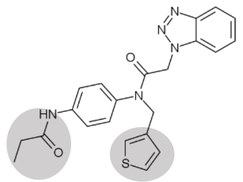
Backup series 2: Benzopyrans

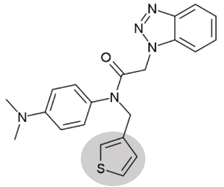


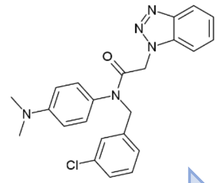


ALP-POS-c59291d4-2
(qPCR, SARS-CoV-2, Radboud)









ALP-POS-c59291d4-2
IC50 12.56 µM

ALP-POS-c59291d4-2
IC50 5.369 µM

ALP-POS-6d04362c-2
IC50 0.391 µM

Assay	Type	August	December	TPP goal
Tier 1		**ALP-POS-c59291d4-2**	**ALP-POS-6d04362c-2**	
Mpro inhibition (Fluorescence)	IC50	1.63 µM	497 nM	<50 nM
Mpro inhibition (RapidFire)	IC50	12.6 µM	391 nM	<50 nM
Tier 2				
VeroE6 antiviral activity (Fluorescence, OC43)	IC50	>20 µM		<5 µM
VeroE6 antiviral activity (CPE)	IC50	not active		<5 µM
VeroE6 antiviral activity (CPE)	IC50	3.65 µM		<5 µM
VeroE6 cytotoxicity	CC50	>100 µM		>100 µM
A549 cytotoxicity	CC50	>20 µM		>100 µM
Calu-3 cytotoxicity	CC50	>100 µM		>100 µM
protease selectivity at 100 µM		<35%		<40%
MDCK-MDR1	Papp			>10 x10^-6 cm/s
human liver	CLint	641 µg/min/mg protein		<10 µg/min/mg protein
microsomal stability	t 1/2	2.16 min		>120 min

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