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

Memorial Sloan Kettering Cancer Center

Sloan-Kettering Institute

In more than 100 laboratories, our scientists are conducting innovative research to advance understanding in the biological sciences and improve human health.

Dana Pe'er

Quaid Morris

Christina Leslie

Joao Xavier

John Chodera

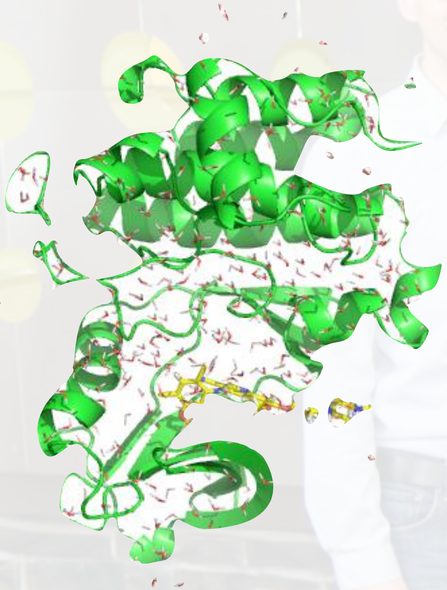
Thomas Norman

csbio@MSKCC

CHODERA LAB

How can computational biophysics play a MAJOR role in the era of CANCER genomics?

modeling



FOLDING @HOME

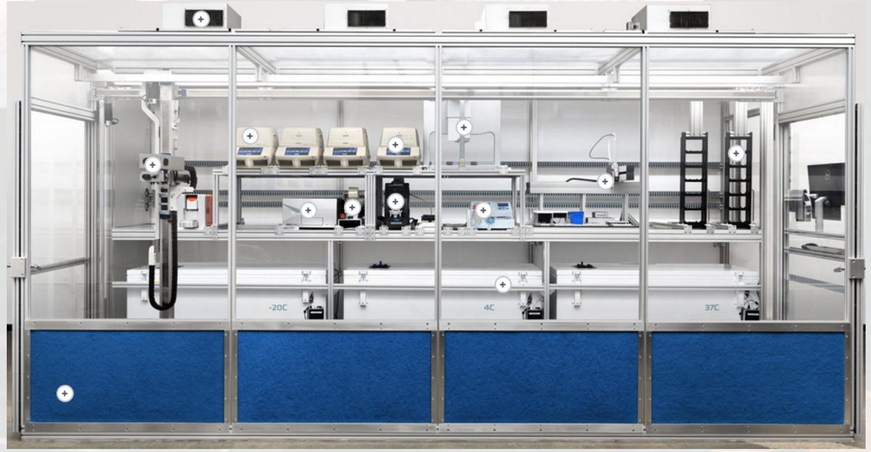
amazon web services™ EC2

$$V(\mathbf{q}) = \sum_{\text{bonds}} K_r(r - r_{eq})^2 + \sum_{\text{angles}} K_\theta(\theta - \theta_{eq})^2$$

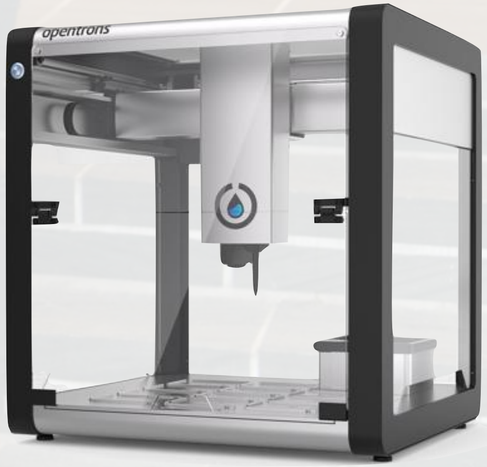
$$+ \sum_{\text{dihedrals}} \frac{V_n}{2}[1 + \cos(n\phi - \gamma)] + \sum_{i<j} \left[\frac{A_{ij}}{R_{ij}^{12}} - \frac{B_{ij}}{R_{ij}^{6}} + \frac{q_i q_j}{\epsilon R_{ij}} \right]$$

automation

chodera lab, Z17



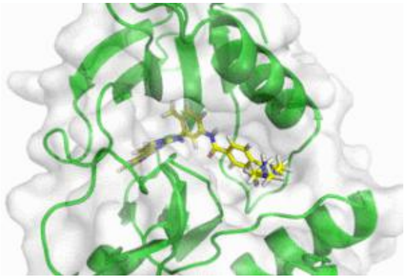
transcriptic cloud wetlab



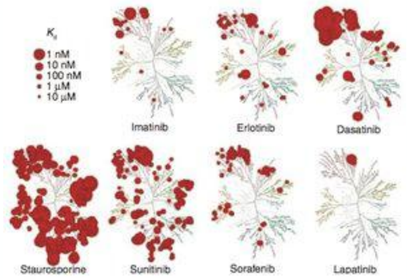
opentrons

CHODERA LAB

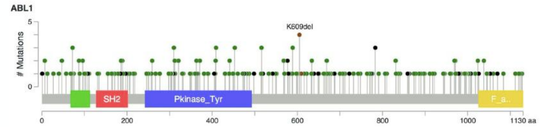
We develop quantitative predictive modeling approaches where they are needed



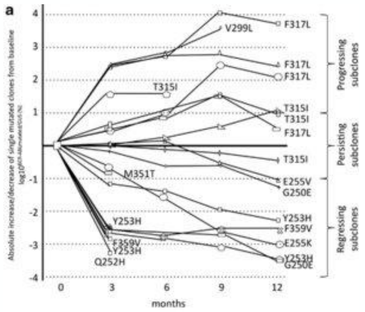
selective inhibitor design: targets/ antitargets



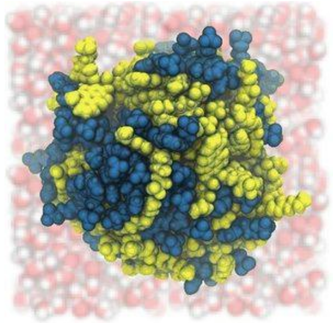
kinase inhibitor selectivity



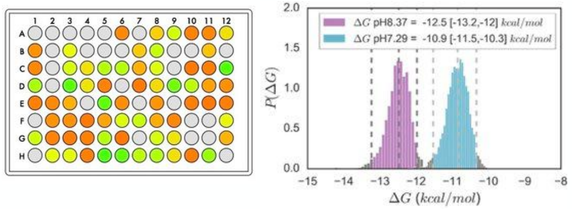
predicting drug sensitivity/resistance



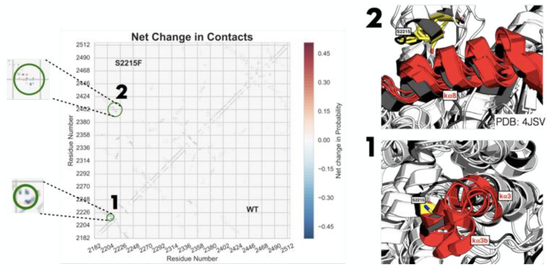
anticipating drug resistance



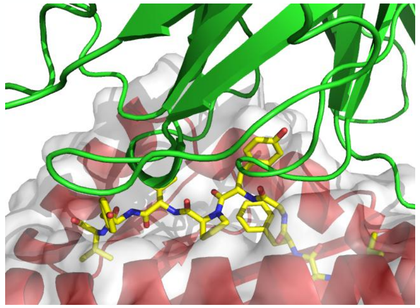
novel drug delivery modalities



automated biophysical assays and inference

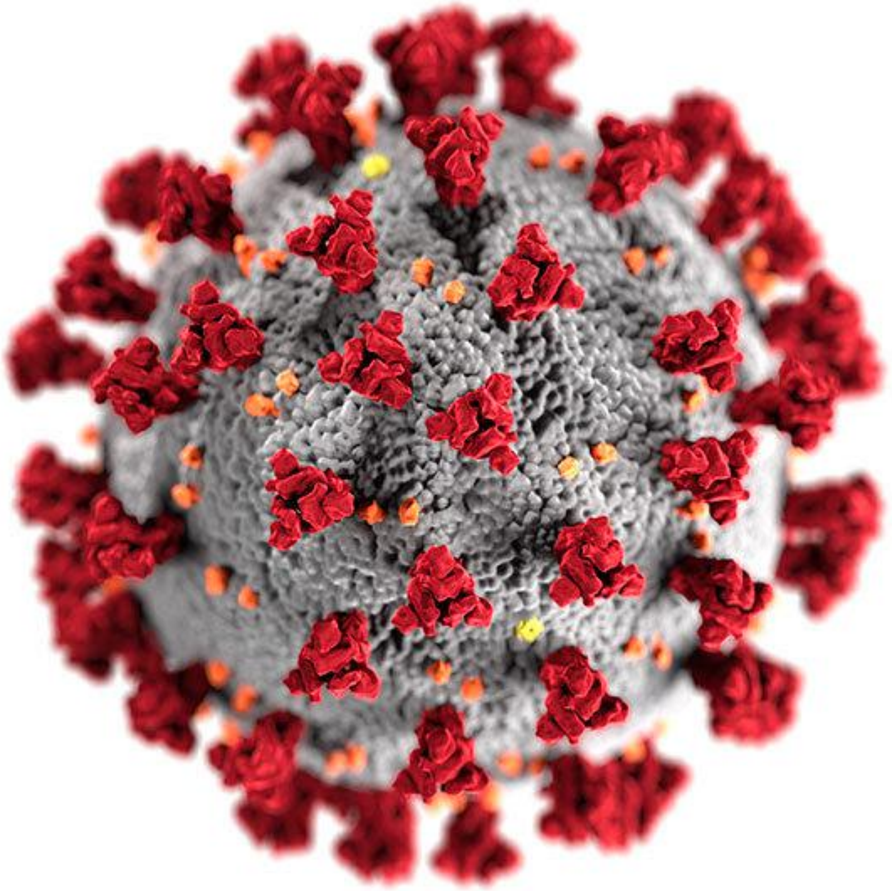


mechanisms of oncogenic activation



cancer immunotherapy

10 Jan 2020



COVID-19 is caused by a novel coronavirus

Researchers uploaded the first draft genome of the novel coronavirus on 10 Jan 2020

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

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

SUMMARY

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

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]

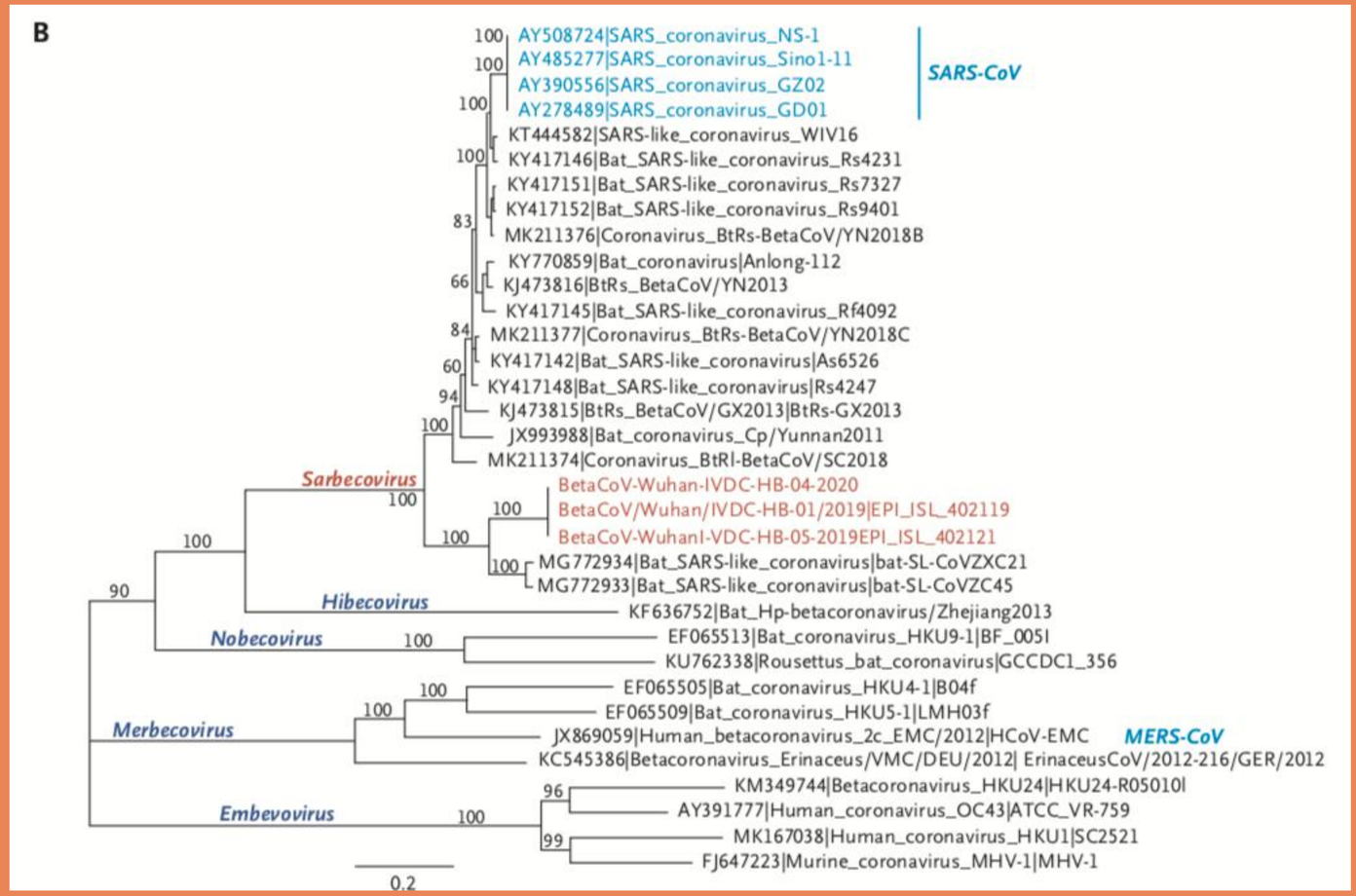
In late December 2019, several local health facilities reported clusters of patients with pneumonia of unknown cause that were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China.[11] On December 31, 2019, the Chinese Center for Disease Control and Prevention (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

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.

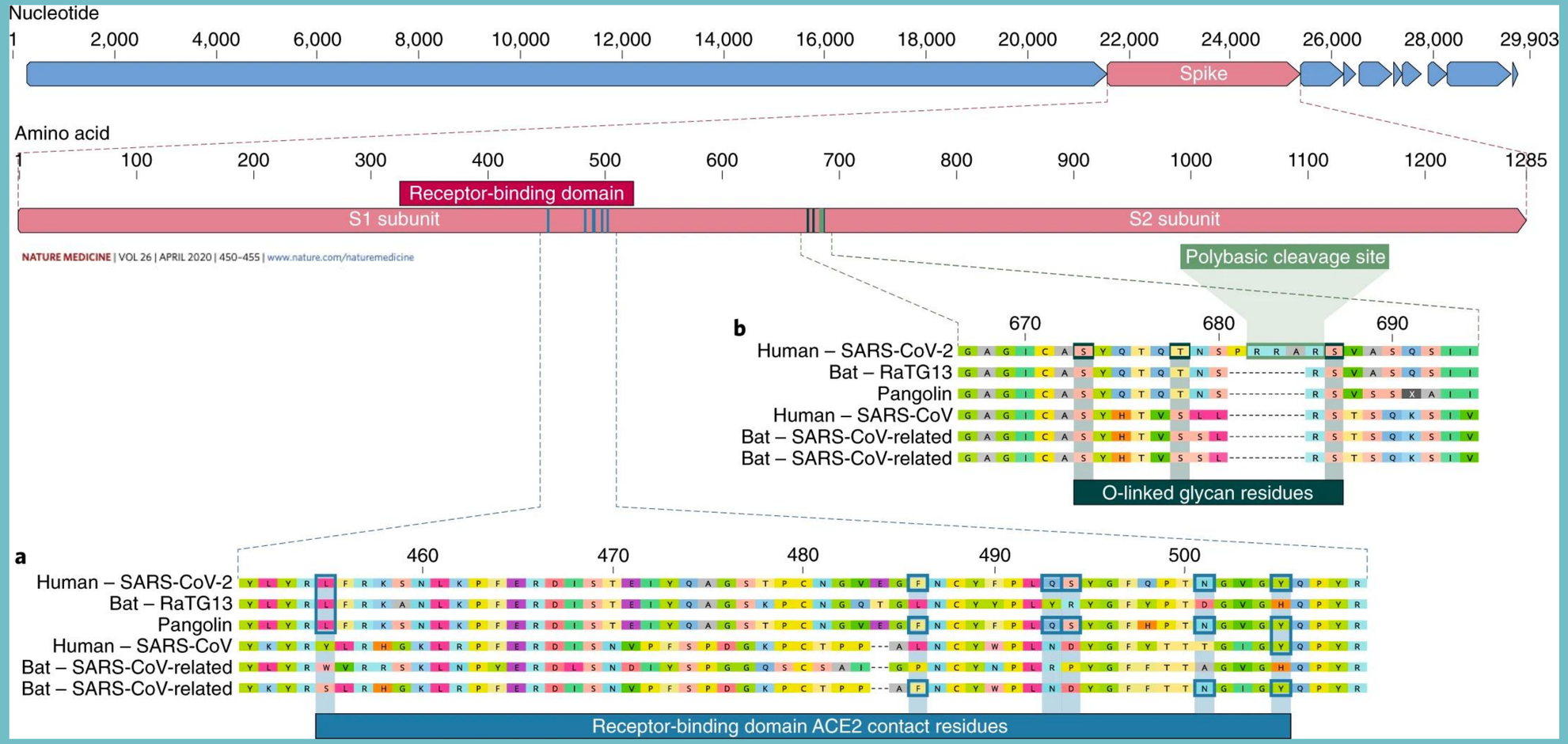
This article was published on January 24, 2020, and updated on January 29, 2020, at NEJM.org.

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



Striking similarity to SARS-CoV and MERS-CoV

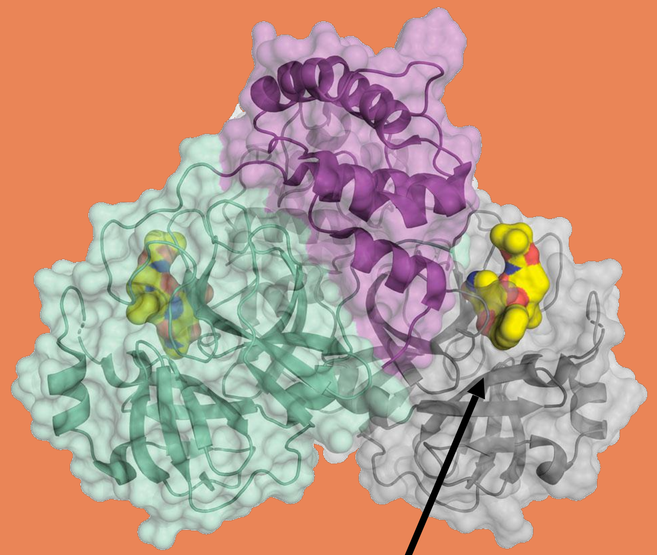
The viral genome sequence was surprisingly similar to SARS-CoV-1: It was ultimately designated SARS-CoV-2

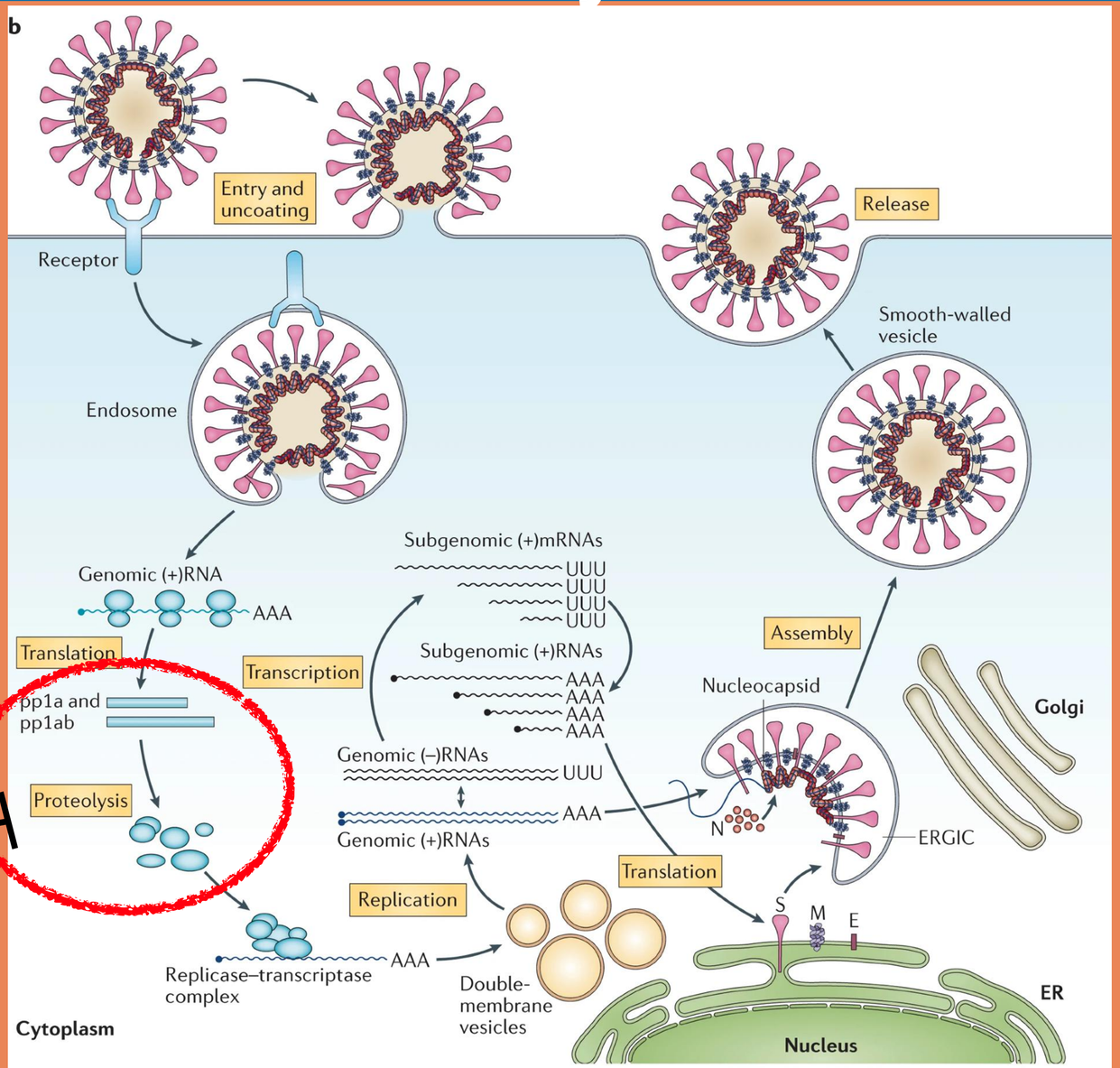


The SARS-CoV-2 main viral protease (Mpro) is essential for a key stage in the viral life cycle

M^{pro}

also: nsp5, 3CL^{Pro}





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

Why would we need a new oral antiviral?

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

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

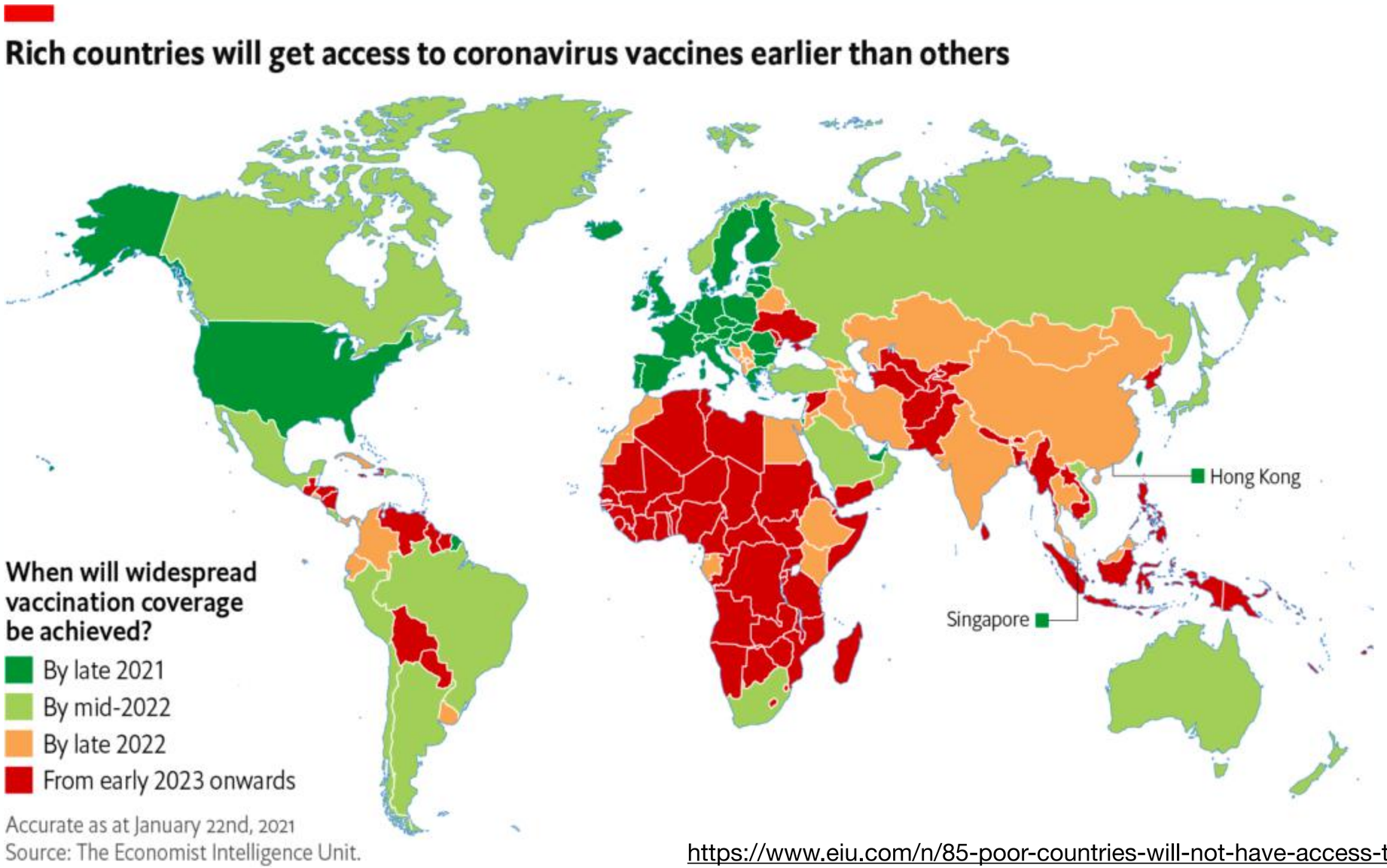
Oral antivirals could be taken early, as opposed to IV drugs

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

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

A simple synthetic route could enable rapid production at low cost

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



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

Drug repurposing is an appealing idea. Too bad is has never worked.

JCIM JOURNAL OF CHEMICAL INFORMATION AND MODELING

ACS AUTHORCHOICE

pubs.acs.org/jcim

Viewpoint

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

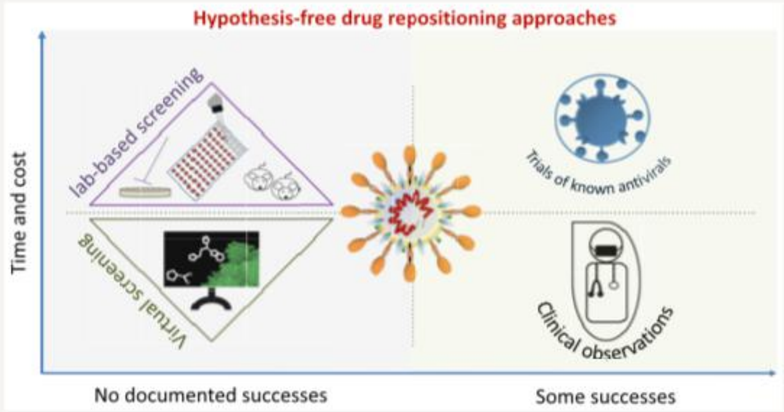
Aled Edwards*

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

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.

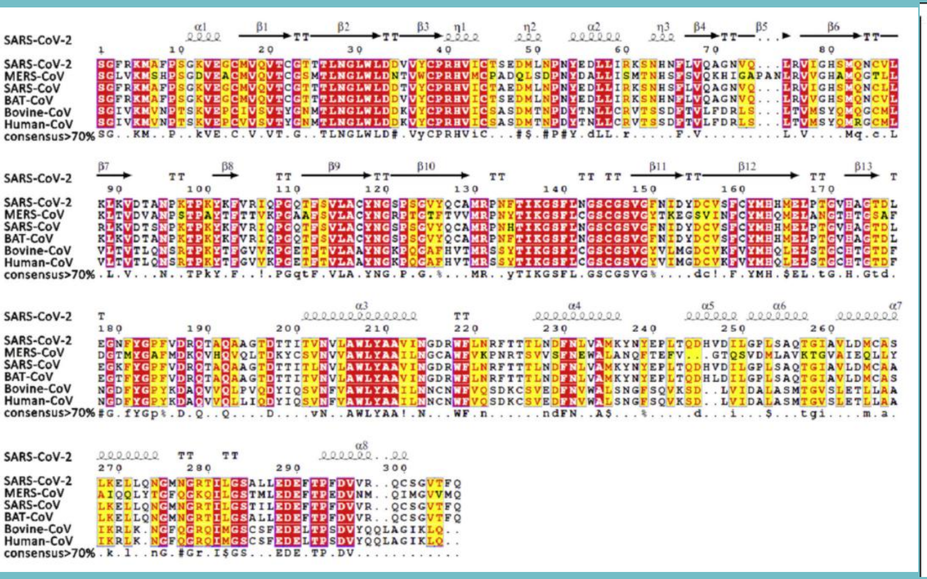


Aled Edwards
SGC Toronto

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

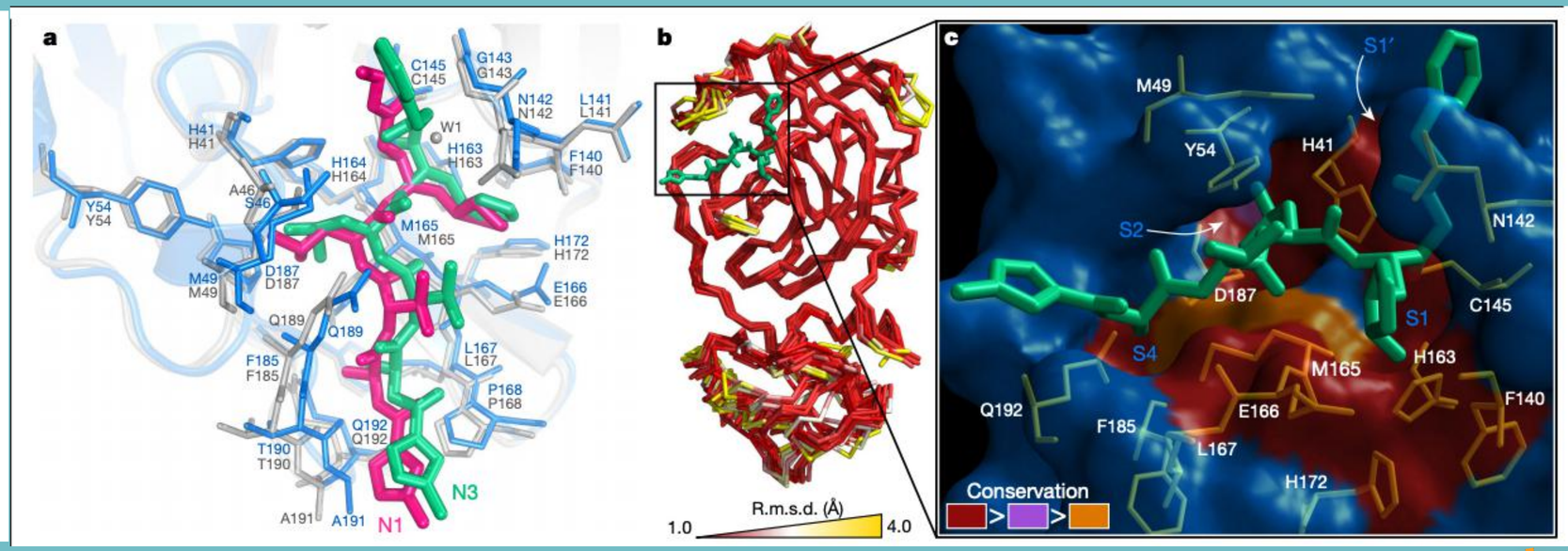
Mpro is an essential enzyme highly conserved among viruses that cause SARS, MERS, and COVID

sequence (24 Jan 2020)



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

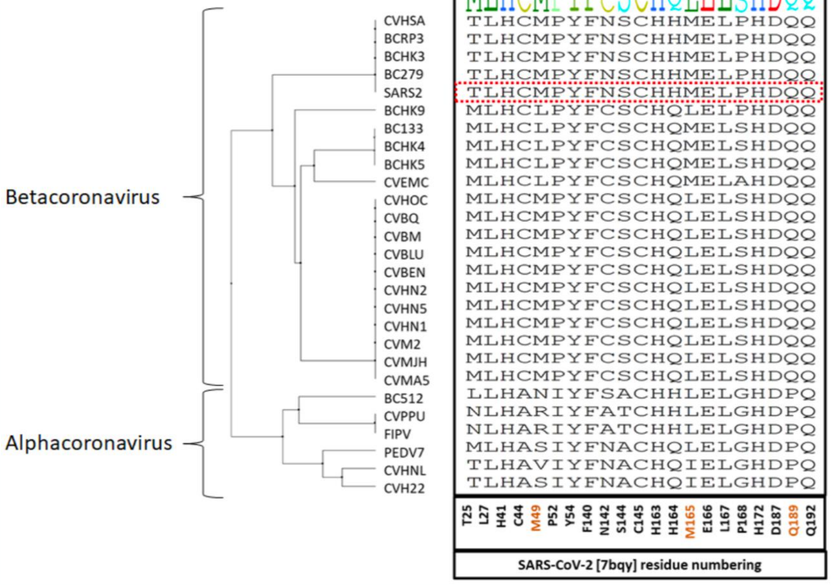
structure (PDB structure released 5 Feb 2020)



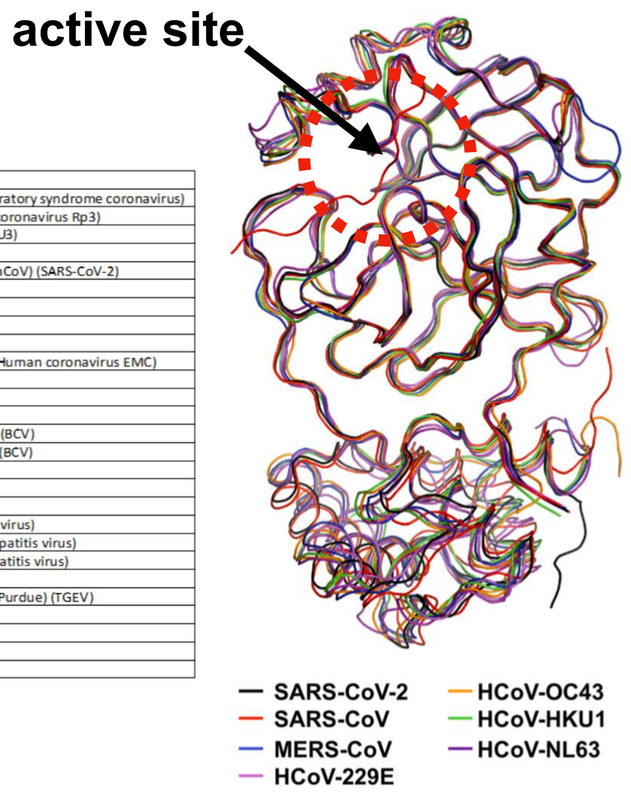
Jin et al. Nature 582:289, 2020
doi:10.1038/s41586-020-2223-y

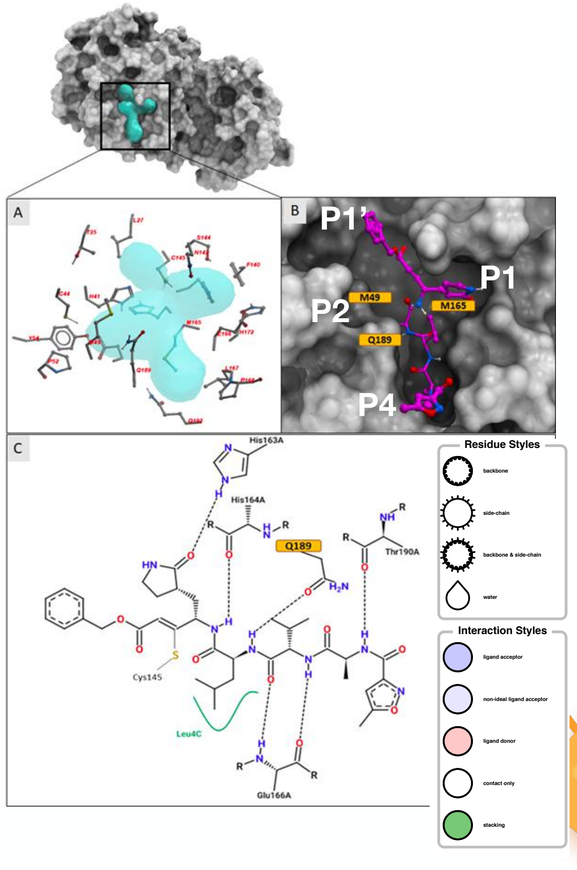
Mpro appears to be a viable target for developing a SARS-CoV-2 antiviral as well as pan-coronavirus antivirals

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



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





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

While no human coronavirus Mpro inhibitors had been approved as a drug…

Antiviral Research 97 (2013) 161–168

Contents lists available at SciVerse ScienceDirect

Antiviral Research

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

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

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

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

ARTICLE INFO

Article history:
Received 23 August 2012
Revised 18 October 2012
Accepted 15 November 2012
Available online 28 November 2012

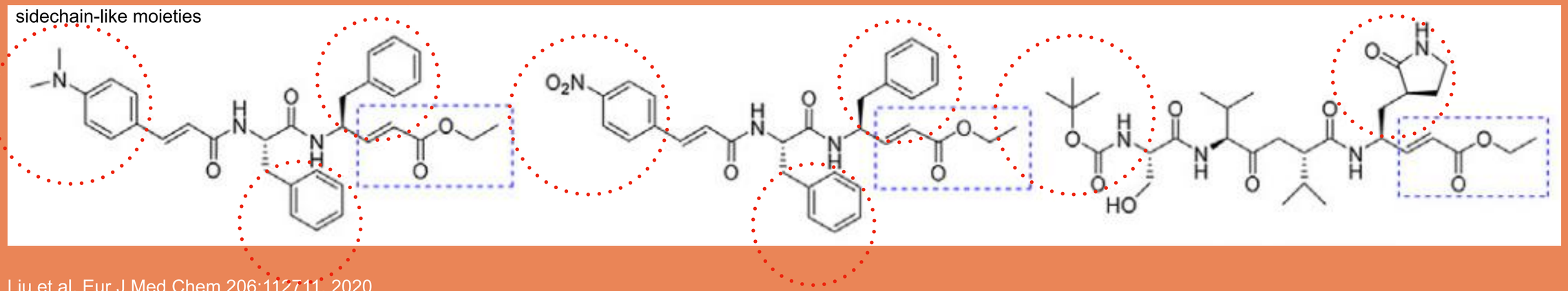
Keywords:
Feline coronaviruses
Feline infectious peritonitis virus
Protease inhibitor
Cathepsin B
Synergy
3CL protease

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.

an Mpro inhibitor had successfully treated cats

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



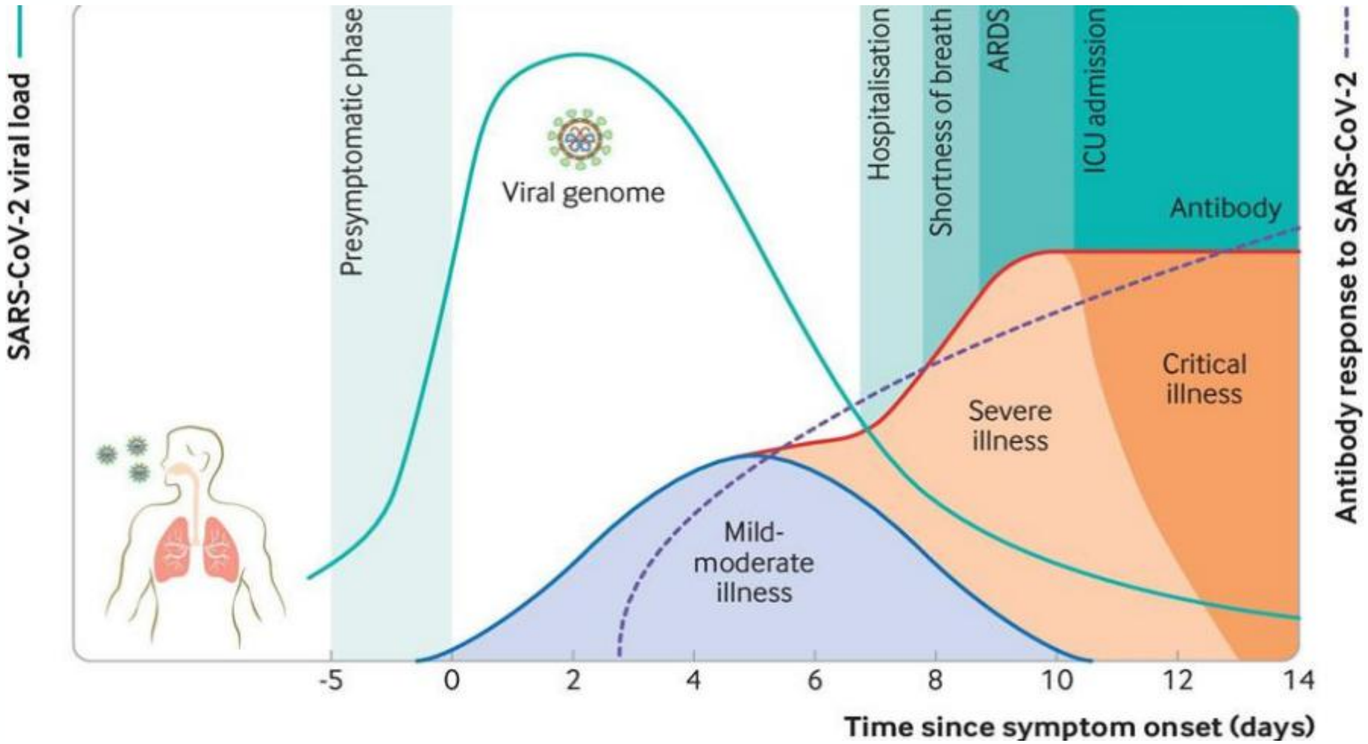
Liu et al. Eur J Med Chem 206:112711, 2020

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

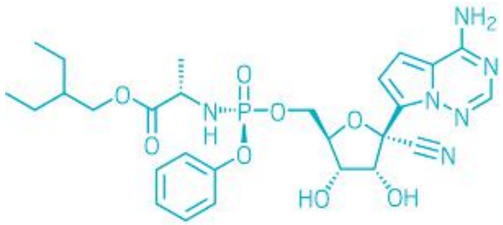
Oral drugs will be much more useful than IV drugs in impacting the course of disease

Oral antiviral
Window of opportunity

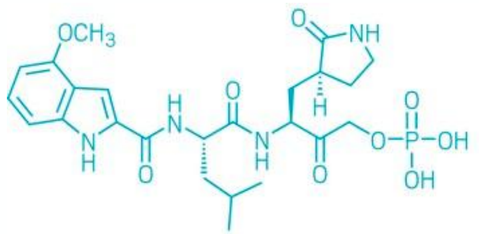
Virus no longer drives disease
Antivirals less effective
Hospitalized, so access to IV drugs



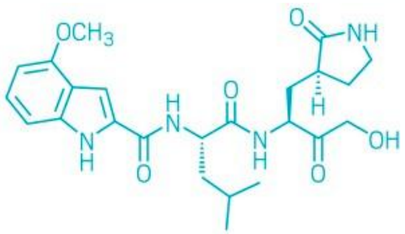
all IV dosing



Remdesivir



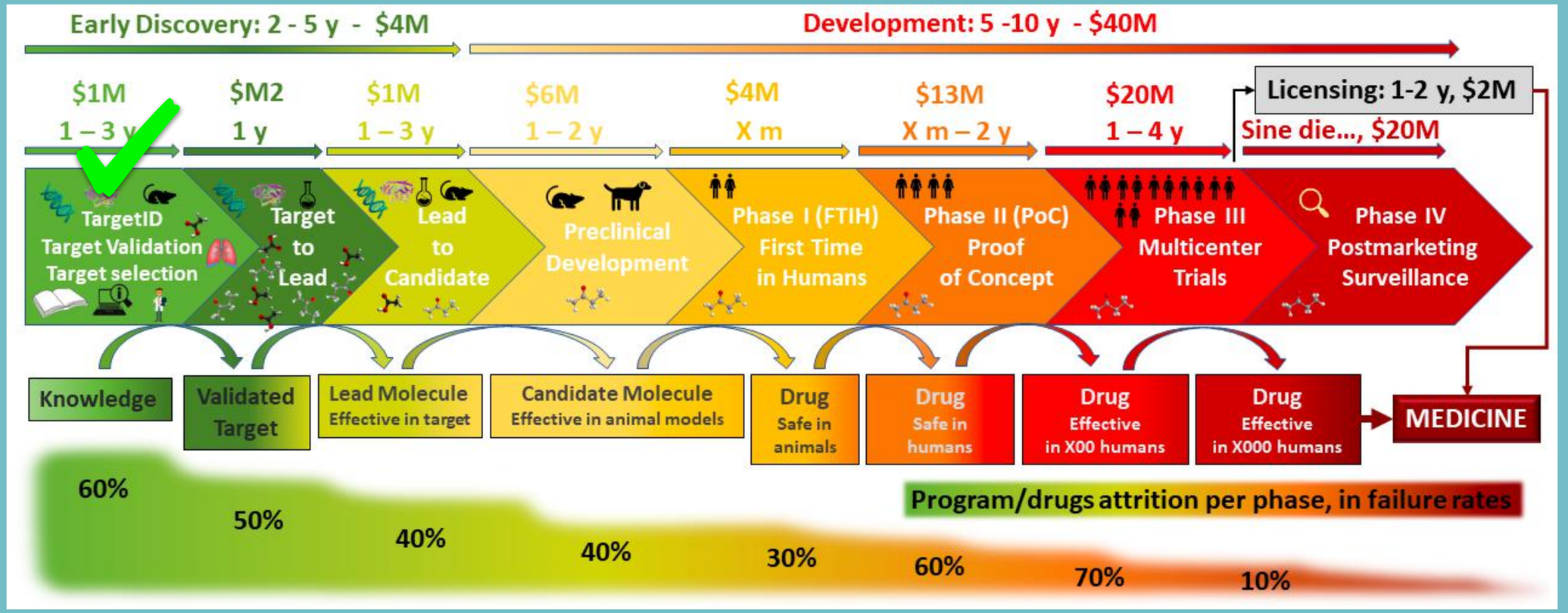
PF-07304814



PF-00835231

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

Drug discovery is usually a long and expensive process



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

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

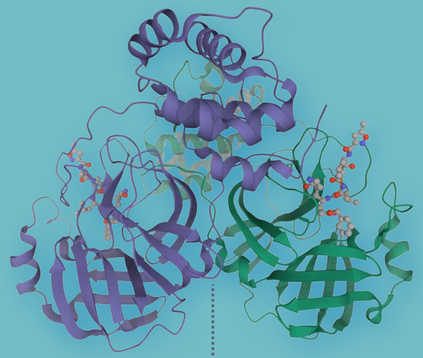
Diamond Light Source prosecuted a high-throughput X-ray fragment screen in a matter of weeks

Frank von Delft
Diamond Light Source / XChem / SGC

February 14

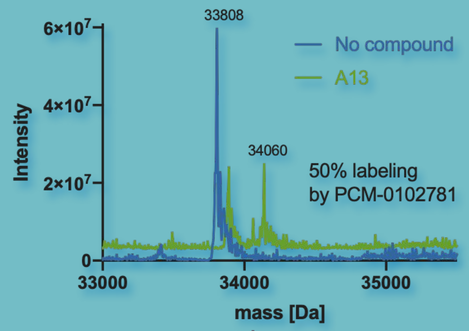
Main protease cloned and produced at Diamond after COVID shutdown of Haitao Yang lab in Shanghai

Martin Walsh



February 20

Atomic resolution structure of the protease determined

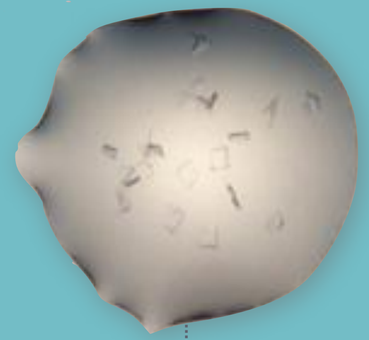


February 25

Covalent screen finds 150 active site hits

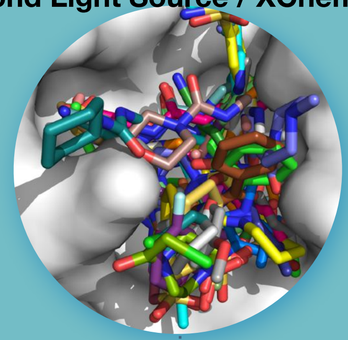
>40 hits validated

Nir London



March 5

1,500 crystals collected in one day (!)

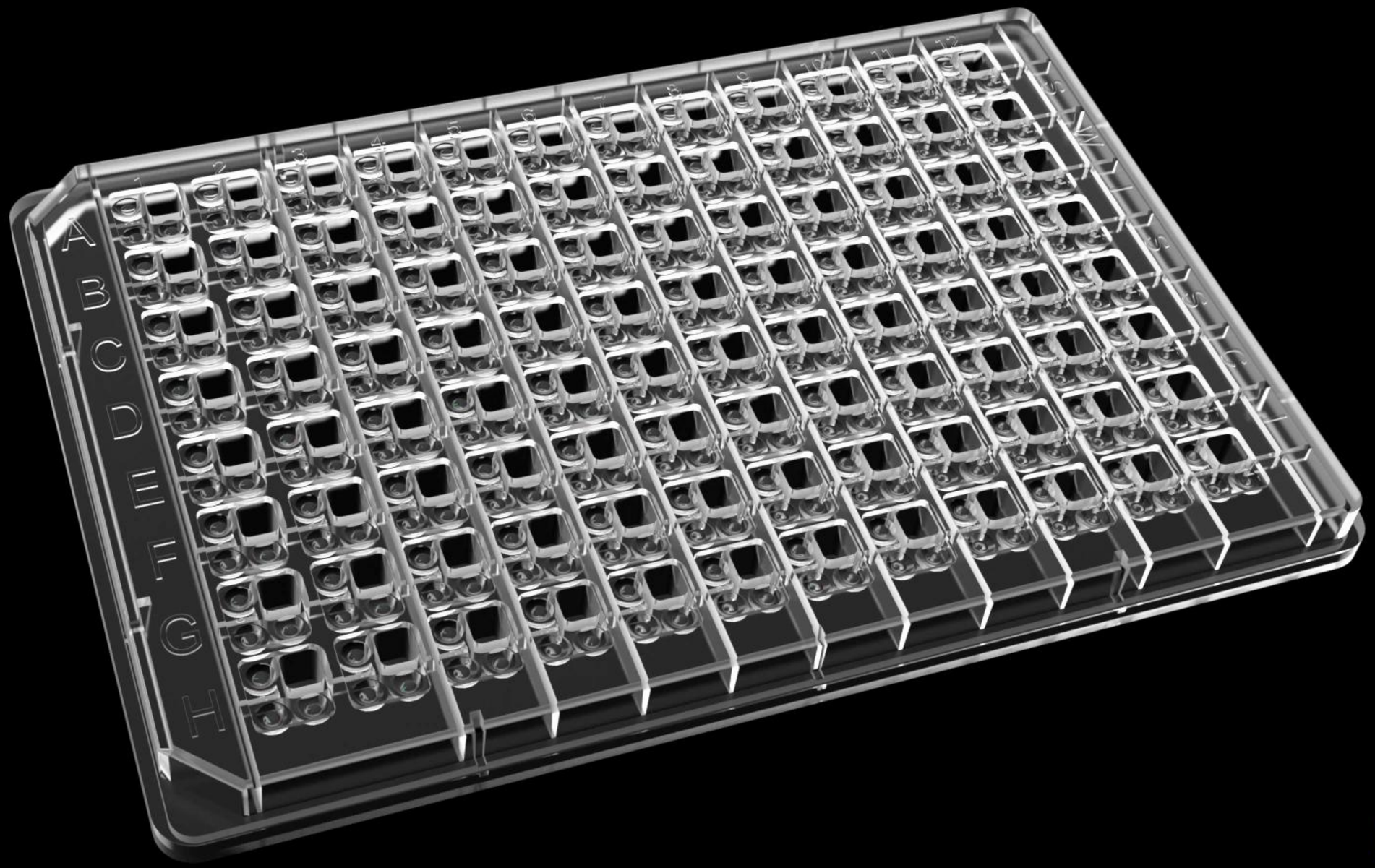


March 18

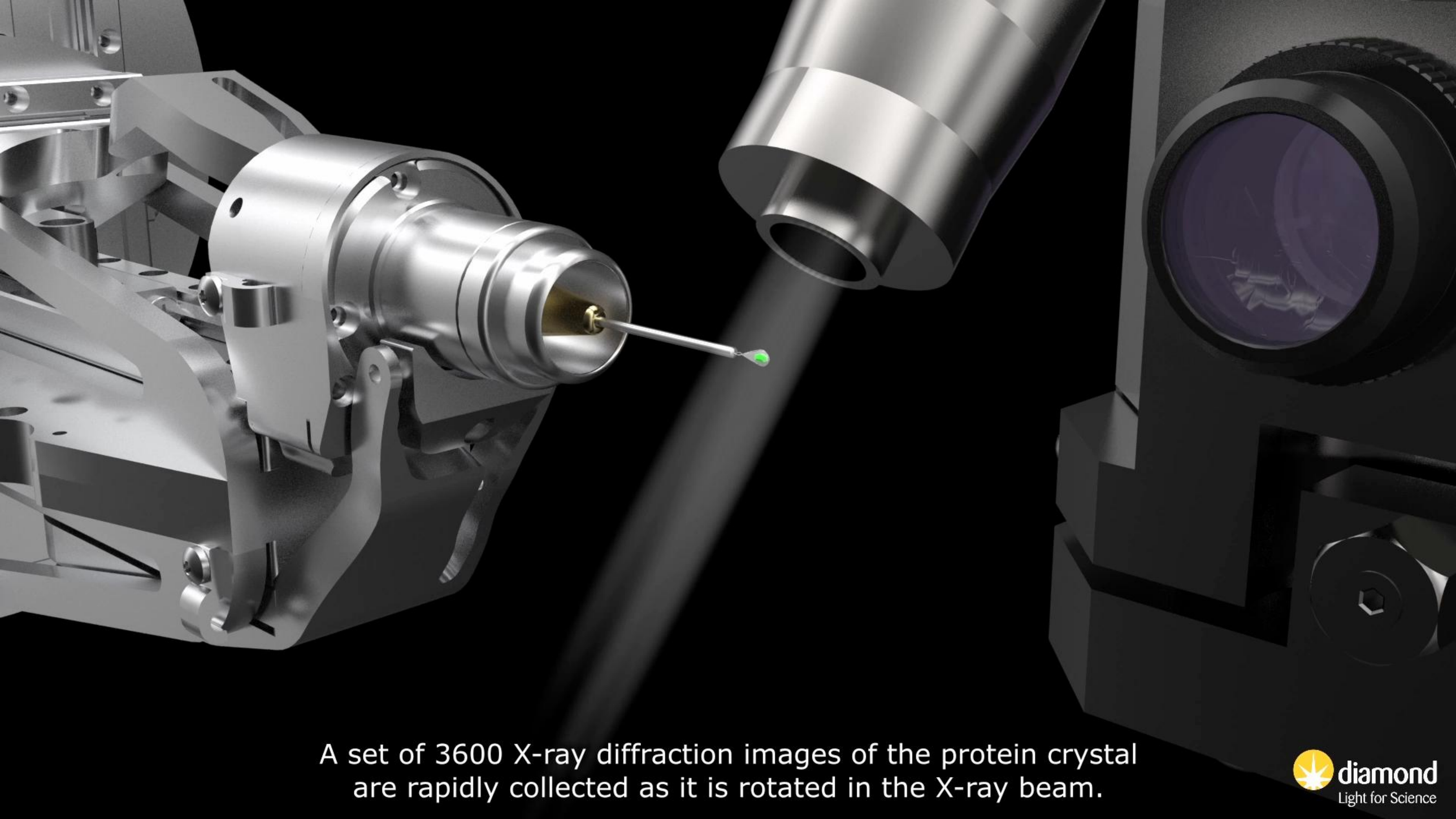
78 fragment-bound structures solved and released to the web

48 covalent fragments
71 active site fragments

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



diamond
Light for Science

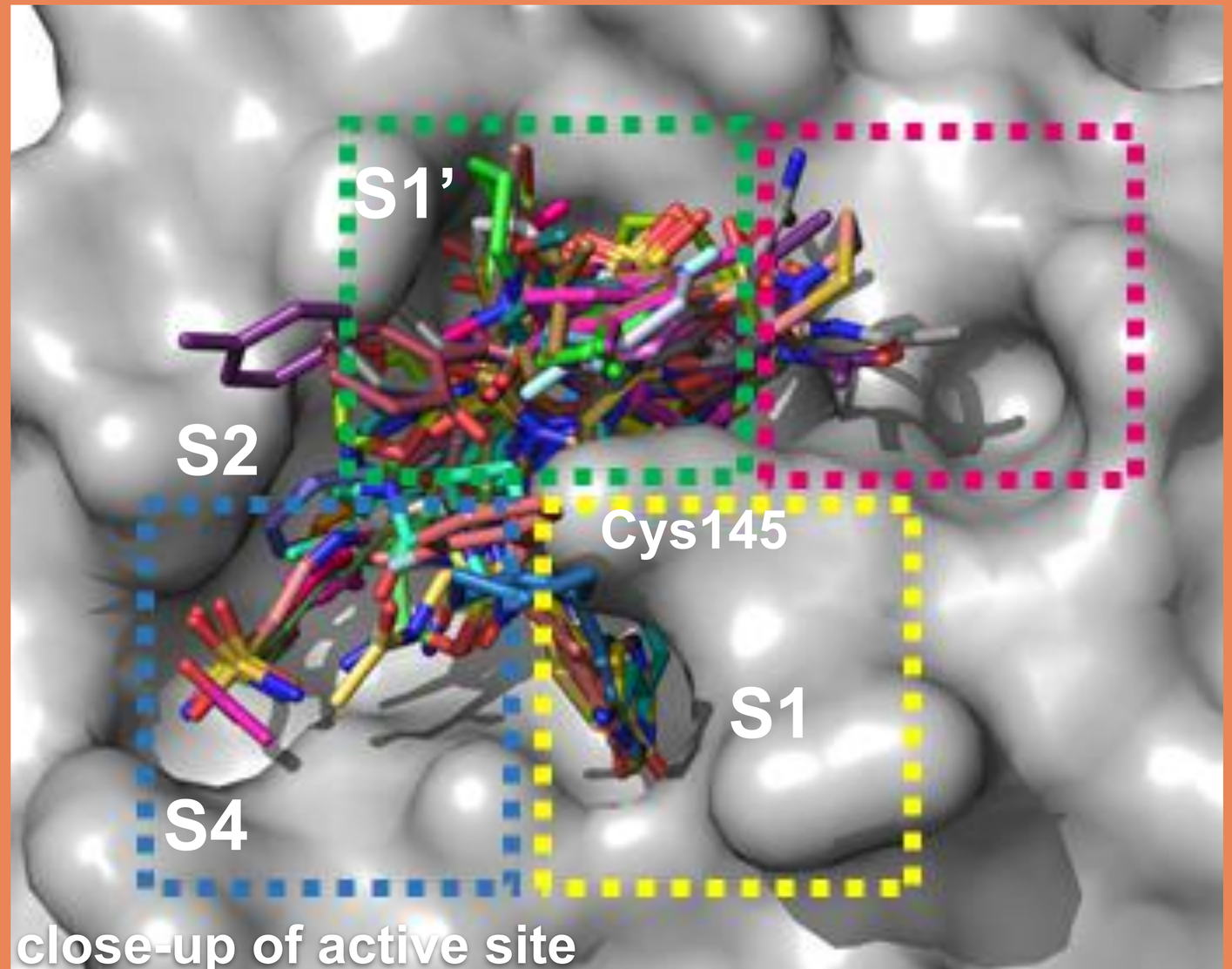


A set of 3600 X-ray diffraction images of the protein crystal are rapidly collected as it is rotated in the X-ray beam.

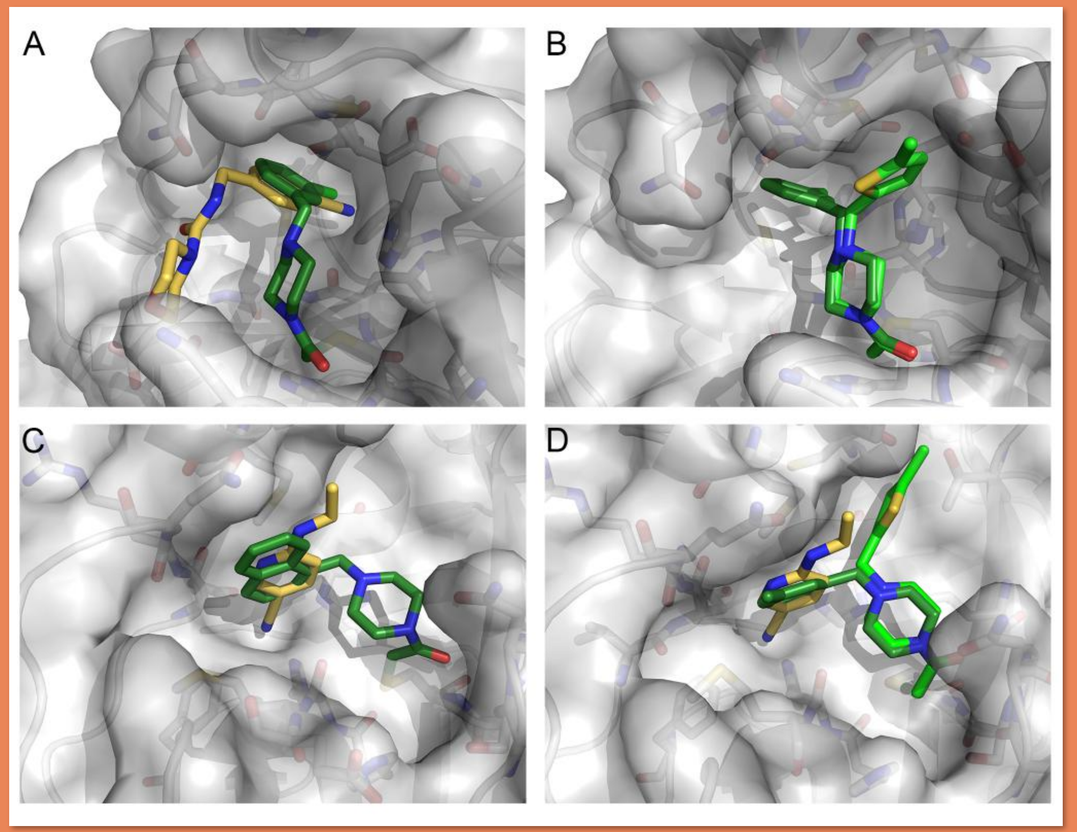
diamond
Light for Science

Fragment hits completely cover the active site

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



close-up of active site



Could we merge our way to potent lead compounds directly?

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

All data was immediately released online

diamond | Coronavirus Science

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

In This Section

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

Main protease structure and XChem fragment screen

Summary

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

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

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

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

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

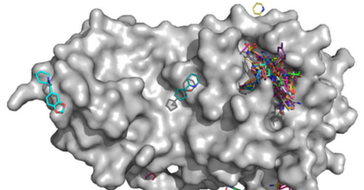
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

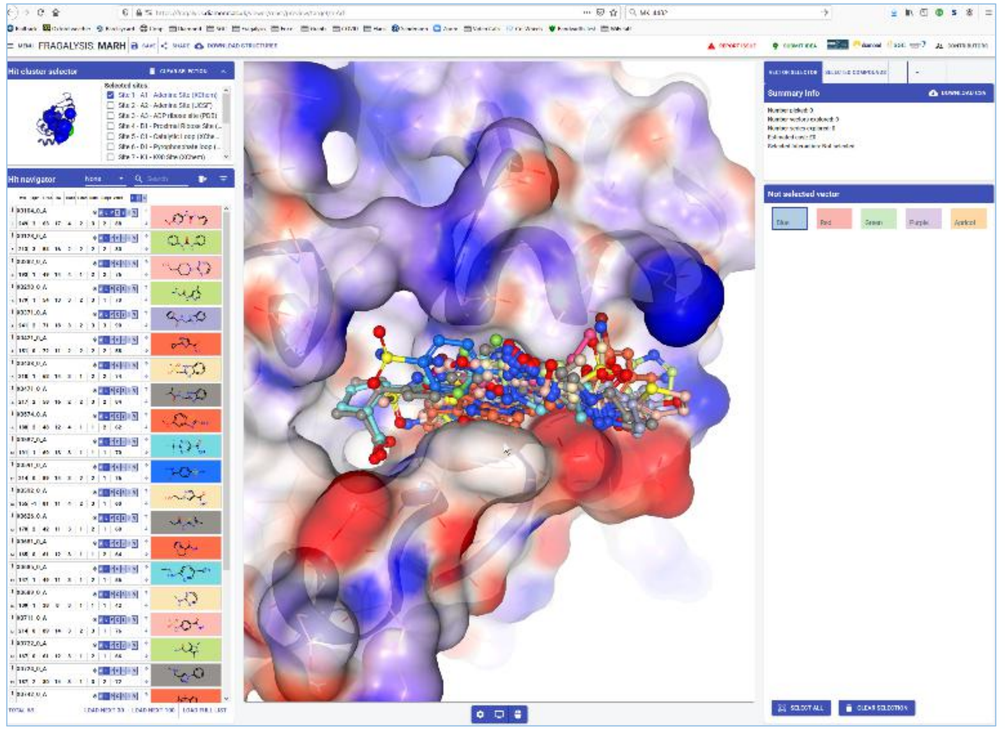
XChem fragment screen

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

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

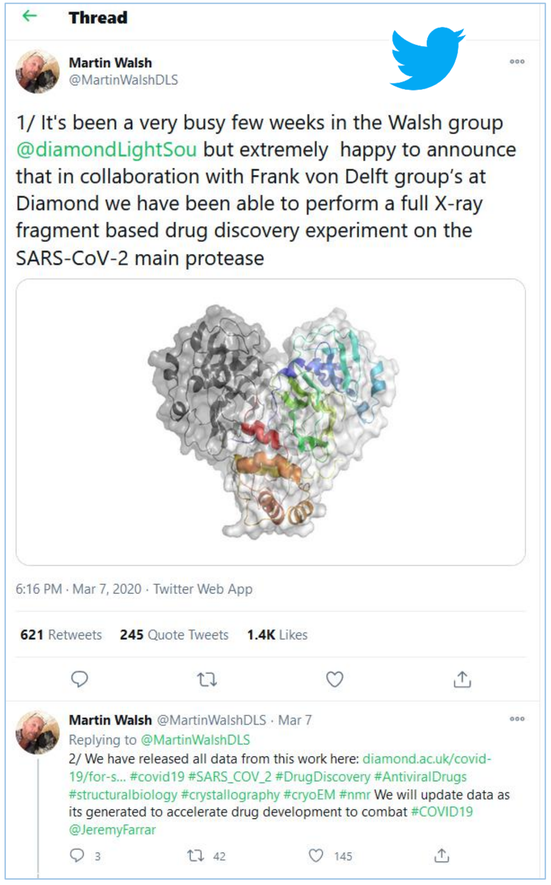
- 23 non-covalent hits in the active site
- 48 covalent hits in the active site
- 3 hits in the dimer interface, one in a calculated hotspot





https://fragalysis.diamond.ac.uk

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



COVID Moonshot

Centre for Medicines Discovery
University of Oxford

XCHEM Diamond Fragment Screening
diamond

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

Nir London
Weizmann Institute

What if we tried ALL OF THEM?

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

Alpha Lee
Cambridge/PostEra

COVID Moonshot

Design a Compound, We Will Make It

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

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

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

SMILES | Add

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

Contact Information

Name* | Email* | Affiliation

Background

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

http://postera.ai/covid

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

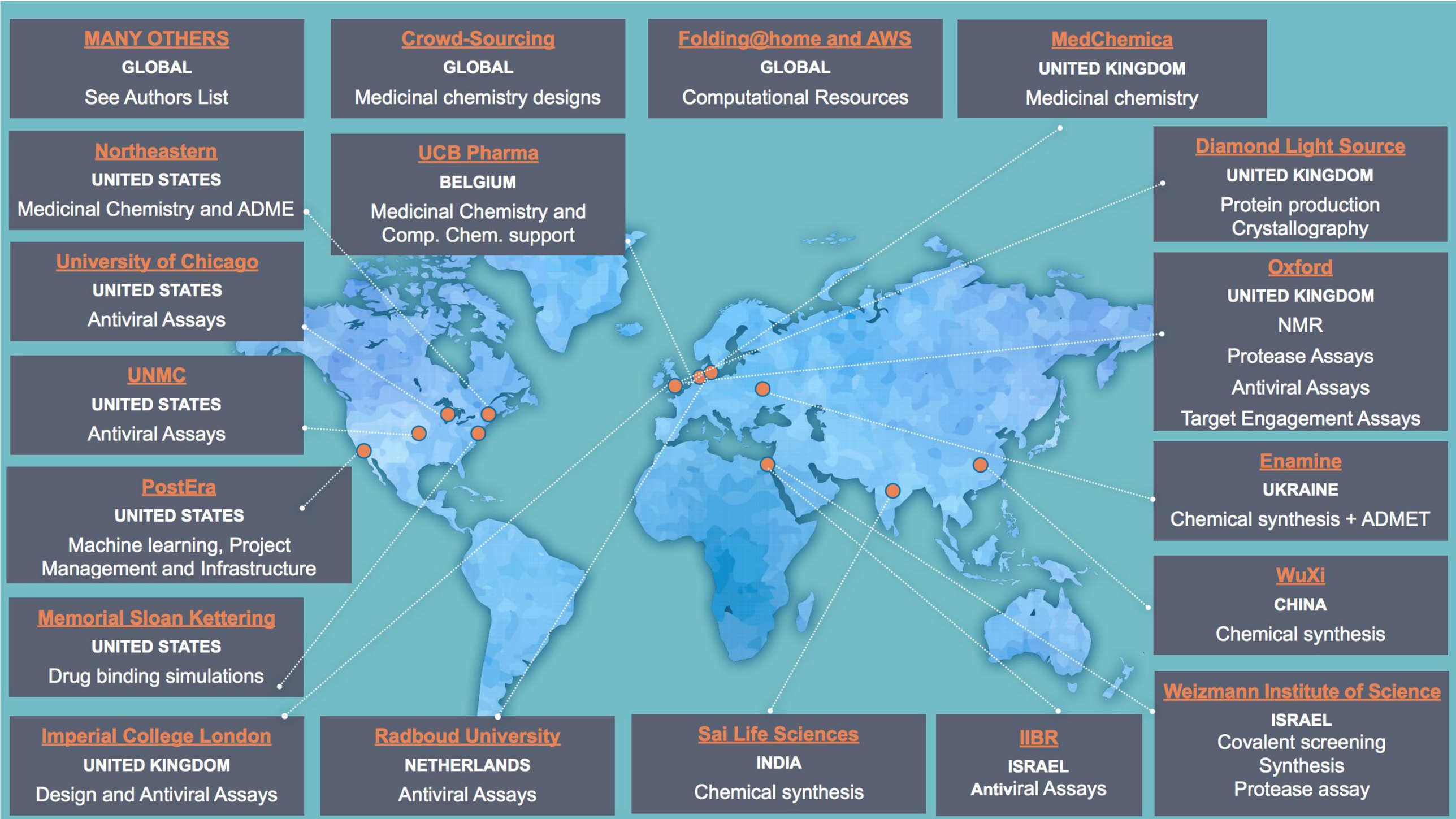
Open science

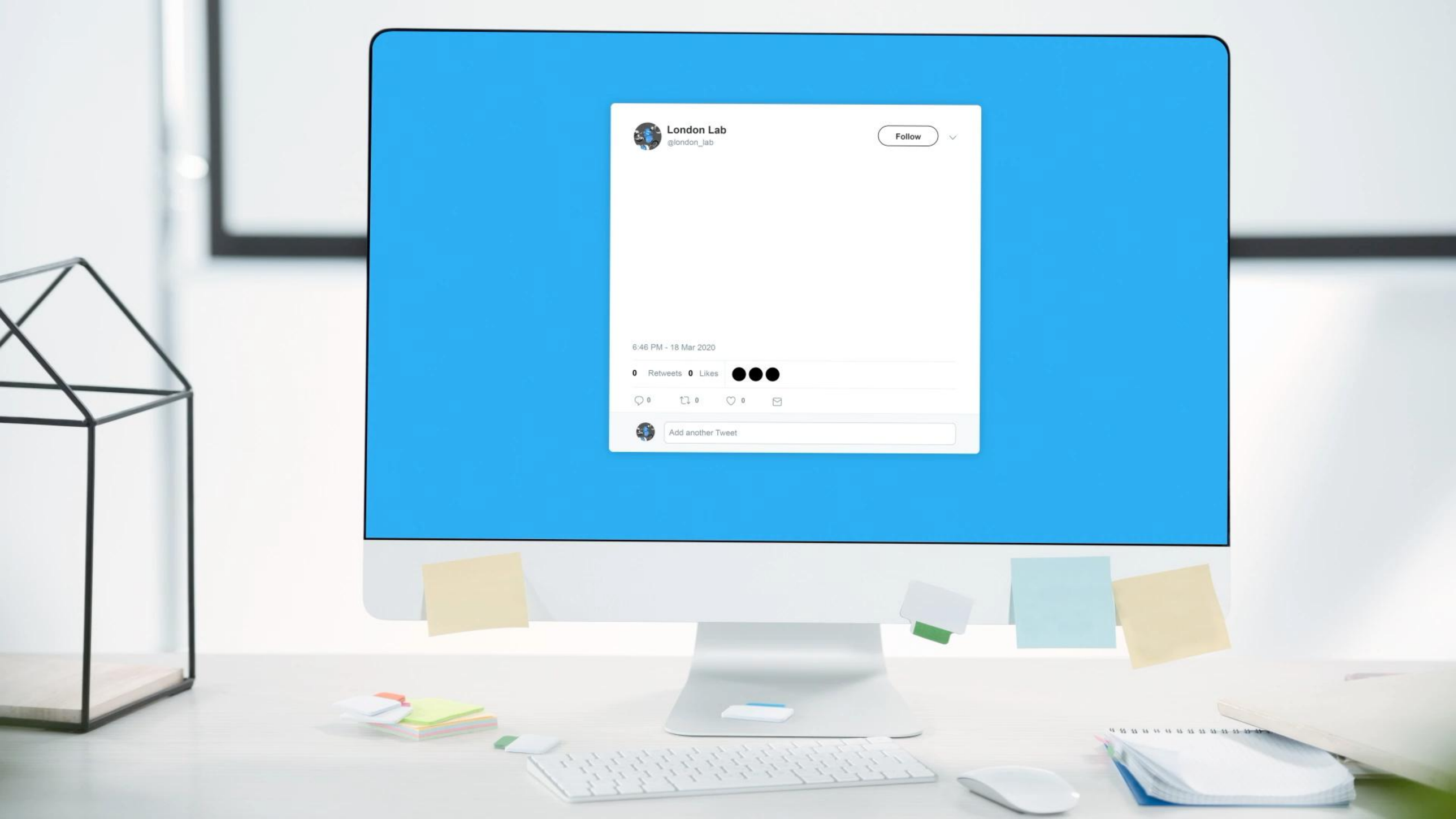
COVID Moonshot

Open data

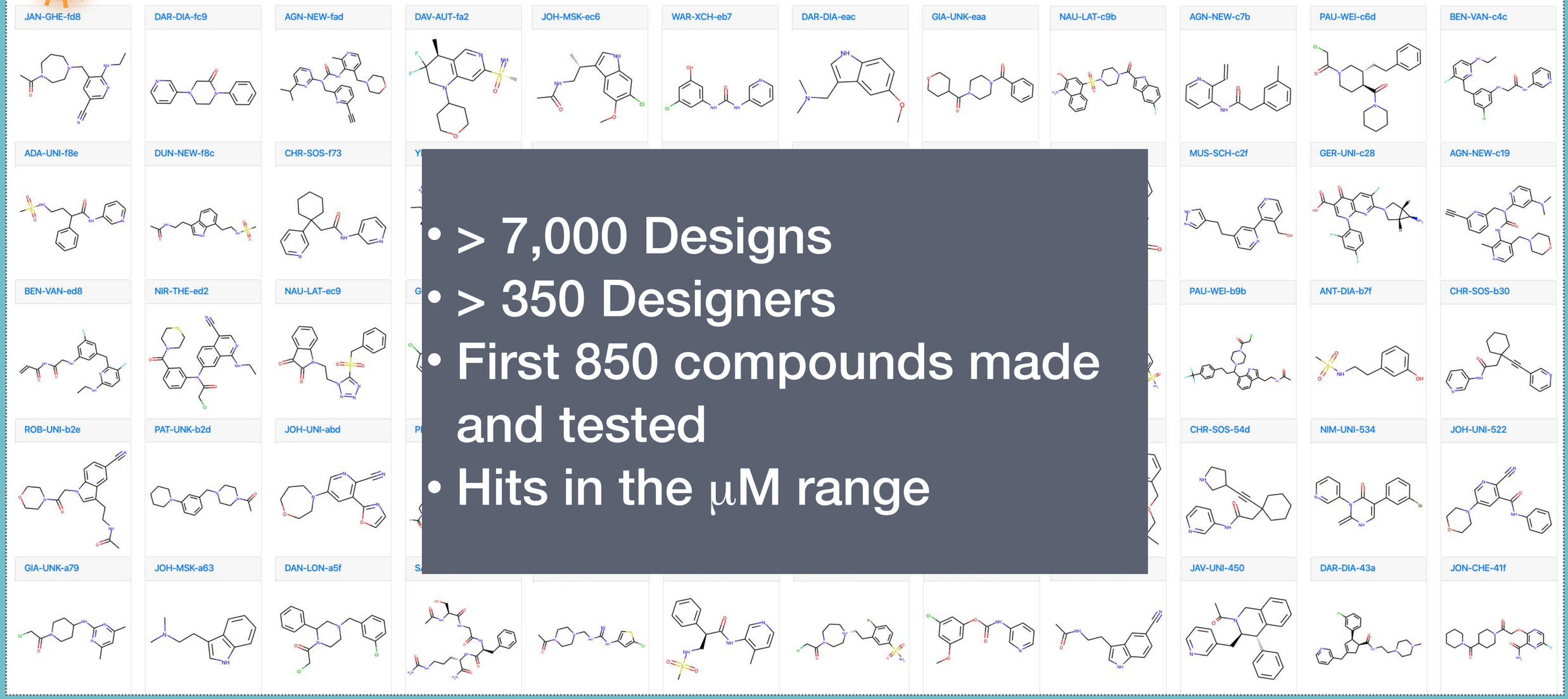
http://postera.ai/covid

Patent-free


MANY OTHERS
GLOBAL
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

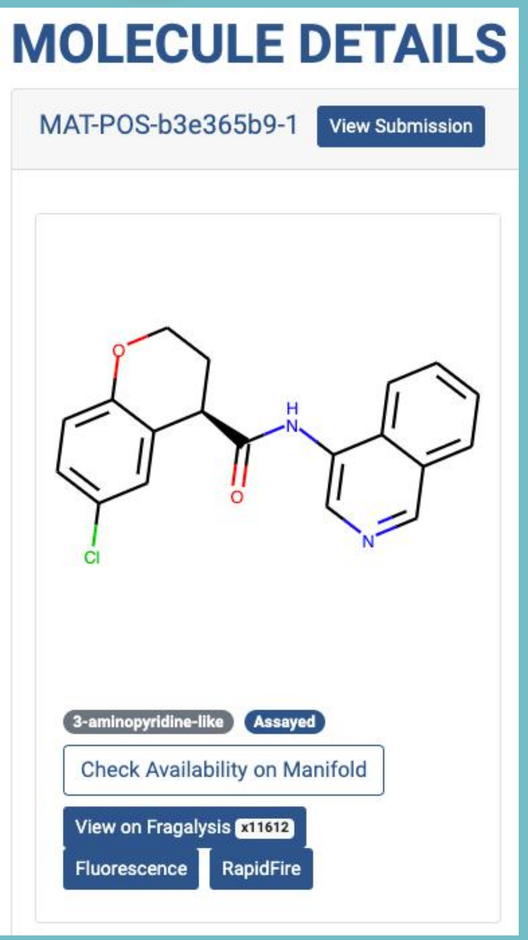

London Lab
@london_lab
Follow
6:46 PM - 18 Mar 2020
0 Retweets 0 Likes
Add another Tweet

…and there was overwhelming response

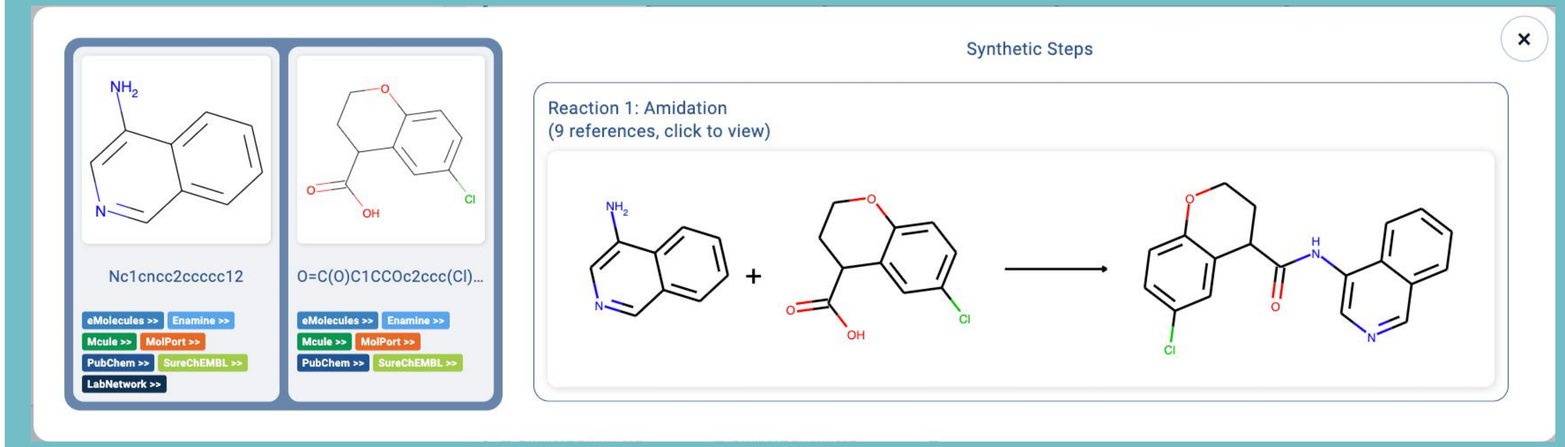


- > 7,000 Designs
- > 350 Designers
- First 850 compounds made and tested
- Hits in the μM range

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!

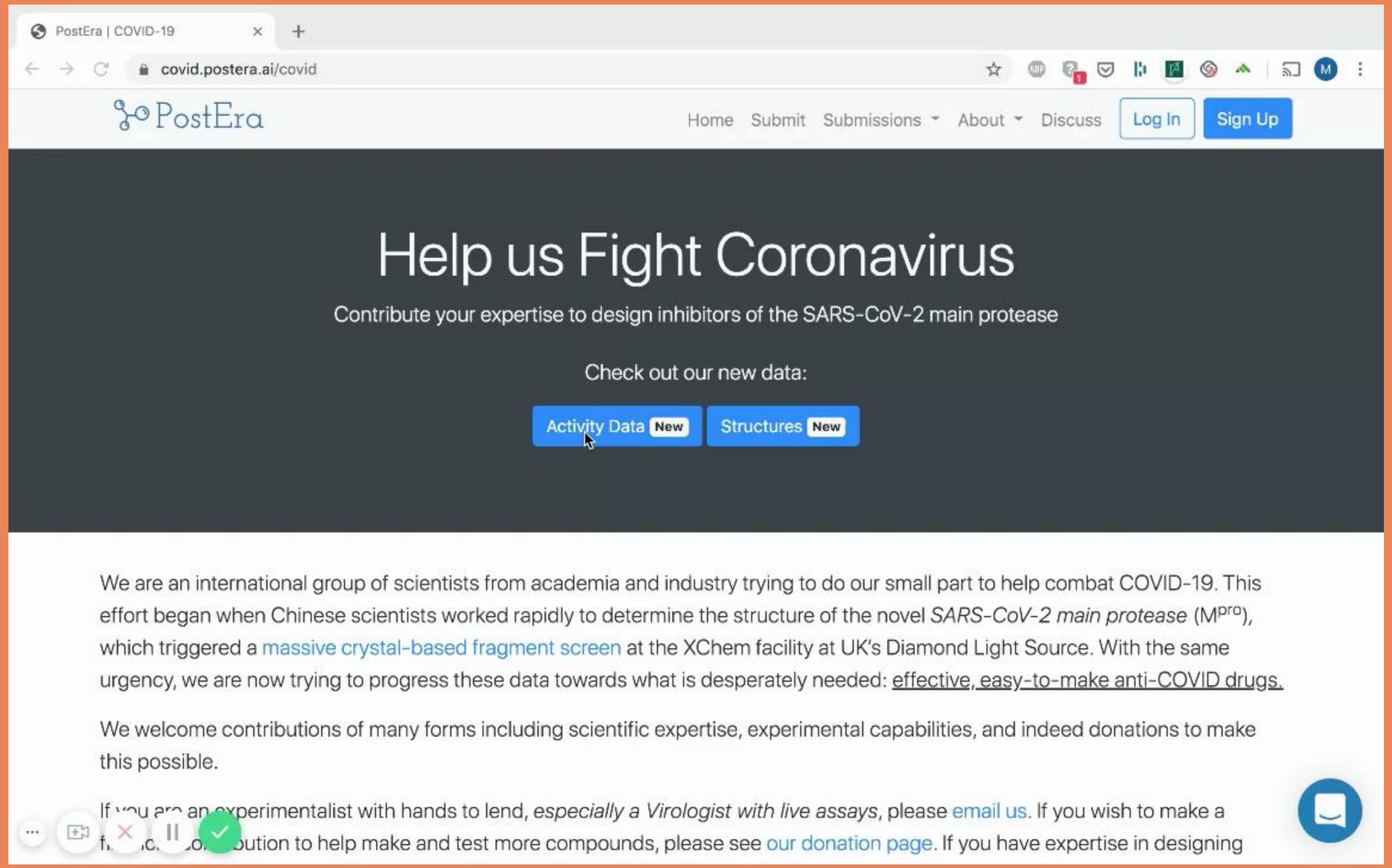
http://postera.ai/covid

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

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

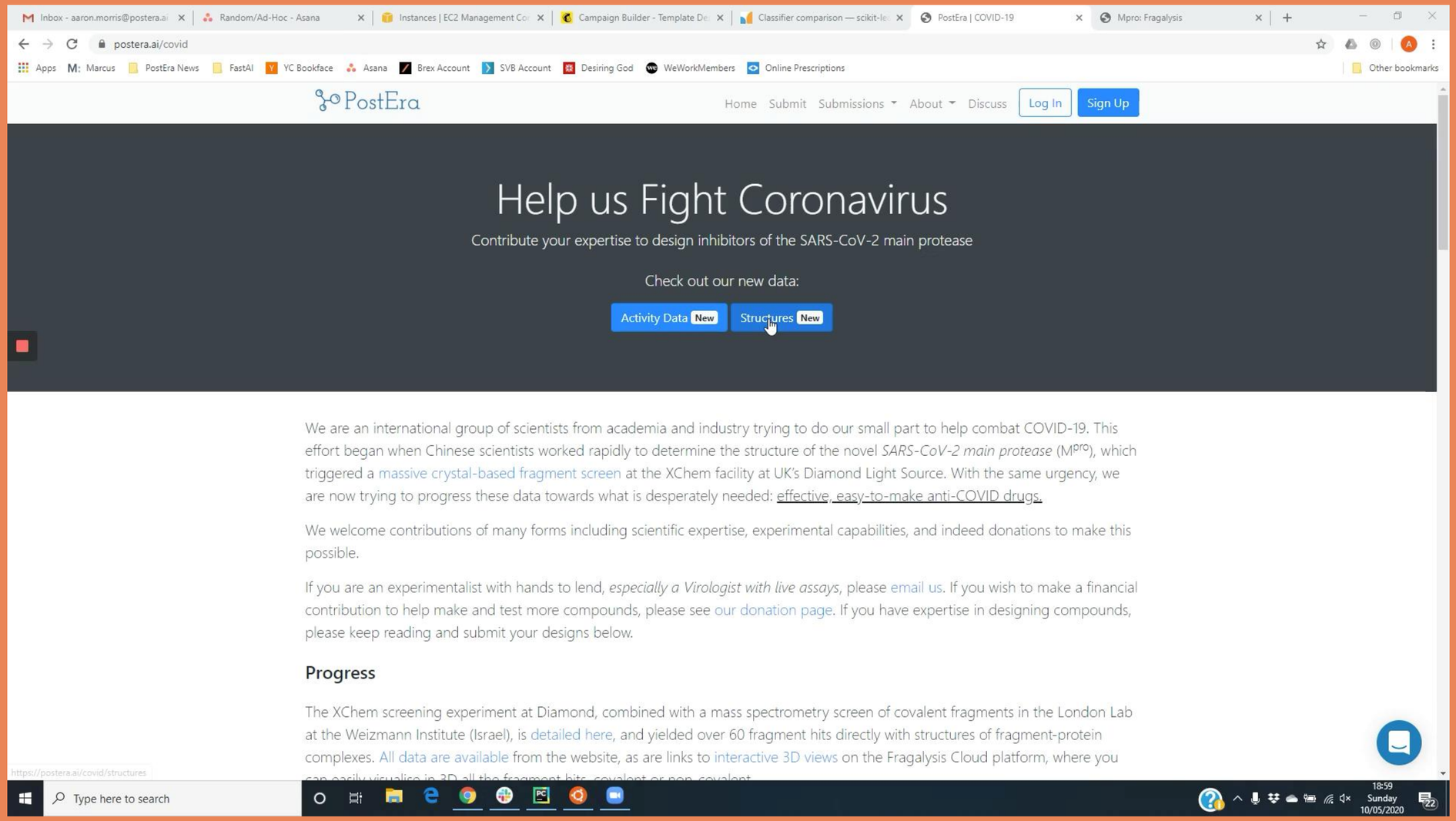
Nir London
Weizmann Institute

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



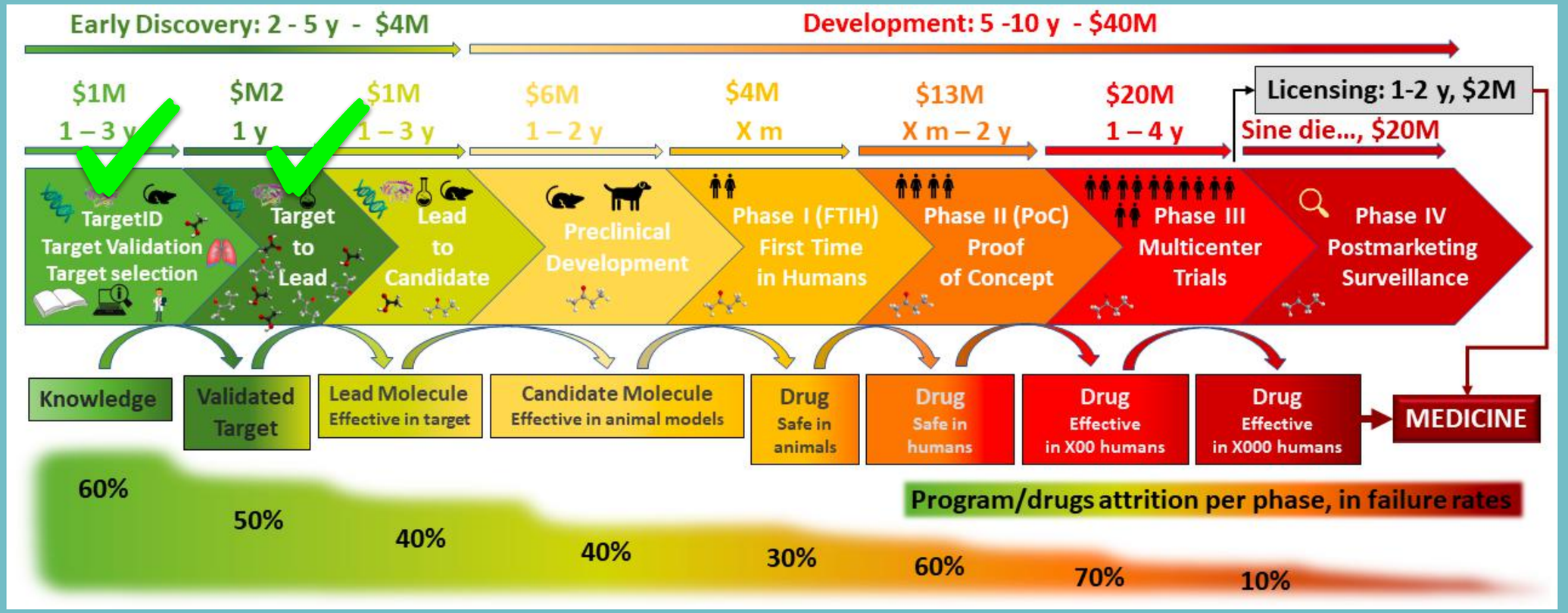
http://postera.ai/covid

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



http://postera.ai/covid

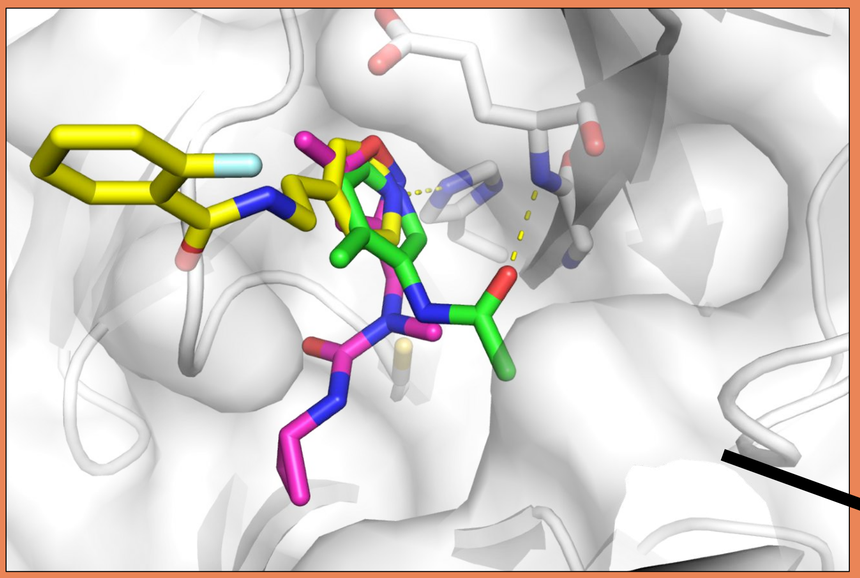
Drug discovery is usually a long and expensive process

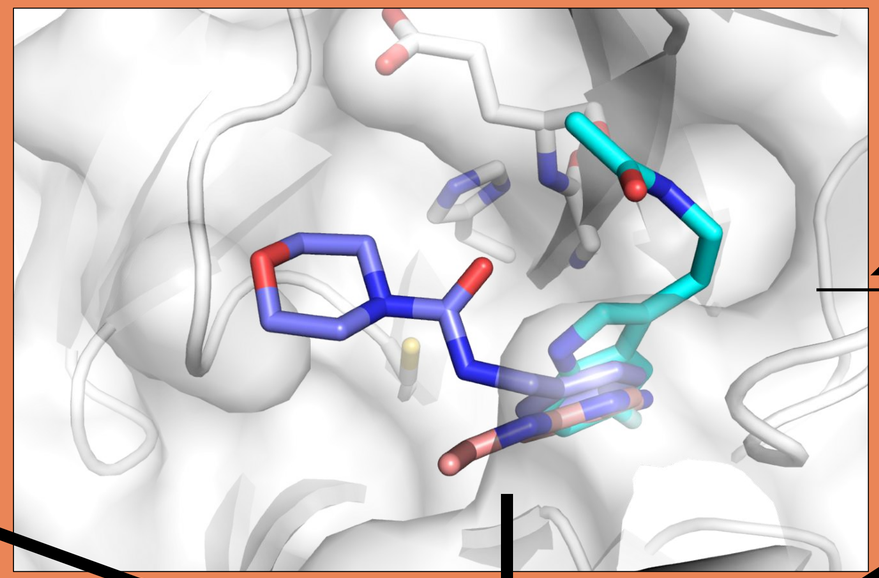


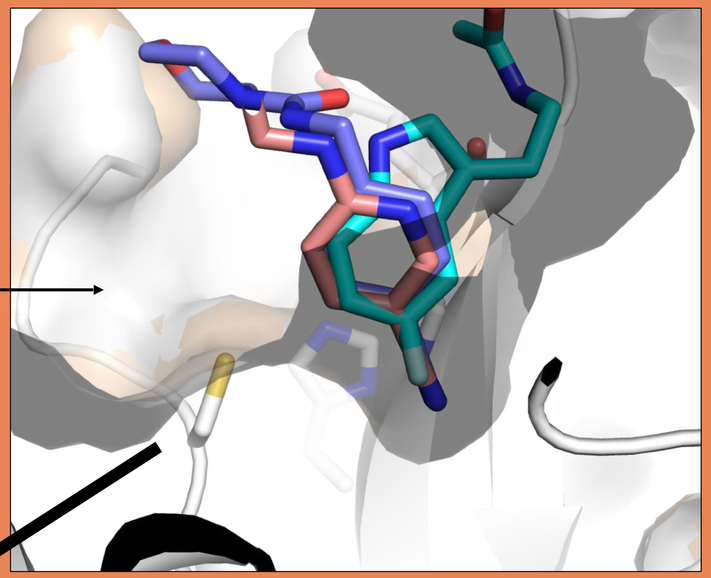
https://doctortarget.com/machine-learning-applied-drug-discovery/

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

Crowdsourcing generated a number of novel chemical series by fragment merging





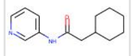


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

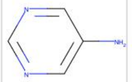
Design Rationale:

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

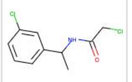
Inspired By:



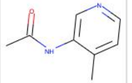
ALE-HEI-f28a35b5-9



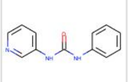
AAR-POS-d2a4d1df-18



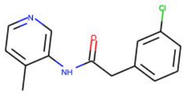
AAR-POS-0daf6b7e-10



MAK-UNK-6435e6c2-8



AAR-POS-d2a4d1df-11



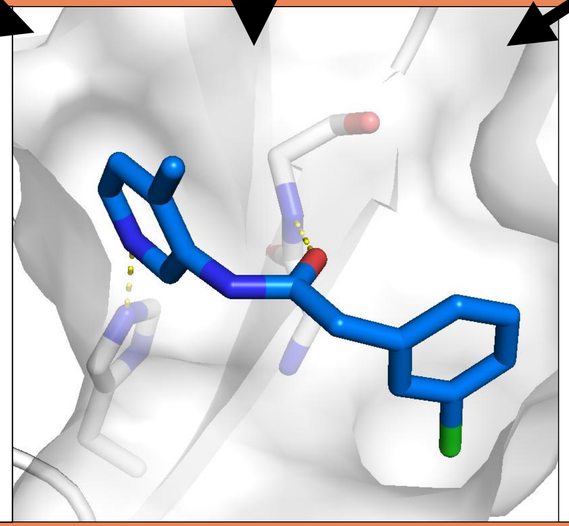
TRY-UNI-714a760b-6

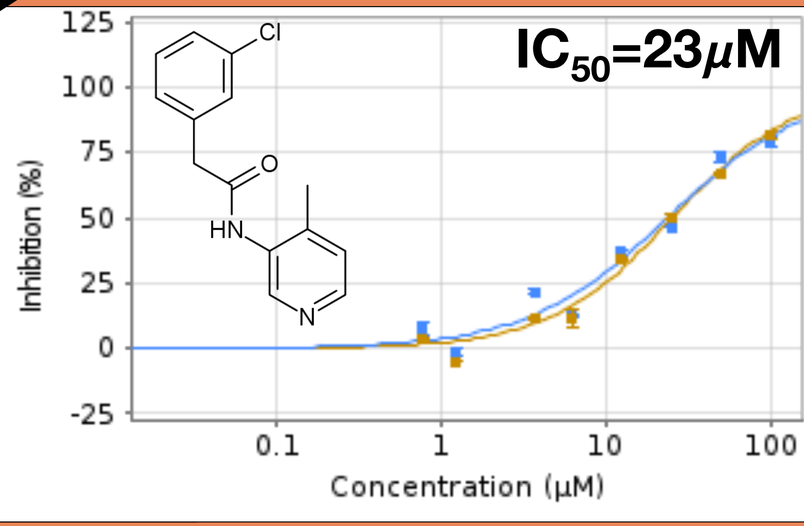
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

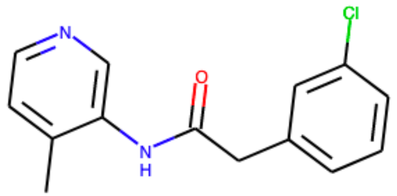
Enamine Mcule MolPort Assayed

View

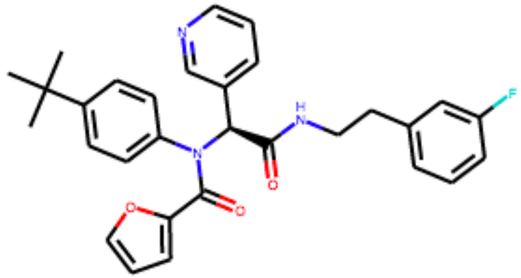




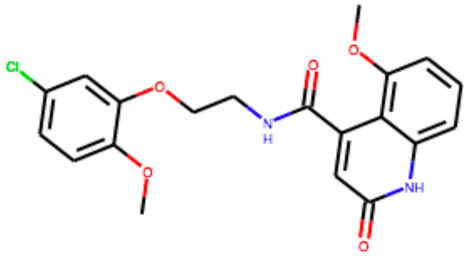
Crowdsourcing yielded multiple lead series



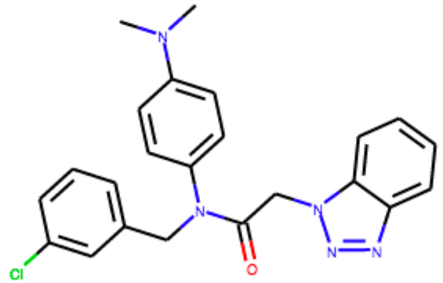
3-aminopyridines



Ugis



quinolones

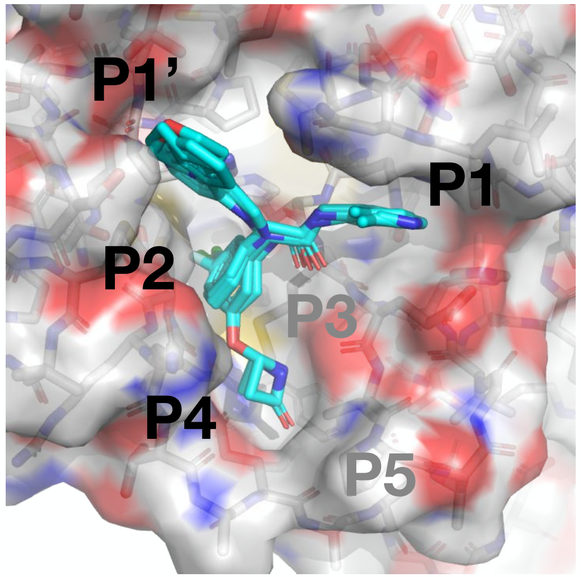


benzotriazoles

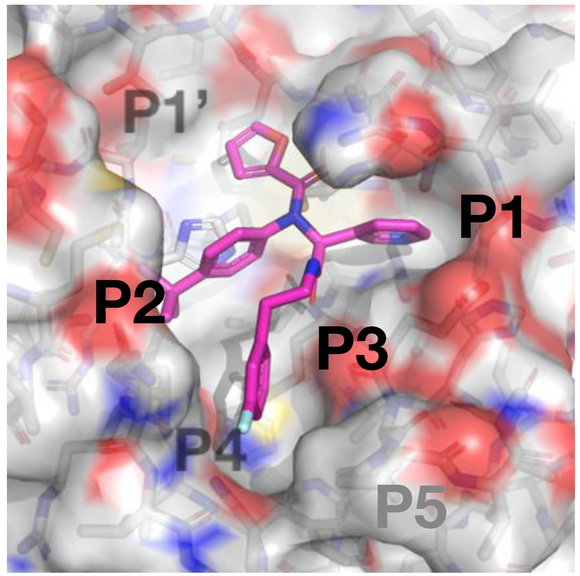
http://postera.ai/covid

[As of 16 Mar 2021]

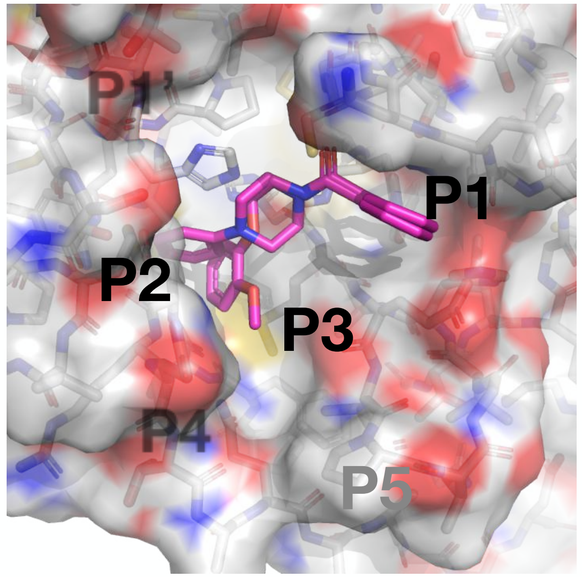
Crowdsourcing yielded multiple lead series



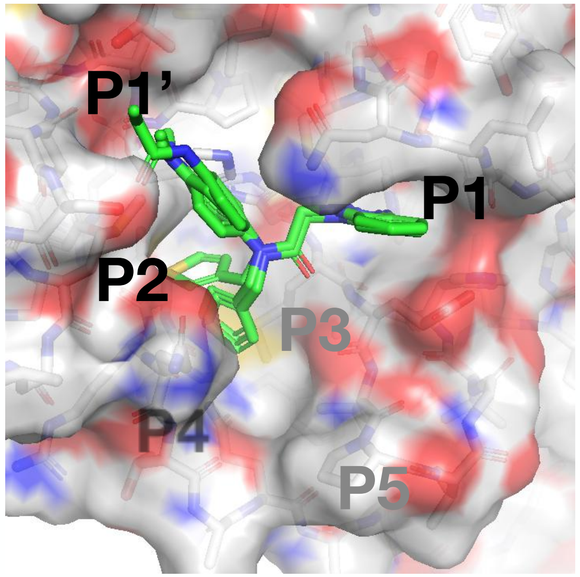
3-aminopyridines



Ugis



quinolones



benzotriazoles

http://postera.ai/covid

[As of 16 Mar 2021]

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

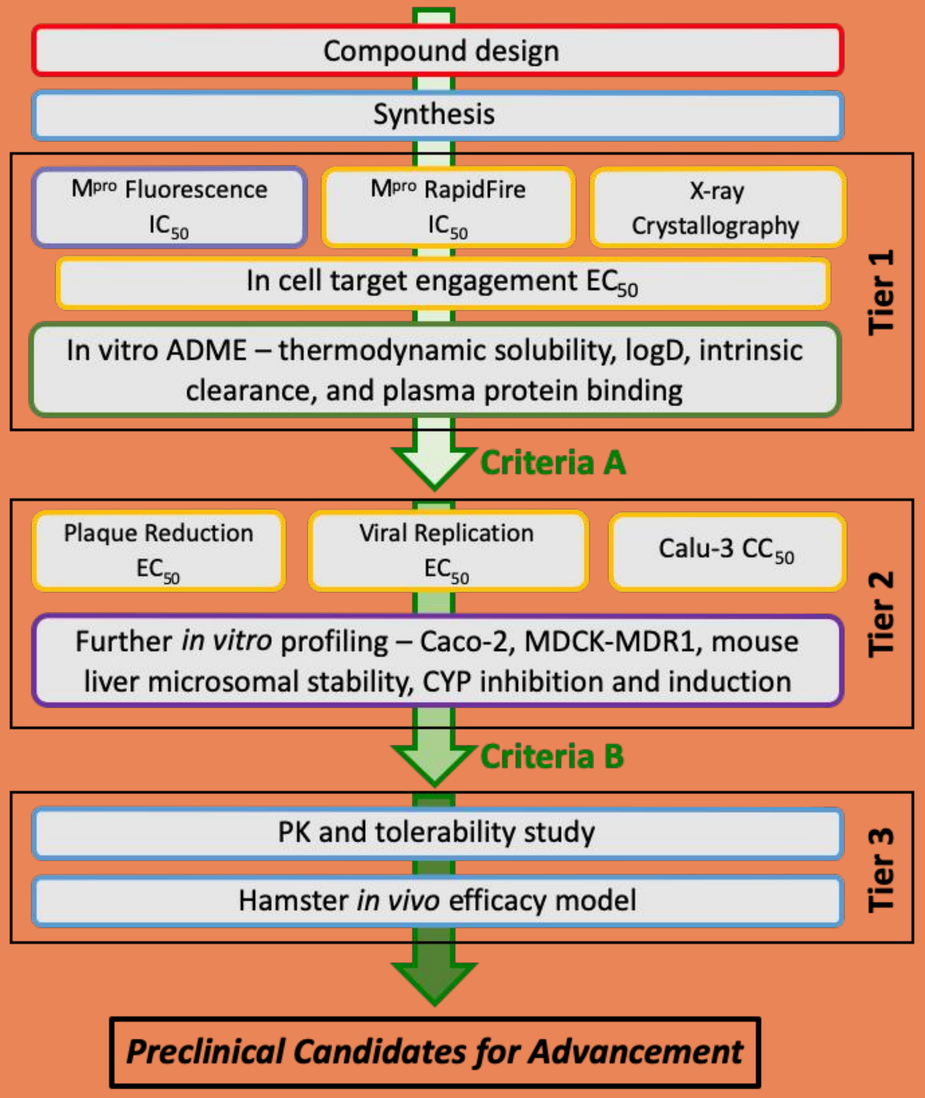
COVID Moonshot

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?

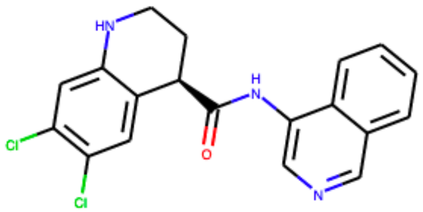
Does it have a favorable safety profile?

Is it orally bioavailable at required concentrations?

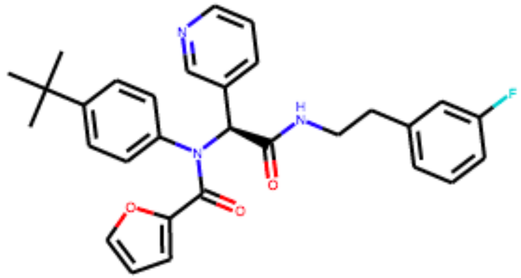
Assay components donated by groups and CROs around the world

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

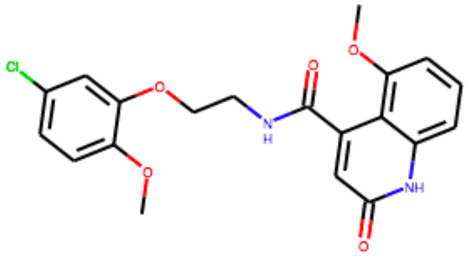
Ed Griffen
Medchemica



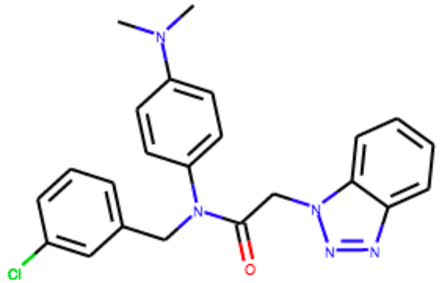
3-aminopyridines
948 compounds
(primary series)



Ugis
403 compounds
(backup series)



quinolones
86 compounds
(backup series)



benzotriazoles
42 compounds
(backup series)

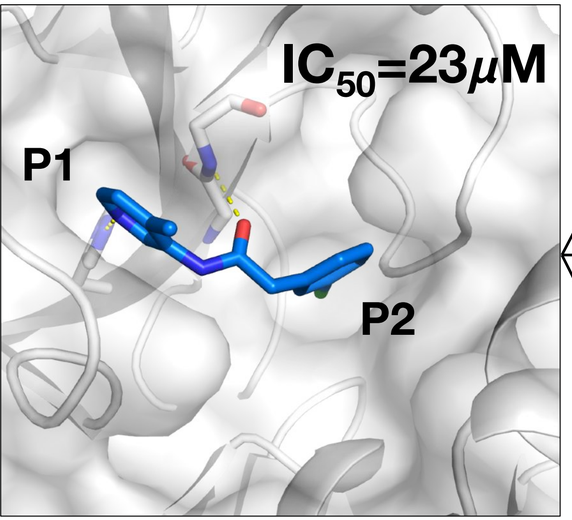
258 X-ray structures (and rapidly growing)
>25% of all SARS-CoV-2 structures!

http://postera.ai/covid

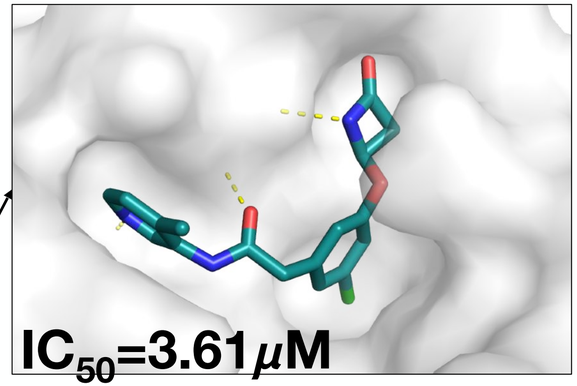
[As of 16 Mar 2021]

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

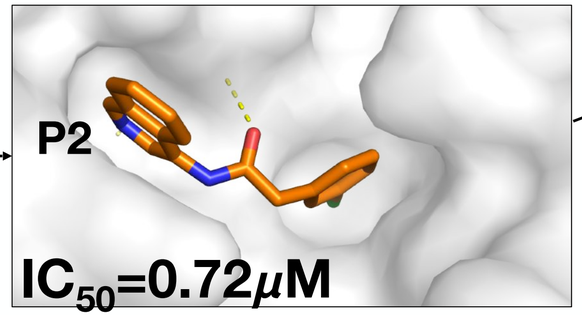
>300 aminopyridine compounds synthesized



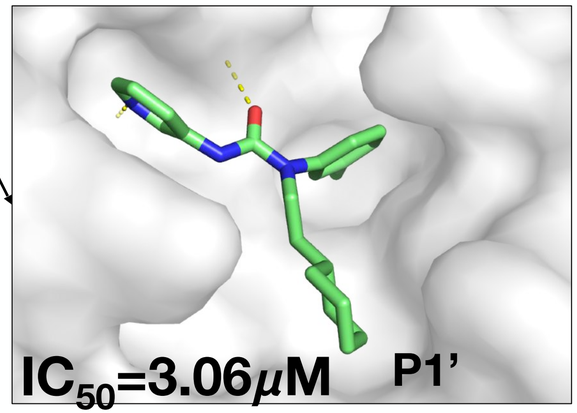
6.4x



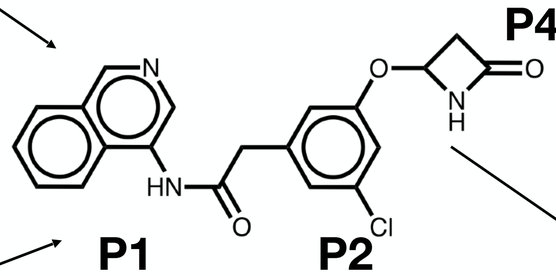
32x

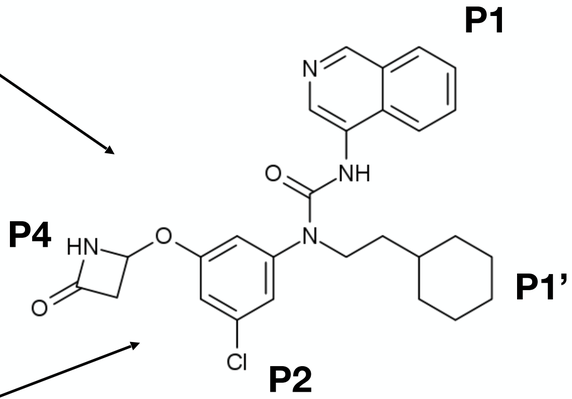


7.5x

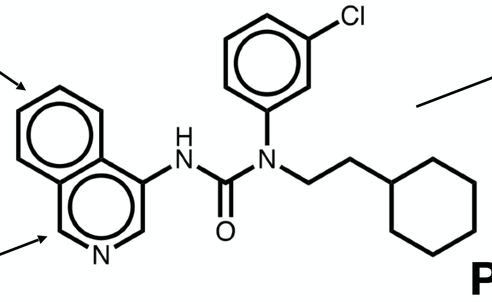


IC_{50}=260 nM





IC_{50}= 105 nM



IC_{50}=270 nM

http://postera.ai/covid