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

THE COVID MOONSHOT: AN OPEN SCIENCE COLLABORATION TO DEVELOP AN ORALLY BIOAVAILABLE INHIBITOR OF THE SARS-COV-2 MAIN VIRAL PROTEASE

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

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

16 July 2023 - CADD GRC - Mount Snow, VT


EAGLE GT
GOODYEAR
EAGLE GT
GOODYEAR

25 FEB 2020

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

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

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


By Pam Belluck and Noah Weiland

Published Feb. 25, 2020 Updated March 9, 2020

One month later...

26 MAR 2020

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

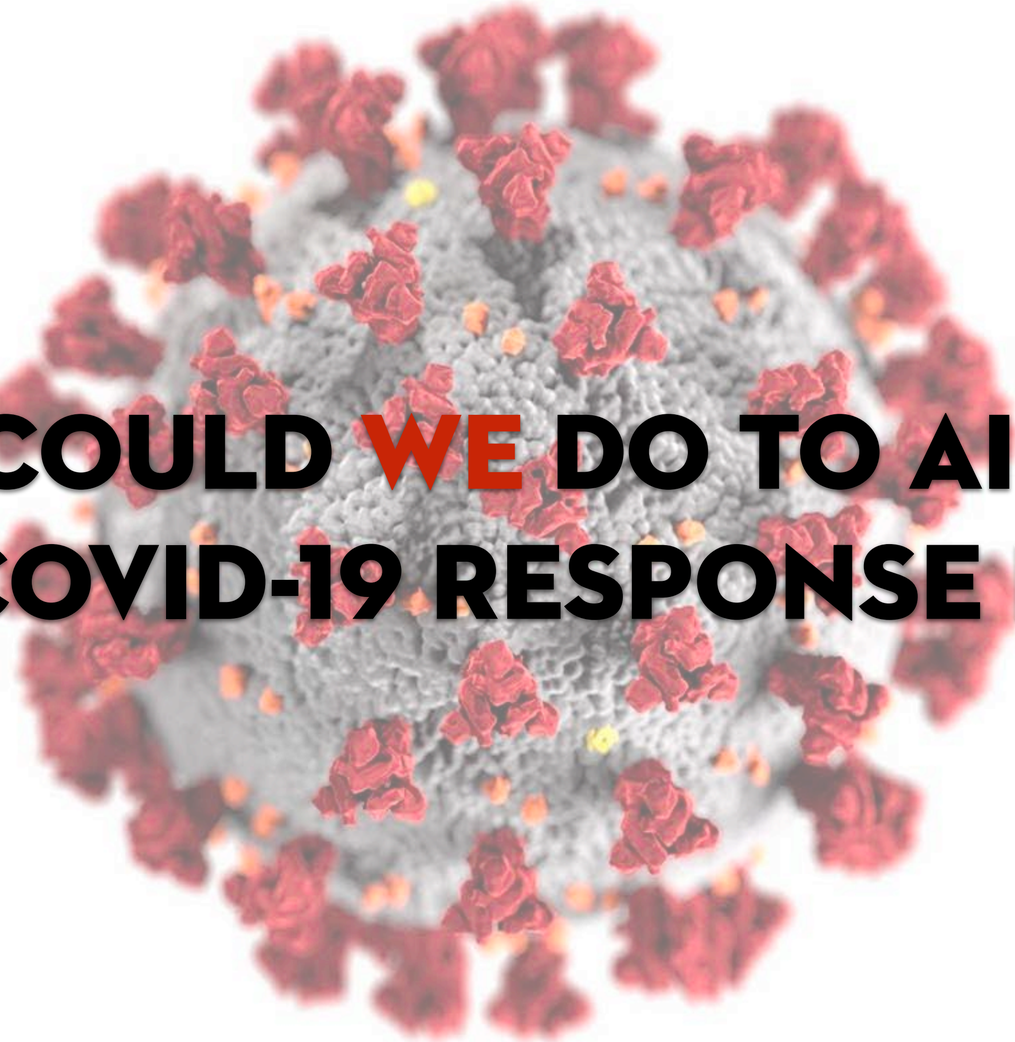
Following a series of missteps, the nation is now the epicenter of the pandemic.

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

By Donald G. McNeil Jr.

Published March 26, 2020 Updated May 28, 2020

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



WHAT COULD WE DO TO AID THE GLOBAL COVID-19 RESPONSE EFFORT?

WE HOPED VACCINES WERE COMING, BUT KNEW THAT ORAL ANTIVIRALS WOULD BE NEEDED

Vaccines would need complete safety if vaccinating ~100% of the public.

Achieving ~100% vaccine uptake is difficult; a drug can be used by those who get sick

An antiviral could avoid resistance seen in vaccines that target highly variable spike

A oral pill without cold storage requirements is much easier to distribute globally

Safe oral antivirals could protect at-risk patients when other options aren't available

THE SARS-COV-2 GENOME WAS PUBLISHED 24 JAN 2020

The NEW ENGLAND JOURNAL of MEDICINE

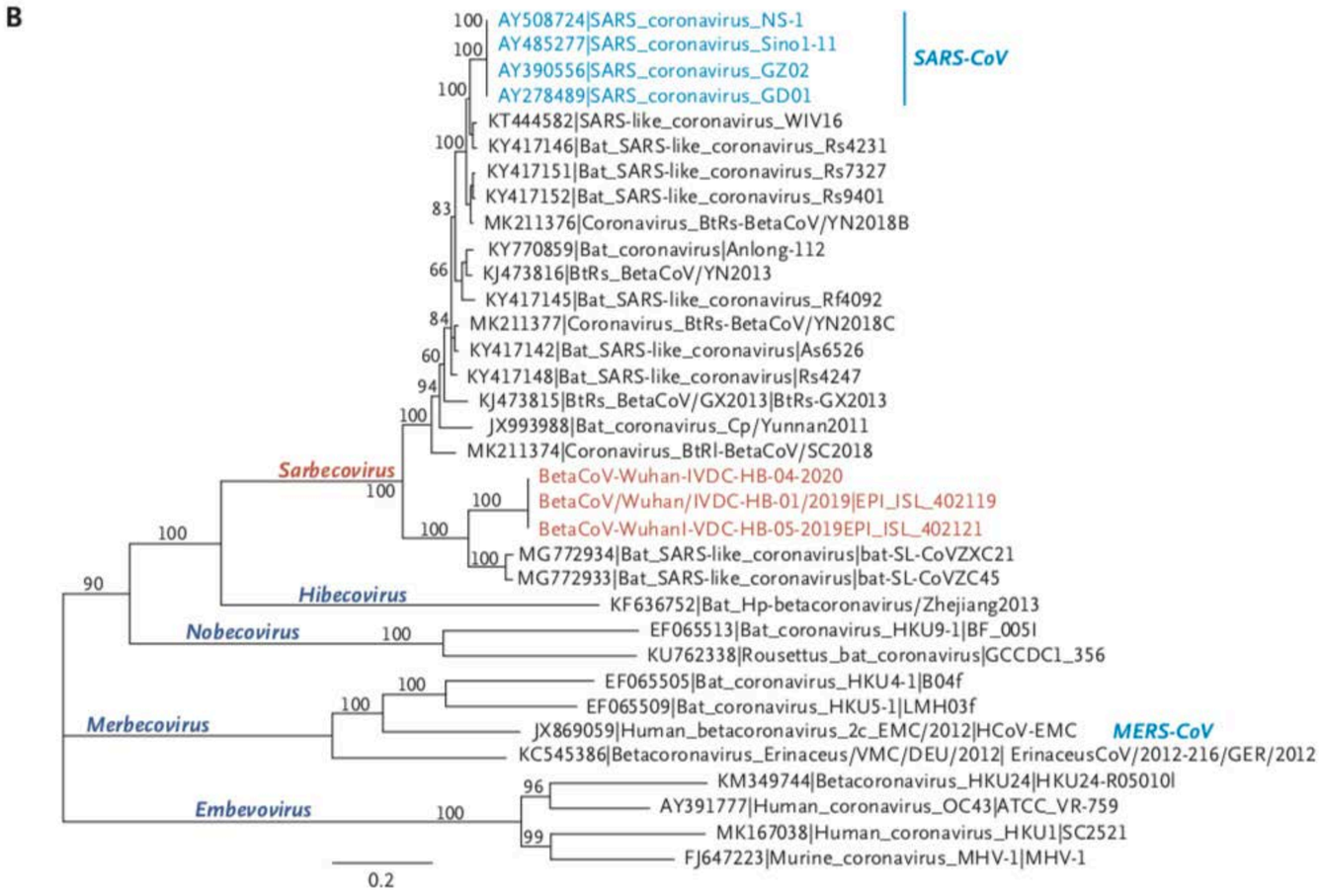
BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

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

SUMMARY

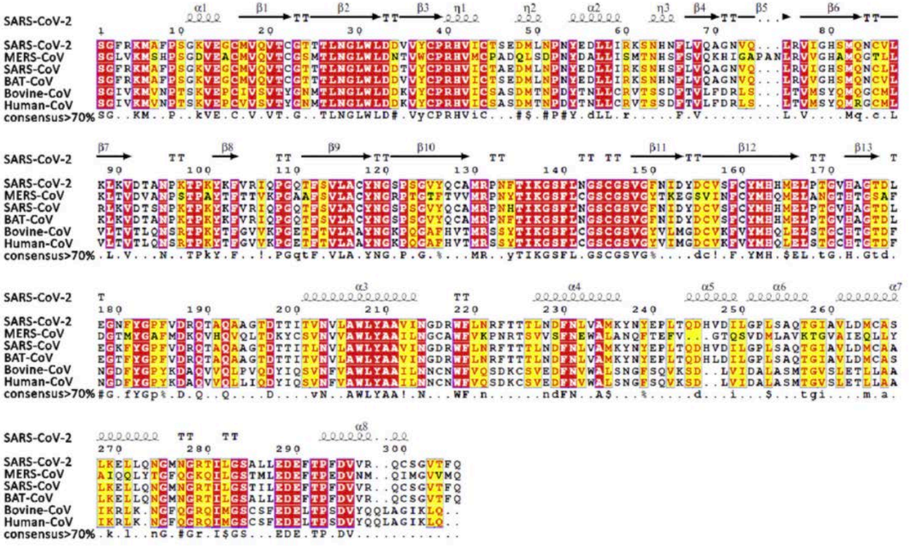
In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used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



The new virus was strikingly similar to viruses responsible for the SARS and MERS outbreaks

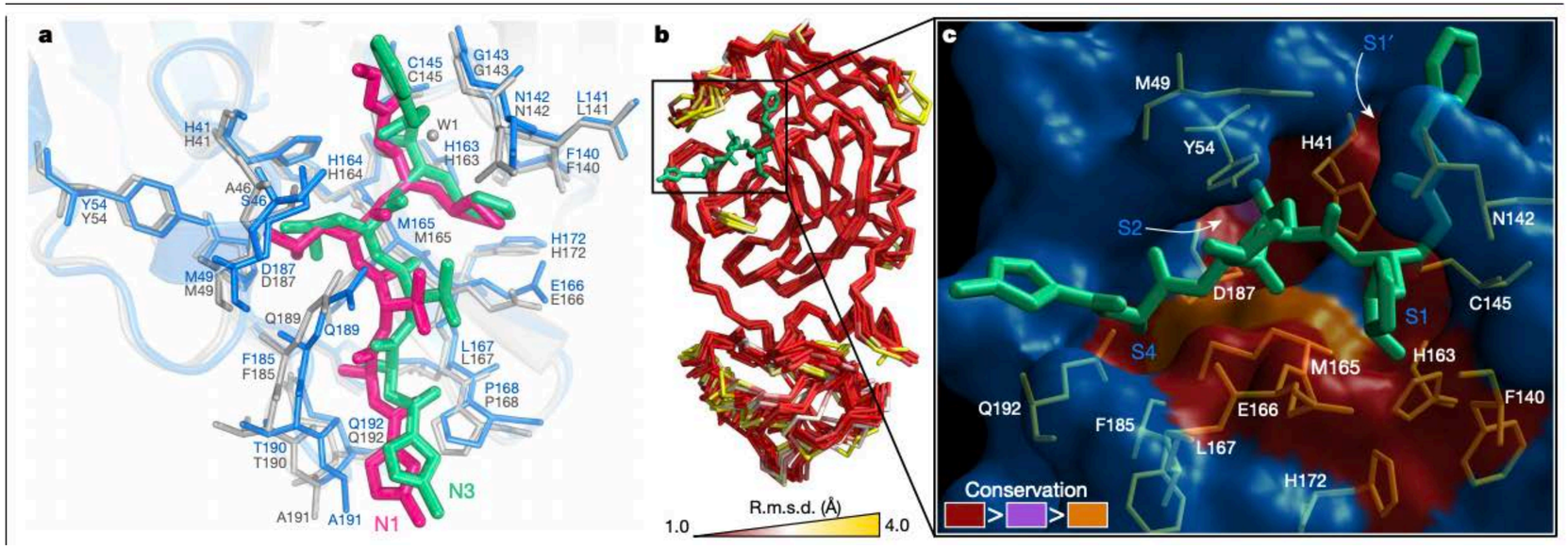
THE MAIN VIRAL PROTEASE (MPRO) IS HIGHLY CONSERVED BETWEEN SARS-COV, MERS-COV, AND SARS-COV-2

sequence (24 Jan 2020)



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

structure (PDB structure released 5 Feb 2020)



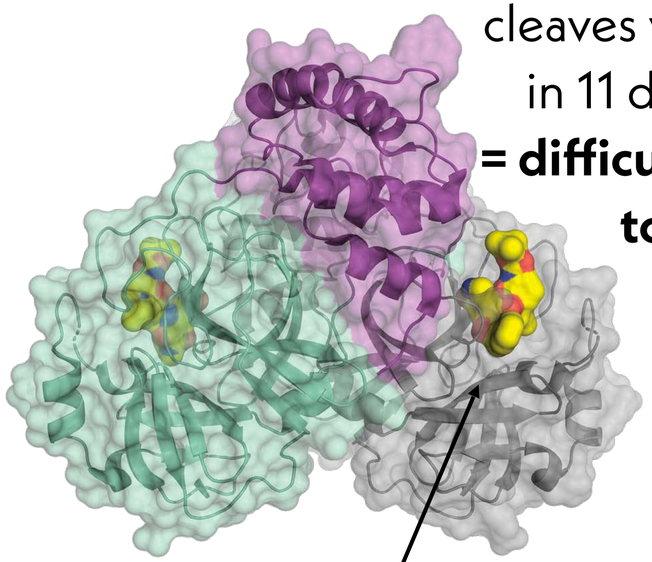
Jin et al. Nature 582:289, 2020
doi:10.1038/s41586-020-2223-y

Could the main viral protease be a viable drug target for COVID-19?

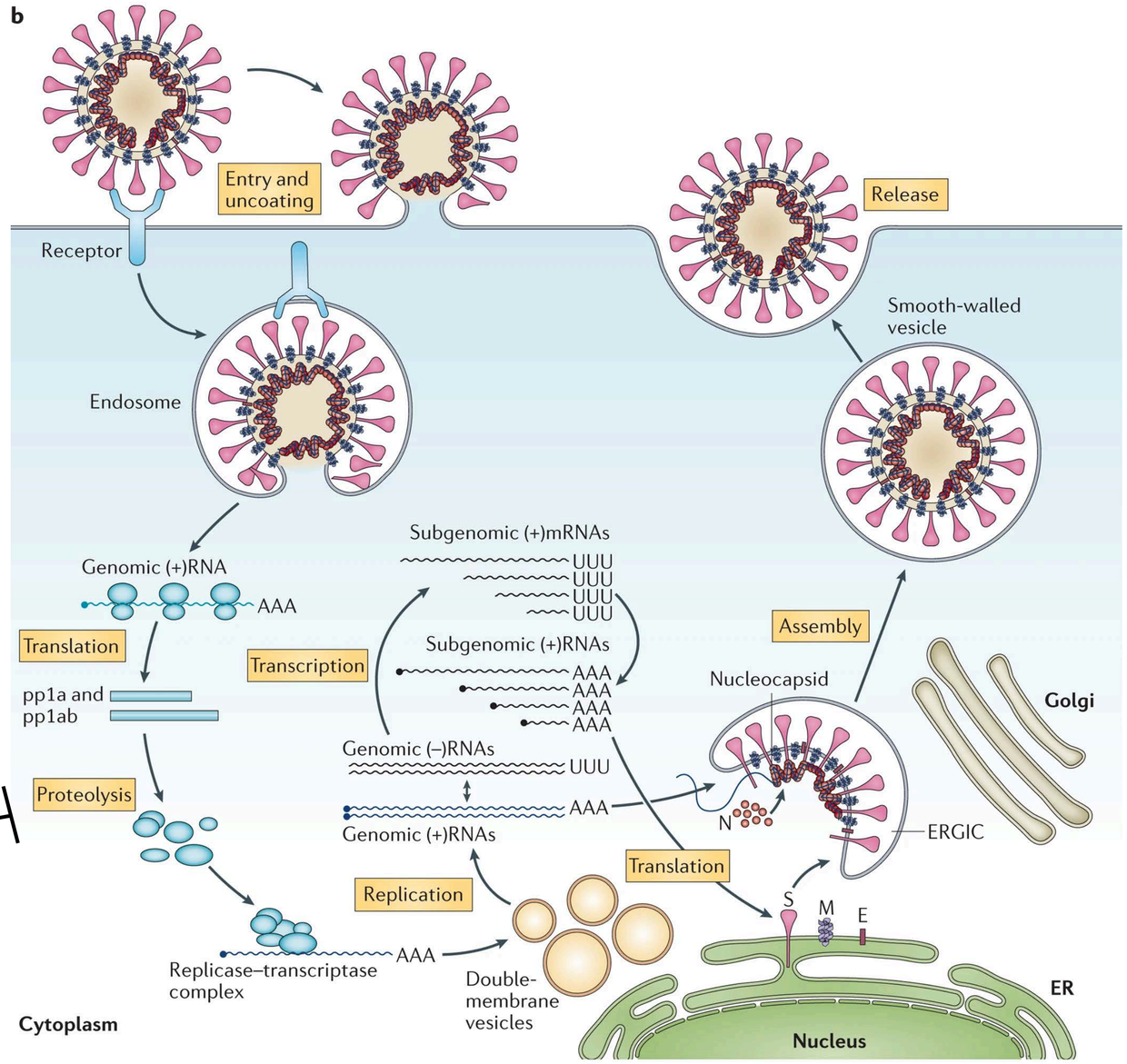
WE KNEW FROM SARS-COV THAT THE MAIN VIRAL PROTEASE (MPRO) IS ESSENTIAL FOR VIRAL REPLICATION

3CL^{Pro}

or **Mpro**

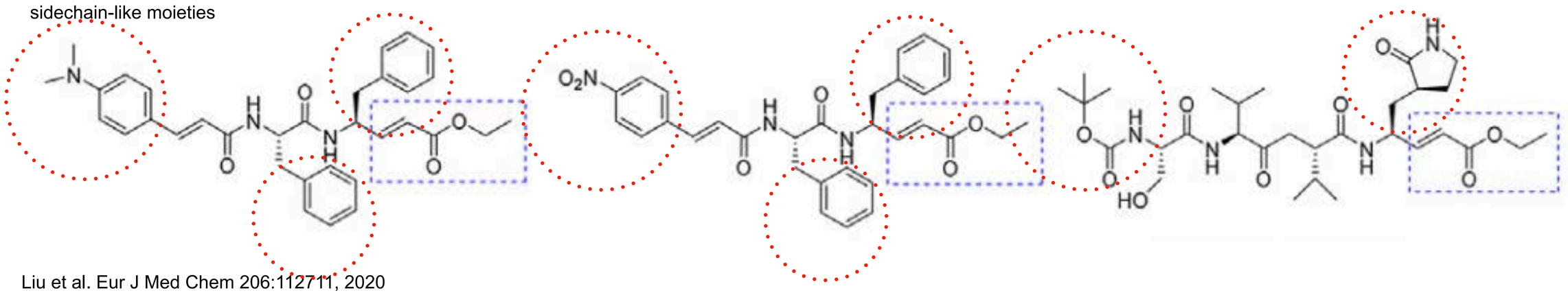


cleaves viral polyprotein
in 11 different places
= difficult for active site to mutate?



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

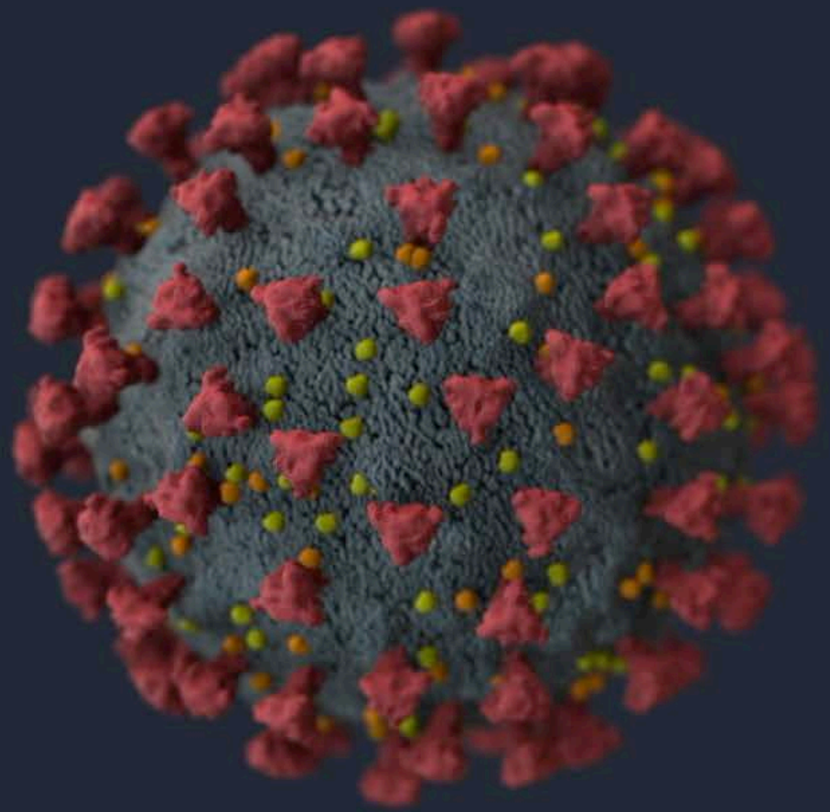
PREVIOUSLY KNOWN SARS-COV MPRO INHIBITORS WERE PEPTIDOMIMETICS, WHICH ARE DIFFICULT* TO DEVELOP INTO ORAL DRUGS



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

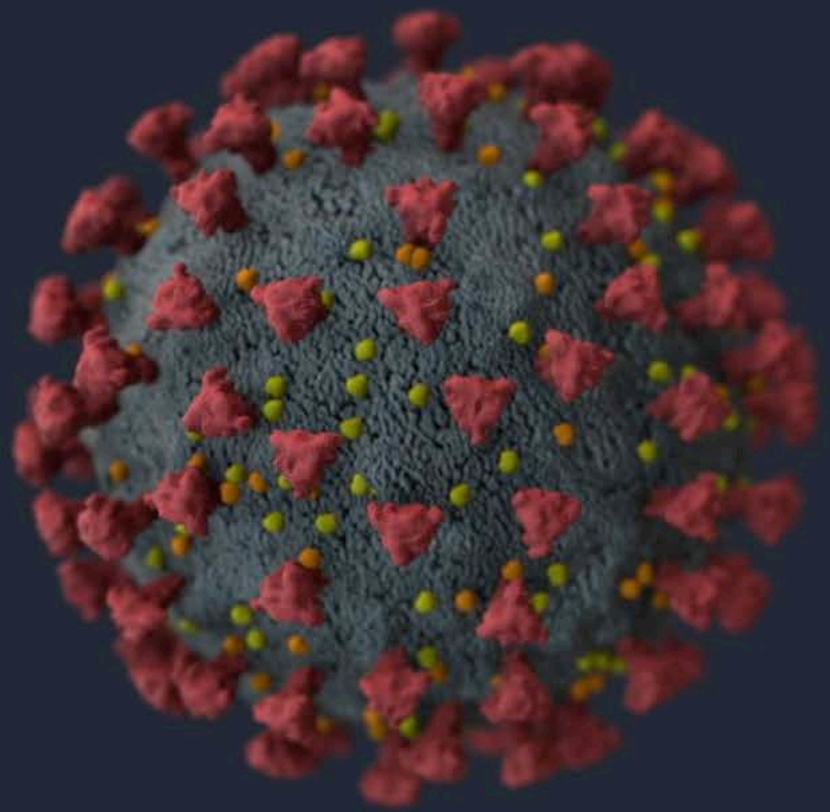
known Mpro inhibitors were also **covalent** inhibitors,
which *can be difficult to optimize* for PK and off-target issues*

*** As you'll hear in the next talk, Pfizer did an *astounding* job of this with nirmatrelvir while we were working on this!**



foolish and naïve!

OUR GOAL



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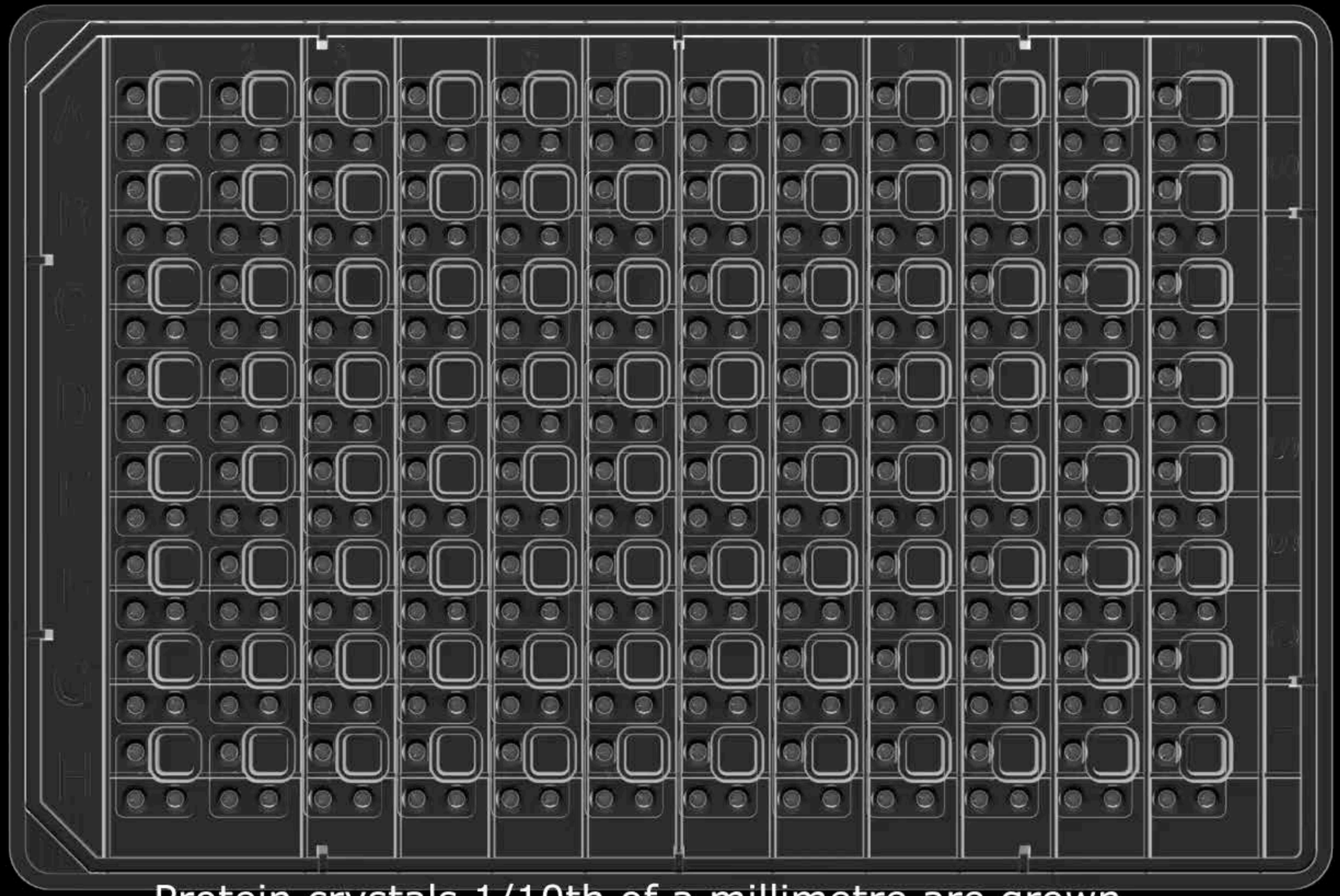
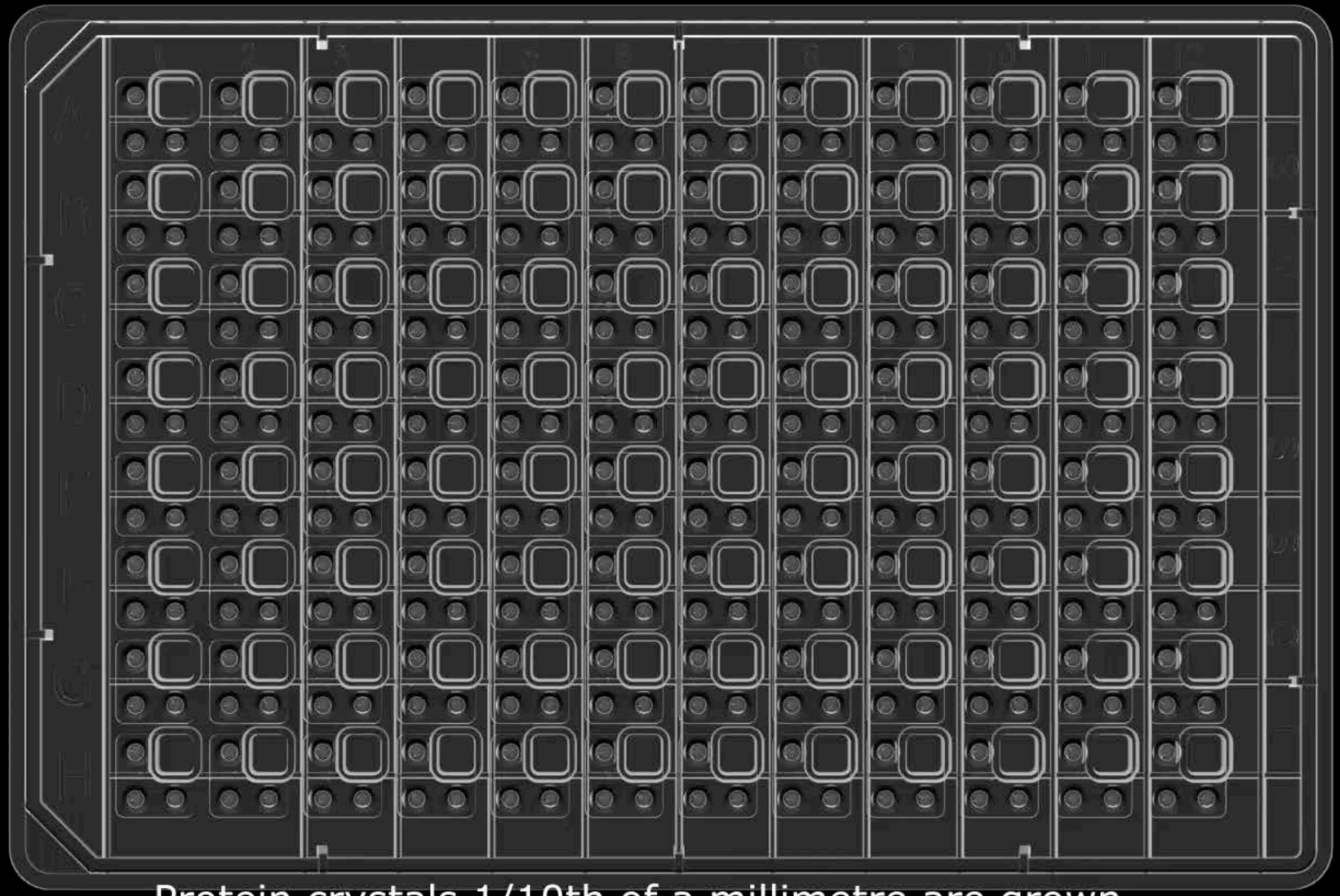
OUR GOAL

Diamond Light Source, UK



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

diamond
Light for Science



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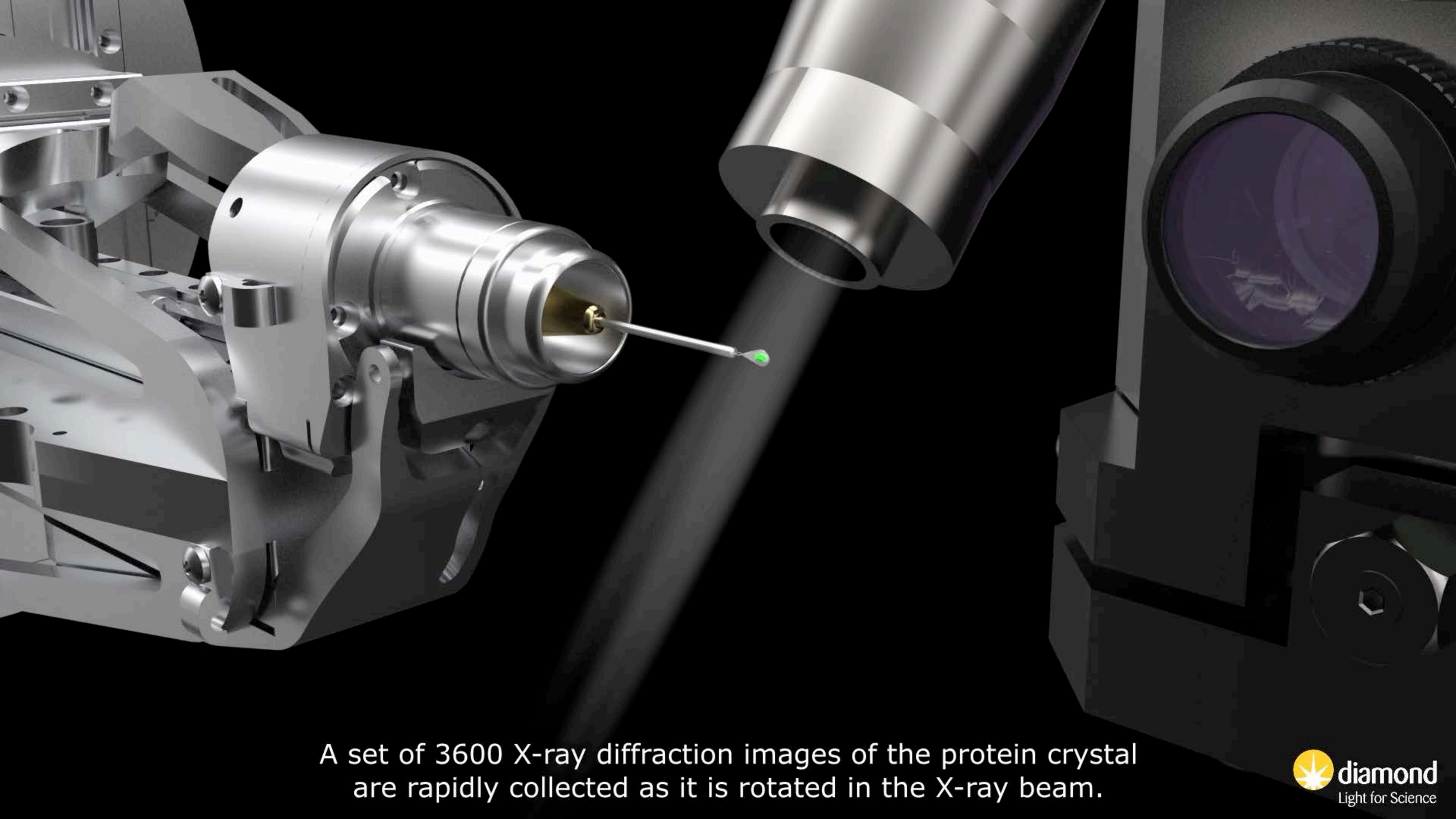
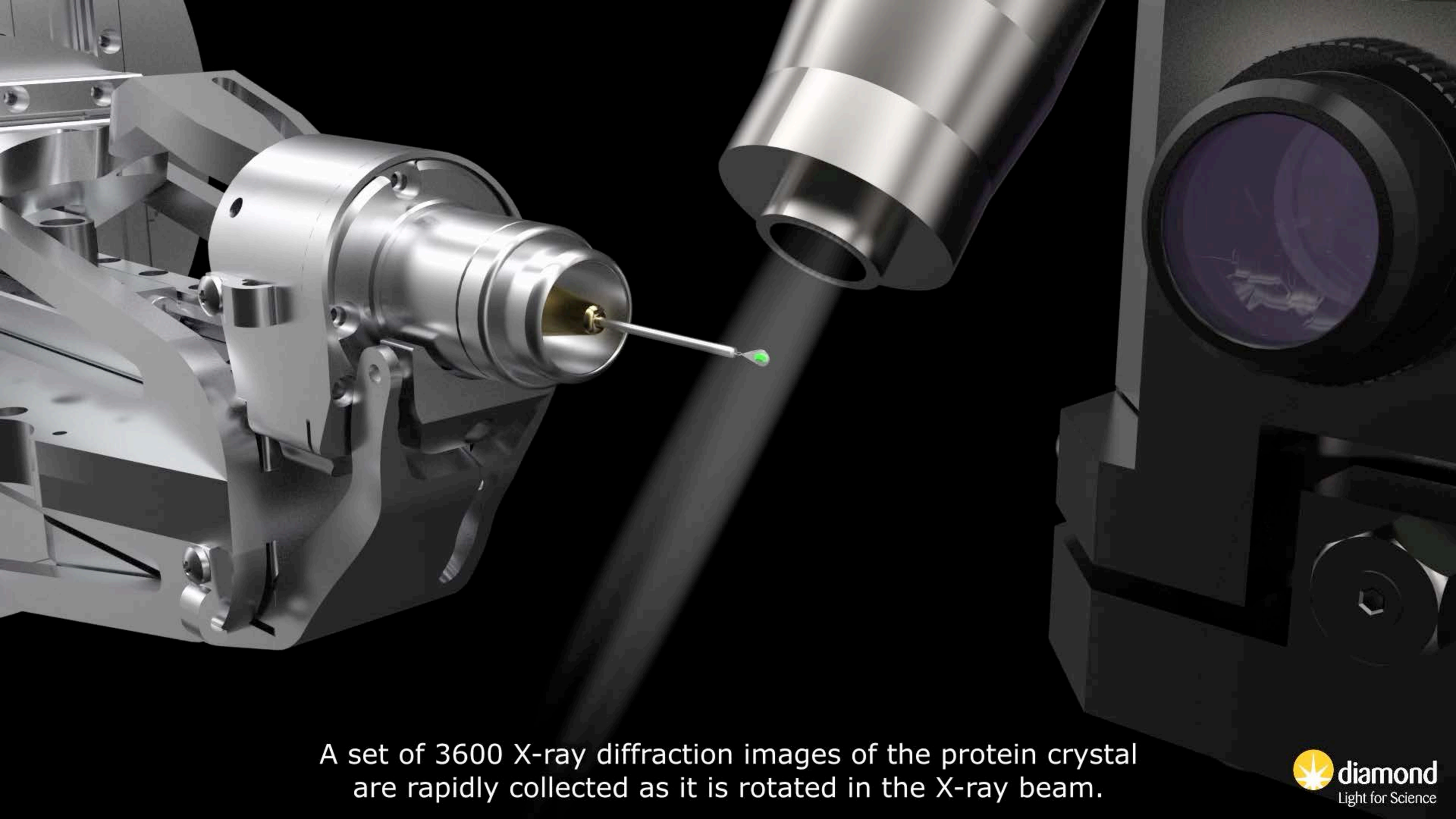


A set of 3600 X-ray diffraction images of the protein crystal are rapidly collected as it is rotated in the X-ray beam.

diamond
Light for Science



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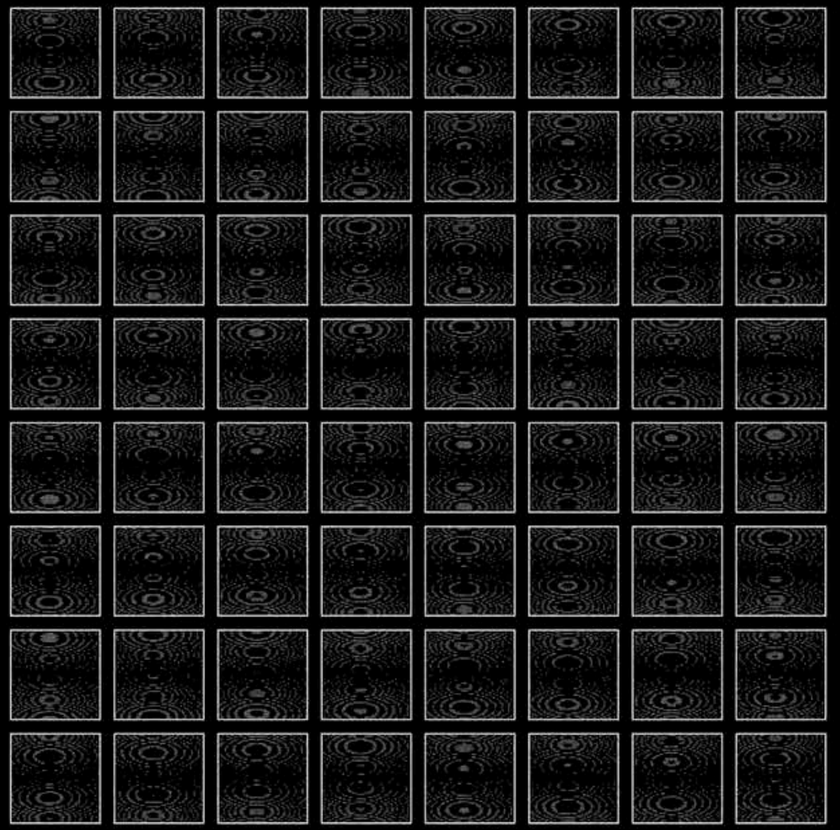
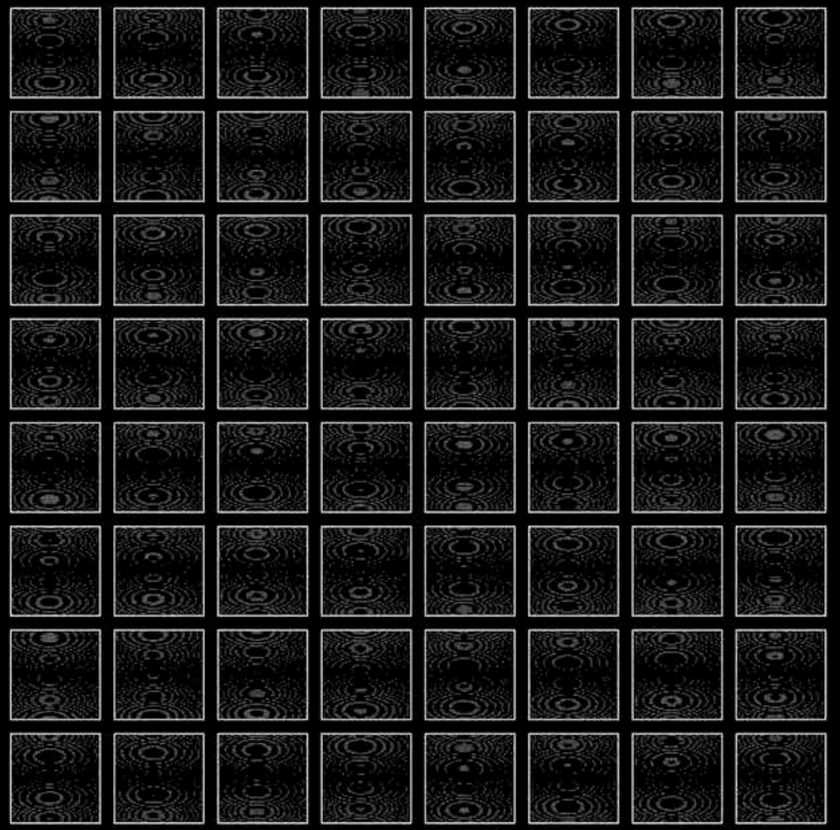


From the diffraction patterns, the three dimensional structure of the SARS-CoV-2 Mpro protein can be determined.

diamond
Light for Science



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diamond
Light for Science

DIAMOND LIGHT SOURCE WAS ABLE TO COLLECT DATA FOR 1,500 X-RAY STRUCTURES IN RECORD TIME

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

Frank von Delft
Diamond Light Source / XChem / SGC

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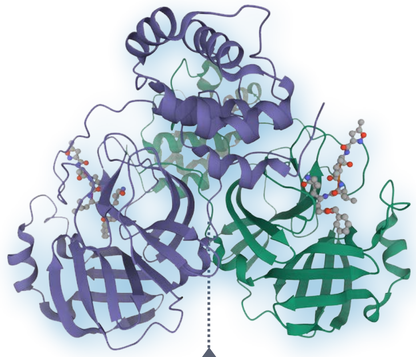
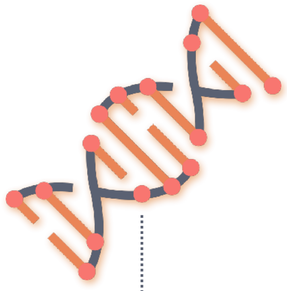


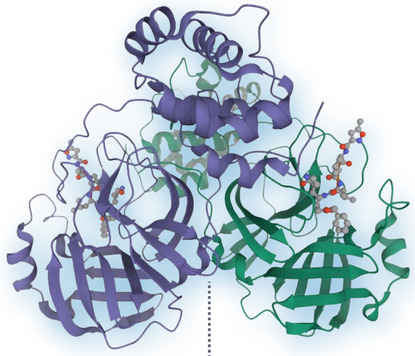
February 5

Haitao Yang lab shares first structure but forced to shut down; sends plasmid sequence to Diamond



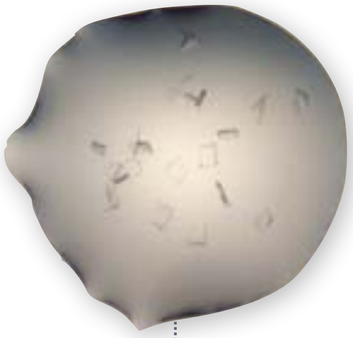
February 14

Main protease cloned and produced at Diamond



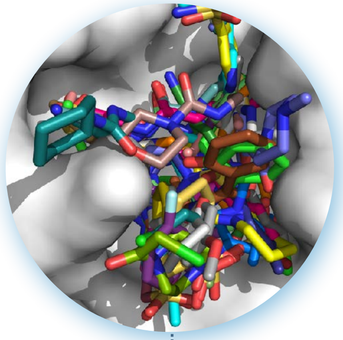
February 20

First protease structure determined at Diamond



March 5

Data for **1,500** crystals for small molecule fragment soaks collected at Diamond



March 18

78 fragment-bound structures solved and released online

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

Frank von Delft
Diamond Light Source / XChem / SGC

ALL DATA WAS IMMEDIATELY RELEASED ONLINE WITH THE GOAL OF ACCELERATING DRUG DISCOVERY

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.

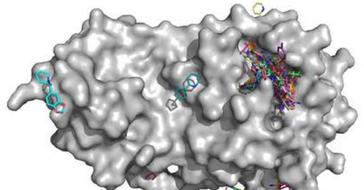
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

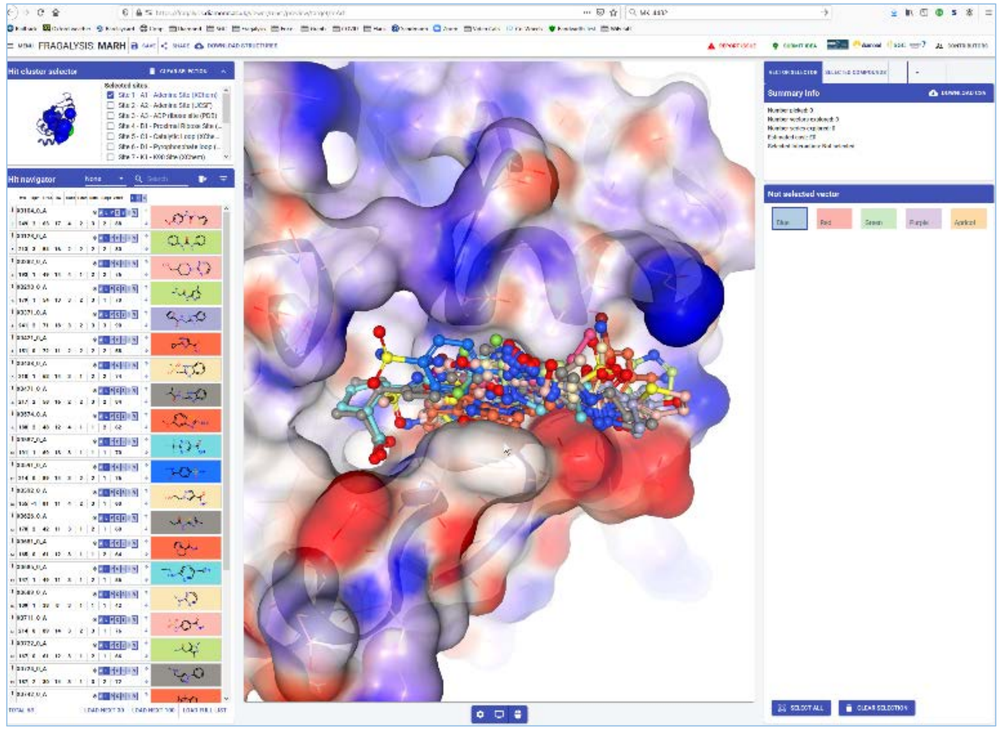
XChem fragment screen

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

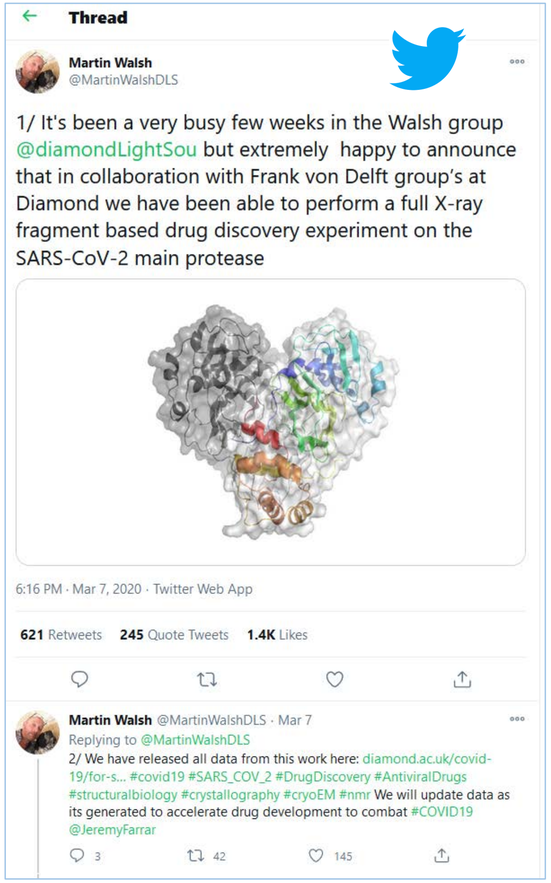




https://fragalysis.diamond.ac.uk

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

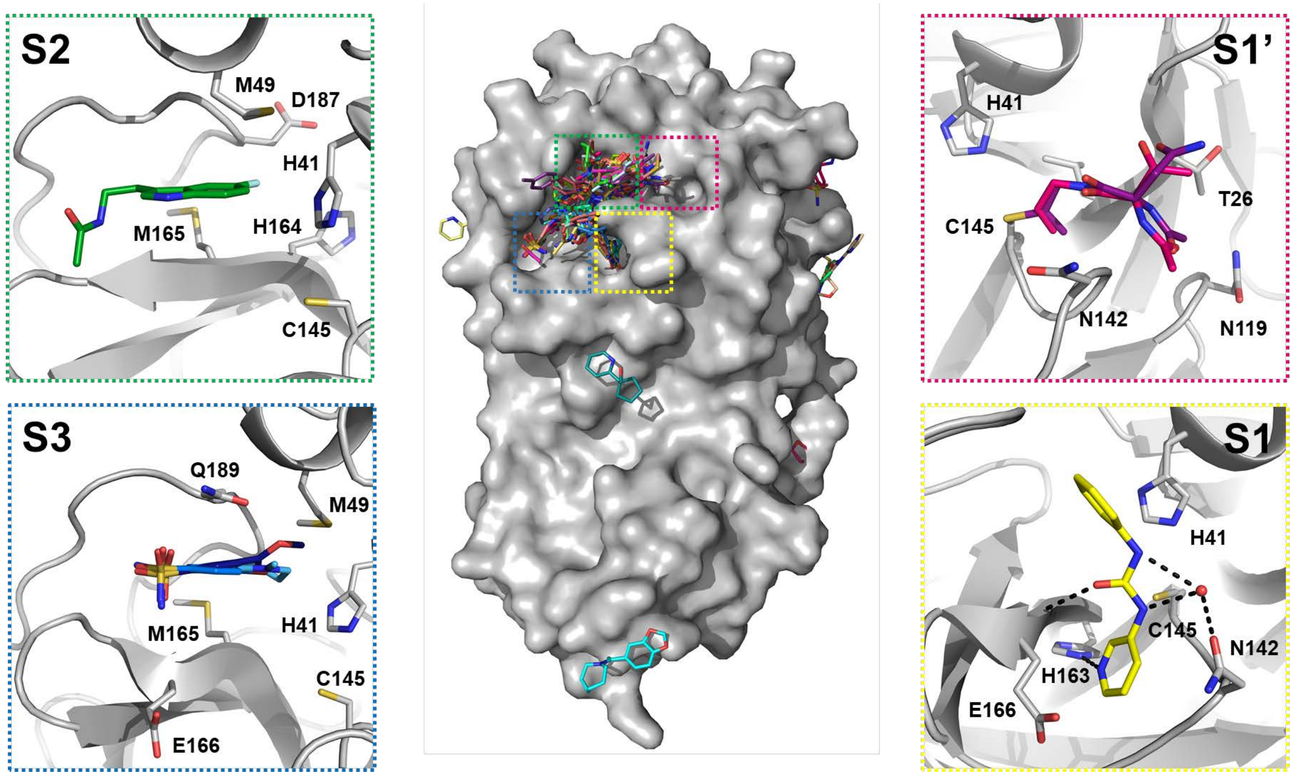
(*pre*-preprinting!)



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

FRAGMENT HITS COMPLETELY COVER THE ACTIVE SITE, SUGGESTING MERGES COULD IMPROVE POTENCY

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



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

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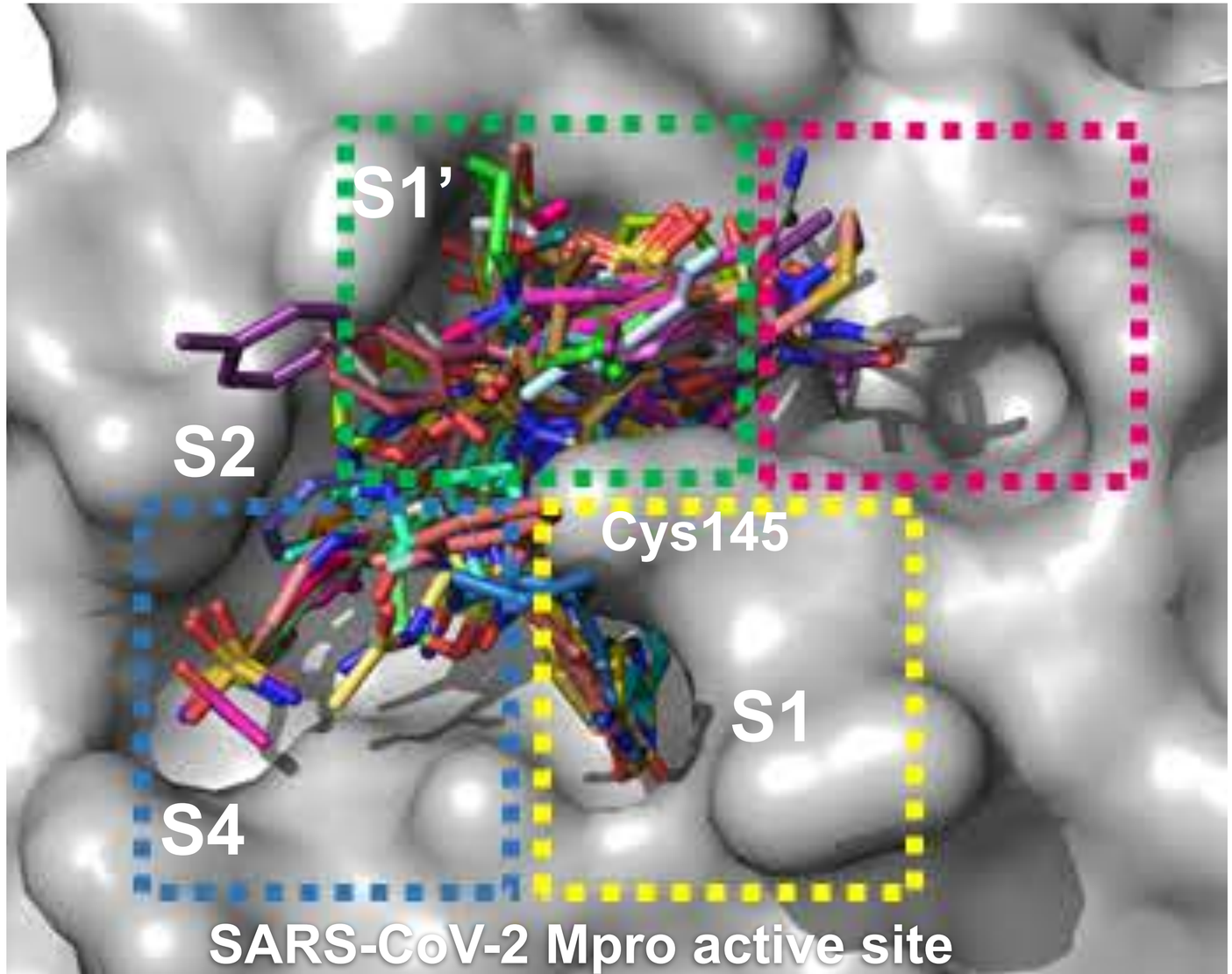

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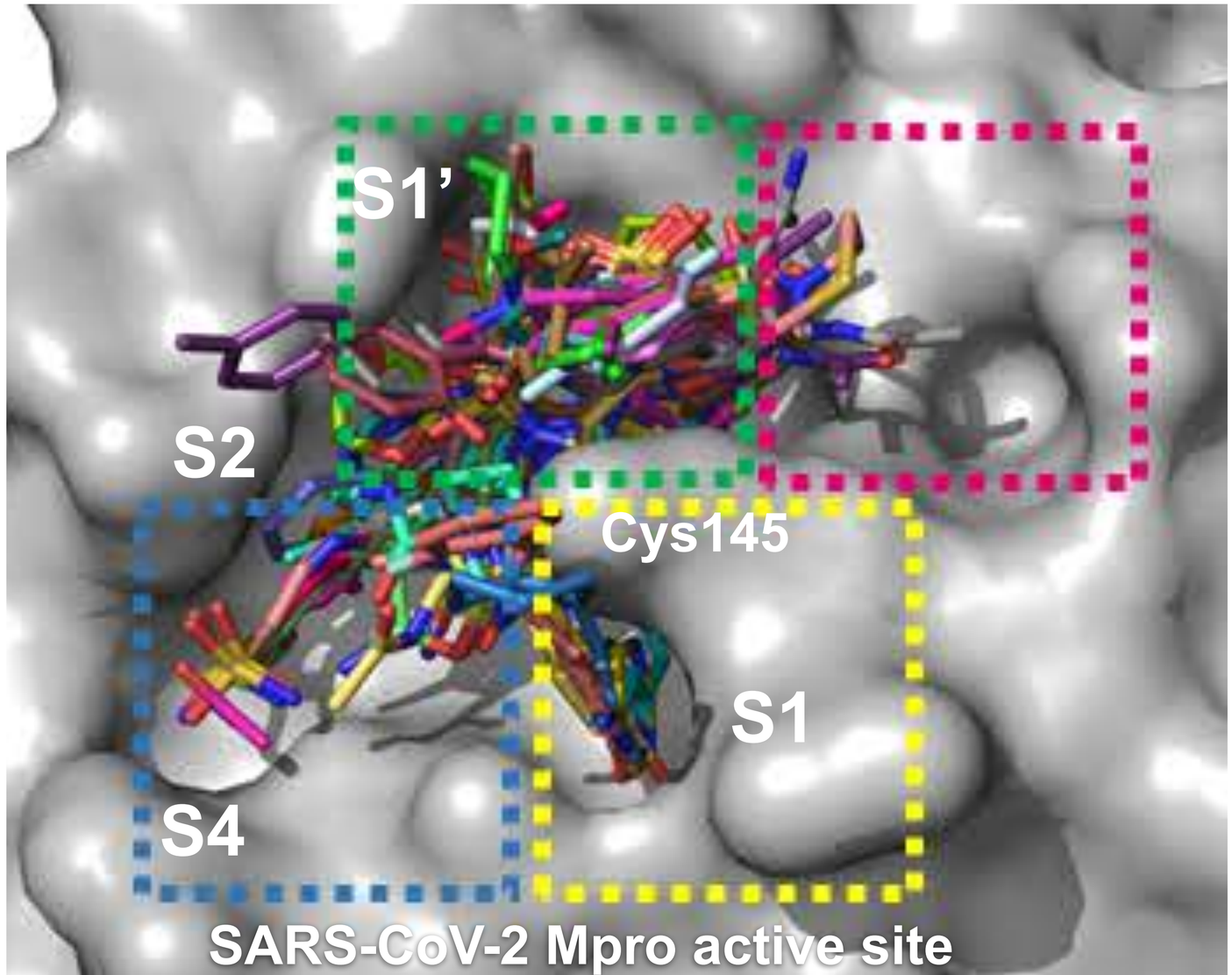

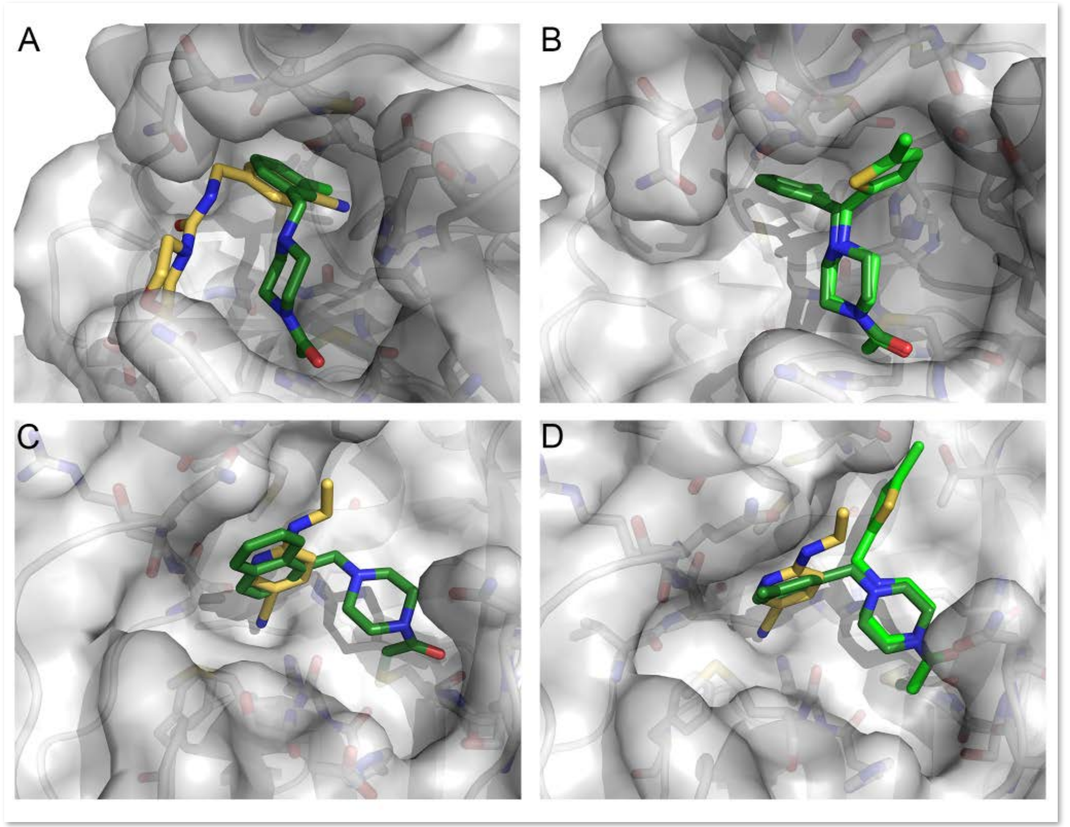

Could we merge our way to potent antivirals directly?

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

WHICH COMPUTATIONAL STRATEGIES WOULD MOST RAPIDLY PROGRESS FRAGMENTS TO EARLY LEADS WITH MEASURABLE POTENCY?

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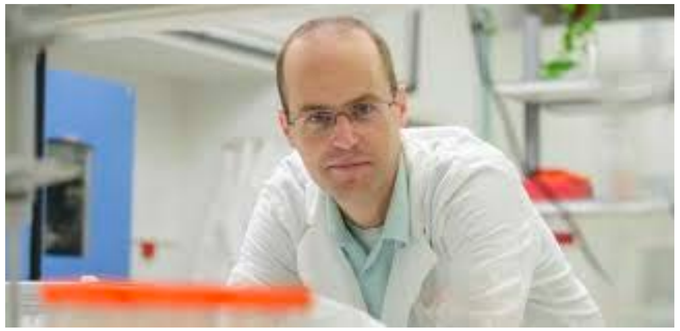
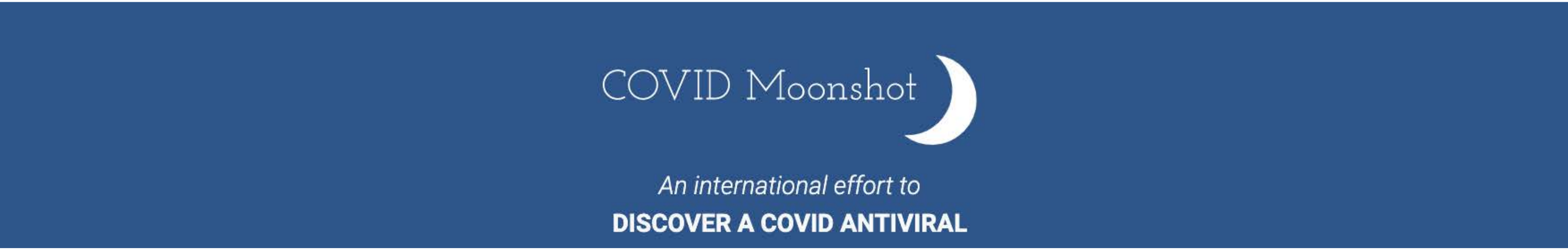


Nir London
Weizmann Institute

"...what if we tried **all of them?**"

FIRST, WE NEEDED A COOL NAME TO MOTIVATE PEOPLE



THE COVID MOONSHOT ADOPTED A GLOBAL OPEN SCIENCE, PATENT-FREE, COLLABORATIVE APPROACH TO DRUG DISCOVERY

Open science

COVID Moonshot

Open data

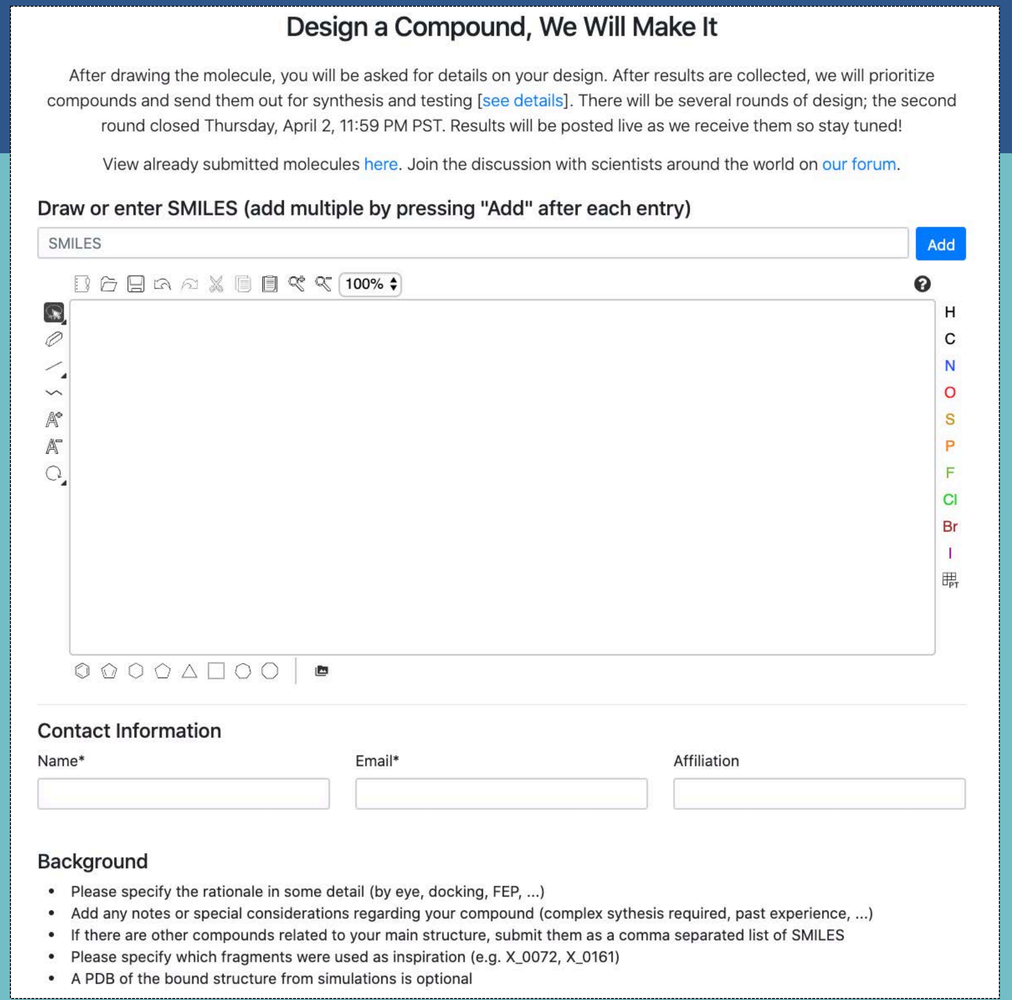
http://postera.ai/covid

Patent-free

Alpha Lee (Cambridge) tapped a company he co-founded, PostEra, to create an open drug discovery commons website

Alpha Lee
Cambridge/PostEra

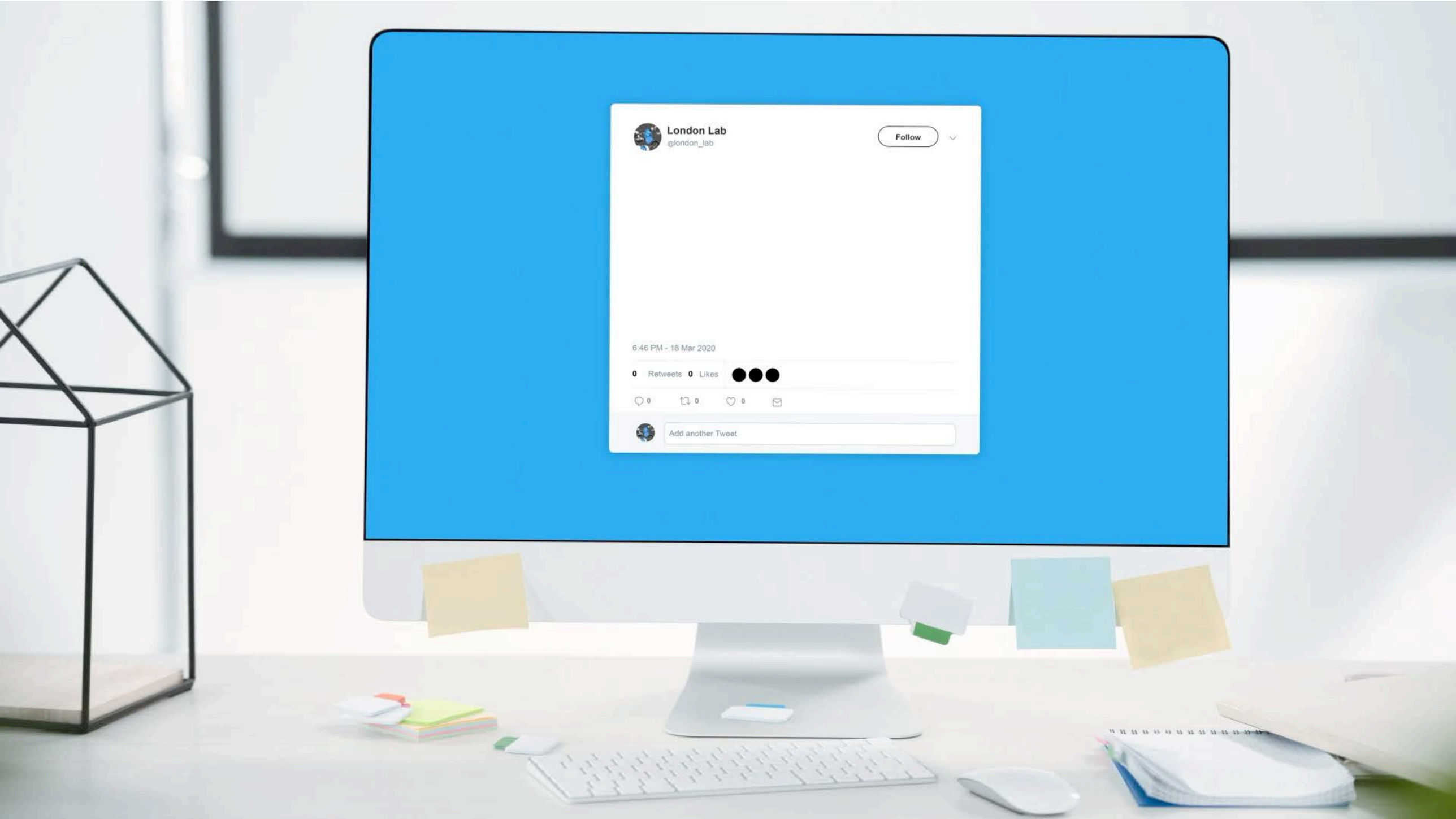
COVID Moonshot

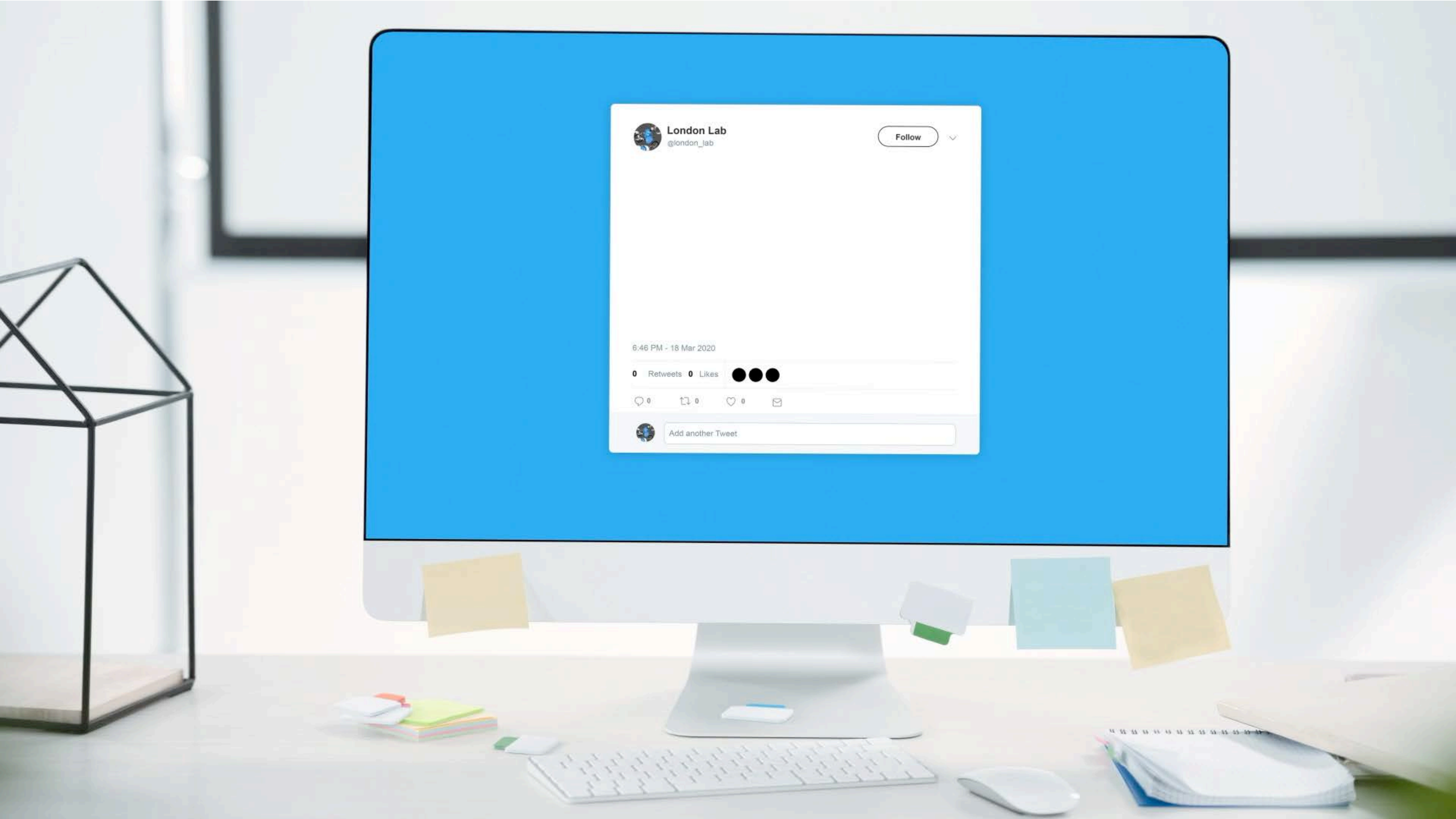


Molecule sketcher!
2D compound design viewer!
Discussion boards!

http://postera.ai/covid

+ Matthew Robinson (PostEra)


London Lab
@london_lab
Follow
6:46 PM - 18 Mar 2020
0 Retweets 0 Likes
Add another Tweet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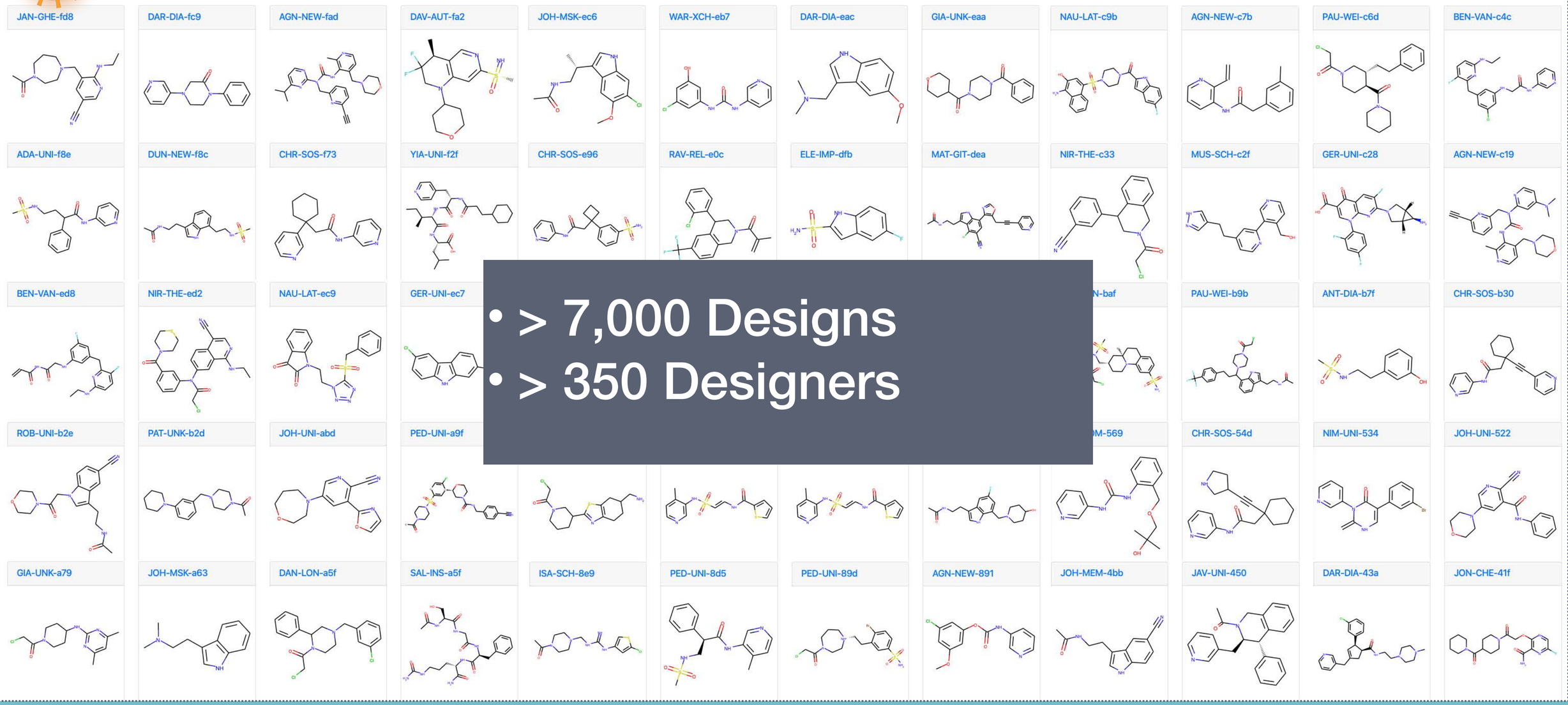
…and there was overwhelming response



- > 7,000 Designs
- > 350 Designers

THERE WERE SOME EXCELLENT IDEAS

MAK-UNK-e05327b2-1

MAK-UNK-e05327b2-2

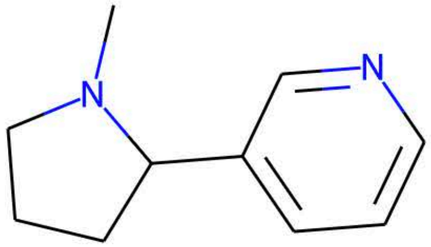
MAK-UNK-e05327b2-3

MAK-UNK-e05327b2-5

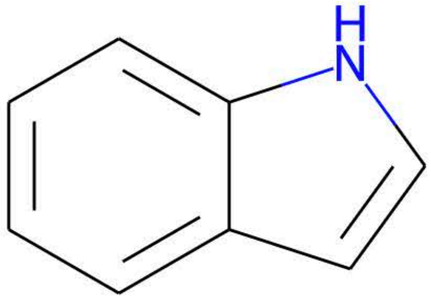
Design Rationale:

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

THERE WERE SOME … INTERESTING … IDEAS TOO



KTA-UNK-dac325de-1



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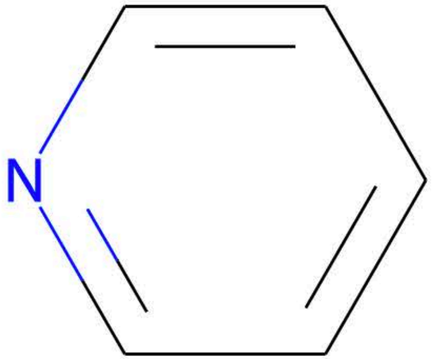
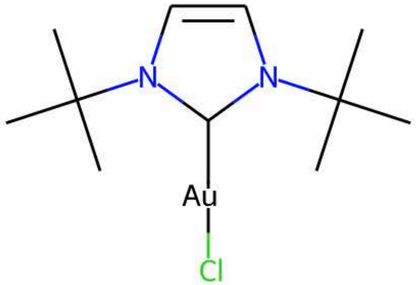


KTA-UNK-dac325de-3

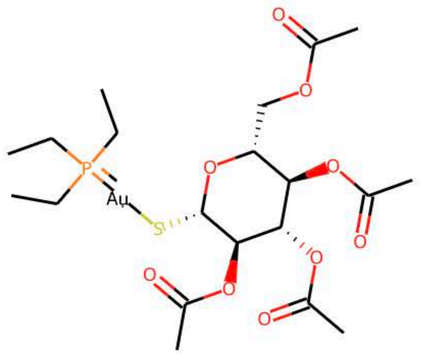
Design Rationale:

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

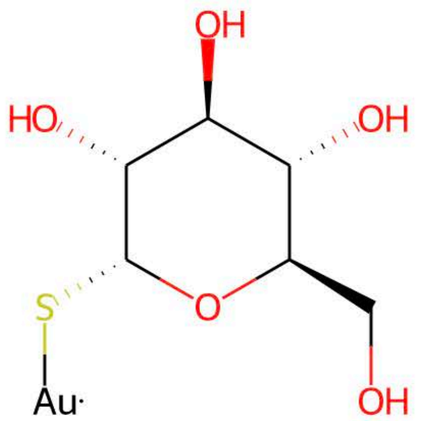
THERE WERE SOME ... INTERESTING ... IDEAS TOO



JOH-UNI-44664832-1



JOH-UNI-44664832-2

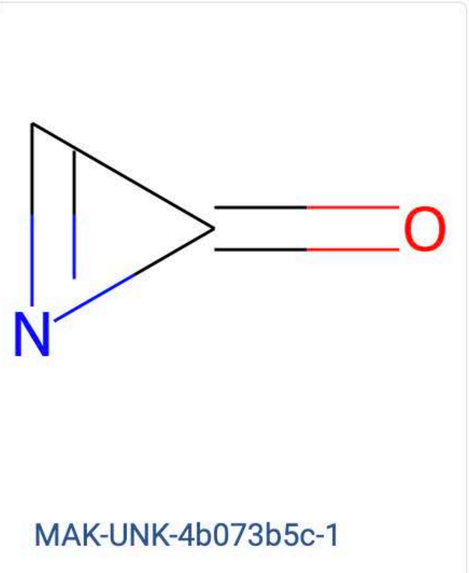


JOH-UNI-44664832-3

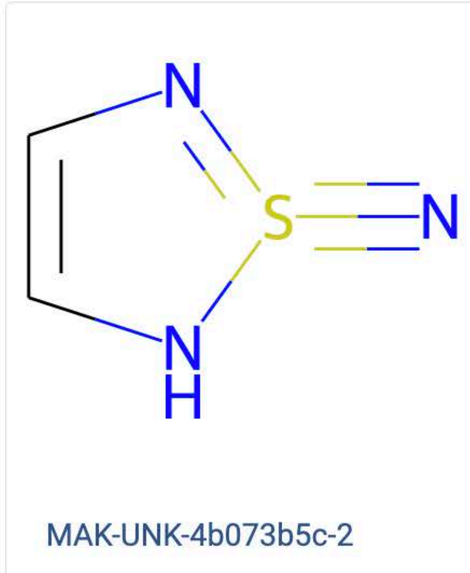
Design Rationale:

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

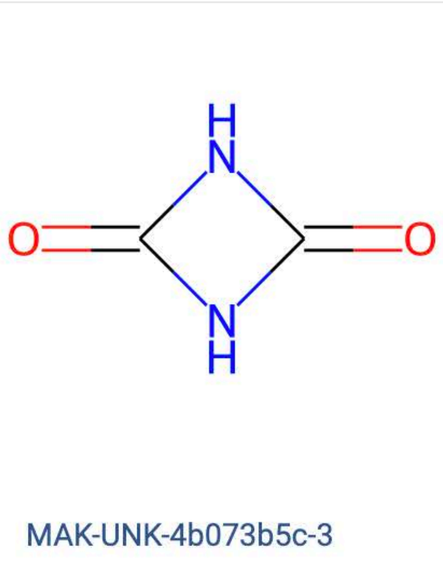
THERE WERE SOME ... INTERESTING ... IDEAS TOO



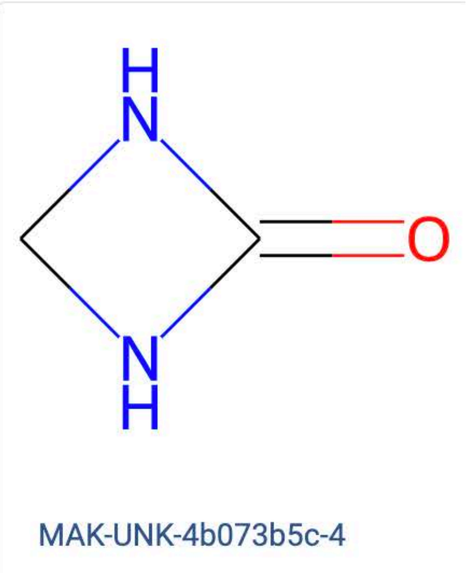
MAK-UNK-4b073b5c-1



MAK-UNK-4b073b5c-2



MAK-UNK-4b073b5c-3



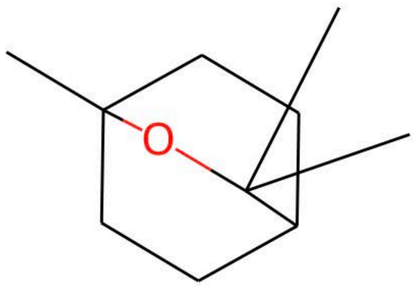
MAK-UNK-4b073b5c-4

Design Rationale:

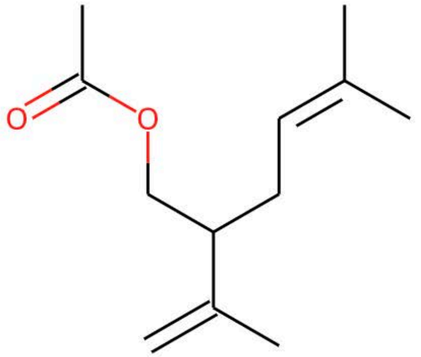
by eye, tiny molecules

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

Molecule(s):



BET-COM-8a5969bb-1

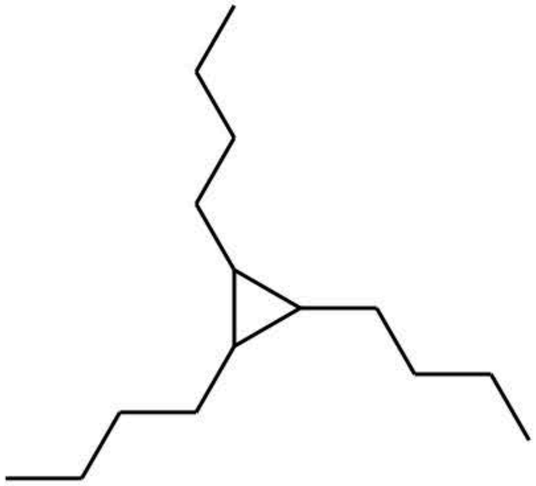


BET-COM-8a5969bb-2

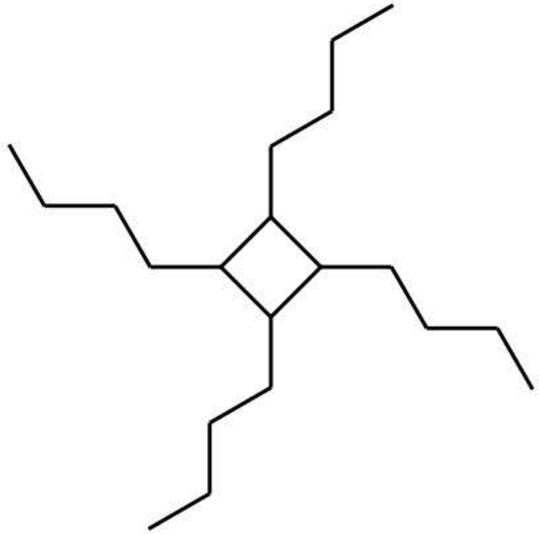
Design Rationale:

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

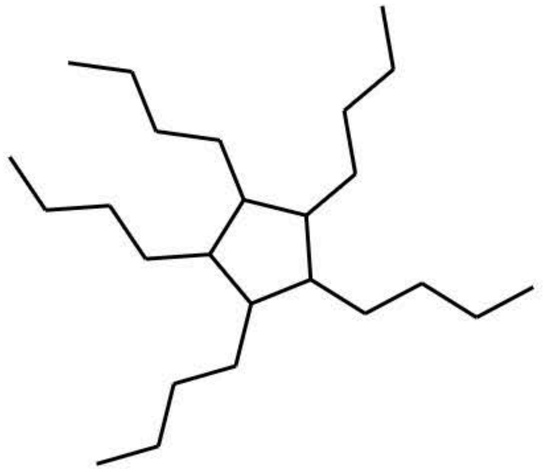
THERE WERE SOME ... INTERESTING ... IDEAS TOO



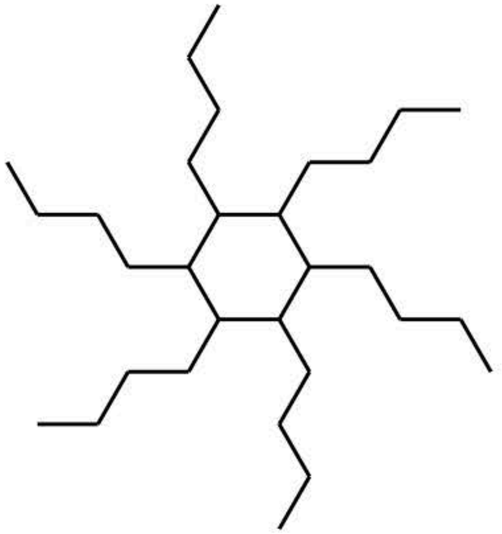
THE-UNK-833274f3-1



THE-UNK-833274f3-2



THE-UNK-833274f3-3



THE-UNK-833274f3-4

Design Rationale:

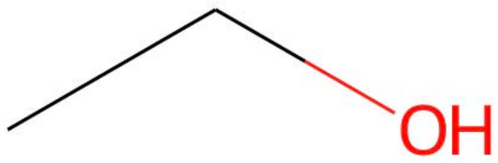
These substances are only carbon, and they have no alarm.

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

Design Rationale:

I used random numbers to find this compound.

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



JAM-UNK-fcc74568-1

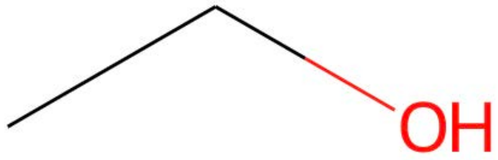
Design Rationale:

Common sense

Other Notes:

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

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



JAM-UNK-fcc74568-1

Design Rationale:

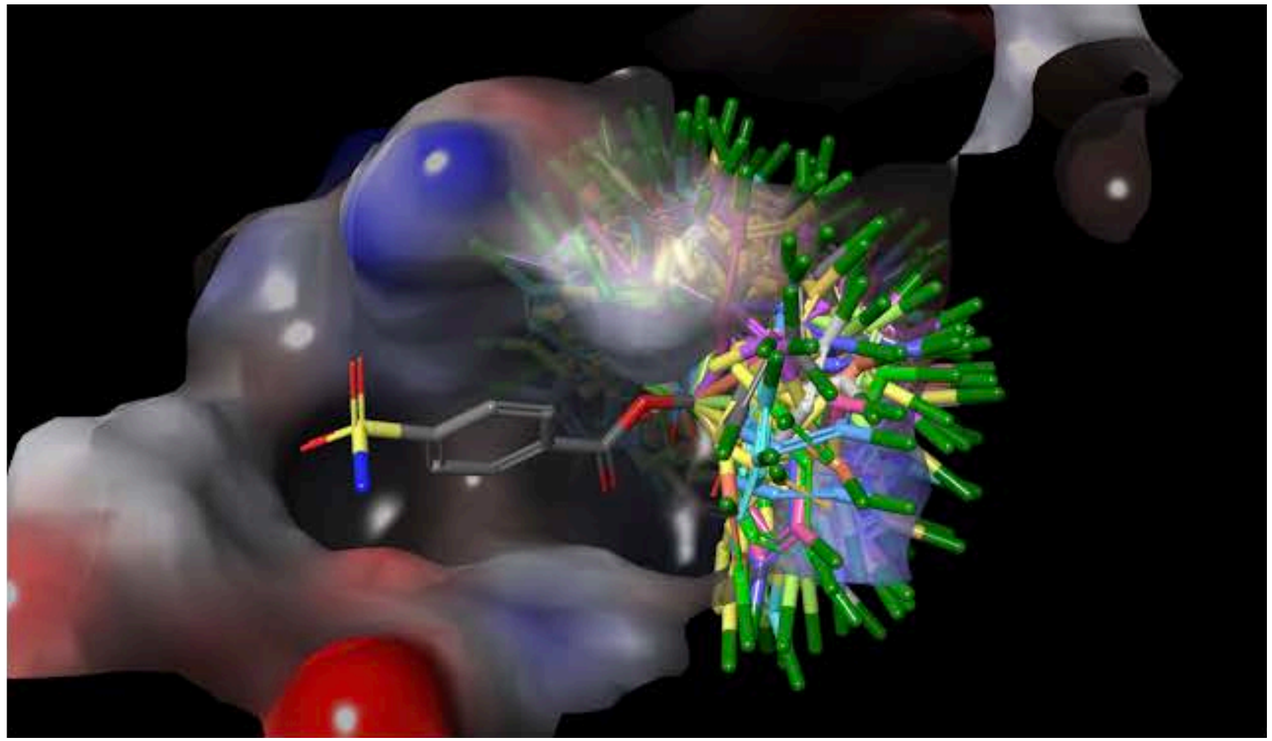
Common sense

Other Notes:

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

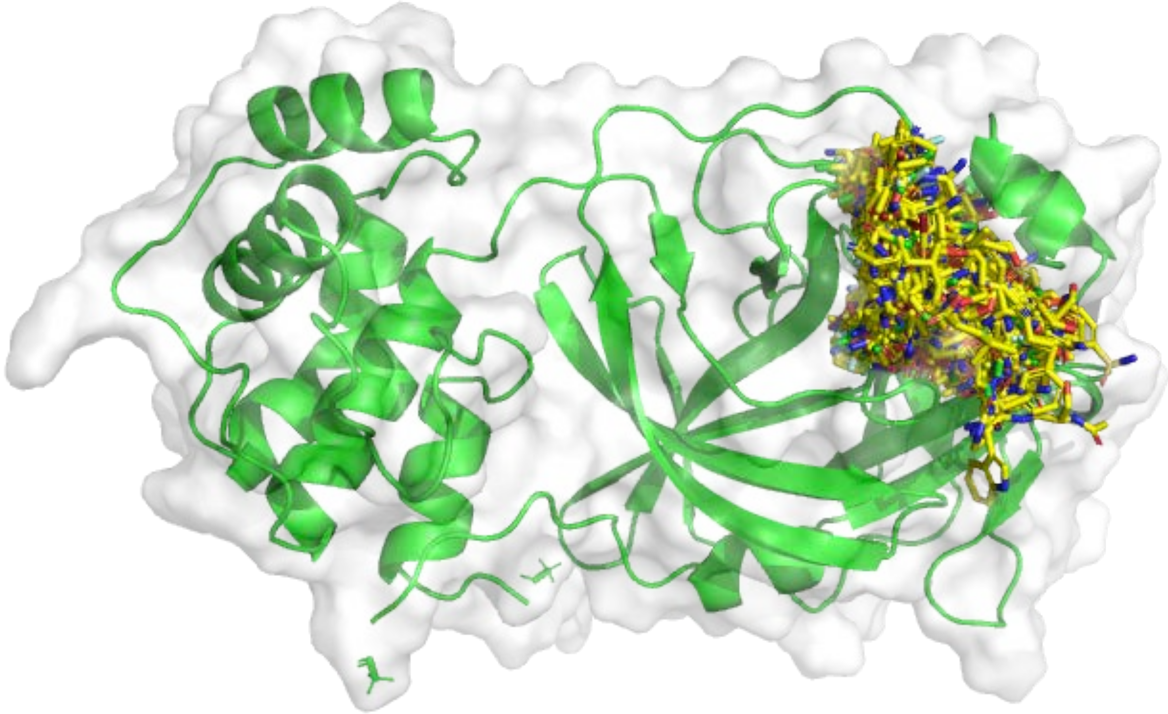
WE USED OPENEYE OMEGA/FRED TO WEED OUT BAD IDEAS

docking of a single compound, showing all possible conformers



Pat Walters blog: http://practicalcheminformatics.blogspot.com

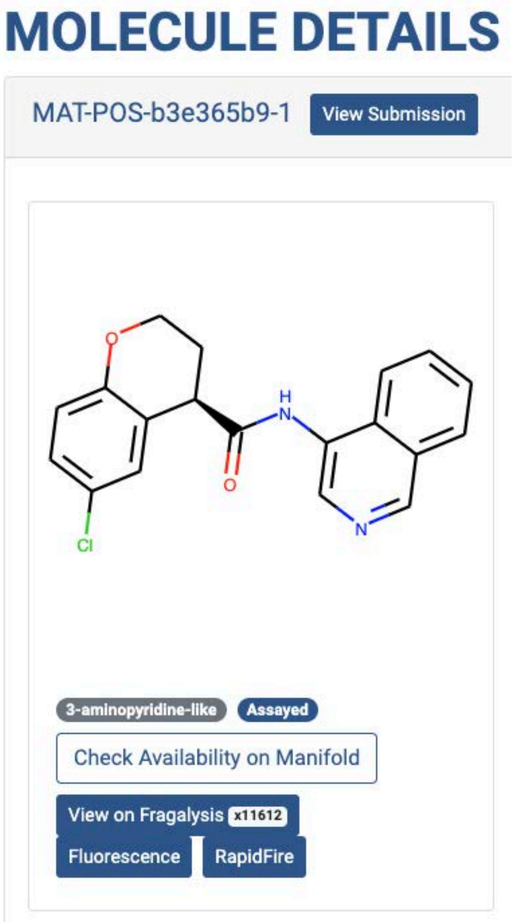
all final docked ligand structures



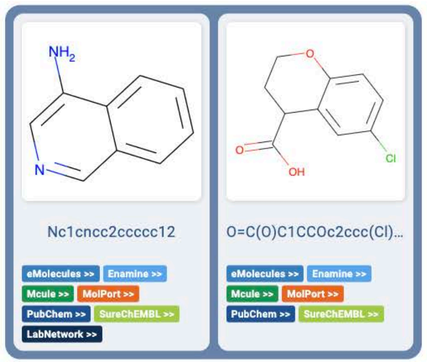
code and docking results: https://github.com/FoldingAtHome/covid-moonshot/tree/master/moonshot-submissions

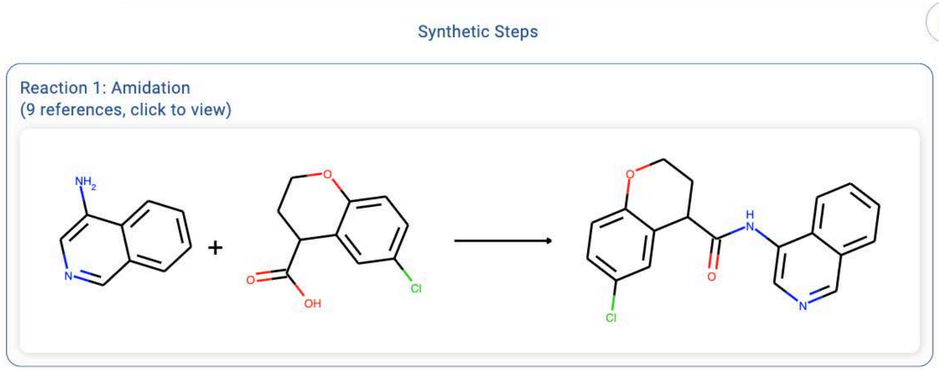
MACHINE LEARNING BASED SYNTHETIC ROUTE PREDICTION MODELS IDENTIFIED DESIGNS THAT COULD BE EASILY SYNTHESIZED

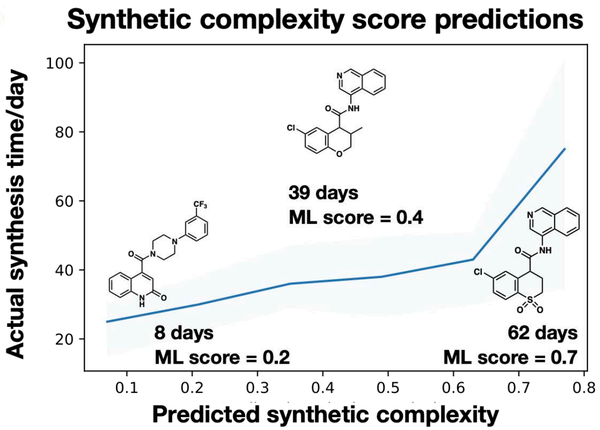
CRO catalogue-aware optimal synthetic route
(Enamine, WuXi, Sai)



http://postera.ai/covid

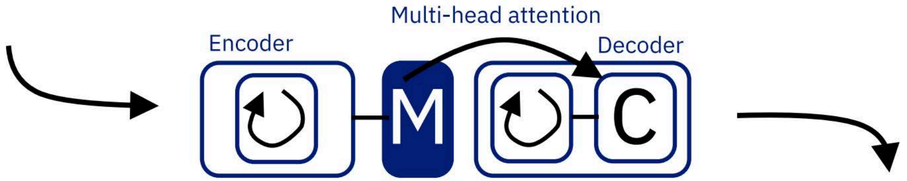






Input: reactants-reagents (atom-wise tokenization)

Br c 1 c c c 2 ...c(c1)c1cc3c4ccccc4c4ccccc4c3cc1n2-c1ccc2c(c1)c1ccccc1n2-c1ccccc1.CCO.
Cc1ccccc1.OB(O)c1ccc2ccc3cccnc3c2n1.c1ccc([PH](c2ccccc2)(c2ccccc2)[Pd]([PH](c2ccccc2)
(c2ccccc2)c2ccccc2)([PH](c2ccccc2)(c2ccccc2)c2ccccc2)[PH](c2ccccc2)(c2ccccc2)c2ccccc2)cc1



c 1 c c c (– n
...2c3ccccc3c3cc(–n4c5ccc(–
c6ccc7ccc8cccnc8c7n6)cc5c5cc6c7ccccc7c7ccccc7c6cc54)ccc32)cc1

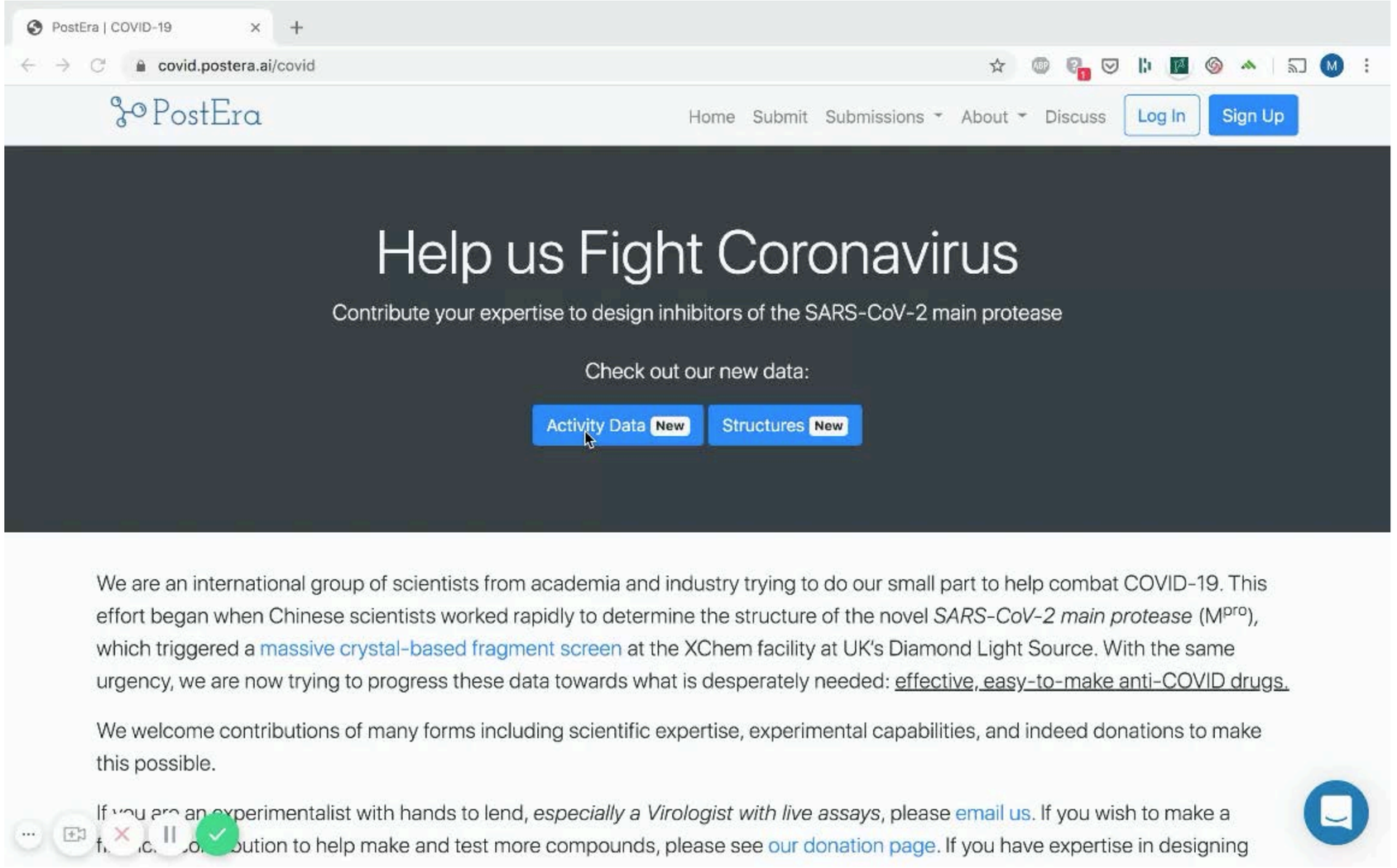
Target: most likely products

Molecular Transformer:
http://postera.ai/manifold

Quickly made 850 compounds in a few weeks!

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

DATA WAS IMMEDIATELY REPORTED BACK TO THE COMMUNITY



http://postera.ai/covid

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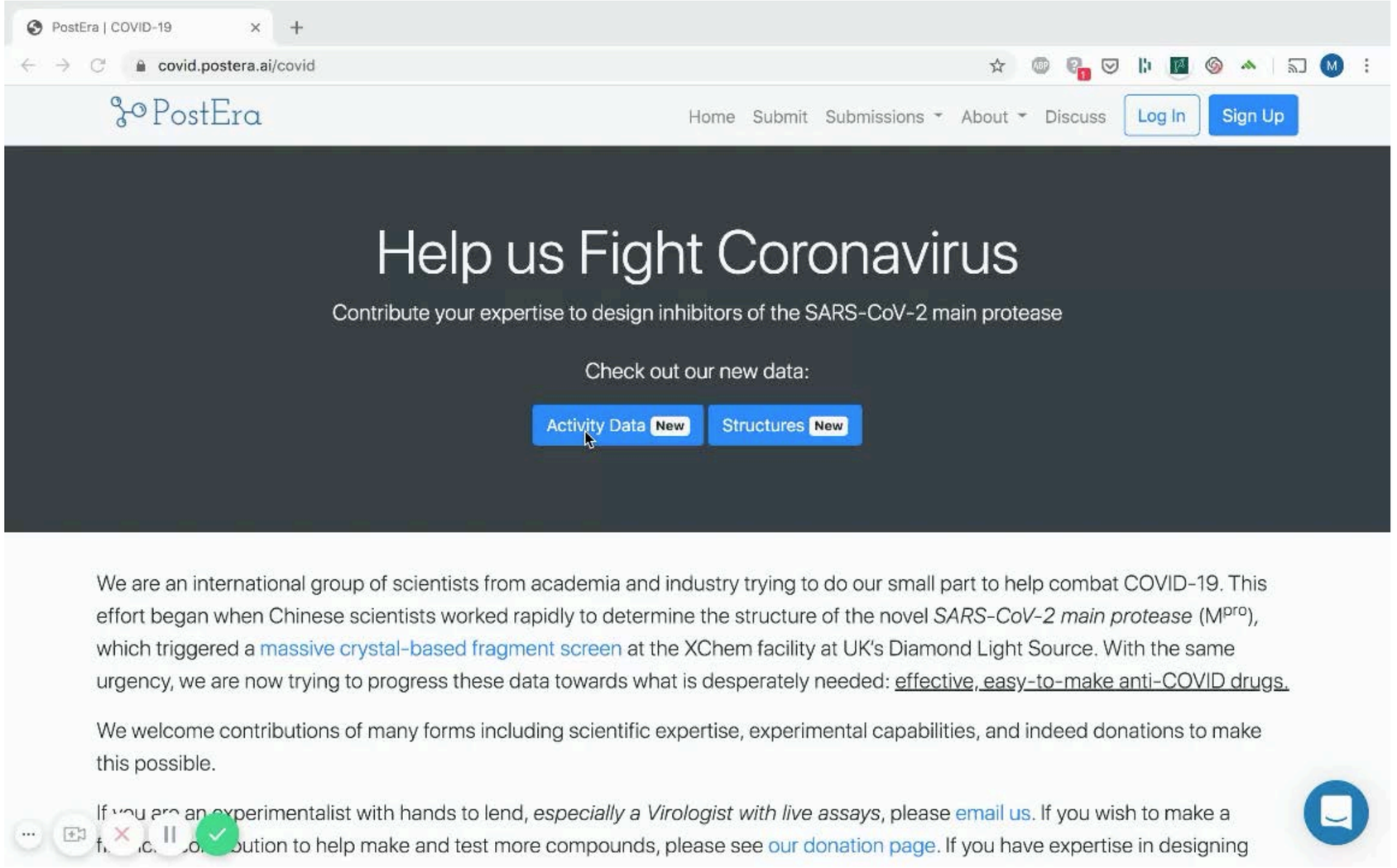
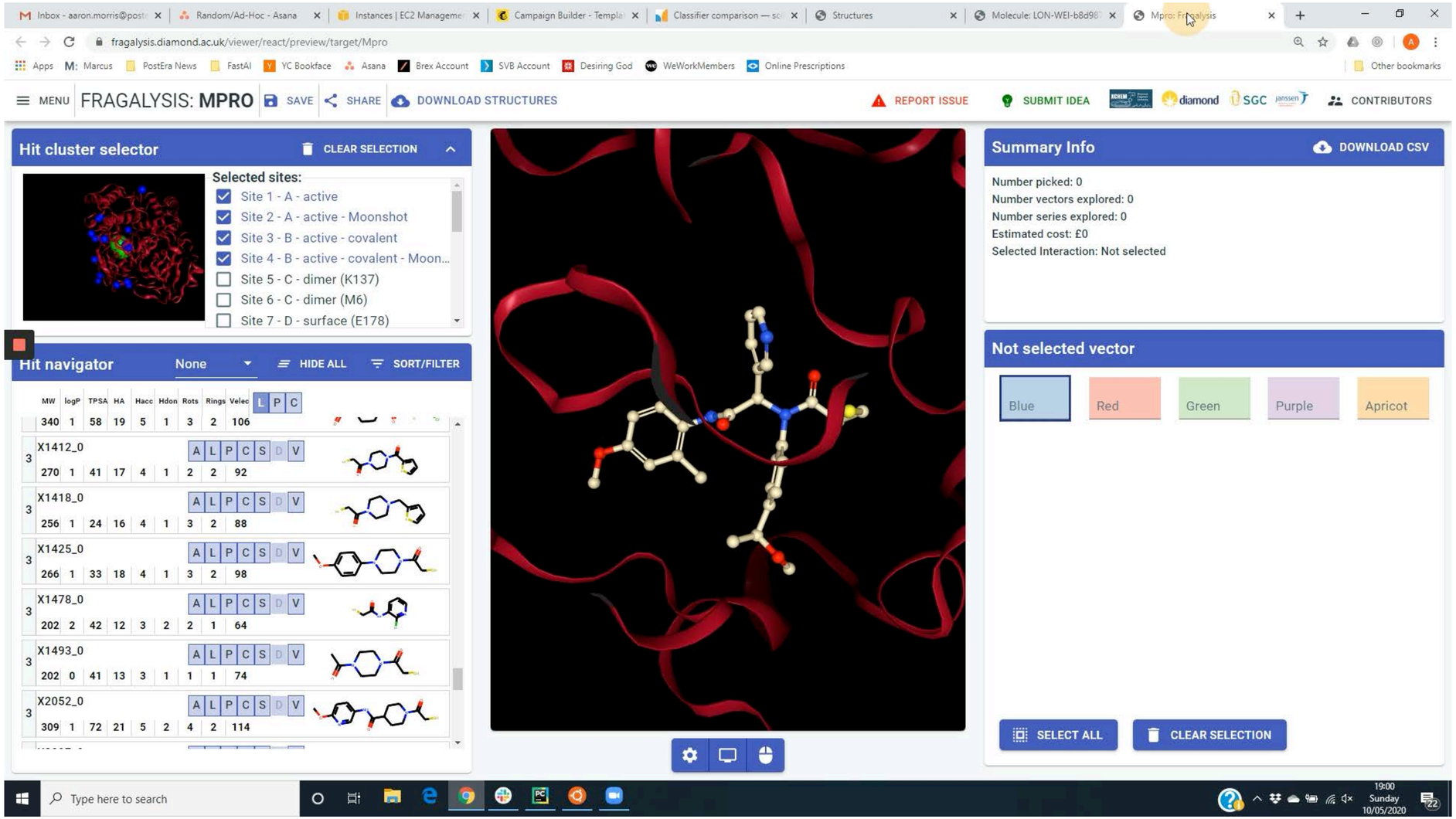


http://postera.ai/covid

DIAMOND'S AUTOMATED BEAMLINE ENABLED US TO GENERATE NEW STRUCTURAL DATA FOR THESE INHIBITORS IN JUST DAYS



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

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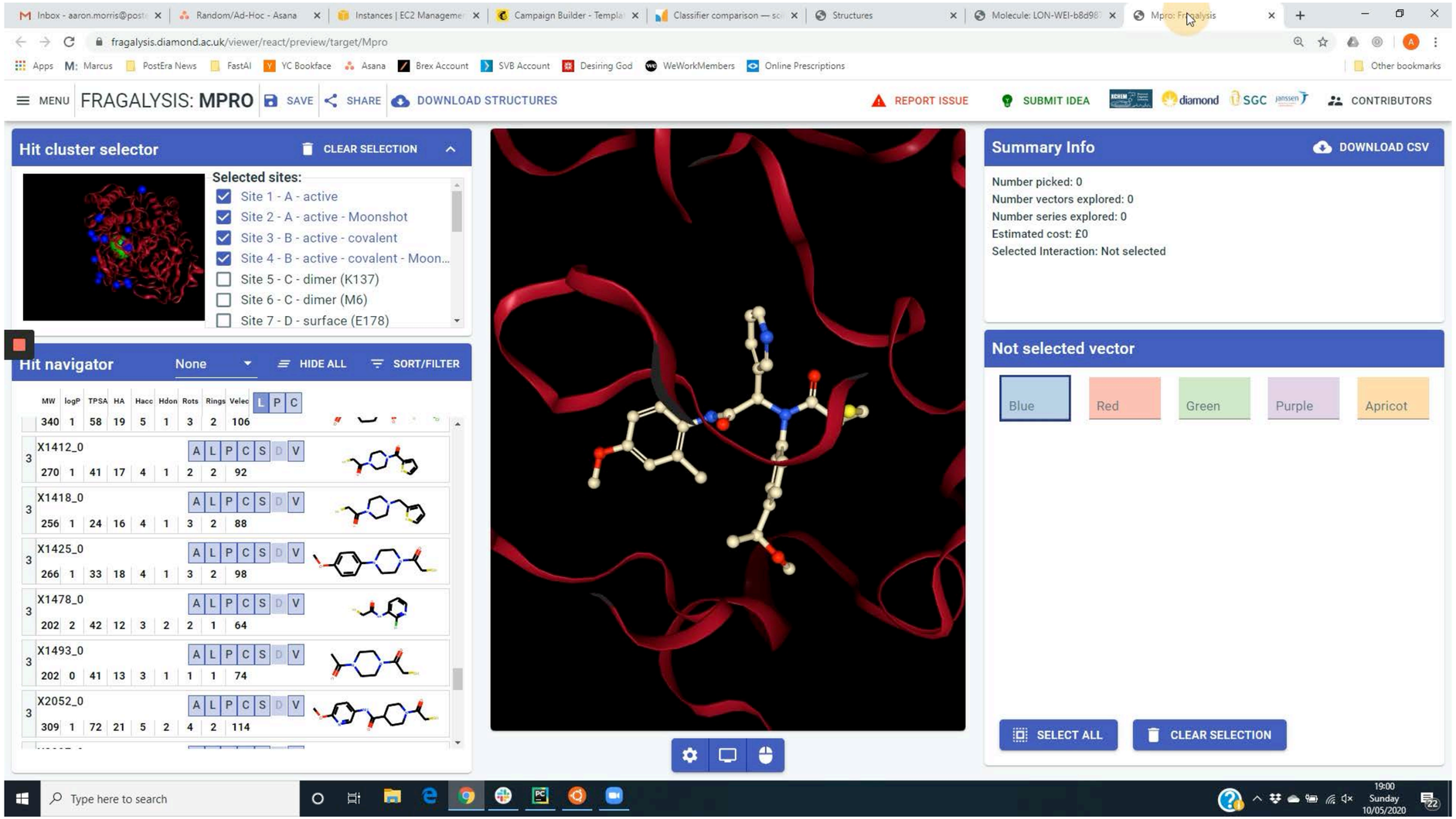
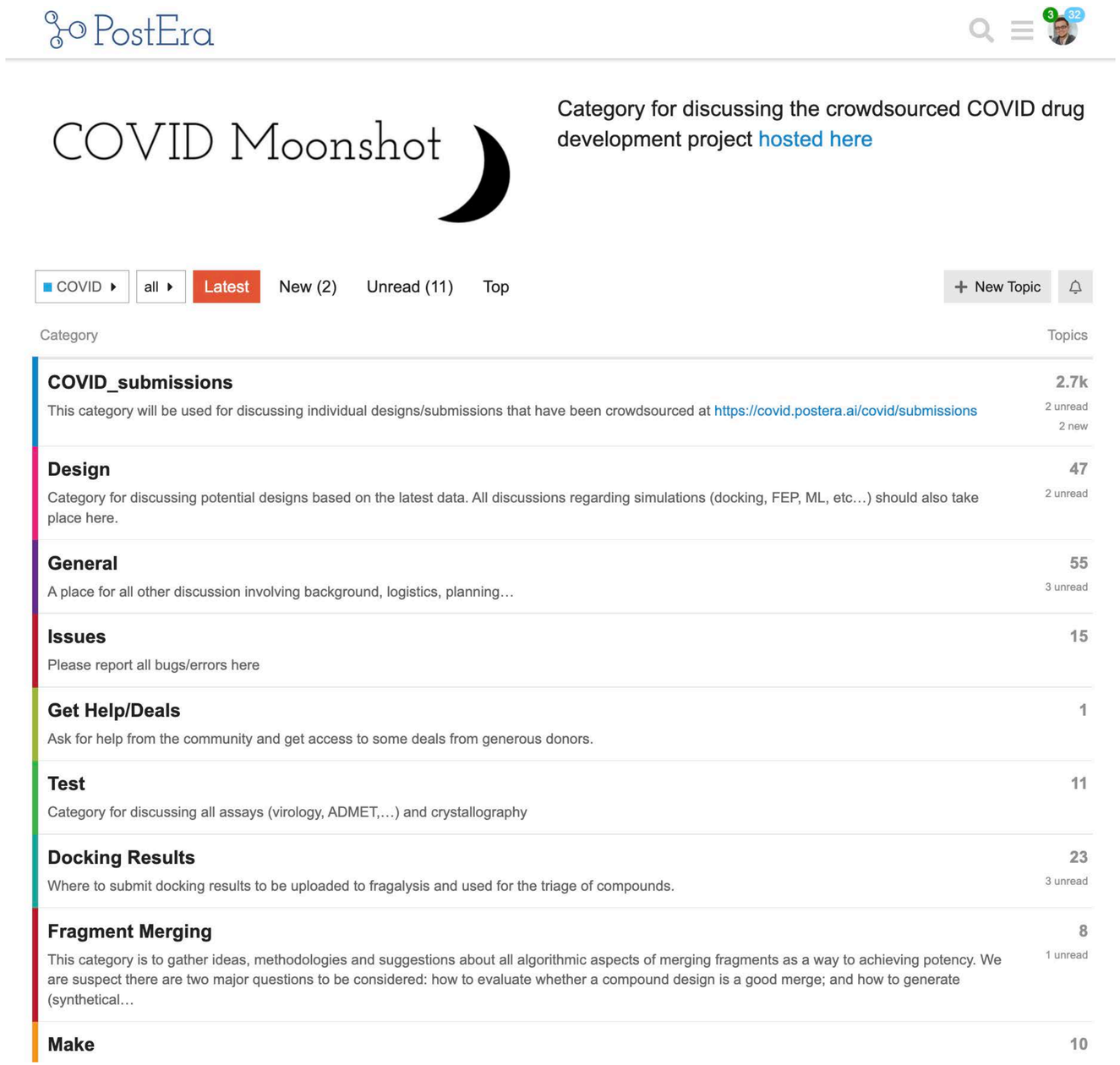


https://fragalysis.diamond.ac.uk/viewer/react/preview/target/Mpro

WE EVEN SET UP A DISCUSSION BOARD



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

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

pwkenny

Peter Kenny

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

Summary Activity Notifications Invites Badges Preferences

STATS

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

259 posts created

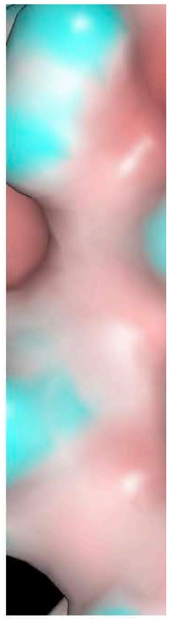
https://discuss.postera.ai/c/covid/5

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

COVID Design

pwkenny Aug '21

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



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

Jorgensen et al MPro inhibitors

COVID General

pwkenny

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

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

Jorgensen et against auton pyridine. For 02c6a514-44

SAR analysis for 3-aminopyridine-like inhibito

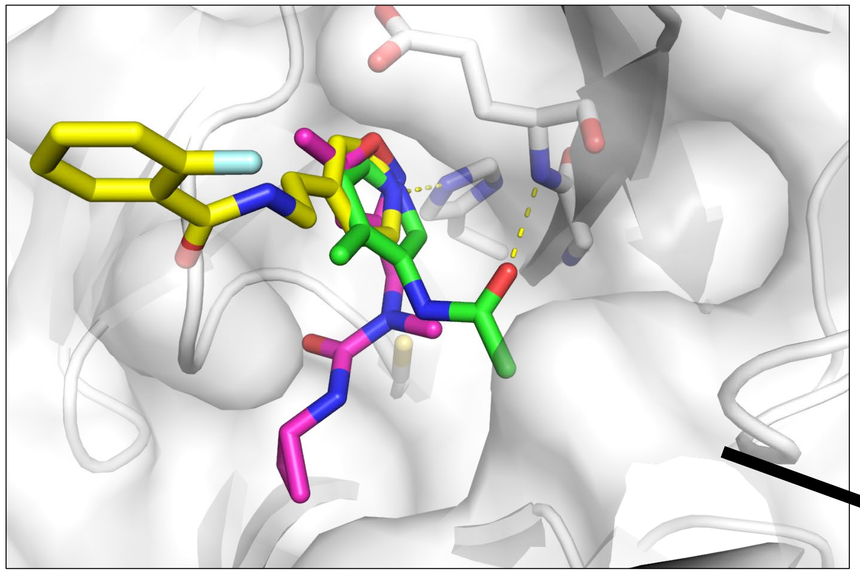
COVID Design

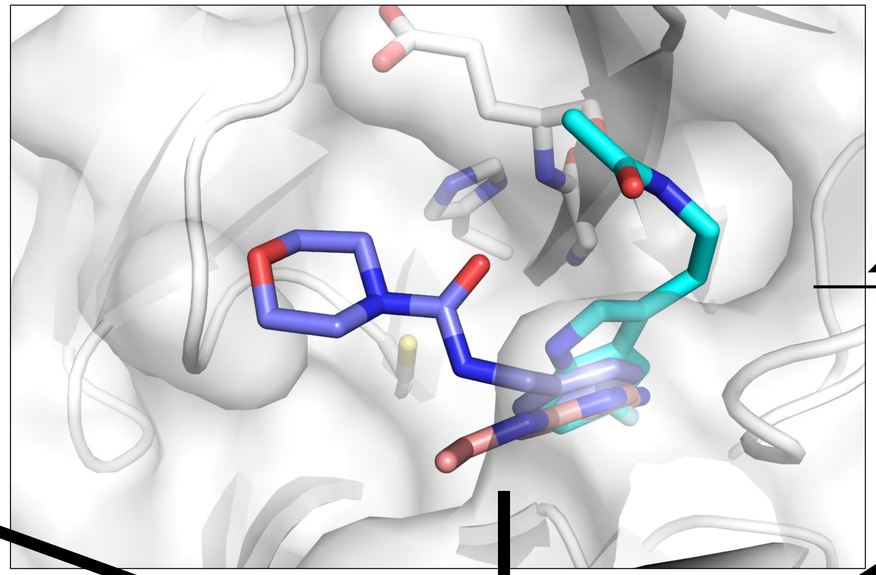
pwkenny

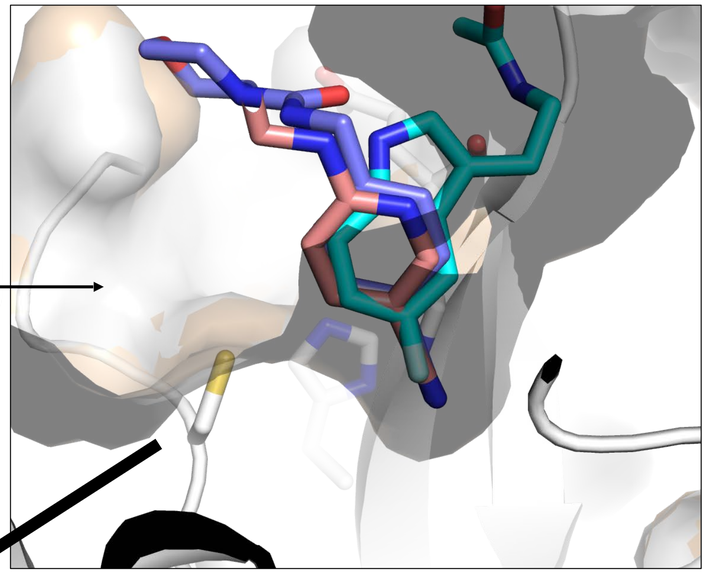
One question of potential interest to COVID Moonshot designers is whether th isoquinoline at P1 relative to pyridine are maintained when the P1 heterocycle opposed to NH). In terms of potency, an isoquinoline at P1 needs to 'pay its w (naphthalene is less aromatic than benzene and therefore more reactive)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

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

CROWDSOURCED DESIGN STRATEGIES GENERATED A NUMBER OF NOVEL CHEMICAL SERIES BY FRAGMENT MERGING





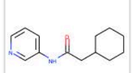


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

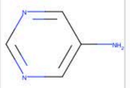
Design Rationale:

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

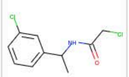
Inspired By:



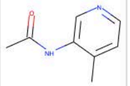
ALE-HEI-f28a35b5-9



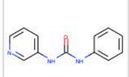
AAR-POS-d2a4d1df-18



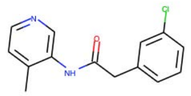
AAR-POS-0daf6b7e-10



MAK-UNK-6435e6c2-8



AAR-POS-d2a4d1df-11



TRY-UNI-714a760b-6

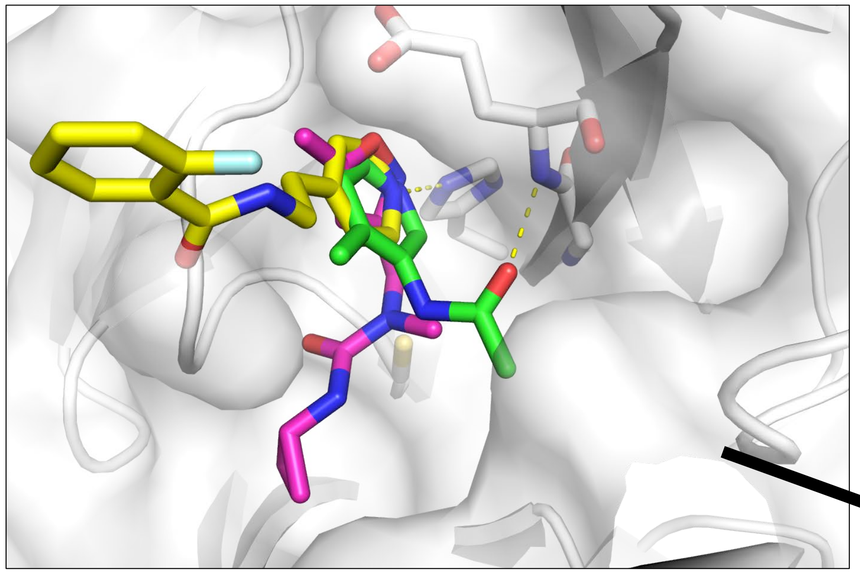
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

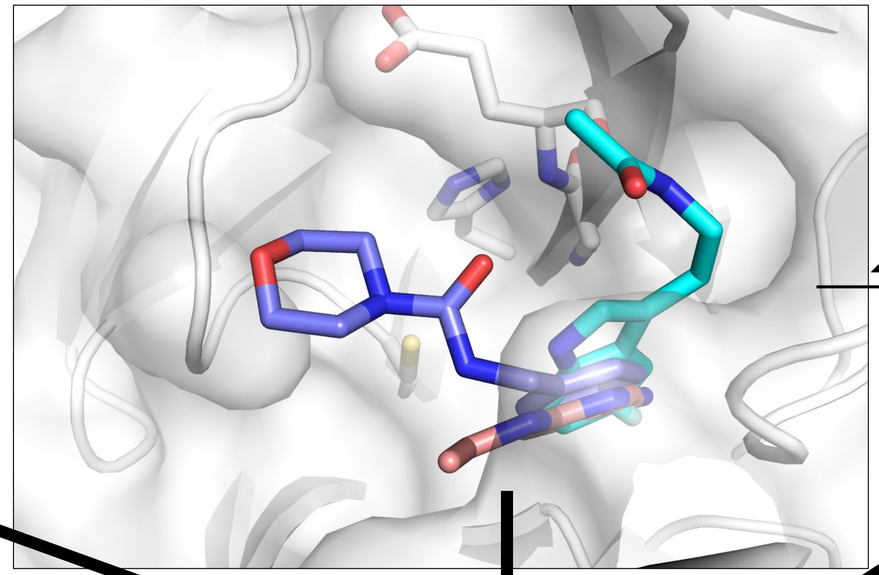
3-aminopyridine-like

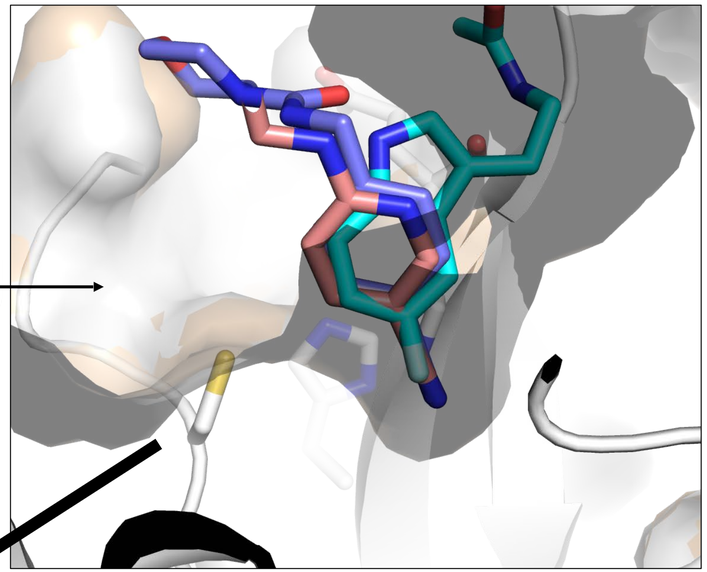
Enamine Mcule MolPort Assayed

View

CROWDSOURCED DESIGN STRATEGIES GENERATED A NUMBER OF NOVEL CHEMICAL SERIES BY FRAGMENT MERGING







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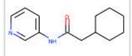
The design of the molecules was done by superimposing the different fragments from the crystal structures (by eye). The reactions should be fairly easy urea formation or amide coupling all from readily available starting materials. Fragments used for the conception of the ideas are the following x0107,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

Inspired By:



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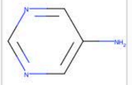

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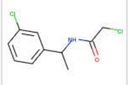

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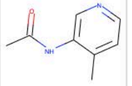

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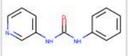

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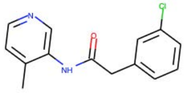


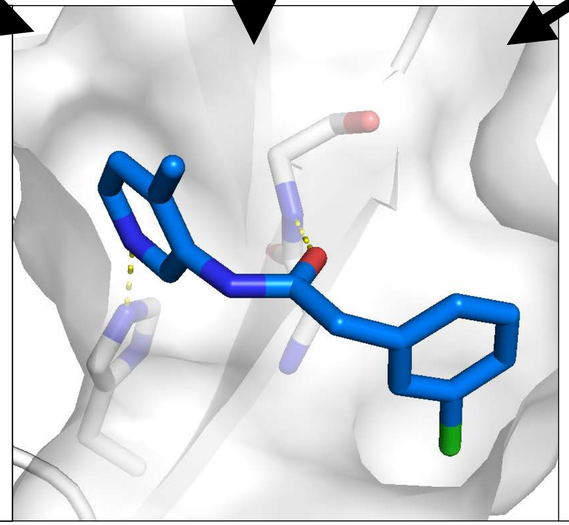
TRY-UNI-714a760b-6

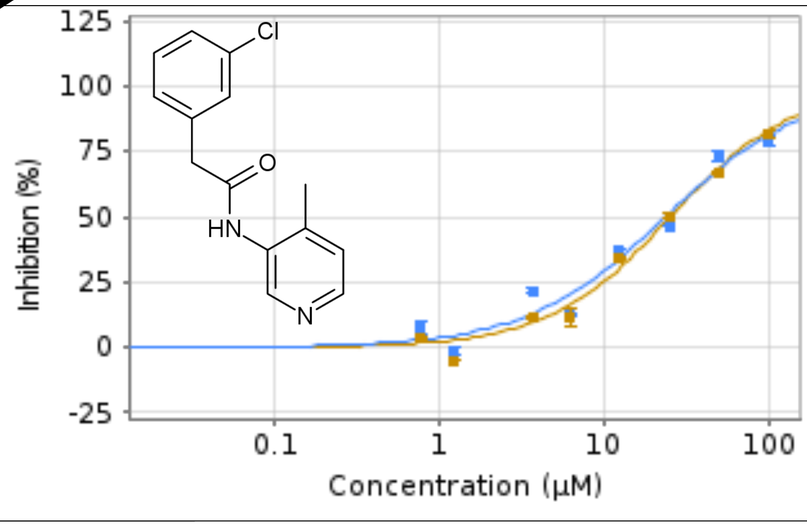
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

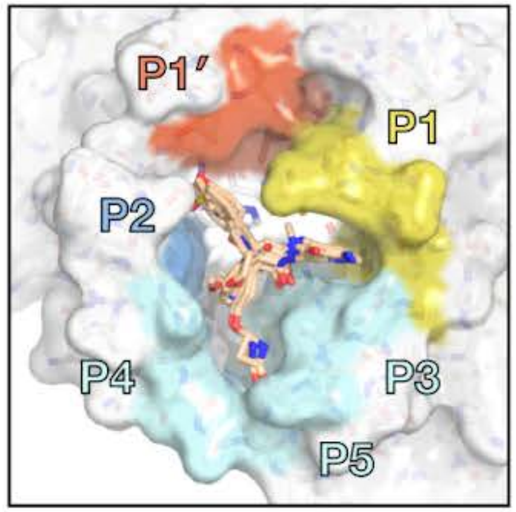
Enamine Mcule MolPort Assayed

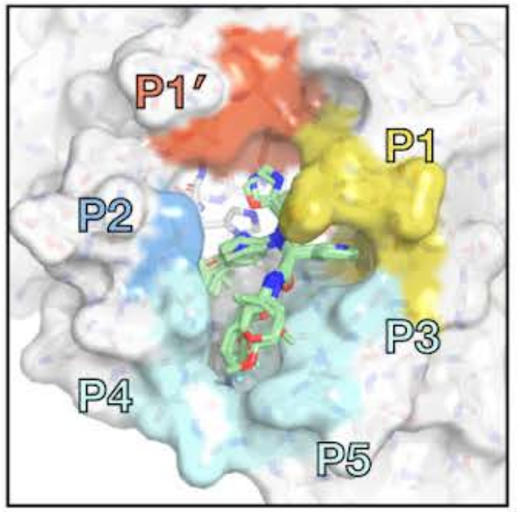
View

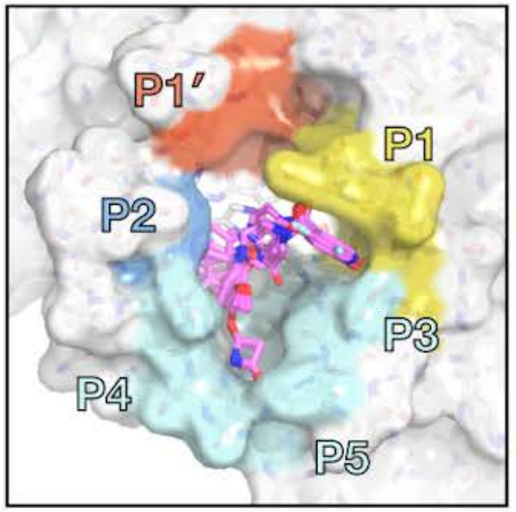


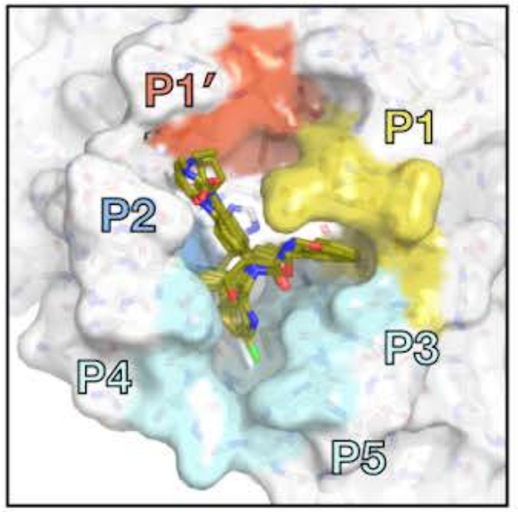


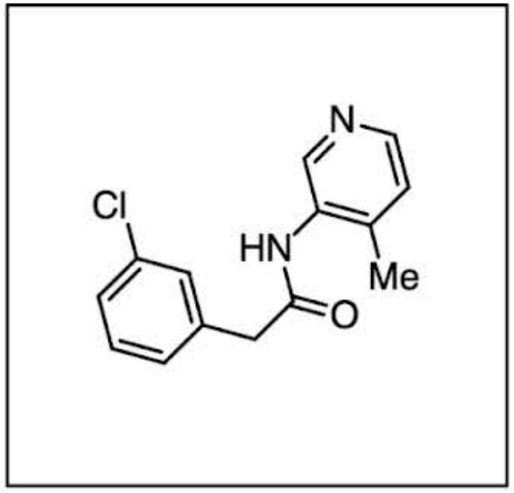
CROWDSOURCING GENERATED MULTIPLE LEADS WITH NOVEL NONCOVALENT CHEMOTYPES



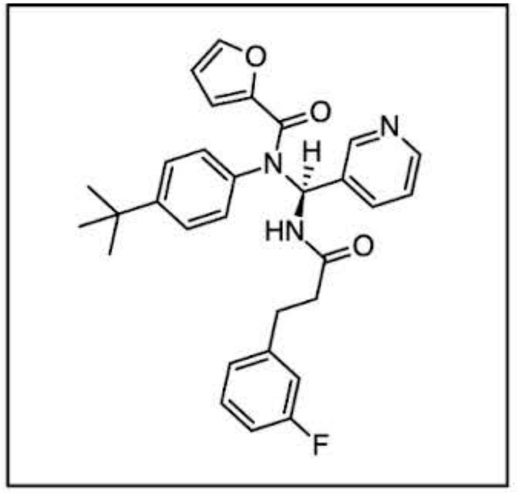




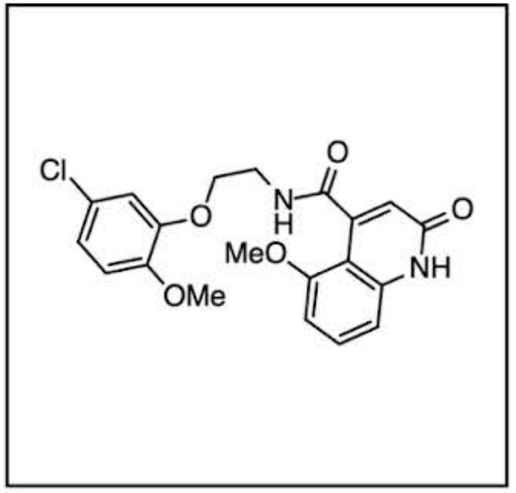




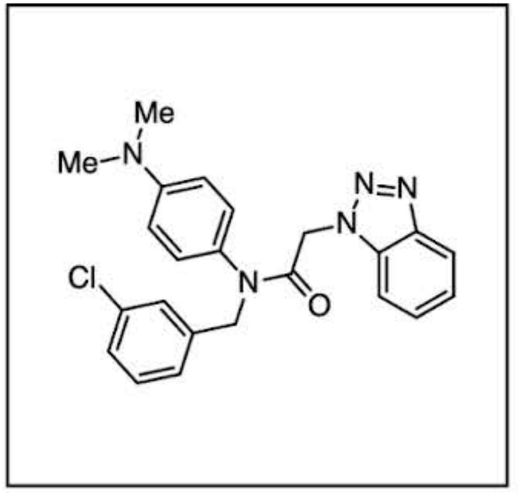
Aminopyridines



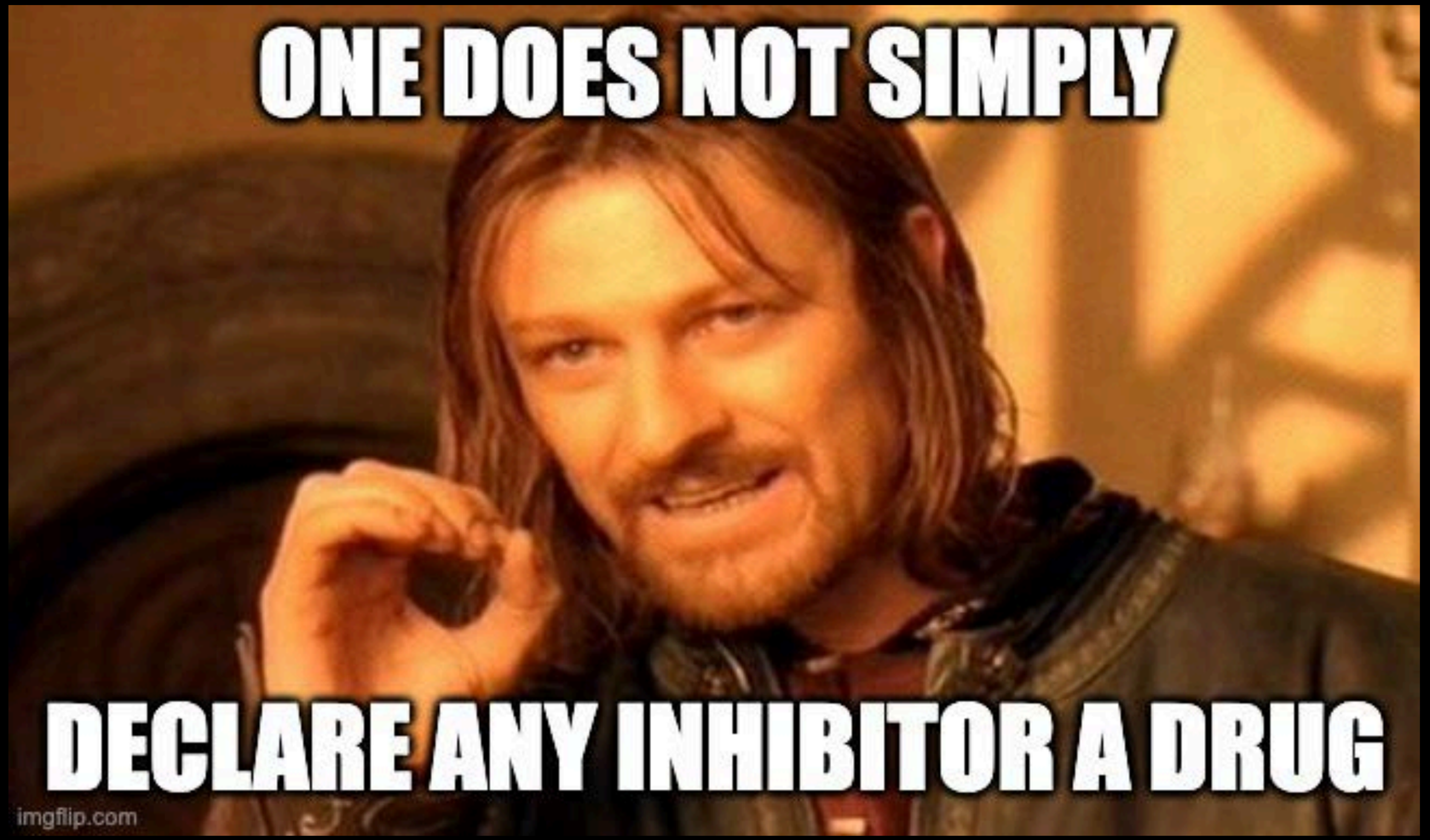
Ugis

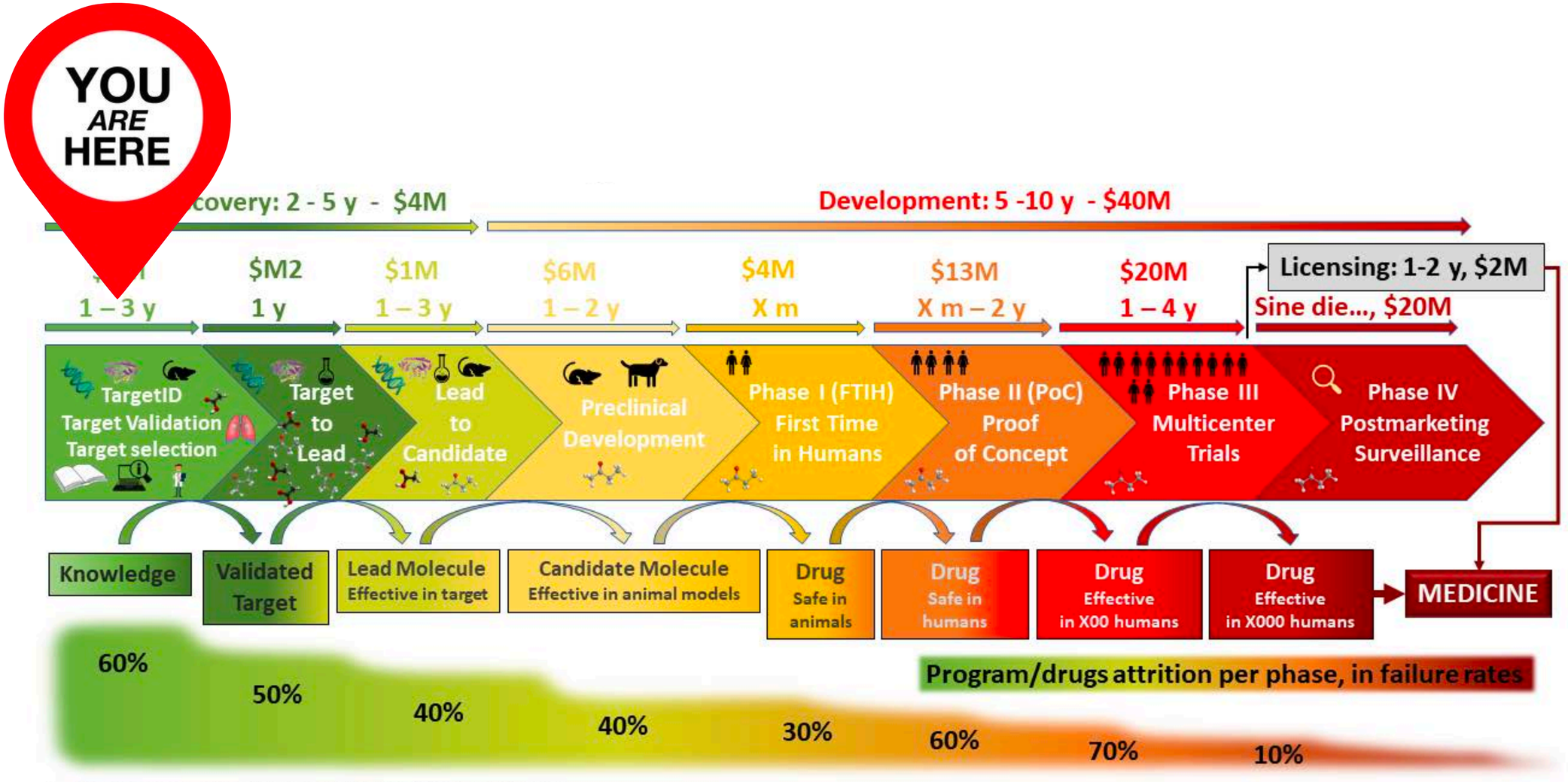


Quinolones

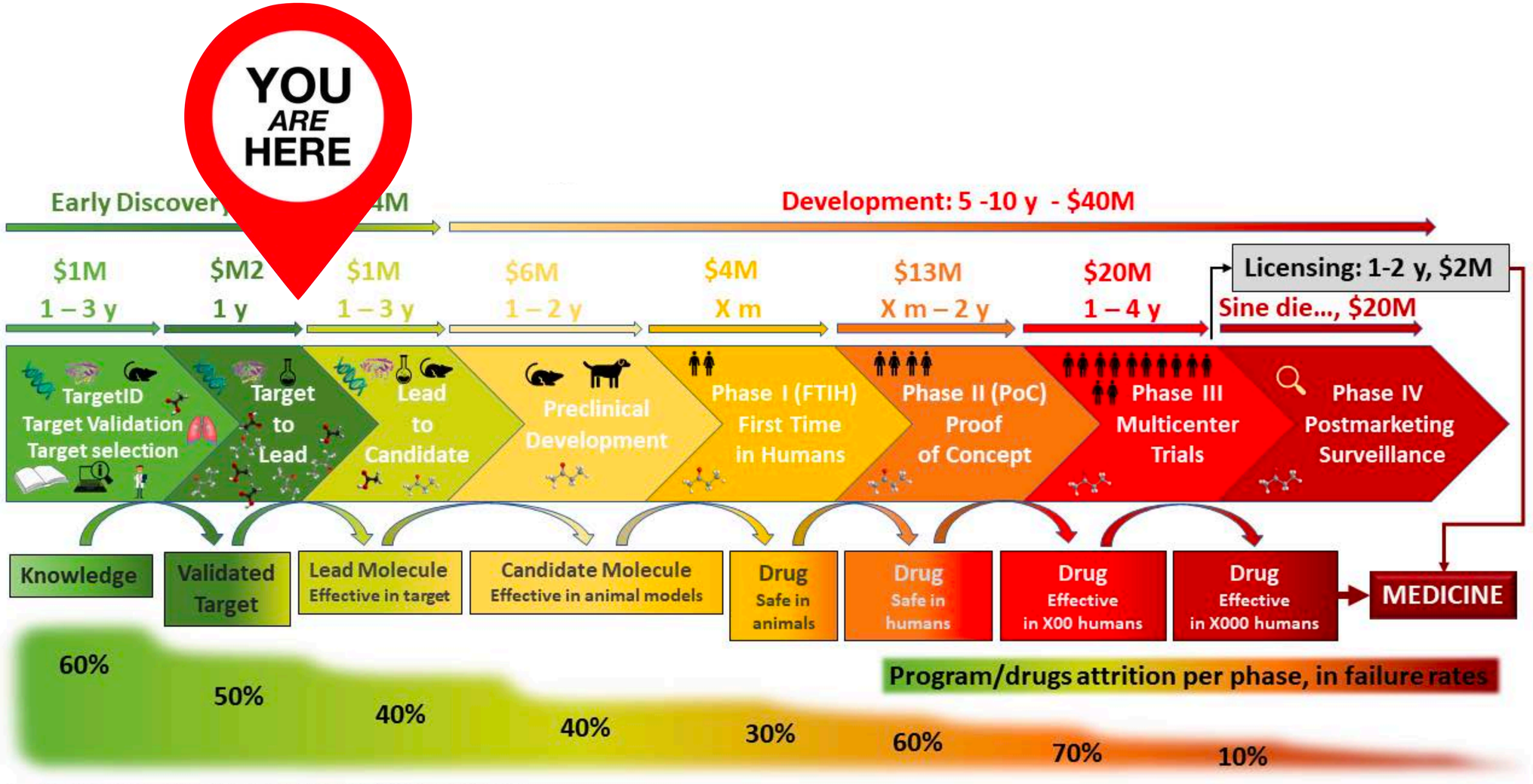


Benzotriazoles


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



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

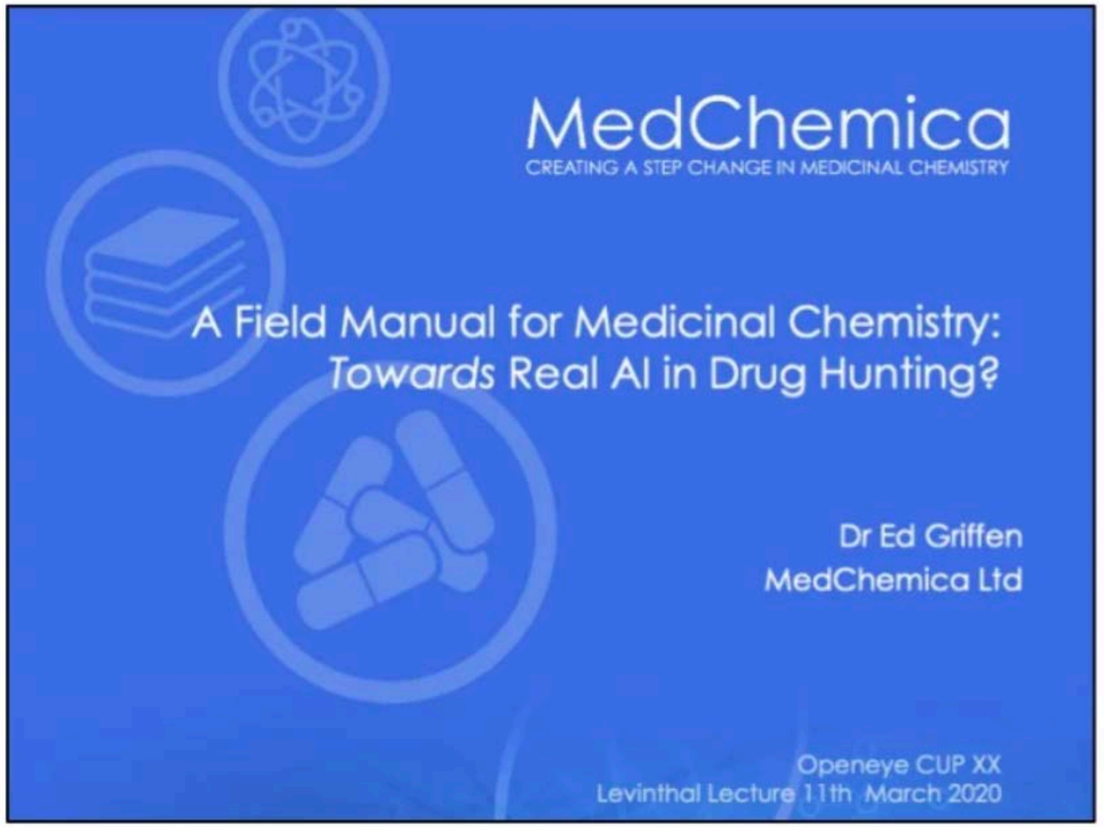


https://doctortarget.com/machine-learning-applied-drug-discovery/

- 4:45 – **Levinthal Lecture:**

  Ed Griffen, Technical Director and Founder, *MedChemica*

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



11 Mar 2022

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

Mar 23, 2020, 2:13 PM

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

Mar 23, 2020, 2:31 PM ✓

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

Mar 23, 2020, 2:42 PM

MEDICINAL CHEMISTRY PROVIDED US WITH GUIDING DESIGN PRINCIPLES

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

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

- **Potency first, covalency later (if needed)**
  - Make the compounds potent and selective first add covalent warhead if needed to avoid complications with a warhead that may react with off-targets

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

We quickly defined a target candidate profile (TCP) to capture the objectives of our drug discovery program

Ed Griffen
Medchemica

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

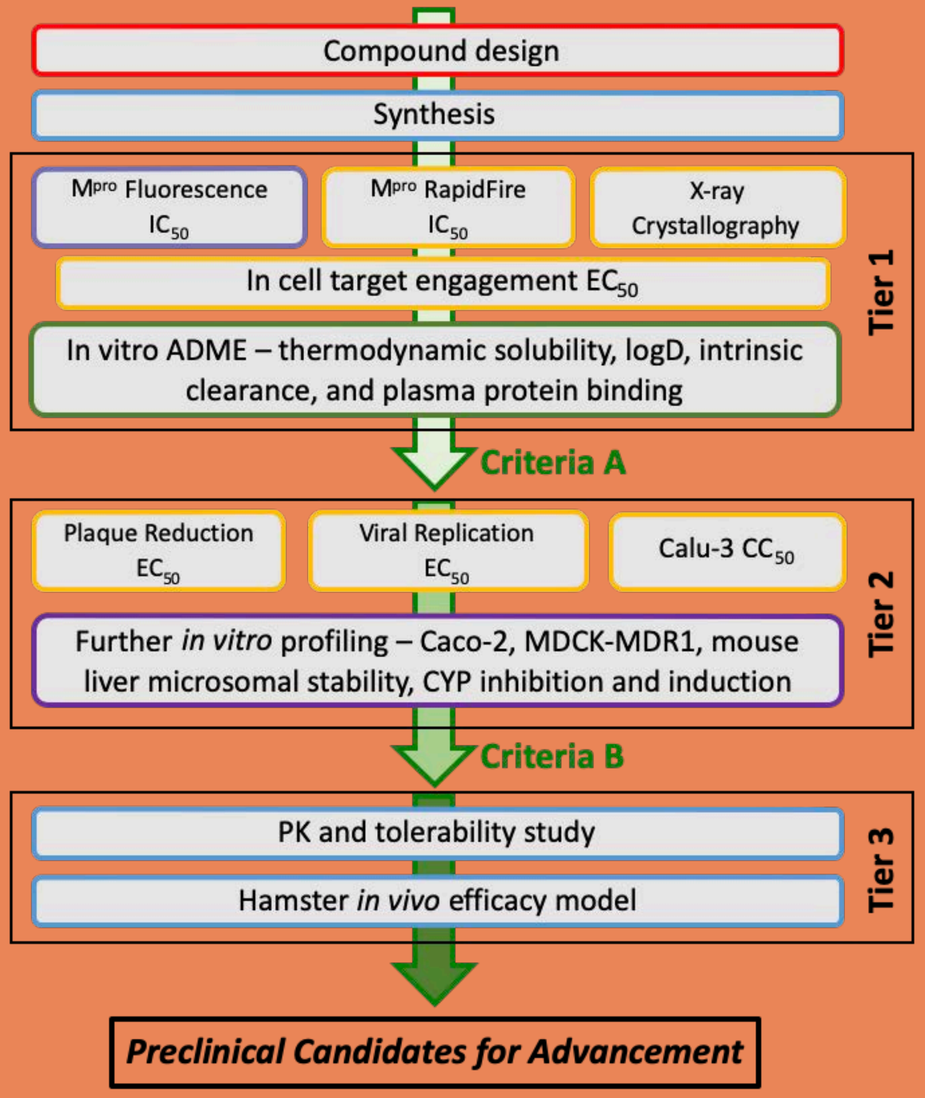
COVID Moonshot

Centre for Medicines Discovery
UNIVERSITY OF OXFORD

XCHEM Diamond Fragment Screening
diamond

Our assay cascade was an attempt to rapidly meet the TCP objectives, but relied mostly on donated resources

Ed Griffen
Medchemica



Does it inhibit Mpro? How does it bind?

Does it enter cells and inhibit Mpro?

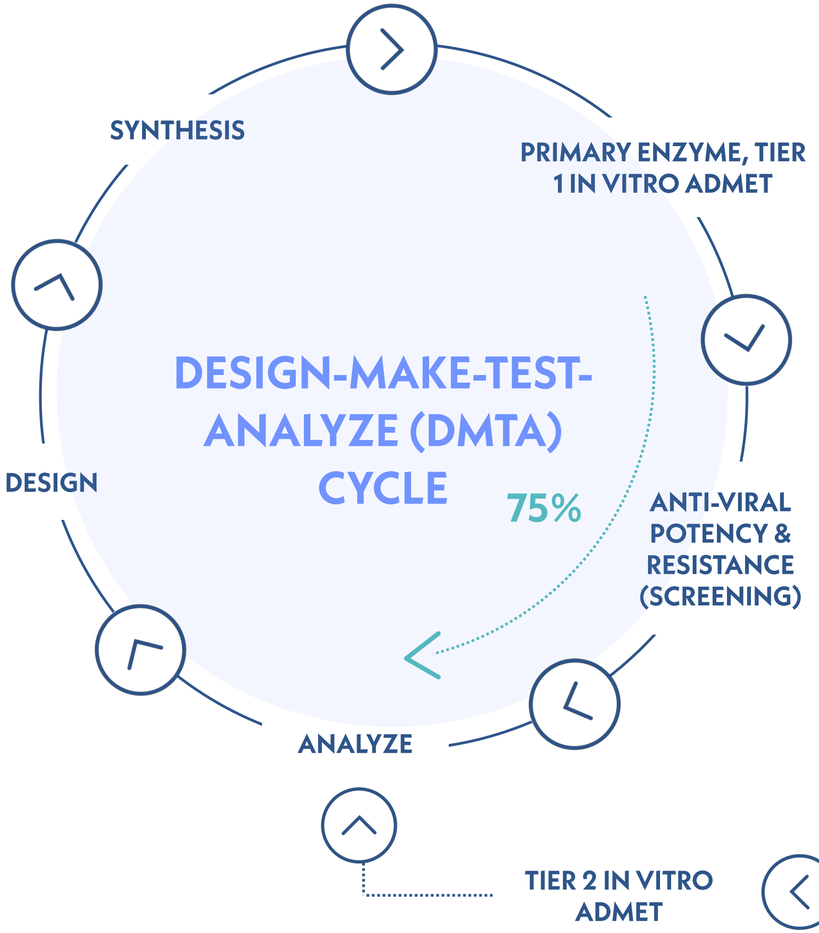
Does it have a chance of working in humans?

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

Does it have a favorable safety profile?

Is it orally bioavailable at required concentrations?

WE SPENT THE NEXT FEW MONTHS IN LEAD OPTIMIZATION DESIGN-MAKE-TEST-ANALYZE (DMTA) CYCLES



LEAD OPTIMIZATION ASSAY CASCADE

20% (~ 500 compounds)

PRIMARY IN VIVO ADMET

6% of total (120 compounds)

TIER 2 IN VITRO ADMET

Anti-viral Animal (profiling)

Anti-viral Cellular (profiling)

45 compounds

TIER 3 IN VITRO ADMET

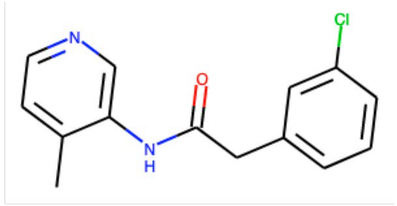
10 compounds

SECONDARY IN VIVO ADMET

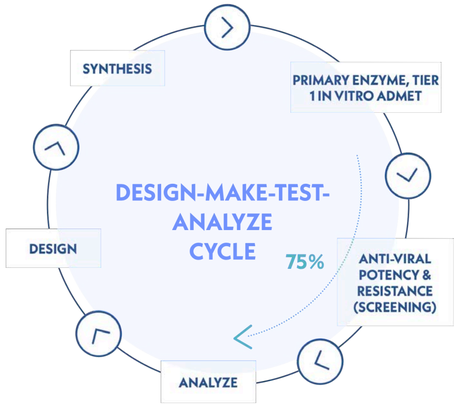
DOSE TO HUMAN PREDICTION

DESIGN-MAKE-TEST-ANALYZE CYCLES SHARE A COMMON OPERATION:

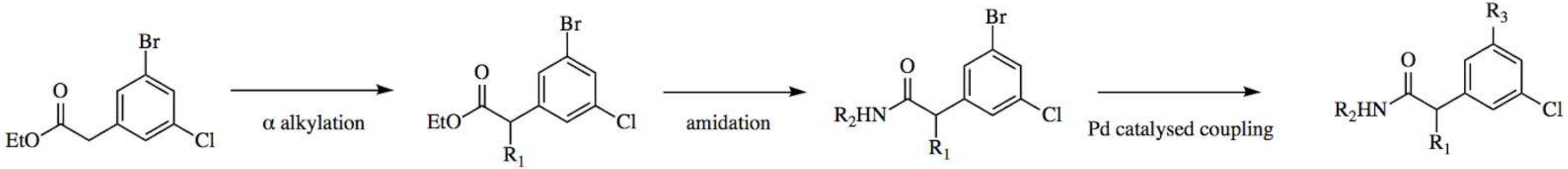
1. Select a current **lead molecule**



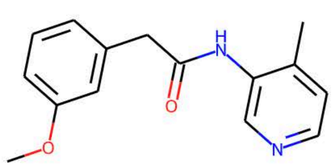
IC_{50} = 25 µM
TRY-UNI-714a760b-6



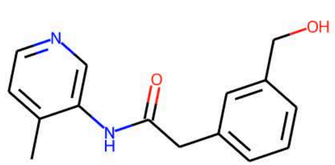
2. Use AI tools to identify a **retrosynthetic pathway** capable of installing new groups to replace part of the molecule



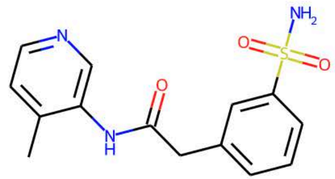
3. Chemists conservatively **select analogues** from the (often very) large enumerated synthetic space



EDJ-MED-e58735b6-1



EDJ-MED-e58735b6-2



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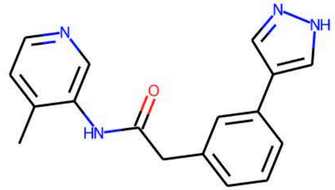
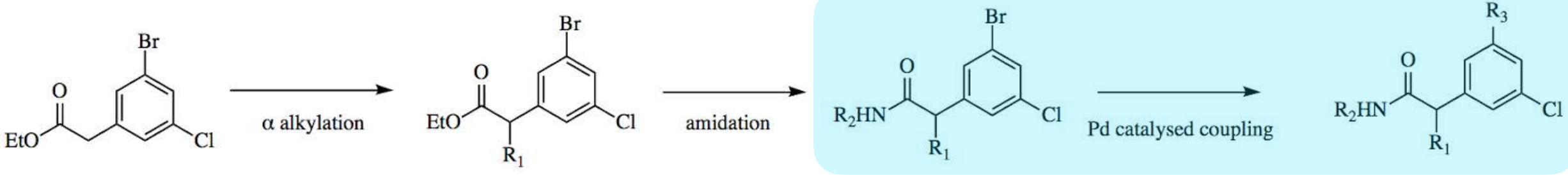
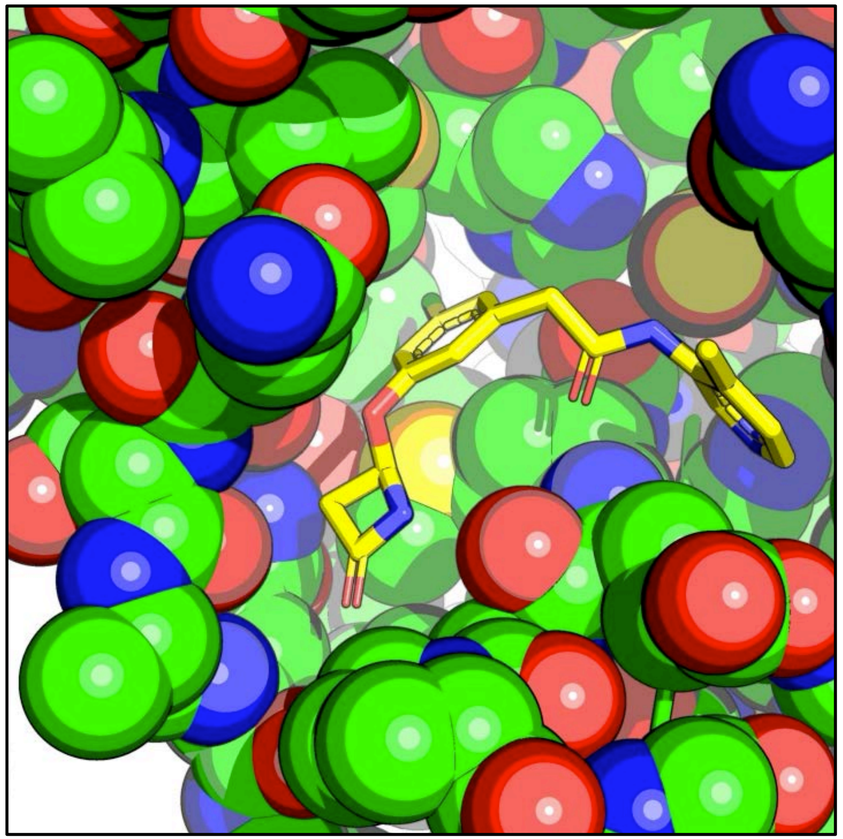


EDJ-MED-e58735b6-4

COULD WE USE PREDICTIVE MODELS TO IDENTIFY PROMISING IDEAS THE CHEMISTS HAD OVERLOOKED?





~15,000
Potential
R3 groups

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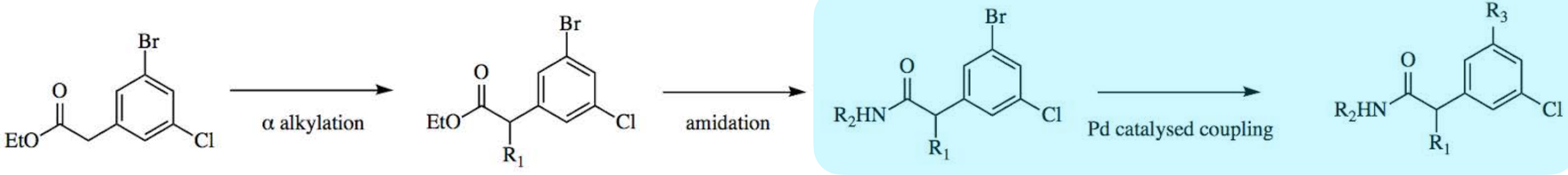

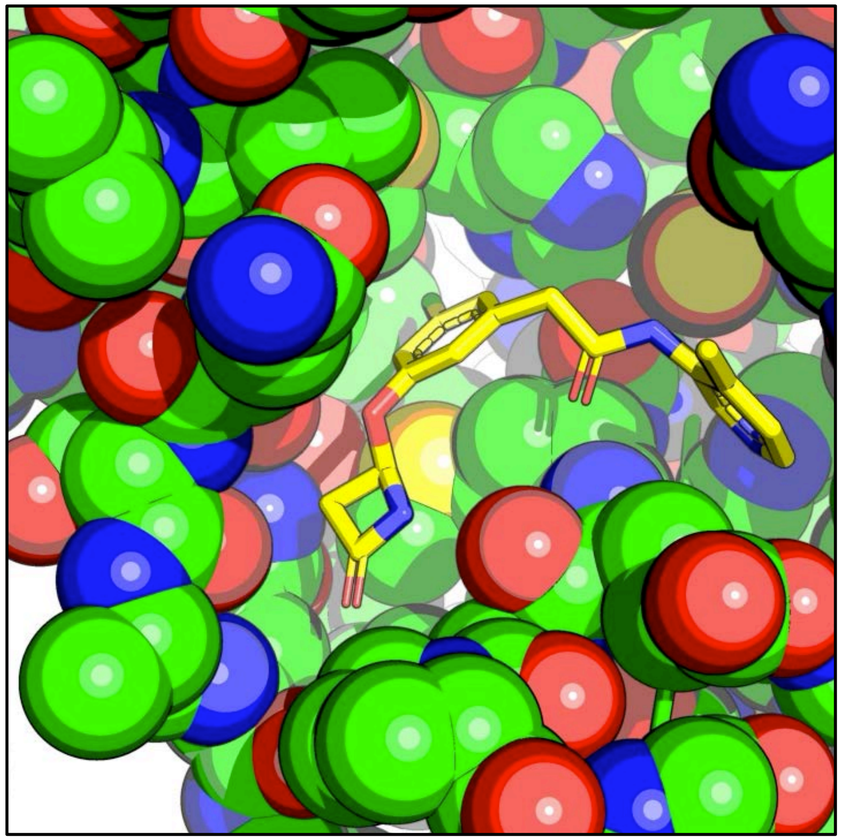

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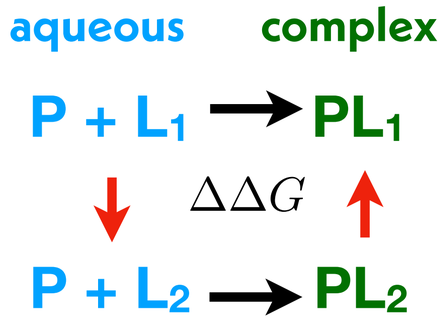
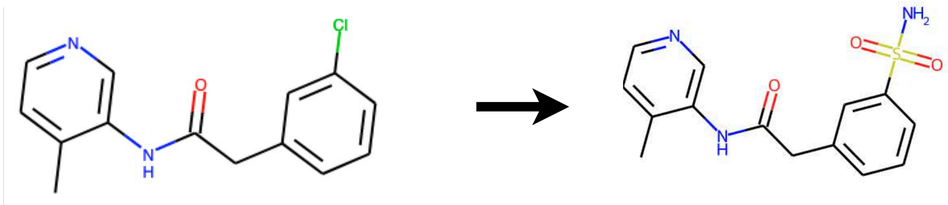
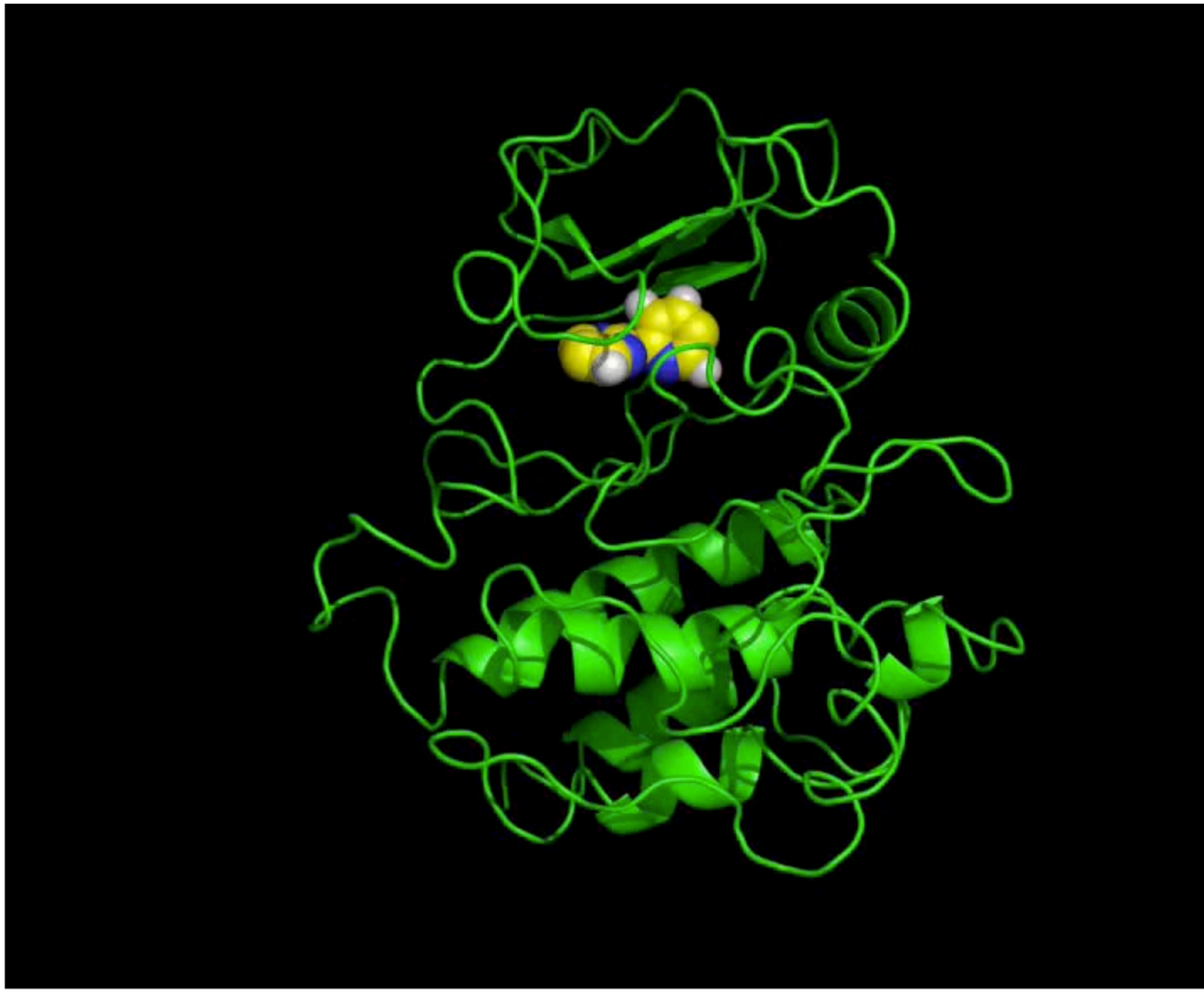
ALCHEMICAL FREE ENERGY CALCULATIONS ARE A USEFUL WAY TO EXPLOIT STRUCTURAL DATA TO PREDICT BINDING AFFINITIES



requires same or **similar scaffolds**
requires **common scaffold to anchor series**





Pioneering work from many: McCammon, van Gunsteren, Kollman, Jorgensen, Chipot, Roux, Boresch, Fujitani, Pande, Shirts, Swope, Christ, Mobley, and many more
LiveCoMS Best Practices: https://livecomsjournal.org/index.php/livecoms/article/view/v2i1e18378

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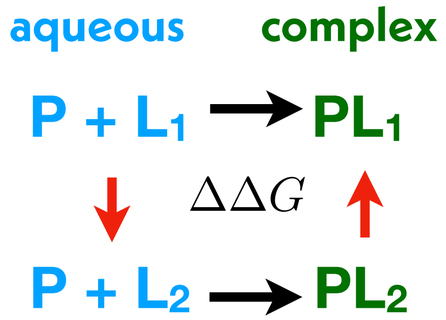

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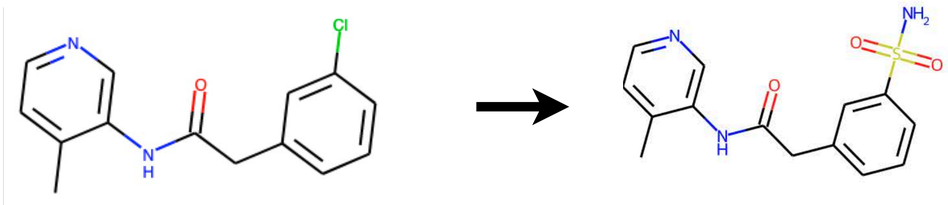

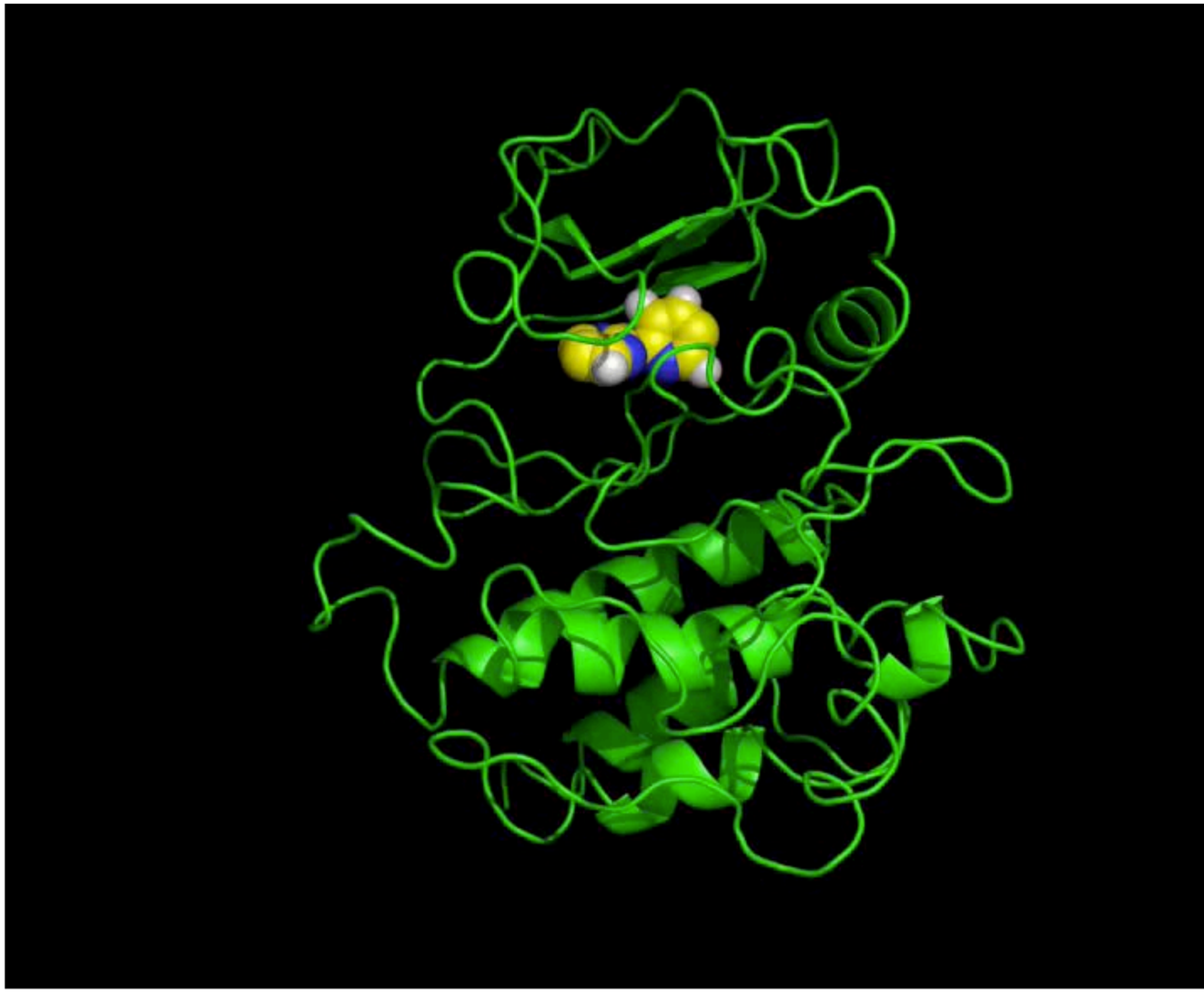

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LiveCoMS Best Practices: https://livecomsjournal.org/index.php/livecoms/article/view/v2i1e18378

open forcefield

An open and collaborative approach to better force fields

OPEN SOURCE

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

OPEN SCIENCE

Scientific reports as blog posts, webinars and preprints

OPEN DATA

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

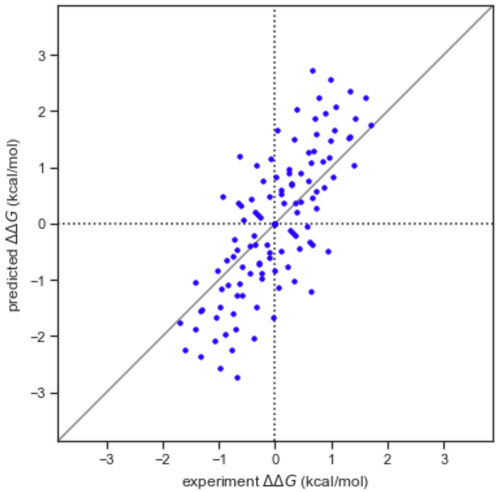
NEWS TUTORIALS ROADMAP

http://openforcefield.org

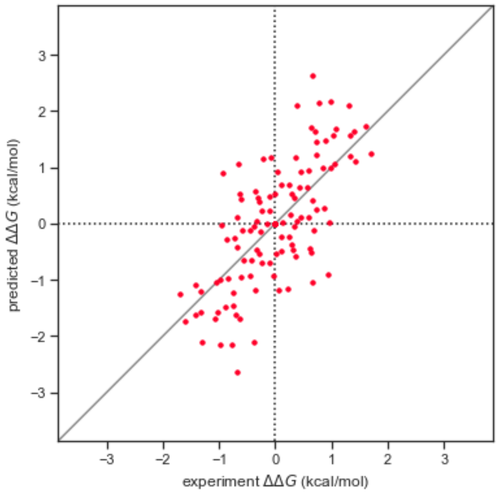
THE OPEN FORCE FIELD INITIATIVE HAS PRODUCED SYSTEMATICALLY MORE ACCURATE FORCE FIELD GENERATIONS

Open Force Field →

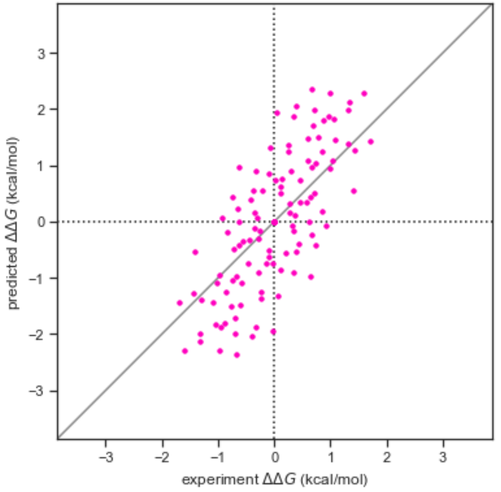
GAFF 1 (1999)



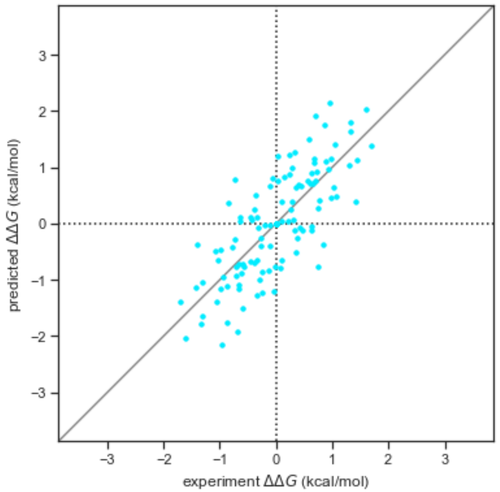
OPLS2.1 (2015)



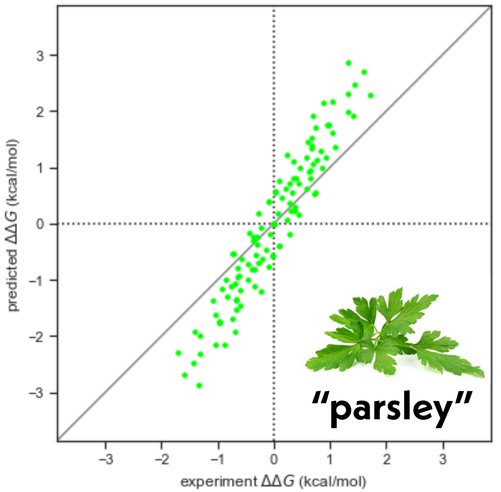
GAFF 2 (2016)



smirnoff99Frosst (2018)

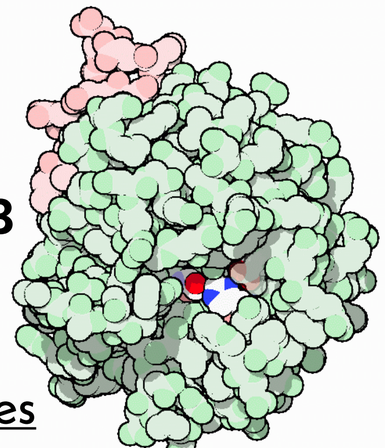


openff 1.0 (2019)



open forcefield

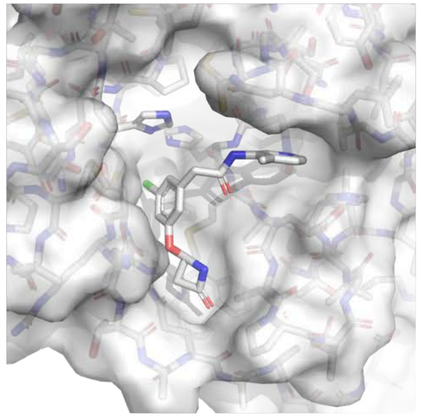
thrombin
PDB101: 1PPB



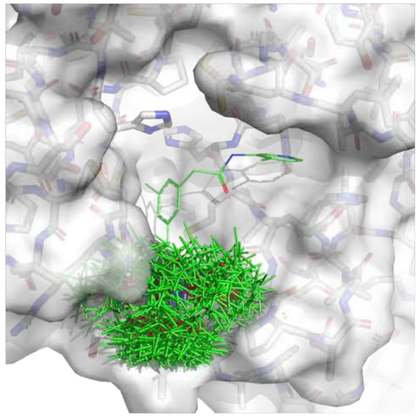
http://github.com/choderalab/perses

QUICK RETROSPECTIVE CALCULATIONS SUGGESTED OUR TOOLS DID A REASONABLY GOOD JOB OF PREDICTING COMPOUND POTENCY

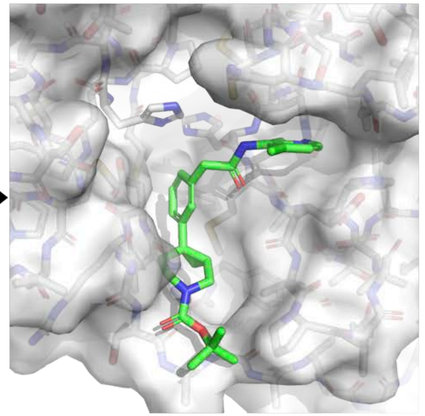
X-ray structure as reference



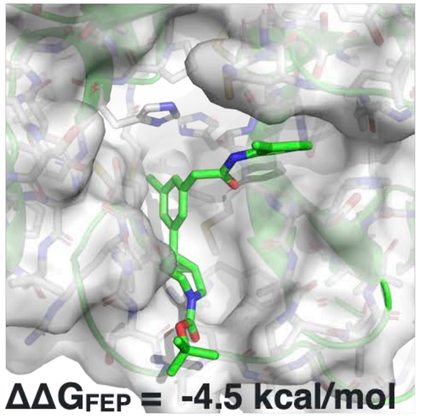
constrained enumeration of poses for proposed molecule



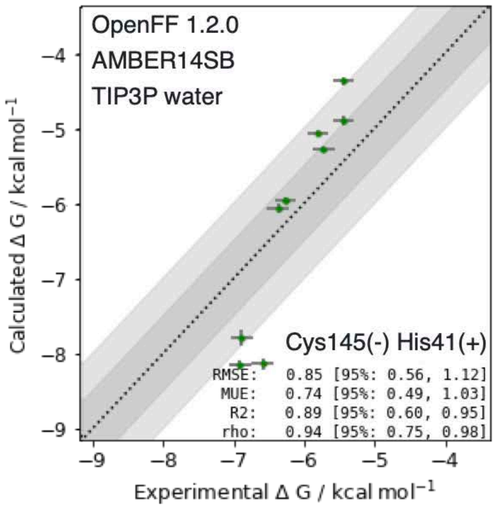
selection of pose with best docking score



free energy calculation final posed structure



3-aminopyridine lead series



DOMINIC RUFA TPCB student

HANNAH BRUCE MACDONALD postdoc

WILLIAM GLASS postdoc

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

Typically, we use fast graphics processing units (GPUs)
to run a few dozen calculations.

Where do we get enough GPUs to score virtual libraries of >15,000 compounds each week?

OUR LAB IS A MEMBER OF THE FOLDING@HOME CONSORTIUM, A WORLDWIDE DISTRIBUTED COMPUTING NETWORK

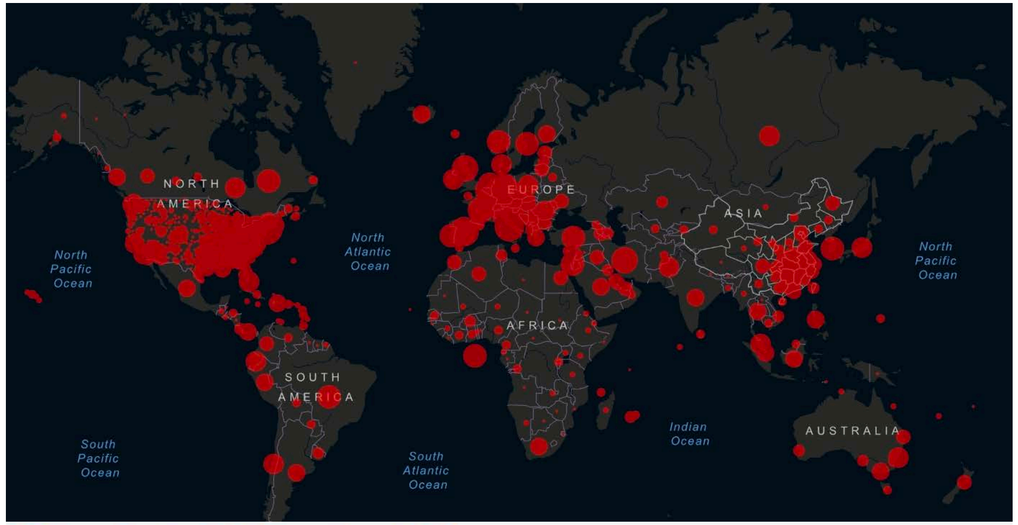
FOLDING @HOME

CHOOSE YOUR PLATFORM

Windows macOS 64bit Linux

FOLDING@HOME CONSORTIUM 2023

GREG BOWMAN | VINCENT VOELZ | ANTONIA MEY | JOHN CHODERA | SONYA HANSON | PILAR COSSIO | DIWAKAR SHUKLA



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!

AS PEOPLE FROM AROUND THE WORLD STARTED RUNNING FOLDING@HOME, WE QUICKLY CREATED THE WORLD'S FIRST EXASCALE COMPUTING RESOURCE

Folding@home blog

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

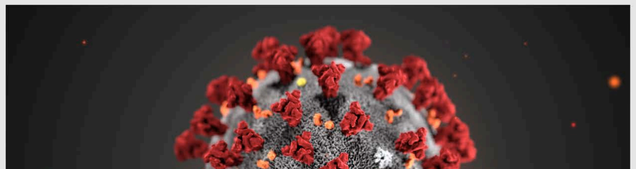
February 27, 2020
by Greg Bowman

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.



Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

Ivy Zhang (CBM)

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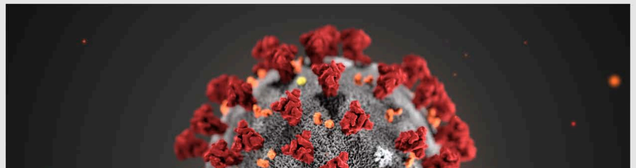
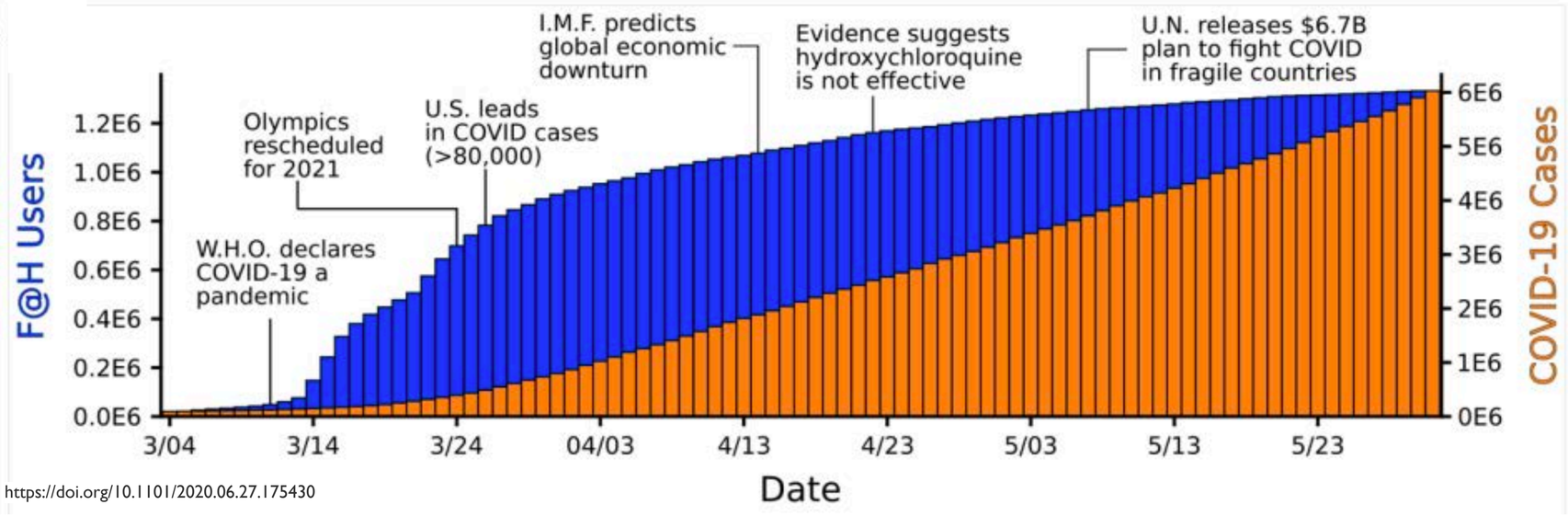




https://doi.org/10.1101/2020.06.27.175430

Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

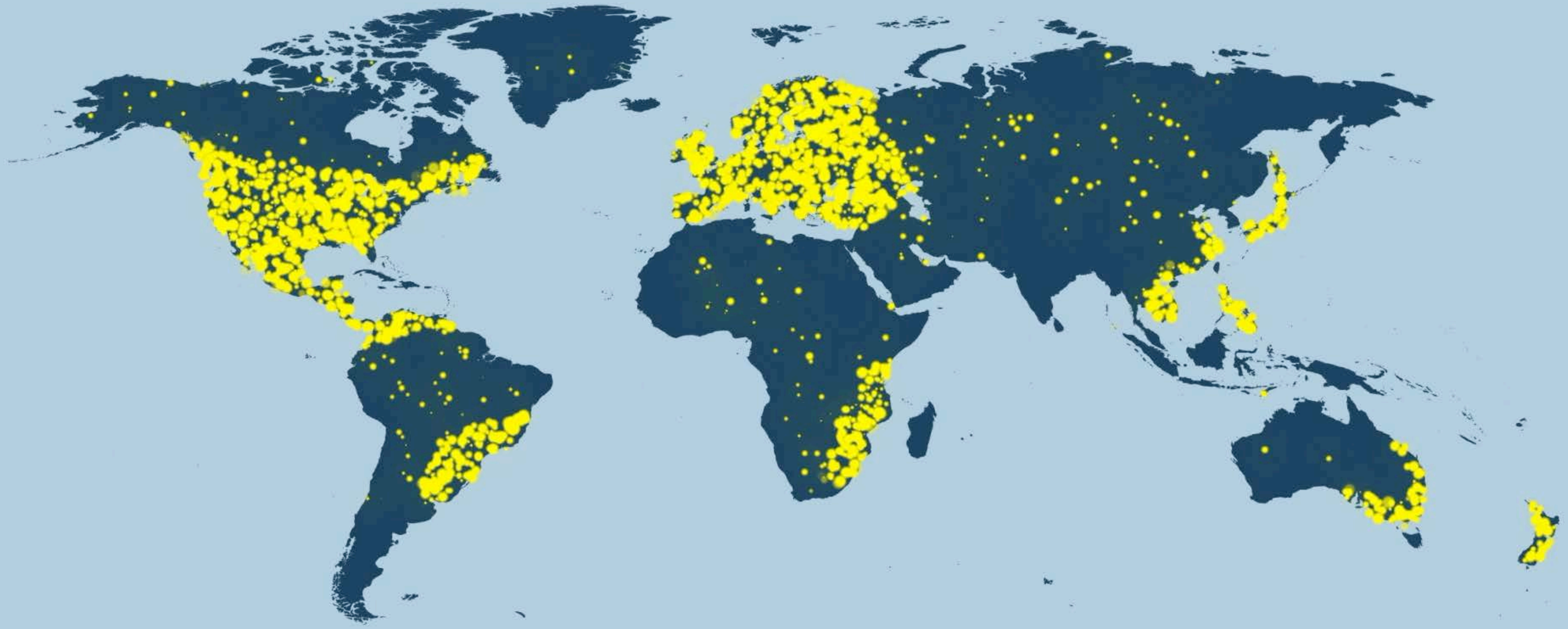
Ivy Zhang (CBM)

~1.5 exaflops

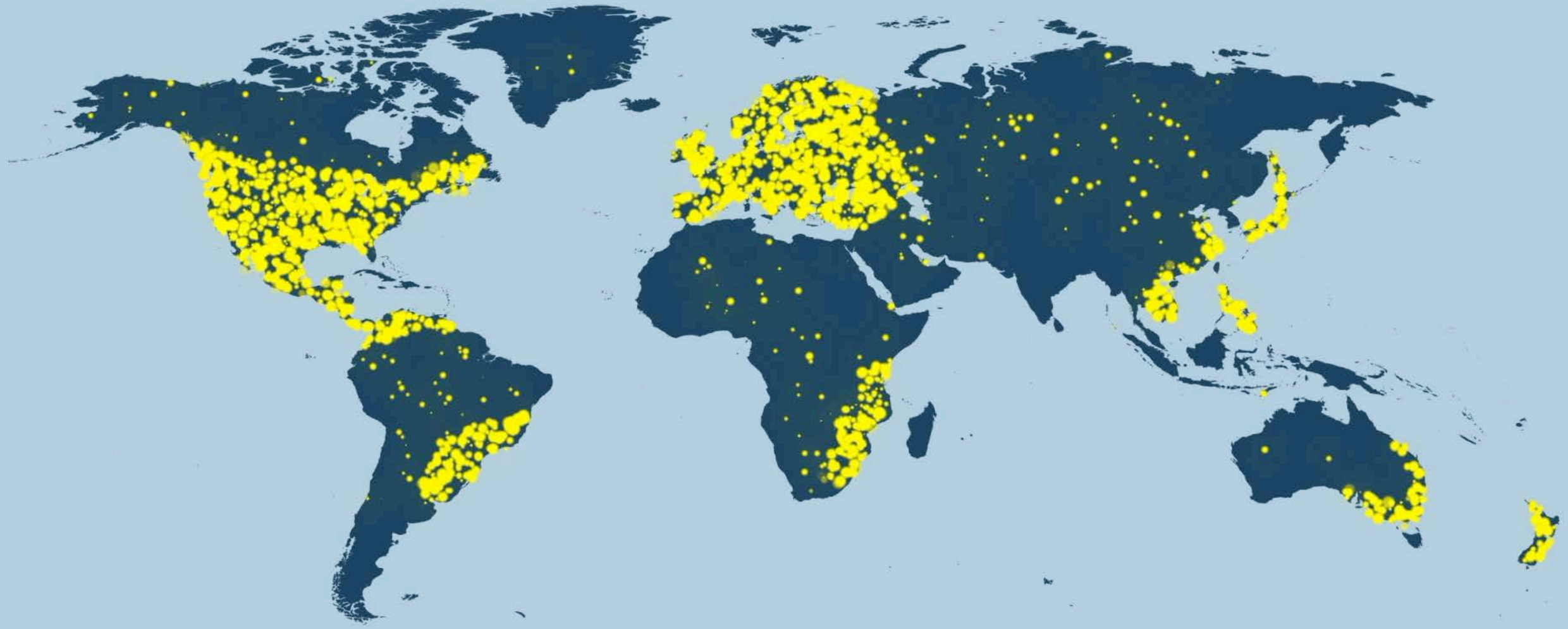
> sum of top-10 supercomputers

This would cost $6.8B/year on AWS.

Nature Chemistry 13:651, 2021



BOTH COMPUTING AND SCIENCE CONTRIBUTORS WERE TRULY GLOBAL



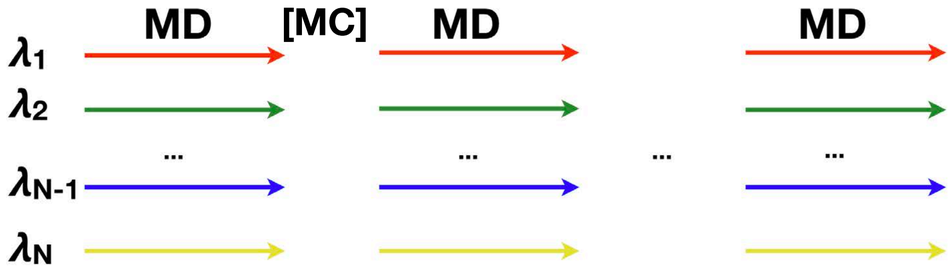
BOTH COMPUTING AND SCIENCE CONTRIBUTORS WERE TRULY GLOBAL

ALCHEMICAL FREE ENERGY CALCULATIONS GENERALLY USE CLEVER BUT COMPLEX MARKOV CHAIN MONTE CARLO ALGORITHMS TO SAMPLE ALCHEMICAL STATES

Independent simulations

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

simple but dangerous

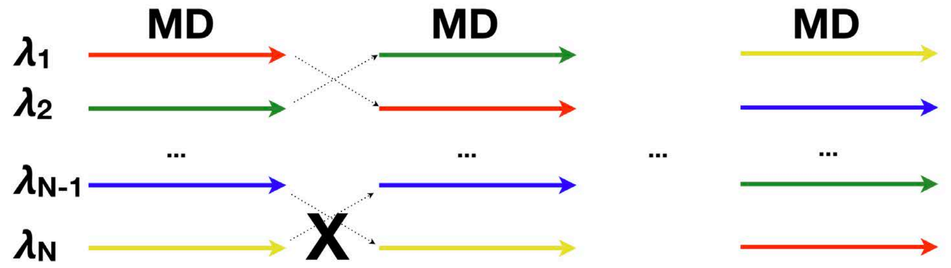


AMBER18 TI
Song, Lee, Zhu, York, Merz 2019
https://doi.org/10.1021/acs.jcim.9b00105

Hamiltonian replica exchange ★

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

reliable but complex and costly



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

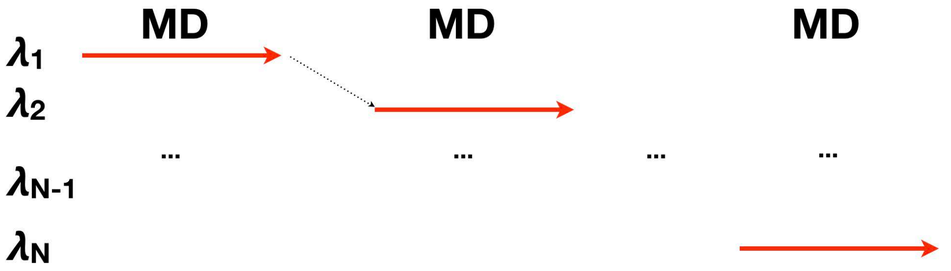
NAMD
Jiang, Thirman, Jo, Roux 2018
http://doi.org/10.1021/acs.jpcb.8b03277

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

Single-replica methods

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

immature and tricky to implement



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

Excursions in Statistical Dynamics

by

Gavin Earl Crooks

B.Sc. (University of East Anglia) 1992
M.Sc. (University of East Anglia) 1993

A dissertation submitted in partial satisfaction of the
requirements for the degree of
Doctor of Philosophy

in

Chemistry

in the

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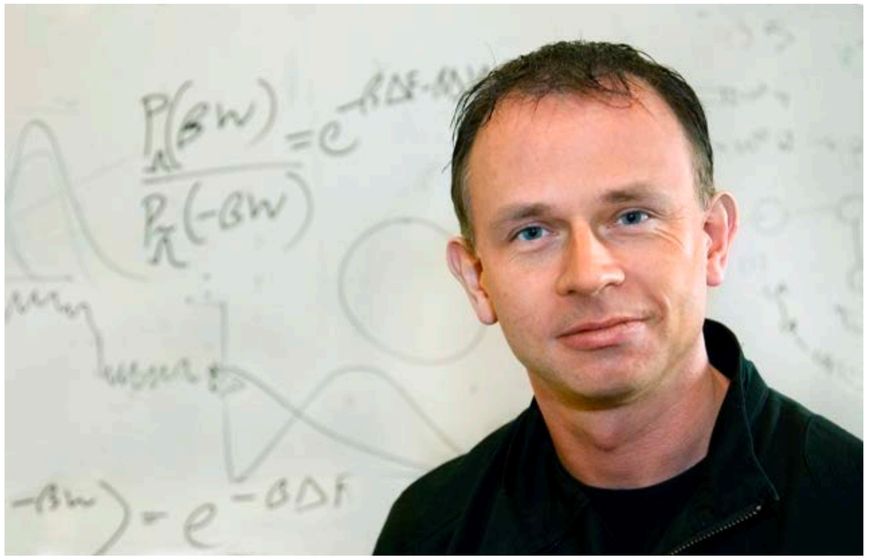
Committee in charge:

Professor David Chandler, Chair
Professor Robert A. Harris
Professor Daniel S. Rokhsar

1999



JOURNAL OF COMPUTATIONAL PHYSICS 22, 245–268 (1976)

Efficient Estimation of Free Energy Differences from Monte Carlo Data

CHARLES H. BENNETT

IBM Thomas J. Watson Research Center, Yorktown Heights, New York 10598

Received February 13, 1976; accepted May 3, 1976

Near-optimal strategies are developed for estimating the free energy difference between two canonical ensembles, given a Metropolis-type Monte Carlo program for sampling each one. The estimation strategy depends on the extent of overlap between the two ensembles, on the smoothness of the density-of-states as a function of the difference potential, and on the relative Monte Carlo sampling costs, per statistically independent data point. The best estimate of the free energy difference is usually obtained by dividing the available computer time approximately equally between the two ensembles; its efficiency (variance × computer time)$^{-1}$ is never less, and may be several orders of magnitude greater, than that obtained by sampling only one ensemble, as is done in perturbation theory.

I. INTRODUCTION

A well-known deficiency of the Monte Carlo [1, 2] and molecular dynamics [3] methods, commonly used to study the thermodynamic properties of classical systems having 10^2 to 10^4 degrees of freedom, is their inability to calculate quantities such as the entropy or free energy, which cannot be expressed as canonical or microcanonical ensemble averages. In general, the free energy of a Monte Carlo (MC) or molecular dynamics (MD) system can be determined only by a procedure analogous to calorimetry, i.e., by establishing a reversible path between the system of interest and some reference system of known free energy. "Computer calorimetry" has a considerable advantage over laboratory calorimetry in that the reference system may differ from the system of interest not only in its thermodynamic state variables but also in its Hamiltonian, thereby making possible a much wider variety of reference systems and reversible paths. Often the path between an analytically tractable reference system and the system of ultimate physical interest will include one or more intermediate systems. These may be interesting in their own right (e.g., the hard sphere fluid), or they may be special systems, important only as calorimetric stepping stones, whose Hamiltonians contain artificial terms designed to stabilize the system against phase transitions [4, 5], induce favorable importance weighting [6, 7], or otherwise enhance the system's efficiency as a computational tool [8–10].

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1999

Vol 437|8 September 2005|doi:10.1038/nature04061 nature

LETTERS

Verification of the Crooks fluctuation theorem and recovery of RNA folding free energies

D. Collin[1]*, F. Ritort[2]*, C. Jarzynski[3], S. B. Smith[4], I. Tinoco Jr[5] & C. Bustamante[4,6]

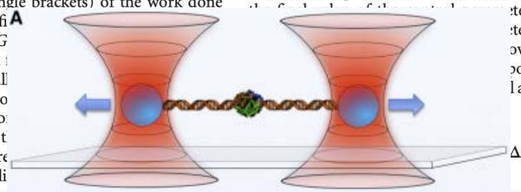
Atomic force microscopes and optical tweezers are widely used to probe the mechanical properties of individual molecules and molecular interactions, by exerting mechanical forces that induce transitions such as unfolding or dissociation. These transitions often occur under nonequilibrium conditions and are associated with hysteresis effects—features usually taken to preclude the extraction of equilibrium information from the experimental data. But fluctuation theorems[1–5] allow us to relate the work along nonequilibrium trajectories to thermodynamic free-energy differences. They have been shown to be applicable to single-molecule force measurements[6] and have already provided information on the folding free energy of a RNA hairpin[7,8]. Here we show that the Crooks fluctuation theorem[9] can be used to determine folding free energies for folding and unfolding processes occurring in weak as well as strong nonequilibrium regimes, thereby providing a test of its validity under such conditions. We use optical tweezers[10] to measure repeatedly the mechanical work associated with the unfolding and refolding of a small RNA hairpin[11] and an RNA three-helix junction[12]. The resultant work distributions are then analysed according to the theorem and allow us to determine the difference in folding free energy between an RNA molecule and a mutant differing only by one base pair, and the thermodynamic stabilizing effect of magnesium ions on the RNA structure.

The Crooks fluctuation theorem[9] (CFT) predicts a symmetry relation in the work fluctuations associated with the forward and reverse changes a system undergoes as it is driven away from thermal equilibrium by the action of an external perturbation. This theorem applies to processes that are microscopically reversible, and its experimental evaluation in small systems is crucial to understand better the foundations of nonequilibrium physics[13]. A consequence of the CFT is Jarzynski's equality[14], which relates the equilibrium free-energy difference ΔG between two equilibrium states to an exponential average (denoted by angle brackets) of the work done on the system, W, taken over an infi
quilibrium experiments, $\exp(-\Delta G$
equality has been developed[6] into a
nonequilibrium single-molecule pul
free-energy profiles or potentials o
coordinates. Experimental testing o
molecule force experiments[16] used t
can be folded and unfolded quasi-re
occur far from equilibrium, the appli
hampered by large statistical unc
sensitivity of the exponential average to rare events[17,18] (low values of W). Moreover, although the equality $\langle W \rangle = \Delta G$ holds for processes occurring near equilibrium, spatial drift in the experimental system usually makes it difficult in practice to extract unfolding free energies using small loading rates (below a few pN s^{-1}). Drift effects decrease noticeably for larger pulling speeds, making it possible to obtain more reliable experimental data (and also good statistics as a large number of pulls can be executed in a reasonable time), but at the expense of a more irreversible unfolding process. Here we show that significant improvements can be obtained by using the CFT, which provides a more robust and more rapidly converging method to extract equilibrium free energies from non-equilibrium processes.

The CFT allows us to quantify the amount of hysteresis observed in the values of the irreversible work done to unfold and refold a macromolecule. Let $P_U(W)$ denote the probability distribution of the values of the work performed on the molecule in an infinite number of pulling experiments along the unfolding (U) process, and define $P_R(W)$ analogously for the reverse (R) process. For the CFT to be applicable, the unfolding and refolding processes need to be related by time-reversal symmetry, that is, in our experiments, the optical trap used to manipulate the molecule must be moved at the same speeds during unfolding and refolding. Moreover, the molecular transition probed always has to start in an equilibrium state (folded in the unfolding process, and denatured or unfolded in the refolding process) and reach a well-defined final state. The CFT[9] then predicts that:

$$\frac{P_U(W)}{P_R(-W)} = \exp\left(\frac{W - \Delta G}{k_B T}\right) \quad (1)$$

where ΔG is the free-energy change between the final and the initial states, and thus equal to the reversible work associated with this process. Note that the CFT does not require that the system studied reaches its final equilibrium state immediately after the unfolding and refolding processes have been completed; it is only the control parameter that needs to attain its final value, whereas the system may continue to equilibrate to a well-defined state that is consistent with
ter. The equilibration occurs
ter, and therefore contributes
over the external variation of a
position of the optical trap or
l approximated by the familiar



$$\Delta x_i \quad (2)$$

where x_i is the distance between the ends of the molecule and N_s is the number of intervals used in the sum (see ref. 6 for a thorough discussion of this issue). Relation (1) quantifies hysteretic effects in the pulling experiment: work values larger than ΔG occur most often

[1]Merck & Co. Inc., Automated Biotechnology Department, North Wales, Pennsylvania 19454, USA. [2]Departament de Física Fonamental, Facultat de Física, Universitat de Barcelona, Diagonal 647, 08028 Barcelona, Spain. [3]T-13 Complex Systems, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, USA. [4]Howard Hughes Medical Institute, [5]Department of Chemistry, [6]Departments of Physics and Molecular & Cell Biology, University of California, Berkeley, California 94720, USA.
*These authors contributed equally to this work.

F COMPUTATIONAL PHYSICS 22, 245–268 (1976)

: Estimation of Free Energy Differences from Monte Carlo Data

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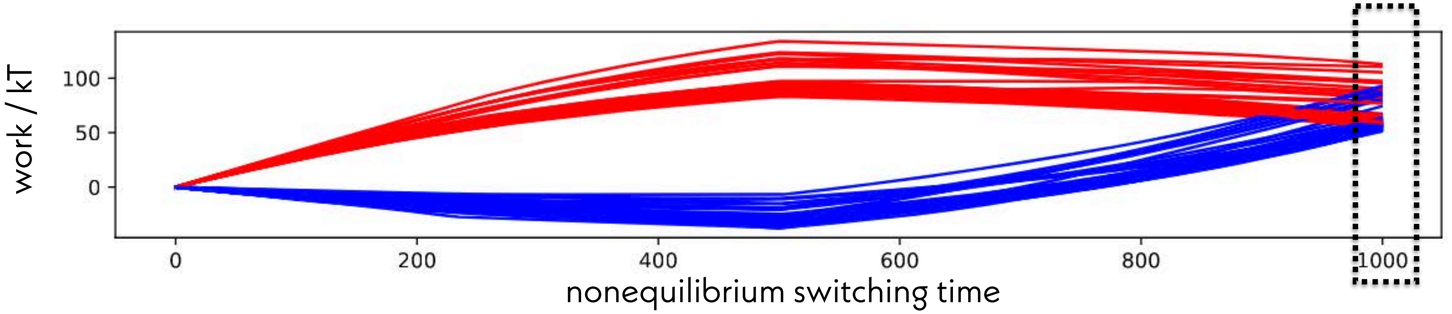
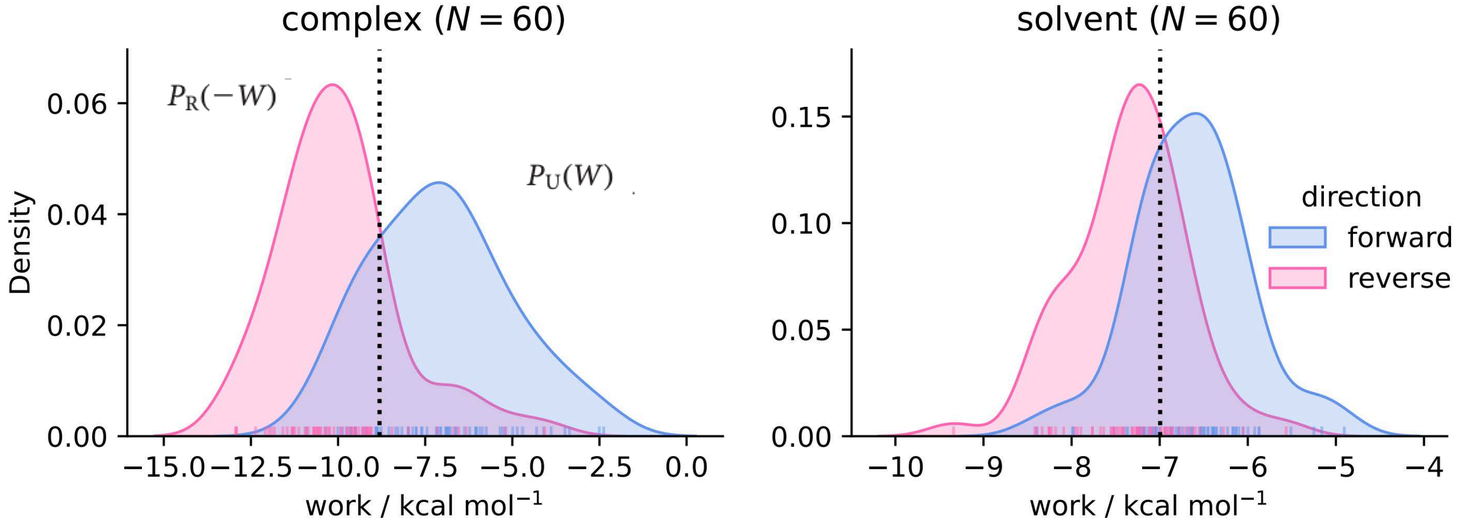
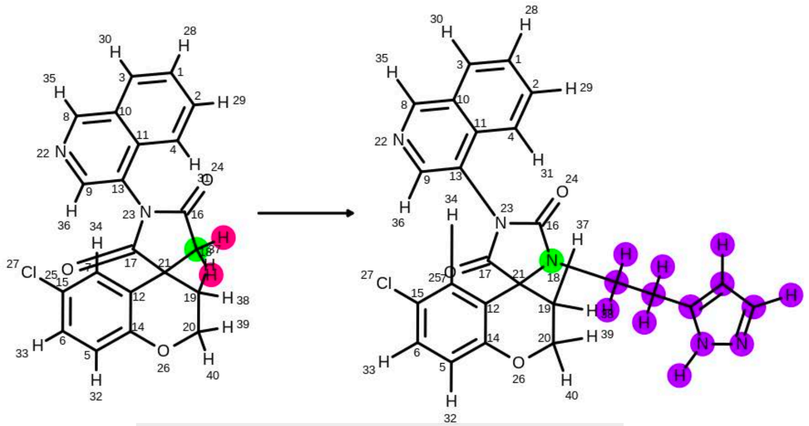
NONEQUILIBRIUM SWITCHING OR CYCLING CAN EASILY BE RUN IN PARALLEL DISTRIBUTED COMPUTING ENVIRONMENTS



$$\frac{P_{\mathrm{U}}(W)}{P_{\mathrm{R}}(-W)} = \exp\left(\frac{W - \Delta G}{k_{\mathrm{B}}T}\right)$$

Crooks fluctuation theorem





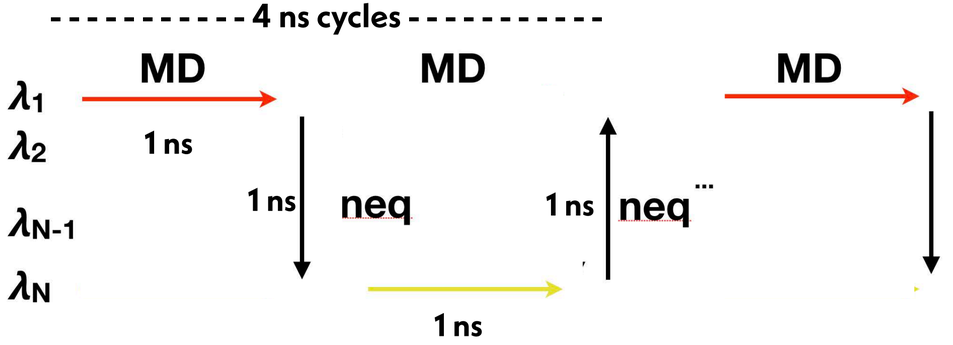
ΔΔG = –1.6 ± 0.1 kcal/mol

(from Bennett acceptance ratio)

Nonequilibrium cycling

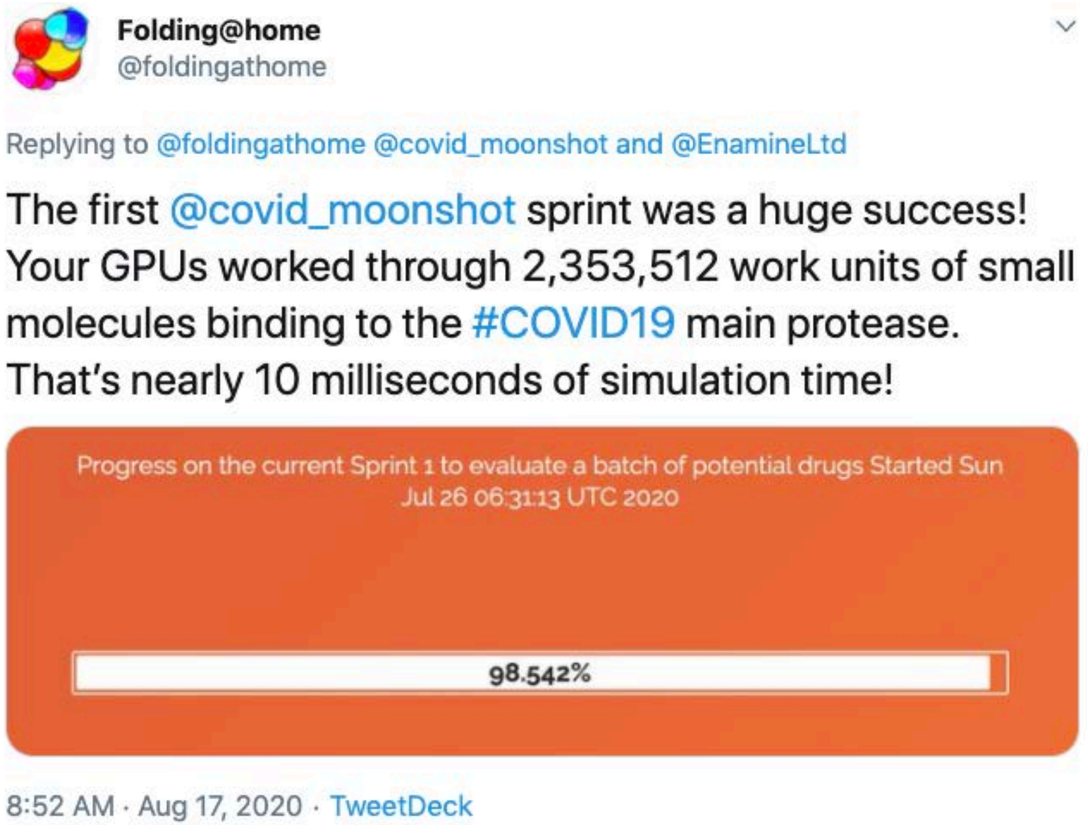
Can approximate nonequilibrium switching if relaxation is fast (or restraints are used to limit motion)

a terrible hack, but it just might work



(Now used in OpenEye Orion NES free energy workflows!)

WE GENERATED A LOT OF DATA, WHICH WE SHARED ONLINE VIA THE AWS PUBLIC DATASETS PROGRAM



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

WE EVEN PUT UP A PROGRESS BAR!

HOW YOU CAN HELP

Fund Us

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

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

GoFundMe

Share Your Compute Power

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

96.5% of sprint completed

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

Folding@home

Contribute Your Expertise

Submit drug design ideas using the form below.

16,638 molecules submitted

1,851 synthesized and tested

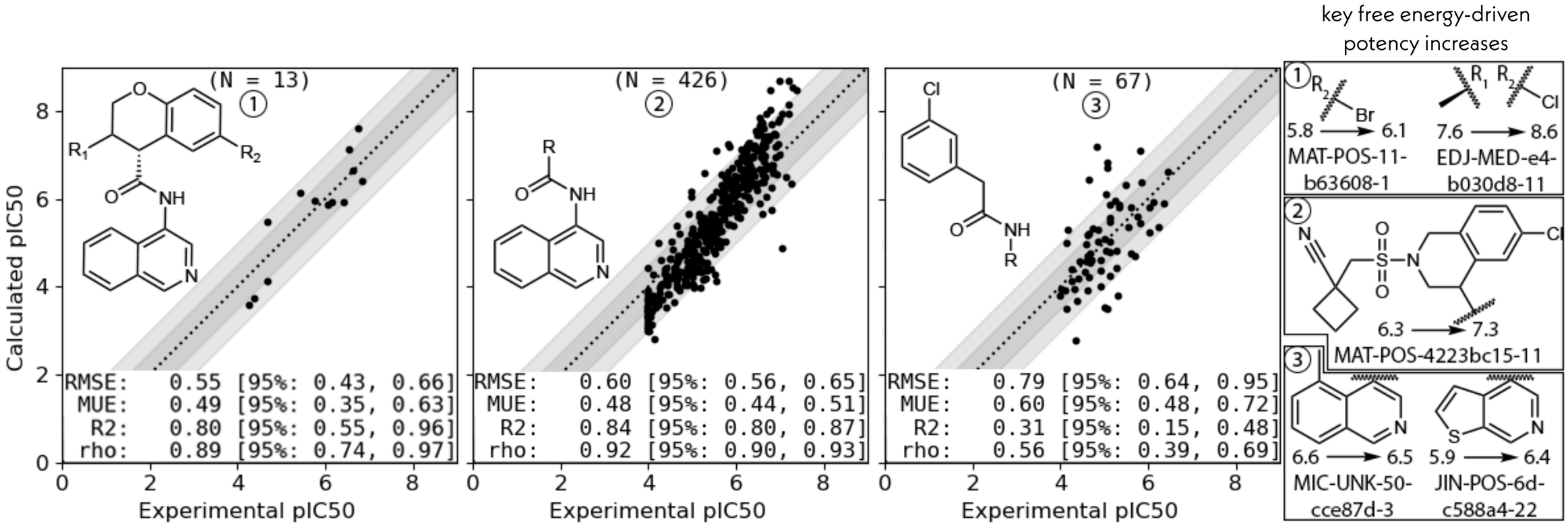
258 structures

Submit Molecule(s)

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

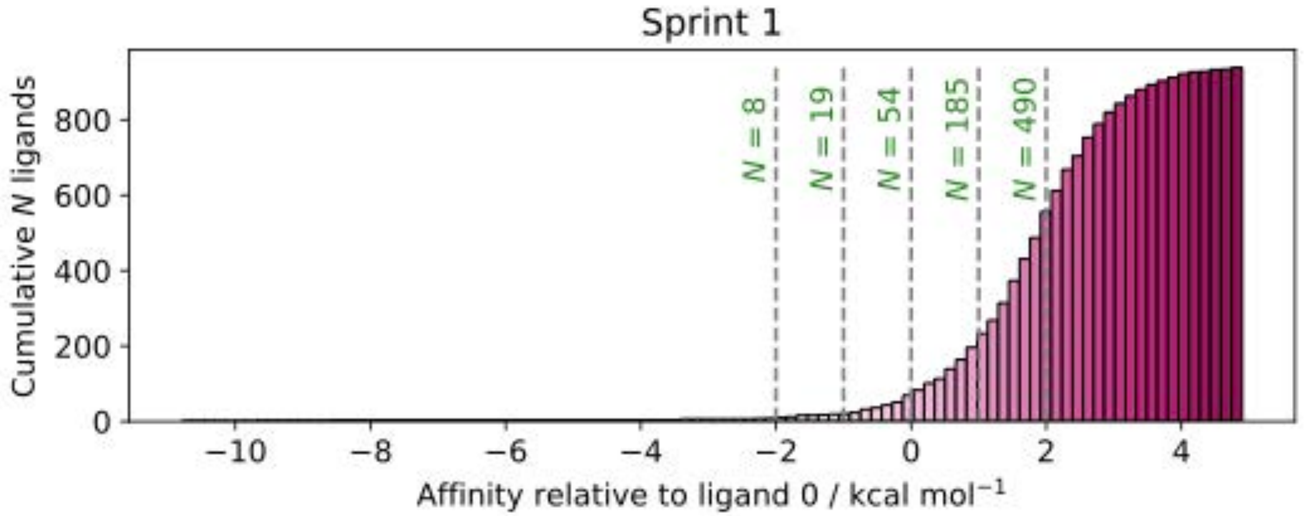
http://postera.ai/covid

ALCHEMICAL FREE ENERGY CALCULATIONS OFTEN HAD REASONABLE ACCURACY



WE LEARNED A LOT ABOUT HOW COMPUTATION COULD AID HUMANS: MOST VIRTUAL LIBRARY COMPOUNDS WERE BAD IDEAS

better worse

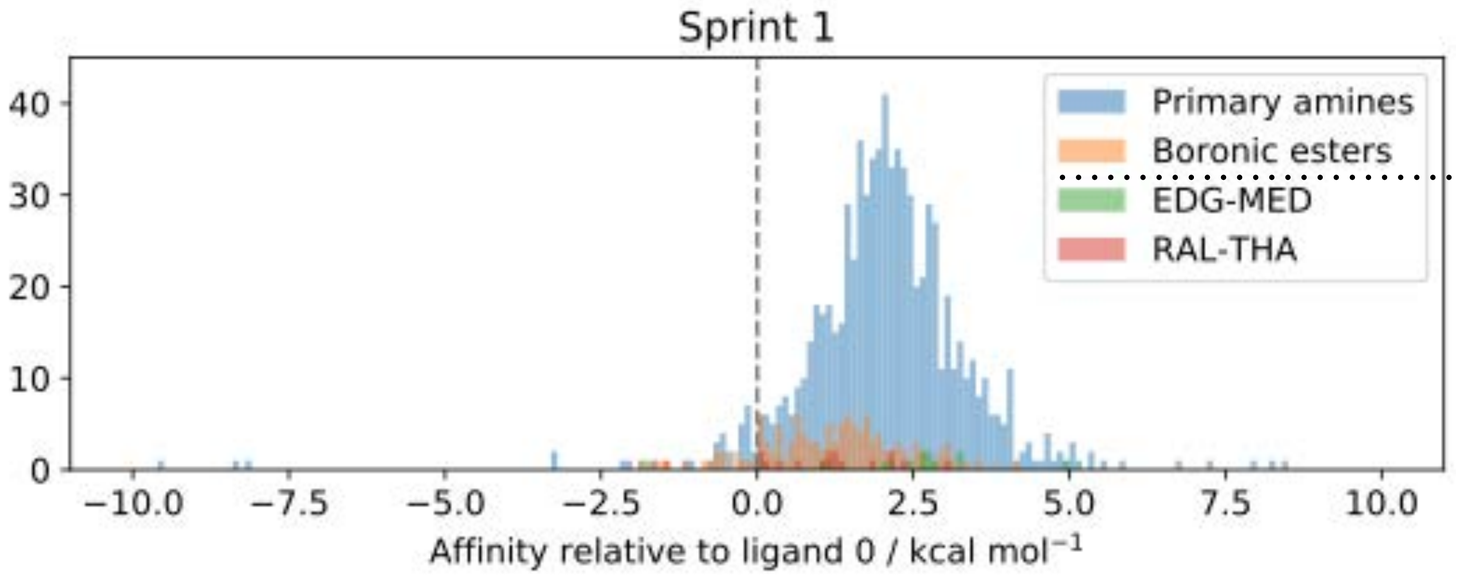


DOMINIC RUFA
TPCB student

HANNAH BRUCE MACDONALD
postdoc

WILLIAM GLASS
postdoc

HUMAN CHEMISTS NOMINATE BETTER COMPOUNDS, BUT ARE LIMITED IN THE NUMBER OF DESIGNS THEY CAN IDEATE



computer

humans

DOMINIC RUFA
TPCB student

HANNAH BRUCE MACDONALD
postdoc

WILLIAM GLASS
postdoc

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

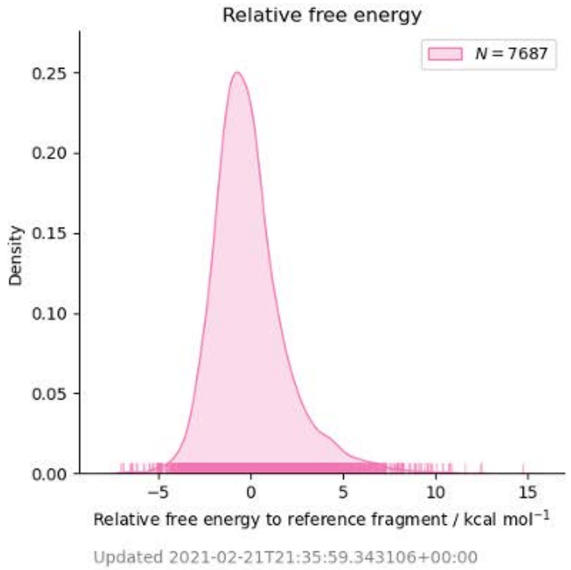
Description

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

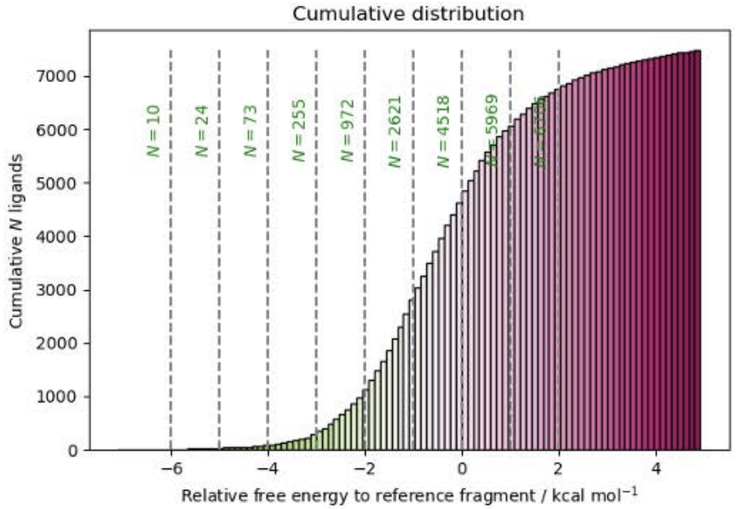
Progress

98.25%

Distributions



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



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

Leaderboard

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

DAVID DOTSON
software scientist

MATT WITTMANN
software scientist

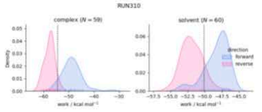
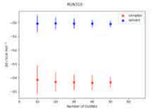
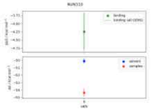
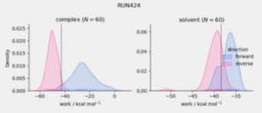
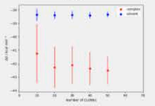
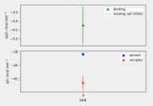
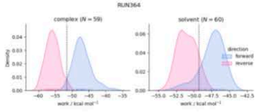
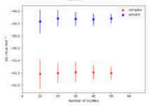
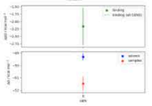
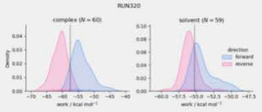
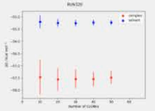
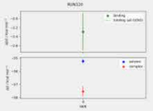
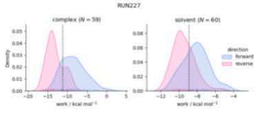
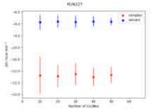
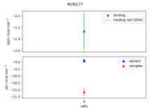
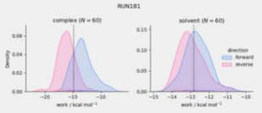
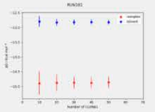
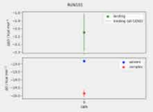
[dashboard]

THE DASHBOARD LET CHEMISTS EASILY INSPECT THE RESULTS

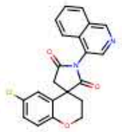
COVID Moonshot Sprint 11 | Summary | Compounds | Microstates | Transformations | **Reliable Transformations** | Retrospective Transformations | Retrospective Compounds

Reliable Transformations

Showing 1 through 100 of 100

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

POTENT HUMAN CHEMIST DESIGNS SOMETIMES UNEXPECTEDLY FLOAT TO THE TOP

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

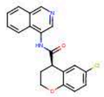
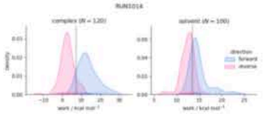
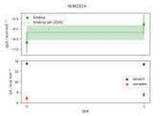
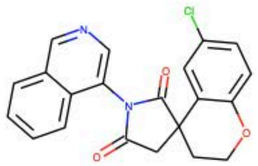
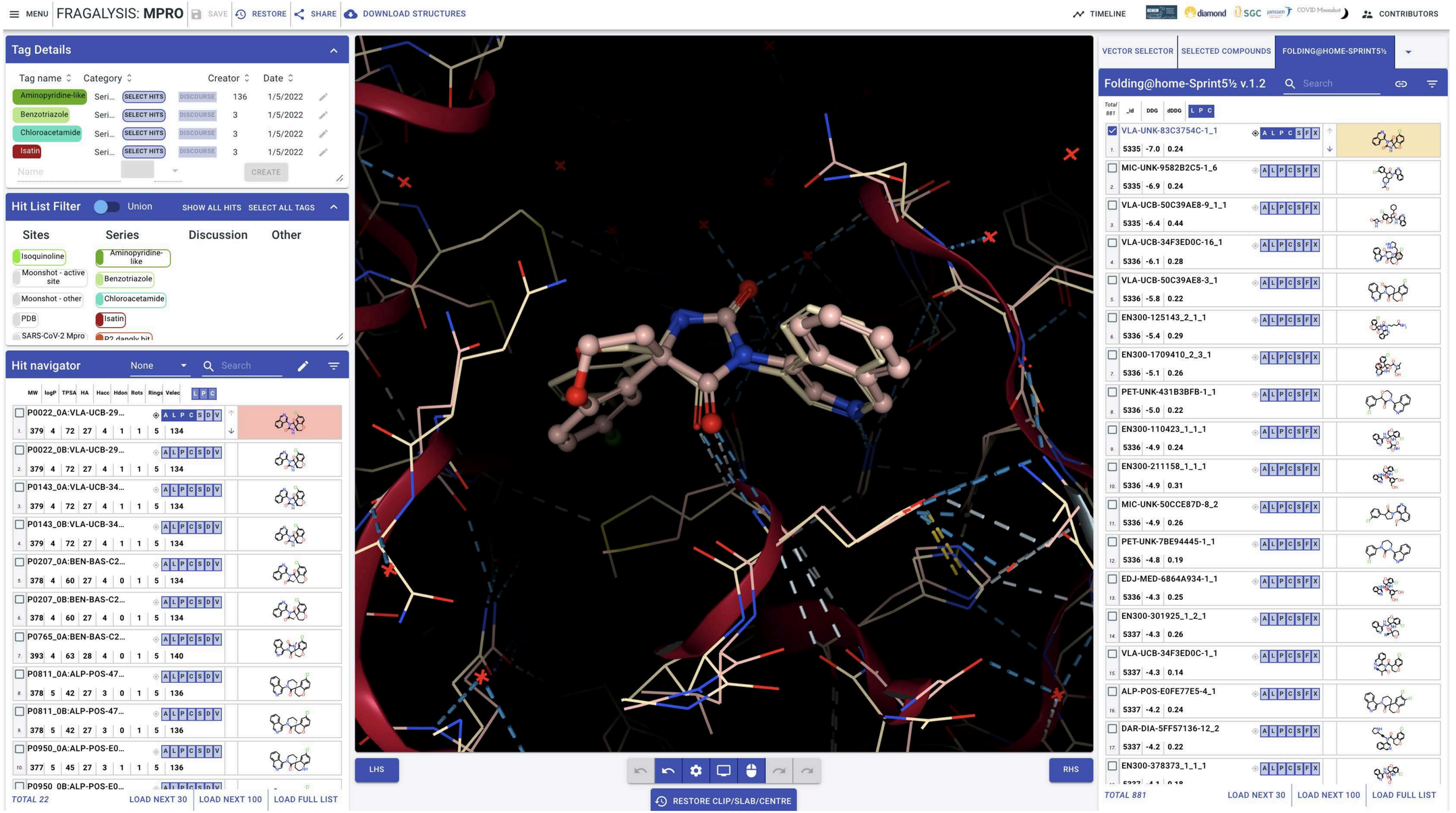
RUN1014	MAT-POS-b3e365b9-1_1		sdf	pdb	BEN-BAS-c2bc0d80-6_1		sdf	pdb	−6.2 ± 0.2	 

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

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

IT WAS SURPRISING HOW WELL POSES COULD BE PREDICTED



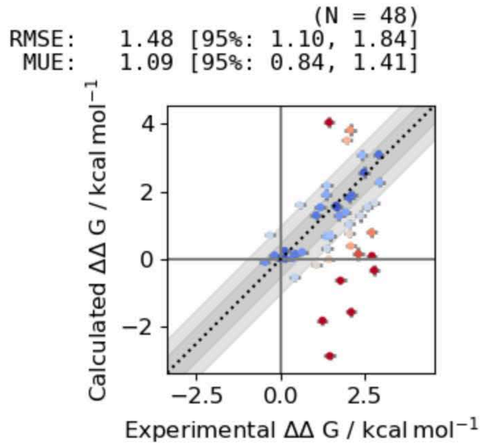
dashboard: https://tinyurl.com/fah-sprint-5-dimer

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

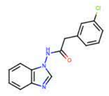
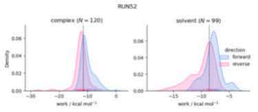
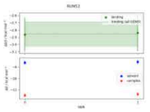
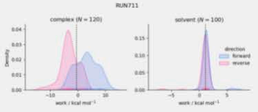
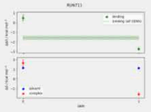
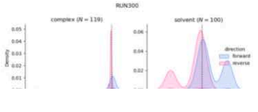
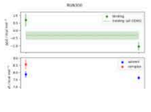
https://fragalysis.diamond.ac.uk/viewer/react/projects/1264/924

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

Retrospective Transformations

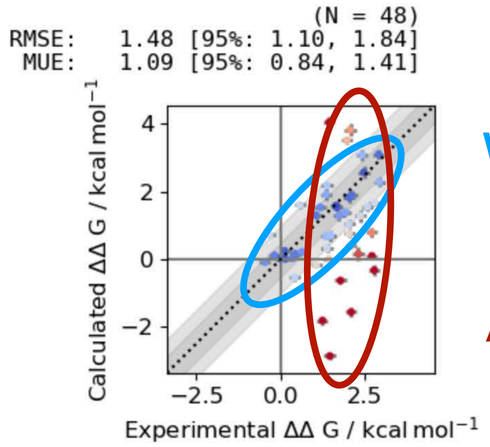


Showing 1 through 48 of 48

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

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

Retrospective Transformations



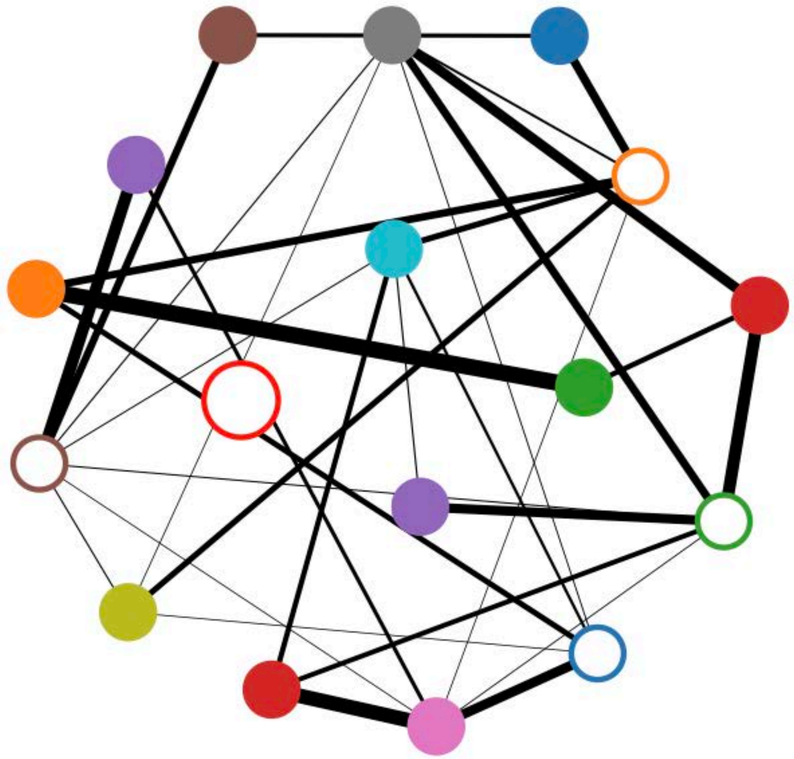
Well-predicted transformations

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

Showing 1 through 48 of 48

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

WE USED NETBFE TO LEVERAGE EXPERIMENTAL MEASUREMENTS FOR MULTIPLE COMPOUNDS IN EACH ALCHEMICAL NETWORK



compound with experimental binding affinity

compound with unknown binding affinity

the maximum likelihood estimator for $\{x_i\}$ is[1,2,16] (assuming that the statistical errors in the measurements follow the normal distribution; see Appendix A for a derivation)

$$\mathbf{F}\cdot\vec{x} = \vec{z} \tag{2}$$

where

$$z_i = \sigma_i^{-2}\hat{x}_i + \sum_{j\neq i}\sigma_{ij}^{-2}\hat{x}_{ij} \tag{3}$$

and $\mathbf{F}$ is the Fisher information matrix:

$$F_{ij} = \begin{cases} \sigma_i^{-2} + \sum_{k\neq i}\sigma_{ik}^{-2} & \text{if } i = j \\ -\sigma_{ij}^{-2} & \text{if } i \neq j \end{cases} \tag{4}$$

The covariance in the estimates of $\{x_i\}$ is given by the inverse of the Fisher information matrix:

$$\mathbf{C} = \mathbf{F}^{-1} \tag{5}$$

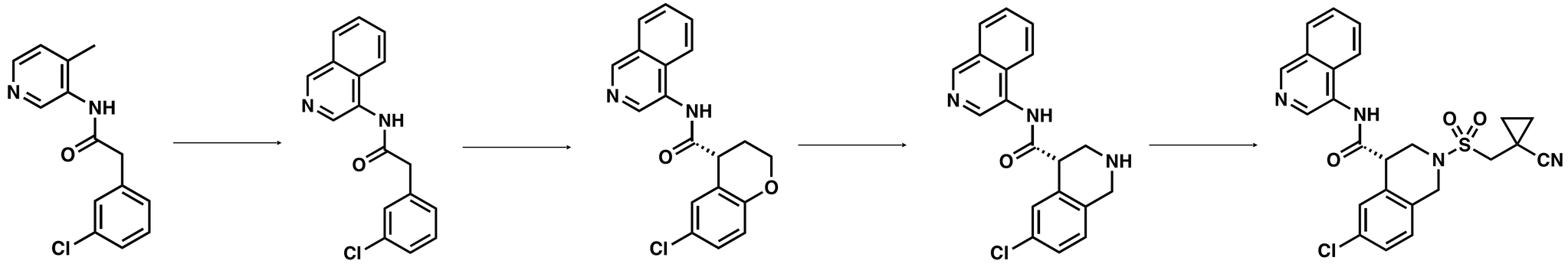
HUAFENG XU
atommapper.com

Optimal Measurement Network of Pairwise Differences
Huafeng Xu. *J. Chem. Inf. Model.* 2019, 59, 11, 4720–4728
https://doi.org/10.1021/acs.jcim.9b00528

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

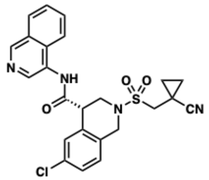
crowdsourced merged fragment hit

first candidate satisfying TCP



PostEra ID	[TRY-UNI-714a760b-6]	[ADA-UCB-6c2cb422-1]	[MAT-POS-b3e365b9-1]	[MAT-POS-3ccb8ef6-1]	[MAT-POS-e194df51-1]
Fragalysis ID / PDB ID	x2646 / 5RH2	x10959 / 7S3S	x11612 / TBD	P0744 / TBD	P1788 / TBD
Enamine Cat No	Z1129289650	Z1530724813	Z4643752419	Z4943052515	Z5129808241
IC_{50}(Mpro)	23.7 [19.5, 28.9] μM	0.721 [0.647, 0.804] μM	0.255 [0.240, 0.270] μM	0.288 [0.273, 0.304] μM	0.0368 [0.0343, 0.0395] μM
EC_{50}(SARS-CoV-2, A549)	n.d.	4.5 μM	7.0 μM	1.9 μM	0.064 μM
$\Delta\Delta G_{exp}$	-2.07 [-1.89,-2.25] kcal/mol	-0.615 [-0.517, -0.715] kcal/mol	0.007 [0.006,0.139] kcal/mol	-1.22 [-1.14, -1.29] kcal/mol	
$\Delta\Delta G_{FEP}$	-1.8±0.1 kcal/mol	-0.7±0.2 kcal/mol	0.0±0.1 kcal/mol	-2.4±0.1 kcal/mol	

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



MAT-POS-e194df51-1

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

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

Cold Spring Harbor Laboratory

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

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

New Results

Follow this preprint

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

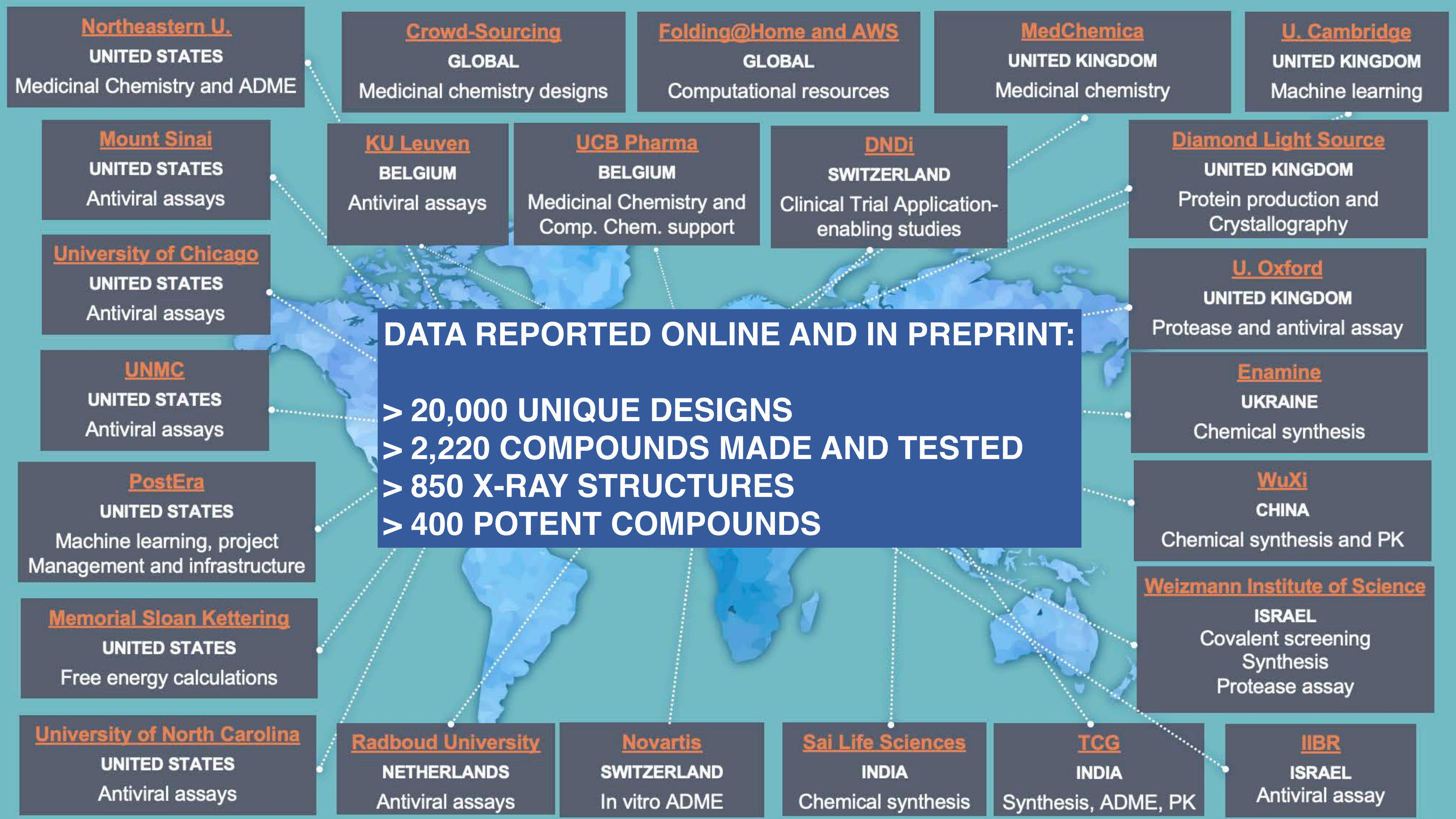
https://doi.org/10.1101/2020.10.29.339317

(updated 2 Mar 2023!)

Over 180 contributors/authors:

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

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

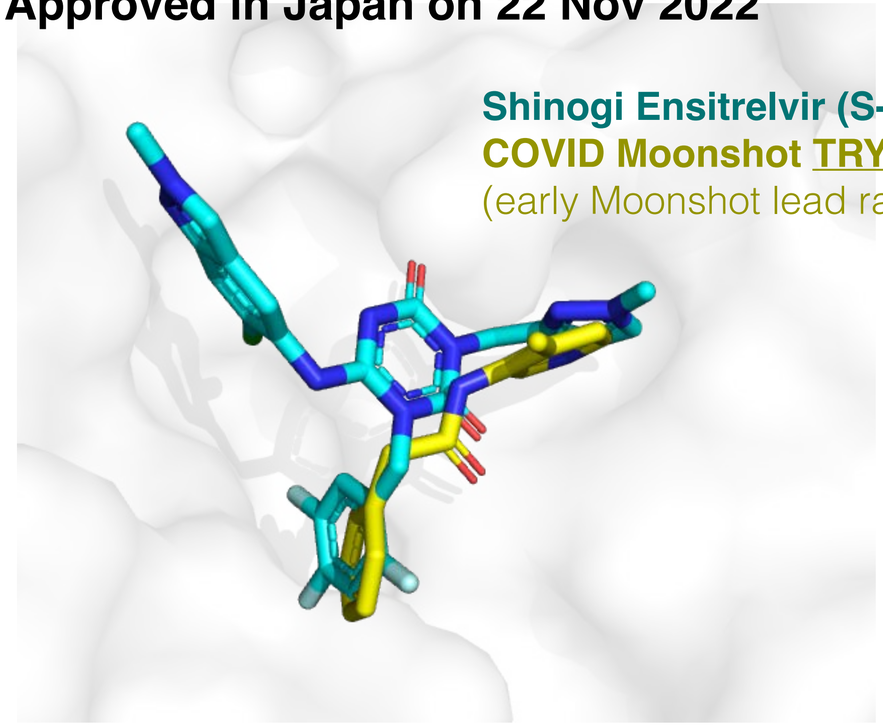

Northeastern U.
UNITED STATES
Medicinal Chemistry and ADME
Crowd-Sourcing
GLOBAL
Medicinal chemistry designs
Folding@Home and AWS
GLOBAL
Computational resources
MedChemica
UNITED KINGDOM
Medicinal chemistry
U. Cambridge
UNITED KINGDOM
Machine learning
Mount Sinai
UNITED STATES
Antiviral assays
KU Leuven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

SHIONOGI RECENTLY REPORTED THE DISCOVERY OF ENSITRELVIR, DISCOVERED WITH THE HELP OF MOONSHOT DATA

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

Shionogi rapidly developed into potent antiviral with excellent PK
(just 1 pill/day for 5 days)

Approved in Japan on 22 Nov 2022



Shinogi Ensitrelvir (S-217622) [PDBID: 8DZ0]
COVID Moonshot TRY-UNI-714a760b-6 [PDBID: 5RH2]
(early Moonshot lead rapidly compound disclosed online)

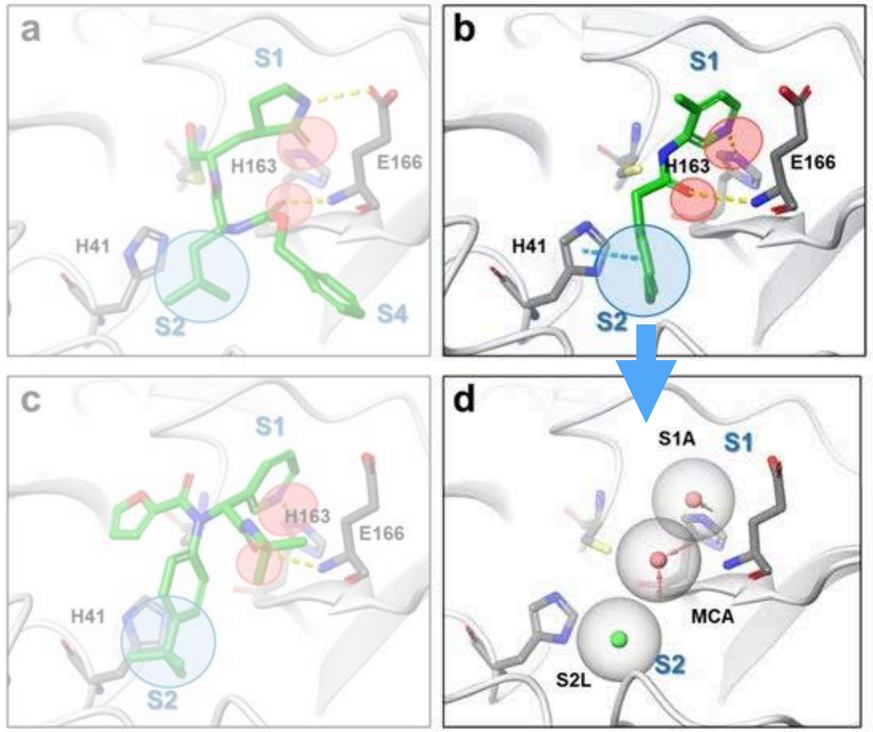
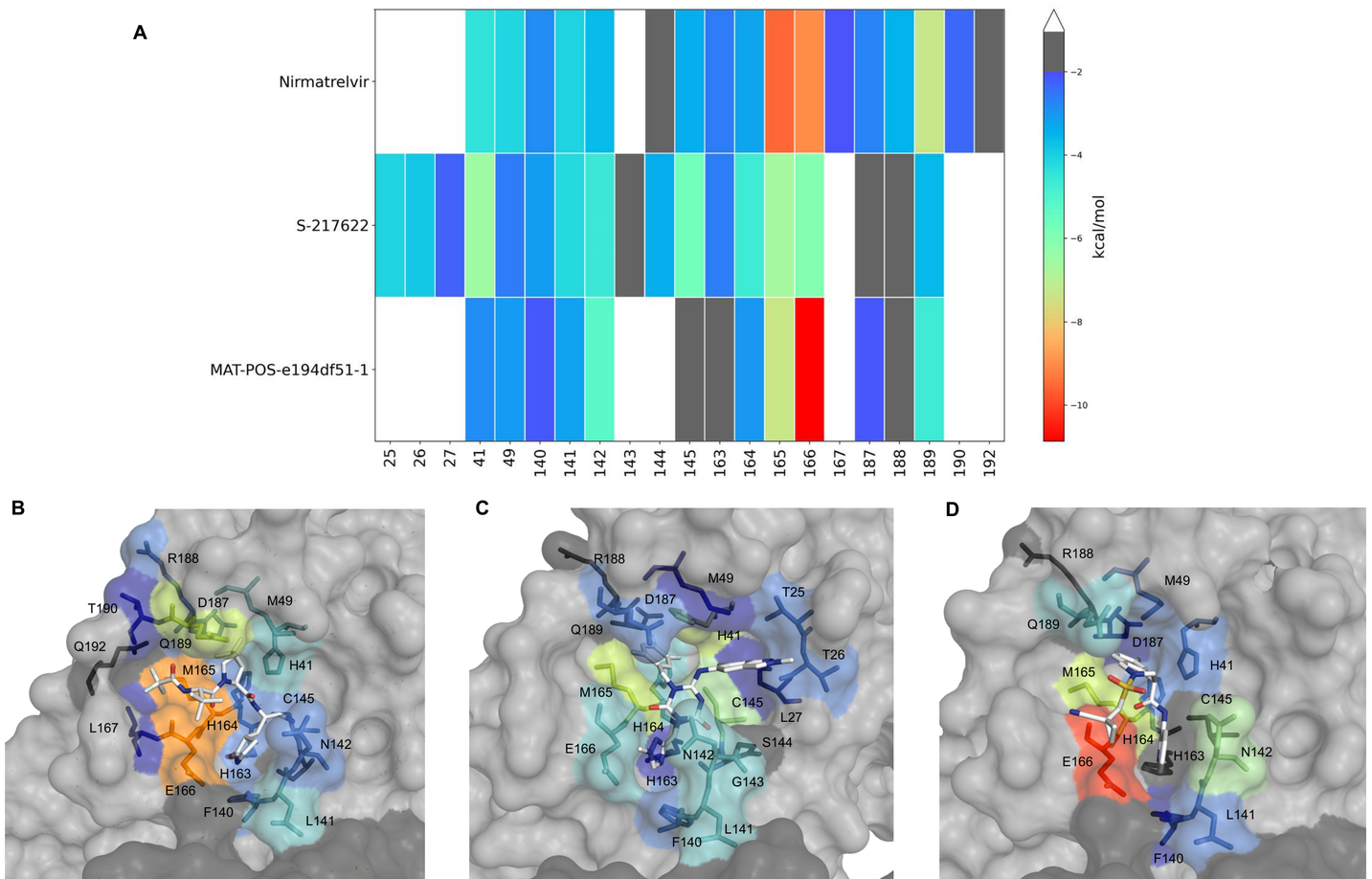


Figure 2. Binding modes of 3CL^{pro} inhibitors, their pharmacophores, and defined pharmacophore filters for virtual screening. (a) Crystal structures of GC376 (PDB: 6WTT), (b) 3-aminopyridine-like compound of the Postera COVID moonshot project (PDB: 5RH2) and (c) ML188 (PDB: 7L0D). The common H-bond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

Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19
J. Med. Chem. 2022, 65, 9, 6499–6512
https://doi.org/10.1021/acs.jmedchem.2c00117

OUR INHIBITOR IS SMALL, NONCOVALENT, AND ENGAGE HIGHLY CONSERVED RESIDUES, PRESENTING A DIFFERENTIATED RESISTANCE PROFILE TO OTHER CLINICAL MPRO INHIBITORS

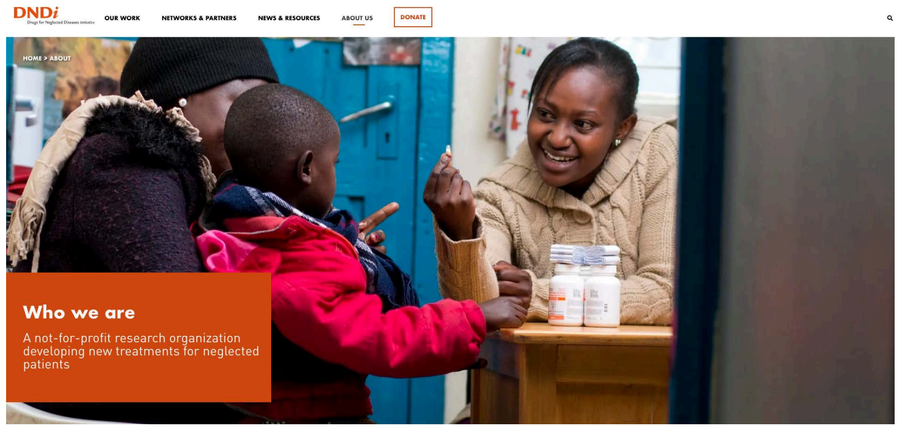


nirmatrelvir (Paxlovid)
Pfizer

Ensitrelvir (S-217622)
Shionogi

MAT-POS-e194df51-1
COVID Moonshot

Analysis by Judy Huang, Sarah Duggan, Celia Schiffer, Melissa Baby
https://doi.org/10.1101/2020.10.29.339317



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

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

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

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

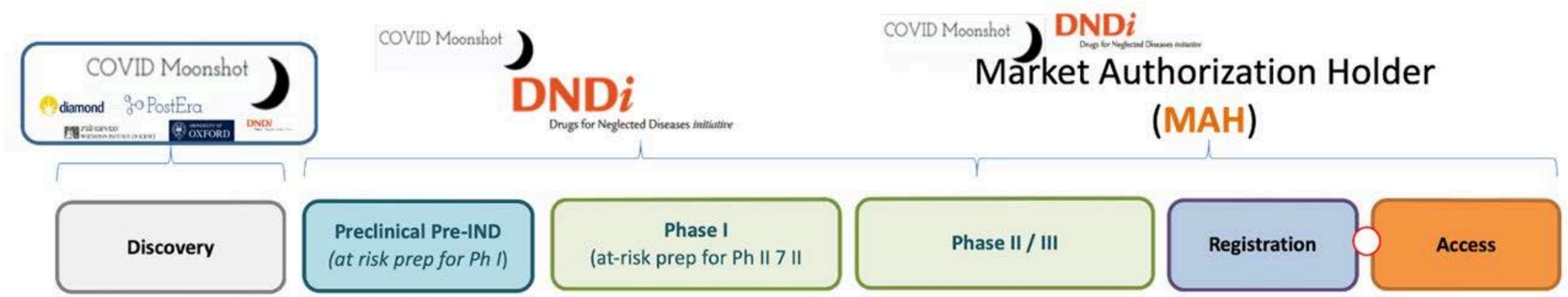
'*Most of the research and funding efforts early in the pandemic focused predominantly on repurposing of existing small molecule drugs and the more rapid development of novel monoclonal antibodies. Now, with the realization that COVID-19 will be a global issue for the foreseeable future we urgently need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

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

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

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

WE'RE AIMING TO BRING AN ANTIVIRAL STRAIGHT TO GENERICS MANUFACTURE WITHOUT A PATENT



We have a potential "straight to generics" pathway, entirely free of patents, with the aim of low-cost global access to meet the needs of underserved low- and middle-income countries (LMICs)

WHAT'S SURPRISING ABOUT ALL THIS?
OUR COMPOUNDS ARE EQUIPOTENT AGAINST SARS-COV-1

Comment

A white-knuckle ride of open COVID drug discovery

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

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

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

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

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

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

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

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

The screens

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

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

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

The tweets

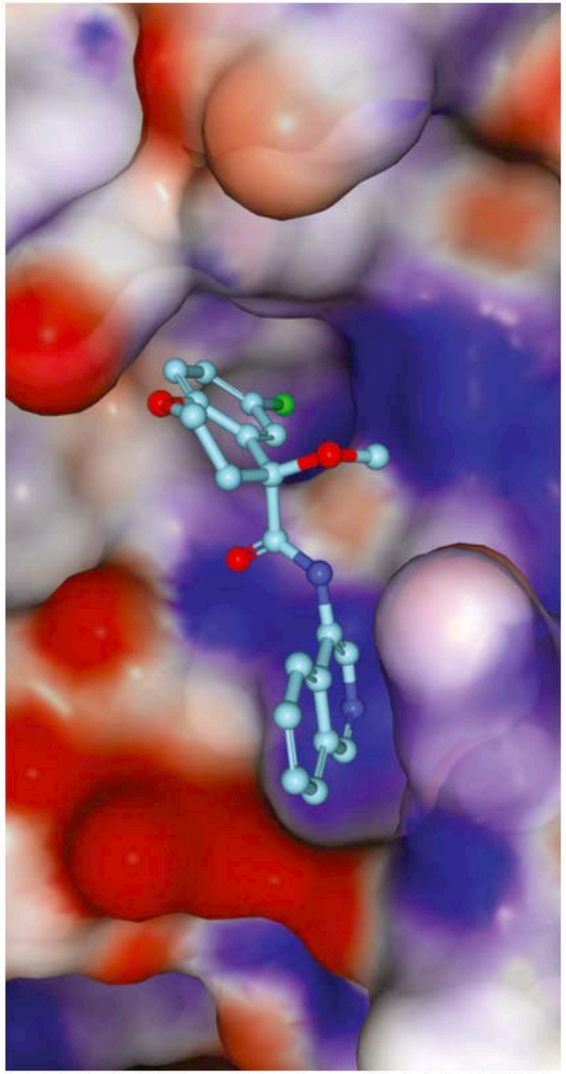
The response surprised us: almost 1,000 retweets in a week, and diverse offers for help. A.L. and M.R., two co-founders of the US–Israeli technology firm PostEra, got in touch to suggest that their machine-learning technology could propose synthetic routes to make new molecules inspired by the fragment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

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

The experiments

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

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



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

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

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

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

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

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

To cells and live virus

By June 2020, the Zoom-based collaboration had identified sets of molecules that clearly inhibited a crucial viral protein. The next step was to test antiviral activity in living cells. These are complex experiments, requiring level-three biosafety labs certified for airborne pathogens.

A.v.D., a translational clinician, coordinated

a shifting coalition of groups. One virologist friend and colleague lived a 10-minute walk away, and they planned experiments on lockdown evening strolls. Other virology groups responded to our tweet for help, and offered a variety of assays. Compounds were shipped, early results trickled in and some compounds unambiguously stalled the virus. These initial successes were crucial, both scientifically and for morale.

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

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

The slog

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

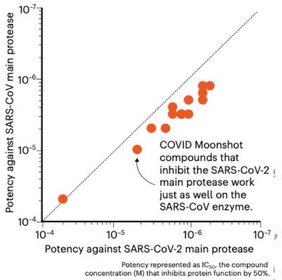
Above all, we can start predicting that these molecules will be straightforward to synthesize and will work as pills that are suitable for vaccine-hesitant or immunocompromised individuals, health-care workers and others in risky situations who could take them prophylactically. Furthermore, we expect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

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

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

MISSED OPPORTUNITY

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



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

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

The moral

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

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

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

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

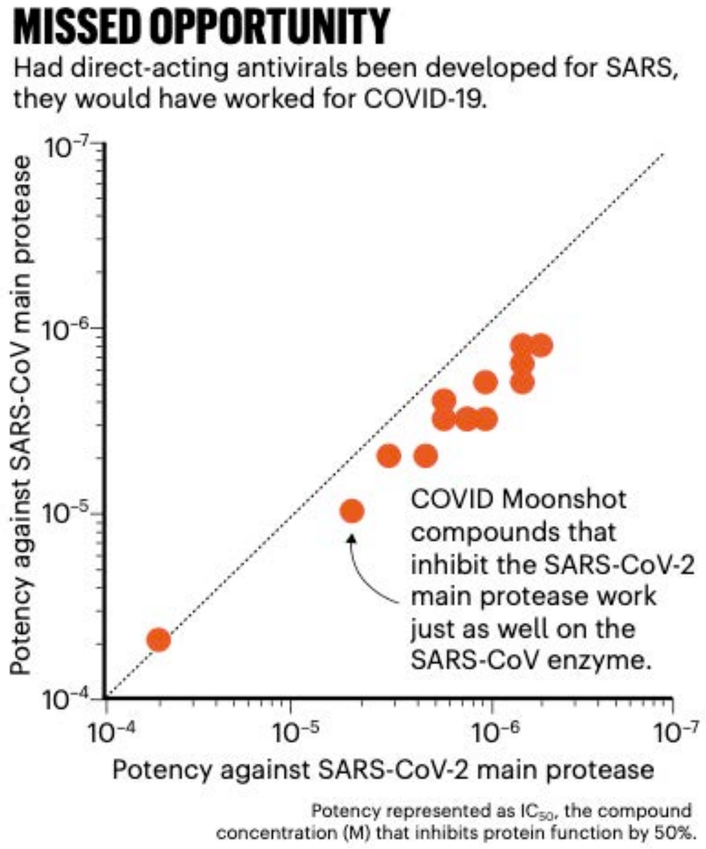
The authors

Frank von Delft is professor of structural chemical biology at the University of Oxford, UK, and principal beamline scientist at Diamond Light Source, Didcot, UK. **John Chodera** is associate member at the Memorial Sloan Kettering Cancer Center, New York, USA. **Ed Griffen** is technical director and co-founder of MedChemica, Ryecraft, UK. **Alpha Lee** is group leader in the Department of Physics, University of Cambridge, UK, and chief scientific officer at PostEra, Boston, Massachusetts, USA. **Nir London** is assistant professor in the Department of Organic Chemistry at the Weizmann Institute of Science, Rehovot, Israel. **Tatiana Matviuk** is principal scientist at Enamine, Kiev, Ukraine. **Ben Perry** is discovery open innovation leader at the Drugs for Neglected Diseases initiative, Geneva, Switzerland. **Matt Robinson** is chief technology officer of PostEra, Boston, Massachusetts, USA. **Mark Calmiano** is a computational chemist at UCB Biopharma, Brussels, Belgium. **Annette von Delft** is a translational scientist at the University of Oxford, UK
e-mail: frank.vondelft@cmd.ox.ac.uk

1. Douangamath, A. *et al. Nature Commun.* **11**, 5047 (2020).
2. Mahase, E. *Br. Med. J.* **373**, n1077 (2021).
3. The COVID Moonshot Consortium *et al.* Preprint at bioRxiv https://doi.org/10.1101/2020.10.29.339317 (2020).
4. Chodera, J., Lee, A. A., London, N. & von Delft, F. *Nature Chem.* **12**, 581 (2020).

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

WHAT'S SURPRISING ABOUT ALL THIS?
OUR COMPOUNDS ARE EQUIPOTENT AGAINST SARS-COV-1



Why couldn't we have done this in 2004 after the 2003 SARS pandemic?

HOW CAN WE PREVENT FUTURE PANDEMICS?

HOW CAN WE PREVENT FUTURE PANDEMICS?

What's the best way to win a race?

HOW CAN WE PREVENT FUTURE PANDEMICS?

What's the best way to win a race?

1. **Run fast.**

2. **Start close to the finish line.**

HOW CAN WE PREVENT FUTURE PANDEMICS?

What's the best way to win a race?

1. **Run fast.**
   Develop a **technology platform** for accelerated discovery of oral antivirals that can rapidly progress fragments to preclinical candidates leveraging machine learning and physical modeling
   Eliminate inefficiencies in human-based discovery by tightly integrating CADD approaches

2. **Start close to the finish line.**
   Repeatedly **exercise this platform** to develop an arsenal of low-cost clinic-ready drug candidates against viruses of pandemic concern
   Leverage platform to generate a variety of antivirals with broad antiviral activity

HOW CAN WE PREVENT FUTURE PANDEMICS?

What's the best way to win a race?

1. **Run fast.**
   Develop a **technology pl** that can rapidly progress
   fragments to preclinical ca l modeling
   Eliminate inefficiencies i CADD approaches

2. **Start close to the finish li**
   Repeatedly **exercise this** iic-ready drug candidates
   against viruses of pandem
   Leverage platform to ger activity

A Pill to Treat Covid-19? The U.S. Is Betting on It.

A new $3.2 billion program will support the development of antiviral pills, which could start arriving by the end of this year.

Dr. Anthony Fauci announced on Thursday that the White House was investing over $3 billion to advance the development of antiviral pills to treat Covid-19 as well as future virus outbreaks.
Agence France-Presse — Getty Images

https://www.nytimes.com/2021/06/17/health/covid-pill-antiviral.html

Consortium formed to discover antivirals for COVID-19 receives NIH funding to develop globally accessible treatments for pandemics

18 May 2022

$68M seed funding for initial 3 years

DNDi
Drugs for Neglected Diseases *initiative*

A consortium led by international scientists from the non-profit, open-science COVID Moonshot has been awarded an initial $68,662,387 from the US National Institutes of Health (NIH) to discover and develop globally accessible and affordable novel oral antivirals to combat COVID-19 and future pandemics.

'*If we had clinic-ready antivirals suitable for SARS-CoV-2 when the pandemic struck in late 2019, we could have perhaps saved millions of lives*,' said Dr Ben Perry, Discovery Open Innovation Leader at the Drugs for Neglected Diseases *initiative* (DND*i*), and a founder of the COVID Moonshot. '*The world needs a diverse stockpile of novel antiviral compounds that can be quickly advanced for the current pandemic and when the next pandemic strikes, and it is essential that these be affordable and equitably accessible to everyone.*'

The consortium has created the artificial intelligence (AI)-driven Structure-enabled Antiviral Platform (ASAP), which will use cutting-edge technology, encompassing advanced structural biology, AI, machine learning, and computational chemistry on Folding@home, the world's largest distributed computing platform, to build a robust antiviral discovery pipeline.

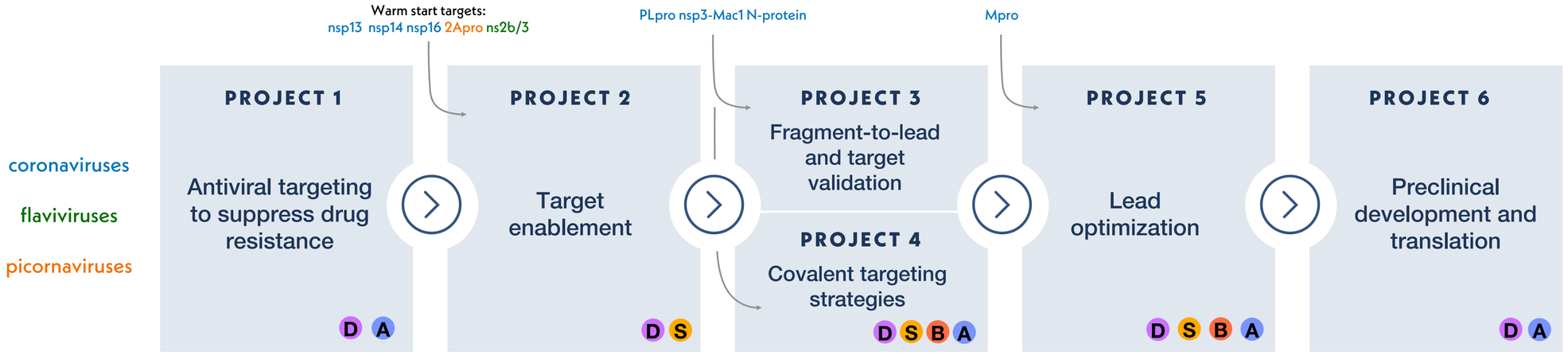
The ultimate objective of the project is to deliver multiple drug candidates ready for evaluation in humans in the event of an ongoing or emerging pandemic threat. The project will maximize the use of an open science model that prioritizes global, equitable, and affordable access.

ASAP is built on the successes of the COVID Moonshot, a global, open-science collaboration that began in March 2020 and rapidly identified potent antivirals targeting the main protease of the SARS-CoV-2 virus, which are currently undergoing a preclinical development program funded by the Wellcome/COVID-19 Therapeutics Accelerator. The open science data publicly shared by Moonshot additionally enabled the identification of another promising COVID-19 drug developed by the Japanese pharmaceutical company Shionogi that is now in late-stage clinical trials.

'*The rapid progress of Moonshot demonstrates the power of AI-driven drug design*,' said Dr Alpha Lee, Chief Scientific Officer of PostEra and a founder of the COVID Moonshot. '*Our algorithms generate molecules with optimized properties that can quickly be made and tested in the lab and help us select the most important experiments. ASAP will take this to the next level.*' Dr Lee is one of the leaders of ASAP.

AI-DRIVEN STRUCTURE-ENABLED ANTIVIRAL PLATFORM (ASAP) IS LIKE A DISTRIBUTED DRUG DISCOVERY BIOTECH

Open science drug discovery for global equitable and affordable access



P1: Karla Kirkegaard (Stanford)
Matt Bogyo (Stanford)
Jesse Bloom (Fred Hutch)

P2: Frank von Delft (Diamond Light Source)
Martin Walsh (Diamond Light Source)
Oxford CMD SRF [service facility]

P3: Alpha Lee (PostEra)
John Chodera (MSKCC)
Frank von Delft (Diamond)
Ed Griffen (Medchemica)
Nir London (Weizmann)
Karla Kirkegaard (Stanford)
Martin Walsh (Diamond)

P4: Nir London (Weizmann)
Matt Bogyo (Stanford)

P5: Ed Griffen (Medchemica)
Ben Perry (DNDi)
Alpha Lee (PostEra)
John Chodera (MSKCC)

P6: Ben Perry (DNDi)
Laurent Fraisse (DNDi)
Annette von Delft (Medchemica)

ADMINISTRATIVE CORE	D DATA INFRASTRUCTURE CORE	S STRUCTURAL BIOLOGY CORE	B BIOCHEMICAL ASSAY CORE	A ANTIVIRAL EFFICACY AND RESISTANCE CORE
John Chodera (MSKCC) Ben Perry (DNDi) Alpha Lee (PostEra) **PIs** **Administrative Director** **Project Coordinator**	**Alpha Lee (PostEra)** Matthew Robinson (PostEra) Frank von Delft (Diamond) John Chodera (MSKCC)	**Frank von Delft (Diamond Light Source)** Daren Fearon (Diamond Light Source) Martin Walsh (Diamond Light Source)	**Nir London (Weizmann)** Haim Barr (Weizmann)	**Kris White (Mount Sinai)** Adolfo García-Sastre (Mount Sinai) Randy Albrecht (Mount Sinai) Johan Neyts (Leuven) [service facility]

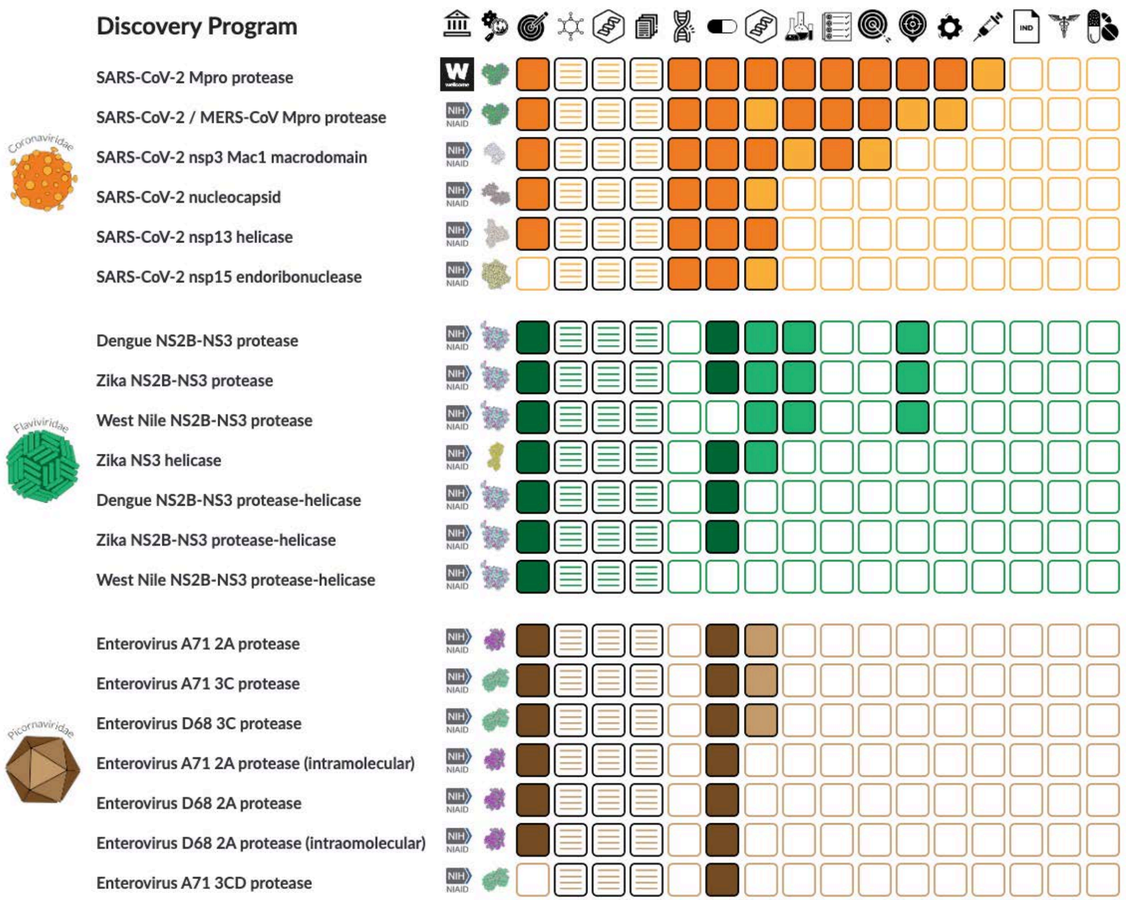
$110M / 5 years planned AViDD Center

http://asapdiscovery.org

WE CAN SHARE ALL THE DATA WE GENERATE FOR ENTIRE DISCOVERY PROGRAMS OPENLY

Pipeline

ASAP direct-acting antiviral discovery programs and research outputs



Click on any shaded box to view data and resources associated with that stage.

http://asapdiscovery.org/pipeline

ASAP Discovery Outputs

Viral Families
Viral families targeted by ASAP

Targeting Opportunities
ASAP identified discovery opportunities for broad antiviral activity

Molecules
ASAP antivirals and assayed compounds

Structures
Structures of ASAP targets with inhibitors

Publications
Scientific publications from ASAP

Mutation Data
Deep Mutational Scanning (DMS) and analysis of circulating variants to identify potential resistance liabilities

Target Product Profiles (TPPs)
Target Product Profiles (TPPs) guiding ASAP discovery programs

Target Enabling Packages (TEPs)
ASAP Target Enabling Packages (TEPs) for initiating structure-based drug discovery programs

Assay Cascades
Assay cascades used by ASAP Discovery programs

Assay Protocols
Assay protocols developed for ASAP Discovery programs

Target Candidate Profiles (TCPs)
Target Candidate Profiles (TCPs) guiding ASAP discovery programs

Hit-to-Lead
Hit-to-lead data packages

Hit-to-Lead
Hit-to-lead data packages

Lead Optimization
Lead optimization data packages

Preclinical program
Preclinical data packages

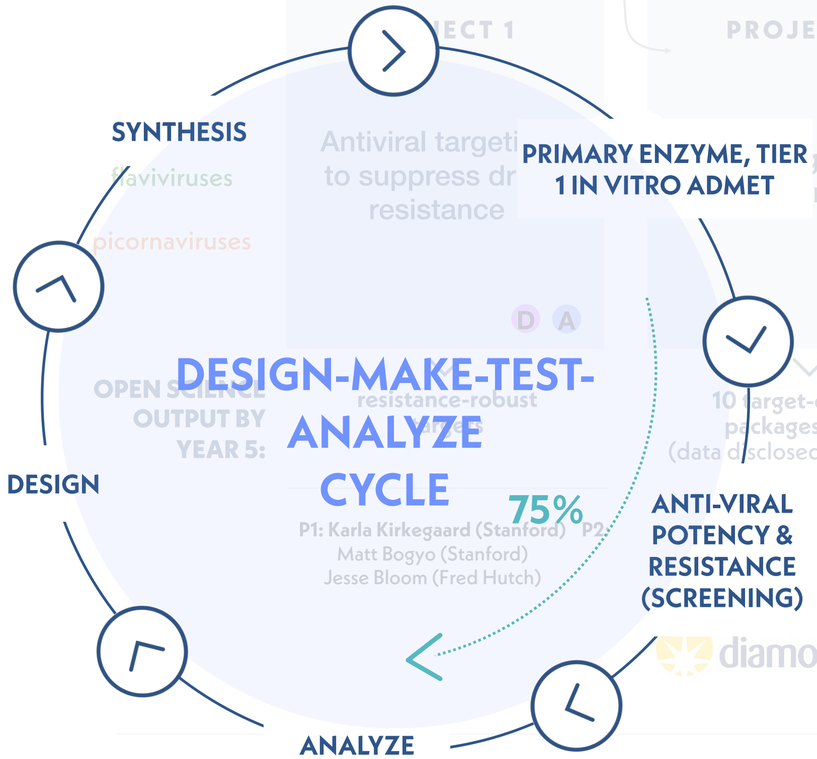
Investigational New Drug (IND) filings
IND (and IND-equivalent) filing packages for ASAP preclinical programs

Clinical trials
ASAP clinical trials

New Drug Approvals
ASAP New Drug Approvals (NDAs)

http://asapdiscovery.org/outputs

ASAP PROVIDES US WITH AN OPPORTUNITY TO FEED THE CADD COMMUNITY WITH DATA FOR BLIND CHALLENGES AND RETROSPECTIVE DATASETS



We will spend **millions of dollars on chemistry** to assess compounds selected by our methods, **all of which will be released openly.**

This provides an **unprecedented opportunity** to prospectively assess computational models and generate curated datasets while producing useful antivirals and discovery data for future pandemics

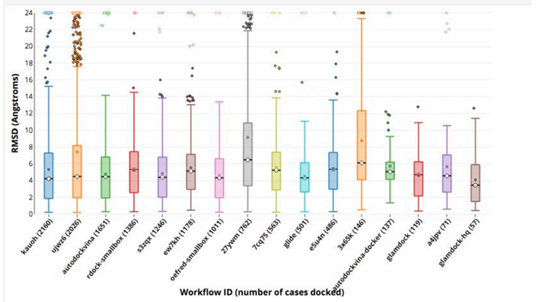
http://asapdiscovery.org

ASAP PROVIDES US WITH AN OPPORTUNITY TO FEED THE CADD COMMUNITY WITH DATA FOR BLIND CHALLENGES AND RETROSPECTIVE DATASETS

ASAP
Accessible Antivirals to Prevent Pandemics

automated blind challenges of containerized tools

continuous blind evaluation of predictive models

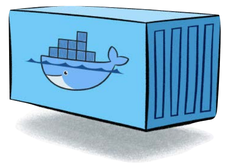


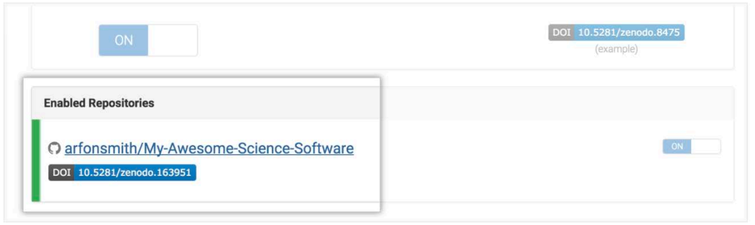
https://drugdesigndata.org/about/celpp

top models used to accelerate discovery

SAMPL challenges

http://www.samplchallenges.org/





CADD community

DOI-based CADD tool repository

retrospective datasets for building and refining predictive models

https://tdcommons.ai/

pharma / academia deploy and use models

ASAP HAS AN OPPORTUNITY TO HELP BUILD SUSTAINABLE CADD SOFTWARE ECOSYSTEMS WORKING WITH OMSF

Open Molecular Software Foundation

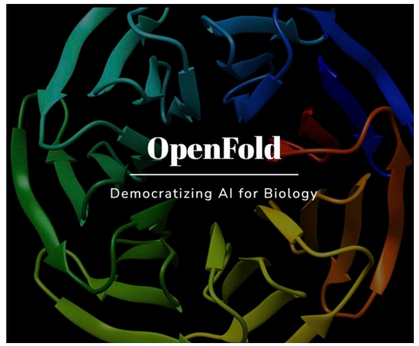
About Services Projects Support

Making bonds

Building open source software and communities in molecular sciences.

open forcefield

open free energy

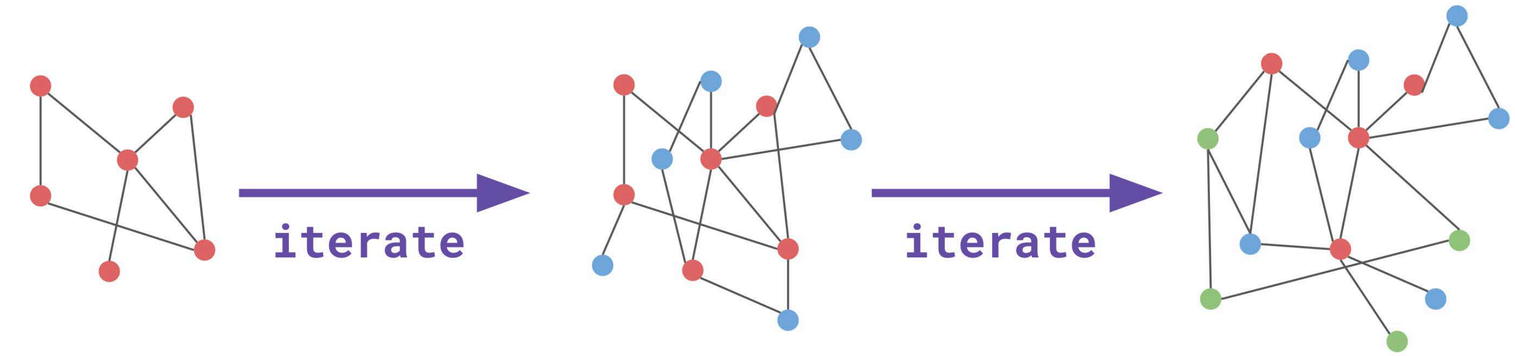


https://omsf.io/projects/project-list/

a 501(c)3 nonprofit organization

ALCHEMISCALE ALLOWS US TO SCALE OPEN FREE ENERGY CONSORTIUM CALCULATIONS TO CLUSTER, CLOUD, AND FOLDING@HOME

alchemiscale



initial network | expanded network | expanded/trimmed network

DAVID DOTSON
Datryllic

https://github.com/openforcefield/alchemiscale

ASAP
Accessible Antivirals to Prevent Pandemics

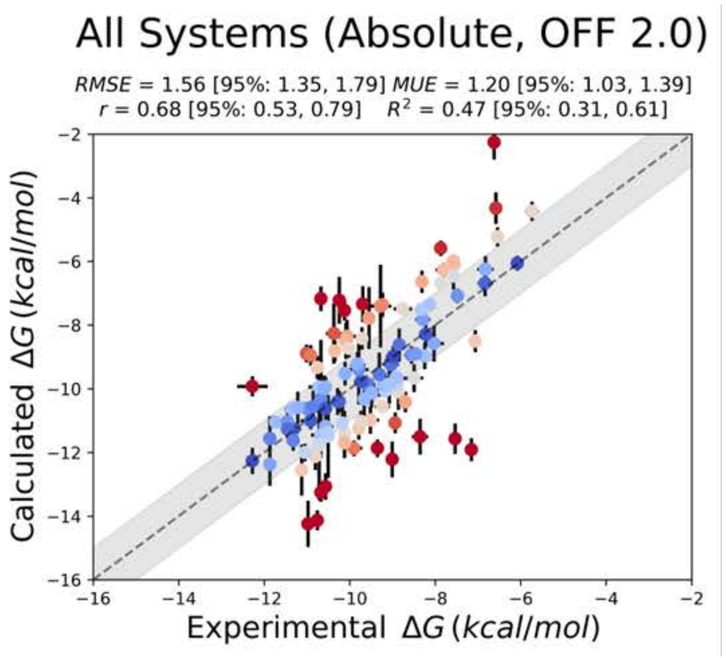
open forcefield

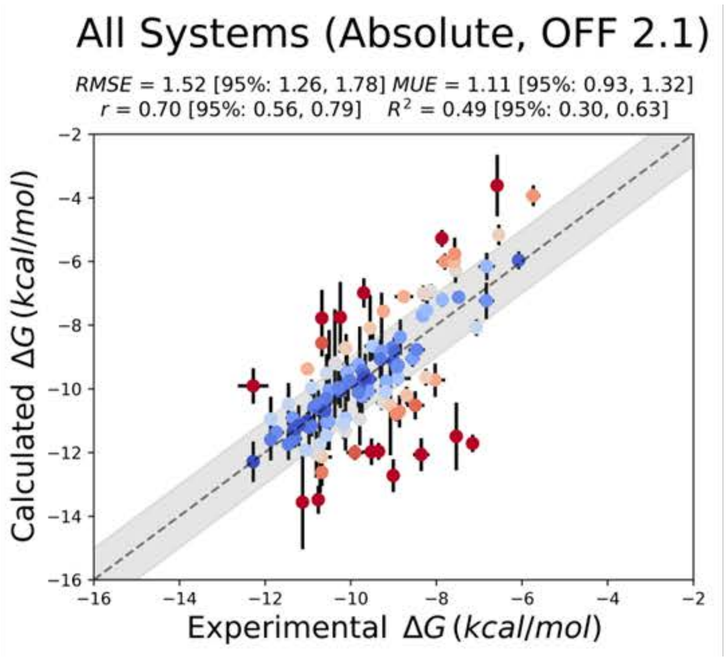
open free energy

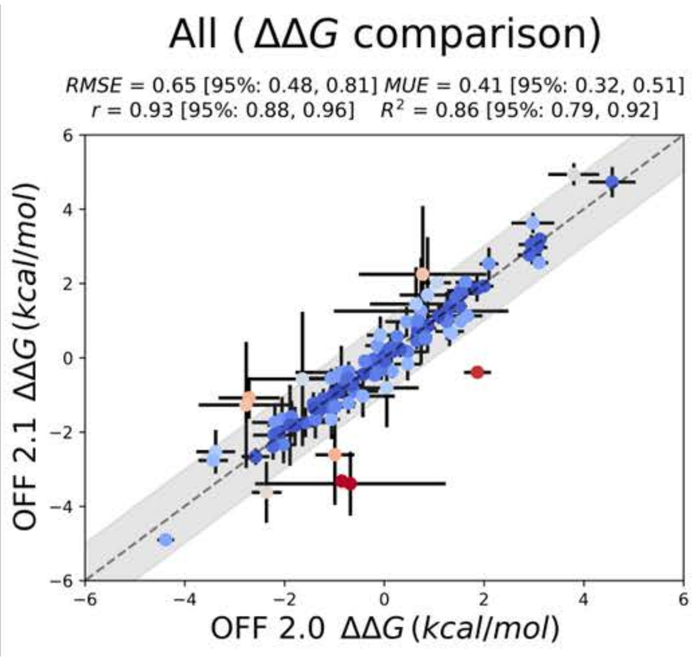
BENJAMIN RIES
Open Free Energy

Check out the Open Free Energy poster from Benjamin Ries on Mon/Tue!

ALCHEMISCALE ALLOWS US TO EASILY ASSESS THE RAPID PROGRESS OPEN FORCE FIELD IS MAKING IN ACCURATE BINDING FREE ENERGIES







JEFFREY WAGNER

Check out Jeffrey Wagner's OpenFF poster on Wed/Thu

ASAP
Accessible Antivirals to Prevent Pandemics

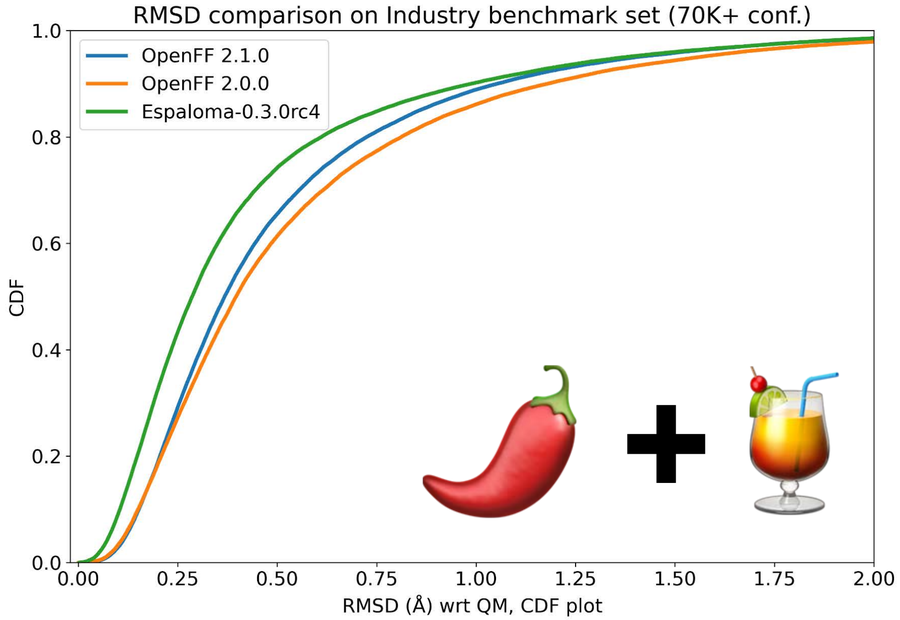
open forcefield

open free energy

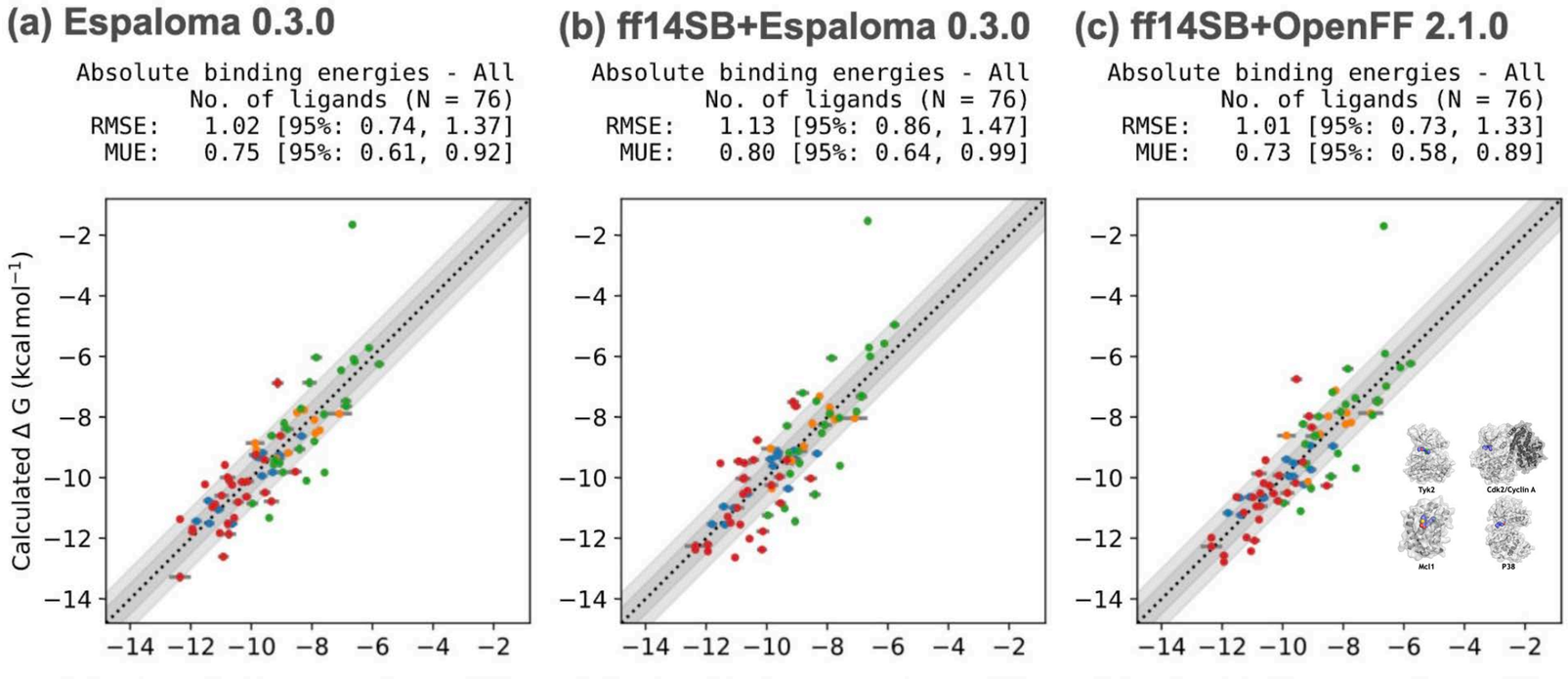
OPEN SOURCE ECOSYSTEMS ALLOW US TO RAPIDLY EXPLOIT NEW TECHNOLOGIES, SUCH AS FULLY MACHINE LEARNED FORCE FIELDS

espaloma is parameterized on over 1M QM calculations and uses **graph nets** to assign MM parameters

reproduces QM minima



Produces excellent protein:ligand binding free energies



KEN TAKABA

Don't miss Ken Takaba's Espaloma poster Wed/Thu on all the details!

OpenMM

open forcefield initiative

YUANQING WANG | **MIKE HENRY** | **PAVAN BEHARA** | **IVÁN PULIDO**

The COVID Moonshot collaboration is worldwide

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

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

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

COVID Moonshot: Enamine Chemists in Kyiv

Tetiana Matviyuk

Slava Kos

Mikhal Shafeev

Oleg Michurin

Olha Tavlui

Yulia Filimonova

Maksym Shevtsov

Volodymyr Voloshchuk

Sergiy Fesh

Oleksandr Zotkin

Volodymyr Pashchenko

Natalia Kozakova

Victor Gulyak

Vitalii Bilenko

Yulia Fil

Kostiantyn Melnykov

Sergiy Kinah

Ivan Logvinenko

Maria Lototska

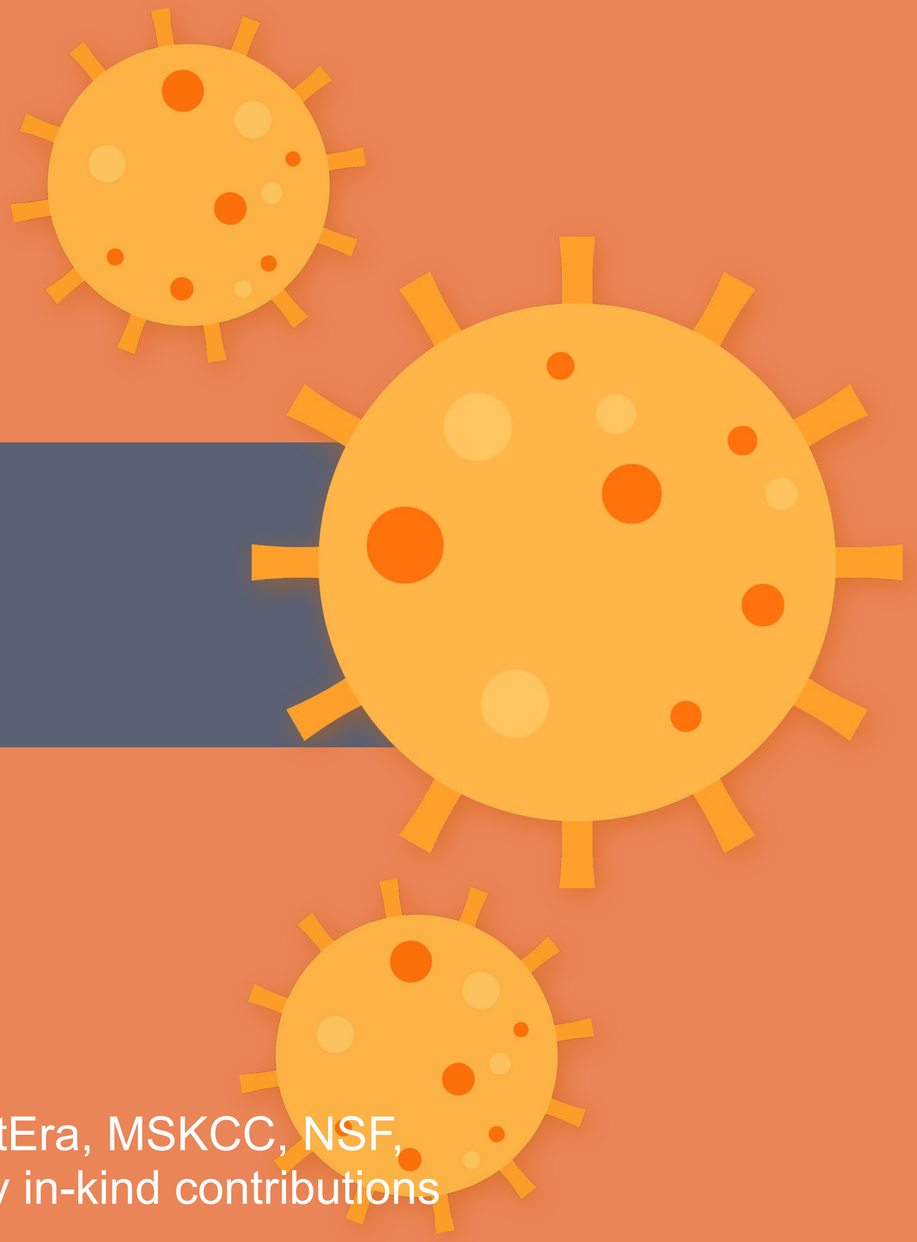
Igor Tsurupa

Eugene Chernyshenko

CHODERA LAB

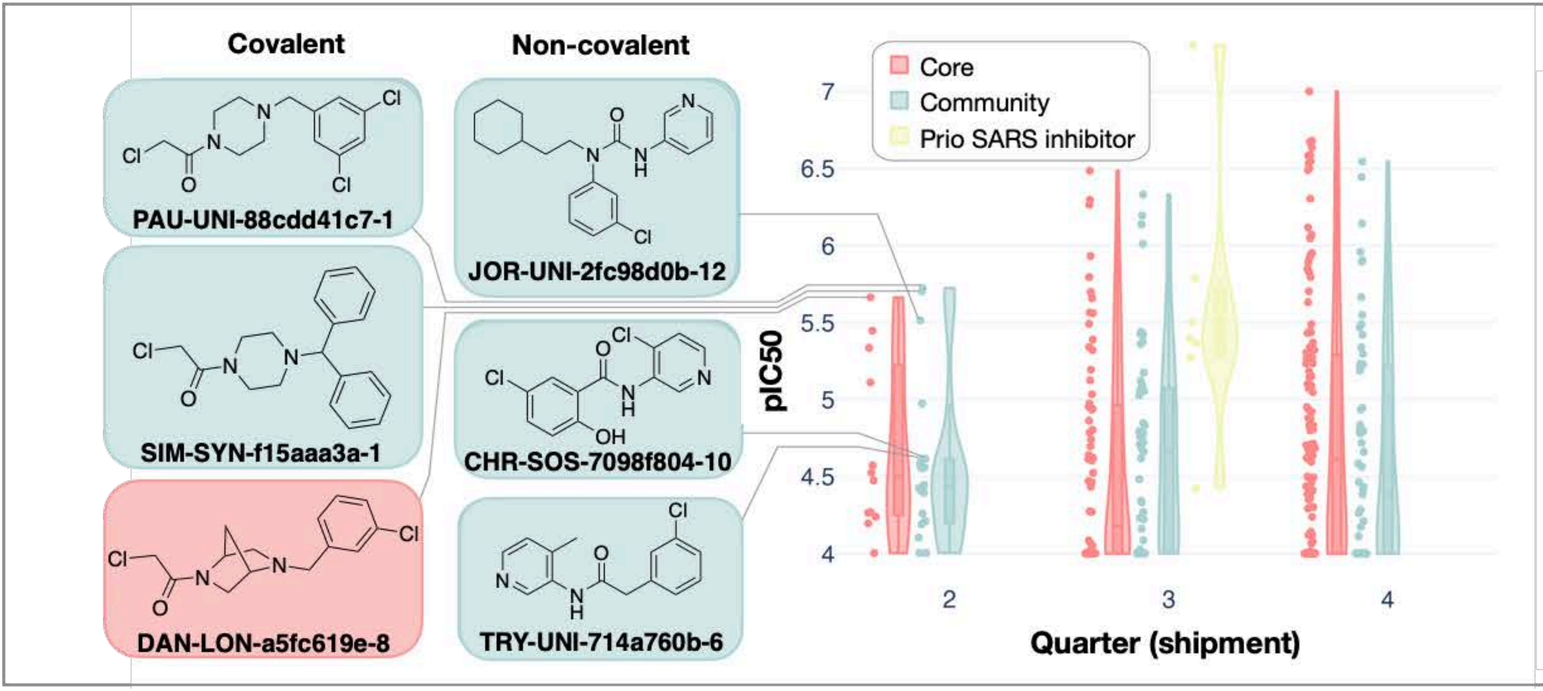
- All funding: http://choderalab.org/funding

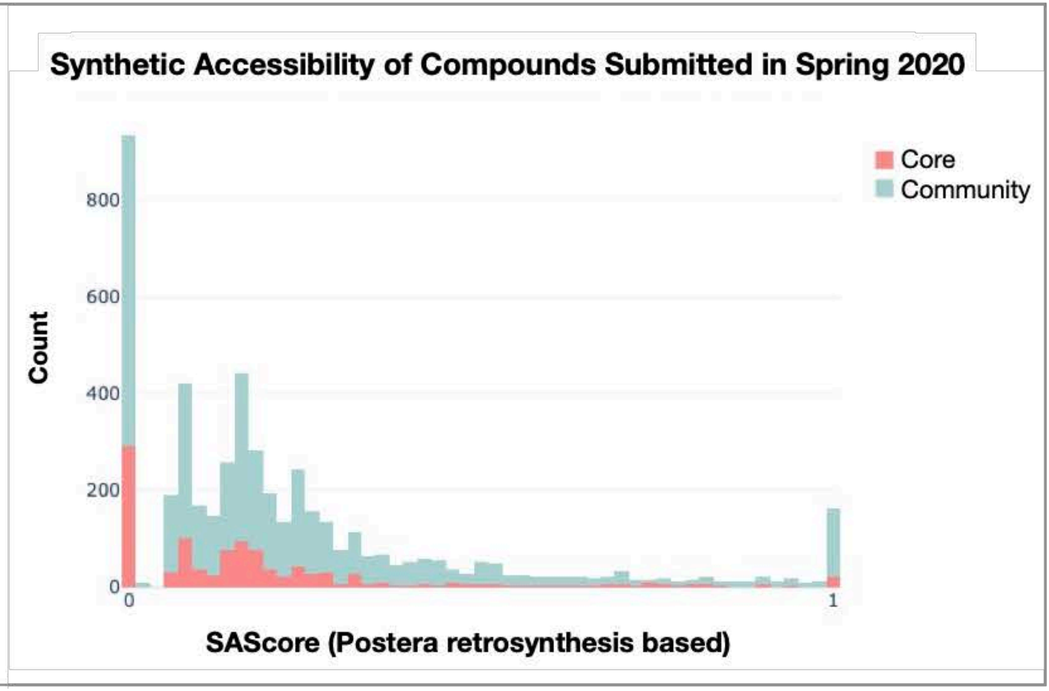
THANK YOU!



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

COMMUNITY SUBMISSIONS GENERATED USEFUL HIT COMPOUNDS EARLY IN THE MOONSHOT PROJECT

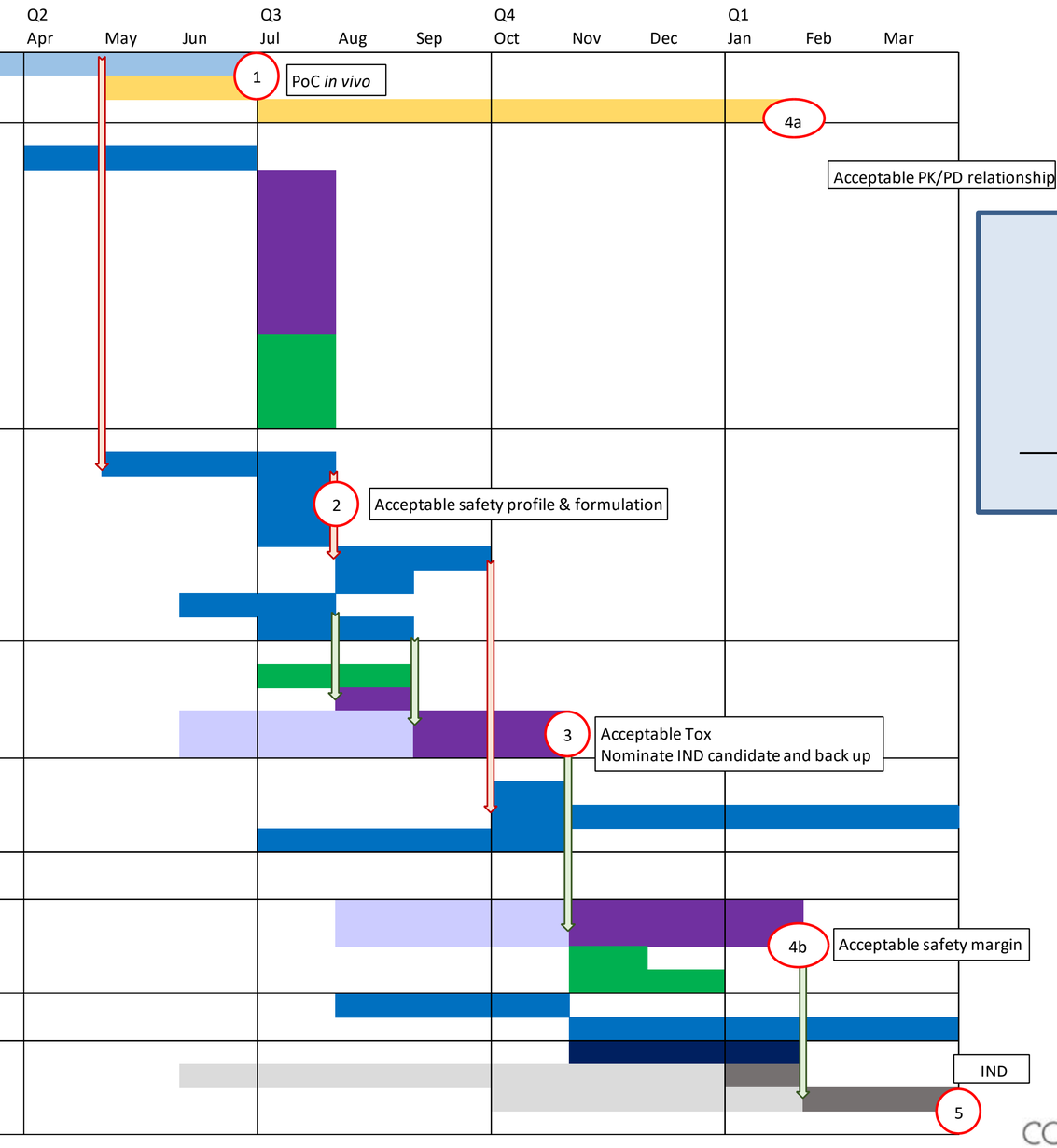




https://www.biorxiv.org/content/10.1101/2020.10.29.339317v4

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

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



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

Efficacy
CMC
Pharmacokinetics
Regulatory
Clinical
Safety

COVID Moonshot

FIN.