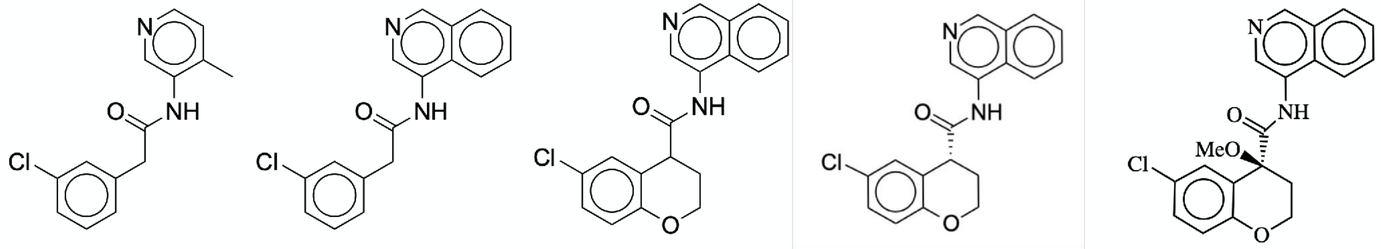
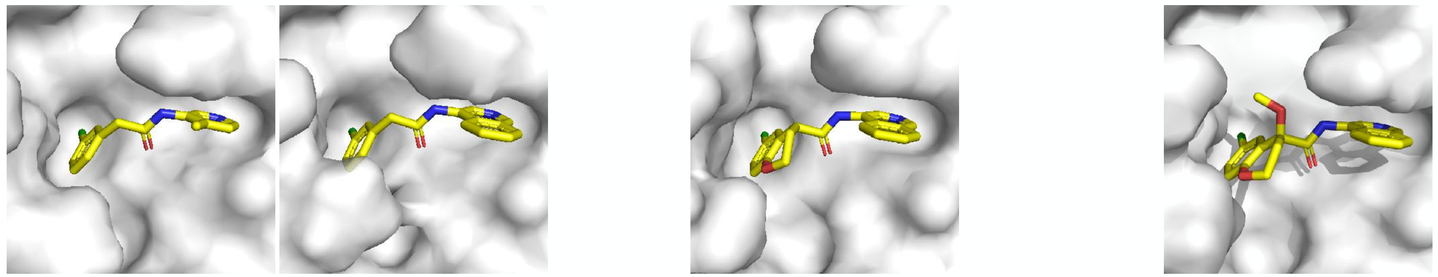
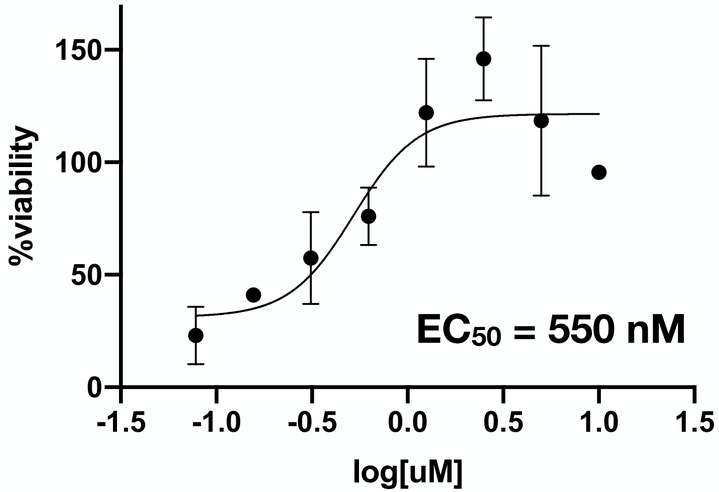
Optimization of the P1-P2 scaffold resulted in incredibly potent compound with ~0.5 µM antiviral activity



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



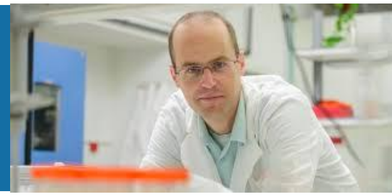
Lead compound active against live SARS-CoV-2



http://postera.ai/covid

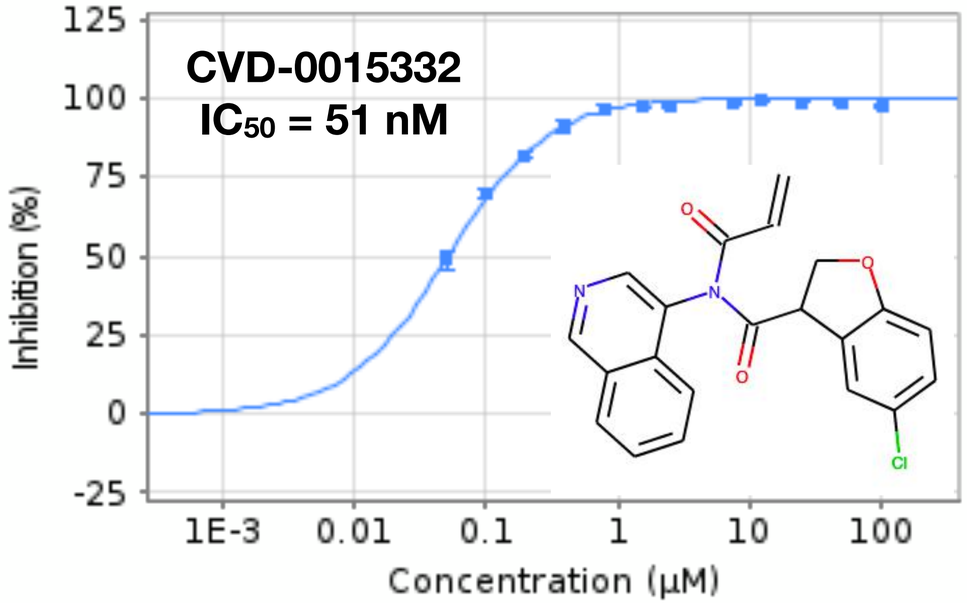
With the Israel Institute of Biological Research

Scaffold is well-poised for covalentization

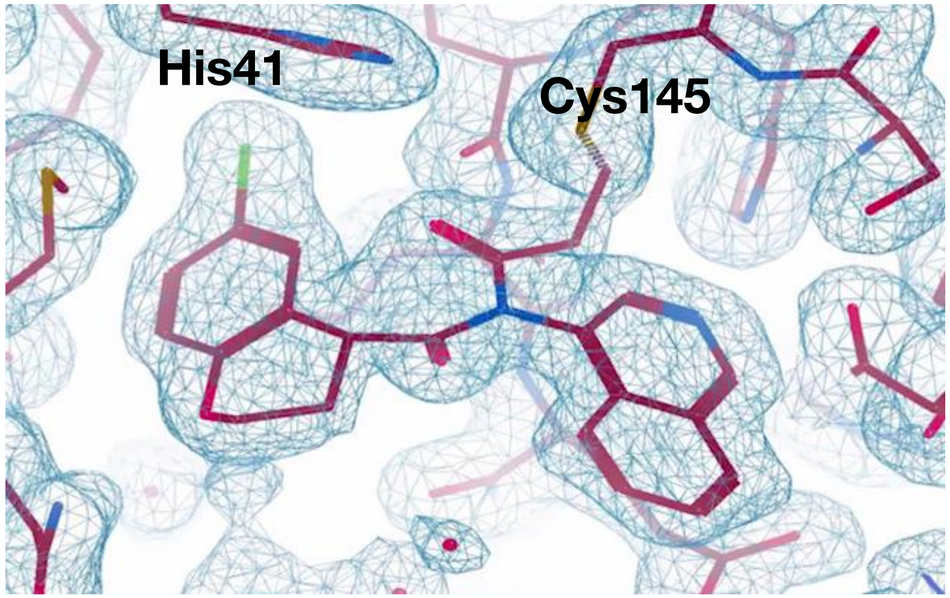


Nir London
Weizmann Institute

MAT-POS-e69ad64a-2



Matt Robinson, PostEra



Diamond Light Source / XChem
Daeron Fearon

http://postera.ai/covid

How can we design optimal P1’/P4 substituents?

http://postera.ai/covid

Our lab had started to use Folding@home to aid experimental collaborators in pursuing COVID-19 drug discovery projects

FOLDING @HOME

Client statistics by OS

OS Type	Native TFLOPS*	x86 TFLOPS*	Active CPUs	Active Cores	Total CPUs
Windows	857	857	67,467	187,104	5,857,235
Mac OS X	91	91	8,083	85,382	217,033
Linux	87	87	6,383	26,457	882,200
NVIDIA GPU	1	2	4	4	348,371
ATI GPU	10,243	21,613	7,178	7,178	426,335
NVIDAI Fermi GPU	36,065	76,097	21,570	21,587	624,822
Total	47,344	98,747	110,685	327,712	8,355,996

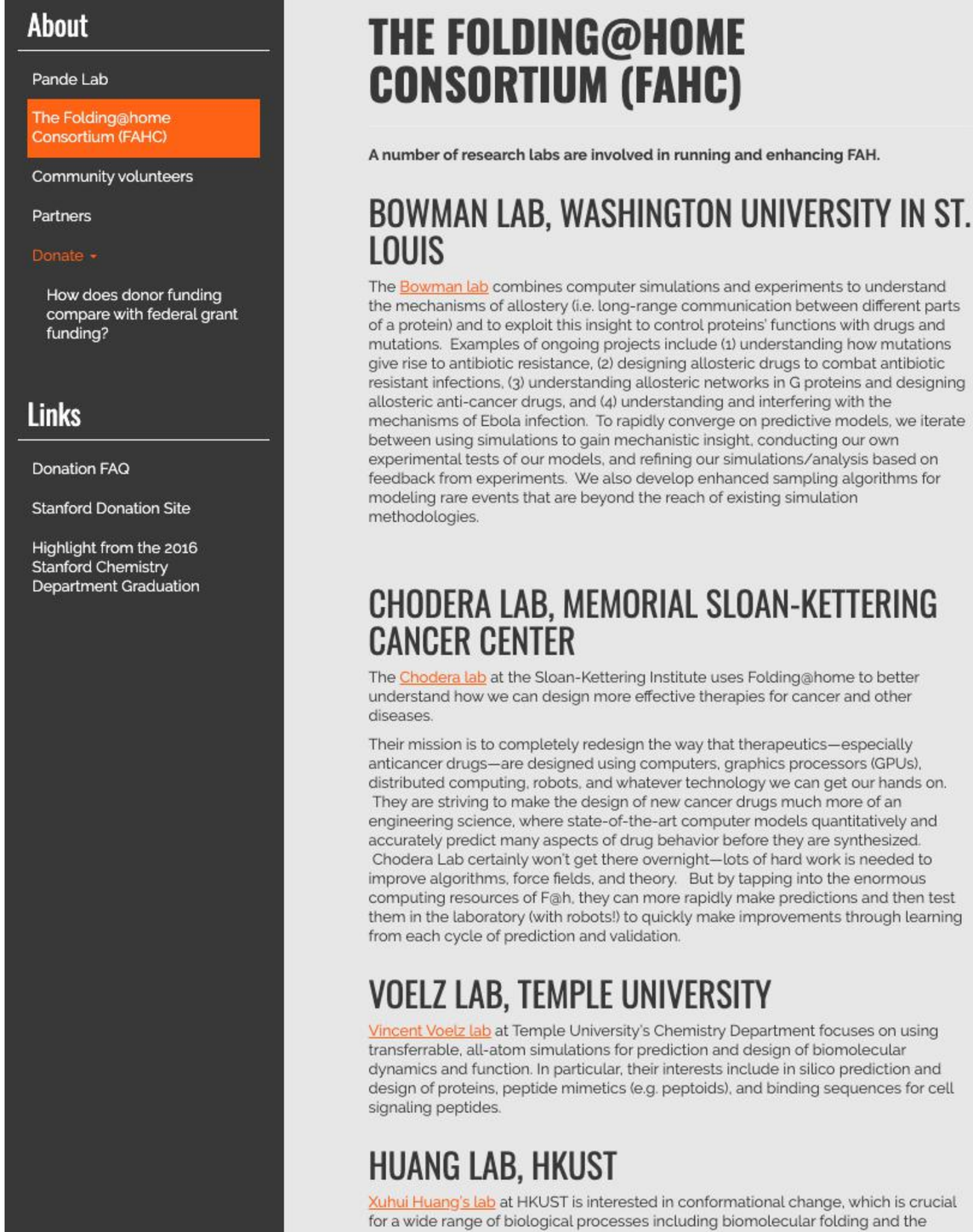
1924085 people have non-anonymously contributed to Folding@home.

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

~100 pflop/s!

we mobilized the folding@home consortium to focus on covid-19

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



About

Pande Lab

The Folding@home Consortium (FAHC)

Community volunteers

Partners

Donate

How does donor funding compare with federal grant funding?

Links

Donation FAQ

Stanford Donation Site

Highlight from the 2016 Stanford Chemistry Department Graduation

THE FOLDING@HOME CONSORTIUM (FAHC)

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

BOWMAN LAB, WASHINGTON UNIVERSITY IN ST. LOUIS

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

CHODERA LAB, MEMORIAL SLOAN-KETTERING CANCER CENTER

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

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

VOELZ LAB, TEMPLE UNIVERSITY

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

HUANG LAB, HKUST

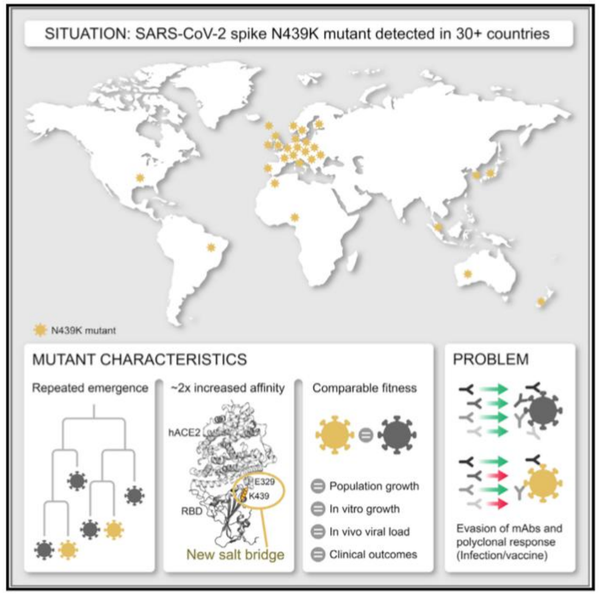
Xuhui Huang's lab at HKUST is interested in conformational change, which is crucial for a wide range of biological processes including biomolecular folding and the

Cell

Article

Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity

Graphical Abstract



Authors

Emma C. Thomson, Laura E. Rosen, James G. Shepherd, ..., Davide Corti, David L. Robertson, Gyorgy Snell

Correspondence

david.l.robertson@glasgow.ac.uk (D.L.R.),
gsnell@vir.bio (G.S.)

In Brief

Epidemiological, clinical, molecular, and structural characterization of the N439K mutation in the SARS-CoV-2 spike receptor binding motif demonstrates that it results in similar viral fitness compared to wild-type while conferring resistance against some neutralizing monoclonal antibodies and reducing the activity of some polyclonal antibody responses.

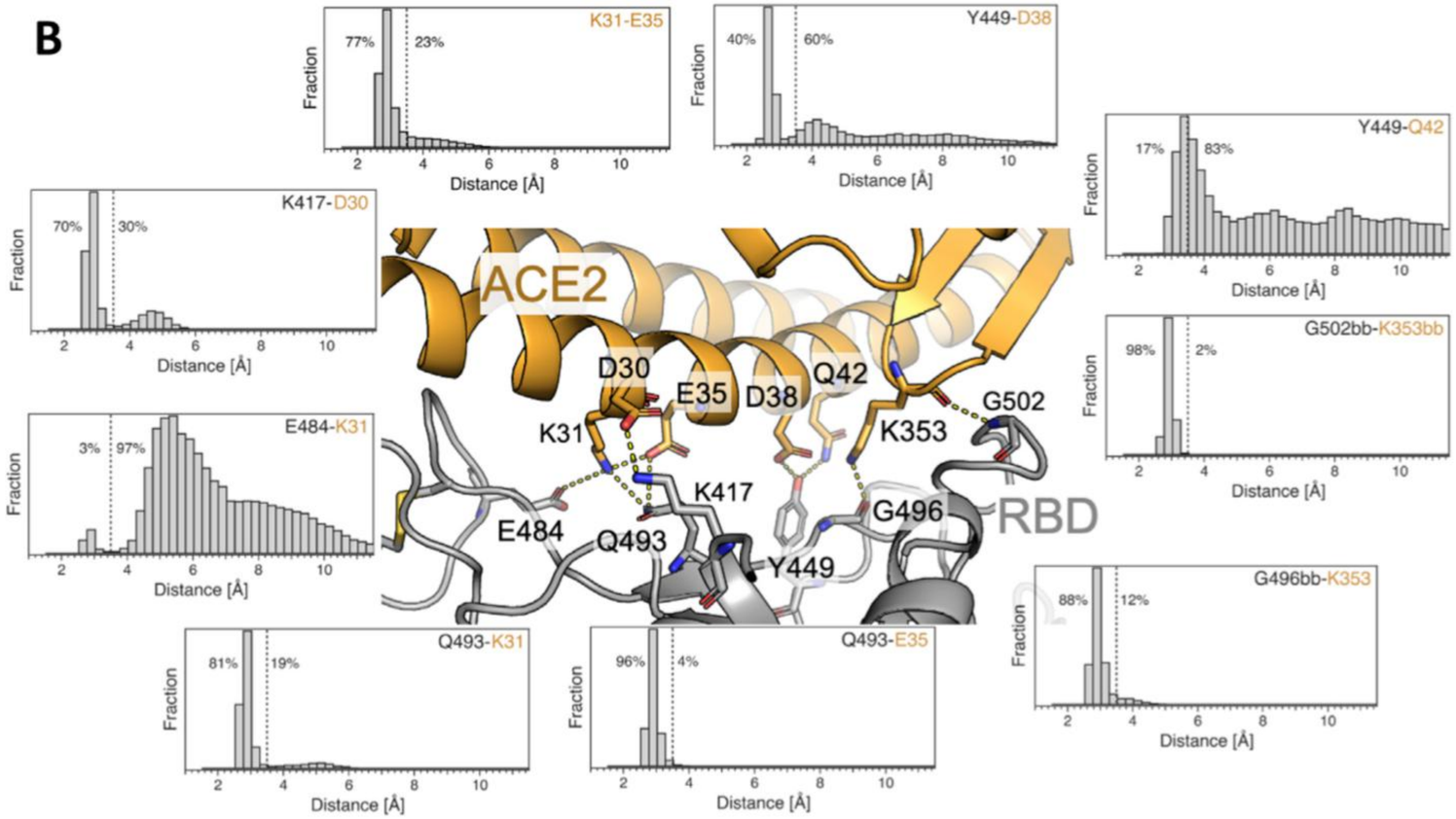
Highlights

- The receptor-binding motif (RBM) is a highly variable region of SARS-CoV-2 spike
- RBM mutation N439K has emerged independently in multiple lineages
- N439K increases spike affinity for hACE2; viral fitness and disease are unchanged
- N439K confers resistance to several mAbs and escapes some polyclonal responses

Thomson et al., 2021, Cell *184*, 1171–1187
March 4, 2021
https://doi.org/10.1016/j.cell.2021.01.037

CellPress

We've been working with Vir Biotechnology and the Bloom and Veesler labs to understand the emergence of new SARS-CoV-2 variants and their capacity for reducing effectiveness of therapeutic and vaccine-elicited antibodies.



We built the first exaFLOP/s computing platform as the public joined in our effort

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

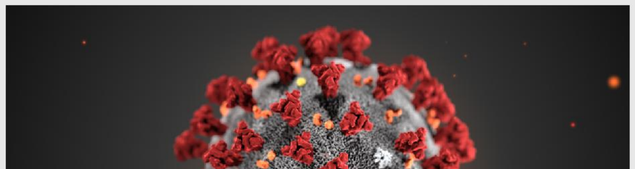
February 27, 2020
by Greg Bowman

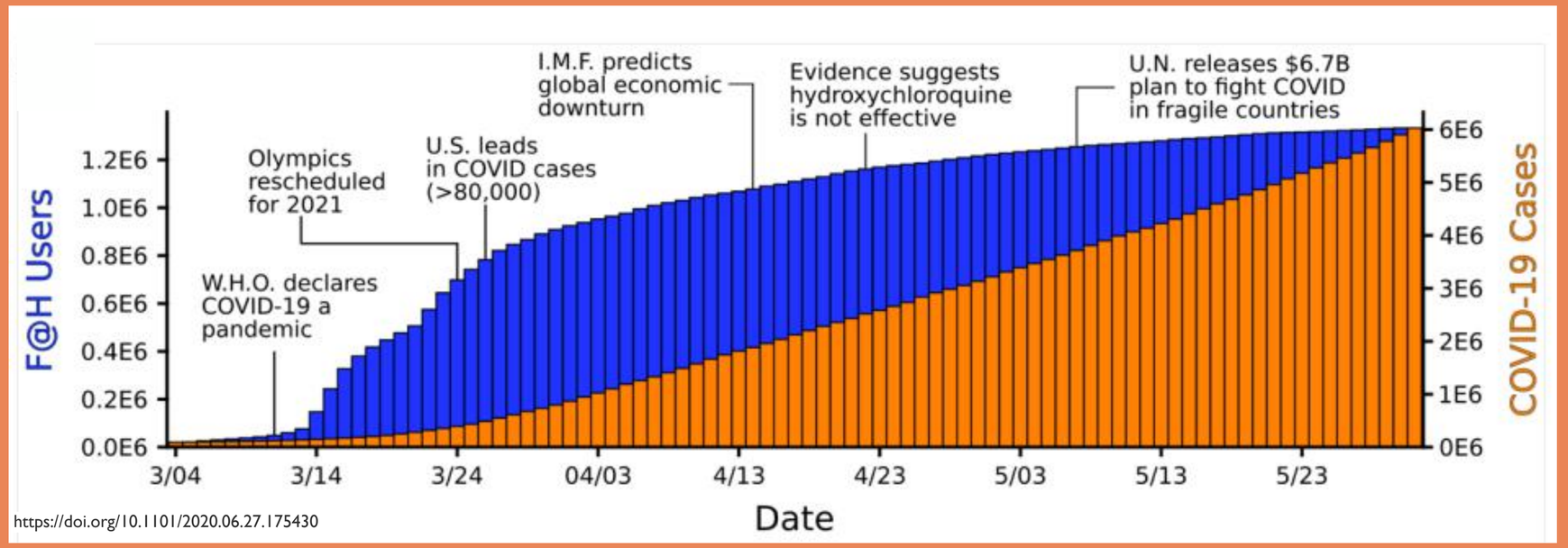
We need your help! Folding@home is joining researchers around the world working to better understand the 2019 Coronavirus (2019-nCoV) to accelerate the open science effort to develop new life-saving therapies. By downloading Folding@Home, you can donate your unused computational resources to the Folding@home Consortium, where researchers working to advance our understanding of the structures of potential drug targets for 2019-nCoV that could aid in the design of new therapies. The data you help us generate will be quickly and openly disseminated as part of an open science collaboration of multiple laboratories around the world, giving researchers new tools that may unlock new opportunities for developing lifesaving drugs.

2019-nCoV is a close cousin to SARS coronavirus (SARS-CoV), and acts in a similar way. For both coronaviruses, the first step of infection occurs in the lungs, when a protein on the surface of the virus binds to a receptor protein on a lung cell. This viral protein is called the spike protein, depicted in red in the image below, and the receptor is known as ACE2. A therapeutic antibody is a type of protein that can block the viral protein from binding to its receptor, therefore preventing the virus from infecting the lung cell. A therapeutic antibody has already been developed for SARS-CoV, but to develop therapeutic antibodies or small molecules for 2019-nCoV, scientists need to better understand the structure of the viral spike protein and how it binds to the human ACE2 receptor required for viral entry into human cells.

Proteins are not stagnant—they wiggle and fold and unfold to take on numerous shapes. We need to study not only one shape of the viral spike protein, but all the ways the protein wiggles and folds into alternative shapes in order to best understand how it interacts with the ACE2 receptor, so that an antibody can be designed. Low-resolution structures of the SARS-CoV spike protein exist and we know the mutations that differ between SARS-CoV and 2019-nCoV. Given this information, we are uniquely positioned to help model the structure of the 2019-nCoV spike protein and identify sites that can be targeted by a therapeutic antibody. We can build computational models that accomplish this goal, but it takes a lot of computing power.

This is where you come in! With many computers working towards the same goal, we aim to help develop a therapeutic remedy as quickly as possible. By downloading Folding@home here [LINK] and selecting to contribute to "Any Disease", you can help provide us with the computational power required to tackle this problem. One protein from 2019-nCoV, a protease encoded by the viral RNA, has already been crystallized. Although the 2019-nCoV spike protein of interest has not yet been resolved bound to ACE2, our objective is to use the homologous structure of the SARS-CoV spike protein to identify therapeutic antibody targets.





https://doi.org/10.1101/2020.06.27.175430

Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

Ivy Zhang (CBM)

This honestly came as a bit of a surprise

Folding@home

Team Monthly | Team | Donor | OS Stats

Active CPUs & GPUs by OS

OS	AMD GPUs	NVidia GPUs	CPUs	CPU cores	TFLOPS	x86 TFLOPS
Windows	75,823	314,952	474,277	3,588,315	680,371	1,384,998
Linux	3,675	41,113	78,124	811,997	85,028	167,152
macOSX	0	0	41,582	230,198	2,578	2,578
Totals	79,498	356,065	593,983	4,630,510	767,977	1,554,728

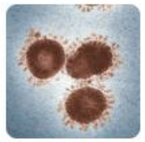
CPUs and GPUs which have returned Work Units within the last 50 days are listed by OS. FLOPS per core is estimated.

TFLOPS is Tera Floating-point OPerations per Second or trillions of math operations per second. Please see our FLOPS FAQ for more information.

Reported on Wed, 25 Mar 2020 23:42:36 GMT

~1.5 exaflops
> sum of top-10 supercomputers

Use Your Computer To Help Folding@Home Solve The COVID-19 Virus Pandemic
Longmont Observer · Yesterday



- 400,000 new people have joined Folding@Home's fight against COVID-19
  Engadget · 2 days ago

View Full Coverage

Folding@home software diverts users' excess processing power to finding coronavirus cure
Dezeen · 22 hours ago

Folding@Home Network Breaks the ExaFLOP Barrier In Fight Against Coronavirus
Tom's Hardware · 5 hours ago

How to Fight Coronavirus With Folding@home and a Gaming PC
How-To Geek · 5 days ago

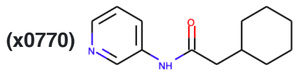
Join Team Hackaday To Crunch COVID-19 Through Folding@Home
Hackaday · 7 days ago

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

There are multiple design vectors to explore

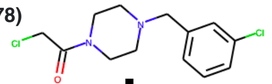
fragment merger produced initial lead compound

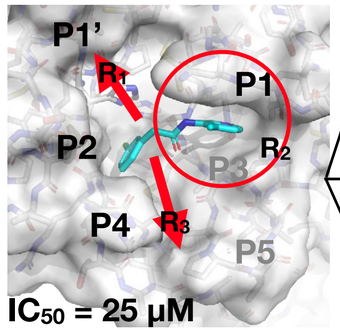
(x0770)



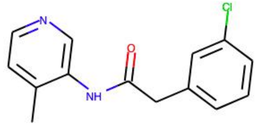
x

(x0678)





IC_{50} = 25 µM

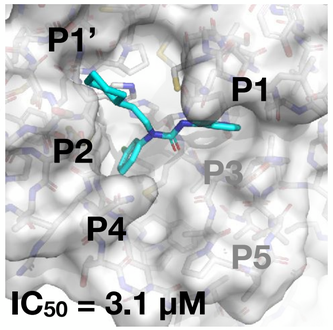


TRY-UNI-714a760b-6 (x2646)
current lead compound

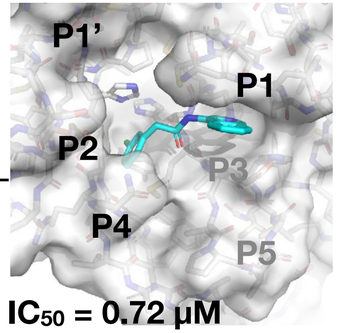
8x

35x

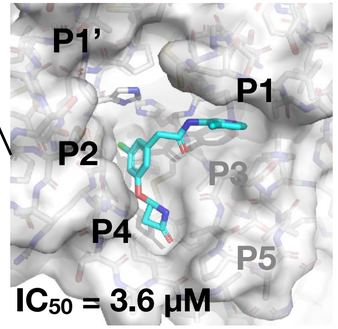
7x



IC_{50} = 3.1 µM

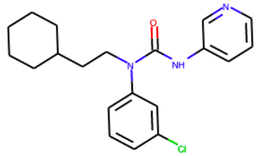


IC_{50} = 0.72 µM



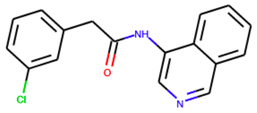
IC_{50} = 3.6 µM

P1' pocket engagement



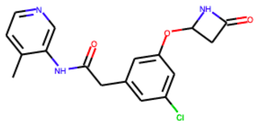
JOR-UNI-2fc98d0b-12 (x10201)

P1 substituent optimization



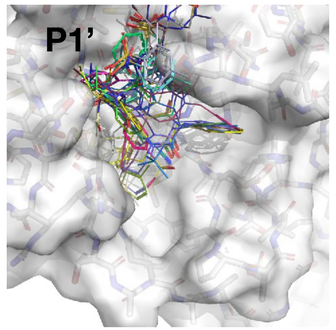
ADA-UCB-6c2cb422-1 (x10959)

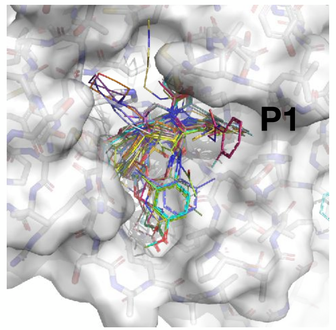
P4 pocket engagement

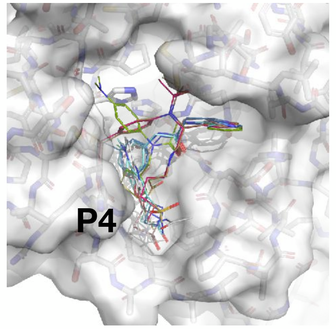


TRY-UNI-2eddb1ff-7 (x10789)

fragment-derived inspiration



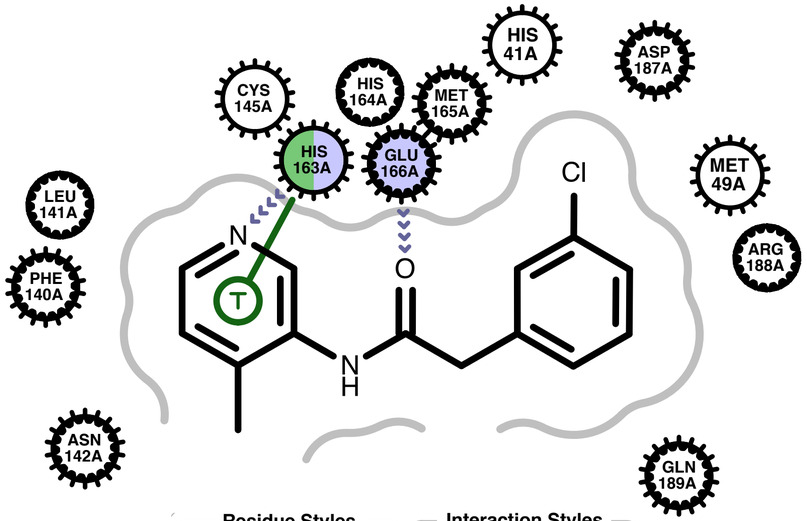




available fragment X-ray structures spanning pockets

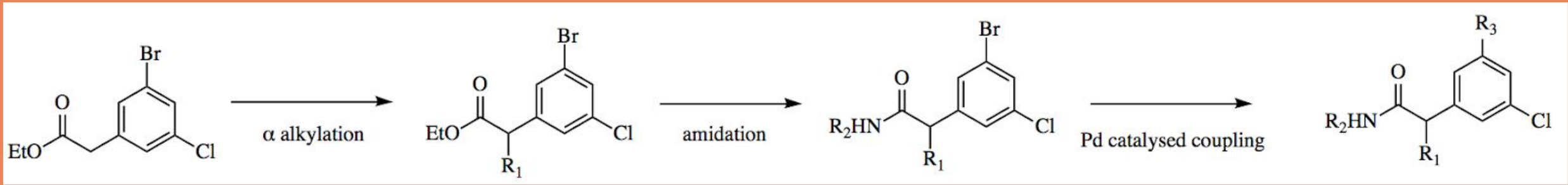
3-aminopyridine scaffold interactions

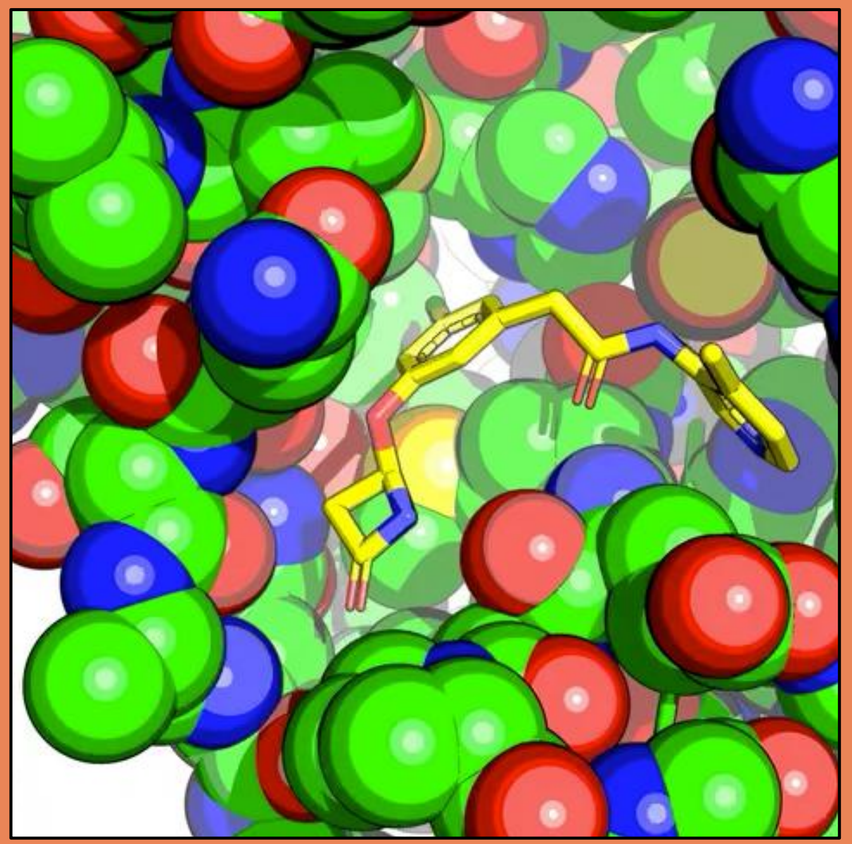
(264 assayed compounds in series)



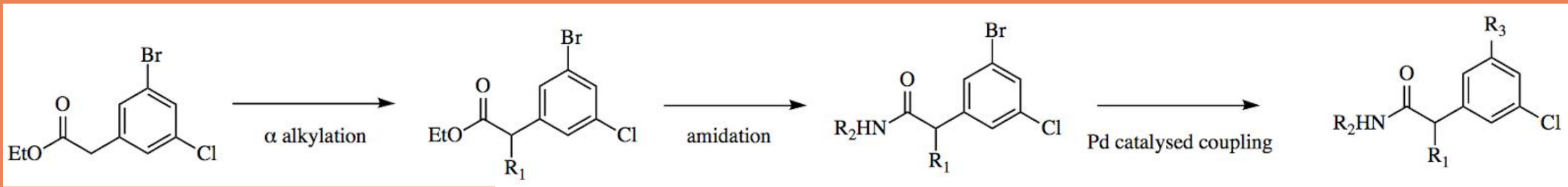
TRY-UNI-714a760b-6 (x2646)
current lead compound

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



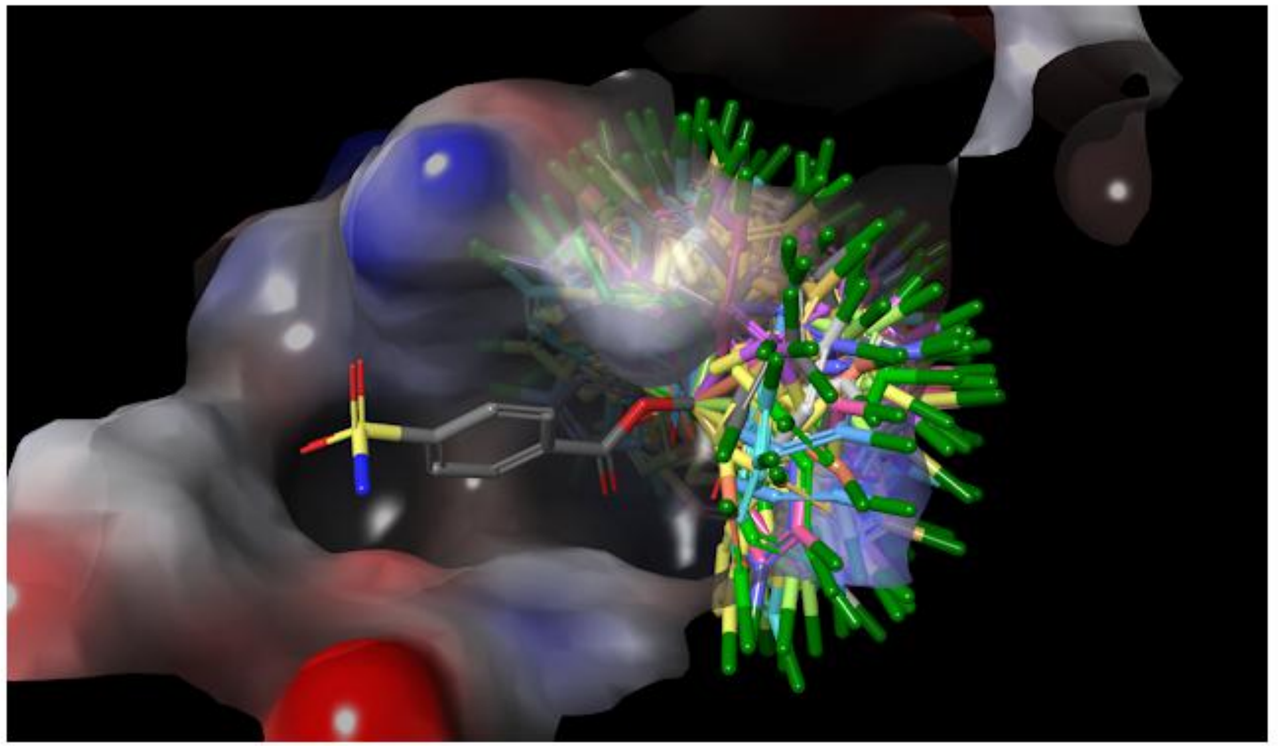


We can enumerate a huge variety of molecules that can be quickly synthesized by changing out the ingredients used in the final step



PAT WALTERS

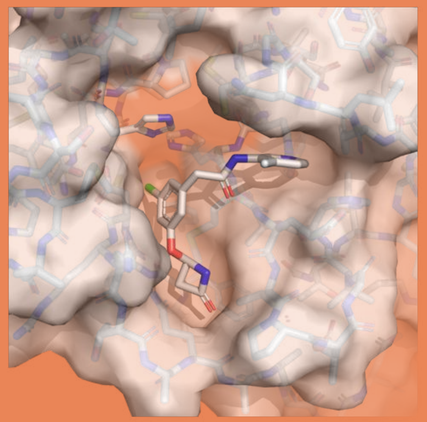
The cool part of this is that, since we kept **BF** fixed, the conformers are already aligned in the binding site.



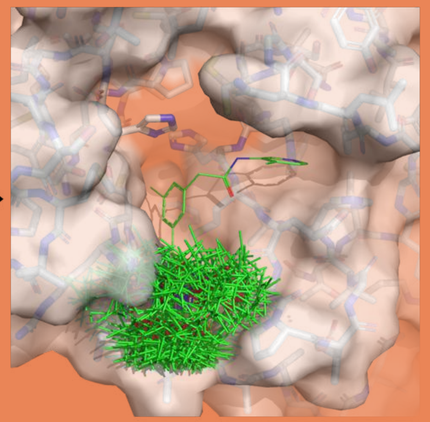
Folding@home can run relative alchemical free energy calculations at planetary scale, performing tens of thousands of transformations/week

Dominic Rufa
Tri-I TPCB PhD student

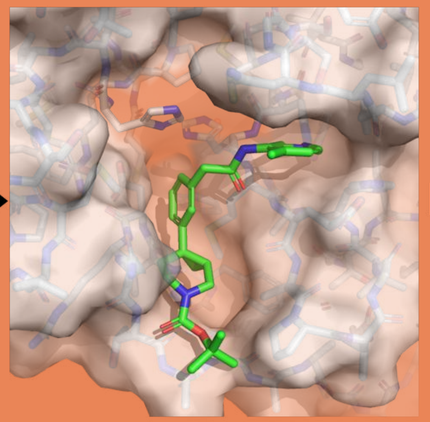
X-ray structure as reference



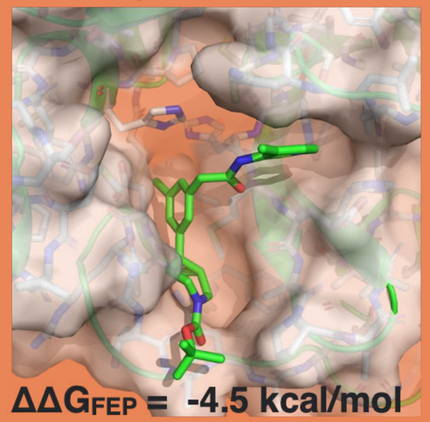
constrained enumeration of poses for proposed molecule



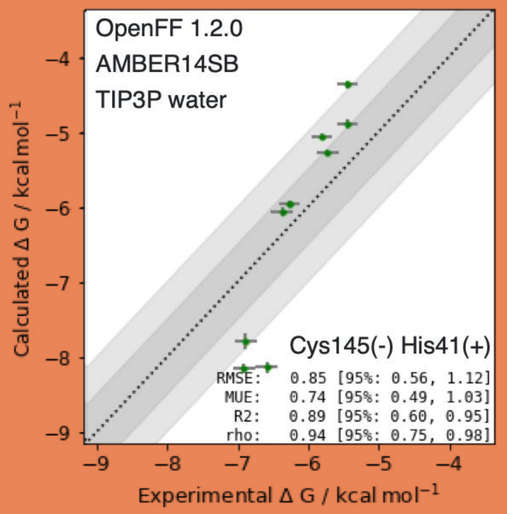
selection of pose with best docking score



nonequilibrium alchemical free energy calculation final posed structure



retrospective performance on 3-aminopyridine lead series



perses: open source relative alchemical free energy calculations
http://github.com/choderalab/perses
Open Force Field Initiative OpenFF (“Parsley”) small molecule force field
http://openforcefield.org

+ Hannah Bruce Macdonald
William Glass
Matt Wittman
David Dotson

TOGETHER, WE ARE POWERFUL

Together, we have created the most powerful supercomputer on the planet, and are using it to help understand SARS-CoV-2/COVID-19 and develop new therapies. We need your help pushing toward a potent, patent-free drug.

Use your PC to help fight COVID-19.

DOWNLOAD FOLDINGATHOME

[Available for Windows, Mac, Linux]

Progress on the current Sprint 2 to evaluate a batch of potential drugs Started Sun Aug 16 01:00:00 UTC 2020

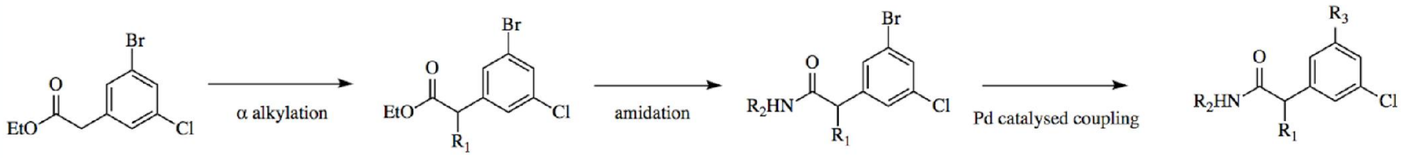
The **progress bar** measures the fraction of compounds we could synthesize that we've evaluated for each sprint

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

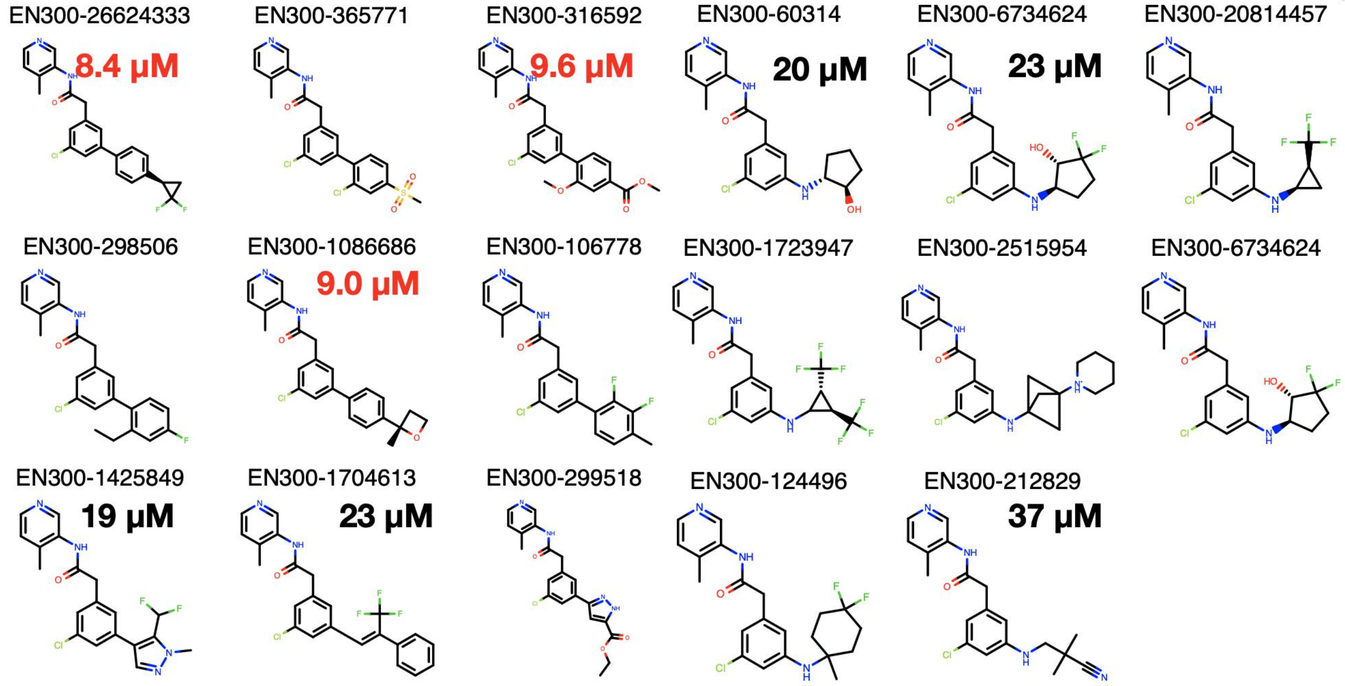
https://registry.opendata.aws/foldingathome-covid19/
https://covid.molssi.org//org-contributions/#folding--home

free energy calculations can rapidly prioritize compounds from large virtual synthetic libraries

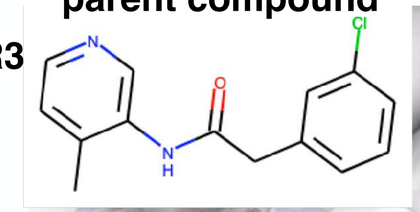
Can we engage S4 from this 5,000-compound virtual synthetic library varying R3



Top free energy calculation compounds and experimental affinity measurements:



parent compound



IC_{50} = 25 μM

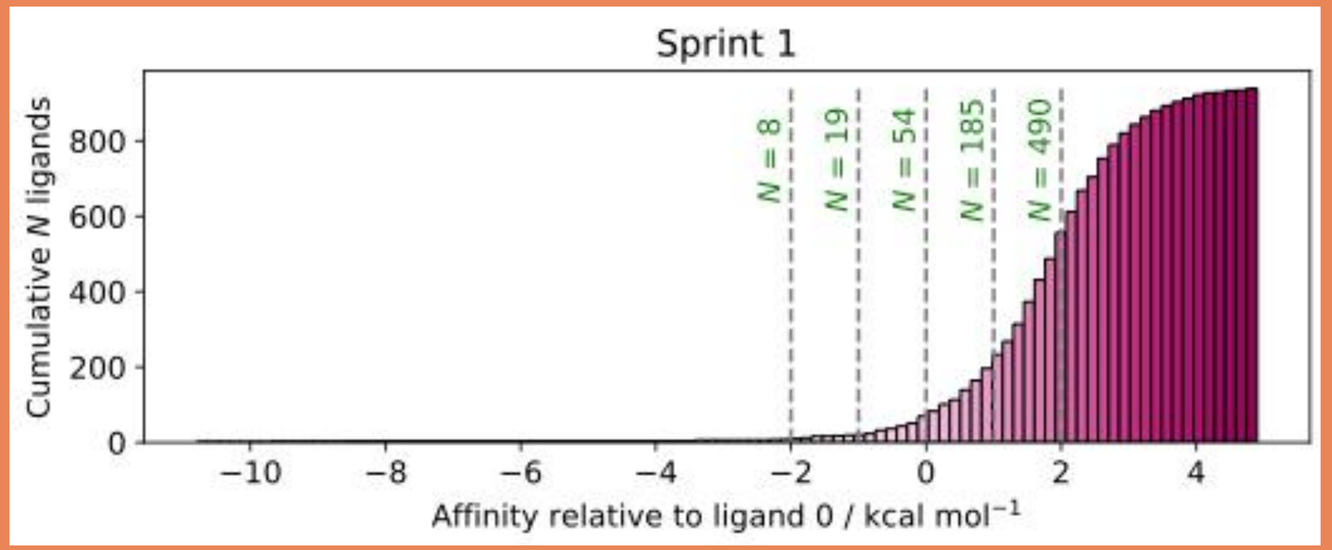
TRY-UNI-714a760b-6

top compounds from free energy calculations

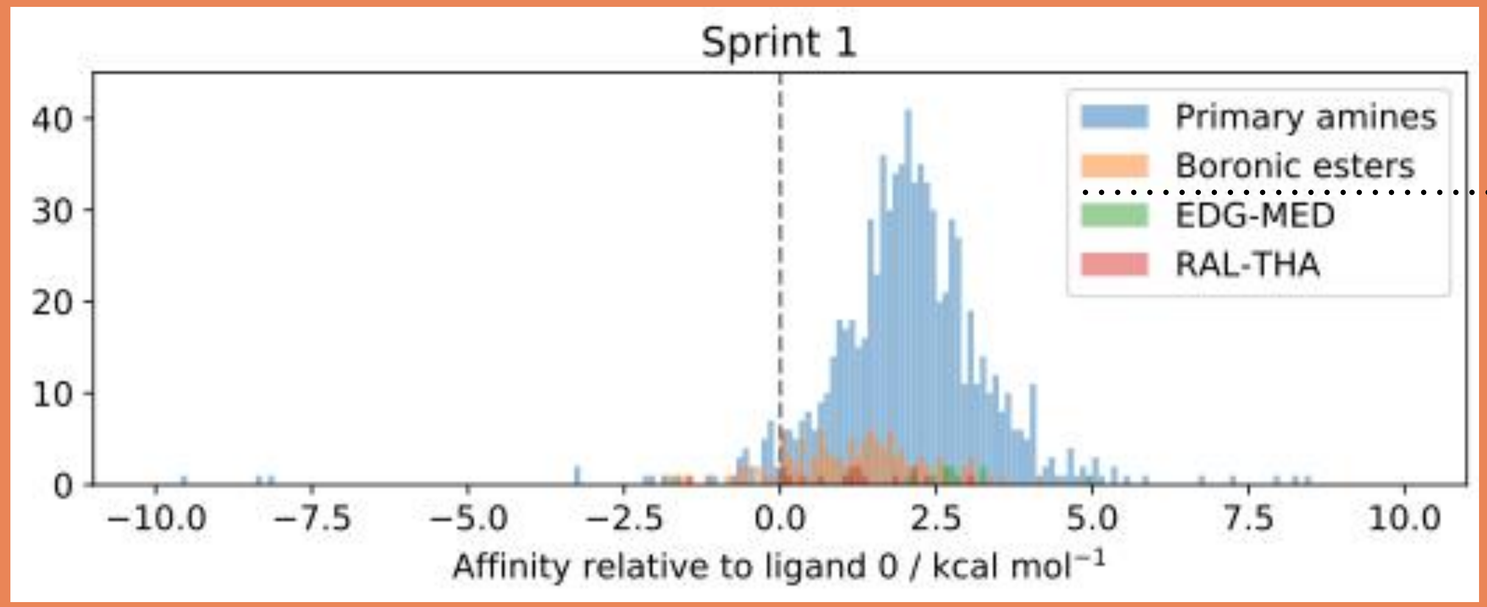
COVID Moonshot: [Moonshot] [Fragalysis] [Dashboard]

Most ideas were bad ideas

better **worse**



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



computer

humans

Sprint 5
Science Dashboard

(compounds are currently being synthesized by Enamine)

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

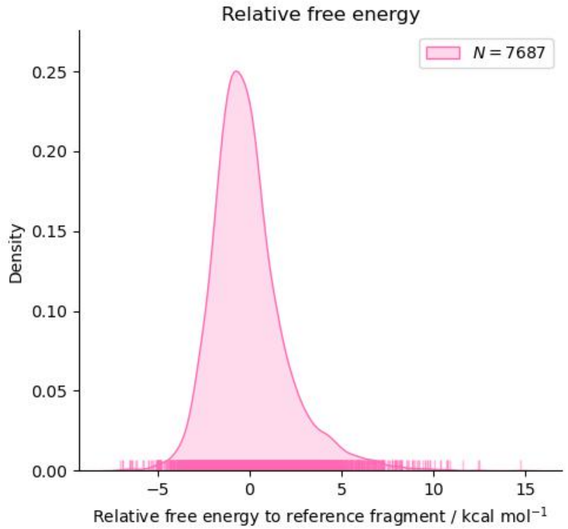
Description

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

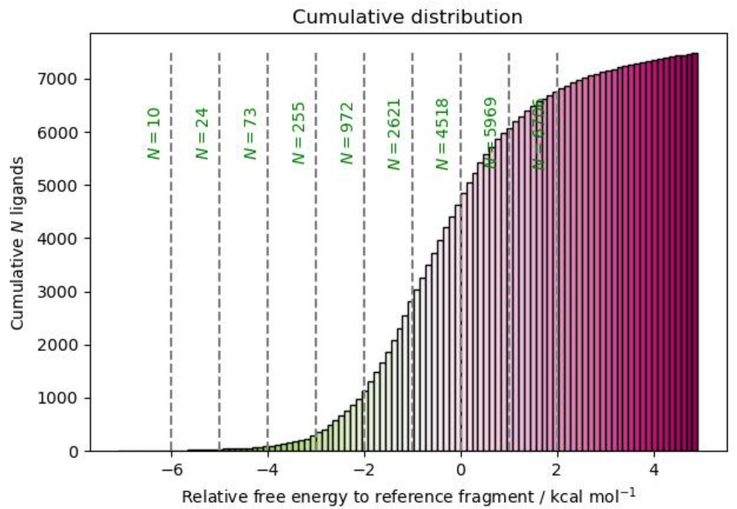
Progress

98.25%

Distributions



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

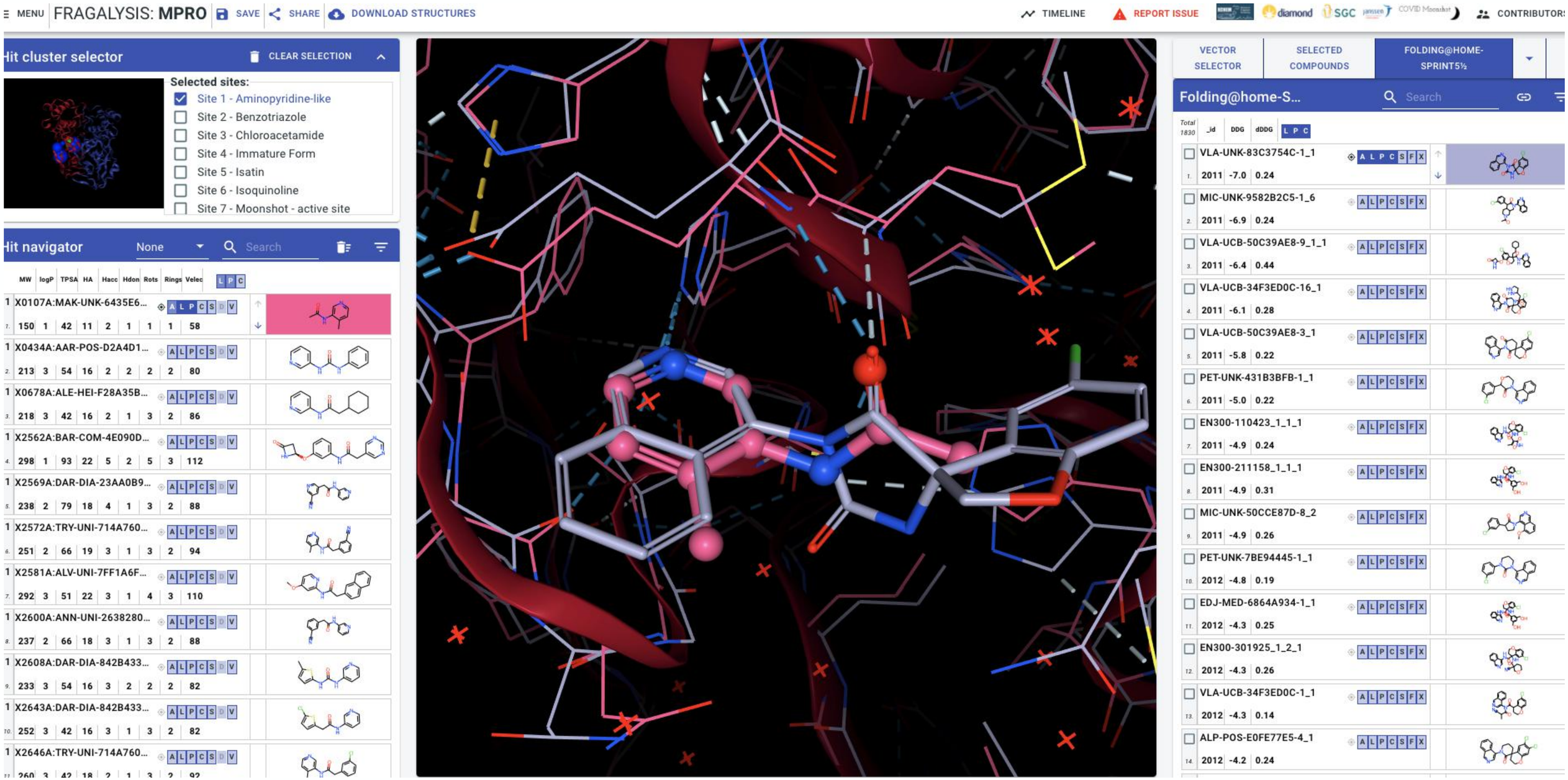


Updated 2021-02-21T21:35:59.343106+00:00

Leaderboard

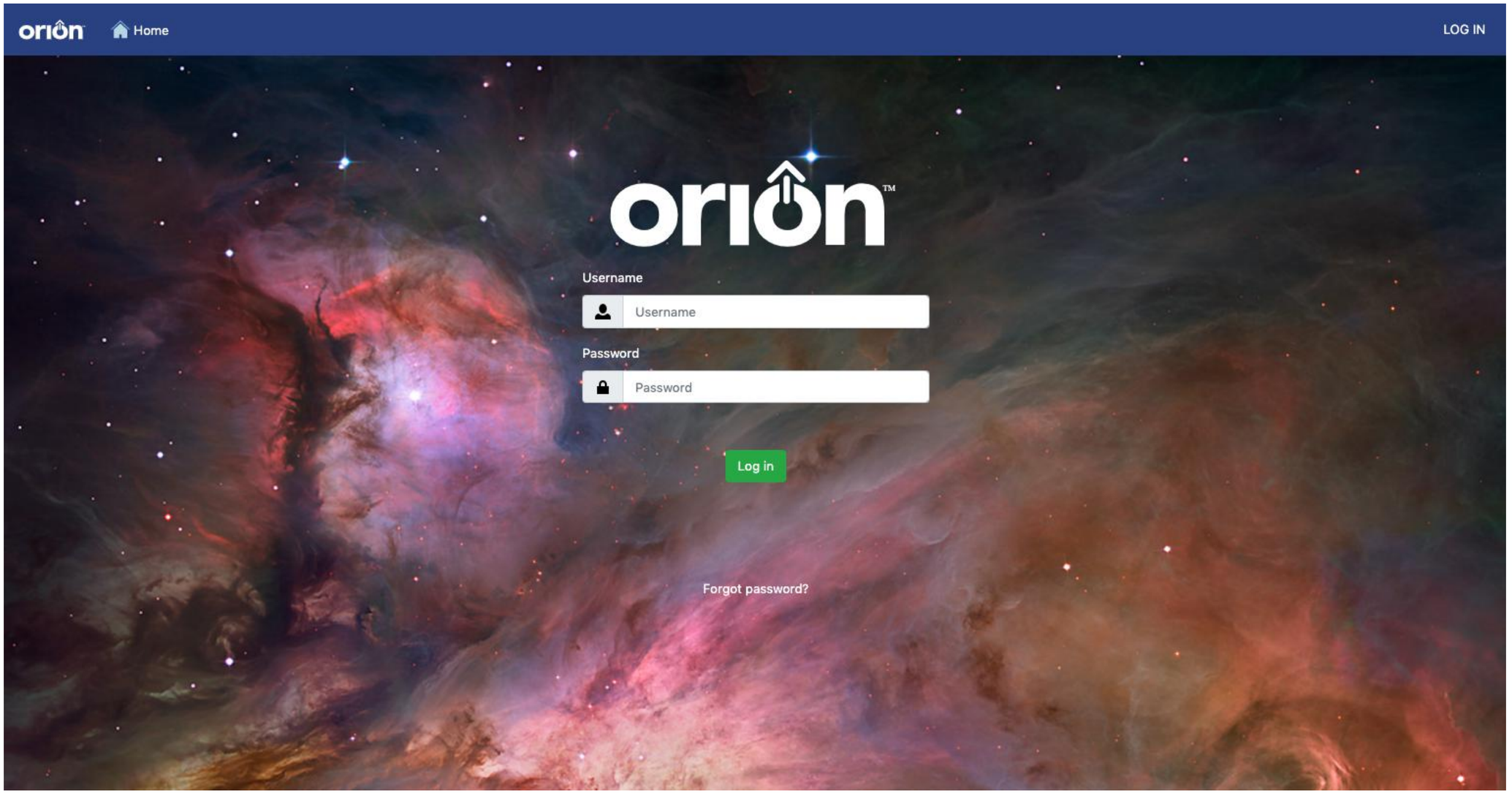
Rank	Compound	SMILES	ΔG / kcal mol^{-1}	pIC50
1	VLA-UNK-83c3754c-1	c1ccc2c(c1)cncc2N3C(=O)[C@@]4(COc5c4cc(cc5)Cl)NC3=O	−15.9 ± 0.2	11.6 ± 0.2
2	ADA-UCB-dc2b944c-1	c1ccc2c(c1)cncc2N3C(=O)CN([C@@]4(C3=O)CCOc5c4cc(cc5)Cl)CC6CCCCC6	−15.5 ± 0.3	11.3 ± 0.2
3	VLA-UCB-34f3ed0c-18	c1ccc2c(c1)cncc2N3C(=O)CN([C@@]4(C3=O)CCOc5c4cc(cc5)Cl)C(=O)N6CCNCC6	−15.4 ± 0.3	11.2 ± 0.2

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



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

we’re working to make these tools available in orion



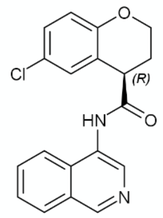
We are close to achieving our TPP objectives

Orally bioavailable inhibitor for therapeutic and prophylactic use

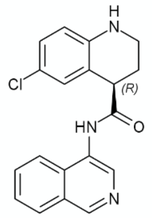
Property	Target range	Progress March 2021
protease assay	IC_{50} < 50 nM (compromise if clean and anti viral activity sufficient)	50nM (mean n=3)
viral replication (Vero-E6)	EC_{50} < 0.2µM	~0.5 µM VeroE6 CPE
plaque reduction (Vero-E6, Calu-3)	EC_{50} < 0.2µM	~0.25 µM Calu3
PK-PD	Cmin > EC90 (plaque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

We have demonstrated antiviral activity agaisnt variants

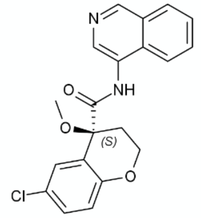
CVD-0013192



CVD-0014805

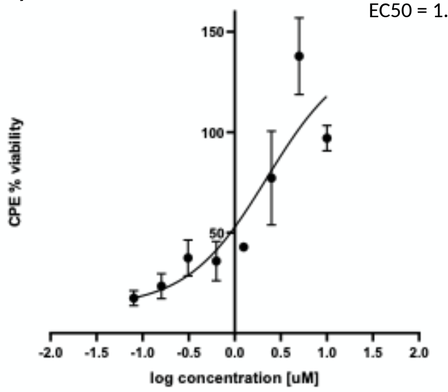


CVD-0013943

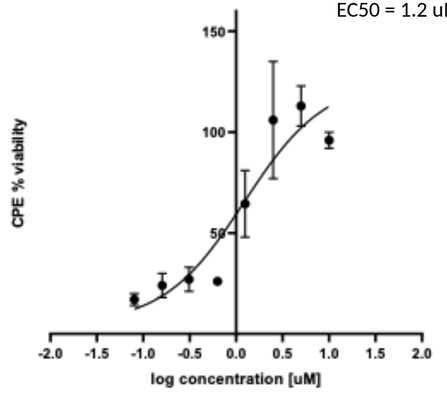


VeroE6
CPE assays

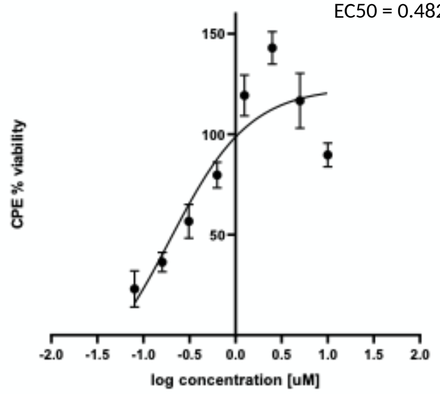
EC50 = 1.57 uM



EC50 = 1.2 uM

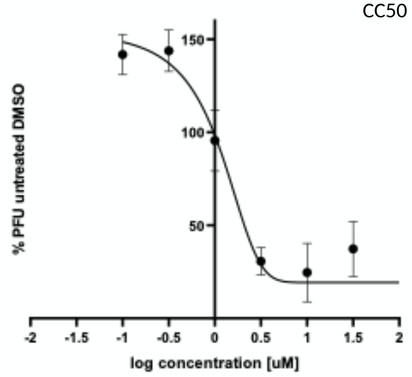


EC50 = 0.482 uM

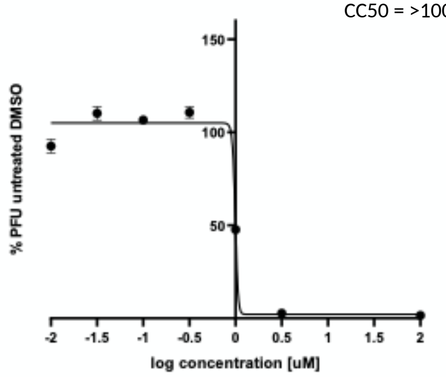


Calu-3
Plaque assay

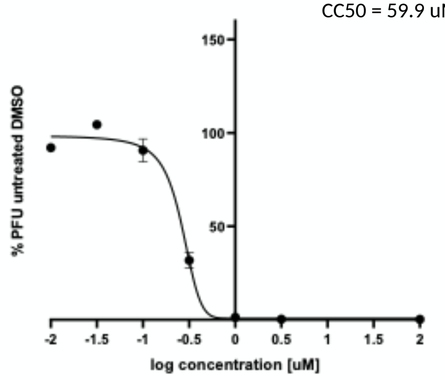
IC50 = 1.09 uM
CC50 = >100 uM



IC50 = 0.986 uM
CC50 = >100 uM



IC50 = 0.244 uM
CC50 = 59.9 uM



Activity of CVD-0013943

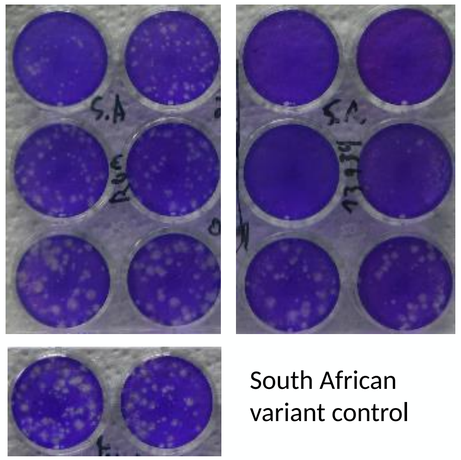
other viral strains:
B1.135 IC50 = 0.469 uM
B1.1.7 ongoing

other cell types
Hela ACE2 IC50 = 3.58 uM

other coronavirus strains
OC43 IC50 = 3.82 uM
MHV ongoing

Remdesivir CVD-0013943

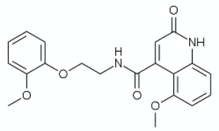
2 μM
1 μM
0.1 μM

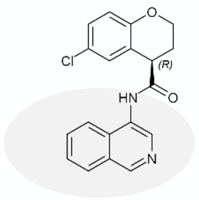


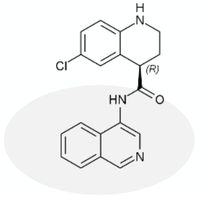
South African variant control

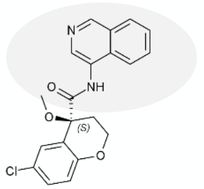
COVID Moonshot

We’re focusing into improving oral pharmacokinetics

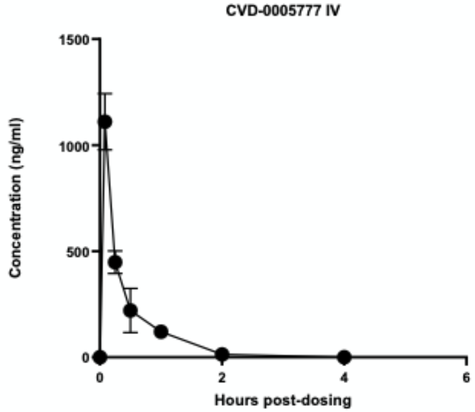




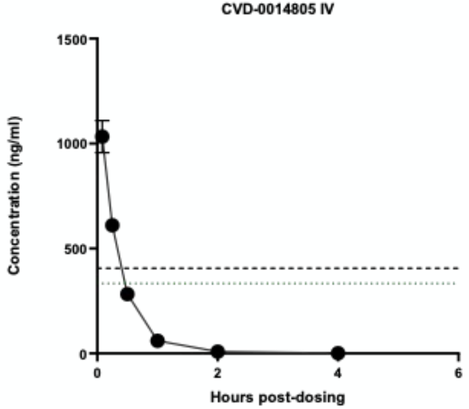


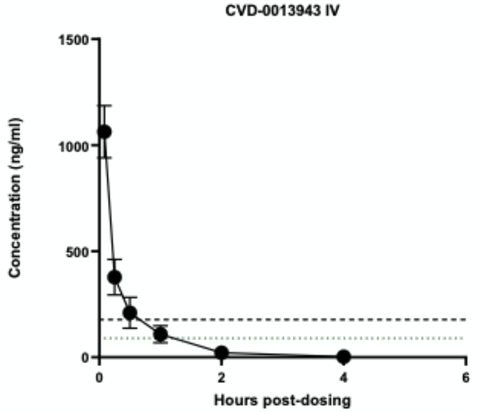


IV 2mg/kg



no IV formulation available for CVD-0013192

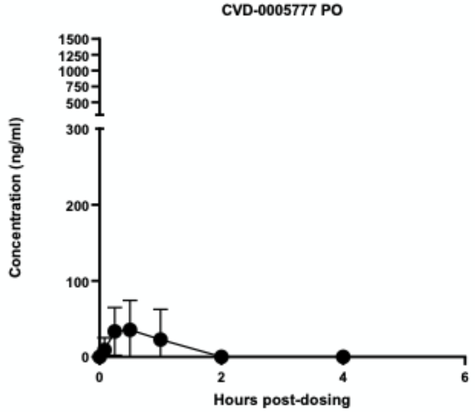


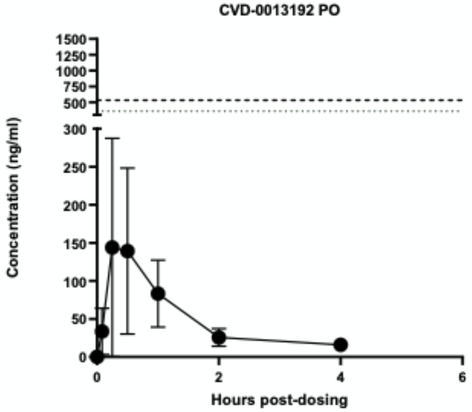


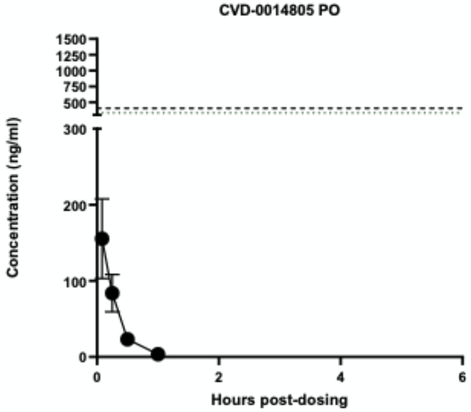
VeroE6 (CPE)

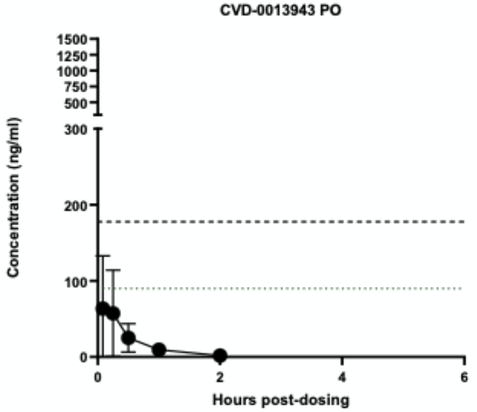
Calu-3 (PFU)

PO 10mg/kg









VeroE6 (CPE)

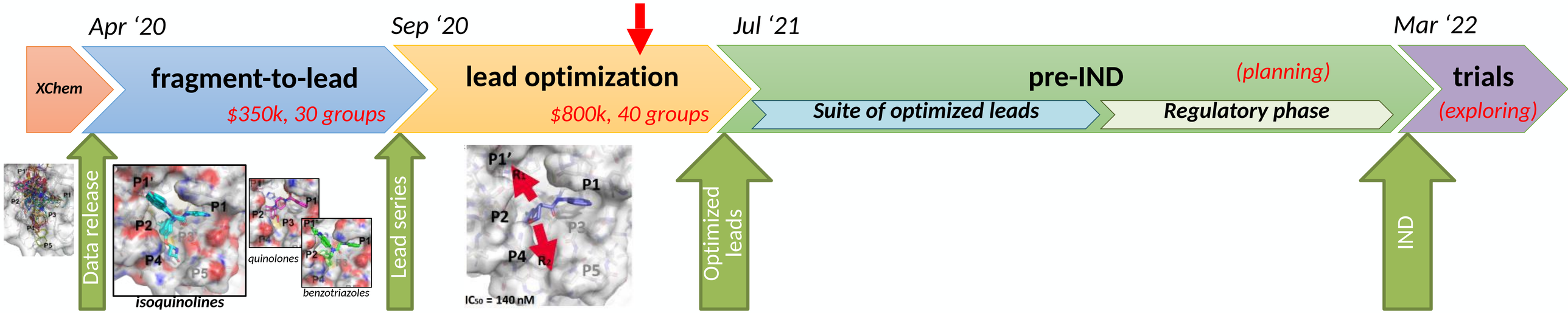
Calu-3 (PFU)

Wistar rat

Balb/c mouse

COVID Moonshot

We’re lining up IND-enabling studies now



COVID Moonshot

The COVID Moonshot collaboration is worldwide

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

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Tim Dudgeon	Informatics Matters
Vladimír Pšenák	M2M solutions, s.r.o
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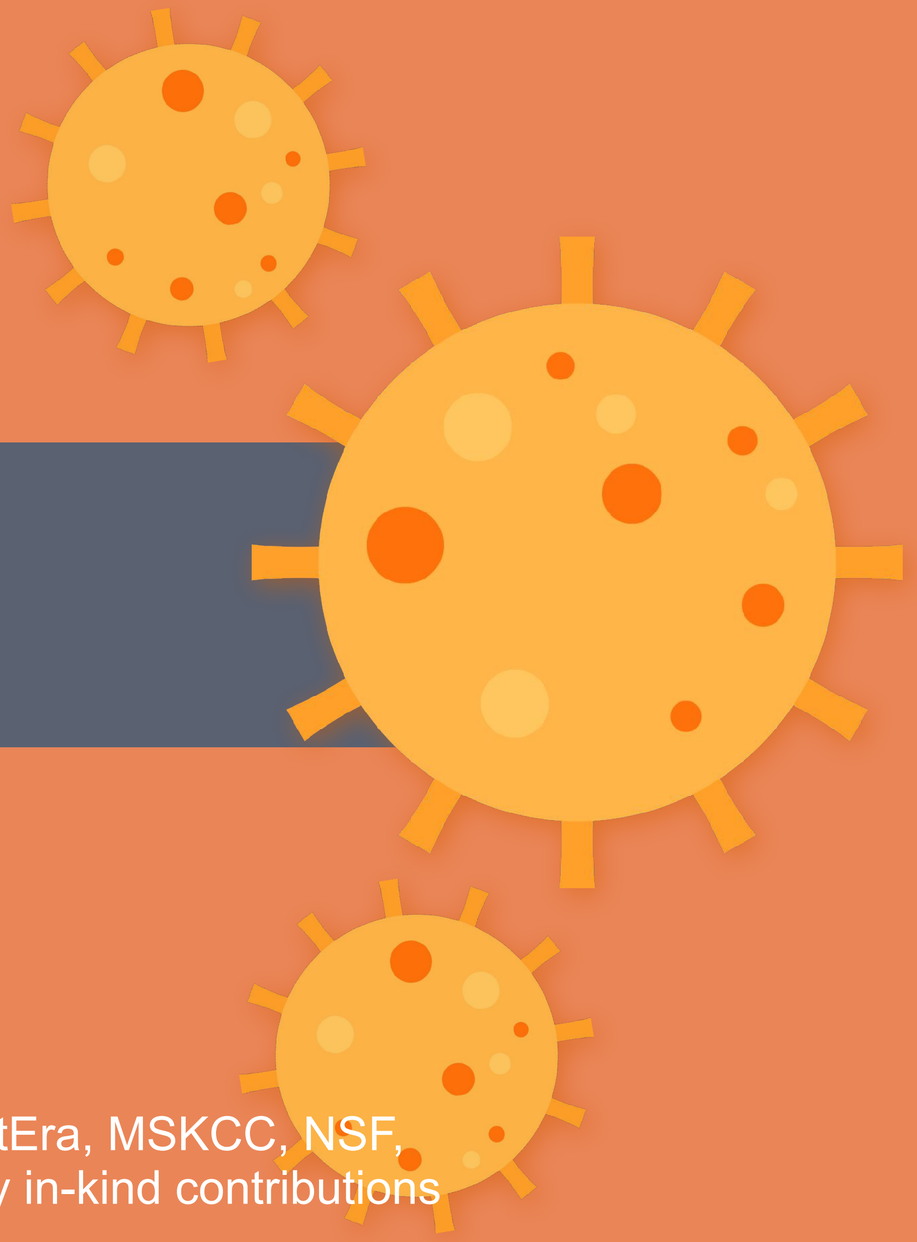
Amir Ben-Shmuel	Israel Institution of Biological Research
Assa Sittner	Israel Institution of Biological Research
Boaz Politi	Israel Institution of Biological Research
Einat B. Vitner	Israel Institution of Biological Research
Elad Bar-David	Israel Institution of Biological Research
Hadas Tamir	Israel 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	
Benjamin Perry	DNDi
Walter Ward	Walter Ward Consultancy and Training
Emma Cattermole	University of Oxford
Lori Ferrins	Northeastern University
Charles J. Evermann	Northeastern University
Bruce F. Milne	University of Coimbra

THANK YOU!

Now, I'd like to answer questions from the audience…



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

Planned *in vivo* efficacy

In collaboration with Kris White and Adolfo Garcia-Sastre (Mount Sinai)

RESEARCH ARTICLE

Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A

Kris M. White[1,2,*,†], Romel Rosales[1,2,*], Soner Yildiz[1,2], Thomas Kehrer[1,2], Lisa Miorin[1,2], Elena Moreno...
+ See all authors and affiliations

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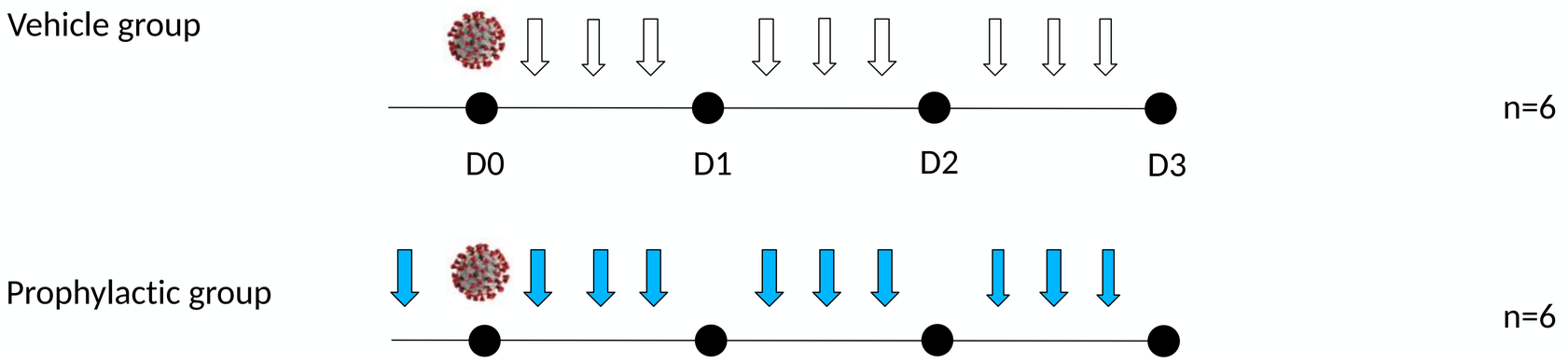
DOI: 10.1126/science.abf4058

Model: K18-hACE2 model
Readout: SARS-CoV-2 Viral load lungs (left lung, day 3)
Lung pathology (day 3)
Weight



Parallel efforts (exemplars)

3CL Mpro small molecules projects

Pharma efforts

Pfizer	Phase 1 (estimate)	peptidomimetic / covalent	IV only
Sosei/Heptares	Late lead op		oral
Novartis	Lead op	both covalent/non covalent	oral
Takeda	Lead op	covalent	oral

Academic effort:

Hilgenfeld/IMI	Lead op	presumably covalent peptidomimetic	IV

Polymerase small molecules projects

Merck/Ridgeback	Phase 2	Molnupiravir (EIDD-2801)	oral
Roche/Atea	Phase 2	AT-527	oral

Other targets (e.g. Helicase)

Takeda	Hit to lead	both covalent/non covalent	oral

Moonshot assets

Nothing to lose and (apparently) inexhaustible goodwill

- Effortless recruitment of collaborators
- No bureaucratic and legal delays
- Extensive donations – cash, labs, time, intellectual input, licenses

Extensive antiviral network

- Cellular assays in place
  - Multiple cell types (VeroE6, Calu-3, A549, hACE overexpressed, Pneumocytes)
  - Novel strains (UK/SA/Brazilian strain)
  - Pan-corona activity (MHV, MERS, SARS, OC43)
- In vivo efficacy lined up
  - Mouse (Mount Sinai, IIBR)
  - Hamster (PHE, Madison)
  - Ferrets (Wendy Barclay, Imperial)

Experienced MedChem team

- Cumulative 100s of years of big pharma experience

Rapid-throughput early screening cascade

- Weekly measurements for biochemical assays (2x) – *immediately public on PostEra*
- Rapid co-crystal structures (~250) – *immediately public on Fragalysis*
- Weekly antiviral CPE measurements (IIBR)

Logistical hubs

- Data: Postera website, CDD Vault, Fragalysis Cloud (structures)
- Compound handling: Enamine
- Compute: Folding@Home globally distributed exaflop supercomputer