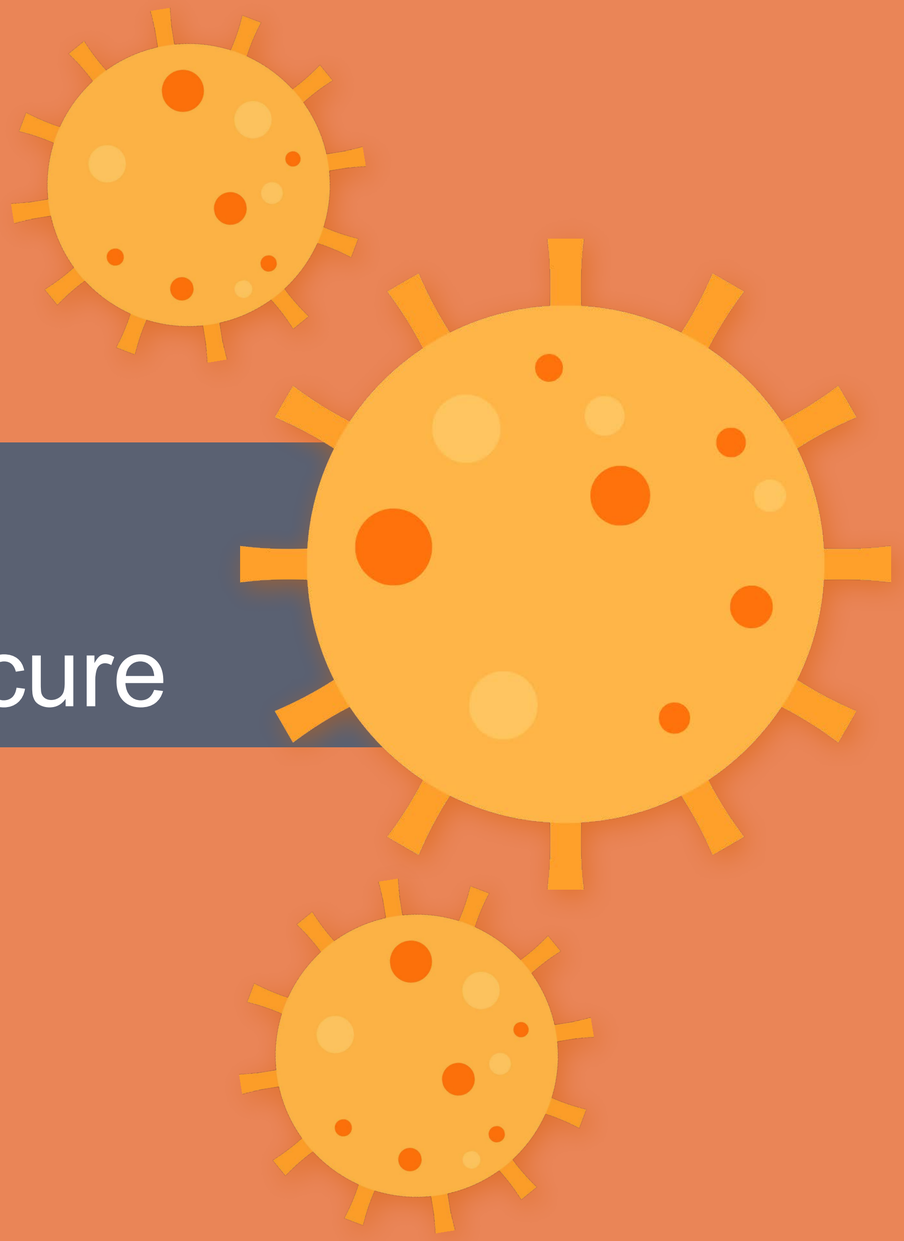
Folding@home

Crowdsourcing computing for a cure



John D. Chodera (MSKCC)
and the Folding@home Consortium

\

Folding@home is a distributed computing platform composed of worldwide volunteers

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!

Folding@home accidentally became the most powerful computer in the world during the pandemic

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

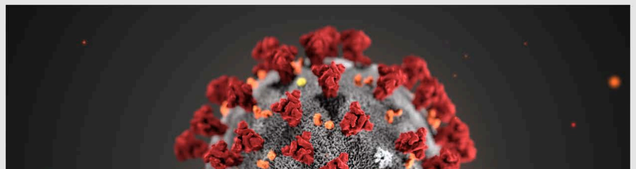
February 27, 2020
by Greg Bowman

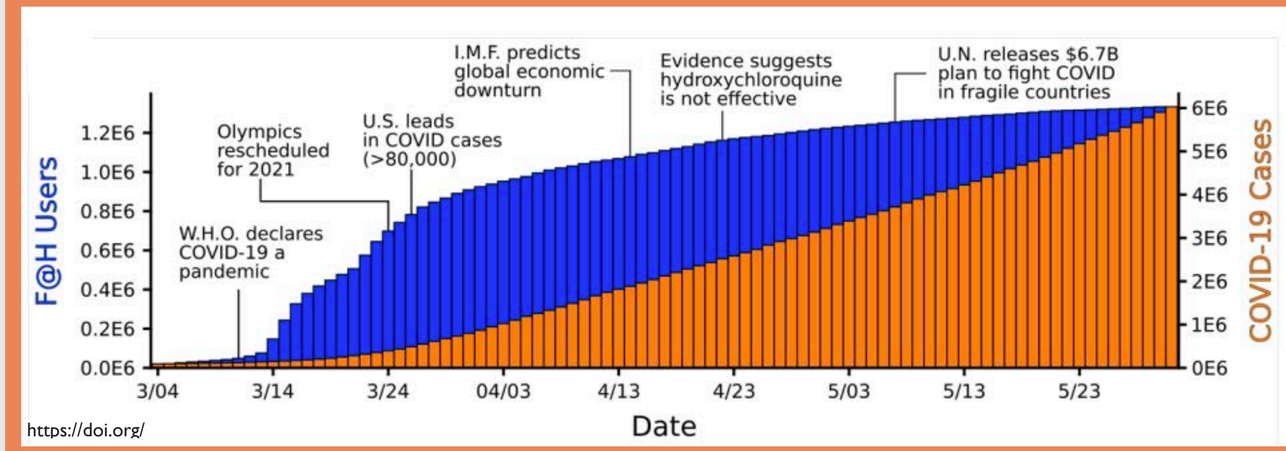
We need your help! Folding@home is joining researchers around the world working to better understand the 2019 Coronavirus (2019-nCoV) to accelerate the open science effort to develop new life-saving therapies. By downloading Folding@Home, you can donate your unused computational resources to the Folding@home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

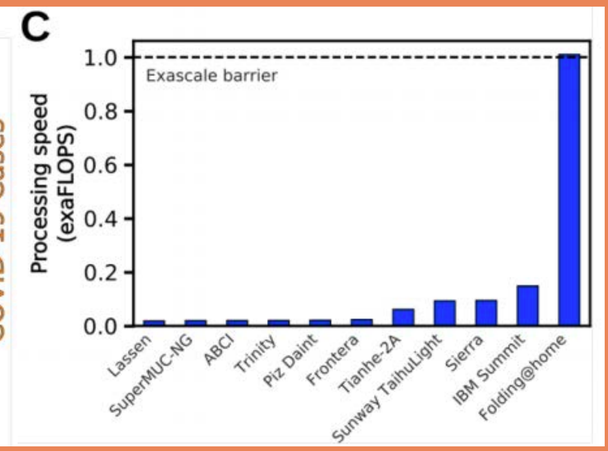
Proteins are not stagnant—they wiggle and fold and unfold to take on numerous shapes. We need to study not only one shape of the viral spike protein, but all the ways the protein wiggles and folds into alternative shapes in order to best understand how it interacts with the ACE2 receptor, so that an 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/



Ariana Brenner (CBM)

Rafal Wiewiora (TPCB)

Ivy Zhang (CBM)

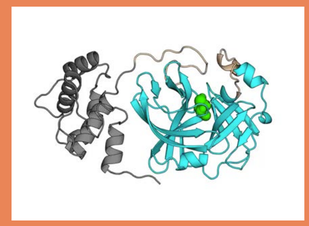
SARS-CoV-2 Simulations Go Exascale to Capture Spike Opening and Reveal Cryptic Pockets Across the Proteome

Maxwell I. Zimmerman, Justin R. Porter, Michael D. Ward, Sukrit Singh, Neha Vithani, Artur Meller, Upasana L. Mallimadugula, Catherine E. Kuhn, Jonathan H. Borowsky, Rafal P. Wiewiora, Matthew F. D. Hurley, Aoife M Harbison, Carl A Fogarty, Joseph E. Coffland, Elisa Fadda, Vincent A. Voelz, John D. Chodera, Gregory R. Bowman

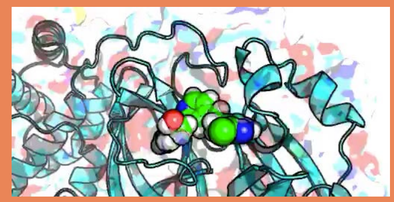
doi: https://doi.org/10.1101/2020.06.27.175430

Folding@home aimed to help the Moonshot with at multiple different stages

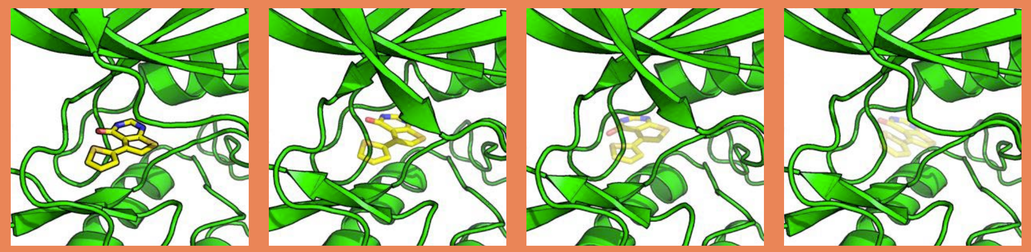
simulations of Mpro flexibility
identification of cryptic pockets
(Bowman lab @ WashU)



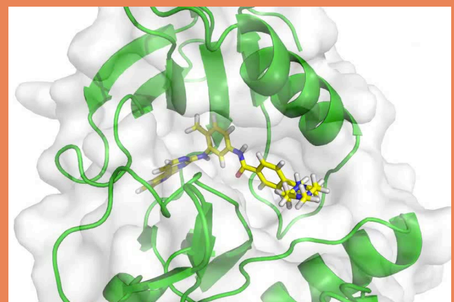
virtual screening to identify
plausible binding modes
(Chodera lab @ MSKCC)



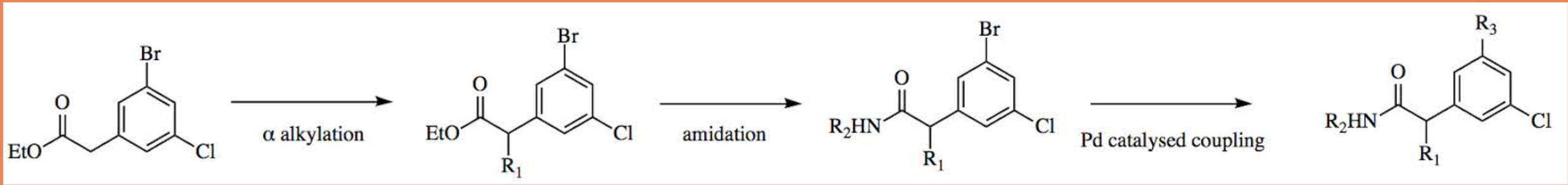
absolute free energy calculations to
prioritize compounds with diverse scaffolds
(Voelz lab @ Temple U)

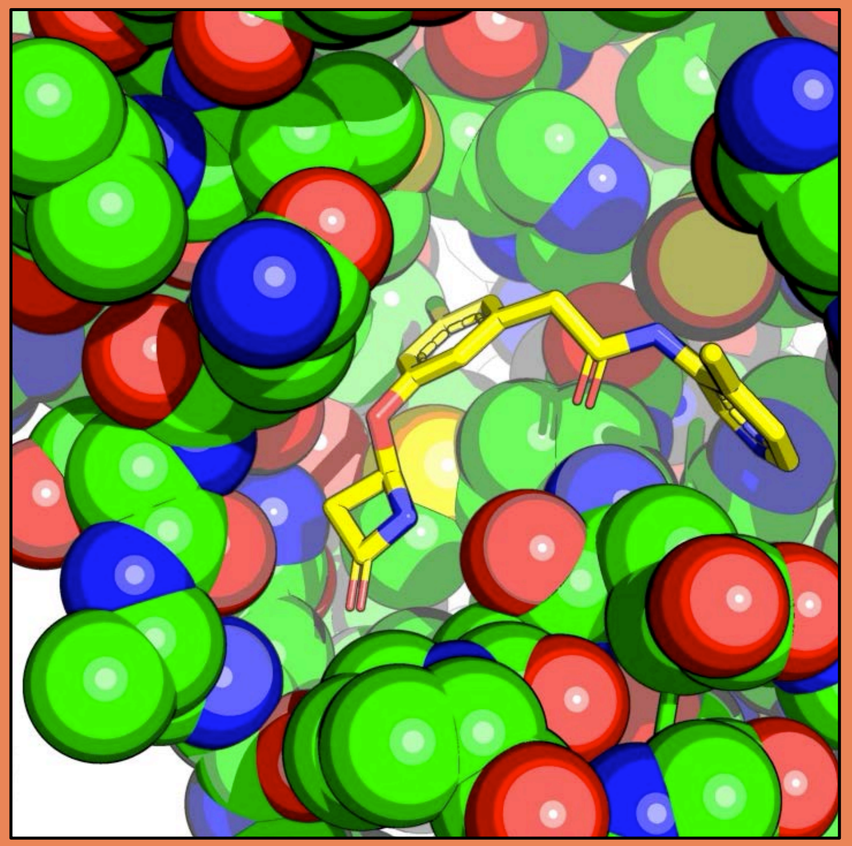


relative free energy calculations
to optimize existing scaffolds with small modifications
(Chodera lab @ MSKCC)



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

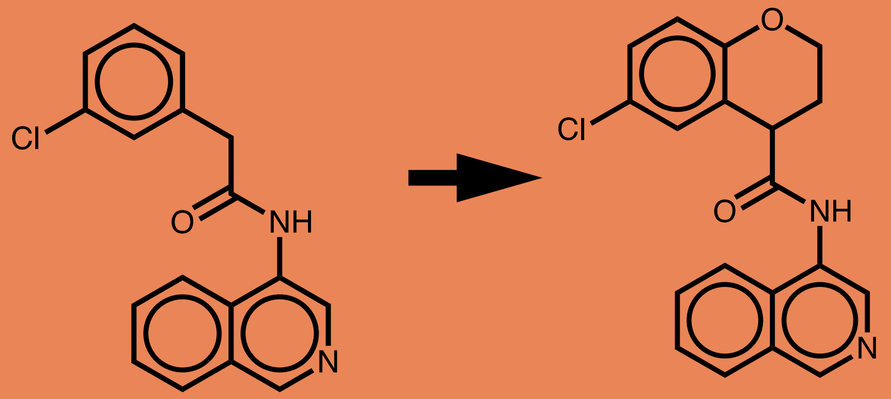




We can use Folding@home to run alchemical free energy calculations to evaluate which designs should bind better

Instead of transmuting **lead** into **gold…**

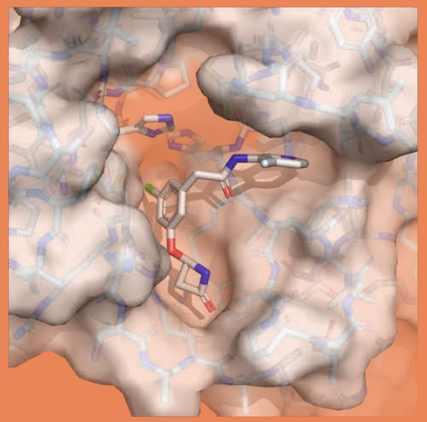
…we change **one molecule** into **another!**



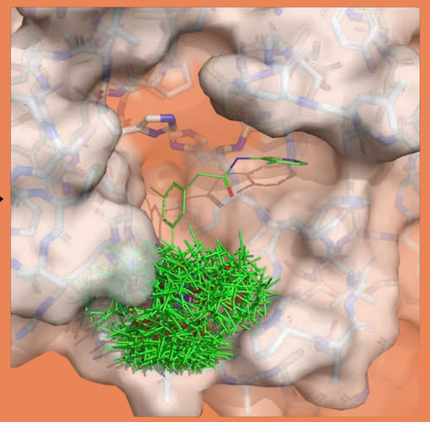
Neither process can be done with chemistry, but we can do it in a computer!

Folding@home has been running free energy calculations at planetary scale in “sprints” of 1-4 weeks in length

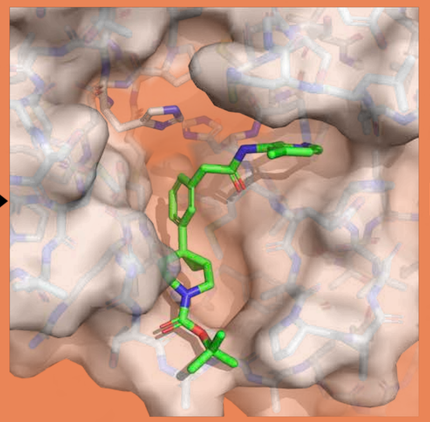
X-ray structure as reference



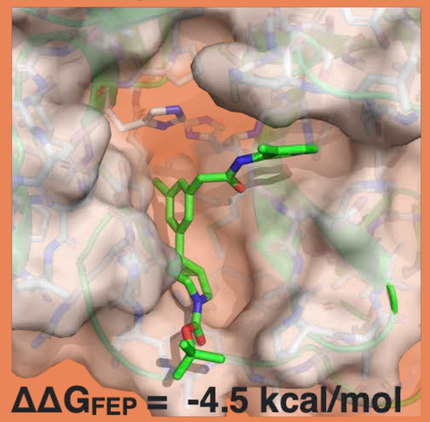
constrained enumeration of poses for proposed molecule



selection of pose with best docking score

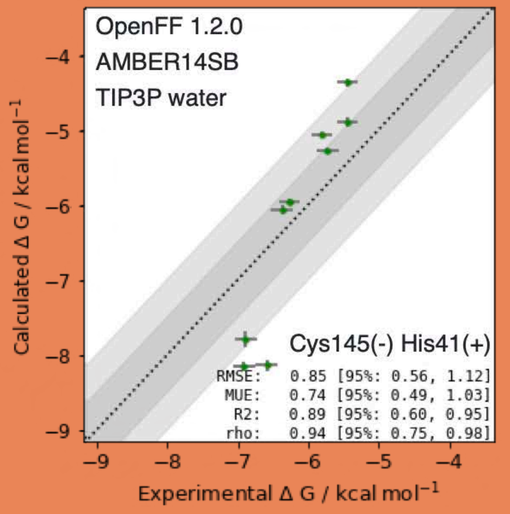


nonequilibrium alchemical free energy calculation final posed structure



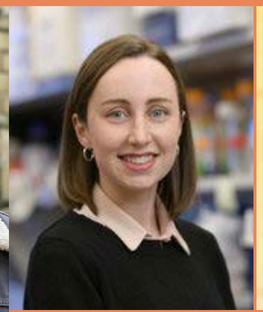
$\Delta\Delta G_{FEP}$ = -4.5 kcal/mol

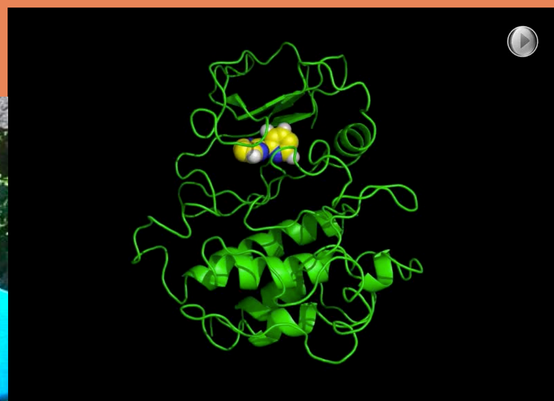
retrospective performance on 3-aminopyridine lead series



perses: open source relative alchemical free energy calculations
http://github.com/choderalab/perses
Open Force Field Initiative OpenFF 1.2.0 (“Parsley”) force field
http://openforcefield.org

William Glass
Postdoctoral Fellow
Hannah Bruce Macdonald
Postdoctoral Fellow
Dominic Rufa
Tri-I TPCB PhD student
Matt Wittmann
Data Scientist Extraordinaire



TOGETHER, WE ARE POWERFUL

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

Use your PC to help fight COVID-19.

DOWNLOAD FOLDINGATHOME

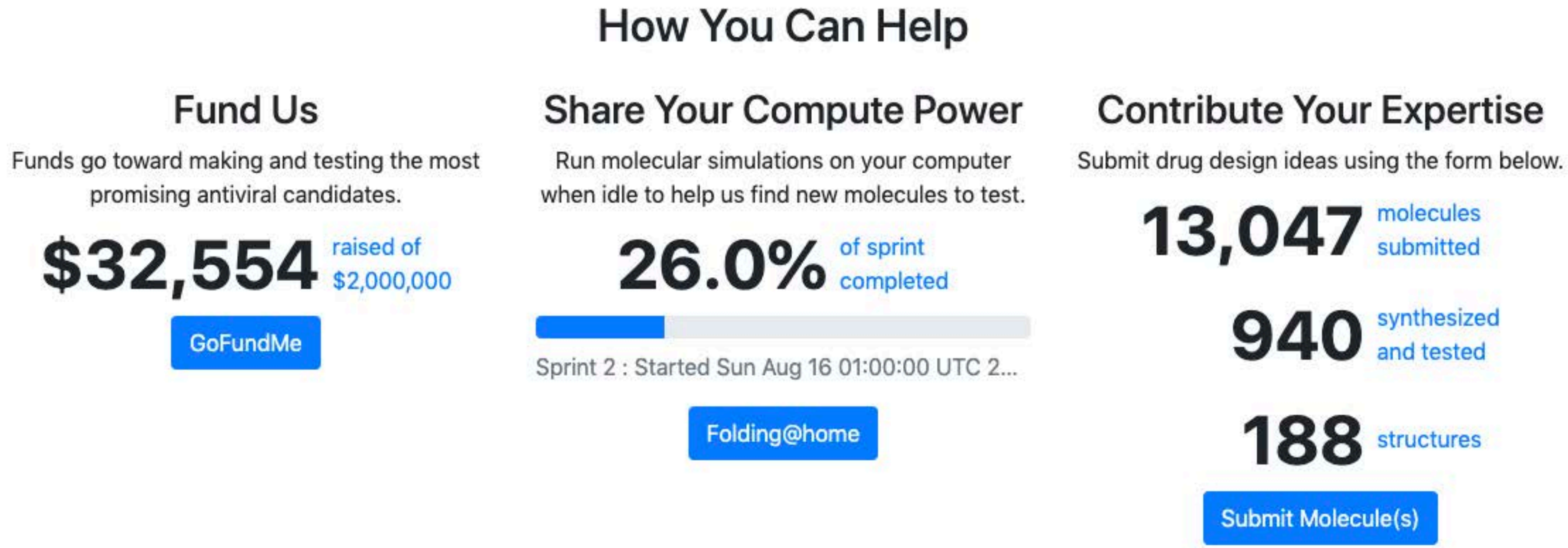
[Available for Windows, Mac, Linux]

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

25.996%

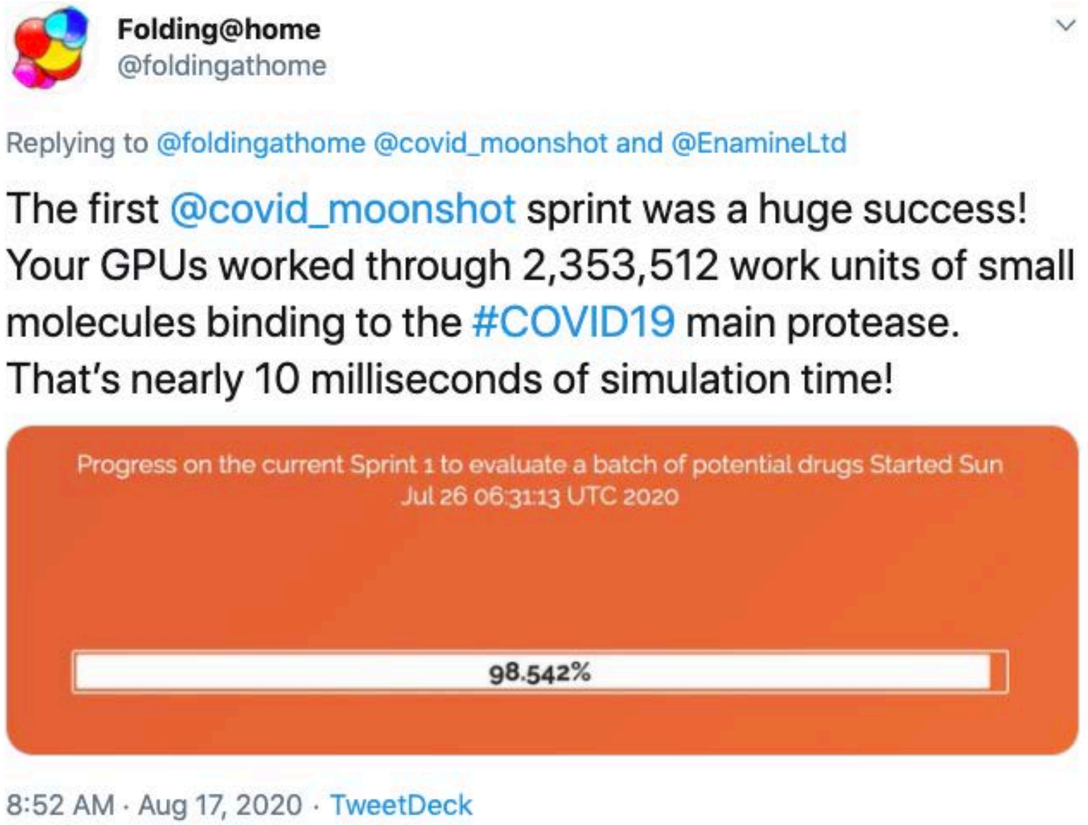
The **progress bar** measures the fraction of compounds we could synthesize that we've evaluated for each sprint

You can also see the progress bar on the COVID Moonshot page, where all experimental data is open and freely available.



http://postera.ai/covid

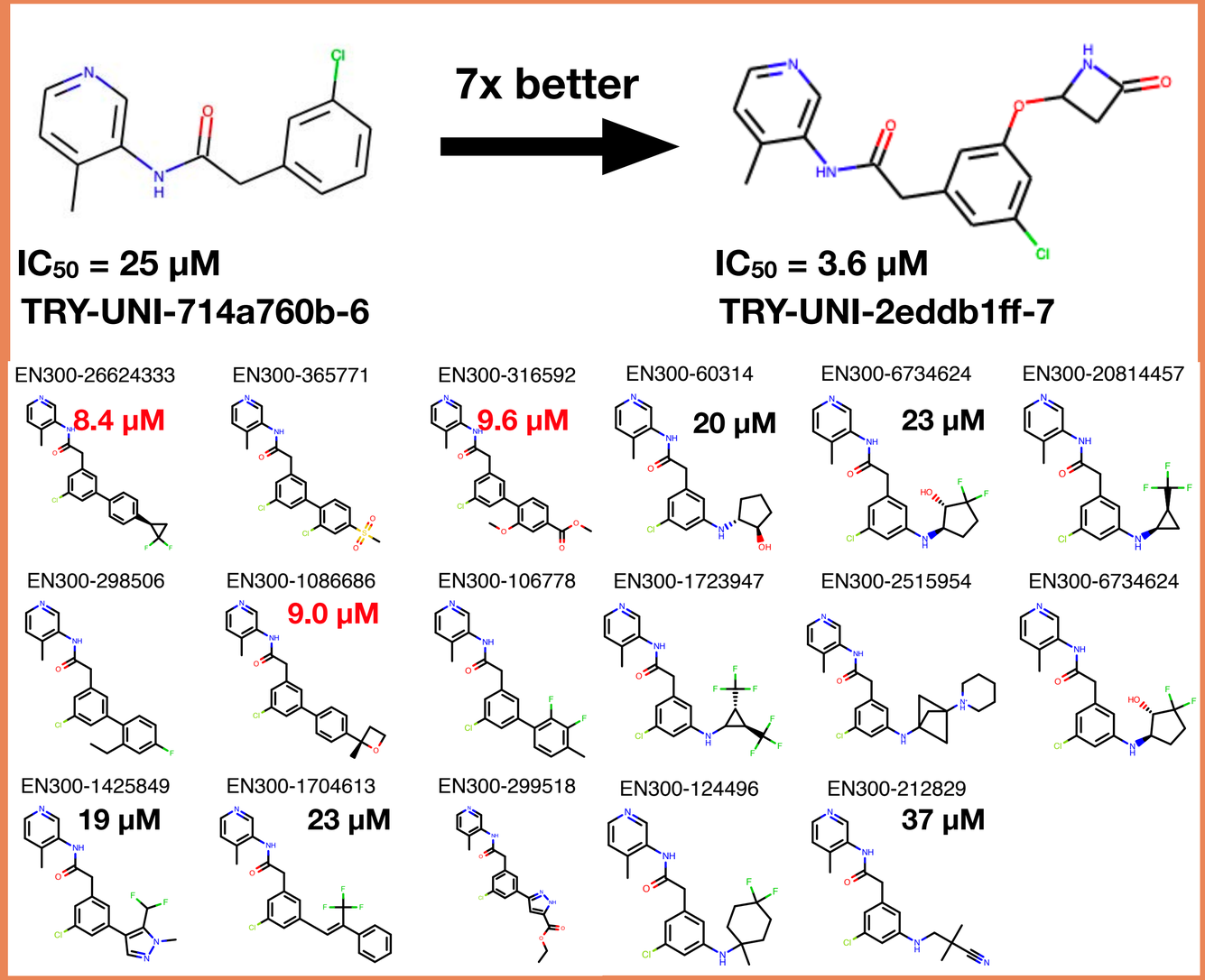
The Folding@home COVID Moonshot sprints represent an incredible amount of computational effort in service of a great cause

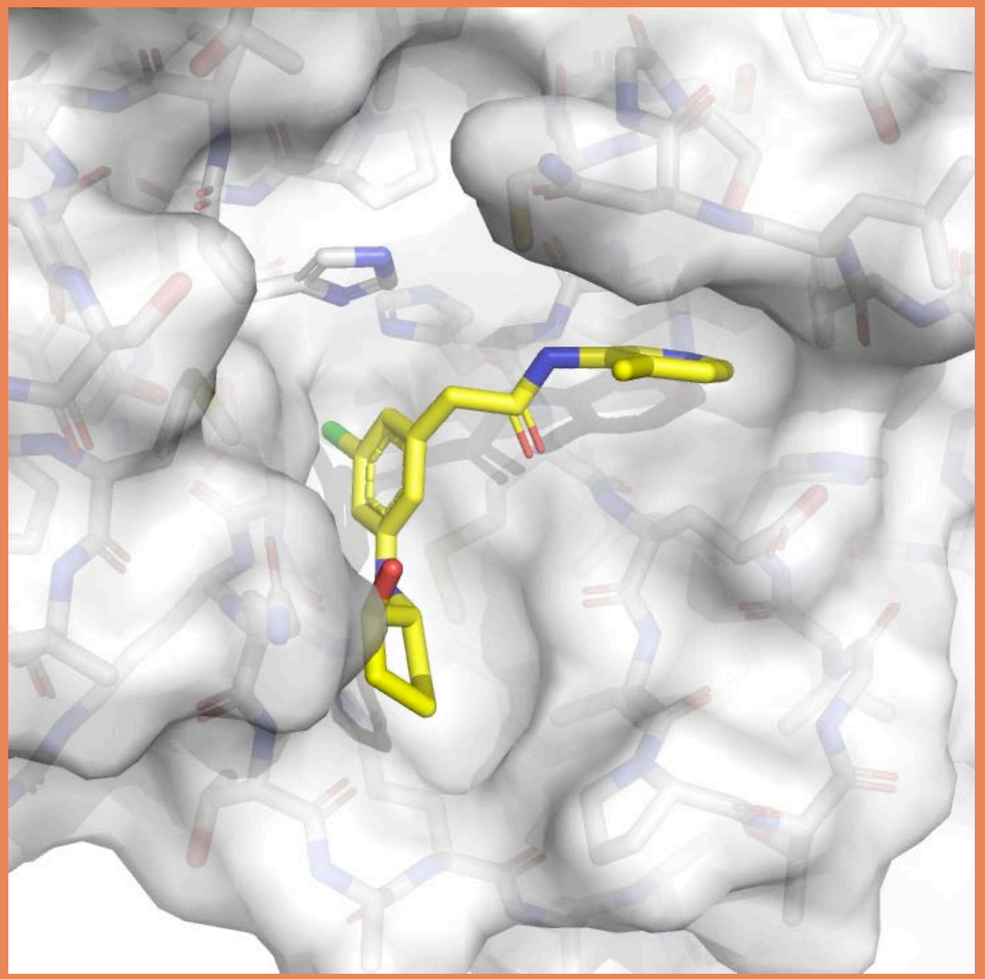


Sprint 1 focused on identifying replacements for an unstable ß-lactam ring for the 3-aminopyridine series

Hannah Bruce Macdonald

MolSSI Investment Postroctoral Fellow, MSKCC

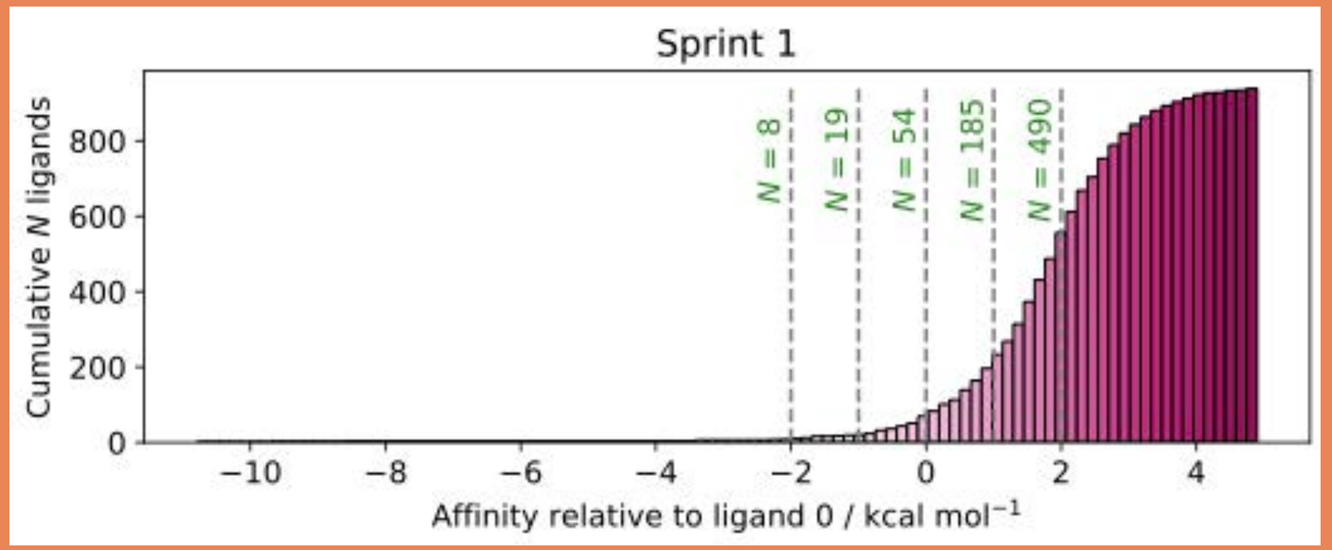




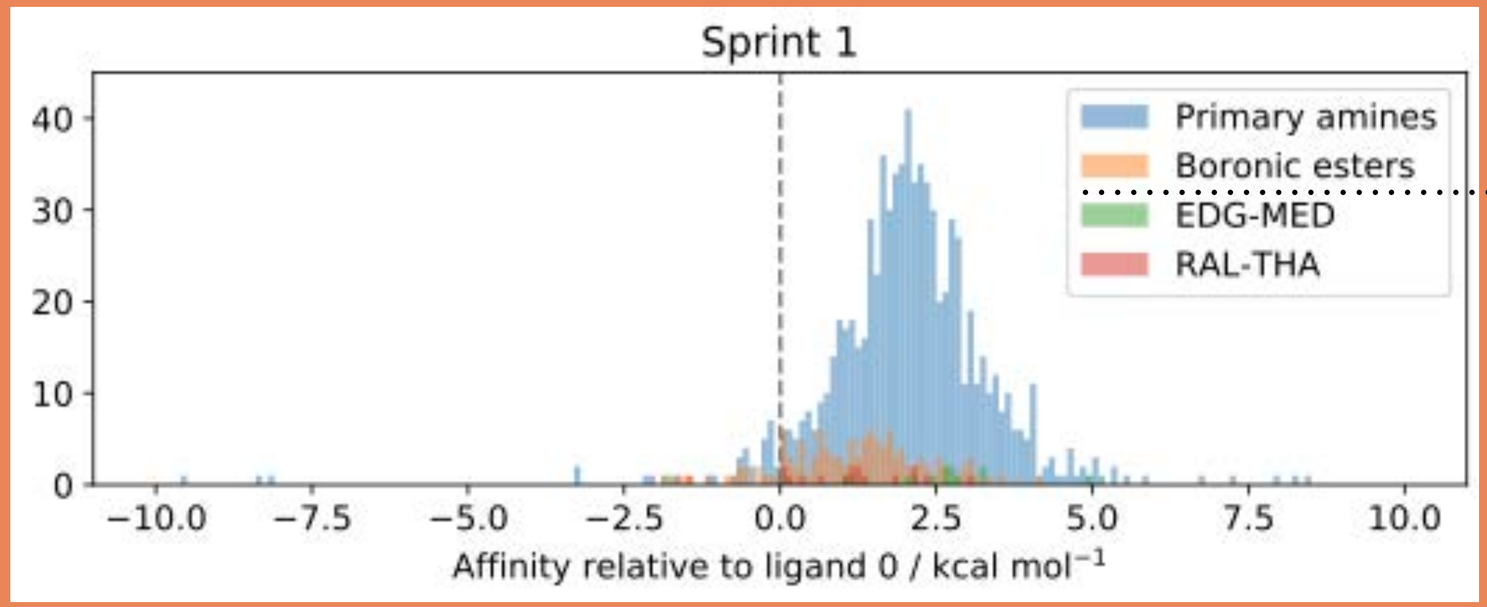
DATA: https://covid.postera.ai/covid/submissions/f42f3716-f86f-41d8-9906-c4fb7b6f5773

Most ideas were bad ideas

better **worse**



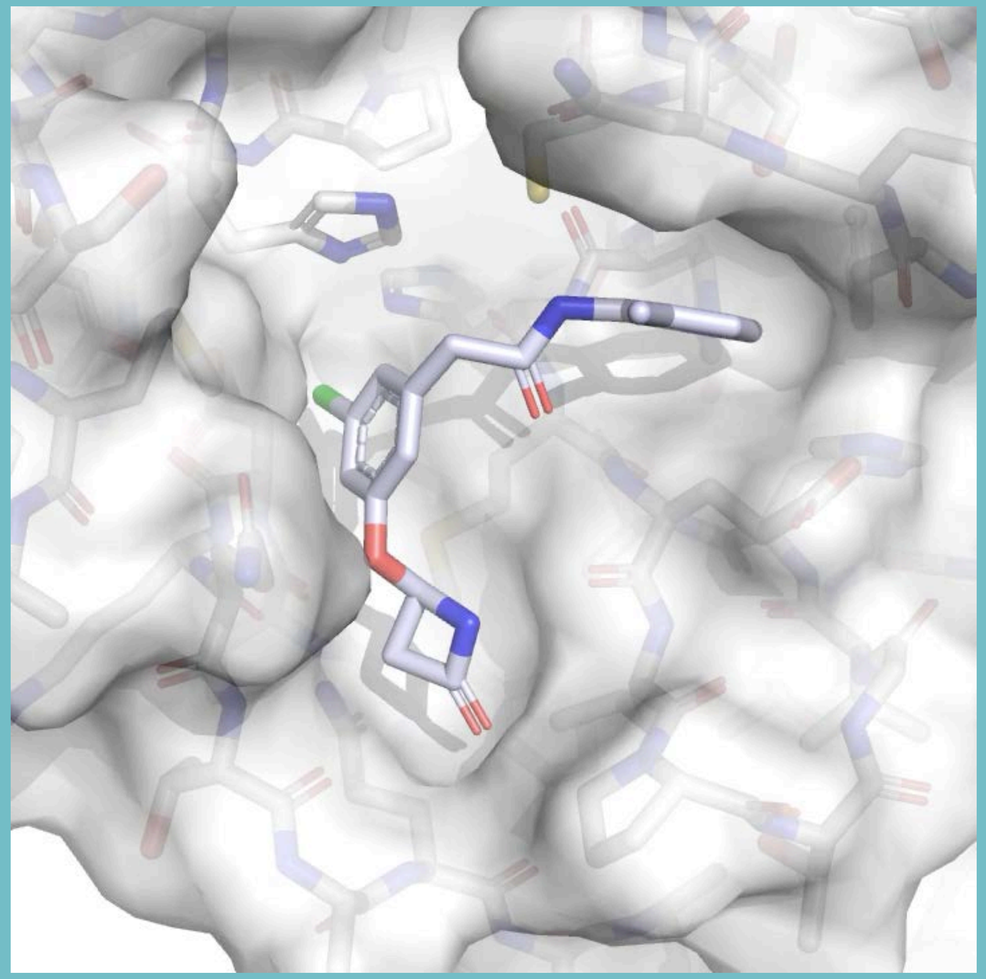
Human chemists seem better than random, but it’s hard to get them to generate enough ideas



computer

humans

Sprint 2 aimed to optimize P4 pocket engagement through an alternative synthetic route



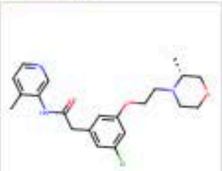
Still waiting for most of the compounds to be synthesized…

Submissions / Submission: CHO-MSK-6e55470f

SUBMISSION DETAILS

CHO-MSK-6e55470f

Molecule(s):



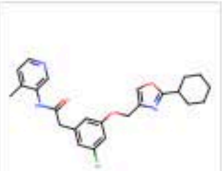
CHO-MSK-6e55470f-1

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCCN2CC0C[C@H]2C)c1

3-aminopyridine-like

Check Availability on Manifold

View



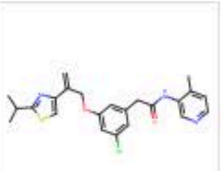
CHO-MSK-6e55470f-2

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCc2coc(C3CCCC3)n2)c1

3-aminopyridine-like Ordered

Check Availability on Manifold

View



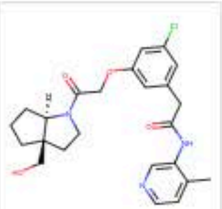
CHO-MSK-6e55470f-3

C=C(COc1cc(Cl)cc(CC(=O)Nc2cnccc2C)c1)c1csc(C(C)C)n1

3-aminopyridine-like Ordered

Check Availability on Manifold

View



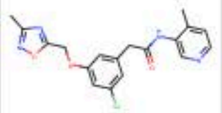
CHO-MSK-6e55470f-4

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCC(=O)N2CC[C@]3(CO)CCC[C@@H]23)c1

3-aminopyridine-like Ordered

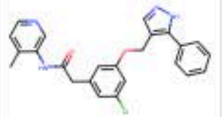
Check Availability on Manifold

View



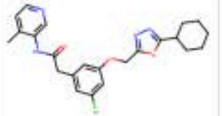
CHO-MSK-6e55470f-5

Cc1noc(COc2cc(Cl)cc(CC(=O)Nc3cnccc3C)c2)n1



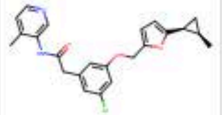
CHO-MSK-6e55470f-6

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCc2cn[nH]c2-



CHO-MSK-6e55470f-7

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCc2nnc(C3CCCCC3)o2



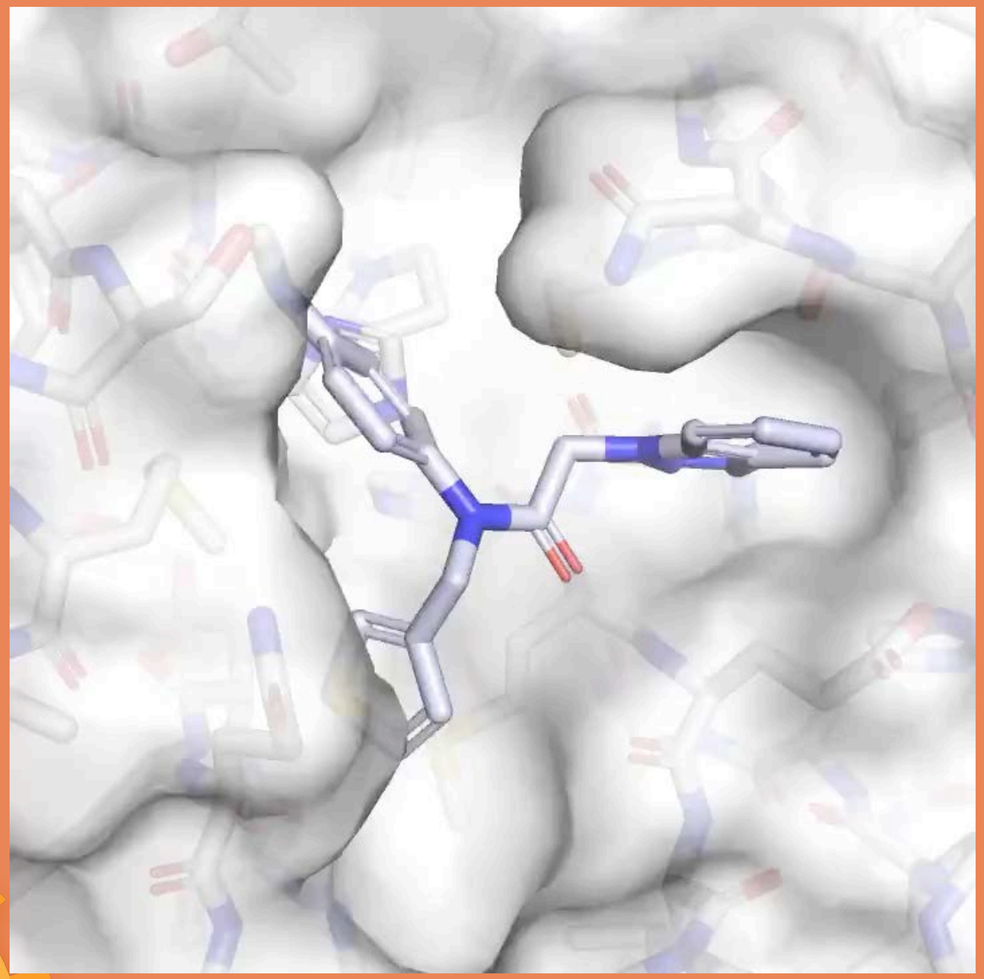
CHO-MSK-6e55470f-8

Cc1ccncc1NC(=O)Cc1cc(Cl)cc(OCc2ccc([C@H]3C[C@H

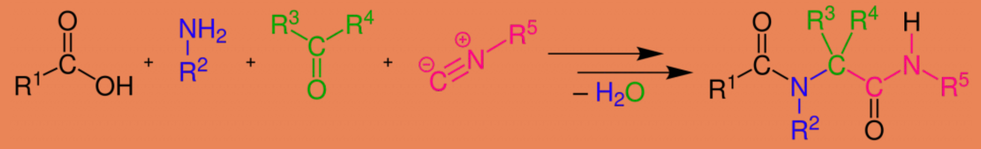
STATUS: https://covid.postera.ai/covid/submissions/6e55470f-7ef5-4164-bbed-66aea806bbe9

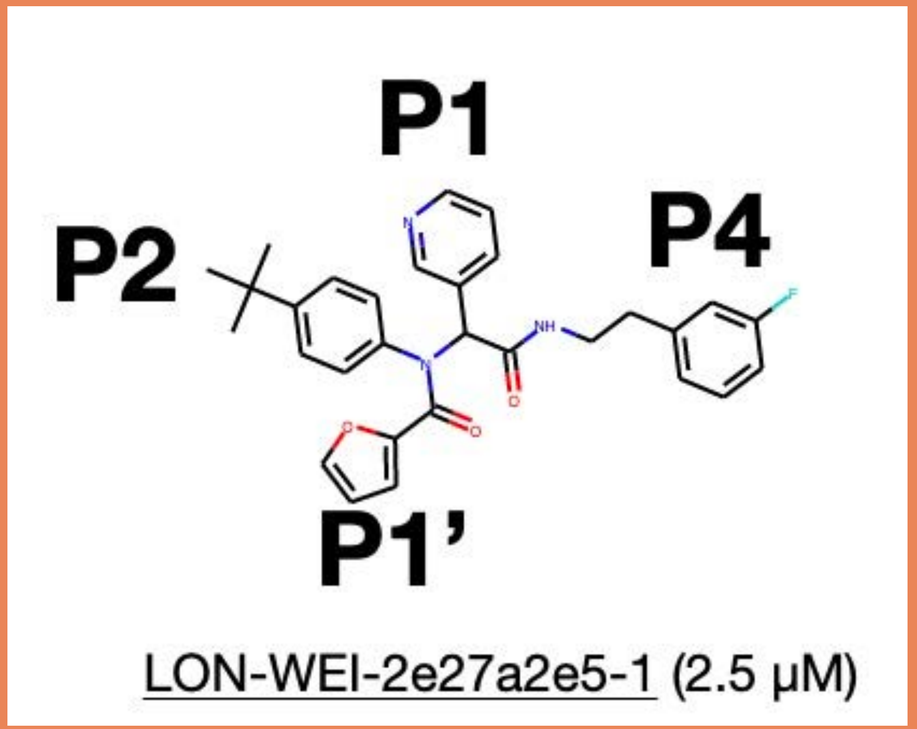
Sprints 3 and 4 focused on other promising lead series where synthesis is still in progres

Sprint 3: benzotriazoles



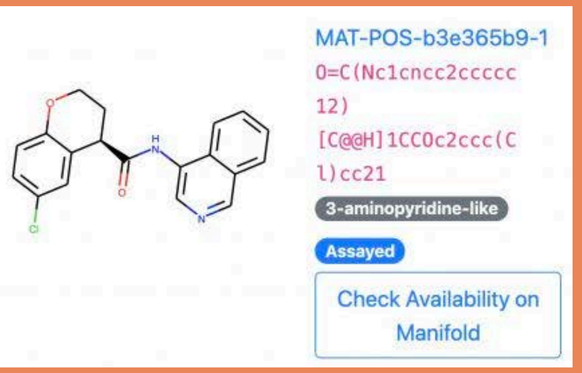
Sprint 4: Ugis





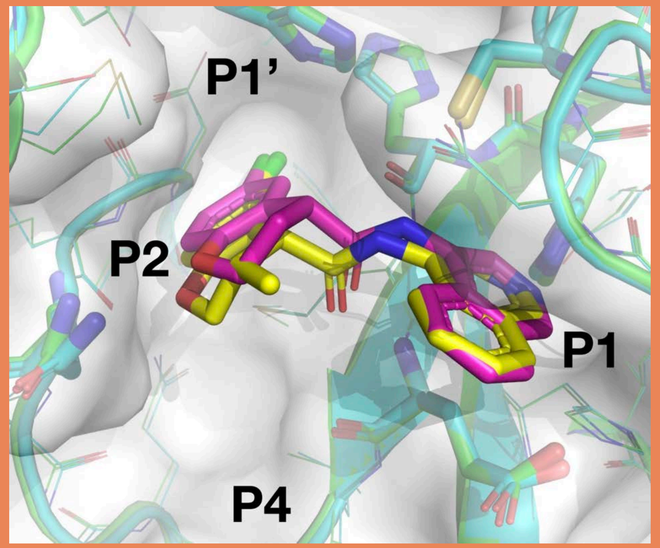
Sprint 5 builds on the 3-aminopyridine series to explore the P1’ pocket

benzopyran-isoquinoline series

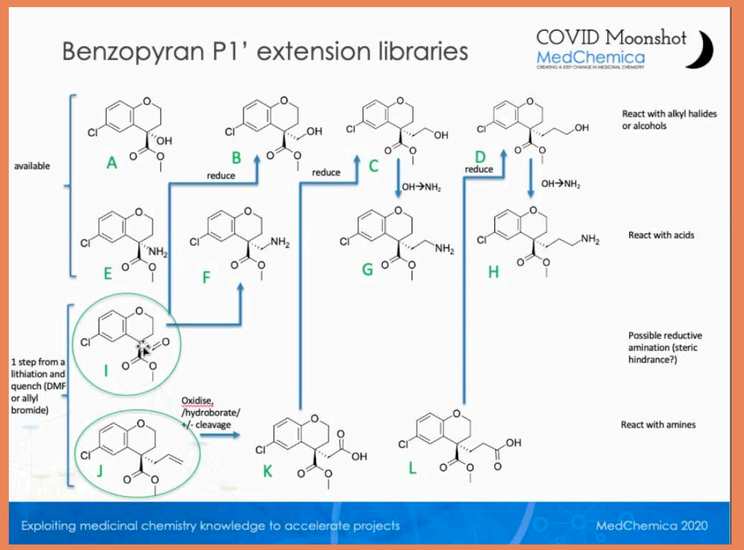


(evolved from 3-aminopyridine series from Sprints 1 + 2)

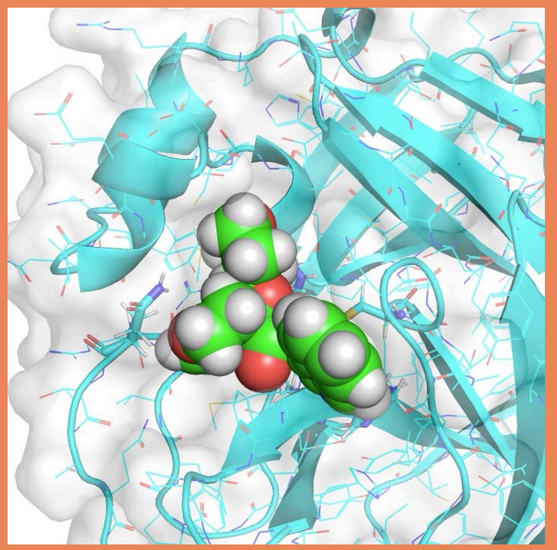
X-ray structures fof this series from Diamond



synthetic routes for ~15,000 compounds from MedChemica/PostEra



initial docked structures for Folding@home



Comparing three strategies in Sprint 5:

1. **Med chemist favorites**
2. **Pharmacophore model**
3. **Free energy calculations**

The Science Dashboard helps us track front-runners

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

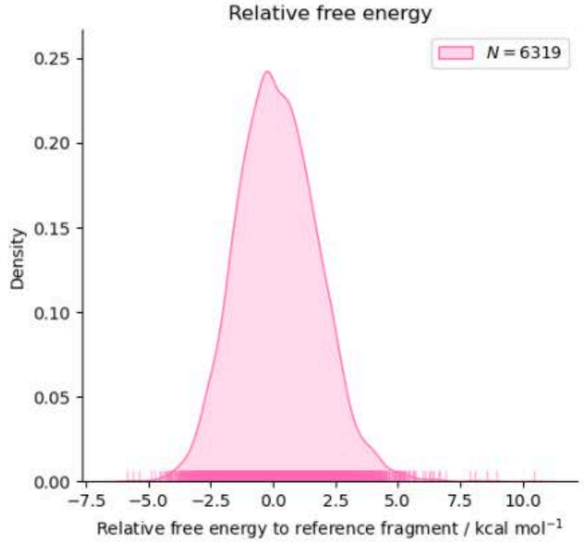
Description

COVID Moonshot Sprint 5 to prioritize benzopyran-isoquinoline series based on x12073 (MAT-POS-8a69d52e-7) to optimize substituents in the P1' pocket with Mpro monomer and neutral Cys145:His41

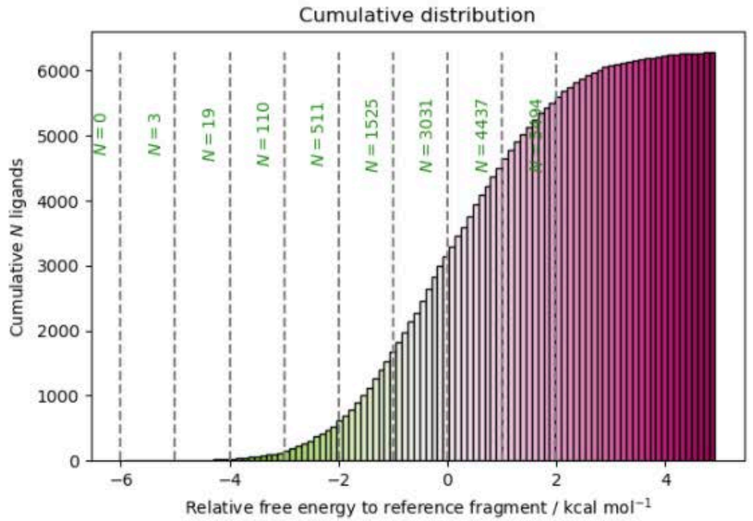
Progress

98.35%

Distributions

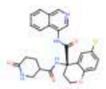


Updated 2020-12-09T19:38:12.118034+00:00



Updated 2020-12-09T19:38:12.118034+00:00

Leaderboard

Rank	Compound		SMILES	ΔG / kcal mol^{-1}	pIC50
1	EN300-42819_1		c1ccc2c(c1)cncc2NC(=O)[C@@]3(CCOc4c3cc(cc4)Cl)NC(=O)C5CCC(=O)NC5	-12.4 ± 0.2	9.0 ± 0.1
2	EN300-208959_1		c1ccc2c(c1)cncc2NC(=O)[C@@]3(CCOc4c3cc(cc4)Cl)NC(=O)C5CNC(=O)CC5C(F)(F)F	-11.9 ± 0.2	8.7 ± 0.1
3	EN300-211158_1		c1ccc2c(c1)cncc2NC(=O)[C@@]3(CCOc4c3cc(cc4)Cl)NC(=O)c5cc(cc(c5)CO)CO	-11.7 ± 0.3	8.6 ± 0.2

All data is being posted to AWS Open Data Registry:
https://registry.opendata.aws/foldingathome-covid19/

Q&A

The Moonshot Team

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