AI-Powered Accelerated Antiviral Discovery

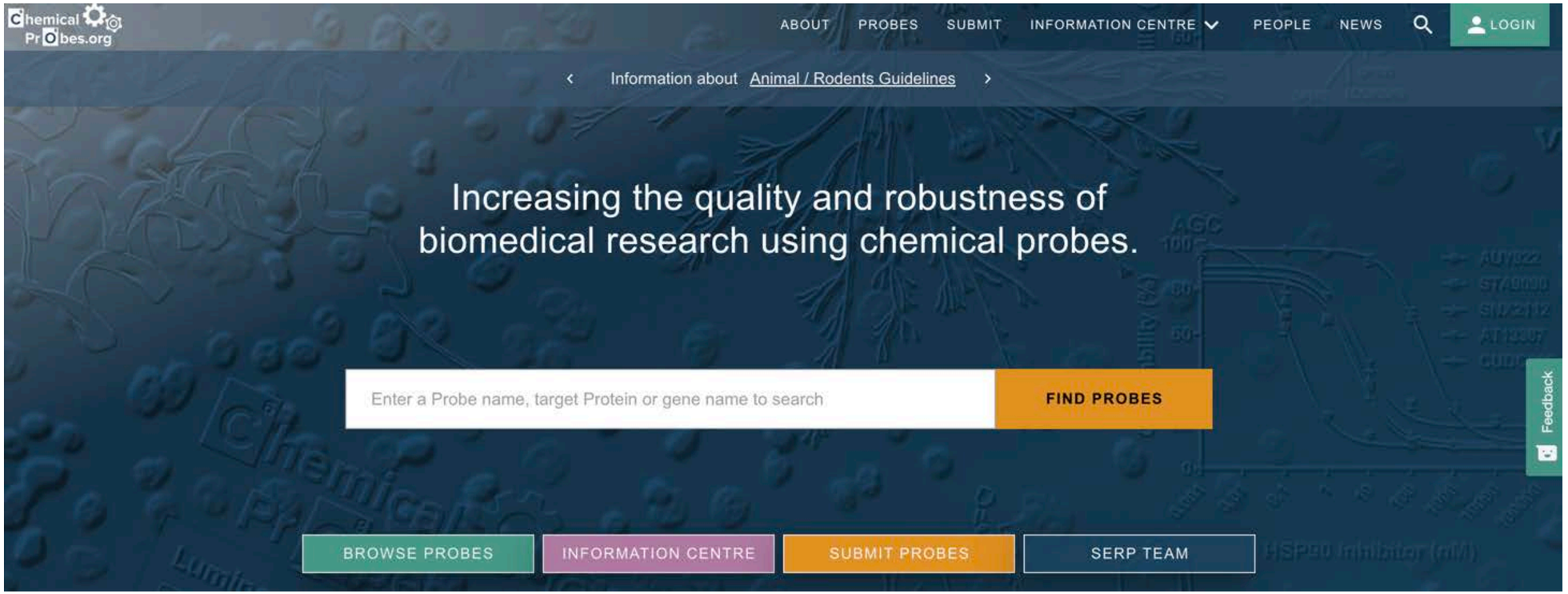
Alpha Lee

University of Cambridge
PostEra Inc (www.postera.ai)
ASAP Consortium (https://asapdiscovery.org/)

CoI statement: AAL is a co-founder and owns equity in PostEra. AAL has ongoing research collaborations with Pfizer and AstraZeneca. PostEra collaborates with pharmaceutical companies and may have ongoing programs in antiviral drug discovery.

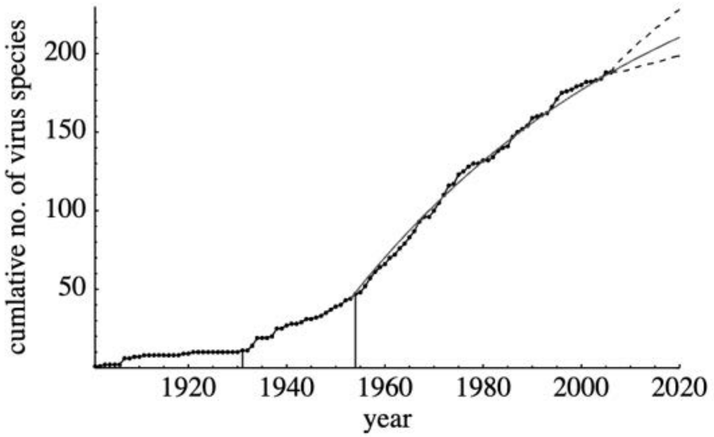
AI accelerates antiviral discovery by speeding up medicinal chemistry

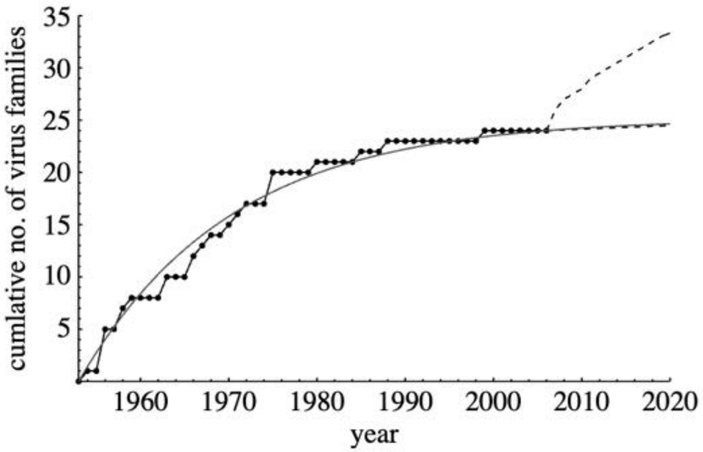
Medicinal chemistry is also crucial to discovering “chemical probes” that validate viral targets



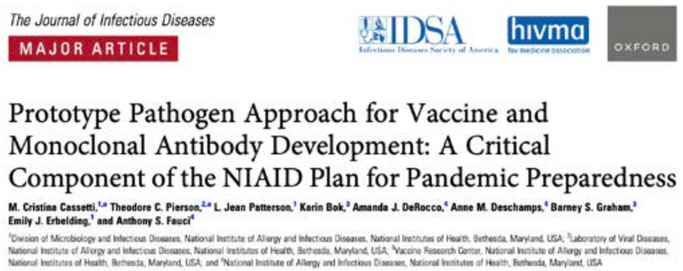
- “Chemical probes” is a well established way to understand how target engagement translates to phenotypic effects
- ~300 human proteins have been probed, but only a few viral proteins…

AI enables an exhaustive chemogenomics approach to pandemic preparedness





Number of identified virus species is increasing, though the number of identified viral families appears to plateau


The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA hivma OXFORD

Prototype Pathogen Approach for Vaccine and Monoclonal Antibody Development: A Critical Component of the NIAID Plan for Pandemic Preparedness

M. Cristina Cassetti,[1,a] Theodore C. Pierson,[2,a] L. Jean Patterson,[1] Karin Bok,[3] Amanda J. DeRocco,[4] Anne M. Deschamps,[4] Barney S. Graham,[3] Emily J. Erbelding,[1] and Anthony S. Fauci[4]

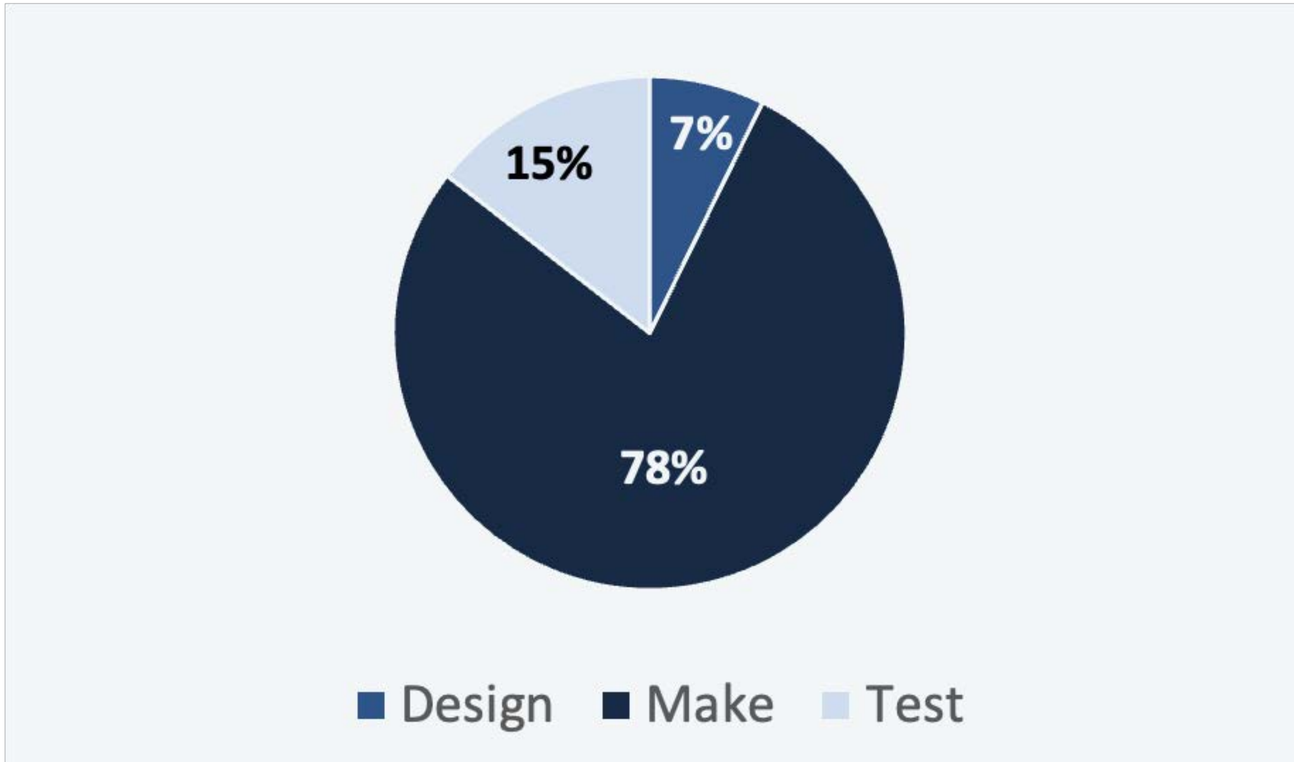
[1]Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; [2]Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; [3]Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA; and [4]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

- SARS-CoV-2 only has 29 proteins
- Many viruses of pandemic concern have far less
- Exhaustively finding chemical probes against every protein in prototypical pathogens is not out of reach

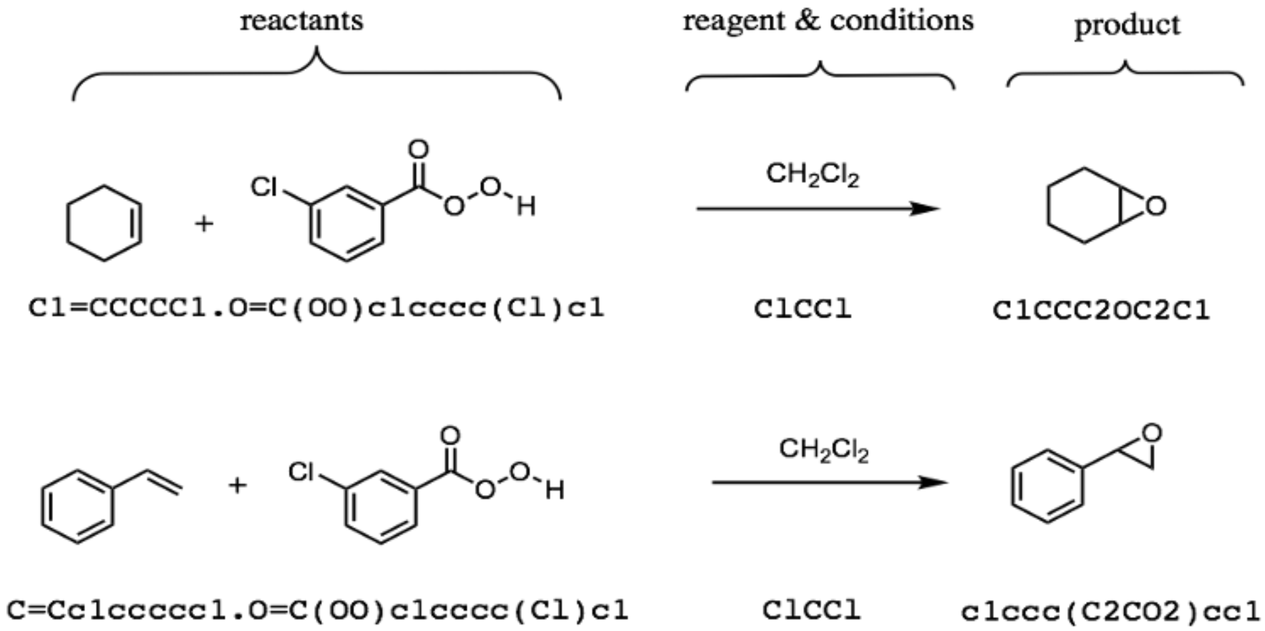
Woolhouse et al., Proc. R. Soc. B 275, 2111 (2008)

AI speeds up synthesis, the slowest step in medicinal chemistry

- Synthesis is the rate-limited step in med chem cycle times
- With AI-driven medicinal chemistry, median synthesis time is 24 days, a 56% improvement on typical synthesis cycles



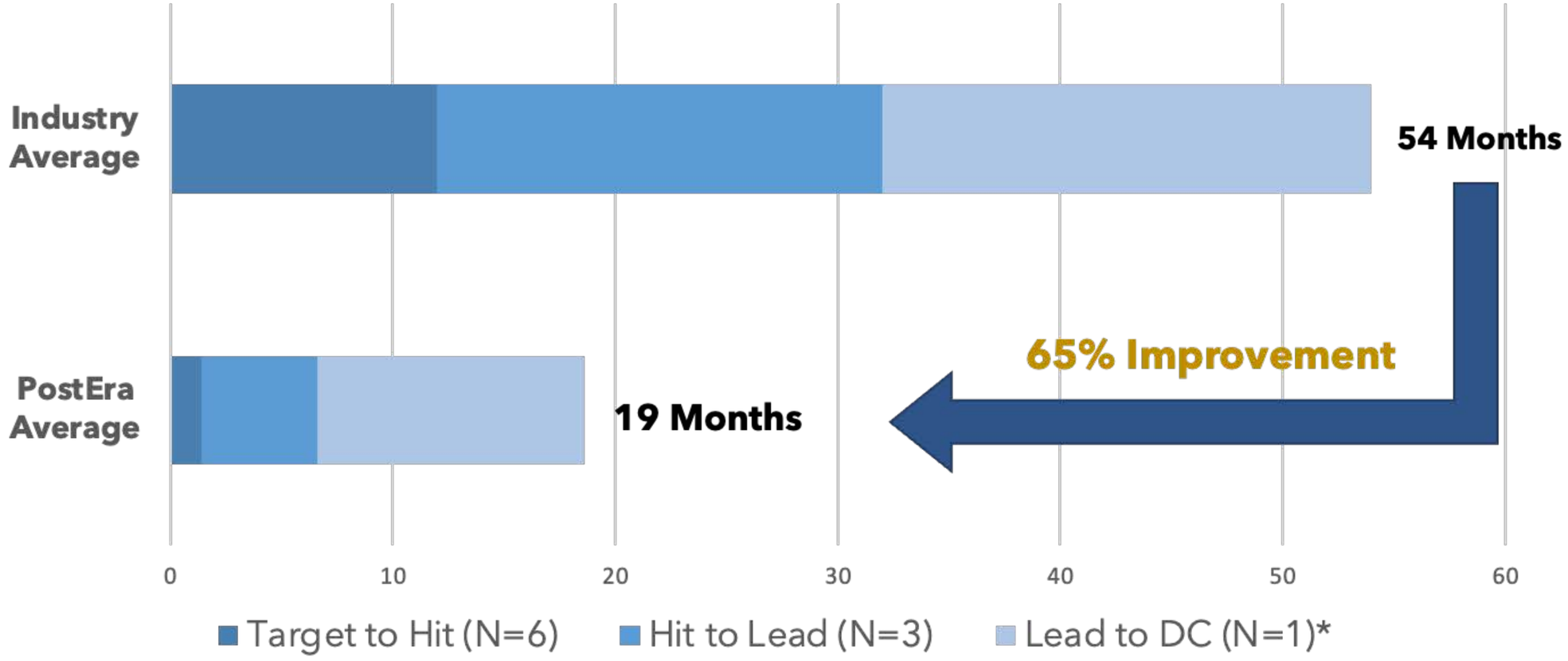
We learn the rules of chemistry using a natural language processing approach



- Our **Molecular Transformer** model is state-of-the-art.
- Molecular Transformer is **10% more accurate** than the best human chemists.

	Jin et al. (2017)	IBM (2018)	Coley et al. (2019)	**Molecular Transformer**
Test set accuracy	79.6%	80.3%	85.6%	**90.4%**

Our AI platform delivers development candidates at pace



COVID Moonshot

An international effort to

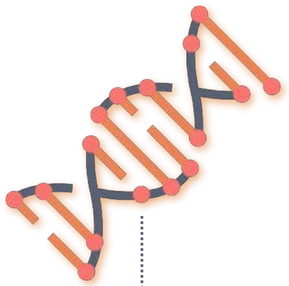
Develop a COVID antiviral

Moonshot's Target Product Profile

- Development candidate nominated
- Currently in IND-enabling studies led by DNDi, funded by a $11M grant from the Wellcome Trust
- **Patent-free from the get-go. Aggressive real-time disclosure of data**.

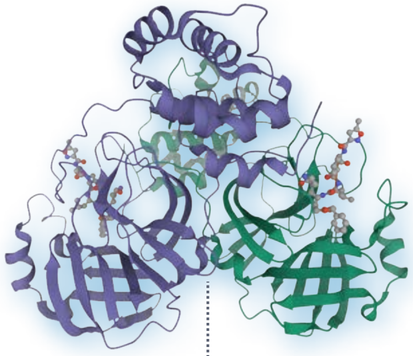
Property	Target range	Cold start Mar 2020 -> Dec 2021
protease assay	IC_{50} < 50 nM	40nM
viral replication	EC_{50} < 0.2µM	0.15 µM in A549 CPE
PK-PD	C_{min} > EC_{90} (plaque reduction) for 24h	Current projected human dose ~220mg QD ; 100mg BID
Coronavirus spectrum	SARS-CoV2 B1.1.7 , 501.V2, B.1.1.248 variants essential SARS-CoV-1 & MERS desirable	Active against B1.1.7 , 501.V2 in cellular assays
Route of administration	oral	BO = 45% in rat
solubility	> 5 mg/mL, >100µM tolerable	750 µM
half-life	Ideally>= 8 h (human) est from rat and dog	Rat 2h, human predicted PK sufficient
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 on analogues Eurofins / CEREP 44 target panel clean Cyp450: clean except 2A4 (3uM) No hERG activity Live phase planned Lead compounds are clean in AMES +/- S9

High-throughput X-ray fragment screen against Mpro amid the first lockdown



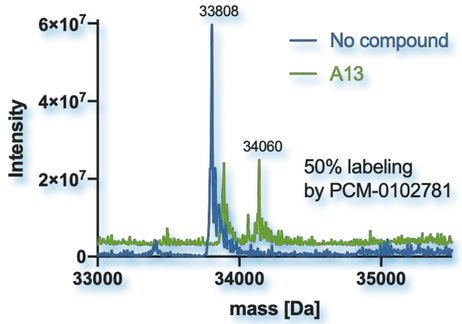
February 14 2020

Main protease cloned and produced



February 20 2020

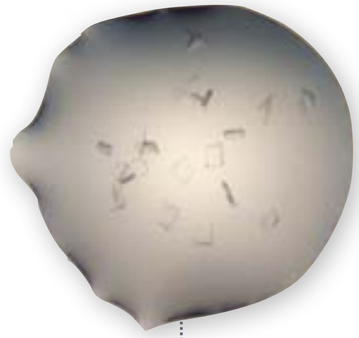
Atomic resolution structure of the protease determined



February 25 2020

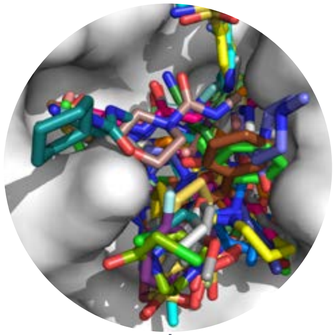
Covalent screen finds 150 active site hits

>40 hits validated



March 5 2020

1,500 crystals collected in one day (!)

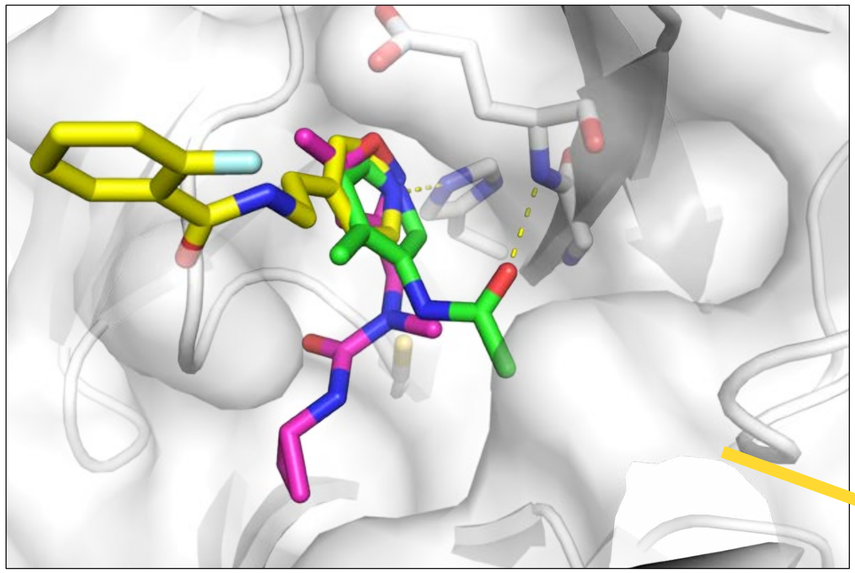


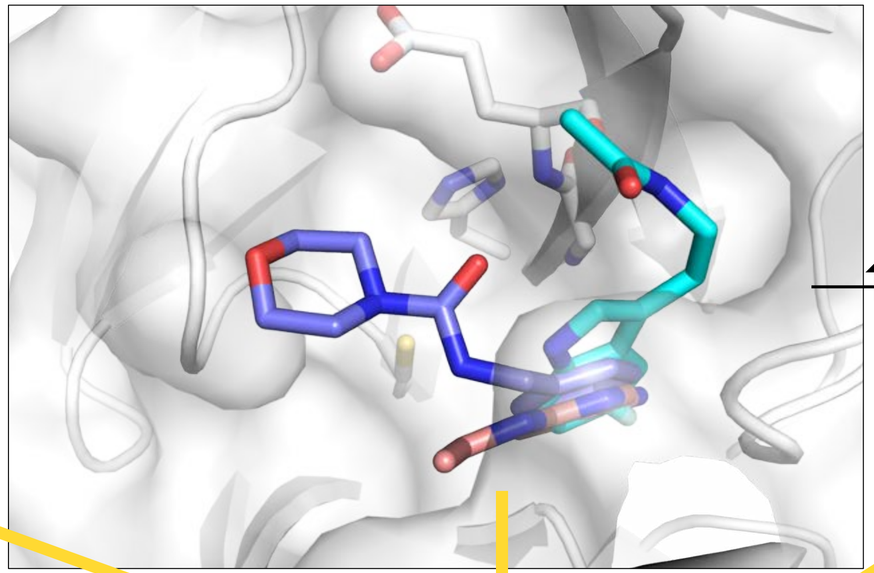
March 18 2020

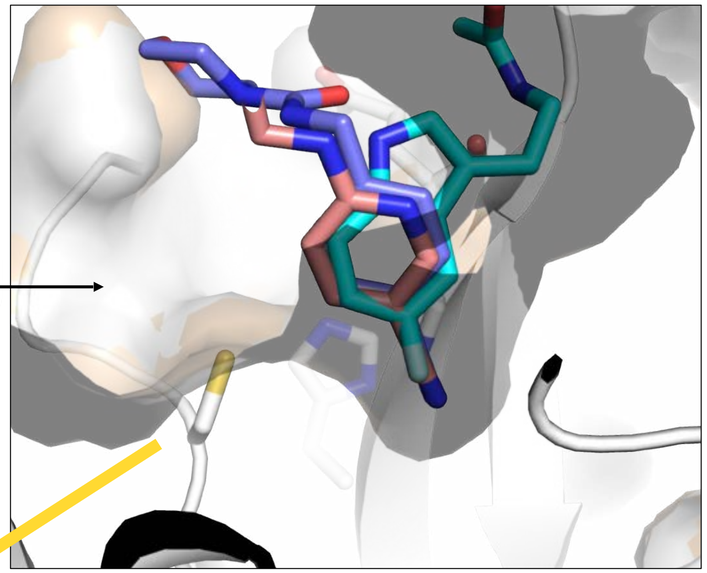
78 fragment-bound structures solved and released to the web

48 covalent fragments
71 active site fragments

Crowdsourcing generated a number of novel chemical series by fragment merging





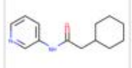


Contributor: Tryfon Zarganis - Tzitzikas, University of Oxford, TDI MedChem

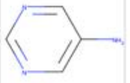
Design Rationale:

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

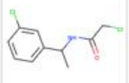
Inspired By:



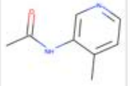
ALE-HEI-f28a35b5-9



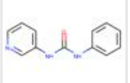
AAR-POS-d2a4d1df-18



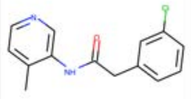
AAR-POS-0daf6b7e-10



MAK-UNK-6435e6c2-8



AAR-POS-d2a4d1df-11



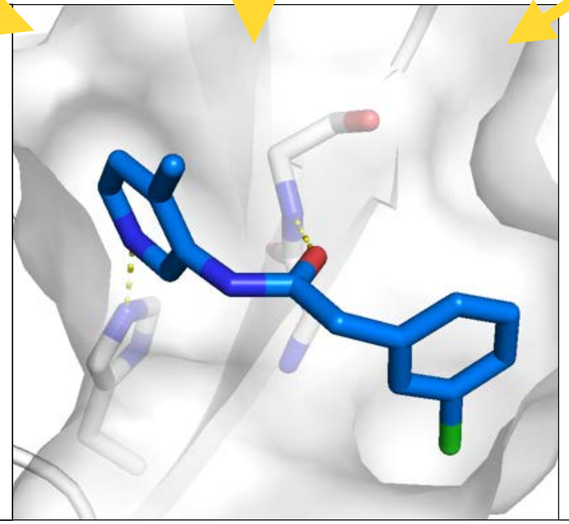
TRY-UNI-714a760b-6

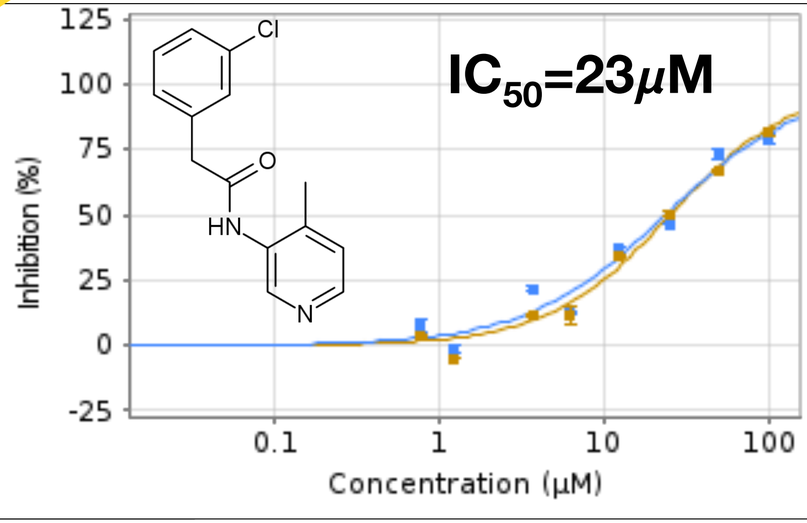
Cc1ccncc1NC(=O)Cc1cccc(Cl)c1

3-aminopyridine-like

Enamine Mcule MolPort Assayed

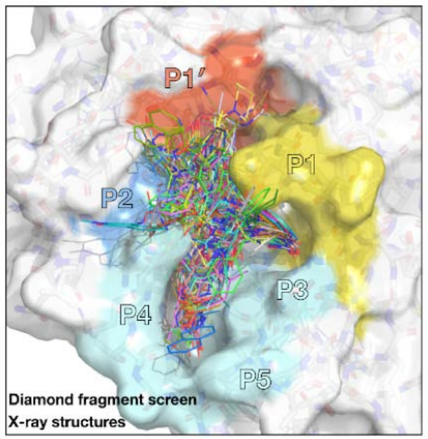
View

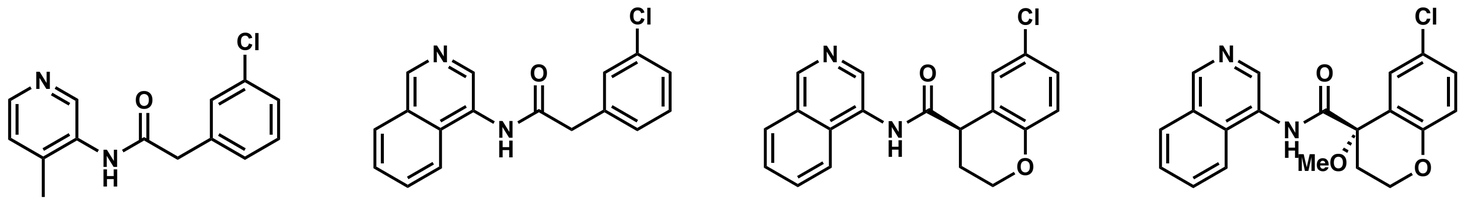




Journey from hit to lead

Crystallographic fragment screen

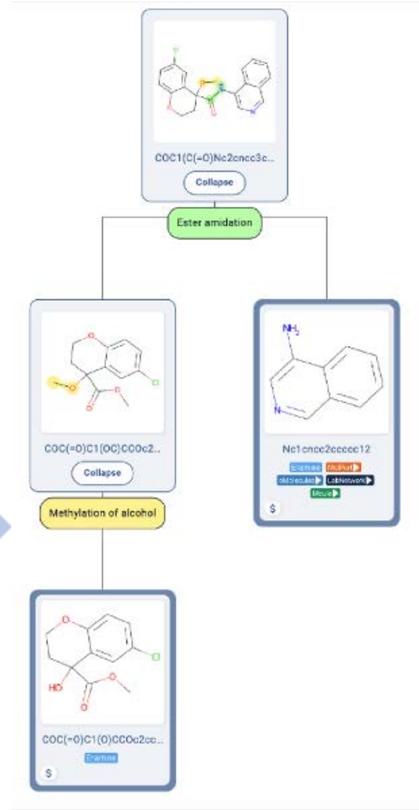


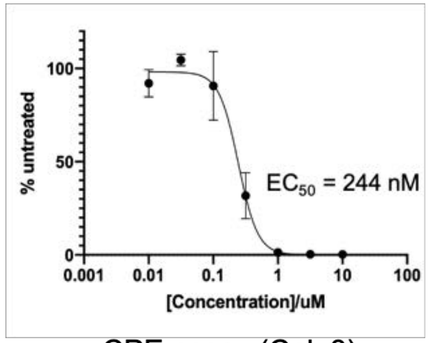


IC_{50} = 24 µM **IC_{50} = 720 nM** **IC_{50} = 140 nM** **IC_{50} = 80 nM**

- Fragment-to-hit
- 1 month from cold start

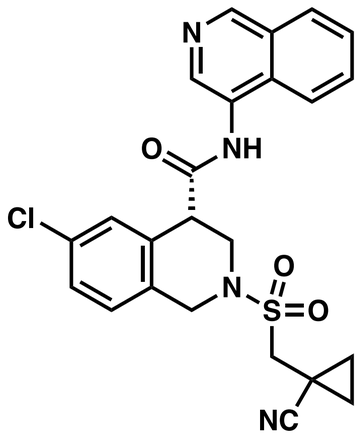
- Potent non-covalent lead identified after 6 months.
- The optimisation process delivered **ligand efficient** molecules that engages tightly with the substrate envelope
- Lead optimisation addressed other important pharmaceutical properties.





CPE assay (Calu3)

Moonshot delivered optimized chemical matter



	A549 (+ p-gp) CPE			HelaAce2 (+ p-gp) CPE			Calu-3 (no p-gp) FFU			VeroE6 (no p-gp) CPE	
	IC50	IC90	CC50	IC50	IC90	CC50	IC50	IC90	CC50	IC50	IC90
Nirmatrelvir	0.218	0.336	>50	0.0604	0.12	> 39.8	2.01	6.08	>100	2.71	3.71
MAT-POS-e194df51-1	0.0638	0.126	>50	0.149	0.365	> 39.8	1.15	4.68	>100		

Robust antiviral activity across different assays

	MAT-POS-e194df51-1		Nirmatrelvir	
	IC50	CC50	IC50	CC50
Alpha variant (B.1.1.7.	0.38	>20	0.12	>10
Beta variant (B.1.351)	1.48	>20	0.21	>10
Delta variant (B.1.617.2)	1.52	>20	0.21	>10
Omicron variant (B.1.529)	0.29	>20	0.07	>10
MA-SARS-CoV-2/WA1	0.43	>20	0.14	>10

Robust antiviral activity across different circulating variants

A rising tide lifted all boats

Journal of Medicinal Chemistry

pubs.acs.org/jmc

Featured Article

Discovery of S-217622, a Noncovalent Oral SARS-CoV-2 3CL Protease Inhibitor Clinical Candidate for Treating COVID-19

Yuto Unoh,[#] Shota Uehara,[#] Kenji Nakahara,[#] Haruaki Nobori, Yukiko Yamatsu, Shiho Yamamoto, Yuki Maruyama, Yoshiyuki Taoda, Koji Kasamatsu, Takahiro Suto, Kensuke Kouki, Atsufumi Nakahashi, Sho Kawashima, Takao Sanaki, Shinsuke Toba, Kentaro Uemura, Tohru Mizutare, Shigeru Ando, Michihito Sasaki, Yasuko Orba, Hirofumi Sawa, Akihiko Sato, Takafumi Sato, Teruhisa Kato, and Yuki Tachibana*

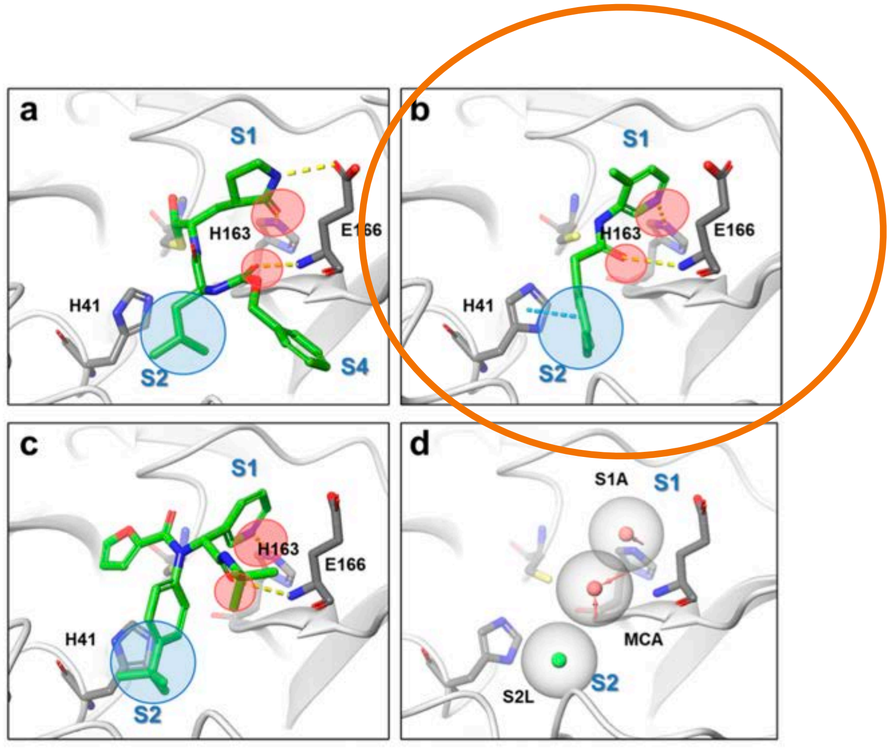


Figure 2. Binding modes of $3CL^{pro}$ inhibitors, their interactions, and defined pharmacophore filters for virtual screening. (a) Crystal structures of GC376 (PDB code: 6WTT), (b) 3-aminopyridine-like compound of the Postera COVID moonshot project (PDB code: 5RH2), and (c) ML188 (PDB code: 7L0D). The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

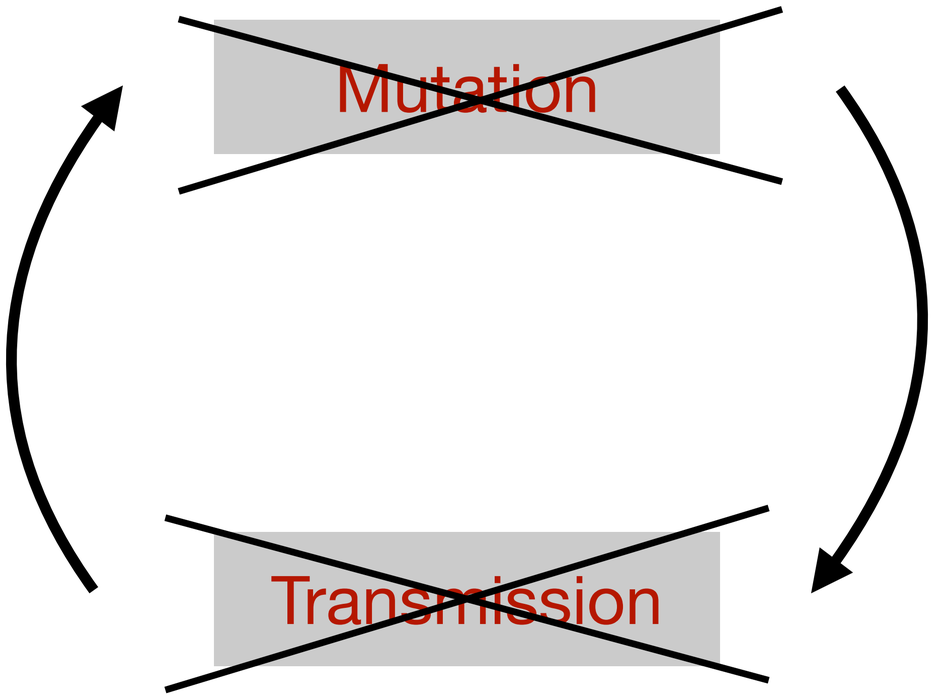
Moonshot's data directly helped Shionogi in their Ensitrelvir discovery campaign

The vision: Reducing the risk of future pandemics through AI technologies

Pandemics are usually driven by a vicious cycle

The vision: Reducing the risk of future pandemics through AI technologies

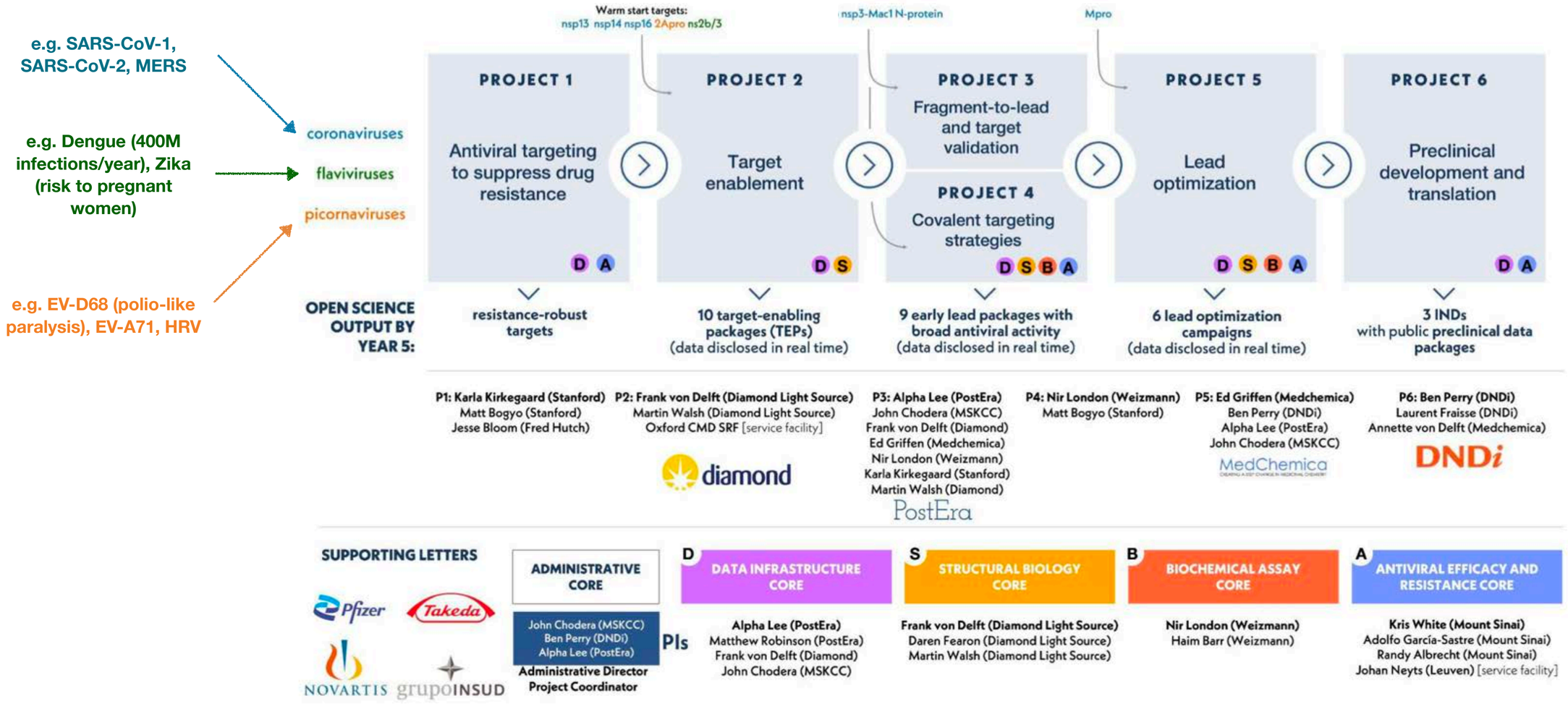
Right targets: Identify resistance-robust targets



Right molecules: Using AI/ML to rapidly design inhibitors that engage resistance-robust binding sites

Right access strategy: Global equitable access. An outbreak anywhere is a pandemic risk everywhere

AI-driven Structure-enabled Antiviral Platform (ASAP): A NIH-funded engine for pandemic preparedness



$68M initial funding over 3 years, with a 5 year funding envelope