COVID Moonshot – end-of-year Webinar

COVID-19 CORONAVIRUS PANDEMIC

Last updated: December 16, 2020, 15:26 GMT

Graphs - Countries - Death Rate - Symptoms - Incubation - Transmission - News

Coronavirus Cases:

74,006,729

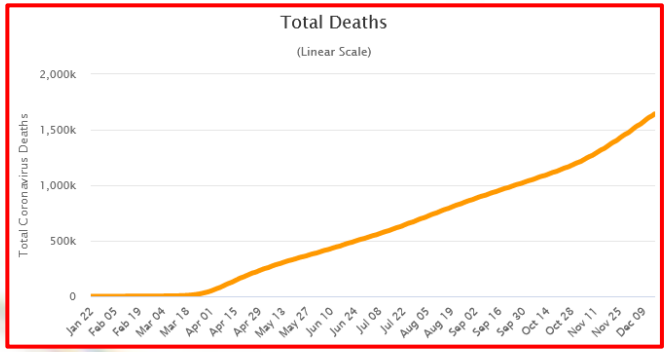
view by country

Deaths:

1,645,774

Recovered:

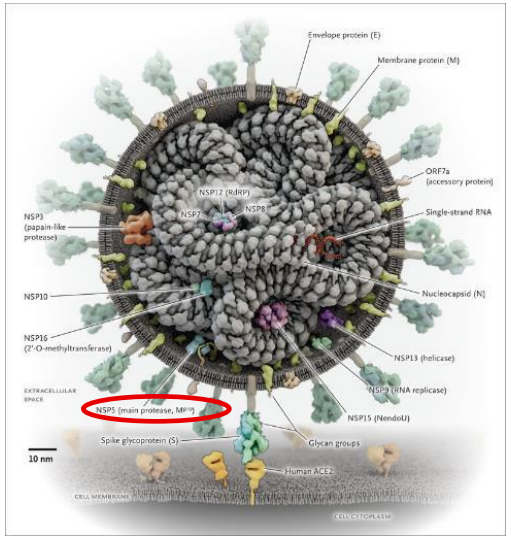
51,980,678

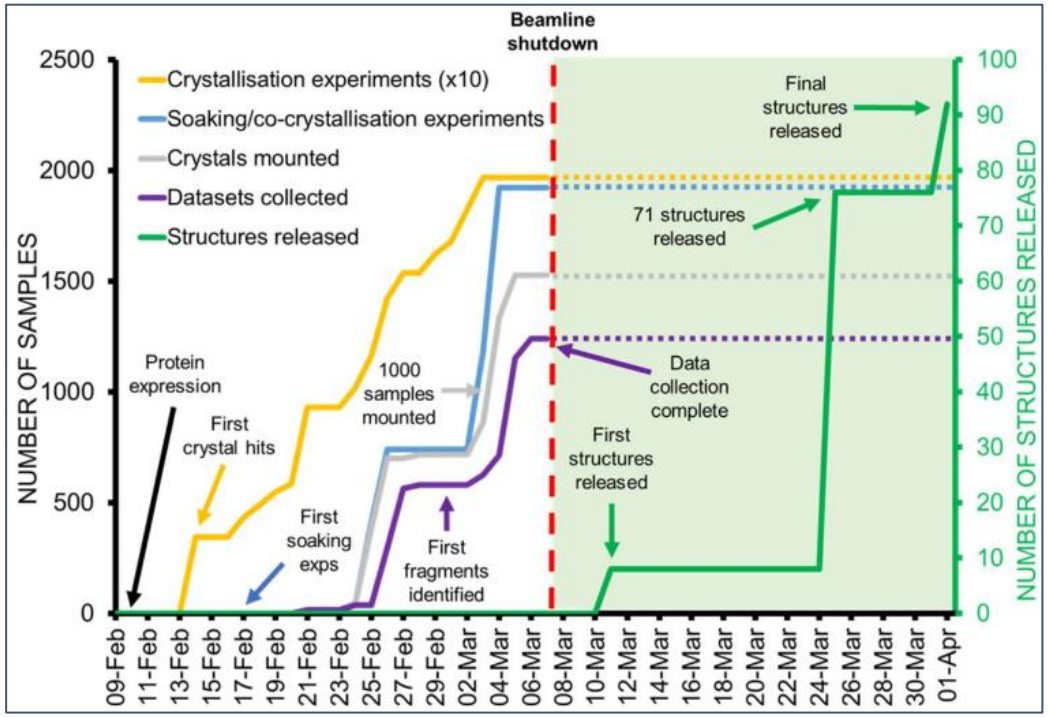


COVID Moonshot

Main protease (Mpro) XChem screen – hits in <2mth

- Mpro: one of 2 proteases – process the viral polyprotein
- Haitao Hao *et al* (Shanghai) – structure by end January(!) – post on website
- Contacted Martin Walsh – request synchrotron help
- Martin & team – reclone, express & crystallize





- Total fragment hits: 23 non-covalent, 48 covalent

Mpro pre-pre-publication of data…

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.

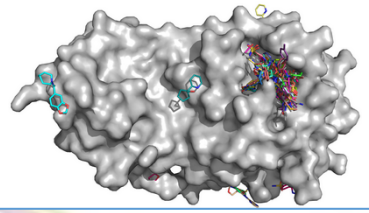
On the 11th of May, the first biochemical and structural data from Moonshot compounds was released and by the 12th of June over 500 compounds had been tested, demonstrating that the design-make-test process is fully in place.

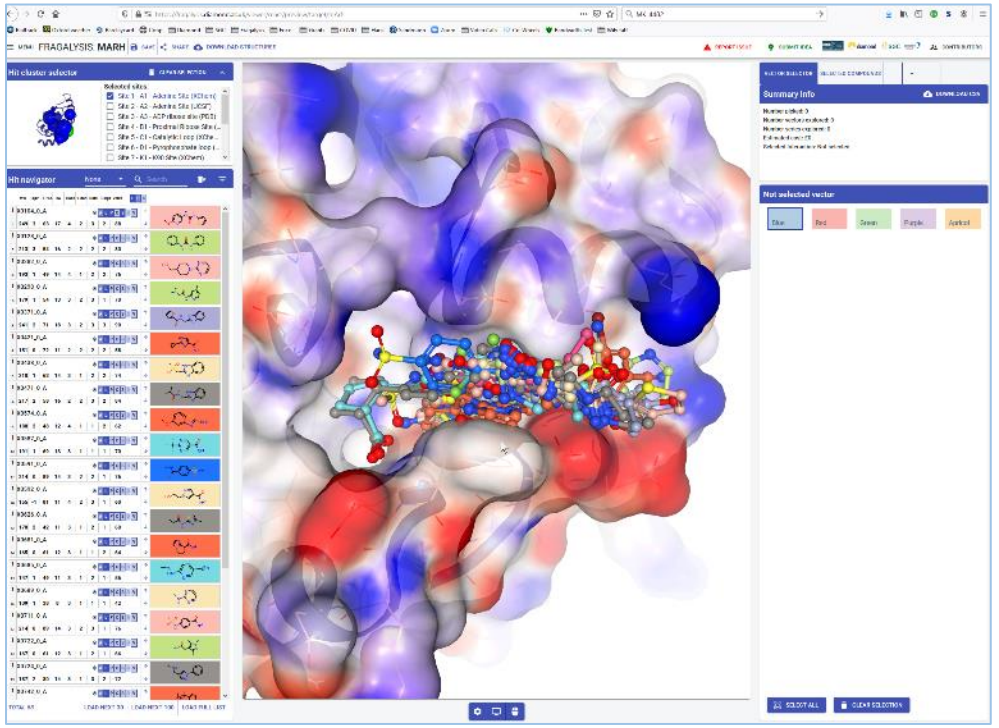
XChem fragment screen

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:

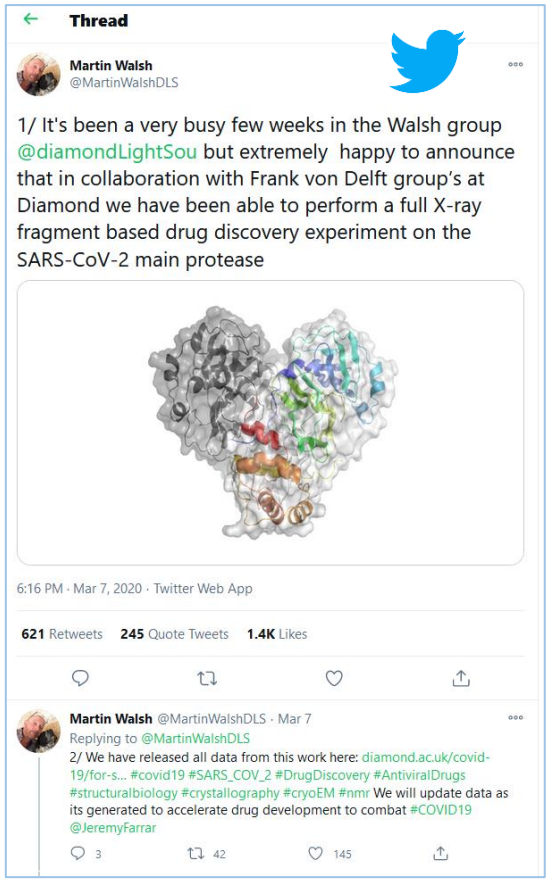
- 23 non-covalent hits in the active site
- 48 covalent hits in the active site
- 3 hits in the dimer interface, one in a calculated hotspot





https://fragalysis.diamond.ac.uk

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



Thread

Martin Walsh
@MartinWalshDLS

1/ It's been a very busy few weeks in the Walsh group @diamondLightSou but extremely happy to announce that in collaboration with Frank von Delft group's at Diamond we have been able to perform a full X-ray fragment based drug discovery experiment on the SARS-CoV-2 main protease

6:16 PM · Mar 7, 2020 · Twitter Web App

621 Retweets **245** Quote Tweets **1.4K** Likes

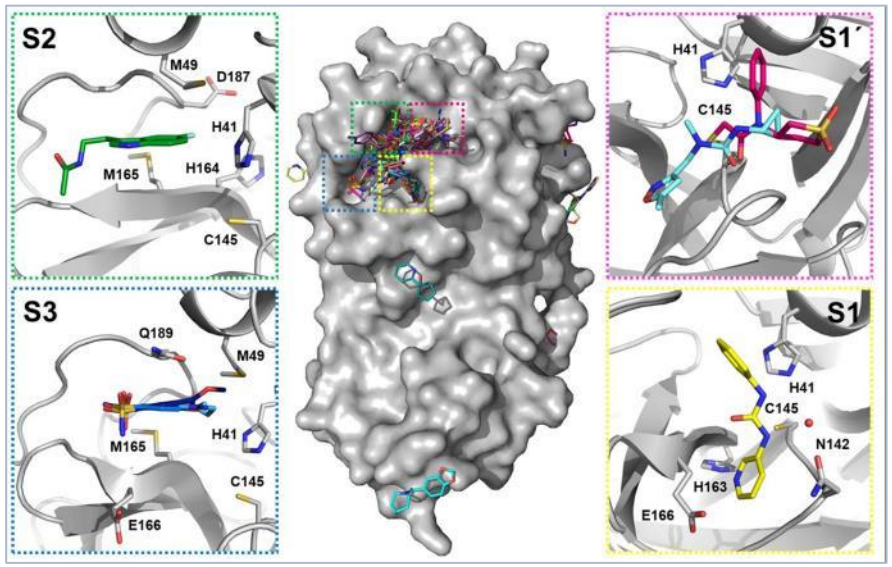
Martin Walsh @MartinWalshDLS · Mar 7
Replying to @MartinWalshDLS
2/ We have released all data from this work here: diamond.ac.uk/covid-19/for-s... #covid19 #SARS_COV_2 #DrugDiscovery #AntiviralDrugs #structuralbiology #crystallography #cryoEM #nmr We will update data as its generated to accelerate drug development to combat #COVID19 @JeremyFarrar

3 42 145

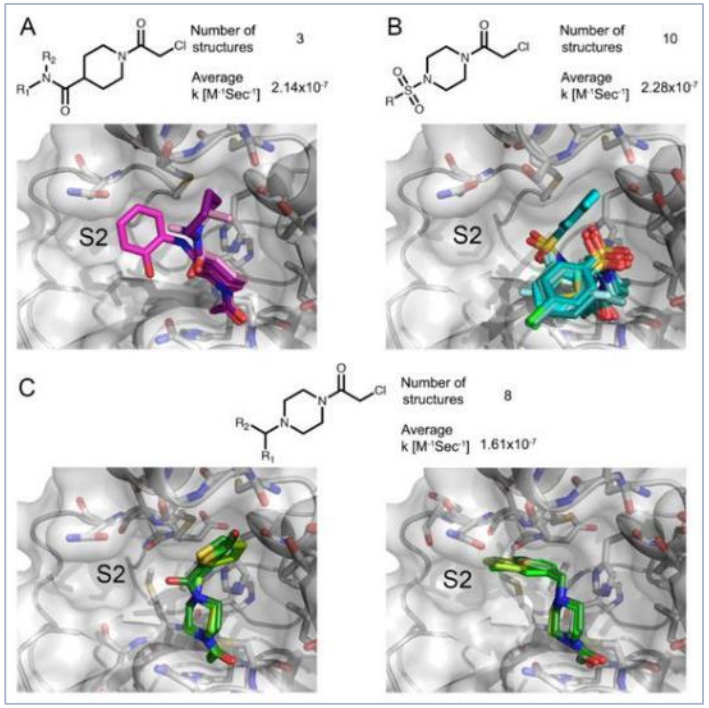
COVID Moonshot

Mpro XChem hits

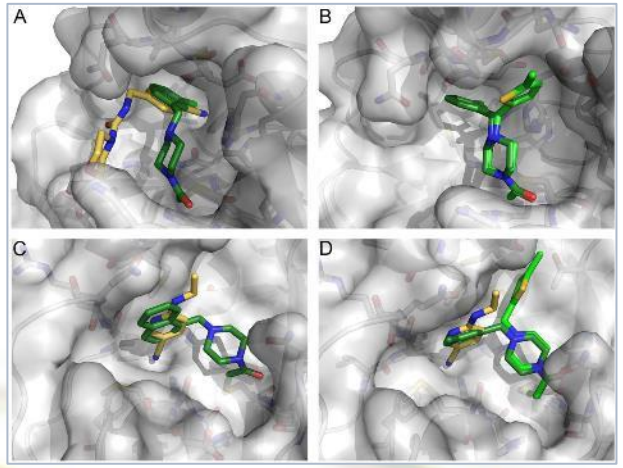
Active site – exhaustively populated



Covalent binding – molecular recognition



Many merging opportunities *(Resnick et al, 2019)*



→ "Merge Space"

Martin Walsh (Diamond)
Nir London (Weizmann Institute)
Frank von Delft (Diamond-XChem)
Douangamath *et al*, Nat Comms, 2020

COVID Moonshot

Merge space – the useful Red Herring

Premise: surely somewhere in Merge Space lurks the drug?

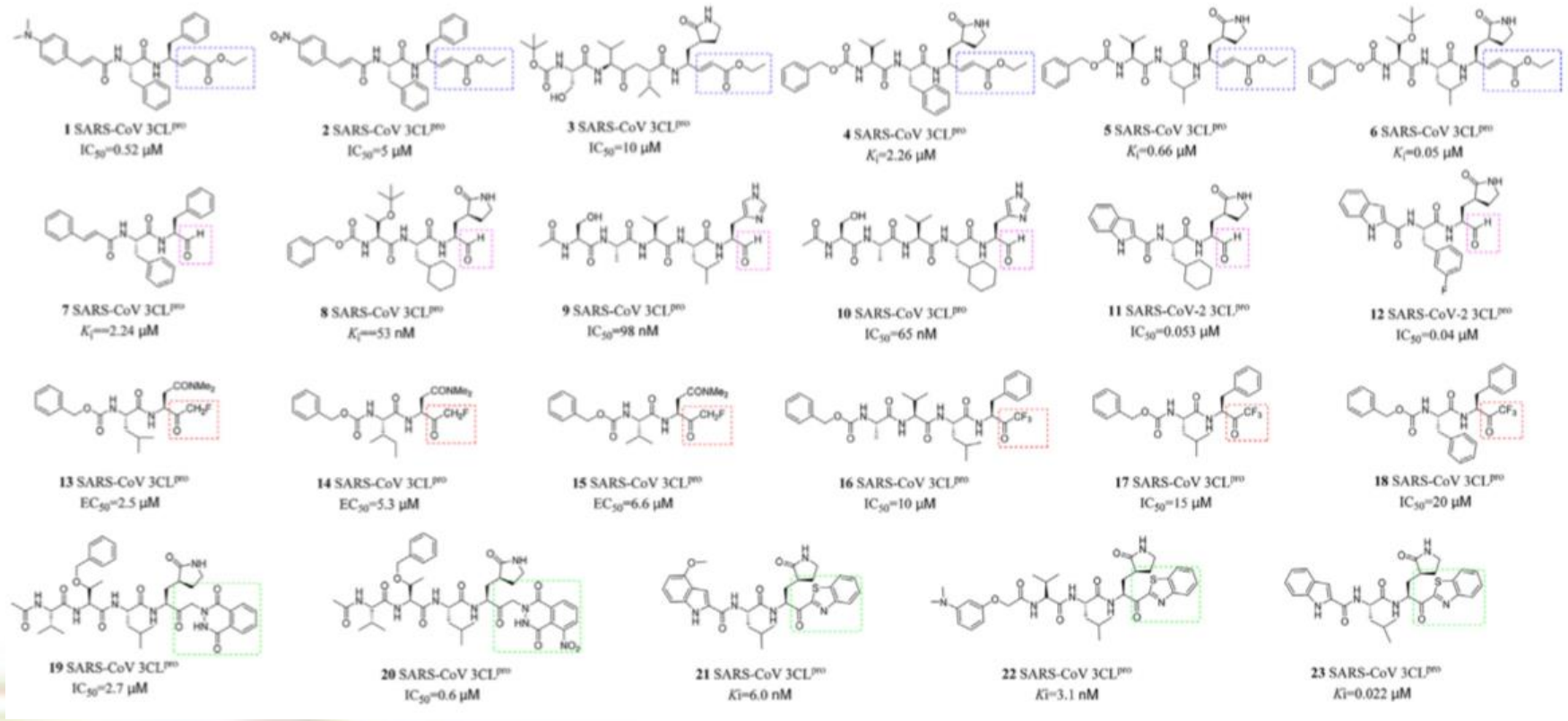
- Simple to make, potent antiviral, clinically safe

?? Can we find them ?? **?? Do it publicly so they're generics ??**

- Conversation (late March):
  - *Nir*: ask Derek Lowe to broadcast on his blog that we need ideas (*SMILES in a google doc?*)
  - *Alpha*: PostEra will build a website and get them made
  - *John*: Folding@Home will rank the submissions
  - *Frank*: Diamond & Oxford will test the compounds
  - All: pool philanthropic and grant funds

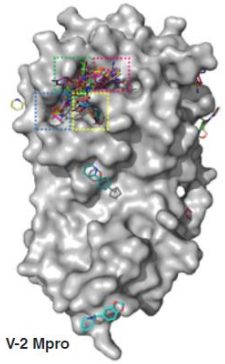
Where are the anti-SARS drugs?

- "*The world does not need another protease inhibitor*" – Al Edwards, private communication, Apr 2020
- Where are they…?
- Lots of covalent peptidomimetics – too hard to develop into drugs?



COVID Moonshot – progressing a new antiviral towards clinic

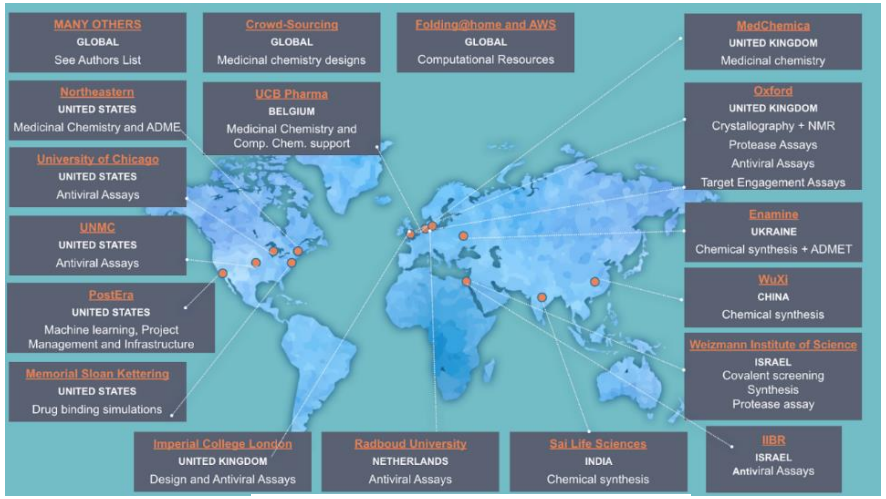
Large spontaneous international collaboration



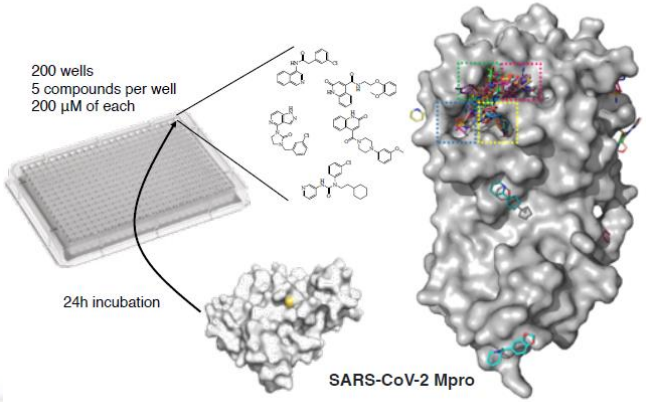
Fragment screen

(Pre-lockdown)

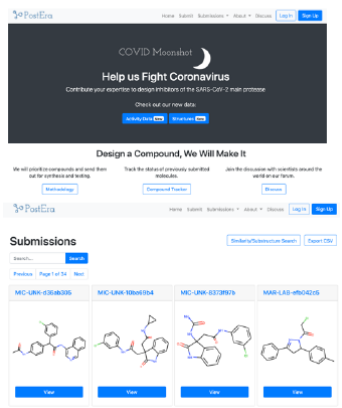
>30 groups
Expertise pro bono - Experiments at cost - Philanthropic funding



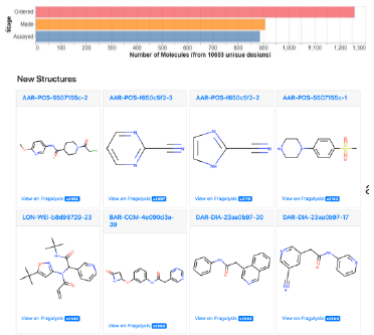
PHASE 0: 1500 fragment soak and X-ray crystallography produces 71 fragment structures [6 Mar 2020]



PHASE 1: IDEATION: 10,000 crowdsourced compound designs submitted [2 Apr 2020]



887 compounds made and assayed
55 compounds IC50 < 10 µM
200 X-ray structures
[21 Jul 2020]



PostEra

PHASE 2: OPTIMIZATION
[proposed work]

DESIGN
med chem strategy review

ANALYZE
COVID Moonshot data exploration portal

ENUMERATE
virtual synthetic library enumeration

TEST
simultaneous X-ray and biochemical data (<1 week)
+ assay cascade

PRIORITIZE
structure-enabled free energy calculations

MAKE
CRO-aware synthesis delegation to minimize synthesis time and cost

COVID Moonshot

Defined target product profile (TPP) for orally bioavailable inhibitor for therapeutic and prophylactic use

Property	Target range	Rationale
protease assay	IC_{50} < 10 nM	Extrapolation from other anti-viral programs
viral replication assay	EC_{50} < 5 µM	Suppression of virus at achievable blood levels
plaque reduction assay	EC_{50} < 5 µM	Suppression of virus at achievable blood levels
route of administration	oral	bid/tid - compromise PK for potency if pharmacodynamic effect achieved
solubility	> 5 mg/mL	Aim for biopharmaceutical class 1 assuming <= 750 mg dose
half-life	> 8 h (human) est from rat and dog	Assume PK/PD requires continuous cover over plaque inhibition for 24 h max bid dosing
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 / therapies, cardiac safety for COVID-19 risk profile 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

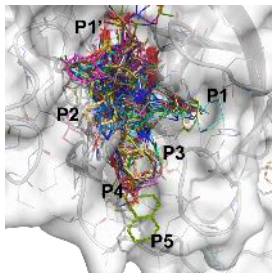
Status and outlook

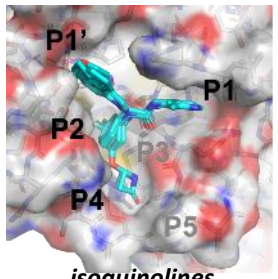
Goal: new potent antiviral: therapeutic & prophylactic
- *simple synthesis*
- *orally available*
- *pharmacologically behaved*
- *pre-clinically safe*

Strategy: work fully open to ensure rapid global availability
- *no IP encumbrance*
- *generic drug*
- *assays/structures/discussions: http://postera.ai/covid*
- *protocols: https://doi.org/10.1101/2020.10.29.339317*

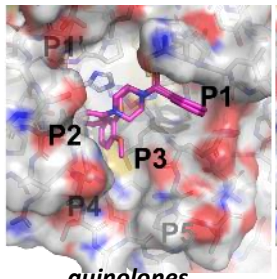
April — *Sept* — *Dec* — *Mar '21*

XChem & data release → **fragment-to-lead** *$350k, 30 groups* → **lead optimization** *$400k, 40 groups* → **toxicity, pre-clinical** *$1.5-2m, 50 groups*

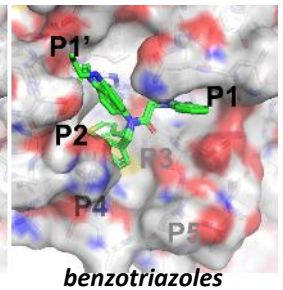




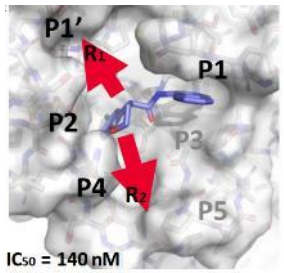
isoquinolines



quinolones



benzotriazoles



6 months: *3 lead series*
100nM enzyme inhibition
cellular antiviral activity
(philanthropic funding)

achieved: *oral availability*
antiviral IC_{50} <1μM
protease selectivity

improving: *potency*
solubility
metabolic stability

seeking: *critical mass funding*
partners (curr: charity, gov)
formulation & manufacturing
clinical trials

COVID Moonshot

Lessons for *(philanthropic)* clinical discovery

- Unless you define it as an endpoint, you'll never get close
  - Define Target Product Profile – TPP
  - Define a flowchart with specific thresholds

- The funding seems impossible to raise from conventional funders

- Very diverse expertise must be involved from the start
  - It *IS* available world-wide, outside of pharma
  - Indirect result of decades of industry investment

- The business models don't yet exist – so everything is worth trying
  - The firmer the advice, the more it should be ignored

- Urgent need for proof-of-principle of new approaches (technological, funding, business)
  - Can Moonshot help shift funders' mindset?