The COVID-19 antiviral race

we're all in this together

In response to the COVID-19 pandemic, international scientists from academia and industry have pooled their expertise and resources to identify candidate compounds that inhibit the activity of the SARS-CoV-2 main protease, in order to develop a clinically effective antiviral.

By Uduak Grace Thomas

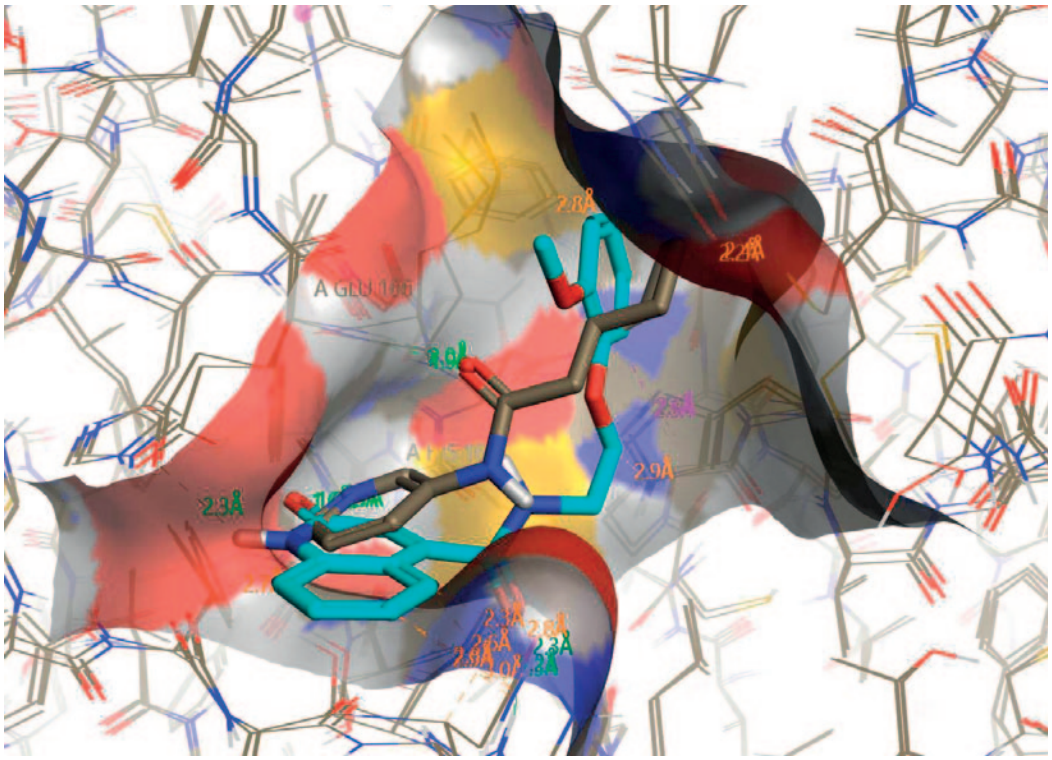
The aptly named COVID-19 Moonshot aims to accomplish this task more rapidly than has historically been done by crowdsourcing potential inhibitors from chemists around that world. In the span of roughly three months, hundreds of scientists have submitted thousands of potential candidates that are now being screened and checked for viability. All the data generated by the collective is shared publicly using a database supplied by Collaborative Drug Discovery. This includes the structures of the protease and the hits identified by screening experiments, as well as the experimental protocols used to select compounds for synthesis and testing.

In participating in the Moonshot, researchers have set aside traditionally siloed approaches to drug discovery research. They have willingly contributed time as well as shared data and knowledge of medicinal chemistry and drug discovery processes to address a massive need. Like millions of people around the world, many in the collective have been carrying out this work while trying to balance day jobs and time with their families. They have also had to deal with closed laboratories that limit their access to equipment, shipping delays, working across different time zones and continents, and in at least one case being infected with COVID-19.

Laying the foundations

There are several activities running in tandem under the COVID-Moonshot umbrella. But the foundation was laid thanks to work carried out by researchers in two laboratories. One of these was Nir London. He heads a computation and chemical biology laboratory at the Weizmann Institute of Science that works on covalent ligand discovery. Among other work, London's team has developed technology that identifies compounds that bind covalently to target proteins and created a library of small compounds that form irreversible bonds with target proteins.

In the course of developing its technology, London's lab formed a partnership with Frank von Delft, the other researcher whose work helped lay the foundation for the Moonshot. Von Delft is the Science Leader of the XChem laboratory at Diamond Light Source and also the principal investigator of the Protein Crystallography group in the Structural Genomics Consortium at Oxford University. His team has developed technology for performing crystallographic fragment screening in a streamlined way that returns results quickly and efficiently. The two teams had previously published a paper showing how combining their respective methods could be used to rapidly



Crystal structure of the SARS-CoV-2 viral protease binding with chemical fragments. *Credit Bruce Lefker*

progress the development of targeted covalent inhibitors.

Earlier this year, von Delft's team gained access to a coronavirus protein – a cysteine protease specifically – from researchers in China who had been studying the strain causing the current outbreak for some time. Using their technology, von Delft's team performed several crystallographic fragment screens against the protein and screened about 1,500 crystals of the full-length protein. They also shared the protein with researchers in London's lab to use their expertise in covalent screening to help prioritise which compounds to focus on.

"The cysteine protease is highly nucleophilic and highly active. We saw really high hit rates, much more than we saw with previous proteins," London explained. It is so reactive that even though London's team ran multiple screens using increasingly stringent conditions, they still received lots of hits. Their screen uses mass spectrometry to help prioritise which fragments best bind the protein, and they varied certain conditions to identify the most potent hits. These were prioritised for crystallography. Both teams then decided to make all the data that they had generated public. Full details of the fragments screened, the libraries used, the covalent and non-covalent hits among other findings from both research laboratories are available at diamond.ac.uk[1,2].

Part of the reasoning for making the data public was to get the scientific community's help with making sense of the large quantity of data that had been generated.

"For a long time, I've been looking at the XChem data and keenly aware that, because we get so many three-dimensional views on all these hits, that there's a lot of information to be exploited," von Delft said in an interview.

"Current formulas for exploiting and knowing what to do with this [data] and how to develop them are really a long way behind, partly because I don't think many computational people knew that this was coming or knew that this was actually available. It's one of those things where an experiment just leaps so far ahead… that it takes a while for people to figure out how to exploit it."

All of this research was happening when the pandemic was at its peak in March, and cities and countries were being locked down. Around this time, one of the researchers tweeted about the fragment screening data that London and von Delft's laboratories had generated and shared. That tweet caught the eyes of Alpha Lee, PostEra's Chief Scientific Officer and Group Leader at the University of Cambridge, and PostEra's co-founder and Chief Technology Officer Matt Robinson. PostEra offers medicinal chemistry services using its machine learning-based platform.

"We pioneered state of the art synthesis prediction tools that can design synthetic routes to complex organic molecules and we integrate that with molecular design tools that we have developed so that we have an integrated platform that closes the whole design-make-test cycle in drug discovery," Lee explained.

The birth of COVID-19 Moonshot

When Lee and Robinson saw the tweet they looked at the structures and realised that this could be way beyond just a scientific discovery – this could be a drug.

"And we have these tools for expanding the fragments and, more importantly, deciding how to synthesise molecules," said Lee. They responded to the tweet and broached the idea of a partnership focused on tackling COVID-19. Armed with a bit of funding, lots of volunteer hours and a community of scientific experts sharing designs and drug discovery strategies, how quickly could new, viable antivirals be identified and synthesised? Thus, the COVID-19 Moonshot was born.

Given the rates of infection at the time, the pressure was on to find a drug candidate. In short order, PostEra had a website up and running (www.postera.ai/covid) to share data and hold the crowd-sourced candidate compounds. The researchers expected that they would receive just a few hundred suggested compound designs. Instead, thousands of submissions poured in from scientists around the world, including those working in industry and academia, retired medicinal chemists, as well as postdoctoral and doctoral students.

"We had two crowd-sourcing waves. The first was for the fragment design molecules. The second wave focused on irreversible or covalent inhibitors, molecules that will just glue up the binding site irreversibly, and that's Nir's expertise," Lee explained. A third wave of crowdsourcing could take place depending on the need, but for now the focus is on consolidating data.

Industry support

To date, the group has received more than 7,000 submissions from 370 medicinal chemists around the world. And the initiative has garnered significant support from industry partners willing to offer their time and expertise. Life sciences company UCB was the first pharma to join the COVID-19 Moonshot, rapidly pivoting its business to lend scientific expertise and experience to the cause through dedicated teams in its discovery research laboratories in Slough, UK and Brainel'Alleud, Belgium. Its scientists have been intimately involved in the strategic development of the initiative – leading the computational chemistry activities critical to assessing and triaging chemical design submissions for synthesis and experimental testing, as well as co-ordinating internal efforts to apply proprietary computational technologies and contribute inhibitor designs from the Computer-Aided Drug Design (CADD) and the medicinal chemistry communities at UCB.

"At its heart, Moonshot is about bringing together some of the brightest brains from across the world to tackle an immediate problem in a genuinely new and refreshing way," Mark Calmiano, Principal Scientist, CADD at UCB, said. "We are learning a lot from so many talented individuals and the progress being made is inspirational, it really feels like we are working on a project with the potential to help so many people."

Additional help soon came from other industry partners. Companies such as Enamine and Sai Life Sciences stepped in offering synthesis services. Collaborative Drug Discovery came forward to provide data management functionality through CDD Vault. Meanwhile, Boehringer Ingelheim contributed reactivity prediction models and Lhasa UK contributed toxicity prediction models.

Integral role of data

One of the first tasks for the team was to sift through the data and identify which ones to progress for additional testing. Early on, as part of their strategy for identifying drug candidates quickly, the researchers decided to focus initially on compounds that target the active site of the main protease enzyme and could be synthesised quickly in large quantities at low cost. They also prioritised compounds that could be synthesised within two weeks. PostEra used its machine learning-based technology to help triage suggestions and derive workable synthesis plans including the number of steps required to make the molecule in question. Given a molecule, PostEra's algorithms search through different ways to disconnect it into its constituent parts.

"Then we have a machine learning method that can suggest which are the best disconnections and whether this disconnection will actually yield fruit in the forward direction," Lee explained. "That gives you two reactants and if both are purchasable, then you are done in one step. If not, then you have to further disconnect these reactants and build out this whole tree of possibilities."

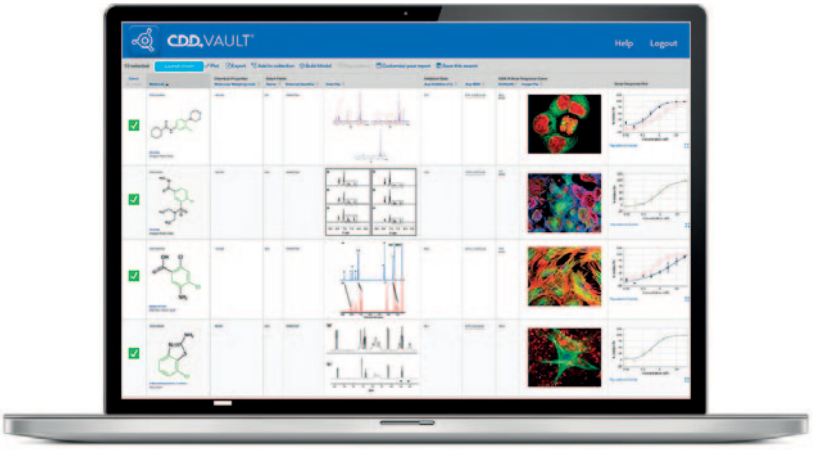
Separate teams are working on computational docking and calculating the binding-free energies of compounds with an eye towards determining

their potency against the COVID protease. Receiving so many candidates has posed some challenges for the team in terms of which ones have the potential to be effective and should be synthesised. For example, scientists contributed a variety of designs with very different scaffolds using various methods and algorithms. These all need to be evaluated and tested and decisions made about which compounds should be prioritised for synthesis. Protein docking methods work well for filtering out which candidate compounds do not fit but, by themselves, they are insufficient for identifying which ones would actually work by effectively inhibiting the protease activity. Researchers are supplementing protein docking technology with methods for exploring the binding-free energies[3] of the submitted compounds to help pare down the list.

As part of their contributions to the Moonshot, Vincent Voelz's laboratory[4] at Temple University is working on calculating the absolute binding energies of the submitted compounds. Separately, John Chodera's laboratory at Memorial Sloan-Kettering Cancer Center is working on some of the docking and relative free energy calculations that will, among other things, help to prioritise compounds with the same scaffold but different substituents. Both laboratories are utilising millions of central processing cores and thousands of graphics processing units that are part of the Folding@home[5] network to handle the computationally-heavy calculations that their work requires. Absolute free energy calculations, for example, can take weeks to complete. Parallelising that work using millions of CPU cores can slash that time significantly.

Docking experiments are also occurring in the laboratory of Robert Glen, a professor of computational medicine at Imperial College London and Director of the Centre for Molecular Informatics at the University of Cambridge. Prior to moving to academia, Glen worked as a senior research scientist at the Wellcome Foundation where he invented marketed drugs and subsequently assisted in the start-up of several successful biotechnology companies. For the Moonshot, he is working with researchers Richard Foster and Holly Foster at Cambridge (CCDC) and Leeds University to come up with ideas for molecules that can be synthesised as well as test which ones could potentially bind to the main protease COVID-19 binding site.

"We dock and score these and then we submit them for synthesis to the group," Glen said in an interview. "Currently there's about 40 molecules that we've suggested that are being synthesised." His team is also helping other groups to dock and score their suggested molecules using the well-known docking program GOLD in collaboration with the Cambridge Crystallographic Data Centre.



Data generated by the project were centrally stored in the CDD Vault informatics platform

"Although we can usually dock the molecules in the right place in the receptor – the big problem is in telling how well the molecules bind. And that's very difficult. Because of this, we've now set up a collaboration with Jimmy Stewart, the developer of MOPAC. We are developing a protocol using semi-empirical quantum mechanics on high performance computing in Cambridge to better estimate binding affinities and select the best molecules."

In terms of assays, London's laboratory is using a high-throughput fluorescence-based activity assay, led by Haim Barr at the high-throughput screening unit of the Nancy and Stephen Grand Israel National Center for Personalized Medicine, to screen the candidate compounds once they are synthesised and shipped from Enamine. Meanwhile two research labs at the University of Oxford, including von Delft's, are using crystallography and mass spectrometry assays to help assess the potency of the synthesised compounds. "Every week there is a new data packet that we upload to CDD Vault to share with everyone through PostEra's website," London explained. "A medicinal chemistry team looks at this data and designs the next set of compounds that Enamine will make and then we'll test." The data is also assessed by a computational chemistry team who are both developing and using existing tools to help further prioritise candidates based on assay data, the designs submitted by the community and the crystal structures. So far "we've synthesised close to 600 compounds and tested more than 500," London said.

As data and results are generated in individual laboratories, information is funnelled back out to

an open forum[6] where the broader scientific community can provide feedback and offer suggestions for next steps. This open approach to the work has resulted in new insights that have helped shaped the work. For example, researchers in the community identified the challenges with protonation states of the protease which affects ligand binding, and highlighted helpful research resources from prior work on SARS-CoV. There are challenges working with covalent designs; and figuring out appropriate ways to model the covalent inhibitor binding has been a group effort.

Although this initiative does not have formalised roles, there are many moving parts requiring a significant amount of co-ordination and planning. In addition to collaborating with teams of researchers operating across multiple countries and time zones, the collective has also needed to work through issues with data flow and formats. Leading the activities of the medicinal chemists involved in the project is Ed Griffen, Technical Director of Medchemica, a UK-based company that provides computational drug discovery services. Prior to launching the company, Griffen was at AstraZeneca where he worked on various aspects of the drug discovery pipeline including lead generation and optimisation and drug synthesis and design. He has also been responsible for developing and setting project strategy, project review as well as identifying and implementing new technologies for improving drug development.

His current efforts with the Moonshot focus on shaping the project direction including identifying things such as what expertise is still needed, potential risks and what goals the group should be working towards.

"One of the first things I did was to draft out a testing cascade and target product profiles," said Griffin. "We have this experienced med chem team who are just all over the data, they understand the risks, they are thinking with real precision about how we design things. I am trying to get that into a picture where we can go 'okay this is what need to do as an overall med chem input into the project'."

One of the medicinal chemists on the team is Bruce Lefker. Previously, he worked for 30 years at Pfizer in various roles in the medicinal chemistry field and has experience with different aspects of the drug discovery process including target identification and optimisation as well as data analytics to support decision making. Lefker had a pre-existing relationship with Nir London from a separate partnership between Pfizer and Weizmann Institute. Lefker joined the Moonshot project early on and has helped to shape a lot of the strategies and processes that help guide its current activities as well as identifying what sort of expertise and data are needed to push the project forward.

One important thing that needed to be addressed early on was getting a robust data system in place. "[For] all of the medicinal chemists who are involved that was one of the first things; where is the data, how can I look at it? How can I slice and dice it in different ways?" Lefker said. Both he and Griffen had used CDD Vault so knew it would meet the needs of the project.

Lessons learned from SARS

The virus is in the same family as several recent viruses that have caused pandemonium in various parts of the world in the last two decades. The selected active site of the COVID-19 main protease was deliberately chosen because this site is conserved across multiple coronaviruses including those responsible for both the SARS and MERS outbreaks. In fact, the protease active site has about 98% similarity with sequence of the SARS protease from the 2003 outbreak. However, because both of those earlier viruses did not have the same global impact that COVID-19 has had, efforts to develop vaccines and viable treatments for them did not gain traction.

When SARS was first appeared, there were some compounds being explored as potential drug candidates. But those efforts did not go very far because treatments for infectious diseases are often not a priority. The investment required to bring a protease inhibitor from initial compound identification through synthesis through clinical trials is substantial and companies may not be able to recoup those costs within the lifetime of a normal patent. It is important to note that the similarities between these viruses does not necessarily mean that drugs that worked for one would work for the other. But if those initial treatments had been taken all the way into the clinic, "we would have had something in the bank that could have been tried out", Griffen noted. PostEra's Lee also highlighted the dearth of research in the 17 years since the initial SARS outbreak and the potential treatments that could have been developed in that time. "It's this missed opportunity that also motivates us. We can't afford to miss another 17 years. We have to start now."

Part of the difficulty with developing inhibitors for cysteine proteases is that they are notoriously difficult to work with. "I've worked on some cysteine proteases in the past [and] they are hard. I have never been involved with a project that

moved that far in this area just because they are a lot harder," Lefker said. There are also challenges with using inhibitors to stop viral activity.

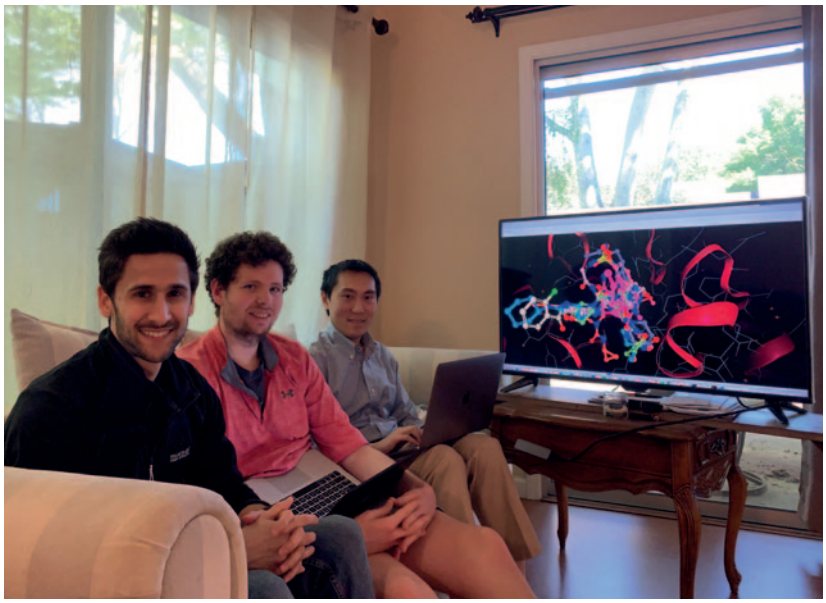
"There are some drugs where if you give a little bit of drug, you'll get some effect and it will be pretty linear. With a virus like this, you can actually cause more harm by giving sub-therapeutic doses. When you are not able to get enough of the drug in the body to fully shut down the virus, the virus will then be under evolutionary pressure to actually mutate and come back and be a worse problem."

Furthermore, whatever drug is developed will need high safety margins. "This is something [that] you have to be able to give to very broad populations as soon as they test positive [even though] they may be pre-symptomatic and they may never develop it," Lefker said.

While at the Wellcome Foundation, Glen worked extensively on antiviral drug development including chain terminators, protease inhibitors and non-nucleoside inhibitors. "This particular protease is difficult for a couple of reasons. One is that the binding site is a very open site so it will be challenging to find molecules that have high affinity and are selective for the protease that is in the virus," he explained. "The second problem is that… the virus, after it has entered the cell, basically creates an environment in the cell within which the protease can work to mature the viral proteases that are being produced. We have to be able to get the compounds into that compartment in the cell. So that can be a challenge."

Keeping in mind the likelihood of another pandemic in future, there is certainly room to explore more open approaches to drug development[7] such as the COVID Moonshot that can help keep some drug development costs down. One of the great things about the COVID-19 Moonshot is the way it has caused the community to coalesce around open drug discovery and to work together in ways that they may not otherwise done. These novel collaboration mechanisms have dramatically increased the speed of innovation and contributed to the current understanding of the virus. With hundreds of scientists and experts working across different time zones, research and development work is going on around the clock.

"This really has been an exciting way of working, both challenging and creative as we seek to design novel compounds aimed at not only SARS-CoV-2 inhibition, but also broad-spectrum inhibition of multiple coronaviruses to better protect our future," Jag Heer, UCB's Director of Medicinal Chemistry, said. "The COVID-19 Moonshot highlights a way of working which I think we will continue to adopt for future global emergencies."



The PostEra team L-R: Aaron Morris (CEO), Matt Robinson (CTO) and Dr Alpha Lee (CSO)

"This is great in the immediate term for generating as much insight and momentum as possible… but also in the long term," PostEra's Lee noted. "Infectious diseases is such an underfunded and financially unattractive area that closing it down just means a project runs out of steam very quickly, whereas if you open it up and get the whole community behind it… that's the only way you get success." And the response from the community to this initiative suggests that an open approach might be the ticket. "The momentum is quite amazing," Lee said.

One of the hallmarks of this initiative is the trust the partners have developed over time, which has allowed the project to move forward quite rapidly. "A main theme of this project is open science, open collaboration, data is released in real time. If this becomes a drug, no one will become rich. It's in the public domain so no IP. All of the compounds are just shipped so no material transfer agreements need to be signed," London said. "It also allows us to be much faster than traditional drug discovery efforts."

Effective drugs are still needed even if a vaccine is developed. Some people may choose not to be vaccinated for various personal reasons, while others might be unable to receive the vaccine for medical reasons. Still others may not have an immunological response to the vaccine for various reasons, while a separate category might need higher doses in order to be safe.

"If we can find an effective safe inhibitor, this is

References

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2 https://www.diamond.ac.uk/covid-19/for-scientists/Main-protease-structure-and-XChem/Downloads.html#.
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the kind of thing that you would want to have in your back pocket," Griffen pointed out. "It's like having a fire extinguisher. You have a fire extinguisher in your house, not because you have a fire but for the day when things go wrong."

And attacking this challenge as a community is starting to pay off. The researchers have identified some molecules that have passed some important checkpoints and could be well on their way to scale-up synthesis and eventually move into animal testing. Although transmission of the virus does appear to be slowing from its peak earlier this year, there is still a sense of urgency given concerns that it could resurge or that a more deadly viral strain could emerge.

"There were papers out in 2013 that looked at gain of function studies in coronaviruses and [COVID-19] was completely predictable, and there are worse options," Griffen pointed out. For example, "if you had a longer duration of asymptomatic development and then worse outcomes, that would be a worse virus. Working on a drug now that inhibits coronaviruses seems like a good kind of societal investment."

Still it could take a long time before effective antivirals for COVID-19 make it to clinics. In addition to this Moonshot, there are other efforts exploring potential treatments including studies that are looking at the efficacy of drugs that have already been approved for other uses.

"New therapeutics take a long time. If we move really fast, it's still going to take us several years," Griffen said. "It's got to be safe because it's going to go to a lot of people." And if efforts to create a vaccine are not successful, then the COVID-19 Moonshot could be one of the best hopes. "I don't want to be in a position where we are the best outcome because that means everything else failed," he continued. "But the science says this is a really hard area to work in so we might be. And the science that's being done is as good, if not better, than any other one I know. We've got a huge amount of global input. I've never seen one like it in 25, 26 years in the pharmaceutical industry."

Although infection rates are currently dropping, "I think we have to look at this as a longer-term problem," Glen noted. "The very limited investment in producing a number of very potent compounds absolutely dwarfs the economic damage that's been done around the world over the last three months. These respiratory viruses can be very deadly when they appear. If we are being sensible, we'll realise that another one can come along in our lifetime and we have to be more prepared. The compounds that we produce now might be too late for this epidemic, but we need to be prepared for the next one. Imagine the transmissibility of COVID-19 with the pathogenicity of MERS-CoV which has a 35% death rate."

Using a cocktail of drugs to target the virus is possible as was done with AIDS. "If we have a cocktail, we can prevent the virus from escaping one single drug because typically it will do that by mutation. That we can avoid by multiple drug therapy," Glen said. Several researchers interviewed for this piece mentioned Gilead Sciences' Remdesivir[8], a drug that works by blocking the synthesis of viral RNA, which has some antiviral activity and is currently being explored for treatment of COVID-19. They noted that it could be used as part of a combination therapy with protease drugs, which work by a different, but synergistic, mechanism.

As the project moves forward, the Moonshot will need additional expertise, including biologists who study respiratory viruses and researchers with expertise in pharmacokinetics and drug toxicity, particularly as drugs move towards clinical testing. These are the most obvious needs for now but there will likely be additional areas of need as things progress.

"We are making new molecules and they will probably show toxicities that we can't predict," Griffen said. It's not until these compounds move into testing that "you find out what the problems are, and you have to solve them." Any drug or cocktail of drugs developed would need to be evaluated to ensure safety and efficacy for various populations, ethnicities, genders and age groups. Furthermore, drugs will need to be assessed to ensure that they do not inhibit the activity of other medications that people might be taking or lose their efficacy because of an interaction with another drug. "Among the team, we've got a good network, so we know who to call to start with," Griffen said. But "if anyone else would like to step up, we'd love to have their support."

Need for funding

There is also a need for additional funding. Currently, much of the work being done on the project is pro bono. Some researchers were also able to realign funding for existing work to support their efforts. But identifying candidates is just the beginning. Getting the candidates into testing is going to require substantial investment. In addition to financial support from donations and small research grants, the Moonshot also has a GofundMe campaign[9] to gather more support for the work. " We are moving as fast as we can, we hope to have some results to inspire more funding," Lee said. "It's

these efforts which will prepare society for the next pandemic or the resurgence of this one."

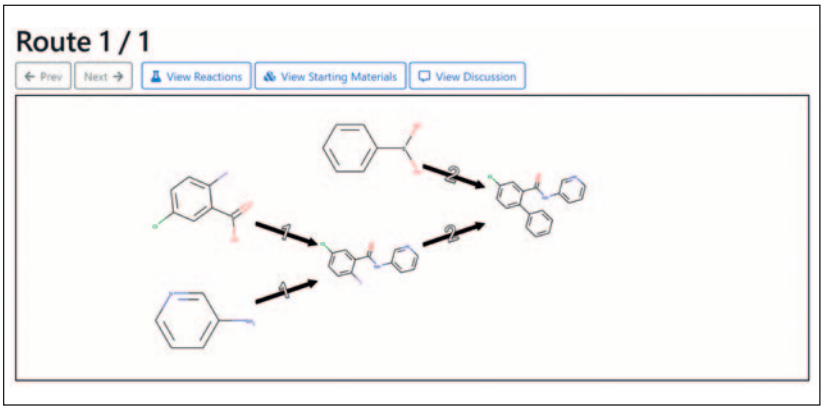
The Moonshot has also highlighted some gaps in the drug discovery pipeline that need to be filled before the next disease crises. For example, von Delft pointed out that much of the work carried out under this initiative is not governed by the kinds of contracts that would be in place under normal conditions, noting that getting these agreements into place has often resulted in delays to projects getting off the ground.

"In a practical sense, what has been useful is to use this urgency to demonstrate what might be possible. To think differently about infrastructure, both scientific and legal. It does not mean that because a moonshot might work in this scenario that it can be replicated infinitely, but there must be a spectrum," he said. "It should be the sort of thing we are looking towards for future pandemics." For example, contracts between universities and companies could be pre-prepared and kept dormant until they need to be deployed in the event of an emergency. "You could see a lot of things that you could line up in advance. When the next pandemic comes, we would know what to do."

Von Delft also pointed out that there are other diseases that impose significant financial burden on healthcare systems around the world but do not receive as much attention as COVID-19. "Why are we not shutting down our societies for Diabetes or Alzheimer's or a number of key public health problems which are burdens on society. I keep wondering whether this sort of thing can scale because COVID isn't the last urgent disease." A lot of things had to come together to make Moonshot possible, including the availability of the crystal structures and screening data, the community's willingness to use their expertise to create designs and help prioritise compounds, access to algorithms and computing power and synthesis infrastructure offered by companies such as Enamine. "It should be the sort of thing we are looking towards for future pandemics. It feels like it might be achievable if you get everything lined up," von Delft said.

As candidates reach threshold potency and move forward into testing, there is cause for cautious hope. But there is still a long way to go and a lot of work to do before safe drugs can move into animal testing.

"We have two or three promising series coming out of different sources, some from crowdsourced designs, some from computations approaches we developed in the lab, and some based on literature compounds from previous coronaviruses," London said. "These are all about single-digit micromolar. We have this one micromolar threshold that we are aiming for and once we cross that threshold, we'll start doing live virus testing." The group expects to cross that threshold in the next couple of weeks and already has collaborators lined up to work on the testing. If those tests work, the next step will be to launch pharmacokinetic testing studies. "Our unstated goal is within half a year to get to studies with compounds that have good PK/PD, good potency in virus assays, and then we can go to models," London said.



PostEra's machine-learning algorithm generates synthesis routes for novel compounds

Ultimately, the proof that a given compound or series of compounds are ready for more widespread testing and potential clinical trials will be when the researchers are able to demonstrate that it works. "I'll believe when we've cleaned out an animal of virus," Griffen said. "All the evidence says it should work but I'd like to see an animal completely sterilised of virus. That will be a huge moment when we can demonstrate that we've done that." DDW

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