Consortium focuses on drug solutions to fight Covid

With the current global inbalance in supply of vaccines against the Covid-19 virus, -particularly in low –to-middle-income countries – so the need for alternative treatment solutions becomes more urgent. The COVID Moonshot project, which came together in March 2020 following a crowd sourcing virtual collaboration, is a non-profit-open-science consortium of scientists from around the world, dedicated to the discovery of globally affordable and easily-manufactured antiviral drugs against COVID-19 and future viral pandemics.

Moonshot has now received a boost of £8 million from Wellcome, on behalf of the Covid-19 Therapeutics accelerator that will push the research towards clinical development.

"With the realisation that COVID-19 will be a global issue for the foreseeable future we urgently need to develop novel antiviral therapeutics. We are therefore thrilled to receive this critical funding from Wellcome and hope it can lead to more support," said Alpha Lee, Chief Scientific Officer at PostEra and Faculty Member at the University of Cambridge.

Labmate UK & Ireland caught up with some of the researchers of the Moonshot consortium to find out some more about their work.

What particular aspect of the research for new molecules and drug discovery is being conducted by UK collaborators at their own laboratories and what techniques are they using?

"PostEra uses AI to decrease the cycle time of the design-make-test cycle, by increasing the speed of chemical synthesis, reducing its unpredictability, and helping drive compound design. This technology is applied throughout the Moonshot campaign, and some of our lead compounds are only 1-step/1-week syntheses," said Alpha Lee

"The chemical synthesis of compounds is the slowest step in the design-make-test cycle of drug design. Moreover, the lead time required to make a molecule is often challenging to predict. PostEra's Manifold platform (https://postera.ai/manifold/) uses AI to search for synthesis routes to target molecules, starting from over 10 billion commercially available chemical building blocks. The mind-boggling number of building blocks, many of which are already richly functionalised, gives our AI platform a unique edge over a manual approach. Using Manifold, we can rapidly triage molecules based on synthetic complexity and design libraries of rapidly synthesisable molecules which probe informative medicinal chemistry hypotheses using PostEra's generative modelling technology.

How do facilities such as Diamond fit into the pattern of Discovery?

"What we have at Diamond is a unique set-up where we can assess the binding of small chemical compounds referred to as fragments to proteins essential for SARS-CoV-2 infection and replication," responded Frank von Delft, Professor of Structural Chemical Biology at the University of Oxford and Principal Beamline Scientist at Diamond Light Source.

"Each protein or 'drug target' is produced in sufficient quantities to allow researchers to grow crystals that can be used to provide high resolution images using x-ray crystallography and the powerful x-rays generated by Diamond. This technique allows researchers to visualise where and how these fragments bind to the sars-cov-2 drug targets being analysed. These data then provide an accelerated platform to aid development of compounds as initial starting points for drug discovery. This is a very early part of the drug design process and it's been the first time the process has been very open to the whole research community."

Past pre-clinical stage, for the potential early drug candidates predicted for near end this year, are future plans already in place for stage 1-3 testing in the low to middle income countries?

"With regards to Molnupiravir – arrangements are in place for licensing to generic manufacturers e.g. in India., although some middle income countries were not covered, explained Annette von Delft, Translational scientist at the University of Oxford. For the Pfizer molecule / Shionogi molecule – no arrangements have been announced to date," she added.

"For the moonshot compounds, we are actively planning the phase I (including funding options) so that we can progress directly into phase I with these compounds, although we will go with whichever location allows us the fastest progress through the clinic. Likewise we are planning ways in which we can accelerate the subsequent clinical trials (phase II / III) although the location for this will be highly dependent on the nature of future manufacturing partners. Our plans remain focused on LMICs."

left to right: Benjamin Perry, Discovery Open Innovation Leader at DNDi; Alpha Lee, Chief Scientific Officer at PostEra and Faculty Member at the University of Cambridge; Frank von Delft, Professor of Structural Chemical Biology at the University of Oxford and Principal Beamline Scientist at Diamond Light Source; Annette von Delft, Translational Scientist at the University of Oxford ; Ed Griffen, Technical Director and co-founder of MedChemica; John Chodera, associate member at the Memorial Sloan Kettering Cancer Center. ©Diamond Light Source, 2021.

Has there been any industry interest as manufacturing partners to date other than the project partners mentioned?

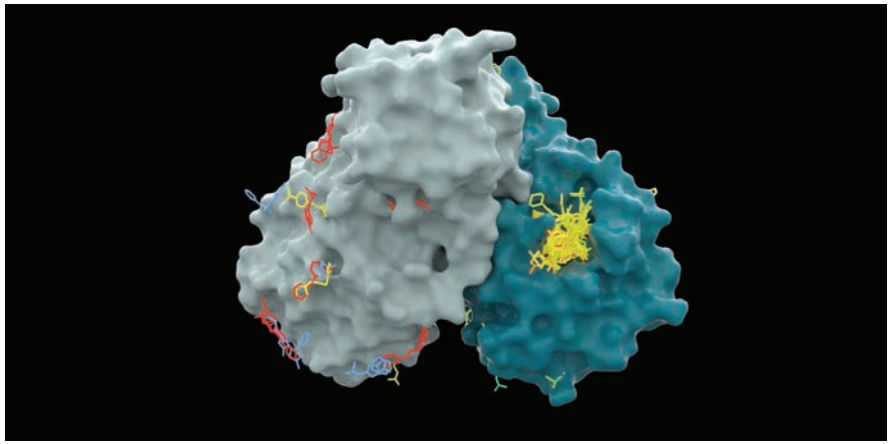
For the COVID Moonshot molecule, we have had early conversations with generic manufacturer's, and there has been some interest from big pharma. We are currently in the process of setting up further conversations.

Apart from the Wellcome Grant, is there any other sources of funding other than through research contributions from European or UK facilities such as Diamond? For example, from Governments, private financing etc - and are you expecting this to happen?

We have received many in-kind contributions to the project, from academic collaborators and pharmaceutical companies such as Novartis and Takeda. Several grants funded the early discovery work (such as Life arc) as well as funding through crowd-sourcing efforts organised by Postera AI.

Collaborators of the Moonshot project include academic and industrial groups such as Diamond Light Source, the UK's national synchrotron; the Weizmann Institute of Science (Israel); the Nuffield Department of Medicine at the University of Oxford (UK); PostEra (US/UK); the Memorial Sloan Kettering Cancer Center (US); various drug discovery consultants including MedChemica Ltd (UK), Thames Pharma Partners (US), and Compass Business Partners (UK); and the Drugs for Neglected Diseases initiative (Switzerland), which is now taking the lead in coordinating the Wellcome-funded drive towards the clinic.

www.diamond.ac.uk



(Molecular) view of a key component of the SARS-CoV-2 virus called MPro (Green/Grey) with drug site targets identified (In yellow). ©Diamond Light Source, 2021.

About DNDi

A non-profit research and development organization, the Drugs for Neglected Diseases initiative (DNDi) works to deliver new treatments for people living with neglected diseases, especially Chagas disease,

sleeping sickness (human African trypanosomiasis), leishmaniasis, filarial infections, mycetoma, pediatric HIV, and hepatitis C. DN Di is also coordinating a clinical trial to find treatments for mild-to-moderate COVID-19 cases in Africa.

Since its creation in 2003 by Médecins Sans Frontières, DNDi has provided 9 new treatments, including new drug combinations for visceral leishmaniasis, two fixed-dose antimalarial drugs, and the first chemical entity it developed, fexinidazole, approved in 2018 for the treatment of both stages of sleeping sickness.

About Wellcome

Wellcome supports science to solve the urgent health challenges facing everyone. We support discovery research into life, health and wellbeing, and we're taking on three worldwide health challenges: mental health, global heating and infectious diseases.

About the Covid-19 Therapeutics Accelerator

The Therapeutics Accelerator is an initiative launched by the Bill & Melinda Gates Foundation,Wellcome, and Mastercard with support from public and philanthropic donors to speed up the response to the COVID-19 pandemic by identifying, assessing, developing, and scaling up treatments. Its partners are committed to equitable access, including making products available and affordable in low-resource settings.

About Diamond Light Source

Diamond Light Source provides industrial and academic user communities with access to state-of-the-art analytical tools to enable world-changing science. Shaped like a huge ring, it works like a giant microscope, accelerating electrons to near light speeds, to produce a light 10 billion times brighter than the Sun, which is then directed off into 33 laboratories known as 'beamlines.' Since operations started, more than 14,000 researchers from both academia and industry have used Diamond to conduct experiments, with the support of approximately 760 world-class staff. More than 10,000 scientific articles have been published by our users and scientists.

Funded by the UK Government through the Science and Technology Facilities Council (STFC), and by the Wellcome Trust, Diamond is one of the most advanced scientific facilities in the world, and its pioneering capabilities are helping to keep the UK at the forefront of scientific research.

About PostEra

PostEra offers medicinal chemistry powered by machine learning. Our technology is built upon pioneering research done at the University of Cambridge. The technology addresses some of the key challenges in drug discovery R&D by integrating molecular design with chemical synthesis. PostEra partners with drug hunters to co-develop cures for patients while also offering some of its synthesis technology via its Manifold web platform. PostEra launched and now helps lead the world's largest open-science drug discovery effort: COVID Moonshot.

About the University of Oxford and the NIHR Oxford Biomedical Research Centre

Oxford University is world-famous for research excellence and home to some of the most talented people from across the globe. Our work helps the lives of millions, solving real-world problems through a huge network of partnerships and collaborations. The NIHR Biomedical Research Centre, Oxford (OxBRC) is based at the Oxford University Hospitals NHS Foundation Trust and run in partnership with the University of Oxford, and was one of five centres funded by the National Institute for Health Research (NIHR) in 2007. The OxBRC is a partnership that brings together the research expertise of the University of Oxford and the clinical skills of staff of Oxford University Hospitals NHS Foundation Trust with the aim of supporting translational research and innovation to improve healthcare for patients.