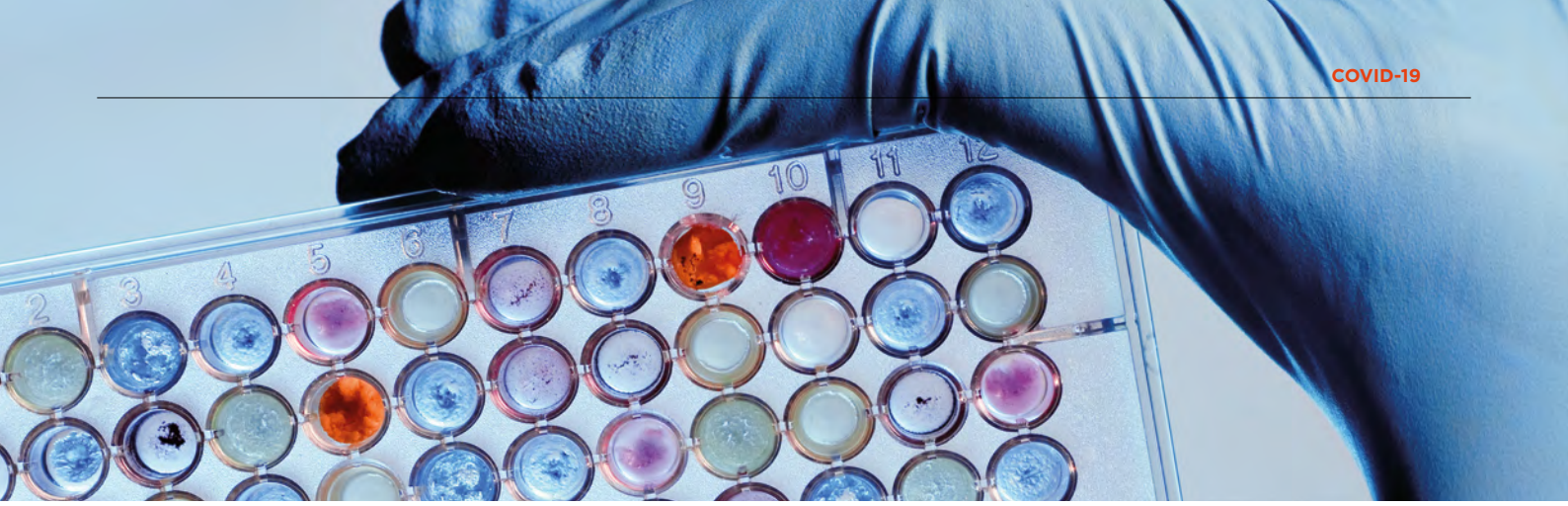
Drug repurposing for the battle against COVID-19

The race has been on since the start of the pandemic to develop vaccines and drugs to fight against the SARS-CoV-2 virus. Vaccine development has proven successful, with vaccine roll-out underway in many countries, but the need remains to identify drugs that can treat the disease for those who have not been vaccinated, or for those where the vaccine is not effective enough to prevent disease. Researchers at the Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP) in Hamburg, Germany, have been using high throughput drug approaches to screen compound libraries for candidate antiviral drugs.

The SARS-CoV-2 virus was identified, isolated and sequenced within a short time of this novel pathogen emerging into the community. However, at that time, the precise details of how the viral infection affects tissues and organs, or how this contributes to the development of disease, were not clear. This knowledge of infection and disease-related mechanisms is normally critical to developing medicines, allowing researchers to target key virus replication, or virus-host interactome associated pathways with small molecule compounds or biologicals. Unfortunately, the growing global crisis meant that researchers did not have time to wait for these disease mechanisms to be fully elucidated before beginning screening for drugs that could directly treat or alleviate the symptoms in COVID-19 patients.

Dr Philip Gribbon, Head of Innovation Area Drug Screening & Compound Repurposing, and his colleagues at Fraunhofer ITMP are experienced in carrying out screening assays to identify compounds that can be repurposed. They understood that screening known drugs and drug analogs against SARS-CoV-2 would allow them to identify candidate compounds with the potential to be rapidly analyzed in *in vivo* efficacy studies, and ultimately clinical trials. Philip explained: “In January 2020, our collaborator – Professor Sandra Ciesek from the Institute for Medical Virology at University Hospital Frankfurt – had access to some of the first clinical isolates of the coronavirus in Europe, and established an assay to screen against the virus on a very short timescale. Working closely with Professor Ciesek, we then began screening Fraunhofer ITMP’s collection of over 5,500 bioactive compounds, including 3,000 clinical stage drugs, for their antiviral activity.”

The Fluent Automation Workstation in use in the laboratory at Fraunhofer ITMP



The workflow for the original assay was a collaborative effort, as Philip described: "Our laboratory uses a Fluent® Automation Workstation to run high throughput screening assays, as this system offers the precision and flexibility that we need to run complex assays in a 96-well, or even 384-well, format. We wanted to capitalize on these capabilities in the fight against the virus, and so we used the Fluent to plate out the compound libraries for the initial SARS-CoV-2 screen. At that point, we sent the plates to a biosafety level 3 (BSL-3) lab in Frankfurt for testing, as whole virus was used in the screening assay. This meant relatively complex plate logistics, due to the limited degree of laboratory automation in the BSL-3 environment but, within three months, we had published the first results online,[1] and eventually uploaded the primary data to ChEMBL and the Image Data Repository databases to assist global research efforts."

Since reporting these initial results, Philip and his team have continued to develop new assays and partner with labs around the world to further our understanding of the virus. Philip added: "Our Fluent platform has been working hard on COVID-19 screening over the last year. We're still using it to support compound plate logistics – for example, we recently shipped 10,000 compounds to a collaborator to screen against the SARS-CoV-2 spike protein – as well as using the system to run selectivity assays and target-based screens against some of the main viral entry and replication-associated targets. We are adapting the Fluent to perform screens using lentiviral infection systems developed by our collaborators at the University Clinic in Hamburg, which express the SARS-CoV-2 spike protein on the surface of lentiviral particles. This will allow us to characterize the effect of different spike mutations on viral entry efficiency and profile compounds or biological-based inhibitors. Some of these assays are highly automated, so the Fluent has certainly proved adaptable to many different workflows."

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All of the data on COVID-19 generated by this research has been made public to support the global community in combating the virus. Philip continued: "We work closely with the teams in the European Bioinformatics Institute and the ELIXIR Research Infrastructure, who set up the EU's COVID-19 data portal. We've tried to be as open as possible about the data that we've been able to generate. For the cell-based assays, we've reported the activities in ChEMBL but, rather than just giving a percentage effect or IC_{50}, we've uploaded the primary image data for the entire screen into a data repository. This means scientists on a global basis can reanalyze the data, and generate additional hypotheses or insights. We're also working with the European Open Science Cloud and the European Commission to use the methodologies we've established for our datasets to help other groups to mobilize their data towards public resources."

Antivirals to treat COVID-19 will be an important part of beating the disease. They serve to support vaccination programs, especially since vaccines are typically not 100 percent effective at preventing the disease, and there is still the risk of new variants emerging that may evade vaccine protection. Drug repurposing efforts allow candidates to be quickly identified and taken into Phase II and III clinical efficacy trials, while potentially reducing the need for the extensive Phase I safety testing normally necessary with novel compounds. Philip concluded: "The high throughput, flexible automation offered by the Fluent platform has supported this effort, and will continue to be invaluable in drug screening, not just for COVID-19, but for a host of diseases. The urgent need created by this pandemic has really identified new areas in which lab automation could prove invaluable in the future."

1. Ellinger, B. *et al.* A SARS-CoV-2 cytopathicity dataset generated by high-content screening of a large drug repurposing collection. *Sci Data*, 2021, **8**,70.

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