

NEWS IN BRIEF

COVID-19 vaccines start moving into advanced trials

Vaccine developers have advanced ten COVID-19 candidates into the clinic, less than 6 months since the SARS-CoV-2 virus was first sequenced. Leading candidates include an adenovirus-based candidate that is in a phase IIb/III trial and an mRNA vaccine that is in a phase II trial.

The University of Oxford and AstraZeneca's AZD1222, currently the most advanced COVID-19 vaccine candidate, consists of a chimpanzee adenovirus vector that has been engineered to carry the SARS-CoV-2 spike protein. Investigators hope that this vaccine will train the immune system to generate neutralizing antibodies against the spike protein, which the virus uses to bind and enter human cells. The immunogenic properties of the adenovirus vector could boost the potency of this approach. A 10,000-volunteer phase IIb/III trial is already underway in the UK, and a

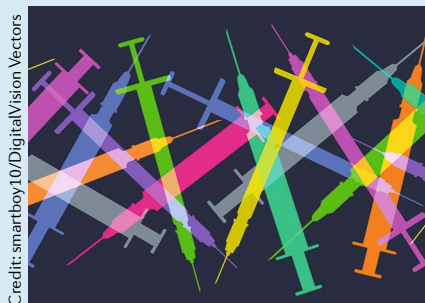
30,000-volunteer trial is planned for the USA this summer.

Moderna's mRNA-1273 is a **nucleotide-based vaccine**. A lipid nanoparticle carries the mRNA for the spike protein into cells, where it is then translated to provide an antigen for the immune system. A **phase II trial** of the vaccine is currently recruiting 600 volunteers.

No adenoviral vector or nucleotide vaccines have yet been approved by regulators in the USA or EU, however. **Other candidates** in clinical and preclinical development include protein subunit vaccines, which rely on purified spike protein to elicit an immune response, and whole-virus vaccines, which use weakened or inactivated forms of SARS-CoV-2 to confer protection.

Some vaccinologists are optimistic that hundreds of millions of doses of vaccines could be available for use within 18 months, or sooner. The USA's Operation Warp Speed, for instance, is aiming for 300 million doses of a COVID-19 vaccine by January 2020. But, the historic precedent is daunting. The average development time for a vaccine is more than 10 years, and the probability of market entry for a preclinical candidate is 6%, found an analysis of **vaccine development** from 1998–2009.

Asher Mullard



Credit: smartboy10/DigitalVision Vectors

First antibody against COVID-19 spike protein enters phase I

Eli Lilly and partner AbCellera have advanced a pioneering antibody against SARS-CoV-2's spike protein into a phase I trial, the first clinical trial of a drug designed specifically to act against the virus that causes COVID-19.

LY-CoV555 initially emerged from a partnership between the NIAID and AbCellera. The partners screened a blood sample from a US patient who had recovered from COVID-19 for promising antibodies. AbCellera subsequently teamed up with Lilly to improve its ability to test and manufacture any resulting candidates. LY-CoV555 aims to prevent the virus from attaching to and entering into human cells, neutralizing the virus and potentially treating and even preventing COVID-19.

The partners anticipate results from the 40-participant phase I safety trial later this month. If safe, they will test the antibody in phase II trials in non-hospitalized COVID-19 patients, as well as in a preventive setting, in vulnerable patient populations. Lilly is also

developing other neutralizing antibodies against SARS-CoV-2, and anticipates testing its candidates as both single agents and in antibody cocktails.

Multiple other companies are advancing their own spike-targeting, neutralizing antibodies. Regeneron is aiming to start a phase I trial of its two-antibody cocktail REGN-CoV2 in June; Celltrion plans to move its CT-P59 into phase I in July; GlaxoSmithKline and Vir plan to bypass phase I, with a phase II trial in July; and Amgen and Adaptive Bio are also working on virus-neutralizing antibodies.

The FDA has only approved one virus-targeting antibody to date — green lighting palivizumab for the prevention of respiratory syncytial virus in 1998. Two antibody-based candidates recently **reduced mortality from Ebola virus**, however. One of these, Regeneron's REGN-EB3, is currently being reviewed for approval by the FDA.

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Targeted degraders clear first safety hurdles

Arvinas's pioneering protein degrader ARV-110 appears generally safe and showed hints of efficacy in preliminary phase I data reported at ASCO in May.

ARV-110 is a bifunctional compound that drives target removal, rather than inhibition, by binding the androgen receptor (AR) with one arm and an E3 ubiquitin ligase with another. This results in the ubiquitination of AR and its subsequent degradation by the proteasome. Arvinas advanced this drug **into a phase I trial** for the treatment of prostate cancer last year. Industry is watching closely, owing to the growing interest in the **targeted degrader modality**.

Arvinas's update on ARV-110 consists of preliminary data from **22 patients** in this first trial. The company said the drug has a "favourable safety profile". Two patients suffered from serious or life-threatening increases in liver enzyme levels, but the company linked both of these to an interaction between ARV-110 and the lipid-lowering agent rosuvastatin. The company has since disallowed use of rosuvastatin in the trial, and it does not believe this safety signal is likely to be a class effect.

The data also hinted at efficacy. In a subset of seven patients with degradable forms of AR, two patients responded to treatment. Both patients had the same mutations in their AR. "For ARV-110 to show signs of efficacy in these patients at this early stage of development is strong validation of our PROTAC technology," said Arvinas CEO John Houston.

This efficacy signal was not as strong or broad as investors were hoping, however. Share prices fell nearly 30% on the release of Arvinas's data.

The trial is ongoing, and Arvinas anticipates another update by the end of the year. The company's ARV-471, an estrogen receptor degrader, is also in phase I development.

Separately, Bristol Myers Squibb reported that its imide drug CC-92480 showed promise **in a phase I** multiple myeloma trial. Imides, acquired by BMS in its US\$74 billion purchase of Celgene last year, are serendipitous degraders: the mechanism of action of lenalidomide and pomalidomide was not well characterized when they were originally developed by Celgene, but research since has shown that these agents bind the E3 ligase cereblon, increasing the enzyme's ability to tag the transcription factors Ikaros and Aiolos with ubiquitin for degradation. With CC-92480, researchers set out **to explicitly optimize** the degradative properties of this molecular glue.

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