BIOCENTURY

APR 2, 2020 | 5:48 PM PDT

Updated on Apr 3, 2020 at 1:47 PM PDT

COVID-19: MANUFACTURING MABS IN PATIENTS

The urgency and scale of the coronavirus outbreak could drive progress in an emerging therapeutic strategy suited to rapid development and distribution -- encoding of antibodies in RNA or DNA.

Neutralizing mAbs against SARS-CoV-2 have arisen as a leading approach among companies designing preclinical therapies for COVID-19. At least 20 groups have disclosed mAb programs (see **"COVID-19 Therapies and Vaccines: Preclinical"**).

Manufacturing is anticipated to be a bottleneck, however, both because of the scale of the outbreak and the 18 months or more it can take to optimize mAb manufacturing.

Two teams are taking a different approach: encoding the therapies in nucleic acids and letting patients' cells produce the antibodies *in vivo.*

Neurimmune Therapeutics AG teamed up with Ethris GmbH Wednesday to develop an mRNA-encoded anti-SARS-CoV-2 antibody that can be administered via inhalation. On Monday, Vir Biotechnology Inc. (NASDAQ:VIR) partnered with Generation Bio Co. to use Generation's close-ended DNA (ceDNA) platform to encode a neutralizing antibody.

Manufacturing nucleic acids is cheaper and easier than proteins, and the nucleic acid products are stable at room temperature, which avoids the need for cold chain distribution.

The concept of encoding a mAb in nucleic acids is not new, but so far has not seen broad uptake. The most advanced program is RGX-314 from RegenxBio Inc. (NASDAQ:RGNX), an AAV8 vector encoding a VEGF-inhibiting antibody fragment in Phase I/II testing for wet age-related macular degeneration (see **"The Quiet Disrupters"**).

Other RNA- and antibody-focused companies, such as Adverum Biotechnologies Inc. (NASDAQ:ADVM) and Moderna Inc. (NASDAQ:MRNA), are also working on encoded therapies alongside their main programs.

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Roger Nitsch, Neurimmune

The need for rapid response in the pandemic could create an opportunity for advancing the technology, possibly pushing it to approval for COVID-19 before any other indication.

A similar situation has arisen on the vaccine side of COVID-19 development, where at least 10 groups are encoding viral antigens in RNA. Like RNA-encoded antibodies, RNA vaccines have yet to receive regulatory approval, but last month, Moderna's mRNA-1273 became first COVID-19 vaccine of any modality to enter the clinic, demonstrating the speed of the approach. The first clinical batch of mRNA-1273 was delivered 42 days after the virus' genome was released; design and manufacturing took 25 days.

NEURIMMUNE AND ETHRIS

Neurimmune is pairing its mAb discovery platform with the mRNA capabilities of Ethris. The partners plan to begin clinical testing in 4Q20.

Neurimmune will screen the blood of recovered COVID-19 patients for neutralizing antibodies using its Reverse Translational Medicine platform, which analyzes healthy immune responses to disease-related proteins (see **"Reversing Forward"**).

Neurimmune's most advanced program from the platform is the anti-β amyloid mAb aducanumab, which Biogen Inc. (NASDAQ:BIIB) is developing for Alzheimer's disease.

Neurimmune President and CEO Roger Nitsch told BioCentury the company felt a responsibility to use its platform to identify antibodies to treat COVID-19, but "given the timeline in antibody GMP manufacturing to make candidates -- 18 months or longer -- we realized, given the urgency of the problem, we can't work with timelines like that."

Instead of developing a standard mAb therapeutic, Neurimmune reached out to Ethris, which Nitsch said can manufacture its mRNA-encoded antibodies in four to five months. The partners will jointly conduct R&D and share costs and revenues.

Neurimmune is in the process of screening recovered patients for anti-SARS-CoV-2 antibodies that are selective for the virus and don't cross-react with human proteins or tissues. The company plans to test the mAbs it selects in virus neutralization assays before handing the candidate to Ethris.

Ethris CEO Gita Dittmar told BioCentury that once the company has an antibody sequence, creating an mRNA molecule is rapid because the process doesn't require cell line development. She said the company can go from *in silico* design to mRNA in four to six weeks. Ethris has contracted with a CMO for GMP manufacturing.

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Gita Dittmar, Ethris

Because of its focus on rare genetic pulmonary diseases, Ethris delivers its mRNA constructs within nanoparticles as an inhaled aerosol formulation, which enables the mAbs to be expressed directly in the lungs within six hours of inhalation.

The delivery mechanism is ideal for treating COVID-19, Dittmar said, because the lungs have a high viral load.

"Neutralization and elimination of the virus in that organ could have a significant effect on the patient's course of disease," she said.

Nitsch said that it is parallel tracking development and manufacturing activity; the companies are speaking with manufacturers and have engaged with both FDA and EMA to plan clinical trials so they can move quickly to the next stage.

Though there are no approved RNA-encoded antibodies, Dittmar said she doesn't foresee any regulatory hurdles, citing the several mRNA products already in the clinic and the approval of two of siRNA therapies from Alnylam Pharmaceuticals Inc. (NASDAQ:ALNY), Onpattro patisiran and Givlaari givosiran.

"The components are things regulators are familiar with," Dittmar said. "It'll be a matter of safety and efficacy profiles of each specific product that gets brought forward."

VIR AND GENERATION BIO

By partnering with Generation Bio, Vir adds a third modality to its COVID-19 attack plan.

Vir expects to begin Phase I/II testing of two mAbs against SARS-CoV-2 in three to five months. The company is also partnered with Alnylam to develop siRNA therapeutics for COVID-19.

Vir told BioCentury that it was interested in Generation Bio's ceDNA technology to combat COVID-19 because it could enable antibody expression in the body for several years.

A mAb therapeutic, on the other hand, would require re-dosing every three to six months to maintain immunity, a Generation Bio spokesperson told BioCentury. "This presents logistical challenges in requiring re-access to all patients and sustained manufacturing capacity to support the repeated treatment of millions of patients globally."

Generation Bio declined to disclose a timeline for the encoded COVID-19 therapy, which will be developed by applying its non-viral gene therapy platform to an antibody Vir isolates from a recovered patient.

The biotech's technology comprises ceDNA, which is stably maintained in the cells but less likely to integrate into the host genome than viral vectors. The ceDNA is delivered in lipid nanoparticles (see **"Crossover Investors Help Generation Bio Land $110M Series C"**).

"This technology, coupled with Vir's potent neutralizing antibodies, has the potential to provide effective, long-lasting protection against SARS-CoV-2," the spokesperson said.

"The components are things regulators are familiar with."

Gita Dittmar, Ethris

Another draw of Generation Bio's platform is its scalable, GMP-ready manufacturing process, which could extend the reach of Vir's mAbs to as many as millions of patients, the spokesperson said.

Unlike Ethris' inhaled technology, which enables the production of antibodies within the lungs, Generation Bio's antibodies will be produced in the liver.

The company has preclinical data showing that its technology can express antibodies within the liver at or above the serum levels required for antibodies to be effective.

Generation declined to comment on the regulatory path for its ceDNA-encoded antibodies.

Not everyone believes that the regulatory pathway will be smooth for DNA- and RNA-encoded antibodies.

AbCellera has a four-year $30 million contract from the Pandemic Prevention Platform (P3) of HHS' Defense Advanced Research Projects Agency (DARPA) to apply its antibody discovery platform to viral pandemics (see **"DARPA's Gambles Might Have Created the Best Hopes for Stopping COVID-19"**).

P3 includes nucleic acid-encoding antibody technology, and aims to develop platforms that can respond to an infectious outbreak within 60 days.

Ester Falconer, head of R&D at AbCellera, told BioCentury that while RNA- and DNA-encoded antibodies would be faster to manufacture and easier to distribute than protein versions of the therapies, the approach is not far enough along to meet the agency's goal for the COVID-19 pandemic.

"In this scenario, you want to be able to go through a path of least resistance to get the treatment out to patients as fast as possible. So that means the traditional protein route for us and our partners," Falconer said.

Further analysis of the coronavirus crisis can be found at ***https://www.biocentury.com/coronavirus****.*