CureVac sues BioNTech over mRNA technology

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A new front has opened in the patent battle over the breakthrough mRNA technology. CureVac in July filed suit in the German Regional Court against BioNTech, seeking fair compensation for infringement of four patents CureVac claims are used to make Comirnaty, the coronavirus vaccine developed and sold by BioNTech and its partner Pfizer. The Tübingen, Germany–based CureVac, whose own mRNA vaccine stalled a year ago after showing just 47% efficacy against COVID-19 in a late-stage trial, said it was not seeking an injunction, nor did it intend to halt the manufacture, sale or distribution of Comirnaty. CureVac's intellectual property portfolio, accumulated over more than 20 years of work in mRNA technology, protects several inventions the company considers foundational to the design and development of BioNTech's mRNA COVID-19 vaccine, including those relating to the engineering of mRNA molecules — sequence modifications to increase stability and enhance protein expression — as well as mRNA vaccine formulations specific to SARS-CoV-2 vaccines. "Many years of our research have also contributed to the success of the mRNA vaccines and made that possible," says CureVac CEO Franz-Werner Haas. "From our point of view, it is self-evident to respect the associated property rights." In response, BioNTech posted a statement on its website that read, in part: "BioNTech's work is original, and we will vigorously defend it against all allegations of patent infringement."

mRNA vaccine maker Moderna is also fending off lawsuits over its COVID-19 vaccine from Alnylam Pharmaceuticals, Arbutus Biopharma and Genevant Sciences.

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mRNA printers kick-start personalized medicines for all

mRNA printers will bring low-cost vaccines and made-to-order treatments for a range of different diseases.

South Africa is setting up mRNA manufacture with new technologies that will ensure vaccines and therapeutics can be made locally and cheaply. Cape Town–based Afrigen joined forces with Belgian firms Univercells and eTheRNA. And the US-based Greenlight Biosciences is about to start a clinical trial of an mRNA vaccine in South Africa, to test a vaccine that will cost about $1 per dose—a fraction of the price of other mRNA vaccines.

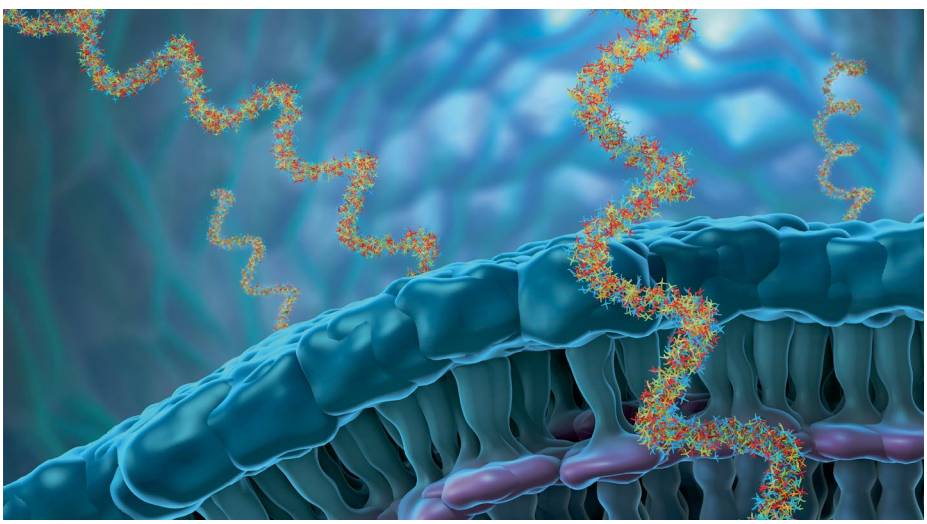
The first wave of COVID-19 vaccines came about as many biopharmaceutical firms pivoted in response to the threat. But during the initial vaccine rollouts, many low-income countries were all but abandoned, highlighting the huge gaps in global supply chains and manufacturing capabilities. "mRNA got done in one year. That's the life cycle of a new product from Apple," says Rahul Singhvi, CEO of Resilience, a biomanufacturing company established in 2020 as an explicit response to the pandemic by investor Robert Nelsen, at Arch Partners.

Yet mRNA manufacturing has not kept pace with innovation—companies often rely on "antiquated approaches," Singhvi says, as they have neither the time nor the resources to invest in better alternatives. At best, they are adding incremental improvements to out-of-date processes, and "that's never going to move the needle." Resilience has raised over $2 billion in equity financing and has big ambitions to put biomanufacturing on a similar footing to semiconductor manufacturing.

Elsewhere, a new wave of biotechs are pursuing plug-and-play approaches. Among them Nutcracker Therapeutics and Creyon Bio are incorporating automation, continuous-flow manufacturing and biochip-based microfluidics devices to accelerate the next cycle of mRNA innovation.

The goal goes beyond manufacturing at lightning speed. An mRNA printer, as popularized by vaccine developer CureVac, could make personalized point-of-care mRNA therapies affordable for more patients around the globe than at present. Although the technology to has yet to be realized, a new era of low-cost on-demand clinical-grade RNA is imminent.

Dan Gibson, chief technology officer at Codex DNA, argues that this is already a reality in research settings. While he was at Synthetic Genomics, Gibson and colleagues, including J. Craig Venter, developed an automated digital-to-biological converter to produce nucleic acids and proteins directly from DNA sequence information. Codex DNA was later spun out to commercialize



mRNA production in the cell is emulated by plug-and-play printers. Christoph Burgstedt / Alamy Stock Photo.

the technology. The resulting BioXP system does not require externally supplied templates, but it generates multiple oligomers, from which it assembles full-length DNA or mRNA sequences as required. In contrast, most mRNA-based vaccines and therapies still rely on externally sourced plasmid DNA.

BioXP users still have to order a reagent kit when they want to generate a given molecule, but Codex DNA is about to introduce a new high-throughput version of the instrument that will allow on-demand printing. Users can build oligo sequences up to 100 base pairs long from a library of shorter, pre-manufactured DNA building blocks made by DNA synthesis technology known as SOLA (for short oligo assembly ligation). The oligos can then be assembled into full-length genes or mRNA molecules, says Gibson, "any time of the day, any day of the week." Pfizer signed an early access agreement with Codex earlier this year, which will allow it to employ the SOLA technology to accelerate mRNA vaccine research and development. (It has also licensed rights to use Hampton, UK–based Touchlight Genetics's doggybone DNA technology for rapid production of template DNA.) Although the nucleic acid molecules generated by the BioXP system are high fidelity, they are not good manufacturing practice (GMP) compliant.

Nutcracker Therapeutics is building a GMP capability into its miniaturized 'GMP-in-a-box' platform for manufacturing low-volumes of therapeutic mRNA molecules. Its focus is on low-volume and personalized oncology therapies, for which existing large-scale mRNA production capacity is not appropriate. The company expects to be producing clinical-grade material for human trials by next year. Its 'Nutcracker Manufacturing Unit' (NMU) relies on single-use microfluidic biochips for each of the three key steps needed to make mRNA: template generation from an externally supplied synthetic DNA sequence, in vitro transcription and lipid nanoparticle formulation of the final product. The entire workflow is monitored by video, and multiple parameters, including yield and impurities, are evaluated in real time. "Once the chip gets loaded into the system, it's a completely closed path," says Samuel Deutsch, Nutcracker's executive vice president of research and early development.

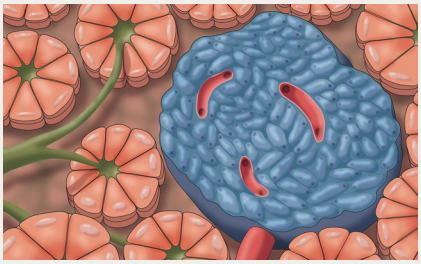
To be fit for the clinic, mRNA molecules generated in this fashion will need regulatory blessing. Upcoming discussions with the US Food and Drug Administration about the company's first investigational new drug filing, for NTX-0250, an RNA therapeutic targeting herpes simplex virus–driven cancers, will therefore have an important bearing on the technology's immediate future. "That will be the litmus test of what the FDA thinks of our technology," says Geoff Nosrati, Nutcracker's chief business officer. The integrity of the software that controls production is an important part of Nutcracker's case, says Deutsch. Access to GMP-grade reagents has also proved challenging. "We've had to break ground in some of these areas," says Nosrati.

Small-scale mRNA production is also in Creyon Bio's sights. The biotech is building a platform that can rapidly manufacture oligonucleotide-based medicines for small populations, such as patients with rare diseases. A key element of its approach is integrating an understanding of the physicochemical properties of oligonucleotide molecules with their sequence-determined biological attributes. Both, ultimately, influence the pharmacological properties of a given molecule, but the range of possibilities in any given scenario is so vast, particularly when chemical modifications are added, that screening is an impossible task. The company could ultimately offer point-of-care drugs to those newly diagnosed with a rare disease. "We see that as a real possibility," says Creyon Bio's cofounder and CEO Christopher Hart. The company's chief medical officer David Dimmock pioneered whole-genome sequencing to diagnose critically ill children at San Diego's Rady Children's Institute for Genomic Medicine. Adding an instrument that would print an appropriate drug therapy on demand would provide obvious benefits. "What's missing is what to print," says Hart.

The collaboration between Afrigen, Univercells and eTheRNA has the opposite goal: it aims to put in place large-scale mRNA manufacturing capacity in regions where it is currently absent. The planned product will be the first African-owned COVID-19 vaccine and a potential rival for the established mRNA vaccines, but there is a wider significance attached to the initiative. Afrigen is mandated to make the manufacturing process available to vaccine producers in more than 15 other countries, as part of its commitment to lead the World Health Organization's first mRNA technology transfer hub. If successful, this project could make a significant contribution to reducing the yawning gap between wealthy countries, which can readily afford the existing mRNA vaccines, and low-and-middle-income countries, which cannot.

Key to the Africa-wide initiative is a highly automated, low-cost manufacturing platform, which Charleroi, Belgium–based Univercells has developed with the help of

Vertex snaps up diabetes stem cell rival



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Vertex Pharmaceuticals has bought Viacyte to expand its type 1 diabetes (T1D) islet cell therapy pipeline. The $320 million cash takeout is an attempt to accelerate Vertex's own stem cell-based cell replacement therapy pipeline for type 1 diabetes (T1D). The deal, expected to close later this year, comes with ViaCyte's drug candidates, human stem cell lines, cell manufacturing facilities and intellectual property, as well as Viacyte's novel hypo-immune gene edited cells.

Vertex first stepped into the T1D stem cell arena in 2019 when it paid $950 million for allogeneic stem-cell product VX-880 from Semma Therapeutics. In unpublished results from one patient treated with VX-880, Vertex reported a dramatic 91% reduction in the need for insulin.

Viacyte's own stem cell derived islet cell therapy, PEC-Direct (VC-02), where the cells are implanted within a pouch that allows vascularization, also demonstrated proof of concept in a single patient, reducing the need for exogenous insulin and improving blood sugar levels. Both VX-880 and VC-02, however, require immunosuppression.

The ideal product would be made up of hypo-immune cells that engraft and survive for long periods without being attacked by the patient's immune system. To this end Viacyte and CRISPR Therapeutics have produced VCTX210, which uses the same device as VC-02 but with genetically edited cells. Vertex and Arbor Biotechnologies are also exploring gene editing alternatives to Cas9.

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funding from the Bill and Melinda Gates Foundation. Its cell-free production platform involves capital expenditure and running costs that are a fraction of those needed for current approaches. By establishing a continuous-flow manufacturing process, which eliminates the need for intermediate storage, the company has been able to reduce the footprint of an mRNA manufacturing suite to about 4 square meters. Yet a system operating at full capacity is capable of producing 2–3 million vaccine doses per week, says José Castillo, co-founder of Univercells and CEO of its RNA platform subsidiary Quantoom Biosciences. A proprietary single-step purification process also contributes to its efficiency. "Each time you purify something you lose something," he says. The system comprises three modules, for PCR amplification of linearized plasmid DNA, in vitro transcription of the template and formulation of the resulting mRNA into lipid nanoparticles. The latter module is not yet completed, and Niel, Belgium–based eTheRNA is providing that element of the process to the Afrigen collaboration. The three modules can be integrated into one end-to-end system but are kept separate for now, to allow quality-control assessment of the amplified DNA before the transcription step.

CureVac, of Tübingen, Germany, has also added automation to its cell-free RNA printer system, with the help of its partner Tesla Automation (formerly Grohmann Engineering), a decades-old German engineering automation firm that Tesla acquired in 2017. This system, too, occupies a small footprint, but that has been a secondary consideration, says Markus Bergmann, the newly appointed general manager of CureVac RNA Printer, a wholly owned subsidiary of CureVac. "The primary target has been the automation." Transcription takes place in an egg-shaped chamber, in which DNA templates immobilized on free-floating magnetic beads undergo several rounds of transcription. This reduces the amount of DNA template required to produce large quantities of mRNA—and reduces or even eliminates the need for the DNase digestion step required in standard approaches.

CureVac expects to start printing mRNA for clinical trials next year. "We are currently working on the requirements that have to be fulfilled," Bergmann says. "We have to show comparability with existing processes and existing production lines." It is initially seeking a manufacturing license from its home region's local authority, the Regierungspräsidium Tübingen, which will allow it to produce defined mRNA molecules. It will then seek GMP certification from the Langen-based Paul Ehrlich Institute, Germany's drug regulator, and from the European Medicines Agency in Amsterdam. The company is not yet disclosing the likely capital cost of a printer or the cost of goods of the molecules it will produce. "In the end, we need to be competitive," says Bergmann.

Greenlight Biosciences uses cell-free microbial lysates to manufacture mRNA. The company has adapted its inexpensive small interfering RNA production technology for insect and fungal pathogen control in agriculture and apiculture to human health applications. "We use microbial strains to produce the building blocks of RNA," says cofounder and CEO Andrey Zarur. Enzymes added to the microbial lysates digest the RNA to generate nucleoside monophosphate monomers. Heat inactivation eliminates the externally added and endogenous nucleases present in the lysate, which are then converted into ribonucleotide triphosphates by a series of thermostable kinase enzymes. The reactions are energized by polyphosphate kinase enzymes isolated from extremophile bacteria living in oceanic hydrothermal vents, which can use inorganic phosphate to produce ATP. "We're reconstituting a primordial soup that has been optimized for industrial production," says Zarur. Polymerization to form full-length mRNA molecules is then directed by an externally supplied DNA template. The company has produced GMP material and, as *Nature Biotechnology* went to press, was about to start a phase 1 clinical trial. It has teamed up with Incheon, South Korea–based Samsung Biologics, in order to scale the process. It has also entered a pact with the Pune-based Serum Institute of India to develop an mRNA vaccine for shingles.

Not all of these approaches will necessarily prove to be successful or competitive, but those that do will strengthen the collective response to future crises. Should another pandemic virus emerge, the world will be a different place from the one across which SARS-CoV-2 started to spread in late 2019. Given the level of human suffering and death that resulted, it needs to be. ❐

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