mRNA made in Africa

BioNTech, the drug company that produced an mRNA vaccine for COVID-19 with Pfizer, has developed a new type of vaccine factory for Africa. The biotech has miniaturized all the processes needed to manufacture mRNA vaccines into a modular unit. The factory, made up of two groups of six 40-foot containers, can be loaded on trucks, planes, boats or trains. Once on site, the so-called 'bioNTainer', containing the 50,000 steps needed to manufacture a mRNA vaccine, can be assembled for plug-and-play manufacturing. The first containers will arrive in Rwanda and Senegal in the second half of 2022 and potentially also in South Africa.

About 99% of Africa's vaccines against all diseases are imported. BioNTech's CEO and co-founder Ugur Sahin hopes the containers will address the manufacturing problem for COVID-19 vaccine production and, in the future, easily adapt to encode new variants, or to manufacture tuberculosis, malaria and cancer vaccines. When fully operational, each unit can produce up to 50 million doses a year following 'good manufacturing process' standards. 'BioNTech's modular production system opens up a new horizon for global vaccine equity," said Paul Kagame, president of the Republic of Rwanda. The Mainz, Germany-based biotech will make the vaccines available at cost and on a non-profit basis, and plans to collaborate with partners "to ensure it is affordable for people in African countries," said Sahin at a press conference announcing the prototype container module. BioNTech is working with the World Health Organization (WHO) to complement its existing mRNA technology transfer hub in South Africa, and the European Union has pledged a $170 billion investment package in Africa.

Also in February, Afrigen Biologics & Vaccines, a WHO-backed tech transfer consortium in South Africa, announced that it has nearly completed its own version of Moderna's mRNA COVID-19 jab. The African vaccine will be manufactured using publicly available sequences and will not include assistance from Moderna. It will enter clinical trials in the fourth quarter of this year.

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and readthrough drugs — were yielding better results in mice at the time, and his team, like most others in the field, dropped the tRNA approach.

Research progress into tRNA therapeutics stalled. Attention shifted to retooling tRNAs to incorporate non-standard amino acids as a way of making recombinant protein therapeutics with new properties. And early patents around the therapeutic use of suppressor tRNA were never licensed or developed further.

The technology back then just "wasn't ready," says Charles Link, an early patent holder who now serves as chief medical officer and executive chairman of Syncromune, an immuno-oncology startup. "At the time, it was hard to conceive of how you could get effective enough delivery and high enough amounts" of suppressor tRNA expression to bring about meaningful clinical benefit.

Even as recently as 2014, when researchers in Portugal showed that suppressor tRNAs held potential for treating or preventing hereditary cancer syndromes caused by nonsense mutations, few investors or academics seemed to take notice. According to Carla Oliveira, a cancer geneticist at the i3S–Institute for Research and Innovation in Health in Porto who led the work, interest in her team's results was "marginal."

That soon began to change — although, for most companies, designing suppressor tRNAs was not the initial focus. Shape Therapeutics, for example, was founded on the work of Prashant Mali, a bioengineer at the University of California, San Diego, who had described and patented two ways of targeting point mutations found in RNA. One involved suppressor tRNAs, an approach the company is now pursuing for the treatment of Rett syndrome, a neurodevelopmental disorder caused by nonsense mutations in the *MECP2* gene. However, it was the other technology, one involving adenosine deaminase enzymes for editing RNAs, that has long been Shape's primary interest.

tRNAs were not initially Tevard's priority either. The company's origins trace back to a platform-agnostic desire to "reverse" Dravet syndrome — hence the name, which is Dravet spelled backward. And early considerations centered around base editing, which explains why Harvard University's David Liu, a pioneer of that technology, is a scientific advisor. But a 2017 encounter between Jeff Coller, an RNA biologist now at Johns Hopkins University, and Harvey Lodish, a cell and molecular biologist at the Whitehead Institute, changed the company's thinking. (Both are Tevard co-founders, along with CEO Daniel Fischer and board chair Warren Lammert, who launched the company for highly person reasons: both men have daughters with Dravet syndrome.)

Coller had shown that the balance between codon abundance in a particular gene transcript and the concentrations of corresponding tRNAs in the cell — a concept known as codon optimality — can greatly change the expression levels of proteins. He and Lodish realized that Tevard could harness that knowledge to develop what it calls 'enhancer' tRNA therapeutics for Dravet syndrome, a rare form of epilepsy mostly caused by heterozygous loss-of-function mutations in the sodium channel gene *SCN1A*. With a cocktail of three enhancer tRNAs, Fischer claims that the company can approximately double the productivity of the working copy of *SCN1A* in affected cells without dramatically altering the expression of other, non-target genes.

Because that enhancer therapy harnesses the potential of the functional gene copy, it could conceivably help all people with *SCN1A*-mutant Dravet syndrome, regardless of the specific defect in the other gene copy. But, as it turns out, both Fischer's and Lammert's daughters, like approximately 25% of all patients with Dravet, harbor premature stop mutations in their *SCN1A* genes — which makes them candidates for a suppressor tRNA approach as well. Tevard is advancing both strategies in partnership with Zogenix, a company that specializes in epilepsy drugs and that will soon be part of Brussels-based UCB under a $1.9 billion buyout plan announced in January.

To enable its suppressor tRNA program, Tevard licensed intellectual property connected to a 2019 paper from Christopher Ahern and his former postdoc John Lueck, who had built a library of hundreds of anticodon-edited tRNAs, dubbed ACE-tRNAs, each capable of suppressing premature termination codons and faithfully incorporating desired amino acids instead. "We covered every known tRNA that could be used as a suppressor in human disease," says Ahern, a molecular physiologist at the University of Iowa in Iowa City who now advises Tevard. (Ahern is also a scientific cofounder of hC Biosciences, which licensed his patents for other applications.)

Ahern and Lueck, in collaboration with Skach from the Cystic Fibrosis Foundation, also showed that ACE-tRNAs prompt only low levels of normal stop readthrough, thereby helping to alleviate one of biggest safety concerns associated with the therapeutic strategy. Other groups have