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We are yet to find out what kind of changes the world will see on the other side of the COVID-19 pandemic. Observers of an optimistic disposition have evoked the emergence of the Italian Renaissance after the Black Death as a precedent, but maybe we shouldn’t set our expectations too high.

One field that is bound to see a renaissance, however, is the development of RNA therapies. Based on their experience in this field, the companies BioNTech (Mainz, Germany, founded in 2008) and Moderna (Cambridge, USA, founded in 2010) both managed to develop mRNA vaccines against the coronavirus in less than 12 months, from sequencing the virus to regulatory approval (Curr. Biol. (2021) 31, R101–R103). Within six months, several hundred million doses of each of these vaccines had been administered.

Other pioneers in the mRNA field include the German companies CureVac and Ethris, as well as Translate Bio in the USA. CureVac, which Ingmar Hoerr co-founded in 2000 on the basis of his doctoral thesis suggesting ways to use mRNA for therapies, secured an early patent on the methodology and was a contender in the vaccine race but fell behind in the second half of 2020. Its vaccine candidate started phase III trials in December 2020 and is still expected to become available in the second half of 2021.

Now that the use of mRNA vaccines has been shown as safe and efficient on an unprecedented scale, these companies can build on the success to finalise and roll out some of the other RNA therapies that they have been developing for years.

The concept of RNA therapy emerged as an alternative to DNA-based gene therapy after early efforts in gene therapy had suffered setbacks, such as the death of Jesse Gelsinger in 1999 (Curr. Biol. (2014) 24, R83–R86). Given that RNA is short-lived and doesn’t interfere with the cell’s genome, the expectation was that there was less of a risk of unexpected long-term side effects, and that public opinion, which in many wealthier countries had turned against genetic manipulation in agriculture, would be more favourable.

The main worry with RNA is its poor stability, especially in a physiological context where ribonucleases are ubiquitous and the body may interpret an unexpected RNA molecule as a virus attack that needs to be eliminated. To address the latter problem, researchers have shown that replacing the uridine nucleoside with the isomer pseudouridine, a variant that also occurs naturally in stable RNAs such as transfer RNAs, protects the molecule from being eliminated as a viral threat. This is the ‘modified RNA’ idea that gave rise to the company name Moderna. The CureVac approach, by contrast, does not rely on these modifications. Instead, the company uses sequence design and different protective envelopes to ensure that the RNA reaches the cell intact.

Conversely, one can also conceptualise mRNA therapy as an alternative to protein therapeutics. It is often difficult to deliver a protein molecule in the correctly folded state, in the right amounts, at the right time and to the exact place in the body where it is needed. Instructing the relevant cell to make that protein may be an alternative, and this instruction can be delivered in the shape of mRNA. The main challenge, still, is how to get the mRNA into the cell safe and sound.

**Cancer hopes**

Apart from infectious diseases as targets for vaccines, cancer could be the most promising field for the application of RNA-based medicines, especially if general approaches are found that target cancer cells with better specificity than conventional chemotherapy. Before the race to develop COVID-19 vaccines made Moderna a household name, Ruchi Jain and colleagues at the company’s research facility developed an mRNA treatment using a modified construct based on the apoptosis mediator PUMA (p53 upregulated modulator of apoptosis) or on caspase-6 to kill the cells of liver tumours by triggering...
apoptosis (Nucleic Acid Ther. (2018) 28, 285–296). To protect healthy liver cells, they inhibited this Trojan horse mRNA via the mechanism of RNA interference (RNAi). For this purpose, they included in the mRNA a target sequence for miR122, a natural microRNA (miRNA) present in healthy liver cells but not in the tumour cells. While these experiments were conducted with rodents, RNAi mechanisms are highly conserved among mammals, suggesting that this can be readily transferred to medical applications in humans.

Like the mRNA vaccines developed in 2020, this RNA therapeutic was packaged in lipid nanoparticles. As these nanoparticles tend to find their way to the liver in any case, the researchers chose liver tumours as their initial target. Regardless of where such products are being applied later on, they will have to be made safe for liver cells.

Several of the companies in the field are following the strategy of ‘vaccinating’ the patient against specific markers found on their cancer cells. BioNTech co-founder Uğur Şahin and colleagues conducted a clinical study on 13 patients with melanoma and reported promising results (Nature (2017) 547, 222–226). The group describes the approach as characterising the specific ‘mutanome’ of a patient’s cancer and mobilising their immunity against this characteristic set of changes.

In February 2021, CureVac expanded its phase I clinical trial for an RNA-based cancer treatment that does not act as an mRNA but as an immune regulator, based on TLR (toll-like receptor) 7/8 and RIG-1 (retinoic-acid-inducible protein 1) activation. It is meant to induce the cancer cells to present antigens that alert the immune system. This candidate product, CV8102, is being tested against four types of cancer, including cutaneous melanoma, adenoid cystic carcinoma, squamous cell carcinoma of the skin and squamous cell carcinoma of the head and neck, both on its own and in combination with antibodies.

“Initial clinical data in cancer has demonstrated the ability of our RNA immunomodulator to trigger a systemic immune response attacking cancer not only at the site of injection but also in other areas of the body,” said Ulrike Gnad-Vogt, head of oncology at CureVac. “The CV8102 trial expansion is expected to provide further insights into clinical efficacy and mechanism of action in patients with advanced PD-1 refractory melanoma, an indication with a high unmet medical need. We are very pleased to see CV8102 progress to the next stage, an important step to further leverage the potential of immunostimulating RNA therapeutics in oncology.”

The company is also conducting a phase I/II clinical trial of a separate mRNA candidate, CV9202, which targets six antigens commonly expressed in non-small cell lung cancer.

mRNA meets medical needs
While RNA vaccines and cancer drugs are typically designed to stimulate or enhance the immune response, applications against autoimmune diseases such as multiple sclerosis (MS) require the opposite functionality. Uğur Şahin’s group at the University of Mainz has recently reported successful animal studies with an RNA vaccine against MS (Science (2021) 371, 145–153). The researchers used the mRNA of the protein targeted by the autoimmune response in MS. They delivered this mRNA to the dendritic cells of the immune system, which are responsible for defining which types of antigens the immune system should recognise as self, and which as foreign. When these dendritic cells present the MS antigen to the immune system, the T cells learn that they should not attack it. With their new approach, Şahin and colleagues were able to demonstrate that the T-cell activity against the MS antigen is indeed reduced in several animal models of MS.

The company Ethris at Planegg near Munich, Germany, is developing novel mRNA design and packaging in order to find treatments for respiratory diseases. The company’s core targets include COVID-19, influenza, pulmonary alveolar proteinosis (PAP), as well as primary ciliary dyskinesia (PCD). Of these development projects, only the COVID-19 therapy developed in partnership with the Swiss company Neurimmune has reached the pre-clinical phase. It is based on supplying mRNA coding for antibodies against the coronavirus directly to the lungs in order to reduce the disease’s impact on respiration.

In its early days, Ethris was also collaborating with Shire Pharmaceuticals (a British company taken over by the Japanese corporation Takeda in 2019) in an effort to find an mRNA treatment for cystic fibrosis. This project is now the main concern of a new company called Translate Bio based in Boston, USA. The company’s most advanced drug candidate, MRT5005, entered phase I clinical trials in 2018. It contains the mRNA for the membrane protein CFTR (cystic fibrosis transmembrane conductance regulator), mutations in
which can trigger symptoms of cystic fibrosis. The idea is that, by offering the mRNA for the intact protein, the treatment should work regardless of which mutation caused the disease. It is designed to be inhaled as an aerosol to reach the lungs directly. Further results of phase I/II reported in March 2021 confirmed that the treatment is safe but haven’t shown consistent patterns of improvement of lung function in the patients treated with several doses — in contrast to initial tests with a single dose, where some improvement was observed. Even though it is not the goal of phase I trials to test effectiveness of the treatment, the apparent lack of improvement may suggest that the approach isn’t performing as well as the developers had hoped.

The company is now aiming to fine-tune the treatment to make it more effective. It also has another, second-generation candidate against cystic fibrosis in its pipeline, as well as potential treatments for other lung diseases, including PCD and pulmonary arterial hypertension (PAH). In collaboration with Sanofi Pasteur, the company is also involved in developing mRNA vaccines and has a candidate vaccine against COVID-19 in clinical trials.

Although cystic fibrosis has been an early target for mRNA therapies, it is proving a challenging one. Rival companies Vertex and Moderna are also thought to have been working on similar therapies for several years but haven’t reported any clinical trials yet. James Dahiman at the Georgia Institute of Technology at Atlanta, USA, and colleagues have recently reviewed the options and challenges of developing RNA or CRISPR treatments for cystic fibrosis (Hum. Gene Ther. (2020) 31, 940–955).

In a study aimed at finding ischaemia treatments, the group of Keiji Itaka at Tokyo Medical and Dental University (TMDU), Japan, delivered the mRNA for the protein brain-derived neurotrophic factor (BDNF) to the brain, using a novel way of coupling the RNA with polymers forming micelles (Biomaterials (2021) 270, 120681). “By selecting polymers with particular properties, we can ensure the mRNA is released when and where it is needed,” first author, Yuta Fukushima, explained.

The BDNF protein itself does not cross the blood–brain barrier and thus cannot be given as a protein therapeutic. The researchers could show that, when they applied their mRNA treatment up to two days after an experimentally induced ischaemia in rats, the protein produced was able to protect the affected area from the damage caused by the lack of oxygen. If the mRNA nanomicelles were administered twice, two days and five days after the ischaemia, the benefits could be detected up to 20 days after the event. For instance, treated rats were shown to have better memory when tested in maze experiments.

The groups of Guangjun Nie and Hai Wang at the Chinese Academy of Sciences have developed yet another delivery vehicle for mRNA therapeutics. Aiming to develop a long-lasting immunotherapy against skin cancer, the researchers embedded the mRNA in a hydrogel material based on the egg protein ovalbumin (Nano Lett. (2021) 21, 2224–2231). While the usual lipid nanoparticles are normally degraded within two days, the researchers could show that the hydrogel can continue supplying the mRNA to the surrounding tissue for around 30 days.

Other medical applications of RNA include the use of antisense RNA to suppress the expression of a harmful protein. The start-up company Sutura based at Birkenhead, UK, for instance, uses antisense RNA combined with a peptide designed to deliver to the RNA site specifically to address genetic diseases. The company’s most advanced development project is a candidate treatment against Duchenne muscular dystrophy, currently in pre-clinical development.

The coming renaissance
Before the COVID-19 pandemic, the field of RNA therapeutics was rich with ideas championed by a small number of start-up companies, but very few of these progressed to clinical trials. The recent application of hundreds of millions of doses of vaccines containing mRNA in lipid nanoparticles has demonstrated that the approach is safe, viable and effective, at least against infectious disease.

Boosted by their newfound fame, cash flow and experience from this unprecedented product rollout, the companies involved are now in a much better position to turn many of their ideas into actual therapies. After the plague years, we can look forward to a renaissance of RNA-based medicines.