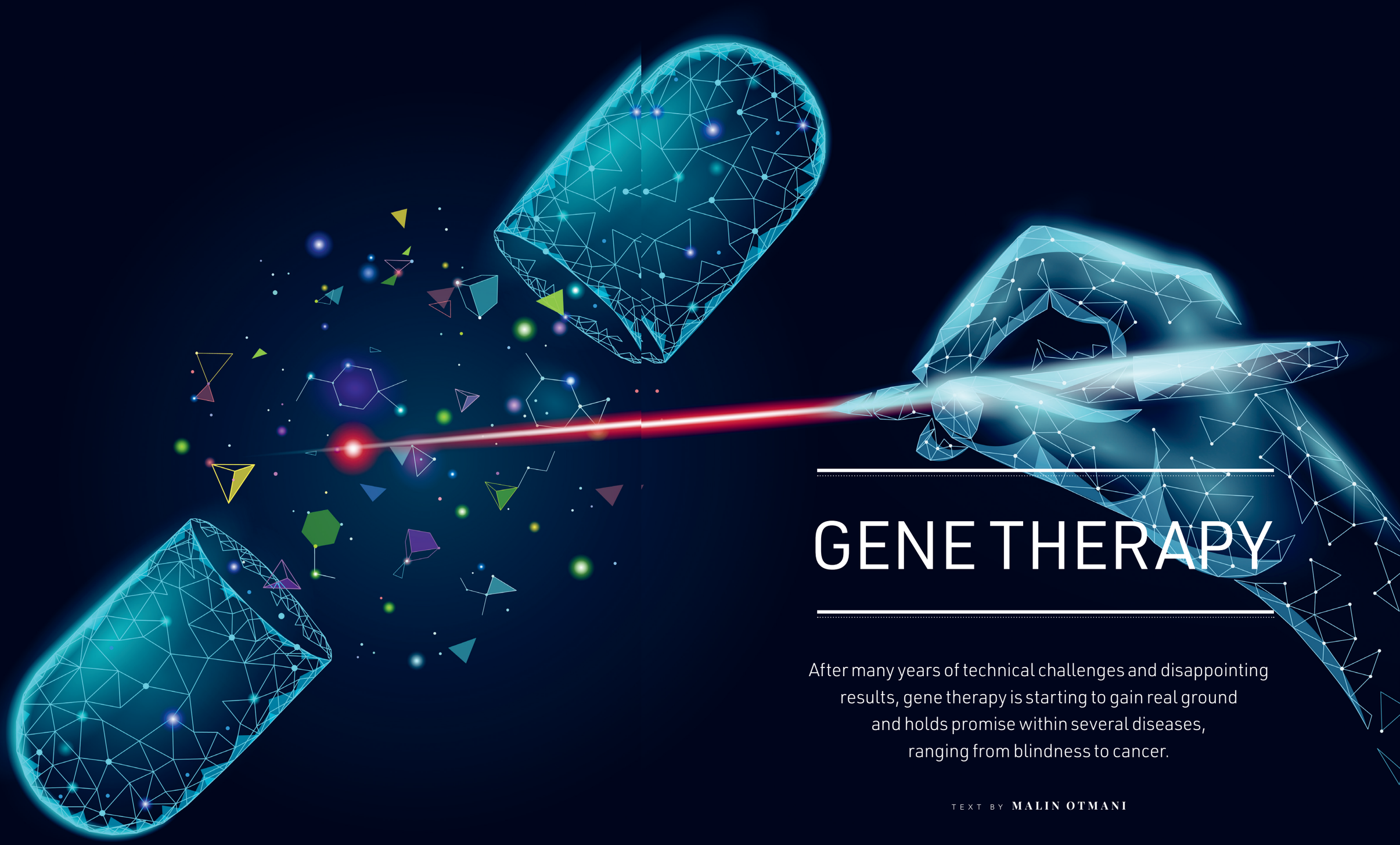


GENE THERAPY

After many years of technical challenges and disappointing results, gene therapy is starting to gain real ground and holds promise within several diseases, ranging from blindness to cancer.

TEXT BY **MALIN OTMANI**

MANIPULATING DNA to treat diseases was in the past equal to science fiction. Throughout the years advances have been made and today the field has had some real breakthroughs. The technology makes it possible to replace defective or missing genes and to give the body instructions on how to produce a specific substance by itself.

Somatic gene therapy can be divided into gene editing (correcting the cell's gene to fix the imbalance), gene replacement (replacing the faulty or non-working gene with a healthy copy of it), gene addition (adding novel genetic code to a different cell to help it combat the protein linked to the damaged gene), and gene inhibition (shutting down the faulty gene).

One hurdle that scientists have had to overcome is making sure a treatment gene zeroes in on the correct cells in the right tissue, and is shuttled into millions of these cells without disrupting the working order of neighboring genes. Another is ensuring that the inserted gene produces enough protein to have an impact. In addition, the therapeutic gene needs to ride in a delivery vehicle that can enter into cells without triggering a harmful reaction from the immune system (Conroy, 2022, Nature).

Laurent Décory, Chief Operating Officer, Aurealis Therapeutics

"When developing gene and cell therapies, massive scientific and medical capabilities, as well as huge investments are required, both for the companies that develop them and for the healthcare systems that have to fund or reimburse them," notes *Laurent Décory*, Chief Operating Officer at Swiss-Finnish company Aurealis Therapeutics. The Basel and Kuopio-based company has developed a cell and gene platform that is based on genetically modified lactic acid bacteria, which are able to synthesize and secrete therapeutic proteins – cytokines, growth factors, antibody fragments – directly in the body.

Choice of vector

Viruses have remained the main choice for delivering therapeutic genes to hard-to-reach cells and there are currently almost 300 clinical trials worldwide investigating viral-vector-based gene therapies (Conroy, Nature, 2022). Roughly half of these use modified adeno-associated viruses (AAVs), which are small viruses that do not cause disease in humans.

Aurealis Therapeutics, however, uses genetically modified lactic acid bacteria. "The advantage is that they have a very high yield, and are much cheaper to manufacture than viral vectors, skin substitutes or CAR T cell therapies for example," says Décory. "This makes me confident that we will be able to provide treatments for large patient populations, with very high cost-effectiveness for healthcare systems and payors."

Therapeutic areas

An area where gene therapy has made perhaps the most progress is within genetic eye disorders. Eyes are well suited for gene therapy because they are shielded from the destructive force of immune-induced inflammation. In 2017, Luxturna was the first in vivo gene therapy to be approved by the FDA. The treatment, developed by Spark Therapeutics, is a one-shot treatment for people with a harmful mutation in the gene RPE65, which causes severe vision loss.

Another disease where gene therapy has proven successful is within blood disorders. For example, earlier this year CSL's Hemgenix, was approved in the EU. It is the first and only one-time gene therapy for the treatment of severe and moderately severe hemophilia B in adults without a history of Factor IX inhibitors. In vivo gene editing using CRISPR aimed at treating sickle cell disease and beta thalassemia (both caused by heritable, single-gene mutations) also hold great promise for the future.

> *"This makes me confident that we will be able to provide treatments for large patient populations, with very high cost-effectiveness for healthcare systems and payors."*
>
> LAURENT DÉCORY

A third disease that has had recent progress with gene therapy is spinal muscular atrophy (SMA). In 2016 the FDA approved Spinraza, a therapy that does not incorporate itself into the genome but must be administered every four months to maintain protein production. Since then, more than 10,000 people have been treated with it worldwide.

Cancer and CAR T cell therapy

Gene therapy also holds great promise within cancer, and especially CAR (chimeric antigen receptor) T cell therapy. The approach uses a patient's own T cells, which are removed and genetically altered so they can build receptors specific to cancer cells. Once infused back into the patient, the modified T cells, which now have the ability to recognize and attack cancerous cells, reproduce and remain on alert for future encounters. The therapy has given hope for critically ill cancer patients. In 2016, the FDA approved the Novartis CAR T cell treatment, Kymriah, for treating acute lymphoblastic leukemia (ALL), and the year after it was approved for use against diffuse large B cell lymphoma. Yescarta, developed by Kite Pharma, has also been approved to be administered to adult patients with two forms of lymph node cancer.

"Until the XXI century, the predominant strategy used in the field to fight cancer was to use oncolytic viruses that were not highly tumor selective (for many decades there was not a chance to engineer viruses as there is today) and trying to deliver results by pure lytic force of the viruses (sometimes even artificially depleting the patient's immune system at the same time)," says *Víctor Cervera-Carrascón*, VP of Business Development at Finnish up-and-coming oncolytic immunotherapy company TILT Biotherapeutics. "These two facts combined delivered unexciting results that took away the interest on the approach."

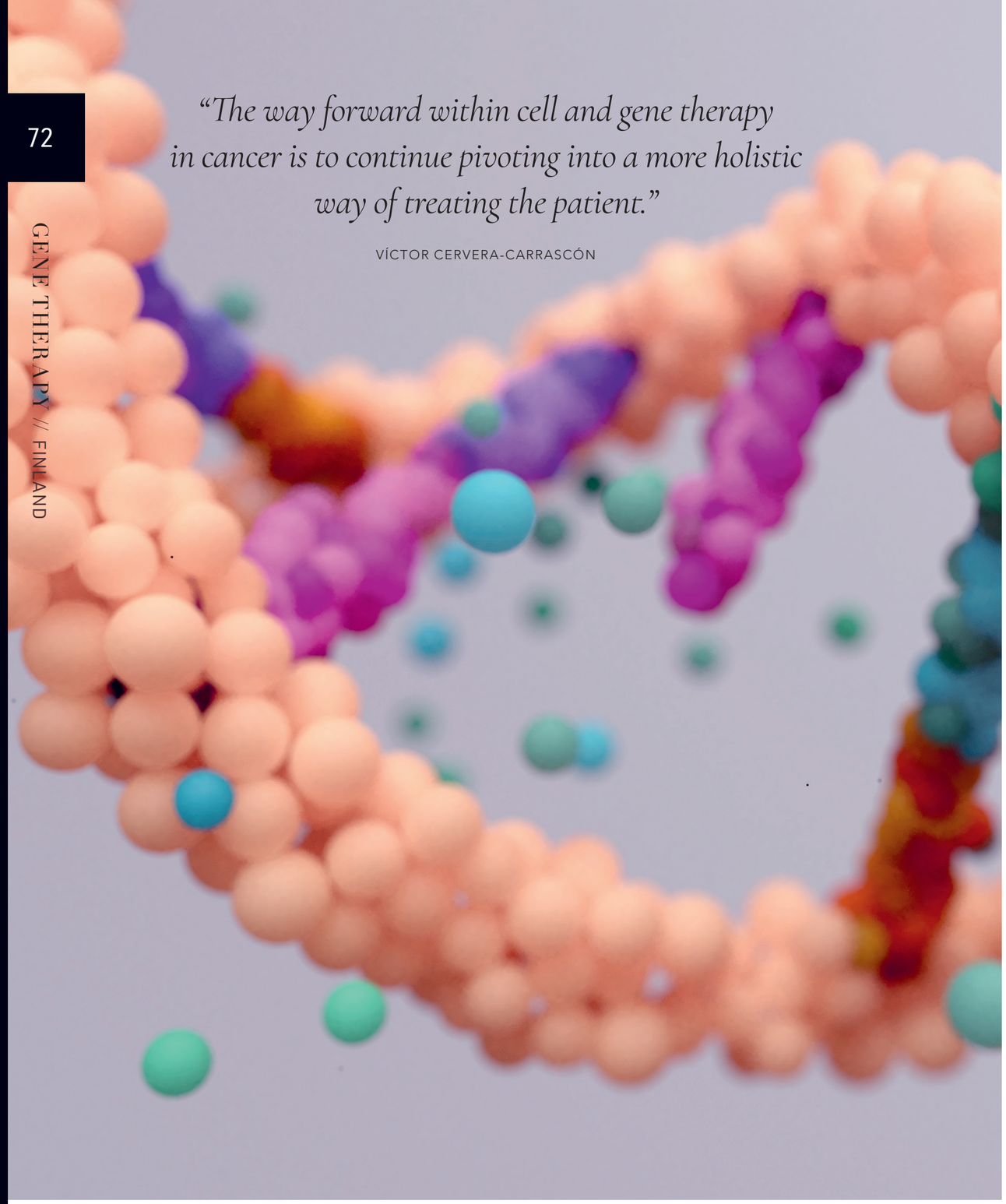
TILT's technology is based on oncolytic viral therapies that modify the tumor microenvironment and eliminate its ability to suppress immune responses to cancer. As a result, T cell therapies, such as checkpoint inhibitors and CAR T therapies, are enhanced. The company's lead therapeutic assets, TILT-123, is a cytokine-armed oncolytic adenovirus.

"Nowadays we can design viruses following different selectivity enhancing resources. In the case of TILT-123 we are using two different selectivity mechanisms which notably restricted the replication to cancer cells even when compared to candidates already engineered for selectivity," explains Cervera-Carrascón.

"Additionally, we do not solely rely on the direct lytic ability of the virus, which of course keeps happening, but we have tailored the virus to simultaneously induce anti-tumor immune reactions by enhancing immunogenic cell death and delivering transgenes that recruit and stimulate immune cells," he says.

TILT-123 (igrelimogene litadenorepvec) has already been dosed to over 60 patients across the globe and this year the company is expecting to close some of its Phase I trials in different indications. "Hopefully, following with a Phase II initiation," says Cervera-Carrascón.

Oncology is also one of Aurealis' therapeutic areas. It is the largest and most invested therapeutic area, according to Décory. "Despite major improvements in treatment and patient outcome, cancers still impact more



than 20 million people, and cause more than 10 million deaths every year. Disease outcomes vary tremendously with cancer location but also specific tumor types, stages or mutations. Cancer treatments have dramatically evolved, from chemotherapy, to targeted therapies, checkpoint inhibitors and now cell and gene therapies. CAR T cell therapies have shown great results, however mainly in blood cancers, in small groups of patients, and at a very high price for healthcare systems," he says.

Aurealis' lead oncology product, AUP-55, is currently in pre-clinical stage. In an ovarian cancer model, treatment with AUP-55 resulted in 91.3% survival and lower tumor load during the study duration of 81 days compared to the 0% survival and massively increased tumor load in untreated animals, describes Décory.

"The acceleration of our pre-clinical program in ovarian cancer, peritoneal carcinomatosis, and potentially in bladder cancer, should allow us to be ready for the clinic in two years from now," he says.

Multi-targeting and the way forward

The Aurealis Therapeutics platform also helps activate the human immune system against other diseases, including chronic wounds and inflammation.

"We believe a cell and gene therapy such as AUP-16, our lead clinical candidate in chronic wounds, can be a game changer here. Both chronic wounds and cancer are complex, multi-factorial diseases and we believe that treating them in a curative way requires multi-targeting, i.e., the ability to directly target multiple biologic targets, with one product. Currently available treatments don't allow that," says Décory.

"To heal a chronic wound, one needs to address all its components. AUP-16 consists of lactic acid bacteria, genetically engineered to produce and release three human therapeutic proteins in-situ: fibroblast growth factor 2 (FGF-2), interleukin 4 (IL-4) and colony stimulating factor 1 (CSF-1). They act as millions of nanoscale bioreactors in the wound. The combined effect of bacteria and synthesized proteins allow re-start and acceleration of the healing of chronic wounds by awakening the immune microenvironment, driving macrophage conversion from pro-inflammatory M1 to anti-inflammatory and regenerative M2 phenotype, granulation of tissue formation by increasing fibroblast proliferation and promoting angiogenesis, and supporting epithelialization," Décory explains, describing the company's 4-in-1 approach.

Víctor Cervera-Carrascón, VP of Business Development, TILT Biotherapeutics

The same logic applies to cancer, he adds. "To destroy a tumor, one needs to address multiple targets simultaneously: innate and adaptive immune system, anti-angiogenesis."

The company recently entered a 139 million USD licensing agreement with XBiome for its chronic wound candidate, AUP-16, in China and just completed a 10 million CHF series A financing round. Following successfully completed Phase 1 study, Aurealis is currently initiating a randomized, placebo-controlled Phase 2 study in diabetic foot ulcers in Italy, Germany and Poland.

"We are starting to prepare another Phase 2 study in venous ulcers, that we hope to start in the first half of next year," says Décory.

The way forward for cell and gene therapy within cancer is to continue pivoting into a more holistic way of treating the patient, believes Cervera-Carrascón.

"Not just designing a product expecting it to work alone in all circumstances but instead to learn in what combination and regimens of administration different types of therapies work best. Of course, that is a difficult job as it requires understanding a myriad of factors that can be overlooked in preclinical studies and even in small clinical trials," he concludes. NLS