TEXT *Ulla Kaltiala* | PHOTOS *Raija Törrönen*

Looking for boundaries to break

Academy of Finland Professor Seppo Ylä-Herttuala wouldn't mind being the target of gene therapy one day. "In fact, we may well be developing cures for our own retirement days," he quips.

No gene-based medicine has yet been approved for the market by western authorities. The road of trials and approvals is long, but the potential applications of gene therapy are extensive, including common diseases associated with lifestyle and aging, such as cardiovascular diseases and cancer.

Professor Ylä-Herttuala's Molecular Medicine group is undoubtedly one of the crown jewels of the University of Eastern Finland. The first in the world to successfully transfer a gene into human arteries using adenoviruses as vectors in 1996, they continue their pioneering research, now coming up with significantly improved, "second generation" gene transfer vectors.

INTRODUCING ADENOVIRAL VECTORS

When the idea of gene therapy was first introduced in the 1970s, it was envisioned as a way of treating inherited diseases by replacing disease-causing genes with normal ones. In the 1990s, horizons were broadened by research groups such as Ylä-Herttuala's who was among the first to start developing gene-based treatments for acquired diseases.

"This was a completely new approach, where the aim was not to repair a disease-causing genetic defect, but to express a therapeutic gene in the tissue affected by the disease."

In most gene therapy studies, altered viruses have been used as gene transfer vectors, due to their unique ability to insert genetic material into cells. "In the first gene transfers to humans, retroviruses were used as vectors because they have the ability to integrate into the host genome in a stable fashion," he explains.

Professor Ylä-Herttuala and colleagues departed fairly far from the mainstream by using adenoviruses as vectors. With adenoviruses, the expression of the transferred genes is only temporary, lasting for up to two or three weeks. "At the same time, they are safer to use than retroviruses, which

have reportedly caused leukemias in trial patients."

Even though disease-causing genes are removed from viral vectors, Professor Ylä-Herttuala prefers using viruses that are not especially harmful in their natural state. Adenoviruses are known to cause only minor infections, such as the common cold.

"Short term gene therapy was a revolutionary idea back then, but it was well received. It makes perfect sense in applications where a high impact is needed for a limited period, such as the treatment of cancers or myocardial infarctions."

"Gene therapy is an option for those who have no other treatment options left – an estimated ten per cent of all cardiac patients. And the numbers are increasing with population aging."

GROWING NEW BLOOD VESSELS

Professor Ylä-Herttuala's team of 35 researchers focuses on developing treatments both for cardiovascular diseases and cancer. "It's actually quite a logical combination, because angiogenesis, the generation of new blood vessels, plays a central role in each of these disease groups."

"In the treatment of cancer, we want to suppress angiogenesis, thus "starving" the malignant tumor, whereas in the treatment of cardiovascular diseases, we want to improve blood circulation by enhancing angiogenesis – the growth of new vessels compensating for obstructed ones. Many other diseases can be treated following the same principles."

For Professor Ylä-Herttuala and his team, the main therapeutic genes of interest are those regulating the vascular endothelial growth factor (VEGF) family. These growth factors are proteins occurring naturally in the body, and they are among the most powerful modulators of angiogenesis. The research group has already shown in phase II clinical gene therapy studies that VEGF-adenovirus can improve vascularity in leg muscles and increase perfusion in the heart muscle.

HERE COME DESIGNER GENES

An ongoing clinical trial carried out in cooperation with the Kuopio University Hospital is taking cardiovascular gene therapy to a new level. The treatment is targeted at patients with severe coronary artery disease who can no longer benefit from traditional treatments. "We are using a new and more effective, modified VEGF gene – kind of a designer version – and the medicine is injected directly into the damaged area of the ventricle wall via catheter."

"This way, angiogenesis is enhanced exactly where it's needed. The sufficient dosage is much smaller than in our early trials, which also reduces the risk of potential side effects. New vessels take only a few weeks to grow, so we expect to see relatively fast relief of chest pains."

Patients with chronic lower limb ischemia also participate in the trial. Animal trials have already shown the effectiveness of the treatment: "You would have had to be blind not to see the new blood vessels."

Such a treatment could significantly improve the lives of hundreds of thousands of cardiac patients in Europe alone. "Gene therapy is an option for those who have no other treatment options left – an estimated ten per cent of all cardiac patients. And the numbers are increasing with population aging."

Professor Ylä-Herttuala and colleagues have also discovered that VEGF gene therapy has a vasculoprotective effect which can be achieved with much smaller doses of the therapeutic gene than those required to enhance angiogenesis.

This discovery has led to the development of a new gene-based treatment targeted to prevent the blocking of blood vessels after vascular surgery.

"In fact, we may well be developing cures for our own retirement days."

This is a common problem in haemodialysis graft access surgery, which is the target market of the product.

The product, Trinam, is about to enter phase III clinical trials conducted by Ark Therapeutics Group. This private biomedical group originates from businesses established by Professor Ylä-Herttuala with Professor **John Martin** and Mr **Stephen Barker** of University College London.

THE RACE IS ON

The gene-based medicines selected by the Group for commercial development are manufactured in Ark's accredited facilities located on the university campus in Kuopio. Their first gene-based product, Cerepro, targeted to treat operable high-grade glioma, a form of brain cancer, has already gone through phase III clinical trials. Its commercialization suffered a setback, though, at the end of 2009 when the European Medicines Agency refused its marketing authorization.

Cerepro is an adenovirus-mediated treatment which, after brain tumor surgery, harnesses healthy brain cells to help prevent a new tumor from growing. Once treated, healthy brain cells surrounding the tumor removal site start expressing the enzyme thymidine kinase. As part of the treatment, the patient is given the drug ganciclovir. It reacts with thymidine kinase, producing a substance which specifically kills dividing cells, leaving healthy, non-dividing brain cells intact. Professor Ylä-Herttuala and colleagues have shown that the treatment can double the life expectancy of malignant glioma patients.

He is confident that after more extensive clinical trials, Cerepro will eventually be approved for the market. "Gene-based drugs are a new concept and they face tighter scrutiny than traditional drugs."

According to him, the transfer of genetic material into the human body with adenoviruses doesn't raise as many fears as does the use of retroviruses as vectors. "It's already quite an achievement to have established an approvable adenoviral gene medicine platform."

The adenoviral vectors Professor Ylä-Herttuala and colleagues now use in clinical trials are a far cry from those they have already developed since the approval of the first ones. "You have to complete the trials with the vectors you began with. But in recent years, we have made significant improvements to adenoviral as well as lentiviral and baculoviral vectors."

An adeno-associated viral vector may be among those his team will take into clinical phase in the future. They have been working on a gene-based treatment for familial hypercholesterolemia, in which patients lack LDL receptors in the liver. "With gene therapy, we could induce the production of the receptor protein, and adeno-associated viral vectors seem promising for a longer-term therapeutic effect. We have already shown the decrease of LDL levels by 50 to 70 percent in a one-year follow-up in animal trials."

Although Professor Ylä-Herttuala has been at the forefront of gene therapy research for years, he is still looking forward to breaking some more boundaries. For that aim, intensive cooperation with the world's other top research teams is crucial. On the other hand, there is an ongoing race to enter the markets of the western world with the first approved gene-based medicine. China has already approved a gene therapy product for the treatment of head and neck carcinoma.

"There are many promising products, some of which will definitely make a breakthrough in the years to come. Inherited, metabolic and immunodeficiency diseases are among the therapeutic targets, as well as retinal degenerative disease and other eye diseases," he concludes.