Editorial

Gene therapy: The ultimate cure for hereditary diseases

In 1972, Theodore Friedmann and Richard Robin proposed gene therapy in their paper published in *Science*, opening with “gene therapy may ameliorate some human genetic diseases in the future”. Since then, almost half a century has passed and the field has been making slow but steady progress in turning their imagined future into reality. Gene therapy was first included in clinical trials in the 1980s, but it was not approved for clinical use in humans until 2003, in China. Since then, gene therapies for treatment of various genetic diseases have been approved in Europe and the USA.

At the 2019 meeting of the American Society of Gene & Cell Therapy in Washington, DC, USA, researchers from the University of California, Los Angeles (CA, USA), announced a new gene therapy treatment yielding striking results in patients born with X-linked myotubular myopathy, a rare hereditary disease that causes muscle myopathy and hypotonia. In this unpublished, phase 1 – 2a trial (NCT03199469), nine male patients aged 8 months to 6 years received intravenous infusion of adeno-associated virus (AAV) that introduced wild-type *MTM1* gene into their muscle cells, leading to substantial growth of their muscle fibers. Seven of them were able to either sit up or walk with assistance after treatment, without which they could barely breathe or move on their own.

In a Phase 1 – 2a clinical trial (NCT02519036) supported by Ionis Pharmaceuticals and F Hoffmann-La Roche, published in June 13 in the *New England Journal of Medicine*, Sarah Tabrizi and colleagues from University College London (UK) tested an antisense oligonucleotide (*IONIS-HTTR*Rx) in adults with early Huntington’s disease and found that the treatment reduced the concentration of mutant huntingtin without serious adverse effects. In another Phase 1 – 2a clinical trial (NCT01512888), published in April 18 in the same journal, researchers from St Jude Children’s Research Hospital in Memphis (TN, USA) tested a lentiviral gene therapy for infants with X-linked severe combined immunodeficiency. The results showed that the gene therapy combined with low-exposure, targeted busulfan conditioning had minor acute toxic effects and resulted in improved immunity in each of the eight treated patients.

These exciting results are bringing new hope to patients with rare and devastating genetic diseases such as these. The US Food and Drug Administration (FDA) approved three gene therapy products in 2017, including voretigene neparvovec-rzyl, the first approved gene therapy treatment for patients with confirmed biallelic RPE65 mutation that causes retinal dystrophy. More than 25 gene therapies are currently in phase 3 or have found treatment efficacy in phase 1 – 2 trials in 2019. The FDA anticipates approving 10 – 20 cell and gene therapy products per year by 2025, which will most probably include gene therapies targeting the diseases mentioned above, as well as sickle cell anemia, heart disease, and cystic fibrosis.

Although we have reasons to be optimistic, challenges remain before gene therapy can jump from bench to bedside for multiple reasons. To begin with, on-target delivery of the gene to the right cells and tissues that are affected by the disease is crucial to the success of gene therapy. Most treatments now being developed use inactivated viral vectors, such as AAV or lentiviruses, to deliver corrected genes or genome-editing machinery to correct the abnormal gene. However, these vectors usually accumulate in the liver, potentially narrowing the spectrum of readily targetable diseases. Remarkable efforts have been made to optimise gene delivery vectors to convey transgenes to desired cell populations. In their work published on March 6 in *Molecular Therapy*, Suh and colleagues from Rice University in Houston (TX, USA) developed a protease-activatable AAV vector, named provector, that responds to elevated extracellular protease activity commonly found in tissue microenvironments of heart disease. In an in-vivo model of myocardial infarction, provector can deliver transgenes preferentially to regions of the damaged heart with high matrix-metalloproteinases activity, with a concomitant reduction in delivery to many off-target organs, including the liver.

In addition, risks of cutting-edge technologies and the rarity of gene therapy for targeted hereditary diseases are the source of several bioethical and financial challenges. Off-target effects of current genome-editing technologies remain a major concern and hurdle to move it into a clinical setting with reasonable and controlled safety. Even for approved gene therapy, in the long run, treatment could cause adverse symptoms or organ damage and other side effects that haven’t been reported yet in patients. Therefore, both health-care providers and patients must balance these risks with the health benefit that gene therapy provides, especially when it comes to treating a rare genetic disease that might have the potential to cause severe problems over several decades. Furthermore, the high costs of developing treatments tailored to a small number of patients could make some gene therapies prohibitively expensive, and insurance coverage might be difficult to obtain.

To overcome these challenges, all stakeholders—policymakers, pharmaceutical companies, scientific researchers, and health providers—must work together to ensure that safe, effective, and affordable gene therapies become available to patients in need. For scientific researchers, the development of the best delivery methods and improvement of the genome-editing technologies will lead to safer and more effective and affordable gene therapies. *EBioMedicine* looks forward to publishing high-quality translational research on this front. For those who are suffering from devastating hereditary diseases and in urgent need of effective treatments, gene therapy is still one of the best promises for the ultimate cure.