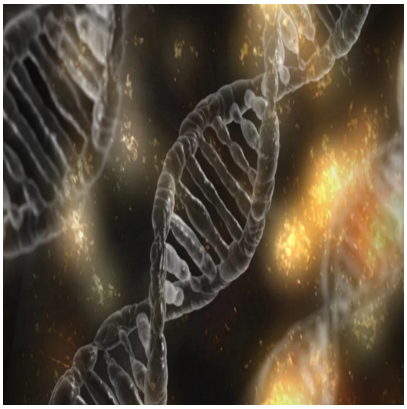

Rustam Gilfanov: Boundaries of Genetic Modification — Breakthroughs, Achievements, Failures, and Limits

Description

Every year, genetic modifications find new areas of application, one way or another. Technologies that were innovative a few years ago are eventually becoming standard tools of clinical practice.

Many people have high hopes for genetic technologies, believing they could cope with incurable diseases (sometimes even before birth) and slow down aging.

The FDA defines [1] gene therapy as a technique that modifies a person's genes to treat or cure a disease. Mechanisms for such modifications can involve *ex vivo* (outside the body) and *in vivo* (inside the body) changes.

There are numerous methods of gene modification: scientists and medics apply vector gene delivery, alter genomes of specific cell types, and edit damaged genes. Now, we can say for certain that those technologies no longer belong to research labs only and are successfully used to improve the lives of real patients. However, they cannot be considered a panacea, as their possibilities remain limited.

Ex vivo modification

One of the first relatively successful cases [2] of applying gene therapy for patient treatment took place in 1990. For a four-year-old Ashanti de Sylva, who suffered from severe combined immunodeficiency, gene therapy became an alternative to hematopoietic cell transplantation, a low-efficiency method accompanied by severe adverse effects. During the treatment, the patient's lymphocytes were taken, modified *ex vivo* using a retroviral vector, and delivered back to her body.

Numerous *ex vivo* modifications have been introduced to clinical practice to help against various disorders, with CAR-T therapy being one of the most promising methods. In 2017, Novartis became the first pharmaceutical company to get FDA approval [3] for using CAR-T cells to treat acute lymphoblastic leukemia patients aged 3-25. The new product was named Kymriah.

The therapy is based on genetic modification of patients' T cells. It forms chimeric antigen receptors on

the cell surfaces that can bind with the protein expressing tumor cells. During the clinical trials, 83% of patients achieved complete or partial remission 3 months after the start of CAR-T therapy. The 12-month survival rate reached 79%, while the survival rate of acute lymphoblastic leukemia patients undergoing the standard chemotherapy never exceeded 30%.

After Novartis, approval was given to CAR-T therapies by other pharmaceutical companies, such as Yescarta and Tecartus by Gilead Sciences and Abecma by BMS. That is not the complete list, and the scientific community is confident it will continue to expand.

Products like those are becoming more and more popular, even though present-day gene therapy has significant limits. CAR-T technologies are now applied only if the standard first-, second-, and even third-line treatment fails to provide any results, and the treatment itself may cause multiple severe adverse effects. Besides, therapy involving genetically modified lymphocytes is extremely expensive.

Another major drawback [4] of this method is the uncertainty over its potential long-term impact, relapses, and side effects, some of which can be fatal.

CAR-T medicines were initially designed to treat oncohematology disorders, but their scope of application turned out to be broader than expected. Recent studies demonstrate that genetically modified T cells can help patients recover from myocardial infarction [5].

Still, those drugs are mainly used in oncohematology. As of yet, CAR-T therapies are ineffective against solid tumors, but scientists are actively working on overcoming this barrier [6].

In vivo modifications

A much-discussed success (that turned into a less-discussed failure) was Glybera, approved for use in the USA and Europe in 2012. The drug aimed to help patients suffering from the deficiency of lipoprotein lipase, the enzyme breaking down complex fats. Low levels of this enzyme cause accumulation of subcutaneous and visceral lipoprotein complexes, leading to serious health issues such as pain, diabetes, liver disorders, and infertility.

Glybera is based on an adeno-associated virus carrying the lipoprotein lipase gene. Its intramuscular injections compensate for the enzyme deficiency, i.e., actually cure the patient. When the drug was released, it was the most expensive medicine on the market. The series of injections (approximately 60 doses were required) initially cost USD 1.5 mln; eventually, the price dropped to 1 mln.

As of 2018, only 31 patients administered this expensive drug; its high price and the rarity of the disease made Glybera production unprofitable. As a result, uniQure decided not to renew its marketing authorization [7] and focus instead on gene therapy for hemophilia B, a more common congenital disease.

In general, such therapies remain costly. Researchers are hesitant to introduce drugs based on adeno-associated vectors to clinical practice for treating rare disorders, as high expenses make their production unprofitable for the industry.

Nevertheless, certain progress has been made. Pfizer and Spark Therapeutics are trying to defeat hemophilia B [8], gene therapy turned out to be effective against hemophilia A [9], and the patient with

sickle cell anemia is showing signs of recovery [10].

The most expensive drug currently used for *in vivo* gene therapy is Zolgensma, manufactured by pharmaceutical giant Novartis. One injection of this medication for spinal muscular atrophy costs USD 2.1 mln.

This rare neurodegenerative disorder, caused by SMN1 gene mutation, affects 1 patient out of 10,000. Its symptoms develop in early childhood and progress with age, as children gradually lose their ability to move, eat, and swallow without assistance. Lack of treatment leads to a fatal outcome. Once administered, Zolgensma normalizes SMN1 functioning and prevents the disease from progressing. It has been proven to increase patients' survival rate; some even regain their body functions and start eating and even walking themselves.

The drug is so expensive that patients cannot afford it; it often has to be purchased by the state or charity funds. Its exorbitant price is not the only drawback of Zolgensma, yet the medicine will not get cheaper in the near future.

Zolgensma was a real breakthrough, but more data is needed to assess its long-term efficiency, as the current period of monitoring patients who got the injection does not exceed 5 years. Besides, the therapy demonstrated severe side effects; there is even one known lethal case, but it is uncertain whether the death was caused by administering the drug.

The examples above are just a few gene therapies adopted by clinical practice for *in vivo* treatment. Those techniques seem highly promising, yet there is not enough data to confirm their long-lasting effect.

CRISPR gene editing

A 2015 *Nature* article on CRISPR/Cas9 technology [11] called it a "game-changer" and compared its development to the introduction of PCR to laboratory practice. "Molecular scissors" have indeed provided vast clinical opportunities for editing genes with utmost precision, "cutting off" defective genes and replacing them with normally functioning ones.

CRISPR is used with relative success for treating ?-thalassemia, sickle cell anemia, and Duchenne muscular dystrophy. However, it has not fully become a systemic clinical practice.

Cancer therapy is another promising area of application for "molecular scissors." During their research, Chinese scientists used CRISPR to edit the genes of patients with non-small-cell lung carcinoma and disrupt a gene encoding the PD1 protein. The researchers concluded the technology is safe for clinical practice; however, further studies expressed concerns over the long-term health effects of genome editing.

In general, doubts about CRISPR accuracy are the main obstacle to making it a routine clinical practice. Researchers still cannot be 100% sure that "scissors" will do their cutting as intended, raising questions over the potential outcomes of such editing.

In 2015, Chinese geneticists conducted an experiment that was widely discussed in the scientific community [12]. They attempted to modify human embryos, editing the gene that provokes ?-

thalassemia. The defect was fixed, but the success rate was only 5-10%. Besides, the alteration was far from perfect: apart from planned changes, researchers also detected several “out-of-target” mutations.

However, another experiment by Chinese scientists led to more serious debates. He Jiankui, a biophysics researcher, announced in fall 2018 that two genetically modified twin girls had been born, with their genome CRISPR-edited before birth [13]. The girls’ father was HIV-positive, and the experiment aimed to create embryos immune to the virus.

It is known that several couples took part in the experiment, and at least three genetically edited children were born. Jiankui’s statement became a scientific sensation, yet it stirred controversy over ethical issues.

CRISPR technology is still far from perfect, so long-term results of editing children’s genomes remain unknown. It is unclear what unintended mutations it may provoke and what health effects they may cause in the future.

Potential consequences include higher risks of cancer and other diseases due to genetic mosaicism, a condition when a single organism possesses cells with several genomes. Jiankui’s research lab plans to monitor the girls’ health until they turn 21 and publish regular reports.

In general, most scientists agree that no matter how tempting the idea of prenatal genome altering may sound, gene editing as a tool is still too imprecise to achieve those goals.

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