SDG 15: Life on Land and human health through the scope of modern technologies

Communicated by Z.G. Aytasheva*, A.N. Bekmukhanbetova*, A.T. Kadyrbekova*, A.M. Khassen*, and D.Ye. Bazarkulova*

***Department of Molecular Biology and Genetics, Faculty of Biology and Biotechnology, Al-Farabi Kazakh National University, Almaty, Republic of Kazakhstan**

On 6-th November graduate students of the Reproductive Genetics Program learning the course of Human Genome and Proteomics were focused on the topic of the United Nations Sustainable Development Goal 15 (SDG 15) “Life on Land”. So, they discussed current efforts of physicians and geneticists to effectively treat hereditary diseases using modern research tools.

What our society should know about heavy genetic disorders, and how the humankind is treating these diseases using updated techniques?

Modern technologies, including gene therapy and genome editing, have literally turned upside-down the treatment of severe hereditary diseases, offering efficient and quick solutions, thereby largely improving patient’s outcomes and quality of life. This huge step forward points out the potential of precision medicine, although provision of accessibility and affordability still remains under question from point of equal possibilities for common healthcare.

Graduate students- geneticists during the discussion on the Goal 15 of Sustainable Development ("Life on Land")

Spinal muscular atrophy (SMA) is caused by mutations in the SMN1 gene, which is critical for the motor neuron life span. Zolgensma, a gene therapy approved in the U.S., and recently in Russia, offers adenovirus-associated (AAV9) vectors to supply with a functional copy of the SMN1 gene to motor neurons in the spinal cord, compensating for the hereditary deficit of this protein [1]. Beginning from 2014, clinical trials have shown that a single dose of Zolgensma provides long-term relief, as patients remain ventilator-free for over six years, according to the NCT04042025 study. Alas, liver toxicity has been noticed as an undesirable side effect of AAV therapy, and two children have died from acute liver failure after receiving the drug [2]. Despite these risks, Zolgensma is regarded as a life-saving option for children with SMA, offering an

alternative to an almost certain fatal outcome. The balance between its therapeutic outcomes and safety risks remains a key perplexity in its use.

Thalassemia is also a hereditary blood disorder caused by gene mutations during the hemoglobin synthesis. Alpha-thalassemia is linked to mutations in the HBA1 and HBA2 genes, whereas beta-thalassemia is associated with mutations in the HBB gene. Recent progress in gene therapy, including the Zynteglo treatment, aim to correct these mutations. Approved in 2019, this therapy involves introduction of a normal beta-globin gene into the patient's stem cells, reducing the need for blood transfusions. One of the first patients, who received this treatment, was 9 years-old Ada, a child with beta-thalassemia, which was able, as a result, to stop regular transfusions after the therapy. The treatment took place at the Children's Hospital of the University of California, San Francisco, and total process lasted four months. Although Ada's hemoglobin levels have not fully reached the normal rate, she, like other patients, will be monitored for 15 years. Regardless of a risk of blood cancer, no such cases were recorded during those studies. The Zynteglo treatment inspires patients with severe beta-thalassemia, but its high cost (2.8 million dollars per vial) limits accessibility. It is anticipated that six and more genome-editing technologies including most popular CRISPR/Cas9 may reduce the price as make such treatments more affordable and effective [3].

Leber Congenital Amaurosis (LCA) is a severe hereditary retinal dystrophy that leads to significant vision loss or blindness in early childhood and is ascribed to 5% of all inherited retinopathies. LCA primarily affects the photoreceptors and retinal pigment epithelium (RPE), essential for vision, and involves mutations in more than 25 annotated genes, including RPE65. [4] Mutations in RPE65 break down the conversion of all-trans-retinyl esters to 11-cis-retinol, impairing photoreceptor response to light and leading to blindness. Molecular genetic testing confirmed LCA diagnoses and enabled more individual treatment procedures. Luxturna, the first FDA-approved gene therapy for LCA, implies an adenovirus-associated vector (AAV2) to deliver a functional RPE65 gene to retinal cells, restoring the visual cycle and improving vision. Clinical trials have indicated its safety and efficiency, with patients demonstrating substantial functional vision improvements and greater independence in daily activities [5].

The CCR5 gene encodes a receptor on the surface of immune cells (T-lymphocytes) that human immunodeficiency virus (HIV) exploits while entering cells. The CCR5Δ32 mutation is a deletion of 32 base pairs that converts the receptor into nonfunctional, preventing from HIV entry into cells. Individuals with this mutation in the homozygous form (CCR5Δ32/Δ32) are naturally resistant to the virus. HIV operates the CCR5 receptor to enter cells. The absence of functional CCR5 inhibits HIV infection. Timothy Ray Brown, the “Berlin Patient”, who suffered from both HIV and leukemia, received a bone marrow transplant from a donor with the CCR5Δ32 mutation. The transplant replaced the patient’s immune cells with those of the donor, which were HIV- resistant, allowing the recipient to achieve long-term remission. Thereby, “Berlin Patient” inspired the development of gene therapy techniques, such as gene editing (e.g., CRISPR-Cas9), to artificial disabling CCR5 , and creating strong HIV resistance[6]. This strategy offers a more accessible and less risky alternatives to bone marrow transplantation.

Progress of gene therapy and gene editing technologies offer promising solutions to global health challenges, such as HIV, genetic disorders like SMA, thalassemia, and LCA, improving patient outcomes and quality of life. These innovations drive medical progress and foster new, more effective treatment options, marking significant steps forward in healthcare. However, to ensure equitable access, it is crucial to make these therapies affordable and available to all, requiring long-term collaboration between researchers, healthcare providers, and organizations worldwide, as well as regionally in Central Asia.

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