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Special Issue: Genome Editing and Gene Therapy

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Abstract—Gene therapy is one of the most rapidly developing fields of molecular medicine. Gene therapy allows simple transfer of genetic methods aimed at correcting pathological processes into clinical practice. However, a number of technical problems still exists limiting broad use of gene therapy approaches. This special issue discusses modern methods and approaches used for the development of novel, effective, and safe agents for gene therapy.

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The central dogma of molecular biology stated in the second half of the previous century described the flow of genetic information within a biological system [1]. Understanding of these mechanisms raised the idea that any pathology caused by molecular defects can be genetically corrected, restoring normal cell activity at the molecular level. This approach was called gene therapy. Towards 1980, methods of molecular cloning were developed, which allowed the application of theoretical principles of gene therapy into practice. Initially, gene therapy was aimed at expression of additional genes coding for products essential for normal cell activity. Discovery of RNA interference [2] led to the development of tools for downregulating the expression of an "undesirable" gene. The new concept of "smart" drugs was recently proposed. Such gene therapy products combine the coding, structural, and enzymatic functions of nucleic acids and can activate mechanisms of translational repression of a particular transcript in response to specific external stimuli [3, 4].

Various approaches are used for the development of gene therapy agents. Methods for long- and short-term expression of therapeutic transgenes were developed. However, the problem of integration of therapeutic transgenes into the patient's genome is still not solved. Retroviruses could not be used as a basis for gene integration because of safety concerns in their application. Only several years ago, CRISPR-Cas systems able to integrate a needed gene into a specific genome locus were discovered [5]. These systems can help to reduce significantly the risk of insertional oncogenesis – a frequent side effect of using retroviruses.

Despite certain progress, development of gene therapy agents is still facing a number of technical limitations that slows the development of this extremely promising field of molecular medicine. Reviews and original articles included in this special issue describe different approaches for the development of gene therapy agents and discuss different ways to overcome arising technical problems.

The review of Savitskaya and coauthors [6] describes different known CRISPR-Cas systems that can be used for genome editing. The perspectives of using such systems in biotechnology and medicine are also discussed. The review of Chugunova and coauthors [7] gives an idea about the current state of methods used for gene inactivation and editing, as well as methods used for incorporation of foreign genes into the genome of model organisms. The possibility of using genome editing for treatment of human muscular dystrophies is discussed is the review of Saada and coauthors [8]. Tsvetkov and coauthors [9] present their study of the regulatory role of the PI3Kα isoform in functioning of the cardiovascular system. They show that PI3Kα is a promising target for gene therapy of tumor cells.

The review of Lukashev and Zamyatnin, Jr. [10] discusses methods of targeted delivery of gene therapy agents to and into target cells. Viral vector-based delivery methods are mainly discussed. The topic of delivery of targeted gene therapy agents is further developed in the review of Sergeeva and coauthors [11] devoted to gene therapy agents based on RNA molecules and delivery methods using liposomes and polymeric nanoparticles.

Since mutations in mitochondrial DNA are often associated with severe hereditary human disorders, gene

therapy can be useful not only for the genetic material stored in the nucleus, but also for mitochondrial DNA. Samoylova and coauthors [12] describe the development of methods of DNA delivery to mitochondria. These methods could be used in the future for the development of gene therapy approaches aimed at correction of mitochondrial genetic disorders.

In 30 years of existence and development of gene therapy approaches, a large number of techniques improving the efficiency and safety of gene therapy agents have been developed. However, these tools are still not sufficient for solving all important problems associated with correction of genetic disorders. Methods increasing the efficiency of gene therapy agents are being improved continuously. The main techniques are presented in the articles of this special issue.

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