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ГЕННАЯ ТЕРАПИЯ БОЛЕЗНЕЙ ЧЕЛОВЕКА: ПОСЛЕДНИЕ ДОСТИЖЕНИЯ И БЛИЖАЙШИЕ ПЕРСПЕКТИВЫ РАЗВИТИЯ

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Gene Therapy for Human Diseases: Recent Achievements and Near-Term Development Prospects

Резюме

В статье кратко изложены недавние успехи в генетической медицине, которые проложили путь для дальнейшего развития генной терапии и заложили основу для разработки технологий следующего поколения. Рассмотрены вопросы, связанные с основным препятствием для более широкого применения методов генной терапии, в частности, с иммунным ответом на векторы доставки генов и продукты чужеродных трансгенов. В этом контексте обсуждается роль новых технологий, позволяющих обойти иммунное препятствие, таких как разработка модифицированных капсидов адено-ассоциированых вирусов (AAV) и методов временного удаления антител из кровотока, а также переноса гена в ткани с помощью наночастиц. Наряду с технологиями первого поколения генной терапии, ориентированных на доставку трансгенов в ткани-мишени, резюмируются последние достижения в разработке совершенно нового подхода к генной терапии, основанного на точной модификации последовательностей генома человека — технологии редактирования генов. И наконец, обозначены перспективные технологии редактирования генов следующего поколения, такие как технологии редактирования, нацеленные на РНК и технологии редактирования эпигенома, которые являются более специфичными и точными, эффективными и применимыми к различным группам заболеваний. В заключение делается вывод, что генная терапия является на сегодняшний день самой захватывающей и революционной биотехнологией современности как из-за недавнего прогресса, так и из-за возможностей, которые она может обеспечить в ближайшем будущем.

Ключевые слова: *генная терапия, аденоассоциированный вирус (AAV), капсиды, наночастицы, редактирование генов, эпигенетика*

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Abstract

The article briefly summarizes recent advances in genetic medicine that paved the way for the further development of gene therapy and set the stage for the development of next generation technology. Issues related to the main obstacle for wider application of gene therapy methods, in particular, with the immune response to gene delivery vectors and transgene products are considered. In this context, the role of new technology allowing to bypass the immune obstacle, such as development of modified capsids of adeno-associated viruses (AAV) and methods for temporary removal of antibodies from the bloodstream, as well as gene transfer into tissues using nanoparticles, is discussed. Along with the technology of the first generation gene therapy focused on the delivery of transgenes into target tissues, latest advances in the development of a completely new approach to gene therapy which is based on precise modification of the human genome sequence, gene editing technology, are summarized. Finally, promising next-generation gene editing technology is outlined, such as RNA-targeted editing technology and epigenome editing technology, which are more specific, precise, efficient and applicable to different groups of diseases. The article concludes that gene therapy and, in particular, human genome editing is perhaps the most exciting and revolutionary biotechnology of our time, due to both recent developments and opportunities it might provide in the nearest future.

Key words: *gene therapy, adeno-associated virus (AAV), capsids, nanoparticles, gene editing, epigenetics*

Conflict of interests

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Introduction

As far back as 1970s, gene therapy, replacing or complementing disease-causative defective DNA with exogenous healthy or beneficial DNA, was recognized as providing viable treatment options for genetic disorders in human [1]. In 1980s, the concept of using a viral vector to transfer genes into mammalian cells was developed [2], and in 1990, and the first approval for testing gene therapy using a viral gene transfer vector encoding adenosine deaminase (ADA) enzyme in a 4-year-old patient suffering from X-linked severe combined immunodeficiency (SCID-X1) due to ADA deficiency of (adenosine deaminase) [3] was obtained in 1990. This was followed by a decade of new trials; however, two of them failed, so, the further gene therapy trials were suspended. In the first case, gene therapy for ornithine transcarbamylase deficiency using an adenovirus (Ad)-mediated delivery vector unexpectedly led to severe vector toxicity, multiple organ failure, and death of an 18-year-old man [4]. In the second case, gene therapy of six patients with SCID-X1, mediated by gamma-retroviral vector (γRV) encoding interleukin-2 receptor gamma chain, was associated with uncontrolled exponential proliferation of clonal mature T cells and integration of retroviral vector in the immediate vicinity of LMO2 proto-oncogene promoter (The LIM only protein 2) which resulted in aberrant transcription and expression of LMO2 [5]. These events were followed by a period of closed clinical trials. However, in the following years, new and safer viral vectors were discovered, including a large number of adeno-associated viral (AAV) vectors [6]. The use of these vectors in new genetic medicine development programs promoted the further progress in the methods of gene therapy of human diseases; their summary and prospects for development in the years to come are presented in this review.

GENE THERAPY FOR HUMAN DISEASES

Viral transgene delivery vector therapy

Over the past five years, gene and cell therapy for human diseases enjoyed renaissance; after decades of efforts in this direction, the first treatment methods approved for clinical practice have emerged (see figure). These include oligonucleotide-based therapy methods (Spinraza for spinal muscular atrophy, Exondys 51 and

Vyondys 53 for Duchenne muscular dystrophy), three cell therapy methods (Kymriah for acute lymphoblastic leukemia, Yescarta for large B-cell lymphoma, Tescartus for recurrent or refractory mantle cell lymphoma in adults), and two gene therapy methods *in vivo* (Luxturna for hereditary retinal dystrophy, Zolgensma for the treatment of patients with proximal spinal muscular atrophy). These treatment methods have different clinical indications and target tissues including neuromuscular diseases, hereditary blindness, and cancer. The importance of these approved treatment methods can hardly be overestimated: they drastically change the life of patients with severe hereditary pathologies and create a foundation for the development of treatment methods for many other human diseases. For example, a successful *in vivo* transfer of a normal copy of the defective gene into human retina and central nervous system with the help of Luxturna and Zolgensma drugs, using AAV-virus as a vector, in Leber congenital amaurosis and spinal muscular atrophy, respectively, facilitated the development of (AAV-based) of hemophilia [7] and Duchenne muscular dystrophy [8] treatment methods, respectively. Likewise, the early development of the method of *ex vivo* lentiviral and retroviral genes transfer to T cells that resulted in the development of adoptive cell immunotherapy (a personalized type of nonspecific cell immunotherapy with activated lymphocytes) was expanded to cover the modification of hematopoietic stem cells that allowed managing hereditary diseases such as sickle cell anemia and beta thalassemia [9]. This early success of gene therapy and the possibility of their extrapolation to other pathologies and patient populations cannot but win admiration. However, the next generation methods are even more impressive, as they can significantly expand the use of these agents for the management of many other human diseases. For example, the main obstacle to a wider implementation of gene therapy methods is still the immune response to gene delivery vectors and alien transgene products. Therefore, the control of human immune system is the trend of research where one of the most effective "breakthroughs" in the field of gene therapy can be made in the near future. Thus, despite the remarkable success of many AAV-based gene therapy methods, up to 50 % of patients are currently excluded from such treatment due to pre-existing immunity to viral capsids [10]. The recent investigations in the field of immune system control were successful and resulted in the development of methods (that are currently undergoing clinical trials) capable of bypassing this immune barrier. These methods use modified AAV capsids that evade the pre-existing neutralizing antibodies [11, 12] and the methods for temporary removal of antibodies from bloodstream [13]. Immunosuppression regimens can also provide both bypassing the pre-existing immunity and prevention of the adaptive immunity to the vector, which, where necessary, can enable subsequent repeated dosing [14, 15].

Non-viral delivery vector (nanoparticle-based) therapy

Furthermore, a significant progress was achieved in the development and profiling the non-viral vectors (nanoparticles) of gene delivery which increased the applicability of used treatment methods [16]. Given the clinical success of miRNA delivery by nanoparticles and the first approval of an miRNA-based drug (Onpattro) for hereditary transthyretin amyloidosis (ATTR) treatment in 2018, it can be assumed that in the future these technologies will have a huge impact on gene therapy [17]. One of the advantages of using nanoparticles as gene delivery vectors is their ability to avoid detection by immune system, which restricts gene delivery by viruses. Furthermore, the chemically defined compositions of nanoparticles provide unique opportunities for their functionalization and tissue targeting, which can finally be critical for the success of gene transfer *in vivo* outside retina and liver.

Genome editing technology

In contrast to first generation gene therapy methods that were focused on the delivery of transgenes, the genome editing technology provides a completely new approach to treatment based on the precise modification of human genome sequences (see figure). There are four basic methods of genome editing — using meganuclease, zinc finger nuclease (ZFN), TALE nuclease (TALEN), and CRISPR/Cas9 nuclease. While genome editing treatment methods were first included into clinical trials as early as in 2010 as a T cells HIV (human immunodeficiency virus) prevention method [18], the first example of disease modifying efficacy was demonstrated only in 2019 in the clinical trials based on CRISPR editing of the genes for sickle cell anemia and beta thalassemia (CTX001) [19]. This pathbreaking success combined with promising safety parameters for the edited T-cell genes and hematopoietic stem cells in human trials [19-21] laid the foundation for the long-awaited results of current and forthcoming clinical trials on genome editing *in vivo* including the current trial of AAV-based retina genome editing (EDIT-101) [22] and the scheduled trial of CRISPR delivery to the liver based on non-viral nanoparticles (NTLA-2001) [19, 23].

Despite this progress, it should still be recognized that the expansion of genome editing technology to target tissues outside retina and liver is associated with numerous issues. In order to encourage and promote research in the field of cell and genome therapy (CGT), including the development of genome editing technologies, the corresponding consortia and government programs were established in the United States, China, Russia and some countries of the European Union. Thus, in the United States, the financing of the regenerative medicine sector that includes gene therapy increased sharply from USD 6 billion in 2019 to USD 19.9 billion in 2020 [24]. Due

to the political support of the country's leadership, CGT research in China have reached unprecedentedly high level. Currently, China, featuring with rapidly growing biotechnology sector with more than 45 national and 4 joint companies with foreign partners, ranks second after the United States in terms of the number of submitted patent applications and registered clinical trials in the field of genetic medicine and is considered to be one of the most advanced world centers of cell and gene therapy. Russia has also established a state program for the development of genetic technologies for 2019–2027; its total funding is 127 billion rubles [24]. Efforts made in this area of scientific research by the leading countries of the world should undoubtedly significantly accelerate the development of treatment methods based on genome editing, in the following ten years or more.

Actual gene editing technologies use nuclease-based systems to cut DNA strands and stimulate DNA repair pathways to make the required sequence changes. Although the clinical trials of these technologies have just started, the numerous, more specific and accurate, effective and applicable to various groups of diseases next generation editing technologies are ready for clinical trials [25, 26]. For example, the invention of basic editing and primary editing allowed precise changing of genome sequences in the absence of DNA breaks and regardless the endogenous DNA repair pathways activity [25]. RNA-targeted editing technologies allow temporary and reversible gene expression modification with no need for permanent changes in genome sequences (see figure) which potentially results in higher efficiency and safety [26]. Finally, the advantages of epigenome editing technologies are the customization, reversibility, and the potential for sustainable results after short-term editor activity that are inherited through cell division [27]. In parallel with these advanced editing modalities, the list of possible DNA targeting systems continues to expand, especially with the exponentially increasing variety of CRISPR-Cas (Clustered regularly interspaced short palindromic repeat sequences/CRISPR-associated protein) systems obtained from the modified variants of various bacteria species and various classes of CRISPR targeting mechanisms [26]. The rapid pace of technological innovation in these areas of editing, according to the researchers, will change our current understanding of gene therapy and significantly expand the range of human diseases to which these approaches can be applied.

Gene regulatory elements editing technology

Another innovation area that will significantly impact the field of gene therapy in the near future is the functional genomics and our understanding of the human genome regulation, that is, epigenetics. For example, the functions of ~ 6000 of ~ 20,000 human genes are currently not known [28]. Therefore, simultaneously with the possibility of treatment using gene editing, CRISPR technologies can also facilitate the functional decomposition of these genome sequences [29]. It should be mentioned that previously scientific investigations and therapeutic interventions were conventionally almost exclusively focused on genes, although 98 % of our genome consists of non-coding DNA, containing epigenetic regulators responsible for >90 % of susceptibility to common diseases [30]. In fact, the first example of the therapeutic efficacy of a gene editing approach based on CRISPR technology (CTX001) as a strategy for compensating for lost beta-globin in hemoglobinopathies involves editing a distal gene regulatory element to alter gene expression rather than editing the underlying genetic mutation [31]. Due to the efforts of ENCODE (The Encyclopedia of DNA elements) international consortium, more than two million of these regulatory gene elements were mapped in hundreds of human cell types and tissue samples; however, the function of very few of these sites is known [32]. Therefore, annotating this "dark matter" of genome can lead to the development of completely new areas in the biology of diseases and classes of therapeutic targets that will allow the use of fundamentally new treatment methods, i.e. gene therapy, genome editing, etc.

Universal cellular therapy methods technology

Interestingly, that the rate of development of technological innovations in gene and cellular therapy is significantly ahead of the rate of their approval and safe implementation in clinical practice. In some cases, this is due to the inadequacy of the existing safety and efficacy requirements to some new therapeutic technologies. For example, the current regulatory models that require a large number of patients to establish safety and efficacy are not applicable to therapeutic technologies aimed at eliminating a mutation found in one patient or in a very small number of patients. Therefore, one of the most promising strategies in this direction is the development of a single composition that will allow to treat a much larger population of patients. Universal cellular therapy methods, created by applying gene editing to obtain allogeneic donor invisible cells that can elude detection by the host's immune system (see figure), can be used both in regenerative medicine and in adoptive cell immunotherapy [33]. Several clinical trials are currently underway to study treatment methods using this design [19], and the conclusions of these trials will significantly affect the future of gene and cellular therapy. However, despite the high-potential prospects of this approach, it is not aimed at correcting genetic mutations *in vivo* and has no effect on the development of transformative technologies such as basic editing and primary editing that can correct individual particular mutations. Similarly, the recent report on oligonucleotide-based therapy targeting a particular genetic mutation and the successful treatment of

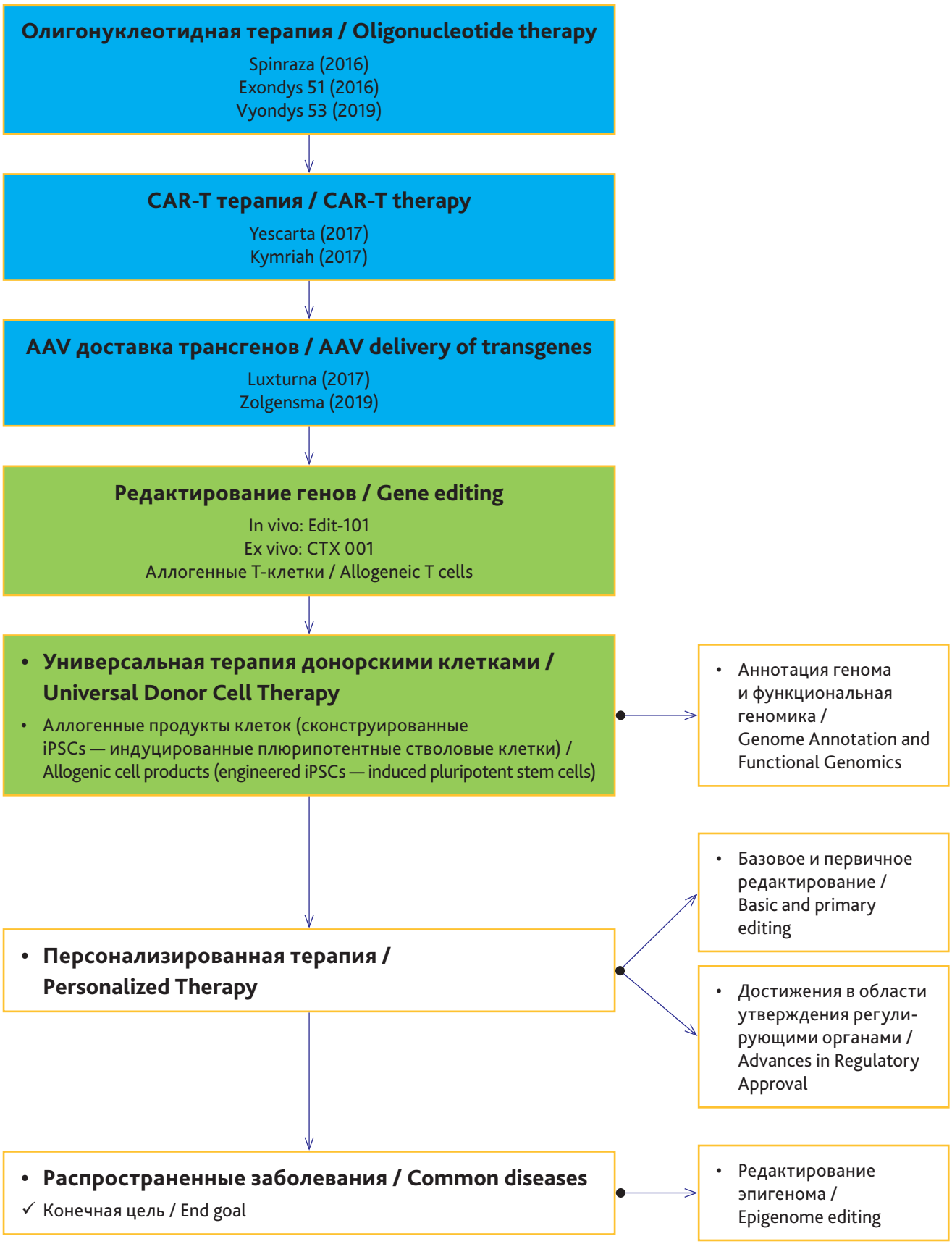

Figure. *Milestones in the development of gene therapy for common diseases.*
Note: Approved treatments and their year of approval are represented by blue boxes, while experimental treatments are represented by green boxes. To reach later milestones, further research is needed to develop alternative therapeutic approaches and address fundamental scientific questions (shown as markers)

a patient with Batten disease can only be considered as a potential program and motivation for such efforts [34]. Consequently, the significant advances in cellular and gene therapy are expected to emerge in the near future in the field of regulatory sciences, as well as the solution of unique challenges using innovative personalized technologies, as we move towards the therapy.

Conclusion

The development of genetic technologies is prioritized in the world's leading countries, and gene therapy, in particular, human genome editing is currently the most exciting and revolutionary biotechnology of the present day [35]. The unrivaled level of control over the delivery of nucleic acids, modulation of immune system, and the precise manipulation of human genome are the technologies that could not have been imagined ten years ago; they will undoubtedly give an impetus to the formation and development of new fields of medicine during the decade to come. At the same time, this emerging glimpse of a new world of technical possibilities has been inspiring the development of new research fields, such as synthetic biology, cell reprogramming and high-performance functional genomics that will undoubtedly continue to transform the concept of biomedical studies.

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Список литературы / References:

1. Friedmann T., and Roblin R. Gene therapy for human genetic disease? Science 1972; 175: 949–955. https://doi.org/10.1126/science.175.4025.949.
2. Williams D.A., Lemischka I.R., Nathan D.G. et al. Introduction of new genetic material into pluripotent haematopoietic stem cells of the mouse. Nature 1984; 310: 476–480. https://doi.org/10.1038/310476a0.
3. Blaese R.M., Culver K.W., Miller A.D. et al. T lymphocyte-directed gene therapy for ADA-SCID: initial trial results after 4 years. Science 1995; 270: 475–480. https://doi.org/10.1126/science.270.5235.475.
4. Raper S.E., Chirmule N., Lee F.S. et al. Fatal systemic inflammatory syndrome in a ornithine transcarbarmylase deficient patient following adenoviral gene transfer. Mol. Genet. Metab. 2003; 80: 148–158. https://doi.org/10.1016/j.ymgme.2003.08.016.
5. Hacein-Bey-Abina S., Kalle C.V., Schmidt M. et al. LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 2003; 302: 415–419. https://doi.org/10.1126/science.1088547.
6. Gao G., Vandenberghe L., aWilson J.M. New recombinant serotypes of AAV vectors. Curr. Gene Ther. 2005; 5: 285–297. https://doi.org/10.2174/1566523054065057.
7. Pasi K.J., Rangarajan S., Mitchell N. et al. Multiyear follow-up of AAV5-hFVIII-SQ gene therapy for hemophilia A. N. Engl. J. Med. 2020; 382: 29–40. https://doi.org/10.1056/NEJMoa1908490.
8. Mendell J.R., Sahenk Z., Lehman K. et al. Assessment of Systemic Delivery of rAAVrh74.MHCK7.micro-dystrophin in Children With Duchenne Muscular Dystrophy: A Nonrandomized Controlled Trial. JAMA Neurol. 2020; 77: 1–10. https://doi.org/10.1001/jamaneurol.2020.1484.
9. Thompson AA, Walters MC, Kwiatkowski J et al. Gene therapy in patients with transfusion-dependent beta-thalassemia. N. Engl. J. Med. 2018; 378: 1479–1493. https://doi.org/10.1056/NEJMoa1705342
10. Boutin S., Monteilhet V., Veron P. et al. Prevalence of serum IgG and neutralizing factors against adeno-associated virus (AAV) types 1, 2, 5, 6, 8, and 9 in the healthy population: implications for gene therapy using AAV vectors. Hum. Gene Ther. 2010; 21: 704–712. https://doi.org/10.1089/hum.2009.182.
11. Tse L.V., Klinc K.A., Madigan V.J. et al. Structure-guided evolution of antigenically distinct adeno-associated virus variants for immune evasion. Proc. Natl Acad. Sci. USA. 2017; 114:E4812–E4821. https://doi.org/10.1073/pnas.1704766114.
12. Maheshri N., Koerber J.T., Kaspar B.K. et al. Directed evolution of adeno-associated virus yields enhanced gene delivery vectors. Nat. Biotechnol. 2006; 24: 198–204. https://doi.org/10.1038/nbt1182.
13. Leborgne C., Barbon E., Alexander J.M. et al. IgG-cleaving endopeptidase enables in vivo gene therapy in the presence of anti-AAV neutralizing antibodies. Nat. Med. 2020; 26: 1096–1101. https://doi.org/10.1038/s41591-020-0911-7.
14. Corti M., Elder M., Falk D. et al. B-cell depletion is protective against anti-AAV capsid immune response: a human subject case study. Mol. Ther. Methods Clin. Dev. 2014; 1: 14033.
15. Meliani A., Boisgerault F., Hardet R. et al. Antigen-selective modulation of AAV immunogenicity with tolerogenic rapamycin nanoparticles enables successful vector re-administration. Nat. Commun. 2018; 9: 4098. https://doi.org/10.1038/s41467-018-06621-3.
16. Lokugamage M.P., Sago C.D., Dahlman J.E. Testing thousands of nanoparticles in vivo using DNA barcodes. Curr. Opin. Biomed. Eng. 2018; 7: 1–8. https://doi.org/10.1016/j.cobme.2018.08.001.
17. Akinc A, Maier MA, Manoharan M, et al. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. Nat. Nanotechnol. 2019; 14: 1084–1087. https://doi.org/10.1038/s41565-019-0591-y

18. Tebas P., Stein D., Tang W.W. et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N. Engl. J. Med. 2014; 370: 901–910. https://doi.org/10.1056/NEJMoa1300662.
19. Mullard A. Gene-editing pipeline takes off. Nat. Rev. Drug Discov. 2020; 19: 367–372. https://doi.org/10.1038/d41573-020-00096-y.
20. Stadtmauer E.A., Fraietta J.A., Davis M.M. et al. CRISPR-engineered T cells in patients with refractory cancer. Science. 2020 Feb 28; 367(6481):eaba7365. doi: 10.1126/science.aba7365. Epub 2020 Feb 6.
21. Xu L., Wang J., Liu Y. et al. CRISPR-edited stem cells in a patient with HIV and acute lymphocytic leukemia. N. Engl. J. Med. 2019; 381: 1240–1247. https://doi.org/10.1056/NEJMoa1817426.
22. Maeder ML, Stefanidakis M, Wilson CJ, et al. Development of a gene-editing approach to restore vision loss in Leber congenital amaurosis type 10. Nat. Med. 2019; 25:229–233. https://doi.org/10.1038/s41591-018-0327-9.
23. Finn J.D., Smith A.R., Patel M.C. et al. A single administration of CRISPR/Cas9 lipid nanoparticles achieves robust and persistent in vivo genome editing. Cell Rep. 2018; 22: 2227–2235. https://doi.org/10.1016/j.celrep.2018.02.014.
24. Федеральная научно-техническая программа развития генетических технологий на 2019 — 2027 г. [Электронный ресурс]. URL:https://legalacts.ru/doc/postanovlenie-pravitelstva-rf-ot-22042019-n-479-ob-utverzhdenii/ (дата обращения: 20.12.2021).
Federal Scientific and Technical Program for the Development of Genetic Technologies for 2019 — 2027. [Electronic resource]. URL:https://legalacts.ru/doc/postanovlenie-pravitelstva-rf-ot-22042019-n-479-ob-utverzhdenii/ (date of the application: 20.12.2021) [In Russian].
25. Anzalone A.V., Koblan L.W., Liu D.R. Genome editing with CRISPR-Cas nucleases, base editors, transposases and prime editors. Nat. Biotechnol. 2020; 38: 824–844.
26. Pickar-Oliver A., Gersbach C.A. The next generation of CRISPR-Cas technologies and applications. Nat. Rev. Mol. Cell Biol. 2019; 20:490–507. https://doi.org/10.1038/s41580-019-0131-5
27. Thakore P.I., Black J.B., Hilton I.B., et al. Editing the epigenome: technologies for programmable transcription and epigenetic modulation. Nat. Methods. 2016; 13:127–137. https://doi.org/10.1038/nmeth.3733.
28. Dey G., Jaimovich A., Collins S.R. et al. Systematic discovery of human gene function and principles of modular organization through phylogenetic profiling. Cell Rep. 2015; 10:993–1006. https://doi.org/10.1016/j.celrep.2015.01.025.
29. Shalem O., Sanjana N.E., Zhang F. High-throughput functional genomics using CRISPR-Cas9. Nat. Rev. Genet. 2015; 16:299–311. https://doi.org/10.1038/nrg3899.
30. Hnisz D., Abraham B.J., Lee T.I. et al. Super-enhancers in the control of cell identity and disease. Cell. 2013; 155:934–947. https://doi.org/10.1016/j.cell.2013.09.053.
31. Wu Y., Zeng J., Roscoe B.P. et al. Highly efficient therapeutic gene editing of human hematopoietic stem cells. Nat. Med. 2019; 25:776–783. https://doi.org/10.1038/s41591-019-0401-y.
32. ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012: 6; 489(7414): 57-74. https://doi.org/10.1038/nature11247.
33. Lanza R., Russell D.W., Nagy A. Engineering universal cells that evade immune detection. Nat. Rev. Immunol. 2019; 19:723–733. https://doi.org/10.1038/s41577-019-0200-1.
34. Kim J., Hu C., Moufawad E.l. Achkar C. et al. Patient-customized oligonucleotide therapy for a rare genetic disease. N. Engl. J. Med. 2019; 381: 1644–1652. https://doi.org/10.1056/NEJMoa1813279.
35. Федорин В.В. Генетическое редактирование человека: перспективы, неизбежность и вопрос морально-этической оправданности. Философская мысль. 2020; 12: 30-41. https://doi.org/10.25136/2409-8728.2020.12.34403.
Fedorin V.V. Human genetic editing: prospects, inevitability and the issue of moral and ethical justification. Philosophical thought. 2020; 12: 30-41. https://doi.org/10.25136/2409-8728.2020.12.34403 [In Russian].