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Adeno-associated viruses in gene therapy for spinal muscular atrophies: trend or triumph?

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ABSTRACT

The development of gene therapy in the 21st century is largely based on application of viral vectors, which have shown their effectiveness along with a fairly high safety profile. Among the vector systems, one of the leading places was taken by adeno-associated viruses (AAV), on the basis of which drugs were created for the treatment of severe hereditary monogenic diseases, including spinal muscular atrophies (SMA). Their use, on the one hand, is justified by the flexibility of AAV as a platform for the creation of gene therapy drugs, and on the other hand, it is often perceived as a kind of trend that has significant limitations. In this review, the focus is on two main aspects: AAV as a vector for the treatment of diseases from the SMA group and possible directions of development in this area and in gene therapy in general.

The review operates with recent data published after clinical trials and experimental studies during last decade, and also critically examines the possibilities of gene therapy using AAV, mentioning other existing approaches, incl. medical therapy for SMA.

Attention is also paid to the situation in the field of using AAV for the treatment of other hereditary diseases and the most acute problems faced by the use of drugs created on the basis of this promising vector system.

Keywords: gene therapy; AAV; neuromuscular dystrophy; spinal muscular atrophy.

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Аденоассоциированные вирусы в генной терапии спинальных мышечных атрофий: тренд или триумф?

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АННОТАЦИЯ

Развитие генной терапии в XXI веке в значительной степени опирается на использование вирусных векторов, которые показали не только свою эффективность, но и достаточно высокий профиль безопасности. Среди векторных систем одно из ведущих мест заняли аденоассоциированные вирусы (ААВ), на основе которых были созданы препараты для лечения тяжелейших наследственных моногенных заболеваний, в том числе спинальных мышечных атрофий (СМА). Использование ААВ, с одной стороны, обосновано их гибкостью как платформы для создания генотерапевтических препаратов, а с другой зачастую воспринимается как своеобразный тренд, у которого есть существенные ограничения. В данном обзоре акцент сделан на два основных аспекта: ААВ как вектор для лечения заболеваний из группы СМА и возможные направления развития в этой области и в генной терапии в целом.

Обзор оперирует актуальными данными, опубликованными в ходе клинических и экспериментальных работ последних лет, а также критически рассматривает возможности генной терапии с помощью ААВ с упоминанием и других существующих подходов, в том числе медикаментозной терапии СМА.

Внимание также уделено ситуации в области использования ААВ для лечения иных наследственных заболеваний и наиболее острым проблемам, с которыми медики сталкиваются в процессе применения препаратов, созданных на основе этой перспективной векторной системы.

Ключевые слова: генная терапия; аденоассоциированные вирусы; нейромышечная дистрофия; спинальная мышечная атрофия.

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INTRODUCTION

To date, the majority of effective gene therapy (GT) drugs for monogenic, oncologic, neurodegenerative, and blood system diseases use recombinant vectors produced by genetic engineering methods using various viruses. The resulting vectors of GT lack genes associated with or directly determining the pathogenicity of wild-type viruses and their ability to replicate, which ensures the safety of viral GT drugs. Although the use of genome-integrating retroviruses, lentiviruses, and genome-editing technologies in GT is gaining attention, it will remain outside the focus of present review.

Gene therapy using recombinant adeno-associated viruses (AAVs) is a rapidly developing field with promising successes and challenges discussed in this report. Application of AAVs in GT of monogenic hereditary diseases, including neuromuscular disorders is of particular interest. Recently AAVs have become an efficient and flexible aspect for gene delivery to human cells.

STRUCTURE AND TISSUE TROPISM OF ADENO-ASSOCIATED VIRUSES AND PROMOTER SELECTION FOR TARGET-GENE EXPRESSION

AAV genome structure

Adeno-associated virus is a small virus (20–25 nm) that belongs to the *Parvoviridae* family. Its genome is represented by a single-stranded DNA of approximately 4.7 kb in length and includes several obligatory elements that ensure replication in the normal life cycle in coinfection with adenovirus. The term "adeno-associated" was coined due to this coinfection required for wild-type AAVs to replicate [1]. These elements include:

- replication (Rep) genes encoding four non-structural proteins (Rep78, Rep68, Rep52, and Rep40) involved in replication, transcription control, integration, and encapsulation;
- viral cofactor gene, which encodes an assembly-activating protein;
- structural capsid genes (*Cap* or *Vp1*, *Vp2*, and *Vp3*).

Recombinant AAVs are generated by deleting all open reading frames from the viral genome, resulting in their transformation into a replication-defective virus or vector. This approach significantly enhances safety and provides vector capacity which is limited to 4.5–4.7 thousand nucleotide pairs because of the small size of AAV capsids.

The only genomic fragments that remain in AAVs after vector creation are two inverted terminal repeats (ITRs) crucial for viral DNA or transgene replication. Minimal ITRs contain a binding site for the viral Rep protein, which aids in the integration of the vector genome into the preformed capsid particle.

AAV capsid and its contribution to tropism of the resulting vectors

The capsid envelope of AAVs provides protection against nucleases and recognition by the innate immune system and determines the virion's tropism. There are 13 known serotypes of AAVs with differing expressed surface antigens and amino acid sequences [1, 2]. These serotypes are characterized by a pronounced tissue tropism. Regarding GT drug development selection of a vector with a specific tropism enables transduction in cells of a particular tissue and reduces delivery to nontarget organs.

Of the 11 major serotypes cloned to date, AAV2 is the most well-characterized. It is known for its safety and efficacy and its high packing and transducing capacity. AAV2 is often used as a basis for creating hybrid vectors, in which the ITRs of one serotype are packaged into the capsid of another serotype to modify its tropism in tissues. The promising new AAV variants AAVrh10 and AAVrh74 have been isolated from rhesus macaques. Compared with AAV2, these serotypes have a higher transduction efficiency, and preexisting immunity against these serotypes is less common in humans [3, 4].

Adeno-associated virus transduction occurs through the interaction of the capsid with glycans and proteoglycans, such as heparan sulfate, expressed in various tissues. Primary binding is followed by interaction with more specific membrane receptors, and the virus is internalized. Fibroblast growth factor receptor 1 is the receptor for AAV2 [5], hepatocyte growth factor receptor is for AAV2 and AAV3 [6], and platelet-derived growth factor receptor is for AAV5 [7], and the universal AAVR receptor [8] is known.

The AAV2 serotype is commonly used for developing GT drugs, whereas the AAV9 and AAV8 vectors are used for treating nervous system diseases. Furthermore, clinical trials are underway for drugs with new capsids, such as AAV-LK03, SPK-100, and AAV-HSC15; however, their safety has not yet been fully characterized.

Promoter variants for transgene expression and their efficiency

Promoters commonly used include cytomegalovirus (CMV) promoter, chicken beta-actin (CBA) promoter, and CAG (synthetic promoter consisting of CMV enhancer, CBA promoter, and rabbit beta-globin splicing acceptor). The recipient organism's native promoters are used for more specific gene delivery [9, 10]. Administration of high doses of vectors with native promoters does not result in serious adverse events, even at doses up to 2×10^{14} viral particles per kilogram. However, studies on animal models have shown that several copies of the AAV9 vector can cause serious toxicity [11]. How the presence of a native promoter affects the final number of viral particles in transducted

tissue and the safety of the vector remains unknown. The development of BIIB089 for the treatment of spinal muscular atrophy (SMA) was discontinued because of its high toxicity and insufficient efficacy. Unfortunately, information on the structure of the vector used is not available [12, 13].

Cytomegalovirus and CAG promoters are commonly used to treat diseases of the central nervous system (CNS). However, studies have shown that two other promoters, mPGK and hSYN, provide stronger transgene expression in the brain and spinal cord than CAG and CMV [14]. Despite this, their introduction into the clinic has been slow. The *GAD* gene encoding glutamic acid decarboxylase was administered in patients with Parkinson's disease in clinical trials using the first neuron-specific NSE promoter in 2005. However, it took more than 15 years to progress to phase II by early 2021 [13, 15].

ADENO-ASSOCIATED VIRUSES AS A TOOL FOR GENE THERAPY

Current status of gene therapy using AAVs

The first drug for GT that delivered the target gene using AAVs was Glybera (alipogene tiparvovec*[1], Uniqure NV, the Netherlands). It received marketing authorization from the European Medicines Agency (EMA) in 2012 [16]. Although intended for the treatment of hereditary lipoprotein lipase deficiency, it was withdrawn from the market in 2017 owing to low demand and high production costs [17].

The approval of voretigene neparvovec* (Luxturna; Spark Therapeutics, USA) [18] by the US Food and Drug Administration (FDA) in 2017, based on modified AAV2, and of onasemnogene abeparvovec (Zolgensma; Novartis, Switzerland) [19] in 2019, based on AAV9, has significantly increased interest in GT by recombinant AAVs. These drugs are currently approved in the USA, EU, UK, Australia, Canada, and South Korea. Additionally, Zolgensma is approved in Israel, Taiwan, Brazil, and Japan. In 2022, eladocagene exuparvovec* (Upstaza; PTC Therapeutics, USA) received approval from the EMA [20]. The drug is an AAV2 vector carrying the gene that encodes L-decarboxylase of aromatic amino acids and used for the treatment of conditions associated with hereditary deficiency of this enzyme. In 2022, etranacogene dezaparvovec (Hemgenix; Uniqure NV, The Netherlands), an AAV5-based drug carrying the gene for clotting factor IX and intended for GT of hemophilia B, was approved for the treatment of hemophilia in the USA [21]. Furthermore, in 2023, FDA approved valoctocogene roxaparvovec (Roctavian; BioMarin Pharmaceutical, USA), which uses AAV2 as a vector carrying blood clotting factor VIII for hemophilia A treatment [22]. Moreover, delandistrogene moxeparvovec-rokl (Elevidys; Sarepta Therapeutics, USA) has been approved for Duchenne muscular dystrophy treatment. The drug is a recombinant AAV vector carrying the microdystrophin gene [23].

Two drugs are in the registration stage and were developed for the treatment of genetic disorders. First, lenadogene nolparvovec* (Jonathon, GenSight Biologics S.A., France) is based on AAV2 with the *ND4* gene and is intended for the treatment of Leber's hereditary optic neuropathy [24]. Second drug, resamirigene bilparvovec* (AT132; Astellas Gene Therapies, USA) was developed for X-linked myotubular myopathy treatment and carries the myotubularin 1 (*MTM1*) gene using AAV8. In ASPIRO trial [25], 2 of 17 boys who received AT132 intravenously at a dose of 3×10^{14} viral genomes per kilogram of body weight developed fatal hepatic failure. These two boys received a much higher dose (4.80×10^{15}–7.74×10^{15} viral genomes total) because of their higher body weight. Whether the hepatic failure was caused by concomitant diseases or a higher dose of AAV was unclear [25]. In the second quarter of 2023, drug developers met with the US FDA and decided to carry on with ongoing clinical trials [24].

Immunogenicity and oncogenicity of AAV-based vectors

Mechanisms of the immune response to AAVs and approaches to reduce immunogenicity. A primary issue with the use of viral vectors is their immunogenicity, which makes it unsafe to reintroduce preparations based on them. The development of the immune response to AAV involves both humoral and cellular links of innate immunity. The activation of humoral immunity results in the formation of capsid-specific antibodies, including neutralizing antibodies. Preexisting antibodies, including those resulting from previous exposure to wild-type AAV, can diminish or completely impede transduction by the therapeutic vector, thereby reducing treatment efficacy. Antibodies that are generated in response to the initial administration of a genetic vector do not affect transduction; however, they prevent the reuse of AAV of a specific serotype. Furthermore, cross-reactivity of antibodies to AAV of other serotypes may occur.

The cellular immune response includes the activation of cytotoxic T-cells approximately 4–12 weeks after the genetic vector is introduced. Studies on animal models indicate that Toll-like receptors mediate the development of the T-cell response by recognizing AAV capsid antigens [26, 27].

Cellular immunity activation upon recognition of AAV capsids is a crucial factor that affects the safety and efficacy of GT. A possible outcome of such a response is hepatotoxicity, which was observed in a clinical study that used AAV of several serotypes, including AAV2, AAV8, AAV10 [28], and AAV9. *In vitro* studies have indicated that the immune response in the liver is triggered by a liver-specific population of macrophages called Kupffer cells [29]. The strong affinity of AAV9 to liver cells poses a significant risk of hepatotoxicity, and a dose-dependent effect of adverse events may be

[1] All marked * drugs are not registered in the State Register of Medicines of the Russian Federation. Available from: https://grls.rosminzdrav.ru/GRLS.aspx.

observed in some patients. Clinical studies [30–32] have shown that prophylactic administration of prednisolone prevented onasemnogene abeparvovec hepatotoxicity. The current protocol for onasemnogene abeparvovec includes prophylactic administration of prednisolone at the lowest doses and for the shortest duration possible. This treatment has no significant effect on pediatric patients.

Adeno-associated virus has an advantage over other viruses as a vector for GT because it elicits a minimal cellular and humoral immune response. The main immune response to AAV is in the form of neutralizing antibodies (nAbs) to the capsid, which prevent AAV from binding to the receptor and entering the cell upon reintroduction. However, the presence of nAbs does not affect the safety of the initial administration of AAV, but significantly reduces its efficacy.

The prevalence of acquired immunity to serotypes AAV2 and AAV3 is high, with 30–80% of people exposed to AAV2 in early childhood and a similar prevalence observed for AAV3. In contrast, nAbs to AAV5 and AAV6 are less common, found in 10–20% and up to 30% of the population, respectively. Infection with AAV7 and AAV8 is rare, affecting no more than 5–6% of individuals. Therefore, nAbs in one or more serotypes of AAVs in a certain number of individuals in the population is possible [33, 34]. This may reduce the effectiveness of GT using this virus, considering possible cross-immunity.

Moreover, transplacental transmission of nAbs from the mother is notable. For instance, nAbs to AAV9 (mainly immunoglobulins of class G) can be detected in the first 6 weeks after birth. Typically, their titer becomes undetectable after 4–6 months. In a clinical study investigating the use of onasemnogene abeparvovec based on AAV9 in patients with SMA, 5.6% of children exhibited an increased level of nAbs to AAV9 (>1:50) upon retesting. Thus, in actual clinical practice, the nAb titer is assessed before administering AAV-based GT drugs [35].

Patients with nAbs are typically excluded from AAV clinical trials. However, the blood–brain and blood–retinal barriers protect the CNS and vision organs from systemic immunity, making it unnecessary to exclude such patients. Therefore, the development and optimization of methods for local administration of GT drugs into the CNS and other immunoprivileged organs are relevant. However, systemic leakage of AAV from the CNS may also occur depending on the delivery route. This was observed in a phase II clinical trial of a drug designed for intracerebroventricular (ICV) delivery of the *GDNF* gene using AAV2. Dissemination of the vector into the cerebrospinal fluid resulted in adverse events and low therapeutic efficacy [36, 37].

Low oncogenicity as a key advantage of AAVs

One advantage of selecting AAVs for delivering therapeutic genes is that they are not typically integrated into the host genome, except in a few cases observed in animals, and instead exist in the cell as episomes. This characteristic significantly decreases the mutagenicity of these vectors [2, 38].

No direct oncogenic effects of AAVs in humans have been reported [39]. However, rare cases of AAV transgene integration into the genome of other mammals have been documented [40, 41]. In a study involving systemic administration of AAV2 and AAV9 to newborn MPSVII mice with hereditary combined deficiency of hexosaminidase A and B (Sandhoff disease model), increased incidence of hepatocellular carcinoma was observed as the animals matured. Analysis of the tumor genetic material showed that the AAV genome was inserted into the Rian locus of mouse chromosome 12, leading to dysregulation of neighboring genes. This finding is significant regarding AAV-induced mutagenesis; however, this locus is only present in rodents. Therefore, this discovery does not contradict the current understanding of the safety of AAVS in humans [42, 43].

SPINAL MUSCULAR ATROPHY AS A KEY INDICATION FOR GENE THERAPY

Characteristics and etiology of diseases from the group of SMAs

Spinal muscular atrophy are a group of inherited diseases of the peripheral nervous system characterized by damage to motor neurons of the brain and spinal cord. Amyotrophic lateral sclerosis (ALS) is a similar disease in pathogenesis and clinical manifestations, affecting both upper and lower motor neurons, leading to paralysis and muscle atrophy [44]. The molecular and genetic mechanisms of ALS are unclear.

Most SMA cases are caused by mutations or deletions in the survival of motor neuron 1 (*SMN1*) gene and are inherited in an autosomal recessive manner. This gene is in chromosome 5q and encodes a survival motor neuron (SMN) protein [45, 46]. The *SMN1* gene has a paralog, *SMN2* that differs by splicing in exon 7. *SMN2* also encodes SMN protein, but SMN production is deficient when *SMN1* is completely deleted. SMA severity is determined by the number of copies of the *SMN2* gene. The more copies of the gene, the milder the symptoms of the disease.

Rare cases of SMA are caused by lesions in the following genes: *VAPB* (chromosome 20), *DYNC1H1* (chromosome 14), *BICD2* (chromosome 9), and *UBA1* (X chromosome).

Similar to other neuromuscular diseases that affect motor neurons, SMAs are incurable monogenic diseases caused by loss-of-function mutations (resulting in reduced or absent protein function) in a specific gene (or its deletion), making them potential targets for GT.

The following types of SMAs are distinguished [47].

- Type 0 manifests itself in the prenatal period in the form of decreased fetal activity; newborns experience heart defects and areflexia, and death occurs due to respiratory failure during the first 6 months of life.

- Type I (infantile SMA or Werdnig–Hoffman disease) is intrauterine or manifests in the first 6 months of life; muscle hypotonia, hyporeflexia, and difficulty sucking and swallowing are observed, and without treatment, most patients do not survive to 2 years of age.
- Type II (intermediate form or Dubowitz syndrome) first appears at 6–18 months of age. Children are unable to sit, stand, or walk unaided, and respiratory problems often lead to early death.
- Type III (Kugelberg–Welander disease) usually occurs between 18 months and adolescence. Children can walk independently but have difficulty running and climbing stairs. The disease progresses slowly, life expectancy is longer (sometimes up to normal) compared with other types and depends on the development of respiratory complications or other conditions that include scoliosis and contractures.
- Type IV develops in adulthood and manifests as slowly progressive weakness and proximal muscle atrophy.

Marketed approaches for the treatment of SMAs

The pathogenetic treatment of SMA is based on increasing SMN protein levels with the goal of reducing symptoms, improving motor function, and preventing life-threatening complications.

Currently, the following drugs have been approved by the FDA and EMA:

1. Nusinersen (Spinraza; Biogen, USA) is the first approved drug for the treatment of all types of SMA in pediatric and adult patients. It is an antisense oligonucleotide that inhibits the splicing of exon 7 of the *SMN2* mRNA, resulting in the synthesis of a longer, more functional form of the SMN protein [48]. Spinraza is administered intrathecally, and the first four doses (after the first dose on day 0) are administered every 2 weeks (second and third dose) and on day 63 from the time of the first dose (fourth dose). Maintenance therapy consists of a single injection of the drug every 4 months [49].
2. Risdiplam (Evrisdi; Genentech, USA) is an oral drug used for the treatment of SMA. Similar to nusinersen, it is an *SMN2* splicing modifier [50]; however, it uses a small molecule rather than an oligonucleotide as the active ingredient. Risdiplam is indicated for patients with SMA type I, II, or III or for patients with up to four copies of the *SMN2* gene (EMA). FDA has approved the drug for use in all patients with SMA regardless of the number of copies of the *SMN2* gene.
3. Onasemnogene abeparvovec (Zolgensma; Novartis, Switzerland) is a GT drug for SMA that uses an AAV9-based vector to carry the *SMN1* gene. It is administered through a single intravenous infusion. FDA and EMA approved the therapy in 2019, but with different indications. Zolgensma has been approved by both EMA and FDA for use in patients with inherited mutations in the *SMN1* gene. This includes patients with type I SMA or up to three copies of the *SMN2* gene and pediatric patients below 2 years old with biallelic mutations in the *SMN1* gene [51, 52].

AAV9 as an optimal vector for SMA treatment

As previously stated, SMA is caused by a mutation in a specific gene, and GT is the etiotropic treatment. A further advantage of GT in SMA is that AAV-mediated transduction of neural tissue can result in long-term gene expression. This is because mature neurons are nondividing cells, and therefore, there is no mitosis in them, resulting in no associated drop in expression from episomal sequences delivered by AAV.

The sole registered viral preparation for GT of SMA with Zolgensma is an AAV9-based vector that carries the *SMN1* gene. Gene expression is driven by a CMV enhancer and a hybrid CBA promoter. AAV9-based vectors have unique characteristics [53] that enable them to cross the blood–brain barrier (BBB), making them suitable for gene delivery to the CNS using relatively minimally invasive intravenous administration in other diseases.

Systemic administration of AAV9 transduces astrocytes in adult mice and neurons and lower motor neurons in newborn animals [54]. The systemic administration of the AAV9 vector in SMA is justified by the fact that mutation in the *SMN1* gene leads to damage in various parts of the body, including motoneurons of spinal ganglia, the nervous system, heart [55], pancreas [56], and skeletal muscles [57].

The AAV9 vector used in Zolgensma is self-complementary, resulting in improved efficacy after a single injection. Currently, data on the efficacy and safety of onasemnogene abeparvovec therapy are available at an average of 7.1 years after treatment initiation. In the START study (NCT02122952), all 10 patients who received the therapeutic dose of the drug were alive, did not require constant ventilation, and continued to show efficacy in preserving previously acquired or achieving new motor skills [58–60]. The clinical study [61] reported adverse events caused by drug administration, limited to an increase in serum hepatic aminotransferases levels approximately 3 weeks after treatment initiation, without other clinical manifestations. Administration of prednisolone effectively mitigated this increase of hepatic enzyme activity.

The phase 3 clinical trial (STR1VE) results showed that onasemnogene abeparvovec was more effective than the control group (a group of patients in a study that examined the natural course of SMA) in terms of the ability to sit unsupported for 30 s. At 18 months of age, 59% of patients demonstrated this ability compared with 0% in the control group (p <0.0001). In the clinical trials, 90.9% of patients were alive after 14 months and did not require continuous ventilation, compared with only 25% of the controls. The trials involved 54 patients below 6 months old, and 2 patients died of causes unrelated to the drug [62, 63].

The SPR1NT study investigated the use of onasemnogene abeparvovec in patients with preclinical

SMA. All 29 participants survived, did not require continuous ventilation, and exhibited age-appropriate motor development [64, 65].

Problematic aspects of using AAV9 in the treatment of SMA

The long-term effects of onasemnogene abeparvovec administration are still being studied in the 15-year follow-up of patients who participated in a clinical trial [66]. Currently, the oldest patient included in the START study is 8.5 years old (8 years after drug administration) [62]. Some scientists have shown that the efficacy of the therapy may decrease in certain patients. This may be attributed to a decrease in the expression of the target gene in transduced cells due to their rapid division in a growing organism [67].

AAV9 can transduce various cells and tissues throughout the body when administered systemically. To achieve more targeted delivery to the CNS, it is advisable to use neuro- or astrocyte-specific promoters. Besse et al. [68] tested this concept. The researchers created an AAV9 vector that expresses SMN, controlled by the human synapsin (SYN) promoter, called AAV9-SYN-SMN. Then, they investigated the impact of ICV administration of AAV9-SYN-SMN on the survival and neuromuscular functions of SMN knockout (SMNΔ7) mice. The AAV9-PGK-SMN vector, which encodes SMN under the phosphoglycerate kinase (PGK) promoter, was used as a control. Both intravenous and ICV injections were administered, with the latter resulting in maximal SMN expression in CNS tissues. The SMN level in the brain and spinal cord of SMNΔ7 mice was 6–9 times higher when injected with AAV9-SYN-SMN vector intracerebroventricularly or with AAV9-PGK-SMN vector intravenously. The maximum dose of AAV9-SYN-SMN induced SMN expression in the spinal cord and brain at a level comparable to that of AAV9-PGK-SMN administered intravenously. However, the efficacy of AAV9-SYN-SMN was inferior to that of AAV9-PGK-SMN administered by different routes. SMN levels in peripheral tissues were similar when administered both intracerebroventricularly and intravenously.

Accumulated clinical data demonstrate the safety of AAVs, justifying their use for therapeutic gene delivery. One promising direction is the development of novel methods to enhance the efficiency of delivery and GT for CNS diseases.

POSSIBLE DIRECTIONS FOR DEVELOPMENT OF GT USING ADENO-ASSOCIATED VIRUSES

Approaches for the modification of AAV vectors

Altering the sequence of AAV capsid proteins can significantly affect transduction efficiency, enabling modifications to control transduction and tissue tropism. Currently, the following techniques and approaches appear to be the most promising:

1. Insertion of specific peptide ligands into capsids to deliver therapeutic genes to targeted cells and tissues. The inclusion of these peptides in the capsid ensures the recognition and binding of the vector to specific proteins on the cell surface. Some modifications of peptide ligands also enhance the penetration of the virus into the cell [69]. Peptides enhance AAV transduction in skeletal muscle cells [70], lungs [71], blood vessels [72–74], pancreatic islets [75], and various tumor cells [76, 77].

Although the insertion of ligands and peptides into the capsid can promote specific binding of the vector to cellular receptors and increase transduction efficiency, these modifications have limitations. The insertion site is restricted to specific locations on the capsid, and modifying these sites could adversely affect receptor-mediated viral entry. Therefore, designing peptide insertions rationally requires identifying capsid sites that are resistant to modification. Additionally, the specificity of many peptides or ligands depends on their conformation. Disrupting the correct three-dimensional structure during insertion may result in reduced efficiency compared with an unmodified vector. Finally, the modified capsid may be neutralized by preexisting antibodies.

2. Using the natural diversity of open AAV serotypes to create mosaic/chimeric capsids. Mosaic vectors consist of capsid proteins from multiple AAV serotypes. Chimeric AAVs are created through directed evolution or genetic engineering, which alters the amino acids in the capsid. Directed evolution involves either error-prone PCR or DNA shuffling. Error-prone PCR is performed under specific conditions that increase the polymerase error rate, resulting in capsid variants with random mutations. DNA shuffling involves restriction enzymes to fragment the cap genes of selected serotypes. These fragments are then randomly recombined into full-length capsid genes, followed by amplification of the variants. Chimeric capsids are obtained, and selective screening with the preferred cell type is performed to select variants with the most suitable characteristics [69, 78].

The genetic engineering approach uses capsid structure and sequence information to create new chimeric viruses. This is achieved by transferring specific capsid residues or domains from one serotype to another to achieve the desired phenotype.

Changing the ratio of proteins of each serotype can achieve the necessary efficiency of transduction for a specific cell type. For instance, Rabinowitz et al. [79] demonstrated that creating a capsid based on serotypes AAV3 and AAV5 in a 3:1 ratio enables the viral particle to bind to both heparin and mucin on the cell surface. In contrast, AAV3 binds only to heparin, and AAV5 has tropism only to mucin [79]. To maintain high transduction efficiency while achieving tropism to a specific tissue type, it is advisable to create

chimeric vectors that include part of the capsid proteins from the wild-type virus and part from the capsid modified with a peptide ligand [80].

3. Exogenous modification of the capsid. These approaches range from the use of bispecific antibodies to bind the virus to receptors and specific cellular capture [81] to biotinylation followed by conjugation of targeting ligands [82, 83]. Furthermore, specific enveloping agents are used to coat the capsid for conjugation with ligands and can prevent viral neutralization by antibodies [84, 85]. Encapsulating AAV2/9 vectors in cationic lipids significantly improves their transduction [86].

4. Use of tissue-specific promoters. To achieve the expression of the therapeutic gene in a specific cell type, tissue-specific promoters can be selected. For instance, synapsin or CamKII promoters can be used for specific transgene expression in neurons [87–89], GFAP or ALDH1/1 promoters for expression in astrocytes [90, 91], and myelin basic protein promoters for oligodendrocytes [92, 93].

AAB9 modification as an approach to the development of new-generation drugs for GT of SMA

A critical discovery in CNS vector transduction was the identification of the AAV9 serotype due to its high tropism in nervous system tissues [54]. A single intravenous or intrathecal injection of an AAV9-based vector has been shown to result in effective and extensive transduction of the spinal cord and CNS, which has spurred research and development of GT using this serotype. AAV9 is currently considered the preferred vector for delivery to the CNS through systemic administration. It is extensively used in clinical trials with minimal indications of peripheral or central toxicity [94].

As previously stated, onasemnogene abeparvovec AAB9 has tropism in various tissues, particularly liver cells, which can result in increased hepatic transaminases. In a study by Pulicherla et al. [95], a vector with reduced liver tropism was obtained using the error-prone PCR method while efficiently transducing cardiac and skeletal muscles. Modifications were made to the GH-loop (amino acids 390–627), which is a capsid region required for receptor binding and influencing the tropism and immunogenicity of the vector.

Using the rational engineering approach, researchers obtained a variant of the AAB9.HR capsid. This vector maintains AAV9's ability to penetrate the BBB when administered intravenously to newborn mice, while reducing peripheral tissue transduction [96].

The CREATE method, which uses Cre-induced recombination, produced the AAV-PHP.B vector. This vector demonstrated a 40-fold increase in the transduction efficiency of adult mouse CNS cells after intravenous injection compared with AAV9. In addition to astrocytes, this vector transduced $CC1^+$ oligodendrocytes and several subtypes of neurons [97]. However, the obtained serotype is only effective in animals possessing the Ly6A receptor and is not suitable for primates or clinical use [98].

Gene therapy for other neuromuscular diseases

Gene therapy is being used in preclinical and clinical studies to study various neuromuscular disorders of monogenic origin.

For instance, familial ALS is caused by a mutation in the *SOD1* superoxide dismutase gene. This mutation leads to the accumulation of misshapen SOD1 protein, which damages cells. A possible treatment for ALS involves the use of AAV carrying a microRNA that targets *SOD1*. The initial use of this vector in two ALS patients resulted in reduced SOD1 levels in spinal cord tissue after intrathecal infusion [99], but did not lead to any clinical improvement. Thus, further studies are required.

Spinal muscular atrophy with respiratory distress syndrome type 1 (SMARD1) is an autosomal recessive motor neuron disease caused by mutations in the *IGHMBP2* gene (11q13). Unfortunately, SMARD1 currently has no cure and primarily affects children. In a mouse model, GT with AAV9 restored the level of target protein, motor function, and neuromuscular physiology and increased the lifespan of animals [100]. This finding has led to the initiation of clinical trials for this drug.

Duchenne muscular dystrophy is caused by mutations in the *DMD* gene, which encodes the subsarcolemmal protein dystrophin. The *DMD* gene is relatively large, at 11,500 bp, making it challenging to package into an AAV-based vector. However, studies have shown that disease symptoms can be alleviated using shorter forms of the dystrophin protein [101, 102]. Several clinical trials are currently underway using AAVs of different serotypes (AAVrh74, AAV8, and AAV9) encoding micro/mini-dystrophin [103, 104]. In 2023, Elevidys was approved by FDA based on recombinant AAVrh74 capsid [23].

Pompe disease, also called glycogen storage disease II, is a muscle disease caused by acid alpha-glucosidase (*GAA*) gene mutations. Enzyme replacement therapy has been used to treat the disease for many years; however, its effectiveness has been limited. It is inherited in an autosomal recessive pattern and affects various organs, including the heart and CNS. As an alternative, GT has been proposed because it has shown efficacy in animal models by reducing glycogen accumulation in the myocardium and motoneurons [105]. Currently, several clinical trials are underway for gene replacement therapy using AAV vectors of different serotypes (AAV1, AAV2/8, AAV9) carrying the *GAA* gene for intramuscular or intravenous administration [104].

X-linked myotubular myopathy is another neuromuscular disease candidate for GT. In dogs, the administration of AAV with the myotubularin gene (*MTM1*) resulted in a significant improvement in muscle strength and survival [106]. However, a clinical trial revealed severe hepatotoxicity in patients receiving high doses of AAV8 with the *MTM1* gene, resulting

in two deaths. The mechanisms that caused these adverse events are not fully understood. It is possible that the presence of antibodies in patients with AAV or comorbidities may have influenced the development of adverse events [107].

Development of direct GT methods with delivery to the CNS

Delivery of genes to the CNS and organs responsible for hearing and vision presents a significant challenge owing to physiological barriers such as the BBB. To overcome this limitation, various methods, including intraocular, intravitreal, and subconjunctival injections, have been applied to target the visual and auditory organs and treat neurosensory disorders. Direct infusion of AAV is the most commonly used method for delivering therapeutic genes to the brain. However, other delivery strategies, such as ICV, intracisternal, and intrathecal routes into the cerebrospinal fluid or bloodstream, may be useful for treating multifocal diseases.

The administration of drugs directly into the CNS requires a surgical procedure that involves the insertion of a needle or a flexible fused-silica catheter into the parenchyma through trepanation holes drilled in the skull. The patient is anesthetized and held inside a stereotactic frame during the procedure. Intracerebral injection of AAV was the first vector delivery method and is still commonly used in clinical trials because of its generally well-tolerated nature [94, 108–111].

Intranasal delivery is a noninvasive alternative that can restore therapeutic lysosomal enzyme levels. These enzymes can diffuse into the CNS after secretion. Additionally, intramuscular or intraspinal injections of AAV are used to treat certain motor neuron diseases [94].

Local administration of the vector has significant advantages over systemic administration. First, it allows for the maximum concentration of the vector in the target tissues. Second, it reduces the extent of biodistribution and associated risks of immunogenicity and toxicity.

Multilevel injections into the spinal cord parenchyma have been successfully applied in preclinical conditions in mouse models of ALS [112–114] in motor neuron diseases. However, the translation of such approaches to larger mammals and clinical trials is challenging because of the high risks of surgical intervention. In addition to the risk of viral or bacterial infection, bleeding, and edema inherent in any neurosurgical intervention, the main limitation associated with stereotactic AAV injection is the vector's limited diffusion into the parenchyma. To enhance vector diffusion in animal models, a convection-enhanced delivery technique has been used, or the vector is coinjected with heparin [115] or mannitol [116]. In animal models, researchers have studied the administration of vectors through intraventricular, intracisternal, and intrathecal routes.

As previously stated, the BBB is a complex biological barrier composed of layers of brain endothelial cells connected by tight contacts, pericytes, and astrocytes. Attempts to compromise its integrity to facilitate the delivery of therapeutic agents, such as mannitol, have been linked to significant side effects [116, 117].

Importantly, the injected transgene is expressed in different cell types depending on the age of the organism. For instance, in newborn mice, the transgene is expressed in neurons, whereas in adults, it is expressed in astroglia [54]. Similar results were obtained in rhesus macaques. Neurons were observed to be transduced after intravenous infusion of AAV9 into newborn animals, whereas glia was predominantly transduced when the vector was administered to young monkeys [54, 118, 119].

Another serotype of AAV that can penetrate the BBB during intravenous administration is the AAVrh10 variant. According to Tanguy et al. [120], AAVrh10 has a higher transduction efficiency than AAV9 in most of the central and peripheral nervous systems. Interestingly, the distribution of AAVrh10 did not alter with increasing vector dose, whereas a dose-dependent effect was observed for AAV9 transduction, indicating that the two vectors have different transduction mechanisms.

CONCLUSIONS

Vectors based on AAVs are the leading platform for gene delivery and treatment of various human diseases. The progress in this field of GT has been significantly boosted by novel biotechnological methods for the rational development of AAV capsids and optimization of genome design. Preclinical and clinical studies have demonstrated the efficacy of GT using AAV which are now considered an optimal therapeutic vector which is supported by their efficacy and safety profiles. The natural properties of various AAV serotypes and targeted modifications of the capsid allow efficient transduction of various cells and organs in the organism, including nervous tissue. Marketing authorisarion of onasemnogene abeparvovec — a GT drug for the treatment of SMA was a crucial step in the development of similar therapies for other neuromuscular diseases.

The long-term effects regarding efficacy and safety of AAVs are still being studied. Current directions in the development of GT mediated by these viruses include creating new capsid modifications, modifying promoters and enhancers, and exploring new routes and delivery methods to achieve specific tissue tropism, improve safety, and enable highly- effective treatments for neuromuscular and neurodegenerative disease.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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