编号：YY001-20221010001

标题：AAV-mediated gene therapy: Advancing cardiovascular disease treatment

简介：Gene therapy has revolutionized the field of medicine, offering new hope for those with common and rare diseases. For nearly three decades, adeno-associated virus (AAV) has shown significant therapeutic benefits in multiple clinical trials, mainly due to its unique replication defects and non-pathogenicity in humans. In the field of cardiovascular disease (CVD), compared with non-viral vectors, lentiviruses, poxviruses, and adenovirus vectors, AAV possesses several advantages, including high security, low immunogenicity, sustainable and stable exogenous gene expression etc., which makes AAV one of the most promising candidates for the treatment of many genetic disorders and hereditary diseases. In this review, we evaluate the current information on the immune responses, transport pathways, and mechanisms of action associated with AAV-based CVD gene therapies and further explore potential optimization strategies to improve the efficiency of AAV transduction for the improved safety and efficiency of CVD treatment. In conclusion, AAV-mediated gene therapy has great potential for development in the cardiovascular system.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105807

编号：YY001-20221010002

标题：Immunogenicity and toxicity of AAV gene therapy

简介：Gene transfer using adeno-associated viral (AAV) vectors has made tremendous progress in the last decade and has achieved cures of debilitating diseases such as hemophilia A and B. Nevertheless, progress is still being hampered by immune responses against the AAV capsid antigens or the transgene products. Immunosuppression designed to blunt T cell responses has shown success in some patients but failed in others especially if they received very high AAV vectors doses. Although it was initially thought that AAV vectors induce only marginal innate responses below the threshold of systemic symptoms recent trials have shown that complement activation can results in serious adverse events. Dorsal root ganglia toxicity has also been identified as a complication of high vector doses as has severe hepatotoxicity. Most of the critical complications occur in patients who are treated with very high vector doses indicating that the use of more efficient AAV vectors to allow for dose sparing or giving smaller doses repeatedly, the latter in conjunction with antibody or B cell depleting measures, should be explored.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105806

编号：YY001-20221010003

标题：Gene Therapy Advances: A Meta-Analysis of AAV Usage in Clinical Settings

简介：Adeno-associated viruses (AAVs) are the safest and most effective gene delivery vehicles to drive long-term transgene expression in gene therapy. While animal studies have shown promising results, the translatability of AAVs into clinical settings has been partly limited due to their restricted gene packaging capacities, off-target transduction, and immunogenicity. In this study, we analysed over two decades of AAV applications, in 136 clinical trials. This meta-analysis aims to provide an up-to-date overview of the use and successes of AAVs in clinical trials, while evaluating the approaches used to address the above challenges. First, this study reveals that the speed of novel AAV development has varied between therapeutic areas, with particular room for improvement in Central Nervous System disorders, where development has been slow. Second,

the lack of dose-dependent toxicity and efficacy data indicates that optimal dosing regimes remain elusive. Third, more clinical data on the effectiveness of various immune-modulation strategies and gene editing approaches are required to direct future research and to accelerate the translation of AAV-mediated gene therapy into human applications.

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编号：YY001-20221010004

标题：AAV gene therapy vectors in the TMJ

简介：Objectives: The goal of this project was to evaluate the use of two adeno-associated viral vector serotypes, adeno-associated viral vectors (AAV)-2 and AAV-6, approved for and used for gene therapy in humans, for the delivery of therapeutic genes to the temporomandibular joint (TMJ) and the attendant sensory nerves. Methods: Young adult wild-type C57BL/6 mice were intra-articularly inoculated with AAV-2 and AAV-6 encoding the reporter gene gfp, the expression of which was assessed in the TMJ as well as along nerves innervating the TMJ. Results: AAV-2 and AAV-6 serotypes were characterized by varying levels of tissue tropism demonstrating different efficacy of infection for articular chondrocytes, meniscal fibroblasts, and trigeminal neurons. Specifically, AAV-2 infected both neurons and articular chondrocytes/meniscal fibroblasts, whereas AAV-6 showed selectivity primarily for neurons. Conclusions: The results of this study are clinically significant in the successful application of gene therapy vectors for TMJ disorders, as this new knowledge will allow for appropriate targeting of specific therapeutic genes to selective tissues (neurons vs. chondrocytes/fibroblasts) as needed by using specific viral vector serotypes.

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编号：YY001-20221010005

标题：AAV-vector based gene therapy for mitochondrial disease: progress and future perspectives

简介：Mitochondrial diseases are a group of rare, heterogeneous diseases caused by gene mutations in both nuclear and mitochondrial genomes that result in defects in mitochondrial function. They are responsible for significant morbidity and mortality as they affect multiple organ systems and particularly those with high energy-utilizing tissues, such as the nervous system, skeletal muscle, and cardiac muscle. Virtually no effective treatments exist for these patients, despite the urgent need. As the majority of these conditions are monogenic and caused by mutations in nuclear genes, gene replacement is a highly attractive therapeutic strategy. Adeno-associated virus (AAV) is a well-characterized gene replacement vector, and its safety profile and ability to transduce quiescent cells nominates it as a potential gene therapy vehicle for several mitochondrial diseases. Indeed, AAV vector-based gene replacement is currently being explored in clinical trials for one mitochondrial disease (Leber hereditary optic neuropathy) and preclinical studies have been published investigating this strategy in other mitochondrial diseases. This review summarizes the preclinical findings of AAV vector-based gene replacement therapy for mitochondrial diseases including Leigh syndrome, Barth syndrome, ethylmalonic encephalopathy, and others.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105810

编号：YY001-20221010006

标题：Circumventing the packaging limit of AAV-mediated gene replacement therapy for neurological disorders

简介：Introduction: Gene therapy provides the exciting opportunity of a curative single treatment for devastating diseases, eradicating the need for chronic medication. Adeno-associated viruses (AAVs) are among the most attractive vector carriers for gene replacement in vivo. Yet, despite the success of recent AAV-based clinical trials, the clinical use of these vectors has been limited. For instance, the AAV packaging capacity is restricted to ~4.7 kb, making it a substantial challenge to deliver large gene products. Areas covered: In this review, we explore established and emerging strategies that circumvent the packaging limit of AAVs to make them effective vehicles for gene replacement therapy of monogenic disorders, with a particular focus on diseases affecting the nervous system. We report historical references, design remarks, as well as strengths and weaknesses of these approaches. We additionally discuss examples of neurological disorders for which such strategies have been attempted. Expert opinion: The field of AAV-gene therapy has experienced enormous advancements in the last decade. However, there is still ample space for improvement aimed at overcoming existing challenges that are slowing down the progressive trajectory of this field.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105811

编号：YY001-20221010007

标题：Early and late stage gene therapy interventions for inherited retinal degenerations

简介：Inherited and age-related retinal degeneration is the hallmark of a large group of heterogeneous diseases and is the main cause of untreatable blindness today. Genetic factors play a major pathogenic role in retinal degenerations for both monogenic diseases (such as retinitis pigmentosa) and complex diseases with established genetic risk factors (such as age-related macular degeneration). Progress in genotyping techniques and back of the eye imaging are completing our understanding of these diseases and their manifestations in patient populations suffering from retinal degenerations. It is clear that whatever the genetic cause, the majority of vision loss in retinal diseases results from the loss of photoreceptor function. The timing and circumstances surrounding the loss of photoreceptor function determine the adequate therapeutic approach to use for each patient. Among such approaches, gene therapy is rapidly becoming a therapeutic reality applicable in the clinic. This massive move from laboratory work towards clinical application has been propelled by the advances in our understanding of disease genetics and mechanisms, gene delivery vectors, gene editing systems, and compensatory strategies for loss of photoreceptor function. Here, we provide an overview of existing modalities of retinal gene therapy and their relevance based on the needs of patient populations suffering from inherited retinal degenerations.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105813

编号：YY001-20221010008

标题：Fantastic AAV Gene Therapy Vectors and How to Find Them-Random Diversification, Rational Design and Machine Learning

简介：Parvoviruses are a diverse family of small, non-enveloped DNA viruses that infect a wide variety of species, tissues and cell types. For over half a century, their intriguing biology and

pathophysiology has fueled intensive research aimed at dissecting the underlying viral and cellular mechanisms. Concurrently, their broad host specificity (tropism) has motivated efforts to develop parvoviruses as gene delivery vectors for human cancer or gene therapy applications. While the sum of preclinical and clinical data consistently demonstrates the great potential of these vectors, these findings also illustrate the importance of enhancing and restricting in vivo transgene expression in desired cell types. To this end, major progress has been made especially with vectors based on Adeno-associated virus (AAV), whose capsid is highly amenable to bioengineering, repurposing and expansion of its natural tropism. Here, we provide an overview of the state-of-the-art approaches to create new AAV variants with higher specificity and efficiency of gene transfer in on-target cells. We first review traditional and novel directed evolution approaches, including high-throughput screening of AAV capsid libraries. Next, we discuss programmable receptor-mediated targeting with a focus on two recent technologies that utilize high-affinity binders. Finally, we highlight one of the latest stratagems for rational AAV vector characterization and optimization, namely, machine learning, which promises to facilitate and accelerate the identification of next-generation, safe and precise gene delivery vehicles.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105812

编号：YY001-20221010009

标题：Delivery of CRISPR-Cas tools for in vivo genome editing therapy: Trends and challenges

简介：The discovery of clustered regularly interspaced short palindromic repeats (CRISPR) genome editing technology opened the door to provide a versatile approach for treating multiple diseases. Promising results have been shown in numerous pre-clinical studies and clinical trials. However, a safe and effective method to deliver genome-editing components is still a key challenge for in vivo genome editing therapy. Adeno-associated virus (AAV) is one of the most commonly used vector systems to date, but immunogenicity against capsid, liver toxicity at high dose, and potential genotoxicity caused by off-target mutagenesis and genomic integration remain unsolved. Recently developed transient delivery systems, such as virus-like particle (VLP) and lipid nanoparticle (LNP), may solve some of the issues. This review summarizes existing in vivo delivery systems and possible solutions to overcome their limitations. Also, we highlight the ongoing clinical trials for in vivo genome editing therapy and recently developed genome editing tools for their potential applications.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105814

编号：YY001-20221010010

标题：Testing preexisting antibodies prior to AAV gene transfer therapy: rationale, lessons and future considerations

简介：Given the increasing number of gene transfer therapy studies either completed or underway, there is growing attention to the importance of preexisting adaptive immunity to the viral vectors used. The recombinant viral vectors developed for gene transfer therapy share structural features with naturally occurring wild-type virus. Antibodies generated against viral vectors obtained through a previous exposure to wild-type virus can potentially compromise transgene expression by blocking transduction, thereby limiting the therapeutic efficacy of the gene transfer therapy; they may also pose potential safety concerns. Therefore, systemic gene transfer delivery requires testing patients for preexisting antibodies. Two different assays have

been used: (1) binding assays that focus on total antibodies (both neutralizing and non-neutralizing) and (2) neutralizing assays that detect neutralizing antibodies. In this review we focus on adeno-associated virus-based gene therapies, describing the immune response that occurs to naturally occurring adeno-associated viruses, the implications for patients with this exposure, the assays used to detect preexisting immune responses, and strategies to circumvent preexisting adaptive immunity to expand the patient base that could benefit from such therapies.
全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105824

编号：YY001-20221010011
标题：Gene Therapy Developments for Pompe Disease
简介：Pompe disease is an inherited neuromuscular disorder caused by deficiency of the lysosomal enzyme acid alpha-glucosidase (GAA). The most severe form is infantile-onset Pompe disease, presenting shortly after birth with symptoms of cardiomyopathy, respiratory failure and skeletal muscle weakness. Late-onset Pompe disease is characterized by a slower disease progression, primarily affecting skeletal muscles. Despite recent advancements in enzyme replacement therapy management several limitations remain using this therapeutic approach, including risks of immunogenicity complications, inability to penetrate CNS tissue, and the need for life-long therapy. The next wave of promising single therapy interventions involves gene therapies, which are entering into a clinical translational stage. Both adeno-associated virus (AAV) vectors and lentiviral vector (LV)-mediated hematopoietic stem and progenitor (HSPC) gene therapy have the potential to provide effective therapy for this multisystemic disorder. Optimization of viral vector designs, providing tissue-specific expression and GAA protein modifications to enhance secretion and uptake has resulted in improved preclinical efficacy and safety data. In this review, we highlight gene therapy developments, in particular, AAV and LV HSPC-mediated gene therapy technologies, to potentially address all components of the neuromuscular associated Pompe disease pathology.
全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105815

编号：YY001-20221010012
标题：Immunogenicity of Novel AAV Capsids for Retinal Gene Therapy
简介：Objectives: AAV vectors are widely used in gene therapy, but the prevalence of neutralizing antibodies raised against AAV serotypes in the course of a natural infection, as well as innate and adaptive immune responses induced upon vector administration, is still considered an important limitation. In ocular gene therapy, vectors applied subretinally bear the risk of retinal detachment or vascular leakage. Therefore, new AAV vectors that are suitable for intravitreal administration for photoreceptor transduction were developed. Methods: Here, we compared human immune responses from donors with suspected previous AAV2 infections to the new vectors AAV2.GL and AAV2.NN-two capsid peptide display variants with an enhanced tropism for photoreceptors-with the parental serotype AAV2 (AAV2 WT). We investigated total and neutralizing antibodies, adaptive and innate cellular immunogenicity determined by immunofluorescence staining and flow cytometry, and cytokine secretion analyzed with multiplex beads. Results: While we did not observe obvious differences in overall antibody binding, variants-particularly AAV2.GL-were less sensitive to neutralizing antibodies than the AAV2 WT. The novel variants did not differ from AAV2 WT in cellular immune responses and cytokine

production in vitro. Conclusion: Due to their enhanced retinal tropism, which allows for dose reduction, the new vector variants are likely to be less immunogenic for gene therapy than the parental AAV2 vector.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105817

编号：YY001-20221010013

标题：AAV-mediated BMP7 gene therapy counteracts insulin resistance and obesity

简介：Type 2 diabetes, insulin resistance, and obesity are strongly associated and are a major health problem worldwide. Obesity largely results from a sustained imbalance between energy intake and expenditure. Therapeutic approaches targeting metabolic rate may counteract body weight gain and insulin resistance. Bone morphogenic protein 7 (BMP7) has proven to enhance energy expenditure by inducing non-shivering thermogenesis in short-term studies in mice treated with the recombinant protein or adenoviral vectors encoding BMP7. To achieve long-term BMP7 effects, the use of adeno-associated viral (AAV) vectors would provide sustained production of the protein after a single administration. Here, we demonstrated that treatment of high-fat-diet-fed mice and ob/ob mice with liver-directed AAV-BMP7 vectors enabled a long-lasting increase in circulating levels of this factor. This rise in BMP7 concentration induced browning of white adipose tissue (WAT) and activation of brown adipose tissue, which enhanced energy expenditure, and reversed WAT hypertrophy, hepatic steatosis, and WAT and liver inflammation, ultimately resulting in normalization of body weight and insulin resistance. This study highlights the potential of AAV-BMP7-mediated gene therapy for the treatment of insulin resistance, type 2 diabetes, and obesity.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105816

编号：YY001-20221010014

标题：AAV-mediated delivery of osteoblast/osteoclast-regulating miRNAs for osteoporosis therapy

简介：Osteoporosis occurs due to a dysregulation in bone remodeling, a process requiring both bone-forming osteoblasts and bone-resorbing osteoclasts. Current leading osteoporosis therapies suppress osteoclast-mediated bone resorption but show limited therapeutic effects because osteoblast-mediated bone formation decreases concurrently. We developed a gene therapy strategy for osteoporosis that simultaneously promotes bone formation and suppresses bone resorption by targeting two microRNAs (miRNAs)-miR-214-3p and miR-34a-5p. We modulated the expression of these miRNAs using systemically delivered recombinant adeno-associated viral (rAAV) vectors targeting the bone. rAAV-mediated overexpression of miR-214-3p or inhibition of miR-34a-5p in the skeleton resulted in bone loss in adult mice, resembling osteoporotic bones. Conversely, rAAV-mediated inhibition of miR-214-3p or overexpression of miR-34a-5p reversed bone loss in mouse models for postmenopausal and senile osteoporosis by increasing osteoblast-mediated bone formation and decreasing osteoclast-mediated bone resorption. Notably, these mice did not show any apparent pathological phenotypes in non-skeletal tissues. Mechanistically, inhibiting miR-214-3p upregulated activating transcription factor 4 in osteoblasts and phatase and tensin homolog in osteoclasts, while overexpressing miR-34a-5p downregulated Notch1 in osteoblasts and TGF-β-induced factor homeobox 2 in osteoclasts. In summary, bone-targeting rAAV-mediated regulation of miR-214-3p or miR-34a-5p is a promising new approach to treat

osteoporosis, while limiting adverse effects in non-skeletal tissues.

全文链接：https://pan.ckcest.cn/rcservice//doc?doc_id=105818

编号：YY001-20221010015

标题：Optimized AAV Vectors for TMC1 Gene Therapy in a Humanized Mouse Model of DFNB7/11

简介：Gene therapy for genetic hearing loss is an emerging therapeutic modality for hearing restoration. However, the approach has not yet been translated into clinical application. To further develop inner-ear gene therapy, we engineered a novel mouse model bearing a human mutation in the transmembrane channel-1 gene (Tmc1) and characterized the auditory phenotype of the mice. TMC1 forms the mechanosensory transduction channel in mice and humans and is necessary for auditory function. We found that mice harboring the equivalent of the human p.N199I mutation (p.N193I) had profound congenital hearing loss due to loss of hair cell sensory transduction. Next, we optimized and screened viral payloads packaged into AAV9-PHP.B capsids. The vectors were injected into the inner ears of Tmc1Δ/Δ mice and the new humanized Tmc1-p.N193I mouse model. Auditory brainstem responses (ABRs), distortion product otoacoustic emissions (DPOAEs), cell survival, and biodistribution were evaluated in the injected mice. We found broad-spectrum, durable recovery of auditory function in Tmc1-p.N193I mice injected with AAV9-PHP.B-CB6-hTMC1-WPRE. ABR and DPOAE thresholds were equivalent to those of wild-type mice across the entire frequency range. Biodistribution analysis revealed viral DNA/RNA in the contralateral ear, brain, and liver but no overt toxicity. We conclude that the AAV9-PHP.B-CB6-hTMC1-WPRE construct may be suitable for further development as a gene therapy reagent for treatment of humans with genetic hearing loss due to recessive TMC1 mutations.

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