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Top stories on advancements in gene therapy for inherited arrhythmogenic diseases: From preclinical studies to initial results in patients

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In recent years, the application of gene therapy to inherited arrhythmias, which had advanced more slowly than in other clinical areas, has witnessed overall progress across different diseases with the publication of new preclinical studies and the starting of clinical trials. This article summarizes the most recent advancements in the field.

AAV9-mediated *KNCQ1* suppression-replacement therapy in a rabbit model of long QT syndrome 1

Mutations in *KCNQ1* causing long QT syndrome 1 (LQT1) usually exert a dominant negative effect that interferes with the function of the wild-type channels, decreasing the likelihood of success with gene replacement therapy. Gene silencing by allele-specific RNA interference against a specific variant is also impractical because of hundreds of different disease-causing variants. The same limitations apply to a genome-editing approach. Recently, the collaboration between the Ackerman and Odening groups[1] showed effective rescue of QT interval duration in a KCNQ1-LQT1 transgenic rabbit using a suppression-replacement therapy approach. The authors combined a *KCNQ1* shRNA that targets the gene in a mutation-agnostic fashion (suppression), binding a gene area that does not contain any known variant with a shRNA-immune *KCNQ1* cDNA that is not affected by the suppression arm (replacement). The construct was delivered with an AAV9 vector by intra-aortic root injection. Rabbits receiving the gene therapy showed reduced QT interval duration compared with sham-treated animals, and isolated cardiomyocytes showed APD_{90} close to the values seen in the wild type. Relevant to the LQT1 phenotype, suppression-replacement gene therapy limited the QT-prolonging effects of isoproterenol in one animal and shortened APD_{90} in isolated cardiomyocytes. This work provides preliminary proof that suppression-replacement gene therapy can mitigate the LQT1 phenotype in a medium-sized animal model. Before a potential clinical application, issues related to the heterogeneity of transduction of the vector carrying a risk of repolarization dispersion and proarrhythmias need to be addressed.

Plakophilin 2 (*PKP2*) gene replacement arrests the progression of cardiomyopathy in a mouse model of PKP2–arrhythmogenic right ventricular cardiomyopathy

Recent work from our group, in collaboration with Rocket Pharmaceuticals,[2] used a PKP2a gene replacement approach delivered through an AAVrh74 vector to prevent the development of cardiomyopathy in the cardiac-specific tamoxifen-activated PKP2 conditional knockout mouse (PKP2cKO). A single intravenous administration of the AAVrh74-PKP2a vector showed successful transgene mRNA and protein expression and appropriate PKP2 localization at the cardiac intercalated disks. Gene replacement resulted in 100% survival of the treated animals for >5 months in contrast to the 100% mortality observed within 50 days of tamoxifen injection in untreated mice. Right and left ventricular function and dimensions were preserved in AAVrh74-PKP2a–treated animals. In a second set of experiments, AAVrh74-PKP2a delivery was effective at arresting the progression of cardiomyopathy and preventing isoproterenol-induced ventricular arrhythmias even when administered after PKP2 loss. A separate study led by Tenaya Therapeutics[3] in the same PKP2cKO mouse model delivered PKP2a replacement therapy with an AAV9 vector and showed similar success in preventing or arresting ventricular dilation and arrhythmia burden. This group also showed that AAV9-PKP2a replacement restored the localization of other desmosomal proteins at the cardiac intercalated disk. Both studies provided preclinical data that were investigational new drug–enabling for phase 1

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clinical trials (NCT05885412, NCT06228924), which are ongoing. The success of 2 separate preclinical studies using different viral vectors raises optimism about the potential success of gene therapy in PKP2- arrhythmogenic cardiomyopathy patients and may provide alternative options in case of specific adeno-associated virus–neutralizing antibodies, a known limitation of gene replacement therapies. However, only clinical studies can address questions such as the safety of the treatment in humans and whether the arrest of disease progression can be maintained over time.

AAV9-LAMP2B gene replacement in patients with Danon disease: Results from the first clinical trial

Greenberg and colleagues[4] published the results of the first phase 1 gene therapy clinical trial for patients affected by Danon disease (NCT03882437). Seven patients, 11–21 years old, received a single intravenous injection of an AAV9-LAMP2B construct and were observed for 24–54 months. All were alive and in stable conditions at follow-up, reaching beyond the age at which most patients die or undergo heart transplantation. Although all patients experienced adverse effects, these resolved by the last follow-up. The severe ones, like thrombotic microangiopathy, ventricular tachycardia, and heart failure, were observed in the only individual with left ventricular ejection fraction of 32%, who eventually underwent heart transplantation. Myocardial biopsy showed successful vector transduction in all patients, reduction of left ventricular mass index and levels of troponin I and B-type natriuretic peptide, and stabilization of left ventricular ejection fraction. The interim results of this study provide insights that could be useful for upcoming adeno-associated virus–related gene therapy protocols in other inherited arrhythmogenic diseases: vector transduction is effective in the heart and, in this case, was stable for ∼4.5 years after infusion, even if the efficiency was well below 100%. These data suggest that gene therapy is likely to be more successful if it is started at an early stage of disease.

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References

1. Bains S, Giammarino L, Nimani S, et al. *KCNQ1* suppression-replacement gene therapy in transgenic rabbits with type 1 long QT syndrome. Eur Heart J 2024; 45:3751–3763.
2. van Opbergen CJ, Narayanan B, Sacramento CB, et al. AAV-mediated delivery of plakophilin-2a arrests progression of arrhythmogenic right ventricular cardiomyopathy in murine hearts: preclinical evidence supporting gene therapy in humans. Circ Genom Precis Med 2024;17:e004305.
3. Wu I, Zeng A, Greer-Short A, et al. AAV9:PKP2 improves heart function and survival in a Pkp2-deficient mouse model of arrhythmogenic right ventricular cardiomyopathy. Commun Med (Lond) 2024;4:38.
4. Greenberg B, Taylor M, Adler E, et al. Phase 1 study of AAV9. LAMP2B gene therapy in Danon disease. N Engl J Med. Published online November 18, 2024. https://doi.org/10.1056/NEJMoa2412392.