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Top stories on gene therapy for genetic heart disease (2024)

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Gene therapy is defined as the modification of gene expression via the introduction of therapeutic nucleic acid with the intention to treat or prevent disease. Mechanistically, gene therapy strategies aim to (1) replace/supplement a defective gene (eg, loss-of-function [LOF] disorders caused by haploinsufficiency) with a functional copy; (2) suppress/silence a defective gene (eg, gain-of-function [GOF] disorders); (3) suppress the normal and mutant allele and replace with normal gene in a hybrid manner (eg, for dominant negative LOF disorders); or (4) directly edit the genome to remove a disease-causative genetic lesion.

Only a handful of gene therapy products have garnered Food and Drug Administration (FDA) approval thus far. In the following sections, we summarize promising gene therapy approaches designed to correct the genetically mediated perturbation(s) that underlie arrhythmogenic right ventricular cardiomyopathy (ARVC) and long QT syndrome (LQTS).

PKP2 gene replacement therapy for ARVC

ARVC is caused by LOF variants in genes that encode desmosomal proteins, predominantly *PKP2*-encoded plakophilin-2, which impair the structural integrity of the desmosome and lead to arrhythmia- and heart failure–predisposing fibrosis and inflammation. The prognosis in individuals with manifest ARVC often is poor.

In the context of this unmet need, 2 groups simultaneously published their preclinical experience with adeno-associated virus (AAV)-mediated *PKP2* gene replacement therapy. First, Bradford et al[1] utilized a *PKP2* knock-in mouse model with the murine equivalent of the human c.2146-1G>C/IVS-10G>C splice-site variant to test the effect of plakophilin-2 restoration. Early administration (postnatal day 2) of a cardiotropic AAV serotype 9 (AAV9) vector containing *PKP2* under the control of a cardiac troponin T (cTnT) promoter (AAV9-cTnT-PKP2) into homozygous c.2146-1G>C/IVS-10G>C mice prevented the electrical and structural hallmarks of ARVC and resulted in 100% survival at 30 weeks.[1] Late administration (4 weeks) of AAV9-cTnT-PKP2 to mice with electrically and structurally manifest disease fully restored plakophilin-2/other desmosomal protein levels and partially improved biventricular systolic function, resulting in improved survival at 20 weeks.[1] An investigational new drug (IND), LX2020 (Lexeo Therapeutics), based on the AAV9-cTnT-PKP2 gene replacement strategy described, recently received FDA approval to enter phase 1b clinical trial (ClinicalTrials.gov Identifier: NCT06109181).

Second, Kyriakopoulou et al[2] demonstrated that infection of c.2013delC/p.Lys628Argfs*12-PKP2 and c.1849C>T/p.Gln573*-PKP2-specific induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) and engineered human myocardium with an AAV serotype 6 (AAV6) vector containing *PKP2* under the control of a noncardiac-specific cytomegalovirus promoter (AAV6-CMV-PKP2) restored levels of plakophilin-2/other desmosomal proteins to physiological levels and enhanced contractile function. Although Kyriakopoulou et al[2] went on to demonstrate that early delivery of AAV6-CMV-PKP2 (postnatal day 5) to an established knock-in mouse model restored plakophilin-2/other desmosomal protein levels and improved basic echocardiographic parameters, the lack of cardiac specificity inherent to AAV6-CMV-PKP2 has raised concerns that it could increase the risk of hepatotoxicity, thereby dampening commercial appeal. Nevertheless, the study by Kyriakopoulou et al[2] provides an additional proof of principle that a "one-and-done" AAV-PKP2 gene replacement strategy may provide a durable and efficacious treatment for *PKP2*-mediated ARVC.

Lastly, no discussion of AAV-PKP2 gene replacement therapy is complete without mentioning preprint works by Wu et al (https://doi.org/10.21203/rs.3.rs-2958419/v1) and van Opbergen et al (https://doi.org/10.1101/2023.07.12.5485

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90). Both gene replacement strategies restored the expression of plakophilin-2/other desmosomal proteins and prevented disease development or attenuated disease progression depending on the timing of administration in an established tamoxifen-activated *PKP2* knock-out mouse model. Importantly, the INDs described in these unpublished works, RP-A601 (Rocket Pharmaceuticals) and TN-401 (Tenaya Therapeutics), have received FDA clearance to enter early-stage clinical trial, and RP-A601 is actively enrolling (ClinicalTrials.gov Identifier: NCT05885412).

Suppression-replacement (SupRep) gene therapy for LQTS

LQTS is caused predominantly by LOF variants in the *KCNQ1*-encoded $K_v7.1$ (LQT1) and *KCNH2*-encoded $K_v11.1$ (LQT2) voltage-gated potassium channels. Importantly, many LQT1- and LQT2-causative variants are missense and incorporate into tetramers where they exert a dominant-negative effect on the wild-type allele.

Because $K_v7.1$ and $K_v11.1$ pore-forming α-subunits expressed from the therapeutic allele are still subjected to the dominant-negative effects of those expressed from the native "mutant" allele, traditional gene replacement strategies may prove suboptimal in LQT1 and LQT2. To overcome this phenomenon, Dotzler et al[3] introduced the concept of dual-component suppression-and-replacement (SupRep) therapy, which combines (1) a short hairpin RNA (shRNA) that binds a 29-nucleotide portion of *KCNQ1* and *KCNH2* devoid of any known genetic variation and "suppresses" expression of both native alleles; and (ii) an shRNA-immune *KCNQ1* or *KCNH2* cDNA genetically engineered using codon redundancy to evade "suppression" by the shRNA while preserving the wild-type protein sequence. As a result, the "suppression" arm creates a variant agnostic blank slate that subverts the dominant-negative pathobiology of many LQT1- and LQT2-causative variants, therefore maximizing the environment for conventional AAV-mediated gene transfer in the "replacement" arm.[3] Thus far, SupRep gene therapy has shown promise in multiple LQT1 and LQT2 patient-specific iPSC-CM models.[3,4] However, unlike the molecular constituents of the desmosome *(PKP2)* and sarcomere *(MYBPC3)* that are the subject of active or upcoming AAV-based gene replacement phase 1 clinical trials where the impact of overexpression likely is negligible, biogenic *KCNQ1* and *KCNH2* GOF has the theoretical ability to be proarrhythmic in the form of short QT syndrome.

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