Screening Method and Gene Therapy Approach for Treating Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)

An innovative and efficacious treatment targeting the genetic drivers of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).

Technology

The Delmar Lab has devised a new clinically-relevant screening method for identifying agents capable of treating/preventing ARVC/D, and relatedly, has developed a promising *Plakophilin-2 (PKP2)* gene therapy-based strategy for treating/preventing ARVC/D. With respect to the former, they generated a conditionally-inducible Plakophilin-2 (PKP2) mouse knock-out model for ARVC/D, as described in *Cerrone et al Nature Comm 2017*, wherein the *PKP2* gene knock-out is cardiomyocyte-specific and tamoxifen-activated. Using this "PKP2-cKO" mouse model as a template, different disease-causing *PKP2* gene truncation mutations can be inserted to initiate ARVC/D, thereby allowing for the screening of agents (e.g., small-molecules, biologics, or gene therapies) capable of treating/preventing the disease in a clinically-relevant background. With respect to the latter, the Delmar Lab and colleagues have previously shown (*Opbergen et al bioRxiv 2023*) that introduction of exogenous full-length *PKP2* (via adeno-associated virus) prolonged survival, prevented arrhythmias, and modified the course of disease progression in PKP2-cKO mice. The Delmar Lab hypothesizes that a smaller functional fragment of PKP2 (consisting of either the N-terminal domain, C-terminal domain, armadillo repeat domains, or various combinations thereof) may have possess similar efficacy as wild-type PKP2 as a gene therapy, yet may carry several key pharmacological advantages due to its smaller size. The Delmar Lab is currently seeking a commercial partner who is interested identifying and developing minimal functional PKP2 fragments capable for treating/preventing ARVC/D.

Background

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a rare inherited heart disease characterized by a fibrous or fibrofatty infiltration into normal heart muscle (mostly in the right ventricle) leading to ventricular arrhythmias (arising predominantly from the right ventricle) which can trigger sudden cardiac death in young (less than 60 yr old) healthy individuals. The disease has an estimated prevalence of 1:2,000 to 1:5,000 individuals, which equates to between 66,800 and 167,000 individuals in the United States in 2023, thereby conferring ARVC/D an orphan disease designation. There are presently no curative treatments for ARVC/D and current treatments options are limited to antiarrhythmic medications, beta blockers, implantable cardioverter defibrillators (ICDs) and catheter ablation. ARVC/D is caused by mutations in genes coding for desmosomal proteins; of which, the plakophilin-2 (PKP2) protein is most commonly mutated (present in ~ 40% of the overall ARVC/D population). Despite

Technology ID
DEL05-02

Category
Life Sciences/Therapeutics/Cardiovas
Disease
Life Sciences/Therapeutics/Gene Therapy
Doug Brawley

Authors
Mario Delmar, MD, PhD

View online page

the clear genetic link between *PKP2* gene mutations and ARVC/D, the currently available treatments do not address the underlying genetic basis of the disease. Consequently, there is an unmet need to develop innovative PKP2-modulating/replacement therapeutics (e.g., small-molecules, biologics, or gene therapies) to more efficiently treat, or potentially cure, this orphan disease.

Application

Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) caused by *plakophilin-2 (PKP2)* gene truncation mutations

Advantages

- **Targets the genetic basis of ARVC/D:** *PKP2* gene replacement corrects the mutated *PKP2* gene underlying ARVC/D
- **Clinically-relevant screen for drug development:** Uses known disease-causing *PKP2* gene mutations to create a ARVC/D murine phenotype for drug screening
- **High selectivity and low systemic toxicity:** *PKP2* gene therapy approaches deliver PKP2 only to cardiomyocytes thereby lowering systemic toxicity risks
- **Minimalistic approach:** A fragment of the *PKP2* gene (as opposed to full-length PKP2) is expected to be easier to deliver via AAVs and carries less risk for adverse off-target effects

Intellectual Property

NYU has filed a PCT application covering the design of *PKP2* wild-type and *PKP2* mutant conditionally-inducible knock-out transgenic mice, the method of using such mice to screen for agents to treat/prevent ARVC/D, and the method of using a minimal *PKP2* functional gene fragment to treat/prevent ARVC/D.

References

1. Delmar et al.(2017) , https://pubmed.ncbi.nlm.nih.gov/28740174/
2. Delmar et al.(2023) , https://www.biorxiv.org/content/10.1101/2023.07.12.548590v1