Development of gene therapy for arrhythmogenic right ventricular cardiomyopathy

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Project Outline

【Background of the Study】

Severe heart failure at a young age refractory to standard therapy is an unmet medical need in cardiovascular medicine. Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare disease caused by genetic variants in genes encoding components of the cardiac intercalated disc. Patients with ARVC exhibit progressive contractile dysfunction in both right and left ventricles and fatal arrhythmias. Among the causative genes for ARVC, desmoglein-2 (*DSG2*) is known to be the most common in Japan. We identified desmoglein-2-deficient cardiomyopathy due to genetic variants in a patient with severe heart failure and demonstrated the therapeutic concept of *DSG2* gene replacement using adeno-associated virus (AAV) vectors in iPSC-derived cardiomyocytes (iPSC-CMs) (*Hum Mol Genet. 2021 Jul 9;30(15):1384-1397*). Furthermore, we found that impaired intercalated disc structure due to pathogenic *DSG2* gene variants is concealed not only in dilated cardiomyopathy but also in various forms of refractory heart failure (*Hum Genome Var. 2024 Dec 20;11(1):47*, *The 89th Annual Scientific Meeting of the JCS*). Although the incidence of ARVC is estimated to be approximately 1 in 5,000 individuals, our genetic analysis data suggest that *DSG2*-related intercalated disc dysfunction may be concealed in a large population of refractory heart failure. We found that desmoglein-2 expression in cardiac tissues was decreased in cases with *DSG2* variants, indicating the necessity of developing gene therapy to restore *DSG2* in the heart.

【Current Progress】

Building upon our established research and development platform utilizing iPS cells (*Stem Cell Reports, 2022. 17(2): 337-351; Circ Genom Precis Med. 2022 Jul 12; JACC Basic Transl Sci, Feb 08, 2023*), we are advancing our studies from both basic and clinical perspectives. Our efforts include the construction of a case registry, the establishment of human iPSC-CM disease models from patients with ARVC, and the development of a mouse model that recapitulates desmoglein-2-deficient cardiomyopathy. Furthermore, we are employing AAV vector for cardiac gene therapy equipped with a heart failure-responsive enhancer, developed by Associate Professor Ken Matsuoka (the Department of Medical Chemistry, Osaka University Graduate School of Medicine). This vector enables robust, cardiac-specific expression even at low doses of AAV, offering the potential for high efficacy and safety.

【Our Aim】

At the University of Osaka Hospital, many patients with severe refractory heart failure receive medical therapy. Our goal is to deliver precise and safe medical therapy based on basic research to these patients. The development of AAV-based gene therapy requires extensive infrastructure, advanced technologies, and robust industry-academia collaboration. We seek partnerships with companies that share our vision for advancing medical therapy. For more details about our research, please refer to the link (→).

Target Disease: Arrhythmogenic right ventricular cardiomyopathy caused by DSG2 gene variants
Patent Information: Patent Application No. 2022-508325; Patent granted on November 18, 2025
Technical Features: A gene therapy vector targeting arrhythmogenic right ventricular cardiomyopathy caused by *DSG2* gene variants
Market Potential and Development Challenges: We aim to develop therapeutic agents targeting gene variants specific to Japanese and East Asian populations
Desired Industry Collaboration: Joint research, GMP manufacturing of AAV gene therapy drugs, and out-licensing