

Adenylyl Cyclase Catalytic Domain Gene Transfer for Heart Failure

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OTHER INFORMATION

KEYWORDS

Gene therapy, adenylyl cyclase, beta-adrenergic receptor, heart failure, cardiac myocytes, intra-coronary infusion, left ventricular hypertrophy

CATEGORIZED AS

- **Medical**
 - Delivery Systems
 - Disease: Cardiovascular and Circulatory System
 - Gene Therapy

RELATED CASES

2018-045-0

BACKGROUND

Heart failure (HF) is a disease of epidemic portions in the United States affecting over 6 million patients with heart failure in the US, with 400,000 new cases per year. It is the most common cause of non-elective admission to the hospital in subjects 65 yrs and older. The introduction of new drugs over the last 30 years that target pathways critical to progression of HF, along with implantable cardiac defibrillators and resynchronization devices have shown some successes, however, both the morbidity and mortality associated with heart failure remains at unacceptable levels, with as many as 30-40% of affected individuals dying within 5 years of diagnosis. Recently, preclinical and clinical trials have tested gene transfer to increase left ventricular (LV) function, especially in heart failure with reduced ejection fraction.

TECHNOLOGY DESCRIPTION

Adenylyl cyclase (AC) is a transmembrane protein in cardiac myocytes and other cells, the effector molecule for beta-adrenergic receptor (βAR) and other G protein-coupled receptors, which regulates the conversion of adenosine triphosphate (ATP) to 30,50-cyclic adenosine monophosphate (cAMP), and thereby initiates a variety of intracellular signaling cascades that influence heart function and additional physiological events. There are 9 membrane bound isoforms (AC1 to AC9); however, increased cardiac expression of AC type 6 (AC6), a dominant AC isoform expressed in mammalian cardiac myocytes, has protean beneficial effects on the failing left ventricle. These beneficial effects, consistent in several species and models appear in large part do not depend upon increased cAMP generation. A phase 2 randomized clinical trial in patients with symptomatic heart failure (HF) and reduced ejection fractions showed that intracoronary AC6 gene transfer appears to be safe and potentially effective, and not associated with increased cardiac arrhythmias. Therefore, AC6 gene transfer may be suitable for treatment of heart failure.

Researchers at VA San Diego and UC San Diego have generated an AC6 mutant (AC6mut) molecule which retains the cellular distribution pattern and favorable signaling effects associated with normal AC6, but which does not generate cAMP upon βAR stimulation—yet has similar favorable effects on LV function as does normal AC6. These data demonstrate that AC6 does not require increased cAMP generation.

In another set of studies, scientists eliminated the two transmembrane domains of normal AC6, yielding a protein with an intact catalytic domain, designated C1C2, that is disengaged from membrane-associated β-adrenergic stimulation, but with an enhanced propensity for intracellular interactions with other proteins, which, ultimately, enhance Ca2+ handling and thus systolic and diastolic heart function. Transgenic mice with cardiac-directed C1C2 are resistant to the delirious effects of LV pressure overload, as can be seen in clinical hypertension

APPLICATIONS

This transgene, C1C2, is sufficiently small to be packaged in an adeno-associated virus (AAV) vector, unlike normal AC6 of AC6mut, increasing the flexibility of delivery. A one-time vascular delivery of a gene transfer product is a novel approach to the treatment of clinical heart failure, and its mechanism of action (increases cardiac myocyte Ca2+ handling) would likely be additive to current therapies.

STATE OF DEVELOPMENT

Transgenic mice with cardiac-directed expression of C1C2 exhibit resistance to sustained adrenergic stimulation compared with transgene (TG) negative (control) siblings. Transgenic mice with cardiac-directed C1C2, a fusion protein of the intracellular C1 and C2 segments of adenylyl cyclase type 6, had normal left ventricular (LV) function, but diminished cAMP generation. Cardiac myocytes from C1C2 mice showed increased Ca2+ release. Furthermore, a virus vector encoding C1C2 will soon be studied.

INTELLECTUAL PROPERTY INFO

The technology is patent pending and available for licensing or collaborations.

RELATED MATERIALS

► Tan Z, Giamouridis D, Lai NC, Kim YC, Guo T, Xia B, Gao MH, Hammond HK. Cardiac-directed expression of adenylyl cyclase catalytic domain (C1C2) attenuates deleterious effects of pressure overload. Hum Gene Ther. 2019 30:682-692. doi: 10.1089/hum.2018.176. Epub 2019 Mar 8. PMID: 30638074 - 03/08/2019

► Gao MH, Lai NC, Giamouridis D, Kim YC, Tan Z, Guo T, Dillmann, WH, Suarez J, Hammond HK. Cardiac-Directed Expression of Adenylyl Cyclase Catalytic Domain Reverses Cardiac Dysfunction Caused by Sustained Beta-Adrenergic Receptor Stimulation. JACC Basic Transl Sci. 2016 Dec;1(7):617-629. doi: 10.1016/j.jacbts.2016.08.004. - 12/26/2016

PATENT STATUS

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United States Of America	Published Application	2019/026418	08/29/2019	2018-045

