Small Molecule Agonists of VDAC2 to Treat Cardiac Arrhythmias and Heart Failure

Tech ID: 24411 / UC Case 2014-397-0

SUMMARY

UCLA researchers have developed a novel small molecule as a potential therapeutic treatment for cardiac fibrillation.

BACKGROUND

Aberrant Ca^{2+} handling in cardiomyocytes is associated with a wide range of human cardiac diseases, including heart failure and arrhythmias.

To uncover novel targets implicated in aberrant Ca^{2+} handling, UCLA researchers developed a zebrafish model called *tremblor* that manifests Ca2+ extrusion defects and fibrillation-like chaotic cardiac contractions as a result ofthe loss of NCX1 sodium/calcium exchanger in cardiomyocytes.

This model was used as a phenotypic screen with a small molecule library developed at UCLA. Small molecules that restore rhythmic and coordinated cardiac contractions in *tremblor in vivo* were identified in this screen and used to pull down a novel mitochondrial target called VDAC2. This voltage-dependent channel protein plays a key role in maintaining Ca^{2+} homeostasis and may therefore be a novel drug target for atrial and ventricular fibrillation and heart failure.

Mechanistically, these compounds potentiate the Ca^{2+} transporting activity of VDAC2 thereby increasing the rate at which excess Ca^{2+} ions are transferred from the cytoplasm into the mitochondria, restoring normal rhythmic Ca^{2+} transients and suppressing cardiac fibrillation. The best compounds from this screen completely rescue the *tremblor* fibrillation phenotype in zebrafish and they have also been shown to be active in isolated adult mouse ventricular cardiomyocytes, human and mouse ES cell-derived cardiomyocytes and an initial in vivo rodent study.

The UCLA team is now working to optimize the PK/PD properties of these small molecule VDAC2 agonists and is planning to begin porcine studies in a well-characterized model of ventricular fibrillation.

APPLICATIONS

Because VDAC2 is a novel drug target for atrial and ventricular fibrillation and heart failure the small molecule agonists under development at UCLA may be drug leads for all of these indications.

ADVANTAGES

- Can effectively regulate cardiac Ca2+ homeostasis and restore cardiac function
- No known side effects

STATE OF DEVELOPMENT

In vivo studies of the present technology have been conducted.

PATENT STATUS

Country	Type	Number	Dated	Case
Germany	Issued Patent	60 2015 072 491.7	08/18/2021	2014-397
Spain	Issued Patent	3233895	08/18/2021	2014-397
France	Issued Patent	3233895	08/18/2021	2014-397
United Kingdom	Issued Patent	3233895	08/18/2021	2014-397

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OTHER INFORMATION

KEYWORDS

Therapeutic, cardiac fibrillation, atrial fibrillation, small molecule, calcium homeostasis

CATEGORIZED AS

- **Medical**
  - Disease: Cardiovascular and Circulatory System
  - New Chemical Entities, Drug Leads
  - Therapeutics

RELATED CASES

2014-397-0

Italy	Issued Patent	502021000089864	08/18/2021	2014-397
Sweden	Issued Patent	3233895	08/18/2021	2014-397
United States Of America	Published Application	2022-012722	04/28/2022	2014-397
United States Of America	Published Application	20170362173	12/21/2017	2014-397

RELATED MATERIALS

- Mitochondrial Ca(2+) uptake by the voltage-dependent anion channel 2 regulates cardiac rhythmicity. ELife (2015)
- Xie Y, Ottolia M, John SA, Chen JN, Philipson KD. Conformational changes of a Ca2+-binding domain of the Na+/Ca2+ exchanger monitored by FRET in transgenic zebrafish heart. Am J Physiol Cell Physiol. 2008 Aug; 295(2):C388-93.
- Zhang Y, Shimizu H, Siu KL, Mahajan A, Chen JN and Cai H. (2014) NADPH oxidase 4 induces cardiac arrhythmic phenotype in zebrafish. J Biol Chem. 2014 Jun 24.
- Langenbacher AD1, Dong Y, Shu X, Choi J, Nicoll DA, Goldhaber JI, Philipson KD, Chen JN. Mutation in sodium-calcium exchanger 1 (NCX1) causes cardiac fibrillation in zebrafish. Proc Natl Acad Sci U S A. 2005

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Novel Non-Peptidomimetic Prenyltransferase Inhibitors
- Hydrodealkenylative C(Sp3)–C(Sp2) Bond Scission
- Compound Library Made Through Phosphine-Catalyzed Annulation/Tebbe/Diels-Alder Reaction

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