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 Ca^{2+} extrusion defects and fibrillation-like chaotic cardiac contractions as a result of the 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 Ca^{2+} homeostasis and restore cardiac function
- No known side effects

STATE OF DEVELOPMENT

In vivo studies of the present technology have been conducted.

PATENT STATUS

<table>
<thead>
<tr>
<th>Country</th>
<th>Type</th>
<th>Number</th>
<th>Dated</th>
<th>Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>Issued Patent</td>
<td>60 2015 072 491.7</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>Spain</td>
<td>Issued Patent</td>
<td>3233895</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>France</td>
<td>Issued Patent</td>
<td>3233895</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Issued Patent</td>
<td>3233895</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>Italy</td>
<td>Issued Patent</td>
<td>502021000089864</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>Sweden</td>
<td>Issued Patent</td>
<td>3233895</td>
<td>08/18/2021</td>
<td>2014-397</td>
</tr>
<tr>
<td>United States Of America</td>
<td>Published Application</td>
<td>2022-012722</td>
<td>04/28/2022</td>
<td>2014-397</td>
</tr>
<tr>
<td>United States Of America</td>
<td>Published Application</td>
<td>20170362173</td>
<td>12/21/2017</td>
<td>2014-397</td>
</tr>
</tbody>
</table>

RELATED MATERIALS

- Mitochondrial Ca(2+) uptake by the voltage-dependent anion channel 2 regulates cardiac rhythmicity. ELife (2015)
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
- Small Molecule Inhibitor of Cholesterol Biosynthesis and Venous Angiogenesis