Cardiac AAV:PKP2 Gene Therapy Reduces Ventricular Arrhythmias, Reverses Adverse Right Ventricular Remodeling, Improves Heart Function, and Extends Survival in a Pkp2-deficient Mouse Model of Arrhythmogenic Right Ventricular Cardiomyopathy

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Disclosures: All authors are shareholders and/or employees of Tenaya Therapeutics, Inc.
# Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

<table>
<thead>
<tr>
<th>ARVC Symptoms</th>
<th>Disease Progression</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early arrhythmias</td>
<td>Concealed Phase</td>
<td>• Presents in young adults</td>
</tr>
<tr>
<td>• Palpitations,</td>
<td>Ventricular Arrhythmia</td>
<td>• Average &lt; 40 years old</td>
</tr>
<tr>
<td>• Lightheadedness</td>
<td>Right Ventricle Failure</td>
<td>• Important cause of sudden cardiac arrest in young adults</td>
</tr>
<tr>
<td>• Syncope (fainting)</td>
<td>Biventricular Pump Failure</td>
<td>• Median age 25 years old</td>
</tr>
<tr>
<td>Progressive development</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Myocardial atrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chamber dilation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fibrofatty muscle replacement</td>
<td></td>
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</tr>
</tbody>
</table>
## Current Therapy for ARVC

No Therapies Address the Underlying Genetic Cause of Disease to Prevent Onset and Prevent Progression

<table>
<thead>
<tr>
<th>Standard of Care</th>
<th>Limitations of Care</th>
<th>New Treatment Paradigm Needed</th>
</tr>
</thead>
</table>
| Anti-Arrhythmic Medications       | • Not fully effective  
• Side effects                                                                         | Options to prevent disease onset                                    |
| Implantable Cardioverter-Defibrillator (ICD) | • Potential for complications  
• Inappropriate shocks  
• Anxiety and impact on quality of life | Options to prevent disease progression                               |
| Ventricular Tachycardia (VT) Ablation | • Invasive procedure  
• Variable success rates                                                                 |                                                                    |
| Exercise Restriction              | • Negative impact on lifestyle and general health                                   |                                                                    |
Majority of ARVC Caused by Desmosome Mutations

- Autosomal dominant inheritance
- ~70K patients with PKP2 mutations in the U.S. alone

Desmosomes Zip Heart Cells Together and Support Gap Junctions to Maintain Electrical Coupling

PKP2 Mutations are the Predominant Genetic Cause of ARVC

- PKP2 43%
- DSP 21%
- DSG2 19%
- DSC2 12%
- TTN 3%
- JUP 3%
- Others 3%

Connexin 43 Plakophilin 2 Desmoplakin
PKP2 Mutation is Associated with Reduction of Protein Levels and Loss of Desmosome Structure in Human Hearts

Loss of Desmosomes in PKP2-mutated Human Heart

Asimaki et al. (2009) NEJM
Potential to Use AAV Gene Therapy for ARVC Due to \textit{PKP2} Mutations

\textbf{TN-401 is a Gene Therapy to Restore the Expression and Function of PKP2 in the Heart}

\textbf{DESMOSOME STRUCTURE}

- Vector = Adeno-Associated Virus (AAV)
  - AAVs are naturally-occurring viruses that do not cause disease
- Promoter = Cardiac-specific
- Expression = Non-integrating and durable
Increasing Use of AAV Gene Therapy

<table>
<thead>
<tr>
<th>Number of Clinical Studies Using AAV, by Start Year</th>
<th>Approved Gene Therapy Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;3,000 patients treated in ~150 AAV gene therapy studies(^1)</td>
<td>(\text{zolgensma}^\text{®}) (ontsemmogene abeparvovec)</td>
</tr>
<tr>
<td>&gt;1,800 patients treated in &gt;40 countries(^2)</td>
<td>(\text{LUXTURN}^\text{®}) (voretigene neparvovec-ryzl for subretinal injection)</td>
</tr>
</tbody>
</table>

\(^1\) Modified from Kuzmin et al., NatRevDrugDiscov 2021

\(^2\) Novartis corporate press release – March 2022
Cardiac-specific *Pkp2* Knockout Mouse Model Recapitulates Human ARVC Phenotypes

**Premature Mortality**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Week Post Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

**Increased Spontaneous PVCs**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Week Post Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>7</td>
<td>&gt;100</td>
</tr>
</tbody>
</table>

**Decreased LV Ejection Fraction**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Week Post Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
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<td>0</td>
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<td>7</td>
<td>4</td>
</tr>
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</table>

**Cardiomyocyte-specific-Cre-ER(T2), Pkp2 fl/fl**

Single Dose Cardiac AAV:PKP2 Gene Therapy Reduces Ventricular Arrhythmias

WT: Normal Sinus Rhythm

Control: Abnormal Ventricular Beats (NSVT & PVCs)

Gene Therapy: Normal Sinus Rhythm

NSVT = Non-sustained ventricular tachycardia
AV = Atrioventricular

• Ventricular Arrhythmia Score includes NSVT, triplets, couplets, AV block and the frequency of PVCs
Single Dose Cardiac AAV:PKP2 Gene Therapy Demonstrates Disease Modification and Survival Benefit

**Prevention of Right Ventricle Enlargement**

![Graph showing RV Area/BW (mm²/g) vs. Weeks Post Induction for WT, Control, and Gene Therapy groups.]

**Prevention of Decline of Left Ventricle Function**

![Bar graph showing Ejection Fraction (%) for WT, Control, and Gene Therapy groups. Significant difference at <0.0001.]

**Extension of Life Span**

![Survival probability graph for WT, Control, and Gene Therapy groups.]

Control n=10
Gene Therapy n=10
Single Dose Cardiac AAV:PKP2 Gene Therapy Restores Desmosomes and Gap Junctions

Desmosome Protein Expression

<table>
<thead>
<tr>
<th></th>
<th>PKP2</th>
<th>DSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td><img src="PKP2_WT.png" alt="Image" /></td>
<td><img src="DSP_WT.png" alt="Image" /></td>
</tr>
<tr>
<td>Control</td>
<td><img src="PKP2_Control.png" alt="Image" /></td>
<td><img src="DSP_Control.png" alt="Image" /></td>
</tr>
<tr>
<td>Dose 1</td>
<td><img src="PKP2_Dose1.png" alt="Image" /></td>
<td><img src="DSP_Dose1.png" alt="Image" /></td>
</tr>
<tr>
<td>Dose 2</td>
<td><img src="PKP2_Dose2.png" alt="Image" /></td>
<td><img src="DSP_Dose2.png" alt="Image" /></td>
</tr>
<tr>
<td>Dose 3</td>
<td><img src="PKP2_Dose3.png" alt="Image" /></td>
<td><img src="DSP_Dose3.png" alt="Image" /></td>
</tr>
</tbody>
</table>

Relative Protein Expression

Cx43 IHC at Gap Junction

WT | Control | Gene Therapy

![Image](Cx43_IHC_WT.png) | ![Image](Cx43_IHC_Control.png) | ![Image](Cx43_IHC_Gene_Therapy.png)
Single Dose Cardiac AAV:PKP2 Gene Therapy Prevents Fibrosis

<table>
<thead>
<tr>
<th>WT</th>
<th>Control</th>
<th>Gene Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Trichrome Staining" /></td>
<td><img src="image2" alt="Trichrome Staining" /></td>
<td><img src="image3" alt="Trichrome Staining" /></td>
</tr>
</tbody>
</table>

Yellow arrows = Fibrosis

![Graph showing % Collagen](image4)

WT Control Gene Therapy
% Collagen
Summary

- Preclinical results using a cardiac-specific Pkp2 knockout mouse model provide encouraging evidence that cardiac AAV:PKP2 gene therapy may be a promising therapeutic option for ARVC patients with PKP2 mutations.

Cardiac AAV:PKP2 gene therapy in a mouse model:
- Reduces ventricular arrhythmias
- Demonstrates disease modification and increased survival
- Restores desmosomes and gap junctions
- Prevents fibrosis
- Preliminary safety evaluation of AAV:PKP2 in wild-type mice shows no adverse effects on cardiac function and no changes in tissues examined.

- TN-401, Tenaya's AAV:PKP2 clinical candidate, is currently advancing into IND-enabling studies.
- Further studies are needed to support these findings.
• To further advance the development of genetic medicines for inherited cardiovascular disease, we encourage genetic testing
  • Genetic testing for ARVC is increasingly available via numerous academic and corporate labs in US and Europe

• Tenaya Therapeutics is partnering with ARVC experts and patient advocacy organizations around the world to better understand and characterize ARVC due to PKP2 mutations
  • Initially through global natural history studies and long-term patient registries
  • For more information: clinical.trials@tenayathera.com
Thank you

We thank Dr. Mario Delmar and NYU for licensing *Pkp2-cKO* mouse