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)

ARVC Symptoms	Disease Progression	Age Group

<u>Early arrhythmias</u>
• Palpitations,
• Lightheadedness
• Syncope (fainting)
 	
<u>Progressive development</u>
• Myocardial atrophy
• Chamber dilation
• Fibrofatty muscle replacement
	Concealed Phase
	↓
	Ventricular Arrythmia
	↓
	Right Ventricle Failure
	↓
	Biventricular Pump Failure
		• Presents in young adults
		  • Average < 40 years old
		
		• Important cause of sudden cardiac arrest in young adults
		  • Median age 25 years old

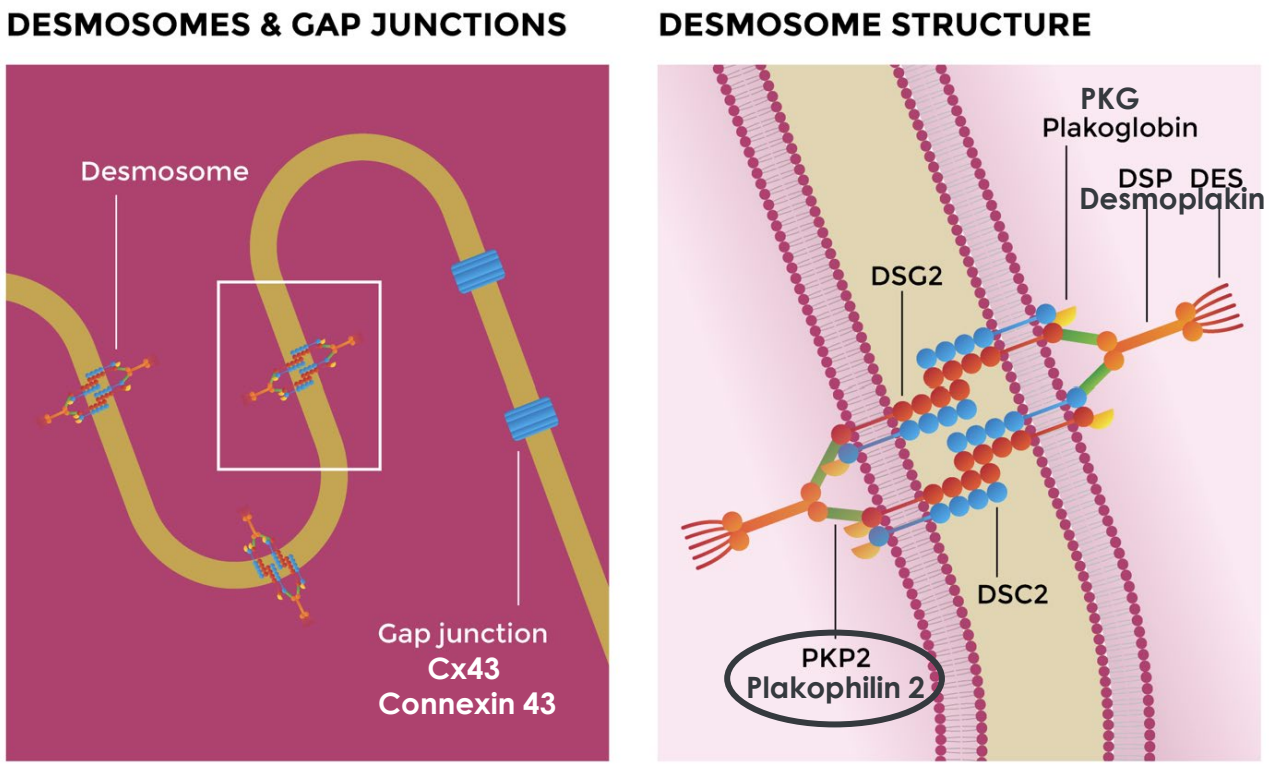
Current Therapy for ARVC

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

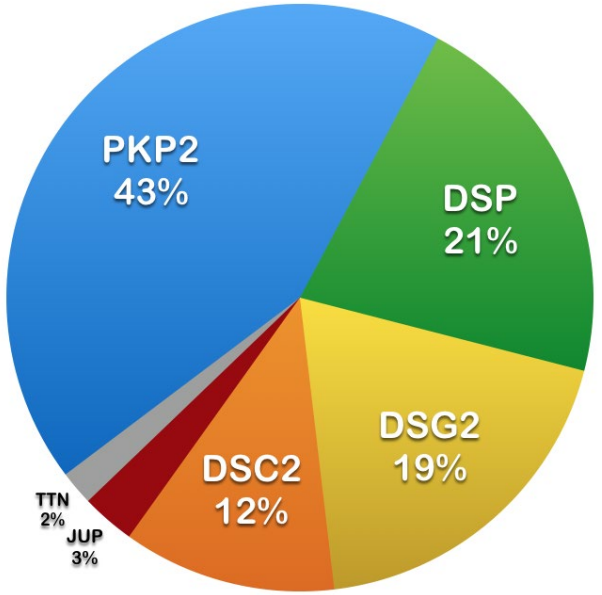
Standard of Care	Limitations of Care	New Treatment Paradigm Needed
Anti-Arrhythmic Medications	• Not fully effective • Side effects	**Options to prevent disease onset**
Implantable Cardioverter-Defibrillator (ICD)	• Potential for complications • Inappropriate shocks • Anxiety and impact on quality of life	
Ventricular Tachycardia (VT) Ablation	• Invasive procedure • Variable success rates	**Options to prevent disease progression**
Exercise Restriction	• Negative impact on lifestyle and general health	

Majority of ARVC Caused by Desmosome Mutations

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

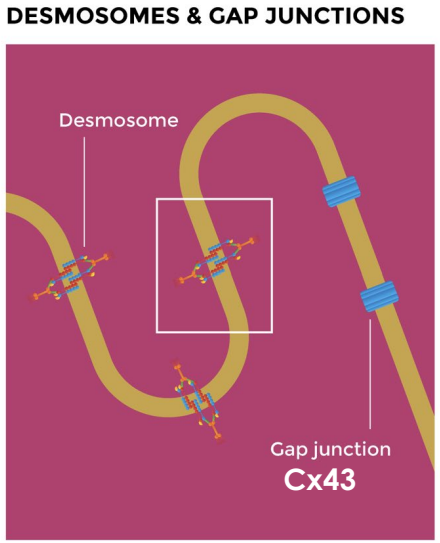


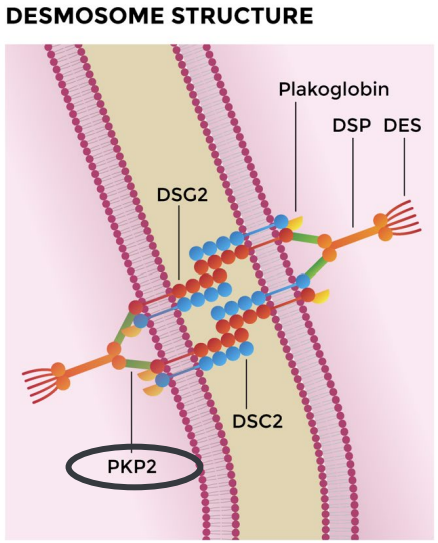
PKP2 Mutations are the Predominant Genetic Cause of ARVC

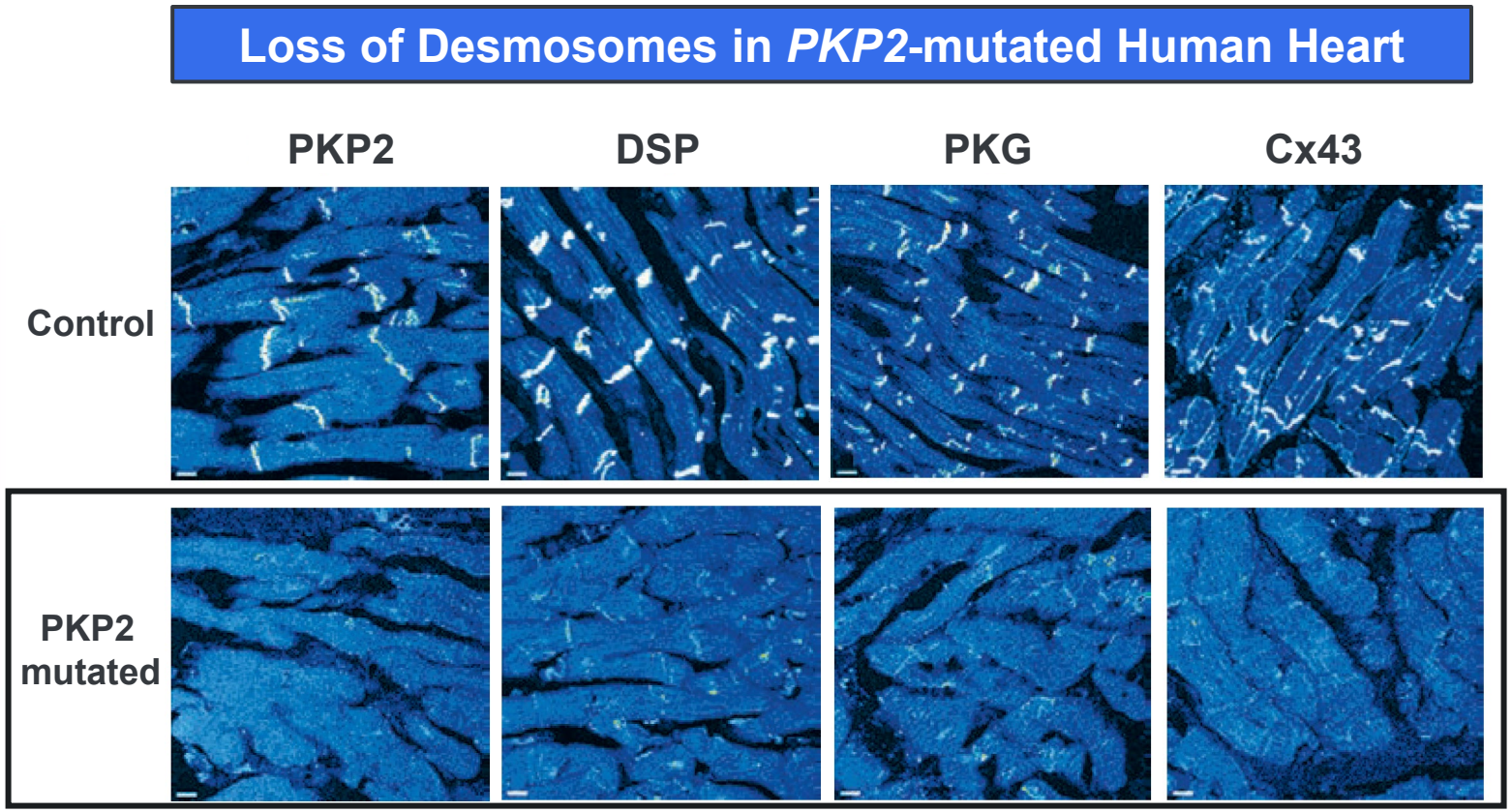


- Autosomal dominant inheritance
- ~70K patients with PKP2 mutations in the U.S. alone

PKP2 Mutation is Associated with Reduction of Protein Levels and Loss of Desmosome Structure in Human Hearts



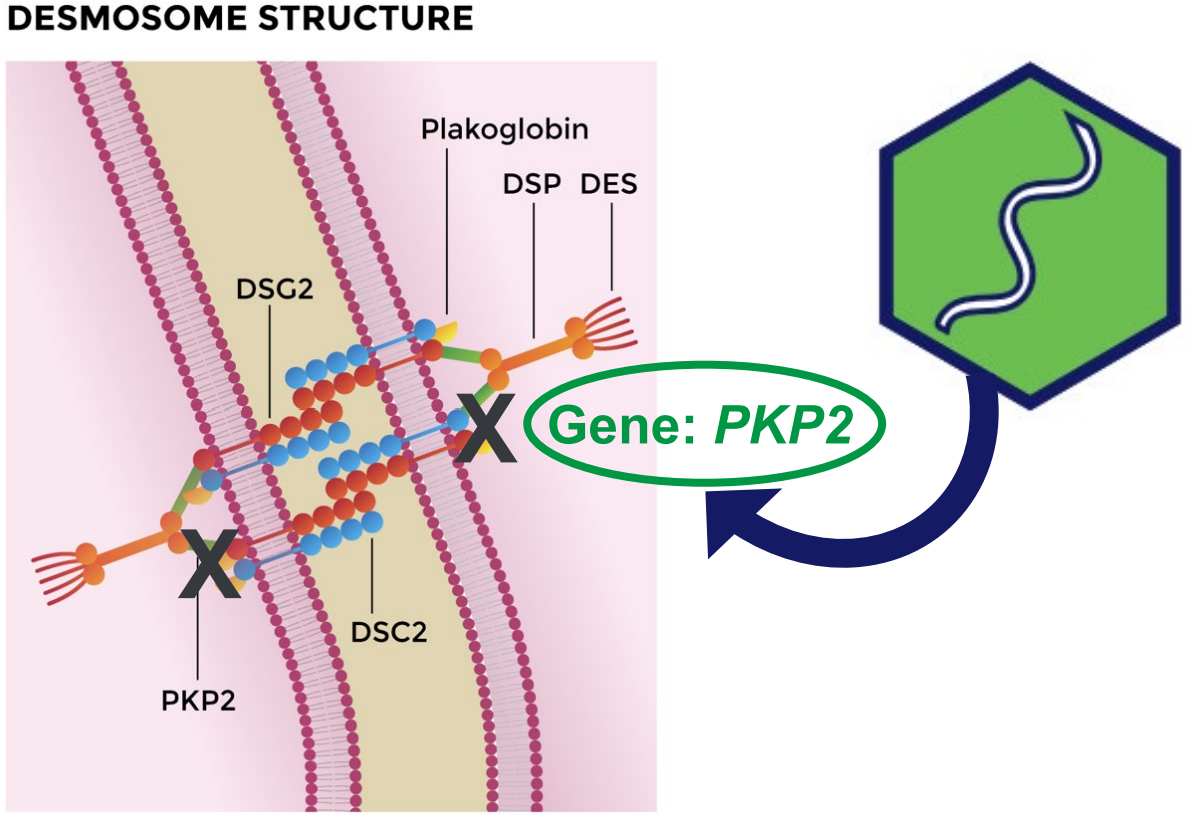




Asimaki et al. (2009) NEJM

Potential to Use AAV Gene Therapy for ARVC Due to *PKP2* Mutations

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



Vector = Adeno-Associated Virus (AAV)

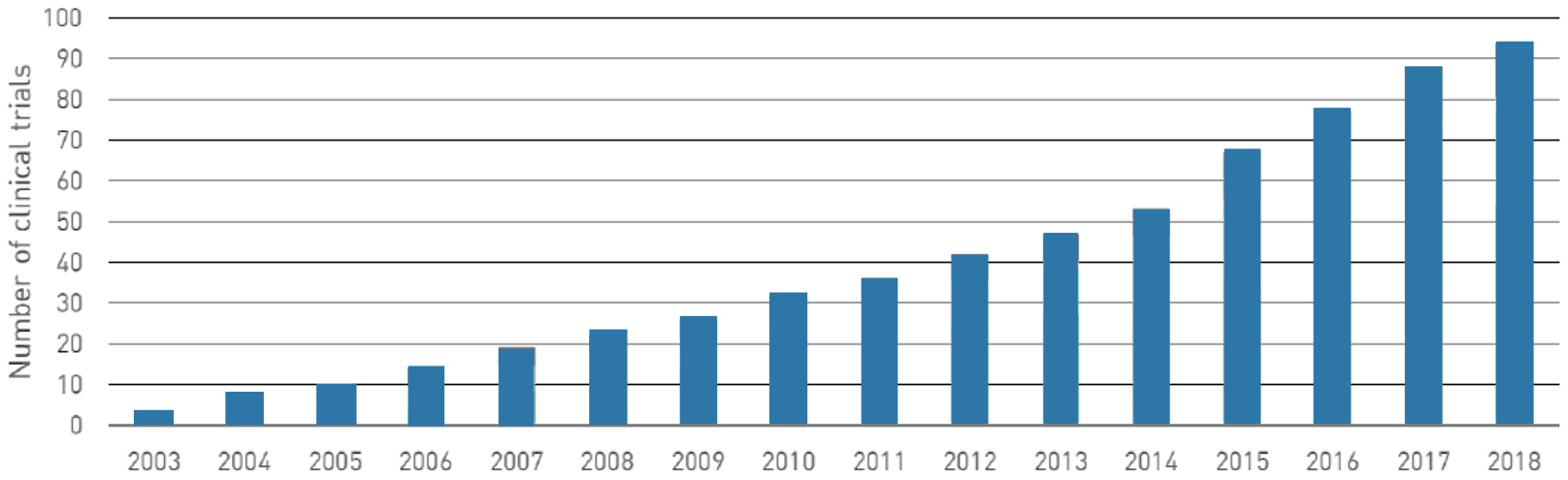
- **AAVs are naturally-occurring viruses that do not cause disease**

Promoter = Cardiac-specific

Expression = Non-integrating and durable

Increasing Use of AAV Gene Therapy

Number of Clinical Studies Using AAV, by Start Year



>3,000 patients treated in ~150 AAV gene therapy studies[1]

Approved Gene Therapy Products

zolgensma® (onasemnogene abeparvovec)

NOVARTIS

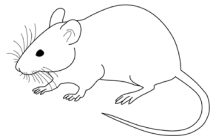
LUXTURNA® voretigene neparvovec-rzyl for subretinal injection

Roche

>1,800 patients treated in >40 countries[2]

[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

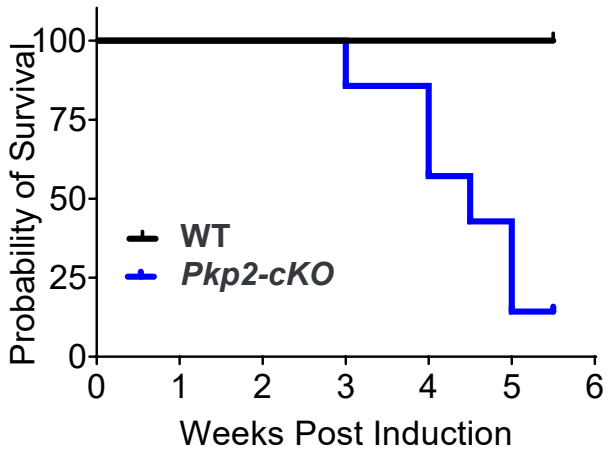


Cardiomyocyte-specific-*Cre-ER(T2), Pkp2* $^{fl/fl}$

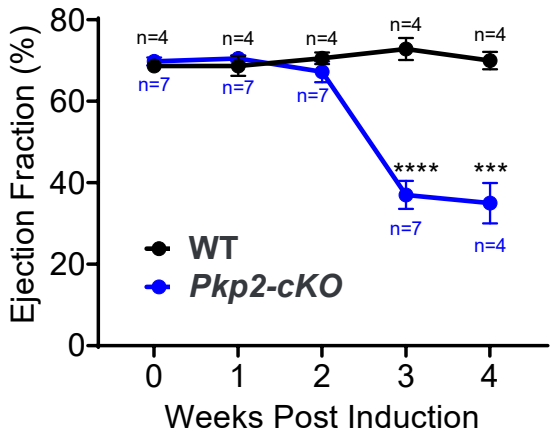
Cerrone et al. (2017) Nat. Comm.

- Life Span
- Cardiac Function
- Electro-physiology
- Fibrosis
- Molecular Desmosome Signature

Premature Mortality



Decreased LV Ejection Fraction



Increased Spontaneous PVCs

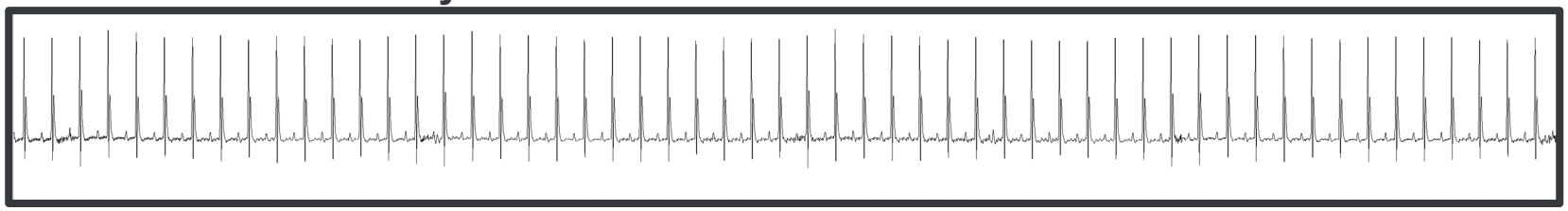
Animal	Week Post Induction		
	Week1	Week2	Week3
1	0	5	>100
2	0	12	12
3	0	2	Died
4	0	66	>100
5	0	20	>100
6	0	1	11
7	4	5	>100

WT = wild type

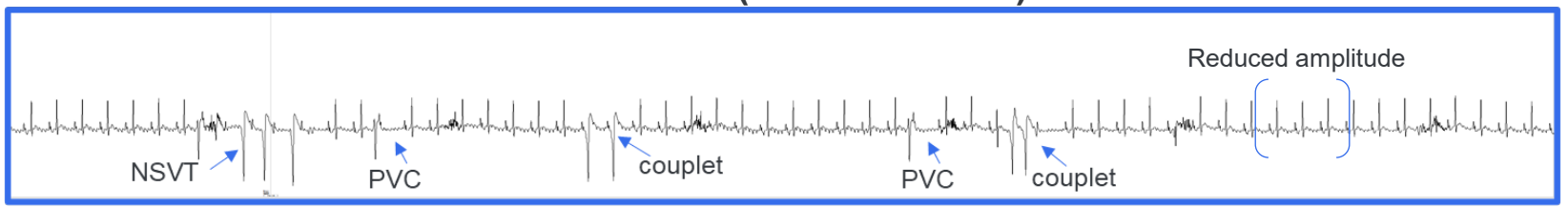
PVC = Premature ventricular contractions

Single Dose Cardiac AAV:PKP2 Gene Therapy Reduces Ventricular Arrhythmias

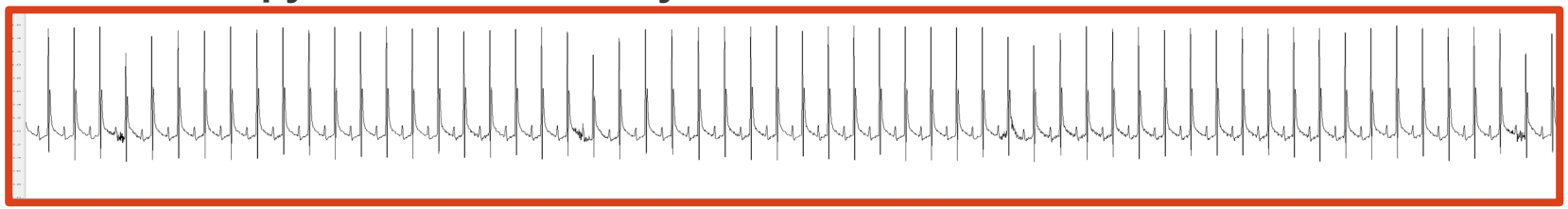
WT: Normal Sinus Rhythm

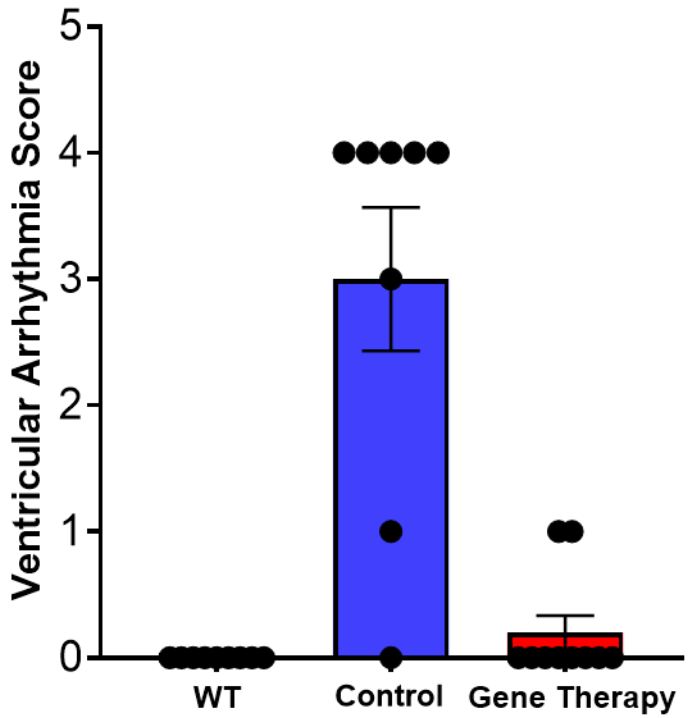


Control: Abnormal Ventricular Beats (NSVT & PVCs)



Gene Therapy: Normal Sinus Rhythm



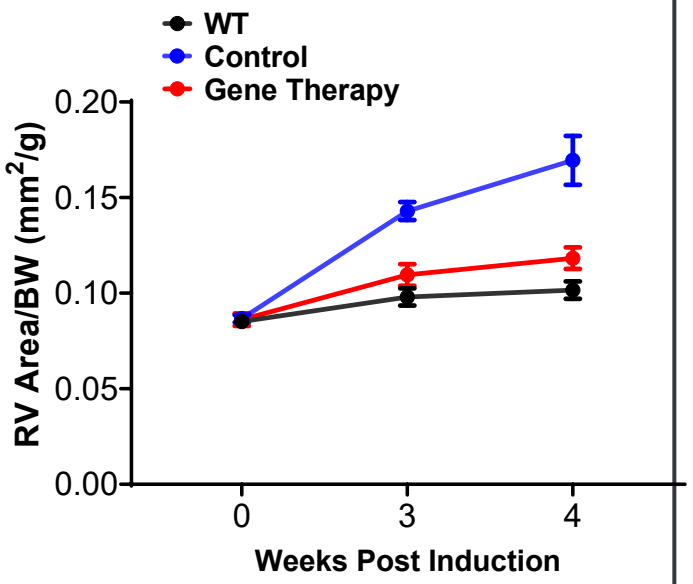


- **Ventricular Arrythmia Score includes NSVT, triplets, couplets, AV block and the frequency of PVCs**

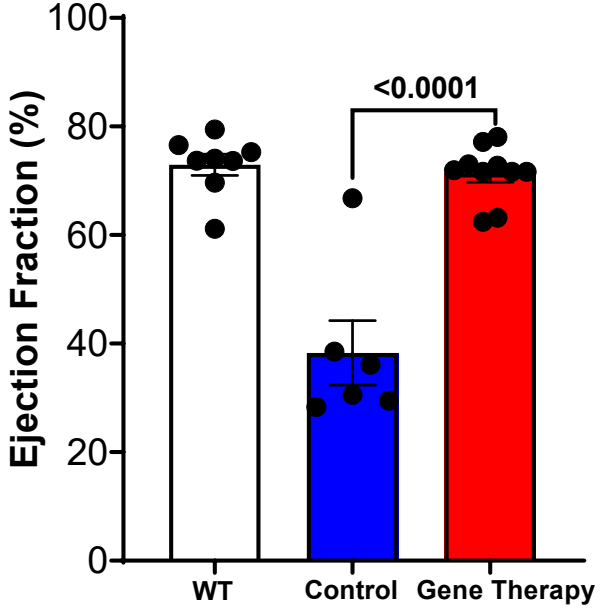
NSVT= Non-sustained ventricular tachycardia
AV = Atrioventricular

Single Dose Cardiac AAV:PKP2 Gene Therapy Demonstrates Disease Modification and Survival Benefit

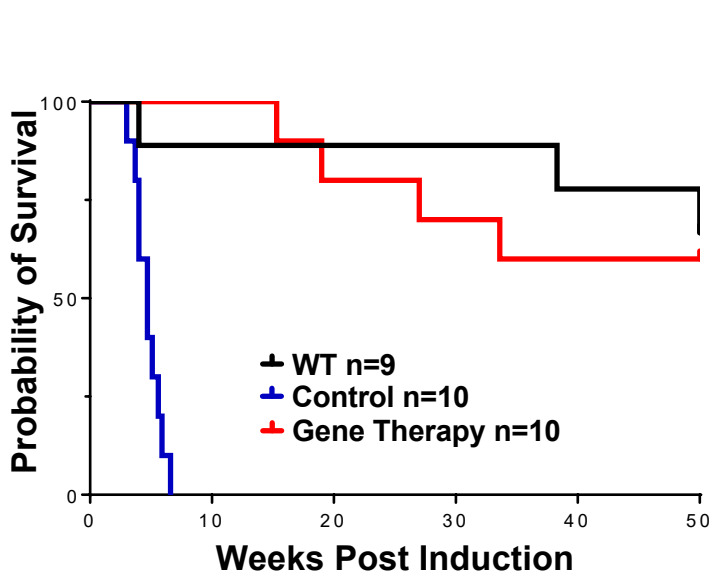
Prevention of Right Ventricle Enlargement



Prevention of Decline of Left Ventricle Function

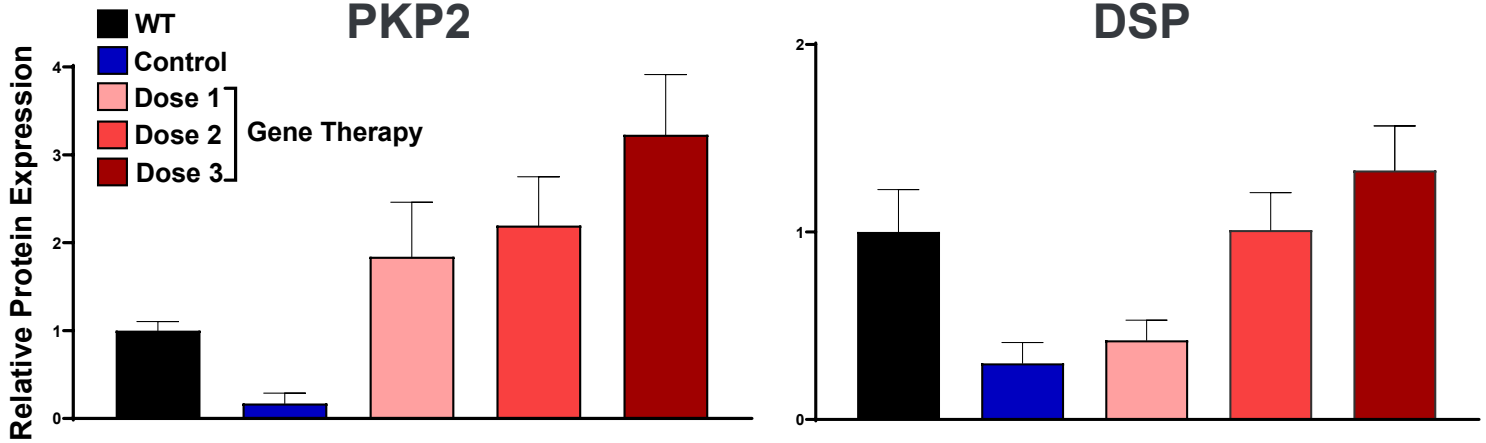


Extension of Life Span

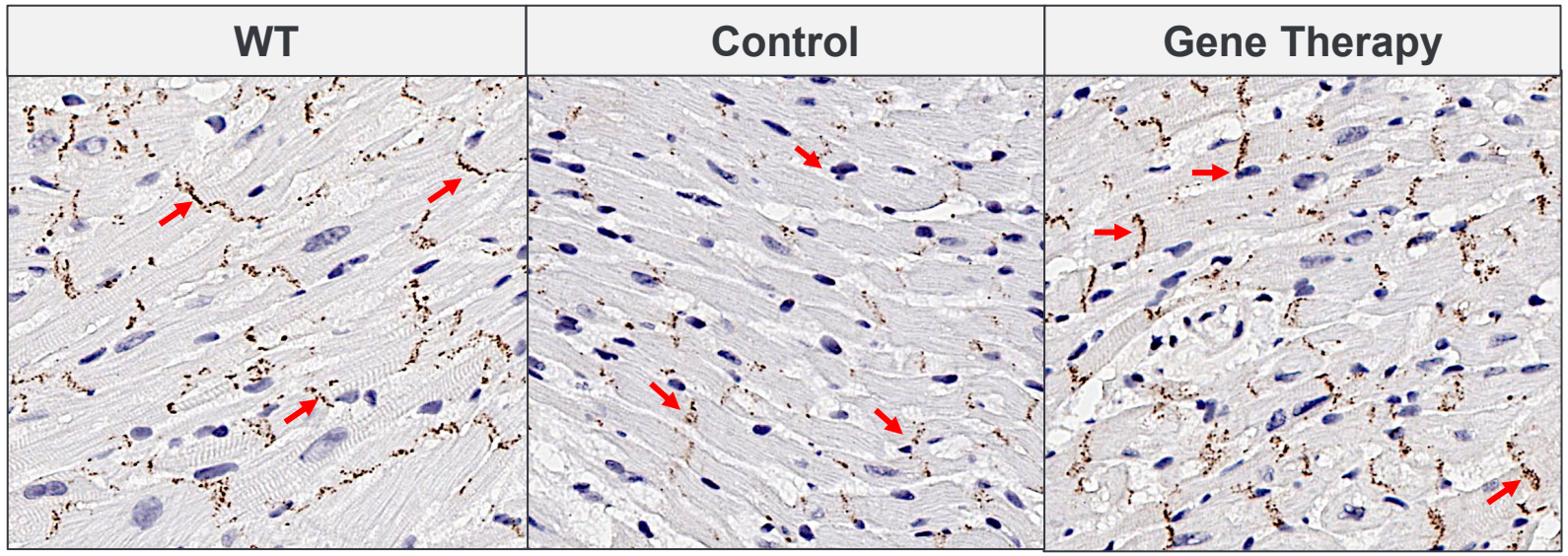


Single Dose Cardiac AAV:PKP2 Gene Therapy Restores Desmosomes and Gap Junctions

Desmosome Protein Expression



Cx43 IHC → at Gap Junction



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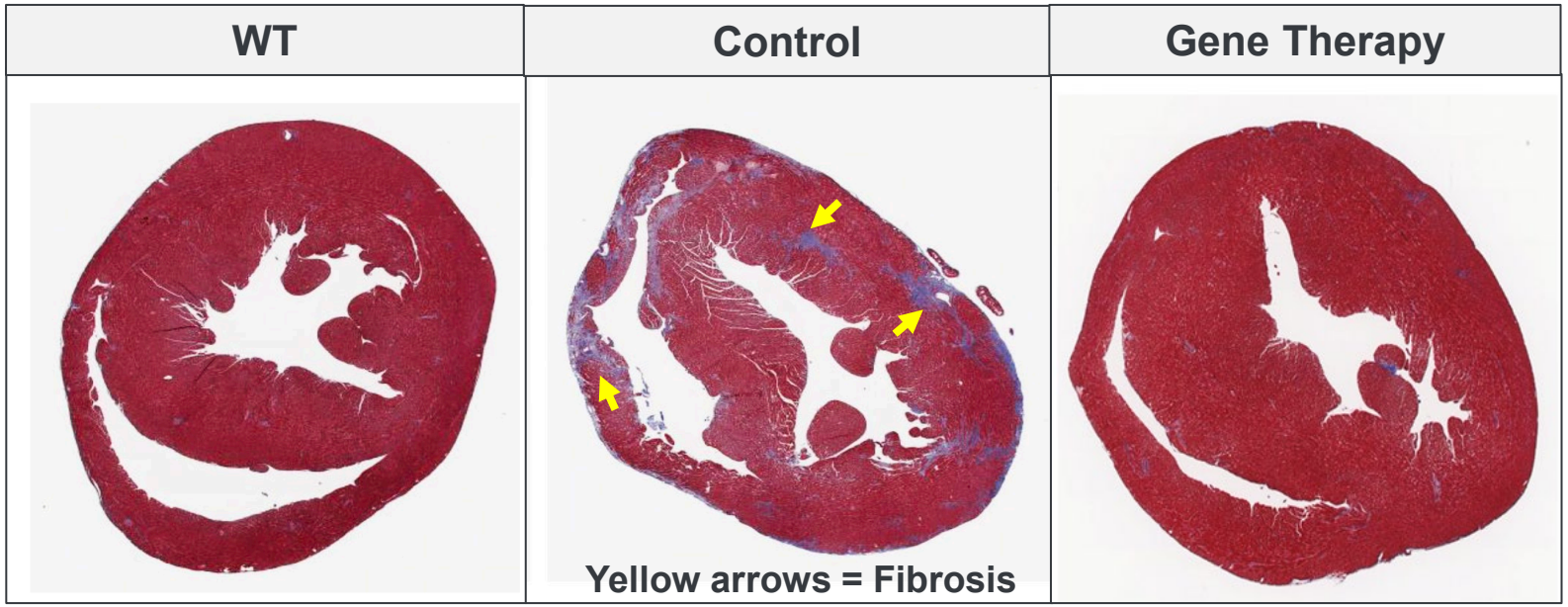
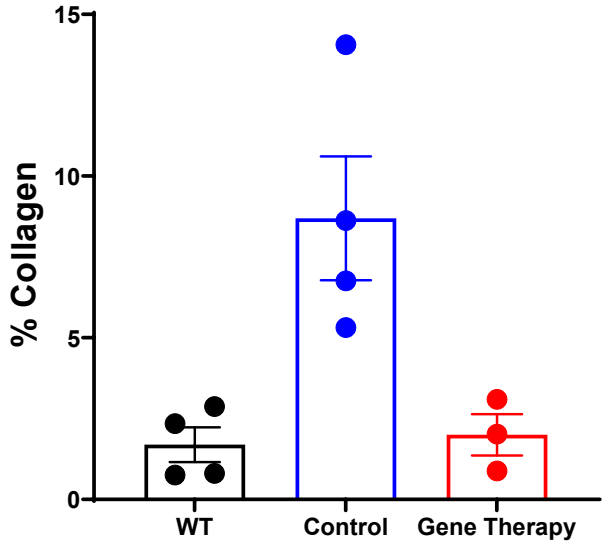
Single Dose Cardiac AAV:PKP2 Gene Therapy Prevents Fibrosis

Trichrome Staining





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**
  - Per HRS/EHRA Expert Consensus Statement on the State of Genetic Testing for the Channelopathies and Cardiomyopathies (2011)
  - 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