Preclinical Efficacy of AAVrh.74-PKP2a (RP-A601): Gene Therapy for PKP2-associated Arrhythmogenic Cardiomyopathy (PKP2-ACM)

Pegasus-ACM Program

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Late-breaking Abstract # 02

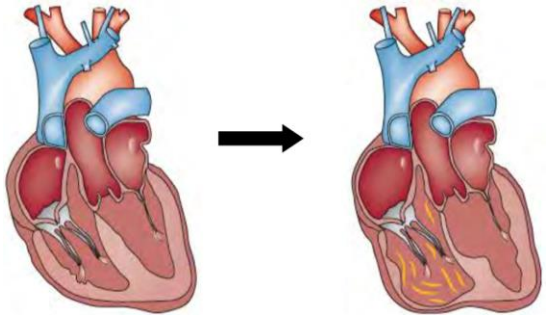
Arrhythmogenic Cardiomyopathy Due to Pathogenic Variants in the PKP2 Gene (PKP2-ACM)

A life-threatening disease, no curative options, clear unmet medical need

Disease Etiology & Clinical Manifestation

- **Pathogenic variants in the *PKP2* gene; Autosomal Dominant**
- Gene encodes for **plakophilin-2 isoform 2a (PKP2a) in heart**
- **PKP2a protein loss at cardiomyocyte junctions impairs intercellular structural and electrical integrity**
- **Fibrofatty infiltration** of the heart muscle (most prominently RV)[1]
- **Ventricular dilation**
- **Ventricular arrhythmias, premature ventricular contractions (PVC)**
- **Sudden cardiac arrest**

Advanced ACM Heart: Cardiomyopathy, Ventricular Dilation, Fibrosis



Electrical Manifestations → Fibrofatty Replacement → Arrythmia, SCD

Mean Age at Presentation: 35y (±18)[1]
Estimated Prevalence (US & EU): ~50,000

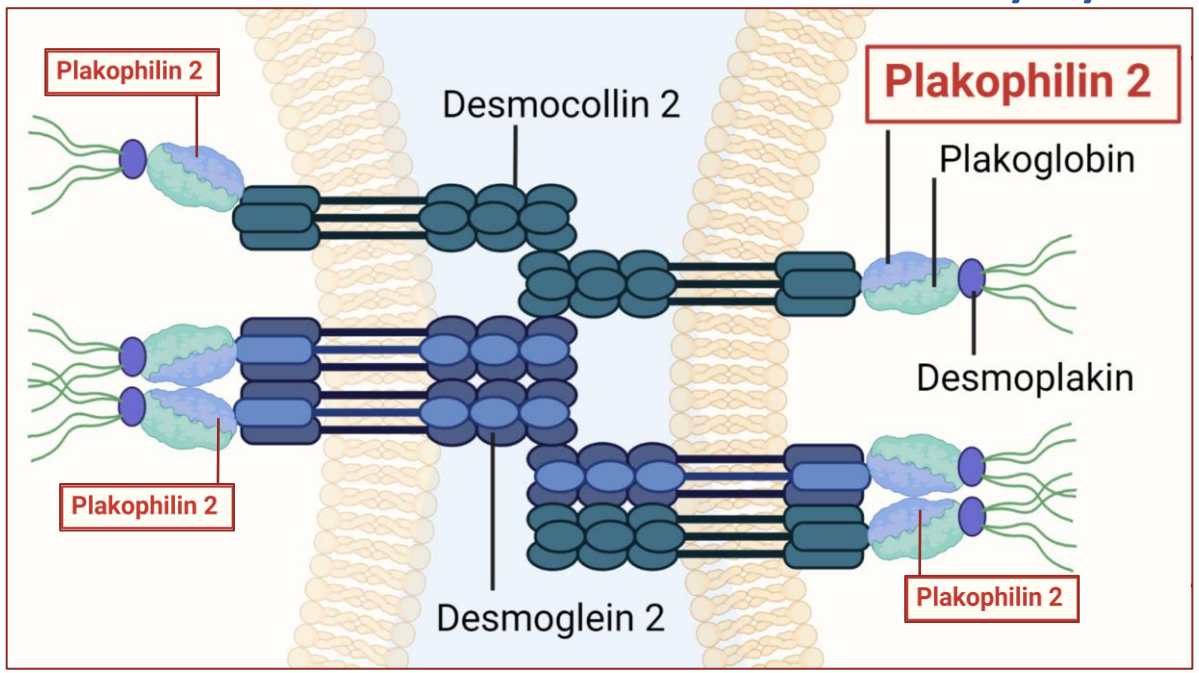
Therapeutic Challenges

- **Available treatments do not modify disease progression**; **no curative therapeutic options**
- Current standard of care includes beta-blockers, anti-arrhythmic agents, ablation, implantable cardioverter defibrillator (ICD); heart transplant for end-stage disease

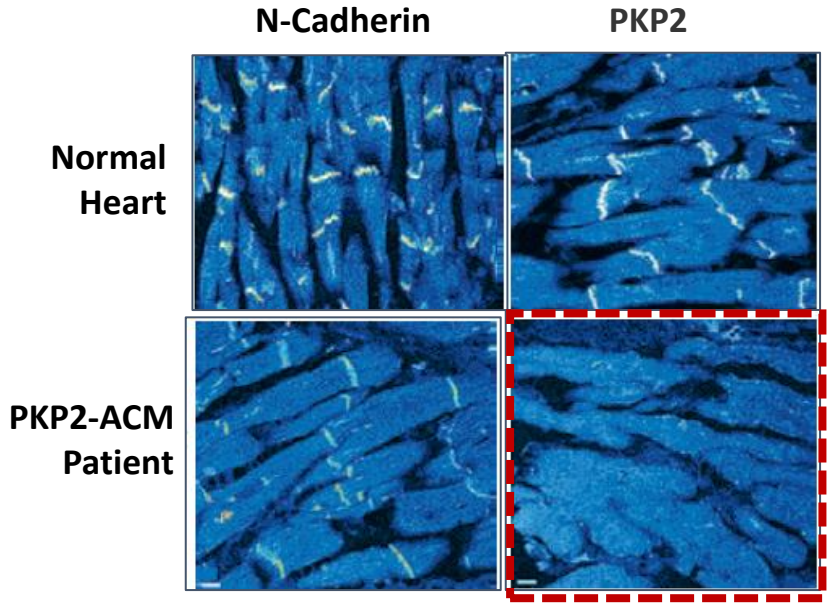
[1]Bhonsale et al., EHJ 2015; Figure adapted from Dalal et al., Circulation, 2006; RV: Right ventricle; ICD: implantable cardioverter defibrillator

Plakophilin-2a Localization to Cardiomyocyte Junctions and Normal Function

PKP2a within Desmosome: Normal Cardiomyocytes



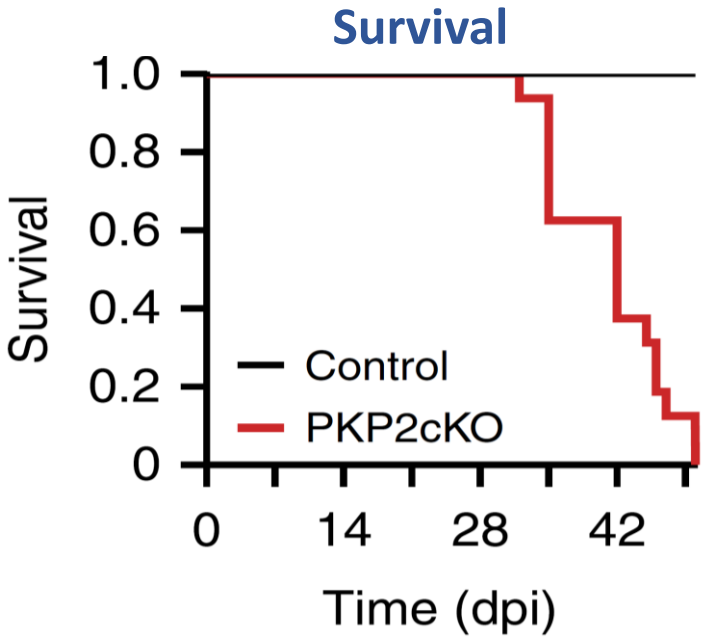
ACM: Diminished Myocardial PKP2

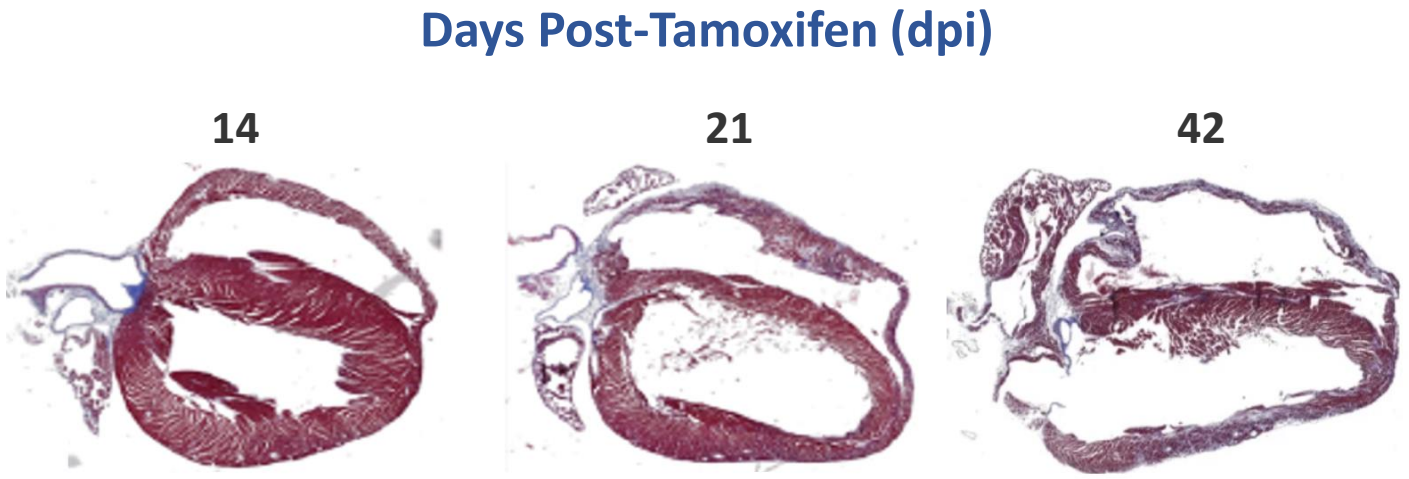


- **Plakophilin-2a is an integral component of the desmosome, a part of the intercalated disc at cardiomyocyte junctions**
- Serves a **multifunctional role; hub of structural and signaling proteins**
  - Scaffold protein involved in **desmosome assembly & cell adhesion**[1]
  - Transcriptional regulation of **calcium homeostasis**[2]
  - **PKP2 deficiency** leads to **loss of desmosome integrity**, **ventricular dilation**, **Ca^{2+} current deficits**, and **subsequent arrhythmia**[3]

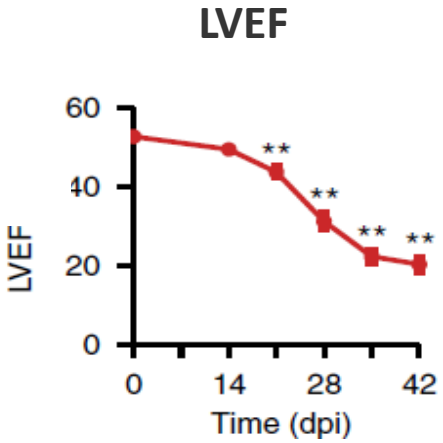
Biopsy figure adapted from: Asimaki et al. NEJM, 2009; [1]Garrod et al., BBA 2008; [2]vanOpbergen et al., Circulation 2022; [3]Cerrone et al., Nat.Comm, 2017

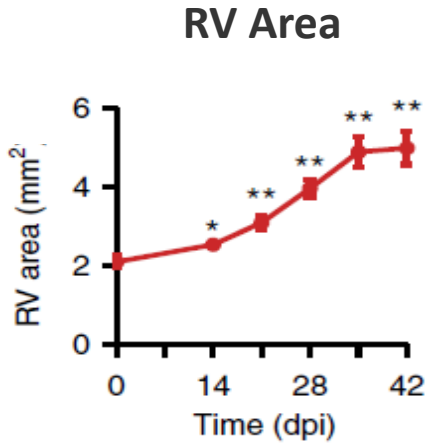
Translationally Relevant Animal Model: Tamoxifen-induced ACM in the PKP2 Cardiac Specific Knockout Mouse (PKP2-cKO)





- 100% mortality by day ~50 following tamoxifen injection
- Cardiac fibrosis starting at 14 dpi
- Decreased ejection fraction & right ventricle function
- Increased right ventricular (RV) area
- PVCs starting at 14-21 dpi and beyond



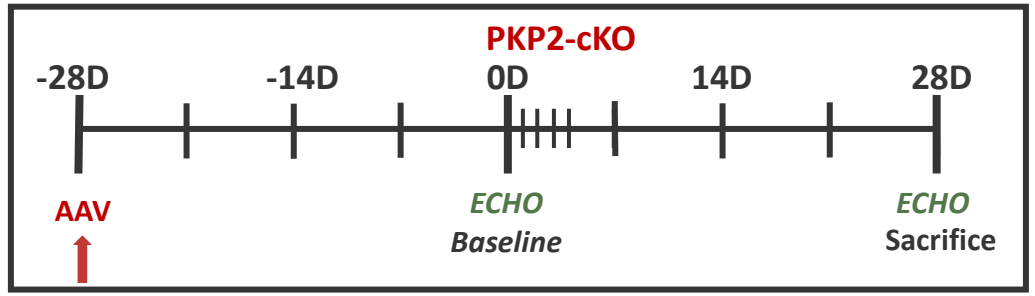


Data from Cerrone et al., Nat Commun. 2017;
cKO: conditional knockout; LVEF: left ventricular ejection fraction; PVC: Premature Ventricular Contractions; dpi: days post-injection

Evaluation of AAVrh.74-PKP2a in Multiple PKP2-cKO Paradigms

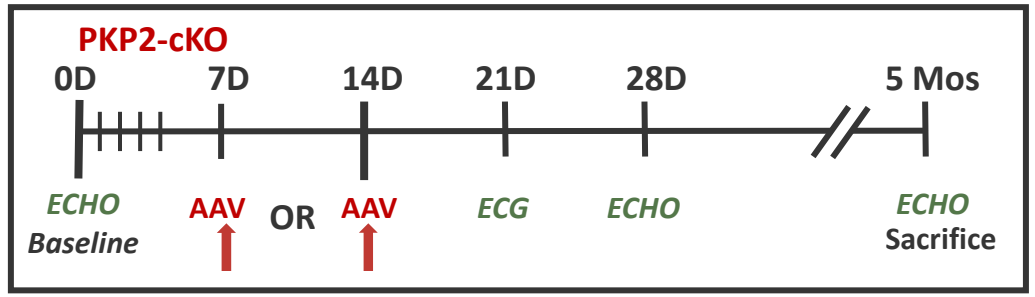
AAVrh.74-PKP2a *Before* PKP2-KO

Evaluated Prevention of ACM Onset

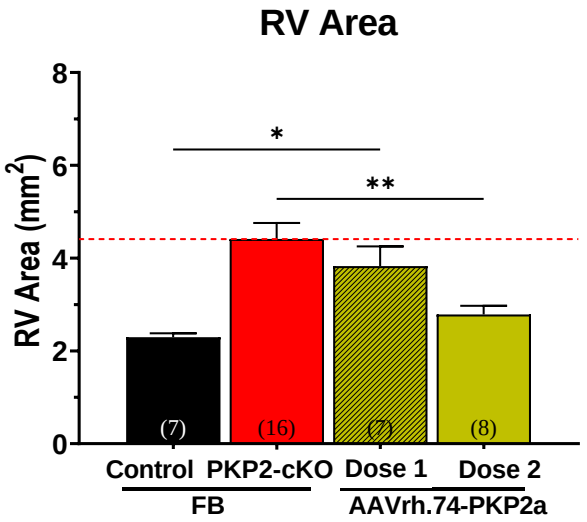


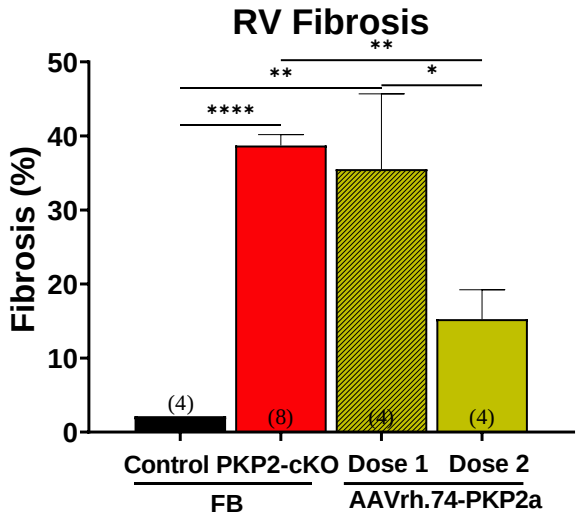
AAVrh.74-PKP2a *After* PKP2-KO

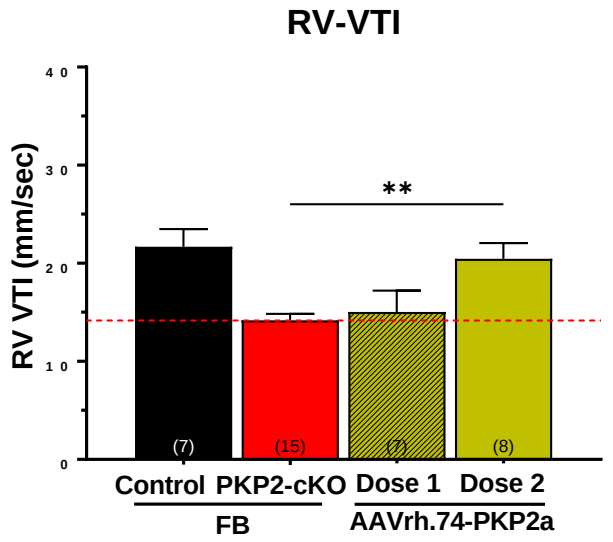
Evaluated Prevention of ACM Progression

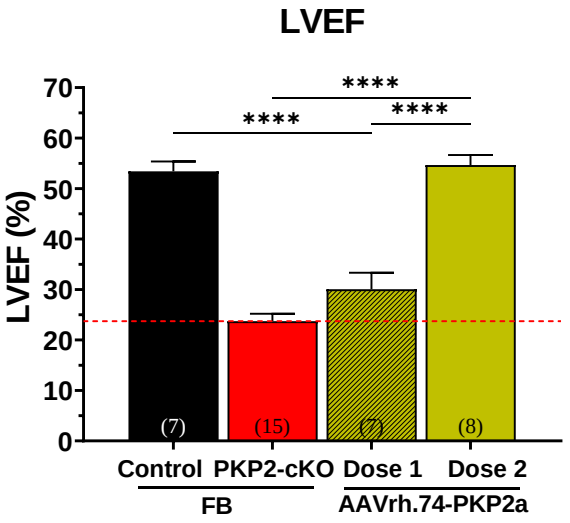


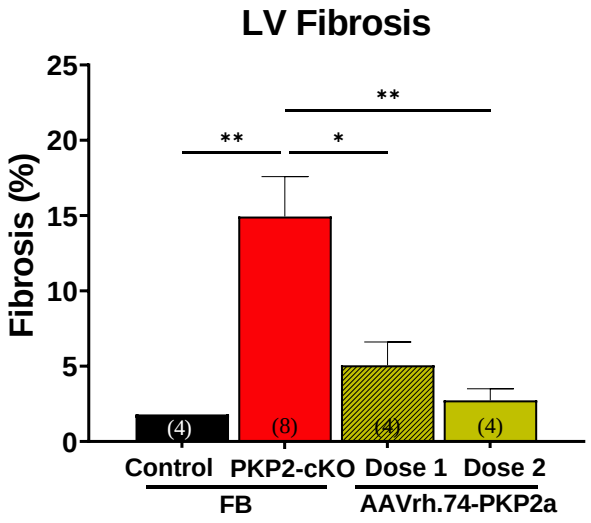
Intravenous AAVrh.74-PKP2a *Before* PKP2 KO Prevents Disease-related Ventricular Dilation, Fibrosis & Systolic Dysfunction in PKP2-cKO Mice









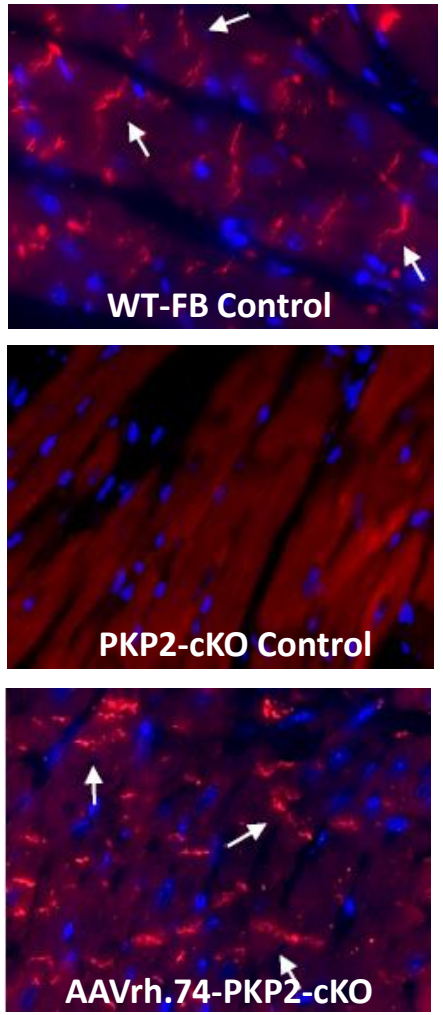


FB = Formulation Buffer Control

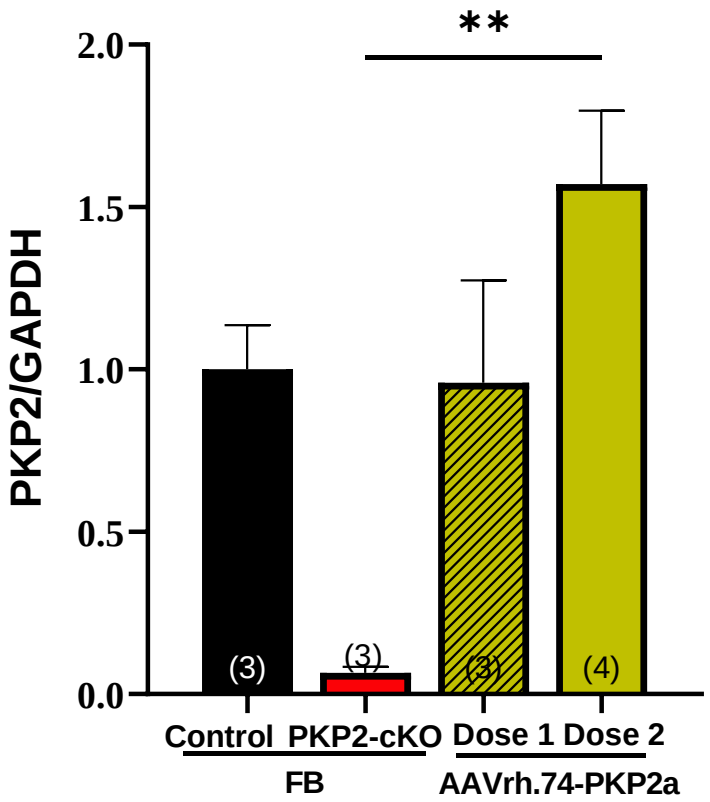
- **Dose-related benefit of AAVrh.74-PKP2a in heart included….**
  - **mitigation of RV enlargement**
  - **preserved RV systolic function**
  - **mitigation of RV & LV cardiac fibrosis**
  - **preserved LV systolic function**

AAVrh.74-PKP2a Transgene Expression in PKP2a-cKO Mouse Model

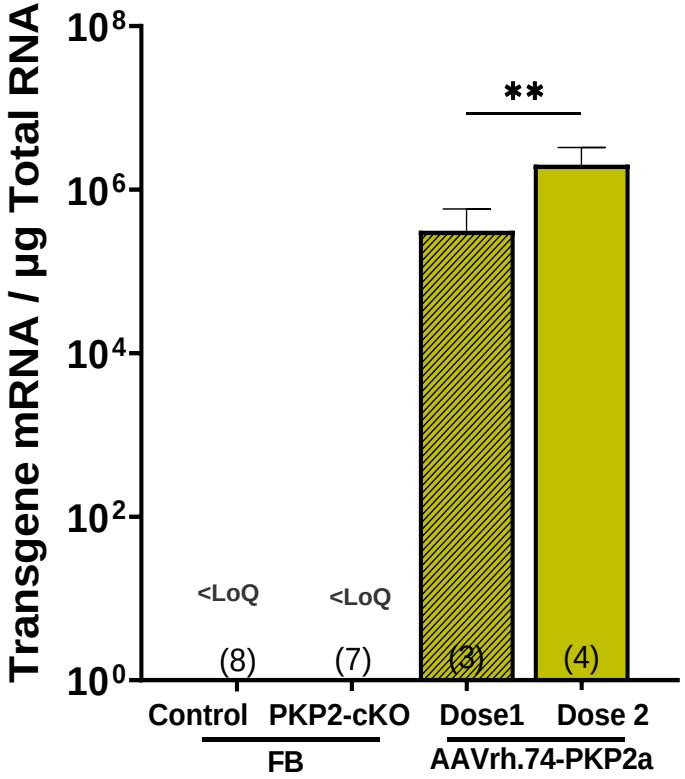
PKP2 by Immunolabeling



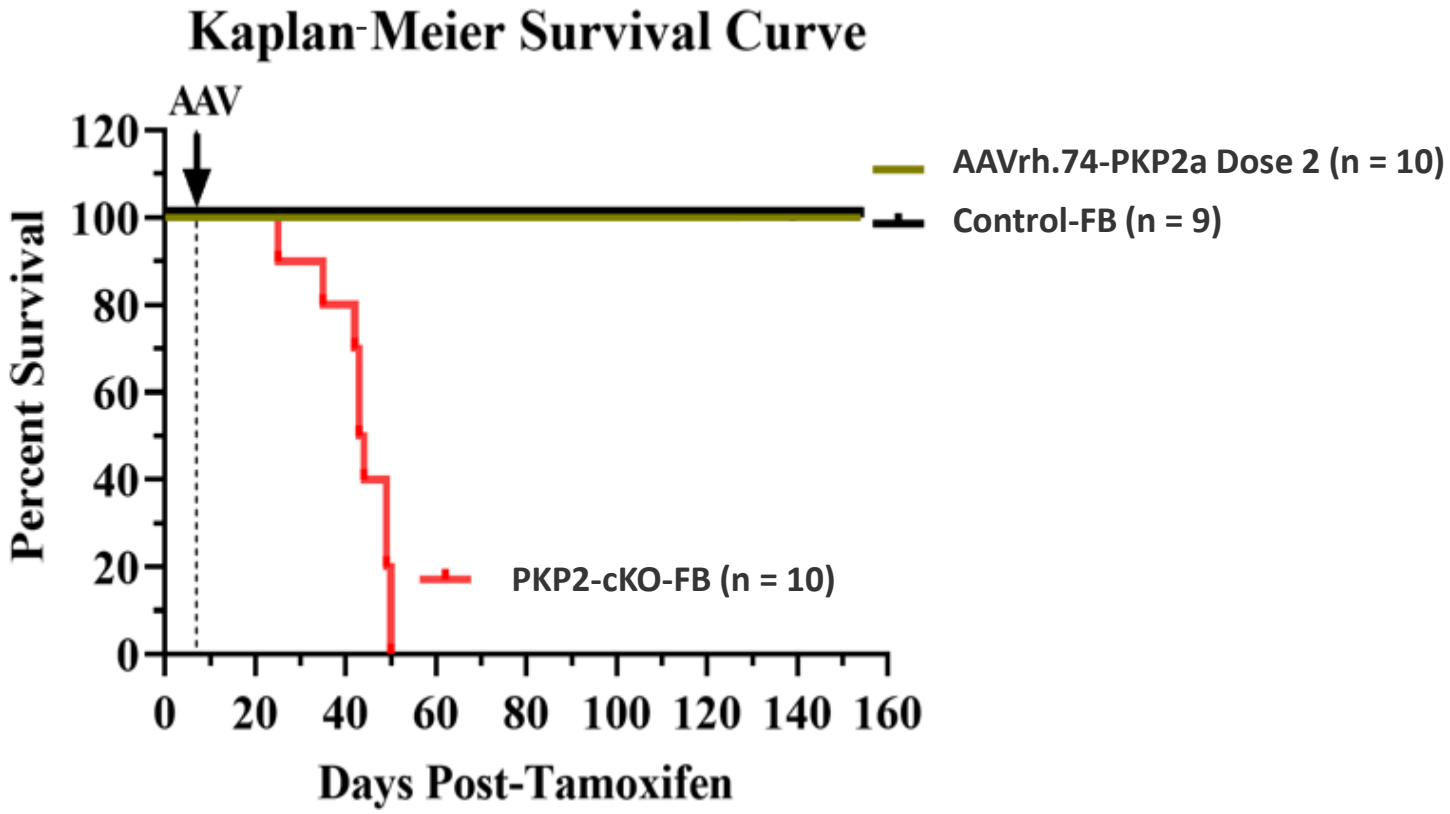
PKP2 Protein (WB)



Transgene mRNA

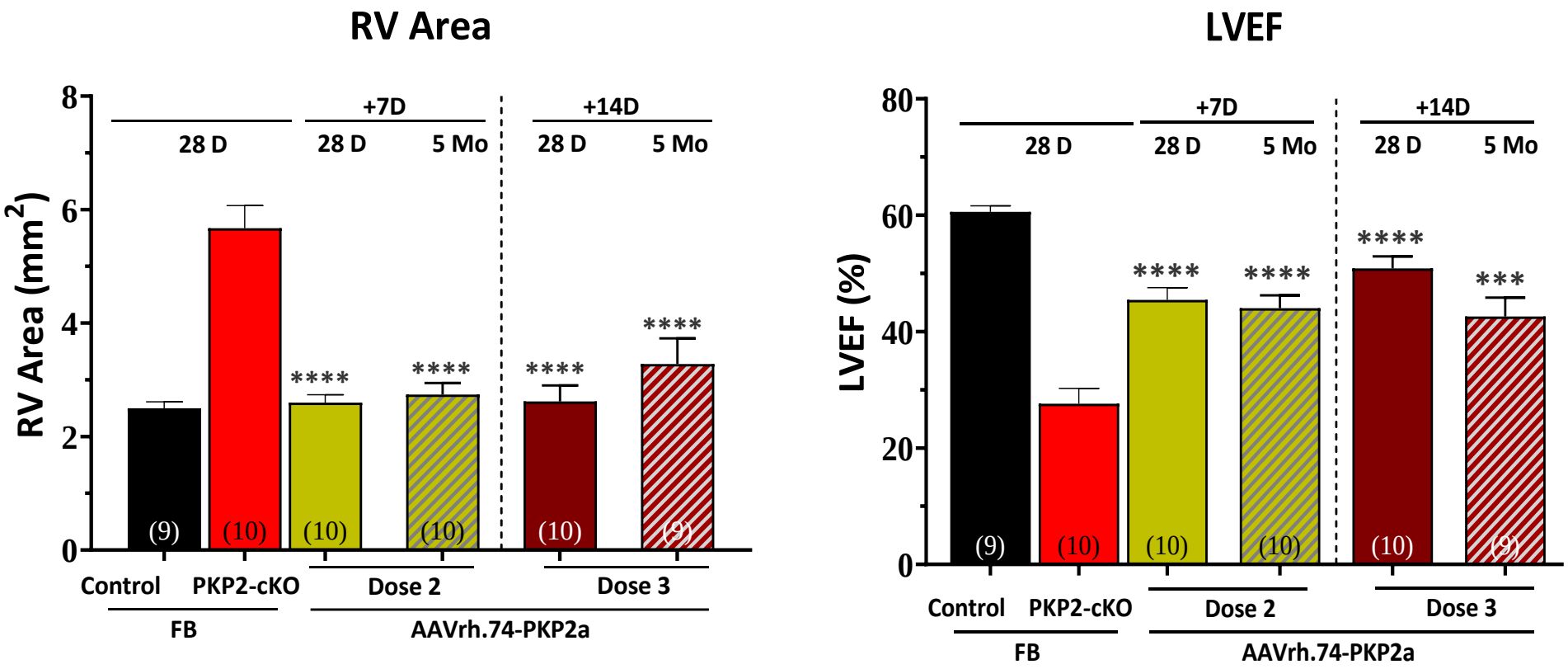


AAVrh.74-PKP2a *After* PKP2-cKO Dramatically Increases Survival



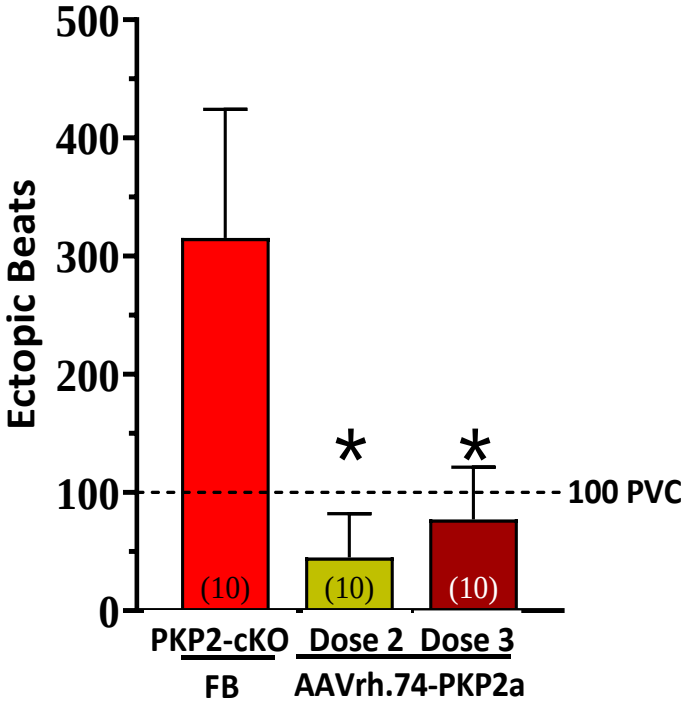
- AAVrh.74-PKP2a delivered ***7 days After*** tamoxifen-induced PKP2-cKO
- **100% survival to 5 months**, compared to 100% mortality by day ~50 in PKP2-cKO-FB

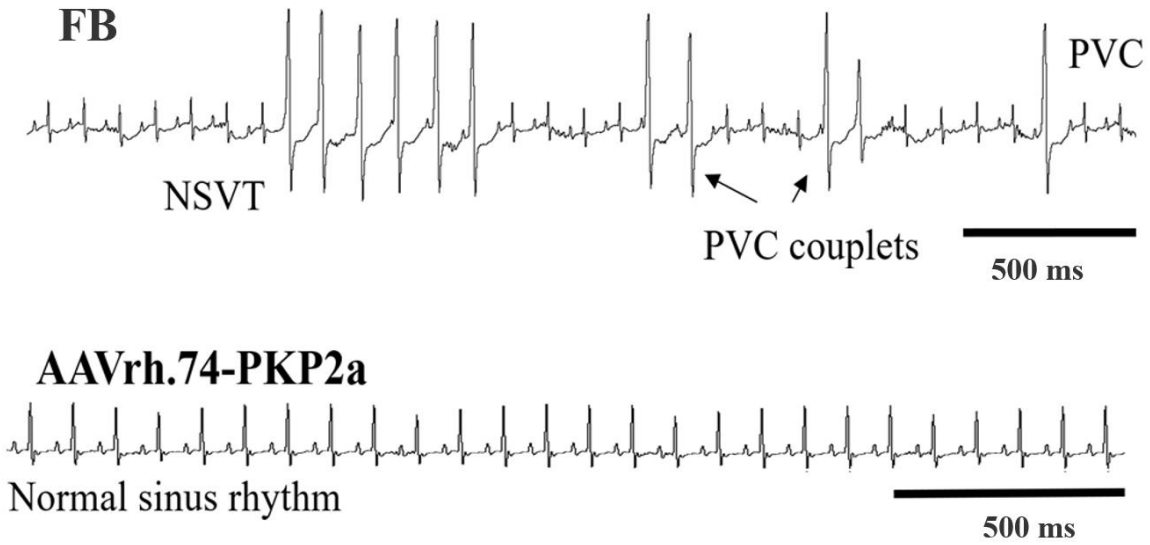
AAVrh.74-PKP2a *After* Disease Induction Prevents ACM Progression



- AAVrh.74-PKP2a was delivered ***7 or 14 days after*** tamoxifen-induced PKP2-cKO
- Mitigation of disease-related increase in RV area & preserved LVEF
- Robust mitigation of disease-related fibrosis in both right & left ventricles

AAVrh.74-PKP2a *After* Disease Induction Mitigates Arrhythmia





- AAVrh.74-PKP2a was delivered ***14 days after*** tamoxifen-induced PKP2-cKO
- Robust mitigation of disease-related Isoproterenol-induced PVC's and ventricular arrhythmia

FB = Formulation Buffer Control; PVC = Premature Ventricular Contractions; NSVT = Non-sustained Ventricular Tachycardia

Efficacy of AAVrh.74-PKP2a in Relevant Mouse Model of PKP2-ACM

Intravenous AAVrh.74-PKP2a, when delivered *after disease onset*…

- resulted in robust transgene expression in heart (protein, mRNA)
- dramatically extended survival in PKP2-cKO mice
- significantly improved arrhythmia burden
- significantly reduced cardiac fibrosis and RV dilation
- significantly improved systolic function
- was safe and well-tolerated up to 5 months, longest timepoint evaluated in the PKP2-cKO model

Efficacy & Safety/Toxicology Profile of Intravenous AAVrh.74-PKP2a Supports Clinical Development

- Firmly established dose-related efficacy in relevant animal model
- Completed comprehensive Safety/Toxicology in rodent & NHP
- No adverse effects up to highest dose evaluated in rodents (to 6 months) or NHP
- Collectively, preclinical efficacy & safety package support clinical development of AAVrh.74-PKP2a (RP-A601) as potential therapeutic in patients with PKP2-ACM
- IND endorsed by FDA May 2023; enrollment to commence at University of California San Diego Medical Center and Children's Hospital of Philadelphia

For Clinical Trial inquiries, please contact: *clinicaltrials@rocketpharma.com*

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