Measuring Protein Expression in Cardiac Gene Therapy

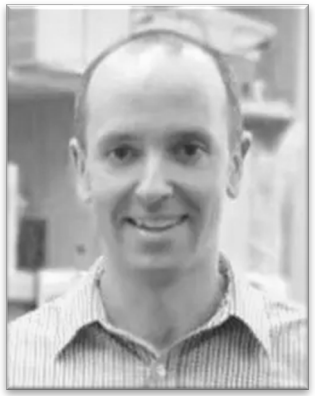
August 26, 2025

Today's speakers

Faraz Ali, MBA
Chief Executive Officer

Kathy Ivey, Ph.D.,
Senior Vice President, Research

Whit Tingley, M.D., PhD
Chief Medical Officer



Guest Speaker:
Michael Previs, Ph.D.
Associate Professor of Cellular, Molecular, and Biomedical Sciences at the University of Vermont

Forward-looking statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Securities Exchange Act of 1934, as amended, that are based on our management's beliefs and assumptions and on information currently available to our management. Forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified. All statements other than statements of historical facts contained in this presentation, including statements regarding business strategy, plans and 2025 strategic priorities; the clinical, therapeutic and market potential of and expectations regarding our product candidates, platforms and proprietary capabilities; clinical development plans for TN-201, TN-401 and TN-301; preclinical efforts and timelines; availability and content of data from MyPEAK™-1 and RIDGE™-1; targeted populations for clinical trials and treatments; the sufficiency of Tenaya's cash runway to fund operations, as well as statements regarding industry trends, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "purpose," "focus," "plan," "potential," "may," "future," "anticipated," "objective," or the negative of these terms or other similar expressions. We have based these forward-looking statements largely on our current expectations and projections about future events and trends that we believe may affect our financial condition, results of operations, business strategy and financial needs.

These forward-looking statements are subject to time, risks, uncertainties and assumptions described in our filings with the SEC, including, but not limited to the section titled "Risk Factors" in our Form 10-K for year ended December 31, 2024, and other documents we have filed, or will file with the SEC. These filings, once filed, are or will be available on the SEC website at www.sec.gov. Such risks include, among other things: the availability of data at the referenced times; the timing of the initiation, progress, completion and potential results of our clinical trials and preclinical studies; our ability to advance product candidates into, and successfully complete, clinical trials and preclinical studies; the potential for clinical trials of our product candidates to differ from preclinical, preliminary, interim or expected results; the timing or likelihood of regulatory filings and approvals; our estimates of the number of patients who suffer from the diseases we are targeting and the number of patients that may enroll in our clinical trials; our ability to successfully manufacture and supply our product candidates for preclinical studies, clinical trials and for commercial use, if approved; our ability to commercialize our product candidates, if approved; future strategic arrangements and/or collaborations and the potential benefits of such arrangements and/or collaborations; our estimates regarding expenses, capital requirements and needs for financing, and our ability to obtain capital; our ability to retain the continued service of our key personnel and to identify, hire and retain additional qualified professionals; our ability to obtain and maintain intellectual property protection for our platforms, programs and product candidates; our ability to contract with third-party suppliers and manufacturers and their ability to perform adequately; the pricing, coverage and reimbursement of our product candidates, if approved; and developments relating to our competitors and our industry, including competing product candidates and therapies; general economic and market conditions; and other risks. These risks are not exhaustive. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in, or implied by, any forward-looking statements. You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee future results, levels of activity, performance or achievements. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. The forward-looking statements made in this presentation relate only to events as of the date on which such statements are made. Except as required by law, we undertake no obligation to update publicly any forward-looking statements for any reason after the date of this presentation. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

This presentation discusses product candidates that are under clinical study and have not yet been approved for marketing by the U.S. Food and Drug Administration. No presentation is made as to the safety or efficacy of these product candidates for the use for which such product candidates are being studied.

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Our purpose: To transform and extend lives through
the discovery, development and delivery of potentially curative therapies
that target the underlying causes of heart disease.

Singular focus on the heart

3 clinical-stage programs

Multiple near-term gene therapy data readouts

Deep expertise in cardiology, genetics and rare disease drug development

Foundational capabilities fuel innovation and first-in-class potential

Track record of execution

Gene therapy pipeline coming into focus

Program	Modality	U.S. Prevalence	Development Stage	Status
Clinical-Stage Programs				
TN-201 for *MYBPC3*+ HCM • FDA Orphan Drug, Fast Track and Rare Pediatric Disease designations • Orphan Medicinal Product designation from European Commission	AAV9 gene therapy	> 120K(1)	**MyPEAK™-1 Phase 1b/2**	Cohort 1 enrolled Cohort 2 enrolled
			Seroprevalence study	Completed >100 participants
			Natural history study	> 220 participants enrolled
TN-401 for *PKP2*+ ARVC • FDA Orphan Drug and Fast Track designations • Orphan Medicinal Product designation from European Commission	AAV9 gene therapy	> 70K(2)	**RIDGE™-1 Phase 1b**	Cohort 1 enrolled Cohort 2 enrolling
			Natural history and seroprevalence study	> 100 participants

1. Sedaghat-Hemedani, et al., *Clin Res Cardiol*. 2018
2. Groeneweg, et al, *Circ Cardiovasc Gen 2015* & McKenna, et al, *Nature Rev Cardio* 2021

MYBPC3 = Myosin binding protein C-3
HCM = Hypertrophic cardiomyopathy (HCM)
AAV9 = Adeno-associated virus serotype 9

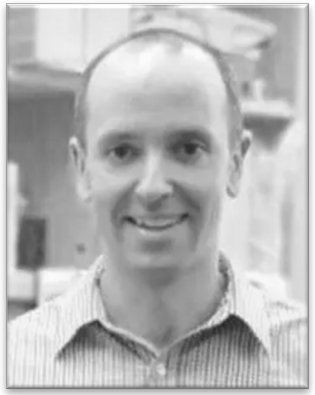
PKP2 = Plakophilin-2
ARVC = = Arrhythmogenic right ventricular cardiomyopathy

Agenda and speakers

Today's agenda

- **Introductory remarks**
  Faraz Ali
- **Tenaya Gene Therapy Program Update**
  Dr. Whit Tingley
- **Measuring Protein Expression in Cardiac Gene Therapy**
  Dr. Kathy Ivey in conversation with Dr. Michael Previs
- **Q&A**

Featured Speaker



Dr. Michael Previs, Ph.D.
Associate Professor, Molecular Physiology and Biophysics
Larner College of Medicine, University of Vermont

- Development of quantitative mass spectrometry-based proteomic techniques to examine muscle structure
- Understanding the molecular mechanisms by which MyBP-C protein regulates the heart's ability to contract
- Co-led the discovery that MYBPC3-associated HCM is a disease of haploinsufficiency, not a poison peptide
- Received Ph.D. in Cell and Molecular Biology Program at the University of Vermont

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Tenaya's Cardiomyopathy Gene Therapy Programs – An Update

Whit Tingley

1H’25 Scorecard: Important progress advancing our two lead gene therapy programs

TN-201 for MYBPC3-associated HCM

- ✓ MyPEAK-1 additional Cohort 1 data at ACC
- ✓ *MYBPC3*+ HCM disease burden presented at ACC
- ✓ MyPEAK-1 high-dose Cohort 2 fully enrolled
- ✓ MyPEAK-1 DSMB clearance to expand at either dose level

TN-401 for PKP2-associated ARVC

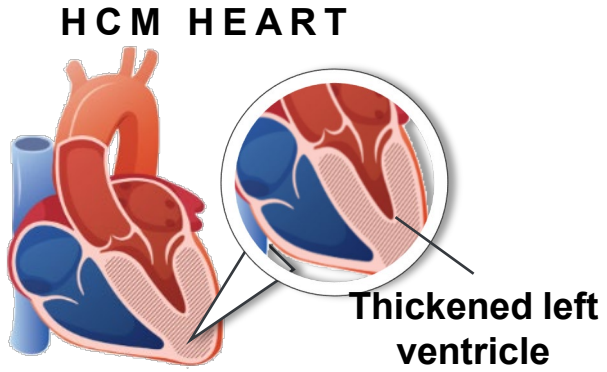
- ✓ RIDGE Natural History study data presented at HRS
- ✓ RIDGE-1 Cohort 1 fully enrolled
- ✓ RIDGE-1 DSMB clearance to expand enrollment at 3E13 vg/kg dose and dose escalate to 6E13 vg/kg
- ✓ RIDGE-1 First Cohort 2 patient dosed

MYBPC3-associated HCM is estimated to affect 120,000 people in the U.S. alone[1]

A severe and progressive autosomal dominant condition affecting adults, teens, children and infants

~57% of identified genetic variants underlying familial HCM are *MYBPC3* mutations[2]

>30% of genetic variants underlying childhood-onset HCM are *MYBPC3* mutations[3]

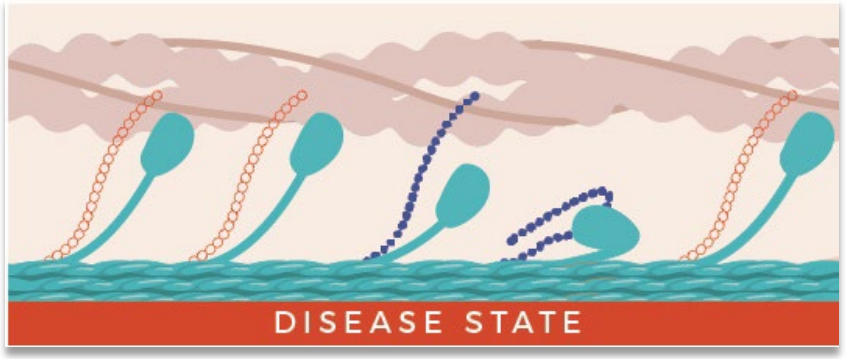


- Significant functional impairment
- Social and psychological impacts
- Symptoms include shortness of breath, fainting, chest pain, fatigue, palpitations, arrhythmias
- Elevated risk of sudden cardiac death and heart failure

1. Sedaghat-Hemedani, et al., *Clin Res Cardiol* 2018
2. Ho, et al, *Circulation* 2018
3. Marston, et al, *Eur Heart Jrnl* 2021

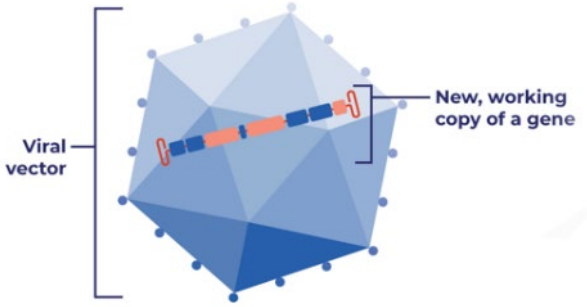
TN-201 is the first gene therapy being developed for *MYBPC3*-associated HCM[1]

MYBPC3+ Pathophysiology

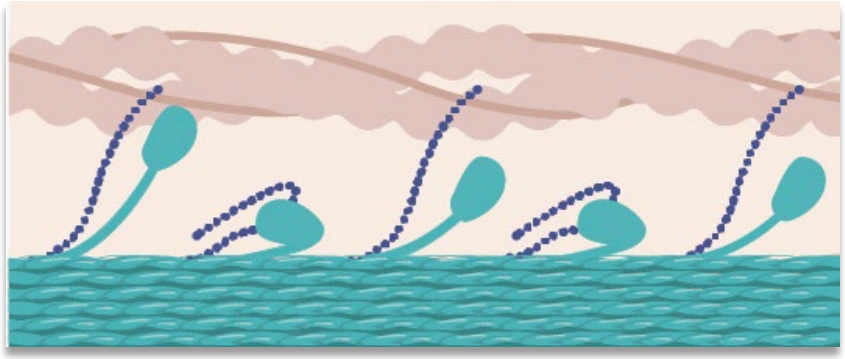


- MyBP-C is an essential structural protein regulating cardiac contractility via interactions with sarcomeric proteins
- Heterozygous mutations in the *MYBPC3* gene lead to lower levels of MyBP-C protein.
- Lower MyBP-C results in increased contractility, thickening of the left ventricle and impaired diastole

TN-201 Mechanism of Action



- TN-201 targets the underlying genetic cause of disease by delivering a full length copy of the *MYBPC3* gene to cardiomyocytes
- TN-201 utilizes an AAV9 capsid and a proprietary promoter with cardiac tropism



- Addition of a *MYBPC3* gene increases MyBP-C protein levels and is expected to halt disease progression, reverse disease pathophysiology, and improve symptoms and patient quality of life after a single dose

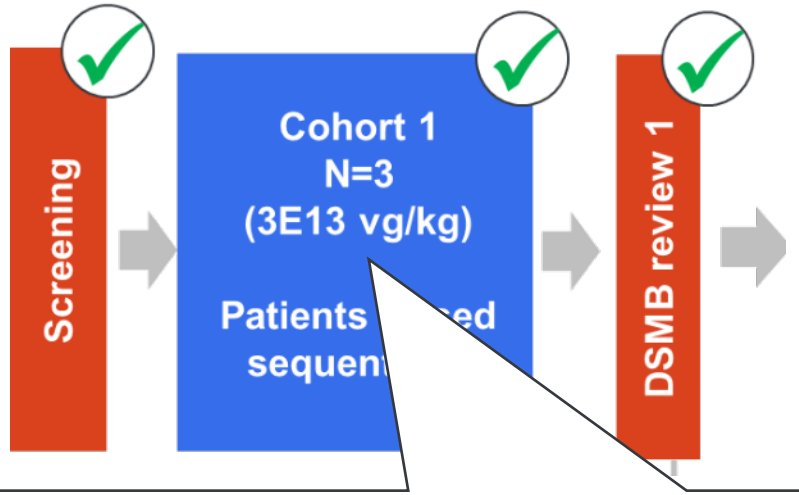
MyBP-C = Myosin-binding protein C

MyBP-C protein missing in sarcomere

MyBP-C protein present in sarcomere

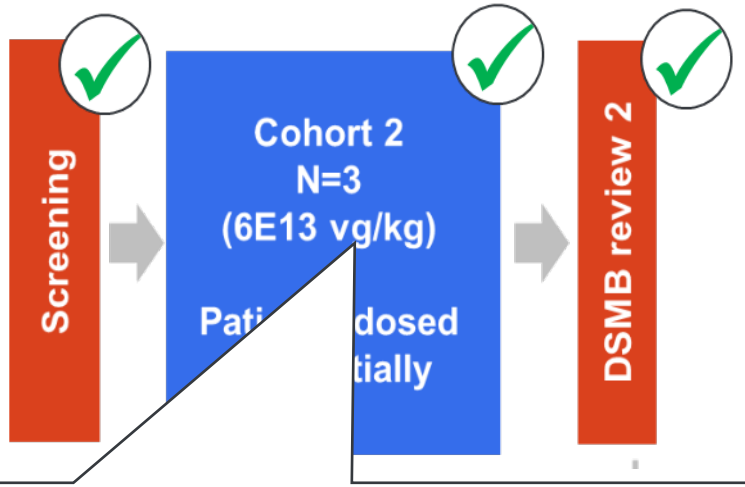
Q4’2025 TN-201 MyPEAK-1 readout:

What to expect



Cohort 1
Longer-term (>=1 year) follow-up for 3 patients at the 3E13 vg/kg dose

Aiming for continuation of encouraging safety, biopsy and clinical results observed at ACC.25



Cohort 2
Initial readout focused on safety and biopsy results for the 3 patients at the 6E13 vg/kg dose

Looking for tolerability at the higher dose and increases in the presence of TN-201 DNA, TN-201 RNA and MyBP-C protein levels vs. Cohort 1

PKP2-associated ARVC is estimated to affect >70,000 people in the U.S.[1]

A severe and progressive genetic heart disease lacking therapeutic treatment options

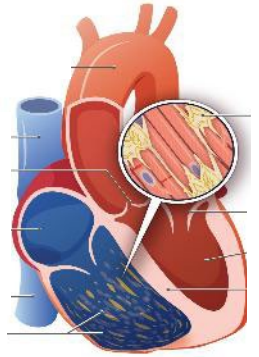
>15% of heart-related deaths in patients < 35 are due to ARVC[2]

23% of ARVC patients present with sudden cardiac death[2]

40% of ARVC patients carry pathogenic *PKP2* mutations[3]

- Early symptoms include palpitations, lightheadedness, fainting [1]
- Significant impact on quality of life due to arrhythmias, ICD shocks and restrictions on physical exertion [4]

ARVC HEART



Scar tissue leads to electrical misfiring between cells

Enlarged right ventricle with fat and scar tissue

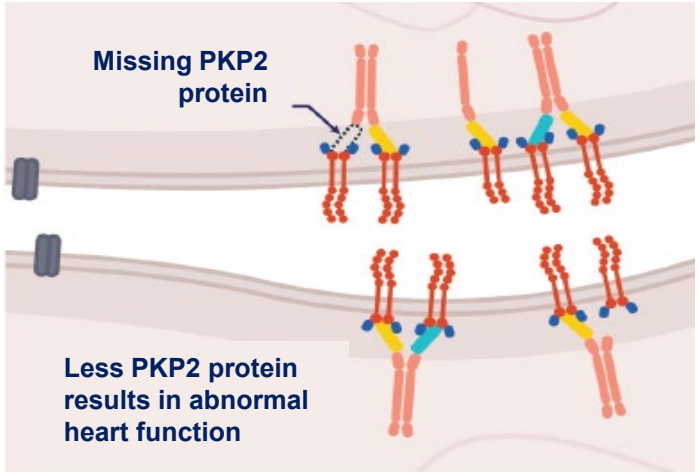
1. Peters, et a, Int J Cardiol 2004; McKenna, Nat Rev Card, 2021
2. Dalal, et al, Circ, 2005
3. Hemida, et al, Eur J Heart Failure, 2018
4. SADS Foundation

SCD= sudden cardiac death
RV = right ventricle
LV = left ventricle
ICD = implantable cardiodefibrillator

TN-401 gene therapy for *PKP2*-associated ARVC

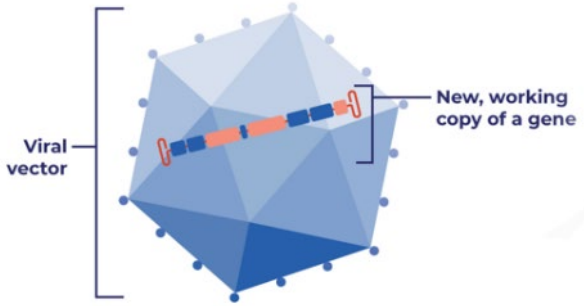
PKP2+ Pathophysiology

Desmosome and Gap Junctions in *PKP2*-associated HCM Heart

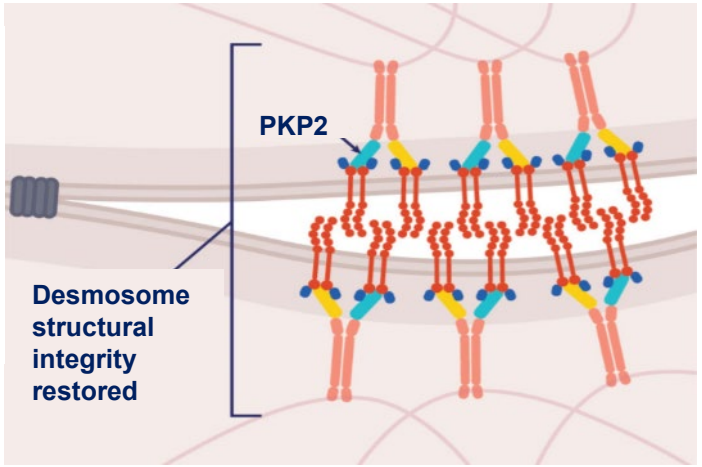


- Mutations of the *PKP2* gene lead to lower levels of Plakophilin-2 (PKP2) protein[1]
- PKP2 is an essential structural protein in the desmosomes, connecting cardiomyocytes supporting electrical and mechanical signaling and overall tissue strength

TN-401 Mechanism of Action



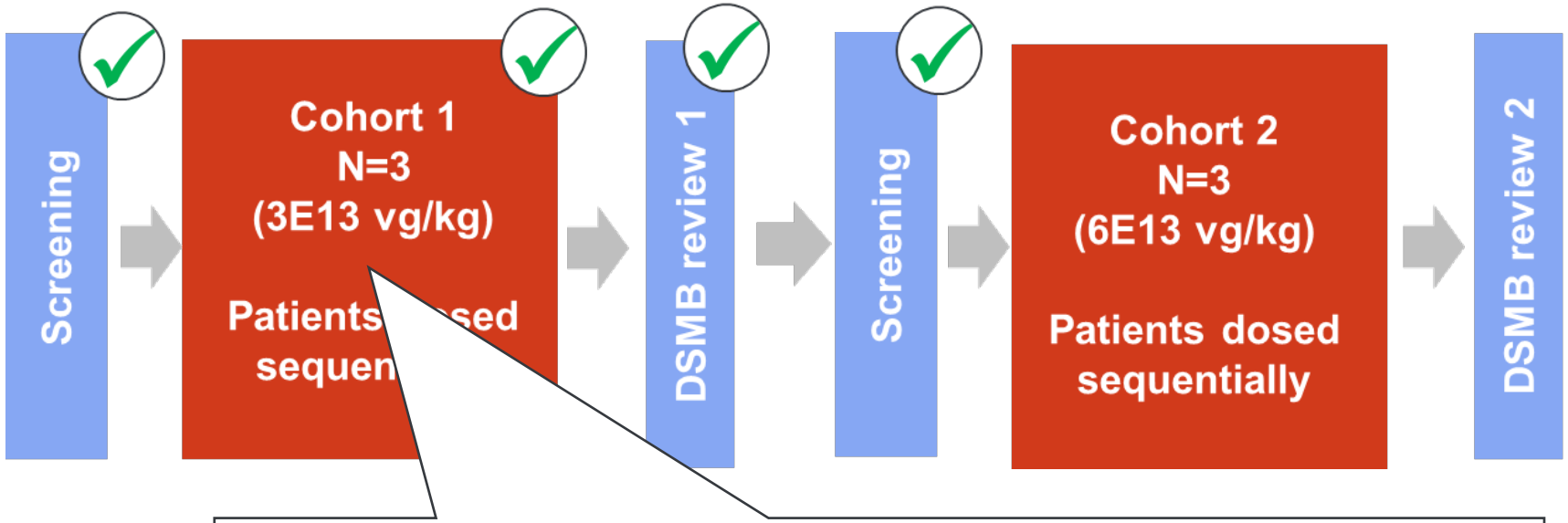
Treated with TN-401



- TN-401 targets the underlying genetic cause of disease by delivering a full-length *PKP2* gene to cardiomyocytes via an AAV9 capsid
- An increase in PKP2 protein levels is expected to restore desmosomal structures with the potential to halt disease progression, reverse symptoms and improve patient quality of life

1. McKenna, et al, Nature Rev Cardio 2021

Q4’2025 TN-401 Data Readout:
What to Expect



Cohort 1
Data release will include initial Cohort 1 (3E13 vg/kg) data focused on safety and biopsy results

Readout will focus on tolerability and the presence of TN-401 DNA, TN-401 RNA and PKP2 protein level changes from baseline

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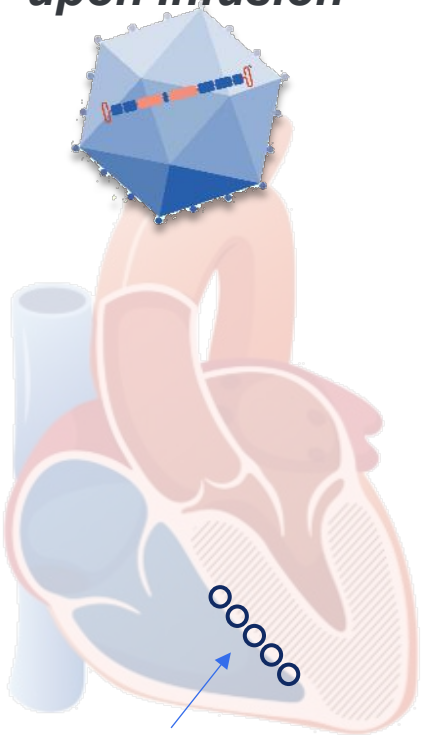
Measuring Protein Expression in Cardiac Gene Therapy

Dr. Kathy Ivey in conversation with Dr. Michael Previs

Biopsy measurements – What are we looking for?

Gene Therapy Mechanism of Action

Gene Therapy upon Infusion



Biopsy samples

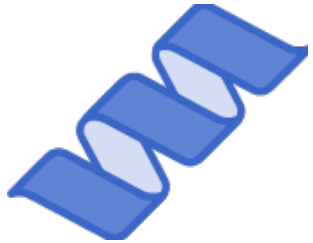
1 **DELIVERY: Transduction (DNA)**

2 **EXPRESSION: Transcription (RNA)**

3 **EXPRESSION: Translation (Protein)**

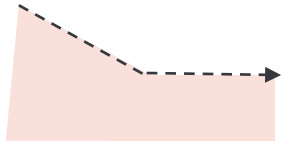
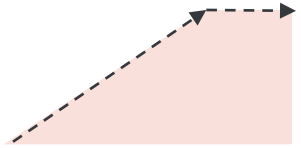
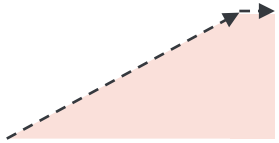
Gene therapy enters cardiomyocytes. The healthy gene delivered forms a stable episome in cell

The healthy gene is transcribed by cell's machinery to produce messenger RNA



mRNA is then converted to the missing protein

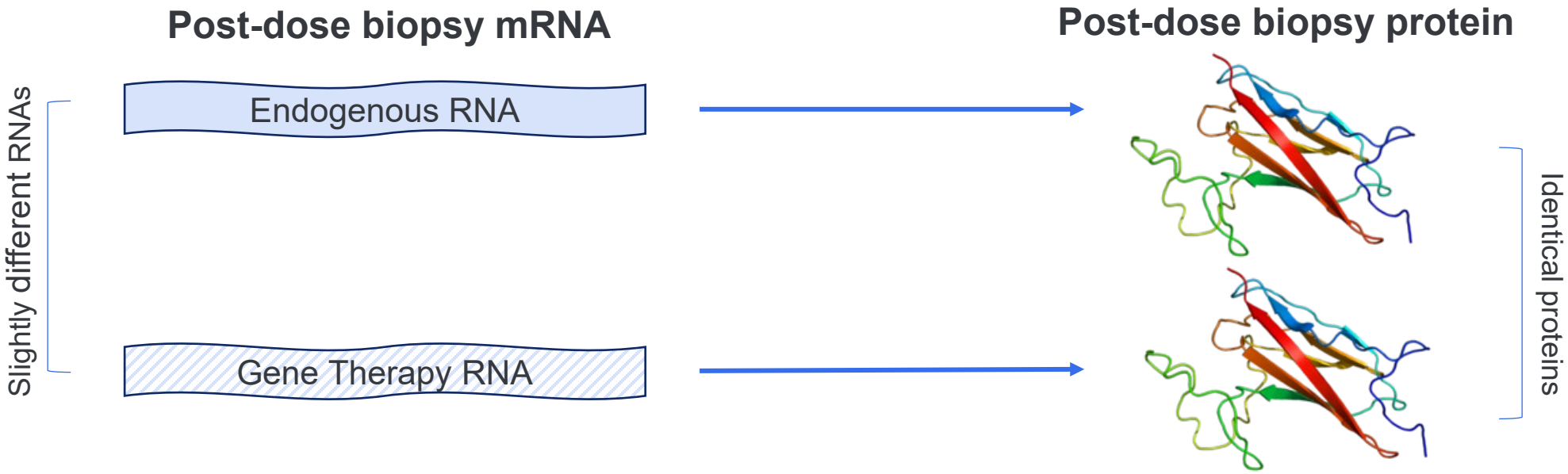
Cardiac biopsies are collected to quantify these leading indicators of TN-201 or TN-401 efficacy

Measurement assays	Anticipated result over time
TN-201 or TN-401 DNA is measured by ddPCR Quantifies the number of TN-201 vector copies in heart tissue	 • Total VCN initially decreases as TN-201 or TN-401DNA is cleared from non-CM cells • TN-201 or TN-401 DNA **delivered to CMs remains stable over time**
TN-201 or TN-401 mRNA is measured by RT-qPCR Quantifies expression of TN-201 mRNA specifically (distinct from endogenous)	 • TN-201 or TN-401 **mRNA increases** as the corresponding DNA stabilizes and is transcribed in cardiomyocytes
MyBP-C or PKP2 protein is measured by LCMS Quantifies abundance of total MyBP-C (normalized to myosin).	 • Protein levels **increase from the patient's baseline** as TN-201 or TN-402 mRNA is translated into new MyBP-C or PKP2 protein

ddPCR = digital droplet polymerase chain reaction | RT-qPCR = reverse transcriptase, quantitative polymerase chain reaction
LCMS = liquid chromatography – mass spectrometry| VCN = vector copy number | CMs = cardiomyocytes

Why do methods matter?

Protein produced from gene therapy and protein produced by the patient's one working gene are indistinguishable



Therefore, we needed a solution that was highly sensitive, quantifiable, and repeatable

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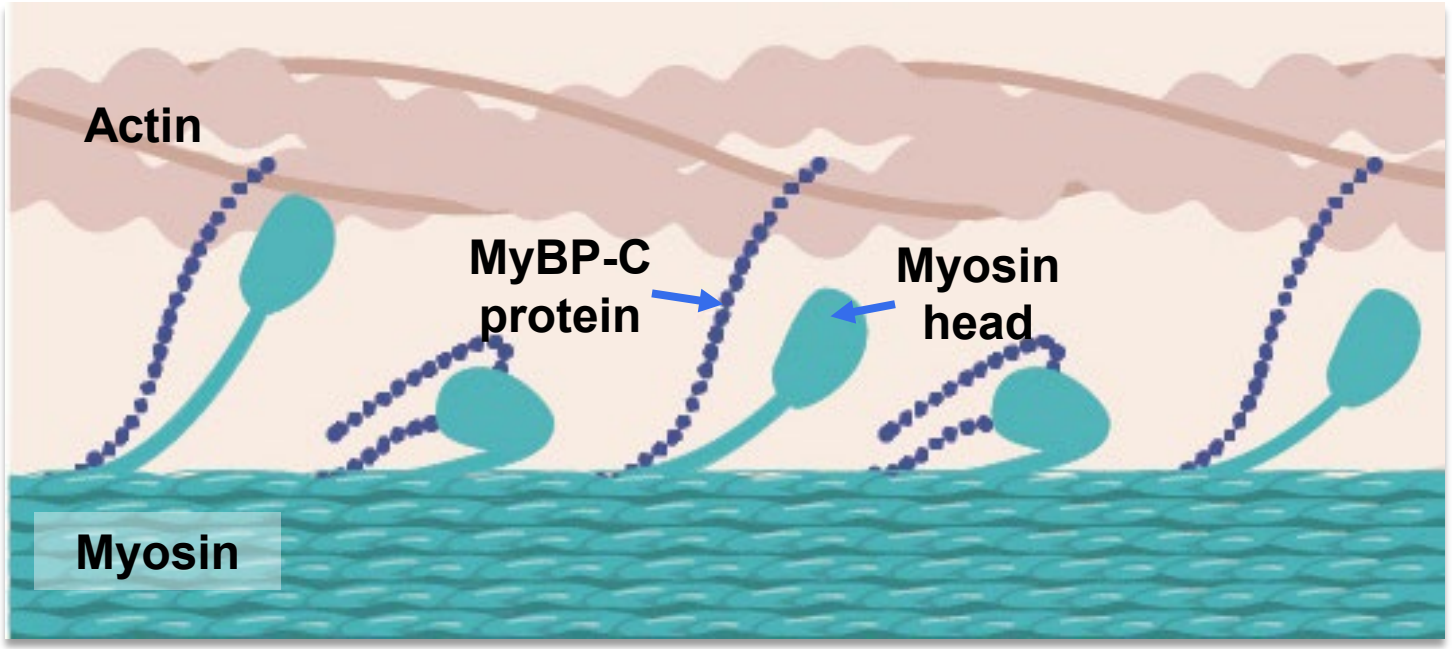
Dr. Kathy Ivey in conversation with Dr. Michael Previs

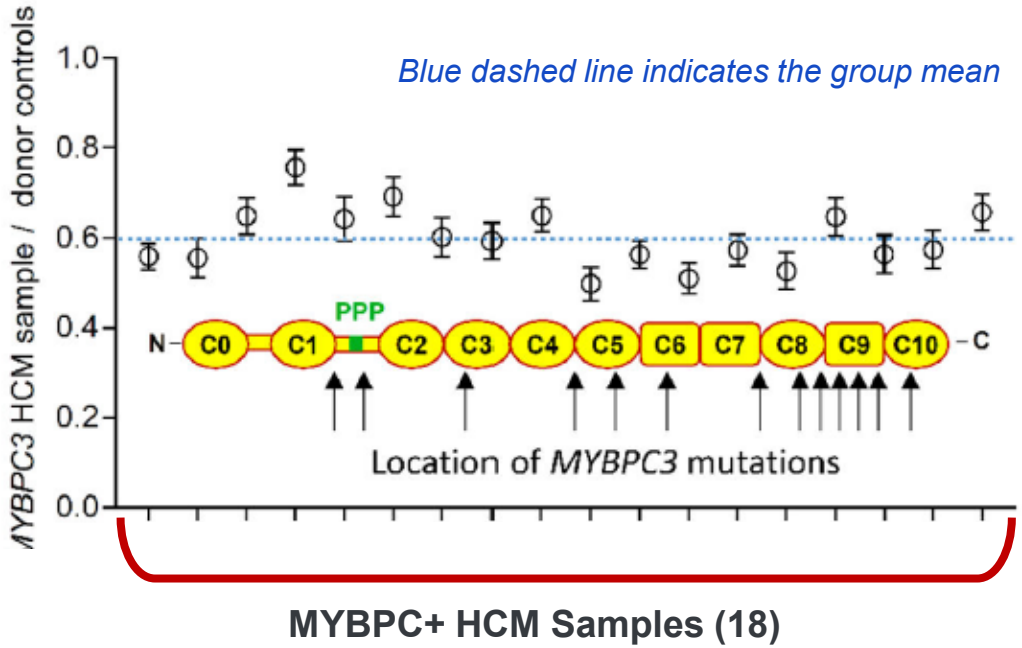
Role and function of MyBP-C protein in the sarcomere

MyBP-C modulates the force and speed of each contraction

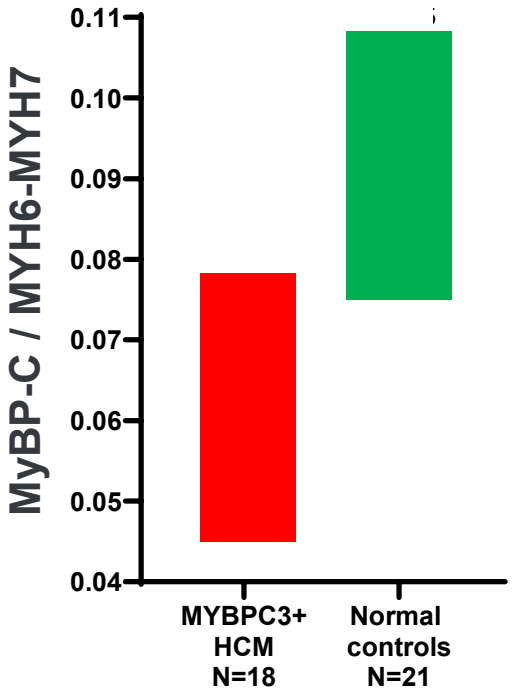


MYBPC3-associated HCM is a disease of haploinsufficiency

Relative abundance of MyBP-C in the individual HCM samples when compared to the donor control group [1]



Range of MyBP-C protein levels in MYBPC3-associated HCM samples and normal controls [1]



1. O'Leary, et al; *J Mol Cell Cardiol* 2019 (updated)

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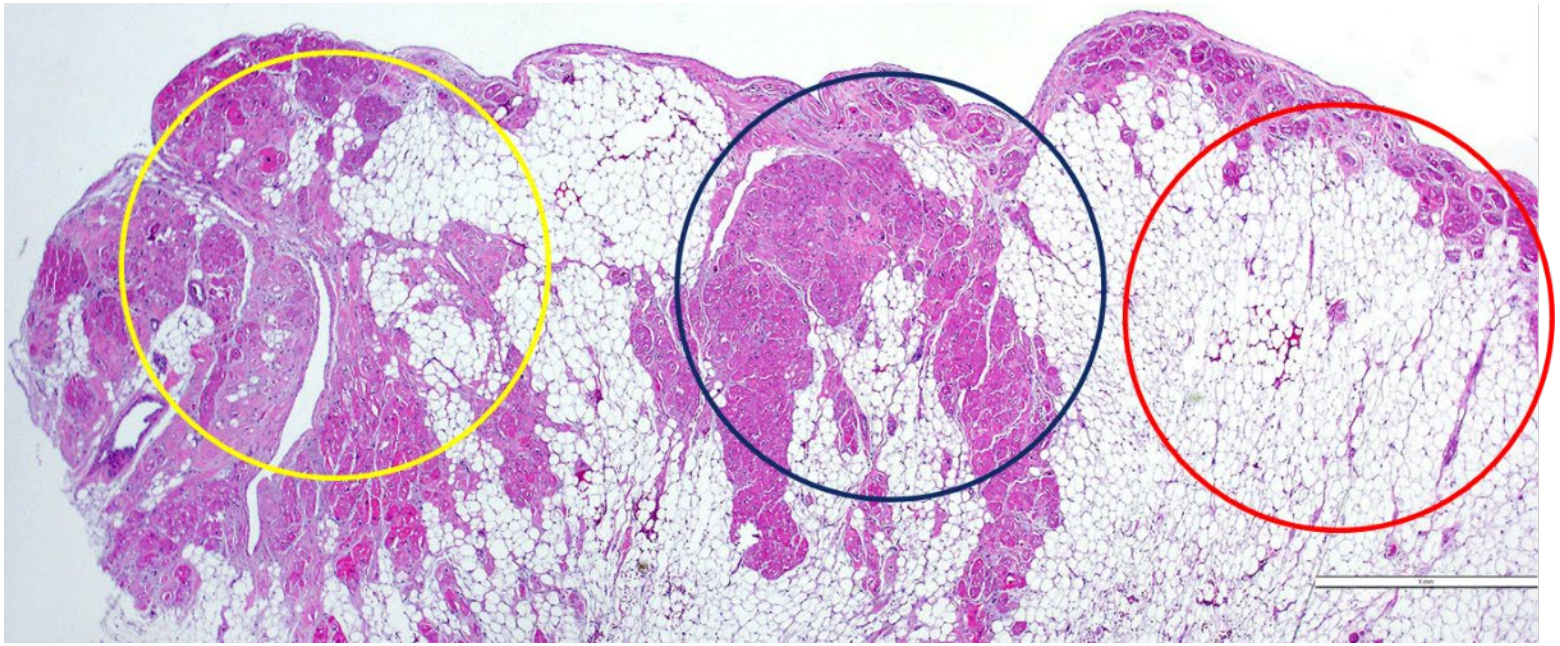
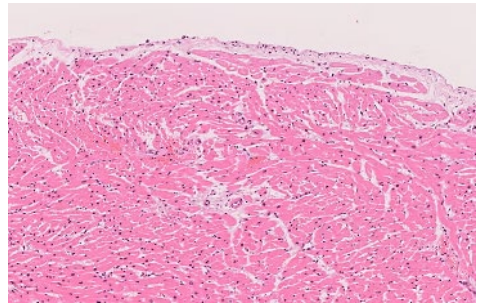
Variability in tissue sample quality happens

Heart tissue in cardiomyopathy patients is heterogenous
resulting in variability in biopsy quality and in the number of cardiomyocytes per sample.
Mass spectrometry overcomes this challenge.



ARVC donor heart tissue with fibrofatty replacement
Biopsy tissue pieces are approximated by circles (~1-2 mm^3)



Normal heart tissue

https://heartpathology.com/genetic-diseases/FigC-arvd-4x.jpg

https://medicine.nus.edu.sg/pathweb/normal-histology/heart/

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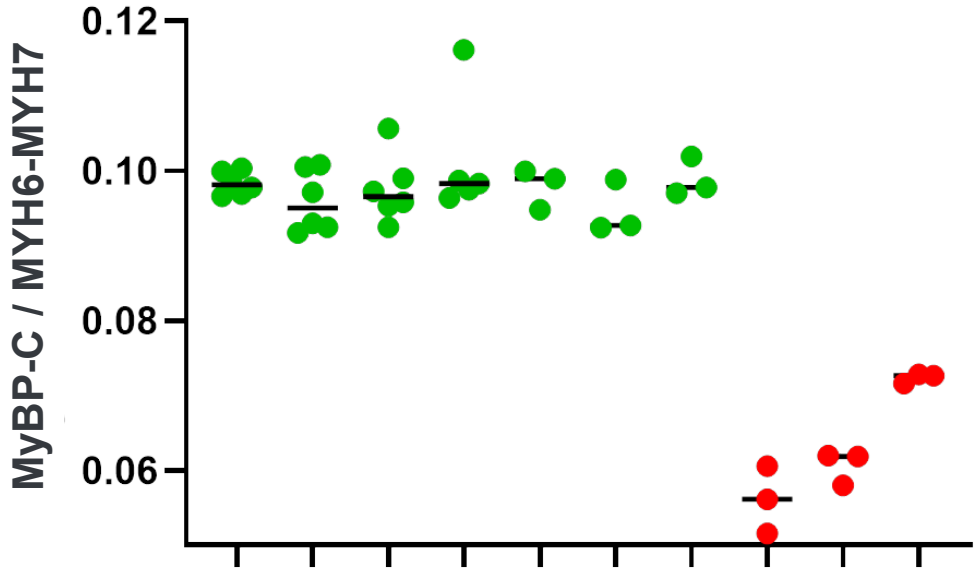
Normalizing MyBP-C to myosin mitigates variability in measurements of MyBP-C expression

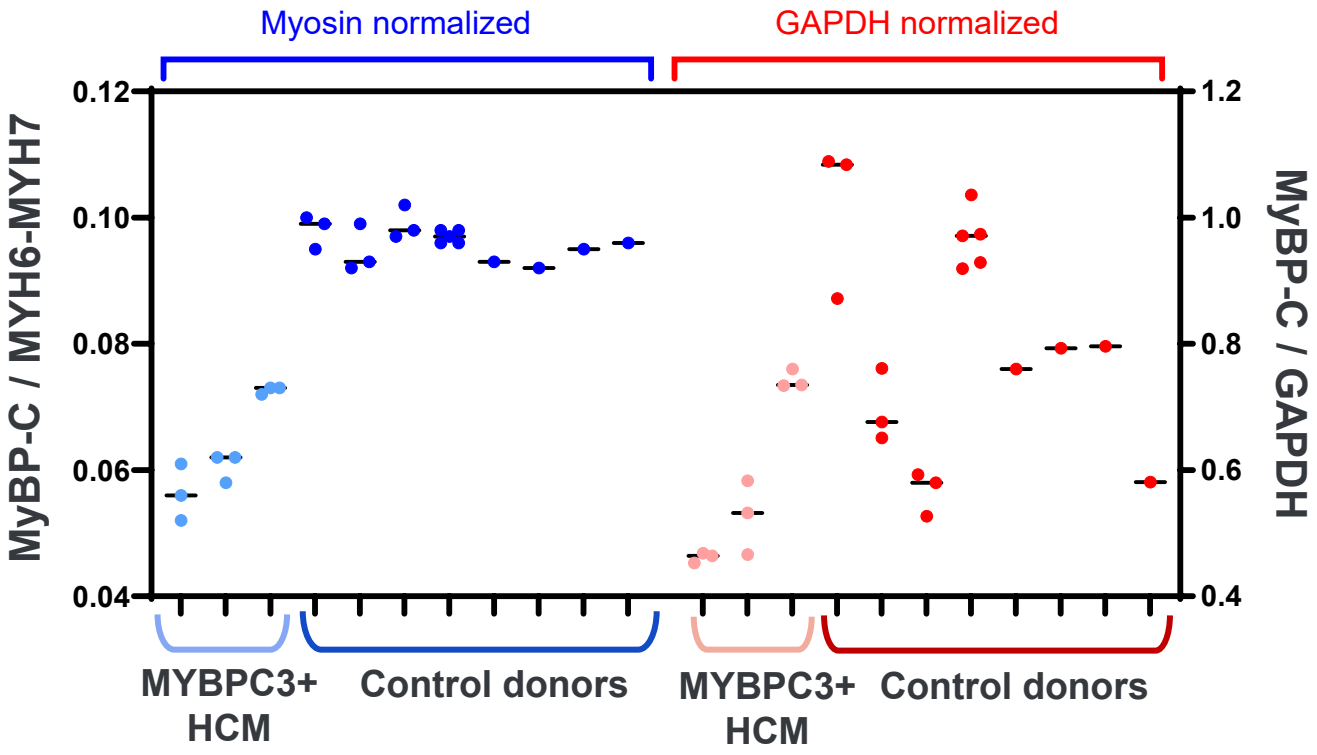
MyBP-C levels are tightly regulated within cardiomyocytes present in biological replicates from donor control heart and MYBPC3-associated HCM samples[(1)]



1. O'Leary, et al; *J Mol Cell Cardiol* 2019 (updated)

Normalizing MyBP-C to other “housekeeping” proteins results in apparent variability in MyBP-C expression

When MyBP-C is normalized to GAPDH rather than myosin, MyBP-C expression seems highly variable.



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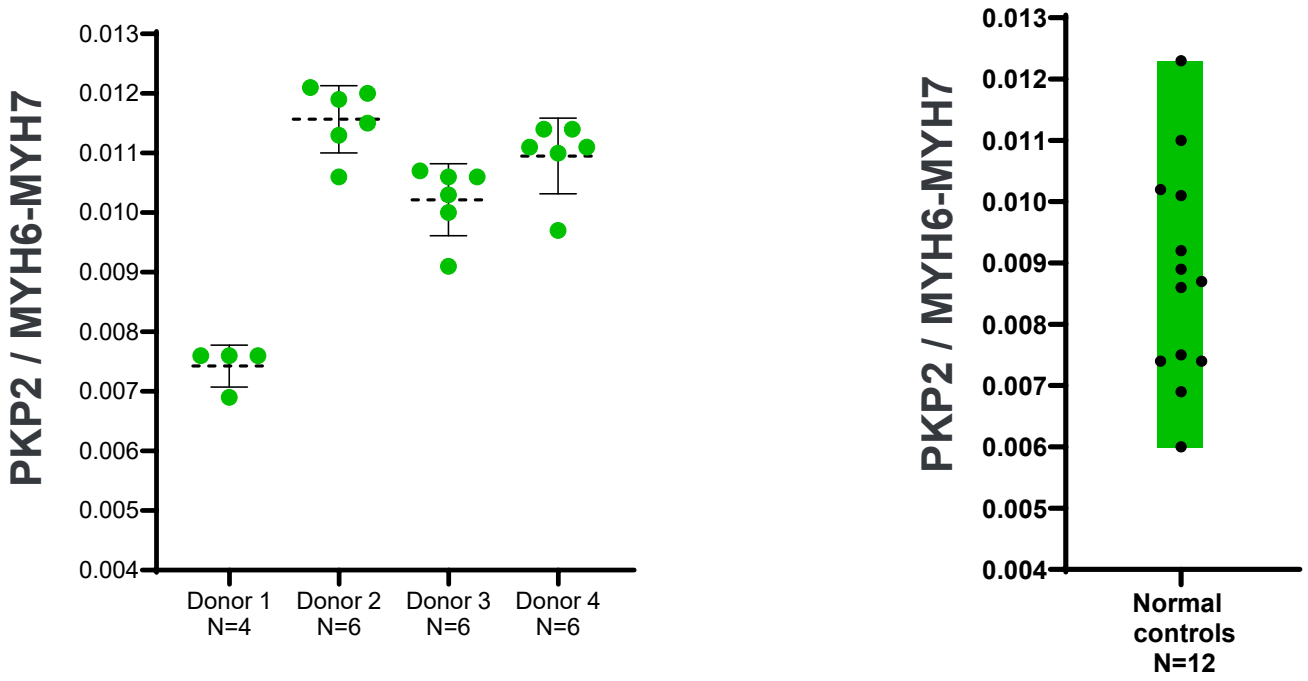
Variability for PKP2 within donors is lower than across donors

Variability in PKP2 levels measured from independent pieces of the same donor control hearts is low and reproducible but the levels vary from donor control to donor control



Q&A
Closing remarks