Scaling New Heights in the Fight Against Heart Disease

Corporate Presentation

January 2023

TENAYA™ THERAPEUTICS

Forward-looking Statement

This presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended 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 and plans, 2023 milestones, including, timing for, dosing of patients in the Phase 1b clinical trial evaluating TN-201, data from the Phase 1 trial of TN-301 and the submission of the TN-401 IND, the clinical, therapeutic and market potential of and expectations regarding our product candidates, platforms and manufacturing capabilities, clinical development plans for TN-201 and related availability of data from the Phase 1b trial, the plan to commence the MAD stage of the Phase 1 trial of TN-301; the sufficiency of Tenaya's cash resources to fund operations into the first half 2025, as well as statements regarding industry trends, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "vision," "mission," "anticipate," expect," "intend," "may," "objective," "ongoing," "plan," "potentially," 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 toa number of risks, uncertainties and assumptions described in our filings with the Securities and Exchange Commission, including, but not limited to the section titled "Risk Factors" in our Quarterly Report on Form 10-Q for the fiscal quarter ended September 30, 2022. Such risks include, among other things: the timing or likelihood of regulatory filings and approvals; the impact of any future communications from the FDA regarding Tenaya's TN-201 IND; the timing of the initiation, progress, completion and potential results of our preclinical studies and clinical trials; our ability to advance product candidates into, and successfully complete, preclinical studies and clinical trials; the availability of data at the referenced times; 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; the potential for clinical trials of our product candidates to differ from preclinical, preliminary, interim or expected results; the commercializing of our product candidates, if approved; our ability to successfully manufacture and supply our product candidates for preclinical studies, clinical trials and for commercial use, if approved; future strategic arrangements and/or collaborations and the potential benefits of such arrangements; 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.

Our vision is to **transform and extend** the lives of people and families fighting heart disease.

Our mission is to **discover, develop and deliver curative therapies** that address the underlying causes of heart disease.

Our therapies and capabilities are designed to provide new hope and new options for **millions of individuals and families** affected by heart disease, from **rare** genetic cardiomyopathies to the most **prevalent** forms of heart failure.

Tenaya Focus on Heart Disease

Why the Time is Now for Next Generation Precision Medicine Therapies

Heart Disease is Still the Leading Cause of Death in the World

- **>30MM** U.S. adults diagnosed with heart disease
- **~40K** U.S. children born each year with congenital heart disease
- Mortality rates are rising despite advances in standard of care

Increasing Genetic Insight and Diagnosis

- Guidelines recommend genetic testing for cardiomyopathies
- Accessible genetic testing for >150 genes for >35 conditions
  Genetic cardiomyopathies can run through families

Increasing Clinical Validation for Precision Medicine Approaches

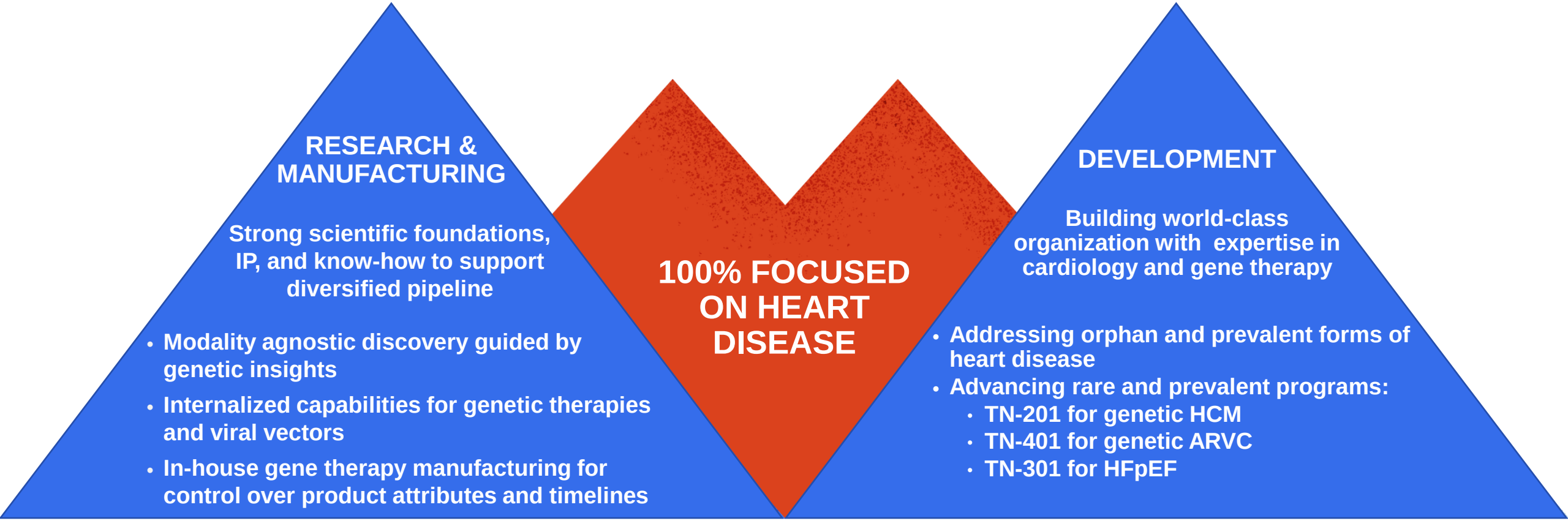
- Approvals for disease-specific therapies for cardiomyopathies
- Early but promising clinical data for cardiac gene therapies
- Potential for smaller studies with larger effect sizes

Stronger Drug Development Toolkit

- Better *in vitro* and *in vivo* disease models
- New modalities (gene therapy, gene editing, etc.)
- Methods to improve delivery and expression and specificity of genes in the heart (e.g., capsids, promoters, catheters)

Tenaya Overview

Combining Cardiovascular and Genetic Medicines Expertise to Target the Underlying Causes of Heart Disease



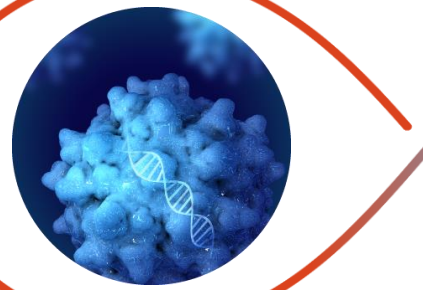
Breaking News: TN-201 IND cleared by FDA
Phase 1b expected to begin dosing patients 3Q 2023

HFpEF = Heart failure with preserved ejection fraction
HCM = Hypertrophic cardiomyopathy
ARVC = Arrhythmogenic right ventricular cardiomyopathy
IND = Investigational New Drug

Multi-Modality Drug Discovery Engine

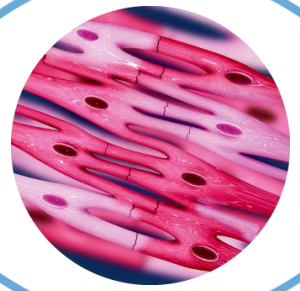
Three Product Platforms Powered by Proprietary Capabilities

GENE THERAPY



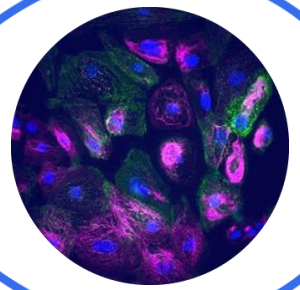
Restore cell function by using viral vectors to deliver healthy copies of genes or other therapeutic payloads

CELLULAR REGENERATION



Regenerate new heart cells *in vivo* by using viral vectors to deliver proprietary combinations of genes

PRECISION MEDICINE

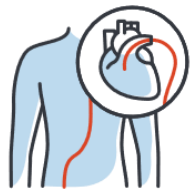


Expand pipeline by using human iPSC-CM disease models and analysis of human genetics to identify new targets and therapies

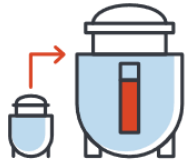
DISEASE MODELS

CAPSID ENGINEERING

PROMOTERS AND REGULATORY ELEMENTS



DRUG DELIVERY



MANUFACTURING

iPSC = induced pluripotent stem cells
CM = cardiomyocyte

Tenaya Pipeline

Deep, Diverse, Wholly-Owned Pipeline Addressing Rare and Prevalent Indications

Program	Modality	Discovery	Preclinical Development	Pre-IND	Phase 1	Phase 2/3	US Prevalence	Commercial rights	Designations
Advanced Pipeline									
TN-301	Small Molecule	**Heart failure with preserved ejection fraction**					> 3MM	TENAYA THERAPEUTICS	
TN-201	AAV	***MYBPC3*+ Genetic Hypertrophic Cardiomyopathy**					> 115K	TENAYA THERAPEUTICS	Orphan drug (U.S. and EU)
TN-401	AAV	***PKP2*+ Genetic Arrhythmic right ventricular cardiomyopathy**					> 70K	TENAYA THERAPEUTICS	Orphan drug (U.S.)
Earlier Pipeline									
DWORF	AAV	**Dilated cardiomyopathy**					> 1MM	TENAYA THERAPEUTICS	
Reprogramming	AAV	**MI-related hear failure**					> 4MM	TENAYA THERAPEUTICS	
Undisclosed Targets	AAV						Rare and Prevalent	TENAYA THERAPEUTICS	
Platform Enhancements	Genetic Therapies							TENAYA THERAPEUTICS	

IND = Investigational New Drug
AAV = Adeno-associated virus
MYBPC3 = Myosin Binding Protein C3

DWORF = dwarf open reading frame micropeptide
PKP2 = Plakophilin-2
MI = Myocardial Infarction

TN-201

Gene Therapy Program for *MYBPC3*-Associated Hypertrophic Cardiomyopathy (HCM)

TN-201: Gene Therapy Program for *MYBPC3*+HCM

Addressing the Leading Genetic Cause of Hypertrophic Cardiomyopathy

Disease Overview

Pathophysiology

- Mutation in *MYBPC3* disrupts contractile apparatus (sarcomere)
- Cardiomyocyte hypertrophy, disarray and fibrosis
- Stiff heart muscle contributes to poor heart filling (diastolic dysfunction)
- Abnormal heart rhythms

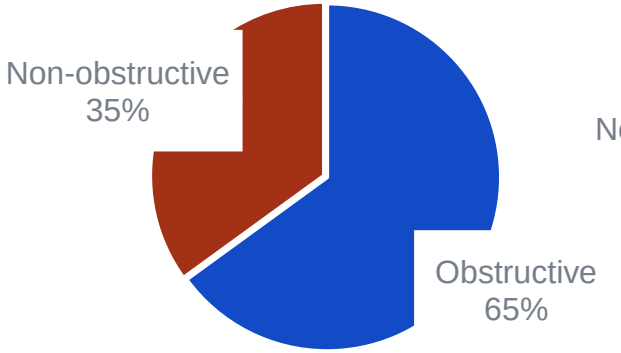
Disease Symptoms and Severity

- Heterogeneous presentation
- Heart failure and sudden cardiac death can occur in adults and children
- Premature infant death in the most severe cases
- Disease severity higher with pathogenic sarcomeric gene mutations such as MYBPC3 vs general HCM

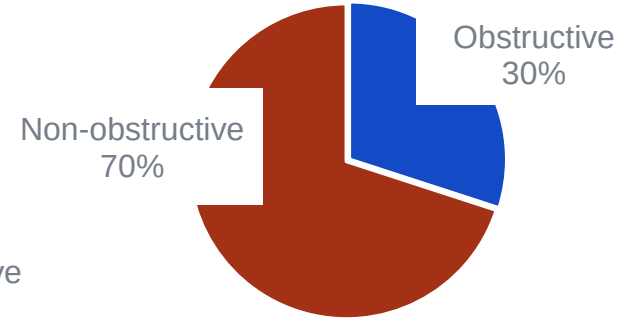
Epidemiology

- *MYBPC3* mutations accounts for ~19% of all HCM
- Estimated >115K patients in U.S. alone
- Majority of patients have non-obstructive form of disease

HCM*



MYBPC3+HCM*



* Percentages are approximate

Standard of Care

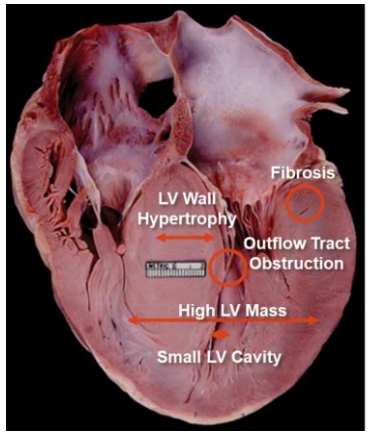
- No treatments address the underlying genetic cause
- Myosin inhibitor (mavacamten) approved for use in obstructive HCM patients

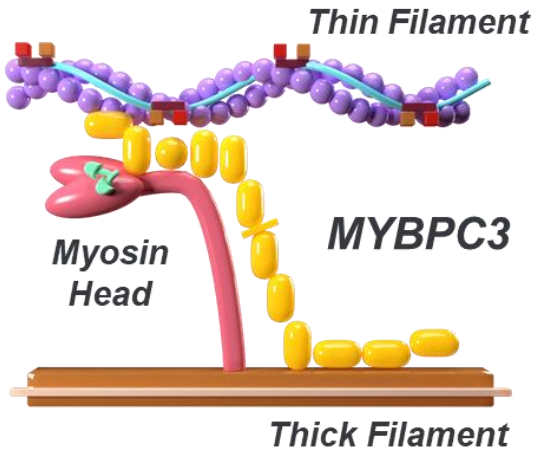
MYBPC3 = Myosin Binding Protein C3
HCM = Hypertrophic Cardiomyopathy

TN-201: Gene Therapy Program for *MYBPC3*+HCM

Targeting the Underlying Cause of Disease for all forms of *MYBPC*+HCM

Tenaya Product Candidate





TN-201 Program Overview	
Target Cell	Cardiomyocyte
Modality	AAV9
Gene	*MYBPC3*
Mechanism	"Lock and key", replace a healthy copy of *MYBPC3* in patients with loss-of-function mutations
Stage	IND Cleared – Phase 1b dosing to begin Q3'2023

Consequences of *MYBPC3* Mutations

- Reduced levels or functionality of MYBPC3 protein
- Decreased inhibition of myosin in the sarcomere
- More myosin heads engaged on actin filament
- Hypercontractility and impaired relaxation

TN-201 Target Profile

- Target underlying cause of disease (*MYBPC3* mutations)
- Disease-modifying therapy with durable response after a single intravenous infusion
- MOA relevant for both obstructive and non-obstructive HCM
- MOA relevant for both severe, rapidly progressing homozygous infants and heterozygous children and adults

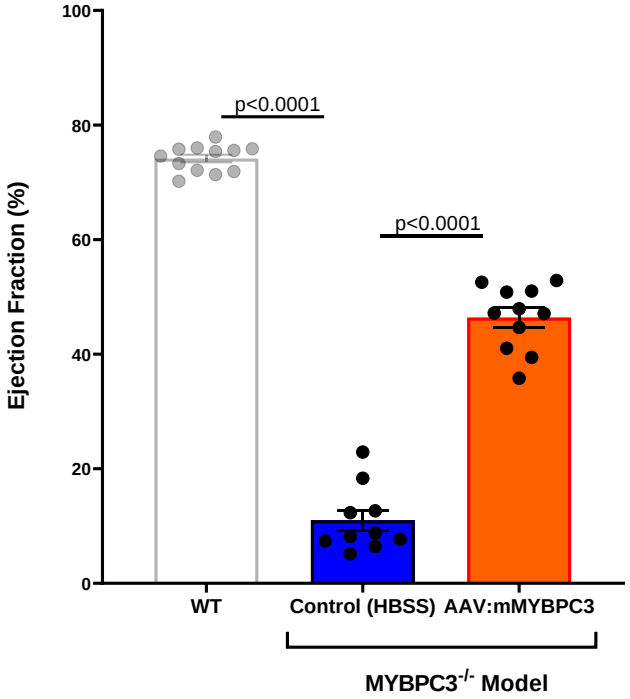
MYBPC3 = Myosin Binding Protein C3
HCM = Hypertrophic Cardiomyopathy
AAV9 = Adeno-Associated Virus Serotype 9
IND = Investigational New Drug

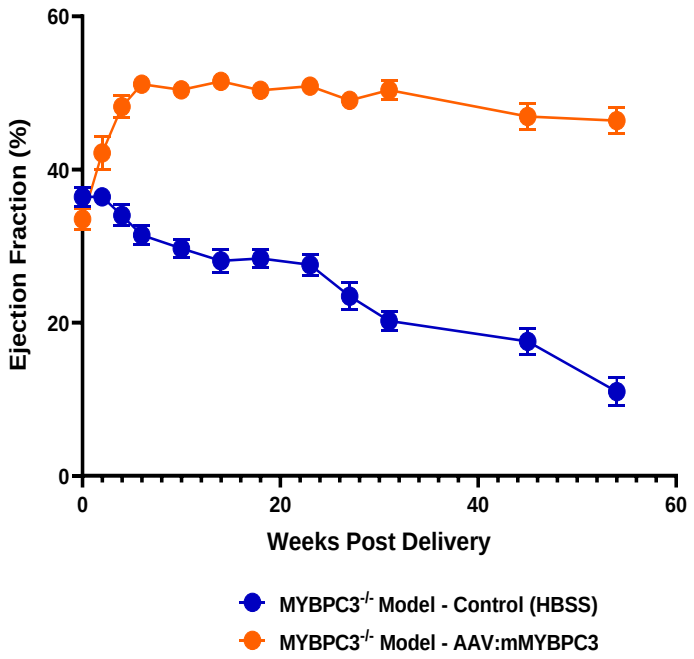
TN-201: Gene Therapy Program for *MYBPC3*+HCM

Durable Disease Reversal and Survival Benefit Observed with a Single Dose in a Severe Homozygous KO Mouse Model

Significant and Durable Improvement in Heart Function (13 Months Post-Treatment)

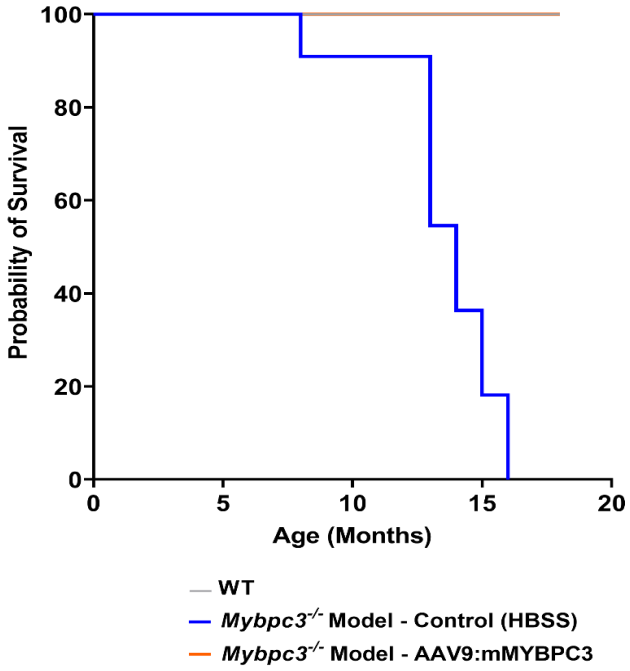
- Animals treated at 2 weeks of age, impact on heart function seen within 6 weeks
- Initial EF improvement of > 20% eventually grows to > 30%





Survival Benefit (18 Months Post-Treatment)

- 100% survival in AAV:*MYBPC3* arm
- 100% mortality in control arm



KO = Knock out
EF = Ejection Fraction
WT = Wild type

MYBPC3 = Myosin Binding Protein C3
AAV = Adeno-Associated Virus
HBSS = saline solution

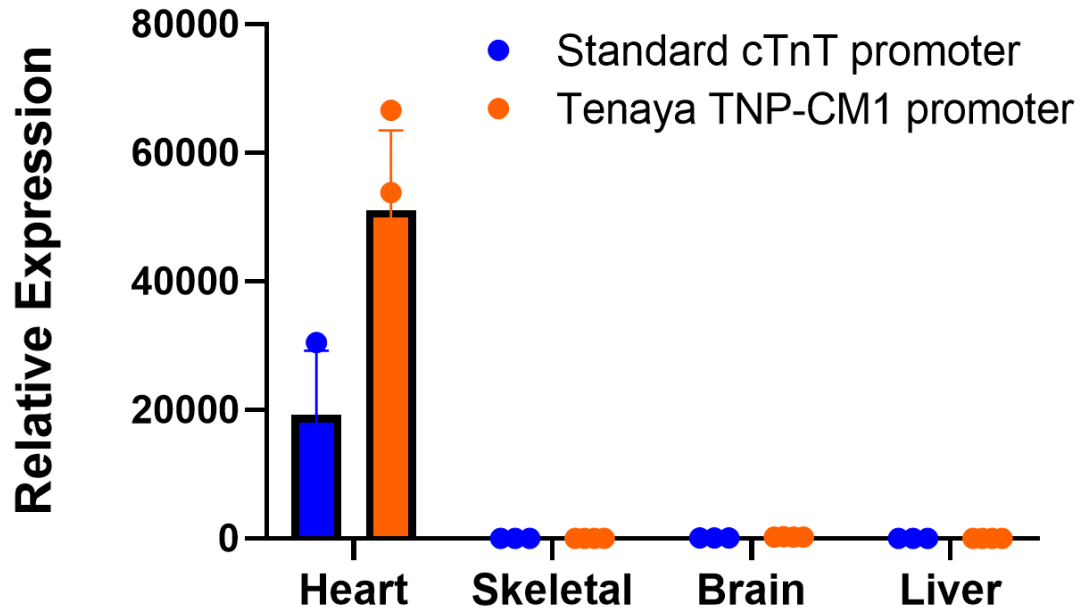
Lombardi, et al; ESGCT 2021

TN-201: Gene Therapy Program for *MYBPC3*+HCM

Improved Results from Proprietary Cardiac-Specific Promoter and Cassette Engineering Efforts

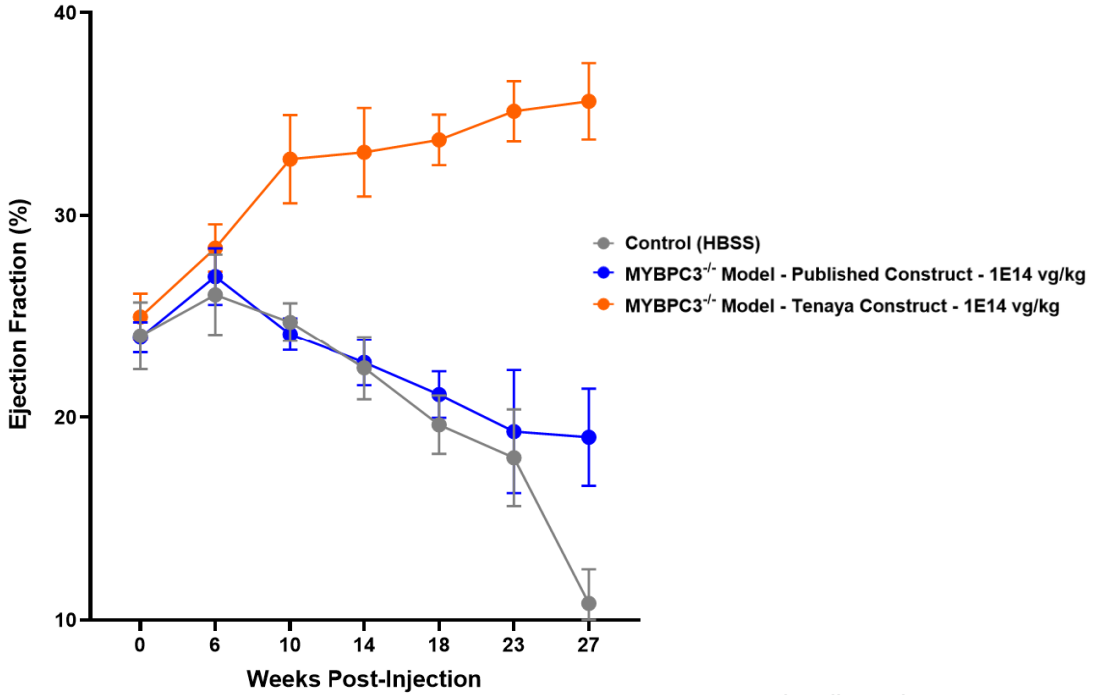
In Vivo Comparison (WT mice)

- High selectivity for heart vs. other organs
- 2x-3x higher MYBPC3 mRNA expression with proprietary Tenaya promoter vs standard cTnT promoter
- Performance also confirmed in hiPSC-CMs and tested in NHPs



In Vivo Comparison (Mature MYBPC3$^{-/-}$ Mice)

- Animals treated at 3 months of age with even more advanced disease
- Significantly better heart function in head-to-head comparison of Tenaya construct vs. historical construct



Lombardi, et al; ASGCT 2021

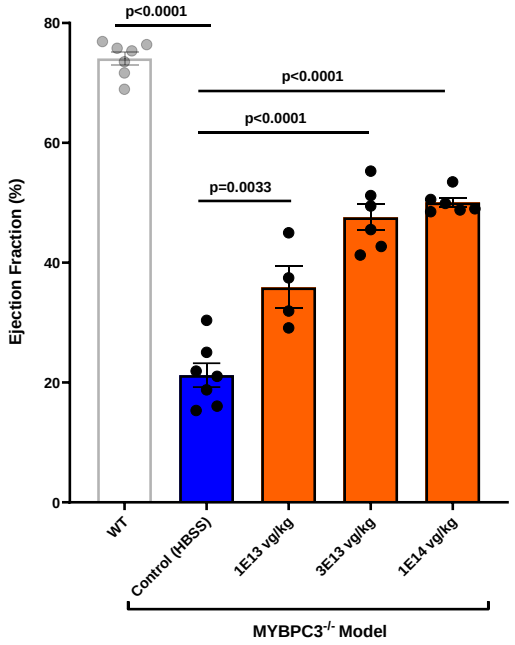
MYBPC3 = Myosin Binding Protein C3
WT = wild type
hiPSC-CM = human induced pluripotent stem cell cardiomyocyte

cTnT = cardiac troponin
NHP = non-human primate

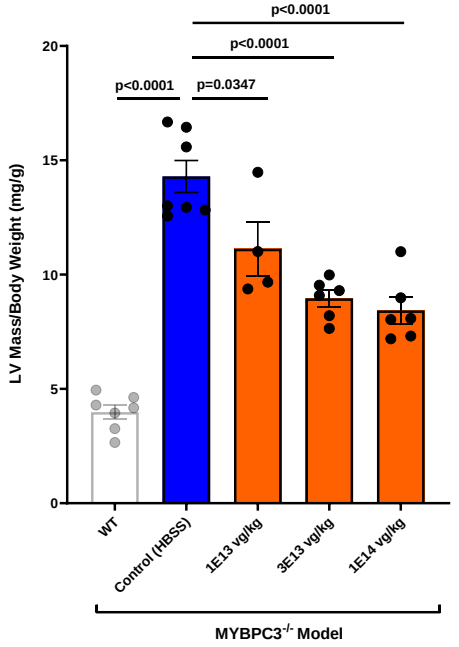
TN-201: Gene Therapy Program for *MYBPC3*+HCM

Dose-Dependent Disease Reversal at Clinically Relevant Doses in a Severe Homozygous KO Mouse Model

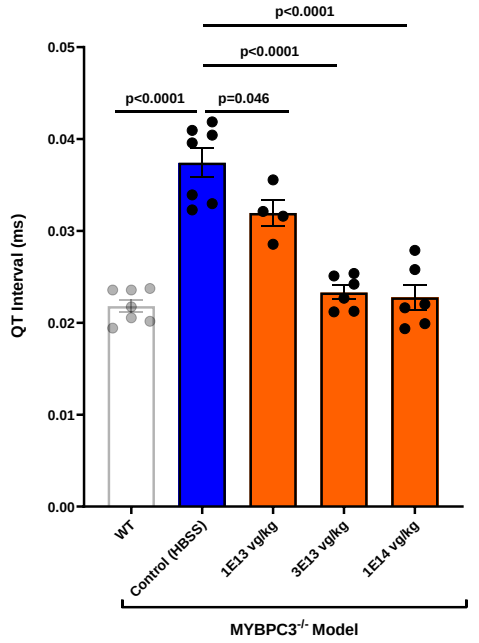
Improvement in Measures of Heart Contraction (8 Months Post-treatment)



Improvement in Measures of Heart Mass (8 Months Post-treatment)



Improvement in Measures of Electrophysiology (8 Months Post-treatment)



TN-201 shows near maximal efficacy at 3E13 vg/kg in preclinical model
Initial dose of 3E13 vg/kg selected in Phase 1b clinical study

MYBPC3 = Myosin Binding Protein C3
IND = Investigational New Drug
KO = Knock out

Lombardi, et al; ASGCT 2021

TN-201: Gene Therapy Program for *MYBPC3*+HCM
Overview of Phase 1b Clinical Study

Study Objectives

Assess the safety, tolerability and clinical efficacy of a one-time intravenous dose of TN-201 gene therapy

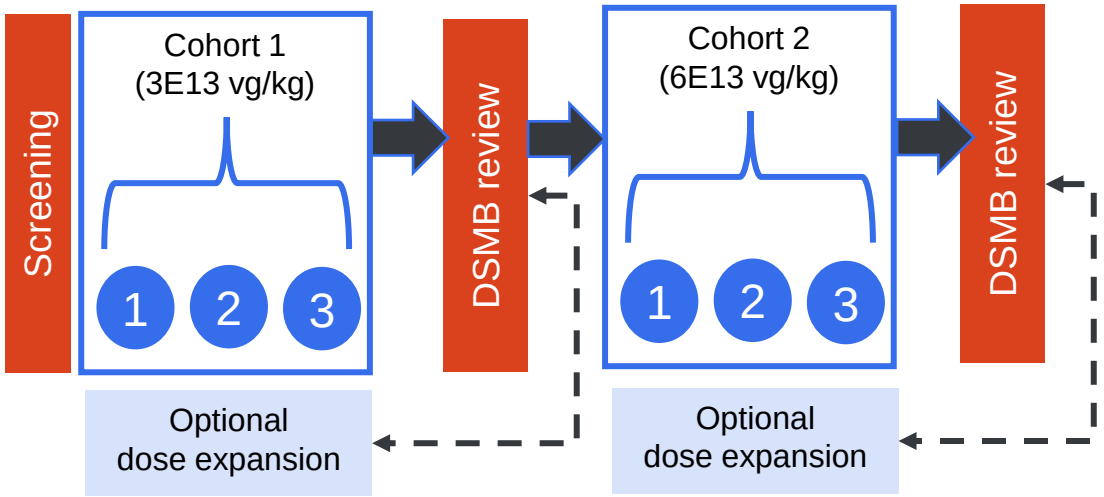
Eligibility

- MYBPC3 mutation carriers
- Symptomatic (NYHA Class II or III)
- Adults (age 18-65)
- Non-obstructive HCM
- ICD present
- Low AAV9 neutralizing antibodies

Phase 1b Design

Open-label, multi-center dose-escalation and dose-expansion study

- Preventive immunosuppressive regimen + close safety monitoring
- Regular assessments for safety, PK and PD
- 5-year safety and efficacy follow-up



Endpoints

- **Safety and tolerability**
- **Pharmacokinetics (PK)**
  - Transgene and mRNA via cardiac biopsies (8wk & 52wk)
- **Pharmacodynamics (PD)**
  - Imaging biomarkers by echo (e.g., LV Mass)
  - Plasma biomarkers (e.g., NT-proBNP)
- **Exploratory efficacy endpoints**
  - NYHA class
  - Exercise capacity (e.g., 6MWT, Peak VO2)
  - Patient-reported outcomes (e.g., KCCQ)

Tenaya anticipates dosing the first patient in Q3 2023; Initial clinical data 2024

MYBPC3 = Myosin Binding Protein C3
HCM = Hypertrophic Cardiomyopathy
NYHA: New York Heart Association

AAV9 = Adeno-associated virus serotype 9
ICD = Implantable cardioverter defibrillator
DSMB: Data Safety Monitoring Board

LV = left ventricular
NT-proBNP = measure of cardiac wall stress

6MWT = 6-minute walk test
KCCQ = Kansas City Cardiomyopathy Questionnaire

TN-201: Gene Therapy Program for *MYBPC3*+HCM
MyClimb Natural History Study

Global natural history study to improve understanding of disease progression and unmet need in *MYBPC3*+HCM with an initial focus on pediatric patients

MyClimb Natural History Study

- **Evaluate natural history of pediatric patients with cardiomyopathy due to mutations in the *MYBPC3* gene**
  - Ages 0-18 years
  - Includes infants with homozygous and compound heterozygous mutations
  - Retrospective and prospective data collection
- **Intended to complement existing disease registries focused primarily on adult patient HCM populations**
- **May support and expedite the development of TN-201 in the pediatric patient population**

Tenaya has activated more than 15 sites in the US and Europe and enrolled more than 80 subjects.

MYBPC3 = Myosin Binding Protein C3
HCM = Hypertrophic Cardiomyopathy

TENAYA™ THERAPEUTICS

TN-301

Small Molecule HDAC6 Inhibitor for Heart Failure with Preserved Ejection Fraction (HFpEF)

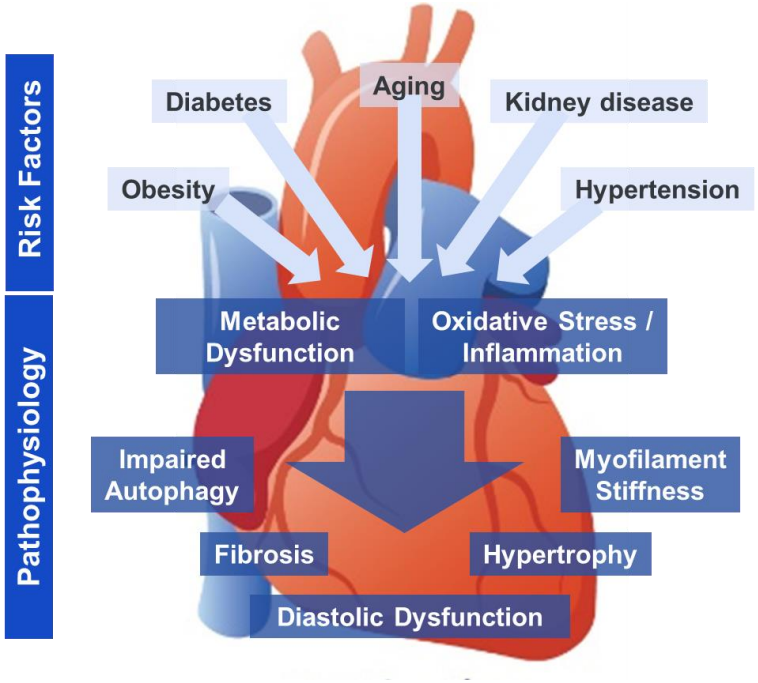
TN-301: Small Molecule HDAC6 Inhibitor for HFpEF

Potential to Address One of the Greatest Areas of Unmet Medical in Adult Heart Disease

Disease Overview

What is HFpEF?

- Complex syndrome characterized by poor relaxation and filling of the left ventricle (diastolic dysfunction)
- Defined as heart failure with LVEF ≥50%
- High overlap with diabetes and obesity



Disease Symptoms and Severity

- **~24%** of HFpEF population has NYHA Class III or IV disease
  - Fatigue, shortness of breath, tissue swelling, edema
  - Diminished quality of life and reduced capacity for physical activity
- **75%** mortality rate over 5-year period following first hospitalization

Epidemiology

- **~50%** of all heart failure
- **>3MM** patients in the U.S.; **13MM** worldwide
- Incidence is on the rise

Standard of Care

- Standard heart failure medications (beta blockers, calcium channel blockers, ACEs, ARBs) to alleviate symptoms
- SGLT2 inhibitors (e.g., empagliflozin) originally approved for diabetes have recently demonstrated positive impact on HFpEF

HFpEF = Heart Failure with Preserved Ejection Fraction
HDAC = histone deacetylase
NYHA = New York Heart Association
LVEF = Left Ventricular Ejection Fraction
ACEs, ARBs = Angiotensin-Converting Enzyme and Angiotensin Receptor Blockers
SGLT2 = Sodium-glucose cotransporter-2

TN-301: Small Molecule HDAC6 Inhibitor for HFpEF

HDAC6 Inhibition Represents a Promising Novel Target for HFpEF

Tenaya Product Candidate	
TN-301: HDAC6 Inhibitor Program	
Target	**Histone deacetylase 6 (HDAC6) enzyme**
Modality	**Highly selective small molecule HDAC6 inhibitor**
Mechanism	**HDAC6 inhibition has a multi-modal MOA that leads to alternations in cellular processes impacting metabolism, inflammation and cardiac function**

- HDAC6 is localized to cytoplasm
- Does *not* modify histones and does *not* directly regulate gene expression

- TN-301 1000x selective inhibition of HDAC6 vs other HDACs
- TN-301 selectivity for HDAC6 is higher vs other partially selective HDAC6 inhibitors in clinical development

Multi-Modal MOA

	Inflammation	Metabolic Dysfunction	Fibrosis	Hypertrophy	Impaired Autophagy	Diastolic Dysfunction
Cardiac fibroblasts (in vitro)			✓	✓		
hiPSC-cardiomyocytes (in vitro)		✓				
BAG3 DCM mouse model (in vivo)	✓	✓			✓	
Diet induced obesity mouse model (in vivo)	✓	✓				
HFpEF mouse model (ex vivo analysis of heart & adipose tissue)	✓	✓	✓			
HFpEF mouse model (in vivo)		✓	✓	✓	✓	✓

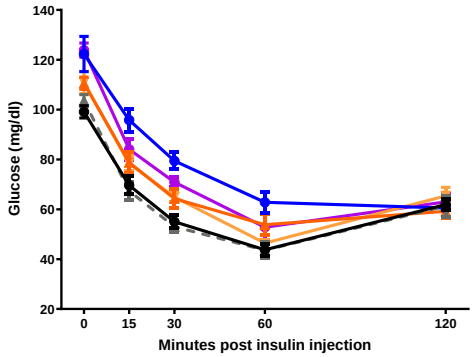
HFpEF - heart failure with preserved ejection fraction
MOA - Mechanism of action
DCM - Dilated cardiomyopathy

TN-301: Small Molecule HDAC6 Inhibitor for HFpEF

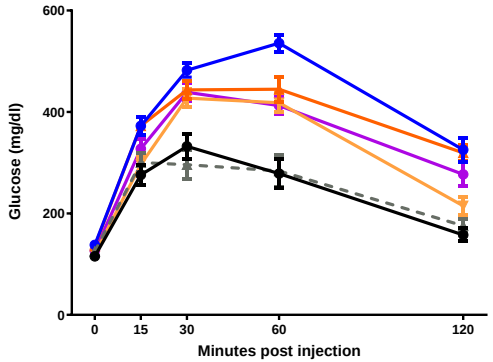
HDAC6 Inhibition Improves Hallmarks of Disease in Multiple Preclinical Models

Improvement in Overall Metabolism

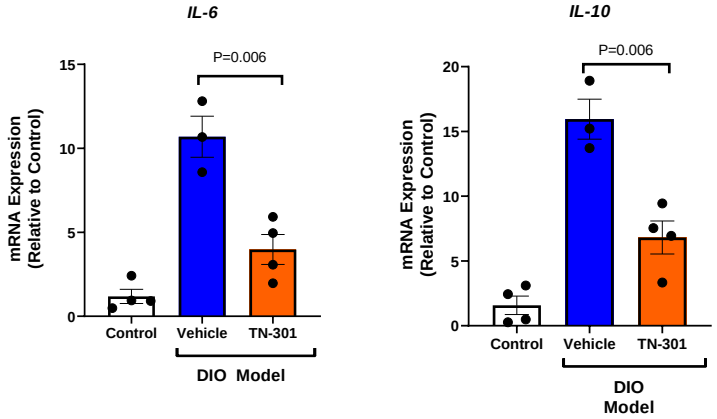
Glucose Tolerance



Insulin Sensitivity

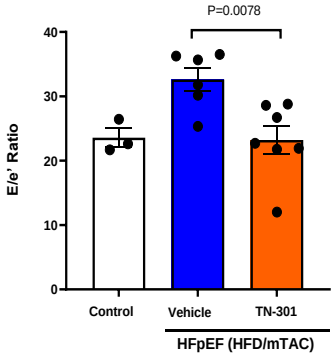


Reduced Inflammatory Markers

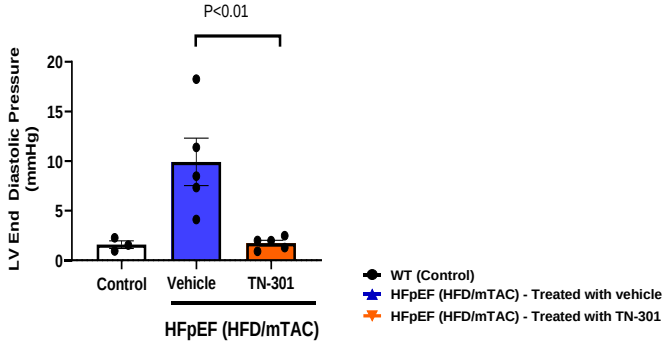


Improvement in Diastolic Function

E/e'

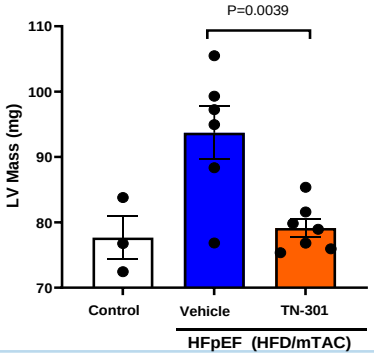


LVEDP

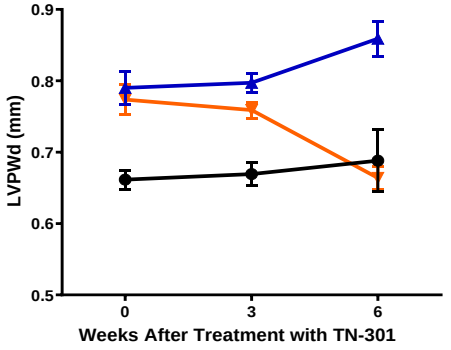


Reduced Hypertrophy

LV Mass



LV Wall Thickness



HFpEF - heart failure with preserved ejection fraction
LVEDP – Left Ventricular End Diastolic Pressure
DIO = Diet-induced obesity

E/e' – Measure of Left Ventricular Filling pressure
LV = Left ventricular
WT = Wild type

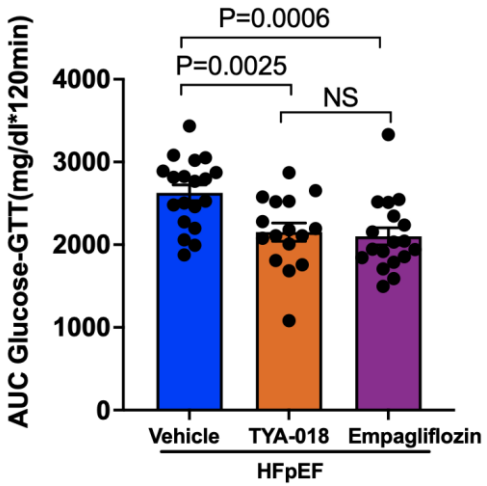
Yang, et al; ESC 2021

TN-301: Small Molecule HDAC6 Inhibitor for HFpEF

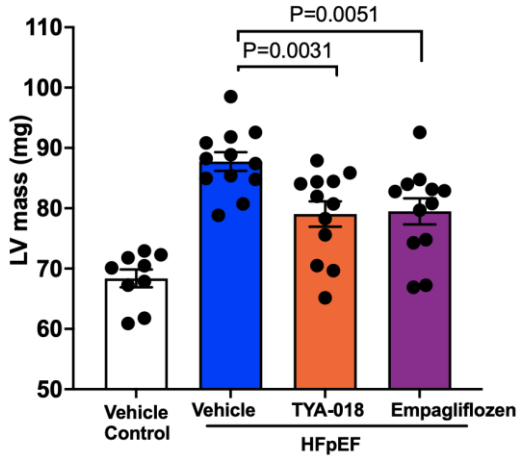
Comparable Efficacy to SGLT2 Inhibition Observed in Murine HFpEF Model

Head-to-head comparison of HDAC6i with empagliflozin validates preclinical HFpEF model and illustrates potential translation of preclinical results to clinical utility with differentiated mechanism

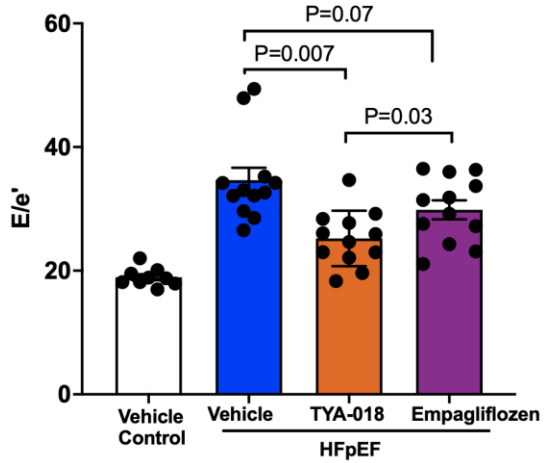
Improvement in Glucose Tolerance — **Single dose**



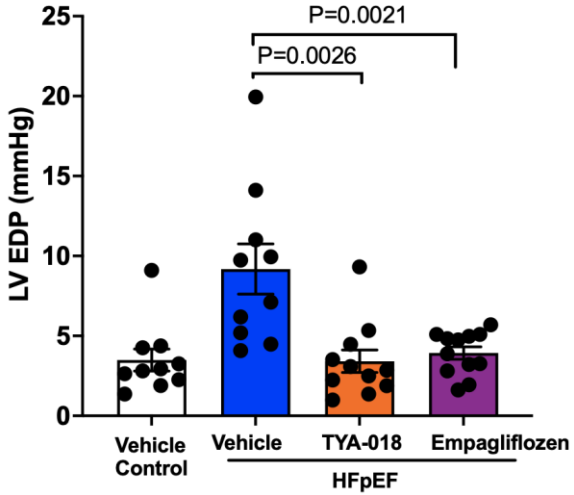
Improvement in LV Mass — **Chronic dosing**



Improvement in Diastolic Function — **Chronic dosing**



Improvement in LV End Diastolic Pressure — **Chronic dosing**



Yang, et al; ESC-HF 2022

- TYA-11018 (TYA-018) is an HDAC6i analog of TN-301 demonstrating equivalent activity and efficacy in various *in vitro* and *in vivo* models.
- Empagliflozin = SGLT2 inhibitor (Jardiance® Boehringer Ingelheim/Eli Lilly, FDA approved for HFpEF as of February 2022)

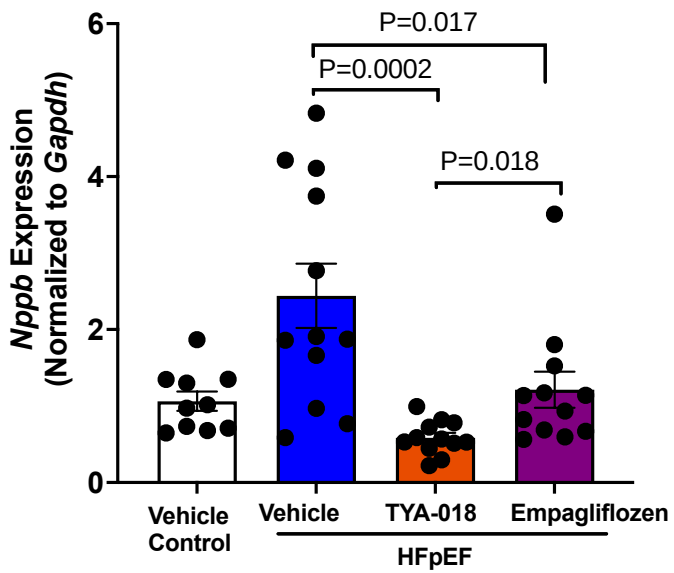
SGLT2 = Sodium-Glucose Cotransporter-2
HFpEF = Heart Failure with Preserved Ejection Fraction
LV = Left Ventricle

TN-301: Small Molecule HDAC6 Inhibitor for HFpEF

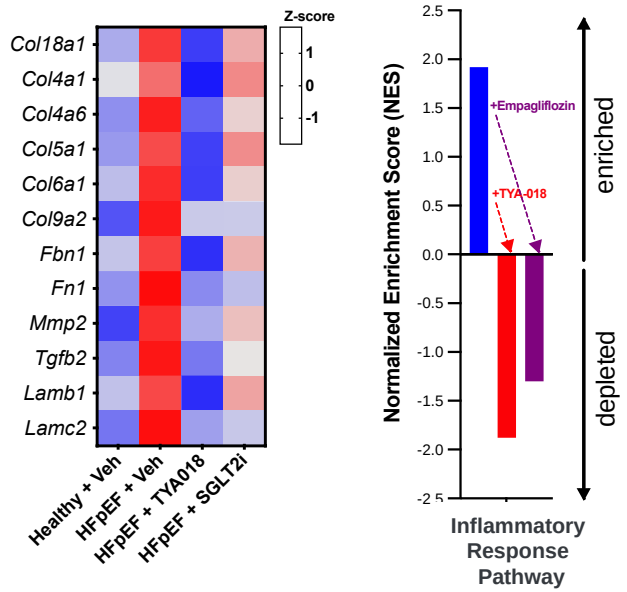
Superior Efficacy to SGLT2 Inhibition Observed in Murine HFpEF Model

Head-to-head comparison of HDAC6i with empagliflozin validates preclinical HFpEF model and illustrates potential translation of preclinical results to clinical utility with differentiated mechanism

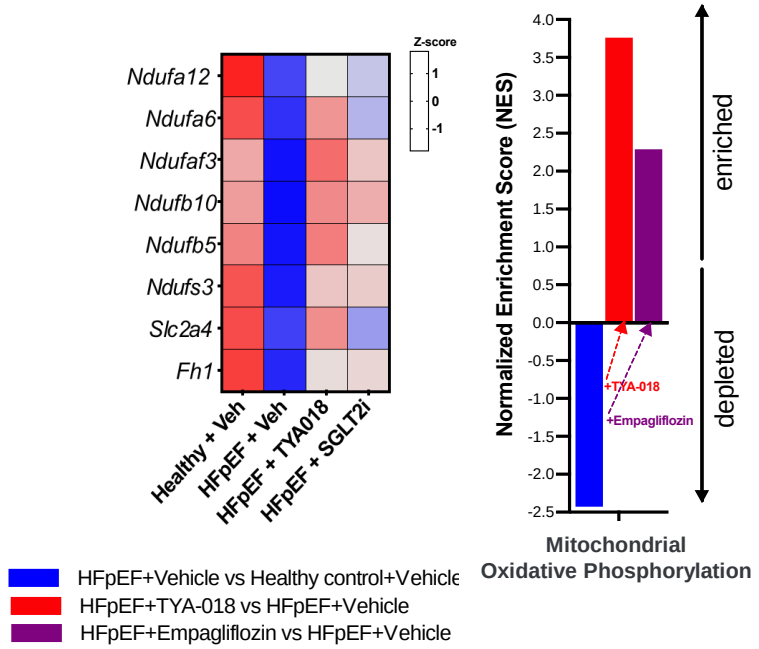
Improvement in Markers of Cardiac Stress



Reduction in Inflammatory Gene Expression



Increased Mitochondrial Energy Production



HFpEF+Vehicle vs Healthy control+Vehicle
HFpEF+TYA-018 vs HFpEF+Vehicle
HFpEF+Empagliflozin vs HFpEF+Vehicle

- TYA-11018 is an HDAC6i analog of TN-301 demonstrating equivalent activity and efficacy in various *in vitro* and *in vivo* models.
- Empagliflozin = SGLT2 inhibitor (Jardiance® Boehringer Ingelheim/Eli Lilly, FDA approved for HFpEF as of February 2022)

Ranjbarvazri, et al; AHA 2022

SGLT2 = Sodium-Glucose Cotransporter-2
HFpEF = Heart Failure with Preserved Ejection Fraction
LV = Left Ventricle

TN-301 HDAC6i Small Molecule Program for HFpEF
First-in-Human Phase 1 Study to Assess Safety and Tolerability

Study Objective

Establish safety profile, confirm target engagement and identify dose ranges for later studies

Primary Endpoint

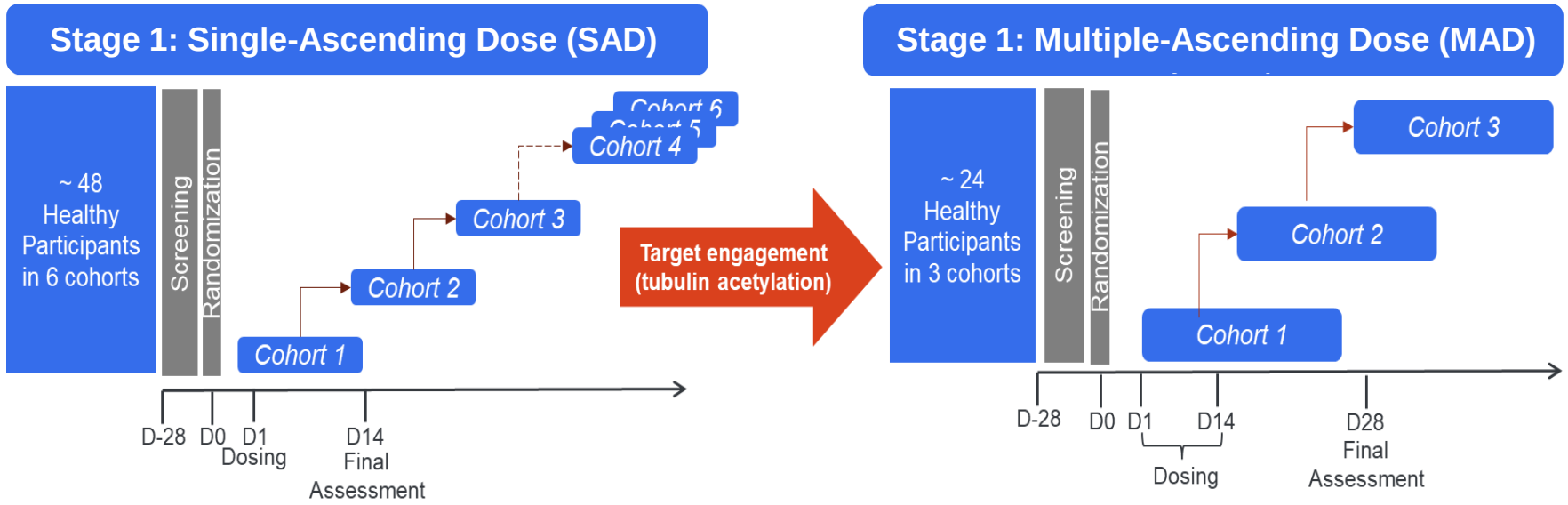
Safety and tolerability

Secondary Endpoints

Pharmacokinetics and pharmacodynamics

Design

Two-stage, single and multiple ascending dose, blinded, randomized (3:1), placebo-controlled



Initial target engagement (tubulin acetylation in blood cells) observed
MAD Stage of study to commence in 1Q 2023
Phase 1 data (SAD + MAD) anticipated in 2H 2023

TN-401

PKP2 Gene Therapy Program for Genetic Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

TN-401: Gene Therapy Program for *PKP2*+ARVC

Addressing the Leading Genetic Cause of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Disease Overview

Pathophysiology

- Mutations in *PKP2* gene affect desmosomes responsible for holding cardiomyocytes together (electro-mechanical coupling)

Disease Symptoms and Severity

- Patients present with palpitations, lightheadedness, syncope
- May develop myocardial atrophy, chamber dilation, fibrofatty muscle replacement
- Average patient presents in young adulthood (< 40 years old)
- Important cause of cardiac arrest in young patients (median cardiac arrest 25 years old)

Epidemiology

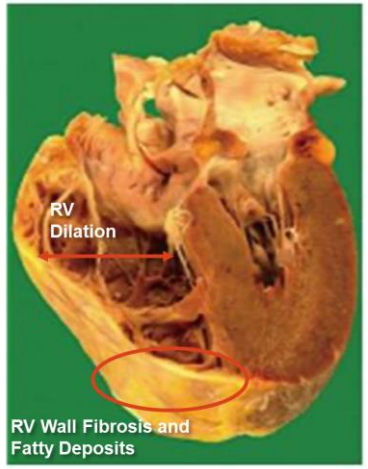
- *PKP2* mutations accounts for ~40% of all ARVC
- Estimated >70K patients in U.S. alone

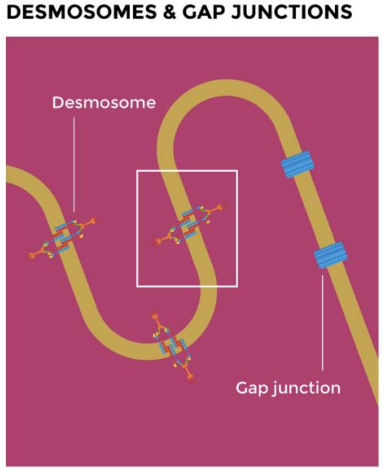
Standard of Care

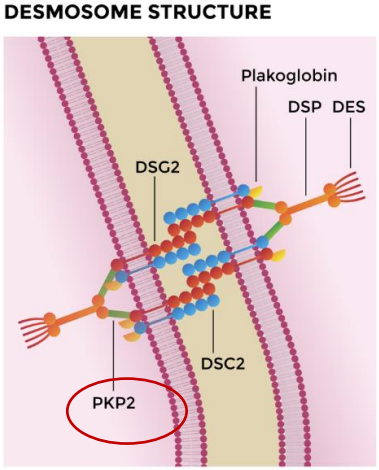
- ICDs, beta blocker, diuretics and antiarrhythmics
- No treatments address the underlying genetic cause

Tenaya Product Candidate

TN-401: PKP2 Program	
Target Cell	Cardiomyocyte
Modality	AAV9
Gene	*PKP2*
Mechanism	"Lock and key", replace a healthy copy of *PKP2* in patients with loss-of-function mutations
Stage	IND enabling







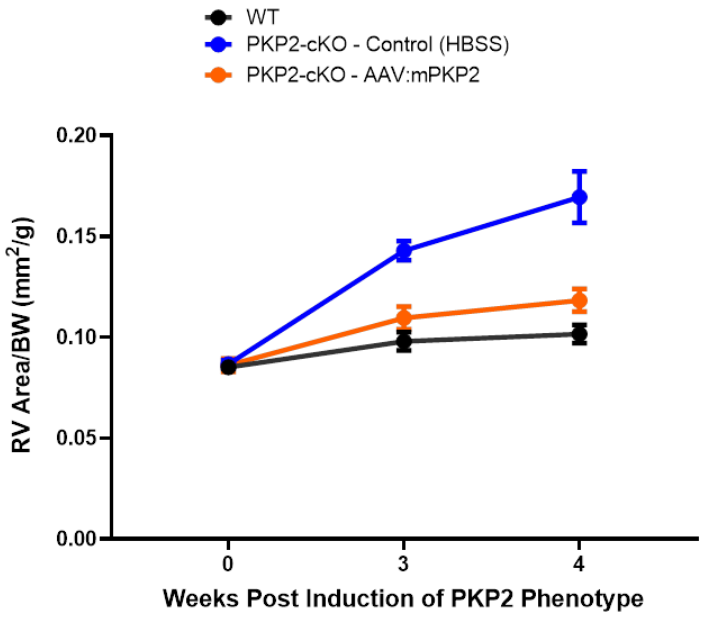
PKP2 = Plakophilin-2
RV = Right Ventricle
AAV9 = Adeno-Associated Virus Serotype 9

ICD = Implantable cardioverter defibrillator
IND = Investigational New Drug

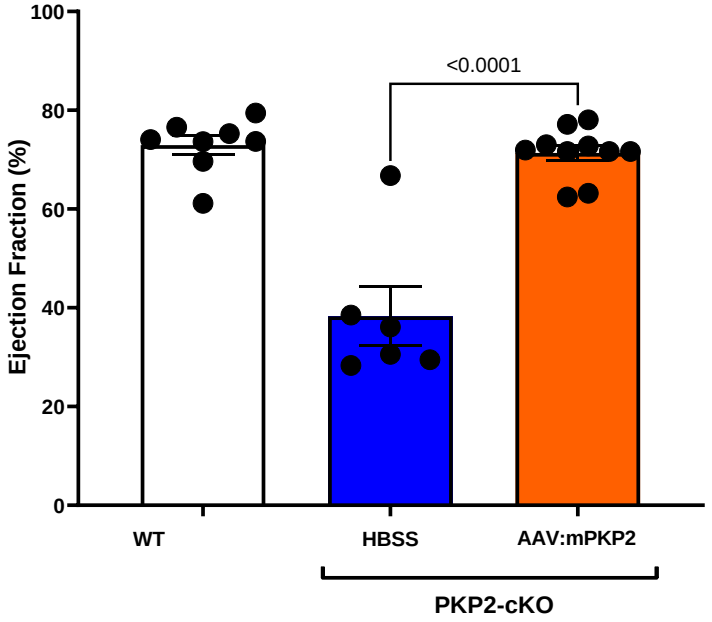
TN-401: Gene Therapy Program for *PKP2*+ARVC

Single-dose AAV:*PKP2* Shows Disease Modification and Survival Benefit

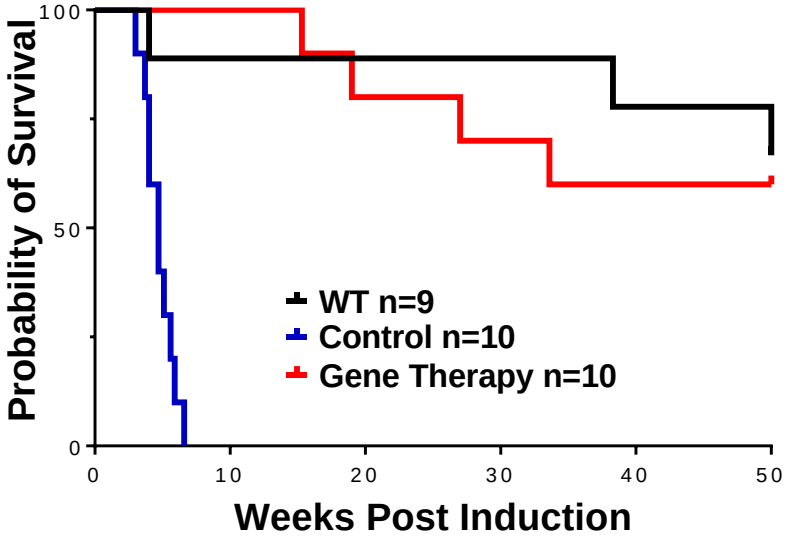
Prevention of Right Ventricle Enlargement



Prevention of Decline of Left Ventricle Function



Survival Benefit



Yang, et al; HRS 2022

PKP2 = Plakophilin-2
ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy
AAV = Adeno-Associated Virus

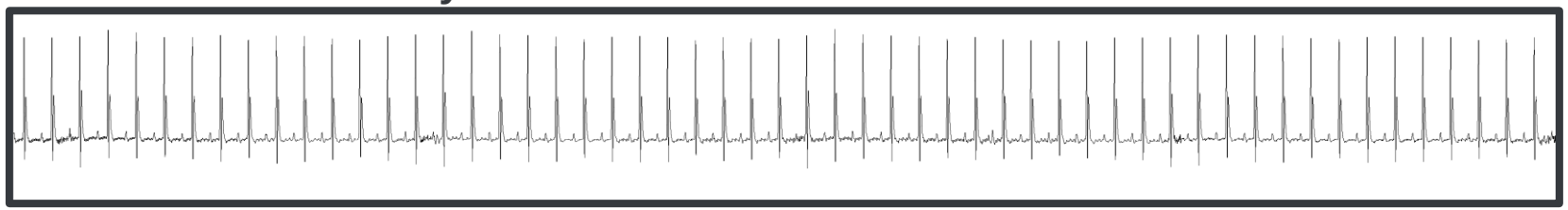
WT = Wild Type
cKO = Conditional Knock-Out

TN-401: Gene Therapy Program for *PKP2*+ARVC

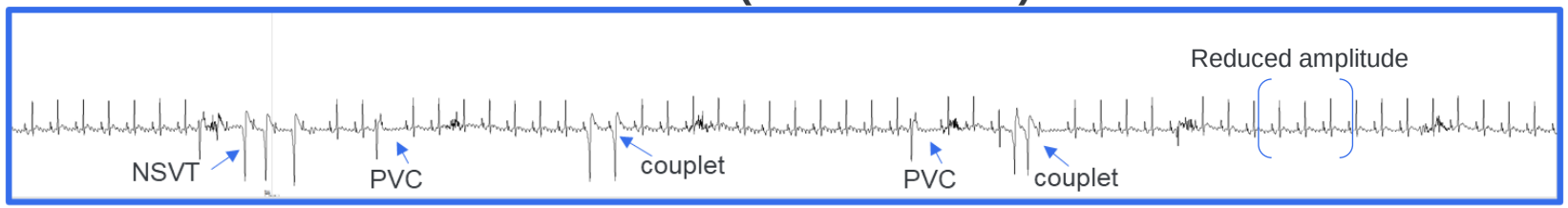
Single-dose AAV:PKP2 Prevents Ventricular Arrhythmias

Prevention of Ventricular Arrhythmias
Including Non-sustained Ventricular Tachycardia (NSVT) and Premature Ventricular Contractions (PVCs)

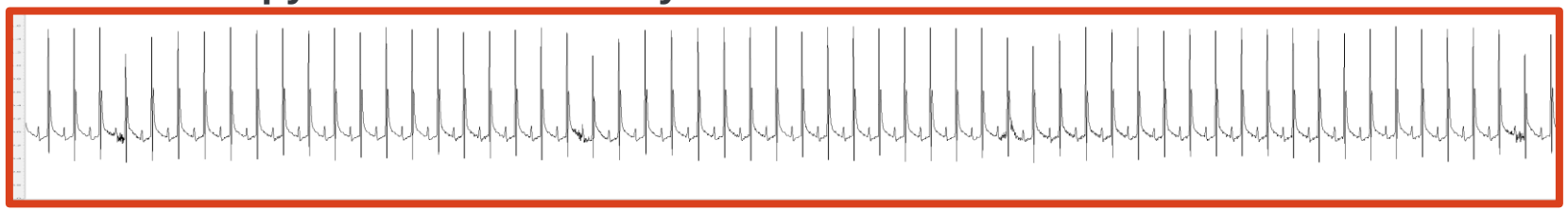
WT: Normal Sinus Rhythm

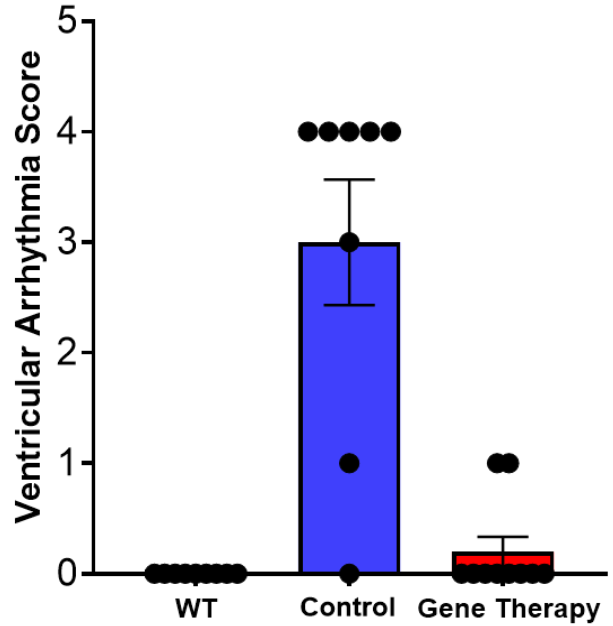


Control: Abnormal Ventricular Beats (NSVT & PVCs)



Gene Therapy: Normal Sinus Rhythm





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

Yang, et al; HRS 2022

PKP2 = Plakophilin-2
ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy
AAV = Adeno-Associated Virus

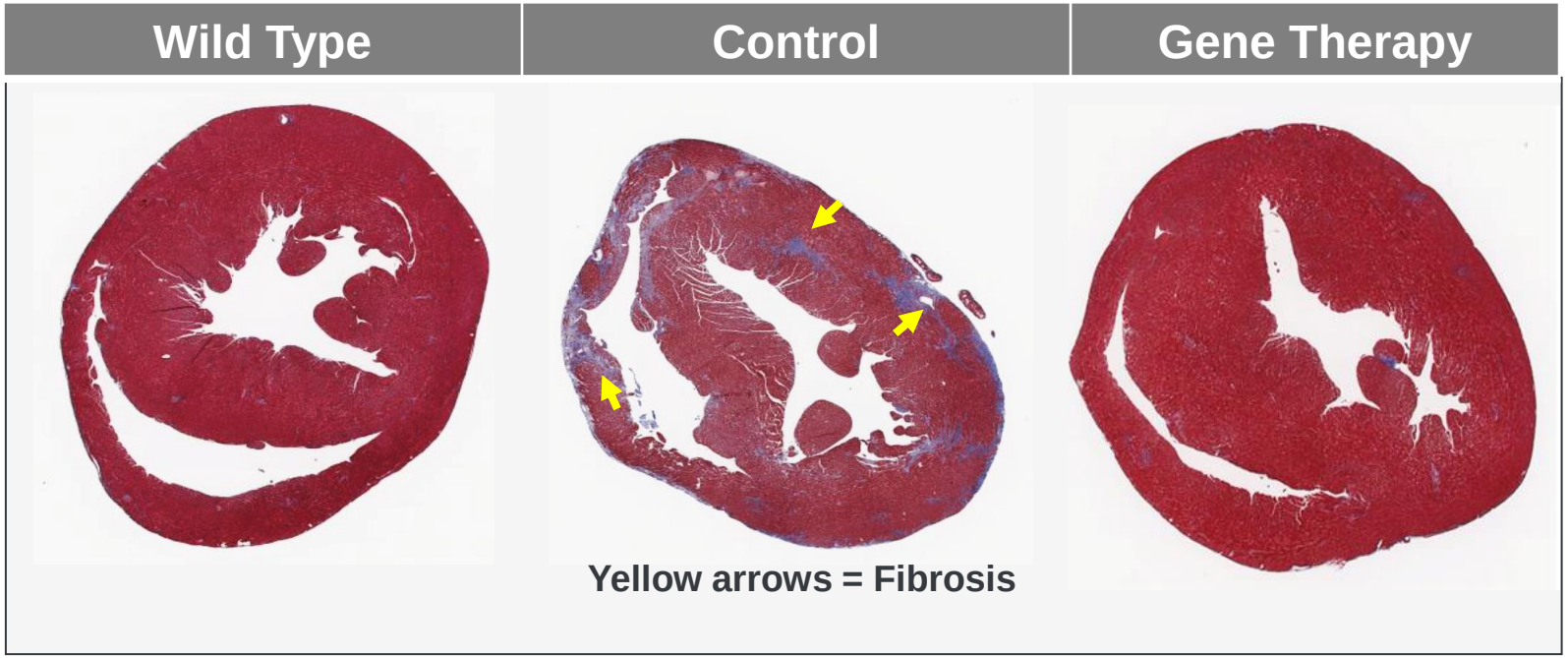
WT = Wild Type
AV = Atrioventricular Block

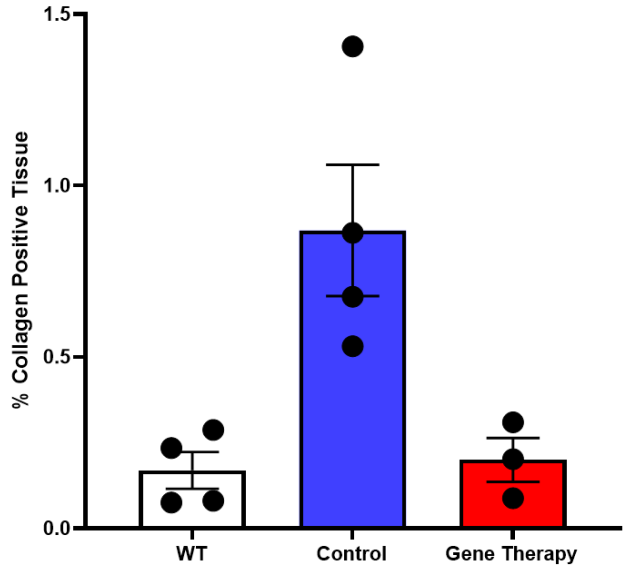
TN-401: Gene Therapy Program for *PKP2*+ARVC

Single Dose Cardiac AAV:PKP2 Gene Therapy Prevents Fibrosis

Prevention of Fibrosis in *Pkp2:*cKO ARV Mouse Model

Trichrome Staining





Yang, et al; ASGCT 2022

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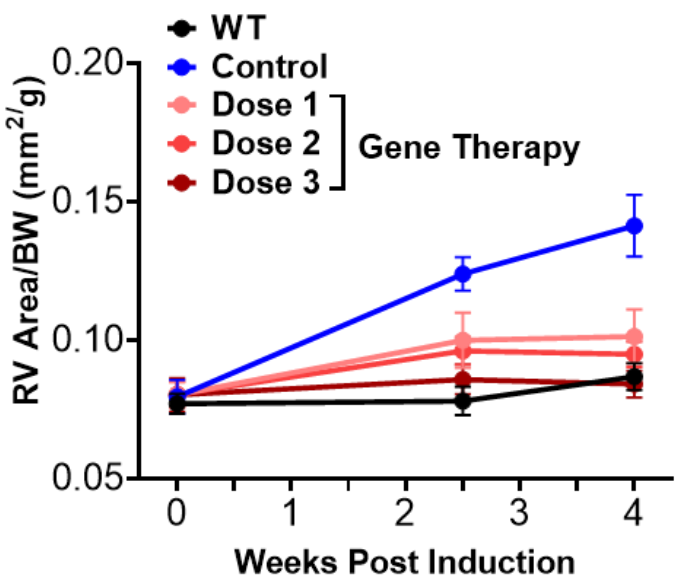
ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy
AAV = Adeno-Associated Virus

cKO = Conditional Knock-Out
WT = Wild Type

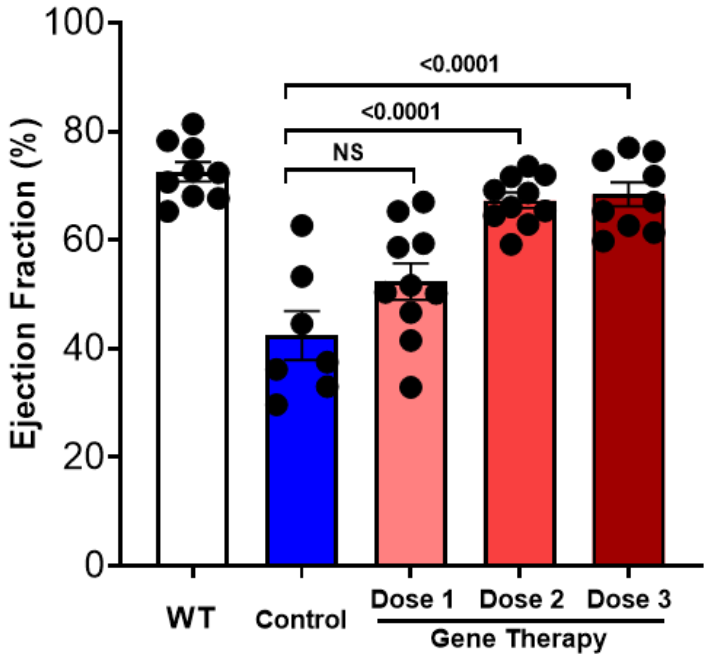
TN-401: Gene Therapy Program for *PKP2*+ARVC

AAV:PKP2 Shows Dose-dependent Improvements

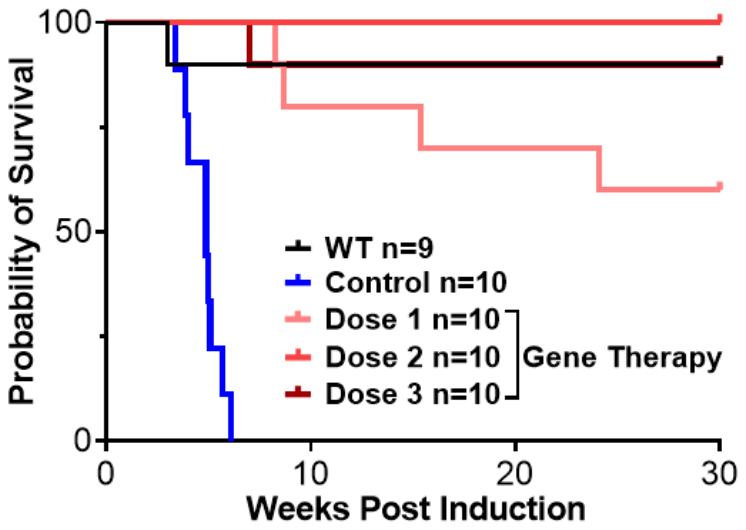
Prevention of Enlargement of Right Ventricle



Prevention of Decline of Left Ventricle Function



Survival Benefit



Yang, et al; HRS 2022

PKP2 = Plakophilin-2
ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy
AAV = Adeno-Associated Virus

WT = wild type

TENAYA™ THERAPEUTICS

Core Capabilities

Capabilities

Internalized and Integrated 5 Core Differentiated Approaches to Support Pipeline

DISEASE MODELS

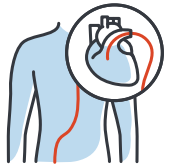
- >40 human iPSC-derived cardiomyocyte (iPSC-CM) models mimicking human disease phenotypes
- Use of imaging/ML algorithms for screening
- *In vivo* pharmacology group + onsite vivarium with ~17 rodent models

CAPSID ENGINEERING

- > 1B capsids screened from > 30 libraries
- Capsids optimized for higher heart selectivity and liver de-targeting
- Proprietary capsids ID-ed to target cardiomyocytes (CMs) and cardiac fibroblasts (CFs)

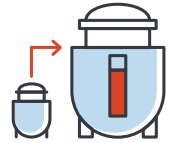
PROMOTERS AND REGULATORY ELEMENTS

- Promoters optimized for more selective and robust expression in heart vs other organs
- Novel regulatory elements for more specific and/or robust expression in CMs vs CFs



DRUG DELIVERY

- Product-specific routes of administration (ROA) include IV infusion plus localized infusion and direct injection
- Novel injection catheter developed based on best-in-class design



AAV MANUFACTURING

- Internalized PD, AD & QC
- Vector Core (50L scale)
- Pilot Plant Operation (200L scale)
- Modular cGMP facility to support clinical studies (1000L+ scale)

Rapid Prototype Iterations (→ Speed)

Lower Doses, High Productivity (→ Safety, Cost, Quality)

Precise Product Delivery (→ Efficacy, Safety)

iPSC = induced Pluripotent Stem Cells
ML= Machine Learning
IV = Intravenous

PD = Process development
AD = Analytical development
QC = Quality control

Capabilities: Disease Models

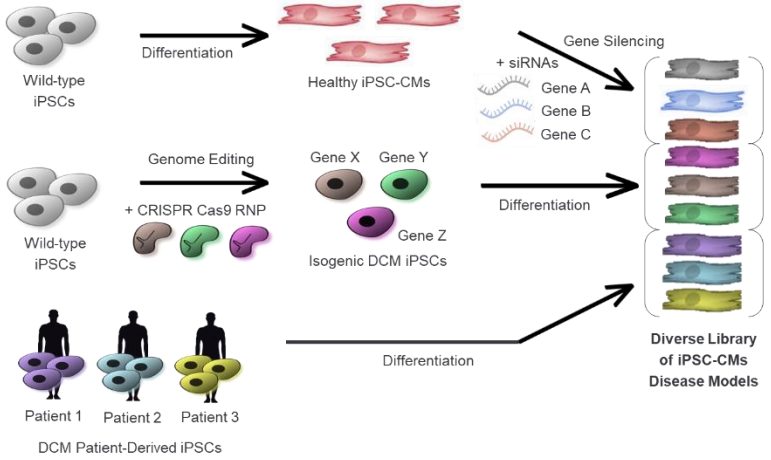
Proof of Concept Established for Identifying New Targets

(1) Generate Proprietary Library of Human iPSC-CMs

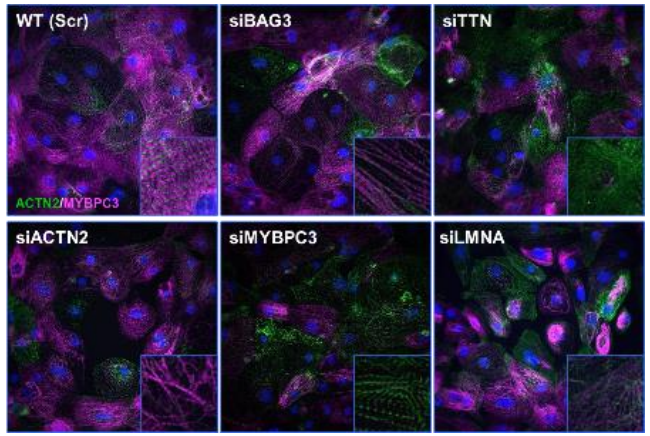
iPSC-CMs from gene silencing

iPSC-CMs from gene editing

iPSC-CMs from affected patients

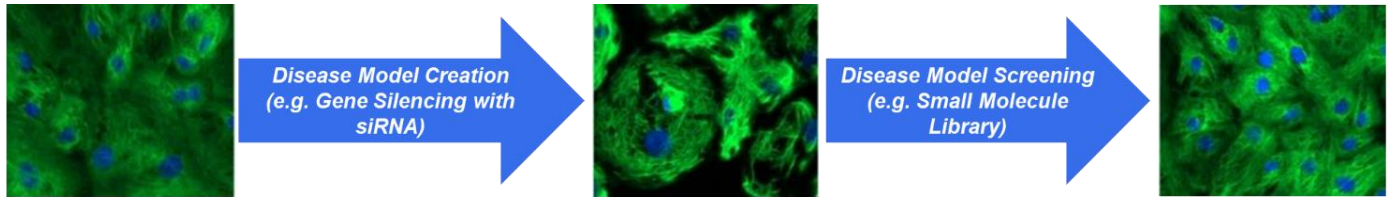


(2) Quantify Disease Phenotypes Using High Resolution Imaging



- Sarcomere-related measures e.g., density and disarray
- Use of 3D/EHTs to measure contractility defects

(3) Screen and Validate Targets Using AI/Machine Learning Algorithms for Further Development ID & Drug Discovery



Normal Appearance (and Function) of Wild-Type iPSC-CM Cells

Abnormal Appearance (and Function) of Disease Model iPSC-CM Cells

Normalized Appearance (and Function) of Disease Model Cells with Screen Compound

- HDAC6 target discovered *in vitro* in a screen iPSC-CMs carrying *BAG3* mutation associated with DCM
- Effect of Tenaya HDAC6i compounds validated *in vivo* in *BAG3* KO model as well as two HFpEF models
- Using human genetics to prioritize other biologically relevant targets identified through ongoing screens

iPSC = induced Pluripotent Stem Cells
CM = Cardiomyocyte
EHT = Engineered Heart Tissue

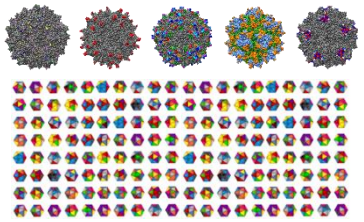
DCM = Dilated Cardiomyopathy
HFpEF = Heart Failure with Preserved Ejection Fraction
KO = Knockout

Capabilities: Capsid Engineering

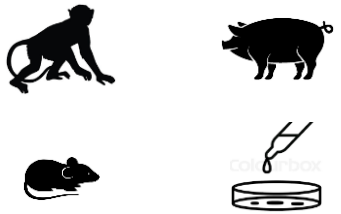
Identifying Novel Capsids with Superior Attributes After Multiple Rounds of Screening in NHPs and Validation in Multiple Species

Focused AAV Screening Efforts Using Multiple Strategies

Screened ~1 billion variants from ~30 diverse libraries

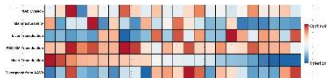


Screening and validation *in vivo*, *in vitro*, and *in silico* models (current focus on NHPs)



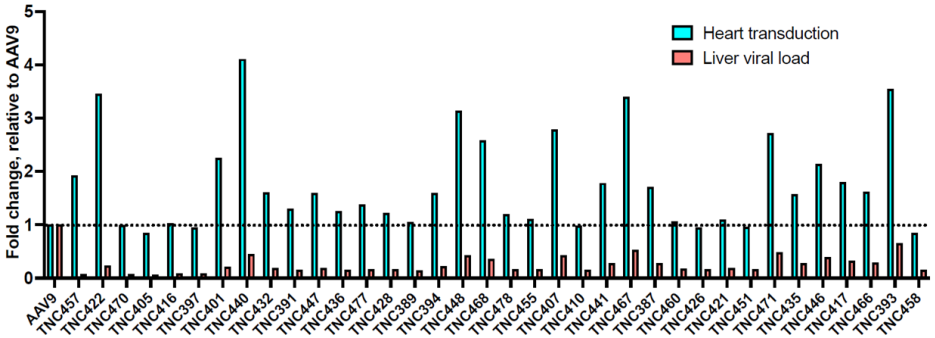
Multiple criteria

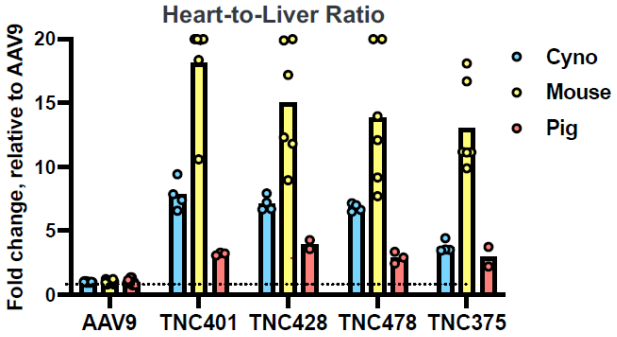
- ↑ heart transduction
- ↓ liver transduction
- ↓ antigenicity
- ↔ manufacturability



Novel AAV Capsids for Heart that Outperform Parental Vectors

- 2nd generation novel capsids demonstrate reduced trafficking to the liver in NHPs vs. AAV9
- Top novel capsids show improved heart-to-liver ratio across all 3 species tested





Chen, et al; ESGCT 2022

2nd Generation Capsid Characteristics

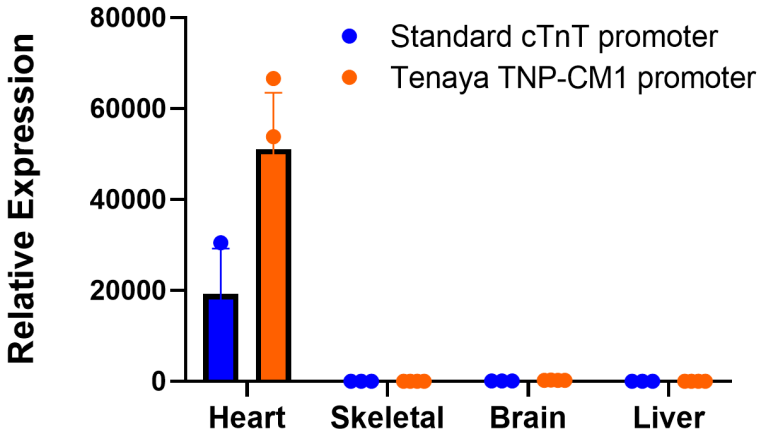
- ✓ Superior heart transduction → may lead to more efficacious therapy
- ✓ Superior liver de-targeting → may improve the safety profile
- ✓ Superior NAb evasion → may enable treatment of a greater number of patients

AAV = Adeno-Associated Virus
NHP = Non-Human Primate
AAV9 = Adeno-Associated Virus Serotype 9

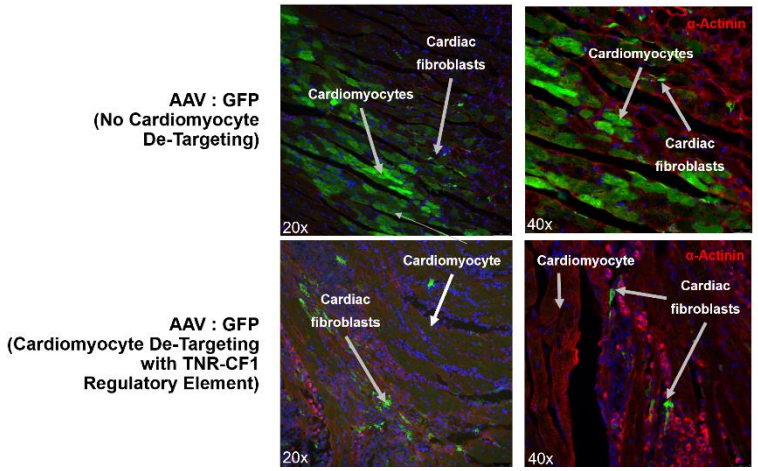
Capabilities: Promoters and Regulatory Elements

More Selective and Robust Transgene Expression in the Heart Intended to Improve Overall Efficacy and Safety

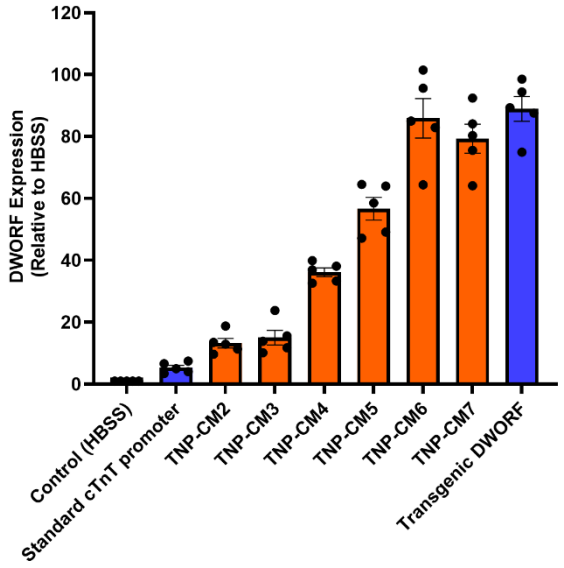
Selective Expression in Heart vs Other Organs



Selective Expression in One Heart Cell Type vs Another



Fine Tune Gene Expression Within a Heart Cell



Example: MYBPC3 program

- Novel promoter enables selective expression in heart vs other organs
- Promoter enables higher expression vs. regular cTnT promoter

Example: Reprogramming project

- Novel regulatory element enables expression in CFs but shuts down translation in CMs
- Optimized co-expression of 3 genes from a single construct

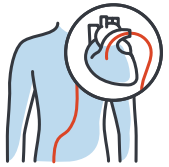
Example: DWORF project

- Suite of novel promoters and constructs to fine-tune level of transgene expression + enable higher expression vs. regular cTnT promoter

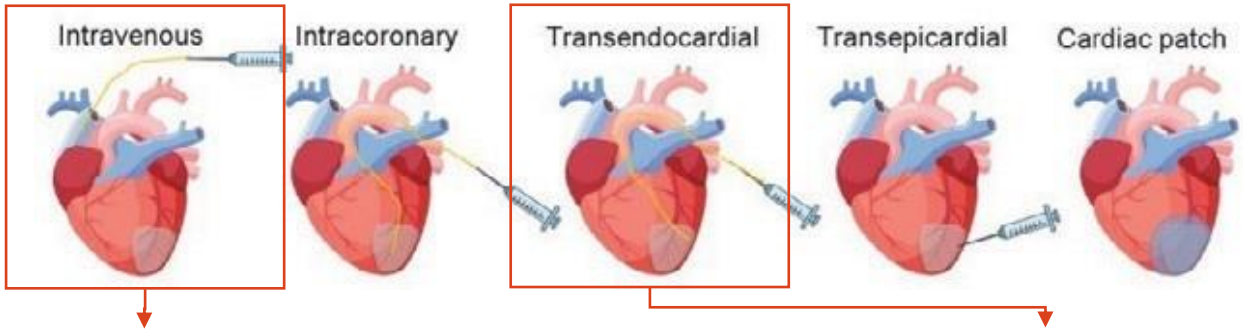
cTnT= cardiac troponin T
CF = cardiac fibroblast
CM = cardiomyocyte

Capabilities: Drug Delivery

Optimizing Delivery of AAV-Based Therapies with Different Routes of Administration (ROA) and Delivery Devices

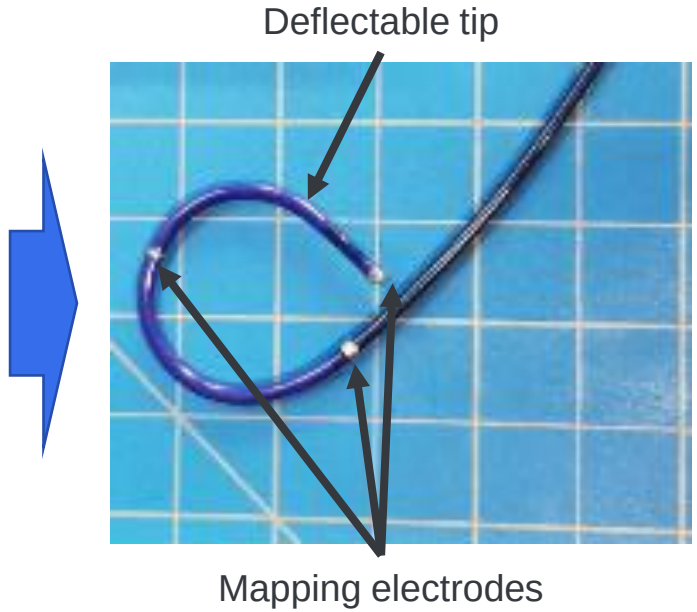


Different delivery methods can affect the relative uptake and biodistribution of therapies in heart vs. to peripheral organs. Discoveries in drug delivery can widen therapeutic index of product candidates by reducing dose required for therapeutic benefit.



- Initial product candidates emerging from Gene Therapy platform (e.g., MYBPC3 program) need broad distribution across the heart tissue more suited to infusion-based approaches.
- Prioritized head-to-head comparison of different infusion-based ROAs to compare IV vs other potential approaches in a large animal model.

- Initial product candidates emerging from Cellular Regeneration platform (e.g., Reprogramming program) require more precise delivery directly around LV scar area more suited to injection-based approaches.
- Developed prototype for novel trans endocardial injection catheter designed with expert interventional cardiologists and based on similar catheters successfully used in clinical trials. Prototype tested in a large animal model.

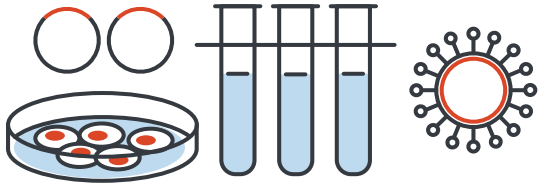


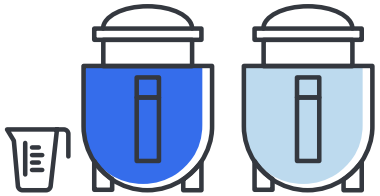
AAV = adeno-associated virus
MYBPC3 = Myosin Binding Protein C3
LV = Left ventricular

Capabilities: Manufacturing

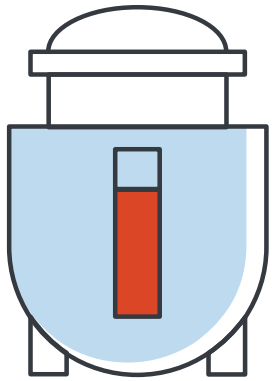
cGMP Genetic Medicines Manufacturing Center Supports TN-201, TN-401 and Future AAV-Based Programs

In-house team of ~45 FTE for Process Development, Analytical Development, and Quality Control





HEK293 Sf9/rBV



Sf9/rBV

Starting Materials	*Vector Core (Shake flask - 50L)*	*Pilot Plant Op (200L)*	*cGMP Facility (1000L+)*
IP and know-how to enable scale to large (> 5000L) bioreactors to produce AAV for prevalent indications	Consistently high purity vector for small and large animal studies enables rapid iterations and candidate selection	Scale-up process to support IND-enabling GLP tox and efficacy studies	More control over process, product attributes, quality, costs, and timelines

cGMP = Good Manufacturing Practices
FTE = Full-time employees
AAV = adeno-associated virus
IND = Investigational New Drug
GLP = Good Laboratory Practices

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Milestones

Key 2022 Accomplishments and 2023 Milestones

	2022	2023
TN-201 **AAV gene therapy for *MYPBC3*+ HCM**	✓ Completed manufacture of Phase 1 clinical supply ✓ Submitted IND	✓ Q1 2023: Received IND clearance • **Q3 2023: Begin patient dosing in Phase 1b trial** • Ongoing: Enroll global non-interventional studies
TN-301 **Small molecule HDAC6 inhibitor for HFpEF**	✓ Presented new preclinical data at ESC-HF ✓ Submitted IND and initiated Phase 1 SAD/MAD clinical trial ✓ Achieved target engagement	• Q1 2023: Begin MAD portion of Phase 1 trial • **2H 2023: Report Phase 1 SAD/MAD data**
TN-401 **AAV gene therapy for *PKP2*+ ARVC**	✓ Presented preclinical data at HRS & ASGCT ✓ Initiated non-interventional natural history and seroprevalence study	• **2H 2023: Submit IND to U.S. FDA** • Ongoing: Produce drug supply for Phase 1 trial • Ongoing: Enroll global non-interventional study
Research and Manufacturing	✓ Presented preclinical data on AAV capsid engineering efforts ✓ Launched operations of cGMP for Genetic Medicines Manufacturing Center at 1000L	• Ongoing: Present data from early-stage research efforts and platform enhancement innovations

$150MM Cash as of Q3'22* + ~$77MM Net Proceeds from Financing in Q4'22 = Sufficient to fund planned activities into 1H 2025

HFpEF - heart failure with preserved ejection fraction
HCM = Hypertrophic Cardiomyopathy
ARVC = Arrhythmogenic Right Ventricular Cardiomyopathy

cGMP = current Good Manufacturing Practice
IND = investigational new drug application
AAV = adeno-associated virus

SAD = Single-ascending dose
MAD = Multiple-ascending dose

* Cash, cash equivalents and investments in marketable securities (current and noncurrent) as of September 30, 2022

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Thank you