Scaling New Heights in the Fight Against Heart Disease

Corporate Overview

November 2021

Disclaimer

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 our future financial condition, results of operations, business strategy and plans, and objectives of management for future 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 "anticipate," "believe," "can,' "contemplate," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "potentially," "predict," "project," "should," "target," "will" or "would," 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 a 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, 2021. Such risks include, among other things: 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 timing or likelihood of regulatory filings and approvals; the negative impacts of the COVID-19 pandemic; 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; the sufficiency of our existing cash and cash equivalents to fund our future operating expenses and capital expenditure requirements; our ability to retain the continued service of our key personnel and to identify, hire and retain additional qualified professionals; the implementation of our business model and strategic plans for our business; 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 Strategy

Why The Time is Now for Next Generation Precision Medicine Therapies Focused on Heart Disease

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

- In the US, >30MM adults diagnosed with heart disease and ~35K children are born each year with congenital heart disease
- There are > 250 known genetically defined disorders where the primary source of morbidity and mortality involves the heart
- Analysis shows mortality rates due to heart failure are rising
- Genetic cardiomyopathy can run through families




Increasing Genetic Insight and Diagnosis

- ACC/AHA 2020 guidelines recommend genetic testing
- Advent of accessible genetic testing in the USA for > 150 genes for > 35 conditions involving arrhythmia and/or cardiomyopathy

Increasing Clinical Validation for Precision Medicine Approaches

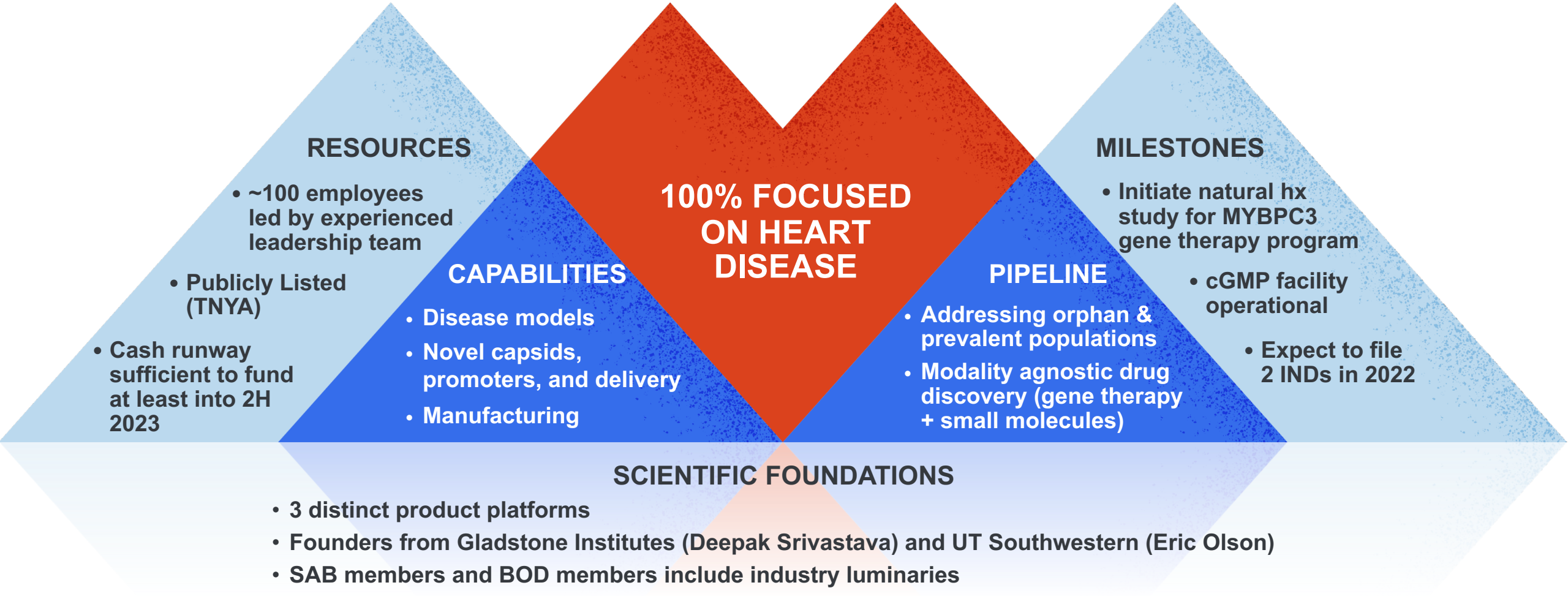
- Initial approval for disease-specific therapies for genetic cardiomyopathies (e.g. ATTR-cardiomyopathy)
- Early clinical data for AAV gene therapy targeting cardiac muscle (e.g. Danon Disease)
- Overall move towards smaller studies with larger effect sizes

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

Tenaya is Advancing Projects from Multiple Scientific Platforms to Address the Underlying Causes of Heart Disease for Both Prevalent and Orphan Indications



Tenaya Executive Team

Diverse Leadership Team Brings Together Experience in Gene Therapy, Cardiovascular R&D, Manufacturing, and Commercialization for Both Prevalent and Orphan Indications

Faraz Ali, MBA

Chief Executive Officer

bluebirdbio
REGENXBIO
genzyme
GE Healthcare

Timothy Hoey, PhD

Chief Scientific Officer

OncoMed PHARMACEUTICALS
AMGEN
Tularik

Whit Tingley, MD, PhD

Chief Medical Officer

Genentech
A Member of the Roche Group
Cytokinetics
UCSF
CARDIODX

Leone Patterson, MBA

Chief Financial and Business Officer

ADVERUM
NOVARTIS
EXELIXIS

Kee-Hong Kim, PhD

SVP, Manufacturing

agilis
Shire
AVALANCHE BIOTECH
Dendreon

Jay Vora, PhD, MBA

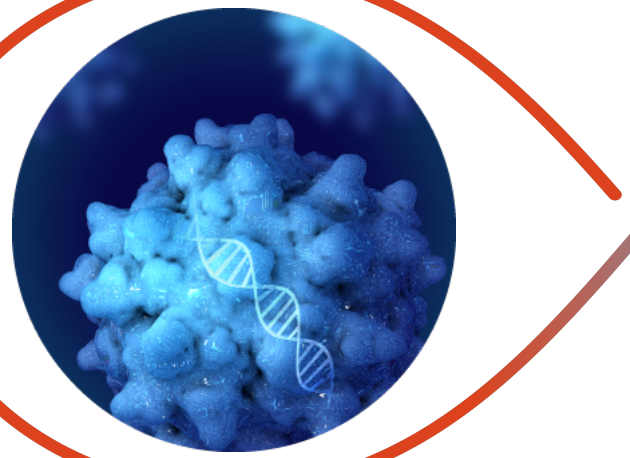
SVP, Program Mgmt

Sangamo THERAPEUTICS
REGENXBIO
BIOMARIN

Tenaya Platforms

Three Distinct and Connected Platforms Bring Together Differentiated Science, Capabilities, and IP Into a Multi-Modality Drug Discovery Engine.

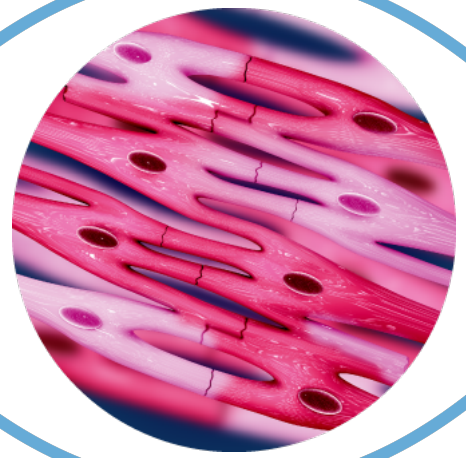
GENE THERAPY



PROBLEM:
Heart cells that are defective (e.g. due to mutations)

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

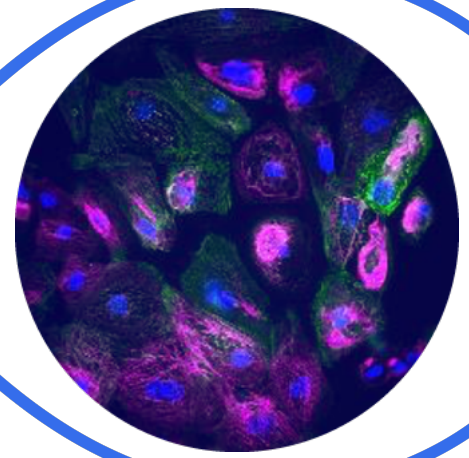
CELLULAR REGENERATION



PROBLEM:
Heart cells that are lost (e.g. due to heart attack)

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

PRECISION MEDICINE



PROBLEM:
Lack of new targets with human validation

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

Tenaya Pipeline

Deep, Diverse, Wholly-Owned Pipeline Addressing Rare and Prevalent Indications. Two Programs Have Initiated IND-Enabling Activities and Expected to File INDs in 2022.

	Program	Modality	Indication	USA Prevalence	Discovery	Preclinical Development	Ph I	Ph II	Ph III	Commercial Rights
Gene Therapy	**MYBPC3**	AAV	Genetic Hypertrophic Cardiomyopathy (gHCM)	> 115K	TN-201		• **Expected to file IND 2022** • **Data presented ASGCT 2021 and ESGCT 2021**			TENAYA THERAPEUTICS
Gene Therapy	**PKP2**	AAV	Genetic Arrhythmogenic RV Cardiomyopathy (gARVC)	> 70K			• **Data presented at ESGCT 2021**			
Gene Therapy	**DWORF**	AAV	Dilated Cardiomyopathy (DCM)	> 1MM			• **Data presented via publications 2016-2020**			
Gene Therapy			Heart Failure w/ Reduced Ejection Fraction (HFrEF)	~ 4MM						
Precision Medicine	**HDAC6i**	Small Molecule	Heart Failure w/ Preserved Ejection Fraction (HFpEF)	> 3MM	TYA-11631		• **Expected to file IND 2022** • **Data presented ESC-HF 2021**			TENAYA THERAPEUTICS
Precision Medicine			Genetic Dilated Cardiomyopathy (gDCM)	> 300K						
Cellular Regeneration	**Reprogramming**	AAV	Heart Failure Due to Prior Myocardial Infarction (MI)	> 4MM			• **Data presented ASGCT 2020**			TENAYA THERAPEUTICS

TENAYA™ THERAPEUTICS

Capabilities

Tenaya Capabilities

Internalizing and Integrating 5 Core Differentiated Approaches to Support Pipeline

DISEASE MODELS

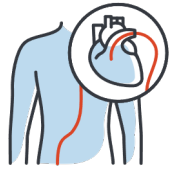
- >40 human iPSC-derived cardiomyocyte (iPSC-CM) models mimicking human disease phenotypes
- Use of imaging/ML algorithms for screening
- *In vivo* pharmacology group + onsite vivarium with ~15 rodent models

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)

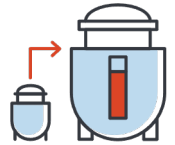
PROMOTERS AND REGULATORY ELEMENTS

- Promoters optimized for more selective and more robust expression in heart vs other organs
- Novel regulatory elements for more specific and/or more 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 FIH studies (1000L+ scale)

Rapid Prototype Iterations (→ Speed)

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

Precise Product Delivery (→ Efficacy, Safety)

Capabilities: Disease Models

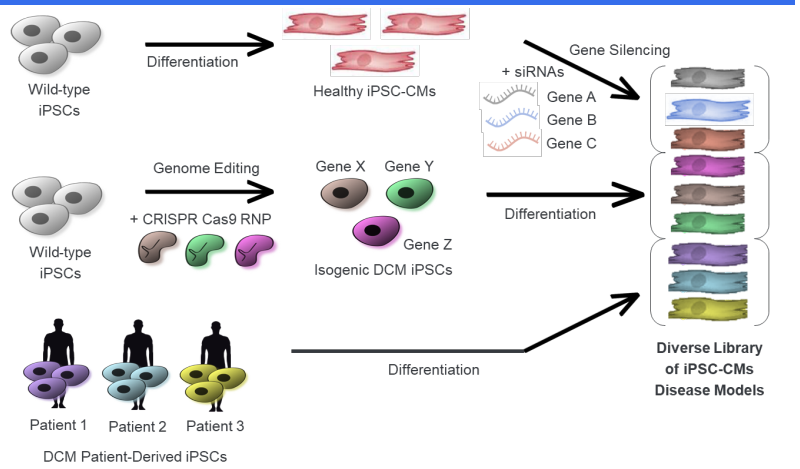
Proof of Concept Established for Phenotypic Screening of Proprietary iPSC-CM Disease Models + High Resolution Imaging + Machine Algorithms

(1) Generate Proprietary Library of Human iPSC-CMs

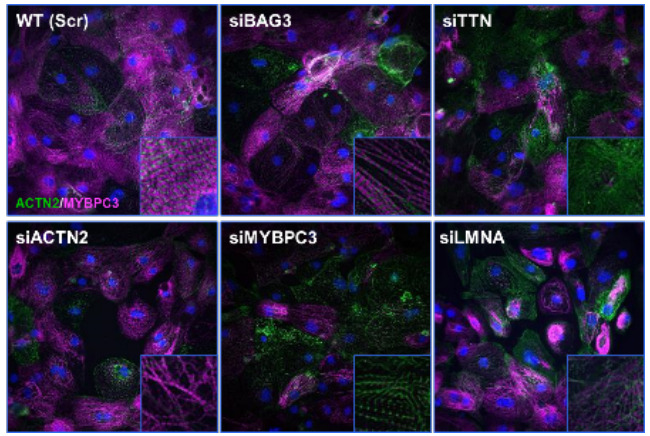
iPSC-CMs from gene silencing

iPSC-CMs from gene editing

iPSC-CMs from affected patients

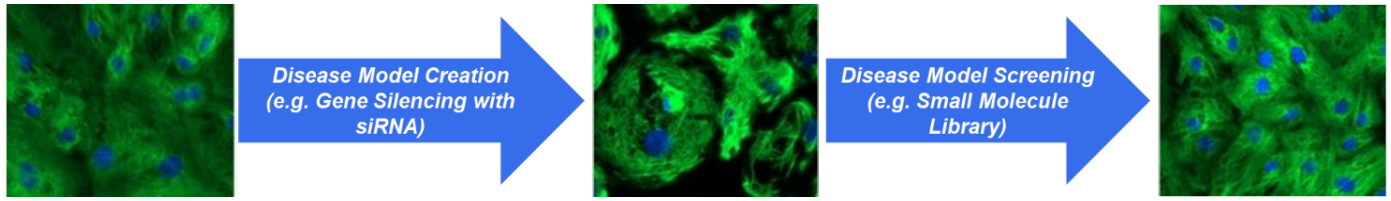


(2) Quantify Disease Phenotypes Using High Resolution Imaging



- 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

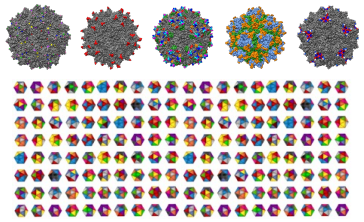
- HDAC6 target discovered *in vitro* in a screen iPSC-CMs carrying *BAG3* mutation associated with DCM
- Effect of Tenaya HDAC6i compounds validated *in vivo* in *BAG3* KO model as well as two HFpEF models
- Using human genetics to prioritize other biologically relevant targets identified through ongoing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

Capabilities: Capsid Engineering

Robust AAV Capsid Evaluation Efforts Utilize *In Vitro, In Vivo, and In Silico* Models Across Species to Identify High Performance Capsids with Unique Properties

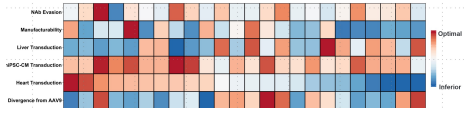
Focused AAV Screening Efforts Using Multiple Strategies

Screened 1 billion variants from ~30 diverse libraries



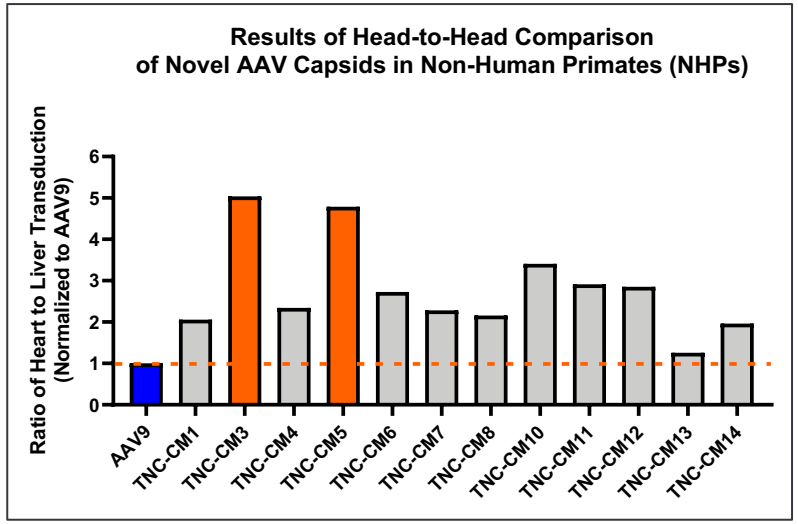
Screening and validation in multiple models, focus on NHPs

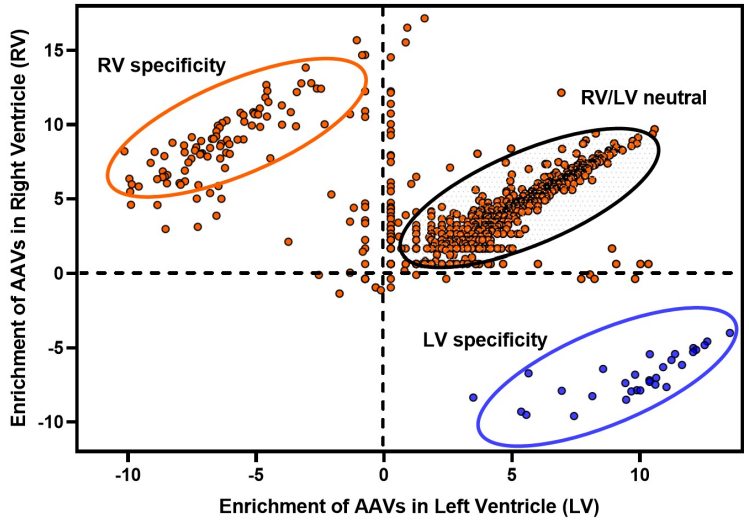
Multiple criteria (↑heart transduction, ↓off-target e.g. liver transduction, ↓antigenicity)



Novel AAV Capsids for Heart that Out-Perform Parental Vectors and Display Unique Properties

- ✓ Capsids with 5x better heart : liver ratios (in NHPs) as well as improved antigenicity profile vs AAV9
- ✓ Capsids with higher enrichment in left- vs right-ventricle (in NHPs)

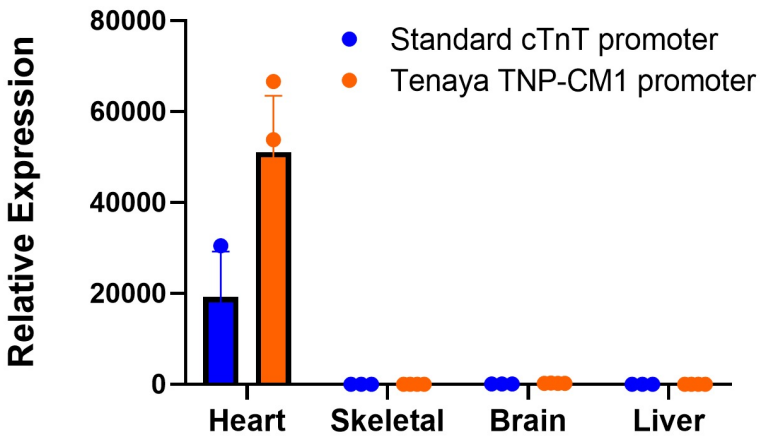




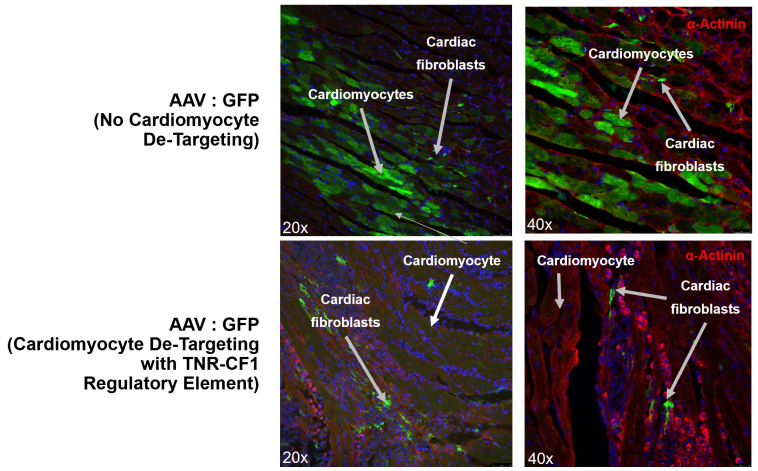
Capabilities: Promoters and Regulatory Elements

Novel Promotors and Regulatory Elements Provide More Selective and Robust Transgenes Expression Intended to Improve Efficacy and Safety

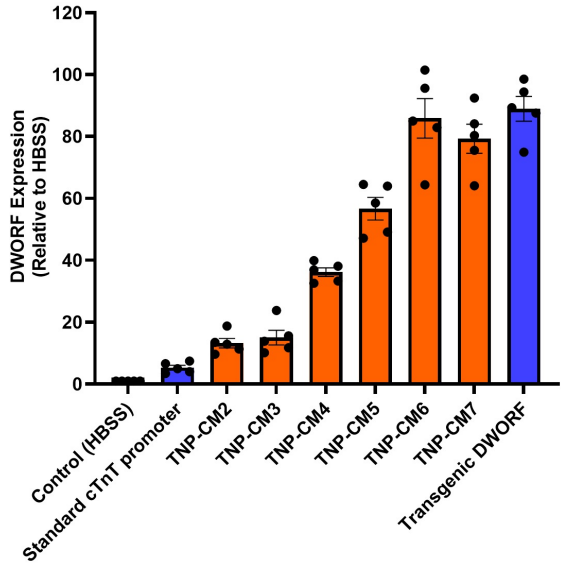
Selective Expression in Heart vs Other Organs



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

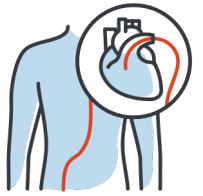
- Novel regulatory element enables expression in CFs but shuts down translation in CMs
- Optimized co-expression of 3 genes from a single construct

Example: DWORF project

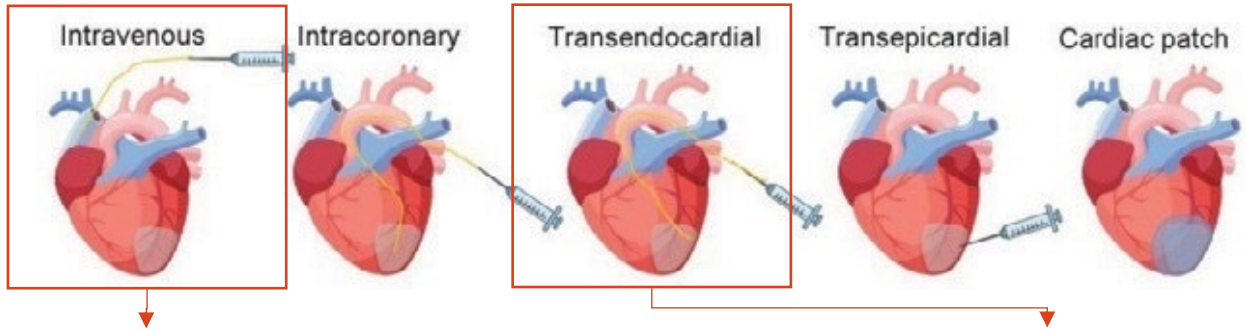
- Suite of novel promoters and constructs to fine-tune level of transgene expression + enables higher expression vs. regular cTnT promoter

Capabilities: Drug Delivery

Exploration of Different Delivery Devices and Routes of Administrations (ROAs) to Optimize Delivery of AAV-Based Therapies

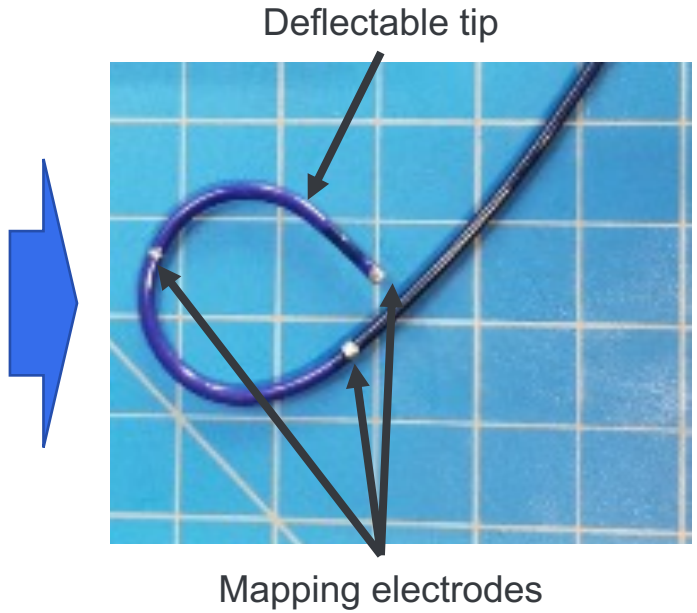


Different delivery methods can affect the relative uptake and biodistribution of therapies in heart vs to peripheral organs. Discoveries in drug delivery can widen therapeutic index of product candidates by reducing dose required for therapeutic benefit.



- 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.

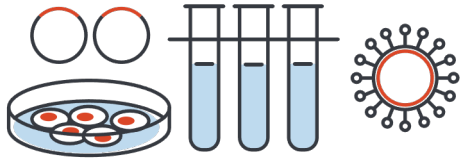
- Initial product candidates emerging from Cellular Regeneration platform (e.g. Reprogramming program) require more precise delivery directly around LV scar area more suited to injection-based approaches.
- Developed prototype for novel trans endocardial injection catheter designed with expert interventional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

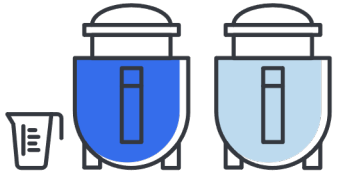


Capabilities: AAV Manufacturing

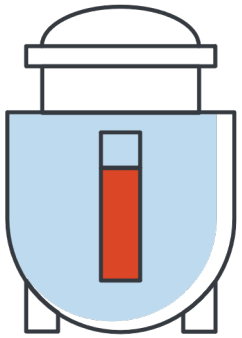
Investment in End-to-End AAV Manufacturing Capabilities Including cGMP Facility Supports MYBPC3 Program and Future AAV-Based Programs

In-house team of ~25 FTE for Process Development (PD), Analytical Development (AD), and Quality Control (QC)
Team will continue to grow as cGMP facility gets closer to becoming operational





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	Scale-up process to support IND-enabling GLP tox and efficacy studies	More control over process, product attributes, quality, costs, and timelines

No reliance on academic centers

Expect to not rely on CDMOs for AAV drug product mfg for initial clinical studies

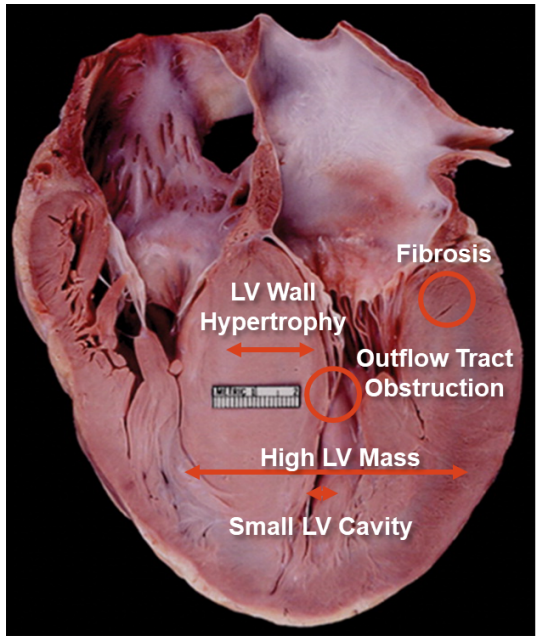
Therapeutic Programs

MYBPC3 Gene Therapy Program

MYBPC3 Gene Therapy Program

Addressing the Leading Genetic Cause of Hypertrophic Cardiomyopathy (HCM) in Adults and Children Affecting > 115K Patients in the US Alone

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

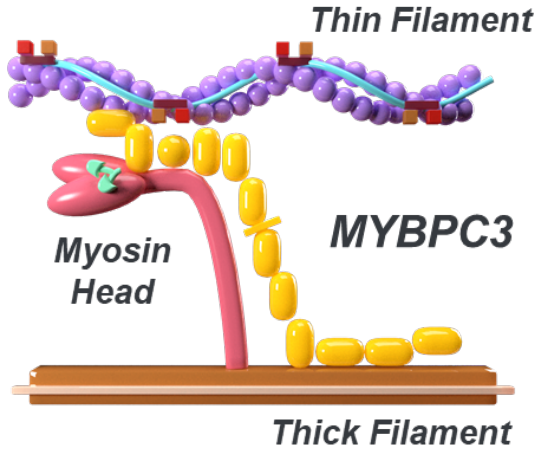
- Heterogeneous presentation
- Heart failure, sudden cardiac death can occur in adults and children
- Premature infant death in the most severe cases

Standard of Care

- No treatments address the underlying genetic cause

Tenaya Product Concept

MYBPC3 Program (TN-201)	
Target Cell	Cardiomyocyte
Modality	AAV
Gene	*MYBPC3*
MOA	"Lock and key", replace a healthy copy of *MYBPC3* in patients with loss-of-function mutations
Stage	IND enabling

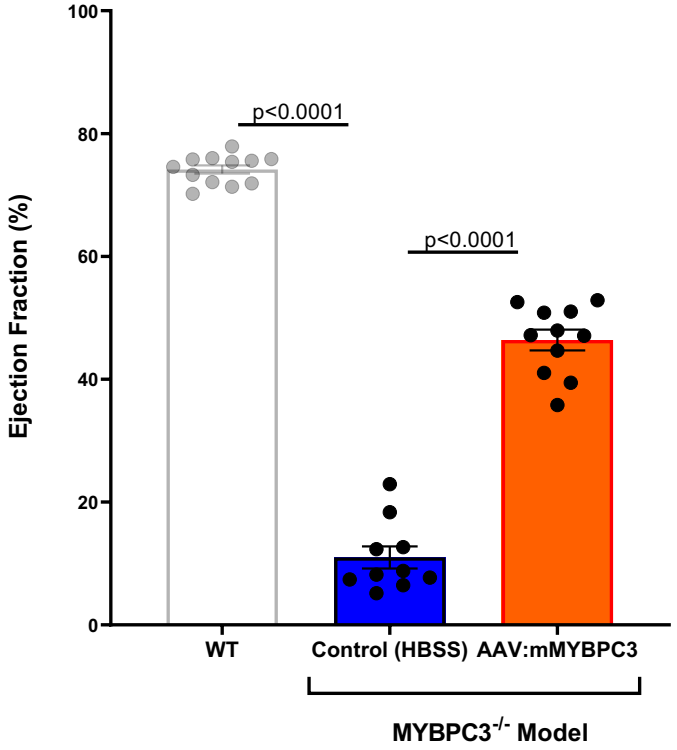


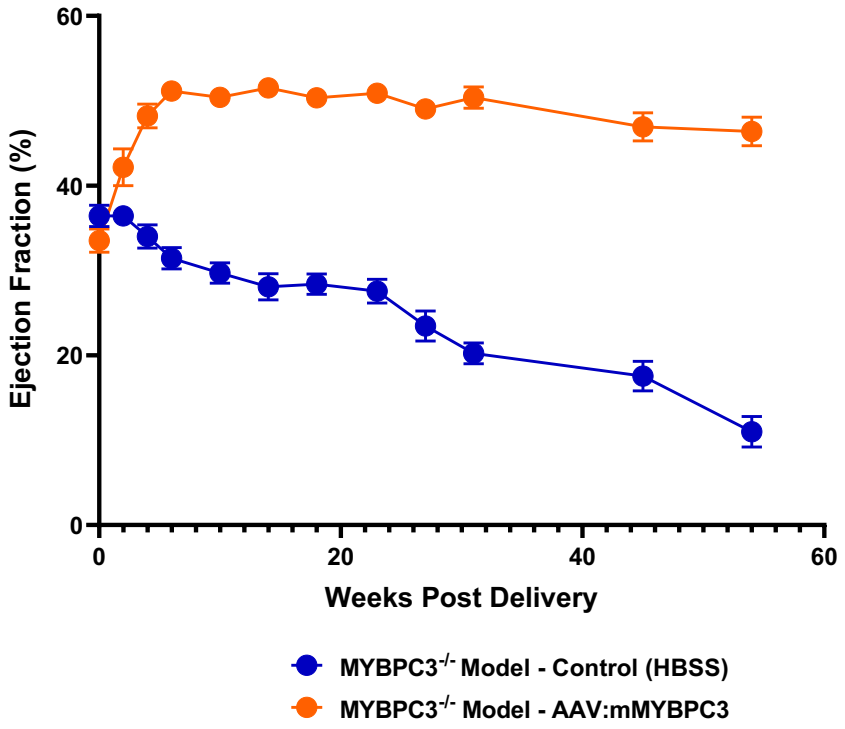
MYBPC3 Gene Therapy Program

Significant Disease Reversal and Survival Benefit Using AAV:MYBPC3 in Severe Model. Effect Maintained 18 Months Post-Treatment After Single Dose.

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

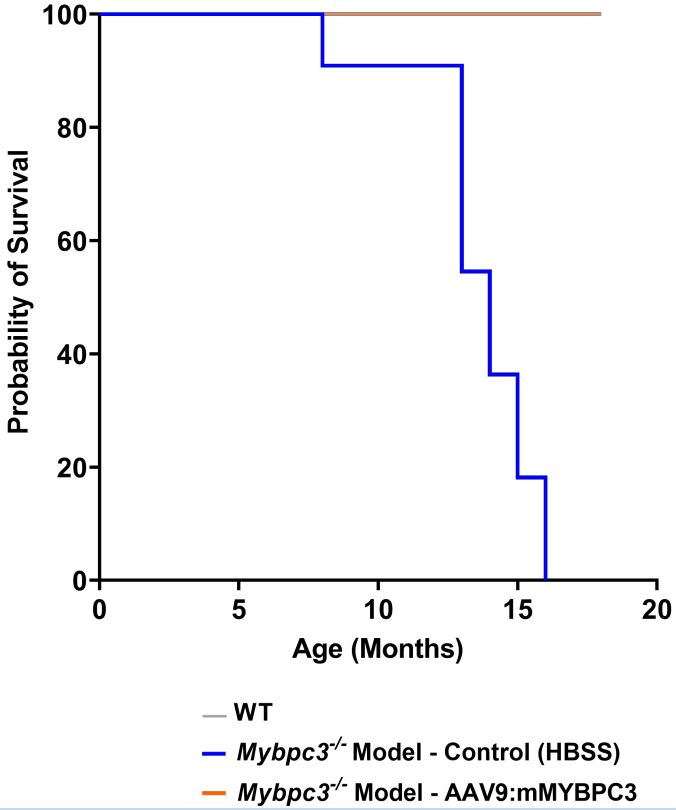
- Animals treated at 2 weeks of age, impact on heart function seen within 6 weeks
- Initial EF improvement of > 20% eventually grows to > 30%





Survival Benefit (18 Months Post-Treatment)

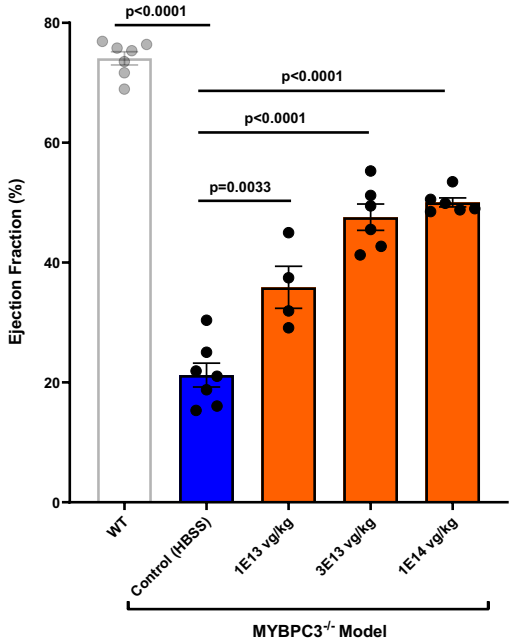
- 100% survival in AAV:MYBPC3 arm
- 100% mortality in control arm



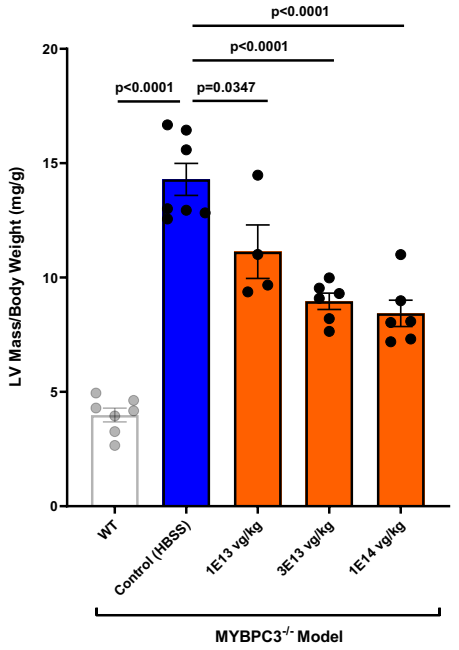
MYBPC3 Gene Therapy Program

Dose Dependent Disease Reversal at Clinically Relevant Doses

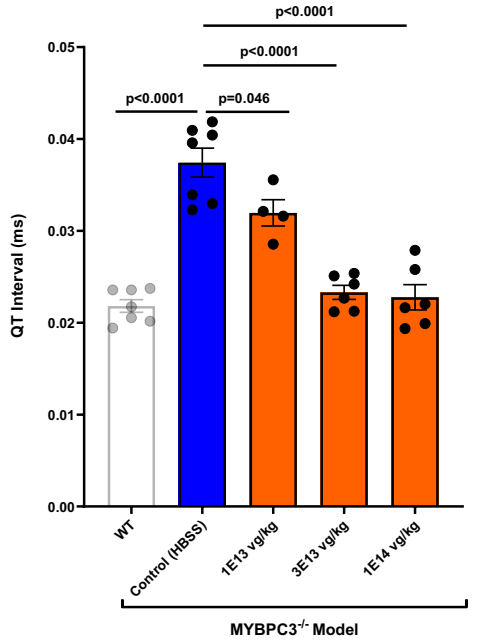
Improvement in Measures of Heart Contraction (8 Months Post Treatment)



Improvement in Measures of Heart Mass (8 Months Post Treatment)



Improvement in Measures of Electrophysiology (8 Months Post Treatment)



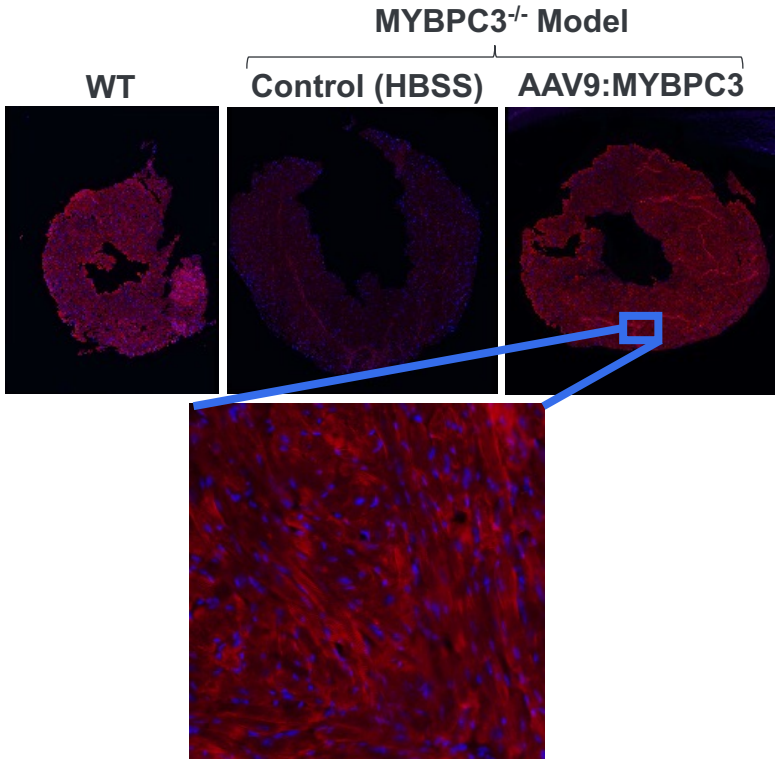
- TN-201 effect appears to plateau around 3E13 vg/kg
- It may be feasible to consider doses for TN-201 in the 3×10^{13} vg/kg to 1×10^{14} vg/kg range during clinical development.
- This dose range is within ranges reported by other companies in connection with an FDA-approved product and clinical studies of product candidates using AAV9 for gene therapy, including where the primary intended organ for the product candidate is the heart.

MYBPC3 Gene Therapy Program

Uniform Distribution, Sufficiently High Heart Penetration, and Normal Levels of Protein Expression Obtained with AAV9:MYBPC3 at Clinically Relevant IV Doses (3E13 - 1E14 vg/kg)

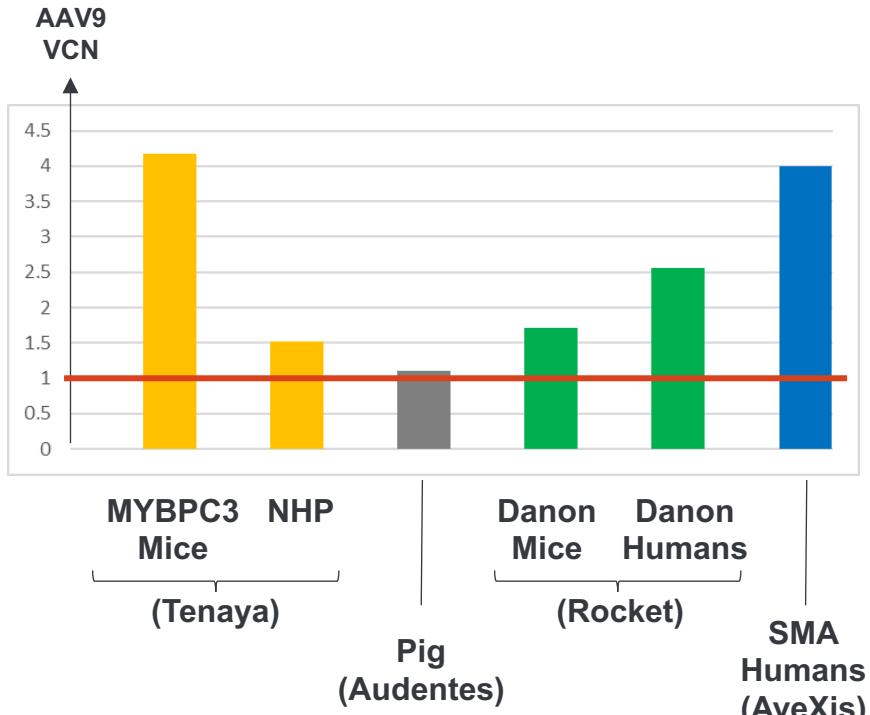
Uniform Distribution of AAV9:MYBPC3 Across Murine Heart

- Broad transduction of cardiomyocytes and MYBPC3 protein expression across myocardium

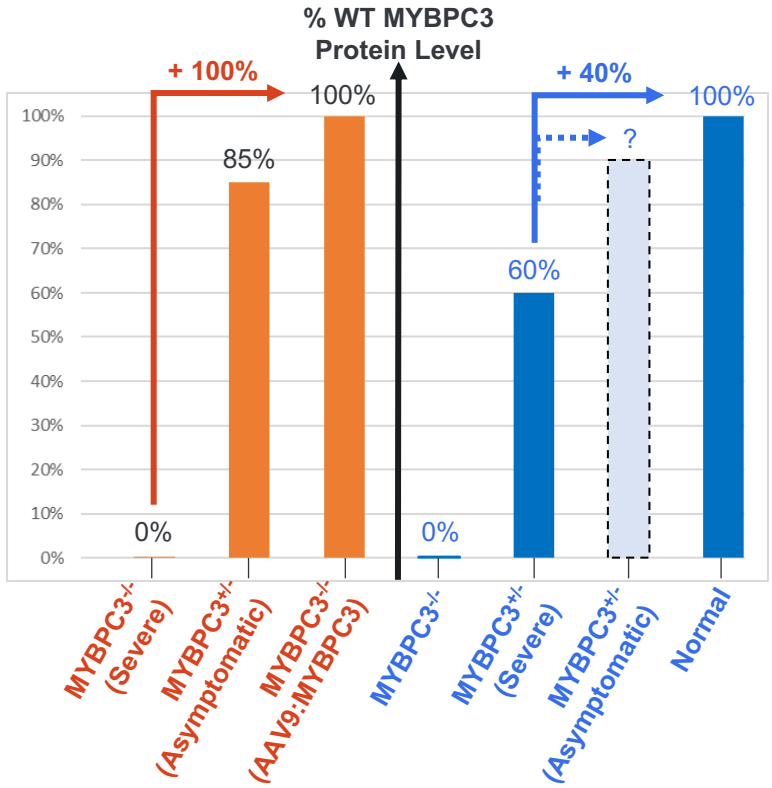


Sufficiently High Heart Transduction with AAV9 Across Multiple Species

- VCN in heart consistently above desired 1 vg/dg threshold (i.e. each cardiomyocyte on average has ≥1 copy of gene delivered)



Sufficiently High Protein Levels with AAV9:MYBPC3 in Murine Heart



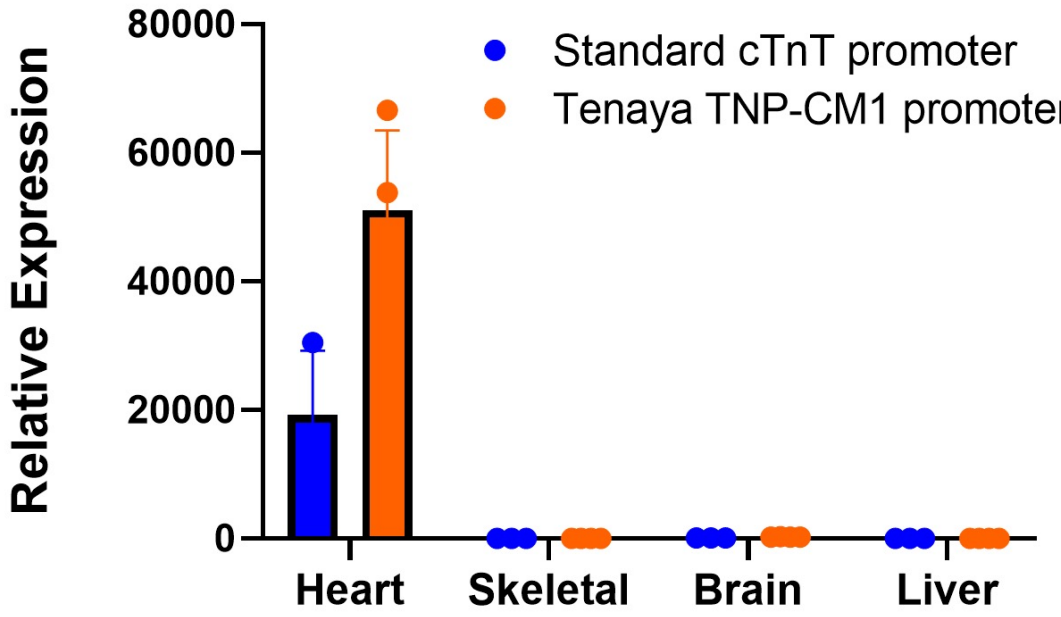
- Achieving 100% WT level expression in MYBPC3$^{-/-}$ model
- Projected need ≤ 40% WT level expression in MYBPC3$^{+/-}$ humans

MYBPC3 Gene Therapy Program

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

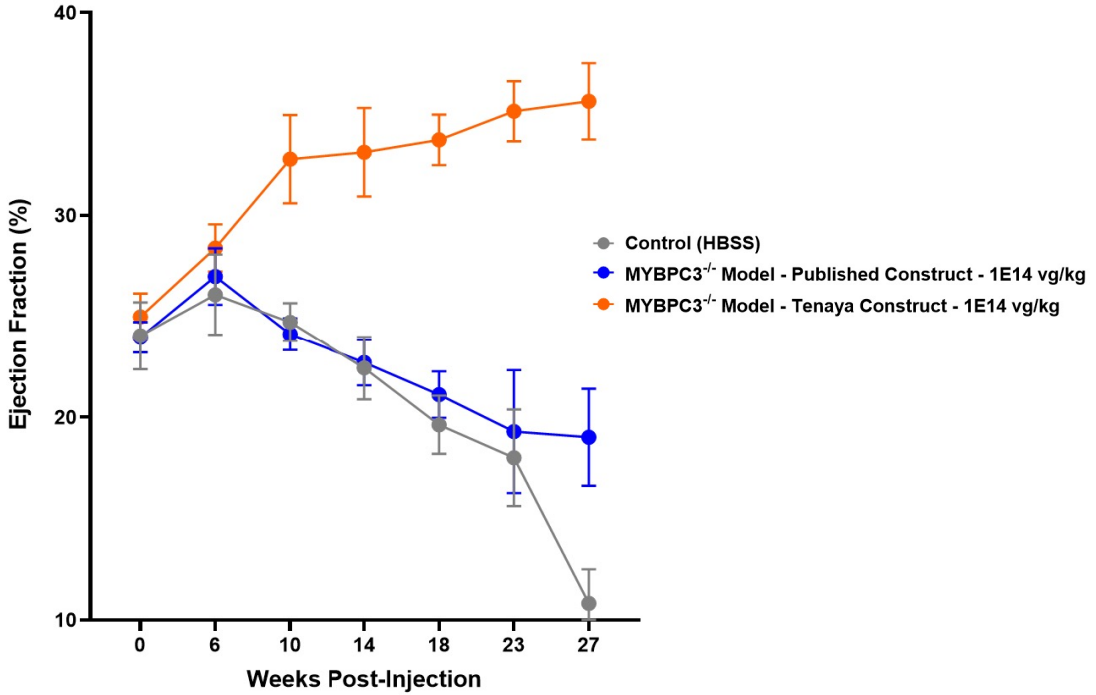
In Vivo Comparison (WT mice)

- 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
- Significantly better heart function in head-to-head comparison of Tenaya construct vs historical construct in relevant disease model



MYBPC3 Gene Therapy Program

Initiated Global Natural History Study to Improve Understanding of Disease Progression and Unmet Need in Individuals Carrying Mutations in the *MYBPC3* Gene, with An Initial Focus on Pediatric Patients

MyClimb Natural History Study

- **Objective is to evaluate the natural history of pediatric patients with cardiomyopathy due to mutations in the *MYBPC3* gene**
  - Ages 0-18 years
  - Includes infants with homozygous and compound heterozygote mutations
  - Retrospective and prospective data collection
  - Expect to involve ~40 sites, initially focused on US and EU
- **Study complements existing disease registries focused on adult patient HCM populations and may support the development of TN-201 in the pediatric patient population**
- **First site activated and first patient enrolled in Q4 2021**

MYBPC3 Gene Therapy Program

TN-201 is in IND-Enabling Studies and expect to file an IND in 2022

Progress

- ✓ Significant and durable reversal out to 18 months
- ✓ Survival benefit
- ✓ Dose-dependent effect at clinically relevant doses
- ✓ Differentiation vs data with other gene therapy constructs
- ✓ US PTO Notice of Allowance supporting TN-201 IP
- ✓ No unexpected safety signals
- ✓ Manufacturing process locked (at 200L scale)
- ✓ Feedback from multiple regulatory agencies
- ✓ Orphan Drug Designation
- ✓ Positive engagement with KOLs & patient adv orgs

Next Steps

✓ Initiated IND-enabling studies	2021
✓ Plan to initiate global natural history study	2021
❑ Expect to file IND	2022

TENAYA THERAPEUTICS

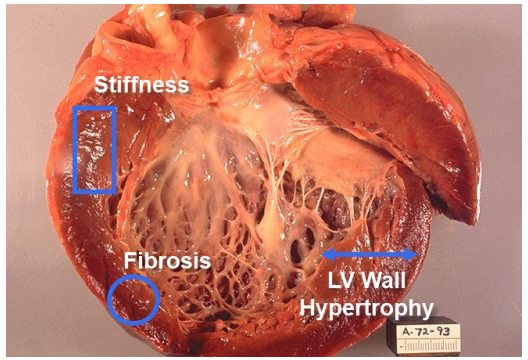
Therapeutic Programs

HDAC6i Small Molecule Program

HDAC6i Small Molecule Program

Addressing HFpEF, the Leading Cause of Heart Failure Affecting > 3MM Patients in US Alone

Disease Overview



Pathophysiology

- Poor relaxation and filling of the left ventricle (diastolic dysfunction)
- High overlap with diabetes and obesity

Disease Symptoms and Severity

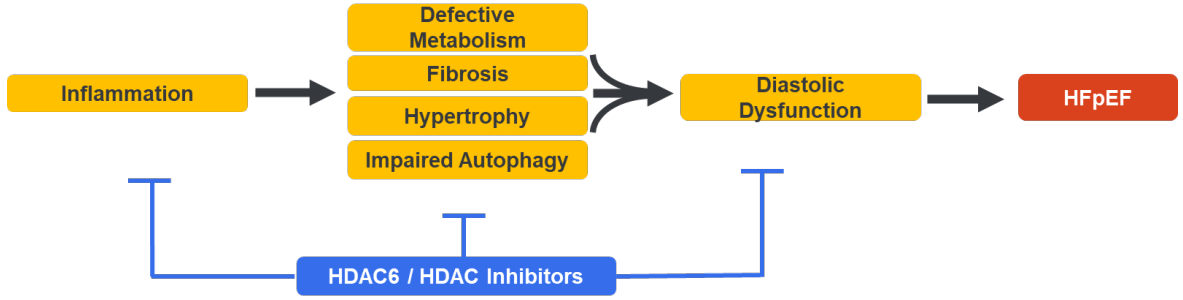
- ~24% of HFpEF population has NYHA Class III or IV disease, impacting QOL and limiting physical activity
- Mortality for HFpEF patients who were previously hospitalized as high as 75% over 5-year period

Standard of Care

- Few effective treatments; no disease modifying therapies that improve clinical outcomes

Tenaya Product Concept

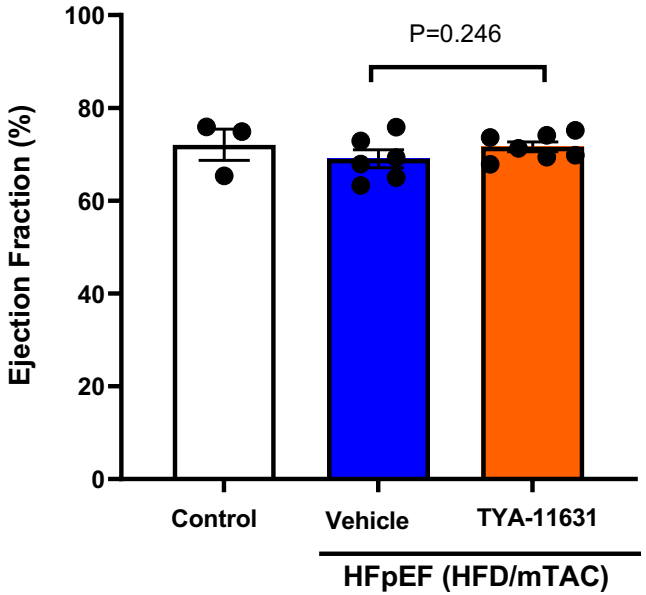
HDAC6i Program (TYA-11631)	
Target Cell	Not a cell-specific effect. Target is in many cells, not just limited to heart cells.
Modality	Small molecule
Target	HDAC6
MOA	Potential multi-modal effect involving inflammation, hypertrophy, fibrosis, lipid & metabolic pathways, insulin sensitivity, autophagy, and protein quality control
Stage	IND enabling



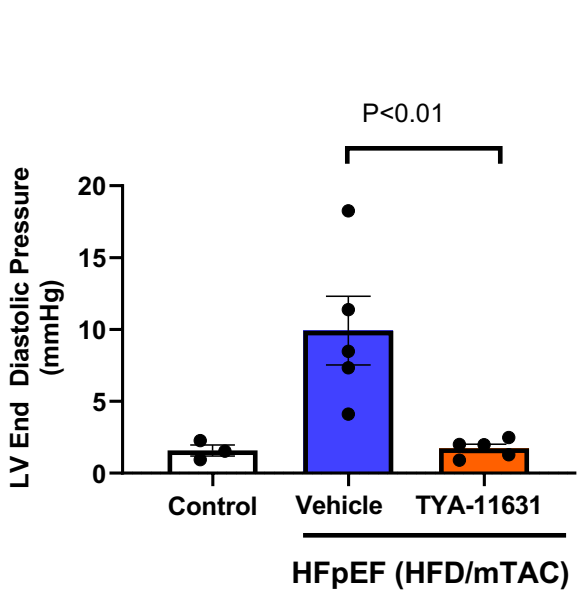
HDAC6i Small Molecule Program

Reversal of Diastolic Dysfunction (to Control Levels) Demonstrated in Multiple HFpEF Models

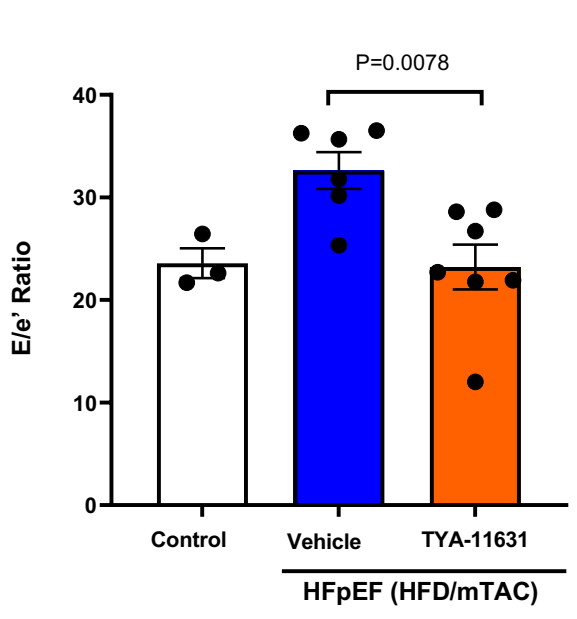
Preserved Ejection Fraction

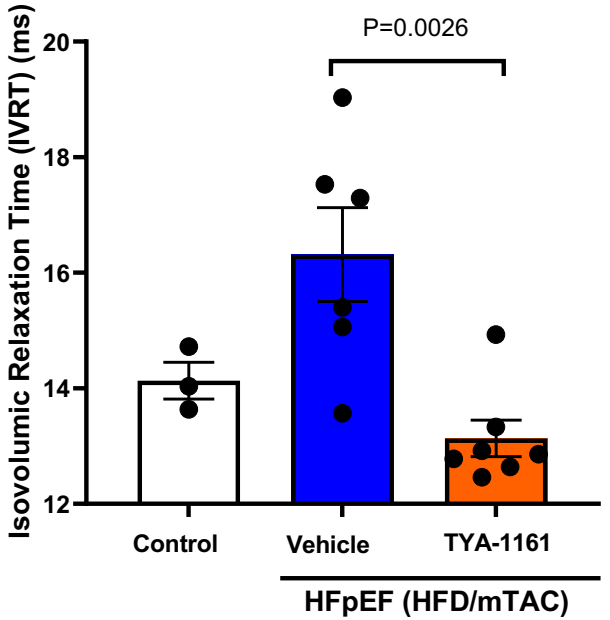


Improvement in LV End Diastolic Pressure



Improvement in LV Relaxation and Filling



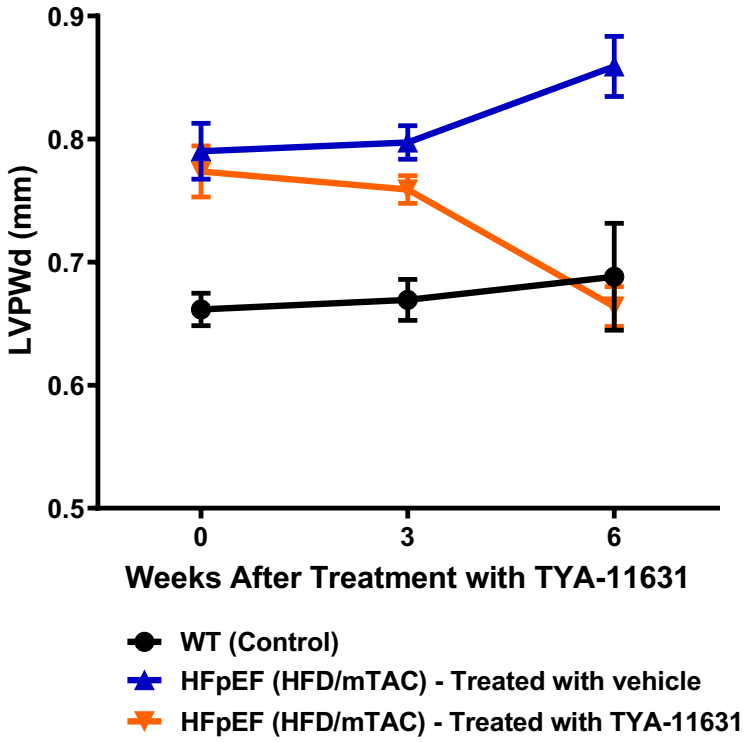


- Model: Pressure overload (mTAC) + 8 weeks of high fat diet (HFD)
- Data after 6 weeks of treatment

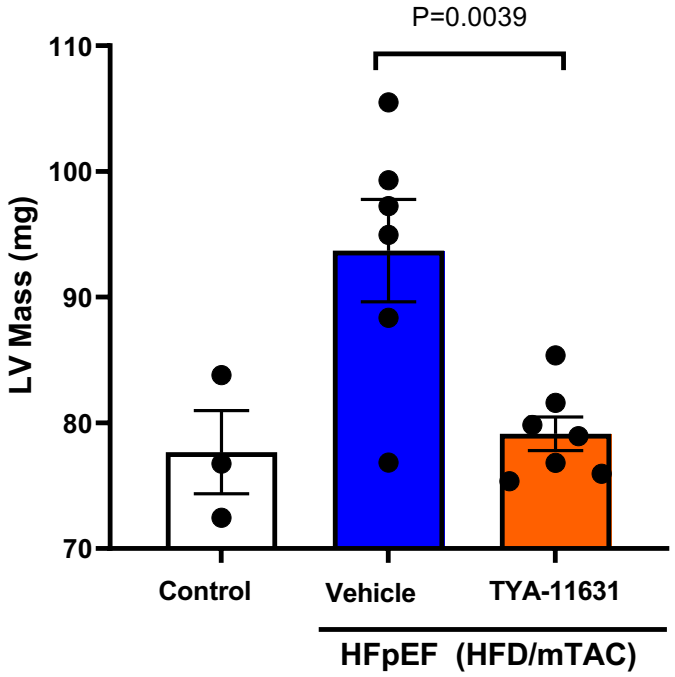
HDAC6i Small Molecule Program

Reversal of Adverse Organ Remodeling (to Control Levels) Demonstrated in Multiple HFpEF Models

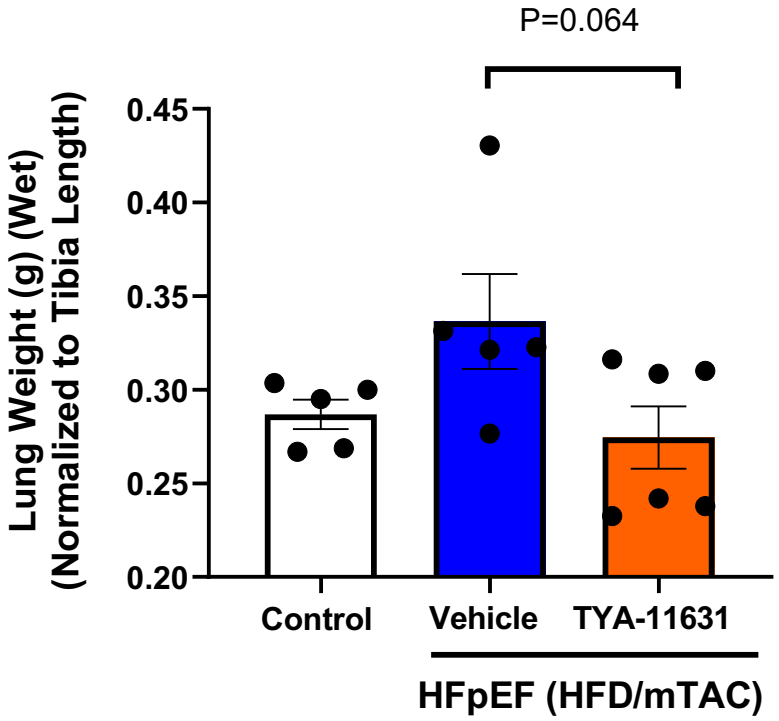
Improvement in LV Wall Thickness



Improvement in LV Mass



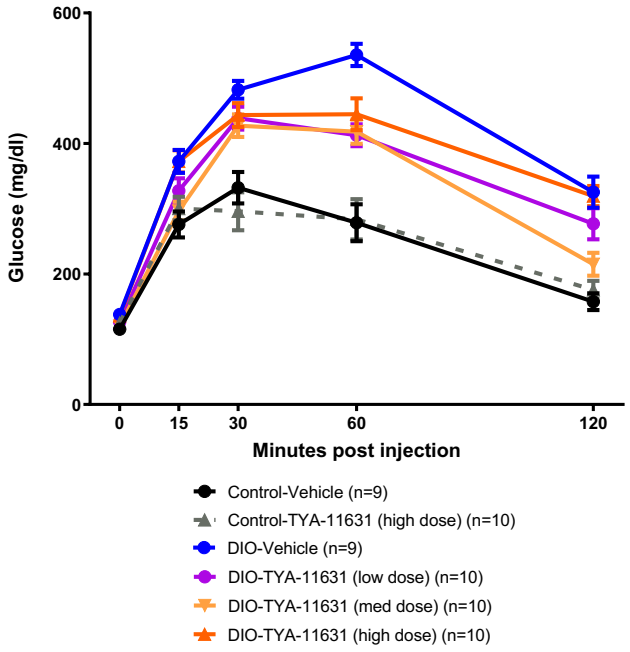
Improvement in Lung Mass



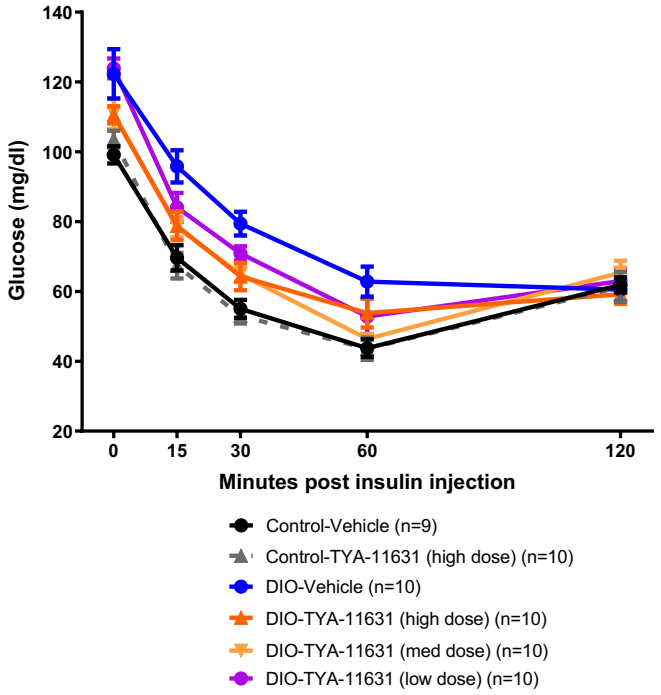
HDAC6i Small Molecule Program

TYA-11631 Improves Glucose Tolerance, Insulin Resistance, and Inflammation in Diet Induced Obesity (DIO) Mouse Model in Dose Dependent Manner, Potentially Addressing Important Link Between HFpEF and Diabetes

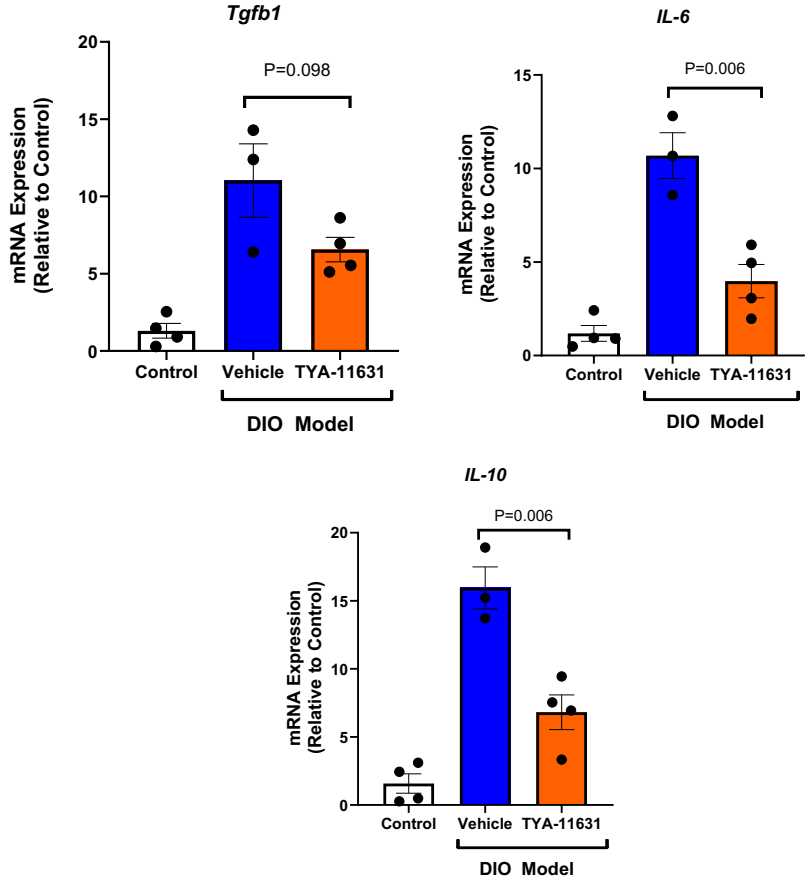
Improvement in Glucose Tolerance After Single Dose of TYA-11631



Improvement in Insulin Sensitivity After TYA-11631 Treatment for 4 weeks



Reduction in Inflammatory Markers After a Single Dose of TYA-11631

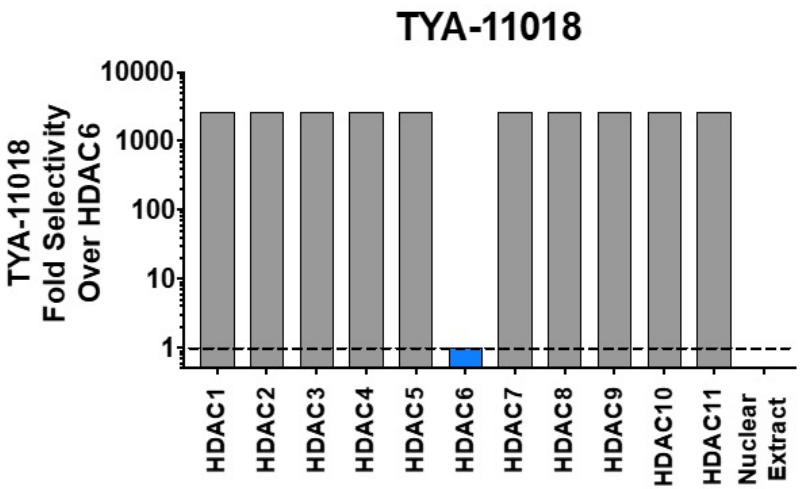


HDAC6i Small Molecule Program

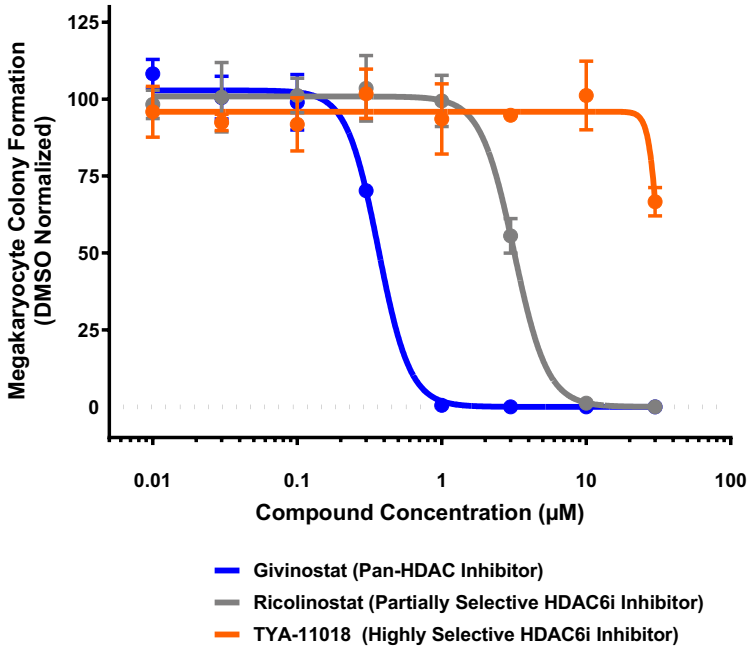
High Specificity for HDAC6 vs Other HDACs Supports Safety Attributes

TYA-11018 demonstrates 1000x Biochemical Selectivity for HDAC6 vs. Other HDACs

- "HDAC" denomination is a misnomer as HDAC6 is a cytoplasmic enzyme primarily involved deacetylation of α-tubulin
- Tenaya compounds have very high selectivity for HDAC6 over other HDACs



Significantly Reduced Risk of Thrombocytopenia vs Other Pan-HDACi or HDAC6i



Overall Clean Profile from In Vitro and In Vivo Testing

- No cellular toxicity observed in mammalian cell culture
- No genotoxicity observed *in vitro* mammalian cell micronucleus test or AMES test
- No treatment-related mortality, adverse effects in clinical signs, body weight, food consumption, clinical pathology, and pathology found in pilot rat or cyno tox studies

HDAC6i Small Molecule Program

TYA-11631 is in IND-Enabling Studies with Several Important Upcoming Milestones

Progress

- ✓ Lead chemical compound selected (TYA-11631)
- ✓ Disease reversal in two different models of HFpEF and one model of gDCM
- ✓ Demonstration of multi-modal mechanism of action relevant to HFpEF pathophysiology
- ✓ IP filed on multiple chemical series
- ✓ No safety signals in multiple species (rat, cyno)
- ✓ Robust PD marker identified that can be measured in human plasma during clinical studies for early measure of target engagement

Next Steps

✓ Initiated IND-enabling studies	2021
✓ Plan to initiate cGMP manufacturing	2021
❑ Expect to file IND	2022

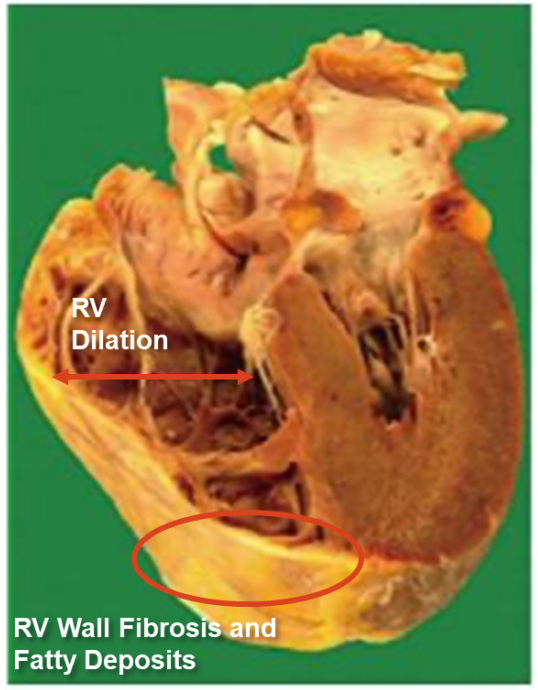
Therapeutic Programs

PKP2 Gene Therapy Program

PKP2 Gene Therapy Program

Addressing the Leading Genetic Cause of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) Affecting >70K Patients in the US Alone

Disease Overview



Pathophysiology

- Mutations in *PKP2* involve desmosomes responsible for holding CMs together
- Fibrofatty muscle replacement, atrophy, chamber dilation, typically starting in right ventricle

Disease Symptoms and Severity

- Average patient presents in young adulthood (< 40 yo) with symptoms of arrhythmias (palpitations, lightheadedness, and fainting).
- Important cause of cardiac arrest in young patients (median cardiac arrest 25 yo)

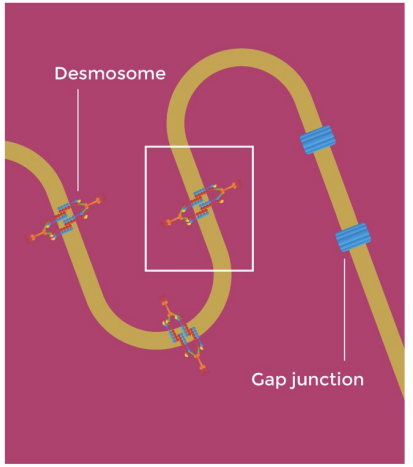
Standard of Care

- No treatments address underlying genetic cause

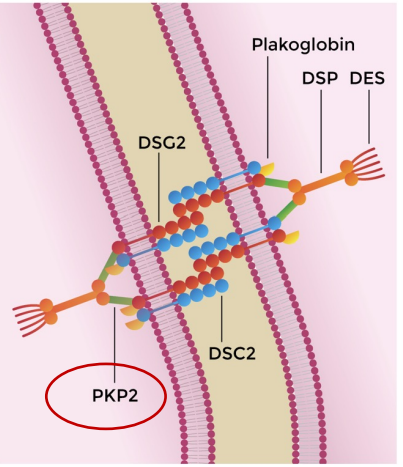
Tenaya Product Concept

PKP2 Gene Therapy Program	
Target Cell	Cardiomyocyte
Modality	AAV
Gene	*PKP2*
MOA	"Lock and key", replace a healthy copy of *PKP2* in patients with loss-of-function mutations
Stage	Candidate selection

DESMOSOMES & GAP JUNCTIONS



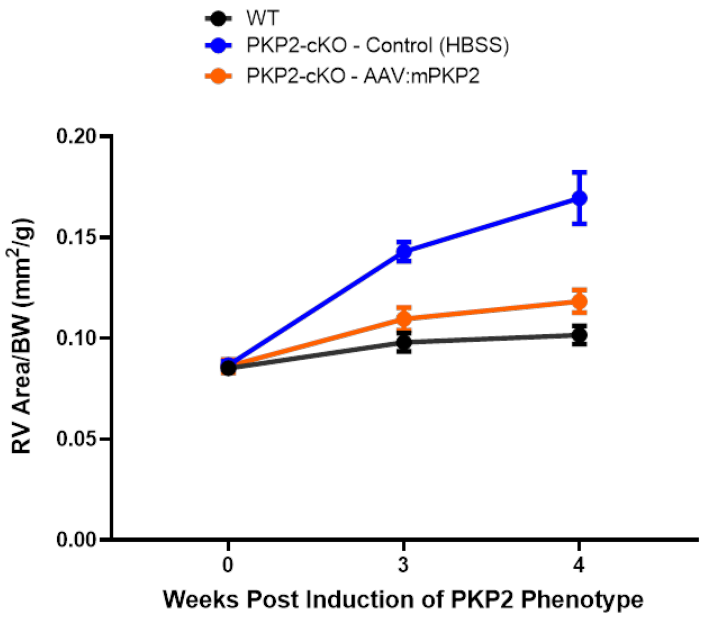
DESMOSOME STRUCTURE



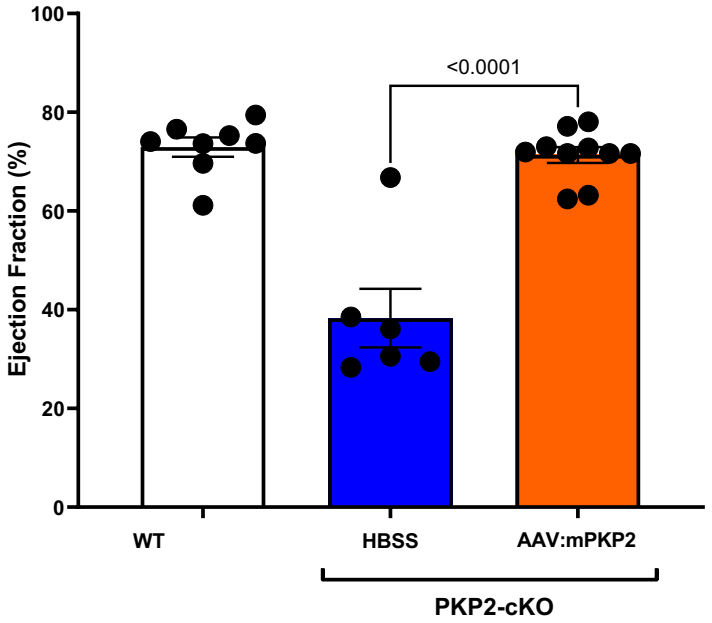
PKP2 Gene Therapy Program

Disease Modification and Survival Benefit With AAV:PKP2

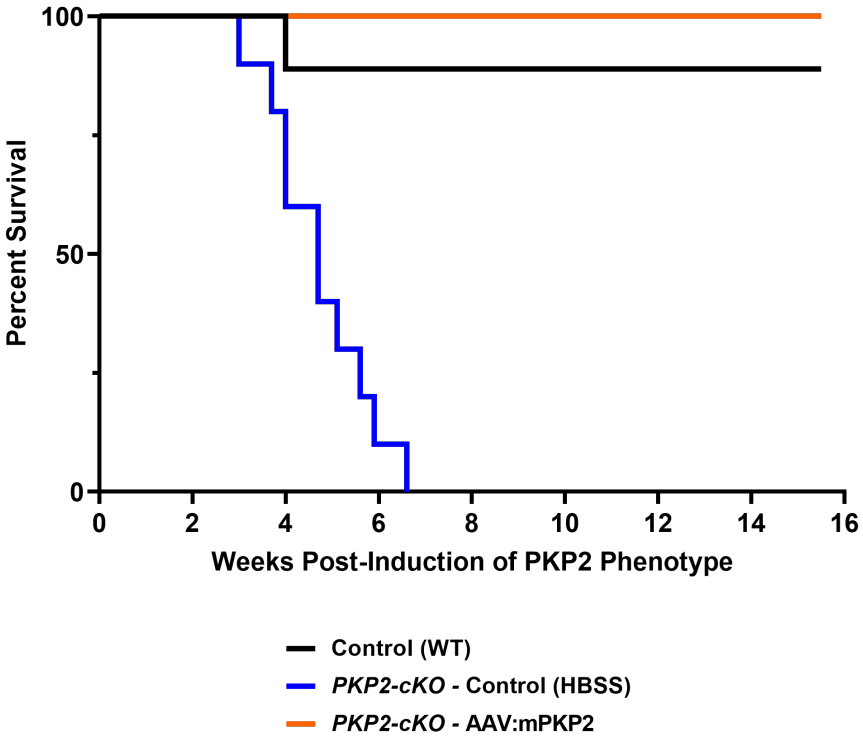
Prevention of Right Ventricle Enlargement



Prevention of Decline of Left Ventricle Function

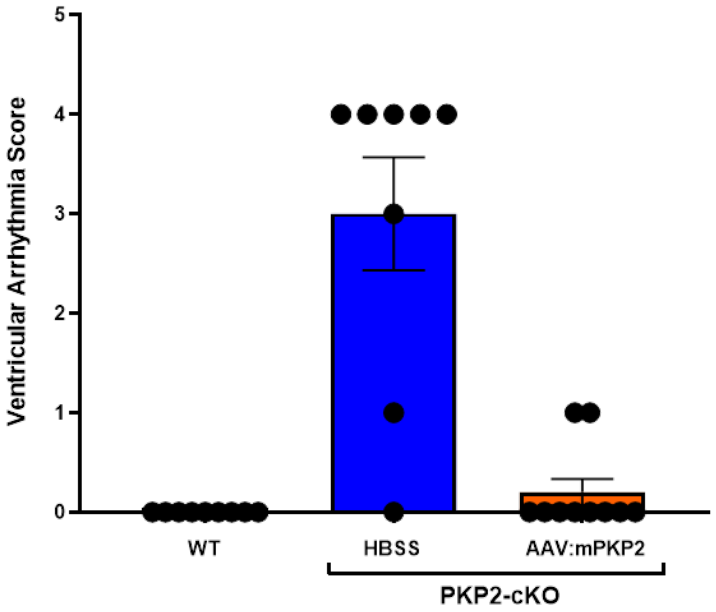


Survival Benefit



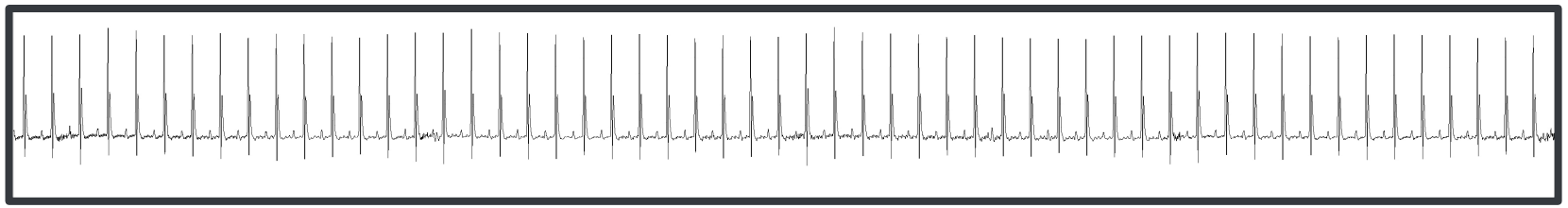
PKP2 Gene Therapy Program
Prevention of Arrhythmia Using AAV:PKP2

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

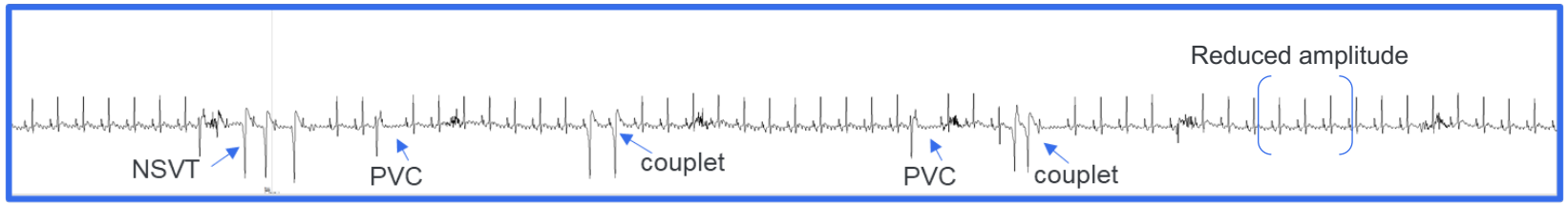


- Ventricular Arrythmia Score includes NSVT, triplets, couplets, AV block and the frequency of PVCs

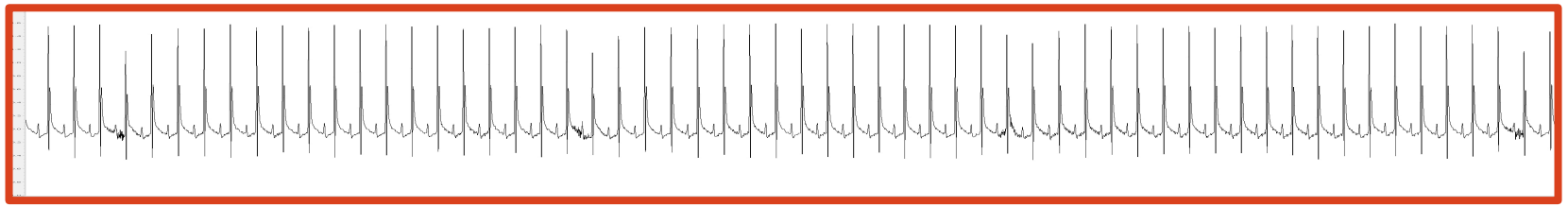
WT: Normal Sinus Rhythm



PKP2-cKO – Control (HBSS): Abnormal Ventricular Beats (NSVT & PVCs)



PKP2-cKO – AAV:mPKP2: Normal Sinus Rhythm



TENAYA™ THERAPEUTICS

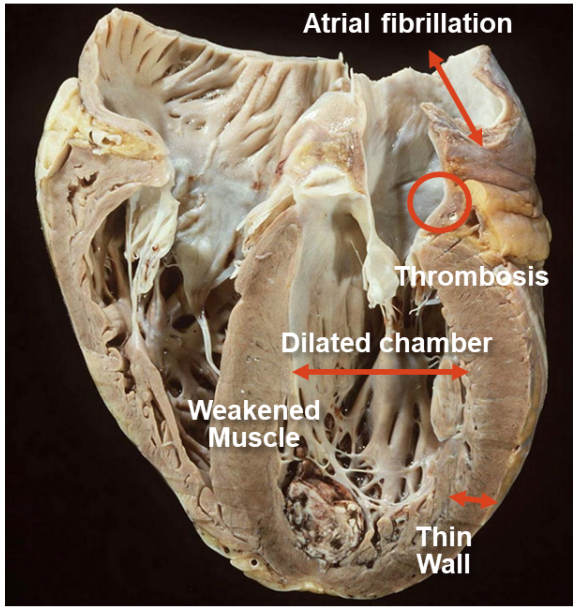
Therapeutic Programs

DWORF Gene Therapy Program

DWORF Gene Therapy Program

Addressing Dilated Cardiomyopathy (DCM) Affecting > 1MM Patients in US Alone via AAV-Delivery of DWORF to Improve Heart Remodeling and Function

Disease Overview



Pathophysiology

- Thin LV walls, enlarged chamber, insufficient contraction, reduced blood flow, ventricular arrhythmias

Disease Symptoms and Severity

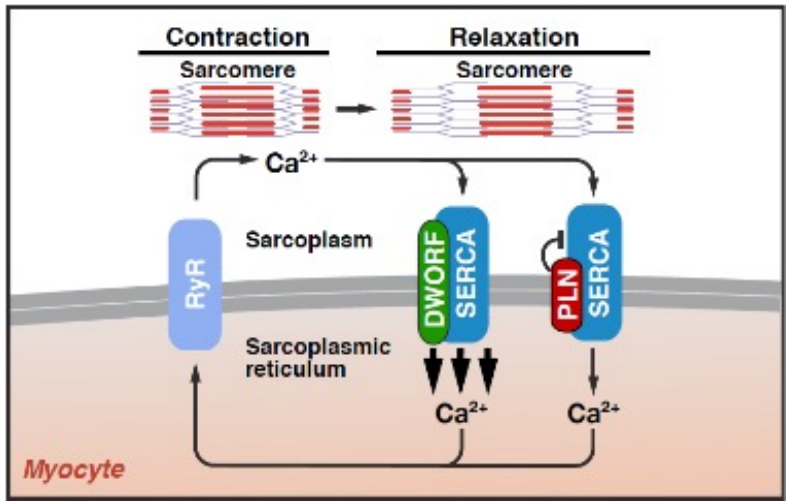
- Progressive and life-threatening disease with premature morbidity and mortality
- Leading cause of need for heart transplants

Standard of Care

- DCM patients are treated with SOC therapies developed for HFrEF
- Premature morbidity and mortality rates remain unacceptably high

Tenaya Product Concept

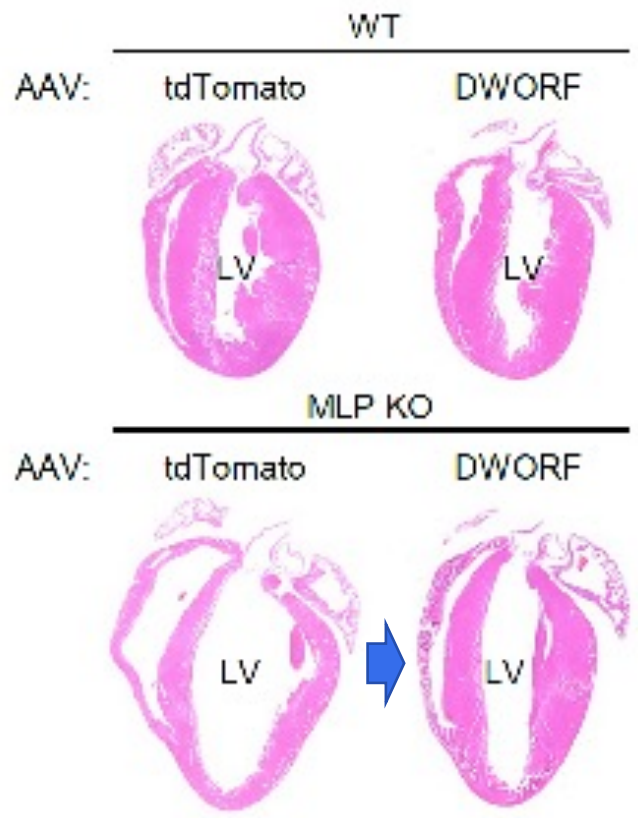
DWORF Gene Therapy Program	
Target cell	Cardiomyocyte
Modality	AAV
Gene	*DWORF*
MOA	DWORF binds SERCA2a Ca^{2+} pump leading to stronger contractions
Stage	Candidate selection



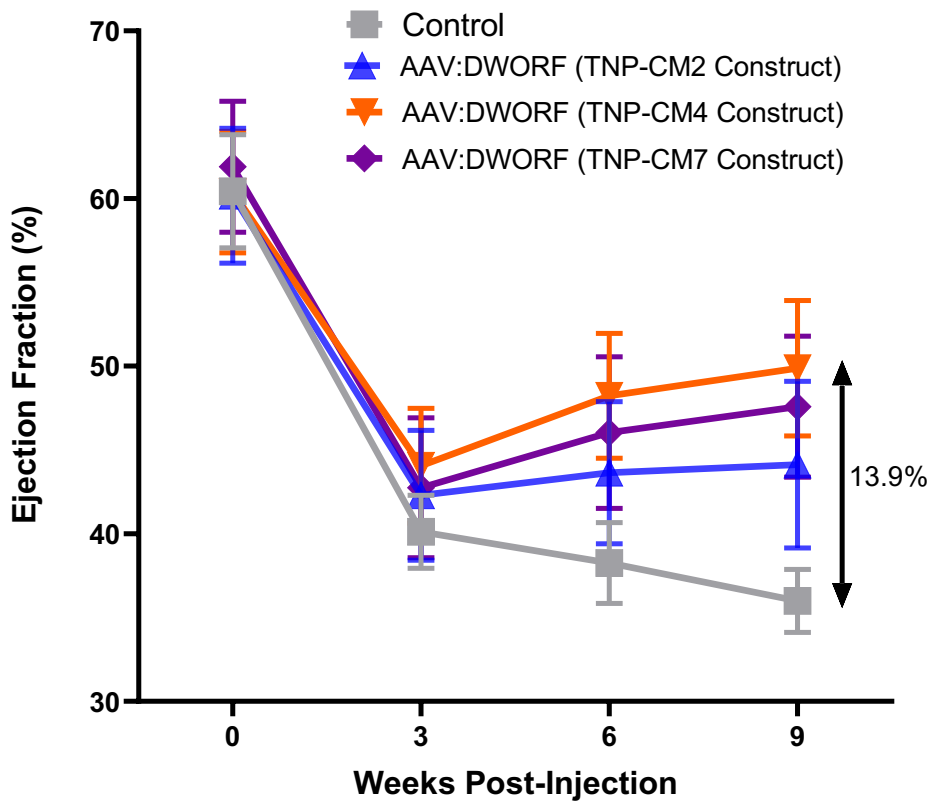
DWORF Gene Therapy Program

In Vivo Proof-of-Concept for Effect of AAV:DWORF Over-Expression on Improvement of Heart Size and Heart Function of Mouse Model of gDCM (MLP KO)

Improvement in Heart Remodeling with AAV:DWORF in MLP KO Model (Olson Lab)



Improvement in Heart Function with AAV:DWORF in MLP KO Model (Tenaya Data)



TENAYA™ THERAPEUTICS

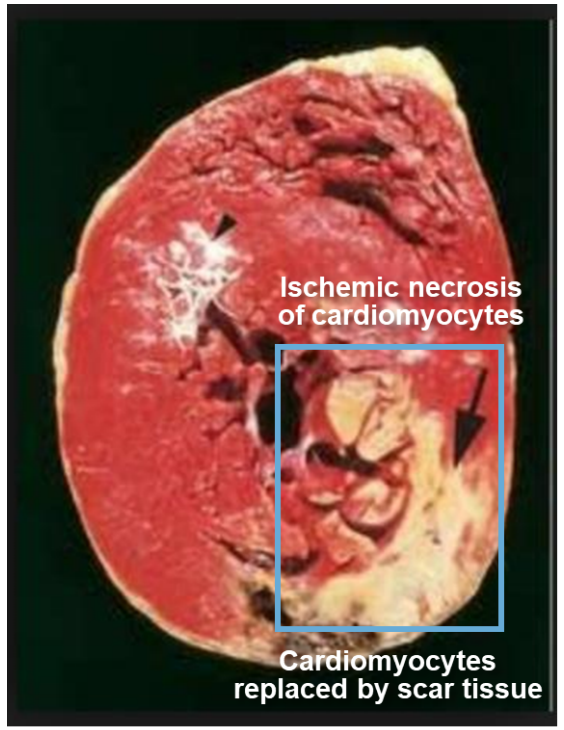
Therapeutic Programs

Reprogramming Cellular Regeneration Program

Reprogramming Cellular Regeneration Program

Replacing Lost Muscle Cells After Myocardial Infarction (MI) that Affects > 800K Patients Each Year in the US Alone with AAV-Based Approach to Cardiomyocyte Regeneration

Disease Overview



Pathophysiology

- Myocardial infarction (MI) can kill up to 1 billion CMs (25% of LV)
- Loss of CMs permanently impairs contraction, leading heart failure and potentially fatal arrhythmias

Disease Symptoms and Severity

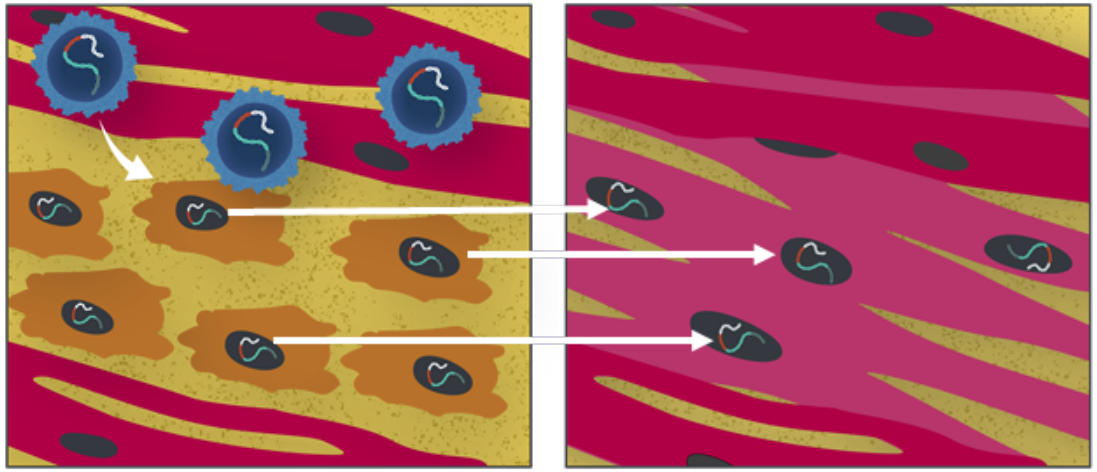
- ~ 5%-10% of MI survivors die within first year and ~50% are re-hospitalized within one year.

Standard of Care

- Treatments reduce the recurrence of MI or reduce the size of an acute MI for patients who arrive on time
- No known therapies replace the lost CMs after MI

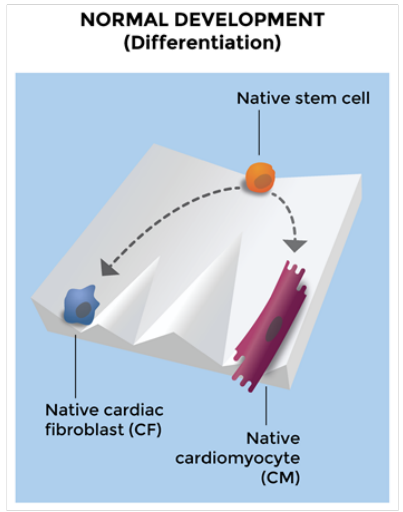
Tenaya Product Concept

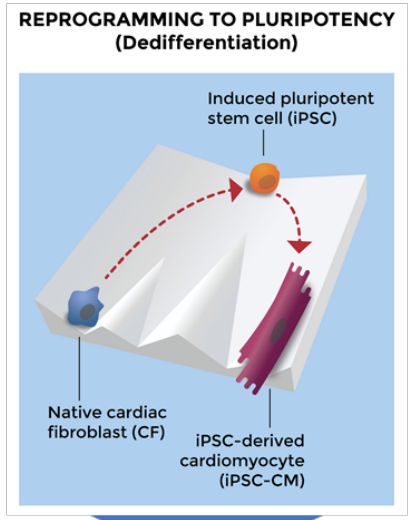
Reprogramming Program	
Target cell	Cardiac fibroblast (CF)
Modality	AAV
Genes	Myocardin$^{\Delta 3}$ + ASCL1 + miR-133
MOA	Convert resident CFs around scar area to new CMs that connect with existing CMs leading to stronger contractions
Stage	Candidate selection

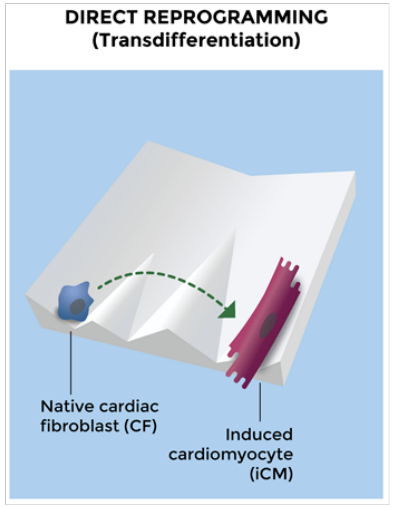


Reprogramming Cellular Regeneration Program
Overview of Direct Reprogramming Approach to Cellular Regeneration

Waddington Model for Cellular Differentiation







Reprogramming to Pluripotency

- Expression of 4 transcription factors to convert any somatic cell into an induced pluripotent stem cell (iPSC)
- Idea can be used to *indirectly* create any cell type in the body by first going through the iPSC state
- First established by Shinya Yamanaka (2006)

Direct Reprogramming

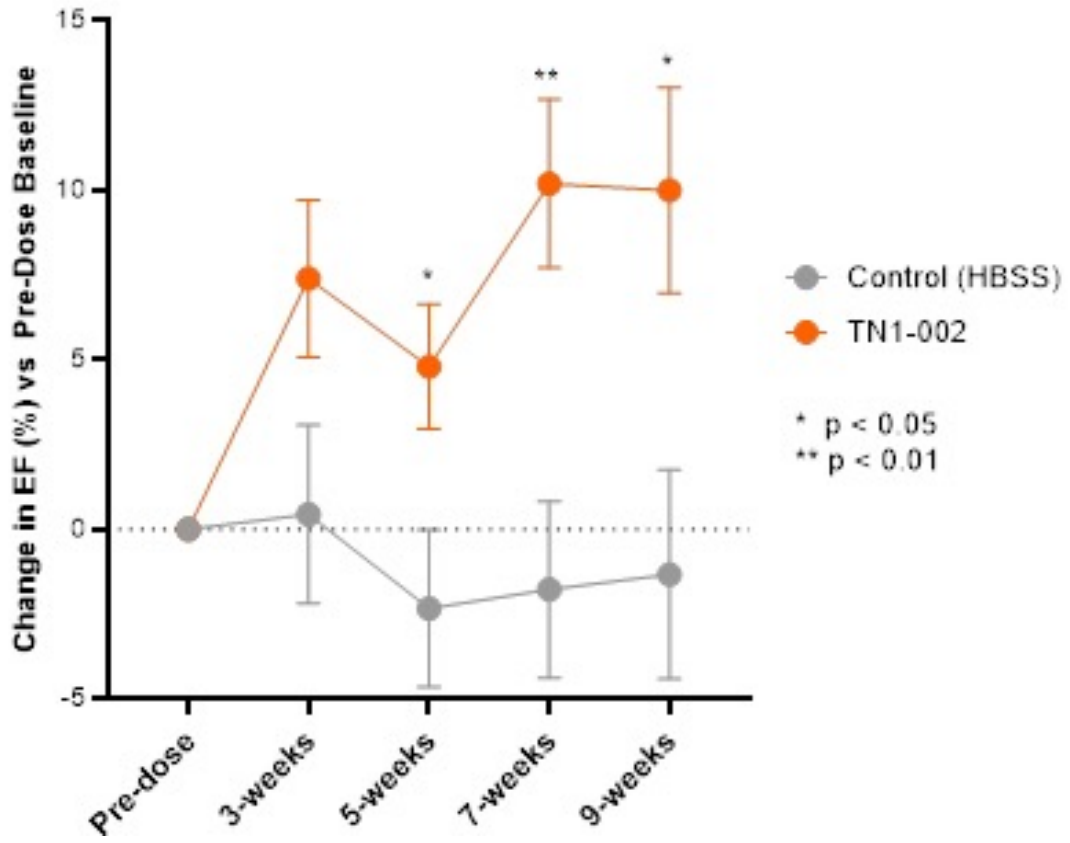
- Expression of specific factors to directly convert one somatic cell type to another without going through an intermediate pluripotent state
- Idea can be used to *directly* reprogram cardiac fibroblasts to create new cardiomyocytes
- First established by Deepak Srivastava (2010)

Tenaya Therapeutics Approach

Reprogramming Cellular Regeneration Program

In Vivo Proof-of-Concept with TN1-002 Construct in Pig Model of Heart Failure Due to Prior MI

Significant Improvement of Heart Function and Heart Morphology in Human-Sized Heart



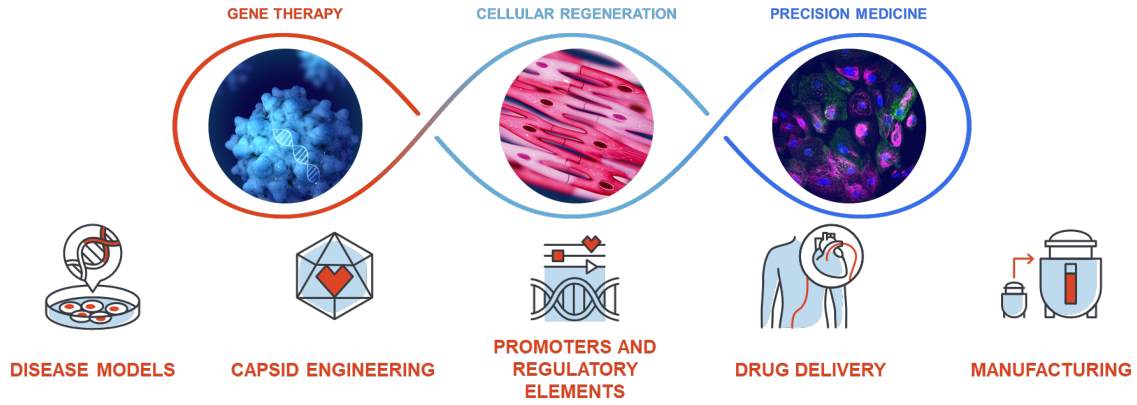
- >10% improvement in absolute ejection fraction (EF) vs pre-treatment baseline and vs controls
  - TN1-002 treated animals ΔEF range from -2% to +24% (vs -10% to +13% for untreated controls)
  - 7 / 10 treated animals were considered “responders” (ΔEF > +5%)
  - ΔEF in responders accompanied by improvement in other parameters (e.g. stroke volume, LV size, strain analysis, and scar size)
  - ΔEF in responders correlates to TN1-002 transgene expression
- Results compare favorably to other published data for large animal models for cell or gene therapies for heart disease
- Meta-analysis of multiple HFrEF therapies illustrates each ΔEF of +5% expected to reduce mortality by ~15%

Anticipated Tenaya Catalysts

	2021	2022	2023+
Programs	✓ **MYBPC3**: Plan to launch natural history study ✓ **HDAC6i**: Plan to initiate cGMP manufacturing	• **MYBPC3**: Expect to file IND • **HDAC6i**: Expect to file IND	• **PKP2**: Expect to file IND • **DWORF**: Expect to file IND • **Reprogramming**: Expect to file IND

Platforms & Capabilities

New Programs



Cash Balance of $280.5MM*: Sufficient to Fund At Least Into 2H 2023

* Cash, cash equivalents and investment in marketable securities as of September 30, 2021