FIRST DEMONSTRATION OF SIGNIFICANT & DURABLE IMPROVEMENT OF CARDIAC FUNCTION IN PIG MODEL OF ISCHEMIC HEART FAILURE WITH DIRECT REPROGRAMMING DELIVERED PRECISELY TO INFARCT BORDER VIA GUIDED INTRAMYOCARDIAL INJECTION CATHETER

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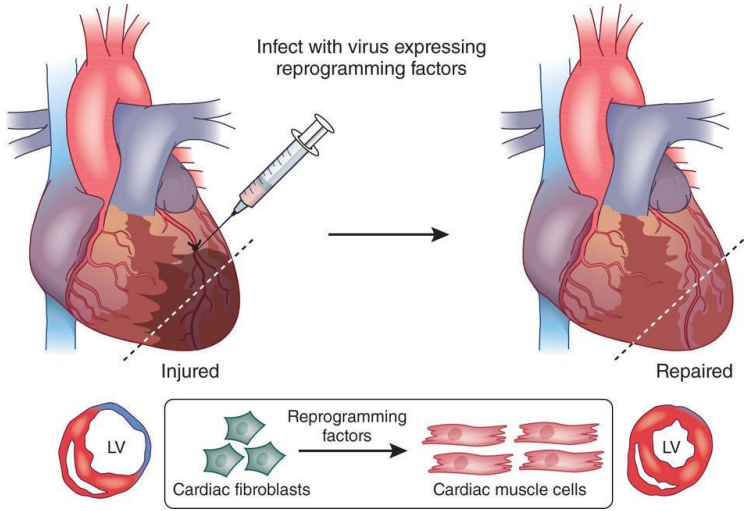
Disclosure: Kathy Ivey is an employee of and shareholder in Tenaya Therapeutics, Inc.

CARDIAC REPROGRAMMING AS A POST-MYOCARDIAL INFARCTION (MI) THERAPY

Rationale for Cardiac Reprogramming

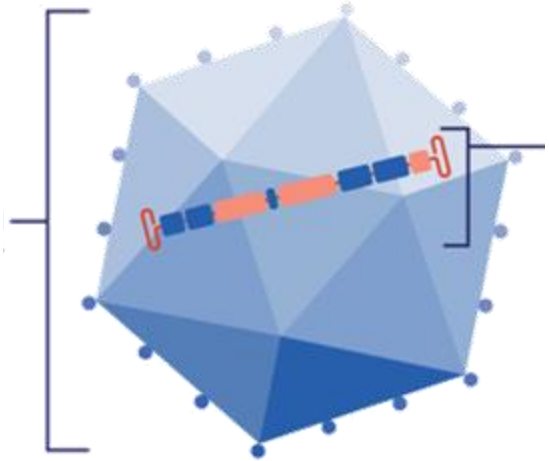
- Myocardial infarction (MI) can kill up to 1 billion cardiomyocytes (CMs) – up to 25% of left ventricle (LV)
- Adult CMs are post-mitotic and do not divide
- Loss of CMs permanently impairs contraction, leading to heart failure and potentially fatal arrhythmias
- Cardiac fibroblasts (CFs) proliferate, and induce scarring and fibrosis after injury
- CFs comprise ~50% of cardiac cells, post-MI – providing a reprogrammable pool
- Proof-of-concept demonstrated in rodent models of MI[1]

In Vivo Cardiac Reprogramming to Convert Fibroblasts into Cardiomyocytes after MI



1. Qian et al., *Nature*, 2012; Song et al., *Nature,* 2012; Inagawa et al., *Circ Res*, 2012; Mathison et al., *J Am Heart Assoc.,* 2012; Jayawardena et al., *Circ Res.,* 2015
2. Nam et al., *Nature Medicine*, 2013

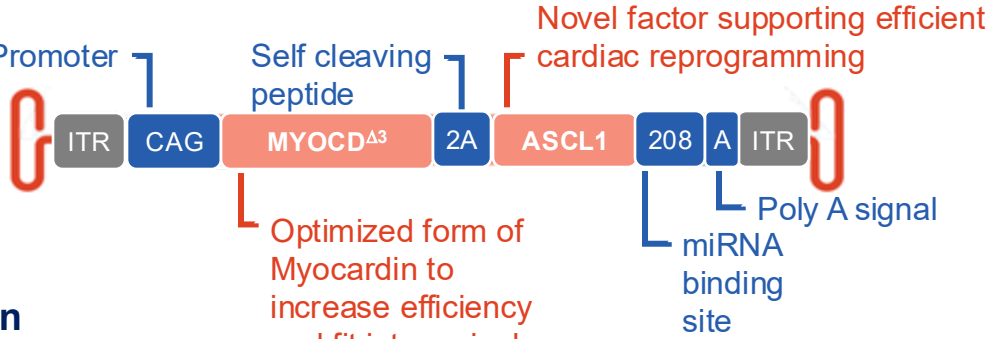
TN-101: A CARDIAC REPROGRAMMING GENE THERAPY IN A SINGLE AAV



AAV5 Capsid

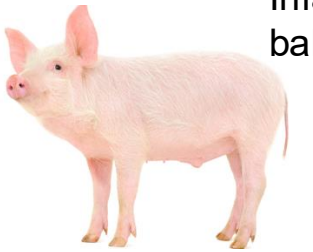
Expression Cassette

Encapsulates specific combination of genes to reprogram cells



Zhou et al., *Circulation*, 2023

OPEN HEART INJECTION OF TN-101 IN PIG MODEL OF CHRONIC MI



Yucatan mini-pig

Infarction induced via balloon occlusion

Open-chest direct epicardial injection of TN-101

Total Dose: 1E14 vg/pig

Day 0
MI

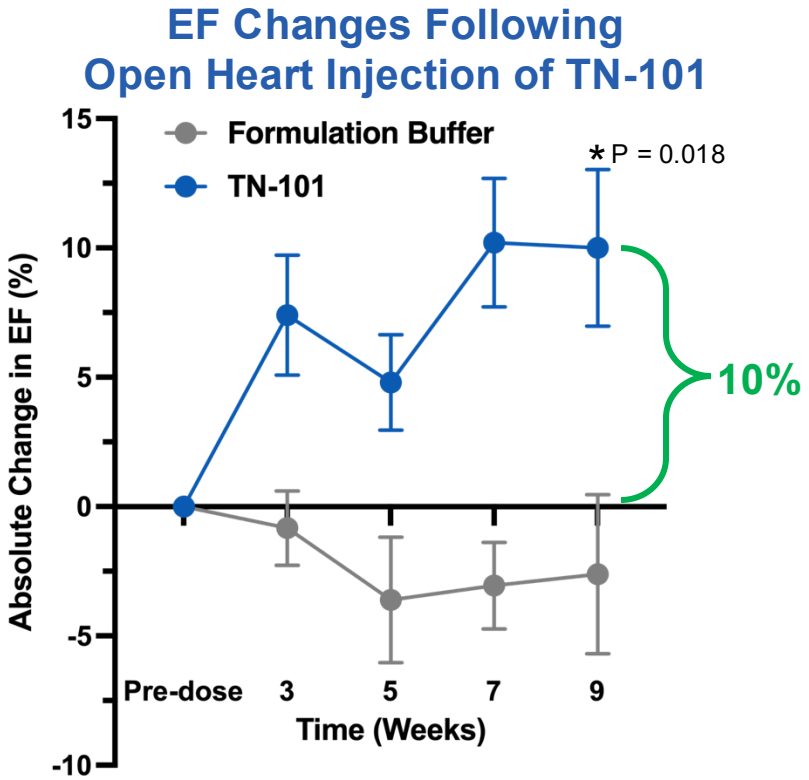
Week 4
Dose

Week 13
Necropsy

9-week in-life data collection

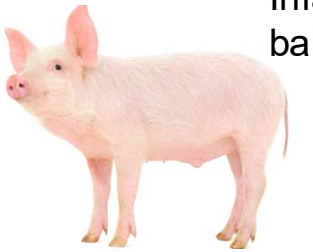
Echo, EKG, and blood collection at baseline, pre-dose, and 3-, 5-, 7-,and 9-weeks post-delivery

TN-101 IMPROVED EJECTION FRACTION (EF) BY 10% IN PIG MODEL OF CHRONIC MI WITHOUT INDUCING ARRHYTHMIAS



- 10% improvement in EF from pre-dose baseline
- No test article-related arrhythmias noted by 24-hour EKG monitoring at 3-, 5-, 7- and 9-weeks post-treatment
- No test-article related adverse histological changes in major organs at 9-weeks post-treatment

INJECTION CATHETER DELIVERY OF TN-101 IN PIG MODEL OF CHRONIC MI



Yorkshire pig

Infarction induced via balloon occlusion

Electrical mapping-guided intramyocardial injection catheter delivery of TN-101

Total Dose: 2.5E14 vg/pig

Day 0
MI

Week 4
Dose

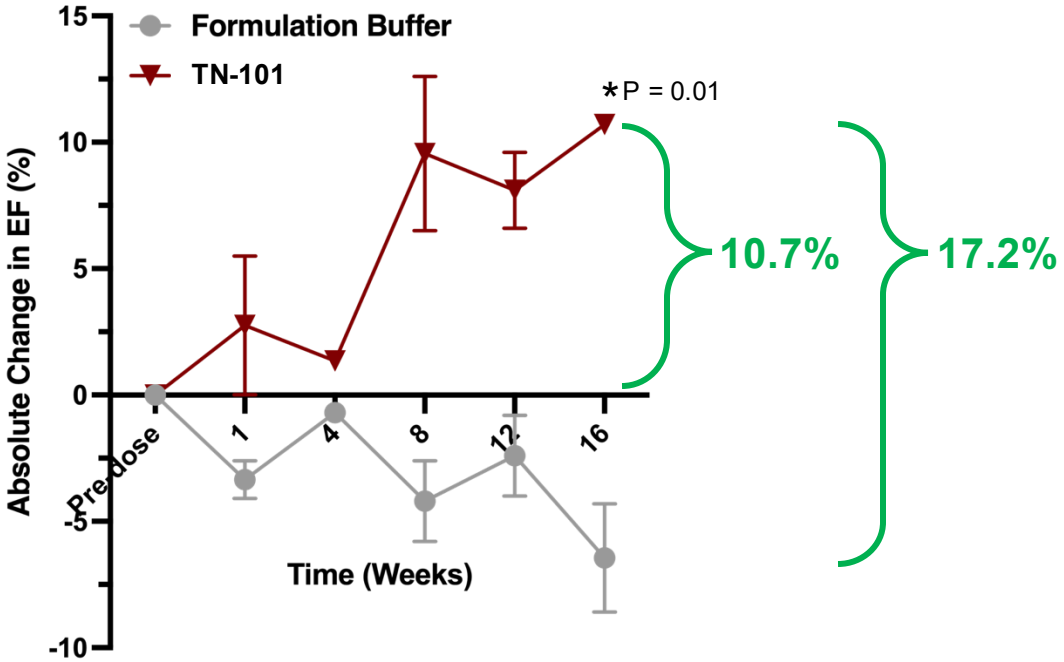
Week 20
Necropsy

16-week in-life data collection

Detailed clinical observations
Standard 2D echocardiography
Clinical chemistry

TN-101 DURABLY IMPROVED HEART FUNCTION IN PIG CHRONIC MI MODEL WHEN DELIVERED BY INTRAMYOCARDIAL INJECTION CATHETER

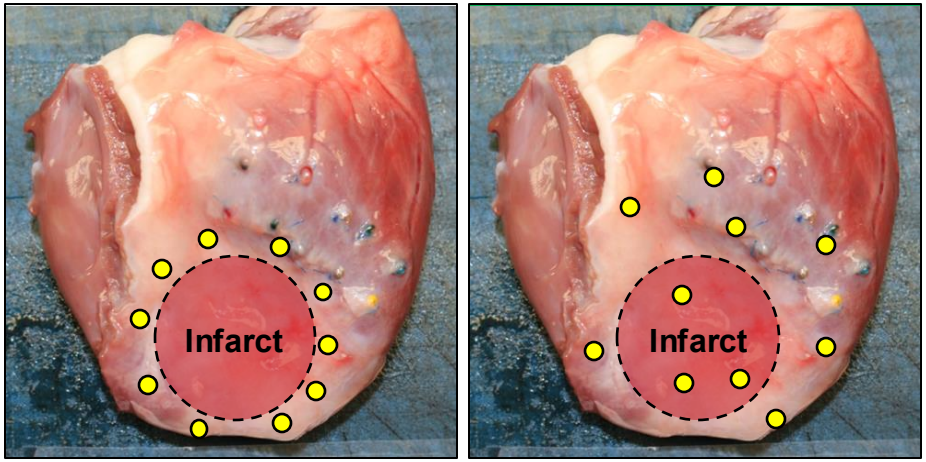
EF Changes Following Injection Catheter Delivery of TN-101



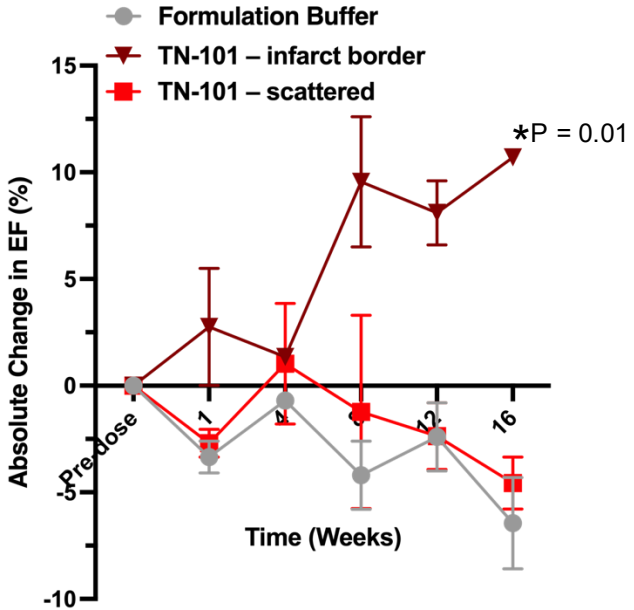
- >10% improvement above pre-dose baseline
- >17% improvement above saline-treated control group
- Benefit noted by 8 weeks post-treatment and sustained to 16 weeks

CARDIAC REPROGRAMMING EFFICACY IS DEPENDENT ON TARGETED DELIVERY TO THE INFARCT BORDER

Delivery to Infarct Border | **"Scattered" Delivery**



Injection sites



- Only the group that received delivery to the infarct border showed improved EF
- Group dosed in a scattered pattern had EF comparable to saline-injected controls; none of these animals showed EF improvement

CONCLUSIONS: TN-101 HAS POTENTIAL TO IMPROVE POST-MI HEART FAILURE

Efficacy

- Validated in multiple relevant models: post-MI mouse, rat, pig, & in human cardiac fibroblasts[1]
- Clear mechanism that is differentiated from cell therapy approaches

Safety

- Capsid with higher tropism for cardiac fibroblasts vs. cardiomyocytes
- Reprogramming factor expression is de-targeted from pre-existing cardiomyocytes (CMs) and downregulated after reprogramming is complete via inclusion of CM-specific miRNA binding sites
- Demonstrated compatibility with localized and image-guided delivery using clinically relevant ROA
- Efficacy at a low overall dose level compared to systemically-delivered AAV gene therapies supports promising risk/benefit profile and cost of goods for this prevalent indication

NEXT STEPS

1. Incorporate FDA regulatory feedback already received into design of IND-enabling studies

2. Select appropriate injection catheter with electrical mapping to support targeted delivery in IND-enabling safety studies

3. Initiate IND-enabling studies in established pig MI model

Cardiac Reprogramming via TN-101 Has the Potential to Be a First- and Best-in-Class Cardiac Regeneration Therapy

TENAYA™ THERAPEUTICS

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Scientific Sessions

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