January 2020

TRIPLE-GENE Therapeutics

Advanced Gene & Cell Therapies for Cardiovascular Disease

Thomas D Reed, PhD: Co-Founder

Biotech Showcase, January 15, 2020

TRIPLEGENE

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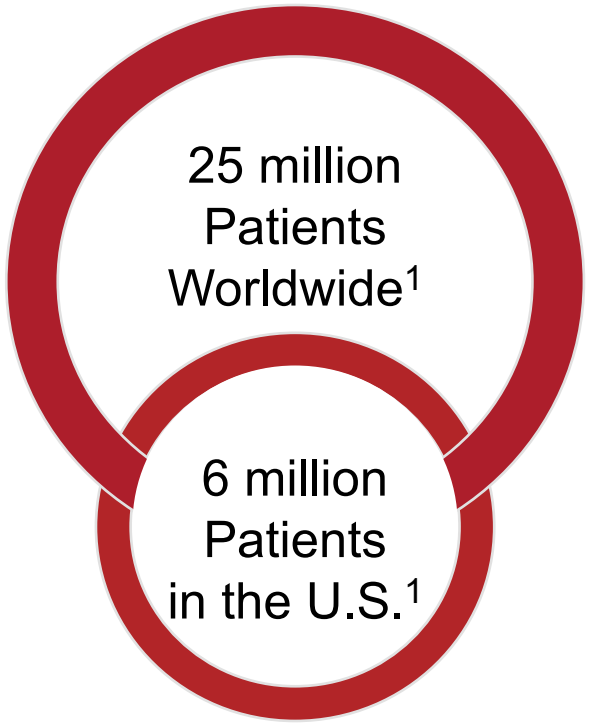
Heart Failure – A Significant Unmet Medical Need



Overall economic burden
Worldwide: **$108 billion**[4]
U.S.: **$32 billion**[1]

Mortality
50% of heart failure patients die within 5 years from diagnosis.[1]

Hospitalization
Heart failure is the **number 1** cause of hospitalization in patients aged >65 years.[2]

Comorbidities
The vast majority of HF patients have **3 or more comorbidities**.[3]

Existing treatments improve quality of life in the short-term and offer some improvement in long-term survival though at high cost and with associated complications[5]

1. http://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_heart_failure.htm
2. http://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf
3. Cowie MR et al. Oxford PharmaGenesis; 2014. http://www.oxfordhealthpolicyforum.org/AHFreport
4. Cook C et al. *Int J Cardiol*. 2014;171(3):368-376.
5. Comparison of prognosis data from 1990 (Matoba et al, Jpn Circ, Jan 1990 accessed at https://www.ncbi.nlm.nih.gov/pubmed/2332933) and from 2016 (Mozzafarian et al, Circulation 2016)

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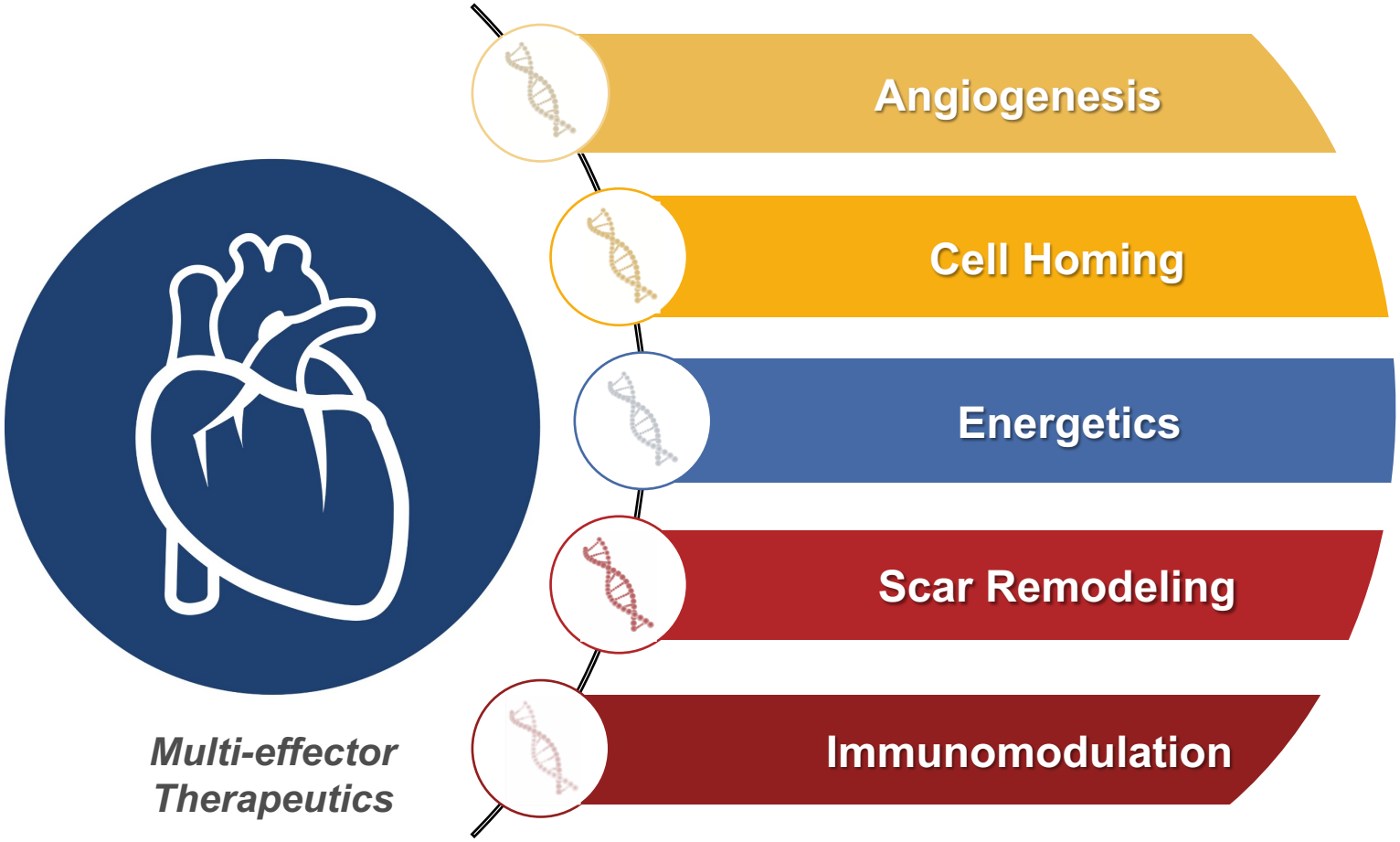
Heart Failure is a Complex and Multifaceted Disease



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Monogenic Cardiac Gene Therapies Fail Efficacy Endpoints

Table 2. Gene therapy clinical trials

Molecular target	Delivery mode	Phase	Name	Patient number	Treatment outcomes	Clinical trial identifier	References
VEGF	Adenovirus	II	KAT	103	Significant increase in myocardial perfusion		[52]
	Plasmid	I	VIVA	178			[53]
	Adenovirus	I	KAT301	30	Enhanced myocardial perfusion	NCT01002430	[54]
	Plasmid	III	EUROINJECT-ONE	80	No difference in myocardial perfusion		[55]
	Plasmid	II/III	NORTHERN	93		NCT00143585	[56]
	Adenovirus	III	REVASC	17			[57]
FGF4	Adenovirus	II/III	AGENT-3	416	No beneficial effect	NCT00346437	[58]
		II/III	AGENT-4	116		NCT00185263	
		I	AGENT	79	Trend for improved myocardial perfusion		[59]
		I	AGENT-2	62			[60]
AC6	Adenovirus	I/II	AC6 Gene Transfer	56	Dose-related improvement of cardiac function	NCT00787059	[61]
SERCA2a	AAV1	I/II	CUPID	51	Decreased HF symptoms remodeling	NCT00454818	[62–65]
		II/III	CUPID-2b	250	No improvement in the clinical course of HF	NCT01643330	[66]
		II	AGENT-HF[a]	10		NCT01966887	
		II	SERCA-LVAD[a]	5		NCT00534703	
SDF1	Plasmid	I	ACRX-100	17	Improvements 6-minute walk	NCT01082094	[67]
		II	STOP-HF	90	Improvements 6-minute walk	NCT01643590	[68]
		IIb	STOP-HF2[b]	180			

Abbreviations: AAV, adeno-associated virus; AC6, adenyl cyclase 6; FGF, fibroblast growth factor; HF, heart failure; LV, left ventricle/ventricular; SDF1, stromal-derived factor 1; SERCA2a, sarcoplasmic reticulum Ca^{2+} ATPase; VEGF, vascular endothelial growth factor.
[a]Terminated.
[b]Ongoing.

Chen *et al*. *Stem Cells* (2017) 35(5):1131-1140.

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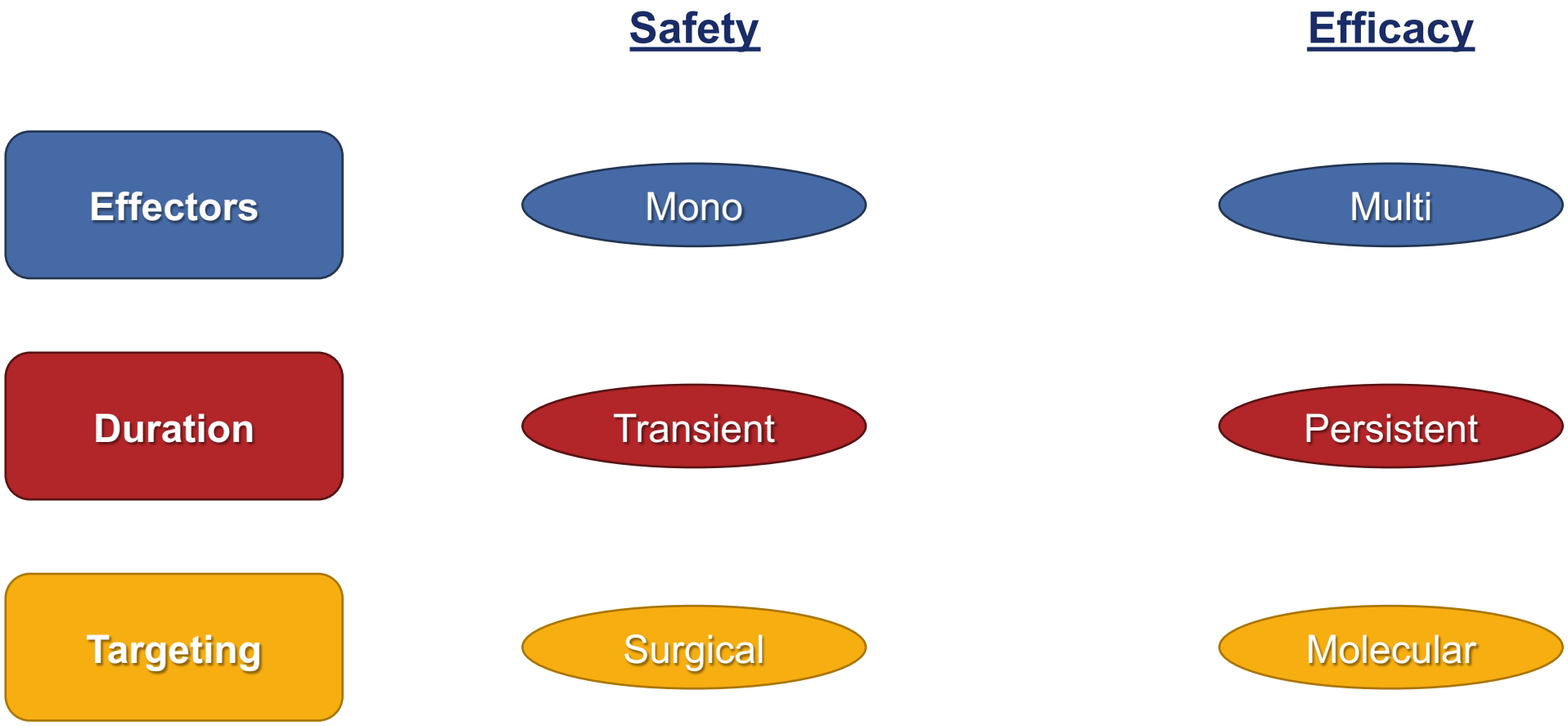
Cardiovascular Gene Therapy Design Matrix (Balancing Safety & Efficacy)



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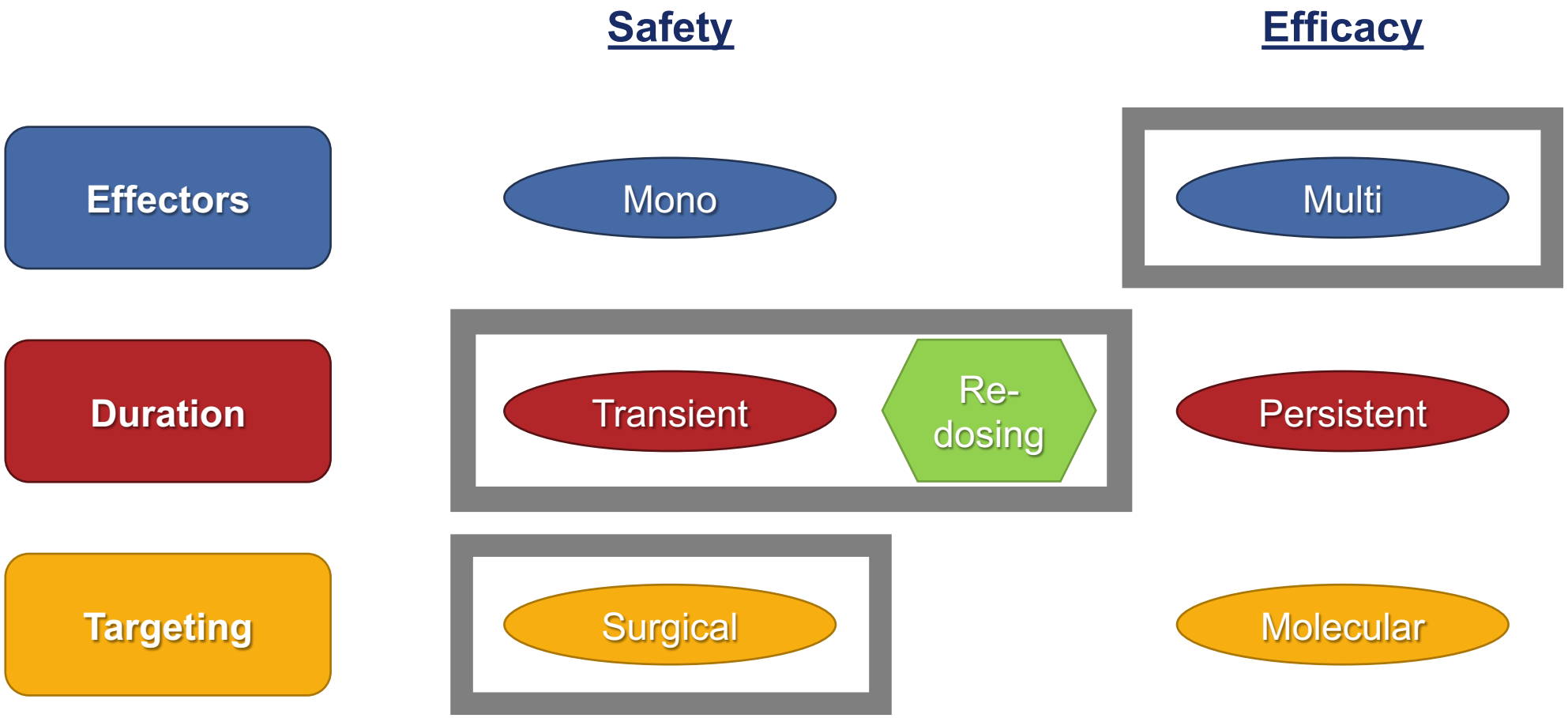
Cardiovascular Gene Therapy Design Matrix (Balancing Safety & Efficacy)



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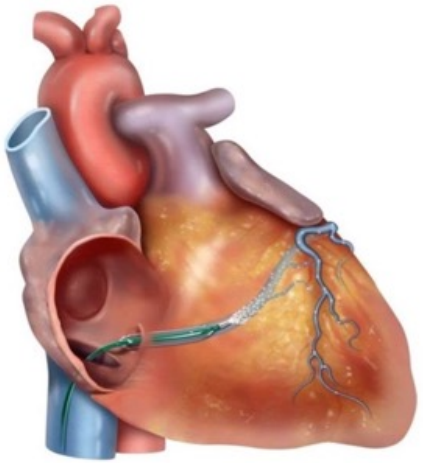
3GTx Technology Differentiation



Drawbacks of Existing Therapeutic Approaches

- **AAV vectors** have limited payload, thus restricting the size and number of delivered genes.
- **Non-viral vectors** have higher payload capacity and show minimal immunogenicity, but low transfection efficiencies raise concerns about under dosing.
- Delivery routes into the heart for gene-based therapeutics are varied yet some methods lack cardiac specificity or carry risks.

Advantages of 3GTx Approach: [(Non-viral)(RCSI)]

Non-viral delivery of multigenic vector targets underlying molecular mechanisms of pathological myocardial remodeling.

- Retrograde Coronary Sinus Infusion (**RCSI**) allows for delivery via capillary filtration increased by the hydrostatic and osmotic pressures, with efficiency of transduction dependent on the volume and time of infusion.

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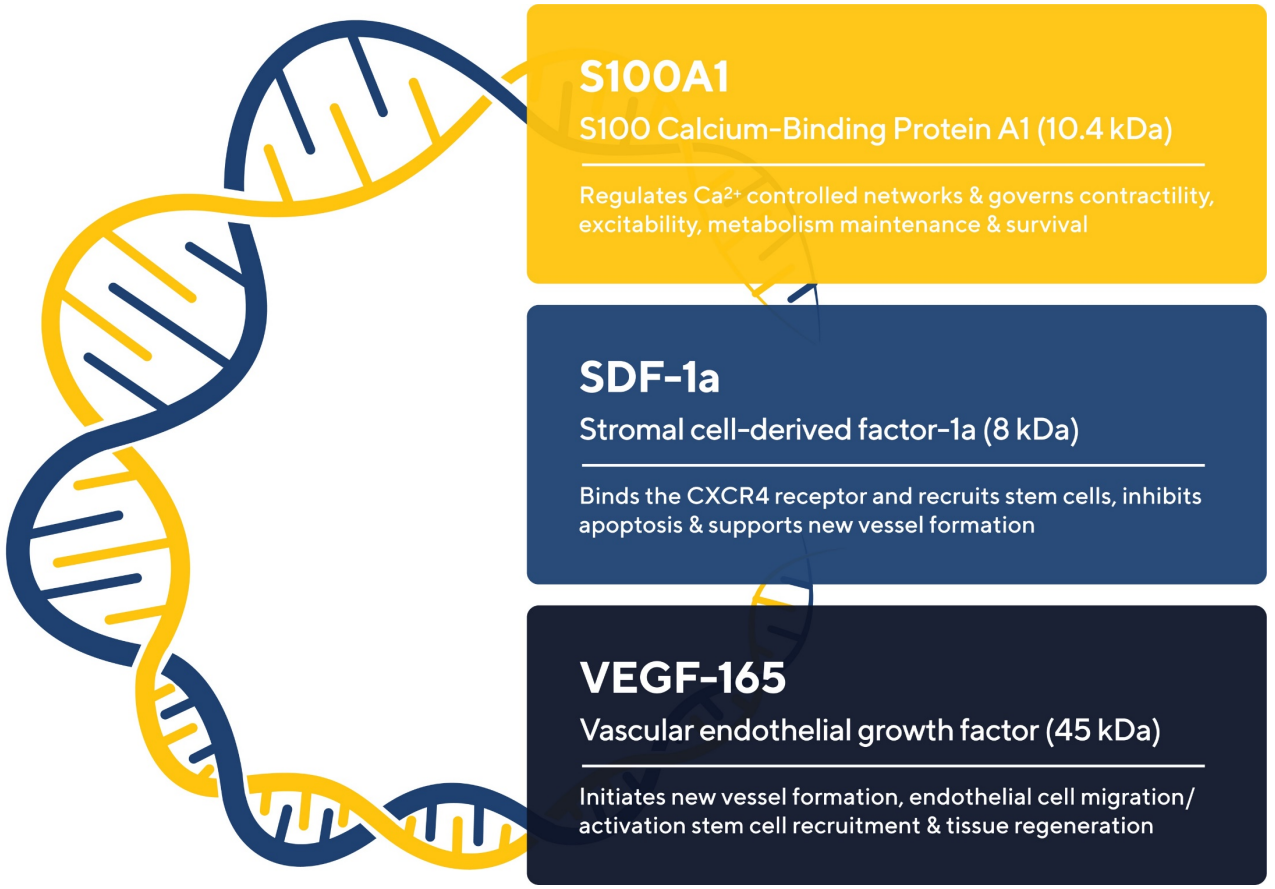
INXN-4001: A Triple Effector Plasmid for Treating Heart Failure

- A multigenic plasmid DNA approach to treat cardiac diseases is based on positive in vitro, pre-clinical and clinical data compared to other studies in which single genes have been utilized.
- **INXN-4001 is a non-viral triple effector plasmid** designed with self-cleaving linkers for constitutive expression of human S100A1, SDF-1α, and VEGF165.
- **Three effector genes in INXN-4001 are designed to address multiple malfunctions** of cardiomyocytes in patients with heart failure.
- Utilizing a single plasmid comprising all three genes, instead of each individual gene on separately delivered plasmids, **controls for delivery and transfection** of the three genes.



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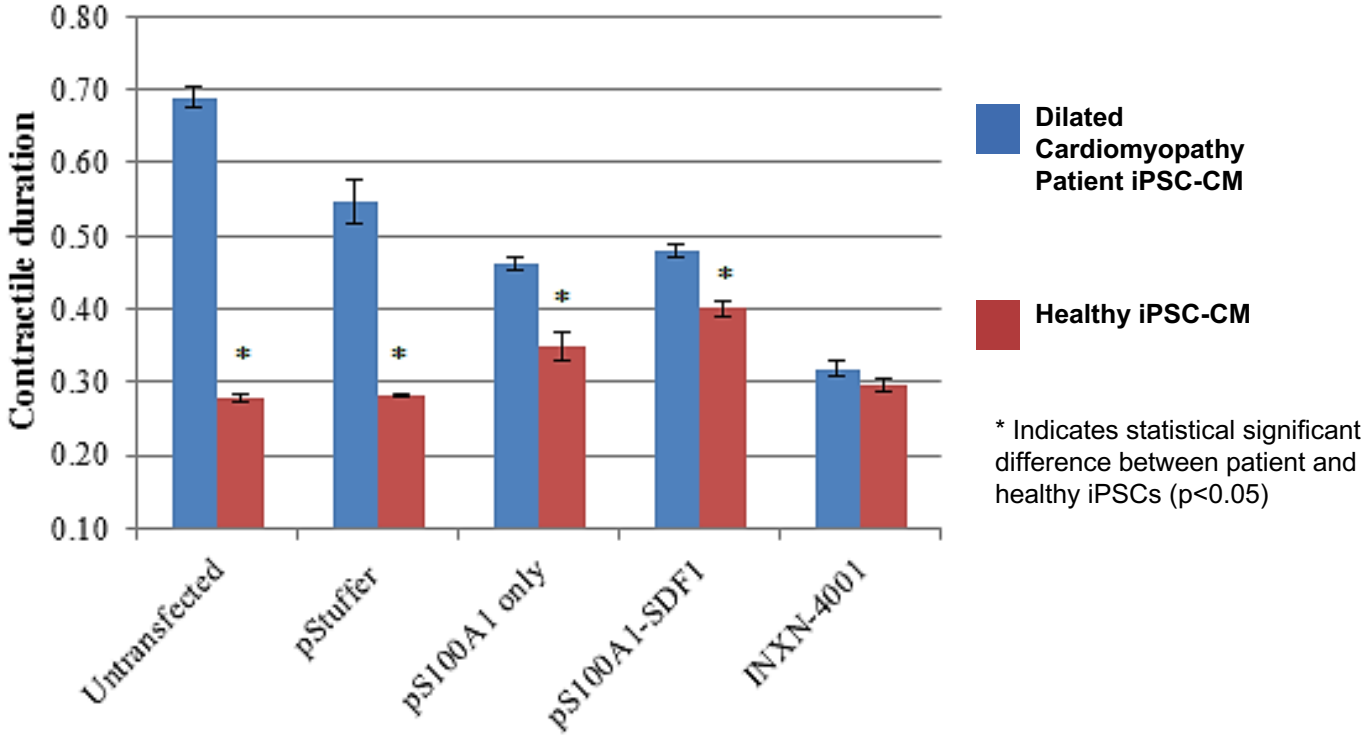
Utility of Multigenic Approach Demonstrated in Human Diseased Cardiomyocytes

INXN-4001 Transfection Improves Contractile Duration of Patient Cardiomyocytes *in vitro*



Transfection of INXN-4001 demonstrated significant improvement in beat rate, contractile duration and contraction rate of DCM iPSC-CM to the levels demonstrated by control cells and did not result in increased cell death compared to controls.

Patel DS, Wu JC, Reed TD, and Patel AN. Mol Ther. 2019;27(4S1):Abstract 777.

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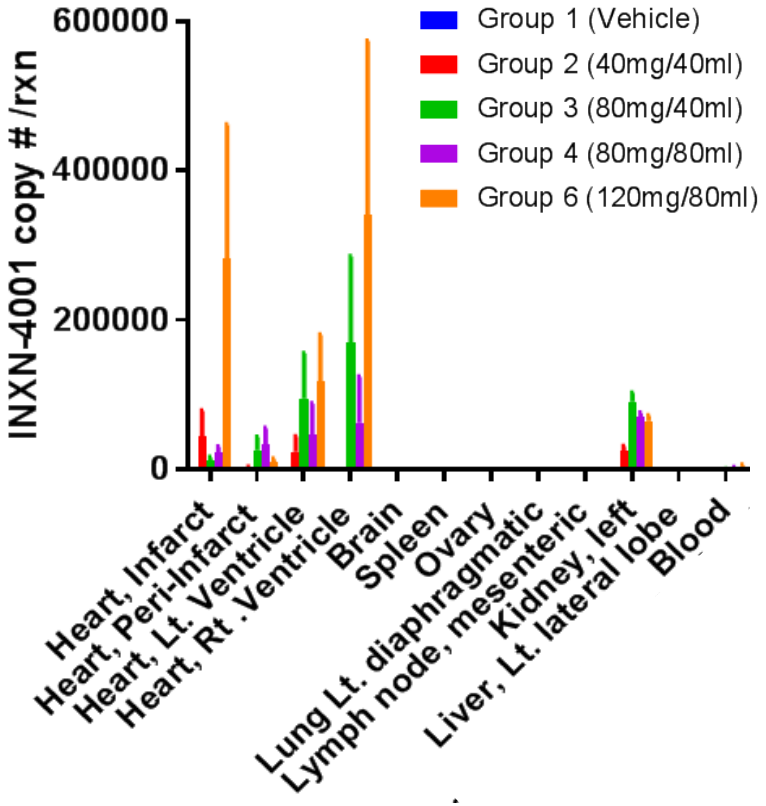
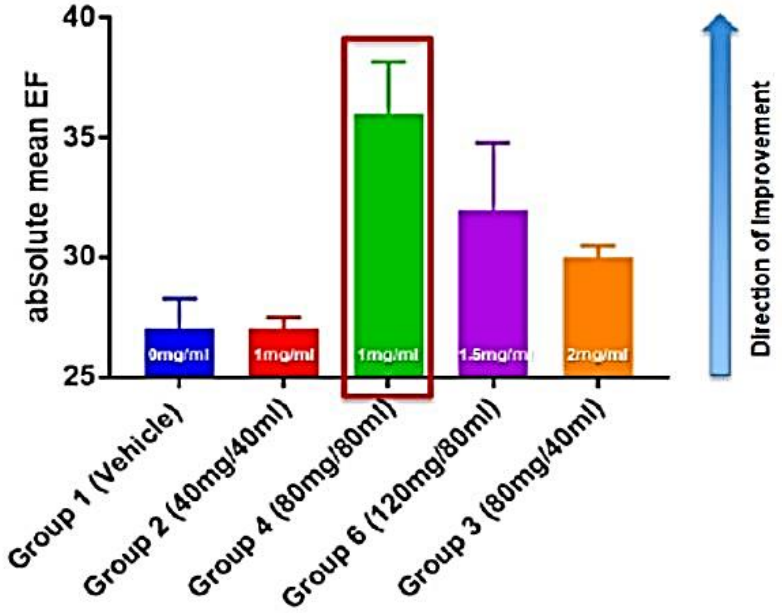
Favorable Biodistribution and Function of INXN-4001 in Pig Model

Biodistribution of INXN-4001 in Pig Indicates Cardiac Specific Delivery



Comparison of Myocardial Functional Parameters Across INXN-4001 Doses in Pig Model Indicates Increase in EF

2598-001 cMRI Absolute Mean Ejection Fraction (EF)



Coronary sinus delivery of INXN-4001 in a large animal ischemic heart failure model demonstrated:

- Decreased left ventricular end systolic volume and increased absolute mean ejection fraction (indicators of myocardial function)
- No increase in arrhythmias compared to controls

Reed TD, Patel DS, Rodenberg EJ, Shirley B, Johnson M, and Patel AN. Mol Ther. 2019;27(4S1):Abstract 775.

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INXN-4001 Phase I Study Design and Status

First-in-human, phase I, open label, safety study of INXN-4001 delivered via RCSI in patients with outpatient LVAD

(clinicaltrials.gov Identifier: NCT03409627)

Cohort 1
(n=6)
INXN-4001
80mg / 40ml

DSMB Review

Cohort 2
(n=6)
INXN-4001
80mg / 80ml

- 12 stable patients with implanted LVAD for mechanical support of end stage HF allocated into 2 cohorts (6 subjects each) to evaluate the safety of infusing the same amount of INXN-4001 (80mg) in 2 volumes (40mL and 80mL) at 20mL/min rate.

Safety

Collected during clinic visits at: pretreatment, day 3, then 1, 3, 6, 9, and 12 months after dosing via RCSI.

- Clinical labs
- Physical exams
- ECG
- Medical history

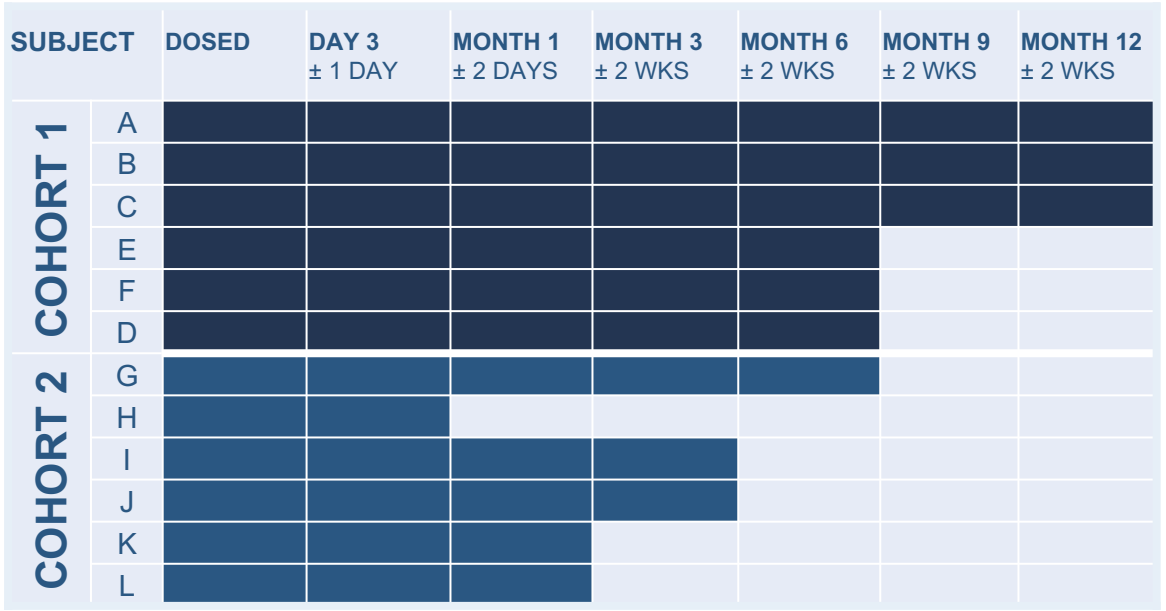
Function

- KCCQ questionnaire
- 6-min walk test (6MWT) prior to and during an LVAD wean interval
- Daily activity data using Actigraph wearable biosensor.

INXN-4001 study has successfully completed enrollment of 12 patients on NOV 5, 2019.

As of January 9, 2020:

- **Overall, 3 patients completed all assessments**
- **Cohort 1 completed 6 months assessments**
- **Cohort 2 completed 1 month assessments** (except 1 patient)



American Heart Association Annual Meeting Presentation November 2019. Poster #Su4176. https://3gtx.com/media/american-heart-association-aha-annual-meeting-november-2019

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Safety & Feasibility

Baseline Characteristics

- Per medical history of 12 dosed patients, 59% of them were ischemic, 33% were non-ischemic, and 8% represented other etiology of heart failure.
- Overall, 58% of patients were class III and IV NYHA, while the rest (42%) fell in class I and II.

Feasibility of INXN-4001 Delivery via RCSI

- Thirteen RCSI procedures took place by NOV 5, 2019, and 12 patients were successfully dosed.
- One procedure failed due to anatomical difficulty of accessing coronary sinus - this patient exited, then re-entered the study, and was successfully dosed.

Safety

- There were no product-related AEs reported so far.
- There was one SAE possibly related to RCSI procedure (acute kidney injury/exacerbation).
- Among 6 cardiac events, 4 were serious, but none related to INXN-4001 therapy.

FIGURE 1. Heart Failure Characteristics at Baseline

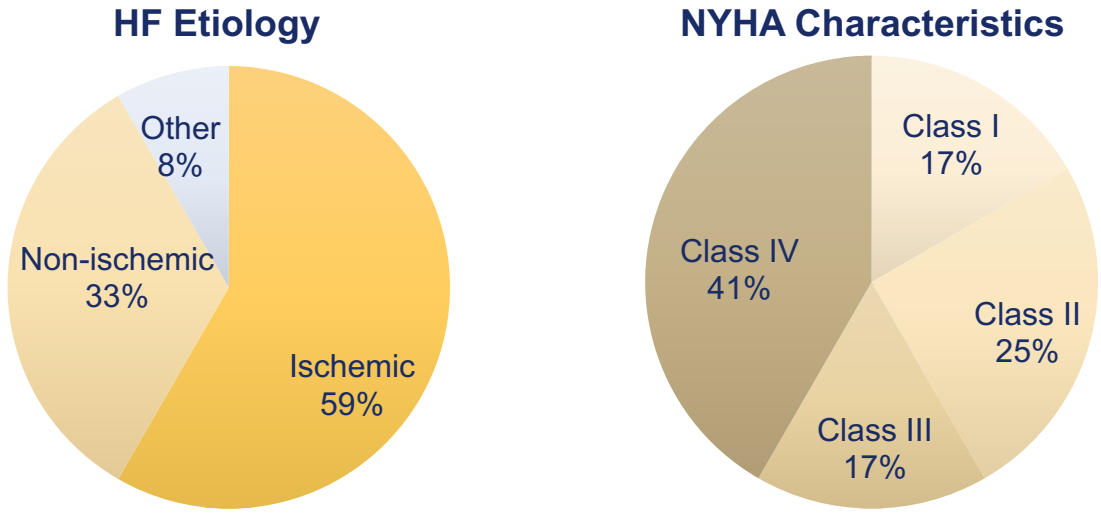

TABLE 1. Safety Review

# AE	Procedure-Related	Product-Related	# Cardiac AE
42 (incl. 13 SAE)	1 (possibly related / not cardiac)	0	6 (none related to Product or Procedure)

TABLE 2. Cardiac Adverse Events

Timeline	Total	Procedure-Related	Product-Related
DAY 0	1	0	0
DAY 3	0	0	0
MONTH 1	0	0	0
MONTH 3	1	0	0
MONTH 6	2	0	0
MONTH 12	2	0	0

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KCCQ Scores

The Kansas City Cardiomyopathy Questionnaire quantifies -

- Physical function
- Symptoms
  (frequency, severity and recent change)
- Social function
- Self-efficacy and knowledge
- Quality of life

Published Reference:
https://cvoutcomes.org/pages/3214 (accessed on 11/9/19)

- Scores range from **0** to **100**
- 100 is the least burden of symptoms
- Change of **≥5 points** considered clinically significant.

- **Observed high variation of KCCQ scores in patients at baseline**
  - Patients A-K ranging from 29% to 93%
- **Observed a trend in the change of KCCQ score with time per patient:**
  - Patient A: increase from 60% to 90% after 6 months
  - Patient B: increase from 29% to 38% after 6 months
  - Patient E: increase from 33% to 75% after 6 months

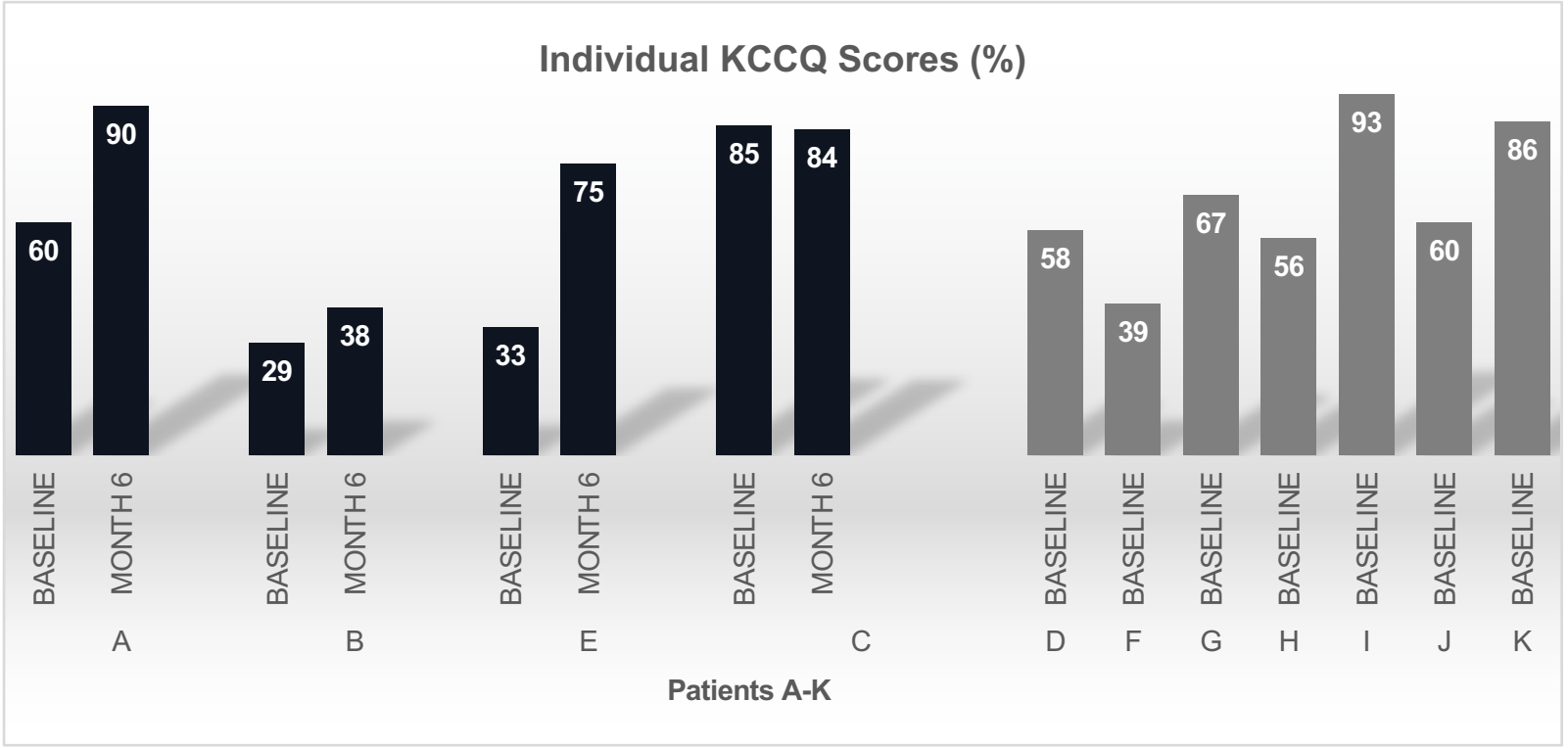

FIGURE 2. Individual KCCQ Scores for 11 patients (A-K) at baseline (n=11) and (when available) after 6 months from INXN-4001 infusion (n=4). (Results shown per data on OCT 25, 2019)

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Six Minute Walk Test Distance

Observed trends to benefit in the distance walked during the Six Minute Walk Test after 6 months post INXN-4001 treatment

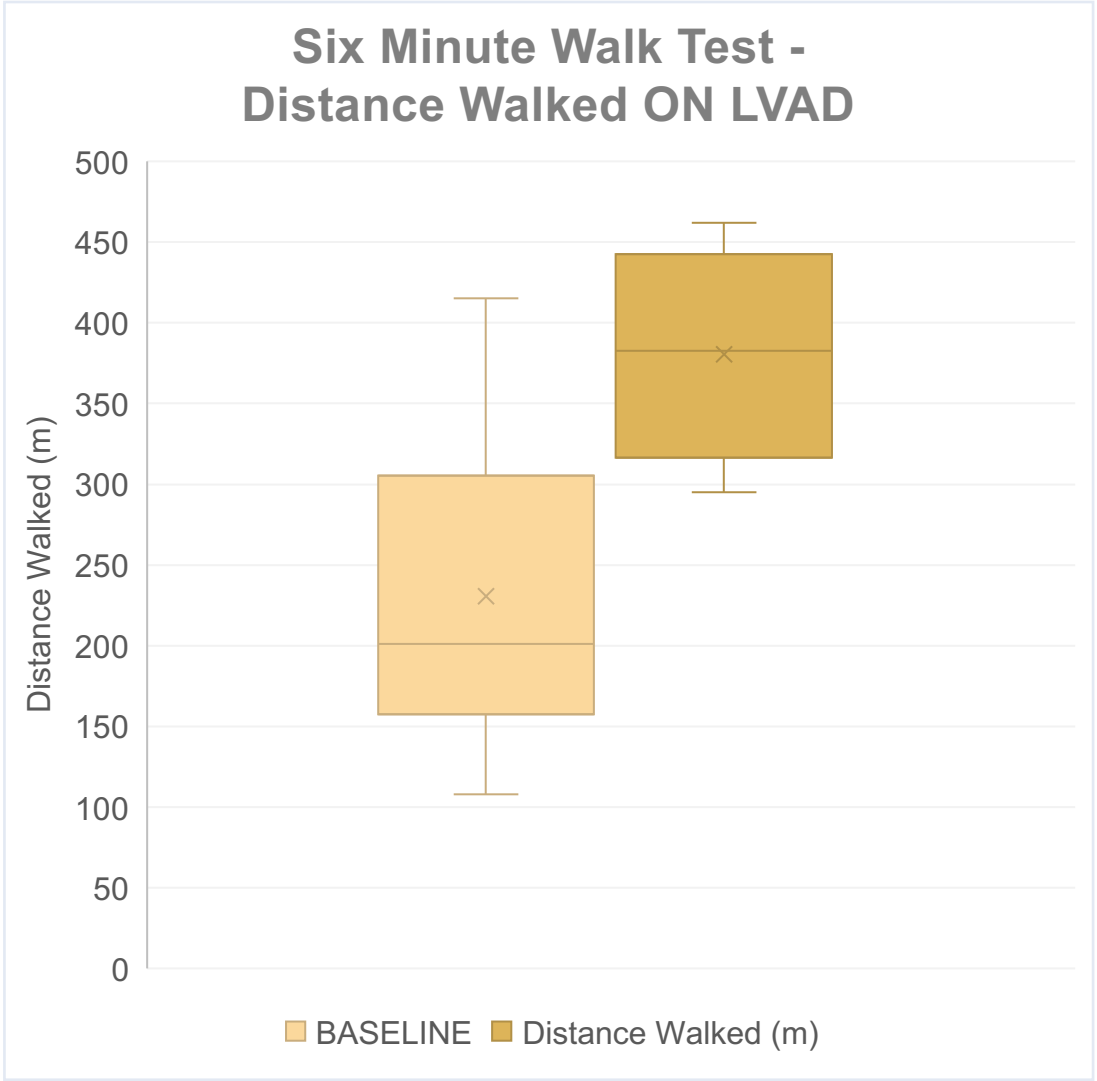

FIGURE 3. Distance walked by patients ON LVAD support during 6MWT at baseline (n=9) and after 6 months from RCSI procedure (n=4). (Results shown per data on OCT 25, 2019).

Published References:
https://erj.ersjournals.com/content/37/1/150 (accessed on 11/9/19)

Distance (m)	For Healthy	For Stable HF
Range	From 380 to 782	From 308 to 482
MEAN ± SD	571 ± 90	395 ± 87

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Left Ventricular Ejection Fraction (LVEF%)

LVEF refers to the amount of blood being pumped out of the left ventricle each time it contracts.

Observed trends to benefit after 6 months post INXN-4001 treatment in the LVEF% representing heart function measure.

Published References:
https://www.acc.org/tools-and-practice-support/clinical-toolkits/heart-failure-practice-solutions/left-ventricular-ejection-fraction-lvef-assessment-outpatient-setting (accessed on 11/9/19)

LVEF Range	
Normal	50% to 70%
Mild dysfunction	40% to 49%
Moderate dysfunction	30% to 39%
Severe dysfunction	Less than 30%

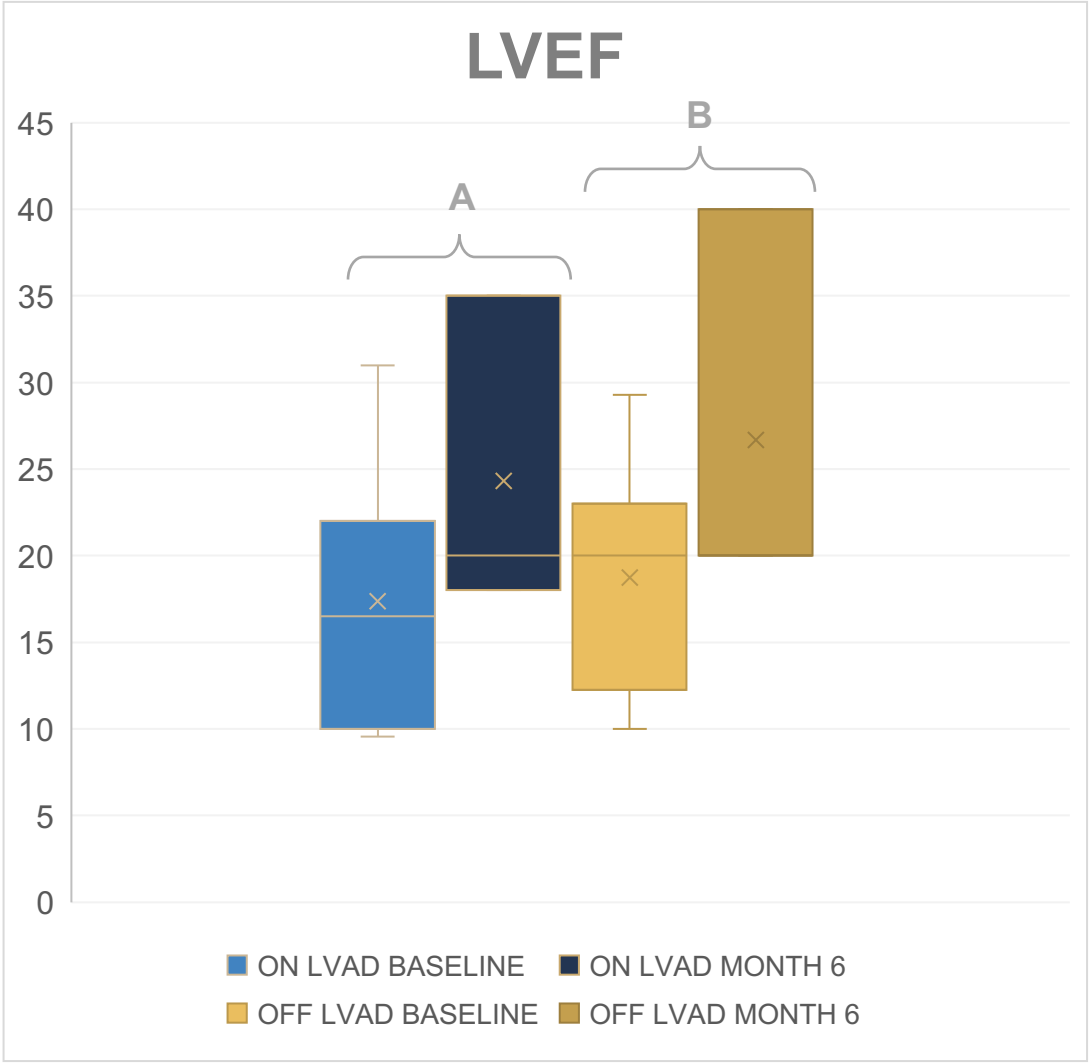

FIGURE 4. LVEF for patients (A) ON LVAD support at baseline (n=11) vs. 6 months post RCSI (n=3) and (B) for patients OFF LVAD support after 6MWT at baseline (n=10) and after 6 months from RCSI (n=3). (Results shown per data on OCT 25, 2019).

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Market Opportunities *(including follow-on indications)*

Heart Disease

Chemotherapy-Induced Cardiomyopathy	
US Patients	15,000 patients[1]
Estimated Market Opportunity	$600M[2]

Non-Ischemic Cardiomyopathy	
US Patients	300,000 patients[3]
Estimated Market Opportunity	$600M[4]

Myocardial Infarction	
US Patients	3.4M patients[5]
Estimated Market Opportunity	$1.8B[6]

Vascular Disease

Peripheral Artery Disease (PAD)	
US Patients	33M patients[7]
Estimated Market Opportunity	$2B[8]

Critical Limb Ischemia (CLI)	
US Patients	2M patients[9]
Estimated Market Opportunity	$800M[10]

1. Estimated using total projected patients with 10 types of cancer (GLOBOCAN database), treated with anthracycline or similar, assuming 11% develop cardiomyopathy (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2848530/)
2. Assumes illustrative price of $40k per patient
3. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4206366/
4. Assumes 5% market penetration and $40k illustrative price
5. Sum of 2018 patients treated: Activase, Brilinta, Enoxaparin Sodium, Integrilin, Lovenox, Plavix (Evaluate Pharma)
6. Sum of 2018 revenues: Activase, Brilinta, Enoxaparin Sodium, Integrilin, Lovenox, Plavix (Evaluate Pharma)
7. Assumes 30% of patients present with claudication symptoms (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2733014/)
8. 0.5% market penetration, $40k illustrative price
9. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6617560/
10. 1% market penetration, $40k illustrative price

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Summary

- Novel triple effector targeted cardiac gene therapy
- FDA cleared for first-in-human clinical trials
- No toxicity or safety issues related to INXN-4001 identified to date
- Promising trends in LVEF and KCCQ scores observed
- Completed enrollment and dosing in Phase I trial for INXN-4001
- **TRIPLE-GENE** is exploring funding opportunities for both advancing INXN-4001, as well as expanding our pipeline of advanced cardiovascular gene therapies

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Acknowledgements

- Our collaborators and investigators at clinical sites -
  - Dr. David A. Bull and Dr. Kapildeo Lotun from the Banner University Medical Center in Tucson, AZ
  - Dr. Timothy Henry and Dr. Gregory Egnaczyk from the Carl and Edyth Lindner Center for Research and Education at The Christ Hospital in Cincinnati, OH
  - The Hart Clinical Consultants in Deland, FL

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TRIPLE-GENE Leadership Team

Thomas D. Reed, PhD – Co-Founder and Managing Director

Dr. Reed is the Co-Founder of Triple-Gene as well as the Founder and CSO of Intrexon Corporation. During his 20+ year tenure at Intrexon, Dr. Reed has contributed to the invention and/or acquisition of numerous advanced technologies designed to improve the safety and efficacy of gene and cell therapies, which are the subject matter of numerous US and international patents. Within the last ten years, Dr. Reed has contributed to the design of oncology, cardiovascular, and rare disease therapies now advancing in the clinic. Prior to starting Intrexon, Dr. Reed's scientific training focused on characterizing the structure and function of genes contributing to cardiovascular development and pathophysiology.

Ewa Jaruga-Killeen, PhD – Clinical Director

Dr. Jaruga-Killeen is the Clinical Director for Triple-Gene, as well as the Director of CSO Program Management at Intrexon Corporation. During her six year tenure at Intrexon, Dr. Jaruga-Killeen has managed cross-divisional research operations for diverse programs across Health, Food, Environment, and Consumer-focused initiatives. She worked closely with the CSO and Intrexon operations teams to manage various stages of the product development life cycle, including product ideation, Target Product Profile definition, through R&D, pre-clinical, and clinical stages of development.

Thomas Samuelson, MBA – Board Member

Mr. Samuelson is a member of Triple-Gene's Board of Directors. He is also a Vice President at Precigen, focusing on the intersection of finance and operations. His primary responsibilities include mergers / divestitures, capital allocation, financial planning /analysis, and business development across Precigen's health verticals. He sits on the board of a number of Precigen subsidiaries and joint ventures. Mr. Samuelson joined Precigen from the healthcare investment banking group at JP Morgan where he covered specialty gene and cell therapies. He is a graduate of Williams College and MIT.

Amit Patel, MD, MS – Co-Founder and Medical Advisor

Dr. Patel is the Co-Founder of Triple-Gene LLC formerly Xogenex LLC. He has invented, developed and translated many cardiovascular devices, drugs, and biologics over the past 20 years. He has been funded by the NIH, DOD, DARPA, and numerous private and venture based organizations with over a $100 million in primary funding. Dr. Patel is currently an active clinical cardiothoracic surgeon and interventionist.

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Thank You

Thomas D. Reed, PhD

Managing Director, Triple-Gene

Founder and Chief Science Officer, Intrexon Corporation

Email: TDR@3gtx.com
Phone: +1 561-410-7006

Triple-Gene LLC
561.410.7013

3gtx.info@3gtx.com
https://3gtx.com/
https://3gtx.com/technologies/rcsi/#overview

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