

Bioheart, Inc.

MYOHEART-SDF-1TM Trial

Myogenesis Heart Efficiency and Regeneration Trial

National Institutes of Health

Recombinant DNA Advisory Committee (RAC)

March 11th, 2008

Clinical Trial Protocol

Carl J. Pepine, MD

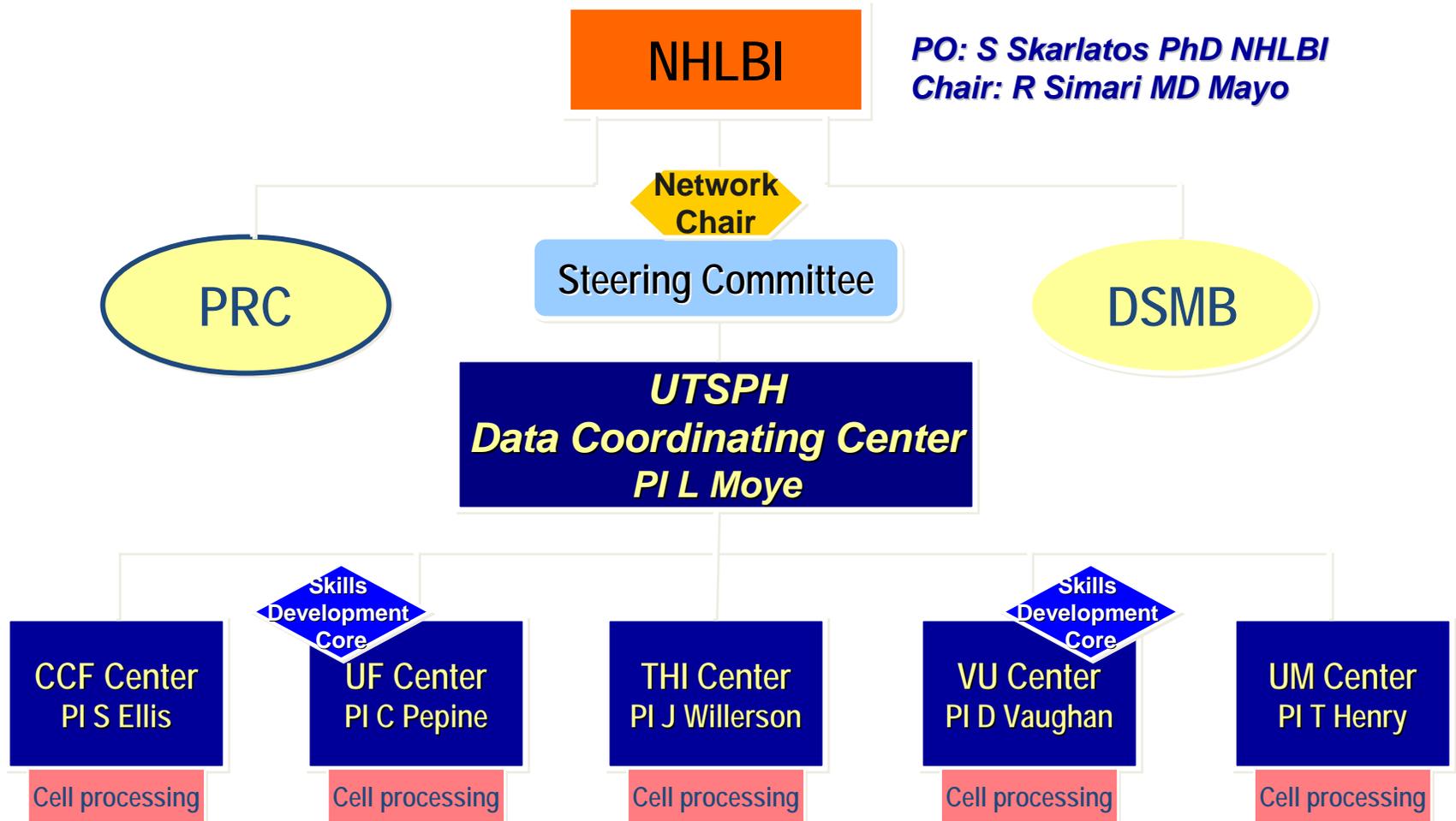
Eminent Scholar, AHA - Suncoast Chapter Chair

Professor of Medicine

Chief, Division of Cardiovascular Medicine

University of Florida

Cardiovascular Cell Therapy Research Network: CCTR



NHLBI-CCTR: Goal and initial phase I/II clinical trials

Goal:
Accelerate research into use of cell-based therapies in management of CV diseases

TIME

Effect of timing of early (3-7 ds) post-MI BMC administration on measures of LV function

Late TIME

Effect of late (2-3 wks) post-MI BMC administration on measures of LV function

FOCUS

Effect of transmyocardial (NOGA) BMC administration on measures of LV function in patients with chronic IHD

Investigational Product Components

- **Autologous Skeletal Myoblasts Expanded followed by *Ex Vivo* Transduction**
- **Adenovirus Serotype 5 Vector expressing Stromal Derived Factor-1**
- **Multi-Electrode Percutaneous Catheter (MyoStar™) with Cardiac Navigation Guidance (NOGA™) Transendocardial Delivery System**

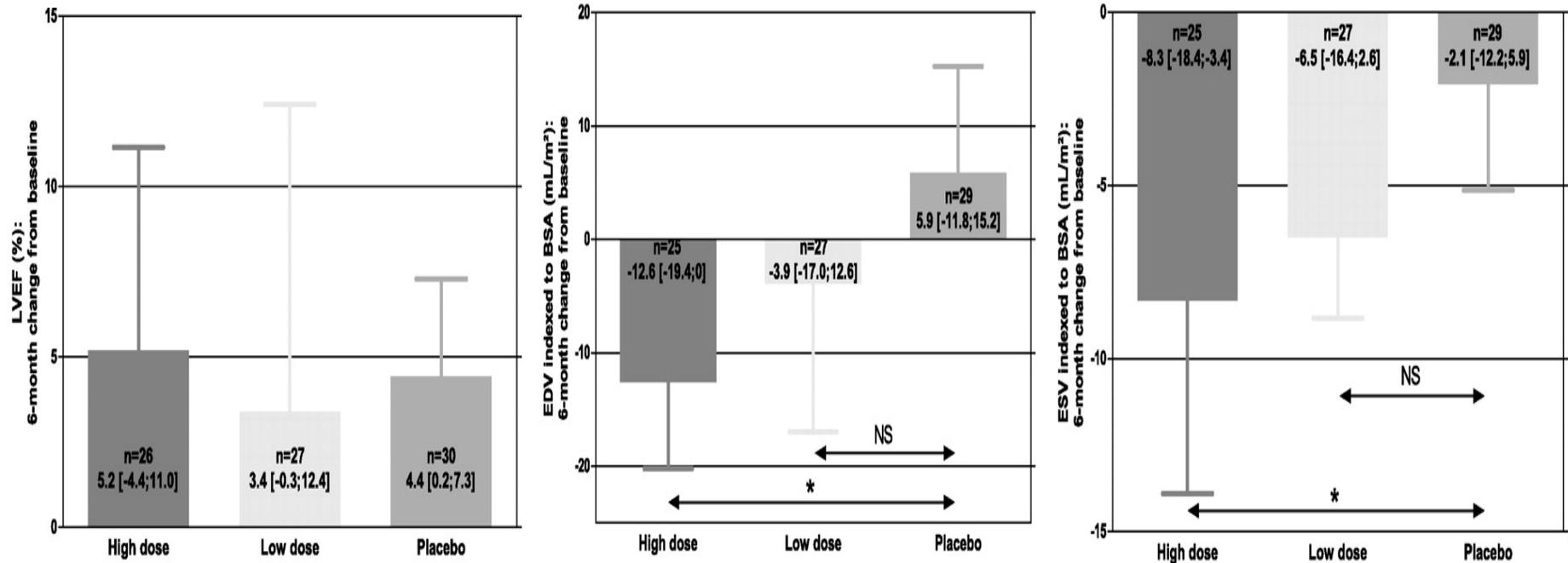
Myoblast Clinical Experience

Myoblasts have been evaluated in at least 11 clinical trials involving more than an estimated 235 study subjects. Of these, 75 patients have been treated under Bioheart-sponsored protocols worldwide to date.

Bioheart Trial	# of Patients	Status	Primary Endpoints
EU Phase I/II	5 Phase I 15 Phase I/II	Study Completed Q2 2003	<ul style="list-style-type: none"> ◆ Serious adverse events ◆ Global ventricular function
MYOHEART (US Phase I)	20	Final Patient Enrolled Q4 2006	<ul style="list-style-type: none"> ◆ Serious adverse events
SEISMIC (EU Controlled Phase II)	40 (14 control)	Final Patient Enrolled Q3 2007	<ul style="list-style-type: none"> ◆ Serious adverse events ◆ LVEF
MARVEL Trial (US/EU Double-Blind Phase II/III)	330 anticipated (110 controls)	Currently Enrolling	<ul style="list-style-type: none"> ◆ Serious adverse events ◆ 6-minute walk distance ◆ Quality of life score

First Randomized Placebo-Controlled Study of Myoblast Transplantation Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC): Six-month change from baseline in LV Measures

Menasche, P. et al. Circulation 2008;117:1189-1200

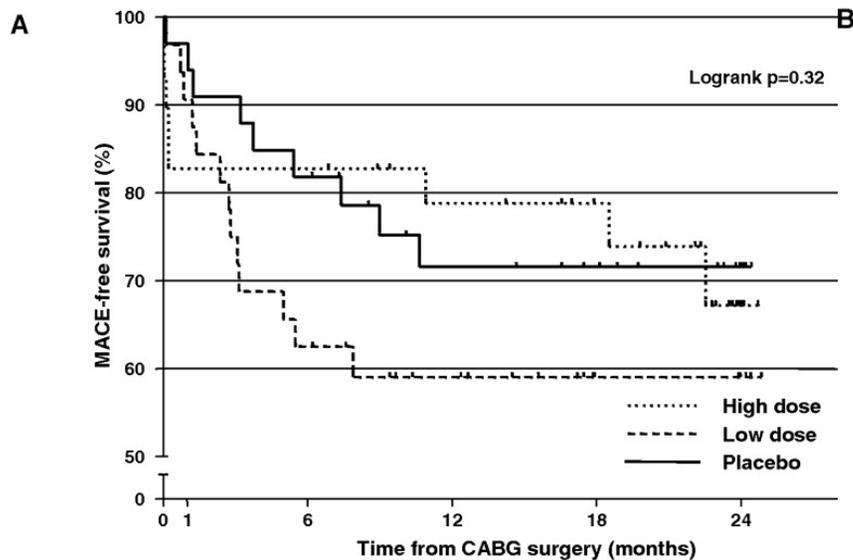


High dose= 800 x10⁶ cells*; Low dose =400 x10⁶ cells
*P<0.05 in a multiple comparison with the use of the Dunn procedure.

First Randomized Placebo-Controlled Study of Myoblast Transplantation Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC): Adverse Outcomes

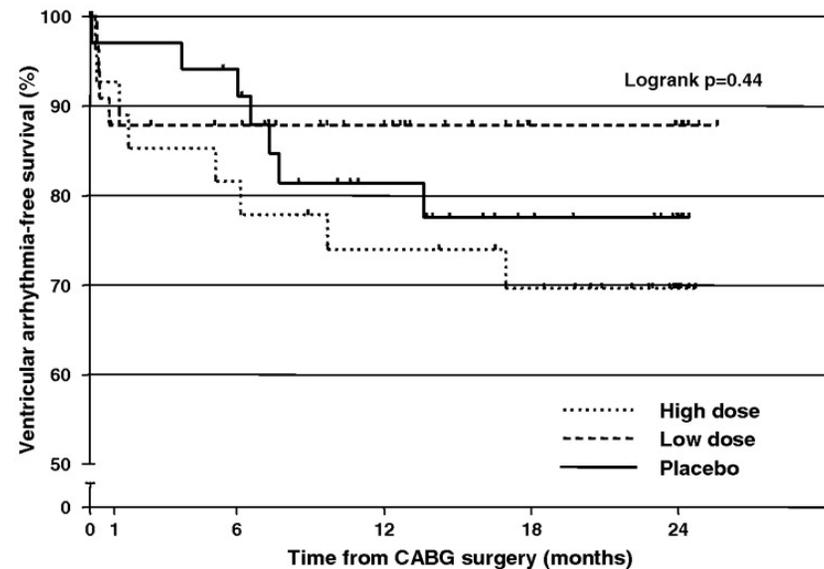
Menasche, P. et al. Circulation 2008;117:1189-1200

Time to first MACE



# at risk	High dose 30	24	24	20	16	3
	Low dose 33	29	20	14	5	3
	Placebo 34	32	27	20	17	8

Time to first ventricular arrhythmia



# at risk	High dose 30	24	24	20	16	3
	Low dose 33	29	20	14	5	3
	Placebo 34	32	27	20	17	8

(A) major cardiac adverse events (MACE) as composite of all cause death, MI, CHF, resuscitated sudden death and stroke.
(B) arrhythmias assessed by interrogation of ICDs as sustained VF or polymorphic VT, sustained monomorphic VT at 120 bpm, wide complex tachycardia of unclear type, sustained AtFib or flutter, bradyarrhythmia and shock delivered by ICD, bradyarrhythmia pacing or antitachycardia pacing.

MyoCell-SDF-1™ Delivery System

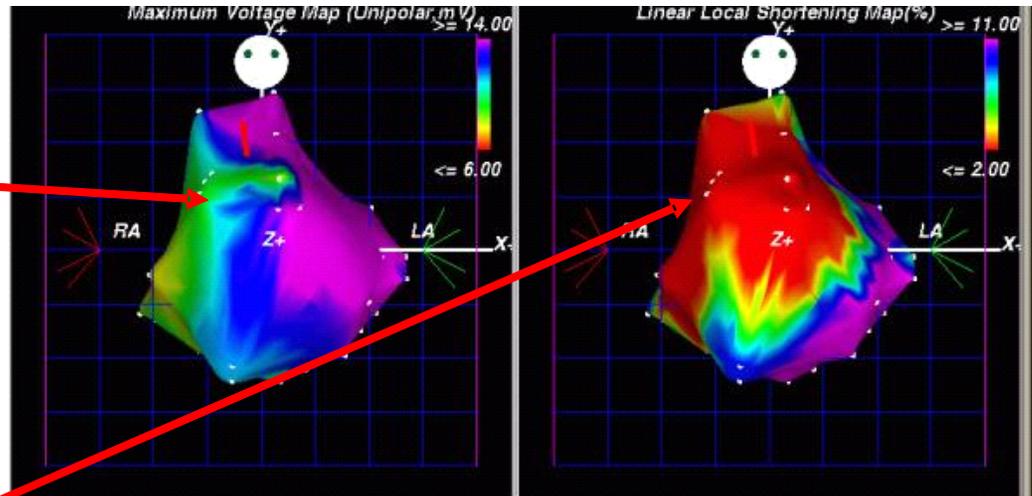
NOGA® XP
CARDIAC NAVIGATION SYSTEM

MYOSTAR™
INJECTION CATHETER

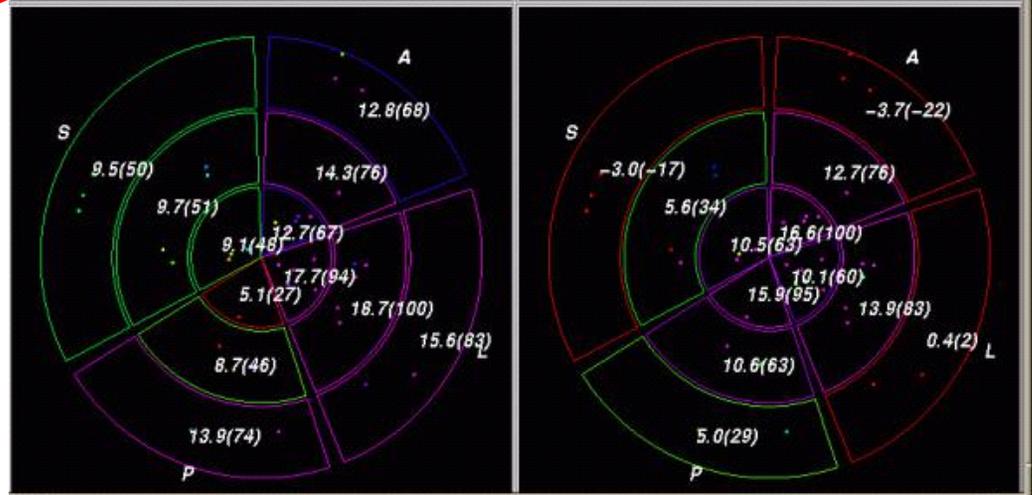
Voltage Map

LLS Map

Voltage Map:
septal and anterior
areas show viable
tissue (green/purple)



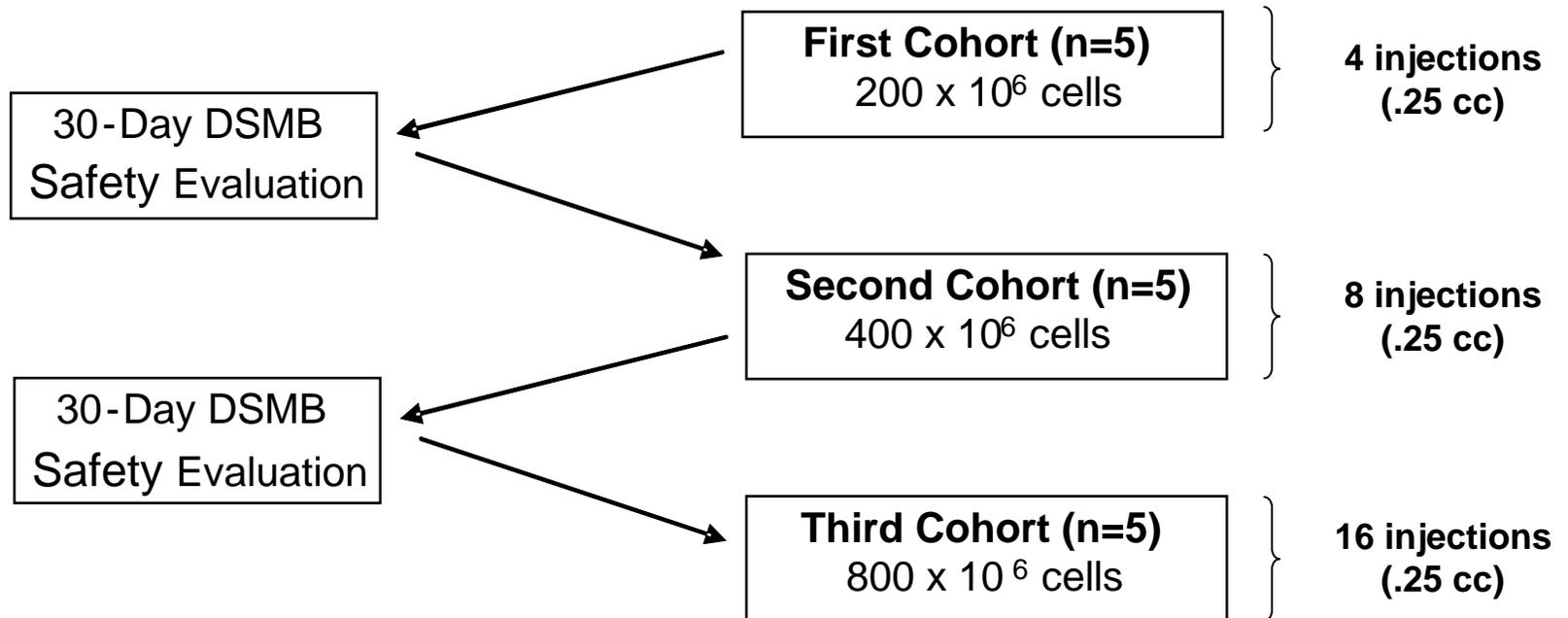
LLS Map:
wall movement in
septal and anterior
areas show
“hibernating” tissue (red)



MYOHEART-SDF-1™ Trial

A Phase I, Open-Label, Non-Randomized,
Dose Escalation, Multi Center Study

Fifteen (15) patients will be enrolled at up to five (5) study centers:



MYOHEART-SDF-1™ Trial

A Phase I, Open-Label, Non-Randomized,
Dose Escalation, Multi Center Study

Study Objectives

1. To assess the safety and feasibility of MyoCell™ SDF-1 (autologous myoblasts modified to express SDF-1) following implantation into the myocardial tissue of CHF subjects fitted with ICDs who experienced prior MI (\geq 12 weeks);
2. To assess the safety and feasibility of the Multi-Electrode Percutaneous Catheter (MyoStar™) with Cardiac Navigation Guidance (NOGA™) Transendocardial Delivery System for delivering MyoCell™ SDF-1.

MYOHEART-SDF-1™ Trial

A Phase I, Open-Label, Non-Randomized,
Dose Escalation, Multi Center Study

Safety Endpoints

- Incidence and nature of AEs through 12 months
- Development of clinically significant abnormal vital signs and lab values, including evaluation of plasma/SDF-1 blood levels post-treatment and through 12 months
- Summary information from 12-lead ECG and Holter monitoring as well as ICD downloads through 12 months

Efficacy Measurements

- Functional Improvement: NYHA Class, 6MWT
- Mechanical Improvement: Strain Echo, PET

MYOHEART-SDF-1™ Trial

Eligibility Criteria

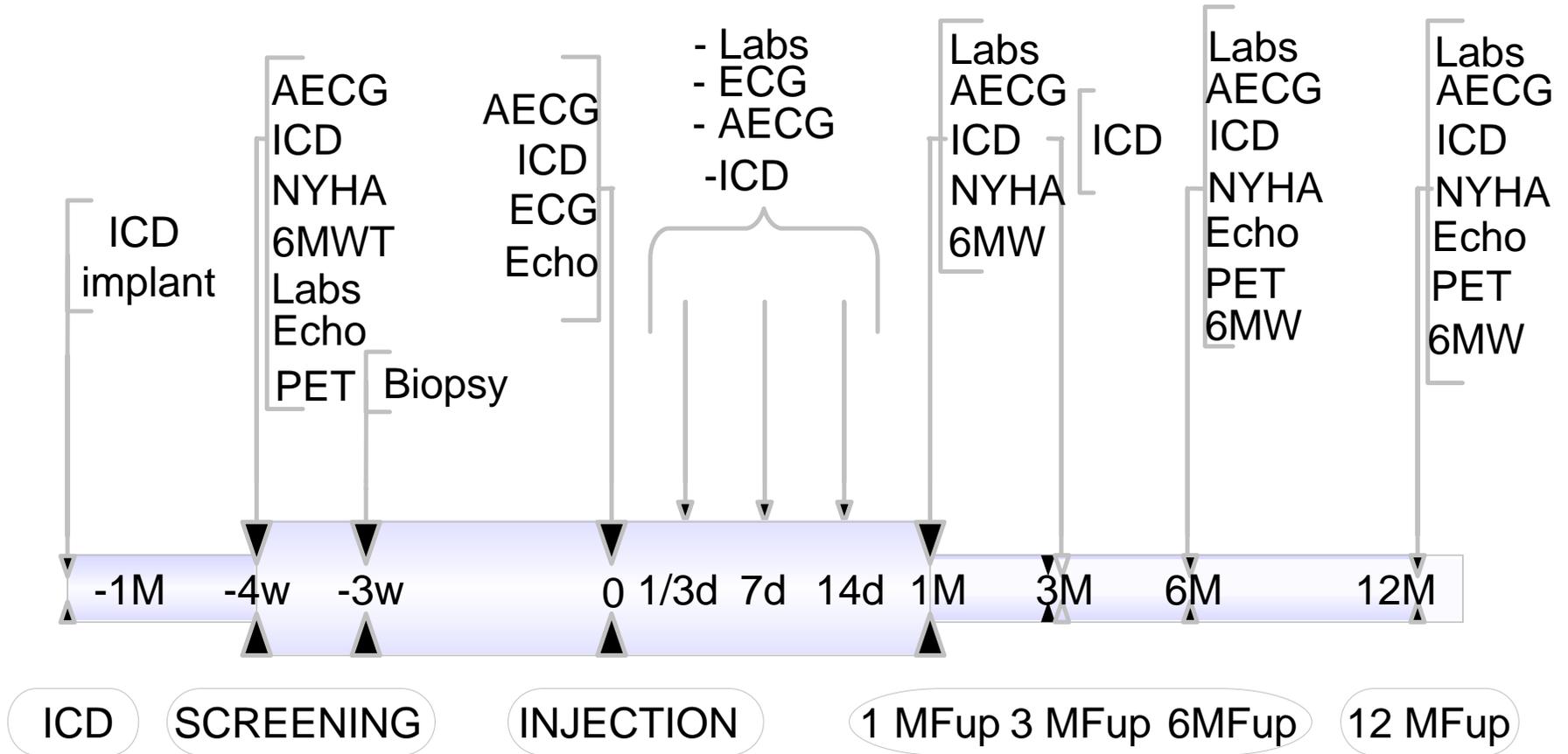
Primary INCLUSION Criteria

- Prior MI \geq 12 weeks old at implant
- Patients with prior placement of an ICD \geq 90 days prior to implant
- NYHA Class II – III
- Age \geq 30 and \leq 80 years old
- Need for revascularization excluded by coronary angiogram or noninvasive stress test within 6 months of screening
- Target region wall thickness of \geq 6 mm by echocardiography
- LVEF \geq 15% and \leq 35%
- Able to provide informed consent

Primary EXCLUSION Criteria

- MI within 12 weeks of scheduled implant
- NYHA class I or IV
- CABG within 5 months or PCI within 3 months of implant
- Any cardiac valve replacement or significant aortic stenosis
- HF secondary to valvular disease
- Severe arterial access tortuosity
- Prior angiogenic or myocardial laser therapy
- Sustained VT or VF 90 days prior to screening
- End stage renal disease

MYOHEART-SDF-1™ Study Flow



Preclinical Studies

Marc Penn, MD, PhD, FACC

Medical Director, Coronary Intensive Care Unit

Director, Experimental Animal Laboratory

Associated Director, Cardiovascular Medicine Fellowship

Departments of Cardiovascular Medicine and Cell Biology

Cleveland Clinic Foundation

Barry Byrne, MD, PhD, FACC

Professor and Associate Chair of Pediatrics, Molecular
Genetics & Microbiology

Powell Gene Therapy Center

University of Florida

Stromal Cell-Derived Factor-1 (SDF-1)

- Chemokine – receptor CXCR4/CXCR7
- Induces stem cell homing to bone marrow
- Lethal knockout secondary to abnormal hematopoietic development
- SDF-1: CXCR4 blocks apoptotic cell death

Why express SDF-1 in the setting of ischemic cardiomyopathy?

Transient re-establishment of SDF-1 expression leads to:

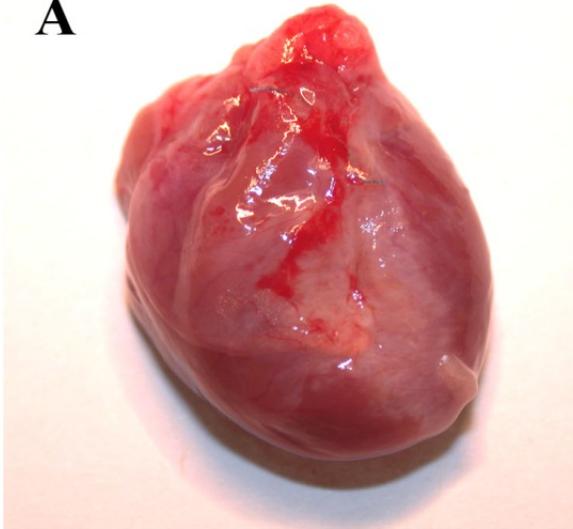
- Homing of bone marrow derived stem cells to the injured myocardium
- Neovascularization of the infarct zone
- Down-regulation of cardiac myocyte CXCR4 expression
- Recruitment of cardiac stem cells into the infarct border zone
- Improved cardiac function

Direct Adenoviral Injection vs. Injection of Adenovirally Transduced SKMB

Study with AdVEGF-165

LAD Ligation Model Leads to Transmural Infarction

A



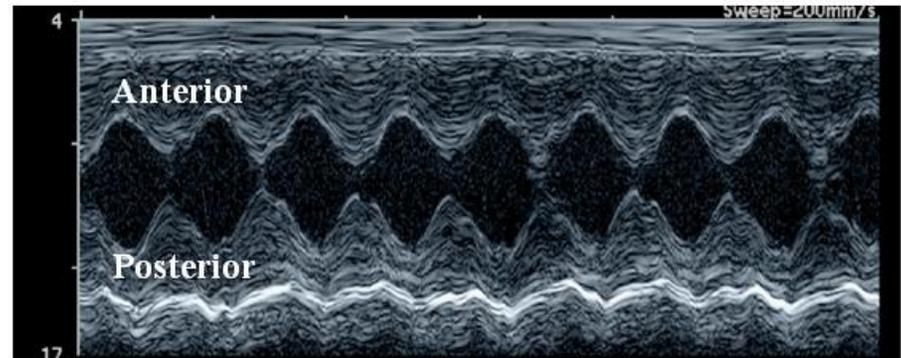
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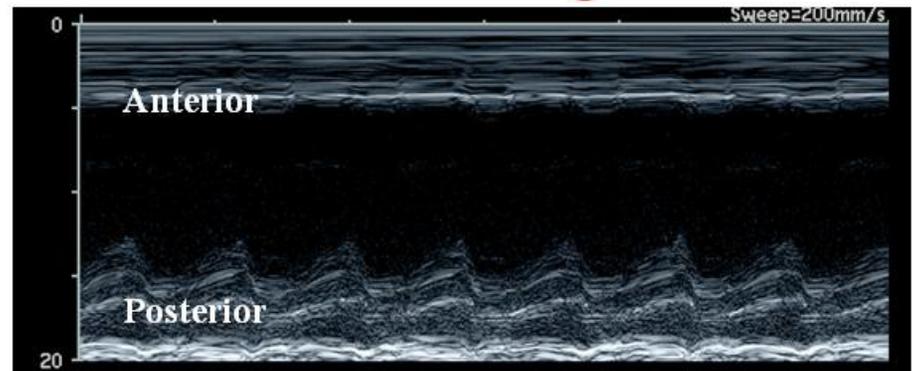
Model of Ischemic Cardiomyopathy

- Lewis Rat LAD ligation
 - SKMB (2 million, 5 divided doses)
 - Ad VEGF-165 (10^7 pfu)
 - SKMB Tx for 24 h with Ad VEGF-165 (10^7 pfu)
- 2D and M-mode echo
 - Anterior and posterior wall thickness
 - Shortening fraction
- Cells injected 8 w after AMI around infarct zone

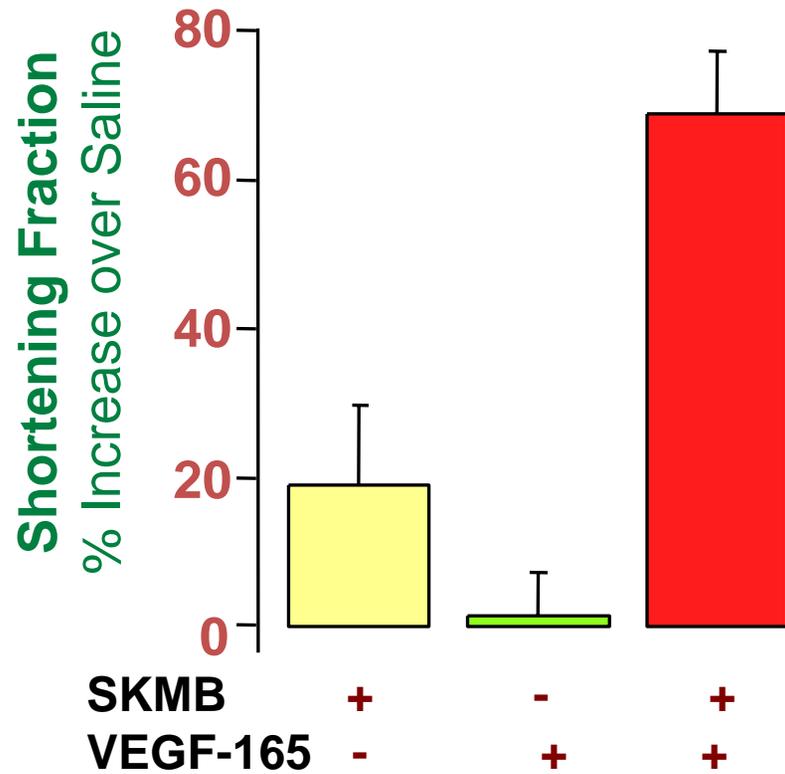
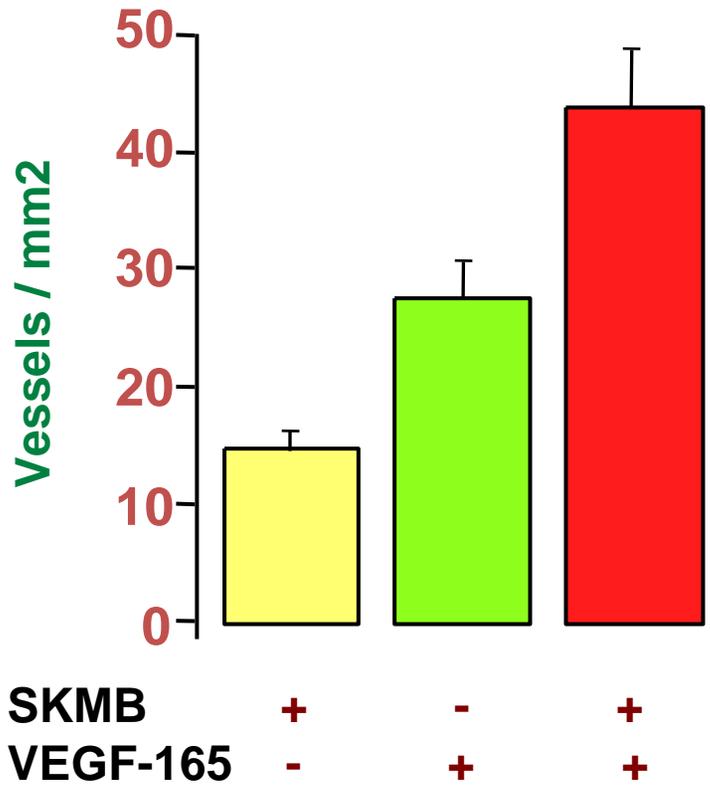
No MI



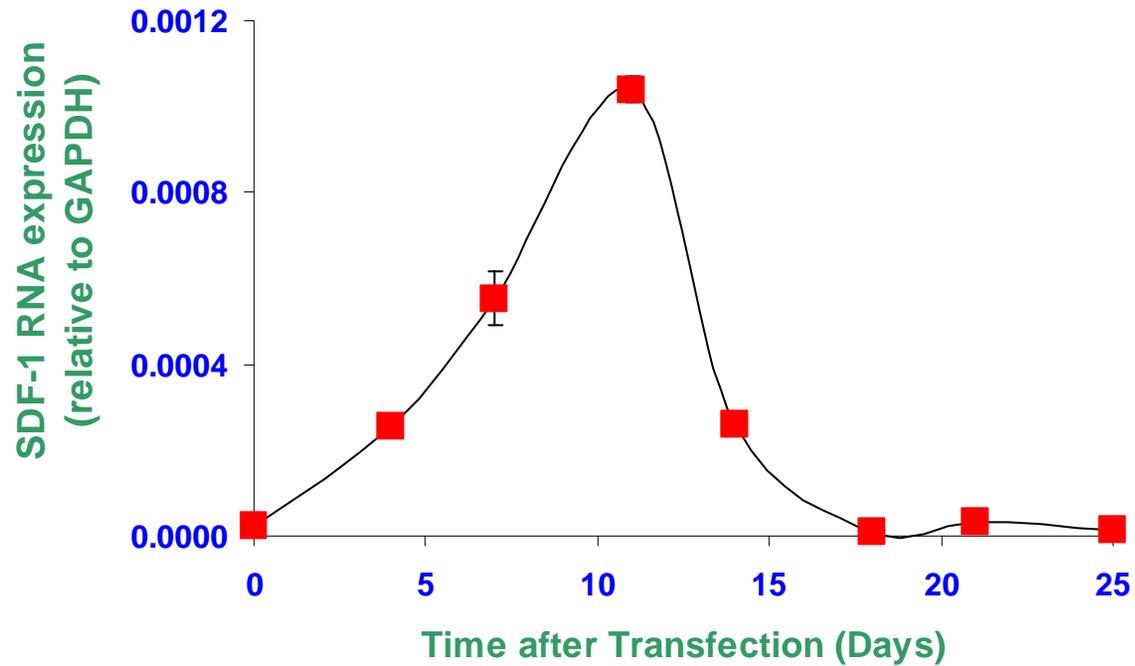
8 w after LAD ligation



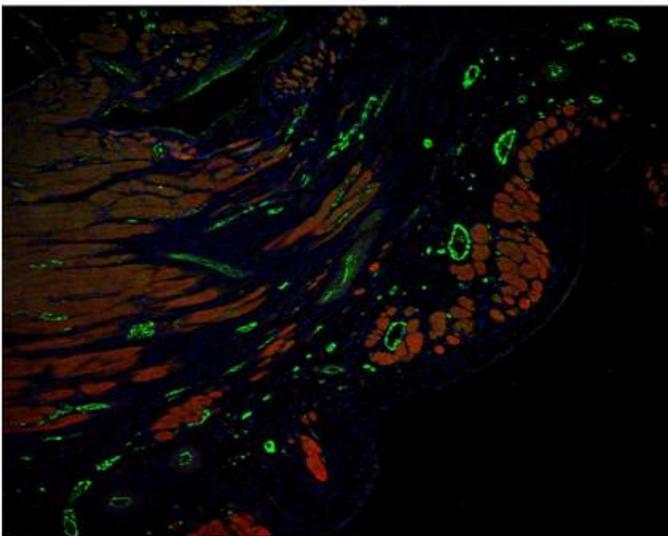
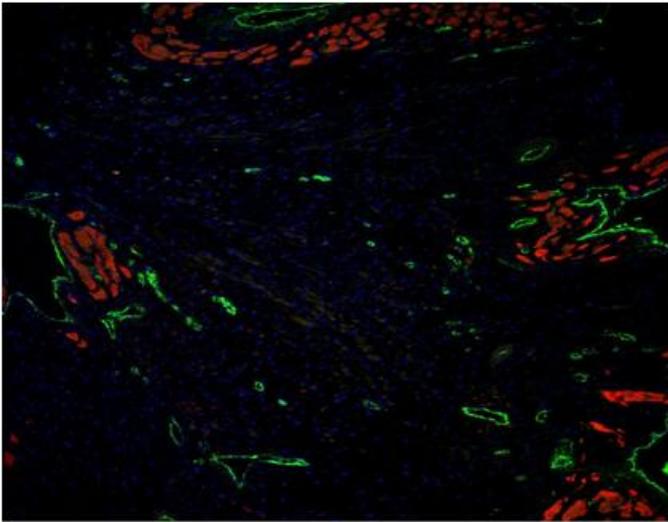
SKMB vs. Adenoviral Gene Transfer



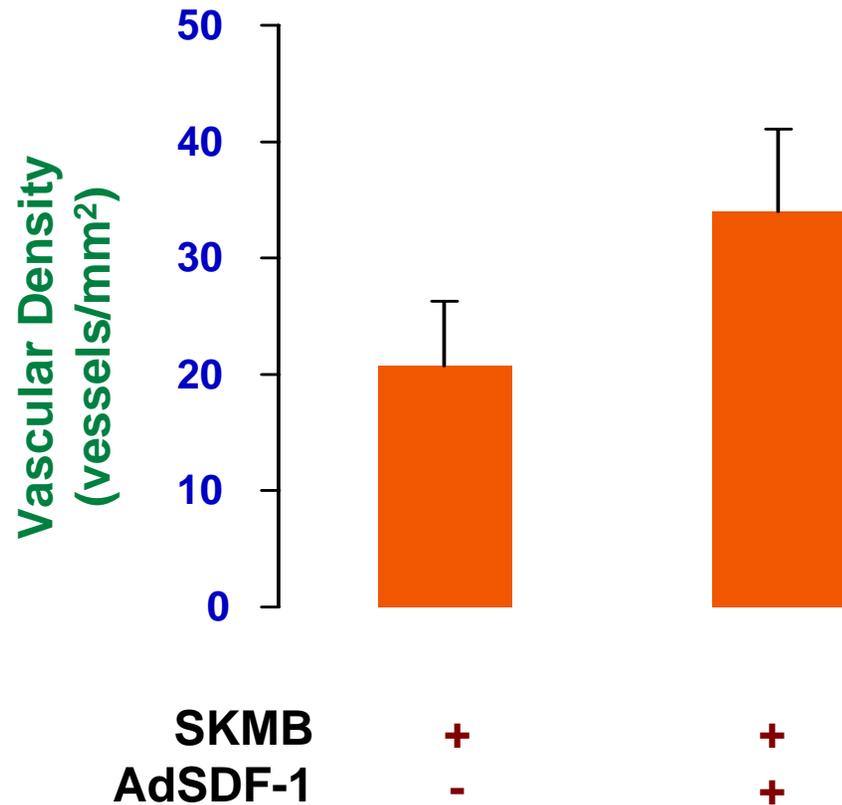
Expression Profile of AdSDF-1 Transduced SKMB



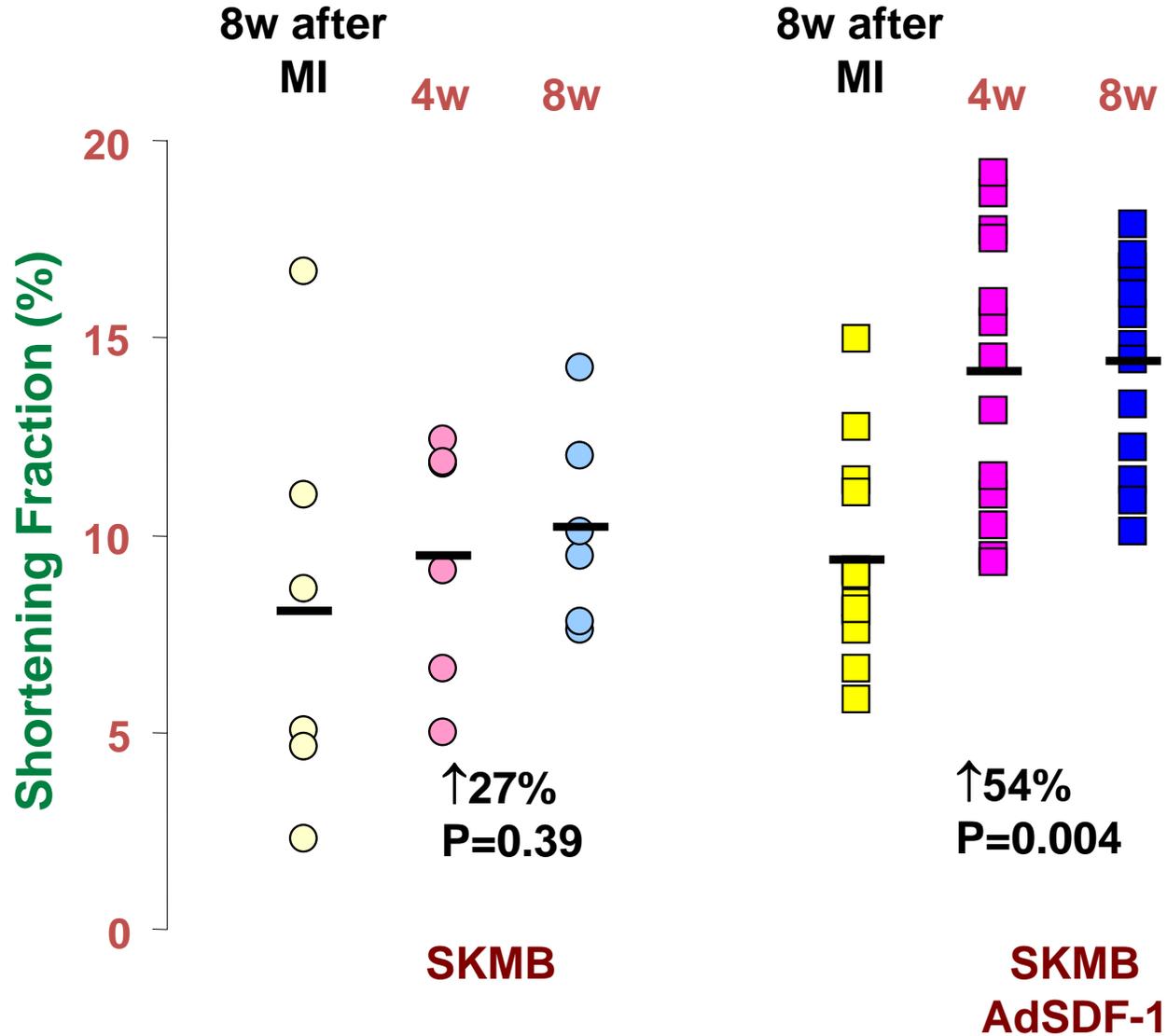
SDF-1 is Angiogenic



vWF for Endothelial Cells



LV Shortening Fraction



Preclinical Studies

1. Autologous Ad-SDF-1 Myoblast Transplantation: 90 Day Toxicity Study in a Swine Myocardial Infarction Model.
2. Tumorigenicity Evaluation of Human Ad-SDF-1 Myoblast Cells in Athymic (Nude) Mice.
3. Effect of SDF-1 on Stem-cell Homing and Tissue Regeneration in Ischemic Cardiomyopathy.
4. SDF-1 Expressing Myoblasts Improve Cardiac Function Compared to Myoblasts Alone in Porcine Model of Ischemic Cardiomyopathy.
5. Mechanical and Electrical Effects of Cell Based Gene Therapy For Ischemic Cardiomyopathy are Independent.
6. AAV SDF-1 Modified Skeletal Myoblast Therapy for Heart Failure.
7. Cellular, But Not Direct, Adenoviral Delivery of Vascular Endothelial Growth Factor Results in Improved Left Ventricular Function and Neovascularization in Dilated Ischemic Cardiomyopathy.

Autologous Ad-SDF-1 Myoblast Transplantation: A 90 Day Toxicity Study in an MI Model in Swine

Safety/Pharmacology/Toxicology Outcomes:

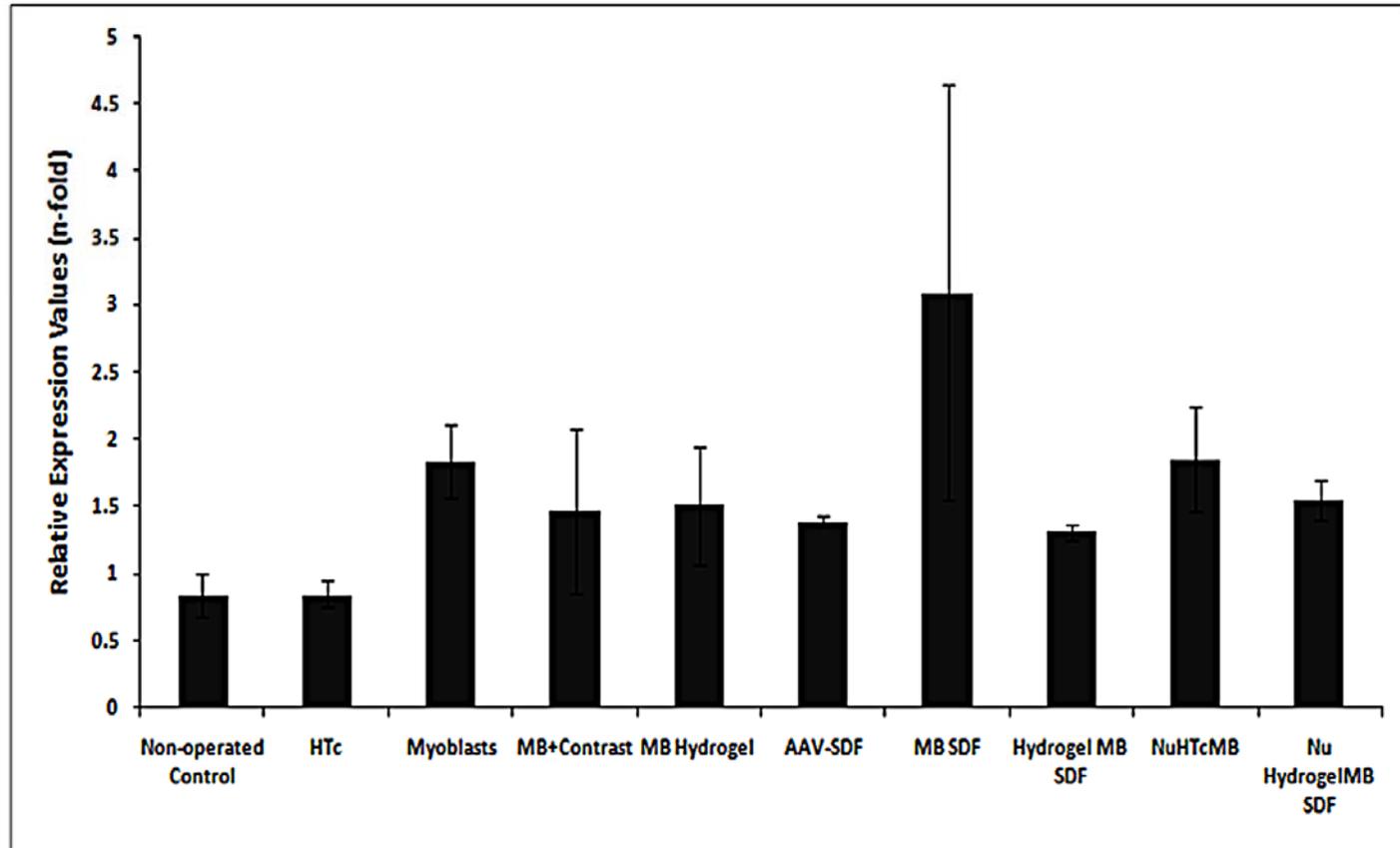
- Injection of the Ad-SDF-1 transduced myoblasts was not associated with clinical findings, including: weight loss, blood pressure changes, electrocardiographic changes or changes in hematology, coagulation, or clinical chemistry parameters (n=9 male, 8 female).
- No arrhythmias resulting from Ad-SDF-1 transduced skeletal myoblast implantation out to 90 days.
- All animals enrolled on study survived to the scheduled necropsy with the exception of animal number 219. Animal number 219 was found dead 9 days post injection with the cause of death believed to be related to the MI.

Tumorigenicity Evaluation of Human Ad-SDF-1 Myoblasts in Athymic (Nude) Mice

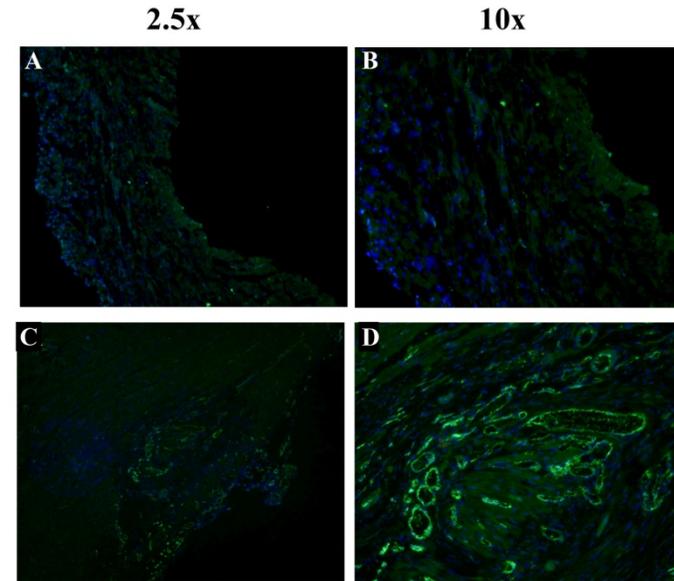
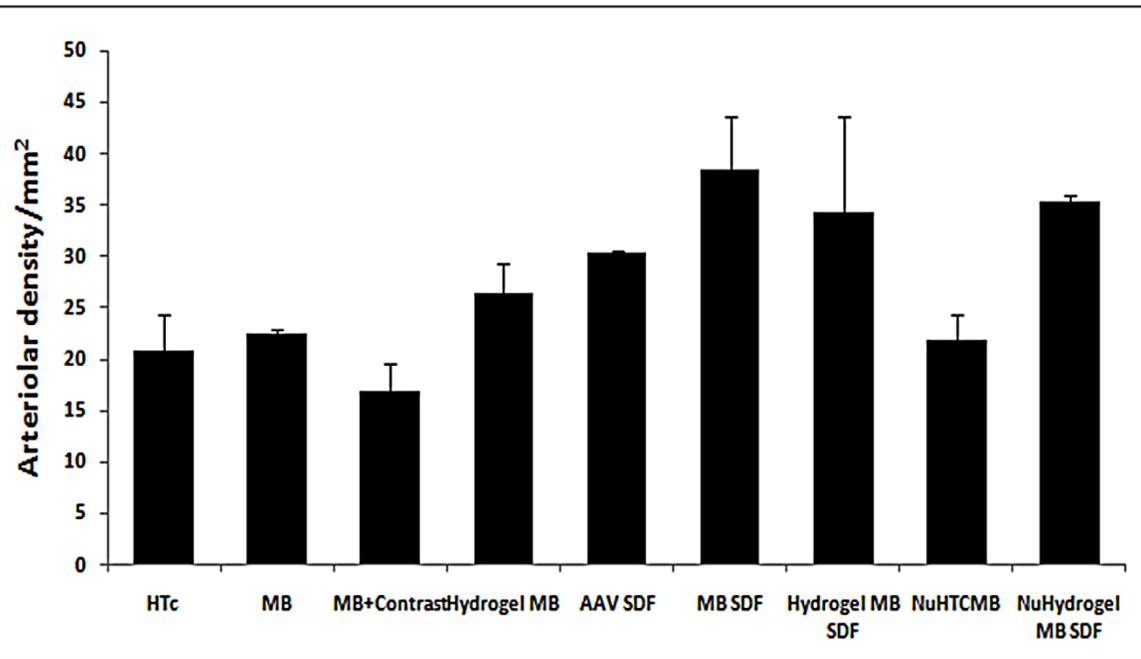
Safety/Pharmacology/Toxicology Outcomes:

- In comparison to the positive and negative control cell lines, the Human Myoblasts + Ad-SDF-1 were well tolerated.
- There were no adverse trends in body weight, clinical observations, or clinical pathology parameters in response to test article.
- Observed injection site fibrosis likely due to the injection process.

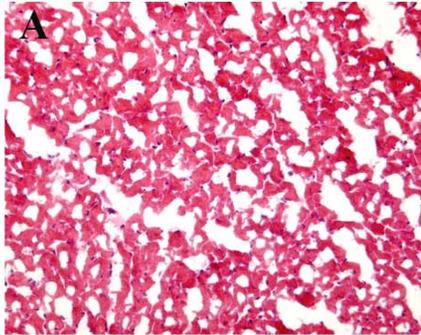
Level of SDF-1 Expression at 8 weeks Post AAV-SDF-1 Modified Human Myoblasts in Nude Rats



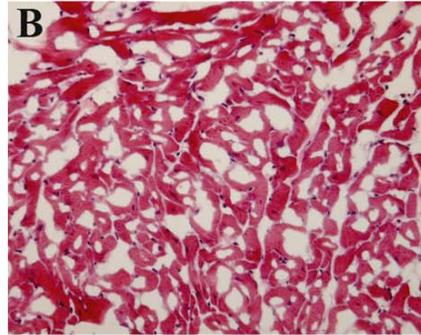
SDF1 modified SKMB Increase Vascular Density post MI



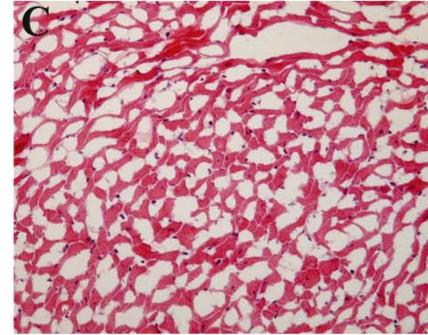
Comparison of Infarct Zone 8-weeks following AAV-SDF1 SKMB



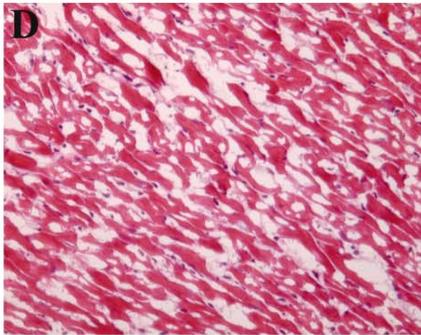
Non-operated Control



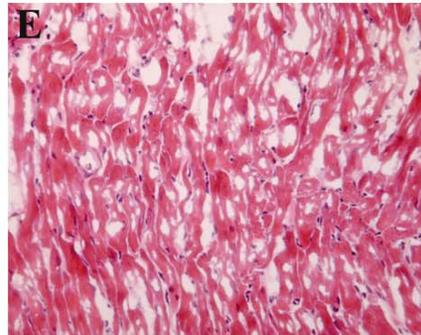
HTc



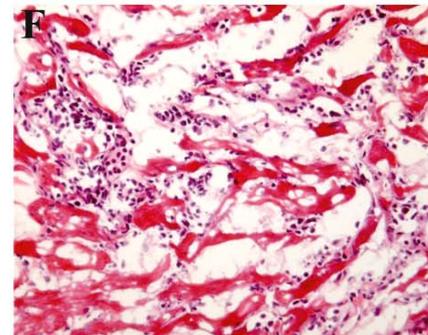
MB



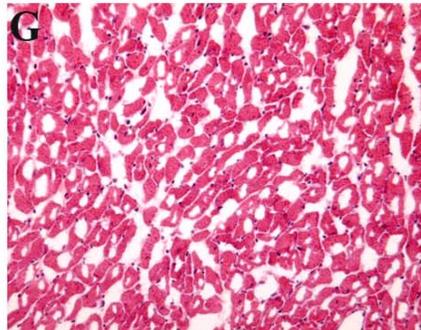
MB+C



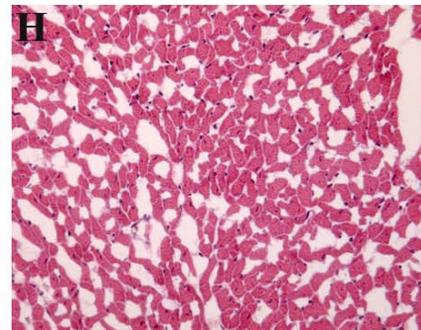
HyMB



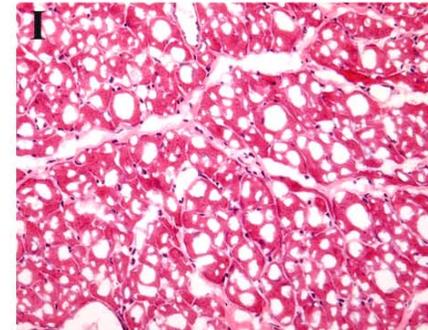
HyMB



SDF



MB SDF



HyMB SDF

Conclusions

- Modified SKMB are able to express SDF-1 up to 15 days which serves as homing signal for myocardial repair.
- Delivery of Modified SKMB is well tolerated in swine by the intended clinical route.
- Short term and long term expression of SDF-1 via SKMB did not lead to tumor formation in rodents.
- SDF-1 Expression in SKMB leads to increased vascular density and improved EF post MI.