Autologous vs. Allogeneic Cells for Cardiovascular Repair

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Disclosures

Company Name	Current Relationship
Juventas Therapeutics	Founder, CSO, Equity, Inventor, BOD
SironRx Therapeutics	Founder, CMO, Equity, Inventor
Cleveland Heart Lab, LLC	Founder, CMO, Equity, Inventor
Oakwood Medical Ventures	Venture Partner
Aastrom Biosciences, Inc	SAB Member
Athersys, Inc.	Sponsored Research
SDG, Inc.	Sponsored Research
MPI Research	Consultant
NIH, Heart Failure Network	DSMB Member
BIOMET, Inc.	DSMB Member
VBL, Inc.	DSMB Member
CardioVIP, Inc.	Member BOD

Why Allogeneic Cell Interest

- Allogeneic cells can be sourced from young healthy donors
- Elderly patients with co-morbid conditions have stem cells of with decreased functional capacity

- Allogeneic cells are anti-inflammatory and could be available for delivery at the time of primary PCI
- Autologous cells need to be harvested, collected and possibly propagated meaning delivery is delayed

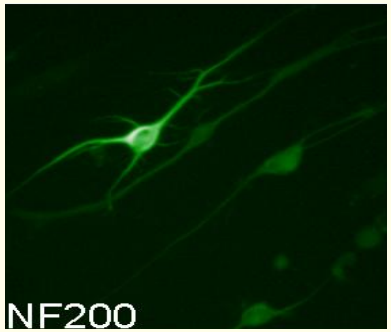
Allogeneic Cells of Interest

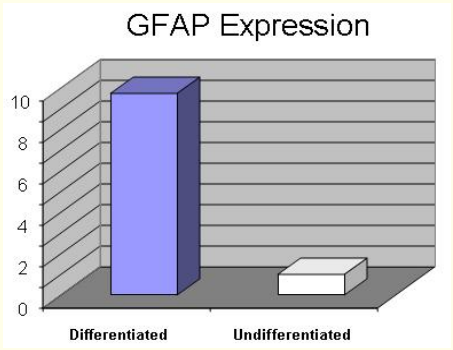
- Generally derivatives of Mesenchymal Stem Cells (MSC)
  - Clinical data for
    - Mesenchymal Stem Cells
    - Multipotent Adult Progenitor Cells
  - Tissue sources
    - Bone marrow
    - Placenta
    - Amniotic membrane

Lineage Differentiation Assays for MAPC

Neuronal

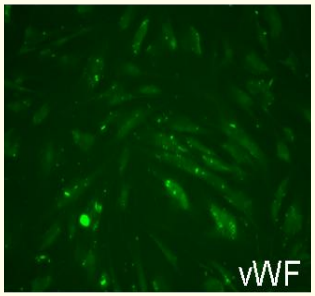
Ectoderm

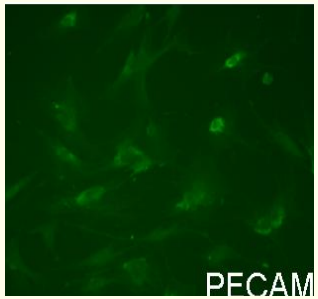


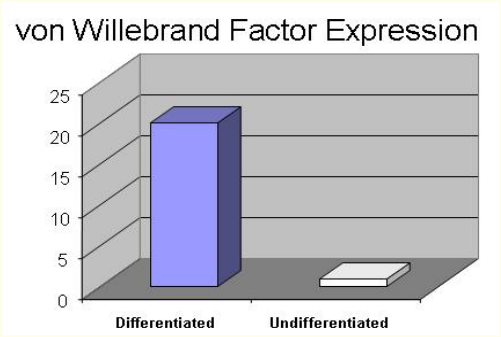


Endothelial

Mesoderm

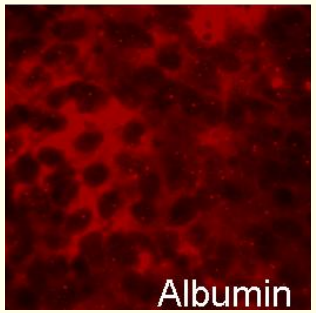


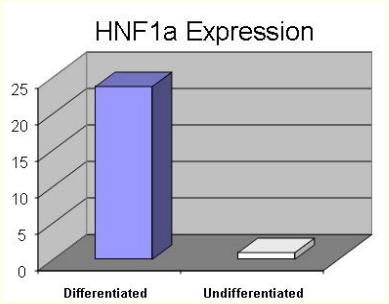


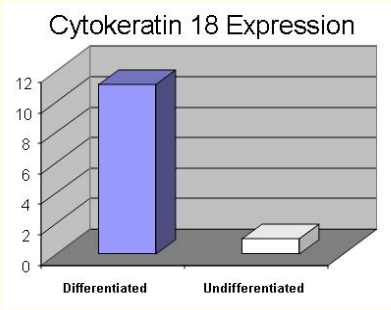


Hepatic

Endoderm



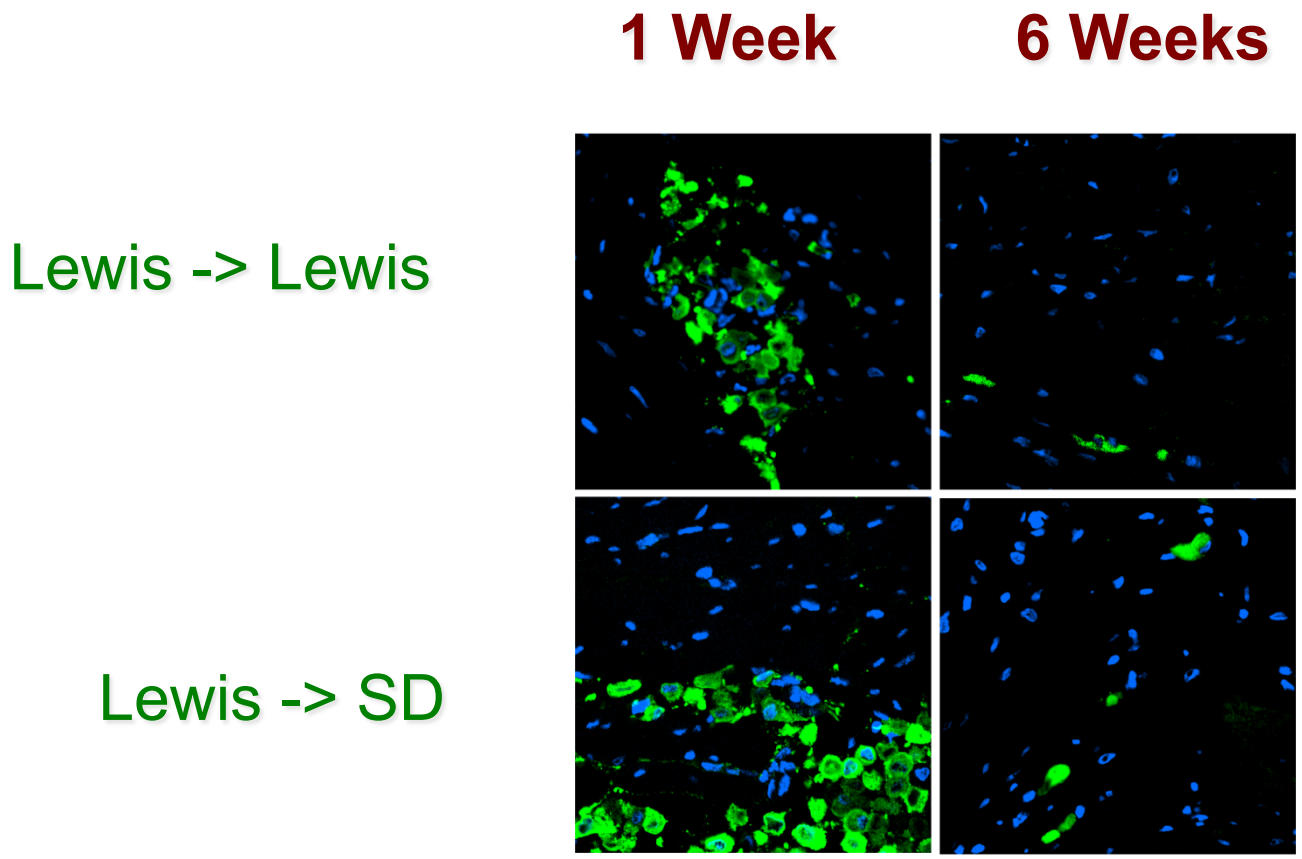




MAPC for Cardiac Cell Therapy in AMI

- Allogeneic potential without the need for immunosuppression
- MAPC have tri-lineage differentiation potential
- Proliferative and genetically stable
- Thousands of doses from a single donor
- True – “off the shelf” cell product

Allogeneic and Syngeneic MAPC Survival and Engraftment

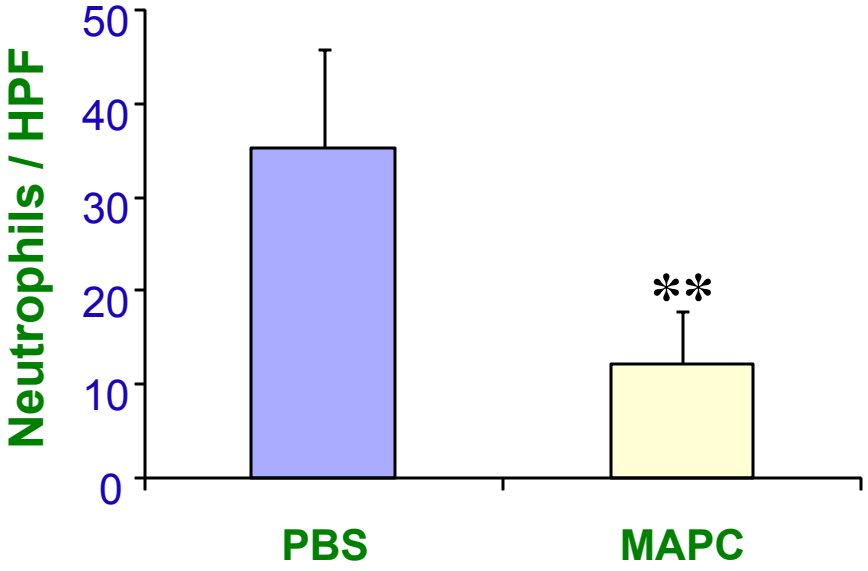


MAPC Reduces Inflammation

Rat AMI Model

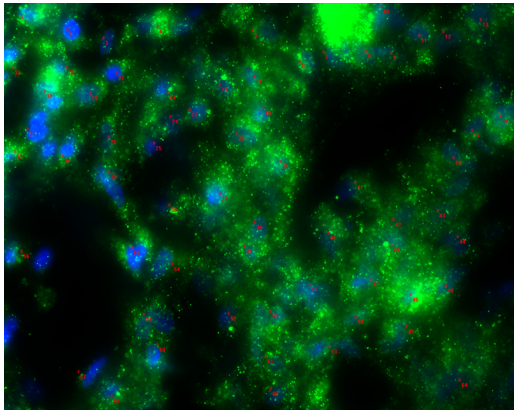
- **LAD ligation and direct MAPC injection in infarct zone**
- **Sacrifice after 3 days**

Neutrophil count in infarcted hearts

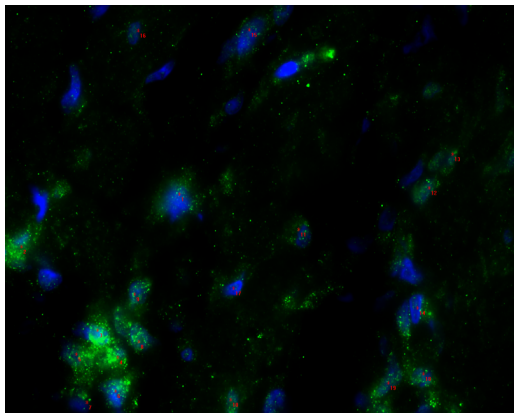


Elastase staining in infarct zone

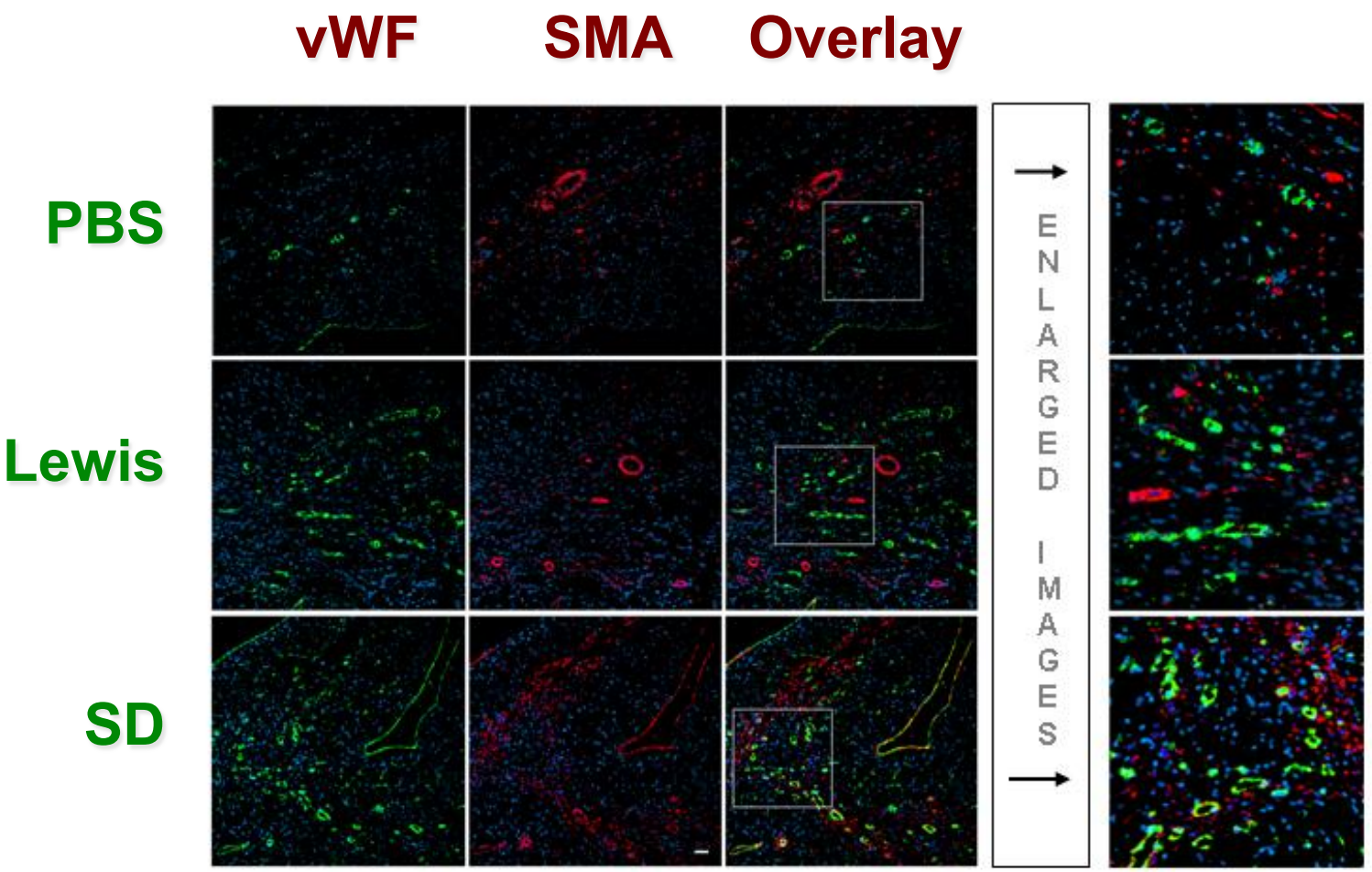
PBS



MAPC

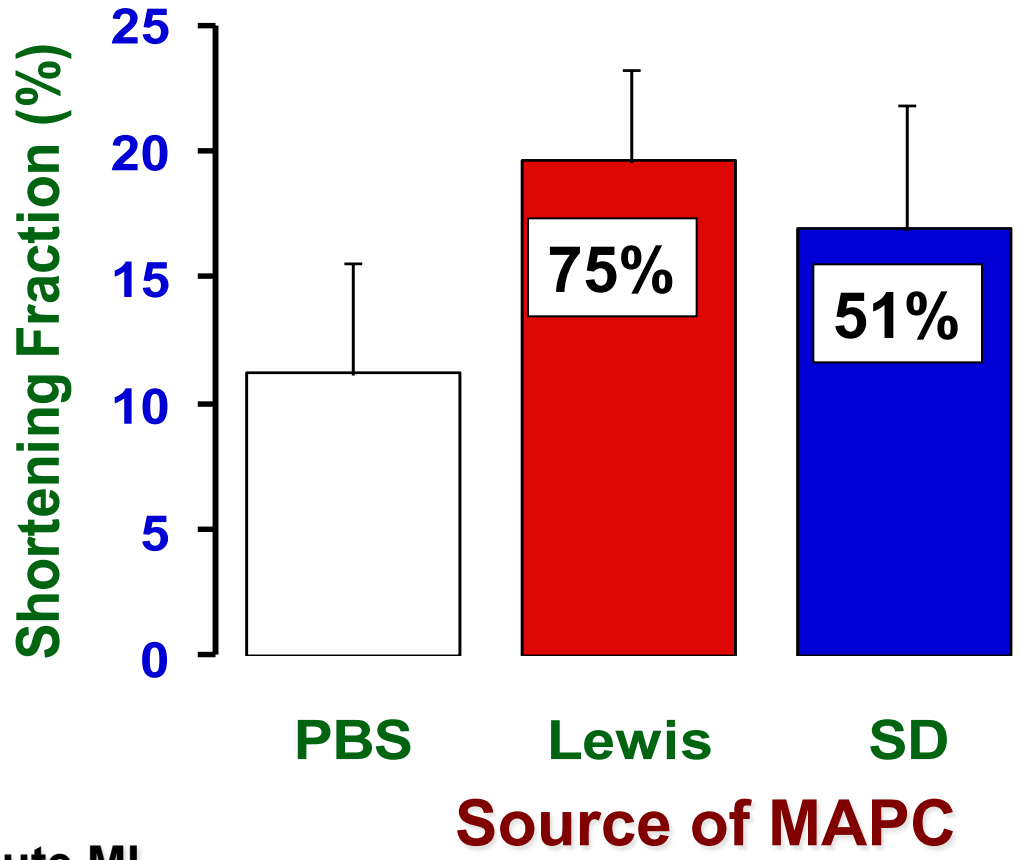


Vascular Effects of MAPC



6 weeks after Acute MI
10 million MAPC or Saline at time of MI

MAPC into Lewis Rat at Time of Acute MI



6 weeks after Acute MI
10 million MAPC or Saline at time of MI

MAPC vs. MSC

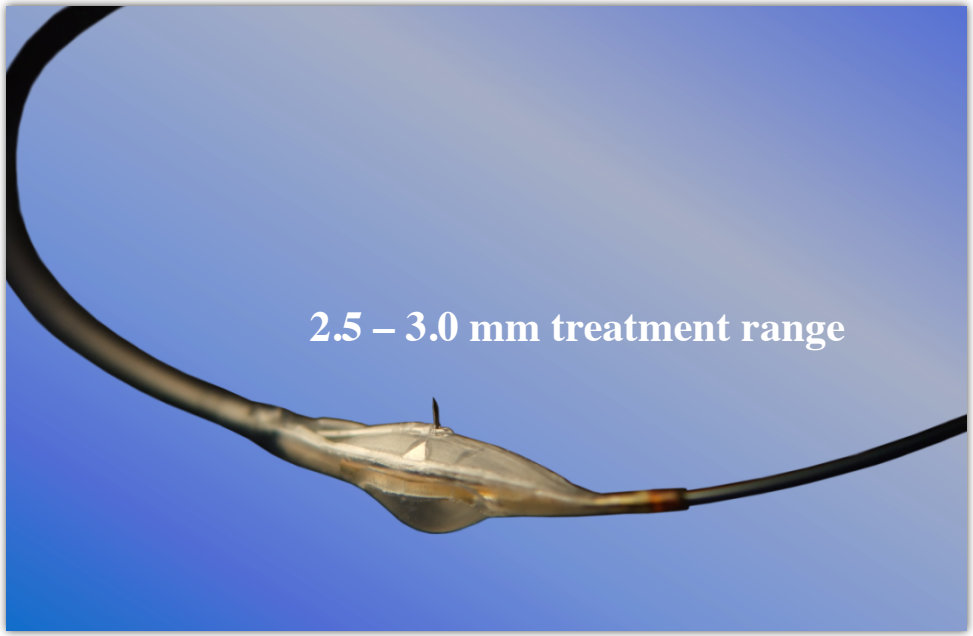
• Stem Cell Survival	No	Yes
• Inhibit Myocyte Death	Yes	Yes
• Cardiac Differentiation	No	No
• Anti-inflammatory	Yes	Yes
• Home to injured myocardium	No	Yes
• Similar Effects Allo vs. Auto	Yes	Yes
• Angiogenic	Yes	Yes
• Paracrine factor mechanism	Yes	Yes

Clinical Strategy

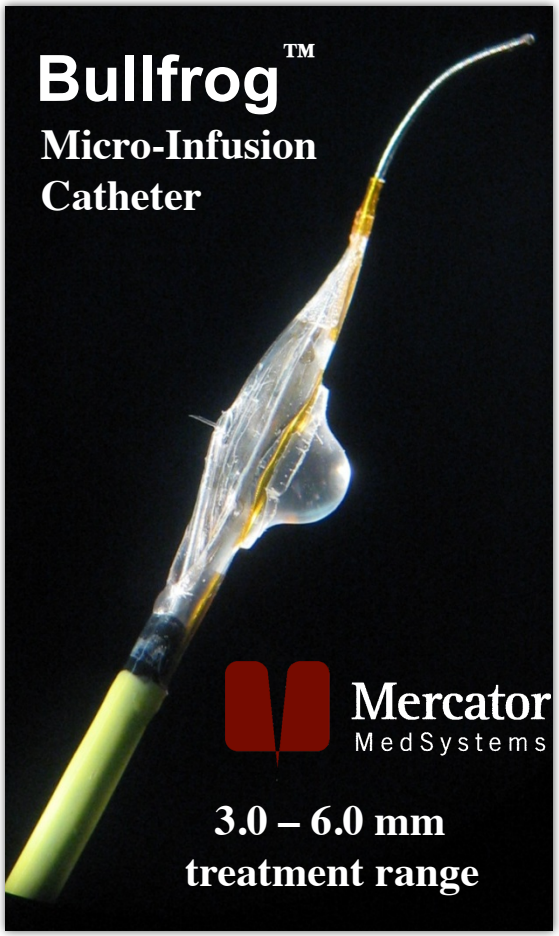
- Off the shelf cell product for allogeneic use
- Wanted easy to implement cell delivery strategy so that cells can be delivered at time of primary PCI

Adventitial Micro-Infusion Catheter Operation

Cricket™ Micro-Infusion Catheter



Both 510(k) cleared for delivery to vessel wall or perivascular area

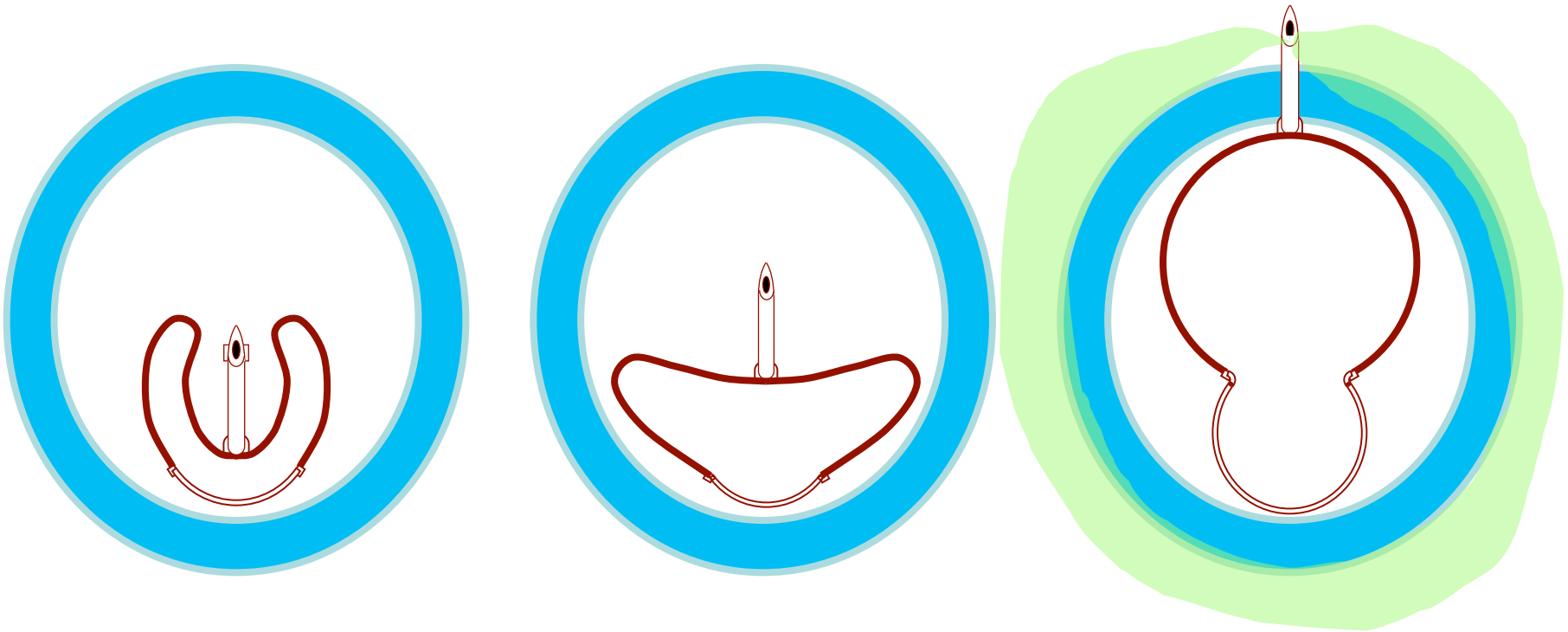


Adventitial Micro-Infusion Catheter Operation

Balloon shields microneedle

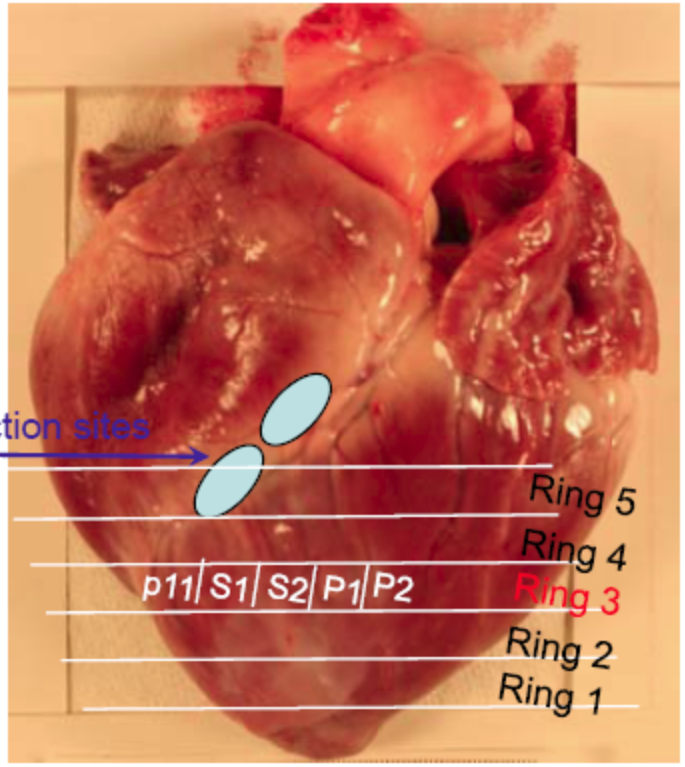
Needle is deployed with inflation

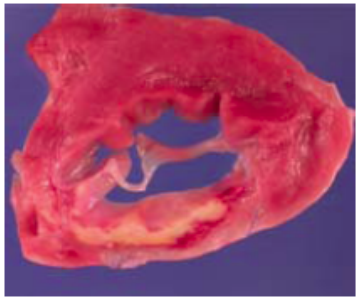
Needle reaches adventitia for infusion



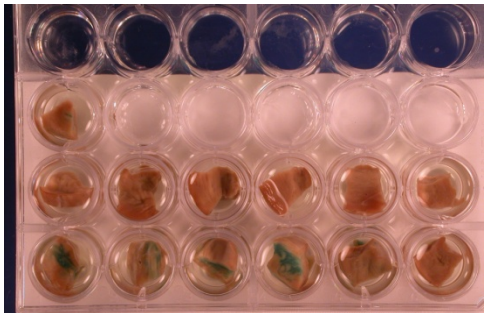
Biodistribution Following Transarterial Delivery in Porcine LAD AMI Model

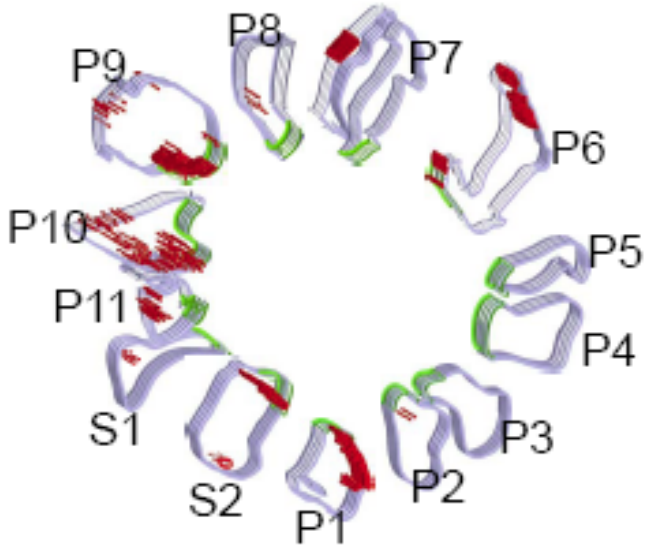
Transarterial catheter delivery of pig MultiStem® cells, 2 weeks, animal 132





Distribution of b-gal cells within Tissue Block, Ring #3





Clinical Synopsis Completed Phase I

- Phase I study, open label, dose escalation
  - STEMI, LVEF between 30-45%
  - Administration of MultiStem in coronary artery (via transarterial catheter) delivered 2-5 days after AMI
  - Multiple sites

- Objectives
  - Primary endpoints: safety: arrhythmias, acute toxicity, hospitalization, death, mechanical complication
  - Secondary endpoints: functionality measure

Demographics

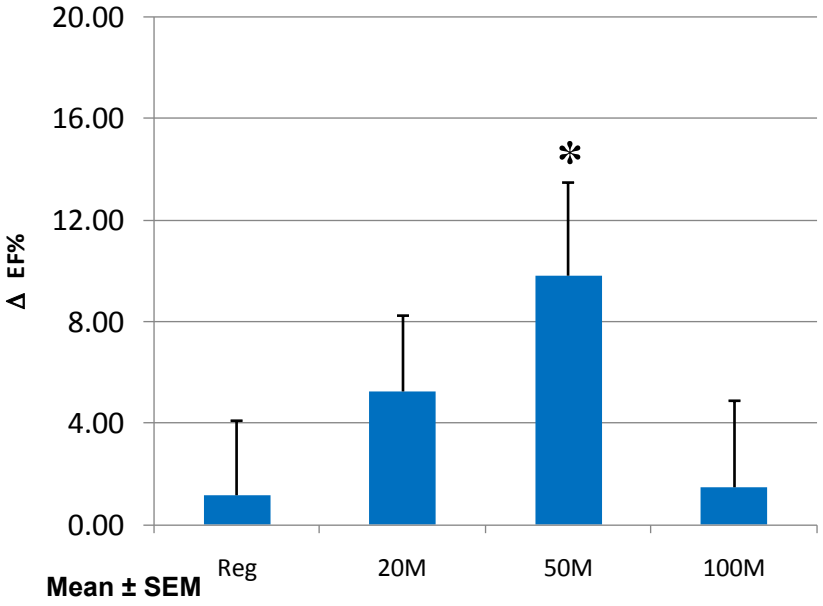
	Registry	20M	50M	100M
# enrolled	6	6	7	6
Mean age	53	64	54	53
Sex (m/f)	5/1	3/3	4/3	5/1
BMI	32.3	34.9	29.1	27.4
Diabetes	2 (33.3%)	2 (33.3%)	1 (14.3%)	1 (16.6%)
Hyperlipidemia	4 (66.6%)	4 (66.6%)	6 (85.7%)	3 (50%)
Hypertension	3 (50%)	4 (66.6%)	5 (71.5%)	4 (80%)
Smoker	3 (50%)	5 (83.3%)	4 (57.1%)	4 (80%)
Target vessel				
LAD	6 (100%)	4 (66.6%)	5 (71.5%)	6 (100%)
RCA	0	2 (33.3%)	2 (28.6%)	0
Time to reperfusion, hr	3.8	4.3	8.6	4.5
Baseline LVEF, %	42.3	40.2	41.9	47.8
TIMI flow	3	3	3	3
CK-MB ng/mL pre MultiStem (min-max)	na	2.4-138.7	4-146.6	1.5-228.9
CK-MB ng/mL 18 h post MultiStem (min-max)	na	2.3-39.35	1.6-5.0	1.3-12.1

MultiStem Safe and Well Tolerated at All Dose Levels

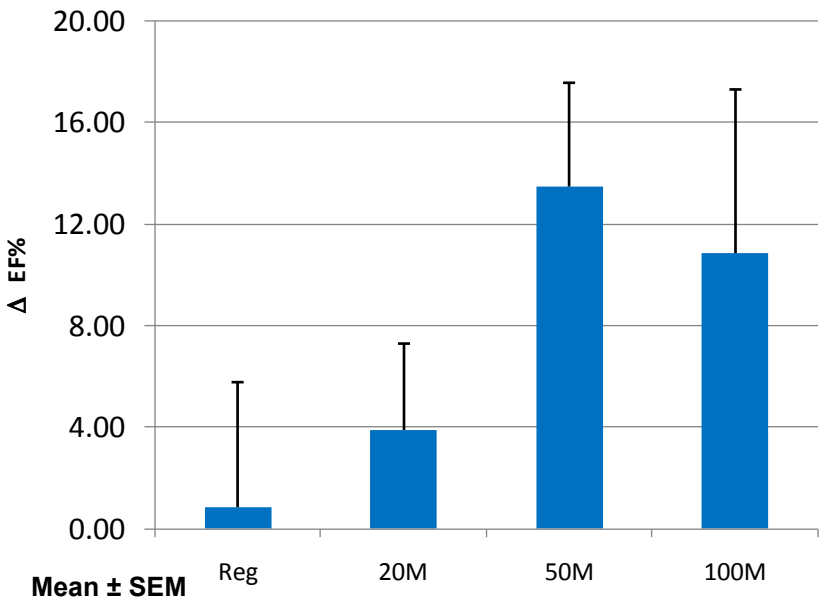
- No clinically significant changes in vital signs, allergic reactions, or infusion-related toxicities associated with MultiStem administration
- No dose limiting toxicities and no infusional toxicities or clinically significant events deemed to be definitely related to MultiStem over 30 day post-acute observation period
- Favorable safety profile over 4 month period following treatment

Ejection Fraction 4-Month Change from Baseline

All subjects

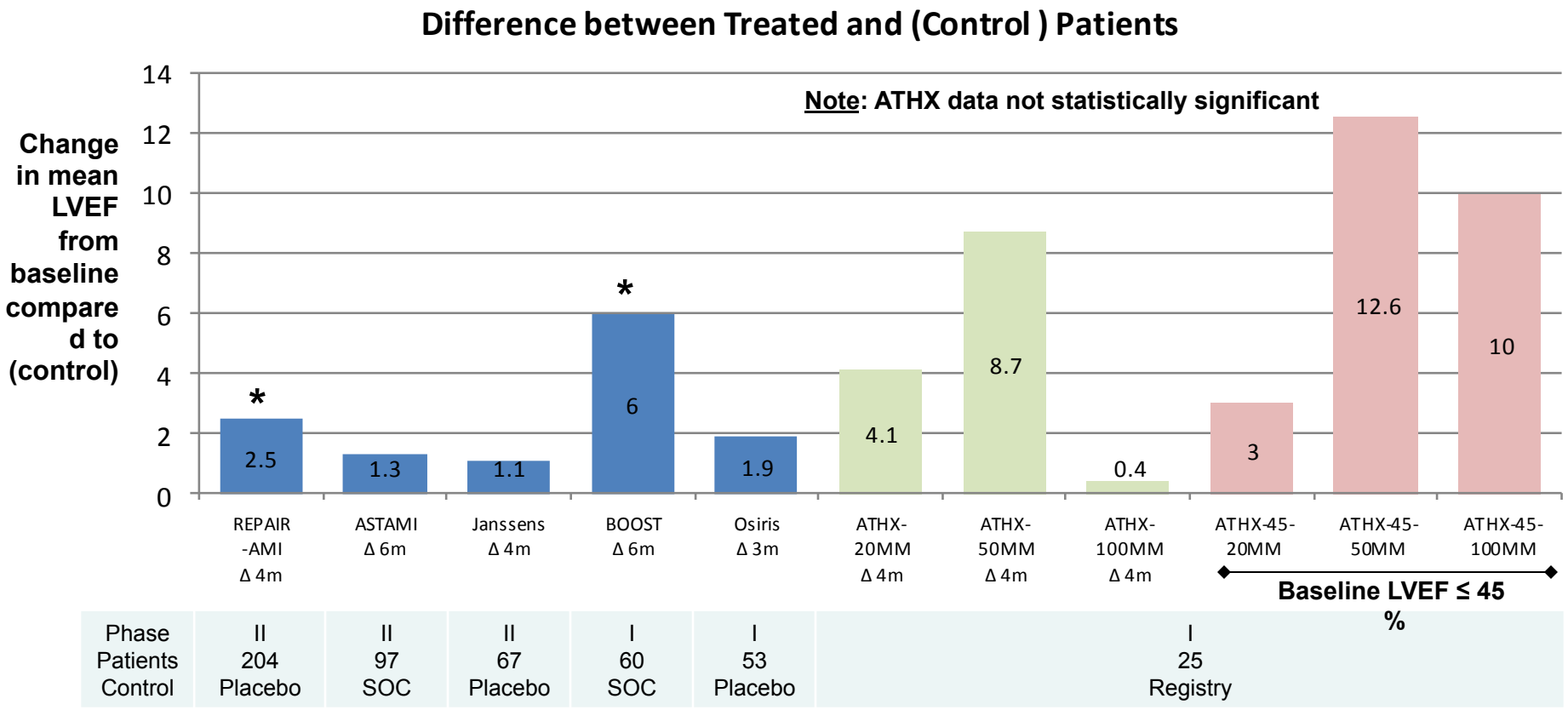


Subjects with baseline LVEF ≤ 45



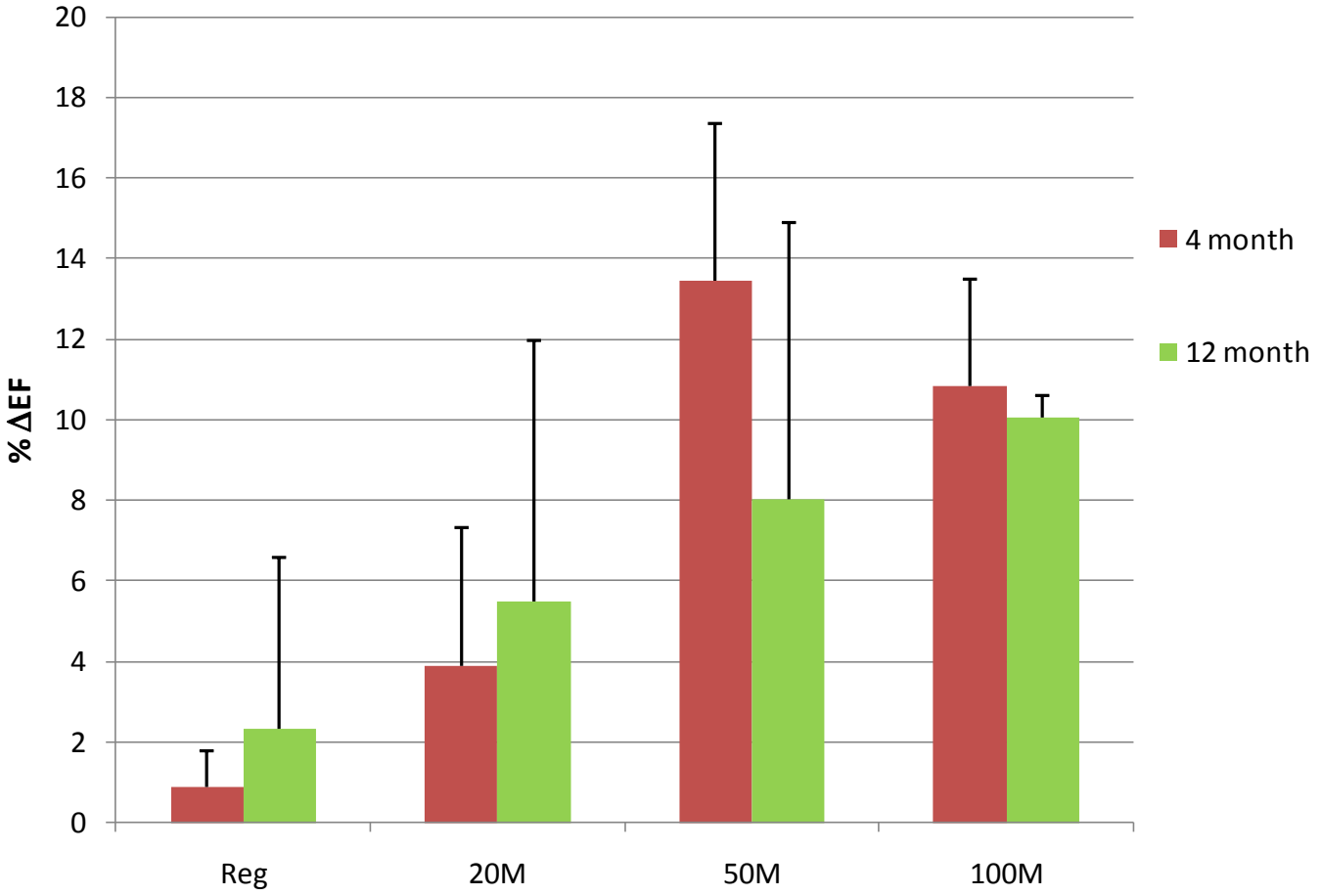
* p<.02, absolute improvement in mean 4-month LVEF relative to baseline

Cell Therapy in AMI – Context Setting
LVEF Comparison at Early Timepoint (3-6 Months)



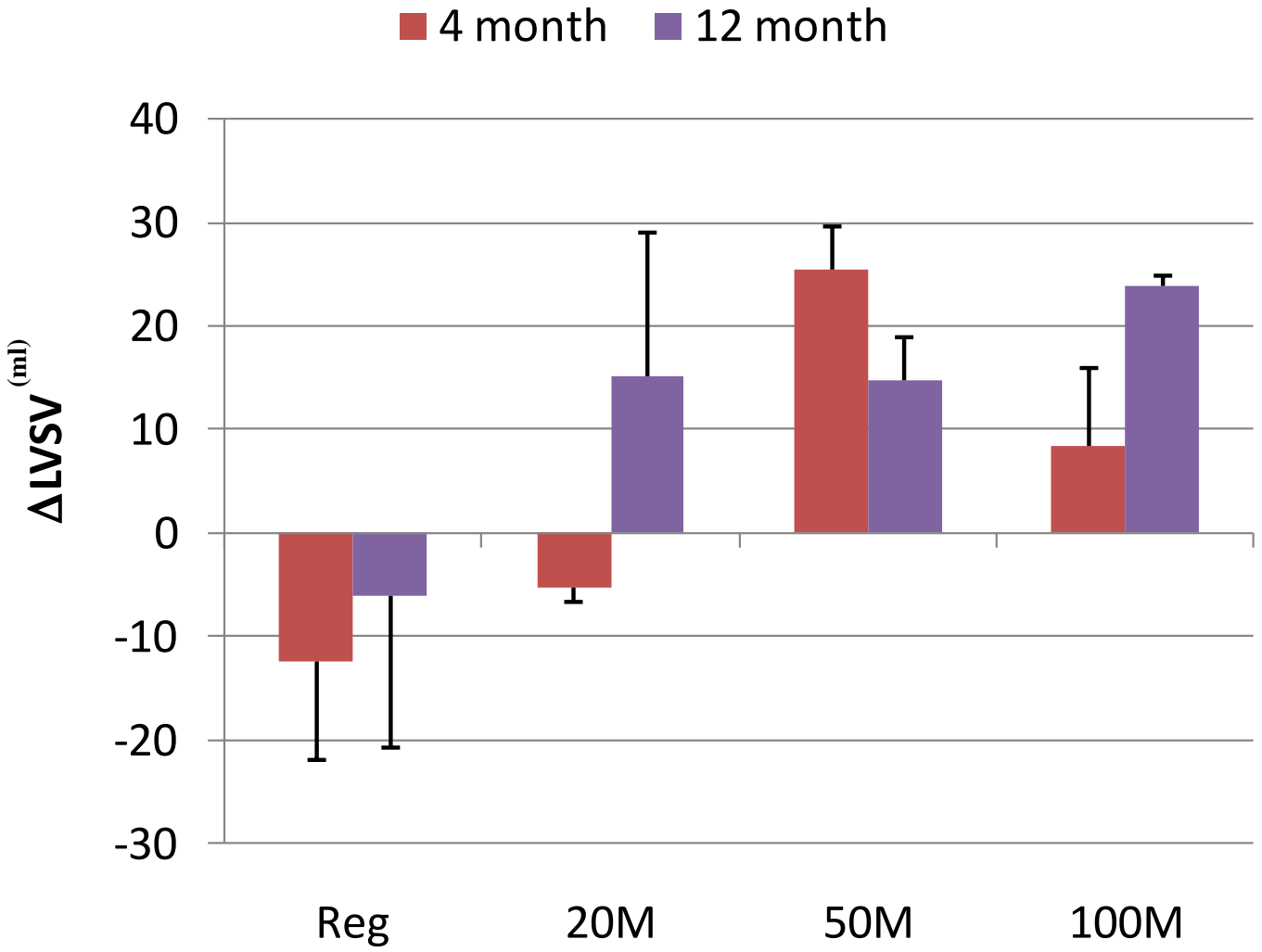
Source: Athersys; N Engl J Med 2006;355:1210-21 (REPAIR-AMI); Circulation 2006;113:1287-1294 (BOOST); N Engl J Med 2006;355:1199-209 (ASTAMI); Lancet 2006;367:113-21 (Janssens); J Am Coll Cardiol 2009;54:2277-86 (Osiris)

Change in LVEF from Baseline Over Time for %EF≤45



Mean ± SEM

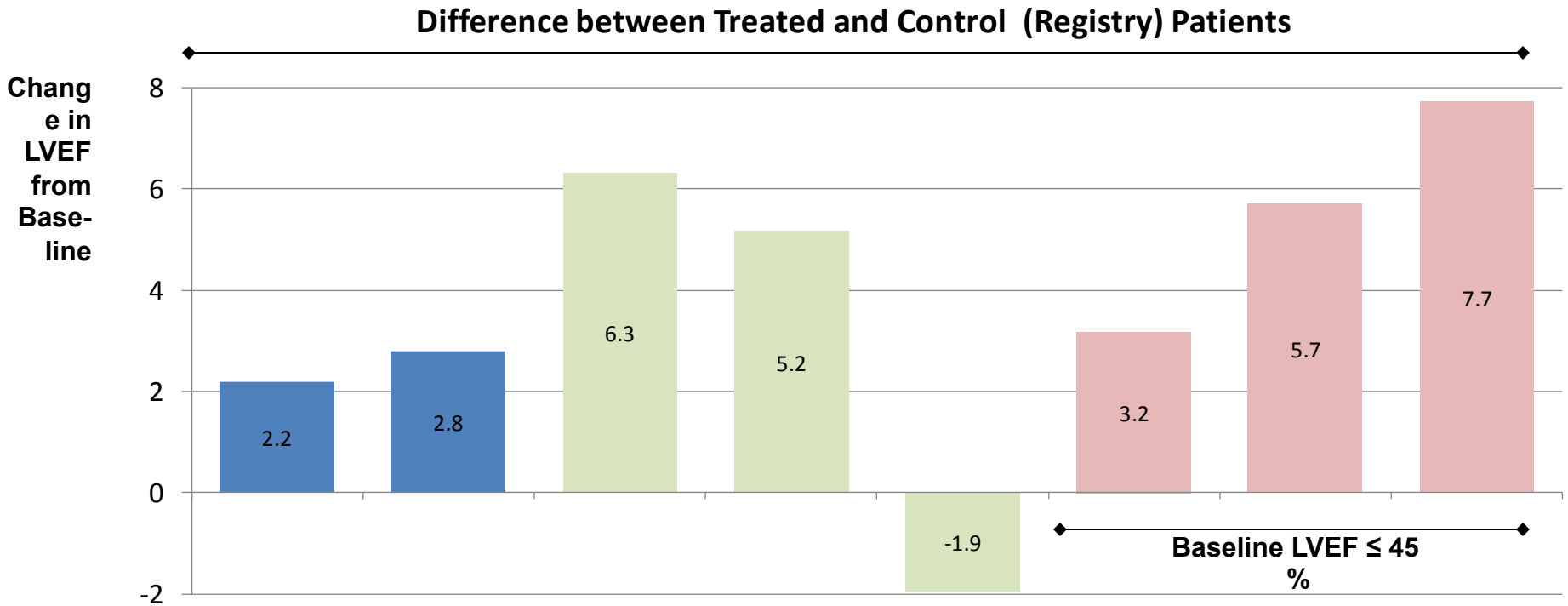
Stroke Volume (LVSV)



Subjects with baseline LVEF <45

Mean ± SEM

LVEF Comparison at Later Timepoint (12 months +)



N, T/C	101/103	30/30	5/5	7/5	6/5	4/3	5/3	**2**/3

Clinical Indications for Allogeneic Stem Cells beyond CV

- GVHD
  - MSC – Treatment of GVHD
  - MAPC – Prevention of GVHD
- IBD
  - Both MSC and MAPC
- STROKE
  - MAPC

Preparation and Planning: Phase 2 Study

- Objectives
  - Demonstrate that MultiStem can provide statistical benefit to AMI patients
  - Improvement in global EF and other cardiovascular performance, and clinical measures
- Basic study parameters
  - LVEF range of >30 to <45, dosed with MultiStem approximately 2 days after PCI
  - Placebo, low dose and high dose (1:1:1)
  - Single injection

Allogeneic MSC AMI Data

- Single infusion within 7 days of AMI
  - 5 year f/u on-going
  - 1 year f/u
    - Decreased cardiac hypertrophy
    - Less ventricular tachycardia
    - Delayed hospitalization/CHF

Additional Data Coming

- POSEIDON Trial
  - Ischemic CM patients
  - Patients receive autologous verse allogeneic MSC
  - Released at AHA next month

Summary

- Allogeneic cell sources appear to have therapeutic potential
- Anti-inflammatory mechanism may support earlier administration to optimize mechanism
- Patients with EF > 45% did not benefit globally from cell therapy
- The combination of MultiStem and Cricket catheter can be used to deliver cells *any time* after AMI
- For AMI allogeneic cells may fit clinical flow better