VIVA Highlights at TCT Asia Pacific 2016

The Promise of Cellular Regenerative Therapies for CLI

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The Goal of 'Therapeutic Angiogenesis':

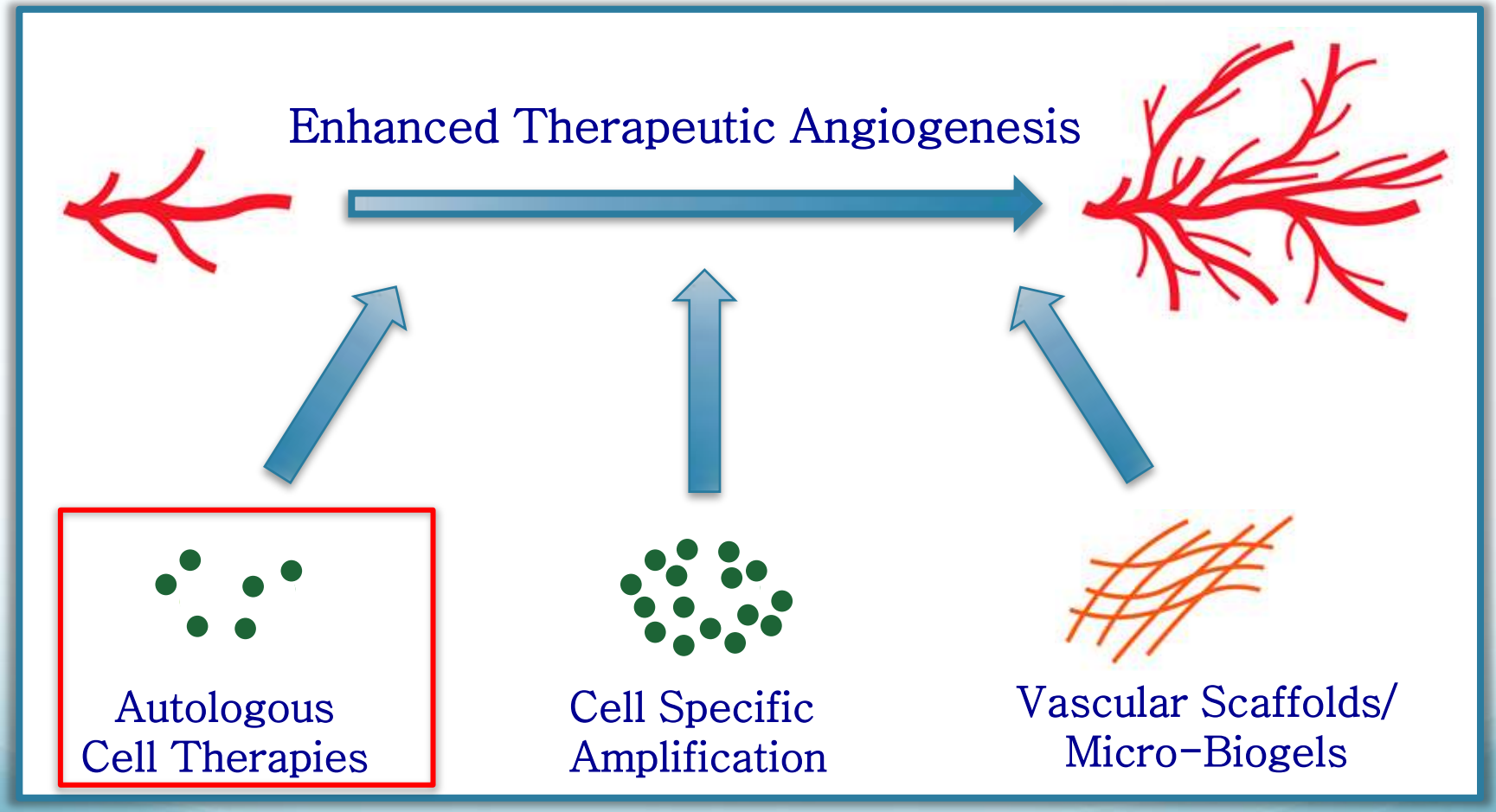
The application of *regulatory genes*, *proteins* and/or *progenitor cells* to patients with vascular disease to *enhance tissue perfusion* through the development of new blood vessels.

In other words: Enhance the body's natural process of regeneration.

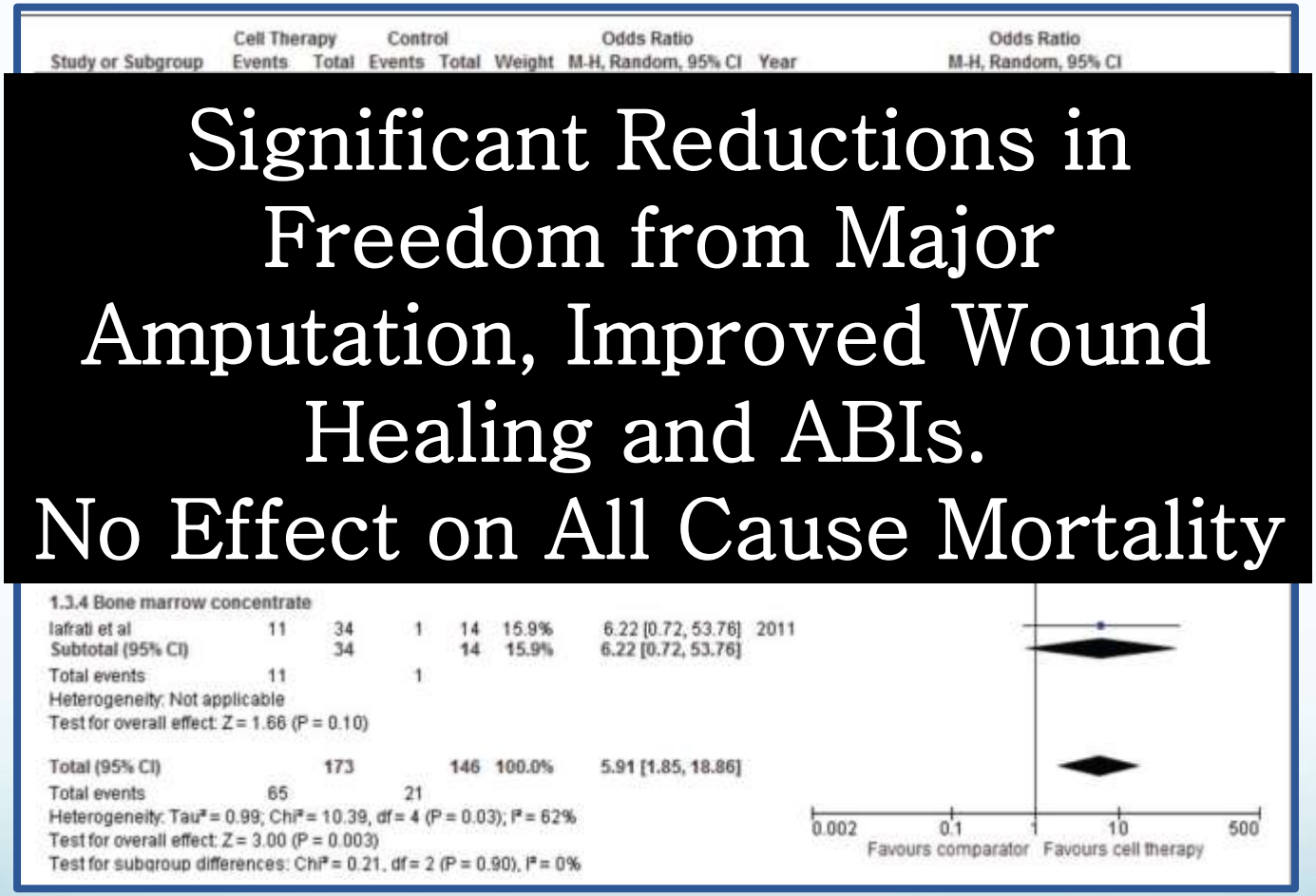
What are the Potential Challenges Faced by these Early Phase Trials?

- What is the ideal mode of administration, cell number for optimal effect, pattern/method/location of administration?
- Time to peak effect, interval dosing? Is a single administration sufficient for optimal effect?
- Is the “no option/poor option” CLI patient too far advanced to salvage and how should that be assessed?
- How do we translate cellular signals of angiogenesis into clinically relevant ‘patient-centric’ endpoints in assessment of effectiveness and safety?

Emerging Paradigms in Cellular Regenerative Medicine



Meta-Analysis of 16 RCTs of Various Cell Therapies Show a Favorable Trend



Odds ratio of improvement in ABI (>0.1 or >15%) in patients with CLI treated with cell therapy versus no cell therapy (random effects model).

Liew et al., Angiology 2015

Phase I BioMet Study Description

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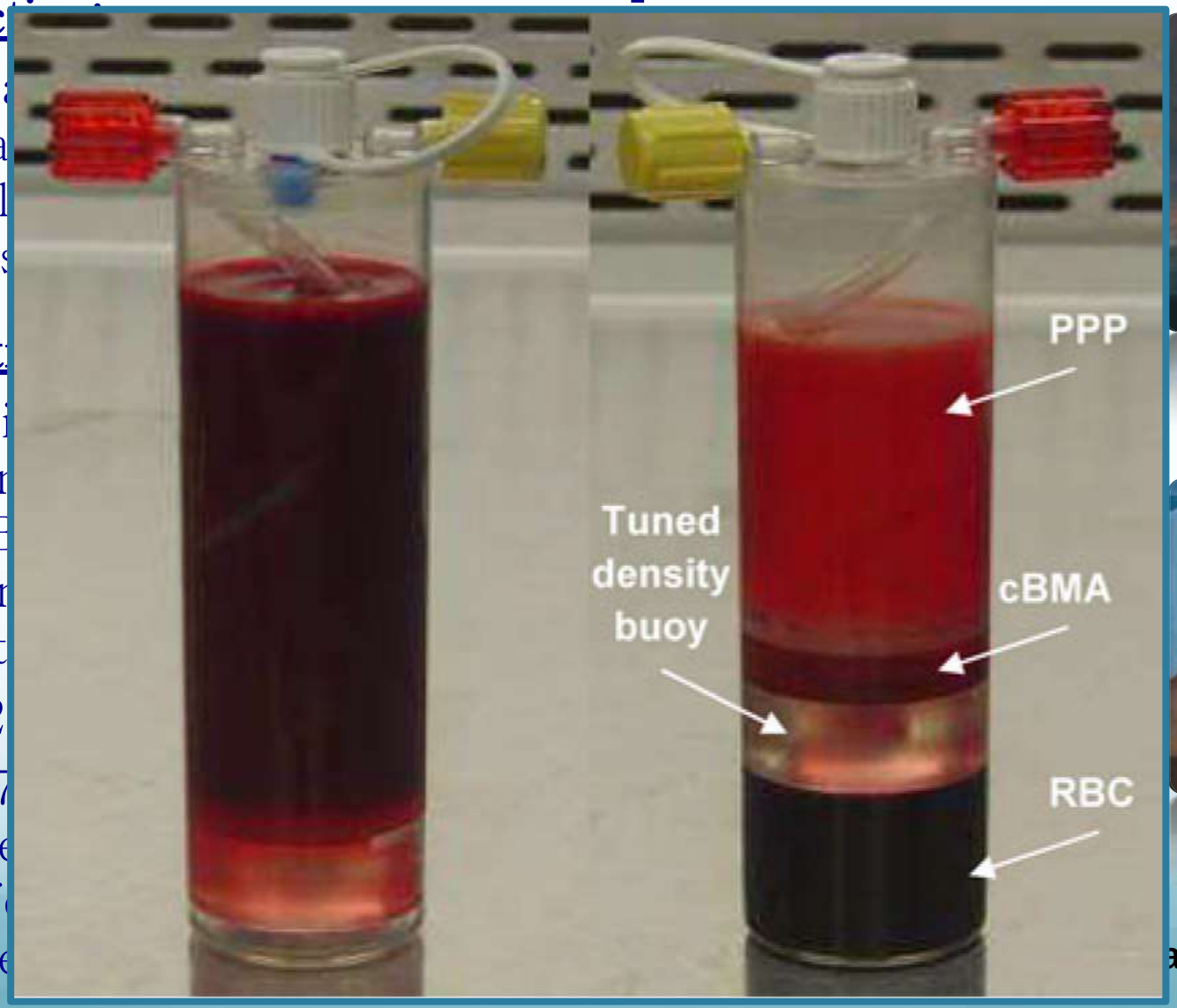
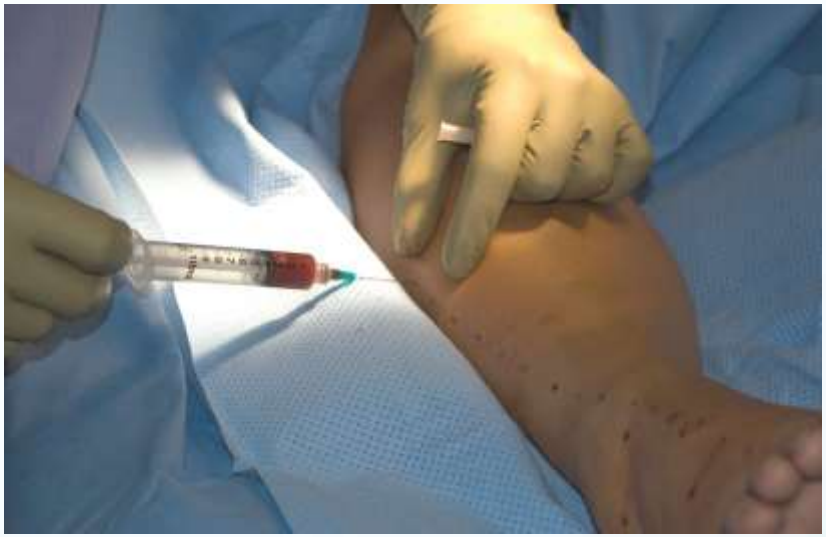


al., JVS 2011

Phase I BioMet Study Design

- Open label, non-randomized single center (IUSM, 2005-2009)
- 29 subjects (30 limbs)
  - All failed previous bypass/endotherapy→"no option"
  - 1st 14 limbs treated with BMA processed by Ficoll density gradient separation
  - Last 16 limbs treated with BMA processed with MarrowStim™ PAD Kit



Murphy, et. al., JVS 2011

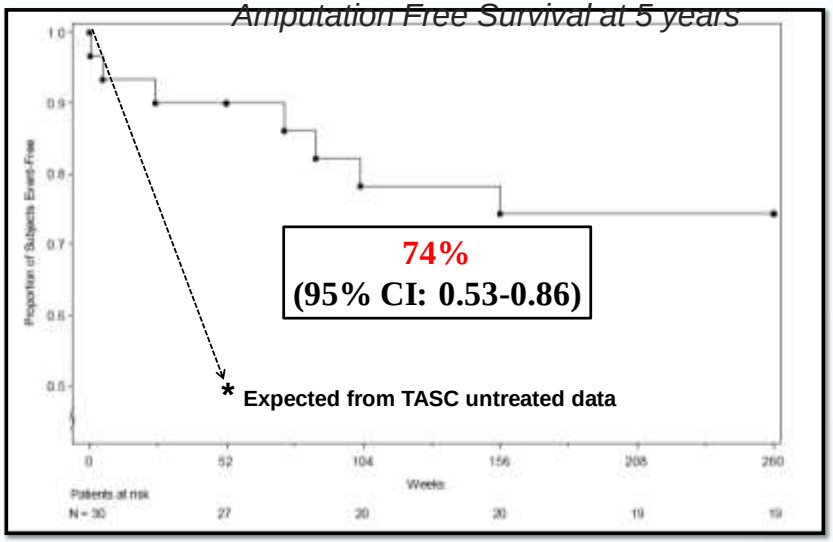
Phase I BioMet Study Results

- Amputation-free survival at 1 year = 86%
  - 3 amputations, 2 deaths
  - 1 amputation/death in same subject
- No reports of procedure-related deaths
- 2 reports of procedure-related SAEs
  - neither related to MarrowStim™ PAD Kit
- Significant improvements at 12 weeks
  - TBI (p=0.02), Rest Pain (p=0.02), VascuQol (p=0.008)

Murphy, et. al., JVS 2011

Phase I BioMet Study
Long Term 5 Yr. Results

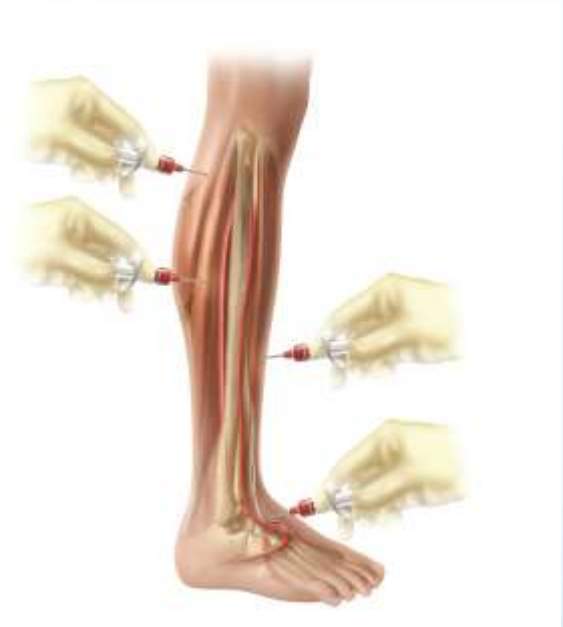
- 21 of 24 (87.5%) patients who completed initial 1-year f/u responded to detailed questionnaire
- Interval from initial treatment:
  - 188.2 ± 12.3 weeks (range:129-278 weeks)
- <u>5 year results</u>:
  - AFS = 74% *(95% CI, 0.53-0.86; P < 0.05)*
  - Freedom from major amputation = 78% *(95% CI, 0.57-0.89; P < 0.05)*
  - Freedom from MALE = 65% *(95% CI, 0.45- 0.79; P < 0.05)*
- 3 patients (14.2%) had major cardiac events
- No incidences of malignancies or diagnoses of proliferative retinopathy
- 15 patients (71.4%) report continued improvement in pain-free walking
- 19 patients (90.4%) felt study was of significant medical value and would participate again
- MOBILE I Trial results to be disclosed later this year



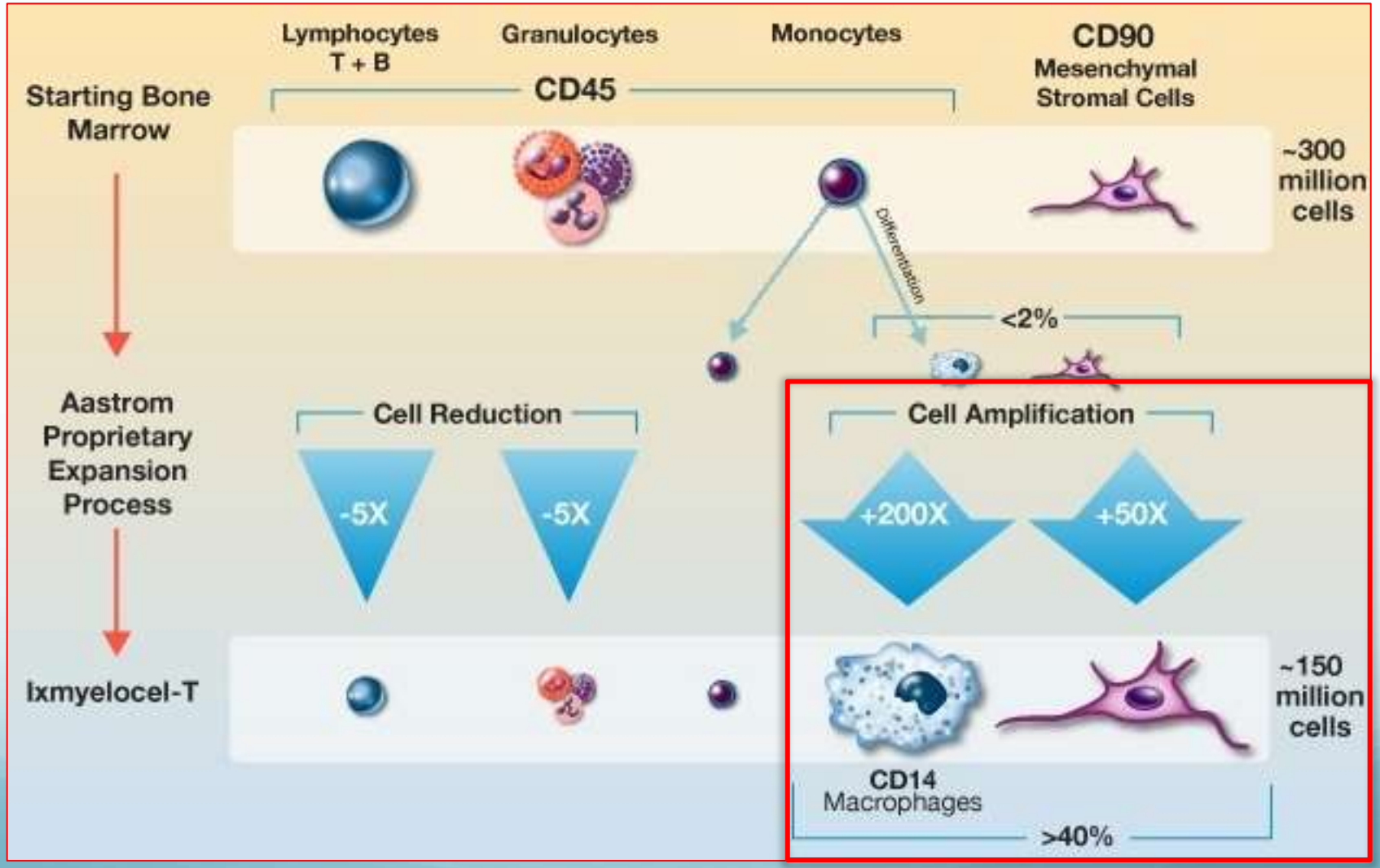
Murphy, NCVH Presentation 2014

The MOBILE Study

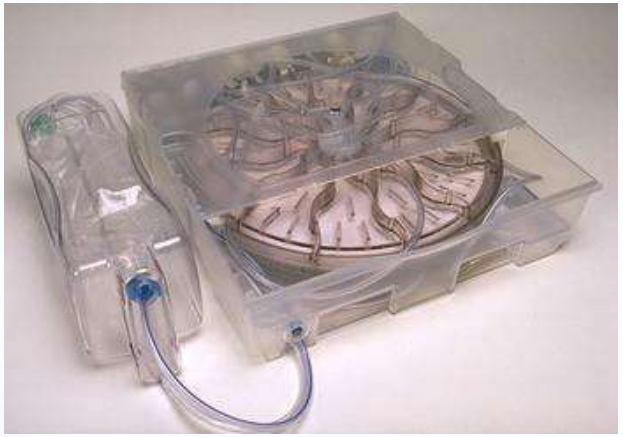
- Pivotal IDE Study (data lock June 2016)
- Prospective, double-blind, multicenter
- Placebo-controlled (sham treatment)
- 3:1 (treatment:placebo) randomization
- Crossover available
- 152 subjects, 30 investigational sites
- Primary endpoint: Rate of treatment failure (major amputation/death) at 52 weeks



Stem Cell Sub-Set Amplification Ixmyelocel-T



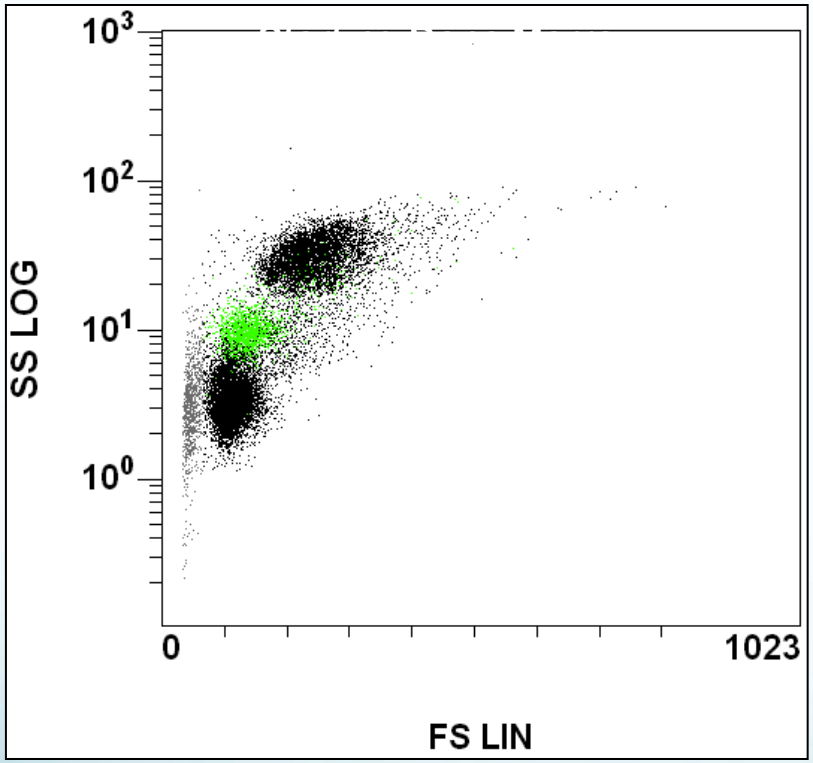
Bone Marrow Harvest – Cells Undergo Expansion in Bioreactor

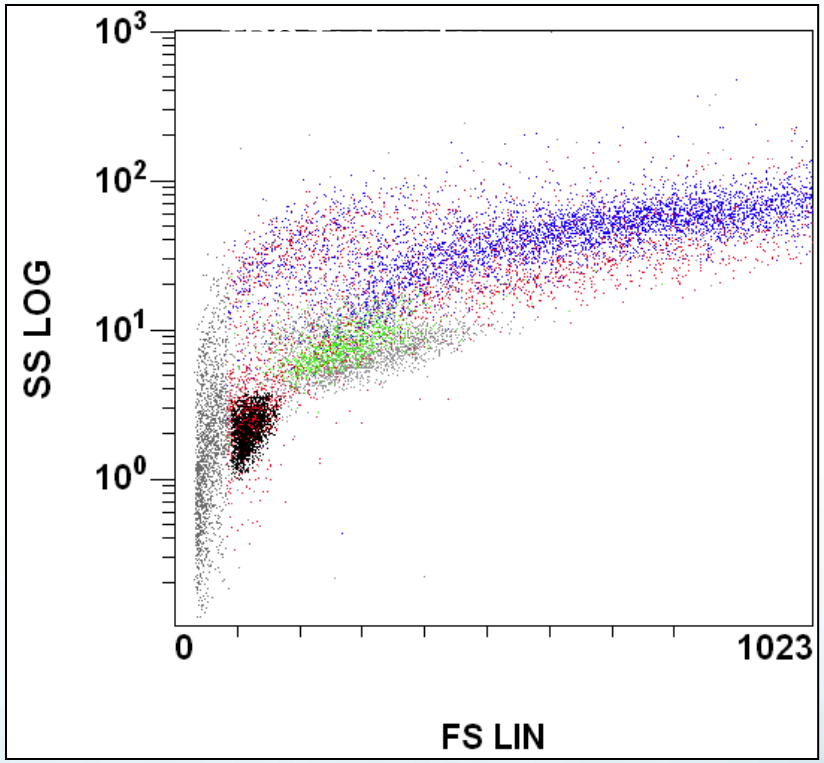


- ~50cc bone marrow aspirate
- Processed using a proprietary, automated, closed culture system (~12 day process).
- 35-295 x 10^6 viable cells: mesenchymal stromal and CD45+ hematopoietic stem cells
- Re-administered IM

Powell SVS 2010

Amplification of Early Stage Cells Found in Bone Marrow



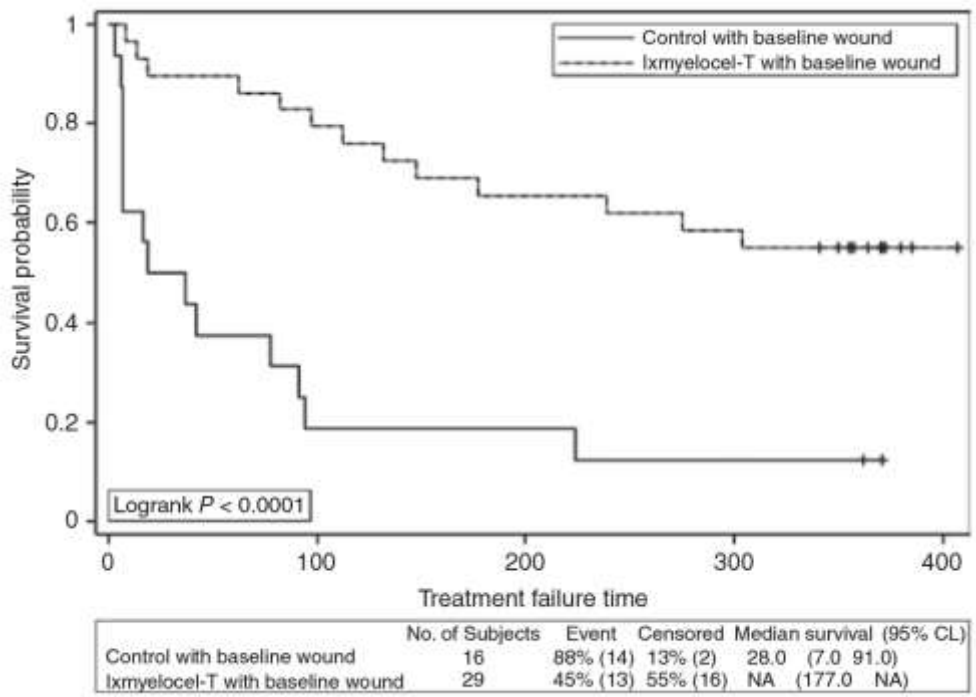


Frequency Distribution of Cell Types Shifts Towards Stem and Progenitor Cells

Powell SVS 2010

Cellular Therapy With Ixmyelocel-T to Treat Critical Limb Ischemia: The Randomized, Double-blind, Placebo-controlled RESTORE-CLI Trial

Richard J Powell[1], William A Marston[2], Scott A Berceli[3], Raul Guzman[4], Timothy D Henry[5], Amy T Longcore[6], Theresa P Stern[6], Sharon Watling[6] and Ronnda L Bartel[6]



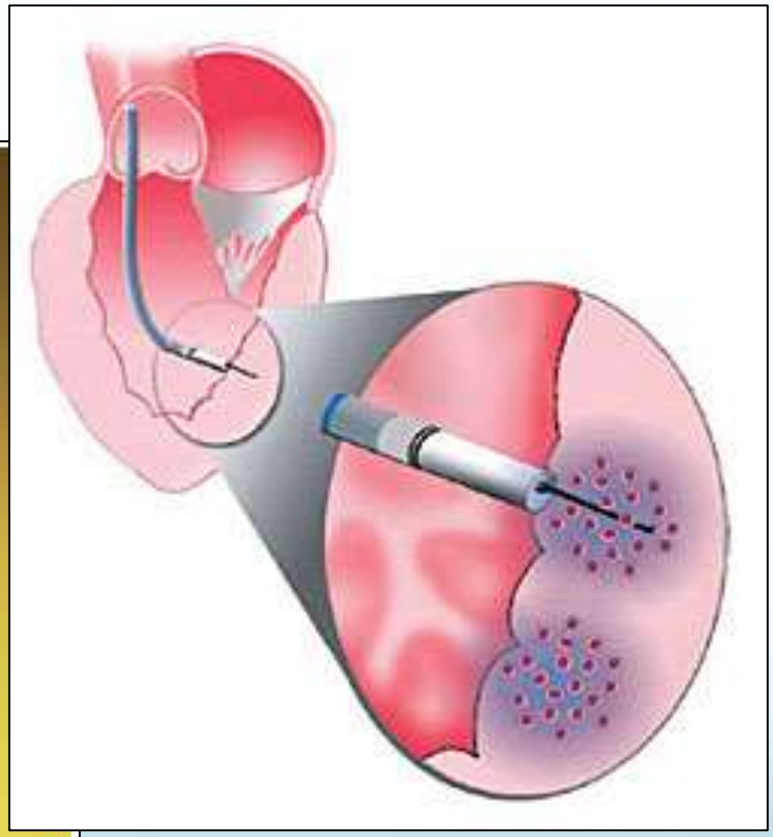
	No. of Subjects	Event	Censored	Median survival	(95% CL)
Control with baseline wound	16	88% (14)	13% (2)	28.0	(7.0 91.0)
Ixmyelocel-T with baseline wound	29	45% (13)	55% (16)	NA	(177.0 NA)

- Phase II RTC trial of “no option” CLI patients
- No difference in AFS b/t two groups; treatment w/ Ixmyelocel-T resulted prolongation of TTF
- Post hoc: those w/ baseline wounds had reduction in treatment failure

Powell et al., Moll Ther 2012

Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial

Amit N Patel, Timothy D Henry*, Arshed A Quyyumi, Gary L Schaer, R David Anderson, Catalin Toma, Cara East, Ann E Remmers, James Goodrich, Akshay S Desai, David Recker, Anthony DeMaria, for the ixCELL-DCM Investigators*



NOGA MyoStar™ Catheter

Patel, et. Al. Lancet April 2016

Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial

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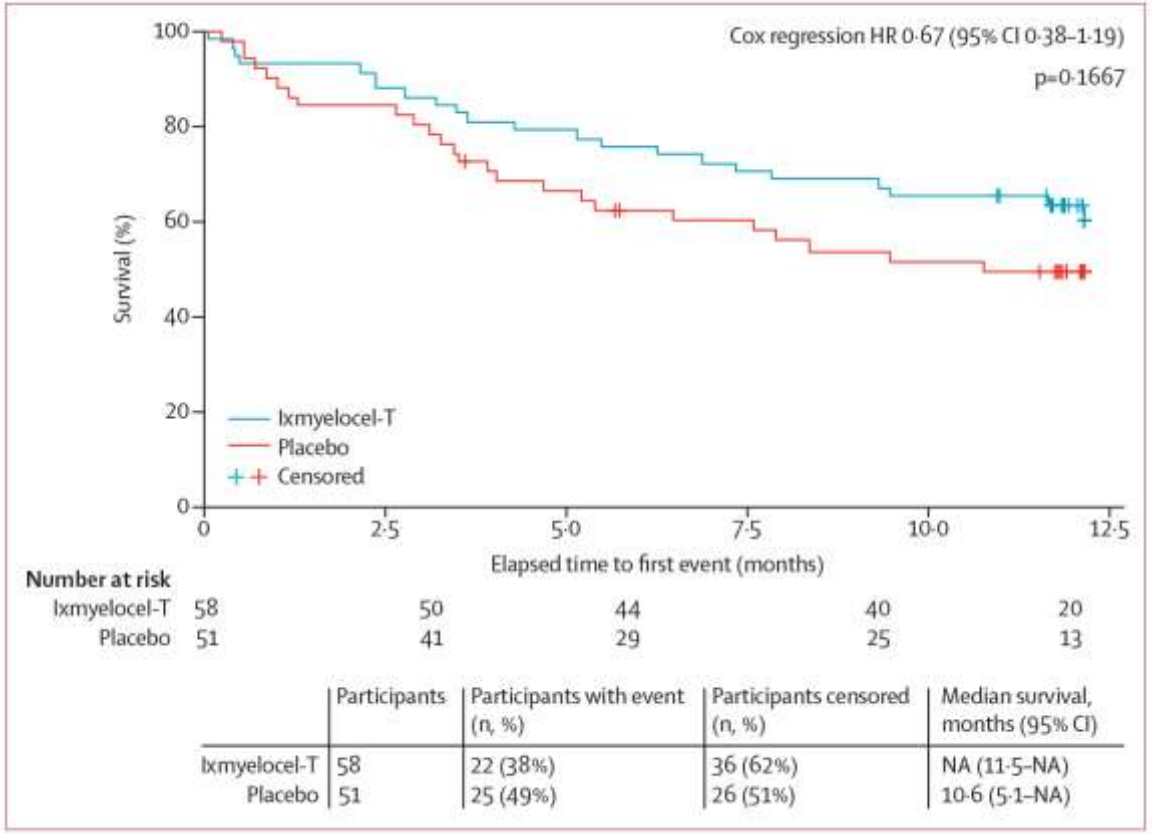


	Participants	Participants with event (n, %)	Participants censored (n, %)	Median survival, months (95% CI)
Ixmyelocel-T	58	22 (38%)	36 (62%)	NA (11·5–NA)
Placebo	51	25 (49%)	26 (51%)	10·6 (5·1–NA)

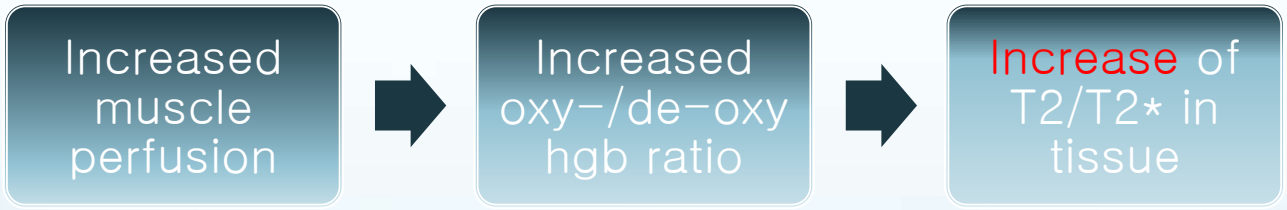
Kaplan–Meier analysis of time to first occurrence of primary endpoint event for ixmyelocel–T versus placebo (n=109) NA=not applicable.

Patel, et. Al. Lancet April 2016

- Same amplification process used in RCT Phase IIB trial of no-option I-DCM patients: Reduction in all cause CV mortality, re-admissions for acute CHF at 12 mos. No change in NYHA class, EF, 6MWT.
- FDA Orphan drug status.
- Ixmyelocel-T may be re-considered to treat CLI patients

Blood Oxygenation-Level Dependent (BOLD) Magnetic Resonance Imaging (MRI) to Assess Change in Tissue Perfusion

- Based on principle that deoxygenated hemoglobin leads to magnetic field distortions (T2* effect) in its vicinity
- Oxyhemoglobin is diamagnetic (resistant to magnetic field) while de-oxyhemoglobin is paramagnetic
- Increase in tissue perfusion alters the local ratio between oxy- and deoxyhemoglobin



The BOLD Effect

- Originates from changes in intravascular hemoglobin oxygenation

Lebon, et al., Magn Reson Med 2010; 64:527-35

Potential Advantages of BOLD

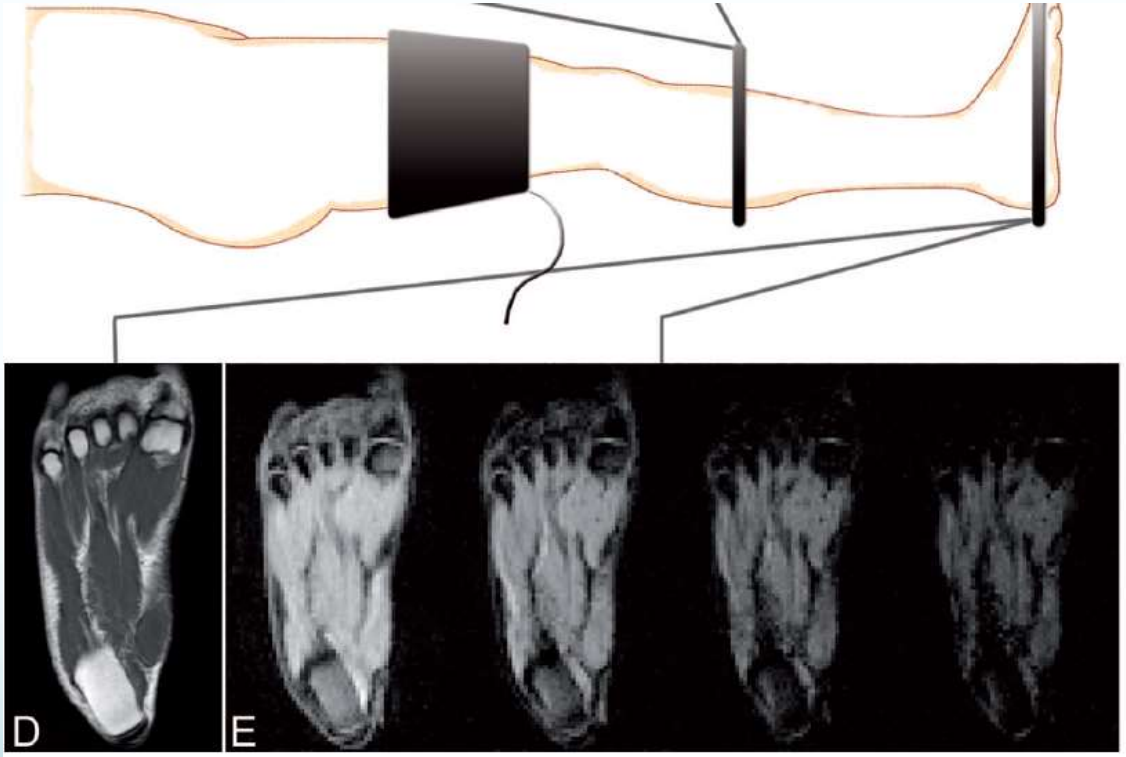
- High temporal resolution
- Good spatial resolution to discern *regional perfusion*
- Non-invasive (MR compatible; legs only)
- *May* provide direct, quantifiable method to direct and quantify a therapeutic response to cellular therapies

Forster BB, Radiology 2006; 241: 329-30

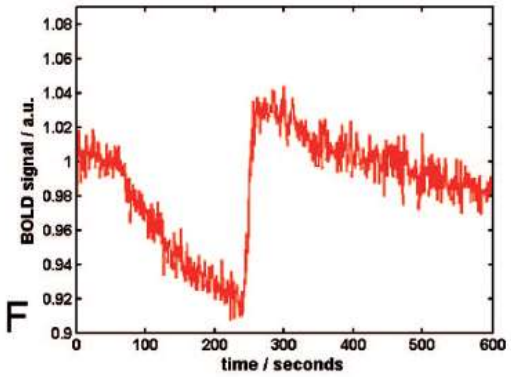
Pedal BOLD:
Skeletal Muscle Perfusion Protocol

- Evaluate changes in BOLD signal due to changes in muscle perfusion
- Utilize a reactive hyperemia protocol for functional evaluation of skeletal muscle
- T1 anatomical reference images utilized to place ROIs within target muscle groups

The Basic Principles: Pedal BOLD Assessment

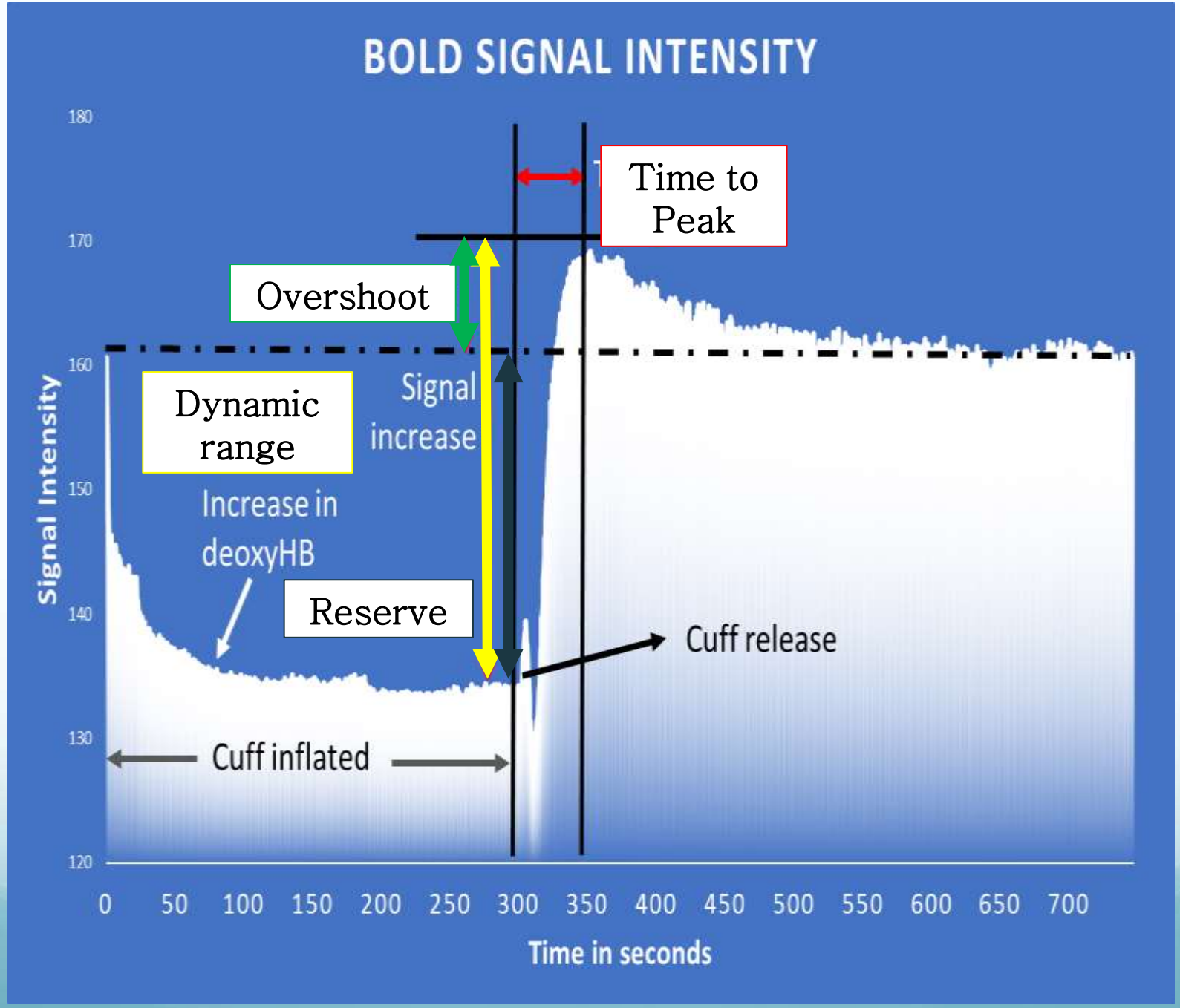


T1 Gradient Echo (7,17,27,37 msec)



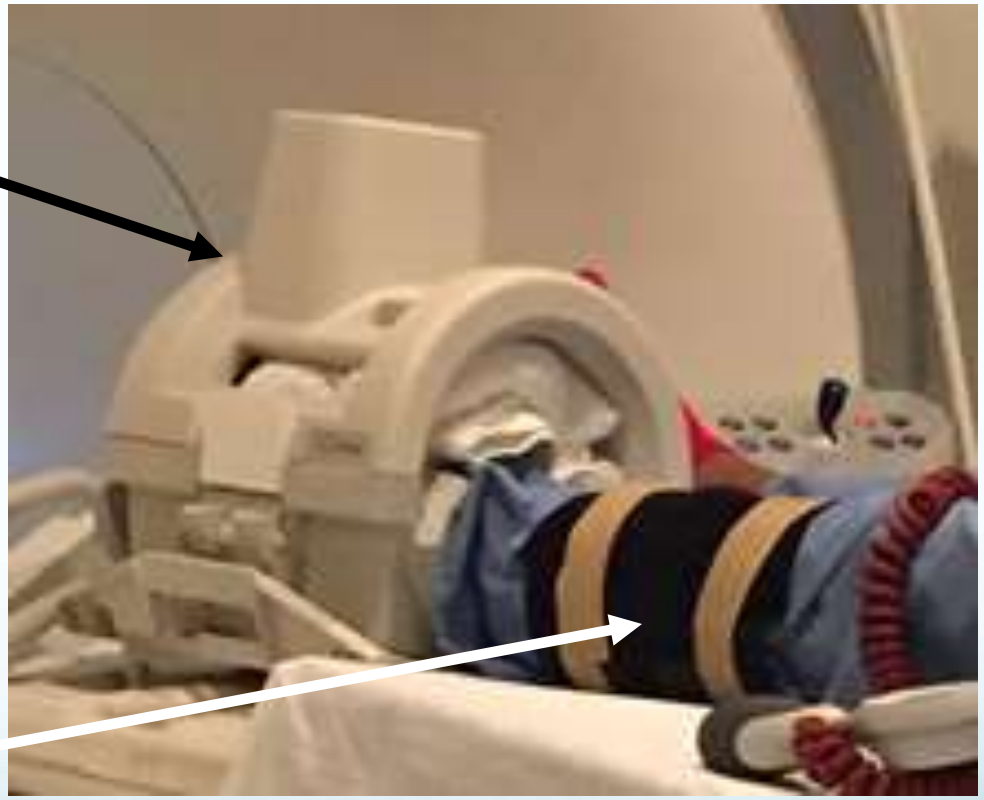
Dynamic T2* map

Kos, et al., Invest Radiol 2009; 44: 741-747


BOLD SIGNAL INTENSITY
Time to Peak
Overshoot
Dynamic range
Signal increase
Increase in deoxyHB
Reserve
Cuff release
Cuff inflated
Signal Intensity
Time in seconds
180
170
160
150
140
130
120
0
50
100
150
200
250
300
350
400
450
500
550
600
650
700

Pedal BOLD MR Scanning Procedure

MR vascular coil to evaluate ROI: the foot/ankle

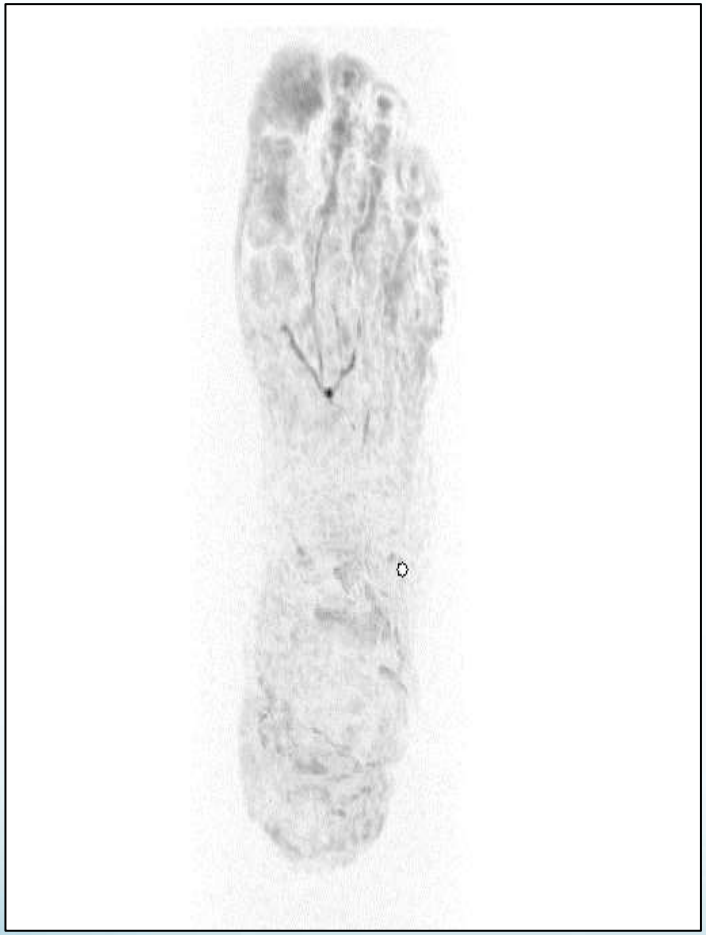


MR compatible BP cuff placed on calf to induce reactive hyperemia

MRA Analysis

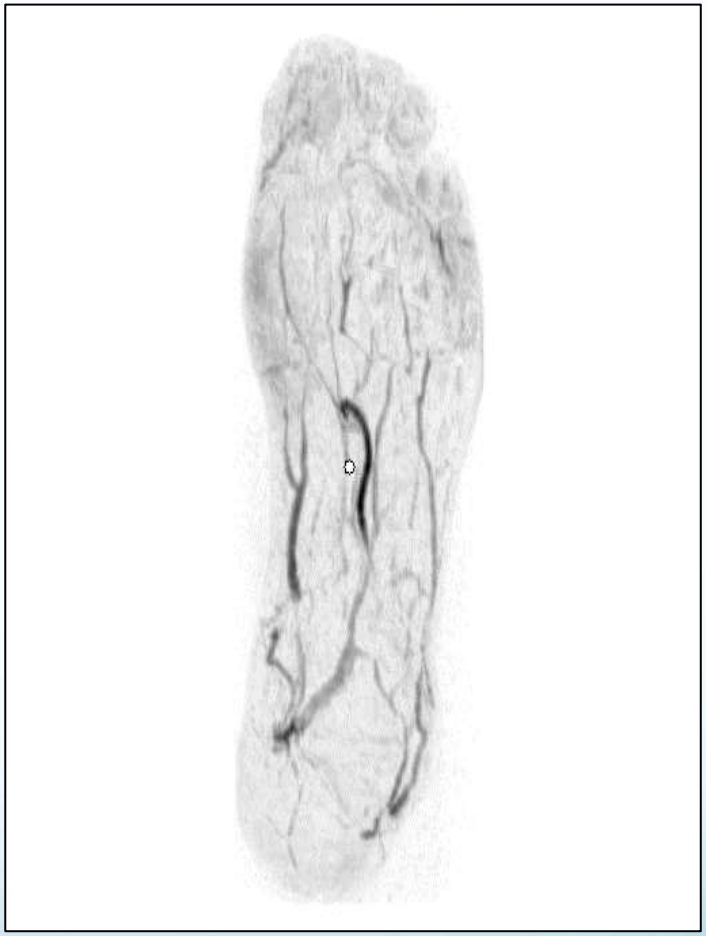
(Comparison: Baseline vs. 30d Follow-up)

01-001



Baseline

1. DPA 100% occlusion
2. MPA 100% occlusion
3. LPA 100% occlusion



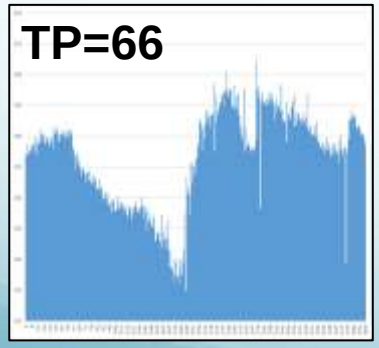
Follow-up (30 Days)

1. DPA 0%
2. MPA 100% occlusion
3. LPA 77% stenosis

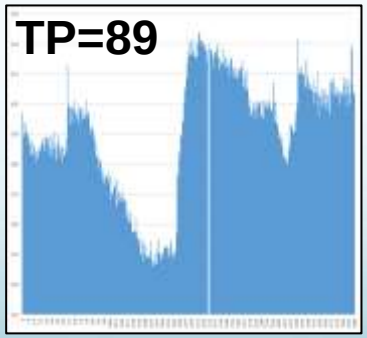
Pedal BOLD MR in PAD

(Baseline vs 30d Follow-up)

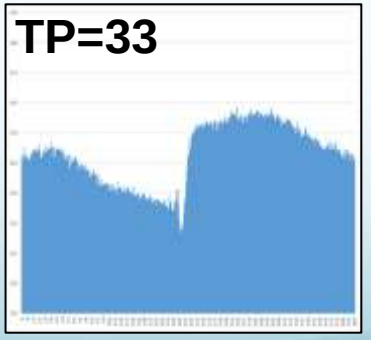
		Overshoot	Reserve	Dynamic range	Time to peak
01-001	Baseline	4.32%	12.36%	16.67%	129
	30 days	9.65%	10.47%	20.12%	74
01-002	Baseline	3.07	4.43	7.50	215
	30 days	10.51	4.29	14.80	110



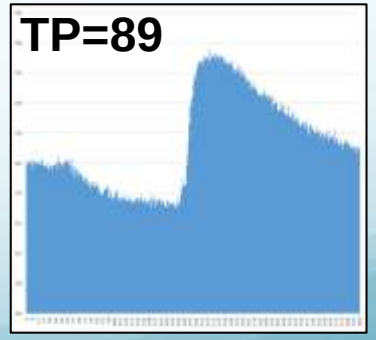
01-001 Baseline



Follow-up (30days)



01-002 Baseline



Follow-up (30days)

The Promise of Pedal BOLD Imaging

- Studies to validate ability of pedal BOLD to detect changes in pedal tissue perfusion pre- and post-revascularization and correlate with traditional non-invasive assessments are ongoing
- BOLD assessed changes in pedal tissue perfusion *may* prove to be a key tool in defining the effectiveness of cellular therapies to enhance tissue perfusion and optimize their biologic effect

The Promise of Cellular Regenerative Medicine

I don't know where we are going from here, but I promise it won't be boring….

David Bowie