Novel Therapies in CLI: Stem Cells & Growth Factors

Are They Clinically Beneficial or Horizon Therapies?

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A Horizon Therapy?

"So many of our dreams at first seem impossible, then they seem improbable, and then, when we summon the will, they soon become inevitable…"

Christopher Reeve
(aka Superman)

The Goal of 'Therapeutic Angiogenesis':

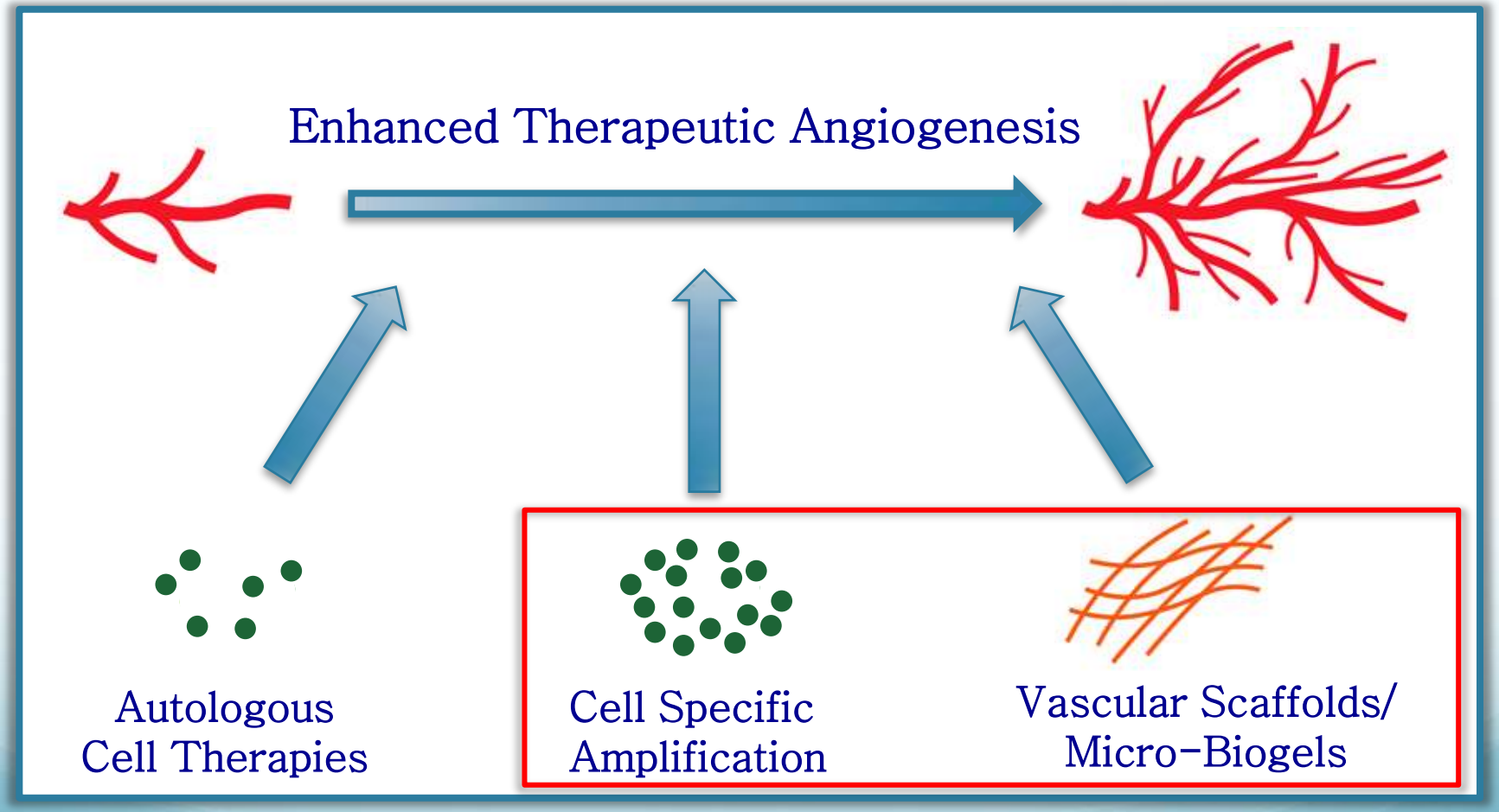
The application of *regulatory genes*, *proteins* and/or *progenitor cells* to patients with vascular disease to *enhance tissue perfusion* through the development of new blood vessels.

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

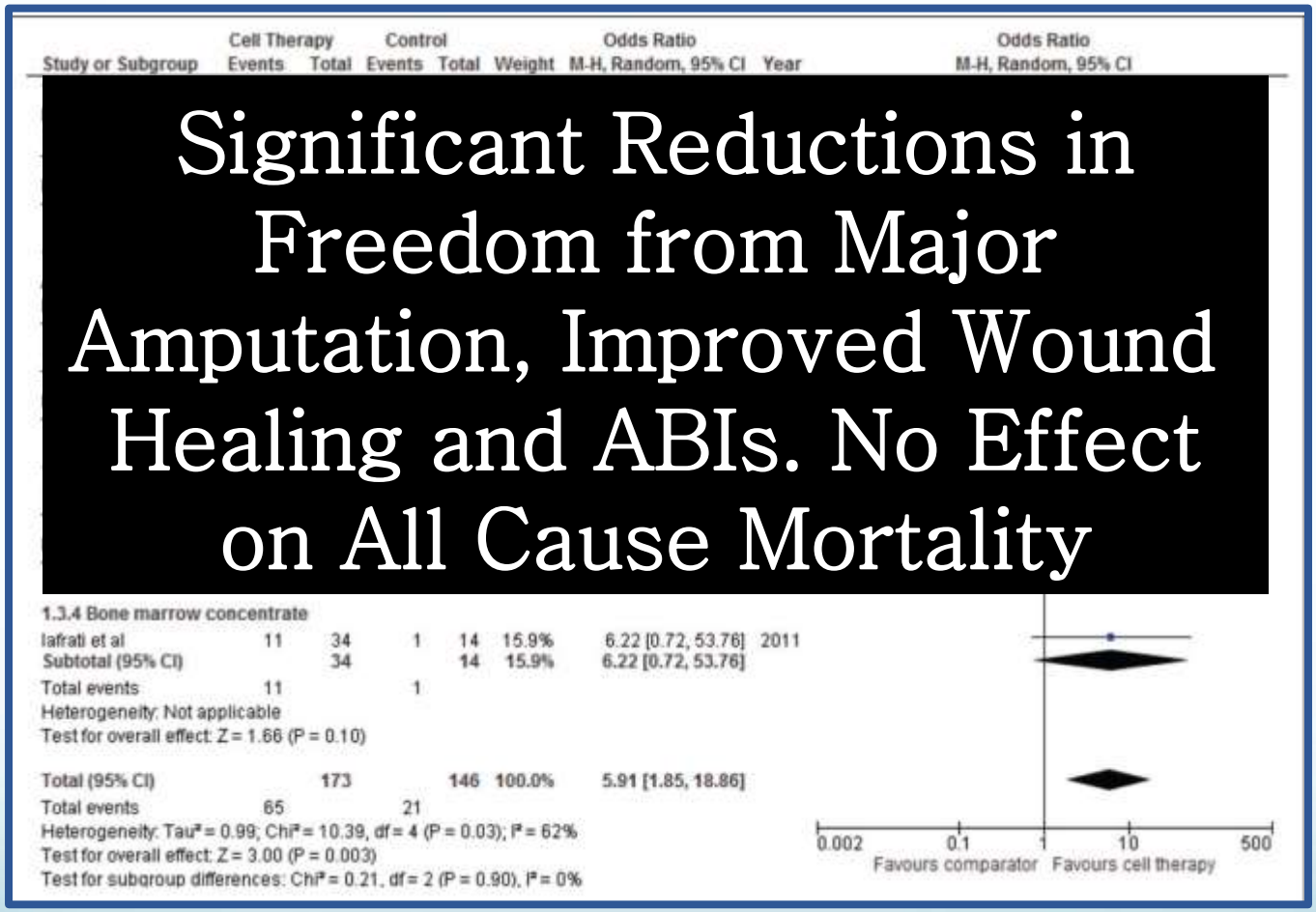
What are the Potential Challenges Faced by these Early Phase Trials?

- 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

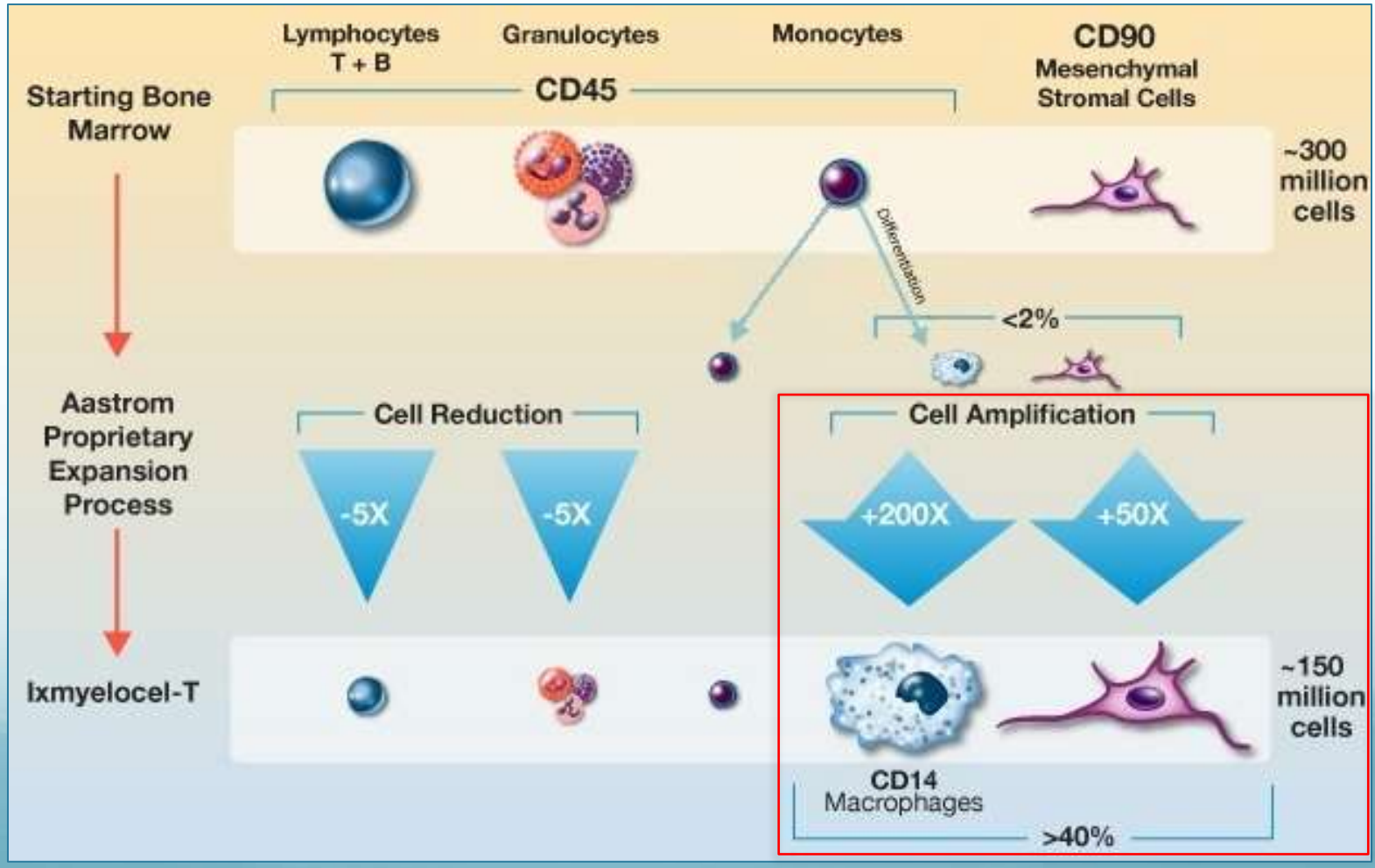


Odds ratio of improvement in ABI (>0.1 or >15%) in patients with CLI treated with cell therapy versus no cell therapy (random effects model).

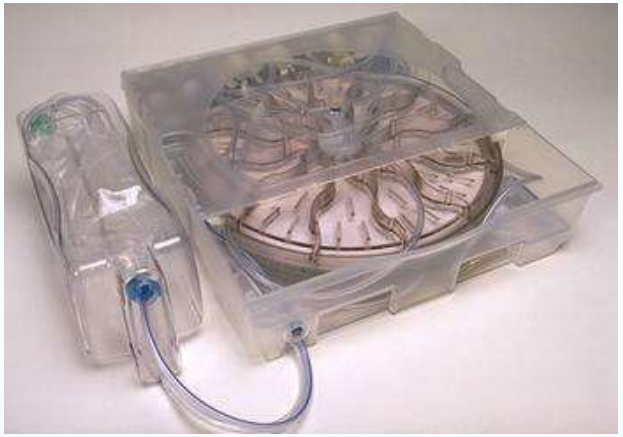
Liew et al., Angiology 2015

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*



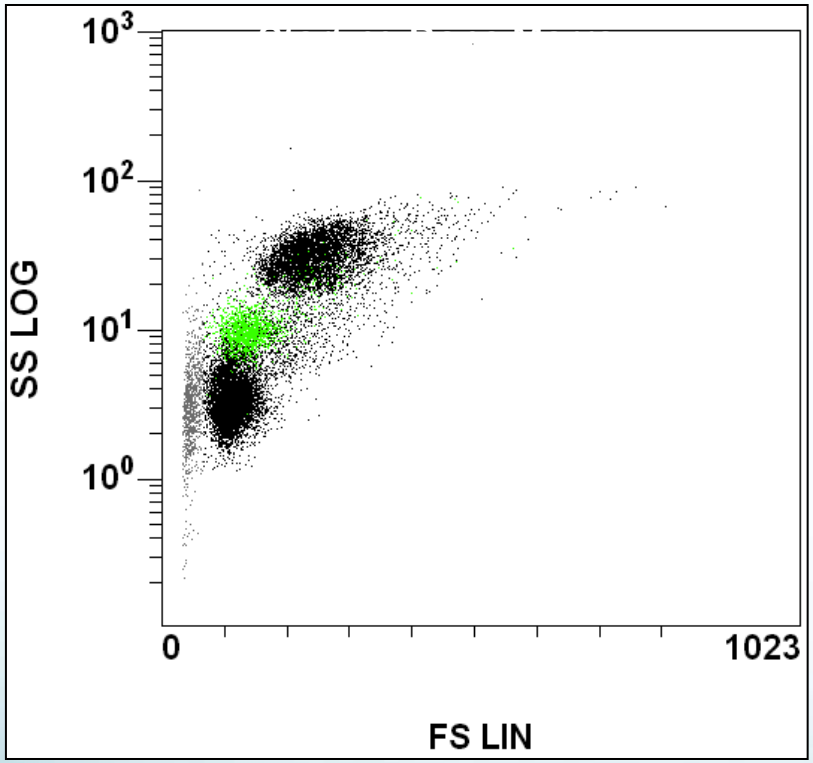
Bone Marrow Harvest – Cells Undergo Expansion in Bioreactor

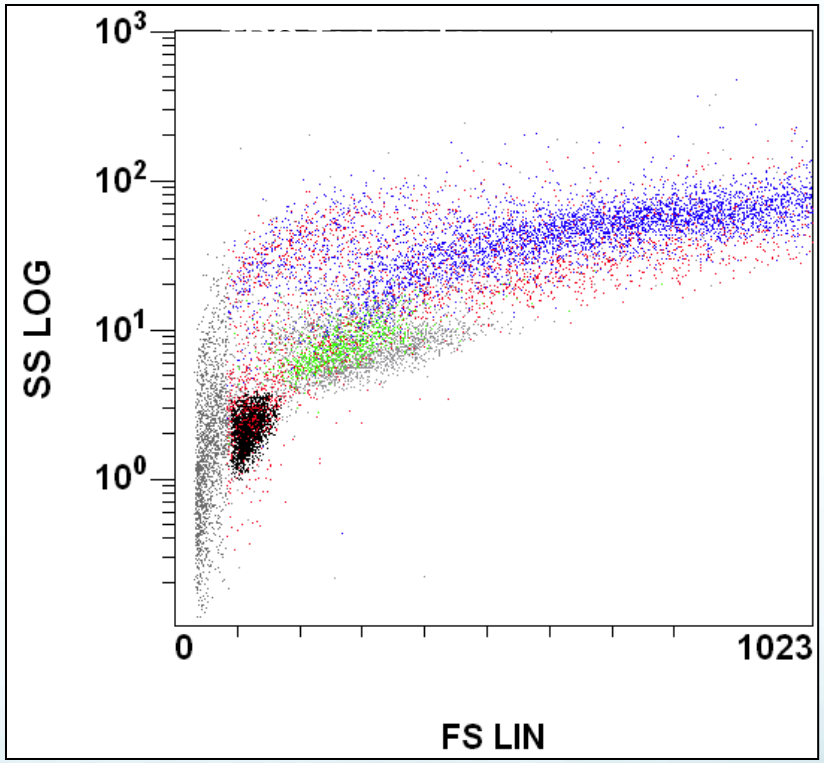


- ~50cc bone marrow aspirate
- Processed using a proprietary, automated, closed culture system (~12 day process).
- 35-295 x 10^6 viable cells: mesenchymal stromal and CD45+ hematopoietic stem cells
- Re-administered IM

Powell SVS 2010

Amplification of Early Stage Cells Found in Bone Marrow



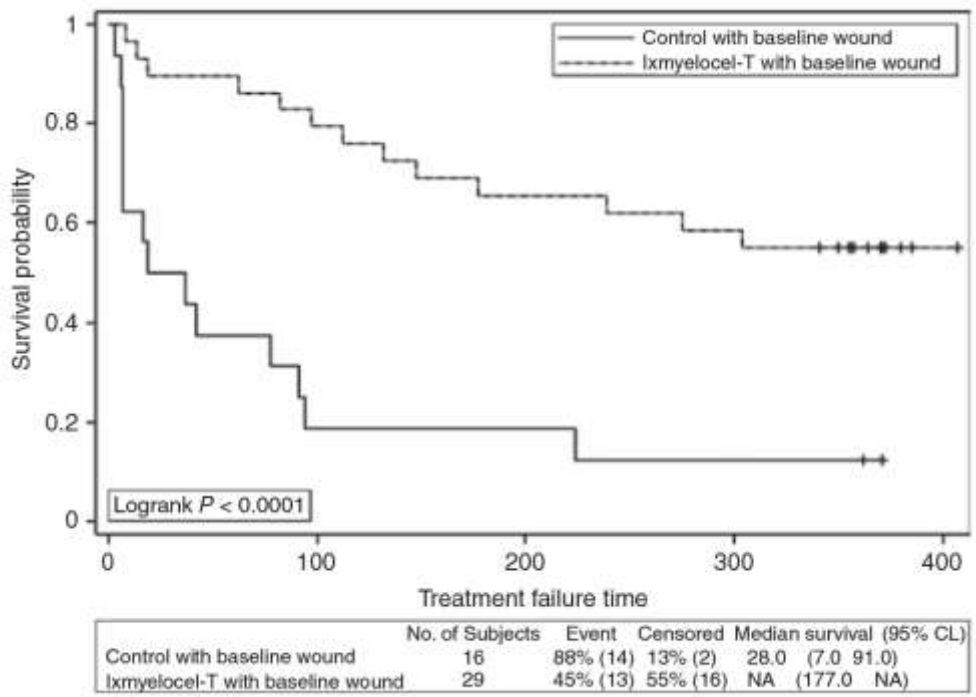


Frequency Distribution of Cell Types Shifts Towards Stem and Progenitor Cells

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

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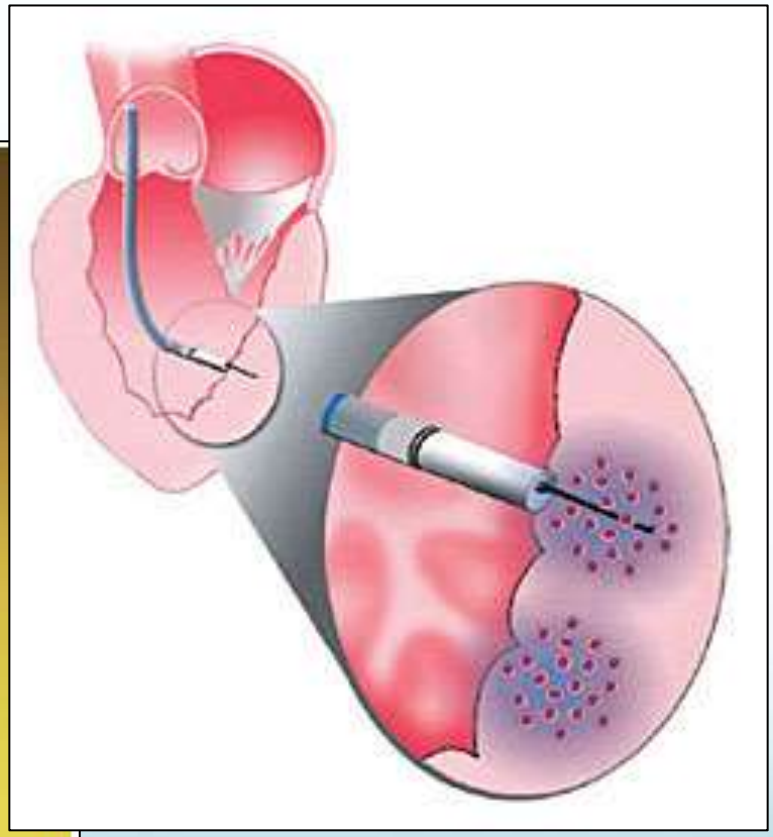
NOGA MyoStar™ Catheter (BioSense Webster, Inc)



Powell et al., Moll Ther 2012

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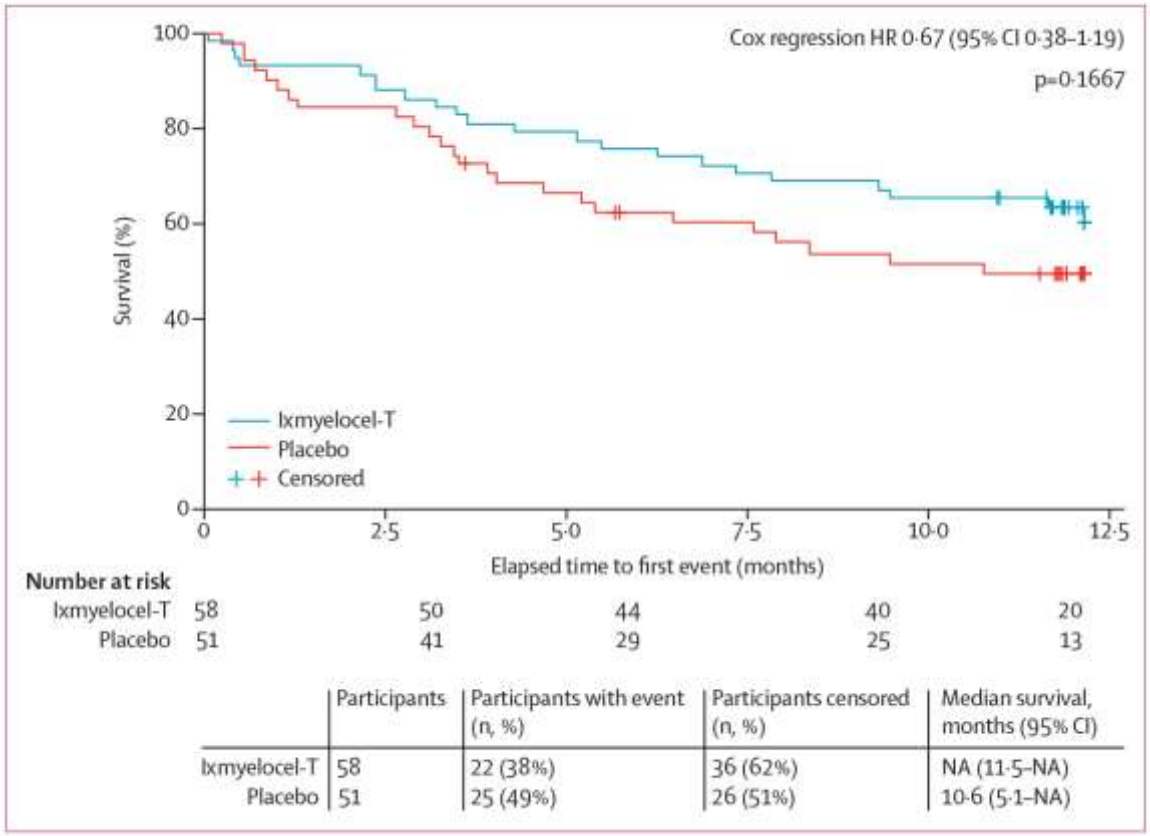


	Participants	Participants with event (n, %)	Participants censored (n, %)	Median survival, months (95% CI)
Ixmyelocel-T	58	22 (38%)	36 (62%)	NA (11·5–NA)
Placebo	51	25 (49%)	26 (51%)	10·6 (5·1–NA)

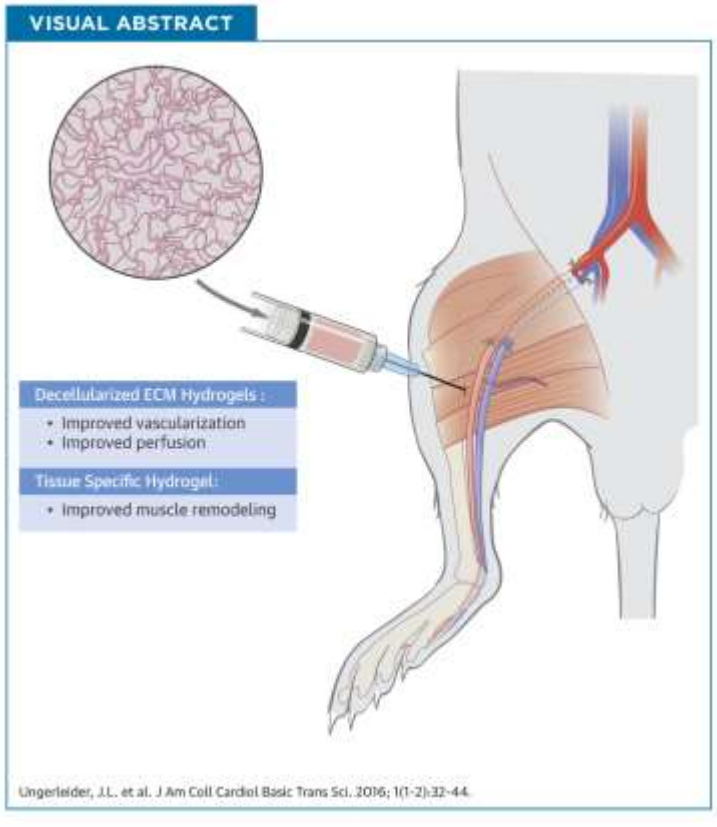
Kaplan–Meier analysis of time to first occurrence of primary endpoint event for ixmyelocel-T versus placebo (n=109) NA=not applicable.

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 (Vericel, Inc)

Extracellular Matrix Hydrogel Promotes Tissue Remodeling, Arteriogenesis, and Perfusion in a Rat Hindlimb Ischemia Model

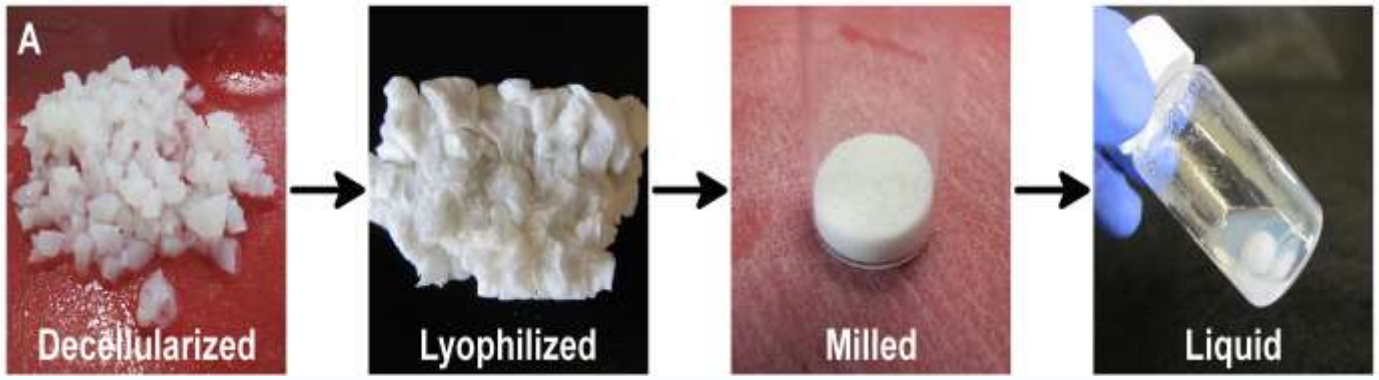
Jessica L. Ungerleider, BS,[a,*] Todd D. Johnson, PhD,[a,*] Melissa J. Hernandez, BS,[a] Dean I. Elhag, BS,[a] Rebecca L. Braden, MS,[a] Monika Dzieciatkowska, PhD,[b] Kent G. Osborn, DVM, PhD,[c] Kirk C. Hansen, PhD,[b] Ehtisham Mahmud, MD,[d] Karen L. Christman, PhD[a]



- Biologic hydrogels: Acellular extracellular matrix (ECM) based materials
- Tissue-specific (skeletal muscle) biocompatible, injectable
- Injected alone: SKM progenitor + cell recruitment & arteriogenesis
- Improved functional perfusion in an ischemic hindlimb model

Ungerleider et al. JACC Basic Trans Sci, 2016

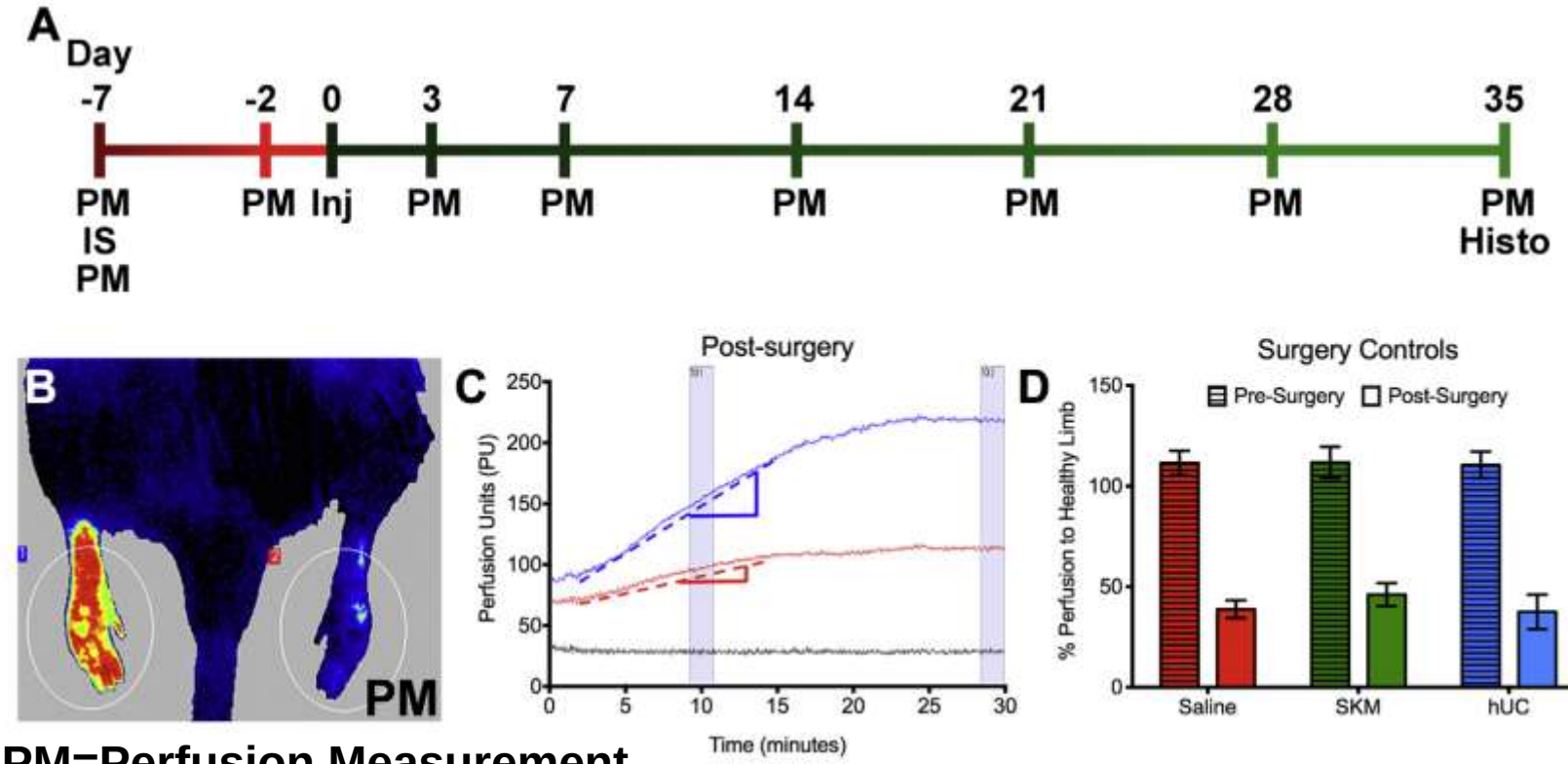
SKM Hydrogel Production



- Porcine skeletal muscle harvested, minced, repeated rinsings, exposure to buffered alcohols & proteases → lyophilized and milled.
- SKM ECM re-suspended in buffered saline and injected SQ into rat hindlimb to induce gelation.
- Skeletal muscle perfusion and migration of skeletal cell precursors assessed.

Ungerleider et al. JACC Basic Trans Sci, 2016

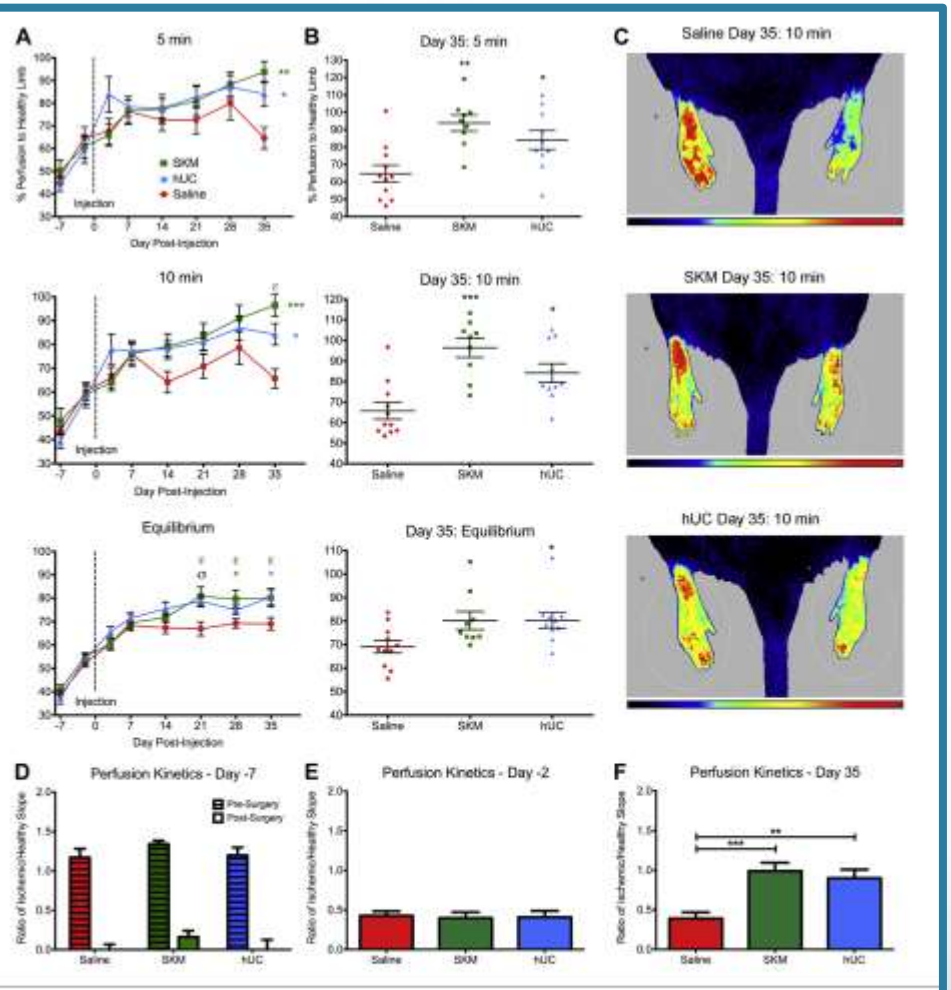
Functional Perfusion Study Post-SKM ECM Hydrogel Injection into Rat Ischemic Hindlimb



PM=Perfusion Measurement

Ungerleider et al. JACC Basic Trans Sci, 2016

Hindlimb Tissue Perfusion and Perfusion Kinetics



(A) Hindlimb perfusion measurements over the 42-day period for animals treated with either the skeletal muscle matrix (SKM) ($n = 9$), human umbilical cord matrix (hUC) ($n = 10$) hydrogels, or saline ($n = 11$). Readings are shown after the animal had been under anesthesia for 5 min, 10 min, and after reaching perfusion equilibrium. **Vertical dotted line** indicates time of treatment injection on day 0. **(B)** Individual animal perfusion readings on day 35. **(C)** Example representative perfusion images for each treatment group after the animal was under anesthesia for 10 min. Healthy limbs are on the **left** and ischemic/treated limbs are on the **right**. Note: Because the units for perfusion are arbitrary, color comparisons cannot be performed between 2 different animals. **(D)** Perfusion kinetics for pre-surgery and post-surgery. **(E)** Pre-injection perfusion kinetics on day −2 (pre-injection). **(F)** Final perfusion kinetics on day 35. A 2-way analysis of variance was conducted to compare within and between treatment groups. $\wp < 0.05$ for SKM compared to SKM at day 7 as determined by a Dunnett's multiple comparisons test. $^*p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$, and $\#p < 0.05$ for both treatment groups compared to saline using a Tukey post hoc test.

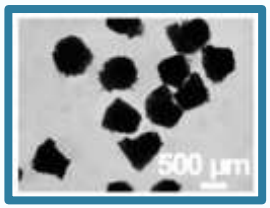
- SKM hydrogel injection improved perfusion over control.
- Moreover, SKM hydogel improved skeletal muscle remodeling by recruitment of skeletal muscle progenitors and increasing density of arterioles through 35 days
- SKM hydrogels improved the local cellular micro-environment (inflammation, down-regulation of cell death, up-regulation of cell-adhesion

(Ventrix, Inc)

Primed 3D injectable microniches enabling low-dosage cell therapy for critical limb ischemia

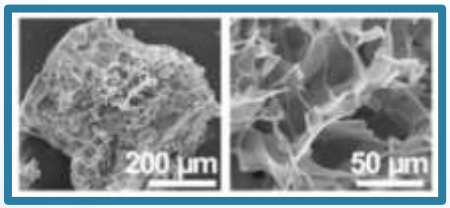
Yaqian Li[a,b,1], Wei Liu[a,1], Fei Liu[a,c,1], Yang Zeng[a], Simin Zuo[a], Siyu Feng[d], Chunxiao Qi[a], Bingjie Wang[a], Xiaojun Yan[a], Ali Khademhosseini[e,f,g,h,i], Jing Bai[a], and Yanan Du[a,b,2]

A



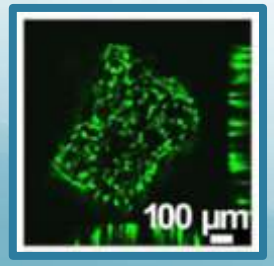
Cryo-gelation fabrication of biogradable gelatin micro-cryogels (GM) that create cellular niches

B



GMs have specific shape, size, pore size and swelling capacity. Biocompatible GMs can be “loaded” with a specific number of SCs

C



Uniform size, number, viability and attachment is achieved. The GM elasticity protects the SC from the mechanical forces of IM injection

Yaqian, et al. PNAS 2014

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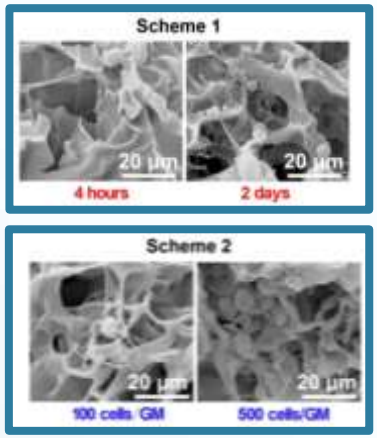
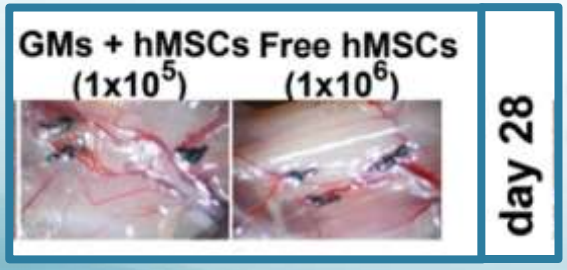
D



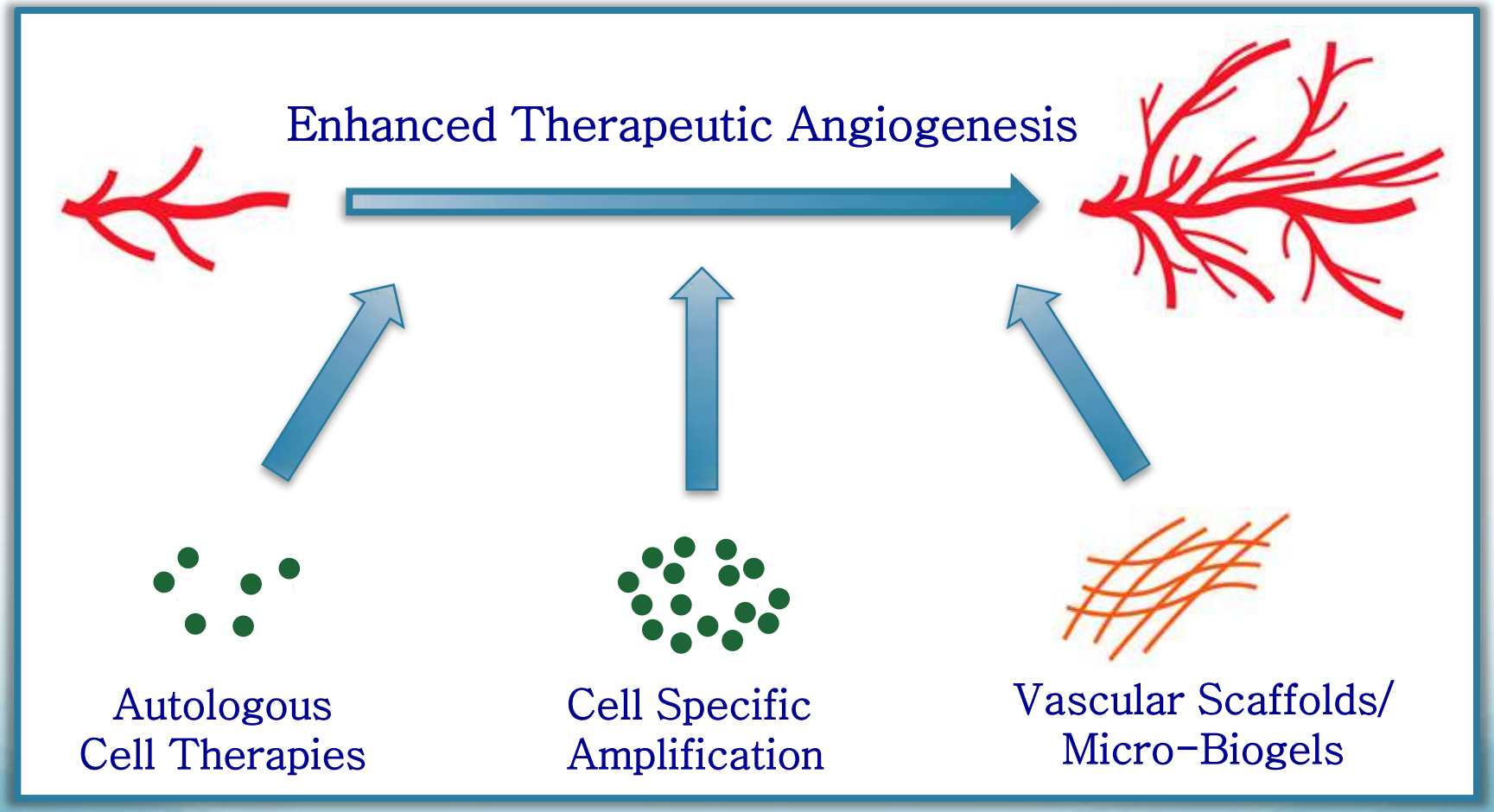
Amount of extracellular matrix formation is modulated by incubation of GM/SCs for specific durations and cell densities

E



Injected “primed” GM+SCs resulted in a higher density of microvessels v. “free” SCs at a lower number of SCs. Greater tissue perfusion and limb salvage scores were observed.

Emerging Paradigms in Cellular Regenerative Medicine



The horizon appears closer every day!

The Promise of Cellular Regenerative Therapies

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

David Bowie