2017 MID-ATLANTIC
CONFERENCE

7th ANNUAL CURRENT CONCEPTS IN
VASCULAR THERAPIES

2017

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4/21/2017

Cell and Gene Therapies for Non-Reconstructable Critical Limb Ischemia

Critical Limb Ischemia

- Defined as chronic limb ischemia with either rest pain or tissue loss (non-healing ulcers or gangrene)
- Prognosis
  - 25% major limb amputation within 1 year
  - 25% die of cardiovascular complications within 1 year
  - 50% mortality at 5 years
- Treatment
  - Medical
    - ASA, statin
    - Wound care
  - Intervention
    - Amputation
    - Revascularization
      - Surgical bypass
      - Endovascular intervention

Non-reconstructable Critical Limb Ischemia

- No option for intervention
  - No suitable target vessel for bypass
  - Small vessel disease in the foot
  - Extensive co-morbidities
- Dismal prognosis
  - Almost 40% amputation rate at 6 months
- Quality of Life comparable to patients with advanced cancer
- Treatment Options
  - Intensive wound care (NPWT, debridement, abx) at a dedicated wound center
    - Some reports with up to 55% healing rates
    - Slow, laborious, unpredictable outcomes
  - Pharmacotherapy (antiplt, vasodilators, hyperbaric O2) of unproven benefit
  - Primary amputation
    - Non-reconstructable disease accounts for ~ 60% of secondary amputations
      - Failed revasc 2/2 disease progression, recurrent ischemia, persistent infection/necrosis despite patent revascularization

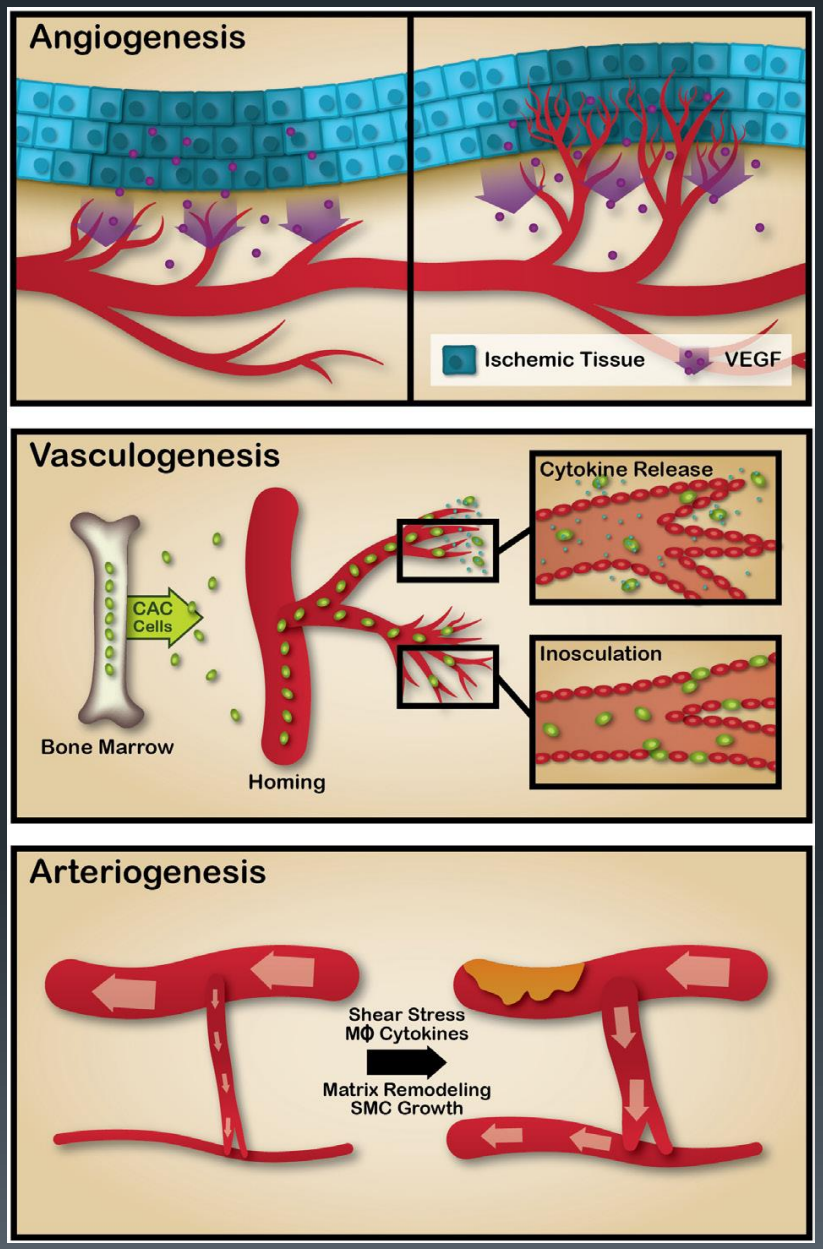
Primary Amputation as a Viable Option in a Subset of Patients with Non-reconstructable Critical Limb Ischemia

- Maintenance of ambulation has been shown to be an important factor in preserving independence and quality of life
- Amputation and prosthetic rehabilitation may be an excellent option to achieve independence and preserve quality of life
  - Good-risk patients after BKA (SM Taylor et al, JVS 2005)
    - Maintenance of ambulation may approach 70%
    - Maintenance of independence may approach 90%
  - Use of iPop may lead to
    - Faster return to ambulation (EM Burgess et al 1969)
    - Lower incidence of revision, and faster return to ambulation (MM Ali et al, Ann Vasc Surg 2013)
- Palliative AKA appropriate for patients too ill to realize the benefit of revascularization
  - Nonambulatory, elderly, knee contractures
  - Preop functional status is most important predictor of postop outcome (SM Taylor et al JVS 2006)

Novel Therapeutic Approaches for Non-reconstructable CLI

- Regenerative Therapies
  Enhance intrinsic cellular/tissue physiologic mechanisms to provide increased blood flow to ischemic limbs
  - Targeting growth factors and gene products involved in angiogenesis and arteriogenesis
  - Stem and progenitor cells participating in vascular repair and proliferation

- Advanced delivery methods
  - Gene therapy
  - Molecular therapy
  - Cellular delivery



- All 3 mechanisms come into play in PAD
- Significant heterogeneity between patients in vascular response to chronic ischemia
  - Same degree of occlusive disease may yield very different functional impairments in different patients
  - Same degree of occlusive disease can yield variable amounts of collaterals

Cook and Losordo. Gene and Cell Therapy for Limb Ischemia. *Circulation* 2015

Therapeutic Angiogenesis for Critical Limb Ischemia

- Concept:
  Use of angiogenic growth factors or stem cells in ischemic limbs to
  - Grow blood vessels
  - Improve blood flow
  - Increase tissue perfusion

- VEGF, FGF, HGF studied in animal models
  - Collateral vessel formation
  - Increased blood flow
  - Increased capillary density

- VEGF, FGF, HGF have been studied in the setting of RCT, with mixed results
  - All have confirmed feasibility and safety
  - No “off-target” angiogenesis
  - No occult tumor growth
  - No progression of diabetic retinopathy

Effect of fibroblast growth factor NV1FGF on amputation and death: a randomised placebo-controlled trial of gene therapy in critical limb ischaemia

Jill Belch, William R Hiatt, Iris Baumgartner, I Vickie Driver, Sigrid Nikol, Lars Norgren, Eric Van Belle, on behalf of the TAMARIS Committees and Investigators

Lancet 2011; 377: 1929–37

- Phase III trial
- 525 patients with non-reconstructable disease, 30 countries
- Randomized to treatment vs. placebo
- 8 IM injections on day 1, 15, 29, 43
- Endpoints
  - Primary:
    - Major amputation or death within 1 yr
- Results:
  - No difference in 12-month amp free survival when compared to placebo (63% vs. 67%, P=0.48)
  - Major amputation/death in 20-25% of patients

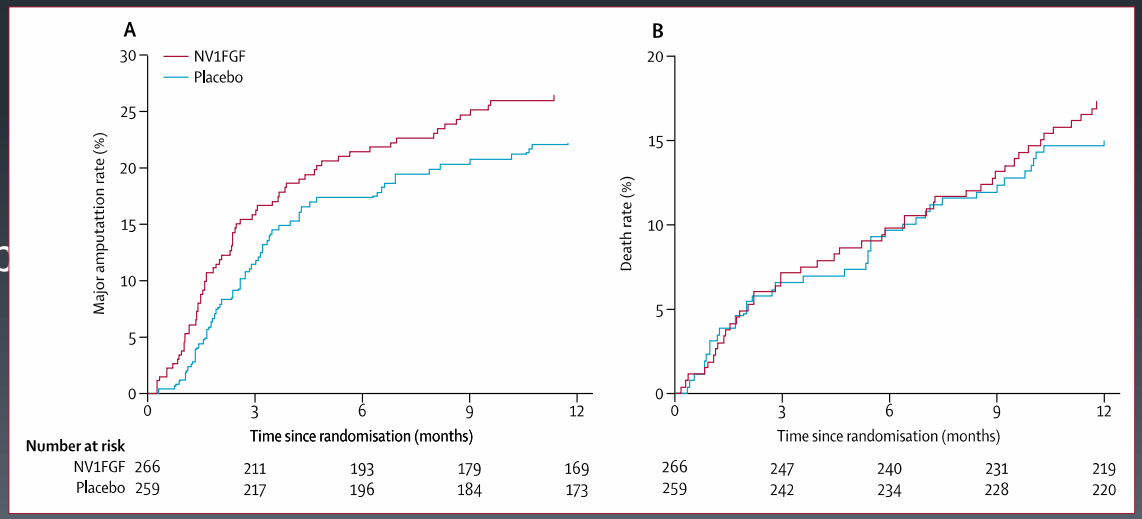


Figure 4: **Cumulative incidence curves over time of components of the primary endpoint**
(A) First major amputation of the treated leg. (B) Death rate over time. NV1FGF=non-viral 1 fibroblast growth factor.

Gene Therapy (2010) 17, 1152–1161

www.nature.com/gt

ORIGINAL ARTICLE

Randomized, double-blind, placebo-controlled clinical trial of hepatocyte growth factor plasmid for critical limb ischemia

H Shigematsu[1], K Yasuda[2], T Iwai[3], T Sasajima[4], S Ishimaru[5], Y Ohashi[6], T Yamaguchi[7], T Ogihara[8] and R Morishita[9]

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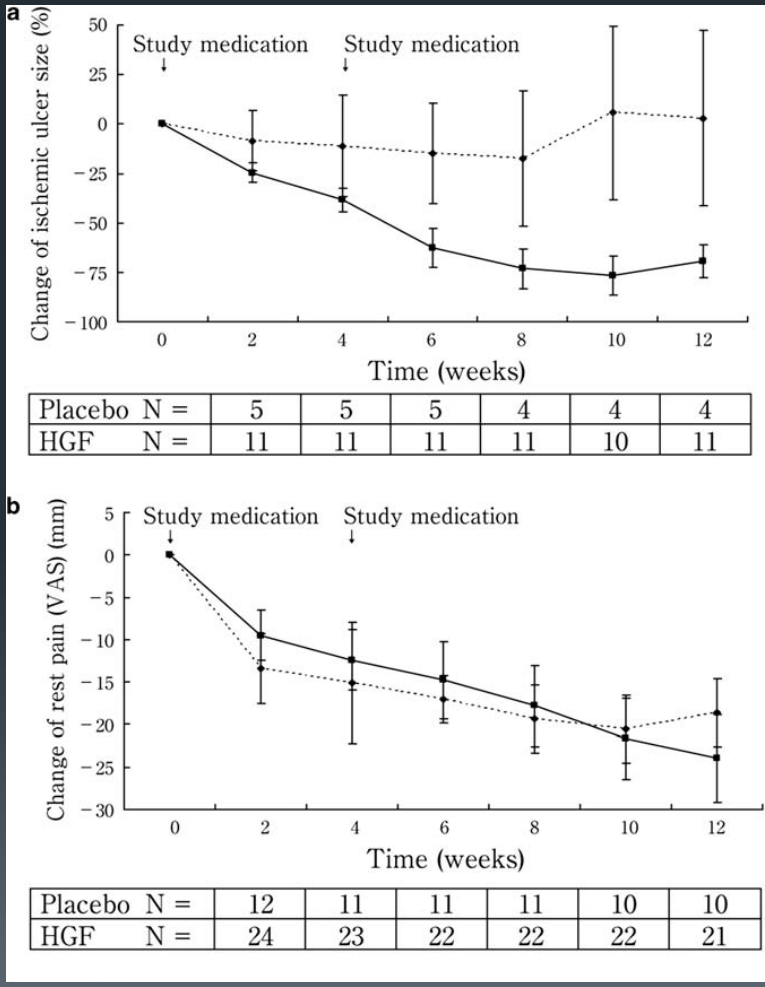
- Multicenter, randomized, double blind, placebo controlled
- 44 pts with non-reconstructable CLI
- Evaluate for efficacy and safety
- End points:
  - Primary
    - Reduction of ulcer size
    - Decrease in rest pain
  - Secondary
    - QoL
- Decrease in ischemic ulcer size
- Other studies with similar results
- Large phase III trial started but terminated in 2016 due to low enrollment



Placebo	N =	5	5	5	4	4	4
HGF	N =	11	11	11	11	10	11

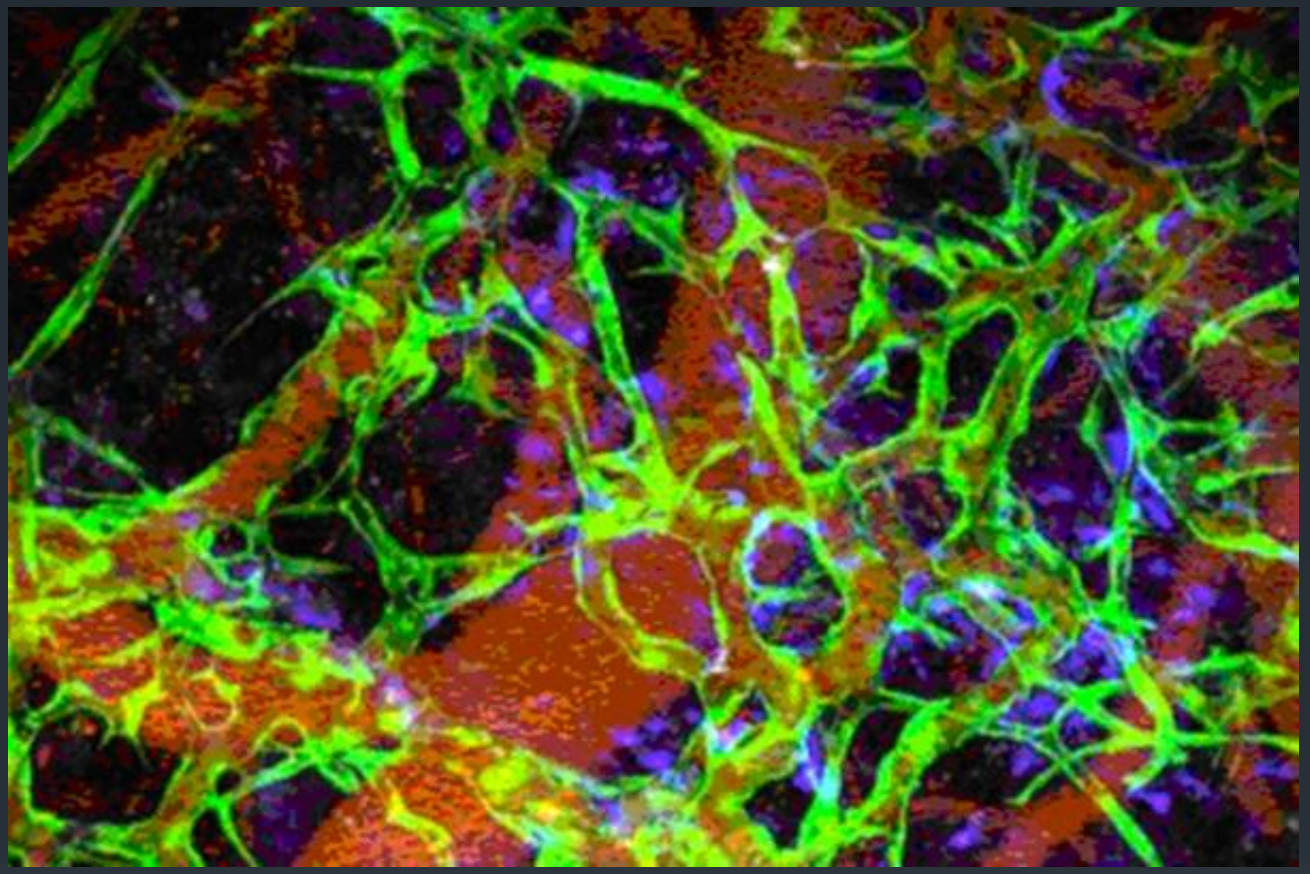
Placebo	N =	12	11	11	11	10	10
HGF	N =	24	23	22	22	22	21

Table 2 – Randomized clinical trial results of angiogenic growth factors versus placebo in patients with critical limb ischemia.

	FGF type 1 (NV1FGF) [14]	FGF plasmid, NV1FGF TAMARIS trial, Phase III [16]	HGF plasmid, AMG0001, AnGes trial [18]
No. of patients	51	525	Drug, 156; placebo, 50
Study design	Phase I, randomized, placebo-controlled	Phase III, randomized, placebo-controlled	Phase II and III, randomized, placebo-controlled
Rutherford class CLI severity	4 and 5	4 and 5	4 and 5
Method of drug delivery	IM injection	IM injection	IM injection
No. of treatments	1 vs 2	4	2 or 3
Study length (months)	6	12	3–36
Study endpoints	Pain reduction; $P < .001$	Amputation free-survival: drug, 65%; placebo, 67%; $P = .48$	Improved ulcer healing; $P < .05$
	Ulcer healing; $P < .01$	Amputation: drug, 26%; placebo, 21%; $P = .31$	Increase in tissue $TcPO_2$; $P < .01$
	Increased $TcPO_2$; $P < .01$	Death: drug, 18%; placebo, 15%; $P = .53$	Reduction in rest pain; $P < .05$
Efficacy demonstrated	Yes	No	Yes
Safety issues		None	None

CLI = critical limb ischemia; FGF = fibroblast growth factor; HGF = hepatocyte growth factor; IM = intramuscular.

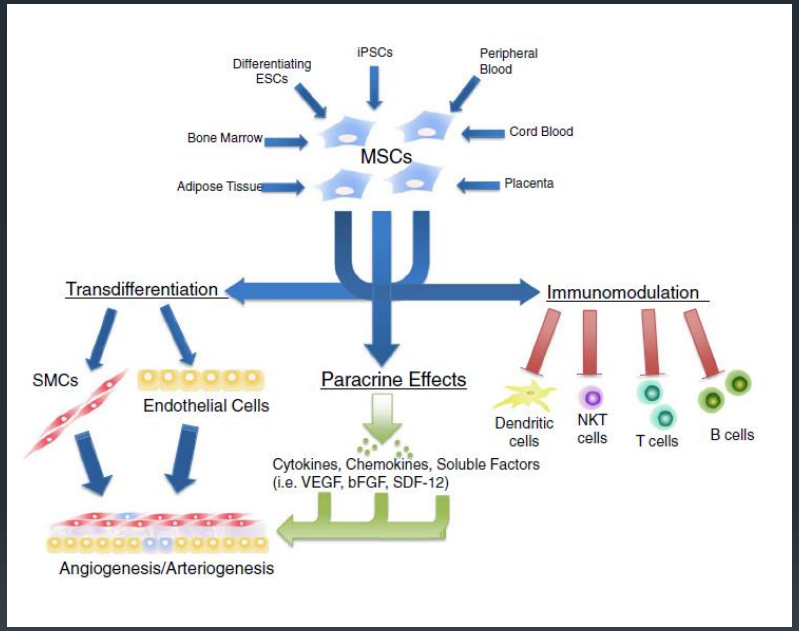
Ko et al, Therapeutic Angiogenesis for critical limb ischemia. *Seminars in Vascular Surgery*, 2014



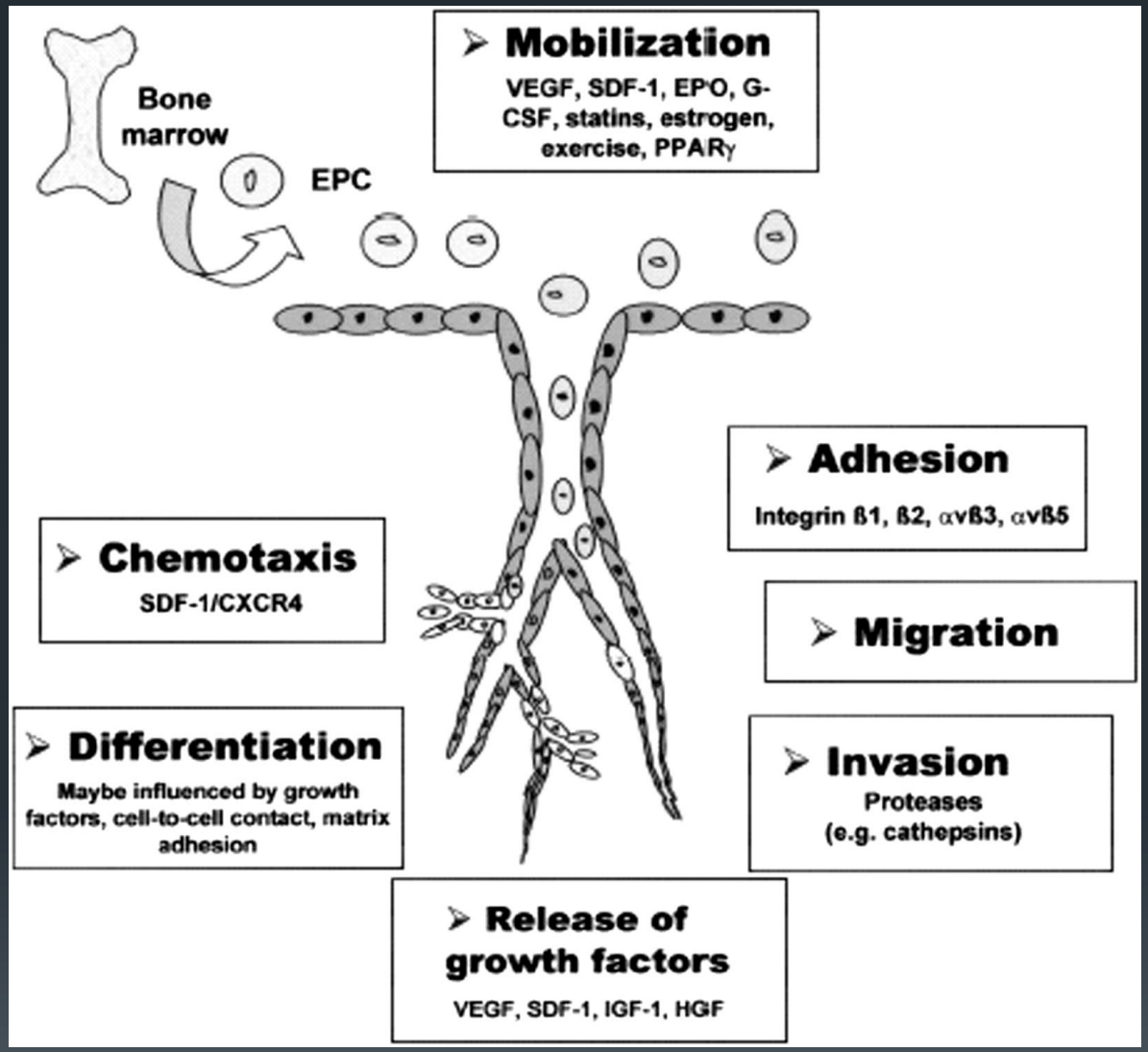
Stem Cell Therapies

Mesenchymal Stem Cells (MSCs)

- Multipotent non-hematopoietic stem cells
  - Found in myriad tissues
    - 1st isolated from bone marrow
    - Optimal source for therapeutic use yet TBD
  - Capacity for self-renewal
  - Differentiation into many different cell types
- Home to and survive in ischemic environments
  - Transdifferentiation -> become vascular cell types
  - Paracrine effects -> stimulate angiogenesis/arteriogenesis via growth factor release
- Currently most actively studied at preclinical and clinical levels
  - Ease of isolation
  - Capacity for ex vivo expansion



Yan, J et al, *Stem Cell Rev and Rep*, 2013



Once in ischemic tissue, stem cells have capacity to perform all functions required during angio/arteriogenesis

Mesenchymal Stem Cells

- Preclinical studies showed promising results in animal models
  - MSCs transplanted into ischemic areas express endothelial markers and promote angiogenesis, arteriogenesis
    - Leading to significantly increased limb blood flow recovery
- Intramuscularly injected MSCs localize to ischemic hind limb
  - No significant migration to other tissues
- Multiple active clinical trials to study the effect of stem cell therapy in CLI

Table 2 On-going MSC clinical trials

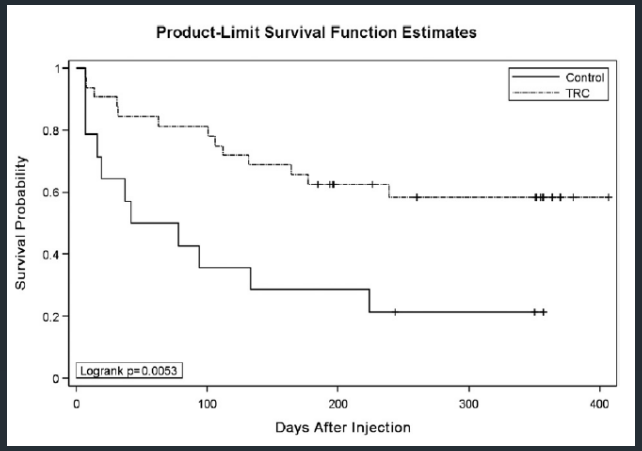
Identifier	Location	Study status	Phase	Cell product	Estimated enrollment	Injection method	Main study design	Time frame	Outcomes measures
NCT01079403	Spain	Unknown	I/II	(A)Adipose-MSC	36	IA	RT, PA, S/E	12 months	ABI, DSA, MRA
NCT01483898	USA	On-going	III	Ixmyelocel-T	594	IM	RT, PA, E, DB	18 months	AFS, WH
NCT01351610	Germany	On-going	I/II	(A)BM-MSC	30	IV	RT, PA, S/E	12 months	ABI, QoL, RP, TcPO2, WH
NCT01257776	Spain	On-going	I/II	(A)Adipose-MSC	36	IA	RT, PA, S/E	12 months	ABI, AFS, DSA
NCT01456819	Malaysia	On-going	II	(A)BM-MNC + MSC	50	IM	RT, PA, E	12 months	ABI, DSA, ETT, VAS, TcPO2, WH
NCT01216865	China	Not yet recruiting	I/II	Cord-MSC	50	IM	RT, PA, S/E	6 months	ABI, AFS, Pain, WT, WH
NCT01211028	France	On-going	I/II	(A)Adipose-MSC	15	IM	NR, SGA, S	6 months	AE
NCT00883870	India	On-going	I/II	(AI)MSC	20	IM	RT, PA, S/E, DB	6 months	ABI, TcPO2
NCT01484574	India	On-going	II	(AI)BM-MSC	126	IM	NR, SGA, S/E	24 months	ABI, AFS, MRA, QoL, TcPO2, WT
NCT01686139	Israel	Not yet recruiting	I/II	(AI)BM-MSC	20	IM	NR, SGA, S	6 months	AE, Pain, VAS, WH

Yan, J et al, *Stem Cell Rev and Rep*, 2013

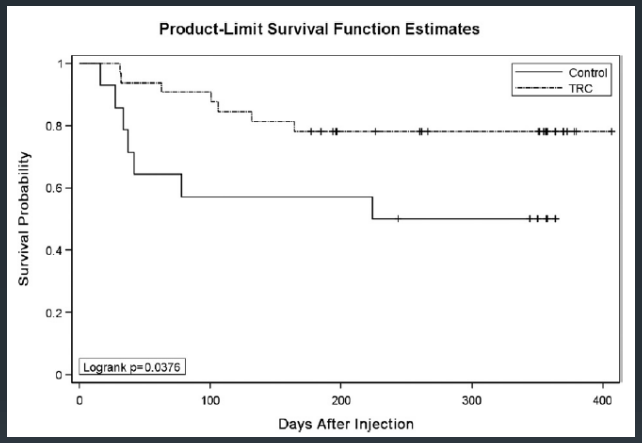
Interim analysis results from the RESTORE-CLI, a randomized, double-blind multicenter phase II trial comparing expanded autologous bone marrow-derived tissue repair cells and placebo in patients with critical limb ischemia

Richard J. Powell, MD,[a] Anthony J. Comerota, MD,[b] Scott A. Berceli, MD,[c] Raul Guzman, MD,[d] Timothy D. Henry, MD,[e] Edith Tzeng, MD,[f] Omaida Velazquez, MD,[g] William A. Marston, MD,[h] Ronnda L. Bartel, PhD,[i] Amy Longcore, MS,[i] Theresa Stern, PhD,[i] and Sharon Watling, PhD,[i] *Lebanon, NH; Toledo, Ohio; Gainesville, Fla; Nashville, Tenn; Minneapolis, Minn; Pittsburgh, Pa; Miami, Fla; Chapel Hill, NC; and Ann Arbor, Mich*

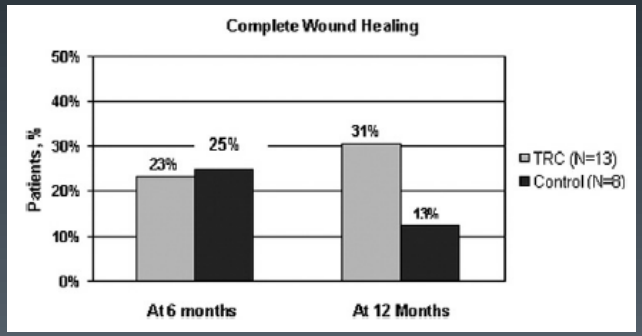
- Prospective, randomized, double-blinded, placebo controlled multicenter trial (18 US centers)
- 86 unreconstructable CLI patients
- BM aspirate expanded ex vivo, then injected into 20 sites in ischemic LE
- Endpoints
  - Primary:
    - Safety
  - Secondary
    - Major amputation-free survival
    - Time to 1st occurrence of treatment failure (amp, death, new gangrene, doubling of wound size)
    - Major amputation rate
    - Wound healing
- Results
  - No difference in adverse events
  - Increased time to treatment failure and amputation-free survival in treated group
  - Decreased major amp rate (19% vs 43%)
  - Improved wound healing



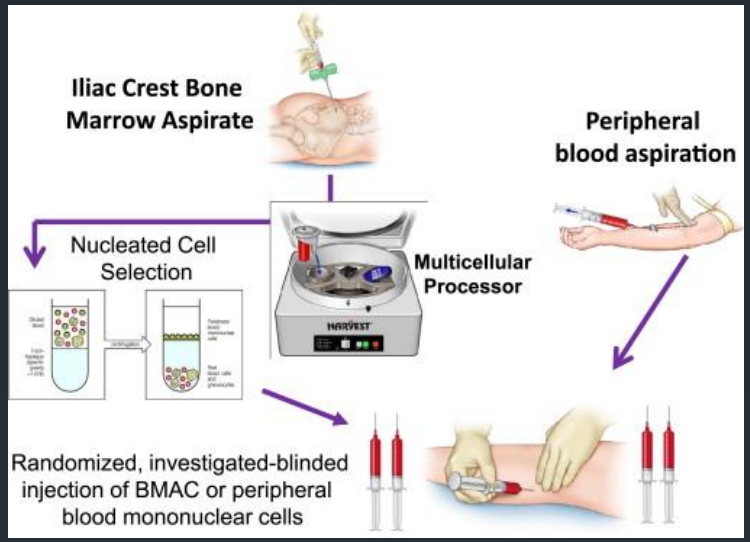
Treatment failure

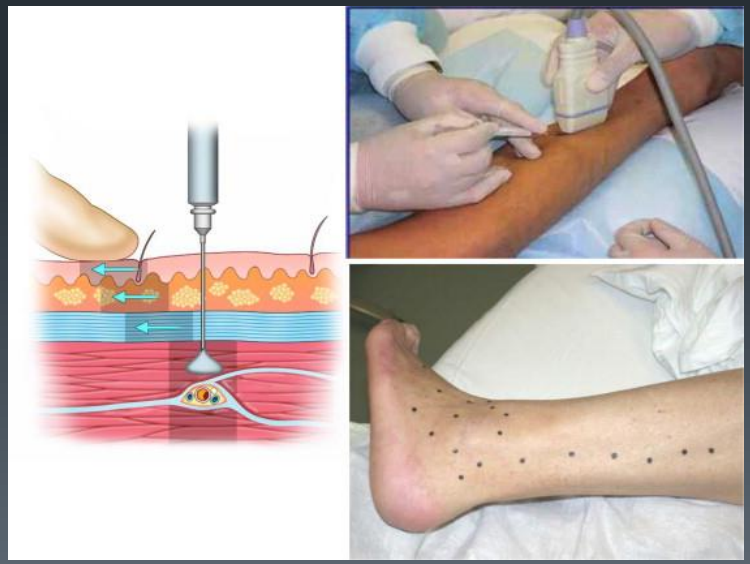


Amp free survival



- REVIVE-CLI
  - Phase III RCT based on findings of RESTORE-CLI
  - Started in 2013
  - Enrolled 40 pts with non-reconstructable disease (594 planned)
  - Halted due to slow enrollment and company shift of focus to dilated cardiomyopathy
- FDA approved phase II pilot study
  - BMAC allows for immediate IM injection of stem cells prepared in the OR
  - 48 pts randomized 2:1 BMAC:placebo
  - 3 months f/u in pts with CLI (tissue loss)
    - Major amputation in 39% treated vs. 71% in placebo patients
    - Duration to amputation was increased
  - Phase III trial now under way





- MOBILE
  - Phase III trial, currently in progress
  - Double blind RCT
  - BMAC vs placebo
  - 152 participants
  - Outcomes assessed
    - Time to major amputation or death
    - Several secondary outcome measures incl perfusion and QoL
    - 5 year amputation free survival
- Estimated study completion May 2020
  - Treatment and 1yr f/u has been completed
  - Long-term follow up is ongoing
  - No initial data analysis published to date

Conclusions

- There is no FDA-approved biological therapy for CLI
- Biologic therapies have shown promise in the treatment of patients with CLI several studies
- Work by promoting tissue angiogenesis in the skeletal musculature
  - tissue regeneration and promotion of distal wound repair
- Recent clinical trials have shown that these biologic therapies are safe
- On-going phase III trials are focusing on stem cell therapy (BMAC)
  - Powered to determine if amp-free survival can be increased
  - Help elucidate frequency of therapy, dose optimization
- Currently no large phase III gene therapy trials underway
  - Phase I/II trials involving genetically engineered stem cells overexpressing vascular growth factors – recruiting
- The effect of concomitant comorbidities, such as DM, on these treatment modalities remains to be elucidated
- Future applications may include biologic therapies in CLI patients before or as an adjunct to endovascular and/or open repair

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Thank you for your attention