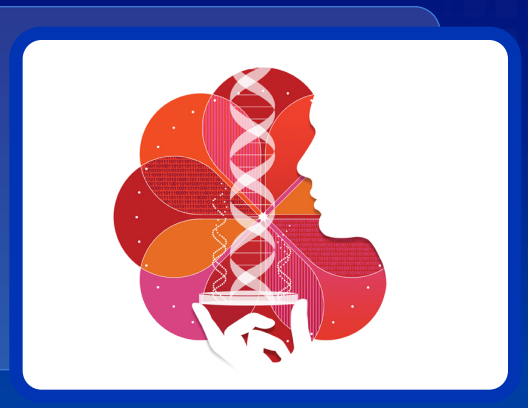

Cardiovascular Cell Therapy Trials

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National Heart Lung and Blood Institute

Outline

- Review of BMC Therapy
- Current Challenges
- NHLBI Cardiovascular Cell Therapy Research Network Trials
- Lessons Learned

Review of BMC Therapy in IHD

- Trials from 2002-2012
- 50 studies; 2625 patients
- BMMNCs (36), BMCs (5),
  CD 133+/CD34+ (6), MSCs/EPCs (3)

Ref: Circ 2012: 126(5):551-68

Characteristics from 50 BMC Trials

- Number of Patients: 10 → 391; (*39*)
- Cell Number: $2x10^6$ → $60x10^9$; (*$100x10^6$*)
- Timing of Delivery: 1 → 18.4 days; (*6.7 d*)
- Average EF: 21% → 62%; (*43%*)
- Follow-up: 3 → 6 months; (*6 months*)
- Blinded/non-blinded patients

* Median in parentheses

Results from 50 BMC Trials

- LVEF ↑ by 3.96% (24 months)
- Infarct size ↓ by 4.03%
- LVESV ↓ by 8.9 ml
- LVEDV ↓ by 5.23 ml
- $100x10^6$ cells were sufficient; $<40x10^6$ were not
- Decrease in all cause mortality, cardiac mortality and stent thrombosis

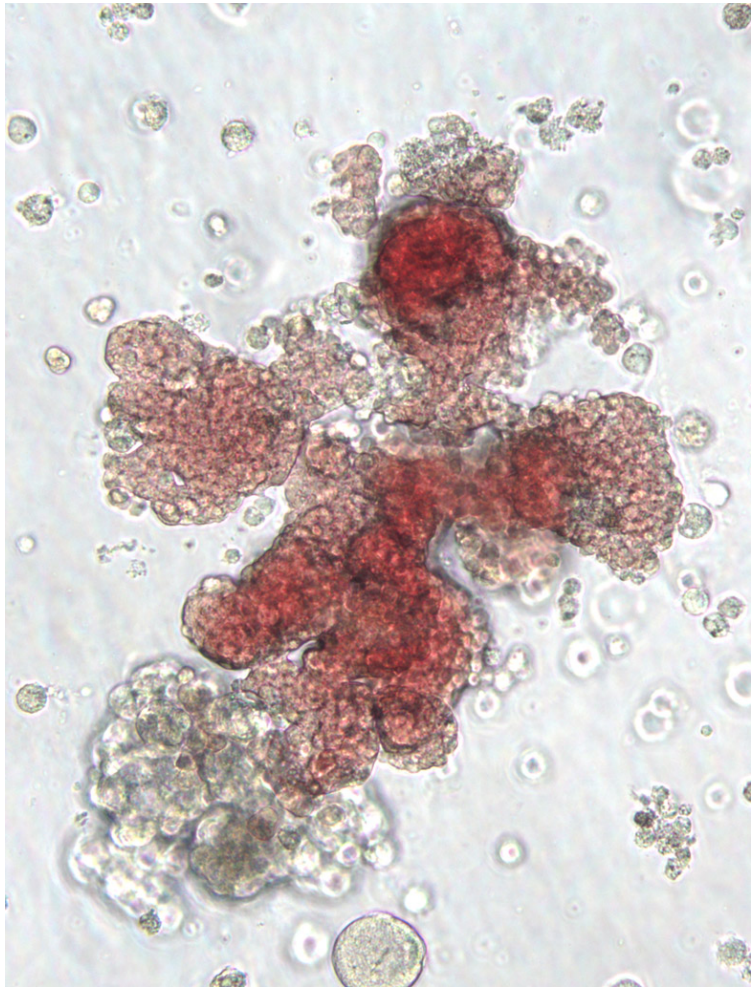
Current Challenges/Issues

- Patient population: are we selecting the right patients (acute MI, HF)
- Cell types and dose: which cells are best? What dose is optimal?
- Timing of delivery: is early post MI or later best?
- Delivery route: intracoronary vs. intramyocardial

Current Challenges/Issues (2)

- Imaging: results vary depending on which imaging tool is used
- Cell Preparation: do we have a standard process?
- Selection of endpoints: should we select one endpoint or more than one?
- Design of protocol: randomized, blinded, small number of patients. Is it safety or efficacy?

Cardiovascular Cell Therapy Research Network (CCTRN)



To promote and accelerate clinical research in the evaluation of novel cell therapy treatment strategies for individuals with cardiovascular disease

Red blood cell colony derived from human embryonic stem cells image from the University of Wisconsin-Madison

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CCTRN Trials

- LateTIME (87 patients) : Effect of Late (2-3 week post MI) BMMNCs administration (150 million cells) on measures of LV function (AHA 2011). First BMC trial to deliver standardized dose of cells.
- FOCUS (92 Patients): Effect of transmyocardial BMMNCs administration (100 million cells) in patients with chronic ischemic disease with LV dysfunction. (ACC 2012)

CCTRN Trial Results

- LateTIME: no improvement in global or regional LV function at 6 months
  - MRI measurements more sensitive
  - Heterogeneity of cells; inflammatory changes
  - Patient population; EF too high to start off

CCTRN Trial Results (2)

- FOCUS: no improvement in LV function, maximal oxygen consumption or lesion reversibility.
  - Assumed ambitious improvements in primary endpoints; at time had no results from other trials
  - **BUT** BMC group had improved LVEF (2.7%) compared with placebo group and maximal oxygen consumption improved in younger patients

Lessons Learned in Protocol Design

- Disappointing results but valuable for designing future trials.
- Select endpoints from different domains: structural evaluations; physiological measurements; biomarkers; functional capacity; quality of life.
- Endpoint event rates or mean changes must be established with predetermined precision.

Other Lessons Learned

- Distributed cell processing was an effective strategy (never carried out before)
- In vitro analyses demonstrated the equivalence of Sepax vs manual procedure
- Development of novel imaging endpoints (regional LV function based on wall motion)
- New ways to recruit patients (use of DVD, identification of the importance of garnering support for the family to recruit a family member)

Thank You

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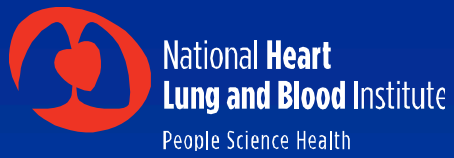

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