Exosomes as next-generation therapeutic candidates

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Disclosure: Founder's equity in, and unpaid advisor to, Capricor Inc.

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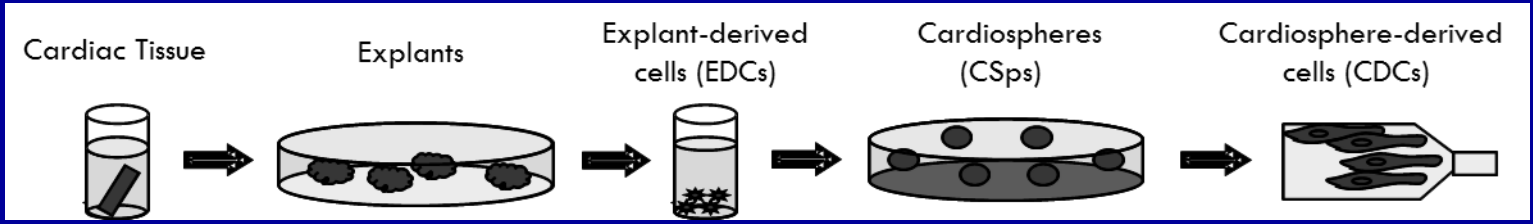
Cardiosphere-derived cells (CDCs)



First described by RR Smith et al., *Circulation* 2007; methods and bioactivity reproduced by at least 26 labs worldwide

Cell Type	Human heart stem cell/cardiac stromal cell
Characteristics	CD105+, CD45-; secreted SDF-1 and exosomes containing distinctive miRs
Clinical Trials	**CADUCEUS**-completed-autologous phase 1 (n=25). Evidence of regeneration in CDC-treated post-MI subjects with mild heart failure (*Lancet*, 2012)
	ALLSTAR-phase 1 (n=14) completed; phase 2 (n=134), enrollment complete-allogeneic CDCs post-MI with mild heart failure
	DYNAMIC-ongoing-phase 2a (n=14)- allogeneic CDCs in patients with advanced heart failure
	HOPE-Duchenne-allo CDCs for DMD cardiomyopathy, enrollment complete
Mechanism of action	Paracrine regenerative effects ▪ **Promote cardiomyomyogenesis** ▪ **Prevent cardiomyocyte apoptosis** ▪ **Anti-fibrotic** ▪ **Anti-inflammatory**

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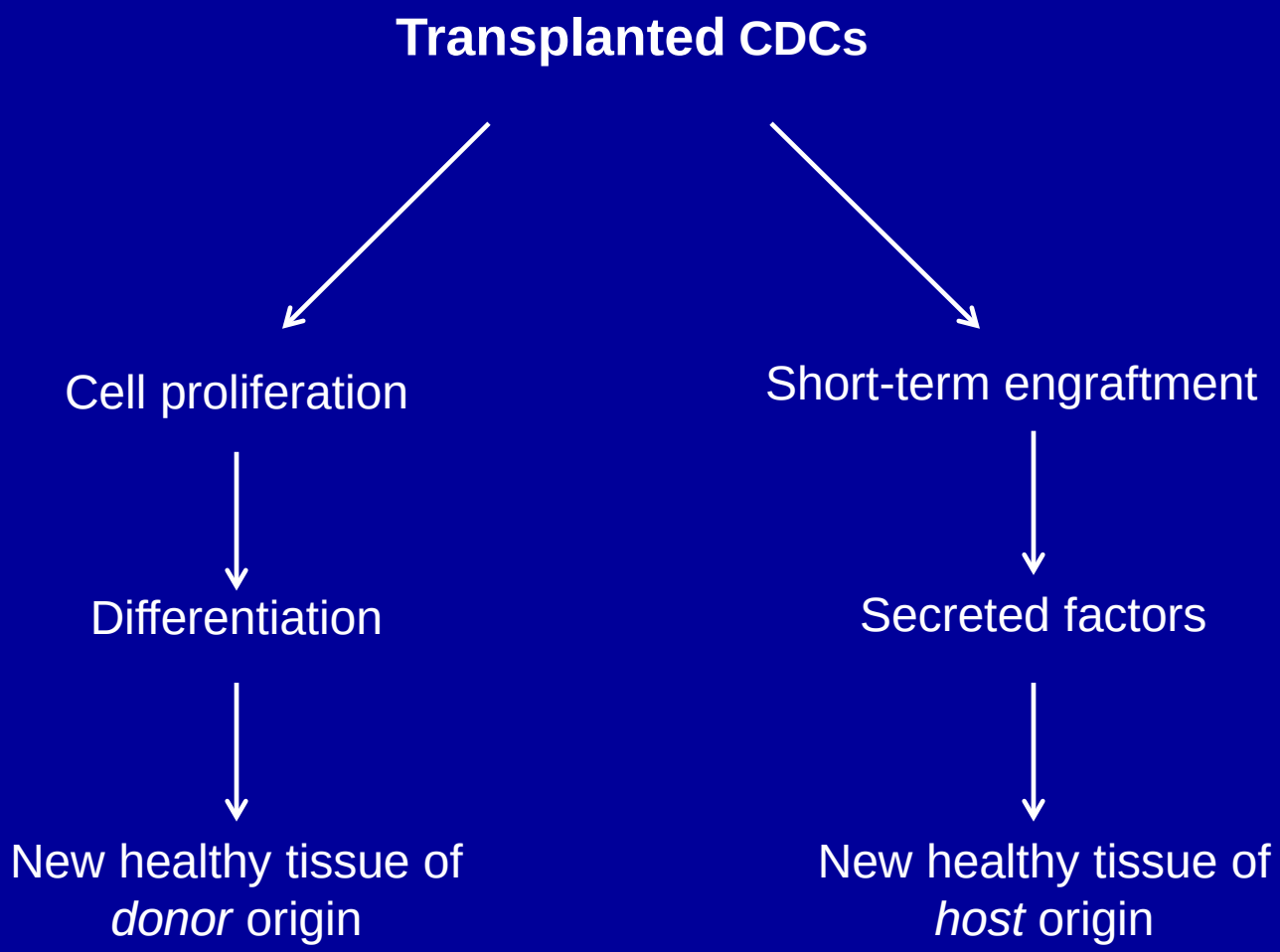
Mechanism



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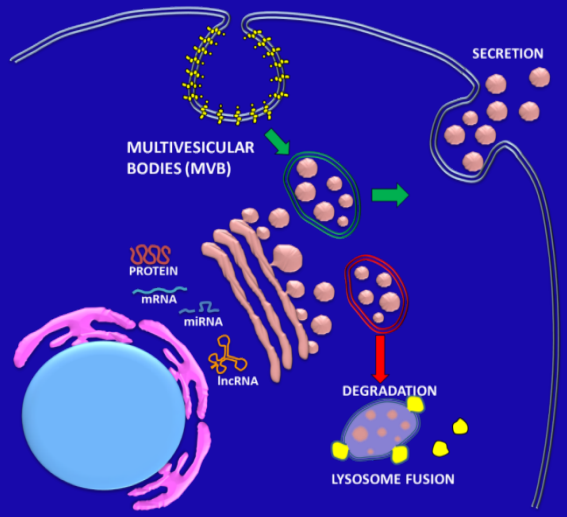
Cell-free therapeutics

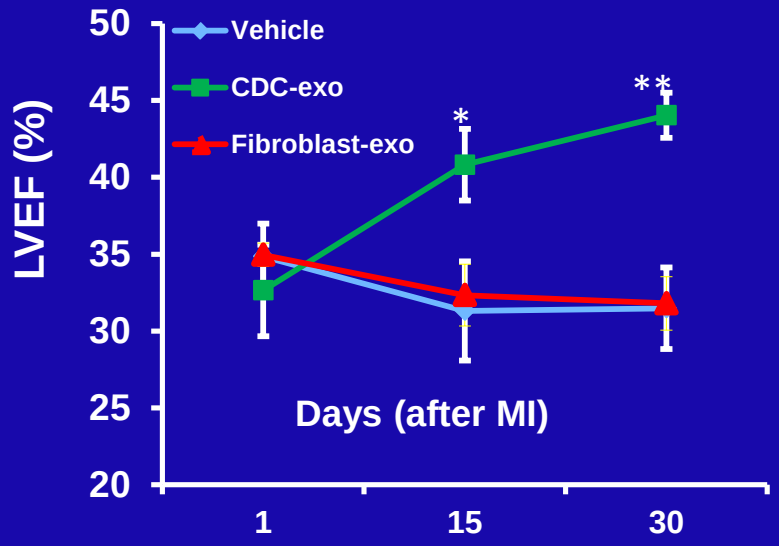
Is there a single entity that can mimic all the salient benefits?

Exosomes are bioactive nanoparticles

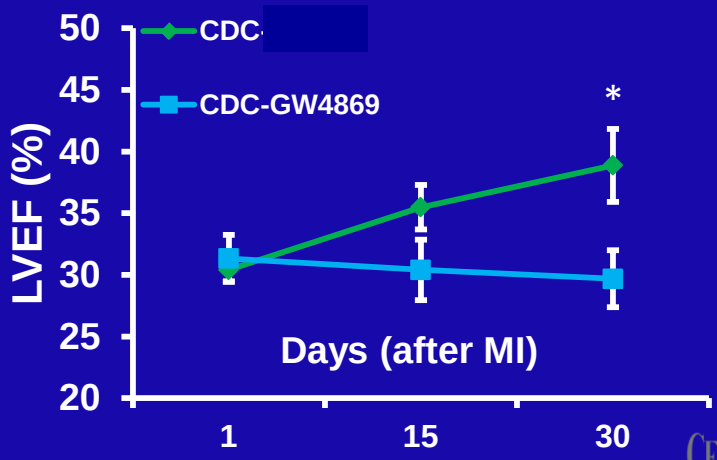


- 30-150 nm particles
- Present in all body fluids
- Released by nearly all cell types
- Loaded with miRs and other bioactive contents
- Payload very cell-specific

CDC exosomes ↑ EF



Blocking exosome biosynthesis abrogates CDC benefit



Ibrahim et al., *Stem Cell Reports* 2014

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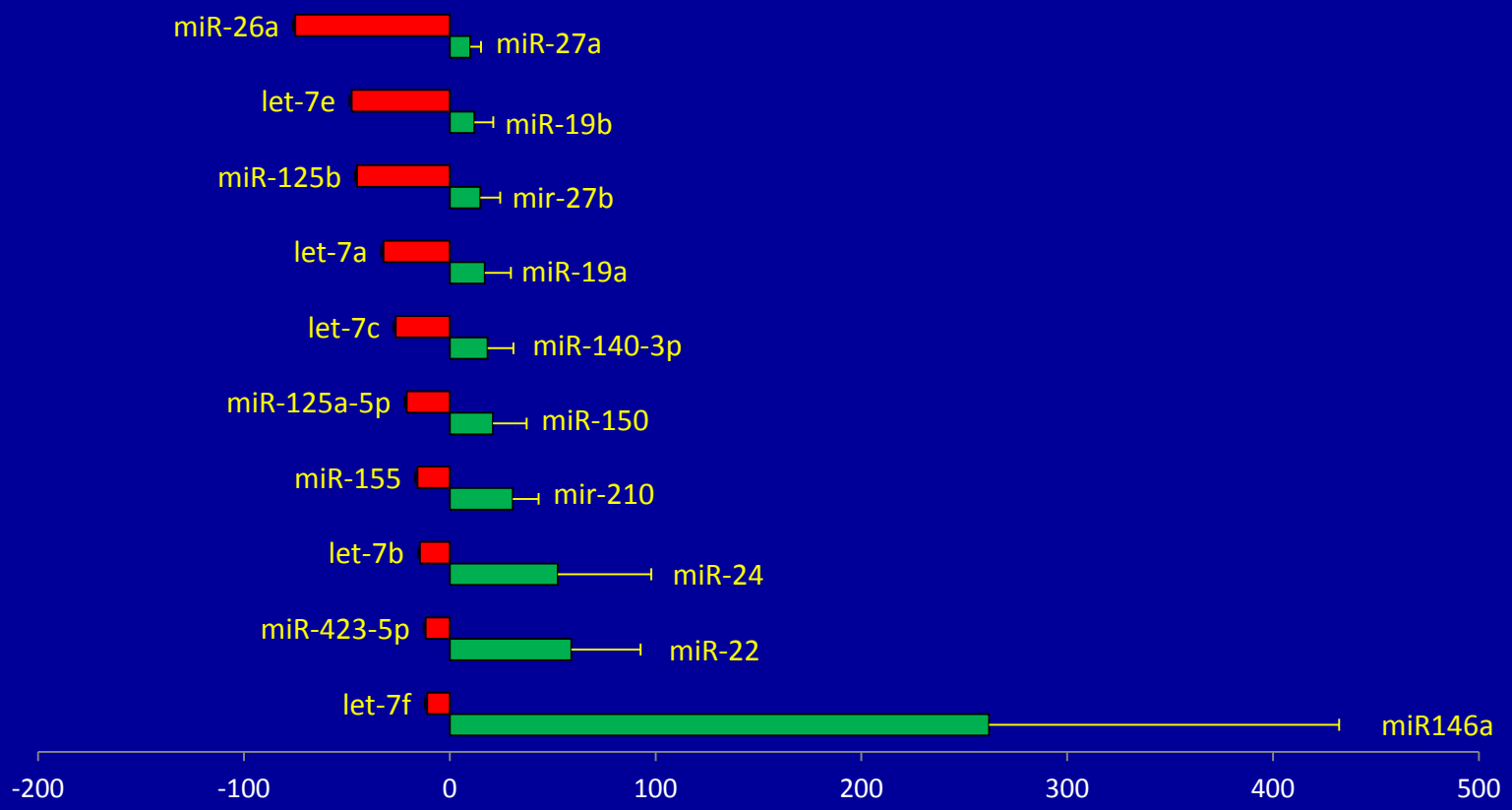
Exosomes mimic CDC effects on multiple biological processes

	CDCs	CDC-XO
• Regenerative	√ 1,2	√ 11,12
• Antifibrotic	√ 1-4	√ 11,12
• Anti-apoptotic	√ 3-5	√ 11,13
• Angiogenic	√ 1,6	√ 11
• Anti-inflammatory	√ 9	√ 12,13
• Immunomodulatory	√ 9,10	√ 12

1. RR Smith et al, *Circ* 2007; 2. Makkar et al., *Lancet* 2012; 3. E. Tseliou et al., *PLoSOne* 2014; 4. E. Tseliou et al., *BRIC* 2014; 5. T-S Li et al, *JACC* 2012; 6. I. Chimenti et al, *Circ Res* 2010; 7. K. Malliaras et al, *Circ* 2012; 8. K. Malliaras et al., *EMBO Mol Med* 2013; 9. M. Aminzadeh et al., *EHJ* 2014; 10. L. Lauden et al, *Circ Res* 2013; 11. A. Ibrahim et al. *Stem Cell Reports* 2014; 12. M. Aminzadeh et al., *Circulation AHA abstracts* 2015; 13. G. DeCouto et al., *Circulation AHA abstracts* 2015

CDC-exosomes exhibit a distinctive miR profile



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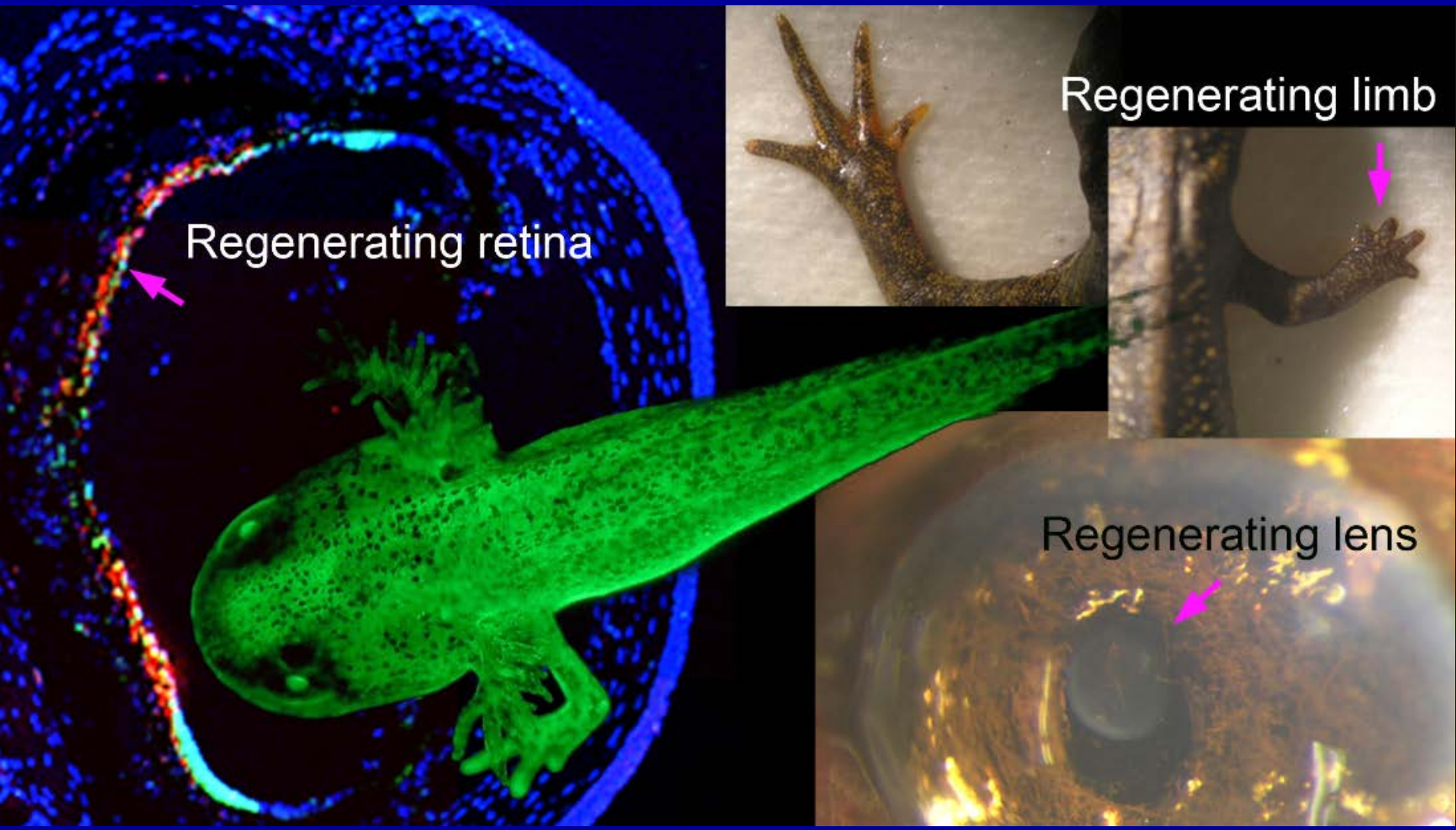
Working hypotheses

- No single RNA species can account for all the benefits of exosomes
- Individual miRs or other RNA species may prevail in any given setting
- The totality of exosomal contents required for full manifestation of bioactivity

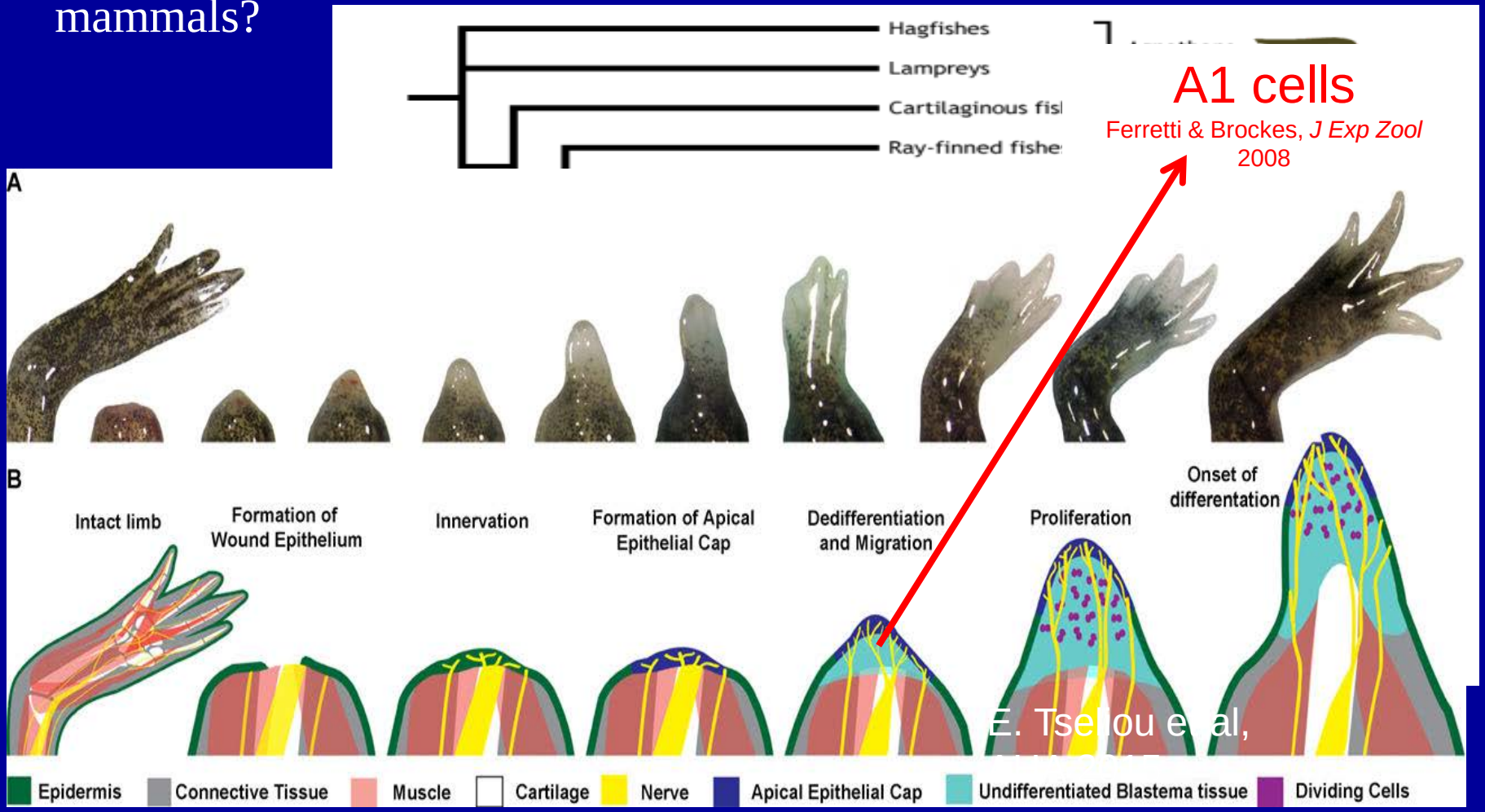
Regeneration in newts>>in mammals



Chiba lab, Tsukuba University, Japan

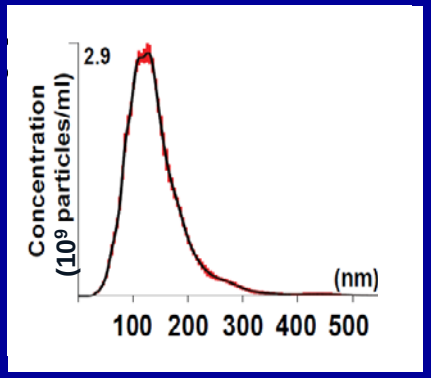
Is newt biology translatable to mammals?

- Separated from mammalian lineage ~**300 million years ago**
- Can newt cells make exosomes? Are the exosomes biologically active in mammals?

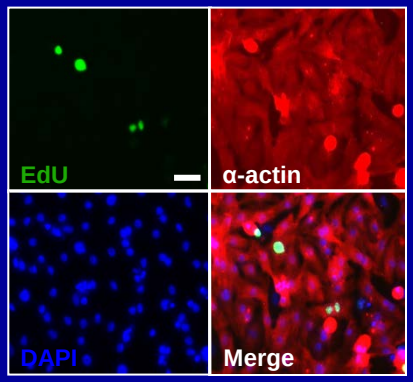


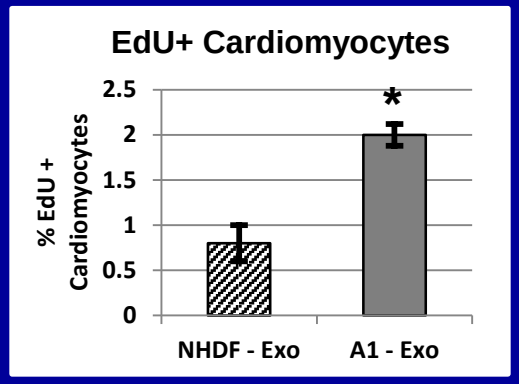
Newt A1 cells make exosomes that are regenerative in rats

Newt exosome size

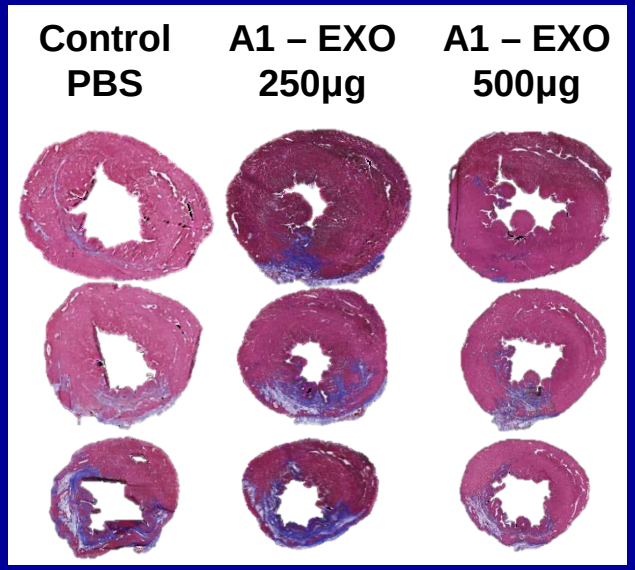


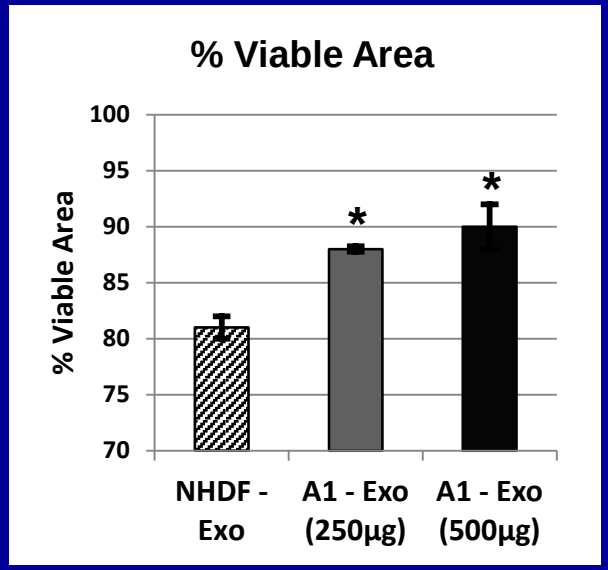
Rat cardiomyocyte proliferation *in vitro*

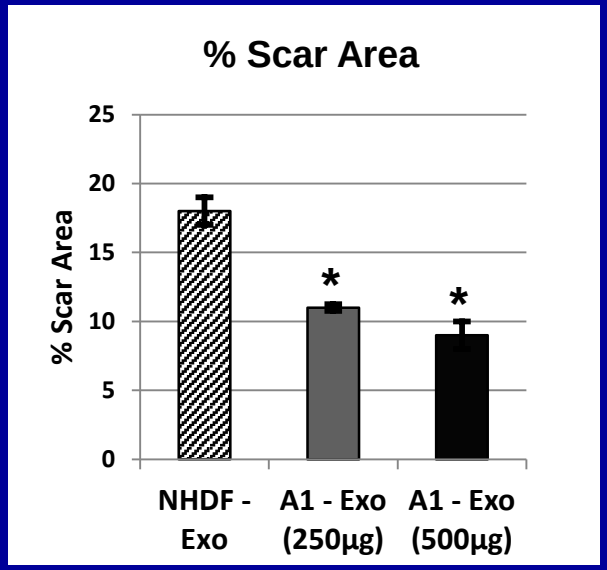




Rat heart morphology two weeks post-infarction: Newt A1- vs. NHDF-exosomes







Will therapeutic exosomes ever reach the clinic?

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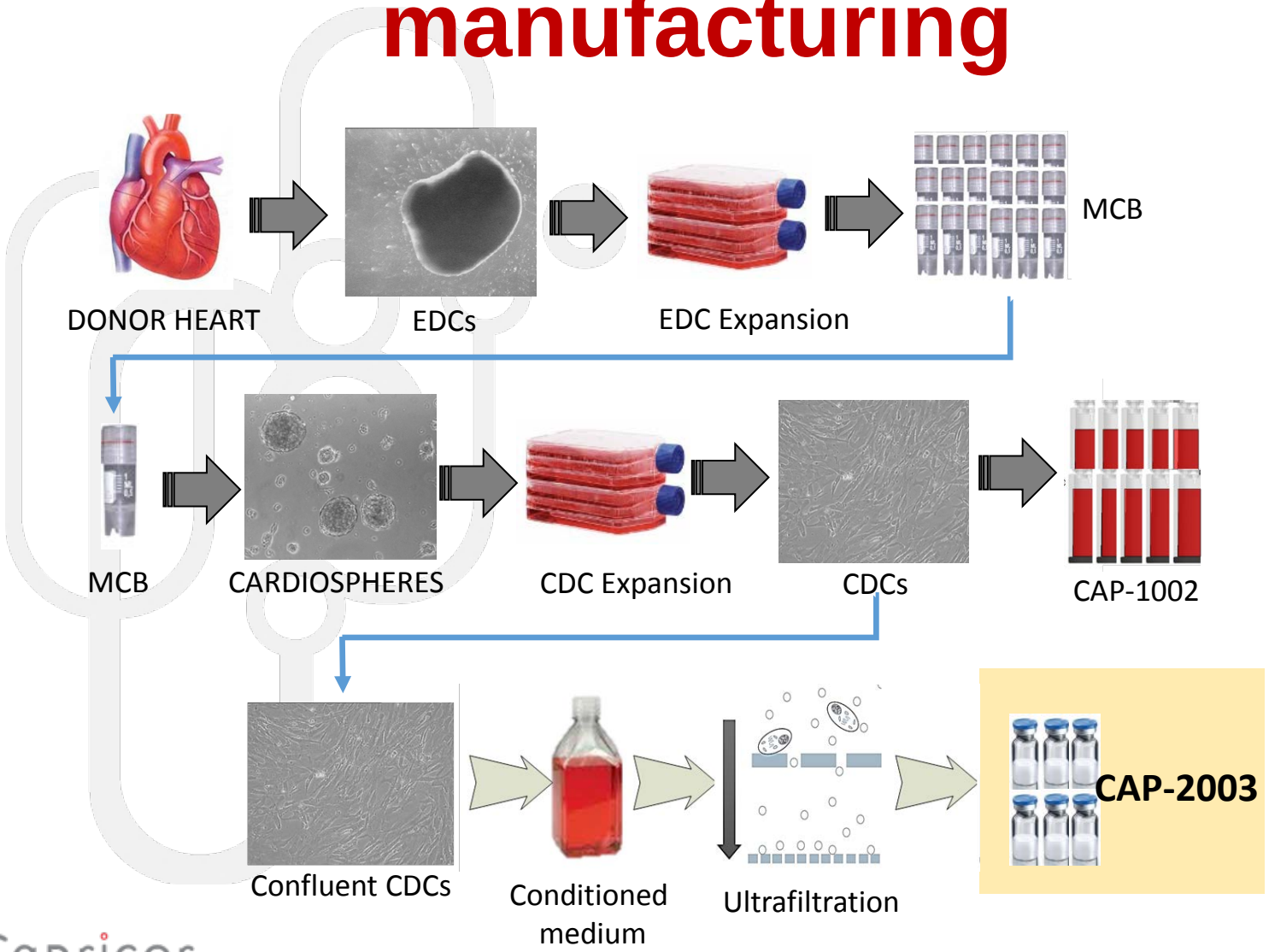
Capricor Overview

- Founded in 2005 (JHU spinoff); NASDAQ listed (CAPR) in 2015
- Employees: 40 FTEs
- Distinctive features:
  - No VC money
  - 100% scientific/medical management
  - Extensive peer-reviewed grant support (CIRM, NIH, DoD)
  - Soup-to-nuts scope: Discovery, development, manufacturing, regulatory and clinical trials design/management

Capricor Therapeutics™

CDC-exosome clinical manufacturing



Capricor Therapeutics™

Summary

- Cardiosphere-derived cells: viable therapeutic candidates
- Exosomes mediate, and reproduce, benefits of CDCs
- Newt exosomes bioactive in mammalian injury
- Clinical development for diseases with prominent fibrosis, inflammation

Acknowledgments

Cedars-Sinai Heart Institute

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