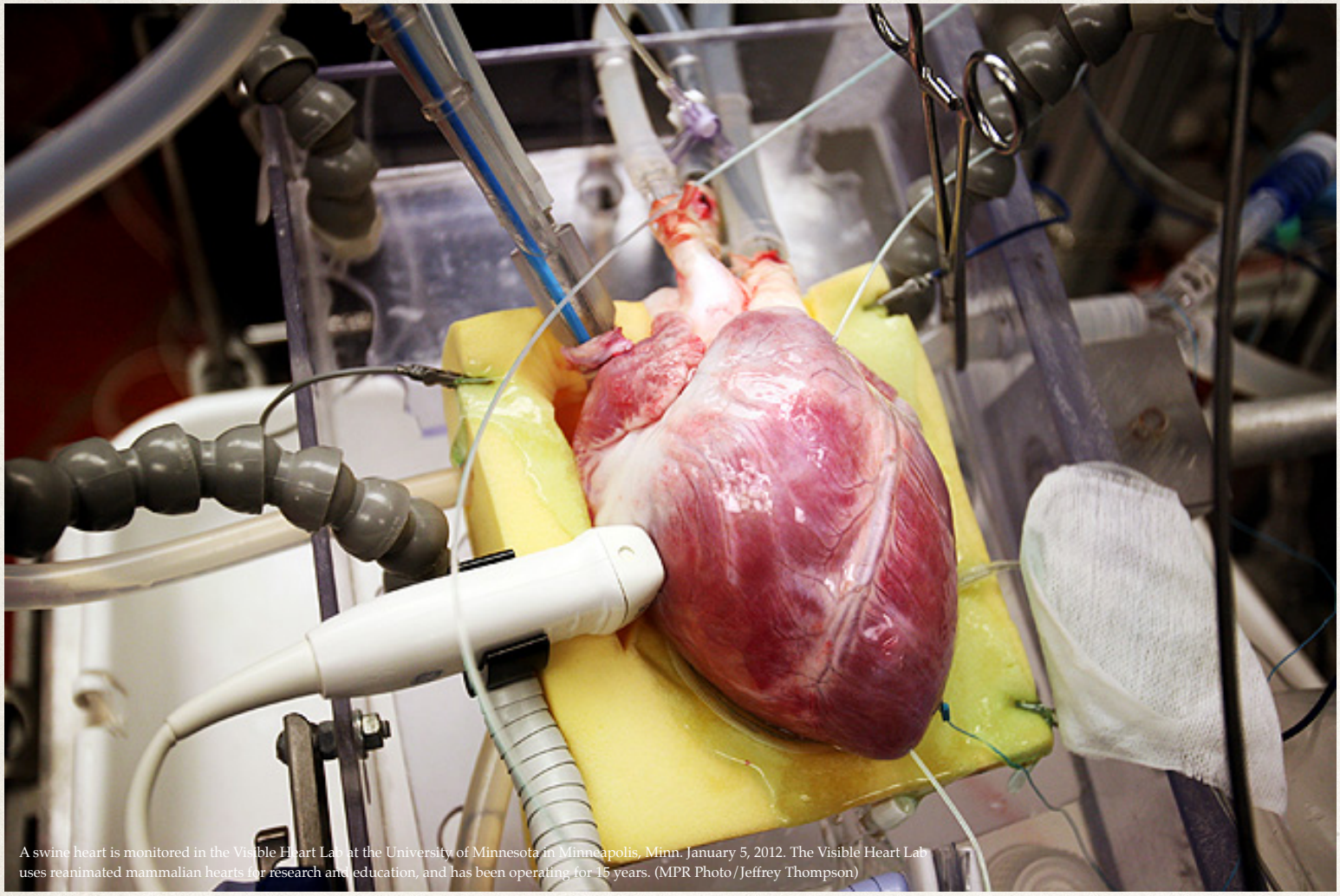


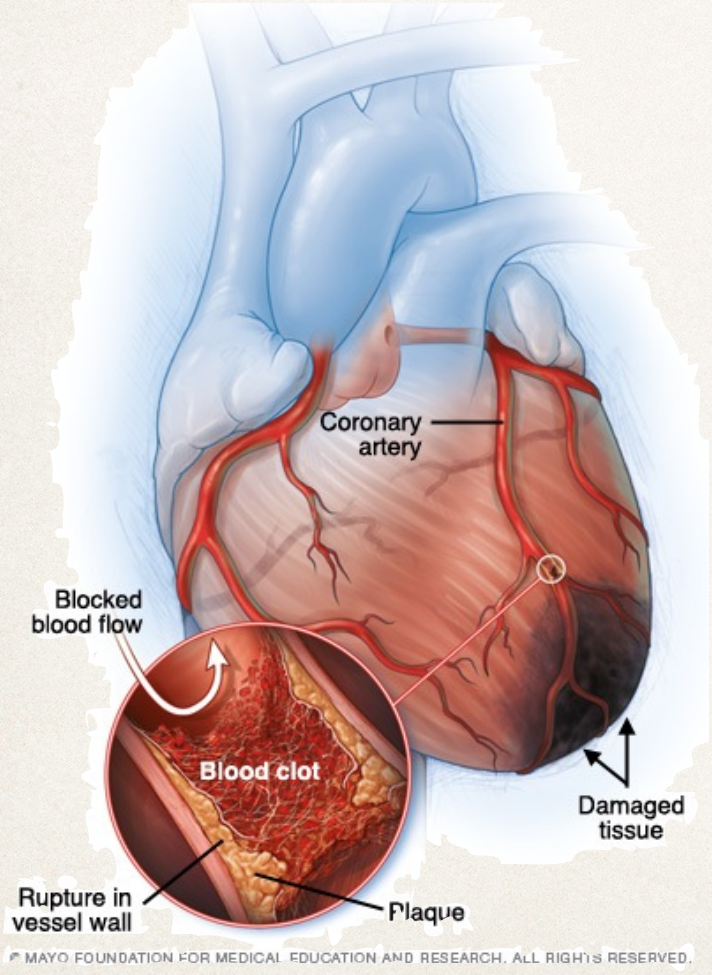
A swine heart is monitored in the Visible Heart Lab at the University of Minnesota in Minneapolis, Minn. January 5, 2012. The Visible Heart Lab uses reanimated mammalian hearts for research and education, and has been operating for 15 years. (MPR Photo/Jeffrey Thompson)

Regenerating Heart Tissue

BMEN 612 - Amin Adibi

21 November 2013

Why would we want to regenerate it?

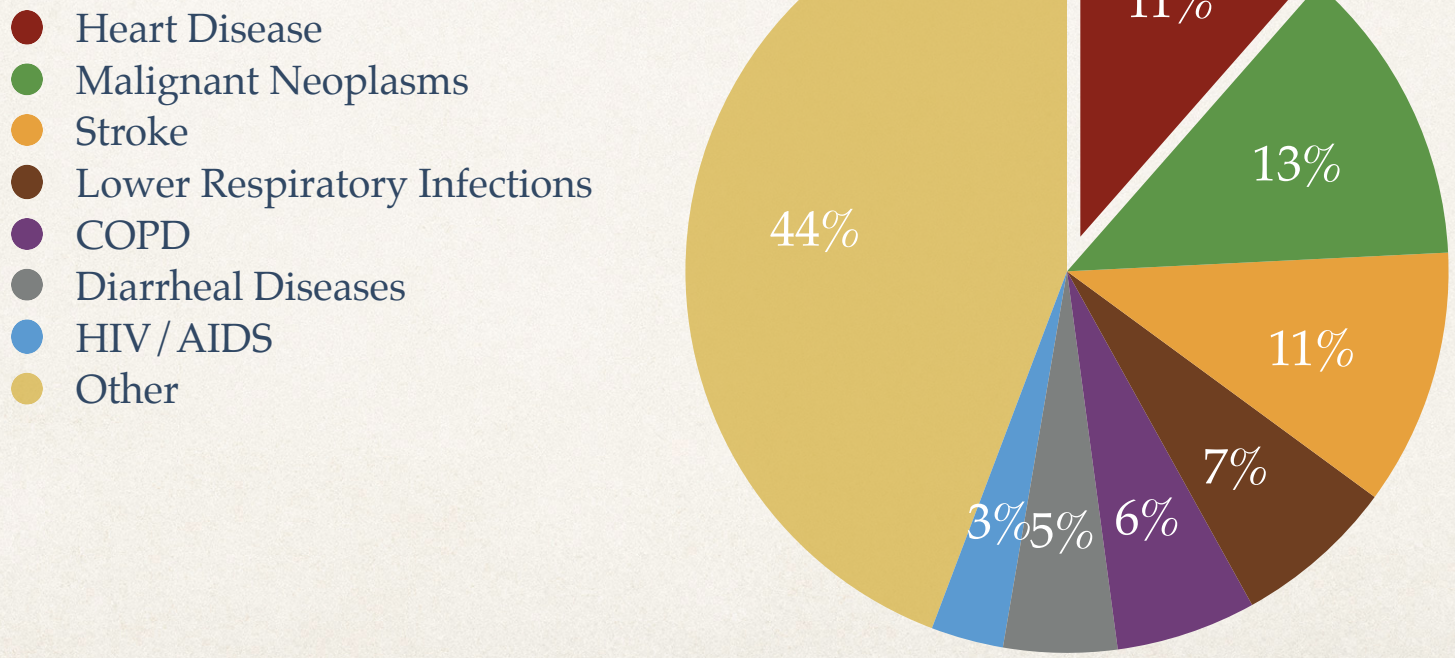


- Heart muscle cells (i.e. cardiomyocyte) die in heart attacks, resulting in dead tissue.
- Up to 1 billion of cardiomyocytes might die in an attack (the total is about 3 billion)
- This results in decreased contraction.
- How do we measure it?

- Ptaszek et al (2012). Laflamme (2005).
  Image from http://www.mayoclinic.com/health/medical/IM00938

Why would we want to regenerate it?

- Heart disease accounts for 7 million annual deaths, 11% of all deaths in the world.



- World Health Organization (2004)

Can't it regenerate itself? Please?

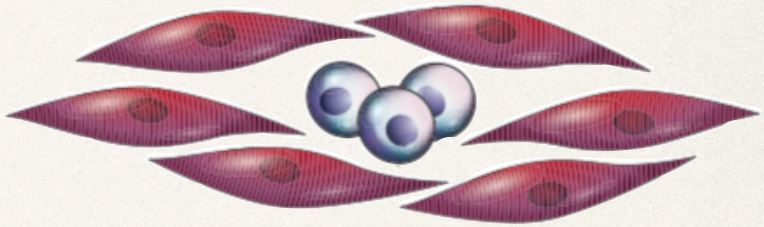
- Unlike zebrafish, salamanders and neonatal mice, there is no cardiac regeneration in humans.

- Cardiomyocyte turn-over rate:
  1% in young people, 0.5% in elderly.
- Turnover increases in response to injury, but is not enough to repair the damaged muscle.

- Boström (2013), Ptaszek et al (2012). Image obtained from http://en.wikipedia.org/wiki/File:Zebrafisch.jpg

Cell Therapy

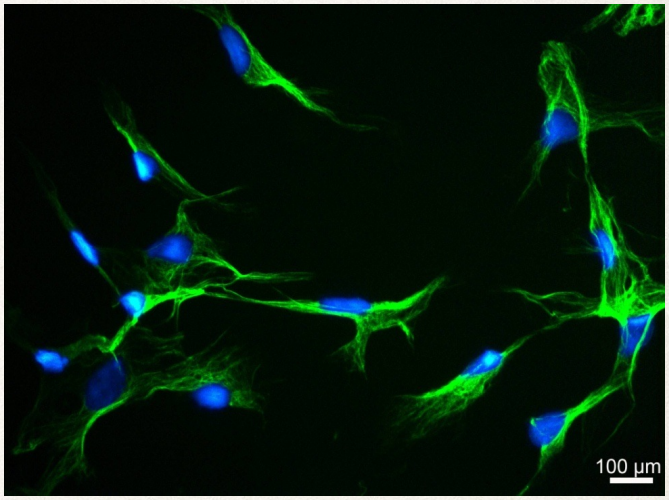
- What is lost? Cells. Maybe we can implant new cells?
- But what kind of cells?
  - Stem Cells.
  - Progenitor Cells.



- Ptaszek et al (2012). Image from Segers et al (2008)

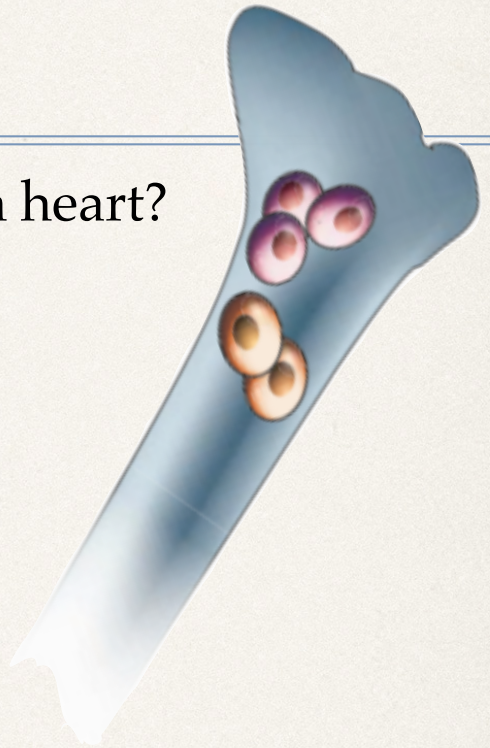
Cell types: skeletal muscle myoblasts

- We want muscle regeneration.
- Let's implant the cells that do it! (Skeletal Muscle Myoblasts)
- Works in rabbits!
- MAGIC Trial → didn't really work!
- No differentiation into heart muscle cells



- Ptaszek et al (2012). Taylor et al. (1998). Menasché (2008). Image from Dorothee et al. (2011)

Cell types: bone marrow cells

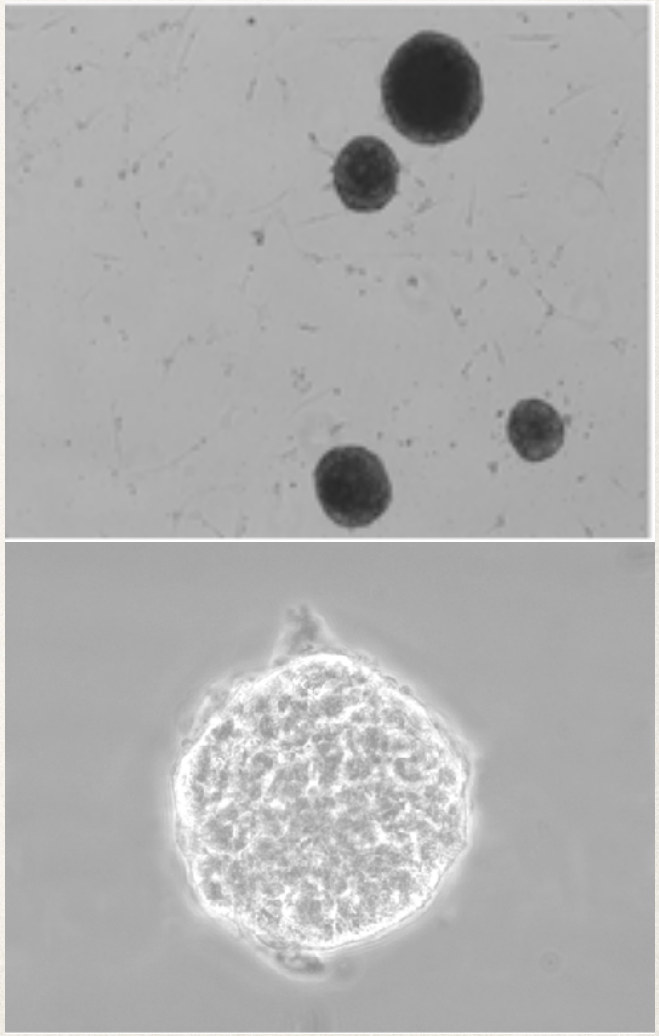


- What is bone marrow (BM)? What does it have to do with heart?
- Cells in bone marrow.
- REPAIR-AMI and STAR-heart trials showed small improvements and no new complications
- STAR-heart showed significant decrease in mortality.
- Studies showed these cells don't differentiate into heart cells.
- Paracrine effects?

- Deb (2003), Quaini (2002), Ptaszek et al (2012). Image from Segers et al (2008)

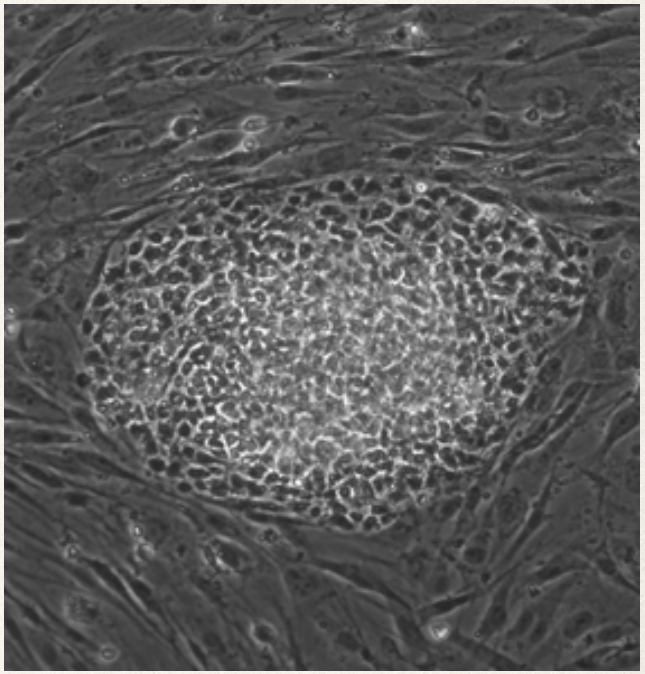
Cell types: cardiac progenitor cells

- What are cardiac progenitor cells?
- Different populations (c-Kit+ , Sca-1+, cardiospheres)
- SCIPIO Trial: c-Kit cells. Myocardial scar reduced. LVEF Improved.
- CADACEUS Trial: cardiospheres from right ventricle biopsies. Myocardial scar reduced No improvement in LVEF.
- Genetic fate mapping, showed these cells do not differentiate into cardiomyocytes. Paracrine factors?
- Barile (2013), Ptaszek et al (2012), Makkar (2012). Images from Barile (2013)



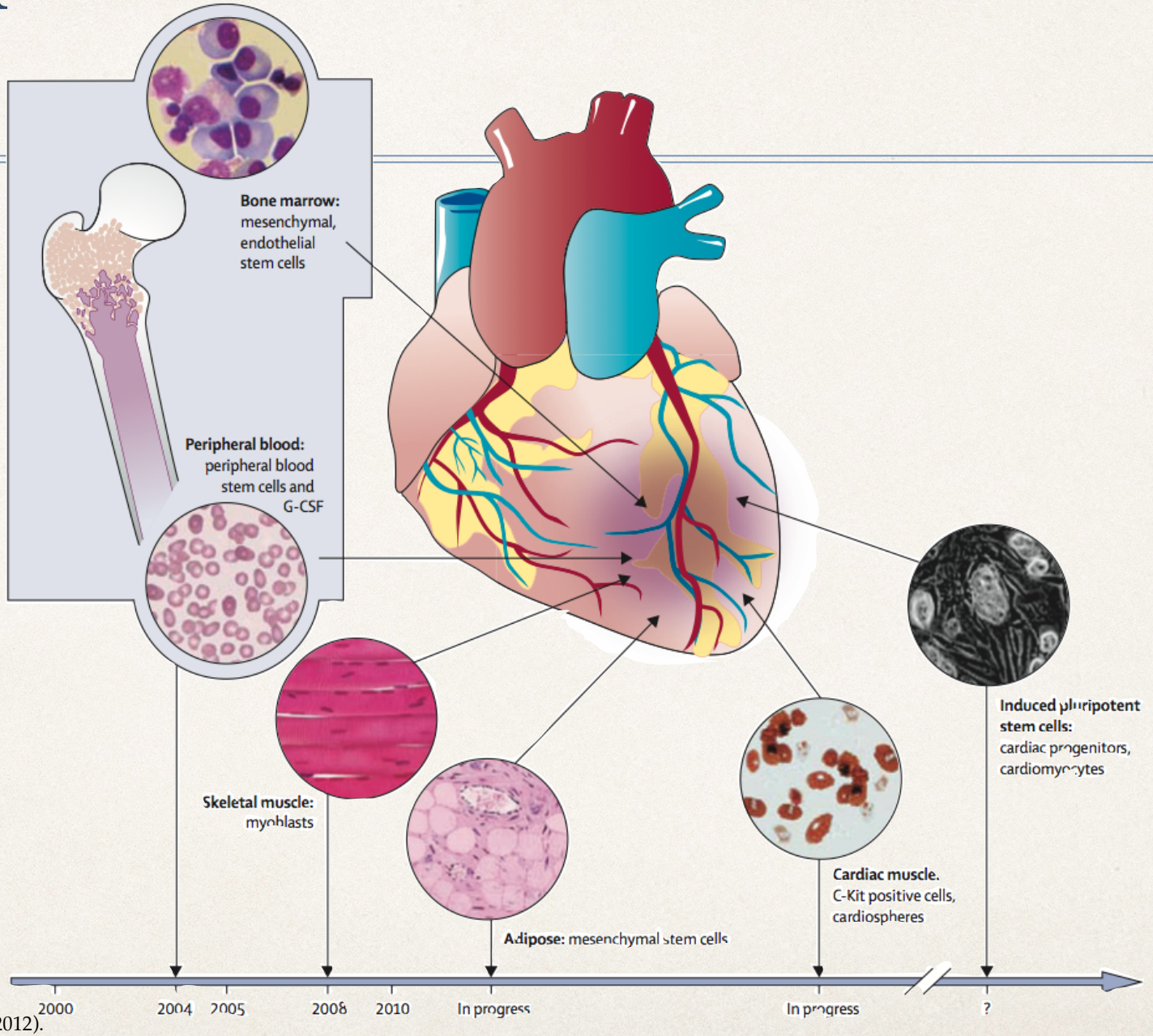
Cell types: iPSCs

- Even if cardiac stem cells are better defined, their rarity might pose a problem.
- Advantages:
  - ethical considerations
  - autologous transplantation
- Issues:
  - viruses
  - removal of pluripotent cells before implantation



- Ptaszek et al (2012). Image from Kim (2010).

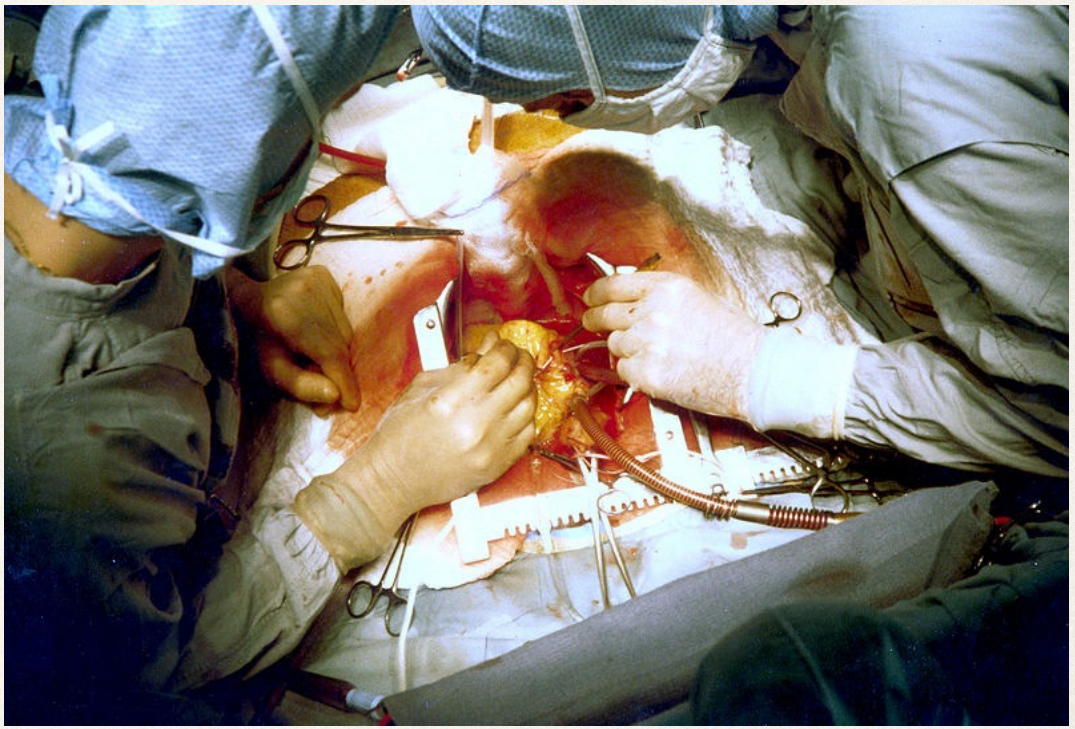
Cell types: timeline



- Image form Ptaszek et al (2012).

Routes of Delivery: open chest injection

- Advantages:
  - direct visualization
  - high efficiency delivery
- Disadvantages:
  - high morbidity
  - hospitalization required
  - high cost



Ptaszek et al (2012). Image from http://en.wikipedia.org/wiki/File:Coronary_artery_bypass_surgery_Image_657B-PH.jpg

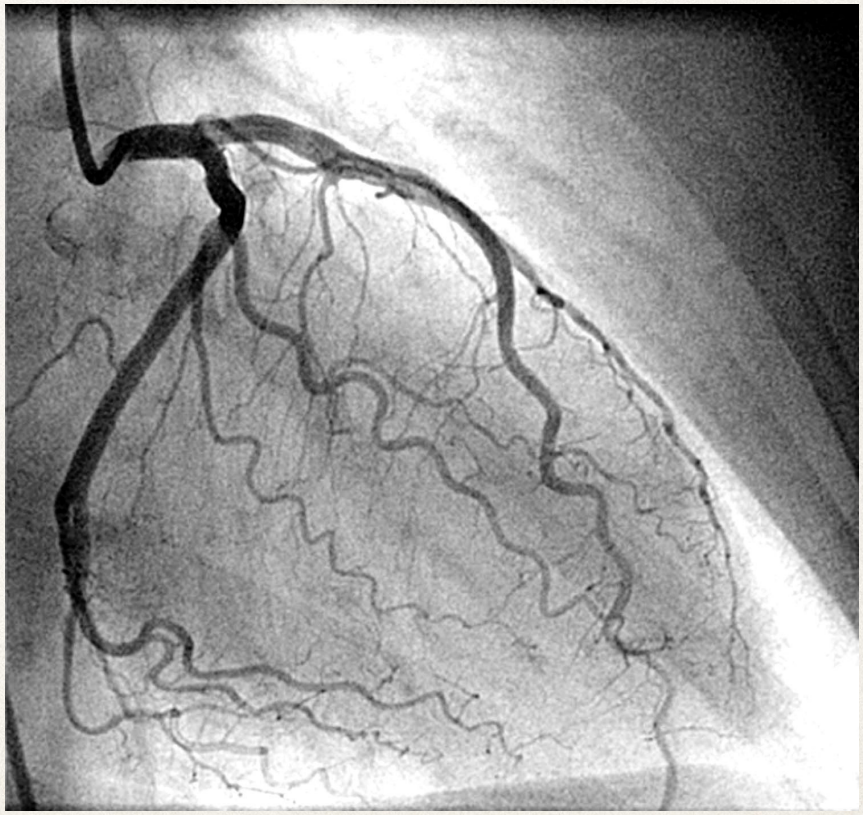
Routes of Delivery: IV Injection

- Advantages:
  - less invasive, low morbidity
  - easy administration
  - cheap
- Disadvantages:
  - dissemination of the delivered cells
  - blocked arteries
  - no visualization

Ptaszek et al (2012). Image fron http://en.wikipedia.org/wiki/File:ICU_IV_1.jpg

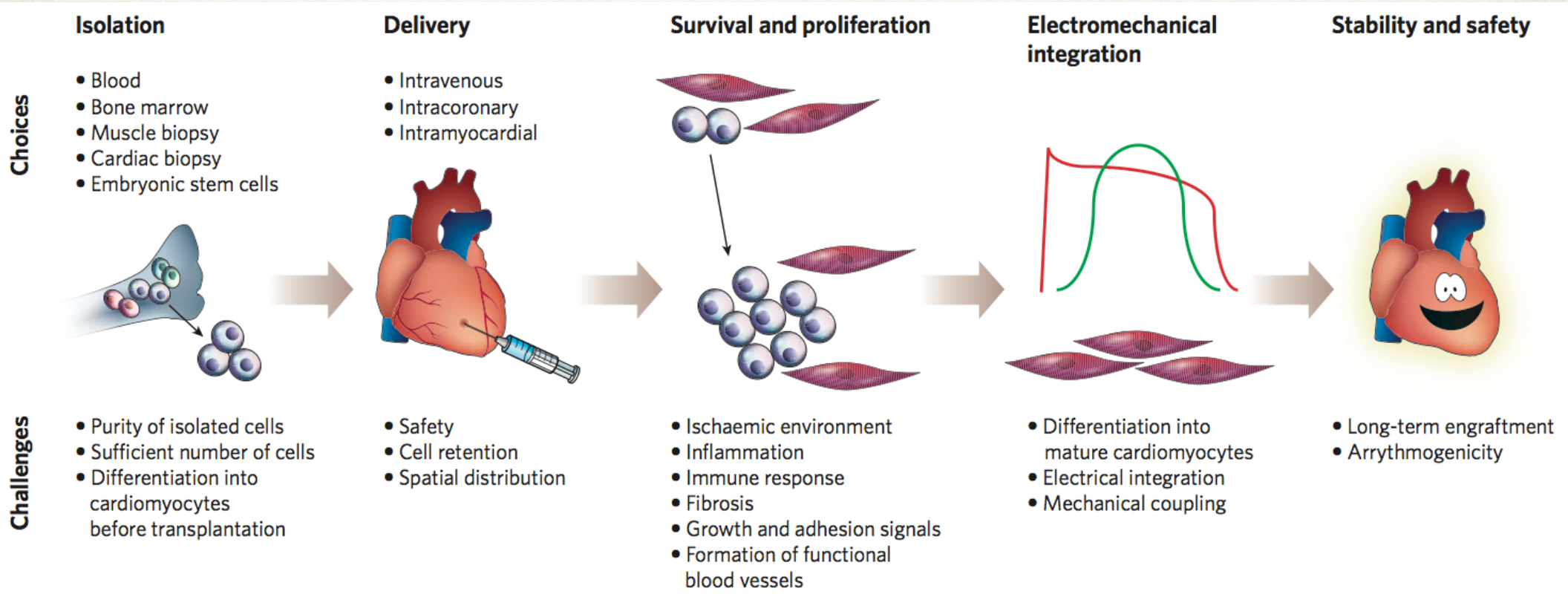
Routes of Delivery: endovascular

- Advantages:
  - less invasive than surgery
  - more localized delivery
- Disadvantages:
  - dissemination of the delivered cells
  - blocked arteries
  - visualization (?)
  - advanced procedure



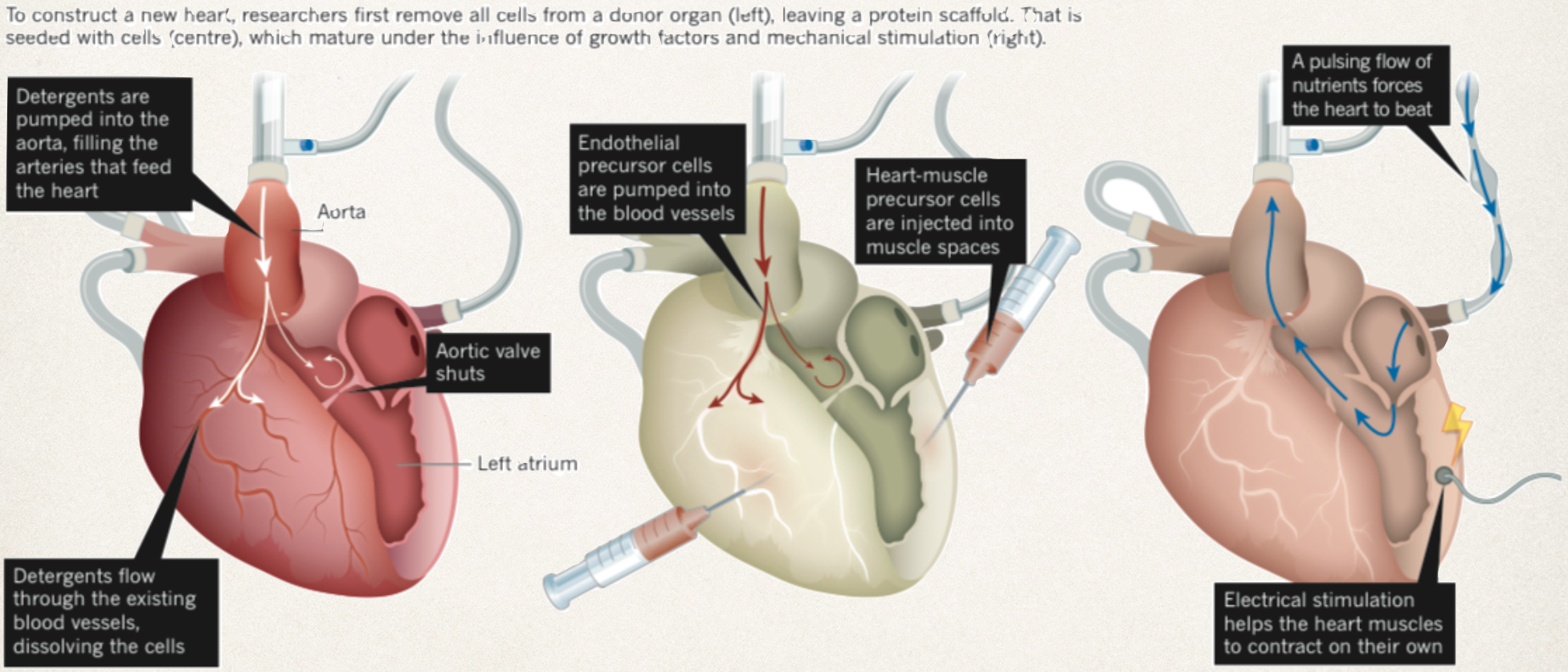
Ptaszek et al (2012). Image from http://drsvenkatesan.files.wordpress.com/2008/10/cag2.jpg?w=500

Cell Therapy: Challenges



Segers et al (2008)

Cardiac Tissue Engineering: decellularized heart



Maher (2012)

Cardiac Tissue Engineering: decellularized heart

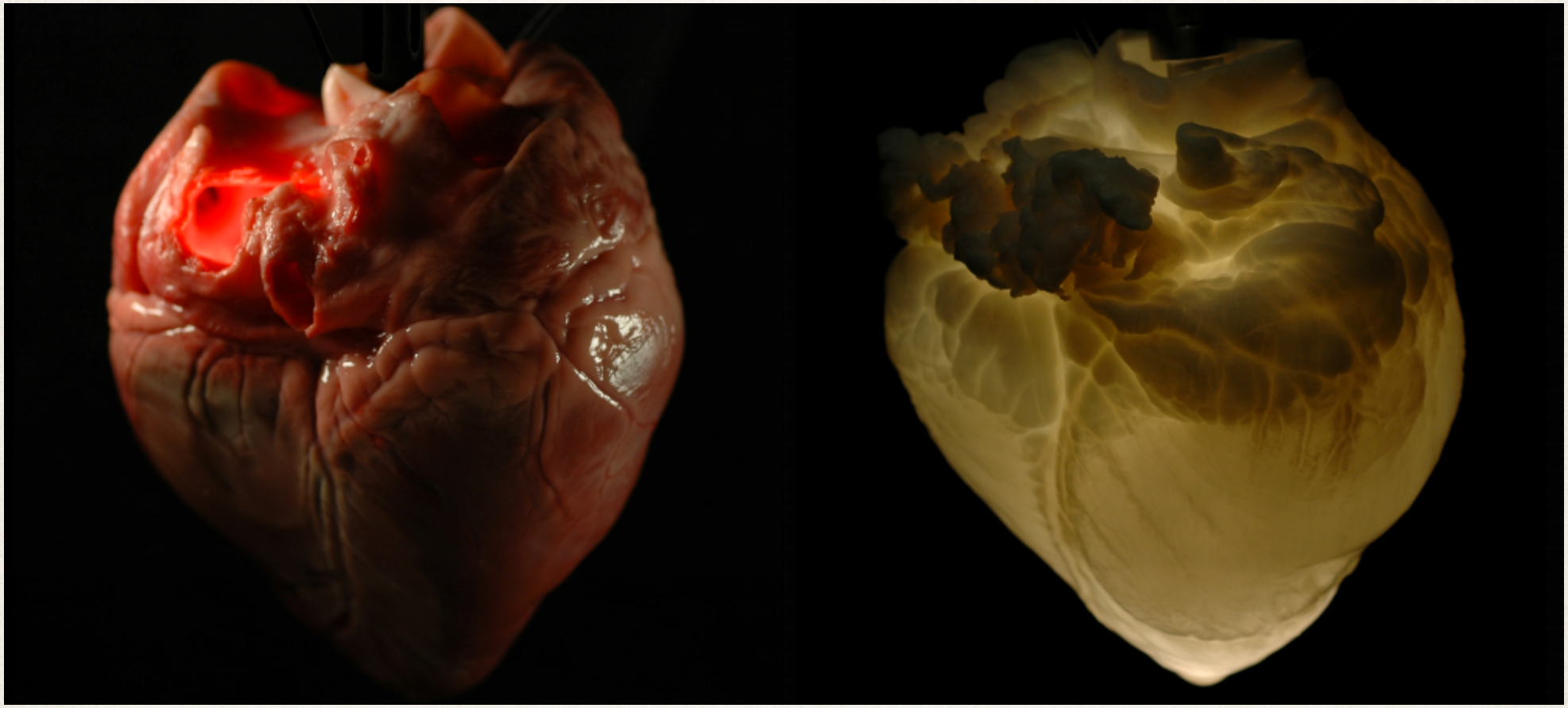
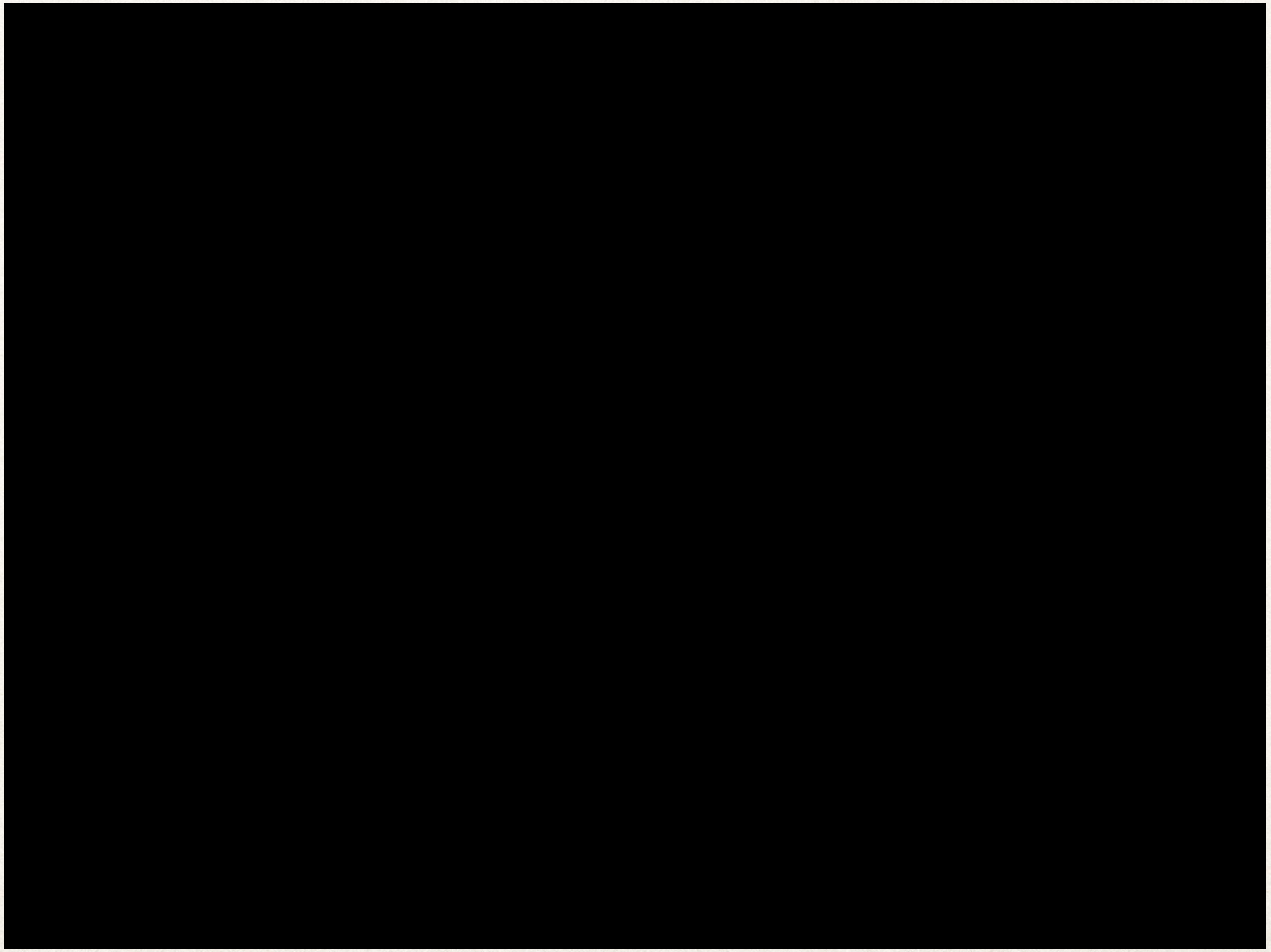


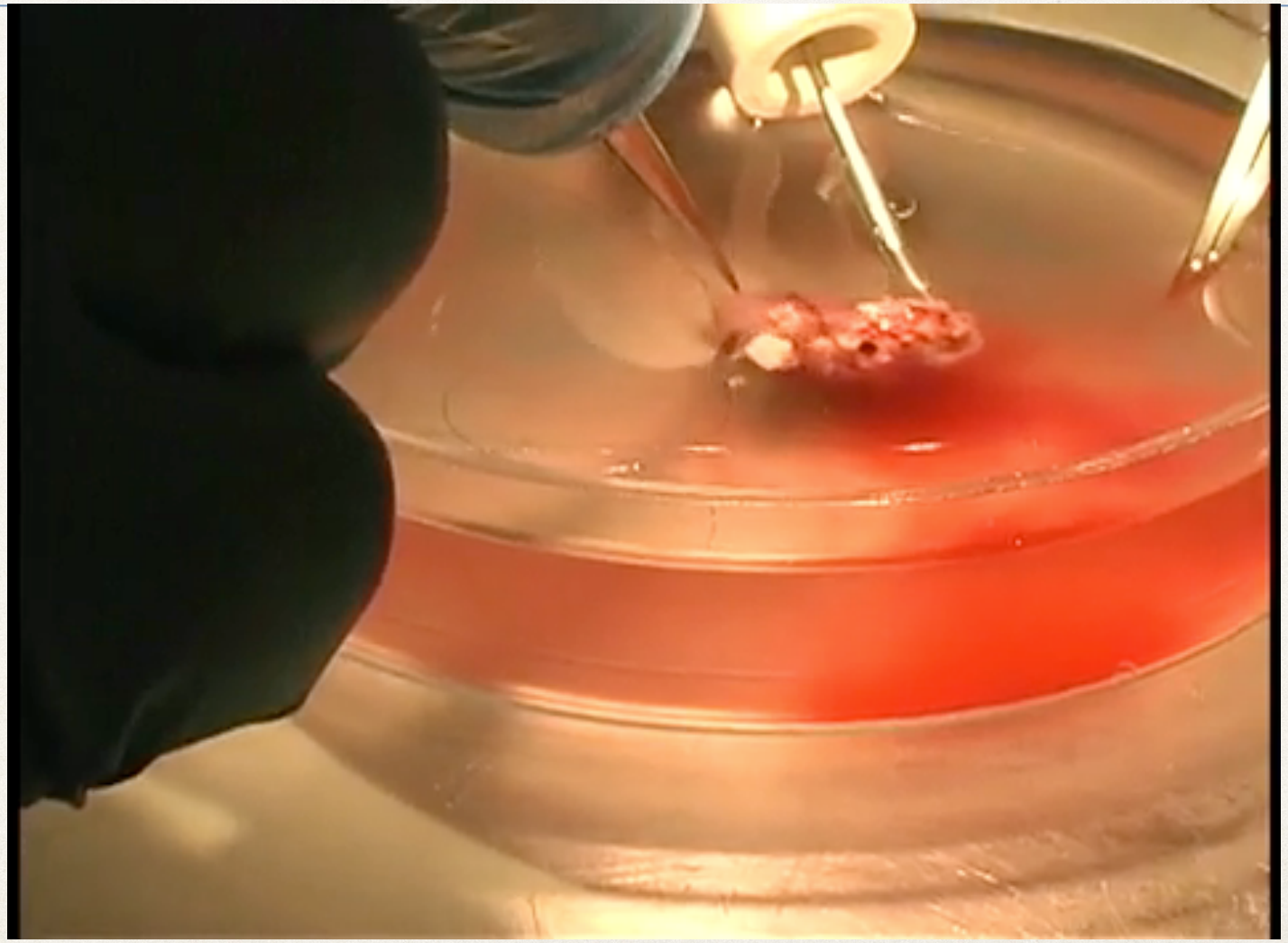
Image from Ott et al. (2008)

Cardiac Tissue Engineering: decellularized heart



Video from Ott et al. (2008)

Cardiac Tissue Engineering: decellularized heart



Video Available from http://www.youtube.com/watch?v=j9XzN0-TQZc

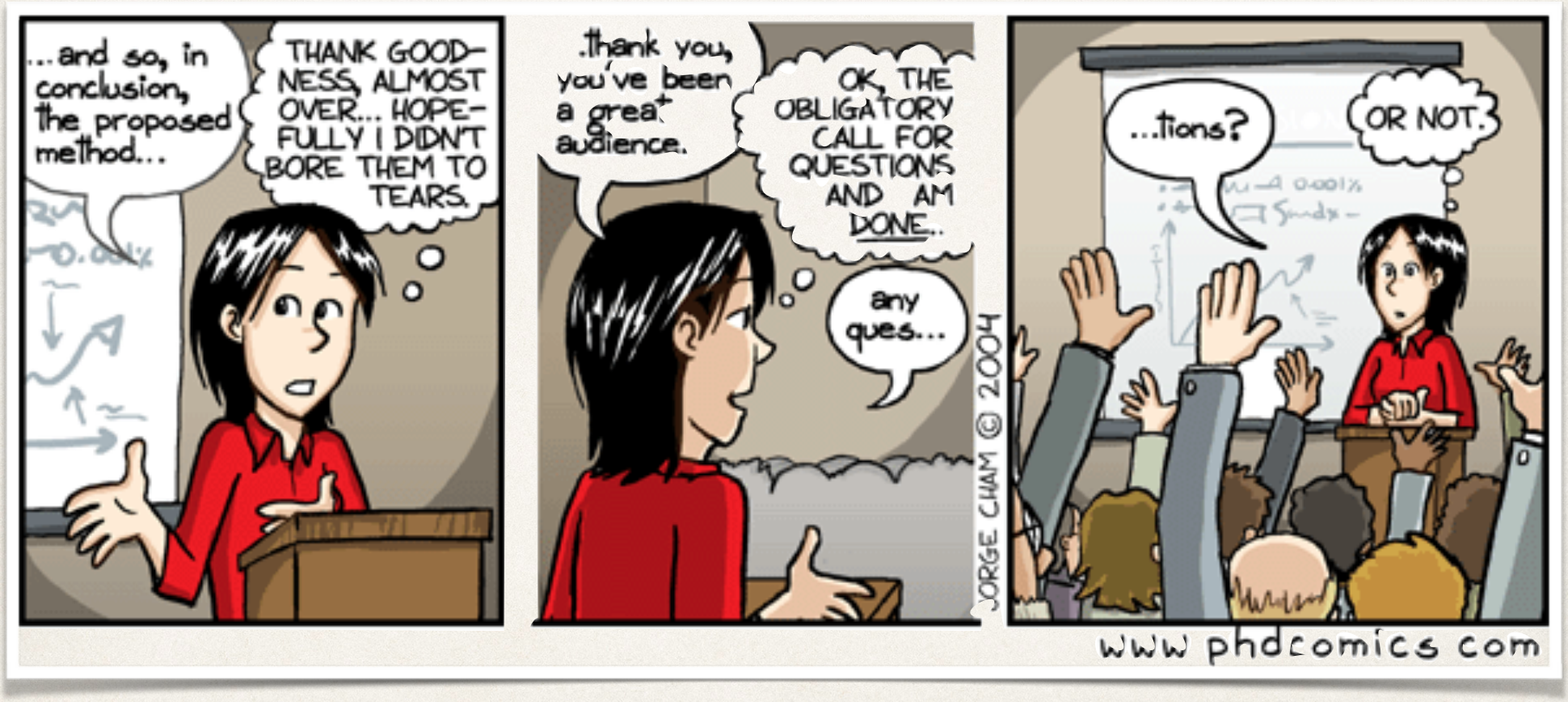
References

- World Health Organization (2004). "Annex Table 2: Deaths by cause, sex and mortality stratum in WHO regions, estimates for 2002". The world health report 2004 - changing history. Retrieved 2013-11-17.
- Statistics Canada (2012), CANSIM table 102-0561 and Catalogue no. 84-215-X. Last modified: 2012-07-25. Retrieved 2013-11-17
- Segers, V. F. M., & Lee, R. T. (2008). Stem-cell therapy for cardiac disease, 451(February). doi:10.1038/nature06800
- Ptaszek, L. M., Mansour, M., Ruskin, J. N., & Chien, K. R. (2012). Towards regenerative therapy for cardiac disease. Lancet, 379(9819), 933–42. doi:10.1016/S0140-6736(12)60075-0
- Laflamme, M. a, & Murry, C. E. (2005). Regenerating the heart. Nature biotechnology, 23(7), 845–56. doi:10.1038/nbt1117
- Taylor, D., Atkins, B., & Hungspreugs, P. (1998). Regenerating functional myocardium: improved performance after skeletal myoblast transplantation. Nature medicine. Retrieved from http://www.nature.com/nm/journal/v4/n8/abs/nm0898-929.html
- Menasché, P., Alfieri, O., Janssens, S., McKenna, W., Reichenspurner, H., Trinquart, L., … Hagège, A. a. (2008). The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. Circulation, 117(9), 1189–200. doi:10.1161/CIRCULATIONAHA.107.734103
- Deb, a. (2003). Bone Marrow-Derived Cardiomyocytes Are Present in Adult Human Heart: A Study of Gender-Mismatched Bone Marrow Transplantation Patients. Circulation, 107(9), 1247–1249. doi:10.1161/01.CIR.0000061910.39145.F0

References

- Quaini, F., & Urbanek, K. (2002). Chimerism of the Transplanted Heart. … England Journal of …, 346(1), 5–15. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMoa012081
- Barile, L., & Gherghiceanu, M. (2013). Human Cardiospheres as a Source of Multipotent Stem and Progenitor Cells. Stem cells international, 2013, Article ID 916837. Retrieved from http://www.hindawi.com/journals/sci/2013/916837/abs/
- Makkar, R. R., Smith, R. R., Cheng, K., Malliaras, K., Thomson, L. E. J., Berman, D., … Marbán, E. (2012). Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet, 379(9819), 895–904. doi:10.1016/S0140-6736(12)60195-0
- Maher, B. Y. B. (2013). HOW TO BUILD A HEART. Nature, 499, 20–22.
- Boström, P., & Frisén, J. (2013). New Cells in Old Hearts. New England Journal of Medicine, 368(14), 1358–1360. Retrieved from http://www.nejm.org/doi/full/10.1056/NEJMcibr1300157
- Klumpp Dorothee, Horch Raymund E. and Beier Justus P. (2011). Tissue Engineering of Skeletal Muscle, Tissue Engineering for Tissue and Organ Regeneration, Prof. Daniel Eberli (Ed.), ISBN: 978-953-307-688-1, InTech, DOI: 10.5772/21197. Available from: http://www.intechopen.com/books/tissue-engineering-for-tissue-and-organ-regeneration/tissue-engineering-of-skeletal-muscle
- Ott, H. C., Matthiesen, T. S., Goh, S.-K., Black, L. D., Kren, S. M., Netoff, T. I., & Taylor, D. a. (2008). Perfusion-decellularized matrix: using nature's platform to engineer a bioartificial heart. Nature medicine, 14(2), 213–21. doi:10.1038/nm1684
- Kim, Kwang-Soo. "Induced pluripotent stem (iPS) cells and their future in psychiatry." Neuropsychopharmacology 35.1 (2010): 346-348.

Questions?


...and so, in conclusion, the proposed method...
THANK GOODNESS, ALMOST OVER... HOPEFULLY I DIDN'T BORE THEM TO TEARS.
thank you, you've been a great audience.
OK, THE OBLIGATORY CALL FOR QUESTIONS AND AM DONE..
any ques...
...tions?
OR NOT.
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