Human embryonic-stem-cell-derived cardiomyocytes regenerate non-human primate hearts

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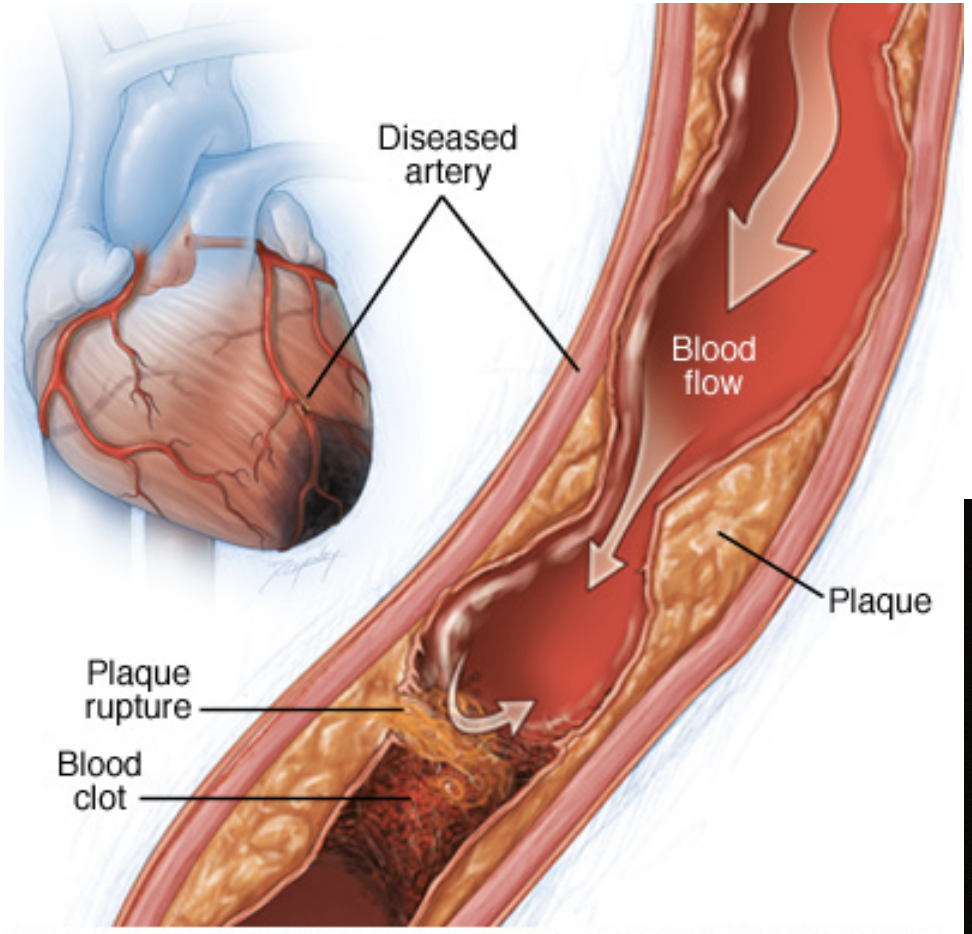
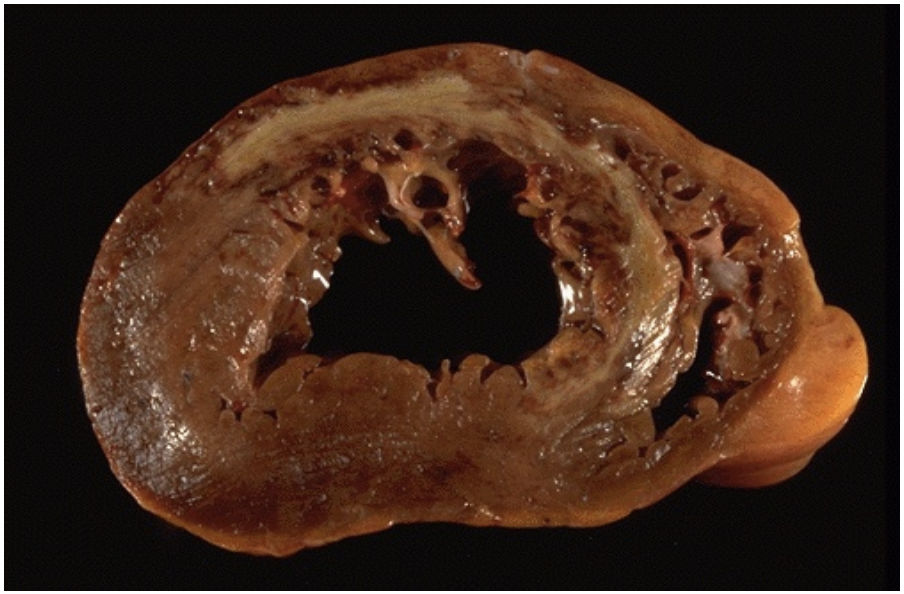
Katrina A. Diaz
Burke Group Literature Seminar
06/21/14

Myocardial ischemia and infarction



- Leading cause of death in first world nations
- 450,000 in USA alone per year; 95% survival



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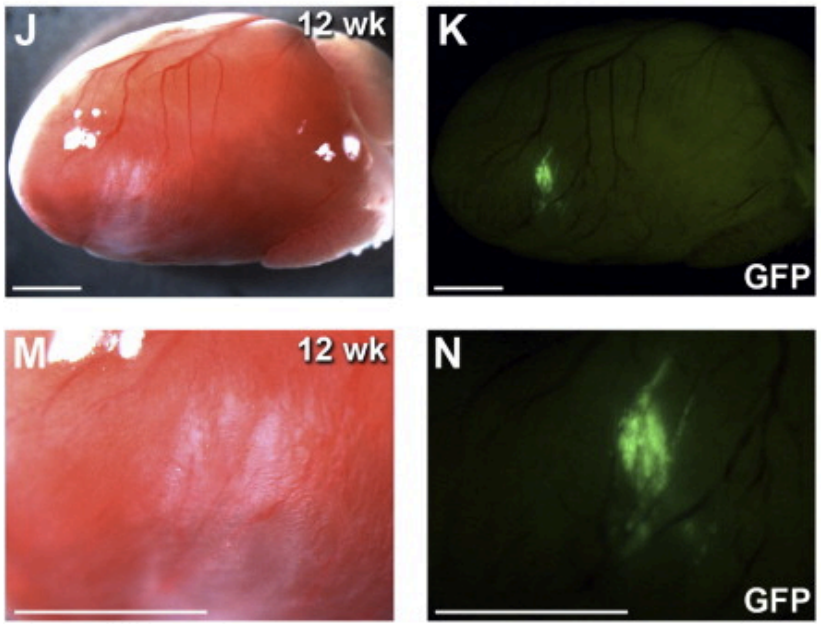
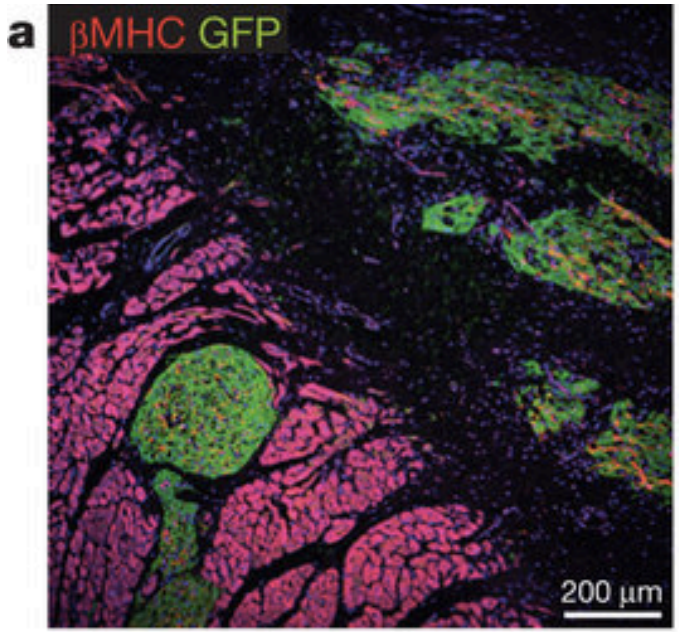
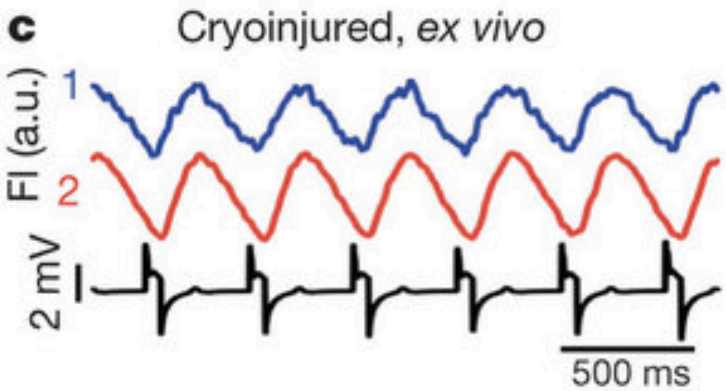
Previous work in heart regeneration



- Rats and mice have too fast of heart rate for human cells to couple to
- Hides arrhythmias

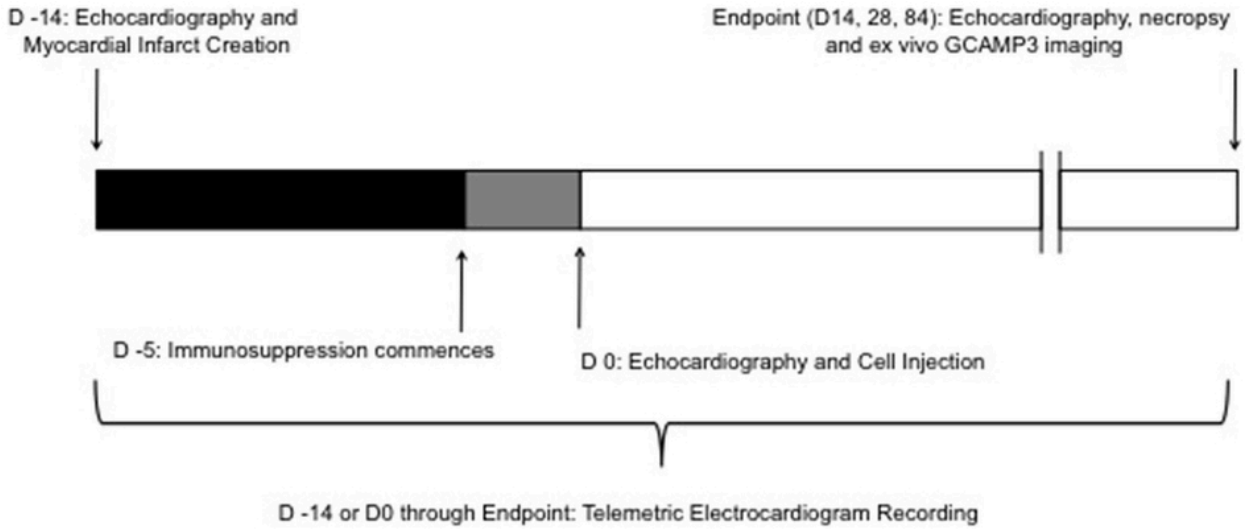


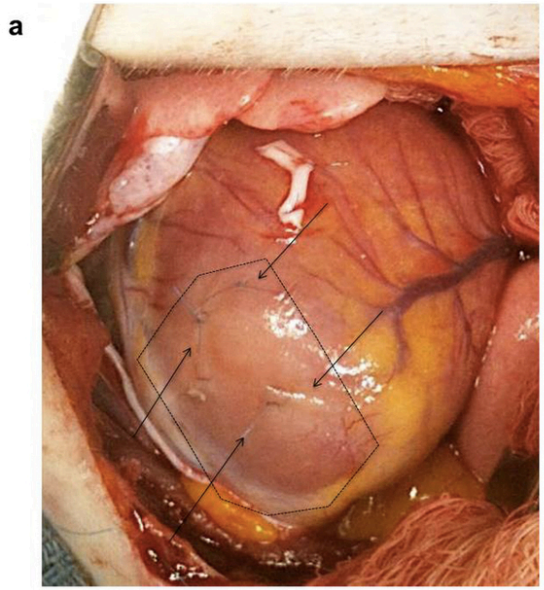


- Guinea pig better synchronicity with human cells
- Cardiac cryoinjury, not ischemia

van Laake et al. (2007). Stem Cell Research, 1(1), 9-24.
Shiba, Y. et al (2012). Nature, 489(7415), 322-325.

Experimental design and hESC-CM injection to infarct region





- 15 aliquots injected in puncture sites
- Retention increased by mattress suture

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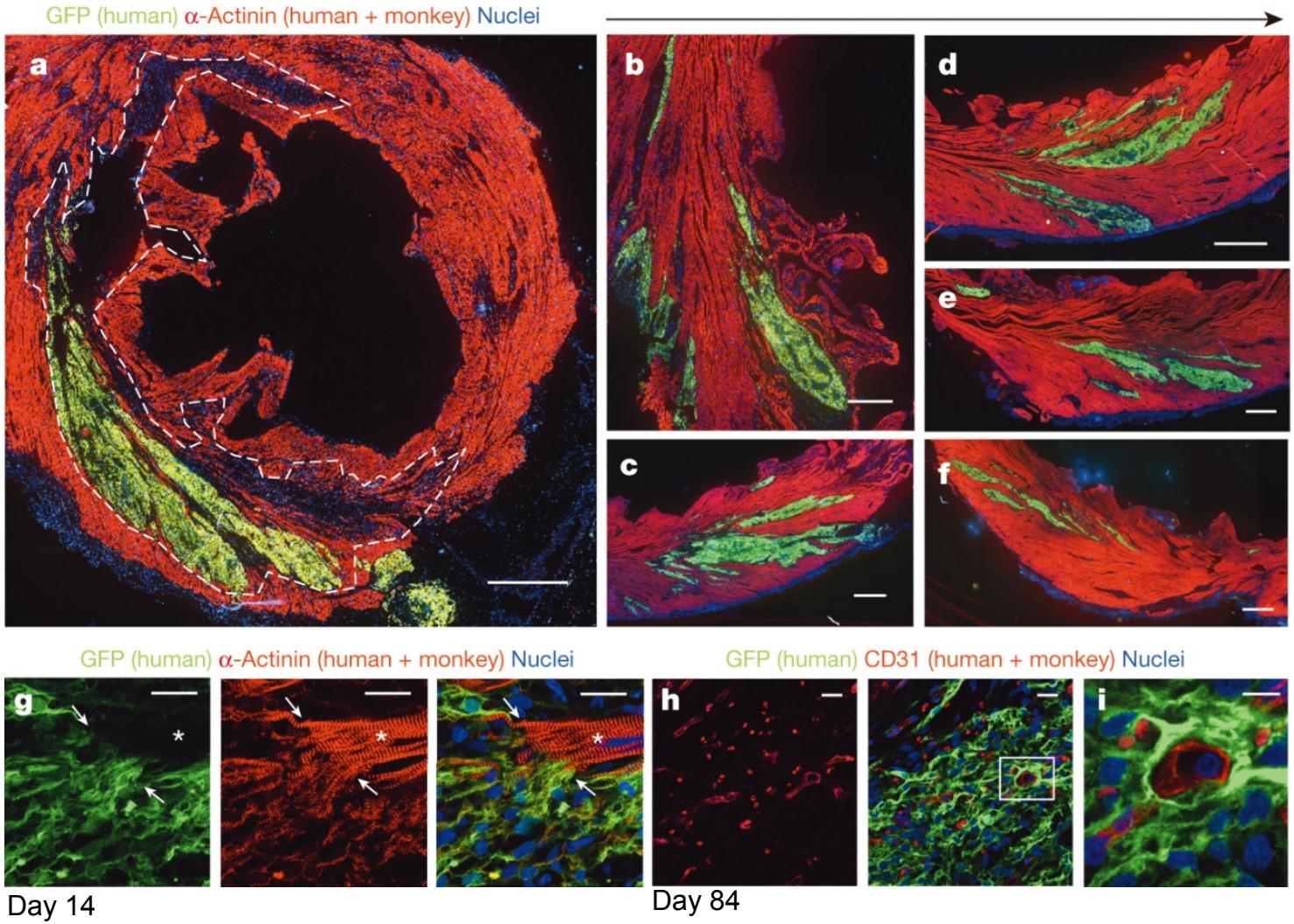
Remuscularization of the infarcted macaque heart with human cardiomyocytes



- 40% restoration of infarct volume (<10% of left ventricle wall)
- >98% of graft expressed sarcomeric protein α-actinin
- Anti-CD41 immunostaining (endothelial) revealed perfusion by host vessel

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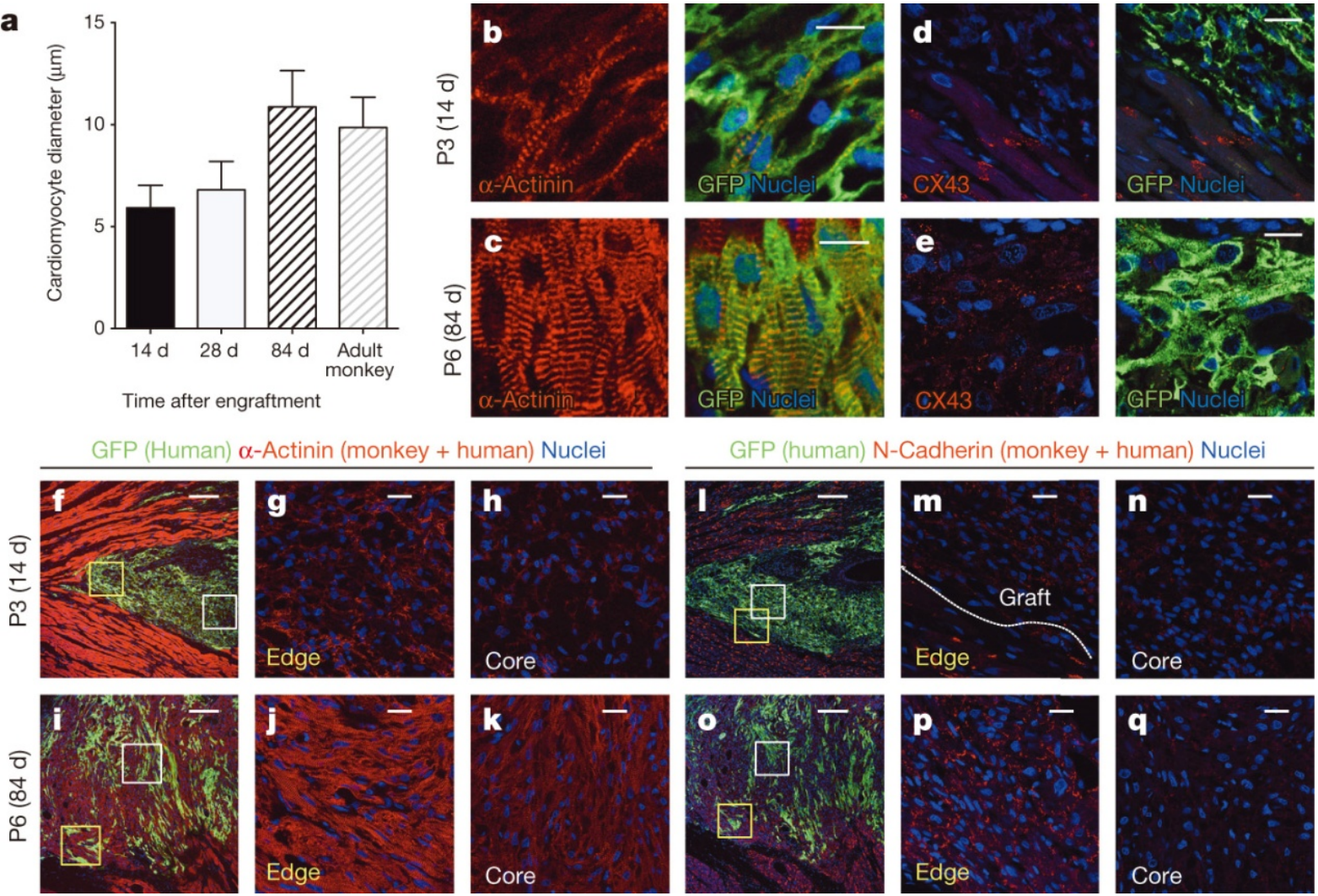
Human cardiomyocyte grafts mature with time from engraftment



- Expression of cadherin, connexin, and intercalated disks
- No graft rejection (minimal lymphocytes present)

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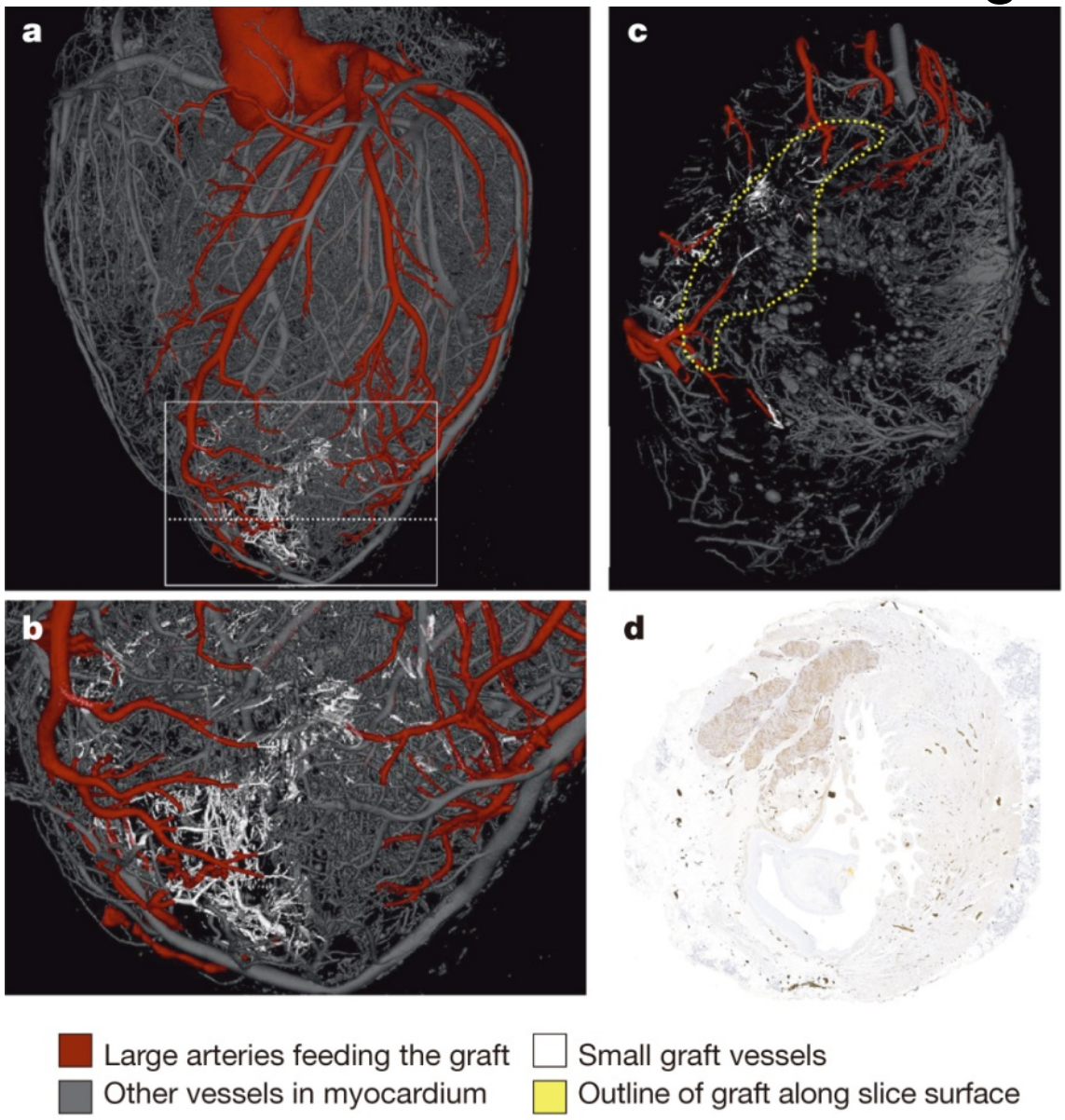
Blood vessels extend from the host coronary network into the graft



- Microcomputed tomography using aligned histology sections and Microfil perfusion

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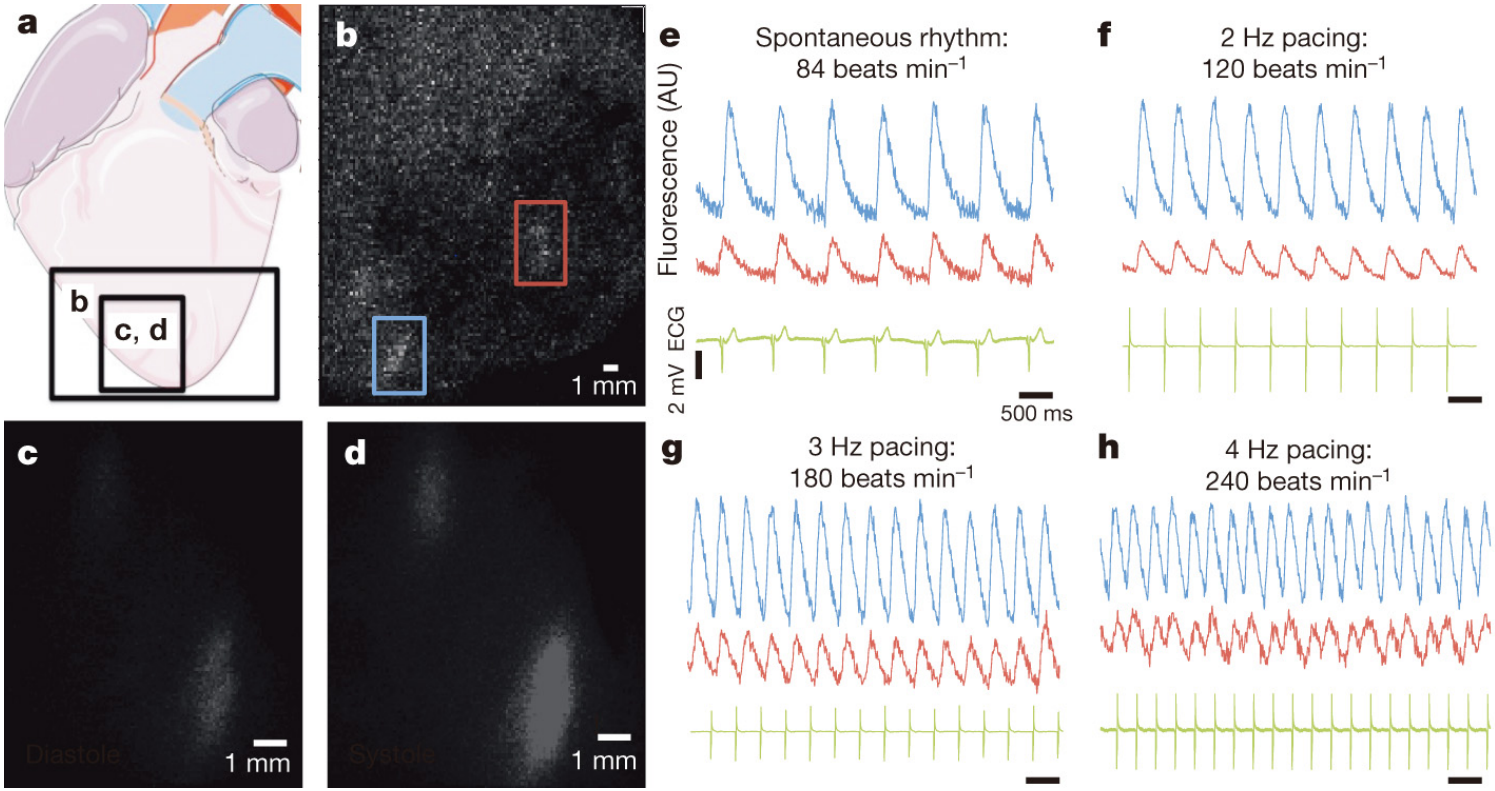
Human cardiomyocytes are electrically coupled 1:1 to the infarcted host macaque heart after transplantation



- Epicardial fluorescent transients synchronous with host ECG QRS up to 240 bpm

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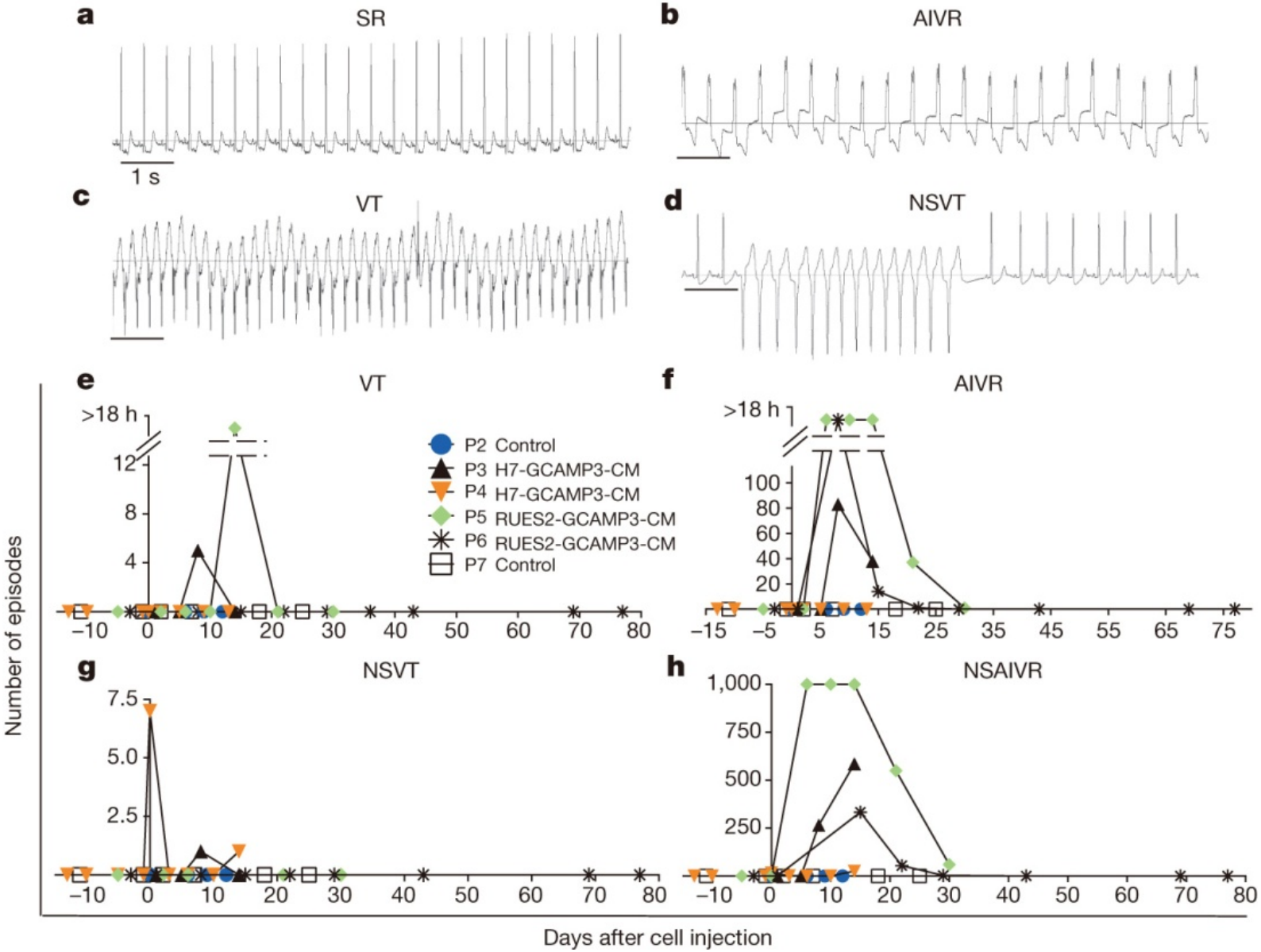
Ventricular arrhythmias after hESC-CM transplantation



- Premature contraction and tachycardia
- Animals conscious and not in distress

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Conclusions and Future Directions

- Extensive remuscularization of the infarcts in all animals, averaging 40% of infarct mass
- All human cardiomyocytes showed complete electrical coupling to the primate heart and responded normally to pacing up to 240 bpm
- Mechanisms and root cause for arrhythmias (size?)
- Greater sample sizes, bigger infarcts, not as clinically relevant
- Despite limitations, these results are very promising for the development of human cardiomyocyte transplantation as a clinical therapy for heart failure