Reprogramming Approaches to Cardiovascular Disease

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&

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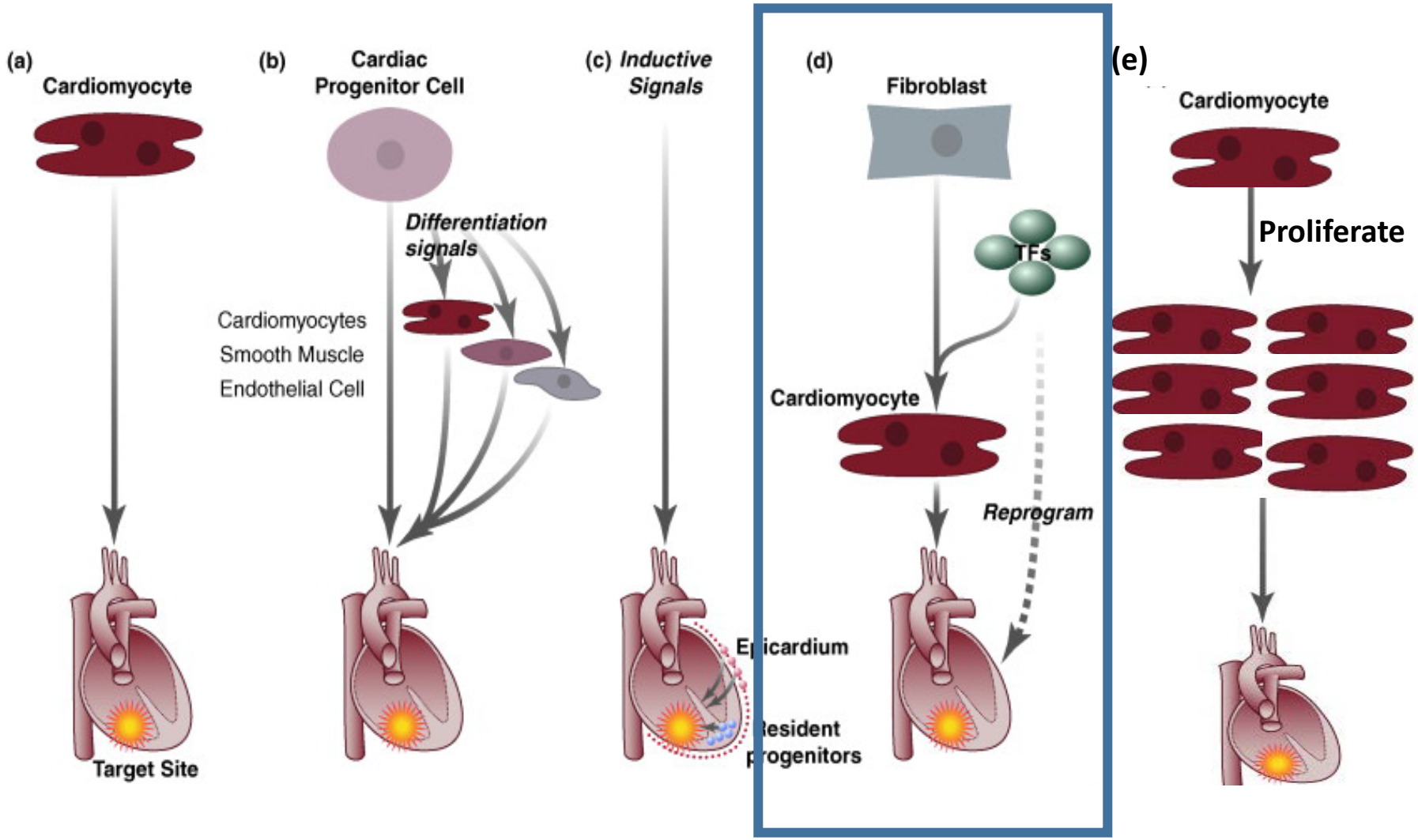
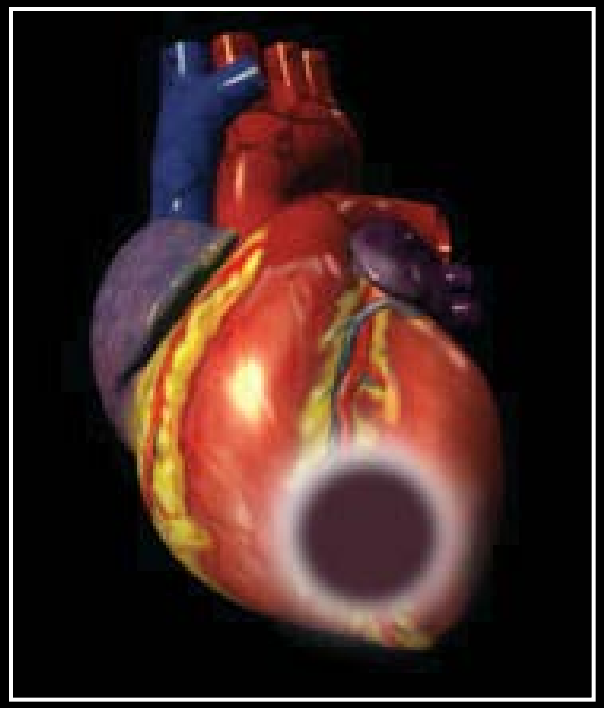
Cell Replacement Strategies to Treat Heart Failure



Modified from Alexander and Bruneau Trends Mol Med. 2010 Sep;16(9):426-34.

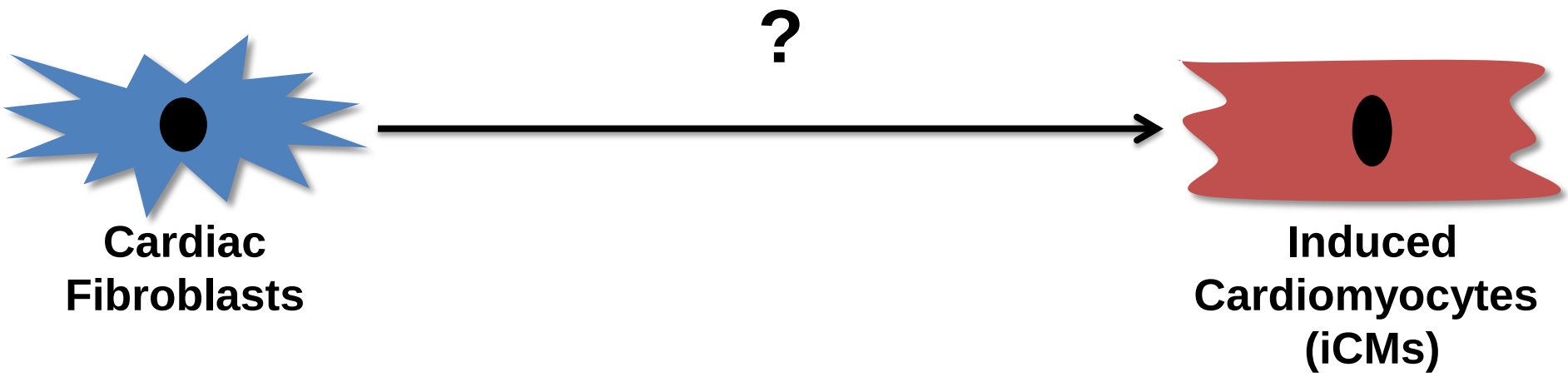
Cardiac Fibroblasts Are Abundant and Induce Scar and Fibrosis



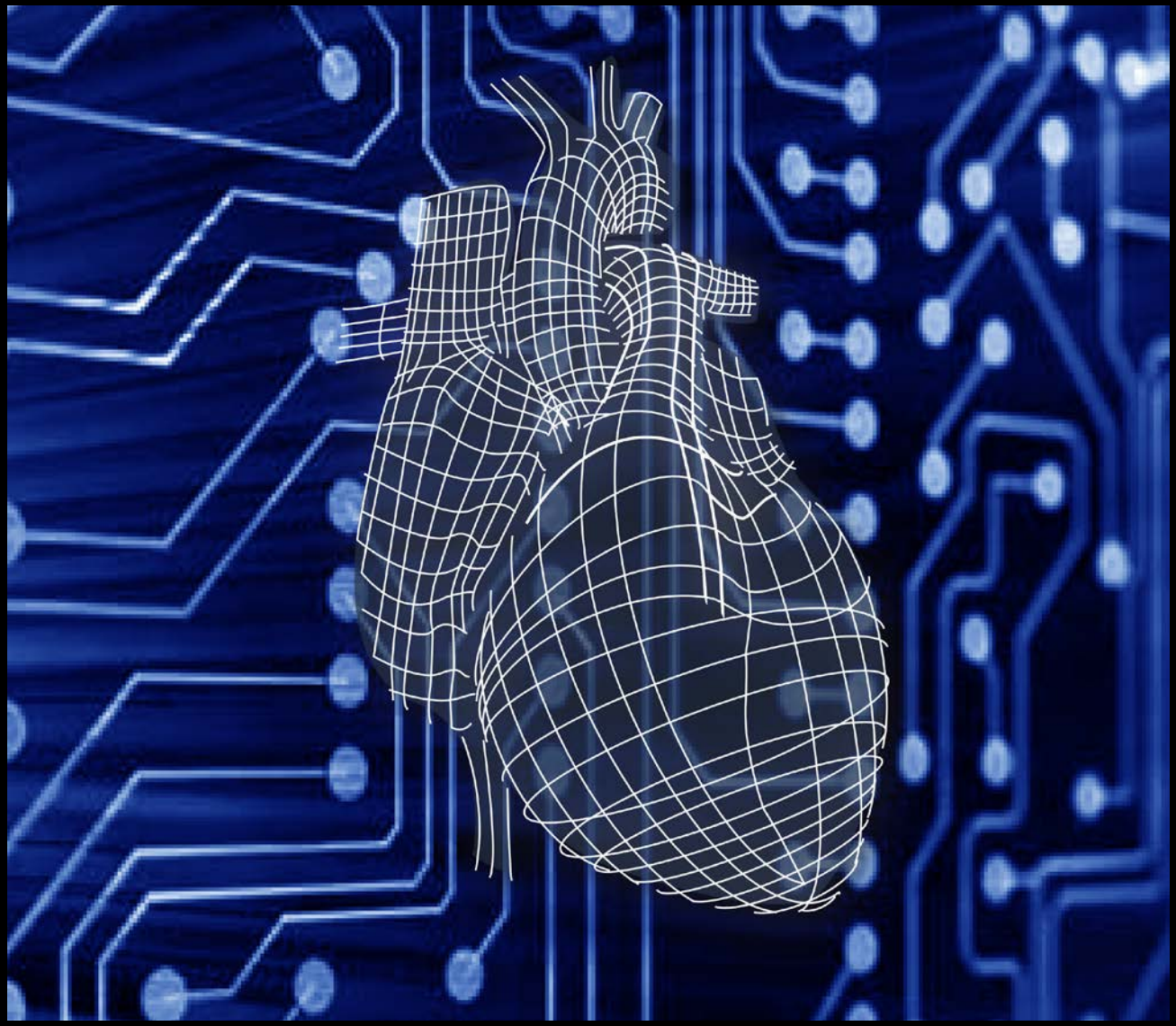
Myocardial Infarction

Fibrosis

Direct Cardiac Reprogramming



Gene Networks That Dictate Fate and State



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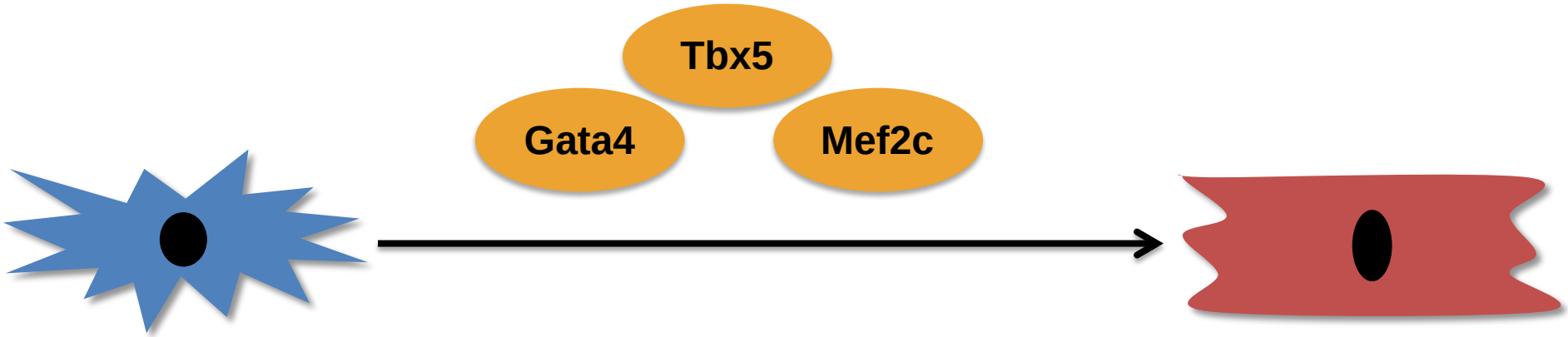
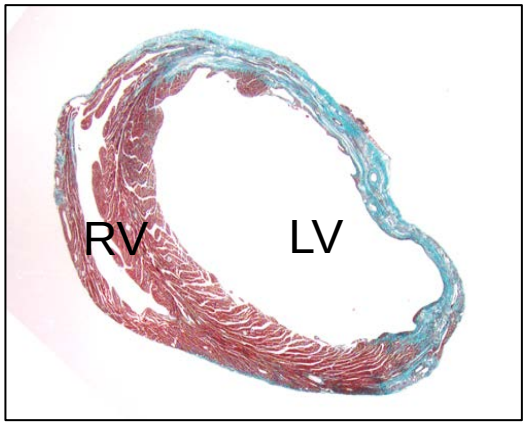
Direct Cardiac Reprogramming



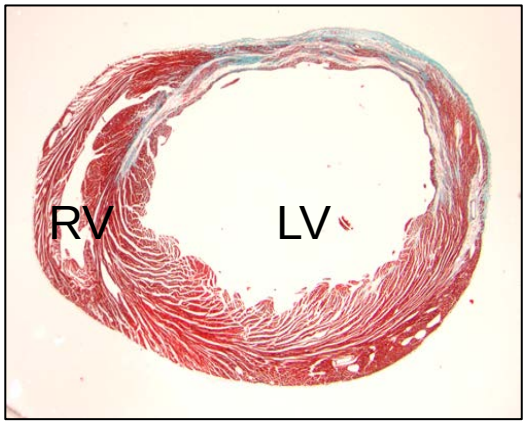
Ieda et al., *Cell*, 2010
Qian et al., *Nature*, 2012
Qian et al., *Nat Protocols*, 2013

In Vivo Cardiac Reprogramming

- Cells electrically couple
- Electrically similar to adult ventricular CMs
- Improved cardiac output by MRI

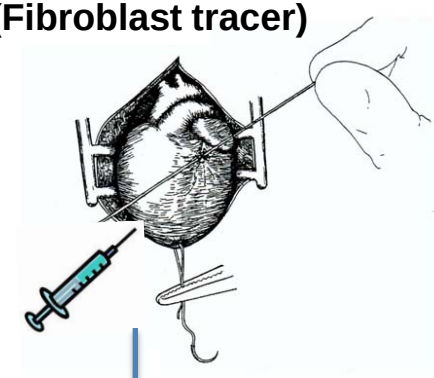


dsRed



Gata4/Mef2c/Tbx5

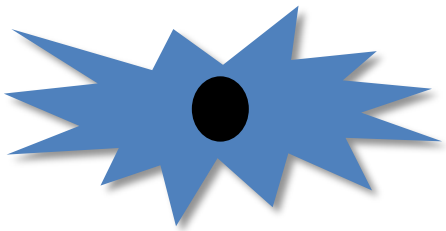
Periostin-Cre-YFP
(Fibroblast tracer)



12 weeks

Qian et al., *Nature*, 2012

Small Molecule Screening to Enhance Gene-Based Direct Cardiac Reprogramming



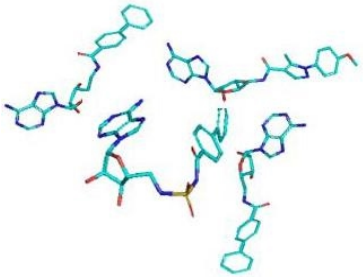
Fibroblasts

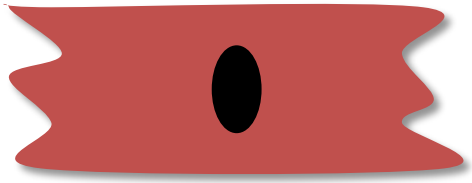
TBX5

GATA4

MEF2C

Small Molecules
(~5500)

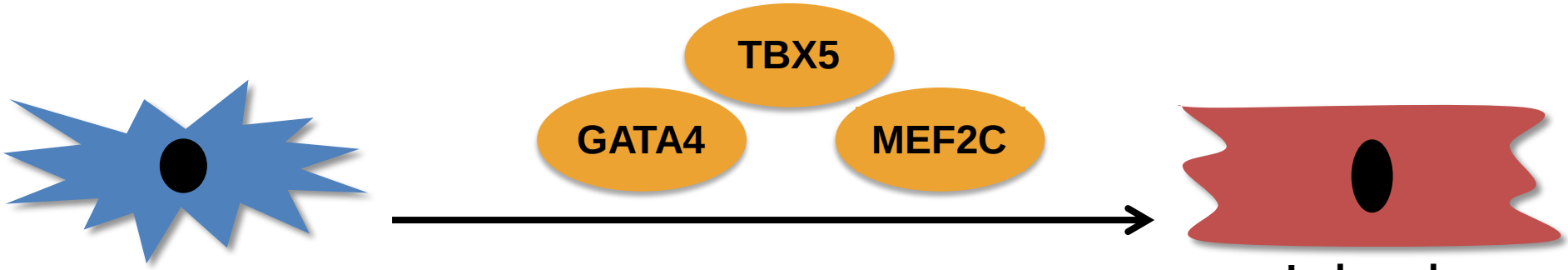




Induced
Cardiomyocytes

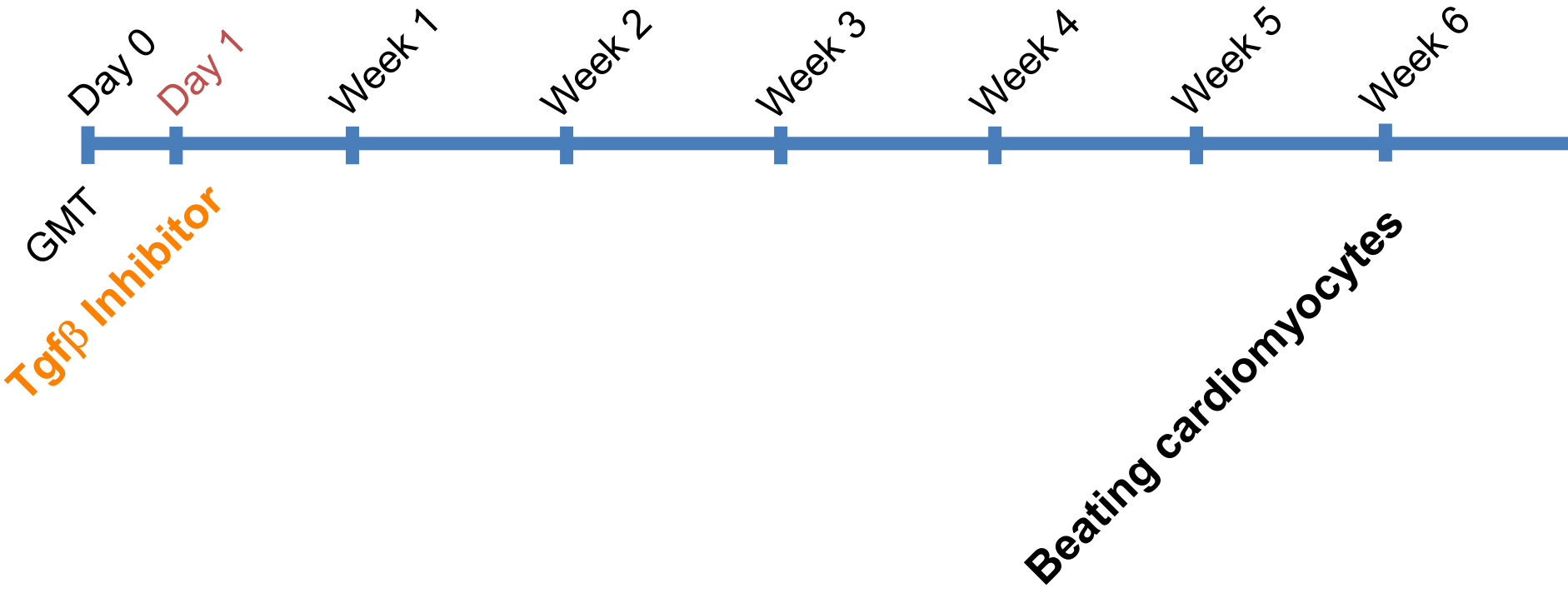
Tamer Mohamed

Wnt and Tgfβ Inhibitors Enhance Efficiency, Quality and Speed of Direct Cardiac Reprogramming

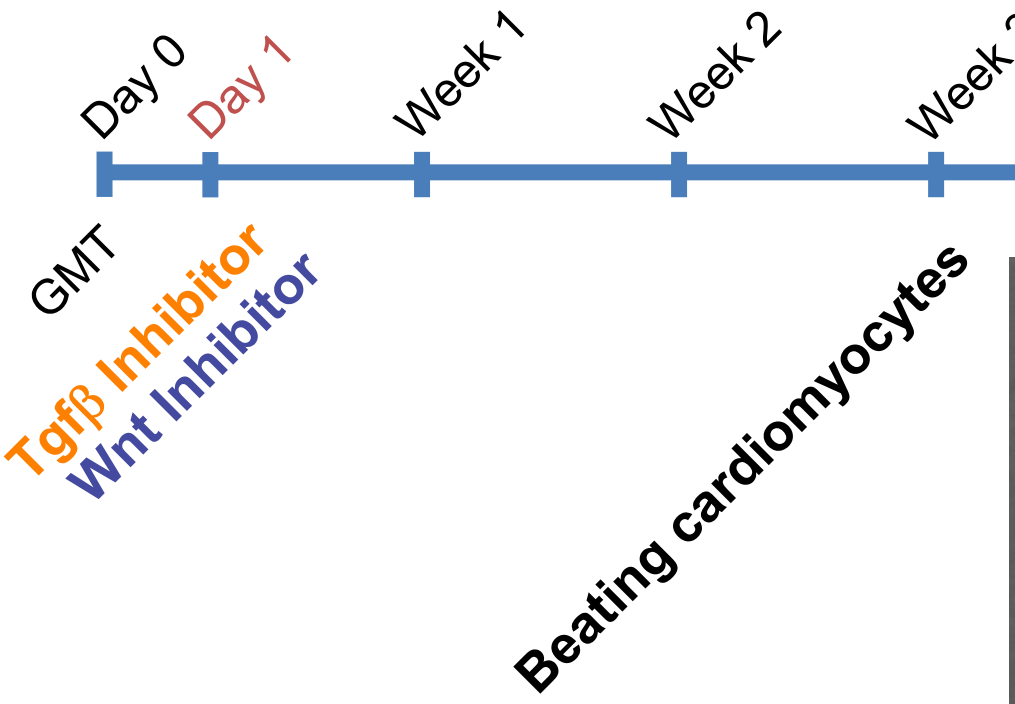


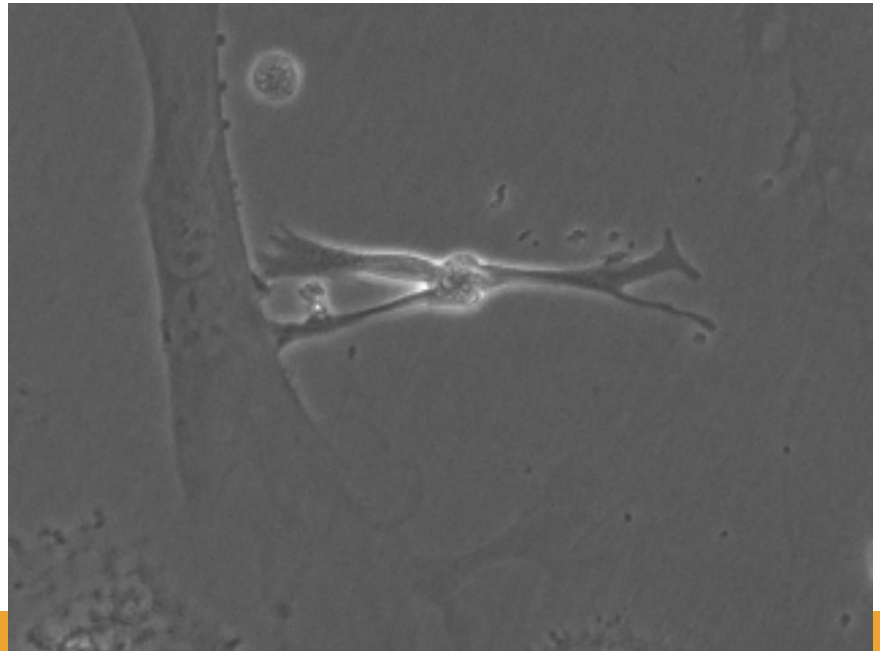
Tamer Mohamed

GMT + Chemicals Induce Beating Cardiomyocytes By 1 Week



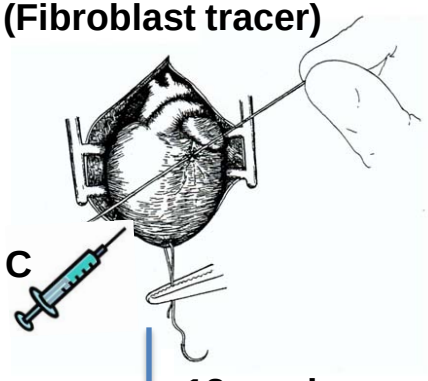
GMT + Chemicals Induce Beating Cardiomyocytes By 1 Week



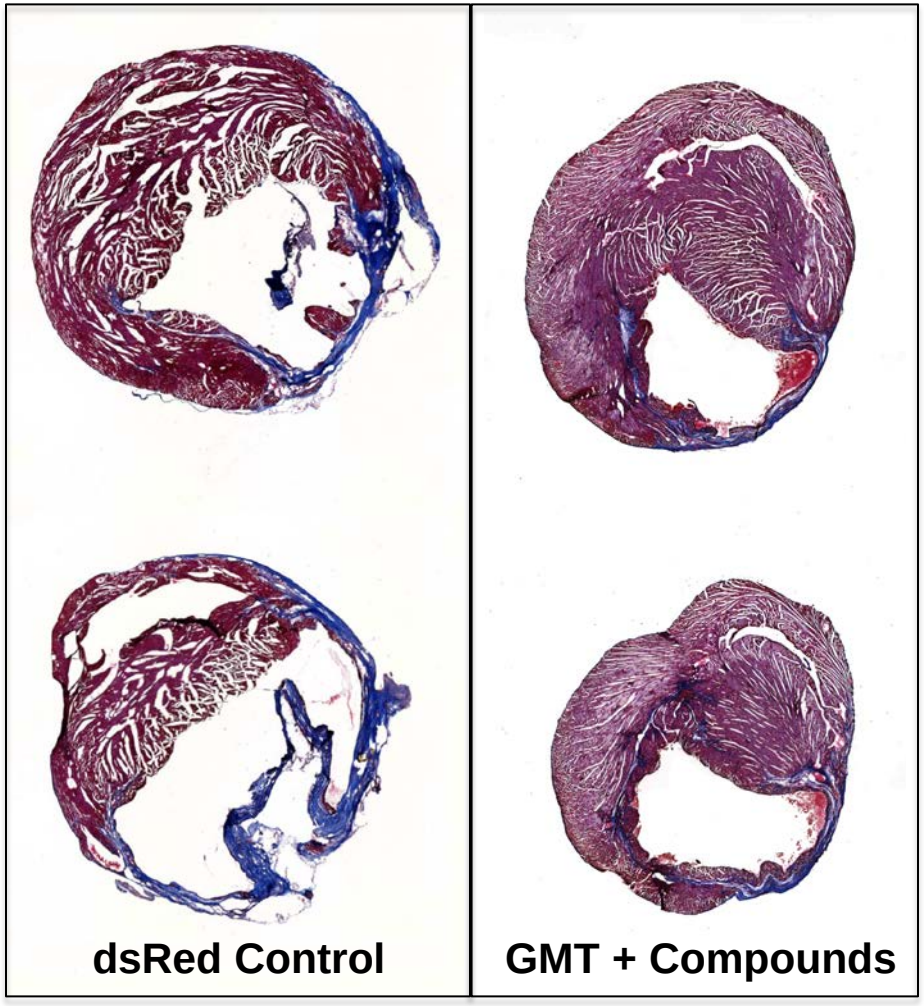


GMT + Chemicals Promotes Greater Cardiac Reprogramming *In Vivo*

Periostin-Cre-YFP
(Fibroblast tracer)



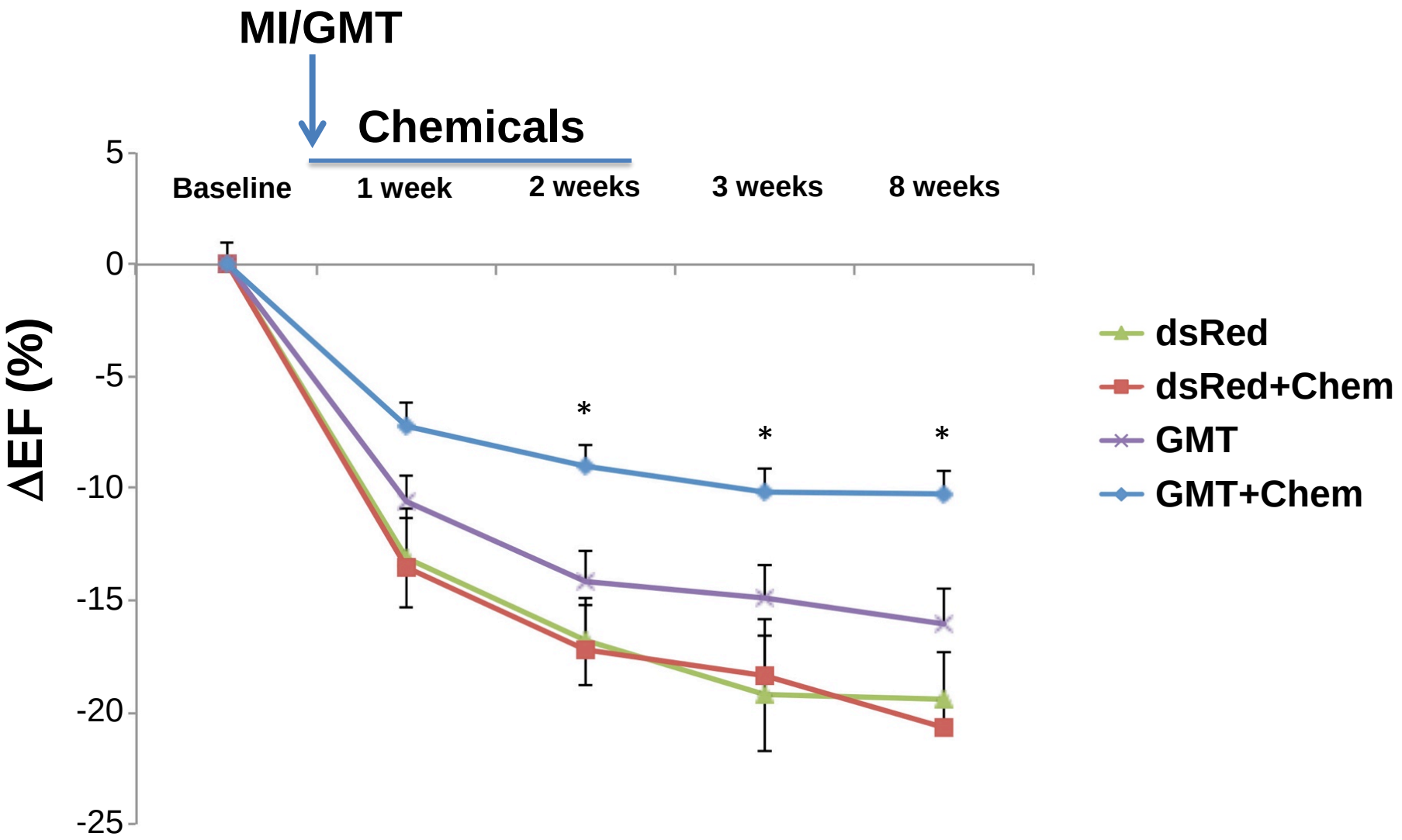
12 weeks



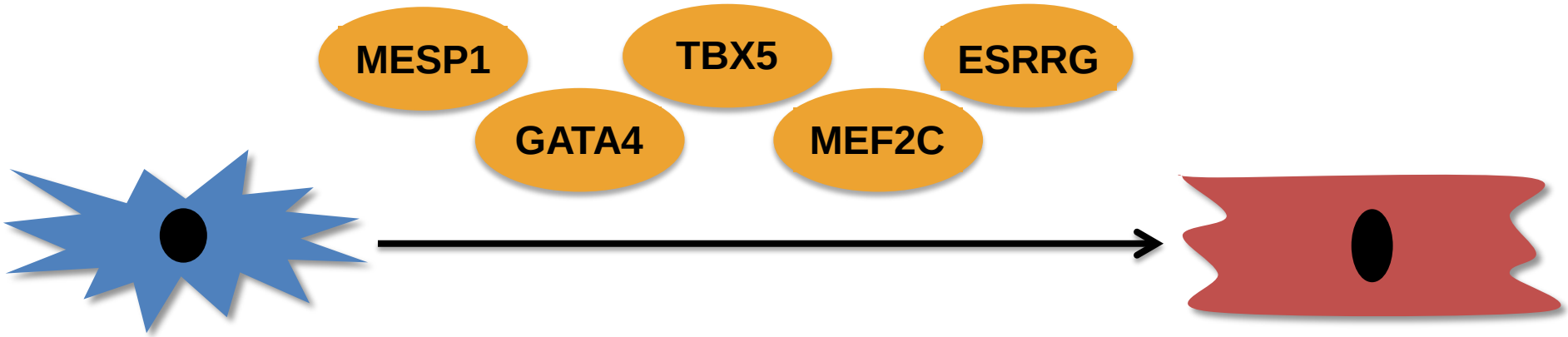
Top

Bottom

GMT + Chemicals Promotes Greater Improvement in Cardiac Function



Human Cardiac Fibroblast Reprogramming Requires Additional Factors



Human Cardiac Fibroblasts

Human Induced Cardiomyocytes (iCMs)

Fu et al., *Stem Cell Reports*, 2013

Pig Experimental Timeline

Palmer Yu

Day 0: Infarct Creation

↓

Day 3: MRI Measurement

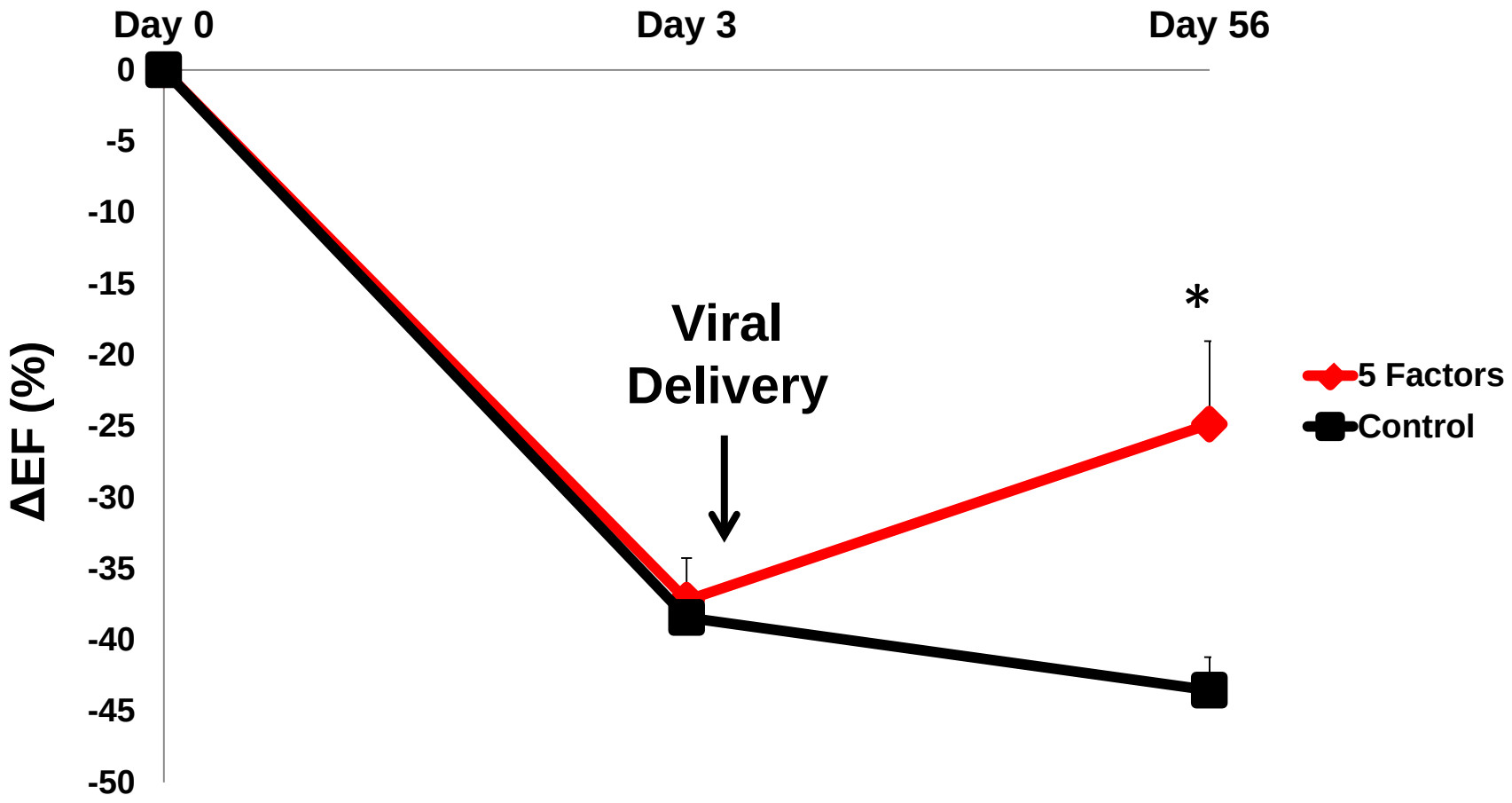
↓

Day 5: Retrovirus Delivery (5F)

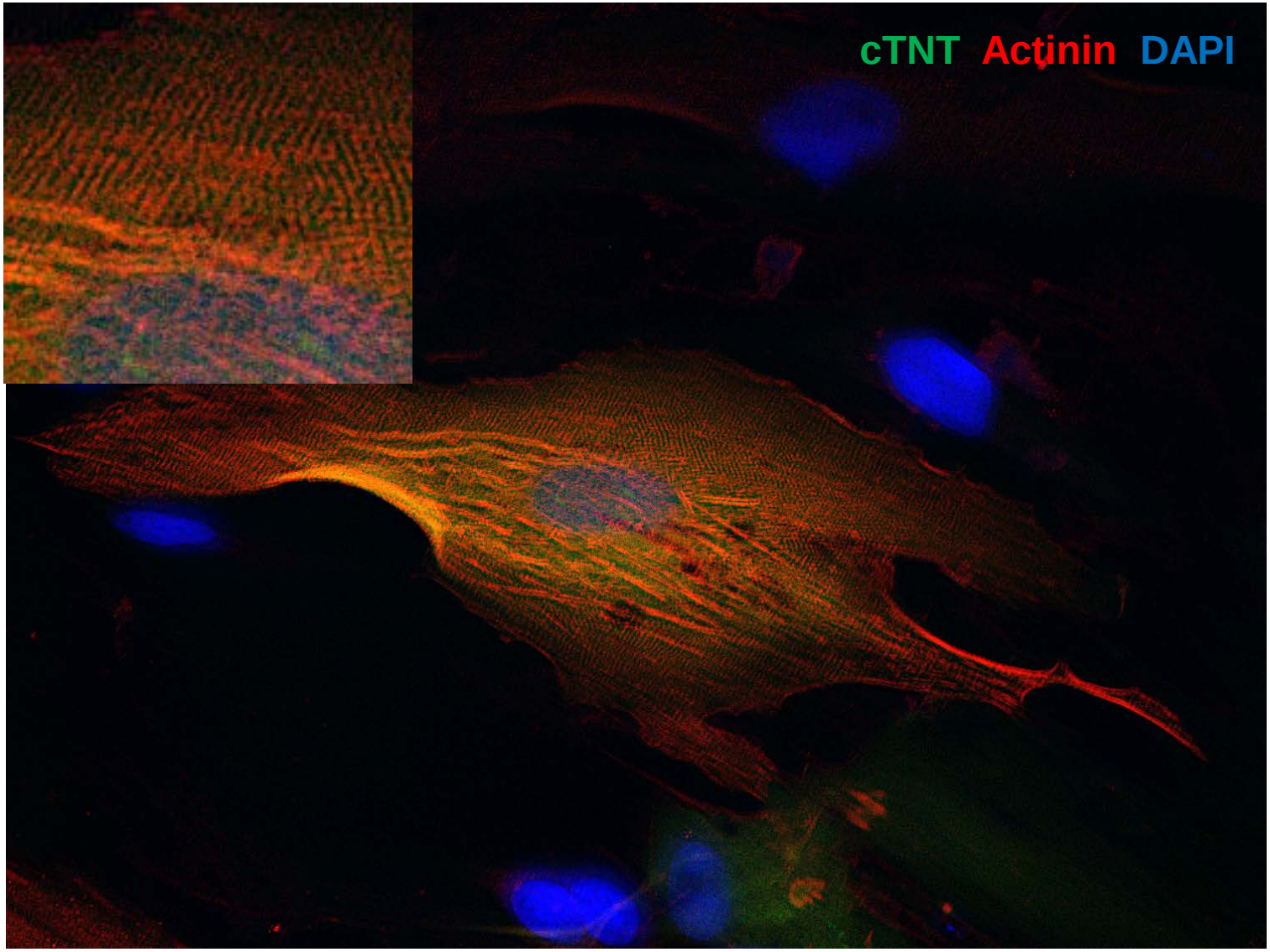
↓

Day 56: MRI, Histology

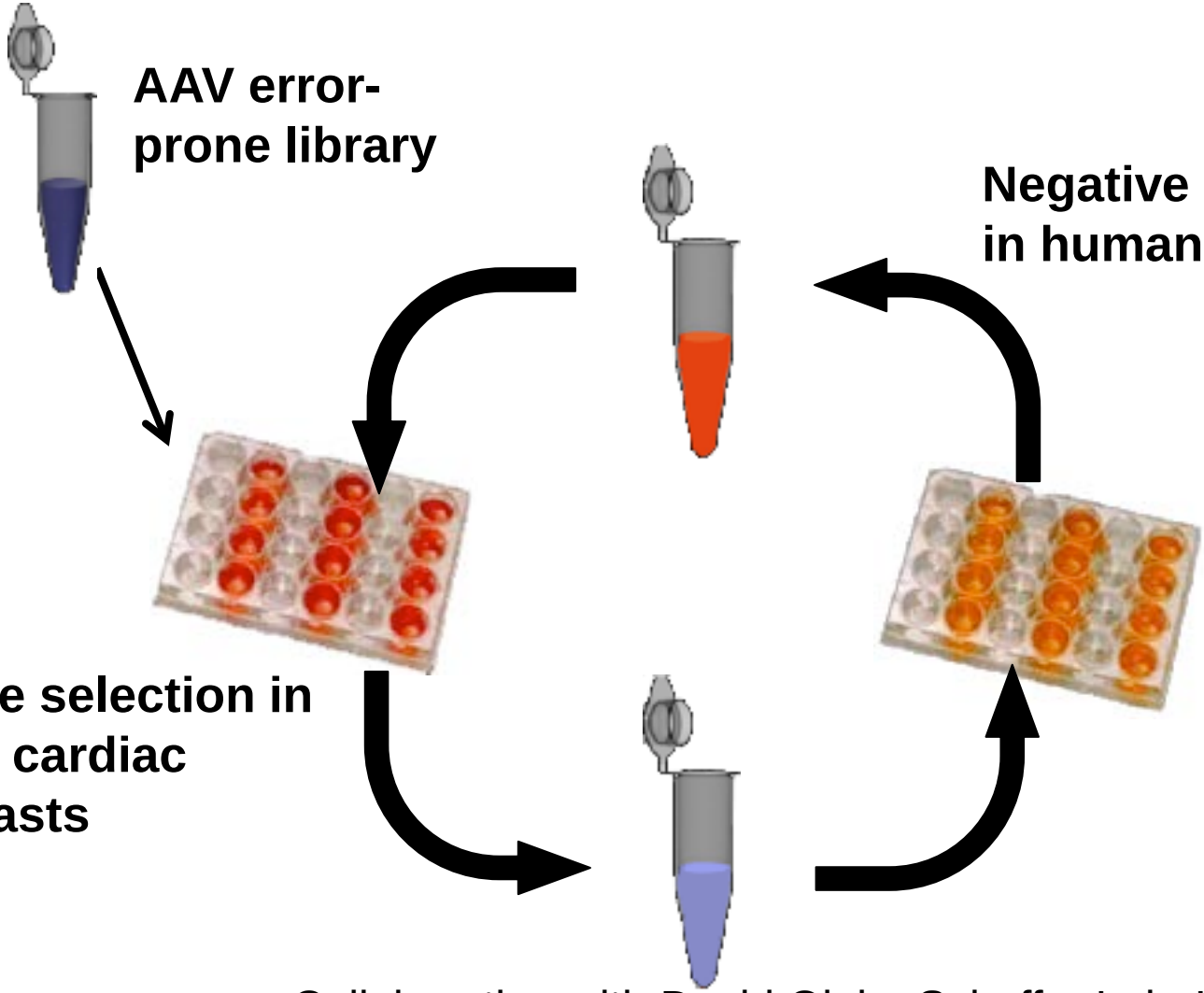
Porcine Cardiac Reprogramming: Improved Cardiac Function Assessed by MRI



Sarcomere Formation With MEF2C/TBX5/Myocardin + Inhibitors Within 3 Weeks in Human Cardiac Fibroblasts

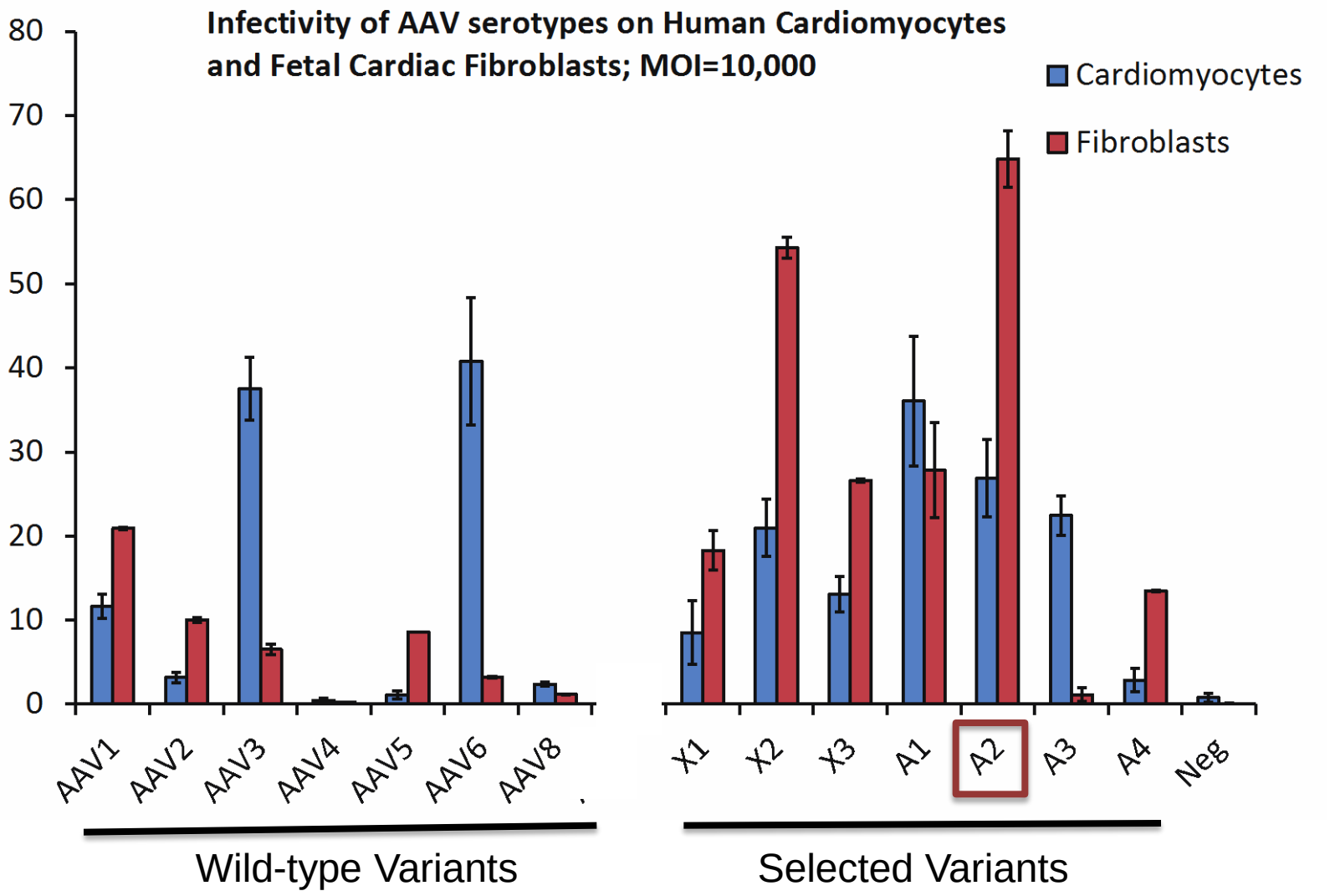


Screening for AAV Variants with Cardiac Fibroblasts Tropism



Collaboration with David Ojala, Schaffer Lab, UC-Berkeley

Selecting for Fibroblast Specific AAV Variants



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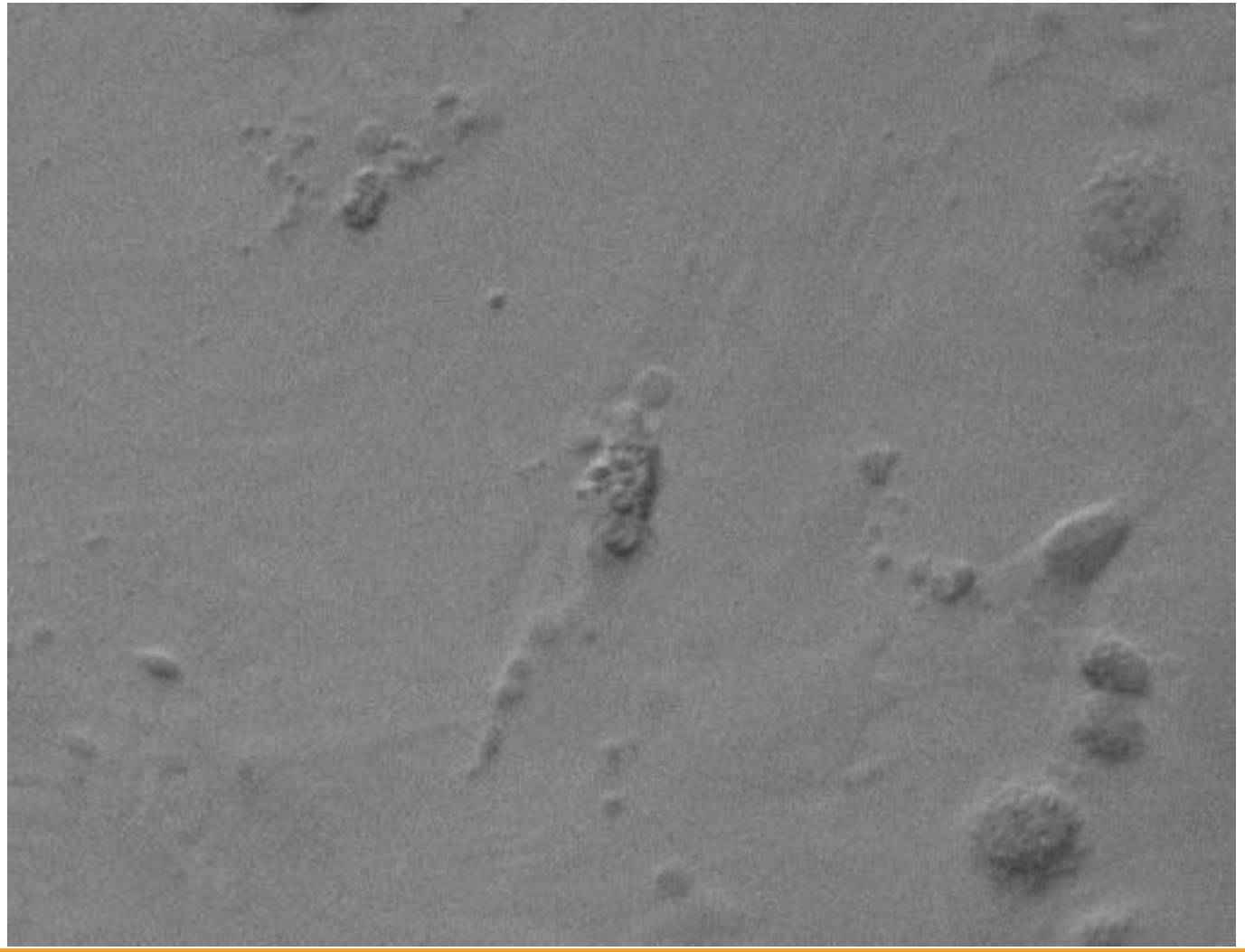
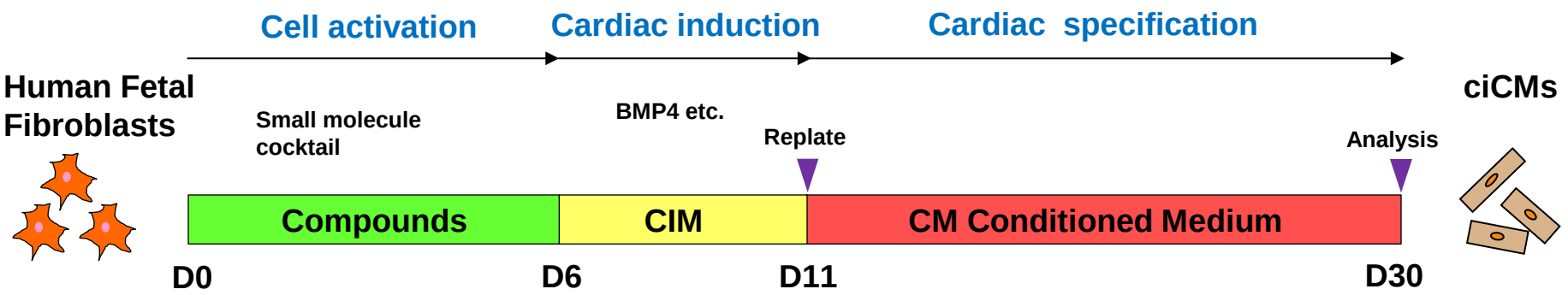
AAV-A2 Delivery Reprograms Cardiac Fibroblasts

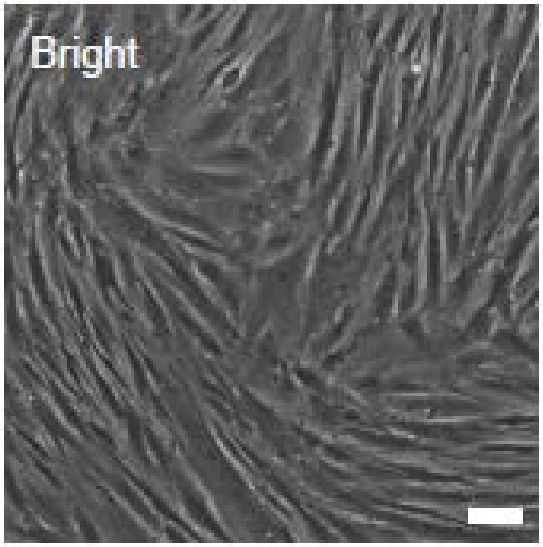
One Week



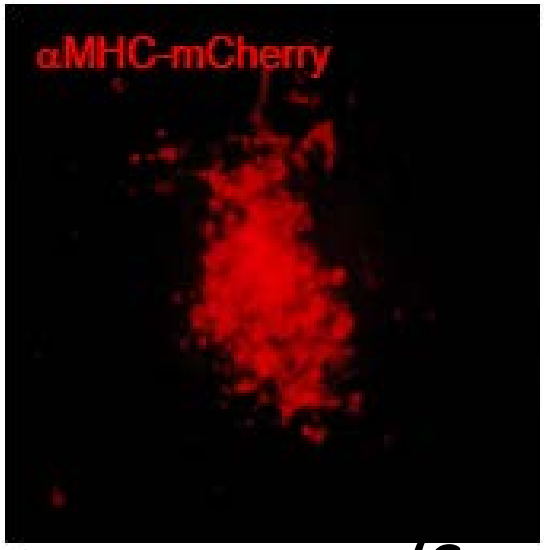
All Chemical Approach to Human Cardiac Reprogramming Through a Progenitor State

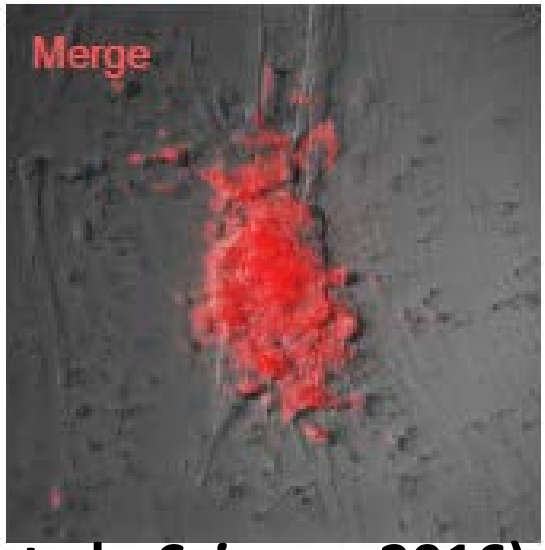


Control Day30



9 Compounds (9C) Day 30



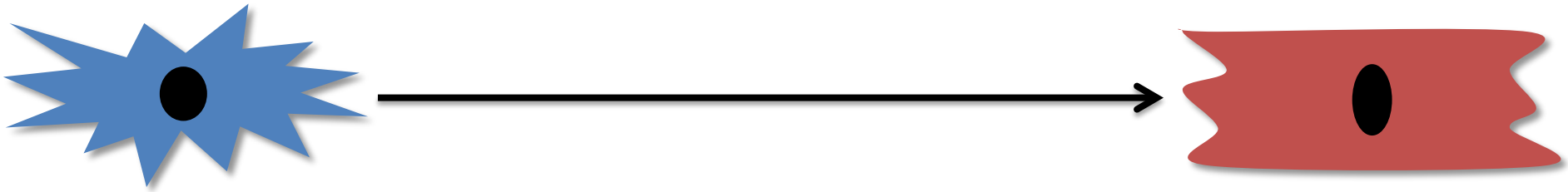


(Cao et al., *Science*, 2016)

Direct Cardiac Reprogramming

Challenges

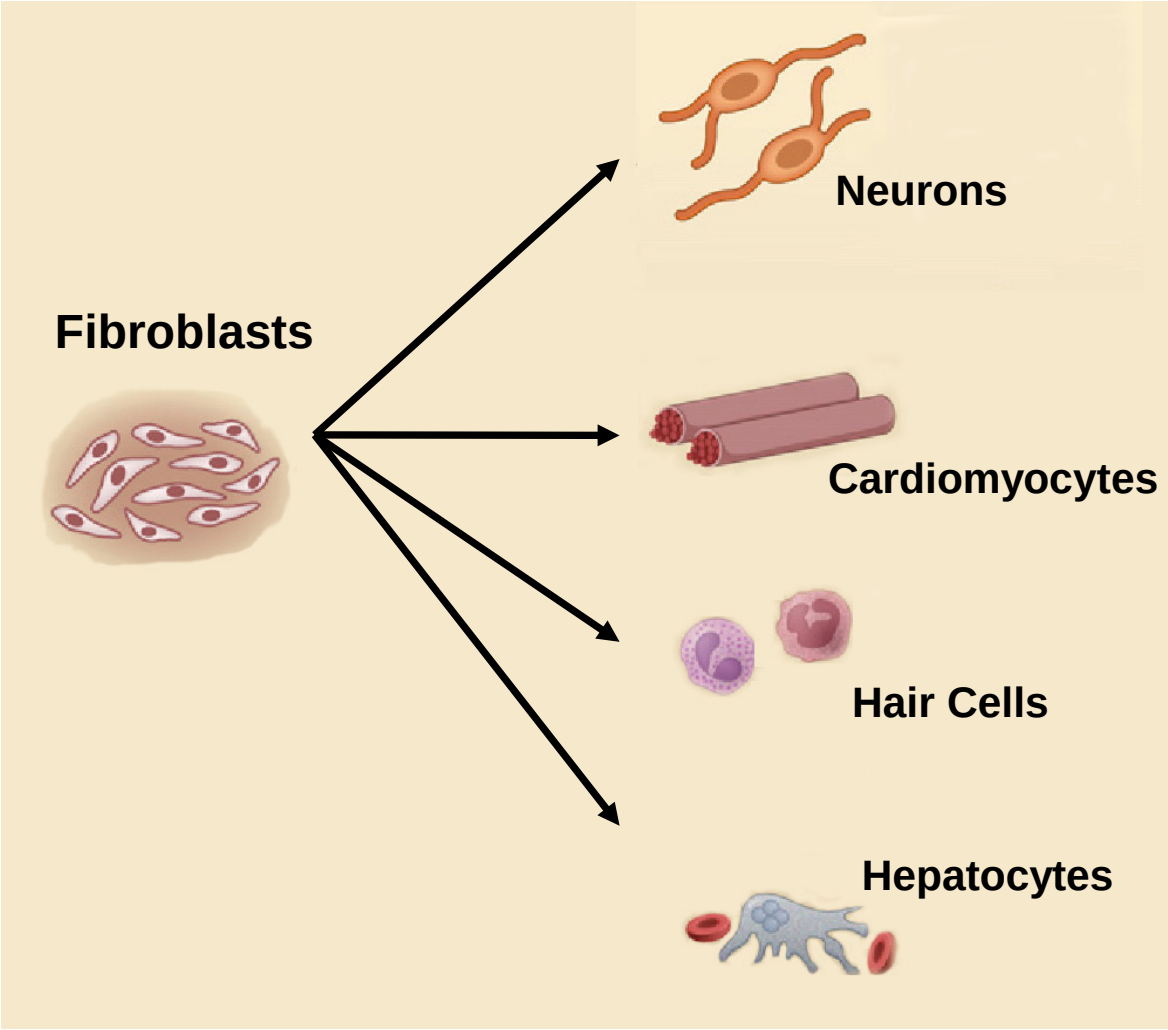
1. Delivery
2. Regulatory for combinatorial approach
3. Safety – e.g., arrhythmias



Cardiac Fibroblasts

Induced Cardiomyocytes (iCMs)

Direct Reprogramming (Transdifferentiation) for Generating Multiple Cell Types



Cell

Leading Edge
Review
A Decade of iPS Cells

In Vivo Cellular Reprogramming: The Next Generation

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