Induced Pluripotent Stem Cells and Direct Cardiac Reprogramming

Solving Barriers for a Powerful Future: The 2016 New Experimental and Clinical Information

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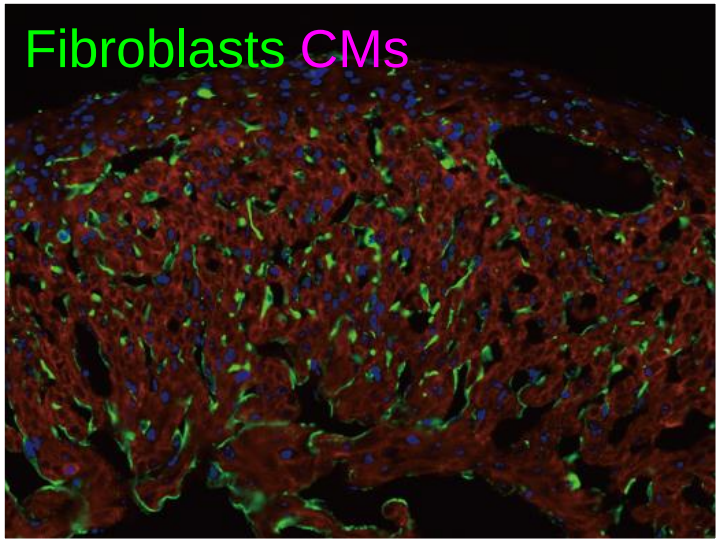
Adult Hearts Have Little Regenerative Capacity

Normal heart

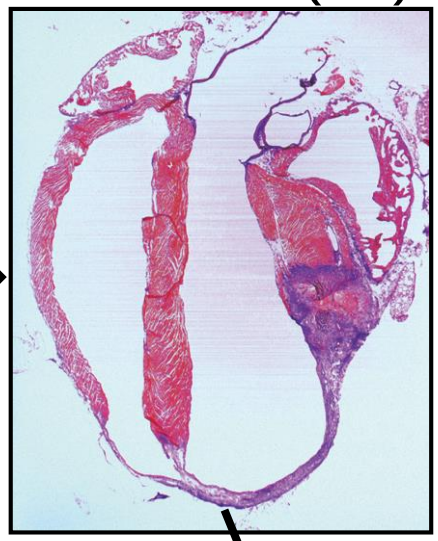


(Ieda et al., Dev Cell, 2009)

Normal heart

Cardiomyocytes

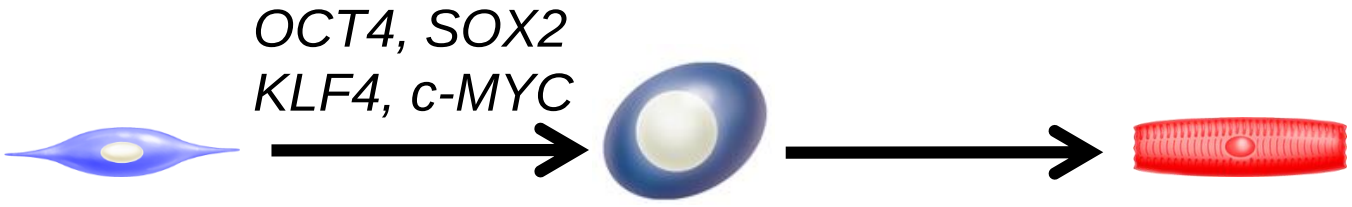
Myocardial infarction (MI)



Fibroblasts

Strategies for Cardiac Regeneration

1. Transplantation of induced pluripotent stem cells (iPSCs)-derived cardiomyocytes



(Takahashi, et al. *Cell* 2007)

2. Direct reprogramming of resident cardiac fibroblasts into cardiomyocytes (direct cardiac reprogramming)

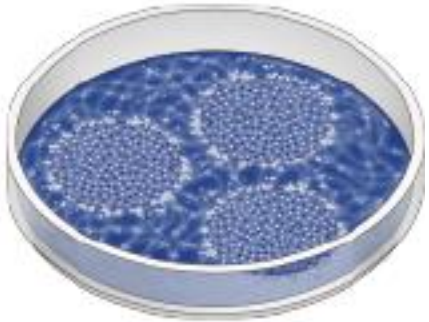
(Ieda, et al. *Cell* 2010)

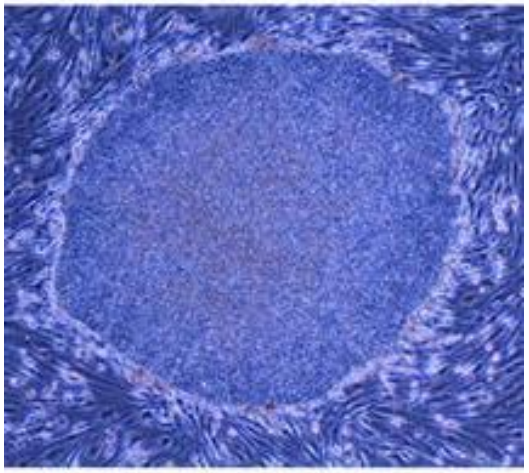
Combination of Stem Cell-specific Factors Convert Fibroblasts to iPSCs

Fibroblasts

OCT4, SOX2
KLF4, c-MYC

induced pluripotent stem cells (iPSCs)





myocytes

iPSCs

Neuron

Blood

Liver

平成24年10月８日（月）

産経新聞

号 外

山中氏にノーベル賞

医学・生理学

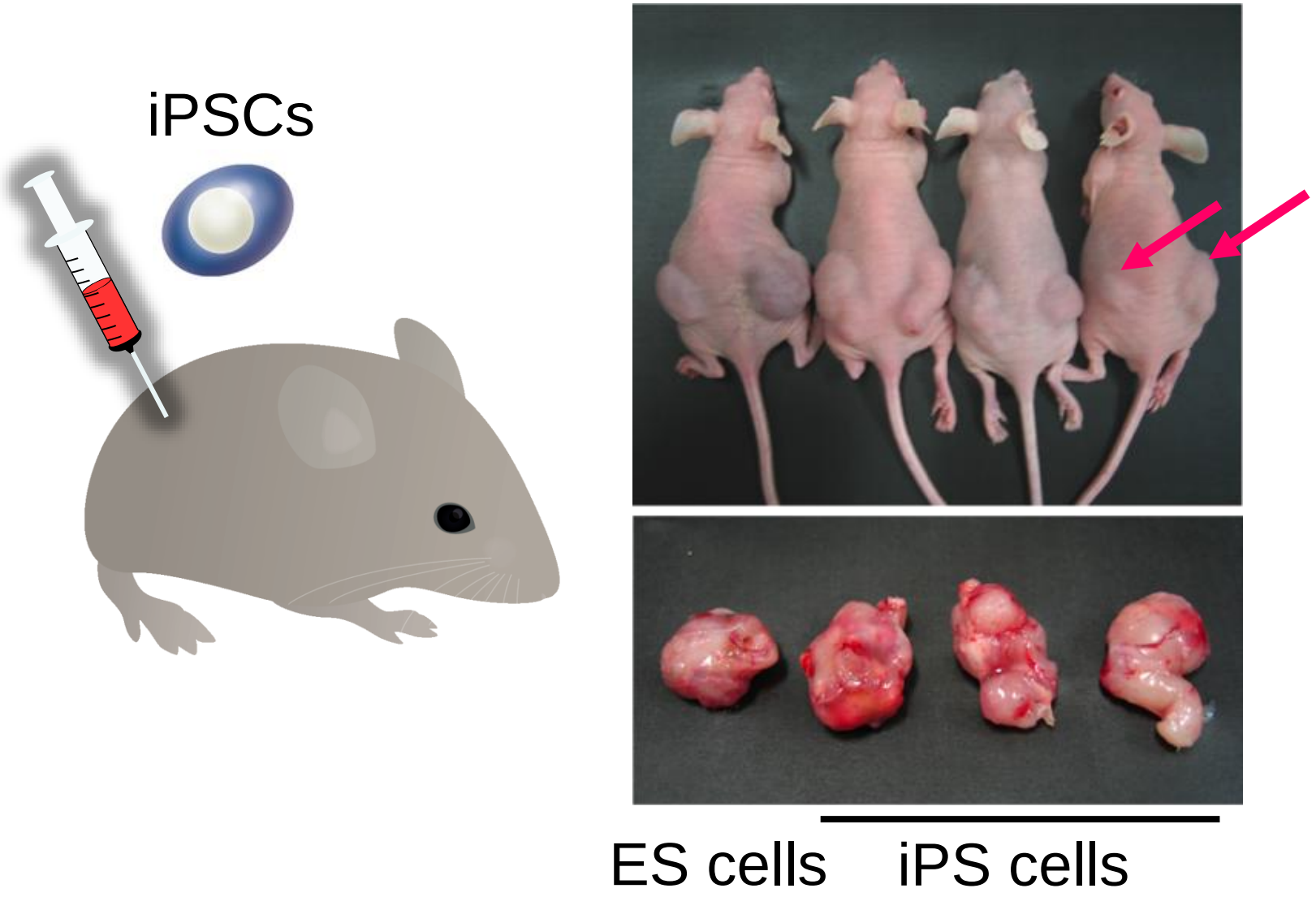
iPS細胞を開発

0120-34-4646

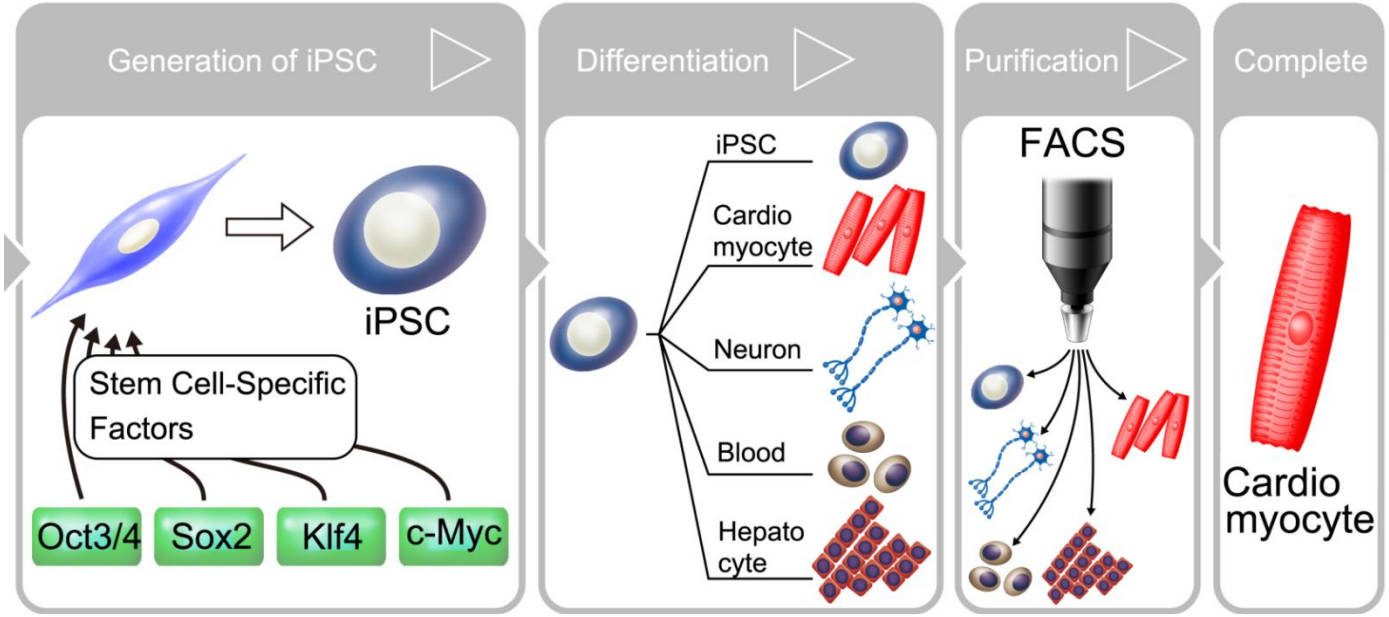
MSN産経ニュース http://sankei.jp.msn.com

(Takahashi, et al. *Cell* 2007)

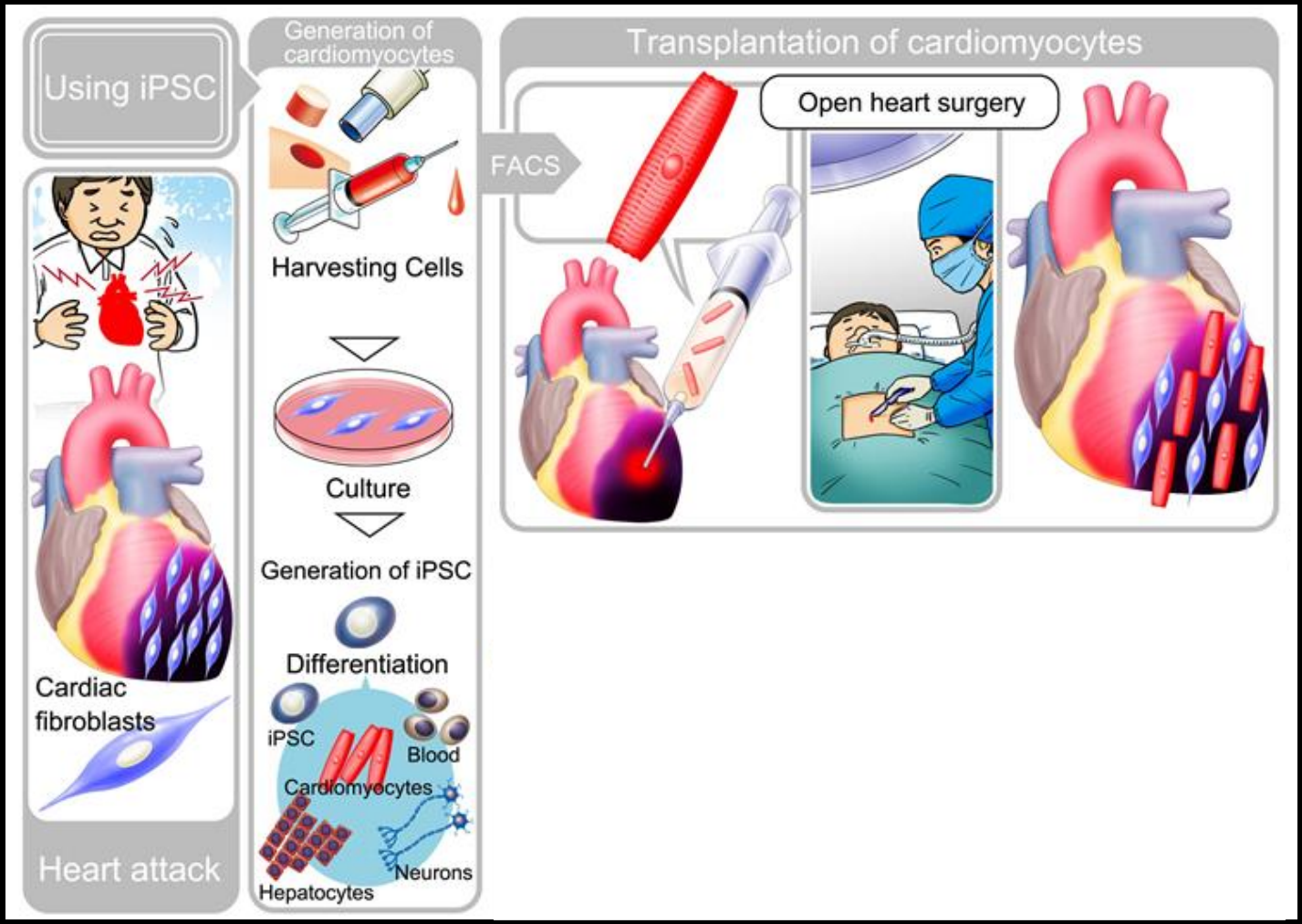
iPSCs Make Tumors



Generation of CMs through iPSCs



Regeneration using iPSC-CMs

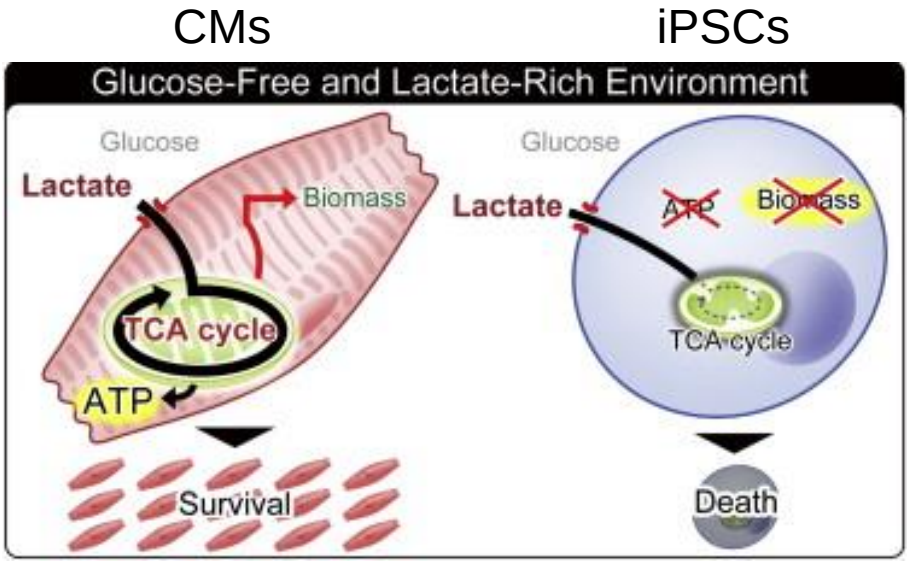


iPSC-CM transplantation

1. Complicated/ long process
2. Tumor by iPSC contamination
3. Poor survival of the cells

Purification of CMs with Culture Conditions

CMs can use lactate for ATP synthesis



Mitochondria rich

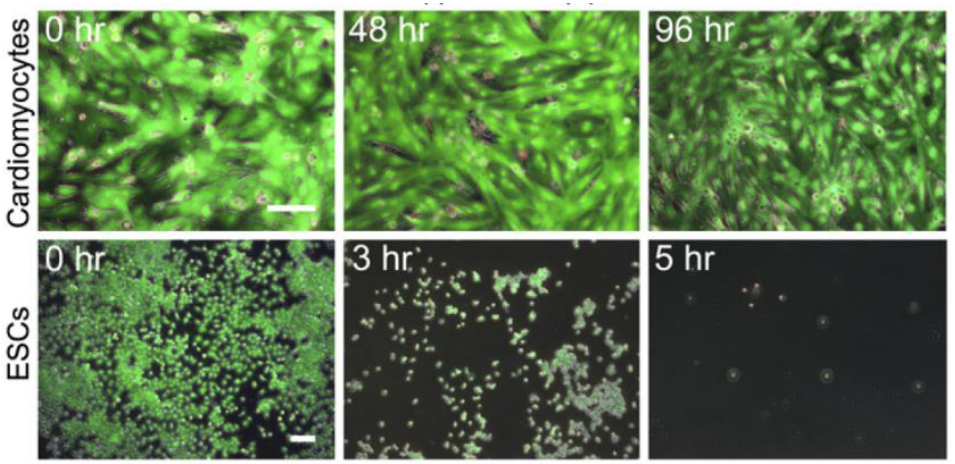
Use lactate for ATP synthesis

Mitochondria poor

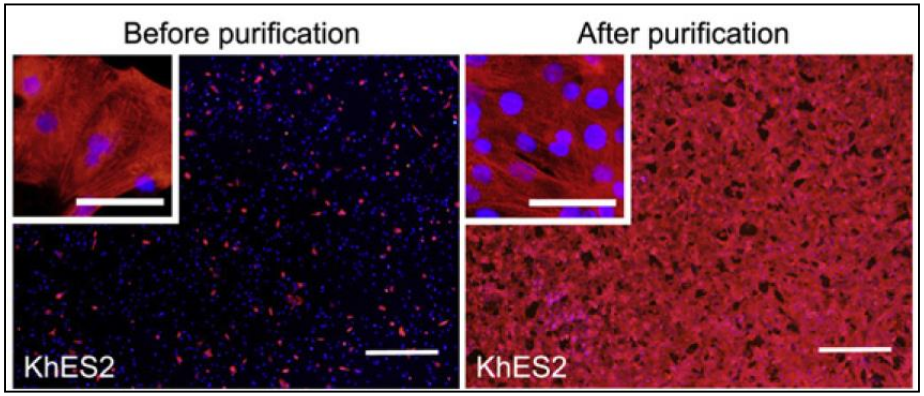
Use only glucose for ATP synthesis

Glucose-/lactate+ culture media may purify CMs and kill iPSCs

CMs survived under glucose-/lactate+



Purification of CMs > 90%



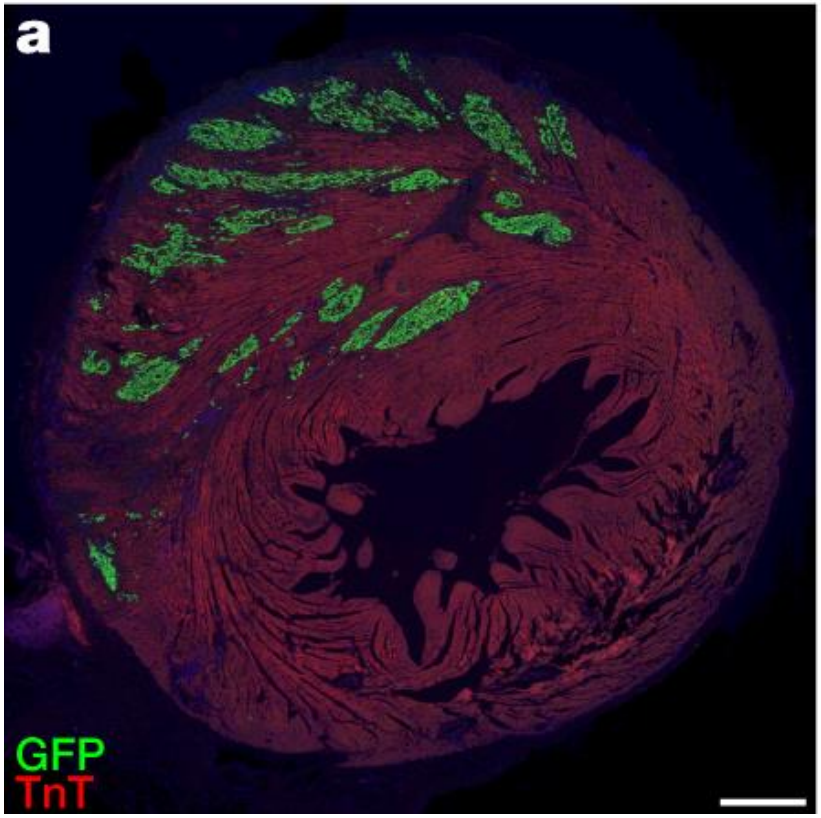
(Tohyama et al., Cell stem Cell, 2013)

Monkey iPSC-CMs Regenerate MI Hearts

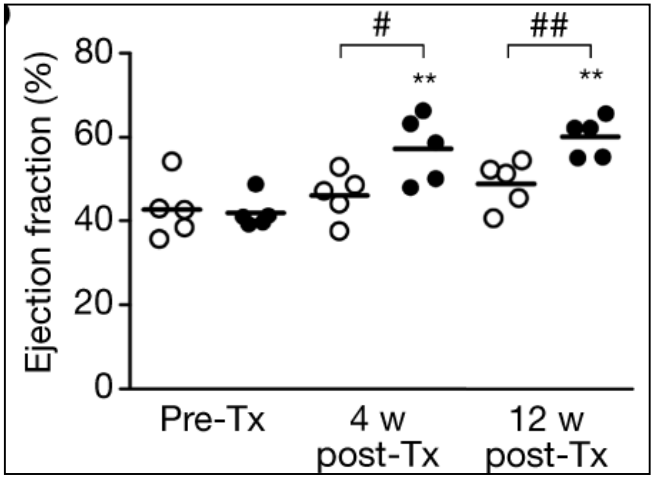
Autologus iPSCs
Expensive!

Allogenic iPSCs
(iPSC bank)

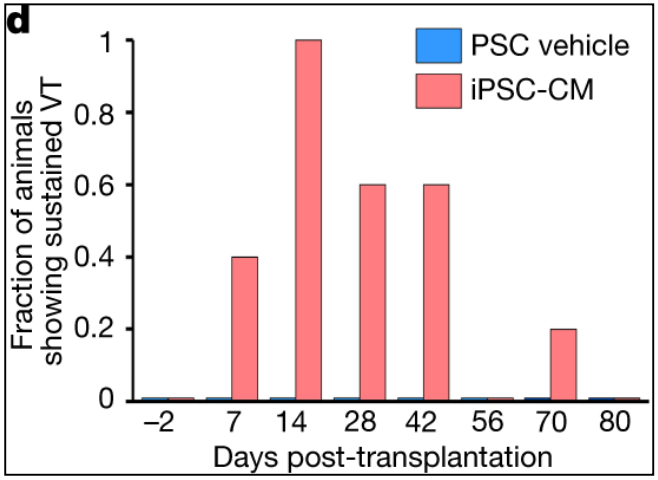
Allogenic monkey iPSC-CMs survived
In MI hearts with immunosuppresants



iPSC-CMs Improved EF



iPSC-CMs induced VT



(Shiba et al., Nature, 2016)

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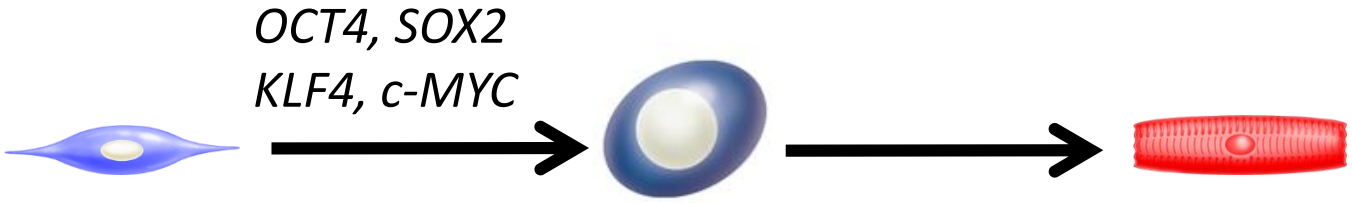
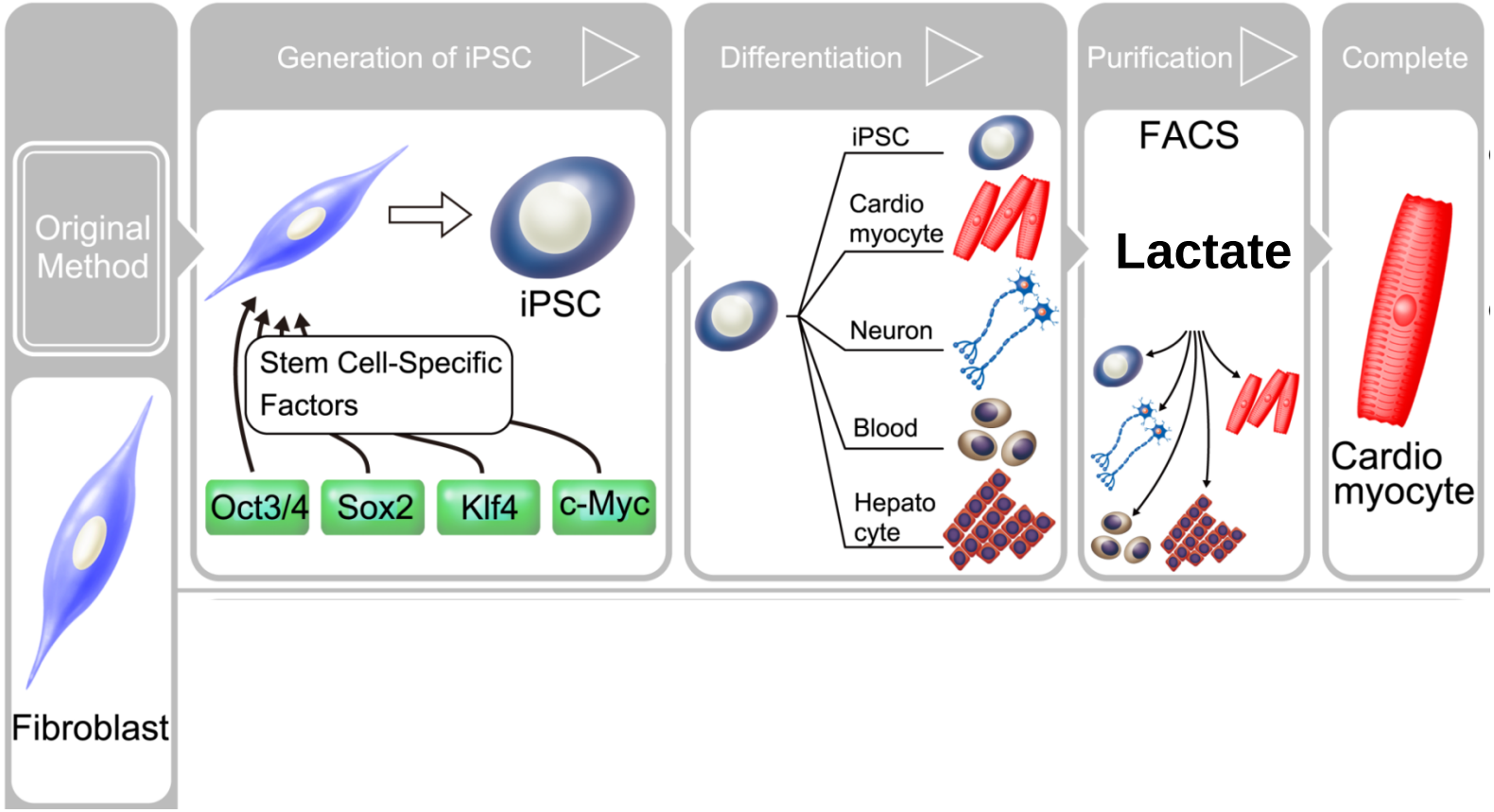


(Takahashi, et al. *Cell* 2007)

2. Direct reprogramming of resident cardiac fibroblasts into cardiomyocytes (direct cardiac reprogramming)

(Ieda, et al. *Cell* 2010)

Generation of Cardiomyocytes from Fibroblasts



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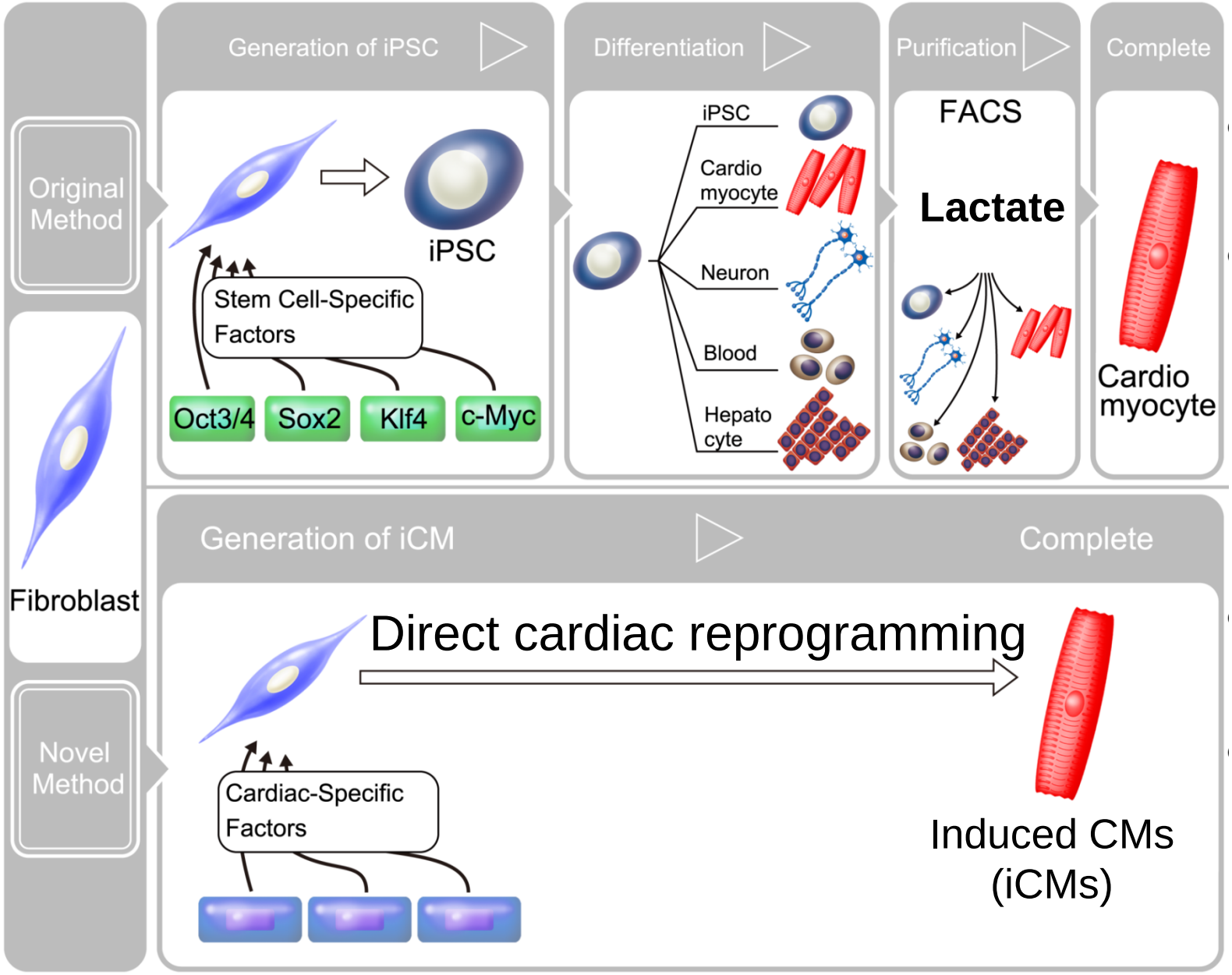
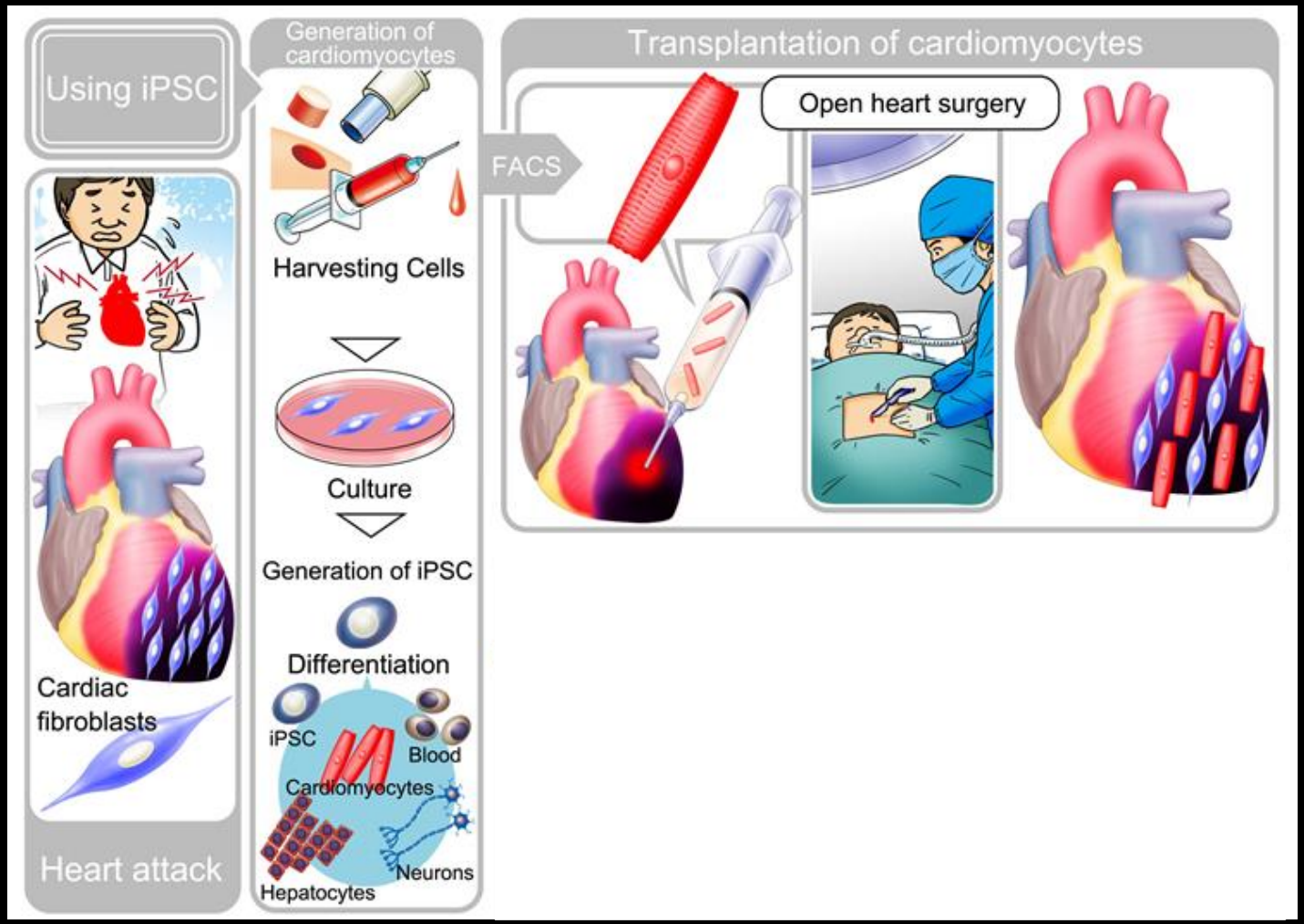


Regeneration using iPSC-CMs



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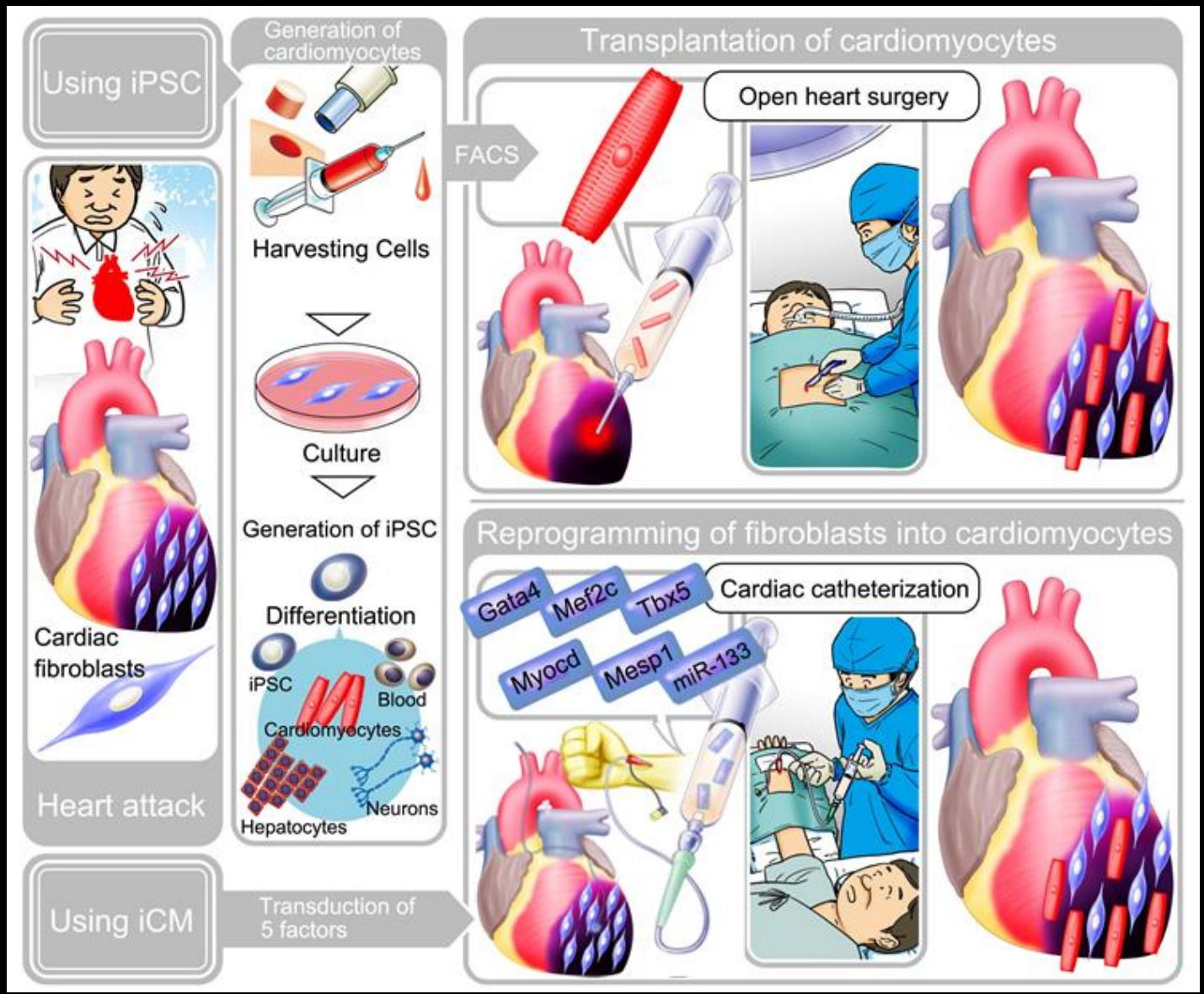
3. Poor survival of the cells

Regeneration by Cardiac Reprogramming



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Cardiac reprogramming

1. Simple/ fast process
2. No risk of tumor formation
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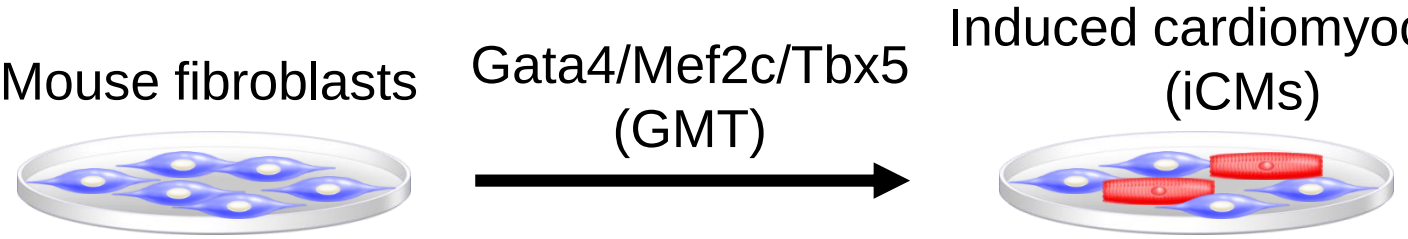
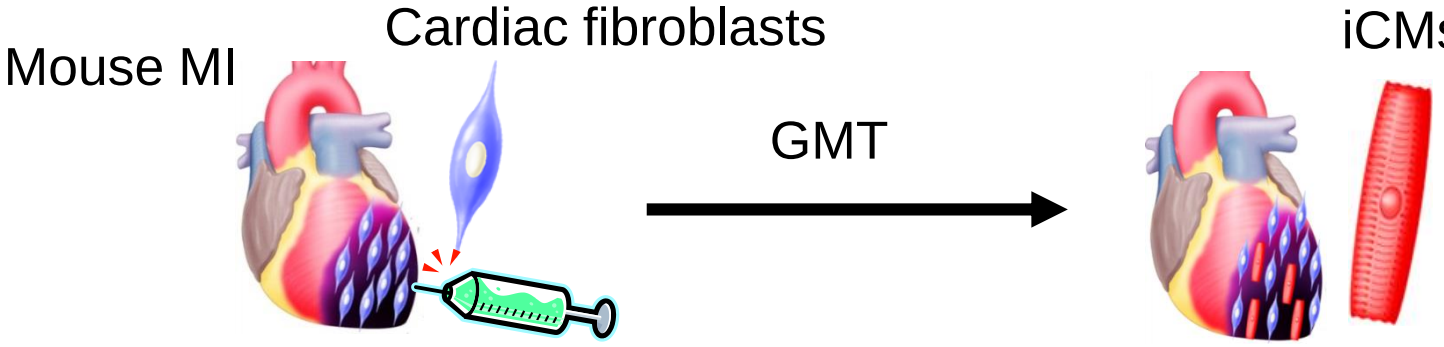
Discovery and Progress of Cardiac Reprogramming

1. Cardiac reprogramming in mouse and human cells



(Ieda et al Cell, 2010) (Wada et al., PNAS, 2013)
(Muraoka et al., EMBO J, 2014)
(Yamakawa et al., Stem Cell Reports, 2015)

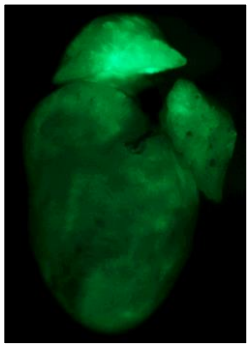
2. Heart regeneration by in vivo cardiac reprogramming



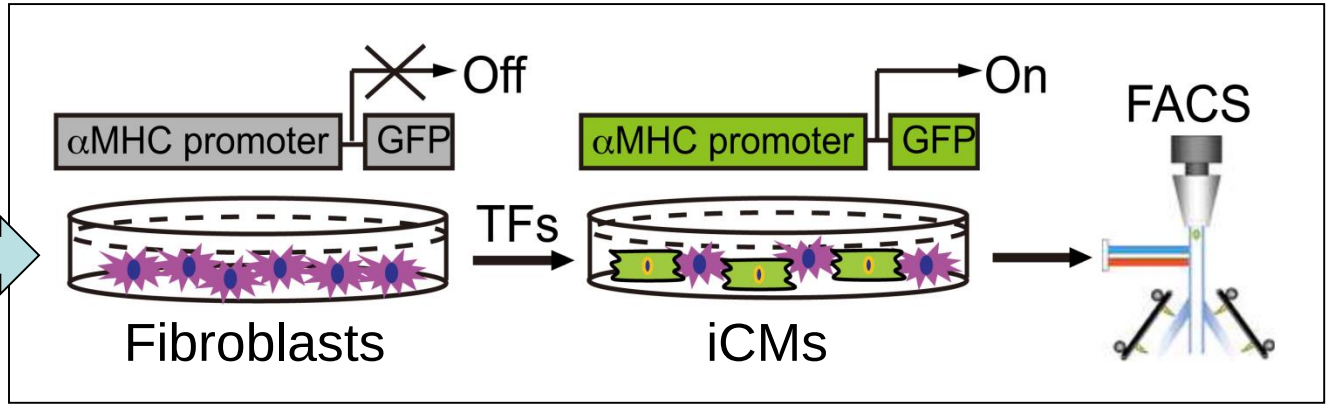
(Inagawa et al Circ Res, 2012)

Gata4/Mef2c/Tbx5 Are Cardiac Reprogramming Factors in Mouse

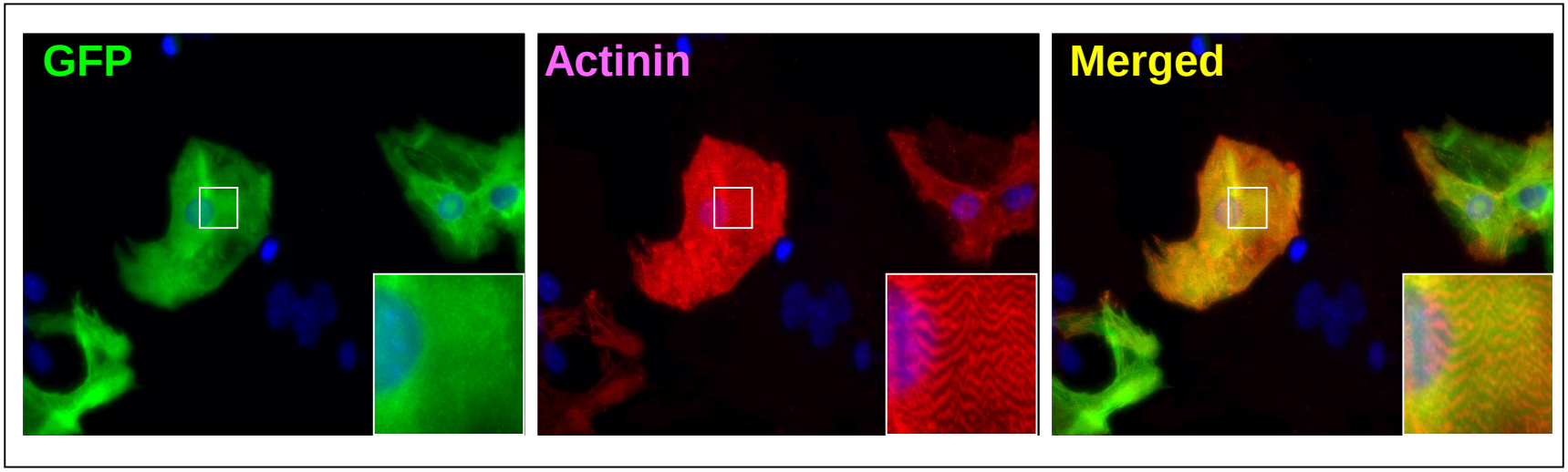
αMHC-GFP TG mouse



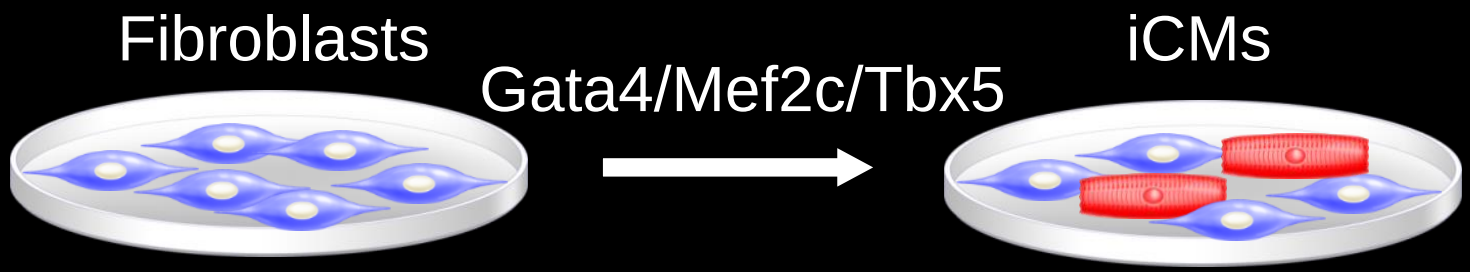
Screening for cardiac reprogramming factors

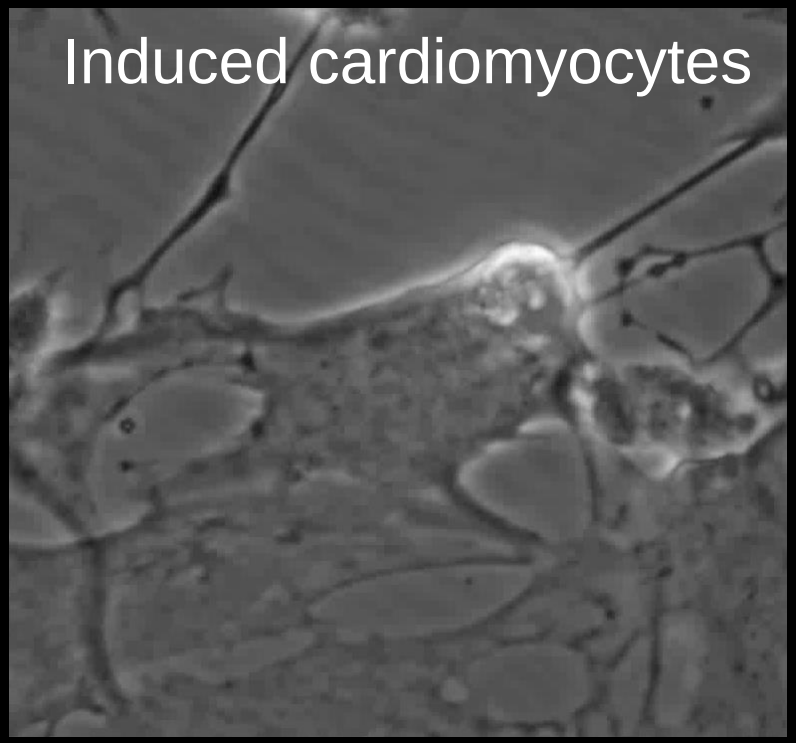


GMT converted fibroblasts into iCMs



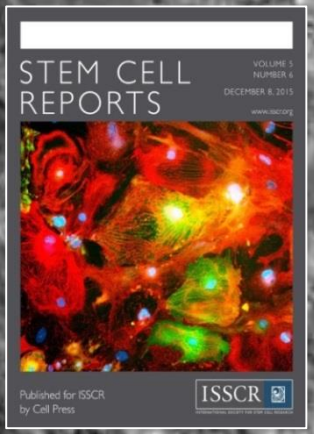
Gata4/Mef2c/Tbx5 Are Cardiac Reprogramming Factors





(Ieda et al., Cell, 2010)

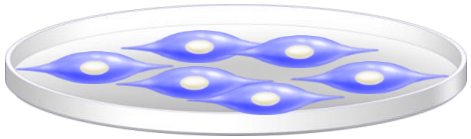
Addition of Cytokines Improved Cardiac Reprogramming Efficiency



(Yamakawa et al., Stem Cell Reports, 2015)

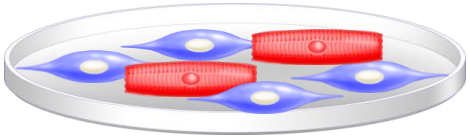
How about in human?

Human fibroblasts



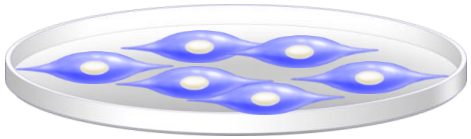
Gata4/Mef2c/Tbx5/
+ ?

Human iCMs



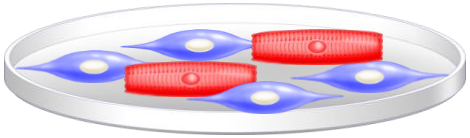
Gata4/Mef2c/Tbx5/Myocd/Mesp1 Are Human Cardiac Reprogramming Factors

Human fibroblasts

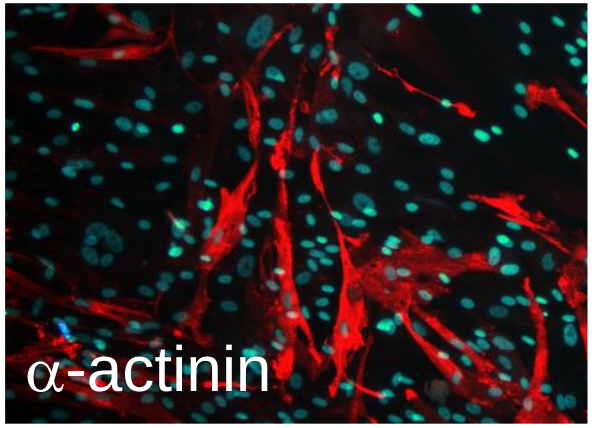


Gata4/Mef2c/Tbx5/
Myocd/Mesp1

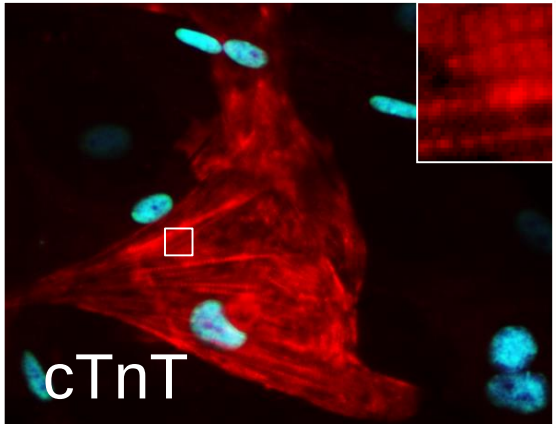
Human iCMs

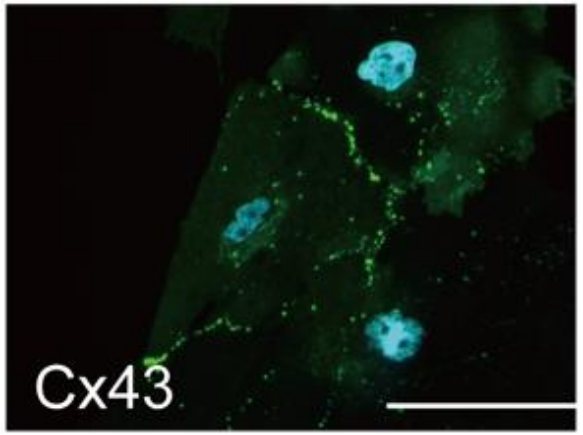


Gata4/Mef2c/Tbx5/
Myocd/Mesp1 (GMTMM)



Human iCMs



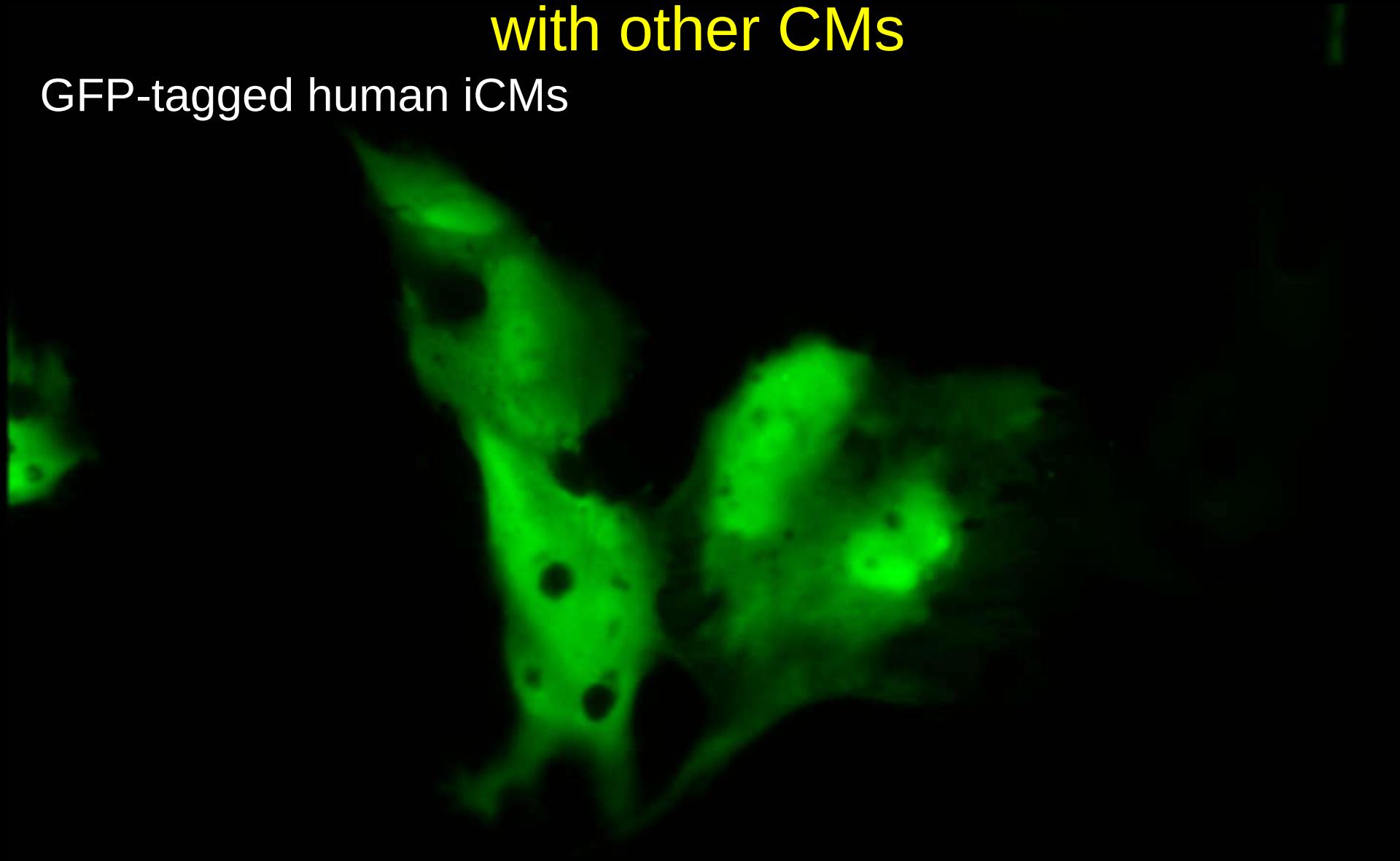


(Wada et al., PNAS, 2013)

(Muraoka et al., EMBO J, 2014)

Human iCMs Beat Synchronously in co-culture with other CMs

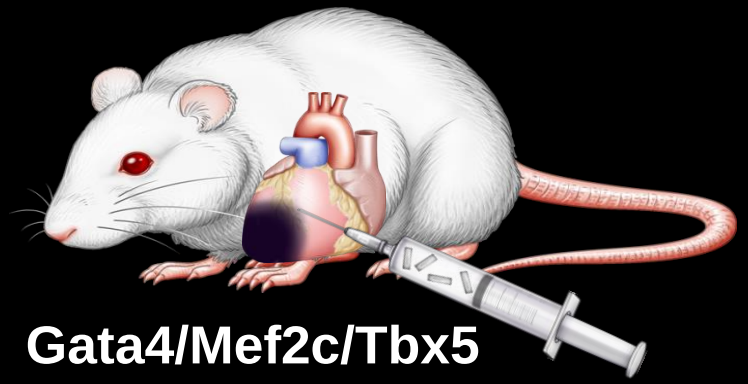
GFP-tagged human iCMs



(Wada et al., PNAS 2013)

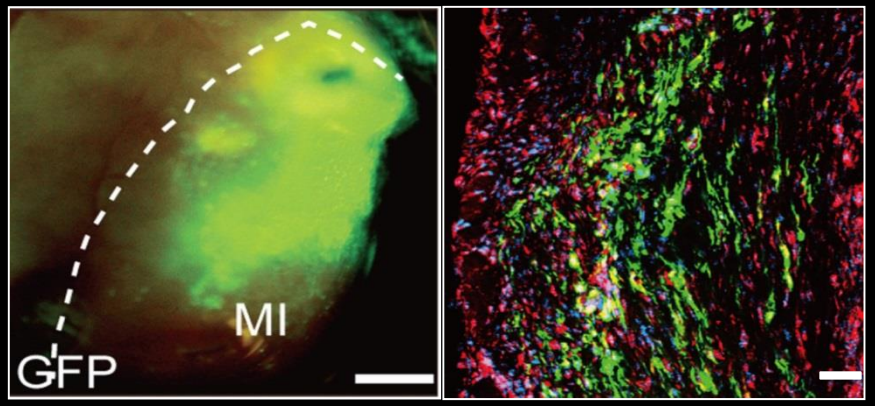
In Vivo Cardiac Reprogramming by GMT

Mouse MI model

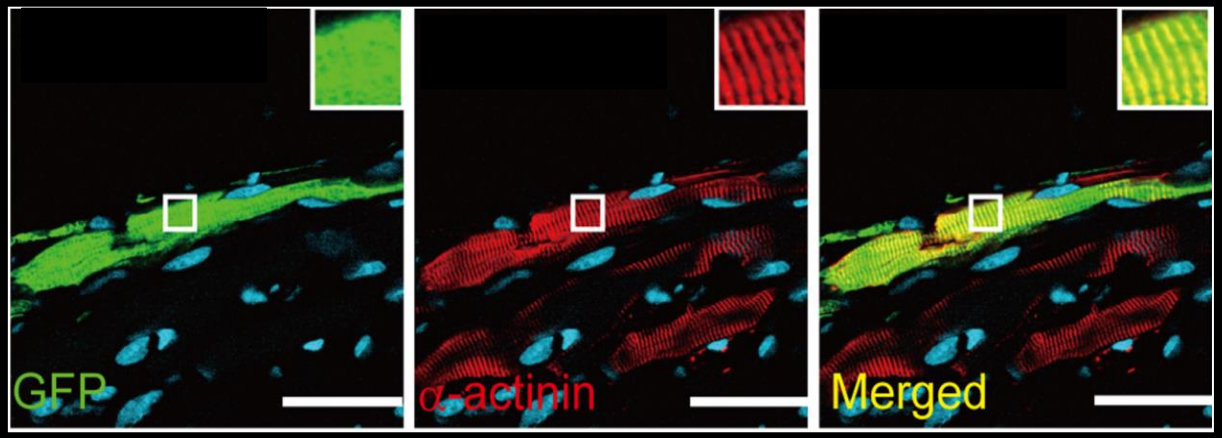


Gata4/Mef2c/Tbx5 (GMT)

Retrovirus GFP infected fibroblasts



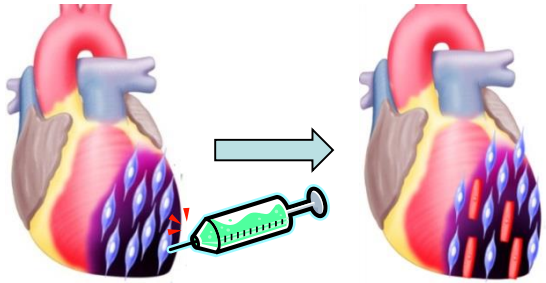
GFP Actinin Merged



(Inagawa et al Circ Res, 2012)

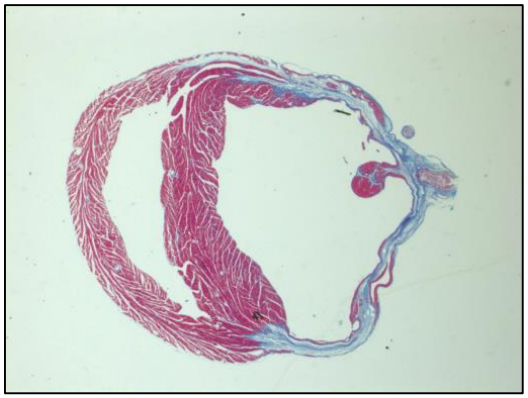
In Vivo Reprogramming Improved Cardiac Function

Gata4/Mef2c/Tbx5

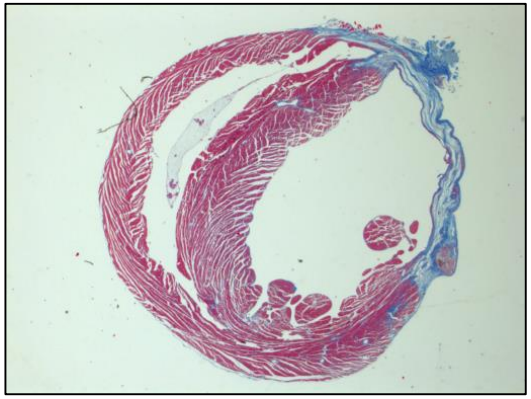


Gata4/Mef2c/Tbx5 reduced fibrosis

Control



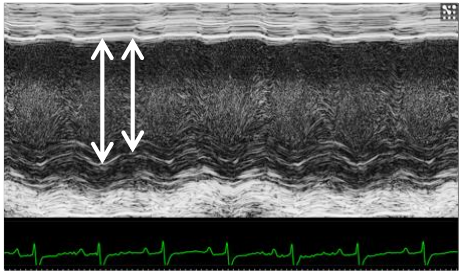
Gata4/Mef2c/Tbx5



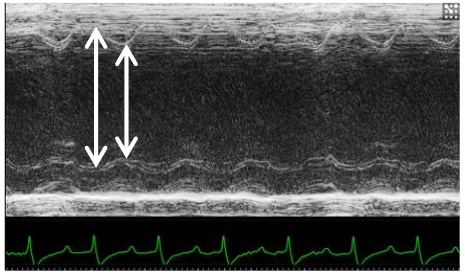
Gata4/Mef2c/Tbx5 improved cardiac function

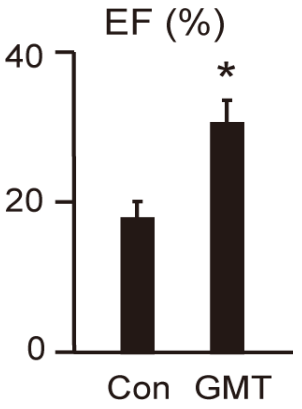
Echocardiogram

Control



Gata4/Mef2c/Tbx5





Discovery and Progress of Cardiac Reprogramming

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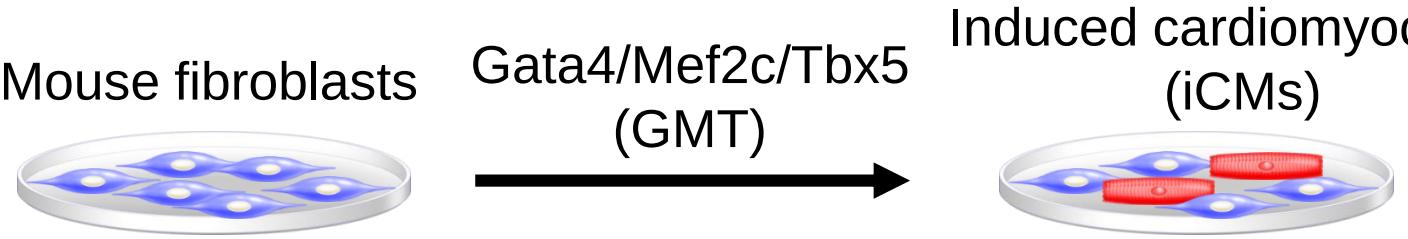

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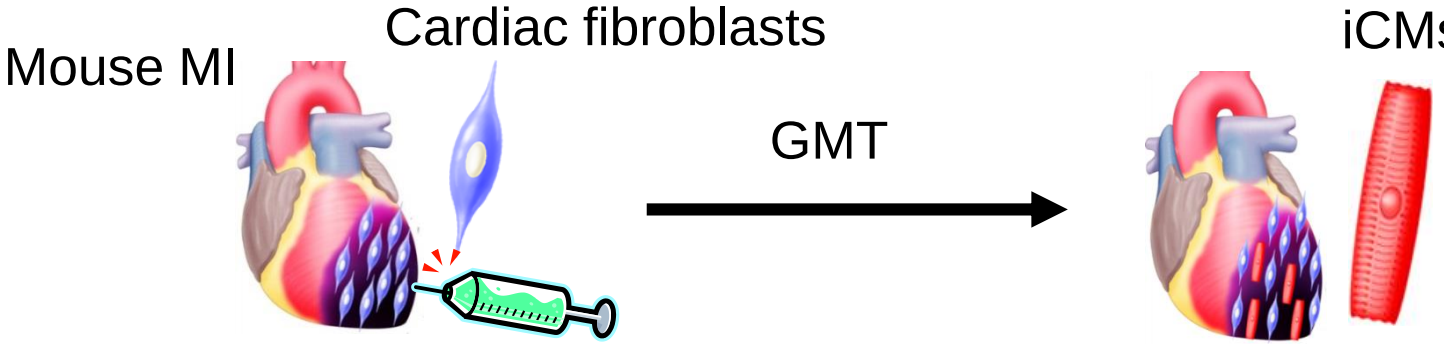
2. Heart regeneration by in vivo cardiac reprogramming



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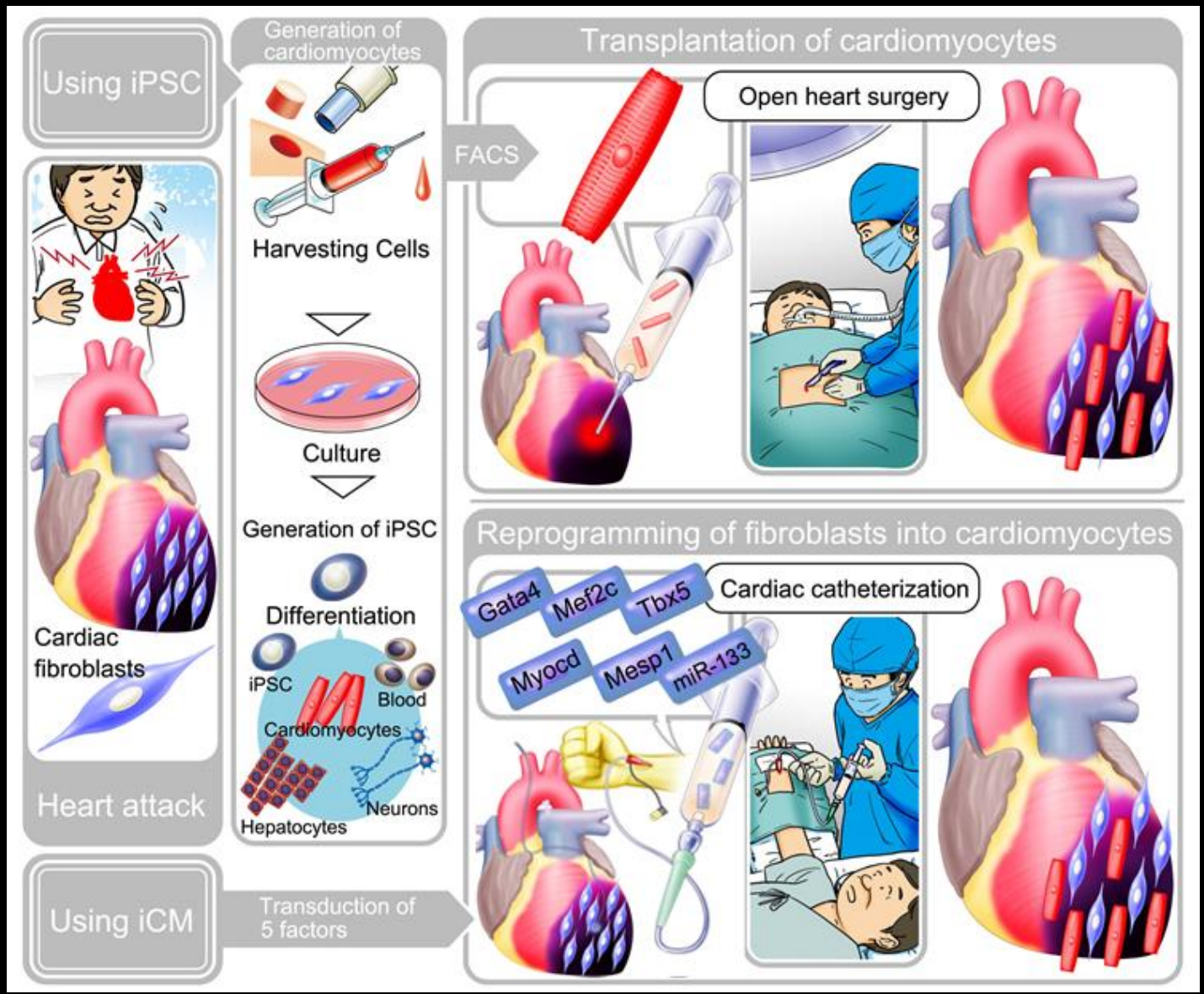

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Acknowledgements

Keio University School of Medicine

Ieda lab

Department of Cardiology

Naoto Muraoka, Kazutaka Miyamoto
Taketaro Sadahiro, Mari Isomi,
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Hidenori Kojima, Shota Kurotsu,
Fumiya Tamura, Keiichi Fukuda

Department of Pediatrics

Hiroyuki Yamagishi

Department of Cardiac Surgery

Ryo Aeba

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