Disease Modeling and Drug Discovery with Human Pluripotent Stem Cells

Shiang Lim (Max)

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O'Brien Institute

SVI
ST VINCENT'S INSTITUTE
MEDICAL RESEARCH

THE UNIVERSITY OF MELBOURNE

13th December 2019

Disease Modeling and Drug Discovery with Human Pluripotent Stem Cell derived vascularized and innervated cardiac organoids

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Cardiovascular disease – a leading cause of death

17.9 million per year around the would

31% of all global death worldwide

20% of Australians suffer from cardiovascular disease

1.1 million hospitalization in 2015-16, 11% of all hospitalization

$8.8 billion annually in Australia

$351.2 billion annually in USA

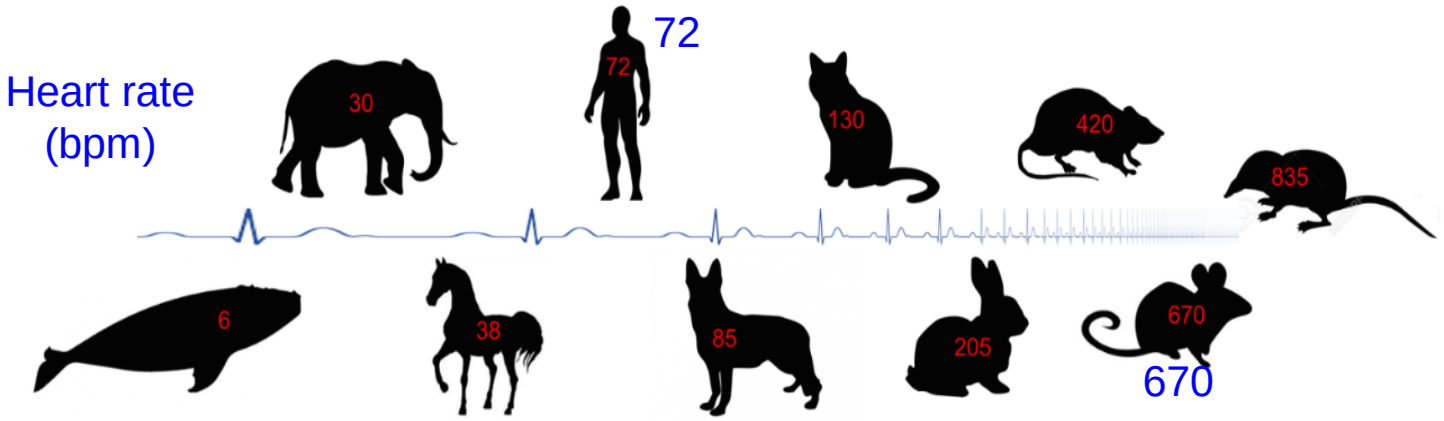
An unmet medical need – Why?

Current treatment options

- Not always compatible with pre-existing conditions & medications
- Undesirable side effects

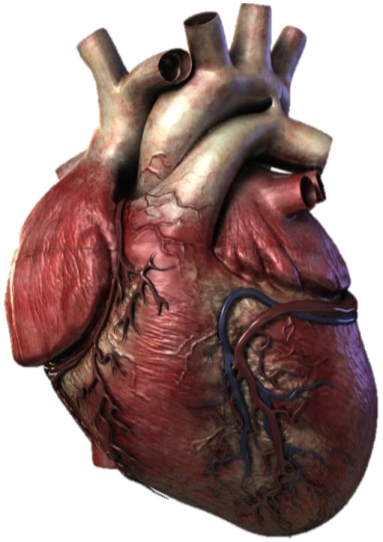
Current heart disease models

- Not clinically relevant
- Too simple

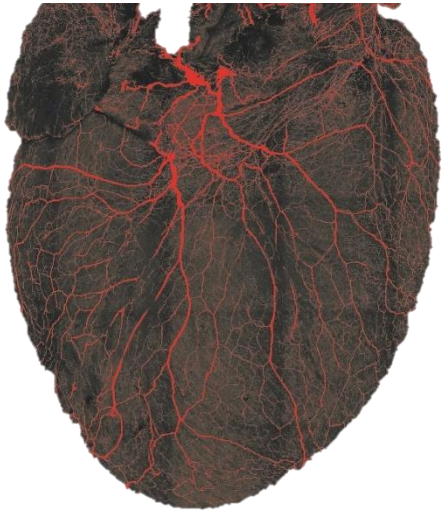


Drug efficacy and toxicity is often human-specific

The human heart is complex



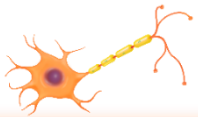
Cardiac vascular system



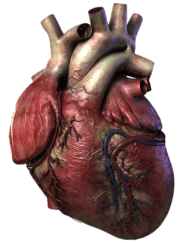
Autonomic nervous system

Heart muscle cells

Blood vessels



Neurons

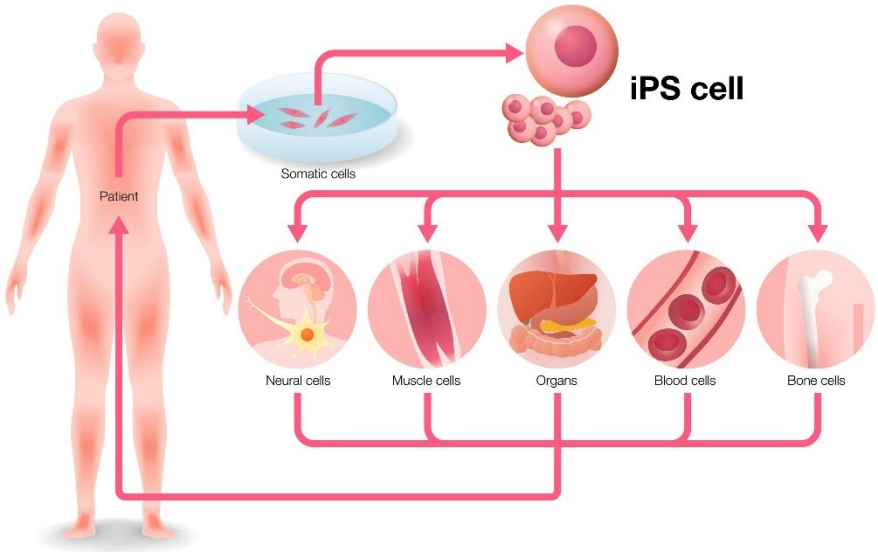


An unmet medical need – Solution?

We need better drug screening model to find better medications

To develop a multicellular cardiac organoid model to faithfully recapitulate heart physiology for predictive drug testing and for novel target identification

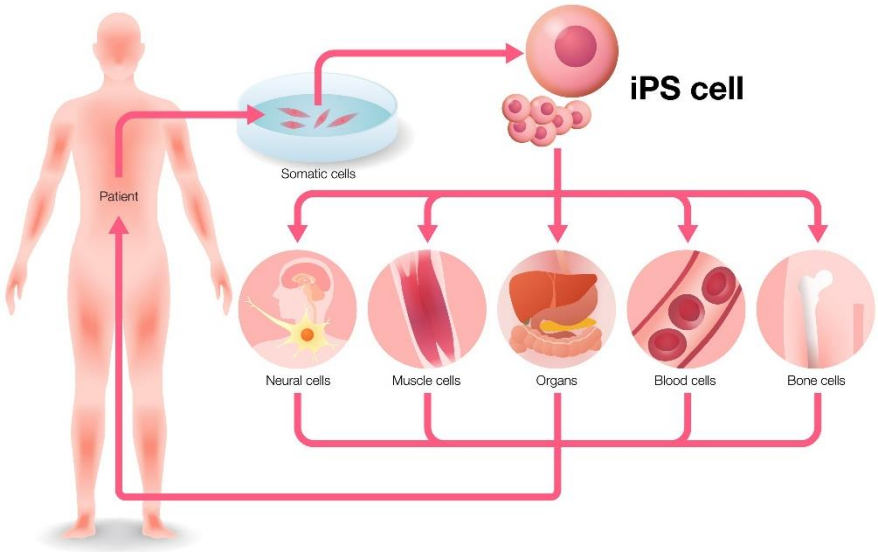
Engineered human 3D heart organoid with integrated blood vessels and a nervous system



Induced pluripotent stem cells (iPSCs)

- Carry an individual's genetic make-up
- Unlimited source of cells
- Transform into all cell types in the body

Engineered human 3D heart organoid with integrated blood vessels and a nervous system



Induced pluripotent stem cells

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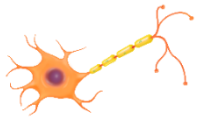
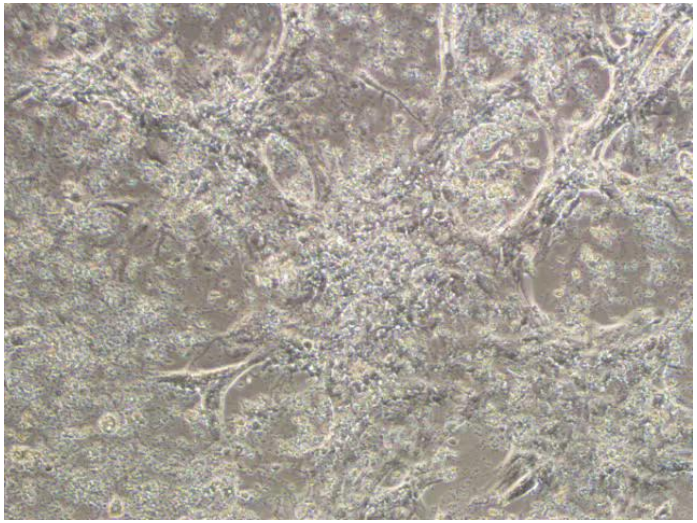
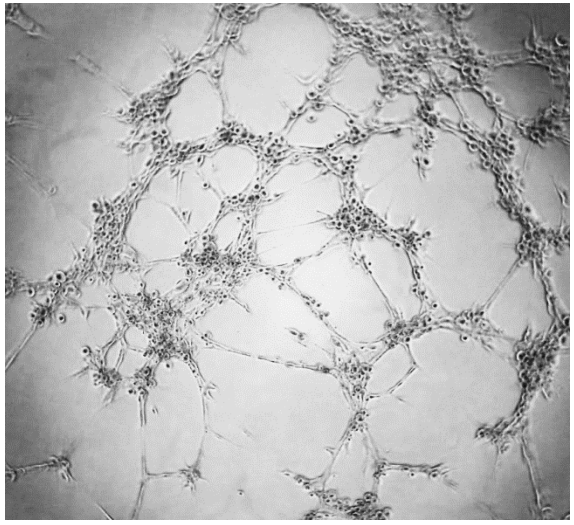
Heart muscle cells

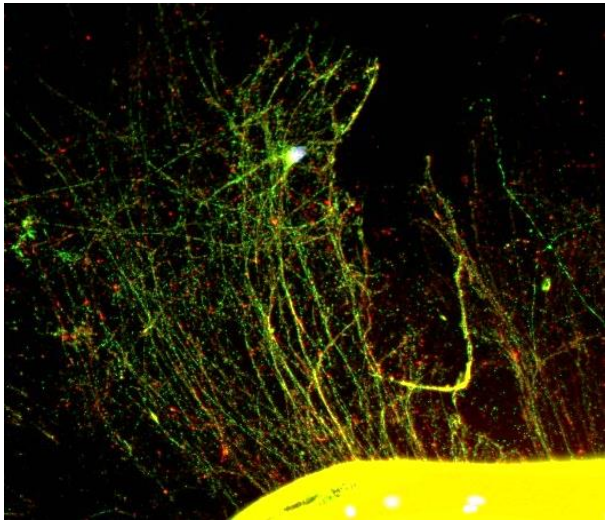
Blood vessels



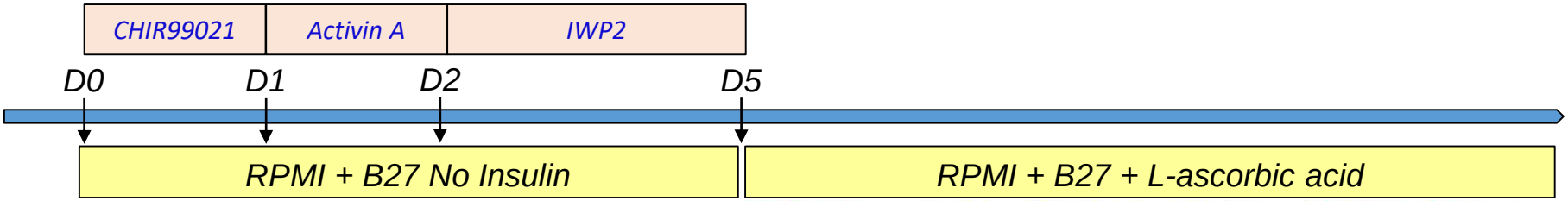
Neurons

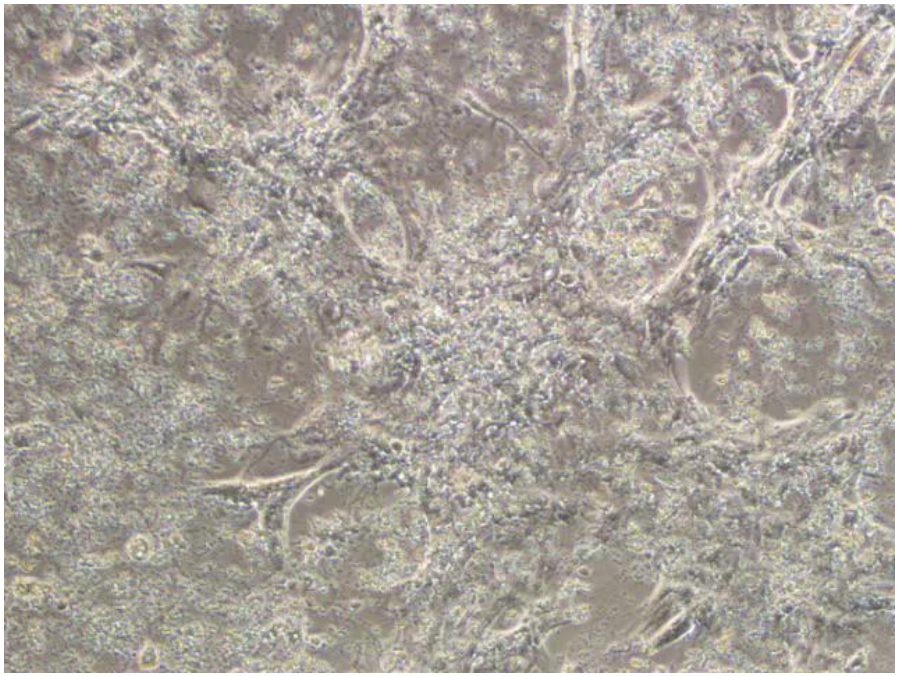


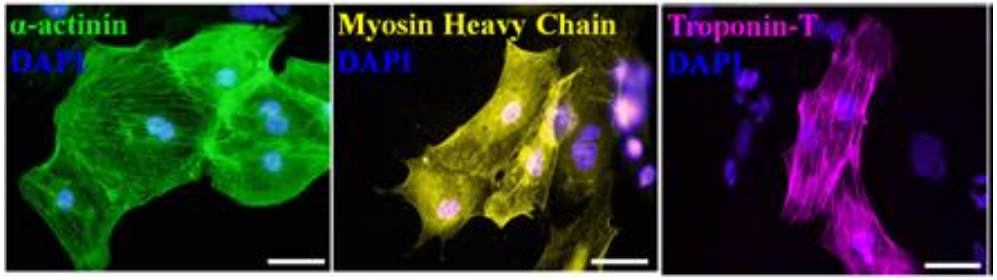


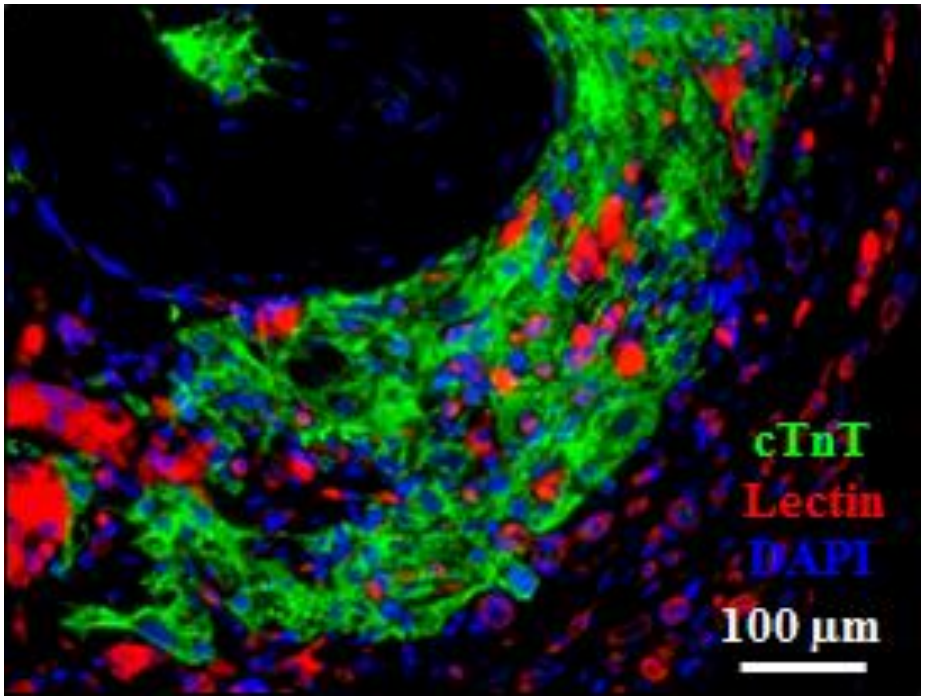


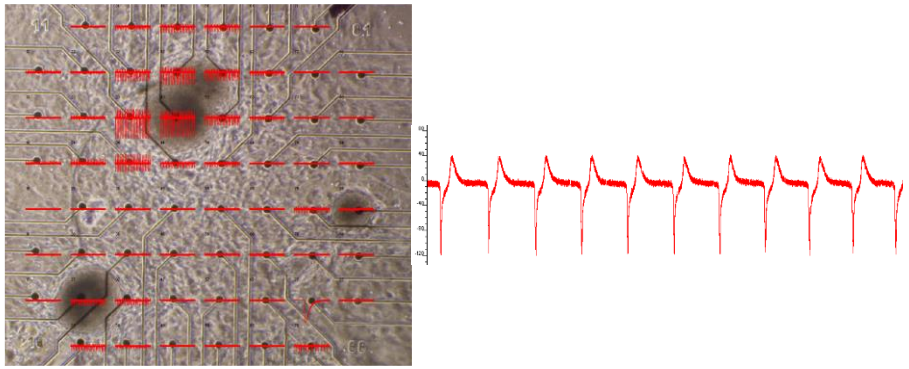
Cardiomyocytes derived from human iPSCs





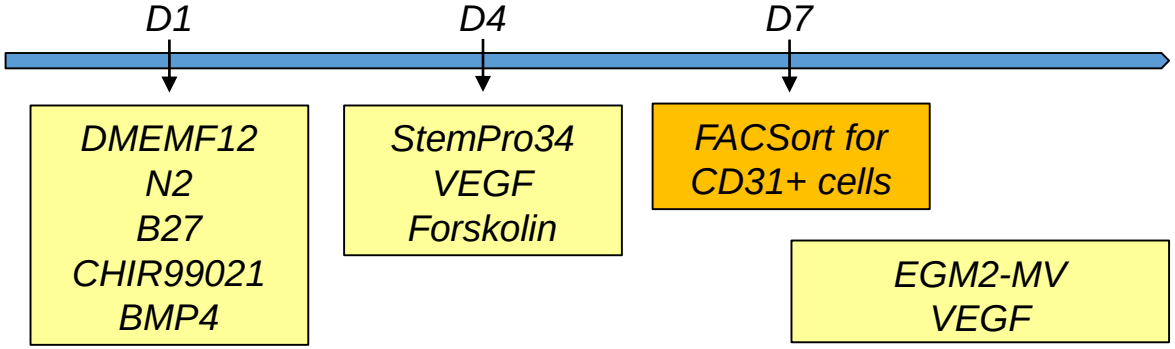


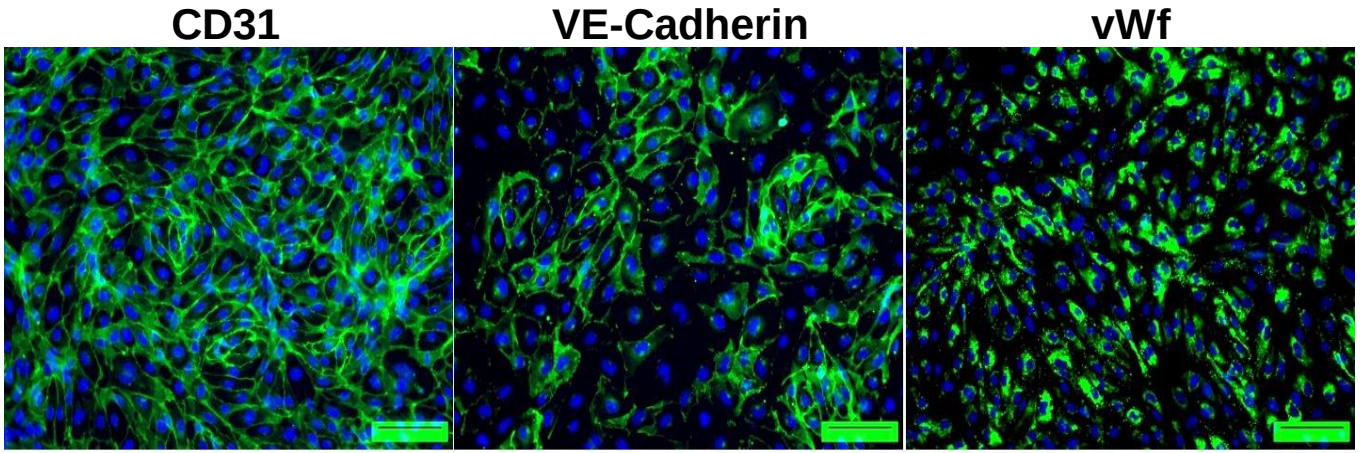


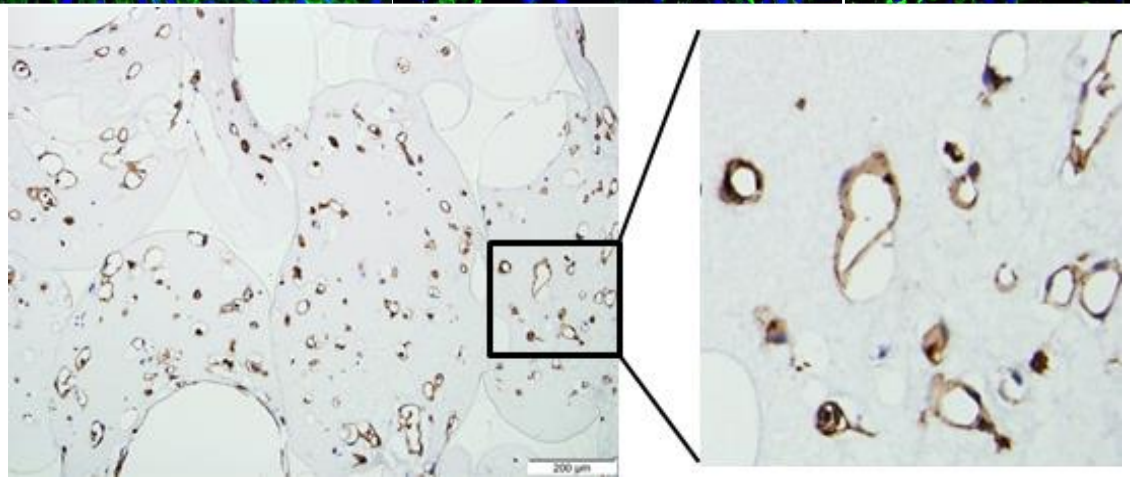


Lim et al. (2013) Stem Cells Transl Med; 3:787
Hoque et al. (2018) Cell Death Disc; 4:39

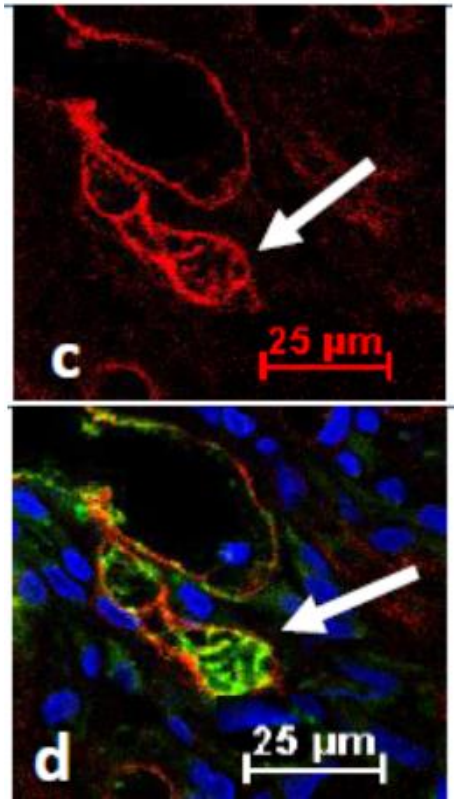
Endothelial cells derived from human iPSCs





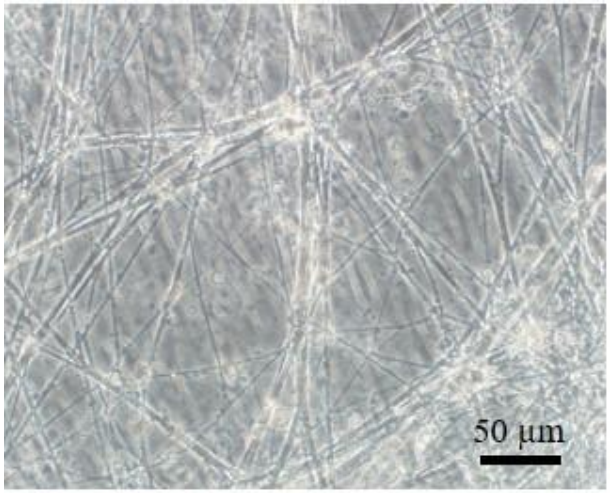


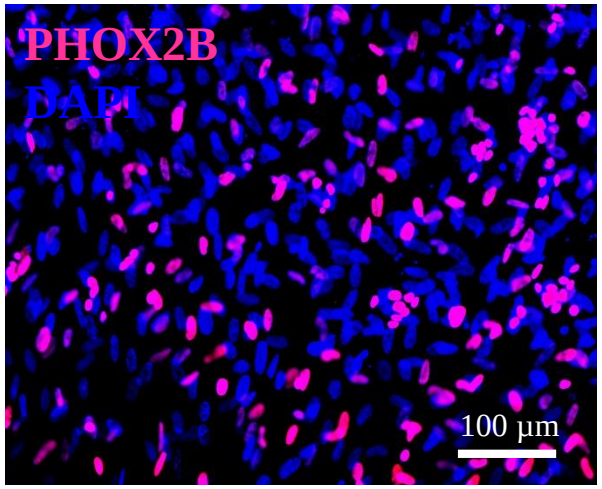
In vivo

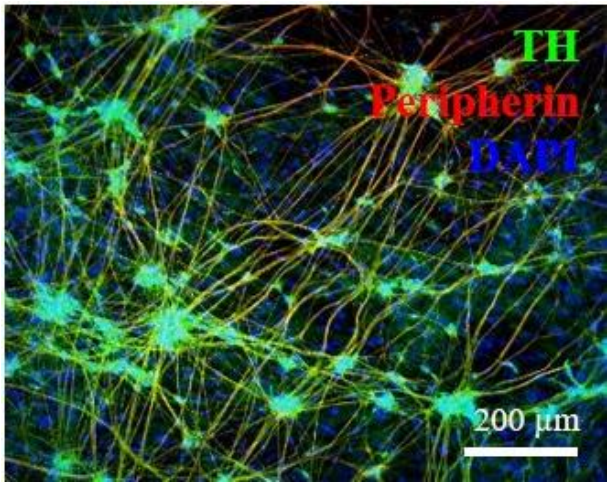


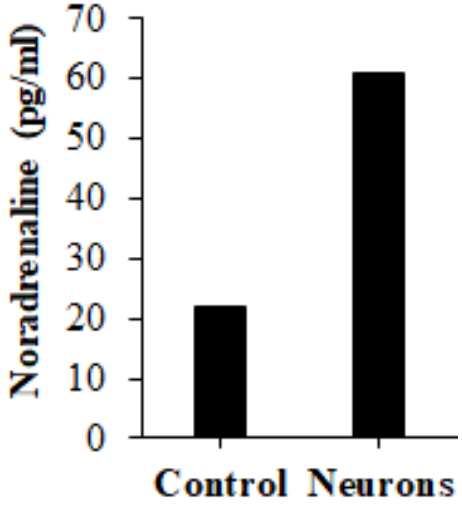
Kong et al. (2019) Acta Biomater, 94:281-294

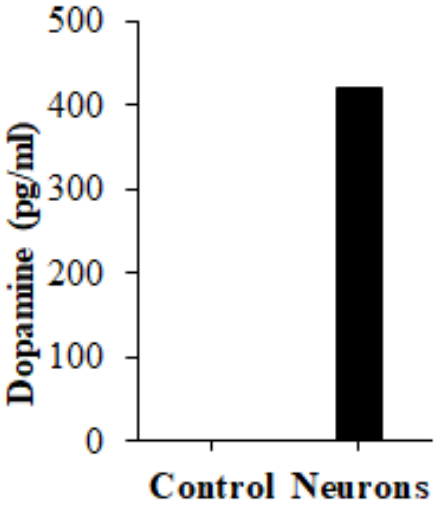
Sympathetic neurons derived from human iPSCs

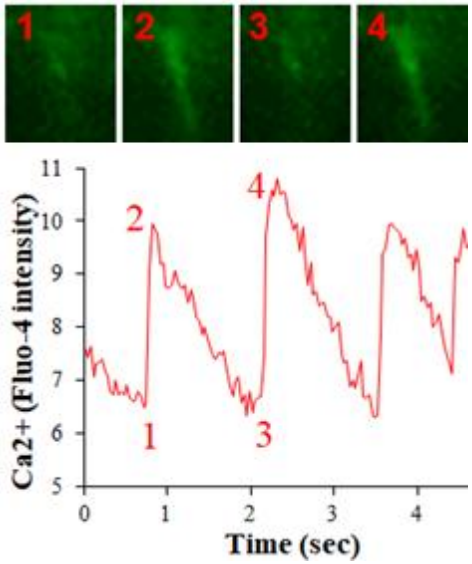


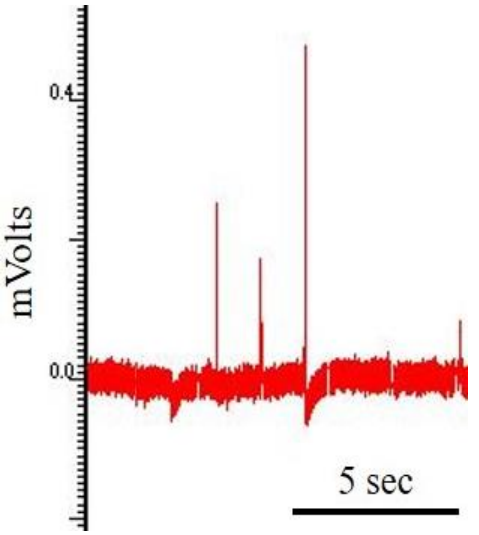






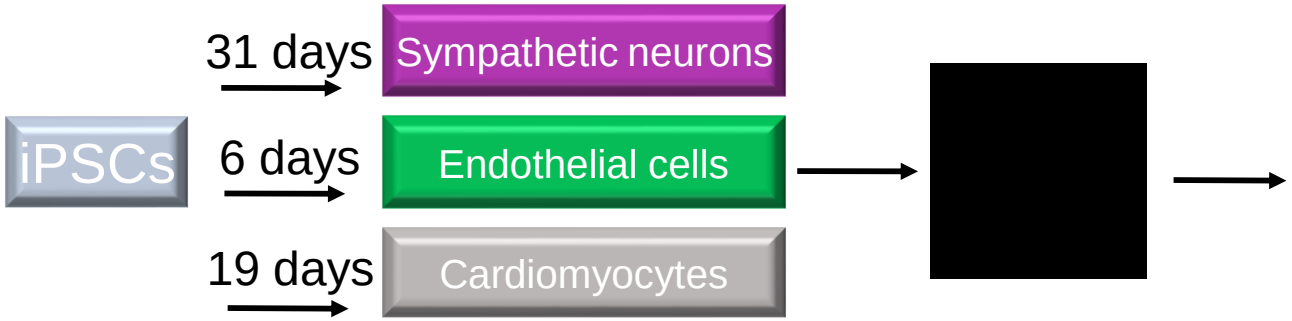


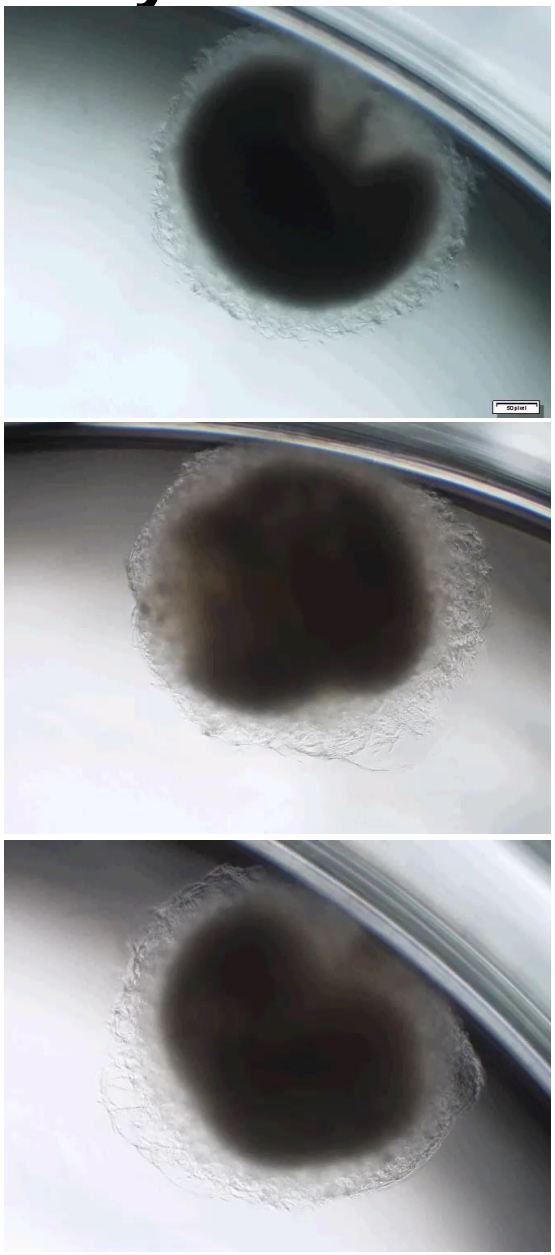




Unpublished data

Engineered human 3D heart organoid with integrated blood vessels and a nervous system

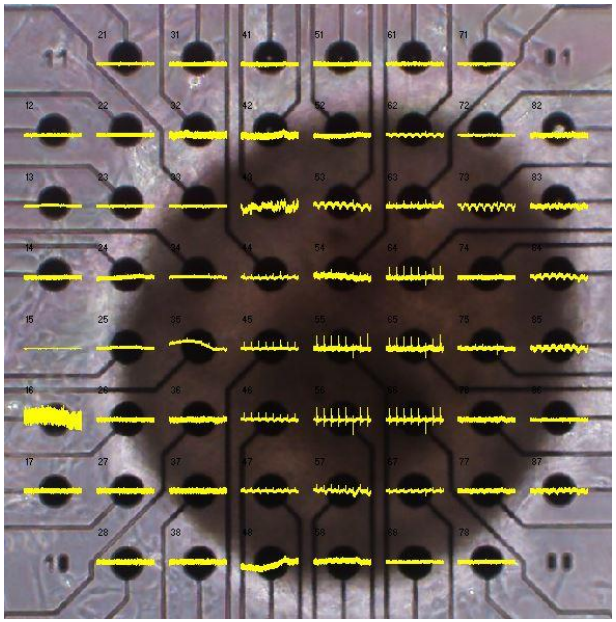


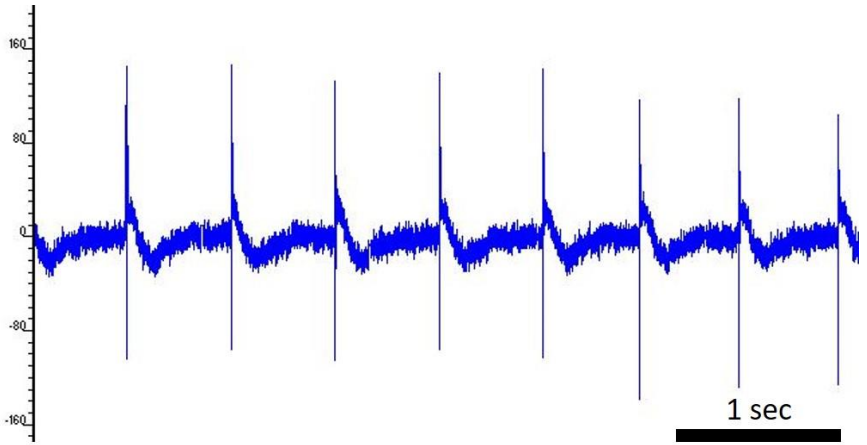


Unpublished data

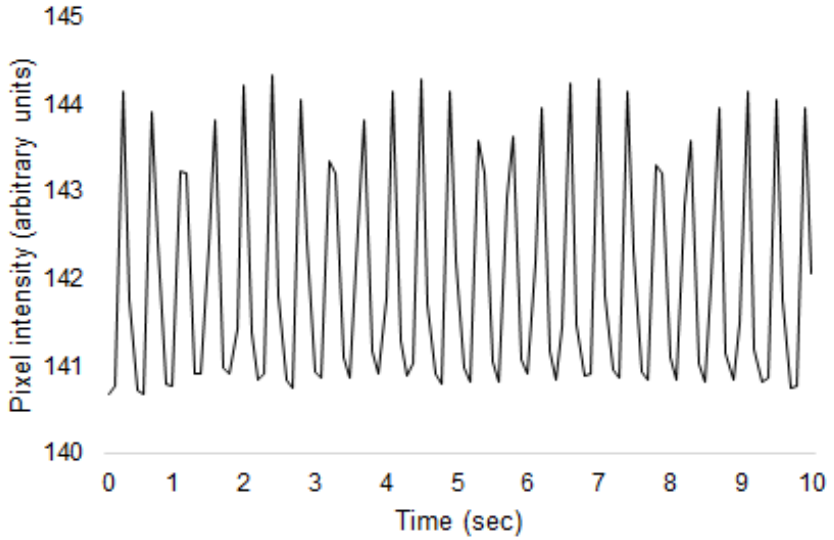
Electrophysiology and contractility of cardiac organoids

Multielectrode array





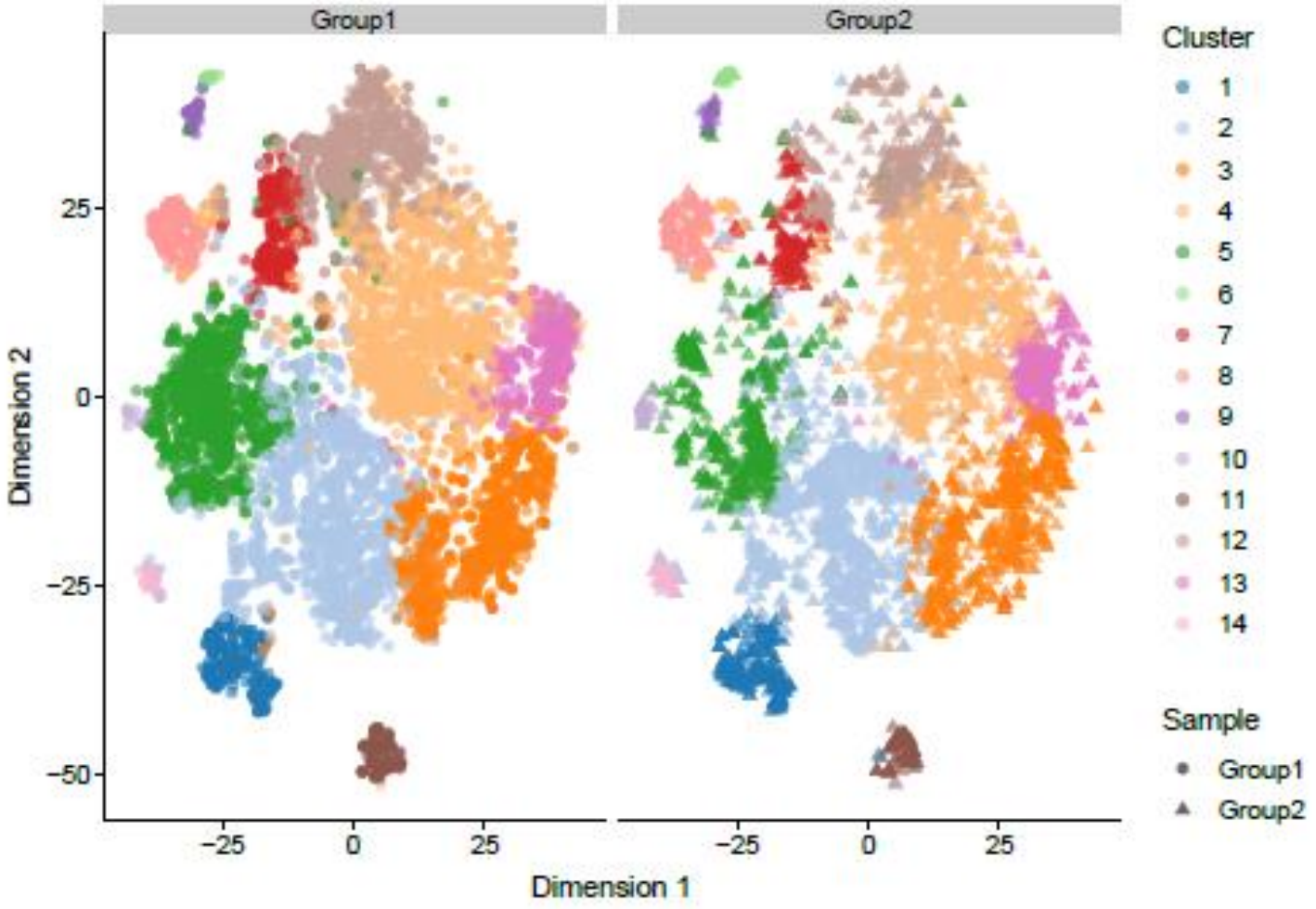
Video microscopy



Beat rate = **168.5 ± 7 bpm** (n=14)

Unpublished data

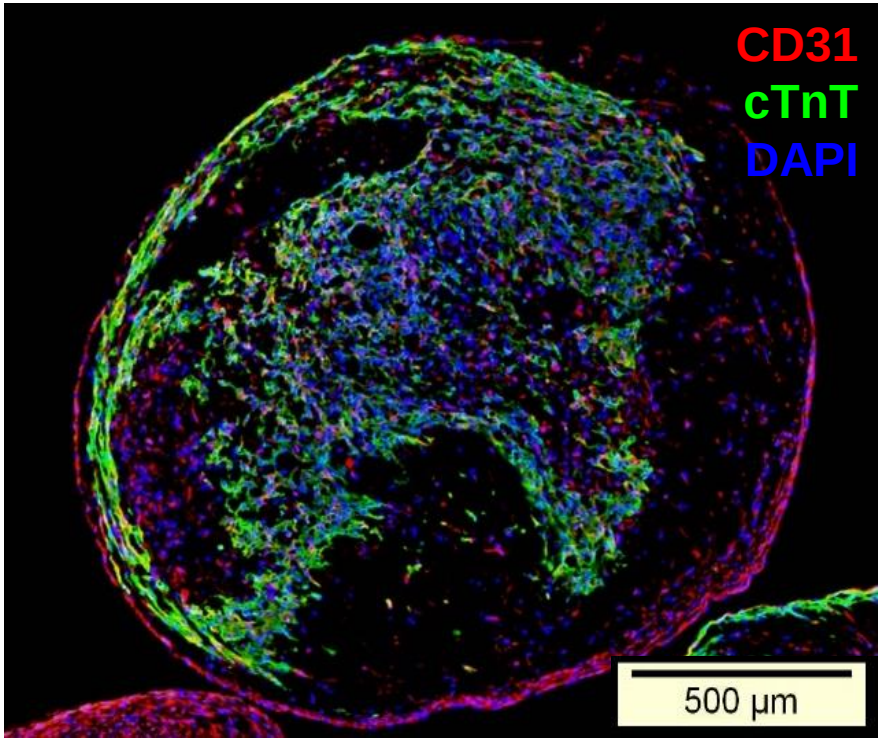
Single cell RNA-seq of cardiac organoids

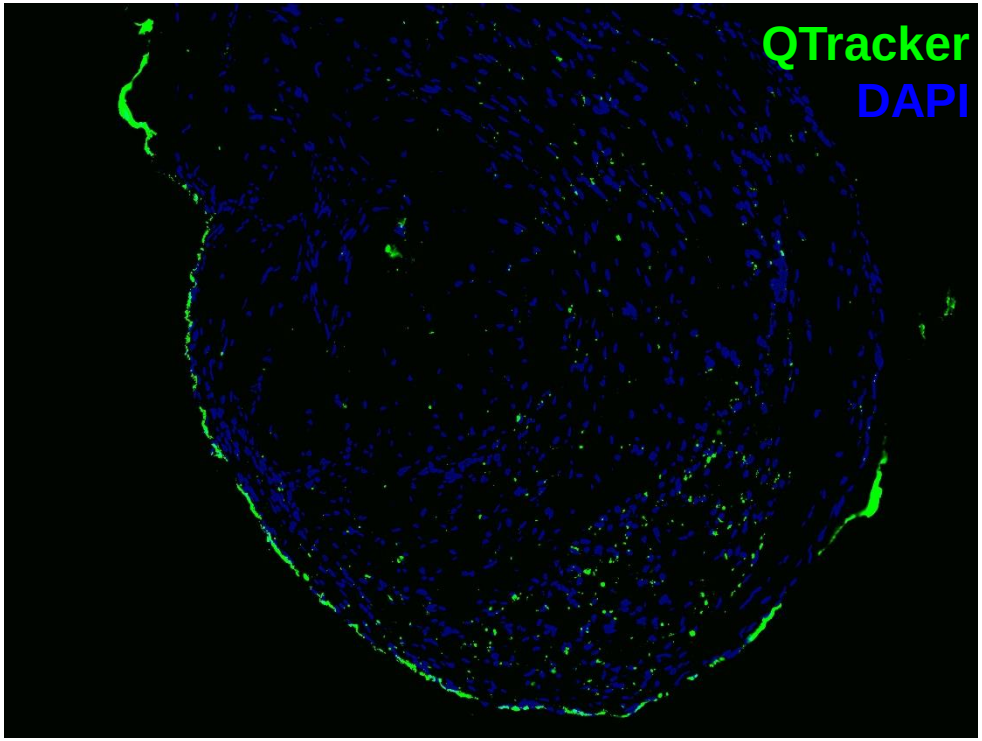


- Identified input cell types
- Highly reproducible

Unpublished data

Cardiac organoids are scalable with optimal diffusion

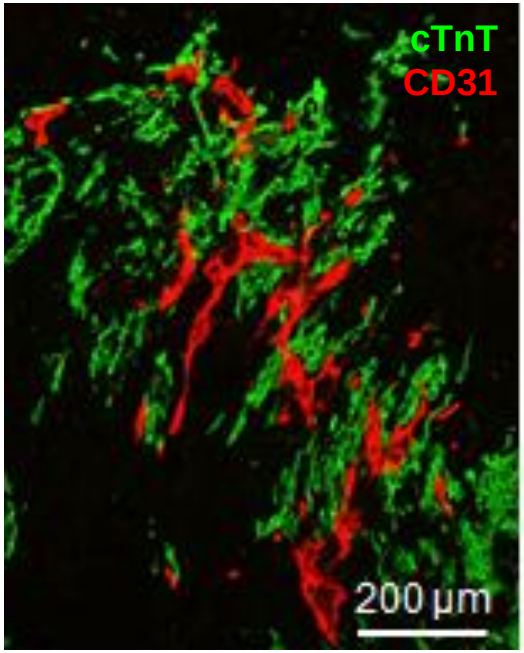


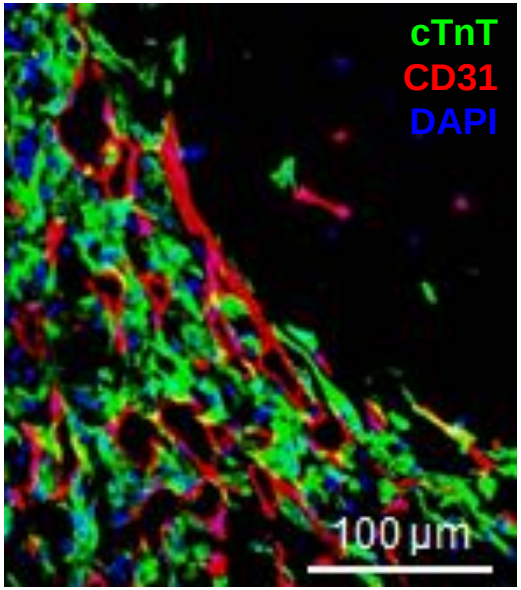


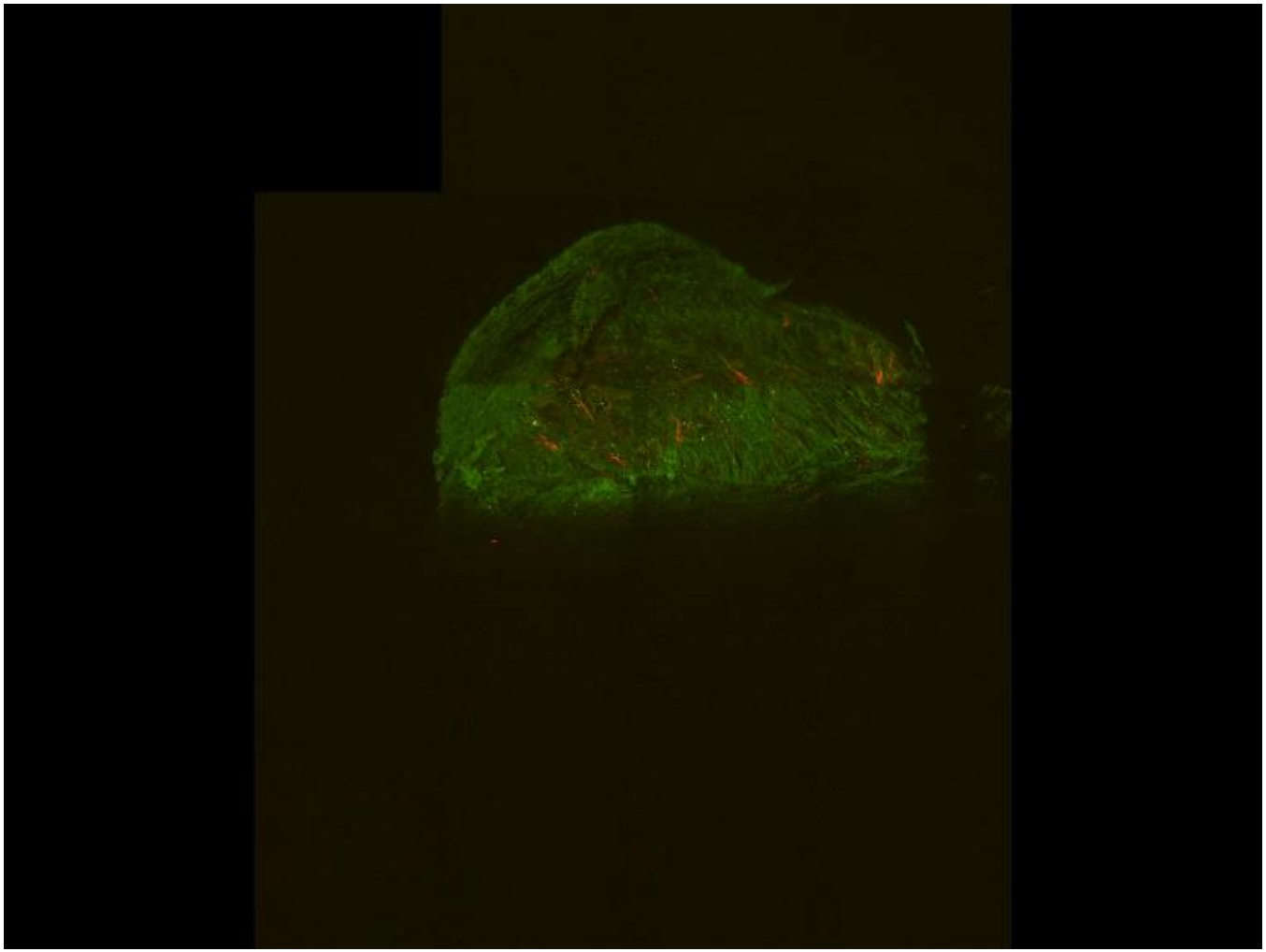
Qtracker = 20 nm in diameter

Unpublished data

Cardiac organoids contain interconnected vessel-like structure with lumens

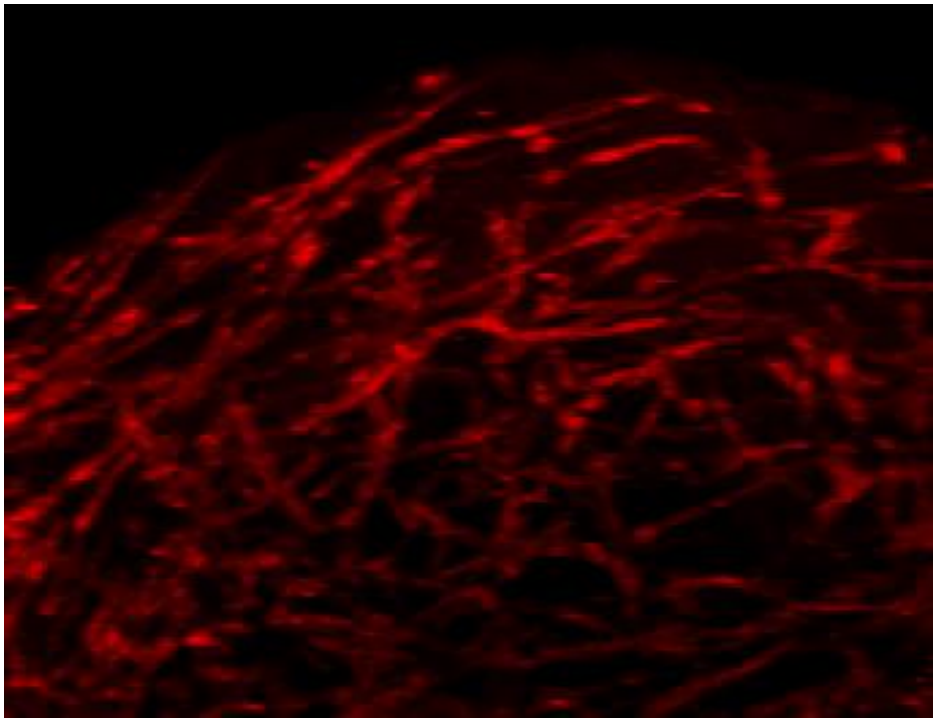




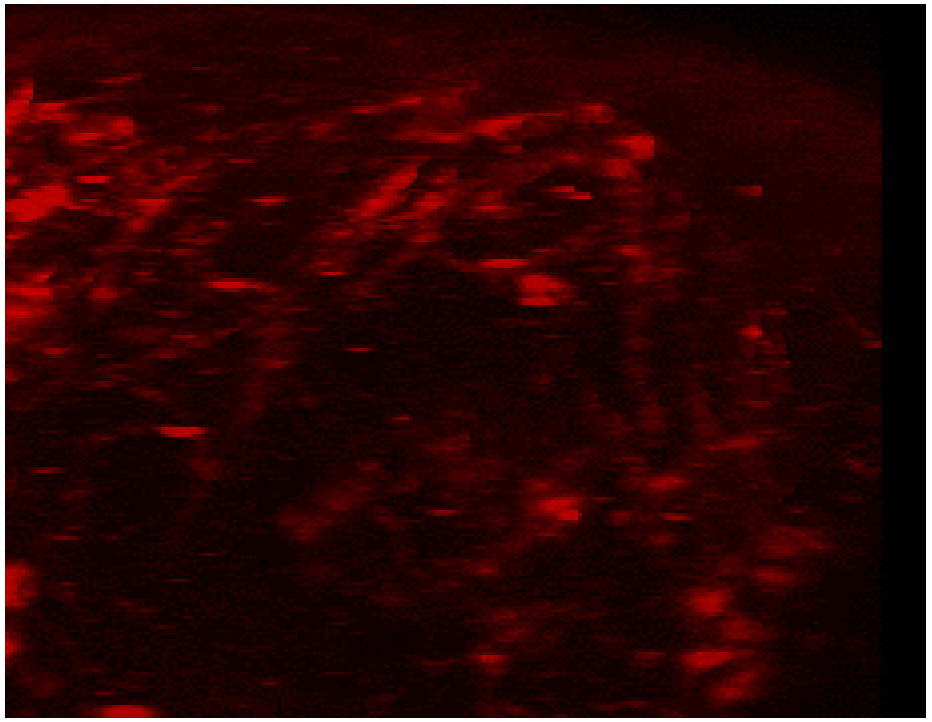


Unpublished data

Cardiac organoids are vascularised and innervated



CD31+ endothelial cells

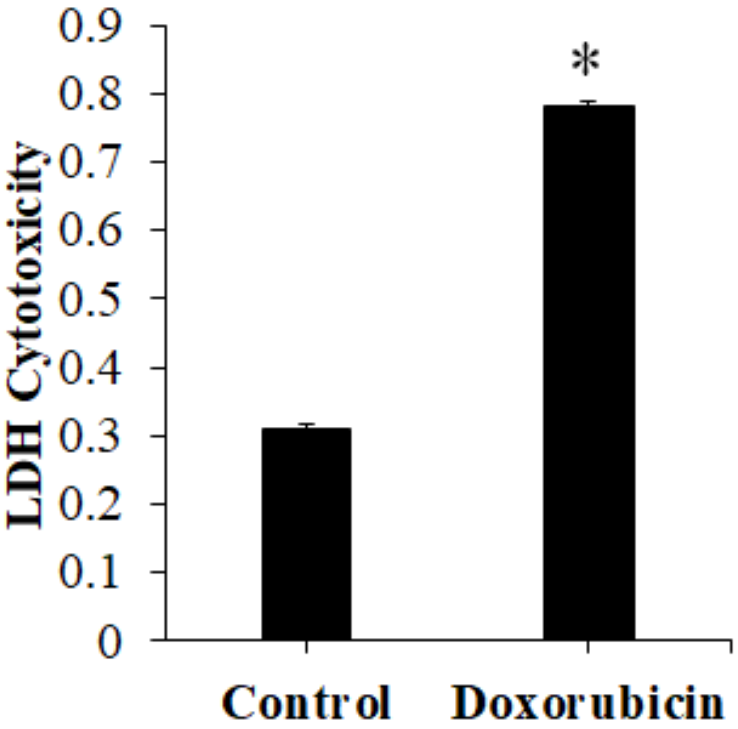


PRPH+ sympathetic neurons

Unpublished data

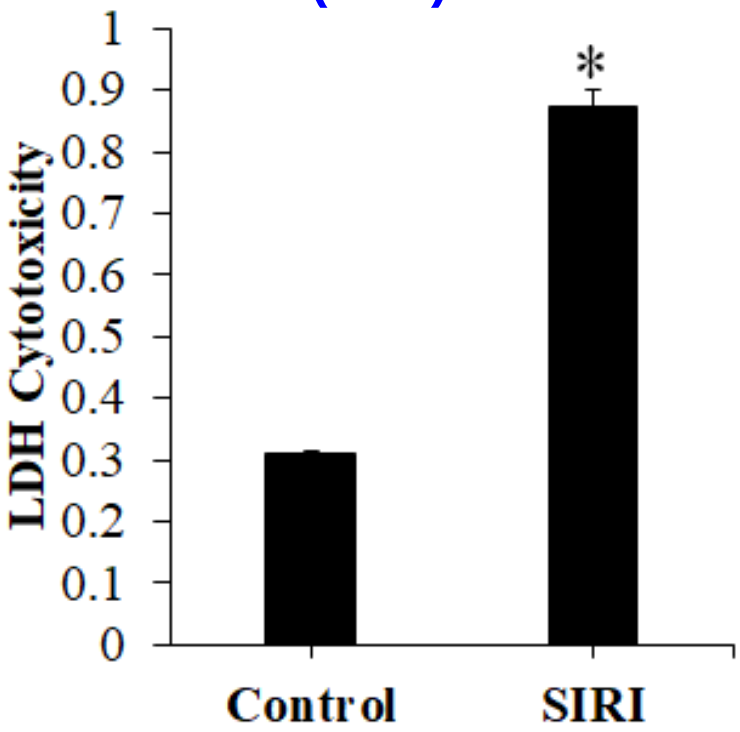
Cardiac organoids can model cardiac injury

Doxorubicin cardiotoxicity



0.5 μM for 24 hours

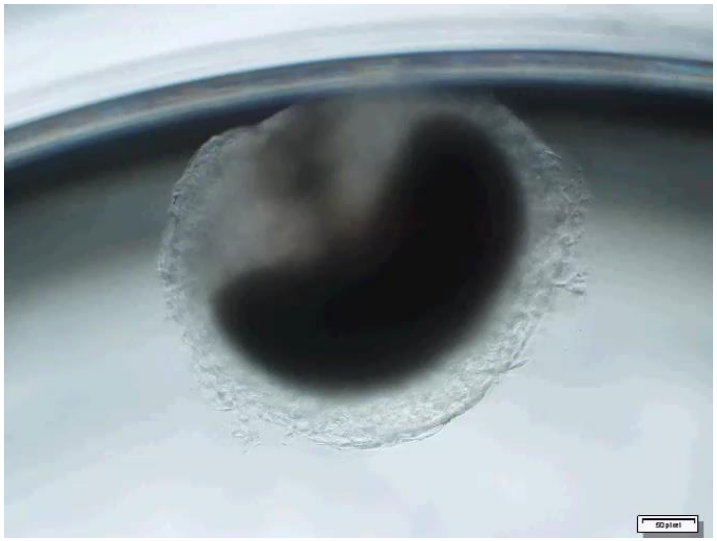
Ischaemia-reperfusion injury (SIRI)

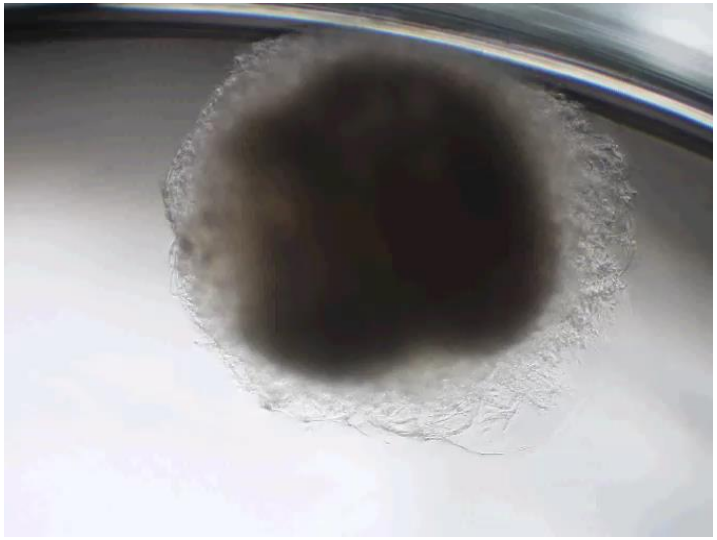


Simulated ischaemia = 2 hours
Simulated reperfusion = 24 hour

Unpublished data

Summary





3D beating heart organoids

- Human-specific
- Vascularised and innerverated
- Reproducible
- Scalable for high-throughput drug screening
- Model cardiac injury
- Future clinical trial in a dish

Acknowledgement

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