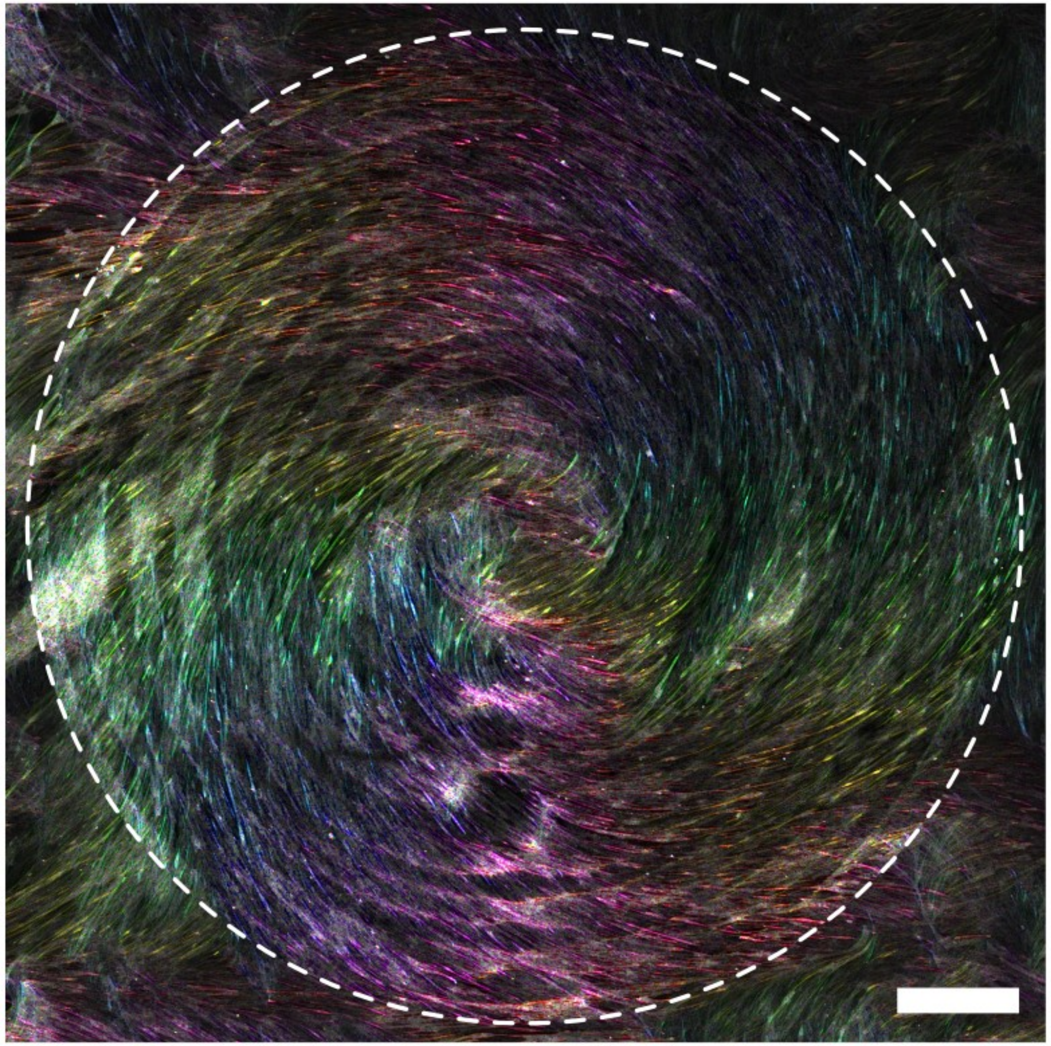
DTU

Instrumented and 3D printed human tissue models

Outline

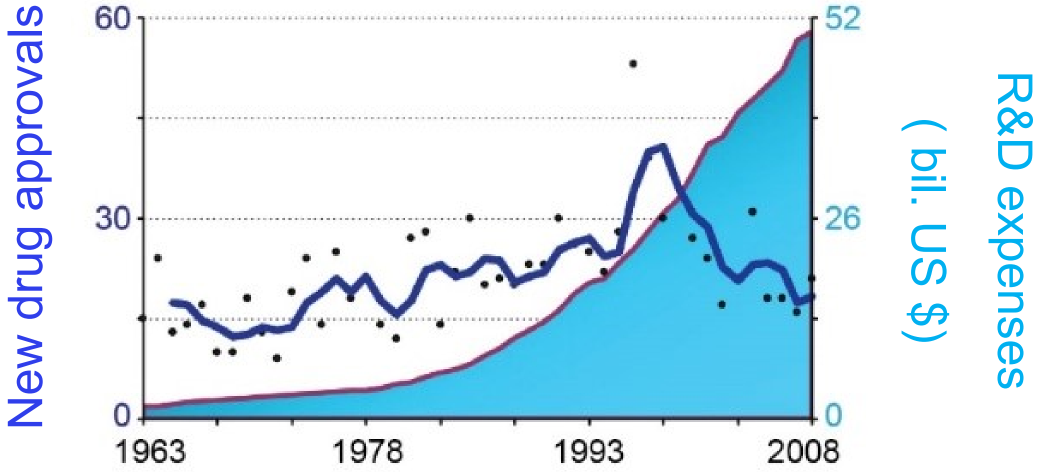
- Engineering human tissue models
- Instrumented cardiac tissue models
  - Multi-material 3D printing
  - Application examples
- Cell-instructive biomaterials
- Embedded Bio-printing
- Summary & Outlook



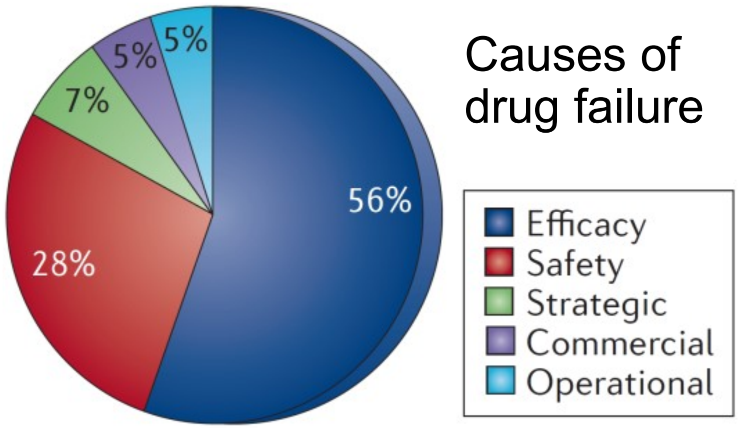
Adapted from SD Cakal et al *biomedical materials 2022*

Engineering human tissue models

Old problems



Kaitlin KI *et al Clin. Pharm. & Therapeutics* 2010



Arrowsmith J, Miller P.

Nature Reviews Drug Discovery. *2013*

The traditional drug development pipeline is deeply flawed

New solutions?
Human iPSC-based models

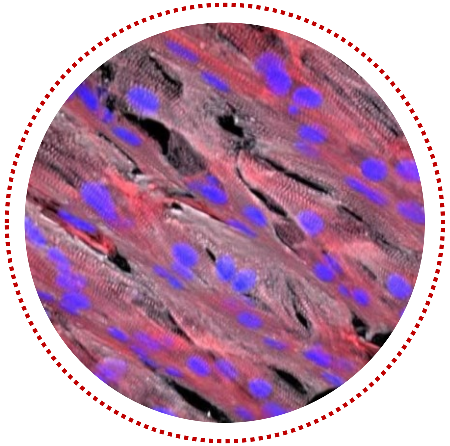
Organoids, *organs-on-chips* & *3D bio-printing*, share

– *Common promises:*

- More predictive preclinical studies
- Replacement of animal models
- Patient models for personalized medicine
- In-depth disease modelling

– Common problems:

- Low maturity
- Lack of complexity (architecture, cell types, biomechanics, biochemical environment)
- Insufficient validation, reproducibility
- Lack of physiologically relevant readouts



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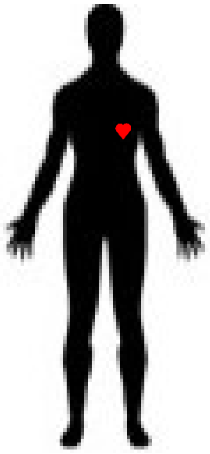
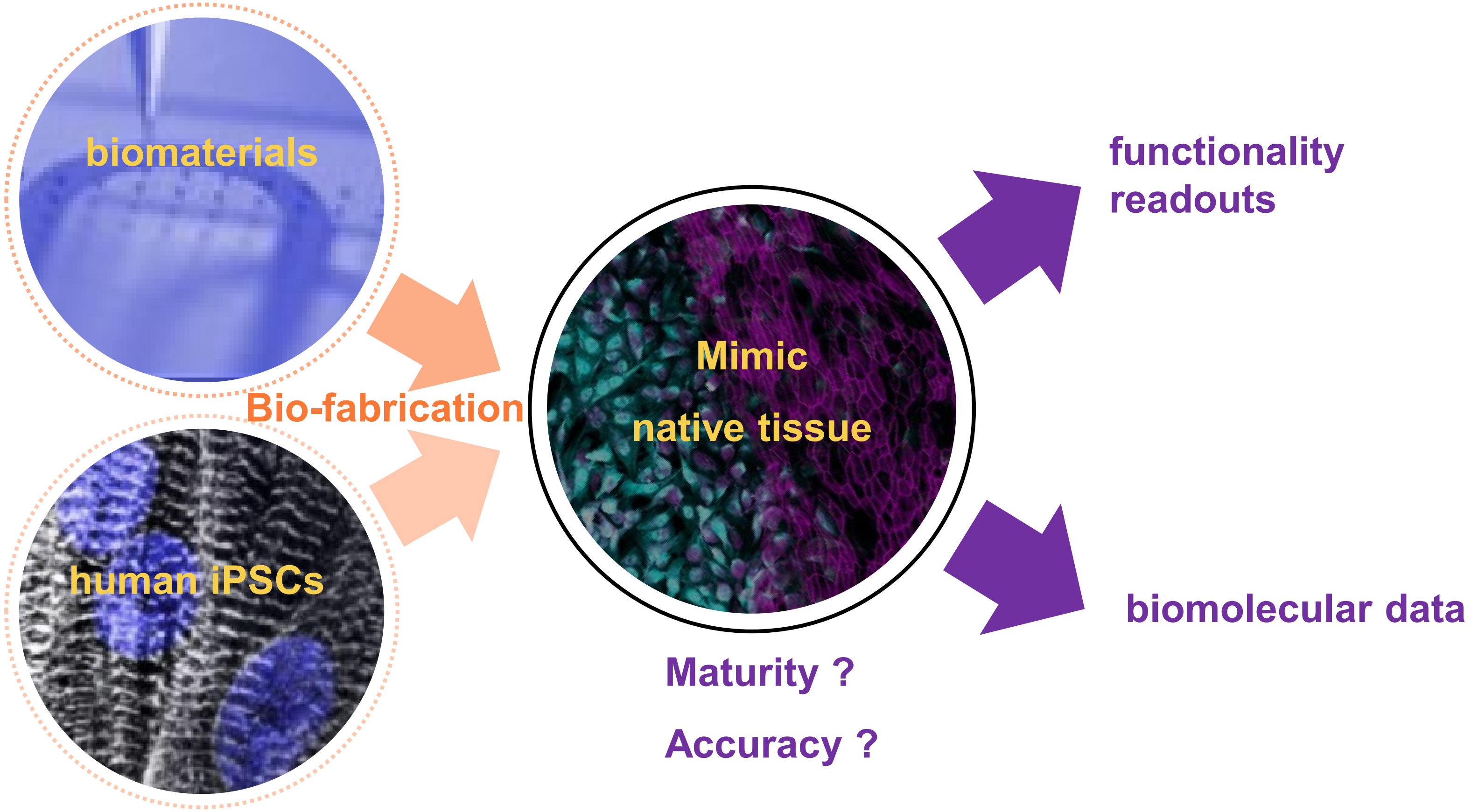


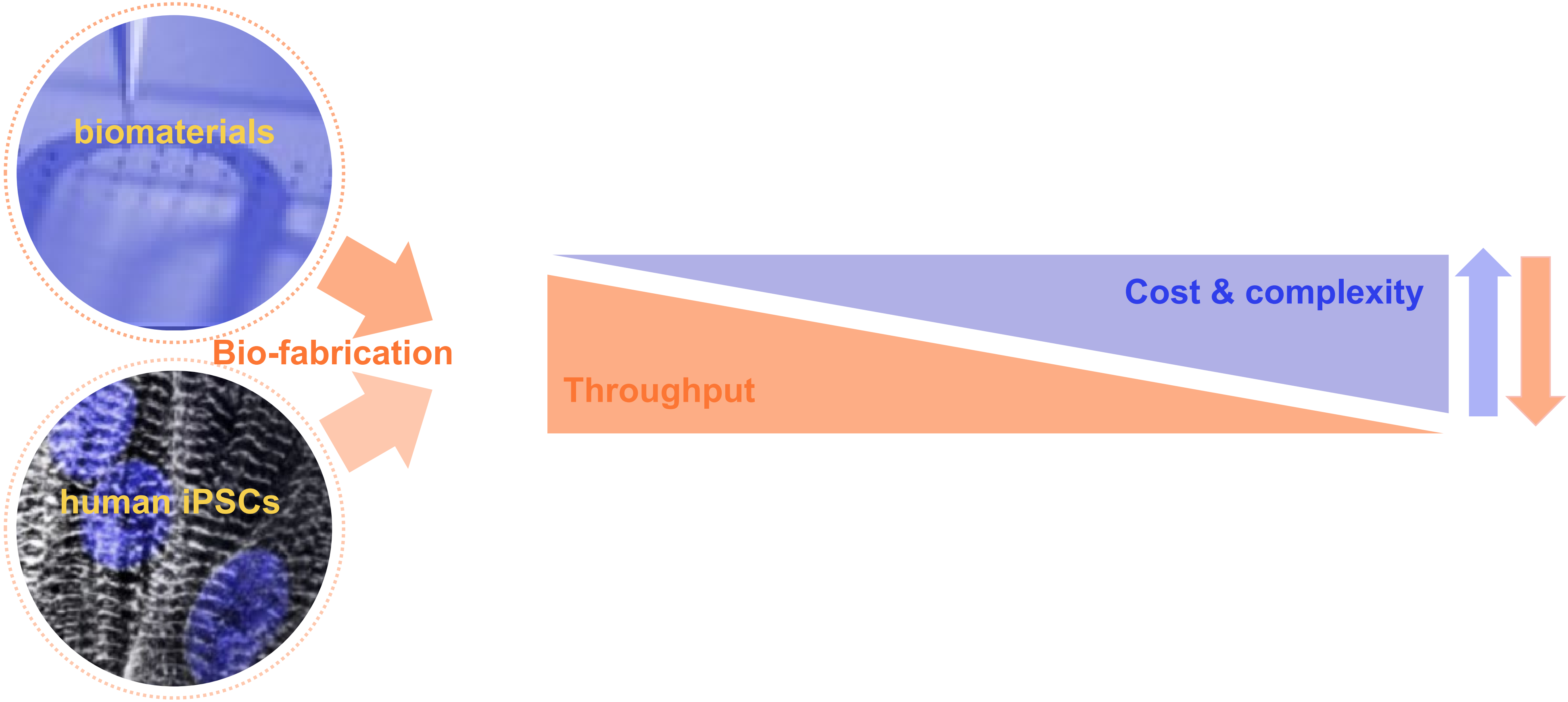
Human stem cell-derived tissues

Lind *et al* Lab on a Chip 2017

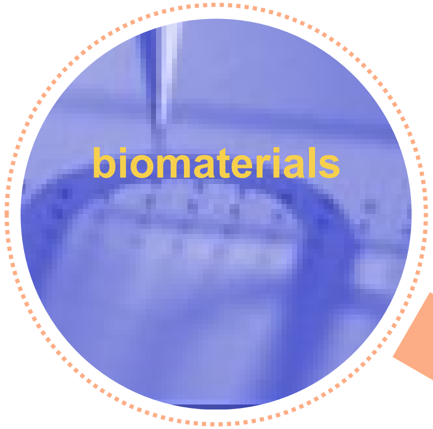
Engineering challenges



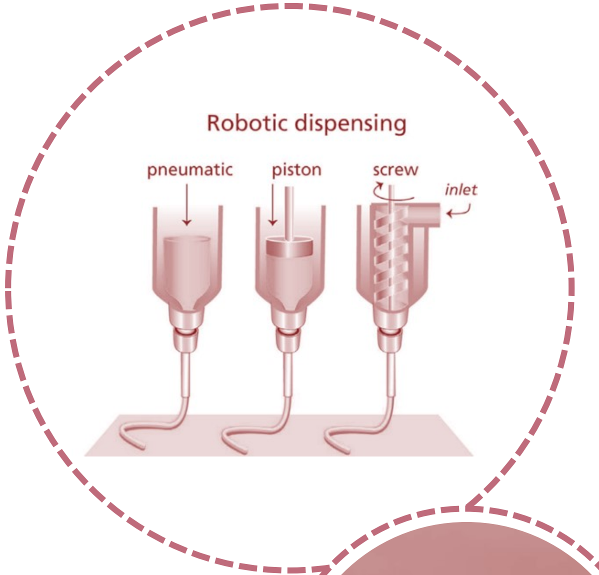
Engineering challenges



Engineering challenges



Multi-material 3D printing

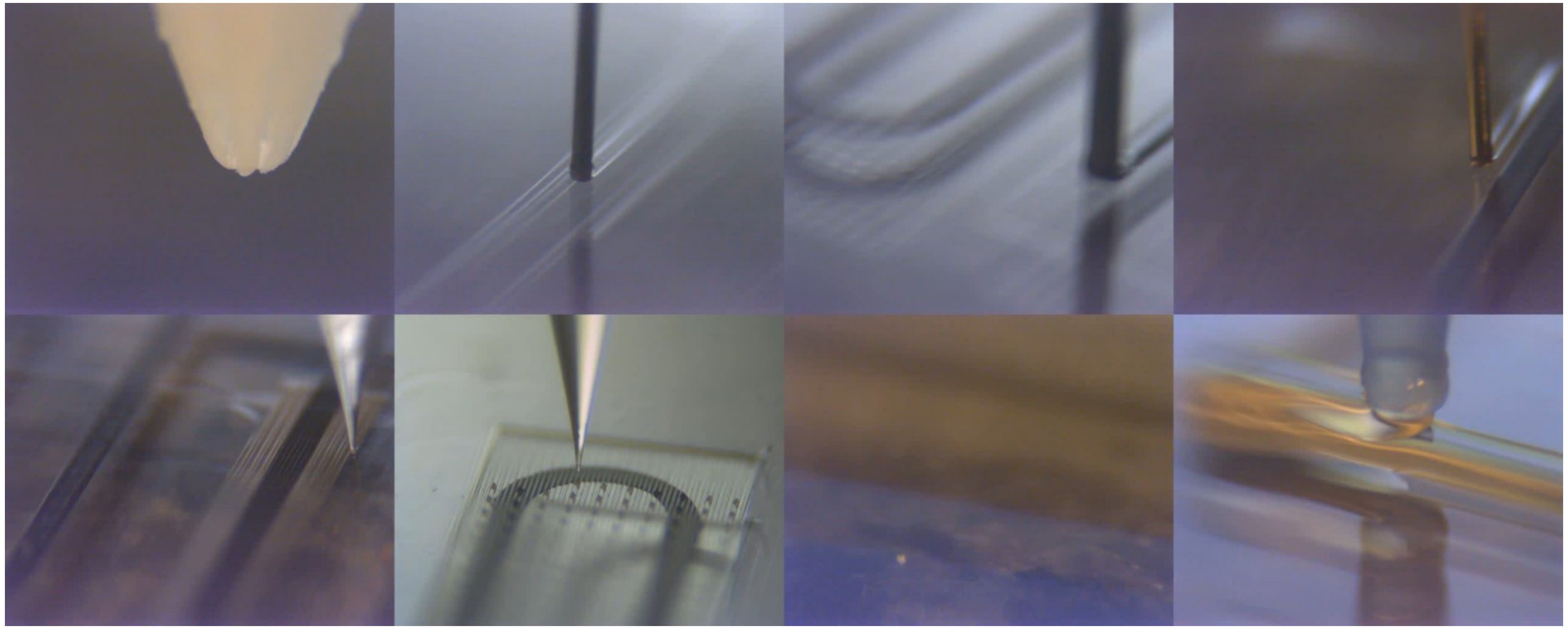


→ **Path to automation**

→ **Customization across complexity space?**

Instrumented human cardiac tissue models

Biofabrication using Multi-material 3D printing



Cardiac Muscle

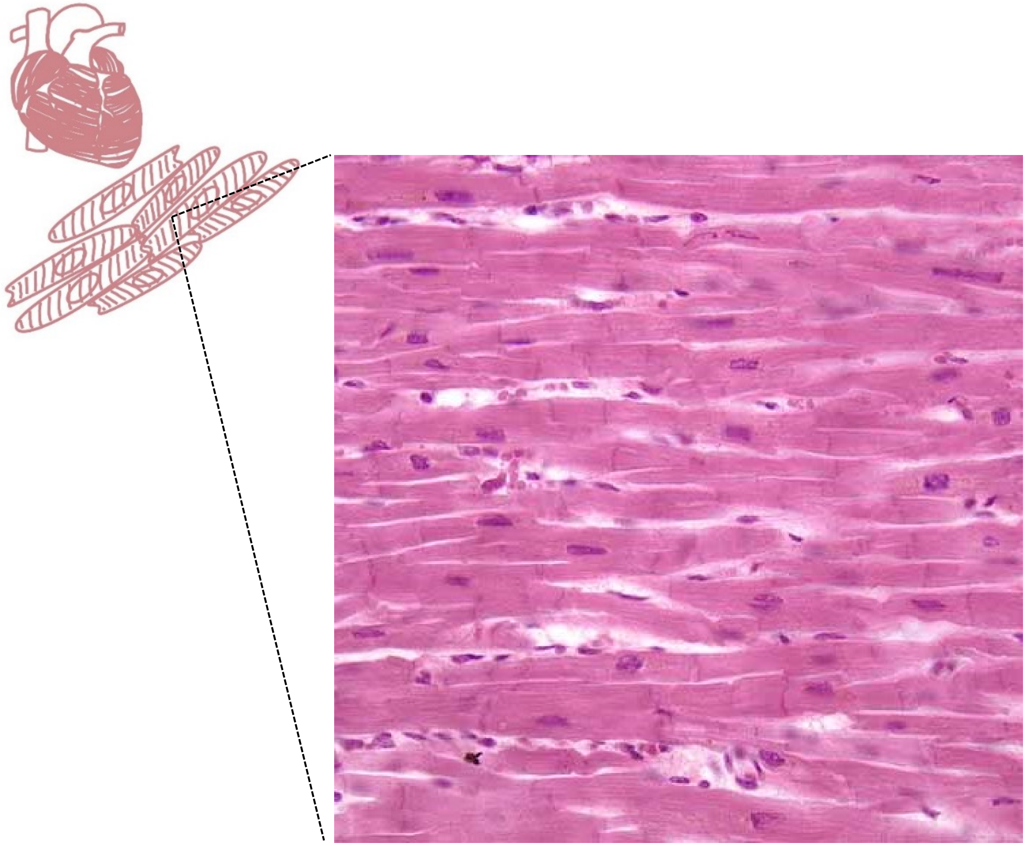
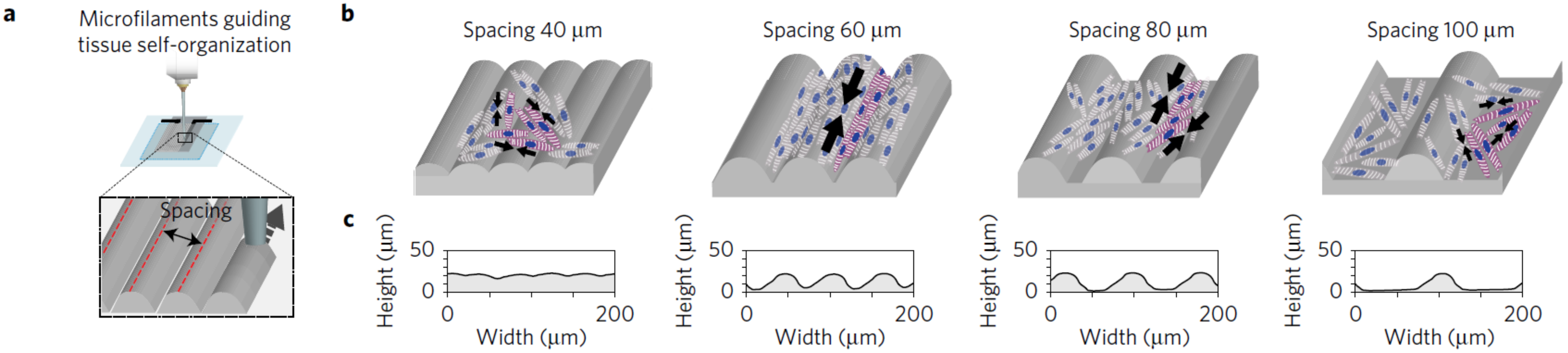


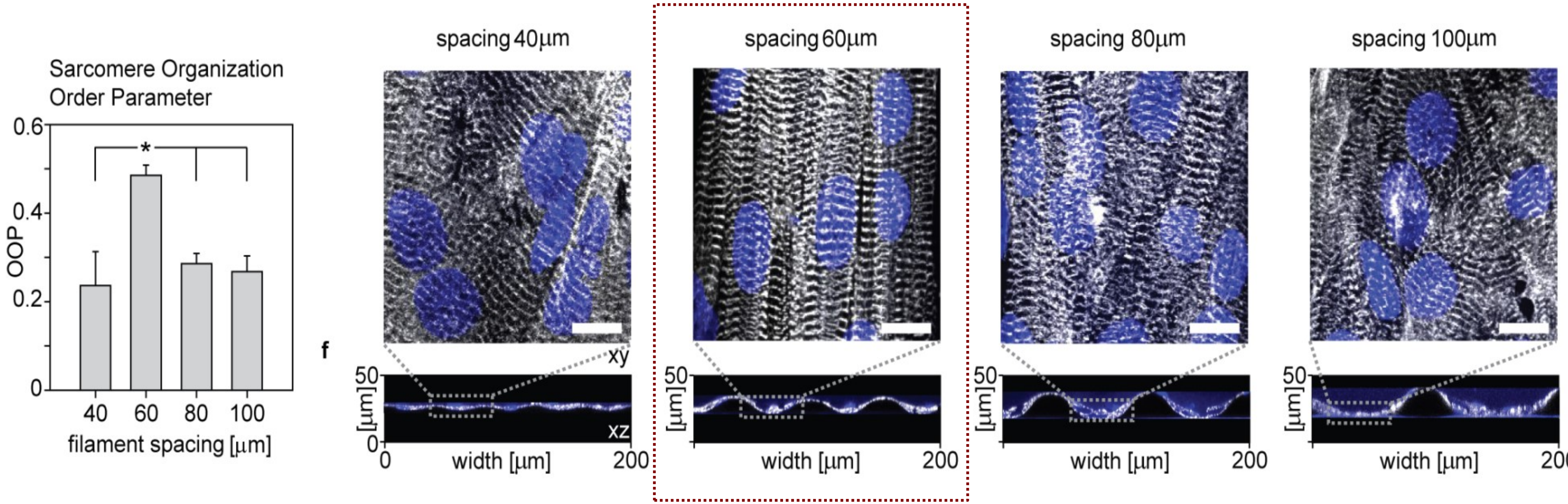
Image courtesy of google

- anisotropic and laminar
- myocyte sheets ~4 cells thick
- highly vascularized

Printed Microstructures Guide Muscle Architecture

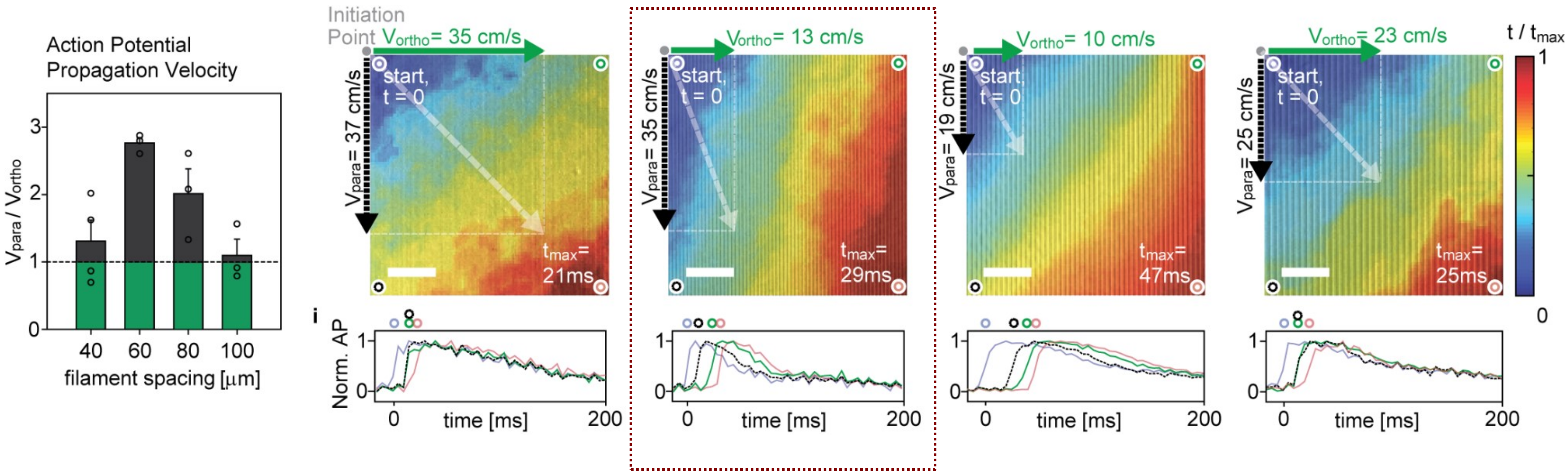


Mimicking native structure



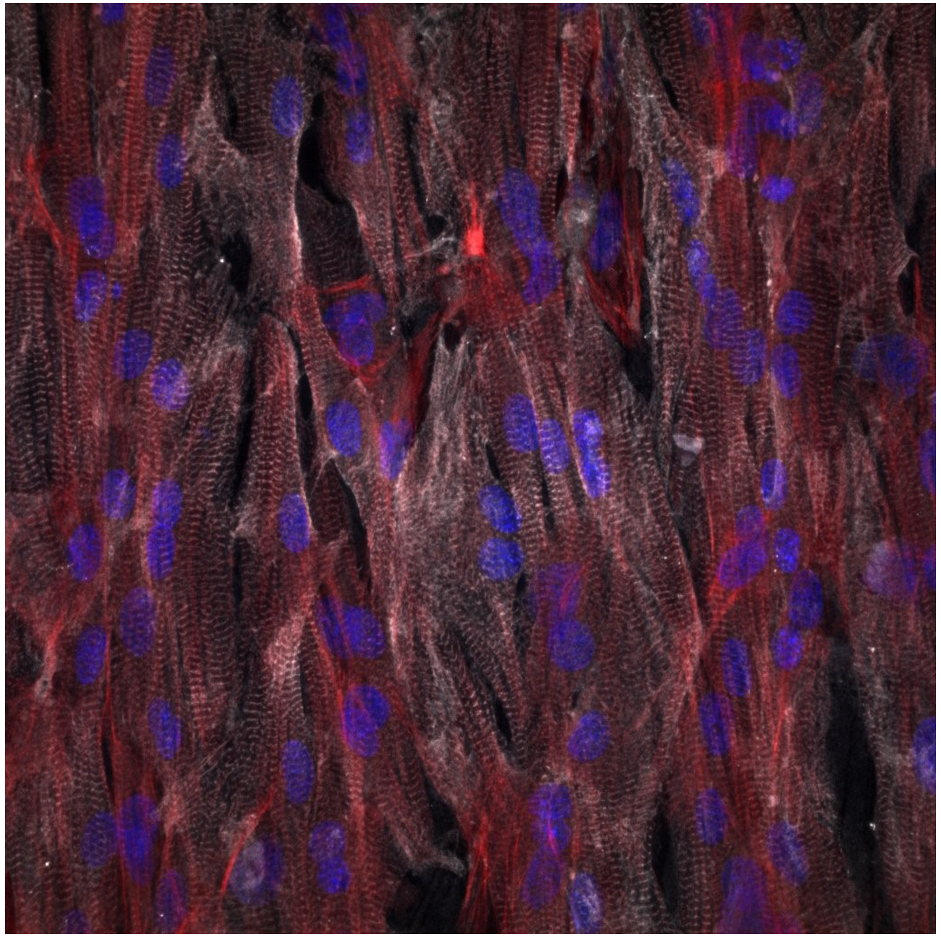
OOP of 0.5 indicative of highly aligned sarcomeres

Mimicking native electrophysiology

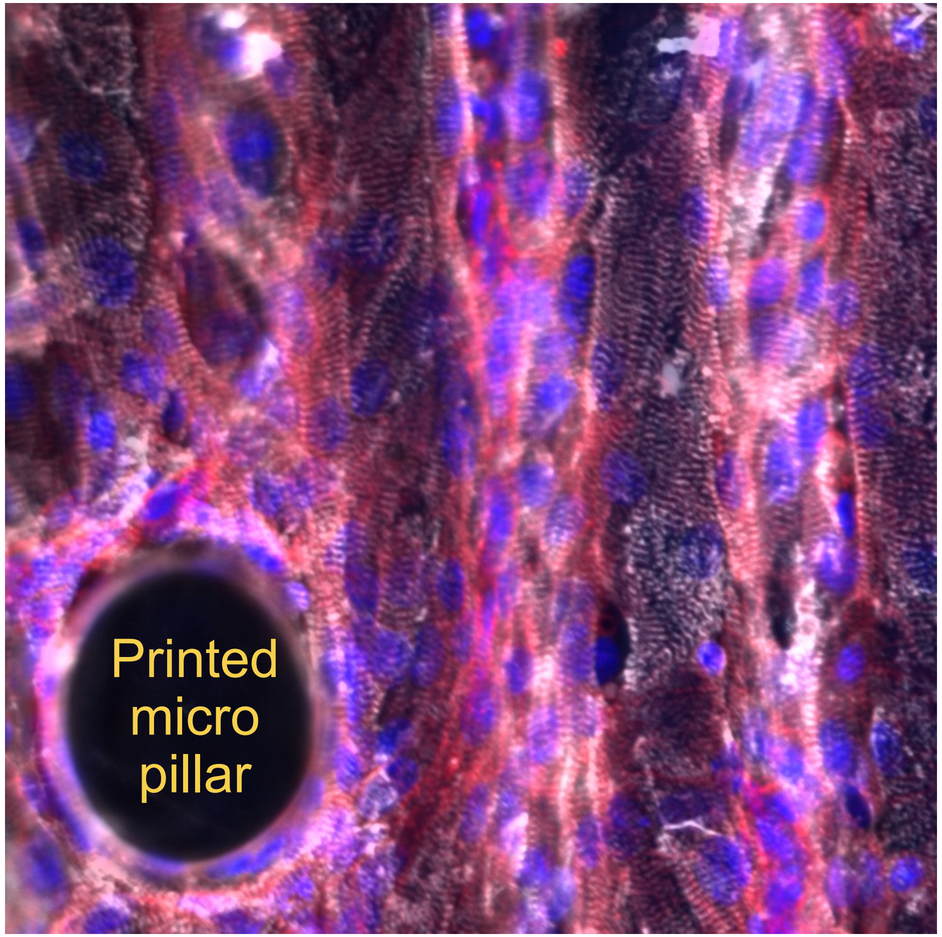


AP propagation speed ratio 2.1 matches native ventricular rat tissue sheets

Adjustable tissue thickness

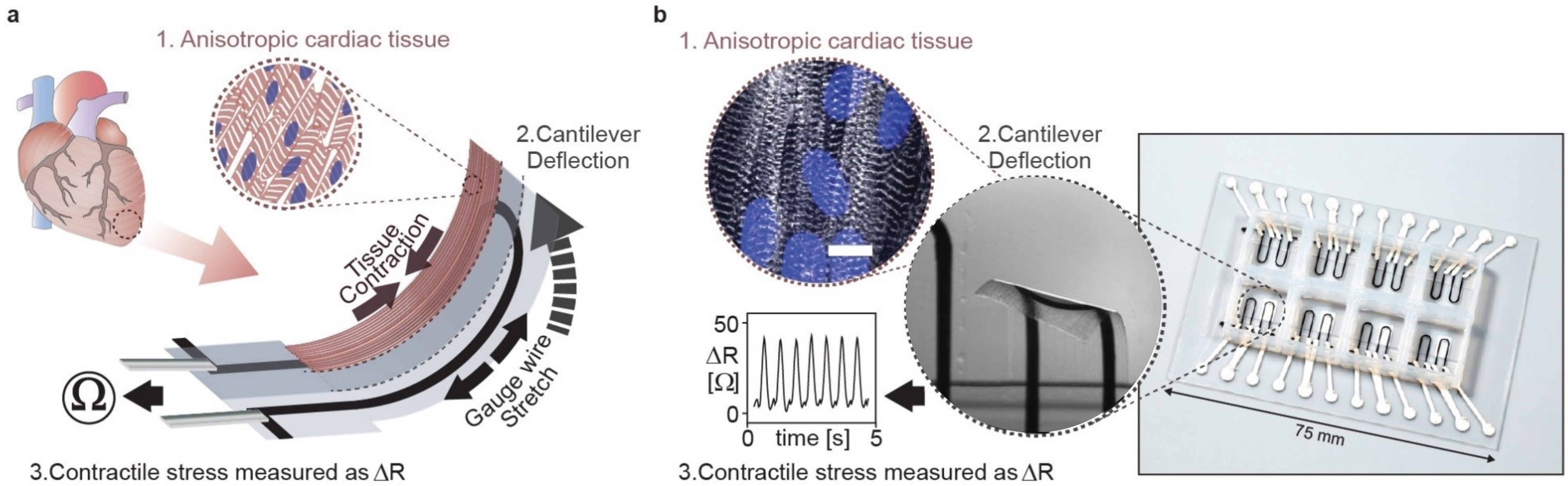


Monolayer CM tissue



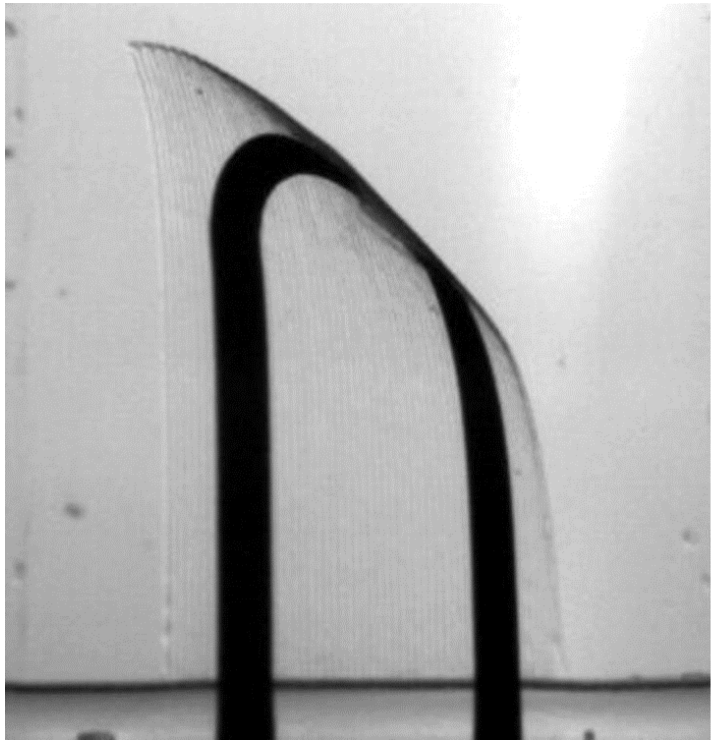
4-layer CM tissue (pillar anchor)

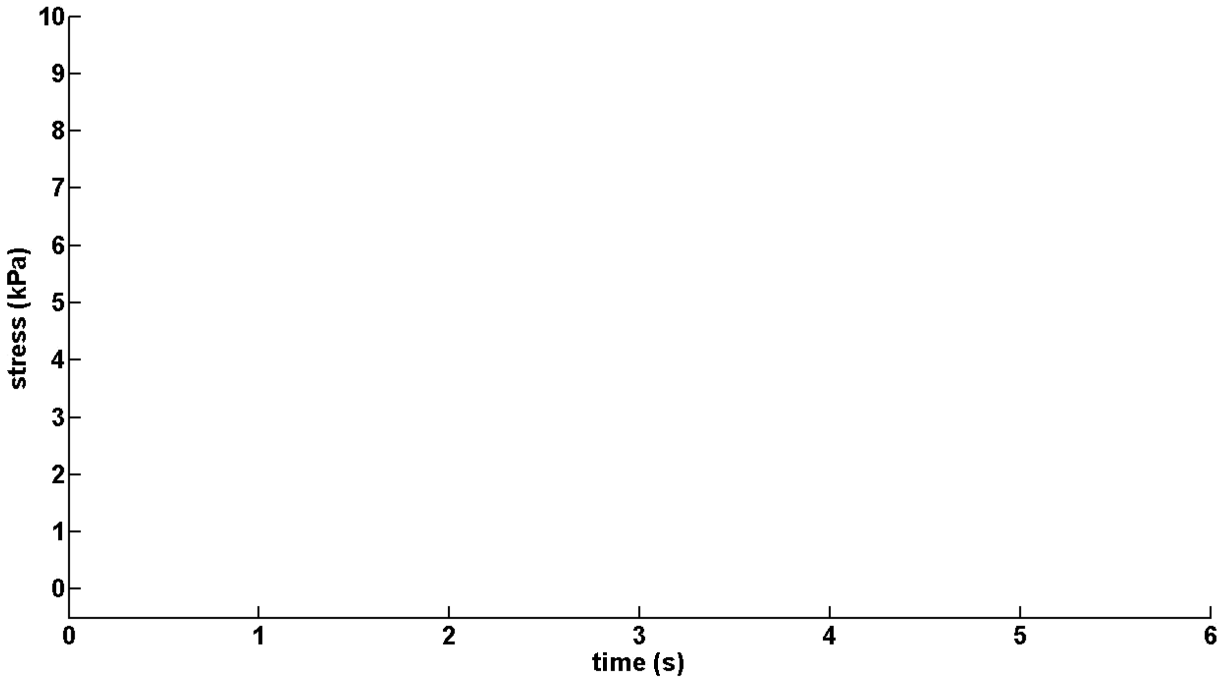
3D printed instrumented Heart on a Chip



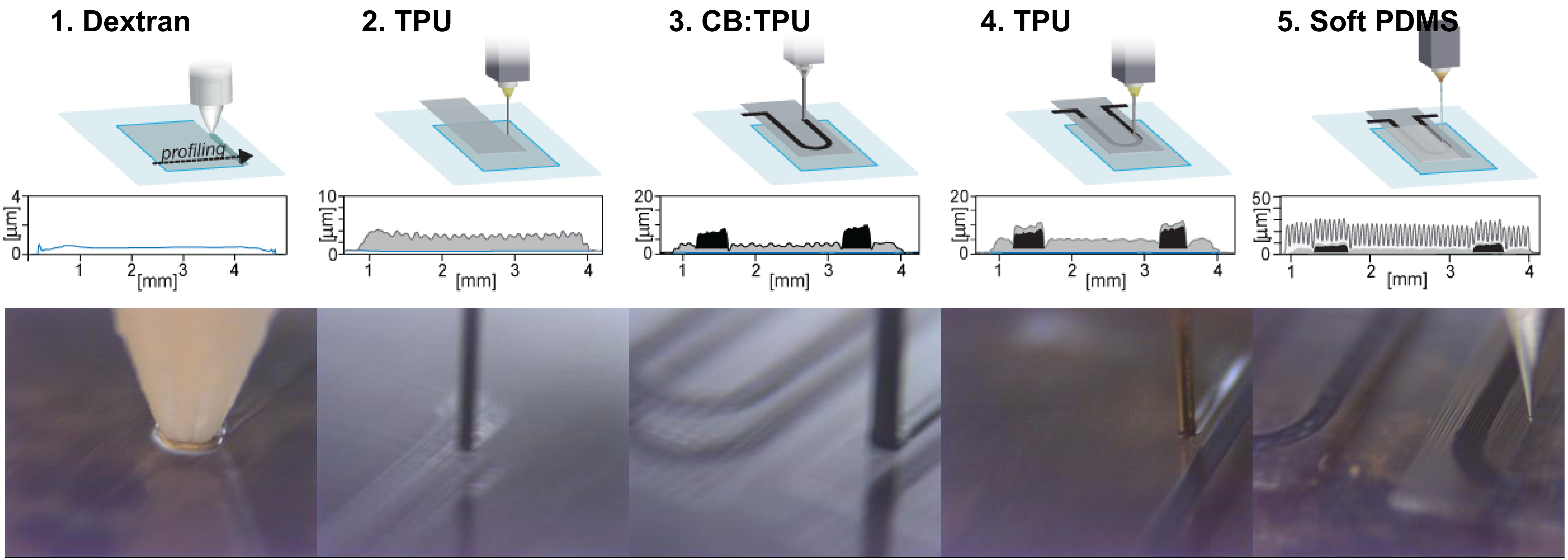
Adapted from JU Lind *Nature Materials* 2017

3D printed instrumented Heart on a Chip



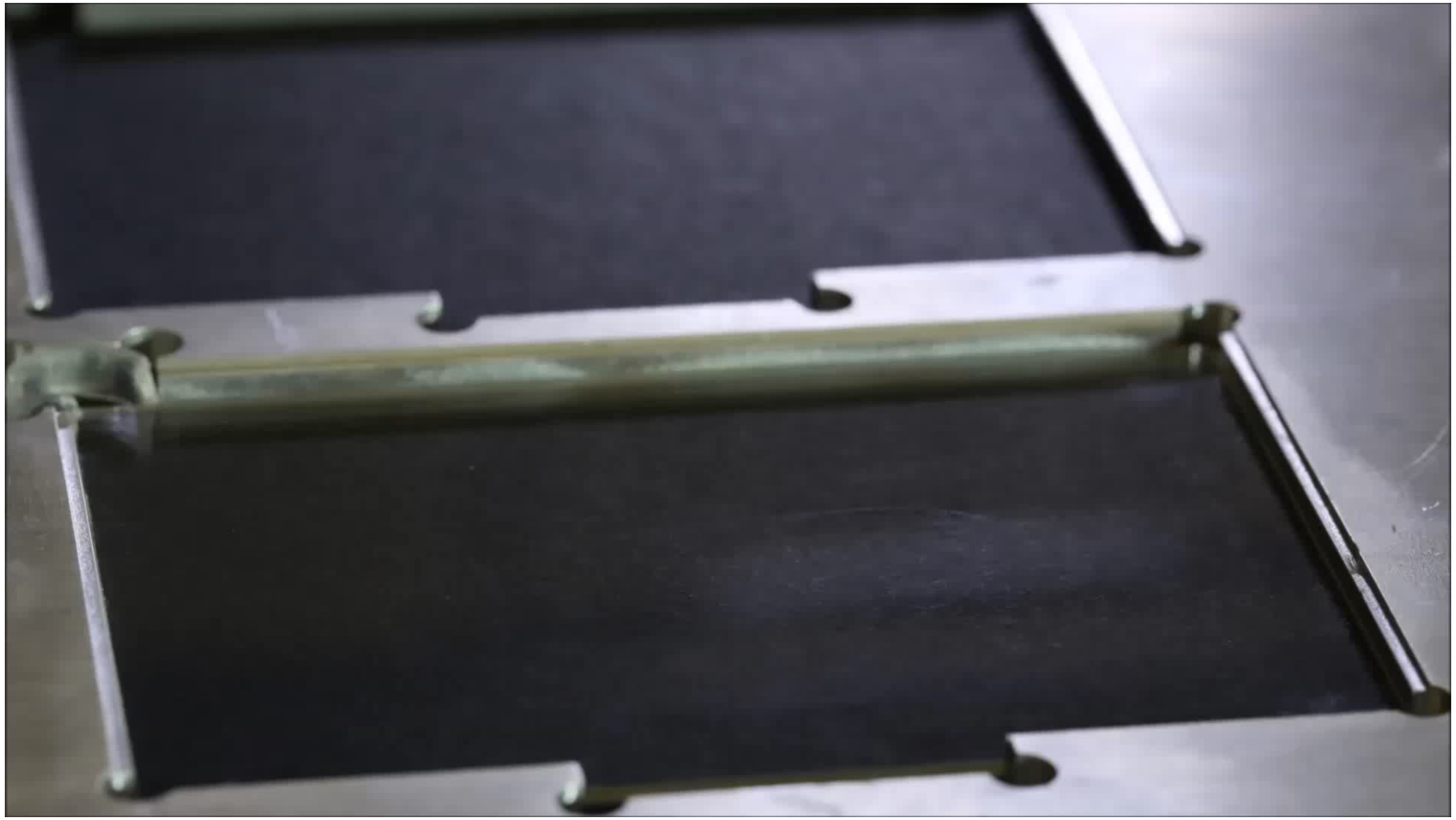


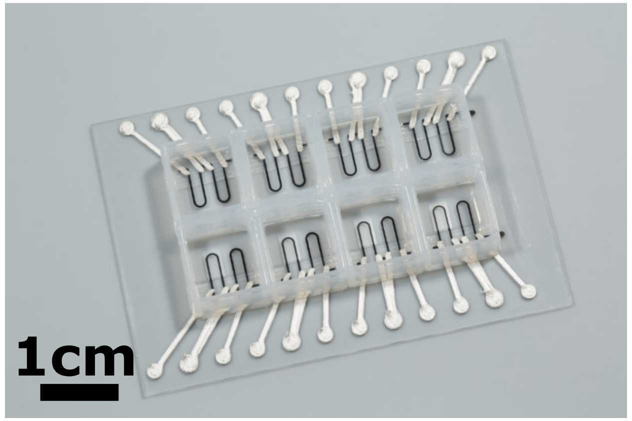
Cantilever layered prints

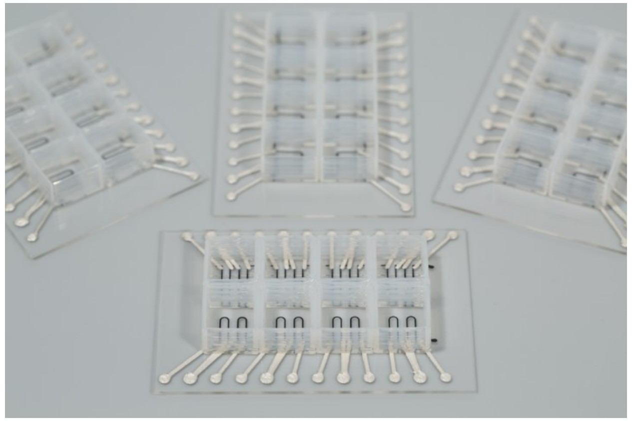


Adapted from JU Lind et al *Nature Materials* 2017

Multimaterial printing of Heart Chips



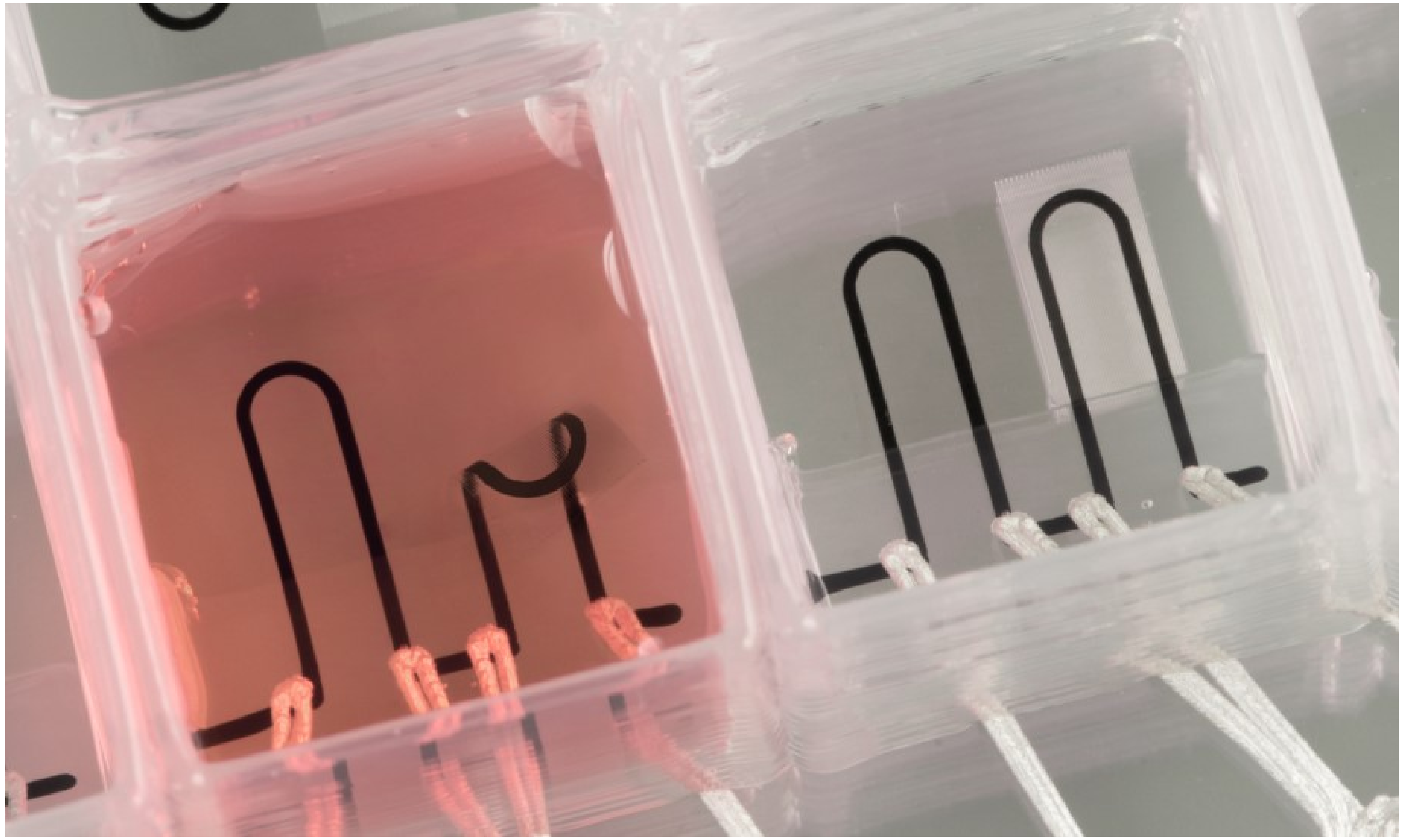




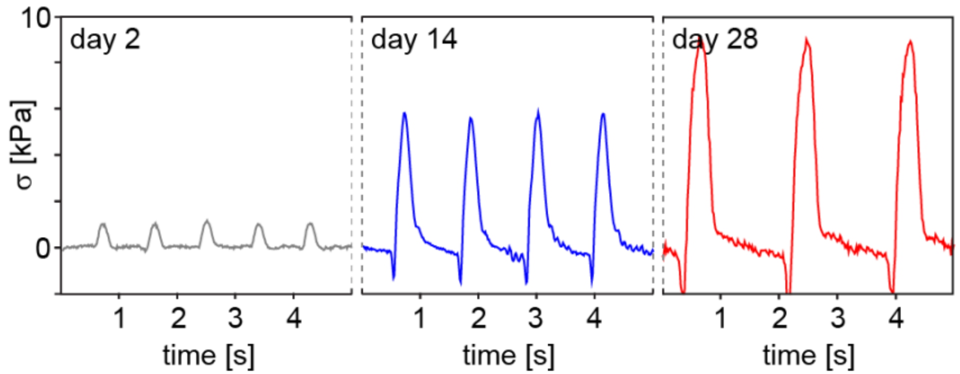
160x

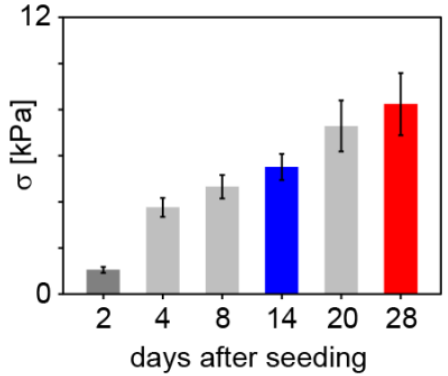
Adapted from JU Lind et al *Nature Materials* 2017

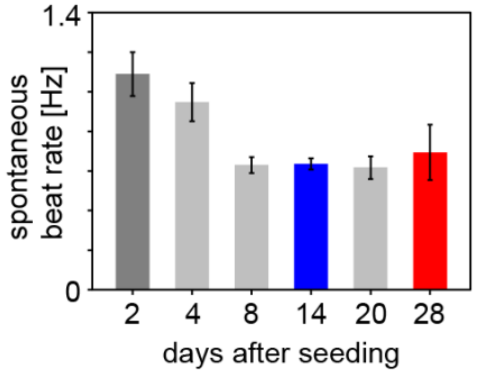
Instrumented heart chip applications

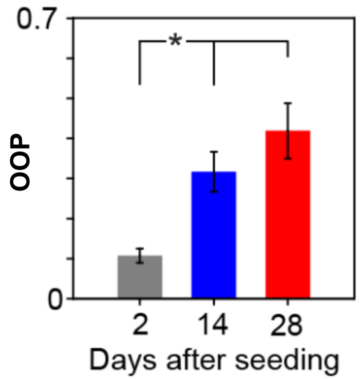


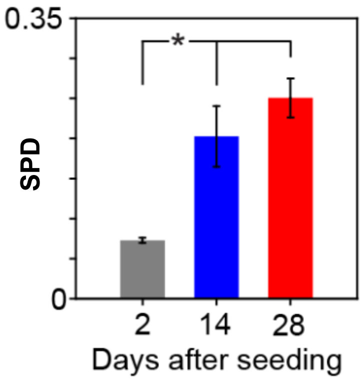
Long term maturation of Human iPS-CM Tissue

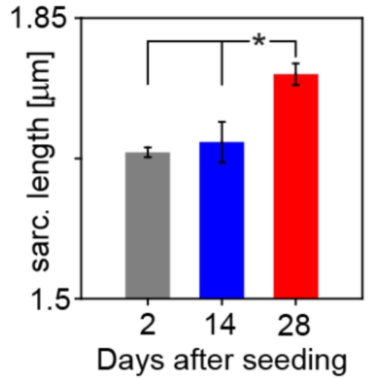




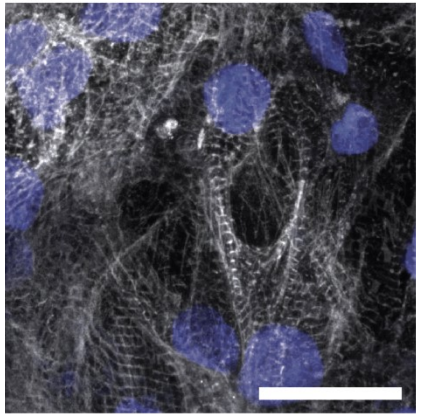






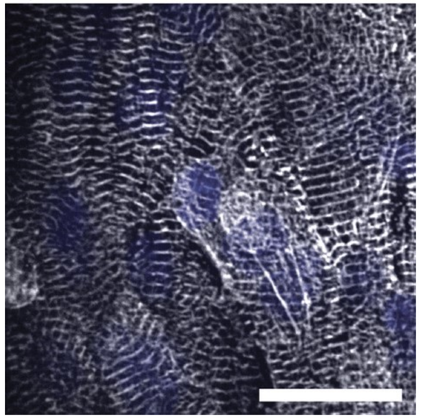


Day 2



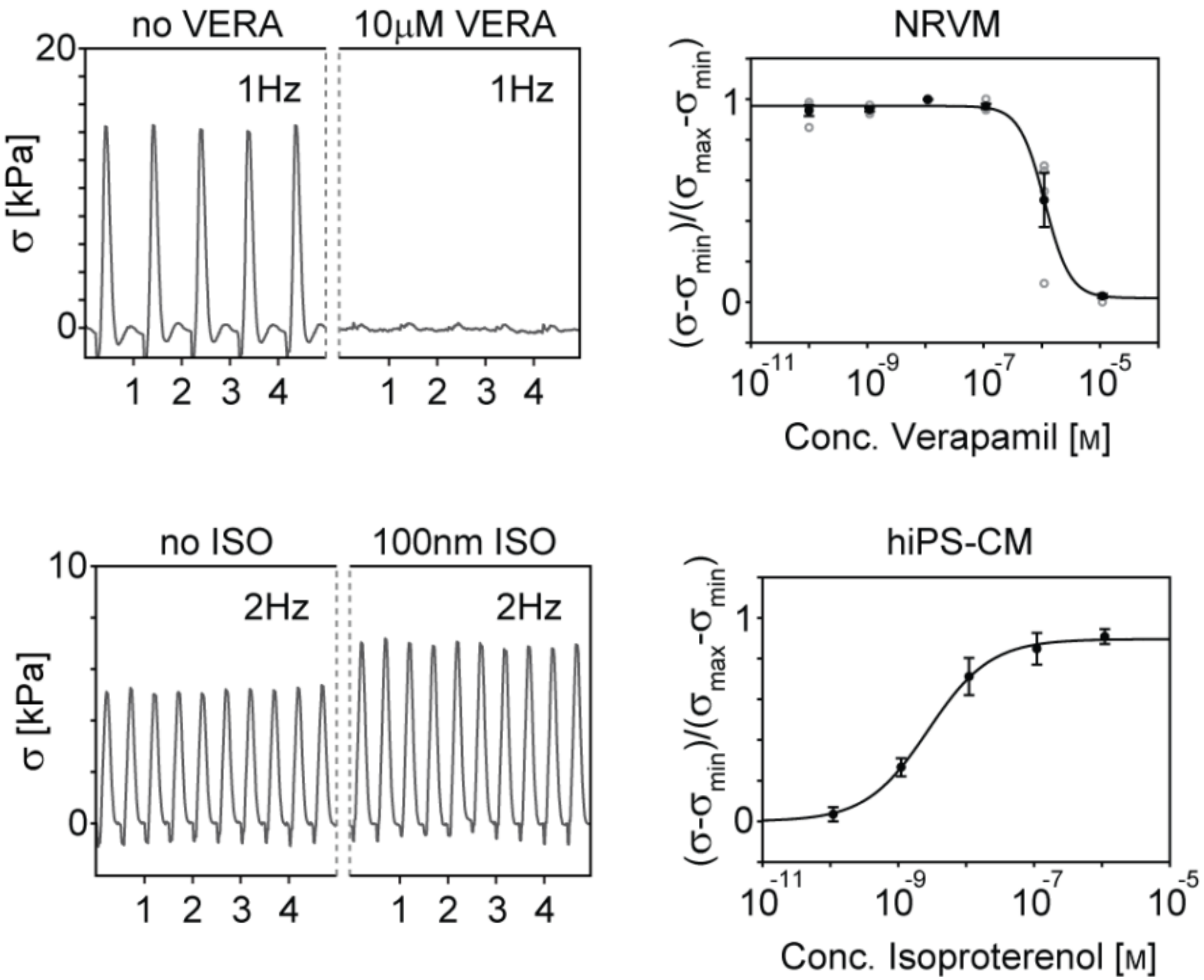
OOP = 0.11

Day 28

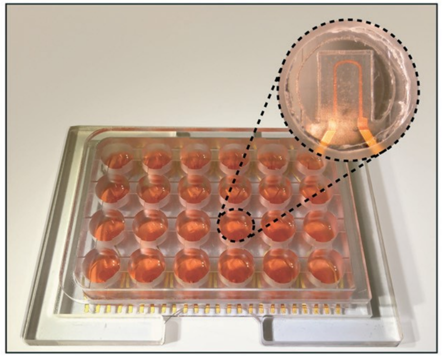


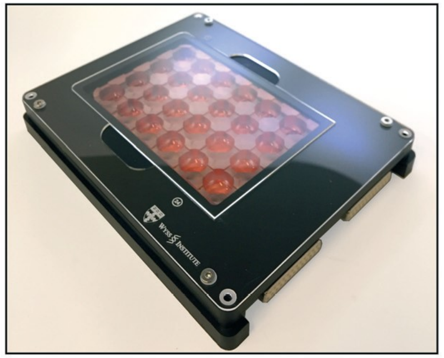
OOP = 0.42

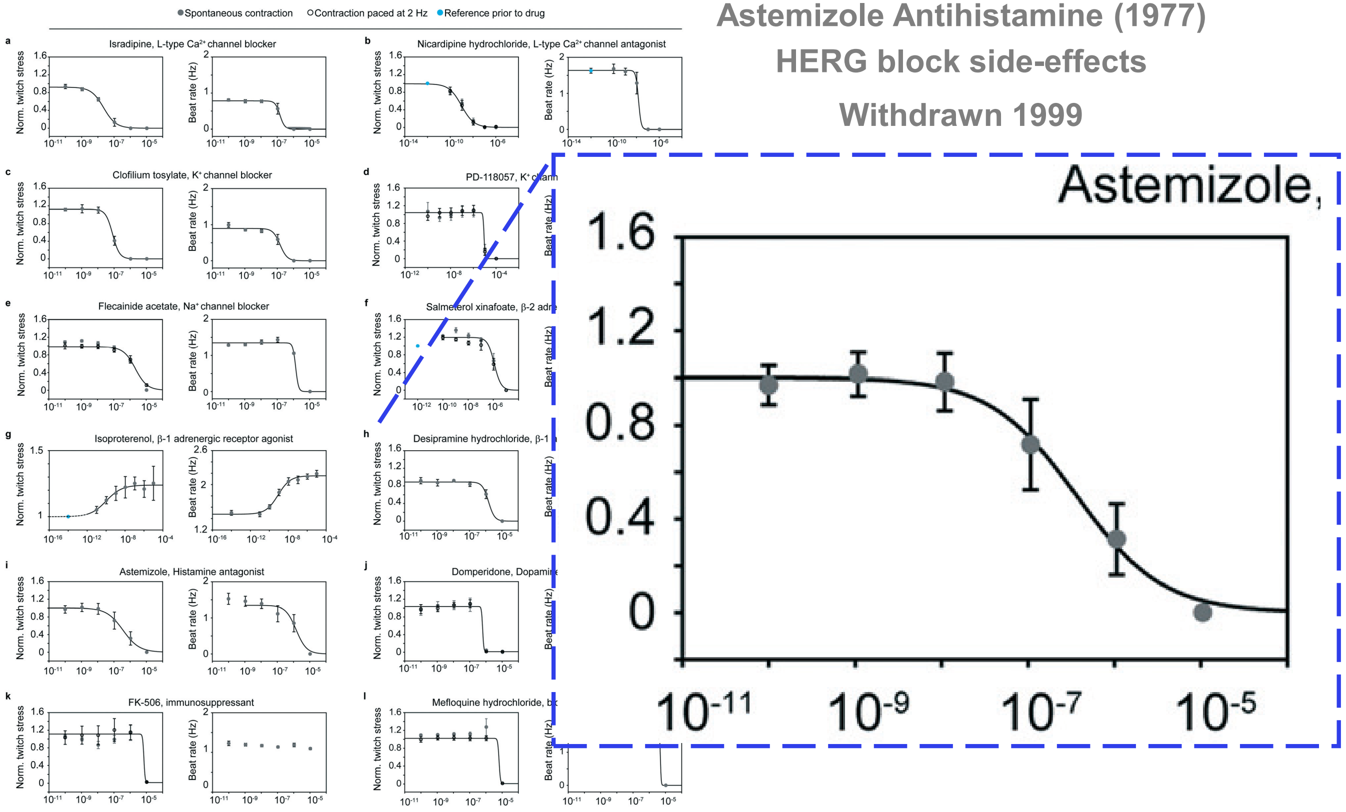
Example drug tests



Drug toxicity tests







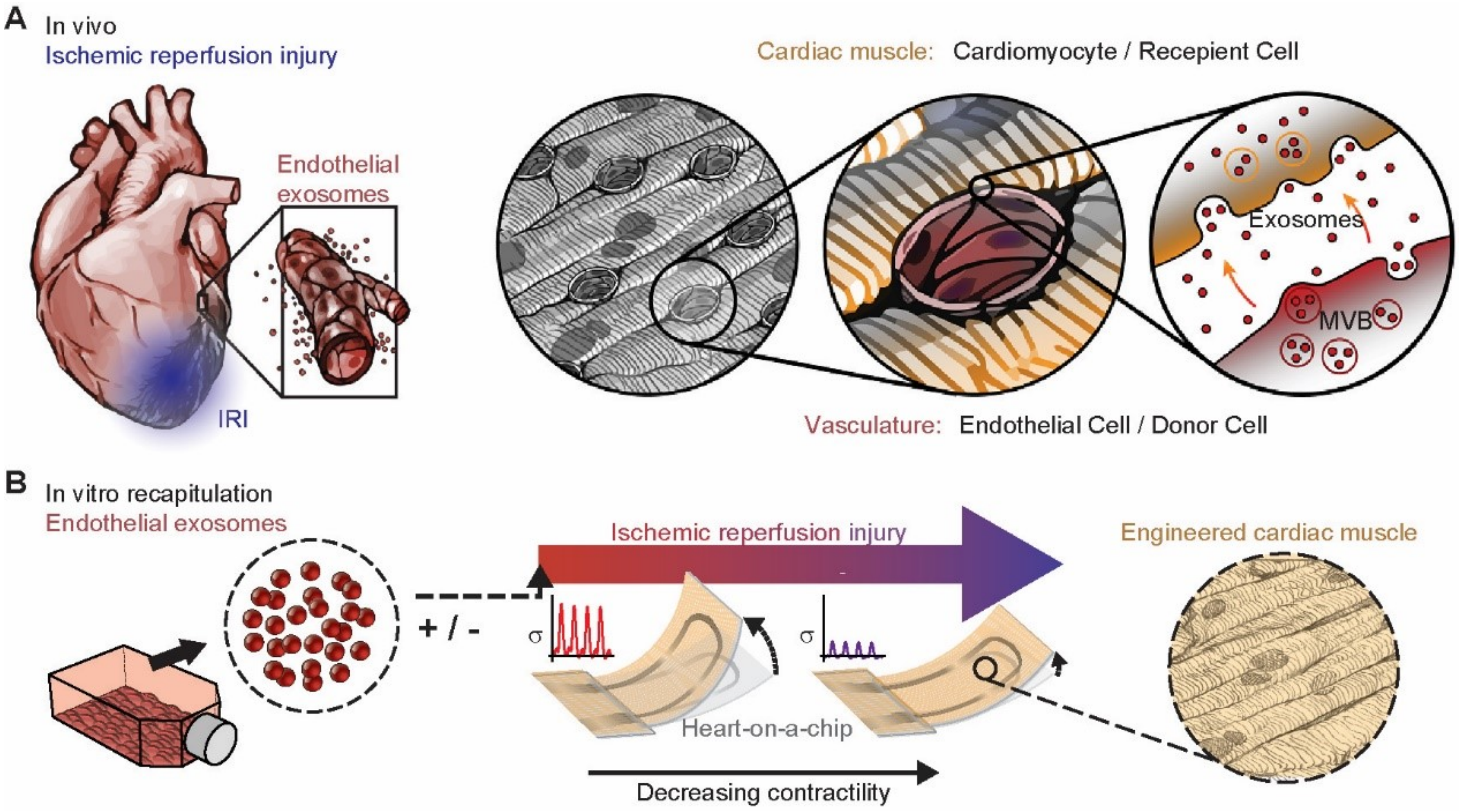
Astemizole Antihistamine (1977)

HERG block side-effects

Withdrawn 1999

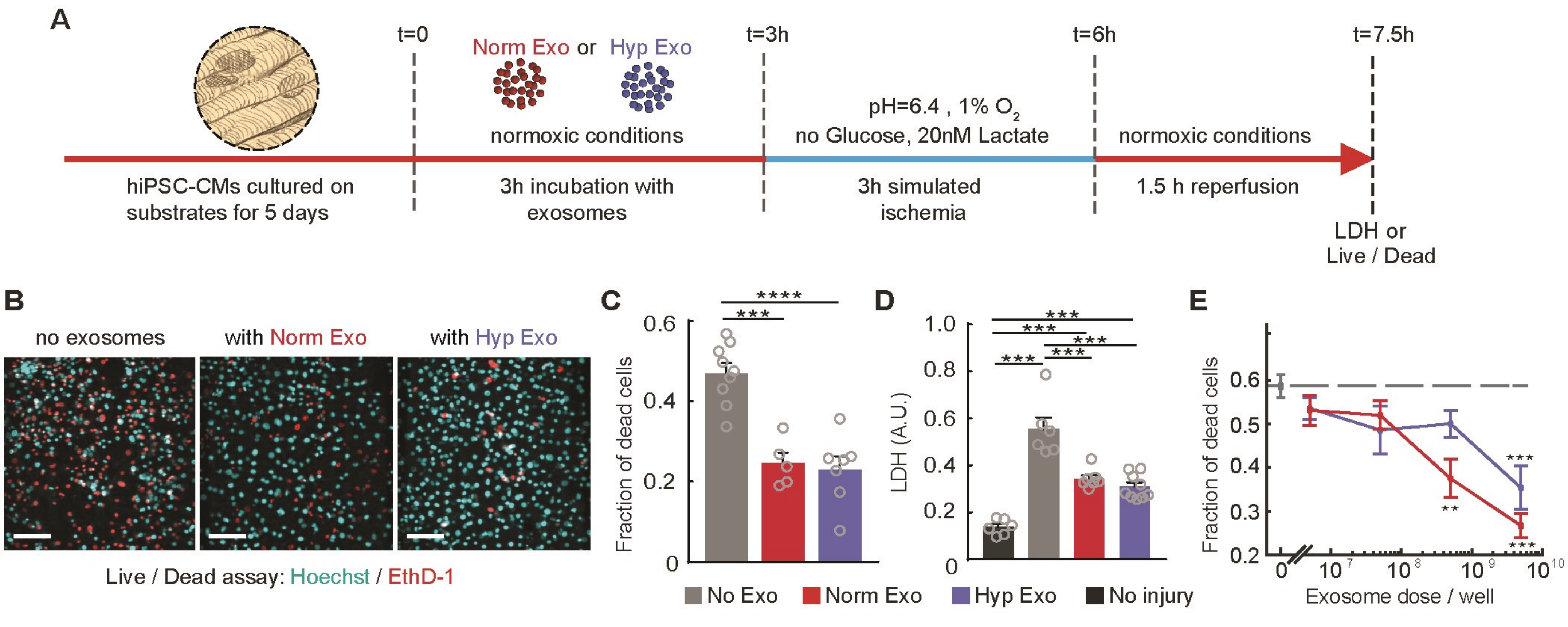
Adapted from JU Lind et al *Lab Chip* 2017

Simulated ischemic heart failure



Adapted from M Yadid et al *Science Translational Medicine* 2020

Simulated ischemic heart failure



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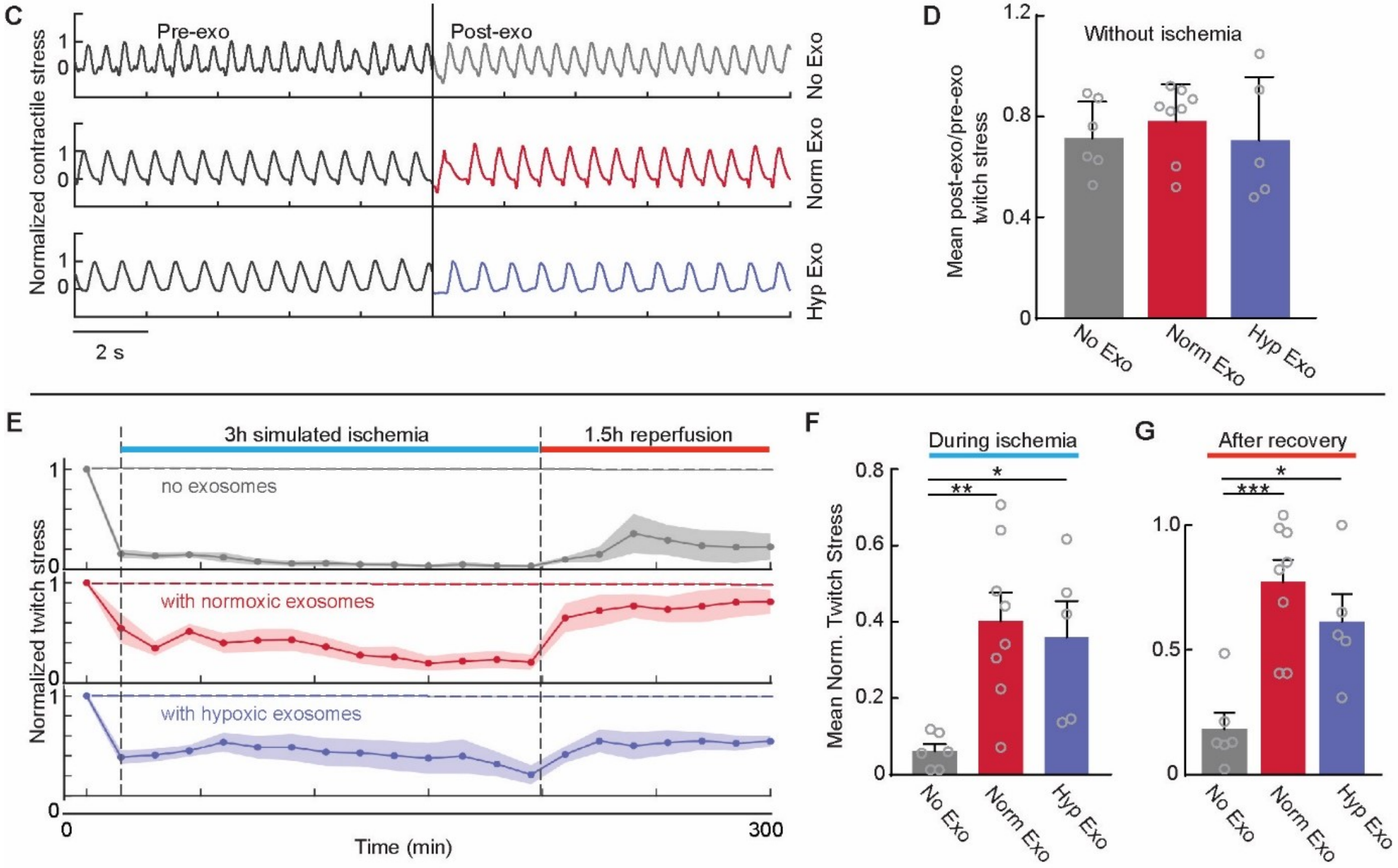
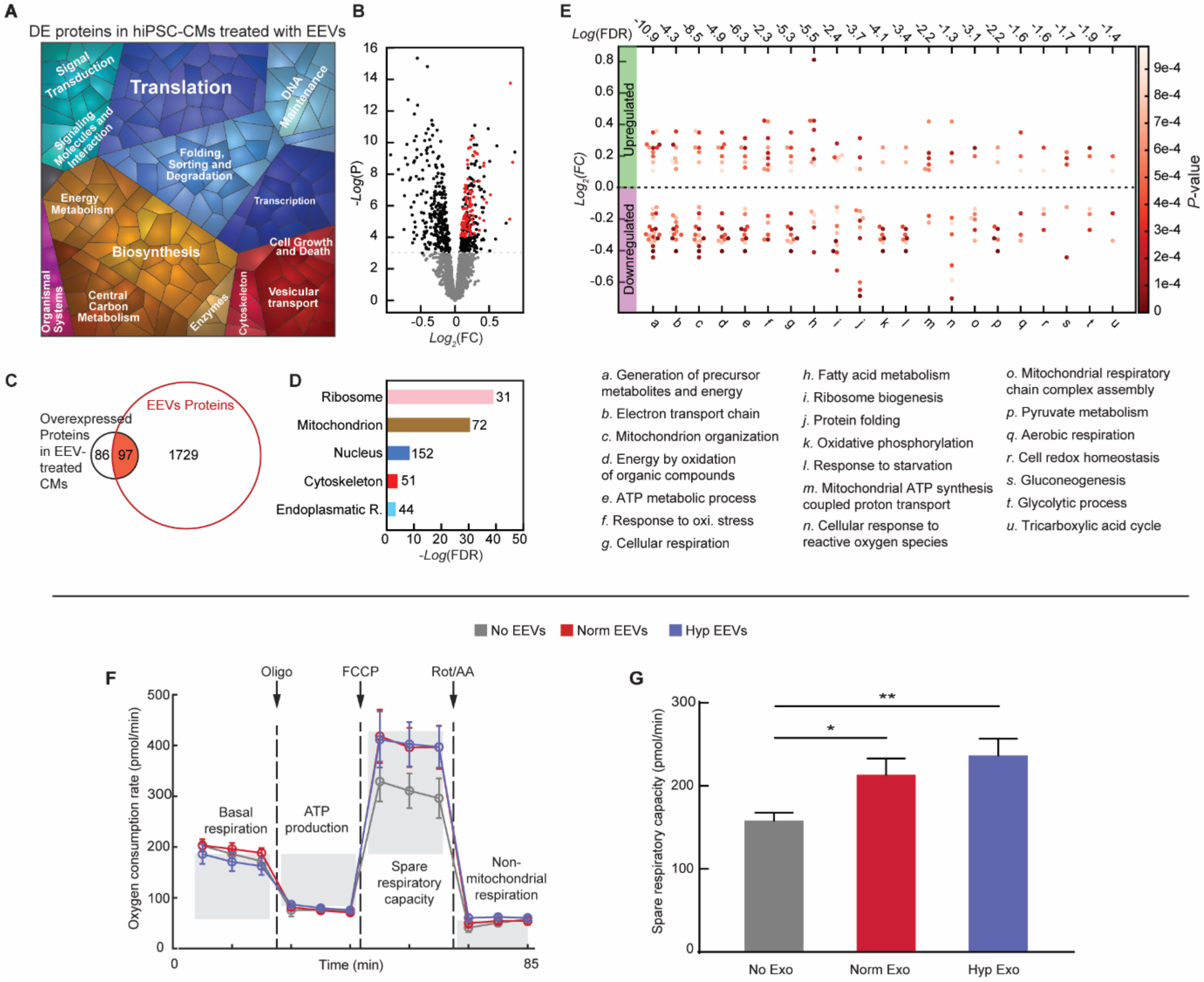


Adapted from M Yadid et al *Science Translational Medicine* 2020

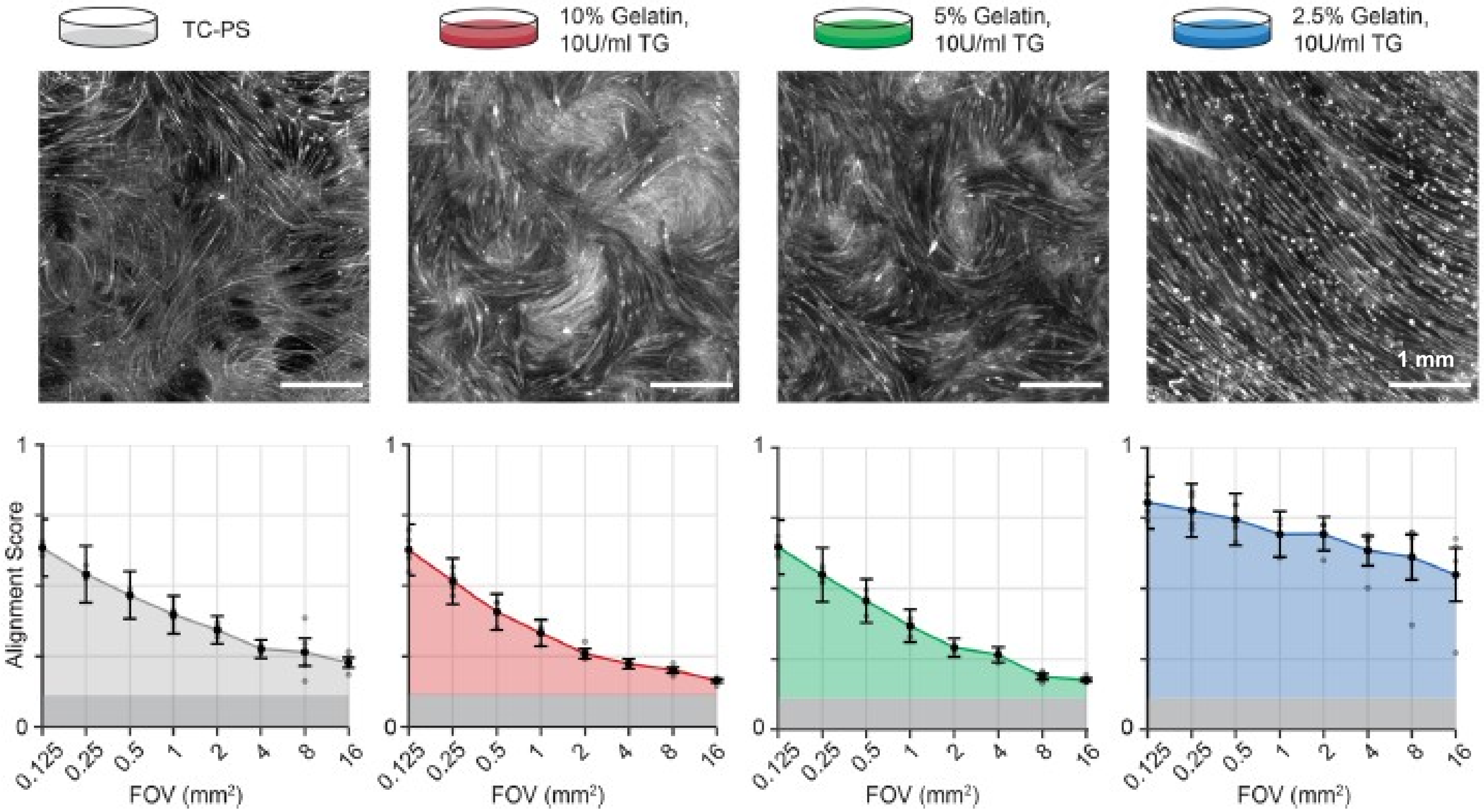
EEVs increase CM respiratory capacity



Adapted from M Yadid et al *Science Translational Medicine* 2020

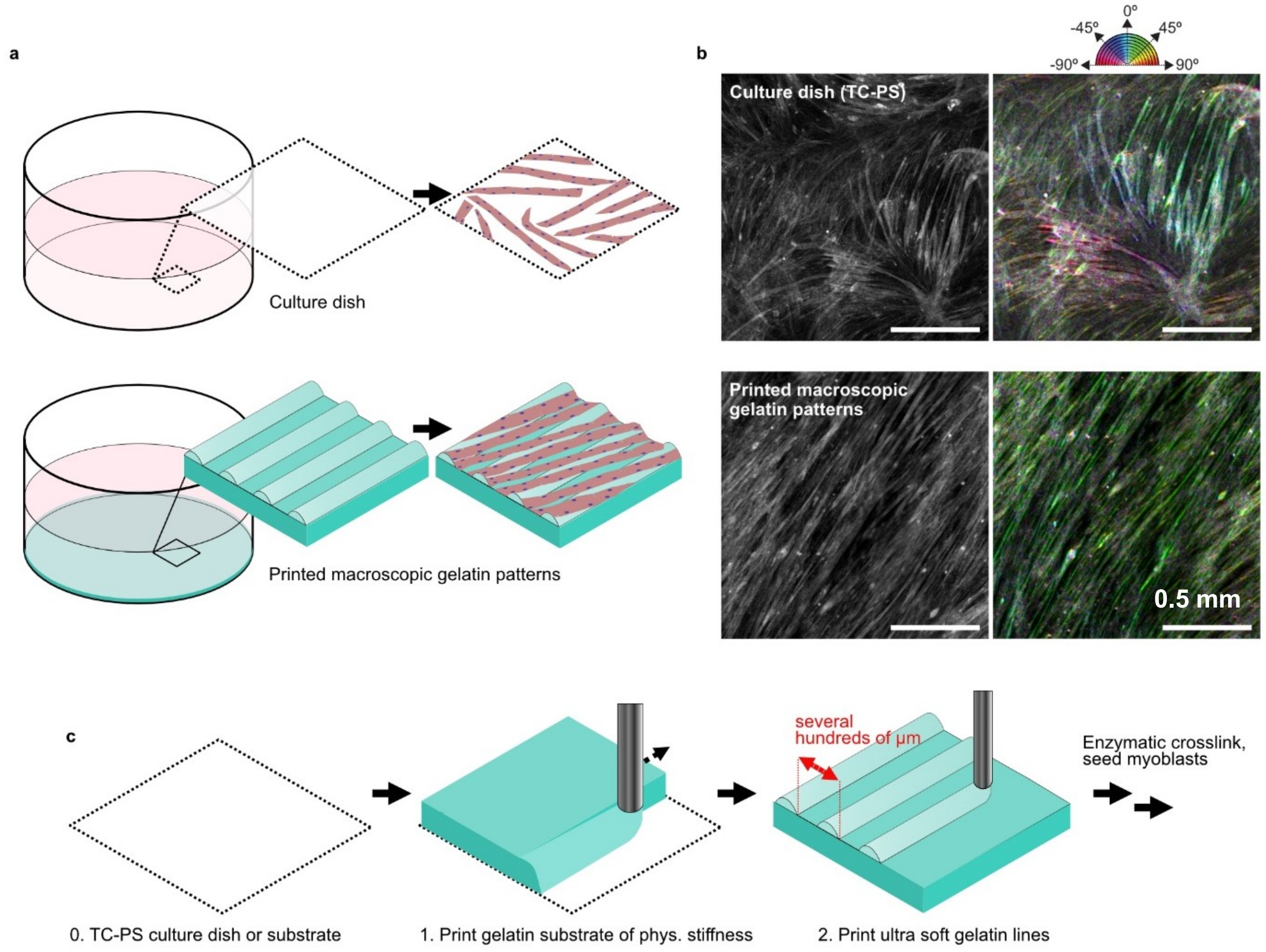
Cell-instructive biomaterials

Spontaneous architecture on ultra soft gelatin



Adapted from JH Jensen et al *Scientific Reports* 2020

Minimally Complex Printed Alignment Structures



Adapted from SD Cakal et al *Biomedical materials 2022*

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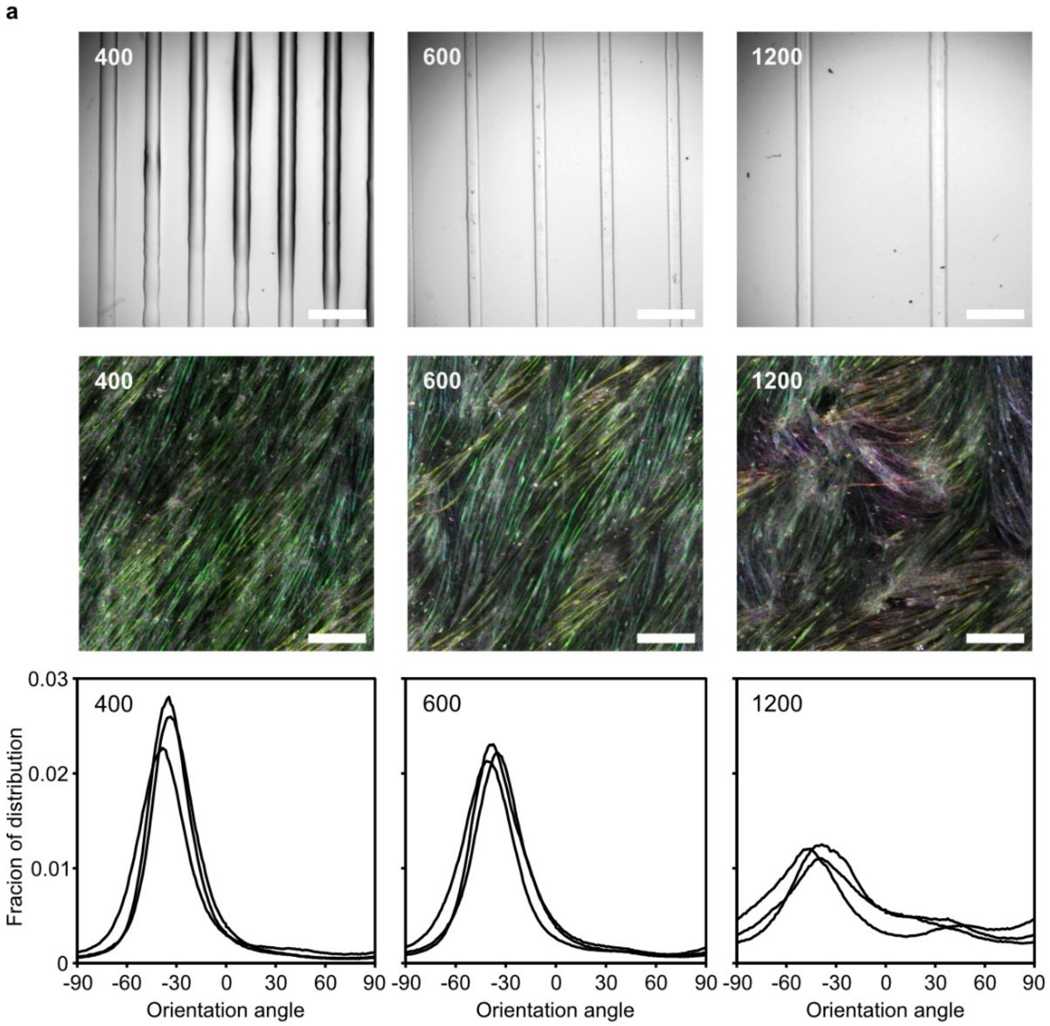

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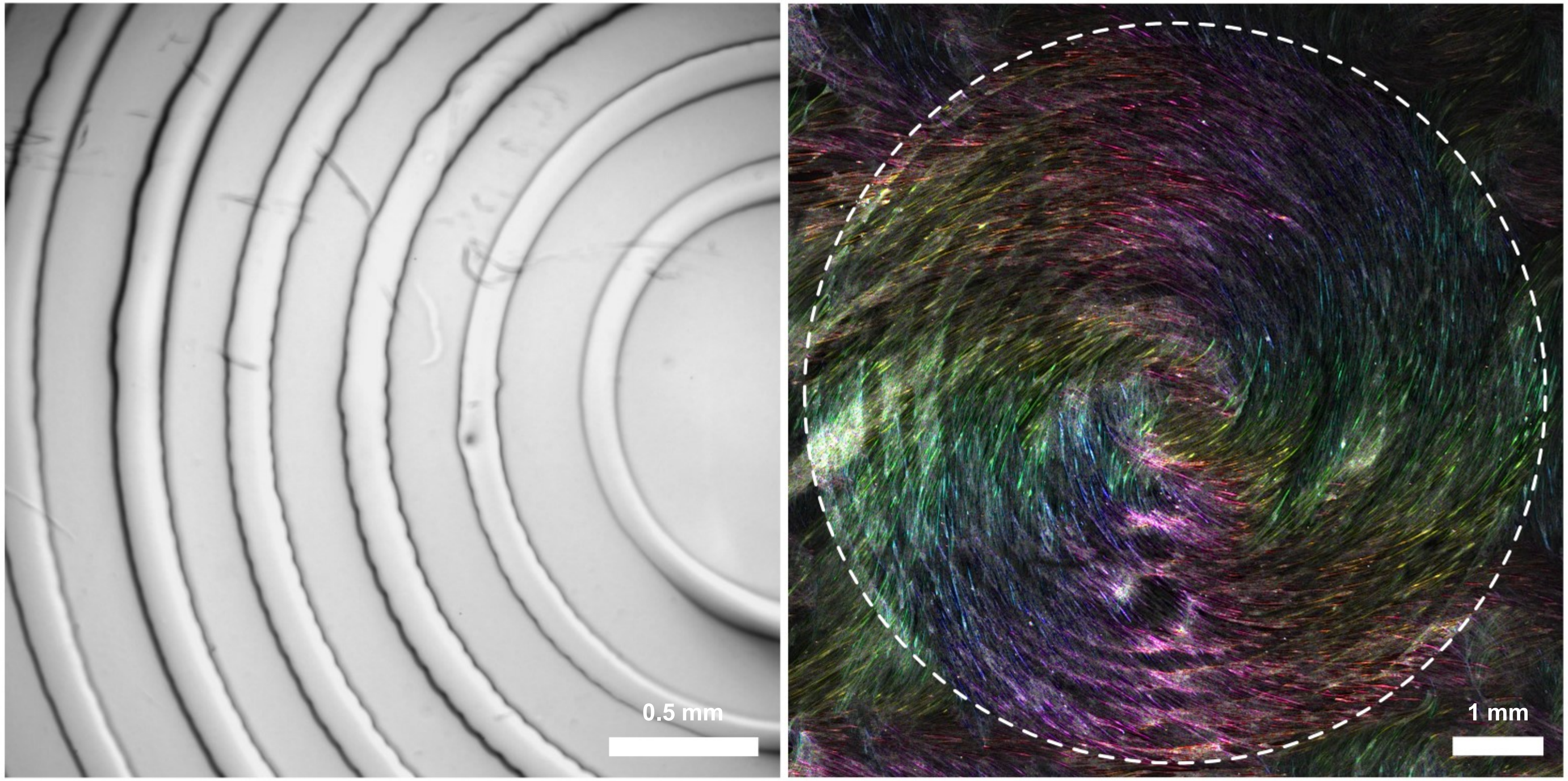

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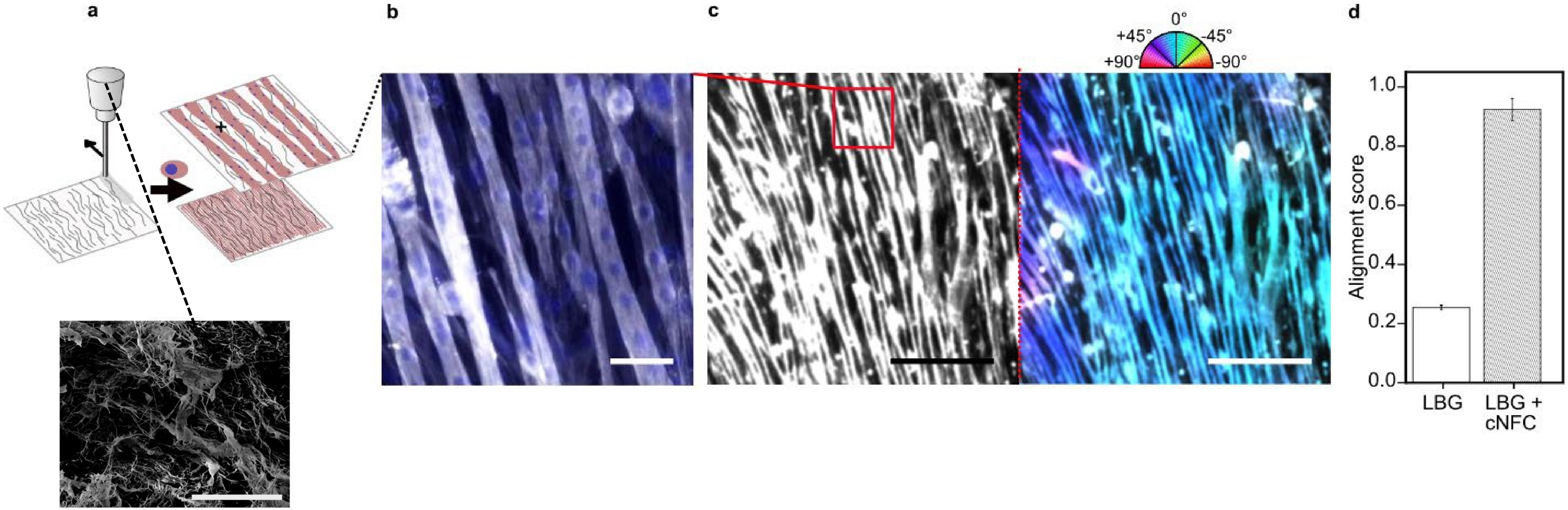
Shear-induced alignment on transparent cellulose nanofiber- gelatin composites



Adapted from Radeke C et al *ACS Applied Materials and Interphases 2023*

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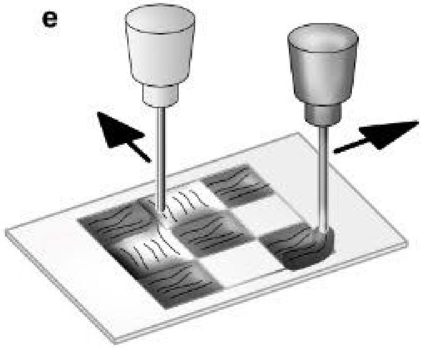

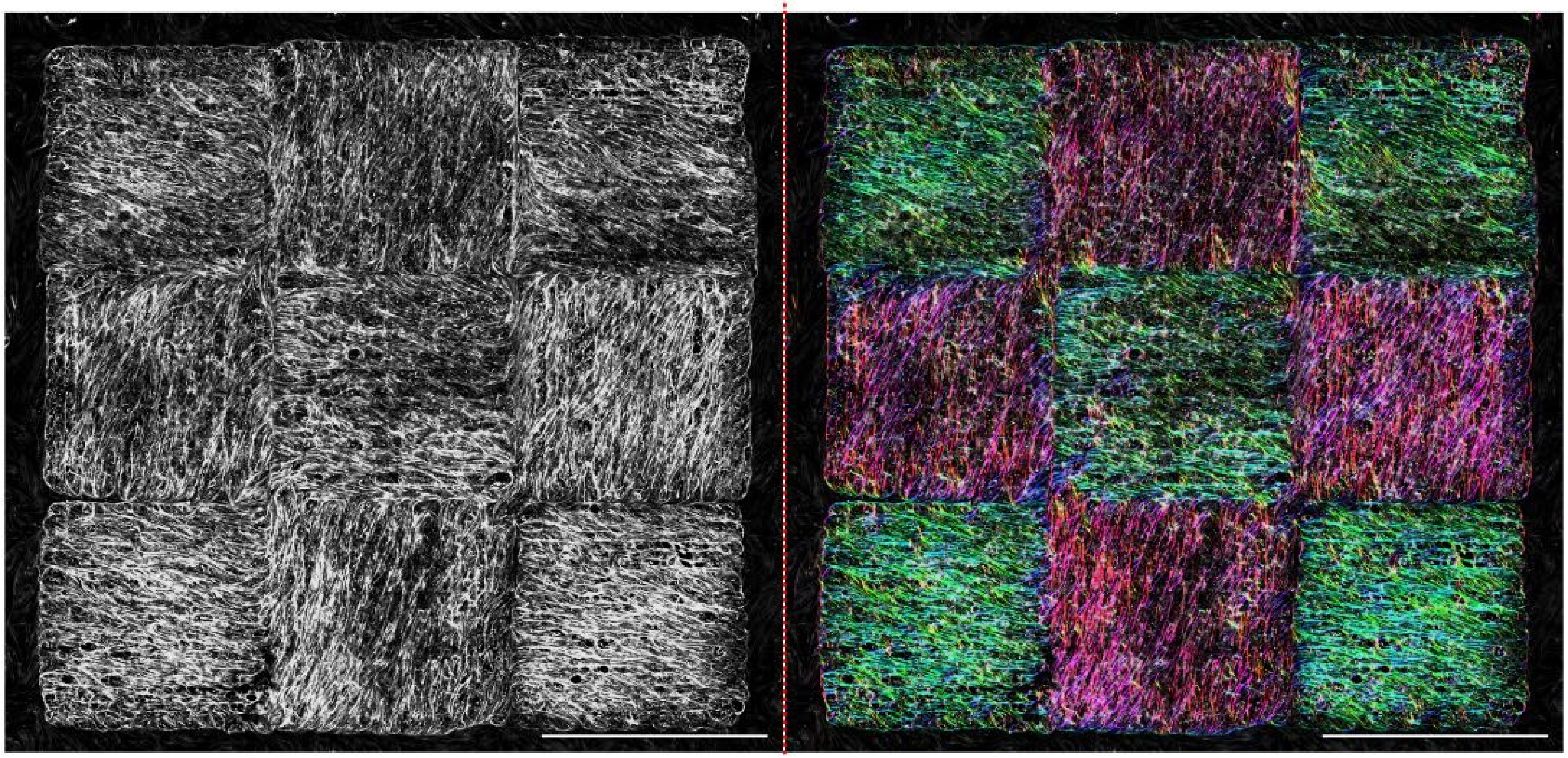

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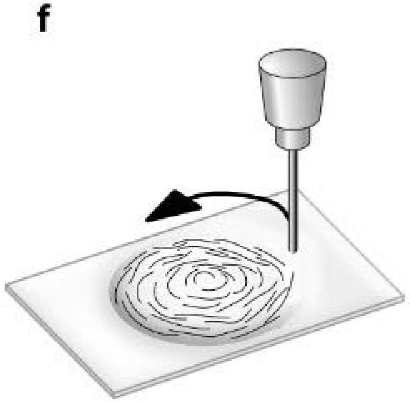

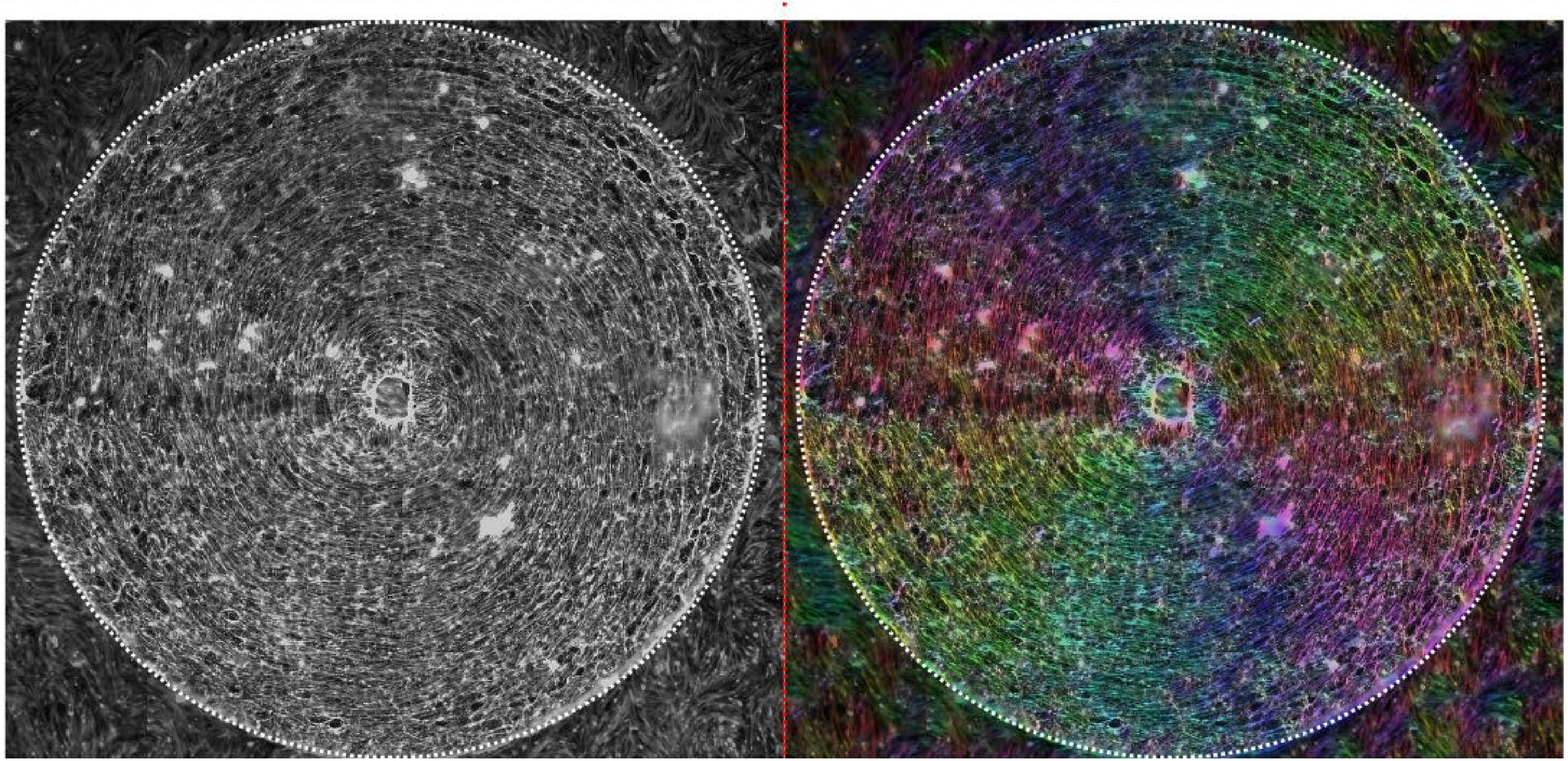

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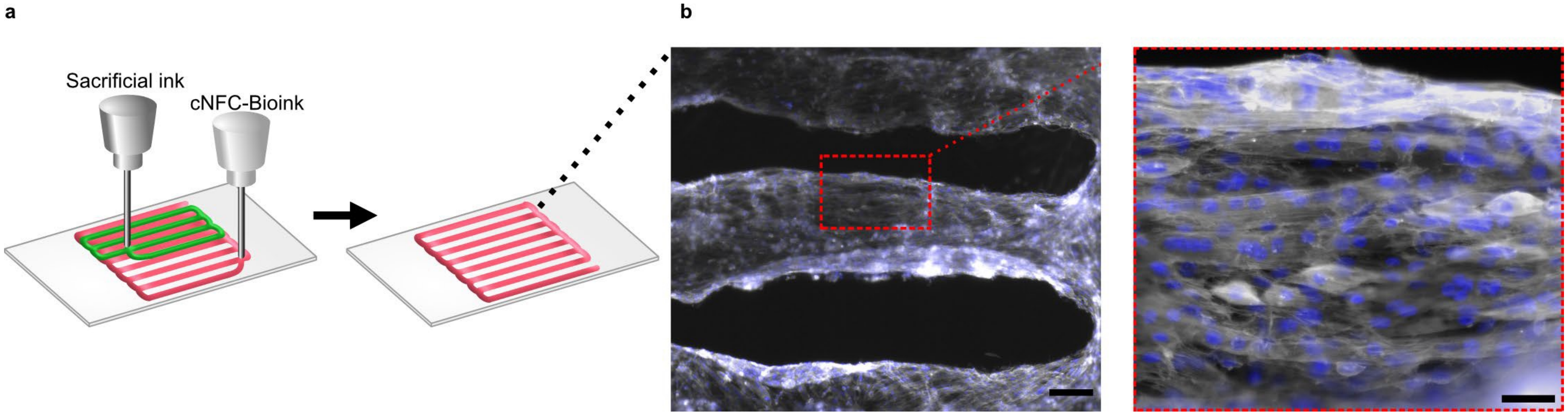
3D bioprinted muscle fibers



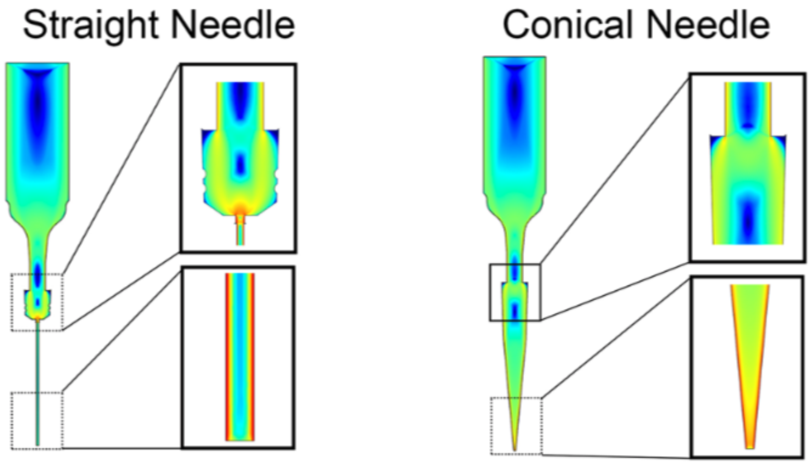
Embedded 3D bioprinting

Bioprinting: shear during print – cell viability

Shear-stress in a tube is

$$\text{Circular tube: } \tau_w = \frac{4\eta Q}{\pi R^3}$$

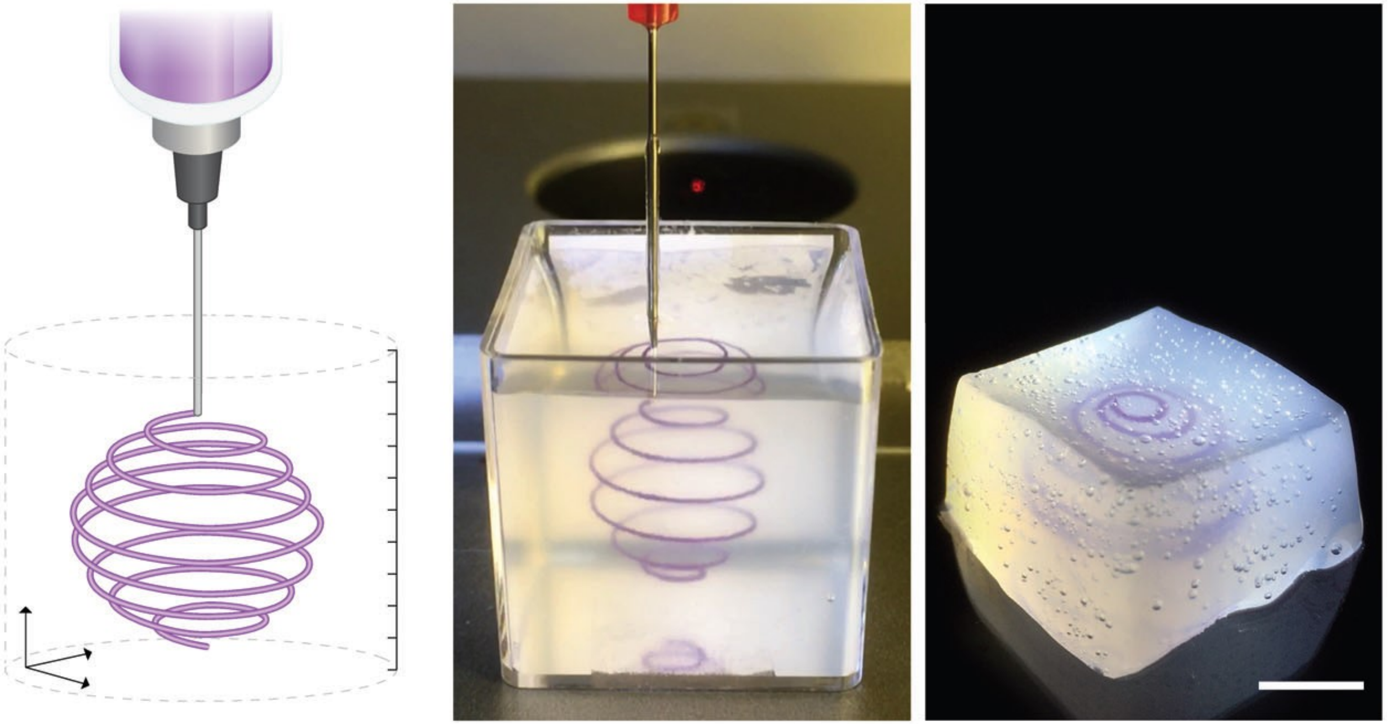
Q is the volumetric flow rate, R = radius, η = viscosity



→ Inherent trade-off between cell viability & phenotype preservation and spatial resolution

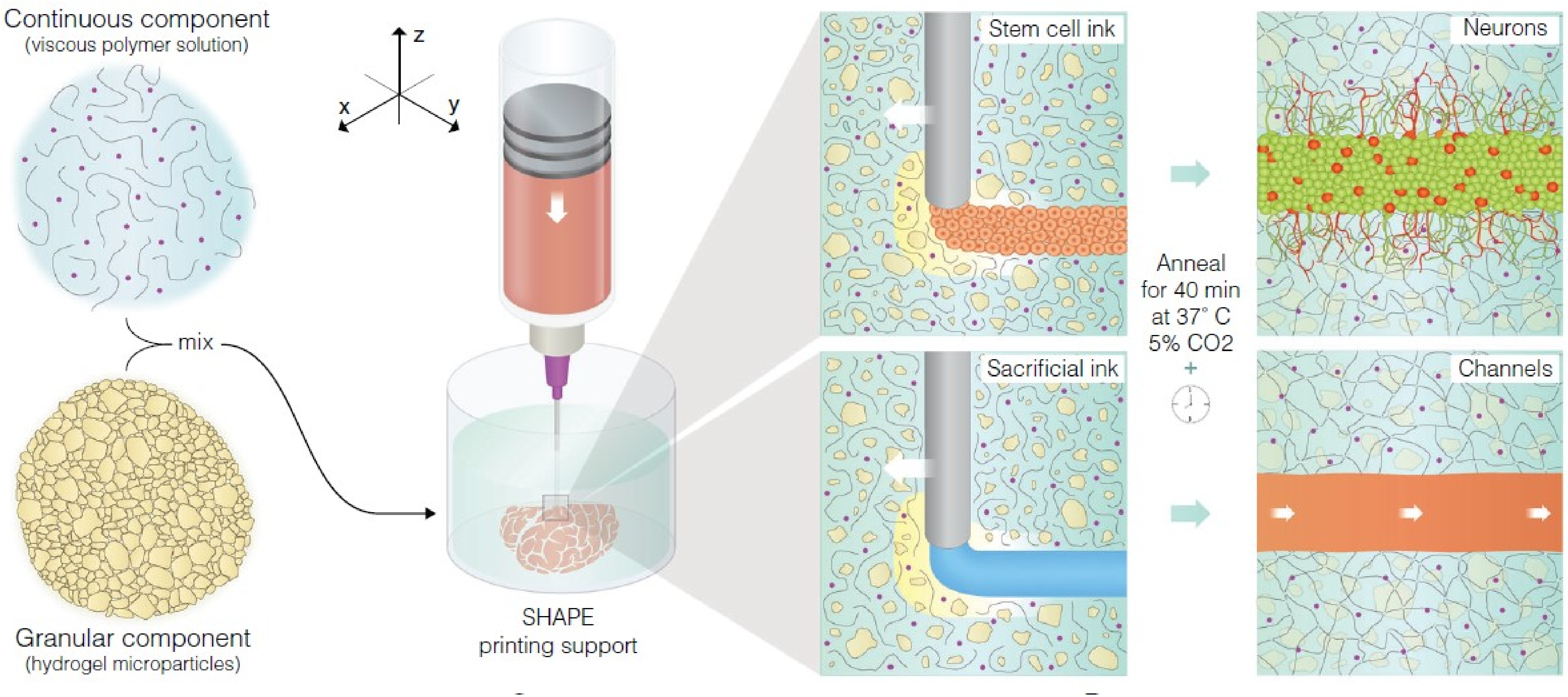
Embedded bioprinting

- Core idea: Printing low viscosity, high-cell concentration inks into support that maintains shape



Adapted from J Kajtez et al *Advanced Science 2022*

Embedded printing in diluted granular gels



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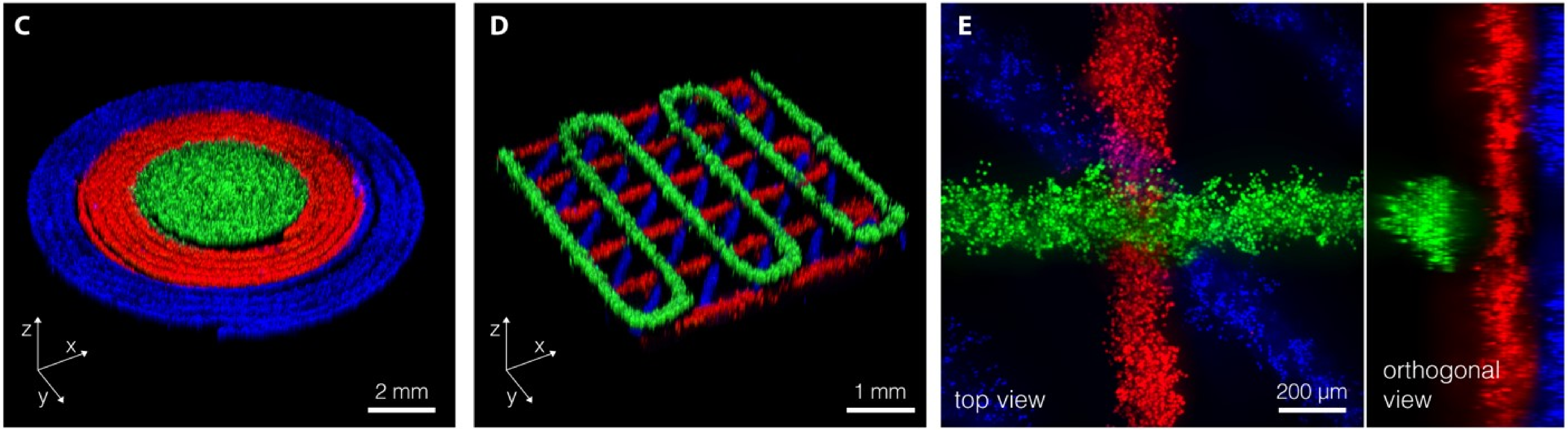

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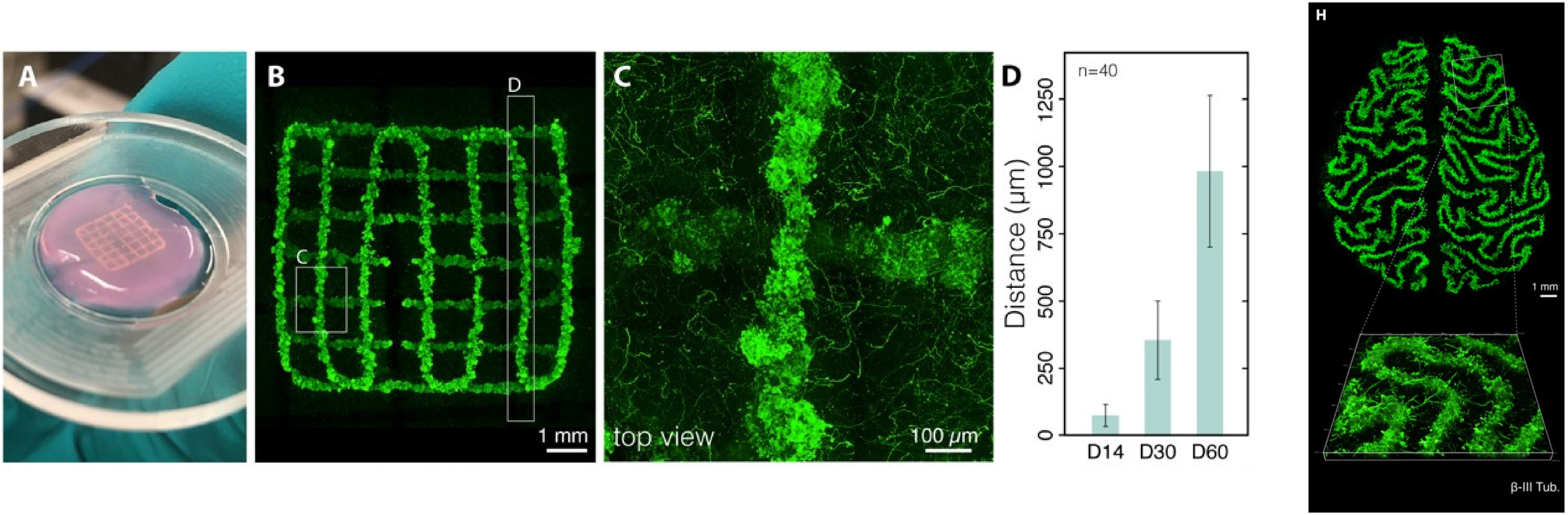
Embedded bioprinting of neuronal tissue models



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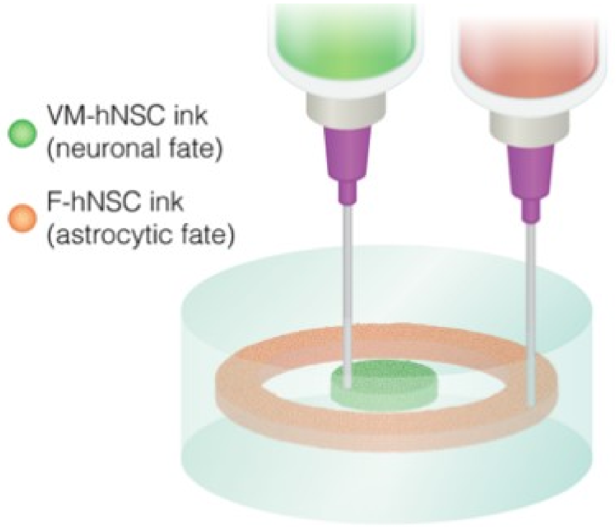
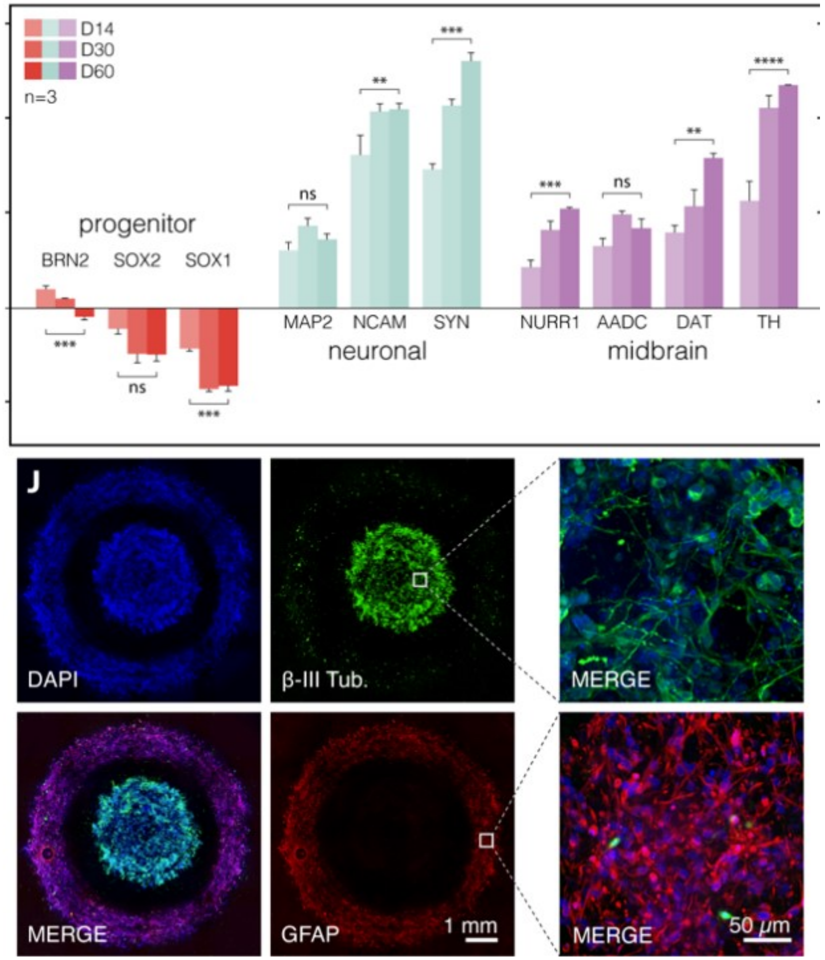
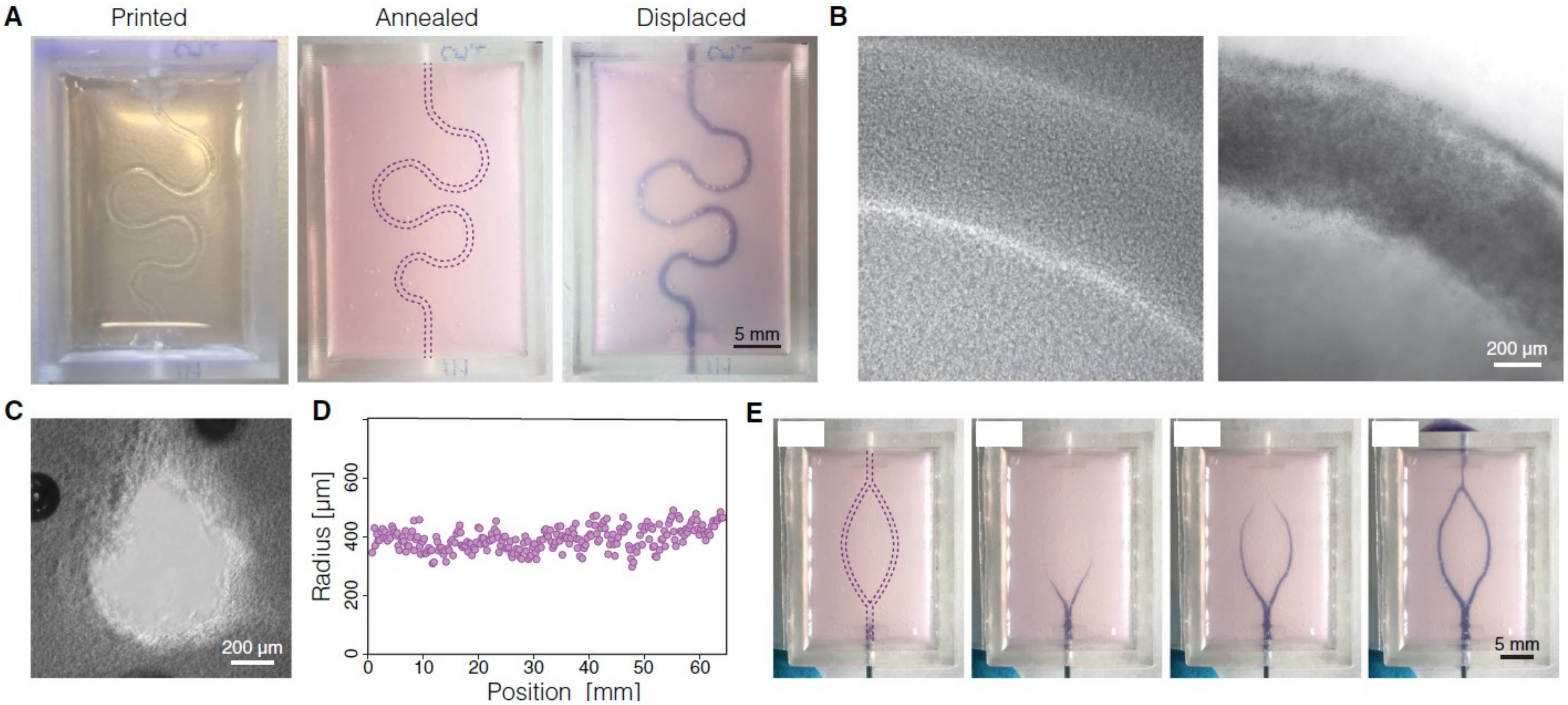
Embedded bioprinting of neuronal tissue models





Adapted from J Kajtez et al *Advanced Science 2022*

Embedded bioprinting perfusable vasculature



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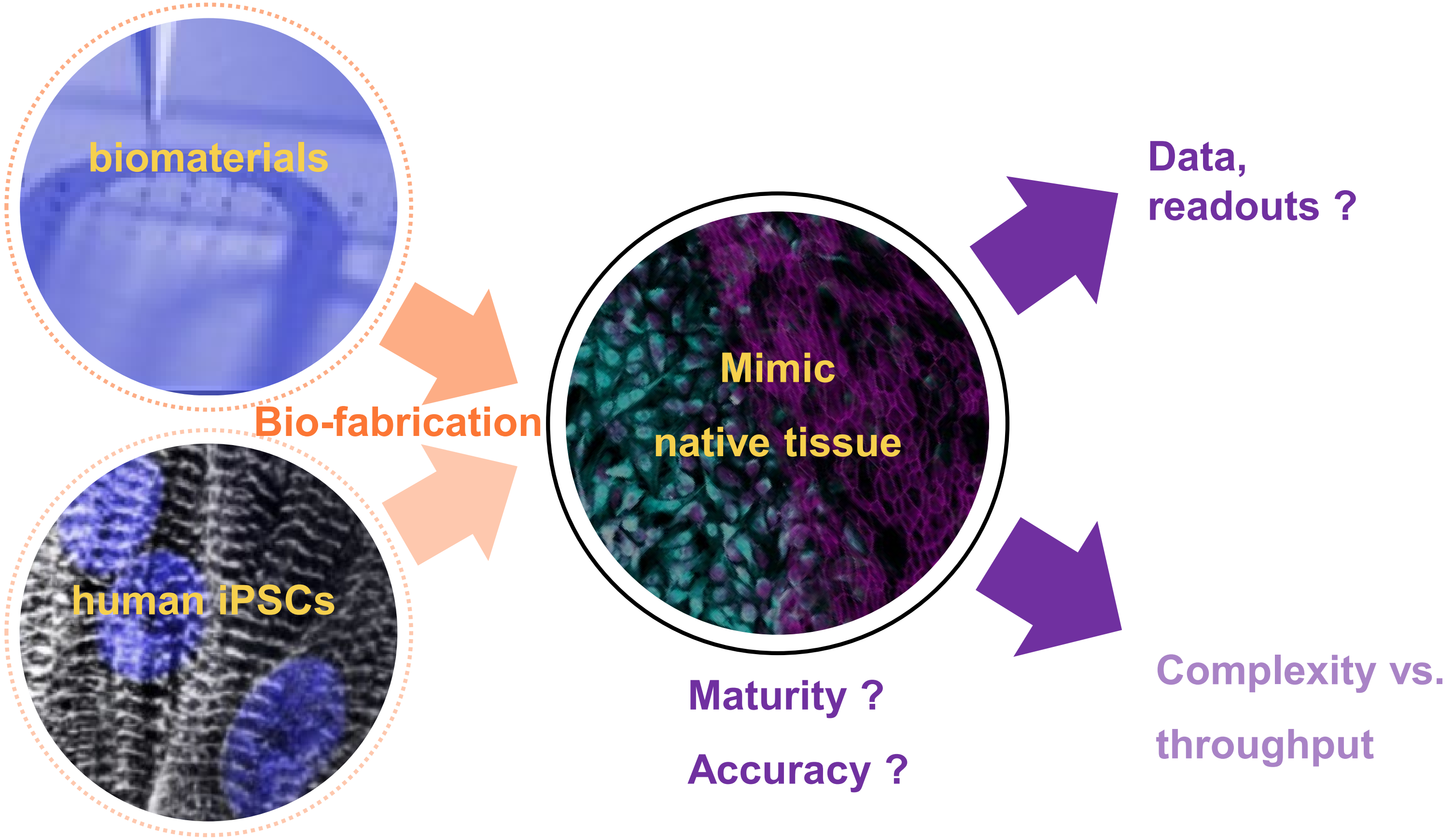
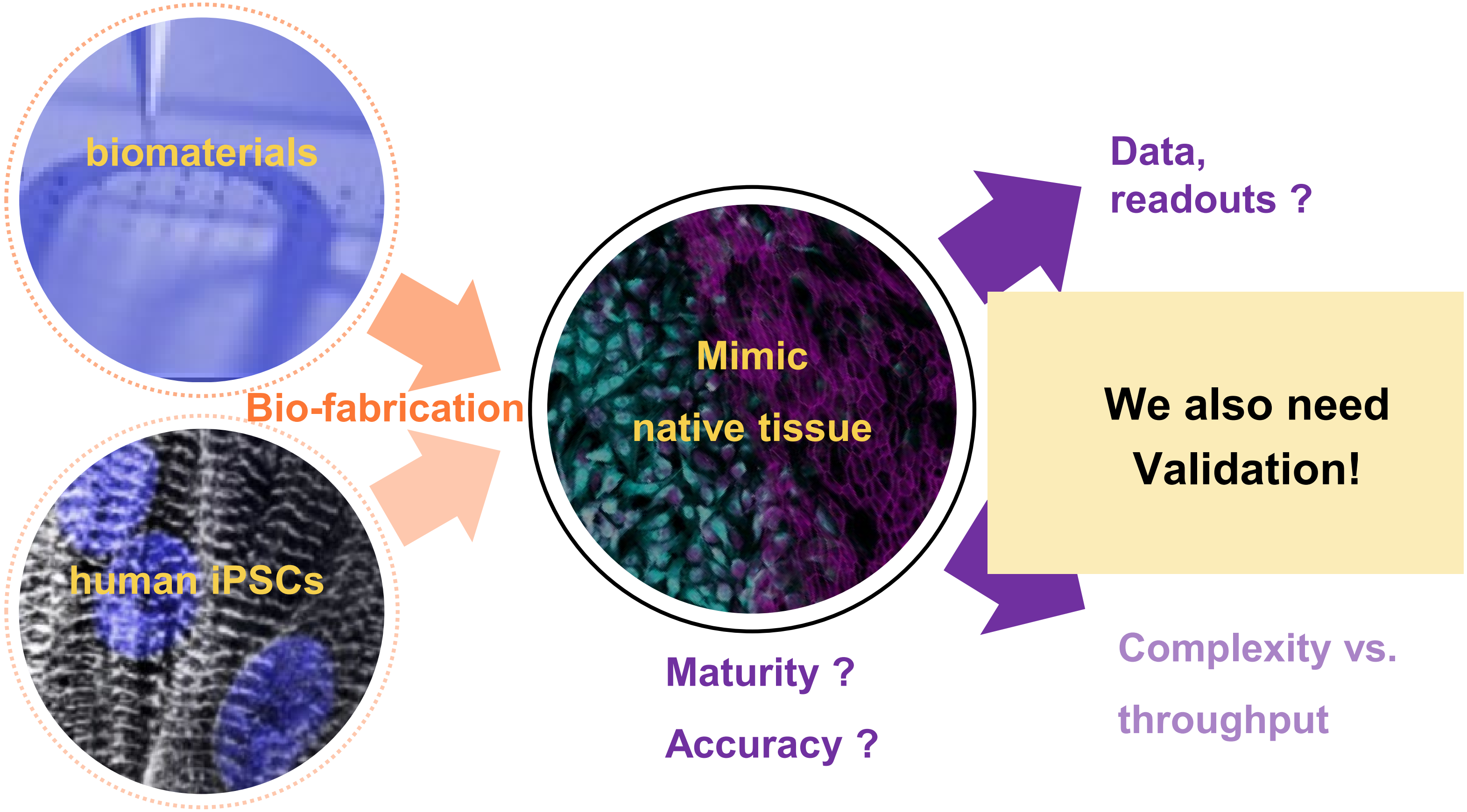
Summary & Outlook

Engineering challenges

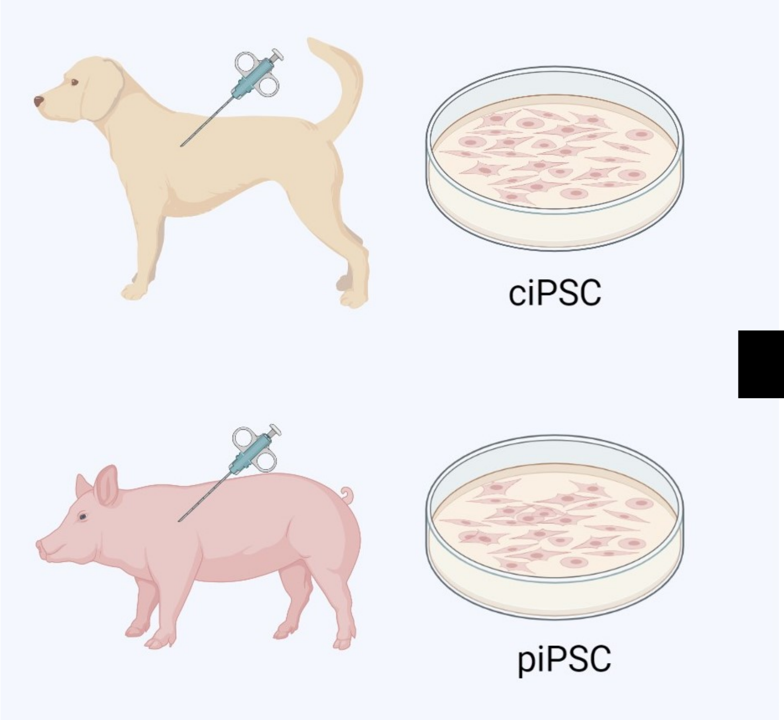


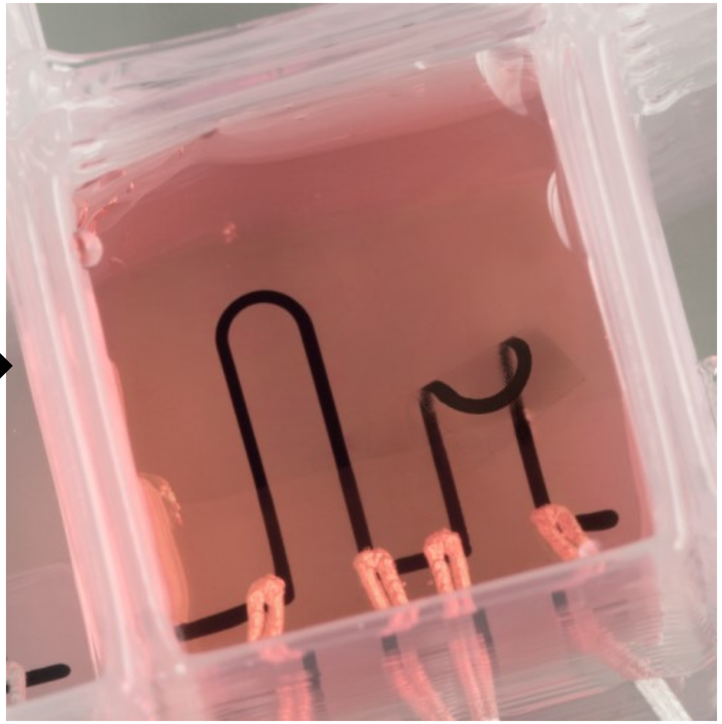
Engineering challenges



Validation

Historic in vivo animal data is unique opportunity for in vitro / in vivo comparisons and validations





Ongoing projects with Kirstine Callø, Kristine Freude Uni. Copenhagen to build iPSCs models from porcine and canine stem cells

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