Engineering an organotypic culture model of endocardial cushion morphogenesis

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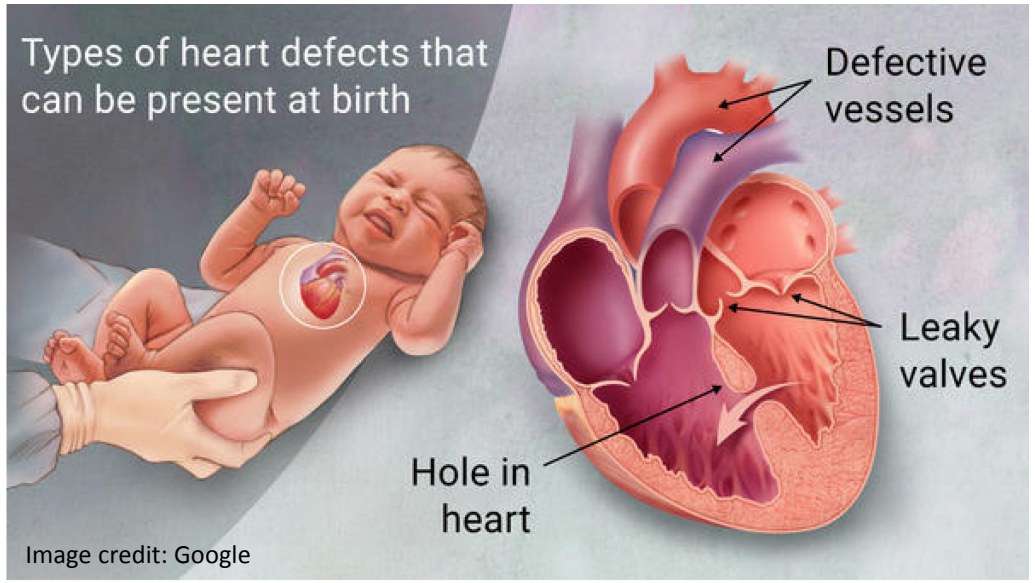
Congenital heart defects


Image credit: CDC

- Most common type of birth defect.
- Affect **1 out of every 100** infants born in the United States.
- Leading cause of infant deaths due to birth defects.
- Genetic etiology is identified in less than 20% of cases.

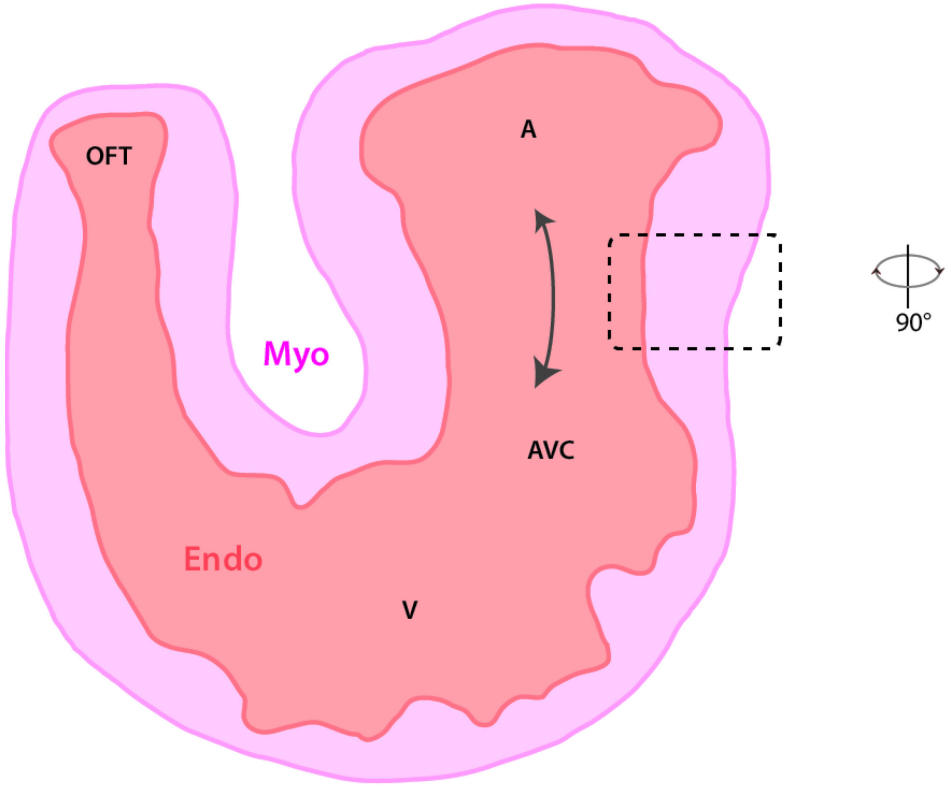
Cardiac developmental toxicity



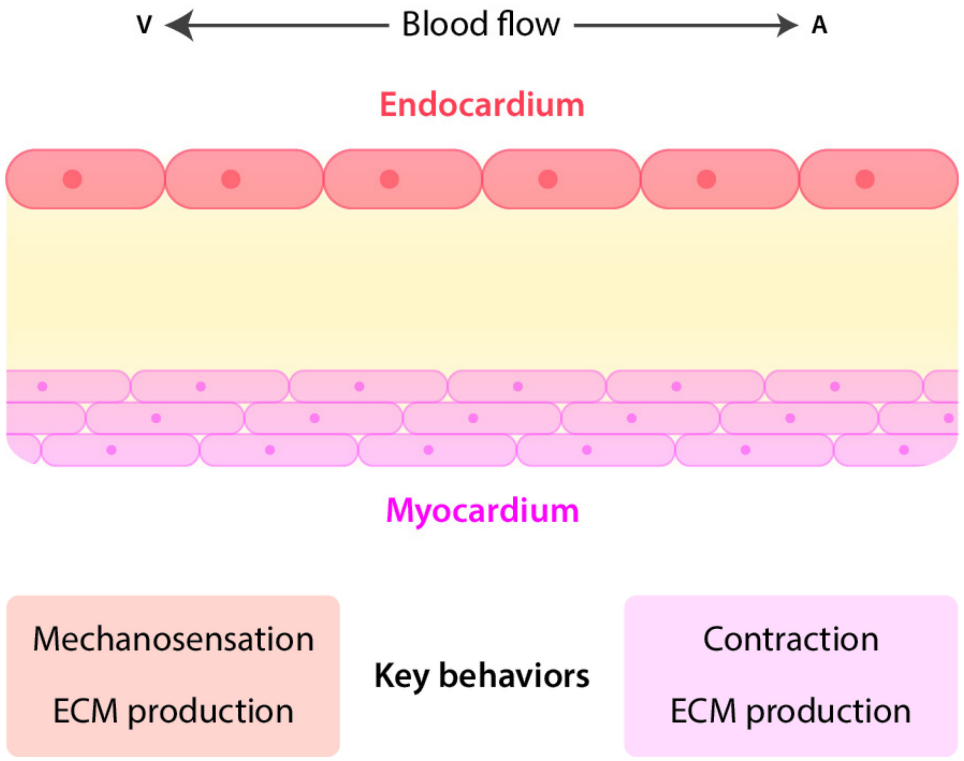
- Due to maternal illness, drug, or environmental exposure.
- Association between exposure to organic solvents (e.g. TCE) and valve and septal defects.
- Endothelial-to-mesenchymal transition (**EndMT**) is sensitive to the effects of organic solvents.

EndMT during cushion morphogenesis

Embryonic heart

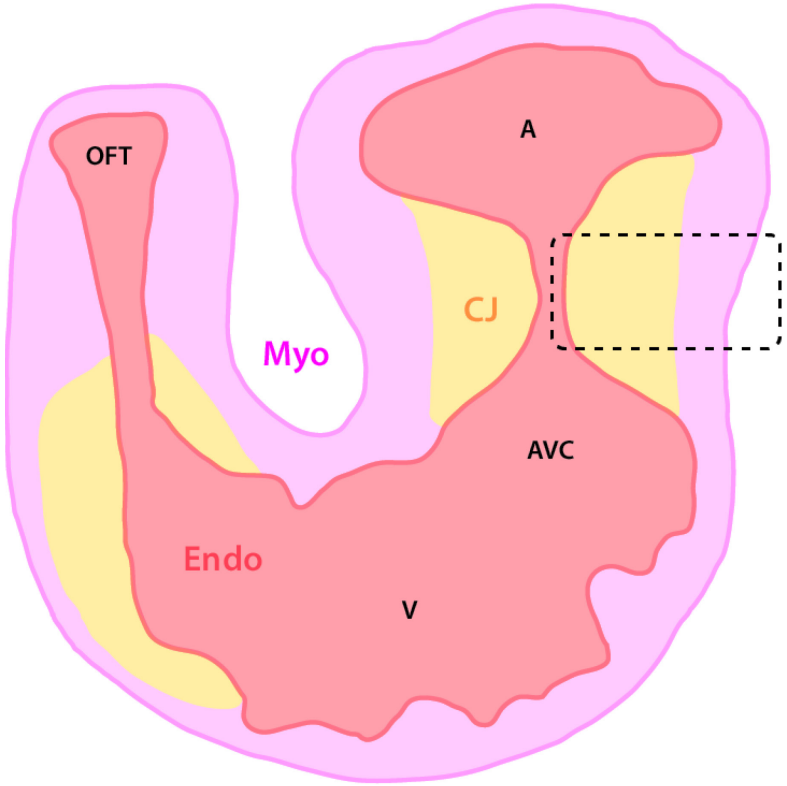


Endocardial cushion

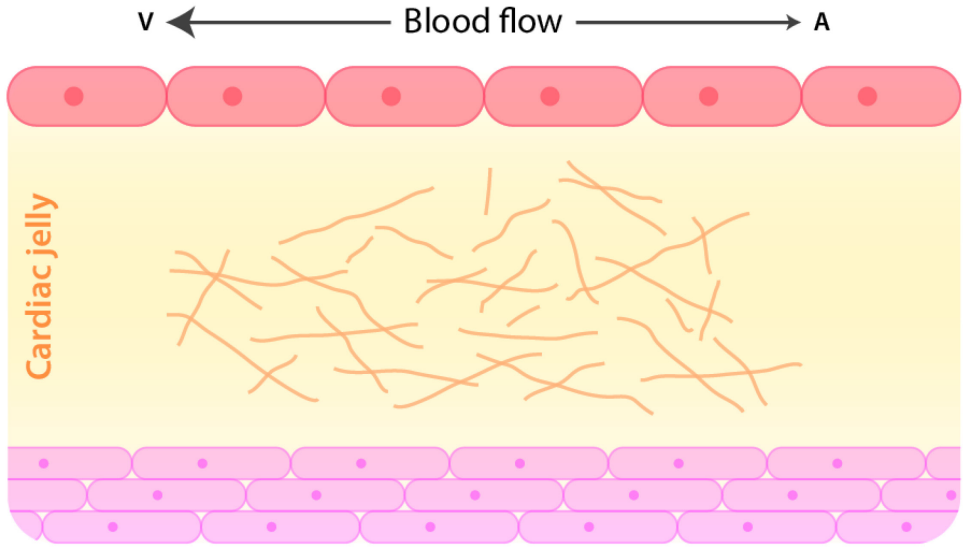


EndMT during cushion morphogenesis

Embryonic heart



Endocardial cushion

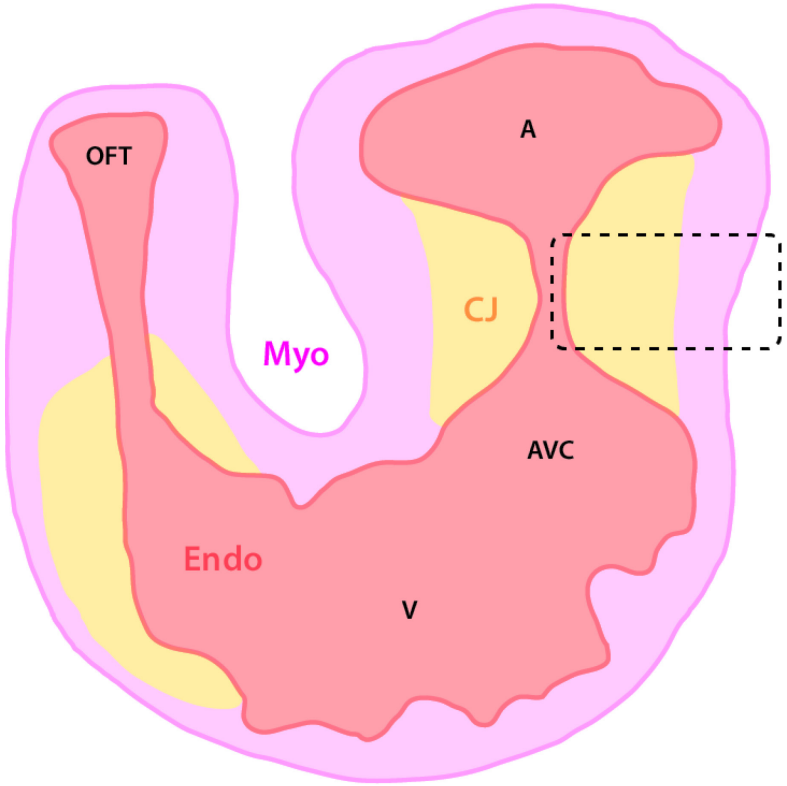


Key ECM components

Hyaluronan Collagen Fibronectin

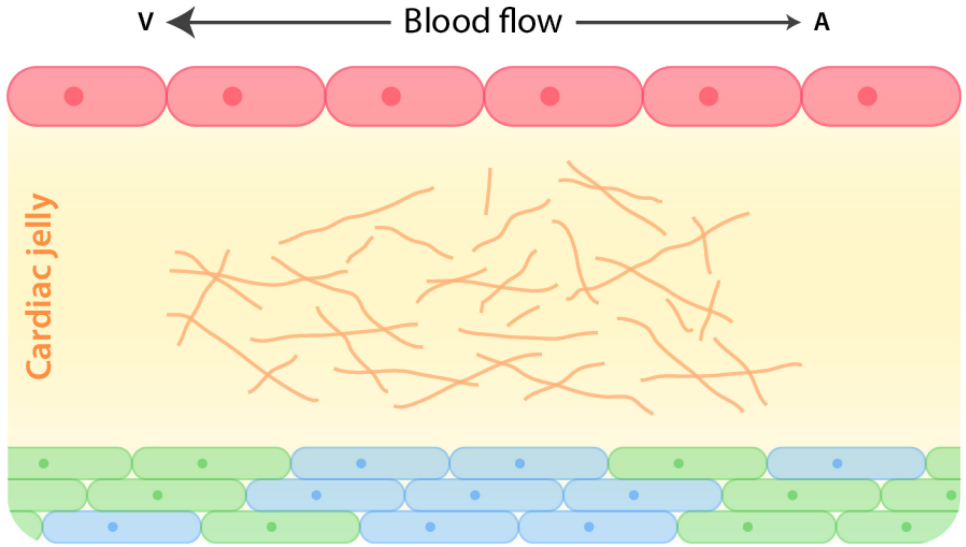
EndMT during cushion morphogenesis

Embryonic heart

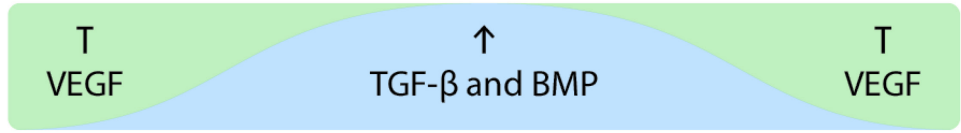


90°

Endocardial cushion

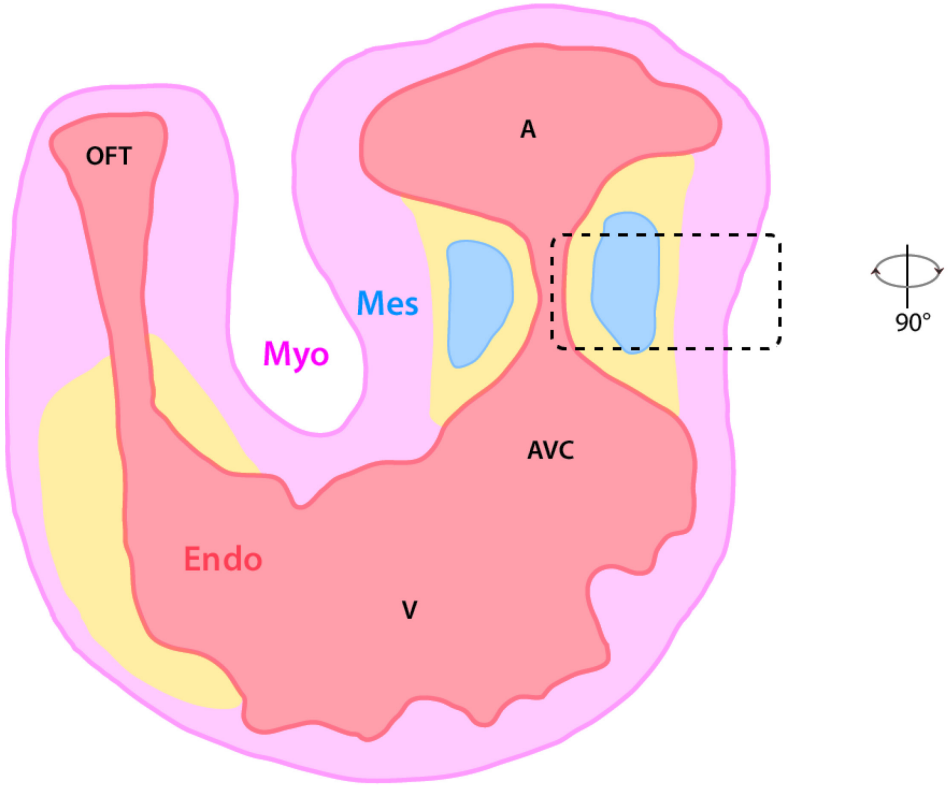


Key EndMT signals

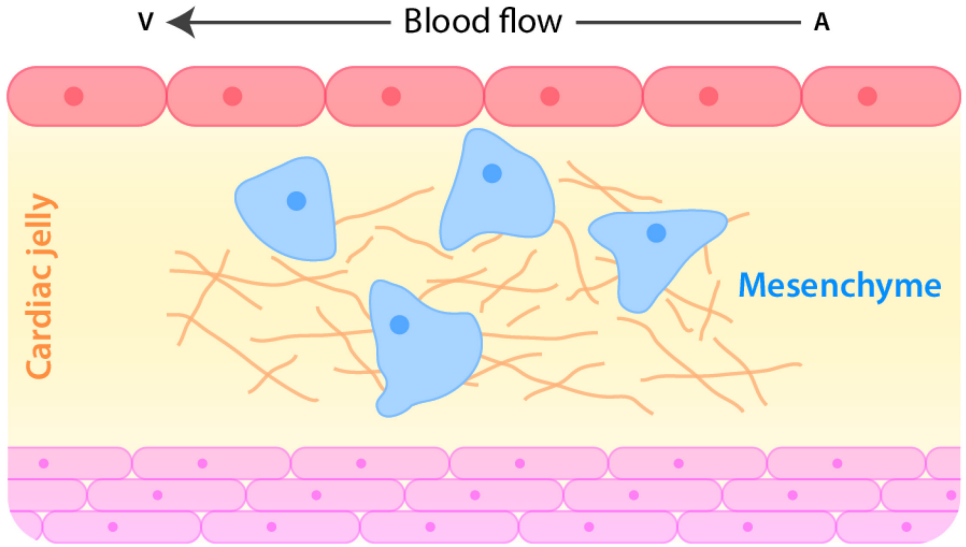


EndMT during cushion morphogenesis

Embryonic heart



Endocardial cushion



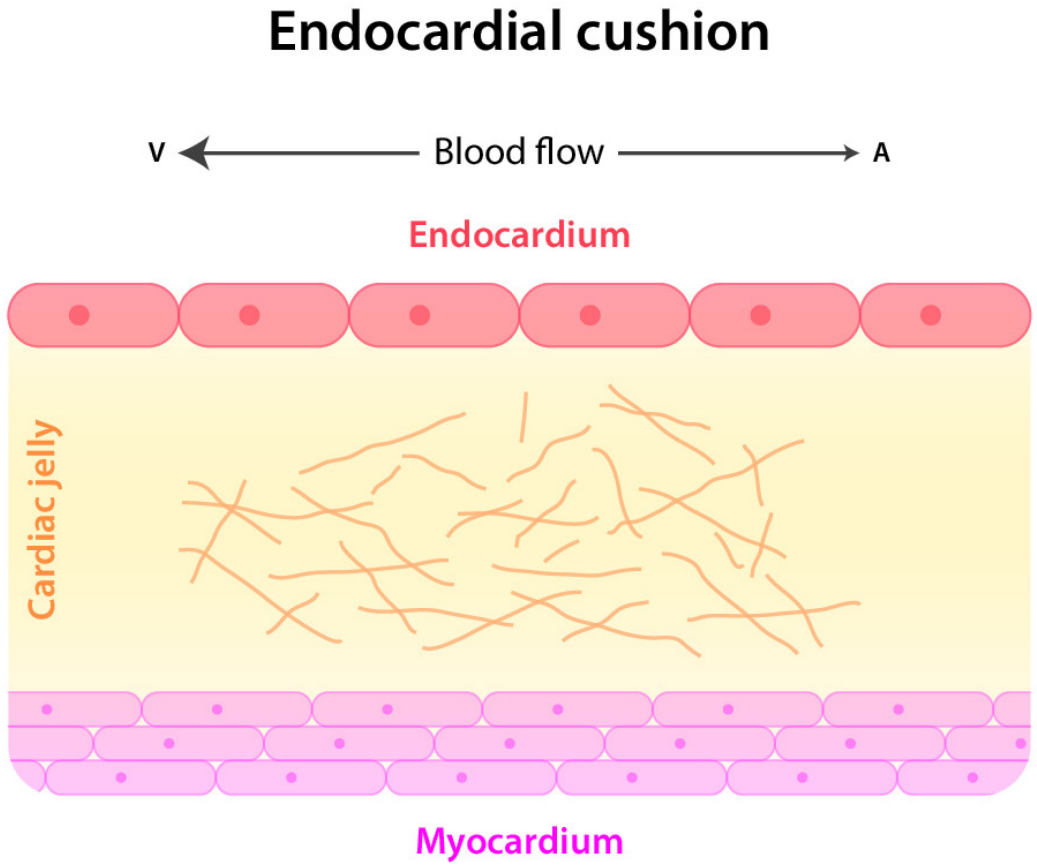
Key behaviors

Proliferation Differentiation ECM production

Project goal

To develop a human cell culture model of **EndMT** to study chemical effects on cardiac septation and valve development.

Key aspects to recapitulate in model



Cell types

Endocardial | Myocardial

Chemical signals

↑ TGF-β | ↑ BMP | T VEGF

Mechanical signals

Cardiac jelly | Blood flow

Key phenotypic changes to measure in model

Endothelial phenotype

Endothelial cells

VE-cadherin

PECAM-1

VEGFR2

Intermediate phenotypes

Mesenchymal phenotype

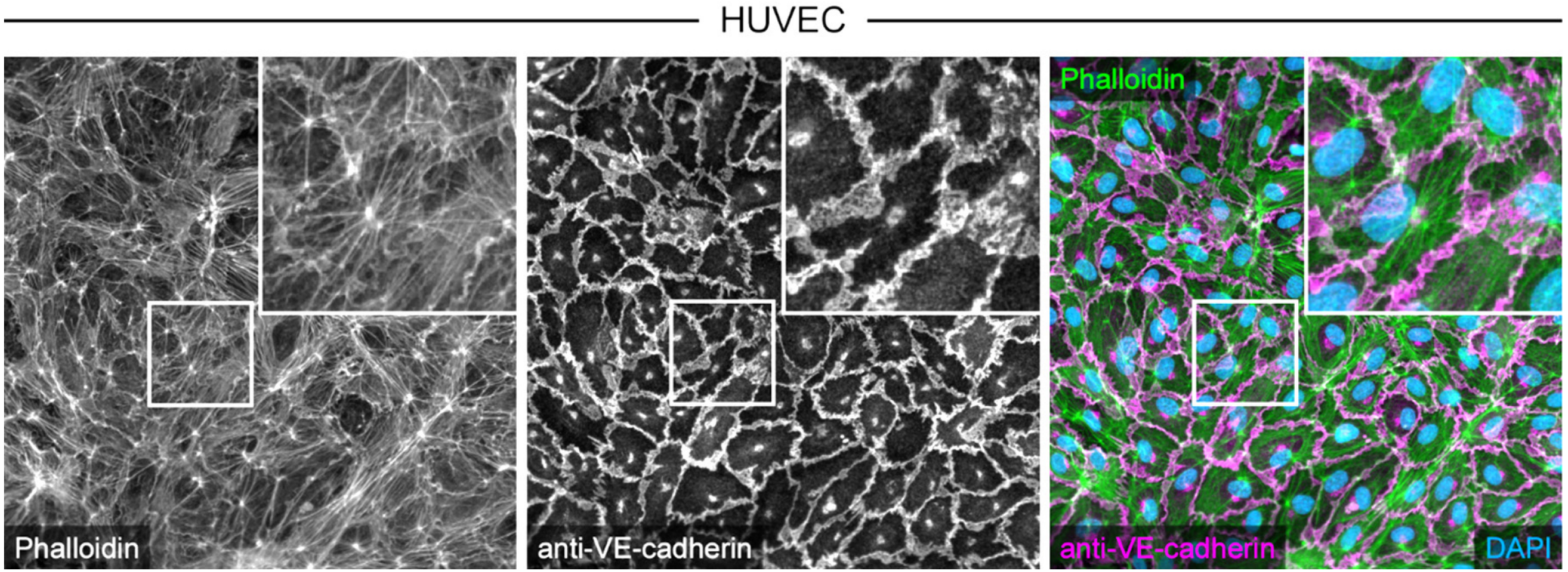
Mesenchymal cells

Snail	α-SMA
Slug	Vimentin
Twist	Fibronectin

Initial approach

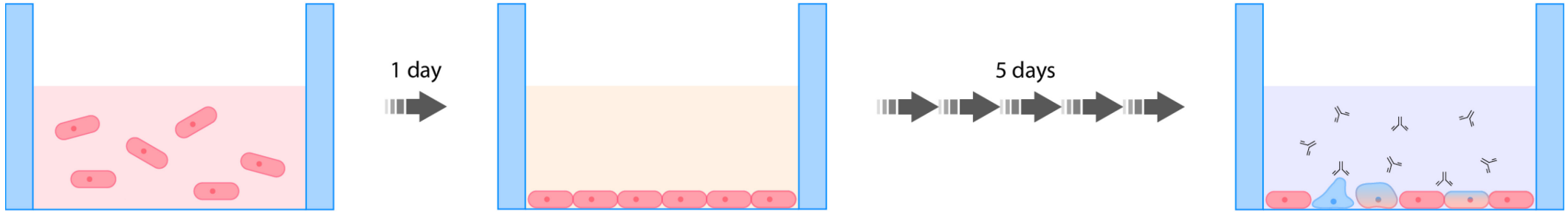
To induce endothelial cells cultured on fibronectin (FN)-coated plastic to undergo **EndMT** using myocardial-derived signals.

Primary and iPSC-derived endothelial cells



Experimental workflow for EndMT induction - I

Cell seeding → 1 day → **Serum starvation** → 5 days → **TGF-β1 treatment** → **Immunostaining**



Cell types

- HUVEC
- hiPSC-EC
- HCAEC
- HMVEC

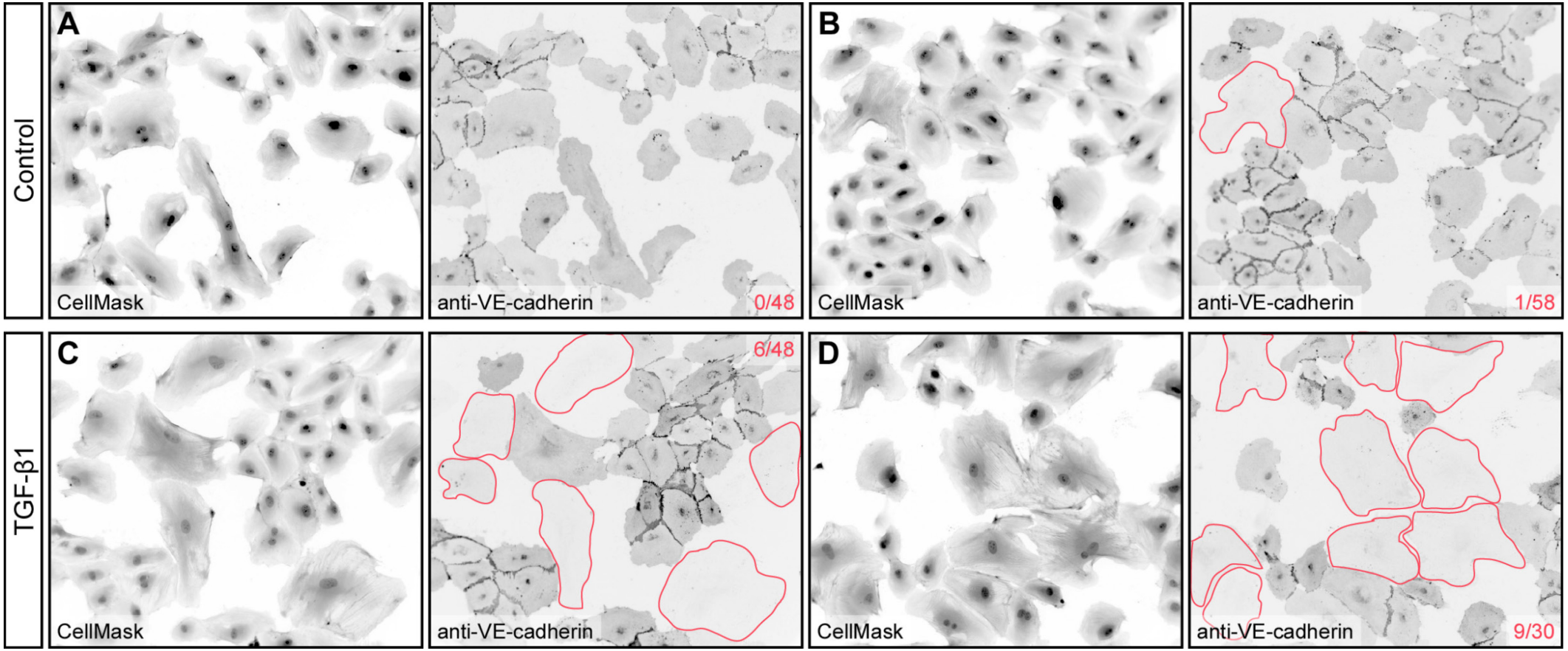
Culture media

- Complete
- Reduced serum
- Reduced serum and lacking growth factors
- Basal

Cell markers

- VE-cadherin
- PECAM-1
- VEGFR2
- Snail
- Slug
- Twist
- α-SMA
- Vimentin
- SM22a

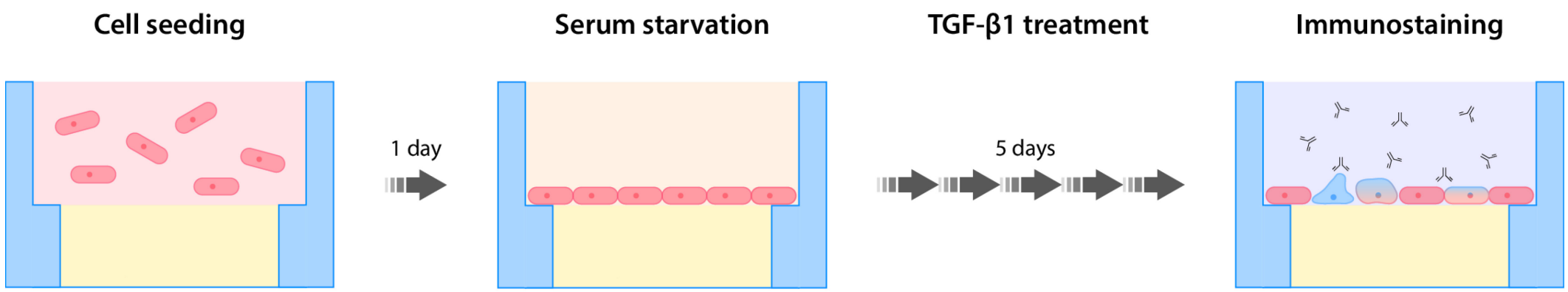
HMVEC undergo EndMT on FN-coated plastic



Revised approach

To induce endothelial cells cultured on hyaluronan (HA)-based hydrogel to undergo **EndMT** using myocardial-derived signals.

Experimental workflow for EndMT induction - II



Cell types

HUVEC

hiPSC-EC

Culture media

Reduced serum

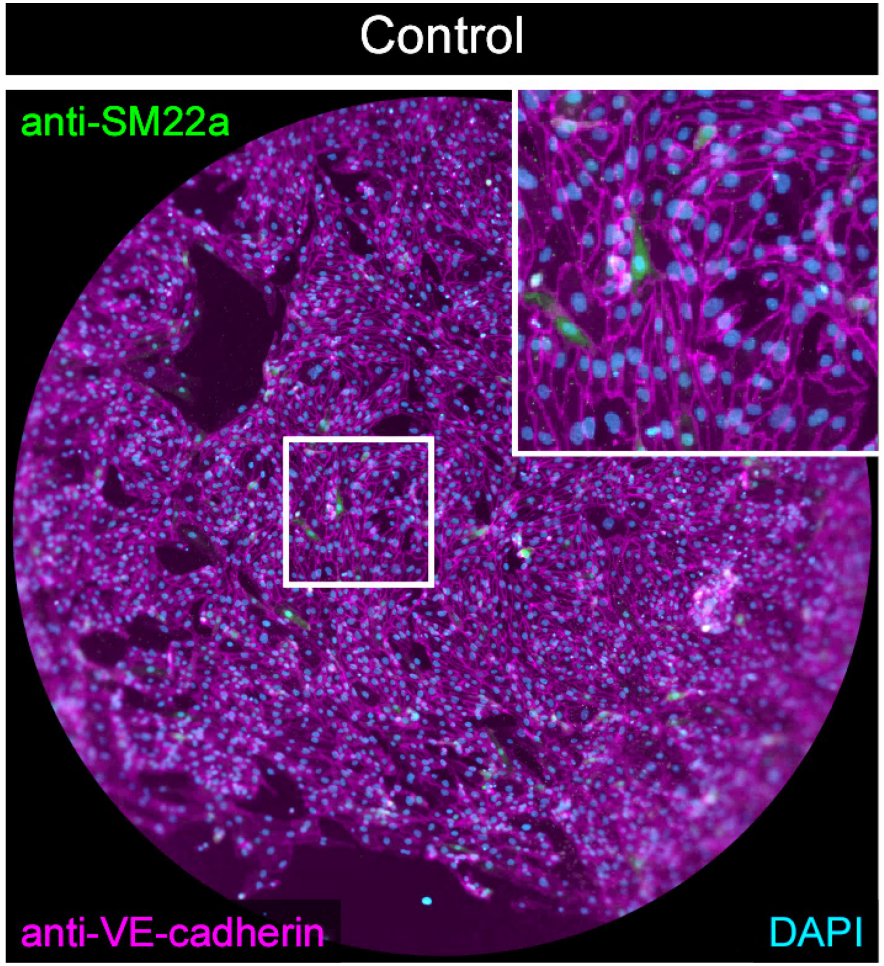
Reduced serum and lacking growth factors

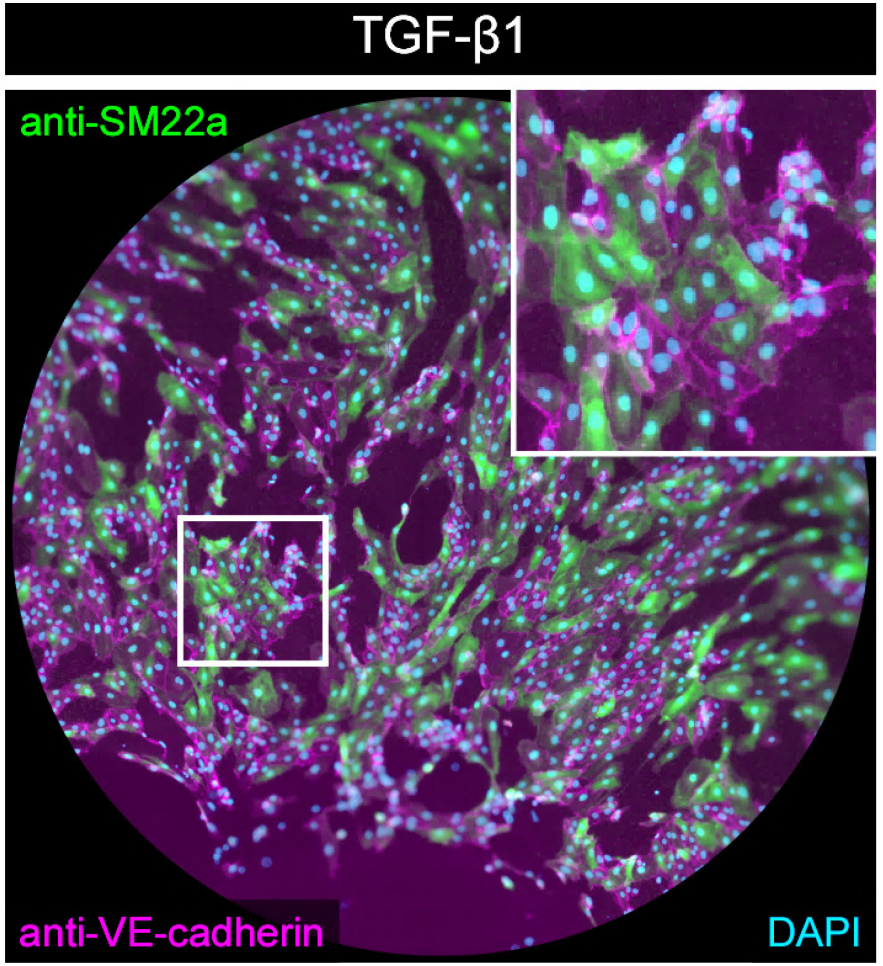
Cell markers

VE-cadherin

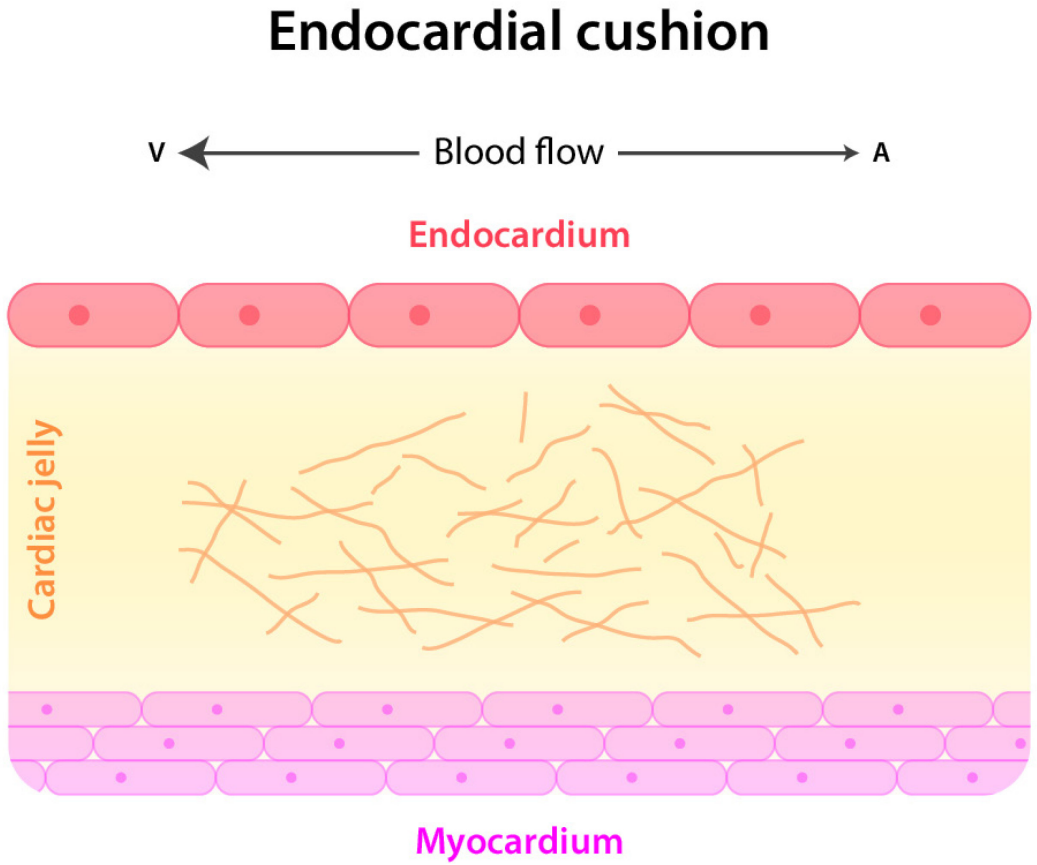
SM22a

HUVEC undergo EndMT on HA-based hydrogel





Next steps in model development



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Mechanical signals

Cardiac jelly | Blood flow

Acknowledgments

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Virtual Tissue Models project

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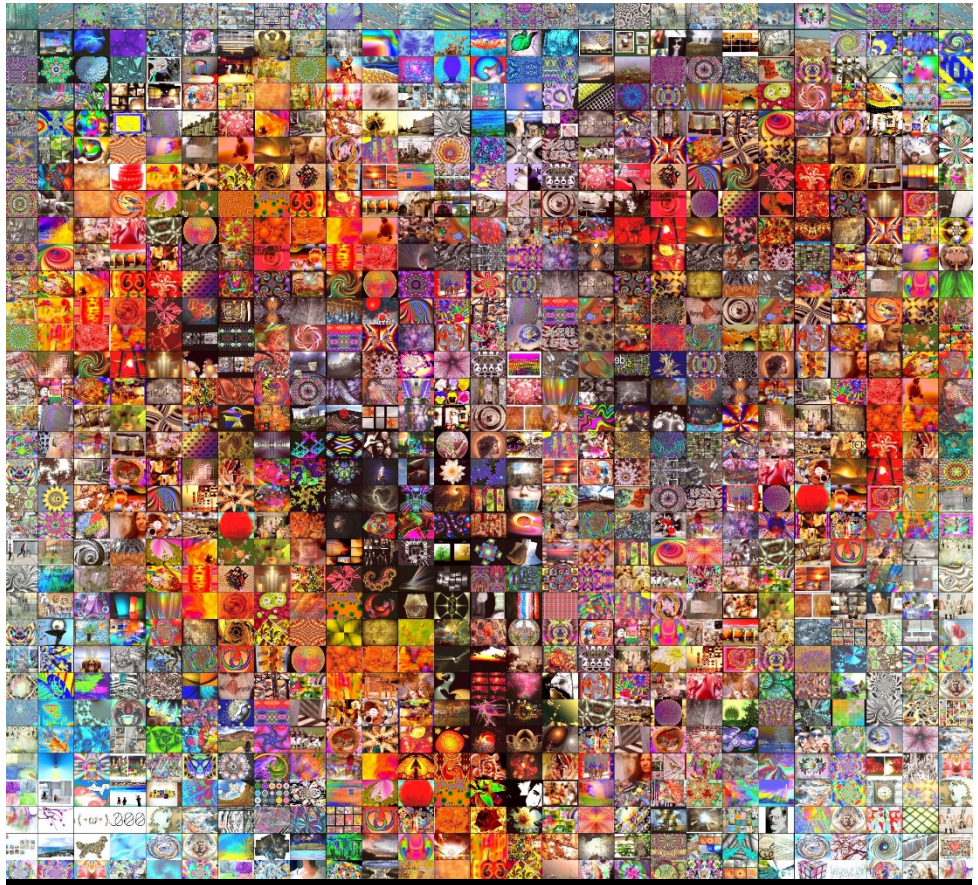

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Questions?