Designing Engineered Biomaterials for Cardiovascular Regeneration

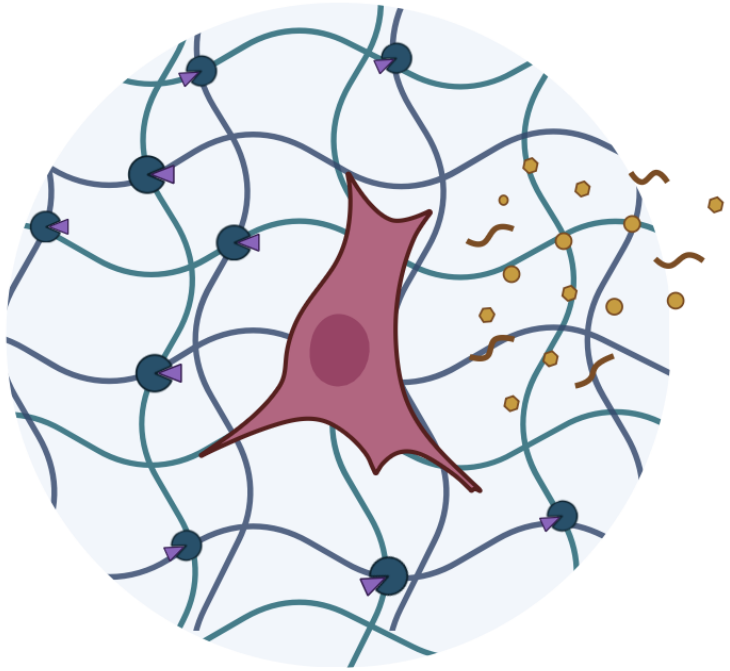
Yuan Yao, PhD

Assistant Professor
Department of Mechanical engineering
Division of Cardiology
Center of Heart Lung Innovation

THE UNIVERSITY OF BRITISH COLUMBIA

Centre for Heart Lung Innovation
UBC and St. Paul's Hospital

Design Therapeutic Biomaterials

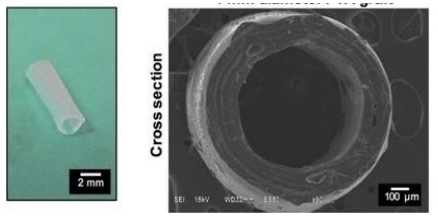


Surface functional groups

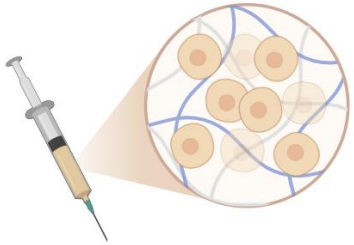
Topography cues

Soluble biochemical molecules

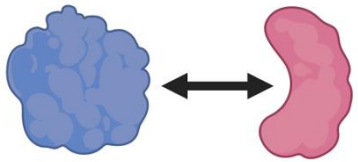
Matrix mechanics



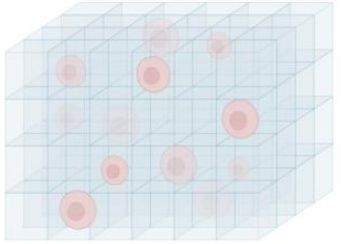
Design of vascular graft



Delivery vehicle for cell transplantation

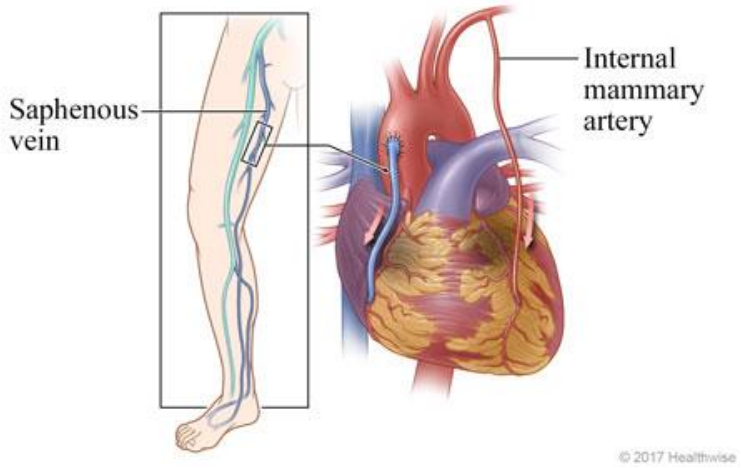


Controlled release of therapeutic proteins

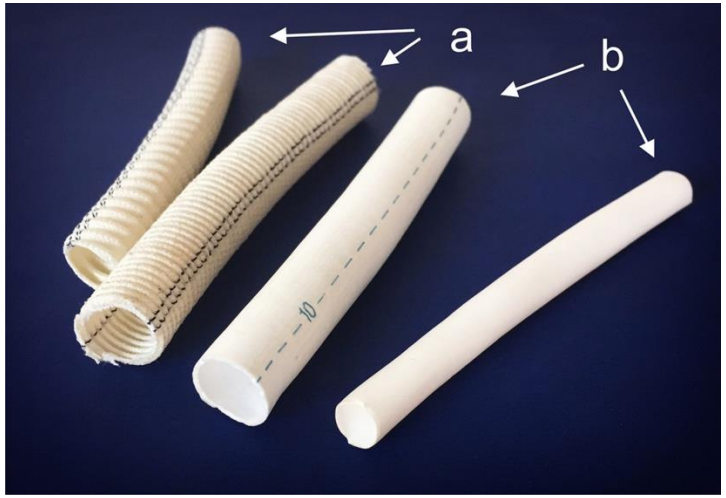


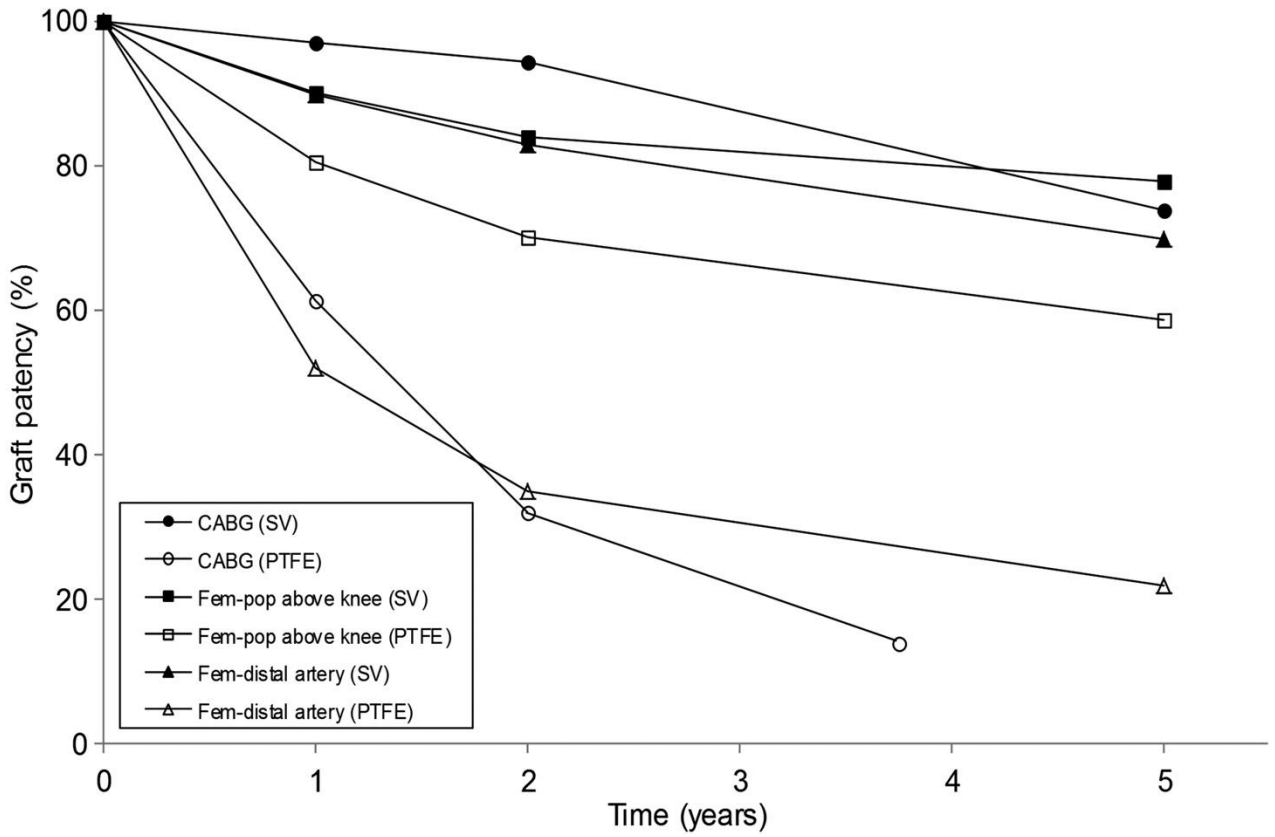
3D cell scaffold

Artificial Small Diameter Vascular Graft



Dacron ePTFE

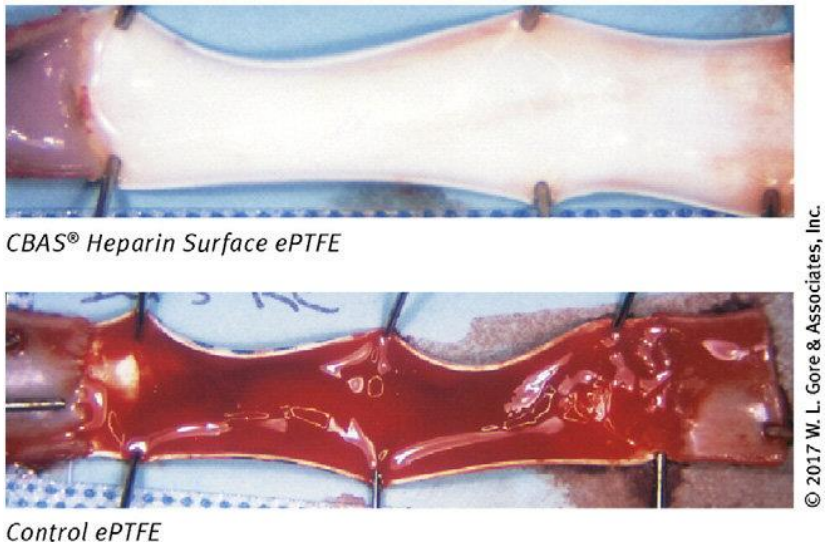




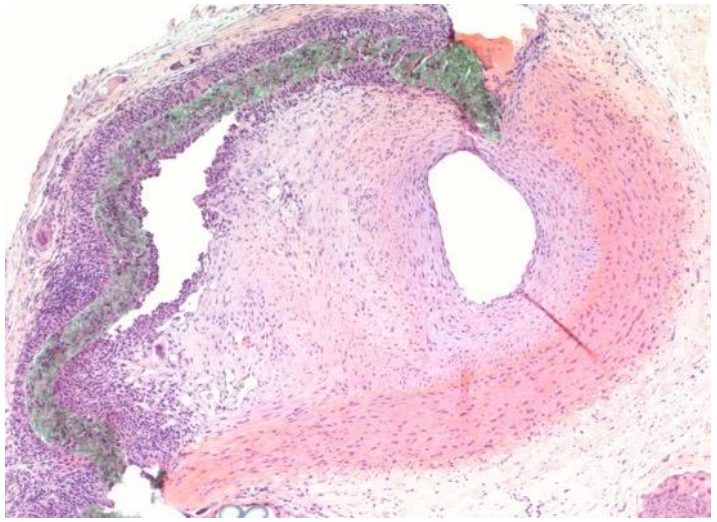
Pashneh-Tala et al. Tissue Engineering: Part B, 2016

Failure of Artificial Small Diameter Vascular Graft

Thrombosis



Intimal hyperplasia

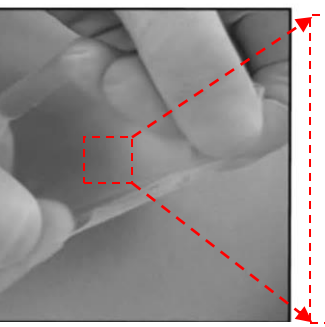


Problems of current synthetic grafts:

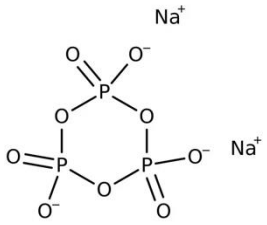
- Lack of endothelial lining
- Mismatch of mechanical properties

Polyvinyl Alcohol Small Diameter Vascular Graft

Polyvinyl alcohol hydrogel as new graft materials

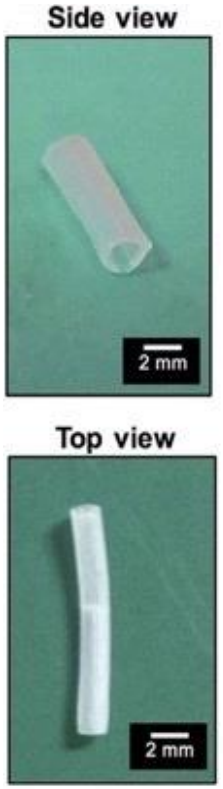


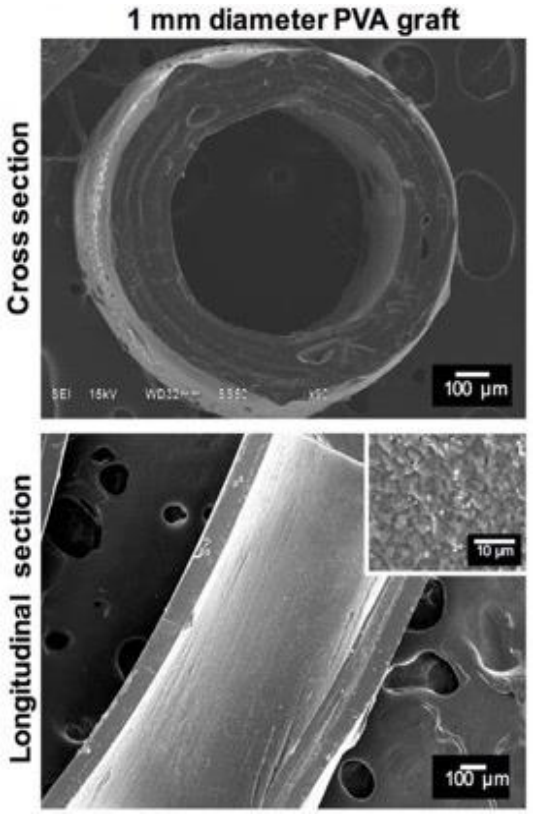
PVA



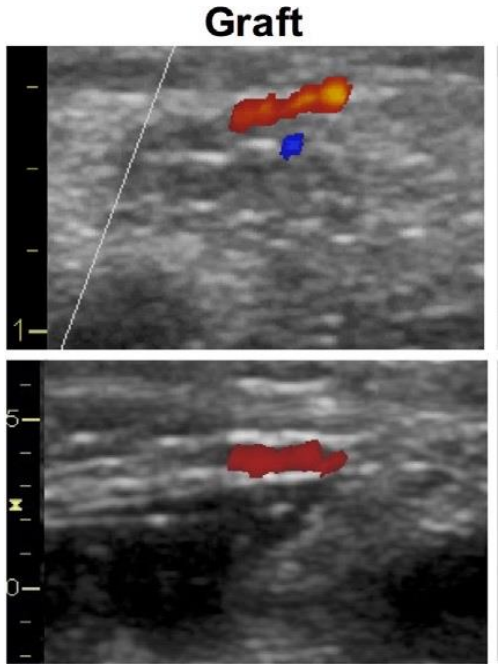
STMP

- ✓ Mild fabrication condition
- ✓ Tunable mechanical properties
- ✓ Low thrombogenicity



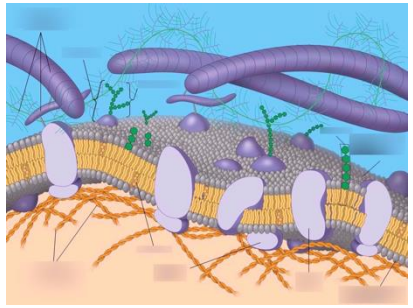


Patent in rabbit femoral artery end-to-end model for 12 days without any anticoagulant



Cutiongco et al. Front. Bioeng. Biotechnol. 4 (2016) 44.

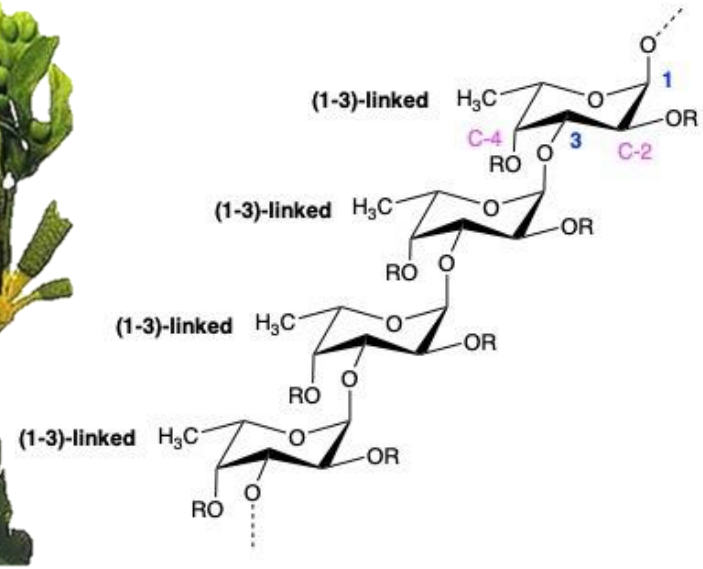
Biochemical Modification to Improve Endothelial Healing



ECM proteins:
Promote cell adhesion;
Limited in vivo stability;
Non-specifically attract platelet adhesion

Anticoagulant:
Reduce blood clotting
But not effective to promote cell growth

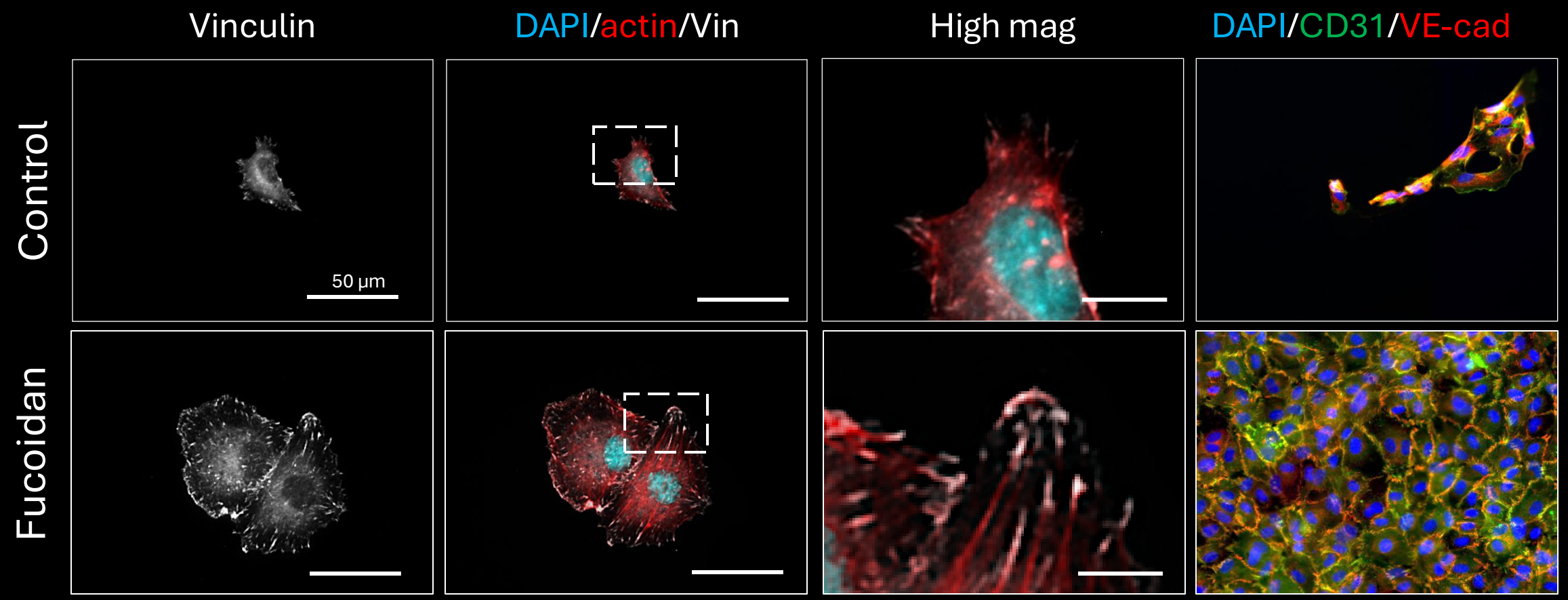
Fucoidan



- Anticoagulant/antithrombotic activity
- Anti-inflammatory activity
- Modulation of vascular cells

Yao et al. Carbohydrate Polymers . 2021, 270, 118347

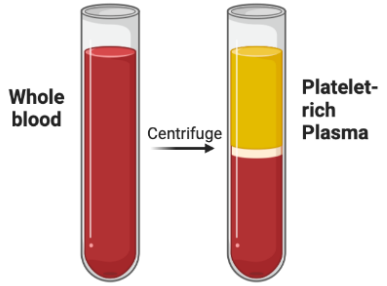
Fucoidan Improves Vascular Endothelial Cell Adhesion

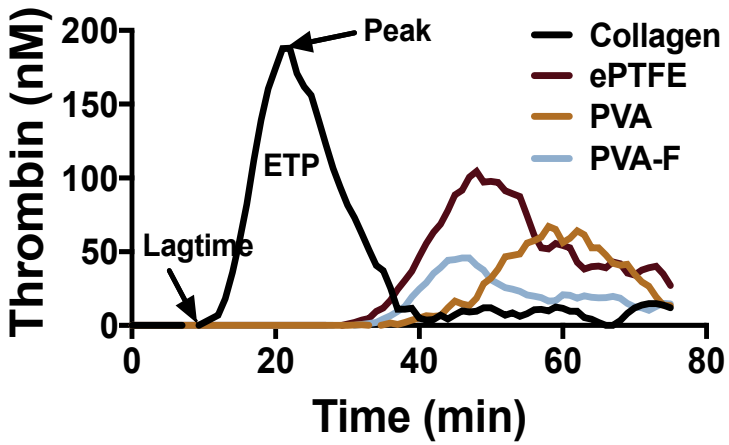


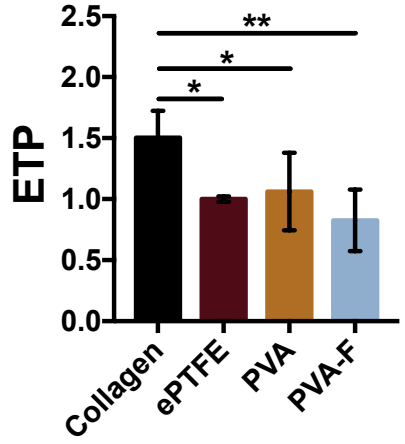
Yao et al. Biomaterials. 2020, 249, 12001
Yao et al. Bioactive Materials. 2023, 22, 535

Fucoidan Maintains Material Low Thrombogenicity

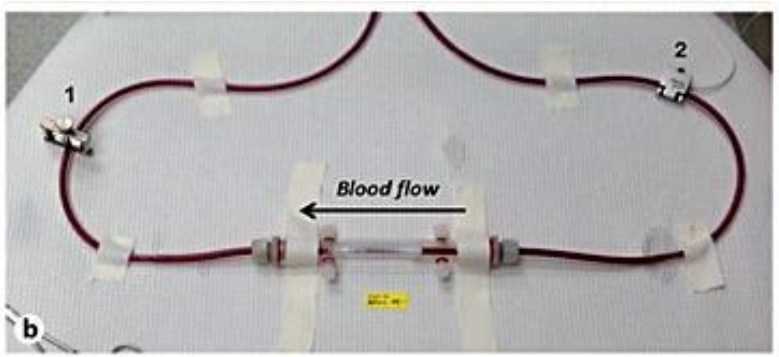
In vitro blood test

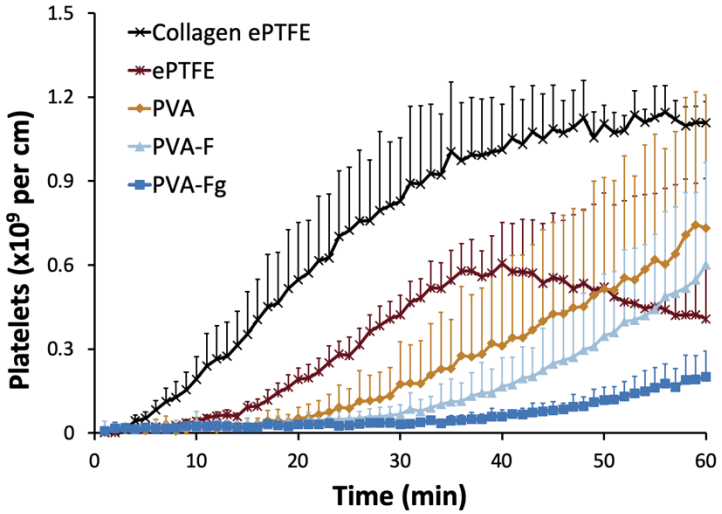


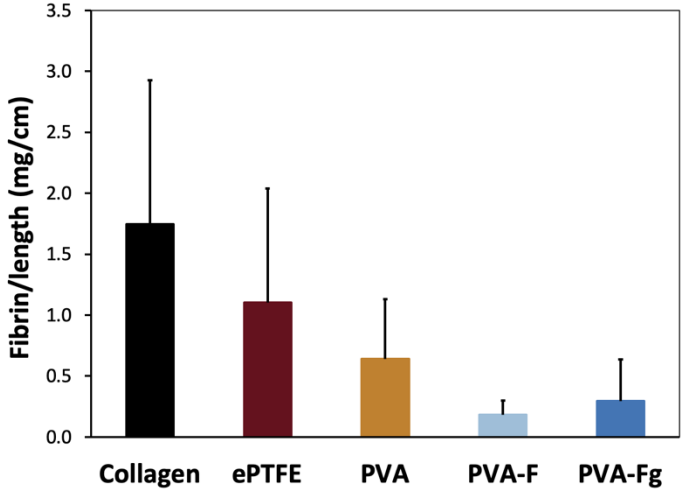




Ex vivo whole blood shunt test



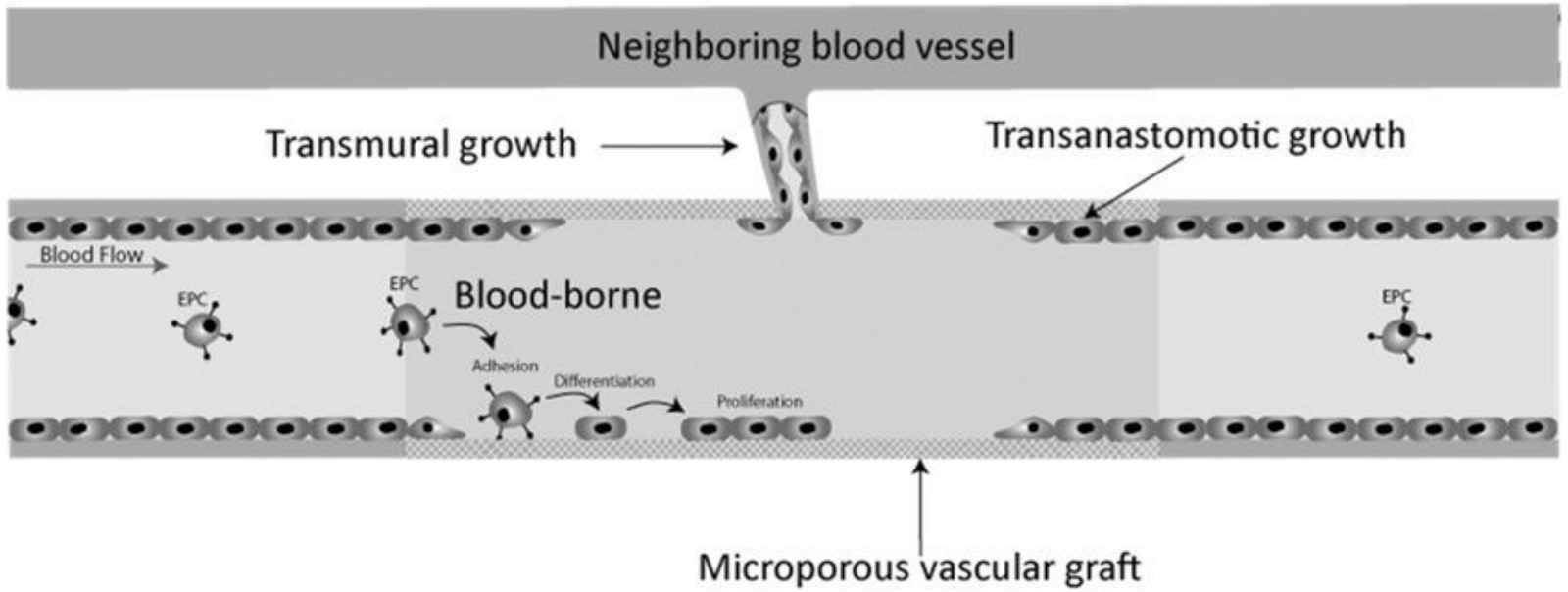




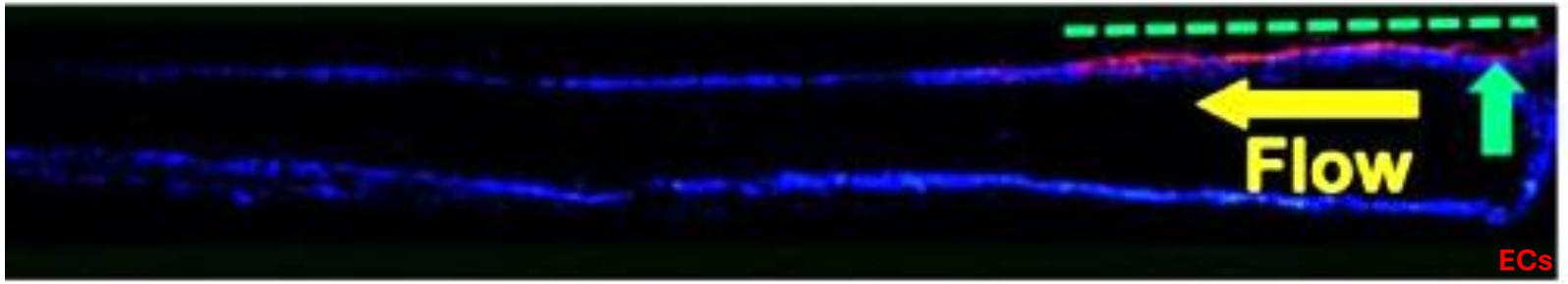
Yao et al. Biomaterials. 2020, 249, 12001

Human Arterial Endothelial Cells Have Limited Migration Capability

- Transanastomotic migration of human vascular endothelial cell is limited



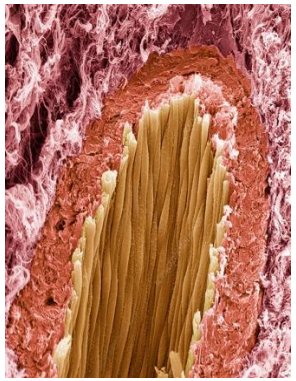
- Most synthetic grafts are only endothelialized at the perianastomotic regions

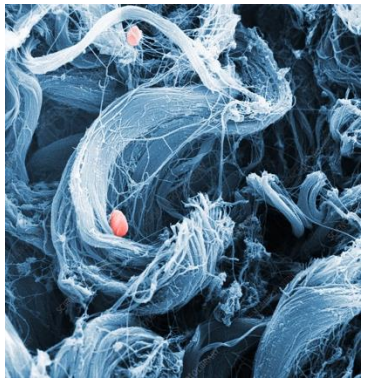


Wen et al. ACS Appl. Mater. Interfaces 2020, 12, 6, 6863–6875;
Heath. Macromol. Chem. Phys. 2017, 218, 1600574

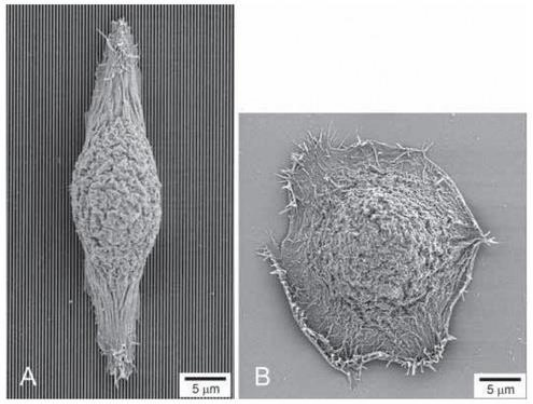
Using Topography Cues to Modulate Endothelial Responses

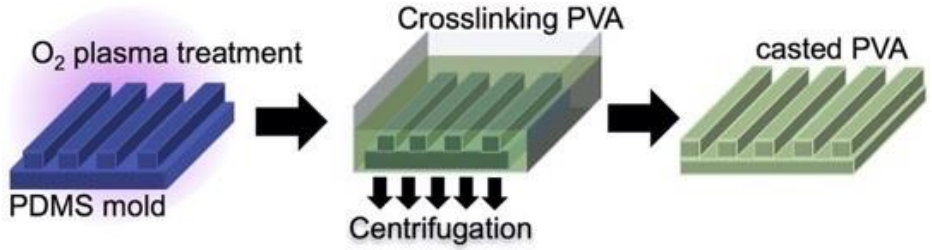
Cells interact with extracellular topography

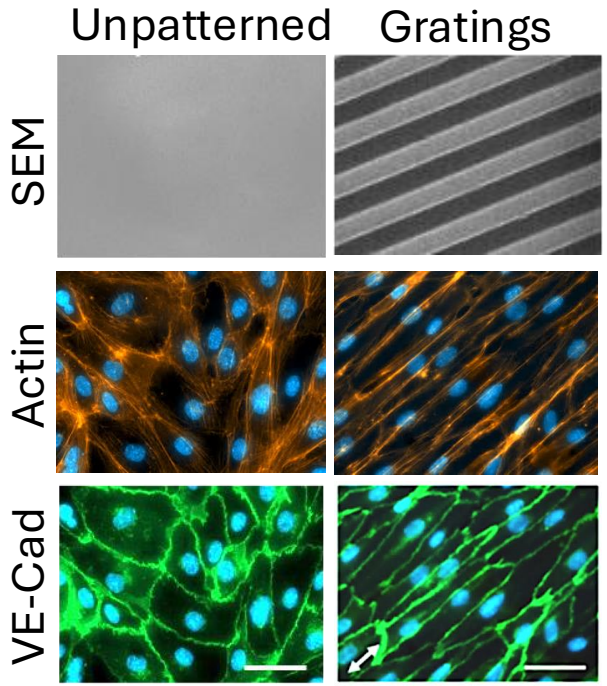




Material topography change cell behaviors

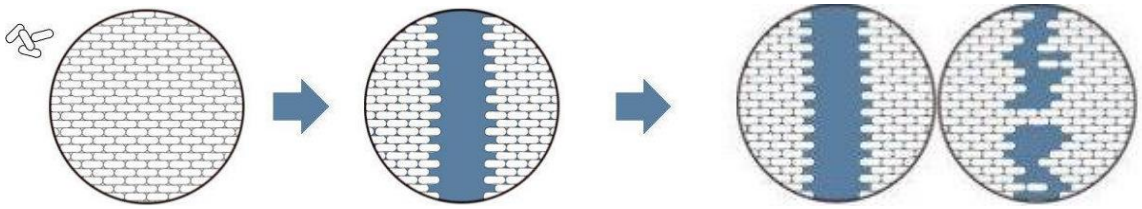


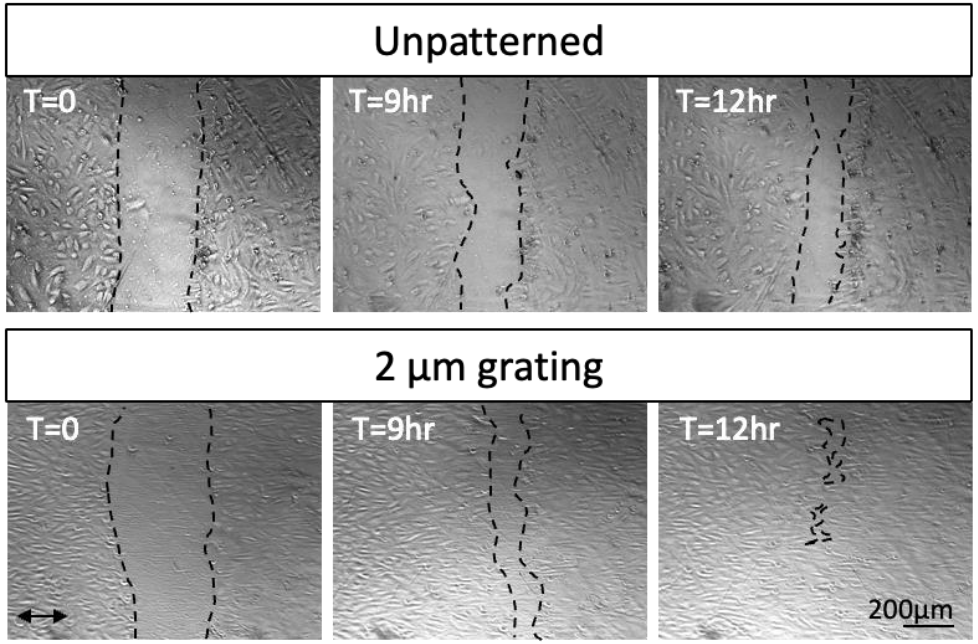


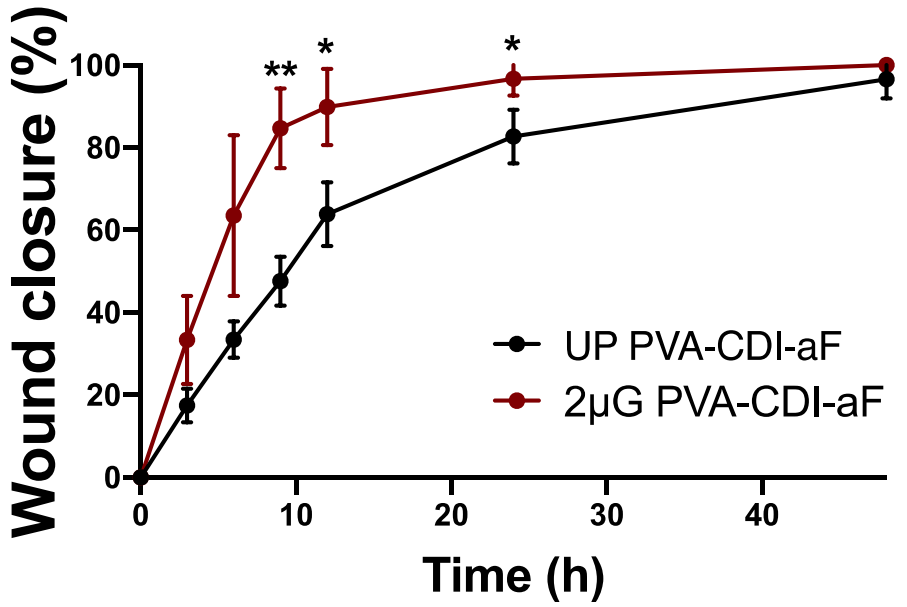


Teixeira et al., J. Cell Sci. 2003, 116, 1881
Yao et al. Bioactive Materials. 2023, 22, 535

Gratings Promote Endothelial Cell Directional Migration

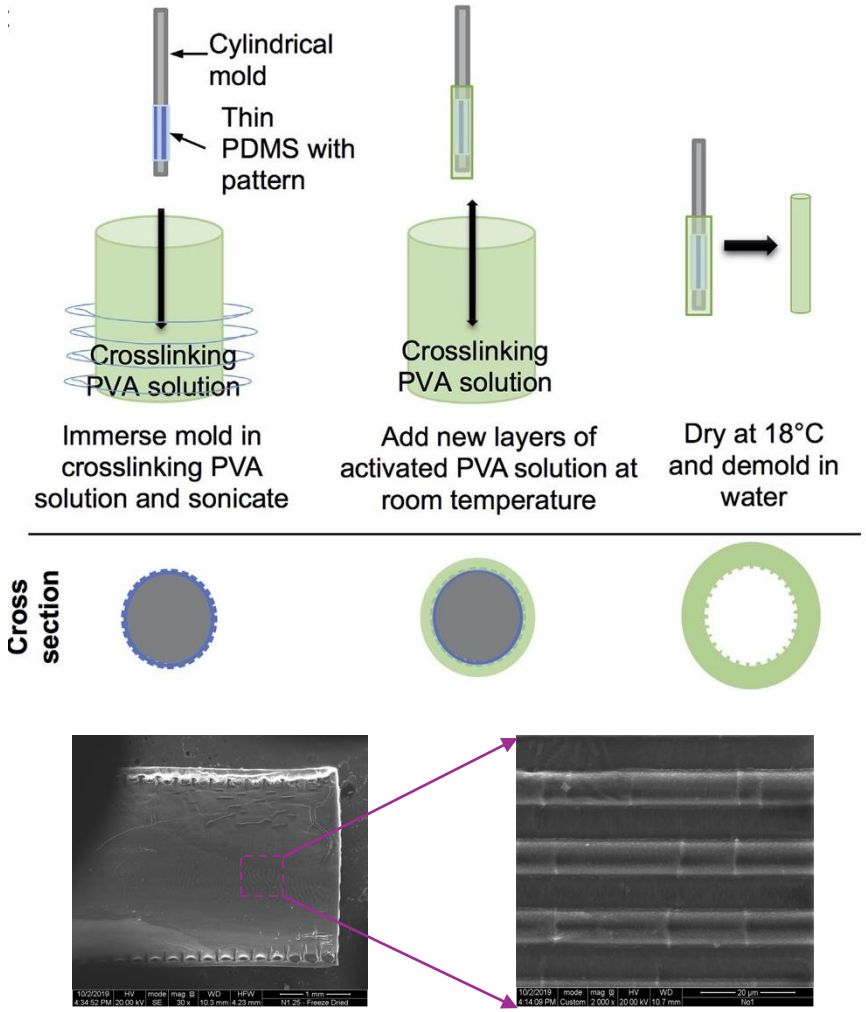


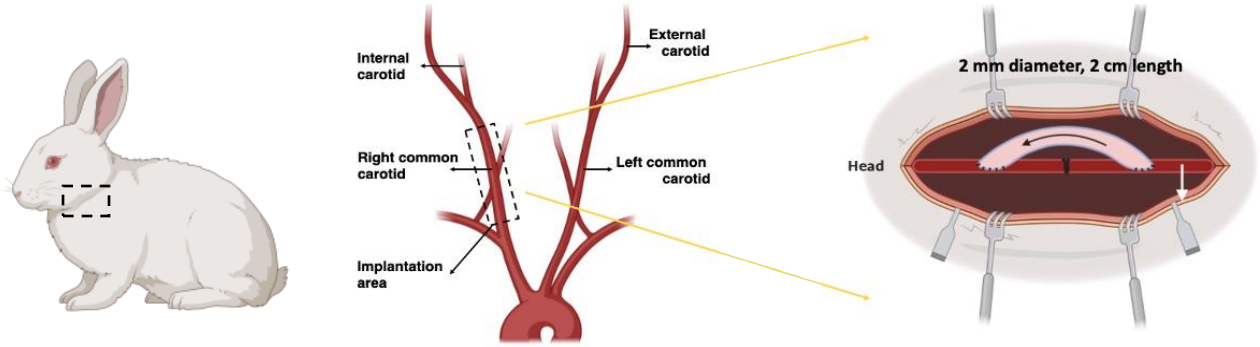


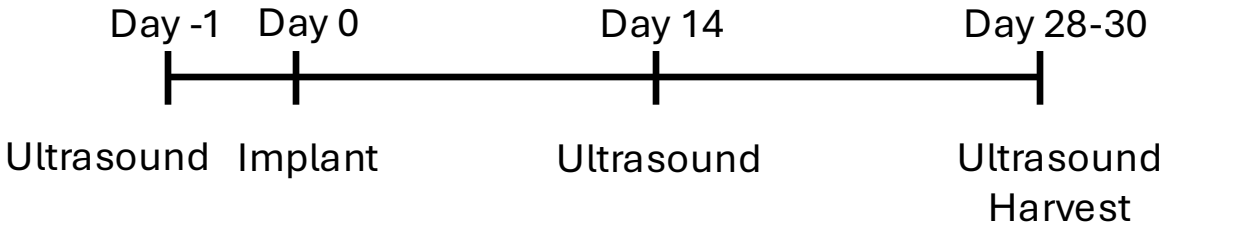


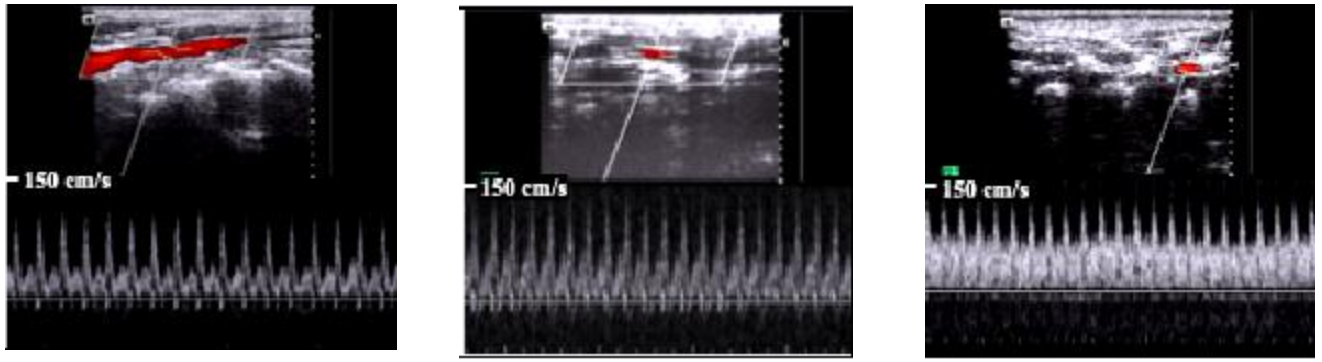
Yao et al. Bioactive Materials. 2023, 22, 535

Graft implantation in Rabbit Carotid End-to-side Model



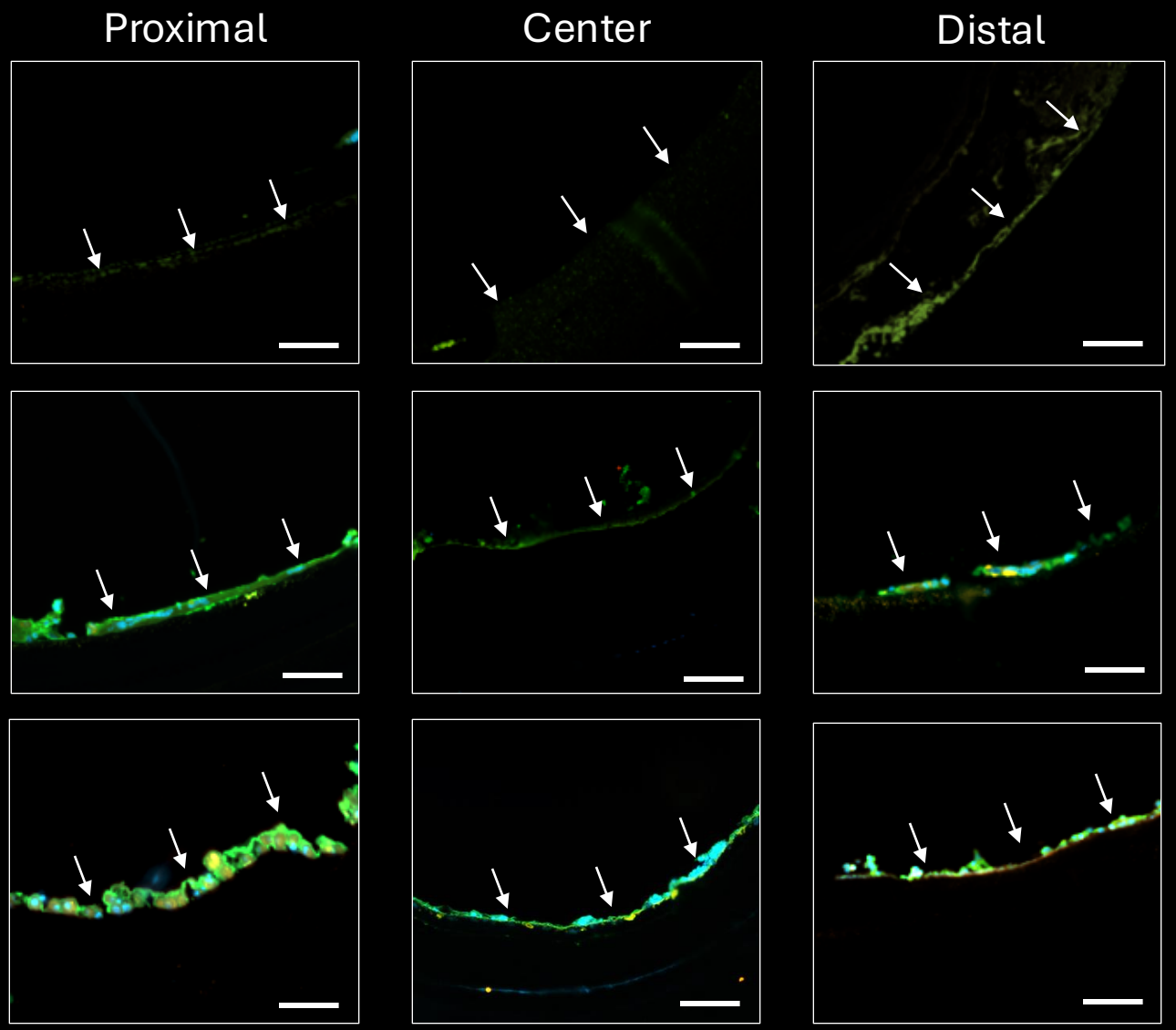






Yao et al. Vascular Tissue Engineering: Methods and Protocols. 2022, 177;
Yao et al. Bioactive Materials. 2023, 22, 535

Fucoidan and Gratings Improved *In Situ* Endothelialization



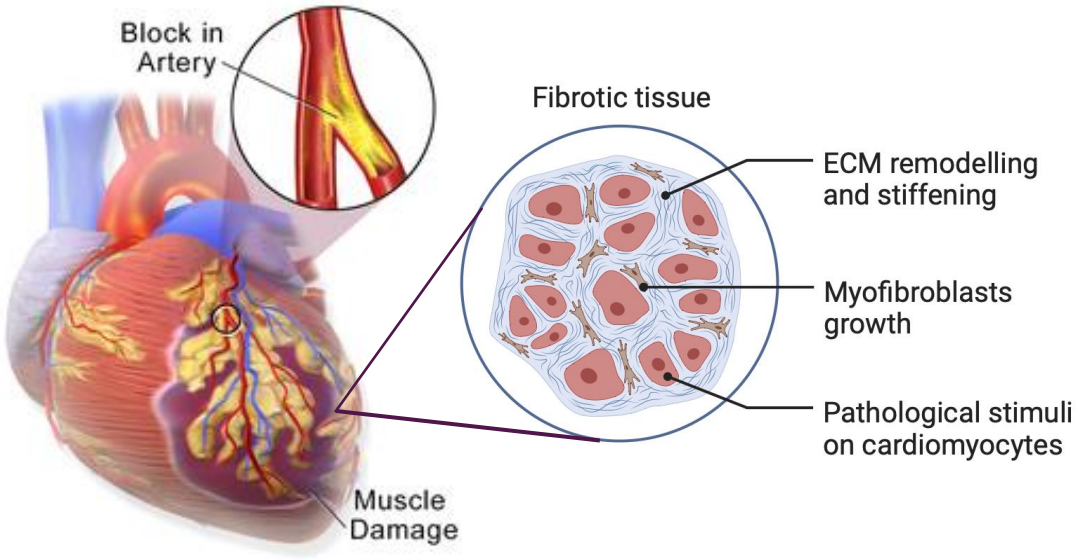
Minimal EC coverage

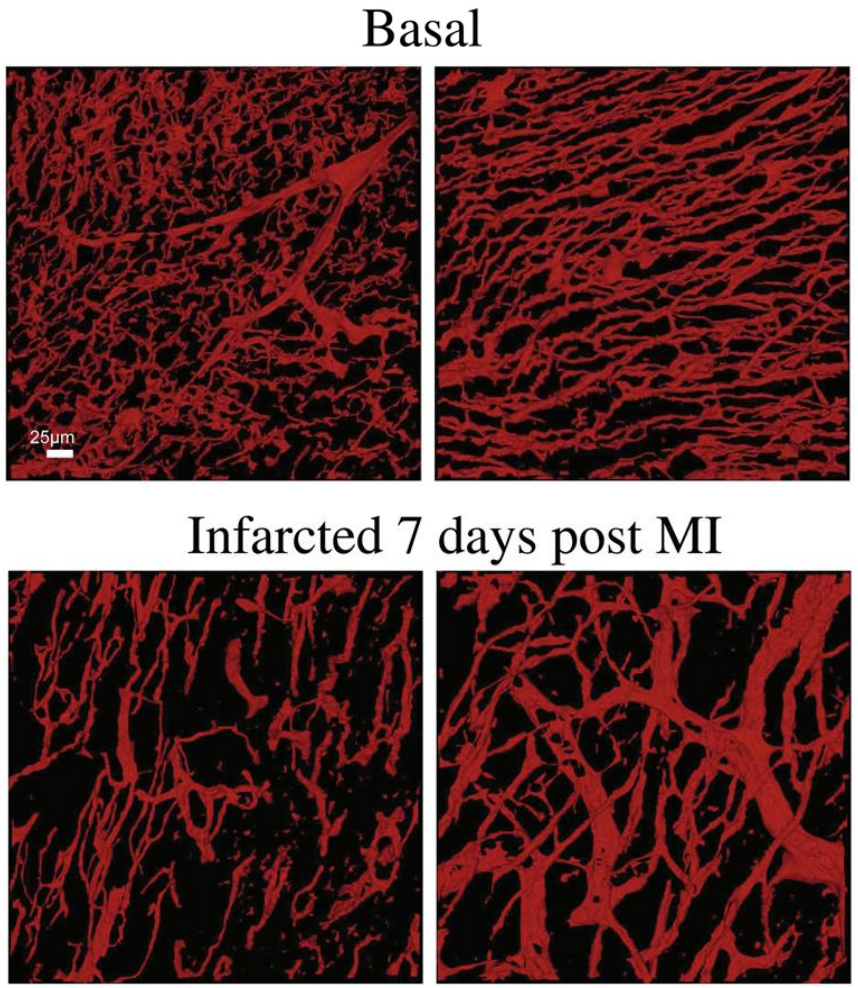
Fucoidan improve EC adhesion

Gratings improve EC healing throughout the graft

Yao et al. Bioactive Materials. 2023, 22, 535

Damaged microvasculature in myocardial infarction





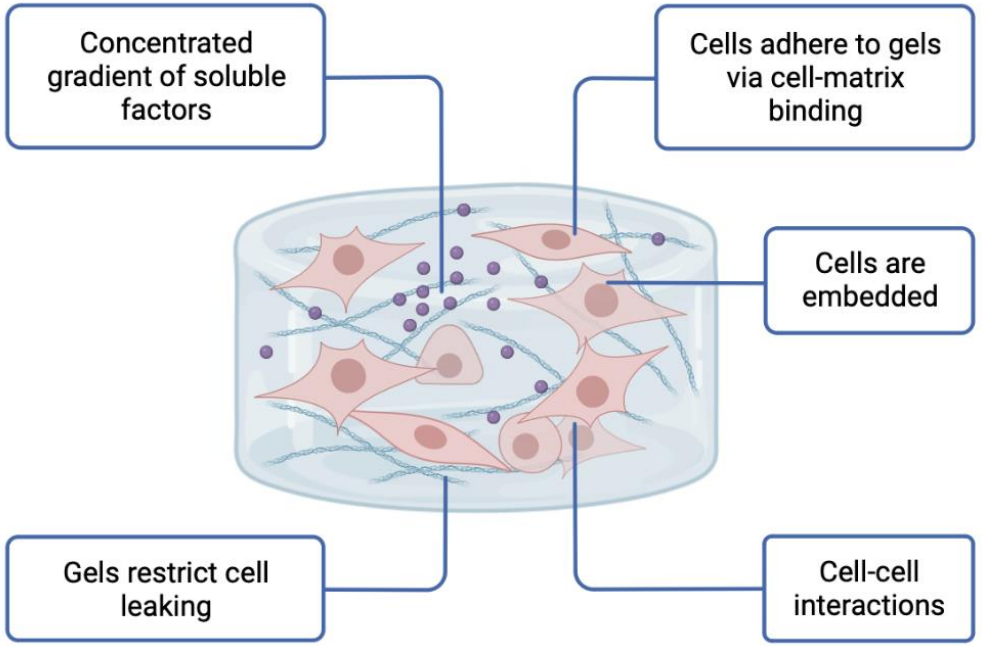
Gkontra, P., Norton, KA., Żak, M.M. et al. Sci Rep 8, 1854 (2018)

Cell transplantation therapy for promoting cardiac healing

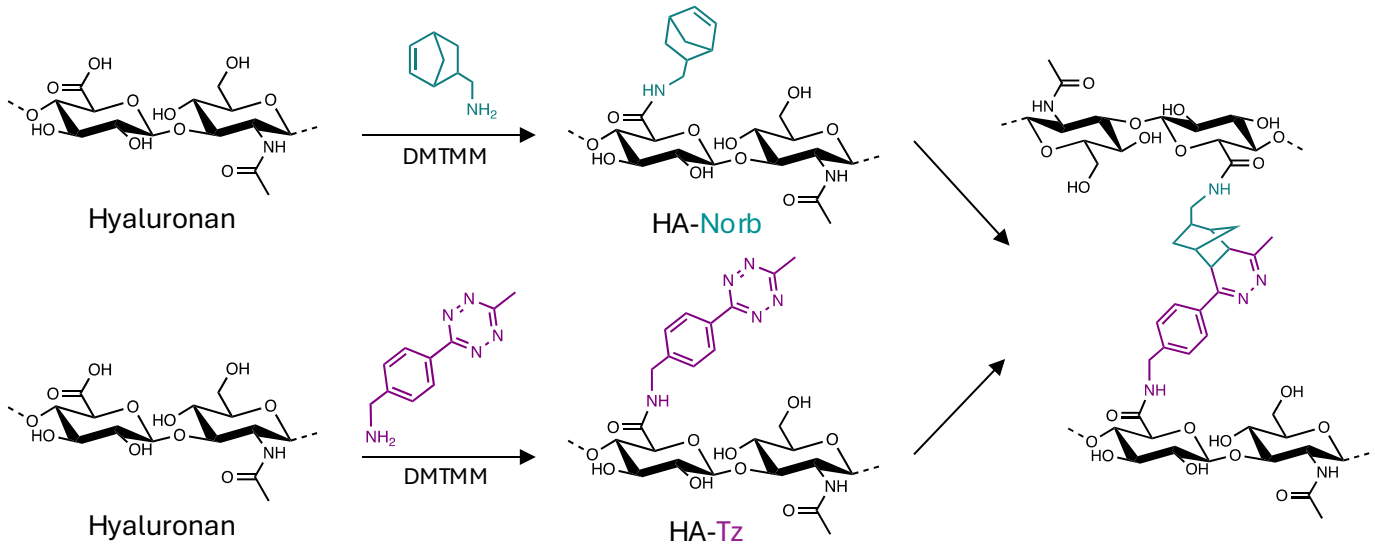
Cell transplantation

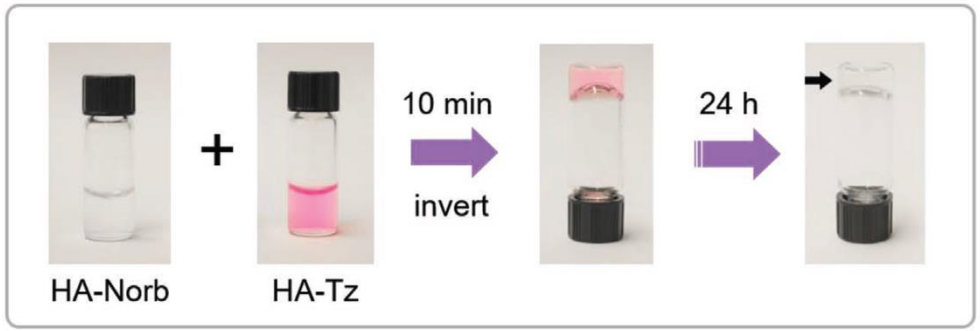
- **Without matrix, 90% cells die after transplantation**
- **Matrigel is not clinically translatable**

Animal-free matrix for cell transplantation

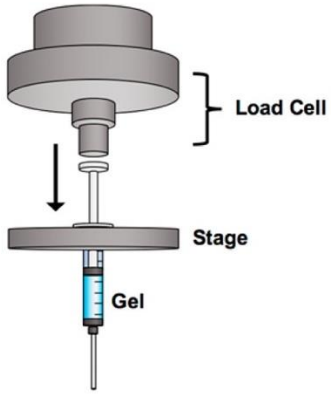


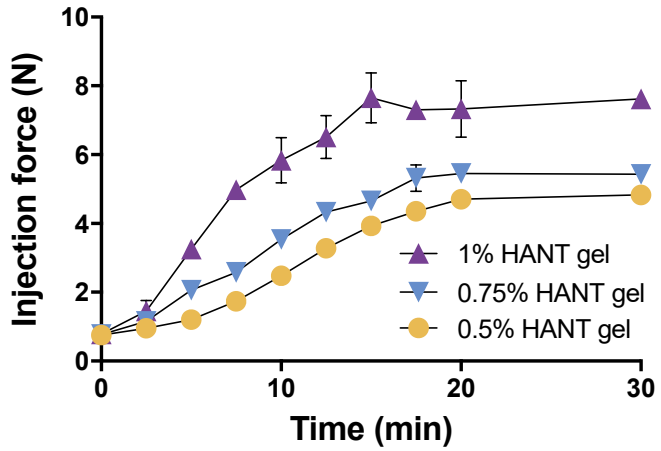
HA matrix has suitable physical properties for VP transplantation



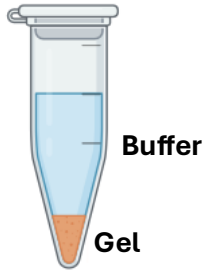


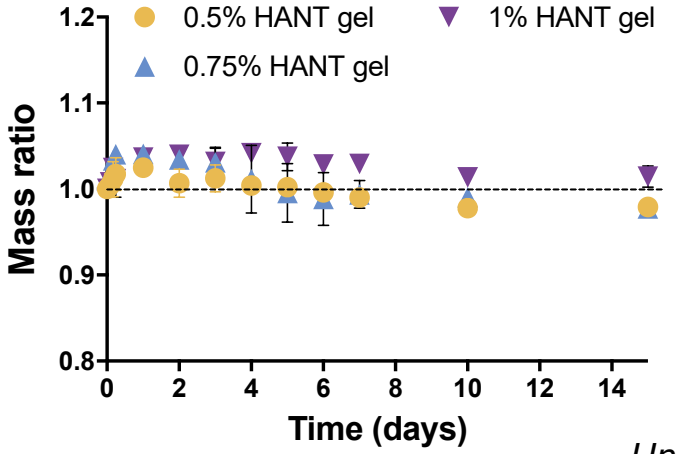
- Hyaluronan gels are injectable (28G needle)





- Hyaluronan gels do not swell significantly over 2 wks

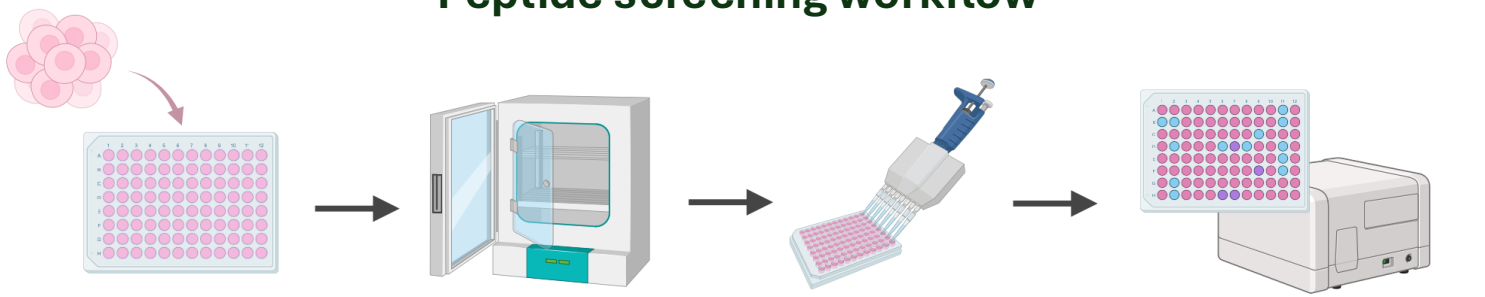




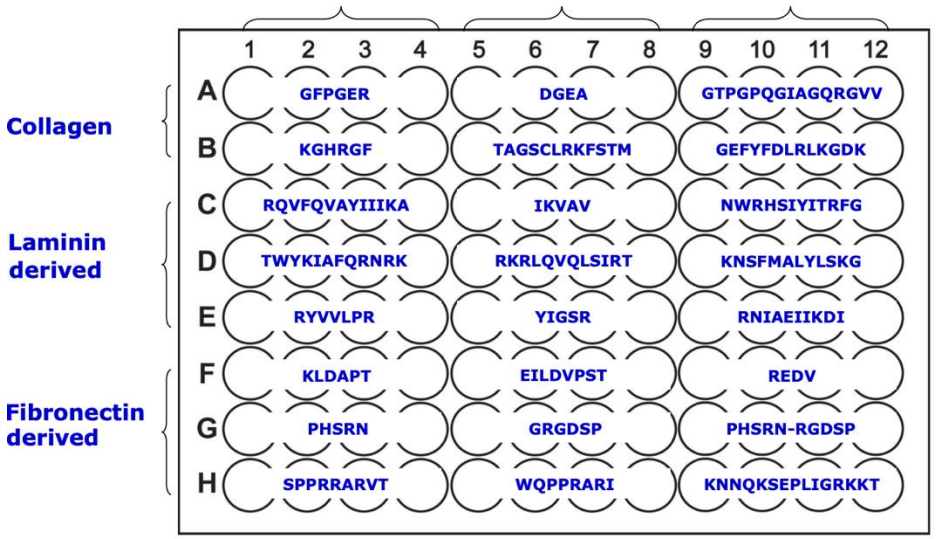
Unpublished data

Screening of cell-adhesive peptides

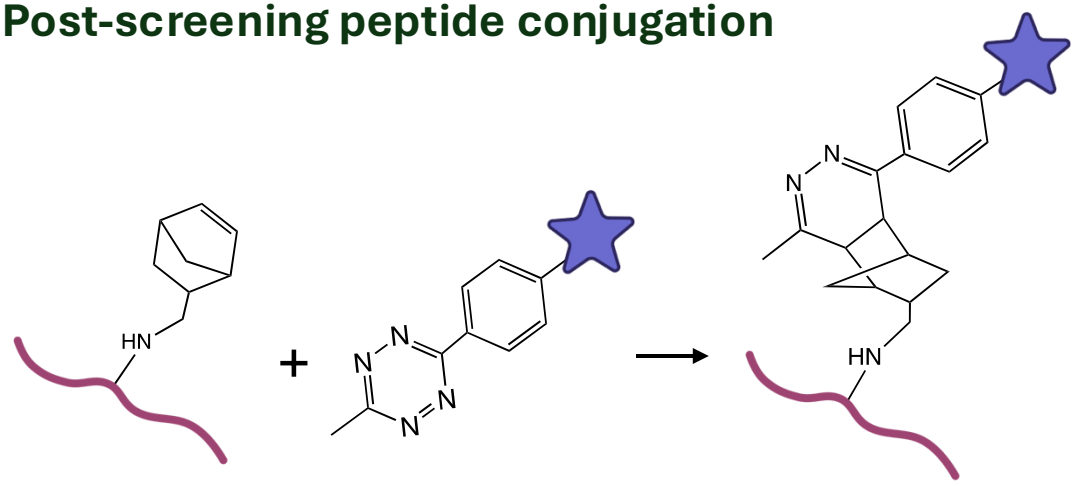
Peptide screening workflow



Peptide map



Post-screening peptide conjugation



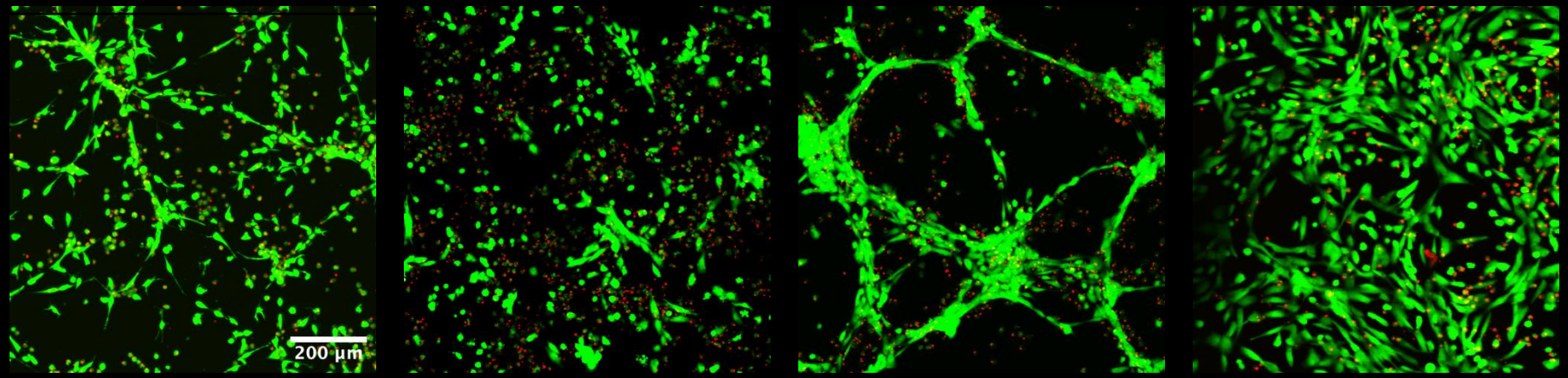
HA-Nb Peptide-Tz HA-peptide

Unpublished data

Matrix modified with peptides are suitable for cell encapsulation

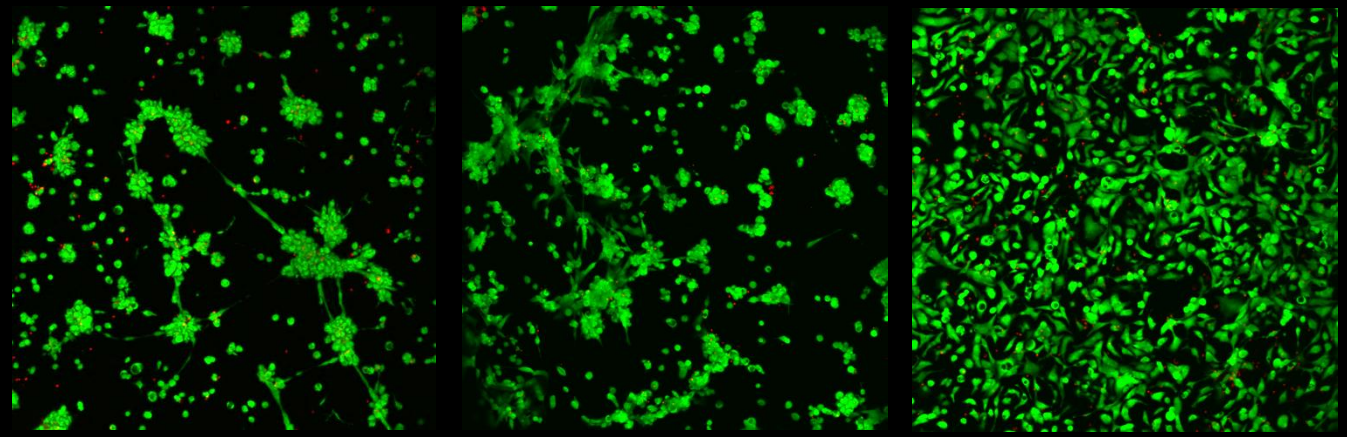
Vascular progenitors

Matrigel | No Peptide | 0.5% Peptide | 1% Peptide



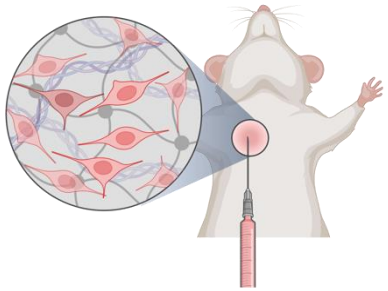
Cardiomyocytes

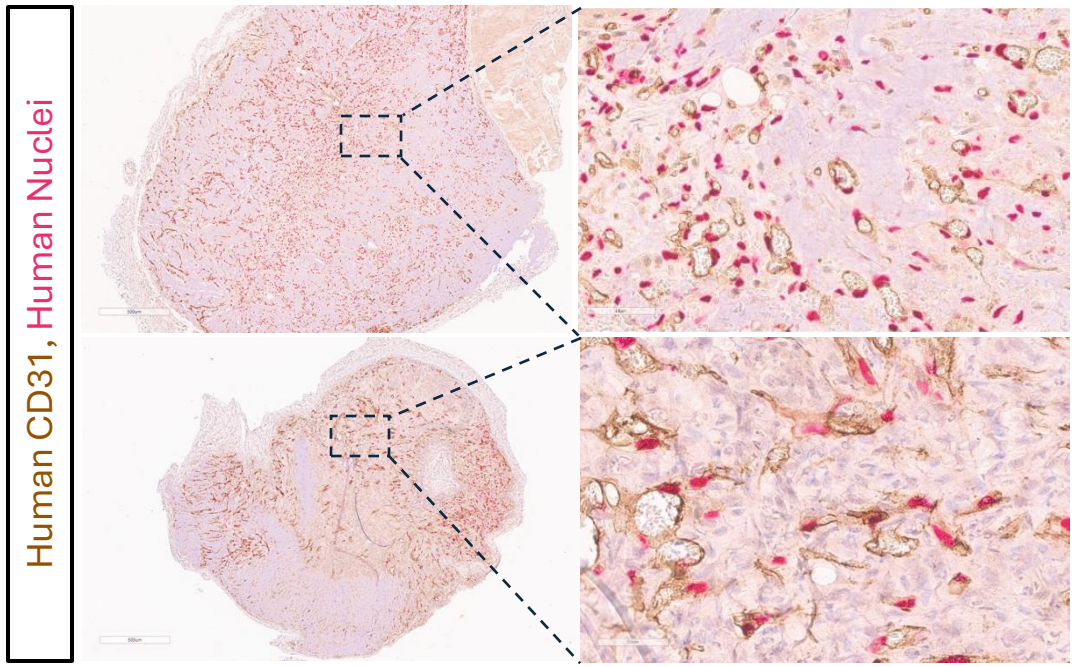
Matrigel | No peptide | 0.5% Peptide

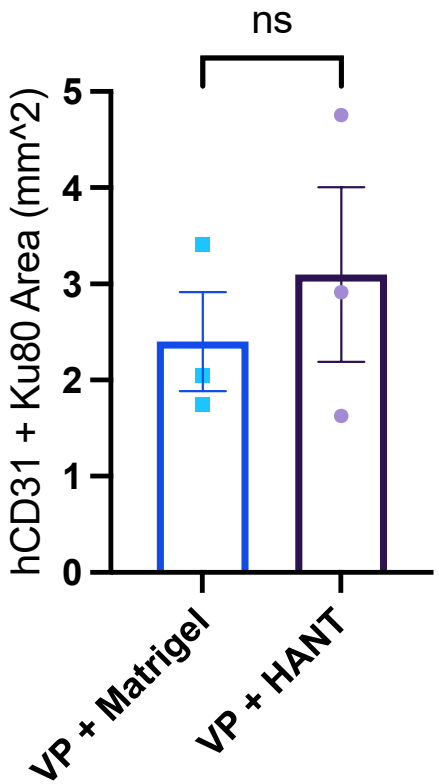


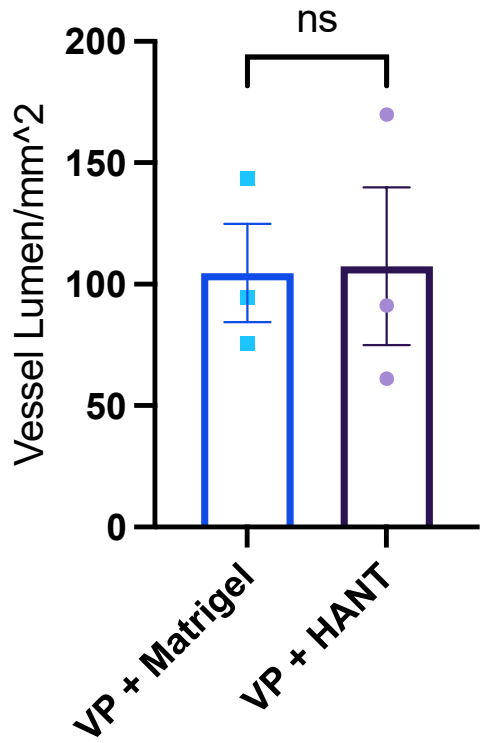
Unpublished data

Animal-free HA matrix supported VP engraftment in mice









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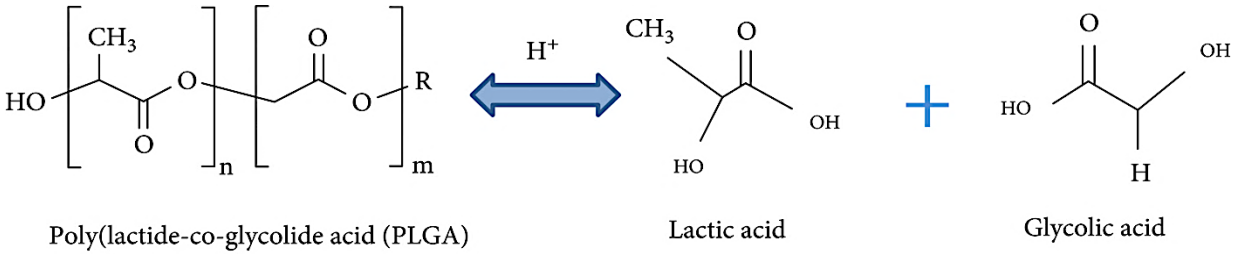
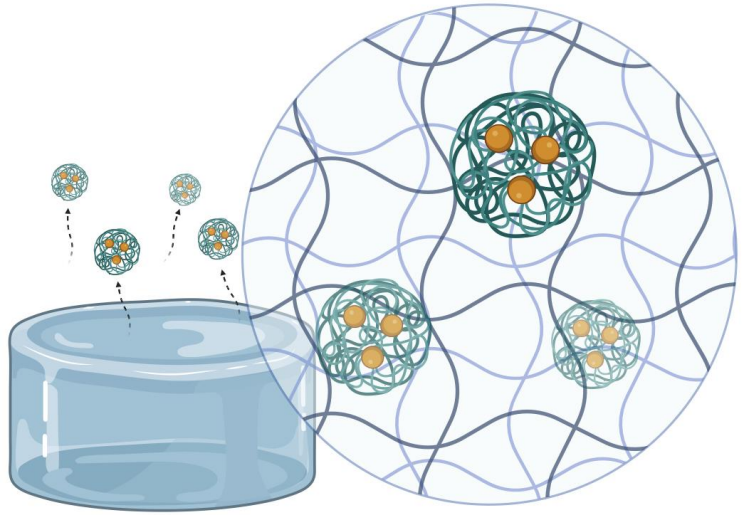
BlueRock THERAPEUTICS

Unpublished data

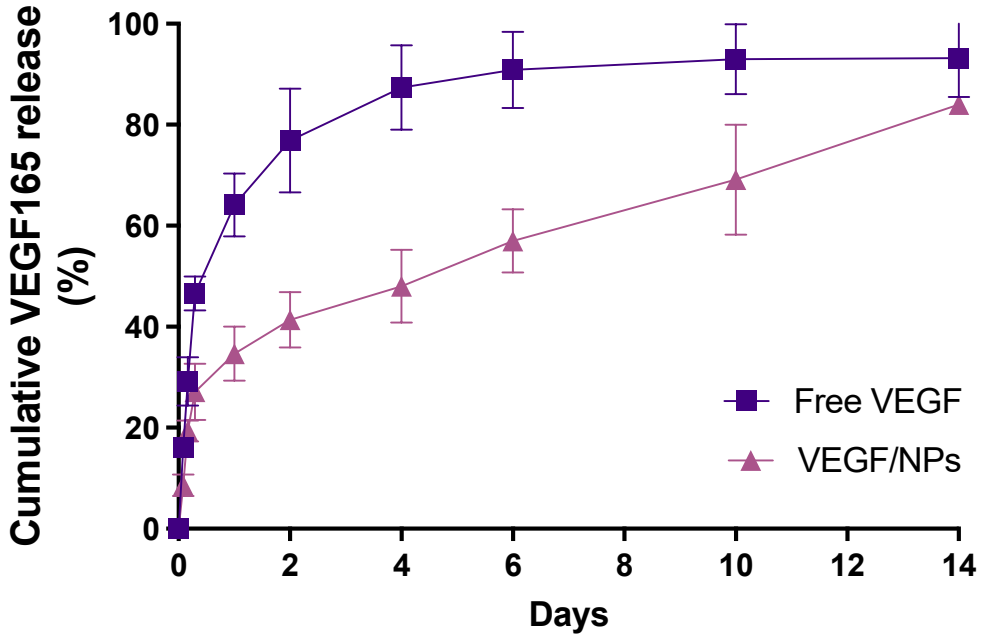
Polymer nanoparticles promoted sustained release of pro-angiogenic proteins



Poly(lactide-co-glycolide acid (PLGA) Lactic acid Glycolic acid



Release of VEGF increased from 4 days to 2 weeks



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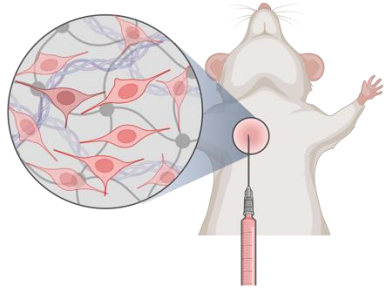
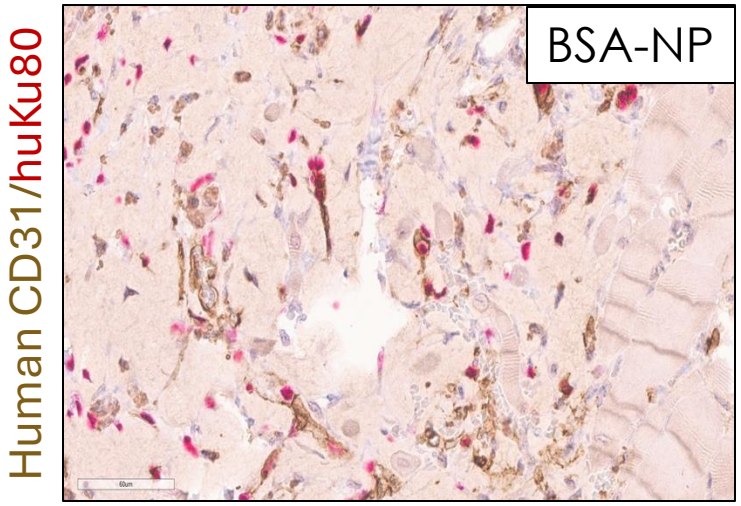
Unpublished data

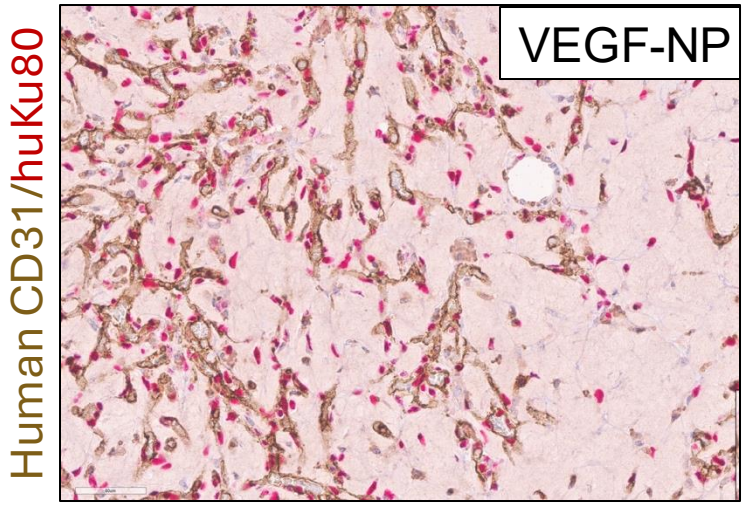
Controlled release of VEGF using nanoparticles reduced cell dose

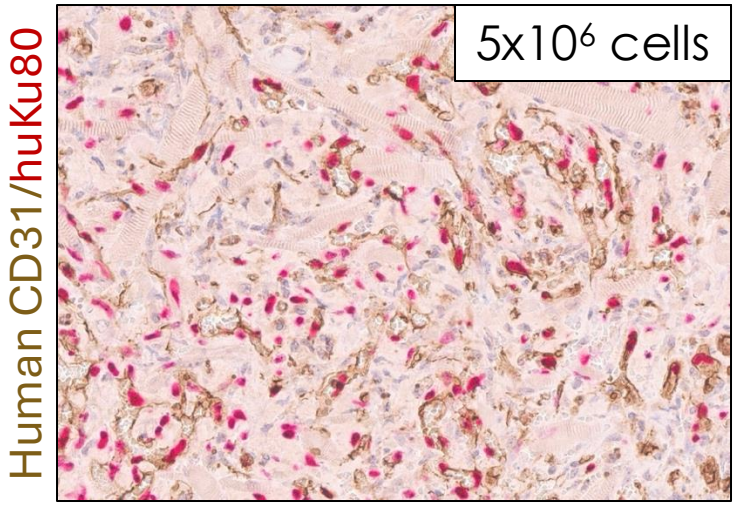


Transplant
$1x10^6$
+/- VEGF-NP
+/-BSA-NP

→ day28 → harvest and analyze







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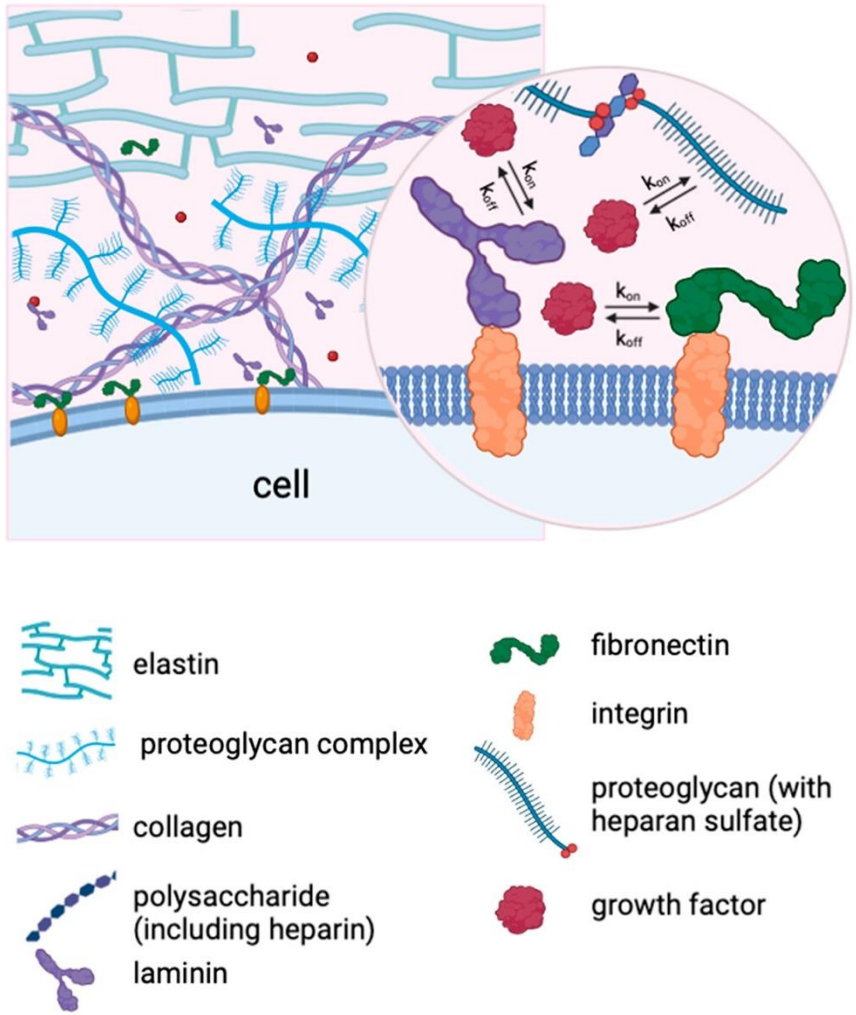
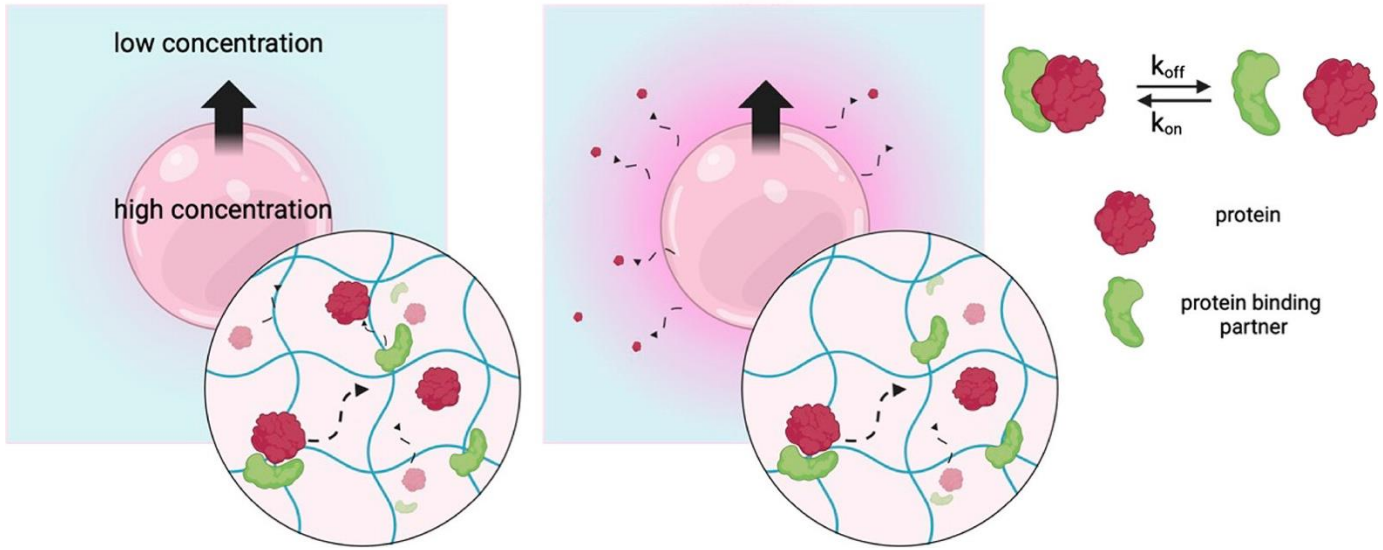
Unpublished data

Affinity-based release of therapeutic growth factors





Release tuned through:

- Strength of affinity interaction (K_D)
- Concentration of binding ligand
- Hydrogel size and geometry

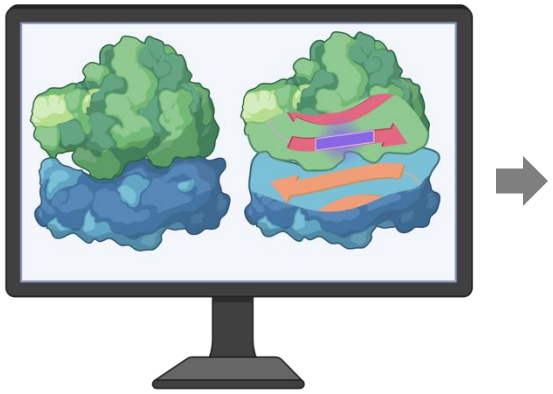
Teal et al. Chem. Mater. 2024, 36 (2), 614-641

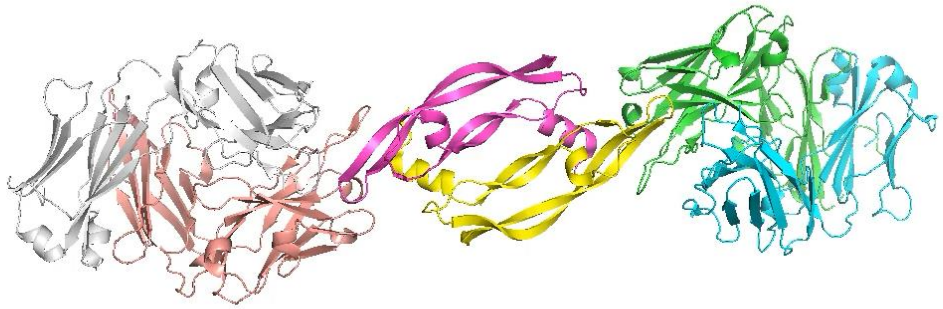
Computational derivation of short protein binding peptide

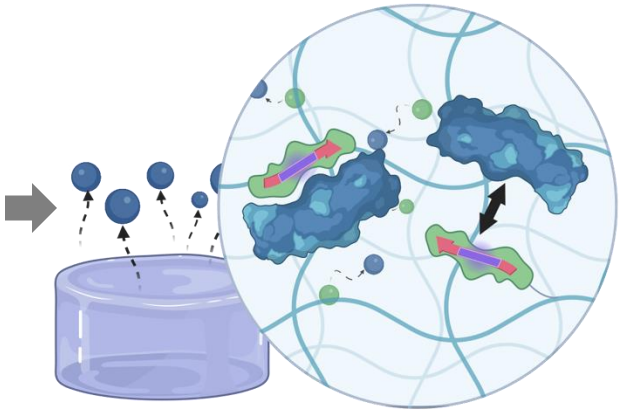
Protein-protein complex

Identify short peptide

Affinity release

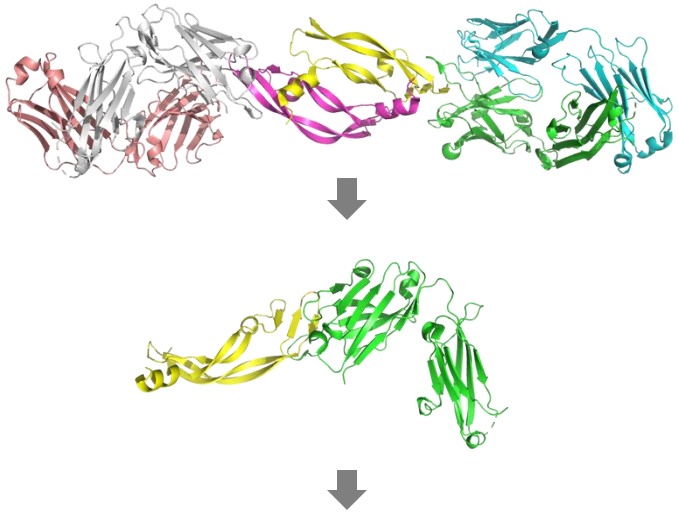


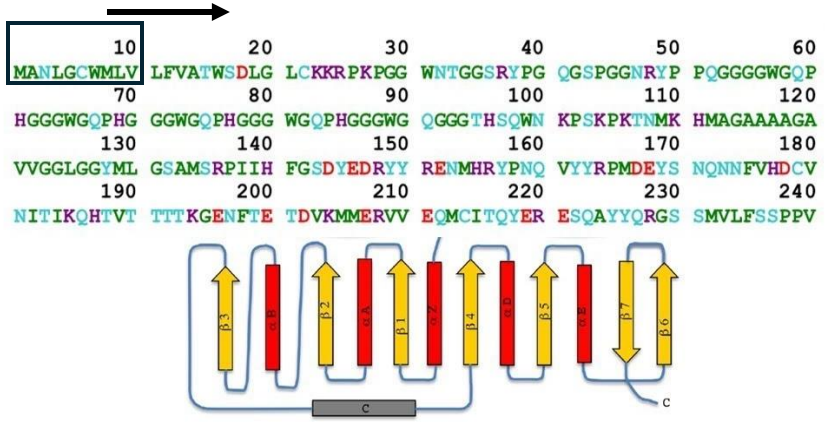


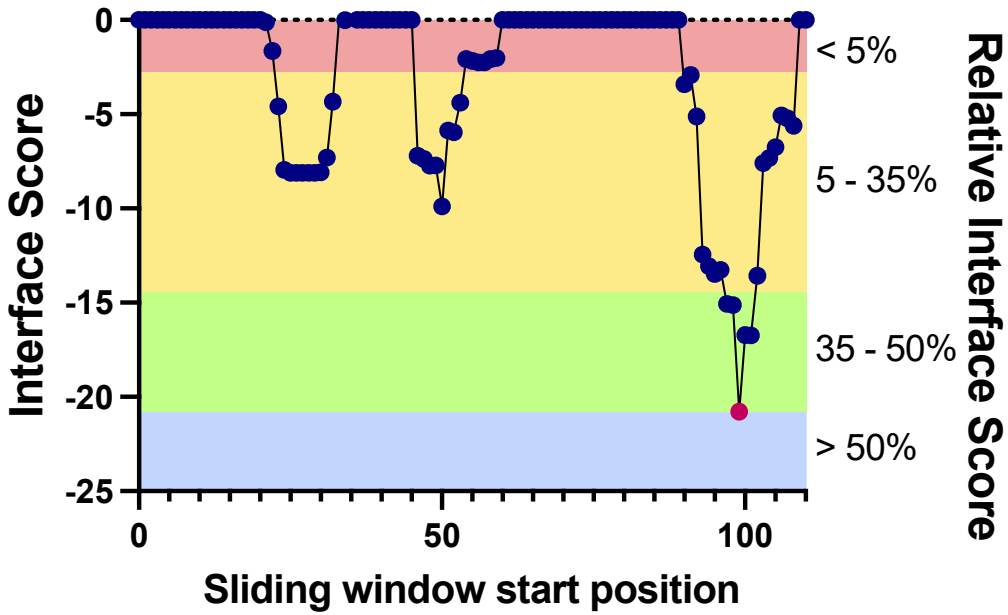


Unpublished data

Deriving short protein binding peptide for protein complex

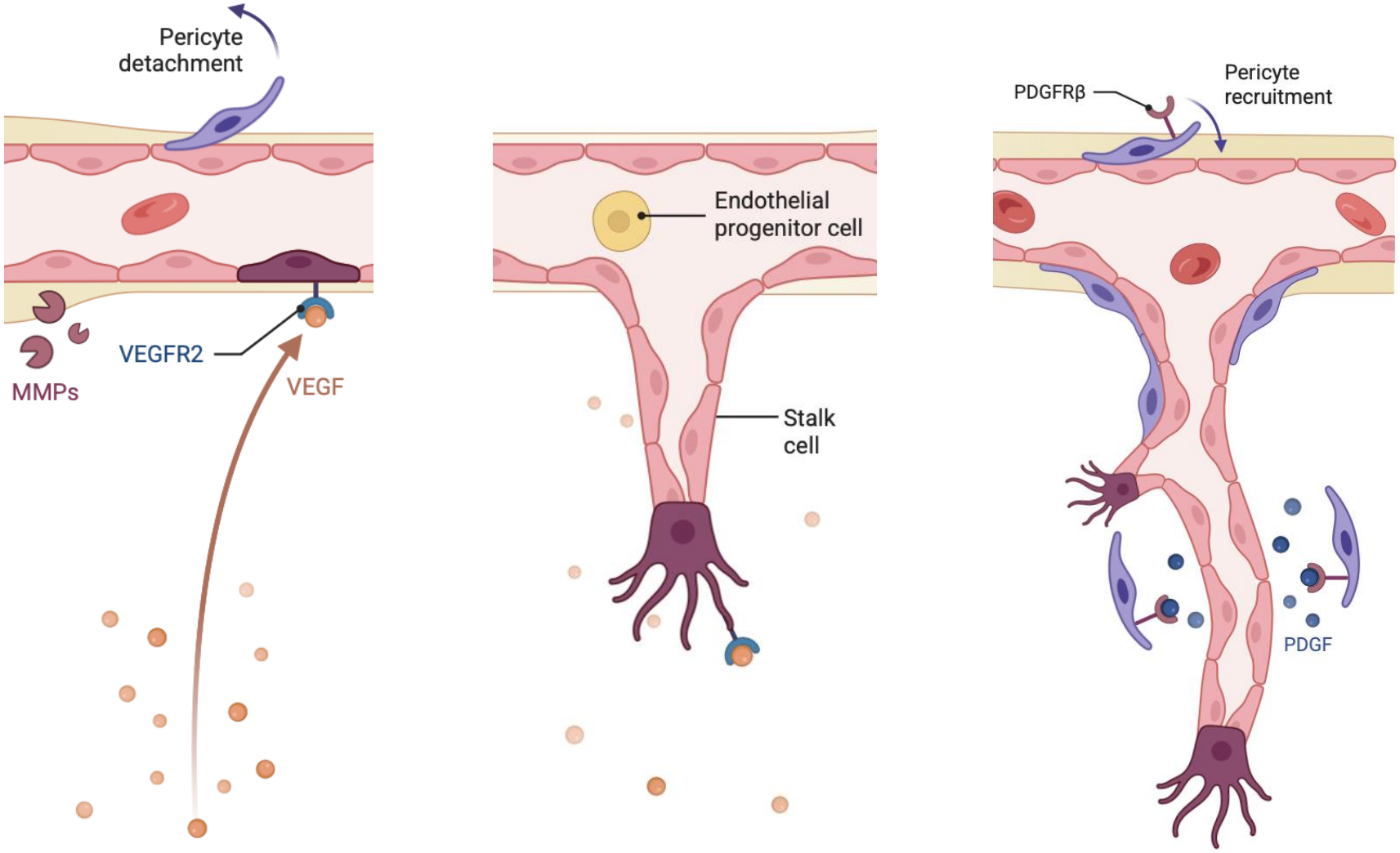






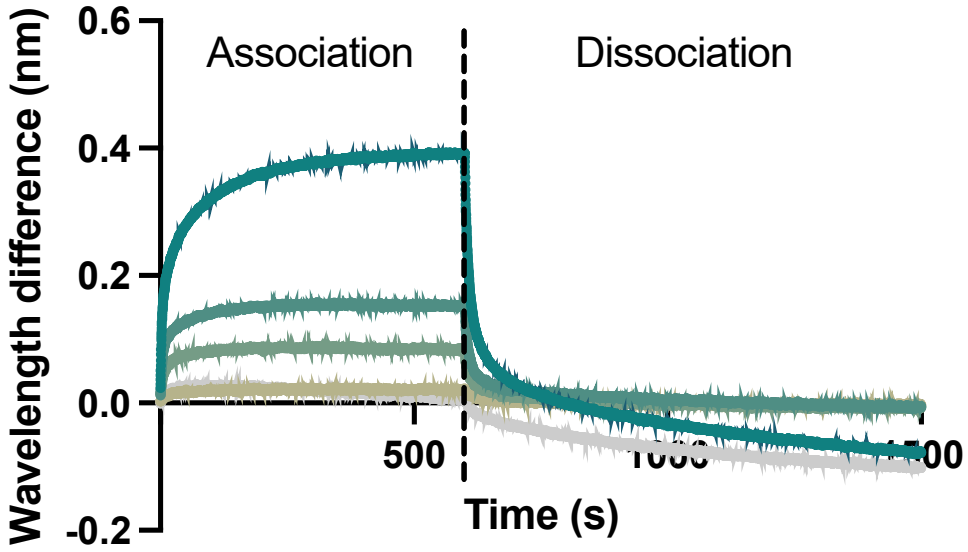
Unpublished data

Temporal presentation of VEGF and PDGF during angiogenesis



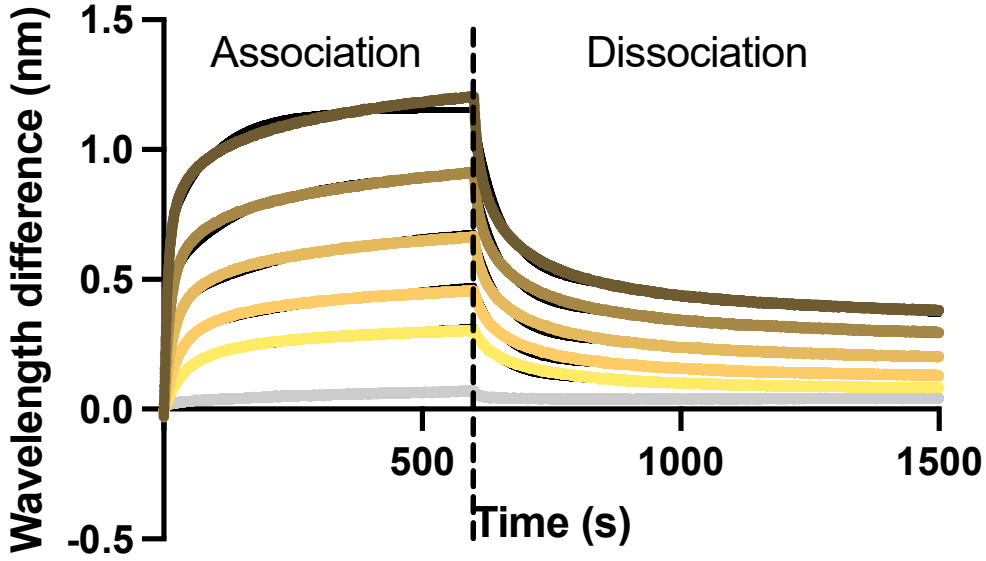
Design binding peptide for sequential release of VEGF and PDGF

VEGF



Dissociation constant K_D: 4.62×10^{-5} M
On-rate K_{on}: 8.59×10^{2} (1/Ms)
Off-rate K_{off}: 3.97×1^{-2} (1/s)

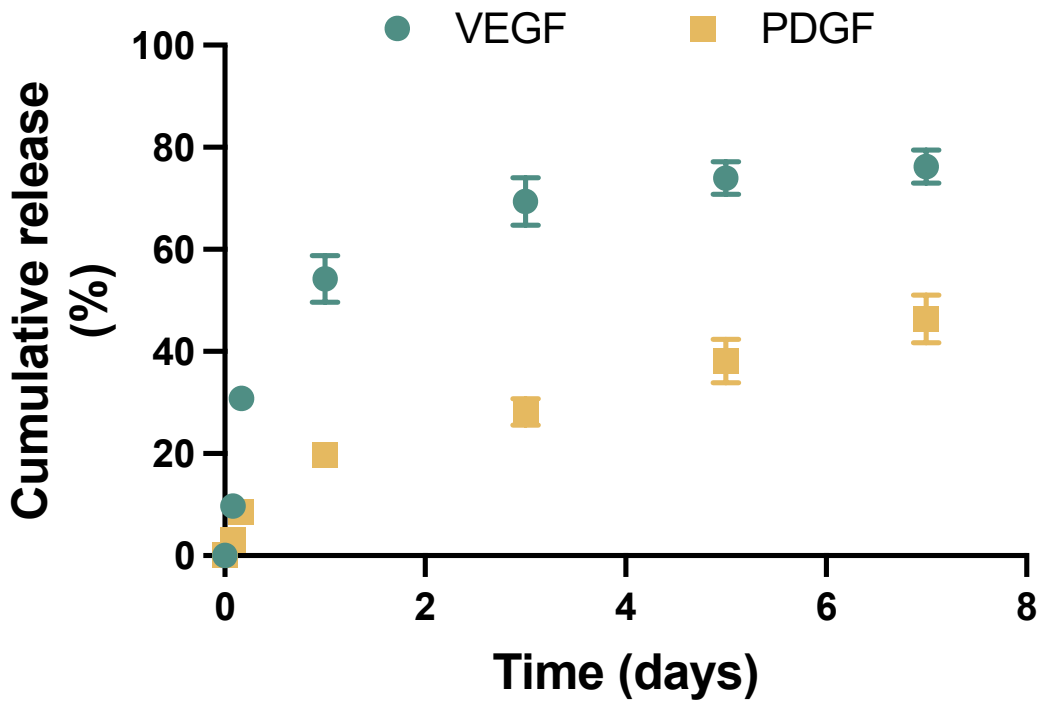
PDGF

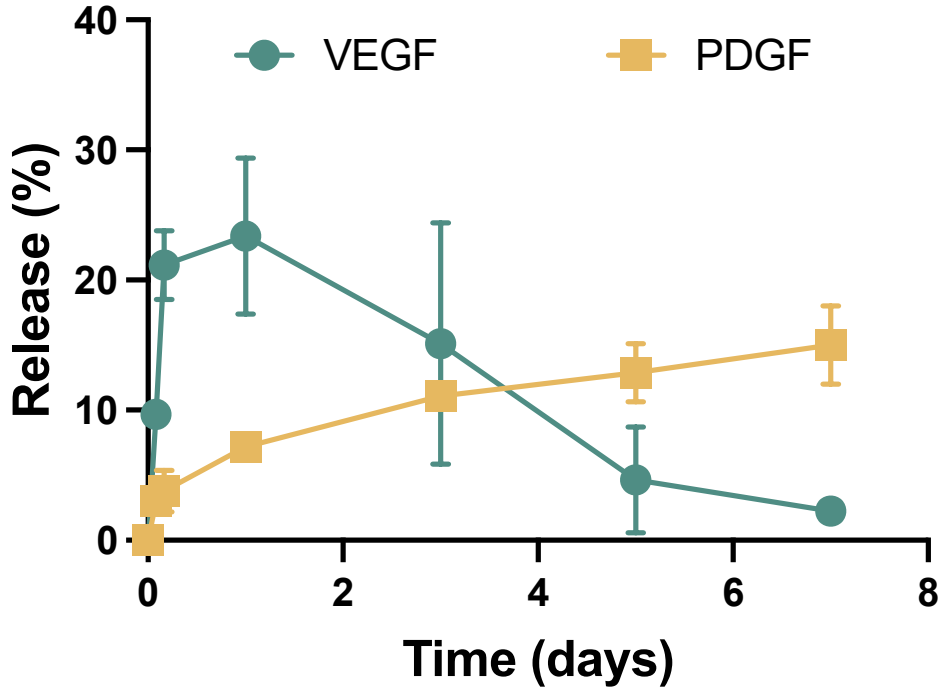


Dissociation constant K_D: 9.27×10^{-7} M
On-rate K_{on}: 1.64×10^{3} (1/Ms)
Off-rate K_{off}: 1.52×10^{-3} (1/s)

Unpublished data

Sequential release of VEGF and PDGF was achieved

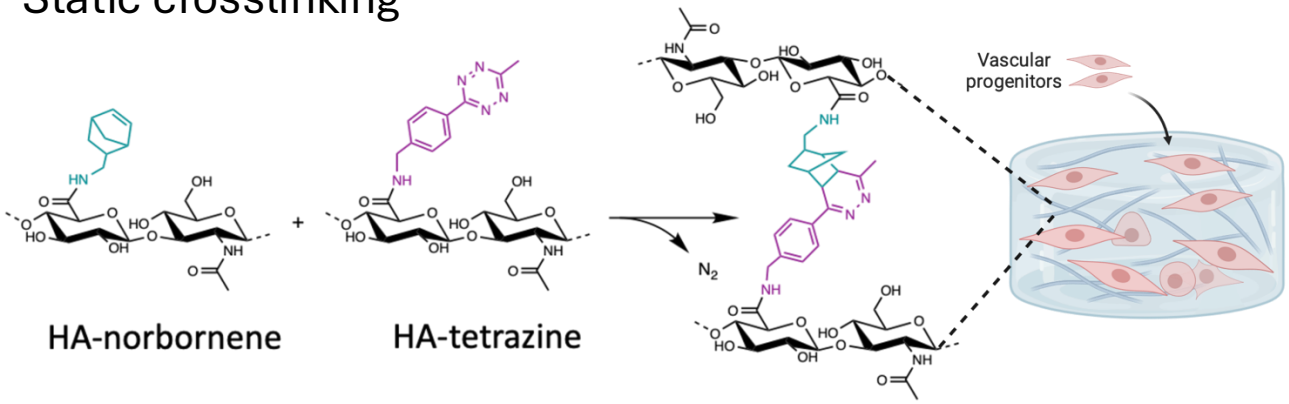




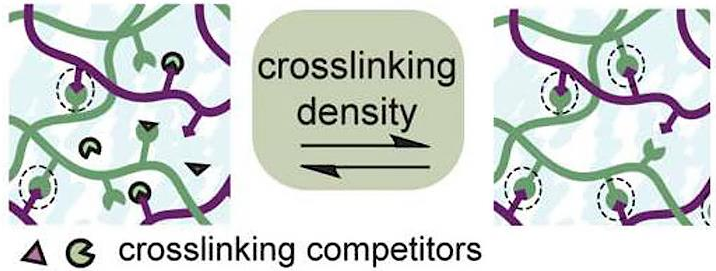
Unpublished data

Ongoing work: Mechano-adaptive hydrogels to regulate vascular morphogenesis

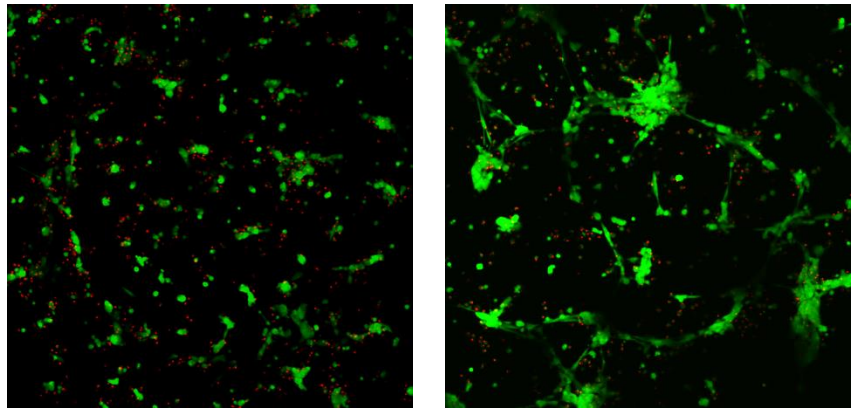
Static crosslinking

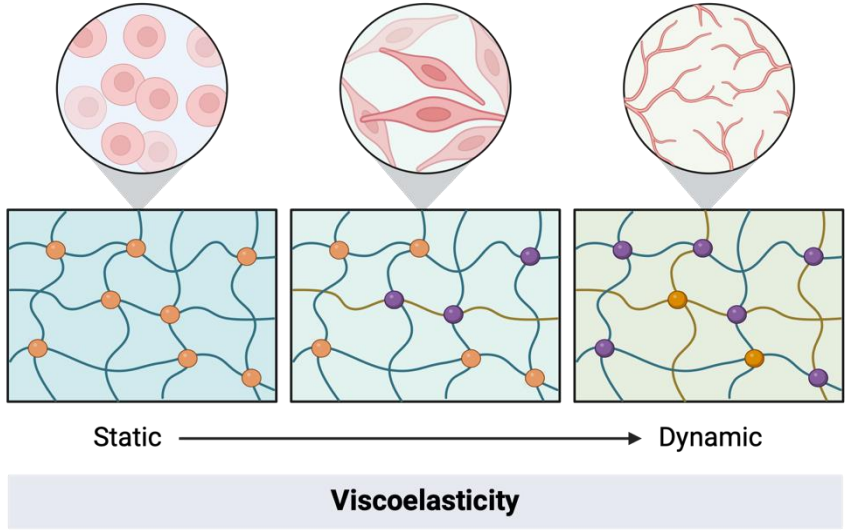


Dynamic crosslinking

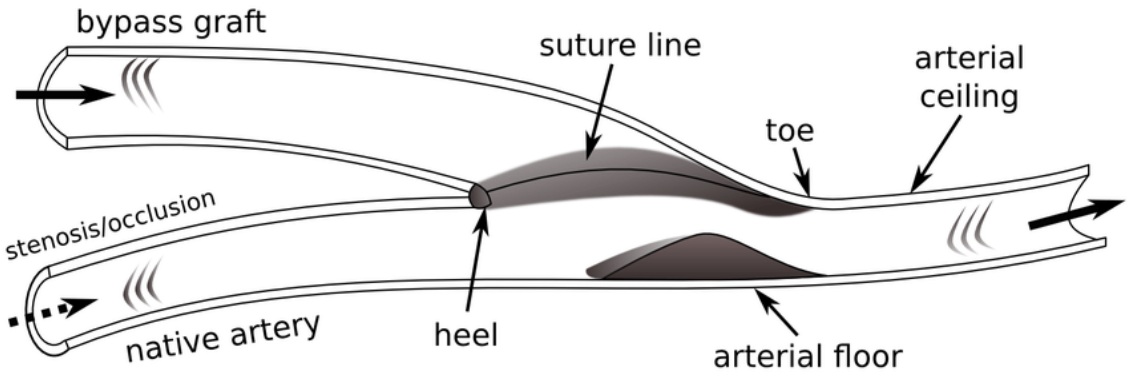


Decrease stiffness



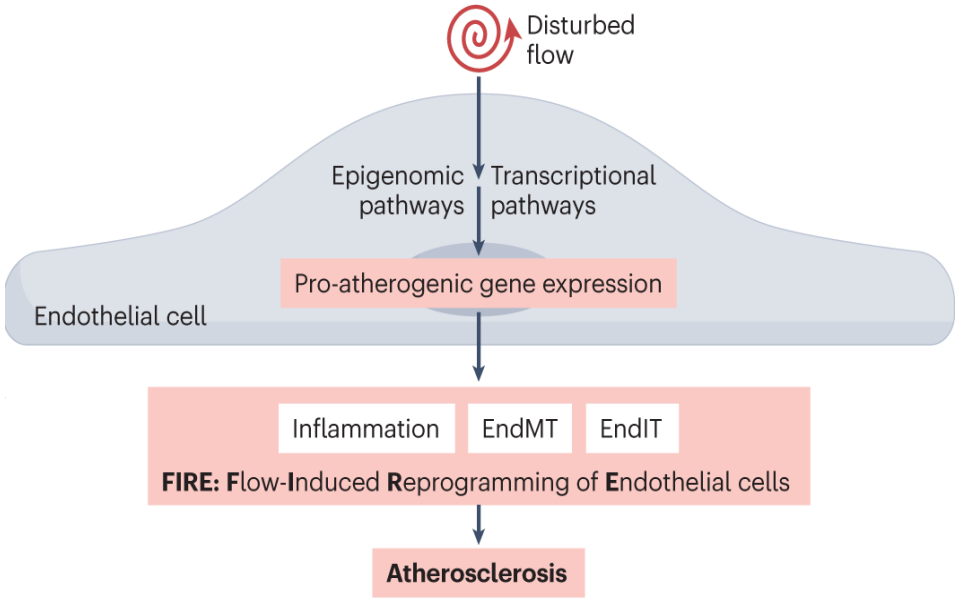


Ongoing work: Flow driven intimal hyperplasia

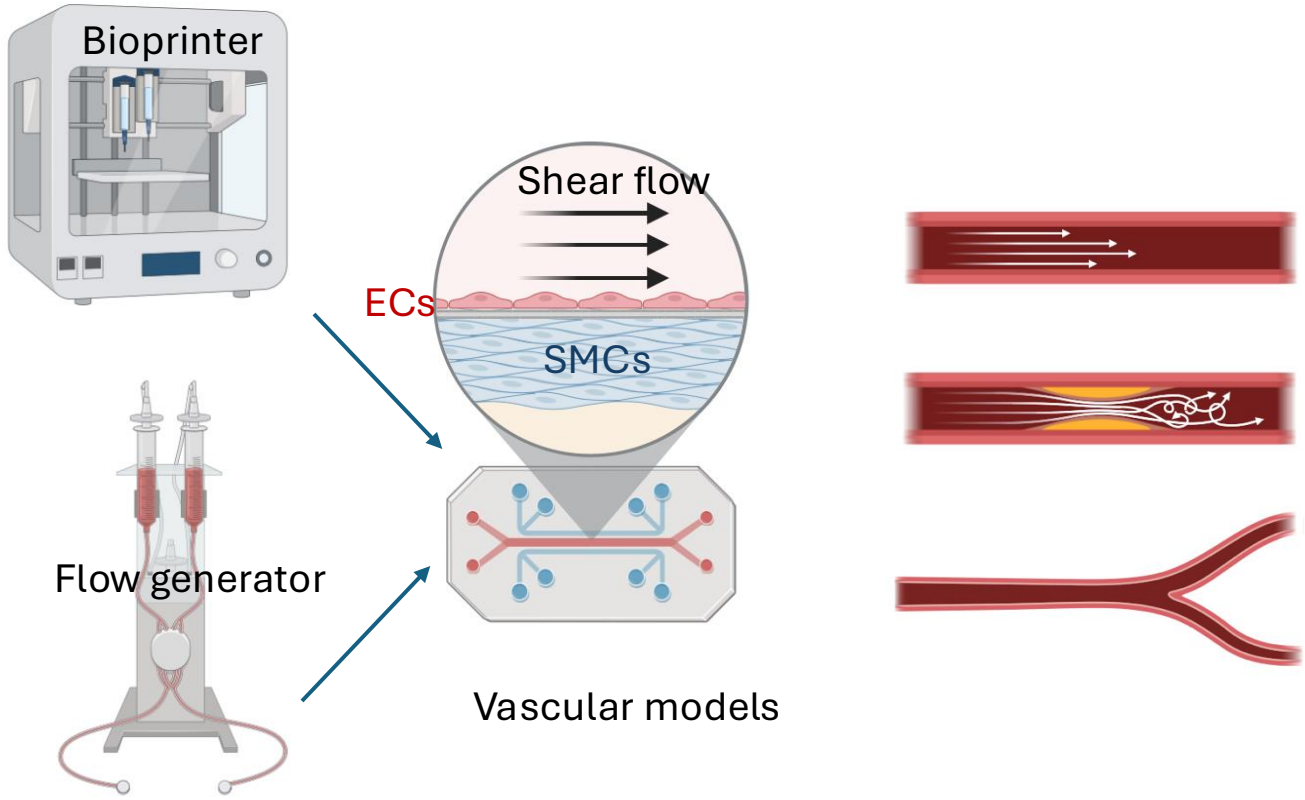


Ongoing work: Vascular model to study flow-induced vascular disease

Disturbed flow stimulates the transition EC to mesenchymal cells



3D bioprinted vascular model with different geometries



Thank you!