



# Engineering the Therapeutic Microenvironment using Nanostructured Biomaterials

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Director, Health Innovation Via Engineering at UCSF

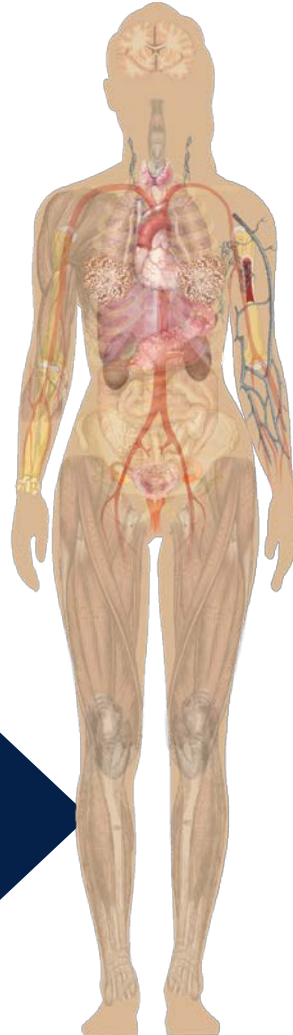
**UCSF**

# The Desai Laboratory for Therapeutic Microtechnology and Nanotechnology



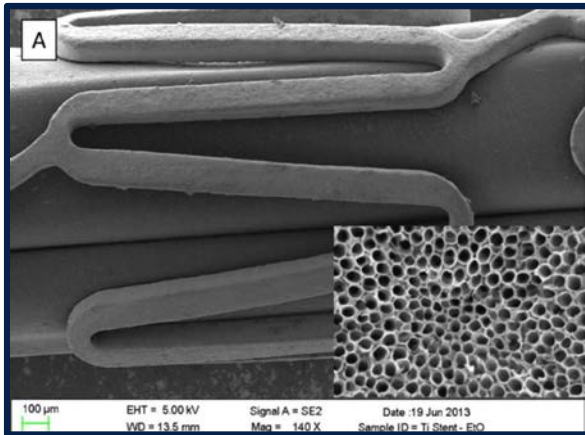
We **design** and **fabricate** micro and nanomaterial solutions for:

- Biomimetic Architectures
- Drug Targeting & Delivery
- Cellular Modulation and Integration in Tissues

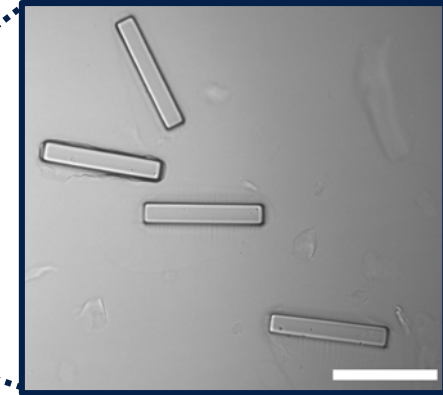


**Therapeutic biomaterials  
for mitigating disease**

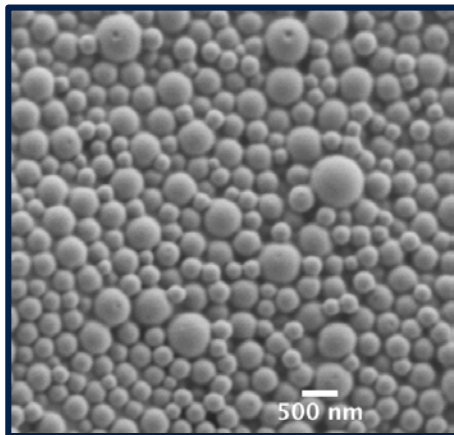
# The Desai Laboratory for Therapeutic Microtechnology and Nanotechnology



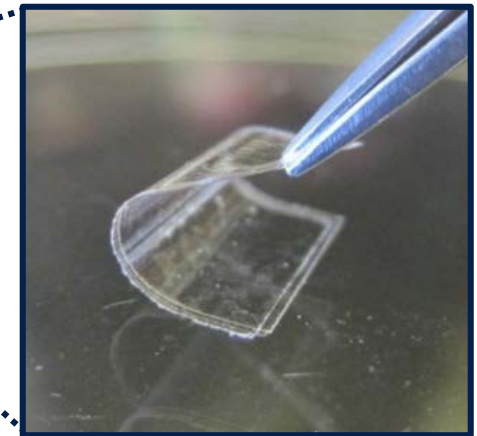
**Devices**



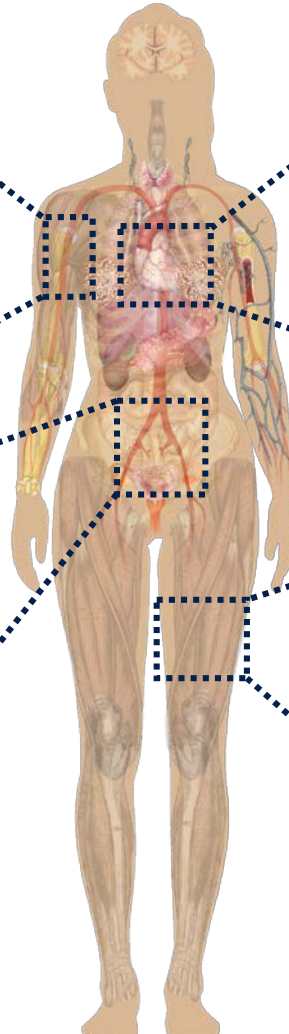
**Topography**



**Nanoparticles**

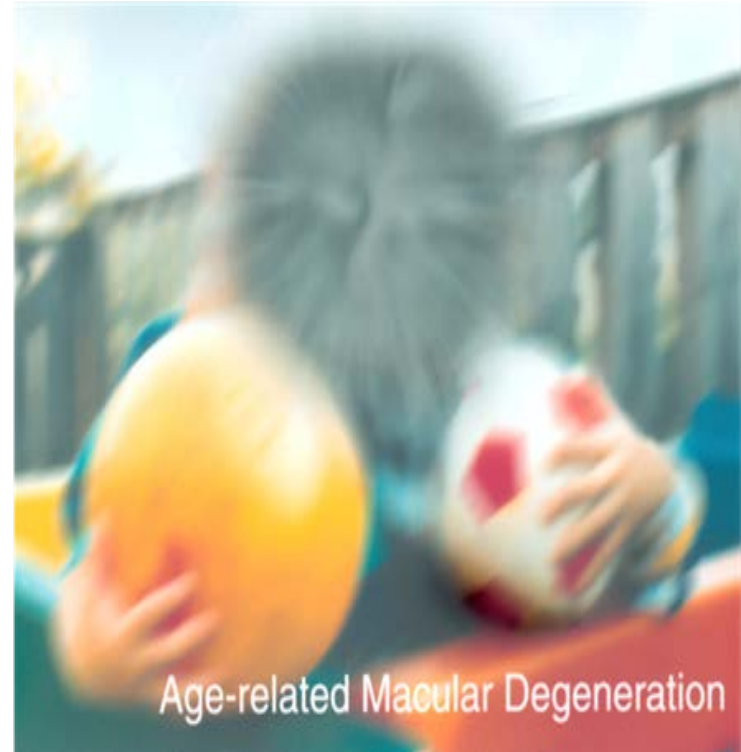


**Thin Films**



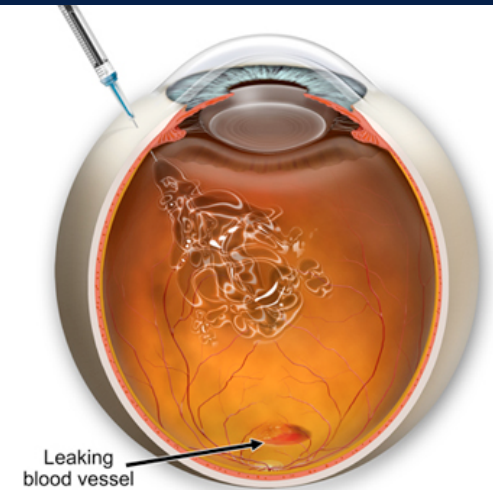
Can we design materials to  
better control drug kinetics?

# Age-related Macular Degeneration (AMD)



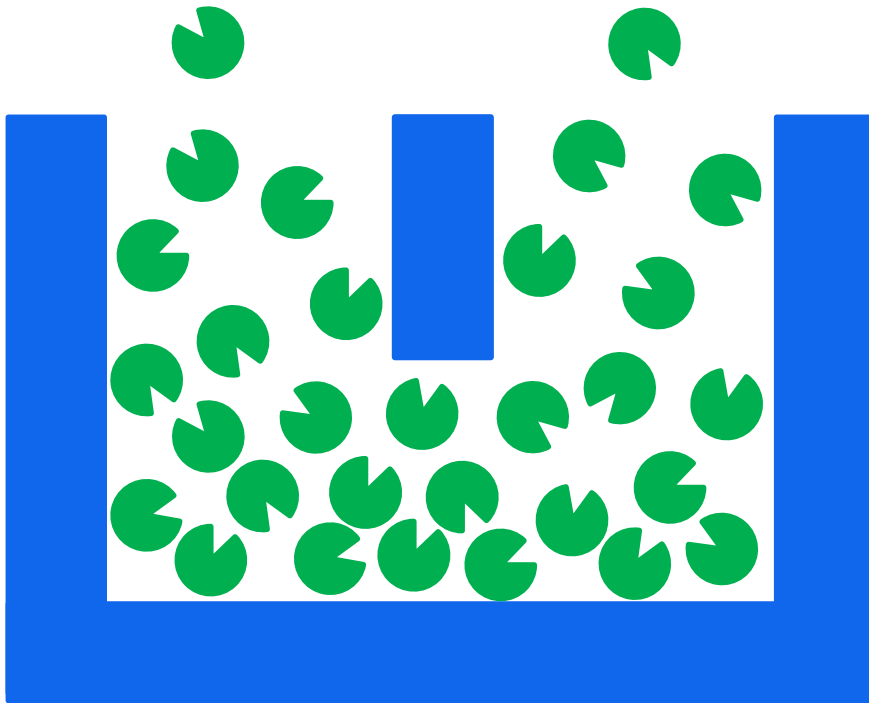
# Clinical Need for Better Delivery Systems for wet-AMD

- Current therapies all use intravitreal injection
  - On average patients dosed 7.7 times per year
  - Peaks and troughs lead to poorer outcomes
  - Repeated injection results in risk of infection, retinal detachment, and cataracts
  - Maximum dose is limited by inflammation and elimination from eye
  
- Requirements?
  - extended delivery duration (at least 4-6 mos)
  - A large drug depot
  - Syringe deployable
  - Device degrades at the end of use (no explant)



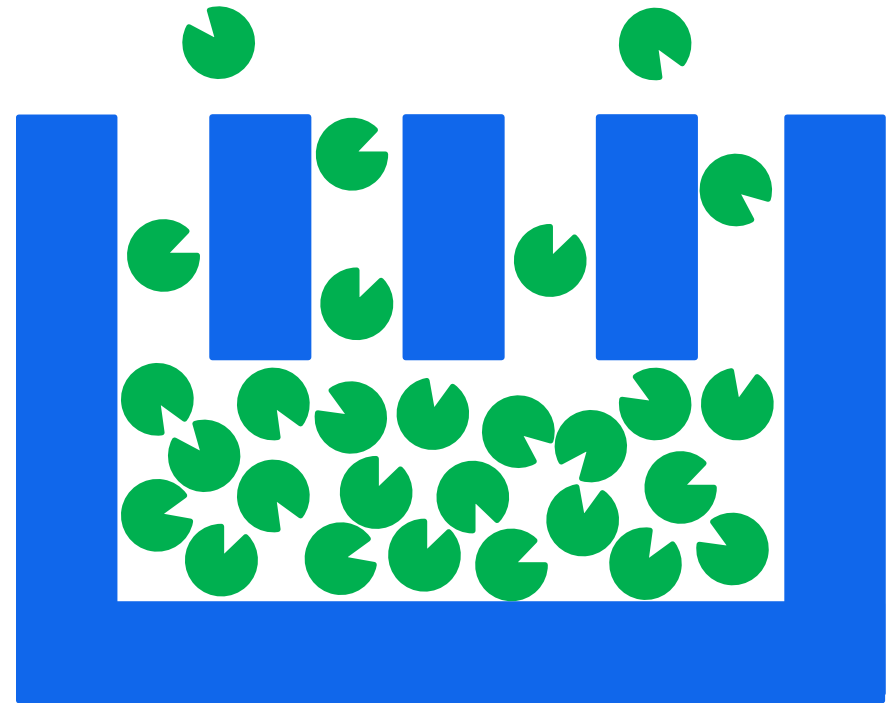
# Achieving Constant Rate Delivery: Micropores vs Nanopores

Pore Size > Molecular Size



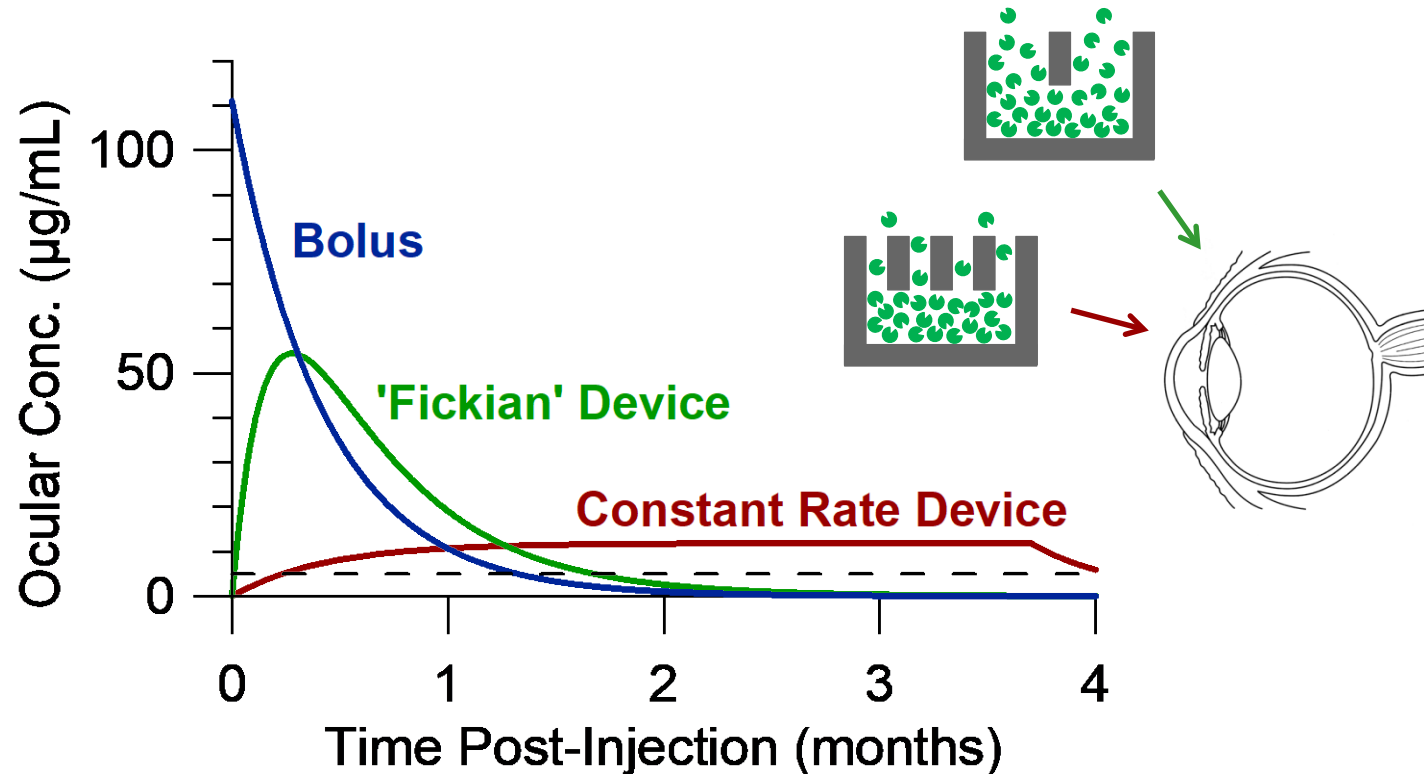
Concentration  
Dependent Delivery

Pore Size ~ Molecular Size



“Single File”  
Constrained Delivery

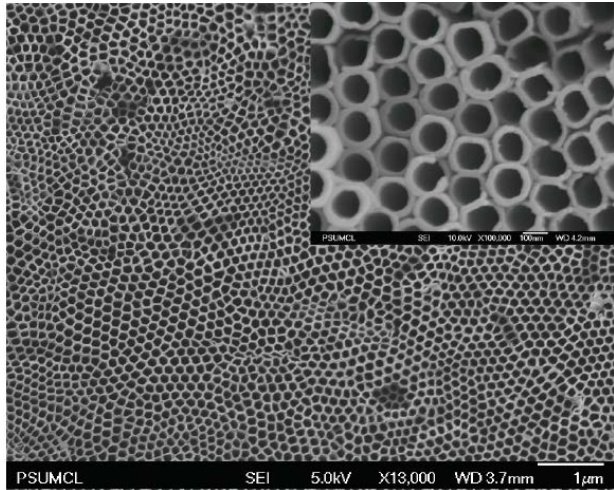
# Modeling Device Pharmacokinetics



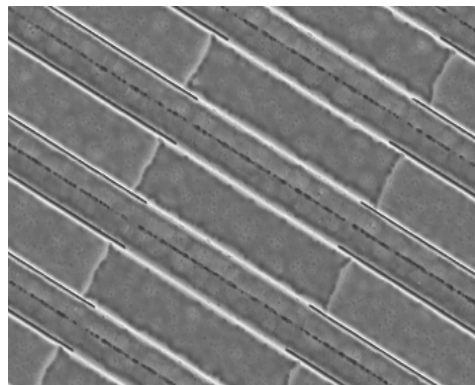
- Continuous delivery can sustain therapeutic concentrations with equivalent payloads



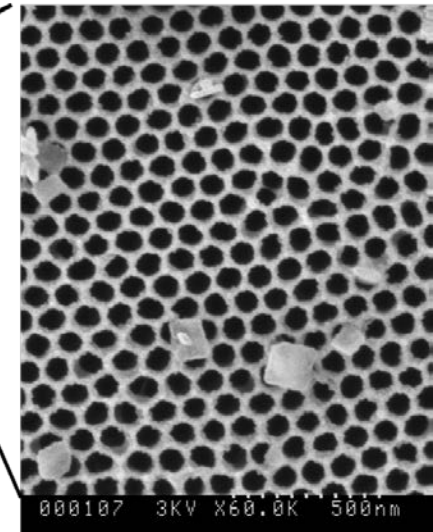
# Therapeutic Delivery from Nanostructured Inorganic Implants



Titania nanotubular membranes

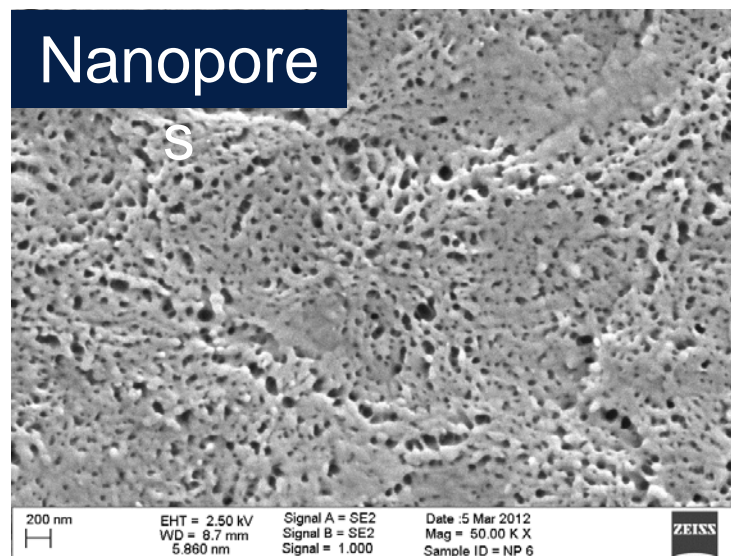
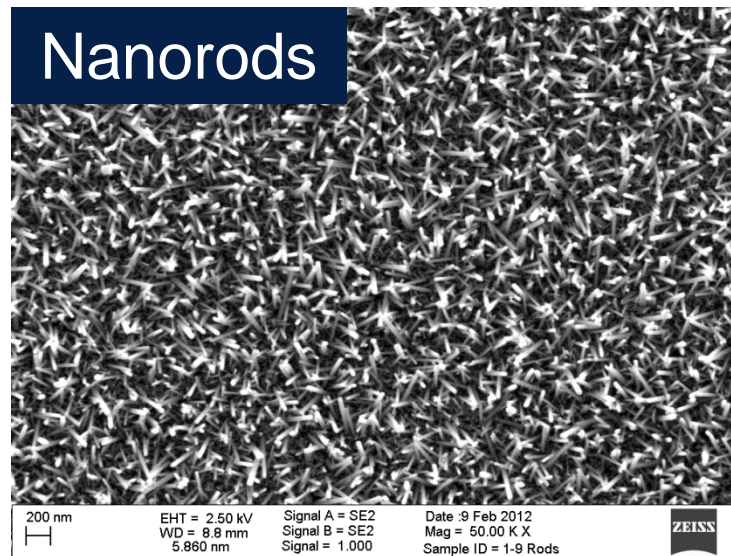
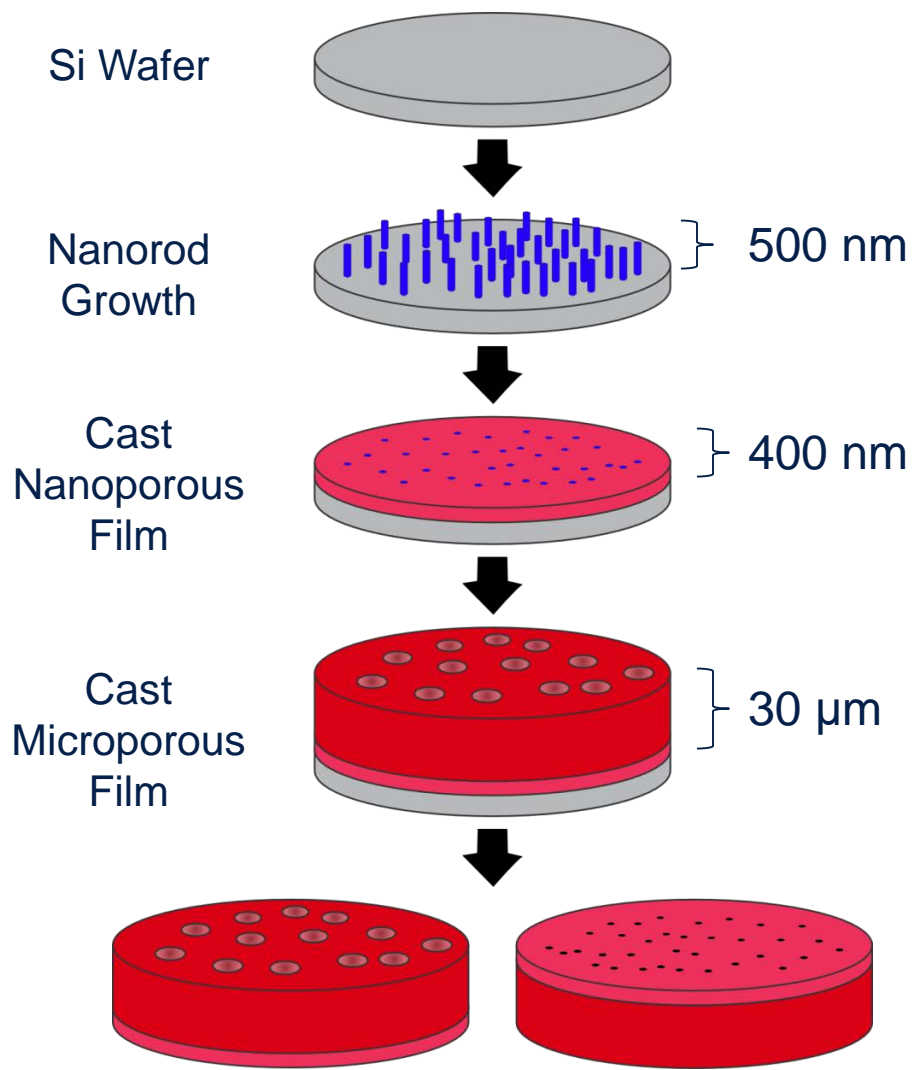


Silicon nanochannels

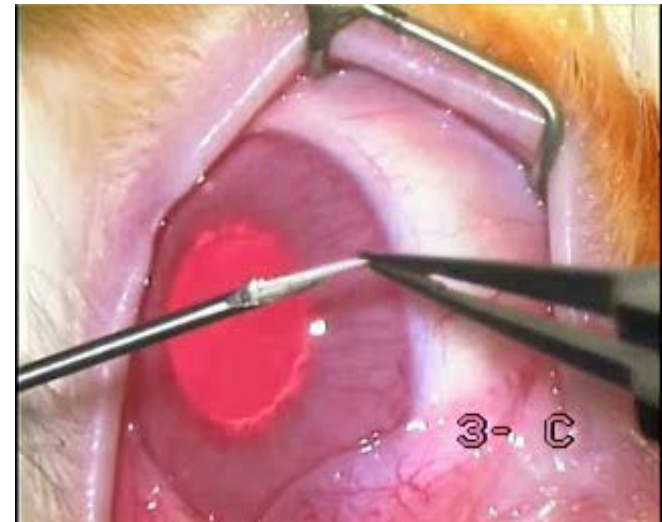
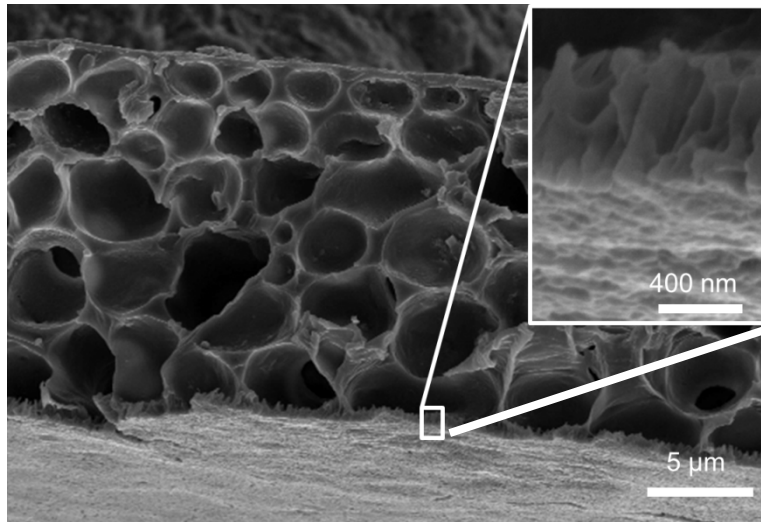


Alumina nanoporous capsules

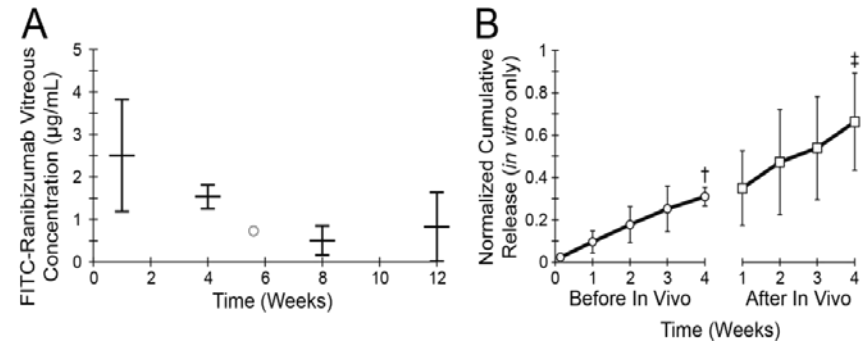
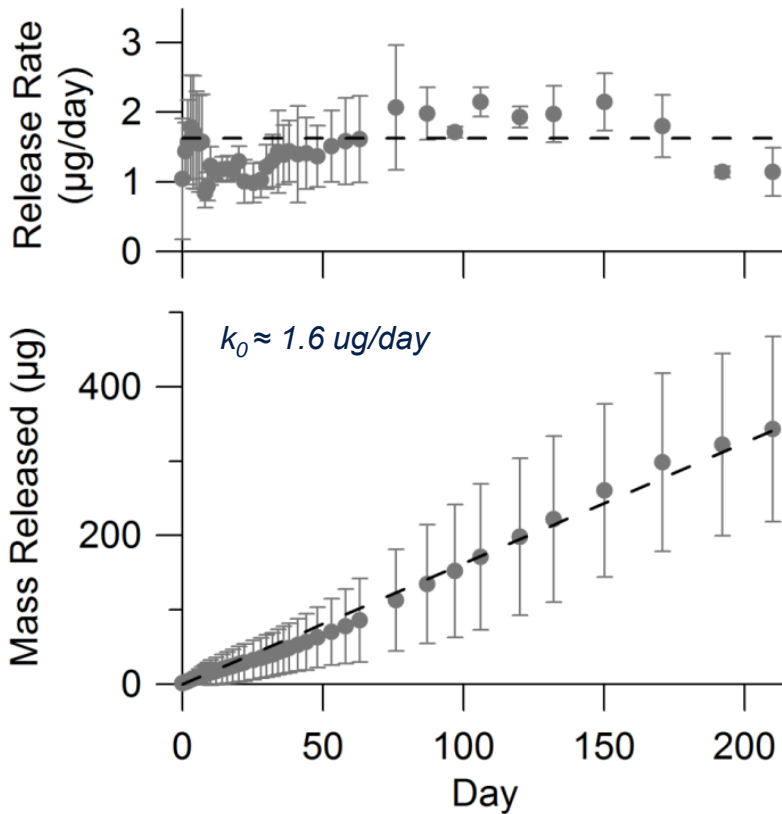
# Nanoporous Polymers from Nanorod Templates



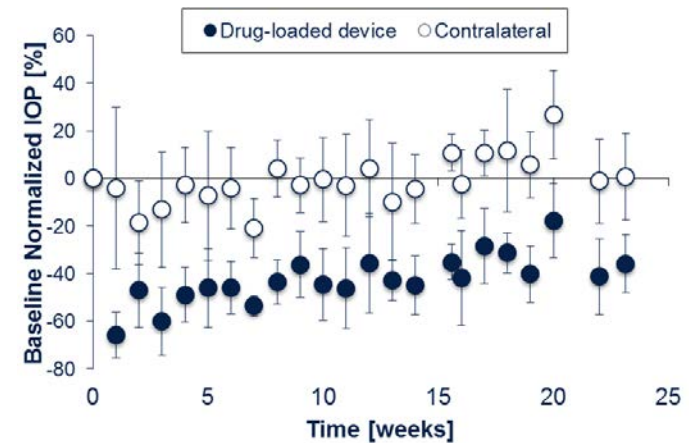
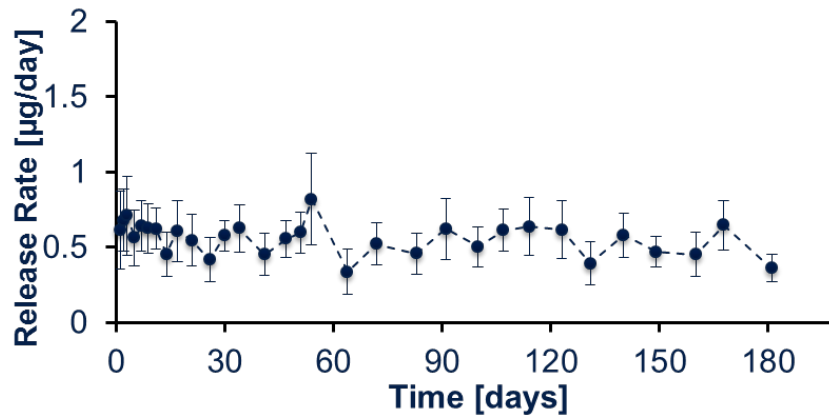
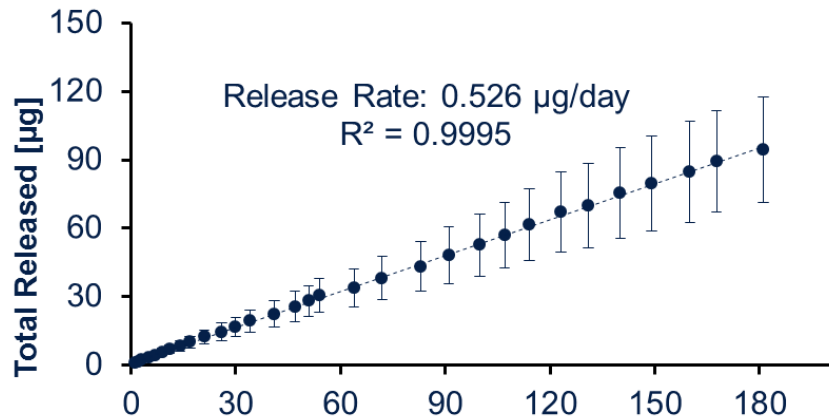
# Supported Nanoporous Membrane Based Devices



# Zero Order Delivery of Antibodies



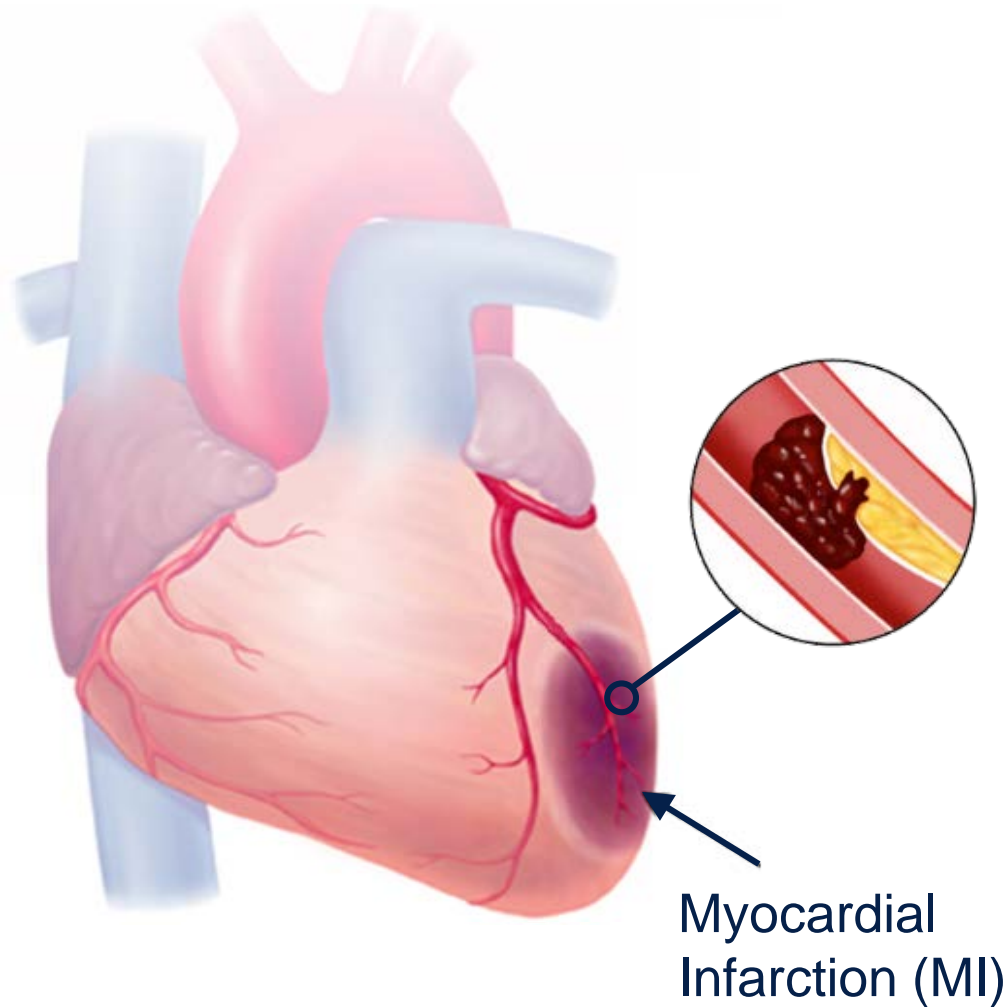
# Zero Order Delivery of Glaucoma Drugs



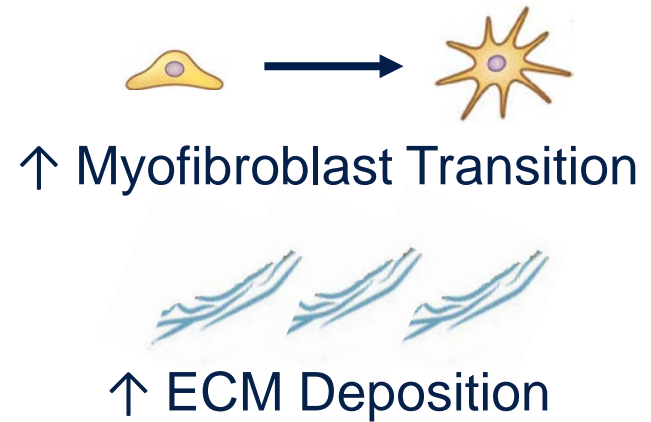
- 6-month therapeutic IOP effect
- Aqueous drug concentration  $93 \pm 25 \text{ ng/mL}$  vs eye drop =  $108 \pm 23 \text{ ng/ml}$

Can we use  
micro/nanostructures to  
reduce fibrosis?

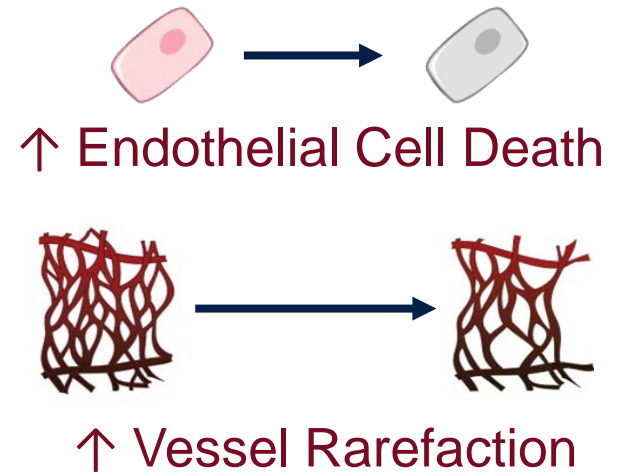
# Prognosis of heart failure remains grim due to pathological remodeling



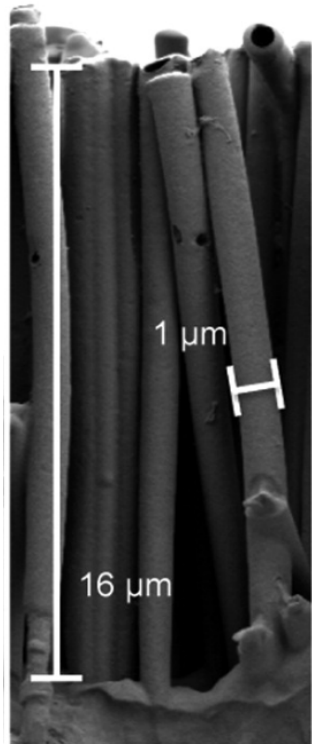
## Fibrosis



## Reduced Vascularization

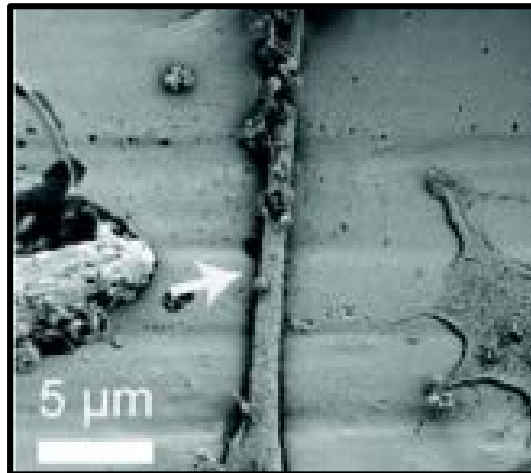


# Microtopographical cues can successfully modulate fibroblast phenotype

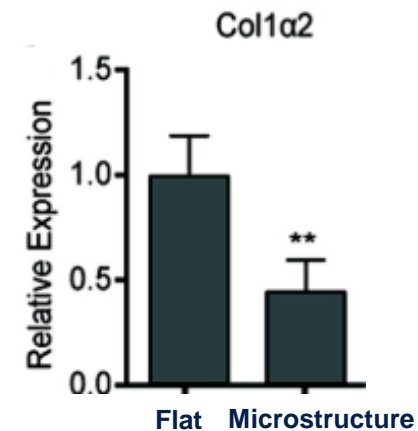
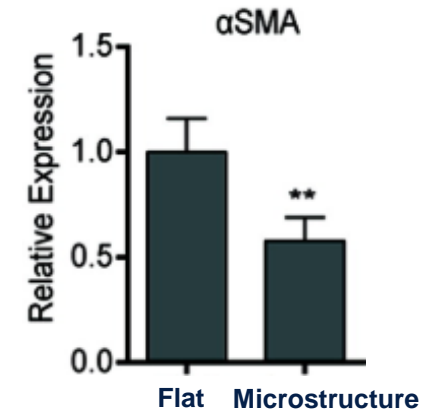


Microstructure Pillars

Flat

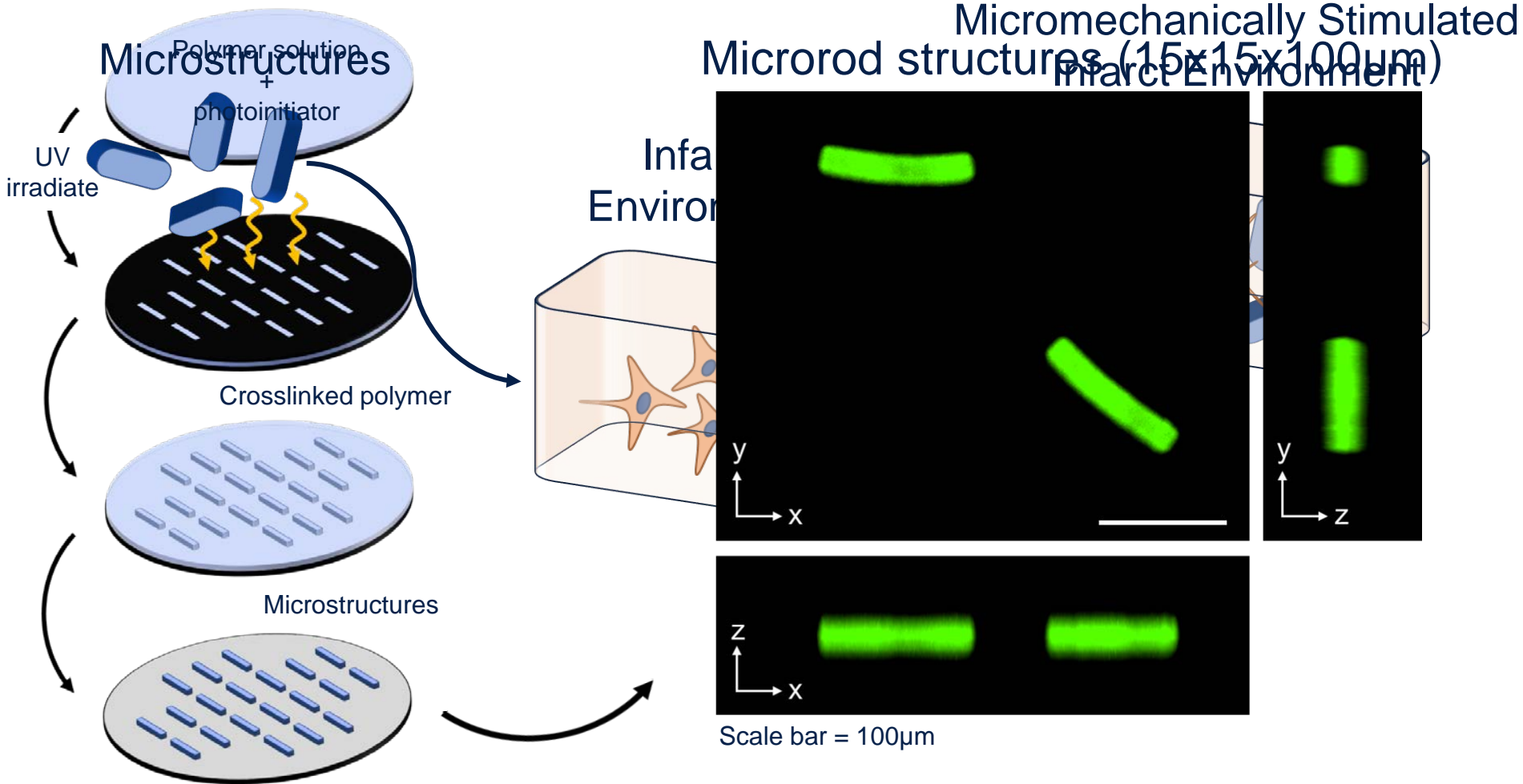


Microstructure





# Microtopography introduces physical cues to alter the post-infarct environment

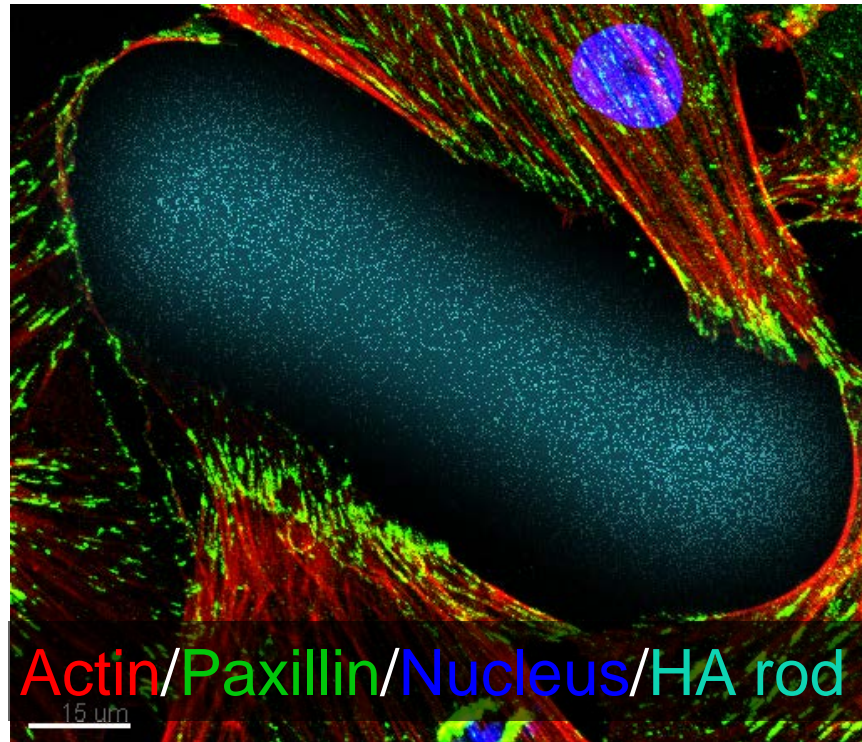


# Hyaluronic acid is an ideal therapeutic polymeric material

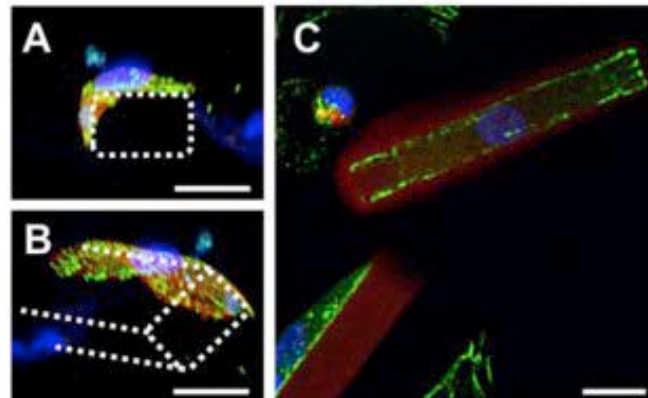
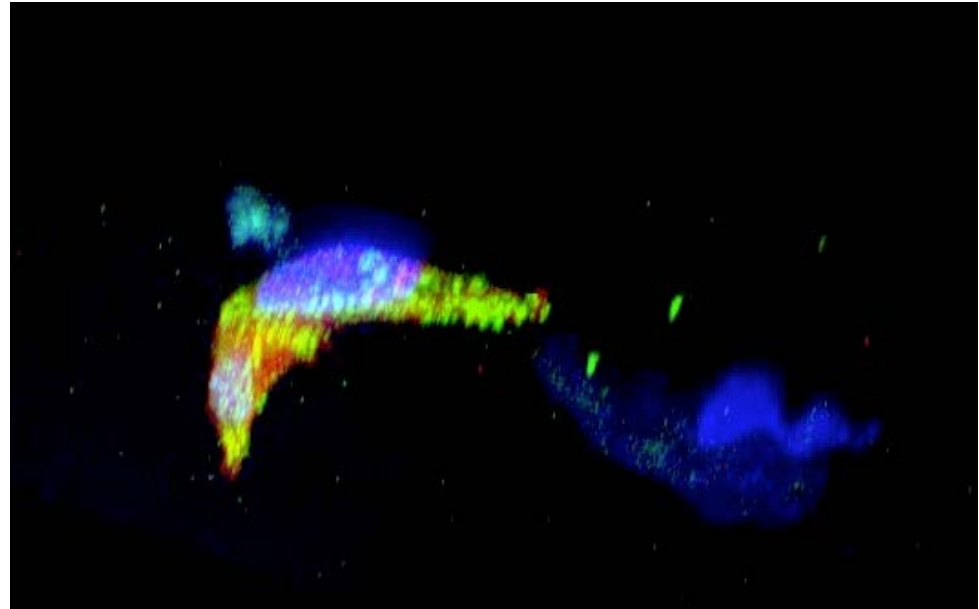
- Naturally occurring
- Biodegradable
- Implicated in wound healing resolution
- Demonstrated efficacy for improving cardiac function after myocardial injury

# Neonatal rat ventricular fibroblasts form distinct focal adhesions to microrods

## Hyaluronic acid microrods (HA microrods)

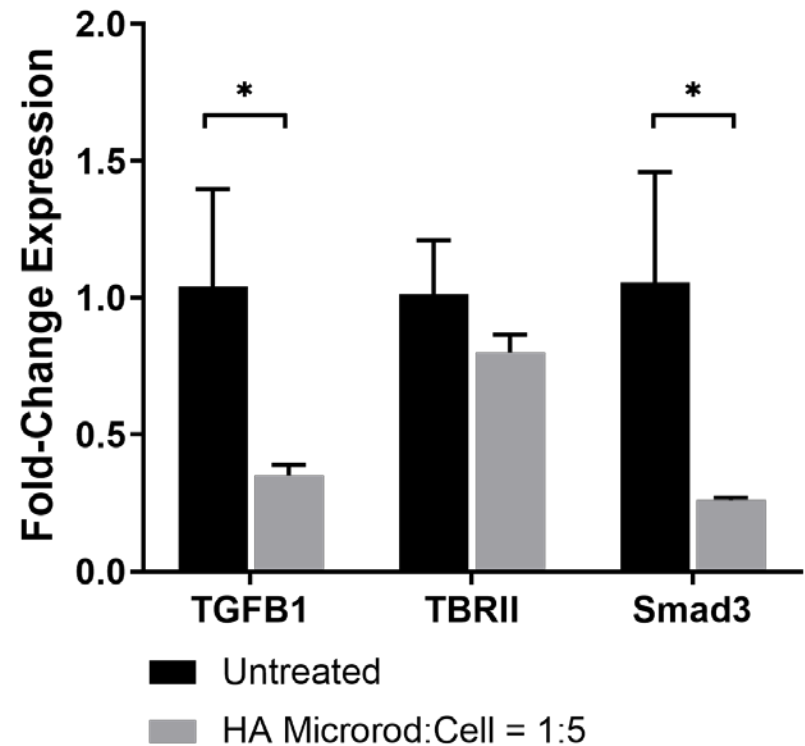
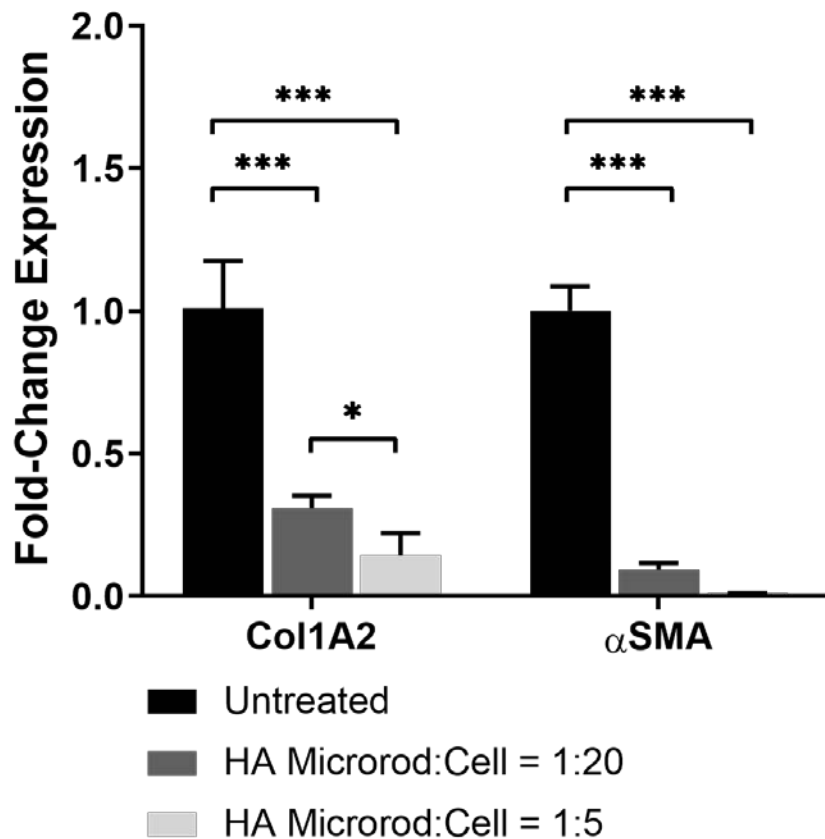


Scale bar = 15  $\mu\text{m}$

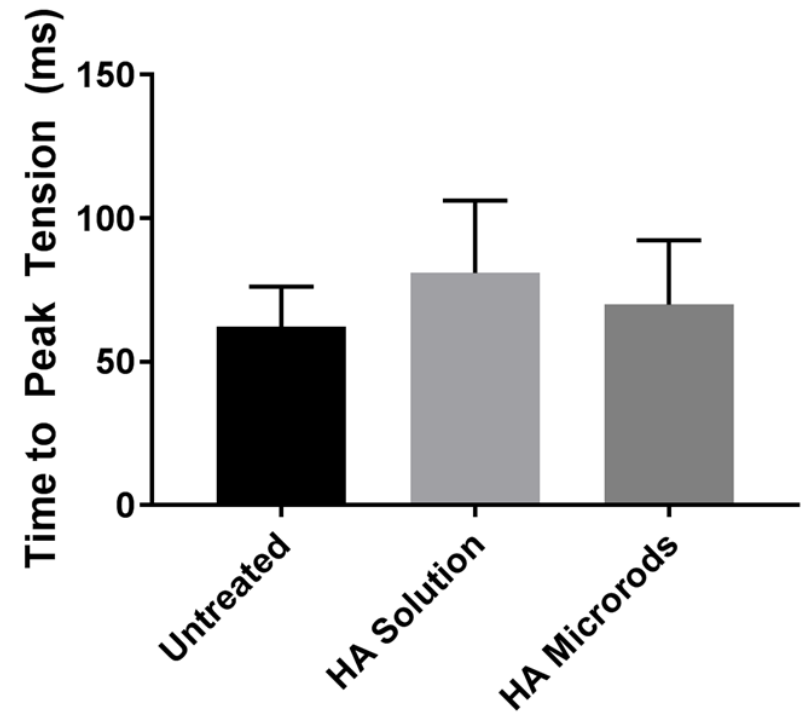
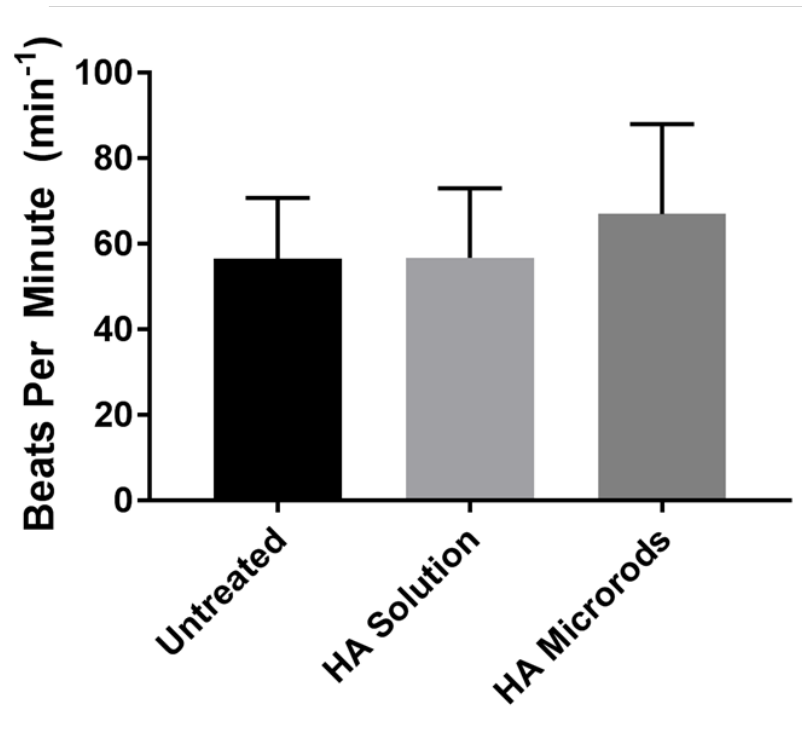


Scale bar = 20  $\mu\text{m}$

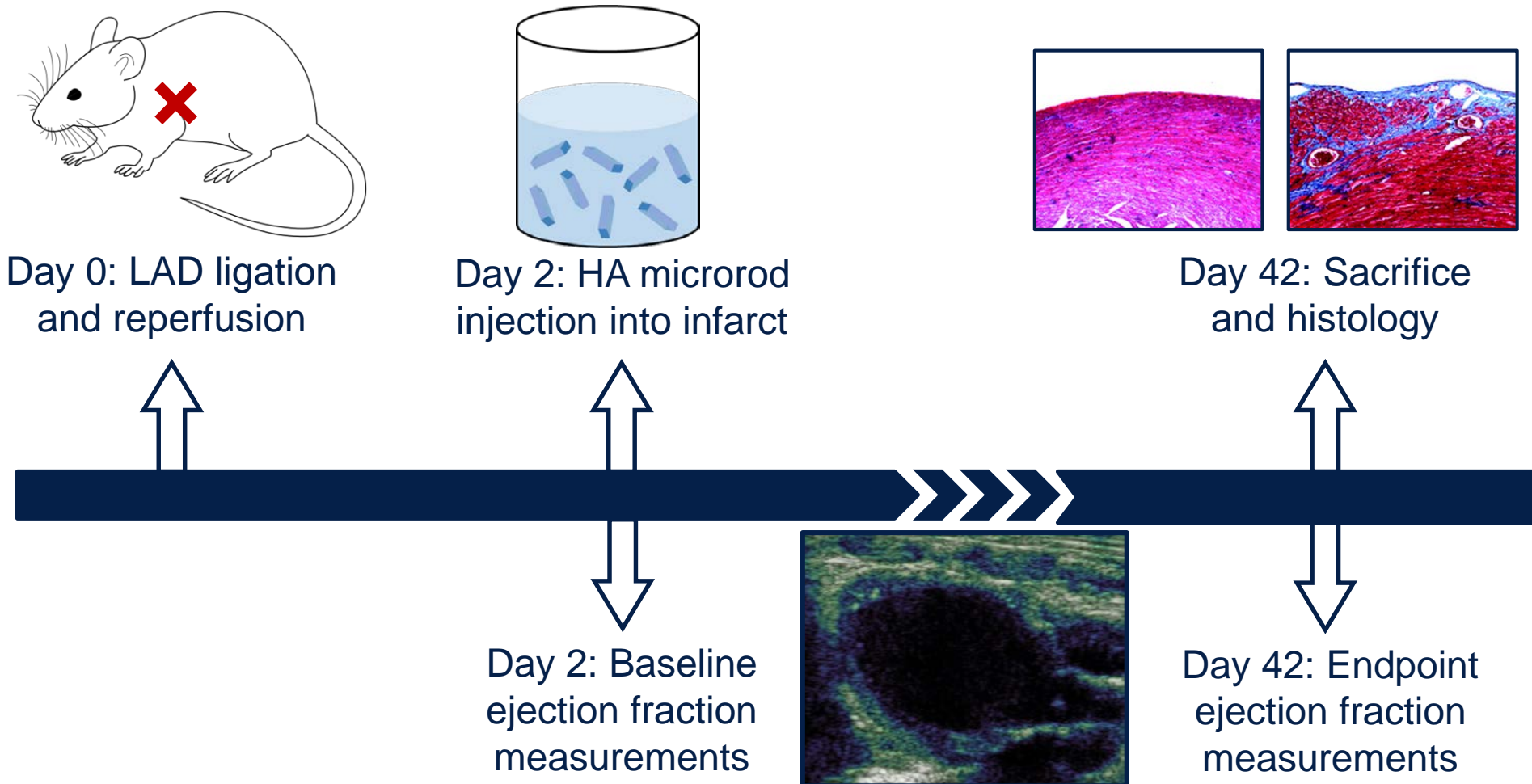
# HA microrods reduce expression of key genes indicative of fibrotic phenotype in fibroblasts



# HA microrods do not interfere with neonatal ventricular cardiomyocyte contractility

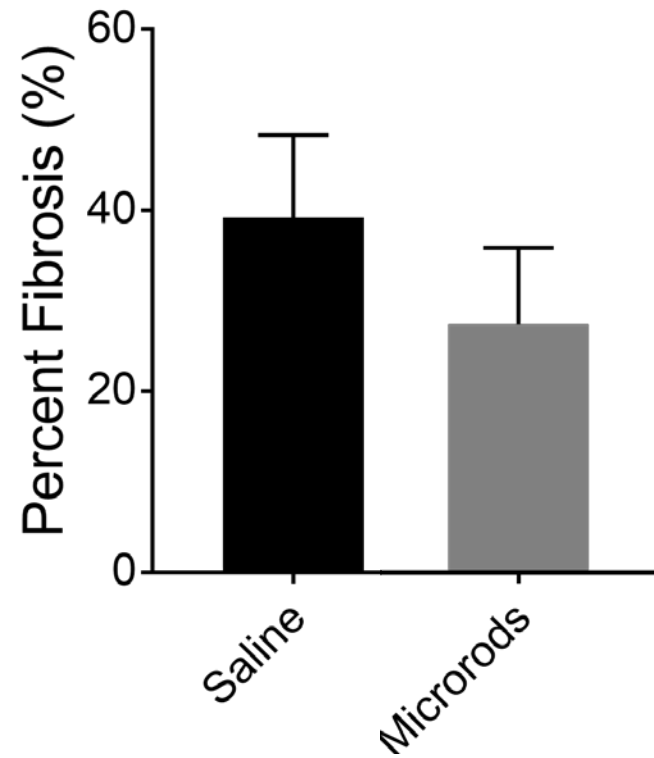
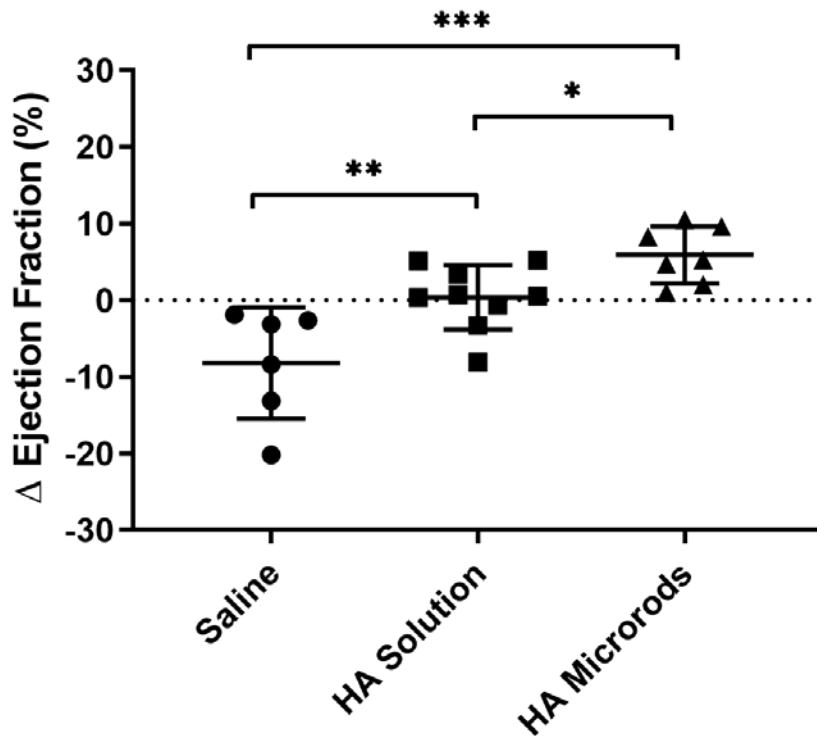


# *In vivo* model of heart failure: rodent ischemia-reperfusion myocardial infarction



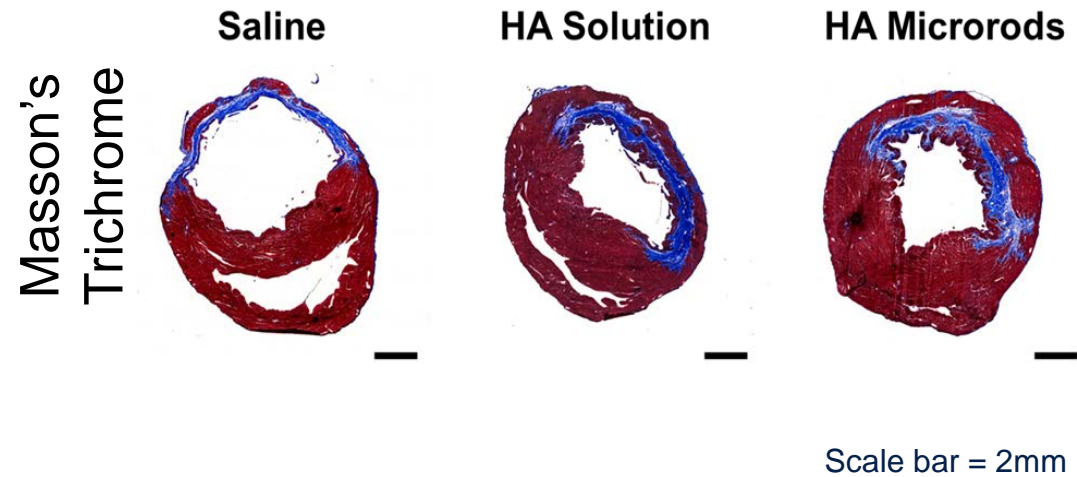
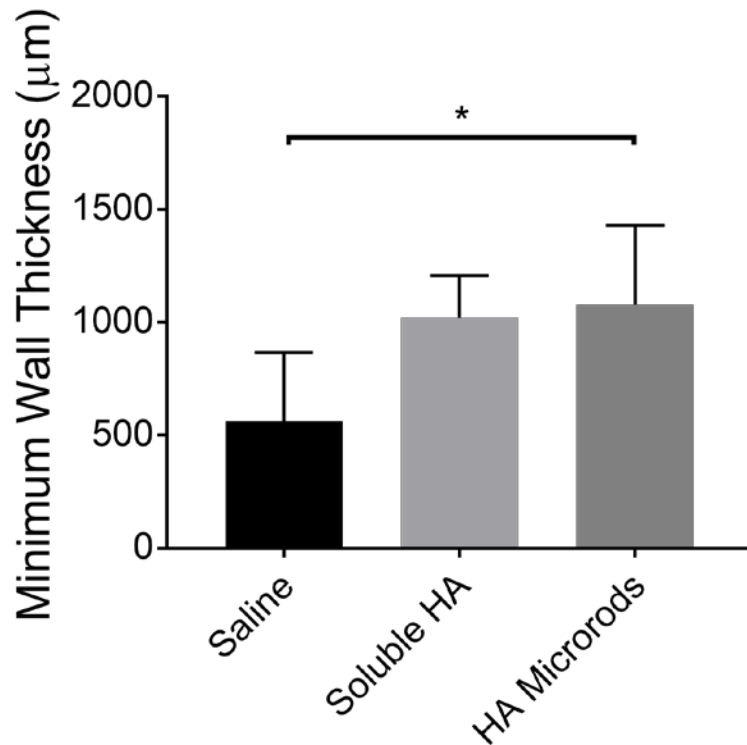
# HA microrods improve cardiac performance 6 weeks after MI and reduce extent of fibrosis

*In vivo* model: Rodent Ischemia-Reperfusion MI



# HA microrods increase left ventricular wall thickness after MI

*In vivo* model: Rodent Ischemia-Reperfusion MI

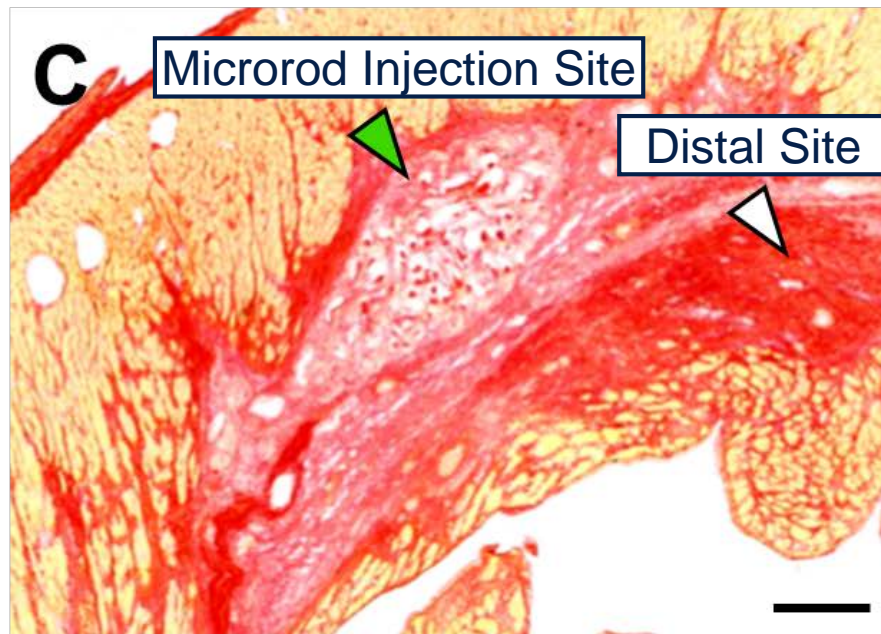




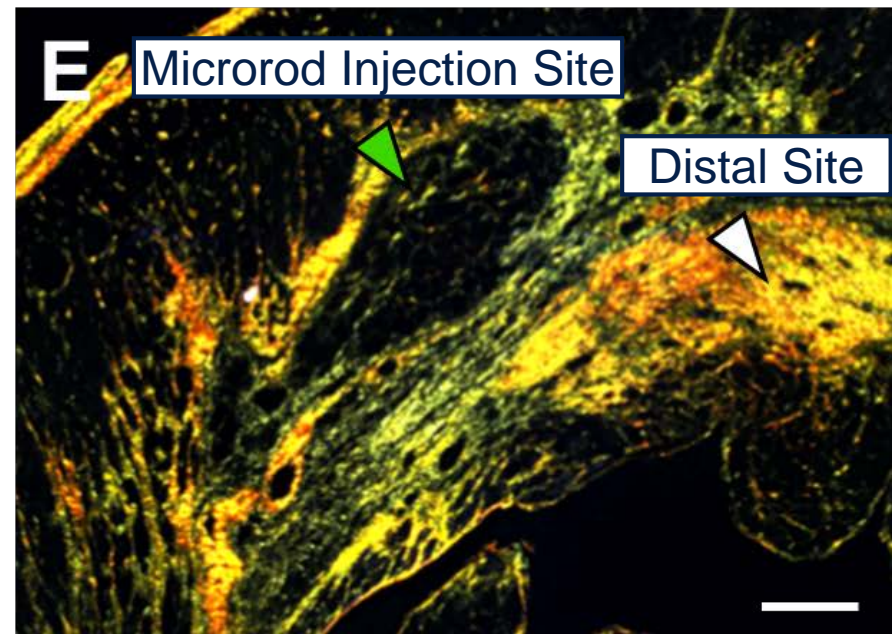
# HA microrods locally reduce collagen deposition within the infarct region

*In vivo* model: Rodent Ischemia-Reperfusion MI

Picrosirius Red  
(Brightfield)



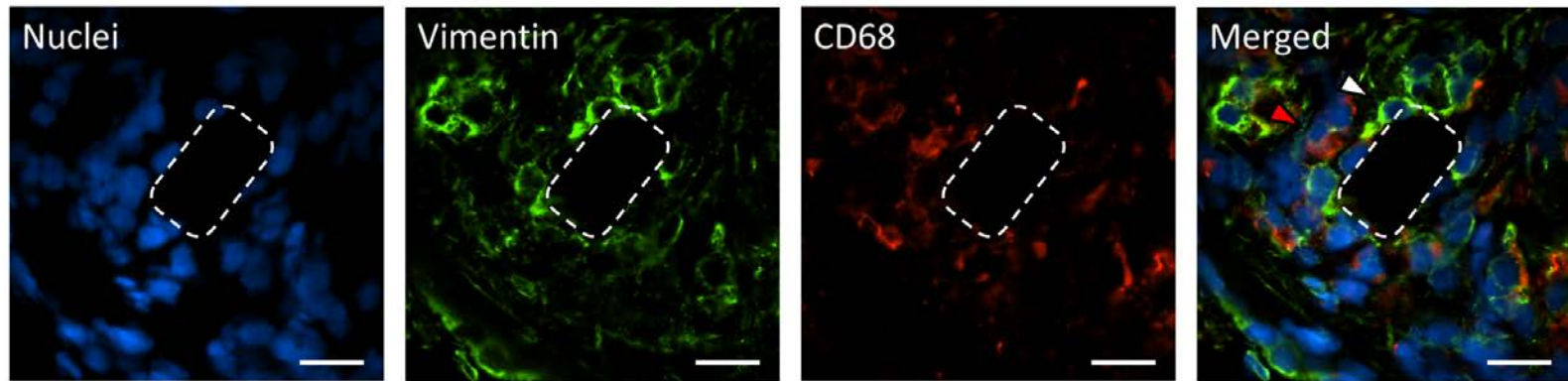
Picrosirius Red  
(Polarized)



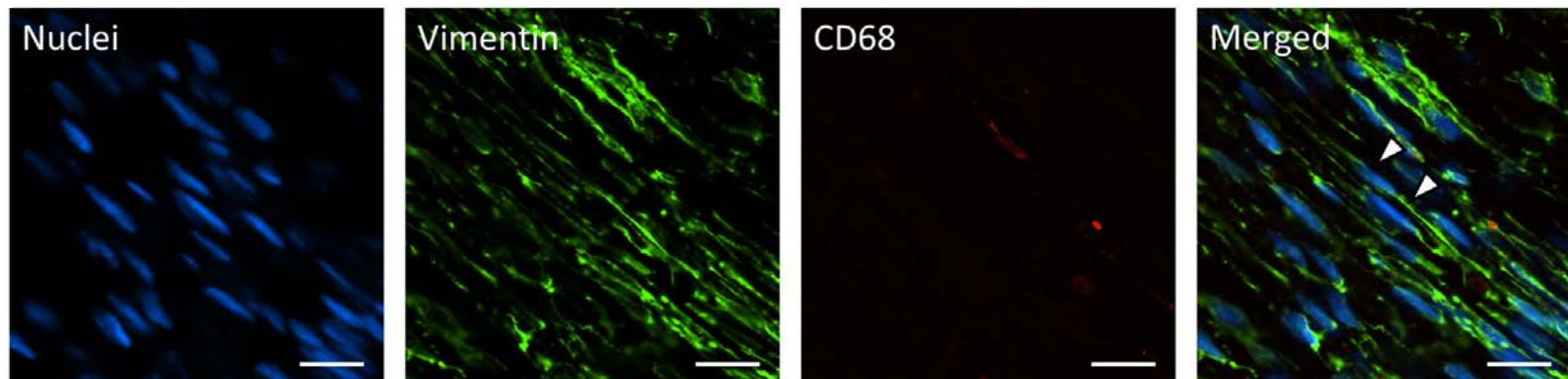
Scale bar = 200 $\mu$ m

# Fibroblasts distal to HA microrods adopt more elongated morphology

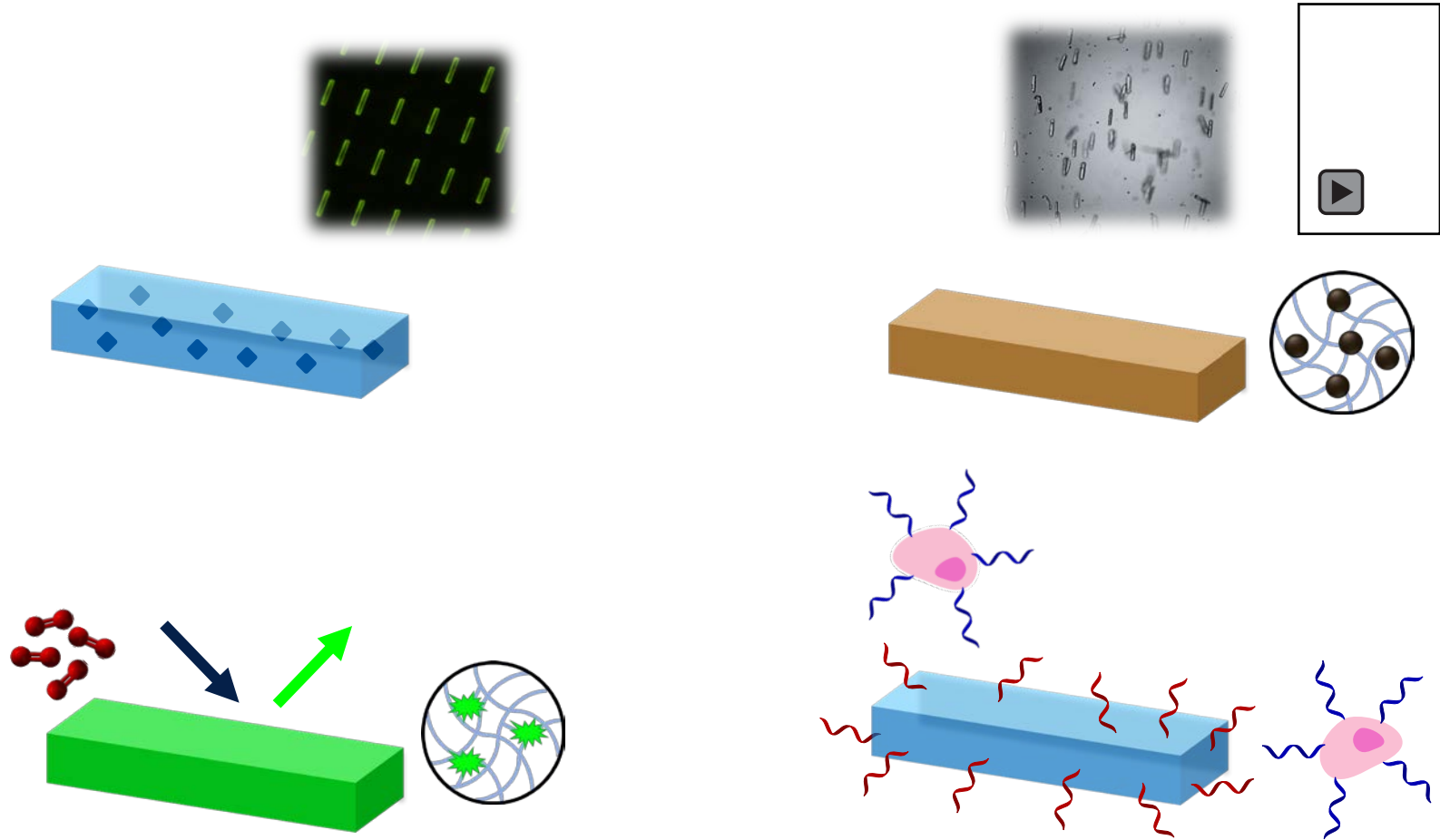
## HA microrod site



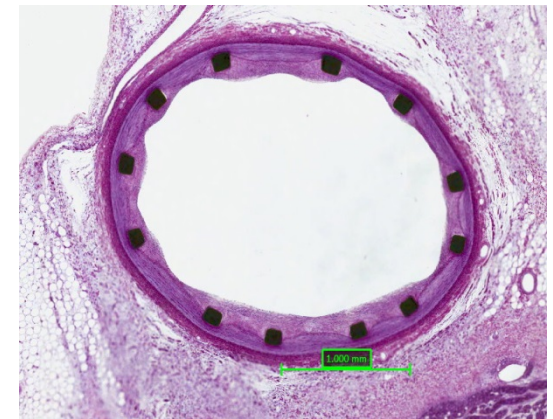
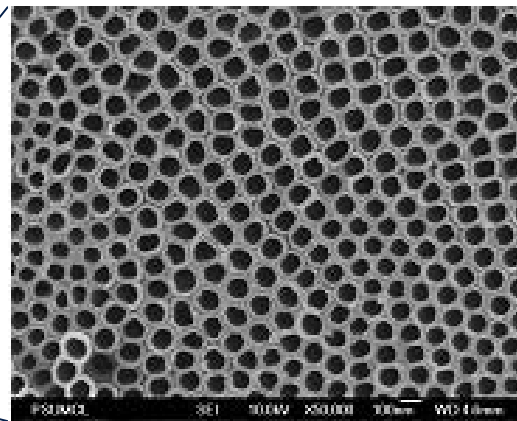
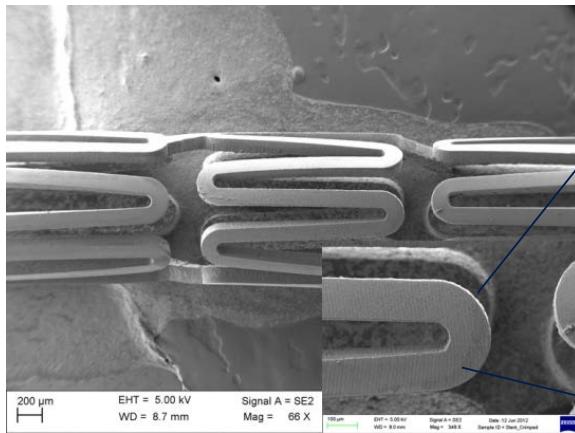
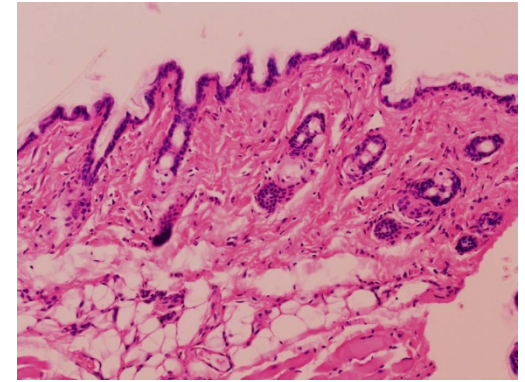
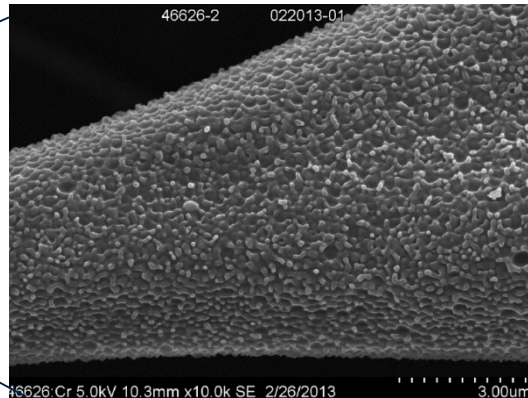
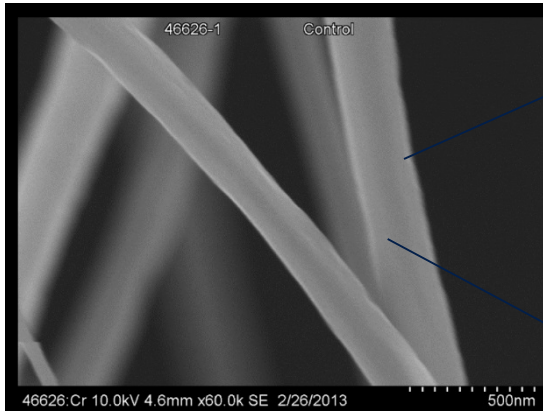
## Distal Site



# Modification of microrods for a range of applications



# “Structured” implants for improved wound healing: Stents and Vascular Grafts



# Bare Metal Stent Drug Eluting Stent



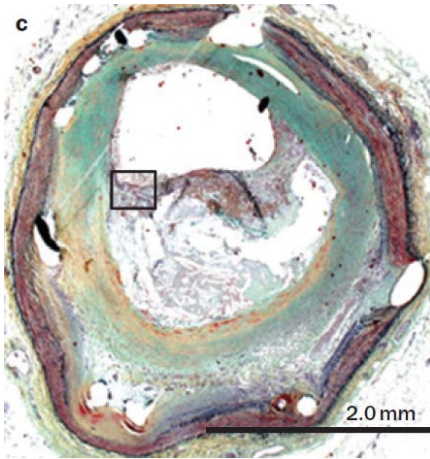
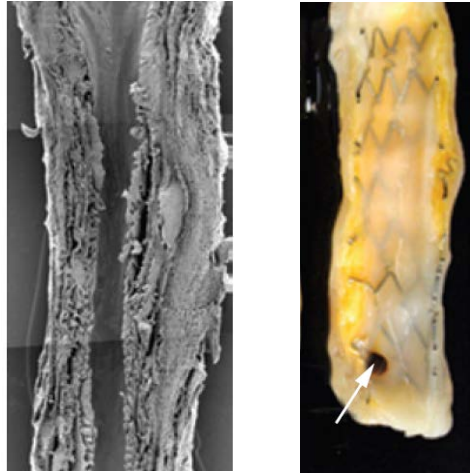
## Bare Metal Stents

- CoCr, Stainless steel, nitinol
- Coated, (bio-)polymer or ceramic

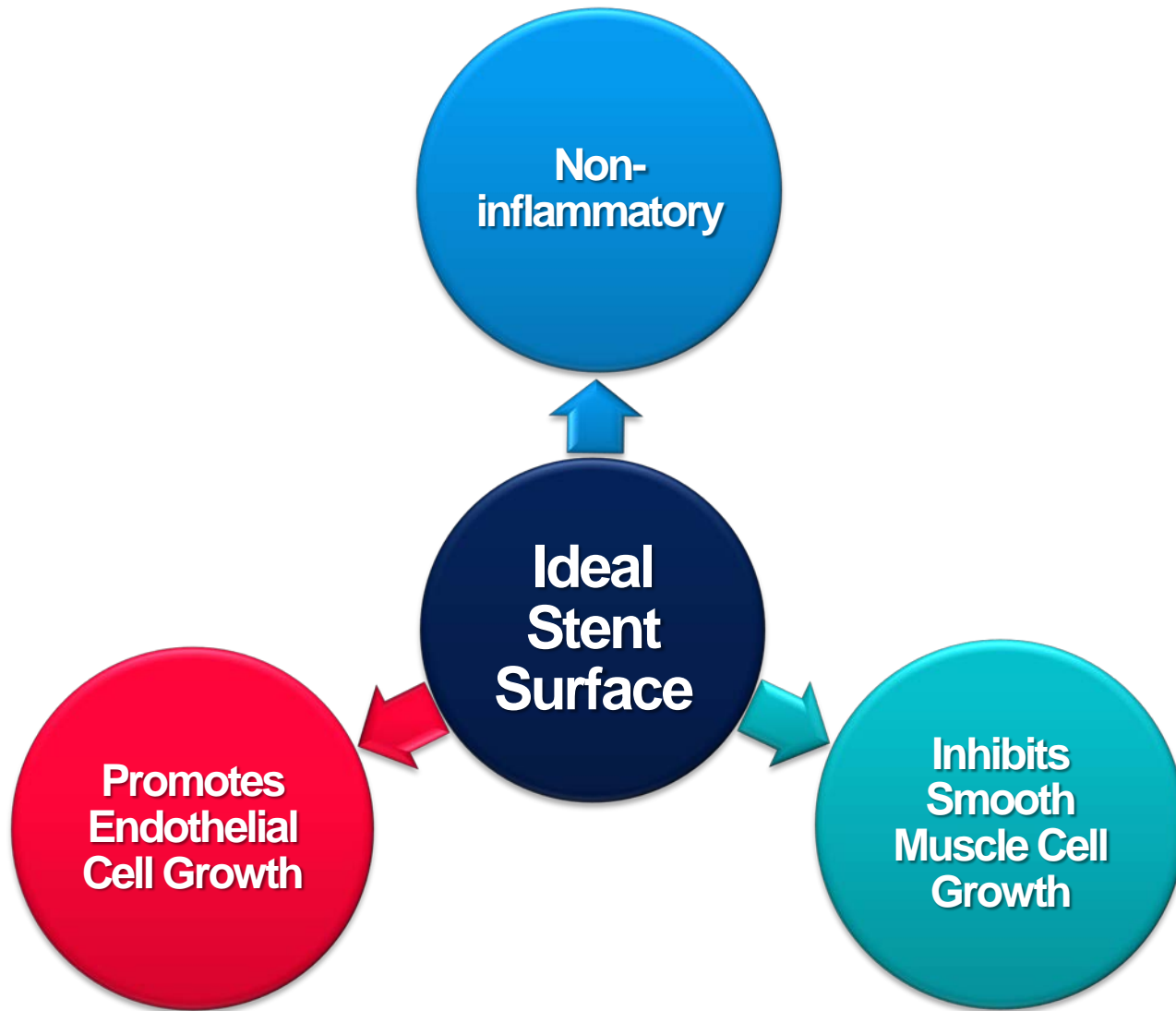
## Drug Eluting Stents

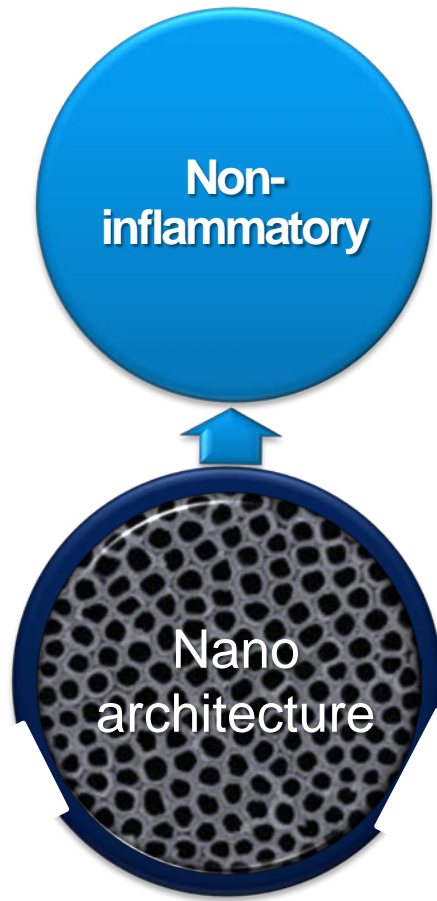
- Anti-Neoplastics (Sirolimus)
- Anti-Proliferative (Paclitaxel)

# In-stent restenosis



- Lumen narrowing
- Granulation tissue
  - Macrophage infiltration
  - Smooth muscle cell
  - Proteoglycan matrix
- Thrombus formation (white arrow)

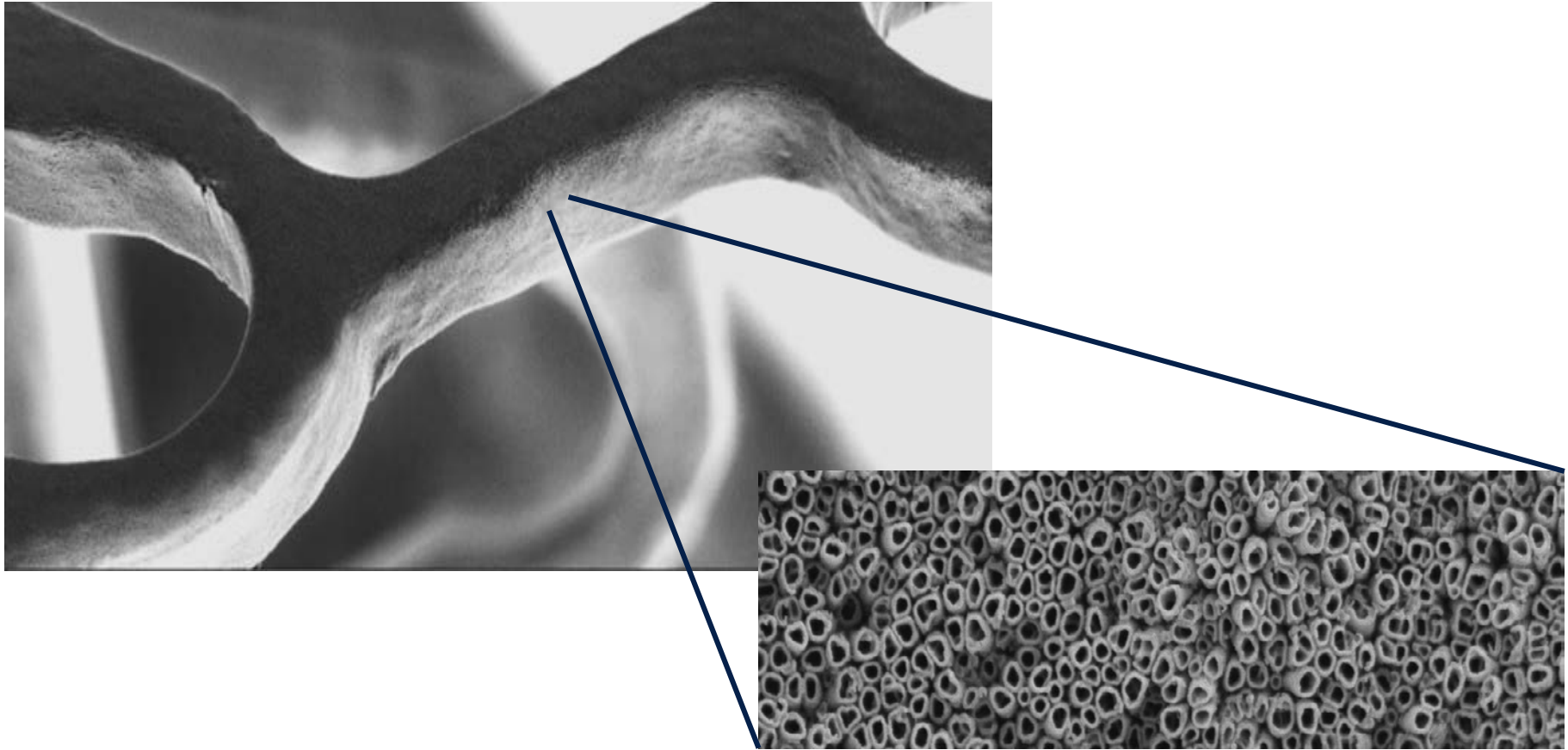




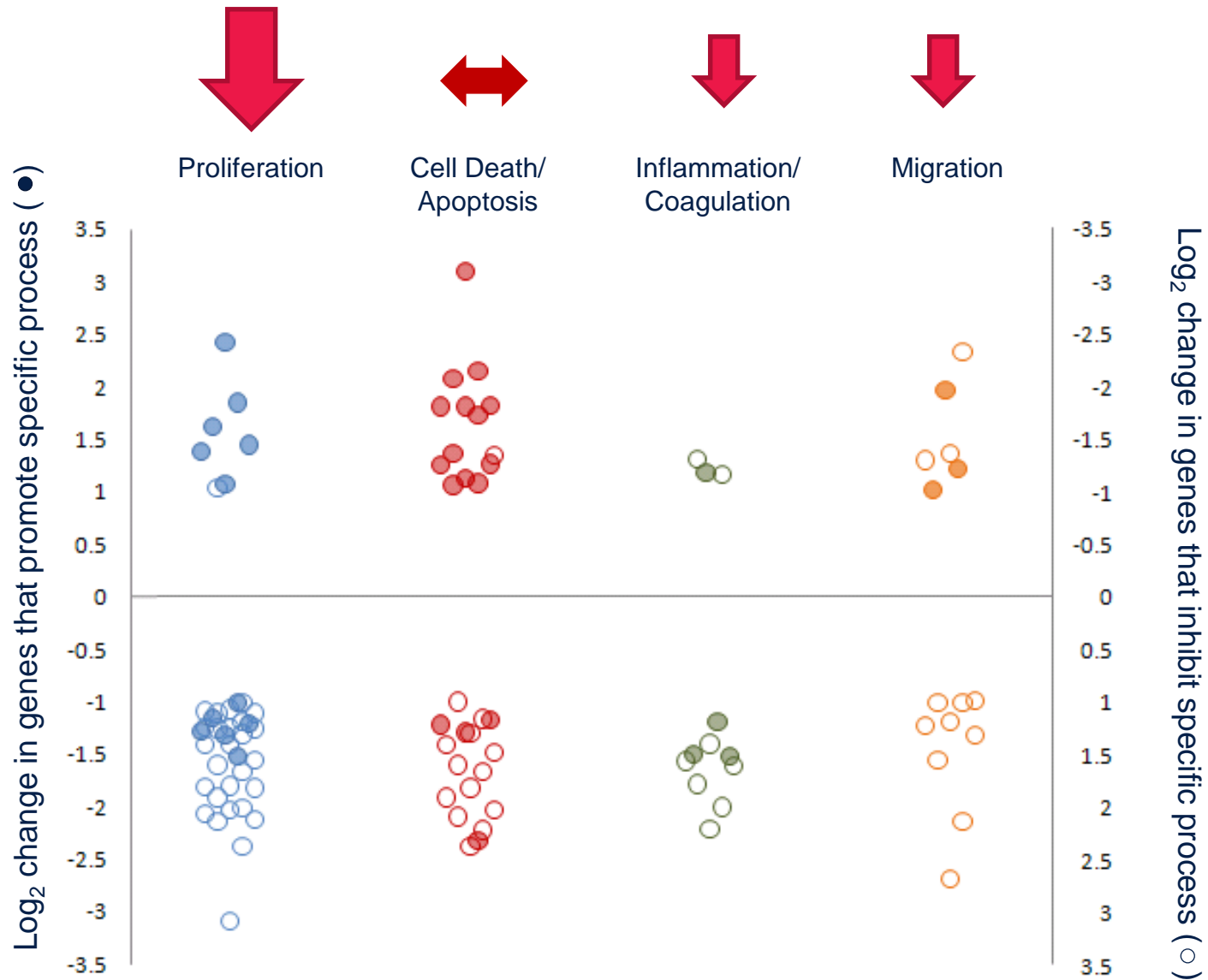
Can nanotopography alone be used to modulate vascular cell response?



# Nanostructured Stents

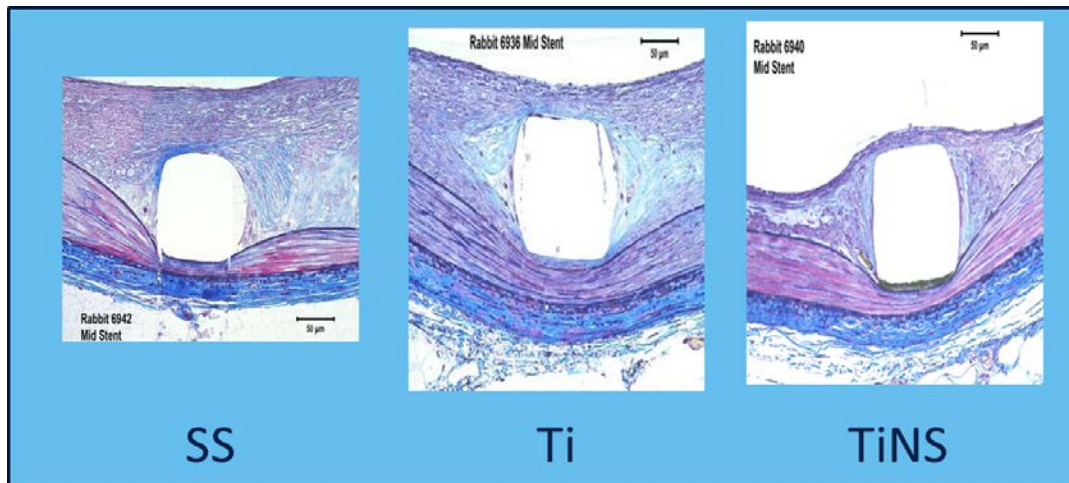
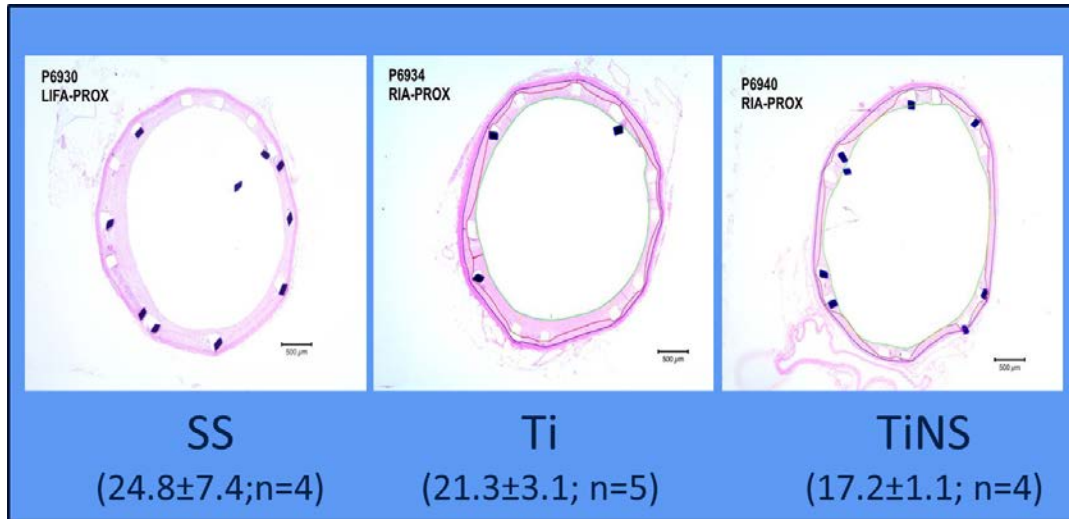


# Smooth muscle cell response to nanotubes



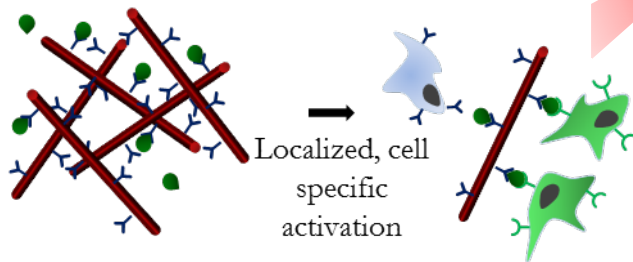
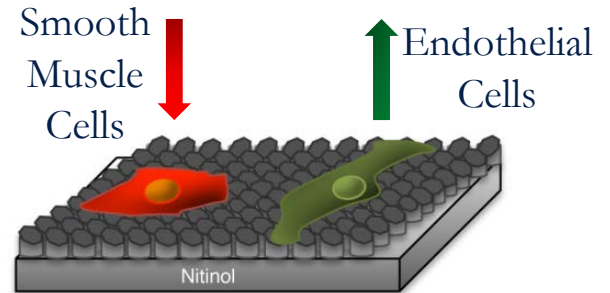
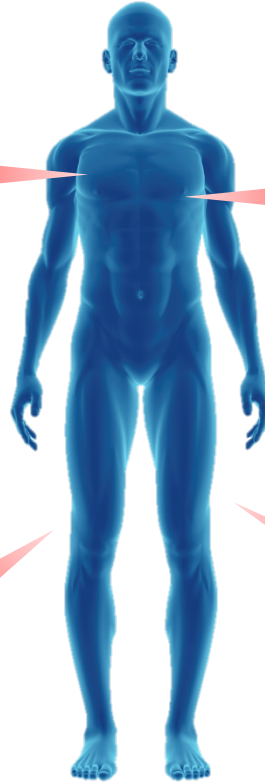
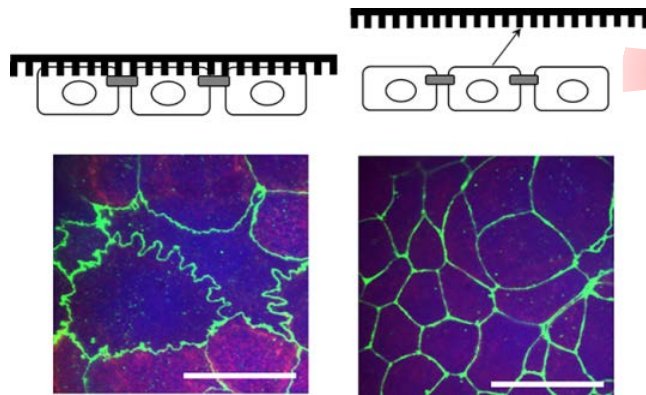


# Nanostructured surfaces reduce stenosis

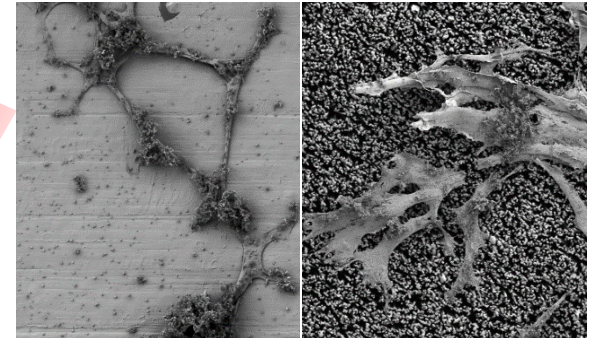


# Designing Therapeutic “Materials” at the Micro and Nanoscale

Epithelial Cells



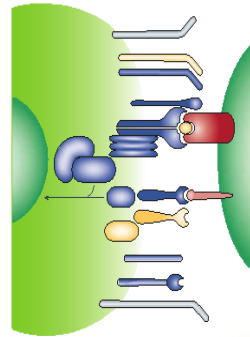
Fibroblasts



# Interfacing Materials with Biologics for Cell Therapy

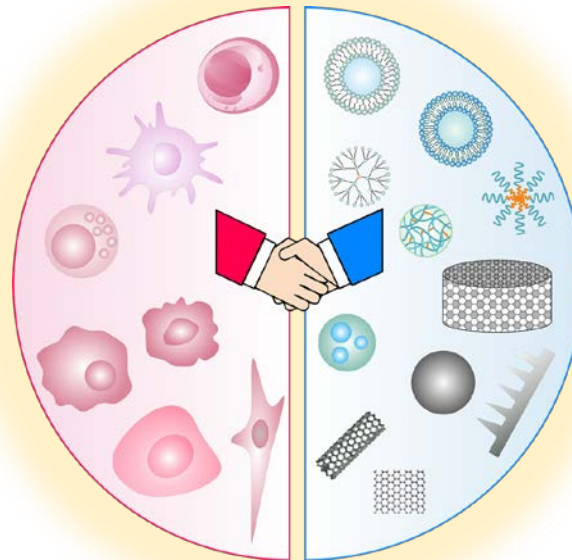
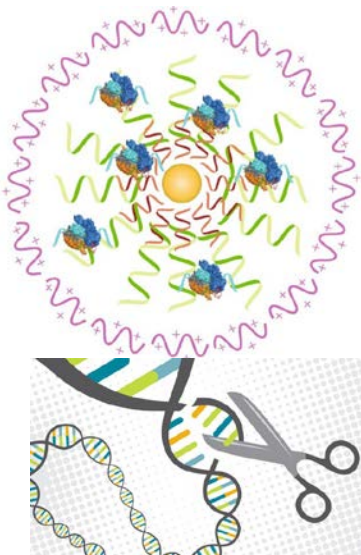
## Cancer immunotherapy

Immune cells

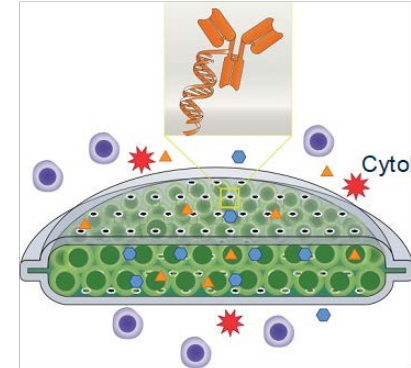


Immune cell engagers

## Gene editing

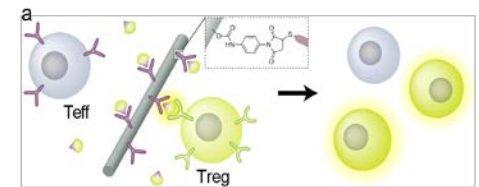


## Diabetes



Immune cells  
Islets  
Insulin  
Glucose

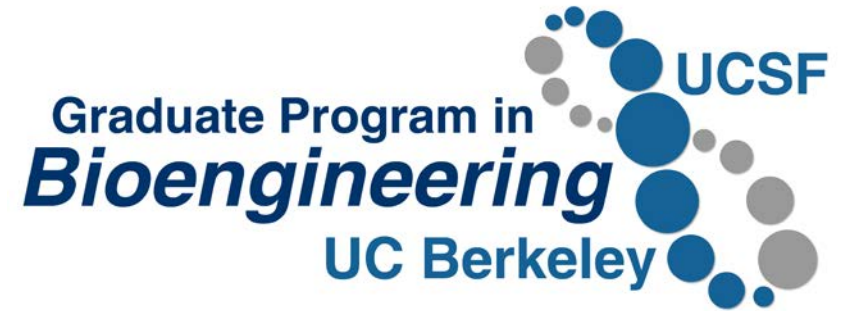
## Autoimmune



IL-2 complexes with Treg-specific nanowires

Treg-specific activation and proliferation

# Acknowledgements



## The Therapeutic Micro and Nanotechnology Laboratory at UCSF



- NIH
- NSF
- JDRF
- Zambon Ltd
- Al Mann Institute
- CIRM
- Catalyst
- Regeneron
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- USAID
- Eli Lilly