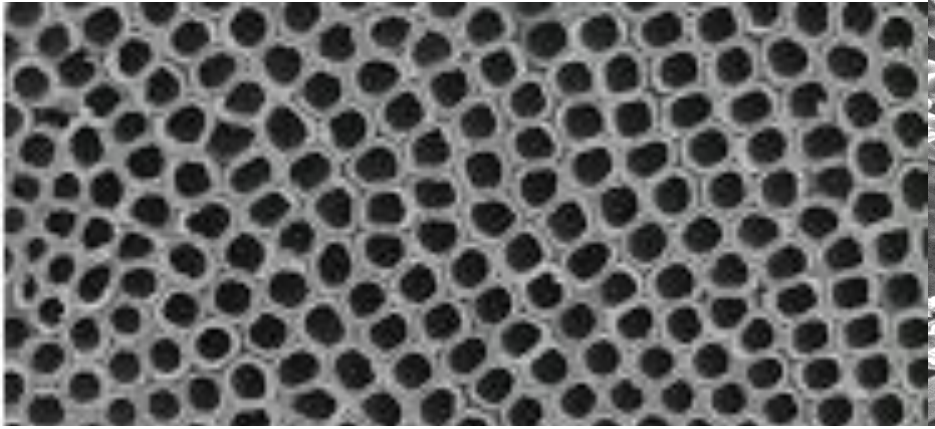
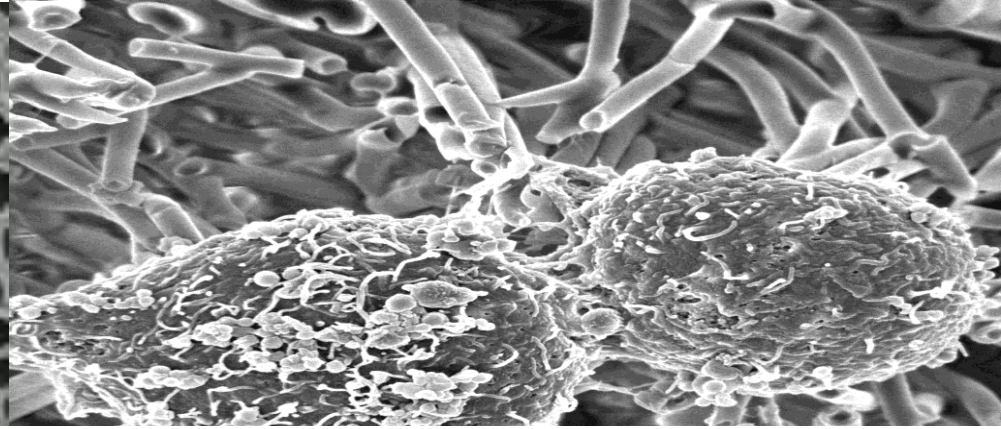
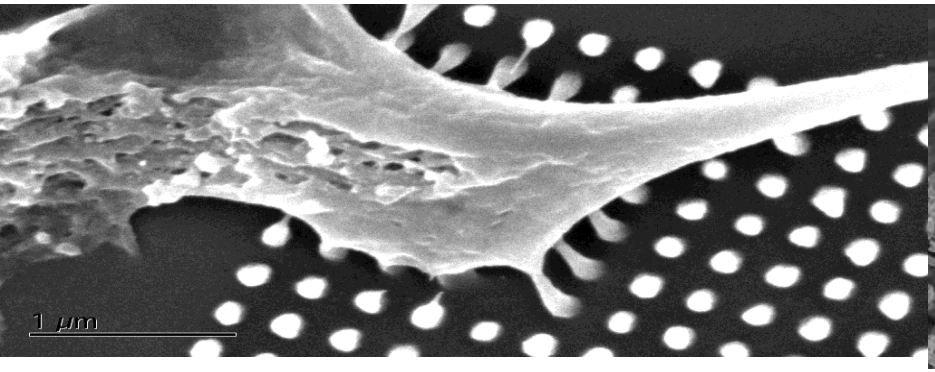
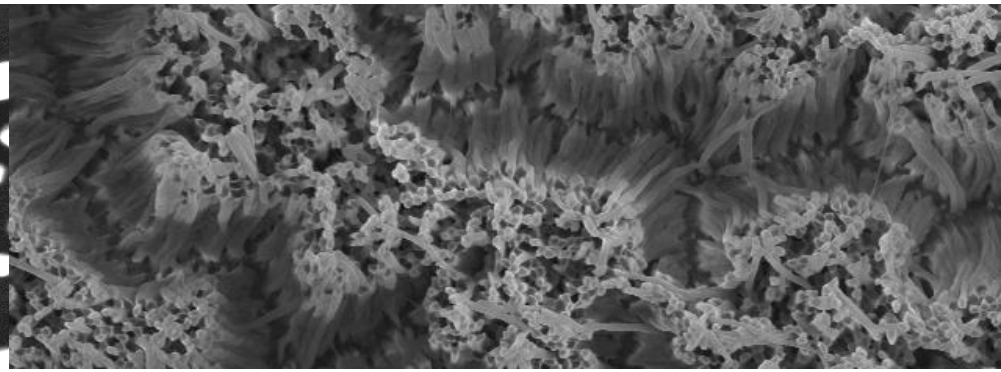




Engineering micro and nanostructured interfaces for therapeutic delivery





Tejal A. Desai

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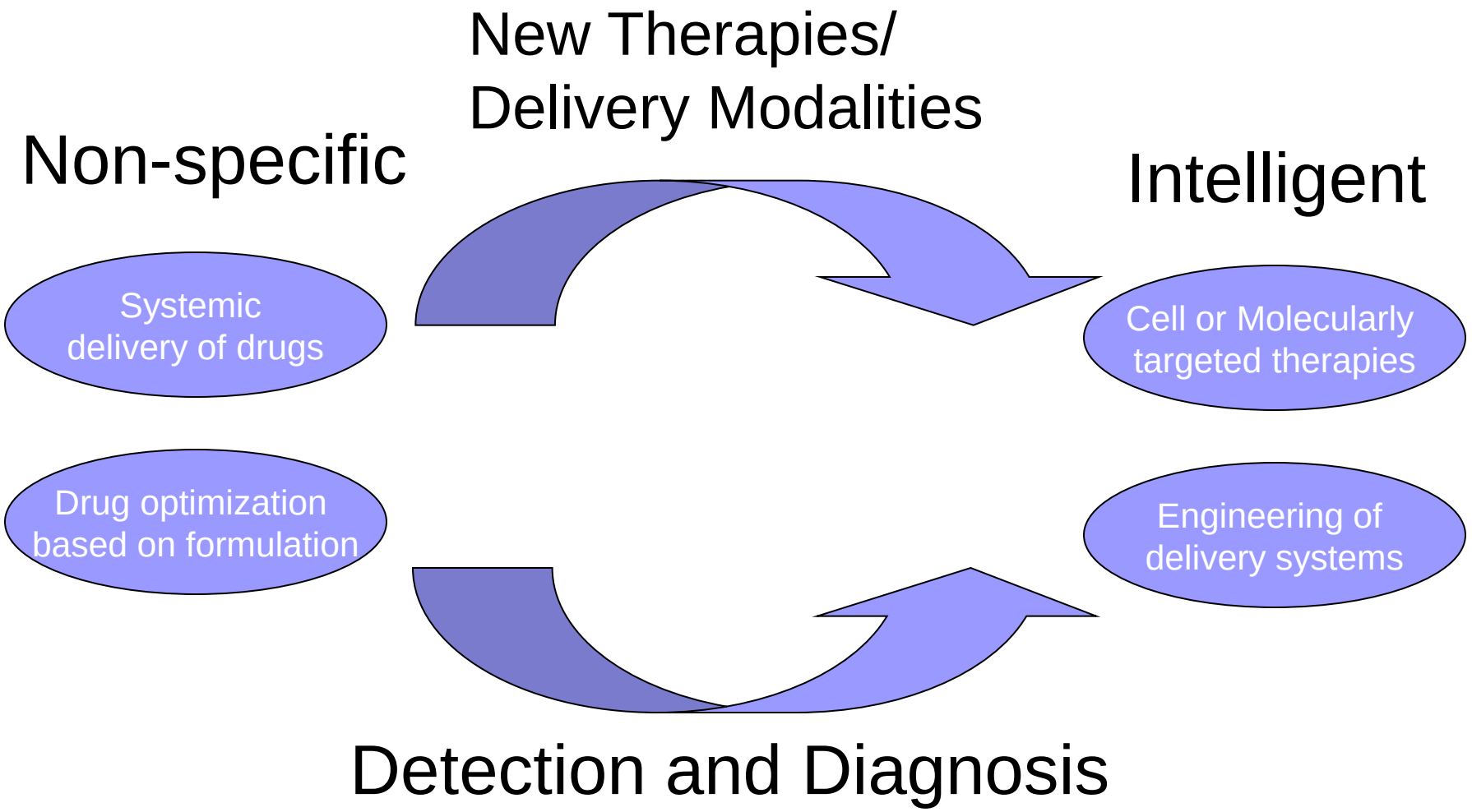
San Francisco

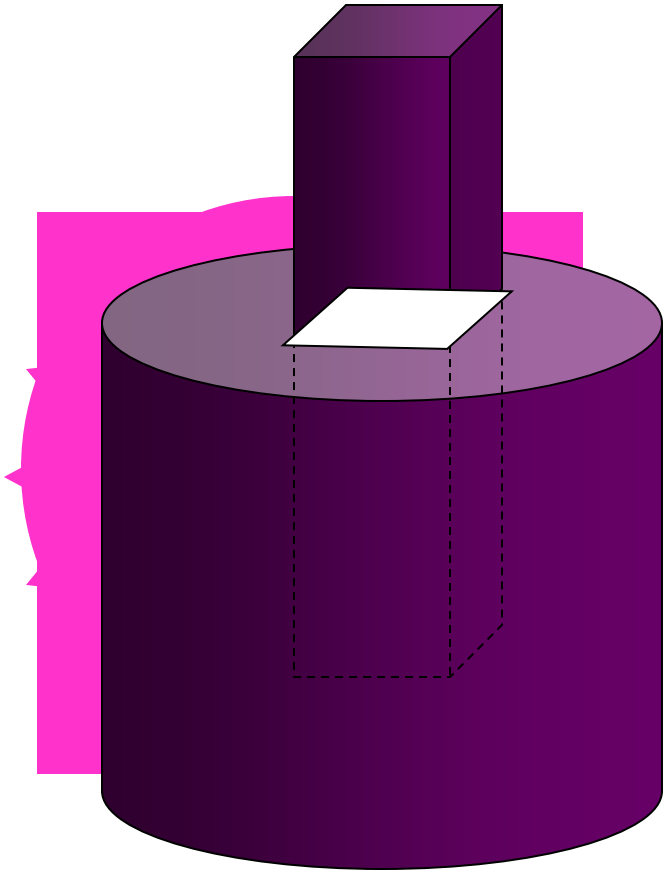
qb3
ucb·ucsc·ucsf

A shift in therapeutic delivery…

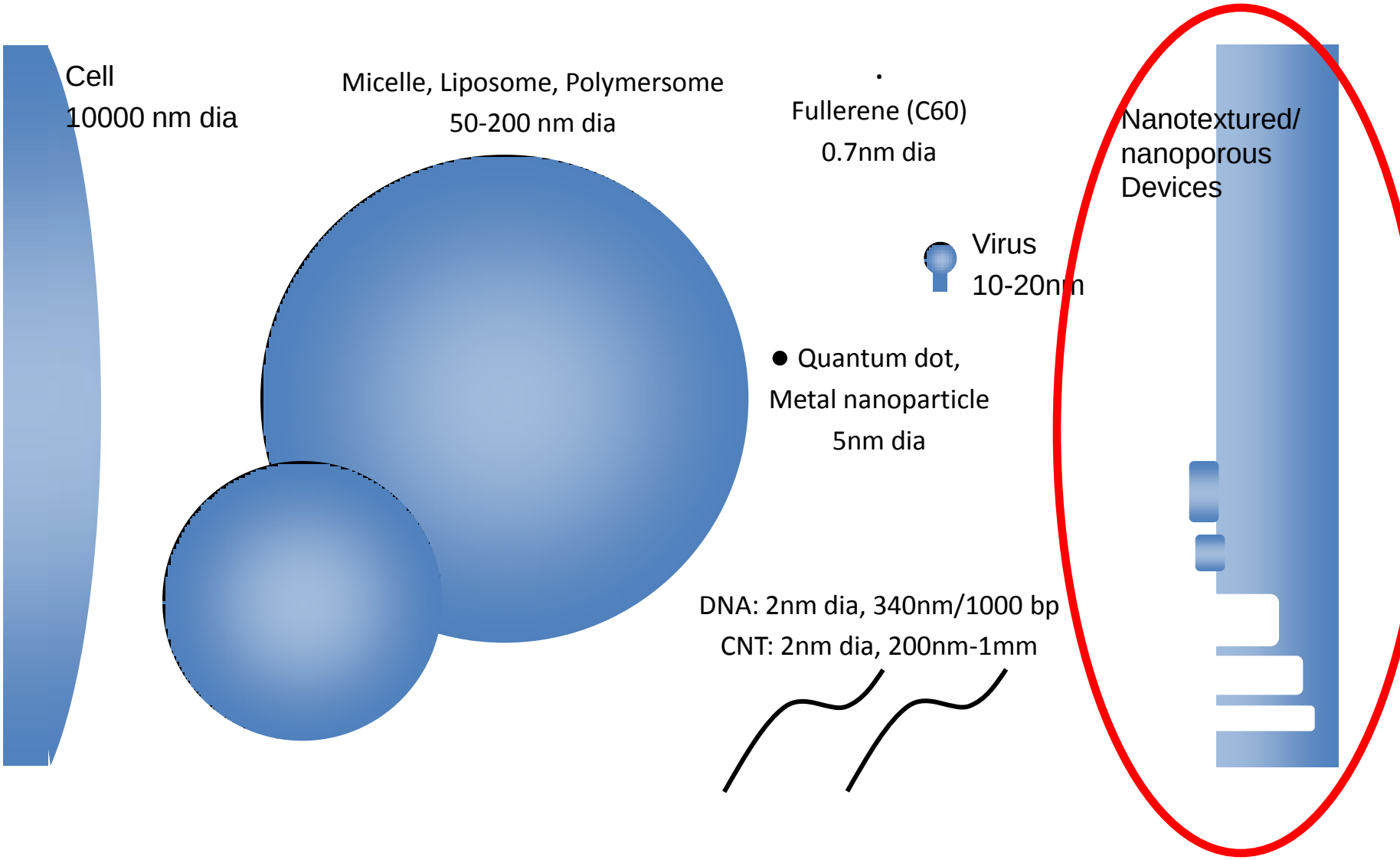


How Can Micro/Nanotechnology Help in Therapeutic Applications?

- Morphological control
- Dimensional control
- Interfacial control

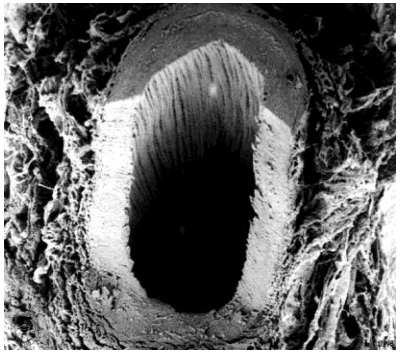


Nanomaterials in biological context

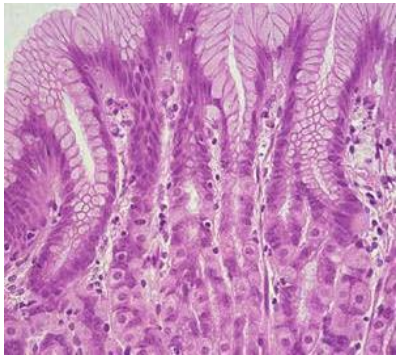


How can we tune device structure to modulate biologic function for therapeutic purposes?

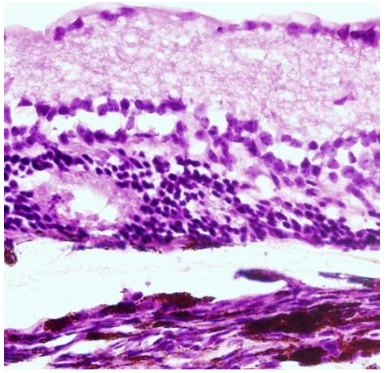
Vascular



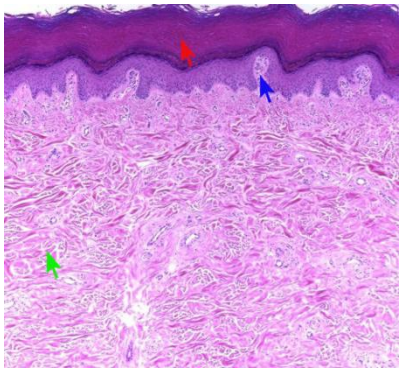
Oral

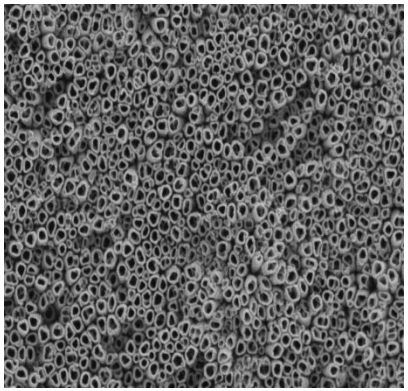


Retinal

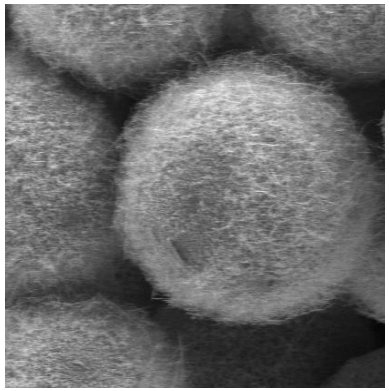


Transdermal

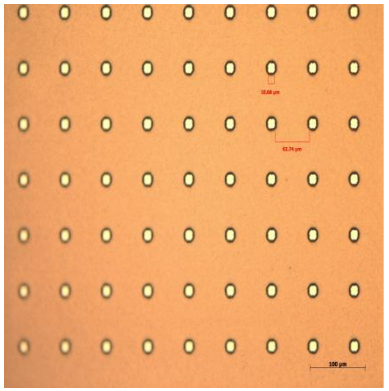




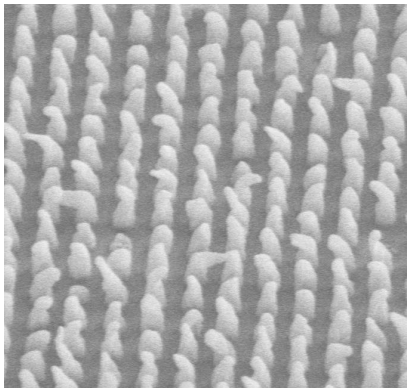
Nanotubes



Nanowires

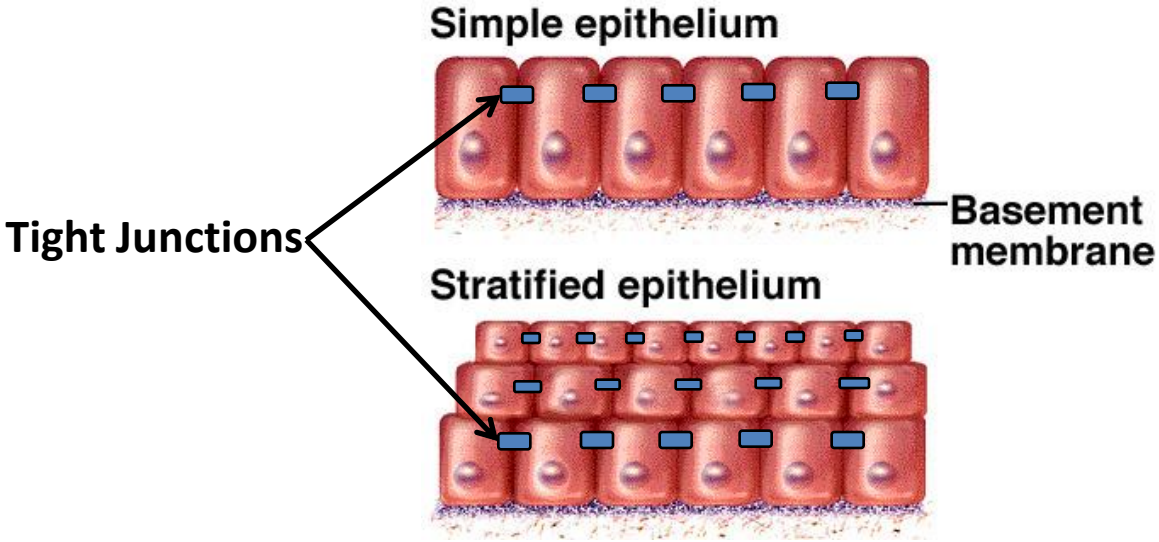


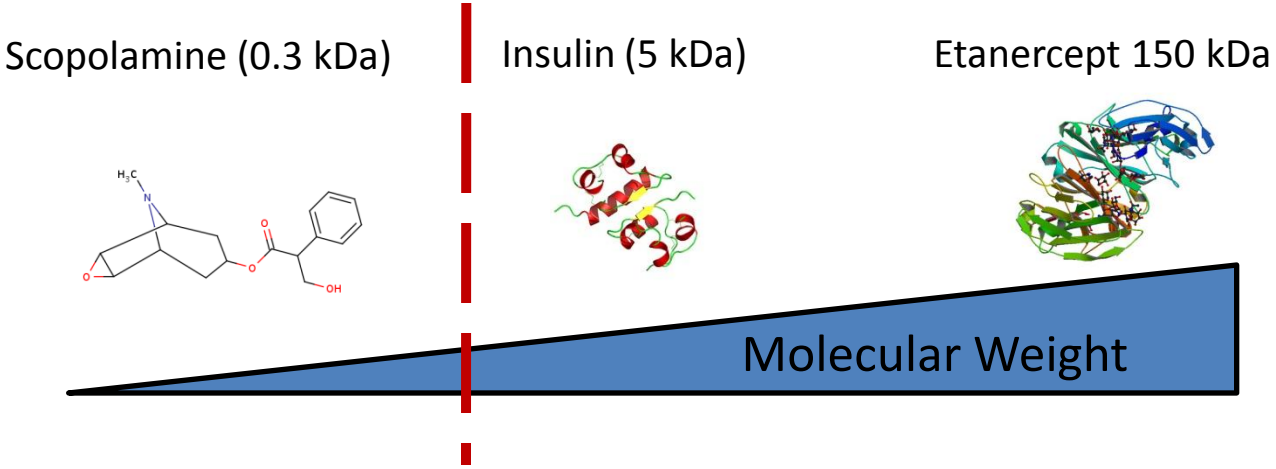
Nanopores



Nanostructure

Challenges in Delivery…



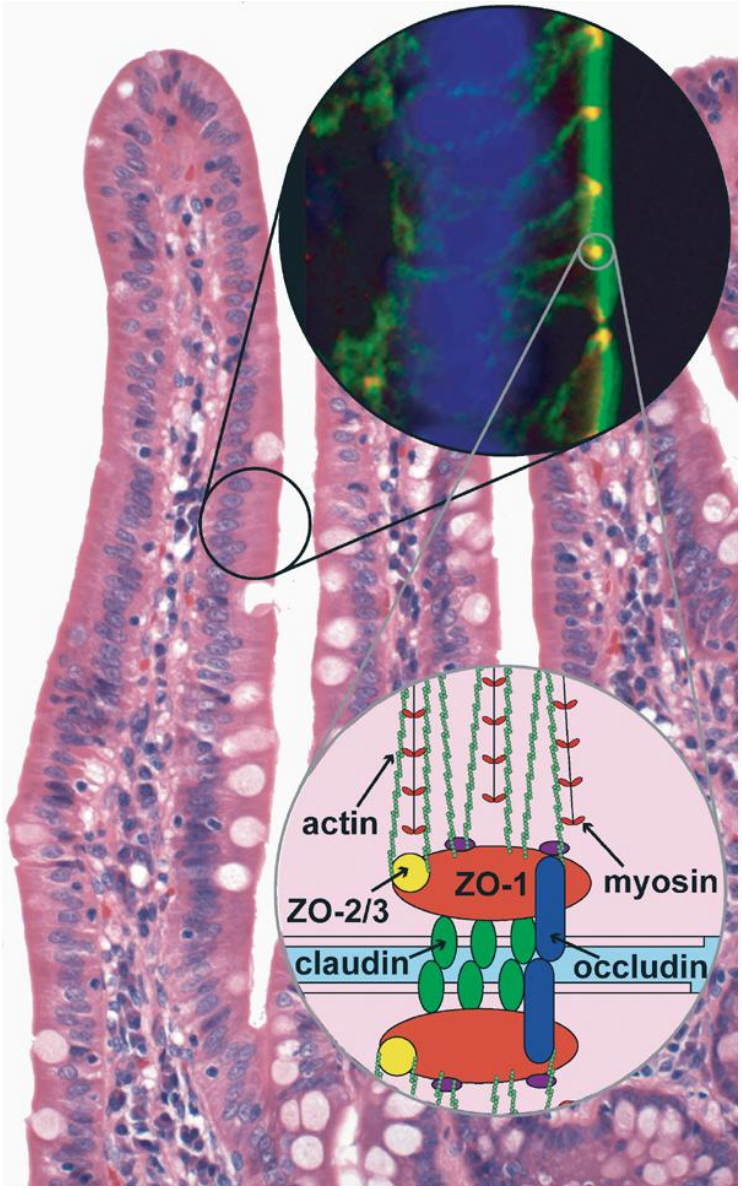


Tight Junctions

- Form a paracellular diffusion barrier
  - Regulates epithelial cell permeability
  - An intermembrane diffusion barrier which restricts the apical-basolateral diffusion of membrane components

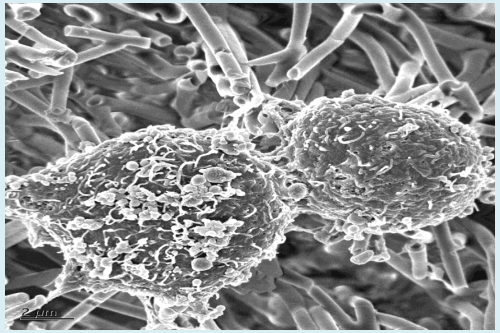
- Physical and Chemical permeation enhancers can be toxic and irreversible

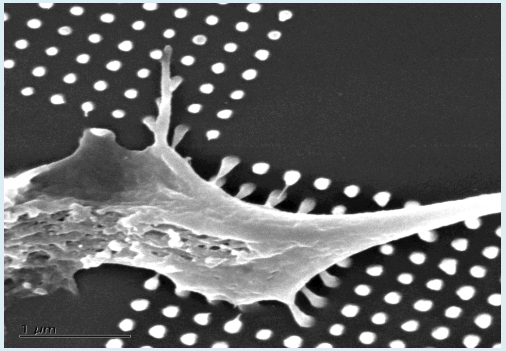
Can device structure be used to reversibly modulate tight junctions?



Nanostructures affect cellular function

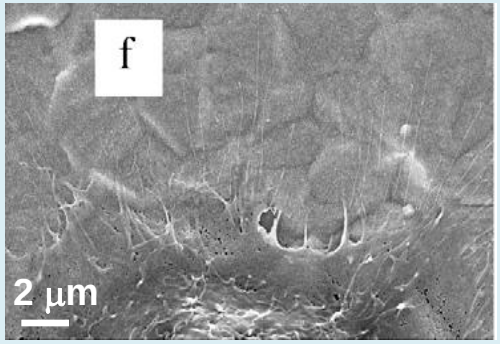
Attachment

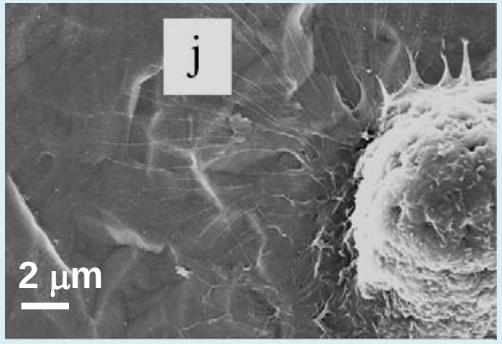




Tao, et. al,
Nanoletters, 2007

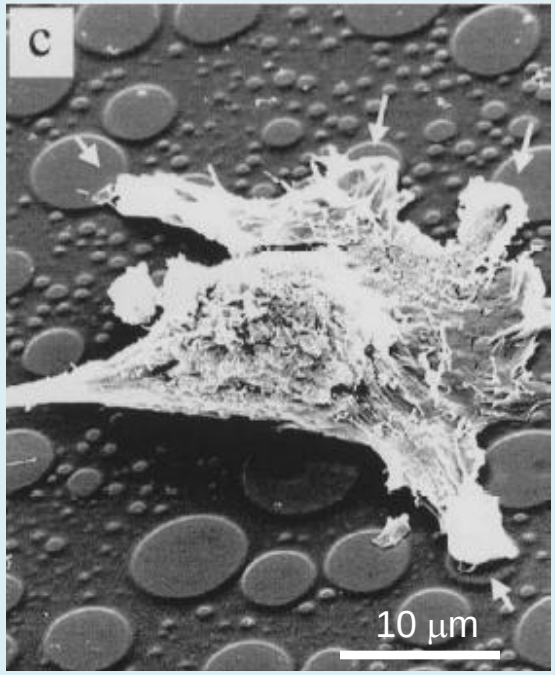
Morphology





Puckett, et. al,
Acta Biomaterialia,
2010

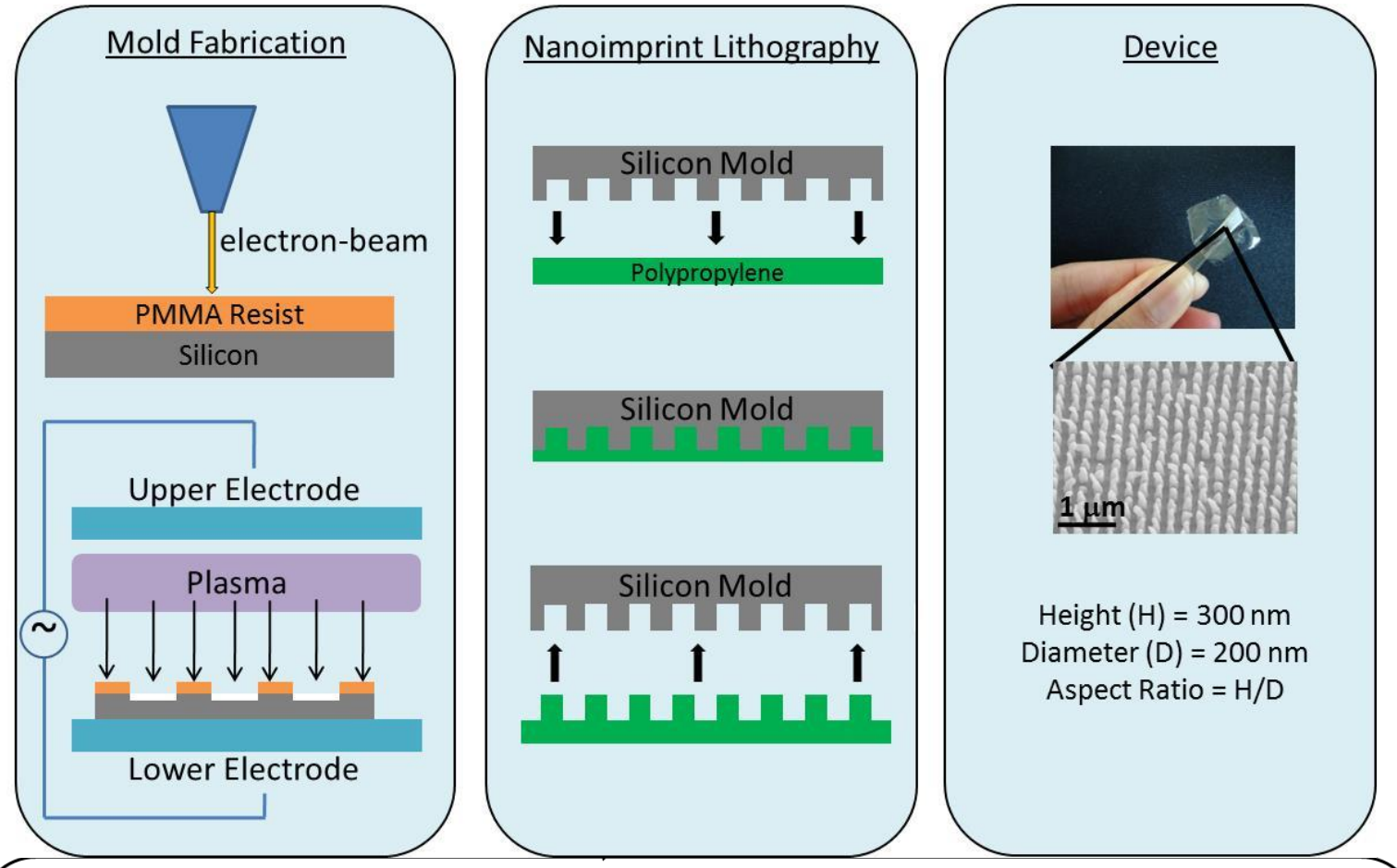
Migration

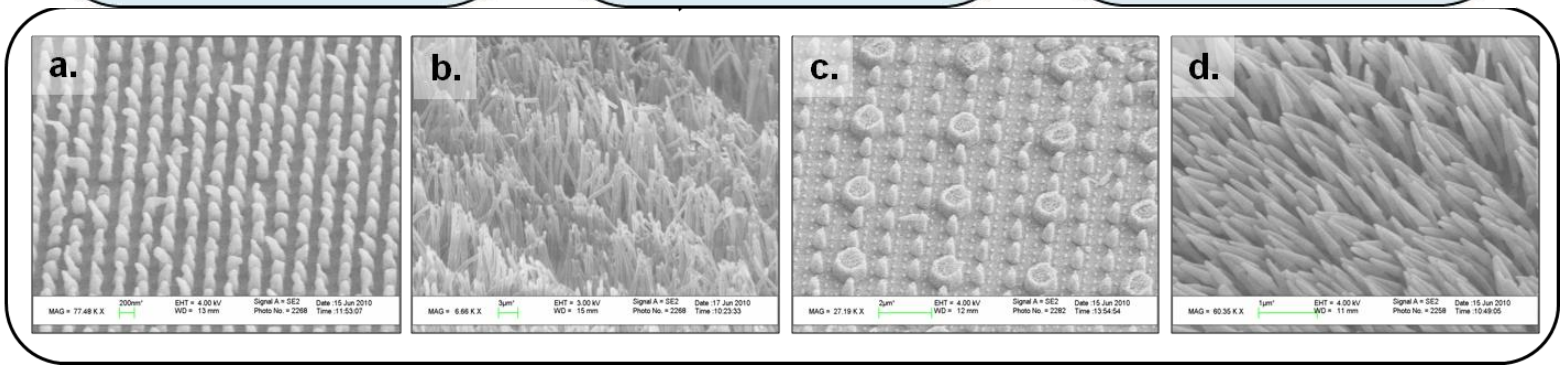


Dalby, et. al,
Tissue Engineering,
2002

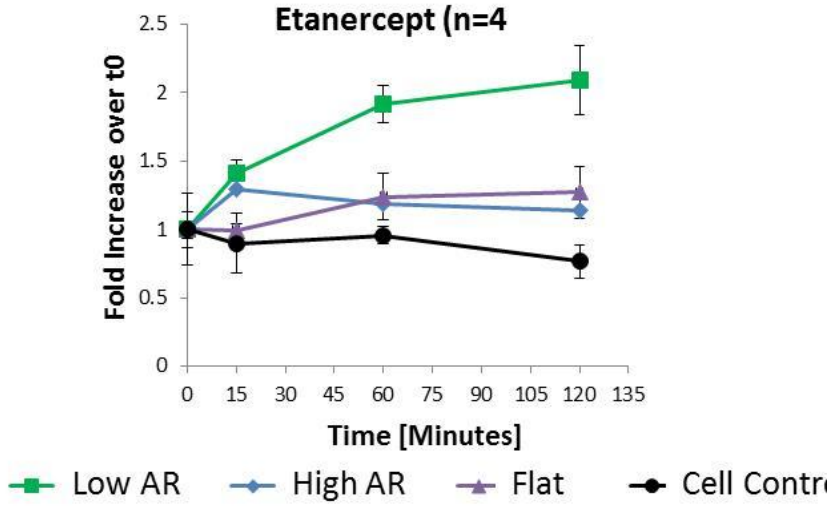
Can we use nanostructure to enhance epithelial permeability?

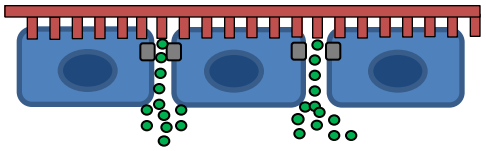
Nanostructured Thin Film Fabrication

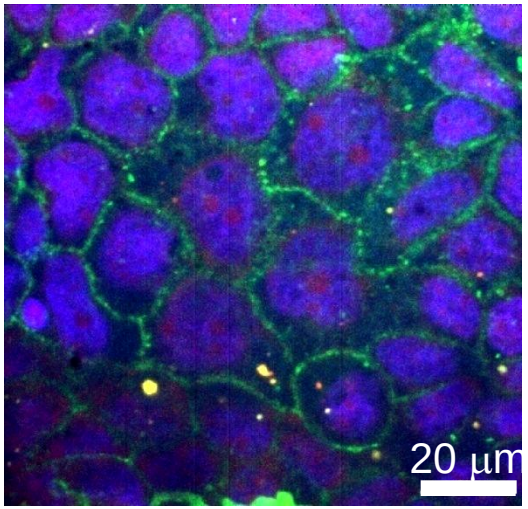




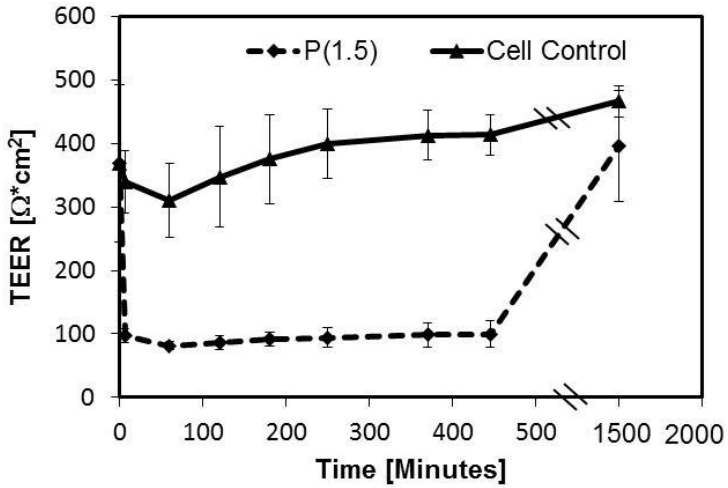
Nanostructures Enhance Paracellular Transport of large proteins





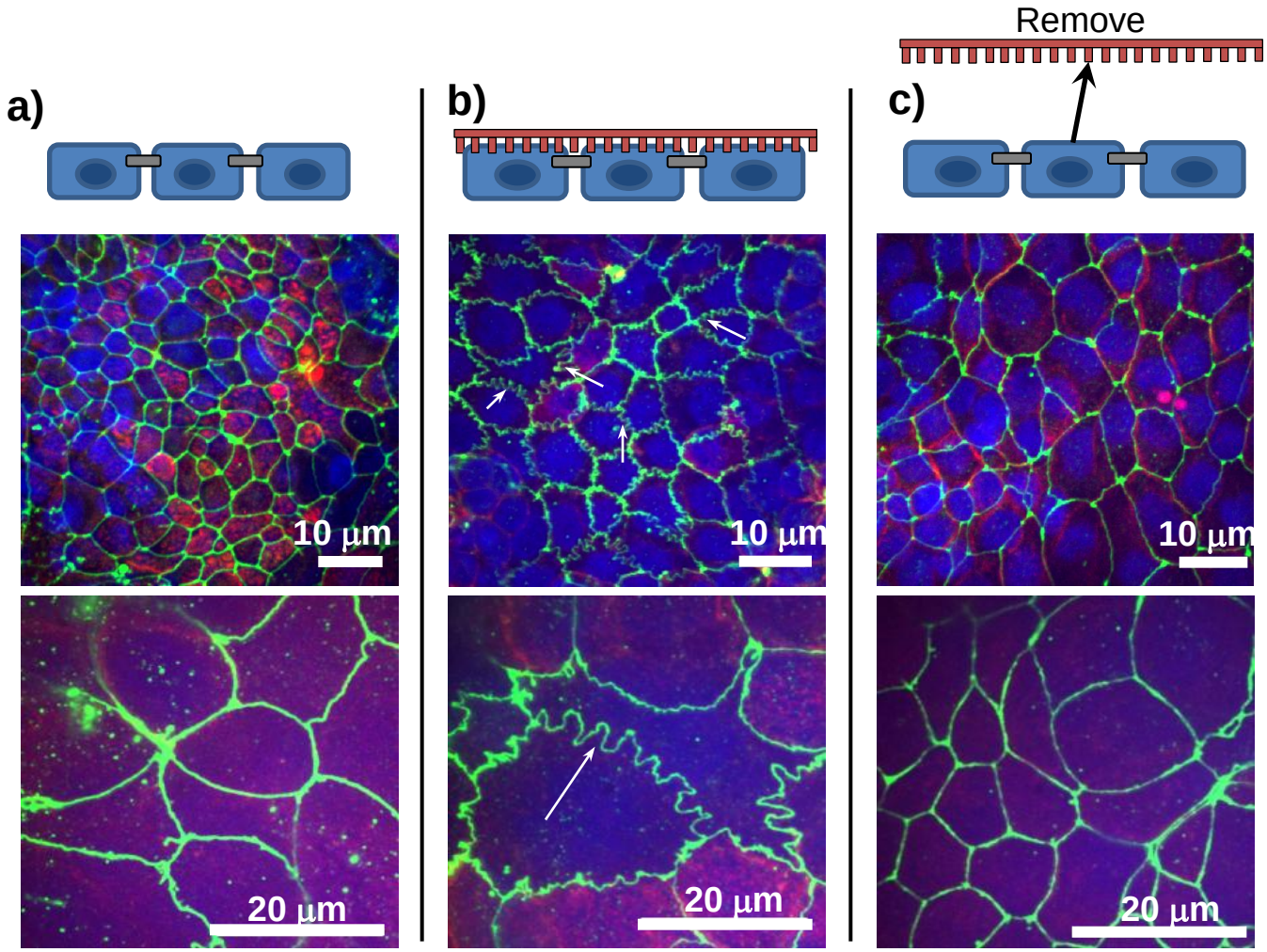


FITC-IgG
Caco-2 cells



FITC-IgG is located in the intercellular space, indicating paracellular transport

The process is reversible and involves remodeling of tight junctions

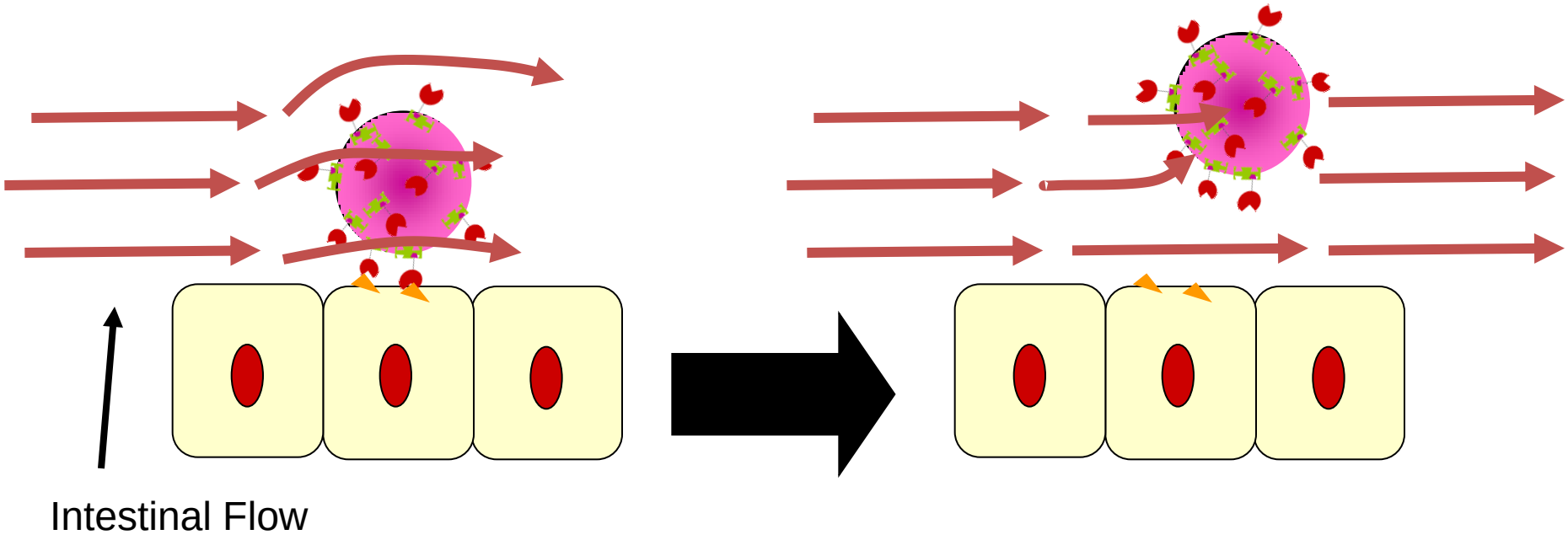


ZO-1 (tight junction protein), Caco-2 nuclei, F-Actin

K. Kam et al., Nanoletters 2013

CAN WE USE “NANOSTRUCTURE” TO ENHANCE PARTICLE ADHESION?

How could we engineer better particle stability under flow conditions?



Adhesion in Biology:

Can we exploit this for drug delivery?

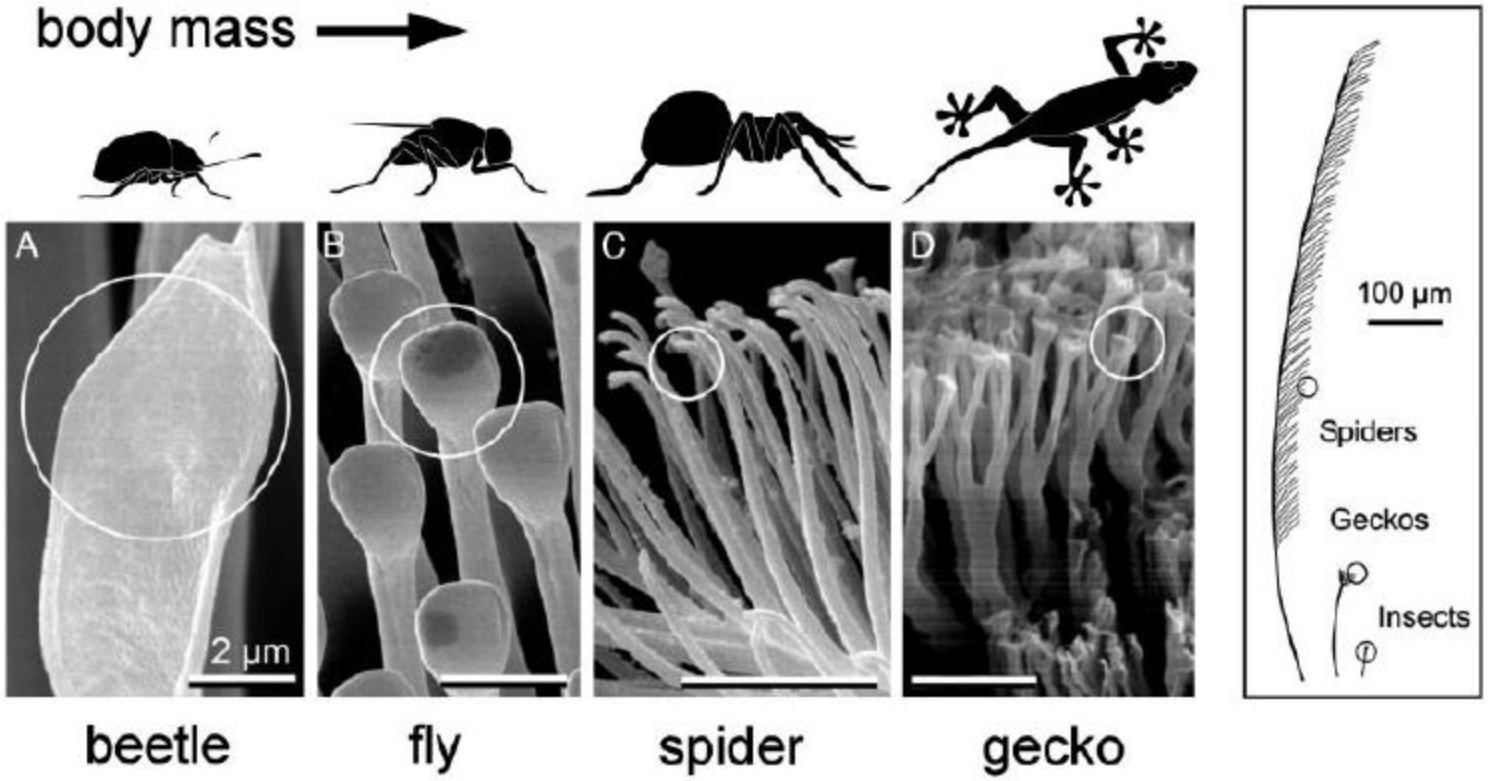
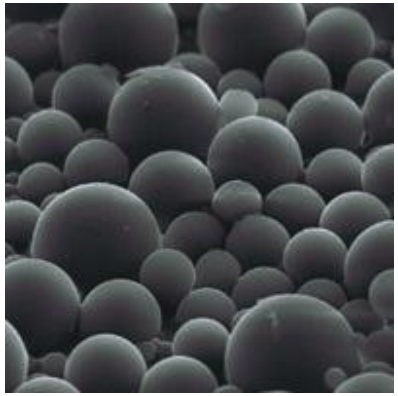
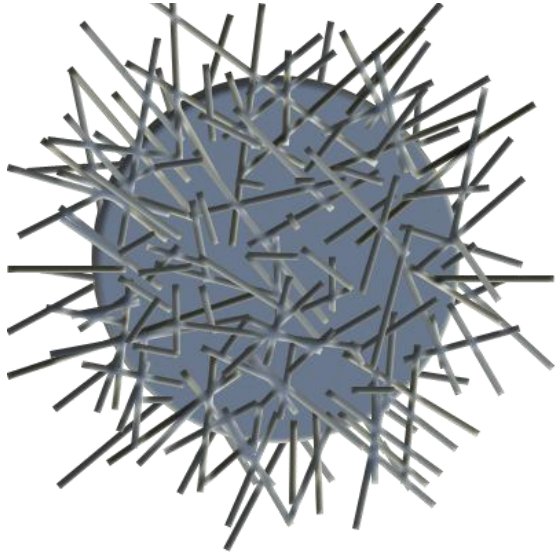


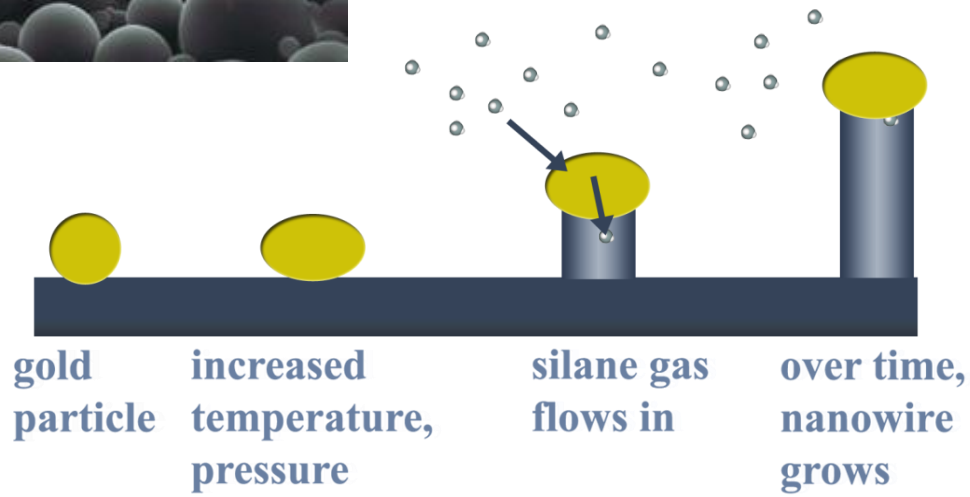
Figure 8: Biological examples of micro and nanoscale features in adhesion[34]

Nanowire Particle Fabrication

Vapor-Liquid-Solid Nanowire Growth Process

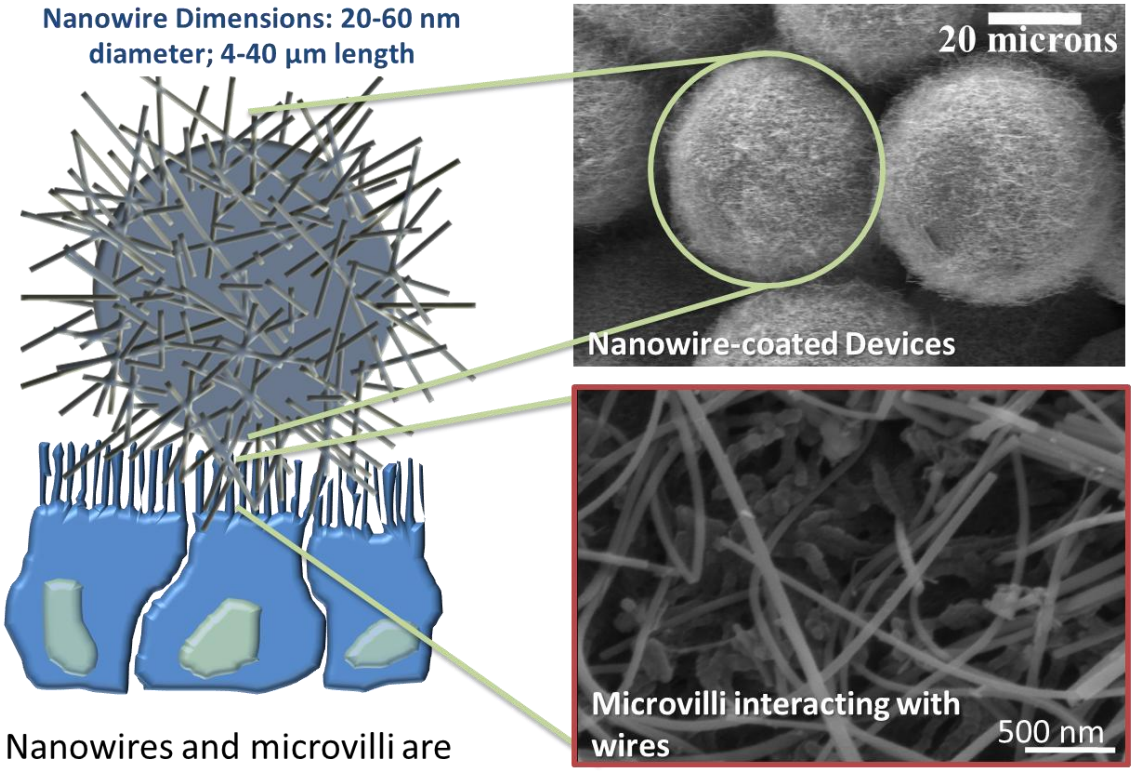




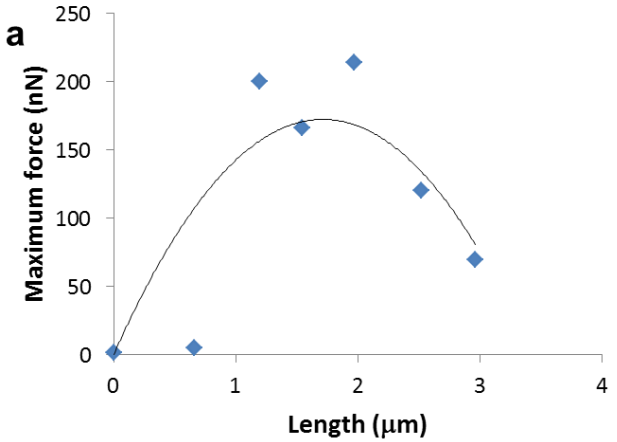


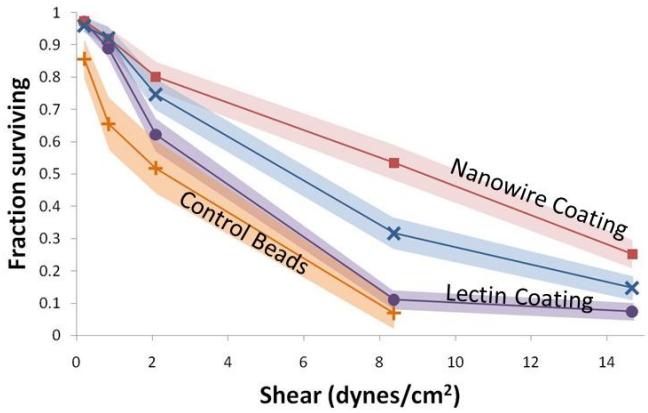
Beginning Substrate: 30-50 micron glass beads

Nanostructured Microparticles



Nanowires and microvilli are similar in scale

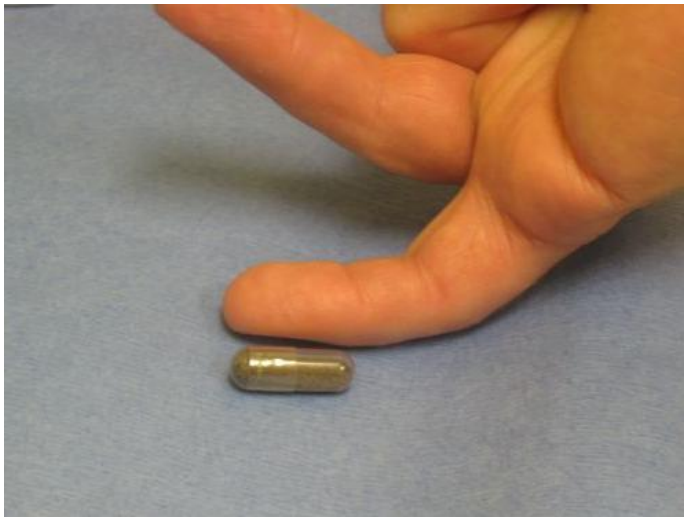




K. Fischer et al., Nanoletters 2010. 2011

Nanowire Particles at 15 and 180 miin

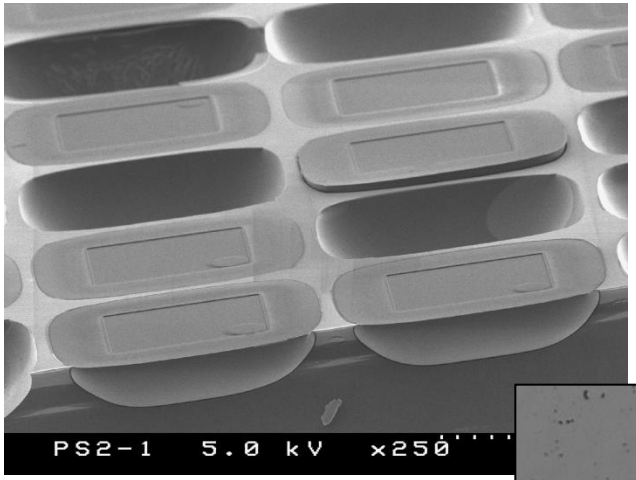
Uncoated particles at 15 min



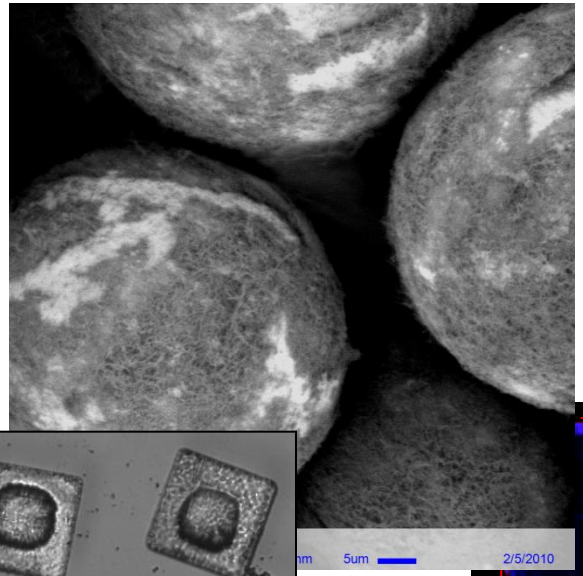
K. Fischer et al., Biomaterials 2012

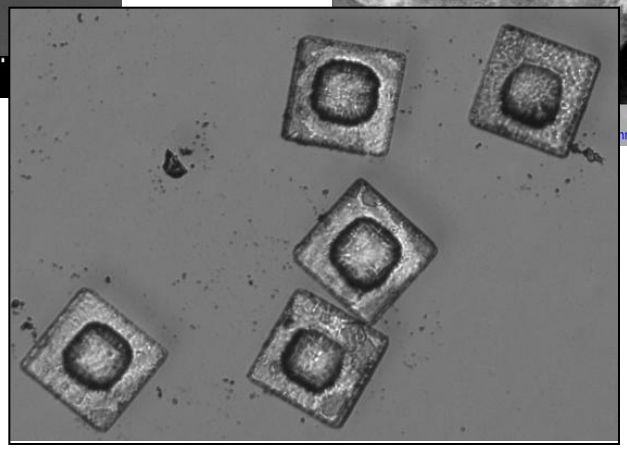
Devices with Enhanced Bioadhesion

Planar microdevices

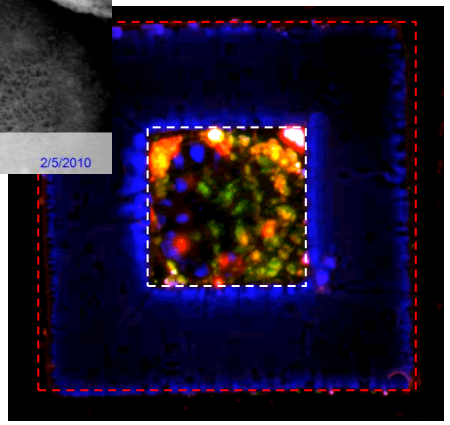


Nanowire Microparticles





Thin film particles

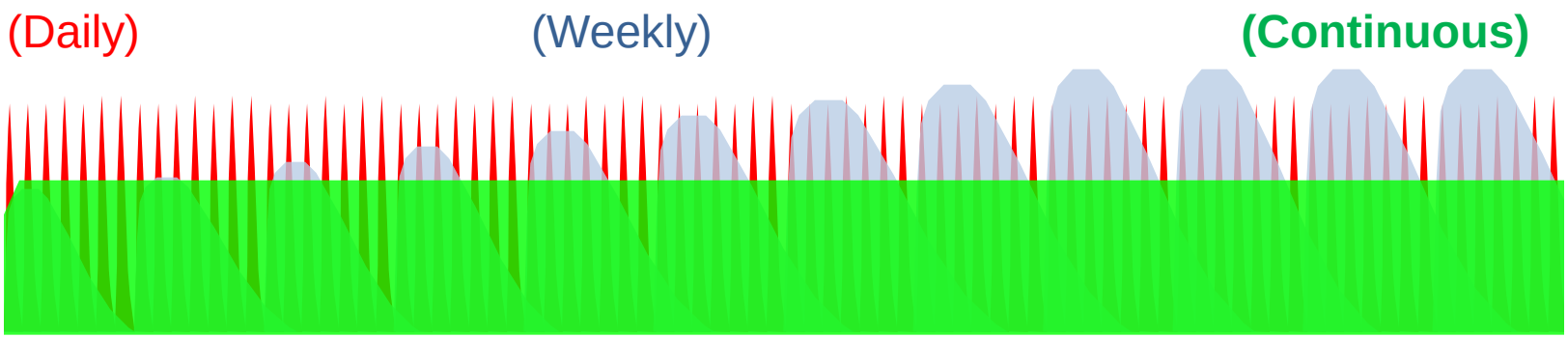


Multi-drug loaded microdevices

We are interested in using “structure” to enhance binding and improve mucosal delivery

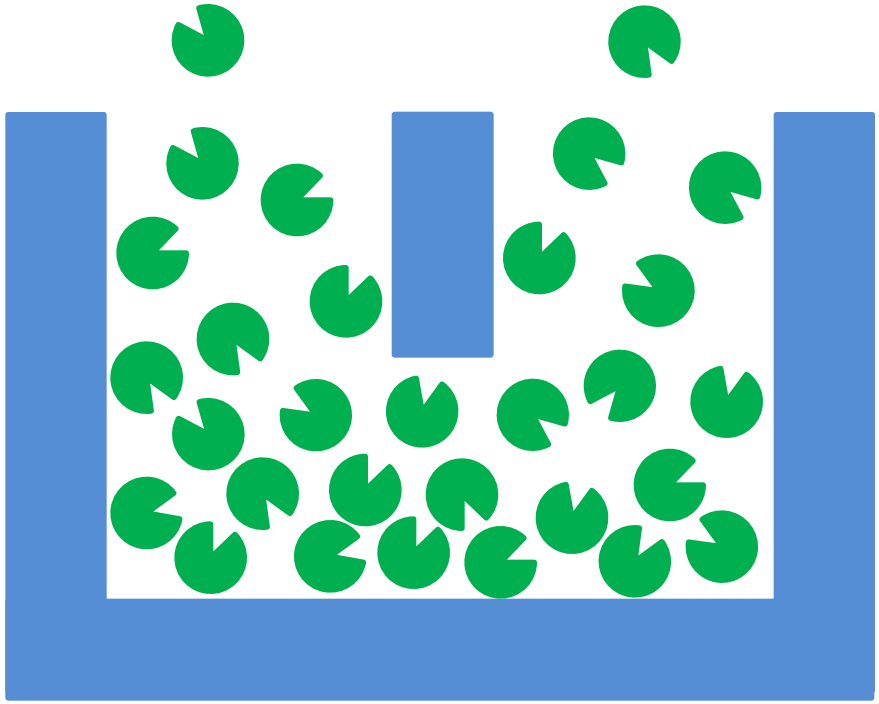
CAN WE USE “NANOSTRUCTURE” TO CONTROL DRUG KINETICS?

How are drug currently delivery?



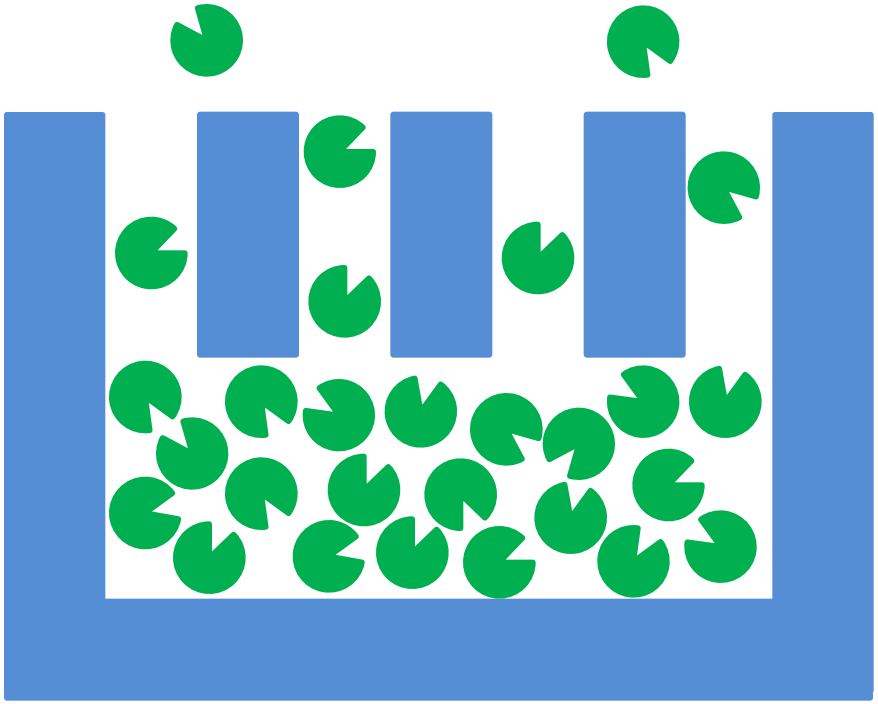
Achieving Constant Rate Delivery: Micropores vs Nanopores

Pore Size > Molecular Size



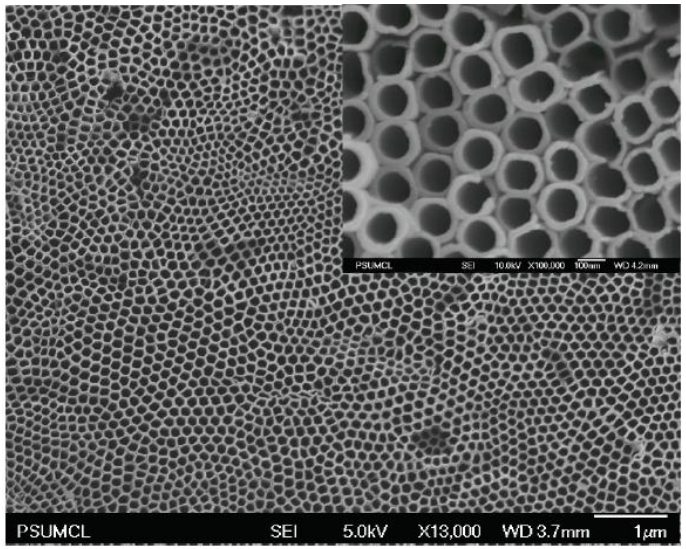
Concentration Dependent Delivery

Pore Size ~ Molecular Size

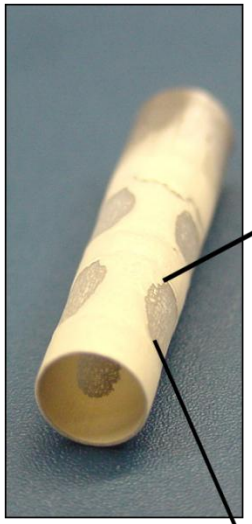


“Single File” Constrained Delivery

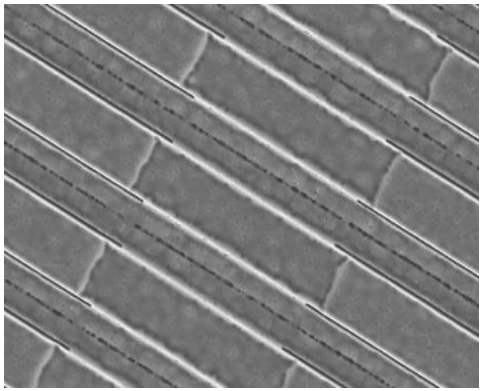
Inorganic Nanoporous Devices

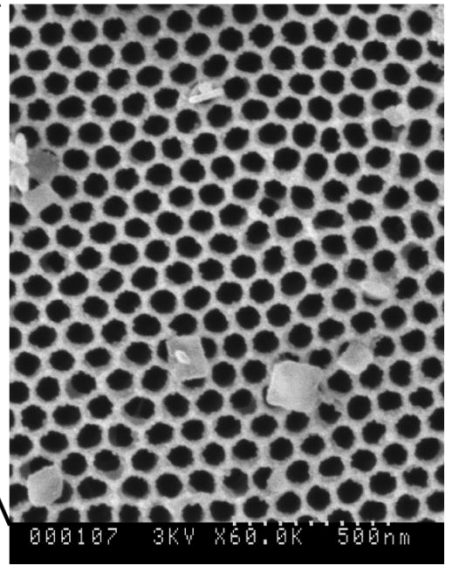


Titania nanotubular membranes



Silicon nanochannels



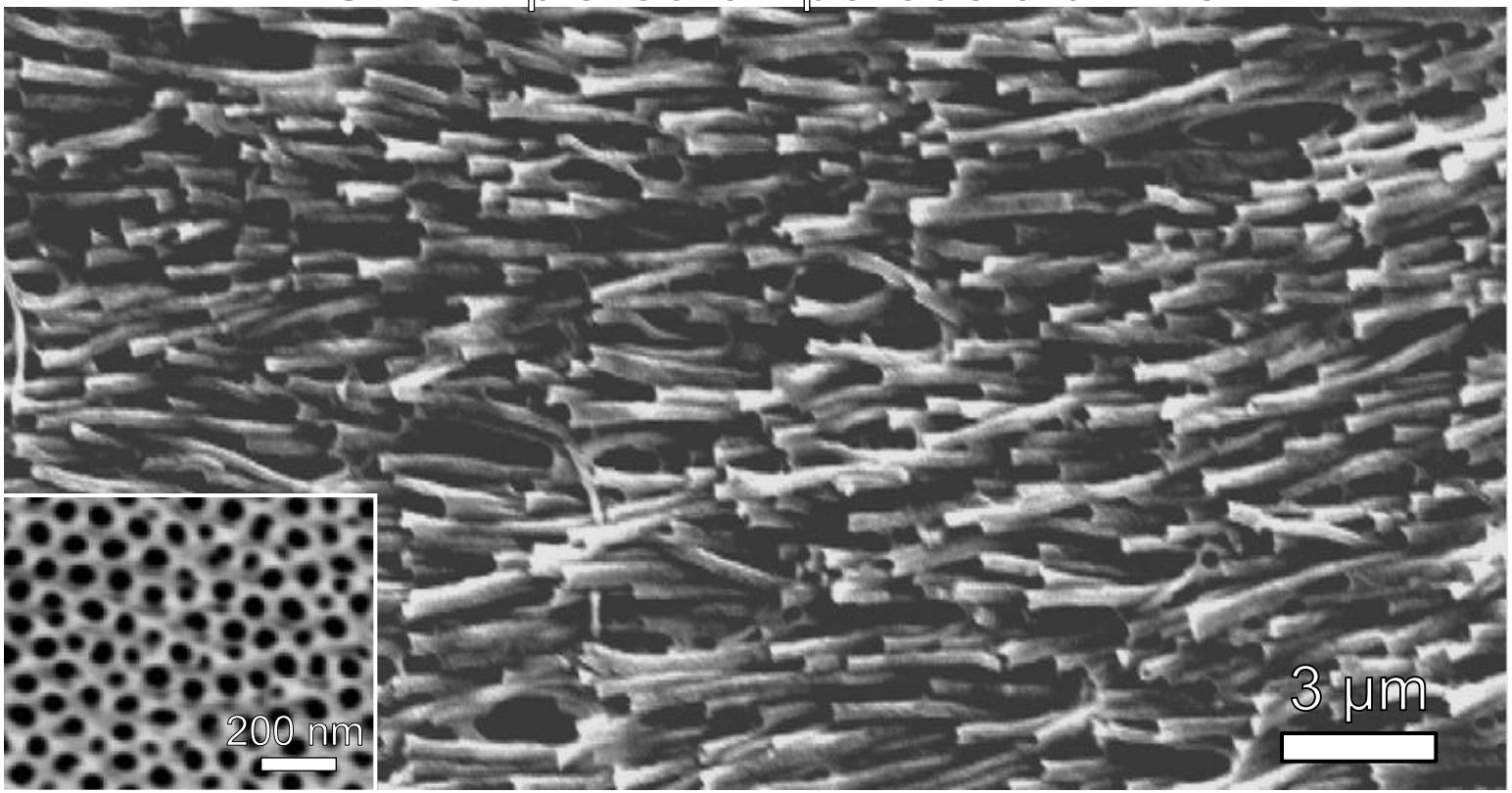


Alumina nanoporous capsules

We have developed a variety of fabrication techniques to produce well controlled nanoscale channels and pores in a variety of materials

Nanotemplating polymers

PCL templated on porous alumina



- Inorganic templates offer more control over the nanostructures produced

S. Tao & T. Desai, *Nanoletters* 7, 1463-1468 (2007).

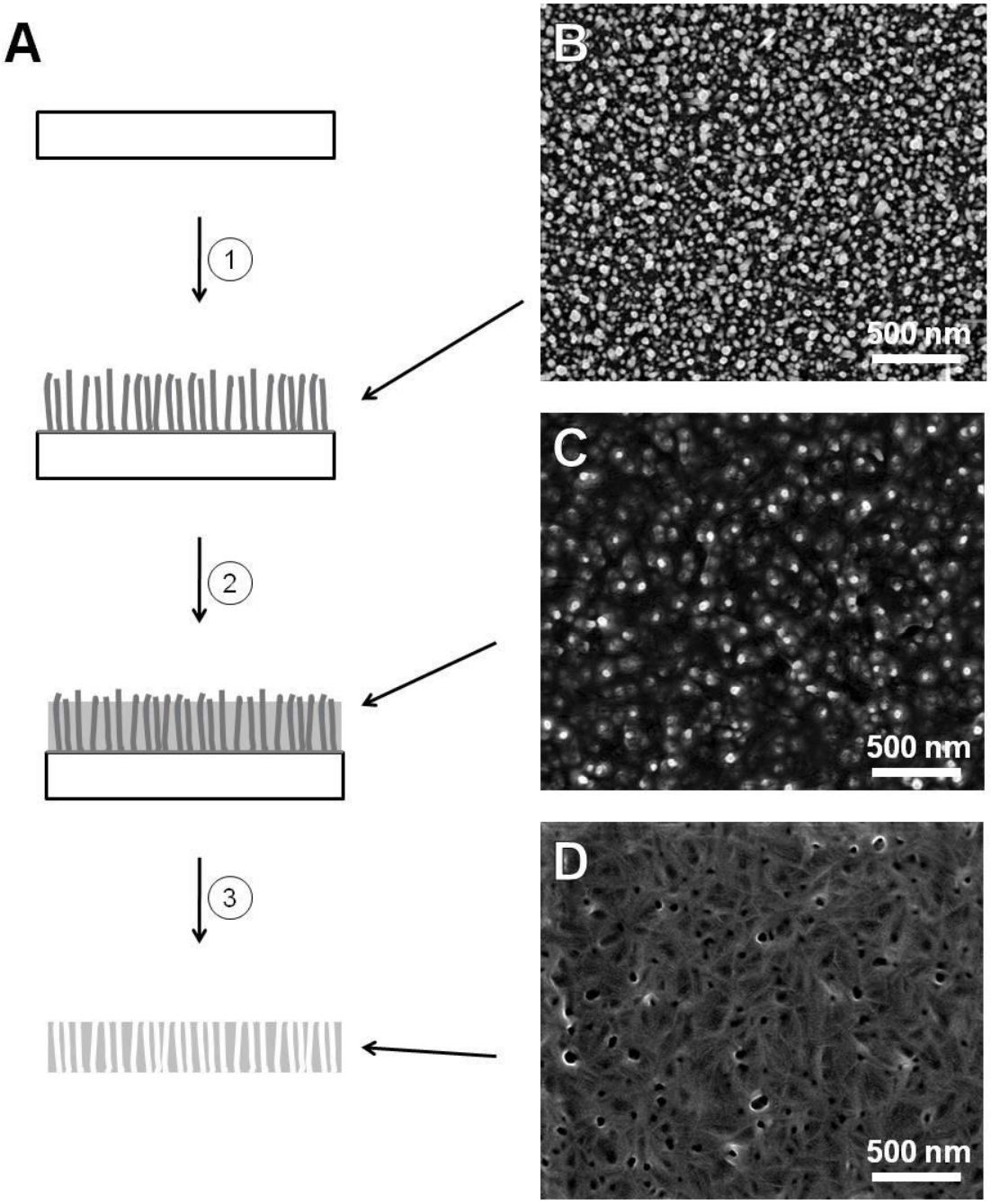
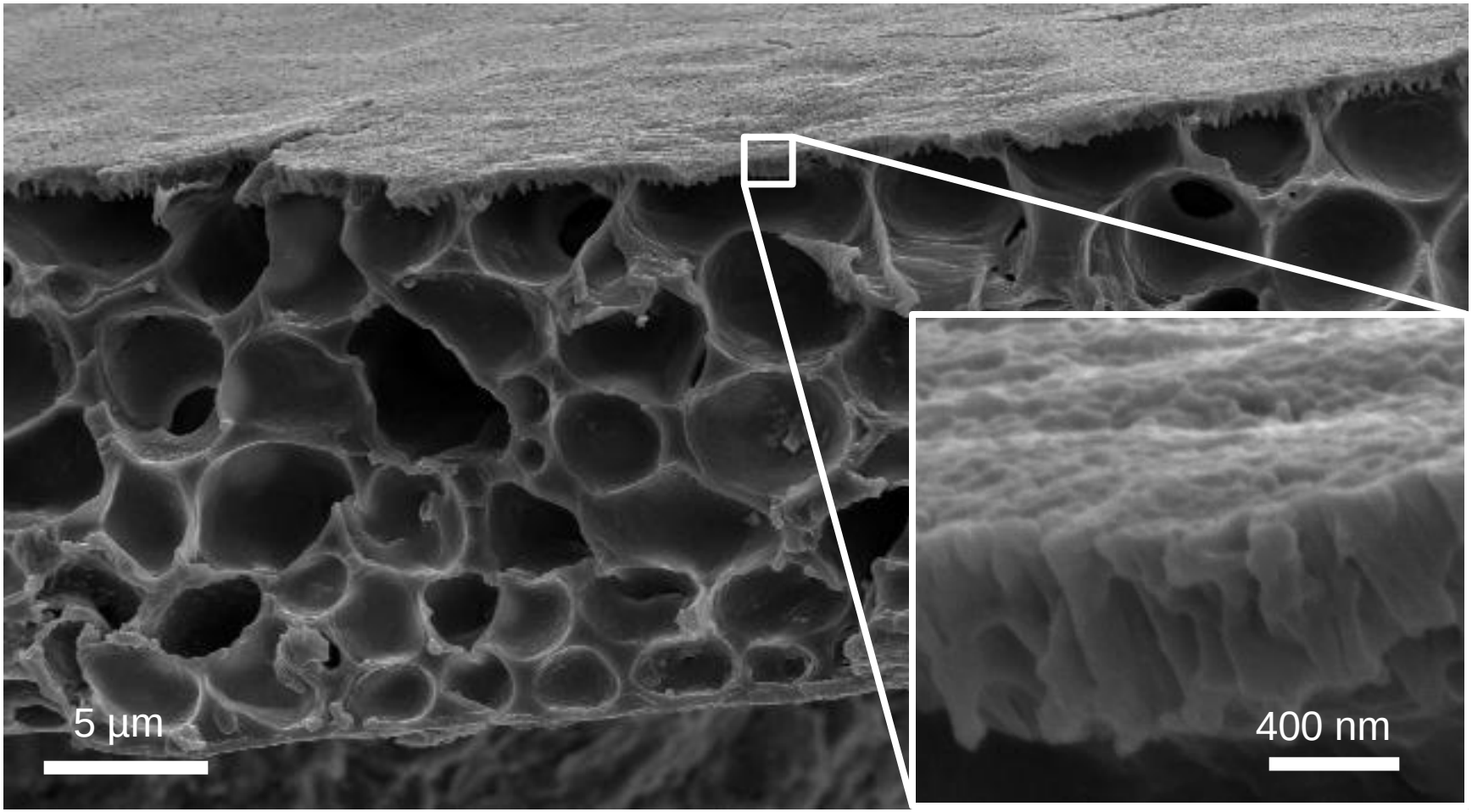


Figure 1: Fabrication of nanoporous poly(caprolactone). (A) Processing sequence showing [1] hydrothermal growth of zinc oxide, [2] casting of poly(caprolactone), and [3] etching of zinc oxide to produce nanostructured polymer. Characteristic scanning electron microscope images of (B) zinc oxide nanowires, (C) poly(caprolactone) coated zinc oxide nanowires, and (D) nanostructured

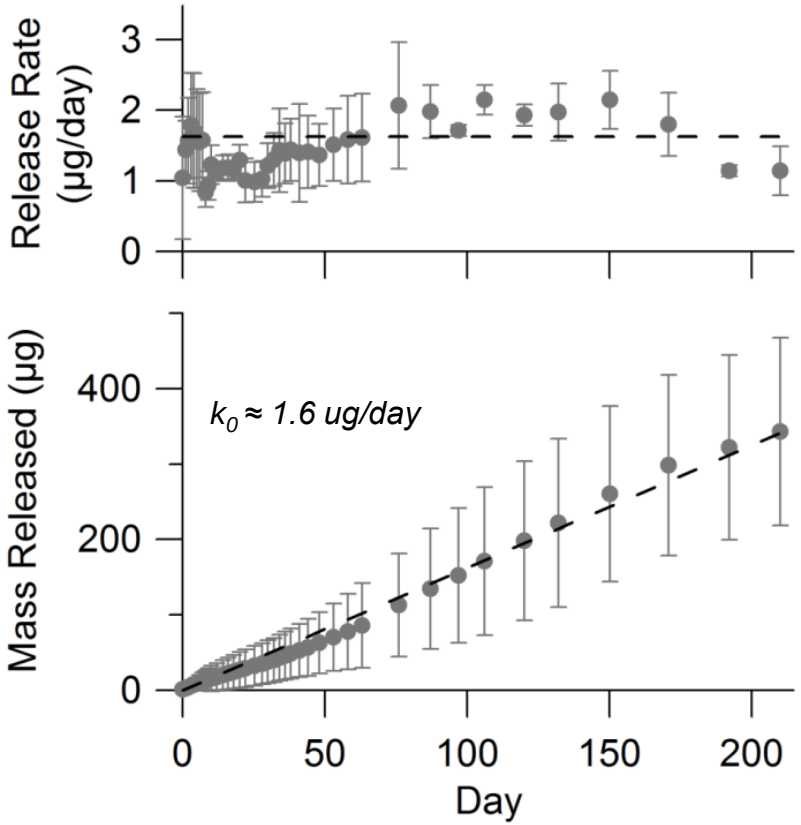
poly(caprolactone).

Bernards and Desai, *Advanced Materials* (2009).

Micro and Nanostuctured PCL films

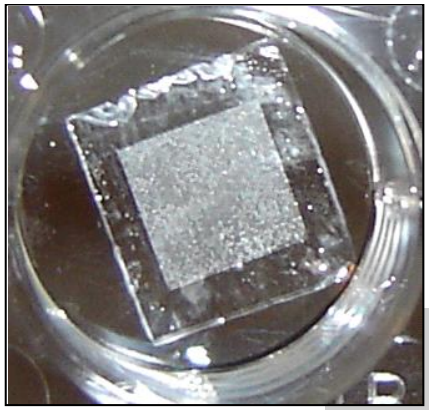


Nanostructure enables controlled drug release kinetics

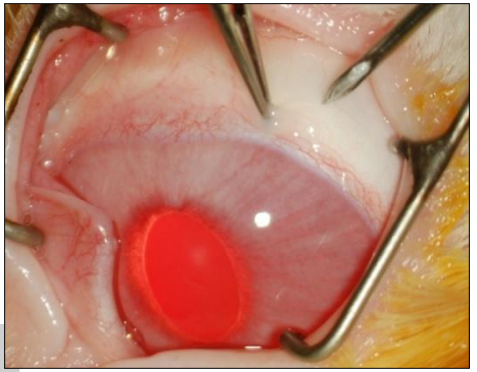


Bernards DA, Lance KD, Ciaccio NA, Desai TA 2012 *Nano Letters*

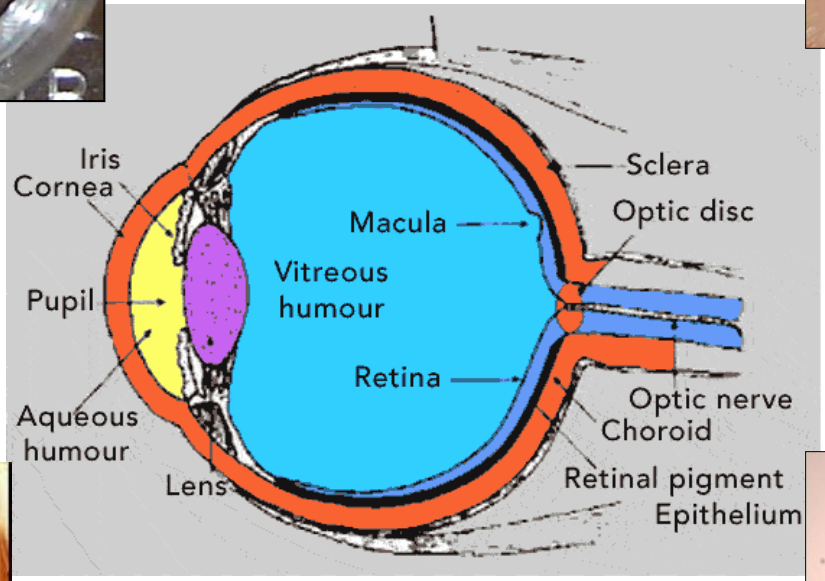
Nanoporous Films for Ocular Delivery

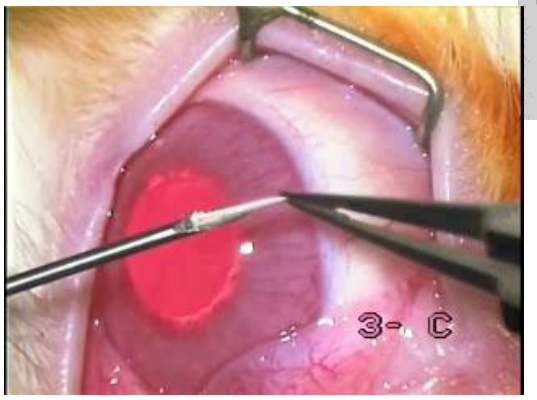


Unfurling films with nanopores

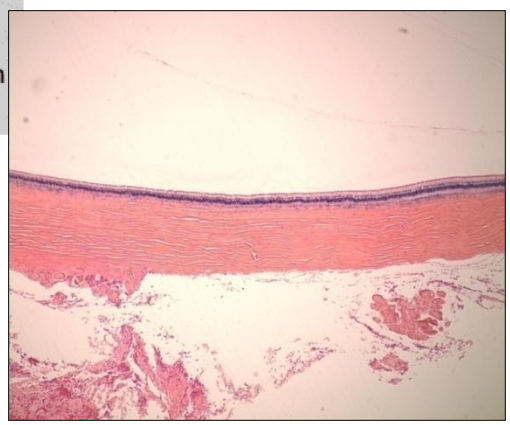


Catheter Injectable





No in vivo inflammation



Micro+Nano delivery platforms can change the way we administer therapy

- New Device Architectures:
  - containing both therapeutic payloads and biophysical cues
  - that can gain access to biological barriers
  - combine affinity-based + size & shape + surface properties

- Enable our ability:
  - to time the release multiple drugs
  - to deliver in a controlled manner
  - to house engineered cellular "factories"
  - To facilitate tissue integration and bioadhesion

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