



Silicon-Based Biomedical Nanotechnologies

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Special Advisor on Nanotechnology

The National Cancer Institute

Outline

- Brief Overview of Silicon-Based Nanotechnologies for Cancer Diagnostics and Therapeutics
- Focus on Silicon-Based Nano- & Micro-Particulates
- Generalized Considerations on Characterization, Standardization, and the Regulatory Issues on Nano- & Micro-Particulates (“Nanovectors”)

Silicon-Based Nanotechnologies for Cancer Dx and Rx

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in Cancer

- **Diagnostics**
 - Micro/Nano-Arrays
 - Micro/Nano-Fluidics
 - Nanowires / FET Sensors
 - Micro/Nano-Cantilevers
 - Selective Molecular Enrichment Substrates
- **Therapeutics**
 - Implants
 - Transdermal Delivery Implements
 - Inhalation Delivery Implements
 - Micro/Nano-Particulates
 - Oral Administration
 - Intravascular Delivery

Disclosure

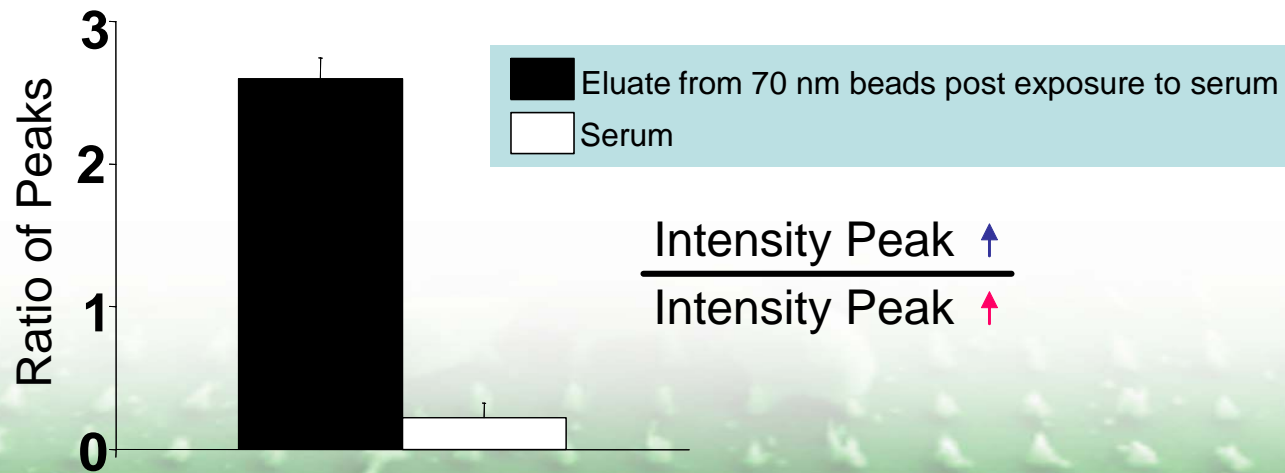
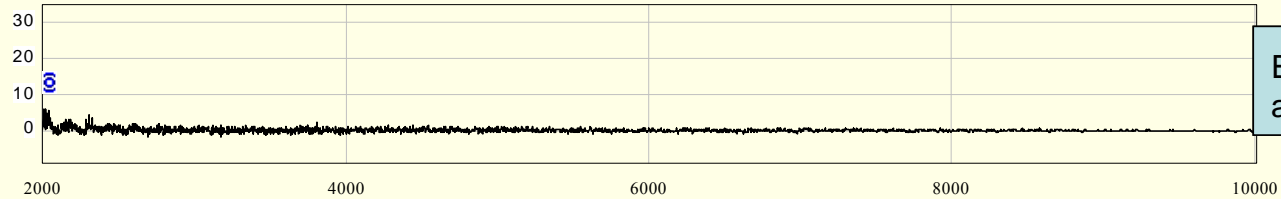
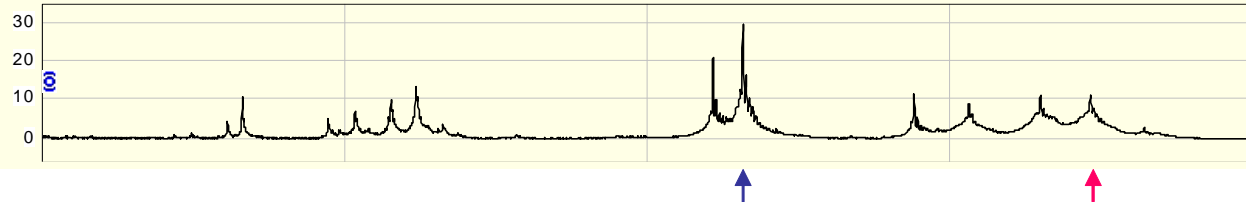
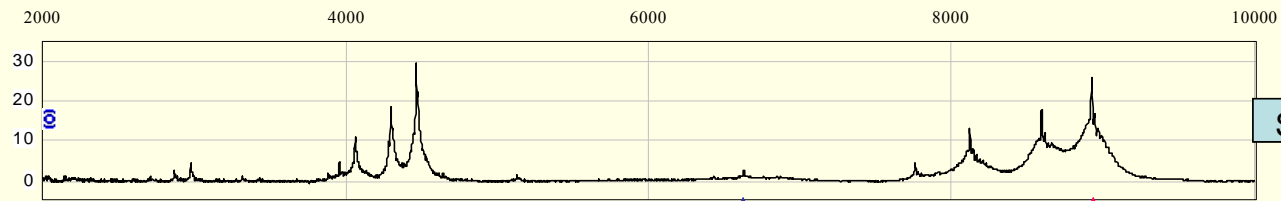
- Mauro Ferrari has a financial interest in iMEDD, Inc of Foster City, California
- iMEDD owns intellectual property on the fields highlighted in the next slide

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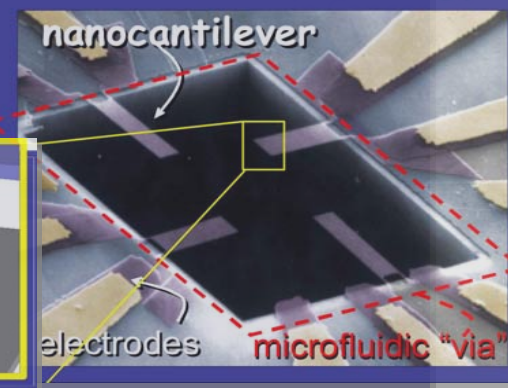
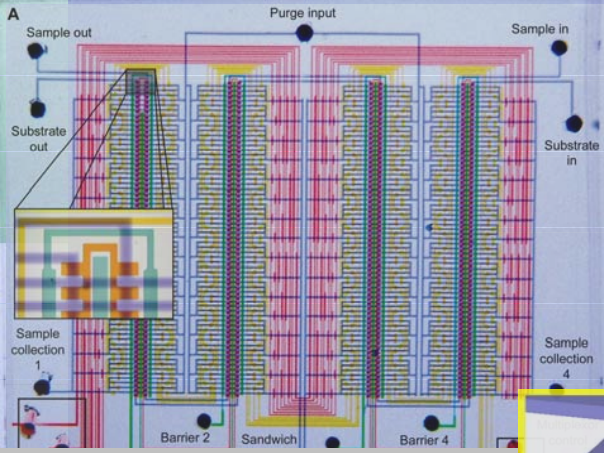
iMEDD has IP in
underlined fields



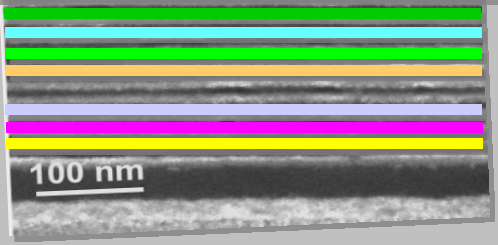
The Nanolab

mfluidics- massively multiplexed plumbing for nanotechnologies

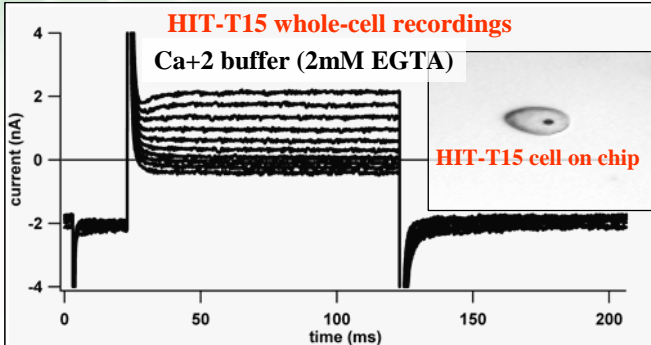
Electrophysiology



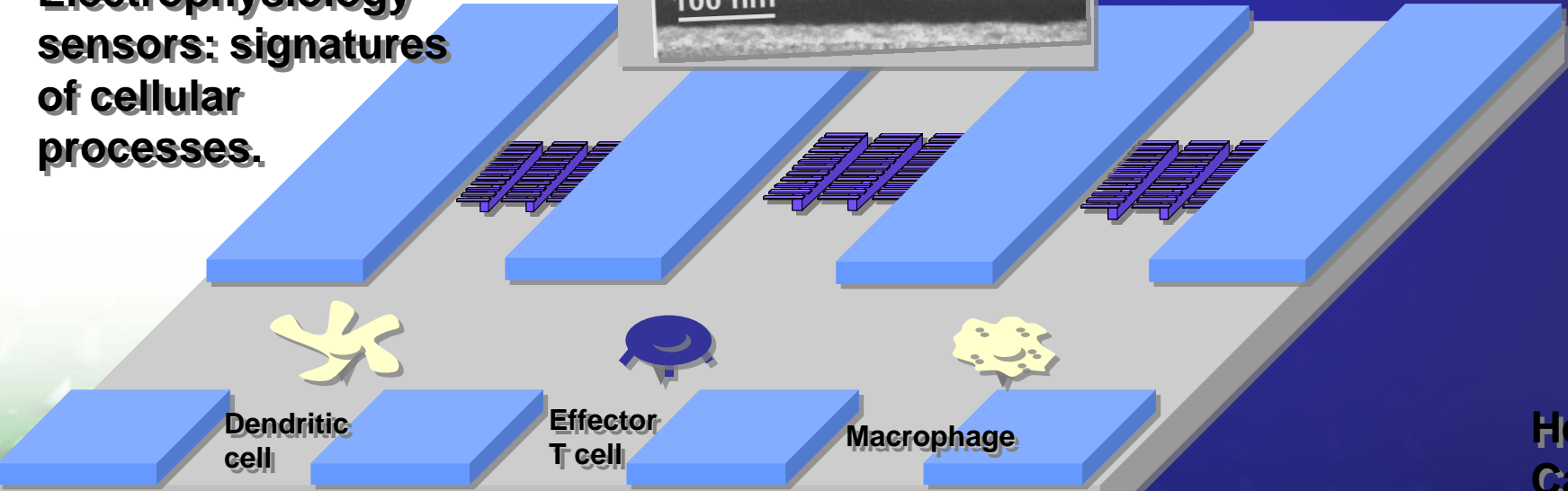
Nanowire Sensors
Signatures of gene & protein expression



Nanomechanics
Protein-protein & Protein-DNA interactions



Electrophysiology sensors: signatures of cellular processes.



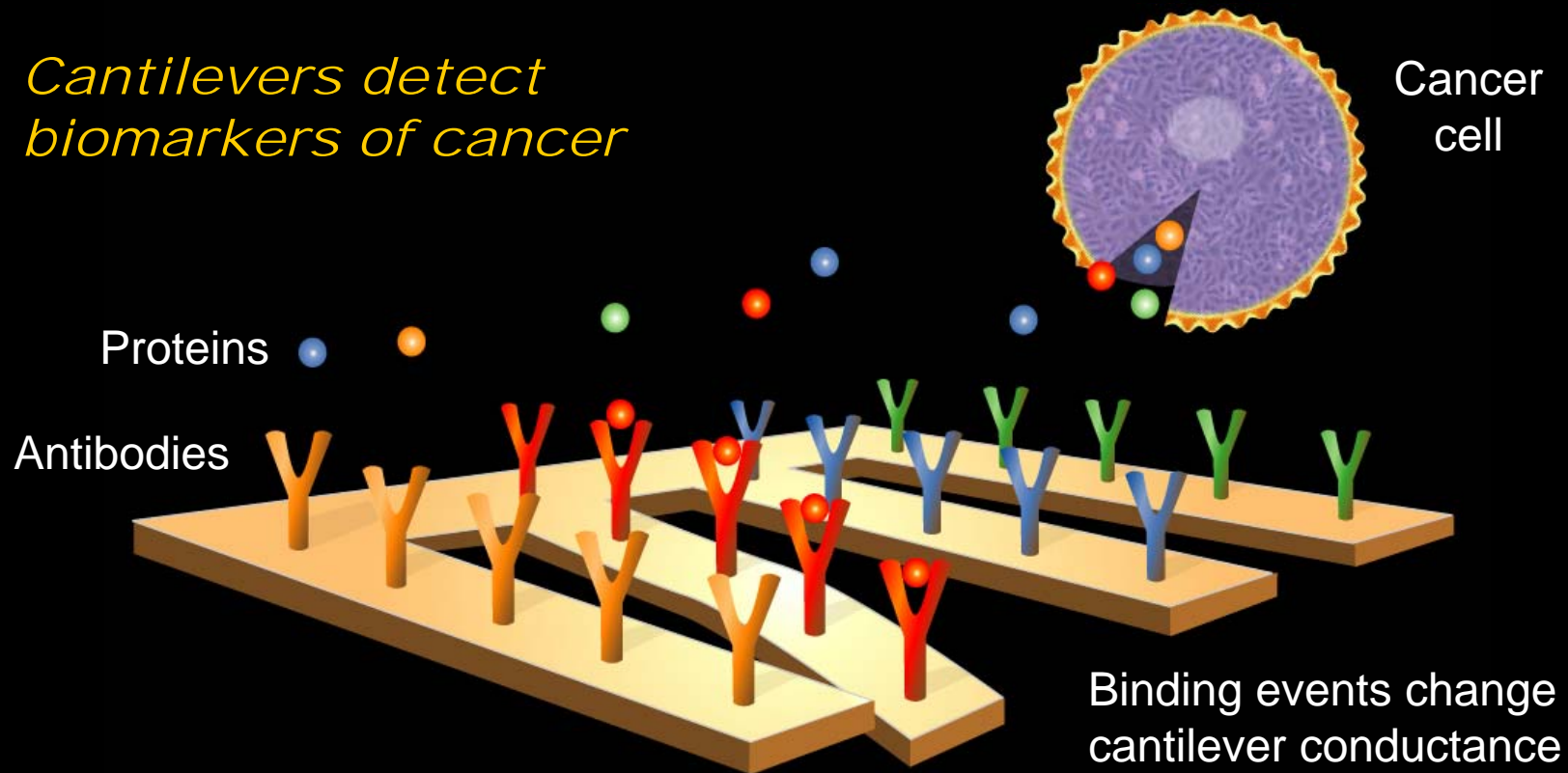
Silicon-based environments embedding:

- **Non-Si Nanowires (InOx, USC; Mark Reed, Yale)**
 - Target: improved properties
- **Carbon Nanotubes (Marcus Lab, Mike Biercuk, Harvard)**
 - Targets: improved properties, logic controls, innovative quantum electronic concepts

Nanotech detects multiple molecular signatures

Nanoscale Cantilevers

Cantilevers detect biomarkers of cancer

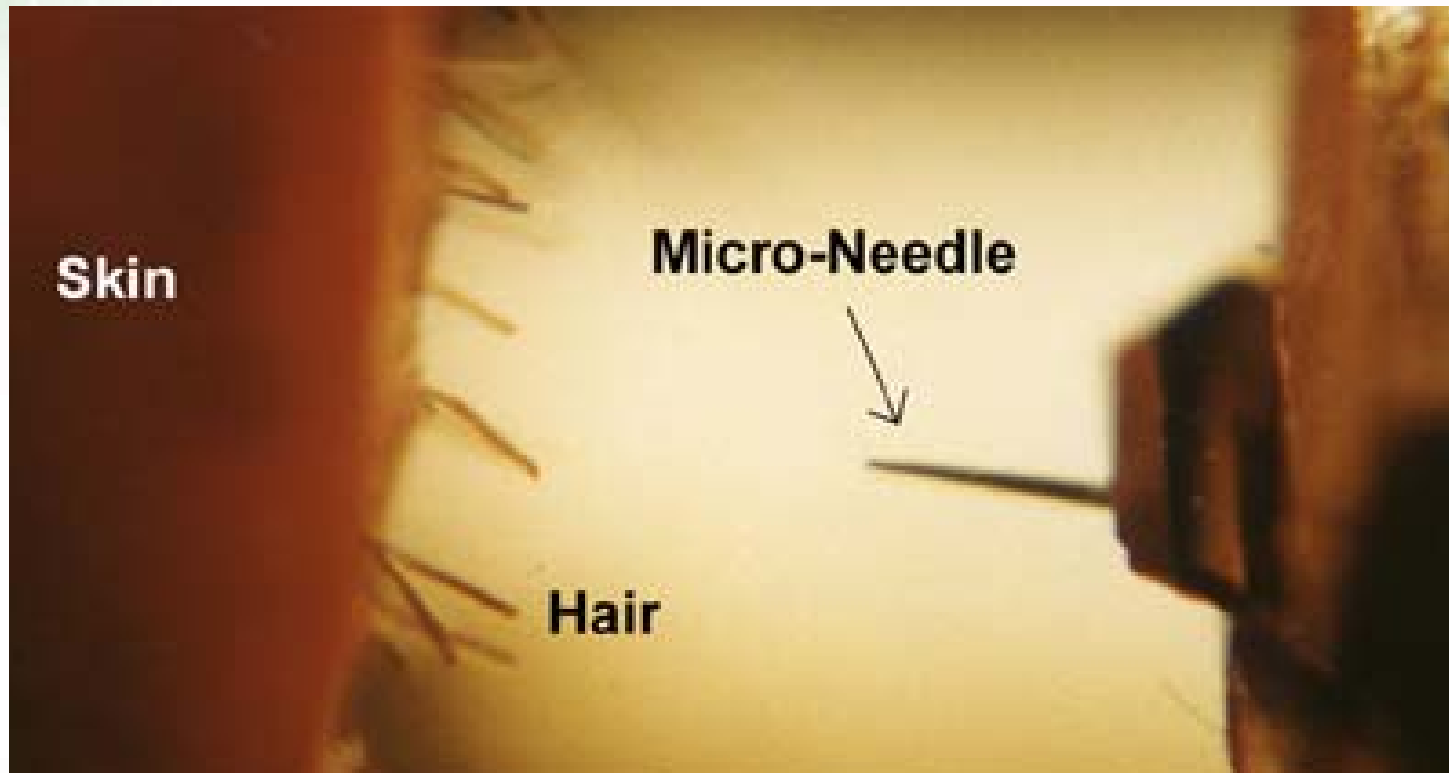


In general, for silicon:

- What is micro today will be nano tomorrow
- Bridging micro and nano is natural
- Scale-up not an issue

Microneedles for Painless Injections/Extractions

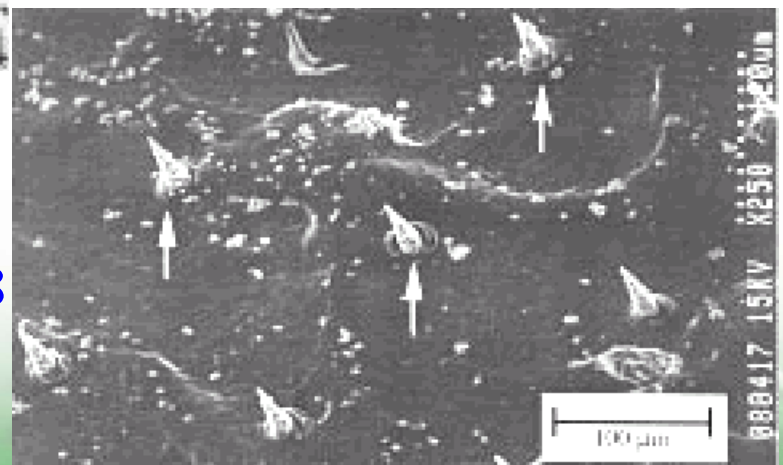
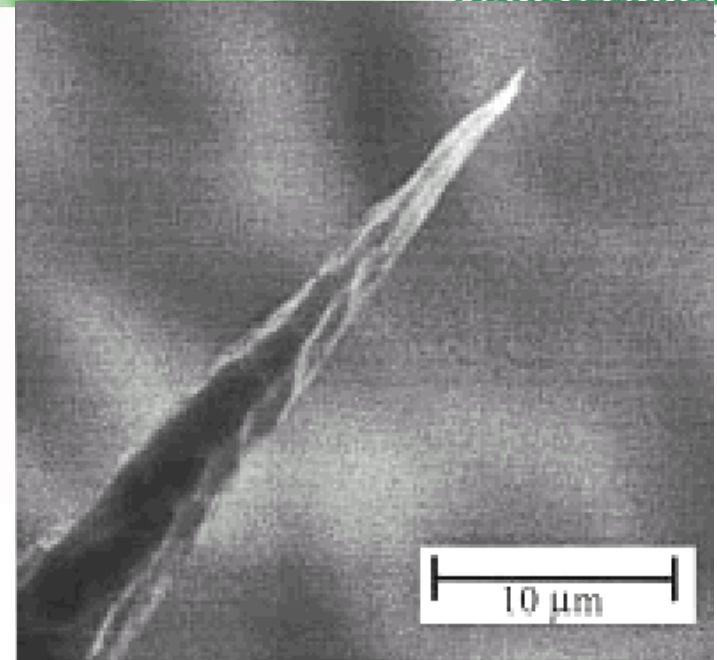
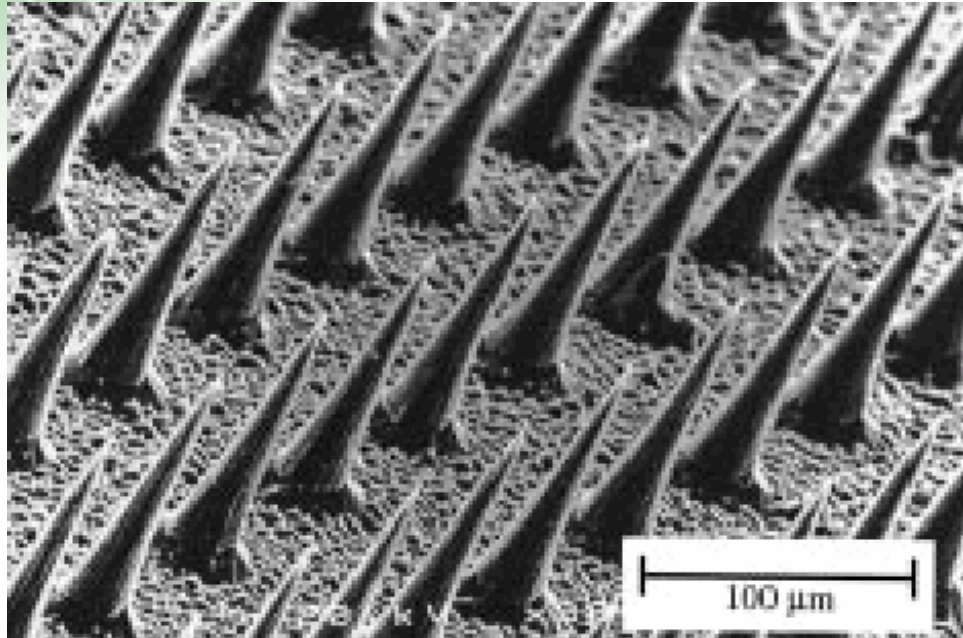
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Kumetrix, Inc., 2000

Better Yet, Arrays of Microneedles

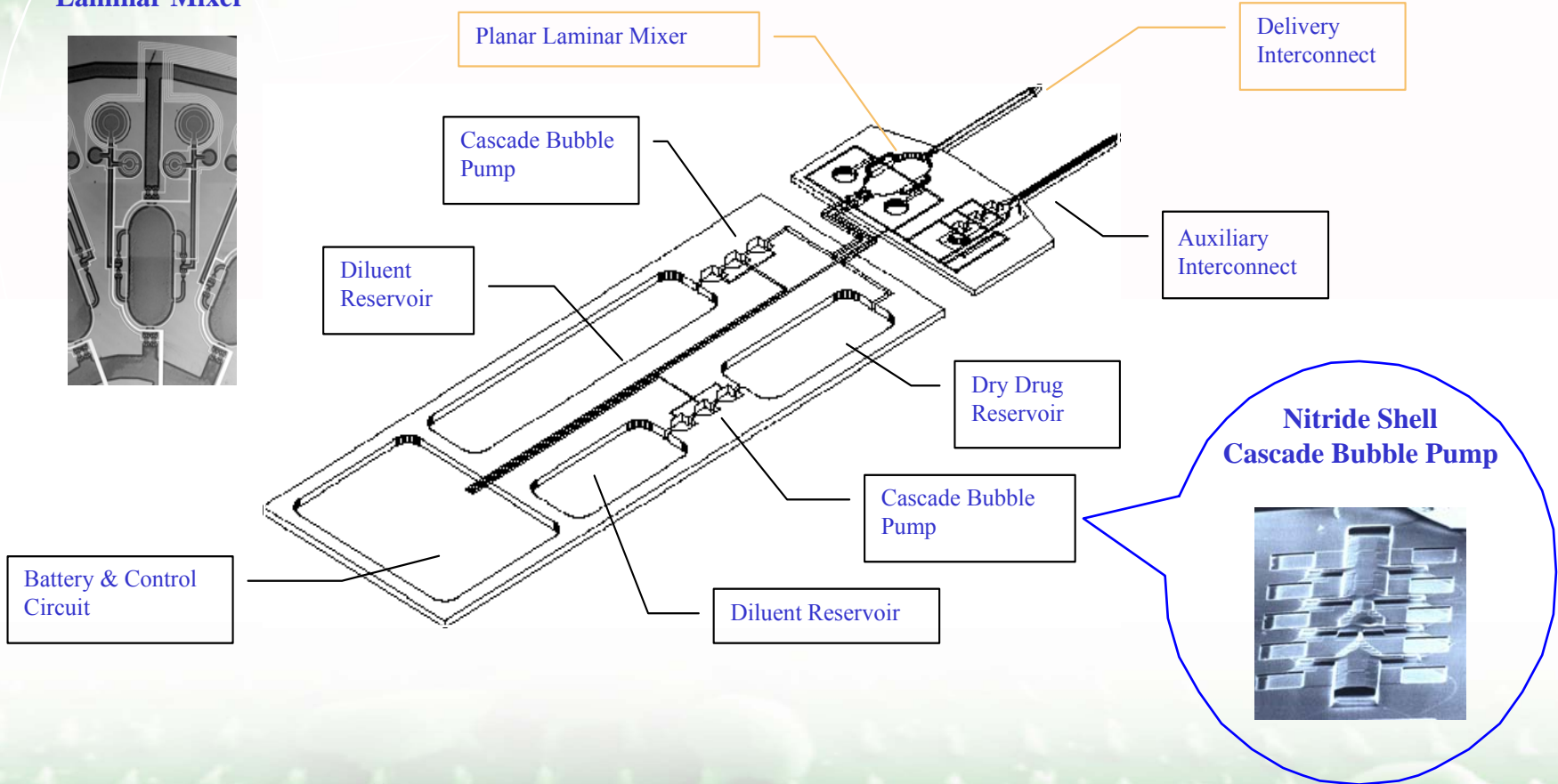
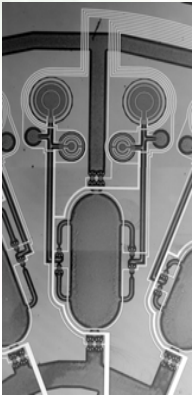
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Nanotechnology
er



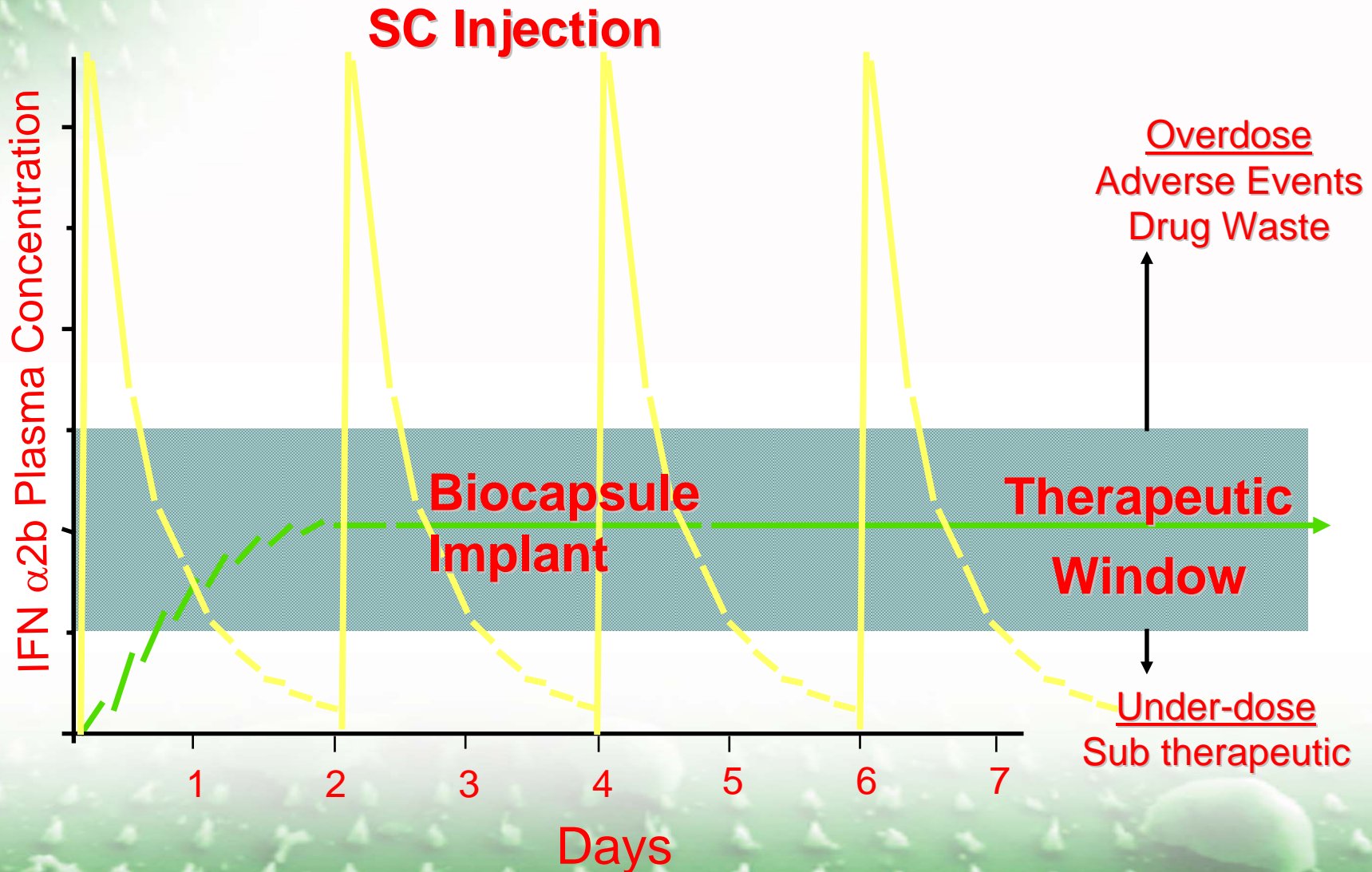
Henry, *et al.* (GA Tech), *Jo. Pharm. Sci.*, 1998

THE PERSONAL RECONSTITUTION & DELIVERY SYSTEM

**Fabricated
Laminar Mixer**



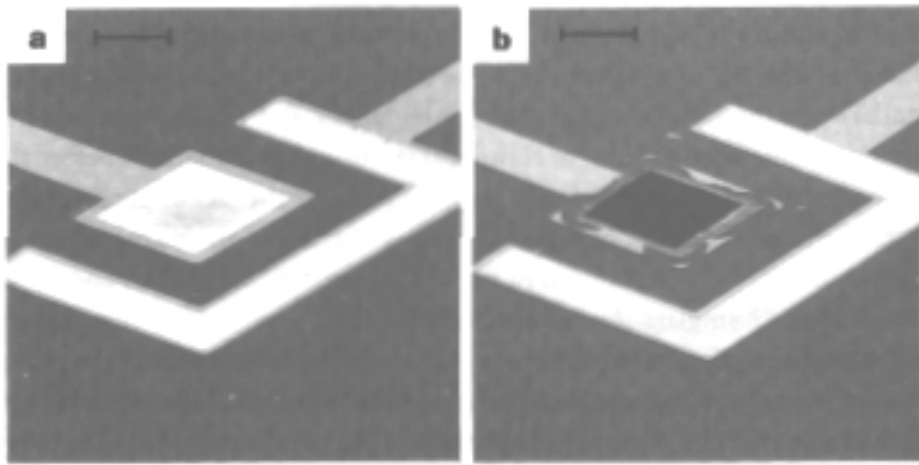
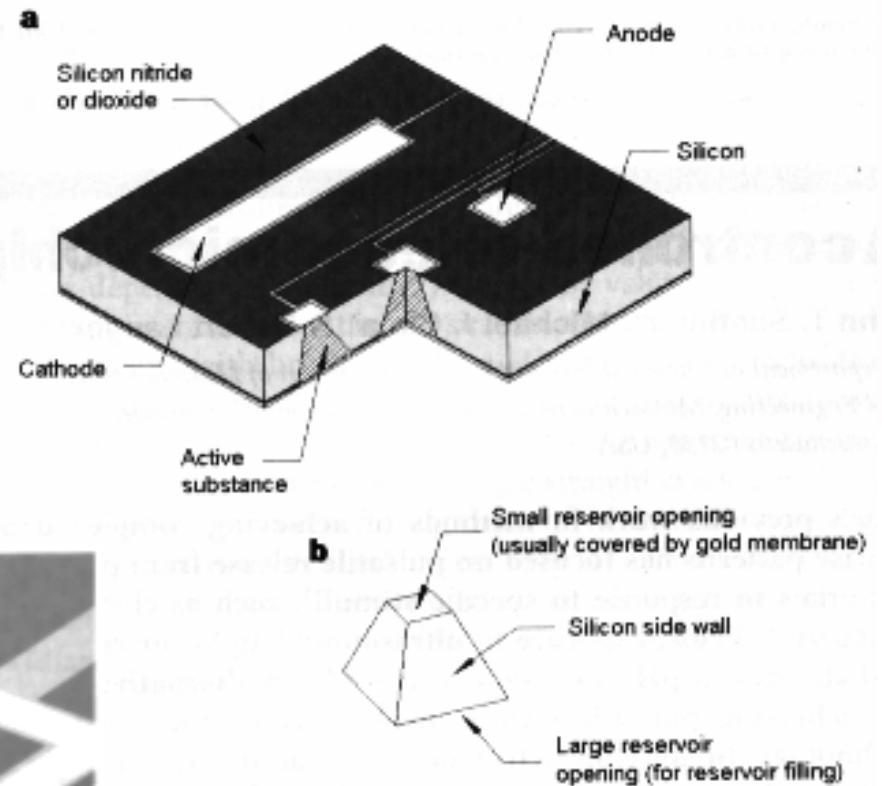
On the notion of time-controlled release: simplest case = zeroth order kinetics



Electrochemical Controlled Drug Release

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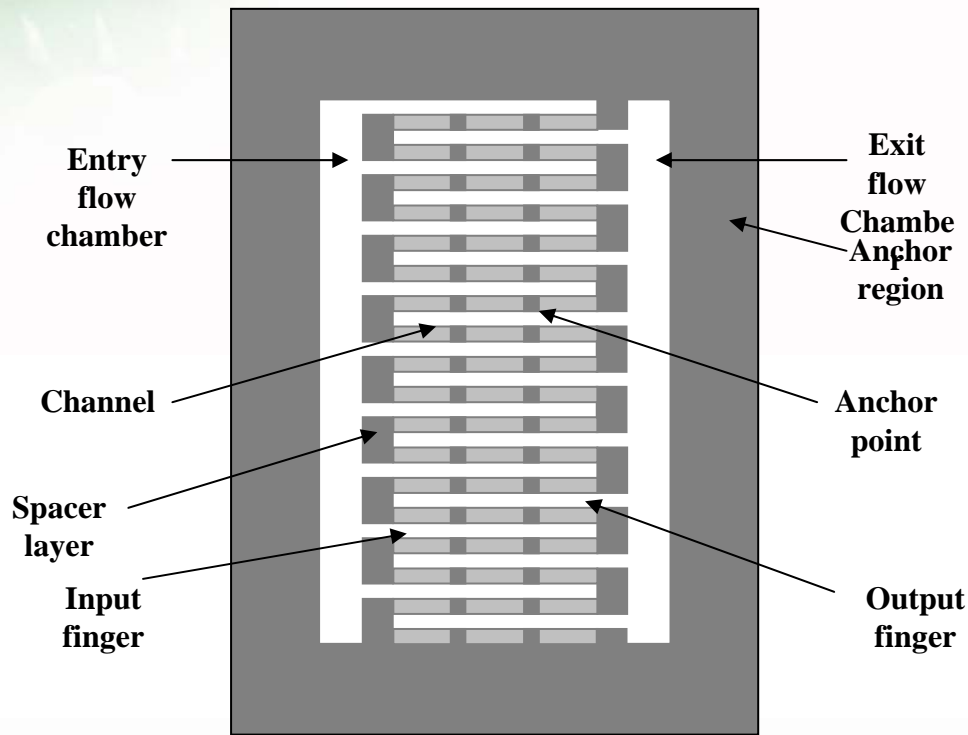
- Circuitry controls local electrochemical environment
- Galvanic erosion of gold cap releases drug



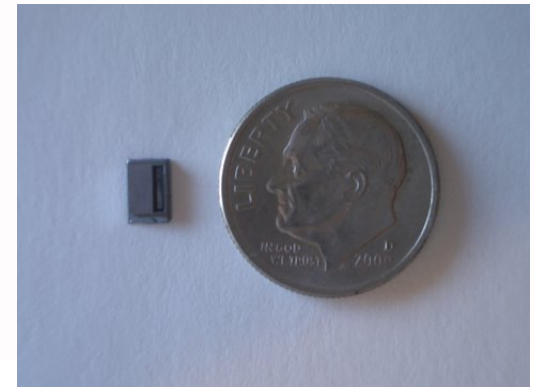
Santini, Cima, and Langer, 1999 (MIT)

iMEDD IP: NanoGATE & Bulk Nanochannel Membrane and Assembled Prototype Implant

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Top and cross-sectional view of the bulk nanopore membrane structure on the structural wafer



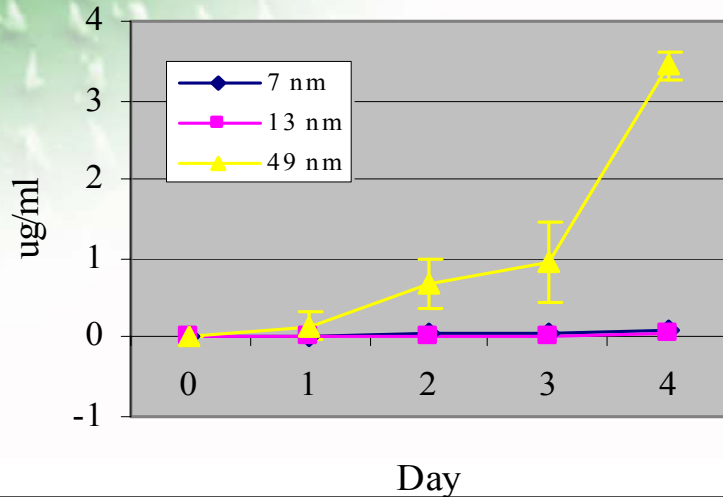
Bulk nanopore membrane (or nanochannel delivery system, nDS1)



Prototype implant

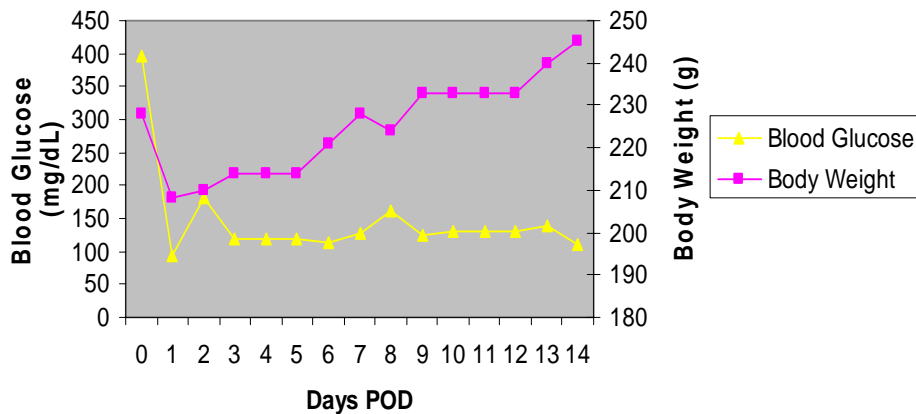
Cell Transplant Biocapsule

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- ◆ Implant containing cells to produce insulin (or other therapeutic agent)
- ◆ Nanochannel silicon membrane protects transplanted cells from immune attack

Animal # 2 (Insulinoma)



*Courtesy Prof. Tejal Desai
& iMEDD*

Nanoporous “Wafer” Implants

- Leigh Canham (x-DRA), principal scientist
- pSIMedica (UK): Drug-delivery
- pSIVida (Aus); Brachytherapy
- Nanoporosity renders material biodegradable with kinetics that can be controlled from minutes to forever
- Also see work by Ulrich Goesele (Duke, Fraunhofer & Max Plank Institutes)



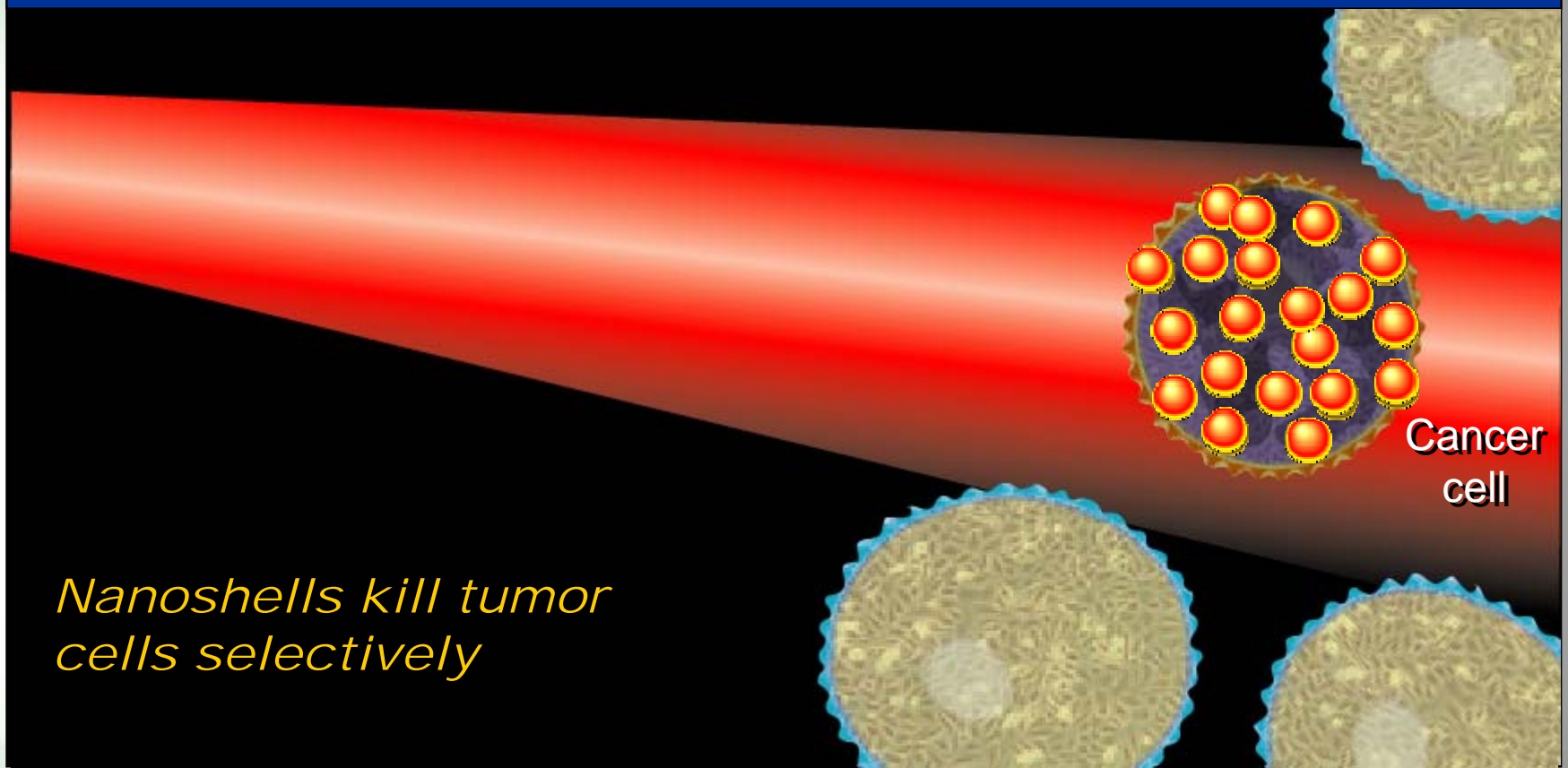
Silicon-Based Nano- & Micro-Particulates

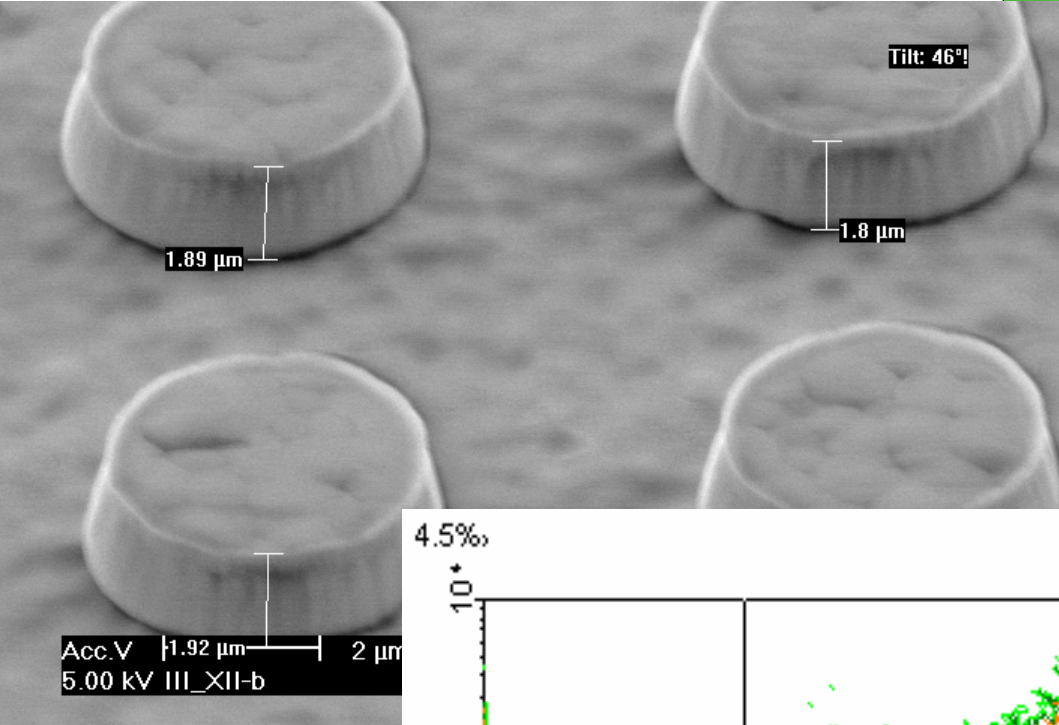
Silicon/silica in > 20 primary micro/nanoparticle types for targeted delivery applications, from literature

Nanotech enables targeted delivery of therapeutics

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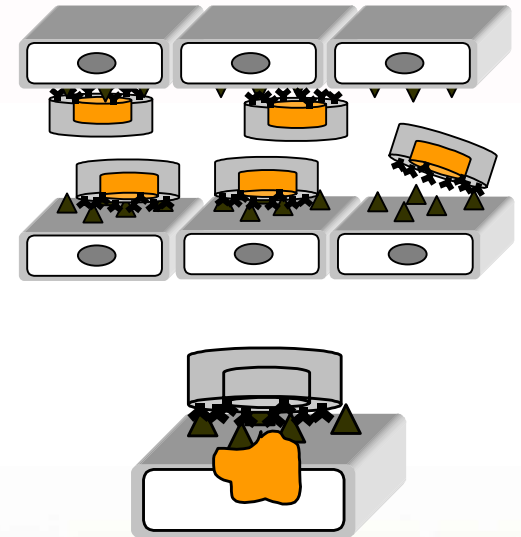
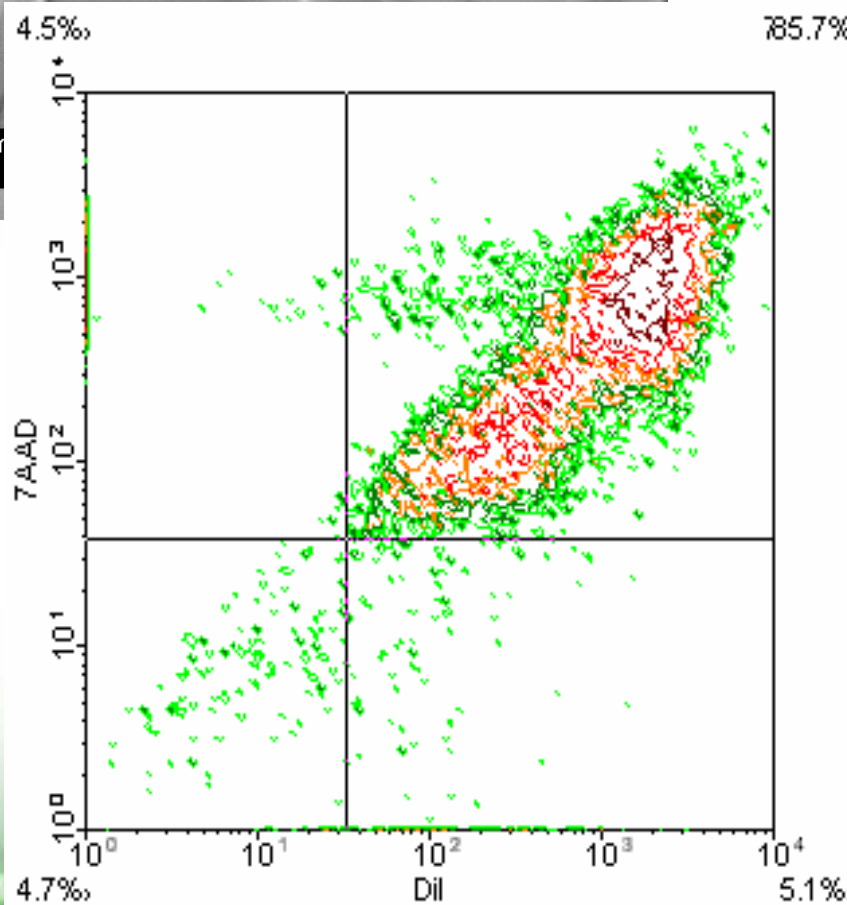
Nanoshells





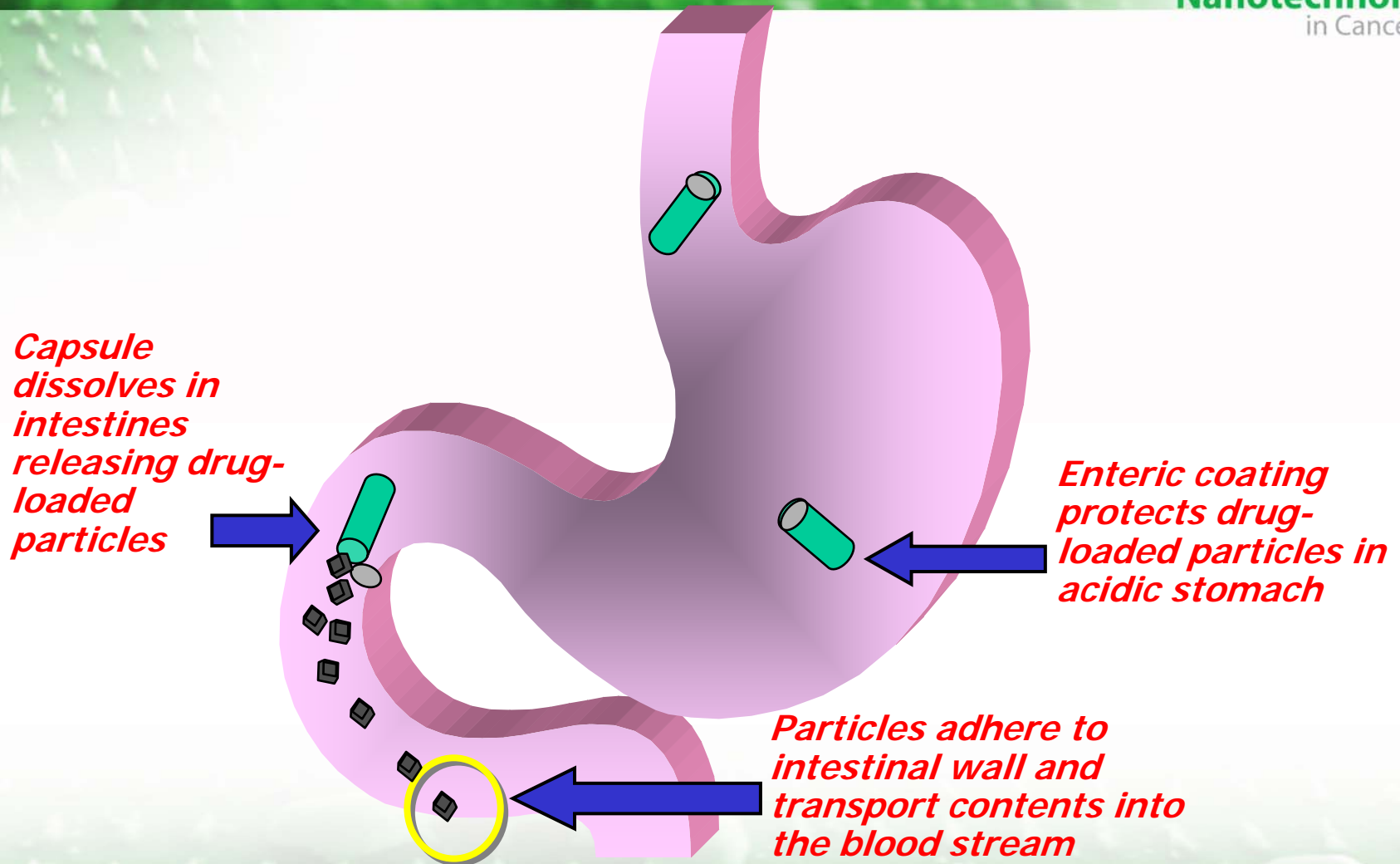
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iMEDD, Inc.
NO LONGER
funded by NCI



Targeted Oral Delivery Nanotech (Illustration)

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Anatomy of Intestinal Epithelium

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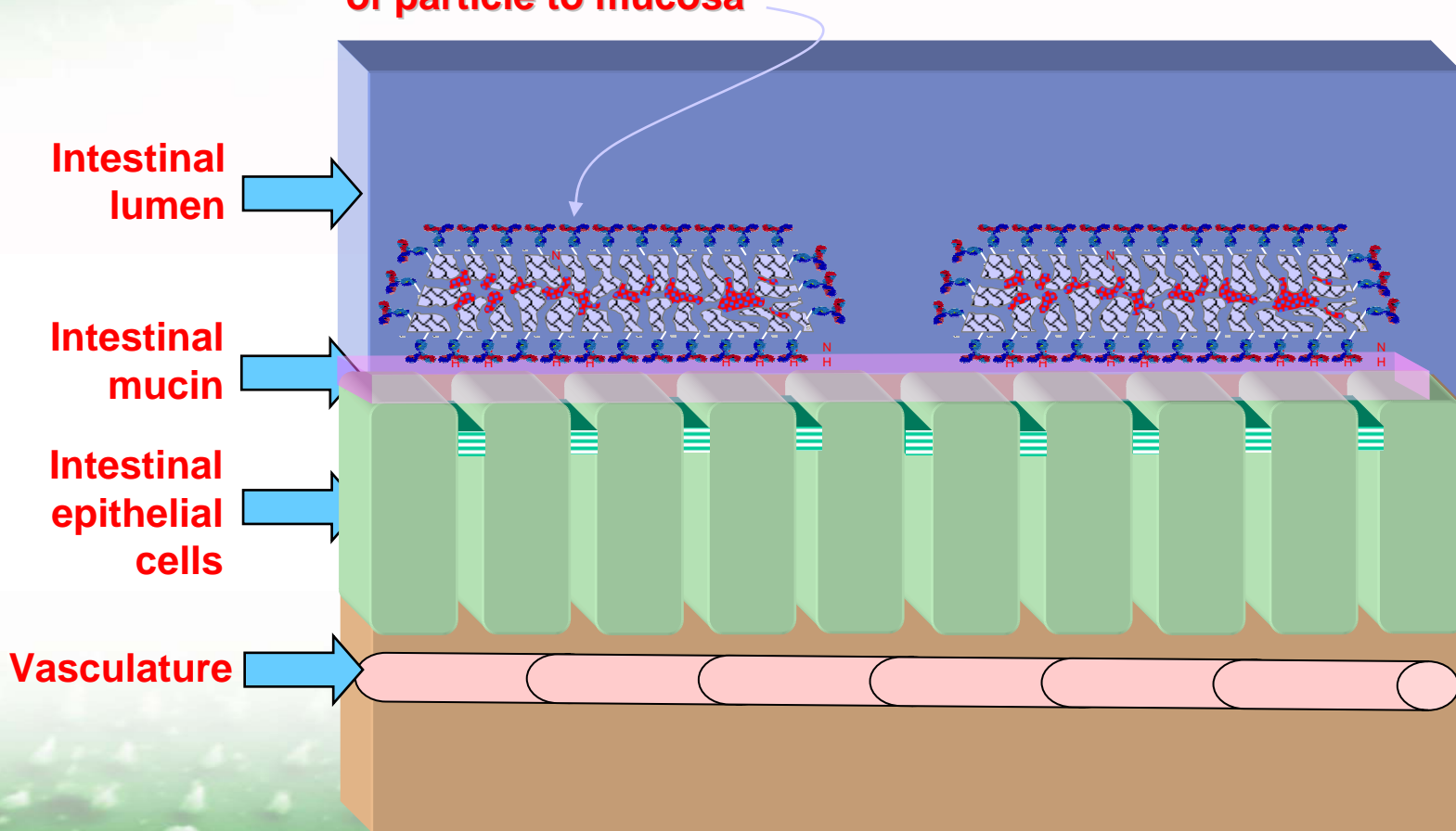


Microfabricated Trans-Mucosal Patch (iMEDD IP)

For Delivery of
Biologically Active Peptides and Proteins

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1. Lectin mediates binding
of particle to mucosa



Microfabricated Trans-Mucosal Patch

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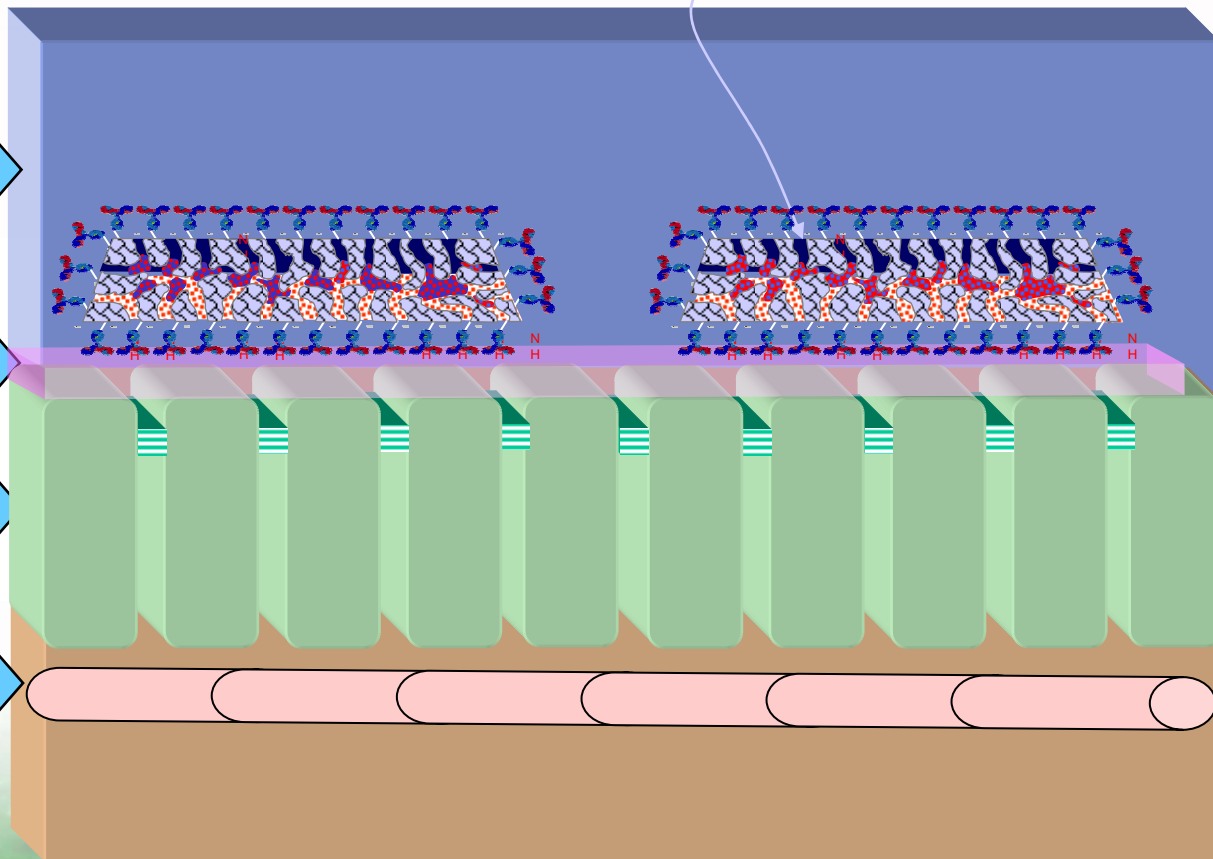
2. Thru-particle hydration
releases drug + enhancer

Intestinal
lumen

Intestinal
mucin

Intestinal
epithelial
cells

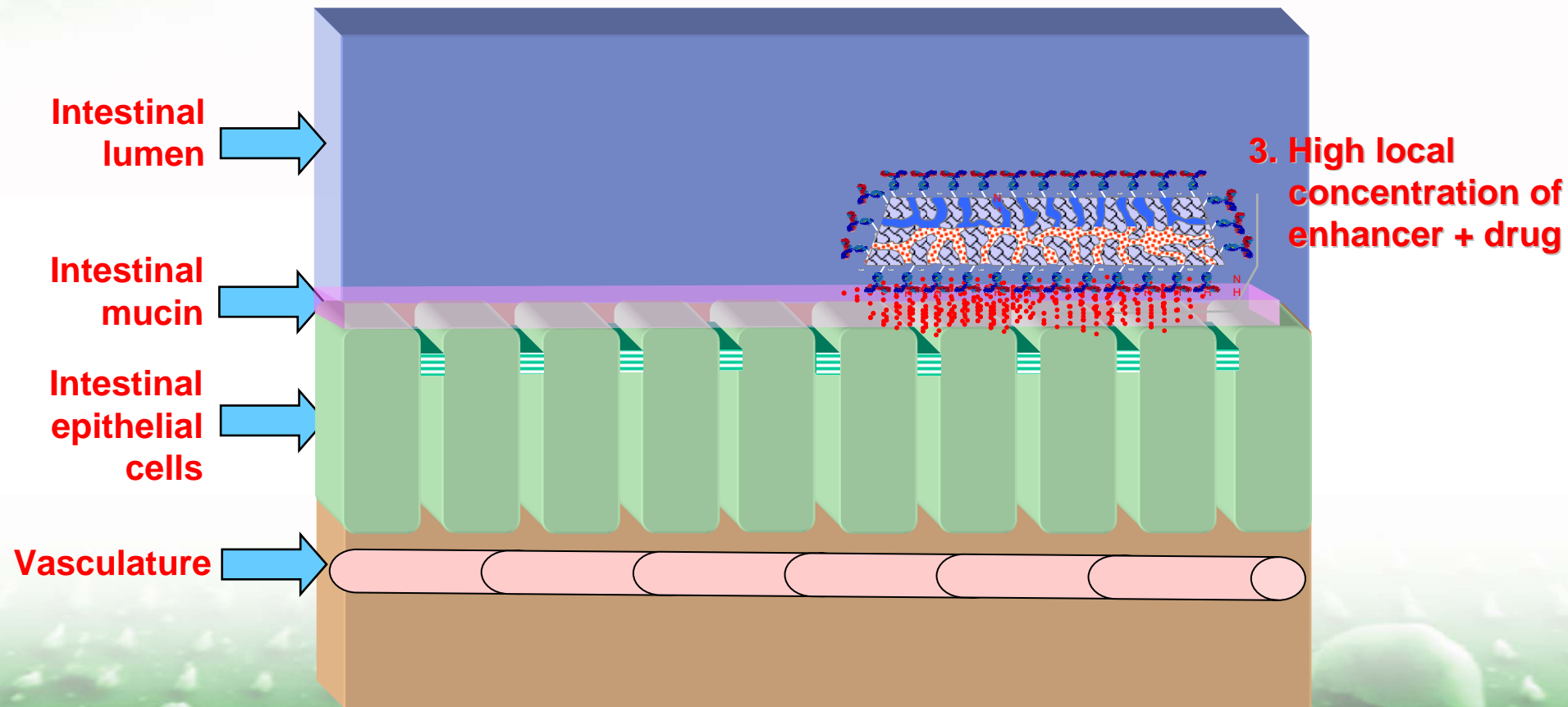
Vasculature



Microfabricated Trans-Mucosal Patch

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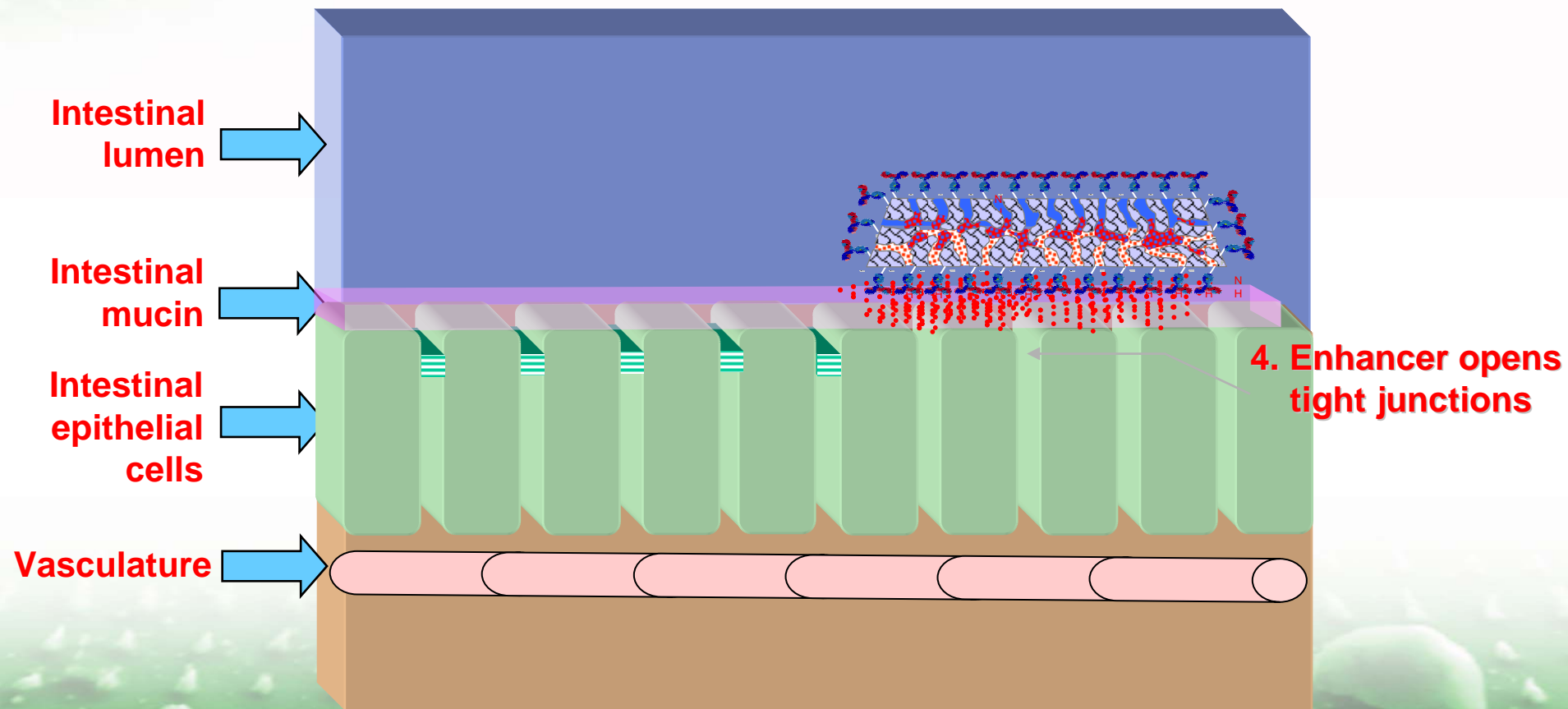
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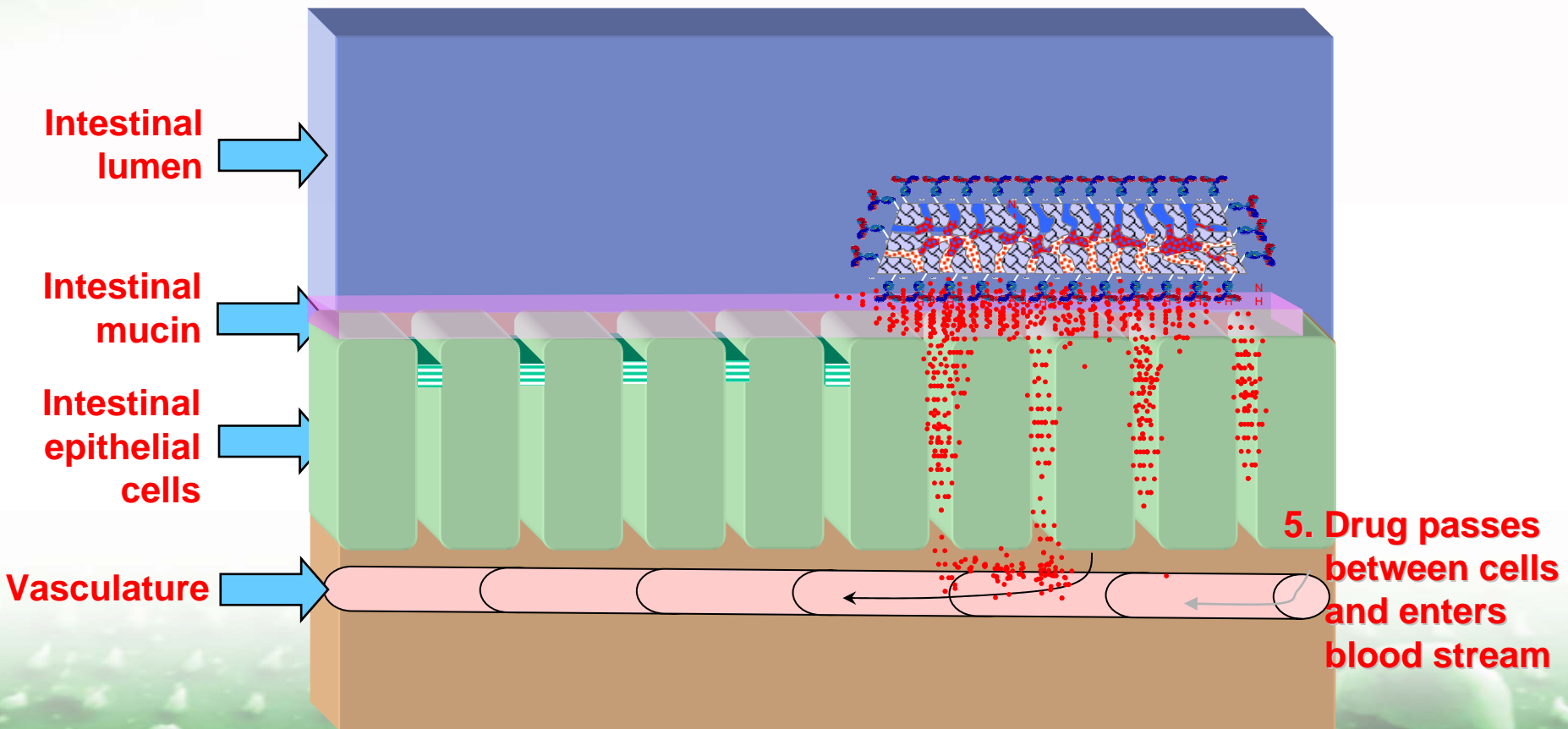
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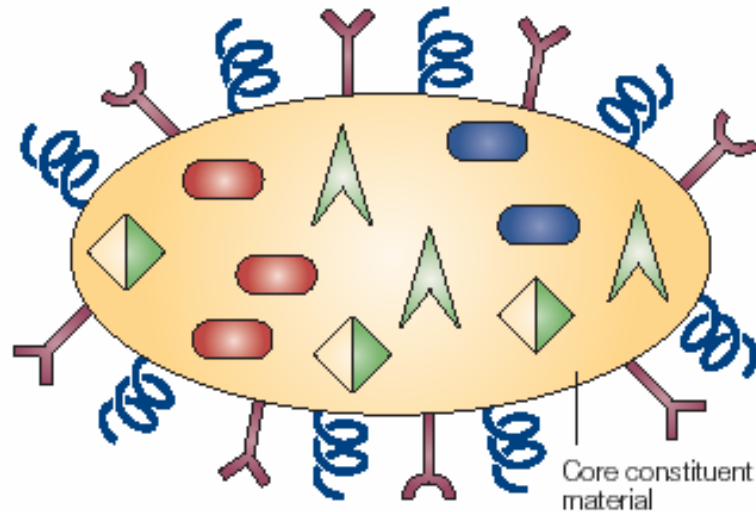
Generalized Considerations on Nano- & Micro-Particulates ("Nanovectors")

Multifunctionality IS the defining advantage in nanovector delivery

- Providing preferential, effective concentrations of therapeutic agents and imaging enhancers at lesion sites, by a combination of
 - Multimodal targeting, such as affinity-based + size & shape + surface properties + remote activation... (probabilities of localization are additive)
 - Overcoming of biological barriers, such as endothelial, epithelial, increased osmotic pressure, macrophage uptake, (probabilities of reaching lesion are multiplicative)
 - Providing co-localized combination therapy

Mauro Ferrari "Cancer Nanotechnology: Opportunities and Challenges", Nature Reviews Cancer, vol.5, n. 3, 161-171 March 2005

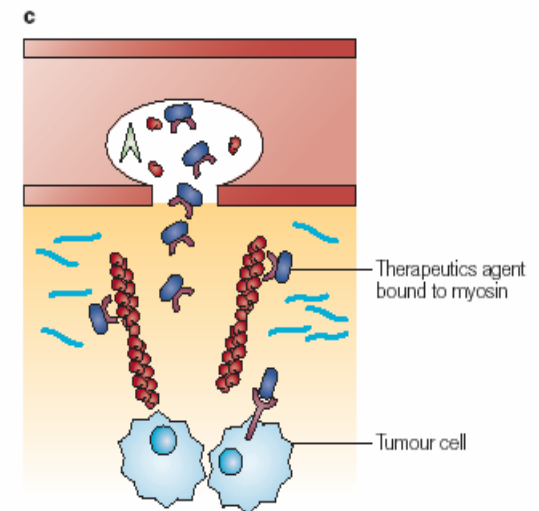
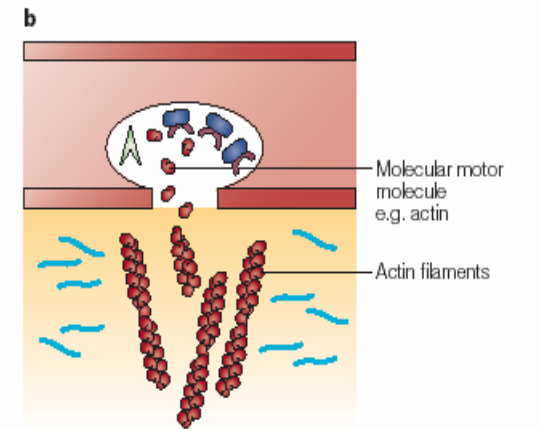
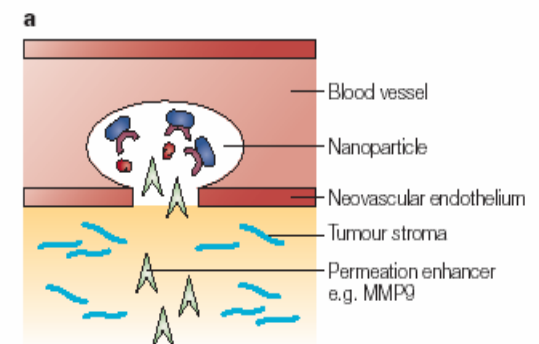
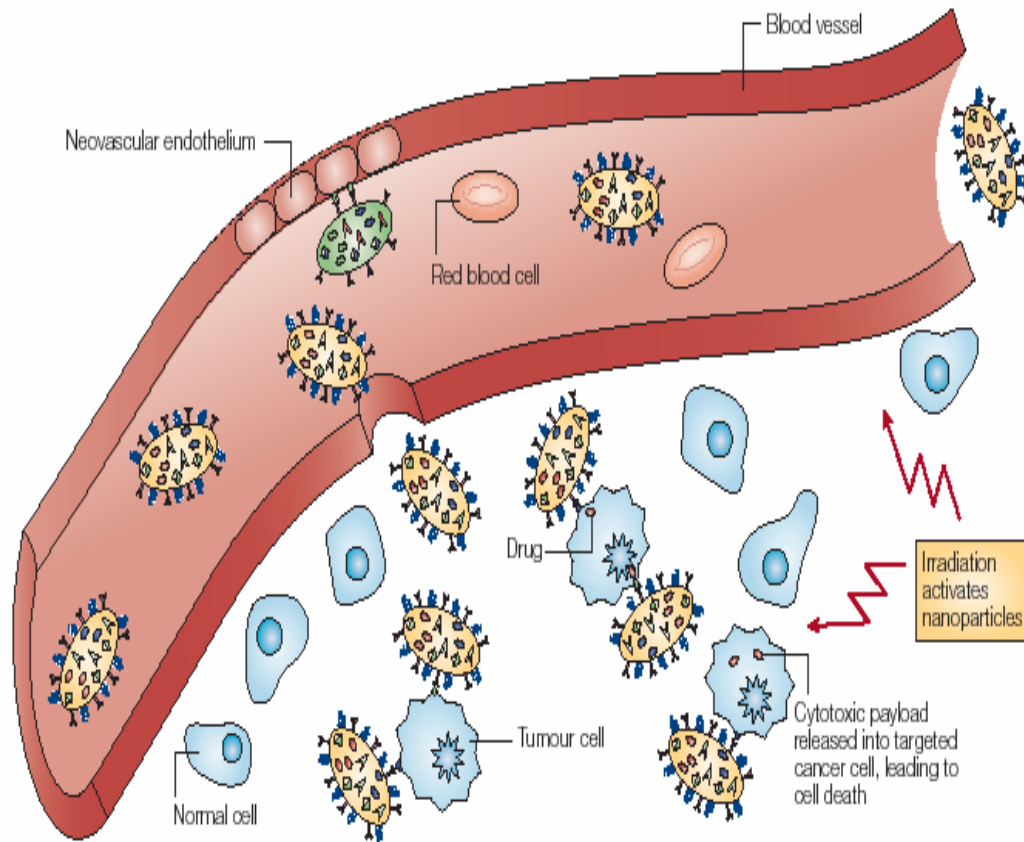
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| Therapeutic or imaging payload | Biological surface modifier |
|--------------------------------|-----------------------------|
| Drug A | PEG |
| Drug B | |
| Targeting moieties | |
| Contrast enhancer | |
| Permeation enhancer | |



Nanovectors: Multifunctionality



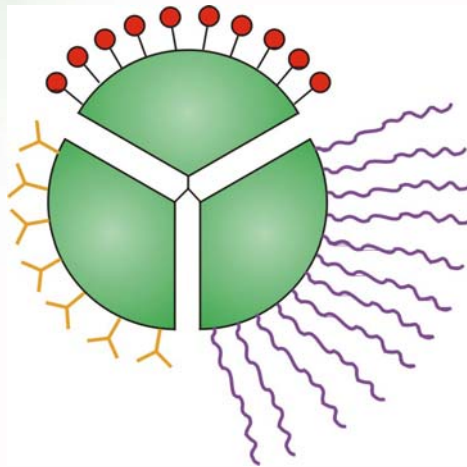
Central issue

- **Regulatory pathway for multifunctional, multicomponent nanovectors????**
 - “Multicomponent” is the transforming advantage
 - Immediate need: “Master file approach” to nanovectored Rx
 - Immediate need: Clarity on Device vs. Drug vs. Biological
 - Immediate need: Guidance document from FDA
 - General need: Mechanisms for further communications FDA/applicant
- **Lack of clear guidance induces:**
 - Dormancy/skepticism of private sector / pharma
 - The “low-hanging fruit approach”, not in the public’s best interest
 - The “avoid the nano-word” syndrome
 - Diminished enthusiasm by funding agencies
 - Expanded latitude for general misinformation / unfounded fears

Issue #2: Standardization – how to compare

- Liposomes, Micelles, Solid Lipid, Micro/nanobubbles
- Dendrimers, Dendrisomes
- Lipid-encapsulated PFC emulsions
- Iron-oxide, drugable entities
- Nanoshells
- Q-Dots
- Silicon, SiO₂ micro/nanoparticles
- Biodegradable micro/nanospheres
- Leashed polications
- DNA-based constructs
- Engineered viral particles
- Buckeyballs
-

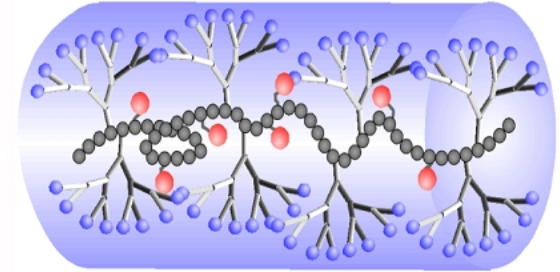
Issue # 3: How to handle combinatorial numbers / approaches?



Dendrimer

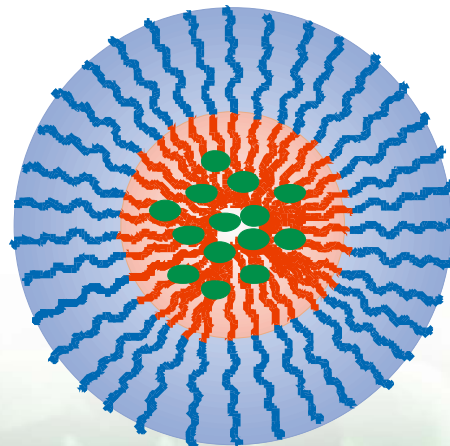


Dendritic hybrid

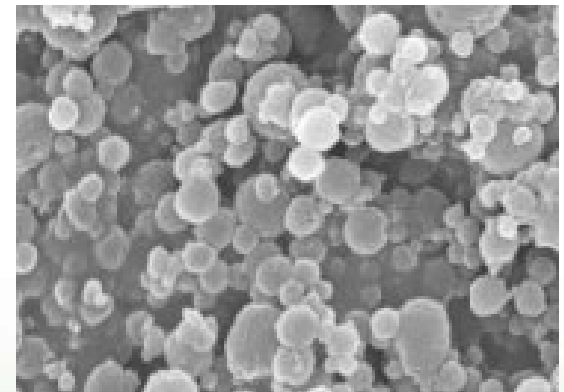


Dendronized polymer

Single Molecules
2-200 nm



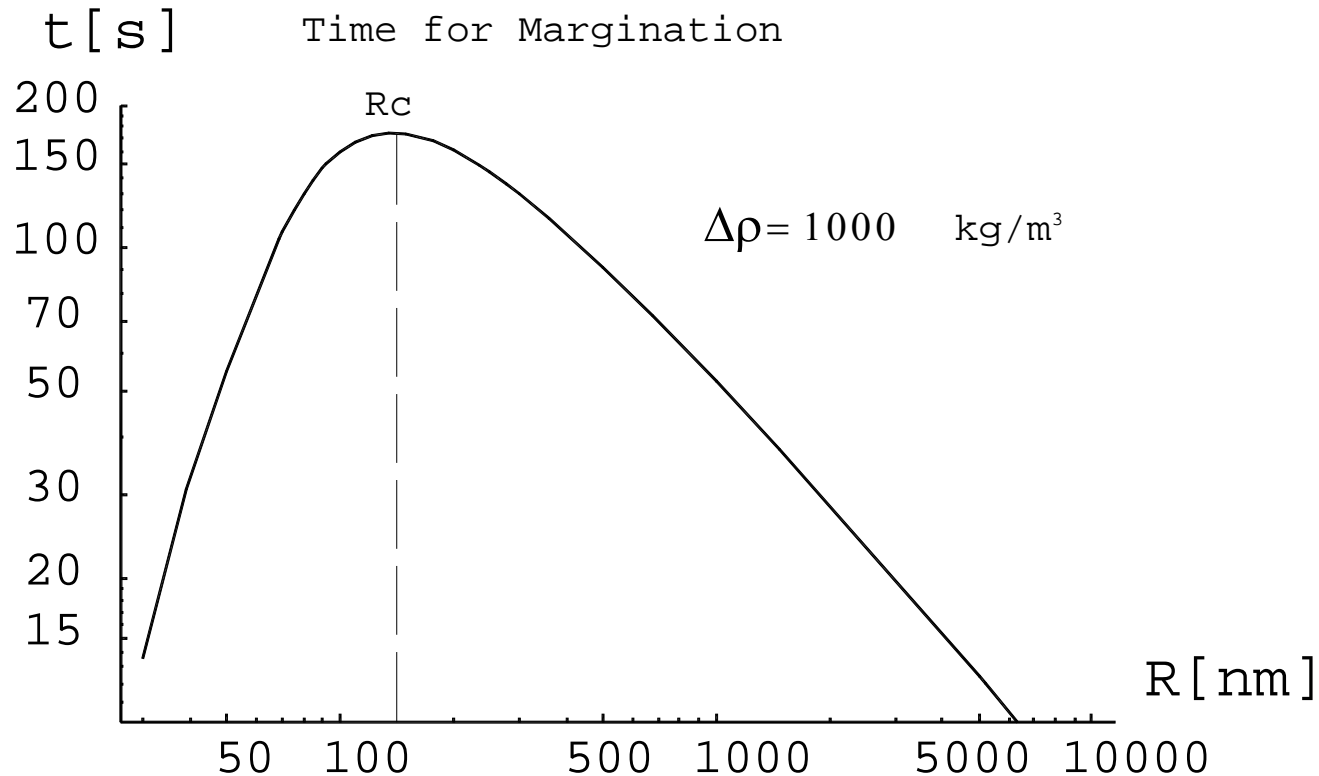
Polymer micelle



Degradable nanoparticle

Molecular assemblies
20-1000 nm

Issue # 4: Integration of mathematical models



- The time for margination is influenced by the relative density $\Delta\rho$ and electromagnetic properties (Hamaker constant A) of the particle
- A critical radius R_c exists for which the margination time is maximum
- The maximum is influenced by $\Delta\rho$ and A and can be tuned!

Underlying Issue: Characterization

- Toxicology: Special needs?
- Characterization methodologies for properties that determine efficacy: Special needs, yes.

Summary: Key Issues

- **Regulatory pathway for multi-component nanovectors ?**
- Standardization – how to compare ?
- How to handle combinatorial numbers?
- Integration of mathematical models!

- Novel characterization methods required ?
 - Integrated NCL & community efforts

Discussion and Contacts

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- Ferrari.5@osu.edu
- Ferrarma@mail.nih.gov