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Remotely Controlled Drug Delivery Implant for Telemedicine

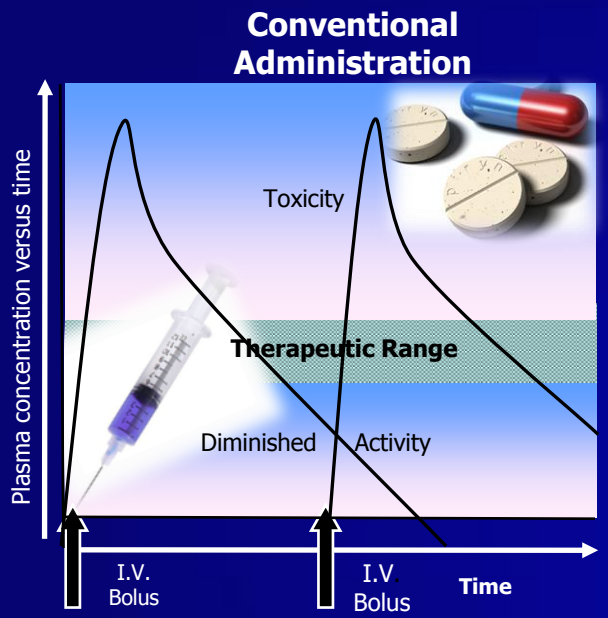
August 17th, 2015

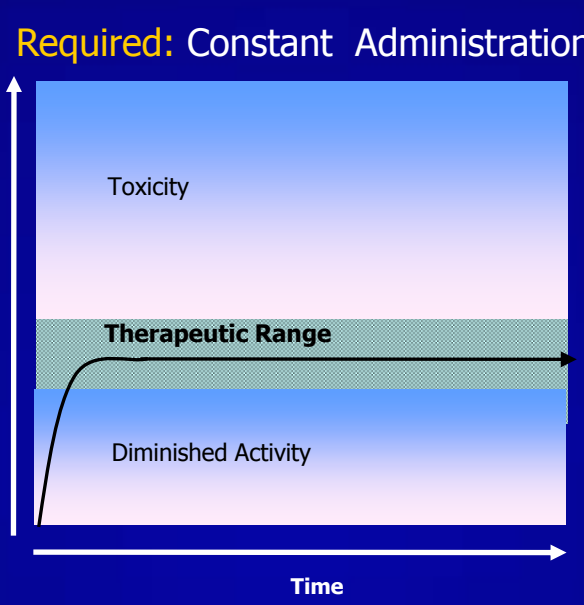
Alessandro Grattoni, Ph.D.
Chairman and Professor,
Department of Nanomedicine
Houston Methodist Research Institute, Houston

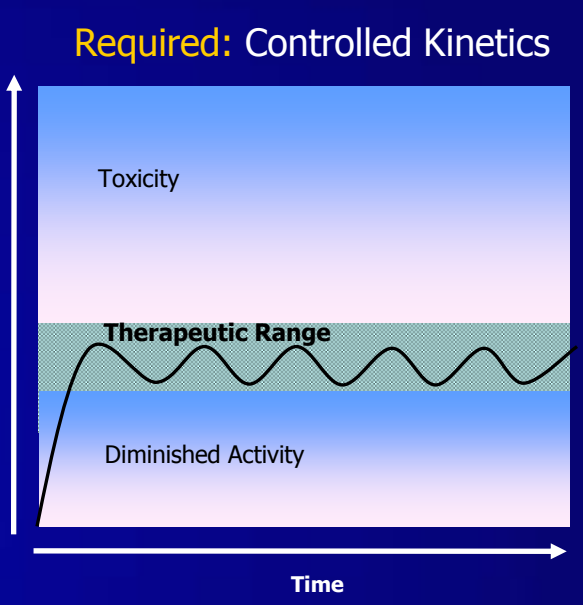
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NANOMEDICALSYSTEMS

The Need for Alternative Drug Delivery Strategies

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- ✓ Multiple Injection
- ✓ Low efficacy
- ✓ Large drug doses
- ✓ Side effects
- ✓ Poor quality of life

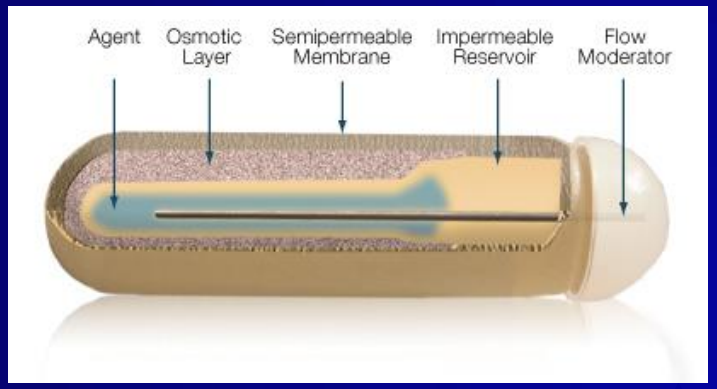
- ✓ Constant Release Rate
- ✓ Improved efficacy.
- ✓ Controlled Release Profile
- ✓ Enabling Chronotherapy.

- ✓ Reduction of the drug dose.
- ✓ Reduction of side effects
- ✓ Improvement of quality of life

Existing Technologies

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Osmotic Pumps



Biodegradable Polymers



Long-acting depots



Wearable External Pumps

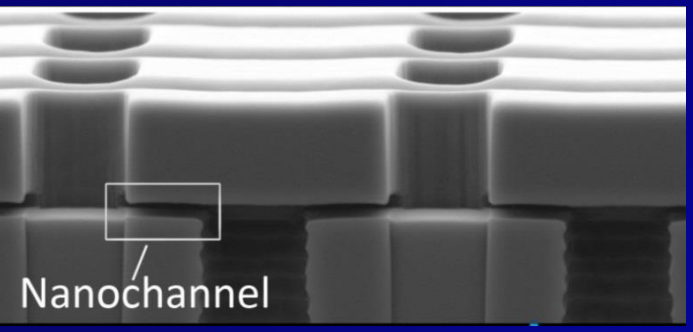


MicroCHIP devices



Nanochannels
No Need for Pumps!

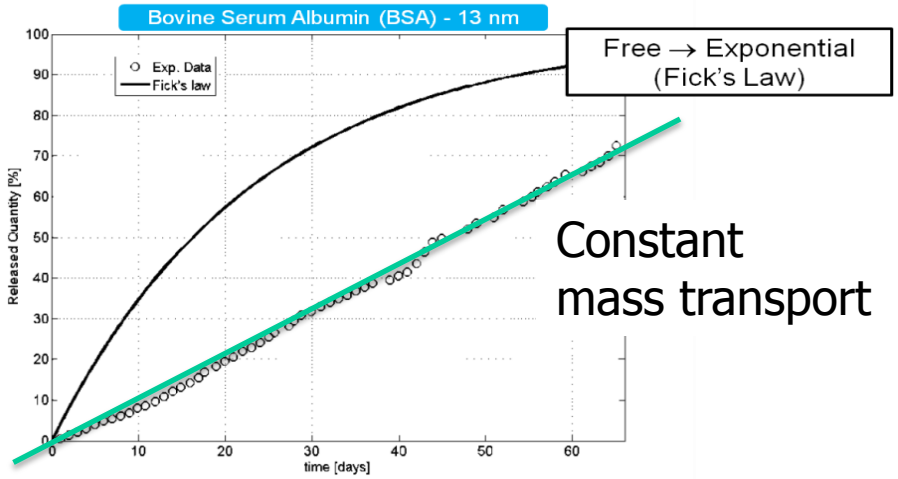
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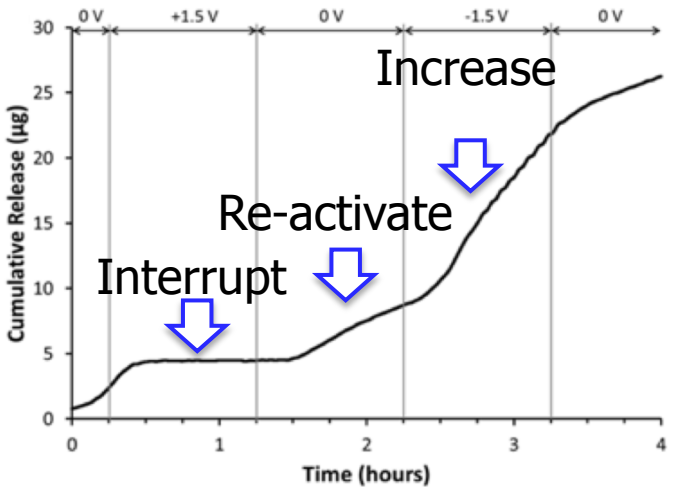
Opportunity: Fluids at the nanoscale do not follow *continuum*-based laws of mass transport

Hypothesis: hindered-diffusion, electro-osmosis, ionic concentration polarization can be used to achieve controlled molecular transport across nanochannels.

Diffusion



Electrokinetic Transport



No Pumps





No Valves

nDS Project

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Objectives

development of silicon based nanochannel membranes for:

1. ***Passive*** and ***Active*** release of molecules, drug and nanoparticles form implants, over extended period of time.
2. ***Cell Transplantation***

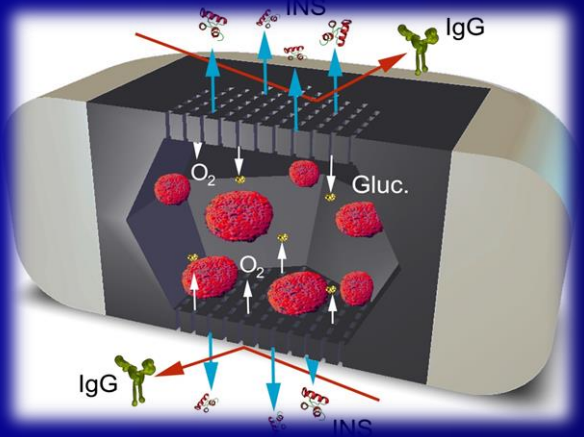
nDS1 Constant Release

Concentration-driven transport



nDS NanoGland

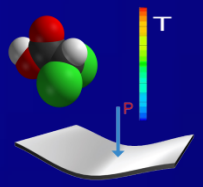
Cell Transplantation



nDS2 Active *ad-hoc* Release

Electrokinetic transport

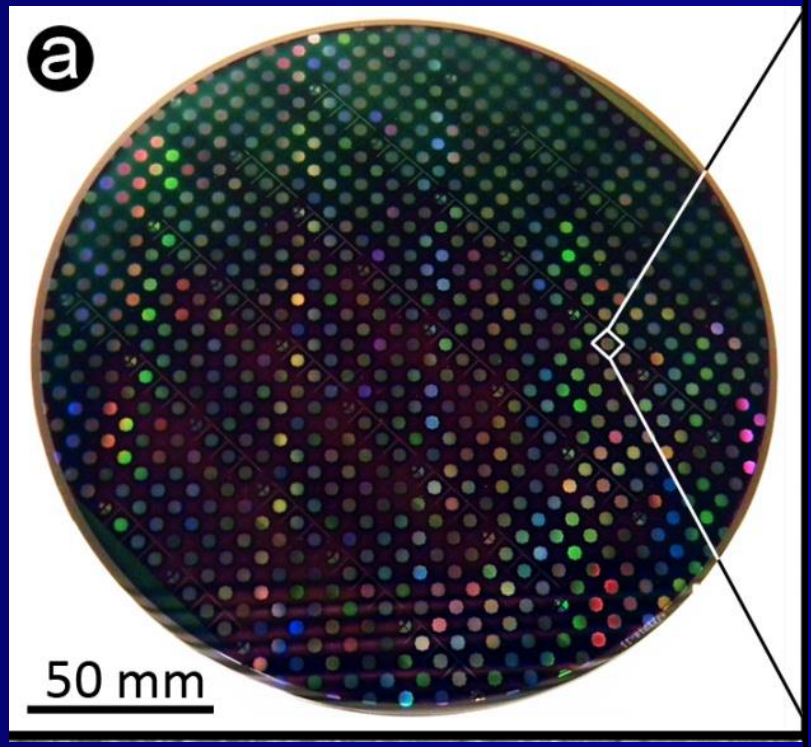


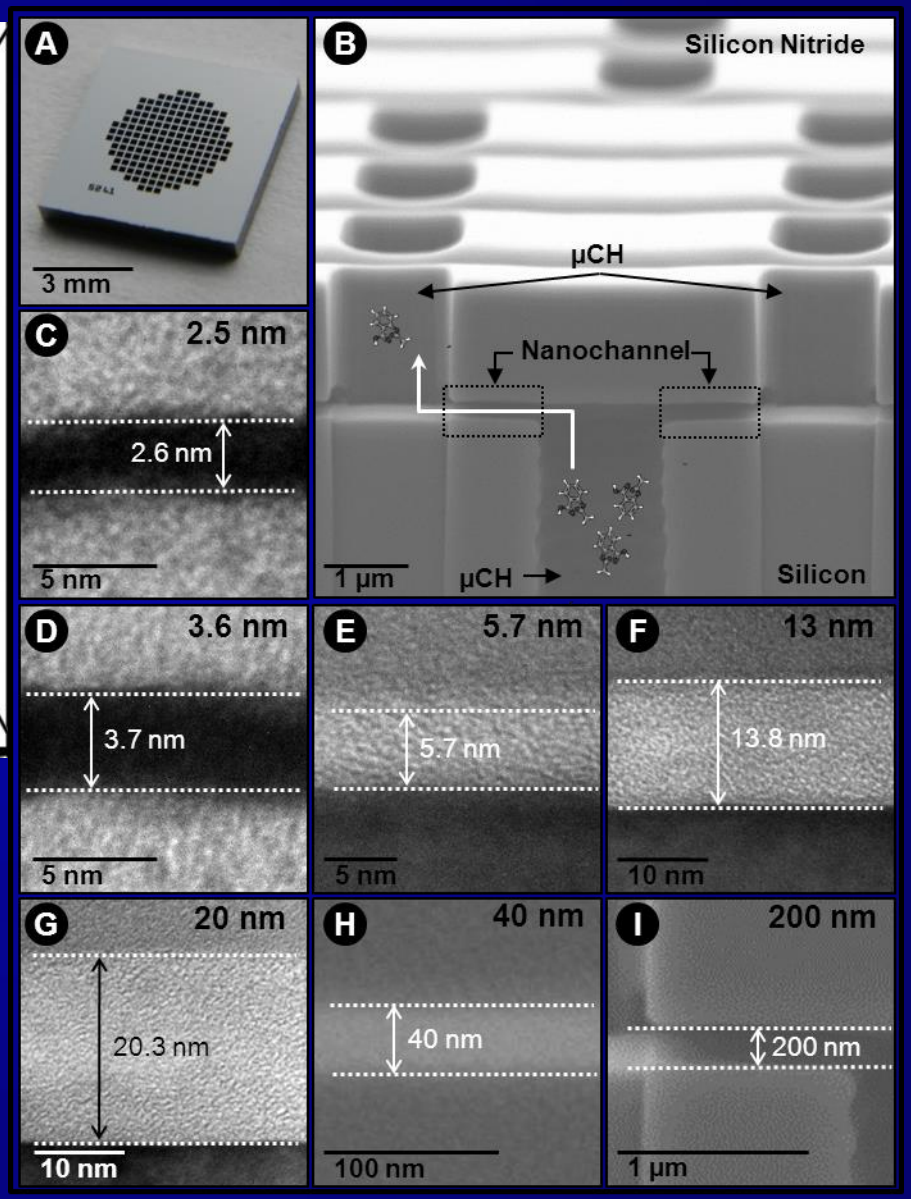




Nanochannel Membrane

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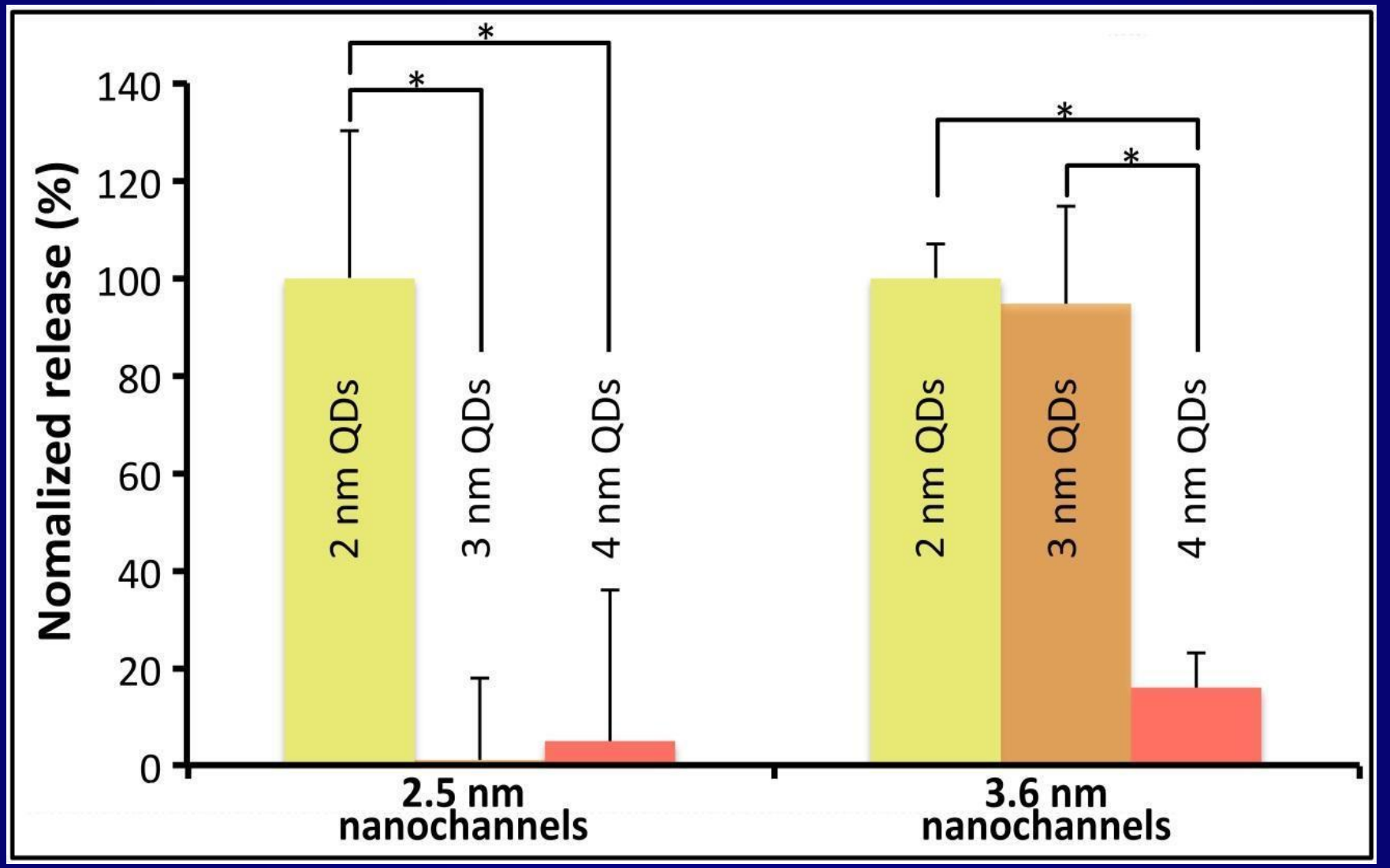




Grattoni, Fine et al. *Lab Chip,* 2010
Grattoni et al. *Pharma. Res.,* 2010

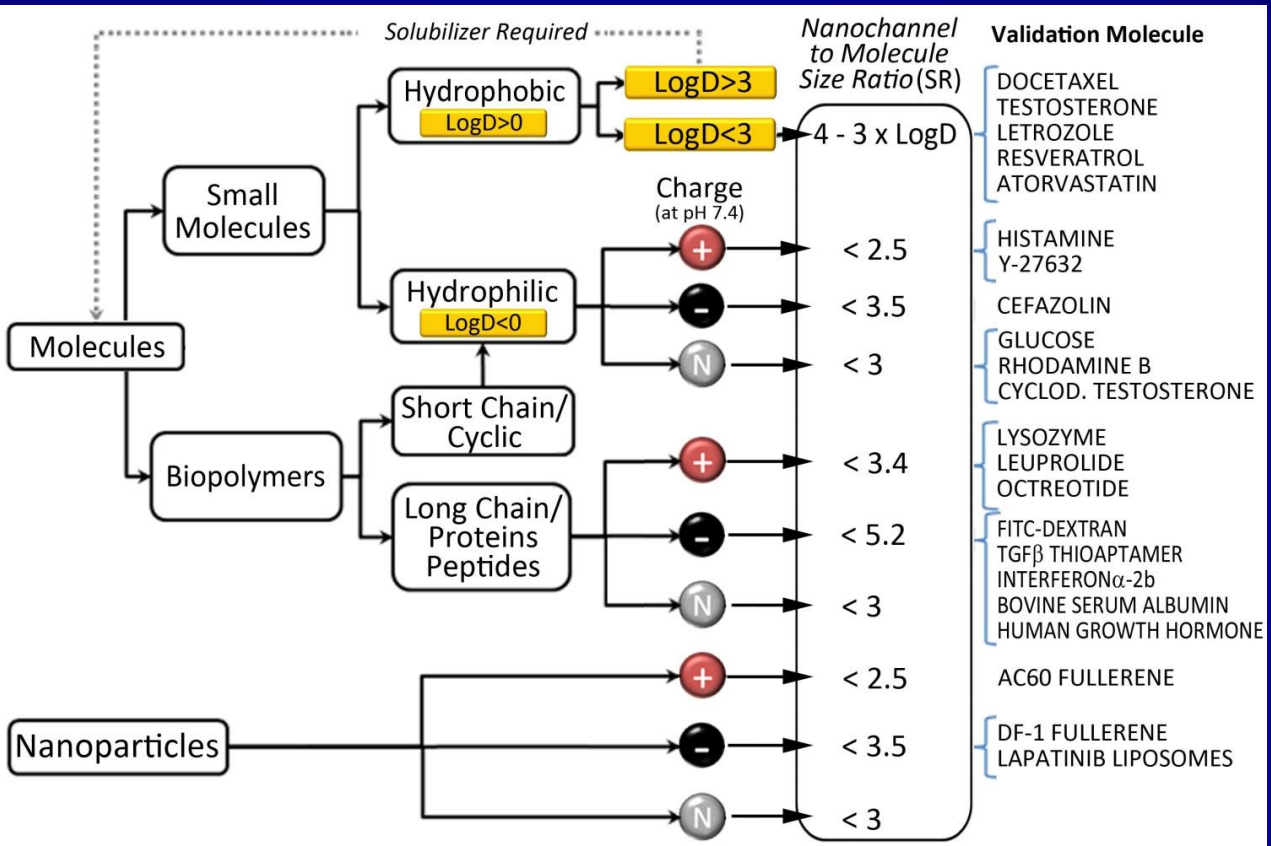
Ultraselective Filtration

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Rational Selection

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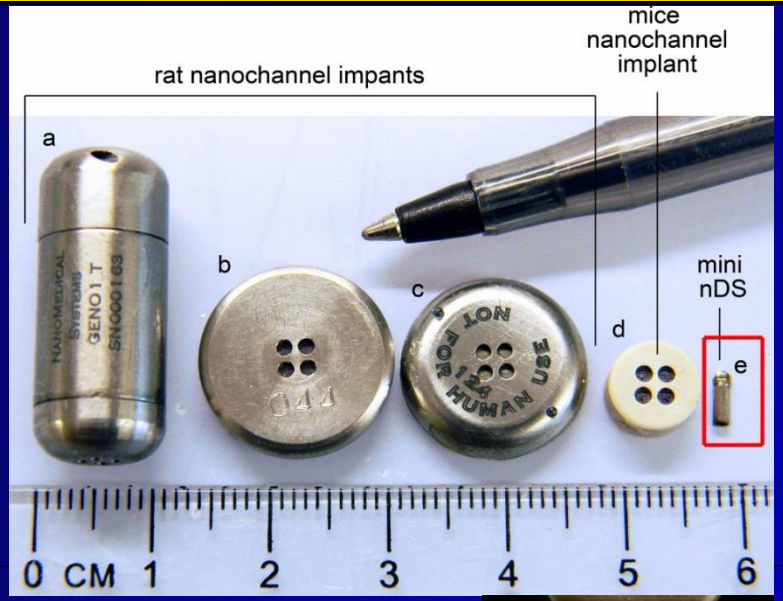


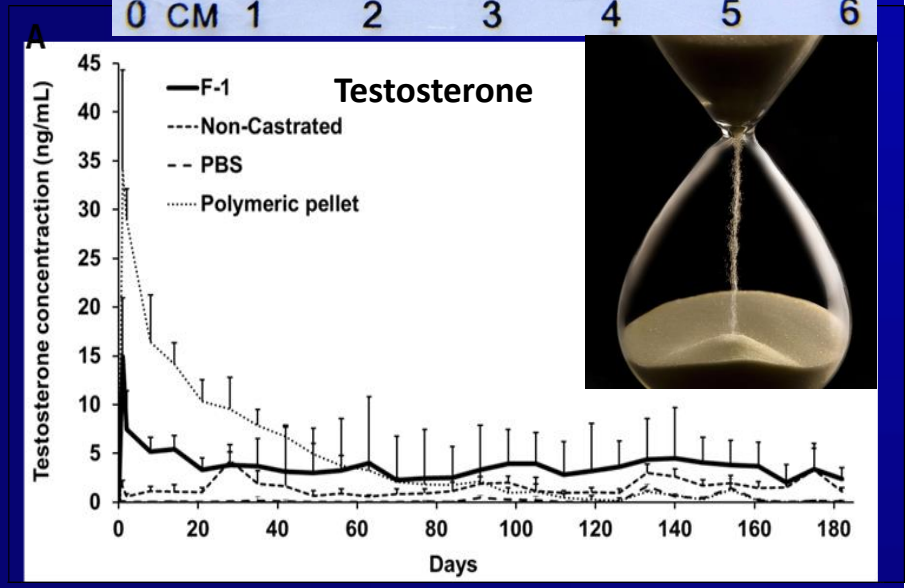
Molecule	MW (Da)	LogD (pH 7)	Charge (pH 7)	Mol Size (Å)	nCH size (nm)	SR
Interferonα-2b	19,200	-	-2	42	22	5.2
hGH	22,100	-	-5	52	20	3.8
Leuprolide	1,209	-	2.3	14	3.6	2.6
Octrotide	1,019	-	1.4	14	3.6	2.6
Letrozole	289	2.5	0	18	3.6	2.0
Y-27632	247	-1.2	1	15	3.6	2.4

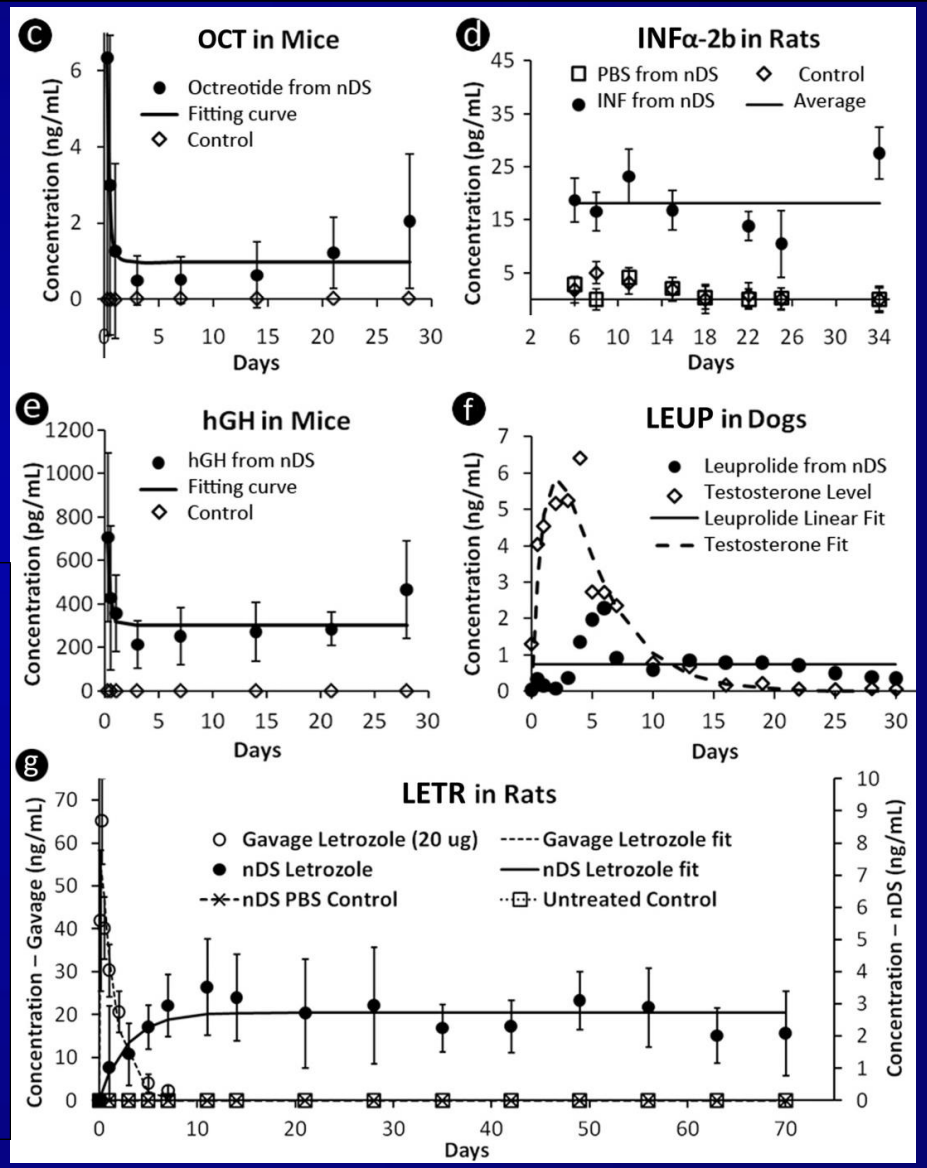
Ferrati et al. *J. Controlled Release,* 2013

in vivo Constant Release of Drugs

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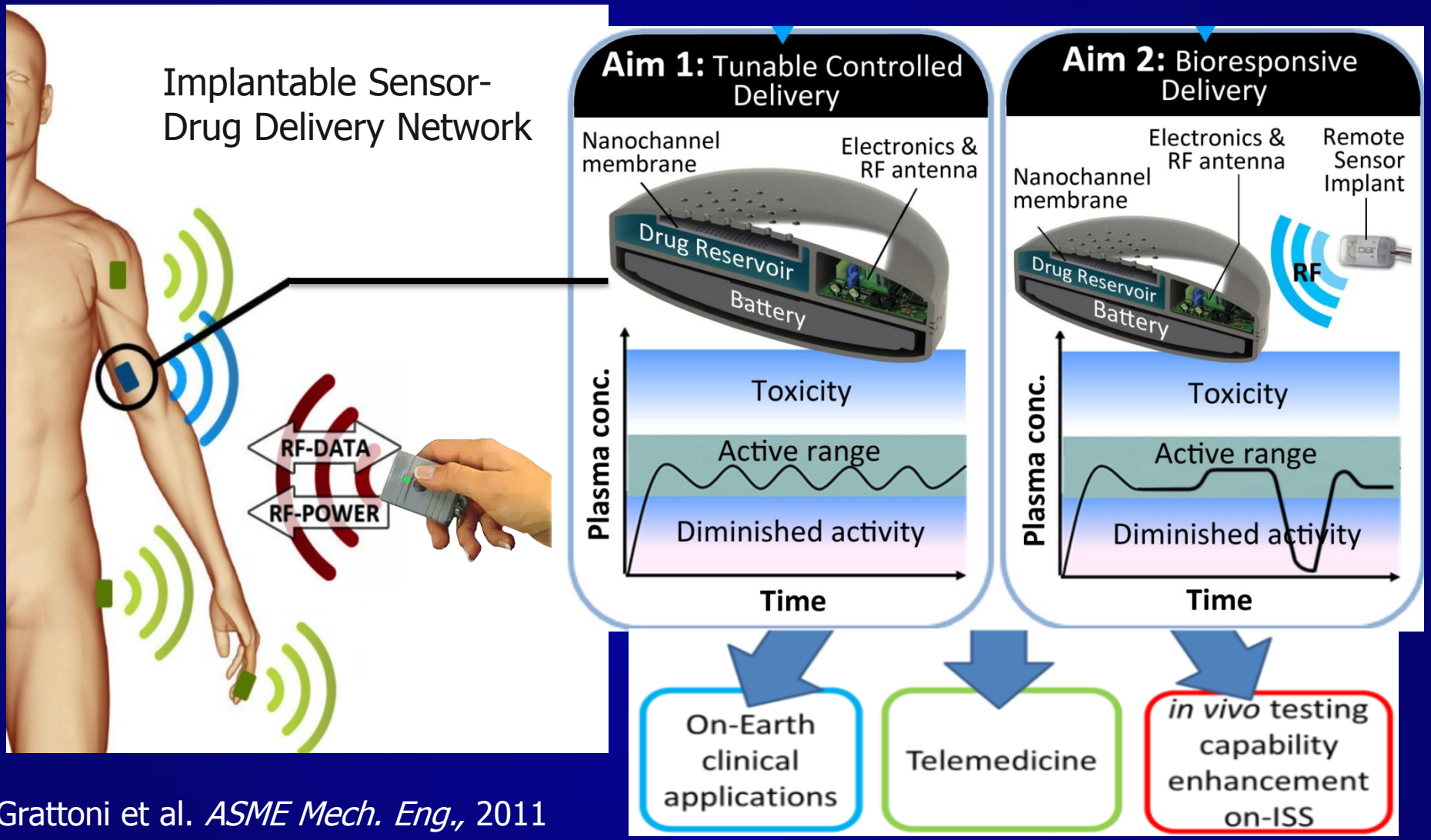


Nicolov et al. *J. Urology,* 2014
Ferrati et al. *Advanced Healthcare Materials,* 2014

Ferrati et al. *J. Controlled Release,* 2013

Remotely Controlled Drug Delivery

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Grattoni et al. *ASME Mech. Eng.,* 2011

Grattoni et al. *Aviat. Space Envir. Med.,* 2012

Grattoni, Fine et al. *Adv. Health. Mat.* 2013

Drug Delivery on ISS

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Microgravity provides a unique environment for life-science investigation: Accelerated and spontaneous models of osteoporosis, muscle atrophy, kidney stones formation, loss of biological clock

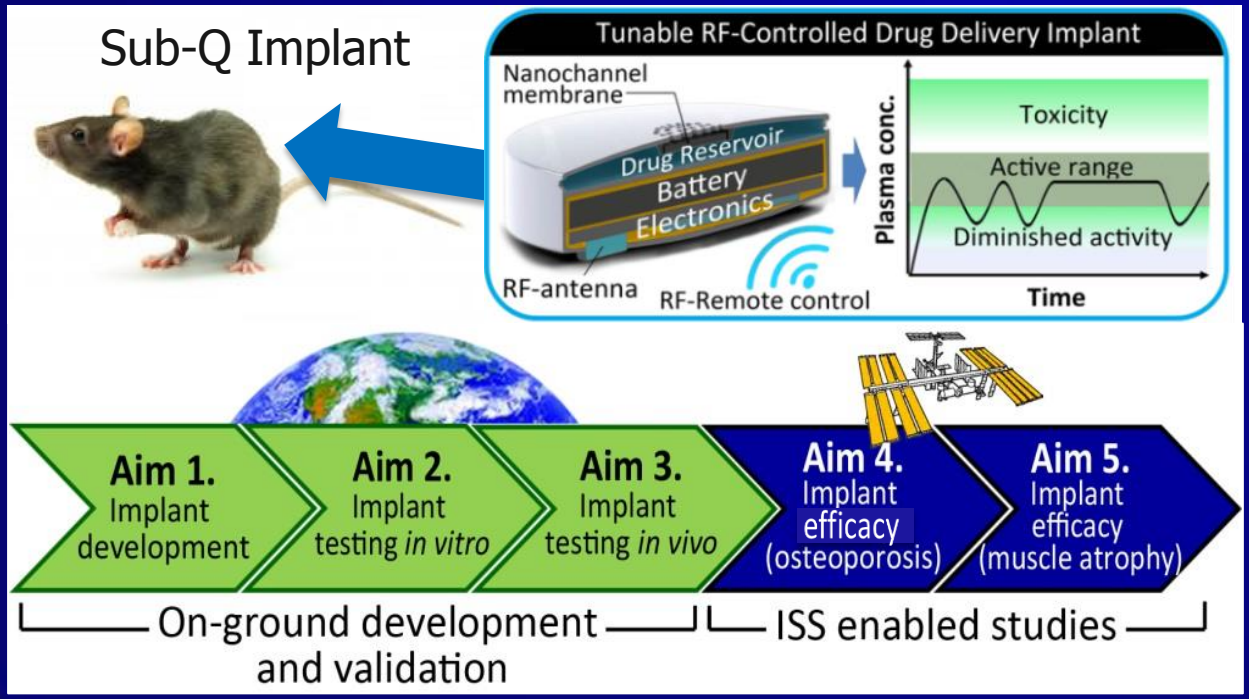
The Challenge:

- tight restrictions in animal handling
- very few options for the administration of therapeutics on the ISS
- limitation of the spectrum of investigations in microgravity
- limitation in the utilization of the extraordinary ISS laboratory



Animal enclosure module
Source: NASA

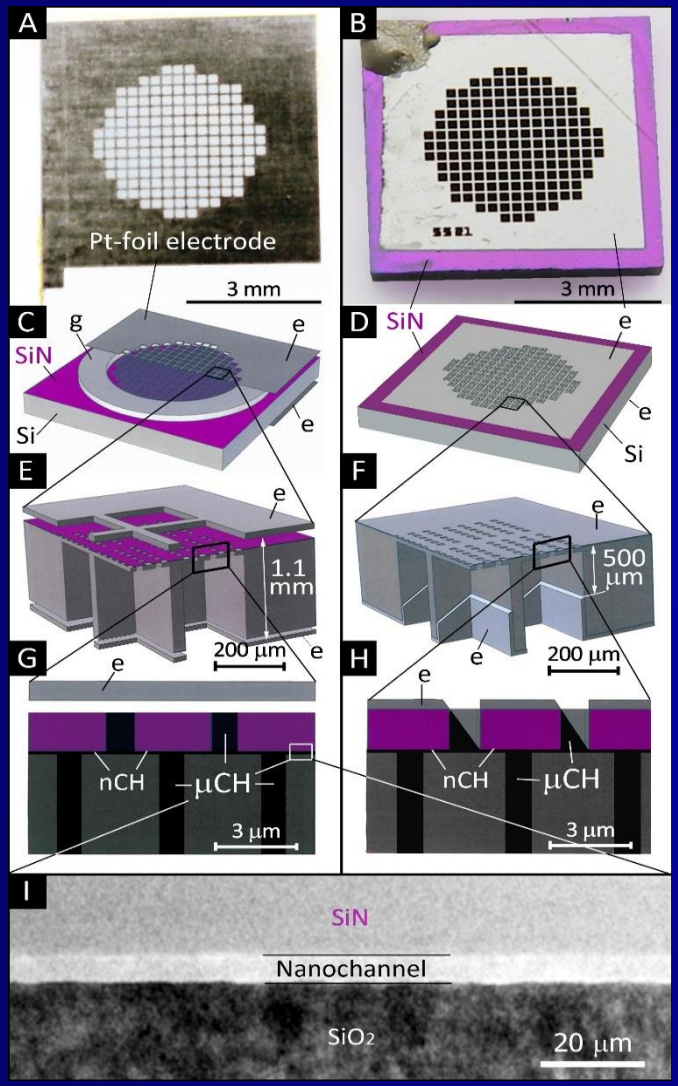
The Solution:

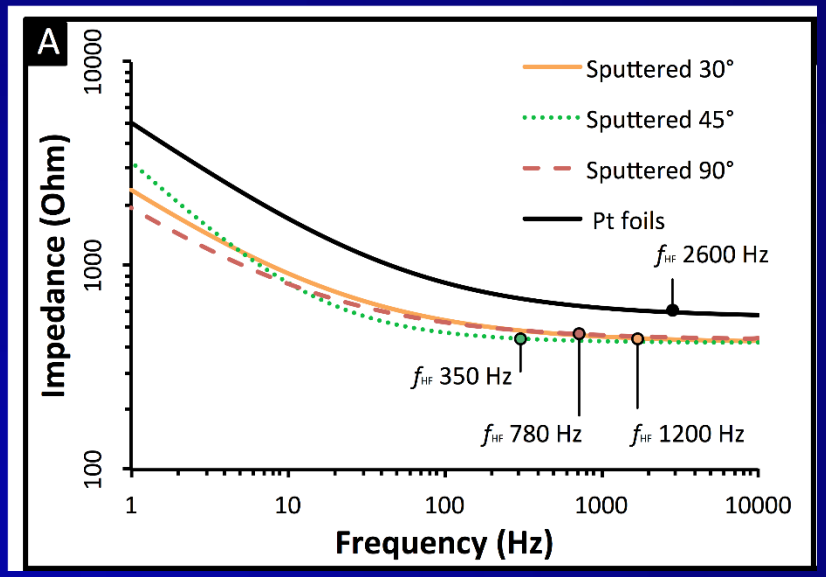


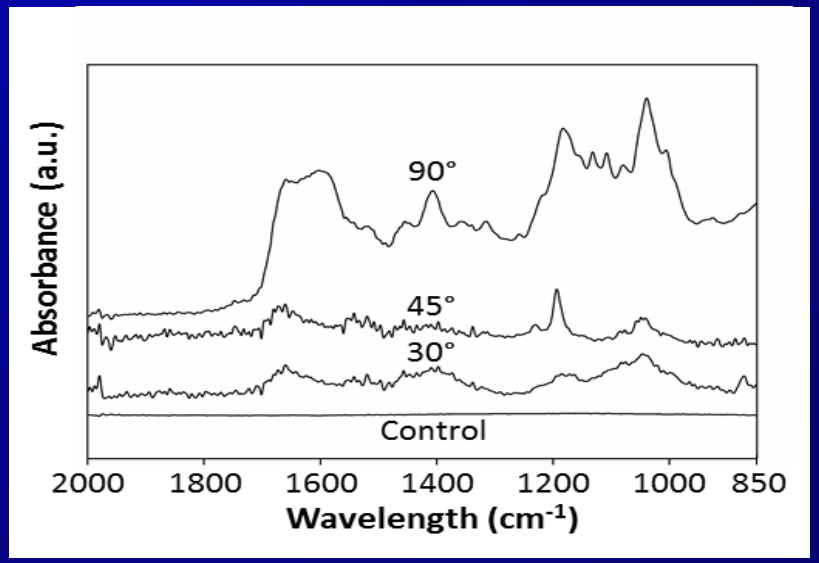
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NanoMedical Systems

Electrode Fabrication and testing







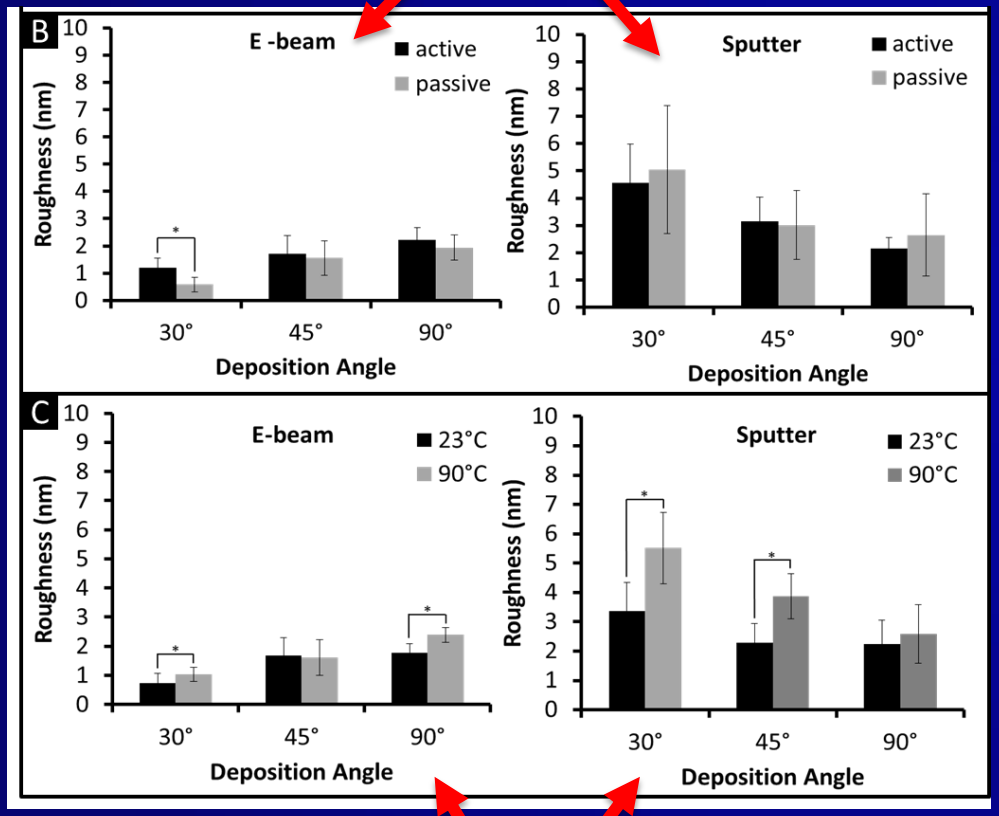
Geninatti, et al. *Biomed. Microdev.,* 2014
Geninatti, et al. *Nanoscale,* 2015

Electrode Fabrication and testing

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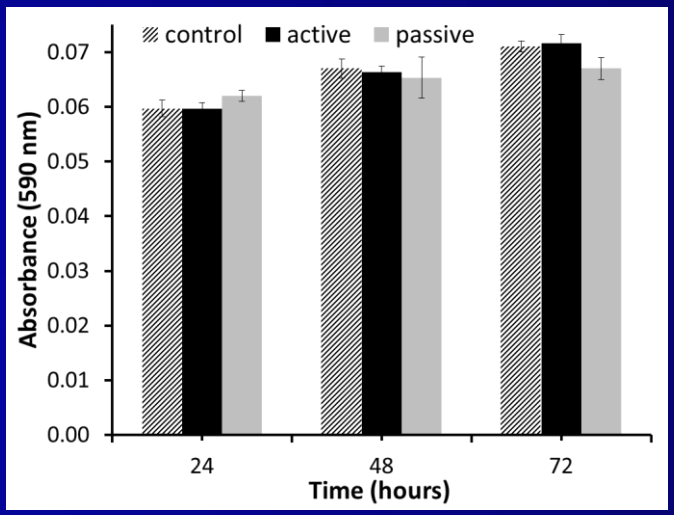
Degradation testing:

Effect of 1.5 VDC applied electric potential



Effect of temperature

Assessment of biocompatibility

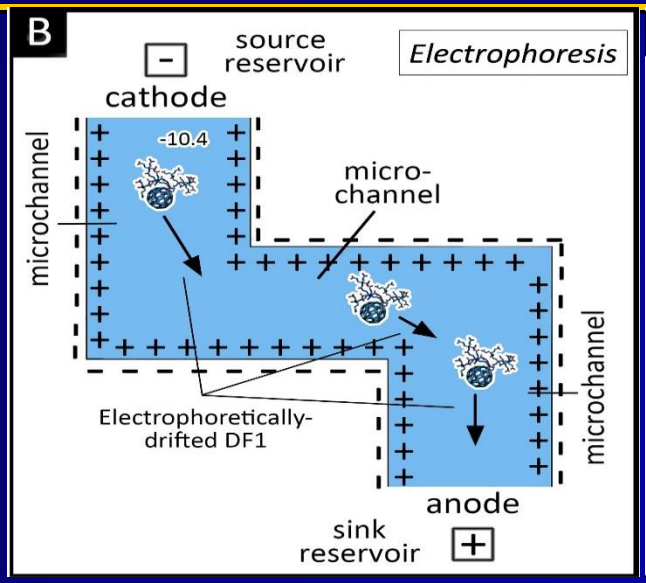


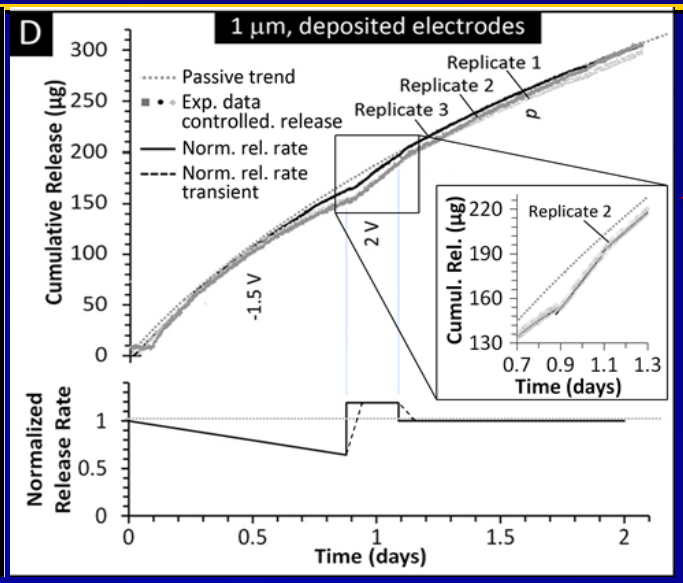
MTT proliferation assay with human dermal fibroblasts

Geninatti, et al. *Biomed. Microdev.,* 2014

Electrophoresis vs ICP

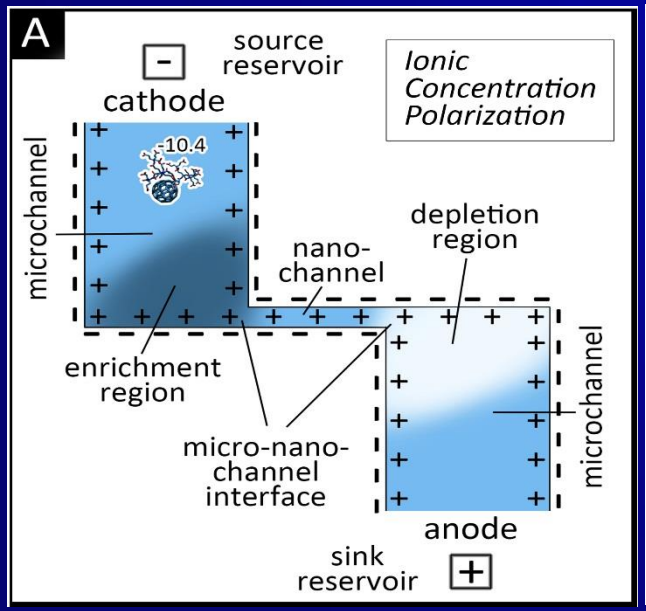
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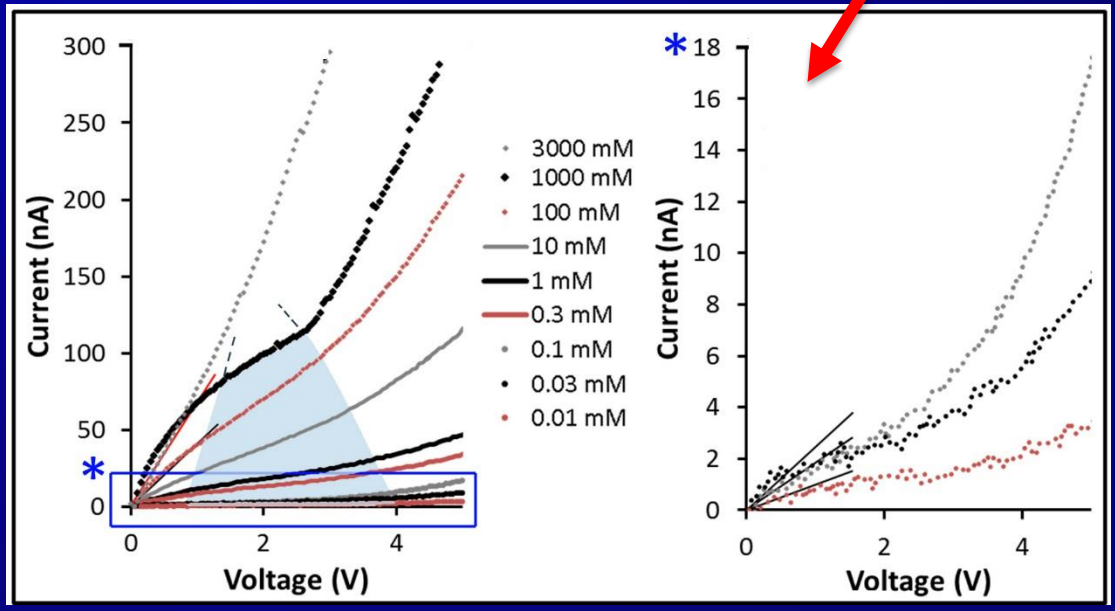




Electrophoresis in "large" channels

Ionic Concentration Polarization (ICP) in "small" channels



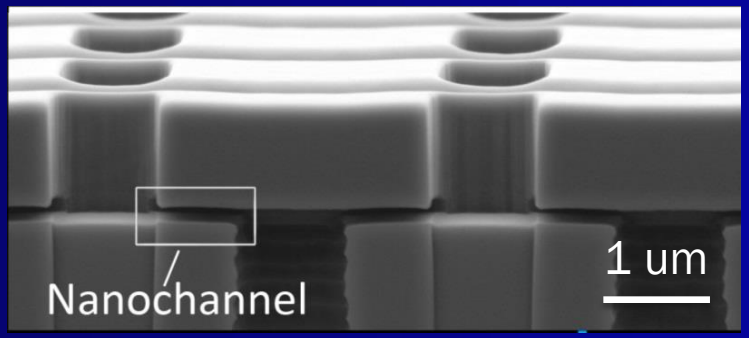


Geninatti, et al. *Nanoscale,* 2015

Control of Molecular Transport

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The nDS is an implantable, silicon- based membrane used for the **ACTIVE** release of molecules, drugs or nanoparticles, over extended period of time.

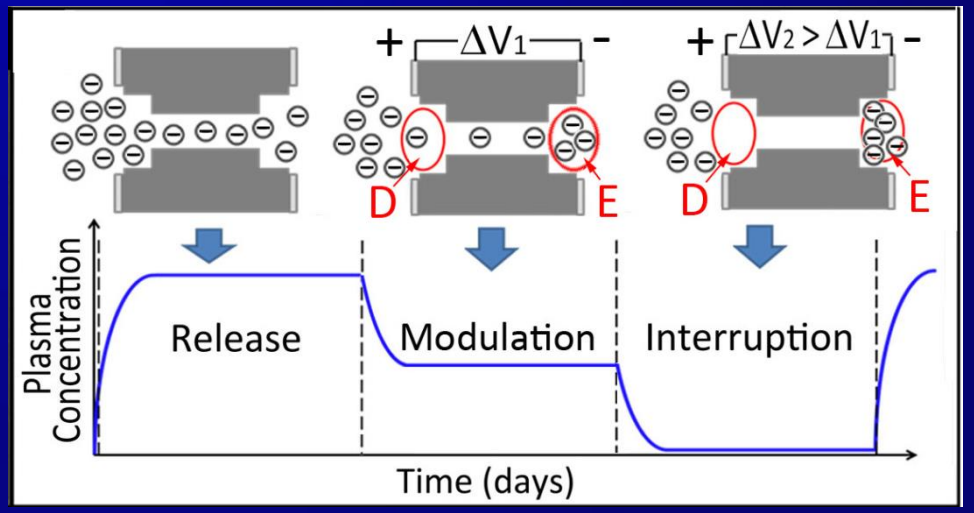


SEM micrograph of the nDS architecture.

A membrane contains hundreds of thousands of nanochannels as small as 2 nm.

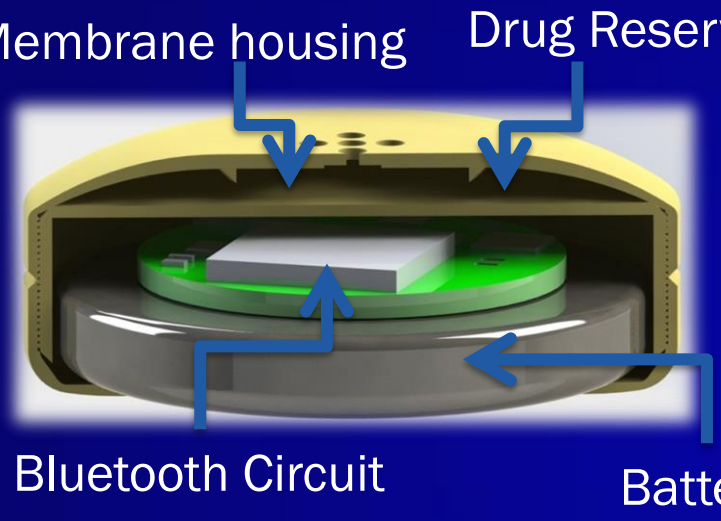
The application of an electric field across nanochannels allows the modulation or the interruption of drug release through:

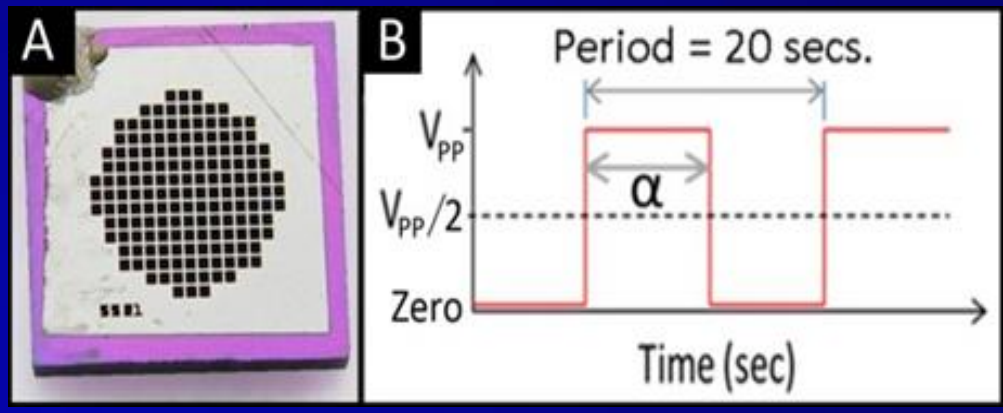
- Ionic Concentration Polarization (ICP)
- Electrophoresis



RF-Remotely Controlled nanochannel Delivery System (nDS2)

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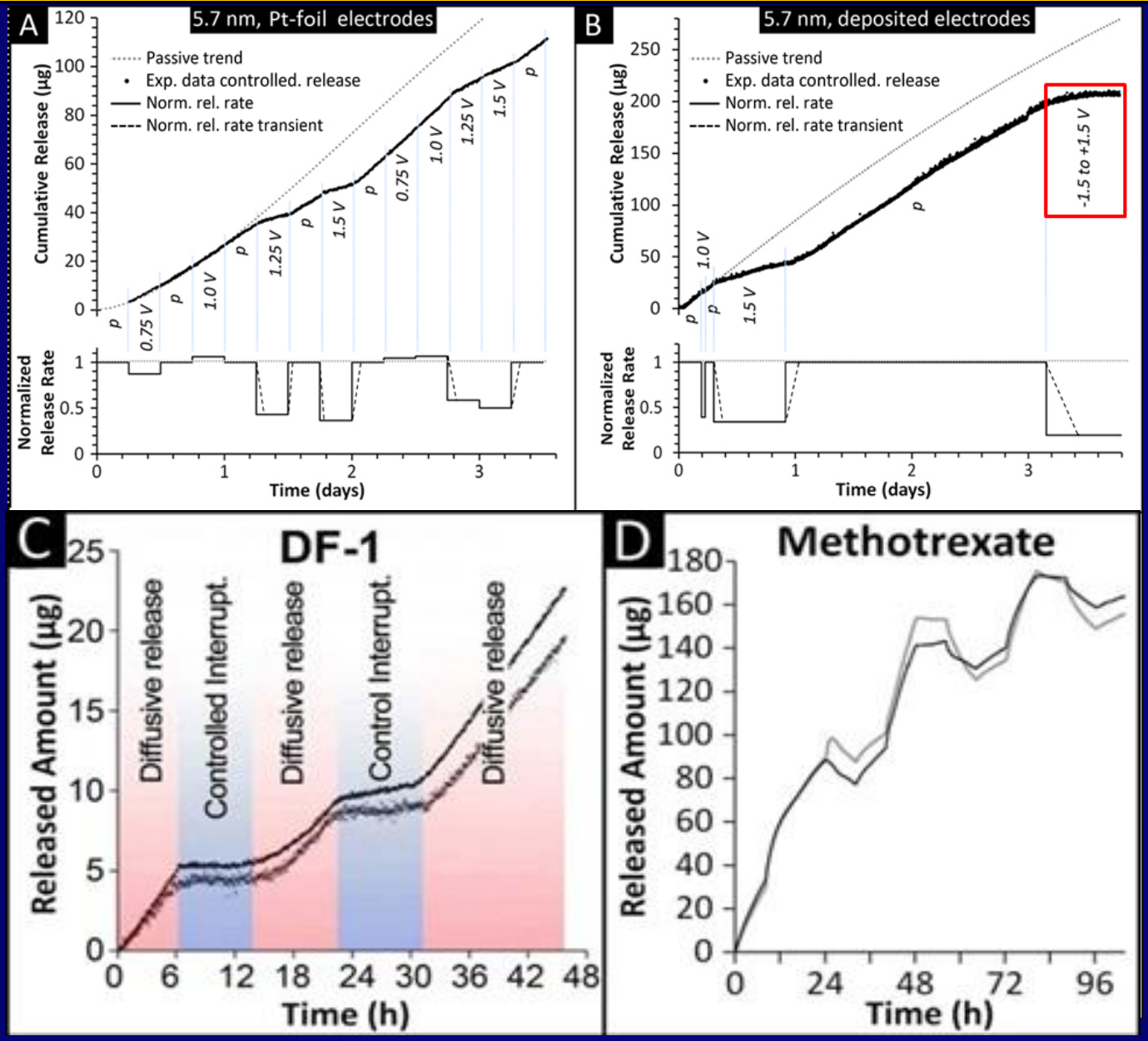




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Tunable Release Results

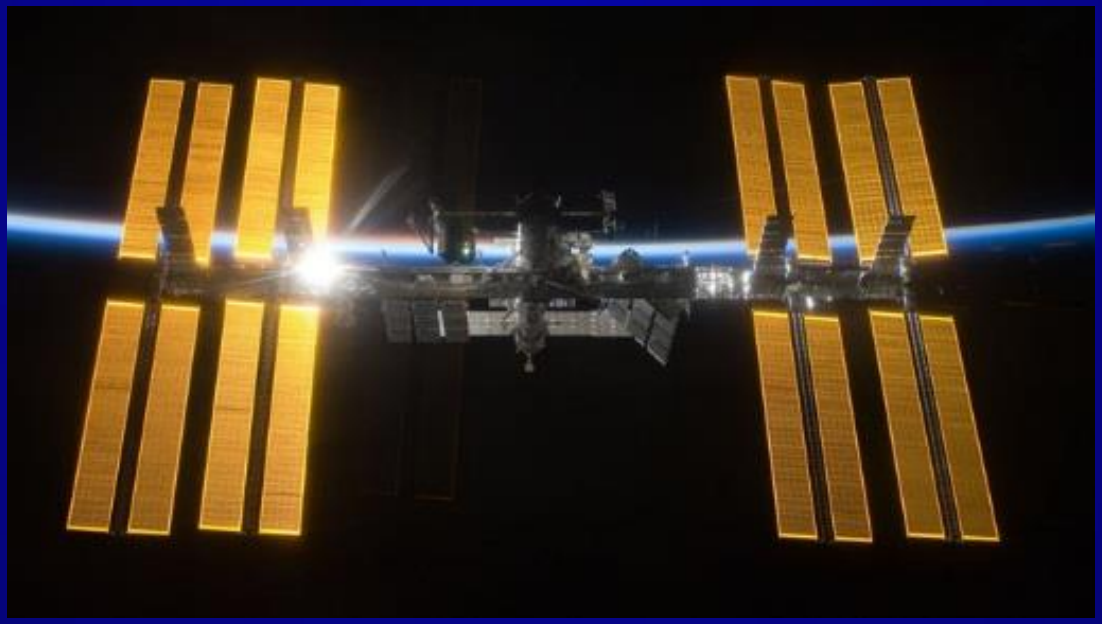
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Geninatti, et al. *Nanoscale,* 2015

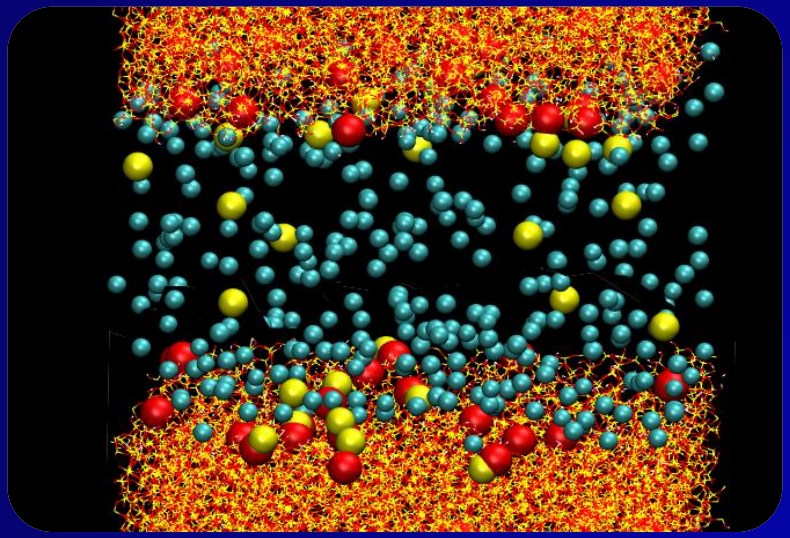
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Study of Constrained Transport in Space



Challenges of Studying Constrained Molecular Transport

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Molecular Dynamics

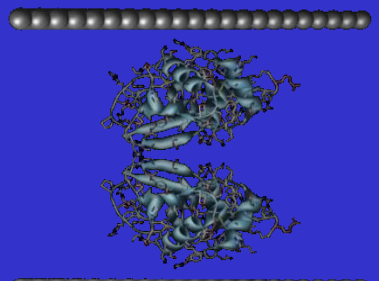
At nanoscale coupled interaction effects take over the molecular transport.

- Interactions
- Adsorption
- Size & Shape
- Charges
- Osmosis

Makes the difference

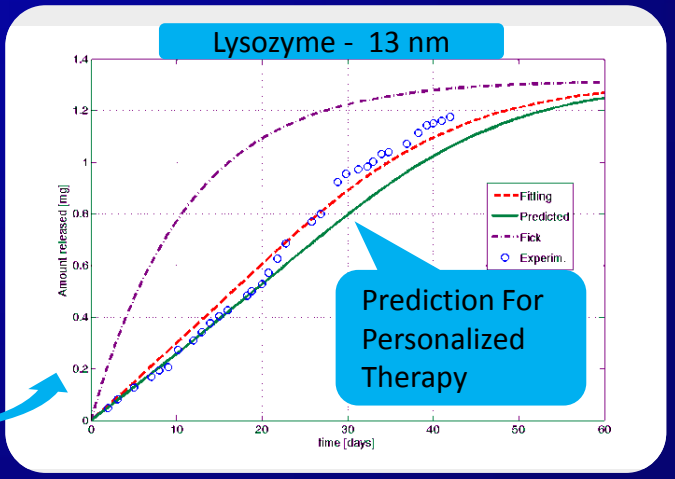
Challenge: decoupling single effects at nanoscale.

New Physics



$$\frac{\partial v}{\partial t} = \left(\frac{kT}{6\pi r \eta} \frac{2b}{(1-bv)^3} - \frac{2a}{6\pi r \eta} \right) \left(\frac{\partial v}{\partial x} \right)^2$$

$$+ \left(\frac{kT}{6\pi r \eta} \frac{1}{(1-bv)^2} - \frac{2a}{6\pi r \eta} v \right) \frac{\partial^2 v}{\partial x^2}$$



Pimpinelli et al. *Applied Physics Letters,* 2013

Ziemys et al. *J. Computational Physics*, 2011

Hypothesis & Approach

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Hypothesis

Microgravity will allow to scale-up from Nano to Micro, and to shine light into decoupled nanoscale effects in a tightly controlled experimental setup.

Approach

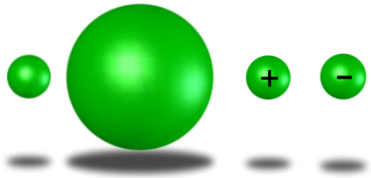
Microscopy analysis of fluorescent microparticles in micro-confinement

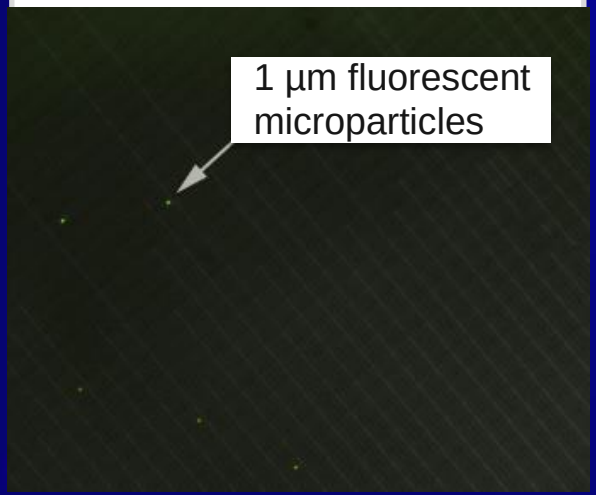
Benefits

- Reduced complexity
- Improved capabilities and analysis
- Greater control of size & shape
- Controlled surface

Micro-nanoparticles

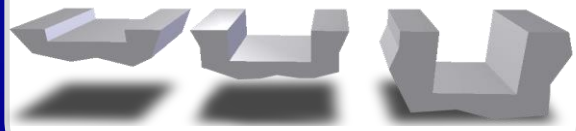
Size (µm): 1, 4

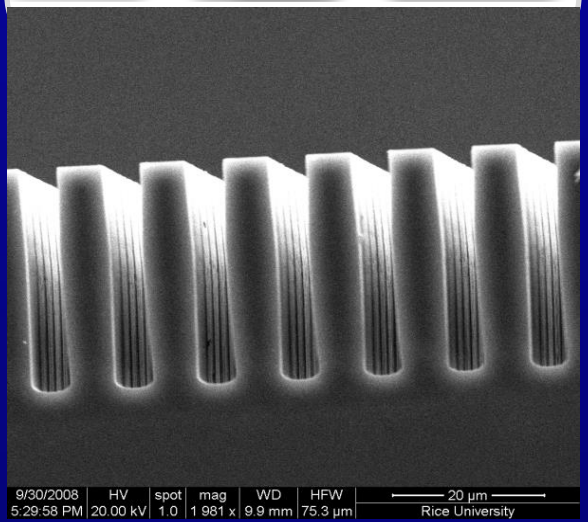


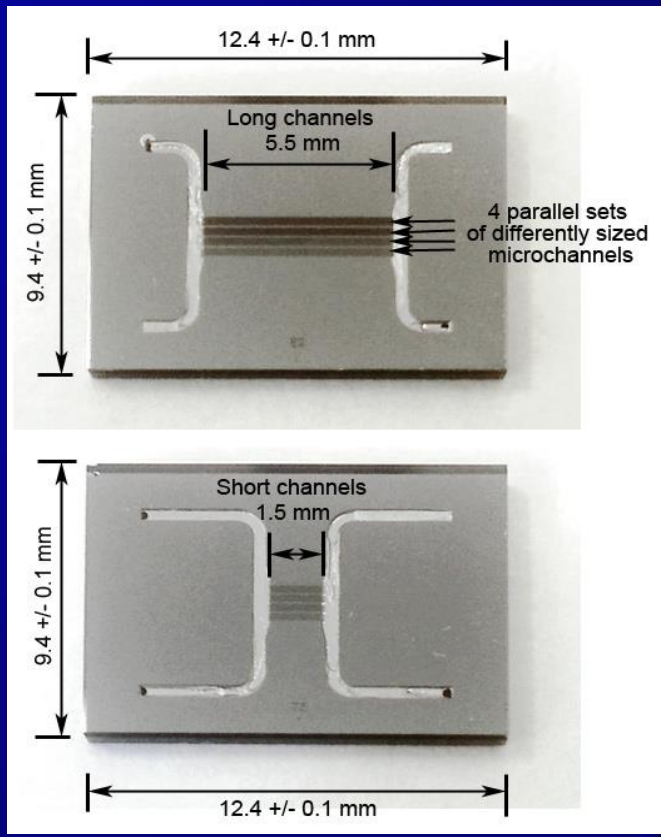


Silicon Microchannel

Depth (µm): 2.5 - 10

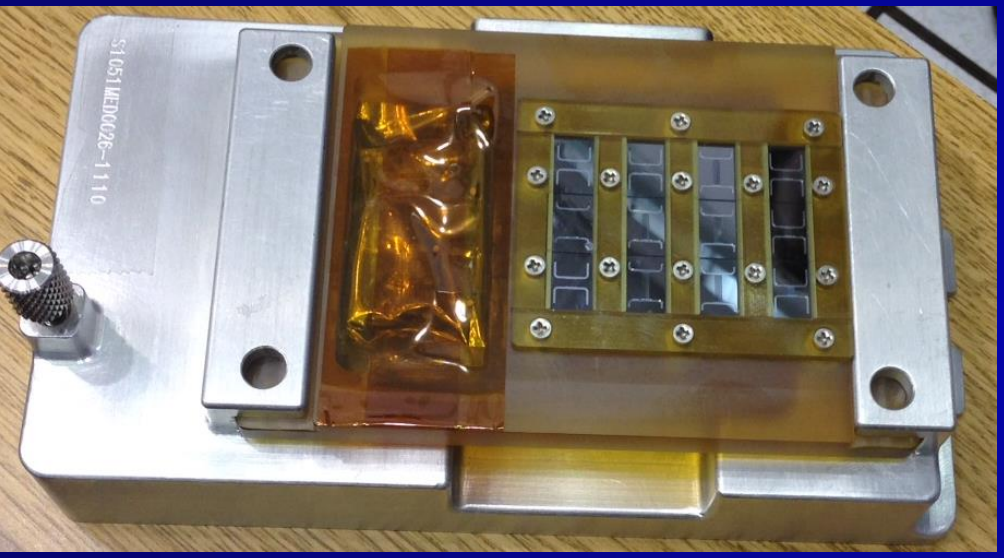




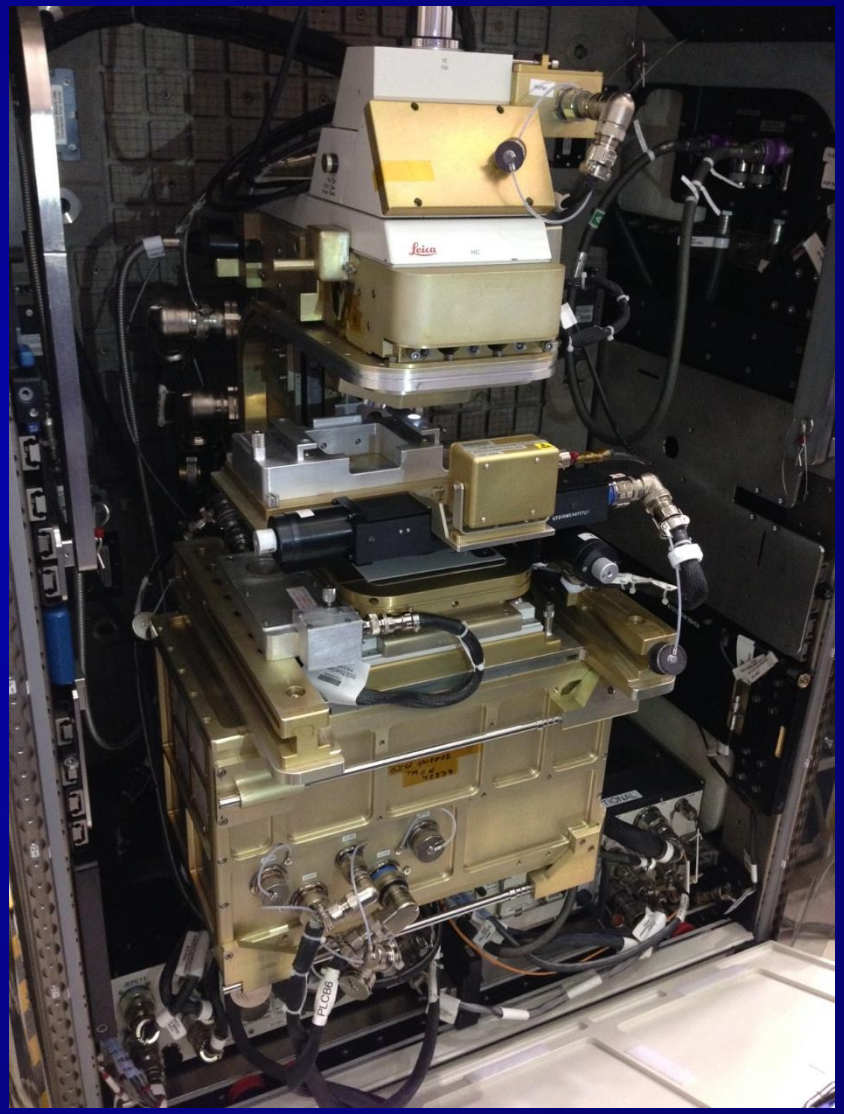


Pre-ISS Flight Testing

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Experimental Setup



LMM replica (Glenn NASA facility)

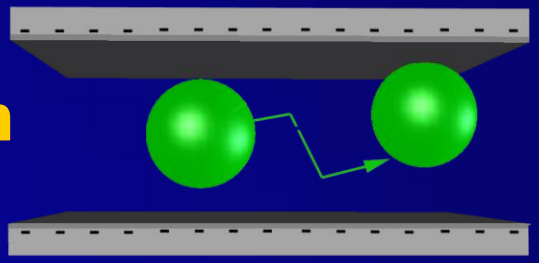
CASIS™

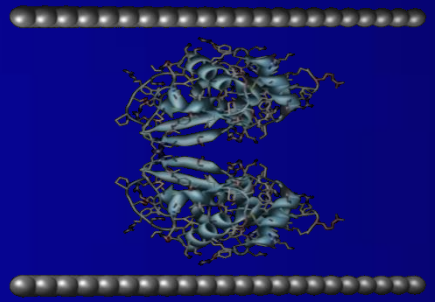
Concluding Remarks

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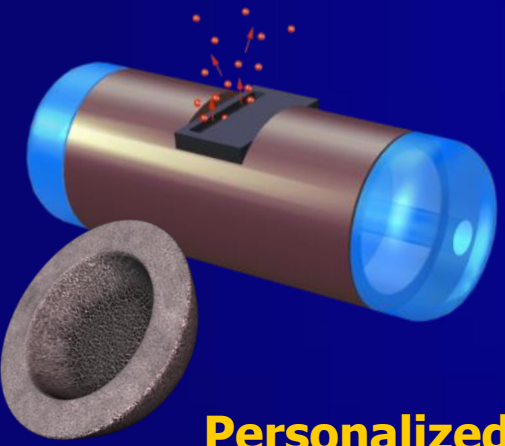


Molecules and nanoparticles on-Earth and in Microgravity





Laws of Nanoscale Mass Transport In Nanostructured Materials



Personalized Therapeutics for Medicine on Earth and in Space, and Military Applications.

New-technologies for Space Exploration

New sieving technologies for Ultraselective Filtration

Acknowledgments

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- Lyle Hood, Ph.D.
- Thomas Geninatti, Ph.D.
- Usha Tekkedath, Ph.D.
- Marco Farina, M.S.
- Jeffrey Schmulen, M.S.
- Carly Figueira, Ph.D.
- Jenaro Huidiboro, Ph.D.



CASIS

- Chad Brinkley
- Kenneth Shields
- John Shubert

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