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Technion - Israel Institute of Technology

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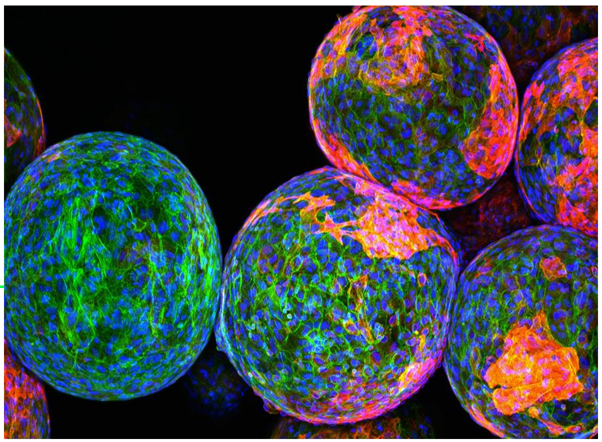
המכון לננוטכנולוגיה ע"ש ראסל ברי
הטכניון-מכון טכנולוגי לישראל

Laboratory for Advanced Functional/Medicinal Polymers and Smart Drug Delivery Technologies



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ISRAEL INSTITUTE OF TECHNOLOGY

Neubauer Asst. Prof. Shady Farah, PhD

TAMC Retreat on: Design, Simulation, Optimization and Fabrication of Medical Implants

, Dan Caesarea hotel, Israel May 10th, 2022

PI & LAB RESEARCH INTERESTS

Shady Farah, PhD

- **Oct 2019, Neubauer Assistant Professor,** The Wolfson Faculty of Chemical Engineering, Haifa, Israel.
- **2014-2019, Post-Doctoral Associate,** Massachusetts Institute of Technology (MIT), at Daniel G. Anderson/Robert S. Langer Lab, Department of Chemical Engineering, the David H. Koch Institute for Integrative Cancer Research at MIT, Boston Children's Hospital/Harvard Medical School, USA.
- **2009-2014 PhD in Medicinal Chemistry,** The Hebrew University of Jerusalem (HUJI), School of Pharmacy; Faculty of Medicine. Supervisor: AJ Domb.
- **2008-2009 MSc in Medicinal Chemistry:** HUJI, School of Pharmacy; Faculty of Medicine, Direct PhD track.
- **2006-2008 B.Sc. in Medicinal Chemistry:** HUJI, School of Pharmacy; Faculty of medicine,

Functional and Medicinal Polymers, 3D Printing of Medical Implants, Localized delivery from Crystals, Controlled Drug Release, Drug Crystals for Long-term Delivery, Smart Materials and Composites for Medical Needs, Cells Encapsulation and "Live Drug Factories" for Chronic Diseases, Tissue Engineering, Functional Polymeric Nanoparticles, Bioactive Surfaces and Crosslinked Polymers, Antimicrobial and Antiviral Polymers, Shape-Memory Polymers, Hydrogels, Personalized Medicine, Polymeric Systems for Cancer-Targeted Delivery. Biodegradable Polymers,

LAB Equipment & Infrastructure

Chemistry Lab

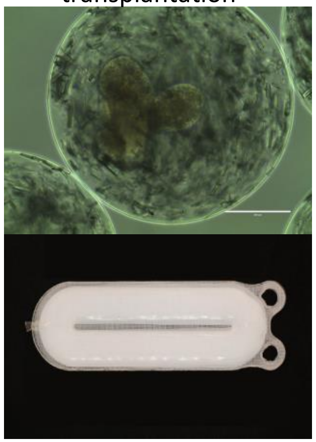
Biology Lab

Medicinal Polymers and Drugs Analysis

3D Printers

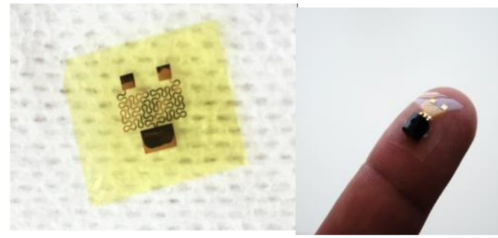
1. Fibrosis & Implants Rejection Problem

1) Cell encapsulation and transplantation

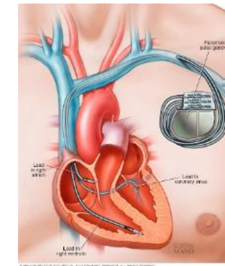


2) Implanted sensors (e.g. CGM)

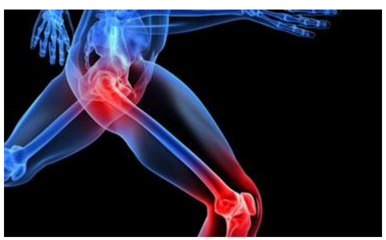
3) Nerve/muscle enervation (STIMs)



4) Any pacing/pacemaker



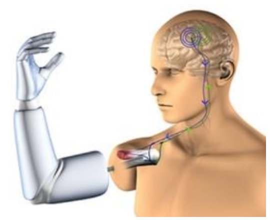
5) Hip/knee replacement



6) Tissue repair/reconstruction

7) Tissue engineering/ regeneration.

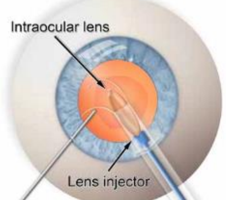
8) Prosthesis and neural interfacing



9) Controlled drug release

10) Vital sign monitoring

11) Intraocular lens replacement

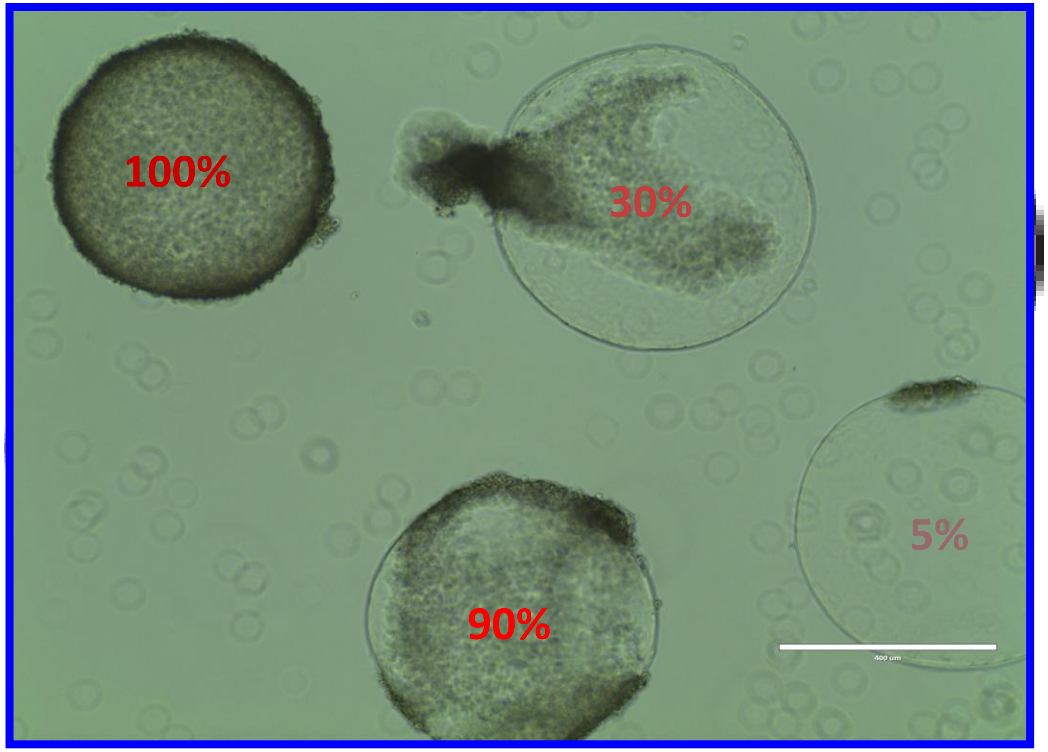


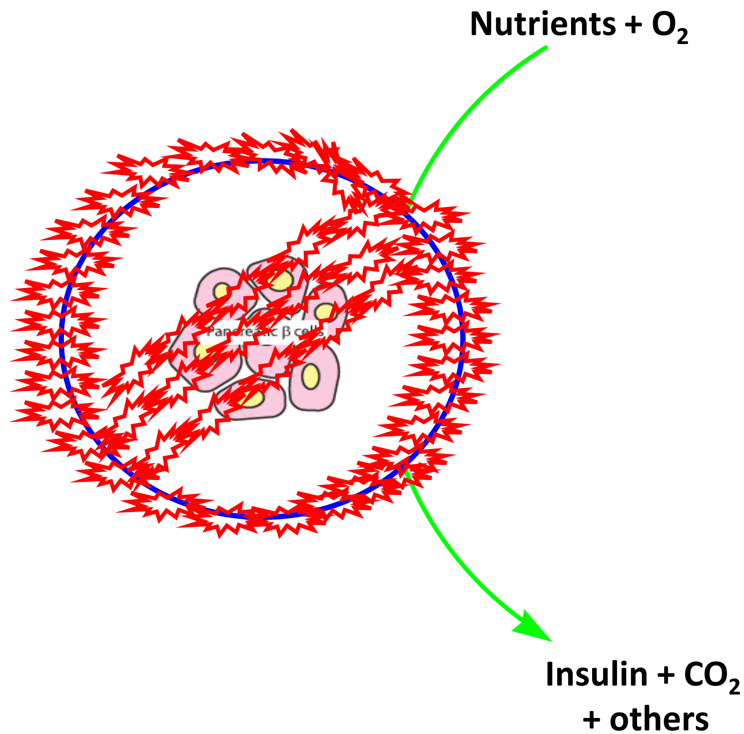
12) Vascular replacement

13) Cosmetic implants

Immunologic Basis of Foreign Body Response

Alginate Capsules for Islets Encapsulation for T1D Treatment





Implant Failure

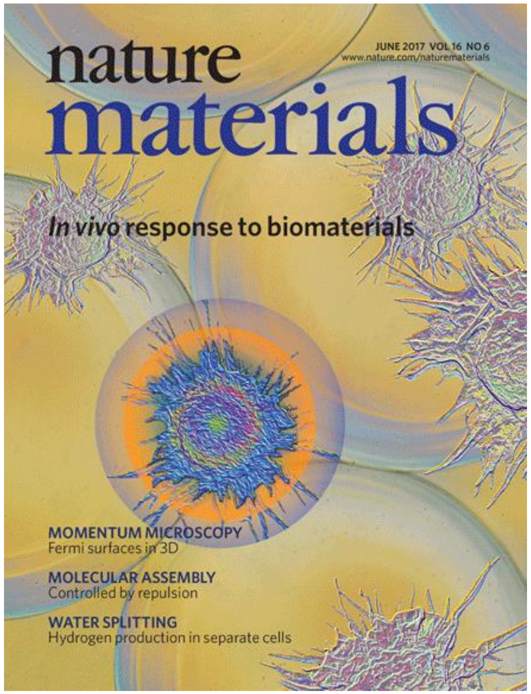
Drug Delivery from Crystals

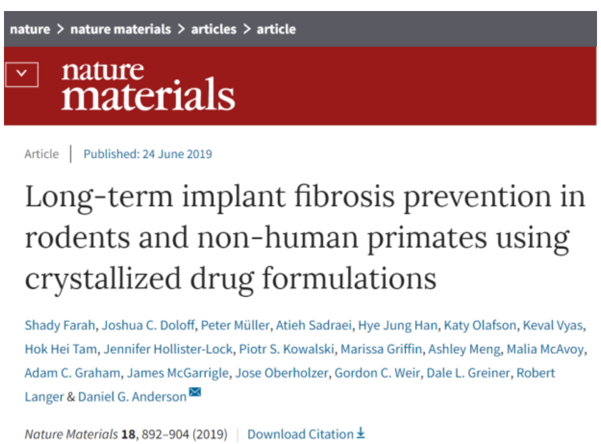
Polymers Functionalization and Chemical Modifications

Biomedical Implant → Foreign Body Reaction (FBR) → **Fibrosis problem!**

Grainger, *Nat. Biotech*. 2013

1.1 Preventing Fibrosis via Non-Polymeric Approach (Drug Delivery from Crystals)





nature > nature materials > articles > article

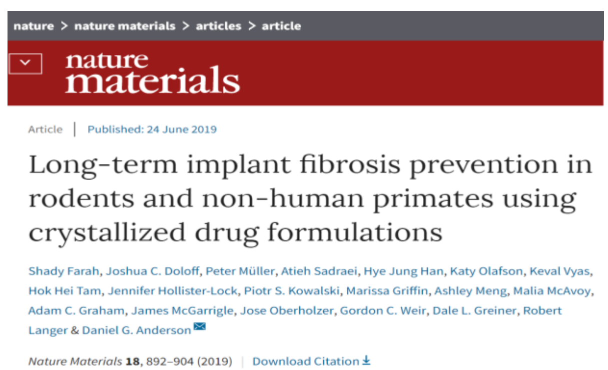
nature materials

Article | Published: 24 June 2019

Long-term implant fibrosis prevention in rodents and non-human primates using crystallized drug formulations

Shady Farah, Joshua C. Doloff, Peter Müller, Atieh Sadraei, Hye Jung Han, Katy Olafson, Keval Vyas, Hok Hei Tam, Jennifer Hollister-Lock, Piotr S. Kowalski, Marissa Griffin, Ashley Meng, Malia McAvoy, Adam C. Graham, James McGarrigle, Jose Oberholzer, Gordon C. Weir, Dale L. Greiner, Robert Langer & Daniel G. Anderson

Nature Materials **18**, 892–904 (2019) | Download Citation



nature > nature materials > articles > article

nature materials

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Bedazzled biomaterials: Crystallized drugs prevent implant fibrosis

Jessica D. Weaver

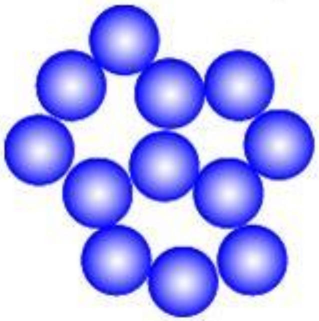
See all authors and affiliations

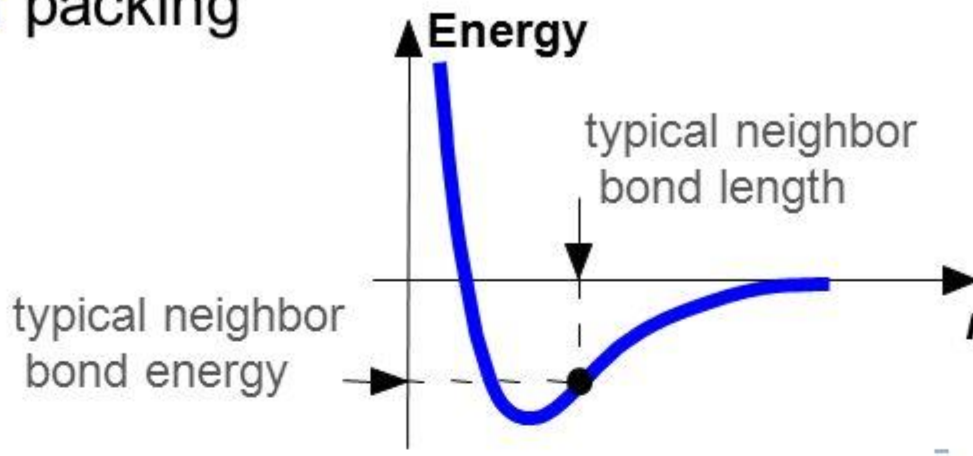
Science Translational Medicine 24 Jul 2019:
Vol. 11, Issue 502, eaay3579
DOI: 10.1126/scitranslmed.aay3579

Article Info & Metrics eLetters

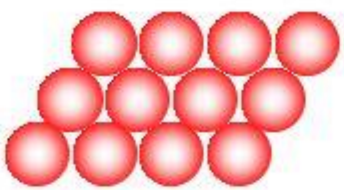
Energy and Packing

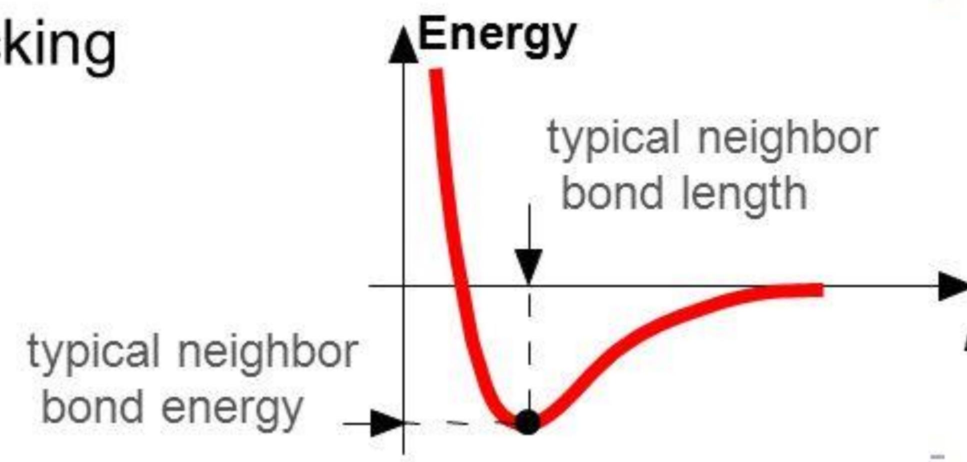
- Non dense, random packing





- Dense, ordered packing





Dense, ordered packed structures tend to have lower energies.

Drug Crystals/Crystallization

Polymer-free Release system

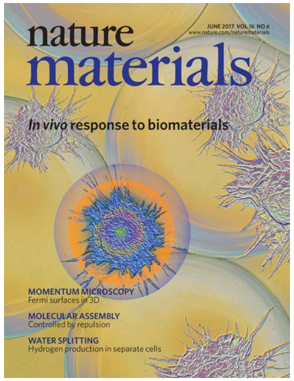
– Crystals low dissolution rate is utilized for the controlled release of the drug.

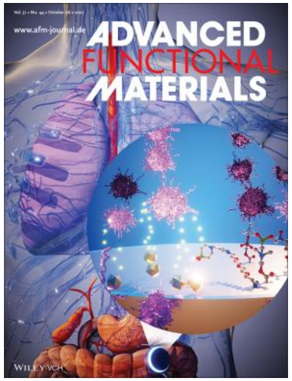
– Drug chemical and physical stability is enhanced.

Advanced Functional Materials, (2021), 44, 2170329
Polymers for Advanced Technologies (2022)

<u>Selected Publications:</u>

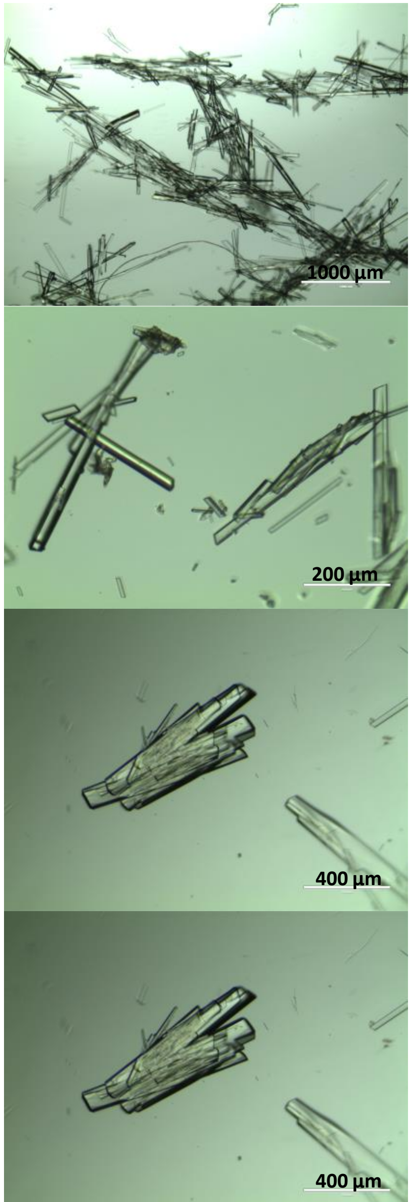
Nature Materials | VOL 18 | AUGUST (2019) | 892–904
ACS Appl. Mater. Interfaces (2018) 10109010-9022
Journal of Controlled Release 271 (2018) 107–117
Journal of Controlled Release 168 (2013) 70–76
International Journal of Pharmaceutics 445 (2013) 20–28
Pharmaceutical Research (2013), 30, 7, 1735–1748
Langmuir (2012) 28 15 6207-6210



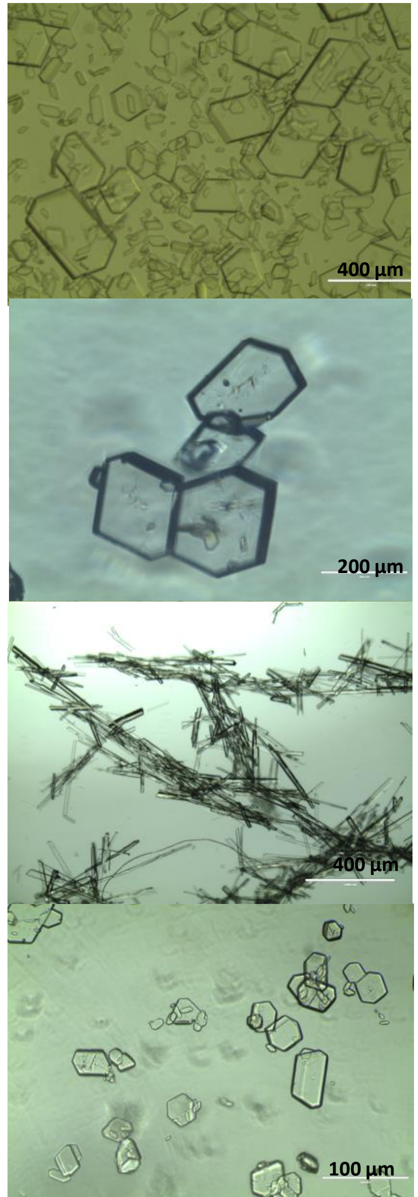


Crystallization Techniques

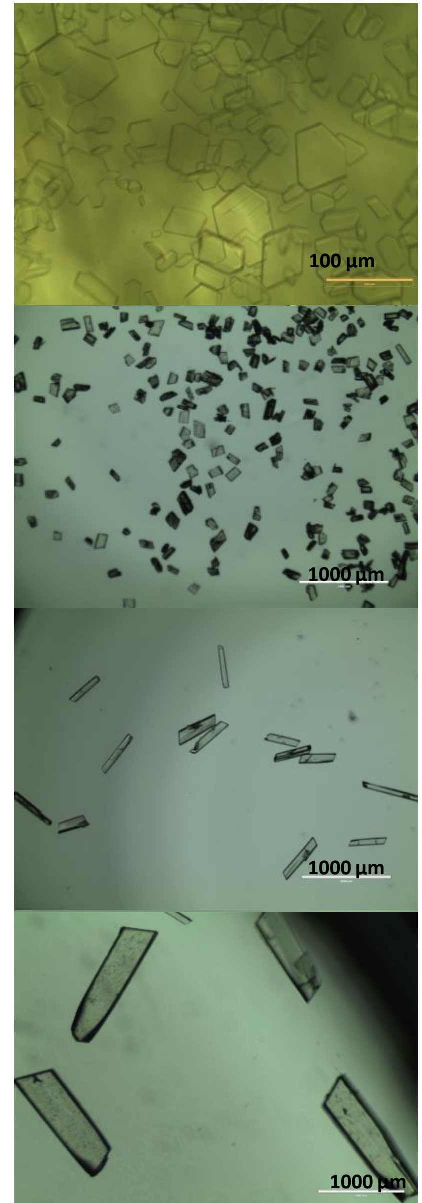
Method I – Solvent Evaporation



Method II – Temperature induced crystallization



Method III – Solvent/Anti-solvent mixture



Method III - Crystal Size: 30 µm

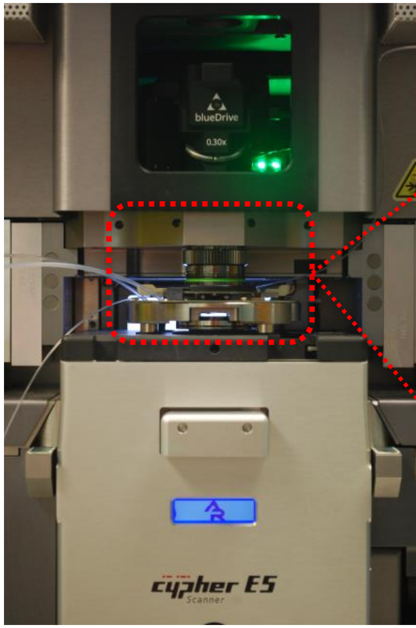
100 µm

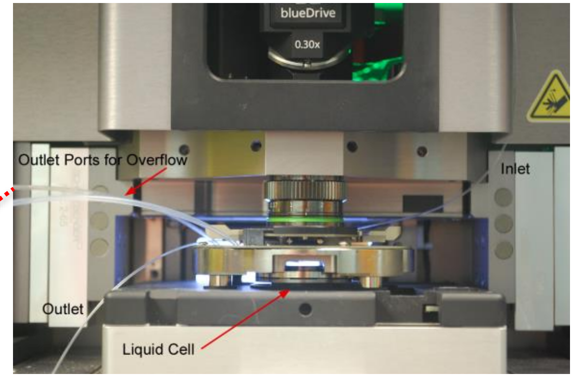
500 µm

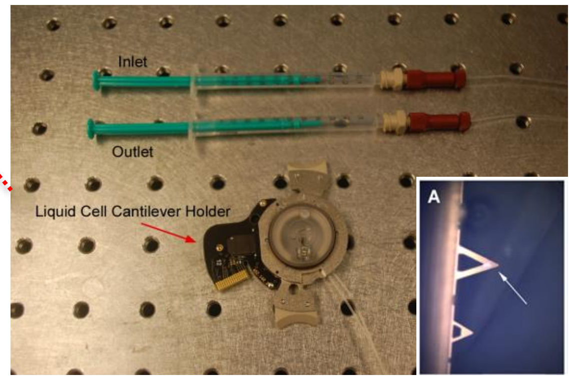
1000 µm

S. Farah et al. Nature Materials 2019 Farah S. et al., Patent (PCT) 2017

Mechanism of Release- in situ AFM



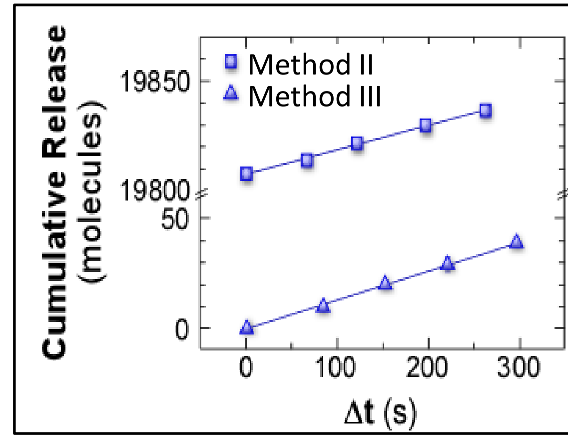


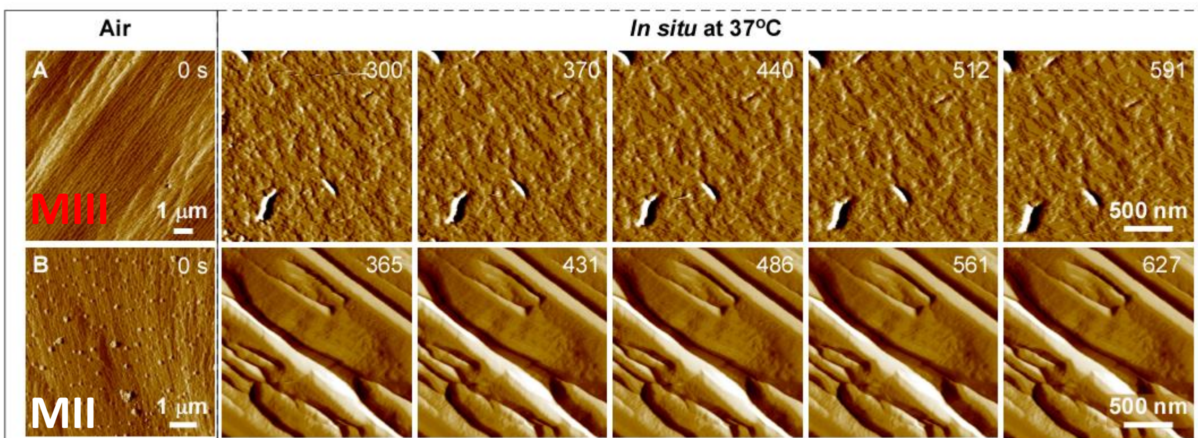


$$v = \frac{\Delta x}{\Delta t} = \frac{x_2 - x_1}{t_2 - t_1} = \left[\frac{nm}{s}\right]$$

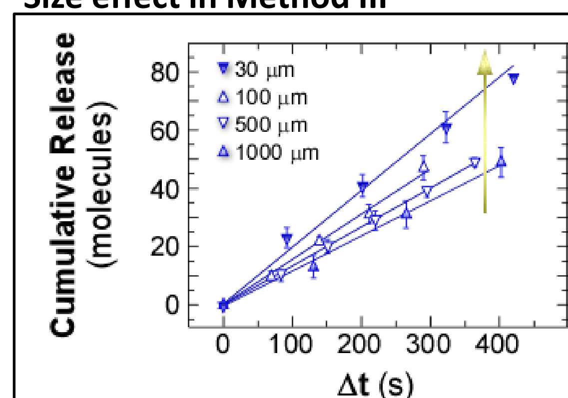
$$n \propto l \int v \, dt$$

$$\frac{dn}{dt} = \rho v l = \left(\frac{molecules}{nm2}\right)\left(\frac{nm}{s}\right)(nm)$$



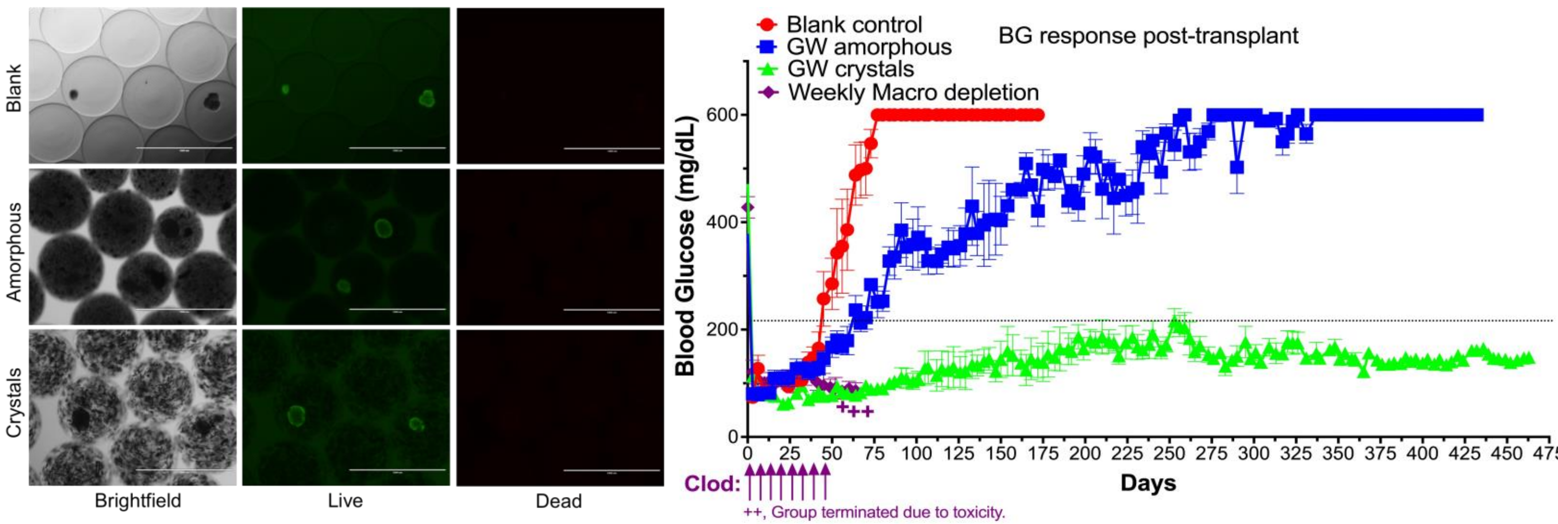


Size effect in Method III

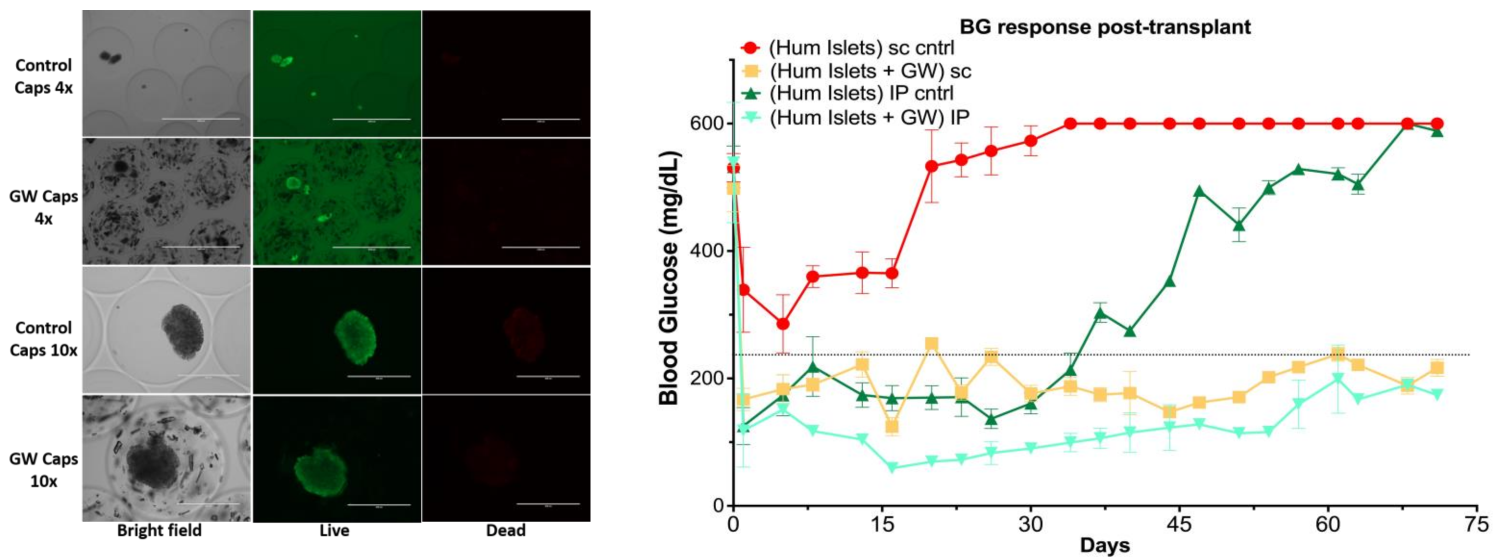


S. Farah et al. Nature Materials 2019 Farah S. et al., Patent (PCT) 2017 (With University of Houston, Tx)

Application 1- Cells Encapsulation (Rat β-Cells in Diabetic Mice-STZ BL6)

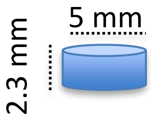


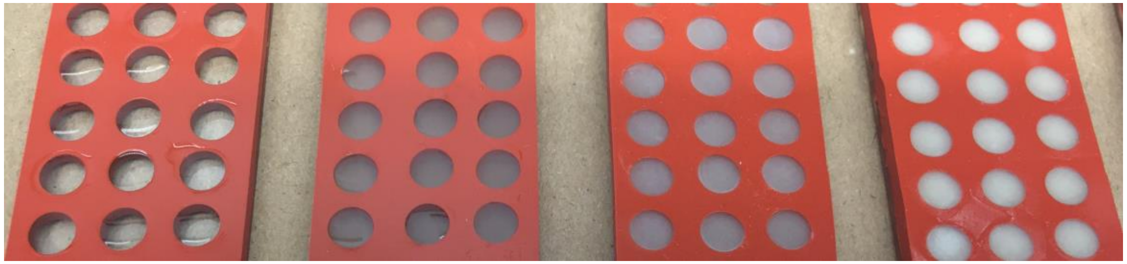
Application 1- Cells Encapsulation (Human β-Cells in Diabetic Mice-STZ BL6)

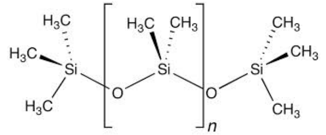


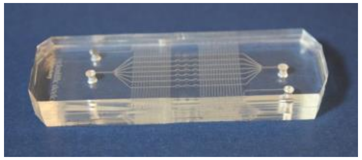
Application 2- Encapsulate crystals in materials for devices fabrication-PDMS

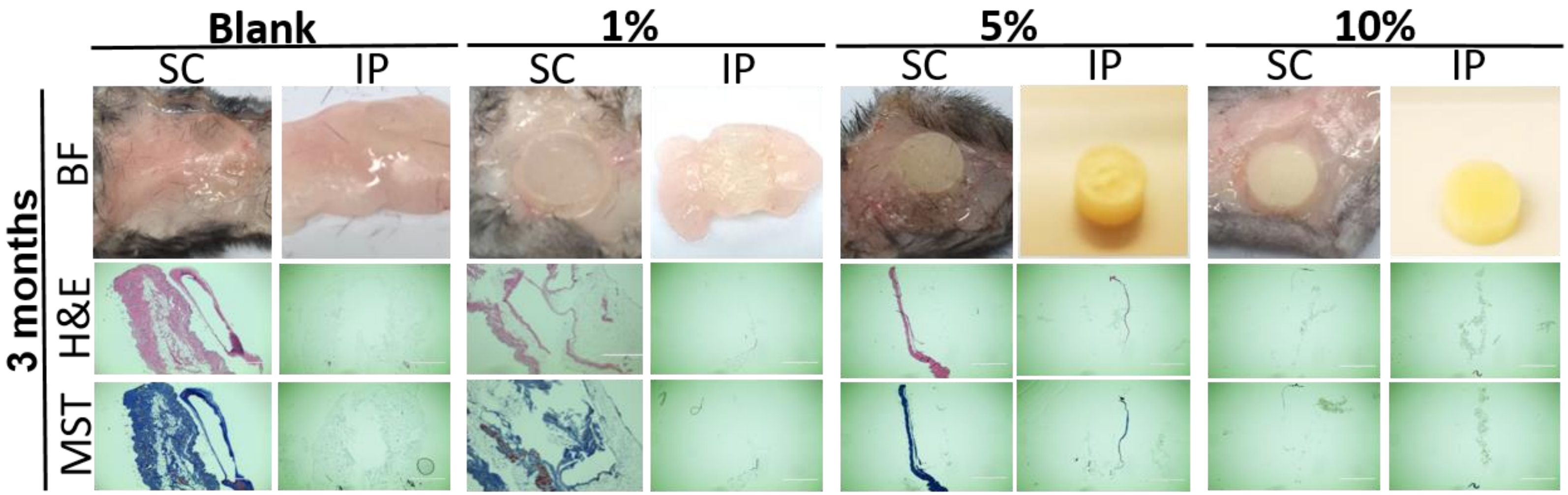
(C57BL/6 mice)

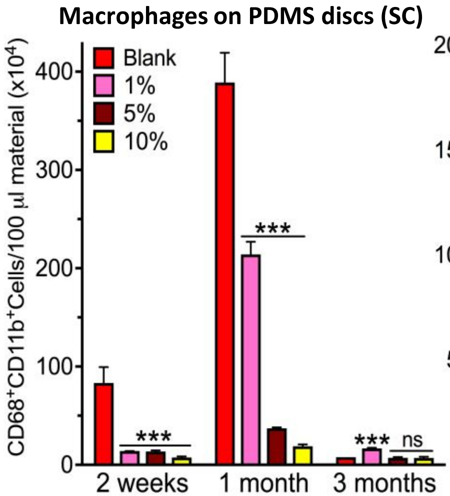


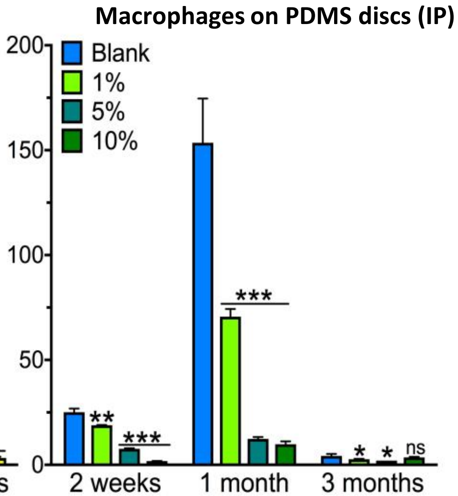


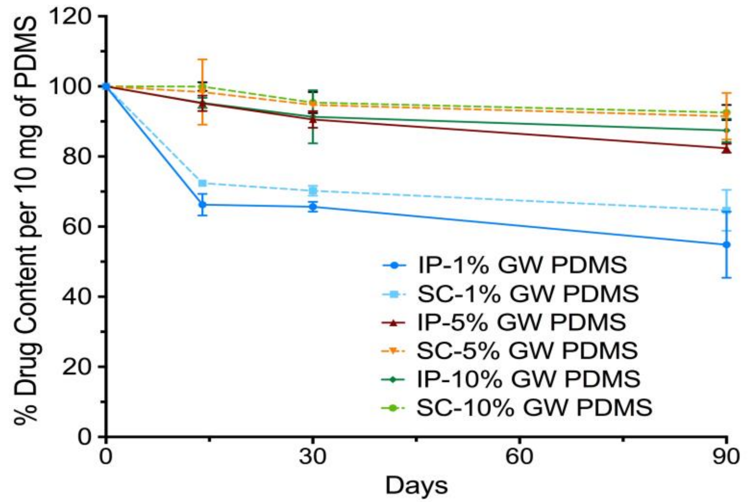








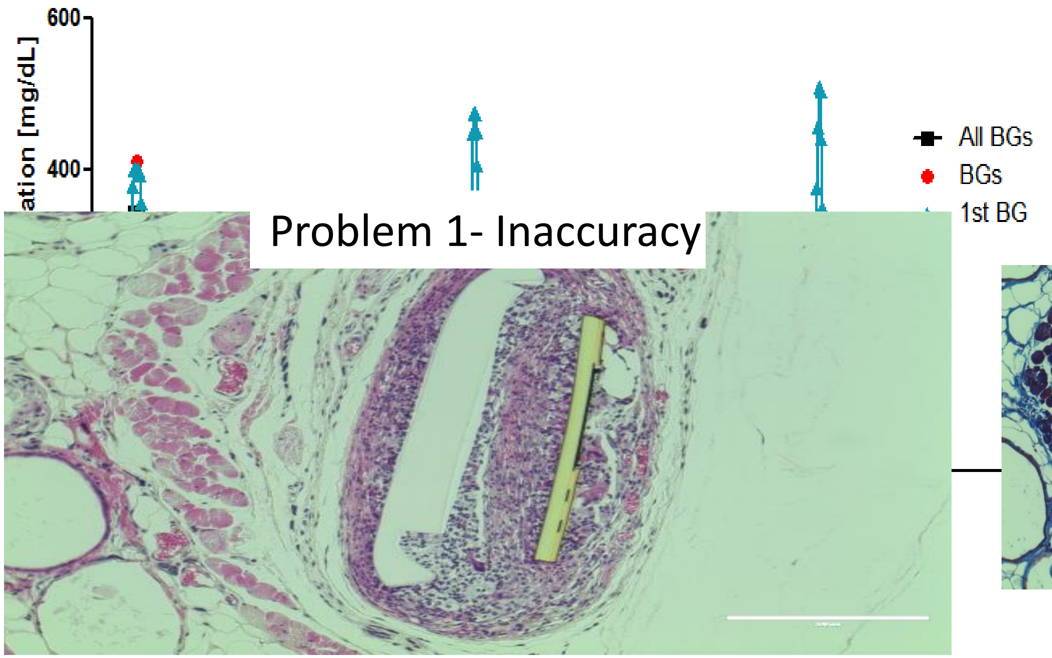




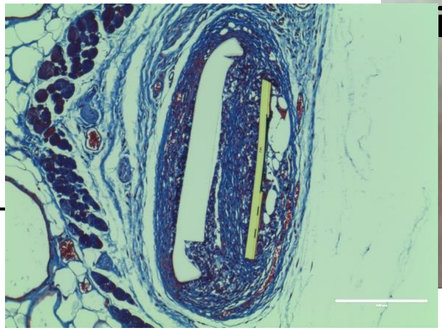
Application 3- Multi-components devices- CGM

Coat

Mice model)



Problem 1- Inaccuracy



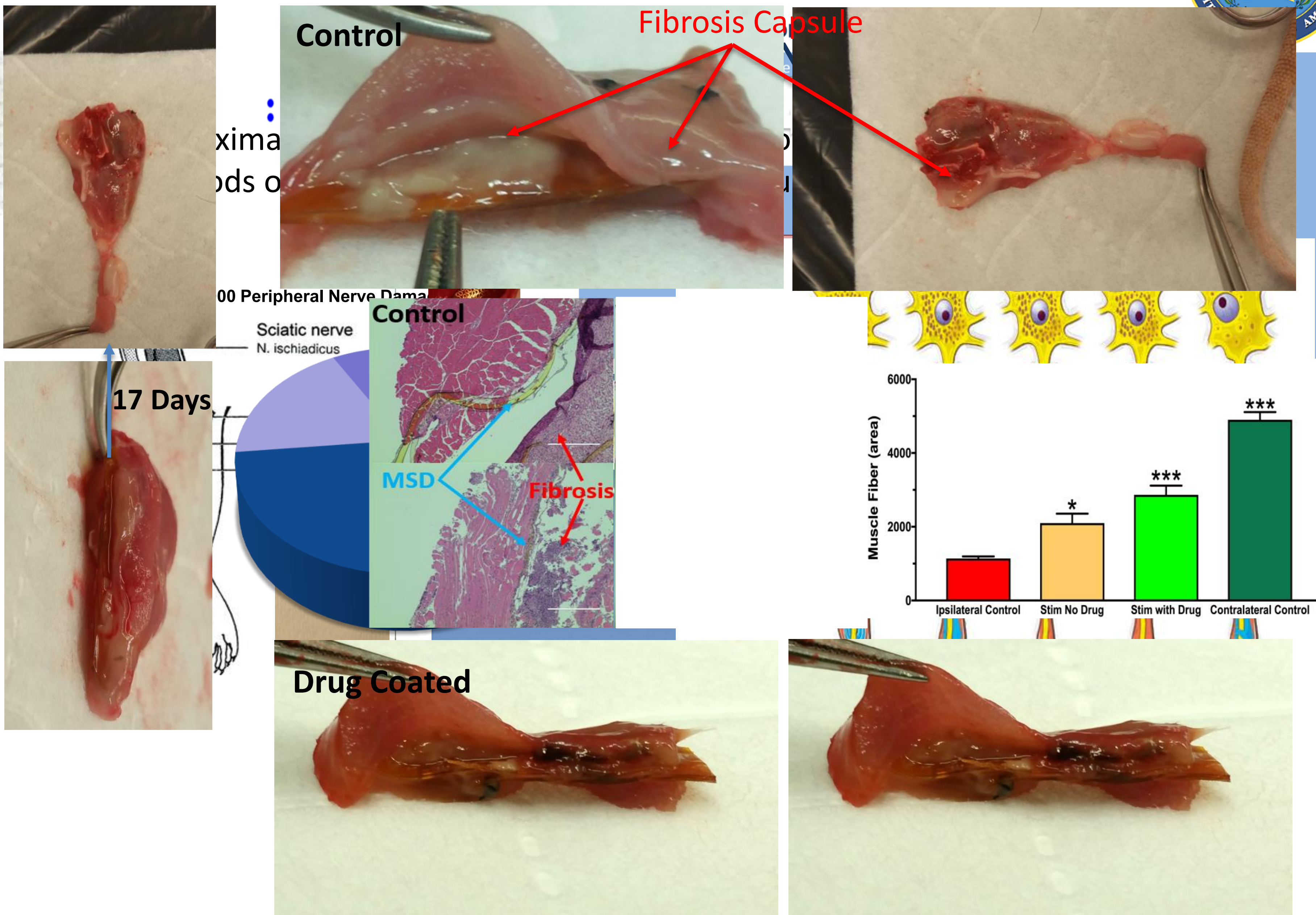
Problem 2- Short term Fibrosis

H&E

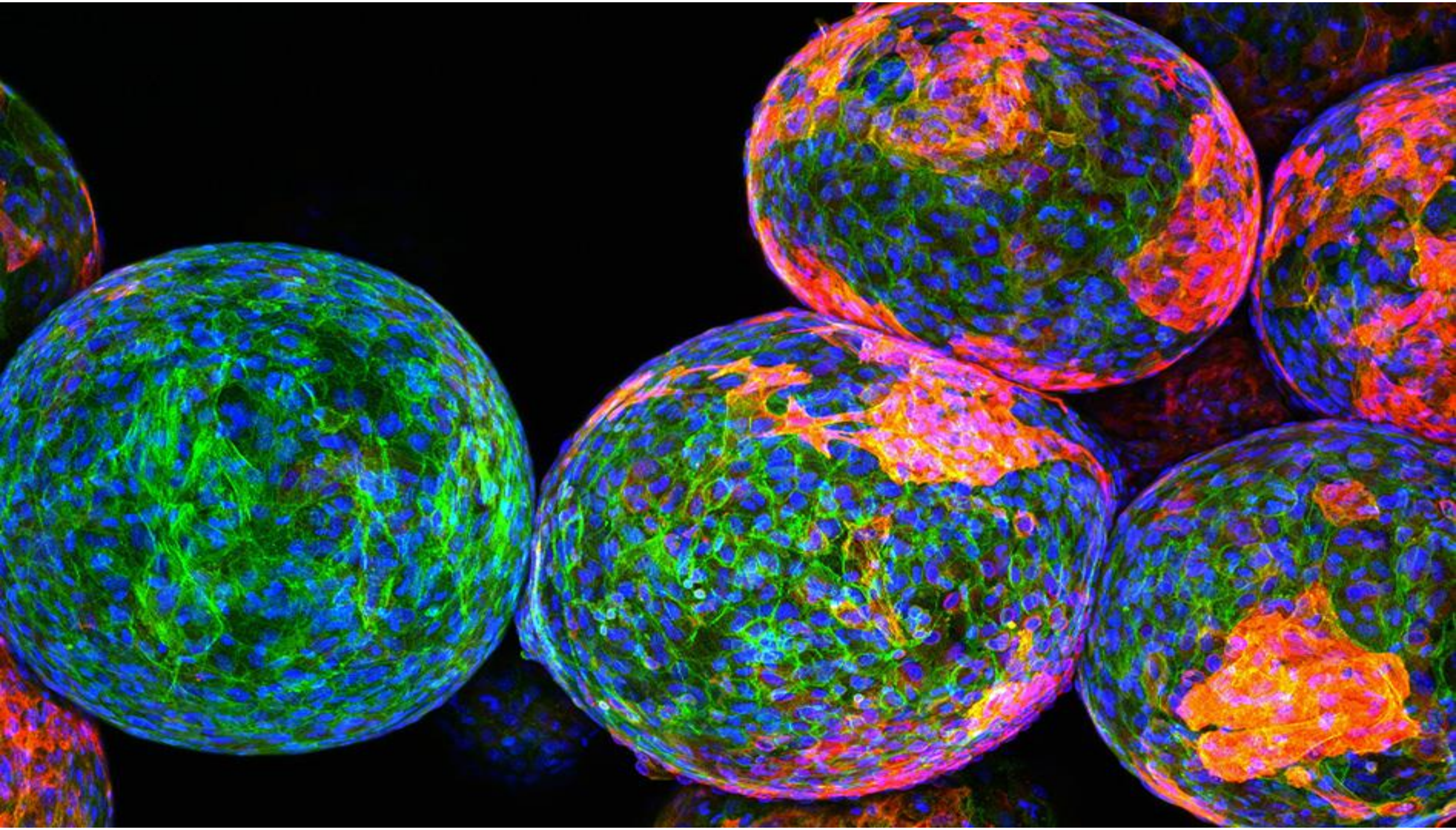
Trichrome

Application 4- Multi-components devices – Muscle stimulating device (MSD)

Mimic neuromuscular stimulation during long-term denervation→ Reduce Muscle atrophy



1.2. Antifibrotic Polymers – Cells Encapsulation

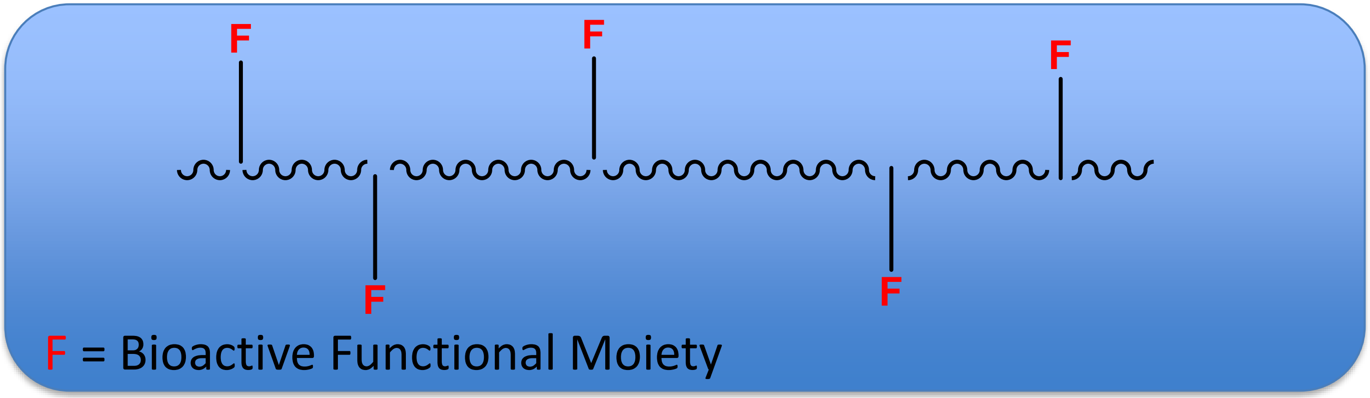


Massachusetts Institute of Technology

ChemE

KOCH INSTITUTE for Integrative Cancer Research at MIT

Bioactive Functionalized Polymers- Medicinal Polymers



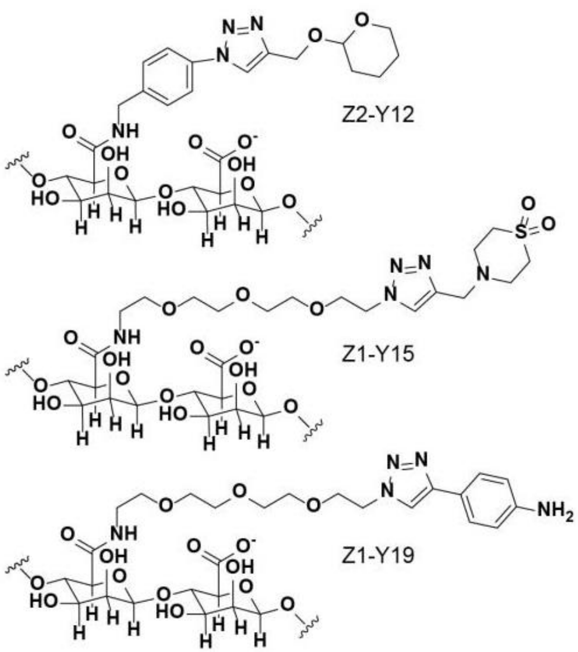
F = Requirements:

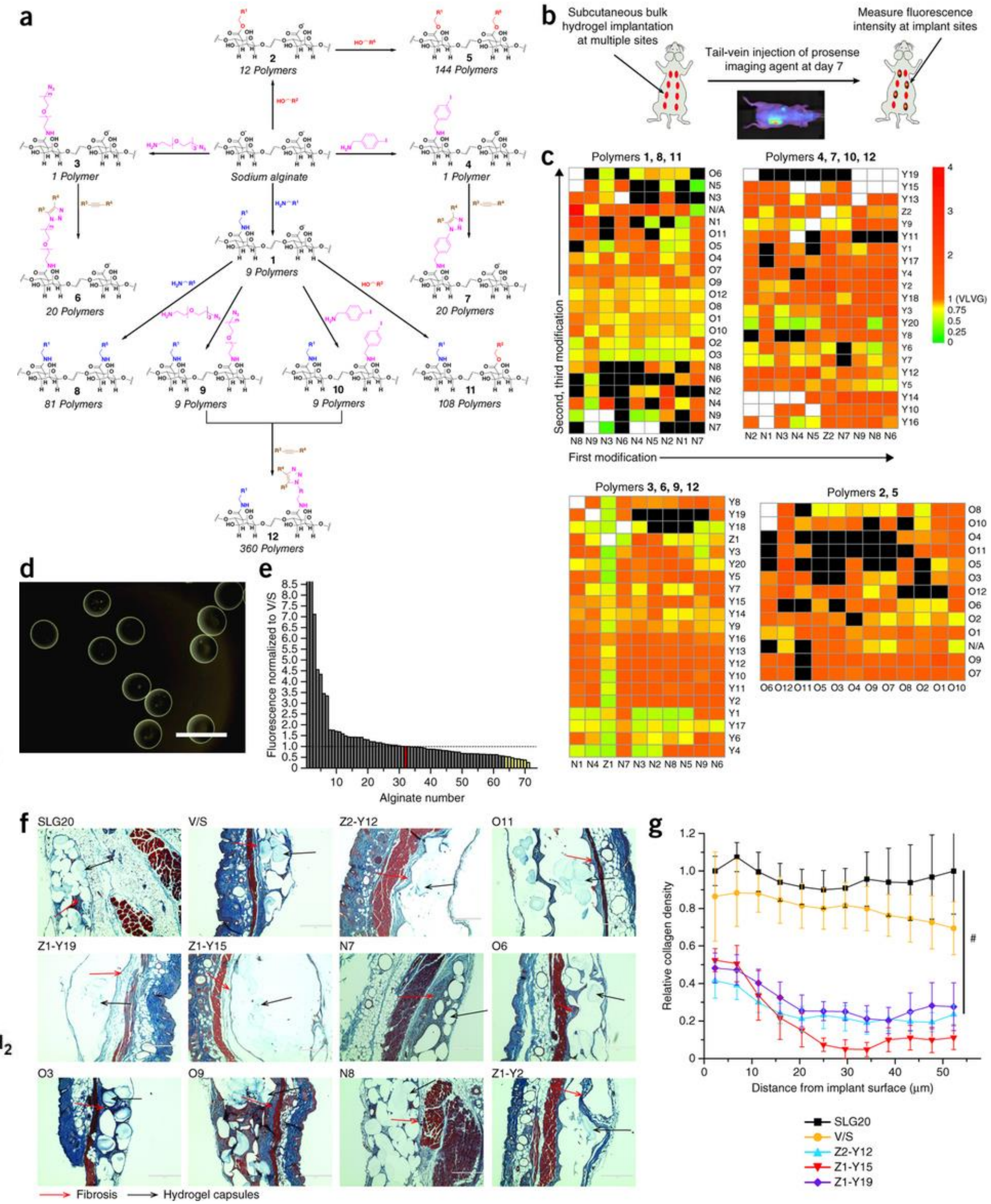
- Bioactivity
- Stability and long term function (?)
- Non/low-toxicity and Biocompatibility
- Specificity

Antifibrotic Polymers

Chemical Modifications and Polymers for Reducing FBR

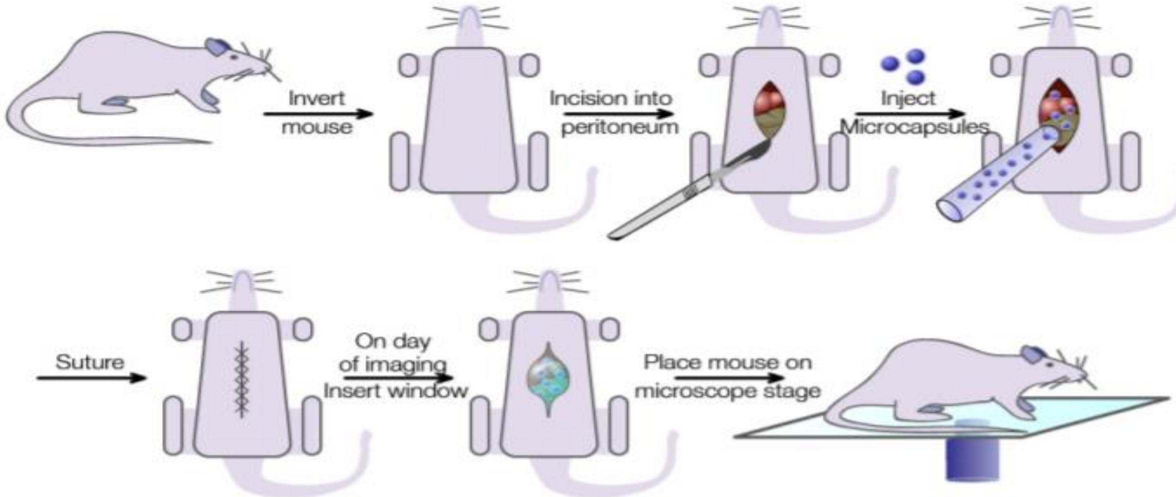
Click Chemistry





Arturo Vegas et al. Nature Biotechnology 2016
Arturo Vegas et al. Nature Medicine 2016

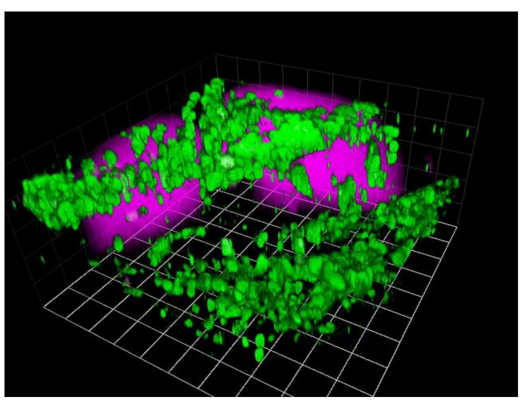
Live Imaging: Biomaterial-Immune Reaction



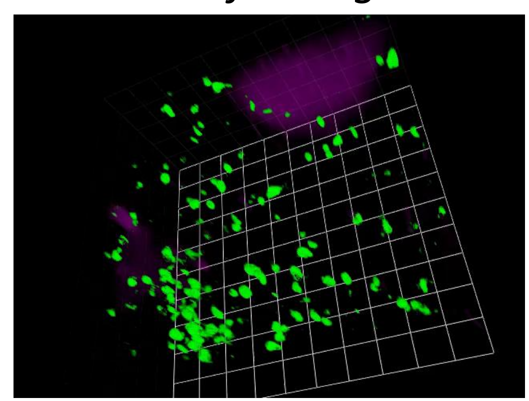
Supplemental Figure S14. Preparation of mice for intravital imaging. The flow of processes involved in preparing mice for implantation with alginate hydrogel spheres, loaded with quantum dots, for *in vivo* intravital fluorescence imaging of macrophage recruitment around and onto implanted spheres.

Nature Materials **volume14**, pages643–651 (2015)

Plain Alginate



Modified Alginate



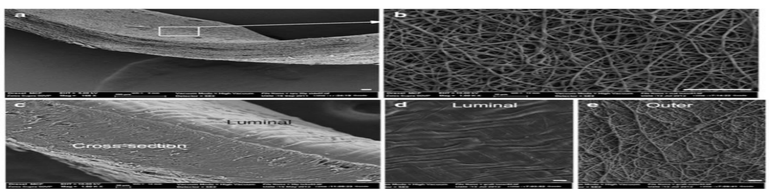
Arturo Vegas et al. Nature Biotechnology 2016

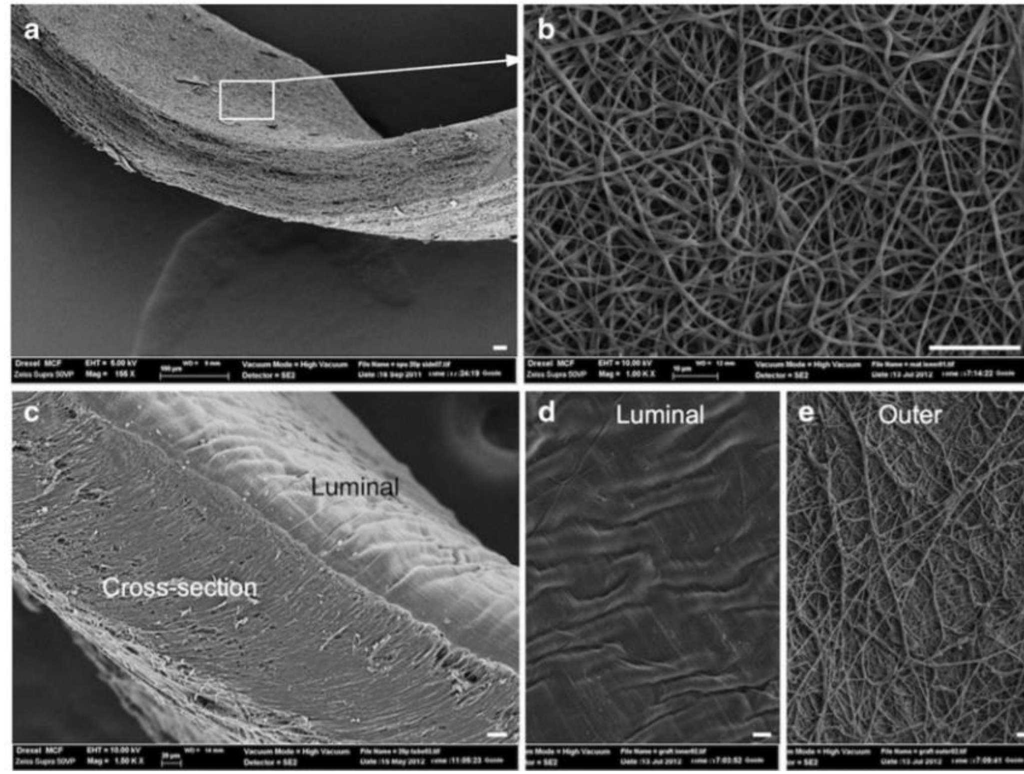
3. Antiproliferative Surfaces in Implanted Biomedical Devices

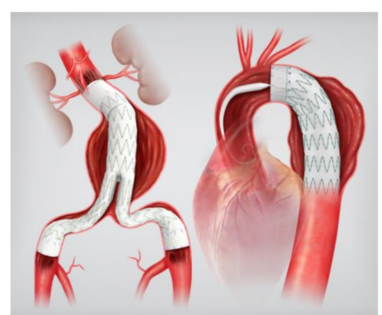
3.1 Drug Eluting Vascular Grafts

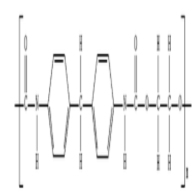
Purpose: Developing rapamycin-eluting electrospun polyurethane (PU) vascular grafts suppress local smooth muscle cell (SMC) proliferation.

Hybrid PU Graft: Bi-Layered Graft









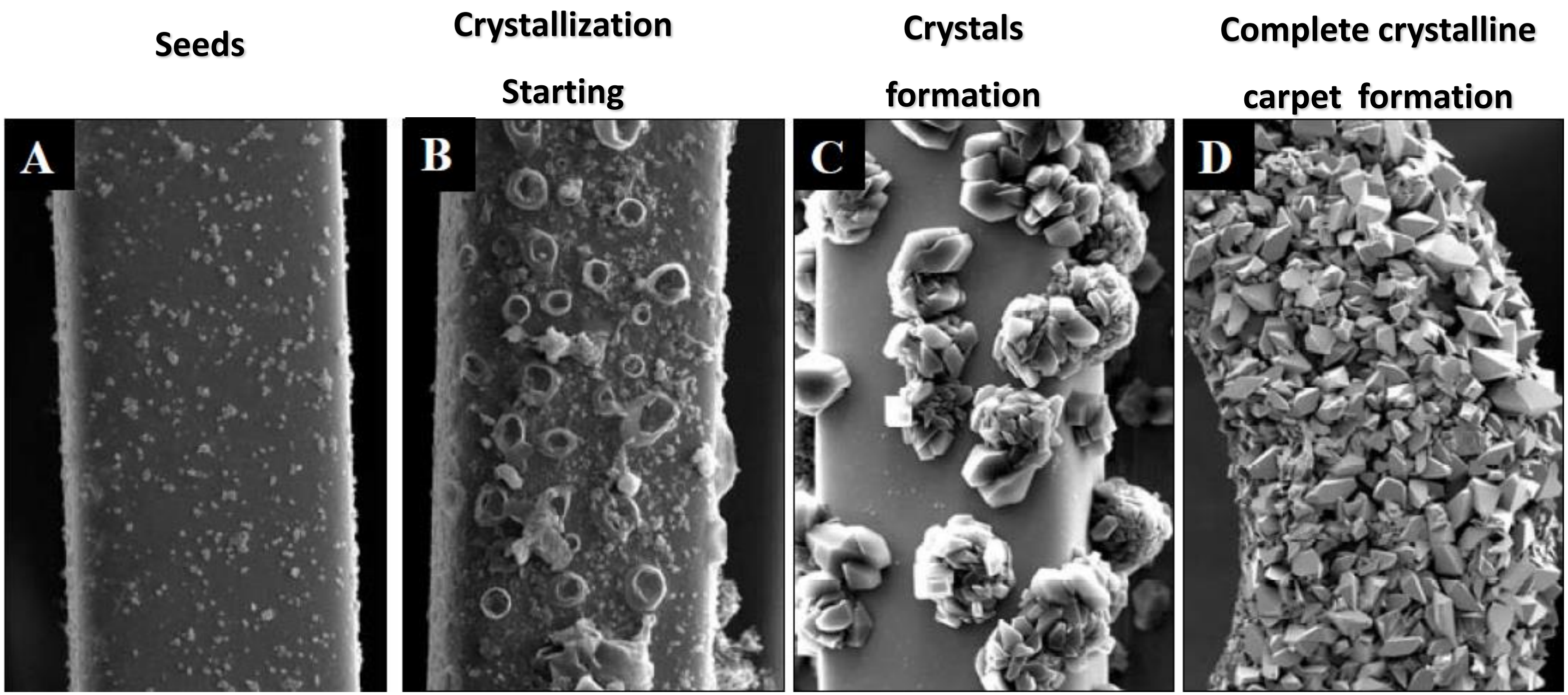
In collaboration with
Prof. Peter I.Lelkes

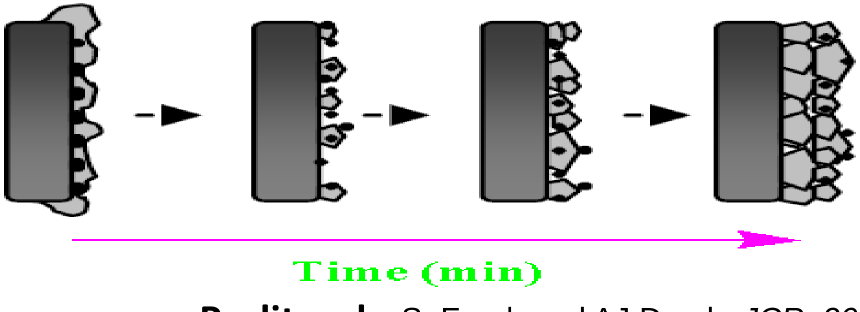
Jingjia Han*, S. Farah*, *Pharm. Res.* 2013, 30,1735–1748.
Jingjia Han*, S. Farah*, *Cardiovascular Pathology,* 2013, 22, e52.

3.2. Medical Devices- Stents- Coatings Surface Crystallization Proceeding:

kinetics of the drug load process

Crystallization: 0 Sec **30 Sec** **3 min** **10 min**



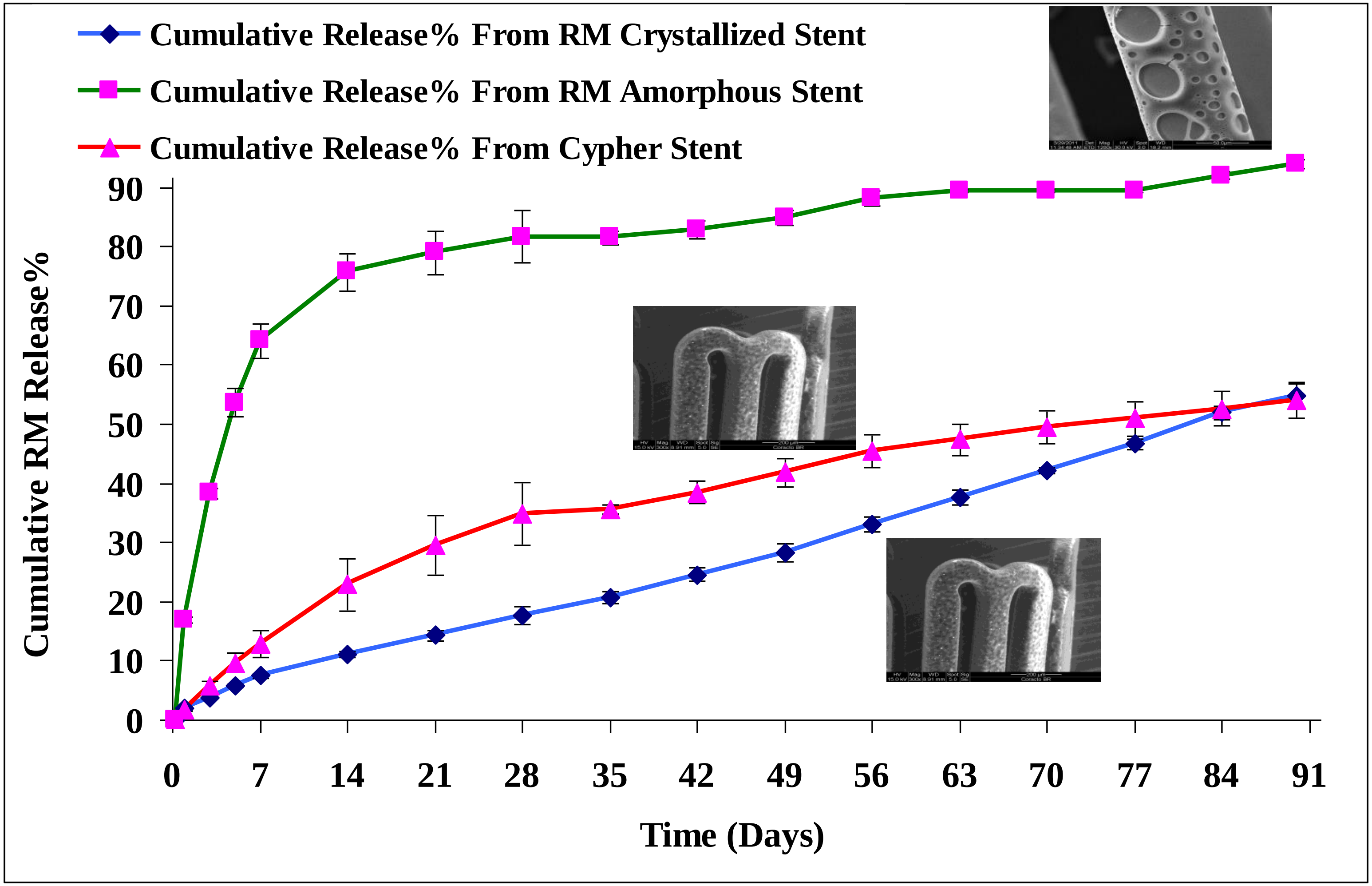


S. Farah et al., *Int. J. Pharm*. 2013, 445, 20–28.
W. Khan* and S. Farah* et al., *JCR*, 2013. 168, 70-76.

Paclitaxel S. Farah and AJ Domb, *JCR, 2018*, 271, 107-117.
Tacrolimus S. Farah et al

Comparison Rapamycin Release in PBS for 90Days:

Cypher (18mm-150µg), Crys and Amorph (15mm-100µg)



S. Farah et al., *Int. J. Pharm*. 2013, 445, 20–28.

W. Khan* and S. Farah* et al., *JCR*, 2013. 168, 70-76.

Paclitaxel S. Farah and AJ Domb, *JCR*, *2018*, 271, 107-117.

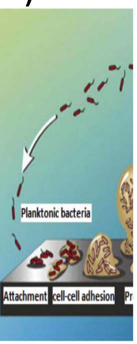
Tacrolimus S. Farah et al

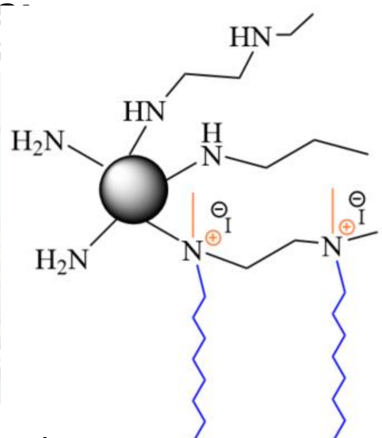
4. Biomedical implants with Antimicrobial Non-Releasing surfaces:

Bacteria Surface Growth and Biofilm Formation

Model

1) Dent





1% w/w

QA-PEI NPs

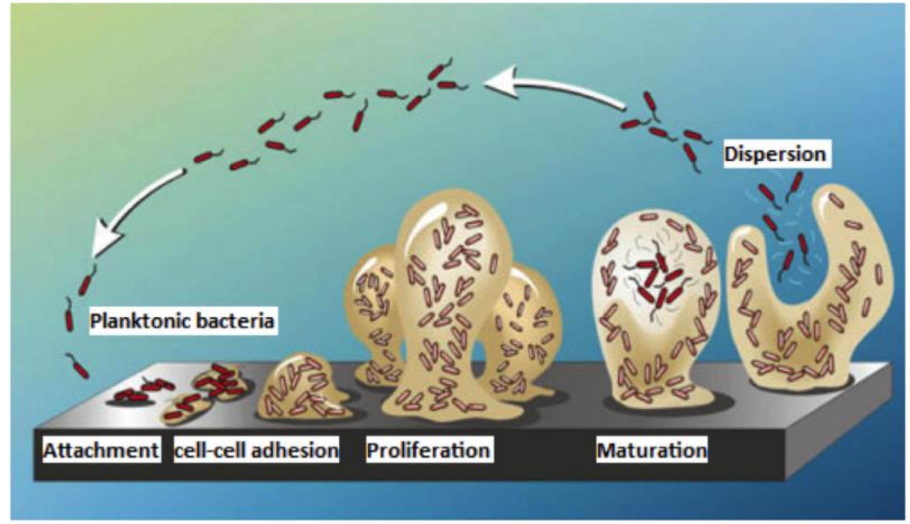
100-150 nm

2) Static Water Purifications

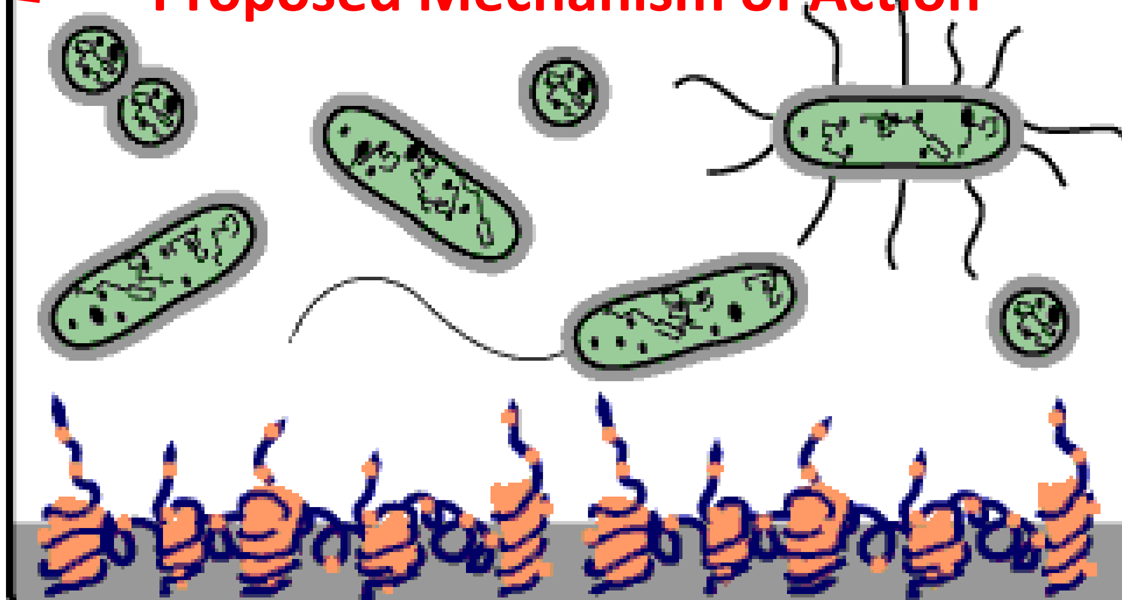
5% w/w

3) Recurrent bacterial peritonitis (Catheters induced)

5% w/w

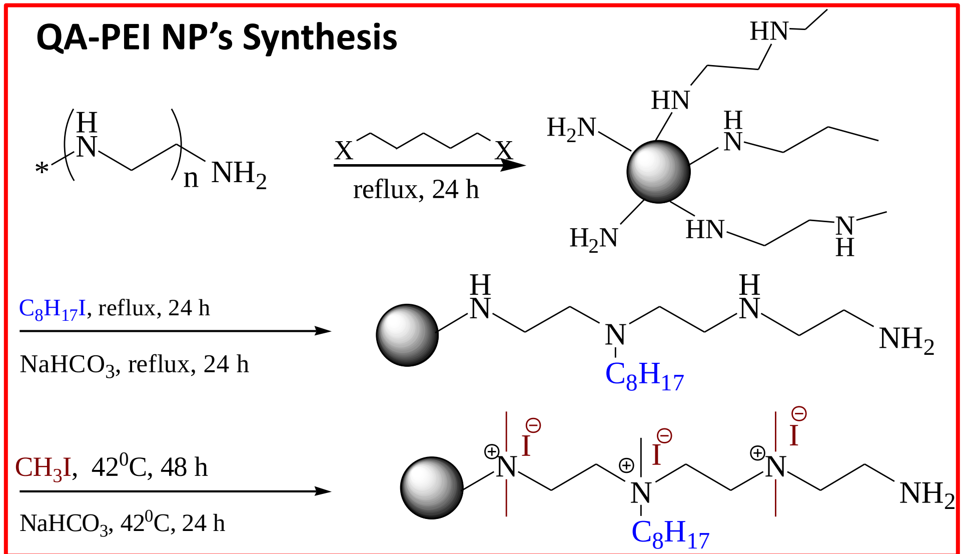


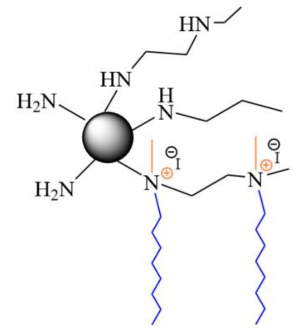
Proposed Mechanism of Action



Antimicrobial Non-Releasing surfaces: **Quaternary ammonium - antimicrobial polymers**

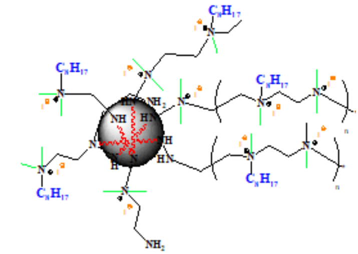
QA-PEI NP's Synthesis





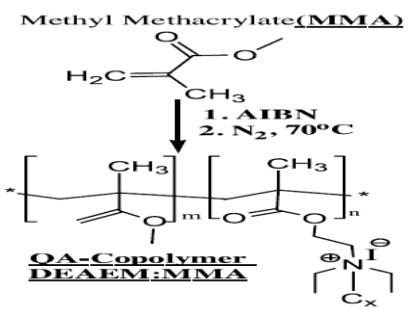
QA-PEI

S. Farah et al. *Polym . Adv .Technol 2013, 24, 452-446.*



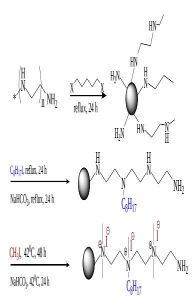
30:70 (C18:C8) QA-PEI

S. Farah et al. *Colloids Surf. B Biointerfaces 2015, 128, 614-619.*



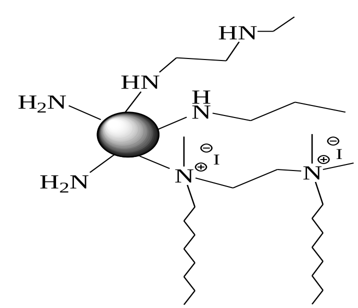
S-QA-PEI

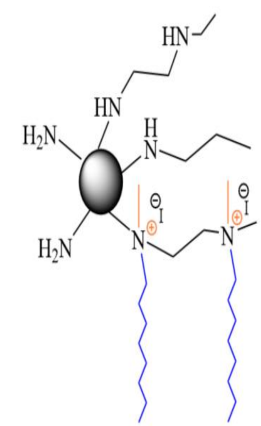
S. Farah et al. *Polym. Adv. Technol. 2014, 25 689–692*



QA-PVP

A Ortega, S Farah et al., *IET nanobiotechnology*, 2015, 9, 342-348





QA-DEAEM

S. Farah et al. *Colloids Surf. B Biointerfaces 2015, 128, 608-613.*

5. 3D Printing of implants and New Synthesized

Three-dimensional printing for new biodegradable polymers after modification with amino acid or saccharide. When the polymers were exposed to ultraviolet light UV, they undergo a polymerization process and turn from a liquid to a solid.

- In our lab we have two kind of 3d printers :

Asiga Max x (Dlp)

Resolution:
27µm

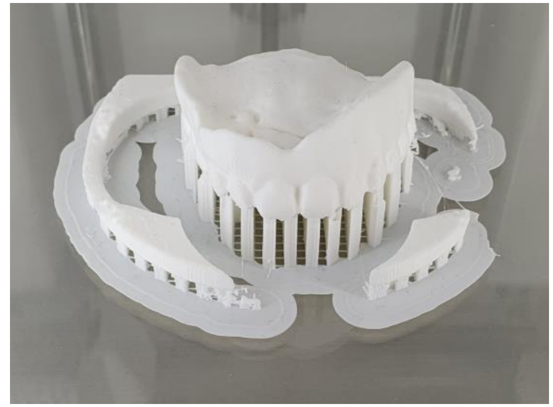
Ultimaker (FDM)

Resolution:
20µm

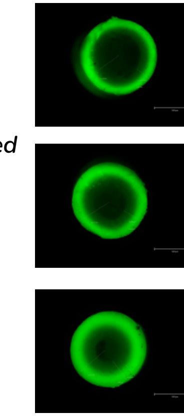
DLP stands for **digital light processing**, and is a type of **vat polymerization**. Vat polymerization 3D printing technologies make use of a (liquid) photopolymer resin which is able to cure (solidify) under a light source.

Fused deposition modeling, or **FDM 3D Printing**, is a method of additive manufacturing where layers of materials are fused together in a pattern to create an object

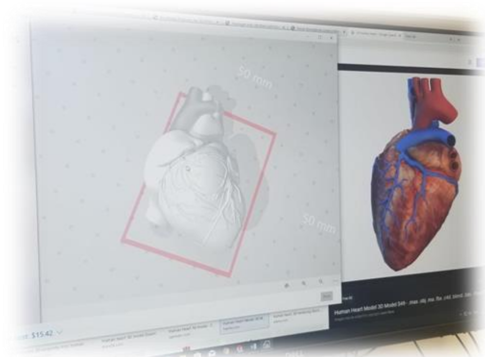
Degradable Implants Models



Drug Loaded Implants

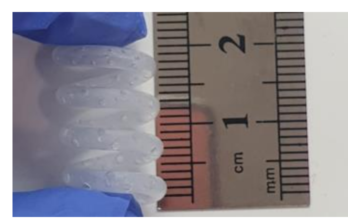


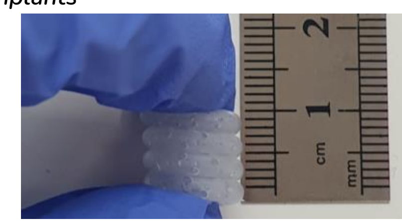
3D printed heart model



Multicomponent Implants

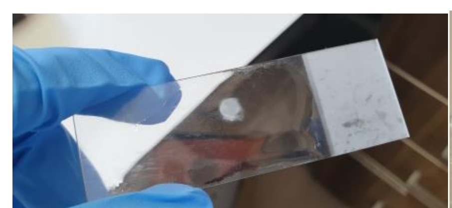
Flexible implants





3D printed microchannel for unique chemical reactions

Pinpoint Controlled Printing

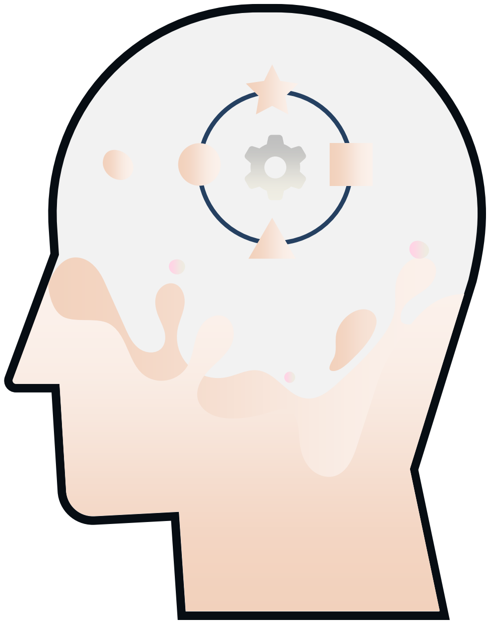


5.1 3D printing of personalized catheters with smart coating for improved functionality, biocompatibility and anti-bacterial characteristics

Assistant Professor Shady Farah, Chemical Engineering - Technion

Assistant Professor Tamar Segal-Peretz, Chemical Engineering - Technion

Associate Professor Boaz Mizrahi, Biotechnology & Food Engineering - Technion



TAMC Funded Project

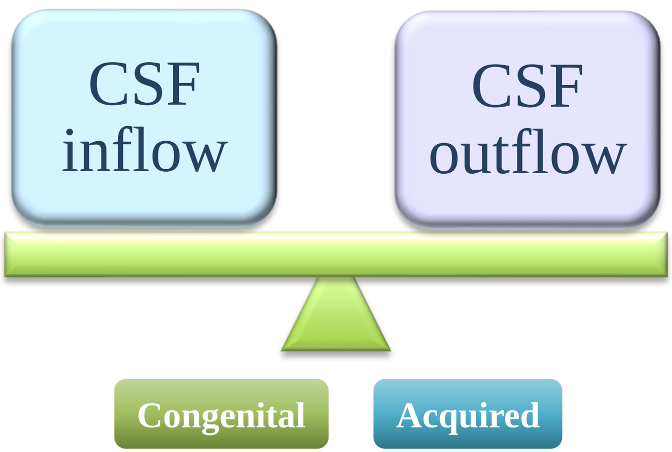
Hydrocephalus mechanisms

Imbalance between the CSF inflow and outflow, via three mechanisms :

-Obstruction = Non-communicating hydrocephalus

-Impaired absorption = Communicating hydrocephalus

-Excessive production



Hydrocephalus outcome

- Worldwide affects more than **380,000** new individuals annually.
- Mortality rate of <u>untreated</u> hydrocephalus ranging 20–87% !!!!!

Pediatric: 88/100,000
(Congenital- 68-316 per 100,000 births)

Adult –
Age 19 to 64 – 11/100,000
Elderly- age 65+ - 175/100,000
Age 80+ - 400/100,000

Isaacs, Albert M et al. "Age-specific global epidemiology of hydrocephalus: Systematic review, metanalysis and global birth surveillance." *PloS one* 2018.
Dewan MC. Et.al. Global hydrocephalus epidemiology and incidence: systematic review and meta-analysis. J Neurosurg. 2018.

Main shunt complications:

1 **Mechanical failure**

- **Obstruction**
- **Fractured tubing**
- **Over-drainage**
- **Migration**

2 **Infection**

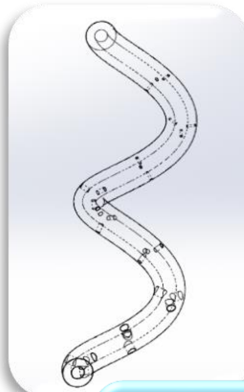
3 **Other complications**

- **Seizures**
- **Intracerebral hemorrhage**
- **Etc.**

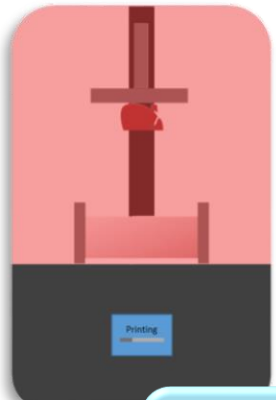
Our Concept

3D Printing & post-printing processing and coating

Neuroimaging prior to insertion of the shunt



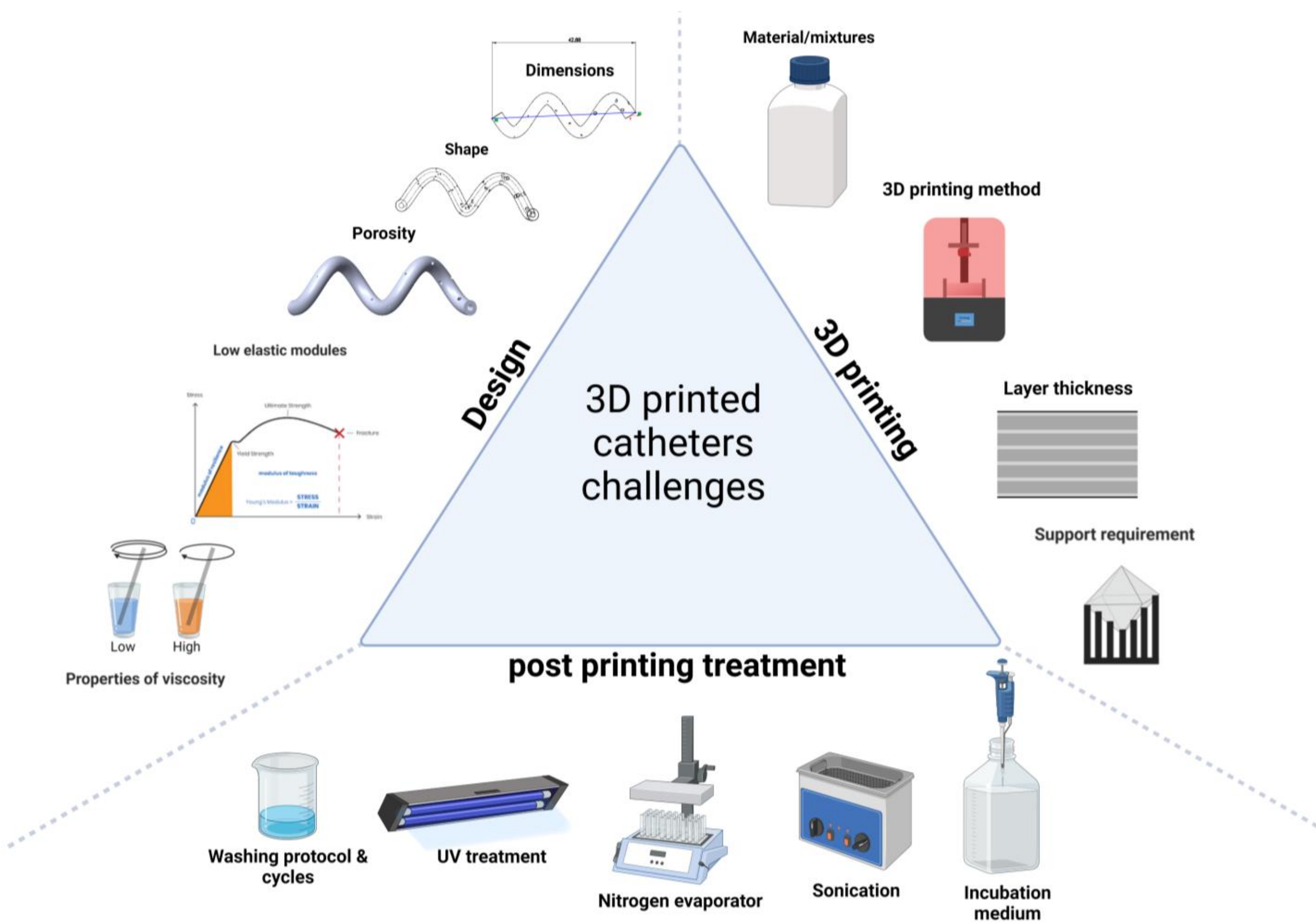
Design a personalized shunt



3D printing and processing

Insert shunt with minimum complications

Parameters impacting implantable catheter functionality:



Parameters impacting implantable devices functionality:

Design

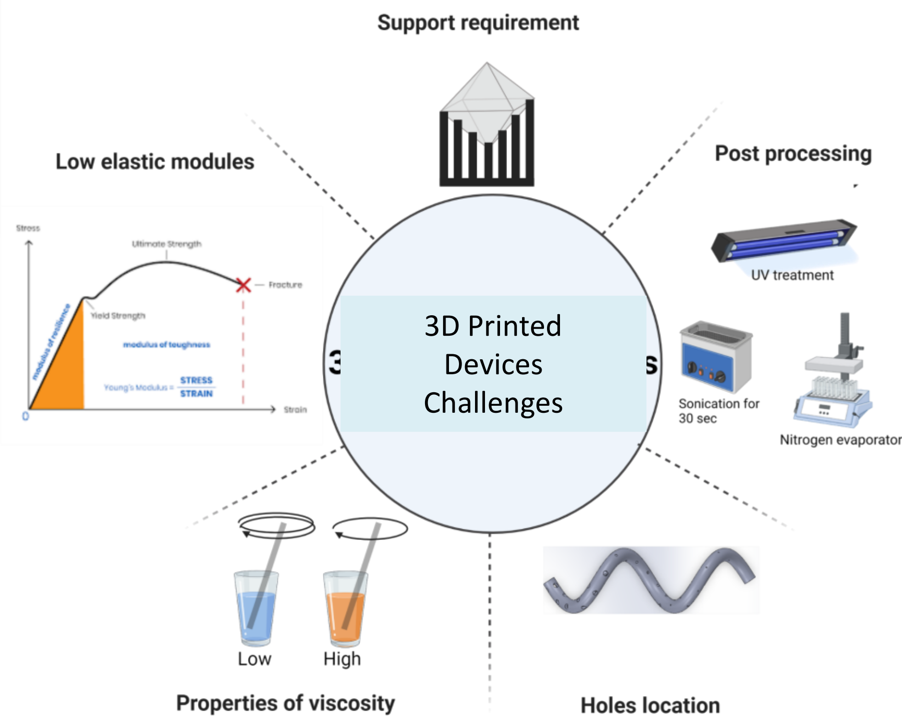
- Shape
- Capacity
- Surface area
- Porosity
- Dimensions

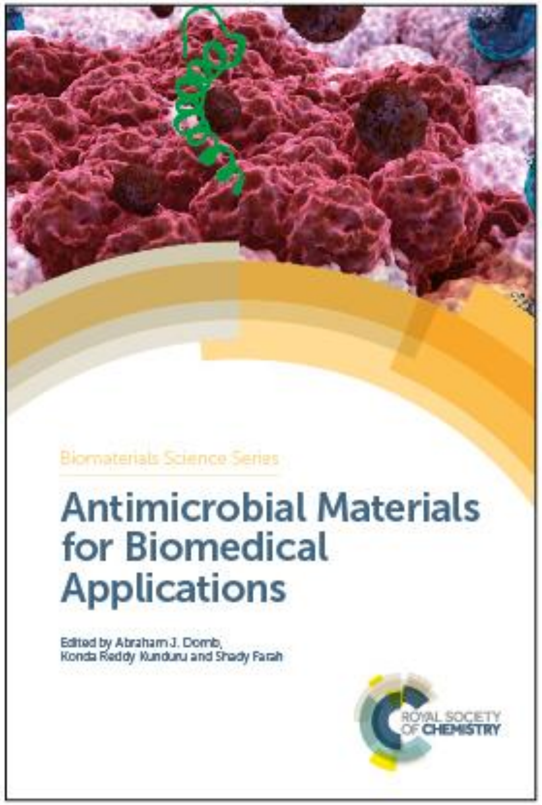
Printing

- Material/mixtures
- 3D printing method
- Temperature
- Layer thickness
- Infill density

Post-printing treatment

- Washing protocols & cycles
- Solvent's nature
- Implants processing
- UV curing
- Incubation medium





Antimicrobial Materials for Biomedical Applications

Abraham J Domb Hebrew University of Jerusalem, Israel
Konda Reddy Kunduru University of Hyderabad, India
Shady Farah Technion-Israel Institute of Technology, Israel

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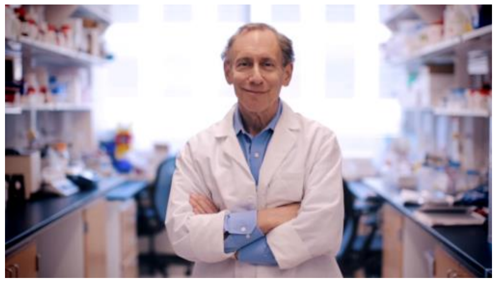
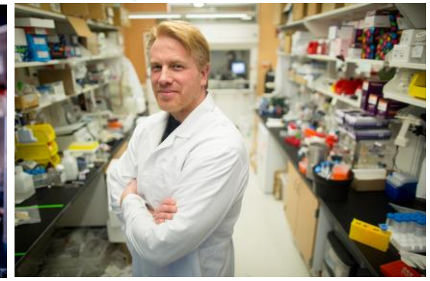
Until every child is well

KOCH INSTITUTE for Integrative Cancer Research at MIT





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הועדה לתכנון ולתקצוב

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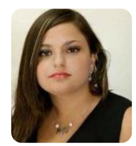
Biomedical engineer



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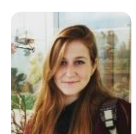
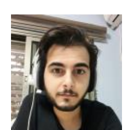
Nagham Muallem-Safuri, MD, Researcher

Medical implants Engineering



Neta Kutner, MSc student

Biochemical engineer



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Laboratory for Advanced Functional/Medicinal Polymers and Smart Drug Delivery Technologies

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Thank You very much for your attention!