Tech Session 3: Immuno Delivery

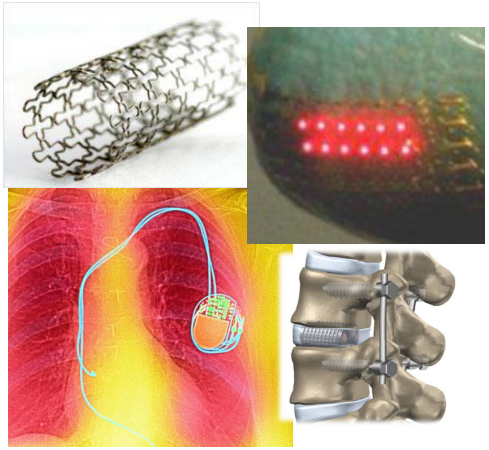
Prof. Joshua C. Doloff

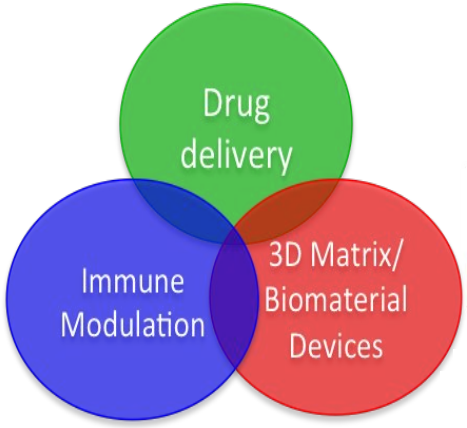
Johns Hopkins University

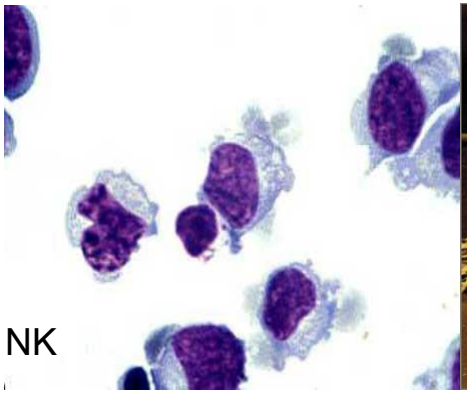
CRS 2022 Annual Meeting & Expo

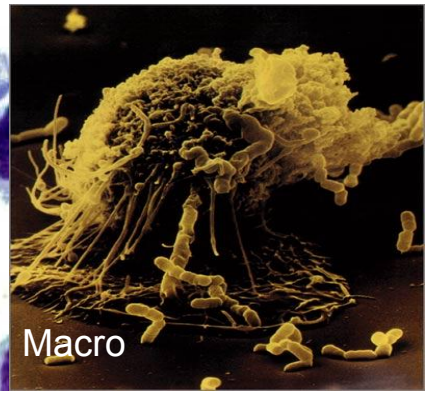
July 11 – 15, 2022 | Montreal Congress Center, Montreal Canada

Advanced Delivery Science









Tailored drug delivery systems: Treating Cancer & Preventing Device/Graft rejection

Joshua C. Doloff, Ph.D.
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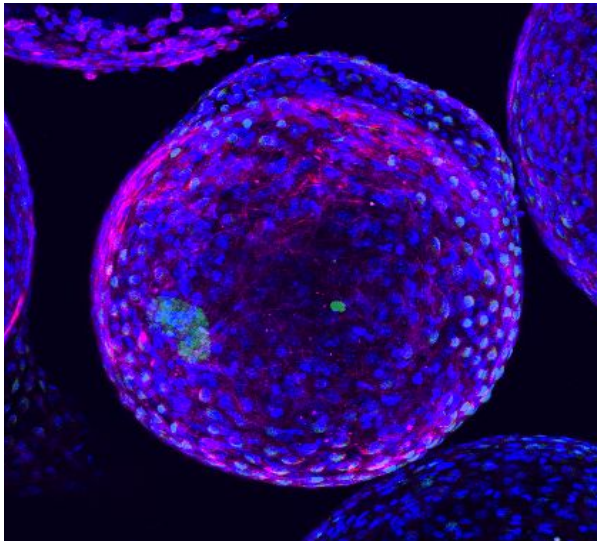
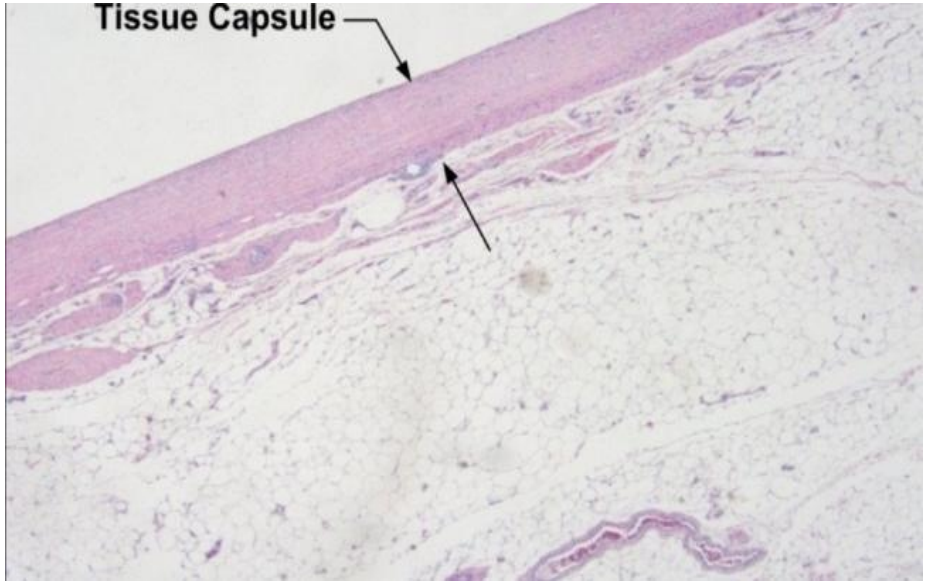
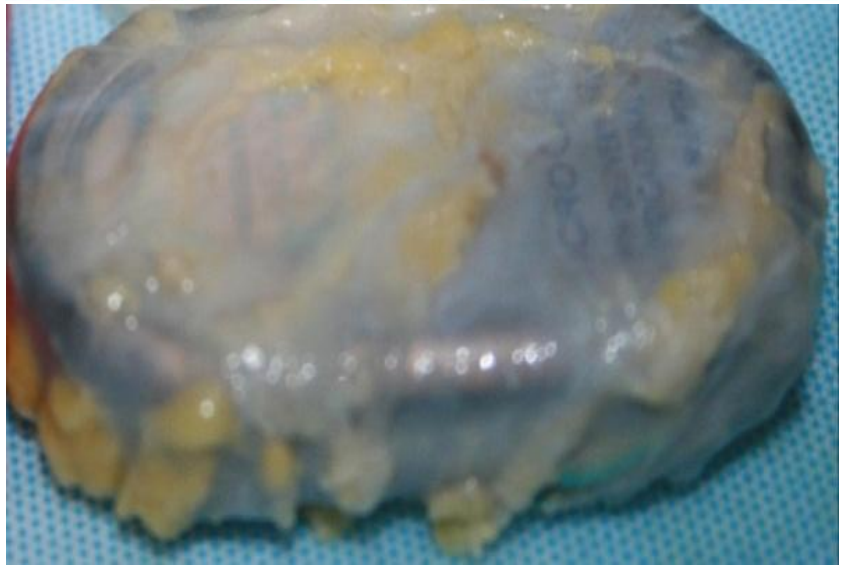
Johns Hopkins Univ.

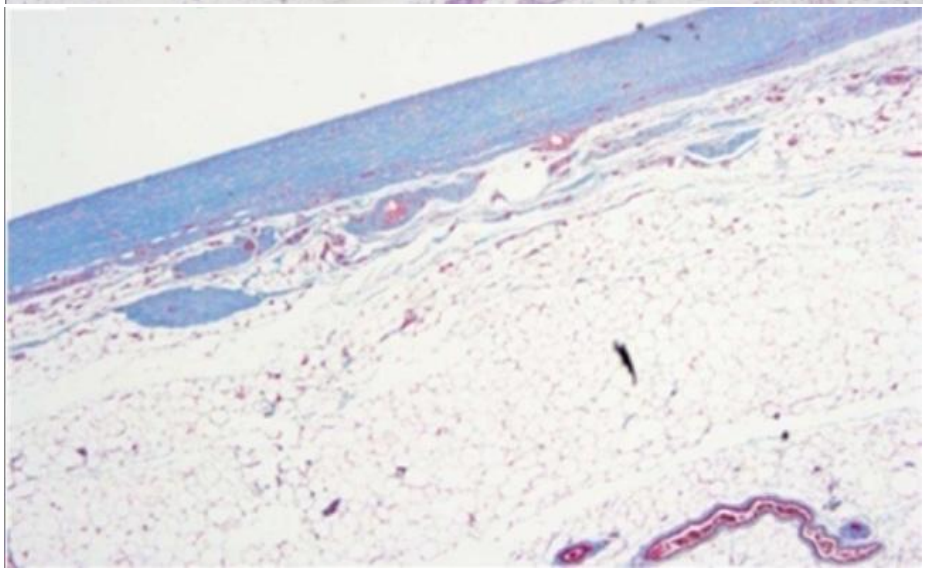
CRS Annual Meeting
Immuno Delivery SIG
Young Investigator
7-14-2022



Fundamental challenge for Medical Devices: Fibrosis



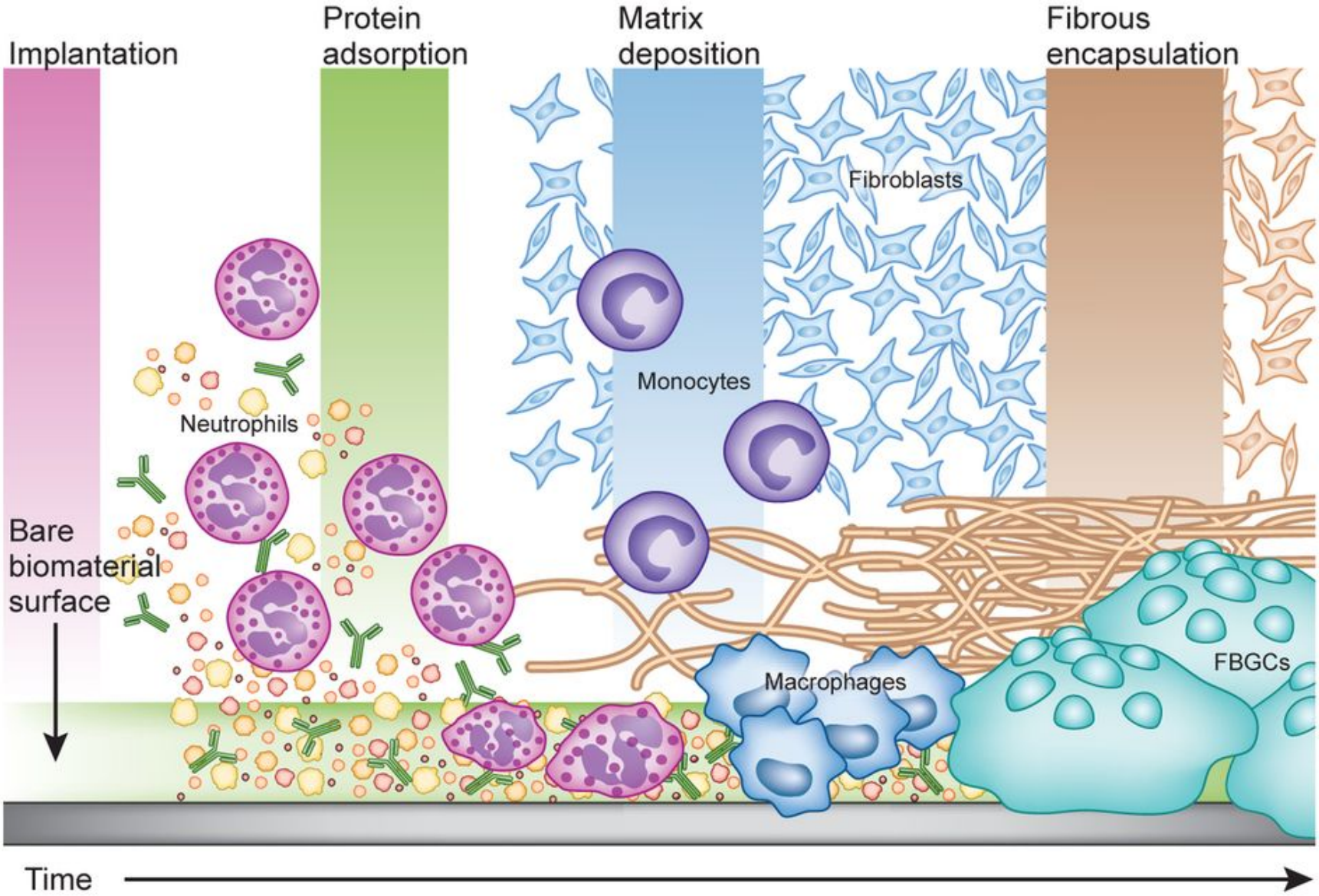




Farra et al., *STM* 2012

Biomaterial-induced Innate Immune-driven Foreign Body Reaction

Note: updates in the model



Grainger, *Nat. Biotech*. 2013

Choice of animal model is important: need to be careful

Fibrosis observations can be animal/strain-dependent

Compliant (non-fibrotic)

BALB/c mice

Some Rat strains

Strong Fibrotic Response

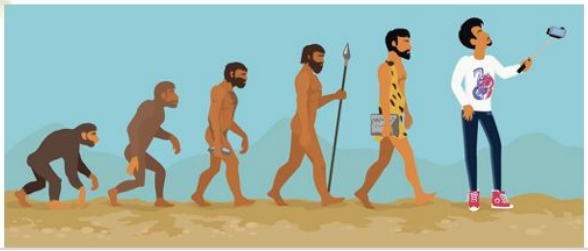
C57BL/6 mice

Pigs (i.e., large white)

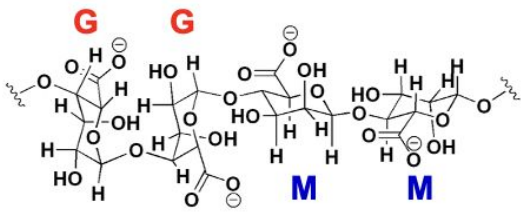
New Zealand White Rabbits

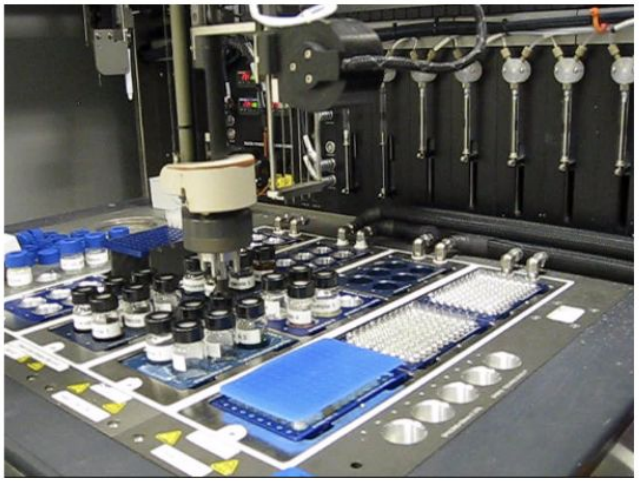
Multiple NHP species
(cynomolgus, baboon, etc.)

Humans



Synthesis to Evaluation: Material Development Workflow





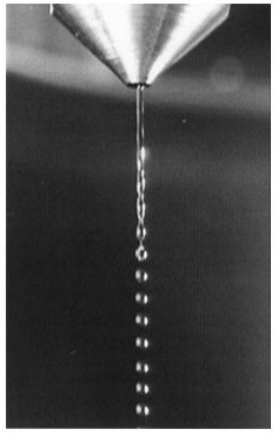
high-throughput mouse

novel material design

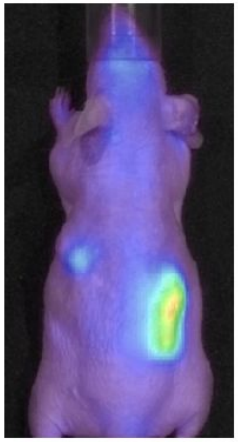
automated, combinatorial synthetic execution

material characterization

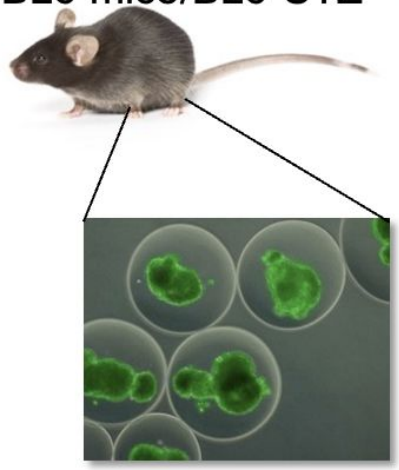
capsule formation, design, islet encapsulation



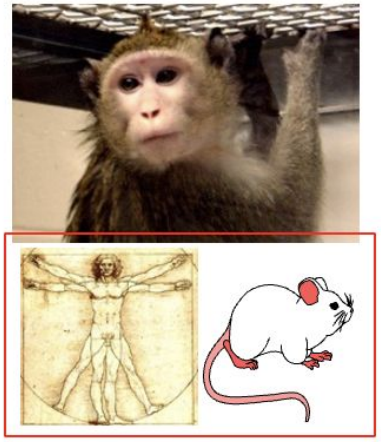
Prosense subcue testing



material fibrosis IP BL6 mice/BL6-STZ



material fibrosis NHP or Humanized



Veiseh*, Doloff*, Ma* et al. *Nat Mater* 2015; Vegas et al. *Nat Biotech* 2016; Doloff et al. *Nat Mater* 2017; Farah*, Doloff*, et al., *Nat Mater* 2019

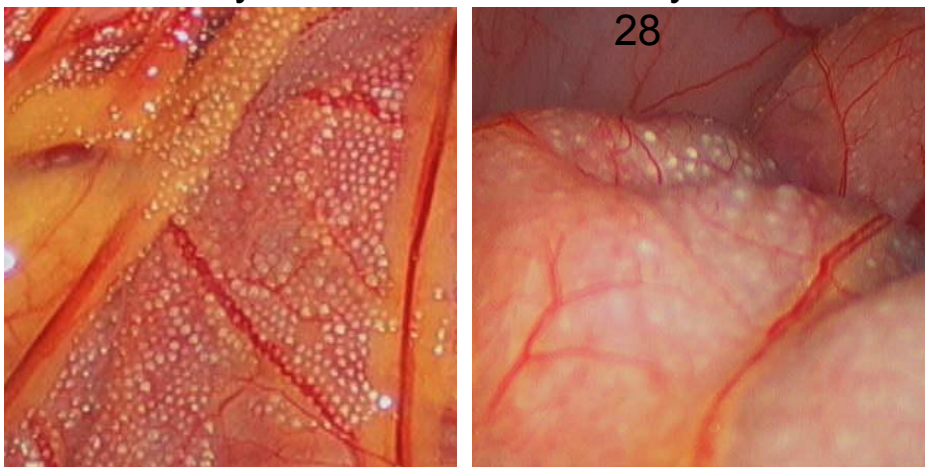
Macrophage depletion/inhibition prevents fibrosis

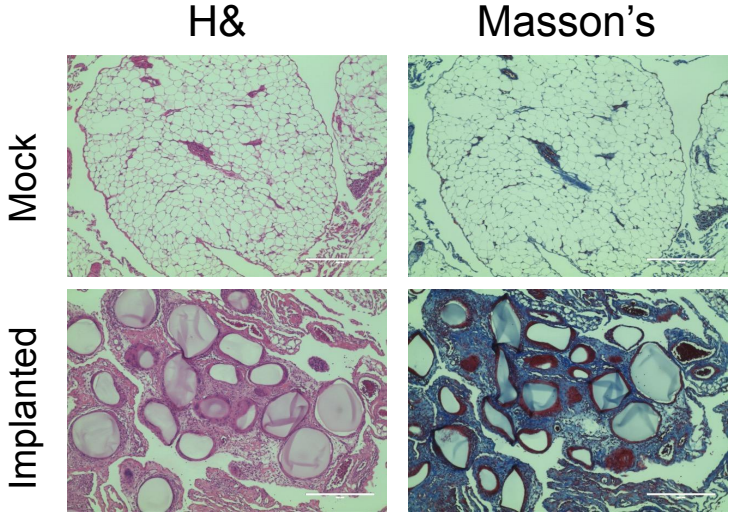
B cells also involved

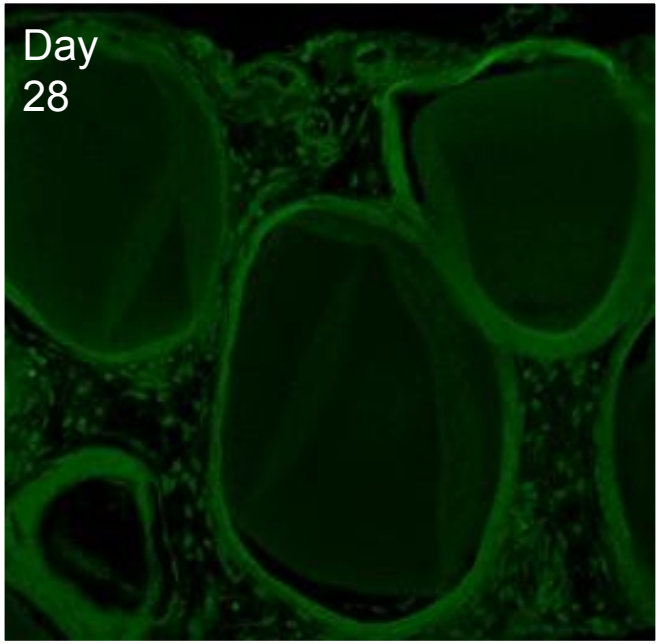
Background	Mutation	T cell deficient	B cell deficient	NK cell deficient	Additional deficiencies	Fibrosis Status
C57BL/6	None	-	-	-	-	✓, Fibrosed
C57BL/6	NOS2	-	-	-	Macros lack iNOS	N/A
C57BL/6	C3	-	-	-	No Complement	✓, Fibrosed
C57BL/6	IL15	-	-	+	Other immune dysregulation	N/A
C57BL/6	Nude	+	-	-	-	✓, Fibrosed
C57BL/6	*mu*MT	-	+	-	-	✓, ↓
C57BL/6	Rag2	+	+	-	-	✓, Mostly Fibrosed
C57BL/6	Rag2/IL2rγ	+	+	+	Macro dysfunction	✓, No Fibrosis
C57BL/6	MAFIA*	-	-	-	Macro depletion	✓, No Fibrosis
C57BL/6	α-MΦ	-	-	-	Macro depletion or inhibition	✓, No Fibrosis ✓, No Fibrosis
C57BL/6	α-Neu	-	-	-	Neutro depletion	Fibrosis
C57BL/6	α-MΦ & α-Neutro	-	-	-	Macro & Neutro depletion	✓, No Fibrosis
C57BL/6	α-CXCL13	-	+	-	Lack of B cells	✓, ↓

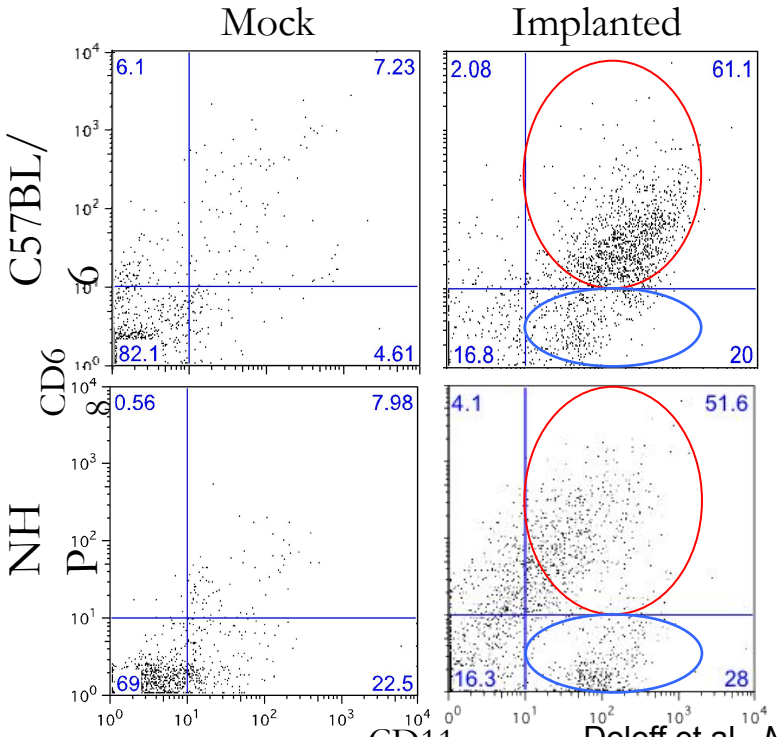
Doloff et al., *Nat Mater*

Primate immune response mirrors that in C57BL/6 mice





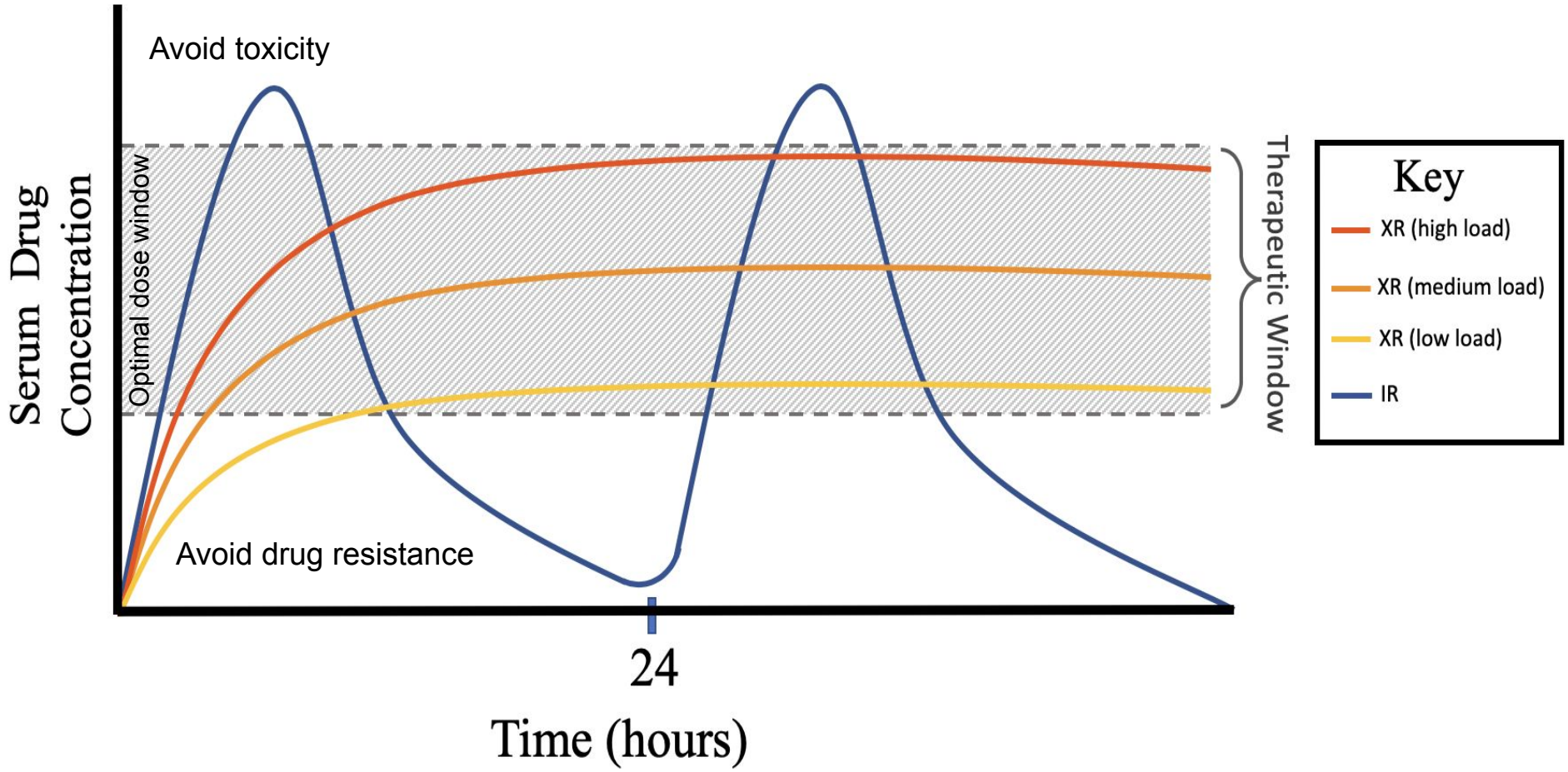




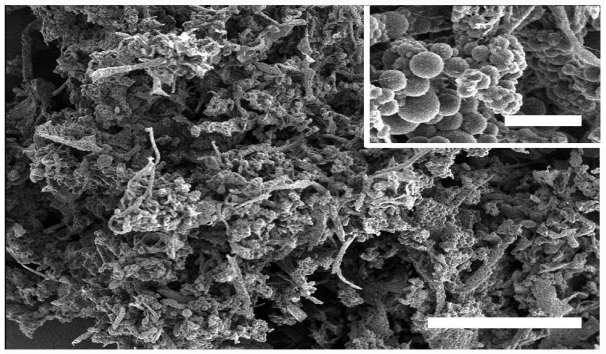
Doloff et al., *Nat Mater*

Drug Formulations for Long-term or Pulsatile release

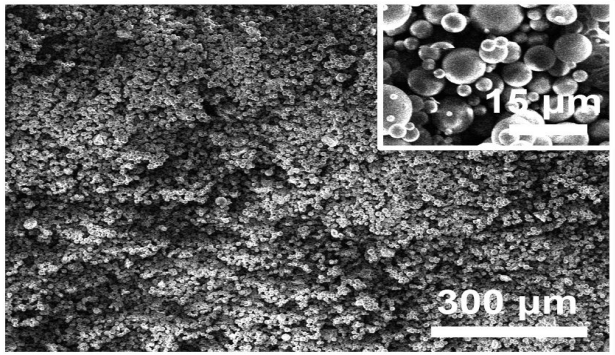
Pharmacokinetics of Extended Release



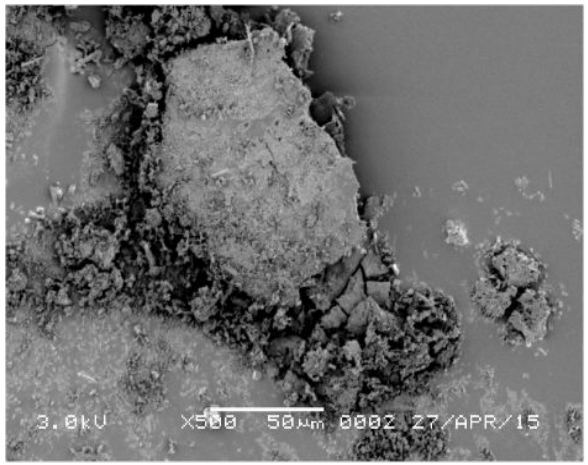
Improving long-term drug release kinetics

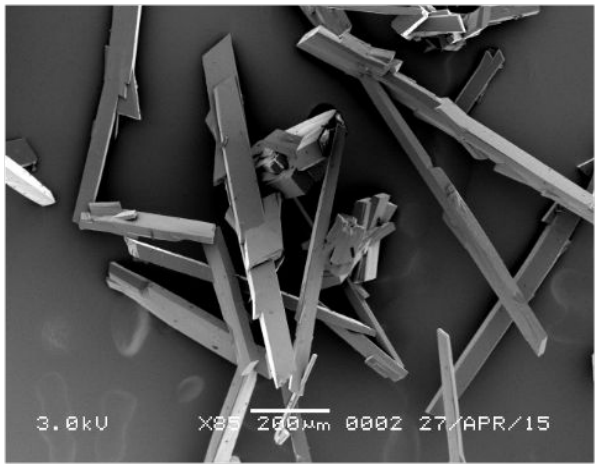


polyurethane (PU)
non-degradable

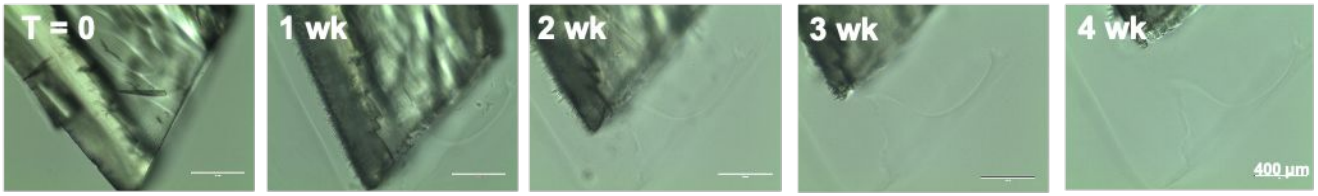


poly (L-lactic acid) (PLLA)
degradation time >2 years





w/ Shady Farah

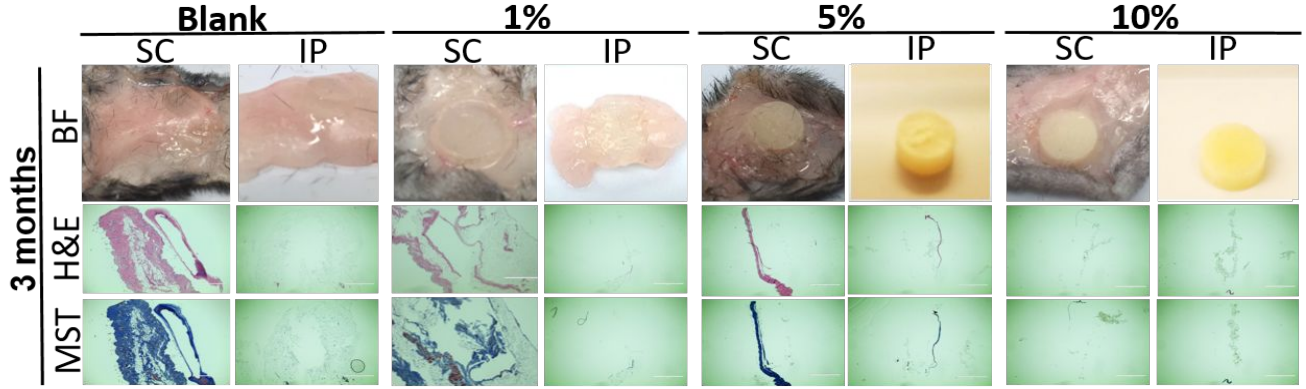


The Wolfson Department of Chemical Engineering
Technion - Israel Institute of Technology

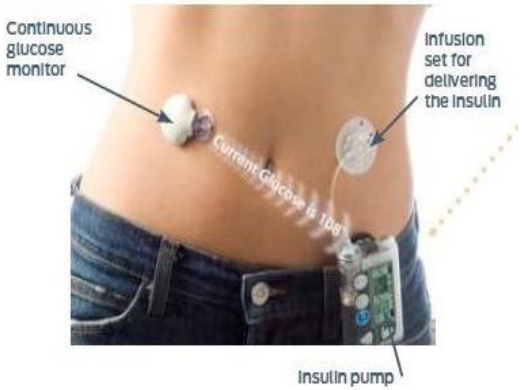
Farah* & Doloff* et al. *Nature Materials* 2019

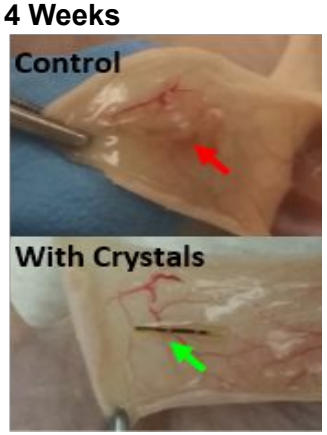
Use of anti-fibrotic in multiple device platforms

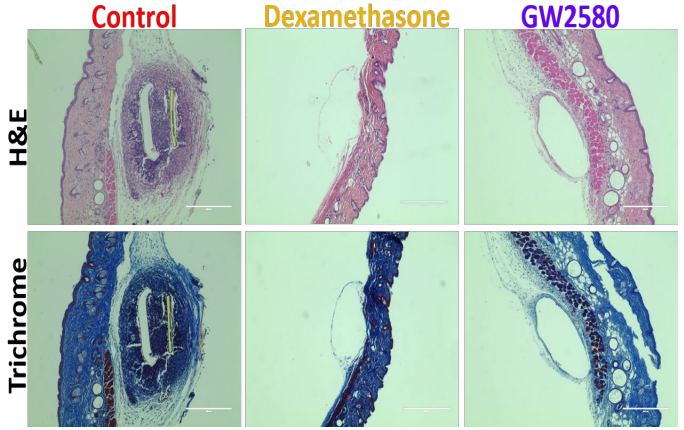
PDMS Carriers:



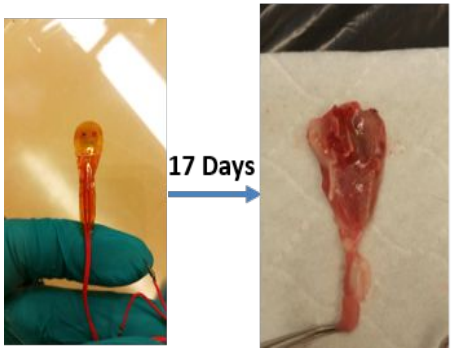
CGMs:

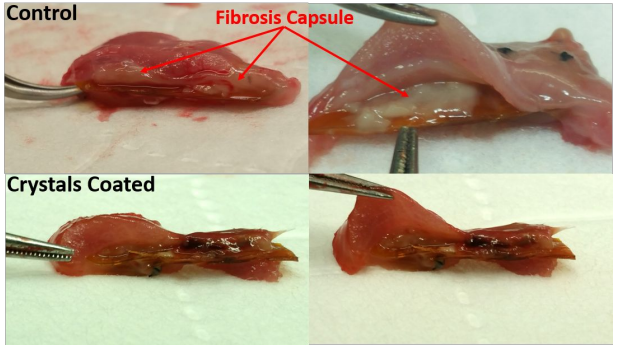


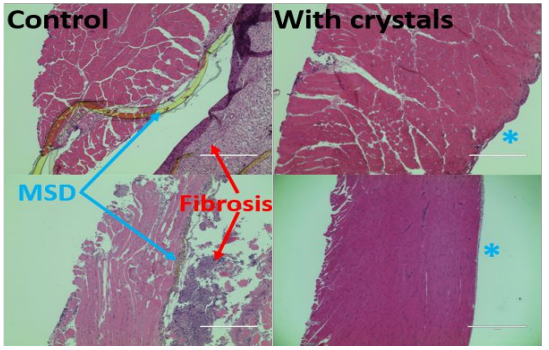




MSDs:

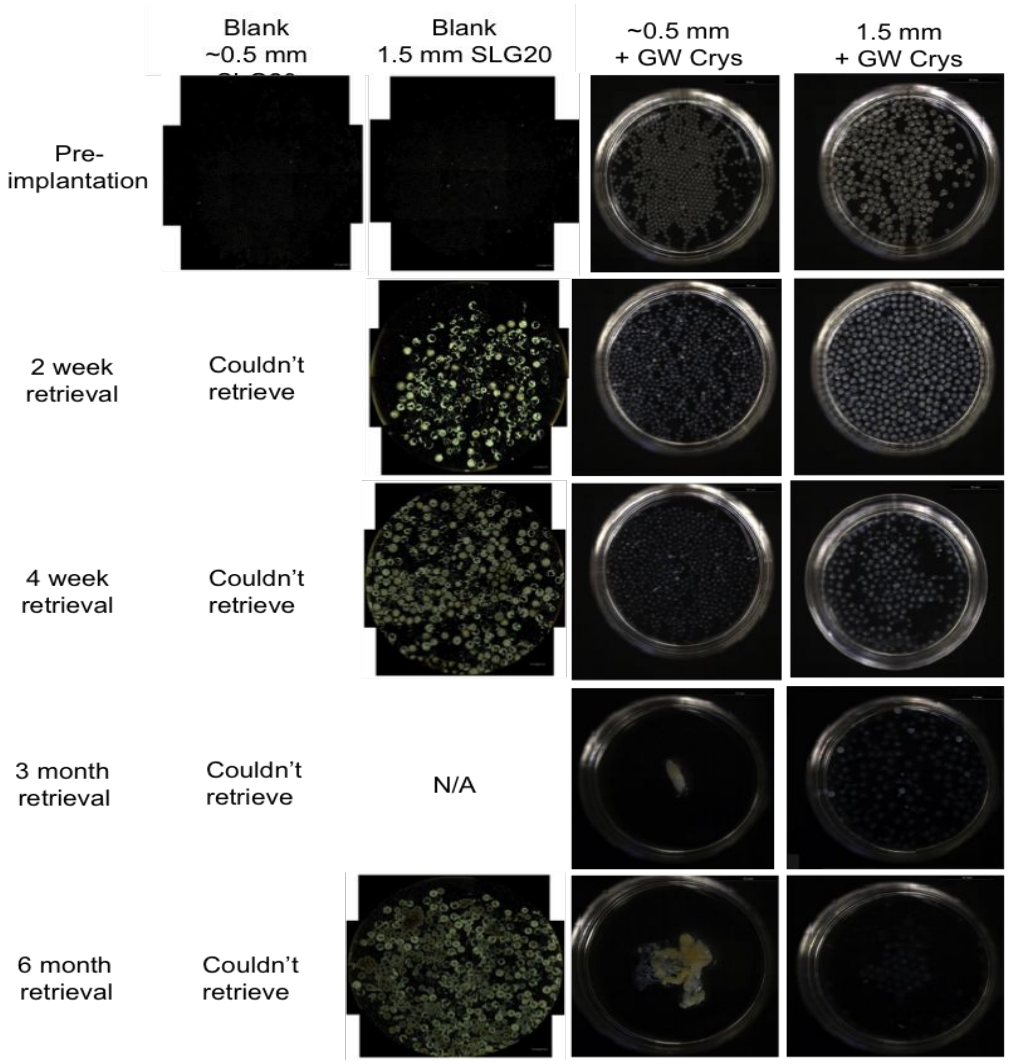


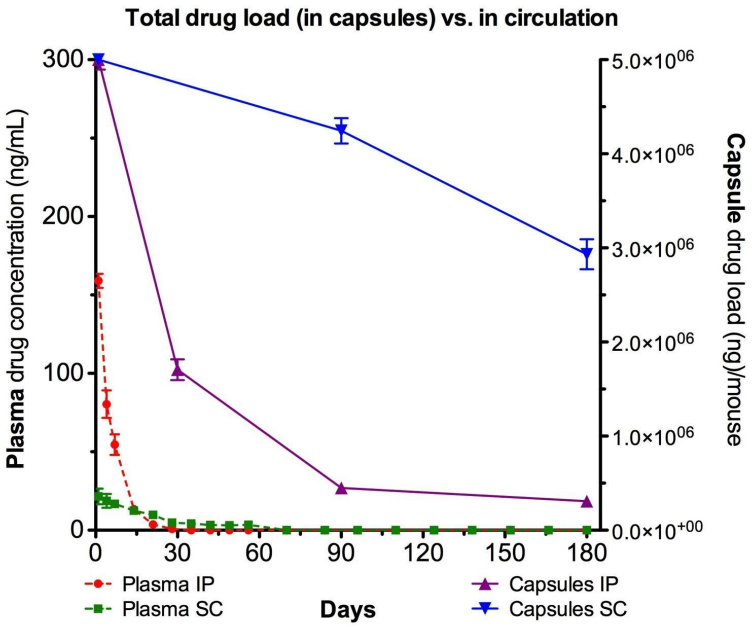




Farah* & Doloff* et al. *Nature Materials* 2019

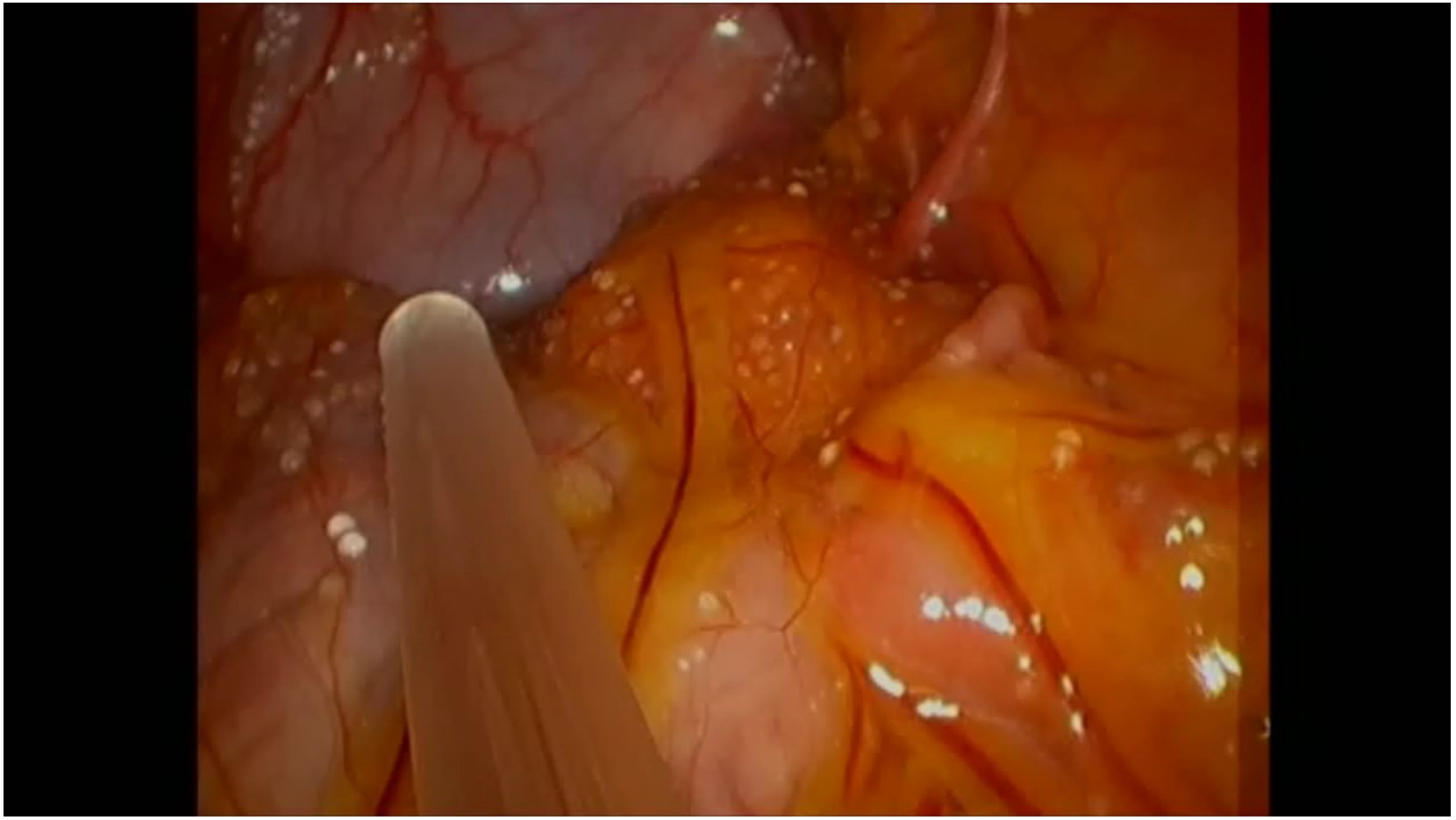
Validated in Non-human primates



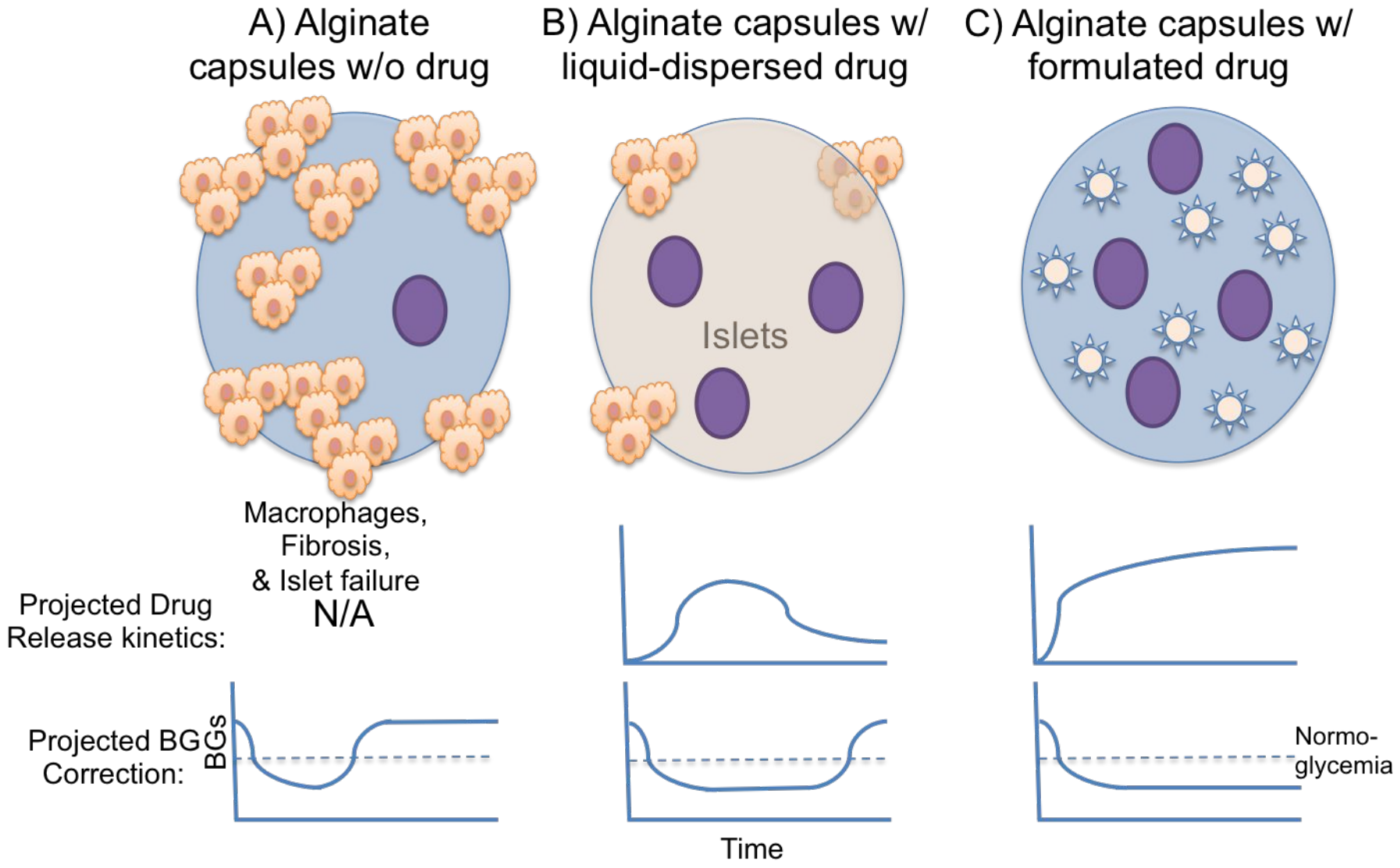


Farah* & Doloff* et al. *Nature Materials* 2019

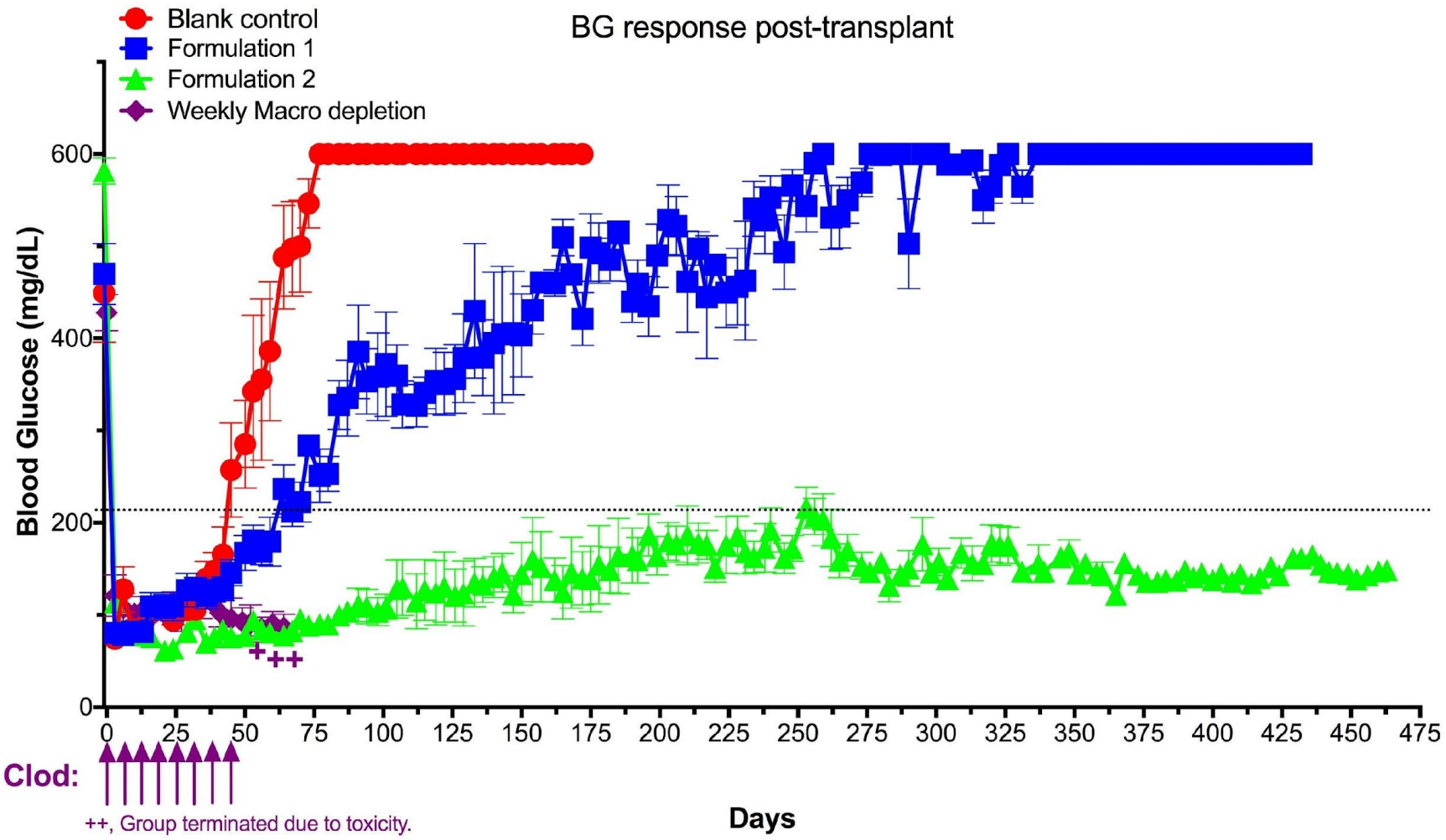
Anti-fibrotic technologies (e.g., architecture, chemistry, and drug delivery) synergize in non-human primates



Improving drug release kinetics & *in vivo* testing



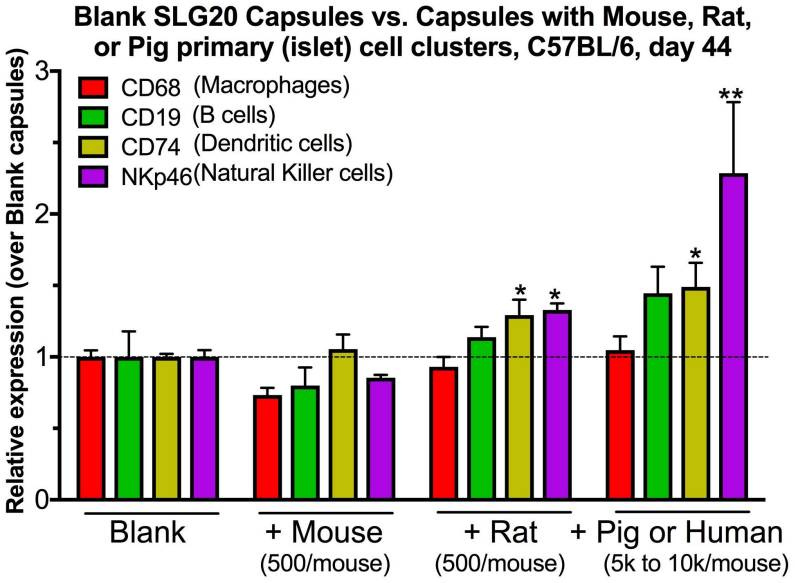
Macrophage inhibition with crystals elongates normoglycemic cures with rat islets in diabetic STZ-C57BL/6 mice

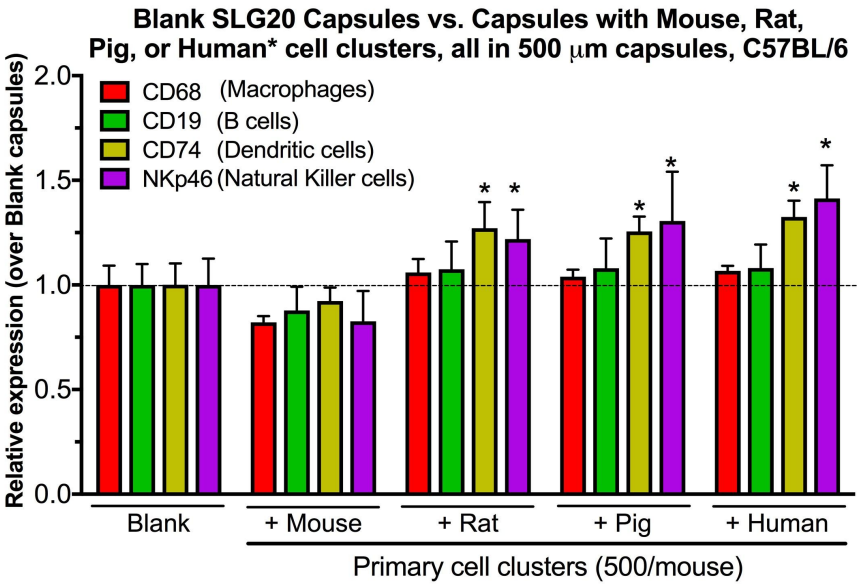


Performed with various cells: primary rat, human, and iPS-derived.

Farah* & Doloff* et al. *Nature Materials* 2019

Issues with Cell graft loading Density & Origin



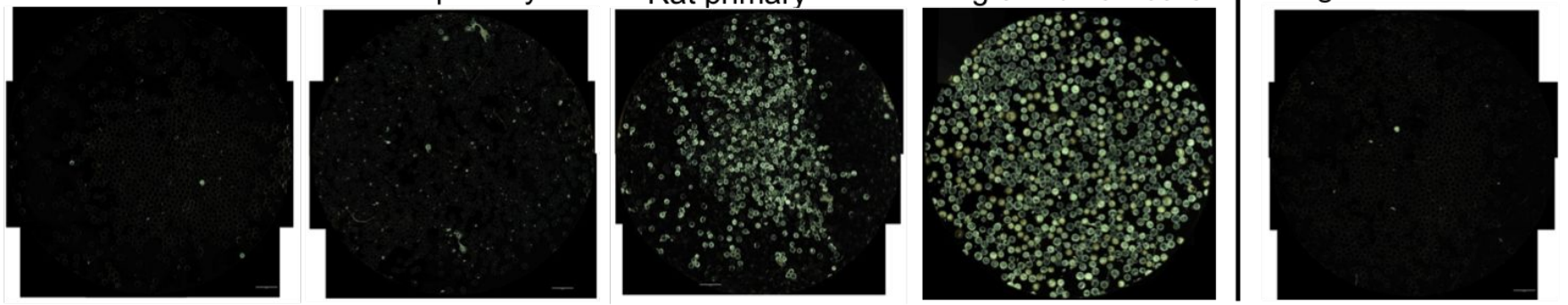


After ~1.5 months in 500 μm SLG20 capsules, in fully Immune Competent mice

Blank | Mouse primary | Rat primary | Pig or Human cells*

Immune compromised NSG mice

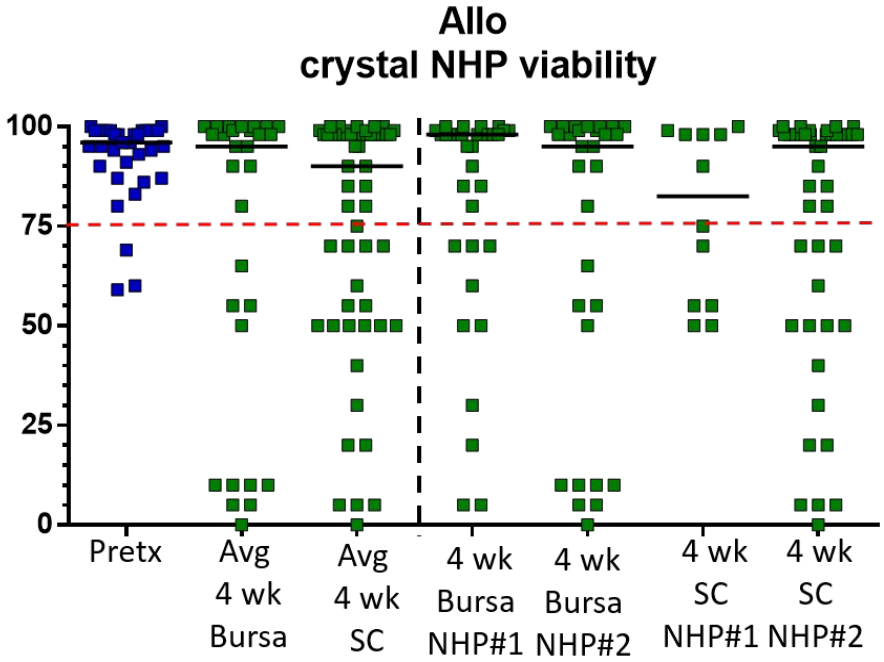
Pig or Human cells*

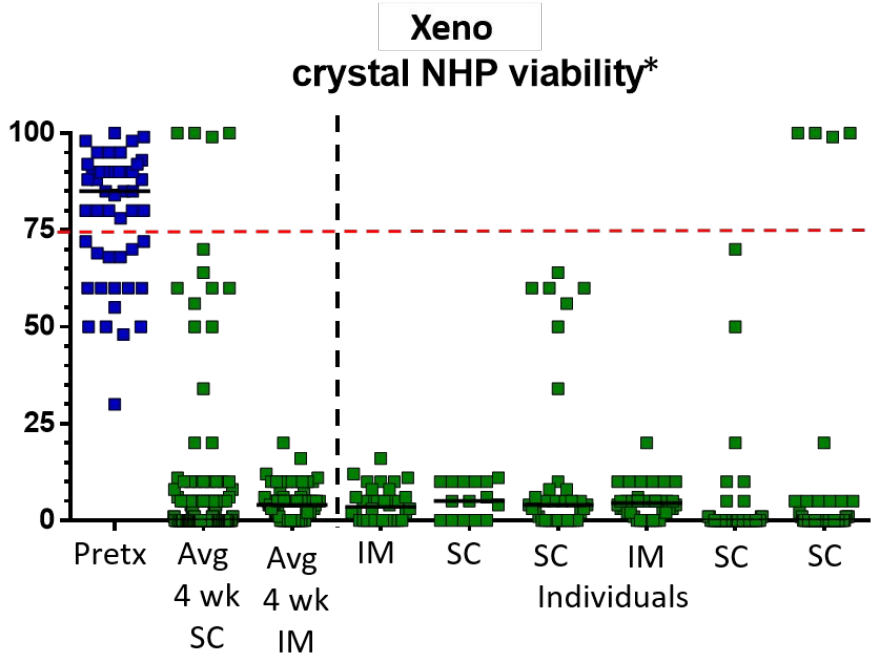


Issues with Cell graft Origin (cont.)

Allo primary NHP islets vs. Human stem-cell derived grafts

in transplanted cynomolgus monkeys

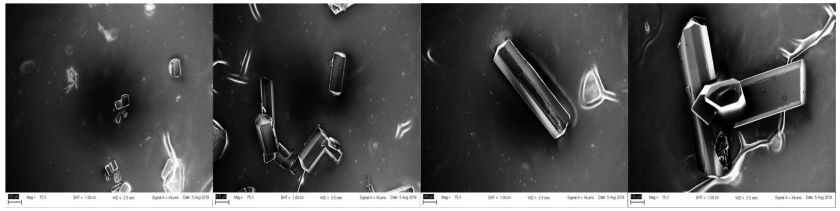




Crystallized drug formulations with new functions

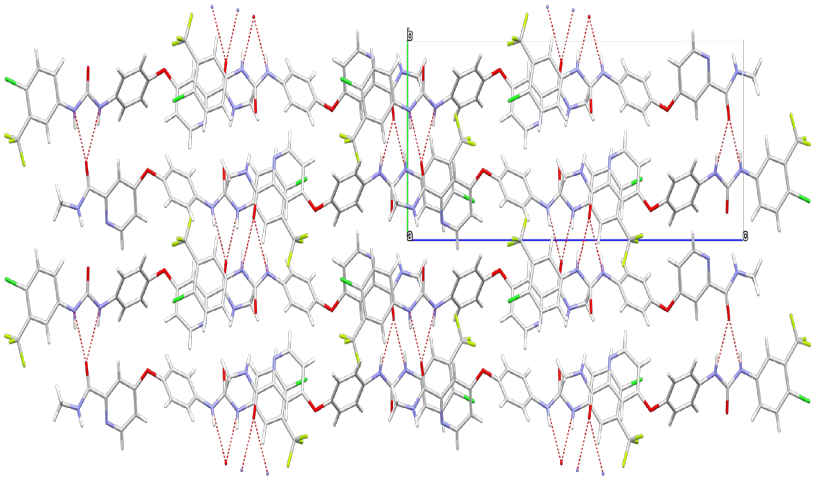
- Tailor drug formulations and release for different applications:

Optimize sizing/manufacturing:

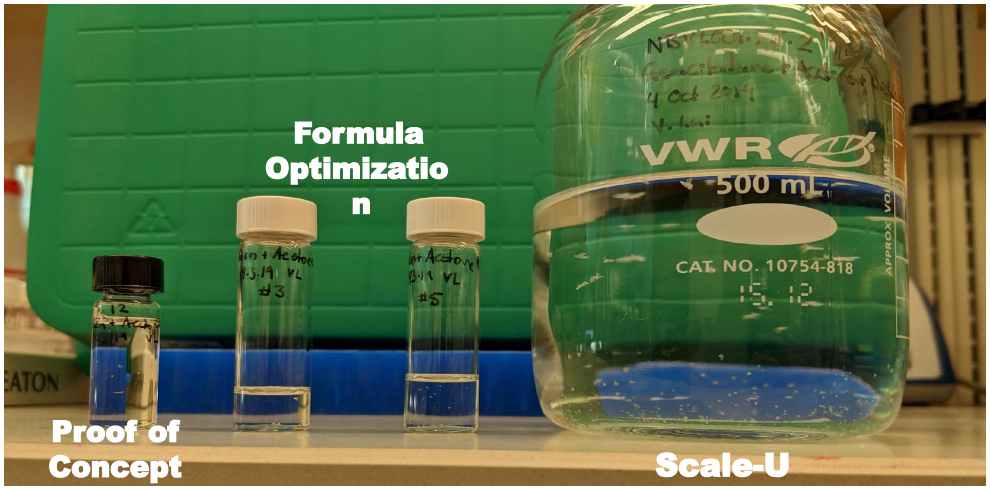


10-50µm 100-300µm 400-700µm 1-2mm

Method of crystallization/release kinetics:

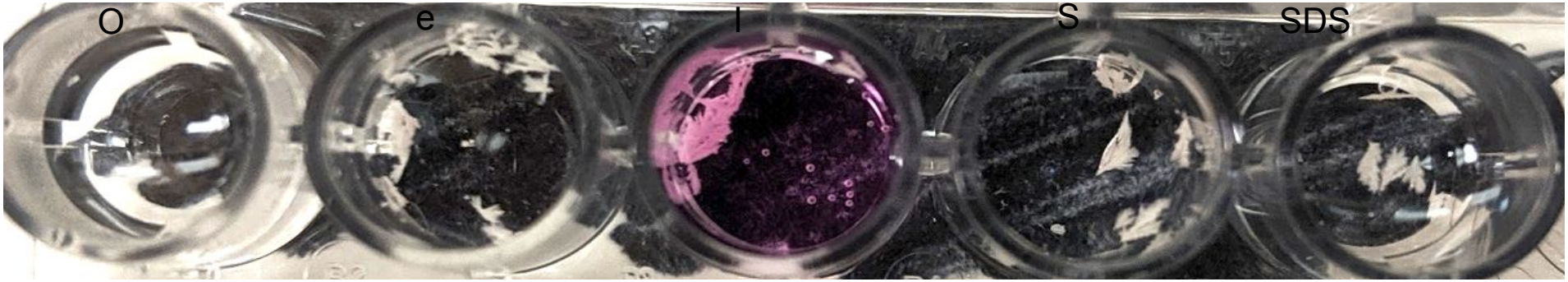


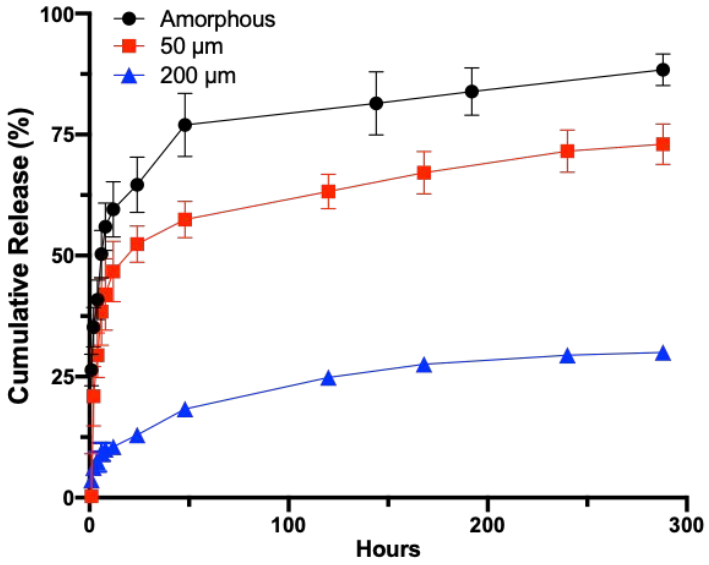
Optimize scale-up for general use and *in vivo* studies:

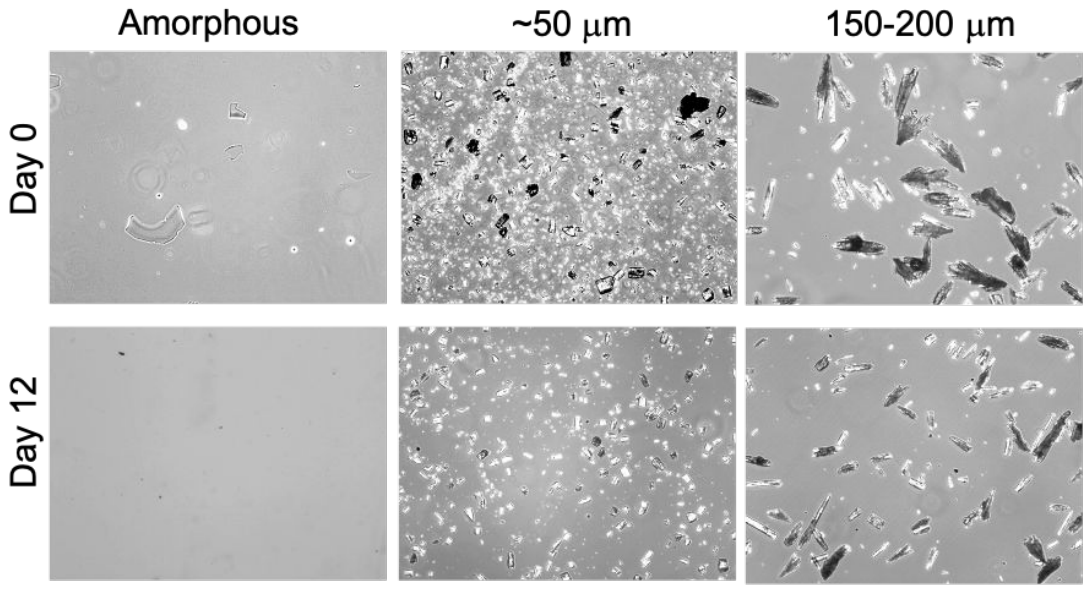


Lai*, Neshat*, et al. *CMBE* 2021

Crystal Stability and Tunability Characterization: via *In vitro* release





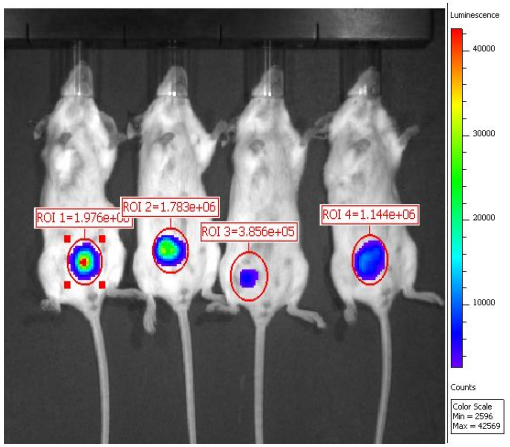


Lai*, Neshat*, et al. *CMBE* 2021

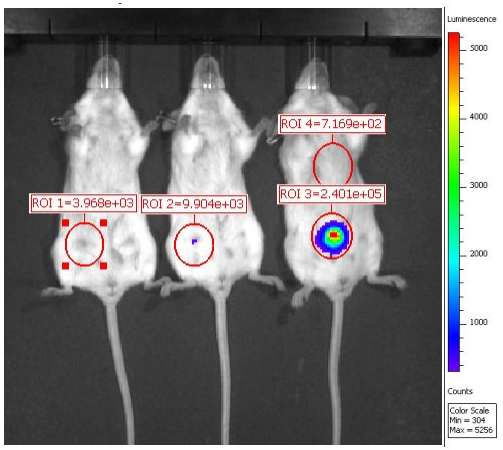
Anti-tumor efficacy

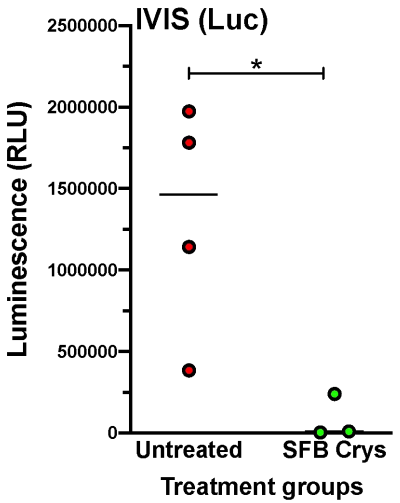
injection of Tumor cells w/ or w/o Drug as well as retrospective

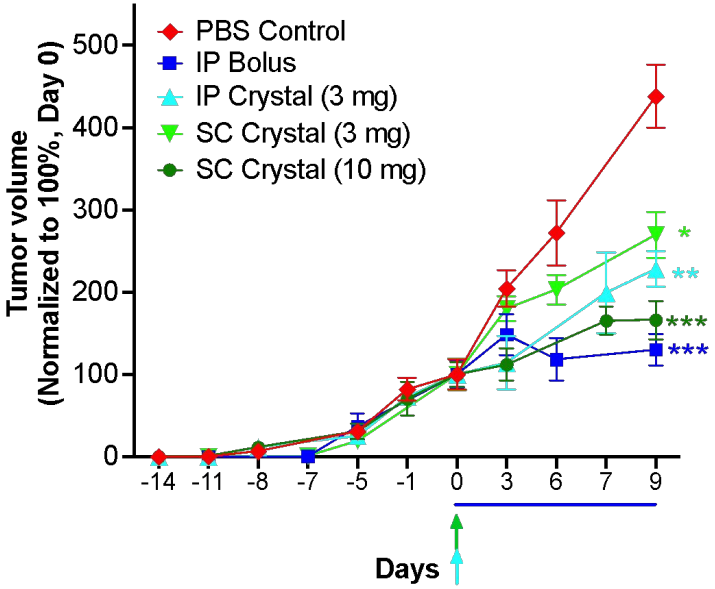
Vehicle

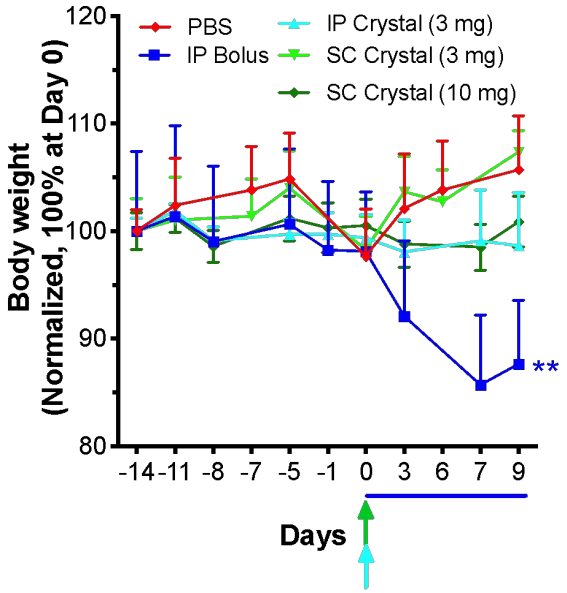


+ Sfb crystals (2









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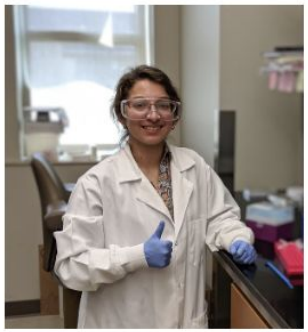
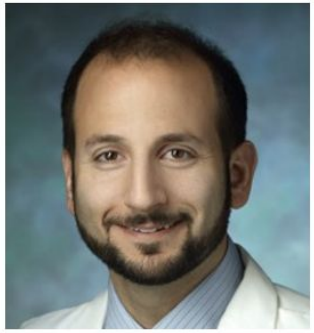


Amanda Rakoski



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