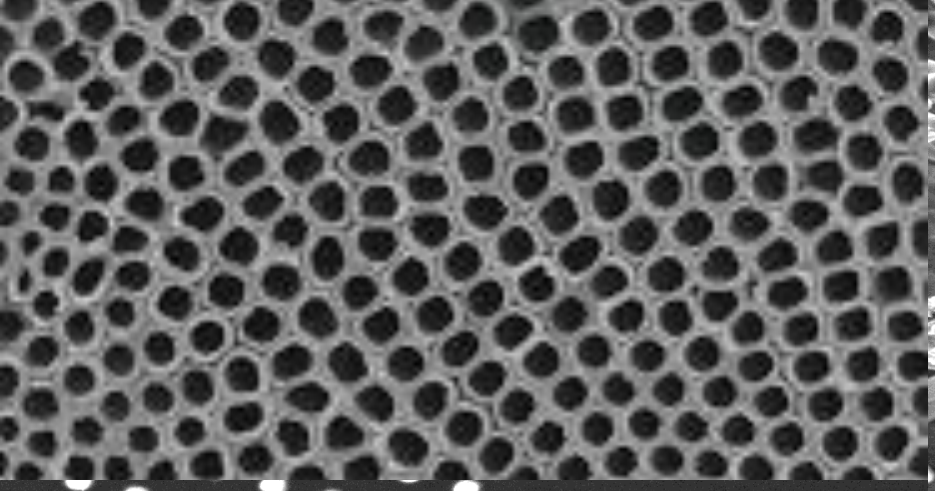
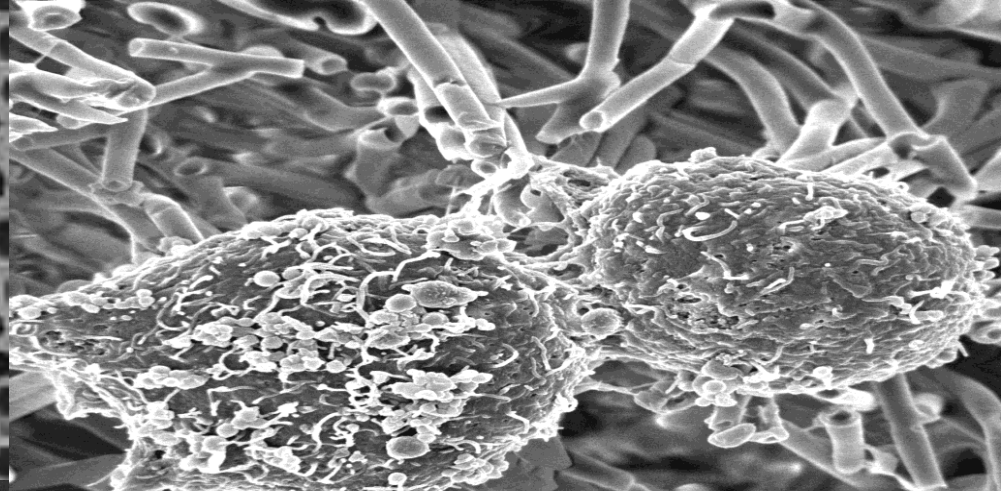
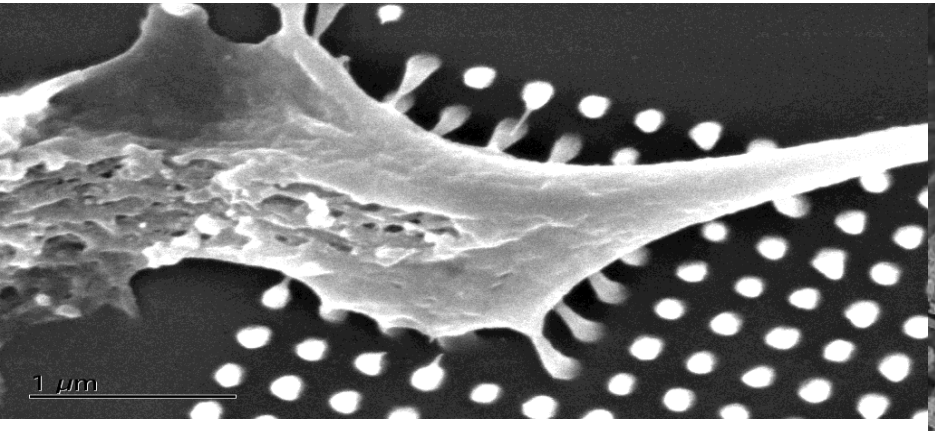
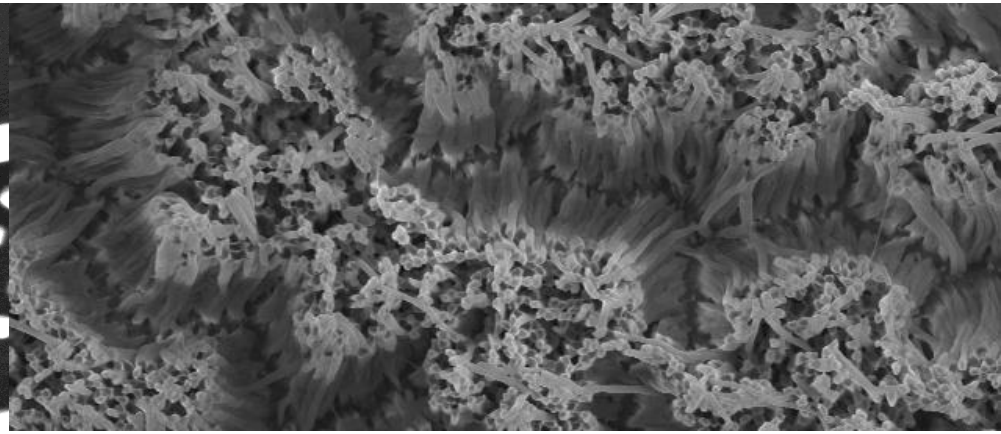




Using Nanostructured Materials to Modulate the Immune System





Tejal A. Desai

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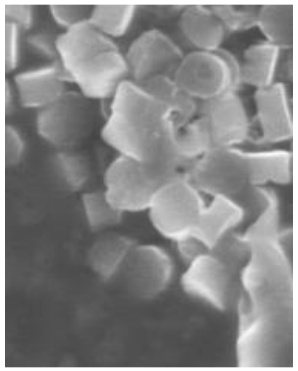
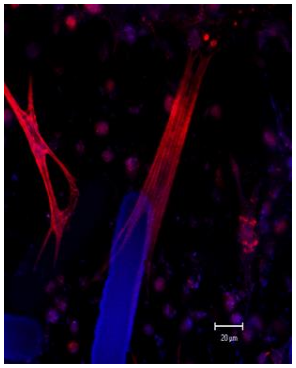
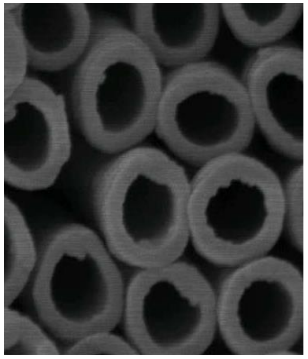
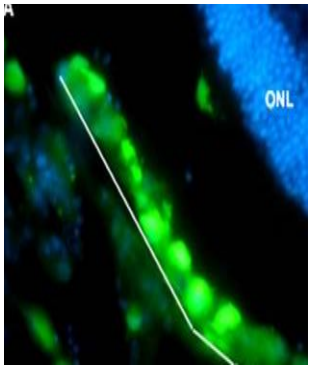
San Francisco

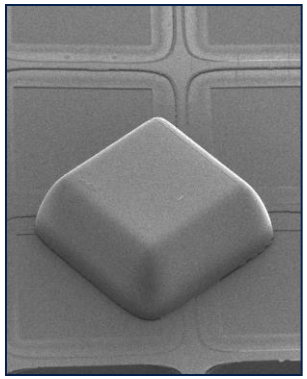
qb3
ucb·ucsc·ucsf

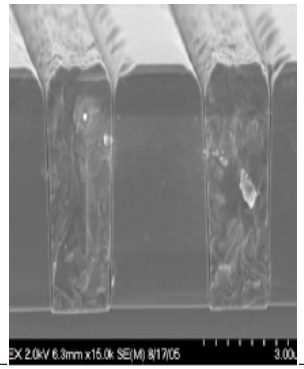












Micro and Nanostructures

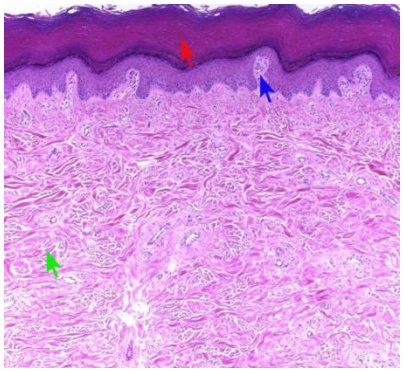
Cell –Material Interactions

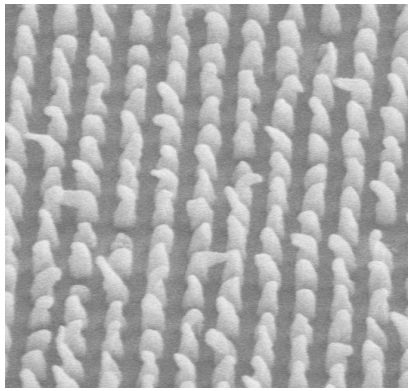
Therapeutic Delivery Systems

UCSF

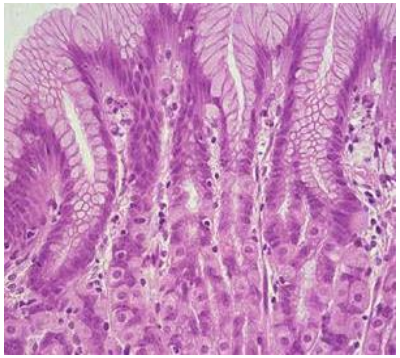
How can material structure modulate cellular function for therapeutic purposes?

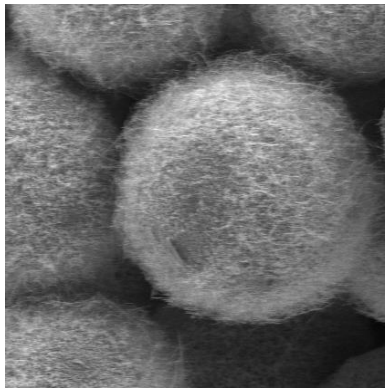
Transdermal



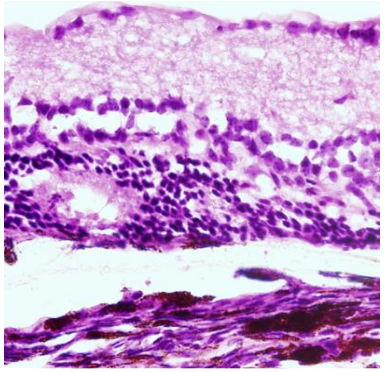


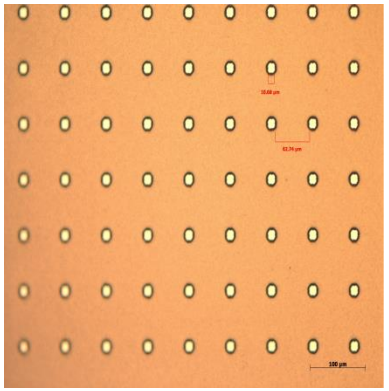
Oral



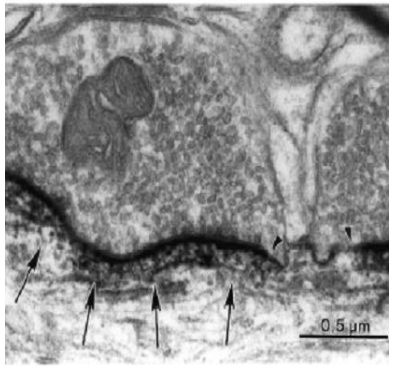


Retinal



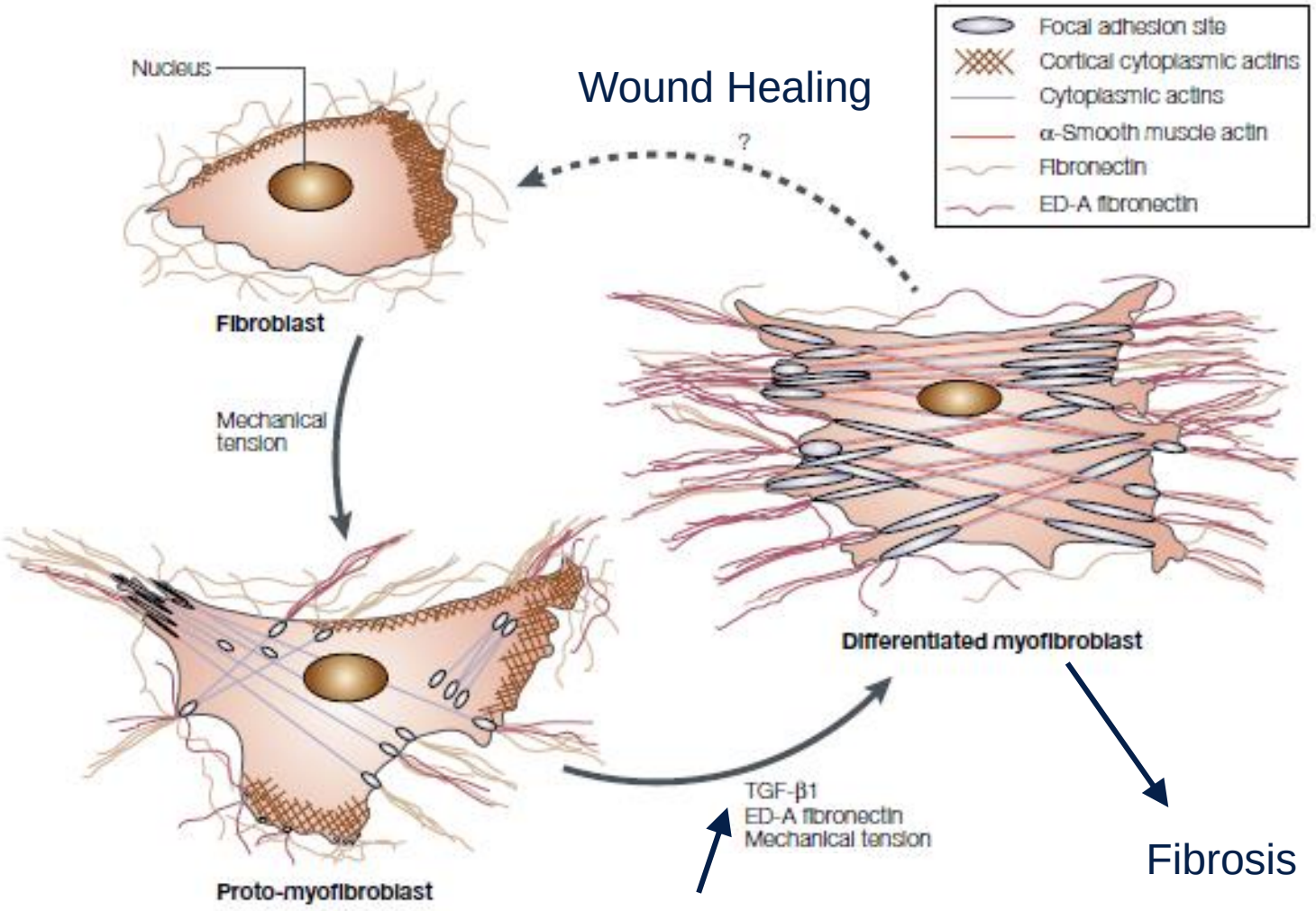


Cardiac



Can we tune material structure to modulate fibrosis?

Fibrosis: Fibroblasts Activated by Aberrant Mechanical Tension and TGFβ



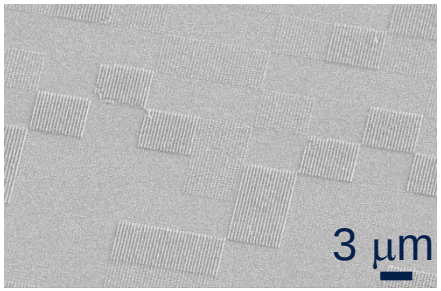
TGFβ

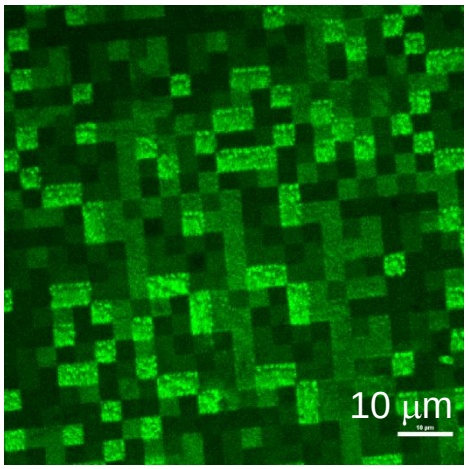
UCSF

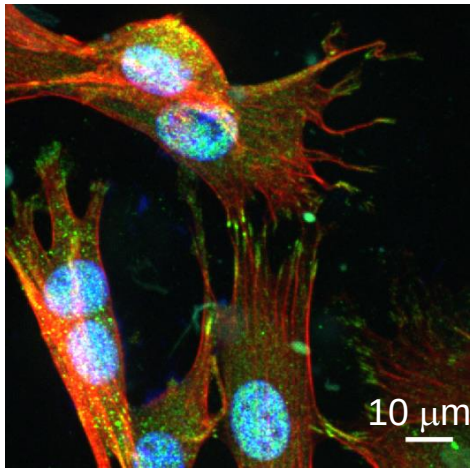
High Aspect Ratio Features Provide Anti-fibrotic Signals

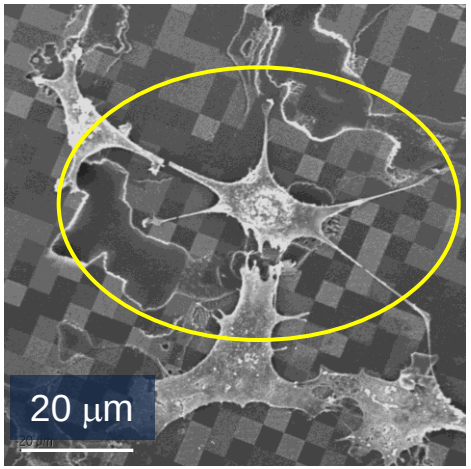
FITC-IgG Adsorption **Vinculin, F-Actin, DAPI**

P(1)









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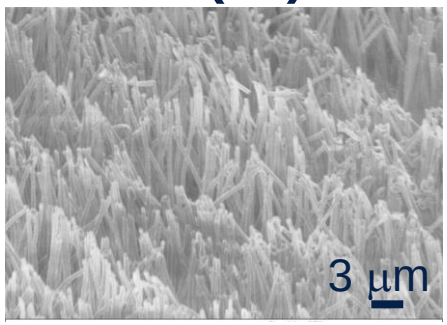
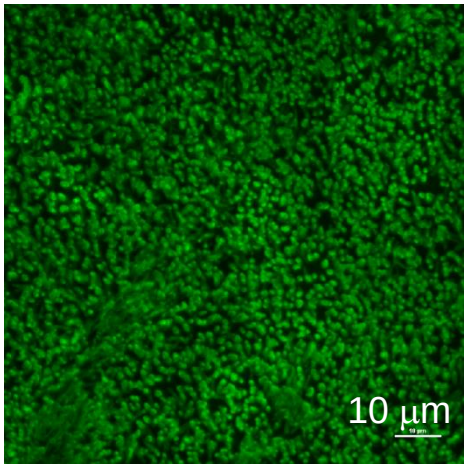
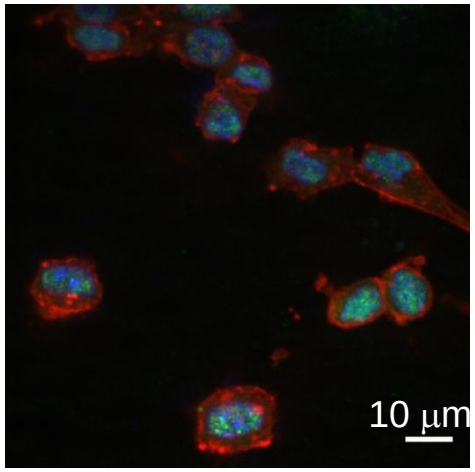
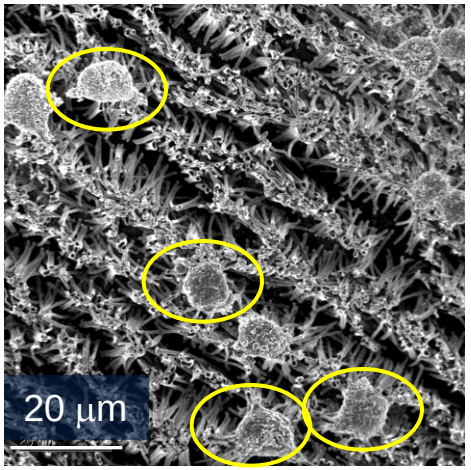




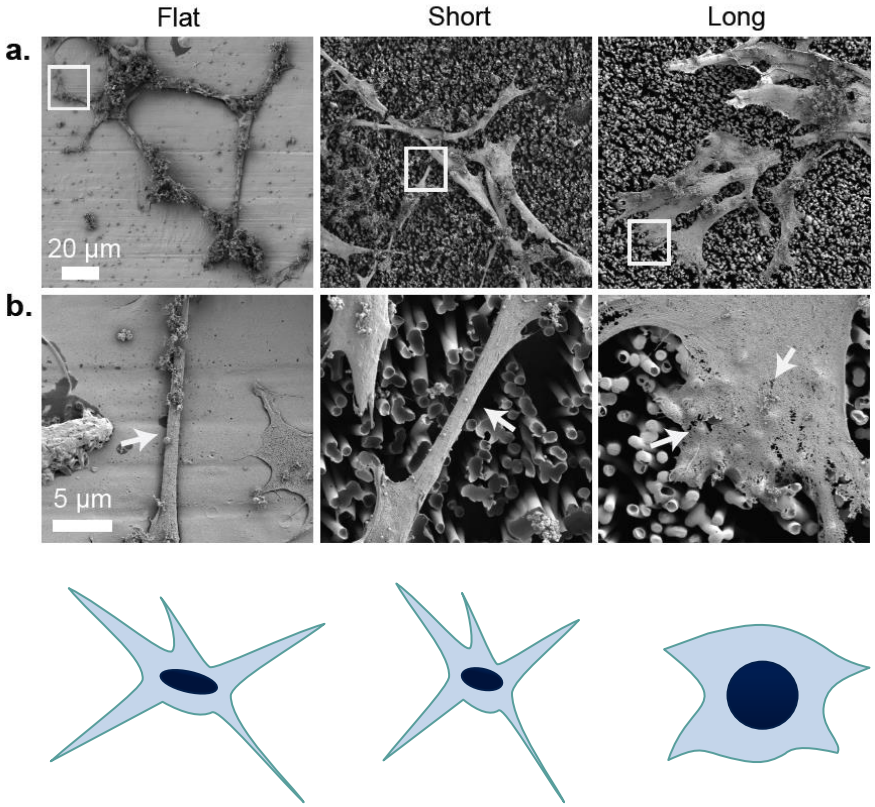


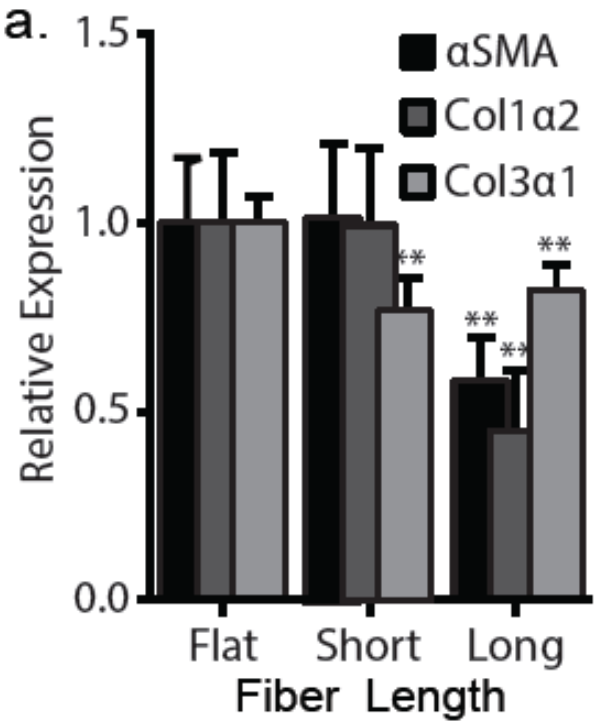


Kam, et. al, Nanoletters 2013; Tissue Engineering 2014

UCSF

Long aspect ratio structures inhibit fibroblast activation *in vitro*

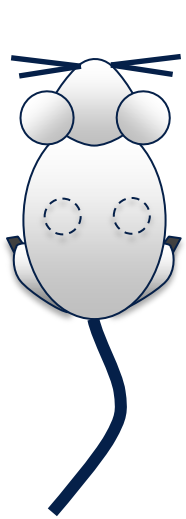


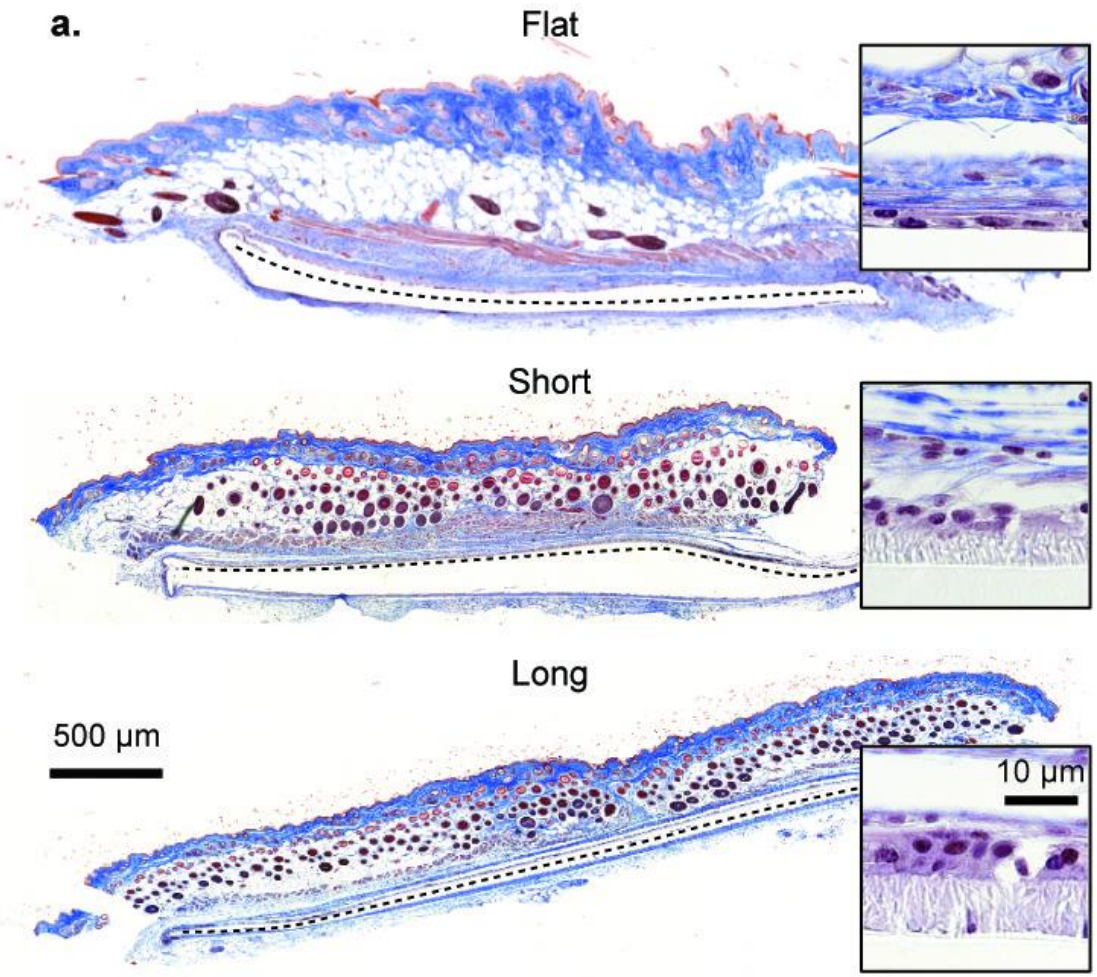


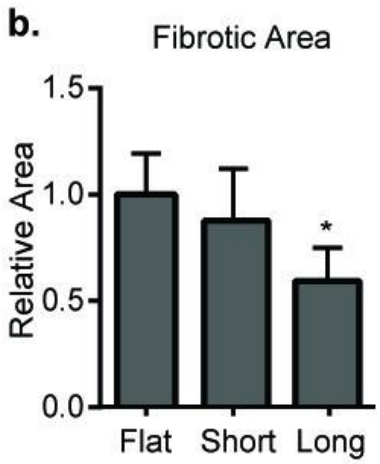
Allen, Ryu et al., 2016

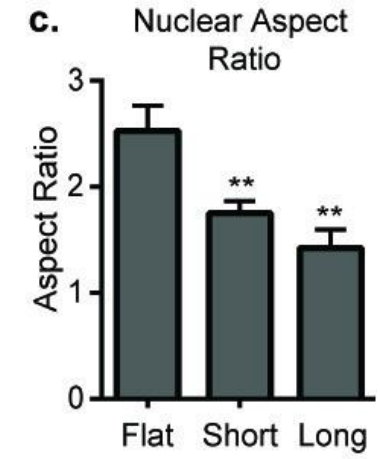
UCSF

Long Structures Decrease Fibrotic Response *in vivo*

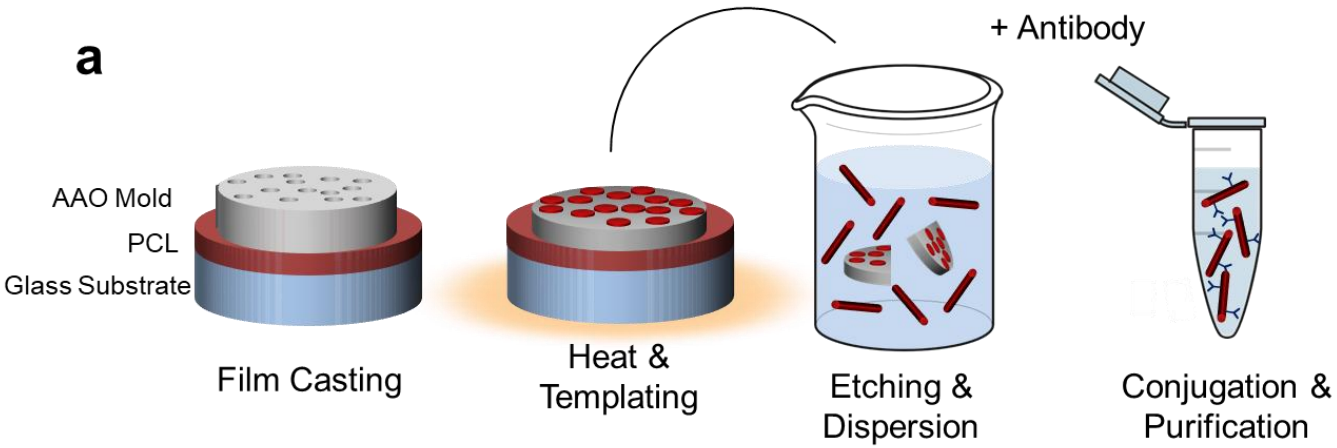




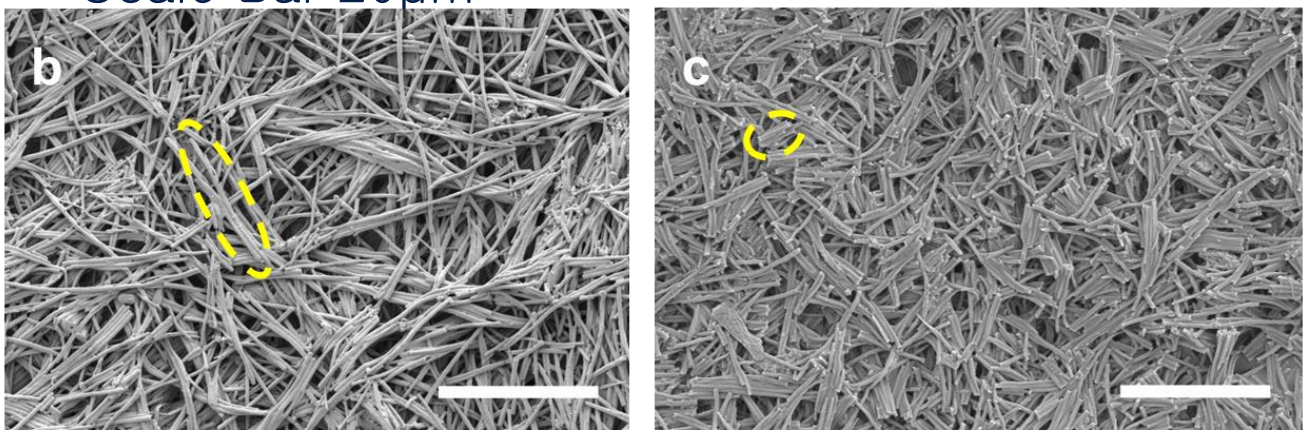




Nanorod fabrication scheme



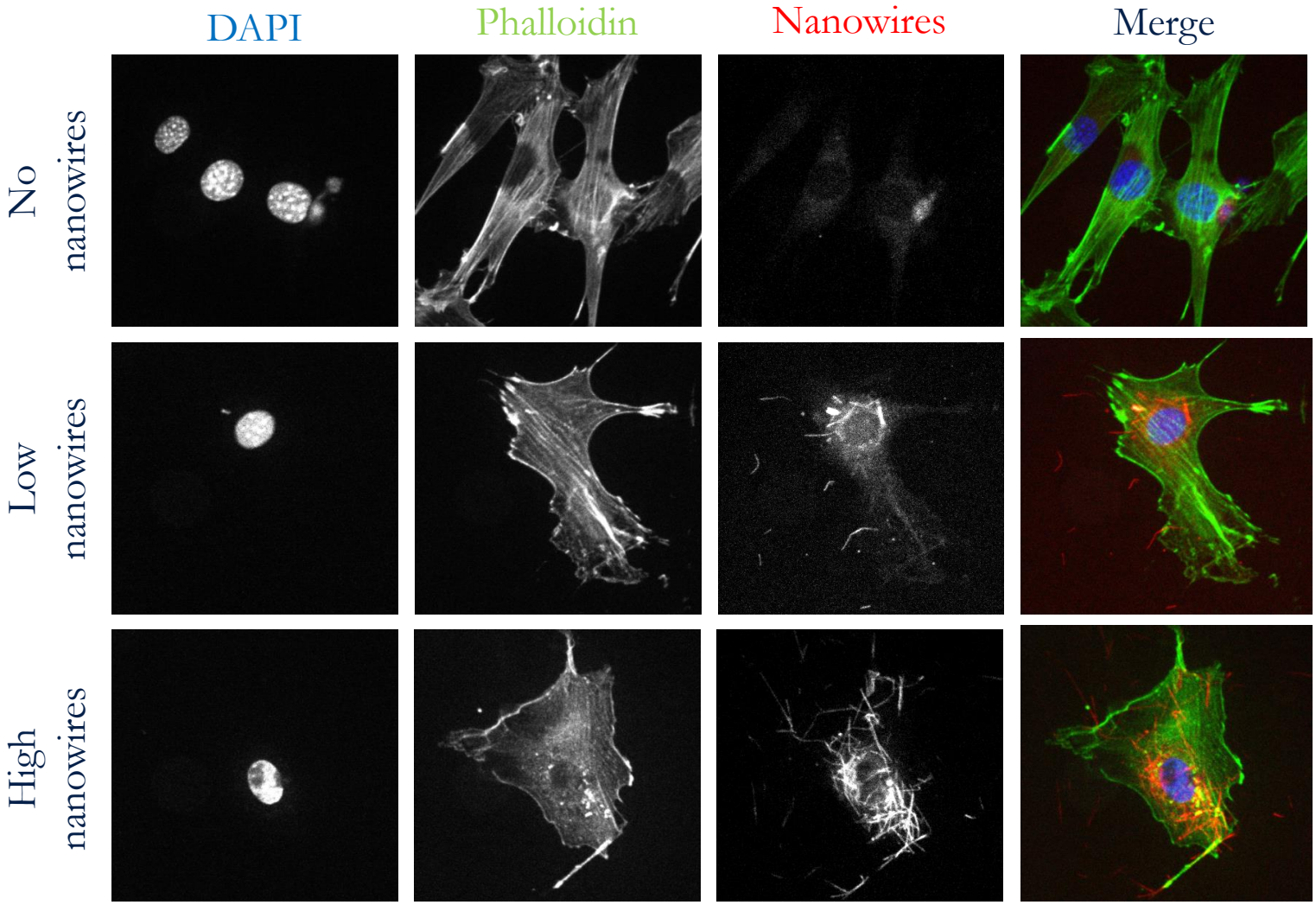
Scale Bar 20μm



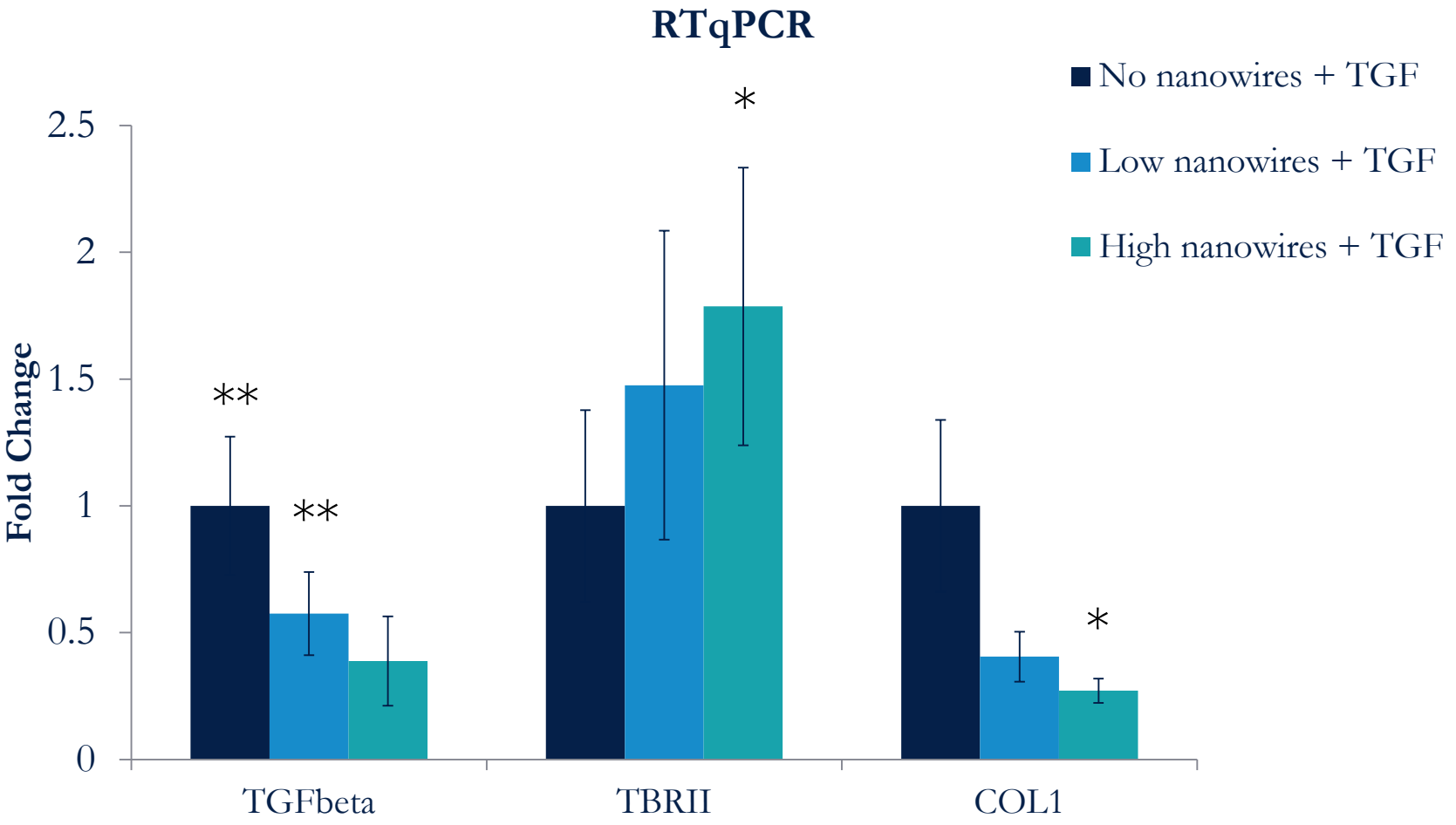
Zamecnik et al., ACS Nano 2017.

UCSF

Nanowires alter cellular morphology and actin cytoskeleton



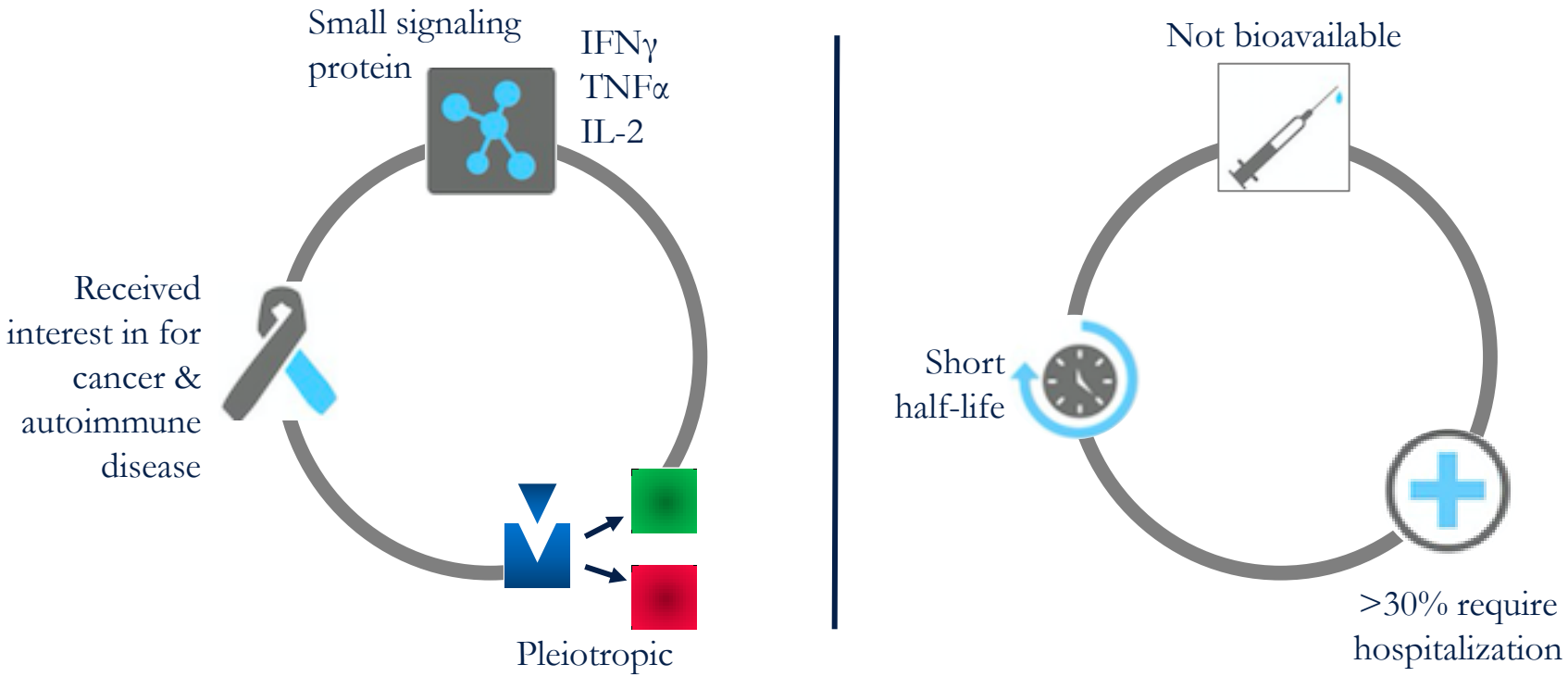
Nanowires decrease TGFβ and collagen transcription



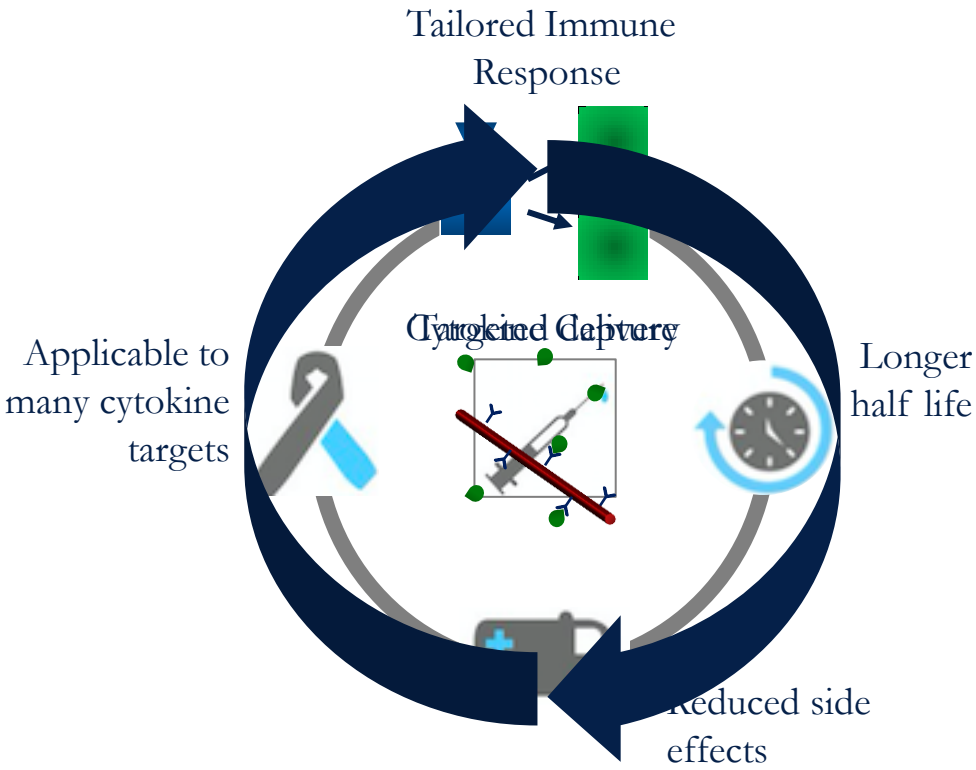
Can we use “nanostructure” to enhance immunotherapy?

Systemic Cytokine Therapy

Features vs. Challenges

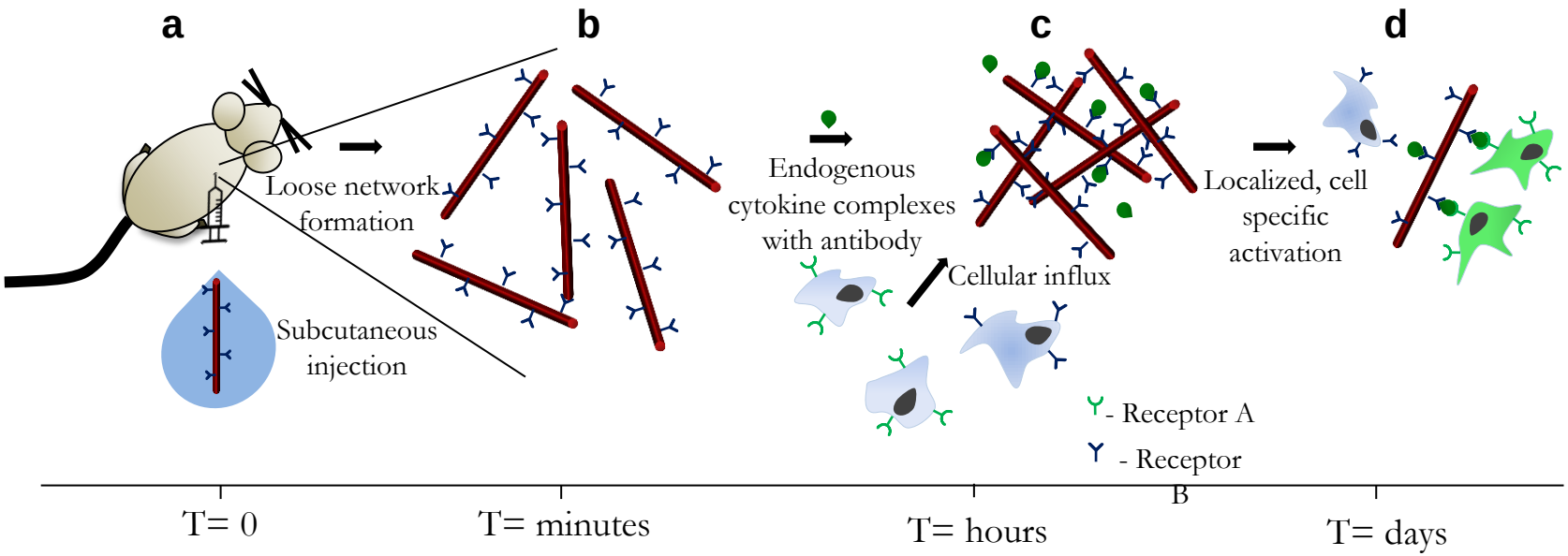


Strategy



Endogenous cytokine capture for prolonged & localized immune activation

Nanostructures as an injectable cytokine trap



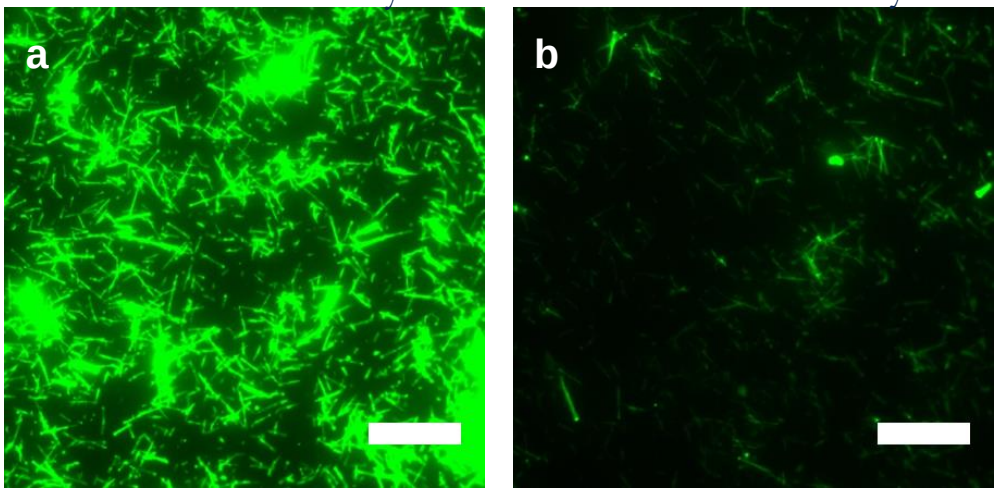
Zamecnik et al., ACS Nano 2017.

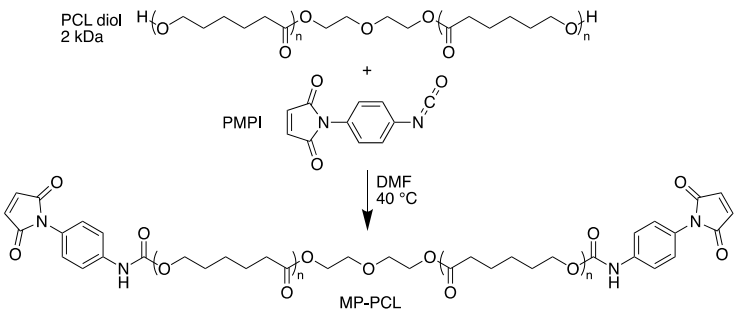
UCSF

Nanowires can conjugate to IgG species and sequester cytokines

Reduced Antibody

Native Antibody





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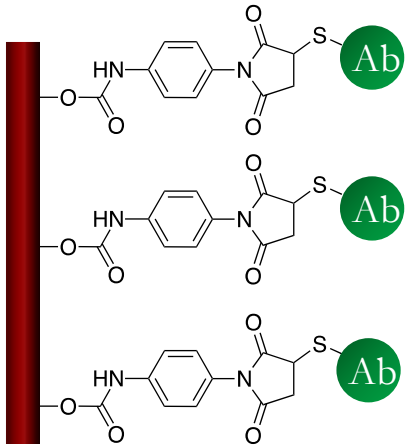

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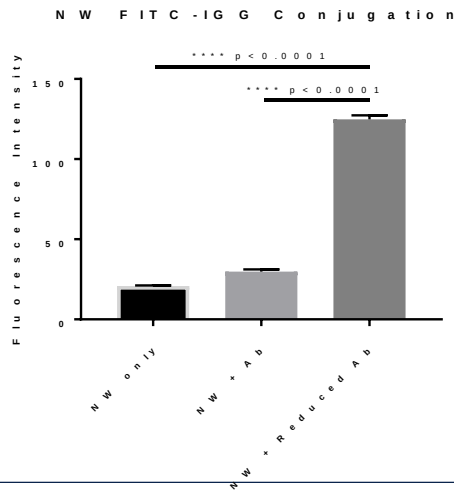

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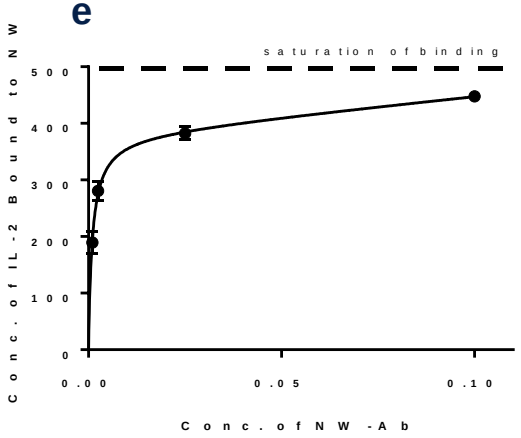
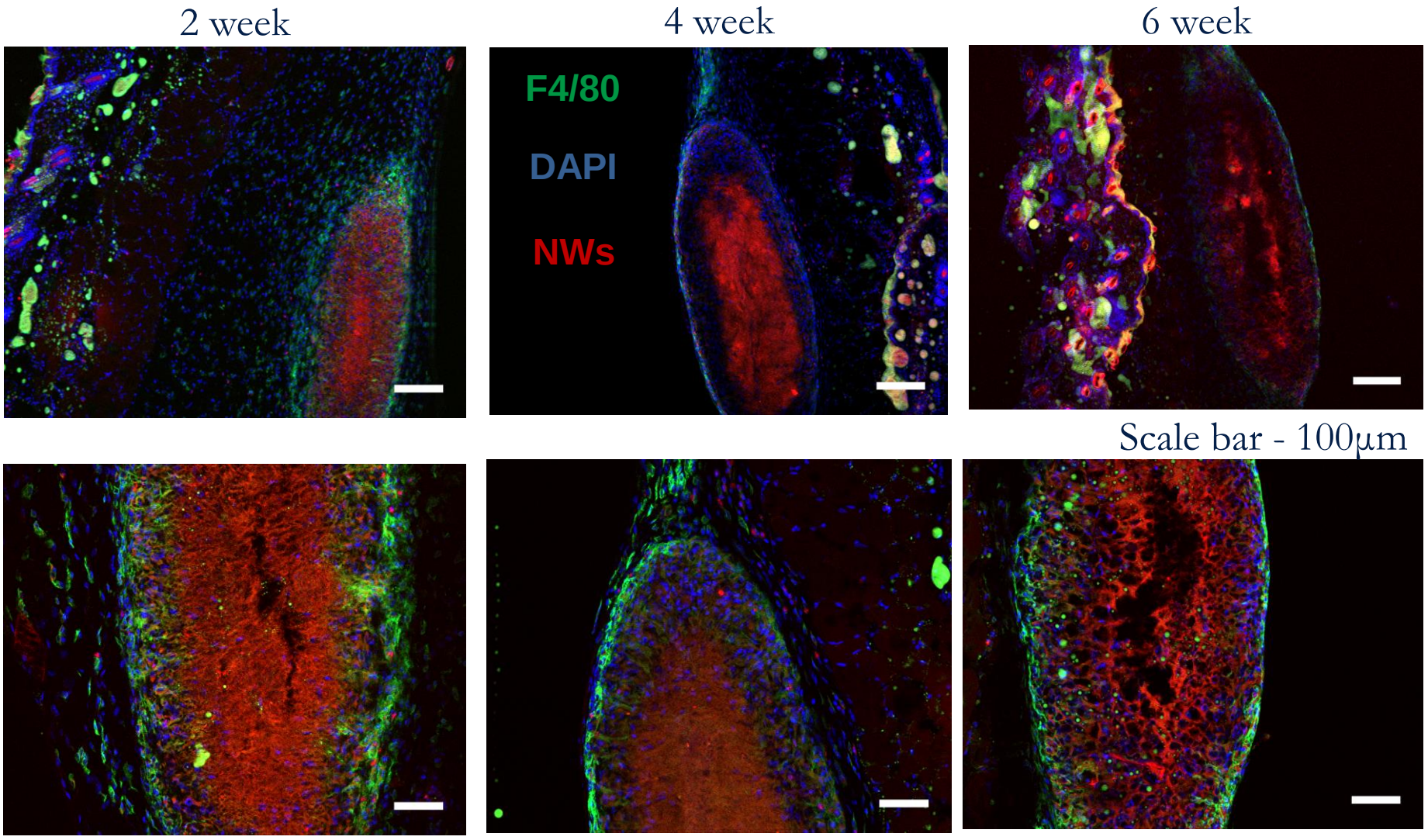


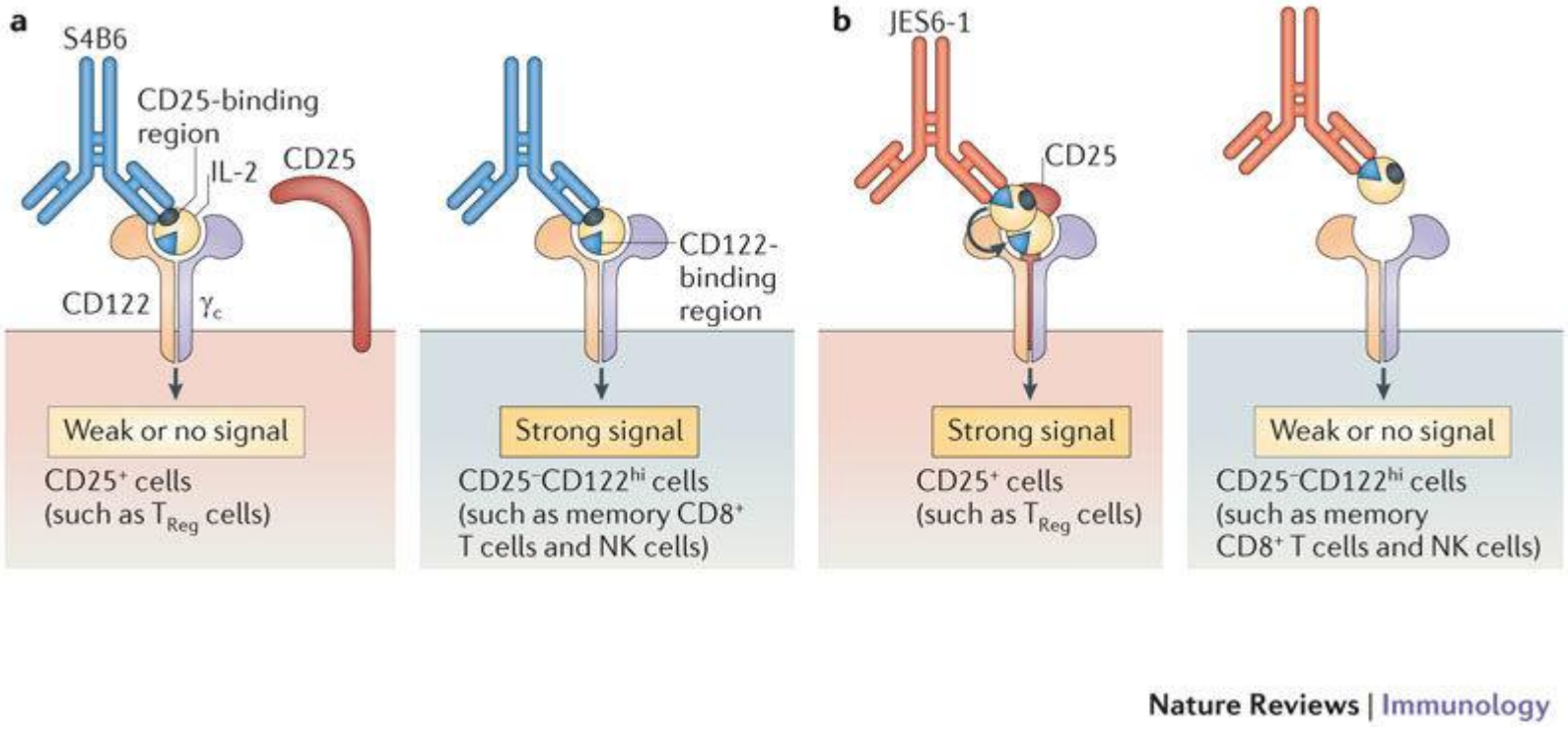
Scale Bar 20μm

UCSF

Nanowires persist *in vivo* for >6 weeks



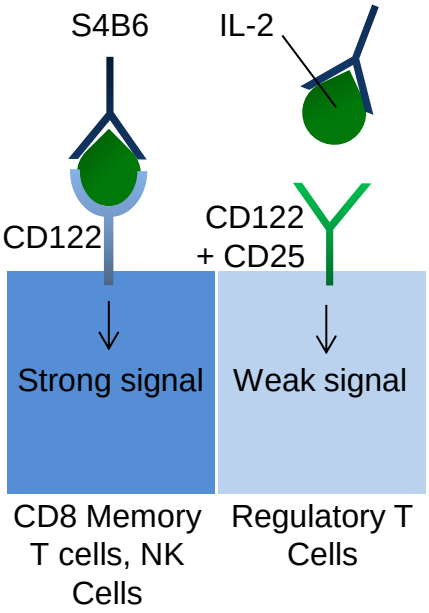
Can we use this strategy to activate T cells ***specifically*** and ***locally***?



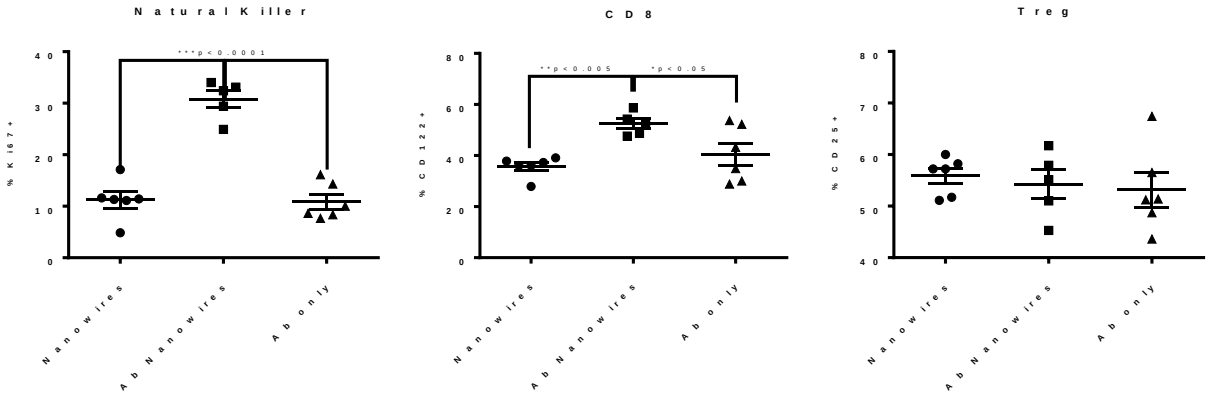
Sprent et al., 2012

UCSF

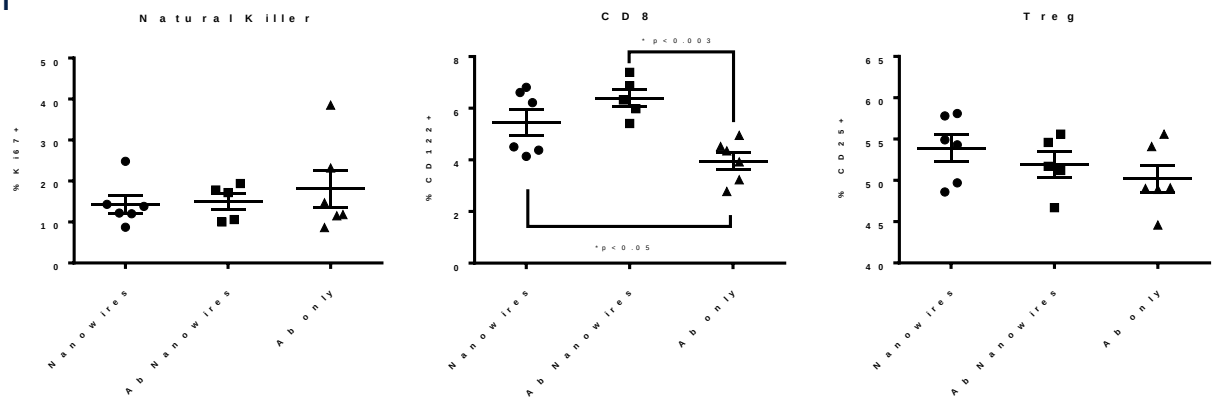
S4B6 antibody-conjugated wires locally activate NK andd CD8 Cells *in vivo*



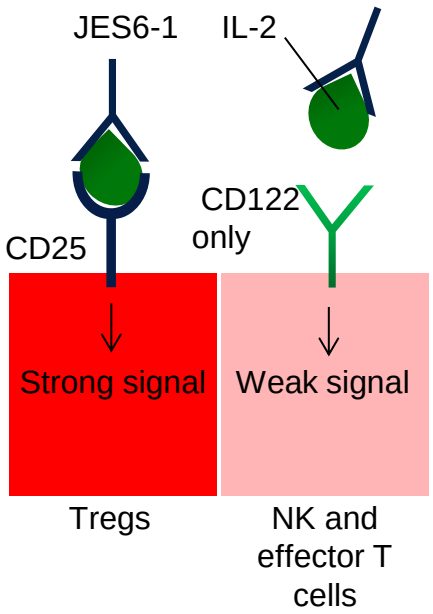
Skin

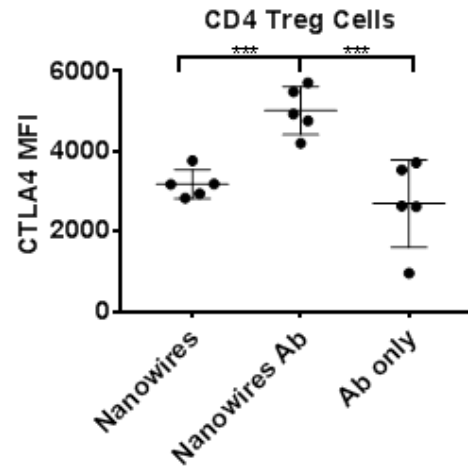


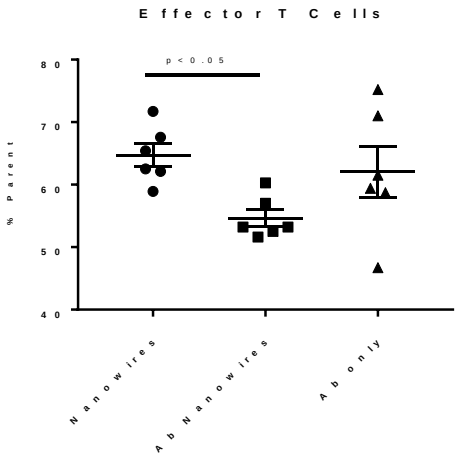
Lymph Node

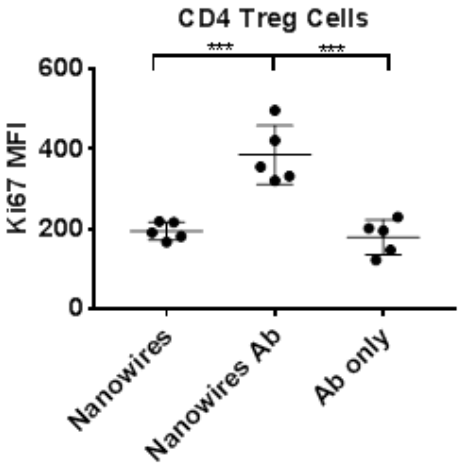


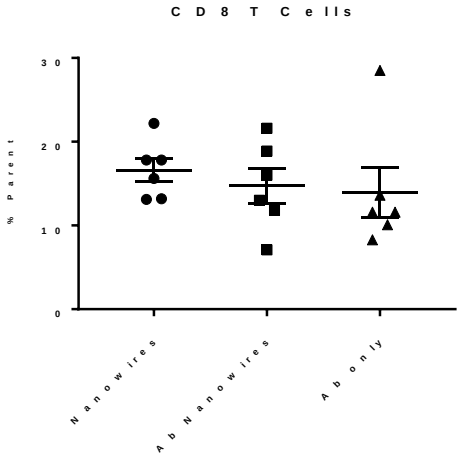
JES6-1-NWs locally activate Tregs and inhibit Teffs in the skin





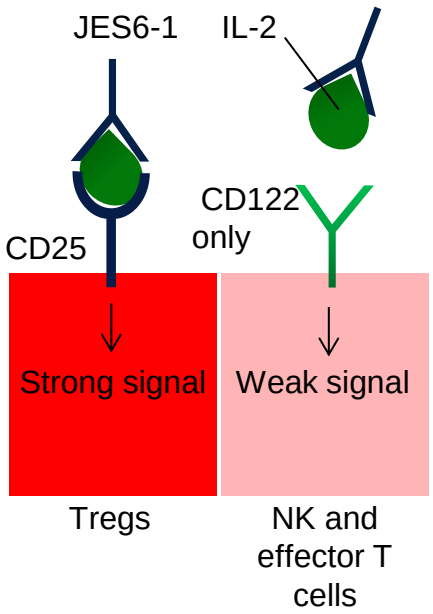


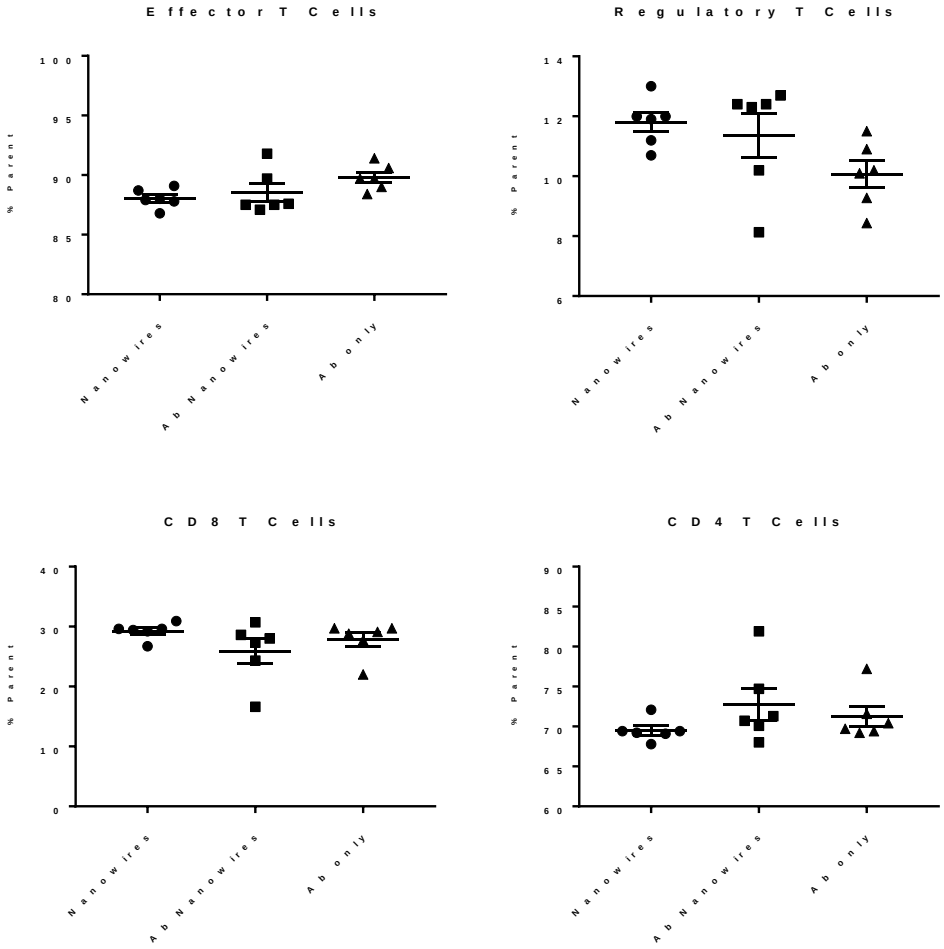




UCSF

JES6-1 NWs have little effect in the draining lymph nodes

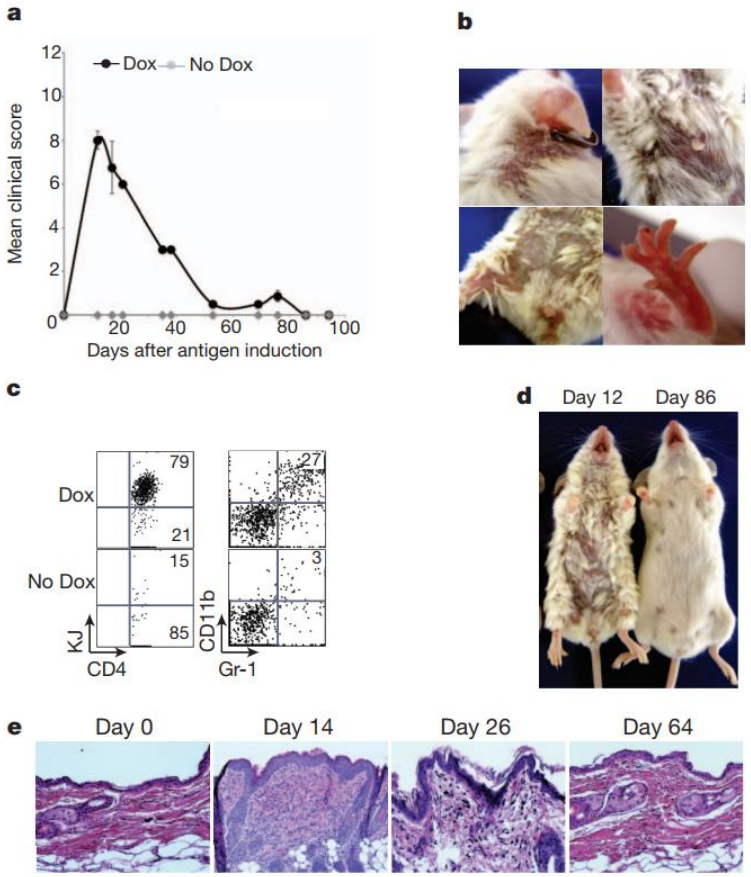




Disease Model –K5-TGO-DO11 Autoimmune Skin Disease

- K5-TGO-DO11 transgenic mouse that exhibits antigen specific immune response to OVA
- OVA under control of tetracycline promotor in keratinocytes,
- Leads to acute dermatitis and influx of CD4's into the skin

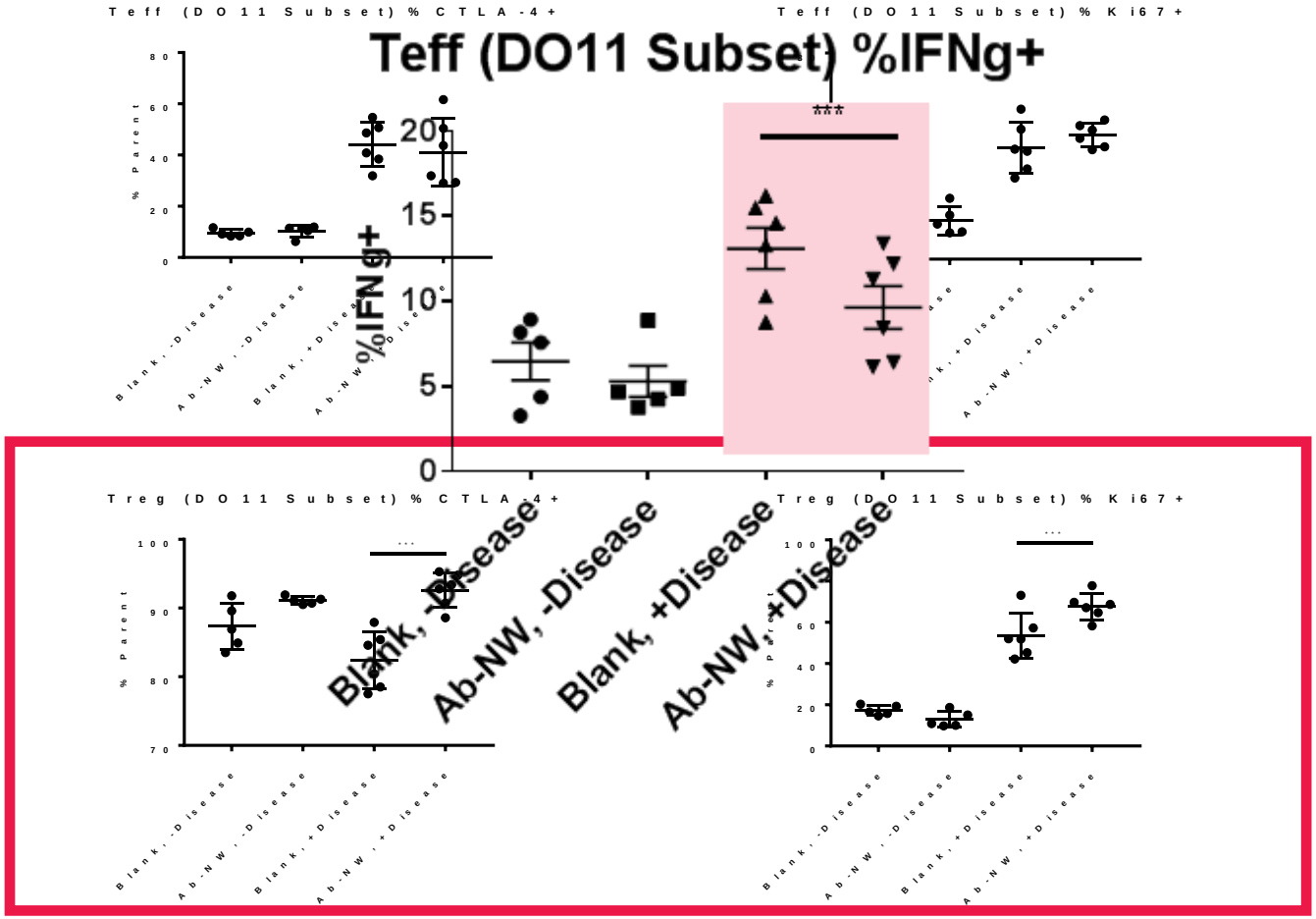
Hypothesis – local augmentation of Treg activation before antigen is turned on will ameliorate disease phenotype



Rosenblum *et al*, Nature, 2011

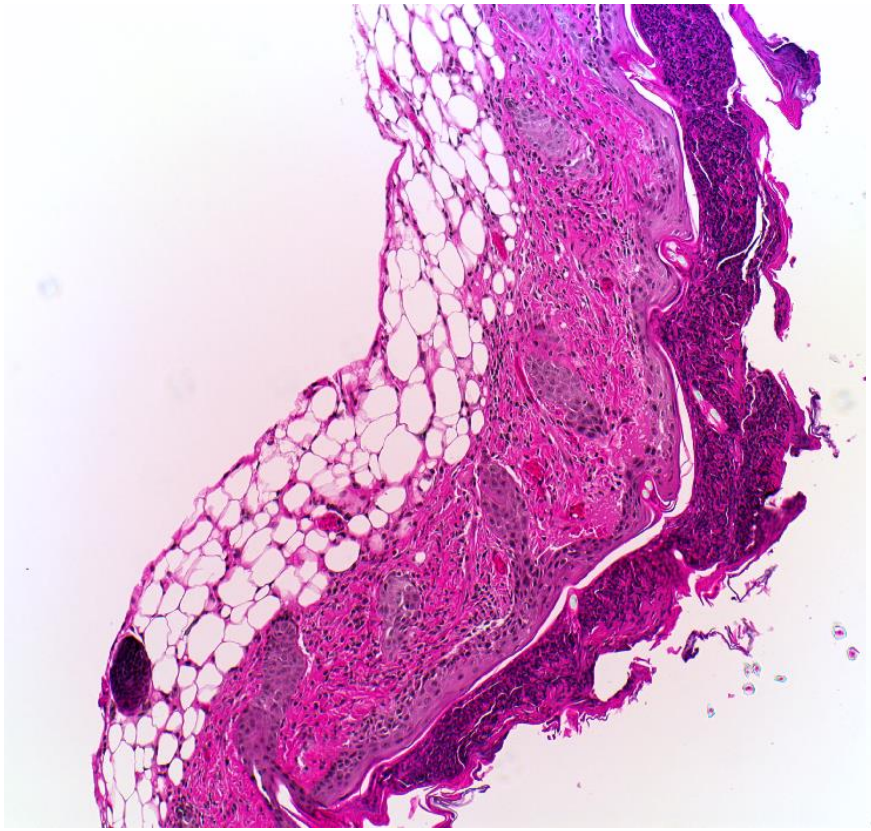
UCSF

Ab-NWs selectively activate antigen specific Tregs - but not effector cells - in the skin



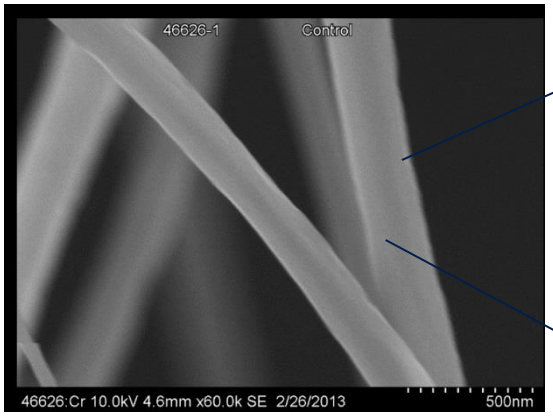
Decreased epithelial hyperplasia and myeloid infiltrate observed in vivo

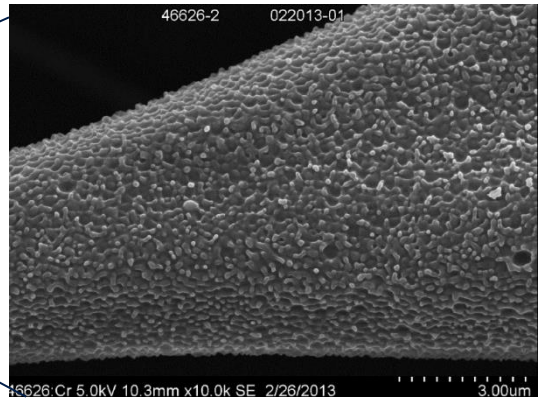
No Treatment (Blank wires)

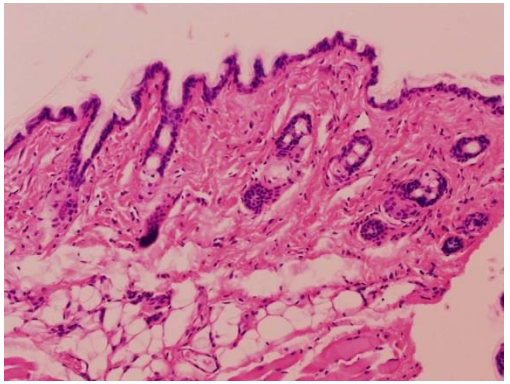


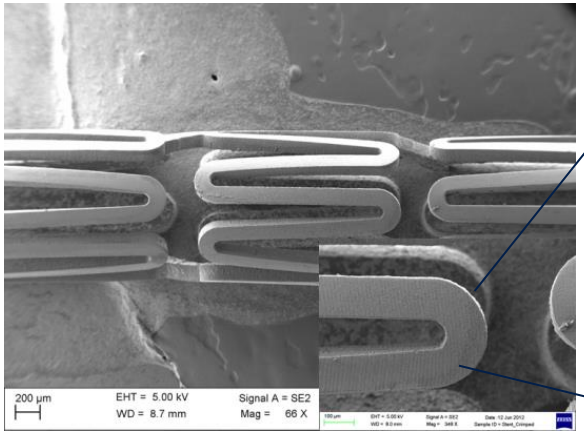
Treated (AB-NWs)

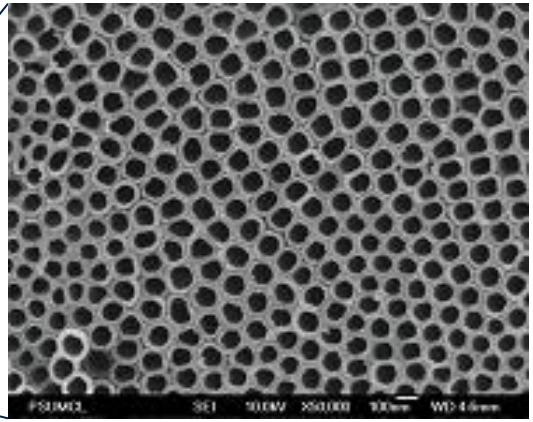
“Nanostructured” implants for improved wound healing: Stents and Vascular Grafts

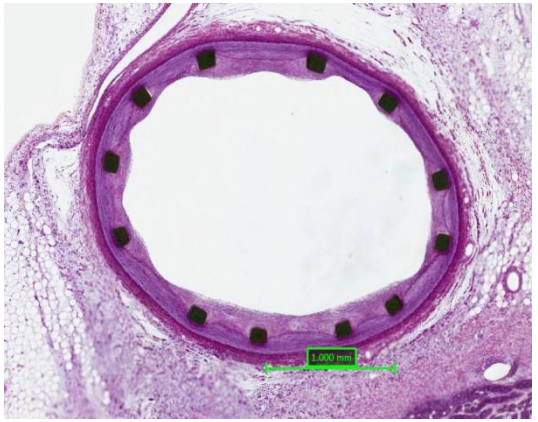












Lee et al, Nanoletters 2014; ACS Biomaterial Science, 2016

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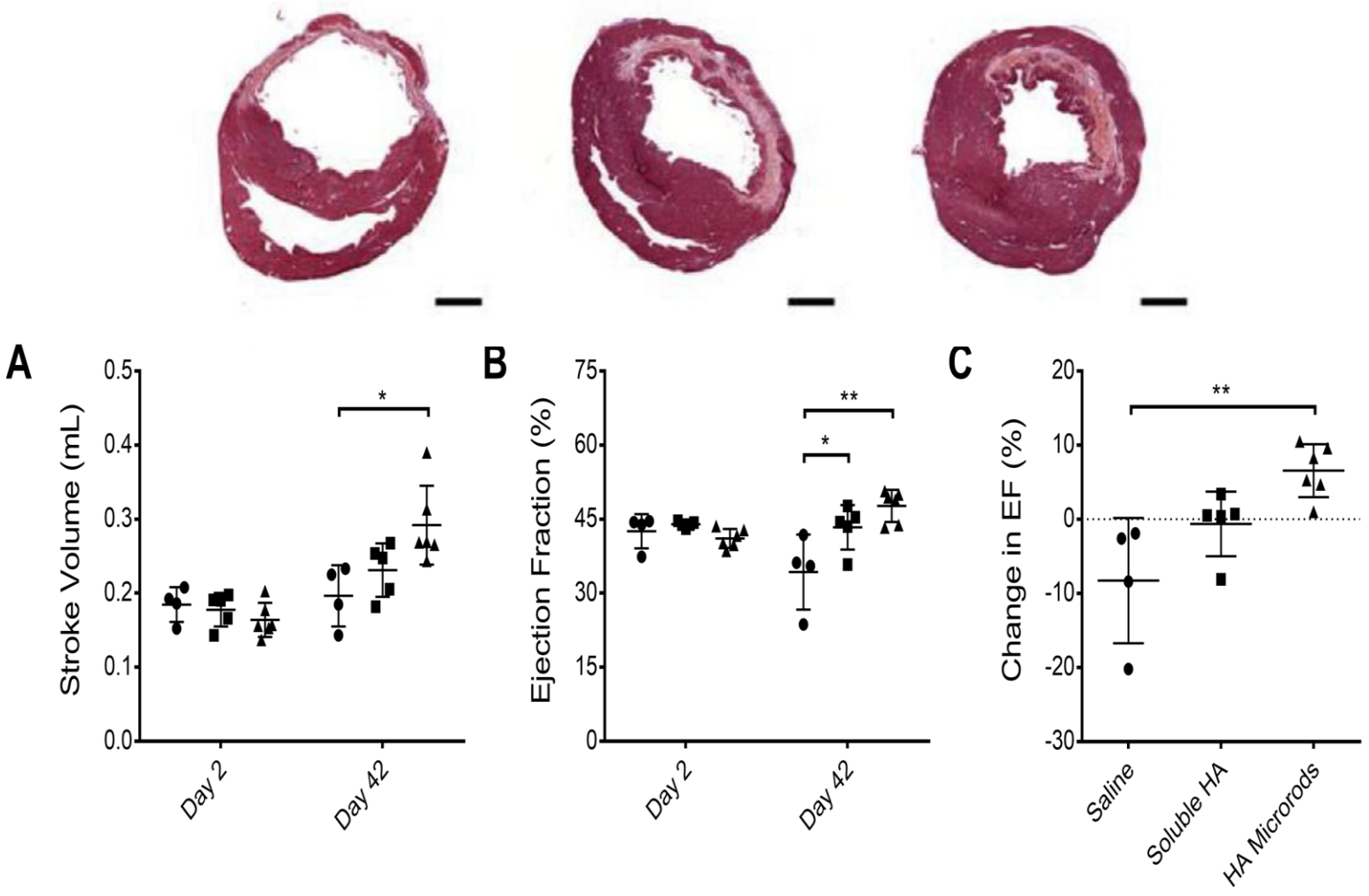
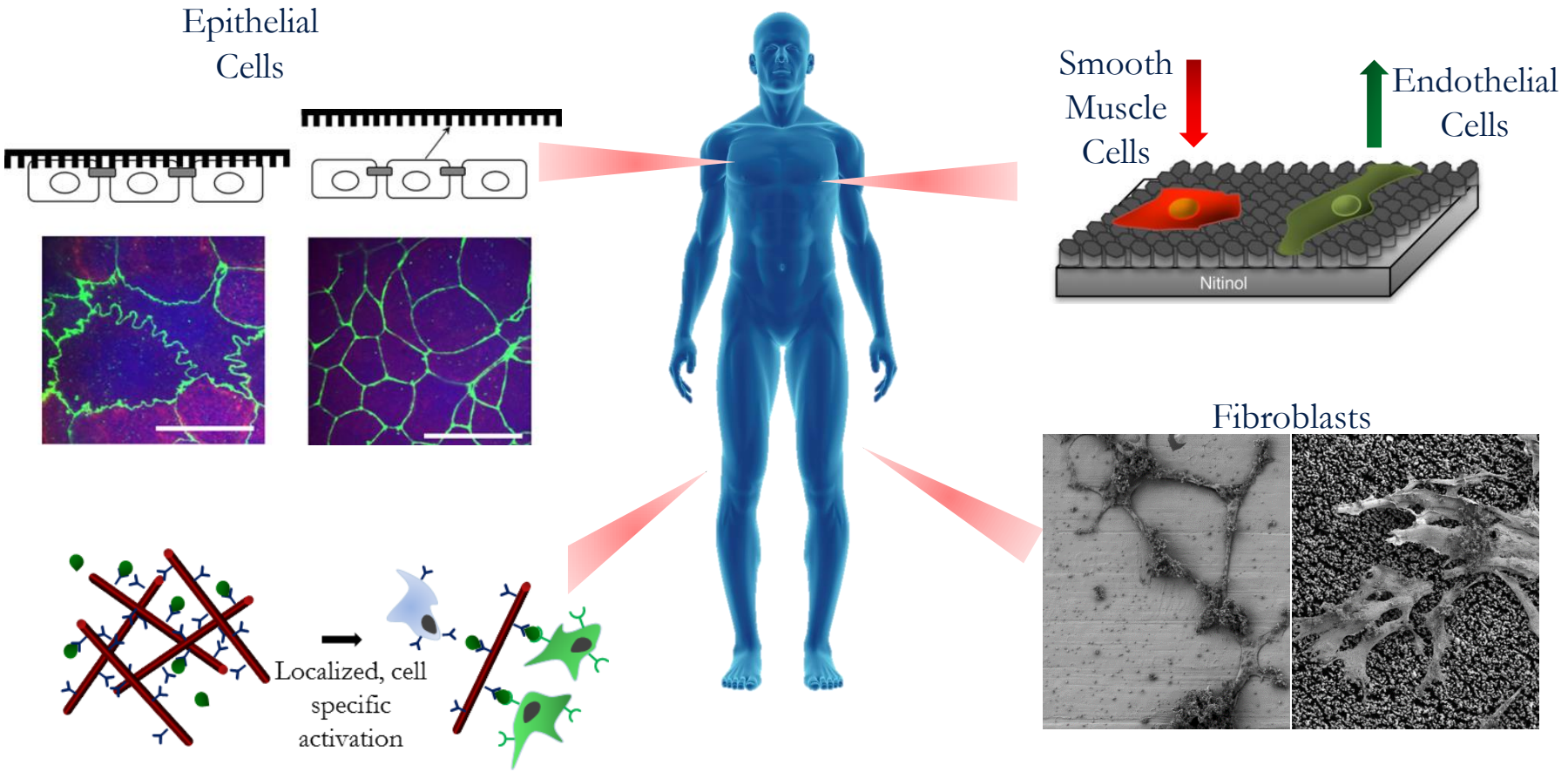
Injected Microstructures preserve *and* improve cardiac output after MI



Le LV et al., Biomaterials 2018

UCSF

Harnessing micro- and nano-topographical cues for therapy



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- Abbvie
- Santen
- Gates Foundation

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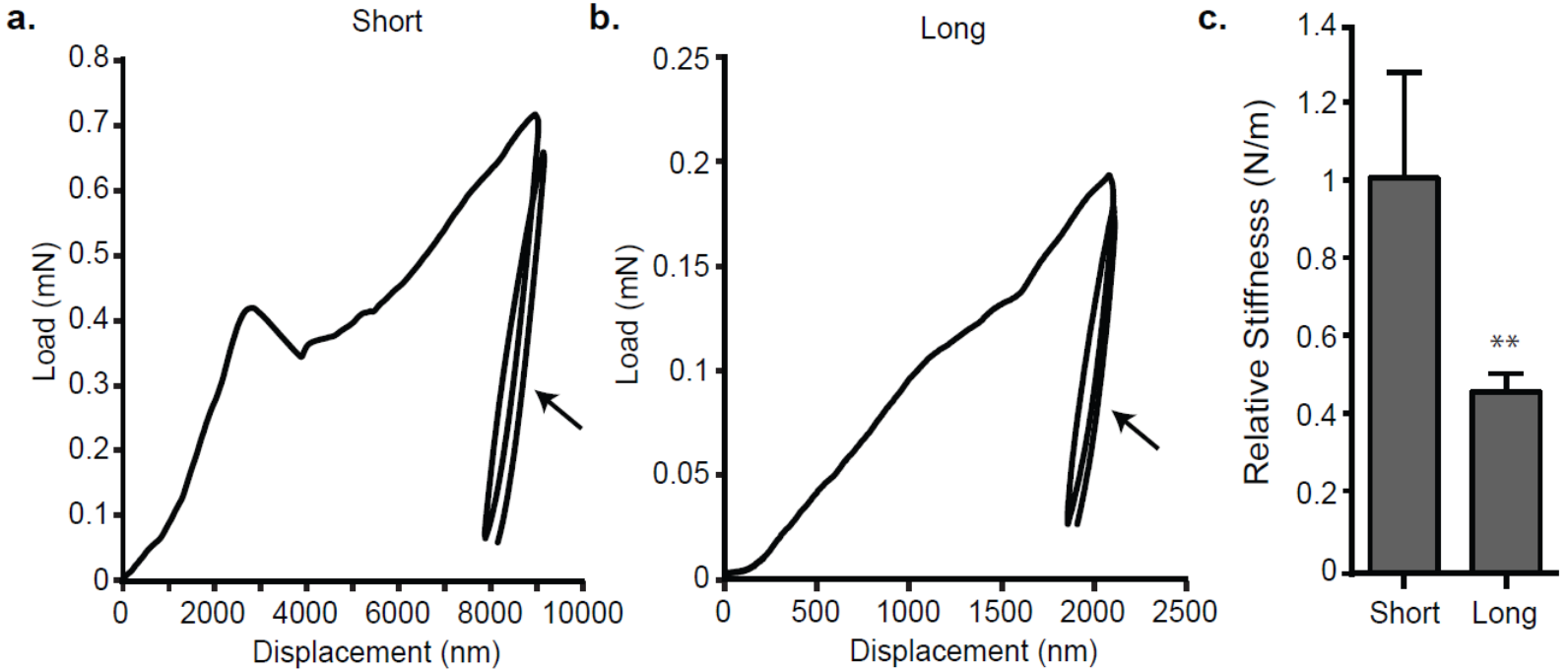
Characterizing mechanics of fibers



Nanoindentation:

- 1590 N/m for short versus 750 N/m for long microfibers (** $p < 0.01$, $n \geq 12$)
- constant prescribed displacement rate of 10 nm/s

with Julia Greer at Caltech

UCSF