Using Nanostructured Materials to Modulate the Immune System

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How can material structure modulate cellular function for therapeutic purposes?

Transdermal  | Oral   | Retinal   | Cardiac
---|---|---|---
![Transdermal Image]  | ![Oral Image] | ![Retinal Image] | ![Cardiac Image]
Can we tune material structure to modulate fibrosis?
Fibrosis: Fibroblasts Activated by Aberrant Mechanical Tension and TGFβ
High Aspect Ratio Features Provide Anti-fibrotic Signals

FITC-IgG Adsorption  Vinculin, F-Actin, DAPI

Kam, et. al, Nanoletters 2013; Tissue Engineering 2014
Long aspect ratio structures inhibit fibroblast activation \textit{in vitro}

\textbf{a.}

\begin{itemize}
\item Flat
\item Short
\item Long
\end{itemize}

\textbf{b.}

\begin{itemize}
\item 20 \mu m
\item 5 \mu m
\end{itemize}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure1}
\caption{Comparison of fibroblast morphology and expression levels under different fiber lengths.}
\end{figure}

\textbf{Allen, Ryu et al., 2016}
Long Structures Decrease Fibrotic Response *in vivo*


Submitted

8
Nanorod fabrication scheme

a

Film Casting
AAO Mold
PCL
Glass Substrate

Heat & Templating

Etching & Dispersion
+ Antibody

Conjugation & Purification

Scale Bar 20μm

Nanowires alter cellular morphology and actin cytoskeleton

<table>
<thead>
<tr>
<th>DAPI</th>
<th>Phalloidin</th>
<th>Nanowires</th>
<th>Merge</th>
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</thead>
<tbody>
<tr>
<td><img src="no_nanowires.png" alt="Image" /></td>
<td><img src="low_nanowires.png" alt="Image" /></td>
<td><img src="high_nanowires.png" alt="Image" /></td>
<td><img src="merge.png" alt="Image" /></td>
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</tbody>
</table>

No nanowires

Low nanowires

High nanowires
Nanowires decrease TGFβ and collagen transcription

RTqPCR

- No nanowires + TGF
- Low nanowires + TGF
- High nanowires + TGF

Fold Change

- TGFbeta
- TBRII
- COL1

**

*
Can we use “nanostructure” to enhance immunotherapy?
Systemic Cytokine Therapy

Features vs. Challenges

- Small signaling protein
- IFNγ
- TNFα
- IL-2
- Received interest in for cancer & autoimmune disease
- Pleiotropic

Not bioavailable

- Short half-life
- >30% require hospitalization
Endogenous cytokine capture for prolonged & localized immune activation
Nanostructures as an injectable cytokine trap

**Zamecnik et al., ACS Nano 2017.**
Nanowires can conjugate to IgG species and sequester cytokines.
Nanowires persist *in vivo* for >6 weeks

Scale bar - 100μm
Can we use this strategy to activate T cells specifically and locally?
S4B6 antibody-conjugated wires locally activate NK and CD8 Cells \emph{in vivo}
JES6-1-NWs locally activate Tregs and inhibit Teffs in the skin.

Strong signal
Weak signal

Tregs
NK and effector T cells
JES6-1 NWs have little effect in the draining lymph nodes.

**Diagram:**
- JES6-1
- IL-2
- CD25 only
- Strong signal
- Weak signal
- Tregs
- NK and effector T cells

**Graphs:**
- Effector T Cells
- Regulatory T Cells
- CD8 T Cells
- CD4 T Cells
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
Ab-NWVs 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
Injected Microstructures preserve and improve cardiac output after MI

Le LV et al., Biomaterials 2018
Harnessing micro- and nano-topographical cues for therapy
Acknowledgements

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- Abbvie
- Santen
- Gates Foundation
Characterizing mechanics of fibers

Nanoindentation:
• 1590 N/m for short versus 750 N/m for long microfibers (** p < 0.01, n ≥ 12)
• constant prescribed displacement rate of 10 nm/s

with Julia Greer at Caltech