Bacterial Interactions with Medical-Device Materials

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Overview

• Infection is now a leading cause of failure in many biomedical devices.

• Surface modifications to control bacterial colonization
  Examples:
  - antifouling surfaces
  - topography/patterning
  - antibiotics (elution; tethering; triggered release)

• The next paradigm for biomaterials design and development will include infection control.
Implanted Biomedical Devices

Total knee replacement
Engineered roughness to control load transfer

Wulff’s Law (~1890):
bone adapts to load (or lack of load)
Various Levels of Implant Surface Roughness

Roughness variations both vertically and laterally

Osteoblast Adhesion and Spreading Depends on Surface Roughness

S. epidermidis efficiently colonizes satin finish surface

Hardware-Associated Infection

Spinal Hardware

• Discectomy – 0.5% to 5%
• Discectomy and fusion – 5% - 8%
• Fusion without implants – 1% to 5%
• Fusion with implants – 1% to 13%

“The primary risk in the use of an external fixator is infection…”

Intramedullary Attachment for Above-the-Knee Prostheses

Battlefield/Civilian Trauma

Courtesy of Dr. Ahmad Nassr
Mayo Clinic

J Bone Joint Surg Am.
2010;92
(Sup. 2):
180-186

Courtesy of UMDNJ
The Number of New Antimicrobials is Declining

Number of New and Approved Molecular Entity (NME) Systemic Antibiotics Per Five-year Period, Through 3/11.

Infectious Diseases Society of America (IDSA)
Clin Infect Dis. 2011;52:S397-S428
Antibiotic Resistance is Increasing

Adapted from: Antibiotic Resistance Threats in the United States, 2013. Centers for Disease Control & Prevention
Bacterial Biofilms

* Bacteria colonize surfaces and develop into biofilms

* Bacteria in the biofilm state can be as much as 10,000 times resistant to antibiotics than planktonic bacteria

Five stages of biofilm development.
From “Understanding biofilm resistance to antibacterial agents”
David Davies
Nature Reviews Drug Discovery 2, 114-122 (February 2003)

Wu et al. submitted to Microscopy and Microanalysis (2014).

Cryo-SEM of S. aureus

2 μm
Cell/Bacteria - Material Interactions

- Cell-interactive surface
- Promotes healing
- Susceptible to infection
Cell/Bacteria - Material Interactions

Cell-interactive surface
Resists bacteria
Can inhibit healing

Cell-repulsive surface
Cell/Bacteria - Material Interactions

- **Cell-interactive surface**
  - Promotes healing
  - Resists bacteria

- **Cell-repulsive surface**

- **Differentially interactive surface**
Cell/Bacteria - Material Interactions

Surface modifications to control bacterial colonization
- Topography
- Patterning
- Antimicrobials
- Self-assembly
  LbL thin films
  microgel coatings
Bio-inspired Surface Topography

Optical profilometry of embossed PDMS surface
2 \( \mu \)m width, 2 \( \mu \)m spacing, 3 \( \mu \)m depth

**Brennan et al.**

Courtesy of A. Brennan
Univ. Florida
Surface Topography Inhibits Bacterial Colonization

*P. aeruginosa* clinical isolate in BSA-modified TSB

![Patterned Surface Images](image1)

Day 2  Day 7  Day 14  Day 21

![Smooth Surface Images](image2)

Day 2  Day 7  Day 14  Day 21

Courtesy of A. Brennan
Univ. Florida

Brennan et al.
“Antifouling” Coatings

PEG gel

Poly(ethylene glycol) [PEG]

PEG monolayer
e.g. oligo-EG thiol, silane

Jeon, Andrade, de Gennes, et al.

Prime & Whitesides
*JACS* 115: 10714-10721 (1993)
Surface-Patterned PEG Microgels
Laterally modulated cell adhesiveness

Wang, Firlar, et al
J. Polymer Sci B: Polymer Physics (2013)

Immunofluorescence imaging of adsorbed Fibronectin (FITC) on PEG microgel patterned surface

Wang et al., Biofouling 28 (9) (2012) 1023-1032
The Staphyloccocal Adhesion Rate Decreases with Inter-Gel Spacing ($\delta$)

Osteoblasts Adhere to and Spread on Microgel-Modulated Surfaces

Exploits differences in:
- Size
- Cell membrane/wall
- Adhesion mechanisms

Active Bacterial Killing: Drug-Eluting Devices/Surfaces

TP: triclosan-coated polyglactin 910 suture
TM: triclosan-impregnated monofilament

Degradable Non-degradable (Antibiotic eluting bone cement)


Courtesy of S. Rothenburger
Self-Assembled Antimicrobial-Containing Coatings

Layer-by-Layer (LbL) thin-film self assembly

G. Decher
Science 277: 1232-1237 (1997)

Non line-of-sight rapid deposition technology
Multilayer Components

polymers

antimicrobials

clay

polymers

proteins

Courtesy of S. Sukhishvili
Stevens Institute of Tech.
**pH-Triggered Self-Defensive Coatings**

(Tannic Acid/Gentamicin)$_{300}$

<table>
<thead>
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<th>pH</th>
<th>Released Gent, %</th>
<th>Released Gent, μg</th>
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</tbody>
</table>

Mass spec
0.2 M NaCl

Sukhishvili et al.
ACS Nano, submitted (2014)
Biomacromolecules 11(12) 3448-56 (2011)
pH-Triggered Self-Defensive Coatings

Sukhishvili et al.
ACS Nano, submitted (2014)
Biomacromolecules 11(12) 3448-56 (2011)
pH-Triggered Self-Defensive Coatings

Local Release

Bacterial surface coverage, %

Time, weeks

0 1 2 3 4

control
TA/Gent

Sukhishvili et al.
ACS Nano, submitted (2014)
Biomacromolecules 11(12) 3448-56 (2011)
Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Anionic PEG-AA copolymer microgels

PLL primer layer silicon wafer
Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Laterally modulated cell adhesiveness

Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Some cationic antimicrobials:
- vancomycin
- gentamicin
- tobramycin
- amikacin
- antimicrobial peptides/peptoids
- etc..

Q. Wang et al,
Appl. Matls. & Interfaces
V4, 2498-2506 (2012)
Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Q. Wang et al,
Appl. Matls. & Interfaces
V4, 2498-2506 (2012)

Cationic antimicrobial

PLL primer layer

silicon wafer

L5 antimicrobial peptide

PAWRKAFRWAWRMLKKAA
Lactoferrin derived
$M_w = 2274$ Da
6 positive charges at pH 7.4

NJ 9709
S. epidermidis
Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Q. Wang et al,
Appl. Matls. & Interfaces
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Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

Adhesion-promoting protein
(e.g. Fibronectin PI ~ 5.5)

PLL primer layer

Q. Wang et al,
Appl. Matls. & Interfaces
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V4, 2498-2506 (2012)
Hierarchical Microgel Self-Assembly to Create Infection-Resisting Multifunctional Surfaces

> Non line-of-sight deposition
> Laterally modulated cell adhesiveness
> Post-deposition antimicrobial loading
> Self-defensive antimicrobial release

Q. Wang et al,
Appl. Matls. & Interfaces
V4, 2498-2506 (2012)
Bacteria can infiltrate ~micron-sized interstices while tissue cells are constrained to the surface.


Microgel Self-Assembly within Nanofiber Mats

Peptide-Loaded Microgel-Modified Nanofibers Resist S. aureus Colonization

unmodified scaffold

Microgel/peptide-modified scaffold

Cryo-SEM of fractured hydrated fiber mat

Osteoblast Response to Microgel-Modified Nanofiber Mats

Q. Wang et al,
Triggered Antimicrobial Release

L5-loaded microgel-modified PCL-chitosan nanofibers after soaking in DMEM for 4 days at 37 °C then inoculated w/ S. aureus and cultured in TSB for 8 h.

Self-defensive surface
A Next-Generation Paradigm for Biomaterials Science and Engineering

The current generation of biomaterials has to a great extent been defined by a major paradigm shift from the pre-1990's perspective of creating biologically inert synthetic surfaces to the current perspective of creating surfaces that controllably interact with host tissue.

From this shift, a new international community emerged that marries skills from cell and molecular biology with those from physical sciences and engineering to an extent almost unthinkable twenty years ago.

The biomaterials community now needs a similar paradigm shift so it can not only regulate tissue-cell/material interactions but do so while simultaneously controlling bacterial-cell/material interactions.
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http:www.stevens.edu/ses/biomaterials/conference

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