Polymers in Biology, Bioengineering and Medicine

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Polymers in Biology

Traditional 2D Cultures:
- polystyrene w/ & w/out surface modifications

Emerging 3D Cultures:
- Collagen
- Matrigel
Many Cells Behave Differently in 2D vs 3D Culture

Tumorigenic cells (middle panel) can be reverted to a near-normal morphology by down-modulation of EGFR signaling. The effect is not observed in 2D.

Designing Polymer Niches for Cell Culture:

Cells

Encapsulation

Seeding

Permissive

Size scale,
Kinetic of degradation,
Transport

Promoting

ECM-like Molecules,
Growth Factors,
Differentiation Factors

Synthetic

Natural
Polymers as ECM mimetics

Cells also Sense and Respond to Mechanical Environment

What biologists could use....

• Tools to temporally control presentation of molecules
• Spatial control of ligands to guide cell attachment and protein interactions on multiple scales ranging from nms to 10s of μms scale
• Better mimics of the extracellular matrix and the in vivo environment
• Presentation of complex (heterogeneous) and multiple functionalities
What polymer scientists and engineers are trying to develop....

- Materials that allow temporal control of cell interactions
- Spatial control of chemistry and mechanics at multiple scales
- Spatiotemporal control of functionalities in three-dimensional settings
- Presentation of complex and multiple functionalities
- Mimicking properties of natural materials and integrating multiple functionalities
- Using materials to direct cell-cell and cell-tissue interactions
Polymer Science in Bioengineering

New Chemistries

- Delivery of new molecular targets
- High through-put assays
- Directing cellular interactions and tissue regeneration

Advanced Processing

Control on multiple time and size scales
Polymer Assisted Delivery of Therapeutics

- Human genome project --> Accelerated discovery of biomolecular products (proteins, plasmid DNAs, various forms of RNA)
- Broad challenges:
  - Stability of molecules
  - Non-specific interactions with cells
  - Limited intracellular entry of nucleic acids
  - Delivering new classes of molecules (e.g., miRNA)
- Significant efforts in targeting and functional cues to enhance delivery (e.g., loading into biomaterials, complexation and chemical fusion)
Polymer Chemistry-Structure-Property Relationships for Intracellular Delivery

Role of the Microenvironment in Regulating Therapeutic Effects

Polymers for stimulatory and/or inhibitory effects

- Through directed cell adhesion
- Chemical structure of adhesion cue
- Physical properties and architecture of the ECN
- Presence of supplemental molecules to up or down-regulate adhesion-receptors

Kong & Mooney, Nature Reviews, 6, 455 (2007)
Polymer-Directed Cell-Interactions

Controlling Cell Adhesion

- Grafting to and grafting from approaches
- Diverse chemical and biological functionalities
- Chemistry vs topography
- Clustering of ligands
- Decouple mechanics from chemistry
- Highly regulated structures
- Tunable surfaces

Density/Spacing of Cell-Adhesive Ligand

Spatial Control of Cell Attachment
Responsive substrates allow temporal and external control of material properties and functionalities.
High Throughput Screening Methods

6 x 6 array of 100 nl gels with varying chemical functionality.

On-chip, IHC or FISH
Polymer-Directed Cell Assembly

Directing Cell-assembly
Local Delivery of therapeutics

Fetal rat forebrain cells (E16-17)

Directing expansion and differentiation of stem cells
Improving cell-based therapies

Mark Saltzman, Yale
Collectively, these extrinsic factors trigger signaling pathways that affect diverse aspects of cell behavior, modifying differentiation, proliferation, expression of ECM, activation of growth factors, and even preventing apoptosis. Using this information to engineer and manipulate cell behavior relevant to medical problems.
Polymer Science in Medicine

Fundamental Studies

Sophisticated approached
Broad diversity of chemistry
Long-term potential
What if?

Clinical Application

Minimalist approach
History of human application
Processing and manufacturing
Safety and practicality
Nearer-term impact
Cell Therapies in Clinical Medicine

Existing Therapies

• Bone marrow transplants
• Blood transfusions
• Islet transplantations
• Autologous chondrocyte implantation
• Over 2000 clinical trials related to cell therapies:
  – Stem cells delivered to ischemic heart regions
  – Neural precursor cells for treating Parkinson’s disease
  – ……
Cell Delivery in Clinical Medicine

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  - ......

Motivation for Polymer Development

- Cell-based therapies will continue to grow as a clinical method to treat diseased or injured tissues.
- To date, treatments are often sub-optimal because carriers are needed for the cells.
- Minimally, carriers are needed that can immobilize cells while allowing them to grow.
- How to exploit polymers for these applications.
Polymers in Medicine

• How to learn from and mimic wound healing? Or Development?
• How much micromanaging of cellular behavior is necessary? What level of information is required?
• Controlling polymer structure and chemistry on multiple size and time scales
• Expand the repertoire of polymers used in human medicine and/or exploiting processing of existing materials to impart new properties
Polymers in Biology, Bioengineering, and Medicine: Needs and Opportunities

- Expand the repertoire of polymers that are considered ‘biomaterials’ and exploit advanced processing methods
- Marriage of knowledge from genomics, proteomics, tissue morphogenesis, evolution of disease, stem cells and their differentiation, …with the design of polymers
- Better integrate multiscale modeling as a tool to guide experimental design and test hypotheses.
- Exploiting advanced tools in imaging, molecular analysis, etc. to better characterize and quantify cell-bimolecule polymer constructs on multiple scales
- Seamless collaborations between basic sciences, engineering, and clinical sciences
Janelia Farm

- HHMI’s first research campus
- 281 acres, 760,000 gross sq ft, 380,000 sq ft of laboratories
- Opened: Fall 2006
- Cost: $500M USD
- Focus: collaborative and innovative research that calls for the development of cutting-edge technological tools.
- Targets of recruitment: Early-career-stage investigator who enjoy engaging in research themselves and working closely with others
- People: Group Leaders, Fellows, Students, Core Support, Visitors (individuals and project teams)
- Steady state: 24 Group Leaders and collective population of ~120 scientists