NEUROENGINEERING

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9/23/2011
What is neuroengineering?

- Neuroengineering combines engineering and computational approaches to problems in basic and clinical neuroscience.
Research and education in neuroengineering encompasses the fields of engineering, mathematics, and computer science. This is coupled with molecular, cellular, and systems neurosciences. Neuroengineers focus on developing novel therapeutic options for neurological disease, defect, and injury.
Neurological Disorders

- Over 600 known neurological disorders
  - Diseases of the CNS and PNS
    - Epilepsy
    - Alzheimer’s
    - Parkinson’s
  - Diseases that attack the nervous system
    - Infections
    - Cancers
  - Physical Injury
  - Stroke
  - Cancer
  - Congenital ‘Defects’
    - Deafness, Blindness, etc.

- For most, treatment options are extremely limited
- The disease/disorder mechanism is highly varied, as is the prognosis.
Some of the Primary Goals of Neuroengineering

- Analyze the function of the nervous system
- Develop methods to restore damaged neurological functions
- Create artificial neuronal systems
Several Neuroengineering Subfields

- Diagnostic Devices and Systems
- Assistive Devices
- Smart Prosthetics
- Neural Cell/Tissue Engineering
- Brain-Computer Interfaces
- Neural Stimulators
- Neural Prosthesis: Implanted Sensors and Devices
  - Artificial cochlea
  - Artificial retina
  - Hippocampal prosthesis
Neural Prosthetics

- Bridging the gap between neuroprosthetic design, tissue engineering, and neurobiology

Hochberg, 2006, Cyberkinetics Corp

New Approaches Being Tested

Implanted drug pumps: These provide temporal and spatial delivery.

Implanted Neural Recorder/Stimulator: Record EEG and Attenuate to stop/attenuate faulty brain activity.

The biological approach: The transplantation of biomolecule-releasing cells provides spatial delivery of drug/regrowth of neuronal pathways.
The Interface: One Type of Electrode Used

Major Interest Area

- Controlling host response
  - Long term stable electrode/neuron interface
    - Gliosis
    - Promoting Neuronal Circuitry
Gliosis upon Electrode Implantation

- Acute
- Chronic

Neuronal Ingrowth and Circuitry Development

Neural Stem Cell ➔ Functional Neurons
How to Combat Gliosis and/or Enhance Neuronal Ingrowth?

- Material Structure
- Material Chemistry
- Material Surface Morphology
- Material Coatings
  - Cell Adhesion Molecules
  - Anti-Inflammatory Agents
  - Encapsulated cells Coating the device
  - Target and draw in NPCs

How to grow neuronal cells in culture...From proliferation to differentiation

- Similar set of approaches.

- So, there is a subset of neuroengineering that focuses on developing materials for integration with neural systems, either *in vivo* or *in vitro*. 
Materials Inspiration

CNS Development
Activity Independent Mechanisms

Stem Cell
Differentiation
Migration
Maturation

"Hardwired" or Environmentally Influenced

Environmental Factors Influencing Activity
Independent Mechanisms

ECM Composition and Concentration
Growth Factors
Morphogens
Cell-Cell Interactions
Mechanical Environment

We can control or mimic many of these factors
Can Flexural Stiffness/Matrix Stiffness Dictate/Homogenize stem cell differentiation?
Solution – Nanostructured polymers

Injection Molded – Potential Translation to Manufacturing

Use for maintenance in the lab, or translate for use as electrode material
Test Platform – To determine if Neuronal Differentiation was susceptible to mechanical compliance

**PGS**

*Poly(glycerol-sebacate)*

- Tunable tissue-level elasticity
- Biodegradable
- Biocompatible – components are FDA approved
- Better *in vivo* & *in vitro* cell response vs. PLGA
- Micro-scale castability
- Molecular structure allows for linkages with other molecules

**Melt Polycondensation reaction of 1:1 molar amounts of glycerol and sebacic acid**

1. 120 °C, under N₂ flow, 24 hours
2. 120 °C, 50 mmHg, 24 hours

Highly viscous, transparent, slightly yellow material. Low number of crosslinks, and OH groups attached to backbone

PGS Microcasting

Array of pillars. 12 μm pitch region. Pillars ~ 3 μm in height.

Array of pits due to overlapping holes in Si mold. 3 μm pitch section.
Some preliminary work with neurospheres

We expected an increase in neuronal differentiation over glass control samples.
Mechanical Stimulation of Neuronal Differentiation

Control of Neuronal Division??
Surface Engineering for Neuronal Differentiation
Surface Engineering for Neuronal Differentiation

Chemically/Mechanically mimic the neuronal environment during differentiation
Surface Engineering for Neuronal Differentiation
Chemistry: Cell Adhesion Molecules

- NCAM-1
- Integral membrane protein
- Inhibits attachment of astrocytes, etc.
- Supported Neurite Outgrowth

Stimulate NPCs

- When microglia are treated with Interferon γ or Interleukin-4, NPCs differentiate into neurons

Schwann Cells were encapsulated within a fibrin gel. The gel was placed in contact with rat spinal cord coated with fibroblast ‘sieve-filled’ coating.

Neurites penetrated the sieves.

How to Combat Gliosis and Promote Neuronal Differentiation – Need a Multi-Tiered Approach

- Engineered Surfaces
  - Enhance Neuronal Growth
  - Discourage Microglia/Macrophage/Astrocytic Response
- Add Soluble Cues
- Modify the Mechanics of the Implant
- Implant Placement

Much more work to be done...

- Will require collaboration at the intersection of neuroprosthetics, tissue engineering and neurobiology.