Introduction to BioMEMS & Medical Microdevices

Biocompatibility, FDA and ISO 10993

Companion lecture to the textbook: Fundamentals of BioMEMS and Medical Microdevices, by Prof. Steven S. Saliterman, http://saliterman.umn.edu/
ISO Definition of a Medical Device

- Any instrument, apparatus, appliance, material or other article, including software, whether used alone or in combination, intended by the manufacturer to be used for human beings solely or principally for the following purposes:
  - Diagnosis, prevention, monitoring, treatment or alleviation of disease;
  - Diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
  - Investigation, replacement or modification of the anatomy or of a physiological process;
  - Control of conception.

- ISO 10993 applies to medical devices used in vivo.
  - Biosensors, integrated smart stents, advanced drug delivery systems, and actuator driven devices in biomedical applications for diagnostics and therapeutics.
Topics

- Biocompatibility
- Foreign Body Giant Cells (FBGS)
- ISO 10993 biocompatibility tests
- Addendum – Tested Materials
Biocompatibility testing answers two fundamental questions:
- Is the material safe?
- Does it have the necessary physical and mechanical properties for its proposed function?

The extent to which a material needs to be characterized depends on:
- Type of material,
- End use of the device (is it a medical device?),
- Function of the material within the device.
- Availability of existing data on the material.
Foreign Body Reaction

- Phagocytic attack and encapsulation of the device.
- When an implanted material comes in contact with blood, a layer of host proteins adsorb to the material surface.
  - Proteins fibrinogen, fibronectin, and vitronectin; immunoglobulin G (IgG); and the complement-activated fragment C3b.
- Neutrophil infiltration leads to inflammation
  - Neutrophils normally phagocytose microorganisms and foreign bodies.
  - Monocytes, macrophages and lymphocytes lead to chronic inflammation.
  - Granulation tissue develops as endothelial cells and fibroblasts proliferate.
- Macrophages fuse forming foreign body giant cells.
- Fibrous encapsulation of the device occurs.
- All materials inside and outside the device, including materials encountered during the manufacturing and preservation process have a potential to evoke a foreign body response.

Host Foreign Body Response…

Foreign Body Giant Cells...

- SEM photomicrographs showing fusion of macrophages into foreign body giant cells:
  - Individual macrophage aggregation on silicon dioxide (day 7) (left).
  - Enlarging giant cell with fusion of cytoplasm and consolidation of nuclei (day 14) (right).

Cellular response to implanted materials…

Biofouling

Biofouling is the process whereby functioning of a medical device is interfered with by the biological response of the host.

This commonly occurs when macrophages and foreign body giant cells (FBGCs) attach to the implanted device, accumulate, grow and interfere with normal operation.

Surface coating of biomaterials seems one good approach to lessen the inflammatory response, lessen macrophage adhesion and FBGCs growth, and improve wound healing.

The foreign body response by the host is largely independent of the material’s being polymeric, ceramic or metallic; being hydrophobic or hydrophilic; or being hard or soft.
The status of the proteins on a material surface is believed to determine the ultimate biocompatibility of a given polymer.

Producing a more biocompatible surface requires achieving specific responses between the polymer surface and the adjacent cells and to reduce non-specific interactions.

- Methods include passivating the polymer surfaces to minimize non-specific protein interaction.
- Functionalizing the polymer surface with biomolecules to induce specific protein adsorption and cell responses.

Non-fouling (i.e., protein adsorption-resistant) polymer coatings for biomaterials provides a more rigorous approach to reduce inflammatory responses. Such polymer surface coatings must satisfy the following constraints:

- Use of nontoxic (biocompatible) materials,
- Effectively inhibit in vivo biofouling,
- Appropriate thickness and permeability to allow analyte transport,
- Techniques to deposit coating onto a variety of materials and architectures.
- Must be mechanically, chemically, and electrically robust to withstand surface deposition, sterilization methods, implantation procedures, and in vivo environment.
- Polyethylene glycol (PEG), \( \text{HO}(-\text{CH}_2\text{CH}_2\text{O}-)_n\text{H} \), is an example.
Hydrophobic surfaces tend to absorb proteins.
  - From unfolding of proteins on the surface and release of bound water molecules.

Cationic proteins bind to anionic surfaces and anionic proteins bind to cationic surfaces.

Proteins tend to adsorb in monolayers.

A minimum PEG molecular weight is required to provide good protein repulsion (500-2000).
  - Mechanism may be resistance of the polymer coil to compression.
Purple dots are non-fouling chemical moiety such as \((\text{CH}_2\text{CH}_2\text{O})_n\) (Polyethylene glycol)

(A) Cross-linked network of long polymeric chains.
(B) Polymers grown off the surface.
(C) Oligo-non-fouling headgroups on a self-assembled monolayer (such as thiol)
(D) Surfactant absorbed to the surface (green dots are hydrophobic tails).
Surface Engineering...

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NFS Compositions…

**TABLE 1.2.10.2 “Non-Fouling” Surface Compositions**

<table>
<thead>
<tr>
<th>Synthetic Hydrophilic Surfaces</th>
<th>Natural Hydrophilic Surfaces</th>
</tr>
</thead>
<tbody>
<tr>
<td>• PEG polymers and surfactants</td>
<td>• Passivating proteins (e.g., albumin and casein)</td>
</tr>
<tr>
<td>• Neutral polymers</td>
<td>• Polysaccharides (e.g., hyaluronic acid)</td>
</tr>
<tr>
<td>poly(2-hydroxyethyl methacrylate)</td>
<td>• Liposaccharides</td>
</tr>
<tr>
<td>polyacrylamide and poly(N-methyl acrylamide)</td>
<td>• Phospholipid bilayers</td>
</tr>
<tr>
<td>poly(N-vinyl 2-pyrrolidone)</td>
<td>• Glycoproteins (e.g., mucin)</td>
</tr>
<tr>
<td>poly(N-isopropyl acrylamide) (below 31°C)</td>
<td><strong>Other Molecules</strong> (see Ostuni et al., 2001).</td>
</tr>
<tr>
<td>• Anionic polymers</td>
<td></td>
</tr>
<tr>
<td>• Phosphoryl choline polymers</td>
<td></td>
</tr>
<tr>
<td>• Sulfo betaines, carboxy betaines, taurine-functionalized materials</td>
<td></td>
</tr>
<tr>
<td>• Poly(2-methyl-2-oxazoline)</td>
<td></td>
</tr>
<tr>
<td>• Gas discharge-deposited coatings (especially from PEG-like monomers)</td>
<td></td>
</tr>
<tr>
<td>• Self-assembled n-alkyl molecules with oligo-PEG headgroups</td>
<td></td>
</tr>
</tbody>
</table>

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**Thermodynamics of Protein Absorption**

<table>
<thead>
<tr>
<th>Table 1.2.10.1</th>
<th>Thermodynamics of Protein Adsorption</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favoring Adsorption</strong></td>
<td></td>
</tr>
</tbody>
</table>
| $\Delta H_{ads}$ | - van der Waals interactions (short range)  
- ion–ion interactions (long range) |
| $\Delta S_{ads}$ | + desorption of many H$_2$O’s  
+ unfolding of protein |
| **Opposing Adsorption** |  |
| $\Delta H_{ads}$ | + dehydration (interface between surface and protein)  
+ unfolding of protein  
+ chain compression (PEO) |
| $\Delta S_{ads}$ | - adsorption of protein  
- protein hydrophobic exposure  
- chain compression (PEO)  
- osmotic repulsion (PEO) |

Flowchart for Biological Evaluation

Device under consideration.

- Perform material characterization:
  - Is the device in contact with the body directly or indirectly?
    - Yes: Proceed with biological evaluation.
    - No: No need for biological evaluation.
  - Is the material the same as an existing commercially available device?
    - Yes: Are the same manufacturing methods, chemical composition, body contact, and sterilization methods used?
      - Yes: Is there sufficient justification and/or test data available?
        - Yes: Select and complete the appropriate tests from Table 15.1.
        - No: Proceed with biological evaluation.
      - No: Categorize by nature and duration of contact.
    - No: Select and complete the appropriate tests from Table 15.1.
# ISO 10993 Biocompatibility Test Categories

<table>
<thead>
<tr>
<th>Device Categories</th>
<th>Biological Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cytotoxicity</td>
</tr>
<tr>
<td><strong>Body Contact</strong></td>
<td>Contact duration</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td>A x x x</td>
</tr>
<tr>
<td></td>
<td>B x x x</td>
</tr>
<tr>
<td></td>
<td>C x x x</td>
</tr>
<tr>
<td><strong>Mucosal Membrane</strong></td>
<td>A x x x</td>
</tr>
<tr>
<td></td>
<td>B x x x o o</td>
</tr>
<tr>
<td></td>
<td>C x x x o x x o</td>
</tr>
<tr>
<td><strong>Breached or compromised spaces</strong></td>
<td>A x x o</td>
</tr>
<tr>
<td></td>
<td>B x x x o o</td>
</tr>
<tr>
<td></td>
<td>C x x x o x x o</td>
</tr>
<tr>
<td><strong>Blood Path, Indirect</strong></td>
<td>A x x x x</td>
</tr>
<tr>
<td></td>
<td>B x x x x o</td>
</tr>
<tr>
<td></td>
<td>C x x o x x x o</td>
</tr>
<tr>
<td><strong>Tissue/Bone/ Dentin Communicating</strong></td>
<td>A x x o</td>
</tr>
<tr>
<td></td>
<td>B x x x x x</td>
</tr>
<tr>
<td></td>
<td>C x x x x x x o</td>
</tr>
<tr>
<td><strong>Circulating Blood</strong></td>
<td>A x x x x o</td>
</tr>
<tr>
<td></td>
<td>B x x x x x x</td>
</tr>
<tr>
<td></td>
<td>C x x x x x x o</td>
</tr>
<tr>
<td><strong>Implant Devices</strong></td>
<td>A x x x o</td>
</tr>
<tr>
<td></td>
<td>B x x x x x x</td>
</tr>
<tr>
<td></td>
<td>C x x x x x x o</td>
</tr>
</tbody>
</table>

*“A = limited (≤ 24 h), B = prolonged (24 h to 30 days), C = permanent (>30 days).*

The ISO 10993 International Standard pertains to:

- Surface devices on the skin, mucosal membranes, breached or compromised surfaces.
- External communicating devices with blood, tissue, bone, dentin.
- Implantable devices.

Its purpose is to protect humans and to serve as a framework for selecting tests to evaluate biological responses.

In so doing consideration has been given to minimize the number and exposure of test animals.
Characterization Methods

- Identification of a materials constituents and:
  - Changes of the material over time,
  - Changes with exposure to different environments,
  - Lot-to-lot consistency for manufacturing purposes.

- Methodologies:
  - Infrared spectral analysis (IR),
  - Thermal analysis,
  - Density analysis,
  - Molecular weight distribution,
  - Mechanical properties,
  - Surface properties,
  - Extract Characterization.
Infrared Spectral Analysis (IR)...

Wave number vs % Transmission

Infrared scan of polypropylene

Albert, DE. “The important role of material and chemical characterization in device evaluation. Medical Device Technology, Octo Media Ltd, June 2004
Useful in material identification and for following polymer degradation.

Molecules absorb specific frequencies that are characteristic of their structure. These absorptions are resonant frequencies, i.e. the frequency of the absorbed radiation matches the transition energy of the bond or group that vibrates.

A basic IR spectrum is essentially a graph of infrared light absorbance (or transmittance) on the vertical axis vs. frequency or wavelength on the horizontal axis.

Typical units of frequency used in IR spectra are reciprocal centimeters (sometimes called wave numbers), with the symbol cm$^{-1}$
Purified Water Extracts…

Albert, DE. “The important role of material and chemical characterization in device evaluation. Medical Device Technology, Octo Media Ltd, June 2004
Isopropyl Alcohol Extracts…

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Albert, DE. “The important role of material and chemical characterization in device evaluation. Medical Device Technology, Octo Media Ltd, June 2004
Cytotoxicity refers to cell damage caused by materials, either by direct contact or by leachable substances (extracts).

Cell damage may occur by a variety of means including activation of the complement system.

- The complement system involves a number of serum factors that are activated in the presence of antigen-antibody binding, bacteria and viruses, or foreign materials.
Determination of cytotoxicity includes:

- Microscopic (qualitative) evaluation
  - Morphology
  - Vacuolization
  - Detachment
  - Cell lysis
  - Membrane integrity

- Quantitative evaluation
  - Cell death
  - Inhibition of cell growth
  - Cell proliferation
  - Cellular secretions
Mouse Fibroblast Cells…

Normal

Cytotoxicity
Exposure to Toxic Extract

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Image Courtesy of NAMSA - North American Science Associates
Sensitization refers to a material's ability to induce specific delayed-type hypersensitivity in the body upon initial exposure:

- **Haptens**,  
- **Langerhans cells** and **T-cell lymphocytes**,  
- **Lymphokines**.

**Testing:**

- **Guinea pig maximization test** (GPMT),  
- **Closed-patch test** (Buehler test),  
- **Murine Local Lymph Node Assay**.
Guinea Pig Maximization Test …

- For the induction phase, a sample volume of 0.1 mL is injected at the prepared site. Seven days later the topical induction is performed.
  - A saturated filter paper or gauze is applied over the skin injection site by an occlusive dressing and torso wrap for a period of two days.
- The challenge phase is performed two weeks later by administering the sample topically to sites not previously used for the induction phase.
  - The dressings are applied for one day and removed.
  - The appearance of the skin is then reviewed and graded at one and two days.
Irritation

- Irritation refers to a *non-specific inflammatory* response to a single, repeated or continuous application of a material.
- Areas tested:
  - Skin,
  - Eyes,
  - Oral mucosa,
  - Genitalia,
  - Rectum.
- Rabbits and human subjects are often used.
Shown is erythema and edema (swelling) about the intracutaneous injection sites on a rabbit test animal.

For rabbits, the samples may be solid, powders or liquids and are applied directly to the skin for 4 hours.

The appearance at each application site is assessed at 1, 24, 48 and 72 hours. Repeated exposure may be performed.
Systemic Toxicity – Whole Body

- Systemic toxicity (body at large):
  - **Acute toxicity** - within 24 hours,
  - **Subacute toxicity** - single dose or multiple doses of a test sample during a period from 14 to 28 days,
  - **Subchronic toxicity** - at 90 days, but not exceeding 10% of the life cycle of the device,
  - **Chronic toxicity** - single or multiple exposures to medical devices, materials and extracts during at least 10% of their lifespan of the test animal.
Gene or point mutations, small deletions, mitotic recombination or microscopically visible chromosome changes.

Studies available:
- *Ames bacterial reverse mutation assay*,
- *Mouse lymphoma assay*,
- *Chinese hamster ovary cells*,
- *Mouse bone marrow micronucleus test*. 
On the left are negative controls, and on the positive controls, the latter showing a karyotype with chromosomal aberrations.
Implantation

- Tests for assessment of the local effects of implant material on living tissue.
- Comparison is made with reactions observed to medical devices whose clinical acceptability has already been established.
- Short term studies of less than 12 weeks implantation, and long term studies of greater than twelve weeks may be performed.
- Solid implant materials for testing must be prepared in the same manner as they are intended for implantation, including form, density, hardness, surface finish, sterilization, and handling.
- Non-solid materials such as liquids, pastes and particulates may also be used, and be contained in polyethylene, polypropylene or polytetrafluoroethylene tubes. Controls of similar size, shape of surface finish should be used.
Histological Changes

Slight irritation - mild infiltration of lymphocytes

Severe lymphohistiocytic response.

Fibrous encapsulation around a previously implanted test material.

Image courtesy of NAMSA
Types of Histological Findings…

- The extent of fibrous capsular involvement around the device and adjoining tissue.
- Tissue inflammatory changes, including polymuclear leucocytes, lymphocytes, plasma cells, eosinophils, macrophages and multinucleated cells.
- Presence of tissue necrosis, capillary wall breakdown or other deterioration.
- Material debris, fatty infiltration and granuloma formation.
- Quality and quantity of tissue ingrowth into porous materials.
Hemocompatibility tests evaluate the effects of medical devices or materials that are in contact (or indirect contact) with blood, on blood components.

- **Hemolysis** is the abnormal breakdown of blood cells.
- **Thrombosis** is the clotting of blood with obstruction of a blood vessel and potential for embolization.
Toxin Exposure…

Normal Red and White Blood Cells

White Blood Cell Karyorrhexis
(breakdown of the nucleus)

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Image courtesy of NAMSA
Degradation is the unwanted breakdown of implanted medical device materials.

Ideally in an implanted device all materials of degradation are ultimately removed by the body without toxicity.

- Polymer degradation.
- Ceramic degradation.
- Metal and alloy electrochemical effects,
Chemical bond scission due to hydrolytic and oxidative processes.

Enzymes, proteins and other cellular activity can alter the rate and nature of degradation.

Ultraviolet cleavage of chemical bonds.

Gamma and electron radiation that cause embrittlement, discoloration and thermal instability.

Metal induced degradation from impurities, additives or hybrid construction.
Summary

- **Biocompatibility** testing answers two fundamental questions:
  - Is the material safe?
  - Does it have the necessary physical and mechanical properties for its proposed function?
- **Biofouling** is the process whereby functioning of a medical device is interfered with by the biological response of the host.
- The **ISO 10993 Standard** is to protect humans and to serve as a framework for selecting tests to evaluate biological responses.
ISO 10993 Subparts discussed:

- Characterization
- Cytotoxicity
- Sensitization
- Irritation
- System Toxicity
- Genotoxicity
- Implantation
- Hemocompatibility
- Degradation
Addendum – Tested Materials

- Biosensors
- Stents
- Micro-Nano-Needles
- Micro-Nano-Reservoirs
- Micro-Nano-Pumps
- Micro-Nano-Actuators
- Tissue Engineering
- Coatings
- Self-Assembled Monolayers
## Biosensors

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosensor</td>
<td>Zinc oxide nanowire</td>
<td>Intracellular $K^+$ detection</td>
<td>In vitro on human adipocytes and frog oocytes cells</td>
<td>Successfully measured $K^+$ ions concentration with small interference from other species</td>
</tr>
<tr>
<td>Epoxy-polyurethane membrane</td>
<td>Protective membrane for Ag/AgCl reference electrode</td>
<td>In vivo subcutaneously in rats</td>
<td>Stable for 4–8 months</td>
<td></td>
</tr>
<tr>
<td>Polydimethyl siloxane (PDMS)</td>
<td>Noninvasive contact lens</td>
<td>Ex vivo on rabbit eyes</td>
<td>Successfully measured glucose concentration</td>
<td></td>
</tr>
<tr>
<td>Sulfonic acid functionalized hydroxyl-terminated hyperbranched polyester</td>
<td>Antibiofouling coating</td>
<td>In vitro test on blood</td>
<td>Successfully integrated biocompatible, antibiofouling, and anticoagulation coating on biosensor</td>
<td></td>
</tr>
<tr>
<td>Parylene probes with Platinum electrode, Stent-316 stainless steel, Ti-Ni-Ta alloy. Au-Cr film</td>
<td>Cyborg eyes</td>
<td>In vivo on Zophobas morio beetles</td>
<td>Exhibited stable chronic insect sensory recordings</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stent-type thermal flow for measuring nasal respiration</td>
<td></td>
<td>Response time 260 milliseconds, and output frequency of 2 Hz</td>
<td></td>
</tr>
</tbody>
</table>
## Stents

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th><em>In Vivo</em> and <em>In Vitro</em> Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stents</td>
<td>Poly (D, L-lactic-co-glycolic acid) (PLGA) with sirolimus and triflusol</td>
<td>Bare metal stent</td>
<td><em>In vivo</em> on porcine carotid artery model</td>
<td>Exhibited significant reduction in restenosis</td>
</tr>
<tr>
<td>Formula 418 Cook</td>
<td>FDA approved stent</td>
<td><em>In vivo</em> on American Yorkshire pig</td>
<td>Successful reception of wireless data up to a range of 50 cm</td>
<td></td>
</tr>
<tr>
<td>Medical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid crystal</td>
<td>Liquid crystal polymer (LCP)</td>
<td>Hermetic packaging for wireless housing</td>
<td><em>In vivo</em> on domestic pigs</td>
<td>Enabled precise and accurate measurements of wireless transmitted data</td>
</tr>
<tr>
<td>Stents</td>
<td>Polyethylene stent with magnetoeelastic sensor array</td>
<td>Wireless transmission</td>
<td><em>In situ</em> on female domestic swine</td>
<td>Successful reception of wireless signals up to a range of 7.5 cm</td>
</tr>
</tbody>
</table>

## Micro-Nano Needles

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-Nano needles</td>
<td>Carbon nanosyringe arrays</td>
<td>Intracellular delivery</td>
<td>In vitro on cancer cells and human mesenchymal stem cells</td>
<td>Successfully delivered different cargos in cytoplasm of cells</td>
</tr>
<tr>
<td>AFM silicon tip to nanoneedle</td>
<td></td>
<td>Intracellular delivery</td>
<td>In vitro on HeLa cells</td>
<td>Delivered proteins directly in cell</td>
</tr>
<tr>
<td>MWCNT nanoneedle attached to tungsten tip</td>
<td></td>
<td>Intracellular biosensing</td>
<td>—</td>
<td>Exhibited detection of Glucose, ascorbic acid, cytochrome in volumes &lt;1 pL</td>
</tr>
<tr>
<td>Silicon based microneedle array</td>
<td></td>
<td>Intradermal delivery</td>
<td>In vivo on mice skin</td>
<td>Successfully delivered protein to dermal layer</td>
</tr>
<tr>
<td>Electrodeposited metal microneedle</td>
<td></td>
<td>Intradermal delivery</td>
<td>In vivo on guinea pig skin</td>
<td>Delivered 90% of cargo within the skin</td>
</tr>
<tr>
<td>Ultra-sharp silicon microneedle</td>
<td></td>
<td>Transdermal delivery</td>
<td>In vivo on human skin</td>
<td>Force of insertion of single microneedle less than 10nN.</td>
</tr>
<tr>
<td>Hollow silicon microneedles</td>
<td></td>
<td>Transdermal delivery</td>
<td>In vivo on diabetic rat</td>
<td>Unsuccessful delivery of insulin</td>
</tr>
</tbody>
</table>

## Micro-Nano-Pumps

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-Nano pumps</td>
<td>Polyetheretherketone (PEEK)</td>
<td>Material for tubing and fittings</td>
<td>Single cell manipulation</td>
<td>Achieved 98.5% cell manipulation success rate for a 1.3 mm thick diaphragm and dispensed volume varied from 500 nL to 250 nL at flow rate of 250 nL/s.</td>
</tr>
<tr>
<td></td>
<td>Poly(methyl methacrylate) (PMMA)</td>
<td>Diaphragm material</td>
<td>Single cell manipulation</td>
<td></td>
</tr>
<tr>
<td>Parylene C</td>
<td>Material for bellow fabrication, housing for actuator assembly in electrochemical pumps</td>
<td></td>
<td></td>
<td>Measured flow rates varied from 1 μL to 34 μL/min and power required is less than 3 mW.</td>
</tr>
<tr>
<td>Silicone</td>
<td>Material for catheter</td>
<td>In vivo subcutaneous drug delivery in Mice</td>
<td></td>
<td>Minimized flow resistance and demonstrated optimal delivery to site with one sided valve in catheter to avoid back flow.</td>
</tr>
<tr>
<td>SAM-N-(triethosilylpropyl)-O-polyethylene oxide Urethane (PEOU)</td>
<td>Antithrombogenic coating</td>
<td>Ex vivo on rats</td>
<td></td>
<td>Imparted hemocompatibility to silicon based device.</td>
</tr>
</tbody>
</table>
# Micro-Nano-Actuators

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vitro Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-Nano actuators</td>
<td>Electrostatic comb-drive</td>
<td>Mechanical testing of single cells</td>
<td>In vitro on epithelial cells</td>
<td>Measured stiffness, hysteresis, and visco-elasticity of adherent cells</td>
</tr>
<tr>
<td>Polyvinylidene fluoride</td>
<td>with silver electrode encapsulated in PMMA</td>
<td>Induces bone formation</td>
<td>In vivo in right hind limb of Merino ewe</td>
<td>Piezoelectric actuator stimulated bone growth and exhibited bone area increment</td>
</tr>
<tr>
<td>C2C12-collagen film</td>
<td>integrated with Silicon MEMS device</td>
<td>Molecular actuator utilizing glucose as power source</td>
<td>—</td>
<td>Depicted successful locomotive motion</td>
</tr>
<tr>
<td>Parylene C encapsulated</td>
<td>nickel based magnetic actuator</td>
<td>Clearing biological accumulation on catheter pore</td>
<td>In vitro on murine vascular smooth muscle cell line</td>
<td>Magnetic actuator successfully removed cellular accumulation</td>
</tr>
<tr>
<td>Polypyrrole based</td>
<td>electrostatic actuation</td>
<td>Actuation controlled catheter tip movement</td>
<td>—</td>
<td>Required faster actuation speed to image using catheter.</td>
</tr>
</tbody>
</table>

# Micro-Nano-Reservoirs

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-Nanoreservoirs</td>
<td>Gold</td>
<td>Sacrificial anode in controlled-release microchip</td>
<td>In vivo subcutaneously in Female rats</td>
<td>Gold corrosion found to be biocompatible. Voltage application reduced leukocyte concentration to control level</td>
</tr>
<tr>
<td>Poly(L-lactic acid) (PLLA)</td>
<td></td>
<td>Biodegradable microreservoir body</td>
<td>In vivo subcutaneously in female Sprague-Dawley rats</td>
<td>PLA showed slow degradation as compared to the PLGA membrane.</td>
</tr>
<tr>
<td>Poly(lactic-co-glycolic acid)</td>
<td></td>
<td>Biodegradable membrane for microreservoir</td>
<td>In vivo subcutaneously in female Sprague-Dawley rats</td>
<td>Different molecular weights of membrane degrades over a span of time and showed pulse drug delivery behavior</td>
</tr>
<tr>
<td>Carbon nanotubes coated by Poly (lactide)-poly(ethylene glycol) CNT-PLA-PEG</td>
<td>Nanoreservoir</td>
<td>In vivo in C57BL/6 mice</td>
<td>Biocompatible polymer coated CNTs showed less toxicity in in vivo and in vitro. Increased the drug efficiency from 12 to 50%</td>
<td></td>
</tr>
</tbody>
</table>

## Tissue Engineering

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Tissue engineering</td>
<td>Core-polyethylene glycol/polyacrylic acid</td>
<td>Artificial cornea</td>
<td>In vitro for core-corneal epithelium cells for periphery-corneal fibroblasts cells</td>
<td>Successfully demonstrated cell growth with contingency on covalent tethering of collagen</td>
</tr>
<tr>
<td>Periphery poly(hydroxyethyl acrylate)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resorbable chitosan</td>
<td></td>
<td>Increases implants stiffness, adds hemostatic and antiseptic properties and improves adhesion</td>
<td>In vivo in Wistar rats</td>
<td>Successful recording of physiological signals for over 12 months</td>
</tr>
<tr>
<td>Stroma tissue</td>
<td></td>
<td>Artificial human cornea</td>
<td>In vitro fibroblast culture to reconstruct stromal tissue</td>
<td>Successfully bioengineered cornea and seeded endothelial and epithelial cells.</td>
</tr>
<tr>
<td>Biodegradable polyurethane scaffolds</td>
<td></td>
<td>Enhancement of mechanical properties</td>
<td>In vivo on skin of Wistar rats</td>
<td>Completely resorbed scaffold after 3 months with slight inflammatory response</td>
</tr>
</tbody>
</table>

## Coatings

<table>
<thead>
<tr>
<th>Devices</th>
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<th>In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coatings</td>
<td>Dexamethasone loaded nitrocellulose coatings</td>
<td>Anti-inflammatory coating for neural implants</td>
<td>In vivo on adult male Sprague-Dawley rats</td>
<td>Sustained drug release for over 16 days</td>
</tr>
<tr>
<td></td>
<td>Micropatterned titanium dioxide</td>
<td>Anti-inflammatory</td>
<td>In vitro on human neutrophils from blood</td>
<td>Pattern size dependent anti-inflammatory coating</td>
</tr>
<tr>
<td></td>
<td>Poly(N-isopropylacrylamide) hydrogel microparticles</td>
<td>Anti-inflammatory</td>
<td>In vivo on murine peritoneal cavity</td>
<td>Reduced leukocyte adhesion and attenuated the expression of pro-inflammatory cytokines</td>
</tr>
<tr>
<td>Nanosilver</td>
<td>Anti-inflammatory</td>
<td>In vivo on Sprague-Dawley female rat</td>
<td>Reduced cytokine concentration and lowered lymphocyte and mast cell infiltration</td>
<td></td>
</tr>
<tr>
<td>Perfluorocarboxylate ionomer (PFCI)</td>
<td>Anticracking</td>
<td>In vivo subcutaneously in Guinea pigs</td>
<td>Reduced mineralization on coating and exhibited better cracking resistant property</td>
<td></td>
</tr>
</tbody>
</table>

### Coatings Continued

<table>
<thead>
<tr>
<th>Devices</th>
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<th>In Vitro Testing Model</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Carboxymethyl-PEG-carboxymethyl</td>
<td></td>
<td>Antibiofouling</td>
<td>In vitro on blood samples</td>
<td>Exhibited hemocompatibility</td>
</tr>
<tr>
<td>NDGA porous collagen scaffolds</td>
<td></td>
<td>Angiogenesis stimulating antibiofouling and</td>
<td>In vivo subcutaneously in rats</td>
<td>Coating showed stability for 4 weeks</td>
</tr>
<tr>
<td>Boophilin coated ethylene glycol</td>
<td></td>
<td>Hemocompatible</td>
<td>In vitro activity assay</td>
<td>Better anti fouling performance as compared to PEO brush</td>
</tr>
</tbody>
</table>

# Self-Assembled Monolayers

<table>
<thead>
<tr>
<th>Devices</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Self-assembled monolayer</td>
<td>Flufenamic acid coated 11-mercapto-1-undecanol</td>
<td>Late stent thrombosis</td>
<td><em>In vitro</em> on human aortic endothelial cell (HAECs) cultures</td>
<td>Favored endothelialization</td>
</tr>
<tr>
<td></td>
<td>Carboxyl terminal</td>
<td>Deploying probes</td>
<td><em>In vivo</em> on adult rats</td>
<td>Successfully deployed PDMS probes</td>
</tr>
</tbody>
</table>