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.
Biocompatibility

- 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 immunoglobulin G (IgG), and the complement-activated fragment C3b.
- Neutrophil infiltration leads to inflammation
  - Neutrophils normally phagocytose microorganisms and foreign bodies.
  - Monoctyes, 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 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.

Biofouling
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 Surfaces...

- Non-fouling (i.e., protein adsorption-resistant) polymer coatings 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), HO(-CH2CH2O-)nH, is an example.

Historical Observations...

- 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 moieties 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...
ISO 10993 Biocompatibility Test Categories…

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)...

- 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...

- Purified water extracts of various polymers.
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.

Cytotoxicity Assessment...

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
Sensitization

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.

Dermal Irritation...

- 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.
Genotoxicity

- 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.

Chromosomal Aberrations...

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.

Types of Histological Findings...

- The extent of fibrous capsular involvement around the device and adjoining tissue.
- Tissue inflammatory changes, including polynuclear 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

- 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.
Degradation

- 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.

Polymer Degradation...

- 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.

**Addendum – Tested Materials**
- Biosensors
- Stents
- Micro-Nano-Needles
- Micro-Nano-Reservoirs
- Micro-Nano-Pumps
- Micro-Nano-Actuators
- Tissue Engineering
- Coatings
- Self-Assembled Monolayers
### NFS Compositions

<table>
<thead>
<tr>
<th>Natural Hydrophilic Surface</th>
<th>Synthetic Hydrophilic Surface</th>
<th>Other Materials (see Zhou et al., 2015)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Polysaccharides (glycans and lectins)</td>
<td>• Polysaccharides (glycans and lectins)</td>
<td></td>
</tr>
<tr>
<td>• Peptides</td>
<td>• Peptides</td>
<td></td>
</tr>
<tr>
<td>• Lipid bilayers</td>
<td>• Lipid bilayers</td>
<td></td>
</tr>
<tr>
<td>• Protein films</td>
<td>• Protein films</td>
<td></td>
</tr>
<tr>
<td>• Polyelectrolytes</td>
<td>• Polyelectrolytes</td>
<td></td>
</tr>
<tr>
<td>• Polynucleotides</td>
<td>• Polynucleotides</td>
<td></td>
</tr>
</tbody>
</table>


### Thermodynamics of Protein Adsorption

#### Table 1.2.10.1 Thermodynamics of Protein Adsorption

**Freezing Adsorption**
- $\Delta G_{f}$
- $\Delta H_{f}$
- van der Waals interactions (short range)
- ion-ion interactions (long range)
- adsorption of many H-2's
- unbinding of protein

**Osging Adsorption**
- $\Delta G_{os}$
- hydration (interface between surface and protein)
- unbinding of protein
- dual compression (P0C)
- adsorption of protein
- protein-hydrophobic expander
- crack compression (P0C)
- osmotic repulsion (P0C)


### Biosensors

<table>
<thead>
<tr>
<th>Device</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vitro and In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioreactor</td>
<td>ZnO, cantilever</td>
<td>Induction of H1 detection</td>
<td>In vitro human adipocytes and Bong oxygen cells</td>
<td>Successfully measured H1 loss concentration with good repeatability and high sensitivity. Stable for 6 months.</td>
</tr>
<tr>
<td>Polymer planar waveguide resonators</td>
<td>Polymers and metallic nanofibers</td>
<td>Phase and amplitude sensing</td>
<td>In vivo human heart</td>
<td>Successfully measured glucose concentration. Suggested integrated biosensor, linking, and antibacterial coating.</td>
</tr>
<tr>
<td>Polymer planar and waveguide resonator sensors (silicon)</td>
<td>Polymers and metallic nanofibers</td>
<td>Phase and amplitude sensing</td>
<td>In vivo human heart</td>
<td>Successfully measured glucose concentration. Suggested integrated biosensor, linking, and antibacterial coating.</td>
</tr>
<tr>
<td>Polyurethane planar and waveguide resonator sensors (silicon)</td>
<td>Polymers and metallic nanofibers</td>
<td>Phase and amplitude sensing</td>
<td>In vivo human heart</td>
<td>Successfully measured glucose concentration. Suggested integrated biosensor, linking, and antibacterial coating.</td>
</tr>
</tbody>
</table>

### Stents

<table>
<thead>
<tr>
<th>Device</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stents</td>
<td>Poly (L-lactic-co-glycolic acid) polymer coated with antimicrobial peptide and intraluminal PTFE membrane coated</td>
<td>Healed stented site</td>
<td>Canine arterial injury model</td>
<td>Exhibited significant reductions in neointimal hyperplasia</td>
</tr>
<tr>
<td>Stents</td>
<td>Lipid crystal polymer (LCP)</td>
<td>Hemostatic packaging for retrieval system</td>
<td>In vivo on bovine jugular vein models</td>
<td>Successful retrieval of stents, no complications</td>
</tr>
<tr>
<td>Stents</td>
<td>Polylactide-co-glycolide, silicon rubber</td>
<td>Functional in vivo</td>
<td>In vivo on canine aorta models</td>
<td>Successful deployment and retrieval of stents</td>
</tr>
</tbody>
</table>


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### Micro-Nano Needles

<table>
<thead>
<tr>
<th>Device</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon nanotube arrays</td>
<td>Carbon nanotubes</td>
<td>Intracellular delivery</td>
<td>In vitro on cancer cell lines and human mesenchymal stem cells</td>
<td>Successfully delivered therapeutics to cancer cells</td>
</tr>
<tr>
<td>Microneedle</td>
<td>Microneedle</td>
<td>Intracellular delivery</td>
<td>In vivo on skin cells</td>
<td>Enhanced penetration of drugs, vaccines, and other therapeutic agents</td>
</tr>
<tr>
<td>Microfabricated needle attached to microneedle tip</td>
<td>Microneedles</td>
<td>Intracellular delivery</td>
<td>In vivo on skin cells</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
<tr>
<td>Silicon-based microneedle array</td>
<td>Silicon-based</td>
<td>Intracellular delivery</td>
<td>In vivo on skin cells</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
<tr>
<td>Electrodeposited metal microneedle array</td>
<td>Electrodeposited metal</td>
<td>Intracellular delivery</td>
<td>In vivo on skin cells</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
<tr>
<td>Hollow fiber microneedles</td>
<td>Hollow fiber</td>
<td>Intracellular delivery</td>
<td>In vivo on skin cells</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
</tbody>
</table>


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### Micro-Nano-Pumps

<table>
<thead>
<tr>
<th>Device</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microfluidic pump (MFP)</td>
<td>Microfluidic</td>
<td>Single-cell manipulations</td>
<td>In vitro on single cells</td>
<td>Improved cell isolation and manipulation</td>
</tr>
<tr>
<td>Parylene C</td>
<td>Parylene C</td>
<td>Intracellular delivery</td>
<td>In vitro on cell lines</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
<tr>
<td>Silicone</td>
<td>Silicone</td>
<td>Intracellular delivery</td>
<td>In vitro on cell lines</td>
<td>Enhanced delivery of therapeutic agents</td>
</tr>
<tr>
<td>SAW-sensor (Shear wave acoustic wave sensor)</td>
<td>SAW-sensor</td>
<td>Intracellular delivery</td>
<td>In vitro on cell lines</td>
<td>Enhanced sensing and monitoring of cell behavior</td>
</tr>
</tbody>
</table>

### Micro-Nano-Actuators

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vitro and In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parylene-C-based</td>
<td>Flexible polymer</td>
<td>Mechanotransduction of neuronal cells</td>
<td>In vitro on primary neuronal cells</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Polydimethylsiloxane (PDMS)</td>
<td></td>
<td></td>
<td></td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>CNT/CNT-CNT hybrid</td>
<td>Conductive polymer</td>
<td>Mechatronic motion</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Polyimide</td>
<td>Thermoplastic polymer</td>
<td>Multifunctional</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
</tbody>
</table>


### Micro-Nano-Reservoirs

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vitro and In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Micro-Nano-reactors</td>
<td>Gold</td>
<td>Multipurpose</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td></td>
<td>Conductive</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td></td>
<td>Conductive</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Carbon nanotubes</td>
<td>Conductive polymer</td>
<td>Multifunctional</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
</tbody>
</table>


### Tissue Engineering

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vitro and In Vivo Testing Model</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue engineering</td>
<td>Collagen</td>
<td>Artificial</td>
<td>In vitro on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Polyethylene glycol (PEG)</td>
<td></td>
<td>Conductive</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Bone tissue</td>
<td>Artificial</td>
<td>Conductive</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
<tr>
<td>Injectable polymers</td>
<td>Conductive</td>
<td>Conductive</td>
<td>In vivo on rat brain</td>
<td>Successful control of neuronal firing</td>
</tr>
</tbody>
</table>

### Coatings

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coatings</td>
<td>Osmiobranchial brachial artery overlay coatings</td>
<td>Anti-inflammatory coating for wound repair</td>
<td>In vivo: chick embryos</td>
<td>Seals wounds effectively over 14 days</td>
</tr>
<tr>
<td></td>
<td>Maropitant laminar device</td>
<td>Anti-inflammatory</td>
<td>In vitro: human macrophage cell lines</td>
<td>Patent-size dependent anti-inflammatory</td>
</tr>
<tr>
<td></td>
<td>Poly-tyrosine-polyethylene</td>
<td>Anti-inflammatory</td>
<td>In vivo: mouse pancreatic islets</td>
<td>Reduced inflammatory response and increased the expression of functional activity</td>
</tr>
<tr>
<td></td>
<td>Nanofiber</td>
<td>Anti-inflammatory</td>
<td>In vivo: Sprague-Dawley rats</td>
<td>Reduced cytokine expression and increased immune cell infiltration</td>
</tr>
<tr>
<td></td>
<td>Perfluorocarbon-based</td>
<td>Antitick</td>
<td>In vivo: Chinese pools</td>
<td>Reduced biosorption of coating and exhibited better working surface property</td>
</tr>
</tbody>
</table>


### Coatings Continued

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiopulmonary ECM-coated with collagen scaffold</td>
<td>Anti-adhesive</td>
<td>In vivo: adult rabbits</td>
<td>Limited tissue compatibility and reduced liability for 14 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asparagine</td>
<td>Anti-proteolytic and anti-inflammatory</td>
<td>In vivo: adult rabbits</td>
<td>Better adhesion performance compared to PEO-hydrogel</td>
</tr>
<tr>
<td></td>
<td>Bioceramic</td>
<td>Biocompatible</td>
<td>In vivo: adult rabbits</td>
<td>Improved mechanical properties and reduced inflammatory response</td>
</tr>
</tbody>
</table>


### Self-Assembled Monolayers

<table>
<thead>
<tr>
<th>Devices</th>
<th>Material</th>
<th>Functionality</th>
<th>In Vivo and In Vitro Testing Model</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self-assembled monolayer</td>
<td>Polypeptide and coated</td>
<td>Anti-adhesive</td>
<td>In vivo: rat and mouse</td>
<td>Improved adhesion and reduced inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Tissue overlay</td>
<td>Anti-proteolytic and anti-inflammatory</td>
<td>In vivo: adult rabbits</td>
<td>Improved adhesion and reduced inflammatory response</td>
</tr>
<tr>
<td></td>
<td>Collagen-hemostatic</td>
<td>Biocompatible</td>
<td>In vivo: adult rabbits</td>
<td>Improved adhesion and reduced inflammatory response</td>
</tr>
</tbody>
</table>