

SESSION ID: 184

PRESENTATION TYPE: Workshop

SECONDARY PRESENTATION TYPE: CE Basic,Symposium,Workshop IAT/ITS

Designation: Innovations in Applied Toxicology (IAT)

TITLE: Challenges in the Development of Medical Devices with Minimal Toxicity Potential

SESSION DESCRIPTION:

During the last two decades, there has been an increase in the use of medical devices for various diagnostic and treatment conditions in the health-care sector. To meet this growing demand, more new and novel materials/chemicals involving cutting-edge technologies are being used in developing those devices and advanced biomaterials. The first speaker will begin the discussion on the toxicological impact of such device materials on patient health. Sometimes, while short term biocompatibility studies utilizing ASTM and ISO 10993 methods may show passing results, but the long term implant studies may fail. Given the complex characteristics of these new medical devices, the host defense system including inflammation (innate immunity), acquired immunity and foreign body reactions must be considered in determining biocompatibility (safety) and efficacy (function). Relationship of surface chemistries to reduction or enhancement of adverse response to the activity of macrophages, lymphocytes and giant cells will be explored. The next talk will focus on how nano particles are being used for localization and treatment of cancer. The role of nanocomposite materials and stem cells in the development of artificial human organs such as trachea, facial organs, coronary grafts and heart valves will be discussed. The current status on potential cytotoxicity of nano particles will be reviewed and how results from testing of ultra-high concentrations (which are in no way related to the actual doses used in clinic) are creating unnecessary alarm in public. Discrepancies between *in vitro* and *in vivo* results involving nanomaterials will be described along with the need for a unifying protocol for reliable and realistic toxicity studies. The third speaker will provide insights into a fascinating field of 3-D polymer scaffolds for tissue engineering. Experimental data will be presented on the use of stereolithography based fabrication with polymers (polylactic acid, polypropylene fumarate and chitosan etc.) to simulate internal structure of hepatic lobule and liver vasculature for tissue regeneration, wound healing and personalized medicine. These scaffolds exhibit structural and mechanical properties that mimic native tissue and may enable cell ingrowth, vascularization and transport of nutrients and waste products. But these technologies have their own unique challenges associated with translation of the devices into clinical use such as device sterility, presence of contaminants, bioabsorbable polymers, unpolymerized monomers and potential toxicity of photoinitiator compounds used in fabrication. However, careful optimization of resin formulation led to elimination of cytotoxicity while maintaining accuracy and high resolution. Successful demonstration of long-term cell growth of human bone marrow derived mesenchymal stem cells on zirconium oxide hybrid scaffolds for bone tissue engineering will be discussed. The next speaker discusses the relative merits of studying the biocompatibility of devices in disease animal models or implanting in clinically relevant tissues rather than in routine muscle or subcutaneous spaces. For example, elastase induced brain aneurysm model in rabbits not only affords the possibility of monitoring the clinical effectiveness of the neurovascular coil but also assessing the device biocompatibility. The thrombogenic potential of cardiovascular stents as well as local tissue effects can be studied by implanting them in the coronary artery of swine for different time points. Lastly, one of the limitations in developing metallic devices is biocorrosion. When a blood contacting, biodegradable iron wire is implanted in rat abdominal aorta extracellular matrix, there was substantial corrosion (confirmed by Raman Spectroscopy and EDS) in 22 days. In contrast, there was only minimal corrosion when the device is in the arterial lumen exposed to blood even after 9 months. The same rat arterial

implantation model offers a unique opportunity to study genotoxicity, implantation and systemic toxicity of the device, thus saving time and animals. The final speaker will give an outline of the regulatory approval process for medical devices in European Union. The salient features of Medical Device Directive and the Active Implantables Device Directive and how products conforming to these guidelines will be granted a CE mark. There will be a discussion on the recently released guidance by European Commission's SCENIHR to assess human health risks of medical devices containing nano materials. In summary this workshop will provide an overview of toxicity issues concerning nano materials, 3-D tissue scaffolds, synthetic organs and solutions to overcome them. Role of device chemistry and host defense mechanism in long term test failures, need to use clinically relevant new animal models and European guidelines for medical device approvals with special emphasis on devices containing nano materials.

ENDORSER 1: Medical Device and Combination Product Specialty Section

ENDORSER 2: Association of Scientists of Indian Origin Special Interest Group

ENDORSER 3: Nanotoxicology Specialty Section

Session Role Order: 1

Session Role: Chair

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SOT Member: Yes

Funding: No SOT Funding

Presentation Title: Chair

Session Role Order: 2

Session Role: Co-Chair

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SOT Member: Yes

Funding: No SOT Funding

Presentation Title: Co-Chair

Session Role Order: 3

Session Role: Presenter

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SOT Member: Yes

Funding: No SOT Funding Needed

Presentation Title: Biocompatibility and the Foreign body Reaction to Medical Devices

Presentation Description: The use of biomaterials in tissue engineering, regenerative medicine and nanomedicine offers new challenges in the determination of biocompatibility (safety) of these respective medical devices for ultimate clinical application. Given the complex characteristics of these new medical devices, the host defense system including inflammation (innate immunity), acquired immunity, foreign body reaction, and wound healing responses must be considered in the determination of biocompatibility (safety) and efficacy (function). Fundamental and clinical studies in our laboratory have focused on the development of a mechanistic understanding of the effect of biomaterial surface chemistry on the formation and activity of monocytes, macrophages, lymphocytes, and foreign body giant cells in the foreign body reaction. Correlative *in vitro* and *in vivo* studies have identified certain surface chemistries that facilitate a reduction or enhancement of the foreign body reaction, respectively, at material/tissue interfaces. While studies utilizing ASTM and ISO Standards have shown short-term biocompatibility for some biomaterials, these biomaterials, when utilized in clinical devices for long-term implication, have shown failure mediated by the foreign body reaction. Examples of this phenomenon will be presented. Results from our fundamental studies have demonstrated that different surface chemistries may result in different responses such as cell adhesion, apoptosis and foreign body giant cell formation. These results broaden our perspectives on macrophages and foreign body giant cells at the material/tissue interface and strongly suggest that it may be possible to influence the functional profiles of macrophages/foreign body giant cells at sites of biomaterial implantation with material-surface chemistry. Our ultimate goal is to identify biological design criteria that will prove useful in the development of new biomaterials for tissue engineering and nanomedicine application where both short- and long-term biocompatibility are required.

Session Role Order: 4

Session Role: Presenter

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SOT Member: No

Funding: SOT Full Funding

Presentation Title: Nanomaterials – Its Use in Biomedical Applications Including Development of Artificial Organs: Do the Benefits Outweigh the Risk?

Presentation Description: In recent years, nanoparticles (NPs) have increasingly found practical applications in technology, research and medicine. The small particle size coupled to their unique chemical and physical properties is thought to underlie their exploitable biomedical activities. In my laboratory nanoparticles has been developed and investigated for localisation and treatment of cancer as well as development of human organs. These organs includes trachea, facial organs and cardiovascular, including coronary artery bypass graft, stents, transcatheter heart valves made from nanocomposite materials and stem cells. Here, I review current toxicity studies of NPs with clinical potential. Mechanisms of cytotoxicity are discussed and the problem of extrapolating knowledge gained from cell-based studies into a human scenario is highlighted. The so-called 'proof-of-principle' approach, whereby ultra-high NP concentrations are used to ensure cytotoxicity, is evaluated on the basis of two considerations; firstly, from a scientific perspective, the concentrations used are in no way related to the actual doses required which, in many instances, discourages further vital investigations. Secondly, these inaccurate results cast doubt on the science of nanomedicine and thus, quite dangerously, encourage

unnecessary alarm in the public. In this context, the discrepancies between *in vitro* and *in vivo* results are described along with the need for a unifying protocol for reliable and realistic toxicity reports.

Session Role Order: 5

Session Role: Presenter

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Funding: No SOT Funding Needed

Presentation Title: Strategies in Stereolithography-Based Fabrication and Toxicity Evaluation of 3D Polymer Scaffolds for Tissue Engineering

Presentation Description: Stereolithography is a rapid prototyping technique which has become a valuable tool for fabrication of tissue engineering scaffolds. This fabrication technology produces complex structures in a layer-by-layer manner based on spatially controlled solidification of liquid resins by photopolymerization. The versatility in design and precise nature of stereolithography permits fabrication of complex scaffolds with physiologically relevant architectures. For example, scaffolds have been fabricated using stereolithography to simulate the internal unit structure of the liver, the hepatic lobule, including accurate branching angles of liver vasculature and a hepatocyte chamber. Scaffolds with well-defined pore sizes, pore interconnectivity, and porosities have been fabricated using stereolithography with a variety of polymers (e.g. polyethylene glycol, polylactic acid, polycaprolactone, polypropylene fumarate, trimethylene carbonate, chitosan). Toxicological evaluation of stereolithography-fabricated scaffolds includes consideration of device sterility, effects of post-processing conditions, potentially toxic residual components, assay interferences, and challenges with assessment of biodegradable constructs. Scaffolds fabricated from biocompatible polymers may result in adverse health responses due to the presence of contaminants, unpolymerized monomers, and/or residual photoinitiators from fabrication. For example, we and others have demonstrated significant cytotoxicity associated with low concentrations of many photoinitiator compounds used in fabrication. Our studies have also focused on optimization of resin composition to eliminate cytotoxicity while maintaining accuracy and high resolution of fabrication. We have successfully demonstrated long-term cell growth of human bone marrow-derived mesenchymal stem cells on 3-D zirconium-oxide hybrid scaffolds for bone tissue engineering. Additional challenges are introduced in biocompatibility assessment when using biodegradable/bioabsorbable polymers for scaffold fabrication, as these materials are constantly evolving in the physiological environment.

Session Role Order: 6

Session Role: Presenter

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SOT Member: No

Funding: SOT Full Funding

Presentation Title: Regulatory Approval of Medical Devices in Europe—A Perspective From a Regulator and a Toxicologist

Presentation Description: The speaker will give an outline of the regulatory approval process for medical devices in European Union. The salient features of Medical Device Directive and the Active Implantables Device Directive and how products conforming to these guidelines will be granted a CE mark. There will be a discussion on the recently released guidance by European Commission's SCENIHR to assess human health risks of medical devices containing nano materials.

Session Role Order: 7

Session Role: Presenter

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SOT Member: Yes

Funding: No SOT Funding Needed

Presentation Title: Biocompatibility of Medical Devices—Is Using Disease or Clinically Relevant Animal Models a Better Approach in Safety Assessment?

Presentation Description: The presentation deals with three case studies from published literature. The first test system deals with neurological coils used to treat brain aneurysm. As per the current biocompatibility procedures, device extract is injected into rodents for acute, subacute/chronic toxicity and implantation in rodent muscle or subcutaneous tissue. But a better method would be to create brain aneurysms in rabbits by injecting elastase directly into the right carotid artery. The resulting aneurysms are embolized with platinum coils via a catheter. At 10 weeks after implantation, the histological analysis showed mild to moderate inflammation and long term studies showed acceptable vascular response. It was reported that the coils induce apoptosis by TNF-alpha mediated extrinsic and Bcl-2 mediated intrinsic pathways. The next example is on studying the cardiovascular stent induced thrombosis in swine model. Since stents are smaller in size, they cannot be implanted in traditional dog femoral or jugular vein. Therefore they are tested in noninjured swine coronary arteries at 30, 90 and 180 days after implantation. The stented vessels are explanted and evaluated for luminal thrombus by histology and SEM. The smooth muscle cell loss and endothelialization of the vessels can be evaluated for local tissue implantation effects. The same animals can be utilized for serum enzymes, clinical chemistry and organ histopathology. So the swine model offers an advantage to assess not only acute/chronic thrombosis but also systemic toxicity and local tissue implantation effects. Lastly, one of the limitations in developing metallic devices is corrosion. When a blood contacting, biodegradable iron wire is implanted in rat abdominal aorta, the incidence of corrosion was found to depend on anatomic location. There was substantial corrosion in the iron wire encapsulated within arterial wall extracellular matrix within 22 days. In contrast, the device exposed to blood inside the arterial lumen experienced minimal biocorrosion even after 9 months which was confirmed by Raman Spectroscopy and scanning electron microscopy/energy dispersive spectrometry. Similar results were observed with magnesium wires. The same rat arterial implantation model can also be used to study other biocompatibility parameters - *in vivo* genotoxicity, implantation and systemic toxicity saving time and animals.