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Welcome from the President

Welcome Surface Science Professionals, Colleagues and Friends,

On behalf of the Surfaces in Biomaterials Foundation (SIBF), I welcome you to BioInterface 2016. The BioInterface Symposium has been presented annually by the Foundation since 1991. The Foundation was founded based on the premise that the interface between the body and a medical device is critical to the device’s performance. From another perspective, the Foundation also facilitated the interface between various industries and with academia to address challenges with bringing medical devices through to the clinic. As was the case in previous Symposia, this year’s technical program provides a forum where a diverse group of scientists can openly discuss and debate recent innovations and research topics. The BioInterface Symposium has a strong applied focus and brings together engineers, scientists, clinicians, and regulatory experts from all aspects of the biomedical community. Throughout the years, this conference has been characterized by many in our industry and academia alike as a preeminent technical symposium that allows easy connection between attendees; I am confident that this year’s technical program will more than live up to this description.

I encourage you to take this opportunity to engage and interact with your fellow attendees who represent the leading corporations, startups and educational institutions that research and produce the innovative medical devices and products that help people to live longer, healthier and more productive lives.

Thank you for attending this year’s meeting. We hope your experience at the 2016 BioInterface Symposium stimulates your thinking and provides you with information and solutions that will be beneficial in your ensuing scientific endeavors.

Sincerely,

Chander Chawla
President, Surfaces in Biomaterials Foundation

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MONDAY — OCTOBER 3, 2016
Theme: Sensing at the BioInterface
Sensors in Drug Delivery

Traditional glucose sensors used in diabetes treatment rely on electrochemical monitoring of enzymatic oxidation of glucose, in the presence of O2. The state of the art involves a transcutaneous electrode tipped with glucose oxidase. Such electrodes last about three days before they need to be replaced, due to poisoning of the enzyme, and skill is required to avoid infection due to the cutaneous puncture. As an alternative, we have investigated the use of hydrogels based on phenylboronic acids, which bind glucose and alter their swelling state as a function of glucose concentration. Thin layers of such hydrogels can be confined inside microdevices, and their swelling, which alters either capacitive or inductive properties of the microdevice, can be monitored by wireless means. In principle, such devices can be implanted, and the goal would be at least one year’s function before replacement.

In this talk, we will describe hydrogel/device configurations that have been studied, based on lightly cross-linked copolymers of methacrylamidophenylboronic acid (MPBA) and acrylamide (AAm). Such devices are shown to respond appropriately to changes in glucose concentration, and to changes in fructose concentration, but in different ways. The fructose response is due solely to enhanced ionization of the MPBA groups with increasing fructose concentration. The same mechanism is present with glucose, but glucose is also able to bind two MPBA units at once, increasing the effective crosslink density and causing shrinkage to occur. Swelling response to both molecules can be modified by incorporating amine comonomers into the hydrogel. The difference in responses to fructose and glucose has been probed by mechanical testing. Fructose- and glucose-swollen hydrogels were subjected to mechanical compression. In the presence of fructose, the resulting stress was essentially constant following compression. Glucose-swollen hydrogels exhibited a sharp stress peak, following a slow relaxation to a plateau stress value. This relaxation is attributed to rearrangement of glucose-mediated crosslinks. Finally, we have carried out long term stability studies of MPBA/AAm copolymer hydrogels, and find that they lose their swelling response over time, this loss occurring more rapidly with increasing temperature. We believe this effect is due to oxidate deborylation of the MPBA groups.

REFERENCES


Bio: Ronald A. Siegel received is ScD from MIT in 1984 under Robert Langer. His early career was spent at the University of California, San Francisco. In 1998 Mr. Siegel moved to the University of Minnesota, where he is Professor of Pharmaceutics and Biomedical Engineering. He was Department Head of Pharmaceutics from 1999-2009. During 1998-1998 he was President of the Controlled Release Society. Mr. Siegel’s research interests are in drug delivery, biosensing, and polymer science.
The bio-interface (tissue/sensor) for sensing is different from bio-interfaces at passive implanted devices or regulation/repair/delivery devices. The manner in which the device function is affected by the bio-environment differs between the types of implanted device. The in vivo tissue reaction (FBR) of an active analytical device (biosensor) affects the device function. And vice versa, the implant of the sensor can affect the tissue response. For a sensor this is particularly true for biomolecules that represent the basal blood levels, such as glucose. For example, the requirement of a sensor that detects and quantifies specific biomolecules (analyte) is dependent on the ability of the analyte to reach and be recognized by the sensor. For a delivery device, the pharmacokinetics of drugs in the tissue around a delivery device is affected by the tissue reaction. For a semi-passive longer term device such as a pacemaker, how the FBR may cause degradation of the device is critical. How this in vivo tissue interface differs from various implanted devices will be contrasted. The implication being the bio-interface interaction with the device directly affects the design and longevity of each type of functional device.

Bio: Raeann Gifford started her continuous glucose monitoring (CGM) sensor development at iSense (acquired by Bayer Diabetes Care) in Portland, OR. She has a Ph. D. in Bioanalytical Chemistry from the University of Kansas (KU). Raeann conducted international University (Tokushima Univ, Japan) and Research Institute (Acreo, Sweden) sensor collaborations. Her industry experience includes sensor innovation at Bayer Diabetes Care. Currently Raeann is Sensor Program Director in Operations at Medtronic Diabetes.
BioInterface Workshop: Natalie Wisniewski

Chief Technology Officer, Profusa, Inc.

Tissue-integrating Sensors

At Profusa, we are pioneering subcutaneous sensors that continually and wirelessly report health status to a mobile device. Our long-term in vivo sensors are based on fluorescent, soft, tissue-like sensors that integrate with the tissue in which they are injected. Because of their tissue integrating properties, they have a very high surface area for quick responsivity and have been shown to last for more than 2 years in humans. Our first product which will be available commercially in Europe in 2016, is a continuous tissue-oxygen sensor, which has applications in hypoxia, critical limb ischemia, wound care, high altitude performance, exercise physiology, COPD, tumor metabolism, and other ischemia-related conditions. Over 60 sensors have been tested successful in humans and 2000 in pigs. Our R&D efforts focus on adapting the same sensor platform for glucose, lactate, alcohol and host of other medically relevant molecules. This talk will share some of our experience in bringing a new sensor technology to market including funding acquisition, transition to the clinic, the industrial design process, manufacturing, regulatory, marketing, reimbursements and other start-up considerations.

Bio: Dr. Wisniewski co-founded Profusa, Inc., a company dedicated to long-term continuous biosensing to provide unprecedented insights into our overall health. Dr. Wisniewski is a scientific leader in biomaterial-tissue interactions, specifically the foreign body response and how it affects implanted sensors. Her novel work on tissue-integrating sensors expands the paradigm of biocompatibility from surface chemistry to include biomechanics and bioelectronics to enable long-term continuous sensors in the body. She currently serves on the Board of Directors and as CTO at Profusa.
We are seeing explosive growth in wearable health monitors for healthcare and fitness applications. Many of these devices stick to the skin. This talk will explore the challenges of the skin as a substrate and considerations for selection of the proper adhesive. In addition we will cover biofunctionalization of materials to enable sensing of particular analytes for these applications.

Bio: Diana Eitzman received her Ph. D. in Chemical Engineering from the University of Minnesota. She has over 20 years of experience at 3M in technology and product development. She has managed laboratories in 3M’s Industrial and Healthcare Markets. Ms. Eitzman is currently the Director of 3M’s Medical Materials & Technologies Laboratory.
Abstract: We are seeing explosive growth in wearable health monitors for healthcare and fitness applications. Many of these devices stick to the skin. This talk will explore the challenges of the skin as a substrate and considerations for selection of the proper adhesive. In addition we will cover biofunctionalization of materials to enable sensing of particular analytes for these applications.

Bio: Amy McNulty received her PhD in Physiology from the University of Toronto. She has over 20 years of experience in tissue regeneration and repair industries and over 15 years in the regulated medical device industry. Ms. McNulty has managed product development at Smith and Nephew as well as KCI (Acelity) and currently is a Director of Research at 3M in the Chronic and Critical Care Solutions Division.
Sensors, Wearables, and Mobile Technologies

Although tremendous strides have been made in health care over the years, over one billion people still lack access to health care systems. The global health challenges of today include chronic medical conditions, infectious diseases, and the conditions closely associated with poverty including malnutrition, diarrheal diseases, and pneumonia. In this presentation the current state of wearable sensors will be discussed. This will be followed by a more in depth discussion of an implantable optical glucose monitoring technology as needed for the chronic condition of diabetes. Lastly, a polarized light mobile phone based technology for detection of the infectious disease, malaria, will be described.

Bio: Gerard L. Coté is the Director for the Center for Remote Health Technologies and Systems and holds the Charles H. & Bettye Barclay Professorship within the Department of Biomedical Engineering at Texas A&M University. He is recognized as a world-wide expert in optical sensing for diagnostic and biomedical monitoring applications. He is a Fellow of four societies, coauthor of over 300 publications, proceedings, patents, and abstracts, and is co-founder of four medical device companies.
Nanomagnetic Biosensing as a Platform Technology for Early Disease Detection and Prevention
MONDAY — OCTOBER 3, 2016
Mechanisms by Which Biologic Scaffolds Influence Cell Behavior

Biomaterials can be generally classified as synthetic versus biologic, or degradable versus nondegradable. The utility of biomaterials for various clinical applications has historically focused upon mechanical and material variables such as composition, strength, and porosity, among others. However, the ultimate determinant of clinical success or failure is the host response to the material itself. The immediate host response to an implanted biomaterial involves the von Bahr effect (adsorption of plasma proteins), followed by an acute and chronic innate cellular immune response. The phenotype of cells which respond to the material in the early phase contributes to the microenvironmental conditions which orchestrate downstream events. The signals which are associated with favorable versus unfavorable outcomes are only partially known and will be the subject of the present discussion.

Bio: Dr. Stephen Badylak, DVM, PhD, MD is a Professor in the Department of Surgery, and deputy director of the McGowan Institute for Regenerative Medicine at the University of Pittsburgh.

Dr. Badylak has practiced both veterinary and human medicine, and is now fully engaged in research. Dr. Badylak began his academic career at Purdue University in 1983, and subsequently held a variety of positions including service as the Director of the Hillenbrand Biomedical Engineering Center from 1995-1998.

Dr. Badylak holds over 50 U.S. patents, 200 patents worldwide, has authored more than 300 scientific publications and 40 book chapters, and has edited a textbook entitled Host Response to Biomaterials. He has served as the Chair of several study sections at the National Institutes of Health (NIH), and is currently a member of the College of Scientific Reviewers for NIH. Dr. Badylak has either chaired or been a member of the Scientific Advisory Board to several major medical device companies. More than eight million patients have been treated with bioscaffolds developed in Dr. Badylak’s laboratory.

Dr. Badylak is a Fellow of the American Institute for Medical and Biological Engineering, a member of the Society for Biomaterials, a charter member of the Tissue Engineering Society International, a past president of the Tissue Engineering Regenerative Medicine International Society (TERMIS) and a Founding International Fellow of TERMIS.

Dr. Badylak’s major research interests include:
- Naturally Occurring Biomaterials, including Extracellular Matrix, and Biomaterial/Tissue interactions
- Developmental Biology and its Relationship to Regenerative Medicine
- Relationship of the Innate Immune Response to Tissue Regeneration
- Clinical Translation of Regenerative Medicine
- Whole Organ and Tissue Reconstruction and Regeneration
TUESDAY — OCTOBER 4, 2016
Engineering Interfaces for Regenerative Medicine
“Off-the-Shelf” Heart Valves and Vascular Grafts Grown In Vitro

We have developed a novel tissue-engineered vascular graft, which is allogeneic upon a decellularization performed prior to implantation and thus “off-the-shelf.” It is grown from remodeling of ovine dermal fibroblasts entrapped in a sacrificial fibrin gel into tissue tube that is then decellularized using sequential detergent treatments. The resulting cell-produced matrix tube possesses physiological strength, compliance, and alignment (circumferential).

We have shown excellent results implanting these tubes into the sheep femoral position at 6 months, including complete recellularization and positive remodeling) without mineralization, dilatation, or immune response (Syedain et al, 2015). Similar results have recently been obtained in a pivotal preclinical model as an AV graft for 6 months, including periodic access with a dialysis needle (Syedain et al, unpublished). We have also recently shown somatic growth of these tubes implanted into the pulmonary of young lambs for almost 50 weeks, through adulthood (Syedain et al, 2016).

Using the concept of a tubular heart valve, where the tube collapses inward with back-pressure between 3 equi-spaced constraints placed around the periphery to create one-way valve action, we have reported unprecedented results implanting valves fabricated from these tubes mounted on 3-pronged crown frames into the sheep aortic position for 6 months (Syedain et al, 2015). We have also used the principle of a tubular heart valve to innovate a tubular pediatric heart valve based on attaching two tubes together with degradable suture to provide the constraints (Reimer et al, 2015) and developed initial experience in a young lamb model (Reimer et al, 2015).

Bio: Prof. Tranquillo received his Ph. D. in Chemical Engineering in 1986 from the University of Pennsylvania. He was a NATO Postdoctoral Fellow at the Center for Mathematical Biology at Oxford for one year before beginning his appointment in the Department of Chemical Engineering & Materials Science at the University of Minnesota in 1987. He has served as the head of the Department of Biomedical Engineering since its inception in 2000. Prof. Tranquillo has used a combined modeling and experimental approach to understand cell behavior, in particular, directed cell migration, and cell-matrix mechanical interactions. More recently, his research program has focused on the role of these cell behaviors in cardiovascular and neural tissue engineering applications. His research program has resulted in over 110 peer-reviewed original research publications, being recognized with his selection for the TERMIS-AM Senior Scientist Award in 2015. He is a Fellow of the American Institute of Medical and Biological Engineering, International Academy of Medical and Biological Engineering, and the Biomedical Engineering Society, and he is also a Distinguished McKnight University Professor.
Materials as Conduits for Directing Cell Behavior

The long term function of medical devices necessitates integration of the device with surrounding cells. This includes modulating protein and platelet responses, regenerating injured cells, recruiting desired cells and preventing planktonic bacteria from adhering to the device surface. Furthermore, the surface of the device must be able to respond at different time scales as the healing process progresses.

In this presentation, new polymeric materials will be presented that prevent blood clotting events, promote re-endothelialization and achieve significant log reduction rates of clinically important bacteria. The polymer and additives can be mixed in different formulations to provide tunable behaviors that can be applied to a range of different applications. As one example, additives, such as metal organic frameworks, can be mixed into medical polymers at concentrations that maintain the mechanical properties of the materials, but impart cell signaling function that lead to improved growth of cells. By improving the cell growth rate/regeneration, in the absence of infection, the material conduits are integrated in a manner that may lead to long term efficacy.

Bio: Melissa Reynolds, Ph. D. is a Boettcher Investigator and Associate Professor at Colorado State University in the Departments of Chemistry, Biomedical Engineering and Chemical and Biological Engineering. She is also currently the Associate Chair for Graduate Education in the department. She received a B. Sc. in Chemistry from Washington State University and a Ph. D. from the University of Michigan. Her research focuses on the molecular design and fabrication of biomimetic materials for use in medical device applications, including the development of metal organic frameworks as biocatalysts.

She has been recognized as an emerging investigator by the Journal of Materials Chemistry and Webb-Waring Biomedical Research Early Career Award, and an NSF CAREER Award. The group’s research on metal organic frameworks received a 2013 TechConnect National Innovation Award. Her research has been funded by NSF, NIH, DOD, Boettcher Foundation, state funding and corporate funding. In addition to her academic interests, Ms. Reynolds is co-founder of Diazamed, a CSU supported company that works to commercialize research.
Session 1: Conrado Aparicio  
Associate Professor, University of Minnesota

The Use of Oligopeptides and Recombinamers to Improve Performance of the Biomaterials Surface

Functionalization of dental biomaterials with multiple bioactivities is desired to obtain surfaces with improved biological and clinical performance. In our lab we have been developing bio-inspired coatings and scaffolds made of recombinant biopolymers or oligopeptides targeting bone regeneration and antimicrobial properties. Statherin-derived peptides for biomimetic mineralization, antimicrobial peptides derived from the parotid salivary protein, and laminin-derived peptides for inducing permucosal sealing formation are some examples of molecules we have used to biologically activate biomaterials surfaces. We have also co-immobilized different oligopeptides on the same substrate to produce multi-functionalized surfaces. These surface modifications aimed to improve dental and orthopedic implant clinical outcomes or to induce dentinal-pulp regeneration.

Bio: Mr. Aparicio is Associate Professor at the University of Minnesota since 2008 and Deputy Director of the Minnesota Dental Research Center for Biomaterials and Biomechanics. His research interests include: biomaterials surface-modification with bone regenerating and antimicrobial properties, biomineralization, and interactions at the bio/non-bio interface. He is co-author of over 80 papers in peer-reviewed journals. Editor of Elsevier book “Biomineralization and Biomaterials.” Additionally, he is co-inventor of several patents, one of them licensed to a dental implant manufacturer. Mr. Aparicio has been an invited and keynote lecturer in International and National research forums. Including the 25th European Conference on Biomaterials, Materials Research Society 2013 Spring Meeting, IX International Congress on Chemical Sciences, Technology and Innovation, Biointerface 2010, and graduate and master programs in several North American, Asian, and European Universities. His work is funded by NIH/NIDCR, European Commission, 3M Foundation, and several biomedical companies, among others. Mr. Aparicio's awards include: 3M Non-Tenured Faculty award, IIId European Award in Basic Research in Dentistry, and 2002 Best Paper in Materials Science: Materials in Medicine, among others.
BioDep - Tailored Interfaces Using Pure Biologic Coatings

Traditional methods for applying biomolecules onto surfaces include multi-step processes wherein the substrate is cleaned, activated and then coated with a primer layer. Additional layers are then applied using slow, cumbersome wet chemical techniques and the biomolecule is finally either tethered to the end of a linker or is encapsulated within a polymer. The result is a complex mixture of synthetic and biological materials present on the surface.

An alternative approach has recently been devised which enables 100% pure biomolecule coatings to be deposited as cross-linked and stable nano-coatings. The deposited materials are bonded onto the substrate and are entirely free of linkers, binders or primers. By passing a nebulised biomolecule through a low energy plasma discharge, the biological materials are activated and become cross-linked or coagulated and are thereby deposited as dry and stable nano-coatings. As the plasma can also activate the substrate, it is possible to bind the biologic directly onto almost any solid surface.

Using this technique, biomolecules have been deposited on to substrates as diverse as plastics, ceramics, metals and even on to living tissue. The technology has been use to successfully deposit a range of proteins, polysaccharides and complex autologous mixtures and the resultant surfaces have been characterised using both in vitro and in vivo techniques. This technique opens the possibility to produce enhanced biological interfaces for improved biocompatibility, enhanced healing and reduced costs.

Bio: John O’Donoghue is the inventor behind a number of breakthrough surface modification technologies. His first invention, entitled CoBlast, has been developed as a mission critical coating on ESA’s Solar Orbital mission and is now finding widespread applications in industrial, military and medical applications. BioDep is a new technology developed by John and focussed on solving a number of issues in the medical device and wound healing sectors. John has a degree in Mechanical Engineering and a Masters degree in Biomedical Engineering and has been an active participant in the Biointerface community for many years.
TUESDAY — OCTOBER 4, 2016
Structural Heart Valve/General Mechanic
Towards the Understanding of the Biocompatibility of Nitinol Biomedical Devices

This presentation explores the effects of oxidation and passivation on the corrosion resistance, ion release, and biocompatibility of medical grade Nitinol. High spatial and angular analytical techniques such as SEM, FIB, AES, as well as synchrotron techniques (microdiffraction, SAXS, and XPS) were used to characterize the composition, phase distribution, and thickness of Nitinol surfaces after various treatments. We will discuss these findings in terms of anodic polarization behavior, galvanic corrosion, and Ni ion release data of implant devices. There is a strong inverse relationship between the thickness and structure of surface oxide and the localized and uniform corrosion resistance of the material. Properly passivated Nitinol surfaces consist of Ni-free amorphous titanium oxide, whereas thermal oxide surfaces are composed of crystalline TiO2 (rutile) with Ni-rich phases (Ni and Ni3Ti). Long-term extraction tests show minimal Ni release rate for passivated Nitinol, whereas thermally oxidized Nitinol shows an increased ion release. Furthermore, galvanic testing between Pt and Nitinol with different surface processing provides insight into the effects of passivation. In this presentation, we also review corrosion-related failure analyses of medical explants. These observations, in combination with scientific investigations, provide comprehensive research that probes the structure of Nitinol biomedical devices surfaces and their interactions with biological fluids. In addition, this presentation will also present scientifically sound strategies for increasing the inertness of Nitinol devices in vivo.

Bio: Alan R. Pelton is Chief Technical Officer of G.RAU Inc., which he founded in 2014 and conducts medical device testing and consulting. From 1993-2014, he was CTO at NDC. He received his Ph.D. in MSE at UC Berkeley and M.S. and B.S. in MetE at SDSM&T. He was a MSE postdoctoral fellow at Stanford University, followed by appointments as Research Metallurgist at Ames Laboratory/ISU and Assistant Professor at the University of Notre Dame.
Tailoring Radiopacity of Thin-wall Vascular Implant Alloys

A short list of off-the-shelf metal alloys have been utilized in the construction of vascular implants. Radiographic density of the alloy has been one of the design inputs for coronary vascular stents, since a design strategy has been to reduce wall thickness to enhance deliverability of the intravascular device to the treatment site. Some candidate alloys have radiographic density that is too high such that the implant can interfere with fluoroscopic imaging of adjacent anatomy and devices. Other alloys have desirable mechanical properties, but the materials do not provide sufficient radiopacity to allow visibility of the implant relative to surrounding biological matter. This is the story of purposeful alloy formulation to create an alloy with radiographic density and mechanical properties compatible with new stent designs. The principles could be applied to alloys for heart valve frames should off-the-shelf alloys not have proper radiopacity, bulk material properties, and surface characteristics for new frame designs.

Bio: Metallurgical Engineer and Senior Manager of Boston Scientific Global Technology & Services Analytical Laboratory for 22 years. Twelve prior years in Defense and Aerospace industry as metallurgical engineer. B.S. Metallurgical Engineering from Michigan Technological University, and MBA from University of St. Thomas.
Session 2: Juergen Scherer
Senior Scientist, EAG, Inc.

Surface and Other Analytical Characterization Methods for Implantable Medical Devices

The ultimate success of many of today’s implantable biomedical devices is often associated with the surface properties of the materials used in the device. This is because the surface is the interface between the body and the device and its chemistry directly affects how the two interact. Therefore, characterizing and understanding the nature of the device surface is critical in both the development and production stages of the product. Material characterization has also received increased emphasis from biomaterial regulatory agencies such as the FDA. This presentation will discuss some of the more advanced surface analysis techniques available to fully understand the surface of implantable devices and will show examples of their applicability.

- Dozens of different analytical tools are available to characterize biomedical device materials, each with their own advantages and limitations.
- Surface sensitive tools must be used when the outermost atomic layers are to be studied.
- Surface sensitive analytical techniques include Auger Electron Spectroscopy (AES), X-ray Photoelectron Spectroscopy (XPS), and Time-of-Flight Secondary Ion Mass Spectrometry (TOF-SIMS).
- Examples of surface studies include device cleanliness/contamination, metal oxide thickness/passivation, and plasma or corona treatments on polymers.

Bio: Dr. Juergen Scherer is a Senior Scientist at EAG Laboratories where he specializes in the characterization of surfaces and interfaces of materials and products ranging from semiconductors to biomedical devices. This includes the study of passivation layers and corrosion, as well as surface segregation of reactive species which can affect the performance and reliability of a device. Dr. Scherer received his Ph.D. in Physics from the University of Kaiserslautern, Germany in 1995.
Preclinical Models for Surgical or Trans-Catheter Heart Valves

Transcatheter heart valve therapies have transformed the treatment of patients with severe aortic valve disease. The expansion into new patient populations has highlighted the production of superior devices for this space requires careful design and development processes. From concept through to clinical trial initiation, all stages of the process rely on the input of engineers, scientists and clinicians alike to bring a successful product to market. Preclinical Models are key to the successful development and testing of this class of complex medical devices. There are many facets to valve evaluation and a one size fits all approach doesn’t work with all types of valves. The surgical staff at American Preclinical Services (APS) has developed multiple methods in a variety of animal models for testing different types of valves, annuloplasty rings and other structural heart repair devices. From early biocompatibility and feasibility testing to pivotal GLP studies for FDA submission, APS has the experience to help along the way. APS performs more than 200 valve related procedures each year. With onsite CT, angiography and echocardiography, extensive in-life evaluation of your test article can be completed in a timely fashion. APS also has extensive experience and capabilities in histological evaluation of your valve as well as analytical evaluation of bioprosthetic valves for ICP-MS quantification of calcium accumulation. Evaluation of devices in the large animal models can often be leveraged for some of the biocompatibility requirements for device implantation, thus reducing the overall project costs. Overall, APS can be a valuable partner in bringing your structural heart projects to fruition.

Bio: Ms. Gross has served as a scientist and surgeon at American Preclinical Services, LLC since early 2006. Ms. Gross has over 12 years of experience in the preclinical contract research industry as a scientist and research surgeon (cardiovascular and abdominal). In 2004 she received her Bachelor of Arts degree in Biology from the University of Minnesota. From 1999-2006 she worked as an assistant scientist (research surgeon and Study Director) performing device training, feasibility research, and GLP safety studies for Experimental Surgical Services (ESS) at the University of Minnesota. Ms. Gross has successfully performed as the Study Director for numerous studies focusing on endovascular, cardiovascular, gastric and endoscopic devices. Furthermore, Ms. Gross has performed and/or assisted in thousands of surgical procedures in a variety of species (swine, canine, ovine, rabbits, bovine, caprine, and non-human primates). She has assisted in the development of research models for heart failure and she has extensive experience in endoscopic procedures, cardiopulmonary bypass, valve replacement, coronary artery bypass, peripheral graft placement, and abdominal surgical implants of various types. In early 2006 Ms. Gross accepted a position at APS as Assistant Scientist and has since been promoted to Senior Scientist/Senior Surgeon.
TUESDAY — OCTOBER 4, 2016
Polyurethane Biodegradation and the New Generation of Biostable Polyurethanes
Session 3: James Anderson M.D., Ph.D.
Distinguished University Professor in the Departments of Pathology, Macromolecular Science and Biomedical Engineering, Case Western Reserve University

Historical Perspective of Polyurethane Biostability

This presentation provides information on the early history of polyurethanes and begins with the discovery and development of polyurethanes by Otto Bayer and colleagues in 1937, and leads up to studies by our group at Case Western Reserve University in the 1980’s and 1990’s. A biased and incomplete perspective on biomedical polyurethane biostability/biodegradation will be presented. References are provided for those wishing more detailed information.

While initially thought to be biostable, biomedical polyurethanes utilized in several different types of medical devices exhibited material changes suggestive of biodegradation. These three examples are detailed in the superb review by Leonard Pinchuk in 1994 (1). These three examples were the MEME breast implant which utilized Scotfoam as a covering and exhibited biodegradation behavior following implantation. The second example, in the early 1980’s, was the observation by Parins that Pellethane 2363-80A polyether polyurethane pacemaker lead material underwent degradation leading to surface cracking. The third example was the observation of creep behavior in the biomedical polyurethanes utilized as bladders in artificial hearts and left ventricular assist devices in the early 1980’s. These observations lead to the development of an in vitro test utilizing cobalt ions and hydrogen peroxide to provide reactive oxygen species (ROS) which provided oxidative chain cleavage in the soft segment polyether component of the Pellethane and Biomer materials. Results from these studies will be presented. The potential for biodegradation leading to ultimate failure of biomedical polyether polyurethanes led to the development of replacement polyurethanes.

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9. Christenson, Elizabeth M., Anderson, James M., and Hiltner, Anne. Oxidative mechanisms of poly(carbonate urethane) and

Bio: James M. Anderson, M.D., Ph.D., is a Distinguished University Professor in the Departments of Pathology, Macromolecular Science and Biomedical Engineering at Case Western Reserve University in Cleveland, Ohio. He is an elected member of the National Academy of Engineering (NAE), National Academy of Medicine (NAM), and the American Association of Physicians (AAP). His research interests are in the areas of biomaterial biostability/biodegradation and macrophage/foreign body giant cell interactions in the foreign body reaction to implanted medical devices, prostheses and biomaterials.
Development of Replacement Polyurethanes for Implantation and Their Use as Platforms for New Biomaterials Development

Their wide range of possible surface and bulk properties make polyurethanes interesting as biomaterials. A proven model structure allows tailoring properties for use in specific devices and implants when no other materials may be suitable.

Typical biomedical polyurethanes are copolymers containing ‘hard blocks’ with dominant thermal transitions above body temperature, and flexible ‘soft blocks’ that as homopolymers would be liquids at 37 C. The choice and concentration of these blocks and their interactions via hydrogen bonding are well-known determinants of the bulk properties and processability of neat polyurethanes. We developed a structure consisting of hard blocks, two or more soft blocks, and surface-modifying end groups (SME) as a ‘biomaterials tool kit’ which we used in many applications including glucose sensor membranes, drug delivery devices, antimicrobial thermoplastics, and biostable implantable prostheses. Most thermoplastic (TPU) and solvent-based ‘segmented’ polyurethane-ureas (SPU) are step growth polymers synthesized from di-functional reactants including diisocyanates, diols, and/or diamines. Inclusion of one or more monofunctional oligomeric reactants terminates chain growth, positioning the oligomeric tail as mobile end groups. Certain end groups are surface active and capable of self-assembly during and after fabrication of device components. The choice of mid-blocks and end groups allows independent control of bulk and surface properties because small concentrations of end groups have a large effect on surface properties but little effect on the bulk.

Our development of so-called replacement biomaterials preceded routine use of the toolkit structure described above, which evolved during several R&D projects, and scale up of these simpler polyurethane compositions. Starting in 1989 the Polymer Technology Group (PTG) received requests from device groups and NHLBI to develop equivalent versions of some industrial polyurethanes being used as biomaterials. At the time, risk-averse suppliers began ‘contraindicating’ their polymers in implantable devices due to the high risk/benefit ratio for these relatively small-volume uses. These included Dow Pellethane® and Corvita Corethane® TPUs, DuPont/Ethicon Biomer™ SPU, and DuPont Lycra spandex fiber. This left pacemaker, VAD, and other implant manufacturers without a source of polymer for established products, and it threatened new cardiovascular devices that were entering clinical trials after years of development.

At PTG we built both batch and continuous reactors to produce replacements for these biomaterials and characterized their physical/mechanical properties and biostability in collaboration with Case Western and Medtronic. Results were published and added to FDA Masterfiles for each PTG product including Elasthane™ polyether-urethane, Bionate polycarbonate-urethane, and BioSpan® SPU. These polymers also served as platforms for developing new biomaterials including PurSil® and CarboSil® silicone-polyurethanes, Bionate II polycarbonate-urethane, and BioSpan-S. Silicone-containing polyurethanes with optional silicone or perfluorinated end groups proved to be more biostable than conventional polyether or polycarbonate polyurethanes when compared at equal hard segment content. These polymers are now used in ‘implantables’ that require toughness and in vivo stability, including cardiovascular, orthopedic, and neuro-stimulation devices.

Bio: Bob Ward is president of ExThera Medical Corporation in Martinez, CA, and founder of the Polymer Technology Group of Berkeley, now DSM Biomedical. Bob is a chemical engineer and polymer scientist with 45 years of experience in the development and manufacturing of medical devices, and many polymeric biomaterials used in implantable applications. He has been involved in four successful medtech start-up companies. Novel and replacement biomaterials, and components developed and manufactured under his direction have been used in dozens of devices and prosthetic implants including glucose sensors, artificial hearts, vascular grafts, pacemakers, orthopedic implants and contact lenses. ExThera, his latest venture, has developed a broad-spectrum hemoperfusion device that safely removes a long list of pathogens and toxins from whole blood in the treatment of (drug-resistant) bacteremia and viremia. Clinical trials are underway.
Polyurethanes containing low amounts of siloxane have been commercially available in various forms since the 1970s, however incorporation of significant amounts of siloxane only became commercially available for medical devices in the 1990s. Numerous papers have demonstrated excellent oxidative and in vivo biostability as well as optimal mechanical properties for this class of implantable biomaterials. In 2006, one of these siloxane-based polyurethanes, Elast-Eon 2A, received FDA approval for use in cardiac leads under the trade name Optim insulation. After >2,000,000 implants worldwide and 10 years of implant history, cardiac leads with Optim insulation continue to demonstrate excellent clinical performance.

In contrast to the clinical experience, a 2012 publication describing a temperature accelerated (85°C) in vitro hydrolysis study predicted catastrophic Optim insulation degradation after 6 years of implantation. The improper use of time-temperature superposition, several inaccurate assumptions, and the absence of in vivo validation called into question the claimed in vitro-to-in vivo correlation. Subsequent studies of cardiac leads explanted from humans after periods of up to 7 years have demonstrated that Optim remains highly biostable in vivo. Multiple labs have confirmed that extreme temperature (up to 85°C) aqueous exposure can induce degradation in Optim and other polyetherurethanes commonly used for implant applications. Interestingly, even exposure to 85°C in the absence of water can induce similar levels of degradation in these materials, indicating that hydrolysis is not the primary cause of extreme temperature degradation. In both in vitro and in vivo studies at body temperature, Optim demonstrates an initial ~22% drop in molecular weight with no reduction in mechanical properties, believed to be due to allophanate bond disruption, followed by stability out to the maximum duration tested, 7 years. While the direct measurement of very low concentrations of allophanate bonds in Optim insulation remains elusive, viscosity and molecular weight data have provided compelling evidence of their presence.

Bio: Christopher Jenney received his Ph. D. in Biomedical Engineering at Case Western Reserve University in 1999. His graduate research examined the impact of surface chemistry on the inflammatory response to biomaterials. He immediately began working for St. Jude Medical as a Biomaterials researcher. In his 17 years at St. Jude Medical Chris has worked as an individual contributor and leader in the areas of biomaterials, cardiac lead product development, quality engineering, and post-market monitoring. Chris is currently leading a team of biomaterials researchers with applications across St. Jude Medical’s broad product portfolio. With an industry focus, Chris and his team scout emerging and commercially-available materials technologies that can be utilized in temporary and implantable medical devices.
Biostable Polyisobutylene-based Polyurethanes

The surface of polyisobutylene (PIB) is exclusively of primary and secondary H atoms rendering this elastomer resistant to hydrolysis and oxidation. Indeed, PIB is the most inert general-purpose rubber known. We synthesized unique polyurethanes (PUs) having PIB soft segments protecting conventional hard segments. Our series of publications document the mechanical properties and hydrolytic-oxidative resistance of these thermoplastic elastomers in vitro and in vivo. We will first cast a bird’s eye view of various PIB-based biomaterials in which biostability is of the essence. Subsequently, we discuss PIB-based PU and contrast its biostability with commercial “biostable” PUs.

Bio: Joseph P. Kennedy is distinguished professor of polymer science and chemistry at The University of Akron. He was an industrial researcher for 13 years (Celanese, Exxon) following which he started his academic career in 1970. His main interest is the creation of new useful polymers and devices for medicine and premium industrial applications. He is the inventor of over 100 issued U.S. patents, some of them in production generating billions of dollars of revenue. He is the author of 4 books and over 700 publications, and he is the recipient of numerous prestigious national and international awards. His latest book “How to Invent and Protect Your Inventions” was published in 2012.
TUESDAY — OCTOBER 4, 2016
Point Counterpoint
A material's useful life in the human body is defined by the length of time that the material is able to perform its function in a given application. Depending on the functional requirements of the material, one application may result in a drastically different useful life compared to a different application using the identical material. This is precisely the reason that the FDA and other regulatory bodies do not “approve” materials, but rather, they approve devices. Trends in healthcare, which include earlier diagnoses and more effective treatments, have led to an increasing and sharply rising change in the time a typical patient will live with a chronically implanted medical device. This expanded longevity combined with the push toward smaller devices has driven the materials traditionally used in many medical device applications to, or even beyond, their performance limits. Because of this, now more than ever, the industry needs new materials to fill the performance gap created by miniaturization coupled with increasing longevity expectations.

In this panel discussion, we will explore the topic of how one should think about introducing new materials for use in chronically implanted devices which are designed to have longevity expectations in the decade plus range.

- Kimberly Chaffin, PhD, PE, Medtronic
- Patrick Willoughby, R&D Mechanical Engineer, Boston Scientific
  Bio: Pat received his B.S. degree from the University of Pittsburgh and his M.S. and Ph.D. degrees from the Massachusetts Institute of Technology. All three degrees are in mechanical engineering, with a focus on precision engineering and medical devices. Since graduate school, he has been with Boston Scientific (BSC). At BSC, Pat has primarily focused on mechanical and material aspects of leads in the Cardiac Rhythm Management division, as well as consulting on a variety of projects around Boston Scientific.

- Christopher Jenney, Sr. Director, St. Jude Medical Sylmar, CA
  Bio: Christopher Jenney received his PhD in Biomedical Engineering at Case Western Reserve University in 1999. His graduate research examined the impact of surface chemistry on the inflammatory response to biomaterials. He immediately began working for St. Jude Medical as a Biomaterials researcher. In his 17 years at St. Jude Medical Chris has worked as an individual contributor and leader in the areas of biomaterials, cardiac lead product development, quality engineering, and post-market monitoring. Chris is currently leading a team of biomaterials researchers with applications across St. Jude Medical’s broad product portfolio. With an industry focus, Chris and his team scout emerging and commercially-available materials technologies that can be utilized in temporary and implantable medical devices.

- Elizabeth Cosgriff-Hernandez, Texas A&M
  Bio: Elizabeth Cosgriff-Hernandez, Ph.D. is an Associate Professor of Biomedical Engineering at Texas A&M University. She received a B.S. in Biomedical Engineering and Ph.D. in Macromolecular Science and Engineering from Case Western Reserve University under the guidance of Professors Anne Hiltner and Jim Anderson. Her dissertation research was focused on elucidating the structure-property relationships and biodegradation mechanisms of polyurethane elastomers. She then completed a UT-TORCH Postdoctoral Fellowship with Professor Tony Mikos at Rice University with a focus in orthopaedic tissue engineering. Dr. Cosgriff-Hernandez joined the faculty of the Biomedical Engineering Department at Texas A&M University in 2007. Her laboratory specializes in the synthesis of hybrid biomaterials with targeted integrin interactions and scaffold fabrication strategies (e.g. injectable foams, 3D printing emulsion inks, reactive, in-line blending electrosprining). She also serves on the scientific advisory board of ECM Technologies and as a consultant to numerous companies on biostability evaluation of medical devices. Dr. Cosgriff-Hernandez is an Associate Editor of the Journal of Biomedical Materials Research, Part B and serves as a standing member and co-chair of the NIH study section on Musculoskeletal Tissue Engineering.

- Tim Lodge, Regents Professor, University of Minnesota
WEDNESDAY — OCTOBER 5, 2016
Neurovascular
We have developed a shape memory polymer (SMP) foam embolic device for treating cerebrovascular aneurysms. The SMP implants include a passively actuated open-celled foam that expands radially from the central platinum-alloy coil. The foams enable more of the aneurysm volume to be filled with a high surface area foreign body that encourages more rapid and complete acute clotting. Chronically, the foams result in filling of the aneurysm with connective by forming collagenous scars. We are working to demonstrate the value proposition of these devices as having better volume filling capacity than bare metal coils and reduced recanalization due to the collagen ingrowth.

We have conducted pilot biocompatibility, two in vivo safety/efficacy studies and multiple in vivo efficacy studies of a foam-over-coil device. In the first in vivo study, twenty-seven SMP polyurethane foams were implanted in a porcine aneurysm animal model to determine biocompatibility, localized thrombogenicity, and the ability to serve as a stable filler material within an aneurysm. Aneurysms were explanted at time points of 0, 30 and 90 days. In these studies the foams were manually inserted into vein sacks by the vascular surgeon at the time of model aneurysm creation. Partial healing was observed at 30 days, and nearly complete healing had occurred at 90 days. These foams exhibited exceptional biocompatibility and stability throughout each implantation period. In the second in vivo study, 90 and 180 day comparative time points were gathered for four animals (two at each explant time point) that each had two aneurysms: one treated with bare platinum coils and the other treated with SMP foam. The porcine sidewall vein pouch carotid aneurysm model was used. The conclusion of the study is that the SMP foams were superior to bare platinum coils in every facet of treatment endpoints including acute clotting, protection of the parent vessel and, most importantly, chronic healing response. For the in vivo study results, all treated aneurysms showed significant occlusion, especially at the dome apex, as indicated by the lack of contrast agent infiltration during fluoroscopic imaging. Also, all device components were clearly identified under fluoroscopy and the implant coils demonstrated consistent delivery, placement, and foam expansion.

The Biointerfaces 2016 talk will present the rational for pursuing embolic scaffolds, background material and device properties, benchtop and in vivo study results and discuss the tradeoffs of conducting this work in an academic setting and translating the technology to industry.

Bio: Dr. Maitland has worked as an engineer in aerospace, national defense and biomedical applications since 1985. His research projects include endovascular interventional devices, optical therapeutic devices and basic device-body interactions/physics including computational and experimental techniques. He has over 80 archival publications and 19 issued patents. His current focus is commercial translation of porous shape memory polymer medical devices.
Endoluminal devices such as metallic flow diversion (FD) and aneurysm bridging (AB) stents are used for treatment of intracranial aneurysms. Treatments are associated with thrombogenic events mandating the use of dual antiplatelet therapy in all cases. We show that the Pipeline(TM) Flex Embolization Device with Shield Technology(TM) has significantly lower peak thrombin compared to the other three FD devices (p<0.05), with statistically similar results to the less thrombogenic AB devices. We conclude that surface modification of endoluminal stents could be an effective method to mitigate thrombogenic complications. The Lazarus Cover (TM) device is an innovative differentiating technology that is complementary to Medtronic’s Solitaire stent retriever platform. This technology is designed to address clinical needs with a novel nitinol “mesh cover” that folds over a stent retriever device during clot retrieval and “candy wraps” the stent with the clot inside. Of the 695,000 acute ischemic stroke victims in the U.S., about 240,000 are eligible for treatment with a stent retriever, like the Solitaire device. However, while these devices are available at more than 500 hospitals in the U.S., only about 13,000 procedures were performed in 2014.

The Lazarus Cover(TM) device is an adjunctive device used in stent retriever procedures and obtained CE Mark authorization in November 2014 for commercial distribution in the European Union; the U.S. regulatory approval process is pending.

**Bio:** Mr. Wainwright is Sr. R&D Manager at Medtronic Neurovascular managing multiple stent based product developments. Previously, he obtained his Ph. D. from the University of Pittsburgh, in Bioengineering with research based on organ specific extracellular matrix for cardiac repair. Mr. Wainwright worked at UPMC hospital supporting ventricular assist device patients. Prior to that he worked at Cordis on peripheral self-expanding stent design and processes.
In the late 2000’s, several companies invented braiding technology and/or braided devices to treat the most difficult fusiform and saccular brain aneurysms. As these braided stent and spheroid devices were implanted in pre-clinical models and patients, new observations about blood deposition, coagulation, and hemodynamic forces were uncovered. My talk will focus on the WEB Intra-saccular Flow Disrupter and highlight the insights and unexpected results that led to new hypotheses about the forces involved at the interfaces between blood, aneurysm sac, and braided device.

Bio: Dr. Ram Kadirvel is an Associate Professor of Radiology at Mayo Clinic. His research focuses on understanding the healing mechanisms of intracranial aneurysms following endovascular treatments. His research group has carried out preclinical evaluations for numerous endovascular devices, including the HydroCoil, the Woven Endobridge, and the Pipeline Embolic Device, that directly led to clinical implantation. Dr. Kadirvel has received a number of research grants and his research has contributed to the publication of over 80 peer reviewed papers. He serves on grant review panels of NIH and American Heart Association. Prior to joining Mayo Clinic, he received his doctoral degree in Biochemistry from University of Madras, India.
Session 5: William Merritt  
Northern Arizona State University

Development of Synthetic Thrombus for Use in Neurovascular Modeling

In vitro thrombus models can be used for device testing and optimizing thrombus extraction procedures to reduce ischemic strokes. Many factors contribute to the variance of mechanical properties in thrombi samples, such as the heterogeneity of thrombus structure and the composition differences in each individual donor’s biology. Other factors, such as the availability of donor thrombi, biological hazards, and biologic material handling procedures, make acquiring, storing, and testing human thrombi inconvenient. The aim of this research is to develop a synthetic thrombus substitute with mechanical properties that are consistently reproducible and comparable to the mechanical properties of a human thrombus. This thrombus substitute will allow for convenient and reproducible in vitro testing of thrombus retrieval devices.

Biomaterials analyzed in this study include hydrogels (i.e. alginate), polymer constructs (i.e. PPODA-QT), and related composite combinations. These materials were chosen to simulate the gel-like nature of a thrombus. The biomaterials are capable of displaying a wide variance of mechanical properties based on adjustable composition. Rheological testing of the biomaterials and donor thrombi provides data on Young’s modulus, dynamic Young’s modulus, shear modulus, viscosity, and hardness. A high precision DHR-2 rheometer (TA Instruments, New Castle, DE) is used for these tests. An in vitro neurovascular model is used to test thrombus placement and integrity under simulated blood flow conditions.

Human thrombus has a dynamic Young’s modulus from 129 to 181 Pa and a shear modulus range from 247 to 373 Pa. These properties, as described in the literature, have been verified with human and animal thrombus samples acquired from our collaborating institution (Barrow Neurological Institute, Phoenix, AZ). The rheometer was used to find elasticity and viscosity properties of the alginate and PPODA-QT formulations. Results have shown that alginate (1 – 2 w/v %) and PPODA-QT (Mw < 900 Da) have similar properties to thrombi, can be formulated to the above specifications, and can be tested in an in vitro model. The thrombus was placed, via the introducer, into the aneurysm vessel model. The artificial blood was pumped at an average inlet flow rate of 200 cc/min with a mean pressure drop of 90 mmHg using a programmable pulsatile pump (CardioFlow 1000 system, Shelley Medical, London, Ontario). The thrombus maintained its position and integrity throughout testing (up to 24 hours).

Through testing and gradual alterations to the composition of the biomaterials, an acceptable synthetic substitute for thrombi can be achieved. This synthetic thrombus, with consistently reproducible mechanical properties, can help reduce the need for acquiring and maintaining human biological materials. Future testing will utilize the synthetic thrombus for in vitro testing of thrombus retrieval devices at NAU’s Bioengineering Devices Lab (BDL).

Bio: William Merritt is a Research Assistant (since February 2016) at Northern Arizona University (NAU) in the Bioengineering Devices Lab (BDL), which is part of the Center for Bioengineering Innovation (CBI). The BDL Research Assistants design and develop new biomaterials and applications, and are certified to test various solids and fluids for material properties. All Research Assistants develop, maintain, and utilize BDL’s material testing equipment and vascular flow models to better understand how various materials and devices interact with the body.
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Bio: Anne Marie Holter is a Research Assistant at Northern Arizona University (NAU) in the Bioengineering Devices Lab (BDL), which is part of the Center for Bioengineering Innovation (CBI). The BDL Research Assistants design and develop new biomaterials and applications, and are certified to test various solid and fluid materials for material properties. All Research Assistants develop, maintain, and utilize BDL’s material testing equipment and vascular flow models to better understand how various materials and devices interact with the body.
WEDNESDAY — OCTOBER 5, 2016
Characterization Methods & Molecular Imaging (Part 1)
Mass spectrometry science drives the study of the molecules that enable life. In fields such as genomics, proteomics or metabolomics we experience a growing interest in the examination of the spatial organization of biomolecules directly from complex surfaces with many interfaces. Tissues harvested for molecular pathology are just one prime example. Molecular biology thrives on a myriad of molecular imaging techniques that aim at the investigation of the relation between spatial organization, structure and function of molecules in biological systems. One of them, mass spectrometry based imaging (MSI), is developing rapidly as an innovative molecular imaging tool. MSI is an extraordinary new tool that eliminates the need to know in advance the specific molecules that define disease states and it can be used in this unbiased manner to discover underlying pathways or constellations of molecules that define healthy, diseased, or regenerated tissues. This technology is particularly ideal for investigating heterogeneity within tissue samples because the spatial organization of the molecular information is retained. Molecular heterogeneity of healthy and diseased tissue (often present in the same sample) is typically studied to determine what happens at the interface of health and disease. More and more researchers realize that a single technology provides only a subset of the molecular information needed to obtain an in depth understanding of this universal clinical problem. Multimodal approaches enable the study of clinical samples at a variety of molecular and spatial scales. The molecular complexity on the genome, proteome and metabolome level all needs to be taken into account. The distribution of several hundreds of molecules on the surface of complex (biological) surfaces can be determined directly in complementary imaging MS experiment with MALDI and SIMS. This enables molecular pathway analysis as well as the analysis of the role and evolution of the different molecular signals during e.g. tumor development.

New developments in both SIMS and MALDI are pushing the limits of the technology that provides novel hitherto unknown molecular details in the study of interfaces. One of these technologies, the use of tandem mass spectrometry in SIMS, enables the direct identification of large organic molecules from complex tissue surfaces. In this lecture we will describe new technological developments and their applications that now allow for true translational research. Multimodal MS based molecular imaging will drive future precision tissue diagnostics and is one of the enablers of systems medicine.

Bio: Prof. Dr. Ron M.A. Heeren (1965) is a distinguished professor and Limburg Chair at the University of Maastricht. He is the director of the Maastricht MultiModal Molecular Imaging (M4I) institute and heads the division of imaging Mass Spectrometry. He has developed innovative approaches towards high spatial resolution and high throughput molecular imaging technologies to study the complexity of interfaces. He has a strong interest in translational molecular imaging for tissue typing in personalized medicine.
Session 6: Nathan Havercroft
ION-TOF USA, Inc.

Label-Free 3D Analysis of Biological Tissue with Micron Spatial and 240k Mass Resolution using a New SIMS Hybrid Mass Analyser

Time-of-flight secondary ion mass spectrometry (TOF-SIMS) is an established, highly sensitive analytical technique for mass spectrometry (MS) imaging applications with a lateral resolution below 100 nm. Monitoring the uptake of nanoparticles, drugs or other chemicals into cells are only a few examples for the application of this label-free chemical analysis technique.

Chemical information is obtained by bombarding the surface with a focused primary ion beam and analyzing the generated secondary ions in a TOF mass analyzer.

However in complex biological samples identification of unknown compounds can be hampered by mass interferences and a high number of possible candidates for a single mass peak.

In order to overcome these limitations, the 3D nanoSIMS project [1] has developed a revolutionary new SIMS instrument that combines the high lateral resolution and speed associated with TOF-SIMS with the high mass resolution and high mass accuracy of an orbital trapping mass analyzer. The instrument is equipped with a newly developed gas cluster ion beam column allowing a lateral resolution down to the micron level. First results obtained from different biomaterials are presented here.

Amiodarone-dosed NR8383 cells and a native coronal mouse brain section were analyzed using either a 20 keV argon gas or a bismuth cluster primary ion beam. For MS of the generated secondary ions a new hybrid SIMS instrument was utilized, featuring a hybrid mass analyzer that combines a fast TOF analyzer (TOFSIMS.5, ION TOF GmbH, Muenster, Germany) with an orbital trapping analyzer (QExactive(TM) HF [2], Thermo Scientific, Bremen, Germany).

High lateral resolution TOF-SIMS images show the sub-cellular distribution of iodine, a moiety of the drug amiodarone with respect to the nucleus of the cell.

First gas cluster Orbitrap(TM) SIMS images from mouse brain sections demonstrate the simultaneous localization and identification of various compounds. On tissue, the high mass resolution (FWHM of 240,000 at m/z 200) was used to identify lipids and metabolites with sub-ppm mass accuracy. Identification of numerous lipid signals at the single cell level could be easily performed using exact mass measurement and comparison with databases. Additionally, ions were selectively fragmented by tandem MS (MS/MS) in order to confirm chemical structure or help on assignment of unknown signals.

With this unique instrument numerous applications in the field of biomaterials can be studied, including interactions between tissue and biomaterials and process control in fabrication. Laterally resolved, label-free, and non-targeted imaging of biomaterials at micron resolution is now possible.

REFERENCES

Bio: Nathan Havercroft is the General Manager of ION-TOF USA, Inc. where he has worked in various roles for 15 years. His experience in surface analysis goes back to 1994 when he began studies with Prof. Peter Sherwood at Kansas State University.
Secondary ion mass spectrometry (SIMS) has increased in popularity for analysis of biologically relevant samples. This is partly due to SIMS’s ability to gain chemical and spatial information at unmatched lateral resolutions and in sample-limited situations. The use of an ion beam for desorption and ionization of surface molecules in SIMS measurements affords for this notable spatial resolution over, for example, laser-based MS approaches. However, the excessive energy of the primary ions yields extensively fragmented surface molecules, and makes identification of the detected secondary ions a nontrivial endeavor. At the start of the last decade, biological SIMS efforts were transformed with the development of cluster primary ion sources. These so-called “soft-ionization” sources, reduced fragmentation of parent species, and extended the applicability for biologically focused SIMS-based measurements by unlocking the possibility to detect and identify lipids, metabolites, and other small biomolecules more readily. This has led to a paradigm shift in secondary ion analysis. The combination of high mass resolution and accuracy mass analyzers with tandem mass spectrometry approaches in SIMS measurements has revealed biochemical information that was previously unattainable. Here, I will discuss development and implementation of the Fourier transform ion cyclotron resonance (FTICR) SIMS instrument, which is coupled with a C60 primary ion source. This instrument can provide greater mass resolving power (m/m50% >3,000,000) and mass accuracy (<1 ppm) than conventional mass spectrometers used in SIMS measurements. In an early application, we demonstrated the usefulness of this instrument in the characterization of eukaryotic cells (Dictyostelium discoideum). FTICR-SIMS was able to generate multiple molecular ion maps at the nominal mass level and it provided good coverage for fatty acyls, prenol lipids, and sterol lipids. The FTICR-SIMS also has the ability to isolate and perform tandem MS on ions of interest. Using this capability, we were able to confirm the location of cholesterol in brain tissue and map a specific fatty acid in a drosophila imaginal wing disc. The recently released PHI nano TOF II with a parallel MS/MS imaging system delivers an unmatched 1 Da mass isolation window, providing greater confidence in the origin of fragment ions generated during tandem MS of the precursor ions. Using the combination of these two instruments, we are exploring the ionization and detection of lanthanide and actinide species in samples, a capability that has implications in medicine, bioremediation, and international security efforts. We are also reevaluating matrix- and metal-enhanced SIMS techniques using these advanced mass analysis approaches.

Bio: Christopher R. Anderton received his Bachelor of Science degree in Chemistry at the University of Colorado at Colorado Springs in 2005. He attained his Ph.D. in Chemistry at the University of Illinois at Urbana-Champaign in 2011, under Mary L. Kraft, where his graduate work focused on multi-technique correlative analysis (secondary ion mass spectrometry, atomic force microscopy, and scanning electron microscopy) of supported lipid membranes. Afterwards, he was an U.S. National Research Council Postdoctoral Associate at the National Institute of Standards and Technology under Anne L. Plant, where he studied how eukaryotic cells respond to changes in the physicochemical properties of their extracellular environment. In 2013 he joined the Mass Spectrometry Group at the Environmental Molecular Sciences Laboratory, which is located on the Pacific Northwest National Laboratory campus. Currently, he focuses on developing new mass spectrometry imaging instrumentation and capabilities to elucidate chemical interactions occurring within microbial communities, soils, and the rhizosphere.
Design, Materials and Characterization of Primary Batteries for Implantable Devices

Primary batteries have been the power source for the majority of implantable medical devices such as pacemakers, cardioverter defibrillators (ICDs), deep brain stimulators (DSB) and drug pumps. Over the years, several primary battery chemistries with different energy density and power density have been developed for implantable applications. The chemistry selection and battery design are tailored to the specific device use needs. The fundamental understanding of the interactions among different components within the battery is necessary in developing implantable battery technology to ensure reliable performance over device life. This presentation will give an overview of the design, material selection and performance characterization of primary batteries for Medtronic devices, and highlight the applications of a number of spectroscopy techniques such as X-ray Photoelectron Spectroscopy, X-ray Diffraction, Scanning Electron Microscopy with Energy Dispersive X-ray Spectroscopy and multinuclear Solid State NMR to elucidate the chemical and microstructural changes of the battery cathode during discharge.

Bio: Kevin Chen is a senior principal scientist in the Energy Systems Research & Technology group of Medtronic Energy and Component Center. His work at Medtronic has been in the research and development of new battery chemistry for powering implantable medical devices. Dr. Chen received a B.S. in Chemistry from NanKai University in China, and a Ph.D. in Inorganic Chemistry from Northwestern University. He completed his post-doctoral work in surface chemistry of materials at Northwestern University.
Probing the Morphology, Nanomechanics and Tribology of Biomedical Gels with AFM

This work applies atomic force microscopy (AFM) methods to crosslinked polyacrylamide and polyvinyl pyrrolidone lubricious coatings as well as crosslinked fibrin-based gels for tissue engineering applications. Analytical methodologies are explored under variable hydration or aqueous immersion; in much of the latter the sharp AFM tip is replaced with a colloid microprobe.

Beyond rich morphologies, the imaging contrast derived from normal and shear force measurements and tip-sample adhesion hysteresis reveals variable material responses as a function of preparation histories (crosslinking, macrotribology, induced orientation). Some defect structures termed craters, pinholes, fissures and wrinkles largely “heal” during hydration (high RH or aqueous immersion), in some cases with a concomitant appearance of crystallites apparently due to the diffusion and aggregation of crosslinking additives. Nanomechanical probing during hydration cycles identifies reversible glass-to-rubber transitions, where the critical transitional humidity depends on degree of crosslinking. Tip-sample adhesion is also strongly sensitive to humidity-actuated glass-rubber transitions (again dependent on crosslinking), and moreover reveals significant differences between thin and thick coatings in the case of polyacrylamide.

Shear-force methods further reveal crosslinking-derived differences in coating behavior, especially pertinent to wear on lubricious coatings. Colloid-probe AFM methodologies were developed and utilized to explore both normal and anisotropic shear response on oriented fibrin gels under aqueous immersion. In all cases mapped measurements, up to several tens of microns in lateral scale, reveal spatial heterogeneities in mechanical response as well as their relationship to morphology.

The overarching emphasis of this presentation is on (i) AFM force measurement to obtain information well beyond simple surface topography; (ii) the enabling “humidity knob”, as well as full aqueous immersion, to study changes in polymeric materials due to hydration; (iii) the importance of multichannel data acquisition and high data throughput to creative applications of AFM.

**Bio:** Greg Haugstad has been active for 32 years in analytical research spanning essentially all classes of materials, from (i) pre-graduate work on temperature-dependent electrical properties of metals and microwave absorptive (stealth) nanocomposites, to (ii) ultrahigh vacuum, synchrotron-photoemission based graduate research on electronic properties of semiconductor interfaces, to (iii) postdoctoral research on ionic crystals and soft materials in ambient and hydrated environments with a focus on nanoscale structure and tribo-mechanical properties. His research as a staff scientist of the past 22 years has expanded from his postdoctoral work emphasizing scanning probe methods (AFM, etc.) and industrial collaboration, with a large component dedicated to biomedical materials and interfaces. Greg travels broadly to meet with collaborators; chair symposia and present work at international meetings; and teach short courses on scanning probe methods.
Topography, roughness and mechanical properties of biomaterials are crucial parameters influencing cell adhesion/motility, morphology and mechanics as well as the development of stem/progenitor cells [1,2,3,4]. Atomic force microscopy (AFM) is a powerful tool not only to study the morphology in terms of high resolution imaging and roughness measurements, but also to map mechanical and adhesive properties. Combining these remarkable abilities with advanced optical microscopy allows for extensive characterization of biomaterials. AFM has become a multipurpose technology which is much more than simple imaging. Interaction forces from single molecule unbinding to cell adhesion and analysis of surface and mechanical properties of biomaterials and cells make AFM to a key technology in biomaterial research. Nano-mechanical analysis of cells increasingly gains in importance in different fields in cell biology like cancer research [5] and developmental biology [6]. Figure 1, maps of topography and storage and loss modulus of a living fibroblast, illustrates the type of information gained. We present an overview of modern techniques to characterize biomaterials including measurements of mechanical parameters such as storage/loss modulus to better understand their interaction with cells and influence on cell behavior.

REFERENCES

Bio: Dr. Stefan Kaemmer earned his Master in Chemistry and PhD in Physical Chemistry from the Technical University of Braunschweig/Germany. He worked as a Staff Scientist for Bruker Corp. for over 10 years before joining JPK Instruments and setting up their US Operations. Dr. Kaemmer has extensive experience in Atomic Force Microscopy and Nanooptics.
Contact angle measurements are used widely to assess wettability, cleanliness, surface chemistry and the potential for creating a high strength adhesive bond. The most common method of measuring contact angles involves the use of sessile drops on flat surfaces. Alternatively, tensiometers are used to evaluate curved solids, such as rods and fibers. Traditionally in tensiometry, the solid is immersed or withdrawn from a liquid while measuring force. Proper analysis of the interplay between capillary forces and buoyancy allows for indirect estimation of contact angles.

Tubes and fibers produced for industrial applications may have different inner and outer surfaces. For example, during extrusion of plastic tube, molten polymer usually passes through a liquid cooling tank where its outer surface is rapidly quenched while in contact with various sizing fixtures; in contrast, its inner surface cools slowly in the presence of a gas without further mechanical manipulation. Consequently, the inner and outer surfaces of extruded tubes and hollow fibers may have distinct morphologies. Moreover, the chemistry of the inner surface may be intentionally modified to improve hydrophobicity and/or the outer surface may be rendered more hydrophilic to improve adhesion.

In recent work we developed a new tensiometry technique for evaluating the wetting inside capillary tubes and hollow fibers. Rather than immersing, capillary tubes of diameter \( D \) were brought into contact with a liquid such that their bottoms just touched the surface of the liquid. A meniscus formed around the inner and outer diameter, wetting the inside of the tube with a contact angle of \( \theta \). If \( \theta \) was < 90°, liquid rose upward (z-direction), reaching a final height of \( h \). We isolated the forces associated with liquid rising inside the tubes and then used those values to estimate work, viscous dissipation and potential energy change.

In this work we show how our experimental technique can be used to estimate contact angle inside of capillary tubes. The technique was first validated with transparent tubes using four liquids. Advancing contact angles measured with the tensiometer agreed well with those estimated from final rise height. As this tensiometry technique does not require a view of the liquid, it can be used to measure the wettability inside opaque tubes. We demonstrated this with poly(ether ether ketone) (PEEK) tubes.

**Bio:** Chuck Extrand is Director of Research at CPC in St. Paul, MN. Over his 20+ year industrial career, he has developed a broad range of materials-based technologies for markets including life science and microelectronics. He holds fourteen U.S. patents and has published more than 100 papers in technical journals, books and conference proceedings. Prior to starting an industrial career, Chuck worked in Japan at the National Institute for Materials and Chemical Research and in Paris at the Collège de France and the Ecole Normale Supérieure. He received a PhD in polymer engineering from The University of Akron and a BS in chemical engineering from the University of Minnesota.
Biology is ultimately a complex puzzle across orders of magnitude in scales. Understanding the connection that structure-property relationships have across those length scales is the necessary first step prior to designing biomimetic materials. However, there is a lack of standardized methodology and instrumentation for measuring mechanical properties across the nano- meso- micro length or force scales or that allows for quantitative comparison between samples and across laboratories. Contact mechanics based Instrumented Indentation enables examination of mechanical properties of compliant materials with far greater resolution and accuracy than ever before.

The two important challenges in indentation of soft samples involve detecting the sample surface (before indentation) and taking care of the adhesion between the tip and the sample surface. During tip-sample approach, the specimens may undergo damage on approach and contact, and very compliant samples might not be sensed at all. This is important for soft materials as the error in zero point determination will influence the measurement. Monitoring the dynamic response during tip-sample approach provides a very sensitive way to determine the location of the surface prior to indentation and provides a force-stiffness measurement along with force-displacement curve acquisition.

The direct measurement in the adhesion and zero point contact measurement bypasses the inaccuracies made by using simple assumptions. Using proper analyses, the adhesion, surface energy, and modulus can be determined from the curve. This experimental technique has a great potential for studying soft materials, non-uniform, and challenging samples in a wide range of in operando conditions with meaningful results. In this presentation a new instrumentation approach specially designed for biological materials will be presented.

Bio: Dr. Syed Asif received his PhD in Materials Science at Oxford in 1993. He is an expert in nanomechanics and related scientific instrument development. He has more than twenty years of experience in the field of nanomechanics with an emphasis on quantitative dynamic measurements. His expertise was essential to the development of Hysitron’s Ubi™ nanomechanical platform and in-situ nanomechanical instruments.
WEDNESDAY — OCTOBER 5, 2016
3D Printing and Bioplotting for Medical Applications
Additive manufacturing (AM), also known as 3D printing, has created avenues of potential in the medical devices industry through newly enabled design possibilities and personalized medicine. Forecasts project significant growth of AM in the medical device space by 2025 (Smithers 2015). FDA’s Center for Devices and Radiological Health (CDRH) has cleared and approved several types of 3D-printed medical devices through its existing regulatory pathways and CDER has also approved a 3D printed drug product. The speed of technology’s adoption has led to a growing need for AM medical device best practices. Many printer types and optimizations of print parameters can be used, however only a few combinations will achieve accurate and reproducible final parts which make these choices critical to quality. Furthermore, AM devices can include complex geometries and part geometry may vary with each unit built. This complexity and personalization may lead to difficulty measuring final part quality with existing techniques. Consequently, there is a great need for new quality metrics and measurement techniques.

One of the FDA’s strategic priorities is to support new approaches to improve product manufacturing and quality, including enabling development and evaluation of novel and improved manufacturing methods. The Agency is using an interdisciplinary approach to evaluate the technology using optical, physical, and biological methods.

This presentation will briefly overview the FDA’s regulatory pathways, describe some technical considerations specific to additive manufacturing of medical products, and summarize several ongoing additive manufacturing research projects at the FDA.

**Bio:** LT James Coburn joined the FDA in 2009 and is now a Senior Researcher in the FDA’s Center for Devices and Radiologic Health (CDRH). He is helping to spearhead the Agency’s efforts in Additive Manufacturing. He performs research on patient-based design factors for device development, sits on several Standards committees, and has led interagency outreach efforts related to the maker movement. LT Coburn is the Lead Investigator for the Agency’s Additive Manufacturing Core Facility and he Co-Chairs the FDA Additive Manufacturing Working Group.
Additive manufacturing (AM), also known as 3D printing, has created avenues of potential in the medical devices industry through newly enabled design possibilities and personalized medicine. Forecasts project significant growth of AM in the medical device space by 2025 (Smithers 2015). FDA’s Center for Devices and Radiological Health (CDRH) has cleared and approved several types of 3D-printed medical devices through its existing regulatory pathways and CDER has also approved a 3D printed drug product. The speed of technology’s adoption has led to a growing need for AM medical device best practices. Many printer types and optimizations of print parameters can be used, however only a few combinations will achieve accurate and reproducible final parts which make these choices critical to quality. Furthermore, AM devices can include complex geometries and part geometry may vary with each unit built This complexity and personalization may lead to difficulty measuring final part quality with existing techniques. Consequently, there is a great need for new quality metrics and measurement techniques.

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The development of methods for interfacing high performance functional devices with biology could impact regenerative medicine, smart prosthetics, and human-machine interfaces. Indeed, the ability to three-dimensionally interweave biological and functional materials could enable the creation of devices possessing unique geometries, properties, and functionalities. Yet, most high quality functional materials are two-dimensional, hard and brittle, and require high crystallization temperatures for maximal performance. These properties render the corresponding devices incompatible with biology, which is three-dimensional, soft, stretchable, and temperature sensitive.

We overcome these dichotomies by: 1) using 3D printing and scanning for customized, interwoven, anatomically accurate device architectures; 2) employing nanotechnology as an enabling route for overcoming mechanical discrepancies while retaining high performance; and 3) 3D printing a range of soft and nanoscale materials to enable the integration of a diverse palette of high quality functional nanomaterials with biology. 3D printing is a multi-scale platform, allowing for the incorporation of functional nanoscale inks, the printing of microscale features, and ultimately the creation of macroscale devices. This three-dimensional blending of functional materials and ‘living’ platforms may enable next-generation 3D printed devices.

Bio: Michael C. McAlpine is the Benjamin Mayhugh Associate Professor of Mechanical Engineering at the University of Minnesota. Previously, he was an Assistant Professor of Mechanical and Aerospace Engineering at Princeton University (2008-2015). He received a B.S. in Chemistry with honors from Brown University (2000) and a Ph. D. in Chemistry from Harvard University (2006). His research is focused on 3D printing functional materials & devices, including the three-dimensional interweaving of biological and electronic materials using 3D printing. He has received a number of awards, including the NIH Director's New Innovator Award, a TR35 Young Innovator Award, an Air Force Young Investigator Award, the Intelligence Community Young Investigator Award, a DuPont Young Investigator Award, a DARPA Young Faculty Award, an American Asthma Foundation Early Excellence Award, a Graduate Student Mentoring Award, the Extreme Mechanics Letters Young Lecturer, and an invitation to the National Academy of Engineering Frontiers in Engineering.
There is a growing trend towards personalization of medical care, as evidenced by the emphasis on outcomes based medicine, the latest developments in CT and MR imaging and personalized treatment in a variety of surgical disciplines. At the same time, 3D printing continues to gain more acceptance from the medical device regulatory bodies and is finding its way as the end manufacturing method for a number of devices, both in the US and internationally. 3D printing holds unique promise to deliver on personalized medicine due to its ability to mass customize patient specific implants. This presentation will cover two unique cases describing how 3D printing’s advantages are currently being leveraged in the clinical market.

The first clinical application of 3D printing that will be reviewed is a first-of-its-kind bio-resorbable (PCL) tracheal splint produced for young children with severe disorders of the windpipe. The ongoing commercialization efforts, the results of first in human cases, and the preparation to enter into clinical trials will be covered in the presentation.

Separately, a patient-specific approach to hip replacement will be demonstrated. For patients suffering from massive bone loss, or undergoing complex revisions on hip replacements, the treatment options can be very limited. In many cases, patient-specific approaches are proving to be the most suitable for these complex revision, congenital, or tumor resected patients in need of a new hip joint. Current work being done to produce 3D printed titanium implants with ideal fixation, ideal loading, and porous structures for osteo-integration will be reviewed.

**Bio:** Janelle Schrot manages a biomedical engineering team at Materialise which focuses on cardiovascular applications of Materialise’s technology. Her group particularly focuses on translating medical image data to three dimensions for research, design, testing and additive manufacturing environments. Ms. Schrot has focused on additive manufacturing and its uses within the cardiovascular field for the last eight years. She is Her background is in product design engineering and she holds a degree in mechanical engineering from Grand Valley State University. Ms. Schrot on the advisory board for Society of Manufacturing Engineers (SME) Medical Additive Manufacturing Workgroup.
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