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# Preface

The Office of Science and Engineering Laboratories (OSEL), one of seven Offices within CDRH, contributes to the Center's mission by providing laboratory data and consults. OSEL serves as the laboratory science nucleus for the Center. Specifically, OSEL helps provide a scientific foundation for the Agency's regulatory decision- making by developing independent laboratory information for regulatory and other public health activities of CDRH. In addition to providing consultation to the Center's regulatory experts, OSEL researchers are involved in mission-oriented science activities including test methods development, risk assessments, forensic investigations, product evaluations, and technology assessment.

The research in OSEL is broad and cross-cutting, with research conducted in the physical, life, and engineering sciences as related to the effects of medical devices on human health. CDRH relies upon this work to support its efforts ensuring public safety in areas as varied as medical imaging, medical device software, breast implants, and drug eluting stents.

OSEL laboratory science provides an important foundation for the regulatory mission of the Center and the Agency and in implementing the primary directive to protect the public health. Among the many accomplishments of OSEL:

1. The scientific research conducted in OSEL laboratories is significant, with great public health impact. One such example is the Huber needle investigation. Huber needles are used to access ports that are implanted under the skin of chronically ill patients for continued access to the veins for blood withdrawal and for delivering medication, nutritional solutions, blood products, and imaging solutions. These needles should be designed to penetrate the port without cutting and dislodging any silicone cores (or slivers) from the ports into which they are inserted.

   When FDA received reports of leakage after accessing a port with a Huber needle (labeled to be non-coring), OSEL scientists assisted the Agency by conducting laboratory testing of Huber needles from multiple manufacturers. The testing showed that certain Huber needles produced cores when inserted into ports.

2. OSEL created a new laboratory, the Functional Performance and Device Use Laboratory, to assess the needs of medical device users in varied-use environments, using multiple-device user interfaces to expand understanding of how medical device design influences use errors and physical performance. The creation of this laboratory was in response to the adverse events data showing that

as many as one-third of medical device failures causing patient harm and reported to the FDA appear to be failures of medical device *use* rather than failure of the device itself. One priority discussed in the CDRH 2011 report, "*A Vital Framework for Protecting and Promoting Public Health,"* was improving medical device safety. A key approach to this laboratory's research would be "to help reduce use error, enhance patient and user safety, improve product usability and efficiency, and enhance user satisfaction with medical devices."

3. All Centers in FDA continue to receive products containing nanotechnology and nanomaterials. The FDA Nanotechnology Taskforce recognized that characterization of nanomaterials is a key component of FDA research; and there is a need to establish a core laboratory facility accessible to all of the Centers, and whose primary function is to provide specialized equipment and tools that are basic to all nanomaterial-related research projects. The Core facility was established in OSEL/CDRH in 2011 with the purchase of three pieces of equipment:

OSEL continues its outreach to the scientists and engineers of tomorrow. Since first begun in 2003, the OSEL student science poster exhibit has become a much-anticipated annual event. What began as an in-house event to provide a forum for young future scientists in OSEL to discuss their work with one another has now become a symposium for collaboration among interns from other FDA components, federal agencies, and various academic institutions—both at the high-school, and college and university levels. The annual exhibit continues to expand and draw interest from non-FDA science and health-care professionals.

The OSEL Annual Report offers timely information about the Office's organization and intramural science activities; provides a summary of the Office's direct laboratory support for pre-market review and post-market evaluation; and provides a bibliography of scientific publications, presentations, and research seminars for the fiscal year reported. The information is within the framework of OSEL's organization structure: divisions are first described, followed by descriptions of the research laboratories. The section on 2011 highlights lists examples of specific successful OSEL research projects and laboratory accomplishments. This report also cites a few examples of the regulatory support work that OSEL provides to the Center's post-and pre-market offices.

We hope you find this document useful and informative. We welcome your comments on the programs described in this report.

For additional information, please visit the OSEL web site at http://www.fda.gov/cdrh/osel or contact us at 301-796-2530.

Steven K. Pollack, Ph.D.
Director
Office of Science and Engineering Laboratories
Center for Devices and Radiological Health, FDA

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## Regulatory Support Activities

Research conducted in the OSEL supports the regulatory activities of the Agency as follows:

- Strategically manage research with the aim of providing a scientifically sound basis for responding to current needs and anticipating future regulatory challenges; and

- Provide technical consults in support of the Center's pre-market, post-market, and compliance activities.

Both activities are coordinated within OSEL in an effective manner so as to best meet Center's regulatory science needs. Laboratory research is the cornerstone upon which the Office provides the regulatory support function. (The research is described in subsequent sections.) It is largely based on investigations related to the mechanistic understanding of device performance or test procedures, enabling the Center and device manufacturers to gain an improved understanding of issues related to safety and efficacy. In general, although the research is directed toward issues identified at the *pre-market* approval level, the reality is that the research has the largest impact on the post-market end of the Center's business because most often the research is *anticipatory* in terms of potential issues of medical devices identified at the pre-market level.

The regulatory support function of the Office is provided through consults supporting both pre-market decisions and post-market actions using expertise developed in the laboratory. A consult is a request for expert advice or information of a specific nature, and provides information that contribute to sound regulatory decisions. Consults are often based on acknowledged scientific/engineering principles or on independent data generated in OSEL laboratories.

In 2011 OSEL provided the following:

| | |
|---|---|
| Number of consults on pre-market issues | **1780** |
| Number of consults on post-market issues | **142** |

The information provided by a consult is used in some of the following ways:

- Evaluate a pre-market submission (IDE, HDE, PMA, 510(k));
- Support a compliance action (regulatory case support/development, Health Hazard Evaluation, Health Risk Assessments, etc.);
- Assist scientific collaboration;

- Respond to a consumer inquiry;
- Provide feedback on guidance documents;
- Provide revisions to one-pagers for the new device approval page;
- Support health hazard evaluation/health risk assessments in device determinations/classifications.

For many post-market as well as pre-market regulatory issues, the consults/reviews and investigations conducted by OSEL independently assess the claims made by manufacturers or other parties concerning safety or effectiveness. In other cases, OSEL reviews may assess the adequacy of a design, a failure investigation, a production process, or a quality process employed by the manufacturer. These reviews and analyses rely on in-house expertise and are often augmented by expertise solicited from colleagues in academia, other government laboratories, or even other industry sectors. OSEL laboratory investigations may be undertaken in instances where the veracity of a performance claim needs to be independently verified by testing or when the claimant lacks the resources to conduct the investigation.

OSEL also provides analytical support to post-market regulatory activities in a variety of ways:

- Provide scientific and engineering reviews and analyses;
- Conduct laboratory investigations of product performance;
- Participate in inspections of medical device establishments;
- Conduct forensic reviews and investigations;
- Identify device safety and performance issues;
- Provide training to FDA and industry; and
- Contribute to Center-wide Matrix teams on issues identification as well as science-based analysis of post-market device performance.

Finally, developing standards and measurements methods is a significant activity of this office. OSEL continues to provide innovative solutions to public health problems by constructing generic techniques that lead to the creation of national and international standards that will enhance product safety and effectiveness. OSEL staff actively participate in developing standards at the national and international levels by performing research to establish standard procedures, and by shouldering standards committees responsibilities to manage, develop and support standards development.

# Office of Science and Engineering Laboratories 2011 Highlights

*Development of a Nanoparticle-based Phantom for Assessment of Retinal OCT Device Performance* **(Optical Diagnostic Devices Laboratory, Division of Physics)**

Optical coherence tomography (OCT) is an FDA-cleared imaging modality now being used 16 million times annually to image the eye with devices from at least 6 different manufacturers. Although OCT is extensively used, there are no standardized test methods that ensure the accuracy and consistency of OCT data. Controlled test objects known as phantoms can fill this gap by serving as a stable, well-characterized reference, which is imaged for preclinical assessment as well as periodically during clinical use for quality assurance. Optical Diagnostic Devices Laboratory (ODDL) researchers have recently designed, fabricated and validated a novel nanoparticle-based phantom specifically for benchmarking the performance of retinal OCT devices. The phantom comprises a precisely shaped transparent polymer with embedded gold nanoshells placed at the retinal plane of a model eye that realistically replicates the focusing characteristics of the human eye. The nanoparticles reflect light from the OCT scanner beam, enabling accurate measurement of the device's point spread function. This provides a detailed representation of the device's spatial resolution and its variation throughout the imaging volume. The phantom, which is easy to use and portable, has been evaluated on a research-grade retinal OCT device in ODDL. The fabrication methods and evaluation results form the basis of a manuscript that has recently been submitted for publication in a scientific journal. Through its research on novel, phantom-based test methods for optical imaging, ODDL is facilitating science-based evaluation and regulatory clearance of innovative, minimally invasive devices with the potential to impact public health.

*Brain Computer Interfaces* **(Biophysics Laboratory, Division of Physics)**

Dr. Cristin Welle and staff of the Biophysics laboratory developed a platform to assess physiological, anatomical, chemical and behavioral responses to invasive recording electrodes in the brain. This is an important development because of the need to improve and assure the long-term safety and reliability of these novel implants. Neural implants have the potential to provide an unparalleled capability for individuals using prosthetic devices to interact with their external environment. Currently, these devices have fallen short of their potential due to a longitudinal decline in their ability to detect neural signals. This failure may result from biological reactions that result from inserting a foreign object into the brain, or from gradual decay of the electrode materials, although

the precise failure mechanisms have yet to be determined. The Division of Physics entered into a collaborative research endeavor with DARPA's (Defense Advanced Research Projects Agency) Reliable Neural Interface Technology (RE-NET) program based on a common interest in the long-term safety and reliability of neural implants. Dr. Welle's expertise in cortical electrophysiology, two-photon imaging and small animal survival surgery has been leveraged to develop innovative test platforms to identify biomarkers predictive of long-term implant success. The DP platform to identify physiological markers that are predictive of failure will see several types of neural electrodes implanted in a genomically controlled mouse model. Single-unit and local field potential electrophysiological data will be recorded weekly for 12 months. Additionally, *in-vivo* two-photon imaging on a weekly basis from individual animals will observe neural death and morphological changes, and automatic computerized detection of freely moving behaviors will be correlated with the electrophysiology to link features important to motor control. In parallel, DP researchers will perform accelerated aging protocols in an artificial brain to assess chronic electrode integrity and function through electrochemical analysis. These investigations identify the factors that are critical to electrode longevity and establish test platforms that can be used to aid the regulatory decisions regarding penetrating neural interfaces.

*CDRH-Transportation Security Laboratory Interagency Project on Electromagnetic compatibility (EMC)* **(Electromagnetic and Wireless Technologies Laboratory, Division of Physics)**

The Transportation Security Laboratory (TSL), Department of Homeland Security (DHS) sought the expertise of OSEL's Division of Physics to assess the potential electromagnetic interference (EMI) risks for airline passengers with personal electronic medical devices (PMEDs) screened with new advanced imaging technology (AIT) systems. This project is being performed under an interagency agreement between FDA and TSL/DHS. It follows previous interagency agreements with TSL in such areas as the study of the potential effects on personal medical devices (PMEDs) from exposure to magnetic fields from metal detector security systems. The present project involves testing and research centered on the potential effects on PMEDs from exposure to the emissions from new millimeter wave body scanner systems. This technology operates by emitting very low levels of electromagnetic fields at very high frequencies (millimeter waves) to create an image of the subject to search for contraband. Because of the dearth of information about medical device exposures to such high-frequency emissions, the OSEL laboratory research project developed novel methods to test and assess effects on PMEDs. The PMEDS included implantable cardiac pacemakers and implantable cardioverter defibrillators, implantable neurostimulators, and drug infusion pumps such as body-worn insulin pumps. The test methods were adapted from earlier OSEL studies involving use of a simulated human body torso. A new simulated torso had to be made

for the present study because of the nature of the millimeter wave fields, since they can be more highly attenuated in the body than fields at lower frequencies.

To assess the exposures, measurements were made of the emissions at several locations in and around the millimeter wave AIT system. These measurements help in developing a unique system to simulate the emissions from the AIT that was used to develop a simple and more easily implemented way to reproduce the AIT exposure. Using the novel testing methods and materials, testing was performed over a range of different makes and models of the implantable and body-worn PMEDs at various positions and orientations in and around the AIT unit. The programming and functioning of each PMED was carefully monitored during these tests. Findings indicated no effects on the functioning of any PMEDs at any of the locations or orientations. The risks for effects on the PMEDs studies for this AIT were assessed to be very low. In addition to the PMED study, the emissions measurements were assessed for radiation safety in reference to the American National Standards Institute (ANSI) Institute for Electrical and Electronics Engineering (IEEE) C95.1 Standard for human exposure to non-ionizing electromagnetic radiation. The emissions measurements revealed very low exposures for the person being scanned or nearby security personnel. Exposures were found to be at least 1000 times below the limits of the human exposure standards.

*Comparative Study of Temperature Measurements in Ex-vivo Swine Muscle and a Tissue-Mimicking Material during High Intensity Focused Ultrasound Exposures* **(Ultrasonics Laboratory, Division of Solid and Fluid Mechanics)**

High-intensity focused ultrasound (HIFU) is a leading-edge, minimally invasive technology for surgery without incisions. Dozens of active development efforts are underway around the globe for applications such as ablating pathologic tissue and stopping internal bleeding. As with many emerging technologies, HIFU has a need for reliable standardized test methods. Existing test methods have been complicated, poorly characterized, and often unreliable. To enable meaningful testing by sponsors and developers, Ultrasonics Laboratory scientists within the Division of Solid and Fluid Mechanics have developed tissue-mimicking materials (TMMs) for characterizing new HIFU products. When TMMs containing thermal sensors are used to measure ultrasound-induced temperature rise, it is important that measurement results reasonably represent those that occur in biological tissue. Therefore, the thermal behavior of the TMM under HIFU exposure was compared to that of *ex vivo* tissue (freshly excised swine muscle). Temperature traces obtained at various pressure levels demonstrated similar types of heating profiles in both the tissue and TMM, the exact nature of which depended on whether bubbles formed during the HIFU exposure. Knowledge gained from this research will facilitate the evaluation of preclinical data submitted by device sponsors, and will aid in developing bench testing guidance and standards. A peer-review paper describing the methodology and results was published recently in *Physics in Medicine and Biology*.

*Contact Lens Contamination Project* **(Division of Chemistry and Materials Science)**

In 2006-2007, a series of widespread Fusarium and Acanthamoeba outbreaks threatened contact lens users in the United States and abroad, making public health authorities increasingly aware of the need for better pre-market testing methods to evaluate contact lens product safety. Experts advised that a single grouping for silicon hydrogels was not adequate to predict potentially harmful lens-solution interactions. Scientists in the Division of Chemistry and Materials Science were charged with performing scientific testing of various physical properties of conventional and silicon hydrogel lenses to determine how they could be grouped to safely predict solution interactions. DCMS staff worked with staff within the Office of Device Evaluation (ODE) to devise a laboratory research strategy that would target some of the most important properties of polymer materials that affect material-solution interactions. This served to familiarize them with both DCMS research capabilities and proposals of analytical methods to answer key questions. The team mapped their strategy based on the hypothesis that silicon hydrogels could be grouped with most of the same properties (water content and charge) as conventional hydrogels, with the exception of one property (hydrophobicity).

The work done by DCMS involved five different research areas: water states, pore sizes, hydrophobicity, and protein and lipid uptake. In each of these areas, DCMS staff used their extensive research experience and scientific knowledge to devise experimental strategies to answer the questions that the team had about silicon contact lens properties and interactions. DCMS researchers also relied heavily on a number of advanced instruments available in OSEL for research, including microscopy, thermogravimetric tools and wet laboratory resources. When combined with results from additional studies being done by staff in the Division of Biology, the results of these experiments allowed the team to devise an improved grouping strategy to help predict interaction of current and future care product components with wide-ranging contact lens materials. ODE will be proposing the new grouping strategy to the contact lens industry and other regulatory bodies as a new standard grouping system that can be used to predict potential harmful lens-solution interactions. The use of this grouping system will greatly simplify lens testing for manufacturers; and as more and more silicon hydrogel lenses and lens care products come to market, it will help ensure consumer safety by preventing harmful lens-solution combinations. Labeling changes can also be made to warn about specific care product interactions where depletion of preservative might allow microbial contamination, or otherwise harmful interactions might occur. The work has not only resulted in several submitted scientific publications and an invited presentation to the Contact Lens Association for Ophthalmology (CLAO) conference, but it is also being used at FDA to help develop improved guidance and standards documents for contact lenses and care products.

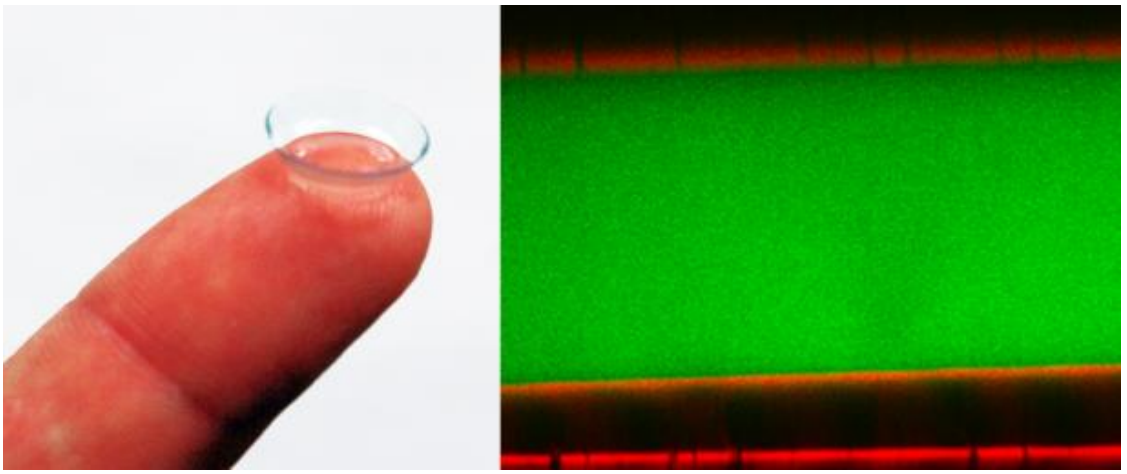


Fig. 1 Image of fluorescent probe penetration in a contact lens obtained using confocal laser scanning microscopy (CLSM)

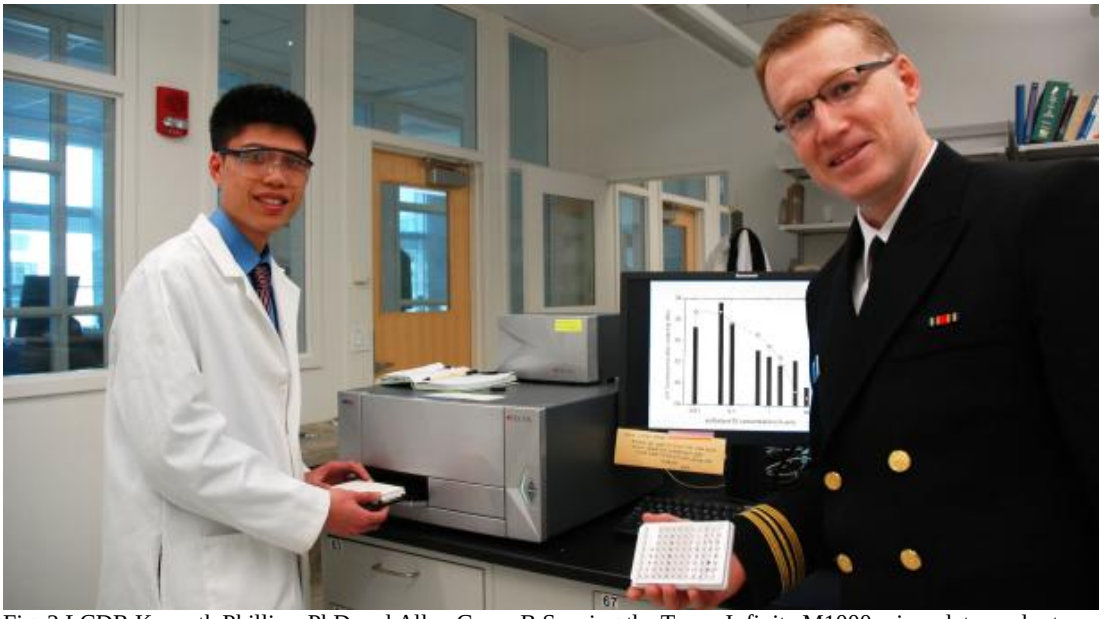


Fig. 2 LCDR Kenneth Phillips, PhD and Allan Guan, B.S. using the Tecan Infinite M1000 microplate reader to measure biomolecular contamination on contact lens materials

*Creation of the Functional Performance and Device Use Laboratory* **(Functional Performance and Device Use Laboratory, (Division of Physics)**

As many as one-third of medical device failures causing patient harm reported to the FDA appear to be failures of medical device use rather than failure of the device itself. In 2011, CDRH released the report *Regulatory Science in FDA's Center for Devices and Radiological Health: A Vital Framework for Protecting and Promoting Public Health*, which highlighted recent progress in regulatory science. One priority discussed in the report was improving medical device safety, and the newly created Functional

Performance and Device Use Laboratory in OSEL's Division of Physics was cited as a key approach to "help reduce use error, enhance patient and user safety, improve product usability and efficiency, and enhance user satisfaction with medical devices."

Creating this new laboratory included identifying the physical space and purchasing essential equipment to build broad scientific capabilities that include:

- an extensive toolbox of hardware and software that will allow the creation of mock-up device user interfaces that can be modified to understand which features increase or decrease the probability of use-related errors;
- an advanced motion-capture system including eye gaze tracking to allow quantitative analysis of how users make and respond to use-related errors; and
- a mobile laboratory to permit usability analyses of medical devices by diverse users in varied-use environments.

The Functional Performance and Device Use Laboratory is now ready to assess the needs of medical device users in varied-use environments, using multiple device user interfaces to expand understanding of how medical device design influences use errors and physical performance.

*Development of Novel Test Methods for Evaluation of Safety and Performance Quality of Optical Therapeutic Techniques and Devices* **(Optical Therapeutics and Medical Nanophotonics Laboratory, Division of Physics)**

To support the Center's regulatory product safety activity, the OSEL/Division of Physics' Optical Therapeutics and Medical Nanophotonics (OTMN) Laboratory maintains the facilities and resources for developing independent test methods for preclinical testing and evaluating the fundamental characteristics, performance quality, and safety of new medical therapeutic devices that employ the latest minimally invasive medical laser and optical technology. In CY 2011, researchers developed alternative test methods for evaluating the safety and efficacy of optical therapeutic techniques and devices in the areas of ophthalmology and ultrashort femtosecond laser therapeutics. They have successfully demonstrated the advanced features of the following test methods:

(1) **Two novel standard test methods for intraocular lens (IOL) implant characterization**. Researchers developed test methods for preclinical evaluation of fundamental optical properties of IOL implants such as dioptric power and light scattering characteristics. The first method is based on an innovative optical coherence tomography (OCT) sensor approach for testing the dioptric power of IOL implants by precisely measuring IOL surface profiles and surface radii. The IOL dioptric power is a key parameter whose precise preclinical measurement is a part of the review process for all IOLs and is important to the effectiveness of IOLs. The proposed test method combines the advanced properties of both high-resolution

OCT imaging and flexible *in-situ* compatible fiber-optic sensing approaches. Thus, the method ensures noncontact, accurate, and objective measurements of IOL optical power under *in-situ* conditions. It should provide CDRH and the device community with an alternative tool to evaluate IOL parameters with more precision, accuracy, and speed, thereby enhancing the safety and effectiveness of IOL implants.

The second test method was developed for characterizing quantitatively light scattering effects in IOLs, which are caused by the existence of optical glistenings. The problem of light scattering glistenings in IOLs is of significant concern because it directly affects the optical quality of a patient's vision with IOLs. Currently utilized test methods have not been adequate to examine light scattering from IOLs. The proposed test method is based on a newly established sensing approach using a ballistic-photon removing integrating-sphere method (BRIM). BRIM increases the test method's sensitivity. It provides a quantitatively simple and effective *in vitro* laboratory method for accurate and objective characterization and grading of glistenings in various IOL of different design and/or material, regardless of their dioptric powers. Furthermore, this innovative technique may be exploited in more general applications for measuring light scattering in various biological and nonbiological media.

(2) **Test methods for multifunctional investigation of femtosecond laser (FSL)-tissue interactions and evaluation of safety and efficacy of FSL based technologies and devices.** The development of novel FSL technologies and medical devices is an emerging field with significant public health impact in a variety of biomedical areas ranging from precise single-cell and robotic tissue surgeries to nanobiophotonics. An example of recently developed FSL-based technology is the application in cataract/lens replacement surgery that is the most commonly performed surgical procedure in the world. Some of these new technologies, however, have exhibited specific safety and efficacy-related concerns, which require independent test methods for safety and efficacy evaluation. Researchers have established a state-of-the-art FSL-based system that is used for developing multifunctional test methods used to evaluate critical characteristics of both FSL systems and tissues involved in the FSL-tissue interactions. The test methods provide monitoring and quantification of the dynamic behavior of fundamental FSL parameters such as wavelength, intensity, polarization, pulse dispersion and spatial beam characteristics, and the optical tissue properties including its absorption and scattering characteristics. These methods ensure an independent source of data for a better understanding of how FSL radiation propagates through and affects tissue in clinically relevant procedures. This will allow for safer and more efficient application of FSL therapies that should result in fewer complications and negative results.

*Development of a Standard for Validation of Computer Modeling of Electromagnetically Induced Heating of Human Tissues* **(Electromagnetic and Wireless Technologies Laboratory, Division of Physics)**

CDRH is faced with a rapidly increasing number of pre-market applications using computational methods for safety and efficacy assessments. Usually sponsors employ commercially available software platforms, and they rely on their accuracy and validity. However, many software platforms lack robust code validation, and much computational data lacks validation of the actual computation itself. The Division of Physics (DP) in OSEL is working with IEEE (The Institute of Electrical and Electronics Engineers) and IEC (International Electrotechnical Committee) to improve this situation. FDA's Dr. Wolfgang Kainz (of OSEL's Division of Physics), Chairman of Technical Committee 34 of the IEEE's International Committee on Electromagnetic Safety, and his committee developed a document to standardize validation procedures for computational codes using the Finite Difference Time Domain (FDTD) Method. The document P62704-1 is titled, "General Requirements for using the Finite Difference Time Domain (FDTD) Method for SAR Calculations." This method applies specifically to the calculation of induced heating from electromagnetic fields, but can also be used generally for validating any code using the FDTD method. It can be applied to MRI and other devices designed to induce, intentionally or unintentionally, tissue heating. Importantly, it specifies detailed validation procedures for code and the computation itself. A breakthrough was achieved in 2011 when the IEEE Standards Board approved this document as a dual logo IEEE/IEC Standard. This new dual logo status makes it possible to recognize the document as a CENELEC standard. CENELEC is the European Committee for Electrotechnical Standardization and is officially recognized by the European Commission as the competent European Standards Organization. Many CENELEC Standards are incorporated in EU Directives and are therefore mandatory. With this initiative, OSEL/DP expands its visibility in the United States and Europe by contributing internationally to standards that improve the safety and efficacy of medical devices.

*First Approval of a Digital Breast Tomosynthesis (DBT) Imaging Device* **(Medical Imaging Laboratory, Division of Imaging and Applied Mathematics)**

While the past decades have witnessed substantial innovation in breast imaging, screen-film and digital mammography are still found to miss approximately 30% of breast cancers. These misses are often ascribed to the 2D nature of this imaging technique, in that the images fail to disclose cancers masked by superimposed fibroglandular tissue. For this reason 3D breast imaging techniques are being developed. One such technology is digital breast tomosynthesis (DBT), a 3D imaging technique that involves the acquisition of multiple lower-dose images (or projections) of the breast at different angles.

Evaluating DBT has been a substantial challenge for the Agency. In particular, nonclinical assessment techniques are just starting to be developed; and clinical studies that may be used to support effectiveness claims are complicated by a low prevalence of cancer in the intended population, differences between screening and diagnostic mammography uses, and most of all, inter- and intra-observer variability when interpreting the 2D and 3D images. All of these factors conspire to make evaluating DBT extremely challenging.

OSEL/DIAM research and expertise related to the conduct and evaluation of non-clinical data and imaging reader studies was directly relevant to CDRH's review of the first DBT PMA submission. Based on this research and knowledge, CDRH was able to quantitatively demonstrate that the sponsor had selected appropriate endpoints, *describe* how the data from multiple studies could be understood together, and *determine* what would be expected of the device performance when released for clinical use, given the limitations of the pre-market study design. Taken together, these analyses overwhelmingly made the case that DBT in combination with digital mammography significantly improved radiologist performance for breast cancer detection compared to digital mammography alone. The Radiological Devices panel unanimously concluded that the data and information submitted by Hologic supported the safety and effectiveness of this new technology and the Hologic DBT device was officially approved for marketing in February 2011. OSEL/DIAM researchers provided scientific support regarding the approval of this particular device, but laid forward a clear and manageable regulatory pathway for other DBT and 3D breast imaging devices under development by other manufacturers.

*Hermeticity Project* **(Materials Performance Laboratory, Division of Chemistry and Materials Science)**

Parylene coatings are commonly used in a number of medical device applications due to their robust properties and ease of application. Parylene is a protective polymer coating material used to uniformly protect any component configuration on such diverse substrates as paper, glass, plastic, resin, and metal, to name a few. Recently, parylene (and engineered parylene derivatives) have been used in new medical devices, where an accurate assessment and understanding of liquid transport and its relationship to the polymer structure is critical in design and evaluation (for example, moisture barrier coatings for implantable electronics). Traditional methodologies for assessing the long-term hermeticity, and consequently the reliability, of these devices are not applicable, so researchers in DCMS sought out collaborations with faculty at the University of Pennsylvania and Drexel University to develop tools and methodologies to evaluate structure-performance-reliability of these coated devices. Using a combination of analytical techniques, they were able to determine the effects of processing on the parylene coating structure, which subsequently affects its barrier properties. If

manufacturers are made aware of this, they may be able to adjust their processing in order to maximize the hermetic seal of PPX, for device reliability, thereby reducing implant failures and need for explant or revision surgeries.

In 2011, DCMS hosted Professor Yossef A. Elabd of Drexel University, who is a leading expert in the area of transport phenomena in polymers, and doctoral candidate Eric Davis under the Scholar in Residence Program. During his time working in OSEL, Professor Elabd had the opportunity to collaborate and exchange ideas with several DCMS scientists. He also taught a Staff College course titled "Transport phenomena in Polymers". These exchanges noted several areas of scientific overlap and applicability, and the discussions which ensued will provide critical knowledge to a number of regulatory issues in the medical device area. Projects that have been initiated include research on drug delivery through complex and biodegradable media and investigating the extraction of low molecular weight toxins/colorants from polymers, all of which can be better understood from the fundamentals of transport phenomena in polymers. Additionally, expertise in novel experimental approaches (such as Time-resolved Fourier transform infrared-attenuated total reflectance (FTIR-ATR) spectroscopy and quartz spring microbalance (QSM)) were exchanged. Laboratory facilities, and analysis methods have been developed collaboratively between Professor Elabd, Eric Davis, and DCMS staff.

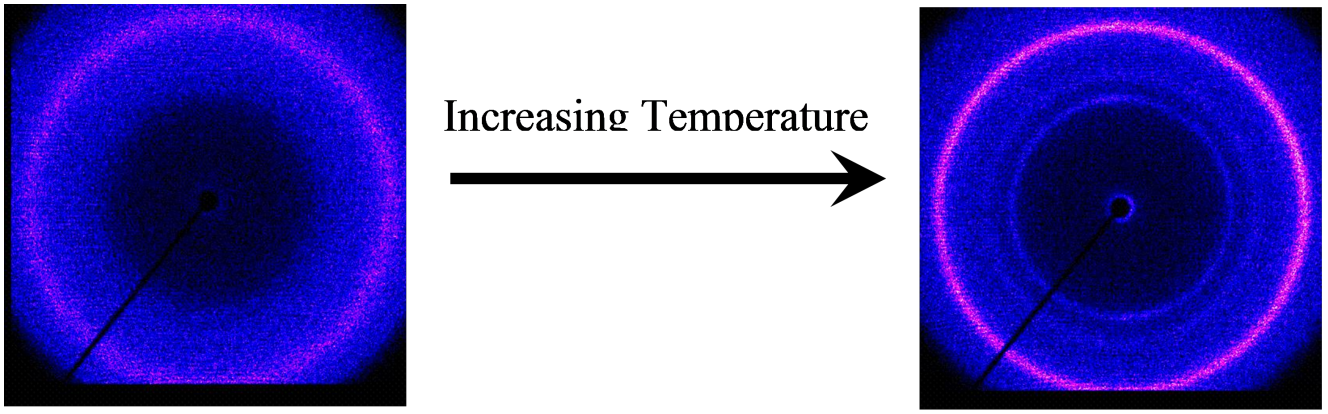



Fig. 3 2D wide-angle X-ray scattering patterns collected from Parylene C before and after exposure to temperature. These data suggest that strict control over manufacturing and post processing of these materials is critical to maintaining the desired properties and performance in devices.

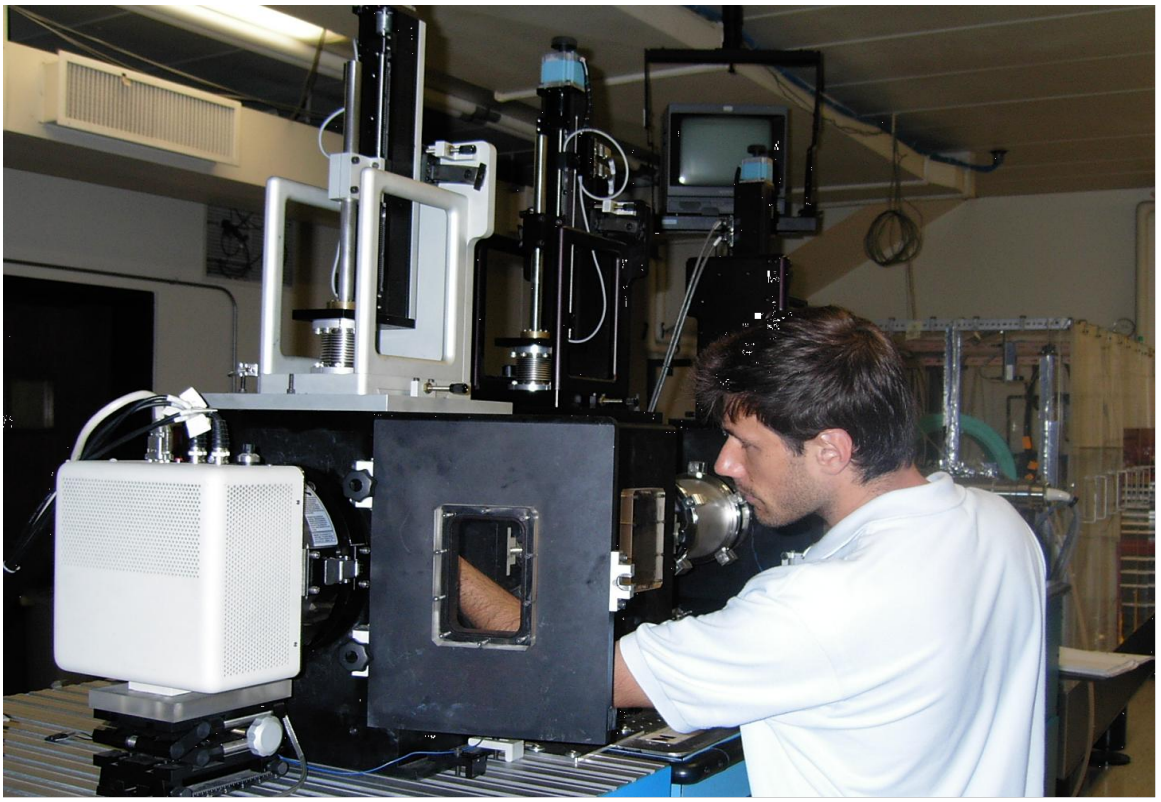


Fig. 4 Dr. Nicholas M. Benetatos preparing specimens for *in-situ* X-ray scattering experiments

*Hydrogel Project* **(MATERIALS PEFORMANCE, Division of Chemistry and Materials Science)**

Hydrogels are crosslinked hydrophilic polymer structures that are used in many biomedical applications including adhesion barriers, surgical sealants, soft tissue fillers, drug carriers, ophthalmic visco-surgical devices, etc. Hyaluronan (HA or hyaluronic acid) is a hydrogel material present in identical form in most tissues in animals and humans. It has high viscoelasticity and rheological properties. Molecules of HA can absorb a large volume of water, expand in the extra cellular space ,and then hydrate and lubricate tissues and joints. Natural HA exists as a high molecular mass polymer and can be degraded, absorbed and cleared by catabolic metabolism following enzymatic (hyaluronidase) degradation. Due to its biocompatible properties, HA has been used in a number of biological and medical applications including soft tissue fillers, drug carriers, ophthalmic visco-surgical devices and adhesion barriers.

In 2003, FDA became aware of a post-market issue regarding Gynecare Intergel ionized ferric hyaluronic acid (Intergel FeHA) adhesion prevention solution in which there appeared to be a higher frequency of adverse effects (e.g., foreign body reactions and/or non-infectious peritonitis) associated with this device. To address the issue, FDA conducted a coordinated assessment of information obtained through the adverse events report database associated with this device, including adverse effects associated with off-label use in laparoscopy and non-conservative procedures such as hysterectomy.

DCMS staff used a chemistry and material science perspective to search for factors that might contribute to the increased risk of adverse effects following Intergel deployment in some patients. Scientists synthesized Fe-HA gels in the laboratory and explored processing conditions such as crosslink density, pH, and mixing time, in order to span the spectrum of possible product variations. They studied its physical properties e.g., wettability or ability to spread or get between two surfaces, as well as chemical properties, such as *in vitro* enzymatic (hyaluronidase) degradation products and half-life (t ½). Through these studies, we were able to gain a thorough understanding of the chemical and physical properties that affect the safety and effectiveness of a device incorporating the material.

The research of this laboratory provided FDA with scientific tools to detect early evidences of safety problems by improving product tests. While these and other findings have resulted from work performed because of problems of one particular device and one material, researchers believe the issues and properties of the material can possibly be applied to other soft polymeric materials and hydrogels that are deployed into and onto the body.

*Interlaboratory Testing of ASTM F1717, Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model* **(Solid Mechanics Laboratory, Division of Solid and Fluid Mechanics)**

Spinal implant constructs consist of numerous components such as pedicle screws, hooks, rods, connectors, and plates that are used to immobilize and stabilize the spine until fusion occurs between the vertebrae. Mechanical characterization of spinal implants is prescribed in ASTM F1717 Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model, which outlines static and dynamic test methods for compression bending, torsion, and tension bending. This method is recognized by FDA and is a routine part of submissions for new devices. Though the test method has been on the books for many years, round-robin testing to illustrate expected variability in results within and between laboratories had never been conducted, making it more difficult for reviewers to interpret test results both for a single device and in comparisons between devices. FDA encouraged ASTM to conduct an interlaboratory study to collect data to generate a precision and bias statement for the method. DSFM was one of six facilities across the country that participated in the interlaboratory study. Engineers within DSFM performed static torsion and compression bending tests, and provided valuable feedback to the ASTM sub-committee as first-time users of the test method which facilitates further refinement of the standard. Additionally, DSFM provided hands-on training in conducting this test method to 15 engineers, 3 medical officers, and 1 biologist within the Orthopedic Spine Devices Branch in the Office of Device Evaluation who evaluate test data generated from this standard to help make recommendations on device performance in marketing applications. Having first-hand experience in a test method provides invaluable information about the actual mechanics of conducting a test that can be used in assessing results for new devices.

*In vitro Thrombogenicity Testing of Blood-Contacting Materials and Medical Devices* **(Fluid Dynamics Laboratory, Division of Solid and Fluid Mechanics)**

Patient complications due to blood clots and embolization are major clinical concerns associated with many blood-contacting devices. Due to the lack of widely accepted *in vitro* thrombosis test methods to evaluate medical devices, FDA and industry currently rely on costly and time-consuming animal studies for evaluating device thrombogenicity. To address this issue, OSEL scientists are working with experts within the FDA, the medical device community, and academia to develop *in vitro* test methods for thrombogenicity evaluation of medical materials and devices. One major challenge in developing *in vitro* thrombogenicity test methods is to control the coagulability of the blood so that it remains stable over the testing period but clots when exposed to thrombogenic conditions. To this end, OSEL scientists comparatively tested blood from

four different species (human, bovine, ovine, and porcine) to determine how anticoagulation conditions impact thrombus formation during dynamic testing with a recirculating blood flow loop.

In the experiments, the clotting potential of the blood, which was originally anticoagulated with acid-citrate-dextrose solution A (**ACDA**) to prevent clotting during withdrawal and shipment, was controlled by adding calcium and heparin to a concentration of 1 to 2 U/ml. Over the testing period, the blood was stable and did not clot under static conditions for any of the species. However, the preliminary results showed that when the blood was subjected to high shear stresses in a stenotic flow model, various sizes of thrombi formed with human, ovine, and porcine blood; but only minimal thrombi formed with bovine blood. These results suggest that recalcified ACDA-anticoagulated blood treated with low-concentration heparin may be useful for *in vitro* thrombosis evaluations of medical devices but also that appropriate anticoagulation levels need to be tailored for blood from different species. In addition to laboratory research, OSEL scientists are also actively working with national and international standards organizations to develop and revise several hemocompatibility testing standards, including the widely-used ISO 10993-4 standard ("Selection of tests for interaction with blood"). The results of this work were presented at the 2011 Annual Meeting of the American Society of Artificial Internal Organs.

*Medical Device Electromagnetic Compatibility (EMC) with Radio Frequency Identification (RFID)* **(Electromagnetic and Wireless Laboratory, Division of Physics)**

The OSEL Division of Physics has a long history of discovering electromagnetic (EM) sources that interfere with medical devices; RFID is no exception. RFID (radio frequency identification) is an automatic identification method that can read a tag from several meters away. Unlike conventional barcodes, RFID does not require line of sight between the reader and tags. To achieve this, an RFID reader transmits radio frequency (RF) energy to a tag. This tag then uses RF energy to respond to the reader with its unique identifying information. FDA is promoting RFID technology to track and trace drugs through the supply chain to help mitigate counterfeit drugs. RFID is also used widely in many hospitals to track the location of medical devices. In previous years, FDA demonstrated adverse effects of RFID readers on a number of implantable cardiac pacemakers. In 2011 FDA researchers, in collaboration with industry, tested the effects of RFID readers on implantable neurostimulators. One effect seen was a loss of proper stimulation from one model of neurostimulator when exposed to low-frequency RFID readers. The research conducted is entirely proactive, as there have been no credible incident reports of neurostimulators being adversely affected by RFID to this date. The study was published in the *Biomedical Engineering Online* (October 2011). FDA and industry are using the information collected in the study to develop RFID EMC (electromagnetic compatibility) standards that currently do not exist. These standards

assist and speed up the review process for pre-market submissions. Additionally, the information and experiences learned about RFID technology have assisted CDRH in the pre-market approval of RFID-enabled medical devices.

*New Left Bundle Branch Block Criteria to Predict Patient Benefit* **(Biophysics Laboratory, Division of Physics)**

In the past 2 years, there have been two FDA panel meetings to seek input on new PMA applications to expand the indications for cardiac resynchronization therapy. Key discussions have revolved around the paucity of evidence regarding the appropriate QRS duration in the presence of left bundle branch block for CRT to be indicated. In response, the Biophysics Laboratory, led by Dr. David Strauss has completed and continues to pursue a series of studies to improve biomarkers to diagnose left bundle branch block and to predict which patients will benefit from CRT. In 2011, Dr. Strauss published new electrocardiographic criteria to diagnose left bundle branch block in the *American Journal of Cardiology*. Dr. Loriano Galeotti, also from the Biophysics Laboratory, has subsequently studied the sensitivity and specificity of the new LBBB criteria using computer simulations of heart activation and has shown that the criteria have equivalent sensitivity with greatly improved specificity compared to conventional criteria. This was presented at an international scientific conference in April 2012. Researcher Zak Loring has evaluated the ability of the new criteria to predict benefit from CRT as a sub-study to the pivotal MADIT-CRT trial. In addition, Dr. Strauss evaluated the presence of scarring by cardiac MRI in patients with left vs. right bundle branch block and presented the results at the American Heart Association in November 2011. This research on CRT and left bundle branch block may change professional society guidelines and FDA labeling for which patients should receive cardiac resynchronization therapy. This will prevent unnecessary devices from being implanted and reduce patient harm and complications.

*Quality System Inspection* **(Software: Regulatory Support and Research, Division of Electrical and Software Engineering)**

In 2011, biomedical software engineer Lisa Simone provided her expertise as part of an inspection team at a medical device manufacturer's facility. DESE was called upon to collaborate in this challenging inspection to assist field investigators in identifying specific deficiencies in the firm's quality management system. In medical devices that contain software, it can be extremely difficult to assess if a firm follows their processes for design controls, especially in the areas of validation, risk/hazard analysis, and design changes.

In collaboration with the inspection team, Ms.Simone identified a trend in customer complaints that the firm had not been aware of. This trend involved incorrect or missing

patient results in a laboratory information system, and incorrect or missing notifications to clinicians that test results were out of range. These types of failures can directly lead to patient harm or death if inappropriate drug dosing (too little or too much) or clinical decisions are made based on incorrect information. At the start of the inspection, the firm had 13 open complaints in this area, 10 of which had not been assessed for risk-to-health, safety or for accountability to FDA for an average of 287 days. Ms. Simone pinpointed critical software files and identified several coding defects which directly caused many of these customer complaints. Some defects were basic violations of software coding practices, while others were new defects that were introduced during the correction of previous defects. As a result of the investigation and her analysis, the firm issued 2 Correction and Removals, and 11 Class II recalls.

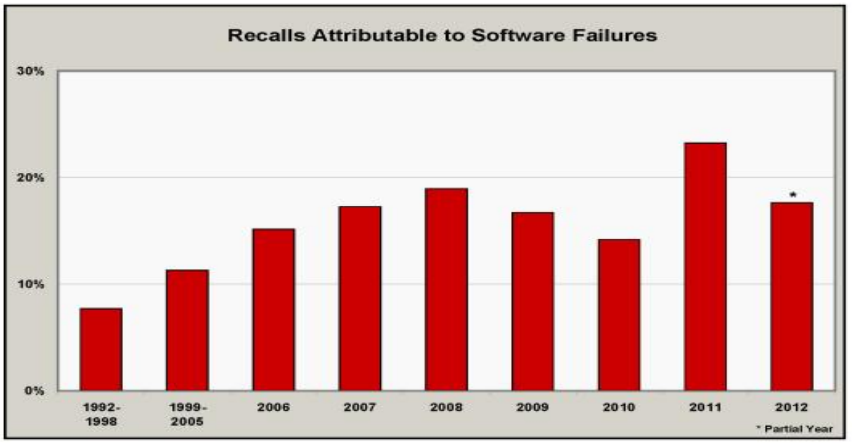



Fig 5

*Simulation Codes for Medical Imaging* **(Medical Imaging Laboratory, Division of Imaging and Applied Mathematics)**

Investigators in DIAM use computer simulations to answer critical questions regarding the safety and efficacy of new medical imaging products without resource-intensive pre-clinical and clinical studies. Since creating open-access our simulation codes to the wider medical imaging research community through a free online repository (http://code.google.com/hosting/search?q=label:DIAM), the web pages have been visited more than 4000 times and the software tools have been downloaded more than 500 times from more than 80 different countries. These software tools are facilitating investigations on new approaches for the design and optimization of medical imaging systems. Successful results from various research groups have already been presented at international scientific meetings such as the upcoming 2012 SPIE Medical Imaging Symposium.

*Software and Book Developed for Nerve Excitation Model* **(Biophysics Laboratory, Division of Physics)**

J. Patrick Reilly and Alan Diamant, two OSEL research fellows, are publishing a book titled, Electrostimulation: Theory, Applications, and Computational Model. The book is accompanied by a public release of the source code and executables of their "Spatially Extended Nonlinear Node" (SENN) model that is described in the book. The software and a brief user's guide will be offered as a free download on a web site maintained by the publisher, Artech House. The applications for electrical stimulation device and associated software are broad and important. The book and software provide an intuitively simple model for estimating electrical dose at the site of nerve or muscle excitation. The method, now available to the public, is of value to both reviewers and researchers. Electrical dosimetry for electrical stimulation devices is evaluated by Division of Physics staff, typically, on a case-by-case basis. The SENN model is universally applicable and provides an estimate for effective electrical stimulation without excessive stimulation. The book describes the "Threshold Factor" using the SENN neuro-electric model to give a numerical rating of any form of electrical stimulation. The "Threshold Factor" correlates with the volume of tissue containing neurons that may be excited by an electrical stimulus. The model and book unify our understanding of electrical dose. A large number of medical devices employ electrical stimulation of the spinal cord, deep brain, cerebral cortex, peripheral nerve, and auditory nerve, and are used in cardiac pacemakers, electrical defibrillators, muscle stimulators and magnetic stimulators. The earliest application of the SENN model was used to set MRI safety limits for induced electrical stimulation, and this was done in collaboration with CDRH. Now this useful model has been converted to one that can be easily used on a personal computer, along with a book to guide its use.

# Division Descriptions

## DIVISION OF BIOLOGY (DB)

DB participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of biological sciences. Specifically, DB conducts research to support the Center's mission to assure the safety and effectiveness and promote the improvement of medical devices in the areas of biological risk assessment, biosensors/nanotechnology, genomic and genetic technologies, infection control and

sterility, tissue-device interactions, toxicity/biocompatibility, and radiation bioeffects. Through laboratory studies, researchers evaluate the potential adverse effects of medical devices on host biological systems and, in collaboration with engineering divisions, identify the source and impact of product degradation on organ systems both under acute and chronic conditions. The Division staff develops measurements methods and analytical procedures to characterize and evaluate devices and products, studies molecular and cellular mechanisms and bioeffects of biomaterials, and supports the Center's enforcement and product testing activities.

The DB staff members are primarily biologists, chemists, and biomaterials scientists.

**Laboratories**

- Biomolecular Mechanisms
- Cardiovascular and Interventional Therapies
- Emerging Biosensors and Biotechnologies
- Infection Control
- Toxicology and Biocompatibility

## DIVISION OF CHEMISTRY AND MATERIALS SCIENCES (DCMS)

DCMS participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of chemistry and materials sciences. Specifically, the DCMS focus is on developing experimental data, test methods and protocols for regulatory and scientific activities involving multicomponent mass transfer, reaction kinetics, absorption and swelling of network polymers, polymer processing, modeling of physiological processes, and materials degradation. Research activities in the division include synthesis and characterization of polymeric and nanocomposite materials; computational modeling of microstructures and microstructure development; evaluating drug and small-molecule elution, diffusion, and leaching from device materials; developing sensor evaluation protocols; measuring and modeling structural transitions and phase stability; hydrogel and biopolymer synthesis and characterization; and shelf-life and service life prediction. DCMS tests the performance of chemical processes of importance to medical devices, such as mass transfer through membranes used in dialysis and blood oxygenation, and manufacturing processes used to fabricate materials and evaluate tools and protocols for device performance.

The technical disciplines of the DCMS staff include physical chemistry, analytical chemistry, polymer science, pharmacology, materials science, materials engineering, biomedical engineering, and chemical engineering.

**Laboratories**

- Active Materials
- Chemical Contamination
- Materials Performance

## DIVISION OF ELECTRICAL AND SOFTWARE ENGINEERING (DESE)

DESE participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of electrical engineering and software. Specifically, the DESE works in the application of electronics, software engineering, and systems engineering body of knowledge to the regulation of medical devices and electronic products that emit radiation. The Division addresses the cutting edge of medical devices through all phases of the product life cycle and all aspects of the product manufacturer's business, from research and development through procurement, production, and ongoing customer support. DCMS hosts the following resources and capabilities: analog and digital circuit design, data acquisition and display, embedded microprocessor and PC-based systems, software-based virtual instruments, quality management and risk management as applicable to electronics and software, testing for hazards arising from the use of electrical and electronic technology in medical products, and electronic design including components, circuits, and analytical techniques for controlling high voltages and/or currents.

DESE staff members are primarily electronics and electrical engineers, physicists, biomedical engineers, and general engineers.

**Laboratories**

- Medical Electronics
- Software (Regulatory Support and Research)

## DIVISION OF IMAGING AND APPLIED MATHEMATICS (DIAM)

DIAM participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of medical imaging and applied mathematics. Specifically, DIAM provides scientific expertise and carries out a program of applied research in support of CDRH regulation of radiation-emitting products, medical imaging

systems, and other devices utilizing computer-assisted diagnostic technologies. Medical imaging research encompasses ionizing and non-ionizing radiation from data capture through image display and observer performance. The computer-assisted diagnostics work of DIAM is focused on the appropriate mathematical evaluation methodologies for sophisticated computational algorithms used to aid medical practitioners interpret diagnostic device results. The Division is charged with developing and disseminating performance assessment methodology appropriate to these modalities. DIAM operates a calibration laboratory for ionizing radiation detection instruments and participates in a full range of programs in support of the Public Law 90-602 mission of the Center.

DIAM staff members are primarily physicists, mathematicians, and physical science technicians.

**Laboratories**

- Image Analysis
- Imaging Physics
- Ionizing Radiation Metrology

## DIVISION OF PHYSICS (DP)

DP participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of physics. Specifically, DP conducts research and engineering studies to support the Center’s mission to assure the safety and effectiveness of medical devices and electronic products, and to promote their improvement. Scientific and technical specialties in the division include optical physics and metrology, sensors, fiber optics, electromagnetics, electromagnetic compatibility and electromagnetic interference, biophysics, functional imaging, cardiac, electrophysiology, neuroscience, and minimally invasive optical and electromagnetic technologies. The Division develops measurement methods, instrument calibration capabilities and analytical procedures to characterize and evaluate devices and products such as computational modeling, and supports the Center’s enforcement and product testing activities. DP evaluates interactions of electromagnetic and optical energy with matter, analyzes implications for the safety and effectiveness of devices and products, and develops and evaluates procedures for minimizing or optimizing human exposure from such devices.

The technical disciplines of DP staff include physics, mathematics, biophysics, biomedical engineering, electronics, neuroscience, and general engineering. A newly formed laboratory is in human-device interfaces. The Human-Device Interface Laboratory is designed to support research in human factors and medical device use. The

facility will examine the people who interact with medical devices, the ways they use devices, and the environments or settings in which they use them.

**Laboratories**

- Biophysics
- Electromagnetic and Wireless Technologies
- Functional Performance (Human) Device Interface
- Optical Diagnostic Devices
- Optical Therapeutics and Medical Nanobiophotonics

## DIVISION OF SOLID AND FLUID MECHANICS (DSFM)

DSFM participates in the Center's mission by conducting research, participating in device review activities, developing consensus standards both domestic and international, developing regulatory guidance, testing forensic and regulatory samples, and providing educational programs in the area of solid and fluid mechanics. Specifically, the core responsibilities of this division involve issues for which mechanical interactions or transport are of primary concern, such as those involving motion; structural support, stabilization, or vibrations; device and material mechanical integrity; materials durability; and biologically relevant parameters of device and materials. The Division has expertise in the areas of fluid dynamics, solid mechanics and materials, acoustics and ultrasonics. DSFM develops measurement methods, instrument calibration capabilities, and analytical procedures to characterize and evaluate devices, device materials, and products, and supports the Center's enforcement and product testing activities. DSFM staff also evaluate interactions of ultrasound energy with matter and the implications of these interactions on the safety and effectiveness of devices and products.

Technical disciplines of the DSFM staff include mechanical engineering, materials science, biomedical engineering, general engineering, and physics.

**Laboratories**

- Fluid Dynamics
- Solid Mechanics
- Ultrasonics

## MANAGEMENT SUPPORT STAFF (MSS)

MSS provides leadership and support to the Office of the Director, Division Directors, and laboratory professionals on all administrative, general management, and knowledge management issues. MSS is responsible for planning, developing, and implementing

Center and OSEL programmatic matters concerning financial management, personnel, procurement, contracts, inter-agency agreements, employee training, and facilities. MSS is also tasked with managing and administering OSEL resources designed to support on-going programs. The staff ensures the proper distribution of operating and payroll dollars, facility plans, procurement and property, travel requests and ADP needs. MSS advises the Office of the Director on potential issues that may affect resources, staffing, and management issues to comply with policies and avoid potential conflicts. In addition, MSS directs and conducts special assignments or projects for the Center as well as the Office Director.

# Office of Science and Engineering Laboratories

# Research Laboratories and Selected 2011 Accomplishments

## *Biomolecular Mechanisms Laboratory* (Division of Biology)

The Biomolecular Mechanisms Laboratory conducts research applying new technologies in the areas of genetics and immunology as related to device and diagnostic development (translational science) and safety assessment. Laboratory projects facilitate the development of expertise necessary for authoritative consultation on novel, controversial, and complex medical devices.

Specific goals include the following:

- Investigating potential biological safety problems with new biomaterials and devices that are unlikely to be addressed by industry or academia
- Understanding the biological basis of adverse events reported for marketed medical devices
- Providing the research base for new performance standards for industry and CDRH reviewers

Current research areas address the following:

1. Biocompatibility issues affecting approval of new devices and nano-sized materials;
2. Basic studies in vascular biology relevant to cardiovascular device adverse events;
3. Medical Counter Measures studies on the rapid detection and threat mitigation of bio-terror agents, including Ebola virus;
4. Issues in the acceptance of genetic analyses related to personalized medicine, including detection of genetic biomarkers and whole genome sequencing;
5. Review of cross-center future products such as drug or biologic/device combination products.

These studies harmonize medical device review issues and address the Center's regulatory need for methods to ensure the safety and efficacy of medical devices and diagnostic tests. To achieve these goals studies are focused on 1) understanding the basis for adverse biological reactions at the molecular and cellular levels, and 2) practical innovations that incorporate new technologies.

**Accomplishments**

*Genetic Toxicology Assay Development for Small Medical Devices and Nanomaterials*

Device safety assessment includes testing for genetic interactions as hazard identification for cancer risk. The most common assays used world-wide are bacterial mutation assays. However, biocompatibility assays generally require prohibitive numbers of small medical devices such as cardiovascular stents or dental implants in order to test a standard quantity of material. Laboratory staff have developed and tested alternative methods that require one-fifth to one-tenth the amount of material required for the standard bacterial assays, while maintaining assay sensitivity. These assays may also be problematic for assessing metal nanoparticles, which may be excluded from the cells. Biomolecular Mechanisms scientists are thus investigating the utility of this assay for assessing nanomaterials and investigating the effect of nanomaterials as inhibitors or facilitators of the detection of genotoxins in combination.

*Genetic Toxicology Expertise*

Staff performed more than 30 formal consults in the areas of genetic toxicology and chaired the CDRH Genetic Toxicology Guidance document committee and the FDA wide GeneTox Network. The Network hosted outside speakers developing new assays for genetic toxicology assessment and employing Next Gen Sequencing technologies. Three publications in genetic toxicology addressed the integration of new technologies, the analysis of the causes of hereditary genetic damage, and the development of a new *in vivo* genotoxicicity assay that can be performed in humans as well as in experimental animals.

## ***Biophysics Laboratory*** (Division of Physics)

The Biophysics Laboratory covers a broad range of expertise spanning cardiac electrophysiology, retinal imaging, peripheral nerve physiology, neural implants effects, quantitative MRI and MR thermometry.

Medical devices that rely on electrophysiology and electrical stimulation for safety and efficacy cut across all medical specialties. The most important examples are devices that work in the heart and nervous system including the following: cardiac pacemakers, defibrillators, retinal stimulators for blindness, brain stimulators (for Parkinson's disease, pain, motor function, hearing), electroconvulsive therapy, magnetic brain stimulation, cochlear implants, middle ear hearing devices, spinal cord stimulators, vagus nerve stimulators, and peripheral nerve stimulators (including those for locomotion, breathing, bladder and bowel control). The less obvious examples are devices for the electrical detection of cancer (from breast, colon and cervix), the transdermal electrical extraction of glucose for monitoring, and a number of "complementary and alternative medicine"

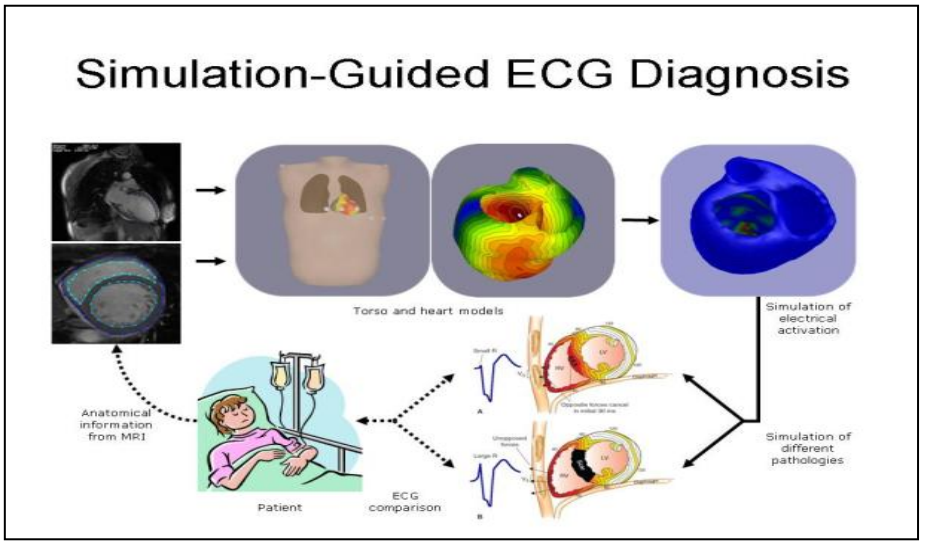



Fig 6 Electrocardiogram is used to help diagnose and locate myocardial scar with the help of an anatomically based computer model.

devices. The scientific discipline of electrophysiology forms a unified basis for the scientific evaluation of all of these devices. The scientific issues involve the basic electrophysiology of a number of body systems and the biomedical engineering of the devices.

In the area of MRI technology, many of the advanced MRI techniques are cleared for clinical use but lack standardization. These include functional BOLD MRI, Diffusion Tensor imaging and Dynamic contrast enhanced imaging. The research involves understanding sources of variability in these methods to facilitate the adoption of these methods as imaging-based biomarkers in clinical trials. Much of the work pertains to developing suitable phantoms and assessing reproducibility. In addition to the research in MRI-based biomarkers, the laboratory is also involved in other MRI-related medical device research such as the analysis of adverse events, and thermometry. This expertise also directly supports the regulatory activities pertaining to the pre-market review of MRI devices.

The research in this laboratory ranges from work directly applied to a single device type (the retinal stimulator), to broader work that is relevant to a class of devices (cardiac stimulators for treating arrhythmias and heart failure), and to far-reaching work on the development of optical stimulation of excitable tissue (supported extramurally). In addition to these areas of research, this laboratory is heavily involved in direct regulatory activities with staff performing as lead reviewers, expert consultants, subject matter experts to FDA Advisory Panels, authors of guidance documents, and the revision of international medical device standards.

**Accomplishments**

*Novel Circuitry for Recording Neuronal Spike Activity*

A collaboration between FDA and the Naval Research Laboratory (NRL), was instrumental in demonstrating a new technology, invented at NRL, to record neuronal spike currents using large (up to 80K) microwire focal plane array imaging chips. This is the first report using a modified high definition imaging chip to record extracellular action potentials of neurons as *spikes of current*. Retinal ganglion cell current spike waveforms recorded with the array are similar to those recorded with more conventional AC voltage amplifiers. The method opens up the development of more novel circuitry for recording neuronal spike activity. The paper, titled "A novel high electrode count spike recording array using an 81920 pixel transimpedance amplifier-based imaging chip" by Lee Johnson, Ethan Cohen, Doug Ilg, Richard Klein, Perry Skeath and Dean A. Scribner, will appear in the *Journal of Neuroscience Methods* in 2012.

*Standardization of Magnetic Resonance Imaging for Clinical Endpoints in Neurology*

Drs. Sunder Rajan and David Soltysik of the Biophysics Laboratory are leading an effort to improve clinical endpoints for safety and effectiveness testing of medical devices. Functional MRI with blood-oxygen-level-dependent (BOLD) contrast is a popular, nonnvasive tool that can assess brain activation and can be used as a biomarker. The validation of BOLD as a biomarker has the potential to improve patient selection, treatment selection, and demonstrate treatment efficacy. It is potentially capable of providing objective endpoints for depression, pain, and stroke studies. Furthermore, the developing standards in using BOLD as a biomarker will make its use more reliable and efficient. In an effort coordinated by Dr. Rajan, Dr. Soltysik is studying the sources of variability in BOLD methods to develop phantoms to standardize the imaging. An indication of early success is the publication of a study that measured variability (due to head position) of BOLD contrast images: D.A. Soltysik, D. Thomasson, S.S. Rajan, J. Gonzalez-Castillo, P. DiCamillo and N. Biassou: Head-repositioning does not reduce the reproducibility of fMRI activation in a block-design motor task, *Neuroimage* 2011: vol 56, issue 3, 1329- 1337.

## ***Emerging Biosensors and Biotechnology Laboratory*** (Division of Biology)

The area of biosensors and biotechnology encompass a wide range of FDA-regulated products such as diagnostic devices, nanotechnology, implantable devices and therapeutic devices. The role of the Emerging Biosensors and Biotechnology Laboratory is to support the scientific basis for the FDA's regulatory decision-making throughout the total product

life cycle by developing independent laboratory information to answer immediate regulatory questions and to aid in regulatory decision-making. In addition, the laboratory includes as its mission the opportunity to explore new emerging technologies as potential areas of research in proactive investigations for future regulatory needs. The laboratory currently has three main focus areas: (1) Emerging biosensors, bioassays and lab-on-a-chip platforms for point-of-care diagnostics/personalized medicine and device safety, (2) nanoparticle characterization and application to diagnostic devices, and (3) radiation safety and novel radiation-based therapeutic agents. Staff in the Emerging Biosensors and Biotechnology Laboratory assess many facets of these new and emerging technologies by studying how device design and device components can affect performance and hence safety and effectiveness. The laboratory staff actively collaborate both within FDA (other OSEL laboratories, Office of Device Evaluation(CDRH), Center for Drug and Evaluation Research, Center for Food Safety and Nutrition, and the Center for Veterinary Medicine) with other government agencies (Naval Research Laboratory, National Cancer Institute) and academia (University of Maryland, University of Maryland Baltimore County, Northwestern University) and the research has resulted in scientific reviews of medical devices, peer reviewed manuscripts, invited presentations and seminars, consensus standards development and the development of guidance documents to assist reviewers and industry.

**Accomplishments**

*Nanotechnology*

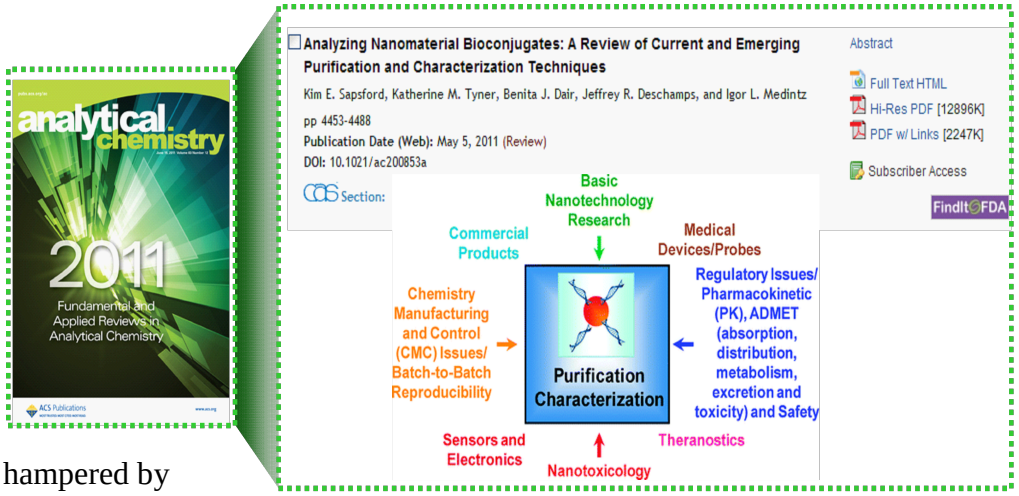



Fig 7

Nanotechnology offers great potential in the development of a vast array of new products to advance public health. While *in vivo* nanoparticle applications are currently hampered by cytotoxicity concerns (an area the laboratory is working on in collaboration with other DB staff), the market for *in vitro* diagnostic (IVD) tests using nanoparticles is rapidly expanding as evident from the published literature. The resulting new technologies and devices are likely to be developed and FDA approval sought much sooner than for their *in vivo*-based counterparts. The use of nanoparticles-- in particular quantum dots, carbon nanotubes (CNTs) and gold nanoparticles--in rapid diagnostic/screening applications is currently being evaluated. The research is evaluating the use of nanotechnology in diagnostic assays and rapid screening tools.

The studies have resulted in a number of peer-review publications and a bookchapter, including a review in the ACS journal Analytical Chemistry titled "*Analyzing*

*Nanomaterial Bioconjugates: A Review of Current and Emerging Purification and Characterization Techniques*" that made the "***top 10 list of most read articles***" during the second quarter of 2011 for Analytical Chemistry and the "***top 20 list of most read articles***" for the previous 12 months. Knowledge gained from these studies and those of others has been used to help draft a guidance document currently under review at the Center level; "*Draft Guidance for Industry and Food and Drug Administration Staff. Guidance Document: Medical Devices Incorporating Nanotechnology*", in which a number of DB staff took lead writing roles. DB staff have also been actively involved in developing a syllabus for a comprehensive nanotechnology training program to be offered to FDA reviewers titled "FDA Applied Sciences Course in Nanotechnology."

*Lab-on-a-chip (LOC)*

Point-of-care (POC) *in vitro* diagnostics (IVD) has the potential to transition diagnosis from a centralized laboratory into the doctors' office to provide the patient and physician with more timely diagnosis and therefore treatment and represent the next generation of medical diagnostic devices regulated by FDA. Lab-on-a-chip (LOC) technologies, in particular, will play a key role in this transition and incorporate advances in many areas of science including materials, electronics, optics, reagents and nanotechnology. Understanding the many aspects of these POC IVD technologies, including signal generation and transduction mechanisms, bioconjugation and labeling techniques, microfluidic generation, nanotechnology, systems integration and automation and ultimately evaluating how these impact overall device performance will be essential to performing critical scientific review of such regulatory submissions, thus ensuring safe and effective products.

Research in this area is multi-disciplinary in nature, and as such the laboratory has established active collaborations with experts in other government agencies (National Cancer Institute and Naval Research Laboratory) and academia (University of Maryland and University of Maryland Baltimore County). Research in this area has resulted in ~18 peer-review publications, including journals such as *Lab-on-a-Chip*, *Analytical Chemistry*, *ACS Nano* and *Biosensors & Bioelectronics*, and ~5 books/book chapters since 2008 for the laboratory. The hands-on expertise acquired will assist in the later development of test methods, guidance documents, and the review of standards for these types of technologies.

*Quantum Dot Nanoparticle Sensors for Heparin Contamination Screening*

The threat of economic adulteration of products by foreign manufacturers with the aim of increasing profits is, unfortunately, of real concern in our now globalized economy. Given the increasing number of medical devices and device components that are manufactured in foreign facilities that may be subject to less regulation prior to exportation, the need to provide FDA inspectors with accurate screening tools is

essential. This was clearly demonstrated in 2008 when contamination of the heparin supply with oversulfated chondroitin sulfate (OSCS) resulted in severe anaphylactoid reactions in exposed patients. Current FDA-required tests for OSCS detection, while robust and sensitive, are expensive, require dedicated laboratories and trained personnel, are highly technical, and are not suitable for rapid screening of samples in the field.

The research in this area is to design rapid, inexpensive, quantitative, robust and field deployable high-throughput methods for detecting OSCS contamination in heparin samples. The project uses a quantum dot (QD) peptide-based fluorescent biosensing platform and is assessing its ability to detect contaminants, such as OSCS. Additionally, these types of platforms could be applied to the detection of alternative contaminates that are either proteolytic in nature (such as Botulinum Neurotoxin A) or activate protease activity. This project expands FDA scientific knowledge concerning the potential of QD nanoparticles, FRET and FRET-based protease technologies as sensing platforms using fluorescence transduction, which may be used to evaluate future FDA regulatory submissions.

## ***Fluid Mechanics Laboratory*** (Division of Solid and Fluid Mechanics)

The Laboratory of Fluid Dynamics, located in the Division of Solid and Fluid Mechanics, maintains a research program focused on the fundamental factors governing the interaction of flowing fluids with medical devices and the development of test methodologies to objectively characterize such interactions and their consequences.

**Accomplishments**

*Using Computational Fluid Dynamics to Assess Blood Damage and Medical Device Safety: An FDA Critical Path Initiative Project*

Computational fluid dynamics (CFD) is a subset of computer modeling used to simulate the flow of fluids and to calculate the physical forces acting within the fluid. CFD is already being used to develop and prototype blood-contacting medical devices, such as prosthetic heart valves and ventricular assist devices (VADs). However, the use of CFD to demonstrate *product safety* in FDA pre-market device applications and post-market investigations requires sufficient computational and experimental validation. This is especially true in the final step of the process as biological responses (e.g., red blood cell rupture, blood clot formation) are predicted based on the purely physical results (e.g., pressures, velocities, shear stresses) obtained from the computational simulations. To understand factors affecting the accuracy of CFD in predicting flow characteristics and blood damage, we conducted an interlaboratory study of a benchmark nozzle model that included participants from academia, industry, and the FDA. The study consisted of three independent parts: (1) experimental measurements of velocities in transparent models of

the nozzle, (2) computational predictions of flow through the nozzle device geometry, and (3) experimental blood damage testing of the nozzle. The simple benchmark nozzle model, which mimicked the flow fields in several medical devices, consisted of a gradual flow constriction, a narrow throat region, and a sudden expansion region where a fluid jet exited the center of the nozzle with recirculation zones near the model walls. In collaboration with scientists at the Rochester Institute of Technology and Pennsylvania State University, transparent acrylic versions of the nozzle were fabricated and the fluid velocities and pressures were measured to provide experimental validation for the companion interlaboratory CFD study.

In the second part of the project, computational modelers from around the world were invited to simulate the flow fields in the nozzle model prior to having access to the experimental velocity data. Twenty-eight groups from six different countries participated in the interlaboratory computational study in which the nozzle flow rate was adjusted so that the throat Reynolds number (Re) was varied from 500 to 6500, as in the experimental study. At all Re's, the largest discrepancies between the computational predictions appeared downstream of the throat. At Re=500, laminar simulations agreed well with experimental velocity data. As the Re was increased, agreement between the measured results and those predicted by the participants became much more variable. While choice of turbulent model is one factor of many that affect simulation accuracy, the analysis of results has helped us to develop a suite of best practices (e.g., appropriate flow model, inlet/outlet length, maintaining mass conservation) for using CFD in medical device evaluations that is impacting both the development of standards and an FDA Guidance Document on reporting computational modeling results in medical device submissions. The experimental flow results from the interlaboratory study were published in 2011 in the *ASME Journal of Biomechanical Engineering*. The results of the computational interlaboratory comparison have been accepted for 2012 publication in the *Journal of Cardiovascular Engineering & Technology*.

## ***Functional Performance and Device Interface Laboratory*** (Division of Physics)

**Accomplishments**

*Emerging Research from the Functional Performance and Device Use Laboratory*
In 2011, the CDRH Science Prioritization Process (C-SPP) identified “Evaluating Use Environments and Human Factors” as one of seven major themes for the Center because understanding the many ways that medical device users interact with devices in typical environments and conditions of use is considered critical to facilitate device use and minimize user error. The report also cited improving health in special populations, including pursuing new methods of assessing persons with disabilities, as another high-priority area.

The Functional Performance and Device Use Laboratory was established to expand our understanding of how medical device design influences use errors and physical function during device use. As capabilities of the new laboratory were created, staff began collaborating with colleagues within CDRH to address regulatory science priorities identified in the C-SPP process. Projects in development include investigating whether providing speech output on infusion pumps will reduce the commission and increase the detection of programming errors; studying unique use-related hazards of medical device operation during public health emergencies and mass casualty events; experimental and computational modeling study of metal-on-metal hip implants to understand their mechanisms of wear and conditions that might contribute to device failure; and analysis of potential sources of use errors related to design features of floor based patient lifts.

The breadth of these newly initiated projects focus on human factors but touch on nearly all of the priorities highlighted by the C-SPP. Results of these projects have great potential to inform pre-market review and post-market surveillance strategies and development of guidance and standards for the manufacturing of safe and effective medical devices.

## ***Infection Control Laboratory*** (Division of Biology)

The Laboratory of Infection Control is an interconnected program of laboratory research that provides consults for medical device-associated infections/sterility, and biological evaluation of medical devices (biocompatibility) for premarket submissions (510(k), IDE, PMA) and postmarket submissions (30-Day notice change for PMA), public health notifications, safety alerts, recalls, Health Hazard Evaluations, Health Risk Assessments, 522 surveillance studies, field inspections, develop or update regulatory guidance documents, national and international standards designed to promote a scientific basis for pre-market and post-market regulatory decision making in CDRH.

Members of the Infection Control Laboratory have accomplished much in research and regulatory arenas regarding biological evaluation of medical devices and in sterility/infection control. Both of these areas are issues that cover nearly all medical devices and have major public health impact.

### Accomplishments

*Infection Control and Device Design*

The influence of device design (physical design, materials used in fabrication) in reprocessing single-use and reusable medical devices to prevent transmission of infectious agents is one of the critical issues the laboratory is currently studying.

Reprocessing reusable devices is a multi-step process designed to maximize patient safety. Cleaning the device is a critical first step. A properly cleaned device should be free of contaminants such as biological matter (e.g., blood, tissue, mucus, etc.) and non-biological materials (e.g., lubricants, detergents, brush bristles, etc.). The presence of such materials can potentially compromise the effectiveness of disinfection or sterilization processes. Several published reports have documented the transmission of infectious material from improperly reprocessed reusable medical devices.

Incidents of improperly cleaned (e.g., arthroscopic shaver handles, endoscopes) and/or disinfected (e.g. endoscopes) *reusable* devices have prompted FDA to issue Safety Communications, Alerts and Notices (Medical Devices) and to require manufacturers to validate the cleaning of reusable devices with test soils and quantitative measurements of residual soils after cleaning. In the past, an acceptable assessment of cleanliness was a visual examination of the device to ensure it was free of contaminants. However, modern devices are increasing in complexity with internal design features that are easily visible to the naked eye, such as narrow opaque lumens, hinges, stopcocks, protective sheaths, rough surfaces, etc. Thus, the design of reusable devices (physical design, use of materials to fabricate) can influence infection control.

The laboratory is presently developing methods to detect and remove the chemical warfare agent Ricin, a natural toxin, on various medical device surfaces. Ricin is relatively easy to make or obtain, is stable, and may contaminate reusable devices either deliberately or accidentally, peanut lectin is used as a surrogate of Ricin. The laboratory data showed the following:

- Reverse osmosis system can remove small toxins from water
- Commercially available wipes containing sodium hypochlorite as the active ingredient rapidly denatures peanut lectin.

Laboratory staff are involved with all Center discussions concerning reprocessing of reusable medical devices and infection control in general, including the following:

- Helped draft the guidance document "Processing/Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling" (May 2011)

- Gave presentations on the subject of medical device reprocessing and use – the FDA Public Workshop on Reprocessing Reusable Medical Devices (June 8-9, 2011), and FDA's Perspective of "Clean" at the Association for the Advancement of Medical Instrumentation (AAMI) and FDA Summit: Medical Device Reprocessing (October 11-12, 2011).

## ***Medical Electronics Laboratory*** (Division of Electronics and Software Engineering)

**Accomplishments**

*Medical Device "Flight Data Recording" and Animation*

Safety critical devices such as those found in the transportation and power industries routinely record operational data via "flight data recorders" or data loggers to enable analysis of adverse events. Here, the data can be used to help determine the cause of the adverse event and subsequently to eliminate or mitigate future events. The data can also be used to assess and optimize device performance issues under different use and environmental conditions. The recordings can also serve another purpose, which is to help verify that design changes take into account adverse event scenarios and mitigate them properly by playing them back as test cases.

As medical devices become more complex and interoperable, so too is the need for recording medical device data. To address this issue we are developing a set of "flight data recording" requirements that can be used in medical devices (or networks of medical devices) to help eliminate or mitigate future adverse events.

It is not enough to be able to record adverse event data. There is a need to "play back" or animate the data in a manner that is helpful to investigators. This issue becomes particularly complex for interoperable devices. Here, it may be necessary to integrate and animate data from multiple medical device flight data recorders to gain a comprehensive understanding of an adverse event. Researchers are developing techniques to perform this animation integration.

## ***Optical Diagnostic Devices Laboratory*** (Division of Physics)

The rapid proliferation of novel diagnostic medical devices employing minimally or noninvasive optical technology is revolutionizing modern health care. These devices now perform a variety of critical *in vivo* tasks in the clinic, such as oximetry monitoring, atherosclerotic plaque assessment, high resolution retinal imaging, and early detection of lung, cervical and gastrointestinal cancers. These systems are based on a variety of optical mechanisms including fluorescence, reflectance and coherence-domain imaging.

Given their increasing complexity, optical technologies represent a significant new regulatory challenge to FDA. There are distinct gaps in understanding the biophysical mechanisms of action, device- and tissue-specific light propagation effects, and tissue damage by ultraviolet, visible and infrared radiation. Basic mechanism studies are needed to facilitate the development of relevant evaluation criteria early in the regulatory

process, thus enabling thorough and swift reviews of cutting-edge optical technologies. The Optical Diagnostic Devices laboratory works to generate fundamental data through studies of light-tissue interaction mechanisms, device performance and tissue safety for a variety of optical technologies. Furthermore, the laboratory is developing phantom-based performance test methods and advanced computational models of light propagation in tissue to elucidate device working mechanisms and facilitate the device review process. This program is located within the Division of Physics (DP).

**Accomplishments**

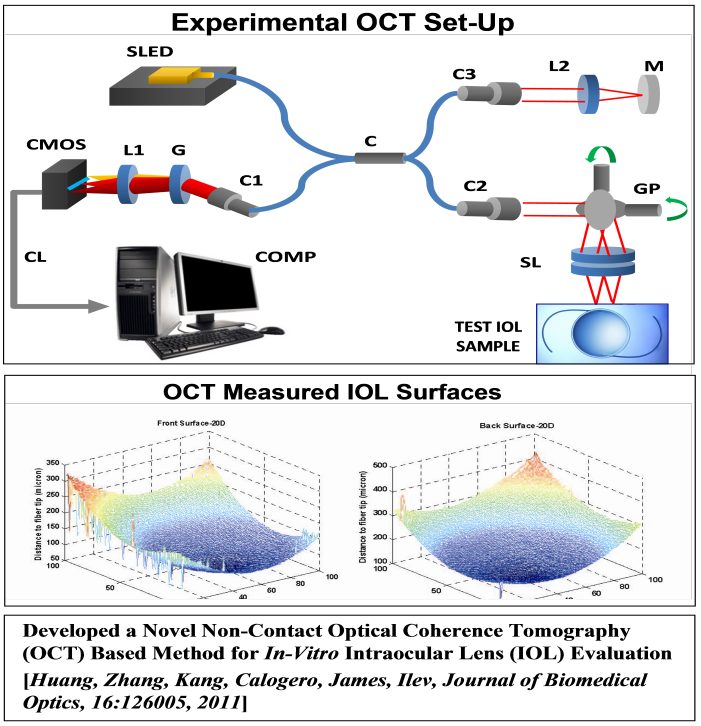
*Imaging Neuronal Tissue Directly below a Stimulus Electrode in Real-Time*

A common problem in determining neural stimulation safety at FDA is the lack of established scientific techniques to study the effects of electrical stimulation on the neurons directly below a stimulus electrode in real time. This is because most stimulus electrodes are made of opaque metals that block conventional optical imaging methods. Noting that plastic tubes made of Teflon fluoropolymers became optically transparent in saline, FDA developed a method to image neuronal tissue directly below a stimulation electrode using optical coherence tomography (OCT). A collaboration between Dr. Ethan Cohen of the Biophysics Laboratory and Anant Agrawal and Dr. Josh Pfefer of the Optical Diagnostic Devices Laboratory (both laboratories are in the Division of Physics), resulted in discovery of how to image the retinal tissue layers swelling in response to epi-retinal electrical pulse train stimulation over the course of time, determining what levels of stimulation were safe for the retina, and documenting changes to the optical properties of the tissue. The paper titled "Optical coherence tomography imaging of retinal damage in real time under a stimulus electrode" by Ethan Cohen, Anant Agrawal, Megan Connors, Barry Hansen, Hamid Charkhkar, and T. Joshua Pfefer was published in 2011 in the *Journal of Neural Engineering*.

## ***Optical Therapeutics and Medical Nanophotonics Laboratory*** (Division of Physics)

Minimally invasive biophotonics techniques and devices have been recently developed as potential alternatives to conventional medical methods for diagnosing, monitoring and treating a variety of diseases, drug discovery, proteomics, and environmental detection of biological agents. These technologies offer a non-contact, effective, fast and painless way for sensing and monitoring various biomedical quantities. Medical devices utilizing minimally invasive biophotonics technology are rapidly finding their way into the mainstream for early disease diagnosis and improved patient acceptance and comfort. Optical therapeutics approaches are being proposed that use high-intensity ultra-short laser radiation, precise delivery fiber optics and near/mid-infrared biosensing and monitoring. CDRH recognizes the need to prepare for evaluating devices being

developed to optically diagnose and treat various diseases, including pre-cancerous and cancerous conditions.




**Developed a Novel Non-Contact Optical Coherence Tomography (OCT) Based Method for *In-Vitro* Intraocular Lens (IOL) Evaluation**
**[*Huang, Zhang, Kang, Calogero, James, Ilev, Journal of Biomedical Optics, 16:126005, 2011*]**

The Optical Therapeutics and Medical Nanophotonics(OTMN) Laboratory of CDRH/OSEL's Division of Physics is responsible for providing and maintaining state-of-the-art knowledge and expertise in the biophotonics, nanobiophotonics, biomedical optics and medical laser field to assist the Center and Agency in evaluating new medical therapeutics devices that employ the latest minimally invasive optical technologies. The OTMN Laboratory also assists with the regulation of hazardous optical and laser radiation emissions potentially harmful to the general population, and with the latest measurement devices to evaluate new optical therapeutics products. OTMN Laboratory research and regulatory-related projects are focused in the following major areas:

1. Evaluating safety and effectiveness of new optical therapeutics technologies and devices concerning critical optical parameters and safety issues related to various medical therapeutic lasers, fiber-optic technologies, and new therapeutic monitoring and biosensing systems.

2. Developing standard test methods and test protocols for laboratory evaluation of fundamental optical radiation characteristics including spectral (from the ultraviolet to mid-infrared), timescale (from millisecond to femtosecond), and spatial parameters of key coherent (lasers) and non-coherent light sources, and also fiber-optic components used in recently developed optical therapeutics devices.

3. Studying working light-tissue interaction mechanisms for optimizing effectiveness and safety of new optical therapeutics devices, which includes studying light-tissue interaction mechanisms at cellular/intracellular levels using state-of-the-art nanobiosensing, nanoimaging and therapeutics techniques.

**Accomplishments**

*Novel Applications of Diagnostic X-rays in Activating a Clinical Photo-Agent Utilized in Photodynamic Therapies*

Photodynamic therapies (PDT) for cancer treatment with photo agents possess a high degree of specificity for broad spectrum of aggressive cancers and may be used where current conventional cancer treatments such as surgery, radiation therapy, and chemotherapy are limited. Porphyrin-based clinical photo-agents used for PDT become activated in killing cancers through visible light illumination. Unfortunately, due to a very shallow visible light penetration depth (~2mm) in tissues, the current PDT strategy has largely been restricted to the treatment of surface tumors, such as the melanomas. Dr. Darrell Tata and Dr. Erkinay Abliz of the Division of Physics OTMN Laboratory reported on the development of a novel non-invasive methodology utilizing "soft" energy diagnostic X-rays to indirectly activate a clinical photo-agent routinely utilized in PDT: Photofrin II (Photo II) through X ray-induced visible light emission from biological cell-sized phosphor particles. This concept was designed and tested in a human brain cancer cell line model. Positive findings reveal a shut-down (> 90% relative to controls) in the cellular metabolic activity of human brain cancer cells. The positive *in-vitro* bioeffect provides a platform for future scientific studies to provide useful endpoints for evaluating this optical therapeutic technique. The research was published in a paper titled, "Novel applications of diagnostic X-rays in activating a clinical photodynamic drug: Photofrin II through X-ray induced visible luminescence from 'rare-earth' formulated particles," in the November 2011 issue of the *Journal of X-ray Science and Technology*.

*Development of Standard Test Methods for Intraocolar Lens (IOL) Implant Characterization*

A novel approach for precise preclinical testing intraocular lens (IOL) implants was developed in the OSEL/OTMN Lab (Dr. Ilko K. Ilev and Robert James) in collaboration with ODE (Don Calogero) and Johns Hopkins University (Yong Huang, Dr. Kang Zhang and Dr. Jin Kang). It is based on a noncontact common-path Fourier domain optical coherence tomography (OCT) sensor method for evaluating the dioptric power of IOL implants by precisely measuring IOL surface profiles and surface radii. This method ensures noncontact, accurate, and objective measurement of IOL optical power under *in-situ* conditions. It provides CDRH and the device community with an alternative tool to evaluate IOL parameters with more precision, accuracy and speed, thereby enhancing the

safety and effectiveness of IOL implants. The new test method was published in the December 2011 issue of the *Journal of Biomedical Optics* and was included as an alternative technique for IOL testing specified in the International Standards for IOL quality evaluation.

## ***Software Laboratory*** (Division of Electrical and Software Engineering)

The scope of this laboratory's activities is to support CDRH pre-market and post-market software evaluation activities by establishing relevant in-house expertise and identifying, qualifying, quantifying, and communicating conformity assessment techniques and criteria which the Center can use to fulfill its mission.

Software is one of the most ubiquitous enabling technologies for many, if not most, classes of medical devices. Devices that incorporate this technology are inherently extremely complex and require that engineers must be able to skillfully peel back many layers of abstraction from the underlying mathematical, behavioral and physical models that govern device operation, to their hardware and software realizations, and down to the physical characteristics of component parts.

**Accomplishments**

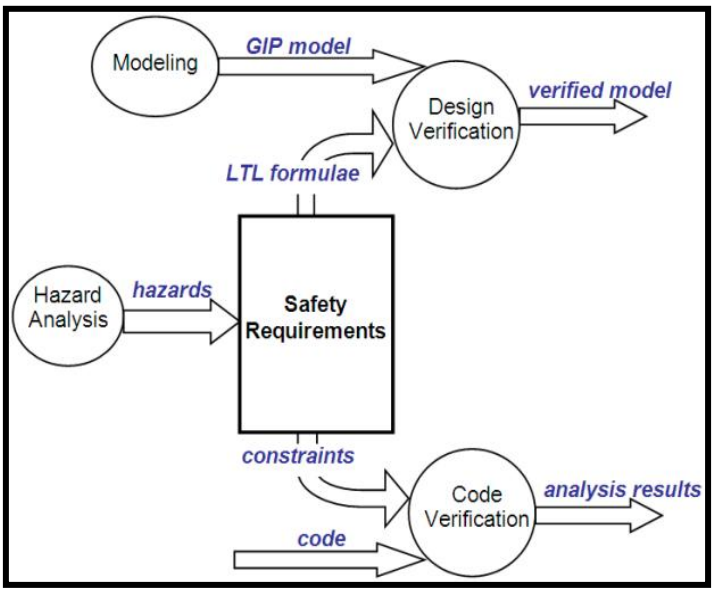
*Architecture Analysis*

All medical devices are built upon some form of architecture, be it hardware, software, or both. If the quality of the architecture is poor, it is likely that the dependability and performance of the device will be poor as well. DESE researchers are developing software architecture analysis methods that examine a devices code by deconstructing it into its constituent components. In this form, researchers can examine how they are organized and interconnected. If there are components that are overly dependent on a certain component or not even used, it can be a sign of current or future problems. The deconstruction process also facilitates analysis of design documentation. Components or interconnections identified from the code may not be addressed in the design documentation, indicating possible design specification problems.

*Software Safety Model for Infusion Pumps*

As the complexity of infusion pump design increases, so does the likelihood of its

Fig 9 Model-based engineering paradigm




failure. A significant number of these failures are due to a lack of principled engineering practices and associated safety issues. This is particularly true in the case of software based systems, where failure modes are difficult to predict. To address this issue, we are using formal methods to investigate a means of assessing the safe execution of infusion pump software.

The approach uses a model-based engineering development paradigm. In this methodology, software design models are derived from device safety requirements using executable modeling notations that simulate code execution. Once the models are encoded, they can be verified using rigorous mathematical methods. The verified models can then be used as unambiguous safety reference implementation standards against real world pumps.

## ***Solid Mechanics Laboratory*** (Division of Solid and Fluid Mechanics)

The goal of the Solid Mechanics Laboratory is to help CDRH understand the response of medical devices and their constituent materials to applied stress for both pre-market evaluations and post-market reported adverse events. The materials of interest include traditional engineering materials such as metals and polymers, but also extend to biological materials and those used in tissue engineered scaffolds. Though the spectrum of relevant materials is broad, common stress analysis principles can be applied to evaluate their behavior.

### Accomplishments

*The Effects of Vertebroplasty on Strain in Adjacent Intervertebral Discs and Vertebrae*

Vertebroplasty is currently the gold standard surgical treatment for painful vertebral compression fractures in the spine. This minimally invasive procedure consists of injecting poly(methyl methacrylate) (PMMA) bone cement into a fractured vertebral body to stabilize the fracture and relieve associated pain. However, it has been recently reported that approximately 25% of the patients experience subsequent fractures within one year of the treatment and the vertebrae adjacent to the cemented level represented a majority of these new fractures (Chosa et al. 2011). These data suggest that vertebroplasty may negatively impact spine biomechanics, reducing the overall safety of this device based on the need for additional surgeries to treat the new fractures. Therefore, DSFM researchers conducted a biomechanical study on female cadaveric spines to quantify the effects of vertebroplasty on strain in adjacent intervertebral discs (IVD) and vertebrae (VB). The results indicated that cyclic loading significantly increased strains in the vertebroplasty treated specimens when compared to a control group that did not undergo vertebroplasty. This increased compressive strain in the vertebroplasty group manifested locally as approximately 11% and 3% higher strains in the superior adjacent IVD and VB, respectively. These results provided insight into the mechanical impact of vertebroplasty on adjacent spinal tissues and are useful in clinical treatment strategies for women who suffer painful vertebral fractures. In addition, the methods developed in this study may be used pre-clinically in new device submissions to evaluate the safety of future vertebral augmentation devices.

## ***Toxicology and Biocompatibility Laboratory*** (Division of Biology)

This is an interconnected program of laboratory research, risk assessment, and standards development activities designed to provide a scientific basis for regulatory decision making in CDRH. Researchers evaluate the potential adverse effects of medical device materials and chemicals, including nano-sized particles, using *in vivo* and *in vitro* experimental models and approaches. Scientists use data to reduce uncertainties in assessing risks to patients exposed to physical and chemical exposures, and ultimately protect their health.

**Accomplishments**

*Risk assessment and Biocompatibility Methods Development*

***A) Computational Toxicology Modeling***

The biological safety of medical devices is typically assessed by conducting biocompatibility testing of an extract of the device or the device itself; however, there is growing interest in an alternate approach that involves characterizing the chemical composition of the device extract and conducting a risk assessment on the compounds identified in the extract. One limitation to the practical implementation of this chemical characterization/risk assessment approach is the lack of toxicity data for many compounds released from device materials. To address this need, the OSEL Laboratory of Toxicology and Biocompatibility is developing a new approach to assess the risk of these compounds in the absence of experimental data. This approach is based on the use of computational toxicology models, such as Quantitative Structure-Activity Relationship (QSAR) models and a modified version of the Threshold of Toxicological Concern (TTC) approach that has been used by other FDA Centers for many years. In 2011, a database of predicted toxicity values was developed for easy and user-friendly access by CDRH reviewers. This new method has already been used a number of times to assess the safety of medical devices and represents a promising approach for the biological evaluation of device materials.

### *B) Identification and validation of biomarkers of kidney damage*

Elevated serum creatinine and blood urea nitrogen (BUN) are typically used as indices of kidney injury; however, greater than 50% kidney function could be lost before elevations of these markers are detected. Since limitations exist with the use of these standard markers of kidney damage, and since early detection of even subtle renal injury is important for the implementation of renal protective strategies, there is a need to identify more sensitive biomarkers of altered renal function. Identification of new, more sensitive and clinically relevant biomarkers is consistent with the goals of the Critical Path Initiative to develop a "new product development toolkit," including new sensitive and clinically relevant biomarkers of safety and effectiveness. The specific goal of this effort is to bridge the gap between basic and applied science and product development so that the safety and effectiveness of new products can be demonstrated in faster time frames, with more certainty, and at lower costs.

Investigators in the OSEL Laboratory of Toxicology and Biocompatibility have made considerable progress to identify and validate biomarkers of kidney damage. Early work in this area involved an evaluation of the ability of new biomarkers to detect acute kidney injury (AKI) at earlier time points and at lower doses of nephrotoxicants than existing tests. A suite of these new biomarkers has undergone a qualification process at FDA for use in preclinical testing, a process in which our data was used in a meta-analysis. With this exciting development, OSEL investigators are now focused on the use of these biomarkers to address regulatory issues of concern for CDRH and other FDA product centers. In 2011, OSEL scientists, with the National Center of Toxicology Research (NCTR) and Harvard University collaborators, characterized the kidney-damaging effects of melamine and cyanuric acid, substances used in the intentional adulteration of pet food

and infant formula. With funding from the FDA's Office of the Chief Scientist challenge grant program, these investigators characterized the progression of kidney and heart damage in a rat model of hypertension and obesity. Given the prevalence of these conditions in the general population, use of this rat model may provide a more clinically relevant approach for the preclinical safety evaluation of some devices than the use of a normotensive (normal blood pressure) and lean animal.

*Nanotechnology and Nanotoxicology*

### *A) Distribution of intravenously-injected silver nanoparticles in pregnant mice and developing embryos*

Silver nanoparticles are used in FDA-regulated products, primarily for antimicrobial efficacy as catheter coatings and integrated into wound dressings. Although research investigating the *in vivo* biodistribution and toxicity of nanomaterials is increasing, very few studies have been conducted to evaluate nanomaterial translocation across the placenta and if adverse effects occur to the developing embryo. OSEL scientists, with collaborators from the FDA Center for Food Safety and Nutrition, George Washington University, Wright-Patterson AFB, and University of Florida, completed a study to evaluate the distribution of silver nanoparticles (10-nm and 50-nm diameter) in pregnant mice and embryos during gestation. The results showed an expected distribution of the nanoparticles primarily to the liver and spleen and that the particles do not appear to cross the placenta to the embryos in significant amounts. Electron microscopy, along with elemental analysis, indicated that the silver appears to be trapped in the mouse placenta and visceral yolk sac, preventing significant silver nanoparticles from reaching the embryo. The study resulted in a publication in 2011 in the journal *Nanotoxicology*.

Austin CA, Umbreit TH, Brown KM, Barber DS, Dair BJ, Francke-Carroll S, Feswick A, Saint-Louis MA, Hikawa H, Sieben KN and Goering PL. Distribution of silver nanoparticles in pregnant mice and developing embryos. *Nanotoxicology*, E-pub ahead of print, October 2011.

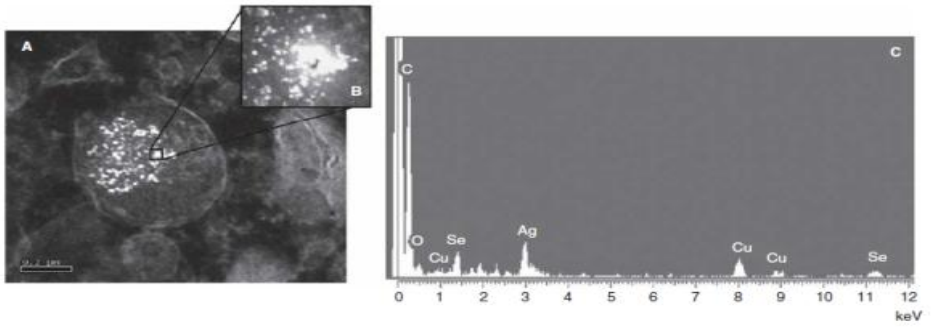



Fig 10 Transmission Electron Microscopy images (Panels A, B) and an Energy Dispersive X-ray Spectroscopy spectrum demonstrating silver in visceral yolk sac tissue on gestation day (GD) 10 of pregnancy following I.V. injection of a 35 µg Ag/mouse dose of silver nanoparticles (50 nm diameter) on GDs 7, 8, and 9.

### *B) Understanding the cellular interactions with materials surface nanotopographies*

Nanophase materials, such as nanofibers, nanotopographical surfaces, nanocoatings and nanocomposites are becoming very popular in the medical device industry to exploit their unique properties, such as better tissue integration, replacement and repair. However, significant basic and applied research is still needed to understand the risk associated with such nanoscale manipulations. OSEL scientists, with collaborators from NIST and NIDCR (NIH), have completed a study to understand how surface nanotopographies can influence the osteo-integration in medical devices, such as orthopedic and dental implants. The results showed convincing evidence that cells *in vitro* react with more sensitivity and specificity to nanostructured surfaces. This unique osteo-integration phenomenon is directly related to the nanoscale roughness provided by these nanotopographical surfaces.

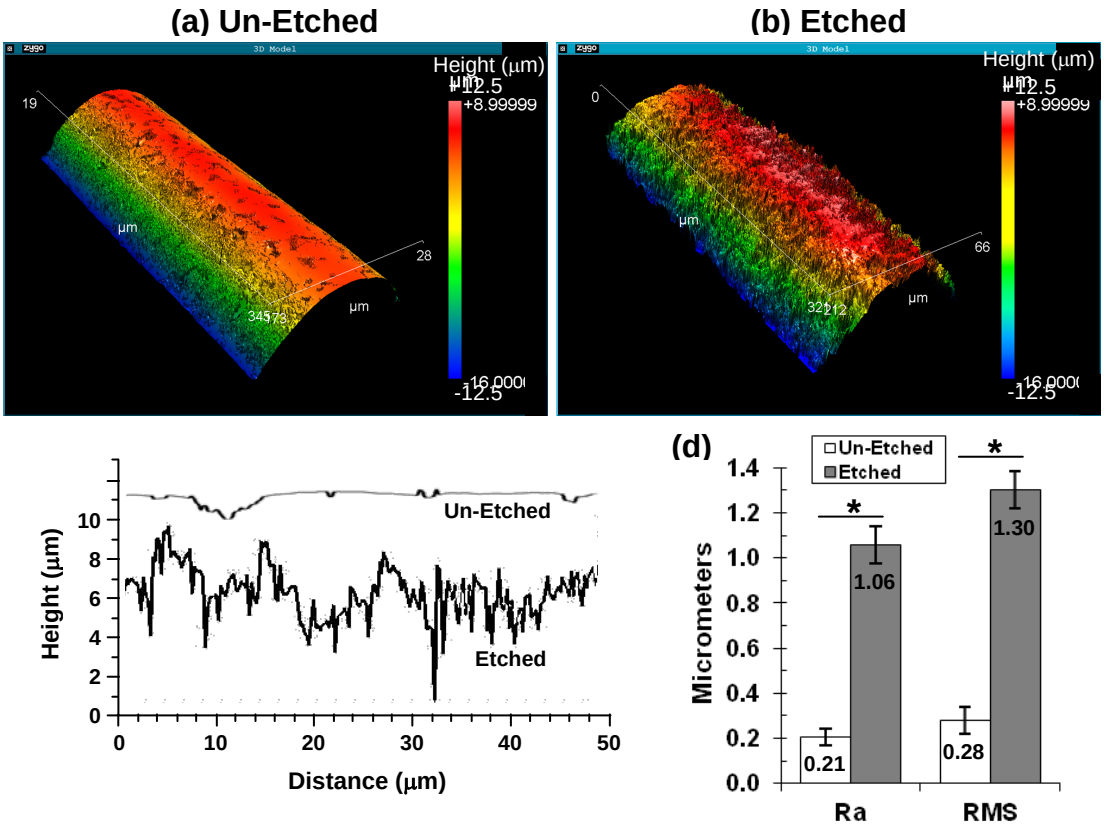



Fig 11 Surface roughness of etched surface were 5-times rougher as compared to un-etched surfaces (a,b). Representative surface profiles (c) and roughness parameters (d) of un-etched versus etched surfaces.

## ***Ultrasonics Laboratory*** (Division of Solid and Fluid Mechanics)

The Ultrasonics Laboratory continues to develop test methods and computational techniques for analyzing the safety and effectiveness of ultrasound ablation devices known as high intensity focused ultrasound (HIFU). Current accomplishments include developing two techniques for non-invasive measurement of high intensity fields to avoid sensor damage; formulating a coagulating blood mimicking fluid for use in HIFU *in vitro* phantoms; characterizing the occurrence of cavitation in a tissue mimicking material during HIFU exposures and assessing its effect on temperature measurements; determining the thermal effects when ultrasound is incident on bone; and utilizing computational techniques to evaluate the effects of nonlinear propagation characteristic of HIFU beams on acoustical and thermal measurement endpoints. Further, the laboratory has begun studies into the neurological effects of blast waves.

### Accomplishments

*Theoretical Framework for Quantitatively Estimating Ultrasound Beam Intensities using Infrared Thermography*

Determining intensity fields produced by high-intensity focused ultrasound (HIFU) devices is important in the development and pre-clinical testing of the devices, as well as in planning clinical procedures. Direct measurement can be challenging because the intense fields can cause sensor damage. An alternative approach for obtaining the intensity distribution is to infer it from the temperature field arising from the absorption of ultrasound energy in a phantom composed of tissue-mimicking material (TMM). Laboratory scientists have developed a theoretical model that uses infrared (IR) camera measurements of the temperature field as input data. Possible complications due to convection currents and heat diffusion are accounted for in the model. It was found that, when compared to the intensity field determined directly from acoustic propagation simulations, intensity profiles could be obtained from the simulated IR temperature data with an accuracy of better than 10%, at pre-focal, focal, and post-focal locations. These efforts will facilitate developing and characterizing an innovative and important surgical technology. A peer-review paper describing the methodology and results was published in 2011 in the *Journal of the Acoustical Society of America*.

# APPENDIX A – OSEL Publications

January 1, 2011 – December 31, 2011 (ordered by publication date)

## Division of Biology

Posnack NG, Lee NH, Brown R, Sarvazyan N. Gene expression profiling of DEHP-treated cardiomyocytes reveals potential causes of phthalate arrhythmogenicity. *Toxicology*, 279(1-3):54-64, **January11, 2011**.

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Yang MH, Sun S, Kostov Y, Rasooly A. A simple 96-well microfluidic chip combined with visual and densitometry detection for resource-poor point of care testing. *Sensors Actuators B Chem*, 153(1):176-81, **March 31, 2011**.

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Elespuru RK. Assessment of heritable genetic effects using new genetic tools and sentinels in an era of personalized medicine. *Environ Mol Mutagen*, 52(4):253-63, **May 2011**.

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Kent M, Platt SR, Rech RR, Eagleson JS, Howerth EW, Shoff M, Fuerst PA, Booton G, Visvesvara GS, Schatzberg SJ. Multisystemic infection with an Acanthamoeba sp in a dog. *J Am Vet Med Assoc*, 238(11):1476-81, **June 1, 2011**.

Potnis PA, Tesfamariam B, Wood SC. Induction of nicotinamide-adenine dinucleotide phosphate oxidase and apoptosis by biodegradable polymers in macrophages: implications for stents. *J Cardiovasc Pharmacol*, 57(6):712-20, **June 2011**.

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## Division of Chemistry and Materials Science

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## Division of Electrical and Software Engineering

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## Division of Solid and Fluid Mechanics

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# APPENDIX B – OSEL Presentations

January 1, 2011 – December 31, 2011 (ordered by date)

## Division of Biology

Tyner KM, Wokovich AM, Godar DE, Doub WH, Sadrieh N. The state of nano-sized titanium dioxide (TiO2) may affect sunscreen performance. *Int J Cosmet Sci.* 2011 Jun;33(3):234-44. doi: 10.1111/j.1468-2494.2010.00622.x. Epub 2011 **January 25, 2011**.

Fisher B. General principles and study designs for reproductive and developmental toxicology studies in small molecules; outcome, analysis, interpretation, and assessment (Seg 1, 2, and 3). Reproductive Toxicity (CDER Training Course), Silver Spring, MD, **March 3, 2011**.

Brown R. Categorization of compounds released from medical device materials into Cramer Classes using Toxtree software. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Brown RP, Hutchinson RW. Biodegradable materials for tissue engineering: applications and safety assessment. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Brown RP, Zhang Q, Barber DS, Komiyama AC, Goering PL. Plasma, urine, and tissue concentrations of hexavalent chromium associated acute kidney injury in Sprague Dawley rats. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Freeman A, Komiyarna A, Fazio J, Hamilla S, Dinesdurage H, Brown RP. Evaluation of the sensitivity of endpoints in the ISO 10993-11 systemic toxicity standard using positive control compounds. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Goering P. Opportunities for research and training in a federal regulatory agency. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Hoffmann D, Krishnamoorthy A, Ramirez Gonzalez V, Zhang Q, Goering PL, Brown RB, Waikar S, Vaidya VS. Urinary fibrinogen: A mechanistic translational biomarker for vascular dysfunction and inflammation in the kidney. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Hutchinson RW, Brown R, Cheeseman MA, Cammack J. The application of the threshold of toxicological concern concept to the preclinical safety assessment of non-pharmaceutical medical products, including medical devices and combination drug-device products. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Kulkarni P, Dinesdurage H, Brown RP. Rapid toxicity screening of polymeric materials using the Microtox Assay. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Zhang Q, Gamboa da Costa G, Beger R, Schnackenberg L, Sun J, Pence L, Bhattacharyya S, Jacob C, Brown RP, Goering PL. Urinary biomarker detection of melamine-cyanuric acid-induced kidney damage in rats. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Bagley B, Kulkarni P, Kueshner N, Brown R, Moilanen L. In silico mutagenicity prediction for leachable components of dental devices. Society of Toxicology Annual Meeting, **March 15, 2011**.

Betz M. My career as a bioengineer. Century High School Career Fair, Sykesville, MD, **March 18, 2011**.

Breger J, Fisher B, Isayeva I, Wang N. Encapsulation of islets in 'click' crosslinked alginate capsules and response to glucose challenge. Graduate Research Interaction Day, College Park, MD, **April 6-6, 2011**.

Breger J. Design of click hydrogels for cell encapsulation. Joyce Breger's Dissertation Defense, College Park, MD, **April 8, 2011**.

Wang NS, Breger J. Design of Click hydrogels for cell encapsulation (dissertation defense), **April 18, 2011**.

Goering P. Comparison of cytotoxic and inflammatory responses of silicone nano- and microparticles, and gold nanoparticles, in RAW 264.7 macrophages. Toxicology and Risk Assessment Conference 2011, Cincinnati, OH, **April 25-27, 2011**.

Shoff ME, Hitchins V. Important variables when using Acanthamoeba to evaluate contact lens solutions. Association for Research in Vision and Ophthalmology 2011 Annual Meeting, Ft. Lauderdale, FL, **May 1-5, 2011**.

Tu E, Shoff M, Joslin C. The addition of benzalkonium chloride to Moxifloxacin confers anti-acanthamoebal activity in an *in vitro* model. Association for Research in Vision and Ophthalmology 2011 Annual Meeting, Ft. Lauderdale, FL, **May 1-5, 2011**.

Clavet C, Lucas A, Chaput M, Gonzalez J, Hitchins V. Effects of contact lens, lens cases and "soil" on disinfection activity in multipurpose contact lens solution against Fusarium solani. American Society for Microbiology, 111th General Meeting, New Orleans, LA, **May 21-24, 2011**.

Lucas A. Environmental fate of Polyhexamethalene Biguannide. American Chemical Society, 5th Mid Atlantic Regional Meeting, College Park, MD, **May 21-24, 2011**.

Mu Y, Keene A, Weaver J, Fisher B. Development of a clinically relevant assay using dendritic cell surface markesr to predict human allergic potential of medical device materials. CYTO 2011, Baltimore, MD, **May 21-25, 2011**.

Haugen S, Hitchins, V. A method to quantitatively assess residual solid soils in reusable medical devices. Reprocessing of Reusable Medical Devices, Silver Spring, MD, **June 9, 2011**.

Goering PL. What we know and don't know about the bioeffects of nanomaterials: challenges in developing experimental approaches for safety assessment. CFSAN MOD Seminar Series I,

Beltsville, MD, **June 16, 2011**.

Yang XC. Elicitation of noninferiority margin. Joint Statistical Meetings 2011, Miami Beach, FL, **July 30 - August 4, 2011**.

Brown R, Kuldami P, Gordon E. Advancing computational toxicology modeling in the Center for Devices and Radiological Health. Workshop on Computer Methods for Medical Devices, **September 9, 2011**.

Kulkami P, Brown R.Validation of Toxtree software for predicting the carcinogencity of compounds released from medical device materials. Workshop on Computer Methods for Medical Devices, **September 9, 2011**.

Elespuru R. Genotoxicity assessment of nanomaterials: Update. Genetic Toxicology Association, **September 14, 2011**.

Rajani A. Miniaturization of a Salmonella typhimurium genotoxicity assay. Genetic Toxicology Association, **September 15, 2011**.

Coelho S, Ito S, Wakamatsu K, Miller S, Beer J, Hearing V. Distribution patterns of eumelanin and pheomelanin in human skin. International Pigment Cell Conference XXIst, Bordeaux, France, **September 21-24, 2011**.

Elespuru R. Analysis of the relative contribution of genetic, developmental and environmental causes to the origin of birth defects. International Congress of Human Genetics, 12th, Montreal, Canada, **October 11-15, 2011**.

Breger J, Fisher B, Isayeva I, Baeva L, Wang N. Optimization of the 'click' reaction for therapeutic cell encapsulation utilizing RIN-5F cells. Biomedical Engineering Society 2011 Annual Meeting, Hartford, CT, **October 12-15, 2011**.

Hitchins V. FDA's perspective of "clean" for reprocessing medical devices. Association for the Advancement of Medical Instrumentation and FDA, AAMI/FDA Medical Device Reprocessing Summit, **October 12, 2011**.

Choi J, Reipa V, Hitchins V, Goering P, Malinauskas R. Human blood biocompatibility of silver nanoparticles. AIChE (American Institute of Chemical Engineers), Annual Meeting of Chemical Engineers, **October 16, 2011**.

Brown R. The basic elements of biocompatibility studies. FDA, Basic Nonclinical Bioresearch Monitoring, **October 17, 2011**.

Elespuru RK, Rajani A. Evolution of colon cancer is reflected in DNA mutational sequence profiles. Environmental Mutagen Society 42nd Annual Meeting, Montreal, Canada, **October 15-19, 2011**.

Elespuru RK, Rajani A. Miniaturization of a Salmonella Typhimurium genotoxicity assay. Environmental Mutagen Society 42nd Annual Meeting, Montreal, Canada, **October 15-19, 2011**.

Fisher B. (Developmental) toxicity testing in the 21st century: Leveraging for alternative models.

Middle Atlantic Reproductive and Teragology Association (MARTA), 2011 MARTA Meeting, **October 20, 2011**.

Brown R. Biological effects of cobalt and chromium released from CoCr alloy: Research activities in the CDRH/OSEL Laboratory of Toxicology and Biocompatibility, National Institute of Standards and Technology, Failure of Metal-on-Metal Hip Implants Meeting, **November 17, 2011**.

Wood S. Development of anti-Ebola MHC tetramers as a surrogate marker to evaluate cell-mediated immunity in vaccines:a computational approach, NIAID Research update, **November 21, 2011**.

## Division of Chemistry and Materials Science

Guo J, Cho S, Luu HD. Determination of Bisphenol-A Compounds Leachable from Polycarbonate- and Polysulfone-based Hemodialyzers. Society of Toxicology 50th Annual Meeting, Washington, DC, **March 6-10, 2011**.

Berger J, Fisher B, Isayeva I, Wang N. Encapsulation of Islets In 'Click' Crosslinked Alginate Capsules and Response to Glucose Challenge. Graduate Research Interaction Day, College Park, MD, **April 6-6, 2011**.

Patwardhan DV. Biomaterials- A FDA Perspective. Society for Biomaterials Annual Meeting and Exposition 2011, Orlando, FL, **April 13-16, 2011**.

Guo J, Saylor DM, Patwardan DV. The Impact of Sex-Based Differences in atherosclerotic Plaque on Drug Release from Drug Eluting Stents (DES). Controlled Release Society 38th Annual Meeting and Exposition, National Harbor, MD, **July 30-August 3, 2011**.

McDermott MK. Nitroxide antioxidants for the prevention of oxidation in crosslinked ultra-high molecular weight polyethylene. Implant Research Center, 5th UHMWPE International Meeting, **September 22, 2011**.

Breger J, Fisher B, Isayeva I, Baeva L, Wang N. Optimization of the 'Click' Reaction for Therapeutic Cell Encapsulation Utilizing RIN-5F Cells. Biomedical Engineering Society 2011 Annual Meeting, Hartford, CT, **October 12-15, 2011**.

Takmakov P. In-vitro system to investigate causes of long-term implant failure. USUHS, Neuroscience Program Poster Session, **December 1, 2011**.

## Division of Electrical and Software Engineering

Fitzgerald B. Utility of shareable distributed mega-computing platform for storing, managing, and analyzing extreme-scale observational data. DIA/FDA CDER/CBER Computational Science Annual Meeting 2011, Arlington, VA, **March 14-15, 2011**.

Sudarsan SD. Signal detection using text mining in large document repositories. George Mason University Department of Computer Science Grand Seminar, Fairfax, VA, **April 12, 2011**.

Silberberg J. Electromagnetic compatibility (APEMC 2011), edition 4 of IEC 60601-1-2. The Korean Institute of Electromagnetic Engineering and The Korean Institute of Electromagnetic Engineering and Science (KIEES), 2011 Asia-Pacific Symposium & Exhibition, **May 18, 2011**.

Ganesan D, Lindvall M, Cleaveland R, Jetley R, Jones P, Zhang Y. Generic safety requirements for developing safe insulin pump software. IEEE/IFIP Conference on Software Architecture 9, Boulder, CO, **June 20-24, 2011**.

Silberberg J. Edition 4 of IEC 60601-1-2, Japan Society of Medical and Biological Engineering, Study group for Medical and Welfare EMC, the 2nd meeting, **September 3, 2011**.

Silberberg J. Edition 4 of IEC 60601-1-2 (Medical electrical equipment ), Swedish Society for Medical Engineering and Physics, Medicinteknikdagarna Conference, **October 11, 2011**.

Jones PL. AAMI, Safety Assurance Cases for Medical Devices, Thoughts on assurance cases, **October 29, 2011**.

## Division of Imaging and Applied Mathematics

Abboud S, Lee K, Vinehout K, Paquerault S, Kyprianou IS. A comparison of methods for estimating the line spread function of a CT imaging system. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Brunner CC, Renger B, Hoeschen C, Kyprianou IS. Investigation of a method to estimate the MTF and NPS of CT towards creating an international standard. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Chen W, Petrick N, Sahiner B. Assessment of updated CAD without a new reader study: effect of calibration of computer output on the computer-aided reader performance in CADx. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Paquerault S, Yarusso LM, Sahiner B, Kettermann A, Hadjiiski LM, Chan HP. Analysis of the number of distinct findings obtained by multiple readers in an MRMC study: When do findings obtained from the addition of new readers become redundant, or otherwise negligible?. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Petrick N, Zeng R, Gavrielides MA, Kim HJG McNitt-Gray MF, Clunie D, Borradaile K, Ford R, Fenimore C, Lu ZQJ, Zhao B, Buckler AJ. Evaluation of 1D, 2D and 3D nodule size estimation by radiologists for spherical and non-spherical nodules through CT thoracic phantom imaging. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Rupcich F, Schmidt TG, Kyprianou I, Badal A. Energy deposition in the breast during CT scanning: quantification and implications for dose reduction. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Sahiner B, Petrick N, Paquerault S, Chen W, Nguyen T. Agreement between two versions of a CADx system: a simulation study. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Wang S, Summers RM, Petrick N, Van Uitert RL, Periaswamy S. 3D supine and prone colon registration for computed tomographic colonography scans based on graph matching. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Zeng R, Myers KJ. Task-based comparative study of iterative image reconstruction methods for limited-angle x-ray tomography. Medical Imaging 2011, Lake Buena Vista, FL, **February 12-17, 2011**.

Wear KA, Maruvada S, Gammell PM, Liu Y, Harris GR. Comparison of hydrophone phase response obtained via time domain spectroscopy measurement and Hilbert Transformation. Therapeutic Ultrasound, 11th International Symposium on, New York, NY, **April 11-13, 2011**.

Wear KA. Improvements in measurements of BUA and SOS in human calcaneus. International Symposium on Ultrasonic Imaging and Tissue Characterization, Wear KA, **June 13, 2011**.

Sharma D, Badal A, Fang Y, Badano A. HybridMANTIS: a novel method for faster Monte Carlo simulation of x-ray imaging detectors. American Association of Physicists in Medicine 2011, **July 1, 2011**.

Chen W. A Semi-parametric Roc approach to assessing biomarkers subject to a measurement error and limit of detection. Joint Statistical Meetings 2011, Miami Beach, FL, **July 30-August 4, 2011**.

Samuelson F, Brown D. Application of Cover's Theorem to the evaluation of the performance of CI observers. International Neural Network Society and Institute of Electrical and Electronics Engineers Computational Intelligence Society, 2011 International Joint Conference on Neural Networks, **July 31, 2011**.

Sechopoulos I, Abboud S, Ali E, Badal A, Badano A, Feng SSJ, Kyprianou I, McNitt-Gray M, Samei E, Turner A. Introduction to the AAPM Task Group No. 195 - Monte Carlo reference data sets for imaging research. American Association for Physicists in Medicine 2011 Annual Meeting, Vancouver, Canada, **July 31-August 4, 2011**.

Sharma D, Badal A, Fang Y, Badano A. Hybridmantis: A novel method for faster Monte Carlo simulation of X-ray imaging detectors. American Association for Physicists in Medicine 2011 Annual Meeting, Vancouver, Canada, **July 31-August 4, 2011**.

Badal A, Badano A. Fast and accurate estimation of organ doses in medical imaging using a GPU-accelerated Monte Carlo Simulation Code. American Association for Physicists in Medicine 2011 Annual Meeting, Vancouver, Canada, **July 31-August 4, 2011**.

Badano A, Kumcu A, Platisa L, Platisa M, Vansteenkiste E, Deblaere K, Philips W. Trends in reader behavior for a signal detection task in multi- and single-slice volumetric images. Medical Image Perception Society XIV Conference, Dublin, Ireland, **August 9-12, 2011**.

Gallas B, Gavrielides M. Reader studies of concordance, a generalized AUC. Medical Image Perception Conference, **August 9, 2011**.

Gallas BD, Badano A, Platisa L, Kumcu A, Platisa M, Vnsteenkiste E, Deblaere K, Philips W. Model and human observer studies in volumetric images for detection tasks with varying complexity. Medical Imaging 2011, Dublin, Ireland, **August 9-12, 2011**.

Gu S, Badal-Soler A, Kyprianou I. Digital high-resolution heart phantom. Validation of Computer Methods for Medical Devices, Silver Spring, MD, **September 7-9, 2011**.

Platisa L, Marchessoux C, Kimpe T, Vansteenkiste E, Philipsa W. Channelized hotelling observers for signal detection in stack-mode reading of volumetric images. ICIP 2011, **September 14, 2011**.

Gallas BD, Pinsky P. Enriched designs for assessing predictive performance – analysis of bias and variance. FDA/Industry Statistics Workshop 2011, Washington, DC, **September 19-21, 2011**.

Sze C, Shama D, Vivek, Badano A. Depth-of-interaction estimates in a micro-columnar scintillator structure from optical transport Monte Carlo MANTIS simulations. IEEE, Institute of Electrical and Electronics Engineers, Nuclear Science Symposium and Medical Imaging Conference 2011, **October 23, 2011**.

Sahiner B. Computer-assisted decision systems in radiology – the hope, the hype and the hard truth: Applications II: Emerging applications, Radiological Society of North America 2011, **November 26, 2011**.

Cho H, Hadjiiski L, Sahiner B, Chan H, Paramugal C, Helvie M, Nees A. Interactive content-based image retrieval (CBIR) computer-aided diagnosis (CADx) system for ultrasound breast masses using relevance feedback. Radiological Society of North America 2011, **November 26, 2011**.

Petrick N. Challenges in breast imaging - evaluation of current and emerging technologies in breast imaging, Radiological Society of North America 2011 Refresher Course, **November 27, 2011**.

Garra BS, DeStigter KK, Lawton K, Rielly M, Noordvyk A. Computerized reporting & outcomes tracking of remotely reported examinations in a low resourced rural environment: requirements and practical solutions, Radiological Society of North American 2011, **November 27, 2011**.

Gavrielides M, Zeng R, Sahiner B, Myers K, Petrick N. Effect of overlapping reconstruction on lung nodule volume estimation with multi-detector CT. RSNA 2011, Chicago, IL, **November 27-27, 2011**.

Petrick N, Linguraru MG, Sandberg J, Summers RM. Hepatic volumetric nomograms from automated analysis of abdominal CT. RSNA 2011, Chicago, IL, **November 27 - December 2, 2011**.

Rupich F, Kyprianou I, Badal A, Gilat T. A technique for comparing CT acquisition methods [intended to reduce patient dose] with respect to breast dose and a task-based image quality metric. RSNA 2011, Chicago, IL, **November 27-27, 2011**.

Zbijeqski W, Badal-Soler A, Kyprianou I, Siewerdsen JH. Scatter properties of compact geometry cone-beam CT systems. RSNA 2011, Chicago, IL, **November 27-27, 2011**.

## Division of Physics

Agrawal A, Connors M, Pfefer J, Chang R, Stafford C, Hwang J. System-independent assessment of OCT axial resolution with a "bar chart" phantom. SPIE Photonics West 2011, San Francisco, CA, **January 22-27, 2011**.

Kim DH, Ilev IK, Han YG. A thickness measurement method for biological samples using lensed-fiber sensors. SPIE Photonics West 2011, San Francisco, CA, **January 22-27, 2011**.

Wang Q, Pfefer J, Le D, Ramella-Roman J. Broadband UV-Vis optical property measurement in layered turbid media. SPIE Photonics West 2011, San Francisco, CA, **January 22-27, 2011**.

Witters D. Considerations for RFID and wireless technology in healthcare. RFID & RTLS in Healthcare Symposium, Orlando, FL, **February 20, 2011**.

Strauss DG. Novel ECG-MRI methods to improve patient selection for ICDs. Magnetic and Electrical Technologies Meeting, Maastricht, Netherlands, **February 24-25, 2011**.

Ilev IK. Advanced multifunctional imaging and sensing approaches in biophotonics and nanobiophotonics. George Washington University Seminar, Washington, DC, **March 4, 2011**.

Witters D. Safety and effectiveness for wireless technology in healthcare. Symposium on Medical Information and Communications Technology 2011, Yokohama City, Japan, **March 4, 2011.**

Kainz W. RF hotspots in multi transmit RF MR coils. Thermal Workshop on RF Hotspots, Zurich, Switzerland, **March 21-22, 2011**.

Johnson LJ, Cohen E, Ilg D, Klein R, Skeath P, Scribner DA. A novel 81,000 electrode spike recording array using a trans-impedance amplifier-based imaging chip. Dr. Jack Judy, DARPA BAA, **April 8, 2011**.

Cohen E. Quantitative measurement of retinal damage in real-time under a stimulus electrode using OCT, University of Maryland, Metropolitan Biophotonics Symposium 2011, **April 15, 2011**.

Le D, Wang Q, Ramella-Roman J, Pfefer J. Evaluation of a fiber-optic system for broadband UV-Vis optical property measurement in layered tissue. Metropolitan Biophotonics Symposium, 3rd Annual, University of Maryland, College Park, MD, **April 16, 2011**.

Aloraefy M, Sapsford K, Roman JR, Pfefer J. Implementation and validation of a FRET-based biosensor for continuous glucose sensing. Metropolitan Biophotonics Symposium 2011, College Park, MD, **April 16, 2011**.

Ilev IK. All-in-one imaging and sensing approaches in biophotonics. University of Maryland, College Park, (Invited talk at Metropolitan Biophotonics Symposium 2011), **April 16, 2011**.

Cohen E, Agrawal A, Pfefer JT, Connors M, Hansen B, Charkhkar H. OCT imaging of retinal damage in real-time under a stimulus electrode. Association for Research in Vision and Ophthalmology, ARVO 2011, **May 1, 2011**.

Cohen E. OCT imaging of retinal damage in real-time under a stimulus electrode. NEI/FDA, 2011 NEI/FDA Endpoints Symposium, **May 6, 2011**.

Pantchenko O. To develop a method for testing electromagnetic compatibility between implantable neurostimulators and low frequency radio frequency identification emitters. Advancement to Candidacy Examination, Santa Cruz, CA, **May 16-16, 2011**.

Chou CK, Angelone LM, Guy AW. Electrically conductive objects in contact with biological tissues during RF exposure. Bioelectromagnetics Society 33rd Annual Meeting, Nova Scotia, Canada, **June 12-17, 2011**.

Witters D. A roundtable discussion: issues and challenges in it network management. Association for the Advancement of Medical Instrumentation Meeting 2011, **June 15-15, 2011**.

Soltysik D, Thomasson D, Rajan S, Gonzalez-Castillo J, DiCamillo P. Head-repositioning does not reduce the reproducibility of block-design motor fMRI activation. Human Brain Mapping 2011, Quebec City, Canada, **June 26-30, 2011**.

Strauss D. Novel methods to improve patient selection for ICDs and CRT. Karolinska University Hospital, ,**August 11, 2011**.

Gray R. Cardiovascular device development and collaborations. University of Virginia-FDA Medical Device Technology Innovation Partnerships, **September 26, 2011**.

Woolsey N, Ilev I, Calhoun W. Characterizing light polarization effects through corneal tissue using lasers. Biomedical Engineering Society 2011 Annual Meeting, Hartford, CT, **October 12-15, 2011**.

Mewton N, Strauss DG, Liu CY, Marchlinsky FE, Tereshchenko L, Killian T, Cox C, Verrier RL, Nearing B, Rizzi P, Wu KC, Spooner P, Lim JAC. Myocardial scar and fibrosis in patients at risk for sudden cardiac death as defined by 12-lead ECG QRS score and QRS-T angle. American Heart Association Scientific Sessions 2011, Orlando, FL, **November 12, 2011**.

Strauss D, Mewton N, Verrier R, Nearing B, Killian T, Marchlinsky F, Tereschenko L, Cox C, Spooner P. Screening entire health system ECG databases to identify patients with abnormal myocardial substrate at potential increased risk for arrhythmic death. American Heart Association, AHA Scientific Sessions 2011, **November 12, 2011**.

Strauss DG, Selvester RH, Wagner GS, Loring Z, Gerstenblith G, Weiss RG, Wu KC. Scar size and etiology of right vs. left bundle branch block: insights from cardiac magnetic resonance and alcohol septal ablation. American Heart Association Scientific Sessions 2011, Orlando, FL, **November 12, 2011**.

## Division of Solid and Fluid Mechanics

Herbertson L. Medical Devices Regulations, Penn State University, **March 3, 2011**.

Stewart, Hariharan, Paterson, Burgreen, Reddy, Day, Giarra, Manning, Deutsch, Myers, Berman, Malinauskas. Results of the FDA interlaboratory computational study in a nozzle with a sudden contraction and conical diffuser. 2nd International Conference on Computational and Mathematical Biomedical Engineering – CMBE2011, Fairfax, VA, **March 30-April 21, 2011**. (Extended abstract published in 2nd International Conference on Computational & Mathematical Biomedical Engineering (2011), P. Nithiarasu and R. Löhner (eds), Swansea University, UK, pp. 391-394).

Liu Y, Maruvada S, Herman BA, Harris GR. Temperature-dependent physical properties of a HIFU blood-mimicking fluid, 11th International Symposium on Therapeutic Ultrasound, **April 1, 2011**.

Di Prima Ma. Material and Design Considerations for Orthopedic Devices. University of Texas at Dallas Department of Mechanical Engineering, Seminar, **April 4, 2011**.

Soneson JE. Practical limits of the parabolic approximation for focused ultrasound beams. International Symposium on Therapeutic Ultrasound 2011, **April 11, 2011**.

Liu Y, Maruvada S, Herman B, Harris G. Temperature-dependent physical properties of egg white for HIFU applications. Therapeutic Ultrasound, 11th International Symposium on, New York, NY, **April 11-13, 2011**.

Myers M, Giridhar D. Quantitative transducer characterization using infrared thermography. therapeutic ultrasound, 11th International Symposium on, New York, NY, **April 11-13, 2011**.

Vesnovsky O., Farrokh B, Topoleski LDT, Grossman LW. The Influence of machining on micro-hardness properties of CoCrMo alloys. Transactions of the Society for Biomaterials, **April 13, 2011**.

Wear KA, Maruvada S, Gammell PM, Liu Y, Harris GR.Time domain spectrometry for measurement of the hydrophone phase response. 55th Annual Convention of the American Institute of Ultrasound in Medicine, New York, NY, **April 2011**.

Maruvada S, Liu Y, Herman BA, Harris GR. Evaluation of a tissue-mimicking material during HIFU exposure. Advanced Metrology for Ultrasound in Medicine conference, **May 12, 2011**.

Hariharan P, Giridhar D, Robinson RA, Myers MR. Techniques for performing quantitative measurements of HIFU intensity distributions noninvasively. Acoustical Society of America, 161st meeting, **May 23, 2011**.

Duraiswamy N**,** Weaver JD, Retta SM, Stewart SFC, Wu C. Evaluating soft tissue leaflet stresses in non-circularly deployed heart valves. ASAIO Annual Conference, Washington, DC, **June 10, 2011**.

Herbertson, Kameneva, Olia, Daly, Smith, Noatch, Malinauskas. Interlaboratory study of flow-induced hemolysis using the FDA benchmark nozzle model. ASAIO annual conference, Washington, DC. Abstract: *ASAIO J*, 57(2):95, **June 10-12, 2011**.

Lu, Chiang, Malinauskas. Presentation at ASAIO (by Q. Lu). Anticoagulation of blood from different species for potential use in *in vitro* thrombosis tests of medical devices. ASAIO annual conference, Washington, DC., Abstract: *ASAIO J*, 57(2):111, **June 10-12, 2011**.

Malinauskas, Giarra, Day, Burgreen, Herbertson, Stewart. Validation of CFD techniques used to evaluate medical devices: Interlaboratory study #2 – FDA benchmark blood pump model. American Society for Artificial Internal Organs - ASAIO annual conference, Washington, DC. Abstract: *ASAIO J*, 57(2):93, **June 10-12, 2011**.

Hariharan, Giarra, Reddy, Day, Manning, Deutsch, Myers, Stewart, Burgreen, Paterson, Malinauskas. Multi-laboratory uncertainty analysis of PIV-measured flow quantities relevant to blood damage in the FDA nozzle model. ASME 2011 Summer Bioengineering Conference Farmington, PA, **June 22-25, 2011**. (Extended abstract published in proceedings.)

Gammell PM, Liu Y, Maruvada S, Wear KA, Harris GR. Phase measurement with a simplified ultrasonic time delay spectrometry system. 38th Annual Review of Progress in Quantitative Nondestructive Evaluation, University of Vermont, Burlington, Vermont, **July 2011**.

Gammell PM, Liu Y, Maruvada S, Harris GR. Detector module for a simplified ultrasonic time delay spectrometry system. 38th Annual Review of Progress in Quantitative Nondestructive Evaluation (QNDE), University of Vermont, Burlington, Vermont, **July 2011**.

McCabe J, Burton E, Morgan A, Budinich C, Woodard G, Liu YB, Myers M, Moratz C. Mouse blood-brain barrier integrity and neuro-immune sequelae from non-impact pressure alterations by high-intensity focused ultrasound. Neurotrauma Symposium, 29th Annual National, Hollywood Beach, FL, **July 10-13, 2011**.

Moratz C, Burton E, Morgan A, Schrot J, McCarron R, Liu YB, Myers M, McCabe J. Rat blood-brain barrier disruption and neuroimmune alterations from non-impact pressure alterations by high-intensity focused ultrasound and blast overpressure shock tube exposure. Neurotrauma Symposium, 29th Annual National, Hollywood Beach, FL, **July 10-13, 2011**.

Dreher MR , Sharma1 KV, Woods DL, Reddy G, Donahue D, Levy E, Karanian JW, Chiesa OA, Pritchard W, Tang Y, Willis S, Lewis AL, Wood BJ. Drug tissue penetration and coverage from doxorubicin eluting radiopaque embolization beads, Controlled Release Society, 38th Annual Meeting and Exposition, **August 1, 2011**.

Marrey R, Gong XY, Nagaraja S, Dreher M, Weaver J, Gupta S, Rebelo N. Computational considerations for stent non-radial fatigue. FDA/NHLBI/NSF Fourth Annual Workshop on Computer Methods for Medical Devices, Silver Spring, MD, **September 2011**.

Lao C. A predictive model for cancer and non- cancer mortality in beagle dog study. FDA/Industry Statistics Workshop 2011, Washington, DC, **September 19-21, 2011**.

Woods T. FDA safety guidelines for medical devices in the MR environment. Biomedizinische Technik, the German Biomedical Conference, Technical Committee on MR Technology in Medicine, **September 28, 2011**.

Liu C, Chinnakonda M, Duraiswamy N. Fluid-structure interaction analysis of a prosthetic aortic valve using abaqus/explicit smoothed particle hydrodynamics. ASME Frontiers in Medical Devices Conference, Irvine, California, **September 2011**.

Chen C, Khismatullin DB, Liu Y, Maruvada S, Myers M. *Ex Vivo* Study of ethanol enhanced cavitation activity in tissue exposed to high intensity focused ultrasound. Biomedical Engineering Society 2011 Annual Meeting, Hartford, CT, **October 12-15, 2011**.

Choi J, Reipa V, Goering P, Hitchins V, Malinauskas R. Physicochemical characterization and *in vitro* hemolysis evaluation of silver nanoparticles. AIChE (American Institute of Chemical Engineers) conference, Minneapolis, MN, **October 16-21, 2011**.

Harris GR. Piezoelectric polymer hydrophones and the regulation of medical diagnostic ultrasound devices by the U.S. Food and Drug Administration. (Invited), Joint Meeting of Washington DC Chapter of Acoustical Society of America and The Catholic University of America School of Engineering, Washington, DC, **November, 2011**.

Dornish M, Kaplan D. Tissue engineered medical product standardization – the ASTM International Committee F04. TERMIS-NA (Tissue Engineering and Regenerative Medicine International Society - North America) Annual Meeting. Houston, TX, **December 11, 2011**.

Ferlin KM, Fisher JP, Kaplan DS, Centrifugation adhesion assay for characterizing the phenotype of chondrocytes. TERMIS-NA (Tissue Engineering and Regenerative Medicine International Society - North America) Annual Meeting. Houston, TX, **December 11, 2011**.

## Office of the Director

Malghan S. Howard University, School of Pharmacy, Graduate school seminar- Nanotechnology regulatory science challenges and research directions, **October 21, 2011**.

Malghan S. NIST-ANSI, International Workshop on Challenges to increased use of documentary nanotechnology standards, Nanotechnology Standards: Regulatory Science Applications at FDA, **December 13, 2011**.

# APPENDIX C – OSEL Academic Affiliations

January 1, 2011 – December 31, 2011

| | |
|---|---|
| **Agrawal, Anant** | Virginia State University<br>Department of Mathematics<br>and Computer Science<br>Member, Master's thesis committee |
| **Badano, Aldo, Ph.D.** | University of Maryland, College Park<br>Adjunct Prof<br>Fischell Department of Bioengineering |
| **Bassen, Howard I**. | University of Maryland<br>College of Engineering<br>Lecturer |
| **Dair, Benita J., Ph.D.** | University of Maryland<br>Fischell Department of Bioengineering<br>Adjunct Professor |
| **Di Prima, Matthew, Ph.D.** | University of Texas at Dallas<br>School of Engineering and Computer Science<br>Visiting Researcher |
| **Dreher, Maureen, Ph.D.** | University of Maryland<br>Fischell Department of Bioengineering<br>Adjunct Professor |
| **Goering, Peter L., Ph.D.** | University of Maryland<br>School of Medicine<br>Baltimore, MD<br>Adjunct Professor<br><br>The George Washington University<br>Department of Biological Sciences<br>Washington, DC<br>Adjunct Associate Professor |
| **Gray, Richard, Ph.D.** | University of Alabama at Birmingham |

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|---|---|
| | Department of Biomedical Engineering<br>Associate Professor<br><br>University of Alabama at Birmingham<br>Center for Glial Biology in Medicine<br>Scientist<br><br>Vanderbilt University<br>Department of Biomedical Engineering<br>Adjunct Associate Professor<br><br>Vanderbilt University<br>Vanderbilt Institute for Integrative Biosystems Research and Education<br>External Associate |
| **Ilev, Ilko, Ph.D.** | University of Maryland<br>Fischell Department of Bioengineering<br>Adjunct Professor<br><br>George Washington University<br>Department of Electrical and Computer Engineering<br>Doctoral Thesis Committee |
| **Jetley, Raoul, Ph.D.** | University of Arkansas at Little Rock<br>Department of Computer Science<br>Adjunct Faculty Member, and<br>Member, Doctoral Dissertation Committee |
| **Kainz Wolfgang, Ph.D.** | University of Houston<br>Department of Electrical and Computer Engineering<br>Member, Doctoral thesis committee |
| **Krauthamer, Victor, Ph.D.** | Uniformed Services University of the Health Sciences<br>Department of Anatomy, Physiology, and Genetics<br>Adjunct Assistant Professor<br><br>American University<br>Department of Biology<br>Adjunct Associate Professor<br><br>George Washington University<br>Department of Biology |

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|---|---|
| | Adjunct Associate Professor |
| **Mehrabi, Ali, Ph.D.** | Strayer University<br>Adjunct professor<br>Undergraduate Math<br><br>Stratford University<br>Adjunct professor<br>Graduate and Undergraduate courses in Networking, CIS, MIS, and Telecommunications |
| **Myers, Kyle J., Ph.D.** | University of Arizona<br>Optical Sciences Center<br>Adjunct Professor<br><br>Georgetown University Medical<br>Department of Radiology<br>Adjunct Associate Professor |
| **Myklebust, Joel, Ph.D.** | George Washington University<br>Department of Electrical and Computer Engineering<br>Adjunct Assistant Professor |
| **Nagaraja, Srinidhi, Ph.D.** | University of Maryland<br>Fischell Department of Bioengineering<br>Adjunct Professor |
| **Petrick, Nicholas, Ph.D.** | University of Michigan<br>Medicine School<br>Adjunct, Research Assistant Professor |
| **Pfefer, T. Josh, Ph.D.** | University of Maryland<br>Department of Chemical and Biomolecular Engineering<br>Doctoral thesis committee |
| **Rajan, Sunder, Ph.D.** | Georgetown University Medical<br>Department of Radiology<br>Adjunct Associate Professor |

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|---|---|
| **Sapsford, Kim E., Ph.D.** | University of Maryland<br>Department of Bioengineering<br>Adjunct faculty |
| **Waynant, Ronald W., Ph.D.** | Catholic University of America<br>Electrical Engineering Department<br>Adjunct Associate Professor<br><br>Uniformed Services University<br>of the Health Sciences<br>Adjunct Professor |
| **Wear, Keith A., Ph.D.** | Georgetown University<br>Radiology Department<br>Adjunct Professor<br><br>Henry M. Jackson Foundation<br>for the Advancement of Military Medicine<br>Guest Scientist |
| **Weininger, Sandy, Ph.D.** | Drexel University<br>Lecturer and course/program developer |

# APPENDIX D – OSEL Science Sharing Seminars

January 24, 2011 – October 17, 2011

### *January 24*

*Contact Lens-Related Eye Infections: How We Got Here, Where We Are Going*
Megan Shoff, Ph.D. (OSEL)

### *March 7*

*Tissue Imaging in Pathology: Quantitative Analysis of Biomarker Expression*
Mario Gavrielides, Ph.D., OSEL

### *March 8*

*Computational Modeling in Device Regulation: Prospects for the Future*
Sandy Stewart, Ph.D., OSEL

### *March 21*

*Tissue Imaging in Pathology: The Challenge of Color Reproduction from Acquisition to Display*
Wei-Chung Cheng, Ph.D. (OSEL)

### *April 4*

*Electrical Activity and Wave Propagation in the Heart, with Application to Defibrillators and Pacemakers*
Richard A. Gray, Ph.D. (OSEL)

### *April 18*

*Postmarket Surveillance Using Administrative Billing Data to Evaluate the Safety and Effectiveness of Uro-Gynecological Mesh*
Cara Krulewitch, CNM Ph.D., FACNM (OSB)

### *May 2*

*The Use of Quantitative Decision Analysis to Assess the Optimal Time to Remove a Temporary Device: the IVC Filter Case*
Telba Irony, Ph.D. (OSB)

***May 16***

*Diagnostic Ultrasound: Bioeffects, Safety, Regulation, and Prudent Use*
Jerry Harris, OSEL, Shahram Vaezy, OIVD, and Robert Phillips (OSEL)

***June 13***

*Innovative Optical Methods for Cancer Detection and Retinal Imaging*
Josh Pfefer, Ph.D. (OSEL)

***June 27***

*From Fluids to Goops to Solids: Characterization of Hydrogels and Implications for Performance*
Katherine Vorvolakos, Ph.D. (OSEL)

***July 11***

*Artificial Pancreas: Challenges with Glucose Sensors, Insulin Pumps, and Algorithms*
Arleen Pinkos, MT(ASCP) (OIVD), Charles "Chip" Zimliki, Ph.D. (ODE), and Irada Isayeva, Ph.D. (OSEL)

***July 25***

*The Infusion Pump Initiative: A Holistic Approach to Developing Better Infusion Pumps*
Victoria Wagman (OCD), Al Taylor (OSEL), Anthony D. Watson, BS, MS, MBA (ODE), Kathleen Cummings (OSB), Valerie A. Flournoy, MS (OC)

***August 8***

*Computational Toxicology as a Tool for Biocompatibility Reviews*
Ron Brown (OSEL)

***August 22***

*Advanced Laser and Optical Technologies for Developing Innovative Test Methods in Biomedicine*
Ilko Ilev, Ph.D. (OSEL)

### *September 19*

*Automated Surveillance to Detect Post-Procedure Safety Signals of Approved Cardiovascular Devices*
Nilsa Loyo-Berrios, Ph.D. (OSB)

### *October 3*

*UV Bioeffects in Humans – Fundamentals of Tanning Process and Deleterious Effects of UV on Skin*
Janusz Beer, Ph.D. (OSEL)

### *October 17*

*Electrical Stimulation of Neural Tissue*
Victor Krauthamer, Ph.D. (OSEL), Thomas Radman (ODE)

# APPENDIX E – Laboratory Leaders

## ✓ DIVISION OF BIOLOGY

Division Director: Marilyn Lightfoote (301) 796-0235
Deputy Director: Kevin Milne*

- Toxicology and Biocompatibility: Peter Goering (301) 796-0253
- Biomolecular Mechanisms (molecular biology, immunology, allergy, cell biology, genomics/genetics): Steve Wood* (301) 796-0243
- Cardiovascular & Interventional Therapeutics: John W. Karanian (301) 210-4247
- Emerging Biosensors and Biotechnologies: Kim Sapsford (301) 796-0311
- Infection Control: Vicki Hitchins (301) 796-0258

## ✓ DIVISION OF CHEMISTRY AND MATERIALS SCIENCE

Division Director: Dinesh Patwardhan (301) 796-2622
Deputy Director: Benita Dair (301) 796-2614

- Active Materials: Martin (Ken) McDermott (301) 796-2621
- Materials Performance: Benita Dair (301) 796-2614

## ✓ DIVISION OF ELECTRICAL AND SOFTWARE ENGINEERING

Division Director: Al Taylor (301) 796-2583
Deputy Director: Brian Fitzgerald (301) 796-2579

- Electrical Engineering: Vacant
- Software (Research): Raoul Jetley (301) 796-2547
- Software (Regulatory Support): Joseph Jorgens (301) 796-2588

## ✓ DIVISION OF IMAGING AND APPLIED MATHEMATICS

Division Director: Kyle J. Myers (301) 796-2562
Deputy Director: Nicholas Petrick (301) 796-2563

- Image Analysis: Nicholas Petrick (301) 796-2563
- Imaging Physics: Aldo Badano (301) 796-2534
- Ionizing Radiation Metrology: Mary Walker (301) 796-2558

## ✓ DIVISION OF PHYSICS

Division Director: Victor Krauthamer (301) 796-2474
Deputy Director: Brian Beard (301) 796-2469

- Biophysics: Sunder Rajan (301) 796-4194
- Electromagnetic and Wireless Technologies: Howard Bassen (301) 796-2472
- Optical Diagnostic Devices: Joshua Pfefer (301) 796-2494
- Optical Therapeutics and Medical Nanophotonics: Ilko Ilev (301) 796-2489
- Functional Performance and Device Use Laboratory: Karen Siegel (301) 796-0653

## ✓ DIVISION OF SOLID AND FLUID MECHANICS

Division Director: Laurence Grossman (301) 796-2502
Deputy Director: Jon Casamento (301) 796-2499

- Fluid Dynamics: Laurence Grossman (301) 796-2502
- Solid Mechanics: Terry Woods (301) 796-2503
- Ultrasonics: Gerald Harris (301) 796-2508

***** denotes Acting

# APPENDIX F – OSEL Organization Chart