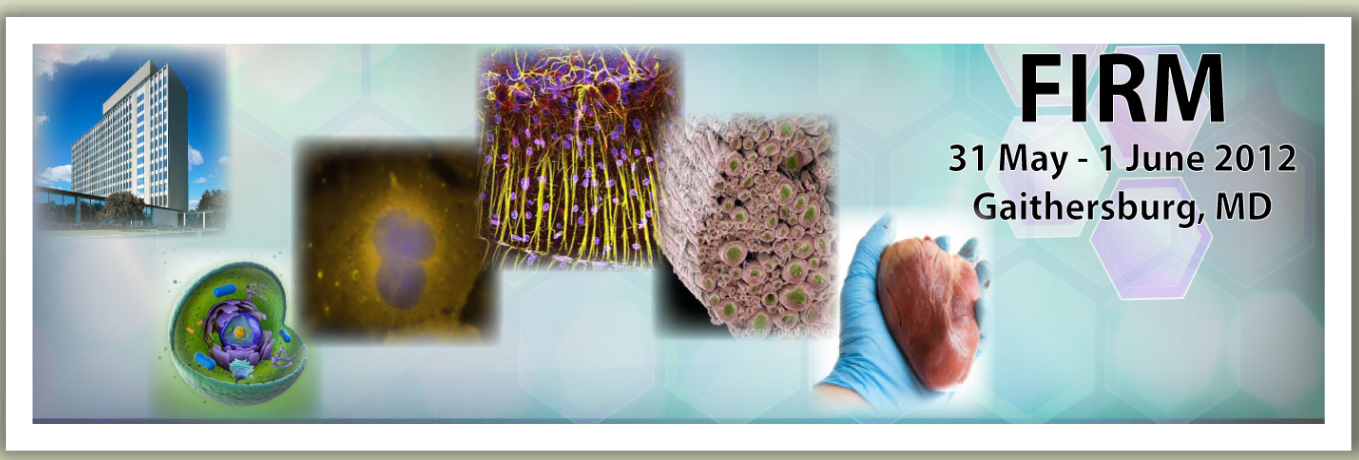
Functional Imaging for Regenerative Medicine

NIST Main Campus, Gaithersburg -
National Institute of Standards and Technology



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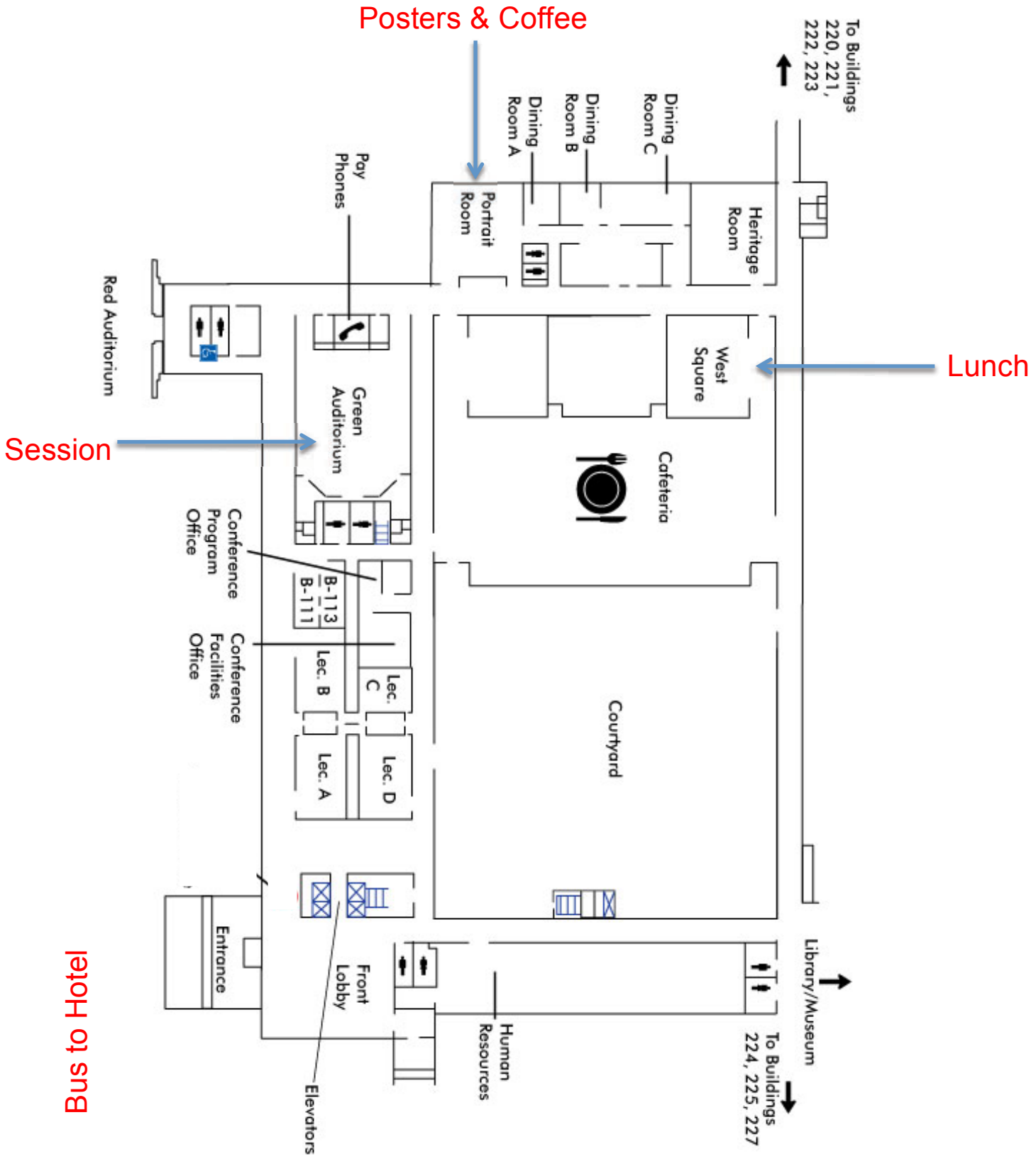

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Workshop Committee Members

Gordana Vunjak-Novakovic (Columbia) – Program Chair
Ralph Weissleder (Harvard) – Program Chair
Marcus Cicerone (NIST) – Organizing Chair
Christine Kelley (NIBIB) – Member
Rosemarie Hunziker (NIBIB) – Member
Martha Lundberg (NHLBI) – Member
Nayda Lumelsky (NIDCR) – Member
Fei Wang (NIAMS) – Member

Thanks to Donna Kimball and Mary Lou Norris (NIST) for logistical support

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Schedule At-A-Glance

31 May

	Session I – Plenary Overview – Green Auditorium	
8:00 am	Introductory Remarks	
8:10 am	Gordana Vunjak-Novakovic	Overview of Tissue Engineering
9:00 am	Ralph Weissleder……	Overview of in vivo imaging
10:00 am	Posters & Coffee	Heritage Room
	Session II A – Cellular Function *in vitro* - Green Auditorium	
10:30 am	Chris Chen……	Cell Adhesion, Forces, and Assembly Into Tissues
11:00 am	Ihor Lemischka……	Pluripotency
11:30 am	Rohit Bhargava……	Chemical Imaging for Molecular Histology
Noon	Lunch	West Square
	Session II B – Cellular Function *in vitro* - Green Auditorium	
1:30 pm	Milica Radisic……	Healthy and Diseased Heart Tissue on a Chip
2:00 pm	Robert Tranquillo……	Monitoring Collagen Transcription Noninvasively During Bioreactor Culture of Engineered Tissues
2:30 pm	Derek Toomre……	Imaging Nanoscale Interactions Between Cells and Their Environment
3:00 pm	Posters & Coffee	Heritage Room
	Session III A – Cellular Function *in vivo* – Green Auditorium	
3:30 pm	Elazer Edelman……	Non-invasive Tracking, Modeling and Predicting the Erosion of Environmentally Responsive Dynamic Materials
4:00 pm	Peter Zandstra……	Feedback Control of Endogenous Signaling to Guide Stem Cell Fate
4:30 pm	Charles Lin……	Live Imaging of the Regenerative Microenvironment
5-6:30 pm	Reception and Posters	Heritage Room
6:30 pm	Bus from NIST to Hotel	

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Session III B – Cellular Function *in vivo* – Green Auditorium

8:00 am	Joseph Wu……	Imaging to Assess Pluripotent Stem Cell Biology
8:30 am	Lihong Wang……	Photoacoustic Tomography: Ultrasonically Breaking through the Optical Diffusion Limit
9:00 am	Robert Guldberg……	Advances in Micro-CT Imaging for Regenerative Medicine
9:30 am	Posters & Coffee	Heritage Room

Session IV A– Whole Organs – Green Auditorium

10:00 am	David Kaplan……	Next Generation Devices for Imaging and Controlling Tissue Regeneration
10:30 am	Farsh Guilak……	Functional Imaging of Cartilage from the Macroscale to the Nanoscale
11:00 am	Shay Soker……	Regenerating Whole Organs
11:30 am	Matthias Nahrendorf……	Optical and Fusion Imaging
Noon	Lunch	West Square

Session IV B – Whole Organs – Green Auditorium

1:30 pm	Al Johnson……	Functional and Structural Imaging of Organ Growth and Repair
2:00 pm	Bret Bouma……	Functional and Microstructural Imaging with OCT
2:30 pm	Sam Wickline ……	Microarchitectural Tissue Classification for Regenerative Medicine: A Potential "Sweet Spot" for Clinical Ultrasound?
3:00 pm	Posters & Coffee	Heritage Room

Session V – Key Challenges & Emerging Opportunities – Green Auditorium

3:30	Panel Discussion with Session Chairs
5 pm	Adjourn

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Sponsors and Partners

MATES
Multi-Agency Tissue Engineering Science

NIBIB

NIST
National Institute of Standards and Technology
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National Heart Lung and Blood Institute

NIAMS

NSF

Society For Biomaterials
Giving life to a world of materials

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OVERVIEW OF TISSUE ENGINEERING

This plenary talk will discuss the state of the art of tissue engineering in three related areas: regenerative medicine, engineered tissue platforms for study of disease and drug screening, and tissue models for advanced biological research. The presentation will focus on the identification of currently used imaging modalities and the new approaches that are needed to move the filed forward. The imaging needs will be reviewed on multiple scales (ranging from molecular to cellular, tissue and organ levels), and for both the *in vitro* and *in vivo* settings. This plenary session will provide an introduction to the more specialized tissue engineering sessions to follow.

AUTHOR

Gordana Vunjak-Novakovic

Gordana Vunjak-Novakovic is the Mikati Foundation Professor of Biomedical Engineering, Vice-Chair of the Department of Biomedical Engineering and a Professor of Medical Sciences at Columbia University. She directs the Laboratory for Stem Cells and Tissue Engineering, and the Stem Cell Imaging Core, and co-directs the NIH Tissue Engineering Resource Center, and the Craniofacial Regeneration Center. She is the lead for bioengineering for the Columbia Stem Cell Initiative. She obtained a Ph.D. in chemical engineering at the University of Belgrade in Serbia where she stayed on faculty and became Full Professor in 1993. Upon moving to the USA, she spent twelve years at MIT, to join Columbia University in 2005. The focus of her research is on engineering functional human tissues using stem cells, biomaterials and bioreactors, for regenerative medicine and study of development and disease. She published 2 books, >50 chapters and >300 journal articles, has 53 patents, and gave >250 keynote and plenary lectures. She is a frequent advisor to government and industry, a study section chair and distinguished editor for NIH, and is serving on editorial boards of 12 scientific journals and numerous advisory boards and councils. In 2000, she was elected Fellow of the American Institute for Medical and Biological Engineering. In 2007, she gave the Director's lecture at the NIH, as the first woman engineer to receive this distinction. In 2008, she was inducted into the Women in Technology International Hall of Fame "for developing biological substitutes to restore, maintain or improve tissue function". In 2009, she was elected to the New York Academy of Sciences. In 2010, she received the Clemson Award of the Biomaterials Society "for significant contributions to the literature on biomaterials". In 2012 she was elected to the National Academy of Engineering "for bioreactor systems and modeling approaches for tissue engineering and regenerative medicine".

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OVERVIEW OF IN VIVO IMAGING

This plenary session will provide a broad overview of advanced imaging methodologies, particularly those useful for tissue engineering and regenerative medicine. The presentation will first highlight general concepts in imaging such as resolution, coverage and imaging probes to obtain molecular detail. A second aspect will be dedicated to microscopic imaging at the single cell level in vivo. Finally, macroscopic imaging at the whole body level will be reviewed. This plenary session will provide an introduction to the more specialized imaging sessions to follow.

AUTHOR

Ralph Weissleder

Dr. Weissleder is a Professor at Harvard Medical School, Director of the Center for Systems Biology at Massachusetts General Hospital (MGH), and Attending Clinician (Interventional Radiology) at MGH. Dr. Weissleder is also a member of the Dana Farber Harvard Cancer Center and a member of the Harvard Stem Cell Institute (HSCI). Dr. Weissleder's research interests include the development of novel molecular imaging techniques, tools for detection of early disease detection, development of nanomaterials for sensing and systems analysis. His research has been translational and several of his developments have led to advanced clinical trials with anticipated major impacts when these methods become routinely available. He is a founding member of the Society for Molecular Imaging Research and has served as its President in 2002. His work has been honored with numerous awards including the J. Taylor International Prize in Medicine, the Millenium Pharmaceuticals Innovator Award, the AUR Memorial Award, the ARRS President's Award, The Society for Molecular Imaging Lifetime Achievement Award, the Academy of Molecular Imaging 2006 Distinguished Basic Scientist Award and the 2008 RSNA Outstanding Researcher Award. He is an elected member of the US National Academies Institute of Medicine. Website: csb.mgh.harvard.edu

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CELL ADHESION, FORCES, AND ASSEMBLY INTO TISSUES

In vivo, local tissue structure defines the cellular environment, constraining how cells interact with surrounding extracellular matrix substrates, neighboring cells, soluble growth factors, and physical forces. These "microenvironmental" cues in turn regulate the behavior of individual cells, such as proliferation, differentiation, migration, and suicide. Using engineered microenvironments, we have begun to expose the complex interplay that occurs between adhesion, force, form, and function in cells. For example, cell adhesion to materials (natural or synthetic) is a central regulator of cellular signaling and function, and is characterized by control loops that affect receptor binding to the substrate, cell spreading and flattening against the material, and the active generation of traction forces as cell contract against these adhesions. These control loops in turn are central to cell proliferation, stem cell lineage commitment, and multicellular patterning and assembly. Major technological challenges remain in order to observe, manipulate, and understand these critical dynamic processes from molecular to multicellular length scales. Addressing such challenges will pave the way for understanding how the dynamic interactions between cells and their surroundings lead to the ultimate translational objectives set by regenerative medicine.

AUTHOR

Christopher Chen

Christopher S. Chen, M.D., Ph.D., Skirkanich Professor of Innovation in the University of Pennsylvania's Department of Bioengineering , is also a faculty member of the Cell Biology and Physiology Program as well as the Cell Growth and Cancer Program. He is director of the Tissue Microfabrication Laboratory and founding director of the Center for Engineering Cells and Regeneration. Dr. Chen has been an instrumental figure in the development of engineered cellular microenvironments in order to engineer cell function. The goal of Dr. Chen's research is to identify the underlying mechanisms by which cells interact with materials and each other to build tissues, and to apply this knowledge in the biology of stem cells, tissue vascularization, and cancer. Dr. Chen has received numerous honors, including the Presidential Early Career Award for Scientists and Engineers, the Angiogenesis Foundation Fellowship, the Office of Naval Research Young Investigator Award, the Mary Hulman George Award for Biomedical Research, and the Herbert W. Dickerman Award For Outstanding Contribution to Science. He serves as a member of the Faculty of 1000 Biology, the Board of Trustees for the Society for BioMEMS and Biomedical Nanotechnology, Editor for BioInterphases and Molecular and Cellular Biomechanics, and member of the Defense Sciences Study Group. He received his A.B. in Biochemistry from Harvard, M.S. in Mechanical Engineering from M.I.T., and Ph.D. in Medical Engineering and Medical Physics from the Harvard-M.I.T. Health Sciences and Technology Program. He earned his M.D. from the Harvard Medical School. He was Assistant Professor in Biomedical Engineering and in Oncology at Johns Hopkins University prior to being appointed Associate Professor at Penn.

PLURIPOTENCY

One major research interest in our laboratory is focused on understanding the regulation of stem cell fate decision processes. A second interest is the use of stem cell approaches to develop patient-specific models of inherited diseases. Both of these efforts currently involve the use of embryonic or induced pluripotent stem cells (ESC and iPSC, respectively). We have taken a broad, quantitative systems biology approach to unravel the regulatory mechanisms that are necessary for maintaining and reacquiring the self-renewing pluripotent state. Specifically, we utilize short hairpin (sh) RNA techniques to perform loss-of-function perturbations in mouse (m) and human (h) ESC. We have developed a genetic complementation strategy to effectively "replace" any gene-product with a version that can be controlled by a small molecule added to cell cultures. Using this approach, we have perturbed the expression of numerous key regulatory molecules such as transcription factors, epigenetic regulators as well as components of signaling pathways. After perturbation, we monitor global molecular changes over time such as chromatin modifications, mRNA levels, microRNA levels and the nuclear proteome. These studies provide a "real time" view of biological information processing that occurs during and is responsible for a transition in ESC fate. An essential component of our studies is computational biology. This has allowed us to analyze and integrate the large amount of information that is acquired. Computational analyses have also facilitated the generation of models of how regulatory networks function during changing cell fates. We have gained numerous novel insights into ESC regulation. Several that will be discussed are: how the Esrrb transcription factor controls pluripotency, genotoxic stress response mechanisms that regulate ESC and translational control as an under-appreciated aspect of cell fate regulation. In our second major research focus, we have utilized iPSC reprogramming to develop models of human genetic diseases. In particular, we have developed patient-specific models of cardiac disorders and are expanding our efforts to include metabolic diseases. Very recently, we have used direct programming technologies to directly convert mouse fibroblast cells into hemogenic endothelium. This tissue is the origin of hematopoietic stem and progenitor cells during fetal development. The programming is fairly efficient and requires four transcription factors. An additional exciting feature of these results is our ability to "kick start" the hemogenic endothelial developmental program, providing an in vitro avenue for in-depth analyses. We are currently extending the direct programming efforts to the human system.

AUTHOR

Ihor Lemischka

Ihor R. Lemischka, Ph.D. is the Director of The Black Family Stem Cell Institute, Lillian and Henry M. Stratton Professor, Developmental and Regenerative Biology Professor, Pharmacology and Systems Therapeutics. He is an internationally renowned stem cell biologist, Dr. Lemischka has patented techniques to isolate stem cells and has significantly advanced the study of stem cell activity and behavior. Dr. Lemischka is working to establish Mount Sinai as the leading stem cell institute in the United States, which he hopes will serve as a model worldwide. Dr. Lemischka hopes to characterize the stem cell's decision-making process and regulatory network, which will then help scientists manipulate stem cell decisions and develop therapies that could treat diseases. A member of the International Society for Stem Cell Research, he has traveled the world to educate the public about stem cell behavior and has delivered countless lectures about stem cell differentiation. Dr. Lemischka earned his postdoctoral degree at Massachusetts Institute of Technology. There,

he served as a postdoctoral research associate and also completed a fellowship at MIT's Center for Cancer Research. Dr. Lemischka then went to the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts where he completed another postdoctoral fellowship. In 1986, he joined the faculty at Princeton University where he rose from Assistant Professor to Professor of Molecular Biology. He remained on the Princeton faculty for 21 years before coming to Mount Sinai.

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CHEMICAL IMAGING FOR MOLECULAR HISTOLOGY

Chemical imaging, in which molecular content is obtained using spectroscopy and images are formed using microscopy, is an emerging area to characterize cells and tissues. We present here a chemical imaging approach based on mid-infrared spectroscopic imaging that combines the spatial specificity of optical microscopy with the molecular selectivity of vibrational absorption spectroscopy. IR spectroscopic imaging is particularly attractive for the analysis of cells and tissue in that it permits a rapid and simultaneous fingerprinting of inherent biologic content, extraneous materials and metabolic state without the use of labeled probes. Recorded data are related to the structural and functional state of the biological material using computation. We describe the computational strategy and statistical considerations underlying decision-making for this modality. A combination of theory, novel instrumentation and signal processing forms an integrated approach to biochemical analyses. First, we describe attempts to automate histopathology without dyes or human input. Results indicate that a rapid assessment of tissue is possible. Applied to engineered 3D tissue models for breast tumors, we show that the imaging technology is useful in rapidly assessing culture quality and that the model systems can act to inform researchers about the involvement of different cell types in cancer progression. Finally, we integrate imaging observations with those from conventional biological experiments to provide a complete view of cancer progression in these systems.

AUTHOR

Rohit Bhargava

Rohit Bhargava is an associate professor of Bioengineering, Mechanical Science and Engineering and Electrical and Computer Engineering as well as the Beckman Institute for Advanced Science and Technology at the University of Illinois at Urbana-Champaign. He is also the Associate Director of the University of Illinois Cancer Center. Rohit received dual B.Tech. degrees (in Chemical Engineering and Polymer Science and Engineering) from the Indian Institute of Technology, New Delhi. His doctoral thesis work at Case Western Reserve University was in the area of polymer vibrational spectroscopy. Subsequently, he worked as a Research Fellow at the National Institutes of Health in the area of cancer pathology and biomedical spectroscopy. Research in the Bhargava laboratories focuses on fundamental optical theory for vibrational spectroscopic imaging, developing new instrumentation, application of spectroscopic imaging to biomedical and polymer problems and numerical analyses. During the past three years, their group has bridged the gap between conventional cell culture and human tissue by developing multicellular, 3D cell cultures with controlled geometries. Current research in the Bhargava group is supported by several federal agencies, industry, private foundations and competitive programs at the University of Illinois. Rohit's work has been recognized with several research and teaching awards and he is routinely nominated to the list of teachers ranked excellent at Illinois.

HEALTHY AND DISEASED HEART TISSUE ON A CHIP

The ability to generate cardiomyocytes from either embryonic stem cells or induced pluripotent stem cells (PSC) provides an unprecedented opportunity to establish human in vitro models of cardiovascular disease as well as to develop replacement cardiac tissue for possible implantation. Although advances in stem cell biology enable us to reliably obtain cardiomyocytes from stem cells, cardiomyocytes derived from human PSC are representative of early human development and are not equivalent to adult cells. Our goal was to develop in vitro models that enable induction of maturation and hypertrophy in human iPSC derived cardiomyocytes. The cells were cultivated in cylindrical microwells. Gel compaction around a template suture enabled matrix remodelling and generation of a highly aligned tissue termed biowire (100mm in diameter and 1cm long). Staining for cardiac troponin T, alpha-actinin and actin revealed the presence of elongated cells aligned in parallel, with frequent striations. To induce maturation, we applied electrical field stimulation while hypertrophic response was achieved through known agonist of hypertrophy such as endothlin-1, angiotensin II and isoproterenol. Gene expression analysis by quantitative PCR indicated a significant downregulation of atrial natriuretic factor (ANF), a marker of fetal development and alpha-myosin heavy chain, expressed in higher quantities in fetal human cardiomyocytes and an upregulation of ion channel genes such as Kir2.1 in electrically stimulated compared to non-stimulated samples. Electrically stimulated samples had a significantly higher maximum capture rate than non-stimulated ones and optical mapping shows a significantly higher conduction velocity in electrically stimulated than non-stimulated controls. Flow cytometry cell analysis revealed an induction of Troponin T expression in electrical stimulated samples and transmission electron microscopy revealed the presence of more mature sarcomeres in stimulated samples, indicating that hESC-derived cardiomyocytes undergo changes compatible with cardiac maturation when cultured in biowires and submitted to electrical stimulation. Our findings have shown that after addition of either of the hypertrophy agonists for one week, the up-regulation of fetal genes indicating adult myocardial disease, such as atrial natriuretic factor, and the current gold standard for cardiac failure, brain natriuretic peptide, was induced. The gene expression data was further corroborated when staining for cardiac troponin T, actin and α-actinin which showed that the cytoskeletal structures of CMs began to deteriorate after the week of treatment. These results indicate that an hESC derived CM engineered heart tissue can respond to both synthetic and biologically derived agonists to undergo changes that correlate with a cardiac hypertrophic state in adults. In order to make the biowire a useful model for high-throughput drug screening studies on-line monitoring of contractile force, impulse propagation, viability and gene expression through novel imaging methods is required.

AUTHOR

Milica Radisic

Dr. Milica Radisic is an Associate Professor at the University of Toronto and Canada Research Chair (Tier 2) in Functional Cardiovascular Tissue Engineering. She obtained B.Eng. in Chemical Engineering from McMaster University in 1999, and Ph.D. in Chemical Engineering from the Massachusetts Institute of Technology in 2004. Before joining University of Toronto in 2005, she was a Postdoctoral Associate at the Harvard-MIT Division of Health Science and Technology. Dr. Radisic has received numerous awards and fellowships,

including MIT Technology Review Top 35 Innovators under 35. In 2006, she was featured on the cover of the book Changing our world: True stories of women engineers. Toronto Star named her one of the people to watch in 2010. She was named "The One to Watch" by the Scientist in June 2010 and she was the recipient of McMaster Arch Award in June 2010. She was a recipient of Connaught Innovation award in January 2011 and Professional Engineers Ontario-Young Engineer Medal in November 2011. Dr. Radisic's research is in the field of cardiac tissue engineering and biomaterials. She utilizes heart cells in combination with biomaterial scaffolds and bioreactors to cultivate functional heart tissue in vitro. Her research on electrical field stimulation was featured on the cover of Toronto Life in the piece titled 25 Ideas That Are Changing the World and CanadaAM in December 2009. Her research interests also include development of injectable biomaterials for cardiac regeneration, microfluidic cell separation and development of in vitro models for cell injection and drug testing. Currently, Dr. Radisic holds research funding from NSERC, CFI, ORF, NIH, CIHR and the Heart and Stroke Foundation. She is a Section Editor-Bioengineering for the International Journal of Artificial Organs. She serves on CIHR BME panel and TERMIS-NA membership committee. Her research findings were presented in over 80 research papers, reviews and book chapters.

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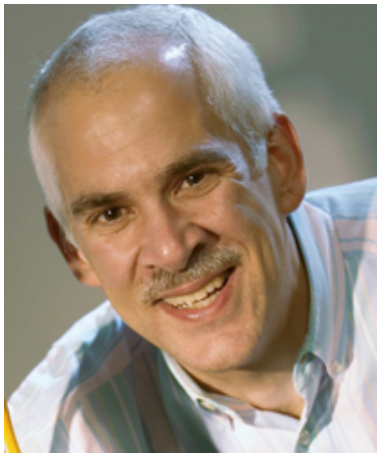
MONITORING COLLAGEN TRANSCRIPTION NONINVASIVELY DURING BIOREACTOR CULTURE OF ENGINEERED TISSUES

Current methods for measuring ECM content in engineered tissues are incompatible with monitoring of ECM production because they require destruction of the tissue. We have implemented a luciferase-based strategy to monitor collagen production noninvasively during bioreactor culture of engineered tissues. Fibrin-based tissue constructs made using fibroblasts and vascular smooth muscle cells stably transfected with a collagen I promoter/luciferase transgene matured with a collagen content comparable to control cells, but could be imaged noninvasively to follow collagen transcription during tissue growth in vitro. We show that vSMC reported collagen I production at the transcriptional level in a static tissue model and that these changes were consistent with changes at the mRNA and protein level. Since these cells report collagen changes instantly and without tissue destruction, they can facilitate construct optimization using multiple stimuli to produce functional engineered tissues. The ultimate tissue growth optimization strategy will require in situ imaging of upstream regulators (multiple phosphoproteins) of all key ECM-related molecules.

AUTHOR
ROBERT TRANQUILLO



Prof. Tranquillo received his Ph.D. in Chemical Engineering in 1986 from the University of Pennsylvania. He was a NATO Postdoctoral Fellow at the Center for Mathematical Biology at Oxford for one year before beginning his appointment in the Department of Chemical Engineering & Materials Science at the University of Minnesota in 1987. He has served as the head of the new Department of Biomedical Engineering since its inception in 2000. Prof. Tranquillo has used a combined modeling and experimental approach to understand cell behavior, in particular, directed cell migration and cell-matrix mechanical interactions. More recently, his research program has focused on the role of cell behavior in cardiovascular and neural tissue engineering applications. His research has resulted in over 90 peer-reviewed publications. Prof. Tranquillo is a Fellow of the American Institute of Medical and Biological Engineering and the Biomedical Engineering Society, and a Distinguished McKnight University Professor.

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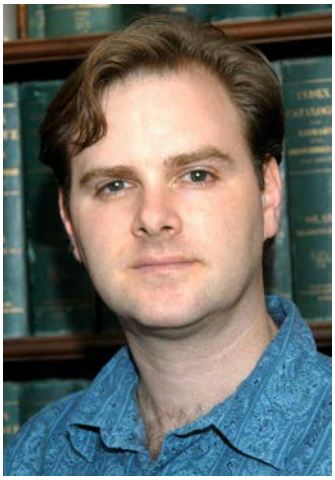
IMAGING NANOSCALE INTERACTIONS BETWEEN CELLS AND THEIR ENVIRONMENT

A challenge for cellular engineering is to understand how cells are organized and respond at the fine spatial-temporal level (e.g. macromolecular assemblies) for these interfaces need to be understood and controlled. Advances in axial and lateral super-resolution imaging hold great promise here for they are allowing investigators to interrogate how cells dynamically sense and interact with their microenvironment (matrix and other cells). Here advances, potential, and challenges of nanoscopy will be discussed followed by case studies on how they can be applied to survey how cells respond to engineered microenvironment. Finally the potential to use light to not only observe, but optogenetically control cellular organization will be illustrated.

AUTHOR

Derek Toomre



Dr. Derek Toomre is an Associate Professor at Yale University School of Medicine in the department of Cell Biology and Director of the Yale "CINEMA" imaging center (Cellular Imaging using New Microscopy Approaches). He did his post-doc in Germany at EMBL with Dr. Kai Simons, and Ph.D. at UCSD with Dr. Ajit Varki. His work focuses on the use of advanced microscopy to imaging membrane traffic, especially spatial control of exo- and endocytosis.
He has authored over 40 articles, 5 reviews, 4 book chapters and 3 patents, which have been licensed to OGS and GE Healthcare. His awards include: a 2007 NIH New Innovator Award, a NAS Kavli fellow, Bayer Scholar award, and a Marie Curie Fellowship.

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NON-INVASIVE TRACKING, MODELING AND PREDICTING THE EROSION OF ENVIRONMENTALLY RESPONSIVE DYNAMIC MATERIALS

Degradable biomaterials continue to emerge as essential components of novel biomedical devices. Innovation in and use of biodegradable materials are limited however by the lack of reliable assays for tracking material fate. *In vitro* degradation by traditional techniques cannot always predict in vivo performance and often confuse erosion, absorption and degradation. Standard methods sacrifice samples or animals preventing sequential measures of the same specimen, and are artificially contaminated by swelling with fluid uptake. Erosion kinetics are poorly predicted using classic gravimetric or GPC analyses. We harnessed fluorescence to follow material mass loss non-invasively in intact specimens, sequentially and identically *in vitro* and *in vivo*. *In vivo* erosion was two-fold faster than rates *in vitro* but correlated linearly. The predictability of this correlation, and its adherence to mathematical models will be of immense value in the development of new devices, their regulatory evaluation and in understanding the biological forces that guide their biological response - minimizing the time, expense and consumption of animals seen with traditional methods. Materials with programmed erosion might now be available for broad array of applications, and for the tracking and correlation of drug release and material erosion from a polymer drug-eluting scaffold, or the fate of cells and materials within tissue-engineered formulations.

AUTHOR

Elazer Edelman

Elazer R. Edelman directs the Biomedical Engineering Center and holds the Cabot Chair in Health Sciences and Technology at MIT. He is Professor of Medicine at Harvard Medical School and Senior Attending Physician the Cardiac Intensive Care Unit at the Brigham and Women's Hospital. His research combines his scientific and medical training, using polymer controlled drug delivery, growth factor biology and biochemistry, tissue engineering, biomaterials-tissue interactions, continuum mechanics, and digital signal processing to examine the cellular and molecular mechanisms of tissue repair. His laboratory helped develop and optimize bare metal and drug-eluting stents, and used device, immune and cell biology to advance studies of endothelial cell and vascular biology, computational modeling of vessel formation, and the homology between endothelial paracrine and angiocrine regulation in cancer and vascular diseases. Edelman's most recent work uses emerging imaging modalities to track the fate and function of environmentally-responsive dynamic materials in both in vivo and in vitro *domains in a correlative fashion. Multiple flurophores enable the simultaneous monitoring of drug release, embedded cell metabolism and secretion, and scaffold integrity. Melding of imaging and materials sciences with wound biology helps explain the differential response of a range of materials in different organs, disease states and applications.*

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FEEDBACK CONTROL OF ENDOGENOUS SIGNALING TO GUIDE STEM CELL FATE

A fundamental limitation in all stem cell-driven culture systems is the rapid accumulation of fate-modifying endogenous signals. Although microengineering technologies can be used to prospectively control the initial levels and impact of endogenous signals, these technologies are typically unable to adapt to dynamic changes in the culture environment. We have developed a number of new tools to characterize and modulate these culture-generated soluble factor-mediated networks. In one example, we have used predictive microfluidic control of regulatory ligand trajectories in individual pluripotent cells to create spatial gradients of differentiation, and have demonstrated how convective fluid flow and local cell organization modulates the impact of endogenous signals. In a second example, we have used an integrated computational and experimental strategy to develop an automated "fed-batch" media dilution approach to reduce the levels and impact of inhibitory paracrine signaling factors, and applied this technology to demonstrate a clinically relevant 11-fold increase in the numbers of human blood stem cells. These results demonstrate the impact of endogenously produced molecules on stem cell fate, and highlight the marked improvements that measurement and control of endogenous feedback signaling can offer stem cell culture. These examples also highlight the need for new technologies to measure and control, in real-time, biologically relevant parameters such as secreted factors and cell compositions.

AUTHOR
Peter Zandstra

Research in the Zandstra Laboratory is focused on the generation of functional tissue from adult and pluripotent stem cells. His groups' quantitative, bioengineering-based approach strives to gain new insight into the fundamental mechanisms that control stem cell fate and to develop robust technologies for the use of stem cells and their derivatives to treat disease. Specific areas of research focus include blood stem cell expansion and the generation of cardiac tissue and endoderm progenitors from pluripotent stem cells. Dr. Zandstra is a Professor in the Institute of Biomaterials and Biomedical Engineering, the Department of Chemical Engineering and Applied Chemistry, and the Donnelly Centre at the University of Toronto. He is also a member of the McEwen Centre for Regenerative Medicine and the Heart and Stroke/Richard Lewar Centre of Excellence. He currently acts as Chief Scientific Officer for the Centre for the Commercialization of Regenerative Medicine (www.CCRM.ca). Dr Zandstra's accomplishments have been recognized by a number of awards and accolades including a Guggenheim Fellowship and the McLean Award. Dr Zandstra's strong commitment to training the next generation of researchers is evidenced by his role as the Director of the undergraduate Bioengineering Program.

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LIVE IMAGING OF THE REGENERATIVE MICROENVIRONMENT

Stem cells are important cell sources for tissue engineering and regenerative medicine. *In vivo*, stem cells reside in specialized microenvironments, called niches, that support and regulate stem cell function. Understanding how the niches are organized and interact with the stem cells *in vivo* is essential for recreating functional niches in engineered tissue constructs ex vivo. Intravital microscopy provides a powerful means to visualize the 3D microarchitecture of the stem cell niche in live animals with cellular resolution. It also provides real-time assessment of cell-based therapy by tracking the homing, survival, and proliferation of the exogenously administered cells, as well as monitoring the host tissue response. Ongoing challenges for intraviatal microscopy will be addressed.

AUTHOR

Charles Lin

Dr. Lin leads an advanced microscopy group at the MGH Wellman Center for Photomedicine and the MGH Center for Systems Biology, where an interdisciplinary team of imaging scientists and biomedical investigators work closely together to develop optical techniques for in vivo cell tracking and molecular imaging. The goal is to use innovative imaging approaches to improve understanding of cell biology in the context of the living organisms, and ultimately to improve cell transplantation, stem cell therapy, and cancer therapy. Dr. Lin is an Associate Professor at Harvard Medical School and an affiliated faculty member at the Harvard Stem Cell Institute and the Harvard/MIT Division of Health Sciences and Technology.

IMAGING TO ASSESS PLURIPOTENT STEM CELL BIOLOGY

The successful derivation of human induced pluripotent stem cells (hiPSCs) by de-differentiation of somatic cells offers significant potential to overcome obstacles in the field of cardiovascular disease. hiPSC derivatives offer incredible potential for new disease models and regenerative medicine therapies. However, many questions remain prior to clinical translation in the future. This talk will highlight anticipated clinical hurdles of pluripotent stem cell therapy, focusing on issues such as donor cell source, differentiation, immunogenicity, and tumorigenicty, and using molecular imaging as a novel technology to assess these biological properties.

AUTHOR

Joseph Wu

Joseph C. Wu, MD, PhD is an Associate Professor in the Department of Medicine (Cardiology) and Department of Radiology at the Stanford School of Medicine. Dr. Wu received his M.D. from the Yale School of Medicine. He completed his cardiology fellowship training followed by a PhD in Molecular Pharmacology at UCLA. He has received numerous awards, including the Burroughs Wellcome Foundation Career Award for Medical Scientists (2007), the NIH Director's New Innovator Award (2008), the NIH Roadmap Transformative R01 Award (2009), and the Presidential Early Career Award for Scientists and Engineers (2010). Dr. Wu's lab uses a combination of gene profiling, tissue engineering, physiological testing, and molecular imaging technologies to better understand molecular and pathophysiological processes. The lab works on biological mechanisms of adult stem cells, embryonic stem cells (ESCs), and induced pluripotent stem cells (iPSCs). For adult stem cells, we are interested in monitoring stem cell survival, proliferation, and differentiation. For ESCs, we are currently studying their tumorigenicity, immunogenicity, and differentiation. For iPSCs, we are working on novel derivation techniques for potential downstream clinical translation. We also work on development of novel vectors and therapeutic genes for cardiovascular gene therapy applications.

PHOTOACOUSTIC TOMOGRAPHY: ULTRASONICALLY BREAKING THROUGH THE OPTICAL DIFFUSION LIMIT

Photoacoustic tomography (PAT), combining optical and ultrasonic waves via the photoacoustic effect, provides in vivo multiscale non-ionizing functional and molecular imaging. PAT is the only modality capable of imaging across the length scales of organelles, cells, tissues, and organs with consistent contrast. Such a technology has the potential to empower multiscale systems biology and accelerate translation from microscopic laboratory discoveries to macroscopic clinical practice. PAT may also hold the key to the earliest detection of cancer by in vivo label-free quantification of hypermetabolism, the quintessential hallmark of cancer.

AUTHOR

Lihong Wang

Lihong Wang holds the Gene K. Beare Distinguished Professorship of Biomedical Engineering at Washington University in St. Louis. His book entitled "Biomedical Optics: Principles and Imaging," one of the first textbooks in the field, won the 2010 Joseph W. Goodman Book Writing Award. He also edited the first book on photoacoustic tomography. Professor Wang has published over 290 peer-reviewed journal articles with an h-index of 58 and delivered more than 310 keynote, plenary, or invited talks. He has received 31 research grants as the principal investigator with a cumulative budget of over $34M. He is the Editor-in-Chief of the Journal of Biomedical Optics. He chairs the annual conference on Photons plus Ultrasound, and chaired the 2010 Gordon Conference on Lasers in Medicine and Biology and the 2010 OSA Topical Meeting on Biomedical Optics. Wang serves as the founding chairs of the scientific advisory boards for two companies commercializing photoacoustic tomography. He received NIH's FIRST and NSF's CAREER awards. He was awarded OSA's C.E.K. Mees Medal and IEEE's Technical Achievement Award for "seminal contributions to photoacoustic tomography and Monte Carlo modeling of photon transport in biological tissues and for leadership in the international biophotonics community". Email: LHWANG@WUSTL.EDU; URL: HTTP://OILAB.SEAS.WUSTL.EDU

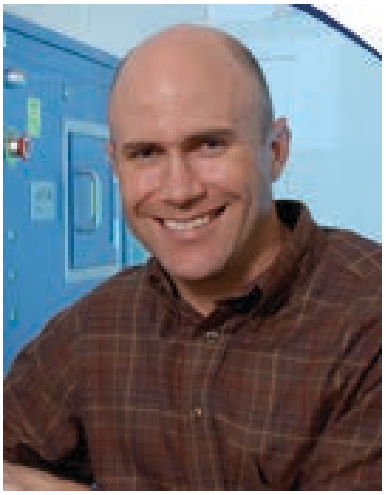
May 31 – June 1, 2012
Gaithersburg, MD

ADVANCES IN MICRO-CT IMAGING FOR REGENERATIVE MEDICINE

Advanced imaging methods play an increasingly important role in the rigorous quantitative evaluation of tissue regenerative strategies. Microcomputed tomography (micro-CT) imaging offers excellent resolution for quantifying 3D tissue morphology and composition but has typically been restricted to analysis of x-ray attenuating tissues such as bone. Even with this limitation, micro-CT analysis has been a valuable evaluation technique for tissue engineering/regenerative medicine (TERM) studies to monitor mineralized matrix synthesis in vitro and quantify functional bone regeneration in vivo. Unfortunately, soft tissues such as blood vessels and cartilage alone are not sufficiently radiodense relative to surrounding tissues to allow micro-CT analysis. However, vascular ingrowth into scaffolds or regions of tissue injury may be imaged nondestructively following perfusion of a radiodense contrast agent. Subsequent morphological analysis can provide quantification of 3D vascular volume, vessel thickness and density, and vascular network connectivity. Recently developed in vivo micro-CT systems and circulating contrast agents offer the potential for longitudinal assessment of vascularization changes over time. Micro-CT imaging in combination with an appropriate contrast agent thus overcomes some of the shortcomings of other vascular assessment techniques by providing high resolution, efficient, volumetric, and quantitative analysis. Contrast-enhanced micro-CT imaging of cartilaginous tissues has also been recently established as a method to assess cartilage regeneration following injury or prevention of degeneration during osteoarthritis. In addition to providing quantitative analysis of articular cartilage morphology, the spatial equilibration of the ionic contrast agents provides a nondestructive indicator of proteoglycan content within the cartilage.

AUTHOR

Robert Guldberg



Dr. Guldberg is a Professor of Mechanical Engineering and Biomedical Engineering at the Georgia Institute of Technology and holds the Parker H. Petit Director's Chair in Bioengineering and Bioscience. He has published over 140 book chapters and journal articles focused on musculoskeletal growth and development, functional regeneration following traumatic injury, and degenerative diseases, including skeletal fragility and osteoarthritis. In November 2009, he was appointed Executive Director of the Institute for Bioengineering and Bioscience at Georgia Tech after serving as Associate Director since 2004. Dr. Guldberg is a Fellow of the American Institute for Medical and Biological Engineering and also currently serves as Chair of the Musculoskeletal Tissue Engineering Study Section at NIH and Chair of the North American Chapter of the Tissue Engineering and Regenerative Medicine International Society (TERMIS).

May 31 – June 1, 2012
Gaithersburg, MD

NEXT GENERATION DEVICES FOR IMAGING AND CONTROLLING TISSUE REGENERATION

New biomaterial systems have been generated from silk proteins over the past few years, exploiting the novel mechanical, biological, optical and electronic features of this family of fibrous proteins. These proteins, derived from silkworm and spider silks, provide useful features such as water-based processing for doping with bioactive compounds, biocompatibility, proteolytic degradability and versatile and robust material formats. Fundamental insight into the rules that govern control of silk protein assembly processes leading to predictable material features has allowed new material systems and devices to be pursued using silks as the key architectural component. In particular, these systems allow us to generate optically addressable implantable devices, electronically interfaced devices and many related themes, towards a new generation of medical needs. These devices can be programmed to degrade, are biocompatible, and provide in vivo views into tissue regeneration that surpass current technologies – such as greater depth and control of optical interrogation, external control of electronic function and readout, and related themes. The potential to use implantable optical and electronic devices, wherein no second surgery is required to remove such devices, opens up entirely new windows of opportunity towards future concepts in medical imaging and control of tissue regeneration.

AUTHOR

David L. Kaplan

David Kaplan holds an Endowed Chair, the Stern Family Professor of Engineering, at Tufts University. He is Professor & Chair of the Department of Biomedical Engineering and also holds faculty appointments in the School of Medicine, the School of Dental Medicine, Department of Chemistry and the Department of Chemical and Biological Engineering. His research focus is on biopolymer engineering to understand structure-function relationships, with emphasis on studies related to self-assembly, biomaterials engineering and functional tissue engineering. He has published over 400 papers and edited eight books. He directs the NIH P41 Tissue Engineering Resource Center (TERC) that involves Tufts University and Columbia University. He serves of the editorial boards of numerous journals and is Associate Editor for the journal Biomacromolecules. He has received a number of awards for teaching, was Elected Fellow American Institute of Medical and Biological Engineering and received the Columbus Discovery Medal and Society for Biomaterials Clemson Award for contributions to the literature.

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May 31 – June 1, 2012
Gaithersburg, MD

FUNCTIONAL IMAGING OF CARTILAGE FROM THE MACROSCALE TO THE NANOSCALE

The mechanical properties of articular cartilage play a critical role in the function of the tissue as the low-friction, load bearing tissue within the synovial joints. Joint loading during normal physical activity causes deformation of the cartilage layer and exposes the chondrocytes within the tissue to a variety of biophysical phenomena that can influence cell behavior. Using a variety of techniques, we present a multiscale approach to imaging and quantifying the mechanical environment and physiology of the chondrocyte, from the level of the whole joint to the cell and subcellular components. Specifically, the goals of these studies have been to 1) apply MRI and other imaging modalities to quantify cartilage strains in vivo; 2) develop atomic force and confocal microscopy techniques in combination with theoretical models to map the mechanical environment of normal and tissue-engineered cartilage at the micro- and nanoscales; 3) Develop in situ fluorescence imaging methods to determine the mechanisms by which chondrocytes respond to mechanical signals. An improved understanding of the relationships between mechanical factors and cell behavior will be critical to the understanding of cartilage function under physiologic and pathologic conditions, as well as the development of tissue engineering approaches for cartilage repair or regeneration.

AUTHOR

Farshid Guilak

Farshid Guilak, Ph.D. is the Laszlo Ormandy Professor of Orthopaedic Surgery at Duke University Medical Center and is the Vice-Chair and Director of Orthopaedic Research. His research focuses on the study of osteoarthritis, a painful and debilitating disease of the synovial joints. His laboratory has used a multidisciplinary approach to investigate the role of biomechanical factors in the onset and progression of osteoarthritis, as well as the development of new pharmacologic and stem-cell therapies for this disease. Dr. Guilak has published over 200 articles in peer-reviewed journal and has co-edited three books. He is the editor-in-chief of the Journal of Biomechanics, associate editor for Osteoarthritis & Cartilage, and serves on the editorial boards of several other journals. He is the Founder and President of Cytex Therapeutics, an early stage startup company focusing on tissue engineering for musculoskeletal diseases.

May 31 – June 1, 2012
Gaithersburg, MD

REGENERATING WHOLE ORGANS

Patients with diseased or injured organs may be treated with transplanted organs. There is a severe shortage of donor organs, which is worsening yearly due to the aging population. Regenerative medicine and tissue engineering apply the principles of cell transplantation, material sciences, and bioengineering to construct biological substitutes that could restore and maintain normal function in diseased, injured and missing tissues and organs. However, progression of these technologies to therapy is hindered by multiple factors such as the supply of sufficient cell numbers and cell types, authentic tissue architecture and vascularization. Recent advances in overcoming these limitations to create large volume tissues and organs will be reviewed. The potential therapeutic applications of these technologies for patients with end-stage tissue and organ failure will be described.

AUTHOR
Shay Soker

Shay Soker PhD is a Professor of Regenerative Medicine, Cancer Biology, Physiology & Pharmacology and Surgical Sciences. Dr. Soker has a particular interest in molecular and cellular biology of the vascular system. During his postdoctoral training at Harvard Medical School, he identified and cloned of a novel VEGF receptor, neuropilin (a study that was published in "Cell"). An expert in the field of angiogenesis, Dr. Soker has a particular interest in molecular and cellular biology of the vascular system. He began working on tissue regeneration and developed programs in. His group developed approaches to enhance the angiogenic potential of cells to improve neo-vascularization of bioengineered tissues.

Dr. Soker's efforts have recently been concentrated on identification of new sources of cells and scaffolds for tissue engineering. Dr. Soker's team has isolated progenitor cells from many tissues and used them to bioengineer tissues, as well as, for cell therapy. In parallel, his group is exploring tissue-derived extracellular matrices as scaffolds for whole organ bioengineering. He had published a seminal manuscript in the journal Hepatology, describing, for the first time, the making of a human liver organoid. He is now using a similar approach to bioengineer kidney, pancreas, intestine and more organs. Dr. Soker served and currently serving as PI and Co-I of numerous research grants from federal and private foundations and industry and as a reviewer for research grant programs.

Dr. Soker has won numerous academic awards including research grants from NIH, US Army, foundations and industry. During his academic career he has mentored more than 25 graduate students and post-doctoral trainees; all have moved on to pursue academic/medical careers. Dr. Soker is frequently invited to present his research in numerous national and international conferences on angiogenesis, tissue engineering and regenerative medicine.

OPTICAL AND FUSION IMAGING

Macroscopic imaging should aid tissue engineering by i) reporting on the delivery, presence and degradation of transplanted materials, cells and tissue, ii) providing information on how the intervention changes the microenvironment in the recipient organism on the cellular and molecular level, and iii) report on the overall therapeutic effects of the treatment on the organ and systems level. Ideally, these data should be obtained noninvasively so one can study the time course; and in parallel, so one can integrate material, physiological and therapeutic observations. This (probably incomplete) wish list is a tall order; however, we have witnessed considerable advance in quantitative non-invasive imaging in small animals. The presentation will discuss multichannel, multimodal and multiscale approaches focussing on optical, PET and MR imaging in murine cardiovascular and cancer models. Further, the talk will feature examples on tracking nanoparticles and drug delivery materials in live mice. The overall goal is to provide an update on emerging macroscopic imaging tools for monitoring tissue engineering in the mouse.

AUTHOR

Matthias Nahrendorf

Matthias Nahrendorf, MD PhD, is an Assistant Professor in Radiology at Harvard Medical School. He attended Medical School at Heidelberg University, followed by residency in Internal Medicine and fellowships at the Biophysics Department in Wuerzburg and the Center for Molecular Imaging in Boston. Since 2006, he is Faculty at the Center for Systems Biology, the Director of the Mouse Imaging Program, and a member of the Immunology Program at Massachusetts General Hospital. His laboratory focusses on imaging of molecular processes in heart failure, atherosclerosis and transplant rejection. Imaging targets are enzymes, immune cells and molecular players with a central role in cardiovascular disease. The Nahrendorf laboratory uses the entire spectrum of modalities, including MR, nuclear, optical and hybrid imaging, to gain insight into inflammation and tissue repair at a systems level, and in an undisturbed in vivo environment.

May 31 – June 1, 2012
Gaithersburg, MD

FUNCTIONAL AND STRUCTURAL IMAGING OF ORGAN GROWTH AND REPAIR

The Duke Center for In Vivo Microscopy (CIVM) is an NIBIB National Resource dedicated to the development of novel preclinical imaging tools and the application of those tools to important biomedical questions. The use of imaging tools to follow tissue repair is clearly one of those important biomedical questions. The goal of this talk is to establish a dialogue with stake-holders in the field of regenerative medicine so that we might develop the tools critical for following tissue regeneration and repair in preclinical models. The development of these preclinical imaging tools is more than simply "turning up the knobs" on clinical machines. This talk will focus on two examples where the unique scaling requirements for imaging the mouse and rat have caused us to think outside of the box for the imaging approach. Our first example focuses on functional changes in the mouse heart following myocardial infarction. We have developed a microCT system explicitly for 4 dimensional functional imaging. A novel geometry and the use of two imaging chains allows us to acquire 4D data @ 44 micron isotropic spatial resolution with 10 ms temporal resolution and imaging times as low as 5 minutes. A dedicated image-processing pipeline automates and standardizes data reduction and analysis. Very high resolution microSPECT has recently been added to provide perfusion measures. Our second example employs magnetic resonance histology to follow neurologic development and repair in the mouse and rat brain. An atlas of the rat brain has been developed with isotropic spatial resolution down to 25 um. The atlas provides a range of tissue contrasts including conventional T2*, susceptibility, and diffusion tensor images. Again, an automated pipeline facilitates and standardizes data reduction. Average data (n=5) have been generated @ nine time points (PND0-PND80). DTI and susceptibility images provide particularly dramatic evidence of changes in white matter. Initial applications to stem cell repair following stroke show exciting potential.

AUTHOR

G. Allan Johnson

Dr. G. Allan Johnson is the Charles E. Putman Professor of Radiology, Physics and Biomedical Engineering. Dr. Johnson graduated magna cum laude (physics/mathematics) from St Olaf College in 1969. He performed his Ph.D. research in (electron spin) magnetic resonance under Professor Walter Gordy from 1969-1974. He joined the Duke Department of Radiology in 1974 where he was responsible for installing the first CT system at Duke. As the Director of Diagnostic Physics for Duke Medical Center, he has translated a number of major technologies into the Duke Health Care system. In 1982-83, he was responsible for installing the world's first clinical high-field (1.5 T) MR system at Duke in collaboration with colleagues at General Electric. Under NIH support he developed the first high-speed health care imaging network at Duke in the early 80's. He developed a network of multidimensional visualization workstations that are used extensively in both routine review and advanced clinical evaluation. In 1986 he founded the Center for In Vivo Microscopy, an NIBIB National Resource. The Center, one of the oldest imaging resources in the country has pioneered technology for acquisition, reconstruction, registration, and visualization of very large (>500 GB) multidimensional imaging arrays. Dr Johnson has founded two companies, holds six patents and is coauthor of ~ 300 peer-reviewed publications. He holds appointments in the Department of Radiology (Medical School), Department of Physics (School of Arts and Sciences) and Biomedical Engineering (Engineering School) as the Charles E. Putman University Professor.

FUNCTIONAL AND MICROSTRUCTURAL IMAGING WITH OCT

Optical coherence tomography (OCT) and its modern Fourier-domain derivatives provide unique capabilities for micro-structural and functional imaging over relatively large tissue volumes in situ. Integrating phase-sensitive Doppler and speckle decorrelation imaging allows rapid volumetric angiography without exogenous contrast agents and opens the possibility for real-time assessment of tissue perfusion, angiogenesis and response to vascular-targeted interventions. By monitoring depth-dependent alterations of the polarization state of reflected light, OCT systems can additionally enable birefringence mapping to characterize the integrity and spatial distribution of collagen, smooth muscle cells and nerve fibers. When coupled with implantable or minimally-invasive sensors and imaging probes, these capabilities could be utilized to guide or serially monitor novel strategies of tissue engineering and regenerative medicine.

AUTHOR

Brett Bouma

Brett E. Bouma, PhD, is a Professor of Dermatology and Health Sciences and Technology at Harvard Medical School and an Associate Physicist in the Wellman Center for Photomedicine at the Massachusetts General Hospital. His doctoral dissertation research, in the physics department of the University of Illinois, Chicago, focused on understanding the interaction of ultrafast laser pulses with optical materials and plasmas.

Following the completion of his graduate work, he entered a post-doctoral fellowship in the EECS department at MIT where he continued his work with ultrafast lasers and began to explore applications in medicine and biology. Since starting a lab at MGH in 1998, he has focused his research on the development and clinical application of novel optical technologies for diagnosis and therapy. Professor Bouma is a Fellow of the Optical Society of America.

May 31 – June 1, 2012
Gaithersburg, MD

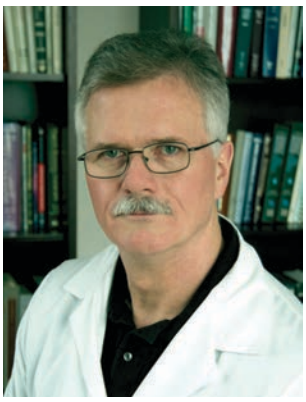
MICROARCHITECTURAL TISSUE CLASSIFICATION FOR REGENERATIVE MEDICINE: A POTENTIAL "SWEET SPOT" FOR CLINICAL ULTRASOUND?

Traditional ultrasound tissue characterization has dealt with differentiation between normal and pathological states by reducing massive data sets to a few quantifiable parameters such as backscattered energy, frequency dependence of scattering, and attenuation. When taken together with knowledge of imaging machine features, these indexes can yield a backscatter cross-section, or the scattering characteristics of individual scattering elements. These metrics generally are applied to an ensemble of scatterers that comprise a tissue or organ, and have a long history of use in the clinic as tools for tissue characterization. However, alone they cannot differentiate pertinent microscopic features of tissue architecture such as specific 3D organization of elements that comprise the fundamental operative unit of the organ in question.

We have recently implemented novel signal processing schemes using various entropy receivers on a pixel-by-pixel basis that can be used to more sensitively differentiate normal from pathological states by focusing on the precise (even subresolution) organization of scatterers rather than their ensemble averaged backscatter cross-sections. We have shown good results in detecting subtle changes in cancer, cardiovascular disease, and in muscular dystrophy, among others. We propose that these methods might be applicable for robust tissue classification to describe specific architectural features of normal and of pathological tissues that can serve as a map to unique physiological structures, or tissue identifiers, at the microscopic level. The import for monitoring physical changes produced by tissue engineering or regenerative medicine to achieve a more physiological microarchitecture would be one relevant application.

AUTHOR

Samuel A. Wickline



Samuel A. Wickline is the J. Russell Hornsby Professor of Biomedical Sciences, and Professor Medicine, Physics, Biomedical Engineering, and Cell Biology and Physiology at Washington University. He received the B.A. degree from Pomona College, Claremont, CA in 1974 and the M.D. degree from the University of Hawaii School of Medicine, Honolulu, HI, in 1980. He completed post-doctoral training in Internal Medicine and Cardiology at Barnes Hospital, St. Louis, MO in 1987 and joined the faculty of the School of Medicine in the Cardiovascular Division before becoming Director of the Cardiovascular Division at Jewish Hospital and subsequently Co-Director of the Cardiovascular Division at Barnes-Jewish Hospital. He established the Washington University "Consortium for Translational Research in Advanced Imaging and Nanomedicine" (C-TRAIN) at the St Louis CORTEX Center devoted to diagnostic and therapeutic development of nanotechnology in concert with corporate and academic partners for broadbased clinical applications. Dr. Wickline also is a founder of 3 local biotech startup companies in St Louis devoted to molecular imaging and targeted therapeutics, and in vitro *molecular diagnostics. He is the author of over 250 research papers, and holds more than 30 issued or filed U.S. patent applications.*

Poster #1.

Candidate Pharmaceuticals Quantitatively Redistribute F-Actin In Astrocytoma Cells

Author and affiliation
S. Lockett[1], T. Turbyville[1], P. Gudla[1], K. Nandy[1], C. Cui[2], J. Jaja[2], K. Reilly[3], J. Beutler[4].
[1]OMAL, Frederick National Laboratory (FNL), [2]Electical and Computer Engineering, University of Maryland, College Park, [3]MCGP, [4]MTL, [3,4]FNL

Abstract
Compound GRIN lenses enable deep brain imaging in live mice. Yet, their field-of-view is only a few 10's of microns, and the axial resolution is poor due to negative spherical aberration. To improve these, a 0.6 NA GRIN lens singlet was used in conjunction with cover glasses, to add positive spherical aberration, and an objective with a correction collar to provide fine adjustment. The FOV was increased to ~150 μm. Also, the lateral and axial resolutions were 618 nm and 5.5 μm, respectively, versus ~1 μm and ~15 μm, respectively, for compound lenses. This improvement enabled observation of large dendritic spines in CA1 of live Thy1-YFPH mice.

Poster #2.

Label-free Optical Classification of Differentiation Lineages of Human Mesenchymal Stem Cells by Broadband CARS microscopy

Author and affiliation
Young Jong Lee,[a] Sebastian Vega,[b] Parth J. Patel,[b] Khaled H. Aamer,[a] Prabhas V. Moghe,[b] and Marcus T. Cicerone[a]

[a]Polymers Division, National Institute of Standards and Technology, Gaithersburg, MD, USA
[b]Department of Biomedical Engineering, Rutgers University, Piscataway, NJ, USA

Abstract
We use broadband coherent anti-Stokes Raman scattering (CARS) microscopy to characterize differentiation of individual human mesenchymal stem cells (hMSCs) cultured in adipogenic, osteogenic, and basal growth media. Using this label-free chemical imaging method, we identify or "digitally stain" subcellular organelles and cell-produced functional markers to determine the differentiation status of individual cells cultured for two weeks. A simple univariate analysis based on the amount of such "digitally stained" functional markers of lipid, mineral, and cytosol, results in three well separated groups of the corresponding lineages. A multivariate analysis of Raman spectra averaged over cytosol regions of individual cells classifies individual cells into three groups – adipocytes, osteoblasts, and undifferentiated stem cells – using appropriate principal components.

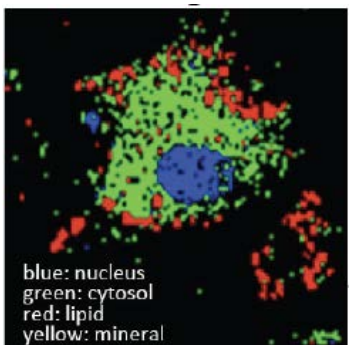


Figure 1: **h-BMSC cultured in adipogenic media and subsequently imaged using BCARS. The image contrast is intrinsic - from molecular vibrations.**

Poster #3.

High-Speed, High-Resolution Functional Coherent Raman Imaging with Broadband Coherent Anti-Stokes Raman Scattering (BCARS) Microscopy

Author and affiliation
Charles Camp and Marcus T Cicerone
National Institute of Standards and Technology, Gaithersburg, MD 20899

Abstract
BCARS microscopy is a powerful, label-free and noninvasive technique for imaging molecular composition and morphology. BCARS uses intrinsic vibrational, providing chemical specificity without the need for sample preparation and staining. Previous generations of BCARS microscopy systems have successfully analyzed a myriad of samples ranging from polymer blends to differentiated stem cells, but with relatively slow image acquisition (~5 min/image). Although orders of magnitude faster than spontaneous Raman microspectroscopy, BCARS imaging was still relatively slow when compared to confocal microscopy techniques. Here we introduce a new generation of high-speed BCARS imaging that uses the latest in fiber laser sources and CMOS detection technology to provide kHz pixel acquisition rates, and image acquisition in ~20 s. The new BCARS system will allow us to noninvasively track chemical processes in cells, in real time.

Poster #4.

Lineage-Dependent Biomechanical Remodeling of Stem Cells During Differentiation

Author and affiliation
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Abstract
Recent evidence suggests that stem cell differentiation can be regulated by modulation of the cell's biomechanics. As a specific example, during adipogenic differentiation of human mesenchymal stem cells (MSCs), the actin stress fibers are reorganized rapidly in order to support the round morphology of adipocytes. Also, when P19 mouse stem cells undergo neuronal differentiation, a significant cytoskeletal transformation occurs in which the microtubules & neurofilaments rearrange and elongate to form the axon and dendrites of the neuron. We therefore investigated the lineage-dependent mechanical changes in stem cells using a variety of quantitative tools and created a sophisticated multi-function engineering model of stem cell differentiation.

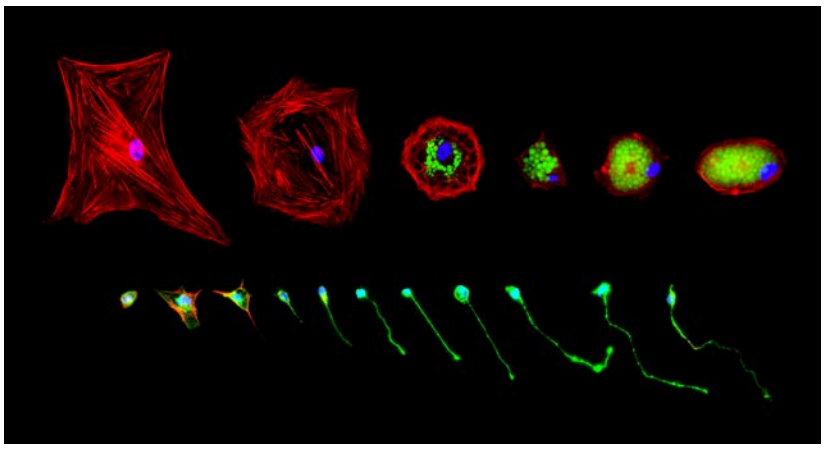

Figure 2: **The top row displays human MSC differentiation into adipocytes (20x). The cells were stained for F-actin (red), lipids (green), and nuclei (blue). The strong and expansive F-actin content of the MSCs atrophies into a thin cortical layer of support as adipogenic differentiation progresses. The bottom row displays the differentiation of P19 mouse embryonal carcinoma stem cells into neurons (20x). These cells were stained for F-actin (red), beta III tubulin (green) and nuclei (blue). After a brief spike in F-actin at the start of differentiation, the beta III tubulin content of the P19 heavily increases to form the axon and dendrites of the neuron.**

Poster #5.

A Method To Resolve Atomic Force Microscopy Feature Definition Issues For Neural Cells Cultured On Nanofibrillar Scaffolds

Author and affiliation
Volkan M. Tiryaki[1], Kan Xie[1], Virginia M. Ayres[1], Ijaz Ahmed[2], David I. Shreiber[2]
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Abstract
A diagnostic approach based on analysis of discrete Fourier transforms of standard atomic force microscopy (AFM) section measurements is developed. The diagnostic approach provides clear feature definition for AFM images of neural cells on nanofibrillar scaffolds. A frequency domain Gaussian high pass filter was determined to be optimal. The diagnosis and custom filter design approach can expand user options towards more knowledgeable use of instrument supplied filters and even beyond the selection supplied with an AFM instrument. Clear feature definition of cells on scaffolds extends the usefulness of AFM imaging in regenerative medicine and contributes to understanding of the directive effects of the nano-environment.

Poster #6.

Quantitative Fluorescence Correlation Spectroscopy (FCS) of Single Molecules with Confocal Microscopy

Author and affiliation
Bonghwan Chon, Kimberly Briggman, and Jeeseong Hwang
Radiation and Biomolecular Physics Division, National Institute of Standards and Technology, Gaithersburg, MD 20899, USA

Abstract
Fluorescence correlation spectroscopy (FCS) is a technique to measure fluorescence emission intensity fluctuations originated from the Brownian motion of dye labeled molecules or particles through a small laser spot, a confocal volume in a confocal microscope, which is a common measurement platform for FCS measurements. A sensitive photon detector records the time trace of fluorescence emission intensities from the single dye molecules or from single fluorescent particles transiently existing in the confocal detection volume. From this intensity trace in time, the correlation function is calculated to extract information about diffusion times and number of diffusing molecules or particles in the volume. Physical models involving the source of the fluctuations are applied and the correlation curves are fitted to quantify their sizes and concentrations. In this study, we present a thorough quantitative evaluation on

how the measurement parameters (laser power, pinhole size, and molecule concentration) in confocal microscopy affect the FCS results of single dye molecules in solution.

Poster #7.

Absorption-based Hyperspectral Imaging and Analysis of Single Erythrocytes

Author and affiliation
Ji Youn Lee[1], Matthew L. Clarke[1], Fuyuki Tokumasu[2], John F. Lesoine[1], David W. Allen[3], Robert Chang[1], Maritoni Litorja[3], and Jeeseong Hwang[1]
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[2] Malaria and Vector Research Laboratory, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA
[3] Sensor Science Division, National Institute of Standards and Technology, Gaithersburg, MD 20899, USA

Abstract
We report an absorption-based hyperspectral imaging and analysis technique to resolve unique physico-chemical characteristics of subcellular substances in single erythrocytes. We constructed a microscope system installed with a spectral light engine capable of controlling the spectral shape of the illumination light by a digital micromirror device (DMD). The hyperspectral imaging system and the sequential maximum angle convex cone (SMACC) algorithm allow us to extract unique spectral signatures (i.e. endmembers) for different types of hemoglobin, such as oxyhemoglobin, methemoglobin, and hemozoin, and scattering from cell membrane in single erythrocytes. Further statistical endmember analysis, conducted on the hyperspectral image data, provides the abundances of specific endmembers, which can be used to build intracellular maps of the distribution of substances of interest. In addition, we perform modeling based on Mie theory to explain the scattering signatures as a function of scattering angle. The developed imaging and analysis technique enables label-free molecular imaging of endogenous biomarkers in single erythrocytes in order to build oximetric standards on a cellular level and ultimately for in vivo as well.

Poster #8.

Surface plasmon resonance imaging to measure cells and substrate interactions

Author and affiliation
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Biochemical Science Division, National Institute of Standards and Technology
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Abstract
We demonstrate the application of surface plasmon resonance imaging (SPRI) as a technique to quantitatively measure cell and protein interactions at a surface. SPRI is essentially a refractive index measurement that that is spatially sensitive to mass changes at the surface sensor. SPRI allows for label-free, real-time, live-cell imaging that contains quantitative information about protein mass changes and

dynamics of the cell/substrate interaction. Changes in protein mass due to secretion from cells and addition to the surface matrix are imaged and quantified concurrently with cellular movement, spread area and points of adhesion.

Poster #9.

Cell cycle dependent TN-C promoter activity determined by live cell imaging

Author and affiliation
Michael Halter[1], Daniel R. Sisan[1], Joe Chalfoun[1], Benjamin L. Stottrup[2], Antonio Cardone[1], Alden Dima[1], Alex Tona[1], John T. Elliott[1], Anne L. Plant[1]
[1]National Institute of Standards and Technology, Gaithersburg MD; [2]Augsburg College, Minneapolis, MN
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Abstract
The extracellular matrix protein tenascin-C plays a critical role in development, wound healing, and cancer progression, but how it is controlled and how it exerts its physiological responses remain unclear. Fully automated image analysis routines, validated by comparison with data derived from manual segmentation and tracking of single cells, are used to quantify changes in cellular GFP in hundreds of individual cells throughout their cell cycle during live cell imaging experiments lasting 62 hours. This work illustrates the application of live cell microscopy and automated image analysis of a promoter-driven GFP reporter cell line to identify subtle gene regulatory mechanisms that are difficult to uncover using population averaged measurements.

Poster #10.

Tissue Phantoms for Dimensional Metrology in Depth-Resolving Optical Systems

Author and affiliation
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Abstract
We report on a novel fabrication approach to build multilayered optical tissue phantoms that serve as independently validated test targets for axial resolution and contrast in scattering measurements by depth-resolving optical coherent tomography (OCT) with general applicability to a variety of three-dimensional optical sectioning platforms. We implement a combinatorial bottom-up approach to prepare monolayers of light-scattering microspheres with interspersed layers of transparent polymer. A dense monolayer assembly of monodispersed microspheres is achieved via a combined methodology of polyelectrolyte multilayers (PEMs) for particle-substrate binding and convective particle flux for two-dimensional crystal array formation on a glass substrate. Modifications of key parameters in the layer-by-layer polyelectrolyte deposition approach are applied to optimize particle monolayer transfer from a glass substrate into an elastomer while preserving the relative axial positioning in the particle monolayer. Varying the dimensions of the scattering microspheres and the thickness of the intervening

transparent polymer layers enables different spatial frequencies to be realized in the transverse dimension of the solid phantoms. Step-wise determination of the phantom dimensions is performed independently of the optical system under test to enable precise spatial calibration, independent validation, and quantitative dimensional measurements.

Poster #11.

Predicting rates of cell state change due to stochastic fluctuations using a data-driven landscape model

Author and affiliation
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Abstract
We model experimental data from a fibroblast cell line that exhibits a wide range of green fluorescent protein (GFP) expression levels under the control of the promoter for tenascin-C. Time lapse live cell microscopy provides data about short term fluctuations in promoter activity, and flow cytometry measurements provide data about the long term kinetics as isolated subpopulations of cells relax from a relatively narrow distribution of GFP expression back to the original broad distribution of responses. We use the steady state distribution of cellular phenotypes and a quantitative description of the short term fluctuations in individual cells to accurately predict the rates at which different phenotypes arise from an isolated subpopulation of cells.

Poster #12.

SUBCELLULAR EFATURE ANALYSIS OF CYTOSKELETON RESPONSES TO ECM RIGIDITY

Author and affiliation
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Abstract
The cytoskeleton drives many of the processes underlying cell shape changes. Developing quantitative metrics for numerically describing the organization of the cytoskeleton is hence valuable for studying cell shape responses. We are interested in understanding how features extracted from epifluorescence microscopy images are related to cytoskeletal proteins generating contractile force, its transmission, and signaling complex organization within cells, when the mechanical rigidity of the extracellular matrix (ECM) is varied. To visualize the cytoskeleton, we used antibody/fluorophore-labeling of cells for di-phosphorylated myosin, filamentous actin, and phosphorylated tyrosine. In order to modulate ECM rigidity, we used a previously described engineered extracellular matrix comprised of a thin film of collagen fibers, which is highly reproducible, mechanically tunable, and exhibits excellent optical characteristics. From high resolution light microscopy images obtained, we spatially fractionated the f-actin cytoskeleton into distinct regions within cells, and used this as a mask to compute cytoskeletal features in all images. By analyzing features extracted from this high dimensional data, we are studying relationships between cell morphology, and protein spatial location, protein activation levels, and their correlations.

Poster #13.

DISSECTING ECM-DRIVEN CELL RESPONSES USING AN ENGINEERED EXTRACELLULAR MATRIX

Author and affiliation
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Abstract
The extracellular matrix, along with other components of the cellular microenvironment, provides specific cues for the maintenance of cell phenotype. A basic component of tissue engineering is hence an understanding the nature of the specific cues ECMs provide cells. ECMs of type 1 collagen are of especial interest in this context because they provide multiple cues to cells: topographical (by varying collagen polymerization), mechanical (by varying collagen density or crosslinking), or receptor-specific cues (by varying multiple aspects of collagen presentation). Traditional bulk gels of collagen as a substrate for cell culture have certain disadvantages in terms of poor physical stability, poor optical properties, and low reproducibility. As an alternative to bulk gels, we had previously engineered thin films of Type 1 collagen, which ameliorate many of these disadvantages. These submicron-thick films comprised of polymerized collagen fibrils are robust, highly reproducible, have excellent light transmission characteristics, and at the same time elicit similar cell responses in spreading and proliferation as those seen on collagen gels,. The films can be modified in multiple ways to change their properties including mechanical stiffness with or without enzymatic crosslinking, extent of fibril formation, and the presentation of glycosyl groups. Using these thin films, we are attempting to understand how specific signals presented to cells by multiple aspects of collagen ECM influence phenotype. In the studies presented here, we examined how collagen mechanical stiffness, the presence or absence of polymerized fibrils, or the presence or absence of glycosylation groups on collagen, influence the modulation of cell adhesion related signaling. Specifically, we examined how these various cues provided by collagen ECM modulate the levels of focal adhesion kinase (FAK), and the activation of the collagen receptor DDR2. Our results suggest that different cell responses are affected by distinct cues presented by collagen, and suggest that the collagen thin films are a useful experimental system to systematically develop metrics for understanding cell-ECM interactions.

Poster #14.

An Engineering Approach to Regenerative Medicine

Author and affiliation
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Abstract
As Regenerative Medicines, (RM), reach the market place, there is a pressing need for an improved understanding of the engineering and economic issues associated with them. In particular there is a need for improved process monitoring and control in the manufacturing of RM products. This presentation will detail the application of engineering techniques to the monitoring and processing of Regenerative Medicines and the impact this work has made on industry. Specifically research activities in the non-invasive monitoring of tissue scaffolds in-process, scaffold characterization post-fabrication, processing of tissue engineered products, label free approaches to cell typing and the development of strategies for in vivo imaging will be described.

Poster #15.

Gradient Index (GRIN) Lens System for High-Resolution *in vivo* Neural Imaging

Author and affiliation
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Abstract
Compound GRIN lenses enable deep brain imaging in live mice. Yet, their field-of-view is only a few 10's of microns, and the axial resolution is poor due to negative spherical aberration. To improve these, a 0.6 NA GRIN lens singlet was used in conjunction with cover glasses, to add positive spherical aberration, and an objective with a correction collar to provide fine adjustment. The FOV was increased to ~150 μm. Also, the lateral and axial resolutions were 618 nm and 5.5 μm, respectively, versus ~1 μm and ~15 μm, respectively, for compound lenses. This improvement enabled observation of large dendritic spines in CA1 of live Thy1-YFPH mice.

Poster #16.

Intravital Imaging of Hematopoietic Cell Dynamics

Author and affiliation

Jeffrey R. Harris[1,2], *Markus Covert*[3], *Tannishtha Reya*[2], *and John P. Chute*[1,2]
[1]*Division of Cellular Therapy,* [2]*Department of Pharmacology and Cancer Biology Duke University Medical Center, Durham, NC, USA*
[3]*Department of Bioengineering, Stanford University*

Abstract

Although we have learned a great deal about the phenotype and function of hematopoietic stem and progenitor cells, we have remained largely in the dark about the dynamic behavior of these cells in context of their native microenvironment. Here we describe a strategy that combines the use of transgenic mice with intravital microscopy to allow in vivo imaging of hematopoietic cell behavior in real-time. The high spatial and temporal resolution has allowed us to visualize the living hematopoietic tissue with exceptional clarity, and observe the architecture and dynamics of transplanted hematopoietic cells in the bone marrow microenvironment. Thus, intravital imaging of the bone marrow microenvironment provides a unique view within the living organism and is a powerful tool for gaining new insight into the regulation of fundamental biological processes such as homeostasis and regeneration.

Poster #17.

Angled Fluorescent Laminar Optical Tomography for Tissue Engineering

Author and affiliation

*Chao-Wei Chen, Andrew B. Yeatts, John P. Fisher, Yu Chen**
Fischell Department of Bioengineering and Department of Electrical and Computer Engineering, University of Maryland, College Park, MD 20742

Abstract

Optimization of regenerative medicine strategies includes the design of biomaterials, cell-seeding methods, cell-biomaterial interactions, and molecular signaling within the engineered tissue. One challenge is to comprehensively observe and quantify the distribution and migration of seeded cells throughout the bulky scaffold. We developed angled laminar optical tomography (aFLOT) as an in vitro tool to non-destructively visualize 3D cell distribution within scaffold. Because of the non-destructive nature of the system, it enables longitudinal inspection of massive amount of samples.

Poster #18.

High Field Magnetic Resonance Spectroscopy, Imaging and Elastography for Cartilage Tissue Engineering

Author and affiliation

Mrignayani Kotech[1], Ziying Yin[1], Temel Kaya Yasar[2], Dieter Klatt[1], Thomas J. Royston[1,2] and Richard L. Magin[1]
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Abstract

Cartilage tissue engineering is a promising technology for cartilage restoration and regeneration therapies. Cartilage is composed of chondrocytes cells (~1%), tissue fluid (~75% of wet weight) and extra cellular matrix (~25%, mainly proteoglycans and type II collagen). In order to mimic native cartilage, tissue engineers focus on production of the ECM component using a variety of approaches to assemble de novo tissue from appropriate cell types, biocompatible gels, biodegradable scaffolds and chondrogenic growth factors. The ultimate success of engineered tissue is normally assessed using histology and biochemical assays. Unfortunately, these techniques of visualizing growth can only be performed only once. Magnetic Resonance Imaging (MRI) is emerging as an alternative, non-invasive tracking tool for tissue engineering because it provides a means for the periodic acquisition of quantitative information (T2, T1ρ, T1, ADC and stiffness) about the development of the engineered tissue, both pre and post-implantation. We present here recent results for tracking cartilage tissue engineering at the early stages of growth in vitro and in vivo.

Poster #19.

Multi Modal Regenerative Imaging

Author and affiliation

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Abstract

Approach proposed incorporates a unique integration of high field magnetic resonance imaging (MRI) and elastography (MRE), to provide anatomical and structural information, and near-infrared optical imaging (NIR), to provide molecular composition, of engineered tissue constructs. We demonstrate: i) specific MRI parameters are highly correlated with particular compositional changes such as bone mineralization; ii) quantitative MRE measures dynamic variations in shear stiffness related to structural transformation of constructs both in vitro and in vivo of MSCs derived constructs; and iii) optical tags illustrate the formation of osteogenesis in a mouse model with excellent sensitivity and specificity.

Poster #20.

Collaborative Research Activities and Resources in Tissue Engineering and Imaging at UC Davis

Author and affiliation
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Abstract
The eloquent processes of cellular organization and tissue formation proceed in a nonlinear fashion. The microenvironment directs tissue formation at many levels including controlling cell shape, adhesion, and migration, enabling signal transport, and supplying appropriate tissue functional properties. The unpredictable remodeling of a tissue underscores the need for noninvasive imaging modalities to follow tissue formation, repair and regeneration. We will describe collaborative efforts on our campus spanning the Dept. of Biomedical Engineering, the School of Medicine, Center for Molecular and Genomic Imaging (CMGI) and the NSF Center for Biophotonics to use various imaging methods to assess tissue formation in vitro and in vivo.

Poster #21.

"Clickable" Cytocompatible PEG-co-Polycarbonate Hydrogels for Encapsulation of MSC

Author and affiliation
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Abstract
Strategies to encapsulate cells in cytocompatible 3-D hydrogels with tunable mechanical properties and degradability without harmful gelling conditions are highly desired for regenerative medicine applications. Here we report a method for preparing poly(ethylene glycol)-co-polycarbonate hydrogels through copper-free, strain-promoted azide–alkyne cycloaddition (SPAAC) click chemistry. Hydrogels with varying mechanical properties were formed by “clicking” azido-functionalized poly(ethylene glycol)-co-polycarbonate macromers with dibenzocyclooctyne-functionalized poly(ethylene glycol) under physiological conditions within minutes.Bone marrow stromal cells encapsulated in these gels exhibited higher cellular viability than those encapsulated in photo-cross-linked poly(ethylene glycol) dimethacrylate. The precise control over the macromer compositions, cytocompatible SPAAC cross-linking, and the egradability of the polycarbonate segments make these hydrogels promising candidates for scaffold and stem cell assisted tissue repair and regeneration.

Poster #22.

Cryo-imaging, the answer to "Where did my cells go?"

Author and affiliation

David L. Wilson,[1] Patiwet Wuttisarnwattana,[1] Mohammed Qutaish,[1] Madhusudhana Gargesha,[1,2] Sasidhar Katari,[2] WouterVan't Hof,[3] Zhenghong Lee,[1] and Kenneth Cooke[1]
[1]Case Western Reserve University; [2]BioInVision, Inc.; [3]Athersys, Inc.

Abstract

We developed and applied a cryo-imaging system which enables assessments of stem cell biodistribution, homing, and engraftment in whole-mouse with single cell sensitivity. A frozen mouse is sectioned and imaged in a tiled, automated fashion, providing anatomical brightfield and molecular fluorescence, 3D microscopic imaging. Stem cells are fluorescently labeled with quantum dots, dyes, and/or gene reporters. Machine learning software accurately detects fluorescent clusters, enabling excellent recovery (up to 90%) of injected cells at early times. Software provides cell counts and densities, and interactive visual microscopic exploration of any cell-containing tissue. We will describe applications including cell therapy of infarct and GVHD, as well as stem cell biology.

Poster #23.

Development of Methodologies for Multimodal *in vivo* Imaging in Rats

Author and affiliation

Daniel Vonwil[1], Jon Christensen[1], Olaf Ronneberger[2], V. Prasad Shastri[1]
[1]Institute for Macromolecular Chemistry and BIOSS-Center for Biological Signalling Studies [2]Department of Computer Sciences, Albert-Ludwigs-University Freiburg, Germany

Abstract

By combining functional methodologies such as fluorescence molecular tomography (FMT), fMRI with μCT and proteomics, functional information that is quantitative, rich in biological information and anatomically accurate can be obtained. Towards this goal of multimodal imaging, we have developed in-house an imaging module that is compatible with both the FMT2500 and the SkyScan1178 μCT systems, thus enabling for the first time the implementation of full body FMT scans and reconstructions of adult rats (~160 g), and accurate superimposition of regions of interest. Ongoing efforts in our laboratory are focused on the refinement of the imaging bed, and the development of small molecule and cell-based probes for functional targeting and function imaging.

Poster #24.

Beyond Fluorescence: Small and Bright Upconversion Nanoparticles for Biological Imaging

Author and affiliation

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Abstract

Lanthanide-doped upconversion luminescent nanoparticles (UCNPs) are promising materials for in vitro and in vivo optical imaging due to their unique optical and chemical properties. UCNPs absorb low energy near-infrared (NIR) light and emit high-energy shorter wavelength photons. Their special features allow them to overcome various problems associated with conventional imaging probes. Here, we present a new type of biocompatible UCNP. They are free of autofluorescence for in vitro cell imaging, and exhibit significantly improved signal-to-noise-ratio (i.e., 300 for Balb-c mice) and outstanding tissue penetration depth (>3cm), and minimal light scattering, all highly desired for in vivo whole animal imaging.

Poster #25.

Small Animal Imaging Program at the Frederick National Laboratory for Cancer Research

Author and affiliation

Joseph D. Kalen[1], Marcelino Bernardo[2], Peter L. Choyke[3], Piotr Z. Grodzinski[4], Lilia V. Ileva[1], Kristin L. Komschlies[5], Nimit Patel[1], Richelle L. Putman[1], Lisa A. Riffle[1], and James L. Tatum[6]. [1]SAIP, LASP, SAIC-Frederick, Inc.; [2]MIP, LASP, SAIC-Frederick, Inc; [3]MIP, CCR, NCI; [4]OCNR, CSSI, NCI; [5]OD, Frederick National Laboratory for Cancer Research; [6]DCTD, NCI

Abstract

The Small Animal Imaging Program (SAIP) Core Facility at the Frederick National Laboratory for Cancer Research provides a comprehensive state-of-the-art "In Vivo" imaging facility to assist NCI investigators to characterize; mouse models, molecular markers for early detection, test new therapies, and monitor tumors in vivo; assist the NCI Nanotechnology Characterization Laboratory to characterize nanoplatforms; and supports the DCTD initiatives in developing standards in small animal imaging, and integrate imaging into drug development. The SAIP offers a wide-range of "in vivo" imaging techniques including: imaging modalities [bioluminescence (Xenogen IVIS SPECTRUM), fluorescence (CRi Maestro), tomographic fluorescence (Perkin-Elmer/Visen FMT-2500), magnetic resonance (Philips 3.0T), X-ray computed tomography (CT), single photon emission computed tomography (Bioscan NanoSPECT/CT), ultrasound and photoacoustics (VisualSonics Vevo 2100-LAZR), and positron emission tomography (Siemens Inveon PET/CT)], and also develops animal handling and image analysis techniques.

Poster #26.

Safely Imaging Stem Cells with a Fluorine-19 Magnetic Resonance Imaging (19F MRI) Tracer

Author and affiliation

B.M. Helfer[1], A. Balducci[1], Z. Sadeghi[2], C. O'Hanlon[1], A. Hijaz[2], C.A. Flask[2], A. Wesa[1]
[1]Celsense, Inc., Department of R&D, Pittsburgh, PA; [2]Case Western Reserve University, Cleveland, OH

Abstract

Labeling stem cells with a 19F MRI tracer enables a quantitative, specific and clinically relevant means of tracking therapeutic cells in vivo. Here we tested the safety and efficacy of a self-delivering 19F MRI tracer, which has been authorized for use in a clinical trial by the FDA for use with a cell therapy product, on human and murine hematopoietic stem cells. The MRI tracer did not alter the differentiation and repopulating activity either in vitro or in vivo, and enabled a pilot study of cell delivery and retention in vivo with 19F/1H MRI. This data supports the use of the tracer in clinical applications for regenerative medicine.

Poster #27.

Terahertz Biomedical Imaging Technology

Author and affiliation

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Abstract

We present spectral imaging results of osseous tissues obtained through terahertz time-domain transmission spectroscopy. Imaging with electromagnetic radiation in the THz frequency regime, between 0.2 THz and 10 THz, has made considerable progress in recent years due to the unique properties of THz radiation, such as being non-ionizing and transparent through many materials. The spectral response of composite bone tissues was investigated using pixel by pixel frequency-domain analysis. Comparisons of the time-domain and spectral characteristics were used to distinguish between regions of differing cellular type, mixed composition, and thickness.

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Poster #28.

Enhanced Homing Permeability and Retention of Stem Cells using Pulsed Focused Ultrasound

Author and affiliation

Scott R. Burks[1], Ali Ziadloo[1], and Joseph A. Frank[1,2]
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[2]Intramural Research Program, National Institute of Biomedical Imaging and Bioengineering

Abstract
Intravenous injection of therapeutic stem cells is the least invasive and most favorable route of administration, but is plagued by inefficient homing of cells to target loci. Pulsed focused ultrasound (pFUS) is a clinically utilized modality that noninvasively and nondestructively produces transient increases in local levels of cytokines, growth factors, and integrins. Consequently, increased homing and retention of mesenchymal stem cells or endothelial precursor cells are observed in pFUS-treated regions after intravenous cell injections. Our results lay the groundwork to enhance cell-based therapies using pFUS as a modality to target multiple types of stem cells to pathological sites.

Poster #29.

A Fiber-Optic-Based Imaging System for Non-Destructive Assessment of Bioengineered Tissues

Author and affiliation
Matthias C. Hofmann,[1] Bryce M. Whited,[1] Tracy Criswell,[2] William C. Vogt,[1] Marissa Nichole Rylander,[1] Christopher Rylander,[1] Aaron M. Mohs,[1,2] Shay Soker,[1,2] Ge Wang,[1] Yong Xu[1]
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Abstract
A major limitation in tissue engineering is the lack of non-destructive methods to assess the development of tissue scaffolds undergoing preconditioning in bioreactors. Due to significant optical scattering in scaffolding materials, current microscope-based imaging methods cannot "see" through thick and optically opaque tissue constructs. To address this deficiency, we developed a fiber-optic-based imaging method capable of non-destructive imaging of cells through a thick and optically opaque scaffold, contained in a bioreactor. This imaging modality is based on local excitation of fluorescent cells, acquisition of fluorescence through the scaffold, and fluorescence mapping based on the position of the excitation light. To evaluate the capability and accuracy of the imaging system, cells were labeled with fluorescent Quantum Dots that enabled us to image them through an opaque scaffold. Without sacrificing the scaffolds, we non-destructively visualized the distribution of the fluorescent cells through a ~500 μm thick scaffold with cell-level resolution and distinct localization. These results were similar to the control images obtained using an optical microscope with direct line-of-sight access. Through a detailed

quantitative analysis, we demonstrated that our method achieved a resolution of the order of 20-30 μm, with 10% or less deviation from standard optical microscopy. Furthermore, we showed that the penetration depth of the imaging method exceeded that of confocal laser scanning microscopy by more than a factor of 2. Our imaging method also enjoys a working distance (> 10cm) much longer than that of a standard confocal microscopy system, which can significantly facilitate bioreactor integration. We envision that this method will enable non-destructive monitoring of cells within a bioengineered tissue construct *in vitro*, as well as, after implantation *in vivo*.

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Presentation Notes

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FUNCTIONAL IMAGING FOR REGENERATIVE MEDICINE

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