TALK ABSTRACTS

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SESSION 1

THE EMERGENT LANDSCAPE OF THE MOUSE GUT ENDODERM AT SINGLE-CELL RESOLUTION

Dana Pe'er

Sloan Kettering Institute

2014 Pioneer Award

To delineate the ontogeny of the mammalian endoderm, we generated 112,217 single-cell transcriptomes representing all endoderm populations within the mouse embryo until midgestation. By using graph-based approaches, we modelled differentiating cells for spatio-temporal characterization of developmental trajectories and defined the transcriptional architecture that accompanies the emergence of the first (primitive or extra-embryonic) endodermal population and its sister pluripotent (embryonic) epiblast lineage. We uncovered a relationship between descendants of these two lineages, whereby epiblast cells differentiate into endoderm at two distinct time points, before and during gastrulation. Trajectories of endoderm cells were mapped as they acquired embryonic versus extra-embryonic fates, and as they spatially converged within the nascent gut endoderm; revealing them to be globally similar but retaining aspects of their lineage history. We observed the regionalized identity of cells along the anterior–posterior axis of the emergent gut tube, reflecting their embryonic or extra-embryonic origin, and their coordinate patterning into organ-specific territories

HOW DO DOCTORS THINK? USING VIDEO GAMES TO MODIFY PHYSICIAN DECISION MAKING

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2015 New Innovator Award

Importance: Diagnostic error is often due to physicians' *heuristics* (intuitive judgments), especially in time-pressured settings. Traditional continuing medical education methods do not remediate heuristics, leaving an important quality gap unadressed.

Objective: To test the efficacy of interactive technologies, such as 'serious games', at recalibrating heuristics, and thereby improving diagnosis.

Design: randomized clinical trial

Setting: online

Participants: We recruited a convenience sample of 320 emergency medicine physicians at the 2017 annual scientific meeting of the American College of Surgeons, selecting those who worked at non-trauma centers in the US.

Interventions: We randomized participants to one of four interventions targeting diagnostic errors in trauma triage in a single-blind trial: an adventure-based video game designed to recalibrate heuristics based on narrative engagement (story-telling); a puzzle-based video game designed to recalibrate heuristics based on analogical encoding (structured case comparison); text-based educational applications, designed to increase knowledge of clinical practice guidelines (active control); and no intervention or usual care (a passive control).

Main Outcomes and Measures: We used a validated virtual simulation as the outcome assessment tool. The simulation included 10 cases, including 4 that we categorized as *representative* (classic or 'archetypal') or *non-representative* ('non-archetypal') of severe trauma. We measured the proportion of under-triage (severely injured patients not transferred to trauma centers) on the virtual simulation and compared under-triage among groups using linear regression models.

Results: 268 (84%) physicians participated in outcome assessment. Physicians exposed to either game under-triaged fewer severely injured patients than those in the control group (-18%, 95%CI -30 to -6%, p=0.004 [adventure game]; -17%, 95%CI -28 to -6%, p=0.004 [puzzle game]). Physicians receiving text-based education under-triaged similar numbers of patients as those in the passive control (+8%, 95%CI -3 to 19%, p=0.15).

Conclusions and Relevance: Theoretically-based clinically-customized video games improved physicians' diagnostic decisions compared with traditional continuing medical education, and could serve as an adjunct to existing quality improvement programs.

HOW TO REACTIVATE SILENCED ALLELES IN GENES WITH MONOALLELIC EXPRESSION

Alexander Gimelbrant

Dana-Farber Cancer Institute

2014 Transformative Research Award

Widespread autosomal monoallelic expression (MAE) is an epigenetic phenomenon affecting thousands of mammalian genes in a manner resembling X-chromosome inactivation (XCI). Similar to XCI, MAE results in an epigenetic mosaic, with clonal cell populations showing highly stable transcriptome-wide patterns of full or partial allelic silencing. In contrast to XCI, very little is known about the mechanisms involved in the establishment and stable maintenance of allelic silencing of MAE genes.

To identify perturbations that can disrupt maintenance of allele-specific silencing, we have developed a new screening approach, Screen-seq, based on targeted RNA sequencing at dozens of MAE loci in parallel. Using this approach, we found, for the first time, conditions that can reactivate some MAE genes. In contrast to previous findings, the strongest reactivation effect was linked to DNA methylation. Allelic imbalance remained unchanged for other MAE genes, indicating that distinct epigenetic mechanisms are involved in MAE maintenance in different loci.

Surprisingly, we also found that allelic imbalance changed for hundreds of genes for which allelic skew appeared to be due to genetic, *cis*-regulatory mechanisms. We will discuss implications of this for understanding the interaction between epigenetic and genetic mechanisms of gene regulation.

SESSION 2

REGULATION OF CELL SIGNALING BY ZINC DYNAMICS

Amy Palmer

University of Colorado

2014 Pioneer Award

The focus of this Pioneer Project was to explore the role of zinc in regulating cell signaling. Zinc is absolutely essential to all forms of life. It is a crucial building block of cells and has been implicated in many fundamental functions, such as DNA synthesis, transcription, metabolism, and apoptosis. For organisms, zinc is required for growth, development and immune function, and perturbation of zinc is associated with numerous pathologies. Given the centrality of zinc in cell biology and human health, it is astounding that at the most fundamental level we still don't understand how zinc status and availability impact basic cellular functions, and the proteins that sense changes in zinc in order to regulate cellular processes remain a mystery. The traditional model of zinc in biology asserts that the ~ 2000 proteins, including > 700 transcription factors, that comprise the zinc proteome bind zinc constitutively. This Pioneer Project has explored a fundamentally different model where zinc acts as a cellular signal and direct regulator of transcription and metabolic processes by titrating occupancy of the zinc proteome.We have used cutting-edge technologies from live cell imaging to transcriptomics, ATAC-seq and proteomics to define zinc dynamics and the downstream consequences of these dynamics in neurons, infected macrophages and during the mammalian cell cycle. We have discovered that sub-nanomolar zinc dynamics alter expression of hundreds of genes in neurons, that zinc influences chromatin accessibility and transcription factor activity, and that zinc plays a role in the proliferation-quiescence cell fate decisions, regulating the mammalian cell cycle in two different phases. As with many exploratory high-risk projects, this Pioneer project also extended in an unexpected direction to develop a new tool called Riboglow to track single molecules of RNA in living cells.

INVESTIGATING THE MECHANISMS OF MOLECULAR MOTORS WITH CRYO-EM

Gabriel Lander

The Scripps Research Institute

2014 New Innovator Award

Cryo-electron microscopy (cryo-EM) proves to be an increasingly powerful tool for studying macromolecular structures with near-atomic precision. While high-resolution structures generally depict cellular machinery in a single conformational state, cryo-EM can also be used to explore the conformational landscape of very large, structurally heterogeneous macromolecular systems. We use a combination of 2D and 3D electron microscopy analyses to investigate the dynein motor complex, which plays a critical role in delivering components to specific locations within a cell. We have produced hundreds of 3D snapshots of the microtubule-bound dynein complex bound to a processivity cofactor, dynactin, to gain a mechanistic understanding of this motor's minus-end directed motion. Our analyses show how multiple dyneins are grouped onto a single molecular scaffold to promote collective force production, increased processivity, and favor unidirectional movement.

HIGH DIMENSIONAL IMAGING OF HUMAN TISSUE USING MIBI-TOF

Michael Angelo

Stanford University

2014 Early Independence Award

Understanding the role of distinct cellular phenotypes in tissue function, development, and pathogenesis requires tools that can rapidly and consistently quantify the expression of multiple proteins while preserving spatial information. With this in mind, we have designed a purpose-built instrument that utilizes high brightness primary ion sources and orthogonal time-of-flight mass spectrometry to rapidly image antibodies tagged with elemental metal reporters in intact tissue sections at sub-cellular resolution. Multiplexed Ion Beam Imaging by Time-Of-Flight (MIBI-TOF) detects elements from hydrogen to uranium, permitting simultaneous measurement of up to 42 labeled antibodies along with histochemical stains and native biological elements. We recently used this capability to analyze infiltrating immune cell populations in archival formalin-fixed paraffin embedded (FFPE) tissue sections from 42 triple negative breast cancer patients. Spatial enrichment analysis showed immune mixed and compartmentalized tumors, coinciding with expression of PD1, PD-L1 and IDO in a cell-type and location-specific manner. Ordered immune structures along the tumor-immune border served as a hallmark of compartmentalization and were linked to survival. We are currently working to build upon this initial effort to develop scoring mechanisms for guiding immune therapy drug selection.

SESSION 3

NEURAL MECHANISMS FOR DYNAMIC ACOUSTIC COMMUNICATION

Mala Murthy

Princeton University

2014 New Innovator Award

Social interactions require continually adjusting behavior in response to sensory feedback. For example, when having a conversation, sensory cues from our partner (e.g., sounds or facial expressions) affect our speech patterns in real time. Our speech signals, in turn, are the sensory cues that modify our partner's actions. What are the underlying computations and neural mechanisms that govern these interactions? To address these questions, my lab studies the acoustic communication system of *Drosophila*. To our advantage, the fly nervous system is relatively simple, with a wealth of genetic tools to interrogate it. Importantly, *Drosophila* acoustic behaviors are highly quantifiable and robust. During courtship, males produce time-varying songs via wing vibration, while females arbitrate mating decisions. We discovered that, rather than being a stereotyped fixed action sequence, male song structure and intensity are continually sculpted by interactions with the female, over timescales ranging from tens of milliseconds to minutes – and we are mapping the underlying circuits and computations. We have also developed methods to relate song representations in the female brain to changes in her behavior, across multiple timescales. Our focus on natural acoustic signals, either as the output of the male nervous system or as the input to the female nervous system, provides a powerful, quantitative handle for studying the basic building blocks of communication.

DNA-NANOTECHNOLOGY ENABLED MEMBRANE ENGINEERING

Chenxiang Lin

Yale University

2014 New Innovator Award

Lipid-bilayer membranes form barriers to define the boundaries of a cell and its subcellular compartments. They undergo modulated structural changes and mediate biochemical reactions to sustain the cell's life cycle. Inspired by such elegance in nature, engineers and biologists have aspired to build artificial membranes to recapitulate the cellular membrane structure and dynamics. Such in vitro preparations provide a complexity-reduced system for the study of functional interactions between membranes and their associating molecules. Here I present our technical innovations in programmable, high-precision membrane engineering. Our general approach is to use designer DNA nanostructures as templates to guide the assembly of lipid bilayers and transduce the programmable feature of the DNA nanostructures to the templated vesicles (Yang et al, Nat Chem, 2016). We show the assembly, arrangement, and remodeling of liposomes with designer geometry, all of which are exquisitely controlled by a set of modular, reconfigurable DNA nanocages, giving rise to membrane curvatures present in cells yet previously difficult to construct in test tubes (Zhang et al, Nat Chem, 2017). Further, we developed complementary approaches to manipulate pre-existing membranes in a biomimetic way (Grome et al, Angew Chem, 2018). Incorporating membrane-interacting proteins into these DNA-templated liposomes allows us to systematically study protein-mediated membrane dynamics, such as SNARE-mediated membrane fusion (Xu et al, JACS, 2016) and extended synaptotagmin-mediated lipid transfer (unpublished), unraveling mechanistic details that are previously hard to investigate. We expect this set of high-precision membrane engineering tools to not only enable quantitative biophysical analyses, but also open new opportunities in synthetic biology (e.g. artificial cells) and therapeutics (e.g. drug delivery).

HIGH RESOLUTION IMAGING OF THE HEART BY OPTICAL COHERENCE TOMOGRAPHY

Christine Hendon

Columbia University

2014 New Innovator Award

Cardiovascular disease is the leading cause of morbidity and mortality in the United States. Progress within the cardiovascular field towards early diagnosis, increased efficacy in therapy and understanding the underlying mechanisms of cardiovascular diseases have been aided in part by advances in medical imaging technologies. Optical coherence tomography (OCT) is a non-invasive imaging modality that provides depth-resolved, high-resolution images of tissue microstructure in real-time. OCT provides subsurface imaging of depths 1-2mm in cardiac tissue with high spatial resolution (10mm) in three dimensions and high sensitivity *in vivo*. Fiber-based OCT systems can be incorporated into catheters to image internal organs. These features have made OCT a powerful tool for cardiovascular imaging, with major contributions to the field of coronary artery disease. Previous work has demonstrated the capability of OCT to visualize important features of the myocardium, including fiber orientation and identification of radiofrequency ablation lesions. Within this talk, I will showcase my laboratory's work towards achieving our objective of characterization of subcellular level features within the myocardium that remodel due to disease. We have designed ultrahigh resolution optical coherence tomography imaging systems with polarization contrast, catheter based probes, and automated analysis applied to a cardiac atlas of 50 human hearts imaged. Through this study, we have established OCT image features corresponding to myofiber and collagen fiber orientation, adipose tissue, endocardial thickness and composition, and venous media. Comprehensive imaging of the entire left atrium, combined with template matching, has allowed us to compare tissue composition distribution between donor hearts. With its high speed, sensitivity, resolution, and we demonstrate that OCT has the potential to characterize features of the myocardium important for evaluating tissue remodelling and arrhythmogenic substrates, such as endocardial thickening, fibrosis, and adipose accumulation, which can be used for substrate guided therapeutic interventions.

CELL-FREE RNA IN A SINGLE DROPLET OF HUMAN SERUM REFLECTS PHYSIOLOGIC AND DISEASE STATES

Sheng Zhong

University of California San Diego

2015 Pioneer Award

Cell-free RNAs (cfRNAs) are present in human serum. It remains unclear to what extent these circulating cfRNAs may reflect human physiologic and disease states. Here, we developed Mols-seq (microliter of liquid sample-sequencing) to efficiently sequence both integral and fragmented cfRNAs from a small droplet (5–7 microliters) of liquid biopsy. We calibrated Mols-seq with standard RNA-seq based on milliliters of input serum and quantified droplet-to-droplet and donor-to-donor variations. We carried out Mols-seq on more than 150 serum droplets from male and female donors ranging from 19 to 48 years of age. Mols-seq detected cfRNAs from more than a quarter of the human genes, including small RNAs and fragments of mRNAs and long non-coding RNAs (lncRNAs). The detected cfRNAs included those derived from genes with tissue (e.g., brain)-specific expression. cfRNA expression completely separated the male and female samples and is correlated with chronological age. Non-cancer and breast cancer donors exhibited pronounced differences in cfRNA expression, whereas donors with or without cancer recurrence exhibited less distinct cfRNA expression patterns. Even without using differentially expressed cfRNAs as features, nearly all cancer and non-cancer samples and a large portion of the recurrence and non-recurrence samples could be correctly classified by cfRNA expression values. These data suggest the potential of using cfRNAs in a single droplet of serum for liquid biopsy-based diagnostics.

TARGETING BIOPHYSICAL CUES TO STUDY, DIAGNOSE, AND TREAT CANCER

Weian Zhao

University of California, Irvine

2014 New Innovator Award

Cancer metastases account for over 90% of cancer deaths, but remain difficult to treat. To improve the efficacy and specificity of treatment for metastatic cancer, we have been developing mechano-responsive cell systems (MRCS) using stem cells and immune cells to directly target tumors using biophysical cues, such as tissue stiffness. MRCS were engineered by lentiviral transduction to have stiffness-sensing promoters of mechanotransduction factors such as Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ). YAP/TAZ is activated when the cell contacts stiff tumor tissues to drive the expression of downstream reporters such as enhanced green fluorescent protein (eGFP) or firefly luciferase (Luc) for imaging, or an anti-tumor agent cytosine deaminase (CD) for treatment. We have demonstrated that MRCS was able to home to metastatic sites in a mouse model of breast cancer, and was able to significantly attenuate cancer progression when compared to saline and non-engineered cell controls. MRCS-treated mice showed less undesirable tissue toxicity compared with constitutively expressed CD. The MRCS can serve as a platform for future diagnostics and therapies targeting aberrant tissue stiffness in conditions such as cancer and fibrotic diseases, and it can also help to elucidate mechanobiology and reveal what cells “feel” in the microenvironment in vivo.

SESSION 4

QUANTITATIVE UNDERSTANDING OF SINGLE CELL RESPONSES TO KINETIC PATHWAY STIMULATION

Gregor Neuert

Vanderbilt University

2014 New Innovator Award

Systems biology research combines experiments with computation to improve our ability to understand and predict the behavior of biological systems. Although to-date, this research has produced several substantial advances, limitations to commonly used experimental and computational approaches exist. On the experimental side, most studies focus on the cellular response to instantaneously changing environments. Such experiments operate under the assumption that such environments are physiologically relevant and ignore the possibility that the rate of environmental change may affect cellular response. Meanwhile, traditional computational approaches result in biological models that make less-accurate predictions than models generated in other scientific fields.

To address the fundamental question of how cells consider environmental rate changes in deciding cell behavior, we monitored cell viability and activation of Mitogen Activated Protein Kinase (MAPK) signaling in response to varying rates of osmotic stress at the single cell level in real time. We discovered a novel threshold rate condition required for cell survival and signaling activation. The set point for the threshold rate condition is determined by the concentration of an evolutionary conserved Protein Tyrosine Phosphatase. These findings show how kinetic environments can cause distinct cellular phenotypes that present a hidden layer in understanding cell biology.

To determine why traditional computational approaches fail to enable accurate predictions of cellular response, we have analyzed single-cell, single-molecule measurements of mRNA during yeast stress response. We use this data to explore why and how the shapes of experimental distributions control prediction accuracy. We show how asymmetric data distributions with long tails cause standard modeling approaches to yield excellent fits but make meaningless predictions. We show how these biases arise from the violation of fundamental assumptions in standard modeling approaches. We demonstrate how single cell modeling yield predictive understanding of transcription control including RNA polymerase initiation, elongation and mRNA accumulation, transport, and decay.

REACTIVATION OF SALIENT EXPERIENCES IN ASSOCIATION CORTEX LINKS CUES TO OUTCOMES

Mark Andermann

Beth Israel Deaconess Medical Center

2014 New Innovator Award

Learning from sensory experiences requires linking cues to diverse, often delayed outcomes. Experiences of cues and outcomes activate brain-wide patterns of neurons. During subsequent quiet periods, memories of recent experiences may become consolidated via synchronous reactivation of these patterns throughout sensory cortex, amygdala, and hippocampus. A key hub that links these areas is lateral sensory association cortex, a region necessary for offline memory consolidation and recall of cue-outcome associations. We examined how reactivation of specific visual cue representations in postrhinal association cortex might link representations of cues and salient outcomes during gradual learning of a task. We imaged hundreds of neurons across weeks as head-fixed mice learned to discriminate between visual cues predicting appetitive, aversive, or neutral outcomes. We observed distinct patterns of neurons that responded to each visual cue during the task. The same patterns were subsequently reactivated during quiet waking in darkness. To identify these cue reactivation events, we developed a novel classifier that could accurately identify each cue presentation from momentary patterns of single-trial population activity, as well as subsequent reactivation of these patterns in darkness. Reactivation rates were higher following low-performance sessions, and were higher for food-predicting cues than for neutral cues, consistent with a role for cue reactivations in associative learning. Indeed, neurons encoding the delivery or anticipation of rewards were often reactivated synchronously with neurons encoding food cues. Strikingly, upon participation in food-cue reactivations, reward-coding ensembles of neurons increased their next-day functional connectivity with the network, while other ensembles decreased their connectivity. We suggest that joint cortical reactivation of cue and outcome representations may provide a substrate for consolidation of cue-outcome associations.

ALTERED LYMPHATIC TRANSPORT AND METABOLISM OF CHYLOMICRONS IN CROHN'S DISEASE

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[1] Washington University

2015 Pioneer Award

Early descriptions of the inflammatory bowel disease Crohn's disease (CD) highlighted lymphangitis as a feature, but surprisingly little research has analyzed lymphatics in CD patients. Dietary fat, packaged in chylomicron lipoproteins, passes through lymphatic vessels during absorption. We examined chylomicron transport during a postprandial response in 22 Crohn's subjects and 17 controls. Inclusion of ^{13}C-triolean in the study meal and a pulse of ^{2}H-glycerol i.v. generated readouts for absorption and catabolism of chylomicrons. CD patients with MRI-confirmed ileal disease activity were recruited, excluding those using steroids or with previous intestinal surgery. Patients were allowed to start prescribed biologics, albeit many were studied before onset of biological therapy. Chylomicron secretion and transport to plasma was linear in control subjects from 30 min after feeding to 2:30. During the first hour of absorption, CD subjects and controls showed similar chylomicron appearance in plasma. However, CD subjects taking anti-TNF targeting medications had heightened chylomicron transport during this time and reduced C reactive protein compared to other CD subjects, and this was correlated to strikingly elevated appearance of glucose insulinotropic peptide (GIP) in plasma. Despite this early functional response in all subjects, the second hour of transport was characterized by a severe dropoff in chylomicron accumulation in plasma of all CD patients that was 85% lower than the rise observed in control subjects during the same time frame. Thus, these translational studies provide the first quantitative evaluation of lymphatic cargo transport from the intestine in CD. These data suggest that transport of cargo begins normally in CD subjects but becomes greatly impaired in a later period. This later period may correspond a deeper region of the small bowel with compromised chylomicron secretion, transport, or both. This possibility and whether GIP accounts for some positive outcomes after anti-TNF therapeutics will be explored as next steps.

SIMULATING HEMODYNAMICS IN THE HUMAN VASCULATURE ON THE SYSTEMIC SCALE AT CELLULAR RESOLUTION

Amanda Randles

Duke University

2014 Early Independence Award

Over the past decade, we have seen an emergence of high-resolution hemodynamic simulation packages targeting the movement of cells in both microfluidic devices and microvasculature. While these detailed simulations can provide much needed insight into device design or cellular behavior in small regions of the body, we are still falling short when it comes to modeling cellular movement and interaction over large spatial and temporal domains. There is a critical gap between multiscale models needed to address scientific questions on the organism scale and available numerical and computational techniques. I will talk about our work to fill address this gap through the development of robust, parallel methods for coupling models across scales and underlying physics representations. In this talk, I will discuss the development of HARVEY, a parallel fluid dynamics application designed to model hemodynamics in patient-specific geometries. I will cover the methods introduced to reduce the overall time-to-solution, enable near-linear strong scaling on the largest supercomputers available to date, and introduce a novel, adaptive model approach to effectively capture cellular behavior at systemic scales. Finally, I will present the expansion of the scope of projects to address not only vascular diseases, but also treatment planning and predicting the movement of circulating tumor cells in the bloodstream.

SESSION 5

FORWARD AND REVERSE GENETICS IDENTIFIES PRIMATE-SPECIFIC LONG NON-CODING RNA GENES AS CONTRIBUTORS TO AND THERAPEUTICS TARGETS IN CANCER AND DIABETES

Leonard Lipovich

Wayne State University

2014 New Innovator Award

The ENCODE Consortium determined that two-thirds of human genes do not encode proteins. Long non-coding RNA (lncRNA) genes comprise an abundant, but still poorly understood, class of non-coding RNA genes. In the FANTOM Consortium, we characterized lncRNAs in human and mouse, highlighting the lack of their interspecies conservation (PubMed ID: 16683030). Unlike protein-coding genes, most human lncRNA genes lack conservation beyond primates (PMIDs: 24463510, 24429298). We interrogated the functional potential of non-conserved lncRNAs, a controversial topic (in view of the assumption that functional non-coding sequences should be conserved), in cancer and diabetes. We discovered and functionally validated primate-specific estrogen-activated oncogenic (and estrogen-repressed tumor-suppressor-like) lncRNAs in human estrogen receptor positive breast cancer cells. We have shown that these spliced, polyadenylated, cytoplasmic, non-conserved lncRNAs regulate cell growth and death (PMID: 28003470).

Over 95% of significant disease-associated variants from Genome-Wide Association Studies are non-coding, but the GWAS field continues to focus on protein-coding candidates. Overlapping all public significant GWAS variants with all Gencode lncRNA exons, we identified, as a top hit, LOC157273, a primate-specific cytoplasmic lncRNA, expressed solely in hepatocytes and found independently by over 20 GWAS of type 2 diabetes, BMI, CVD, and obesity, that we validated as a negative regulator of liver glycogen storage (and that, hence, may contribute to abnormally high fasting glucose levels). We developed oligonucleotide-based drugs targeting this lncRNA. In view of the precedents targeting liver ncRNAs with sequence-based drugs (PMID: 23534542), we posit that siRNA derivatives targeting our lncRNA can be delivered to the liver in vivo for type 2 diabetes treatment. Summarily, we show primate-specific lncRNAs, in cancer and normal cells, with genetic epidemiology and cellular phenotypes jointly pointing to specific roles in disease networks.

[NOTES: This work was supported by the National Institutes of Health (NIH) Director's New Innovator Award 1DP2-CA196375. The complete list of co-authors will be provided during the presentation.]

EXPANSION MICROSCOPY REVEALS A FIBROUS SCAFFOLD OF HUMAN CHROMOSOMES

Hu Cang

Salk Institute of Biological Studies

2014 New Innovator Award

How a human chromosome is folded into an X shape in less than 40 minutes remains elusive since the discovery of mitosis. Chromosome scaffold, a proteinous structure, comprising mainly topoisomerase 2a(top2a) and condensin, spanning the full length at the core of each chromatid, holds the key to the understanding of chromosome folding. However, its structure remains largely unknown. The scaffold was first found fibrous, appearing as an interconnected web of filaments, suggesting that top2a and condensin could oligomerize into filaments on chromatin to re-organize chromatin fibers at the chromosome-scale. However, the filaments were not observed directly, instead, after depleting histones from the chromosomes, leading to debates about whether the observed fibrous architecture was the result of harsh histone depletions. Even whether top2a is an integrated component of chromosome scaffold or merely precipitate during the invasive treatment remains unknown. The difficulty to directly visualize chromosome scaffold reflects the needs for a microscopy with higher resolutions. Here, by integrating STORM/Palm with expansion microscopy, we visualize chromosome scaffold directly, and reveal a fibrous architecture consisting of interlacing top2aand condensin filaments. Furthermore, the fibrous scaffold is found established in two steps. First, top2a and condensin filaments braid together into a single-axis scaffold, which then splits into two, one for each chromatid, giving rise to the iconic X-shape. Lastly, the braid-split process requires cooperation between top2aand condensin, mediated by the C-terminal domain of top2a. Antagonizing the cooperation disrupts chromosome assembly, blocks chrsomatid resolution, and leads to spherical, instead of rod-shaped chromatids. Together, we reveal a braid-split process, through which, filaments of top2a and condensin braid chromatin into a fibrous scaffold, giving rise to a helical order underneath seemingly disordered chromatin fibers.

SYNTHETIC GENETIC SYSTEMS FOR RAPID MUTATION AND CONTINUOUS EVOLUTION *IN VIVO*

Chang Liu

University of California, Irvine

2015 New Innovator Award

This talk will describe the construction of a yeast orthogonal replication system that rapidly and durably mutates user-selected genes without any elevation in genomic mutation rates (Ravikumar *et al.*, *Cell* **175**, 1946-1957, 2018). Applications in scalable protein and enzyme evolution will be discussed, including studying drug resistance, studying how enzymes evolve, engineering enzymes for the production of commodity chemicals, and rapid evolution of antibodies.

EXPLORER: INITIAL HUMAN STUDIES FROM THE FIRST MEDICAL SCANNER THAT SIMULTANEOUSLY CAPTURES 3-D IMAGES OF THE ENTIRE HUMAN BODY

Ramsey Badawi[1] and Simon Cherry[1]

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2015 Transformative Research Award

Positron emission tomography (PET) scanners generate in vivo images of the distribution and kinetics of radiolabeled molecules, providing a powerful and non-invasive window into human physiology, metabolic pathways and molecular targets. However, current PET scanners for humans cover only 15-30 cm of the body axially, leading to long scan times, higher radiation dose, and poor signal collection. The goal of the EXPLORER consortium is to design, construct and demonstrate the world's first total-body PET scanner that images the entire human body at once.

The large increase in efficiency with which the EXPLORER scanner collects signal provides roughly a factor of 40 gain over conventional PET/CT scanners. This allows whole-body PET studies to be acquired with unprecedented count-rates, improving the signal-to-noise ratio of the resulting images. Alternatively, the sensitivity gain can be used to acquire high-quality PET images at radiation doses on the order of that received for a roundtrip intercontinental flight, or with very short (sub-minute) scanning times. Furthermore, the scanner can, for the first time, dynamically image the entire human body in three dimensions. These capabilities could have a profound impact on both biomedical research and clinical practice.

The EXPLORER consortium recently completed the first scanner and has acquired initial scans of human subjects. The 194 cm long PET scanner is also combined with a computed tomography (CT) scanner that provides anatomic context for the PET images. High quality scans, scans with radiation doses of less than $1/10^{th}$ the standard radiation dose, and total-body pharmacokinetic studies with frame times as short as 1 second, have been acquired. The scanner offers new opportunities for human biomedical research and recently received 510(k) approval from the FDA, allowing it to be used for clinical PET studies and setting the stage for broader dissemination of this new imaging technology in the United States.

REGENERATIVE ENGINEERING: CONVERGENCE OF MATERIAL IMPORTANCE

Cato Laurencin

University of Connecticut

2014 Pioneer Award

We define Regenerative Engineering as the Convergence of Advanced Materials Science, Stem Cell Science, Physics, Developmental Biology, and Clinical Translation for the regeneration of complex tissues, organs and organ systems. Biomaterials play a centrally important role. Work in the area of musculoskeletal tissue regeneration has focused on a number of biomaterial technologies. Polymeric nanofiber systems create the prospect for biomimetics that recapitulate connective tissue ultrastructure allowing for the design of biomechanically functional matrices, or next generation matrices that create a niche for stem cell activity. Polymer and polymer-ceramic systems can be utilized for the regeneration of bone. Through the use of inducerons, small molecules fostering induction, the design of regeneration-inducing materials can be realized. Hybrid matrices possessing micro and nano architecture can create advantageous systems for regeneration, while the use of classic principles of materials science and engineering can lead to the development of three dimensional systems suitable for functional regeneration of tissues of the knee. Through convergence of a number of technologies, with advanced materials science playing an important role, we believe the prospect of engaging future grand challenges is possible.

SESSION 6

DEVELOPMENT OF HUMAN INTESTINAL SIMULACRA

Nancy Allbritton[1], Yuli Wang[1], Chris Sims[1], Shawn Gomez[1], Scott Bultman[1], Shawn Gomez[1], and Scott Magness[1]

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2015 Transformative Research Award

Organ-on-chips are miniaturized devices that arrange living cells to simulate functional subunits of tissues and organs. These microdevices provide exquisite control of tissue microenvironment for the investigation of organ-level physiology and disease. Human organ-on-chips are transforming biomedical research providing platforms that accurately replicate human tissues and enable a better understanding of human-to-human physiologic variations. These human organ facsimiles will fundamentally alter drug discovery and development by providing human constructs for screening assays, toxicity measurements and investigation of molecular-level drug actions. We have developed an open, planar format of a 3D polarized epithelium using primary human or mouse gastrointestinal stem cells to fully recapitulate gastrointestinal epithelial architecture and physiology. A planar monolayer comprised of stem/proliferative and differentiated primary cells was developed on a shaped hydrogel scaffold with an array of crypt-like structures. Imposition of chemical gradients across the crypts yields polarized epithelium with a stem-cell niche and differentiated cell zone. The stem cells proliferate, migrate and differentiate along the crypt axis as they do *in vivo*. We have developed a dense mucus layer (400 microns thick) on the luminal epithelial surface that is impermeable to bacteria and acts a barrier to toxins. An oxygen gradient across the tissue mimic permits luminal culture of anaerobic bacteria while maintaining an oxygenated stem cell niche. Our *in vitro* human colon crypt array replicates the architecture, luminal accessibility, tissue polarity, cell migration, and cellular responses of *in vivo* intestinal crypts. Intestinal biopsy samples can be used to populate these constructs to produce patient-specific tissues for personalized medicine and disease modeling. This bioanalytical platform is envisioned as a next-generation system for assay of microbiome-behavior, drug-delivery and toxin-interactions with the intestinal epithelia.

CONTROL OF THE NEONATAL SEPTISOME AND HYDROCEPHALUS IN SUB-SAHARAN AFRICA

Steven Schiff

Pennsylvania State University

2015 Pioneer Award

Hydrocephalus is the most common childhood condition requiring neurosurgery. Of the estimated 400,000 new cases each year, the majority are in the developing world, and neonatal sepsis is the largest single cause. The yearly death toll from neonatal sepsis is about 1 million lives lost, the majority in sub-Saharan Africa and southern Asia. Despite the enormous toll on life, most of the microbial agents causing neonatal sepsis remain unrecovered, and the agents responsibility for postinfectious hydrocephalus (PIH) are almost completely unstudied. This project seeks a comprehensive characterization of the neonatal sepsis underlying PIH, and the evolution of a strategy to achieve control of these conditions. We took as our first principle that a pan-microbial approach was required – a description of the composite of bacteria, viruses, parasites, and fungi that might be causal in combination or in sequence. Employing careful case controls, amplicon and whole genome sequencing, as well as viral oligomer concentration and RNAseq, we undertook an interlocking examination of PIH, the underlying population of neonatal sepsis, and a maternal-infant study, in order to trace the connections from in utero infections to neonatal sepsis and onward to PIH in Uganda. Surprisingly, we uncovered that there was a dominant species of difficult to culture bacteria that was highly virulent in PIH in this region of East Africa. Furthermore, there was a background viral co-infection that was prominent in the infants with bacterial brain infections. In addition, using satellite rainfall measurements, there was a powerful environmental connection to the location and timing of these infections. We can be highly predictive of the type of infection, knowing what village an infant came from, and when the infant developed sepsis. Our findings lead to an entirely novel predictive strategy to control and prevent such infant infections.

REMEMBERING THE PAST: A NEW FORM OF PROTEIN-BASED INHERITANCE

Daniel Jarosz

Stanford University

2015 New Innovator Award

During their lifetimes, individuals commonly experience transient changes in gene expression as a result of different environmental stimuli. These responses are often thought to have little heritable influence once they decay. However, we have recently discovered that such stimuli frequently induce self-perpetuating changes in protein conformations. This occurs most commonly in proteins that regulate information flow: chromatin modifying enzymes, transcription factors, and RNA binding proteins. These conformations can be broadly defined as prions, although their structures do not usually match the cross-beta sheet amyloids of the archetypical prion PrP. However, like known prions, corresponding changes in protein function are heritable from one generation to the next without any change to the genome. In this sense, such protein-based inheritance represents an extreme form of epigenetics. We have begun to characterize the biochemistry of these elements and investigate their influence on disease, development, and evolution. Lessons learned provide insight into mechanisms of pathological and beneficial protein aggregation alike, and how they might be modulated therapeutically.

THE RECREATIONALLY USED "BARBIE DRUG", MELANOTAN II, INDUCES AGGRESSIVE BEHAVIOR IN HUMAN MELANOMA CELLS

Robert Judson-Torres[1], Yuntian Zhang[2], Leor Weinberger[2], and Maike Hansen[2]

[1] University of Utah
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2014 Early Independence Award

While genetic changes are responsible for the initial events of tumorigenesis, transcriptional reprogramming that occurs in the absence of additional alterations to the genome can drive further progression. Consequently, small molecules that impact transcriptional programs within pre-cancerous cells could induce more advanced disease. Melanoma is often derived from pre-malignant lesions such as melanocytic nevi AKA the common mole. As moles are located within the skin, they are exposed to a myriad of stimuli, both unintentionally and, in the case of compounds used for cosmetic purposes, intentionally. Here we sought to determine whether such stimuli could increase the risk of reprogramming melanocytic cells into a more malignant state. We used digital holographic cytometry to conduct morphological and phenotypic analyses of single cells within populations of a panel human melanoma cell lines. We identified a re-occurring semi-stable cell state defined by distinct morphology and gene expression and increased propensities for tumor growth, cell invasion, and metastasis. Melanoma cells transitioned in and out of this state in the absence of genetic alterations. We measured the kinetics of the transition when exposed to a panel of small molecules and observed that Melanotan II – an unregulated compound used for cosmetic purposes that has been associated with nevus eruptions and melanoma initiation – increased the probability of switching into the aggressive state. In conclusion, we have identified a semi-stable and aggressive state of melanoma cells that is induced by a currently used and poorly regulated cosmetic compound.

SESSION 7

3D PRINTED NANO-BIONIC ORGANS

Michael McAlpine

University of Minnesota

2014 New Innovator Award

The development of approaches for the multidimensional integration of functional electronic components with biological tissue and organs could have significant impact in regenerative medicine, smart prosthetics, and restorative health. However, current electronic devices and systems are inherently two dimensional and rigid, thus prohibiting seamless meshing with three-dimensional, soft biology. The ability to three-dimensionally interweave biological tissue with functional electronics could enable the creation of bionic organs for regenerative applications, reversing impairments, or even augmenting functionality. Here, we present a novel strategy for overcoming these difficulties via additive manufacturing (3D printing) of biological cells alongside various classes of functional electronic nanomaterials. Previously, we have generated a functional bionic ear via 3D printing of a cell-seeded hydrogel matrix in the anatomic geometry of a human ear, along with an intertwined conducting polymer consisting of infused silver particles. This allowed for the in vitro culturing of cells around an inductive coil antenna in the ear, which subsequently connects to cochlea-shaped electrodes. Via the New Innovator mechanism, we have extended this concept toward a variety of new paradigms. These have included breakthroughs in 1) 3D printed patient-specific organ models, and 2) the direct writing of electronics and cells on the body, even while undergoing motion, 3) spinal cord regenerative devices and the 3D printing of viable neural progenitor cells, 4) 3D bioprinted cancer models which dynamically mimic metastasis, and 5) 3D printed bionic eyes. Overall, our approach has introduced a disruptive new method to intricately merge biology and electronics via next-generation, multifunctional 3D printing methods. The work outlined here thus constitutes a novel, highly interdisciplinary investigation to addressing outstanding questions in the generation of bionic organs, and we believe that this work has represented a series of key advances in dynamic tissue engineering, regenerative medicine, and 3D interweaving of functional electronics into biological systems.

NEAR DEATH EXPERIENCES AT THE CELLULAR LEVEL

Denise Montell

University of California, Santa Barbara

2014 Pioneer Award

Every day, every cell in our bodies makes an active decision whether to live or die. Apoptosis is a programmed form of cell suicide that is conserved in all multicellular organisms and functions to remove excess or damaged cells during development and stress. Proper regulation of apoptosis is essential to prevent degenerative diseases, cancer, and autoimmune disease. Activation of executioner caspases is a critical step, which until recently has been considered the point of no return. New work demonstrates that cells can survive caspase activation in a process we named anastasis. We have discovered that anastasis is a widespread and evolutionarily conserved cell behavior during normal development and stress. Moreover tumor cells exposed to chemotherapy can survive by anastasis and emerge with greater drug resistance. I will describe the physiological significance of this survival pathway and insights into the underlying molecular mechanisms.

DOES RACIALLY TARGETED FOOD ADVERTISING WORK? BLACK ADOLESCENTS SHOW STRONGER PREFERENCES FOR RACIALLY CONGRUENT FOOD ADS THAN WHITE ADOLESCENTS

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2015 Early Independence Award

Objectives: We examined whether Black and White adolescents preferred racially congruent food ads (i.e., race/ethnicity of the actor matches the viewer's self-reported race/ethnicity) as compared to racially incongruent ads and ads without people.

Methods: We conducted a randomized controlled online experiment with 387 Black and 455 White adolescents ages 13-17 years. Adolescents viewed 8 pairs of ads; each pair consisted of a social media ad and a print ad. One-quarter of ads featured Black individuals, one-quarter featured White individuals, and half of ads did not feature people. Adolescents rated ads on the following dimensions: trendiness, artistic appeal, how much they liked the ad, perceived deliciousness of the featured product, and purchase intentions. We examined Black and White adolescents' preferences for racially congruent ads relative to racially incongruent ads and ads without people.

Results: Black adolescents rated ads featuring Black individuals higher on all five dimensions as compared to ads featuring White individuals ($p < 0.002$) in models adjusted for brand preferences. In contrast, there were no differences in White adolescents' ratings of ads featuring White or Black individuals on 3 of the ad rating dimensions. On the remaining two dimensions, White adolescents rated ads featuring Black individuals significantly higher than ads featuring White individuals (delicious, $p=0.002$; purchase intent, $p=0.040$). While Black adolescents rated ads featuring Black individuals significantly higher than White individuals rated the same ads on 4 out of 5 dimensions, there were no differences in Black and White adolescents' ratings of food and beverage ads featuring White individuals or without people.

Conclusions: Black adolescents reported stronger preferences for racially congruent ads than White adolescents, suggesting racially targeted marketing may be more effective among Black adolescents relative to their White peers. Future research should examine whether Black adolescents' preferences for racially congruent ads influence food purchases and caloric intake.

PROGRAMMING ADAPTABLE HUMAN VASCULAR NICHE CELLS FOR ORGANOTYPIC STEM CELL REGENERATION

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[1] Weill Cornell Medicine

2014 Transformative Research Award

Stem cell self-renewal and fate determination are dependent on niche-derived signals. However, the source of the niche cells and mechanism by which these signals regulate tissue-specific regeneration are not fully defined. Tissue-specific endothelial cells (ECs) by production of defined angiocrine factors establish an instructive vascular niche that choreographs stem cell homeostasis and organ regeneration, such as hematopoietic stem cells (HSCs). To uncover the mechanism by which these organotypic angiocrine signals regulate stem cell reconstitution, we have devised an *in vivo* tissue-specific vascular niche platform for expansion of HSCs and for generating vascularized cardiac, epithelial, hepatic and neural 3D organoids.

Employing this vascular niche model, we show that ECs deploy signals that are essential for the specification, self-renewal and differentiation of human, mouse and non-human primate HSCs. Vascular niche cells are also essential for pluripotent-independent conversion of readily accessible adult ECs into engraftable HSCs. To prove this point, we transduced human or mouse adult mature ECs with Runx1/Spi1/Gfi1/FosB transcription factors along with vascular niche-induction enabling step-wise conversion of these ECs into long-term repopulating immunocompetent HSCs. Clonal populations of converted HSCs expanded on vascular niche in vitro, and fully reconstituted multi-lineage hematopoiesis in rodents. Co-infusion of the ECs along with HSCs augmented hematopoietic recovery, underscoring the significance of tissue-specific vascular niche-signals in stem cell reconstitution *in vivo*.

To translate the potential of vascular niche to the therapeutic setting, we have engineered generic adaptable ECs capable of adaptively vascularizing epithelial, hepatic, pancreatic beta islet, neural and cardiac 3D organoid cultures. Cross talk of adapted ECs with tissue-specific stem cells promotes proper patterning and remodeling of these organoids into functional tissues. Using *in vivo* regenerative models, we show that transplantation of ECs stimulates hematopoietic, hepatic, and lung repair without provoking maladapted fibrosis or tumorigenesis. These approaches have allowed us to uncover the molecular determinants of vascular heterogeneity; bringing us closer to translate the regenerative potential of ECs for organ repair to the clinic. We are in the process of performing the First-In-Human co-transplantation of HSCs with vascular niche cells to accelerate hematopoietic recovery. These upcoming clinical trials will set the stage for reconstructing and remodeling vascular niche *in vivo* for treatment of acquired, inherited, as well as malignant stem cell disorders. More importantly, tissue-specific vascular-stem cell organoid cultures facilitate screening by gene-editing and small molecule libraries to identify unknown vascular niche signals that coordinate stem cell self-renewal and differentiation for functional organ repair.

SESSION 8

REDESIGNING THE T CELL

Wendell Lim

University of California, San Francisco

2014 Transformative Research Award

We are interested in the general principles of how cells use molecular signaling circuits to make complex and precise decisions. We have been using a synthetic biology philosophy to rigorously test our understanding of these principles -- can we design synthetic circuits that endow living cells with novel sensing and response behaviors? Using this approach, we have been able to design next-generation therapeutic T cells with significantly enhances capabilities.

MOLECULAR MECHANISMS GOVERNING THE FUNCTION OF THE BLOOD-BRAIN BARRIER

Chenghua Gu

Harvard Medical School

2014 Pioneer Award

The blood-brain barrier (BBB) provides a safe and constant homeostatic brain environment that is essential for proper neural function. However, tightly regulated BBB is also the biggest obstacle for CNS drug delivery and BBB breakdown proceed neurodegeneration. Thus, understanding the basic mechanisms underlying BBB function will enable us to manipulate the BBB (increase or decrease its permeability) for treating neurological disease. My lab's recent discoveries have changed our understanding of how the BBB restricts blood-brain communication. BBB is formed by a layer of endothelial cells lining the walls of the brain's blood vessels. Historically, the restricted permeability of the BBB has been attributed to the specialized tight junctions between endothelial cells. However, substances can also cross endothelial cells by transcytosis, via endocytic vesicles that are trafficked across the cell. We discovered that transcytosis is *actively inhibited* in brain endothelial cells. We identified a molecular pathway and demonstrated that interfering with this pathway de-represses trancytosis and makes the BBB leaky. Our findings suggest that molecular pathways inhibiting transcytosis could be targeted to open the BBB for drug delivery. I will present our past and ongoing research on identifying novel key BBB molecular regulators and new tool development to study BBB. Our work have a big impact on therapeutics, enabling transient access of drugs to the CNS, and change how neurological diseases are treated. More broadly, our studies of vesicular trafficking in vascular endothelial cells have the potential to reveal general lessons about the regulation of trafficking in other cell types.

NATURAL AND ARTIFICIAL SELECTION ON INFLUENZA VIRUSES

Sarah Cobey

University of Chicago

2014 New Innovator Award

Adaptive immune responses impose strong selection on influenza viruses, but how an individual's immune memory evolves, and how individuals' immune memories collectively shape influenza's evolution and epidemiology, are unclear. We also have only a fuzzy understanding of how widespread vaccination affects these selective pressures. Using case data from the United States, Australia, and New Zealand, I present evidence that the hierarchical nature of immune memory (a phenomenon termed "original antigenic sin" and "imprinting") shapes influenza epidemic activity. Furthermore, the dynamics of immune memory appear to underlie the mediocre effectiveness of the influenza vaccine in recent seasons. This might explain why widespread vaccination in the United States is not having as strong an effect on influenza dynamics as we might expect, and as should be possible if strain mismatch were the only cause of imperfect effectiveness. These results point to several hurdles for the development of universal influenza vaccines.

IN SEARCH OF AN *IN VIVO* BIOPSY: STUDIES IN STIMULUS-RESPONSIVE COLLOIDS FOR BIOSENSING

Andrew Goodwin

University of Colorado

2014 New Innovator Award

Early disease detection and diagnosis requires sensing minute quantities of biomolecules in drawn fluids or imaging localized abnormalities in the body. Improvement upon existing technologies will require development of agents that can change their structure in response to the presence of an elevated biomarker with sufficient sensitivity, ignore the many other biomolecules present, and signal a positive result. This talk will address efforts in the Goodwin Lab to develop such technologies based on specifically-engineered nanoparticles that can bind to analytes to produce changes in detectable signal by many orders of magnitude. In one case, we developed mutually-reactive reagents that produce a fluorescent signal after aggregation and content mixing. In another case, the alignment of fluorocarbon droplets in an acoustic field allowed vaporization and detection by clinically relevant ultrasound. Each of these approaches utilizes mechanisms for in situ biomolecular detection, facilitating the development of in situ biosensors without washing steps or microfluidics.

The second part of the talk will focus on new technologies for increasing ultrasound contrast without the use of injected fluid. Microbubbles are the dominant ultrasound contrast agent owing to their ability to generate nonlinear contrast in the presence of acoustic waves. However, they suffer from poor stability in circulation and an inability to cross the vascular endothelium. Here, a series of mesoporous silica nanoparticles were synthesized with sizes around 100 nm. By specifically tuning both surface chemistry, pore size, and pore morphology, silica nanoparticles could be designed that could maintain their signal in whole blood. Finally, because of the ability of these nanoparticles to generate cavitation processes, these nanoparticles were shown to not only kill cells at distances of up to 400 μm away but also create transport channels for the perfusion of other small molecules such as cancer drugs or growth factors.

BUGS, DRUGS AND THE LOCAL MILIEU: USING MOLECULAR IMAGING TO GAIN NEW INSIGHTS

Sanjay Jain

Johns Hopkins University

2014 Transformative Research Award

The modern patient is increasingly susceptible to severe bacterial infection. However, traditional tools for infection are limited by their dependence on invasive sampling to access infections. While imaging is a powerful noninvasive technology widely used in the clinic, current imaging tools only provide anatomic localization of lesions, and cannot reliably differentiate true infections from other processes or provide detailed information about the local biology (e.g. drug concentrations, microenvironment).

We systematically screened ~1000 random radiolabeled small molecules to identify candidates that were selectively metabolized and accumulated in bacteria to develop several novel and specific imaging tracers for detecting, quantifying and monitoring bacterial infections. In addition, we have also developed several radio-labeled analogs of antimicrobial drugs and used them to study multi-compartment pharmacokinetics. Here we present animal and first-in-human data on three novel positron emission tomography (PET) molecular imaging tracers developed by us: 1) ^{18}F-fluorodeoxysorbitol (^{18}F-FDS), an analog of sorbitol, a Food and Drug Administration (FDA) approved "sugar free" sweetener, metabolized selectively by Gram-negative bacteria, but not mammalian cells, for rapid, specific detection, spatial localization and class discrimination of bacterial infections as well as rapid detection of therapeutic failures due to multi-drug resistant organisms (MDROs) *in situ*; 2) ^{11}C-Rifampin, a FDA approved first-line tuberculosis (TB) drug, for rapid, noninvasive multi-compartment pharmacokinetic (PK) assessments in several privileged compartments to inform human dosing and; 3) ^{124}I-iodo-DPA-713, a synthetic ligand for the translocator protein (TSPO), as a specific imaging biomarker for macrophage-associated inflammation, predictive of treatment efficacy and relapse in animal models.

These imaging tracers have significant potential for rapid diagnosis and monitoring of bacterial infections in patients, including life-threatening infections due to MDROs. Knowledge gained from these studies will not only provide unique mechanistic insights into bacterial pathogenesis, but will also be a major stride towards developing precision medicine tools for infectious diseases.