FAST
FUNCTIONAL ANALYSIS & SCREENING TECHNOLOGIES
CONGRESS

Engineering Functional 3-D Tissue Models

October 28-29

Phenotypic Drug Discovery

October 28-29

Screening and Functional Analysis of 3-D Models

October 29-30

Physiologically-Relevant Cellular Tumor Models for Drug Discovery

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SUNDAY EVENING, OCTOBER 27, 6:00-9:00 PM
SC1 Pre-Conference Dinner Short Course

Scaffolds: Bridging the Gap between 2-D and 3-D
Three-dimensional (3-D) in vitro models aim to bridge the gap between standard two-dimensional (2-D) cell-based assays and the in vivo environment. Scaffolds provide the foundation for this dimensional shift. Well-designed scaffolds provide the necessary local structural, mechanical and environmental cues to direct functional growth. Additionally, scaffolds help preserve the bioactivities of the biomolecules helping control biomolecule distribution and release. This interactive short course is designed to provide practical solutions for moving from 2-D to 3-D. Build your scaffold expertise!

Instructors:
Emerging Technologies for Assembly of Microscale Hydrogels
Ultran Demirici, Ph.D., Assistant Professor, Medicine and Health Sciences and Technology, Brigham and Women’s Hospital, Harvard Medical School

Preparation and Use of 3-D Porous Natural Polymer Scaffolds for in vitro Tumor Microenvironment Models
Stephen J. Forczyk, Ph.D., Biomedical Engineer, Biomaterials Group, Biosystems and Biomaterials Division, National Institute of Standards and Technology

Merging Microscale Technologies and Advanced Biomaterials for Cardiovascular Tissue Engineering
Nasim Annabi, Ph.D., Research Scientist, Ali Khademhosseini Laboratory, Tissue Engineering, Cardiovascular Division, National Institute of Standards and Technology

Automation of 3-D Cell Cultures Using Defined Biomimetic Hydrogels
Markus Rimann, Ph.D., Research Associate, Life Sciences and Facility Management, Zurich University of Applied Sciences

MONDAY EVENING, OCTOBER 28, 6:00-9:00 PM
SC2 Dinner Short Course

Automating a 3-D Culture Screening Laboratory: Meeting the Challenges
The paradigm shift from 2-D to 3-D cell culture models is under way and progressing rapidly. Although the screening community recognizes the functionality that 3-D models can provide, their implementation in any high-throughput screening laboratory is hampered by the lack of appropriate automation tools and technologies. In addition, when using complex models, their costs and readout speed have to be taken into account. This interactive short course offers insights on advancing the automation tools and technologies. In addition, when using complex models, their costs and readout implementation in any high-throughput screening laboratory is hampered by the lack of appropriate automation tools and technologies. In addition, when using complex models, their costs and readout speed have to be taken into account. This interactive short course offers insights on advancing the automation tools and technologies.

Instructor: Anthony M. Davies, Ph.D., Director, Irish National Center for High-Content Screening and Analysis (INCHA)

SC3 Dinner Short Course

Preparation and Use of 3-D Porous Natural Polymer Scaffolds for in vitro Tumor Microenvironment Models
Stephen J. Forczyk, Ph.D., Biomedical Engineer, Biomaterials Group, Biosystems and Biomaterials Division, National Institute of Standards and Technology

Merging Microscale Technologies and Advanced Biomaterials for Cardiovascular Tissue Engineering
Nasim Annabi, Ph.D., Research Scientist, Ali Khademhosseini Laboratory, Tissue Engineering, Cardiovascular Division, National Institute of Standards and Technology

Automation of 3-D Cell Cultures Using Defined Biomimetic Hydrogels
Markus Rimann, Ph.D., Research Associate, Life Sciences and Facility Management, Zurich University of Applied Sciences

TUESDAY EVENING, OCTOBER 29, 6:00-9:00 PM
SC4 Dinner Expert ThinkTank

How to Meet the Need for Physiologically-Relevant Assays?
Moderator: Lisa Minor, Ph.D., President, In Vitro Strategies, LLC

Panelists:
Anthony M. Davies, Ph.D., Director, Irish National Center for High-Content Screening and Analysis (INCHA)
Marina Fitzek, Associate Principal Scientist, Discovery Sciences, AstaZeneca
Aaron Morris, Ph.D., Lab Head, Cancer Biology, Sanofi Oncology
Michelle Palmer, Ph.D., Section Head, Screening and Compound Profiling, GlaxoSmithKline
Caroline Shamu, Ph.D., Lecturer, Systems Biology and Director, ICCB-Longwood, Harvard Medical School
D. Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute and Allegheny School of Medicine

For a detailed description of the Expert ThinkTank please visit www.FASTCongress.com.

*A separate registration is required to attend a short course.
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10:30 An Engineered Model of the Airways with All Primary Human Cells

Sonia Grego, Ph.D., Senior Scientist, Center for Materials and Electronic Technologies, Brown University

We present an application of 3-D levitation tissue culture system based on magnetic nanoparticles to modeling white blood tissue. We demonstrate efficient differentiation of mesenchymal progenitors into adipocytes achieved in parallel with endothelial cells organizing into vessel-like structures in 3-D organoids termed “adipospheres.” This magnetic levitation approach, enabling the retention and self-organization of cell types composing a tissue, may provide advantages for quick and simple organoids termed “adipospheres.” This magnetic levitation approach, enabling the retention and self-organization of cell types composing a tissue, may provide advantages for quick and simple

10:45 Coffee Break

ORGAN SHORT SESSION: LUNG MODEL APPLICATIONS

10:30 An Engineered Model of the Airways with All Primary Human Cells

Sonia Grego, Ph.D., Senior Scientist, Center for Materials and Electronic Technologies, Brown University

Microfluidic systems enable biomimetic cultures for more physiologically-relevant models of organ systems than cell-biomaterial interaction and the design of an appropriate 3-D microenvironment. This presentation will highlight examples showing the importance of microenvironment in influencing cellular behavior and will describe how one can purposefully tune this cell-biomaterial “handsaw.” The potential of specialized 3-D cellular systems in personalized medicine will be discussed.

9:45 Tissue Engineering in Magnetic Levitation 3-Dimensional Culture System

Michael Kotton, Ph.D., Associate Professor; John S. Dunn Research Scholar, Jerold B. Katz Distinguished Professor in Stem Cell Research, The Brown Foundation Institute of Molecular Medicine for Stem Cell and Regenerative Medicine, University of Texas Health Science Center at Houston

We present an application of 3-D levitation tissue culture system based on magnetic nanoparticles to modeling white blood tissue. We demonstrate efficient differentiation of mesenchymal progenitors into adipocytes achieved in parallel with endothelial cells organizing into vessel-like structures in 3-D organoids termed “adipospheres.” This magnetic levitation approach, enabling the retention and self-organization of cell types composing a tissue, may provide advantages for quick and simple organoids termed “adipospheres.” This magnetic levitation approach, enabling the retention and self-organization of cell types composing a tissue, may provide advantages for quick and simple

10:15 Coffee Break

ENGINEERING 3-D SYSTEMS

8:15 Chairperson’s Opening Remarks

Jeffrey Morgan, Ph.D., Professor, Medical Science and Engineering and Co-Director, Center for Biomedical Engineering, Brown University

Microfluidic systems enable biomimetic cultures for more physiologically-relevant models of organ systems than cell-biomaterial interaction and the design of an appropriate 3-D microenvironment. This presentation will highlight examples showing the importance of microenvironment in influencing cellular behavior and will describe how one can purposefully tune this cell-biomaterial “handsaw.” The potential of specialized 3-D cellular systems in personalized medicine will be discussed.

9:05 Designing a Tunable 3-D Heterocellular Breast Cancer Tissue Test System

Karen J.L. Burg, Ph.D., Hunter Endowed Chair and Professor of Bioengineering, Director, Institute for Biological Interfaces of Engineering, Clemson University

The viability of a tissue-engineered product relies on cell-biomaterial interaction and the design of an appropriate 3-D microenvironment. This presentation will highlight examples showing the importance of microenvironment in influencing cellular behavior and will describe how one can purposefully tune this cell-biomaterial “handsaw.” The potential of specialized 3-D cellular systems in personalized medicine will be discussed.

8:25 Integration of Systems Biology and Tissue Engineering in Drug Development

Linda D. Goffin, Ph.D., Professor, Biological Engineering and Mechanical Engineering and Director, Center for Gynepathology Research, Massachusetts Institute of Technology

Intense efforts in recent years to develop new therapies for chronic debilitating inflammatory diseases such as asthma, rheumatoid arthritis and inflammatory bowel disease have yielded many new promising classes of compounds, from kinase inhibitors, protease inhibitors and monoclonal antibodies directed at specific networks. Predicting efficacy (as well as off-target toxicities) in humans remains a significant challenge for therapies directed at these diseases, as intervention in a targeted node of a network may result in unintended compensation along other network paths or in off-target toxicities. To address these problems, systems biology approaches are being developed to predict phenotype, and responses to intervention, by linking extracellular communication networks to intracellular signaling networks using a compendium of data from patient samples, animal models and in vitro studies. Such approaches are being developed in parallel with a confluence of techniques to improve diagnostic tools and criteria, better classify patients according to clinical symptoms and findings and improve the information content of in vitro cell and tissue-based assays. This talk will focus on how to integrate systems biology approaches with 3-D in vitro models of liver and other organs.

11:00 Development of Engineered Trachea-Lung Constructs: The New Respiratory Models to Study Lung Development, Physiology, Pathology or Toxicology

Joan Nichols, Ph.D., Professor, Internal Medicine, Division of Infectious Diseases, University of Texas Medical Branch

Traditional culture assays to examine toxicity or pathogenicity in 2-D systems are flawed due to: 1) dependency on immortalized cell lines which do not adequately reflect biology and response of primary human cells, 2) reliance on single-cell systems that fail to recognize cell-cell interactions with the microenvironment and 3) reliance on artificial 2-dimensional monolayers for modeling complex diseases. Development of good in vitro human tissue models would help to bridge the gap in our current knowledge of lung responses, as well as provide a better understanding of lung development, physiology and pathology. A benefit of our current in vitro lung model is that hypotheses generated from review of data from human disease studies can be tested directly in engineered human tissue models. We are currently using complex 3-D systems to examine cell-based responses, physiologic functions, pathologic changes related to development of lung disease and lung fibrosis.

11:30 Next-Generation Bioengineered 3-D Human Tissue-Equivalent Platform System to Validate High-Volume Vaccine Production

Thomas J. Goodwin, Ph.D., Disease Modeling and Tissue Analogues Laboratory, NASA

An advanced 3-D regenerative tissue-equivalent disease modeling and detection system for most major human organs has been developed using a NASA platform. Normal human cells, tissue-engineered to grow in bioreactors simulating aspects of microgravity, serve as a platform to identify progenitor cell and organoid cellular interactions, modulations in gene expression and cellular differentiation. This technology validates longitudinal DNA and RNA viral proliferation, genomics and host proteomic inflammatory responses. The human lung epithelial cell construct mimics human respiratory epithelium including polarization, tight junctions, desmosomes, microvilli, functional tissue markers and maintains a long-term viral infective state without loss of cellular function. This model is a paradigm shift for high-volume production of virus for vaccine production.

11:45 Lung Cancer Models: Preclinical Models for Disease Development and Evaluation of Novel Therapeutics

Jonathan Garlick, D.D.S, Ph.D., Professor, Oral Pathology, School of Dental Medicine, Tufts University; Director, Center for Integrated Tissue Engineering and Professor, Tufts School of Medicine, School of Engineering and Sackler School of Graduate Biomedical Sciences

Human lung cancer is a leading cause of cancer-related mortality and has a high rate of recurrence and transplantation, yet the current models are not sufficient to predict outcomes and guide treatment strategies. One major obstacle is the lack of advanced preclinical models that closely mimic human lung tissue and disease development. In this talk, I will discuss recent advances in developing and utilizing preclinical models to study lung cancer development, progression, and treatment response.

12:00 pm Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

3-D MODEL SYSTEMS TO COMPREHEND HEALTH VS. DISEASE STATES

1:30 Chairperson’s Opening Remarks

1:35 3-D Intestinal Tissue Models

John March, Ph.D., Associate Professor, Biological and Environmental Engineering, Cornell University

Interactions between human upper intestinal cells and microorganisms populating the intestinal lumen are increasingly being resolved at the molecular level. We are developing in vitro tools to better understand human epithelial cells develop in a 3-D environment and how bacteria and other organisms interact with these cells.

2:05 Organs-on-Chips

Anthony Bahinski, Ph.D., MBA, FAHA, Lead Senior Staff Scientist, Wysup Institute

Development of safe and effective drugs is currently hampered by the poor predictive power of existing preclinical animal models that often lead to failure of drug compounds late in their development. Given the tremendous cost of drug development and the long timelines involved, major pharmaceutical companies and government funding agencies are now beginning to recognize a crucial need for new technologies that can quickly and reliably predict drug safety and efficacy in humans in preclinical studies. Advances in bioengineering, material sciences, microfabrication and microfluidics technologies have enabled the development of microphysiologic systems that mimic the functional units of an organ. These microsystems could potentially further our understanding of disease etiology and fill the critical need for improved model systems to predict efficacy, safety, bioavailability and toxicology outcomes for candidate compounds.

2:35 From iPSC to 3-D Skin Equivalents: Dynamic Platforms to Study Human Disease

Jonathan Garlick, D.D.S, Ph.D., Professor, Oral Pathology, School of Dental Medicine, Tufts University; Director, Center for Integrated Tissue Engineering and Professor, Tufts School of Medicine, School of Engineering and Sackler School of Graduate Biomedical Sciences

Induced pluripotent stem cells reprogrammed from somatic cells can now be developed into a broad spectrum of cell types. This technology provides important opportunities to use this replenishing source of stem cells to fabricate 3-D tissue. This presentation will describe how iPSC can be used to create 3-D, skin-like tissues that harbor the potential to improve drug screening and disease
modeling. We will demonstrate how 3-D human tissues can be used to elucidate the function and screen the safety of iPSC-derived cells before their clinical use and how to best leverage 3-D tissue models to help advance “Disease in a Dish” to “Disease in a Tissue.”

3:05 Refreshment Break in the Exhibit Hall with Poster Viewing

Customized 3-D Cell Cultures and Assays Showcase
All agree that 3-D cell models that are morphologically and functionally similar to native tissue hold the potential to improve in vitro assays. However, it is important to note that there is no one-size-fits-all solution; each cell type requires a different environment and different assays to screen them. This session showcases companies that are driving cell culture and screening assays into the new dimension of studying health vs. disease and drug response.

4:00 Tumor Microtissue Models to Study Gene Function Analysis
Jens M. Kelm, Ph.D., CSO & Co-founder, InSphero AG
Cancer cells in vivo are coordinately influenced by an interactive three-dimensional microenvironment. However, clinical-relevant identification of drug targets and initial target validations are primarily done in two-dimensional cell culture systems resulting in high failure rates. The design of 3-D co-culture models which reflect better heterotypic cell interactions enables investigations on the phenotypic impact of gene function with a model that more closely resembles tumor growth in vivo.

4:20 Automation, A New Dimension in 3D Cell Based Screening
Susanne Braun, Ph.D., Senior Market Manager, Applications & Solutions, Tecan
The adoption of 3D cell cultures for cell based screening has improved assay results significantly. Routine implementation of automation using liquid handling robotics and detection devices is mandatory to achieve high reliability and consistency. Tecan is showing solutions of automated 3D technologies on its Freedom EVO® liquid handling robotic system with its microplate readers and users optimized read out technologies to automatically assess 3D cell based structures.

4:40 Novel 3D Cell Migration Assay for Drug Efficacy and Cytotoxicity Testing Using an iPod
Glauco R. Souza, Ph.D., CSO, Nano3D Biosciences, Inc.
We will introduce a label-free cell based assay which combines 3D cell culturing by magnetic levitation and cell migration to quantitatively evaluate drug efficacy and toxicity using an iPod Touch. Results obtained with this high-content assay are significantly faster (6h to 5 days) than traditional 3D assays which rely on cell proliferation (10 to 30 days). We will present results with primary cells and cell lines that show significant differences in IC50 between 3D and 2D with various compounds: doxorubicin, Ibruprofen, retinoic acid, and SDS.

5:00 Welcome Reception in the Exhibit Hall with Poster Viewing

6:00–9:00 Dinner Short Course* (see page 2 for details)
SC2: Automating a 3-D Screening Laboratory: Meeting the Challenges
Instructors: Stephen Gundry, Research Scientist, Electrical Engineering, The City College of New York, CUNY
Nicolas Attux-Tafa, Ph.D., Research Scientist, École Supérieure de Physique et de Chimie Industrielles ParisTech
Markus Rimann, Ph.D., Research Associate, Life Sciences and Facility Management, Zurich University of Applied Sciences
*Separate registration required

TUESDAY, OCTOBER 29

7:30 am Breakfast Presentation (Sponsorship Opportunity Available) or Morning Coffee

3-D MODELS FOR DRUG SCREENING

8:30 Chairperson’s Opening Remarks
Jonathan Garlick, D.D.S, Ph.D., Professor, Oral Pathology, School of Dental Medicine, Tufts University; Director, Center for Integrated Tissue Engineering and Professor, Tufts School of Medicine, School of Engineering and Sackler School of Graduate Biomedical Sciences

8:35 Tissue Models of Disease and Their Potential for High-Throughput Screening
Victoria M. Viador, Ph.D., Scientific Consultant and former Staff Scientist, Center for Cancer Research, National Cancer Institute, NIH
A standard, simplified in vitro three-dimensional tissue model will be an invaluable tool for mimicking the biology of living tissues, studying the complexity added by disease and testing drug candidates. Thanks to fruitful collaborations between biologists, physicists and engineers, cell-based assays are expanding into the realm of tissue analysis. Accordingly, three-dimensional 3-D micro-organoid systems will play an increasing role in drug testing and therapeutics over the next decade. Nevertheless, important hurdles remain before these models are fully developed for high-throughput screening (HTS). Modeling 3-D tissues to mimic in vivo architecture remains a major challenge. I will highlight recent breakthroughs in the field of tissue biologics and their impact on the success of drug candidates through preclinical optimization. First, I focus on three-dimensional models by tissue or organ type with an emphasis on how faithfully the model is to tissue architecture and functionality, after which I explore models that are most amenable to high-throughput screening with emphasis on detection platforms and data modeling. As technology advances to provide novel 3-D methods of HTS analysis, so do potential pitfalls associated with such methods.

9:05 Alginate-Based 3-D Cell Culture System as an in vitro Tumor Model for Anticancer Studies
Chandralah Godugu, Ph.D., Research Scientist, College of Pharmacy and Pharmaceutical Sciences, Florida A&M University
Three-dimensional (3-D) in vitro cultures are recognized for recapitulating the physiological microenvironment and exhibiting high concordance with in vivo conditions. Taking the advantages of 3-D culture, we have developed an alginatel-based scaffold as an in vitro tumor model for anticancer drug testing and also to track nanoparticle penetration. Further, NSCLC stem cells were developed as 3-D in vitro tumor models and the effect of various anticancer drugs/nanoparticles were further studied and compared with parental cells and stem cell monolayer cultures. Finally, the effect of anticancer drugs on apoptosis induction and other antiprotactic markers were studied and compared with the 2-D cell culture systems. The audience will get a good appreciation of the role of alginateline-3-D cultures and their applications for anticancer drugs and nanoparticles investigations.

9:35 Inhibition of KRAS-Driven Tumorigenicity by Interruption of an Autocrine Cytokine Circuit
Amir Aref, Ph.D., Research Fellow, Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School
Models for disease processes are critically important both for improving understanding and developing new therapeutics. Microfluidic assays provide unique capabilities for mimicking the local microenvironment in terms of multiple cell types and for controlling and monitoring chemical gradients and cellular interactions. Here we present a new model to simulate the epithelial-to-mesenchymal transition, a critical stage in metastatic cancer, and use this model to examine differences in drug response between 2-D and 3-D and between monoculture and co-culture. Together, these studies reveal the potential of this approach in identifying new drug targets that have potential to prevent metastatic disease.

10:05 Coffee Break in the Exhibit Hall with Poster Viewing

10:45 Bioengineering Functional Human Trabecular Meshwork Outflow Systems for Anti-Glaucoma Drug Screening
Yubing Xie, Ph.D., Assistant Professor, College of Nanoscience and Engineering, University at Albany-SUNY
Glaucoma is the leading cause of irreversible blindness, resulting from elevated intraocular pressure (IOP). The current unmet need in the field is a proper in vitro model system that can be used to study outflow physiology and identify IOP-lowering agent. Based on our patented technology, we have successfully demonstrated the feasibility of recreating functional human trabecular meshwork (HTM) on microstructured, porous scaffolds and performing outflow studies and drug testing using the bioengineered HTM. Our results show that bioengineered HTM exhibited in vivo-like morphology, expression of HTM markers, outflow characteristics and drug responsiveness. This in vitro HTM model system provides a new avenue for understanding HTM physiology and pharmacological screening of anti-glaucoma therapeutics.

11:15 Drug Uptake and Diffusion in 3-D Multicellular Microtissues
Jeffrey Morgan, Ph.D., Professor, Medical Science and Engineering and Co-Director, Center for Biomedical Engineering, Brown University
My lab has developed an easy-to-use format for the formation of scaffold-free multicellular spheroids and we’ve devised new algorithms to quantitatively study 3-D drug transport in vitro. We are investigating the role of drug efflux transporters, such as P-glycoprotein (Pgp), and the effects of inhibitors of Pgp on the 3-D uptake and diffusion of drugs through the multiple cell layers of a spheroid. We’ve found that some inhibitors of Pgp also inhibit gap junctions, an activity not previously reported for these drugs. Multicellular spheroids are better mimics of the in vivo environment because their cell density is closer to that of real tissues and they better replicate the in vivo barriers to drug uptake and diffusion. The 3-D model discussed is useful for many different cell types including cancer cell lines, stem cells as well as human cells. Drug uptake and diffusion are critical to the efficacy and potential toxicity of all drugs. The audience will gain an understanding of a new 3-D technology, new algorithms to quantitatively study 3-D drug transport in vitro and new effects of well-known drugs that can only be uncovered using a 3-D system.

11:45 3-D Microtissues for the Discovery of Chemoradiation-Sensitizing Compounds
Michael Atkinson, Ph.D., Coordinator and Leader of Workshop 01, Institute of Radiation Biology, German Research Center for Environmental Health, Technical University of Munich
3-D tumor spheroids have been used as relevant biological models for oncology drug discovery for many years. However, aside from chemotherapeutic interventions, these 3-D models are also highly valuable tools for evaluating radiotherapy in vitro. In the presentation, the novel use of tumor co-culture spheroids for assessing combined chemo- and radiotherapeutic intervention will be illustrated. High-content analytical readouts are used to discriminate between the different cell populations in the 3-D microtissues to quantitatively the therapeutic impact on them.

12:15 pm Close of Engineering Functional 3-D Tissue Systems for Anticancer Studies
Jonathan Garlick, D.D.S, Ph.D., Professor, Oral Pathology, School of Dental Medicine, Tufts University; Director, Center for Integrated Tissue Engineering and Professor, Tufts School of Medicine, School of Engineering and Sackler School of Graduate Biomedical Sciences

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Functional Analysis & Screening Technologies Congress
Phenotypic screening (aka classical pharmacology) has been historically used in drug discovery. While technological developments have made the prevalence of target-based screening more popular, statistical analysis shows that a disproportionate number of first-in-class drugs with novel mechanisms of action come from phenotypic screening. Cambridge Healthtech Institute's Inaugural Phenotypic Drug Discovery meeting will address the advantages of phenotypic screening vs. target-based screening, and focus on assay development, selection of physiologically-relevant models and subsequent target identification.

MONDAY, OCTOBER 28

7:30 am Main Conference Registration and Morning Coffee

ADVENTAGE OF PHENOTYPIC DRUG DISCOVERY

8:15 Chairperson's Opening Remarks

8:30 The Contribution of Mechanistic Understanding to Phenotypic Screening for First-in-Class Medicines

David C. Swinneney, Ph.D., CEO, Institute for Rare and Neglected Diseases Drug Discovery (iRND3)

The level of mechanistic understanding required for drug discovery is a central feature of most strategies. Paradoxically, an understanding of mechanism is not required for regulatory approval. Recent analysis of how medicines were discovered showed that some mechanistic understanding was used to select starting points in the majority of successful phenotypic drug discovery programs. It was concluded that mechanism takes on different connotations depending on context and perspective, and that a target need not be the exclusive definition of mechanism.

8:55 Integrating Novel Technologies to Identify Small Molecules that Drive Translational Research and Therapeutics

Michelle Palmer, Ph.D., Director, Discovery and Preclinical Research, Broad Institute

9:20 Systematic Repositioning of Drugs Using Phenotypic Screening Data

Mark Hurle, Ph.D., Senior Investigator, Bioinformatics and Computational Biology, GlaxoSmithKline

Computational analysis of phenotypic screening data is often geared toward analysis of results from a single screen, identifying targets via annotation of the compounds hit. Hits are also commonly defined via change in a single measurable. By utilizing large numbers of screens and/or measurables, commonalities between targets and phenotypes can be detected. Two examples will be discussed: Connectivity Map, which utilizes genome-wide expression data, and CRUSH (Compound Repositioning Using Screening Hits), which analyzes high-throughput and focused screening data. These pipelines lead to repositioning of compounds and targets against additional diseases.

9:45 Coffee Break

HIGH-CONTENT ANALYSIS

10:15 The Role of HCA in Quantitative Systems Pharmacology

D. Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute and Allegheny Foundation; Professor, Computational and Systems Biology, University of Pittsburgh

We are implementing quantitative systems pharmacology (QSP) as a novel approach to drug discovery and development when combined with phenotypic methods using high-content analysis. We are implementing QSP for understanding the heterogeneity of response within tumors and then developing optimal therapeutics to address this biological complexity. In addition, QSP is being applied to the development and implementation of a 3D, human biomimetic liver acinus model to be used as an early safety assessment platform to optimize the development of lead compounds.

10:40 High-Content and High-Definition Screensings Identified Stem Cell Regulators

Sheng Ding, Ph.D., William K. Bowes, Jr. Distinguished Investigator, Gladstone Institutes; Professor, Pharmaceutical Chemistry, UCSF

Recent advances in stem cell biology may make possible new approaches for treatment of a number of diseases. A better understanding of molecular mechanisms that control stem cell fate function as well as an improved ability to manipulate them is required. Toward these goals, we have developed and implemented high-content and high-definition cell-based screens of chemical libraries to identify and further characterize small molecules that can control stem cell fate in various systems. This talk will provide latest examples of discovery efforts in my lab that have advanced our ability and understanding toward controlling stem cell fate.

11:05 A One-Step High-Content Imaging Assay to Monitor Apoptosis and Cell Cycle State in Mammalian Cells

Caroline Shamu, Ph.D., Lecturer, Systems Biology and Director, ICCB-Longwood, Harvard Medical School

11:30 Sponsored Presentations (Opportunities Available. Contact Ilana Quigley at 781-972-5457 or iquigley@healthtech.com.)

12:00 pm Luncheon Presentation: The BioMAP® Platform of Primary Human Cell Systems for Phenotypic Drug Discovery and Development – Lessons Learned

Elen L. Berg, Ph.D., General Manager and Scientific Director, BioSeek, a division of DiscoverRx

The BioMAP® platform of primary human cell-based disease models has been used since 2004 by companies, academics and the government to profile small molecules, natural products and biologics. From this experience, we have developed guidelines and best practices for the use of these assays in phenotypic drug discovery. Key applications that will be presented include the use of this platform to identify compounds that are more likely to progress in development and for deconvolution of compound mechanisms of action.

PHENOTYPIC SCREENING IN PHYSIOLOGICALLY-RELEVANT MODELS

1:30 Chairperson's Opening Remarks

1:35 Phenotypic Screening and Profiling in Increasingly Physiologically-Relevant Contexts

Anne Carpenter, Ph.D., Director, Imaging Platform, Broad Institute

Our laboratory works with dozens of collaborators worldwide to design and execute large-scale microscopy-based experiments to identify causes and potential cures of disease. Physiologically-relevant model systems are increasingly being used in this work, including co-cultures of two different cell types to better mimic functional tissue and whole organisms such as Caenorhabditis elegans to study entire organ systems. Machine-learning approaches, in some cases guided by biologists’ intuition, have been successfully used to measure subtle phenotypes in these complex model systems.

2:00 Expanding the Use of Primary Cell Systems in Hit Identification and Compound Profiling

Steve Ludbrook, Ph.D., Section Head, Screening and Compound Profiling, GlaxoSmithKline

The current focus on translationally-aligned drug discovery approaches, together with significant technology improvements, offers the potential to accelerate the uptake of primary cell screening systems in the drug discovery process. Examples of primary cell systems will be described, encompassing the increased usage of phenotypic assays in specific program critical path activities, but also primary screening activities for hit identification, with the aim of improving transition from the screening plate to the diseased patient.

2:25 Human Induced Pluripotent Stem Cells and Patient Specific Cell-Based Disease Models for Drug Discovery

Anne Bang, Ph.D., Director, Cell Biology, Sanford-Burnham Medical Research Institute

Patient-specific primary cells and human induced pluripotent stem cells (hiPSC) could aid in the development of clinically useful compounds. We used patient cells to develop a phenotypic assay for muscular dystrophy and conducted a high-content screen with the goals of identifying early treatment candidates. In addition, using hiPSC derived neurons, we performed a high-content screen for compounds that modulate neurite growth. We will discuss our high-content screening results and development of hiPSC based models.

2:50 Sponsored Presentation (Opportunity Available. Contact Ilana Quigley at 781-972-5457 or iquigley@healthtech.com.)

3:05 Refreshment Break in the Exhibit Hall with Poster Viewing
4:00 Identifying Cardioprotectants of an Ischemia-Reperfusion Model in iPSC-Derived Cardiomyocytes

Siobhan Malany, Ph.D., Chemical Biology Team Leader, Sanford-Burnham Medical Research Institute

Small molecules that protect cardiac cells from ischemia-reperfusion mediated death would potentially limit heart damage during heart attack. We have developed a TSBP-well high-throughput phenotypic acute cell-based model of ischemia and reperfusion injury in human iPSC-derived cardiomyocytes (iCells). Hydrogen peroxide treatment simulates the oxidative stress of reperfusion and 2-deoxy-D-glucose simulates the metabolic stress of ischemia. We screened known drug collections for their ability to protect iCells against cell death in a viability assay to better understand pathways involved.

4:25 HCS to Discover RNA Therapeutics for Heart Failure

Mark Menciola, Ph.D., Professor, Bioengineering, UCSD; Professor and Director, Muscle Development and Regeneration Program, Sanford-Burnham Medical Research Institute

There is an urgent need for therapies that reverse the course of ventricular dysfunction in heart failure, which is a leading cause of morbidity and mortality. Our research is focused on developing high-content screening assays and instrumentation to discover targets and screen for molecules active in cardiac regeneration and cardiomyocyte contractility. HCS that incorporates static and kinetic (live imaging) endpoints were used to develop a potential RNA therapeutic for heart failure that targets a clinically validated protein and shows efficacy in a mouse model.

5:00 Welcome Reception in the Exhibit Hall with Poster Viewing

6:00-9:00 Dinner Short Course* (see page 2 for details)

SC3: Introduction to High-Content Phenotypic Screening

Instructor: Anthony M. Davies, Ph.D., Director, Irish National Center for High-Content Screening and Analysis (INCHA)

*Separate registration required

TUESDAY, OCTOBER 29

7:30 am Breakfast Presentation (Sponsorship Opportunity Available) or Morning Coffee

CHEMICAL GENOMICS

8:30 Chairperson’s Opening Remarks

8:35 Coincidence Biocircuits for the Interrogation of Complex Chemical Libraries

James Inglese, Ph.D., National Center for Advancing Translational Sciences, NIH

High-throughput screening, a mainstay of pharmaceutical drug discovery, uses micro-volume assays to interrogate chemical libraries. Reporter gene assays, well-suited for HTS, can offer a wealth of cellular pathways to target; however, existing designs are prone to numerous reporter-based artifacts exacerbated by the use of complex chemical libraries such as natural product extracts. Through evaluating the basis of these 'off-pathway' effects we have devised an approach to improve the fidelity and efficiency of reporter gene-based HTS.

9:00 Chemogenomics Library Screen Reveals a Novel Mechanism for Modulating ApoE Levels in the Brain

Fabien Vincent, Ph.D., Associate Research Fellow, Assay Development and Pharmacology, Pfizer

A strong genetic link exists between the ApoE4 genotype and Alzheimer’s Disease (AD). A loss of function hypothesis is gaining credence and accordingly mechanisms leading to increased production and secretion of ApoE in the brain may be therapeutically beneficial. A proprietary library termed the Chemogenomics Library was designed for the purpose of identifying novel targets and mechanisms using phenotypic screening. The screen revealed HDAC inhibition as a novel mechanism for enhanced ApoE secretion. Importantly, oral administration of HDAC inhibitor MS275 to mice led to a significant increase in ApoE levels in both plasma and the hippocampus, thus validating this novel mechanism in vivo.

9:25 Chemical Genetics Reveals a Kinase-Independent Role for Protein Kinase R in Pyroptosis

Erik Het, Ph.D., Senior Scientist, MedChem, Pfizer

Formation of the inflammasome, a scaffolding complex that activates caspase-1, is important in numerous diseases. Pyroptotic cell death induced by anthrax lethal toxin (LT) is a model for inflammasome-mediated caspase-1 activation. We discovered 7-desacetoxy-6,7-dehydrogurumin (7DG) in a phenotypic screen as a small molecule that protects macrophages from LTProduced death. Using chemical proteomics, we identified protein kinase R (PKR) as the target of 7DG and show that RNA knockdown of PKR phenocopies treatment with 7DG. Further, we show that PKR’s role in ASC assembly and caspase-1 activation induced by several different inflammasome stimuli is independent of PKR’s kinase activity.

9:50 Sponsored Presentation (Opportunity Available. Contact Ilana Quigley at 781-972-5457 or iquigley@healthtech.com.)

10:05 Coffee Break in the Exhibit Hall with Poster Viewing

CASE STUDIES IN PHENOTYPIC DRUG DISCOVERY

10:45 Phenotypic Screening for Lipid Droplet Modulators

Zhu Lin, Ph.D., Biology Team Leader, Division of Pre-Clinical Innovation, National Center for Advancing Translational Sciences, NIH

Intracellular lipid droplets are associated with many dysfunctions such as obesity, coronary artery disease, fatty liver disease, and infectious diseases. There are limited medical interventions that could be used to treat these conditions. We have developed a lipid droplet accumulation phenotypic assay using embryonic Drosophila S2 cells, and utilized the assay to conduct quantitative HTS against 400K compounds. Many hits found from the screening demonstrated efficacy in mammalian cells as well.

11:10 Inhibition of the c-Myc Oncoprotein with a Naturally-Occurring Compound and Its Analogs

Edward Prochownik, M.D., Ph.D., Director, Oncology Research, Children’s Hospital of Pittsburgh Most cancers deregulate the c-Myc (Myc) oncoprotein, which sustains tumor proliferation. This bHLH-ZIP transcription factor interacts with another bHLH-ZIP protein, Max, to regulate transcription. We have developed small molecule Myc-Max disruptors (“Myc compounds”) that inhibit tumor cell proliferation although poor pharmacokinetics limit their in vivo efficacy. We have now identified a promising, naturally-occurring Myc compound and generated several analogs with improved activity while eliminating a highly reactive chemical group, thus improving specificity. These analogs are highly bio-available, well-tolerated and possess significant anti-tumor effects.

11:35 From Phenotypic Screening to Mechanism of Action: What Does the Toolbox Look Like?

Monica Schenone, Ph.D., Research Scientist, Broad Institute

As the biopharmaceutical industry moves from target-based into phenotypic screening of small molecules, elucidating mechanism of action (MoA) is crucial. However, determining the MoA of small molecules identified from phenotypic screens remains a challenge. The tool box for target identification includes direct biochemical methods, genetic interactions and computational inference. In many cases, combinations of approaches may be required to fully understand mechanisms of small-molecule action.

12:00 pm Close of Phenotypic Drug Discovery Meeting
Inaugural Screening and Functional Analysis of 3-D Models
Complex Cellular Models Predictive of Human Response to Improve Early Decision Making

While more informative than cell-free biochemical assays, monolayer or suspension cell culture HTS assays still fail to accurately reflect the human cellular microenvironment. There is a need for physiologically-relevant cellular models for drug screening and functional analysis that provide high predictive value for clinical efficacy and safety of compounds. The three-dimensional cell culture models mimic the human tissue microenvironment and provide more accurate information for compound and target selection, thereby reducing late-stage attrition. Cambridge Healthtech Institute’s Inaugural Screening and Functional Analysis of 3-D Models meeting will explore the use of 3-D models to profile compound action and predict toxicity and efficacy. The meeting will cover assay development using 3-D cellular models, high-content analysis and imaging of 3-D models, and applications of screening 3-D models for compound profiling and target discovery/validolation.

TUESDAY, OCTOBER 29

12:00 pm Main Conference Registration

1:30 Chairperson’s Opening Remarks

1:35 Application of Clonogenic 3-D Assays in High-Throughput Screening and Compound Optimization/Characterization

Aaron Morris, Ph.D., Lab Head, Cancer Biology, Sanofi Oncology

The ability to grow in an anchorage-independent manner is a hallmark of cancer cells. A 3-dimensional clonogenic growth assay in soft agar leverages this phenotype for assessment of cancer-signaling dependencies. We have performed a 3-D multi-cell line parallel phenotypic high-throughput screen with our proprietary compound collection to identify pathways, targets and chemical matter with selective anti-tumor activity. This 3-D soft agar assay has been further optimized to support hit-to-lead optimization efforts and a full range of MoA characterization studies.

2:00 High-Throughput 3-D Cell Culture for Drug Discovery and Human Toxicology

Jonathan Dorick, Ph.D., Isermann Professor of Chemical and Biological Engineering, and Vice President for Research, Rensselaer Polytechnic Institute

The need for increased knowledge of drug candidates at early stages of discovery is driving the development of new, high-throughput, and high-content technologies. The centerpiece of our approach involves the use of a miniaturized three-dimensional mammalian cell culture platform that consists of 500-1,000 individual cell cultures on a microscope-size slide “biochip.” A broad range of human and animal cells have been used on the chip platform, including primary cells and transformed cell lines from multiple tissues, as well as human and animal stem cells. Furthermore, many assays that are traditionally performed in well plates can be adapted to the high-throughput 3-D cell culture chip.

2:25 Development Challenges with 3-D Tumor Spheroid Culture and Endpoint Measurements Relevant to Drug Screening

Marina Fiteek, Associate Principal Scientist, Discovery Sciences, AstraZeneca

The pharmaceutical industry faces increasing pressure to deliver novel differentiated products to fulfill unmet medical needs. We have seen a trend towards increased interest in the use of physiologically-relevant systems applied to drug screening campaigns. Emerging techniques in the 3-D culture area can position cells in an environment which offers the potential for measuring more relevant functional responses. We will describe our experience using different techniques to generate tumor cell-derived spheroids and the methods we have applied to measure their properties. The presentation will be an assessment of the potential benefit and the challenges that need to be overcome to successfully exploit the more physiologically-relevant properties of tumor spheroids and implications for future drug screening.

2:50 Sponsored Presentations (Opportunities Available. Contact Ilana Quigley at 781-972-5457 or iquigley@healthtech.com.)

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing

HIGH-CONTENT ANALYSIS OF 3-D MODELS

4:15 Development of a Novel Reversible Cell Scaffold (RCS) System for Use with High-Content Imaging Platforms

Anthony M. Davies, Ph.D., Director, Irish National Center for High-Content Screening and Analysis (INCHA)

In this presentation we will for the first time showcase a completely novel system of cell culture permitting cells to be first grown in 3-D and then harvested as required. This system has been specifically designed for use with HCSIA imaging platforms, automated liquid handling and HTS. Unlike any other 3-D assay systems currently used, our technology does not rely upon solid gel matrices, scaffolds, micro-patterned surfaces or hanging drop assay systems to achieve reproducible cancer spheroid growth. Indeed many of the inherent technical issues surrounding these technologies are avoided by utilizing this novel 3-D culture technology. This reversible cell scaffold system comprises of two individual components: (i) a low-viscosity liquid support/scaffold; and (ii) an agent that deactivates the scaffold, permitting sedimentation of cellular structures under gravity, permitting either high-content imaging in situ or recovery for further analysis such as gene expression or biochemical analysis. This system of suspension/deactivation has been used to great effect in both high-content imaging and subsequent gene expression studies.

4:40 3-D Models of Metastatic Cancer Targeting Tumor-Initiating Cells via High-Content Analysis

Daniel V. Labbadia, Ph.D., Assistant Professor, Pharmaceutical Sciences, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado

In vitro 3-D models, particularly multicellular tumor spheroids (MCTS), offer a systems biology approach to bridge information from molecular target and 2-D cell-based screening, with in vivo models, to improve the predictability of drug discovery. We will discuss our current research with 3-D models using fluorescent reporter models, suitable for high-content imaging drug discovery. Specifically, we will describe methods to measure local (single-cell and global entire MCTS) changes after small molecule treatment targeting drug resistant invasive phenotypes of cancer.

5:05 Presentation to be Announced

6:00-9:00 Dinner Expert ThinkTank* (see page 2 for details)

SC4: How to Meet the Need for Physiologically-Relevant Assays?

Moderator: Lisa Minor, Ph.D., President, In Vitro Strategies, LLC

Panels:

Anne Bang, Ph.D., Director, Cell Biology, Sanford-Burnham Medical Research Institute

Anthony M. Davies, Ph.D., Director, Irish National Center for High-Content Screening and Analysis (INCHA)

Marina Fiteek, Associate Principal Scientist, Discovery Sciences, AstraZeneca

Aaron Morris, Ph.D., Lab Head, Cancer Biology, Sanofi Oncology

Michelle Palmer, Ph.D., Director, Discovery and Preclinical Research, Broad Institute

Caroline Shamu, Ph.D., Lecturer, Systems Biology and Director, ICCB-Longwood, Harvard Medical School

D. Lansing Taylor, Ph.D., Director, University of Pittsburgh Drug Discovery Institute and Allegheny Foundation; Professor, Computational and Systems Biology, University of Pittsburgh

*Separate registration required
8:25 Chairperson’s Opening Remarks

8:30 Functional Analysis of Therapeutic Antibodies Using ex vivo Tumor Spheroids
Mitchell Ho, Ph.D., Chief, Antibody Therapy Section, Laboratory of Molecular Biology, National Cancer Institute, NIH
Tumor microenvironments present significant barriers to antibody therapy. We established ex vivo tumor spheroids to study molecular mechanisms of antibody drug resistance. The tumor spheroids may prove invaluable for identifying potential targets in addition to providing an innovative platform for analyzing therapeutic antibodies. We compared the global gene expression profiles of spheroids and monolayers and identified genes specific to the 3-D biological structure of mesothelioma. An update on generation of human single-domain antibodies for cancer therapy will also be discussed.

8:55 Third Dimension: The Future of RNAi-Driven Target Identification in Cancer
Geoffrey A. Bartholomeusz, Ph.D., Assistant Professor and Director, siRNA Core Facility, Department of Experimental Therapeutics, Division of Cancer Medicine, University of Texas MD Anderson Cancer Center
3-D spheroid cell cultures, unlike 2-D monolayer cell cultures, demonstrate properties that are highly correlated to tumors. The ease at which spheroid models can be applied in high-throughput screens has resulted in the realization of their importance to address relevant questions in tumor biology. We are developing 3-D spheroid cell culture models to be used in high-throughput screening, and the design of one such model for target identification utilizing high-throughput RNAi screens will be discussed.

9:20 Presentation to be Announced

9:45 A 3-D Culture-Based siRNA Screening Tool for Secretory Epithelium Cancer Targets
Nathalie Picallet-D’Hahan, Ph.D., Senior Researcher, IRTSV/Biornics, CEAM offers the ability to perform in vivo screens for genes involved in the epithelial-plasmacytoid activation of innate immune cells in a physiological context. We propose to combine two heterogeneous cell lines (mimicking both epithelial and fibroblast types) and two conditions (normal and cancerous) to assess the expression of genes that may be involved in the pathogenesis of cancer. Additionally, we have developed a 3-D culture-based siRNA screening tool that allows us to screen for genes involved in the secretion of immunomodulatory factors in a 3-D culture model. The tool offers the ability to perform in vivo screens for genes involved in the epithelial-plasmacytoid activation of innate immune cells in a physiological context.

10:00 Perfecta3D Hanging Drop Plate: A Highly Flexible and Straightforward 3D Screening Tool
Nicky Slawny, Ph.D., Applications Specialist, 3D Biomatrix
Biologically-relevant 3-D tissue culture models for drug discovery are simple to create using Perfecta3D Hanging Drop Plates. Single cell type or co-culture spheroids and organoids are created in high-throughput friendly 96-well or 384-well plates and analyzed with existing manual or automated laboratory equipment to generate more physiologically relevant data.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing

11:00 Functional Analysis of Therapeutic Antibodies Using in vivo Tumor Spheroids
Mitchell Ho, Ph.D., Chief, Antibody Therapy Section, Laboratory of Molecular Biology, National Cancer Institute, NIH
Tumor microenvironments present significant barriers to antibody therapy. We established ex vivo tumor spheroids to study molecular mechanisms of antibody drug resistance. The tumor spheroids may prove invaluable for identifying potential targets in addition to providing an innovative platform for analyzing therapeutic antibodies. We compared the global gene expression profiles of spheroids and monolayers and identified genes specific to the 3-D biological structure of mesothelioma. An update on generation of human single-domain antibodies for cancer therapy will also be discussed.

11:15 Engineering 3-D in vivo Tumor Models of Antineoplastic Drug Resistance: Use of Malignant Spheroids and Non-Malignant Accessory Cells from the Metastatic Microenvironment
Eugen Dhimolea, Ph.D., Research Fellow, Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School
To model the composition and architecture of metastatic lesions and to address the role of the local metastatic microenvironment in the drug resistance exhibited by disseminated cancers, we assembled heterotypic in vivo 3-D tissue cultures comprised of malignant cells growing in dispersed format vs. growing as spheroids, and in the presence vs. absence of non-malignant accessory cells from organs frequently targeted by metastatic disease. We assessed the pathophysiological relevance of these models by testing the activity of more than 100 FDA-approved antineoplastic drugs. The spheroid morphology significantly decreased the efficacy for several classes of conventional DNA-damaging (e.g. anthracyclins) agents as well as recently established targeted therapies (e.g. kinase inhibitors), while being associated with increased cell-killing activity of others. Our 3-D co-culture system provides a practical and clinically-relevant experimental system to study the mechanisms of metastatic microenvironment-related drug resistance and to screen for biologically active compounds that circumvent it.

11:40 Tumor-Microenvironment-on-Chip (TMOC)
Bumsoo Han, Ph.D., Associate Professor, Mechanical and Biomedical Engineering, Purdue University
Targeted delivery of therapeutic and imaging agents to tumors without non-specific accumulation at normal tissues can significantly improve the treatment and diagnosis of cancers. Nanotechnology recently enabled various functional nanoparticles as vehicles for targeted delivery. However, it is extremely challenging to optimize their design and configuration using traditional cell culture and animal models. In order to address this challenge, a new in vitro model was developed to simulate the complex 3-D tumor microenvironments relevant to the transport of nanoparticles.

12:05 pm Three-Dimensional Melanoma Models: From Screening to Skin Reconstructs
Adina Vultur, Ph.D., Staff Scientist, Wistar Institute
The melanoma field has seen unprecedented clinical successes in the last few years; however, tumor heterogeneity and plasticity indicate the requirement for an arsenal of therapeutic strategies to overcome advanced disease. We focus our efforts on investigating genetically-distinct melanoma subgroups using high-throughput 3-D screening assays (with and without a support matrix) and increasingly complex preclinical models from normal human skin reconstructs to patient-derived xenografts. Our melanoma model pipeline has already allowed us to identify compounds and targets with limited activity in the 2-D setting, but with potential in vivo.
Traditional drug screening relies on monolayer cell culture, which is not always predictive of natural physiological state. This is especially problematic in cancer drug discovery, where simple cell cultures are not predictive of a complex tumor microenvironment that consists of various cell types that interact in three-dimensional structures. As the cost of drug development rises, there is increasing pressure for more predictive in vitro models for functional analysis and compound characterization. Cambridge Healthtech Institute’s Inaugural Physiologically-Relevant Cellular Tumor Models for Drug Discovery meeting will focus on the latest advances in 3-D cellular tumor models and complex co-culture systems for functional analysis studies and compound screening/characterization.

TUESDAY, OCTOBER 29

12:00 pm Main Conference Registration

COMPLEX TUMOR MODELS FOR PHENOTYPIC ASSAYS

1:30 Chairperson’s Opening Remarks

1:35 Phenotypic-Based Primary Screen for Angiogenesis Inhibitors
Mohannaj Dhanabal, Ph.D., Group Leader, Lead Discovery Technology, EMD Serono

Angiogenesis, the formation of new blood vessels from the pre-existing microvasculature, is among the key events for many physiological and pathological processes. We describe an angiogenesis assay system that allows rapid and reliable quantification of three-dimensional vessel formation in vitro in a miniaturized format using (BD Matrigel™) onto 384 plates. Such platform is used for screening compounds in a 384-well plate format to a High Content Screening. Finally, we used this to screen more compounds during the drug discovery and development process, which led us to the identification and prioritization of compounds with potent antiangiogenic activity.

2:00 BioDynamic Imaging of Three-Dimensional Drug Response in Spheroids and Cancer Tissue
David Nolte, Ph.D., Professor, Physics, Purdue University

BioDynamic Imaging is a new form of three-dimensional functional imaging. It detects intracellular motions that act as a suite of biomarkers and provides an endogenous form of image contrast inside living tissue. Heterogeneous three-dimensional drug response affecting diverse intracellular motions is mapped out in real time after application of drugs. Delayed penetration, internal hypoxia, quiescent cell populations, and differential responses are captured. Correlation of the dynamic signatures with conventional high-content analysis provides insight into the mechanistic origins of the dynamic images.

2:25 A Chemical Biology Approach to Identify New Microtubules Dynamics Regulators
Laurence Lafançère, Ph.D., CNRS Research Director, Department of Cell Differentiation and Transformation, Institut Albert Bonniot

The emergence of tumor resistance to conventional microtubule-targeting drugs restricts their clinical use. Using a cell-based assay that recognizes microtubule polymerization status to screen for chemicals that interact with regulators of microtubule dynamics, we identified Pyr1, a cell permeable inhibitor of LIM Kinase, which is the enzyme that phosphorylates and inactivates the actin depolymerizing factor cofilin. Pyr1 reversibly stabilize microtubules, blocked actin filament dynamics, and inhibited cell motility in vitro. Pyr1 inhibition of LIM Kinase caused a microtubule stabilizing effect, which was independent of any direct effects on the actin cytoskeleton. Thus, LIM Kinase functions as a signaling node that controls both actin and microtubule dynamics. In addition, Pyr1 retained its activity in multidrug resistant cancer cells that were resistant to conventional microtubule targeting agents. It is also effective in animals, where it delays tumors formation while showing a good tolerability. Thus, Pyr1 is a “first in class” LIMK inhibitor, showing efficacy on mice tumor models. Our results show that LIMK, which is an emerging target for cancer therapy, is indeed a targetable enzyme for cancer treatment.

2:50 Sponsored Presentations (Opportunities Available. Contact Ilana Quigley at 781-972-5457 or iquigley@healthtech.com.)

3:20 Refreshment Break in the Exhibit Hall with Poster Viewing

ORGANOTYPIC CO-CULTURE TUMOR MODELS

4:15 4-D Co-Culture Models of Breast Cancer for Target Identification
Ray Mattingly, Ph.D., Professor, Pharmacology, Wayne State University

We have developed 3-D coculture models that we term MAME (mammary architecture and microenvironment engineering). These MAME models include tumor cells cocultured with a variety of other relevant subtypes, including myoepithelial cells, tumor-associated fibroblasts and macrophages, and endothelial cells of blood and lymphatic origin. Proteolysis can be imaged and quantified using a live-cell assay of the degradation of fluorescein-quenched collagens. Extension of these models into 4-D (3-D plus time) demonstrates processes such as development of positive feedback loops between the cocultured cells, invasion of tumor cells into the angiogenic and lymphangiogenic networks, and allows identification of targets through profiling of cytokine production and responses.

4:40 A Stromal-Based 3-D Co-Culture Model for Chemotherapy Sensitivity Testing
Omar S. Aljitaawi, M.D., Assistant Professor, Internal Medicine, University of Kansas Medical Center

The discrepancy in leukemic cell responses to chemotherapy in vivo, compared to in vitro, is partly related to the interactions of leukemic cells with the 3 dimensional (3-D) bone marrow (BM) stromal microenvironment. We describe an in vitro model that we have developed to investigate the effects of chemotherapy on leukemic cell lines co-cultured with human BM stromal cells in 3-D. This novel model provides an opportunity to study leukemic cell responses to chemotherapy in 3-D.

5:05 Micropatterned Surfaces for the Study of Cancer and Endothelial Cell Interactions with Hyaluronic Acid
Sharon Gerecht, Ph.D., Associate Professor, Chemical and Biomolecular Engineering, Johns Hopkins University

Hyaluronic acid (HA) has been implicated in cellular interactions that are associated with cancer progression. Functional HA surfaces were developed to study interactions between cancer cells and HA. A similar surface patterning approach was used to create HA regions next to fibronectin in two- and three-dimensional settings to study the interactions between cancer and endothelial cells. The ability to observe the dynamic interactions of cancer cells and angiogenesis within HA-rich microenvironment will improve fundamental understanding towards therapeutic targets.

6:00-9:00 Dinner Expert ThinkTank* (see page 2 for details)

SC4: How to Meet the Need for Physiologically-Related Assays?
Moderator: Lisa Minor, Ph.D., President, In Vitro Strategies, LLC
Panelists:
Anne Bang, Ph.D., Director, Cell Biology, Sanford-Burnham Medical Research Institute
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8:30 Functional Analysis of Therapeutic Antibodies Using ex vivo Tumor Spheroids
Mitchell Ho, Ph.D., Chief, Antibody Therapy Section; Laboratory of Molecular Biology, National Cancer Institute, NIH
Tumor microenvironments present significant barriers to antibody therapy. We established ex vivo tumor spheroids to study molecular mechanisms of antibody drug resistance. The tumor spheroids may prove invaluable for identifying potential targets in addition to providing an innovative platform for analyzing therapeutic antibodies. We compared the global gene expression profiles of spheroids and monolayers and identified genes specific to the 3-D biological structure of mesothelioma. An update on generation of human single-domain antibodies for cancer therapy will also be discussed.

9:45 A 3-D Culture-Based siRNA Screening Tool for Secretory Epithelium Cancer Targets
Nathalie Picollo-D’Hahan, Ph.D., Senior Researcher, IRTSV/BiomiCEA
Genetic screening is certainly one of the most powerful approaches to gain insights into gene function and complex biological processes. However, it is becoming evident that functional genomics screens need to be performed in a more physiologically-relevant environment provided by a 3-D context. We propose to combine two technological innovations; both in microfluidic-generated 3-D cultures and parallelized lens-less imaging to perform 3-D RNAi-based HTS and to characterize new biomarkers in prostate cancer. We employed silencing RNAs (siRNA) targeting kinase-related genes to identify 3-D-specific effectors of prostate acini morphogenesis and polarity.

10:25 Coffee Break in the Exhibit Hall with Poster Viewing
Pricing and Registration Information

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