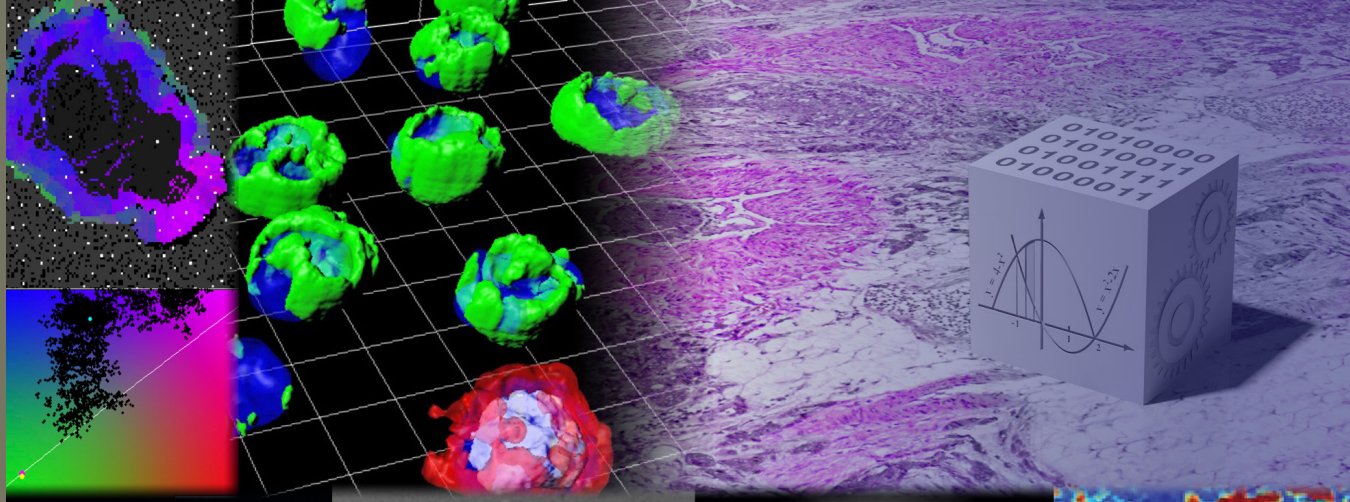
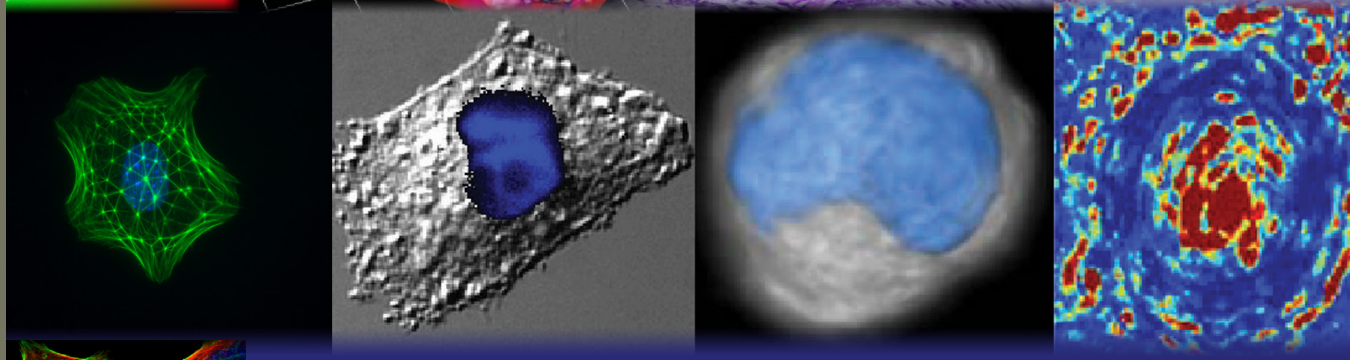
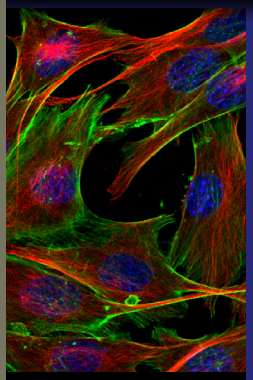
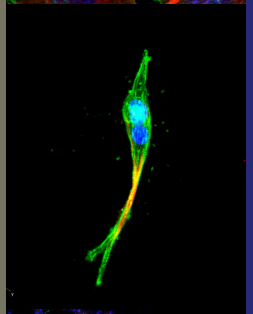
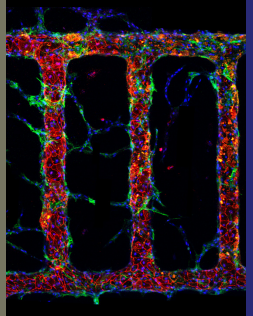
National Cancer Institute

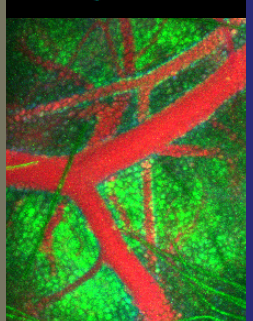












PHYSICAL SCIENCES ONCOLOGY CENTERS

Fourth Annual NCI Physical Sciences-Oncology Centers (PS-OCs) Network Investigators' Meeting

April 17-19, 2013

The Scottsdale Plaza Resort
Scottsdale, Arizona

PS-OC Network Young Investigators' Meeting

April 16-17, 2013

Program Book

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

The following PS-OCs provided images for the front cover:

- Alexander Anderson, H. Lee Moffitt Cancer Center PS-OC
- Peter Kuhn, The Scripps Research Institute PS-OC
- Dong-Hwee Kim and Denis Wirtz, Johns Hopkins University PS-OC
- Abraham Strook, Cornell University PS-OC
- Parag Mallick and Shannon Mumenthaler, University of Southern California PS-OC
- PS-OC Cell Line paper: "The Physical Sciences – Oncology Centers Network. A physical sciences network characterization of non-tumorigenic and metastatic cells." *Sci. Rep.* 3, 1449 (2013)

Dear Colleagues:

On behalf of the National Cancer Institute's (NCI) Office of Physical Sciences-Oncology Program staff, we are pleased to welcome you to the Third Annual NCI Physical Sciences-Oncology Centers (PS-OCs) Network Investigators' Meeting, April 17-19, 2012, at the Scottsdale Plaza Resort in Scottsdale, Arizona.

Over the course of this past year, participants in the PS-OC Program have continued to explore new and innovative approaches to better understand and control cancer through the convergence of the physical sciences and cancer biology. Specifically, within the collaborative network of 12 PS-OCs, trans-disciplinary teams work toward exploring the physical laws and principles that shape and govern the emergence and behavior of cancer at all scales, in an effort to open up new areas and support the development of clinical advances. The NCI envisions teaming cancer biologists and clinical oncologists with scientists from various non-biology disciplines such as physics, mathematics, chemistry, and engineering to generate collaborative teams capable of (1) challenging "accepted" dogma, (2) generating orthogonal (i.e., independent and comprehensive) sets of data, and (3) integrating novel conceptual approaches from these different fields. As these teams continue to mature and learn from each other, new perspectives and novel approaches are emerging to help generate answers to some of the major questions and barriers in cancer research.

The Annual PS-OC Network Investigators' Meeting includes a diverse group of PS-OC participants, ranging from principal investigators to postdoctoral fellows and graduate students, and will highlight scientific efforts within the PS-OC Network, promote new collaborations, and provide a venue for working group discussions.

The meeting this year will include, for the second time, a special session dedicated to the Program's Young Investigators, which occurs April 16-17. With an eye on the future, this session will feature both professional development and scientific presentations from young investigators who are the next generation working at the crossroads of the many disciplines that contribute to the PS-OCs.

We would like to extend special thanks to this year's Meeting Planning Committee (Dr. Paul Davies, Dr. William Grady, Dr. Robert Austin, and Dr. David Agus) as well as our hosts, the Arizona State University PS-OC. Once again, on behalf of the NCI, thank you for your commitment and dedication to this unprecedented endeavor.

With kind regards,

Larry A. Nagahara, Ph.D.
Director
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Jerry S.H. Lee, Ph.D.
Health Sciences Director
Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

Mariam Eljanne, Ph.D., M.S.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Jonathan Franca-Koh, Ph.D.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Michael G. Espey, Ph.D., M.T.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Sean E. Hanlon, Ph.D.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Nastaran Zahir Kuhn, Ph.D.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Nicole Moore, Sc.D.
Project Manager
Office of Physical Sciences-Oncology
National Cancer Institute, NIH

Agenda

WEDNESDAY, APRIL 17

12 noon - 5:30 p.m.	**Registration**	Foyer
12 noon - 5:30 p.m.	**Poster Setup**	La Terraza
1:00 p.m. - 1:05 p.m.	**Tutorial Introductions** Paul Davies, Ph.D. Arizona State University Arizona State University PS-OC	Grand Ballroom
1:05 p.m. - 2:55 p.m.	**Epigenetics Tutorial** Moderator: Stuart Lindsay, Ph.D. Arizona State University Arizona State University PS-OC	Grand Ballroom
1:05 p.m. - 1:35 p.m.	***Epigenetics: Thinking Outside the Cell Membrane Box*** Stuart Lindsay, Ph.D. Arizona State University Arizona State University PS-OC	
1:35 p.m. - 2:05 p.m.	***Chromatin and Transcription From an Epigenomics Perspective*** Steven Henikoff, Ph.D. Fred Hutchinson Cancer Research Center Arizona State University PS-OC	
2:05 p.m. - 2:35 p.m.	***Who Was Bohr and What Might His Effect Have to Do With Cancer?*** Rob Phillips, Ph.D. California Institute of Technology Northwestern University PS-OC	
2:35 p.m. - 2:55 p.m.	***Panel Discussion***	
2:55 p.m. - 3:15 p.m.	**Break**	
3:15 p.m. - 5:05 p.m.	**Origins of Cancer Tutorial** Moderator: Charles Lineweaver, Ph.D. Australian National University	Grand Ballroom
3:15 p.m. - 3:45 p.m.	***Origins of Cancer*** Paul Davies, Ph.D. Arizona State University Arizona State University PS-OC	

3:45 p.m. - 4:15 p.m. ***What Can Astrobiology Teach Us About Cancer?***
Sara Walker, Ph.D.
NASA Astrobiology Institute Fellow
Arizona State University PS-OC

4:15 p.m. - 4:45 p.m. ***Phylomedicine: Evolutionary Lessons and Solutions for Genomic Medicine***
Sudhir Kumar, Ph.D.
Biodesign Institute
Arizona State University

4:45 p.m. - 5:05 p.m. ***Panel Discussion***

5:05 p.m. - 5:35 p.m. **National Cancer Institute Tutorial** Grand Ballroom
Moderator: Mariam Eljanne, Ph.D.
National Cancer Institute, NIH

5:05 p.m. - 5:25 p.m. ***Targeted Cancer Therapies: Transforming the NCI Experimental Therapeutics Program***
S. Percy Ivy, M.D.
National Cancer Institute, NIH

5:25 p.m. - 5:35 p.m. ***Innovative Molecular Analysis Technologies (IMAT) Program***
Tony Dickherber, Ph.D.
National Cancer Institute, NIH

5:35 p.m. - 7:35 p.m. **Poster Session and Reception** La Terraza

THURSDAY, APRIL 18

7:00 a.m. - 5:00 p.m.	**Registration**	Foyer
7:00 a.m. - 8:00 a.m.	**Continental Breakfast**	Foyer
8:00 a.m. - 8:05 a.m.	**NCI Welcome** Larry A. Nagahara, Ph.D. National Cancer Institute, NIH	Grand Ballroom
8:05 a.m. - 8:10 a.m.	**ASU Welcome** Paul Davies, Ph.D. Arizona State University Arizona State University PS-OC	Grand Ballroom
8:10 a.m. - 8:30 a.m.	**Opening Remarks** Michael M. Crow, Ph.D. President, Arizona State University	Grand Ballroom
8:30 a.m. - 10:15 a.m.	**Physics of Cancer** Moderator: Denis Wirtz, Ph.D. Johns Hopkins University Johns Hopkins University PS-OC	Grand Ballroom

8:30 a.m. - 9:00 a.m.
Endogenous Voltage Gradients and Cancer as a Developmental Disorder: Patterning Cues in the Microenvironment That Control Carcinogenesis
Keynote Speaker: Michael Levin, Ph.D.
Tufts University

9:00 a.m. - 9:25 a.m.
Obesity-Associated Increased Interstitial Stiffness as a Potential Modulator of Breast Tumorigenesis
Claudia Fischbach-Teschl, Ph.D.
Cornell University
Cornell University PS-OC

9:25 a.m. - 9:50 a.m.
Cellular Pressure and Volume Regulation and Implications on Cell Mechanics and Cell Motility
Sean Sun, Ph.D.
Johns Hopkins University
Johns Hopkins University PS-OC

9:50 a.m. - 10:15 a.m.
Actin and Myosins in the Nucleus: The Secret Elements in Defining Nuclear Structure?
Primal de Lanerolle, Ph.D.
University of Illinois at Chicago
Northwestern University PS-OC

10:15 a.m. - 10:35 a.m. **Break**

10:35 a.m. - 12:45 p.m. **Energy, Information, and Cancer** Grand Ballroom

Moderator: Robert H. Austin, Ph.D.
Princeton University
Princeton University PS-OC

10:35 a.m. - 11:05 a.m. ***Cancer Attractor States and Cell Population Dynamics: A Framework for Non-genetic, Non-Darwinian Evolution of Cancer Drug Resistance***

Keynote Speaker: Sui Huang, M.D., Ph.D.
Institute for Systems Biology

11:05 a.m. - 11:30 a.m. ***The Atavistic Model of Cancer: Evidence, Objections, Therapeutic Value***

Keynote Speaker: Charles Lineweaver, Ph.D.
Australian National University

11:30 a.m. - 11:55 a.m. ***Exponentially Growing Cells Can Support a Constant Growth Rate by Very Different Metabolic Strategies***

Nikolai Slavov, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

11:55 a.m. - 12:20 p.m. ***Warburg, Shmarburg. Aerobic Glycolysis Is Normal.***

Robert A. Gatenby, M.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

12:20 p.m. - 12:45 p.m. ***Utilizing High-Precision Mass Sensing to Directly Measure Cell Response to Nutrient Depletion and Cellular Nutrient Requirements***

Scott Manalis, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

12:45 p.m. - 2:00 p.m. **Lunch and Working Groups** Cypress Court

For those attending Working Groups, lunch will be served in the Foyer.

Education, Outreach, and Advocate Joint Working Group Las Palmas

Moderator: Mariam Eljanne, Ph.D.
National Cancer Institute, NIH

lookatphysics.com
David Liao, Ph.D.
University of California, San Francisco
Princeton University PS-OC

Communicate Effectively With PS-OC Colleagues, for Patients' Sake!
Deborah Collyar
Patient Advocates In Research (PAIR)
Princeton University PS-OC

CTC Transport Working Group Grand Ballroom A

Moderator: Owen McCarty, Ph.D.
Oregon Health & Science University
The Scripps Research Institute PS-OC

CTC Cytoskeleton Dynamics: Insights From Two Computational Models
Katarzyna Rejniak, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

Modeling the Vascular Behavior of CTCs in a Capillary Flow: In Silico and In Vitro Experiments
Paolo Decuzzi, Ph.D.
The Methodist Hospital Research Institute
The Methodist Hospital Research Institute PS-OC

Redox Potential (RePo) Working Group Grand Ballroom B

Moderator: Robert A. Gatenby, M.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

Force, Hypoxia, and Metabolic Regulation of Tumors
Valerie M. Weaver, Ph.D.
University of California, San Francisco
University of California, Berkeley PS-OC

2:00 p.m. - 3:40 p.m. **PS-OC Perspectives Directed at Clinical Applications** Grand Ballroom

Moderator: Steven A. Curley, M.D., FACS
The University of Texas MD Anderson Cancer Center
The Methodist Hospital Research Institute PS-OC

2:00 p.m. - 2:25 p.m. ***Social Evolution of Cellular Communities Under Stress: Driving Forces of Dynamic Heterogeneity***

Thea D. Tlsty, Ph.D.
University of California, San Francisco
Princeton University PS-OC

2:25 p.m. - 2:50 p.m. ***Clinical Applications of the C Technology and Modeling***

Jorge J. Nieva, M.D.
Billings Clinic
The Scripps Research Institute PS-OC

2:50 p.m. - 3:15 p.m. ***Integrating Multiscale Imaging Data to Predict and Control the Resistant Phenotype in Patients***

Thomas Yankeelov, Ph.D.
Vanderbilt University
H. Lee Moffitt Cancer Center & Research Institute PS-OC

3:15 p.m. - 3:40 p.m. ***Mathematical Models of Tumor Microenvironment Transport Accurately Predict Limitations to Chemo/Radiation Delivery and Outcome***

Vittorio Cristini, Ph.D.
University of New Mexico
The Methodist Hospital Research Institute PS-OC
University of Southern California PS-OC

3:40 p.m. - 4:00 p.m. **Break**

4:00 p.m. - 5:30 p.m. **Integrating the Physical Sciences – Challenges and Opportunities** Grand Ballroom

Moderator: Anna D. Barker, Ph.D.
Arizona State University

4:00 p.m. - 4:15 p.m. ***Introduction***

Invited Speaker: Anna D. Barker, Ph.D.
Arizona State University

4:15 p.m. - 5:45 p.m. ***Panel Discussions***

Robert H. Austin, Ph.D.
Princeton University
Princeton University PS-OC

Robert J. Gillies, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

Valerie M. Weaver, Ph.D.
University of California, San Francisco
University of California, Berkeley PS-OC

Peter Kuhn, Ph.D., M.S.
The Scripps Research Institute
The Scripps Research Institute PS-OC

Steven A. Curley, M.D.
The University of Texas MD Anderson Cancer Center
The Methodist Hospital Research Institute PS-OC

5:45 p.m. - 7:45 p.m. **Poster Session** La Terraza

7:00 p.m. - 9:30 p.m. **PS-OC Steering Committee Working Dinner** La Valencia B

FRIDAY, APRIL 19

7:00 a.m. - 2:30 p.m. **Registration** Foyer

7:00 a.m. - 8:00 a.m. **Continental Breakfast** Foyer

8:00 a.m. - 8:10 a.m. **NCI Update** Grand Ballroom
Jerry S.H. Lee, Ph.D.
National Cancer Institute, NIH

8:10 a.m. - 8:25 a.m. **PS-OC Network Update** Grand Ballroom
Larry A. Nagahara, Ph.D.
National Cancer Institute, NIH

8:25 a.m. - 8:30 a.m. **PS-OC Poster Awards**
Mariam Eljanne, Ph.D.
National Cancer Institute, NIH

8:30 a.m. - 10:15 a.m. **Physical Science Perspectives on Metastasis** Grand Ballroom
Moderator: Valerie M. Weaver, Ph.D.
University of California, San Francisco
University of California, Berkeley PS-OC

8:30 a.m. - 9:00 a.m. ***Coordinate Molecular Regulation of Epithelial Dissemination by Genetic and Microenvironmental Variables***
Keynote Speaker: Andrew Ewald, Ph.D.
Johns Hopkins University

9:00 a.m. - 9:25 a.m. ***Direct Mechanical Modulation of the Invasive Phenotype***
Jan T. Liphardt, Ph.D.
University of California, Berkeley
University of California, Berkeley PS-OC

9:25 a.m. - 9:50 a.m. ***The Evolution of Cooperative Systems in Cancer***
Kenneth J. Pienta, M.D.
Johns Hopkins University
Princeton University PS-OC

9:50 a.m. - 10:15 a.m. ***Effect of Pro-Inflammatory Cytokines and Spheroid Culture on Breast Cancer Cell Adhesion***
Michael R. King, Ph.D.
Cornell University
Cornell University PS-OC

10:15 a.m. - 10:35 a.m. **Break**

10:35 a.m. - 11:25 a.m. **Challenges and Opportunities for Cancer Modeling** Grand Ballroom

Moderator: Kelly J. Bethel, M.D.
Scripps Clinic Medical Group
The Scripps Research Institute PS-OC

10:35 a.m. - 11:00 a.m. ***Observations From a Cancer Doc***

David B. Agus, M.D.
University of Southern California
University of Southern California PS-OC

11:00 a.m. - 11:25 a.m. ***Exploring Possibilities for Next-Generation Computational Cancer Models that Work Together***

Paul Macklin, Ph.D.
University of Southern California
University of Southern California PS-OC

11:25 a.m. - 12:40 p.m. **Challenge of Complexity** Grand Ballroom

Moderator: Thomas V. O'Halloran, Ph.D.
Northwestern University
Northwestern University PS-OC

11:25 a.m. - 11:50 p.m. ***3D Structures of Cancer Proteins Computed From Evolutionary Information Using Statistical Physics***

Chris Sander, Ph.D.
Memorial Sloan-Kettering Cancer Center
Dana-Farber Cancer Institute PS-OC

11:50 a.m. - 12:15 p.m. ***Nucleosome Maps With Base-Pair Resolution Revealing Distinct Nucleosome Positioning Mechanisms in S. Cerevisiae and S. Pombe***

Ji-Ping Wang, Ph.D.
Northwestern University
Northwestern University PS-OC

12:15 p.m. - 12:40 p.m. ***Methods to Define the Fitness Landscape of HIV for Rational Vaccine Design May Provide Clues for Cancer Immunology***

Arup Chakraborty, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

12:40 p.m. - 2:45 p.m. **Lunch and Roundtable Discussions** La Terraza

The Roundtable Session will examine the ideas and findings of the meeting in an informal setting. The discussions will focus on exploring what are the key take home messages from the meeting, how ideas from the meeting will impact future work and directions, the major questions and challenges that can be addressed by physical science perspectives, and opportunities for new collaborations.

Jonathan Franca-Koh, Ph.D.
National Cancer Institute, NIH

Nicole Moore, Sc.D.
National Cancer Institute, NIH

2:45 p.m. - 3:00 p.m. **Wrap-up and Adjournment** La Terraza
Jonathan Franca-Koh, Ph.D.
National Cancer Institute, NIH

Speaker Abstracts

EPIGENETICS TUTORIAL

Epigenetics: Thinking Outside the Cell Membrane Box
Stuart Lindsay, Ph.D.
Arizona State University
Arizona State University PS-OC

This talk will offer an overview of the ways in which information on phenotype can be transmitted from mother cell to daughter cell. Loss of this information is clearly central to the cancer problem. These pathways include transmission of transcription factors, DNA methylation and incorporation of variant histones. One neglected, but important factor, is remodeling of the ECM by means of factors excreted by the cell, which then signal daughter cells embedded in the modified ECM.

Chromatin and Transcription From an Epigenomics Perspective
Steven Henikoff, Ph.D.
Fred Hutchinson Cancer Research Center
Arizona State University PS-OC

This tutorial will describe recent progress in developing methods for genome-wide profiling of epigenomes and transcriptomes, including base-pair resolution mapping of the basic chromatin machinery and nucleosome dynamics. Mapping the full protein complement of chromatin in space and time can lead to insights into chromosome biology, developmental processes and disease.

Who Was Bohr and What Might His Effect Have to Do With Cancer?
Rob Phillips, Ph.D.
California Institute of Technology
Northwestern University PS-OC

The Bohr effect refers to changes in the binding of oxygen to hemoglobin with changes in the pH and was studied in detail by Danish physiologist Christian Bohr, father of the famous physicist Niels Bohr. In this talk, nearly 50 years to the day after the elucidation of the allostery concept by Monod, Changeux and Jacob, I will describe how statistical mechanics can be used to characterize a host of different allosteric transitions. These observations will lead to a phylogeny of ideas that lead to unexpected linkages between the Bohr effect in hemoglobin, precise adaptation in chemotaxis and to the physicochemical description of the chemical modifications to DNA and its attendant proteins. Specifically, the talk will explore the way in which these kinds of unexpected connections between apparently unrelated phenomena might shed light on how genomes are reprogrammed epigenetically both in healthy and diseased cells.

ORIGINS OF CANCER TUTORIAL

Origins of Cancer
Paul Davies, Ph.D.
Arizona State University
Arizona State University PS-OC

Progress against cancer is slow because we have been thinking about the problem the wrong way. We need to ask: why do almost all healthy cells come pre-loaded with a "cancer subroutine" that can be triggered by a variety of insults? Once switched on, cancer develops a distinctive phenotype with familiar hallmarks, and unfolds along a very predictable and deterministic trajectory. It is widespread among mammals, birds, fish and reptiles. Clearly cancer is a deep-rooted part of the story of life, like aging. And as with aging, cancer is not really a disease but a process with evolutionary origins stretching back over a billion years. It follows that, in general, cancer cannot be cured, but its effects can be mitigated by delaying onset and slowing progression. Management via control of physical parameters, rather than destruction by chemicals or beam weapons, offers the best hope.

What Can Astrobiology Teach Us About Cancer?
Sara Walker, Ph.D.
NASA Astrobiology Institute Fellow
Arizona State University PS-OC

Many hallmarks of cancer suggest that it has deep evolutionary roots that extend at least as far back as the dawn of multicellular life, 1 billion years ago. One of the primary aims of astrobiology - which seeks to understand the origin, evolution, distribution and future of life - is to elucidate the earliest stages of the history of life on Earth. Astrobiology may therefore provide new insights into the nature of cancer by tracing its evolutionary history and explaining why cancer cells behave as they do. In this talk I explore the connections between cancer as viewed as an evolutionary throwback and insights provided by astrobiology, and ask: what can astrobiology teach us about cancer? Topics to be discussed include eukaryogenesis, the origin of multicellularity and the history of the co-evolution of life and oxygen on Earth. I conclude with a discussion of potential future directions in cancer research that derive insights from topics discussed.

Phylomedicine: Evolutionary Lessons and Solutions for Genomic Medicine
Sudhir Kumar, Ph.D.
Biodesign Institute
Arizona State University

Nature has been the greatest experimenter on Earth for millennia. New genomic changes continuously arise in all species during their propagation from generation to generation and in an individual's life time. For billions of years, these mutations have been subjected to the process of natural selection. Mutations with significant negative fitness impacts have been eliminated by purifying selection. Fates of selectively neutral mutations with no negative effects have been determined by chance. They are revealed by exploring sequence differences among species in comparative analyses as patterns of conservation and divergence. These molecular evolutionary patterns and their underlying causes are now the foundation of approaches that forecast potentially disruptive mutations found in our personal and somatic genomes. Predictive molecular evolutionary techniques and the associated research are encompassed by Phylomedicine, which is emerging as a discipline at the intersection of molecular evolution, genomics, and biomedicine. I will discuss insights from our Phylomedicine investigations aimed at understanding and predicting genotype-phenotype relationships through an analysis of human genome variation implicated in Mendelian, cancer, and other complex diseases.

NATIONAL CANCER INSTITUTE TUTORIAL

Targeted Cancer Therapies: Transforming the NCI Experimental Therapeutics Program
S. Percy Ivy, M.D.
National Cancer Institute, NIH

The transformation of the National Cancer Institute (NCI)-sponsored cooperative experimental therapeutics clinical trials program will lead to a change from a series of separate organizations conducting early phase cancer treatment trials into a consolidated, integrated NCI Experimental Therapeutics-Clinical Trials Network (ET-CTN). The formation of investigational agent-specific project teams to define the drug development plan will include investigators from the NCI and its grant and contract holders. This group will perform experimental therapeutic clinical trials with drugs held under Investigational New Drug applications (INDs) by NCI's Division of Cancer Treatment and Diagnosis (DCTD), Cancer Therapy Evaluation Program (CTEP). By defining better approaches to the development of novel anticancer agents, the ET-CTN will capitalize on its ability to characterize tumors molecularly. The ET-CTN will identify appropriate biomarkers to select patients most likely to respond to specific agents and to establish the cause(s) of emerging mechanisms of resistance that may result from tumor heterogeneity.

The ET-CTN will accomplish its objectives by forming multi-institutional, multi-disciplinary project teams to define early drug development clinical trials of novel drugs or combination therapies. As novel agents progress from phase 1 to phase 2 trials, investigators across multiple NCI-supported trial mechanisms (National Clinical Trials Network (NCTN), Consortia, phase 2 contractors, as well as the ET-CTN) will collaborate with NCI's Investigational Drug Steering Committee (IDSC) and its disease-specific steering committees to develop novel treatments requiring molecularly-guided patient selection and pathway-driven investigational combination therapies in a wide variety of malignancies. NCI staff will provide standardized central operational, regulatory, and administrative support including data management, trial registration, and Central Institutional Review Board (CIRB) review for approved, early phase trials. NCI staff across several Divisions will assist ET-CTN investigators to develop multi-disciplinary project teams and will evaluate early phase experimental therapeutic trials that are submitted to CTEP.

Innovative Molecular Analysis Technologies (IMAT) Program
Tony Dickherber, Ph.D.
National Cancer Institute, NIH

The NCI Center for Strategic Scientific Initiatives re-launched an updated Innovative Molecular Analysis Technologies (IMAT) program in the fall of 2011, dedicating $10.5 million dollars in new awards each year through unique funding mechanisms (3 year R21s and R33s) to better support investigators through both the early stages of technology development. The IMAT program runs alongside several active programs at the NCI for supporting cancer-relevant technologies, including the Physical Sciences Oncology Centers Program. A variety of IMAT-supported research projects will be highlighted to demonstrate the variety and high level of innovation evident in the IMAT portfolio of supported research. Potential projects of interest and identified technology gaps will also be highlighted.

Endogenous Voltage Gradients and Cancer as a Developmental Disorder: Patterning Cues in the Microenvironment That Control Carcinogenesis

Michael Levin, Ph.D.
Tufts University

One view of cancer is as a developmental disorder: tumors arise when cells lose interactions with the global patterning cues that normally orchestrate individual cell behaviors towards the anatomical needs of the host. Indeed, it has long been known that actively patterning contexts (such as regenerating limbs and developing embryos) can reprogram cancer cells into normal morphogenetic roles. Thus, understanding and learning to control the complex field of instructive cues that guides the growth and form of living tissues is crucial to the prevention, detection, and normalization of cancer. Alongside the well-studied biochemical properties of diffusible gradients and extracellular matrix functions a powerful and still poorly understood system of pattern control: endogenous bioelectricity. Ion channels and pumps present in all cells, not just excitable nerve and muscle, set up spatio-temporal gradients of resting potential (Vmem) that is now known to mediate instructive control over cell shape, migration, proliferation, and differentiation. We have shown that Vmem determines the differentiation of mesenchymal stem cells and neural progenitor cels, and indeed, a number of ion channels are now increasingly recognized as oncogenes. However, the true impact of molecular bioelectricity on cancer biology is just beginning to be appreciated.

Our work over the last decade has shown that these endogenous Vmem gradients are crucial functional determinants of large-scale shape. In a range of model systems, we have shown that these gradients encode positional information and organ identity cues that guide the growth and patterning of multicellular structures. By developing molecular-genetic methods to precisely control (and observe) these gradients in vivo, we have shown that remarkable control over biological shape can be exerted.

Using targeted misexpression of well-characterized channels in the frog system, we have shown the ability to induce formation of whole eyes in any tissue of the body, and to induce regeneration of spinal cord and entire legs; by changing the subtle prepattern of Vmem that precedes and directs gene expression during craniofacial patterning, we have shown the ability to regulate the morphogenesis of the face. In regenerating planarian flatworms, we have shown that such physiological gradients provide non-genetic templates for growth that can permanently change target morphology (the shape to which the animal regenerates) without alteration of DNA sequence.

Recently, we applied these new methods and strategies to the problem of cancer. We showed that (1) Vmem alterations are a non-genetic mechanism for transforming normal stem cell derivatives (pigment cells) into a metastatic state similar to melanoma, (2) that non-invasive monitoring of Vmem by voltage reporter dyes in vivo is a good way to detect tumors before they form (a diagnostic modality), and that (3) Vmem is a tractable control point by which oncogene-mediated tumorigenesis can be suppressed despite high levels of the oncogene protein in cells. Remarkably, the regulation of carcinogenesis by Vmem occurs at considerable distance, consistent with the global nature of Vmem cues as part of the morphogenetic field. In this talk, I will introduce the field of molecular bioelectricity, describe our work on the developmental regulation of cancer by bioelectric properties of the microenvironment in the Xenopus laevis model, and sketch a roadmap for exploiting these powerful biophysical properties of the microenvironment to develop diagnostic and rebooting (normalization) strategies for biomedicine.

Obesity-Associated Increased Interstitial Stiffness as a Potential Modulator of Breast Tumorigenesis

Claudia Fischbach-Teschl, Ph.D.
Cornell University
Cornell University PS-OC

Obesity represents an important risk and prognostic factor for breast cancer including its most common presentation: hormone receptor positive (HR+) disease in postmenopausal women. While much focus has been placed on evaluating the role of altered endocrine signaling in mediating this connection, physicochemical alterations to the microenvironment may also be critical. In particular, fibrotic tissue remodeling occurs at an enhanced rate in obese adipose tissue and, in the context of breast cancer, has been associated with perturbed epithelial morphogenesis due to augmented breast tissue stiffness. Here, we have investigated the hypothesis that obesity increases interstitial extracellular matrix (ECM) stiffness in adipose tissue by elevating the number of contractile and ECM-depositing activated fibroblasts (i.e., myofibroblasts) and that the resulting changes in ECM physicochemical properties promote malignancy by altering both tumor and stromal cell behavior. To address this hypothesis, we have applied a multidisciplinary approach that capitalizes on the engineering, cell biology, and clinical expertise of investigators associated with the Cornell PSOC. Immunofluorescence analysis of both mouse and patient-derived samples suggested that obesity-associated fat is enriched in myofibroblasts and fibrillar ECM molecules relative to fat from lean subjects. Förster resonance energy transfer (FRET) analysis additionally indicated that obesity-associated adipose stromal cells (ASCs) increased fibronectin unfolding, stiffening, and overall matrix quantity relative to those deposited by ASCs from lean mice. In addition, analysis of collagen fibrillar structure in mammary tissue by multiphoton Second Harmonic Generation (SHG) imaging depicted enhanced linearity of collagen fibers in obese mammary fat as compared to lean counterparts. Moreover, mechanical analysis via Surface Forces Apparatus (SFA) confirmed that these changes collectively increase ECM stiffness. Finally, these alterations contributed to altered ASC and tumor cell behaviour ultimately promoting vascularization and malignancy.

Cellular Pressure and Volume Regulation and Implications on Cell Mechanics and Cell Motility

Sean Sun, Ph.D.
Johns Hopkins University
Johns Hopkins University PS-OC

Hongyuan Jiang, Kimerbly Stroka, Kostantinos Konstantopolous
Johns Hopkins University

In eukaryotic cells, small changes in cell volume can serve as important signals for cell proliferation, death and migration. Volume and shape regulation also directly impacts mechanics of cells and tissues. Here we develop a quantitative mechanism of cellular volume and pressure regulation, incorporating essential elements such as water permeation, mechanosensitive channels, active ion pumps and active motor-driven stresses in the cell cortex. The model can predict the cellular volume and pressure for several models of cell cortical mechanics. Furthermore, we show that when cells are subjected to an externally applied load, such as in an AFM indentation experiment, active regulation of volume and pressure leads to complex cellular response. Instead of the passive mechanics of the cortex, the observed cell stiffness depends on several factors working together. Finally, we examine the implications of volume regulation in cell motility, where polarized distribution of membrane channels and pumps can lead to directed cell migration in an actin-independent manner. Quantitative results from experiments and modeling will be discussed.

Actin and Myosins in the Nucleus: The Secret Elements in Defining Nuclear Structure?

Primal de Lanerolle, Ph.D.
University of Illinois at Chicago
Northwestern University PS-OC

The regulation of cytoskeletal dynamics by actin and myosin plays a central role in transformation, tumor growth and metastasis. What about the nucleus? The nucleus has structure, it is organized into domains consisting of active and inactive genes and it is proposed to contain a nucleoskeleton analogous to the cytoskeleton. Actin and myosin, the proteins that regulate cytoskeletal dynamics and cell mechanics, are also abundant in the nucleus. Actin and nuclear myosin I, one of 7 myosins found in the nucleus, are transcription factors. Actin and nuclear myosin I also function as a motor in establishing chromatin domains in the nucleus. Furthermore, the expression of junctional proteins that regulate actin dynamics at the membrane and are associated with various cancers results in the formation of nuclear actin filaments. Importantly, we have discovered alterations in RNA polymerase II localization, decreases in transcription and altered chromatin structure in cells with nuclear actin filaments. Pull-down experiments using G-actin as bait have revealed actin binding to multiple polymerase subunits and chromatin remodeling complexes. Nevertheless, many questions remain. What structures do actin form in the nucleus and how do they impact transcription and chromatin remodeling? We are addressing this question using super-resolution microscopy. However, it may require 3D STED or STORM or a new approach capable of detecting single actin filaments to truly address this question. Do actin and nuclear myosin I act as a motor to power transcription? Or does nuclear myosin I, which has been shown to be a mechanosensor, act as a break to prevent backsliding or the recovery of transcription following a backsliding event? I will briefly describe what is known about motors in the nucleus and then discuss how cell biologists, cancer biologists and physical scientists could collaborate to address important questions related to gene transcription and chromatin structure.

Cancer Attractor States and Cell Population Dynamics: A Framework for Non-genetic, Non-Darwinian Evolution of Cancer Drug Resistance

Sui Huang, M.D., Ph.D.
Institute for Systems Biology

Why would the immense capacity of the genome to produce, without mutations, the entire bodily ecosystem of thousands of distinct cell types that inherit their phenotypes, not also accidentally generate cancer cells? If normal cell types are attractor states in the high-dimensional gene expression state space of the genome, then, inspired by Kauffman (1973), we postulate that cancer cells are forbidden cell types: They fail to mature because they are "stuck" in one of the countless excess attractor states in the vast gene expression state space. The latter is highly structured because of the genome-wide gene-gene interactions which produce attractor states, instabilities, etc. Such dynamics is best understood within the framework of a quasi-potential landscape - an exact mathematical construction of Waddington's epigenetic landscape. In this rugged landscape, evolution has carved developmental trajectories ("chreods") to safely guide developing cells to the terminal, robust attractors that encode normal cell phenotypes. But accidental deviations (due non-genetic or genetic perturbations) may push cells into dead-end "side-valleys" outside the evolved chreods. Here the cells are stuck in unoccupied attractor states that may bear similarity to states of the ontogenetic (embryonic) or phylogenetic (ancient) past. These pathological attractors are not under selection pressure and encode unstable, immature, asocial (selfish) cells with no evolved access to normal attractors. This model proposes the necessary existence of cancer and explains counterintuitive facets of tumorigenesis, such as those that, against current orthodoxy, do not require genetic mutations. Using these concepts I will in this talk focus on Lamarckian dynamics in the inexorable acquisition of cancer drug resistance and present results suggesting that cells do not follow Darwin's principle of "*Survival of the fittest,"* but rather, adhere to Nietzsche's principle of "*What does not kill me makes me stronger"* when developing resistance.

The Atavistic Model of Cancer: Evidence, Objections, Therapeutic Value

Charles Lineweaver, Ph.D.
Australian National University

Paul Davies
Arizona State University

It is clear that cancer has deep evolutionary roots stretching back to the dawn of multicellularity. Our atavistic theory of cancer postulates that the initiation and progression of cancer represents a reversion to ancestral phenotypes that can be triggered by a wide variety of insults. We will present the main aspects of the model (Davies & Lineweaver 2011) and explain why it is an improvement upon, and an extension of, the dominant somatic mutation model and the more recent cancer stem cell model. The atavistic model is based on the connections between three ingredients: phylogeny, ontogeny and carcinogenesis. The relevant deep phylogeny is the more than billion year evolution of cell differentiation and multicellularity. The most relevant aspects of ontogeny are the physiological details of embryogenesis, cell differentiation, normal cell turnover and wound healing. We will briefly review (i) the fundamental (and controversial) connection between ontogeny and phylogeny and (ii) the increasingly evident connections between carcinogenesis and ontogeny (i.e., embryogenesis and wound healing). We will describe how de-differentiation, the Warburg effect, the angiogenic switch, the cadherin switch and many other hallmarks of cancer are most easily explained in the context of the atavistic model. We will also address objections that have been raised against the model and describe potential therapeutic applications. Our model stresses the importance of deep phylogeny in understanding cancer, and invites researchers to apply new observational techniques to a range of basal metazoans to help elucidate the evolution of multicellularity and cancer.

Exponentially Growing Cells Can Support a Constant Growth Rate by Very Different Metabolic Strategies

Nikolai Slavov, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

Alexander van Oudenaarden
Massachusetts Institute of Technology and the University Medical Center Utrecht, Netherlands
Massachusetts Institute of Technology PS-OC

Cells grown in culture generally display at least three sequential growth phases: a lag phase, an exponential phase, and a stationary phase. Cultures of exponentially growing cells are used ubiquitously for biological research since it is widely assumed that cells sampled from this phase represent a single well-defined physiological state. Here we challenge this assumption by demonstrating that cell physiology and gene regulation change continuously during exponential growth at constant growth rate. We quantified metabolic fluxes, oxygen consumption, carbon dioxide production, amino acid concentrations, gene expression (including mRNA levels, protein levels, and post-translational modifications), and sensitivity to both heat and oxidative stress during a full time-course of the diauxic growth of budding yeast. We found that during the first exponential growth phase, cells substantially change their metabolic state, transitioning from a mostly respiratory to a predominantly fermenting state. During this transition ATP production per cell decreases substantially, while the rate of biomass production remains constant. Concomitantly, the sensitivity to stress increases. Together these changes suggest a trade-off between the choice of metabolic strategy and sensitivity to stress. We found that up to 71% of the variance in protein levels can be accounted for by mRNA variance; some of the remaining variance can be explained by changes in amino acid abundance. Our observations show that, in general, exponential growth at a constant rate represents not a single metabolic/physiological state but a continuum of changing states characterized by different metabolic fluxes and distinct trade-offs.

Warburg, Shmarburg. Aerobic Glycolysis Is Normal.

Robert A. Gatenby, MD
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

Robert Gillies, Tamir Epstein
H. Lee Moffitt Cancer Center & Research Institute

Mammalian cells can metabolize glucose aerobically to H_2O and CO_2 generating up to 38 ATP/glucose or anaerobically to lactate producing 2 ATP/glucose. Since Pasteur's experiments in 1857, glucose metabolic pathways have been conceptually linked to local oxygen concentration so that, in the standard model, aerobic metabolism is used in oxygen environments and glycolysis reserved for periods of hypoxia. Glucose metabolism to lactate in the presence of oxygen, commonly observed cancer cells (the Warburg effect), is notable primarily because it violates this "oxygen control" paradigm. In fact, investigators continue to search, unsuccessfully, for a defect in oxidative glucose metabolism in cancer cells nearly 100 years after Warburg's initial observation. We propose an alternative model of cellular bioenergetics in which glucose metabolism is governed by spatial and temporal variations in energy demands. Aerobic metabolism, which rapidly saturates, supplies steady but efficient energy to meet base-load demand. Glycolytic metabolism, less efficient but with 100-fold faster ATP production, responds rapidly to "peaked" increases in ATP demand above baseline. We demonstrate these temporal dynamics give rise to spatial compartmentation as glycolytic enzymes are located peripherally to accommodate rapid increases in ATP demand necessary for membrane response to environmental perturbations while mitochondria are consistently more central. This model provides an alternative to the traditional oxygen control paradigm by linking glucose metabolism to variable energy demands necessary for optimal cell function. In this model, the Warburg effect simply represents the adaptation of tumor cells to increased peaked energy demand that is required for cell motility and proliferation.

Utilizing High-Precision Mass Sensing to Directly Measure Cell Response to Nutrient Depletion and Cellular Nutrient Requirements

Scott Manalis, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

Mark Stevens, Sungmin Son
Massachusetts Institute of Technology

Investigating cancer cell metabolism has been proven as an effective route to both better understand and specifically target cancer therapies. Nonetheless, still relatively little is known about how these cells regulate their growth and metabolism in response to changing environmental cues. The rapid proliferation of cancer cells poses increased demands for energetic and anabolic substrates, both of which are met in part by regulating differential metabolism. Recently, we devised a way to instantaneously change the external nutrient level surrounding a single cell while continuously measuring the buoyant mass of individual cells, which in turn gives precise growth rate (GR). To better characterize cell growth response to nutrient depletion, we took advantage of two murine hematopoietic cell lines for which we've previously characterized the single-cell growth dynamics. Data shows that depletion of key metabolic substrates glucose and glutamine produce an instantaneous GR decrease of 36%-40% and 28%-29%, respectively, larger mass fractions of total uptake than previous measurements suggest for either substrate. To confirm that this effect is dictated by a mechanism other than uptake, depletion of both substrates was preformed. Measurement showed a non-additive GR slowdown of 50%, suggestive of cellular sensing and a downstream, concomitant elimination of other substrates' uptake. In an attempt to localize sensing of our two substrates, we pursued experiments to rescue the effects of their depletion. Individual supplementation of 2-dimethyl-alphaketogluterate or succinate to depletion conditions rescues and partially rescues, respectively, the onset of GR slowdown due to either substrate's depletion. Further experimentation to describe the mechanism driving GR are being pursued, both to explore possible substrates of signal transduction such as cellular redox balance, energy state, or metabolite levels, and to formally rule out other known methods of cellular sensing.

PS-OC PERSPECTIVES DIRECTED AT CLINICAL APPLICATIONS

Social Evolution of Cellular Communities Under Stress: Driving Forces of Dynamic Heterogeneity

Thea D. Tlsty, Ph.D.
University of California, San Francisco
Princeton University PS-OC

The tissues of our bodies exist as communities of cells that exhibit social interactions that are scalable and ubiquitous in nature. Competition for nutrients, cooperation to generate functional products and acts of altruism are common and extend from the subcellular to the systemic. The cellular mechanisms that generate heterogeneity and the emergence of social interactions that underlies development and the formation of functional tissues of the body are still a major mystery.

Stress disrupts the status quo of tissue homeostasis and sets in motion cellular processes that result in dynamic social evolution. Recent work from our group has identified multiple consequences of this disruption that range from changes in cell fate to modulation of the environmental niche. Under certain circumstances restoration of homeostasis and repair is achieved. Under other circumstances, these consequences collude to create a pro-tumorigenic niche.

Surprisingly, the abovementioned stress-induced cellular processes can also activate the ultimate program of heterogeneity, pluripotency. We have identified cells within human adult tissue that can acquire a pluripotent state. These rare cells can be directly isolated from the human body and be shown to create functional derivatives of heart, brain, bone, cartilage, gut and many more tissues. This rare subpopulation is poised to transcribe pluripotency markers, Oct3/4, Sox2 and Nanog at levels similar to those measured in human embryonic stem cells and to acquire a pluripotent state sensitive to environmental programming. *In vitro*, *in vivo* and teratoma assays demonstrated that either a directly-sorted (uncultured) or a single cell (clonogenic) cell population from primary human tissue has the ability to differentiate into functional derivatives of each germ layer, ectodermal, endodermal and mesodermal. In contrast to other cells that express Oct3/4, Sox2 and Nanog, these human endogenous Plastic Somatic cells (ePS cells) are mortal, express low telomerase activity, expand for an extensive but finite number of population doublings, and maintain a diploid karyotype before arresting in G1. These cells may provide insights into the origins of tissue (and tumor) heterogeneity and the dynamic evolution of cellular social interactions.

Clinical Applications of the C Technology and Modeling

Jorge J. Nieva, M.D.
Billings Clinic
The Scripps Research Institute PS-OC

The Scripps PSOC has focused on the knowledge creation around the fluid phase of solid tumors. The initial primary approaches were detection of and characterization of cancer cells in the circulation as well as modeling the pathways, taken by cancer cells, that lead to illness and death of patients. As the message of metastasis, the role of circulating tumor cells is being defined in different primary diseases and at different stages of disease. After establishing the initial relevance of these cells, we can now focus on understanding changes in sub-populations of circulating cells at different time points of the disease. These findings are now converging into a unified theorem on the circulation of cancer cells that has direct implications for the treatment of cancer patients. The Newton model of cancer seeding and re-seeding proposes that in contrast to current day oncology practice, the unique sites of anatomic spread for cancer metastasis are relevant and the approach of treating cancer as a disease with only 3 steps, local, regional, then metastatic, may need to be revised. The oncologic practice of treating all distant metastasis as equivalent may need to be replaced with a model that is increasingly complex. Similarly, the practice of treating all circulating cancer cells as both negative and equivalent, must also be re-examined.

Integrating Multiscale Imaging Data to Predict and Control the Resistant Phenotype in Patients

Thomas Yankeelov, Ph.D.
Vanderbilt University
H. Lee Moffitt Cancer Center & Research Institute PS-OC

Erin Rericha, Vito Quaranta
Vanderbilt University

Clinical Problem: Our efforts focus on harnessing well-constrained biophysical models of tumor treatment response to improve the deployment of targeted therapies. We aim to identify—early in the course of treatment—the appearance of the resistant phenotype in order to limit patients' exposure to toxicities when the therapy is ineffective and provide patients the opportunity to switch to a potentially more efficacious approach.

Physical Science Perspective: The success of a physical science approach to cancer *therapy* requires that tumor mathematical models make testable predictions on clinically relevant scales. A major challenge is to bridge models designed to work with cell-scale data with models designed to incorporate clinical data. We hypothesize that integration of readily-available, multi-scale imaging techniques can build this bridge and ultimately constrain multi-scale model parameters with patient specific measurements. Such constrained models can then be evolved in time to make testable predictions on clinically relevant scales. At the microscale, automated fluorescence confocal microscopy provides cell proliferation, heterogeneity, and migration measurements at the single cell level. At the mesoscale, custom-designed bioreactors support cell growth up to tissue-scale densities, enabling acquisition of both microscopy and MR images. At the macroscale, MRI provides measurements of tumor cell density, proliferation, motility, and delivery of nutrients and treatments. We then integrate these multi-scale data into biophysical models that predict the optimum imaging times to discover the resistant phenotype *in vivo*. In the pre-clinical setting, we are coordinating microscopy measurements with PET/MRI measures so that model predictions of clinical outcomes contain an absolute minimum of non-patient specific parameters. Finally, clinical studies employ a limited battery of PET/MRI data to predict the eventual response of breast tumors after the first cycle of neoadjuvant therapy. These ongoing experiments generate vast amounts of data we are excited to share with the PSOC network to establish new collaborations.

Mathematical Models of Tumor Microenvironment Transport Accurately Predict Limitations to Chemo/Radiation Delivery and Outcome

Vittorio Cristini, Ph.D.
University of New Mexico
The Methodist Hospital Research Institute PS-OC
University of Southern California PS-OC

Eugene Koay[1], Elaine Bearer[2], Steven Curley[3], Mauro Ferrari[1], Sanjiv Gambhir[4], Hermann Frieboes[5], Bryan Smith[4], Jennifer Pascal[3], Zhihui Wang[3]
[1]The Methodist Hospital Research Institute, [2]The University of New Mexico, [3]The University of Texas MD Anderson Cancer Center, [4]Stanford University, [5]University of Louisville

Biobarriers pose a multitude of challenges for delivering drugs to tumors, yet a comprehensive understanding of these challenges remains elusive, hindering the development of more effective, efficient treatment options and better patient outcomes. Computational methods of "mathematical pathology" developed through quantitative analysis of patient data have the potential to provide predictions of treatment outcome in the clinical setting. Here, we show that mathematical modeling of mass transport based on fundamental (bio)physical principles complements experimental and clinical investigations towards understanding and predicting how the tissue-scale transport of chemotherapeutic agents affects outcome. We will present two complementary mathematical models that mechanistically correlate tumor microenvironment to chemotherapy

effectiveness. In the first, we have retrospectively studied the diffusion of chemotherapy drugs in colorectal cancer (CRC) metastases in the human liver by comparing measurements of cell death from histopathological patient samples at MD Anderson and the University New Mexico to the mathematical model of mass transport. The model accurately predicts the fraction of dead tumor cells due to treatment based on various physical, experimentally measurable patient-specific parameters, and agrees well with the patient data (residual analysis; $R^2 = 0.94$). We have also applied this method to lymphoma tumors grown in mice, and obtained similar results. In the second, we show how mathematical modeling of tumor perfusion during contrast-enhanced computed tomography (CT) scans of pancreatic ductal adenocarcinoma describes gemcitabine incorporation into tumor DNA and pathological response to chemoradiation therapy in both prospective and retrospective clinical trials conducted at MD Anderson. This work has the potential to be translated into the clinical setting and may provide relevant information to guide cancer treatment.

PHYSICAL SCIENCE PERSPECTIVES ON METASTASIS

Coordinate Molecular Regulation of Epithelial Dissemination by Genetic and Microenvironmental Variables

Invited Speaker: Andrew Ewald, Ph.D.
Johns Hopkins University

Metastasis begins with the escape, or dissemination, of cancer cells away from the primary tumor. During metastasis there are genetic changes in the cancer cell in parallel with molecular, cellular, and mechanical changes in the tumor microenvironment. Our lab seeks to understand the relative capacity of these inputs to induce epithelial dissemination, alone and in combination. A major barrier is the relative experimental and optical accessibility of mammary tumors in vivo. To overcome this barrier we developed an innovative combination of primary 3D cell culture, nanobiomaterials, timelapse 3D imaging, and molecular genetic techniques. We applied these techniques to resolve the cellular basis of breast tumor dissemination and to visualize in real-time the response of epithelial cells to genetic and microenvironmental perturbations.

To test the importance of the extracellular matrix (ECM) to tumor cell dissemination, we cultured epithelium from primary human breast carcinomas in different ECM gels. We utilized basement membrane gels to model the normal microenvironment and collagen I to model the stromal ECM. In basement membrane gels, malignant epithelium was either indolent or grew collectively, without protrusions. In collagen I, epithelium from the same tumor invaded with protrusions and disseminated cells. Our data reveal that metastatic tumors preferentially disseminate in specific ECM microenvironments. Furthermore, these data suggest that breaks in the basement membrane could induce invasion and dissemination via the resulting direct contact between cancer cells and collagen I.

However, Matrigel and collagen I have different protein composition and different mechanical properties. We next sought to define microenvironmental properties that could induce epithelial dissemination into the non-permissive (Matrigel) environment. We first varied matrix rigidity by varying the crosslinking density of poly(ethylene glycol) (PEG) networks within Matrigel scaffolds. Specifically increasing the rigidity of the microenvironment limited epithelial growth, but did not induce dissemination. We next incorporated adhesive signals into the PEG network using peptide-conjugated cyclodextrin (α-CDYRGDS) rings. The α-CDYRGDS rings threaded along the PEG polymers, enabling independent control of matrix mechanics, adhesive peptide composition, and the density of adhesive sites within the PEG network. Adhesive PEG networks induced dissemination at intermediate values of adhesion and rigidity. Importantly, dissemination was induced in the presence of the basement membrane proteins in Matrigel, and without inclusion of collagen I. We conclude that microenvironmental signals can induce dissemination without either the protein sequence or the fibrillar organization of collagen I.

We next sought to test the relative importance of different molecular events to dissemination. Molecular models of metastasis often focus on loss of intercellular adhesion or activation of an epithelial to mesenchymal transition (EMT). These models converge on the cell adhesion gene *E-cadherin* (*Cdh1*), as *E-cadherin* is frequently mutated in breast cancer and can also be transcriptionally repressed during EMT. However, the specific consequences of individual molecular events are obscured by the many mutations present in each breast tumour. We therefore developed techniques to delete or express genes in fluorescently labelled clones within primary murine mammary epithelium. E-cadherin was required both for simple epithelial architecture and for branching morphogenesis. Furthermore, E-cadherin loss induced collective invasion past basement membrane but not robust epithelial dissemination. Conversely, expression of the EMT transcription factor *Twist1* was sufficient to induce rapid dissemination of epithelial cells into the ECM, despite membrane-localized E-cadherin. Taken together, our data reveal distinct roles for E-cadherin and Twist1 in the early cellular processes of metastasis.

Direct Mechanical Modulation of the Invasive Phenotype

Jan T. Liphardt, Ph.D.
University of California, Berkeley
University of California, Berkeley PS-OC

Quanming Shi[1], Rajarshi P. Ghosi[1,2], Hanna Engelke[1], Chris H. Rycroft[1,2], Luke Cassereau[1,2], James Sethian[1,2], Valerie M. Weaver[-1]
[1]University of California, Berkeley, [2] Lawrence Berkeley National Laboratory

Cells and multicellular structures such as mammary acini can chemically and mechanically remodel their extracellular matrix (ECM) environment but can also respond to changes in ECM properties by differentiating, disorganizing, or branching. Here we show that Ras-transformed mammary acini with thinned basement membranes and weakened cell-cell junctions can directionally interact via lines of mechanically concentrated and aligned collagen. These collagen lines form between acini due to overlap of their collagen transport fields and the nonlinearity of collagen rheology. Gradually, a network forms, in which collagen lines interconnect hundreds of acini over distances of several centimeters. Disorganization of mechanically interacting pairs of acini is more probable, rapid, and extensive than of single acini. When acini were mechanically isolated from the bulk gel and other acini by targeted laser cutting of the collagen, the isolated acini remained strongly contractile but no longer disorganized in 20 of 20 experiments. Thus, mechanical and microanatomical signals necessary for rapid disorganization of mammary acini can emerge out of the interplay of oncogenic transformation, the nonlinearity of collagen mechanics, and acinar contractility, and can spread within contiguous biological matrices.

The Evolution of Cooperative Systems in Cancer

Kenneth J. Pienta, M.D.
Johns Hopkins University
Princeton University PS-OC

The evolution of cooperation has a well-established theoretical framework based on game theory. Existing cancer theory suggests that individual clones of cancer cells evolve independently from one another, acquiring all of the genetic traits or hallmarks necessary to form a malignant tumor. It is also now recognized that tumors are heterotypic, with cancer cells interacting with normal stromal cells within the tissue microenvironment, including endothelial, stromal, and nerve cells. This tumor cell–stromal cell interaction in itself is a form of commensalism, because it has been demonstrated that these nonmalignant cells support and even enable tumor growth. We have added to this theory by regarding tumor cells as game players whose interactions with each other and host cells help to determine their Darwinian fitness. Our data suggests that tumor cells may promote proliferation of each other by means of diffusible products. This raises the possibility that neighboring cancer cells can help each other grow as well as protect each other from a set of host defenses that neither could survive alone. The data also demonstrates that cancer cells can have similar interactions with host myofibroblasts, endothelial cells, and macrophages. We believe that cooperation can evolve as byproduct of mutualism among genetically diverse tumor cells and/or host cells. Conversely, we also demonstrate examples of parasitism whereby one cancer clone grows at the expense of other clones. This hypothesis supplements, but does not supplant, the traditional view of carcinogenesis in which one clonal population of cells develops all of the necessary genetic traits independently to form a tumor. Cooperation through the sharing of diffusible products raises new questions about tumorigenesis and has implications for understanding observed phenomena, designing new experiments, and developing new therapeutic approaches. Discovery in this area can be facilitated by the cooperation of physicists and cancer biologists!

Effect of Pro-Inflammatory Cytokines and Spheroid Culture on Breast Cancer Cell Adhesion

Michael R. King, Ph.D.
Cornell University PS-OC

Yue Geng, Siddarth Chandrasekaran
Cornell University

Hematogeneous metastasis can occur via a cascade of circulating tumor cell adhesion events to the endothelial lining of the vasculature, i.e., the metastatic cascade. Interestingly, the pro-inflammatory cytokines IL-6 and TNF-α, which play an important role in potentiating the inflammatory cascade, are significantly elevated in metastatic breast cancer (BCa) patients. Despite their high metastatic potential, human breast carcinoma cells MDA-MB-231 lack interactions with E-selectin functionalized surfaces under physiological shear stresses. We hypothesized that human plasma, 3-D tumor spheroid culture using hydrophobic PDMS substrates, or cytokine-supplemented culture media could induce a phenotypic switch that allows BCa cells to interact with E-selectin coated surfaces under physiological flow. Flow cytometry, immunofluorescence imaging, and flow-based cell adhesion assay were utilized to investigate the phenotypic changes of MDA-MB-231 cells with various treatments. Our results indicate that plasma, IL-6, and TNF-α promote breast cancer cell growth as aggregates and induce adhesive recruitment of BCa cells on E-selectin coated surfaces under flow. 3-D tumor spheroid culture exhibited the most significant increases in the interactions between BCa and E-selectin coated surfaces by upregulating CD44V4 and sLe^x expression. We found that IL-6 and TNF-α concentrations in blood can regulate the recruitment of BCa cells to the inflamed endothelium. Matrigel invasion assay also indicated that BT20 and MCF7 spheroids were more invasive than BT20 and MCF7 cells grown as monolayers. Interestingly, co-cultured spheroids of BT20, MCF7, and MCF10A cells, created to represent the heterogeneity of more realistic tumors, showed the greatest overall enhancement to blood vessel adhesion and Matrigel invasion. We propose a mechanism that could explain the invasiveness of 'triple-negative' breast cancer cell line MDA-MB-231 via a positive feedback loop of IL-6 secretion and maintenance. Taken together, our results suggest that therapeutic approaches targeting cytokine receptors and adhesion molecules on cancer cells may potentially reduce metastatic load and improve current cancer treatments.

CHALLENGES AND OPPORTUNITIES FOR CANCER MODELING

Observations From a Cancer Doc

David B. Agus, M.D.
University of Southern California
University of Southern California PS-OC

Exploring Possibilities for Next-Generation Computational Cancer Models That Work Together

Paul Macklin, Ph.D.
University of Southern California
University of Southern California PS-OC

Cancer heterogeneity—ranging from genetics to phenotype to prognosis—has emerged as a critical cancer research topic. Computational modelers are grappling with a different sort of heterogeneity: a large and growing variety of modeling techniques, generally applied to different cancer problems, with little interoperability. This complicates model comparison and cross-validation and hampers efforts to interconnect models and data from different groups. This stands in contrast with other fields faced with complex data and dynamics. For example, hurricane forecasting has advanced tremendously over the last 40 years, not only due to improved data collection and individual model refinement, but also because forecasters *combine* them into ensemble models that leverage the variety of model assumptions to mitigate the impact of uncertain whether physics and make better predictions.

In this talk, we will explore possibilities for a next-generation ecosystem of compatible models that can cooperate to combat uncertainty in patient parameters and the biophysics of cancer. There may never be a single best model that correctly incorporates all the important biology of cancer, but ensembles of high-quality models could leverage diverse expertise to improve predictions. And interconnected systems of compatible models may be able to integrate diverse data sets to help explain patient outcomes, assess and refine leading cancer biology hypotheses, and ultimately guide clinicians and their patients in their treatment choices. We will discuss key challenges and a possible way forward to advance this vision, explore potential dividends for interdisciplinary cancer research, education and open science, and invite others to join us in exploring these ideas.

CHALLENGE OF COMPLEXITY

3D Structures of Cancer Proteins Computed From Evolutionary Information Using Statistical Physics

Chris Sander, Ph.D.
Memorial Sloan-Kettering Cancer Center
Dana-Farber Cancer Institute PS-OC

Debora Marks
Harvard University

Amino acid covariation in proteins, extracted from the evolutionary sequence record, can be used to fold proteins, including transmembrane proteins important in cancer. Addressing a fundamental challenge in computational molecular biology, a new prediction method (EVold) applies a maximum entropy statistical physics approach to infer evolutionary couplings between sequence positions from correlated mutations in the multiple sequence alignment of a protein family. When translated to distance constraints, such residue-residue couplings are sufficient to generate good all-atom models of proteins from different fold classes, ranging in size from 50 to more than 300 residues. We use the technique to predict previously unknown 3D structures of proteins of biomedical interest, from their sequences alone. We show how the method can plausibly predict oligomerization, functional sites, and conformational changes in transmembrane proteins. The discovered evolutionary couplings provide insight into essential interactions constraining protein evolution and, with the rapid rise in large-scale sequencing, are likely to facilitate a comprehensive survey of the universe of protein structures by a combination computational and experimental technology. Applications to cancer genomics relate to the interpretation of the functional impact of cancer-related mutations and the design of targeted therapeutics for proteins of currently unknown 3D structure.

Nucleosome Maps With Base-Pair Resolution Revealing Distinct Nucleosome Positioning Mechanisms in S. Cerevisiae and S. Pombe

Ji-Ping Wang, Ph.D.
Northwestern University
Northwestern University PS-OC

Knowing the exact positions of nucleosomes not only advances our understanding of its imperative role in gene regulation, but also the mechanisms that underlie between-species variation in chromatin structure. The fission yeast *S. pombe* and budding yeast *S. cerevisiae* are two highly diverged model organisms widely used to study basic biological processes in eukaryotes. Using a recently developed chemical mapping approach we have produced genome-wide in vivo nucleosome maps for *S. cerevisia* and *S. pombe* with base-pair resolution. These new maps reveal that *S. pombe* shares the same ~10n+5 linker length pattern as *S. cerevisiae*, but with major distinctions in nucleosomal/linker DNA sequence features from *S. cerevisae*. The A/T rich sequences in *S. pombe* are enriched in the +/-20 bp of dyad, while they are disfavored in *S. cerevisiae* nucleosomes. The poly (dA-dT) tracts, known to substantially deplete nucleosomes in *S. cerevisiae* and other eukaryotes, only slightly affect the nucleosome occupancy in *S. pombe*. In addition, they possess preferential rotational positions within the nucleosome core, and are particularly enriched in the central +/-30 bp region as tracts length increases. The *S. pombe* does not have well-defined nucleosome free region immediately upstream of TSS, instead the -1 nucleosome is positioned with regular distance to the +1 nucleosome, and its occupancy is negatively correlated with gene expression. We discovered that the nucleosomes around transcriptional start site show bidirectional phasing in both species when intergenetic distance is relative short. The heterochromatin regions in *S. pombe*, known to be densely packed in the chromatin fiber, however, tend to have sparse nucleosome positioning, mixed with both well-positioned and fuzzy nucleosomes. The fundamental difference observed between *S. cerevisiae* and *S. pombe* suggests that the nucleosome positioning code and chromatin organization in eukaryotes may largely depend on other chromatin-forming proteins including linker histones in addition to the histone octamer core.

Methods to Define the Fitness Landscape of HIV for Rational Vaccine Design May Provide Clues for Cancer Immunology

Arup Chakraborty, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

HIV continues to wreak havoc around the world, especially in poor countries. A vaccine is urgently needed to overcome this major global health challenge. I will describe key challenges that must be confronted to achieve this goal. I will then focus on some work that aims to address a part of these challenges by bringing together theory and computation (rooted in physics), consideration of structures of multi-protein assemblies, basic immunology, and human clinical data. The results of these studies define the evolutionary space accessible to HIV by constructing the fitness landscape of viral proteins as a function of mutations. Our work suggests the design of immunogens that could be components of vaccines that might elicit immune responses which might be able to hit HIV where it hurts upon natural infection. The methods we describe are general, and in principle, could be applied to diverse pathogens (and maybe, even cancer). I will describe our naïve thoughts on how the methods we have developed might be applied to address the issue of heterogeneity in cancer and the implications for the design of cancer immunotherapies.

Poster Abstracts

Poster Number	PS-OC	Author	Title	Page Number
1	Arizona State University PS-OC	Nandakumar	An Integrated Quantitative Analysis of Nuclear Architecture in Neoplastic Progression	39
2	Arizona State University PS-OC	Amouzougan	Apoptosis Escape in Stably Expressing p53 Mutant Breast Cancer Cells	40
3	Arizona State University PS-OC	Cisneros	Cancer and the Origin of Multicellularity	41
4	Arizona State University PS-OC	Petritis	Quantitative Analyses of Protein-Protein Interactions in the B-cell Receptor Signaling Pathway	42
5	Arizona State University PS-OC	Sandersius	Computational Modeling of AFM Indentation on Soft, Heterogeneous Biological Substrates	43
6*	Arizona State University PS-OC	Yang	Doxorubicin Enhances Nucleosome Turnover Around Active Gene Promoters	44
7	Arizona State University PS-OC	Senapati	Dual Recognition of Mixed Proteins and Chromosomal Arrays	45
8	Arizona State University PS-OC	Staunton	Mechanical Properties of Cancer Cells Embedded in 3D Collagen I Matrices Probed by AFM-CLSM	46
9	Arizona State University PS-OC	Doss	Quantitative Analysis of AFM Indentations on Soft, Heterogeneous Samples	47
10	Arizona State University PS-OC	Tran	Single-Cell Gene Expression Analysis of Barrett's Esophagus and Esophageal Adenocarcinoma	48
11	Cornell University PS-OC	Kim	A Novel Statistical Approach for Characterizing the Heterogeneity in Tumor Cell Dissemination	49
12	Cornell University PS-OC	Che	Capture of Tissue Factor-Expressing Tumor Cells Using Tissue Factor Pathway Inhibitor at Low and Physiological Shear	50
13	Cornell University PS-OC	Thege	Early Detection of Pancreatic Cancer With Multiplexed Microfluidic Immunocapture	51
14*	Cornell University PS-OC	Carey	Leading Malignant Cells Initiate Collective Epithelial Cell Invasion in a Three-Dimensional Heterotypic Tumor Spheroid Model	52

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
15	Cornell University PS-OC	Benitez	Microfluidic Extraction of Human Chromosomal DNA From Single Cells for Epigenetic Analysis in Nanofluidic Channels	53
16	Cornell University PS-OC	Porri	Outreach and Dissemination and Microfabrication Facility Activities in the Cornell University Center on the Microenvironment and Metastasis (CMM)	54
17	Cornell University PS-OC	Mak	The MUSIC Assay and Single-Cell Invasion Studies	55
18	Cornell University PS-OC	Chandrasekaran	TRAIL Mediated Apoptosis in the Third Dimension	56
19	Cornell University PS-OC	Song	Understanding the Effect of Adipose Stromal Cells on Vascular Network Assembly	57
20	Cornell University PS-OC	Giannakakou	Using a Microfluidic Device to Capture CTCs and Interrogate Mechanisms Taxane Resistance in the Prospective TAXYNERGY Clinical Trial in Prostate Cancer	58
21	Cornell University PS-OC	Mason	Young Investigator Trans-Network Project: The Role of the 3D Mechanical Environment in Regulating Angiogenesis	59
22	Dana-Farber Cancer Institute PS-OC	De	Aberration in DNA Methylation in B-Cell Lymphomas Has a Complex Origin and Increases With Disease Severity	60
23	Dana-Farber Cancer Institute PS-OC	Kwak	Dissecting Cytokine Signaling in Myeloproliferative Neoplasm at the Level of Single Cells	61
24	Dana-Farber Cancer Institute PS-OC	Xhangolli	Epigenetic Fluctuation of Tumor Suppressor Genes as a Possible Mechanism of Tumor Initiation	62
25	Dana-Farber Cancer Institute PS-OC	Podlaha	Histone Modifications Are Associated With Transcript Diversity in Normal and Cancer Cells	63
26	Dana-Farber Cancer Institute PS-OC	Riester	Risk Prediction for Late-Stage Ovarian Cancer by Meta-analysis of 1,622 Patient Samples: Biologic and Clinical Correlations	64
27	Dana-Farber Cancer Institute PS-OC	Chen	Single-Cell Proteomic Analysis of Lung Cancer Cells and the Implication in Drug Resistance	65
28*	Dana-Farber Cancer Institute PS-OC	Altrock	Time Scales in the Probabilistic Spread of Defective Mutants	66

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
29	Dana-Farber Cancer Institute PS-OC	Werbeck	Tumor-Astrocyte Interactions in Breast Cancer Brain Metastasis	67
30*	Johns Hopkins University PS-OC	Phillip	A Phenotypic Signature of Pancreatic Cancer Metastasis	68
31	Johns Hopkins University PS-OC	Wong	A Platform to Study Metastatic Cancer	69
32	Johns Hopkins University PS-OC	Hung	Cell Migration Analysis Through Cell-Nucleus Correlation	70
33	Johns Hopkins University PS-OC	Wu	Characterization and Modeling of Cancer Cell Motility in 3-D Extra-Cellular Matrix	71
34	Johns Hopkins University PS-OC	Gilkes	Collagen Prolyl and Lysyl Hydroxylases Promote Stiffness and Breast Cancer Metastasis	72
35	Johns Hopkins University PS-OC	Ortiz	Fibrin Microfibers as a Platform for Angiogenesis	73
36	Johns Hopkins University PS-OC	Loza	Image Analysis Based Methods for Quantifying Intercellular Interactions	74
37	Johns Hopkins University PS-OC	Aifuwa	Microtubule Dependent Alterations to Cancer Cell Behavior Promoted by Senescent Fibroblasts	75
38	Johns Hopkins University PS-OC	He	Regulation of the Division Axis in Mammalian Cells Embedded in Three-Dimensional Matrix	76
39	Johns Hopkins University PS-OC	Stroka	Role of Ion Channels and Aquaporins in Cell Migration Through Confined Microenvironments	77
40*	Massachusetts Institute of Technology PS-OC	Korolev	Dynamics of Evolutionary Innovation in Cancer	78
41	Massachusetts Institute of Technology PS-OC	McFarland	Occam's Metastasis	79
42	Massachusetts Institute of Technology PS-OC	Stevens	Single Cell Growth Response to Metabolite Deprivation	80
43	The Methodist Hospital Research Institute PS-OC	Leonard	Abraxane Loading Into Multistage Vector for Liver Metastases Therapy	81
44	The Methodist Hospital Research Institute PS-OC	Frieboes	Analysis of Nanoparticle Uptake by Tumor Vasculature Using Computational Modeling	82
45	The Methodist Hospital Research Institute PS-OC	van de Ven	Analysis of Tumor Perfusion Using an Engineering Approach	83
46	The Methodist Hospital Research Institute PS-OC	Koshkina	Autophagy and Enhanced Chemosensitivity in Pancreatic Cancers Induced by Noninvasive Radiofrequency Field Treatment	84

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
47	The Methodist Hospital Research Institute PS-OC	Koshkina	Gold Nanoparticles Stabilized With Soft Matter Corona: Evidence of Stability and Long Circulation In Vivo	85
48	The Methodist Hospital Research Institute PS-OC	Koshkina	Tumor Selective Hyperthermia Induced by Short-Wave Capacitive RF Field	86
49	The Methodist Hospital Research Institute PS-OC	Srinivasan	Effect of Nanovector Entrapment on Monocyte Rolling and Adhesion to Endothelial Cells	87
50	The Methodist Hospital Research Institute PS-OC	Gehlot	Bio-mathematical Modeling of Yucatan Pigs: A Pilot Report	88
51	The Methodist Hospital Research Institute PS-OC	Wang	Impact of Diffusion Barriers to IFNγ on Breast Cancer Immunotherapy	89
52	The Methodist Hospital Research Institute PS-OC	van de Ven	Improving Nanotherapeutics Delivery Without Reliance on the EPR Effect	90
53	The Methodist Hospital Research Institute PS-OC	Lee	Modeling of Cell and Nanoparticle Transport in the Microvasculature	91
54*	The Methodist Hospital Research Institute PS-OC	Pascal	Predictive Biophysical Modeling of Dose Response of Tumor Cells Treated With Free Drug and Protocells	92
55	The Methodist Hospital Research Institute PS-OC	Savage	Radio Frequency-Induced Tumor Necrosis in a Mouse Model of Breast Cancer	93
56	The Methodist Hospital Research Institute PS-OC	Yokoi	Discovering Biomarkers for the Vascular Permeability to Nanotherapeutics in Different Tumor and Organ Microenvironments	94
57	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Hormuth	An Imaging Driven Biophysical Model to Predict Brain Tumor Growth and Response	95
58	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Jackson	Connecting MRI Physics to Glioma Microenvironment: Simulating T_2 MRI Signal Intensity Based on Model-Predicted Tumor-Associated Vasogenic Edema	96
59*	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Cunningham	Darwinian Dynamics and Current Concepts of Driver and Passenger Mutations	97
60*	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Epstein	Dual-Mode Cellular Energetics and the Warburg Effect	98
61	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Kim	Optimizing Melanoma Treatments: Regulating Autophagy-Mediated Treatment Resistance	99

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
62	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Lloyd	Pathology to Drive Precision Medicine in Oncology: Lessons of Landscape Ecology	100
63	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Damaghi	Proteomics-Based Biomarker Discovery for Acidic Microenvironment of Breast Cancer Tumors	101
64	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Trister	Radiogenomics: Assessing Gene Expression Perturbations in Gliomas With a Patient-Specific Model Informed by Routine Imaging	102
65	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Lloyd	Regional Variations in Intratumoral Selection Forces Produce Predictable Cellular Heterogeneity	103
66	H. Lee Moffitt Cancer Center & Research Institute PS-OC	Robertson	A Treatment Optimization Framework for Undetectable Bone Metastases: Developing an Integrated, Patient-Specific Tool	104
67	Northwestern University PS-OC	Chuang	Chance and Circumstance Govern Macrophage Functional Diversity	105
68*	Northwestern University PS-OC	Wells	Control of Stochastic Switching in Biological Networks	106
69	Northwestern University PS-OC	Oyer	Consequences of Oncogenic Isocitrate Dehydrogenase Mutations and 2-Hydroxyglutarate Production in Prostate Epithelium	107
70	Northwestern University PS-OC	Rosanio	Discovery of DNA-Bendability Motifs Using a Large, Random Library	108
71	Northwestern University PS-OC	Simeon	Effects of DNA Methylation on Nucleosome Stability: Insight Into the Mechanistic Behavior of Cancer Using Computational Studies	109
72	Northwestern University PS-OC	Yang	The Involvement of TET1 in Prostate Cancer	110
73	Northwestern University PS-OC	Hornick	Micromechanical Properties of Mammalian Meiotic Chromosomes: High-Frequency Model of Genomic Instability That Phenocopies Cancer Pathogenesis	111
74	Northwestern University PS-OC	Sun	Micromechanics of Human Mitotic Chromosome	112
75	Northwestern University PS-OC	Sebeson	Nucleosome Positioning Maps Examining the Role of PRC2/Eed in Embryonic Stem Cell Development	113

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
76	Northwestern University PS-OC	Martin	Nucleosomes and Chromatin Architecture in the *Drosophila* Genome	114
77	Northwestern University PS-OC	Yungster	Optimizing Rate Constants in Epigenetic Markov Models	115
78	Northwestern University PS-OC	Zaichuk	A Single-Nucleotide Resolution Map of Nucleosomes in *Schizosaccharomyces Pombe*	116
79	Northwestern University PS-OC	Eastland	Understanding the Role of Disulfides in Metaphase Chromosome Structure and Its Link to Genetic Diseases	117
80	Princeton University PS-OC	Collyar	Communicate Effectively With PS-OC Colleagues, for Patients' Sake!	118
81	Princeton University PS-OC	D'Silva	Deterministic Separation of Cancer Cells From Blood at 10 mL/min	119
82	Princeton University PS-OC	Jiao	Evolution and Morphology of Microenvironment-Enhanced Malignancy of Three-Dimensional Invasive Solid Tumors	120
83	Princeton University PS-OC	Epstein	Evolution of Radiation Resistance in a Complex Microenvironment	121
84	Princeton University PS-OC	Bestoso	Evolution and the Selective Excission of Cryptic Phages in Bacteria Under Antibiotic Stress	122
85*	Princeton University PS-OC	Fuhrmann	Heterogeneity in Cell-Matrix Adhesion as an Indicator of Metastatic State	123
86	Princeton University PS-OC	Zhang	Mesoscopic Evolution in Bacteria	124
87	Princeton University PS-OC	Austin	Metastatic Breast Cancer Cells Collectively Invade Collagen by Following a Glucose Gradient	125
88*	Princeton University PS-OC	Chen	Modeling the Switch From Tumor Dormancy to Rapid Proliferation	126
89	Princeton University PS-OC	Vyawahare	The Positioning Logic and Copy Number Control of Genes in Bacteria Under Stress	127
90	Princeton University PS-OC	Vyawahare	Princeton PS-OC Microfluidic Core Facility	128
91	Princeton University PS-OC	Wu	Rapid Adaptation and Evolution of Drug Resistance of Cancer	129
92	Princeton University PS-OC	Wu	Rapid Evolution of Drug Resistance of Multiple Myeloma in the Microenvironment With Drug Gradients	130

* Young Investigator Speaker

Poster Number	PS-OC	Author	Title	Page Number
93	Princeton University PS-OC	Lee	Single-Cell Sequencing Reveals Genetic Heterogeneity in Cell Population	131
94	Princeton University PS-OC	Hodas	The Thermodynamics of Cancer	132
95	The Scripps Research Institute PS-OC	Emerson	Automated Cell Classification using Low Dimensional Feature Extraction and Representation	133
96	The Scripps Research Institute PS-OC	Schaffer	Cancer Heterogeneity, CTCs, and Metastasis: Staring at the Tip of the Iceberg	134
97*	The Scripps Research Institute PS-OC	Baker-Groberg	Colon Adenocarcinoma Cell Recruitment to Platelets and Thrombi Under Shear	135
98	The Scripps Research Institute PS-OC	Mason	Comparing the Complexity of Metastatic Cancer	136
99	The Scripps Research Institute PS-OC	Bazhenova	Dynamic Changes in Circulating Tumor Cell Levels as a Prognostic Marker in Stage IV Non-Small Cell Lung Cancer (NSCLC)	137
100	The Scripps Research Institute PS-OC	Lee	Modeling and Simulation of Procoagulant Circulating Tumor Cells in Blood Flow	138
101	The Scripps Research Institute PS-OC	Dago	Monitoring Treatment Response in Prostate Cancer by Applying Single Cell-Molecular Characterization of Circulating Tumor Cells	139
102	The Scripps Research Institute PS-OC	Phillips	Multiscale Optical Quantification of Subcellular Structure in Early and Late Stage Isogenic Colorectal Cancer Cell Lines	140
103	The Scripps Research Institute PS-OC	Ruiz	PSCO0056: Identification and Characterization of Circulating Tumor Cells in the Blood of Melanoma Patients	141
104	The Scripps Research Institute PS-OC	Baker-Groberg	Rationale Design of an Ex Vivo Model of Circulating Tumor Microemboli	142
105	University of California, Berkeley PS-OC	LaBarge	Age-Dependent Mechano-Responses in Human Mammary Epithelial Progenitor Cells	143
106	University of California, Berkeley PS-OC	Kim	CD44-based Adhesion and Mechanotransductive Signaling on Engineered Hyaluronic Acid Matrices	144
107	University of California, Berkeley PS-OC	Kurup	Characterizing the Cooperation Between ErbB2 Signaling and ECM Stiffness in Driving Breast Tumor Progression	145
108	University of California, Berkeley PS-OC	Yang	Computational Identification of Cellular Mechanical Properties From Image Data	146

Poster Number	PS-OC	Author	Title	Page Number
109	University of California, Berkeley PS-OC	Schofield	Histological Examination of the Temporal and Spatial Expression of SATB1 Reveal No Correlation With Tumor State but Does Signal a Tumor-Promoting Inflammatory Environment	147
110*	University of California, Berkeley PS-OC	Bainer	Localized Modulation of Genomic Transcriptional Activity Driven by Extracellular Stiffness Cues in 3D	148
111	University of California, Berkeley PS-OC	Shi	Long-Range Mechanical Communication Among Disorganizing Mammary Acini	149
112	University of California, Berkeley PS-OC	DuFort	Mechanical Force Regulates the Nanoscale Dynamics of Focal Adhesions	150
113	University of California, Berkeley PS-OC	Veiseh	Multiplexed Profiling of Breast Cancer Cellular Heterogeneity by Microenvironmental Probes	151
114	University of California, Berkeley PS-OC	Nan	Quantitative Single Molecule Imaging Reveals a Dimeric Ras/Raf Signaling Module	152
115	University of California, Berkeley PS-OC	Greene	Restricting EphA2 Receptor Reorganization Alters Internalization and Signaling in MDAMB231 Cells	153
116	University of Southern California PS-OC	Ruderman	Altered Autoantibody and Cytokine Profiles in a Murine Lymphoma Model	154
117	University of Southern California PS-OC	Lee	Cytokine Profiles Associated With Therapeutic Intervention and Tumor Transplantation in Lymphoma Mouse Model	155
118	University of Southern California PS-OC	Flinders	Epigenetic Adaptation to Drug Treatment in Lymphoma	156
119	University of Southern California PS-OC	Gonzalez-Malerva	Functional Differences of Mutant p53s Expressed in MCF10A Cells and Their Contribution to Breast Carcinogenesis	157
120	University of Southern California PS-OC	Li	Investigating New Therapies for Chemoresistant *p53-/-;Emu-MYC* Lymphoma	158
121	University of Southern California PS-OC	Frieboes	Prediction of Drug Response in Non-Hodgkin's Lymphoma	159
122	University of Southern California PS-OC	Mumenthaler	Microenvironmental Heterogeneity Drives Tumor Evolutionary Dynamics	160
123	University of Southern California PS-OC	Macklin	Progress in User-Friendly, 3-D Multiscale Agent-Based Simulation of Large (500k+ Cells) Cancer Systems	161

* Young Investigator Speaker

Invited Poster Presentations

Poster Number	Invited Poster Presentation	Author	Title	Page Number
124	American Type Culture Collection	Reid	PBCF Provides BioServices to the PS-OC Network Investigators	162
125	CCS Associates	Keating	Key Steps to Consider in Commercialization of an Academic Clinical Assay Platform	163
126	National Cancer Institute	Dickherber	Innovative Molecular Analysis Technologies (IMAT) Program	164
127	National Science Foundation	Parker	Clinical Relevance, Mathematical Models, and Cancer Treatment Decision Support	165
128	National Science Foundation	Tees	Mechanical Properties of Cancer Cells: A Possible Biomarker for Stemness	166
129	National Science Foundation	Bonin	Mechanical Properties of Cells Undergoing Neoplastic Transformation	167

ARIZONA STATE UNIVERSITY PS-OC

1. An Integrated Quantitative Analysis of Nuclear Architecture in Neoplastic Progression

Arizona State University PS-OC
Project 3: ASU PS-OC, Arizona State University

Vivek, Nandakumar, Nanna, Hansen, Glenn Honor, Kathryn Hernandez, Stephanie Helland, Roger H. Johnson, Kimberly J. Bussey, Deirdre R. Meldrum

Arizona State University

Nuclear architecture is intricately associated with cell health. Qualitative two-dimensional assessment of nuclear features, including shape and chromatin distribution, is used for cancer diagnosis. But scant quantitative information exists about changes in three-dimensional nuclear architecture, and the molecular drivers of these changes, as cells progress to malignancy.

We studied an *in vitro* neoplastic progression model representing normal squamous, esophageal metaplasia, dysplasia, and adenocarcinoma to develop quantitative biosignatures predictive of disease stage based upon nuclear architecture and its molecular determinants. Analysis of single-cell transmission-mode optical CT imagery yielded 3D nuclear morphometric biosignatures distinctly different from conventional (2D) diagnostic metrics. After controlling for cell cycle stage, morphological heterogeneity was still abundant in normal cell populations and increased with progression. The expression levels of proteins known to regulate nuclear architecture varied with progression but did not correlate strongly with trends in their spatial localization. Dysplastic cells demonstrated significantly higher expression levels ($p<0.05$) of HP1α relative to normal squamous or adenocarcinoma. No changes were observed in localization pattern detected by immunofluorescence. In contrast, lamin A/C, H3K9me3, and H3K9Ac exhibited differential localization but not expression. To understand the interplay between nuclear structure and chromatin organization, we treated normal, metaplastic, and adenocarcinoma cells with the histone deacetylase inhibitor vorinostat. We observed normalization in nuclear structure and chromatin distribution of abnormal cells. Our morphological observations were associated with an increase in active chromatin marks, a decrease in repressive chromatin marks, and decreased CTCF expression.

The results of our study demonstrate the utility of quantitative 3D nuclear morphology to robustly predict cell health, reinforce the phenotypic impact of nuclear architectural proteins, and demonstrate the variation in their expression as a function of neoplastic progression.

Associated Cancer Types/Areas: esophagus, Barrett's esophagus, adenocarcinoma

Keywords: quantitative,nuclear architecture, molecular drivers

2. Apoptosis Escape in Stably Expressing p53 Mutant Breast Cancer Cells

Arizona State University PS-OC
Anderson Breast Cancer Research Project

Eva Amouzougan, Seron Eaton, Laura Gonzalez, Jin Park, Karen Anderson

Arizona State University

The formation of cancer is driven by genetic mutations in proto-oncogenes and tumor suppressor genes. Proto-oncogenes and tumor suppressor genes play an important role in cellular processes such as in cell cycle regulation and responses to apoptosis. Alteration of these genes has been linked to uncontrolled cell division, immortalization and tumor formation. TP53 is a tumor suppressor gene that regulates the cell cycle and the induction of apoptosis (programed cell death). Mutation in the TP53 gene is associated with tumor development in nearly 50% of all human cancers, including the most aggressive types of breast cancer. Resistance to apoptosis has been associated with tumor progression and resistance to chemotherapeutic agents. The goal of this study was to investigate if different p53 mutations induce different levels of apoptosis altering metastatic potential. Non-tumorigenic immortalized breast epithelial cells (MCF10A) expressing wild-type p53 were transduced with ten prevalent TP53 mutations using retroviral vectors. Using the topoisomerase inhibitor camptothecin (CPT), apoptosis was induced in the MCF10A cell lines. The cells were analyzed by flow cytometry using Annexin V, Pacific Blue. Nearly 60% apoptosis was observed in the MCF10A cells expressing the WT p53 compared with 34% apoptosis in the cells expressing the R248Q mutation. Different level of resistance to apoptosis were observed in the cells expressing various p53 mutations, R273H (56.01%), R175H (49.09%), Y234C (47.33%), Y220C (44.39%), R163C (43.40%) and R248W (42.07%). P53 mutations differently altered the apoptosis-signaling pathway, which may impact malignancy and invasiveness.

Associated Cancer Types/Areas: breast cancer, apoptosis, tumor suppressor genes

Keywords: apoptosis, p53 mutation, chemotherapeutic

3. Cancer and the Origin of Multicellularity

Arizona State University PS-OC

Luis Cisneros[1], Sara Walker[2]

[1]Arizona State University; [2]Beyond Center, National Aeronautics and Space Administration

Cancer represents a breakdown of the normal relationship between somatic and germ cells. It has been suggested (Rainey and Kerr, 2010) that the transition from a single-celled world to reproductive assemblages is facilitated by the onset of defectors that flourish at the expense of the collective. If so, cancer could be a necessary part in the profound relationship between selfish cells and cooperating communities leading to this momentous evolutionary step. Therefore cancerous 'cheats' may play a major role in the origin of cooperative aggregates and the subsequent emergence of fully multicellular life. We use an agent-based model of interacting cells that switch between a reproductive phase and a non-reproductive cooperative phase to explore this hypothesis. The evolutionary strategies that individual cells adopt depend on the their local micro-environment but also modify it. Therefore, structure and organization on a large scale determine the behavior of individual cells, and the dynamics of individual cells in turn determine the properties of the whole. This interplay is addressed in the context of multicellular evolution by weighting the effects of defection on system stability and reproduction. The evolution of collective properties is explored by running large statistical samplings of the model system for different parameters such as abundance of resources, critical phenotypic switching, metabolism, cell differentiation and adhesive properties.

Associated Cancer Types/Areas: general theoretical work

Keywords: origin of cancer, multicellularity, agent-based model

4. Quantitative Analyses of Protein-Protein Interactions in the B-cell Receptor Signaling Pathway
Dynamic State Space Modeling of Cancer Cell Response to Therapy
Arizona State University PS-OC

Brianne Petritis, Mitch Magee, Ben Ober-Reynolds, Justin Saul, Jin Park, Ian Shoemaker, Jason Steel, Kevin Peasely, Joshua LaBaer

Arizona State University

Aberrant protein signaling contributes to the formation and progression of diseases, including Burkitt's lymphoma, a highly aggressive non-Hodgkin lymphoma that affects B-cells. The comprehensive characterization of protein-protein interactions (PPIs) in the B-cell receptor (BCR) pathway will help elucidate the molecular mechanisms during tumor growth and response to treatment. Here, we coupled nucleic acid programmable protein arrays (NAPPA) with surface plasmon resonance imaging (SPRi) to obtain high throughput, quantitative analyses of human PPIs within the BCR pathway. In our initial experiment, 106 proteins in the BCR pathway were displayed on the arrays and queried with 14 purified proteins considered to be central signaling proteins in this network. NAPPA-SPRi detected and quantitatively measured the strength (i.e., affinity) and interaction rate (i.e., kinetics) for 27 known PPIs as well as 190 novel interactions. Differences in protein interaction strength, ranging from μM to sub-pM affinity, were observed within a single array. Moreover, our novel combinatory approach was sensitive enough to distinguish differences in protein interactions between different protein isoforms and positions (N- vs. C-) of the capture tag. We are currently probing the BCR signaling pathway array with additional proteins. We are also studying the effects of protein mutations and post-translational modifications on PPIs. These data will be used to generate a dynamic signaling model of the BCR pathway, which will be tested and refined through transcriptomic and proteomic measurements of Burkitt's-like lymphoma cell models following various perturbations (i.e., genetic mutations, cytotoxic treatment). Our high throughput, quantitative approach could be applied toward characterizing other signaling pathways and may help to identify potential therapeutic targets of disease.

Associated Cancer Types/Areas: Burkitt's lymphoma, non-Hodgkin lymphoma, B-cell lymphoma

Keywords: proteomics, signaling, lymphoma

5. Computational Modeling of AFM Indentation on Soft, Heterogeneous Biological Substrates

Arizona State University PS-OC
Project 1: Center for Biological Physics and Department of Physics

Sebastian Sandersius[1], Bryant L. Doss[1], Jack R. Staunton[1], Timothy Newman[2], Robert Ros[1]

[1]Arizona State University, [2]University of Dundee

Cancer progression is associated with changes in the mechanical properties of cells as well as the extracellular matrix (ECM) in which they are embedded. Atomic force microscopy (AFM) has been used to measure mechanical properties of cancer cells embedded in gels of ECM such as collagen. It is important to measure cell mechanics in such media as it provides environmental conditions more realistic for cells in vivo. Mechanical measurements from such composite media are convoluted and it is not straight forward to deconvolute measurements to obtain information on the mechanical attributes of each constituent within the media. A computational model has been developed to provide theoretical confirmation and calibration of experimental measurements. The Subcellular Element Model (ScEM) has been introduced to compute the dynamics of large numbers of three-dimensional deformable cells in multicellular systems. Within this model framework, each cell is represented by a collection of elastically coupled elements, interacting with one another via short-range potentials, and dynamically updated using over-damped Langevin dynamics. The ScEM can also be used to represent a single cell in more detail, by using a larger number of subcellular elements exclusively identified with that cell. Using the ScEM, force indentation measurements have been simulated and we have profiled the effects of heterogeneity within the viscoelastic substrates.

Associated Cancer Types/Areas: microenvironment, elasticity, metastasis

Keywords: AFM, microenvironment, mechanics, ScEM, modeling, ECM, Langevin, viscoelasticity, rheology, suspensions, composites

6. Doxorubicin Enhances Nucleosome Turnover Around Active Gene Promoters

Arizona State University PS-OC
Project 2: Probing the Physical Properties of Nucleosomes During Cancer Progression

Fan Yang, Christopher J. Kemp, Steven Henikoff

Fred Hutchinson Cancer Research Center

Doxorubicin (also known as Adriamycin) is a DNA intercalator that is among the most commonly used anti-cancer drugs. Doxorubicin causes DNA double-strand breaks in rapidly dividing cells, although whether it also affects general chromatin properties is unknown. Here, we use a metabolic labeling strategy for directly measuring nucleosome turnover to examine the effect of doxorubicin on chromatin dynamics in squamous cell carcinoma cell lines derived from genetically defined mice. We find that doxorubicin enhances nucleosome turnover around promoters of active genes. Consistent with a direct action of doxorubicin, enhancement of nucleosome turnover around promoters gradually increases with time of exposure to the drug. Interestingly, enhancement occurs both in wild-type cells and in cells lacking the p53 tumor suppressor gene or the master regulator of the DNA damage response, Atm, suggesting that doxorubicin action on nucleosome dynamics is independent of the DNA damage checkpoint. In addition, another anthracycline intercalator, aclarubicin, shows similar effects on enhancing nucleosome turnover around promoters. Our results suggest that anthracycline intercalation promotes nucleosome turnover by its effect on DNA topology, with possible implications for cancer chemotherapies that combine traditional DNA intercalators with targeted epigenetic drugs.

Associated Cancer Types/Areas: nearly all cancers and leukemias treated with standard-of-care anthracycline drugs

Keywords: nucleosome turnover, Doxorubicin, transcription initiation

7. Dual Recognition of Mixed Proteins and Chromosomal Arrays

Arizona State University PS-OC
Project 2: Probing the Physical Properties of Nucleosomes During Cancer Progression

Subhadip Senapati, Saikat Manna, Sudipta Biswas

Arizona State University

Atomic force microscopy (AFM) is one of the most important tools to scan and image a surface with nanometer resolution. It can also operate in physiological condition (i.e., in aqueous buffer). That makes it efficient and gives an edge over some other microscope when it comes to imaging or studying biological samples such as proteins, cells etc. Moreover, AFM tip can be functionalized by biomolecules using suitable chemical method and can be used to detect corresponding target molecules immobilized on the surface by recognition imaging and to measure the binding force between them using force spectroscopy which can provide information at single molecular level. Recognition imaging helps us to study a biomolecule with simultaneous topographic image and force spectroscopy gives the interaction force between the molecules on the tip and surface in the form of force-distance curves from which force in the range of pico-newton can be obtained. Here, an easy and convenient method has been described for the functionalization of AFM tips (copper-free click chemistry). Moreover, We have developed a tri-arm linker with antithrombin aptamer and RGD peptide on it and we want to detect thrombin and integrin from a mixture of proteins. Following this, we want to use this technique to image the extracted chromatin of selected cell lines and find out the relation between epigenetic cancer, DNA methylation and H2A.Z incorporation.

Associated Cancer Types/Areas: epigenetic cancer

Keywords: recognition imaging, DNA methylation, H2A.Z

8. Mechanical Properties of Cancer Cells Embedded in 3D Collagen I Matrices Probed by AFM-CLSM

Arizona State University PS-OC
Project 1: Center for Biological Physics

Jack R. Staunton, Bryant L. Doss, Robert Ros

Arizona State University

Mechanical interactions between the cell and extracellular matrix (ECM) are critical to the metastasis of cancer cells, from breaking *out* through the basal lamina of the primary tumor (intravasation) to breaking *in* through the basal lamina at a distal site (extravasation). Increased mechanical compliance confers metastatic cells with a distinct advantage in reaching the other side. In the past several years, experimental perturbations of ECM stiffness *in vitro* have revealed the importance of 'outside-in' signaling in effecting cellular behavior and phenotype, and the physiological relevance of a 3D microenvironment has become increasingly clear. With this in mind, we have established a 3D model system in which to investigate cell-ECM mechanics using an atomic force microscope (AFM) mounted on and synchronized with a confocal laser scanning microscope (CLSM). Along with the use of well-defined spheroconical AFM probes with large radii and tip height, the advancement of novel AFM indentation data analysis methods to correctly determine elastic moduli in a depth-dependent manner enables us to determine the stiffness of cells that are embedded in gels. For the experiments, bovine collagen I matrices ranging ~10-50 μm in thickness and ~0.1-10 kPa in elastic modulus are covalently attached to dishes with optical glass bottoms using common surface chemistry. After polymerization, gels are seeded with metastatic, tumorigenic MDA-MB-231 breast cancer cells, immortalized non-tumorigenic MCF-10A mammary epithelial cells, or with both. Cells are given various amounts of time to adhere and/or invade the gel before fluorescent staining and measurement. Here we report our latest results on the mechanical properties of collagen-embedded normal and cancerous breast cells.

Associated Cancer Types/Areas: breast cancer, 3D microenvironment, metastasis

Keywords: AFM, elasticity, cell mechanics

9. Quantitative Analysis of AFM Indentations on Soft, Heterogeneous Samples

Arizona State University PS-OC
Project 1: Center for Biological Physics and Department of Physics

Bryant L. Doss, Jack R. Staunton, Robert Ros

Arizona State University

Atomic force microscope (AFM) indentations are a common method for producing quantitative mechanical data of eukaryotic cells as well as other biological and elastomer samples. We are interested in performing these experiments on cells embedded in 3D matrices to study the mechanical aspects of cancer development, however the analysis methods that currently exist are insufficient for describing such complex samples. We have developed a number of improvements to the analysis of raw AFM force-indentation data to account for mechanical heterogeneity and determine the actual elastic moduli of two-layer materials based on the apparent Young's modulus in depth-dependent regressions. New piecewise contact geometry models to represent AFM tips are derived to account for both the apex and cone angle, which is necessary to include at deep indentations. Theoretical methods for analyzing bonded two-layer substrates are implemented to quantify how subsurface heterogeneities affect the depth-dependent analysis. We find that the apparent Young's modulus will have a linear slope whose value will depend on the height of the first layer and relative rigidity of the two layers, providing a signature for determining the actual Young's moduli for these materials. Furthermore, in the case where the elastic modulus of one layer is well defined, the other can be determined with very high accuracy (< 6% error). To validate the technique, we use finite element simulations and AFM indentations on polyacrylamide gels. The theory agrees strongly with the finite element simulations for all indentations with softer second layers and shallow indentations with stiffer second layers. Experimentally, the theory can account for some change in apparent Young's modulus, however elasticity gradients in the polyacrylamide cause the slope to be much more pronounced than in a simple two-layer material.

Associated Cancer Types/Areas: microenvironment, elasticity, metastasis

Keywords: AFM, microenvironment, mechanics

10. Single-Cell Gene Expression Analysis of Barrett's Esophagus and Esophageal Adenocarcinoma
Arizona State University PS-OC
Project 3: Arizona State University PS-OC

Thai Tran, Kelsey Haeuser, Edward Siu, Ashlee Harris, Dan Van Blarcom, Vivek Nandakumar, Roger H Johnson, Deirdre R Meldrum

Arizona State University

Esophageal adenocarcinoma (EAC) is among the most lethal and fastest growing cancers in the United States. An estimated 14,000 people are diagnosed with EAC every year and the mortality rate is 97%. The onset of EAC is triggered by a metaplastic transformation of normal squamous (NS) esophageal epithelial cells to Barrett's esophagus (BE) cells in response to acid reflux. BE patients progress through non-dysplastic metaplasia and increasing grades of dysplasia prior to EAC. Since patients with BE are at a 125-fold elevated risk of developing EAC, routine endoscopic surveillance is a commonly adopted patient management strategy. Unfortunately, no methods currently exist to identify such patients in the initial stages of BE. The resulting lack of appropriate patient management strategies significantly drives up the cost of medical care. The crux of this daunting problem is the inherent cell population heterogeneity within the BE tissue segment. The inability of widely-used conventional bulk cell techniques to identify diagnostic biomarkers necessitates new diagnostic methods based on single-cell analysis that quantify genotypic and phenotypic heterogeneity to predict the subset of metaplastic BE patients who will eventually progress to EA. In this study, we investigated cellular heterogeneity in BE and EAC at the single-cell level. We showed that mRNA expression levels of various BE and EAC markers including CDX2, TFF3 and CyclinD1 are highly variable in both BE and EAC cells, suggesting high levels of cell heterogeneity found in both stages of EAC progression. Additionally, we also demonstrated that while most BE and EAC cells did not express the angiogenesis growth factor, VEGF, occasional VEGF-positive cells were observed where VEGF expression is significantly higher in EAC as compared to BE. Future studies will focus on establishing cell heterogeneity in a vast number of patients and correlating such data sets with clinical outcomes to identify predictive biosignatures.

Keywords: single-cell, esophageal adenocarcinoma, Barrett's esophagus

11. A Novel Statistical Approach for Characterizing the Heterogeneity in Tumor Cell Dissemination

Cornell University PS-OC
Project 2: Physical and Chemical Cues in Tumor Cell Migration

Beum Jun Kim, Mingming Wu

Cornell University

Tumor cell genotypic and phenotypic heterogeneity are hallmarks of cancer. However, current *in vitro* assays are often population based, and fail to capture the individualities of tumor cells. In this work, we examined tumor cell motility and chemotaxis at a single cell level using a robust 3D microfluidic chemotaxis assay. Using a malignant tumor cell line, MDA-MB-231, as a model system, we measured cancer cell movements when the cells were subjected to well defined epidermal growth factor (EGF) and chemokine SDF-1α gradients. To characterize the heterogeneity of tumor cell motility, we used Levy flight statistics to model the distribution of the tumor cell movement step size. The Levy flight distribution has been used in a wide range of dynamic systems for describing rare events, including chaotic mixing in fluid flows and food search strategies of flying birds. The occurrences of the rare events are characterized by the exponent of the distribution tail in the power law. Here, we explore the possibilities of using the Levy flight distribution exponent as a measure for the heterogeneity of the cancer cell motility, as such the ability to disseminate to distant sites. The impact of epidermal growth factor and chemokine SDF-1α gradients on cancer cell dissemination will be discussed.

Associated Cancer Types/Areas: breast cancer, metastasis, microenvironment

Keywords: motility statistics, Levy walk, dissemination strategy

12. Capture of Tissue Factor-Expressing Tumor Cells Using Tissue Factor Pathway Inhibitor at Low and Physiological Shear

Cornell University PS-OC
Project 3: Adhesion of Tumor Cells in the Vascular Microenvironment, Cornell University Center on the Microenvironment and Metastasis

Sara Che, Michael L. Shuler, Tracy Stokol

Cornell University

Tissue Factor (TF) is over-expressed in various types of malignant cancer cells, including breast cancer cells, and can promote invasive and migratory behavior in cancer cells. Tissue factor's endogenous inhibitor, tissue factor pathway inhibitor (TFPI), is expressed on endothelial cells, and stops the TF-mediated coagulation by binding the enzymatic partners of TF, factor VII (FVII) and factor X (FX).

Previously, we have shown that TF-expressing breast cancer cells, MDA MB 231, can adhere to immobilized recombinant TFPI under static conditions, while MCF7 with weak TF expression cannot. We further tested adhesion in a microfluidic device. Under low shear (0.4-0.7 dyn/cm2), MDA MB 231, but not MCF 7, bind to immobilized

TFPI; the capture is TF-dependent as pretreatment of MDA MB 231 with an antibody against TF significantly reduced the binding. Adhesion of MDA MB 231 to immobilized TFPI is dependent on shear, TFPI concentration and FVII concentration. At physiological shear (1.0 dyn/cm 2 and higher), there was minimal capture of MDA MB 231 with immobilized TFPI. We are currently investigating the role of inflammation and selectins in mediating capture of MDA MB 231 under physiological shear. This is the first study to demonstrate that TFPI, the natural inhibitor of TF, can capture TF-expressing tumor cells under physiological shear.

Associated Cancer Types/Areas: breast cancer, metastasis, cancer cell adhesion

Keywords: tissue factor, cell adhesion, tissue factor pathway inhibitor

13. Early Detection of Pancreatic Cancer With Multiplexed Microfluidic Immunocapture

Cornell University PS-OC
Cornell University Center on the Microenvironment and Metastasis, Kirby Research

Fredrik Thege[1], Steven Santana[1], Andrew Rhim[2], Brian Kirby[1]

[1]Cornell University, [2]University of Pennsylvania

Pancreatic cancer is the fourth leading cause of cancer related death in the United States. The abysmal patient survivorship, rapid progression and asymptomatic nature of pancreatic cancer make it one of the biggest challenges faced by modern medicine. As early detection is an efficient way to improve patient survivorship, we are developing a novel methodology for early detection of pancreatic cancer using multiplexed microfluidic capture and genetic analysis of circulating pancreas cells. This body of work builds on our success in identifying circulating pancreas cells in both pancreas cancer and pancreatic cyst legion patients using the GEDI technique. By using multiple pancreatic cancer cell markers that are specific and robust to cancer-associated changes in protein expression, we can optimize immunocapture of circulating pancreatic cells. Here, our work on mucin expression, anti-mucin based immunocapture and novel biomarkers for circulating pancreatic cells is presented with our clinical findings. As entry of pancreatic cells into the bloodstream can occur prior to tumor formation, we hypothesize that the release of circulating pancreatic cells is an early event in pancreas cancer progression and that pancreatic cyst lesion patients with circulating pancreas cells are at increased risk of pancreatic cancer. The overarching goal is to establish these measurements as novel biomarkers for early pancreatic cancer risk stratification and to inform clinical action.

Associated Cancer Types/Areas: pancreatic cancer, early detection , circulating tumor cells, metastasis, pancreatic cyst lesions

Keywords: PanCa, CTC, detection

14. Leading Malignant Cells Initiate Collective Epithelial Cell Invasion in a Three-Dimensional Heterotypic Tumor Spheroid Model

Cornell University PS-OC
Project 2: Physical and Chemical Cues in Tumor Cell Migration

Shawn P. Carey, Alina Starchenko, Alexandra L. McGregor, Cynthia A. Reinhart-King

Cornell University

Solid tumors consist of genetically and phenotypically diverse subpopulations of cancer cells with unique capacities for growth, differentiation, and invasion. While the molecular and microenvironmental bases for heterogeneity are increasingly appreciated, the outcomes of such intratumor heterogeneity, particularly in the context of tumor invasion and metastasis, remain poorly understood. To study heterotypic cell–cell interactions and elucidate the biological consequences of intratumor heterogeneity, we developed a tissue-engineered multicellular spheroid (MCS) co-culture model that recapitulates the cellular diversity and fully three-dimensional cell–cell and cell–matrix interactions that characterize human carcinomas. We found that ''invasion-competent'' malignant cells induced the collective invasion of otherwise ''invasion-incompetent'' epithelial cells, and that these two cell types consistently exhibited distinct leader and follower roles during invasion. Analysis of extracellular matrix (ECM) microarchitecture revealed that malignant cell invasion was accompanied by extensive ECM remodeling including matrix alignment and proteolytic track-making. Inhibition of cell contractility- and proteolysis-mediated matrix reorganization prevented leader-follower behavior and malignant cell-induced epithelial cell invasion. These results indicate that heterogeneous subpopulations within a tumor may possess specialized roles during tumor progression and suggest that complex interactions among the various subpopulations of cancer cells within a tumor may regulate critical aspects of tumor biology and affect clinical outcome [1].

Associated Cancer Types/Areas: breast cancer, tumor invasion and metastasis, intratumor heterogeneity

Keywords: intratumor heterogeneity, invasion and metastasis, extracellular matrix

Reference

Carey SP, Starchenko A, McGregor AL, Reinhart-King CA. (2013) Leading malignant cells initiate collective epithelial cell invasion in a three-dimensional heterotypic tumor spheroid model. *Clinical and Experimental Metastasis*. doi: 10.1007/s10585-013-9565-x

15. Microfluidic Extraction of Human Chromosomal DNA From Single Cells for Epigenetic Analysis in Nanofluidic Channels

Cornell University PS-OC
Cell Epigenomic Analysis Core, Cornell University Center on the Microenvironment and Metastasis

Jaime J. Benitez[1], Juraj Topolancik[1], Harvey C. Tian[1], Christopher B. Wallin[1], David R. Latulippe[1], Kylan Szeto[1], Patrick J. Murphy[1], Benjamin R. Cipriany[1], Dong S. Choi[2], Jenny Chang[2], Paul D. Soloway[1], Harold G. Craighead[1]

[1]Cornell University, [2]The Methodist Hospital Research Institute

We describe a microfluidic device for the extraction, purification and stretching of human chromosomal DNA from single cells. A two-dimensional array of micropillars in a microfluidic polydimethylsiloxane (PDMS) channel was designed to capture a single human cell. Megabase-long DNA strands released from the cell upon lysis are trapped in the micropillar array and stretched under optimal hydrodynamic flow conditions. Intact chromosomal DNA is entangled in the array, while other cellular components are washed away from the channel. Quantification of the extracted material reveals that the microdevice efficiently extracts essentially all chromosomal DNA. Genomic DNA from different cell types was extracted using the device and labeled on-chip with methyl-CpG binding domain 1 (MBD1) protein modified with a fluorescent dye. MBD1-bound DNA was released from the device and directly transferred to a nanofluidic channel for single molecule detection of MBD1 molecules. Quantification of bound MBD1 protein and comparison between cell types offers a strategy to assess relative global DNA methylation from single cells.

Associated Cancer Types/Areas: epigenetics

Keywords: microfluidics, nanofluidics, epigenetic analysis

16. Outreach and Dissemination and Microfabrication Facility Activities in the Cornell University Center on the Microenvironment and Metastasis (CMM)

Cornell University PS-OC
Outreach and Dissemination

Teresa Porri, Graham Kerslick

Cornell University

The CMM's Outreach and Dissemination Unit adds value to the physical sciences and oncology communities through two primary mechanisms. First, we train both PSOC-affiliated and outside researchers in topics that are of value in creating an integrated research community through our minicourse series, which provides scientists with one-on-one, in-lab training on topics of interest.

Previous minicourse topics include cell-culture techniques, surface modification, and microfluidics, and upcoming minicourses on imaging techniques are planned. Secondly, we fund early-phase research opportunities between investigators within the PSOC and outside investigators through our ongoing pilot project program.

The CMM Microfabrication Facilities, funded by Cornell and through user fees, also provides an integrated range of equipment and capabilities by which PSOC members can further their research goals. This multidisciplinary core facility has a wide variety of micro and nanofabrication, chemical modification, and analytical tools, along with the expertise to assist PSOC and outside investigators.

Keywords: outreach, core facility, microfabrication

17. The MUSIC Assay and Single-Cell Invasion Studies

Cornell University PS-OC
Project 2: Biomedical Engineering Department

Michael Mak, Cynthia A. Reinhart-King, David Erickson

Cornell University

The mechanical microenvironment has been demonstrated to be critical in inducing cell invasion. Elements such as extracellular matrix (ECM) stiffness, fiber alignment, and density can induce behavioral effects in cells such as increased force generation and migratory directional persistence. While popular cell-in-gel models have been useful in producing qualitative and semi-quantitative analyses of cell invasion characteristics, their inherent structural heterogeneities prevent the assessment of more subtle cell invasion events, such as cell transition dynamics and mechanical strategies during invasion across a physical barrier. In our work, by designing and fabricating well-defined features that modulate the cell local environment on the scale of the cell and its nucleus, we elicited functional responses that are otherwise difficult to observe in a 3D heterogeneous environment. These responses, including contractions, rotations, and back extensions of the cell body, facilitate cell deformations across subnucleus-scaled barriers.

Because metastasis is the leading cause of cancer related deaths, assays that can uncover molecules that target not only death or anti-proliferation signaling pathways but also the functional invasive capacities of cancer cells could yield new therapeutic elements in drug development. We have performed initial tests using a clinically successful anti-breast cancer drug, Taxol, and demonstrated that in addition to anti-growth effects, Taxol also has anti-invasion features, which manifest as a reduction in the treated cell's ability to invade across subnucleus-scaled barriers as well as a depolarization in the cell's migration trajectory.

Our studies were performed using a microfluidic invasion assay that implements the MUlti-barrier Serial Invasion Channels (MUSIC) design. In this device, individual cancer cells are induced to invade across multiple subnucleus-scaled barriers, enabling the quantitative analysis of cell invasion dynamics and multi-sampling per cell. We are actively involved in functional single-cell assay development to help assess cancer invasion, heterogeneity, and pharmacologic effects in high throughput.

Associated Cancer Types/Areas: breast cancer, metastasis and the microenvironment, cell mechanics

Keywords: single-cell mechanics, cell invasion, metastasis

18. TRAIL Mediated Apoptosis in the Third Dimension

Cornell University PS-OC
Department of Biomedical Engineering

Siddarth Chandrasekaran, Jocelyn R. Marshall, Michael R. King

Cornell University

TNF-alpha Related Apoptosis Inducing Ligand (TRAIL) is increasingly being used as a therapeutic drug to kill cancer cells [1]. We have shown that cancer cells cultured as 3D tumor spheroids exhibit increased adhesion to E-selectin and have more migratory and invasive properties [2]. Cancer cells in the circulation are constantly subjected to apoptosis inducing factors secreted by stromal cells. Despite the presence of these factors cells are still able to extravasate and metastasize. We hypothesized that cancer cells that enter the circulation from a primary site would be more resistant to TRAIL mediated apoptosis. To test this hypothesis, we cultured breast cancer cells BT20 and MCF7) as 3D spheroids on polydimethylsiloxane (PDMS) coated plates and dissociated these spheroids and studied the expression of death receptors (DR4 and DR5) that mediate TRAIL induced apoptosis. As a control we also studied the expression of death receptors on cells cultured as 2D monolayers. Our results reveal that tumor spheroids show decreased expression of DR4 and DR5 when compared to cells cultured in monolayer form. We also treated dissociated tumor spheroids with 2 µg/mL of TRAIL and determined the percentage of apoptotic cells using Annexin V-FITC apoptosis kit. It was found that 1.40% of BT20 cells and 0.85% of MCF7 cells cultured as tumor spheroids were in late apoptosis stage as opposed to 11.72% of BT20 cells and 13.29% of MCF7 cells cultured as a monolayer (Fig.1). These results suggest that three-dimensional growth of cancer cells may bestow resistance to TRAIL induced apoptosis, which may change the current view on therapeutically targeting cancer cells using TRAIL. We are currently investigating the mechanisms behind this increased resistance to TRAIL in 3D tumor spheroids by staining for death receptors and lipid rafts to determine their co-localization and determine if there is an alteration of TRAIL receptor internalization in tumor spheroids.

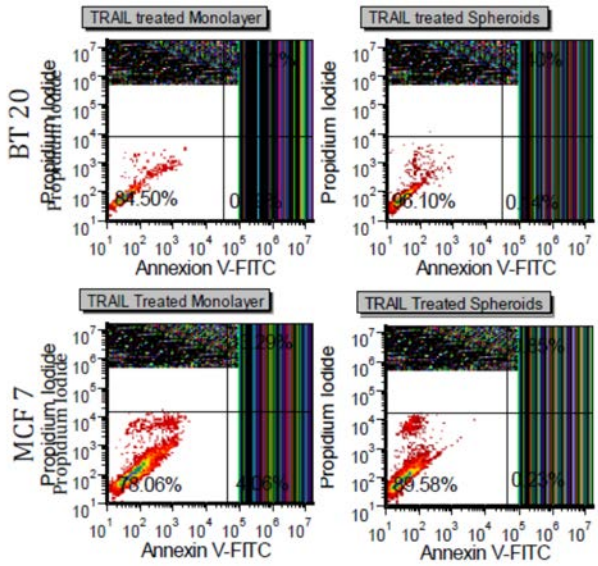


Figure 1. Flow Cytometry histograms showing percentage of cells in different stages of apoptosis (lower left quadrant = viable, lower right quadrant = early apoptosis, upper left quadrant = necrotic, upper right quadrant = late apoptosis).

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Associated Cancer Types/Areas: breast cancer, therapy

Keywords: tumor spheroids, TRAIL, breast cancer

19. Understanding the Effect of Adipose Stromal Cells on Vascular Network Assembly

Cornell University PS-OC

Project 1: Physicochemical Transducer Networks and Their Role in Regulating the Angiogenic Switch Across Multiple Scales

Young Hye Song, Seung Hee Shon, Bo Ri Seo, Abraham D. Stroock, Claudia Fischbach

Cornell University

Adipose-derived stem cells (ASCs) are critical stromal components of various tumors including breast cancer. However, their specific contributions to tumor angiogenesis remain unclear. Here, we have investigated the role of tumor-associated ASCs (tASCs) on biochemical and mechanical modulations of the breast tumor microenvironment and the resulting effects on tumor angiogenesis. Generating tASCs by addition of conditioned media from MDA-MB231 human breast cancer cells led to increased tASC secretion of pro-angiogenic factors, as well as enhanced matrix stiffness due to elevated extracellular matrix (ECM) deposition and contraction relative to control ASCs. To study the individual and combined effects of these variations on invasion angiogenesis, we have utilized conventional tube formation assays on Matrigel and microengineered 3-D invasion assays, respectively. In accordance with their increased proangiogenic capability, conditioned media from tASC promoted capillary tube formation on Matrigel relative to control ASCs. However, when ASCs were embedded in the bulk of microfabricated collagen scaffolds and coated with a monolayer of human umbilical vein endothelial cells (HUVECs), ASCs migrated towards the HUVEC monolayer and prevented endothelial invasion into the collagen scaffold. This barrier function was enhanced with tASCs due to their increased proliferation relative to control ASCs. Interestingly, when ASCs and HUVECs were both incorporated into the collagen bulk of these scaffolds, ASCs promoted the formation of capillary-like structures with increased lumens where pretreatment with TCM further modulated this effect. These results were in agreement with in vivo studies where blood vessels in MDA-MB231 & ASC co-implanted tumors exhibited larger lumens and perimeters as compared to blood vessels in MDA-MB231 control tumors. Collectively, these data suggest ASCs as physicochemical regulators of tumor angiogenesis that may serve as future therapeutic targets, but whose specific contributions to tumor angiogenesis may only be evaluated with appropriately designed culture platforms.

This work was supported by the NCI through the Cornell Center on the Microenvironment and Metastasis (U54 CA143876-01) as well as through RC1 CA146065-01.

Associated Cancer Types/Areas: breast cancer, tumor angiogenesis, tumor microenvironment, tumor stroma

Keywords: adipose-derived stem cells, tumor angiogenesis, tumor microenvironment

20. Using a Microfluidic Device to Capture CTCs and Interrogate Mechanisms Taxane Resistance in the Prospective TAXYNERGY Clinical Trial in Prostate Cancer

Cornell University PS-OC
Research on Circulating Tumor Cells

Paraskevi (Evi) Giannakakou[1], Matthew S. Sung[1], Ada Gjyrezi[1], Guang Yu Lee[1], Alexandre Matov[1], Giuseppe Galletti[1], Luigi Portella[1], Yusef Syed[1], Timothy Lannin[1], Atanas Hristov[2], Duane Hassane[1], Scott Tagawav[1], Brian Kirby[1], David Nanus[1]

[1]Cornell University, [2]University for Information Science and Technology, St Paul the Apostle, Orhid, Macedonia

Prostate cancer progression into castration-resistant prostate cancer (CRPC) is driven by continued androgen receptor (AR) signaling. The taxanes represent the only class of chemotherapy that improves overall survival in CRPC patients. However, clinical drug resistance remains a major clinical challenge. The molecular mechanisms underlying clinical taxane resistance have not been elucidated due to the lack of available metastatic tumor tissue. Circulating tumor cells (CTCs) have emerged as a viable alternate source of tumor tissue which can be used for molecular and functional analyses. Here, we use a geometrically enhanced differential immunocapture (GEDI) microfluidic device that couples an anti-prostate specific membrane antigen (PSMA) antibody with optimized 3D geometry to capture and isolate live CTCs from peripheral blood of CRPC patients. The GEDI-microfluidic device was shown to have a 2-400 fold higher sensitivity for CTC capture than the FDA-approved CellSearch® system. We have developed a suite of functional assays that can be performed on live GEDI-captured CTCs that enable their molecular characterization and allow us to test specific mechanistic hypotheses based on our extensive preclinical data. Included, and herein described, are the determination of AR subcellular localization, extent of effective drug-target engagement assessed by microtubule bundling, identification of RNA species relevant to the mechanism of taxane resistance and computer vision algorithms that will allow for enriched and automated analysis of high-volume image sets of GEDI-captured CTCs. In addition, we will be testing the hypothesis that distinct AR splice variants may affect patient sensitivity to taxane based chemotherapy. This suite of assays are being rigorously applied in a phase II clinical trial in which chemotherapy-naïve CRPC patients will be initially treated with either docetaxel or cabazitaxel and clinically evaluated for an early switch to the other taxane following disease progression. This prospective, randomized, multi-site clinical trial will enroll 100 CRPC patients within one year. Patients will be followed until relapse and each patient will have 15 independent GEDI assays performed across five time points from baseline to chemotherapy crossover to relapse. The depth of coverage this suite of assays provides will offer unique insights for potential mechanisms of clinical taxane resistance and predictive biomarkers for taxane sensitivity in CRPC patient CTCs.

Associated Cancer Types/Areas: prostate cancer, metastasis

Keywords: circulating tumor cells**,** clinical trial, drug resistance

21. Young Investigator Trans-Network Project: The Role of the 3D Mechanical Environment in Regulating Angiogenesis

Cornell University PS-OC
Project 2: Physical and Chemical Cues in Tumor Cell Migration

Brooke N. Mason[1], Mark C. Lloyd[2], Veronica Estrella[2], Tingan Chen[2], Rebecca M. Williams[1], Lawrence J. Bonassar[1], Robert A. Gatenby[2], Robert J. Gillies[2], Cynthia A. Reinhart-King[1]

[1]Cornell University, [2]H. Lee Moffitt Cancer Center

Tumor tissues generally have altered mechanical properties as compared to native, healthy tissue, and solid tumors are associated with an increase in angiogenesis. Newly formed tumor vasculature tends to be malformed, leakier and more tortuous than the capillary network in new tissues. Our in vitro data suggests that matrix stiffness contributes to the differences in tumor vasculature compared to the vasculature in healthy tissue.

In this PS-OC trans-network project, we explore the effects of 3D matrix stiffness on the organization and quantity of angiogenic blood vessels both in vitro and in vivo. To determine if tumor stiffness plays a role in dictating vessel structure, we used non-enzymatic glycation to cross-link collagen without altering collagen density. Using these matrices, we show that changes in the stiffness of the 3D matrix alter the spreading, angiogenic sprouting, and spheroid outgrowth of bovine aortic endothelial cells. Additionally, we show that endothelial cells embedded within glycated collagen matrices dynamically alter their connectivity and formation of intercellular lumens. We have also initiated experiments utilizing collagen gels stiffened via non-enzymatic glycation implanted within a murine dorsal window chamber model. Our ongoing experiments will determine the effects of matrix stiffness on blood vessel formation in real-time in vivo.

Associated Cancer Types/Areas: angiogenesis, microenvironment, matrix mechanics

22. Aberration in DNA Methylation in B-Cell Lymphomas Has a Complex Origin and Increases With Disease Severity

Dana-Farber Cancer Institute PS-OC
Project 2: The Cell of Origin of Human Cancers

Subhajyoti De[1], Markus Riester[2], Franziska Michor[2], Rita Shaknovich[3], Huimin Geng[3], Yanwen Jiang[3], Ari Melnick[3], Leandro Cerchietti[3], Olivier Elemento[3], Huimin Geng[3], Matthias Kormaksson[3], Bruce Woolcock[4], Nathalie Johnson[4], Randy D. Gascoyne[4], Jose M. Polo[5]

[1]University of Colorado, Denver, [2]Dana-Farber Cancer Institute, [3]Cornell University, [4]British Columbia Cancer Research Centre, [5]Monash University

Despite mounting evidence that epigenetic abnormalities play a key role in cancer biology, their contributions to the malignant phenotype remain poorly understood. Here we studied genome-wide DNA methylation in normal B-cell populations and subtypes of B-cell non-Hodgkin lymphoma: follicular lymphoma and diffuse large B-cell lymphomas. These lymphomas display striking and progressive intra-tumor heterogeneity and also inter-patient heterogeneity in their cytosine methylation patterns. Epigenetic heterogeneity is initiated in normal germinal center B-cells, increases markedly with disease aggressiveness, and is associated with unfavorable clinical outcome. Moreover, patterns of abnormal methylation vary depending upon chromosomal regions, gene density and the status of neighboring genes. DNA methylation abnormalities arise via two distinct processes: (i) lymphomagenic transcriptional regulators perturb promoter DNA methylation in a target gene-specific manner, and (ii) aberrant epigenetic states tend to spread to neighboring promoters in the absence of CTCF insulator binding sites.

Associated Cancer Types/Areas: diffuse large B-cell lymphoma, follicular lymphoma

Keywords: lymphoma, methylation, heterogeneity

23. Dissecting Cytokine Signaling in Myeloproliferative Neoplasm at the Level of Single Cells

Dana-Farber Cancer Institute PS-OC

Project 1, Project 2: Single-Cell Profiling Core

Minsuk Kwak[1], Jonathan J. Chen[1], Yao Lu[1], Maria Kleppe[2], Franziska Michor[3], Ross L. Levine[2], Rong Fan[1]

[1]Yale University, [2]Memorial Sloan-Kettering Cancer Center, [3]Harvard University

Myeloproliferative neoplasms (MPNs) are a phenotypically heterogeneous group of chronic myeloid malignancies characterized by abnormal proliferation of one or more myeloid lineages and the transformation to acute myeloid leukemia (AML). The majority of MPNs are caused by the gain-of-function mutations of various signaling proteins including the thrombopoietin receptor (MPLW515L) that lead to constitutive activation of downstream tyrosin kinase signaling cascades such as JAK-STAT signaling pathway. Previously studies have discovered that multiple cytokines were significantly elevated in the serum from MPN diseased mice with MPLW515L-mutation. Using our recently developed bioanalytical assay microchip for highly multiplexed proteomic detection at single cell levels, we performed a highly multiplexed single-cell secretomic analysis of primary bone marrow (BM) cells from murine MPN model with MPL-mutations. Our bioanalytical microchip allows for the multiplexed measurement of inflammatory cytokines secreted from more than a thousand single MPN-mice BM cells. A multiplexed population protein measurement (microELISA) was performed with the supernatant collected from same cells in order to compare with single-cell cytokine secretomic profiles. Based on cytokine secretomic analysis at both single-cell and population levels, we have discovered significantly altered cytokine production from MPL-mutant diseased mice. We have also observed the significant heterogeneity among single-cell cytokine secretomic profiles. Based on distinct single-cell cytokine secretion profiles, multiple cellular subsets of BM population that secreted unique combinations of inflammatory cytokines were identified. To specifically delineate the cellular subpopulations of BM cells that contribute to inflammation state associated with pathogenesis of MPN by producing and releasing cytokines, we sorted different mutant or wild-type cells from BM cell population using fluorescence-activated cell sorting (FACS) based on GFP and cell surface markers and measured the single-cell cytokine profiles of different BM cell subpopulations. We further aim to investigate the roles of specific signaling pathways that govern mutant-driven cytokine productions in malignant or non-malignant cells.

Associated Cancer Types/Areas: acute myeloid leukemia, myeloproliferative neoplasm, cancer heterogeneity, tumor initiating cells

Keywords: myeloproliferative neoplasm, single-cell cytokine secretomic profiles, MPLW515L-mutant MPN mice

24. Epigenetic Fluctuation of Tumor Suppressor Genes as a Possible Mechanism of Tumor Initiation

Dana-Farber Cancer Institute PS-OC
Project 2: Single-Cell Profiling Core

Iva Xhangolli[1], Yu Wu[1], Yosi E. Maruvka[2], Eric C. Holland[3], Franziska Michor[2], Rong Fan[1]

[1]Yale University, [2]Dana-Farber Cancer Institute, [3]Memorial Sloan-Kettering Cancer Center

The classical two-hit hypothesis, although initially used as a model to explain hereditary cancer susceptibility, has recently been disputed due to the statistic low probability of shutting down both copies of the same gene in the same cell. The two hits account for the number of events necessary to inactivate both alleles of tumor suppressor genes. However, one hit, a single allele mutation or deletion, may play a role in tumorigenesis without the inactivation of the second allele. In this study, we are diverging from the two-hit hypothesis considering only the mutation of a single allele. We propose that random variation in the protein level in the cells with only one functioning allele will follow the same pattern as if both alleles were missing. Using high-content, multi-parameter fluorescence imaging cytometry, we will quantify the levels of three tumor suppressors (p16, p19, and PTEN) in various cancer cell lines and correlate them to the cell's fitness such as proliferation capability. Three different types of glial cell lines were taken into consideration: a wild type (homozygous positive) cell line possessing both allele copies of gene *CDKN2A* (p16) and INK4a/ARF locus *CDKN2A* (p19), a heterozygous cell line possessing only one functioning allele of each gene, and a homozygous negative cell line with both allele copies knocked down. This study allows us to evaluate the correlation between protein variation and the rate of cancer initiation at the single-cell resolution and identify the possible cells of origin that account for tumor initiation via epigenetic fluctuation of tumor suppressors.

Associated Cancer Types/Areas: brain/breast cancer

Keywords: tumor suppressor proteins, fluorescence imaging, cell fitness

25. Histone Modifications Are Associated With Transcript Diversity in Normal and Cancer Cells
Dana-Farber Cancer Institute PS-OC

Ondrej Podlaha[1], Subhajyoti De[2] Mithat Gonen[3], Franziska Michor[1]

[1]Dana-Farber Cancer Institute, [2]University of Colorado, [3]Memorial Sloan-Kettering Cancer Center

Mechanisms that generate transcript diversity are of fundamental importance in eukaryotes. Although 95% of human genes produce more than one mRNA isoform, the regulation of this phenomenon is still incompletely understood. Much progress has been made in deciphering the role of sequence-specific features as well as DNA and RNA binding proteins in alternative splicing. Recently, however, several case studies have revealed a direct involvement of epigenetic factors in alternative splicing. We sought to investigate the association of histone modifications with exon inclusion rates on a genome-wide scale and across both normal and cancer cell lines in humans. We found that specific histone modifications – for instance H3K4me2, H3K9ac, H3K9me1, H3K27ac, H3K79me2, and H4K20me1 – are significantly correlated with exon inclusion rates ($p < 1.0 \times 10^{-10}$) within six normal and three cancer cell lines. Furthermore, we identified a set of 115 candidate genes, including 4 cancer-associated genes, for which exon presence or absence associates with specific histone marks. Furthermore, histone modification enrichment alone can predict exon inclusion rates in two independent cell lines (accuracy rate 70%). Our results suggest that the epigenetic regulation of transcript diversity may be a common genome-wide phenomenon representing an avenue of deregulation in tumor development.

26. Risk Prediction for Late-Stage Ovarian Cancer by Meta-analysis of 1,622 Patient Samples: Biologic and Clinical Correlations

Dana-Farber Cancer Institute PS-OC

Markus Riester[1,2], Wei Wei[3], Levi Waldron[1,2], Aedin C. Culhane[1,2], Lorenzo Trippa[1,2], Franziska Michor[1,2], Curtis Huttenhower[1,2], Giovanni Parmigiani[1,2], Michael Birrer[3]

[1]Dana-Farber Cancer Institute, [2]Harvard University, [3]Massachusetts General Hospital

Background: Ovarian cancer causes over 15,000 deaths per year in the United States, the majority of which present as advanced stage high grade, serous tumors. The survival of these patients is quite heterogeneous, and an accurate prognosis would help with the clinical management of these patients. Published microarray-based prognostic gene signatures are, however, not yet sufficiently robust to employ clinically.

Methods: We developed and validated a gene expression signature of survival for advanced stage serous ovarian cancer, integrating 13 publicly available datasets totaling 1,622 subjects. This signature was further tested on early stage serous disease. A second signature was developed for predicting debulking status. We trained prediction models using a meta-analysis variation on the Compound Covariate method, tested models via a "leave-one-dataset-out" procedure, and performed validation in additional datasets not meeting the selection criteria for training data. Selected genes from the debulking signature were validated by immunohistochemistry and qRT-PCR in two independent cohorts of 177 and 78 patients, respectively.

Results: The survival signature stratified patients into high- and low-risk groups (HR=2.17; 95% CI, 1.83 to 2.57) significantly better than the TCGA signature (P = 0.016). *POSTN*, *CXCL14*, *CCL13*, *FAP*, *NUAK1*, *PTCH1*, and *TGFBR2* were validated by qRT-PCR (multivariate AUC 0.8; 95% CI 0.71-0.90) and POSTN, pSmad2/3 and CXCL14 by immunohistochemistry as independent predictors of debulking status (multivariate AUC 0.89; 95% CI 0.84-0.93).

Conclusions: Our predictive signatures provide the most accurate and well-validated prognostic models for early and advanced stage high-grade serous ovarian cancer and prediction of surgical debulking outcome.

27. Single-Cell Proteomic Analysis of Lung Cancer Cells and the Implication in Drug Resistance

Dana-Farber Cancer Institute PS-OC
Project 3: Single-Cell Profiling Core

Jonathan J. Chen[1], Rui Zhao[2], William Pao[3], Franziska Michor[2], Rong Fan[1]

[1]Yale University, [2]Dana-Farber Cancer Institute, [3]Vanderbilt University

Secreted proteins including cytokines, chemokines, and growth factors represent important functional regulators mediating a range of cellular behavior and cell-cell paracrine/autocrine signaling in the immunological system and tumor microenvironment. Detection of these proteins is of great value for the understanding of the mechanisms involved in the tumor microenvironment that contribute to long-term response cancer cells to treatment. Non-small cell lung cancers (NSCLC) which carry mutations in the exons that encode the kinase domain of epidermal growth factor receptor (EGFR) are sensitive to tyrosine kinase inhibitors (TKIs). However, sustained treatment of EGFR mutant tumors eventually leads to acquired resistance. We use PC-9 (wild type), PC-9 ER (polyclonal drug resistant), and PC-9 BR (monoclonal drug resistant) cell lines to study the gain/loss of drug resistance in NSCLC. We describe single cell proteomic analysis on PC-9, PC-9 ER, and PC-9 BR cell lines using flow cytometry as well as a high throughput single cell proteomics platform for the simultaneous measurements of secreted proteins. We observe distinct heterogeneity among the single cell cytokine levels of NSCLC cell lines. Recent evidence indicates that a genetically identical cell population can give rise to diverse phenotypic differences; therefore, it is biologically informative and relevant to measure the secretomic signature of cancer cells at the single cell level. Mediated by an array of signaling molecules, this complex intercellular signaling network leads to tumor environments that are unique despite their apparent homogeneity. Understanding the functional heterogeneity of tumor cells and inter-cellular signaling network within the tumor environments will significantly benefit the strategies and clinical implications for drug resistant cancers.

Associated Cancer Types/Areas: lung cancer, drug resistance, cellular heterogeneity

Keywords: single cell analysis, drug resistance, cellular heterogeneity

28. Time Scales in the Probabilistic Spread of Defective Mutants

Dana-Farber Cancer Institute PS-OC

Evolutionary Dynamics of Brain, Lung, and Hematopoietic Tumors

Philipp M. Altrock[1], Tobias Galla[2], Arne Traulsen[3]

[1]Dana-Farber Cancer Institute, [2]The University of Manchester, [3]Max Planck Institute for Evolutionary Biology

On a phenotypic level of description, malignant cancer mutants compete or coexist with normal cells based on complex interaction patterns. A powerful means to describe such complex frequency dependent interactions is evolutionary game theory. Here, we study the stochastic dynamics of evolutionary games, and focus on the so-called `stochastic slowdown' effect, previously observed in [Altrock et al, Phys. Rev E 82, 011925 (2010)] for simple but general evolutionary dynamics; A beneficial mutation may take longer to take over than a neutral one. The fixation time conditioned on the mutant taking over (i.e., conditioned on the diagnosis of cancer) can show a maximum at intermediate selection strength. We show that this phenomenon is present in the Prisoner's Dilemma, and also discuss counterintuitive slowdown and speedup in coexistence games. In order to establish the microscopic origins of these phenomena, we calculate the average sojourn times. This allows us to identify the transient states which contribute most to the slowdown effect, and enables us to provide an understanding of slowdown in the takeover of a small group of cooperators (normal cells) by defectors (cancer cells) in the Prisoner's Dilemma: Defection spreads fast initially, but the final steps to takeover can be delayed substantially. The analysis of coexistence games reveals even more intricate non-monotonic behavior. In small populations, the conditional average fixation time can show multiple extrema as a function of the selection strength, e.g., slowdown, speedup, and slowdown again. We classify generic 2x2 games with respect to the possibility to observe non-monotonic behavior of the conditional average fixation time as a function of selection strength. Such non-monotonic behavior can have a crucial impact on treatment strategies after diagnosis.

Associated Cancer Types/Areas: micro-evolutionary process of cancer, mathematical methods in cancer biology

Keywords: evolutionary dynamics, prisoner’s dilemma, fixation times, moran process, stochastic slowdown, frequency dependent selection

29. Tumor-Astrocyte Interactions in Breast Cancer Brain Metastasis
Dana-Farber Cancer Institute PS-OC
PSOC- T32 Training Grant: The Cell-of-Origin of Human Cancers

Jillian L. Werbeck, Eric C. Holland

Memorial Sloan-Kettering Cancer Center

Breast cancer is the second leading cause of cancer related deaths in women in the United States. Metastasis is the most lethal complication of breast cancer and yet the mechanisms involved in site specific dissemination and metastasis are still largely unknown. The tumor stroma is a known contributor to cancer progression and has been implicated in many common sites of metastasis such as the bone or lung. However, the role of the tumor stroma in the brain is still poorly understood.

Breast cancer patients who develop brain metastases have a poor prognosis and local and systemic therapies are often palliative at best. One challenge to therapeutic intervention is the presence of the blood-brain barrier, which hinders adequate penetration of therapeutic agents into the brain. Another challenge is the active role of stromal cells, such as astrocytes, which mediate invasion and have been shown to protect tumor cells from apoptosis and chemotherapy.

The goal of this investigation is to characterize the astrocyte response to breast cancer tumorigenesis. We used a glial fibrillary acidic protein-GFP (GFAP-GFP) mouse to isolate astrocytes from the 4T1 breast cancer model, and to look at differences in gene expression between normal and tumor-associated astrocytes. We also characterized the gene expression in astrocytes in response to radiation or dexamethasone treatment.

We demonstrated that tumor associated astrocytes are increased in breast cancer brain metastases. We also identified a novel gene expression signature of astrocytes in the brain tumor microenvironment. Our future goal is to identify novel targets in astrocytes that might have therapeutic potential for patients.

Associated Cancer Types/Areas: breast cancer, metastasis, tumor microenvironment

Keywords: astrocytes, breast cancer, metastasis

30. A Phenotypic Signature of Pancreatic Cancer Metastasis

Johns Hopkins University PS-OC

Jude M. Phillip, Pei-Hsun Wu, Shyam B. Khatau, Wei-Chiang Chen, Jeffrey Stirman, Sonal Gupta, Alexander S. Baras, Jeffrey T. Leek, Anirban Maitra, Denis Wirtz

Johns Hopkins University

According to the American Cancer Society, two out of every five persons in the US will develop cancer during his/her lifetime. Pancreatic cancer is one of the most lethal cancers: at the time of diagnosis, more than 50% of patients present with metastatic disease typically to the liver; having a 5-year survival rate is less than 3%. Since the completion of the Human Genome Project, researchers have focused on trying to understand the genetic basis of metastasis in the effort to better predict disease progression and uncover new therapeutic targets. Studies of genomic sequences of pancreatic cancer patients suggested relatively common signal pathways associated with tumorigenesis, however, possibly due to the inherent heterogeneity of cancer, no molecular signature specific to metastases were observed. Here, we investigated the possibility that pancreatic cancer cells that had successfully metastasized to the liver would display a distinct set of physical properties from those in the primary tumor by examining the morphology of individual cells derived from both primary tumors and liver metastases. We developed a comprehensive morphological analysis to classify irregular cellular and nuclear shapes using a limited number of common shape modes through Eigen shape decomposition and clustering approaches. With the aid of an automated high-throughput microscopy set up, cells were analyzed from 13 previously sequenced patient-derived cell lines. Our results show that the lack of cell and nuclear morphological heterogeneity is a robust and predictive feature of metastatic pancreatic cancer cells and suggest that metastasis is associated with a selection process for biophysical features.

Associated Cancer Types/Areas: pancreatic cancer; primary tumors and liver metastases

Keywords: pancreatic cancer, high throughput cell phenotyping, morphology

31. A Platform to Study Metastatic Cancer

Johns Hopkins University PS-OC
Center for Cancer Physics, Physics of Cancer Microfabrication Core

Andrew D. Wong, Peter C. Searson

Johns Hopkins University

Metastasis is responsible for over 90% of cancer related deaths. While significant advances in visualizing metastasis have been made in vivo, the details of the biological and physical processes that govern invasion and intravasation remain poorly understood. The difficulty in studying metastasis stems from the complexity of the interface where invasion and intravasation take place, between the tumor's local tissue microenvironment and the vascular system. To elucidate the mechanistic events taking place during invasion and intravasation, we have developed a platform that positions tumor cells adjacent to an artificial vessel embedded in an extracellular matrix (ECM). Using live-cell, fluorescence microscopy, we study the complex interplay between highly metastatic cancer cells and a functional artificial microvessel lined with endothelial cells during tumor migration and intravasation. We hypothesize that an engineered platform that recapitulates the interactions between a tumor and a physiologically relevant artificial vessel within an extracellular matrix will allow the systematic study of the physical and biological properties that regulate invasion and intravasation. Since there remain many gaps in our understanding of the biology and physics of invasion and intravasation, further insight into these poorly understood processes may provide new strategies to prevent the spread of cancer and reduce the high mortality rates associated with metastasis.

Associated Cancer Types/Areas: breast cancer, connective tissue cancer, tumor metastasis, tumor microenvironment

Keywords: tumor intravasation, invasion, tumor vasculature

32. Cell Migration Analysis Through Cell-Nucleus Correlation
Johns Hopkins University PS-OC

Shen-Hsiu Hung, Stephen Hugo Arce, Chien-Wen Kuo, Qian Peng, Tina Ren, Kai Cheng, Yiider Tseng

University of Florida

Cell migration is a dynamic process that plays vital role in critical physiology conditions, including tissue developing, wound healing, immune reaction, and metastasis. During such process, the movements of the nucleus, the largest cellular organelle, need to be coordinated with those of the cell. However, the correlation between nuclear and cellular movements is not promptly incorporated into current approach to analyze cell migration. In this study, we utilize this correlation to accurately estimate the intrinsic cell migration capacity over different mesenchymal cell types.

Associated Cancer Types/Areas: ovarian cancer, osteosarcoma

Keywords: cell migration, cellular-nuclear displacement correlation, ovarian cancer

33. Characterization and Modeling of Cancer Cell Motility in 3-D Extra-Cellular Matrix

Johns Hopkins University PS-OC

The Physics of Cadherin-Mediated Intercellular Adhesion and Migration in Cancer

Pei-Hsun Wu, Anjil Giri, Sean X. Sun, Denis Wirtz

Johns Hopkins University

Cancer cell migration through the extra-cellular matrix (ECM) is one of the most important processes during metastasis. Cell migration is a multi-scale process, which integrates molecular kinetics and signaling; cell mechanics and microenvironment. A quantitative understanding of cell motion in three-dimensions will facilitate the development of a system-level understanding of cellular processes in cancer metastasis and further promote identification of new therapeutic targets. Though various mathematical models were proposed to measure cell migration on 2-D surfaces, adequate tools to characterize and model migration in 3-D are lacking. In this work, we observed the migration patterns of individual HT1080 fibrosarcoma cells on 2-D substrate and in 3-D collagen matrices for more than 8 hours. We found that non-Gaussian behavior of cell velocity distribution at various time scales in population level is a universal characteristic for both cell 2-D and 3-D migration and it is as result of the highly varied cell-to-cell motility behaviors. Further, cell velocity in 3-D matrices is anisotropic and velocity profiles display different speed and self-correlation processes at different directions. Together, by including cell-level variation, anisotropic velocity and observation noise in persistent random walk model, we were able to predict the population level of cell motility system in 3-D matrices which corresponding well to experimental observation. Our model further allows the estimation of speed for HT1080 cells in 3-D matrices at more pathophysiological relevant time scale (months) and we found there are small populations of cells that display ~10x higher speed than the general population and could imply that metastatic cells come from small populations of cells within a tumor.

Associated Cancer Types/Areas: fibrosarcoma, metastasis

Keywords: cell motility, cancer, extra-cellular matrix (ECM)

34. Collagen Prolyl and Lysyl Hydroxylases Promote Stiffness and Breast Cancer Metastasis
Johns Hopkins University PS-OC

Daniele M. Gilkes, Pallavi Chaturvidi, Carmen Wong, Denis Wirtz, Gregg Semenza

Johns Hopkins University

Metastasis is the leading cause of death among patients who have breast cancer. Understanding the role of the extracellular matrix in the metastatic process may lead to the development of improved therapies to treat cancer patients. Intratumoral hypoxia is found in the majority of breast cancers and is associated with an increased risk of metastasis and patient mortality. Here we demonstrate that hypoxia-inducible factor 1 activates the transcription of genes encoding collagen prolyl and lysyl hydroxylases that are critical for collagen deposition by breast cancer cells and breast cancer associated fibroblasts. We show that expression of collagen prolyl hydroxylases promotes cancer cell alignment along collagen fibers and increased collagen stiffness. Cancer cells travel farther and faster on hypoxic as compared to control ECM resulting in enhanced cancer cell invasion and metastasis to lymph nodes and lungs. We establish the prognostic significance of collagen prolyl hydroxylase mRNA expression in human breast cancer biopsies and evaluate the novel use of ethyl 3,4-dihydroxybenzoate, a prolyl hydroxylase inhibitor, which decreases tumor fibrosis and metastasis in a mouse model of breast cancer.

Associated Cancer Types/Areas: breast cancer, metastasis, microenvironment

Keywords: HIF-1, P4H, collagen

35. Fibrin Microfibers as a Platform for Angiogenesis

Johns Hopkins University PS-OC

Project 1: Interaction Between HIF-1 and ECM

Sebastian F. Barreto Ortiz, Shuming Zhang, Matthew Davenport, Jamie Fradkin, Hai-Quan Mao, Sharon Gerecht

Johns Hopkins University

Angiogenesis has long been considered to be one of the crucial requirements for tumor development. One of the main characteristics of tumor tissues is their abnormal vasculature that is often redundant, immature, and leaky. However, it is still not fully understood how cancer cells induce the development of these abnormal vascular networks, and how endothelial cells and mural cells interact within these networks. Furthermore, it has been shown that in tumor vasculature pericytes are loosely associated to the endothelial cells, diverging from the normal architecture of blood vessels. In this work, we seek to develop a 3D scaffold to study initial endothelial cell tube formation and further vascular maturation by smooth muscle cell recruitment and investment.

Electrospinning has proven to be a useful technique for developing biocompatible 3D scaffolds for a myriad of biomedical applications. Here we use a unique approach for using this technology to study angiogenesis with the advantage that different cell types, as well as different growth factors, can be added separately at different time points.

With this novel approach, we created single fibrin microfibers with an aligned nano-topography that can be individually manipulated and used as molds to guide endothelial colony forming cell (ECFC) tube formation. Fibers ranging from 100 to 500 μm in diameter were prepared, characterized, and seeded with ECFCs. Cells were shown to align with the fiber's nano-topography, and, remarkably, to deposit ECM proteins circumferentially (perpendicular to the cell's alignment). This organization was shown to be dependent both on the cell's organization and the cylindrical shape induced by the fibers. Furthermore, these ECM structures were proven to be stable after fibrin degradation with plasmin, which enables the formation of hollow vessels made out of ECFCs and their own ECM.

Keywords: angiogenesis, microvasculature, ECM

36. Image Analysis Based Methods for Quantifying Intercellular Interactions
Johns Hopkins University PS-OC

Andrew Loza[1], Bo Li[1], Sean Sun[1], Denis Wirtz[1], Greg Longmore[2]

[1]Johns Hopkins University, [2]Washington University in St. Louis

A common aberrant phenotype in cancer cells is alteration of adhesion. This mechanical cellular difference can have consequences leading to multiple hallmarks of cancer, including evasion of growth suppression, invasion, and metastasis. Alpha-catenin is a key component of adherens junctions, and its loss or mutation is frequently seen in carcinomas. Previous work has shown that alpha-catenin knockdown (α-catKD) results in reduced single E-cadherin bond strength, but cell adhesion is far more complex than single protein interactions. Among other processes, cell adhesion involves strengthening of initial bonds, recruitment of junction components, and formation of cytoskeletal interactions. To quantify intercellular interactions and behavior in-vitro, we use the non-transformed human breast epithelial MCF10A cell line and a stable MCF10A α-catKD cell line. We apply Particle Image Velocimetry (PIV) and cell tracking methods to these cells in homogeneous culture and co-culture. Particle Image Velocimetry is an image correlation technique that estimates local velocities in a dynamic system. Through spatial and temporal analyses of this vector field, we observe that α-catKD reduces spatial correlation as well as the size of domains of coordinated motion. This indicates that the degree of mechanical coupling between mutant cells, a reflection of intercellular adhesion, is decreased when alpha-catenin is lost. In our co-culture system, we observe increased dispersion of α-catKD cells into the surrounding epithelium, indicating that α-catKD significantly changes interactions with wild type cells. The decay curves of the spatial and temporal velocity autocorrelation functions can be used to quantify general coherence of motion, but the rate and form of decay speaks to the underlying physical parameters of the system. We are working to formulate a dynamical model for epithelial motion to extract these physical parameters. Future work will build on this system to model tumors in three dimensions ex vivo.

Associated Cancer Types/Areas: breast cancer

Keywords: alpha-catenin, article image velocimetry, spatial correlation

37. Microtubule Dependent Alterations to Cancer Cell Behavior Promoted by Senescent Fibroblasts
Johns Hopkins University PS-OC

Ivie Aifuwa, Nick Longe, Denis Wirtz

Johns Hopkins University

Cellular senescence is a state of irreversible cell cycle arrest that occurs when cells having the potential to divide encounter oncogenic stress that promotes damage to the DNA. Cell cycle arrest prevents the perpetuation of the damage from one generation to the next and therefore creates an anti-tumor mechanism for the cell. Regardless of this benefit, senescent cells pose additional harm to the organism as a whole. Cells induced into senescence have been shown to develop a marked increase in the secretion of pro-inflammatory cytokines, which have been termed senescence-associated secretory phenotype (SASP). This pro-inflammatory stimulus promotes an aggressive cancer behavior, which includes enhanced tumor invasion, tumor size, proliferation and EMT. Here, we observe with nonaggressive human breast cancer cell line, T47D, that SASP promote significant alterations to cell morphology, cytoskeleton structure, cellular compliance and promote a single cell migratory phenotype. We demonstrate that the cells ability to promote this behavior in response to the SASP is dependent on microtubule cytoskeleton. When cells are depleted of microtubules, cells fail to invade, migrate, alter their morphology and lose cell-cell contact. We further demonstrate that microtubules are not only required to promote this phenotype, but to also maintain it. This study shows that the aggressive cancer cell behavior that occurs in response to SASP is dependent on the integrity and dynamics of the microtubule cytoskeleton.

Associated Cancer Types/Areas: breast cancer

Keywords: senescence, migration, microtubule

38. Regulation of the Division Axis in Mammalian Cells Embedded in Three-Dimensional Matrix
Johns Hopkins University PS-OC
Cadherin-Mediated Adhesion in 3D

Lijuan He, Pei-Hsun Wu, Denis Wirtz

Johns Hopkins University

The regulation of cell mitosis is critical for normal development of tissues and organs. Uncontrolled mitosis has been implicated in natural genetic variations, human aging and the progression of cancer. Previous studies investigating the control of the cell division orientation were performed with cells cultured on two-dimensional (2D) substrates. However, many types of cells divide in 3D matrices, in particular fibroblast and fibrosarcoma cells which are located in collagen I-rich connective tissues. Here, we employed single live-cell imaging assay and quantitative image analysis to probe the regulation of cell division in 3D collagen I matrices. Our results show that cells exhibit modes of cell division in 3D matrix distinct from their counterparts on 2D substrates. The percentages of different cell division modes are sensitive to cell type, the density and the microstructure of the collagen matrix, and cell-matrix interactions. Results also reveal that the direction of the last protrusion before cell division faithfully predicts the cell division axis for the cells with steady protrusion during interphase. This correlation held for vastly different cell types, including human fibrosarcoma, breast cancer, embryonic kidney, and mouse embryonic fibroblast cells, and was unaffected by collagen density, the depletion of integrin receptors or the blocking of matrix metalloproteinase functions. Further analysis suggests that it is the cell shape that mediates the correlation between the directions of cell protrusion and cell division. This study provides novel insights into the mechanisms governing the control of cell division in a 3D microenvironment.

Associated Cancer Types/Areas: cell division, microenvironment

Keywords: cell division, 3D microenvironment, cell-matrix interaction

39. Role of Ion Channels and Aquaporins in Cell Migration Through Confined Microenvironments

Johns Hopkins University PS-OC
Engineering in Oncology Center

Kimberly M. Stroka, Hongyuan Jiang, ZiQiu Tong, Sean X. Sun, Konstantinos Konstantopoulos

Johns Hopkins University

Cell homeostasis and diverse processes, including migration, are tightly regulated by cell volume. During migration through tissues, metastatic cancer cells experience varying degrees of physical confinement. We hypothesized that cell volume regulation is especially important for migration in confined microenvironments, where cells must deform in order to squeeze through physically restrictive spaces. To address this hypothesis, we developed a novel "jet propulsion model" of cancer cell migration in narrow microchannels, based on water and ion flow into and out of the cell. We tested the validity of this model by quantifying live cell migration in a microfluidic-based chemotactic device with 3 μm-wide extracellular matrix-coated channels. As predicted by the model, inhibition of Na^+/H^+ ion channels or knockdown of aquaporin 5 (AQP5) reduced confined cell migration velocity. To further test the model, we osmotically shocked cells at the leading and/or trailing edges within the microfluidic device. Remarkably, cells reversed migration direction within 5 minutes of applying a hypotonic shock at the leading edge or hypertonic shock at the trailing edge; blockage of Na^+/H^+ ion channels, inhibition of actin polymerization, or knockdown of AQP5 interfered with this response. To further understand the repolarization mechanism, we quantitatively analyzed the distribution of NHE-1 (a specific Na^+/H^+ ion channel) and AQP5 within the cells. Both NHE-1 and AQP5 polarized to the leading edge of cells migrating in narrow channels and redistributed to the new leading edge approximately 30 minutes after the osmotic shock. Thus, cell migration initiated in the opposite direction even before NHE-1 repolarized, indicating that confined cell migration driven by an osmotic shock does not require NHE-1 to be localized at the leading edge, which is a key aspect of our model. Together, the results support our "jet propulsion model" of confined cell migration that is dependent on the coordinated extension and retraction of fluid-driven protrusions within the cell.

Associated Cancer Types/Areas: cancer types: breast, sarcoma; cancer areas: metastasis, microenvironment, migration

Keywords: cell volume regulation, osmolarity, confined migration

40. Dynamics of Evolutionary Innovation in Cancer

Massachusetts Institute of Technology PS-OC
Project 4

Kirill Korolev[1], Christopher McFarland[2], Leonid Mirny[1]

[1]Massachusetts Institute of Technology, [2]Harvard University

Cancer is a somatic evolution that is driven by a sequence of evolutionary innovations, collectively known as the hallmarks of cancer. Each innovation is encoded by a heritable "driver" alternation that enables cells to survive and reproduce faster. Since all mutations occur randomly, these beneficial driver alternations arise alongside neutral and deleterious passenger alternations that do not cause cancer, but nevertheless affect its fitness. Here we present a theory of evolutionary innovations in the presence of weak deleterious mutations and apply it to cancer. We find that cancer progression critically depends on the size of the tumor and its mutation rate. Below a critical population size, tumors are overwhelmed by deleterious mutations and tend to regress. Progression to cancer is then akin to crossing an energy barrier in chemical kinetics. The probability of crossing this barrier decreases with increasing mutation rate because natural selection is inefficient when mutations are too frequent. The time to cross the barrier, on the other hand, decreases with mutation rate, and, as a result, cancer incidence peaks at intermediate mutation rates. The theory agrees well with simulations and provides a framework for interpreting cancer clinical data. In particular, our theory provides an explanation for the low ratio of drivers to passengers in highly mutated cancer and for the nonmonotonic dependence of clinical outcomes in breast cancer on the extent of genetic alterations. The theory is also useful in designing and interpreting passenger-mediated treatment strategies.

Keywords: evolutionary dynamics, passenger mutations, cancer progression

41. Occam's Metastasis

Massachusetts Institute of Technology PS-OC

Trans-Network Project: Genotypic Determinants of Metastatic Fitness: A Delicate Balance of Passenger and Driver Mutations

Christopher McFarland[1], Jacob Scott[2], Jonathan Wojtkowiak[3], David Basanta[3], Alexander Anderson[3], Leonid Mirny[4]

[1]Harvard University, [2]Oxford University, [3]H. Lee Moffitt Cancer Center & Research Institute, [4]Massachusetts Institute of Technology

The formation of metastases is a multi-step process, involving (1) migration of cells from the primary tumor into the bloodstream, (2) arrest in foreign stroma, and (3) growth from a colony of only a few cells. The last step is highly inefficient and poorly understood. Here, we explore a minimal computational model of the process where we allow cells to grow in a primary tumor, seed them into new stroma, and then assay for macroscopic metastases. In our model, every step of the process is stochastic: cell division and death, acquisition of new mutations affecting cell fitness, selection of 'seed' cells from the primary tumor, and changes in fitness of acquired mutations when cell enter new stroma. We find that the evolutionary path to metastatic disease is highly inefficient and (epi)genetically diverse, i.e. many different sets of mutations can lead to primary or metastatic growth. Metastatic efficiency depends on many factors even in this minimal model: tumor size, age, heterogeneity, and the relation between stromal micro-environment and primary site, all of which correspond with empirical observations. Metastatic efficiency can be described analytically and depends upon the number of fixed advantageous and deleterious mutations. We can transform these 'genetic' state variables into a equivalent "phenomenological" form that is a function of tumor size and age, offering a potential synthesis of two perspectives on cancer progression. Lastly, our model predicts that metastatic efficiency decreases with mutational load. We directly tested this by applying increasing mutagenic doses to a transformed MCF-10A cell line and then injecting these cells into the tail vein of mice. As mutational load increased, we observed fewer, slower growing metastases, thus affirming the predictions of our model. We hypothesize that treatments strategies exploiting cancer's load of passenger mutations can prevent metastatic disease.

Associated Cancer Types: breast cancer, metastasis, evolution, microenvironment

Keywords: metastasis, evolution

42. Single Cell Growth Response to Metabolite Deprivation

Massachusetts Institute of Technology PS-OC

Coordination of Cell Growth and Division in Normal and Cancer Cells

Mark Stevens, Sungmin Son, Scott Manalis

Massachusetts Institute of Technology

Investigating cancer cell metabolism has been proven as an effective route to both better understand and specifically target cancer therapies. Nonetheless, still relatively little is known about how these cells regulate their growth and metabolism in response to changing environmental cues. In order to measure cellular uptake of metabolites, we devised a way to instantaneously change the external nutrient level surrounding a single cell. This technical advance allows us to precisely define when the cell's environmental conditions are altered, a level of environmental control and temporal resolution not possible in bulk culture approaches. At the same time, we continuously measure the cells mass in a suspended microchannel resonator (SMR), which in turn gives precise growth rate (GR). Initial depletions of glucose and glutamine, two substrates for which uptake as been previously characterized by radiolabel as ~10% and ~2%, respectively, show surprising results. Data shows that depletion of glucose and glutamine produce an instantaneous GR decrease of 36%-40% and 28%-29%, respectively. This represents a significantly larger mass fraction than uptake alone. To confirm that this effect is dictated by a mechanism other than uptake, depletion of both substrates was preformed. Measurement showed a non-additive GR slowdown of 50%. Combining the magnitude of GR slowdown with the instantaneous nature of the response, it suggests an induction of cellular sensing and a downstream, concomitant elimination of other substrates' uptake. Intriguingly, taking downstream glucose sensing as an example, canonical mechanisms of cell response to glucose depletion [e.g., AMP Kinase (AMPK), mammalian target of rapamycin (mTOR)] are unlikely to be able to account for a GR response on the observed timescale.

We hypothesize that the measurement of instantaneous short-term growth response captures the additive effect of substrate uptake loss, and all instantaneous signaling meant to mitigate the adverse effects of nutrient depletion. We envision using instantaneous growth response as a lumped parameter in high throughput studies to probe the contribution of metabolites to growth processes, unbiased by uptake level or previous characterization. Continued experimentation will further characterize the growth rate effect caused by depletion of a broader range of metabolic substrates, enabling comparison of growth rate effects to uptake levels and know metabolic participation.

Keywords: metabolism, growth, signaling

43. Abraxane Loading Into Multistage Vector for Liver Metastases Therapy

The Methodist Hospital Research Institute PS-OC
Project 1: Center for Transport Oncophysics (CTO)

Fransisca Leonard, Tomonori Tane, Jenolyn Francisca Alexander, Xuewu Liu, Mauro Ferrari, Kenji Yokoi, Biana Godin

The Methodist Hospital Research Institute

Abraxane, albumin-bound paclitaxel, has been found to improve anti-tumor response rate, delayed disease progression, and extended overall survival in advanced breast cancer, and non-small lung cancer in comparison to paclitaxel and has been FDA approved for application in both types of cancer.

The objective of this study was to design a vector that will be able to overcome biophysical transport barriers in poorly vascularized tumor lesions. Our previous studies with intravital microscopy have shown that metastastatic lesions in the liver originated from breast and colorectal cancer have significant impairment in the blood supply and transport of molecules. Multistage nanovectors (MSV), based on nanoporous silicon particles loaded with Abraxane (MSV-ABX) were developed to overcome various biophysical barriers and efficiently carry therapeutic payload to the tumor microenvironment. The first stage porous silicon particles rely on biological factors, targeting tumor-associated macrophages, and further creating a depot from which the drug/therapeutic nanoparticles are slowly released in the close proximity to the tumor.

Results from in vitro studies with 4T1 breast cancer cells showed similar activity of MSV-ABX to Abraxane in killing tumor cells in monoculture, while in vivo studies demonstrated promising result where MSV-loaded Abraxane (MSV-ABX) was more effective than Abraxane in therapy of the liver metastasis of breast and colorectal cancer in mouse models. Data from a co-culture study of 4T1 with macrophages was in agreement with in vivo results, suggesting the importance of cancer microenvironment in overcoming the transport barriers by drugs encapsulated in MSV. Moreover, MSV-ABX induced macrophage migration.

These data showed that a retention of MSV-ABX in the proximity of the tumor lesions in the liver enabled overcoming the barriers for drug transport in poorly vascularized lesions based on the diffusion gradients.

Associated Cancer Types/Areas: liver metastasis of breast and colorectal cancer, cancer microenvironment.

Keywords: nanotechnology, microenvironment, metastasis

44. Analysis of Nanoparticle Uptake by Tumor Vasculature Using Computational Modeling

The Methodist Hospital Research Institute PS-OC
Core 1: Biomathematics Core

Hermann Frieboes[1], Min Wu[2], John Lowengrub[2], Paolo Decuzzi[3], Vittorio Cristini[4]

[1]University of Louisville, [2]University of California, Irvine, [3]The Methodist Hospital Research Institute, [4]University of New Mexico

The development of novel strategies applied to the early detection and more efficient treatment of diseases has been enabled by the application of nanotechnology to the biomedical sciences. In particular, powerful chemotherapeutic molecules have been reformulated into liposomes and nanoparticles (NPs) in cancer treatment, evincing improved pharmacodynamics and pharmacokinetics, as well as reduced off-target toxicity. Nevertheless, the dose of active molecules uptaken at target sites remains suboptimal. Since the tumor vasculature determines the transport of any systemically injected agent to cancerous tissue, it is reasonable to assume that the tumoritropic accumulation of NPs are affected by the level of maturation of the vessel network and the concomittant expression of vascular receptor molecules. To verify this hypothesis as well as optimize the tumoritropic deposition of NPs, we develop a ultidimensional computational model to predict the accumulation of systemically injected NPs in tumors. We implement a mesoscale model for the vascular adhesion of NPs with a multi-dimensional tumor growth model that links cellular-level events to the tumor tissue scale while accounting for the time-dependent development of the tumor-induced vasculature.

Associated Cancer Types/Areas: cancer nanotherapy

Keywords: mathematical modeling, computational simulation, nanovector transport

45. Analysis of Tumor Perfusion Using an Engineering Approach

The Methodist Hospital Research Institute PS-OC
Center for Transport Oncophysics

Anne van de Ven[1], Behnaz Abdollahi[2], Carlos Martinez[3], Mauro Ferrari[1], Hermann Frieboes[2]

[1]The Methodist Hospital Research Institute, [2]University of Louisville, [3]Southwestern University

Heterogeneities in the perfusion of solid tumors prevent optimal delivery of nanotherapeutics. Clinical imaging protocols capable of obtaining patient-specific vascular perfusion data are under development but have proven difficult to implement. It is challenging not only to determine which perfusion features hold greater prognostic value, but also to relate measured features to vessel structure and function. With the advent of systemically administered nanotherapeutics, whose delivery is dependent on overcoming diffusive and convective barriers to transport, such knowledge is becoming increasingly important. Here we describe a framework for the automated evaluation of arterial and venous perfusion curves measured at the single vessel level. Primary tumor fragments, collected from triple negative breast cancer patients and grown as xenografts in mice, were injected with a bolus of fluorescence contrast and monitored using intravital microscopy. Two features directly measured from the time-series curves, namely arterial peak and venous delay, were input into a Fuzzy C-mean (FCM) supervised classifier, in order to classify and rank tumors according to degree of perfusion. The resulting tumor rankings correlated inversely with experimental nanoparticle accumulation measurements, enabling prediction of nanotherapeutics delivery without requiring any underlying assumptions about tissue structure or function, or heterogeneities contained within. With proper calibration, these methodologies may enable the study of a variety of nanotherapeutics delivery strategies in different tumor models.

Associated Cancer Types/Areas: breast cancer, tumor vasculature

Keywords: intravital microscopy, tumor perfusion, mathematical modeling

46. Autophagy and Enhanced Chemosensitivity in Pancreatic Cancers Induced by Noninvasive Radiofrequency Field Treatment

The Methodist Hospital Research Institute PS-OC

Nadezhda V. Koshkina[1], Katrina L. Briggs[1], Flavio Palalon[1], Amirali N. Hamir[1], Steven A. Curley[1,2]

[1]The University of Texas MD Anderson Cancer Center, [2]Rice University

It is assumed that radiowaves are safe for humans. However, changes on the molecular level that may be induced by powerful radiofrequency (RF) fields in normal and malignant cells remain poorly understood. In our study, exposure of different pancreatic cancer cell lines to 13.56 MHz radiowaves resulted in substantial morphological and molecular changes, in marked contrast to normal cells that were apparently unaffected. RF treatment activated autophagy but not apoptosis in cancer cells and induced their death. These effects of RF treatment were absent in normal pancreatic epithelial cells in vitro. Excessive numbers of autophagic vesicles in cancer cells persisted 24-48 h after RF exposure and then started to decline. Addition of a subtoxic dose of gemcitabine (GCB) to RF treatment inhibited the recovery of cancer cells from the RF-induced autophagy and enhanced the cytotoxic effect of the latter on cancer cells. Weekly treatment of GCB-resistant ectopic and orthotopic Panc-1 cancers in mice with non-invasive RF treatment combined with GCB had an antitumor effect superior to that of RF or drug treatment alone ($P<0.01$), yet had no evidence of systemic toxicity. Immunohistochemical analysis of orthotopic tumors from mice confirmed the ability of RF treatment to induce autophagy but not apoptosis in cancer cells. This indicated the potential role of this particular cell death mechanism in malignant cells treated with RF field exposure combined with low-dose chemotherapy. This novel therapeutic approach using non-invasive RF treatment in combination with low dosages of a standard chemotherapy drug used for pancreatic cancer in situ was effective without causing toxic effects in normal cells and tissues.

47. Gold Nanoparticles Stabilized With Soft Matter Corona: Evidence of Stability and Long Circulation In Vivo

The Methodist Hospital Research Institute PS-OC
PSOC Project 2: Noninvasive Radio-Frequency Field Induced Thermal Destruction of Malignant Cells in Human Hepatocellular Cancer

Nadya Koshkina[1], Alexei A. Bogdanov, Jr.[2,3], Suresh Gupta[2], Surong Zhang[2], Gang Han[2], Steven A. Curley[1]

[1]The University of Texas MD Anderson Cancer Center, [2]University of Massachusetts ,[3]Moscow State University

As the number of diagnostic and therapeutic applications utilizing gold nanoparticles (GNPs) increases, so does the need for a source of GNPs that are stable in vivo, biocompatible, and suitable for bioconjugation 1, 2. Here we show that GNPs stabilized with a methoxypolyethylene glycol-graft poly-l-lysine corona during synthesis resulted in monodisperse (diameter 41.5±13.5) spherical single-core (9.3±2.3 nm), weakly positively charged nanoparticles carrying amino groups that were amenable to modification. The GNPs were stable against aggregation in the presence of serum proteins, demonstrating no apparent intracellular aggregation after their uptake in endosomes. In addition, the GNPs exhibited no toxicity in human endothelial cells, but showed dose-dependent toxicity in epithelial cancer cells. Radioactive labeling of GNPs with 99mTc-mercaptoacetyltriglycine allowed imaging of GNP biodistribution after systemic administration. Single-photon emission computed tomography revealed (1) long circulation time of GNPs in the bloodstream, (2) zero-order elimination kinetics, and (3) GNP accumulation at sites of experimental inflammation and tumor in mice. Our results demonstrate that the MPEG-pPLL corona confers stealth properties that enable GNPs to exist in a non-aggregating state ultimately improving their biocompatibility, and potential for use in biomedical applications.

Associated Cancer Types/Areas: any type of solid tumor

Keywords: stable gold nanoparticles, cancer delivery, biodistribution

48. Tumor Selective Hyperthermia Induced by Short-Wave Capacitive RF Field

The Methodist Hospital Research Institute PS-OC

Project 2: Noninvasive Radio-Frequency Field Induced Thermal Destruction of Malignant Cells in Human Hepatocellular Cancer

Nadya Koshkina, Mustafa Raoof, Brandon T. Cisneros, Stuart J. Corr, Flavio Palalon, Steven A. Curley

The University of Texas MD Anderson Cancer Center

There is a renewed interest in developing high intensity short wave capacitive radiofrequency (RF) electric fields for nanoparticle-mediated tumor-targeted hyperthermia. However, the direct thermal effects of such a high intensity electric field (13.56 MHZ, 600 W) on normal and tumor tissues are not completely understood. In this study, we investigate the heating behavior and dielectric properties of normal mouse tissues and orthotopically implanted human hepatocellular and pancreatic carcinoma xenografts. We note tumor-selective hyperthermia (relative to normal mouse tissues) in implanted xenografts that can be explained on the basis of differential dielectric properties. Furthermore, we demonstrate that repeated (1-2 times/week) RF exposure of tumor-bearing mice can result in a significant anti-tumor effect compared to control groups without detectable harm to normal mouse tissues.

Associated Cancer Types/Areas: pancreatic cancer, liver cancer

Keywords: radiofrequency, hyperthermia, orthotopic cancer

49. Effect of Nanovector Entrapment on Monocyte Rolling and Adhesion to Endothelial Cells

The Methodist Hospital Research Institute PS-OC
Project 1: Center for Transport Oncophysics (CTO)

Srimeenakshi Srinivasan[1], Yue Geng[2], Sarah R. Ally[1], Fransisca Leonard[1], Michael King[2], Biana Godin[1]

[1]The Methodist Hospital Research Institute, [2]Cornell University

Better understanding of the physics behind the interaction of various cell populations in the tumor site and their relations to intrinsic cancer biology can enable rational design of new and improved cancer therapies. Natural chemotactic migration of monocytes to necrotic areas of the tumor can be exploited and used as a Trojan horse for efficient cell mediated nanovector based delivery of active agents. The objective of this study is to evaluate the effect of NP/MP loading, into monocytes (THP-1), on the physics of monocyte and endothelial cell interaction and their flow dynamics under various shear stresses. THP-1 cells are professional phagocytes and thereby readily took up all types of particles tested, namely gold naoparticles (AuNP), silica beads (SB), liposomal doxorubicin (LDox) and silicon microparticles (SMP). Internalization kinetics was distinct for each case. AuNP/SB/LDox showed rapid loading and within 1-2 h had hundreds of particles associated with each cell. SMP loading into THP-1 also was rapid, however, the number of particles/cell reached a maximum of about 3-5 after 6 h. Cell viability following incubation with the various nanovectors was not affected, except for when incubated for 24 h with high concentration of liposomal doxorubicin. The rolling velocity and adhesion of THP-1 to cells was affected by the type of particle loaded. While SMP loading decreased the rolling velocity, the loading of SB or LDox did not affect it. Based on these observations, we can anticipate that the amount of the NPs/MPs beared by monocytes (potentially derived from patients) can be precisely controlled by varying the initial concentration of the particles/cells and incubation time. Our results also confirm our hypothesis that particle uptake alters the properties of immune cells ability for rolling and adhesion. Further studies will examine the possibility of rationally designing particles to be preloaded into monocytes so these will concentrate preferentially into the tumor regions.

50. Bio-mathematical Modeling of Yucatan Pigs: A Pilot Report

The Methodist Hospital Research Institute PS-OC

Prashasnika Gehlot[1], Jennifer Pascal[2], Vittorio Cristini[2], Steve Curley[1]

[1]The University of Texas MD Anderson Cancer Center, [2]University of New Mexico

Tumors have a very heterogeneous microenvironment because of their limited, unstructured vasculature, making the delivery and distribution of drugs very inconsistent. Because of these heterogeneities, traditional chemotherapy drugs reach primarily well-perfused areas. Research has been primarily directed towards in vitro experiments on cultured cells in monolayers and how drugs affect the individual cell, failing to include the additional biological factors involved in drug delivery through a disorganized vasculature and penetration through tissue to the tumor cells. Mathematical modeling based on fundamental (bio)physical principles in conjunction with large animal model experiments can be used to understand how the tissue-scale transport of chemotherapeutic agents affects tumor response to chemotherapy and thereby address this critical question. Here we will present preliminary results comparing the mathematical model predictions to measurements from histopathological samples from Yucatan pig livers to quantify the role that biobarriers play in limiting the efficiency of drug delivery.

51. Impact of Diffusion Barriers to IFNγ on Breast Cancer Immunotherapy

The Methodist Hospital Research Institute PS-OC
Project 3: Multiscale Cancer Modeling: From Cell Phenotypes to Cancer Spread and Response to Therapy

Zhihui Wang[1], Hiranmoy Das[2], Metin Gurcan[2], Jennifer Pascal[2], Vittorio Cristini[1]

[1]The University of New Mexico, [2]The Ohio State University

Molecular-focused cancer therapies, such as molecularly targeted therapy and immunotherapy, demonstrate only limited efficacy in cancer patients so far. We argue that underestimating the role of biophysical factors that impact the delivery of drugs or cytotoxic cells to the target sites (for associated preferential cytotoxicity or cell signaling modulation) may be responsible for the poor clinical outcome. Therefore, instead of focusing exclusively on the investigation of molecular mechanisms in cancer cells, convection-diffusion processes of cytotoxic molecules and migration of cancer-killing cells within tumor tissue should be taken into account to improve therapeutic effectiveness. Here, we present a mathematical model of the interstitial diffusion and uptake of small cytotoxic molecules (interferon-γ; IFN-γ) secreted by γδ T-cells to predict breast cancer growth inhibition as measured both in vitro and in vivo. Our analysis shows that diffusion barriers of cytotoxic molecules conspire with γδ T-cell scarcity in tissue to limit the inhibitory effects of γδ T-cells on cancer cells. This may increase the necessary ratios of γδ T-cells to cancer cells within tissue to unrealistic values for having an intended therapeutic effect, and render the immunotherapeutic treatment ineffective. Further therapies in practice may seek to overcome these diffusion barriers to transport a sufficient amount of γδ T cells to the tumor site.

Associated Cancer Types/Areas: breast cancer, immunotherapy, microenvironment

Keywords: microenvironment, mathematical modeling, T-cell based immunotherapy

52. Improving Nanotherapeutics Delivery Without Reliance on the EPR Effect

The Methodist Hospital Research Institute PS-OC

Anne L. van de Ven, Melissa D. Landis, Lacey A. Paskett, Hermann B. Frieboes, Jenny C. Chang, Mauro Ferrari

The Methodist Hospital Research Institute

Chemotherapeutics delivery is generally poor in tumors characterized by rapid perfusion and low blood volume fraction. Systemically administered nanoparticles can be engineered to overcome adverse transport conditions to act as intravascular drug depots for the localized delivery of high concentrations of chemotherapeutics. The feasibility of this approach was first demonstrated using melanoma, and is now being further investigated using human triple-negative breast cancer biopsies implanted into mice. Intravital microscopy studies of xenografts selected for differing vascular morphologies have yielded intriguing preliminary data regarding the role of tumor vascularity in drug and particle delivery. The first-pass perfusion of a 40kDa dextran tracer revealed that BCM-2665 tumors are perfused ~6x more rapidly than BCM-4195 tumors and contain ~30% lower volume fraction of blood. Interestingly, flow parameters that adversely impact drug delivery appear to favor the accumulation of plateloid particles. As a result, BCM-2665 xenografts receiving an i.v. injection of 1000x400nm particles show ~10x more particle accumulation than BCM-4195 tumors. The ability of these therapeutic particles to reach tumors appears to be primarily driven by flow-related parameters, which we quantify using a combination of intravital microscopy and mathematical modeling. Taken together, these findings suggest that cytotoxic intravascular drug depots may be a promising strategy for increasing the efficiency of chemotherapeutics delivery to drug-resistant tumors and is the premise of ongoing therapeutic response studies.

53. Modeling of Cell and Nanoparticle Transport in the Microvasculature

The Methodist Hospital Research Institute PS-OC
Center for Oncophysics, Biomathematics Core

Tae-Rin Lee[1], Andy Yun[2], Wing Kam Liu[3], Paolo Decuzzi[1]

[1]The Methodist Hospital Research Institute, [2]Harvard University, [3]Northwestern University

Understanding cell and nanoparticle (NP) transport in the microvasculature is crucial to develop new strategies for targeting circulating tumor cells (CTCs) and solid tumors. However, predicting the actual transport of cells and NPs in whole blood is challenging in that multiple interactions should be accounted for, such as those among red blood cells (RBCs), CTCs, macrophages and NPs. In this presentation, a novel computational approach based on the Immersed Finite Element Method (IFEM) is suggested for simulating the transport of cells and NPs in whole blood. In vitro and in vivo experiments are also presented in support of the computational predictions. The lateral dispersion of CTCs and NPs can be characterized as a function of the cell/NP size and deformability. The cellular interactions among CTC, RBCs and endothelial cells are explicitly incorporated in the IFEM simulation. Finally, the IFEM data are combined with the geometry and flow information of the microvessel to efficiently quantify the nanoparticle dispersion in the entire microvasculature. Stronger lateral drifting forces for NPs above 500nm in diameter and cells are observed along the local hematocrit. Also, CTC rolling and interaction with the vessel wall is increased with cell rigidity. Further development of the model will be in the rational design of NPs and better understanding of CTC vascular behaviors.

Keywords: circulating tumor cell, nanoparticle transport, blood flow

54. Predictive Biophysical Modeling of Dose Response of Tumor Cells Treated With Free Drug and Protocells

The Methodist Hospital Research Institute PS-OC
Center for Transport Oncophysics

Jennifer Pascal[1], Carlee Ashley[2], Zhihui Wang[1], Jeffrey Brinker[2], Vittorio Cristini[1]

[1]The University of New Mexico, [2]Sandia National Laboratories

The natural defenses of the human body create many challenges for chemotherapeutics to reach their intended targets. A largely overlooked limitation of traditional chemotherapy delivery is the transport within the tumor microenvironment. The unstructured and limited vasculature in tumors makes them a very heterogeneous microenvironment causing inconsistencies in the delivery and distribution of drugs. With the recent advances in nanotechnology, an arsenal of tools have become available to synthesize nanoparticles loaded with anticancer drugs that can circumvent many of the transport limitations faced by traditional bolus injections of chemotherapy drugs. Their quantum properties, high surface areas and amenability to modification offer a possible alternative to traditional chemotherapy administration that is several-fold more effective and efficient at killing tumor cells.

Here we compare tumor cell responses to traditional delivery of drugs with delivery using the novel protocells by developing a framework that integrates mathematical modeling with biological cytotoxicity experimental data. This integration provides an approach to gain further insight into how to optimize the aforementioned treatment possibilities. We will present a mathematical model that describes in vitro cytotoxicity assay data for parental and multi-drug resistant human hepatocellular carcinoma cell lines using the common anticancer drug, doxorubicin. The mathematical model was solved analytically and fit to data for both free doxorubicin and doxorubicin-loaded protocells to obtain parameters describing cell death and uptake rates of drug. By extracting these parameters, we are able to *predict* the cells' response to each method of delivery, something that has not yet been achieved by previous researchers. Furthermore, this work explains the differences in free drug and protocell delivery and aids in elucidating the specific advantages observed from utilizing protocells as a drug delivery vehicle.

Associated Cancer Types/Areas: hepatocellular carcinoma, protocells, drug delivery

Keywords: dose response, mathematical modeling, transport oncophysics

55. Radio Frequency-Induced Tumor Necrosis in a Mouse Model of Breast Cancer
The Methodist Hospital Research Institute PS-OC

David Savage, Charles Lindquist, Steven Curley, Rita Serda

The Methodist Hospital Research Institute

Previous work in our lab with liver and pancreatic cancer models has indicated that radio frequency (RF) exposure accelerates the rate of necrosis in solid tumors (data in press). This necrosis occurs independent of thin needle heating source insertion, or of injected particles to serve as a source of induced heat. Moreover, our preliminary data with 4T1 mouse mammary tumors exposed to RF energy during magnetic resonance imaging with a 7 Tesla scanner also showed significant necrosis that increased with each imaging episode. Necrosis was observed in animals with sham and saline injections, and we hypothesize that it is due to the RF energy used to pulse atoms inside of the magnetic field. This study was aimed at determining whether a high power RF field can accelerate and/or induce tumor necrosis, and to characterize the mechanism of action. 4T1 tumors were initiated in nude mice. Once the tumors neared 10% of the animal's body weight, the tumor regions were exposed to a short (4 min) and long (10 min) dose of radiofrequency energy at 600 W and 13.56 Hz. The mice were then sacrificed after 24 hours, and sections of organs and tumors were prepared for histology. Our data is forthcoming, but we anticipate that it will show accelerated necrosis in RF exposed animals when compared to the no treatment controls. Additionally, we are using immunohistochemistry to examine expression of LC3b to determine if autophagy plays a role in RF-induced cell death or survival. The findings of this study may both indicate a novel effect of RF energy on primary breast cancer tumors, and propose a mechanism. Ultimately, this may add further evidence that RF exposure alone is sufficient to induce hyperthermic cell death in large solid tumors.

56. Discovering Biomarkers for the Vascular Permeability to Nanotherapeutics in Different Tumor and Organ Microenvironments

The Methodist Hospital Research Institute PS-OC
Department of Nanomedicine

Kenji Yokoi, Tomonori Tanei, Biana Godin, Anne L. van de Ven, Jenolyn Alexander, Mauro Ferrari

The Methodist Hospital Research Institute

Enhanced permeation and retention (EPR) effect is utilized by nanotherapeutics for preferential accumulation to the tumor. However, the relative benefit of the EPR effect varies from tumor to tumor based differences in the tumor microenvironment and can result in insufficient accumulation of nanotherapeutics. In this study, 4T1 and 3LL murine cancer cell lines, known to have similar sensitivity to pegylated liposomal doxorubicin (PLD) in vitro, were shown to accumulate significantly different quantities of PLD in vivo. PLD accumulation correlated with tumor-specific differences in therapeutic efficacy and vascular permeability, which was modulated by the extent of coverage of tumor-associated endothelial cells by basement membrane. Matrix metalloproteinase (MMP)-9 and its endogenous inhibitor, tissue inhibitor of metalloproteinase (TIMP)-1, played a pivotal role in these phenomena. Differences in PLD accumulation and vascular permeability were organ-specific and significantly correlated with the relative ratio of MMP-9 and TIMP-1 in the systemic circulation of tumor-bearing mice. Our findings support the further development of MMP-9 and TIMP-1 as paired surrogate biomarkers for assessing the vascular permeability to PLD and the application of these biomarkers could be expanded to other types of nanotherapeutics utilizing the EPR effect.

Associated Cancer Types/Areas: metastases to brain and liver

Keywords: nanotherapeutics, EPR effect, biomarker

H. LEE MOFFITT CANCER CENTER & RESEARCH INSTITUTE PS-OC

57. An Imaging Driven Biophysical Model to Predict Brain Tumor Growth and Response

H. Lee Moffitt Cancer Center & Research Institute PS-OC
Pilot Project: An Imaging Driven Biophysical Model to Predict Brain Tumor Growth and Response

David Hormuth, Nkiruka Atuegwu, Thomas Yankeelov

Vanderbilt University

Magnetic resonance imaging (MRI) and positron emission tomography (PET) have matured to the point where they can provide noninvasive, quantitative, and 3D characterizations of, for example, blood flow, vessel permeability, blood volume, cellularity, hypoxia, metabolism, and cell proliferation. One way to capitalize on the wealth of available information is to incorporate it into a realistic biophysical model that can be used to predict tumor growth and therapy response on an individual basis. The mathematical modeling literature typically models tumor growth by developing systems of equations describing, for example, chemotaxis, haptotaxis, and growth factor gradients. By introducing imaging data into these models, terms requiring information available typically only by highly invasive methods or within idealized systems can be replaced with terms supported by *patient-specific* imaging data, thereby making such models more amenable to hypothesis generation and experimental validation. Towards this end, we have built a biophysical model of cell proliferation and angiogenesis that can be initialized and constrained almost entirely by co-registered PET and MR images of molecular, cellular, and physiological data. The present model consists of three coupled partial differential equations which describe tumor cell number, glucose concentration, and endothelial cell density. The system is solved numerically using standard finite difference methods in Matlab. Tumor cell movement and proliferation is determined at each iteration from calculated distributions of tumor cells, endothelial cells, and glucose concentration. Using an initial distribution of tumor characteristics from readily available imaging data, a tumor "forecast" can be developed which predicts tumor status at future time points and this prediction can be directly tested against experimental data. We will present preliminary results on this method's ability to predict tumor growth in the C6 model of rat brain cancer.

Associated Cancer Types/Areas: brain cancer, microenvironment

Keywords: MRI, PET, tumor forecasting, biophysical modeling, imaging

58. Connecting MRI Physics to Glioma Microenvironment: Simulating T_2 MRI Signal Intensity Based on Model-Predicted Tumor-Associated Vasogenic Edema

H. Lee Moffitt Cancer Center & Research Institute
Project 3: Clinical Imaging and the Tumor Physical Microenvironment

Pamela Jackson[1], Andrea Hawkins-Daarud[1], Russell Rockne[1], Robert Gatenby[2], Robert Gillies[2], Alexander Anderson[2], Kristin Swanson[1]

[1]Northwestern University, [2]H. Lee Moffitt Cancer Center & Research Institute

Glioblastomas are predominantly assessed with gadolinium-enhanced T_1-weighted (T_1Gd) and T_2-weighted fluid attenuated inversion recovery (T_2/FLAIR) magnetic resonance imaging (MRI). Hyperintensity on T_2/FLAIR images is understood to correspond with vasogenic edema and infiltrating tumor cells. Magnetic resonance (MR) images do not directly show tumor cells; rather, they capture abnormalities in the microenvironment caused by the presence of tumor cells. Thus, assessing disease extent remains challenging through the obscuring lens of MRI. To better understand how hyperintensity on T_2/FLAIR MR may correlate with actual cell density, we explore a multi-compartmental MRI signal equation which takes into account interstitial fluid native to the tissue and also induced by tumor infiltration. The relative abundance of de novo and tumor induced fluid is produced by a mathematical model of glioma growth and angiogensis. In the mathematical model, gliomas are comprised of vasculature and three tumor cell phenotypes: normoxic, hypoxic, and necrotic cells. Edema is characterized as fluid leaking from abnormal tumor vessels. We simulated spatial maps of tumor cell density, hypoxia, and edema for aggressive virtual tumors with different rates of proliferation and invasion. These spatial maps were then passed into a multi-compartmental MRI signal model for generation of simulated T_2/FLAIR MR images. T_2 values for individual compartments in the signal equation were either from literature or estimated. Additionally, T_2 maps were calculated from simulated images.Simulated MRIs had the appropriate contrast for normal white matter, normal gray matter, and tumor tissue. Normal white matter and tumor T_2 values calculated from simulated images were very similar to values reported in the literature. However, simulated T_2 values for peripheral edema were lower than literature values, suggesting further investigation of model parameters is needed. Once properly calibrated, we believe our MRI signal simulation can help with understating how underlying tissue changes affect the signal seen on MRIs.

Associated Cancer Types/Areas: brain

Keywords: MRI, edema, brain tumor

59. Darwinian Dynamics and Current Concepts of Driver and Passenger Mutations

H. Lee Moffitt Cancer Center & Research Institute PS-OC
Math Core Project

Jessica Cunningham[1], Robert Gatenby[1], Joel Brown[2]

[1]H. Lee Moffitt Cancer Center & Research Institute, [2]University of Illinois at Chicago

The cellular transition from normal to cancer is an evolutionary process characterized by stochastically accumulated mutations but deterministic convergence to well-defined phenotypic "hallmarks." The genetic and epigenetic changes associated with cancer evolution are typically divided into "drivers," defined as necessary for malignant growth and "passengers," which encompass all other mutations including deleterious and those conferring little or no fitness benefit. Here we examine somatic evolution of the malignant phenotype using a discrete, time-branching model employing Darwinian dynamics in the context of the classical evolutionary life history trade-off between fecundity and survivorship. We demonstrate that evolution promotes common phenotypic adaptations (or hallmarks) but through a wide range of genetic pathways. As a result of these diverse genetic trajectories, the fitness value of any gene mutation is dependent on initial cell properties, current selection forces, and prior genotypic and phenotypic changes. Our models quantitatively demonstrate that, while driver mutations are observed, all tumors contained subpopulations with uncommon mutations or combinations of mutations that contribute to optimal fitness but would typically be regarded as "passengers". These populations promote the inevitable adaptation yielding resistance to targeted therapies directed against mutations classified as "drivers." We find the current binary classification of "drivers" or "passengers" is inconsistent with subtleties of tumor biology and could limit success of targeted therapies.

Keywords: Darwinian dynamics, targeted therapy, adaptation of resistance

60. Dual-Mode Cellular Energetics and the Warburg Effect

H. Lee Moffitt Cancer Center & Research Institute PS-OC
Cancer Imaging and Metabolism, Math Core

Tamir Epstein, Robert Gillies, Robert Gatenby

H. Lee Moffitt Cancer Center & Research Institute

Ever since Pasteur showed in 1857 that lactate production in cells increases as oxygen concentrations decrease, glucose metabolism has been viewed as oxygen-dependent, so that in normal physiological conditions only the efficient aerobic metabolic pathway is used (up to 38 ATP/ glucose), while the inefficient glycolytic pathway (2 ATP/glucose) is reserved for periods of hypoxia. The Warburg phenomenon that prevails in cancer cells--glucose metabolism to lactate in the presence of oxygen--is notable primarily because it violates this "oxygen control" paradigm. We present theoretical and experimental evidence for a model of cellular bioenergetics in which glucose metabolism, under physiological conditions, is governed by spatial and temporal variations in energy demand. Aerobic metabolism, a slow but efficient process, supplies the energy necessary to meet base-load ATP demand. Glycolytic metabolism, less efficient but with 100-fold faster energy production rate, is utilized for "peak" demand in response to internal or external perturbations. These temporal dynamics give rise to spatial compartmentalization within cells because glycolytic enzymes must be located peripherally to accommodate local fluctuations in ATP demand when membrane pumps respond to environmental perturbations. Mitochondria, the locus of aerobic metabolism, in contrast are more centrally located. In this model, the Warburg effect is viewed not as a failure of oxidative metabolism but as a physiological response to increased fluctuations in membrane energy demand in cancer cells.

Associated Cancer Types/Areas: cancer metabolism

Keywords: cancer metabolism, Warburg effect

61. Optimizing Melanoma Treatments: Regulating Autophagy-Mediated Treatment Resistance
H. Lee Moffitt Cancer Center & Research Institute PS-OC
The Physical microenvironment in somatic evolution of the malignant phenotype

Eunjung Kim, Vito Rebecca, Keiran Smalley, Alexander R.A. Anderson

H. Lee Moffitt Cancer Center and Research Institute

Autophagy is a self-digestive mechanism that removes unnecessary cellular components. An AKT inhibitor, MK2206, and chemotherapy agents (Carboplatin and Paclitaxel) have been shown to activate autophagy in melanoma cells, although the consequences of autophagy activation in this context are not clear. Here, we developed an integrative approach to investigate the role of autophagy in melanoma treatments. We built a mathematical model comprising ordinary differential equations that explains the dynamics of drug sensitive melanoma cells, drug resistant melanoma cells, and autophagy cells. The basic parameters in the model such as the growth rates and death rates were estimated by comparing model predictions with experimental data. Our simulation results showed that a persistent treatment of MK2206 combined with chemotherapy agents increased autophagy population significantly, resulting in significant increase of resistant population. However, when a slightly different treatment scheme with a different timing and order was applied, the resistant population didn't increase significantly. These simulation results imply that both treatment order and timing play an important role in modulating autophagy-mediated resistant population. To this end, we applied a control theory to determine the optimal timing and order of MK2206, Carboplatin, and Paclitaxel. Our aim is to minimize autophagy mediated resistant population. Our simulations show that a carefully designed pulse drug delivery is more effective than continuous process.

Associated Cancer Types/Areas: melanoma, drug resistance

Keywords: autophagy, drug resistance, optimization, mathematical model

62. Pathology to Drive Precision Medicine in Oncology: Lessons of Landscape Ecology

H. Lee Moffitt Cancer Center & Research Institute PS-OC

Mark Lloyd[1,2], K.A. Rejniak[1], Joel Brown[2], Robert Gatenby[1], E. Minor[2]; M.M. Bui[1]

[1]H. Lee Moffitt Cancer Center and Research Institute, [2]University of Illinois at Chicago

A major goal of modern medicine is increasing patient-specificity so that the right treatment is administered to the right patient at the right time with the right dose. Current applications of this goal for cancer patients have largely focused on identification of genetic or epigenetic properties of tumor cells. However, recent studies have clearly demonstrated substantial genetic heterogeneity between tumors in the same patient and within subclones of a single tumor. Thus, molecular analysis from populations of cells (either a whole tumor or small biopsy of that tumor) is, at best, an incomplete representation of the underlying biology. These observations indicate a significant need to define intratumoral evolutionary dynamics that yield the observed spatial variations in cellular properties.

It is generally accepted that genetic heterogeneity among cancer cells is a manifestation of intratumoral evolution, and this is typically viewed as a consequence of random mutations generated by genomic instability with the cancer cells. We propose that this represents an incomplete view of Darwinian dynamics, which typically are governed by *phenotypic* variations in response to spatial and temporal heterogeneity in environmental selection forces. We propose that careful pathologic feature analysis can provide precise information regarding regional variations in environmental selection forces and phenotypic adaptations. These observations can be integrated using quantitative, spatially-explicit methods developed in ecology to define the underlying heterogeneous biological processes in tumors within individual patients.

Associated Cancer Types/Areas: microenvironment

Keywords: pathology, ecology, personalized medicine

63. Proteomics-Based Biomarker Discovery for Acidic Microenvironment of Breast Cancer Tumors

H. Lee Moffitt Cancer Center & Research Institute PS-OC

Mehdi Damaghi, Jonathan Wojtkowiak, Daniel Verduzco, Veronica Estrella, Robert Sprung, John Koomen, Mark Lloyd, Robert J. Gillies

H. Lee Moffitt Cancer Center & Research Institute PS-OC

The physical microenvironment of tumors is heterogeneous. A combination of poor vascular perfusion, regional hypoxia and increased glycolysis leads to an acidic microenvironment. Chronic acidosis selects for phenotypic alterations and changes in protein expression. The tumor cells that acquire resistance to acid-mediated cytotoxicity have a growth advantage over non-adapted stroma and hence acquire an invasive and metastatic phenotype. Acid-adapted cells have altered protein expression profiles.

In general, there have been numerous genomic- and transcriptomic-based studies to identify biomarkers for diagnosis and therapy prediction of cancers. In contrast, proteomics studies are more rare, although they are higher in actionable information content. Many mechanisms of biological control are exerted post-translationally and, hence proteomics approaches are highly suited for biomarker discovery. Int his work, we have used protoemics approaches to investigate profiles in acid-adapted cells in order to identify diagnostic biomarkers and to illuminate mechanisms of acid-adaptation.

Stable Isotope Labeling by Amino acids in Culture (SILAC) techniques provide an efficient method for quantitative analysis of whole proteome of paired biological samples. In this study we SILAC labeled MCF-7 breast cancer cells grown in neutral pH and adopted chronically to low pH (pH 6.7 for more than 3 months). Using LC-MS/MS the whole proteomes of both samples were compared. Analyses revealed that 31 proteins were higher and 35 were lower expressed in the acid –adapted compared to control cells; Many of these were mitochondrial and glycolytic proteins. Among the increased proteins were two major group of proteins related to autophagy and S100 families. Using multiple reaction monitoring (MRM), qRT-PCR, and western blotting we have re-confirmed the differences in the expression levels of these proteins. Immunohistochemistry (IHC) is underway in mouse tumor xenografts under control and bicarbonate-treated conditions. Bicarbonate neutralizes the acidic pH and expected to reverse the acid-adapted phenotype.

Identification of modulated proteins will elucidate mechanisms of tumor survival and progression and suggest candidate biomarkers for patient assessment.

Associated Cancer Types/Areas: breast cancer, microenvironment, biomarker

Keywords: SILAC proteomics, breast cancer, acidic microenvironment

64. Radiogenomics: Assessing Gene Expression Perturbations in Gliomas With a Patient-Specific Model Informed by Routine Imaging

H. Lee Moffitt Cancer Center & Research Institute
Project 3: Clinical Imaging and the Tumor Physical Microenvironment

Andrew Trister[1], Brian Bot[2], Kellie Fontes[1], Carly Bridge[3], Jason K. Rockhill[1], Maciej M. Mrugala[1], Russell Rockne[3], Erich Huang[2], Stephen Friend[2], Kristin Swanson[3]

[1]University of Washington, [2]Sage Bionetworks, [3]Northwestern University

Background: Gliomas are heterogeneous diseases with a wide distribution of growth kinetics that can be estimated using routine pretreatment imaging and that are prognostic for patient outcome after treatment. Molecular data of glioma patients have been made available through REMBRANDT, TCGA and TCIA. We evaluate the potential genetic drivers among patients with different net proliferation (p) and diffusion rates (D) included in these publicly available datasets.

Methods: The normalized microarray data from REMBRANDT (n=475 patients with grade II-IV glioma) was used to define a set of genes predictive of high grade glioma patients when compared with lower grade gliomas. 647 of these genes were also assessed in patients included in TCGA (n=466 patients grade IV). Eighty-four patients also had preoperative MRI imaging available through TCIA, allowing us to calculate an estimate of D and p. Differential gene expression comparing diffusion and proliferation rates was performed, and gene-set enrichment analysis was used to discover and validate gene-set motifs. Hierarchical clustering was used to compare survival outcomes.

Results: Thirty-seven genes are differentially expressed with D. Genes implicated in cell adhesion, extracellular matrix (ECM) maintenance and the production of focal adhesions are negatively correlated with D. Genes positively correlated with D are related to cell motility and pseudopodia formation. When considering p, 20 genes are differentially expressed. Clustering on these genes revealed two classes; one with a survival advantage (log-rank p=0.0002).

Conclusions: This work demonstrates the potential to assess underlying differences in gene expression in a heterogeneous cancer through patient specific assessment of routinely available imaging. We find that more diffuse tumors will under-express genes involved in focal-adhesions and production of ECM, while they express genes in pathways related to motility and pseudopodia formation. Furthermore, tumors with high p are seen to express genes related to treatment resistance, which may explain worse survival in these patients.

Associated Cancer Types/Areas: brain

Keywords: TCGA, glioblastoma, radiogenomics

65. Regional Variations in Intratumoral Selection Forces Produce Predictable Cellular Heterogeneity

H. Lee Moffitt Cancer Center & Research Institute

Mark Lloyd[1,2], Jessica Cunningham[3], M.M. Bui[1], Robert Gillies[1], Joel Brown[1], Robert Gatenby[1]

[1]H. Lee Moffitt Cancer Center & Research Institute, [2]University of Illinois at Chicago

Recent demonstration of extensive genetic diversity in cancer cells has renewed interest in the dynamics of intratumoral evolution. Because genetic events that drive evolution are randomly distributed, intratumoral heterogeneity appears unpredictable and chaotic- resulting, for example, in cell populations with positive and negative biomarkers or different "driver" pathways in the same tumor. These observations raise concerns that current gene-based strategies to personalize cancer treatment are too simplistic.

We propose intratumoral heterogeneity is the result of predictable phenotypic adaptations to spatially-dependent variations in local micro-environmental selection forces. A mathematical model of intratumoral Darwinian dynamics demonstrates cancer cells will evolve toward two general strategies: (1) "Engineer" phenotypes that primarily invest resources to promote infrastructure such as blood vessels or (2) "Pioneer" phenotypes that, by investing in motility and invasion, co-opt normal tissue infrastructure. Since the latter strategy can be successful only at the tumor-host interface, the model predicts a spatial pattern of cancer cell heterogeneity with "pioneers" at the tumor-host interface and "engineers" more broadly distributed. Image analysis of 15 invasive breast cancers demonstrated consistent variations between cancer cells at the tumor edge and the core including critical biomarker expression. CAIX, a biomarker for poor prognosis that promotes invasion by producing an acidic micro-environment, was found predominantly at the tumor edge while CAXII, a biomarker of good prognosis and high pHe, was found primarily in the tumor core. Both were observed in the same tumor. We conclude that intratumoral genetic heterogeneity is a predictable result of spatial variations in Darwinian dynamics.

Associated Cancer Types/Areas: microenvironment; breast cancer

Keywords: speciation, intratumoral heterogeneity, evolution

66. A Treatment Optimization Framework for Undetectable Bone Metastases: Developing an Integrated, Patient-Specific Tool

H. Lee Moffitt Cancer Center & Research Institute PS-OC

Mark Robertson, Mark Lloyd, Marilyn Bui, Susan Minton, Alexander Anderson

H. Lee Moffitt Cancer Center & Research Institute

Following resection of a primary tumor, patients are often treated with adjuvant therapies to prevent subsequent metastatic disease. Since metastases are often undetectable following treatment of the primary, adjuvant therapies are administered in a generic fashion, based on the dominant signature of the primary and broad population statistics. However, observed heterogeneity within the primary tumor could potentially be used in a computational model to further refine treatment strategies in a patient-specific fashion. We have developed a mathematical model of breast cancer metastasis growing in the bone microenvironment, which can be used to model the effects of adjuvant treatments, including tamoxifen, aromatase inhibitors (AI), and bisphosphonates. Histological and clinical analysis on 40 patients with paired primary and metastatic data from TCC have been used to develop metastatic seed profiles and parameterize the model. The result of this research is an interactive tool that can be used to optimize adjuvant therapies, to minimize metastatic disease (of unknown status) based on data derived from the patient. The optimization routine relies on heterogeneous input from primary tumor histology and other patient-specific data to develop a metastatic seed profile, which is a representation of the probable mix of circulating metastatic tumor cells. This profile is used in an in silico model of the bone microenvironment to test for metastatic growth. Each collection of micro-metastases is tested against variable therapy regimens, using an optimization routine that can look for the therapy with longest remission time or maximum chance of complete cure. As an example, a class of patients with high estrogen-receptor (ER) positivity appears to respond best to an alternating regimen of tamoxifen and AI therapy. The interactive tool developed in this project has translational potential as an application that can assist the clinician with adjuvant therapy decisions, including the optimal choice, schedule and combination. The patient-specific results are a significant refinement of the generic "pathway" guidelines that are currently used in clinical practice. This framework is easily extendable to include other metastatic and primary disease sites.

Associated Cancer Types/Areas: breast, bone

Keywords: treatment optimization, histology, modeling

67. Chance and Circumstance Govern Macrophage Functional Diversity

Northwestern University PS-OC
Dynamic Evolution of Tumor-Immune Network

Yishan Chuang, Joshua Leonard

Northwestern University

Macrophages play a critical role in maintaining the balance between homeostasis and protective inflammation by adopting immunostimulatory (M1) or immunosuppressive (M2) phenotypes. Tumors manipulate this balance between homeostasis and protective inflammation by inducing the production of immunosuppressive stimuli, which shifts macrophages into a tumor-promoting M2 phenotype. However, tumor-associated macrophages can be switched from M2 phenotype back to M1 phenotype with the application of stimuli such as interleukin-12 (IL-12). Our research focuses on understanding the macrophage polarization decision-making process and how we can potentially manipulate it for therapeutic purposes.

Most research to date has focused on the application of coherent signals (either pro-M1 or pro-M2 stimuli alone) even though these stimuli rarely exist independently *in vivo*. To assess how macrophage "calculate" responses when exposed to contradictory signals, we incubate cells with various doses of both IL-10 and IL-12, after which macrophages were "activated" using bacterial endotoxin (lipopolysaccharide, LPS). Contrary to previous reports, the presence of IL-10 prevented IL-12 mediated promotion of an M1 phenotype. Moreover, M2-type responses increased with IL-10 and were largely independent of IL-12 co-treatment. Furthermore, individual macrophages have shown differing responses to identical signal. The communication between individual macrophages may play a critical role in the overall polarization response. Using flow cytometry, we observed the probability of polarization towards an M2 state increased with IL-10 dose, and was independent of IL-12 co-treatment. Interestingly, some cells remained non-responsive to LPS-mediated activation, and this probability of activation was unchanged by cytokine pretreatment. These data represent the first evidence to date that macrophage polarization is a stochastic process and suggest that separate stochastic regulatory processes govern activation and polarization. Such insights reshape our understanding of local immune responses and should help identify novel therapeutic targets and strategies for the treatment of cancer and other diseases involving chronic immune dysfunction.

Associated Cancer Types/Areas: tumor immune network in immunosuppressive tumor microenvironment

Keywords: tumor microenvironment, macrophage polarization

68. Control of Stochastic Switching in Biological Networks
Northwestern University PS-OC
Project Name: Dynamic Nucleosome Signatures in Epigenetic Memory and Cancer Development

Daniel Wells, William Kath, Adilson Motter

Northwestern University

Noise caused by fluctuations in molecular number is a fundamental part of intracellular processes. While the response of biological systems to noise has been studied extensively, there has been limited understanding of how to control this response and exploit it to induce a desired cell state. Here we present a scalable quantitative method based upon large deviation theory to predict and control rare noise-induced switching between different states in genetic networks. Our analysis can be used to generate a dramatically distilled form of the original network—represented as a "metagenetic" network of transition paths, transition rates, and states—whose dynamics can be rationally controlled. Employing this distinct network representation, we consider models of cell differentiation and show how changes in gene activation rates or other tunable factors can lead to desired changes in stochastic switching that induce lineage changes towards pre-specified cell states, promote transdifferentiation, and explain re-specification events. This framework offers a systems approach to controlling biological dynamics and manipulating cell fates.

Associated Cancer Types/Areas: stem cells, development

Keywords: cell reprogramming, biological networks, systems biology

69. Consequences of Oncogenic Isocitrate Dehydrogenase Mutations and 2-Hydroxyglutarate Production in Prostate Epithelium

Northwestern University PS-OC

DNA Sequence-Encoded Nucleosome Positioning and Gene Regulation

Jon Oyer, Jonathan Licht

Northwestern University

Recent technological advances in DNA sequencing have yielded more comprehensive identification of mutations occurring in tumors. These efforts have detected recurrent mutations in a gene encoding isocitrate dehydrogenase (IDH1) in several tumor types. In each of these tumors IDH1 missense mutations at arginine 132 (R132) confer a gain of function and produce an aberrant metabolite, 2-hydroxyglutarate (2HG), as opposed to wild type (WT) activity that produces alpha-ketoglutarate (α-KG). α-KG is a cofactor for the Ten-Eleven Translocation enzymes (TET1/2/3), which catalyze DNA hydroxymethylation. This DNA modification contributes to epigenetic regulation of gene expression, but its specific effects and target genes remain unclear. To test whether IDH1 R132 mutations affect DNA hydroxymethylation and alter cell phenotypes in a manner that promotes prostate tumorgenesis, we generated a gain of function model in prostate epithelium. The prostate epithelial cell line RWPE was infected with retrovirus that expressed either WT or mutant IDH1 (R132H). RWPE cells expressing the R132H mutant produced 2HG at levels comparable to those measured in cancer cell lines with endogenous IDH1 mutations, whereas 2HG was not generated by IDH1 WT overexpression. Relative to WT-expressing cells or uninfected RWPEs we observed that global DNA hydroxymethylation levels were reduced in R132H-expressing cells. Moreover, our data suggest that this trend increases with time. The reduced DNA hydroxymethylation likely results from inhibition of TET2 and/or TET3, because TET1 mRNA was not detected in RWPE cells. Despite molecular changes associated with IDH1 R132H expression, proliferation was not affected when cells were cultured in complete media. However, 2HG conferred a growth advantage to RWPE cells cultured with reduced growth factor levels. Collectively our findings improve the understanding of how IDH1 mutations promote carcinogenesis with the goal of developing effective targeted therapies for the subtype of cancers that harbor IDH1 mutations.

Associated Cancer Types/Areas: prostate cancer, cancer metabolism, cancer epigenetics

Keywords: DNA hydroxymethylation, epigenetics, IDH1

70. Discovery of DNA-Bendability Motifs Using a Large, Random Library

Northwestern University PS-OC

DNA Information and Organization at Supranucleosomal Scales: Chromatin Folding and Higher Order Structure, Heterochromatin, and Domain-Wide Repression

Gabriel Rosanio, Jonathan Widom, John Marko, Olke Uhlenbeck*

**Deceased*

Northwestern University

The ability of DNA to bend or be bent is a mechanistic characteristic central to life. That specific DNA sequences are predisposed to existing in bent configurations has implications ranging from the tight packing of viral genomes into capsids and eukaryotic DNA into heterochromatin through nucleosome-wrapping to gene regulation through physical interactions with transcription factors. Further, highly bendable DNA has been associated with cancer-specific deletion and hereditary neuromuscular diseases among others. Being able to identify the intrinsic properties of DNA sequences that favor bendedness, therefore, is required to understand these fundamental processes and those diseases that arise when these processes are disrupted.

Though studies have been done on the bendability of DNAs of specific sequences, their results have led to differing, though not mutually exclusive, conclusions. Previous studies have suggested that the ability of short, specific DNA motifs to bend leads directly to large-scale bent DNA configurations. Others have indicated that bent DNA conformations in vivo are primarily the consequence of protein-DNA interactions which impose bending upon DNA. While subsequent studies have aimed at determining the bendability of DNAs in the absence of proteins which may enforce a specific geometry on DNA, they are still limited in their ability to explore the full depth and breadth of possible DNA sequence combinations.

Here we present a SELEX-based approach to discover DNA motifs that are highly-bendable in the absence of extraneous proteins. We started with a large pool (~7 x 1012 molecules) of short, random DNAs. Employing iterative rounds of selection based on traditional biochemical looping techniques that utilize low concentrations of T4 DNA ligase to trap DNAs whose ends came close together, we enriched the pool for those DNAs that preferentially exist in near-circular states nearly 6-fold over generic DNAs. Analyzing these DNA molecules with high-throughput sequencing, we have determined that there is a set of motifs that result in inherently cyclizable DNAs, and that the nucleosome positioning sequence (NPS) is a bending motif rather than a nucleosome-binding motif.

Associated Cancer Types/Areas: gene expression

Keywords: chromatin, gene expression

71. Effects of DNA Methylation on Nucleosome Stability: Insight Into the Mechanistic Behavior of Cancer Using Computational Studies

Northwestern University PS-OC

Tomekia Simeon, Mark Ratner, George C. Schatz

Northwestern University

Recent experimental studies suggest that the mechanical properties of a given DNA sequence dictate its nucleosome positioning propensity, and therefore may play an important role in gene regulation. In particular, the nucleosome affinity of DNA sequences is higher in sequences that have dinucleotide repeated every 10 bp. Likewise, CpG methylation of DNA is an epigenetic modification associated with the inactivation of transcription and the formation of a repressive chromatin structure. Understanding the changes in the structure of nucleosomes with various dinucleotide and upon CpG methylation and is necessary in providing insight of the mechanisms of gene repression. The Fragment-Molecular Orbital (FMO) and the Density Functional Theory-Symmetry Adapted Perturbation Theory (DFT-SAPT) methods were utilized to systematically study the stacking effects of two different (linear and bent) DNA fibers of 18 bps length as a function of both twist and rise (which is related to its bending propensity). The DFT-SAPT method provides insight into the π-stacking and hydrogen-bonded interactions of DNA structures on the basis of electrostatic and dispersion contributions. Results indicate sequences with CpG methylation along with specific dinucleotides have lower interaction energies-this is associated to higher nucleosome affinity. These findings suggest that changes in the physical properties of nucleosomes induced upon CpG methylation may contribute directly to the formation of a compacted chromatin structure.

Research Supported by NIH-PSOC grant #U354CA143869.

Associated Cancer Types/Areas: gene expression, epigenetics

Keywords: histone methylation, epigenetic, nucleosomes

72. The Involvement of TET1 in Prostate Cancer
Northwestern University PS-OC
Epigenetics in Prostate Cancer

Angela Yang, Jonathan Zhao, Longtao Wu, Jung Kim, Hongjian Jin, Chunxiao Song, Chuan He, Jindan Yu

Northwestern University

The recent breakthrough findings of TET1 and its catalytic product, 5-hydroxymethylcytosine (5hmC), in embryonic stem cells have substantiated the importance of epigenetic events in the process of development. In light of TET1's functions in reversing DNA methylation, which is a phenomenon frequently altered in various cancer types, it is now imperative to investigate what roles TET1 may play during carcinogenesis.

Here, we are using the model of prostate cancer, which is known to comprise copious number of epigenetic aberrations, to better understand how TET1 and 5hmC are involved in this context. Interestingly, we found that a protein (designated as xxx) of great importance in prostate cancer directly induces TET gene expression, consequently leading to corresponding changes in global 5hmC levels. Moreover, an examination of patient samples of normal and tumor tissues reveals a statistically significant correlation between Protein xxx and TET1. Using knockdown and overexpression assays, we demonstrated through qRT-PCR, western blot and immunofluorescence staining that this protein xxx positively regulates TET1 expression. Bioinformatics analysis of genomic landscapes of this protein, 5mC and 5hmC (performed by ChIP-seq and 5mC- or 5hmC-specific pulldown-seq) showed that binding sites of this protein tend to have lower level of 5mC but increased level of 5hmC. This result also points to a possible recruitment of TET1 by protein xxx to its own genomic loci, which could have significant implications in changing the surrounding chromatin conformation due to TET1's demethylating ability.

This result clearly suggests a potentially important function of TET1 in prostate cancer, likely through DNA demethylation and chromatin structure modification. Although further evidence is needed to strengthen the link between the two proteins, this cooperation between protein xxx and TET1 is a novel mechanism that can provide some new insights into prostate carcinogenesis.

Associated Cancer Types/Areas: prostate cancer, epigenetics

Keywords: prostate cancer, TET1, DNA hydroxymethylation

73. Micromechanical Properties of Mammalian Meiotic Chromosomes: High-Frequency Model of Genomic Instability That Phenocopies Cancer Pathogenesis

Northwestern University PS-OC

Jessica E. Hornick, Francesca E. Duncan, Teresa K. Woodruff, John Marko

Northwestern University

Prior to cell division, eukaryotic cells undergo a dramatic reorganization of chromatin whereby the long strands of DNA are bundled and condensed into the compact structures known as chromosomes. Proper chromosome condensation is essential for accurate segregation of homologous chromosomes or sister chromatids. The folding of the flexible chromatin fiber into a complex structure is due, in part, to the multi-subunit protein, condensin, and cells deficient in condensin fail to fold the chromatin properly, resulting in anaphase bridges and other defects. Meiosis is a specialized process with two sequential cell divisions that occur in the absence of an intervening interphase to produce haploid gametes. Compared to mitosis in healthy somatic cells, meiosis in the mammalian egg is remarkably error-prone, especially in females of advanced reproductive age. Thus, the mammalian egg represents a robust and unique model system to study molecular mechanisms of chromosome segregation errors and aneuploidy similar to what occurs in cancer cells. Measurement of the micromechanical properties of isolated individual chromosomes has provided a powerful tool for understanding the organization of chromosomes in mitotic cells of several species. However, the role of the micromechanical properties of mammalian chromosomes during meiosis is unknown.

Our objective is to analyze the chromosome micromechanics during meiosis in oocytes from young mice and old mice, which have been shown previously to have high rates of aneuploidy. Immature oocytes were collected from either young (6-8 weeks) or old (>14 months) naturally cycling animals and in vitro matured. Chromosomes were isolated from eggs arrested at metaphase of meiosis II and, with micromanipulation, stretched in order to measure the force constant of a single chromosome. We show here individual chromosomes can be efficiently isolated from mouse eggs arrested at metaphase of meiosis II and these meiotic chromosomes have reversible elasticity and a force constant on the piconewton scale. Meiotic chromosomes have a force constant that is significantly higher than has been measured in human mitotic cells (~3000 pN vs. ~300 pN), indicating either a species specific difference or an inherent difference in chromosome makeup between mitotic and meiotic chromosomes. We also demonstrate that chromosomes from young animals have a significantly smaller average force constant (1977±304 pN) when compared to chromosomes from older animals (4290±721 pN). There is a significant difference in the micromechanical properties of chromosomes from oocytes with higher frequency of aneuploidy, suggesting a possible role for the architecture of chromosomes in contributing to chromosome segregation errors.

Associated Cancer Types/Areas: chromosome structure, chromosome segregation errors, aneuploidy

Keywords: condensin, chromosome, cell division

74. Micromechanics of Human Mitotic Chromosome

Northwestern University PS-OC

DNA Information and Organization at Supranucleosomal Scales: Chromatin Folding and Higher Order Structure, Heterochromatin and Domain-Wide Repression

Mingxuan Sun, John Marko

Northwestern University

Eukaryote cells completely reorganize their long chromosomal DNAs to folded mitotic chromosomes to facilitate precise DNA segregation during mitosis. Errors in chromosome folding and segregation can result in severe chromosome damage during cell division. The question of how DNAs are folded into the compact X-shaped chromosomes has been an outstanding problem intricately related to control of cell growth and proliferation and gene regulation, and consequently a problem closely related to many genetic and developmental disorders and cancers. However, the internal organization of mitotic chromosomes remains unclear.

We report biophysical experiments on single mitotic chromosomes from human cells, where isolated single human chromosomes were studied by micromanipulation and nanonewton-scale force measurement to understand chromosome connectivity and topology. This approach can be applied to study the micromechanics of chromosomes from cancer versus non-cancer cells.

We further looked into the effect of RNAi knockdowns of a major chromosome-organizing protein—condensin on mitotic chromosome organization. We found the stiffness of human chromosomes goes down by almost 10 fold in condensin depleted cells, compared to wildtype cells. Immunofluorescent staining of condensin shows a punctuated pattern along the chromosome arms, indicating individual condensin clusters. Our studies provide a quantitative analysis of the effect of condensin on mitotic chromosome condensation.

Associated Cancer Types/Areas: chromosome structure, gene expression

Keywords: chromosome structure, chromosome micromechanics, condensin

75. Nucleosome Positioning Maps Examining the Role of PRC2/Eed in Embryonic Stem Cell Development
Northwestern University PS-OC
DNA Sequence-Encoded Nucleosome Positioning and Gene Regulation

Amy Sebeson, Jon Widom, Ji-Ping Wang, Alec Wang

Northwestern University

The polycomb complex (PRC2) is responsible for regulating embryonic stem cell differentiation, and is also a common enhancer of cancer cell invasiveness and metastasis. However, the precise molecular mechanism for the activation of this complex within the embryonic state is not completely understood. Since transcription is highly dependent on the surrounding chromatin structure, knowledge of the precise locations of nucleosomes is critical for understanding how embryonic stem cells (ESCs) regulate their genomes and how the process of PRC2 recruitment occurs.

To this end, we are generating nucleosome positioning maps in mouse ESCs, PRC2 mutant cells (Eed -/-), cells with the Eed mutation rescued, and MEF cells. Our approach will synthesize information from RNA-seq expression data, whole-genome nucleosome maps and high-resolution enriched nucleosome maps. The later are generated via a solution hybridization enrichment strategy where we isolate large (~150–200kbp) bacterial artificial chromosome (BAC) clones for regions of interest and use them to isolate and sequence mononucleosome DNAs that correspond to those regions.

By comparing nucleosome positions to predicted nucleosome occupancies, we can identify nucleosomes that are remodeled in vivo and hence likely correspond to important regulatory regions. This may allow us to identify new transcription factor (TF) binding sites and enhancer elements. Furthermore, this system is ideal for examining the chromatin landscape surrounding "pioneer" TFs, which could help explain their ability to initiate transcriptional networks. Finally, nucleosome positioning within PRC2-mutant cells may identify the signal for polycomb recruitment, and determine whether PRC2 is necessary for establishing bivalent chromatin signatures in ESCs.

Since genes regulating the embryonic state overlap with mis-expressed transcriptional programs in cancers, a more precise understanding of ESC transcriptional networks will also elucidate molecular mechanisms underlying cancer activation and can help target future therapeutics.

Associated Cancer Types/Areas: metastasis

76. Nucleosomes and Chromatin Architecture in the *Drosophila* Genome
Northwestern University PS-OC
DNA Sequence-Encoded Nucleosome Positioning and Gene Regulation

Rebecca Martin

Northwestern University

Precise timing and location of gene expression is imperative to the development and survival of an organism. Transcription can be regulated, in part by nucleosome occupancy along the DNA. We have established high-resolution genome wide maps of nucleosome positions in the *Drosophila* genome using micrococcal nuclease digestion of chromatin in a homogenous population of cells and high throughput parallel sequencing. These maps have been created both in vivo and in vitro and will be used to analyze the intrinsic organization of *Drosophila* chromatin architecture and to test whether nucleosome-nucleosome spacing is uniquely characterized between heterochromatin and euchromatin regions. Furthermore, in order to examine the role of the non-canonical linker histone, Histone H1 in *Drosophila* chromatin architecture, we have generated genome-wide maps of Histone H1 using chromatin immunoprecipitation/parallel DNA sequencing ("ChIP-Seq") methods We will use this map to determine the global occupancy of H1-containing nucleosomes, its relation to genomic features, and to compare underlying sequence preferences to bulk nucleosomes in vivo and in vitro. The overall aim of this research is to develop a detailed understanding of the key features that govern nucleosome organization in the multicellular metazoan organism, *Drosophila melanogaster*.

Knowledge of aspects of *Drosophila* chromatin architecture, including intrinsic differences between heterochromatic and euchromatic loci, the genomic function of linker histone H1 containing nucleosomes; and competition between nucleosomes and regulatory proteins will help to advance our understanding of higher eukaryotic nucleosome positioning and transcriptional regulation.

Associated Cancer Types/Areas: gene expression

Keywords: chromatin, nucleosomes

77. Optimizing Rate Constants in Epigenetic Markov Models
Northwestern University PS-OC
Dynamic Nucleosome Signatures in Cancer Development and Epigenetic Memory

Nir Yungster, William Kath, Dirk Brockmann, Yupeng Zheng

Northwestern University

Recently, a method was developed for conducting M4K - mass spectrometry-based measurement and modeling of histone methylation kinetics (Zheng et al. 2012). We have made improvements to this method by incorporating previously unused experimental statistics into our model-optimization procedure that results in significantly improved fits to experimental data. Accurately modeling methylation changes to histone proteins is essential to understanding the activities of methyltransferases such as EZH2, which has been linked to human B-cell lymphoma, or MMSET, which has been linked to multiple myeloma (MM). Among MM patients, 15-20% show a t(4:14) chromosomal translocation which leads to the overexpression of MMSET. Zheng et al. used MM cells with high MMSET expression to demonstrate the potency of their M4K approach. By comparing the results from a targeted knock-out of MMSET to a non-targeted knock-out, they obtained a measured decrease in methylation rates.

Our model, with its improved modeling of such rates, can be incorporated in testing the effectiveness of drug therapies that might target the activities of methyltransferases. Among the adjustments we made to improve the calculation of these rates was an alteration to the optimization cost function to weigh deviations between our model and individual data points based on the precision of those experimental values. Additionally, we imposed new error terms to the optimization cost function to ensure that for large time, our dynamical model agrees with the steady-state behavior observed in experiment.

Associated Cancer Types/Areas: multiple myeloma, kinetic modeling

Keywords: histones, epigenetics, modeling

78. A Single-Nucleotide Resolution Map of Nucleosomes in *Schizosaccharomyces Pombe*
Northwestern University PS-OC
DNA Information and Organization at Supranucleosomal Scales

Tetiana Zaichuk[1], Erin Georette[2], Heyrman Moyle[2], Robert A. Holmgren[1], Olke C. Uhlenbeck[1], Jonathan Widom[1], Liqun Xi[1], Qingyang Zhang[1], Quanwei Zhang[1], Jiping Wang[1]

[1]Northwestern University, [2]University of Illinois

The packaging of eukaryotic genomes into nucleosomes plays critical roles in chromatin organization and gene regulation. A recently developed approach based on chemical modification of engineered histones has been used to obtain a base pair resolution map of genome-wide nucleosome positions in fission yeast *Schizosaccharomyces pombe* (*S. pombe*). Evolutionary aspects of nucleosome positioning mechanisms have been assessed by comparing nucleosome chemical maps of *S. pombe* and budding yeast *Saccharomyces cerevisiae* (*S. cerevisiae*). While broadly similar, several aspects of nucleosome biology have diverged. The extent of nucleosome depletion over restrictive polypurine tracts varies between species. In *S. pombe* increased poly (dG) repelling is compensated via diminished poly(dA) repulsion. The enrichment of A/T dinucleotides around the dyad in *S. pombe* is more pronounced. Opposite to *S. cerevisiae*, the A/T fraction at the nucleosome edges and linker regions of *S. pombe* is lower than the genome average. *S. pombe* promoters are more covered and the -1 nucleosome occupancy is correlating negatively with gene expression. The nucleosomes around transcriptional start site have bidirectional phasing when intergenic distance is relatively short. Heterochromatin regions tend to have sparse nucleosome positioning, mixed with both well-positioned and fuzzy nucleosomes.

This study advanced our understanding of relative importance of intrinsic determinants and trans-acting factors in genome-wide species-specific positioning of nucleosome.

Associated Cancer Types/Areas: gene expression, epigenetics

Keywords: nucleosome, *Schizosaccharomyces pombe*, chemical map

79. Understanding the Role of Disulfides in Metaphase Chromosome Structure and Its Link to Genetic Diseases

Northwestern University PS-OC
DNA Information at Larger Length Scales

Adrienne Eastland

Northwestern University

During mitosis, chromatin fibers are packaged by proteins into highly condensed structures that form metaphase chromosomes. Chromosome structures at these different periods of the cell cycle have been intensely studied, yet no clear picture of large-scale structure exists for mitotic chromosomes. Dounce (1973) suggested a possible mechanism for achieving the striking degree of chromatin condensation that occurs at the onset of mitosis might involve formation of interprotein disulfide bridges. Also, Olszewska and Marciniak (1990) claim that changes in redox state can alter chromosome structure during metaphase due to the formation of disulfide bonds. Previous micromanipulation methods investigating mitotic chromosome structure of newt (*Notophthalmus viridescens*) cells in our lab (Poirier and Marko 2002), showed that treating metaphase chromosomes with reducing reagents changed chromosome elasticity and shape.

We hypothesize that this phenomenon was due to the reduction of disulfide bonds in metaphase chromosomes, which is surprising in light of the conventional understanding of the redox state in cells, which is thought to be reducing. Therefore, I proposed using human embryonic kidney (HEK) 293 cells as a model to examine the possibility that disulfide bonds play a structural role in stabilizing metaphase chromosomes. Information derived from this model will provide valuable data for the analysis of normal cell division, gene regulation, and genetic diseases. Collection of metaphase chromosomes from HEK293 cells was completed using a chromosome purification protocol developed by Sone (2002) with minor modifications. The next step is to isolate disulfide-containing proteins using SDS-PAGE combined with mass spectrometry for analysis. This technique will identify reducing-reagent-sensitive proteins that are essential for chromosome structure and function. This research represents the first compositional view of the role of disulfides in maintenance of metaphase chromosome structure and provides a protein framework for future research on this topic.

Associated Cancer Types/Areas: chromosome stability

Keywords: chromosome organization

80. Communicate Effectively With PS-OC Colleagues, for Patients' Sake!

Princeton University PS-OC

Deborah Collyar[1], *Carole Baas*[2]

[1]*Princeton University,* [2]*NCI Office of Advocacy Relations*

Each Physical Sciences in Oncology Center (PS-OC) offers stimulating opportunities to work with new colleagues and explore new areas of science that can potentially reverse the mechanisms that currently allow cancer cells to evade therapies and preventive efforts. To achieve success (i.e. translate progress to humans) internally and throughout the PS-OC network, all members must quickly learn how to work together effectively.

Challenges always arise when bringing different fields together, even when participants are willing. Disparate cultures, concepts, approaches, and terminology can stymie true progress without a clear commitment and path to resolve issues. Too often, science programs overlook the importance of communication strategies that help members bridge pervasive gaps between disciplines. Once these gaps are addressed, enhanced collaborations can commence with other PS-OCs, external stakeholders, and the Public.

This poster presents commonly accepted communication strategies and techniques used for human interaction (not communication systems) in business and healthcare to consider their utility within the PS-OC Program. The intent is to find tools to accelerate effective internal and external communication that supports PS-OC collaborations, and produces better results for cancer patients and those at high risk.

Concepts include:

- Questioning hidden assumptions within each discipline
- Respecting differences
- Adjusting body language
- Considering context
- Listening to feedback
- Creating ACTIONABLE goals
- Solving problems successfully

Since language can be a key obstacle, the "Words Matter" series from Patient Advocates In Research (PAIR) will be highlighted to show how common terms used in physics and cancer biology actually mean very different things. While debate may be attractive, most scientific controversies have little relevance for the Public. This is why the focus relies on building common understandings in order to solve problems that can achieve better cancer prevention, treatment, and care for people.

Associated Cancer Types/Areas: several cancer types or areas may be used to illustrate concepts

Keywords: communication, effectiveness, results

81. Deterministic Separation of Cancer Cells From Blood at 10 mL/min
Princeton University PS-OC
Physical Ecology Design and Capabilities

Joseph D'Silva[1], Kevin Loutherback[2], Liyu Liu[3], Amy Wu[1], Robert H. Austin[1], James C. Sturm[1]

[1]Princeton University, [2]Lawrence Berkeley National Laboratory, [3]Chinese Academy of Sciences

Circulating tumor cells (CTCs) and circulating clusters of cancer and stromal cells have been identified in the blood of patients with malignant cancer and can be used as a diagnostic for disease severity, assess the efficacy of different treatment strategies and possibly determine the eventual location of metastatic invasions for possible treatment. There is thus a critical need to isolate, propagate and characterize viable CTCs and clusters of cancer cells with their associated stroma cells. Here, we present a microfluidic device for mL/min flow rate, continuous-flow capture of viable CTCs from blood using deterministic lateral displacement (DLD) arrays. We show here that a DLD array device can isolate CTCs from blood with capture efficiency greater than 85% CTCs at volumetric flow rates of up to 10 mL/min with no effect on cell viability.

Associated Cancer Types/Areas: breast, prostate

Keywords: circulating, blood, capture

82. Evolution and Morphology of Microenvironment-Enhanced Malignancy of Three-Dimensional Invasive Solid Tumors

Princeton University PS-OC
Project: Stress-Induced Changes in Nuclear Structure

Yang Jiao, Salvatore Torquato

Princeton University

The emergence of invasive and metastatic behavior in malignant tumors can often lead to fatal outcomes for patients. Complex tumor-host interactions and the interactions between the tumor cells leading to such malignant tumor behaviors are currently poorly understood. We have employed a cellular automaton (CA) model to investigate microenvironment-enhanced malignant behaviors and morphologies of avascular invasive solid tumors in three dimensions. Our CA model incorporates a variety of microscopic-scale tumor-host interactions, including the degradation of the extracellular matrix by the malignant cells, nutrient-driven cell migration, and pressure buildup due to the deformation of the microenvironment by the growing tumor and its effect on the local tumor-host interface stability. Moreover, the effects of cell-cell adhesion on tumor growth are explicitly taken into account. Specifically, we find that while strong cell-cell adhesion can suppress the invasive behavior of the tumors growing in soft microenvironment, cancer malignancy can be significantly enhanced by harsh microenvironment conditions, such as exposure to high pressure levels. We ascertain a qualitative "phase diagram" that characterizes the malignant behavior of invasive solid tumors in terms of two competing malignancy effects: rigidity of the microenvironment and cell-cell adhesion. An interesting feature of the diagram is a "phase transition" between noninvasive and invasive behaviors.

Associated Cancer Types/Areas: metastasis, microenvironment

Keywords: invasive tumor, microenvironment, morphology and evolution, 3D simulation

83. Evolution of Radiation Resistance in a Complex Microenvironment
Princeton University PS-OC
The Physical Environment in Cancer Invasion

Tamir Epstein[1], Robert Austin[1], So Hyun Kim[2], Monal Mehta[3], Tif Kahn[3]

[1]Princeton University, [2]Ehwa Womans University, [3]Cancer Institute of New Jersey

Radiation treatment responses in brain cancers are typically associated with short progression-free intervals in highly lethal malignancies such as glioblastomas. Even as patients routinely progress through second and third line salvage therapies, which are usually empirically selected, surprisingly little information exists on how cancer cells evolve resistance. We will present experimental results showing how in the presence of complex radiation gradients evolution of resistance to radiation occurs.

Associated Cancer Types/Areas: brain

Keywords: radiation, resistance, evolution

84. Evolution and the Selective Excision of Cryptic Phages in Bacteria Under Antibiotic Stress
Princeton University PS-OC
Bacterial Model Ecologies

John Bestoso[1], Qiucen Zhang[2], Saurabh Vyawahare[1], James C. Sturm[1], Hyunsung Kim[3], Nader Pourmand[3]

[1]Princeton University, [2]University of Illinois, [3]University of California, Santa Cruz

Bacteria have taken advantage of the lysogenic insertion of phage DNA into their genome by using the expression of phage genes to the bacteria's, not the phage's, advantage. These inserted phage genes have lost their lytic phenotype with time and are called cryptic prophages. In this work, we use de novo whole genome sequencing to compare the evolution dynamics of the emergence of resistance to ciprofloxacin from two distinct but well characterized genomic strains (wild type and Growth Advantage in Stational Phase (GASP) mutants) in a microfabricated complex ecology in which motility confers an evolutionary advantage. While we show somewhat expectedly that the mutated sigma factor in the GASP strain leads to rapid and deterministic fixation of different but spatially correlated mutations in the gyrA gene to the wild-type evolved strain, more unexpected is the excision of the e14 protophage only in the evolved GASP strains. We believe that because motility gives a fitness advantage in our microfabricated complex ecology, the ecological selection pressure of motility leads to the selective excision of the prophage e14, since the prophage e14 confers biofilm formation ability in the wild-type. Supression of biofilm formation by selective excision of the prophage e14 makes sense from an evolution perspective.

Keywords: bacteria, phages, evolution

85. Heterogeneity in Cell-Matrix Adhesion as an Indicator of Metastatic State

Princeton University PS-OC
Pilot Project: Adhesive Heterogeneity as an Indicator of Metastatic State

Alexander Fuhrmann[1], Adam Engler[1], Thea Tlsty[2]

[1]University of California, San Diego, [2]University of California, San Francisco

Cancer cells have great genetic diversity, which may be reflected in the variation in metastatic potential. As it has been difficult to determine a comprehensive set of genetic markers to define a metastasizing cell population, we propose to examine a common behavior, i.e. cell-matrix adhesion, that may be differentially regulated in metastasizing versus non-metastasizing cancer cells. To assess cell-matrix adhesion strength in a heterogeneous population of breast cancer cells, we employed a spinning disc device where cells adhering to matrix-coated substrates were exposed to radially-dependent shear. Within a cell population, those at the center or edge experience low or high matrix detachment forces, respectively. Exposure to acute shear for a highly metastatic cancer cell line, i.e., MDA-MB-231, resulted in a broadly distributed population of cells unlike the sigmoidal, homogeneous shear response observed from non-metastatic, non-malignant, or somatic cell lines, MCF7, MCF10A, NIH 3T3 fibroblasts, respectively. This suggests that adhesion strength differences may scale with cell state with the most metastatic cells coming from high shear regions. Magnesium and calcium concentration differences have been reported between stroma and tumors, which are also involved in regulating integrin activation. While there was an up to 2-fold increase in adhesion strength for MCF7 or MCF10A cells in the presence of 0.5 mM magnesium, MDA-MB- 231 cells exhibited a 10-fold increase in adhesion strength and also developed a sigmoidal, homogeneous shear response when exposed to 0.5 mM magnesium and/or calcium. The average attachment strength as well as the restoration of attachment-homogeneity gradually increases with cation concentration with the most drastic increase occurring between 10uM to 0.5mM, which falls within the physiological range for both stroma and tumor. This observation indicates that variances in attachment strength in the absence of cations may be dependent on cell state. Indeed, when selecting only strongly attaching cells (in the absence of exogenous cations), we found that those cells maintain their strong attachment phenotype, but over time stochastically return to heterogenous adhesion strength. These findings suggest a potential mechanism to differentially regulate metastasizing cell adhesion, and also support using population-based adhesion assays to assess adhesion heterogeneity and select those cells that may have the highest metastatic potential.

Associated Cancer Types/Areas: breast cancer, metastasis

Keywords: cell adhesion, metastasis, heterogeneity

86. Mesoscopic Evolution in Bacteria
Princeton University PS-OC
Bacterial Model Ecologies

Qiucen Zhang[1], Saurabh Vyawahare[2], Alexandra Lau[3], Jonas Pedersen[4], Julia Bos[2], Robert H. Austin[2]

[1]University of Illinois, [2]Princeton University, [3]Mount Holyoke College, [4]University of Denmark

This experimental work uses a master equation approach to model single cell internal error-prone chromosome replication, which we show yields the Gompertz probability distribution function for evolution dynamics. The Gompertz probability distribution can be used to model how some organisms evolve rapidly, after a long lag period, resistance to a drug. At the core of the Gompertz equation lies a hazard term which is not constant but increases exponentially with time. That prediction is verified using filamenting *E. coli* under the influence of the genotoxic antibiotic ciprofloxacin. The mesoscopic ecological niche created within the single individual bacteria by filamenting ultimately yields resistant progeny.

Keywords: bacteria, mesoscopic evolution, resistance

87. Metastatic Breast Cancer Cells Collectively Invade Collagen by Following a Glucose Gradient
Princeton University PS-OC
Physical Ecology Design

Robert Austin[1], Liyu Liu[2], Guillaume Duclos[3], Bo Sun[1], Jeongseog Lee[1], Amy Wu[1], Yooseok Kam[4], Eduardo Sontag[5], Howard Stone[1], James Sturm[1], Robert Gatenby[4]

[2]Princeton University, [2]Chinese Academy of Sciences, [3]Physico-Chimie Curie, [4]H. Lee Moffitt Cancer Center & Research Institute, [5]Rutgers University

We show that MDA- MB-231 metastatic breast cancer cells collectively invade a three dimensional collagen matrix by following a glucose gradient. We observe that due to the 3D physical deformation of the matrix, as measured by the displacement of reporter beads within the matrix, there exists a long range deformation mechanical field inside the matrix which serves to couple the motions of the invading metastatic cell. The invasion front of the cells is a dynamic one, with different cells assuming the lead on a time scale of 24 hours due to certain cells having higher speeds of penetration, which are not sustained. The front cell leadership is dynamic presumably due to metabolic costs associated with the long range strain field which proceeds the invading cell front, which we have imaged using confocal imaging and marker beads imbedded in the collagen matrix.

Associated Cancer Types/Areas: breast cancer, metastasis

Keywords: collective, invasion, glucose gradient

88. Modeling the Switch From Tumor Dormancy to Rapid Proliferation

Princeton University PS-OC
Project 4: Physical Ecology and Design

Duyu Chen, Yang Jiao, Salvatore Torquato

Princeton University

Malignant cancers that lead to fatal outcome for patients may remain dormant for a very long period of time. Although certain mechanisms have been proposed, cancer dormancy is currently not well understood from both a basic and clinical point of view. Modeling, however, can be a powerful way to provide insights into the cancer dormancy mechanisms. Here we employ a cellular automaton model that incorporates a variety of cell-level tumor-host interactions and different mechanisms for tumor dormancy, including the effects of the immune system and angiogenesis. Our model predicts a switch behavior from a dormant state to a rapid proliferation state. Our results show that for certain parameter regimes, our model possesses an emergent behavior that leads to a "switch" in the tumor's state from dormant to active, which can be viewed as a phase transition. Insights from this work may also help to suggest new early detection cancer techniques.

Associated Cancer Types/Areas: brain cancer, pancreatic cancer, metastasis, microenvironment

Keywords: cancer dormancy, immunosurveillance, CA model

89. The Positioning Logic and Copy Number Control of Genes in Bacteria Under Stress
Princeton University PS-OC
Bacterial Model Ecologies

Saurabh Vyawahare[1], Robert Austin[1], Qiuchen Zhang[2], Alexandra Lau[3]

[1]Princeton University, [2]University of Illinois, [3]Mount Holyoke College

Escherichia coli (*E. coli*) cells when challenged with sublethal concentrations of the genotoxic antibiotic ciprofloxacin cease to divide and form long filaments which contain multiple bacterial chromosomes. These filaments are individual mesoscopic environmental niches which provide protection for a community of chromosomes (as opposed to cells) under mutagenic stress and can provide an evolutionary fitness advantage within the niche. We use comparative genomic hybridization to show that the mesoscopic niche evolves within 20 minutes of ciprofloxacin exposure via replication of multiple copies of genes expressing ATP dependent transporters. We show that this rapid genomic amplification is done in a time efficient manner via placement of the genes encoding the pumps near the origin of replication on the bacterial chromosome. The de-amplification of multiple copies back to the wild type number is a function of the duration is a function of the ciprofloxacin exposure duration: the longer the exposure, the slower the removal of the multiple copies.

Keywords: gene positioning, stress, exposure

90. Princeton PS-OC Microfluidic Core Facility

Princeton University PS-OC
Core 1: Microfluidics Core Facility

Saurabh Vyawahare

Princeton University

The Microfluidics Facility (http://www.princeton.edu/microfluidics) is one of the three core facilities of the Princeton PSOC . Our mission is to make micro-fabrication/microfluidic technologies accessible to the widest set of researchers and students, both for research and for education. We own and operate a suite of equipment and clean-room space that allows members to make devices at the micrometer scale, and then use them to perform biological experiments, all at one location. One of our courses is the annual Microfluidics Bootcamp held at the beginning of August. Last year, we hosted 19 students for this week-long course. The course consisted of a series of lectures and hands-on lab work, constituting a broad introduction to microfluidics. Participants successfully built their own microfluidic devices from start to finish and performed several experiments using them. The material from this course is posted on our website. We will conduct our third camp July 29 – August 9, 2013, building on last year's experience.

Keywords: microfluidics

91. Rapid Adaptation and Evolution of Drug Resistance of Cancer

Princeton University PS-OC

Project 4: Physical Ecology Design and Capabilities

Amy Wu[1], Qiucen Zhang[1], Guillaume Lambert[2], Zayar Khin[3], Ariosto Silva[3], Robert A. Gatenby[3], Robert H. Austin[1], James C. Sturm[1]

[1]Princeton University, [2]New York University, [3]H. Lee Moffitt Cancer Center & Research Institute

In order to understand how cancer adapts to chemotherapy rapidly, we build a microfluidic platform to mimic the drug gradients in tumor microenvironment to observe the long-term (multiple generation) dynamics of cancer.

We show that MDA-MB-231 breast cancer cells are able to divide in the high doxorubicin region (>160nM) over 72 hours, in contrast to their behavior in a uniform doxorubicin environment. Characterization of the cell motion showed that their short-range migration (<300 microns over 72 hours) did not help them to gain growth advantage. The profiles of cell growth vs time in different regions in the gradient environment suggest that communication of signals promoting drug resistant growth from cells in regions of low drug concentration to those in adjacent regions of higher concentration may be occurred.

We also study the evolution of drug resistance in multiple myeloma by incorporating the idea of microhabitats, which segregate the population of cells, to enhance the fixation rate of the mutation. This model system has been demonstrated in our previous bacteria model, which shows the acceleration of emergence of antibiotic resistance. In the myeloma system, colonies of drug-resistant cells emerge from regions with low drug concentration toward the regions with high drug concentration in 2 weeks. The IC50 of these resistant cells increased 16-fold compared to their parental wild type. These resistant cells also express more drug pumps then the wild type. By sequencing the whole transcriptome of these myeloma cells, we are looking for genetic signatures for the cells to acquire drug resistance.

Associated Cancer Types/Areas: multiple myeloma, breast cancer, microenvironment

Keywords: evolution, population dynamics, microfluidics

92. Rapid Evolution of Drug Resistance of Multiple Myeloma in the Microenvironment With Drug Gradients

Princeton University PS-OC
Physical Ecology Design and Capabilities

Amy Wu[1], Qiucen Zhang[2], Guillaume Lambert[3], Zayar Khin[4], Ariosto Silva[4], John Kim[5], Nader Pourmand[5], Robert A. Gatenby[6], Robert H. Austin[7], James C. Sturm[7]

[1]Princeton University, [2]University of Illinois, [3]University of Chicago, [4]Salk Institute, [5]University of California, Santa Cruz. [6]H. Lee Moffitt Cancer Center and Research Institute, [7]Princeton University

Drug resistance in cancer is usually caused by the spatial drug gradients in tumor environment. Here, we culture multiple myeloma in a gradient from 0 to 20 nM of doxorubicin (genotoxic drug) across 2 mm wide region for 12 days. The myeloma cells grew rapidly and formed 3D colonies in the regions with less drug concentration. However, we have seen emergent colonies forming in regions with drug concentration above the minimal inhibitory concentration in less than one week. Once the cells have occupied the regions with less drug concentration, they tend to migrate toward the regions with higher drug concentration in a collective behavior. To characterize their resistance, we collect them from this microfluidic system, for further analysis of the dose response. We find that the IC50 (drug concentration that inhibits 50% of controlled population) of the cells, undergone a drug gradient, increase 16-fold of the wildtype cells. We further discover that these resistant cells express more Multidrug Resistance (mdr) protein, which pumps out the drugs and causes drug resistance, than the wildtype. Our current works on RNA-sequencing analysis may answer other expression mechanisms that may confer the drug resistance.

Associated Cancer Types/Areas: multiple myeloma, microenvironment

Keywords: resistance, drug gradients, evolution

93. Single-Cell Sequencing Reveals Genetic Heterogeneity in Cell Population

Princeton University PS-OC

Nano-Analysis Shared Resource, Single-Cell Sequencing

Mei-Chong Lee[1], Fernando Lopez-Diaz[2], Beverly Emerson[2], Muhammad Tariq[1], Shahid Khan[1], Hyunsung Kim[1], Amie Radenbaugh[1], Nader Pourmand[1], Charlie Vaske[2], Robert H. Austin[4]

[1]University of California, Santa Cruz, [2]Salk Institute for Biological Studies, [3]Five3 Genomics LLC, [4]Princeton University

Intratumor genetic heterogeneity has long been observed through various methods, including cell staining, spectral karyotyping, and fluorescent in situ hybridization (FISH), which allow pathologists to directly visualize any chromosomal abnormality in each individual cell. Through these methods, we now appreciate that cancers can contain multiple different clonal populations, where each population might exhibit different cellular properties, including grow rate, gene expression profile, ability to metastasize, and drug sensitivity. Since the establishment of the next generation sequencing, many studies had been performed to analyze and characterize cancer genomes and transcriptomes. But only a few studies have addressed the tumor heterogeneity through next generation sequencing. The current level of sequencing error (0.1%-1%) often masks low-abundance mutations. Majority of the low-abundance mutations are only present in a limited number of cells. In order to improve the sensitivity of detecting low-abundance mutations, we identified the expressed single nucleotide variants (SNVs) at the single cell level using next generation sequencing. Here we describe the genomic analyses of single cells that demonstrate the claim that no two cells are alike, even when they are clonal. In this study, we used the Human breast carcinoma cell line, MDA-MB-231. We treated the cells with a chemotherapy drug, paclitaxel, commercially known as Taxol. We performed RNA sequencing on both single cells and population cells for the untreated and Taxol-treated survivor cells. We identified thousands of low abundance expressed SNVs in single cells that are undetectable at the population level. On average, single cells only share 25% of the private expressed SNVs amongst each other. We also performed deep DNA sequencing to construct the reference genome of the MDA-MB-231 cell line for identifying the RNA-DNA differences. We confirmed the accuracy of our variant calls using pyrosequencing.

Associated Cancer Types/Areas: breast, metastasis

Keywords: single-cell, RNA-Seq, mutations

94. The Thermodynamics of Cancer

Princeton University PS-OC
Information Sciences Institute

Nathan Hodas

University of Southern California

The laws of physics demand that (1) any organism must retain sufficient energy reserves to survive until reproduction and (2) survival requires continual expenditure of energy. Organisms often evolve to minimize such expenditures, expressed as the "principle of least effort." Additionally, evolution also favors short-term, costly choices that are outweighed by long-term free-energy gains. For example, squirrels store nuts for the winter. It often seems that cancer, on the other hand, is favoring short-term reproduction over long-term success, at least with respect to the life of the organism. Is this true, or is cancer, in fact, thermodynamically favorable? Answering this question requires a deeper understanding of the thermodynamics of cancer and of evolution in general.

Each cancer is different, and their evolutionary pathways are complex and stochastic. Yet, all living organisms obey the laws of thermodynamics. Cancer is known to undergo metabolic shifts during its evolution, so energy plays an essential role. Thermodynamic observations made in vitro are essential to understanding the complex interactions between cancer and the body. Dynamically measurements of thermodynamic observables could be used to understand and predict evolutionary pathways, but the precise nature of these observables remains unknown. I suggest theory and experiments that may provide insight into these observables, and how they could be manipulated to optimize treatment protocols to favor successful outcomes, instead of encouraging the cancer down its all-consuming, often fatal, pathway.

Keywords: thermodynamics, evolution

95. Automated Cell Classification using Low Dimensional Feature Extraction and Representation

The Scripps Research Institute PS-OC
RP2: Topology

Tegan Emerson[1], Michael Kirby[1], Peter Kuhn[2], Paul Newton[2], Stephen O'Hara[1], Mohsen Sabouri[2], Anand Kolatkar[2]

[1]Colorado State University, [2]The Scripps Research Institute

We aim to automate the detection of circulating tumor cells utilizing methods in pattern analysis and computer vision. We have proposed a descriptor based on a concentric ring structure which exploits the size and circular nature of the cells implicitly. We have also employed the Fourier transform which has a natural rotational invariance due to its periodicity. Working towards this aim we have generated a curated data set on which to test the descriptor. Using the described feature representation on our curated cells we achieved average correct classification rates of 99.4% in the two class classification problem of separating white blood cells from circulating tumor cells. Based on the strength of these results we will begin searching for subclassifications of cells based on these descriptors. It is our hope to discern additional cell subtypes which may aid in additional diagnostic information.

Associated Cancer Types/Areas: classification of circulating disease-related cells from cancers with epithelial origin

Keywords: classification, feature extraction, circulating tumor cells

96. Cancer Heterogeneity, CTCs, and Metastasis: Staring at the Tip of the Iceberg
The Scripps Research Institute PS-OC
Project 2: Typology

Randolph L. Schaffer[1], Peter Kuhn[1], Kelly Bethel[1], Angel Edago[1], Maddy Luttgen[1], Jim Hicks[2]

[1]The Scripps Research Institute, [2]Cold Springs Harbor Laboratory

Background: Of the over 600 archived blood samples collected from Hepatocellular carcinoma (HCC) patients, we have to date processed 81 samples for the presence of Circulating Epithelial Cells (CEpCs: cytokeratin +, DAPI +, CD45 –), of which 28 had greater than 5 CEpCs/mL (mean=19.6 cells/mL, range 0-473). Preliminary data on several of our archived HCC samples demonstrates the presence of CEpCs in HCC patients both before and during liver transplantation. Of interest, some of the intraoperative samples following regional blood flow occlusion to allow for implantation of the new liver show a dramatically increased number of CEpCs. This is true even in the single control patient in our series who did not have cancer in his liver at the time of transplant. This raised the question of whether all or any of these circulating epithelial cells are tumor cells (CTCs).

Study Design: In collaboration with Cold Spring Harbor Laboratory, we utilized single cell genomic copy number variation (CNV) as a method of CEpC and tissue sample interrogation. The method of copy number profiling and lineage analysis of cancer cells is based on using the distribution of sequence reads from low coverage Illumina Next-Gen DNA sequencing to infer the copy number profile and genomic rearrangements from DNA amplified from individual cells. A typical 'first draft' profile is deduced from 1-2 million uniquely mapping reads after filtering for sequence quality and removal of PCR duplicates. To obtain a copy number profile, the uniquely mapping reads for each sample are grouped representing contiguous locations along the reference genome and the resolution of the profile can be adapted to the read content and the purpose of the test.

Results: We will review the results of CNV analysis performed on tumor samples and CTCs from a patient with HCC who underwent liver transplantation and subsequently developed metastatic HCC 20 months later in the transplanted liver, bone and peritoneal cavity.

Associated Cancer Types/Areas: liver cancer, metastasis, CTCs

Keywords: CTC, metastasis, genomics

97. Colon Adenocarcinoma Cell Recruitment to Platelets and Thrombi Under Shear

The Scripps Research Institute PS-OC
Project: 4DB

Sandra Baker-Groberg, Asako Itakura, András Gruber, Owen J.T. McCarty

Oregon Health & Science University

Cancer metastasis involves separation of cancer cells from a primary tumor, entrance of tumor cells into the blood or lymphatic circulation, adhesion to or entrapment at a distal site, and proliferation to form of a secondary tumor. The anatomical site-specificity of cancer metastasis, the effect of antithrombotic treatments on metastasis, and the role of the vessel microenvironment in cancer metastasis remain to be explored. We aimed to investigate the kinetics and molecular mechanisms of metastatic colon adenocarcinoma cell recruitment to fibrillar proteins and thrombi under shear flow, ex vivo.

SW620 cells ($1x10^6$ cells/mL; colon adenocarcinoma cells from lymph node) were perfused over immobilized fibrillar collagen, fibrinogen, laminin, fibronectin, or von Willebrand factor at physiologically relevant shear rates ranging from 25 to 200 s^{-1}. Platelet aggregates were formed by perfusing citrate anticoagulated whole blood over fibrinogen or collagen. Thrombi were formed by perfusing recalcified whole blood over fibrinogen or collagen in the presence of coagulation. Tumor cells were perfused either during or following platelet aggregate or thrombus formation. The role of polymorphonuclear leukocytes (PMNs) in tumor cell recruitment was investigated by perfusing purified PMNs over both platelet aggregates and thrombi. The degree of transient tumor cell interactions (recruitment, rolling and release) and the number of firmly adhered tumor cells were quantified using fluorescence microscopy.

The extracellular matrix proteins, fibrillar collagen, fibrinogen, laminin, fibronectin, and von Willebrand factor supported tumor cell recruitment and adhesion in a shear-dependent manner, with a maximal degree of binding observed at the lowest shear rate (25 s^{-1}). The rate of transiently interacting SW620 cells varied from nearly 200 cells/mm^2/min on collagen to less than 30 cells/mm^2/min on fibrinogen. Platelet aggregates and thrombi formed on either fibrinogen or collagen supported SW620 cell interactions and adhesion under shear. Increased SW620 cell interactions and binding was observed on platelet aggregates and thrombi formed on collagen as compared to fibrinogen. Moreover, thrombi supported a greater degree of SW620 cell interactions and adhesion as compared to platelet aggregates formed on either collagen or fibrinogen. Interestingly, in the absence of anticoagulation, we observed SW620 preferentially binding to clot-bound leukocytes. Along these lines, addition of purified leukocytes ($1x10^6$ PMNs/mL) to thrombi resulted in a doubling of the number of interacting and bound SW620 cells.

Our findings demonstrate that colon adenocarcinoma cell tethering, rolling and firm adhesion to extracellular matrix proteins, platelet aggregates, leukocytes, and thrombi under flow are enhanced in recalcified blood and reduced by shear. The results suggest that metastasizing cancer cells may preferentially home to sites of blood vessel injury and inflammation that induce local thrombin generation.

Associated Cancer Types/Areas: metastatic colon adenocarcinoma

Keywords: cancer, thrombosis, platelets

98. Comparing the Complexity of Metastatic Cancer

The Scripps Research Institute PS-OC
RP3 Equations of Topology, USC Viterbi School of Engineering

Jeremy Mason, Paul K. Newton

University of Southern California

We present a comparative study of breast, colon, lung, and prostate cancer complexity based on a notion of `network entropy' and metastatic pathway diagrams obtained from ensemble averaged Markov transition matrices for each primary cancer type. The transition matrices are obtained by solving a constrained linear optimization problem so that the steady-state matches the metastatic tumor distribution from autopsy data sets of untreated cancer victims (1914-1943). The two main drivers of network complexity are (i) N, the number of metastatic sites, and (ii) the probability distribution associated with those sites. This is captured by calculating the Shannon entropy associated with the metastatic tumor distributions. We show that the Markov chain model obeys the 2nd law of thermodynamics, namely the Shannon entropy increases as the disease progresses in time from the primary tumor. Since convergence to the steady-state occurs after (roughly) two steps, we rank order all two-step pathway probabilities emanating from the primary tumor location to construct reduced order models based on the top 30 two-step pathways. These models are reduced further to compare the complexity using a fixed percentage (35%) of cumulative two-step pathways. We use the Kullback-Leibler divergence to quantify the `distance' between each metastatic distribution from the `generic' cancer distribution based on all cancer types.

Associated Cancer Types/Areas: lung, breast, colon, prostate, metastasis

Keywords: Markov chain, metastasis, entropy

99. Dynamic Changes in Circulating Tumor Cell Levels as a Prognostic Marker in Stage IV Non-Small Cell Lung Cancer (NSCLC)

The Scripps Research Institute PS-OC
Project 3: Equations of Metastasis

Lyudmila Bazhenova[1], Anders Carlsson[2], Anand Kolatkar[2], Madelyn Luttgen[2], Kelly Bethel[2], Jorge J. Nieva[3], Peter Kuhn[2]

[1]University of California, San Diego, [2]The Scripps Research Institute, [3]Billings Clinic

We have previously reported the performance of immuno-enrichment free High Definition CTC (HD CTC) assay in the enumeration and characterization of circulating tumor cells (CTCs) in NSCLC. In the HD-CTC assay, nucleated cells are fluorescently labeled and imaged using automated microscopy. CTCs are defined as morphologically distinct, cytokeratin positive, CD45 negative cells. Here, we investigate how CTCs and their physical properties relate to prognosis and treatment outcome prediction in 362 blood samples collected longitudinally from 81 Stage IV NSCLC patients. Blood was collected at time of enrolment, 3 weeks later, and every 3 months thereafter. The collection protocol was restarted at disease progression, resulting in a sample number ranging between one and 12 samples per patient. 41 patients were in 1st line therapy, 11 in 2nd, 17 in 3rd, 7 in 4th, 3 in 5th and 2 in 6th line therapy. Average age was 63, range 33 to 90; male to female ratio was 1:1.19. 86% percent of patients had CTCs in at least one blood sample; CTC counts ranged from 0 to 885 CTCs/ml with a mean of 23.5 CTCs/ml. No correlation was found between the absolute CTC concentration and survival. However, in the 26 patients that had had samples collected both at the start of and during first line chemotherapy, an increase in CTC level between the two timepoints were associated with longer survival ($p < 0.001$). This suggests that the change in CTC level after entering 1st line chemotherapy, but not the absolute CTC concentration, carries prognostic information, highlighting the importance of access to serially collected specimens. The mechanism behind the CTC spike's ability to predict outcomes needs to be further elucidated.

Associated Cancer Types/Areas: lung cancer

Keywords: prognosis, CTC, NSCLC

100. Modeling and Simulation of Procoagulant Circulating Tumor Cells in Blood Flow

The Scripps Research Institute PS-OC

Four Dimensional Biopsy – The Physics and Mathematics of Metastasis

Angela Lee[1], Garth Tormoen[2], Owen McCarty[2], Paul Newton[1]

[1]University of Southern California, [2]Oregon Health & Science University

The procoagulant nature of circulating tumor cells (CTCs) poses significant risks for cancer patients, as increased incidence of blood clotting has been observed and reported in the literature. We investigate the fluid phase of cancer in relation to hemostatic processes in the blood by developing mathematical and computational models of cancer cells in flow, including the chemical concentration fields of enzymes diffusing with the flow field in a blood vessel. We have studied idealized computational domains, with one wall (2D and 3D) and circular closed domains in 2D, using simulations built with Green's function solutions (exact solutions). The CTCs are modeled as point particles in both no flow and constant flow conditions, with viscous boundary conditions for the vessel wall. Concentration fields of thrombin, modeled by the advection-diffusion equations, are shown to persist near the blood vessel walls, supporting the physiological observation that blood clots form on the vessel walls. In recirculation zones, where blood flow rates are lower, we show that concentration fields are higher than in open regimes for the same number of CTCs, supporting the view that clot formation occurs more frequently in regions of slowest flow.

Associated Cancer Types/Areas: metastasis, thrombosis

Keywords: circulating tumor cells, blood coagulation, computational fluid-structure interaction

101. Monitoring Treatment Response in Prostate Cancer by Applying Single Cell-Molecular Characterization of Circulating Tumor Cells

The Scripps Research Institute PS-OC

Angel E. Dago[1], Asya Stepansky[4], Anders Carlsson[1], Natalie Felch[1], Madelyn Luttgen[1], Anand Kolatkar[1], James Hicks[2], Mitchell E. Gross[3], Peter Kuhn[1]

[1]The Scripps Research Institute, [2]Cold Spring Harbor Laboratory, [3]University of Southern California, [4]Skyline Genomics, Inc.

The high-definition circulating tumor cell (HD-CTC) assay provides for an enrichment-free approach to CTC identification and molecular characterization. Here, we utilized the HD-CTC approach to study androgen receptor (AR) expression combined with genome-wide copy number variation (CNV) analysis in sequential CTCs samples obtained from a castration resistant prostate cancer (CRPC) patient treated with abiraterone acetate. At baseline, before treatment initiation, we observed a balanced proportion of AR-negative and AR-positive CTCs. During a brief period of clinical response the proportion of AR-positive CTCs drastically declined followed by a rapid increase associated with clinical progression (increased PSA and pain). CNV analysis of single CTCs from the baseline blood draw revealed multiple genomic rearrangements, such as AR amplification along with a pattern of chromosomal gains and losses typical of prostate cancer. During treatment response, however, the frequency of CNV alterations significantly declined, followed by the reemergence of a population with multiple complex alterations. Detailed analysis of the CNV profiles revealed that many abnormalities were commonly shared between the CTC populations, but a number were unique to the AR+ CTC population at the time of therapeutic relapse, including increased MYC amplification and alteration of the AR amplicon that included additional adjacent genes. Remarkably, the reconstruction of tumor lineage based on the CTC genomic profiles enables us to trace and identify the precise treatment time point where the putative therapy-resistant CTC clone emerges until it eventually expanded to become the predominant AR+ CTC population at the point of therapeutic relapse. Overall, our results demonstrated that the integration of the HD-CTC enumeration technology with protein expression and single cell genomic analyses could successfully be applied to real time monitoring of ADT therapy emergent change in a prostate cancer patient, and may provide a direct roadmap for personalized cancer medicine in the near future.

102. Multiscale Optical Quantification of Subcellular Structure in Early and Late Stage Isogenic Colorectal Cancer Cell Lines

The Scripps Research Institute PS-OC
Project 3: Cytophysics, Oregon Health & Science University

Kevin G. Phillips[1], Dhwanil *Damania*[2], *Hariharan Subramanian*[2], *Vadim Backman*[2], *Eric C. Anderson*[1], *Melissa H. Wong*[1], *Owen J.T. McCarty*[1]

[1]*Oregon Health & Science University,* [2]*Northwestern University*

Establishing a connection between genetic, epigenetic, and molecular perturbations among cells contributing to the pathogenesis of cancer and changes in their basic physical features has inspired the pursuit of quantitative biomarkers for disease surveillance through a variety of optical imaging and sensing modalities. Currently, the multiscale label-free optical quantification of cellular structure as a function of tumorigenic potential remains unexplored. Using the patient-matched SW480/SW620 colorectal cancer cell lines as a model of early and late stage disease, we quantified cellular mass-density variations at the nanoscale using partial wave spectroscopic (PWS) microscopy, a multi-spectral reflection mode technique, and at the micron scale using non-interferometric quantitative phase microscopy (NIQPM), a transmission modality. At the nanoscale, SW620 cells exhibited more fluctuations in their mass-density organization, quantified through the disorder strength (L_d) compared to SW480 cells. L_d is a structural signature indicative of increased tumorigenic potential. NIQPM was used to measure the micron scale cellular mass density of the SW cell types through phase reconstruction of transmitted waves through the cells. NIQPM density measurements revealed a systematic bimodal distribution of the subcellular densities of both cell types. The density distributions possessed distinct small-scale features that were sensitive to the increased tumorigenic potential of the SW620 cells. These findings identify unique architectures associated with early and late stage colorectal cancer cell lines at different spatial scales. These quantitative microscopy tools represent an emerging approach in cancer biology that provide unique utility in their ability to quantify the fundamental physical features of cells and the alteration of these features due to genetic, chemotherapeutic, and environmental perturbations.

Associated Cancer Types/Areas: colorectal, culture, metastasis, primary

Keywords: colorectal cancer, early and late stage, subcellular structure

103. PSCO0056: Identification and Characterization of Circulating Tumor Cells in the Blood of Melanoma Patients

The Scripps Research Institute PS-OC

Carmen Ruiz[1], Julia Li[1], Edward McClay[2], Wolfram Samlowski[3], Soldano Ferrone[4], Peter Kuhn[1]

[1]The Scripps Research Institute, [2]Pacific Oncology and Hematology, [3]Comprehensive Cancer Centers of Nevada, [4]Harvard Catalyst

Background: Solid tumors have the ability to metastasize through the generation of circulating tumor cells (CTC) that travel through the blood to colonize distant organs. In addition to providing evidence of early dissemination events, CTCs may act as a marker to (1) predict and/or evaluate patient response to a given therapy, (2) guide the choice of alternative therapies, and (3) monitor recurrence in patients after treatment. While a strategy to efficiently identify CTC in epithelial cancer has been established, up to now, a method for detection of circulating melanoma cells (CMC) has not been validated, partly because of the lack of a suitable and consistently expressed biomarker.

Purpose: Here we investigate the potential of the chondroitin sulfate proteoglycan 4 (CSPG4) as a biomarker to identify melanoma CTC in the peripheral blood of melanoma patients, as it is selectively expressed at high levels in primary and metastatic melanoma lesions, and its restricted distribution in normal tissues.

Methods: Three melanoma cell lines (WM1789, WM278 and WM1617) were used in spiking experiments for antibody validation. Because of the variability of CSPG4 epitope expression by different cell lines, CSPG4 detection has been improved in our assay by using a panel of 7 monoclonal Abs that has high association constants for distinct and spatially discrete CSPG4 epitopes. Expression of CSGP4 was also assessed in blood specimens collected from 12 metastatic melanoma patients and compared to one of the most frequently used melanocytic marker, HMB45.

Results: CTC ($CSPG4^+$, $CD45^-$) cells were identified in 2 patients. They were morphologically different from peripheral blood mononuclear cells (PBMC) and showed atypical features. The combination of CSPG4 with HMB45 did not increase the number of positive patients but resulted in the detection of more CMC in the two patients with $CSPG4^+$ cells.

Conclusion: Phenotypic heterogeneity among melanoma cells suggest that a multi-marker assay needs to be developed for optimal identification.

104. Rational Design of an Ex Vivo Model of Circulating Tumor Microemboli

The Scripps Research Institute PS-OC

What Makes a Microenvironment Permissible for Tumor Growth?

Sandra Baker-Groberg[1], Michael King[2], Paolo Decuzzi[3], Kevin G. Phillips[1], Owen J.T. McCarty[1], Anand Kolatkar[4], Madelyn Luttgen[4], Kelly Bethel[4], Peter Kuhn[4]

[1]Oregon Health & Science University, [2]Cornell University, [3]The Methodist Hospital and Research Institute, [4]The Scripps Research Institute

Metastasis is the major cause of death from cancer. The pathogenesis of hematogenous metastasis is a dynamic process consisting of detachment of tumor cells from the primary site, invasion into the host's blood vessels, transport through the circulation, and arrest, extravasation and proliferation at a secondary site. One of the keys to successful hematogenous metastasis is tumor survival in the bloodstream. The goal of this study is to utilize state-of-the-art optical measurement tools to quantify the mass, volume, and density of circulating tumor microemboli (CTM) to serve as the input parameter set to guide ex vivo microfluidic experiments and multiscale mathematical models to understand the complex physicochemical interactions between CTM, blood cells, and plasma in the vascular microenvironment.

To determine the basic physical features of circulating tumor microemboli (CTM), the Hilbert-transform differential interference contrast microscopy (HD-CTC) assay was utilized to identify cancer cells in a peripheral blood draw from a 54 year old breast cancer patient. The patient presented with bilateral invasive ductal mammary carcinoma and biopsy-proven metastatic disease to bone. The right breast was ER/PR+/HER-2–, the left breast was ER/PR/HER-2+ with a positive axillary node by fine needle aspiration. Immunohistochemistry of a bony site biopsy was ER+, PR–, and HER-2+. An 8 mL blood draw was taken prior to a bilateral mastectomy. CTMs were then plated onto microscope slides, identified using the HD-CTC assay, and their coordinates recorded. The slides containing these cells were then quantitatively analyzed using non-interferometric quantitative phase microscopy (NI-QPM), to determine aggregate mass, and HT-DIC, to determine cluster volume. Together, these parameters enable a determination of the average aggregate density. A total of N = 21 aggregates were analyzed under these label-free imaging modalities.

Mean CTM mass, surface area coverage and volume (± standard deviation) were 167.7 ± 143.4 pg, 625.3 ± 319.4 μm^2 and 631.8 ± 314.7 fL, respectively.

Our findings indicate that breast cancer associated CTMs are comprised of a heterogeneous population whose constituents display a wide range of structural variability. CTM mass, volume, and density displayed coefficients of variations (standard deviation over the mean) in excess of 50%. This data was then used to guide the parameters of an ex vivo model of CTM clusters and was used as an input for the development of a model of CTM transport.

Associated Cancer Types/Areas: cancer types: breast - invasive ductal mammary carcinoma and bone metastases; cancer areas: metastasis, microenvironment, circulating tumor microemboli

Keywords: cancer, microemboli, metastasis

105. Age-Dependent Mechano-Responses in Human Mammary Epithelial Progenitor Cells

University of California, Berkeley PS-OC
Pilot Program and Trans Network Initiative

Mark LaBarge, Fanny A. Pelissier, James Garbe, Masaru Miyano, Martha R. Stampfer

Lawrence Berkeley National Laboratory

Multipotent epithelial progenitors are putative roots of some breast cancers. Progenitors unable to terminally differentiate into luminal or myoepithelial cells increase proportionately in human mammary epithelia with age, suggesting that altered regulation of such progenitors may underlie age-associated increased breast cancer incidence. Because microenvironment influences differentiation into stable terminal states, we asked whether aging altered the ability of the progenitors to differentiate according to microenvironmental cues. Progenitors from younger (<30y) and older (>55y) mammary epithelia were exposed to mechanically tuned microenvironments to determine whether differentiation was impacted by substrata mimicking a range from compliant normal-like to stiffer malignant-like breast. Mechano-responses were age-dependent; progenitors from women <30y, but not >55y, generated terminal differentiated luminal epithelial cells on normal-like substrata and more myoepithelial cells on malignant-like substrata. Stress fiber and focal adhesion measurements suggested mechano-sensing was equivalent in both groups. Transduction of mechanical information to the nucleus via Rho-pathway and the mechano-sensitive YAP/TAZ transcription co-activators was age-dependent. Thus aging altered human multipotent mammary progenitors making them insensitive to mechanical cues that otherwise imposed terminally differentiated states.

Associated Cancer Types/Areas: breast cancer, microenvironment

Keywords: breast cancer, mechano-environment, aging

106. CD44-based Adhesion and Mechanotransductive Signaling on Engineered Hyaluronic Acid Matrices

University of California, Berkeley PS-OC
Fundamental Mechanobiology of Cancer

Yushan Kim, Sanjay Kumar

University of California, Berkeley

Glioblastoma multiforme is the most malignant primary brain tumor and is characterized by the diffuse infiltration of glioma cells into brain. The extracellular matrix (ECM) of brain parenchyma is rich in the glycosaminoglycan hyaluronic acid (HA) but relatively poor in fibrillar proteins. With the use of synthetic HA matrices functionalized with RGD peptide, we present new evidence that the HA receptor CD44 may be responsible for supporting integrin-based adhesion and mechanotransduction of glioma cells. Suppression of CD44 function reduces adhesion to RGD peptide-functionalized HA matrices at both short (30 min) and longer (180 min) adhesion times. Additionally, the adhesion, spread area, and two-dimensional migration speed of glioma cells are sensitive to the stiffness of HA-based matrices not functionalized with adhesive peptides, suggesting that HA receptors themselves are involved in the sensing of the biophysical environment. Invasive motility through transwell membranes is greatest when HA-CD44 adhesion is present, but limited when RGD-integrin adhesion is introduced. While the mechanosensing mechanisms of integrins and cadherins are widely studied, these findings reveal a previously under-appreciated role of cancer cell adhesion and mechanotransduction supported by CD44, and possibly other HA-specific receptors. This has broad implications on the field's fundamental understanding of how glioma cells interact with the tumor microenvironment, and potentially reveals new strategies for therapeutic interventions.

Associated Cancer Types/Areas: brain, invasion

Keywords: CD44, hyaluronic acid/hyaluronan, ECM (extracellular matrix)

107. Characterizing the Cooperation Between ErbB2 Signaling and ECM Stiffness in Driving Breast Tumor Progression

University of California, Berkeley PS-OC

Abhishek Kurup[1], Clare Yu[1], Thea Tlsty[2], Elliot Botvinick[1\]

[1]University of California, Irvine, [2]University of California, San Francisco

Introduction: Evidence suggests that increased Extra Cellular Matrix (ECM) stiffness may cooperate with oncogenes to sensitize mammary epithelial cells (MEC) towards malignancy and increase metastatic potential via mechanotransduction. These studies aim to provide the causative link to the positive correlation of Mammographic Density (MD) and risk of breast cancer. Metastatic potential can be studied by overexpressing the oncogene ErbB2 in varying conditions. ErbB2 is over-expressed in 20 to 30% of invasive breast cancers and up to 85% of Ductal Carcinoma In Situ (DCIS) and therefore is of particular interest. Furthermore, ErbB2 pathways and integrin pathways have much overlap of downstream proteins activation providing the biological basis of cooperation. Previous studies have resorted to changing stiffness in naturally derived ECMs via changing concentration or cross-linking. Either process can change ligand density, porosity, architecture, and diffusivity. Therefore, it is difficult to determine whether the resulting tumor phenotype is due to stiffness changes or other factors. In addition, the current standards for studying 3D breast models call for growing the mammary epithelial cells in an overlay method, i.e. a layer of matrix underneath the cells with 2% Matrigel in the media above the cells. This method chemically fools the cells into a 3D structure. Nonetheless, force balance in physiological settings is more closely related to an embedded 3D model. It is imperative to understand how the relationship between ECM stiffness alone, the ErbB2 pathway, and MEC metastatic potential changes in an embedded culture. We accomplish this by embedding MECs in a 3D culture within the stiffness gradient device (SGD), which can alter stiffness in a concentration independent fashion, as previously published. MCF10A.ErbB2 cells (Muthuswamy Lab) were utilized for their ability to be driven towards malignancy with the addition of an external dimerizer that activates the ErbB2/Her2 pathway. MCF10A cells were used as control.

Materials and Methods: MCF10A and MCF10A.ErbB2 cells were cultured in Matrigel/Collagen mixtures within the SGD. The hydrogels were also embedded with 2 um silica beads to be used as probes for AMR. In the SGD, the ECM is polymerized around a post that is rotated to induce strain, and a stiffness gradient is established without changing architecture and concentration. Stiffness can be tuned from 100 – 1000 Pa within one dish, the range of normal and malignant breast tissue. Optical tweezers based active microrheology (AMR) was used to measure the ECM stiffness maps and correlate to the function and signaling of mechanoreceptors. Hydrogels were stiffened by post rotation. AMR was conducted to calculate the complex shear modulus (G*). G* is a measure of material stiffness (G') and loss (G''). The cells were allowed to reach their growth arrested acini phase, at which time appropriate dishes were stiffened. After an additional 2 weeks, dimerizer was added to the culture. Non-linear imaging in regions of high stiffness and low stiffness was conducted to reveal acini morphology and molecular distributions. MCF10A cells were also cultured in a similar fashion. Experiments were repeated with increased post rotation. Acinar colonies were counted to determine percent invasive and disruptive colonies in stiffened vs. non-stiffened and in dimerizer vs. non-dimerizer cultures. Disruptive colonies were characterized as change from normal morphology, but no invading podia.

Results and Discussions: The results showed a dramatic amplification of invasive behavior when ErbB2 was activated in a stiffened matrix. Compared to MCF10A, MCF10A.ErbB2 showed a higher basal level of invasion and disruption. However, the actual percent of invasion was lower in embedded than previously reported in overlay. In addition, there were also stark differences in disruptive acini percentages between overlay and embedded cultures.

Conclusions: Increasing Her2 activation seems to amplify invasion in pre-stiffened colonies. The differences between overlay and embedded re-highlights the importance of the tumor microenvironment. This study demonstrates the role of stiffness alone in altering MEC phenotype.

108. Computational Identification of Cellular Mechanical Properties From Image Data

University of California, Berkeley PS-OC

Insoon Yang, Claire Tomlin

University of California, Berkeley

We present a computational method to identify cellular mechanical properties from image data or movies. The key idea of the method is to formulate an optimization problem constrained with a level set based-dynamic model of biological cells.

By solving the optimization problem, we can determine mechanical parameters that minimize the difference between the solution of the model and given data, and that are within biologically or mechanically correct ranges. An adjoint-based method is studied to numerically solve the optimization problem in an efficient way. This computational approach only requires the sequence of images: the method can be very useful to estimate the mechanical properties of cells and the forces applied to cells where direct experimental measurements of them are not tractable. The performance of the method is demonstrated with the following examples: (1) identification of the surface tension of bilayer membranes from image data of the vesicle-vesicle adhesion; (2) identification of the forces (per density) of actin and myosin in cell polarization. Furthermore, we discuss how the computational identification of the forces exerted on the multicellular structures of S1 and T4-2 cells will help us understand the mechano-chemical signaling in the growth of multicellular structures of non-malignant and malignant breast cells.

Associated Cancer Types/Areas: breast

Keywords: computational and systems biology, cellular mechanical properties, force estimation

109. Histological Examination of the Temporal and Spatial Expression of SATB1 Reveal No Correlation With Tumor State but Does Signal a Tumor-Promoting Inflammatory Environment

University of California, Berkeley PS-OC

Brett Schofield[1], Phillip Jess[1], Anatoly Urisman[2], Yunn-Yi Chen[2], Jan Liphardt[1]

[1]University of California, Berkeley, [2]University of California, San Francisco

Special AT rich binding protein 1 (SATB1) is a DNA binding protein, primarily found in thymocytes and activated T cells. SATB1 facilitates DNA looping and thus the transcription, or repression of target genes. It was recently reported that SATB1 expression in breast epithelial cells is associated with poor prognosis in breast cancer and a metastatic phenotype in breast cancer cell lines. This result sparked interest in the cancer community and articles have appeared supporting this conclusion. However an equal number of articles have appeared that find no connection between SATB1 and breast cancer [5,6], igniting a debate that has reached the pages of the New York Times. In order to contribute and help provide some clarity to this important and fascinating question our research has focused on the study of whole breast cancer tissue sections. With the use of Immunohistochemical staining we aimed to understand if and when SATB1 is expressed in epithelial tumor cells. By studying the expression of SATB1 in normal, ductal carcinoma in situ (DCIS), invasive and high grade breast carcinomas we were able to glean potential clues as to the role that SATB1 may play in this process. Furthermore, the process of tumorigensis does not occur in an isolated environment but is a delicate interplay of the cancerous epithelial cells with the surrounding environment that is comprised of many components including myoepithelial cells, immune cells, fibroblasts and extracellular matrix proteins to name just a few. By studying whole tissues we can also examine how the expression of SATB1 correlates with a changes in the tissue microenvironment. We find that SATB1 is not preferentially expressed in either normal, DCIS, invasive or high grade cells indicating SATB1 may have a normal function in epithelial cells. However we do note that high SATB1 expression, in epithelial cells, correlates strongly with tumor infiltrating immune cells.

Associated Cancer Types/Areas: breast cancer

Keywords: breast cancer, inflammation, SATB1

110. Localized Modulation of Genomic Transcriptional Activity Driven by Extracellular Stiffness Cues in 3D

University of California, Berkeley PS-OC

Russell Bainer[1], Yoshihiro Yui[1], Shannon Mumenthaler[2], Parag Mallick[3], Ondrej Podlaha[4], Franziska Michor[4], Jan Liphardt[5], Jonathan Licht[6], Valerie Weaver[1]

[1]University of California, San Francisco, [2]University of Southern California, [3]Stanford University, [4]Dana-Farber Cancer Institute, [5]University of California, Berkeley, [6]Northwestern University

The stiffness of the extracellular matrix (ECM) stimulates mechanotransduction pathways that regulate tissue development and tumor progression. We previously showed that a stiff ECM potentiates cell growth and survival, enhances cell migration to drive tumor cell invasion, and drives malignant progression of the mammary gland in culture and in vivo, but the specific transcriptional and molecular events that occur as cells acquire these phenotypic changes are not well understood. To clarify this process, we used expression microarrays, tandem mass spectrometry, and massively parallel RNA sequencing to identify changes in gene expression levels, isoform usage, and protein abundance that occur as intact ascini respond to distinct stiffness environments. We found that in stiffer ECM conditions ascini acquire consistent changes in gene expression related to cell adhesion and mRNA splicing, and specifically induce the expression of a set of genes involved in epithelial cell differentiation that includes multiple SPRR and S100 proteins. Remarkably, these genes map to an apparent stiffness-mediated transcriptional hotspot on chromosome 1q21, a region containing elevated transcription in many cancers but whose activity has not been related to mechanotransduction. We then used a heuristic approach to identify additional candidate force-mediated transcriptional hotspots throughout the genome that contain multiple genes that are coordinately activated or silenced in response to elevated ECM stiffness. These studies provide biological insight into the divergent cellular responses to distinct stiffness environments and suggest that cellular genome regulatory responses to the force environment may specifically target distinct chromosomal regions via a mechanism that remains to be elucidated.

Associated Cancer Types/Areas: breast cancer, microenvironment

Keywords: mechanobiology, chromatin state, genomics

111. Long-Range Mechanical Communication Among Disorganizing Mammary Acini
University of California, Berkeley PS-OC

Quanming Shi[1], Rajarshi P. Gosh[1,2], Hanna Engelke[1], Christopher Rycroft[1,2], Luke Cassereau[3], James X. Sethian[1,2], Valerie M. Weaver[1], Jan T. Liphardt[1,2]

[1]University of California, Berkeley, [2]Lawrence Berkeley National Laboratory, [3]University of California, San Francisco

Cancer development is associated with distinct extracellular matrix (ECM) structure and mechanics. Altered ECM mechanics drive tumor progression. Here we employed 10AT acini model system to study how multi-cellular organoids respond to varied ECM substrates using a combination of imaging techniques and mechanical characterization. We have found that when seeded on collagen substrates, multicellular acini dis-assemble into single cells, with the rates of disassembly varying with substrate stiffness and composition. When on collagen gel, acini generate radiating fibers by progressively pulling on the collagen that extends to hundreds of micrometers. The generation of fiber network precedes disorganization. Furthermore cells migrating along the fibers display markedly alleviated speed.

Long-range substrate deformations are evident in wide imaging fields, where extent of deformation is strongly correlated with density of acini. While modulation of substrate topology by acini most likely rises from sensing and processing mechanical signals emanating from proximal acini in form of compression, tension and shear forces, it has been difficult to isolate mechanical cues from chemical cues. We have developed a strategy to distinguish between mechanical and chemical contributions to acinar disorganization and spreading. Using laser capture micro-dissection we show that, when the mechanical connection of an acinus is severed from the surrounding continuous bed of collagen, thus isolating the acinus on an island of collagen; the acinus shows nearly no disorganization even though the immediately underlying substratum shows huge enrichment of collagen. Also the degree of disorganization shows a positive correlation with the increase in the size of the island of collagen. Since the acini seeded on collagen are immersed in a medium which ensures efficient admixture of chemical cues and accessibility of each acinus to these cues through diffusion; the considerably impaired disorganization of these acini isolated on islands of collagen points towards the indispensability of mechanical forces in acinar disorganization.

Our future aim is to build an integrated model system to account for the coupled metamorphosis of acinus and its substrate at a macroscopic and molecular scale.

Associated Cancer Types/Areas: breast cancer, microenvironment

Keywords: cancer mechanics, collagen, long-range interaction

112. Mechanical Force Regulates the Nanoscale Dynamics of Focal Adhesions

University of California, Berkeley PS-OC
Project 2: From Cells to Tissues: Multiscale Mechano-Chemical Feedback

Christopher DuFort[1,2], Matt Rubashkin[2], Matthew Paszek[2], Guanqing Ou[1,2], Jon Lakins[2], Valerie Weaver[1,2]

[1]University of California, Berkeley, [2]University of California, San Francisco

The three-dimensional architecture and spatial organization of focal adhesions varies systematically and can be directly modulated by mechanical force. The interaction between focal adhesion proteins is spatially regulated by cell generated forces including contractility and is influenced by, or may even dictate the maturation state of the adhesion contact. Cells sense and respond to their external environment through macromolecular complexes called focal adhesions. When mechanically stimulated, these complexes transduce information through activation of adhesion plaque molecules such as talin, vinculin, and focal adhesion kinase. Since the nano-architecture of adhesion complexes has only recently been described under static conditions, it is currently unknown if and how mechanical forces deform and dynamically modify the molecular architecture of these complexes to facilitate mechanotransduction. While the role of focal adhesions as intricate molecular machines is well appreciated, little is known about their overall organization at the nano-scale. It has been previously hypothesized that focal adhesion complexes are highly spatially conserved structures. However, our results suggest that there are specific nano-scale changes to focal adhesion architecture that appear to be directly correlated with regions of varying cell-generated contractility and motility phenotypes. To further our understanding of focal adhesion structure and function, the three-dimensional organization and spatial orientation of proteins comprising focal adhesion complexes with precisions of ~5 nm along the optical axis and diffraction-limited laterally was revealed with a scanning-angle variant of fluorescence interference contrast microscopy.

Work supported by: PSOC U54CA143836-01, R01 CA138818-01A1, DOD W81XWH-05-1-0330 to VMW.

Associated Cancer Types/Areas: breast, microenvironment

Keywords: breast cancer, microenvironment, motility, invasion

113. Multiplexed Profiling of Breast Cancer Cellular Heterogeneity by Microenvironmental Probes
University of California, Berkeley PS-OC

Mandana Veiseh[1], D.H. Kwon[1], A.D. Borowsky[2], C. Toelg[3], H. Leong[3], J. Lewis[3], E.A. Turley[3,4], M.J. Bissell[1]

[1]Lawrence Berkeley National Laboratory, [2]University of California, Davis, [3]London Health Sciences Centre, [4]University of Western Ontario

Tumor heterogeneity is a determining factor in diagnosis and therapy of breast cancer (BCa). We investigated BCa cellular heterogeneity, based on binding characteristics of a microenvironmental hyaluronan (HA) probe, in relation to the degree of BCa aggression. Fluorescent HA probes, multiplexed profiling, and cell sorting strategies were developed and used to detect/capture tumor cell subpopulations with differences in HA binding ($HA^{-/low}$ vs. HA^{high}) and HA receptors expression. Whereas we monitored HA:cell interaction in BCa lines of different molecular subtypes, we concentrated on the most metastatic cell line, MDA-MB-231. The HA probe binding was non-Gaussian in all subtypes, and the highest binding level was detected in the most invasive triple-negative basal subtypes. Binding levels were dramatically reduced upon "reversion" of highly malignant cells to a non-malignant phenotype in 3D cultures, suggesting that level of cellular binding to HA probe provides a measure of malignant behavior. Comparison between HA^{high} and $HA^{-/low}$ subpopulations revealed surprising differences in morphology, proliferation and invasion in culture, which were retained in two in vivo models. HA^{high} subpopulations exhibited higher levels of invasion but surprisingly lower levels of proliferation compared to either unsorted parental cells or the $HA^{-/low}$ subpopulation. Querying HA probe binding in BCa lines reveals a novel form of tumor heterogeneity that predicts malignant behavior. These results may aid in diagnosis and therapy of invasive BCa subpopulations and early identification of cancer patients susceptible to metastasis.

Associated Cancer Types/Areas: breast

Keywords: breast cancer heterogeneity, three-dimensional cultures, hyaluronan probes

114. Quantitative Single Molecule Imaging Reveals a Dimeric Ras/Raf Signaling Module
University of California, Berkeley PS-OC
Mechanobiology of Tumor Progression

Xiaolin Nan[1], Tanja M. Tamguney[2], Eric Collisson[2], Sophie Y.L. Kuo[3], Jan Liphardt[4], Joe W. Gray[1], Frank McCormick[2], Steven Chu[3,4,5]

[1]Oregon Health & Science University, [2]University of California, San Francisco, [3]Lawrence Berkeley National Laboratory, [4]University of California, Berkeley, [5]U.S. Department of Energy

The Ras/Raf signaling node regulates cell proliferation and other essential cellular functions, and deregulated activation of this node is frequently linked to human cancers. Despite extensive research, efforts on targeting Ras and Raf in cancer therapeutics have only had limited success, urging a thorough re-examination of the molecular mechanisms regulating signaling around these oncoproteins. We have employed photoactivated localization microscopy (PALM), a powerful single-molecule imaging technique that delivers nanometer spatial resolution and single-protein counting capability, to study Ras and Raf signaling in intact mammalian cells. We first demonstrate that when combined with quantitative image analysis, PALM is capable of directly resolving individual proteins and protein complexes such as dimers and oligmers in intact mammalian cells. With this quantitative imaging approach, we show that Raf forms dimers under various activation conditions including the presence of Ras-GTP or small molecule Raf inhibitors. These observations provide direct evidence for Raf dimerization and its involvement in cell signaling. More interestingly, quantitative single molecule imaging of cells expressing tunable levels of mutant Ras revealed that Ras-GTP also forms dimers in order to activate Raf/MAPK signaling. Biochemical assays further confirmed that formation of Ras-GTP dimers on the cell membrane is both necessary and sufficient e for Raf/MAPK activation. Taken together, these findings strongly suggest that the Ras/Raf signaling node acts as a dimeric module of which the basic functional unit consists of two copies of Ras and Raf proteins. Our discovery provides the molecular basis for designing alternative and potentially more effective targeted cancer therapies, and demonstrates the power of quantitative single molecule imaging approaches in uncovering the molecular details of oncogenic signaling processes.

Associated Cancer Types/Areas: types of cancer, signal transduction/fundamental molecular mechanisms of cancer

Keywords: single-molecule super-resolution imaging**,** Ras and Raf signaling, dimerization

115. Restricting EphA2 Receptor Reorganization Alters Internalization and Signaling in MDAMB231 Cells

University of California, Berkeley PS-OC

Adrienne Greene, Samuel J. Lord, Aiwei Tian, Jay T. Groves

University of California, Berkeley

The importance of spatial reorganization of receptors and ligands that occurs at the cell-cell interface is becoming increasingly evident in a variety of cell systems. Our lab has developed a unique experimental platform in which live cells are interfaced with supported lipid membranes displaying receptor ligands, creating a controllable and laterally mobile ligand presentation system that recapitulates essential aspects of the cell-cell contact. To probe how protein organization in the membrane influences cell signaling events, we use a spatial mutation strategy in which we pattern supported lipid bilayers into microscale corrals to restrict protein movement within the confines of the corrals and then measure alterations in cell signaling. When MDAMB231 breast cancer epithelial cells overexpressing the receptor tyrosine kinase EphA2 are interfaced with a supported lipid bilayer containing the EphA2 ligand, ephrinA1, EphA2 binds to ephrinA1, and the complex reorganizes into large clusters. Here, we found that the molecular composition of these clusters largely consists of the endocytosis components clathrin and dynamin— at the exclusion of many other molecules—indicating that these clusters might be sites of clathrin-mediated endocytosis. We then developed a highly quantitative assay to measure endocytosis from an ephrinA1-presenting supported lipid membrane. Disrupting both clathrin-mediated endocytosis and metalloproteases using small molecule inhibitors alters ephrinA1 endocytosis. Finally, when receptor-ligand movement and clustering is disrupted using patterned substrates, ephrinA1 endocytosis is altered as a function of clustering, indicating that EphA2 signaling is sensitive to perturbations in spatial organization. The implications of these observations for spatial regulation of EphA2 signaling will be further discussed.

Associated Cancer Types/Areas: breast cancer

Keywords: endocytosis, receptor, reorganization

116. Altered Autoantibody and Cytokine Profiles in a Murine Lymphoma Model

University of Southern California PS-OC

Daniel Ruderman[1], Mitch Magee[4], Shan X. Wang[5], David Agus[1], Daniel Hillis[1,2], Scott Lowe[3], Joshua LaBaer[4], Jung-Rok Lee[5], Garrick Wallstrom[4], Cornelius Miething[3], Iris Applemann[3], Kiki Liu[3], Daniel Ruderman[1],Tom Tombrello[2]

[1]University of Southern California, [2]Applied Minds, [3]Memorial Sloan-Kettering Cancer Center, [4]Arizona State University, [5]Stanford University

We are determining auto-antibody and cytokine levels in a murine model of lymphoma to assess host responses during the course of disease development. We utilize two cell lines Eμ-Myc/Arf-/ (sensitive to chemotherapy) or Eμ-Myc/p53-/- (resistant to chemotherapy), to initiate lymphoma development by intravenous injection into syngeneic C57Bl/6 mice. Anti-tumor antibodies were detected utilizing nucleic acid programmable protein arrays (NAPPA) utilizing sets of approximately 10,000 human proteins. Normalized autoantibody levels were analyzed using statistical methods to detect coordinate changes in autoantibody levels to proteins within curated physiological pathways (Gene Ontology). We find highly significant changes in autoantibody levels around cancer progression and B cell receptor signaling pathways, providing evidence for the immune surveillance of intracellular processes within tumors. In addition, autoantibodies to proteins regulated by p53 show stronger differential expression between Eμ-Myc/p53-/- and Eμ-Myc/ARF-/- mice than non-p53-regulated proteins. Further, in Eμ-Myc/ARF-/- the autoantibody responses showed higher specificity to cell surface proteins than mice bearing Eμ-Myc/p53-/- tumors. We also utilized sensitive Magneto-nanosensor chips to assess the proteins IL-6, VEGF, G-CSF, B2M, TNF-alpha, FLT3-Ligand and Eotaxin levels for quantitation. On Day 14 post-tumor challenge, we detected significant increases in IL-6 and G-CSF in cyclophosphamide-treated mice with both cell lines as compared to untreated mice. Interestingly, in mice challenged with Eμ-Myc/p53-/- cells, we detected significant increases in Eotaxin and FLT3LG as compared to untreated mice. Similarly, in mice challenged with Eμ-Myc/ARF-/- cells, B2M and TNF-alpha were significantly increased on day 14 as compared to untreated tumor-bearing mice. The results of these studies, along with those of other projects in the USC PSOC consortium, provide the foundation to perform additional sample collection in IL-6 knockout mouse model. This model platform will allow us provide results to the data modelers to establish parameters to mathematically predict the host response to tumor development.

Associated Cancer Types/Areas: lymphoma

Keywords: cytokine, antibody, pathway analysis

117. Cytokine Profiles Associated With Therapeutic Intervention and Tumor Transplantation in Lymphoma Mouse Model

University of Southern California PS-OC
Project 4: Integrated Multiscale Analysis of Tumor and Host Response to Therapy

Jung-Rok Lee[1], Cornelius Miething[2], Dan Ruderman[3], Iris Appelmann[2], Dewey Mitchell Magee[4], Scott Lowe[2], Joshua LaBaer[4], Shan X. Wang[1]

[1]Stanford University, [2]Memorial Sloan-Kettering Cancer Center, [3]University of Southern California, [4]Arizona State University

Cytokine expression levels can be manifestation of host-tumor interaction or response to the external stimuli such as therapeutic intervention. These clues can be used to understand the underlying mechanism of the interaction and response. Many modalities have been used to measure cytokine profiles in serum samples. The magneto-nanosensor chip is a very promising measurement platform because of its multiplexing ability and low sample consumption which enable us to conduct longitudinal studies in the mouse model. We have developed the assays for IL-6, VEGF, GCSF, Eotaxin, FLT3LG, TNF-α, and B2M, and these seven proteins in a serum sample are measured at the same time with a single chip. For the cytokine measurement, we developed lymphoma mouse models where drug-resistant (Eμ-myc/p53-/-) and drug-sensitive (Eμ-myc/Arf-/-) cell lines are injected into the mice and one of groups is treated with cyclophosphamide. The serum samples were collected from these mouse models up to 28 days after the tumor cell transplantation, and measured with the magneto-nanosensor chips. We observed that IL-6 and GCSF are up-regulated only in the drug-treated group 6 days after the treatment, and some cytokines behave differently in the mice injected with different cell lines. Some serum samples collected within 24 hours after the drug treatment were also measured to monitor early responses to the treatment.

Associated Cancer Types/Areas: lymphoma

Keywords: molecular detection, protein array, GMR sensors

118. Epigenetic Adaptation to Drug Treatment in Lymphoma

University of Southern California PS-OC

Dynamic State Space Modeling of Cancer Cell Response to Therapy

Colin Flinders[1], *Larry Lam*[1], *Liudmilla Rubbi*[1], *David Agus*[2], *Dan Ruderman*[2], *Matteo Pellegrini*[1], *Parag Mallick*[2]

[1]*University of California, Los Angeles,* [2]*University of Southern California*

Tumors harbor epigenetic alterations that are both heritable as well as dynamic. These epigenetic alterations, particularly DNA methylation, have been shown to correlate with gene expression and act as drivers of tumorigenesis. Furthermore, recent studies have shown that DNA methylation patterns in human patient tumors are significantly enriched for cancer- and development/differentiation-related genes across patients. However, the degree to which DNA methylation alterations have the ability to produce selectable drivers of tumorigenesis and treatment outcome remains unclear. Using genome-scale analysis of DNA methylation alterations, we have shown that chemotherapeutic treatment is capable of acting as a driver of tumor evolution by applying a selective pressure that results in changes at the DNA methylation level. Additionally, we have shown that continuous passage in the presence of a chemotherapeutic leads to an epigenetic adaptation that allows for increased survival at higher concentrations of drug.

Associated Cancer Types/Areas: lymphoma, tumor evolution, tumor heterogeneity

Keywords: epigenetic, evolution, genomics

119. Functional Differences of Mutant p53s Expressed in MCF10A Cells and Their Contribution to Breast Carcinogenesis

University of Southern California PS-OC

Laura Gonzalez-Malerva[1], Eaton S. Seron[1], Anasuya Pal[1], Mayra Guzman[1], Donald Chow[2], Eva Amouzougan[1], Hongwei Yin[2], Jin Park[1], K.S. Anderson[1], J. LaBaer[1]

[1]Arizona State University, [2]Translational Genomics Research Institute

Recent high-throughput tumor sequencing has confirmed a striking prevalence of somatic *TP53* mutations in breast cancer (~35% overall), usually associated with basal-like tumors. Patients with these aggressive tumors have worst clinical outcome, fewer treatment options and respond poorly to current therapies. Mutations in *TP53* can induce dominant negative effects on wild-type (WT) p53 protein, including enhanced tumor growth, increased cell migration, invasion and metastasis. Dominant mutations do not necessarily lead to a null phenotype. Different p53 mutations result in gain-of-function phenotypes such as distinct patterns of growth, tumorigenicity and protein interactions, which suggest that individual *TP53* mutations result in distinct cellular programs. We hypothesized that unique *TP53* mutations would have distinct functional effects on the hallmarks of cancer. To study this, we generated MCF10A stable cells expressing the ten most frequent breast cancer mutations located in the DNA binding domain of *TP53*. We are measuring proliferation, apoptotic resistance, transition to mesenchymal state (EMT), alterations in migration and invasion effects for all these dominant p53 mutants. Compared with wt-p53, the $p53^{G245S}$ and $p53^{H179R}$ mutants displayed disrupted epithelial staining and look more mesenchymal in absence of TGF-β, which correlate with invasive behavior observed. Interestingly the $p53^{R248Q}$ displayed a disrupted epithelial staining, look more mesenchymal and was among the most invasive one in absence of TGF-β, moreover this mutant escape to induction of apoptosis. These preliminary data suggest that different *TP53 mutations result in distinct* cellular programs and influence breast carcinogenesis.

Associated Cancer Types/Areas: breast cancer

Keywords: breast cancer, invasion, EMT

120. Investigating New Therapies for Chemoresistant *p53-/-;Emu-MYC* Lymphoma

University of Southern California PS-OC
Multiscale Complex Systems Transdisciplinary Analysis of Response to Therapy

Yulin Li[1], Colin Flinders[2], Greg Behbehani[1], Dan Ruderman[3], Parag Mallick[1], Dean W. Felsher[1]

[1]Stanford University, [2]University of California, Los Angeles, [3]University of Southern California

Deregulation of MYC oncogene expression is a key feature of human burkitt's lymphoma. The Emu-MYC mouse is a preclinical model that closely mimics human Burkitt's lymphoma. The Emu-MYC lymphomas often spontaneously develop mutations in either p19ARF or p53. P53 mutations render the Emu-MYC lymphoma cells resistant to conventional DNA damage-inducing chemotherapy drugs, such as cyclophosphamide, vincristine, and doxorubicin. We have performed proteomics and microarray experiments to interrogate the mechanisms of chemoresistance of *p53-/-;Emu-MYC* lymphoma. Upon treatment with mafosphamide, a cyclophosphamide analog, we found that *the p53-/-;Emu-MYC* cell upregulated the mTOR pathway and the G2/M cell cyle checkpoint, which may contribute to cell survival upon DNA damage-inducing chemotherapy. Based on this result, we are currently testing some alternative drugs in vitro both as a single agent or in combination for chemoresistant *p53-/-;Emu-MYC* lymphoma. Since *p53-/-;Emu-MYC* lymphoma cells are defective in their G1 checkpoint, disabling the G2/M checkpoint with CHK inhibitors may drive cell cycle progression without DNA repair and promote cell death through mitotic catastrophe. In addition, inhibiting mTOR function with rapamycin or targeting MYC with JQ1 seem to be effective as single agents in vitro.

Associated Cancer Types/Areas: lymphoma

Keywords: lymphoma, MYC, chemotherapy

121. Prediction of Drug Response in Non-Hodgkin's Lymphoma

University of Southern California PS-OC
Project 3: Multiscale Cancer Modeling: From Cell Phenotypes to Growth and Therapy Response

Hermann Frieboes[1], Bryan R. Smith[2], Masakatsu Kotsuma[2], Benjamin Cahill[1], Sanjiv Sam Gambhir[2], Vittorio Cristini[3]

[1]University of Louisville, [2]Stanford University, [3]University of New Mexico

Drug resistance greatly impacts the treatments in non-Hodgkin's lymphoma. There are multiple contributions to drug resistance, including molecular and cell-scale genomic effects as well as tumor-scale physical features. Due in part to drug resistance and other factors, it has proven difficult to offer accurate prognoses for lymphoma patients prior to their treatments aside from a physician's intuition/experience. In order to help tailor chemotherapy to individual patient's tumors and thus help avoid resistance, we model lymphoma drug response using a biologically-grounded tumor model1 that incorporates a detailed representation of intra-tumor physical properties such as diffusion and transport barriers. This model does not focus on either cell-scale or tumor-scale effects, but instead links them in order to provide a more accurate representation of the real tumor in living subjects. Specific inputs to the model include the tumor blood volume fraction, the average geometric mean diameter of blood vessels, the drug diffusion penetration distance, and the drug response measured in vitro. Since these parameters can easily be measured from immunohistochemistry and biopsy specimens prior to therapy, this model offers a novel approach to help determine lymphoma chemotherapeutic treatment that could ultimately be applied as part of the physician's toolkit.

Associated Cancer Types/Areas: lymphoma

Keywords: mathematical modeling, computational simulation, drug resistance

122. Microenvironmental Heterogeneity Drives Tumor Evolutionary Dynamics

University of Southern California PS-OC
Transnetwork Project

Shannon Mumenthaler[1], Jasmine Foo[2], William Pao[3], David Agus[1], Franziska Michor[4], Parag Mallick[5]

[1]University of Southern California, [2]University of Minnesota, [3]Vanderbilt-Ingram Cancer Center, [4]Dana-Farber Cancer Institute, [5]Stanford University

Tumor growth is a complex evolutionary process driven by dynamic feedback between a heterogeneous cell population and selection pressures from the tumor microenvironment. Spatio-temporal heterogeneity in the microenvironment can create physical niches that facilitate cellular adaptation as seen in regions of hypoxia and acidosis where cells may up-regulate glycolysis and become resistant to acid-meditated toxicity in order to survive. In recent studies, using clinically prevalent subtypes of EGFR-related non-small cell lung cancer (NSCLC), we observe that nutrient and drug gradients resulting from a cells' proximity to vasculature, can produce selective pressures driving tumor evolution. We provide a detailed examination of the microenvironmental impact (i.e., oxygen, glucose, and drug) on growth rates of NSCLC cell lines that are either sensitive or resistant to the EGFR TKI, erlotinib. Often we consider drug resistance to be associated with a fitness cost to the cell in the absence of drug. However, here we demonstrate that the situation is more complex, with the local tumor microenvironment influencing the magnitude and the directionality of the selective effect. In fact, the resistant cells actually gain a selective advantage in nutrient-stressed environments compared to the sensitive cells. The resulting growth dynamics were used to inform a stochastic compartment-based tumor model of pre-existing drug resistance where each compartment represents a specific tumor environmental niche. This integrative modeling framework was then used to predict rebound growth kinetics and tumor composition (i.e., % resistance) and in particular, provide insight into the magnitude by which the microenvironment influences these results. These investigations strongly suggest that ignoring the microenvironment or using laboratory environmental conditions to inform tumor dynamics can lead to inaccurate conclusions. Therefore, knowledge of the selective advantage/disadvantage of different cell populations within different regions of the tumor will better guide model predictions, influence overall tumor dynamics, and impact treatment strategies.

Associated Cancer Types/Areas: lung cancer, microenvironment, drug resistance

Keywords: microenvironment, drug resistance, evolutionary modeling

123. Progress in User-Friendly, 3-D Multiscale Agent-Based Simulation of Large (500k+ Cells) Cancer Systems

University of Southern California PS-OC
Multiscale Complex Systems Transdisciplinary Analysis of Response to Therapy (MC-START)

Paul Macklin, Margy Gunnar, Alice Z. Hyun, Liwen Hu, Shannon Mumenthaler

University of Southern California

Modelers have made substantial progress in 3-D agent-based simulation of cancer. Models now routinely include various combinations of transport, mechanics, lineage, evolution, and tumor-host interactions, with calibration to in vitro, in vivo, and clinical data. However, significant challenges remain in pushing these models towards cross-disciplinary educational and clinical application. Many models are still confined to 2D; extension to 3-D, biologically- and/or clinically-relevant problems is computationally difficult. Most simulators lack intuitive user interfaces and instead require direct modification of source code when applying them to new problems. Describing and configuring complex 3-D cell and tissue arrangements is non-trivial. A current lack of standardized model cell and tissue description languages hinders model cross-validation, model recombination, and model and data exchange. These shortcomings make it difficult to apply simulators to new, clinically-relevant problems, and discourages participation in computational oncology by biologists, clinicians, and students.

We present current progress by our lab in addressing these problems. We are developing a mechanistic 3-D agent-based computational framework capable of simulating approximately 500,000 cells on high-end desktop computers, including nonlinear transport, cell volume regulation, and microenvironment-dependent cell phenotype, in complex in 3-5 mm^3 tissues that include plasto-elastic basement membranes and ECM and complex blood vessel networks. We are developing an XML-based standard for exchanging virtual cell lines and tissues (MultiCellXML), along with a suite of user-friendly tools for model configuration, exchange, visualization (e.g., virtual pathology) and analysis. It is our hope that this work will make possible novel integrative computational oncology experiments that can help extrapolate results from in vitro experiments to simulated clinical outcomes, will encourage participation in computational modeling by a broader coalition that includes biologists and clinicians as well as engineers and mathematicians, and will help facilitate more rapid training of the next generation of cross-disciplinary cancer scientists.

Associated Cancer Types/Areas: agent-based cancer modeling, 3-D simulations, mechanics, multiscale modeling, model exchange, cross-disciplinary education

Keywords: 3-D agent-based models, cross-disciplinary education, computational oncology

AMERICAN TYPE CULTURE COLLECTION

124. PBCF Provides BioServices to the PS-OC Network Investigators

Yvonne A. Reid

American Type Culture Collection

The PS-OC Bioresource Core Facility (PBCF), located at ATCC, serves as a biorepository and a distributor of bioproducts and reagents to the PS-OC Network Investigators. The PBCF supplies consistent, reliable and well-authenticated biomaterial to over 50 laboratories worldwide. Biomaterial supplied includes: cancer cell lines and non-tumorigenic counterparts, genomic DNA, total RNA, protein lysates from cells, reagents and protocols (SOPs) for the optimal propagation and cryopreservation of cell lines. Additionally the PBCF provides an annual workshop for young PS-OC network investigators. The annual, hands-on, workshop on basic techniques in molecular biology is scheduled for July 2013 at ATCC in Manassas, VA.

The PBCF is supported by the Office of Physical Sciences-Oncology (OPSO), National Cancer Institute of the National Institutes of Health under Award Number HHSN26121100018I.

CCS ASSOCIATES

125. Key Steps to Consider in Commercialization of an Academic Clinical Assay Platform

CCS Associates

Susan M. Keating, Greg Baxter, Caroline C. Sigman

CCS Associates

Transferring a new technology assay platform from an academic laboratory to a start-up company for development and commercialization as a clinical assay involves not only a shift in approach to system development, but also implementation of a series of steps that will lead to the ultimate goal of successful commercialization of the technology. The academic research environment of continuous, sometimes on-the-fly optimization with limited documentation must change to a more controlled environment of extensive documentation, defined procedures focused on reproducibility and a single, or limited focused application. Key factors to consider in addition to financial/capital resource issues, technology transfer and intellectual property status (not discussed), are early delineation of the business strategy and plan for the first intended use of the platform, as well as the regulatory strategy and organizational structure required to match the commercialization strategy with regulatory requirements. Given the framework, critical steps to follow even during system and assay optimization are implementation of GLP compliant laboratory practices, documenting the assay and system (hardware and software), and bringing these under "design control." Verification and validation studies of the assay and system performance follow, as well as appropriately designed studies to demonstrate clinical validation and utility. Early recognition and initiation of planning to implement these processes at appropriate times in the assay development lifecycle will facilitate the move from the feasibility stage of development to commercialization.

Keywords: commercialization, regulatory issues

126. Innovative Molecular Analysis Technologies (IMAT) program

Tony Dickherber

National Cancer Institute

The NCI Center for Strategic Scientific Initiatives re-launched an updated Innovative Molecular Analysis Technologies (IMAT) program in the fall of 2011, dedicating $10.5 million in new awards each year through unique funding mechanisms (3 year R21s and R33s) to better support investigators through both the early stages of technology development. The IMAT program runs alongside several active programs at the NCI for supporting cancer-relevant technologies, including the Physical Sciences Oncology Centers Program. A variety of IMAT-supported research projects will be highlighted to demonstrate the variety and high level of innovation evident in the IMAT portfolio of supported research. Potential projects of interest and identified technology gaps will also be highlighted.

NATIONAL SCIENCE FOUNDATION/NATIONAL CANCER INSTITUTE PLIERS AWARD

127. Clinical Relevance, Mathematical Models, and Cancer Treatment Decision Support

National Science Foundation
University of Pittsburgh

Robert Parker

University of Pittsburgh

Chemotherapy treatment design is currently an ad hoc process of pre-clinical and clinical trials using one or more agents against particular tumor types. The combinatorial nature alone precludes testing of all possible drug combinations and tumor types. And though designer drugs (e.g., Gleevec) provide treatment advantage when detailed mechanistic information is available, broader-spectrum cytotoxic agents continue to see widespread acceptance, with modest patient benefit. We postulate that a model-based treatment design system, coupled with clinically relevant mathematical models of key disease processes – tumor growth and spread; drug-induced and biological anti-tumor effect; toxicity – could provide a decision-support framework allowing clinical professionals to more effectively deliver personalized chemotherapy regimens that improve patient outcomes (*e.g.*, survival, quality of life, etc.).

We focus at present on the improved use of proven anticancer agents, including gemcitabine (pancreatic and lung cancer) and docetaxel (head/neck and ovarian, among other cancer types). A model-based approach to clinical decision support is developed by combining models of drug pharmacokinetics, tumor growth, drug efficacy, and drug-induced toxicity with a receding horizon control/optimization formulation commonly used to control industrial processes in the field of engineering. The result is an algorithm that incorporates clinical understanding (through mathematical models at a variety of scales), addresses logistical and other clinically relevant constraints (as a function of the receding horizon formulation), and may provide caregivers with alternative treatment schedules that are more patient-centered (outcome, quality of life, or both).

Associated Cancer Types/Areas: types: pancreatic, lung, head, and neck; areas: personalized medicine, decision support

Keywords: chemotherapy, mathematical modeling, systems medicine

128. Mechanical Properties of Cancer Cells: A Possible Biomarker for Stemness

National Science Foundation
Ohio University

David F.J. Tees, Ameneh Mohammadalipour, Monica M. Burdick, Fabian Benencia

Ohio University

There is evidence that cell deformability can be used as a biomarker to distinguish between healthy and cancerous cells. Cell deformability depends on the properties of the cytoplasm, the cytoskeleton and the nucleus, and can be defined in terms of the strain response of the cell to an applied stress. Two different cell mechanical behaviors have been observed: 1) circulating white blood cells behave as liquid drops with a cortical tension; 2) most tissue cells behave as viscoelastic solids. Micropipette aspiration was used to investigate deformability differences between two breast cancer cell lines. Hs578T breast cancer cells have been reported to have a stem-like phenotype, whereas BT-20 cells are more recognized as being non-stem-like. Individual cancer cells were aspirated under controlled pressures into small glass micropipettes with radius, R, smaller than the cell radius. The length of the aspirated section of the cell inside the micropipette, L, was measured. Graphs of cell deformation (L/R) versus applied pressure, showed a linear trend for small deformations for both BT-20 and Hs578T cells, while for large deformations, the graphs were no longer linear. One possible explanation is that above a deformation threshold, the cells were exhibiting liquid-like behavior. When cells were aspirated using a large, constant aspiration pressure, half of the cells entered the micropipettes at constant pressure, a characteristic of liquid drops. It could be concluded that for small deformations, cells exhibit solid-like behavior, while for larger deformations they could exhibit liquid-like or viscoelastic behaviors. Our hypothesis is that the stem-like or non-stem-like phenotype of cancer cells is correlated with differences in mechanical properties. These mechanical properties could be used as a biomarker for stemness of cells, which could eventually lead to a new diagnostic method. This work was supported by grant CBET-1106118 from the National Science Foundation.

Associated Cancer Types/Areas: breast cancer, metastasis

Keywords : cancer stem cells; cell mechanical properties; micropipette aspiration, cancer heterogeneity, ctcs and metastasis: staring at the tip of the iceberg

129. Mechanical Properties of Cells Undergoing Neoplastic Transformation

National Science Foundation
Cell Mechanics of Protein Mobility during Neoplastic Transformation

Keith Bonin[1], Martin Guthold[1], Jed Macosko[1], George Holzwarth[1], Anita McCauley[1], Karin Scarpinato[2], Xinyi Guo[1], Justin Sigley[1], Amanda Smelser[1], John Jarzen[2]

[1]Wake Forest University, [2]Georgia Southern University

We will report on measurements of the mechanical properties of cells that are undergoing neoplastic transformation. The cells in our study consist of normal, immortalized, and tumorigenic versions of human mammary epithelial cells (the Weinberg cell line). The cells are grown on glass substrates that are functionalized with poly-d-lysine. We are measuring the elastic moduli of the cytoplasmic and nuclear regions of the different cells using an Atomic Force Microscope (AFM) with a 5.3 um diameter spherical probe. In the AFM experiments the modulus measurements are performed on cells that are isolated, that are in the center of a small colony, and that are on the periphery of a small colony. We are also measuring the diffusion of mismatch repair proteins in the different cells using a confocal microscope using two methods: Fluorescence Recovery After Photobleaching (FRAP) and Raster Imaging Correlation Spectroscopy (RICS). Finally, we are also measuring the diffusion and transport of different natural organelles such as lysosomes and peroxisomes using particle tracking microscopy, and we are using these measurements to extract the viscosity of the cytoplasm of the three different states of the cancer cells. This paper will report the results and status of all three methods for measuring the mechanical properties of the cells undergoing neoplastic transformation.

Associated Cancer Types/Areas: breast cancer

Keywords: modulus, AFM, FRAP

Agenda

TUESDAY, APRIL 16

2:00 p.m. - 7:00 p.m.	**Registration**	Foyer
3:00 p.m. - 3:05 p.m.	**Welcome and Opening Remarks** Jonathan Franca-Koh, Ph.D. National Cancer Institute, NIH	Grand Ballroom
3:05 p.m. - 3:15 p.m.	**Young Investigator Award Process Tutorial** Sean E. Hanlon, Ph.D. National Cancer Institute, NIH	Grand Ballroom
3:15 p.m. - 4:30 p.m.	**Speed Networking – Connecting Trainees at the Intersection of Physical Sciences and Cancer Biology** Moderators: Nicole Moore, Sc.D. National Cancer Institute, NIH Nastaran Zahir Kuhn, Ph.D. National Cancer Institute, NIH	Grand Ballroom
4:30 p.m. - 4:45 p.m.	**Break**	
4:45 p.m. - 7:00 p.m.	**Young Investigator Professional Development** Moderator: Michael G. Espey, Ph.D. National Cancer Institute, NIH	Grand Ballroom
4:45 p.m. - 5:05 p.m.	***From Bench to Bedside to Bench – A Union of Basic and Clinical Sciences*** Joseph R. Mikhael, M.D. Associate Professor, Mayo College of Medicine Arizona State University PS-OC	
5:05 p.m. - 5:25 p.m.	***The Business of Science - One Person's Experience*** Stuart Lindsay, Ph.D. Regent's Professor, Arizona State University Director, Center for Single Molecule Biophysics Arizona State University PS-OC	
5:25 p.m. - 5:45 p.m.	***Managing Transition (provisional title)*** Xiaolin Nan, Ph.D. Assistant Professor, Center for Spatial Systems Biomedicine Oregon Health & Science University University of California, Berkeley PS-OC	

5:45 p.m. - 6:05 p.m. ***From Incision to Decision: A Surgeon's Experience With Generation of New Knowledge***

John (Kim) M. Jessup, M.D.
Chief, Diagnostics Evaluation Branch, Cancer Diagnosis Program DCTD, National Cancer Institute, NIH
Adjunct Investigator, Laboratory of Experimental Carcinogenesis
CCR, National Cancer Institute, NIH

6:05 p.m. - 6:35 p.m. **Panel Discussion – Q&A**

Joseph R. Mikhael, M.D.
Associate Professor, Mayo College of Medicine
Arizona State University PS-OC

Stuart Lindsay, Ph.D.
Regent's Professor, Arizona State University
Director, Center for Single Molecule Biophysics
Arizona State University PS-OC

Xiaolin Nan, Ph.D.
Assistant Professor, Center for Spatial Systems Biomedicine
Oregon Health & Science University
University of California, Berkeley PS-OC

John (Kim) M. Jessup, M.D.
Chief, Diagnostics Evaluation Branch, Cancer Diagnosis Program, DCTD, National Cancer Institute, NIH
Adjunct Investigator, Laboratory of Experimental Carcinogenesis
CCR, National Cancer Institute, NIH

6:35 p.m. - 6:40 p.m. **Closing Remarks and Adjournment**

Jonathan Franca-Koh, Ph.D.
National Cancer Institute, NIH

WEDNESDAY, APRIL 17

8:00 a.m. - 11:30 a.m. **Registration** Foyer

8:00 a.m. - 8:05 a.m. **Welcome and Opening Remarks**
Michael G. Espey, Ph.D.
National Cancer Institute, NIH

8:05 a.m. - 9:05 a.m. **Session 1: Modeling Cancer** Grand Ballroom
Moderator: Luis Cisneros, Ph.D.
Arizona State University
Arizona State University PS-OC

8:05 a.m. - 8:20 a.m. ***Darwinian Dynamics and Current Concepts of Driver and Passenger Mutations***
Jessica Cunningham, M.S.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

8:20 a.m. - 8:35 a.m. ***Control of Stochastic Switching in Biological Networks***
Daniel K. Wells, M.S.
Northwestern University
Northwestern University PS-OC

8:35 a.m. - 8:50 a.m. ***Dynamics of Evolutionary Innovation in Cancer***
Kirill S. Korolev, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC

8:50 a.m. - 9:05 a.m. ***Time Scales in the Probabilistic Spread of Defective Mutants***
Philipp M. Altrock, Ph.D.
Dana-Farber Cancer Institute
Dana-Farber Cancer Institute PS-OC

9:05 a.m. - 10:20 a.m. **Session 2: Genome to Phenotype**
Moderator: Vivek Nandakumar, M.S.
Arizona State University
Arizona State University PS-OC

9:05 a.m. - 9:20 a.m. ***Doxorubicin Enhances Nucleosome Turnover Around Active Gene Promoters***
Fan Yang, Ph.D.
Fred Hutchinson Cancer Research Center
Arizona State University PS-OC

9:20 a.m. - 9:35 a.m. ***Predictive Biophysical Modeling of Dose Response of Tumor Cells Treated With Free Drug and Protocells***
Jennifer Pascal, Ph.D.
University of New Mexico
The Methodist Hospital Research Institute PS-OC

9:35 a.m. - 9:50 a.m. ***Dual-Mode Cellular Energetics and the Warburg Effect***
Tamir Epstein, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC

9:50 a.m. - 10:05 a.m. ***Modeling the Switch From Tumor Dormancy to Rapid Proliferation***
Duyu Chen
Princeton University
Princeton University PS-OC

10:05 a.m. - 10:20 a.m. ***A Phenotypic Signature of Pancreatic Cancer Metastasis***
Jude M. Phillip, B.Eng.
Johns Hopkins University
Johns Hopkins University PS-OC

10:20 a.m. - 10:35 a.m. **Break**

10:35 a.m. - 11:35 a.m. **Session 3: Cancer Cells on the Move** Grand Ballroom
Moderator: Colin Flinders
University of Southern California
University of Southern California PS-OC

10:35 a.m. - 10:50 a.m. ***Leading Malignant Cells Initiate Collective Epithelial Cell Invasion in a Three-Dimensional Heterotypic Tumor Spheroid Model***
Shawn P. Carey
Cornell University
Cornell University PS-OC

10:50 a.m. - 11:05 a.m. ***Localized Modulation of Genomic Transcriptional Activity Driven by Extracellular Stiffness Cues in 3D***
Russell Bainer, Ph.D.
University of California, San Francisco
University of California, Berkeley PS-OC

11:05 a.m. - 11:20 a.m. ***Heterogeneity in Cell-Matrix Adhesion as an Indicator of Metastatic State***
Alexander Fuhrmann, Ph.D.
University of California, San Diego
Princeton University PS-OC

11:20 a.m. - 11:35 a.m. ***Colon Adenocarcinoma Cell Recruitment to Platelets and Thrombi Under Shear***
Sandra Baker-Groberg
Oregon Health & Science University
The Scripps Research Institute PS-OC

11:35 a.m. - 11:40 a.m. **Closing Remarks and Adjournment**
Michael G. Espey, Ph.D.
National Cancer Institute, NIH

Darwinian Dynamics and Current Concepts of Driver and Passenger Mutations
Jessica Cunningham, M.S.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC
Poster Abstract Number: 59

Control of Stochastic Switching in Biological Networks
Daniel K. Wells, M.S.
Northwestern University
Northwestern University PS-OC
Poster Abstract Number: 68

Dynamics of Evolutionary Innovation in Cancer
Kirill S. Korolev, Ph.D.
Massachusetts Institute of Technology
Massachusetts Institute of Technology PS-OC
Poster Abstract Number: 40

Time Scales in the Probabilistic Spread of Defective Mutants
Philipp M. Altrock, Ph.D.
Dana-Farber Cancer Institute
Dana-Farber Cancer Institute PS-OC
Poster Abstract Number: 28

Doxorubicin Enhances Nucleosome Turnover Around Active Gene Promoters
Fan Yang, Ph.D.
Fred Hutchinson Cancer Research Center
Arizona State University PS-OC
Poster Abstract Number: 6

Predictive Biophysical Modeling of Dose Response of Tumor Cells Treated With Free Drug and Protocells
Jennifer Pascal, Ph.D.
University of New Mexico
The Methodist Hospital Research Institute PS-OC
Poster Abstract Number: 54

Dual-Mode Cellular Energetics and the Warburg Effect
Tamir Epstein, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
H. Lee Moffitt Cancer Center & Research Institute PS-OC
Poster Abstract Number: 60

Modeling the Switch From Tumor Dormancy to Rapid Proliferation
Duyu Chen
Princeton University
Princeton University PS-OC
Poster Abstract Number: 88

A Phenotypic Signature of Pancreatic Cancer Metastasis
Jude M. Phillip, B.Eng.
Johns Hopkins University
Johns Hopkins University PS-OC
Poster Abstract Number: 30

Leading Malignant Cells Initiate Collective Epithelial Cell Invasion in a Three-Dimensional Heterotypic Tumor Spheroid Model
Shawn P. Carey
Cornell University
Cornell University PS-OC
Poster Abstract Number: 14

Localized Modulation of Genomic Transcriptional Activity Driven by Extracellular Stiffness Cues in 3D
Russell Bainer, Ph.D.
University of California, San Francisco
University of California, Berkeley PS-OC
Poster Abstract Number: 110

Heterogeneity in Cell-Matrix Adhesion as an Indicator of Metastatic State
Alexander Fuhrmann, Ph.D.
University of California, San Diego
Princeton University PS-OC
Poster Abstract Number: 85

Colon Adenocarcinoma Cell Recruitment to Platelets and Thrombi Under Shear
Sandra Baker-Groberg
Oregon Health & Science University
The Scripps Research Institute PS-OC
Poster Abstract Number: 97

Participant List

David B. Agus, M.D.
Keck School of Medicine
Viterbi School of Engineering
University of Southern California
(310) 272-7650
agus@usc.edu

Ivie Aifuwa, Ph.D.
Chemical and Biomolecular Engineering
Johns Hopkins University
(732) 887-6104
aifuwa@jhu.edu

Turi Alcoser
Department of Biomedical Engineering
Cornell University
(201) 426-0281
taa49@cornell.edu

Jenolyn Francisca Alexander, M.S., B.Eng.
Department of Nanomedicine
The Methodist Hospital Research Institute
(713) 441-7834
jalexander2@tmhs.org

Philipp M. Altrock, Ph.D.
Department of Biostatistics and Computational Biology
Harvard School of Public Health
Dana-Farber Cancer Institute
(857) 207-6075
paltrock@jimmy.harvard.edu

Eva Amouzougan
Center for Personalized Diagnostics
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
eamouzou@asu.edu

Alexander R. Anderson, Ph.D.
Integrated Mathematical Oncology
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-4316
alexander.anderson@moffitt.org

Karen Anderson, M.D., Ph.D.
Personalized Diagnostics Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
karen.anderson.1@asu.edu

Iris Appelmann, M.D.
Cancer Biology and Genetics Program
Memorial Sloan-Kettering Cancer Center
(646) 888-3340
appelmai@mskcc.org

Melissa Aranzamendez, M.A.
Princeton University
(609) 258-2602
maranzam@princeton.edu

Brian Ashcroft, Ph.D.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
brian.ashcroft@asu.edu

Robert H. Austin, Ph.D.
Department of Physics
Princeton University
(609) 258-2602
austin@princeton.edu

Vanessa Baack
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
vanessa.baack@asu.edu

Russell Bainer, Ph.D.
Department of Surgery
Center for Bioengineering and Tissue Regeneration
University of California, San Francisco
(773) 915-3426
russell.bainer@ucsfmedctr.org

Sandra Baker-Groberg
Oregon Health & Science University
(503) 459-1358
bakers505@gmail.com

Anna D. Barker, Ph.D.
Arizona State University
(480) 727-0898
anna.barker@asu.edu

Sebastian F. Barreto Ortiz
Department of Chemical and Biomolecular Engineering
Johns Hopkins University
(610) 390-4094
barretos@jhu.edu

Gregory T. Baxter, Ph.D.
CCS Associates, Inc.
(650) 963-8103
gbaxter@ccsainc.com

Jaime J. Benitez, Ph.D.
Selected Cell Epigenomic Analysis Core Center on the Microenvironment and Metastasis
Cornell University
(607) 592-4432
jb356@cornell.edu

Kelly J. Bethel, M.D.
The Scripps Research Institute
(858) 472-8848
bethel.kelly@scrippshealth.org

Mona P. Bisase, M.B.A.
The Methodist Hospital Research Institute
(713) 441-4889
mpbisase@tmhs.org

Joel S. Brown, Ph.D.
Department of Biological Sciences
University of Illinois at Chicago
(708) 925-5032
squirrel@uic.edu

Cynthia Buness
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
cynthia.buness@cox.net

Kimberly Bussey, Ph.D.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
kimberly.bussey@asu.edu

Mario Cabodi, Ph.D.
Department of Biomedical Engineering
Boston University
(617) 358-1793
cabodi@bu.edu

Shawn P. Carey
Department of Biomedical Engineering
Cornell University
(860) 877-1247
spc73@cornell.edu

Anders Carlsson, Ph.D.
The Scripps Research Institute
(858) 784-7197
canders@scripps.edu

Arup Chakraborty, Ph.D.
Massachusetts Institute of Technology
(617) 253-3890
arupc@mit.edu

Siddarth Chandrasekaran, Ph.D.
Department of Biomedical Engineering
Cornell University
(817) 889-0683
sc2389@cornell.edu

Sara Che
Biomedical Engineering
Cornell University
(607) 379-1667
spc77@cornell.edu

Duyu Chen
Princeton University
(609) 258-3341
duyu@princeton.edu

Huanhuan Chen, M.S.
Cornell University
(718) 915-6396
hc642@cornell.edu

Matthew A. Cheney, M.A., M.S.
Department of Chemistry
Rice University
Surgical Oncology
The University of Texas MD Anderson Cancer Center
(713) 348-3476
mac5@rice.edu

Luis Cisneros, Ph.D.
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
cisluis@asu.edu

Deborah Collyar
Patient Advocates In Research (PAIR)
Princeton University
(925) 260-1006
deborah@tumortime.com

Stuart J. Corr, Ph.D.
The University of Texas MD Anderson Cancer Center
Rice University
(832) 785-0271
sjcorr@mdanderson.org

Vittorio Cristini, Ph.D.
University of New Mexico
(505) 272-9008
vcristini@salud.unm.edu

Michael M. Crow, Ph.D.
Arizona State University
(480) 965-8972
michael.crow@asu.edu

Jessica Cunningham, M.S.
H. Lee Moffitt Cancer Center & Research Institute
(813) 434-3552
jessica.cunningham@moffitt.org

Steven A. Curley, M.D., FACS
Department of Surgical Oncology
Division of Surgery
The University of Texas MD Anderson Cancer Center
(713) 794-4957
scurley@mdanderson.org

Angel Ernesto Dago, Ph.D.
The Scripps Research Institute
(858) 784-7197
edago@scripps.edu

Mehdi Damaghi, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
(813) 457-8142
mehdi.damaghi@moffitt.org

Jessica Daniels, M.A.
Dana-Farber Cancer Institute
(631) 987-0061
jdaniels@jimmy.harvard.edu

Saheli S. Datta, M.S.
University of California, Berkeley
(510) 672-5090
saheli@berkeley.edu

Paul Davies, Ph.D.
Beyond Center for Fundamental Concepts in Science
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
paul.davies@asu.edu

Pauline Davies
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
pauline.davies@asu.edu

Paolo Decuzzi, Ph.D.
The Methodist Hospital Research Institute
(713) 441-7316
pdecuzzi@tmhs.org

Primal de Lanerolle, Ph.D.
Department of Physiology and Biophysics
University of Illinois at Chicago
(312) 996-6430
primal@uic.edu

Peter DelNero, B.E.
Cornell University
(913) 271-2229
pfd28@cornell.edu

Peter C. Doerschuk, M.D., Ph.D.
Department of Biomedical Engineering
Cornell University
(607) 255-2152
pd83@cornell.edu

Bryant Doss, M.S.
Center for the Convergence of Physical Science and Cancer Biology
Department of Physics
Arizona State University
(480) 965-3860
bryant.doss@asu.edu

Ellen Dreksler
Physics Department
University of California, Berkeley
(310) 597-9578
ellen@berkeley.edu

Christopher C. DuFort, Ph.D.
University of California, San Francisco
(360) 600-5830
chris.dufort@gmail.com

Beverly Emerson, Ph.D.
Regulatory Biology
Salk Institute
(858) 453-4100
emerson@salk.edu

Tegan Emerson
The Scripps Research Institute
(541) 420-6286
teganemerson@yahoo.com

Tamir Epstein, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
(734) 709-1844
tamir.epstein@gmail.com

Mandy B. Esch, Ph.D.
Cornell University
(607) 351-1121
mbe2@cornell.edu

Andrew Ewald, Ph.D.
Departments of Cell Biology and Oncology
Center for Cancer Nanotechnology Excellence
School of Medicine
Johns Hopkins University
(410) 614-9288
andrew.ewald@jhmi.edu

Mauro Ferrari, Ph.D.
The Methodist Hospital Research Institute
(713) 441-7250
mferrari@tmhs.org

Claudia Fischbach-Teschl, Ph.D.
Cornell University
(607) 255-4547
cf99@cornell.edu

Colin Flinders
University of Southern California
(818) 324-5503
colin.flinders@proteowizard.org

Hermann Frieboes, Ph.D.
University of Louisville
(502) 852-3302
hbfrie01@louisville.edu

Alexander Fuhrmann, Ph.D.
Department of Bioengineering
University of California, San Diego
Sanford Consortium for Regenerative Medicine
(623) 252-5907
afuhrmann@ucsd.edu

Zev J. Gartner, Ph.D.
Department of Pharmaceutical Chemistry
University of California, San Francisco
(415) 514-9962
zev.gartner@ucsf.edu

Robert A. Gatenby, M.D.
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-7376
geraldine.rodriguez@moffitt.org

Prashasnika Gehlot, Ph.D.
The University of Texas MD Anderson Cancer Center
(281) 435-2990
pgehlot@mdanderson.org

Daniele M. Gilkes, Ph.D., M.S., B.Eng.
School of Medicine
Johns Hopkins University
(321) 332-2776
dgilkes1@jhu.edu

Robert J. Gillies, Ph.D.
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-8355
robert.gillies@moffitt.org

Marie E. Godla
Department of Biomedical Engineering
Cornell University
(661) 972-2712
meg342@cornell.edu

Laura G. Gonzalez, Ph.D.
Center for Personalized Diagnostics
The Biodesign Institute
Arizona State University
(480) 965-1050
laura.g.gonzalez@asu.edu

William M. Grady, M.D.
Center for the Convergence of Physical Science and Cancer Biology
Fred Hutchinson Cancer Research Center
(480) 965-3860
william.grady@asu.edu

Adrienne Greene
Department of Molecular and Cell Biology
University of California, Berkeley
(510) 684-5828
acgreene@berkeley.edu

Jessica Han
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
jessica.h.han@asu.edu

Nanna Hansen, Ph.D.
Biosignatures Discovery Automation Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
nanna.hansen@asu.edu

Andrea Hawkins-Daarud, Ph.D.
Feinberg School of Medicine
Department of Neurological Surgery
Northwestern University
(312) 695-7136
andjhawkins@gmail.com

Lijuan He, Ph.D.
Johns Hopkins University
(443) 845-5987
lijuanh@jhu.edu

Stephanie Helland
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
stephanie.helland@asu.edu

Barbara L. Hempstead, M.D., Ph.D.
Cornell University
(212) 746-2195
blhemst@med.cornell.edu

Steven Henikoff, Ph.D.
Center for the Convergence of Physical Science and Cancer Biology
Fred Hutchinson Cancer Research Center
(480) 965-3860
steveh@fhcrc.org

Nathan Hodas, Ph.D.
Information Sciences Institute
University of Southern California
(626) 379-4863
nhodas@gmail.com

Eric C. Holland, M.D.
Memorial Sloan-Kettering Cancer Center
(646) 888-2561
hollande@mskcc.org

David A. Hormuth II, M.S.
Department of Biomedical Engineering
Institute of Imaging Science
Vanderbilt University
(615) 936-3328
david.a.hormuth@vanderbilt.edu

Jessica E. Hornick, Ph.D.
Feinberg School of Medicine
Northwestern University
(312) 503-2530
j-hornick@northwestern.edu

Sui Huang, M.D., Ph.D.
Institute for Systems Biology
(206) 732-1200
sui.huang@systemsbiology.org

Shen-Hsiu Hung
Department of Chemical Engineering
University of Florida
(352) 392-0862
shenhsiu@gmail.com

Brian Hurt
University of Southern California
(818) 836-0810
brianhur@usc.edu

Pamela Jackson, Ph.D.
Department of Neurological Surgery
Feinberg School of Medicine
Northwestern University
(312) 695-9417
pamela.jackson@northwestern.edu

Paul Janmey, Ph.D.
University of Pennsylvania
(215) 573-7380
janmey@mail.med.upenn.edu

Phillip Jess, Ph.D.
University of California, Berkeley
(510) 666-2786
phillip.jess@berkeley.edu

Roger Johnson, Ph.D.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
roger.h.johnson@asu.edu

Edwin F. Juarez Rosales
University of Southern California
(415) 699-5846
juarezro@usc.edu

Sheila M. Judge, Ph.D.
Chemistry of Life Processes Institute
Northwestern University
(847) 491-5868
s-judge@northwestern.edu

Benjamin Katchman, Ph.D.
Center for Personalized Diagnostics
Arizona State University
(480) 399-1563
benjamin.katchman@asu.edu

Susan M. Keating, Ph.D.
CCS Associates, Inc.
(650) 691-4400
skeating@ccsainc.com

Laimonas Kelbauskas, Ph.D.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
laimonas.kelbauskas@asu.edu

Shyam Khatau, Ph.D.
Chemical and Biomolecular Engineering
Johns Hopkins University
(508) 904-1985
shyam@jhu.edu

Beum Jun Kim, Ph.D.
Biological and Environmental Engineering
Cornell University
(607) 351-6775
bk37@cornell.edu

Eunjung Kim, Ph.D.
Integrated Mathematical Oncology
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-5186
eunjung.kim@moffitt.org

Hannah S. Kim
Department of Nanomedicine
The Methodist Hospital Research Institute
(713) 441-2172
hkim@tmhs.org

MunJu Kim, Ph.D.
Integrated Mathematical Oncology
H. Lee Moffitt Cancer Center & Research Institute
(412) 360-8181
munju.kim@moffitt.org

Yushan Kim
Department of Bioengineering
University of California, Berkeley
(510) 643-4191
yushan@berkeley.edu

Michael R. King, Ph.D.
Department of Biomedical Engineering
Cornell University
(607) 255-9803
mike.king@cornell.edu

Katsuhiro Kita, Ph.D.
Division of Hematology and Medical Oncology
Weill Medical College
Cornell University
(212) 746-0293
kak2040@med.cornell.edu

Anand Kolatkar, Ph.D.
The Scripps Research Institute
(858) 784-2514
anandk@scripps.edu

Konstantinos Konstantopoulos, Ph.D.
Department of Chemical and Biomolecular Engineering
Johns Hopkins University
(410) 516-6290
kkonsta1@jhu.edu

Kirill S. Korolev, Ph.D.
Massachusetts Institute of Technology
(617) 253-5088
korolev@mit.edu

Steven Kosak, Ph.D.
Robert H. Lurie Comprehensive Cancer Center
Feinberg School of Medicine
Northwestern University
(312) 503-9582
s-kosak@northwestern.edu

Nadezhda Koshkina, Ph.D.
Division of Surgical Oncology
The University of Texas MD Anderson Cancer Center
(713) 792-7183
nvkoshki@mdanderson.org

Peter Kuhn, Ph.D., M.S.
The Scripps Research Institute
(858) 784-9114
pkuhn@scripps.edu

Adriana Kuiper, M.B.A.
Arizona State University
(480) 727-7314
adriana.kuiper@asu.edu

Sanjay Kumar, M.D., Ph.D.
Department of Bioengineering
University of California, Berkeley
(510) 643-0787
skumar@berkeley.edu

Sudhir Kumar, Ph.D.
Center for Evolutionary Medicine and Informatics
Biodesign Institute and School of Life Sciences
Arizona State University
(623) 225-5230
s.kumar@asu.edu

Joshua LaBaer, M.D., Ph.D.
The Biodesign Institute
Arizona State University
(480) 965-2805
jlabaer@asu.edu

Mark A. LaBarge, Ph.D.
Lawrence Berkeley National Laboratory
(510) 485-4544
malabarge@lbl.gov

Larry Lam
Department of Molecular, Cell and Developmental Biology
University of California, Los Angeles
(626) 833-3201
larry.t.lam@ucla.edu

Justin Law
Rice University
(713) 348-3476
justin.j.law@rice.edu

Angela Lee, M.S.
Aerospace and Mechanical Engineering Department
University of Southern California
(909) 263-1885
angelamc@usc.edu

Joo Sang Lee, Ph.D.
Northwestern University
(847) 769-2329
joosang@northwestern.edu

Jung-Rok Lee, M.S.
Stanford University
(650) 796-8791
jungrok@stanford.edu

Tae-Rin Lee, Ph.D.
Department of Translational Imaging
The Methodist Hospital Research Institute
(847) 372-1972
taerin.lee@gmail.com

Wendy Mei-Chong Lee, M.S.
Department of Biomolecular Engineering
University of California, Santa Cruz
(408) 203-5666
wlee@soe.ucsc.edu

Michael Levin, Ph.D.
Biology Department
Tufts University
(617) 627-6161
michael.levin@tufts.edu

Ross L. Levine, M.D.
Memorial Sloan-Kettering Cancer Center
(646) 888-2767
leviner@mskcc.org

Yulin Li, M.D., Ph.D.
Division of Oncology
Stanford University
(814) 404-6088
yulinli@stanford.edu

David Liao, Ph.D.
Department of Pathology
University of California, San Francisco
(908) 455-8787
david.liao@ucsf.edu

Jonathan D. Licht, M.D.
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
(312) 503-1114
akelly1@nmff.org

Stuart Lindsay, Ph.D.
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
stuart.lindsay@asu.edu

Charles Lineweaver, Ph.D.
Planetary Science Institute
Research School of Astronomy and Astrophysics and
Research School of Earth Sciences
Australian National University
61-2-6125-6717
charley@mso.anu.edu.au

Jan T. Liphardt, Ph.D.
Physics Department
University of California, Berkeley
Lawrence Berkeley National Laboratory
(510) 666-2784
liphardt@berkeley.edu

Heping Liu, Ph.D.
The University of Texas MD Anderson Cancer Center
(713) 792-8977
hepliu@mdanderson.org

Liyu Liu, Ph.D.
Institute of Physics
Chinese Academy of Sciences
86-18612111924
liu@iphy.ac.cn

Mark Lloyd, M.S.
H. Lee Moffitt Cancer Center & Research Institute
(813) 541-1238
mark.lloyd@moffitt.org

Fernando Lopez-Diaz, Ph.D.
Salk Institute
(858) 453-4100
lopezdiaz@salk.edu

Andrew Loza, B.Eng.
Washington University in St. Louis
(614) 204-2964
lozaa@wusm.wustl.edu

Madelyn Luttgen
The Scripps Research Institute
(858) 784-7179
mluttgen@scripps.edu

Paul Macklin, Ph.D.
Center for Applied Molecular Medicine
University of Southern California
(310) 701-5785
paul.macklin@usc.edu

D. Mitchell Magee, Ph.D.
Center for Personalized Diagnostics
The Biodesign Institute
Arizona State University
(480) 727-0857
mitch.magee@asu.edu

Parag Mallick, Ph.D.
Canary Center for Cancer Early Detection
Stanford University
Center for Applied Molecular Medicine
University of Southern California
(650) 724-0923
paragm@stanford.edu

Scott Manalis, Ph.D.
Massachusetts Institute of Technology
(617) 253-5039
scottm@media.mit.edu

John F. Marko, Ph.D.
Department of Molecular Biosciences
Department of Physics and Astronomy
Northwestern University
(847) 467-1276
john-marko@northwestern.edu

Jocelyn Marshall, M.S.
Cornell University
(330) 554-7574
jocelyn.r.marshall@gmail.com

Brooke N. Mason, M.S.
Department of Biomedical Engineering
Cornell University
(989) 385-0904
bns39@cornell.edu

Jeremy Mason, M.S.
University of Southern California
(337) 349-8718
masonj@usc.edu

Michael McCoy
Biological Engineering
University of Missouri, Columbia
Biomedical Enginering
Cornell University
(417) 848-6729
mgm274@cornell.edu

Christopher D. McFarland
Harvard University
(518) 860-2834
christopherdmcfarland@gmail.com

Alexandra L. McGregor
Biomedical Engineering
Cornell University
(248) 802-8313
alm358@cornell.edu

Deirdre Meldrum, Ph.D.
Center for Biosignatures Discovery Automation
Arizona State University
(480) 965-3860
deirdre.meldrum@asu.edu

Joseph R. Mikhael, M.D.
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
mikhael.joseph@mayo.edu

Adilson E. Motter, Ph.D.
Department of Physics and Astronomy
Northwestern University
(847) 491-4611
motter@northwestern.edu

Shannon Mumenthaler, Ph.D.
Department of Medicine
Center for Applied Molecular Medicine
University of Southern California
(323) 442-2529
smumenth@usc.edu

Xiaolin Nan, Ph.D.
Department of Biomedical Engineering
Knight Cancer Institute
Oregon Health & Science University
(503) 418-9317
nan@ohsu.edu

Vivek Nandakumar, M.S.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
vivek.nandakumar@asu.edu

David Nanus, M.D.
Division of Hematology/Oncology
Weill Cornell Medical College
Cornell University
(646) 962-2084
dnanus@med.cornell.edu

Timothy Newman, Ph.D.
School of Engineering, Physics and Mathematics
University of Dundee
+44 (0)1382 385880
t.newman@dundee.ac.uk

Paul K. Newton, Ph.D.
Department of Aerospace and Mechanical Engineering and Mathematics
University of Southern California
(213) 740-7782
newton@usc.edu

John Nicoll
Center for Applied Molecular Medicine
University of Southern California
(323) 442-2537
jnicoll@proteowizard.org

Jorge J. Nieva, M.D.
Billings Clinic
(406) 238-2500
jnieva@billingsclinic.org

Thomas V. O'Halloran, Ph.D.
Department of Chemistry
Chemistry of Life Processes Institute
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
(847) 491-5060
t-ohalloran@northwestern.edu

Anna Lisa Palange
The Methodist Hospital Research Institute
(713) 576-9749
apalange@tmhs.org

Robert S. Parker, Ph.D.
Department of Chemical and Petroleum Engineering
Swanson School of Engineering
University of Pittsburgh
(412) 624-7364
rparker@pitt.edu

Jennifer Pascal, Ph.D.
University of New Mexico
(931) 881-4464
japascal@gmail.com

Katherin Patsch, Ph.D.
Center for Applied Molecular Medicine
Keck School of Medicine
University of Southern California
(323) 381-9274
kpatsch@usc.edu

Matteo Pellegrini, Ph.D.
University of California, Los Angeles
(310) 825-0012
matteop@mcdb.ucla.edu

Beatriz Penalver Bernabe, M.S.
Chemical and Biological Engineering Department
Northwestern University
(847) 467-6720
bpenalver@u.northwestern.edu

Brianne Petritis, B.S.
Center for Personalized Diagnostics
Arizona State University
(480) 965-7049
bpetriti@asu.edu

Shelly Peyton, Ph.D.
University of Massachusetts, Amherst
(413) 545-1133
speyton@ecs.umass.edu

Jude M. Phillip, B.Eng.
Chemical and Biomolecular Engineering Department
Institute for NanoBioTechnology
Johns Hopkins University
(917) 224-9054
jphillip@jhu.edu

Benette Phillips, Ph.D.
Robert H. Lurie Comprehensive Cancer Center
Northwestern University
(312) 503-7883
schallma@northwestern.edu

Rob Phillips, Ph.D.
California Institute of Technology
(818) 919-2142
phillips@pboc.caltech.edu

Kenneth J. Pienta, M.D.
Johns Hopkins University
(734) 604-2168
kpienta@umich.edu

Teresa J. Porri, Ph.D.
Cornell Center on the Microenvironment and Metastasis
Cornell University
(607) 220-6006
tp252@cornell.edu

Sue Porterfield, M.S.
Institute for NanoBioTechnology
Johns Hopkins University
(410) 516-3423
sporterfield@jhu.edu

Nader Pourmand, Ph.D.
UCSC-PPS-OC
(831) 502-7315
pourmand@soe.ucsc.edu

Yvonne A. Reid, Ph.D.
ATCC
(703) 365-2737
yreid@atcc.org

Katarzyna A. Rejniak, Ph.D.
Mathematical Oncology Department
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-6918
kasia.rejniak@moffitt.org

Erin C. Rericha, Ph.D.
Department of Physics
Vanderbilt University
(202) 306-5473
erin.rericha@vanderbilt.edu

Jessica Reynolds, M.S.
H. Lee Moffitt Cancer Center & Research Institute
(989) 326-2307
jessica.cunningham@moffitt.org

Mark Robertson-Tessi, Ph.D.
Integrated Mathematical Oncology
H. Lee Moffitt Cancer Center & Research Institute
(813) 745-6818
mark.robertsontessi@moffitt.org

Russell Rockne, M.S.
Feinberg School of Medicine
Northwestern University
(312) 695-7985
russell.rockne@northwestern.edu

Mariam Rodriguez Lee, Ph.D.
The Scripps Research Institute
(858) 784-7197
mrlee@scripps.edu

Robert Ros, Ph.D.
Center for the Convergence of Physical Science and Cancer Biology
Department of Physics
Arizona State University
(480) 965-3860
robert.ros@asu.edu

Gabriel Rosanio
Department of Molecular Biosciences
Integrated Biological Sciences Program
Northwestern University
(847) 491-5504
g-rosanio@northwestern.edu

Dan Ruderman, Ph.D.
Keck School of Medicine
University of Southern California
(323) 664-0734
ruderman@usc.edu

Carmen Ruiz, Ph.D.
The Scripps Research Institute
(858) 784-7197
carmenrv@scripps.edu

Jason H. Sakamoto, Ph.D.
The Methodist Hospital Research Institute
(713) 441-7350
jhsakamoto@tmhs.org

Chris Sander, Ph.D.
Memorial Sloan-Kettering Cancer Center
(646) 888-2602
sanderc@mskcc.org

Sebastian Sandersius, Ph.D.
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
sebastian.sandersius@gmail.com

Michael Sara
Chemistry of Life Processes Institute
Northwestern University
(847) 467-4488
m-sara@northwestern.edu

David J. Savage
The Methodist Hospital Research Institute
(903) 780-6561
dsavage@gmail.com

Randolph L. Schaffer, M.D., FACS
Center for Organ Transplantation
The Scripps Research Institute
(858) 829-4289
schaffer.randolph@scrippshealth.org

Brett J. Schofield
Department of Molecular and Cellular Biology
University of California, Berkeley
(510) 666-2786
brett.scho@berkeley.edu

Amy Sebeson
Northwestern University
(630) 738-1003
acsebeson@gmail.com

Subhadip Senapati, M.S.
Center for the Convergence of Physical Science and Cancer Biology
Center for Single Molecule Biophysics
Arizona State University
(480) 965-3860
ssenapa2@asu.edu

Patti Senechal-Willis, M.S.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
patti.senechal-willis@asu.edu

Haifa Shen, Ph.D.
Department of NanoMedicine
The Methodist Hospital Research Institute
(713) 441-7321
hshen@tmhs.org

Quanming Shi, Ph.D.
Department of Physics
University of California, Berkeley
(510) 666-2786
squanming@gmail.com

Michael L. Shuler, Ph.D.
Cornell University
(607) 255-7577
mls50@cornell.edu

Caroline Sigman, Ph.D.
CCS Associates, Inc.
(650) 691-4400
csigman@ccsainc.com

Nikolai Slavov, Ph.D.
Departments of Physics and Biology
Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology
(609) 933-7517
nslavov@mit.edu

J. Rory Staunton, M.S.
Center for the Convergence of Physical Science and Cancer Biology
Department of Physics
Arizona State University
(480) 965-3860
jrstaunt@asu.edu

Mark Stevens
Department of Biology
Koch Institute for Integrative Cancer Research
Massachusetts Institute of Technology
(206) 250-1043
markms@mit.edu

Tracy Stokol, D.V.M., Ph.D.
College of Veterinary Medicine
Cornell University
(607) 253-3255
tracy.stokol@cornell.edu

Karen A. Strauss, D.P.H., M.S.
Patient Advocate
Northwestern University
(847) 899-3650
straussk@mac.com

Kimberly Stroka, Ph.D.
Institute for NanoBioTechnology
Johns Hopkins University
(410) 516-3857
kstroka@jhu.edu

Jim Sturm, Ph.D.
Princeton University
(609) 258-5610
sturm@princeton.edu

Yvonne Suarez
University of Southern California
(323) 442-2596
yvonnes@usc.edu

Sean Sun, Ph.D.
Johns Hopkins University
(410) 516-4003
ssun@jhu.edu

Kristin R. Swanson, Ph.D.
Feinberg School of Medicine
Department of Neurological Surgery
Northwestern University
(312) 695-7933
kristin.swanson@northwestern.edu

David Tarin, M.D., Ph.D.
University of California, San Diego
(858) 361-3658
dtarin@ucsd.edu

David Tees, Ph.D.
Department of Physics and Astronomy
Ohio University
(740) 593-1694
tees@ohio.edu

Fredrik Thege, M.S.
Department of Biomedical Engineering
Cornell University
(949) 933-1193
fredrik.thege@gmail.com

Atma Thompson
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
atma.thompson@asu.edu

Thea D. Tlsty, Ph.D.
University of California, San Francisco
(415) 502-6115
thea.tlsty@ucsf.edu

Thai Tran, Ph.D.
Center for Biosignatures Discovery Automation
Center for the Convergence of Physical Science and Cancer Biology
Arizona State University
(480) 965-3860
thai.tran@asu.edu

Yiider Tseng, Ph.D.
University of Florida
(352) 392-0862
ytseng@che.ufl.edu

Darren Tyson, Ph.D.
Department of Cancer Biology
Vanderbilt University
(615) 936-1975
darren.tyson@vanderbilt.edu

Anne L. van de Ven, Ph.D.
Department of Nanomedicine
The Methodist Hospital Research Institute
(713) 441-7449
avandeven@tmhs.org

Mandana Veiseh, Ph.D.
Lawrence Berkeley National Laboratory
(206) 235-3362
mveiseh@lbl.gov

Saurabh Vyawahare, Ph.D.
Princeton University
(626) 840-9823
saurabhv@princeton.edu

Sara Walker, Ph.D.
NASA Astrobiology Institute
Arizona State University
(480) 965-3860
sara.i.walker@asu.edu

Damian Walsh
Department of Nanomedicine
The Methodist Hospital Research Institute
(713) 441-7312
dcwalsh@tmhs.org

Ji-Ping Wang, Ph.D.
Northwestern University
(847) 204-7809
jzwang@northwestern.edu

Shan X. Wang, Ph.D.
Stanford University
(650) 723-8671
sxwang@stanford.edu

Elizabeth Wayne
Biomedical Engineering
Cornell University
(215) 840-3214
ecw74@cornell.edu

Valerie M. Weaver, Ph.D.
University of California, San Francisco
(415) 476-3826
valerie.weaver@ucsfmedctr.org

Zhubo Wei, Ph.D.
Cancer Biology Program
The Methodist Hospital Research Institute
(713) 441-1135
zwei@tmhs.org

Daniel K. Wells, M.S.
Northwestern University
(847) 491-4602
danielwells2015@u.northwestern.edu

Jillian L. Werbeck, Ph.D.
Memorial Sloan-Kettering Cancer Center
(315) 345-5571
werbeckj@mskcc.org

Lon J. Wilson, Ph.D.
Department of Chemistry
Rice University
(713) 348-3268
durango@rice.edu

Denis Wirtz, Ph.D.
Departments of Chemical and Biomolecular Engineering, Pathology, and Oncology
Johns Hopkins University
(410) 516-7006
wirtz@jhu.edu

Andrew D. Wong
Center for Cancer Physics
Physics of Cancer Microfabrication Core
Johns Hopkins University
(949) 378-6900
adwong@jhu.edu

Joyce Wong, Ph.D.
Biomedical Engineering and Division of Materials Science and Engineering
Boston University
(617) 353-2374
jywong@bu.edu

Amy Wright, M.B.A.
The Methodist Hospital Research Institute
(713) 441-7267
aswright@tmhs.org

Amy Wu, M.S.
Princeton University
(609) 258-4774
amywu@princeton.edu

Pei-Hsun Wu, Ph.D.
Department of Chemical and Biomolecular Engineering
Johns Hopkins University
(352) 514-6041
pwu@jhu.edu

Fan Yang, Ph.D.
Fred Hutchinson Cancer Research Center
(480) 965-3860
fyang@fhcrc.org

Insoon Yang
Department of Electrical Engineering and Computer Sciences
University of California, Berkeley
(415) 706-1685
iyang@eecs.berkeley.edu

Thomas Yankeelov, Ph.D.
Institute of Imaging Science
Vanderbilt-Ingram Cancer Center
Vanderbilt University
(615) 322-8359
thomas.yankeelov@vanderbilt.edu

Clare Yu, Ph.D.
University of California, Irvine
(949) 212-1549
cyu@uci.edu

Yoshihiro Yui, Ph.D.
Department of Surgery
University of California, San Francisco
(415) 476-3973
yoshihiro.yui@gmail.com

Nir Yungster, M.S.
Northwestern University
(440) 552-9051
niryungster@gmail.com

Peiming Zhang, Ph.D.
Arizona State University
(480) 965-5491
pzhang8@asu.edu

Federal Participants

Joseph Alper, M.S.
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
Life Science and Nanotechnology Consulting, LLC
(303) 641-8107
joe@lsncon.com

Tony Dickherber, Ph.D.
Center for Strategic Scientific Initiatives
Office of the Director
National Cancer Institute
National Institutes of Health
(301) 547-9980
anthony.dickherber@nih.gov

Mariam Eljanne, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 443-3612
eljannem@mail.nih.gov

Michael G. Espey, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-3388
michael.espey@nih.gov

Jonathan Franca-Koh, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-3388
jonathan.franca-koh@nih.gov

Emily Greenspan, Ph.D.
Center for Strategic Scientific Initiatives
Office of the Director
National Cancer Institute
National Institutes of Health
(301) 451-0943
greenspanej@mail.nih.gov

Sean E. Hanlon, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-2481
sean.hanlon@nih.gov

S. Percy Ivy, M.D.
Investigational Drug Branch
Cancer Therapy Evaluation Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
(240) 276-6565
percy.ivy@nih.gov

John M. Jessup, M.D.
Cancer Diagnosis Program
Division of Cancer Treatment and Diagnosis
National Cancer Institute
National Institutes of Health
(240) 276-5952
jessupj@mail.nih.gov

Nastaran Z. Kuhn, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-2472
nas.kuhn@nih.gov

Jerry S.H. Lee, Ph.D.
Office of the Director
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 496-1045
leejerry@mail.nih.gov

Nicole Moore, Sc.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 435-2486
nicole.moore@nih.gov

Larry A. Nagahara, Ph.D.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-3388
nagaharl@mail.nih.gov

Nicholas Panaro, Ph.D.
Nanotechnology Characterization Laboratory
SAIC-Frederick
(301) 693-2222
panaron@mail.nih.gov

Michelle D. Smith
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 496-0893
michelle.smith@nih.gov

Katrina I. Theisz, M.S.
Office of Physical Sciences-Oncology
Center for Strategic Scientific Initiatives
National Cancer Institute
National Institutes of Health
(301) 451-8210
theiszki@mail.nih.gov

About the Program

Mission

The mission of the National Cancer Institute's (NCI) Physical Sciences in Oncology Initiative is to foster the development of innovative ideas and new fields of study that converge perspectives and approaches of physical sciences and engineering with cancer biology and clinical oncology. Through the use of various funding mechanisms and outreach activities, we hope to join these often disparate areas of science to better understand the physical and chemical forces that shape and govern the emergence and behavior of cancer at all levels which will lead to exponential progress against cancer.

Background

To further explore how the NCI could more effectively engage the physical sciences in cancer research, three strategic "think tanks" were convened during 2008 to bring together thought leaders from the fields of physical sciences and engineering with leaders in the fields of cancer biology and clinical oncology.

Four general *themes* emerged from these NCI-sponsored strategic think tanks as new areas of investigation that are critical to understanding and ultimately controlling cancer:

- **Physics (Physical Laws and Principles) of Cancer:** Defining the role(s) of thermodynamics and mechanics in metastasis and determining how this knowledge might be employed in new intervention strategies.
- **Evolution and Evolutionary Theory of Cancer:** Developing a comprehensive theoretical inclusive construct that would provide a foundation for understanding and predicting cancer heterogeneity.
- **Information Coding, Decoding, Transfer, and Translation in Cancer:** Pursuing theoretical and supportive experimental approaches that define what information is and how it is decoded and managed in terms of cell signaling and contextual information translation in cancer.
- **Deconvoluting Cancer's Complexity:** Pursuing theoretical and experimental approaches from the physical sciences to cancer complexity that will inform a new fundamental level of understanding of cancer that may facilitate prediction of viable pathways to develop novel interventions.

Physical Sciences-Oncology Centers (PS-OCs) Program

As a first step of the initiative, a program consisting of a virtual network of PS-OCs was launched in the fall of 2009. The management of the network involves a cooperative agreement collaboration between an NCI project team, the awarded center principal investigators, and the PS-OC Steering Committee.

Each PS-OC will bring together expert teams from the fields of physics, mathematics, chemistry, and engineering in conjunction with researchers in cancer biology and clinical oncology to assemble and develop the infrastructure, capabilities, and research programs required to enable team research to converge disciplines of physical sciences/engineering with cancer biology/oncology.

Goals of the PS-OC Network

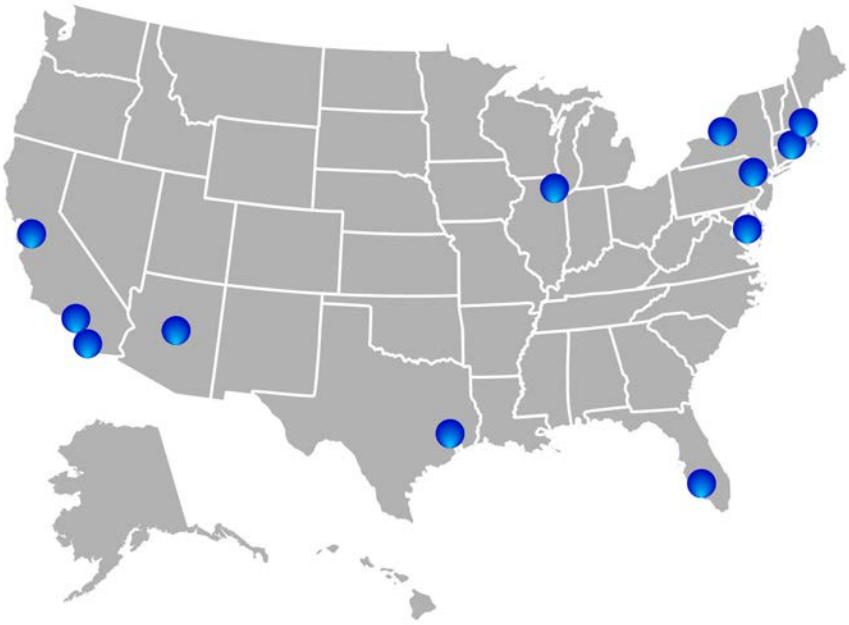
- To generate *new knowledge* and catalyze *new fields of study* in cancer research by utilizing physical sciences/engineering principles to gain a better understanding of cancer and its behavior at all scales, thereby generating answers to some of the major questions and barriers in cancer research.
- To identify new perspectives and approaches which facilitate *paradigm-shifting* science and lead to exponential progress against cancer rather than looking for new tools to do "better" science.
- To build *trans-disciplinary* teams and infrastructure to better understand and control cancer through the convergence of physical sciences and cancer biology.

Physical Sciences-Oncology Centers

The 12 PS-OCs listed below serve as focal points for the Physical Sciences-Oncology Centers Program, which will explore new and innovative approaches based on physical sciences principles to better understand and control cancer, catalyze and generate new bodies of knowledge and fields of cancer study, and support the development of clinical advances.

Our Centers

The National Cancer Institute (NCI) has awarded cooperative agreements to 12 leading institutions to build a collaborative network of Physical Sciences-Oncology Centers (PS-OCs).



Arizona State University Physical Sciences-Oncology Center
Tempe, Arizona
Principal Investigator: Paul Davies, Ph.D.
Senior Co-Investigator: William M. Grady, M.D.

Cornell University Physical Sciences-Oncology Center
Ithaca, New York
Principal Investigator: Michael L. Shuler, Ph.D.
Senior Co-Investigator: Barbara L. Hempstead, M.D., Ph.D.

Dana-Farber Cancer Institute Physical Sciences-Oncology Center
Boston, Massachusetts
Principal Investigator: Franziska Michor, Ph.D.
Senior Co-Investigator: Eric C. Holland, M.D., Ph.D.

H. Lee Moffitt Cancer Center & Research Institute Physical Sciences-Oncology Center
Tampa, Florida
Principal Investigator: Robert A. Gatenby, M.D.
Senior Co-Investigator: Robert J. Gillies, Ph.D.

Johns Hopkins University Physical Sciences-Oncology Center
Baltimore, Maryland
Principal Investigator: Denis Wirtz, Ph.D.
Senior Co-Investigator: Gregg L. Semenza, M.D., Ph.D.

Massachusetts Institute of Technology Physical Sciences-Oncology Center
Cambridge, Massachusetts
Principal Investigator: Alexander van Oudenaarden, Ph.D.
Senior Co-Investigator: Tyler Jacks, Ph.D.

The Methodist Hospital Research Institute Physical Sciences-Oncology Center
Houston, Texas
Principal Investigator: Mauro Ferrari, Ph.D.
Senior Co-Investigator: Steven A. Curley, M.D.

Northwestern University Physical Sciences-Oncology Center
Evanston, Illinois
Principal Investigator: Thomas V. O'Halloran, M.D.
Senior Co-Investigator: Jonathan D. Licht, M.D.

Princeton University Physical Sciences-Oncology Center
Princeton, New Jersey
Principal Investigator: Robert H. Austin, Ph.D.
Senior Co-Investigator: Thea D. TIsty, Ph.D.

The Scripps Research Institute Physical Sciences-Oncology Center
La Jolla, California
Principal Investigator: Peter Kuhn, Ph.D.
Senior Co-Investigator: Kelly J. Bethel, M.D.

University of California, Berkeley Physical Sciences-Oncology Center
Berkeley, California
Principal Investigator: Jan T. Liphardt, Ph.D.
Senior Co-Investigator: Valerie M. Weaver, Ph.D.

University of Southern California Physical Sciences-Oncology Center
Los Angeles, California
Principal Investigator: W. Daniel Hillis, Ph.D.
Senior Co-Investigator: David B. Agus, M.D.

Jerry S.H. Lee, Ph.D.
Health Sciences Director, Center for Strategic Scientific Initiatives
National Cancer Institute, NIH

Dr. Lee serves as the Health Sciences Director for the National Cancer Institute's (NCI) Center for Strategic Scientific Initiatives (CSSI). He provides scientific input to the planning, development, and deployment of programs to carry out the Center's mission to build exploratory initiatives focused on the integration of advanced technologies, trans-disciplinary approaches, infrastructures, and standards, to accelerate the creation of publicly available, broadly accessible, multidimensional data, knowledge, and tools to empower the entire cancer research continuum for patient benefit. Dr. Lee serves and leads various trans-NCI working groups and also represents CSSI at various NIH, HHS, and external committees and other activities to develop effective partnerships across Federal agencies and to build collaborations with key external stakeholders.

Through the CSSI Office of the Director, he is responsible for scientific, programmatic, and operational management of CSSI's broad scientific portfolio (~$145 million per year) carried out by more than 80 staff members within CSSI offices, including The Cancer Genome Atlas Program Office (TCGA PO), Office of Cancer Nanotechnology Research (OCNR), Office of Biorespositories and Biospecimen Research (OBBR), Office of Cancer Genomics (OCG), Office of Cancer Clinical Proteomics Research (OCCPR), and Office of Physical Sciences-Oncology (OPSO). Dr. Lee also currently serves as Acting Director of TCGA PO. Dr. Lee's efforts facilitate the execution of cross-disciplinary strategies and synergies in key areas of research and training to support these emerging fields. His past experience at NIH includes serving as a program manager for the NCI's Innovative Molecular Analysis Technologies (IMAT) program and the NCI Alliance for Nanotechnology in Cancer program, where he was Program Director of fellowships to support multidisciplinary training in cancer nanotechnology. Dr. Lee's previous research experiences in coordinating collaborations among the U.S. Naval Research Laboratory, NCI-Frederick Laboratory, Johns Hopkins University Medical Oncology Division, and Institute for NanoBioTechnology also contribute to carrying out his current efforts.

Scientifically, Dr. Lee has extensive research experience in using engineering-based approaches to examine mechanisms of age-related diseases and cancer progression focused on combining cell biology, molecular biology, and engineering to understand various cellular reactions to external stimuli. Specifically, Dr. Lee's research has emphasized increasing the understanding of RhoGTPase-mediated nuclear and cellular mechanical responses to fluid flow, 3D culture, and contributions to laminopathies such as progeria. He has coauthored numerous papers, two book chapters, and one book, and has spoken at various cell biological and biomedical conferences.

Dr. Lee currently serves as adjunct assistant professor at Johns Hopkins University, where he also earned his bachelor's degree in biomedical engineering and Ph.D. degree in chemical and biomolecular engineering.

Larry A. Nagahara, Ph.D.
Director, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Nagahara is Acting Director of the Office of Physical Sciences-Oncology in the Center for Strategic Scientific Initiatives (CSSI), NCI, where he coordinates and directs program and research activities related to expanding the role of the physical sciences in cancer research, including the Physical Sciences-Oncology Centers (PS-OC) Program. Previously, he served as the Nanotechnology Projects Manager for the NCI's Alliance for Nanotechnology in Cancer program, for which he helped oversee the development of promising nano-based diagnostics and therapeutics projects and turned them into applications that will eventually benefit cancer patients. Dr. Nagahara also currently represents NCI on the Trans-NIH Nano Task Force, which is tasked to develop NIH-wide scientific and policy vision for nanotechnology, as well as NCI's Project Scientist for the NIH's Nanomedicine Development Centers and NIH's Genes and Environment Initiative (GEI) Exposure Biology Program.

Dr. Nagahara has been actively involved in physical sciences and nanotechnology for over 15 years, most notably novel scanning probe microscopy development, carbon nanotube applications, molecular electronics, nanoenergy, and nanosensors. Before joining NCI, he was a Distinguished Member of the Technical Staff at Motorola and led its nanosensor effort. He is also currently an adjunct professor in the Department of Physics at Arizona State University and an Associate Editor of the IEEE *Sensors Journal*. Dr. Nagahara has published over 80 technical papers and 3 book chapters, and has 1 book pending as well as over 15 patents issued/filed in these fields. He is an American Physical Society (APS) Fellow and a Nano50 Awardee and was a member of Motorola's Scientific Advisory Board.

Sean E. Hanlon, Ph.D.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Hanlon serves as a Project Manager for the Physical Sciences-Oncology Centers (PS-OC) Program within the Center for Strategic Scientific Initiatives (CSSI) at the NCI. In this role, he assists in the oversight and scientific management of PS-OC projects by encouraging interdisciplinary collaborations of investigators and researchers within the PS-OC network.

Dr. Hanlon came to the National Cancer Institute through the AAAS Science & Technology Policy Fellowship program. Prior to his selection as a AAAS Fellow, Dr. Hanlon was a postdoctoral fellow at the Lineberger Comprehensive Cancer Center and Carolina Center for Genome Sciences at the University of North Carolina at Chapel Hill. His postdoctoral work used genomics and bioinformatics approaches to address problems in transcriptional regulation on a genome-wide scale. This work helped further the understanding of how cells and organisms ensure that each gene in the transcriptome is expressed and repressed only at the appropriate time. As a postdoctoral fellow, Dr. Hanlon has taught graduate-level courses in genomics and bioinformatics research. Dr. Hanlon received his Ph.D. degree in molecular biology and biochemistry from Rutgers University in 2003, where his work focused on understanding how chromatin structure influences transcription and cell-cycle progression. Dr. Hanlon is interested in enhancing all levels of science education and promoting funding of basic and translational science research.

Mariam Eljanne, Ph.D., M.S.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Eljanne has an M.S. degree in microbial genetics from the University of North Carolina at Charlotte and a Ph.D. degree in human genetics from the University of Pittsburgh. She has 14 years of experience as a research scientist and 6 years in clinical research. After earning her master's degree, Dr. Eljanne managed the Molecular Diagnostics Laboratory for Infectious Diseases at the University of Pittsburgh Medical Center. She then joined the Department of Human Genetics at the University of Pittsburgh, where she worked on gene therapy, stem cell research, and genomic imprinting. Dr. Eljanne studied the methylation pattern of DNA in the mouse, an epigenetic modification of the genome that leads to genomic imprinting. After earning her Ph.D. degree, she joined Cytyc Corporation in Boxborough, Massachusetts, where she worked on breast and cervical cancer diagnostic assay development. In 2004 she moved to Beth Israel Deaconess Medical Center (BIDMC) in Boston as a Senior Research Associate working on prostate cancer diagnostic/prognostic assay development and prostate clinical research. With this clinical research experience from BIDMC, Dr. Eljanne joined the Johns Hopkins School of Medicine Lupus Center as a Research Program Manager, managing several industry-sponsored lupus clinical trials. In 2009 Dr. Eljanne joined the National Institute of Allergy and Infectious Diseases to manage the Vaccine Treatment and Evaluation Units clinical trial contract. Dr. Eljanne's interest lies in understanding the epigenetic modifications of DNA that lead to cancer development and in testing some of the new discoveries in preclinical and clinical settings.

Jonathan Franca-Koh, Ph.D.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Franca-Koh serves as a Project Manager for the Physical Sciences-Oncology Centers (PS-OC) Program within the Center for Strategic Scientific Initiatives at the NCI. In this role, he assists in the oversight and scientific management of PS-OC projects by encouraging interdisciplinary collaborations of investigators and researchers within the PS-OC network.

Dr. Franca-Koh received his Ph.D. degree in cell and molecular biology from the University of London's Institute of Cancer Research in 2003, where his work focused on understanding the role of the *Frat* oncogene in regulating Glycogen Synthase Kinase 3 and the Wnt signaling pathway. Prior to joining the National Cancer Institute, Dr. Franca-Koh worked as a postdoctoral fellow at Johns Hopkins University and as a staff scientist at the J. Craig Venter Institute. His postdoctoral work focused on the molecular mechanisms of chemotaxis using *Dictyostelium discoideum* as a model system. This work led to the discovery of a novel role for the conserved protein kinase *tsunami/fused* in regulating chemotaxis. At the J. Craig Venter Institute, Dr. Franca-Koh developed high-throughput protein-protein interaction technologies and participated in work that led to a comprehensive map of the *E. coli* protein interaction network.

Nastaran Zahir Kuhn, Ph.D.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Kuhn serves as a Project Manager for the Physical Sciences-Oncology Centers (PS-OC) Program within the Center for Strategic Scientific Initiatives (CSSI) at the NCI. In this capacity, she assists in the oversight and scientific management of PS-OC projects by encouraging interdisciplinary collaborations of investigators and researchers within the PS-OC network.

Dr. Kuhn's scientific expertise lies in using an engineering approach to studying microenvironment regulation of breast cancer and stem cell fate. Her doctoral dissertation, completed at the University of Pennsylvania's Institute for Medicine and Engineering, focused on the effects of aberrant mechanical cues from the extracellular matrix on mammary epithelial cell morphogenesis and therapeutic resistance. Dr. Kuhn extensively characterized and identified a progressive increase in the mechanical stiffness of mouse mammary tissue during tumor progression in a transgenic mouse model of human breast cancer, indicating a role for extracellular matrix stiffness in regulation of breast tumor progression and highlighting a possible therapeutic target in breast cancer. In recognition of her graduate work, the Bioengineering Department at the University of Pennsylvania awarded Dr. Kuhn the Solomon R. Pollack Award for Excellence in Graduate Bioengineering Research. Dr. Kuhn completed her postdoctoral fellowship at the NIH in the Cartilage Biology and Orthopaedics Branch of the National Institute of Arthritis and Musculoskeletal and Skin Diseases, where she investigated microenvironment regulation of bone marrow stromal stem cell fate. Namely, Dr. Kuhn identified laminin alpha4 and interleukin-6 as critical stemness factors of adult stem cells, thus allowing these cells to be more efficiently propagated in culture and possibly utilized for regenerative medicine.

Dr. Kuhn received her bachelor of science degree in nuclear engineering from the University of California, Berkeley, and her Ph.D. degree in bioengineering from the University of Pennsylvania. She has coauthored several research publications in both the biological and the physical sciences. In addition, she has taught undergraduate-level courses in cancer biology and graduate-level courses in tissue engineering and regenerative medicine.

Nicole Moore, Sc.D.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Prior to joining the Office of Physical Sciences-Oncology, Dr. Moore was a research chemist in the Biomaterials Group at the National Institute of Standards and Technology (NIST). Her research efforts focused on fabricating biaoctive gradients with click chemistry for high-throughput measurement of cell response to functionalized materials. This work highlighted key concentrations of immobilized biomimetic peptides that direct osteogenic differentiation and induce inflammation promoting rational design of biomaterials. While at NIST, Dr. Moore was awarded an exploratory research grant to develop new technology for measuring intracellular trafficking of nanoparticles and the Material Science and Engineering Laboratory Work-Life and Diversity Award. Dr. Moore received her doctorate in chemical engineering from Washington University in St. Louis, where she systematically explored the effect of peptides on the intracellular trafficking of nanoparticles culminating in the development of a nontoxic and efficient multifunctional polyethylene glycol vehicle for gene therapy. Upon completion of her dissertation, she was awarded a National Research Council Postdoctoral fellowship at NIST in the Biomaterials Group. Dr. Moore earned her bachelor of science degree in biomolecular and chemical engineering from the University of Notre Dame. She has coauthored several research publications in both the biological and the physical sciences. In addition, she is a member of the American Association for the Advancement of Science postdoctoral and graduate student advisory board.

Michael G. Espey, Ph.D., M.T.
PS-OC Project Manager, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Dr. Espey joined the NCI as a Program Manager from the NIH intramural program, where for more than 15 years as a Staff Scientist he conducted basic, preclinical, and translational research. His expertise is in the integration of multiple fields of study including biochemistry, cancer, immunology, infectious disease, and neuroscience. A common thread is his interest in redox mechanisms that interface chemistry with biology. Dr. Espey began his career in clinical pathology as a board-certified medical technologist and worked in the University of Iowa Hospital, Georgetown University Hospital, and the NIH Clinical Center in the hematology, immunology, virology, transfusion medicine, and organ transplant laboratories. He received his Ph.D. degree with distinction from Georgetown University jointly in biology and physiology for work on tryptophan metabolism in the immune system of the brain and secondary lymphoid tissues. As an NIH postdoctoral fellow at the NIDDK, Dr. Espey examined neuroimmunology and inflammation associated with retroviral infection. As an NIH staff scientist, he worked in both NCI and NIDDK on innate immunology, cancer tumor microenvironment redox mechanisms, in particular the interplay between oxygen, nitric oxide, and associated reactive species in terms of cancer biology and therapeutic interventions. Dr. Espey has strong interests in imaging, biophysical instrumentation and drug development. He is the lead NIH FAES Professor for Molecular and Cellular Biology and serves on peer review for over 40 scientific journals.

Karen Jo
Cancer Research Training Award Fellow, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

Ms. Jo is currently serving as a Cancer Research Training Award (CRTA) Fellow for the Physical Sciences-Oncology Centers (PS-OC) Program within the Center for Strategic Scientific Initiatives at the NCI. She began her fellowship in May of 2010 and conducts programmatic analysis of the 12 PS-OCs, with a focus on evaluation of the innovative multidisciplinary training programs within the Network. Additionally, she assists the PS-OC Project Managers in their oversight and scientific management of the PS-OC projects.

Ms. Jo earned a bachelor's degree in finance from the University of Maryland. She is planning to attend medical school after the completion of her fellowship at NCI.

Katrina I. Theisz, M.S.
Operations Coordinator, Office of Physical Sciences-Oncology, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH

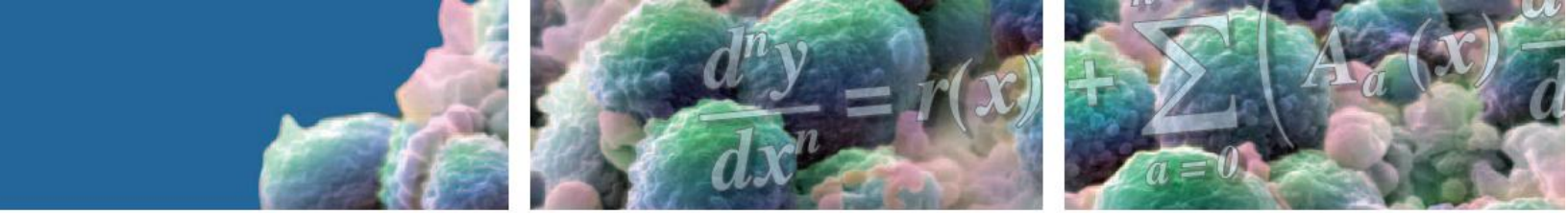
Ms. Theisz joined the Office of Physical Sciences-Oncology in October 2011. Aside from administrative duties including workshop logistics, much of her work focuses on program evaluation. Ms. Theisz completed two master's level counseling internships at Princeton House Behavioral Health in Princeton, New Jersey, and Four Winds Hospital in Katonah, New York, as well as an undergraduate internship at the University Medical Center at Princeton Eating Disorders Program. She received her master of science degree in mental health counseling from Pace University and her bachelor of science degree in psychology from York College of Pennsylvania.

Carole Baas, Ph.D.
Patient Advocate, Office of Advocacy Relations, National Cancer Institute, NIH

Dr. Baas is the national advocate for the Physical Sciences-Oncology Centers (PS-OC) Program within the Center for Strategic Scientific Initiatives (CSSI) at the NCI. Drawing upon her background in research and academia as well as from her personal experience with cancer—Dr. Baas has a Ph.D. degree in biomedical engineering from Texas A&M University and is a survivor of both skin and breast cancer—she serves as a liaison between the scientists and the cancer communities. Her role is to represent the patient perspective, encourage advocacy involvement within the PS-OC network, and promote the dissemination of research findings to the public.

Prior to her involvement in patient advocacy, Dr. Baas was a medical researcher studying high-altitude physiology for the U.S. Air Force and National Aeronautics and Space Administration. Her doctoral work included coursework in medical imaging, biomaterials, medical instrumentation, biofluid dynamics, and physiology, with a secondary focus in human factors engineering. Dr. Baas' dissertation was a mathematical model of the flow of cerebrospinal fluid (CSF) in which she refined existing multicompartmental mathematical models of the CSF system and combined these with a model simulating valve shunt function during the treatment of hydrocephalus. The resulting model was used in a computer simulation describing the behavior of the CSF system under a variety of pathologic situations and illustrating the use of shunting systems in the treatment of these conditions.

Dr. Baas became a cancer advocate following her diagnosis of breast cancer in 2004. She serves a variety of roles within a number of cancer organizations and programs, including the American Cancer Society's Reach to Recovery program; Susan G. Komen for the Cure, as a member of the Advocates in Science Education and Training Working Group; I-SPY2 Clinical Trial for new breast cancer therapeutic agents, as a member of the Data Access & Publication Request Review Working Group; Hope for Two: The Pregnant with Cancer Network, as a peer counselor to help women diagnosed with cancer during pregnancy or postpartum; and the American College of Radiology Imaging Network (ACRIN), an NCI cooperative group, as patient advocate for the Experimental Imaging Sciences Committee. Dr. Baas is a graduate of the National Breast Cancer Coalition's Project LEAD, an intensive program for advocates on cancer biology, genetics, epidemiology, and research design to prepare them to serve as educated voices in breast cancer research and public policy processes; and Clinical Trials Project LEAD, an advanced course focused on understanding and improving breast cancer clinical trials research. Dr. Baas regularly participates as an advocate reviewer for the U.S. Department of Defense Breast Cancer Research Program and for Susan G. Komen for the Cure. She is also involved in public health policy, lobbying Congress on health care issues and funding of cancer research and, at the local level, as one of nine voting members of the Board of Health for Irving, Texas, a suburb of Dallas.

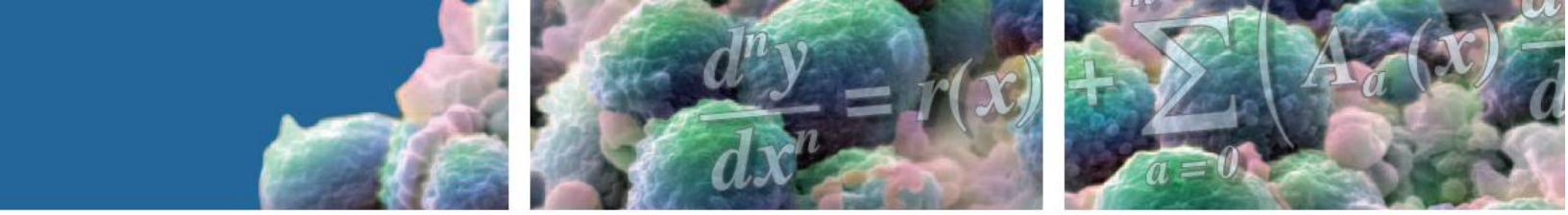


PBCF- Cell Lines

CELL LINES • SOPS • REAGENTS • DERIVATIVES

The PS-OC Network Bioresource Core Facility (PBCF) at ATCC is a central resource for all members of the Physical Sciences-Oncology Network. The PBCF serves as a centralized distributor and repository providing the Network with common stocks of an authenticated set of non-malignant and cancerous cell lines, cell culture reagents, and related standard operating protocols. All related inquiries and orders should be sent via email to: NCI-PBCFContract@atcc.org

PBCF Cat. No.	Name	Tissue	Description	Status
NCI-PBCF-HTB14	U-87	Brain	Malignant glioblastoma; human	**Available**
NCI-PBCF-CRL1690	T98G	Brain	Glioblastoma multiforme; human	**Available**
NCI-PBCF-CRL4010	hTERT-HME1	Breast	hTERT-immortalized mammary epithelium; human	**Available**
NCI-PBCF-HTB22	MCF-7	Breast	Breast adenocarcinoma derived from pleural effusion; weakly metastatic; human	**Available**
NCI-PBCF-1001*	MCF7-B7-TS	Breast	MCF7 derivative; Tamoxifen-sensitive; human	**Available**
NCI-PBCF-1000*	MCF10A-JSB	Breast	MCF10A derivative; metastatic adenocarcinoma; human	**Available**
NCI-PBCF-HTB133	T-47D	Breast	Ductal carcinoma; human	**Available**
NCI-PBCF-CRL1500	ZR-75-1	Breast	Ductal carcinoma; human	**Available**
NCI-PBCF-HTB26	MDA-MB-231	Breast	Highly metastatic adenocarcinoma; human	**Available**
NCI-PBCF-HTB123	DU4475	Breast	Cutaneous metastatic nodule; advanced breast cancer; human	**Available**
NCI-PBCF-CRL-2336	HCC1937	Breast	Primary ductal carcinoma; human	**Available**
NCI-PBCF-HTB132	MDA-MB-468	Breast	Metastatic breast adenocarcinoma derived from pleural effusion; human	**Available**
NCI-PBCF-HTB38	HT-29	Colorectal	Colorectal adenocarcinoma; CpG island methylator phenotype; human	**Available**
NCI-PBCF-CCL228	SW480	Colorectal	Colorectal adenocarcinoma; microsatellite stable; human	**Available**
NCI-PBCF-CCL247	HCT116	Colorectal	Colorectal adenocarcinoma; microsatellite unstable; human	**Available**
NCI-PBCF-HTB37	Caco-2	Colorectal	Colorectal adenocarcinoma, microsatellite stable; human	**Available**
NCI-PBCF- CCL229	LoVo	Colorectal	Colorectal adenocarcinoma, microsatellite unstable; human	**Available**
NCI-PBCF-CCL227	SW620	Colorectal	Metastatic colorectal adenocarcinoma derived from lymph node; human	**Available**
NCI-PBCF-HTB77	SKOV-3	Ovary	Metastatic ovarian adenocarcinoma derived from ascites; human	**Available**
NCI-PBCF-HTB161	NIH: OVCAR-3	Ovary	Metastatic ovarian adenocarcinoma derived from ascites; human	**Available**
NCI-PBCF-HTB75	Caov-3	Ovary	Primary ovarian adenocarcinoma; human	**Available**
NCI-PBCF-CRL5922	NCI-H2087	Lung	Non-small cell lung cancer (NSCLC); human	**Available**



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NCI-PBCF-CRL2503	NL20	Lung	SV-20 large T antigen-immortalized lung epithelium; non-tumorigenic; human	**Available**
NCI-PBCF-CCL256	NCI-H2126	Lung	Metastatic non-small cell lung cancer (NSCLC) derived from the pleural effusion; adenocarcinoma; human	**Available**
NCI-PBCF-CCL256.1	NCI-BL2126	B Lymphoblast	B lymphoblast (normal tissue) derived from NSCLC patient,NCI-H2126; human	**Available**
NCI-PBCF-CRL1469	Panc-1	Pancreas	Pancreatic epithelioid carcinoma; human	**Available**
NCI-PBCF-HTB79	Capan-1	Pancreas	Metastatic pancreatic adenocarcinoma derived from liver; human	**Available**
NCI-PBCF-CRL4023	hTERT-HPNE	Pancreas	hTERT-immortalized pancreatic epithelium, non-tumorigenic; human	**Available**
NCI-PBCF-CRL1740	LNCaP clone FG	Prostate	Metastatic prostate carcinoma derived from lymph node; human	**Available**
NCI-PBCF-CRL1435	PC-3	Prostate	Metastatic prostate carcinoma derived from bone; human	**Available**
NCI-PBCF-HTB81	DU 145	Prostate	Metastatic prostate carcinoma derived from brain; human	**Available**
NCI-PBCF-CRL2876	VCaP	Prostate	Metastatic prostate carcinoma derived from Vertebrae; human	**Available**
NCI-PBCF-CRL11609	RWPE-1	Prostate	HPV-18-immortalized prostate epithelium, non-tumorigenic; human	**Available**
NCI-PBCF-CRL2505	22Rv1	Prostate	Prostate carcinoma derived from primary site; human	**Available**
NCI-PBCF-CRL1619	A375	Skin	Malignant melanoma; human	**Fall 2013**
NCI-PBCF-CRL1676	WM266-4	Skin	Melanoma derived from metastatic site of malignant melanoma; human	**Fall 2013**
NCI-PBCF-HTB65	MeWo	Skin	Metastatic malignant melanoma derived from lymph node; human	**Fall 2013**
NCI-PBCF-HTB68	SK-MEL-2	Skin	Malignant melanoma; human	**Fall 2013**

**** PS-OC investigator deposited cell line***

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PS-OC NETWORK BIORESOURCE CORE FACILITY

PHONE
800.638.6597

FAX
703.365.2750

EMAIL
NCI-PBCFContract@atcc.org

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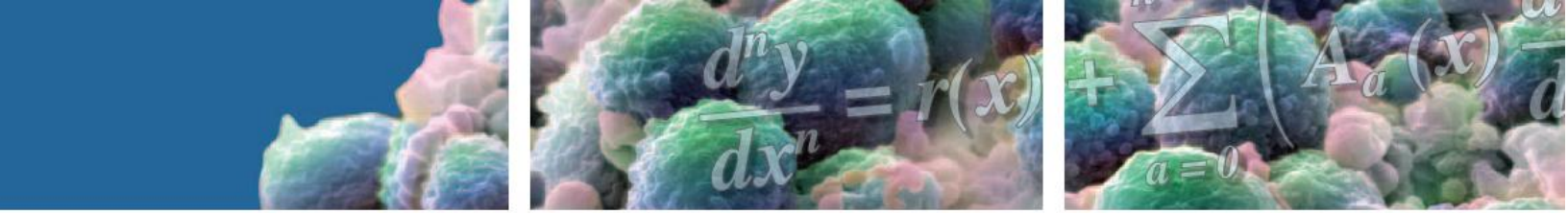

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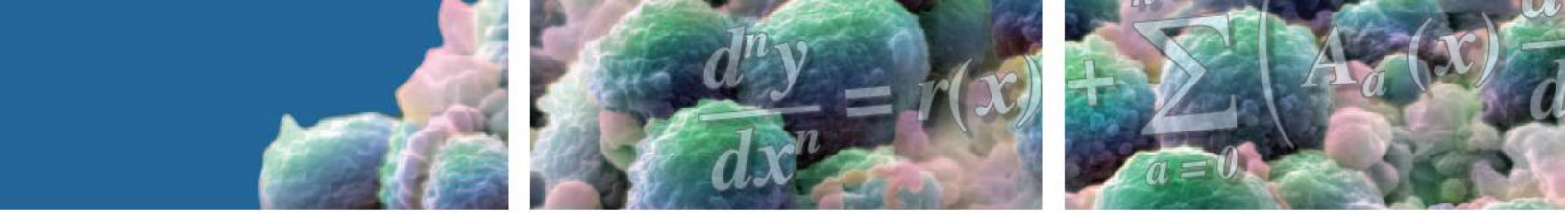

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PS-OC Network Bioresource Core Facility

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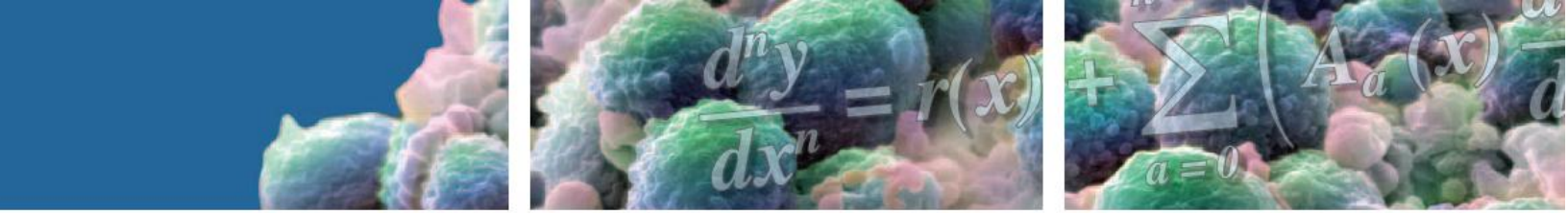
**** PS-OC investigator deposited cell line***

ATCC | PBCF
PS-OC NETWORK BIORESOURCE CORE FACILITY



ATCC

PS-OC Network Bioresource Core Facility

PBCF Workshop

Annual PBCF Workshop on Basic Techniques in Molecular Biology

July 30-August 2, 2013 • 4-Day Course • ATCC, Manassas, VA

The NCI Physical Sciences-Oncology Center Network Bioresource Core Facility (PBCF) workshop is designed to provide an overview of molecular techniques through classroom presentation and laboratory work. This Workshop is intended for PS-OC Young Investigators with no prior experience in molecular biology techniques.

Topics include the following hands-on laboratory techniques:

- **Isolation and characterization of gDNA and tRNA isolated from mammalian cells**
- **Gene cloning**
- **Transfection**
- **Polymerase Chain Reaction (PCR)**
- **Sequencing**
- **Gene expression**
- **FISH (fluorescence *in situ* hybridization)**
- **Introduction to data analysis**

This 4-day workshop employs an integrated approach – utilizing hands-on training to reinforce lecture material, enabling the PS-OC Network Trainees to translate culture techniques into applications in their own laboratories.

To register, email Dr. Yvonne Reid at NCI-PBCFContract@atcc.org

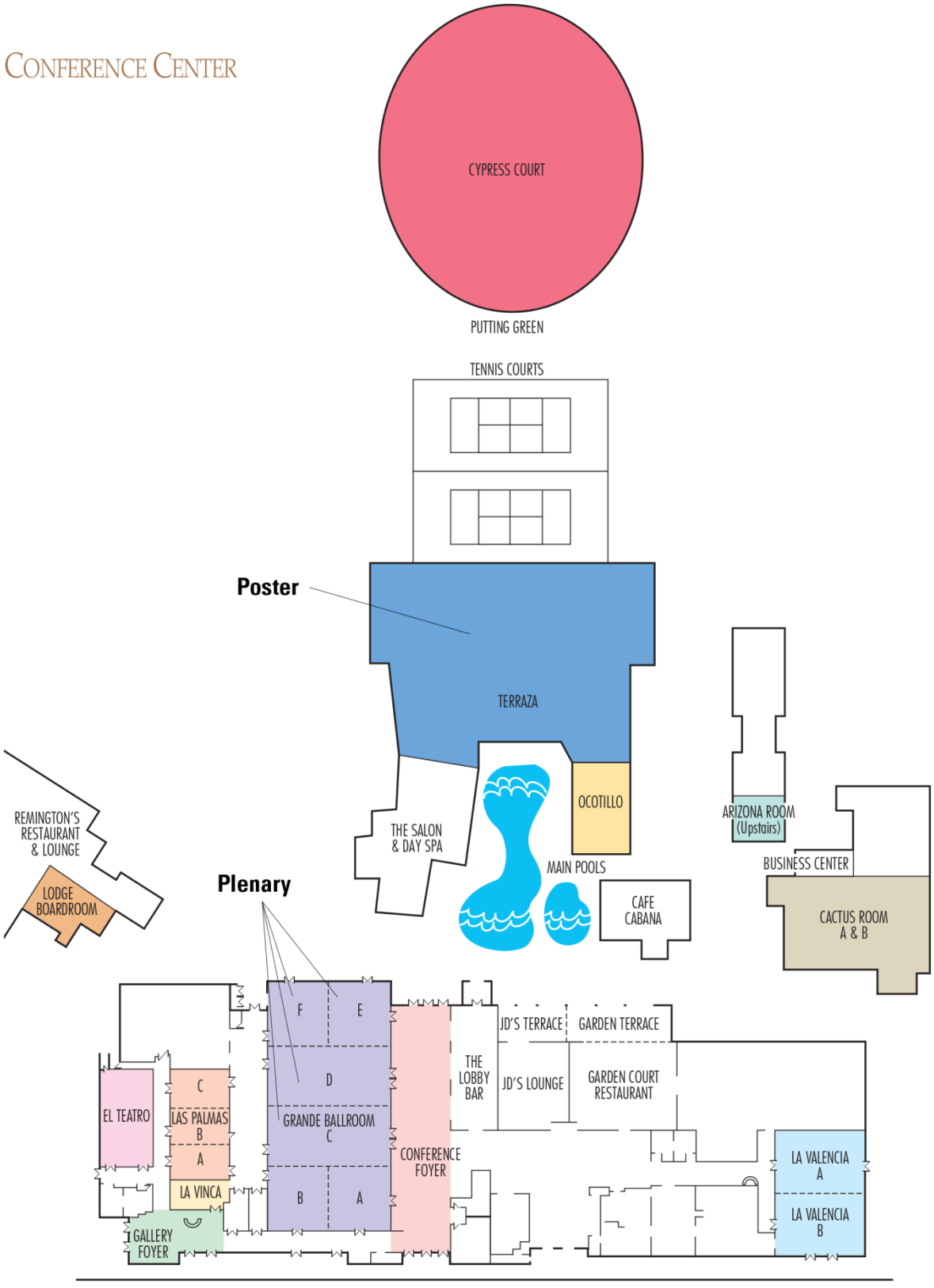
There is no charge to PS-OC trainees for the workshop.
Airfare, hotel, and incidentals are not covered

PHONE
800.638.6597

FAX
703.365.2750

EMAIL
NCI-PBCFContract@atcc.org

Scottsdale Plaza Resort Map



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NIH...Turning Discovery into Health