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5th Simpson Querrey Institute for Epigenetics Symposium

March 28, 2024

“Tumor Metabolism, Epigenetics, and Immunity ”

SQE

WELCOME TO THE 5th SIMPSON QUERREY INSTITUTE FOR EPIGENETICS SYMPOSOUM

"Tumor Metabolism, Epigenetics, and Immunity"

AGENDA

8:15 AM	-	9:00 AM	Continental Breakfast
9:00 AM	-	9:15 AM	Welcome and Introduction Ali Shilatifard, PhD Director, Simpson Querrey Institute for Epigenetics

MORNING SESSION 9:15 AM - 12:05 PM

Each session: 25 minutes presentation; 5 minutes Q&A

Session Chair: Issam Ben-Sahra, PhD

9:15 AM	-	9:45 AM	"*Can We Exploit Tumor Metabolism for New Therapies?"* Celeste Simon, PhD, University of Pennsylvania
9:45 AM	-	10:15 AM	"*The Role of Metabolites in Cancer and Aging"* Marcia Haigis, PhD, Harvard Medical School
10:15 AM	-	10:45 AM	"*Spatial Assessment of Metabolism"* Shawn Davidson, PhD, Northwestern University
10:45 AM	-	11:05 AM	Coffee Break
11:05 AM	-	11:35 AM	"*Effects of Oncogenic Signaling to mTORC1 on Tumor Metabolism"* Brendan Manning, PhD, Harvard T. H. Chan School of Health
11:35 AM	-	12:05 PM	"*Decoding Critical Targets of the LKB1/STK11 Tumor Suppressor in NSCLC"* Reuben Shaw, PhD, Salk Institute of Biological Studies
12:05 PM	-	1:30 PM	Lunch Break

AFTERNOON SESSION 1:30 PM - 6:00 PM

Each session: 25 minutes presentation; 5 minutes Q&A

Session Chair: Lillian Eichner, PhD

1:30 PM	-	2:00 PM	"*Transcriptional Control of Metabolism and Inflammation by Glucocorticoids"* Nina Henriette Uhlenhaut, PhD, TUM School of Life Sciences
2:00 PM	-	2:30 PM	"*Circadian Clock Control of Muscle Stem Cell-Mediated Tissue Regeneration"* Clara Peek, PhD, Northwestern University
2:30 PM	-	3:00 PM	"*Elucidating Compound Lipid Fluxes Within the Tumor Microenvironment"* Christian Metallo, PhD, Salk Institute of Biological Studies
3:00 PM	-	3:30 PM	"*Promoting Lung Recovery: Epigenetic and Metabolic Control of Treg Cell Function"* Benjamin Singer, MD, Northwestern University
3:30 PM	-	3:50 PM	Coffee Break
3:50 PM	-	4:20 PM	*"Transcriptional Repression by HDAC3 Mediates T-cell exclusion from Kras Mutant Lung Tumors"* Lillian Eichner, PhD, Northwestern University
4:20 PM	-	4:50 PM	"*Metabolic Alterations in Tumor and Host in Cancer"* Eileen White, PhD, Rutgers Cancer Institute of New Jersey
4:50 PM	-	5:20 PM	"*Nucleotide Metabolism and Control of Cell Growth"* Issam Ben-Sahra, PhD, Northwestern University
5:20 PM	-	5:50 PM	"*Metabolic Outliers and Human Disease Phenotypes"* Ralph DeBerardinis, MD/PhD, UT Southwestern Medical Center
5:50 PM	-	6:00 PM	Closing Remarks: Drs. Ben-Sahra and Eichner

Benjamin Singer, M.D.

Associate Professor, Medicine (Pulmonary and Critical Care) and
Biochemistry and Molecular Genetics
Northwestern University

Benjamin D. Singer, MD, is the Lawrence Hicks Professor of Pulmonary Medicine and an Associate Professor of Medicine (Pulmonary and Critical Care) & Biochemistry and Molecular Genetics at the Northwestern University Feinberg School of Medicine. Dr. Singer's laboratory asks a key question that has taken on added importance during the COVID-19 pandemic: *How can we promote resolution of lung inflammation and repair of lung damage?*

His research program is thematically centered on how epigenetic mechanisms control the immune response to pneumonia-induced lung injury. He has determined in humans and in experimental systems how a subset of T cells known as regulatory T cells orchestrates resolution and repair, discovering epigenetic mechanisms—chiefly those that involve DNA methylation—that govern regulatory T cell identity and function. His studies led to clinical trials for patients with severe COVID-19 and other inflammatory disorders, and he has gone on to apply his findings to the fields of metabolism, aging, autoimmunity, immunodeficiency, and cancer. He has published high-impact papers in the *JCI*, *Nature*, etc. while at the same time maintaining a translational focus in critical care medicine, caring for patients with life-threatening conditions in the ICU.

Brendan Manning, Ph.D.

Acting Chair & Professor, Department of Molecular Metabolism, Harvard T.H. Chan School of Public Health; Faculty Affiliate, Department of Cell Biology, Harvard Medical School and Dana-Farber/Harvard Cancer Center

Dr. Manning received his BS from the University of Massachusetts, Amherst and his PhD from Yale University, then joined Harvard Medical School for his postdoctoral research. During this time, he discovered that the tuberous sclerosis complex (TSC) tumor suppressors serve as the molecular connection between the PI3K and mTOR pathways, thereby linking a signaling pathway activated in the majority of human cancers to a nutrient-sensing pathway that controls cell growth and metabolism.

In 2004, he joined the faculty of the then newly established Department of Genetics and Complex Diseases at Harvard-Chan (renamed Molecular Metabolism in 2019) to continue research at the interface of signaling and metabolism. The Manning laboratory is primarily focused on defining the functions of the PI3K-mTOR pathway in physiology and diseases with metabolic dysfunction at their core, including cancer, diabetes, neurological disorders and aging. Dr. Manning is a two-time recipient of the National Cancer Institute's Outstanding Investigator Award.

Celeste Simon, Ph.D.

Scientific Director, Abramson Family Cancer Research Institute
Associate Director, Cancer Center, Perelman School of Medicine
University of Pennsylvania

M. Celeste Simon, Ph.D. is the Scientific Director of the Abramson Family Cancer Research Institute and an Associate Director of the Cancer Center at the Perelman School of Medicine at the University of Pennsylvania. Dr. Simon's research is focused on how cells sense and respond to changes in the availability of molecular oxygen and nutrients. This affects normal development, physiology, and numerous diseases, such as the growth of solid tumors. The Simon Laboratory is studying how O2 sensing impacts tumor inflammation, metabolism, metastasis, and overall disease progression. She accesses animal models and cancer patient samples with the ultimate goal of developing novel strategies to treat tumors such as pancreatic cancer, soft tissue sarcoma, hepatocellular carcinoma, and renal cancer.

Dr. Simon currently directs a laboratory of 20 individuals, including graduate students, postdoctoral fellows, clinical fellows, and research technicians. She was an HHMI Investigator for twenty years, and has received numerous awards recognizing her research, such as the Fouad Bashour Award for Distinguished Physiologists, Stanley N. Cohen Award for Biomedical Research, and Elliot Osserman Award from the Israel Cancer Research Fund. In 2014, she was elected to the American Academy of Arts and Sciences, and the National Academy of Medicine in 2018. She received an NCI Outstanding Investigator Award in 2017 and was named a Fellow of the AACR Academy in 2021. She was also elected to the National Academy of Sciences in 2021, named the AACR-G.H.A. Clowes Award for Outstanding Basic Cancer Research in 2023, and received a FASEB Lifetime Achievement Award for her research, leadership, and mentoring. In 2023, she was named an HHMI Emeritus Investigator.

Christian Metallo, Ph.D.

Professor, Salk Institute for Biological Studies
Daniel and Martina Lewis Chair

Christian Metallo is a professor at the Salk Institute for Biological Studies and holds the Daniel and Martina Lewis Chair. He is also an adjunct professor of bioengineering at UC San Diego. His laboratory integrates engineering approaches, stable isotope tracing, mass spectrometry, and molecular biology tools to dissect how metabolic dysregulation contributes to human disease. Key focus areas include cancer, macular disease, neurodegeneration, and diabetes.

Christian received his Ph.D. in Chemical Engineering from the University of Wisconsin-Madison and was an American Cancer Society Postdoctoral Fellow at the Massachusetts Institute of Technology before starting his lab at UC San Diego in 2011. He was the recipient of a Searle Scholar Award and a Camille and Henry Dreyfus Teacher-Scholar Award, and he is a fellow in the American Institute for Medical and Biological Engineering.

Clara Peek, Ph.D.

Assistant Professor, Biochemistry and Molecular Genetics and Endocrinology
Northwestern University

Clara Peek is an Assistant Professor at Northwestern University Feinberg School of Medicine in the Departments of Biochemistry and Molecular Genetics and Medicine-Endocrinology. Dr. Peek received her B.S. degree in Bacteriology at the University of Wisconsin-Madison and Ph.D. in Biochemistry at The Johns Hopkins School of Medicine. She completed her postdoctoral training in the Department of Medicine-Endocrinology at Northwestern University Feinberg School of Medicine.

In 2018, Dr. Peek established her research group which focuses on how molecular circadian clocks control responses to nutrient stress in skeletal muscle fibers and stem cells. The overarching goal of the laboratory is to advance our understanding of circadian timing in metabolic physiology and disease.

Eileen White, Ph.D.

Deputy Director and Chief Scientific Officer, Rutgers Cancer Institute at Rutgers University
Associate Director, Ludwig Princeton Branch of the Ludwig Institute for Cancer Research at Princeton University

Eileen White, PhD is a cancer biologist known for her work establishing that a DNA tumor virus oncogene functions by inhibiting programmed cell death by apoptosis and is a homologue of the human BCL-2 oncogene. She is also known for establishing that tumor cells induce intracellular nutrient scavenging by autophagy, which promotes their metabolism, growth, survival, and malignancy. These findings informed the means to target the apoptosis and autophagy pathways for cancer therapy.

Eileen is Deputy Director and Chief Scientific Officer at the Rutgers Cancer Institute at Rutgers University, and Associate Director of the Ludwig Princeton Branch of the Ludwig Institute for Cancer Research at Princeton University. She is also the Lead PI for the CRUK/NCI Cancer Grand Challenge to address the mechanisms causing cancer cachexia through the CANcer Cachexia Action Network. Amongst Eileen's honors are membership in the US National Academy of Sciences, and she is an elected fellow of the American Association for the Advancement of Science, the American Academy of Microbiology, and the American Association for Cancer Research Academy.

Issam Ben-Sahra, Ph.D.

Associate Professor, Biochemistry and Molecular Genetics
Northwestern University

Dr. Issam Ben-Sahra is an Associate Professor of Biochemistry and Molecular Genetics at Northwestern University, Feinberg School of Medicine. He obtained his Ph.D. in molecular and cellular biology from Côte d'Azur University in Nice, France. During his doctoral research, Dr. Ben-Sahra investigated the molecular and cellular impacts of metformin, an antidiabetic drug, on prostate cancer cell metabolism and growth. He subsequently conducted postdoctoral research in the laboratory of Prof. Brendan Manning within the Department of Molecular Metabolism at Harvard T.H. Chan School of Public Health in Boston. Here, his work brought to light that the pro-growth signaling pathway, mTORC1, controls pyrimidine and purine synthesis.

Dr. Ben-Sahra has been recognized with several prestigious awards, including the Bettencourt-Schueller Prize, the NIH K99/R00 Award, and the LAM Foundation Established Investigator Award. Leveraging advanced LC-MS-based techniques such as metabolomics, isotope tracing, and proteomics, the Ben-Sahra lab is dedicated to exploring the regulation of nucleotide synthesis by signaling networks in both normal and proliferating cells. Moreover, Dr. Ben-Sahra's research team is actively working to unveil novel fundamental roles for pyrimidines and purines in controlling cellular metabolism and function. Ultimately, the Ben-Sahra lab aims to identify new metabolic vulnerabilities that could be strategically targeted to counter neoplasia and inhibit tumor progression.

Lillian Eichner, Ph.D.

Assistant Professor, Biochemistry and Molecular Genetics
Northwestern University

Dr. Eichner obtained her undergraduate degree in Chemistry from Northwestern University. She earned her Ph.D. in Biochemistry from McGill University in Montréal, Canada, studying Nuclear Receptor function in cancer with Dr. Vincent Giguère. Her post-doctoral training was carried out with Dr. Reuben Shaw at the Salk Institute for Biological Studies in La Jolla, CA, where she used genetically engineered mouse models to uncover key insights into the in vivo mechanisms driving LKB1 mutant lung tumor biology.

The Eichner Lab continues to study transcriptional dependencies at the intersection of epigenetics, signaling, and metabolism to reveal and harness therapeutically targetable vulnerabilities in cancer.

Marcia Haigis, Ph.D.

Professor, Department of Cell Biology
Co-Director, Paul F. Glenn Center for the Biology of Aging Research
Director, Gender Equity for Faculty in Science, Harvard Medical School

Marcia C. Haigis is a Professor in the Department of Cell Biology, co-Director of the Paul F. Glenn Center for the Biology of Aging Research, and the Director of Gender Equity for Faculty in Science at Harvard Medical School. She obtained her Ph.D. in Biochemistry from the University of Wisconsin and performed postdoctoral studies at MIT studying mitochondrial metabolism. Dr. Haigis is an active member of the Dana Farber/Harvard Cancer Center, an Affiliate of the Broad Institute, and a member of the Ludwig Center at Harvard Medical School.

Dr. Haigis has made fundamental contributions to our understanding of how mitochondria contribute to human health and diseases of aging. Her pioneering studies identified ways that mitochondria utilize fuels and signal in to support cancer cell proliferation. Research in the Haigis laboratory has also led to a deeper mechanistic understanding of how cancer cells are able to recycle metabolic by-products, such as ammonia to support cancer growth. Most recently, her work has shed light on our understanding of how diet and obesity regulate anti-tumor immunity. Dr. Haigis is the recipient of numerous honors and awards, including the Brookdale Leadership in Aging Award, the Ellison Medical Foundation New Scholar Award, the American Cancer Society Research Scholar Award, the National Academy of Medicine Emerging Leaders in Health and Medicine Program, and the 2023 Samsung Ho-Am Prize in Medicine. Dr. Haigis serves on numerous academic and for-profit scientific advisory boards.

Nina Henriette Uhlenhaut, Ph.D.

Chair, Metabolic Programming, Technical University of Munich
Director, Institute for Diabetes and Endocrinology, Helmholtz Munich

Professor Henriette Uhlenhaut holds the Chair for Metabolic Programming at the Technical University of Munich and is the Director of the Institute for Diabetes and Endocrinology at Helmholtz Munich in Germany. She has a degree in Biotechnology from the Technical University of Braunschweig and a Master's degree in Applied Biology from Georgia Tech. She graduated with a PhD in Molecular Biology from the EMBL – Heidelberg University joint international graduate program.

Her research on the mechanisms of transcriptional regulation employed by the Glucocorticoid Receptor to control metabolism and innate immunity has been recognized by multiple awards, including the German Research Foundation (DFG) Emmy Noether Program and the Heinz Maier Leibnitz Prize, two grants from the European Research Council (ERC) and the EJE Award of the European Society for Endocrinology.

Ralph DeBerardinis, M.D., Ph.D.

Director, Genetic and Metabolic Disease Program, Children's Research Institute
Division Chief, Pediatric Genetics and Metabolism, Department of Pediatrics
UT Southwestern Medical Center

Ralph DeBerardinis, M.D., Ph.D. is a pediatric biochemical geneticist and physician-scientist. His lab studies the role of altered metabolic pathways in human diseases, including cancer and pediatric inborn errors of metabolism. The DeBerardinis lab pioneered the use of metabolomics and isotope tracing to characterize disease-associated metabolic states directly in patients, and to use disease-relevant model systems to explore how metabolic perturbations contribute to tissue dysfunction.

Dr. DeBerardinis directs the Genetic and Metabolic Disease Program in the Children's Research Institute at UT Southwestern Medical Center and serves as Division Chief of Pediatric Genetics and Metabolism in the Department of Pediatrics at UT Southwestern. He is an Investigator in the Howard Hughes Medical Institute and has been elected to the Association of American Physicians and the National Academy of Medicine.

Reuben Shaw, Ph.D.

Director of the NCI-Designated Cancer Center
William R. Brody Chair at the Salk Institute of Biological Studies

Reuben Shaw is the Director of the NCI-Designated Cancer Center and the William R. Brody Chair at the Salk Institute in La Jolla, California. Dr. Shaw got his PhD in 1999 from Tyler Jacks lab at MIT followed by a postdoc in Lew Cantley's lab at Harvard Medical School before starting as an Assistant Professor at the Salk in early 2006. He worked his way up the ranks, and in 2016 he took over as Director of Salk's NCI-Designated Cancer Center from Tony Hunter. He received multiple young investigator awards early in his career and in 2017 received an NCI Outstanding Investigator Award.

20 years ago, Reuben made the unexpected finding that the LKB1 tumor suppressor - which is commonly mutated in lung cancer - was the long-sought-after kinase that activates AMPK following energy stress, including after the diabetes drug metformin. This connection between metabolic sensing and cancer was very unexpected at the time but today is just one of many mechanisms connecting pathways altered in cancer to direct metabolic regulation. Dr. Shaw's lab continues to focus on the AMPK signaling pathway and other metabolic stress pathways, which has led to multiple therapeutic avenues in cancer and other diseases.

Shawn Davidson, Ph.D.

Assistant Professor of Medicine (Pulmonary and Critical Care)
Northwestern University

Dr. Davidson is an Assistant Professor at Northwestern University, specializing in cell metabolism and method development to study disease metabolism in physiological settings. I received my bachelor's degree from Providence College in 2010 and my Ph.D. from the Massachusetts Institute of Technology in 2017, both in Biology. As a graduate student, I received the National Science Foundation Graduate Research Fellowship to develop methods for studying tumor metabolism in vivo. My postdoctoral research at the Broad Institute and Brigham and Women's Hospital focused on bioengineering approaches to study the metabolism of tumor and immune cells.

As a Lewis-Sigler Institute Fellow at Princeton University, our lab pioneered "Iso-Imaging" (stable-isotope tracing coupled with imaging mass spectrometry) for single-cell, spatially resolved metabolic measurements. We continue to apply Iso-Imaging in my lab at Northwestern University. Our work progresses in developing imaging mass for stable-isotope tracers and metabolism; investigating metabolic dysregulation in disease states with pathological assessment and mathematical modeling; developing therapeutic strategies for metabolic targets; researching new in vivo metabolic therapeutic delivery methods; and creating animal models that mimic genetic modifiers in human diseases.

PROMOTING LUNG RECOVERY: EPIGENETIC AND METABOLIC CONTROL OF Treg CELL FUNCTION

Benjamin Singer, M.D., Northwestern University

Severe pneumonia due to pathogens such as influenza A virus and SARS-CoV-2 injures the lung to cause the acute respiratory distress syndrome (ARDS), a clinical entity associated with a mortality rate as high as 40%. Care of patients with severe pneumonia-induced ARDS is centered on supportive interventions such as mechanical ventilation in the intensive care unit (ICU). To identify factors that contribute to prolonged care episodes and mortality in ICU patients, we designed a machine learning approach that discretizes and clusters ICU clinical data by day and applied it to 585 mechanically ventilated patients with severe pneumonia and respiratory failure, 190 of whom had COVID-19. We found that unsuccessful treatment of ICU complications such as ventilator-associated pneumonia contributes to mortality in patients with severe pneumonia, including COVID-19. These results support our premise that activation of repair pathways during recovery from viral pneumonia will shorten the duration of time that patients require the ICU, thus mitigating the ICU's attendant morbidity and mortality.

In prior work, we established an essential role for $CD4^{+}Foxp3^{+}$ regulatory T (Treg) cells in orchestrating resolution and repair of acute lung injury, demonstrating how metabolic and epigenetic interventions that stabilize Treg cell identity *in vivo*—and *ex vivo* before therapeutic transfer—enhance their pro-recovery functions. Recent clinical trials demonstrated the safety and preliminary efficacy of Treg cells administered to patients with viral pneumonia, yet we found that the injured lung microenvironment challenges the mitochondrial function required for optimal Treg cell pro-recovery capacity. How Treg cells adapt their metabolic programs to sustain and optimize their function during an immune response occurring in a metabolically stressed microenvironment remains unclear. Hence, we tested whether Treg cells require the energy homeostasis-maintaining enzyme AMP-activated protein kinase (AMPK) to adapt to metabolically aberrant microenvironments caused by malignancy or lung injury, finding that AMPK is dispensable for Treg cell immune-homeostatic function but is necessary for full Treg cell function in B16 melanoma tumors and during acute lung injury caused by influenza virus pneumonia in mice. AMPK-deficient Treg cells had lower mitochondrial mass and exhibited an impaired ability to maximize aerobic respiration. Mechanistically, we found that AMPK regulates DNA methyltransferase 1 to promote transcriptional programs associated with mitochondrial function in the tumor microenvironment. In the lung during viral pneumonia, we found that AMPK sustains metabolic homeostasis and mitochondrial activity. Induction of DNA hypomethylation was sufficient to rescue mitochondrial mass in AMPK-deficient Treg cells, linking DNA methylation with AMPK function and mitochondrial metabolism. These results define AMPK as a determinant of Treg cell adaptation to metabolic stress and offer potential therapeutic targets in cancer and to promote resilience following tissue injury caused by viral pneumonia.

EFFECTS ON ONCOGENIC SIGNALING TO mTORC1 ON TUMOR METABOLISM

Brendan Manning, Ph.D., Harvard T.H. Chan School of Public Health

The mechanistic target of rapamycin (mTOR) complex 1 (mTORC1) is a key signaling node, universal to eukaryotic cells, which links the sensing of nutrient and growth signals to the coordinated regulation of nutrient metabolism. The activation state of mTORC1 is tightly controlled through a small G protein switch involving the TSC1-TSC2-TBC1D7 protein complex (the TSC complex) and the Ras-related small G protein Rheb. The direct phosphorylation and inhibition of TSC2 within the TSC complex by the protein kinases AKT and ERK provide the major mechanistic links between growth factor and oncogenic signaling and the activation of mTORC1. In the past 15 years, our research has identified downstream mechanisms through which mTORC1 signaling promotes anabolic metabolism while attenuating catabolic metabolism to drive cell growth. As these findings were largely restricted to reductionist cell culture settings, we have recently sought to define the metabolic consequences of aberrant mTORC1 signaling within the tumor microenvironment using a combination of quantitative metabolomics (comparing plasma, tumor, and tumor interstitial fluid) and in vivo metabolic tracing following stable isotope infusion. I will present our latest, unpublished findings, from these ongoing studies.

CAN WE EXPLOIT TUMOR METABOLISM FOR NEW THERAPIES?

Celeste Simon, Ph.D., University of Pennsylvania

Our laboratory investigates responses to changes in oxygen availability, as well as cancer cell adaptations to microenvironmental stresses that significantly contribute to advanced disease. Solid tumors frequently develop in areas subjected to hypoxia and growth factor/nutrient deprivation, due to vascular insufficiency. I will discuss how this influences tumor progression.

ELUCIDATING COMPOUND LIPID FLUXES WITHIN THE TUMOR MICROENVIRONMENT

Christian Metallo, Ph.D., Salk Institute for Biological Studies

Metabolism is central to virtually all cellular functions and contributes to a range of diseases. Therefore, a quantitative understanding of how biochemical pathways are dysregulated in the context of diseases such as cancer is necessary to identify new therapeutic targets. To this end we apply stable isotope tracers, mass spectrometry, and metabolic flux analysis (MFA) to explore metabolism in cells, animal models, and human patients. We are particularly interested in understanding how amino acids and lipid metabolism are coordinated in the context of cancer and diabetes, with an additional emphasis on developing technologies to address new questions. While most cancer metabolism studies focus on intermediary pathways and bioenergetics, we are building frameworks to study the dynamics of membrane lipid metabolism in tumors, focusing on sphingolipid biosynthesis and recycling. These pathways are tightly regulated across the ER, golgi, and autophagosome and operate at different time scales compared to central carbon metabolism. Using high-resolution mass spectrometry, we can resolve isotopologue distributions for complex membrane lipids, and these data are incorporated in the context of MFA models to resolve key exchange fluxes associated with lysosomal biology. To examine these pathways in more physiologically relevant contexts we are applying these methods to tumor slice cultures. These tools and results are allowing us to identify critical enzymes across diverse lipid metabolism pathways involving synthesis and recycling that exhibit high fluxes under distinct settings.

CIRCADIAN CLOCK CONTROL OF MUSCLE STEM CELL-MEDIATED TISSUE REGENERATION

Clara Peek, Ph.D., Northwestern University

Circadian clocks generate rhythmic pulses of glucose metabolism and respiration to divide energy-producing and energy-consuming processes into separate periods in the light-dark cycle. At the cellular level, clocks direct the expression of thousands of genes involved in metabolism, tissue growth, and repair, yet our understanding of how clocks detect signals in the environment to coordinate transcription and metabolic flux at precise stages during development remains poorly understood. A breakthrough in understanding circadian mechanisms in metabolic plasticity came from our discovery that molecular clock transcription factors respond to changes in environmental oxygen. We uncovered a bidirectional link between circadian clocks and the control of the oxygen- and mitochondrial stress-responsive hypoxia-inducible factor (HIF) pathway, which controls adaptation to low oxygen environments, such as during tumorigenesis and ischemic injury. Here, we demonstrate the role for the circadian clock in post-muscle injury myogenesis and tissue regeneration. Indeed, loss of the clock regulator *Bmal1* in adult muscle stem cell populations leads to impaired regeneration after ischemic muscle injury in mice. Furthermore, we observe time-of-day differences in muscle regeneration rates, with more rapid tissue repair following injury during the dark (active) phase. Mechanistically, we found that BMAL1 directs the transcriptional and metabolic response to hypoxia, via regulation of HIF1a target gene expression. Through regulation of hypoxic anaerobic glycolysis, BMAL1 controls the induction of cytoplasmic NAD^+ following tissue injury, which we found to be important for the regulation of myogenesis and immune cell recruitment following injury. Taken together, we have identified the MuSC-autonomous circadian clock as a novel regulator of oxygen-dependent control of myoblast cell fate and muscle tissue regeneration.

METABOLIC ALTERATIONS IN TUMOR AND HOST IN CANCER

Eileen White, Ph.D., Rutgers Cancer Institute of New Jersey

Cancer is a metabolic disease. Oncogenic events alter tumor cell metabolism to produce building blocks and mitigate redox stress while suppressing the high energy consuming functions of normal professional cells. Tumor cells also engage nutrient scavenging pathways (e.g., micropinocytosis for extracellular nutrients and autophagy for recycling of intracellular nutrients) to sustain metabolism. In advanced cancer, factors produced by tumors drive systemic inflammation and the wasting of host tissues, particularly the dedicated nutrient stores of muscle and fat, in a process known as cachexia. Cancer cachexia is responsible for most cancer deaths, but the underlying mechanisms are unclear. Determining who cancer metabolism is altered and how tumors alter the metabolism and function of host tissues can identify new targets for cancer therapy.

NUCLEOTIDE METABOLISM AND CONTROL OF CELL GROWTH

Issam Ben-Sahra, Ph.D., Northwestern University

Cells and organisms must coordinate their metabolic activity with changes in their nutrient environment. Cellular nucleotides play a central role in metabolism at a fundamental level. Purine and pyrimidine bases can be synthesized de novo or recycled through the salvage pathways. Nucleotides carry packets of chemical energy (e.g., ATP, GTP) throughout the cell to the many cellular functions that demand energy, which include synthesizing nucleic acids, proteins, and cell membranes. Our research program aims to unravel the molecular mechanisms through which growth signaling pathways influence the activity of metabolic pathways, with a specific focus on nucleotide synthesis. Previously, our investigations led to the discovery that the mechanistic target of rapamycin complex 1 (mTORC1) stimulates the synthesis of purines and pyrimidines through distinct molecular mechanisms. Building upon this discovery, my laboratory is currently dedicated to exploring the dynamic interactions between signaling and the nucleotide metabolic pathways. I will discuss our ongoing research on how signaling and nucleotide metabolic pathways mobilize building blocks for macromolecular synthesis to control cellular growth and function. We anticipate that our studies will provide novel insights into the molecular relationship between signaling networks and nucleotide metabolism, contributing to a deeper understanding of cellular function, and offering potential avenues for therapeutic interventions in signaling or metabolism-driven diseases.

TRANSCRPITIONAL REPRESSION BY HDAC3 MEDIATES T-CELL EXCLUSION FROM *KRAS* MUTANT LUNG TUMORS

Lillian Eichner, Ph.D., Northwestern University

Histone Deacetylase 3 (HDAC3) function in vivo, which has been predominantly defined in metabolic tissues, is nuanced and directed in a tissue specific fashion. We recently reported a critical tumor cell-intrinsic role for HDAC3 in *Kras* mutant lung tumors. In subsequent work, we identified HDAC3 as a tumor cell-intrinsic transcriptional regulator of the lung tumor immune microenvironment. In *Kras* mutant lung cancer cells, we found that HDAC3 is a direct transcriptional repressor of a cassette of secreted chemokines. Using genetic engineered mouse models, we found that HDAC3 inactivation in vivo induced expression of this gene set selectively in lung tumors and resulted in enhanced T-cell recruitment. Furthermore, we found that inhibition of HDAC3 in the presence of *KRAS* pathway inhibitors dissociated expression of immunosurveillance- from immunosuppressive-related chemokines, and that combination treatment of entinostat with trametinib enhanced T-cell recruitment into lung tumors in vivo. Together, our findings reveal that HDAC3 is a druggable endogenous repressor of T-cell recruitment into *Kras* mutant lung tumors.

THE ROLE OF METABOLITES IN CANCER AND AGING

Marcia Haigis, Ph.D., Harvard Medical School

Mitochondria are dynamic organelles that provide cells with energy and metabolites needed for survival and growth even during dramatic changes in diet, stress and development. Metabolic rewiring is a hallmark of cancer and supports the increased biosynthetic and energetic requirements of cancer cells. The tumor microenvironment provides a unique niche that supports the metabolic reprogramming of the tumor but may be suppressive to cytotoxic T cells. Additionally, metabolites serve as key signaling molecules and enable communication within cells and between cells. Here I will discuss our work in identifying novel molecular mechanisms that allow tumor and immune cells to adapt to external stresses and changes in nutrient availability.

TRANSCRIPTIONAL CONTROL OF METABOLISM AND INFLAMMATION BY GLUCOCOTICOIDS

Nina Henriette Uhlenhaut, Ph.D., TUM School of Life Sciences

The glucocorticoid receptor (GR) is one of the most powerful physiological regulators and one of the most widely used clinical drug targets. Its ligands, glucocorticoids, are both endogenous steroid hormones and synthetic immunomodulators. Once bound to its ligand, the glucocorticoid receptor translocates to the nucleus to control the expression of hundreds of target genes in a cell-type, time-point, and signal-specific manner. To identify and characterize the transcriptional complexes assembled by the GR on metabolic and inflammatory promoters and enhancers, we are combining mouse genetics with NGS techniques (ChIPseq, RNAseq, ATACseq, …), bioinformatics and proteomics. Our latest results on GR coregulator complexes, crosstalking transcription factors, DNA binding site motifs and their interactions with the chromatin landscape in vivo will be presented.

METABOLIC OUTLIERS AND HUMAN DISEASE PHENOTYPES

Ralph DeBerardinis, M.D., Ph.D., UT Southwestern Medical Center

Many human diseases involve alterations of cellular metabolism caused either directly or indirectly by mutations in genes that regulate the metabolic network. We study two kinds of disease that follow this paradigm: cancer and inborn errors of metabolism (IEMs). The incredible metabolic diversity of the human population provides opportunities to identify particular metabolic features that connect with clinically relevant aspects of disease, thus giving rise to new insights about pathophysiology. We have developed approaches using in vivo isotope tracing and metabolomics to assess metabolism directly in diseased tissues from patients, and to use these studies to generate hypotheses that can be tested in experimental models. I will discuss our ongoing efforts in reverse-translational research to identify disease-associated metabolic properties in patients, and to test whether blocking these properties can suppress disease progression in mice and other experimental models. Areas of particular interest include defining the impact of fixed, genetically defined metabolic anomalies on tissue development and the evolution of metabolic properties during cancer initiation and metastasis.

DECODING CRITICAL TARGETS OF THE LKB1/STK11 TUMOR SUPPRESOR IN NSCLC

Reuben Shaw, Ph.D., Salk Institute of Biological Studies

Inactivating mutations in the LKB1 (STK11) tumor suppressor are the third most frequent genetic alteration in non–small cell lung cancer (NSCLC). LKB1 encodes a serine/ threonine kinase that directly phosphorylates and activates 14 members of the AMP-activated protein kinase family. The function of many of the AMPK-related kinases (AMPKRs) remains obscure, and which are most critical to the tumor-suppressive function of LKB1 remains unknown.

Recently we have combined CRISPR and genetic analysis of the AMPKR family in NSCLC cell lines and mouse models, revealing multiple surprises. First, despite an unwavering role in inhibiting mTOR pro-growth signaling, loss of AMPK at initiation in Kras GEMMs results in a block in tumor progression, which we could connect to a loss of lysosome and metabolic adaptive capability. Moreover, we found a surprising critical role for the SIK subfamily.

Conditional genetic loss of Sik1 revealed increased tumor growth in mouse models of Kras - dependent lung cancer, which was further enhanced by loss of the related kinase Sik3 . As most known direct substrates of SIK1 and SIK3 control transcription, gene-expression analysis was performed, revealing specific transcriptional programs that contribute to LKB1-dependent tumorigenesis. Additional pathways by which one might therapeutically target these tumors based on the signaling and metabolic pathways dysregulated from LKB1-deficiency will be discussed.

SPATIAL ASSESSMENT OF METABOLISM

Shawn Davidson, Ph.D., Northwestern University

Isotope tracing has helped to determine the metabolic activities of organs and tumors. Methods to probe metabolic heterogeneity within these tissues are less developed. Recent advances from my lab to develop spatial metabolomics methods have enabled the determination of metabolic activity at the cellular level. Specifically, we couple stable-isotope-labeled nutrient infusion to matrix-assisted laser desorption ionization imaging mass spectrometry ("Iso-imaging") to quantitate metabolic activity in mammalian tissues and tumors in a spatially resolved manner. Integrating spatial metabolomics and isotope-labeling data with other spatial modalities will generate new hypotheses about how to target metabolism to enhance immunotherapy and identify vulnerabilities in cancer.