

# Lipids in Cancer

## *Symposium*

November 12, 2021

Rutgers University, New Brunswick, NJ



New Jersey Institute for Food,  
Nutrition, and Health

## Lipids in Cancer

Rutgers Center for Lipid Research Symposium  
November 12, 2021



Dear Colleagues,

We are pleased to welcome you to the sixth annual symposium of the Rutgers Center for Lipid Research (RCLR) entitled “*Lipids in Cancer.*” We have brought together scientists outside the RCLR family who will share their knowledge, results, and insights into how lipids are involved in cancer. Additionally, a series of short talks will be presented that highlight the research of our postdocs/students. We are certain that you will find the presentations, which are designed to facilitate your interaction with other scientists, stimulating, informative, and enjoyable.



The RCLR is a center of the New Jersey Institute for Food, Nutrition, and Health that promotes multidisciplinary research on the biochemical, biophysical, cellular, and molecular mechanisms involved in lipid metabolism, and extension of these endeavors to elucidate the underpinnings of lipid-based diseases such as obesity, lipodystrophy, diabetes, and heart disease. Our research utilizes model organisms, cells, tissues, and state-of-the-art instrumentation.

The center fosters interaction among faculty, postdoctoral associates, and students by holding monthly research meetings where postdoctoral associates and students have the opportunity to present their research and receive constructive feedback in a warm and friendly atmosphere. Moreover, we provide small grants and travel support to students and postdoctoral associates. We hold an annual symposium and a monthly seminar series that brings renowned scientists to Rutgers. The RCLR founded the Big Ten Academic Alliance Lipid Symposium; this meeting brings lipid researchers at Big Ten schools to interact on a regular basis. In the end, we extend our research findings to address lipid-based diseases, thereby promoting optimum health.

In closing, we convey our appreciation to the IFNH for their support in bringing this symposium to fruition.

Sincerely,  
Harini Sampath and  
George M. Carman

# Lipids in Cancer

Rutgers Center for Lipid Research Symposium  
November 12, 2021

## Program

- 9:15 am **Harini Sampath**  
*Welcome and introductions*
- 9:25 am **Brooke Emerling** (Sanford Burham Prebys Medical Discovery Institute)  
*Introduction of Dr. Lewis C. Cantley*
- 9:30 am **Lewis C. Cantley** (Weill Medical College of Cornell University)  
*The PI3K pathway: at the intersection of obesity, metabolism, oncogenesis, and cancer therapeutics*  
Discussion
- 10:30 am **Dr. Yanxiang (Jessie) Guo** (Robert Wood Johnson Medical School)  
*Autophagy and cancer metabolism in Kras-driven lung cancer*  
Discussion
- 11:20 am **Short talk presentations by RCLR postdocs/students**
- Joanna M. Kwiatek** (Carman Laboratory)  
*Reconstitution of the Nem1-Spo7 protein phosphatase complex into unilamellar phospholipid vesicles reveals its dependence on phosphatidic acid for the dephosphorylation of Pah1*
- Maria Ibrahim** (White Laboratory)  
*Defining the role of autophagy within whole-body mammalian metabolism in health and disease*
- Natalie Burchat** (Sampath Laboratory)  
*Role of intestinal stearyl-CoA desaturase 1 in whole-body lipid metabolism and metabolic health*
- Stephania Guzman** (Bhattacharya Laboratory)  
*Targeting hepatic kisspeptin receptor ameliorates non-alcoholic fatty liver disease*
- Siddhi Pawar** (Xue Laboratory)  
*Role of fungal lipid flippase in *C. neoformans*-host interaction*
- 12:00 pm *Break*

- 1:00 pm **Celeste C. Simon** (University of Pennsylvania)  
*Lipotoxicity in stressful tumor microenvironments*  
Discussion
- 2:00 pm **Brooke M. Emerling** (Sanford Burham Prebys Medical Discovery Institute)  
*Targeting metabolic vulnerabilities of cancer cells by phosphoinositide kinase inhibition*  
Discussion
- 3:00 pm **George M. Carman** (Rutgers University)  
*Awards and Carman Prize in Lipids*
- 3:15 pm Adjourn

## Speaker Biographies



**Dr. Lewis C. Cantley** is the Meyer Director of the Sandra and Edward Meyer Cancer Center at Weill Cornell Medical College and Professor of Cancer Biology in Medicine. Dr. Cantley has made significant advances in cancer research, stemming from his discovery of the signaling pathway phosphoinositide 3-kinase (PI3K) in 1984. His pioneering research has resulted in revolutionary treatments for cancer, diabetes, and autoimmune diseases. The author of over 400 original papers and more than 50 book chapters and review articles, Dr. Cantley is a fellow of the American Academy of Arts and Sciences and a member of the National Academy of Sciences. He graduated summa cum laude with a B.S. in chemistry from West Virginia Wesleyan College (1971) and obtained a Ph.D. in biophysical chemistry from Cornell University (1975). He conducted postdoctoral research at Harvard University, where he was appointed assistant professor of biochemistry and molecular biology in 1978. He became a professor of physiology at Tufts University in 1985 and returned to Harvard Medical School as Professor of Cell Biology in 1992. He became chief of Harvard's new Division of Signal Transduction, and a founding member of its Department of Systems Biology in 2002. In 2007, he was appointed director of the Beth Israel Deaconess Cancer Center. He joined the faculty of Weill Cornell Medical College and NewYork-Presbyterian Hospital in 2012.



**Dr. Jessie Yanxiang Guo** is an Associate Professor in the Division of Medical Oncology, Department of Medicine at the Robert Wood Johnson Medical School and a Resident Member at Rutgers Cancer Institute of New Jersey. Dr. Guo received her Bachelor of Medicine degree (equivalent of US M.D.) from Beijing Medical University, China. She then joined the Institute of Basic Science of Medicine (Beijing, China), where she began her research work in the field of cancer immunology and received her Master of Medicine degree. She received a Ph.D. degree through the Department of Molecular Cancer Biology and Pharmacology at Duke University under the supervision of Dr. Sally Kornbluth, where she received extensive training in biochemistry, cell cycle, cell death, and cancer biology. Dr. Guo joined the laboratory of Dr. Eileen White at Rutgers Cancer Institute of New Jersey as a postdoctoral fellow and moved into the emerging fields of autophagy and cancer metabolism. Through the use of genetically engineered mouse models for human cancers and state-of-the-art metabolomics, she discovered that Ras activation upregulates autophagy and that autophagy is required to maintain mitochondrial function to support Kras-driven lung tumor growth by recycling metabolites. Dr. Guo's current research interests are to elucidate the molecular mechanisms of tumorigenesis and identify and target potential metabolic vulnerabilities in Ras-driven cancers to improve cancer therapy. Her work is funded by the NIH, the American Cancer Society, and the New Jersey Health Foundation.



**Dr. Celeste C. Simon** is the Arthur H. Rubenstein Professor of Cell and Developmental biology, the scientific director of the Abramson Family Cancer Research Institute, and the Associate Director of the Abramson Cancer Center Core Facilities at the University of Pennsylvania Perelman School Of Medicine. Her research focuses on cancer cell metabolism, angiogenesis, and immunology. Dr. Simon earned a B.A. degree from Miami University, an M.S. degree from Ohio State University, and Ph.D. from The Rockefeller University. She carried out postdoctoral research at Rockefeller and Harvard Medical School before joining the faculty in the Departments of Medicine and Molecular Genetics & Cell Biology at University of Chicago. Dr. Simon was appointed as a Howard Hughes Medical Institute Investigator in 1994 and moved to the University of Pennsylvania as Associate Professor of Cell and Developmental Biology in 1999. In 2017, she was awarded the National Cancer Institute Outstanding Investigator Award. She was elected to the National Academy of Medicine in 2018 and to Academy of the American Association for Cancer Research and to the National Academy of Sciences in 2021.



**Dr. Brooke M. Emerling** is an Assistant Professor in the Cell and Molecular Biology of Cancer Program at the Sanford Burnham Prebys Medical Discovery Institute in La Jolla, California. She received her B.A. from the University of California Santa Cruz and her Ph.D. in Molecular and Cellular Biology from Northwestern University. Dr. Emerling did her postdoctoral training at Harvard Medical School under the mentorship of Dr. Lewis C. Cantley. She then became an Instructor of Cancer Biology in Medicine at Weill Cornell Medical College in New York City, where she continued her research on lipid kinase signaling and cancer metabolism. Dr. Emerling's research interest lies in understanding key signaling and metabolic pathways involved in the regulation of cellular function and growth under pathological conditions such as cancer. Her research program centers around dissecting the roles of the family of non-canonical phosphoinositide kinases, the phosphatidylinositol-5-phosphate 4-kinase, in cellular metabolism and cancer signaling. Dr. Emerling was awarded the American Association for Cancer Research Early-Career Award in 2014. Her work is funded by the National Institutes of Health and the American Cancer Society.

**Reconstitution of the Nem1-Spo7 protein phosphatase complex into unilamellar phospholipid vesicles reveals its dependence on phosphatidic acid for the dephosphorylation of Pah1**

Joanna M. Kwiatek, George M. Carman

Department of Food Science, Rutgers University, New Brunswick, NJ 08901

Phosphatidate (PA) phosphatase is one of the most important enzymes regulating lipid metabolism due to its function of catalyzing the dephosphorylation of PA to produce diacylglycerol. The importance of this reaction is exemplified by cellular defects and lipid-based diseases associated with the loss of the enzyme. PA phosphatase is controlled by protein kinases through phosphorylation taking place in the cytoplasm which causes retention of the enzyme in this cellular location. Interaction with the endoplasmic reticulum (ER) membrane-associated Nem1-Spo7 protein phosphatase complex followed by its dephosphorylation, causes the enzyme to hop onto the ER membrane where it either binds to a phospholipid molecule or to its substrate PA to catalyze its reaction. PA phosphatase then scoots along the ER membrane towards another PA molecule for another round of catalysis. In this work, the Nem1-Spo7 complex was reconstituted into unilamellar phospholipid vesicles (liposomes) composed of PA and the major ER membrane phospholipids; the complex was examined for its role in regulating phosphorylated PA phosphatase for its membrane interaction and catalytic function. Recombinant PA phosphatase was phosphorylated by Pho85-Pho80 and incubated with the proteoliposomes. The reconstituted protein phosphatase catalyzed the dephosphorylation of PA phosphatase and facilitated its membrane interaction and ability to catalyze the dephosphorylation of PA at the membrane surface.

**Defining the role of autophagy within whole-body mammalian metabolism in health and disease**

Maria Ibrahim, Eileen White

Rutgers Cancer Institute of New Jersey, New Brunswick, NJ 08901

Macroautophagy (autophagy hereafter) is the mechanism by which cells recycle proteins and organelles to maintain cellular homeostasis during stress and starvation. Under normal conditions, autophagy functions at a low basal level to remove damaged cellular components, thus preventing the gradual accumulation of toxic, intracellular waste material. Cancer cells rely on autophagy -- in many cases, they are more autophagy dependent than normal cells and tissues. This is due to the inherent deficiencies in the surrounding microenvironment caused by increased metabolic and biosynthetic demands imposed by deregulated cell proliferation. A major limitation is that most cancer models have addressed the role of autophagy only in tumors without drawing a direct comparison to autophagy deficiency in normal tissues. We propose to use a GEMM of systemic ablation of essential autophagy gene 7 (*Atg7*) to explore the underlying metabolic phenotype associated with autophagy deficiency and the tumor microenvironment. Acute, whole-body deletion of *Atg7* in adult mice causes a systemic metabolic defect manifested by gradual loss of white adipose tissue, liver glycogen, and muscle mass. Hence, we propose that the overall alterations in energy balance, consumption, and macro-fuel combustion contribute to the metabolic phenotype underlying autophagy deficiency. Intact autophagy promotes both metabolic and immune mechanisms by regulating immune cell homeostasis and function and suppressing inflammation. Additionally, serum cytokine and chemokine analysis demonstrated an increase in interferon induced cytokine, *CCL2*, upon loss of autophagy. We propose loss of autophagy causes systemic alterations in immune infiltration leading to metabolic changes within the host and tumor microenvironment. We hypothesize that loss of autophagy causes systemic metabolic reprogramming by shifting metabolism from intracellular recycling to dependence on a dedicated nutrient source and loss of *CCL2* can rescue the potential deleterious phenotype in autophagy deficient mice.

### **Role of intestinal stearoyl-CoA desaturase 1 in whole-body lipid metabolism and metabolic health**

Natalie Burchat and Harini Sampath

Rutgers Center for Lipid Research, New Jersey Institute for Food, Nutrition, and Health and Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ 08901

Stearoyl-CoA desaturase 1 (SCD1) is an ER-resident enzyme that converts saturated fatty acids into monounsaturated fatty acids (MUFAs). These MUFAs are the preferred substrates for the synthesis of lipid species such as cholesterol esters and triglycerides. The intestine plays an important role in both lipid absorption and assimilation. Cholesterol and free fatty acids but be esterified into cholesterol esters (CE) and triglycerides (TG), respectively, for efficient secretion of chylomicrons for eventual lipid assimilation. Given the important role of SCD1 in modulating the esterification of both CE and TG, we hypothesized that intestinal SCD1 may regulate lipid secretion from the intestine. Intestine-specific knockout (iKO) mice were generated by crossing SCD1 floxed mice with mice expressing Cre recombinase under the control of the villin promoter. Our studies reveal that these mice have a 13% reduction in steady-state plasma lipids, with a specific reduction in plasma triglycerides and free cholesterol. They also have reduced hepatic diacylglycerols and cholesterol esters, with a particular reduction in species containing the MUFA myristoleic acid (14:1). When given an oral bolus of a saturated fat, iKO mice do not have elevated triglyceride levels relative to floxed controls, suggesting reduced efficacy of intestinal lipid and secretion in these mice. In addition to these alteration in lipid handling, iKO mice marked increases in plasma and hepatic bile acids, potentially due to an inability to efficiently esterify cholesterol. Downstream signaling via bile acids is elevated in iKO mice, resulting in activation of TGR5 signaling in brown adipose tissue and the ileum. Thus, our results indicate that deletion of intestinal SCD1 has significant impacts on whole-body energy balance and lipid metabolism.

### **Targeting hepatic kisspeptin receptor ameliorates non-alcoholic fatty liver disease**

Stephania Guzman, Moshmi Bhattacharya

Department of Medicine, Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ, 08901

Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease worldwide affecting about 25% of the global population. In the U.S., NAFLD is a silent national epidemic that affects about 85 million adults and 8 million children, with associated annual medical costs of \$103 billion. The incidence of NAFLD correlates with the rise in obesity, Type 2 diabetes, and metabolic syndrome. A key feature of NAFLD is excessive hepatic fat accumulation or steatosis (ie NAFL), due to dysregulated hepatic fat metabolism which can progress to nonalcoholic steatohepatitis (NASH), fibrosis, cirrhosis and eventually to hepatocellular carcinoma (HCC). Currently, there are no approved pharmacotherapies to treat this disease. The G-protein coupled kisspeptin receptor (KISS1R) and its ligand kisspeptin are expressed in the liver, but their function is unknown. This study provides the first evidence that hepatic KISS1R signaling provides a protective role in the liver against steatosis. Using high fat diet (HFD) fed insulin resistant mice, we demonstrated that a deletion of hepatic *Kiss1r* worsened hepatic steatosis and increased markers for inflammation and fibrosis, in addition to enhancing glucose intolerance and insulin resistance phenotype. In contrast, administration of a potent KISS1R agonist (KPA) protected against steatosis, improved insulin resistance and decreased markers for inflammation and fibrosis. Furthermore, using a diet induced mouse model of NASH (DIAMOND mice), we observed that KPA treatment reduced hepatic fibrosis. Mechanistically, we found that activation of hepatic KISS1R signaling inhibits lipogenesis by activating the master energy sensor, AMPK. Activation of KISS1R also decreased interleukin-1beta levels; this cytokine is involved in all stages of liver disease promoting steatosis, inflammation and fibrosis. In NAFLD patients and in HFD-fed mice, hepatic KISS1/KISS1R expression and plasma kisspeptin levels were elevated

## Short talk abstracts

compared to healthy controls, suggesting a compensatory mechanism to reduce triglyceride synthesis. Overall, this study establishes KISS1R as a novel therapeutic target for the treatment of NAFL and NASH.

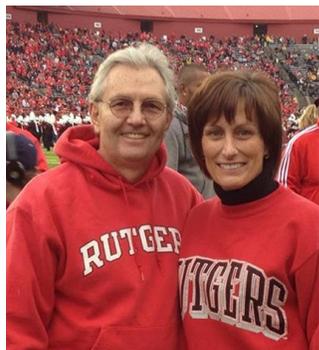
### **Role of fungal lipid flippase in *C. neoformans*-host interaction**

Siddhi Pawar, Orchi Dutta and Chaoyang Xue

Public Health Research Institute; Department of Microbiology, Biochemistry and Molecular Genetics, New Jersey Medical School, Rutgers University, Newark, NJ 07103; Rutgers Center for Lipid Research, Rutgers University, New Brunswick, NJ

*Cryptococcus neoformans* is a facultative intracellular fungal pathogen that infects the lung and then disseminates to the central nervous system to cause deadly cryptococcal meningitis, which accounts for ~15% HIV/AIDS related deaths. Alveolar macrophages are the first line of host defense against *Cryptococcus* infection. However, the mechanism of macrophage-fungus recognition and interaction remains incompletely understood. How *C. neoformans* is able to suppress host immunity and escape the antifungal activity of macrophages is still unclear. Our recent study on fungal lipid translocase (flippase) function revealed a critical role of fungal phospholipids in *Cryptococcus*-macrophage interaction. We found that loss of Cdc50, the regulatory subunit of a P4 type ATPase in *C. neoformans* results in an increased phosphatidylserine (PS) accumulation on the membrane surface. Interestingly, the *cdc50*Δ mutant showed a significant increase in both phagocytosis rate and macrophage killing in vitro tissue culture assays. Furthermore, the mice infected with *cdc50*Δ cells induced a strong Th-1 and Th-17 response, cleared the infection, and prevented secondary dissemination when compared to the mice infected with wild type H99 strain. PS has been recognized as an “eat-me” signal in macrophage recognition of apoptotic cells. We hypothesize PS exposure on *C. neoformans* might aid in macrophage recognition, interaction, and induction of a protective immune response during pulmonary cryptococcosis. Our preliminary data indeed showed that host PS receptors, Tyro-3 and Axl, are highly induced in the infected mouse lung. The long-term goal of our study is to understand the molecular mechanism of lipid flippase mediated host-*C. neoformans* interaction and target lipid flippase function as a novel drug target.

## Carman Prize in Lipids



The George M. and Maureen D. Carman Prize in Lipids is an endowed prize established to encourage research and to provide financial assistance to graduate students and postdoctoral fellows/associates in the School of Environmental and Biological Sciences (SEBS). The prize is awarded for outstanding research achievement in the area of lipid biochemistry. You can contribute to the endowment via the [Rutgers Foundation](https://www.rutgers.edu/foundation) web site and earmark the funds for the Carman Prize in Lipids.

### Recipients



Hyeon-Son Choi  
(2007)



Anibal Soto-Cardalda  
(2008)



Younkyung Kim  
(2009)



Stylianos Fakas  
(2011)



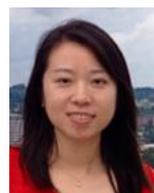
Lesley Wassef  
(2011)



Wen-Min Su  
(2012)



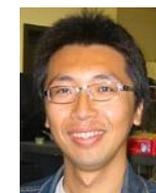
John Douglass  
(2013)



Yixuan Qiu  
(2014)



Marc Tuazon  
(2014)



Lu-Sheng Hsieh  
(2015)



Yeonhee Park  
(2016)



Inna Nikonorova  
(2017)



Prabuddha Dey  
(2018)



Joanna Kwiatek  
(2019)



Kevin Tveter  
(2020)



Natalie Burchat  
(2021)



William Jonsson  
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