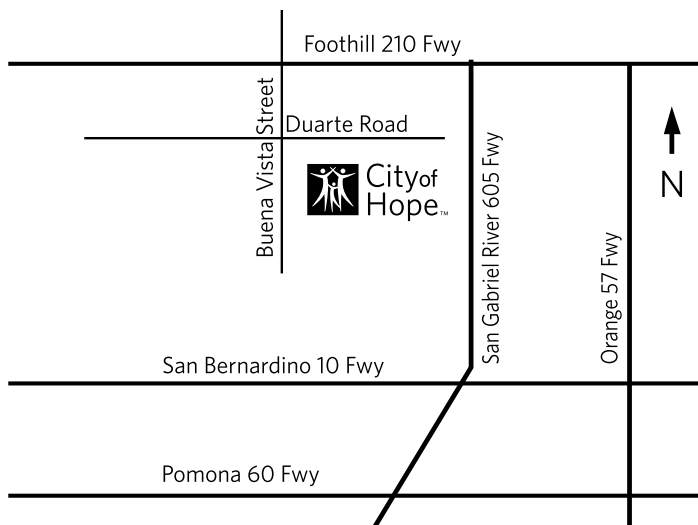


Date
 Monday, November 7, 2011
 8:45 a.m. to 5:20 p.m.

Registration
 Registration is required and free.
 To register, please visit
<http://BeckmanSymposium.coh.org>

Location
 Cooper Auditorium
 Beckman Research Institute
 City of Hope
 1500 E. Duarte Rd.
 Duarte, CA 91010-3000

Information
 For more information, please contact
 Steven Novak:
 Phone: 626-256-8775
 Fax: 626-471-3901
 Email: BeckmanSymposium@coh.org



Cancer as a Metabolic Disease

The 21st Beckman Symposium
 November 7, 2011

City of Hope and Beckman Research Institute





Richard Jove, Ph.D.

Morgan and Helen Chu Director's Chair
Beckman Research Institute
City of Hope

As Director of Beckman Research Institute of City of Hope, I would like to welcome you to the 21st Beckman Symposium, titled "Cancer as a Metabolic Disease." The Beckman Symposia are dedicated to presenting the latest breakthroughs in the areas of basic, translational

and clinical science research. This year's conference has brought together leaders in fields crossing multiple disciplines, and will highlight exciting topics in the areas of microRNA-mediated regulation of cell fate and identity, development and cancer, and immunity, among many other novel opportunities for therapeutic intervention.

City of Hope comprises Beckman Research Institute and the National Medical Center, both of which are located in Duarte, Calif. In 1983, Beckman Research Institute of City of Hope was established as the first of five Beckman Institutes, following a generous gift from the Arnold and Mabel Beckman Foundation.

Beckman Research Institute of City of Hope is unique among the Beckman Institutes in that it has held a National Cancer Institute (NCI) Cancer Center Support Grant for more than 25 years. City of Hope comprehensive cancer center, with five research programs in the areas of basic science research (cancer biology), clinical and translational research (developmental cancer therapeutics, cancer immunotherapeutics, hematologic malignancies), and prevention and control programs (cancer control and population sciences), conducts its activities across the entire Duarte campus, facilitating interactions among basic, translational and clinical researchers. All cancer center members who conduct laboratory research hold appointments as Beckman Research Institute faculty. These collaborative interactions between the cancer center and Beckman Research Institute provide tremendous opportunities for translation of laboratory discoveries directly into new therapies for patients. As a result, City of Hope has numerous ongoing clinical trials that build on the research discoveries of Beckman Research Institute investigators.

The Duarte campus occupies 120 acres, with 64 buildings and more than 300,000 square feet of laboratory space devoted to biomedical research. Beckman Research Institute has 24 scientific shared (core) resources that include Analytical Pharmacology, Functional Genomics, High Throughput Screening, Mass Spectrometry and Proteomics, DNA Sequencing, Nuclear Magnetic Resonance, Synthetic and Biopolymer Chemistry, Transgenic Mouse Lab and X-ray Crystallography, among others.

We would like to thank you for your participation in this year's Beckman Symposium and hope it will provide a forum to present and discuss the latest advances in molecular medicine, essential for the translation of laboratory research into successful clinical practice. This year's topic is particularly timely and also timeless in relevance!

Kind regards,

Richard Jove, Ph.D.
Morgan and Helen Chu Director's Chair

The History of Beckman Research Institute

The Arnold and Mabel Beckman Foundation, in April of 1983, awarded \$10 million to City of Hope's research institute. This was the first major gift made by the foundation and set up the first of five Beckman Research Institutes. Arnold Beckman, Ph.D., during the formal dedication ceremony in January of 1984, said: "We look on our contribution as an investment, probably one of the best investments of our lives. It may not pay dividends in dollars, but it will pay dividends that are far more valuable than dollars — the pride and satisfaction of being associated with an organization that is doing so much for the benefit of mankind."

It is with his words in mind that Beckman Research Institute of City of Hope continues in its mission. In 2008, the institute celebrated its 25th anniversary.

Funds from the foundation were earmarked for buildings, equipment and endowment. In addition, later donations from the Beckman Foundation have contributed to the construction of the Conrad Hilton, Shapiro and Kaplan-Black research buildings, Graff Medical and Scientific Library and, most recently, the Arnold and Mabel Beckman Center for Cancer Immunotherapeutics & Tumor Immunology, a 108,000 square foot research facility.



In addition to the original gift, the foundation has also made annual donations that have provided valuable discretionary funds. Since 1991, Beckman monies have funded the annual Beckman Symposium, bringing world renowned scientists to City of Hope, and the Beckman Fellows Program, which has helped to

launch the careers of eight talented young scientists. During the current funding period, Beckman Foundation funds are being used for development of new state-of-the-art technologies and shared core facilities that enable leading-edge biomedical research at City of Hope.

The mission of the Arnold and Mabel Beckman Foundation, established in September 1977, is to support basic science research, medicine and education. "I accumulated my wealth by selling instruments to scientists," Beckman explained, "so I thought it would be appropriate to make contributions to science." For a quarter of a century, the Beckman Foundation has lived up to its mission by providing vital support to Beckman Research Institute of City of Hope. The new vision for Beckman Research Institute, supported by the foundation, is excellence in innovative biomedical research that impacts on the treatment of cancer, diabetes and related diseases.

The 2011 Beckman Symposium
CANCER AS A METABOLIC DISEASE

Program

8:45 a.m.	Welcome Richard Jove, Ph.D. Director, Beckman Research Institute
8:50 to 9 a.m.	Glutamine and Cancer — Personal Reflections and Early Insights Eugene Roberts, Ph.D. City of Hope
9 to 10 a.m.	Plenary Presentation Therapeutic Targeting of Cancer Cell Metabolism Craig B. Thompson, M.D. Memorial Sloan-Kettering Cancer Center
10 to 10:45 a.m.	Glutamine at the Crossroads of Cell Growth and Autophagy Robert Abraham, Ph.D. Pfizer Biopharmaceuticals
10:45 to 11 a.m.	Break
11 to 11:45 a.m.	Nuclear Receptors and AMPK — Resetting Metabolism Ronald M. Evans, Ph.D. The Salk Institute for Biological Studies
11:45 a.m. to 12:30 p.m.	Targeting Altered Cellular Metabolism in EGFR-Activated Glioblastomas Paul S. Mischel, M.D. David Geffen UCLA School of Medicine

The 2011 Beckman Symposium
CANCER AS A METABOLIC DISEASE

Program

12:30 to 1:45 p.m.	Lunch and Poster Session
1:45 to 2:30 p.m.	Obesity and Cancer Mortality: Lessons from Childhood Leukemia Steven Mittelman, M.D., Ph.D. Children's Hospital of Los Angeles
2:30 to 3:15 p.m.	A Pharmacologic Approach to Treat Colorectal Cancer via Nutrient Depletion Barry M. Forman, M.D., Ph.D. City of Hope <i>(The City of Hope speaker was selected by invited speakers who ranked anonymously submitted abstracts.)</i>
3:15 to 3:30 p.m.	Break
3:30 to 4:15 p.m.	Altered Metabolic Enzymes and Metabolites in Cancer Yue Xiong, Ph.D. University of North Carolina at Chapel Hill Fudan University, Shanghai, China
4:15 to 5 p.m.	Regulation and Function of the mTORC1 and mTORC2 Pathways David M. Sabatini, M.D., Ph.D. Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology
5 to 5:20 p.m.	Panel Discussion

Glutamine at the Crossroads of Cell Growth and Autophagy

Robert Abraham, Ph.D.

Pfizer Biopharmaceuticals

Glutamine is a nonessential amino acid that represents an important source of bioenergetic and biosynthetic precursors during rapid cell growth and proliferation. Cellular transformation is frequently associated with a concomitant increase in glutamine consumption. Glutamine supports anabolic metabolism in large part through its ability to supply carbon to the mitochondrial tri-carboxylic acid cycle via glutaminolysis. Deamination of glutamine during glutaminolysis leads to the generation of ammonia as a potentially toxic by-product. Glutamine is also involved in the activation of mTOR, a protein kinase that coordinates overall cell growth with nutrient supplies. In addition to its well-established roles in building cell mass, glutamine was recently shown to regulate autophagy, an intracellular degradative pathway that can lead to cell attrition as opposed to growth. One mechanism through which glutamine metabolism affects autophagy is via the release of ammonia during glutaminolysis. This presentation will highlight the dynamic interplay among glutamine, mTOR, and the autophagic machinery in cancer cells.

Nuclear Receptors and AMPK — Resetting Metabolism

Narkar, V., Ph.D., Lamia, K., Ph.D., Yu, R., M.D., Ph.D., Downes, M., Ph.D., and Evans, R.M., Ph.D.

Howard Hughes Medical Institute, The Salk Institute, La Jolla, CA

Nuclear hormone receptors (NHRs) are a large family of ligand-activated transcription factors that regulate programs of cellular growth, differentiation and homeostasis. The structurally conserved ligand binding domains of NHRs bind to hydrophobic small molecules including steroid hormones, fat soluble vitamins and bile acids, thereby interpreting small molecule cues to affect transcriptional readouts.

The temporal correspondence between metabolic and circadian rhythms suggests the inherent coupling of these two key physiologic processes. Sleep, inactivity and fasting are opposed by wakefulness, motivated behavior and the fed state. Thus we are interested whether there may be common mechanism for “entraining” both the clock and key metabolic pathways. We provide evidence that the energy sensor AMPK, via actions as an atypical transcriptional regulator, may function as one such dual entrainment trigger.

In regards to the clock, we provide genetic, mechanistic and pharmacologic evidence that AMPK-dependent phosphorylation enables cryptochromes (e.g., Cry1) to act as energy sensors for metabolic entrainment of the circadian clock. In addition, we find that in muscle, AMPK dramatically activates the transcriptional potency of PPAR α to promote running endurance in an exercise dependent fashion. Unexpectedly, the AMPK agonist AICAR creates a similar gene profile and increases endurance even without exercise. Pharmacologic exercise and clock entrainment from AMPK have therapeutic implications in metabolic disease, atherosclerosis and frailty, as well as the potential for athletic abuse.

A Pharmacologic Approach to Treat Colorectal Cancer via Nutrient Depletion

Lily Lai, M.D., Min Lin, M.S., Ramani Ravirala, Ph.D., Sharon Wilczynski, M.D., Ph.D., David Smith, Ph.D., Barry M. Forman, M.D., Ph.D.

City of Hope

In 1927, Otto Warburg demonstrated that tumors possess an elevated rate of glycolytic metabolism and suggested that selective depletion of glucose from tumor cells would provide a very effective form of chemotherapy. In the past decade there has been increasing evidence that obesity and diabetes are associated with a higher risk of cancer development and deaths. For example, there is a consistent two-fold increase in colorectal cancer (CRC) risk in obese/diabetic individuals, resulting in an estimate that 20 to 35% of all CRC cases in the United States are attributed to obesity/diabetes. Despite the strong epidemiological evidence, there is a large gap in our understanding of the effects of altered energy and nutrient metabolism on cancer, and no pharmacological means to reverse this interaction.

We show that the nuclear receptor FXR limits the progression of intestinal tumors and CRC in mouse and man. Patients with detectable FXR expression in their tumors experience a 5.9-year increase in overall survival. Treatment of mice with FXR ligands decreased tumor size and number by increasing tumor apoptosis.

Given the link between FXR and whole body glucose homeostasis, we asked whether FXR ligands might act by altering intratumor glucose levels. We found that FXR activation in vivo (mice) specifically led to an increase in GSK-3 β phosphorylation, decreased mTOR activity and a selective decrease in intra-tumor glucose with no effect on the normal mucosa. These findings provide perhaps the first example of the exciting therapeutic approach first proposed by Warburg over eight decades ago.

Altered Metabolic Enzymes and Metabolites in Cancer

Yue Xiong, Ph.D.

Department of Biochemistry and Biophysics, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, North Carolina 27599, USA. Molecular and Cell Biology Lab, Institutes of Biomedical Sciences, Fudan University, Shanghai 200032, China

Altered metabolic regulation was recognized as the first tumor phenotype and broadly used in the clinic for tumor detection. Two recent findings — direct regulation of metabolic enzymes by frequently mutated cancer genes and frequent mutations targeting gene encoding metabolic enzymes in cancer — have renewed interest in cancer metabolism. Our recent findings revealed a novel regulation of metabolism by the lysine acetylation of many metabolic enzymes. We also found that metabolic intermediates directly participate in the epigenetic control. Importantly, alternations both metabolic enzyme acetylations and metabolites are linked to human cancer development.

Targeting Altered Cellular Metabolism in EGFR-activated Glioblastomas

Paul S. Mischel, M.D.

David Geffen UCLA School of Medicine

Cancer is a disease characterized by mutational activation and enhanced dependence on oncogenic signal transduction cascades. Cancer is also characterized by major shifts in cellular metabolism, including glucose utilization and uptake, energy metabolism and lipogenesis. The molecular circuitry linking oncogenic signal transduction cascades and therapeutically targetable metabolic circuits is only beginning to be understood. This talk will focus on glioblastoma, the most common malignant primary brain tumor of adults and one of the most lethal of all cancers. Glioblastoma is characterized by nearly universal PI3K pathway hyperactivation, including EGFR amplification and mutation. Studies leading to molecular dissection of the signaling networks linking mutated EGFR with altered lipogenesis, cholesterol homeostasis and anaerobic glycolysis will be discussed, including integration of studies performed in cell lines, in vivo models and tumor tissue from patients treated with targeted inhibitors. The talk will describe the identification of therapeutically targetable EGFR/PI3K/SREBP-1 dependent pro-survival metabolic signaling pathways, and will discuss recent studies linking this pathway to altered fatty acid synthesis and cholesterol homeostasis.

Obesity and Cancer Mortality: Lessons from Childhood Leukemia

Steven Mittelman, M.D.

Children's Hospital of Los Angeles

Obesity increases both the incidence and mortality of numerous types of cancer. Obesity is a complex state, associated with numerous physical, physiological, social, economic and genetic differences, making it difficult to tease apart the mechanisms linking obesity to cancer. A recent study found that children who are obese at the time of diagnosis of high-risk acute lymphoblastic leukemia (ALL) have a 50 percent increased risk of relapse compared to lean children. To investigate this, we developed mouse and tissue culture models of obesity and leukemia. We have found that obese mice develop ALL more rapidly, and are more likely to relapse after treatment with first line chemotherapies, even when they are dosed proportional to body weight. Also, we have demonstrated that adipocytes have multiple effects to impair chemotherapy of ALL: They attract leukemia cells, secrete factors which cause ALL resistance to chemotherapy, and they concentrate chemotherapy out of the extracellular environment, making it inaccessible to the ALL cells. Adipocytes also produce important fuels, such as the amino acids asparagine and glutamine, which may help leukemia cells resist certain chemotherapies. These complex effects of adipocytes may help explain why obese individuals have such a substantial increased risk of dying from cancer.

Regulation and Function of the mTORC1 and mTORC2 Pathways

David M. Sabatini, M.D., Ph.D.

Whitehead Institute for Biomedical Research, Massachusetts Institute of Technology

mTOR is the target of the immunosuppressive drug rapamycin and the central component of a nutrient- and hormone-sensitive signaling pathway that regulates cell growth and proliferation. We now appreciate that this pathway becomes deregulated in many human cancers and has an important role in the control of metabolism and aging. We have identified two distinct mTOR-containing protein complexes, one of which regulates growth through S6K and another that regulates cell survival through Akt. These complexes, mTORC1 and mTORC2, define both rapamycin-sensitive and -insensitive branches of the mTOR pathway. I will discuss new results from our lab on the regulation and functions of the mTORC1 and mTORC2 pathways.

Therapeutic Targeting of Cancer Cell Metabolism

Craig B. Thompson, M.D.

Memorial Sloan-Kettering Cancer Center, New York

Proliferating cancer cells exhibit a robust but seemingly wasteful metabolism. Two nutrients, glucose and glutamine, are consumed by tumor cells at rates in vast excess of their utilization by nontransformed cells. The uptake of each of these nutrients is under the control of distinct oncogenes. The PI3K/Akt/TOR signaling pathway plays the primary role in directing cellular glucose uptake and metabolism. Deregulation of this pathway in cancer can be imaged in vivo by FDG-PET scans. Recent evidence suggests that the myc family of oncogenes direct glutamine uptake and mitochondrial catabolism in transformed cells. Glutamine and glucose metabolism facilitate distinct mitochondrially-dependent synthetic reactions required for growth. Recent evidence suggests tumor suppressors are counter-regulators of mitochondrial biosynthesis. In the case of hypoxia, conversion to anaerobic glycolysis is induced by activation of HIF-1 α . In the case of glucose limitation, conversion to fatty acid oxidation is mediated by activation of p53. In addition, a role for intracellular metabolites in oncogenic signaling has also been recently suggested through studies of succinate dehydrogenase and fumarate mutations in cancer. The discovery of cancer-associated mutations in isocitrate dehydrogenase 1 and 2 that produce a novel metabolite, 2-hydroxyglutarate, provides the most compelling example of this principle to date. With these new discoveries in mind, the roles of oncogenes and tumor suppressors in the regulation of metabolic pathways will be discussed. Therapeutic strategies to selectively impair tumor metabolism will be considered.

General Information

The 2011 Beckman Symposium CANCER AS A METABOLIC DISEASE

- Date:** Monday, November 7, 2011
8:45 a.m. to 5:20 p.m.
- Location:** Cooper Auditorium
Beckman Research Institute
City of Hope
1500 E. Duarte Rd.
Duarte, CA 91010-3000
- Registration:** Registration is required and free.
Registration includes lunch.
- Information:** For more information, including a list of hotel accommodations, please contact:
Steven Novak
Phone: 626-256-8775
Fax: 626-471-3901
Email: BeckmanSymposium@coh.org
Or visit our Web site at
<http://BeckmanSymposium.coh.org>

In compliance with the Americans with Disabilities Act, all reasonable efforts will be made to accommodate persons with disabilities at the meeting. If you have any special dietary or accommodation needs, please notify the program coordinator listed above prior to the symposium. This advance notification will help us serve you better.

Cancer as a Metabolic Disease

is the 21st Beckman Symposium to be held at Beckman Research Institute of City of Hope. Supported by funds from the Beckman Endowment, the Beckman Symposia are arranged annually by the research staff organization of City of Hope.

This year's symposium was organized by

Barry M. Forman, M.D., Ph.D.
Wendong Huang, Ph.D.
Lily Lai, M.D.

The objective of Beckman Research Institute of City of Hope is to support innovative and creative research and to educate future scientists in the biological sciences. The institution is committed to providing an environment of academic freedom in which investigators can pursue greater knowledge. Research is to be of the highest possible caliber and directed to an understanding of the molecules and processes of life, including those processes important to the causes, prevention and cure of human disease.

— Mission Statement, Beckman Research Institute of City of Hope



Cover Image:

The image depicts an 18F-fluorodeoxyglucose (FDG) PET scan of a patient with recurrent non-Hodgkin lymphoma, first diagnosed at stage IV-B. Overlaid upon the image are the glycolytic-related metabolic pathways that contribute to the "Warburg effect." These pathways are active in most tumors and establish the molecular underpinnings for the widely used 18F-FDG diagnostic PET scan. This year's Beckman Symposium will feature molecular and physiologic aspects of cancer metabolism with an eye toward identification of therapeutic targets that can be manipulated for novel forms of cancer therapy (scan provided by James Bading, Ph.D., City of Hope).