

Date

Friday, November 20, 2009
8 a.m. to 5 p.m.

Registration

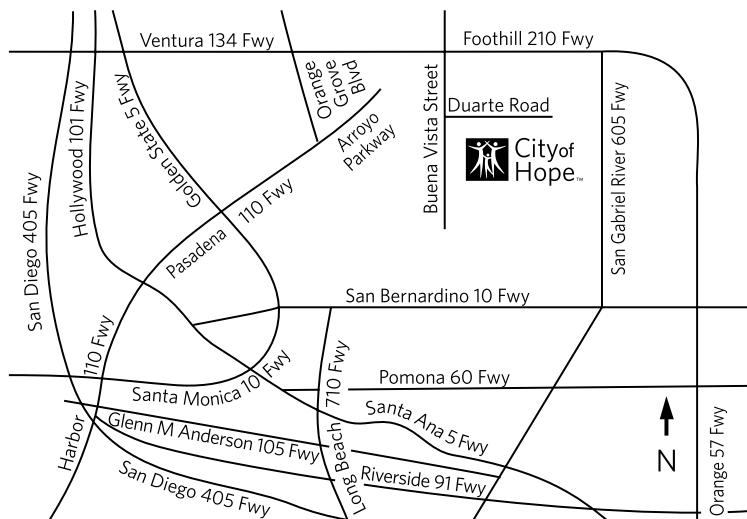
Registration is required and free.
To register, please visit
www.cityofhope.org/beckmansymposium

Location

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

Information

For more information, please contact
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New Frontiers in Molecular Medicine

The 19th Beckman Symposium
November 20, 2009
Beckman Research Institute

Cooper Auditorium
Duarte, California





The Arnold and Mabel Beckman Center for Cancer Immunotherapeutics and Tumor Immunology



Richard Jove, Ph.D.

Director
Beckman Research Institute
City of Hope

As Director of Beckman Research Institute at City of Hope (BRI/COH), I would like to welcome you to the 19th Beckman Symposium, titled “New Frontiers in Molecular Medicine.” 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 stem cell biology, signaling pathways, small molecule therapeutics, protein interactions, and cell differentiation, among many other novel opportunities for therapeutic intervention.

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

BRI/COH 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. The 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 science researchers. All Cancer Center members who conduct laboratory research hold appointments as BRI/COH faculty. These collaborative interactions between the Cancer Center and BRI/COH 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 BRI/COH investigators.

The Duarte campus occupies 120 acres, with 64 buildings and more than 270,000 square feet of laboratory space devoted to biomedical research. The BRI/COH has 23 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. Additional shared resources under development include Stem Cell and Viral Vectors.

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. Sit back, relax, and enjoy the outstanding scientific program!

Kind regards,

Richard Jove, Ph.D.

Symposium Program

8 to 8:30 a.m.	Registration Continental Breakfast	11:30 to 12:20 p.m.	Signal Transduction in Cancer and the DNA Damage Response Tony Hunter, Ph.D. Salk Institute for Biological Sciences, CA
8:30 to 8:40 a.m.	Welcome Michael A. Friedman, M.D. President and Chief Executive Officer, Director, City of Hope Comprehensive Cancer Center	12:20 to 1:20 p.m.	Lunch — Courtyard
	Opening Remarks Richard Jove, Ph.D. Director, Beckman Research Institute	1:20 to 2:10 p.m.	Prodding and Engineering Cell Death Pathways James A. Wells, Ph.D. University of California, San Francisco, CA
8:40 to 9:30 a.m.	Phenotypic Switching and the Molecular Anatomy of Tumor Progression George Vande Woude, Ph.D. Van Andel Institute, MI	2:10 to 3 p.m.	Dissecting and Drugging Pathologic Protein Interactions with Hydrocarbon-Stapled Peptides Loren D. Walensky, M.D., Ph.D. Harvard Medical School, MA
9:30 to 10:20 a.m.	Transcriptional Effects of Persistently Active Stat3 in Cancer Cells James E. Darnell, Jr., M.D. The Rockefeller University, NY	3 to 3:20 p.m.	Break
10:20 to 10:40 a.m.	Break	3:20 to 4:10 p.m.	New Frontiers in Molecular Medicine: Development of Proof-of-Concept Chemical Probes Targeting Selected Cysteine Proteases, Kinases, Orphan Nuclear Receptors, and Carboxylate Transporters William R. Roush, Ph.D. The Scripps Research Institute, FL
10:40 to 11:30 a.m.	New Uses for Stem Cells in Understanding Neurodegenerative Disease Lee L. Rubin, Ph.D. Harvard University, MA	4:10 to 5 p.m.	A Chemical Approach to Stem Cell Biology Peter G. Schultz, Ph.D. The Scripps Research Institute, CA

Transcriptional Effects of Persistently Active Stat3 in Cancer Cells

James E. Darnell, Jr., M.D.

Cancer cell production of IL-6 and IL-6 activation of STAT3 may well be the major cause of persistent activation of STAT3 that contributes to human oncogenesis. A brief review of this conclusion will be followed by a discussion of results of acute removal of phosphorylated STAT3 on transcriptional events (high throughput ChIP sequence) one hour later, in head and neck and prostate cancer cell lines. The objective is to learn the transcriptional targets of STAT3 under conditions of continuous low level ligand stimulation in different tumors.

Signal Transduction in Cancer and the DNA Damage Response

Tony Hunter, Ph.D.

Several protein kinases not previously implicated in cancer have recently been shown to harbor mutations in tumor cells by kinome resequencing. We have analyzed cancer-associated mutations in DAPK3 and two isoforms of PKC and found that they decrease kinase activity, suggesting they normally play tumor suppressor roles and are mutationally inactivated in some cancers. In response to DNA double-strand breaks (DSBs), cells sense the DNA ends at the break and then activate the protein kinase ATM. We have found that the tumor suppressor protein CtIP is essential downstream of ATM, for resection of the 5' end at DSBs, which in turn is a prerequisite for activation of the ATR kinase and subsequent repair of the break by homologous recombination.

New Frontiers in Molecular Medicine: Development of Proof-of-Concept Chemical Probes Targeting Selected Cysteine Proteases, Kinases, Orphan Nuclear Receptors, and Carboxylate Transporters

William R. Roush, Ph.D.

Recent studies at Scripps Florida targeting the development of selective chemical probes for certain cysteine proteases, kinases, orphan nuclear receptors, and monocarboxylate transporters will be presented. In several cases, the starting point for the probe development efforts derived from ultra-high throughput screens performed at Scripps Florida under the auspices of the NIH's Molecular Libraries Program and the MLPCN network.

New Uses for Stem Cells in Understanding Neurodegenerative Disease

Lee L. Rubin, Ph.D.

Most people who think about the connection between stem cells and neurodegenerative disease do so in the context of cell replacement therapy — adding cells back to repair a damaged nervous system. However, this is only one way in which a stem cell-focused approach can help us find new treatments. In principle, human stem cells can be differentiated into large numbers of the very types of neurons and glial cells that are affected by nervous system disorders. These cells can then be used to set up “screens” that may help us both understand more clearly the pathological basis of the different diseases as well as find better therapeutics.

A Chemical Approach to Stem Cell Biology

Peter G. Schultz, Ph.D.

We are using a variety of cell based screens to identify and characterize the mechanisms of small molecules that affect stem cell self-renewal and differentiation, and the reprogramming of somatic cells. Examples will be discussed including the expansion of cord blood derived HSCs, *in vivo* neurogenesis, the selective differentiation of MSCs to chondrocytes and osteoblasts, reversible beta cell proliferation, MEF and SKP reprogramming, human ESC self-renewal and differentiation, and the selective killing of cancer stem cells.

Phenotypic Switching and the Molecular Anatomy of Tumor Progression

George Vande Woude, Ph.D.

During malignant progression, tumor cells switch from a proliferative to an invasive phenotype through epithelial-mesenchymal-transition (E-M-T). Subsequently, metastatic growth requires transformation from an invasive to a proliferative phenotype by mesenchymal-epithelial-transition (M-E-T). Using a model in which we are able to induce E-M-T or M-E-T, we observe that E-M-T occurs with loss of E-Cadherin expression and the gain of c-MET expression. β -Catenin expression levels do not change with phenotypic switching; however, β -Catenin localization shifts from the cell membrane to nuclear/cytoplasm. Our results suggest a role for β -Catenin in modulating c-MET expression and E-M-T gene regulation. This model is a valuable tool for investigating both E-M-T and M-E-T in the metastatic progression of numerous carcinomas.

Dissecting and Drugging Pathologic Protein Interactions with Hydrocarbon-Stapled Peptides

Loren D. Walensky, M.D., Ph.D.

Protein interactions mediate innumerable cellular activities in health and disease. Whether fleeting or stable, homeostatic or pathologic, protein partnerships and their sites of contact form the basis for discovery of biological pathways, disease mechanisms, and opportunities for therapeutic intervention. Harnessing Nature's evolutionarily-honed peptides to investigate and subvert disease-causing protein interactions has been hindered by their loss of natural architecture, vulnerability to degradation, and cellular impermeability. We have applied a chemical strategy termed “hydrocarbon-stapling” to remedy the shortcomings of synthetic peptides, yielding unique discovery tools and prototype therapeutics that target pathologic protein interactions for clinical benefit.

Prodding and Engineering Cell Death Pathways

James A. Wells, Ph.D.

Apoptosis, or programmed cell death, represents an ultimate fate decision in cell biology. This process is critical for cellular differentiation and remodeling of tissues, and for anti-viral and anti-tumor defense. A distinct molecular feature of apoptosis is the widespread, but controlled cellular proteolysis, which is predominantly mediated by eight members of the caspase family of cysteine proteases. These enzymes are like demolition experts that cleave protein targets critical for cellular life. We have designed new enzymes and small molecules to study and activate individual caspases and the proteins they cleave.

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. Dr. Beckman, 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 at City of Hope continues in its mission. In 2008, the Institute celebrated its twenty-fifth 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 Beckman Center for Cancer Immunotherapeutics and 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 cutting-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," Dr. 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 objective of the 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

New Frontiers in Molecular Medicine

is the 19th Beckman Symposium to be held at Beckman Research Institute at 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

David Horne, Ph.D.

Richard Jove, Ph.D.

Takahiro Maeda, M.D., Ph.D.

John Termini, Ph.D.

John Williams, Ph.D.

Richard Yip, Ph.D.

Special thanks goes to

Silvia da Costa, Ph.D.

Steve Novak, Ph.D.

Sarah Torres

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 prior to the symposium. This advance notice will help us serve you better.

Cover Image:

Hypothetical model of crossed masked Erbitux and Matuzumab based on Donaldson et al., Cancer Biology and Therapy (2009).

While monoclonal antibodies are routinely used in the clinic, a number of these target antigens are also present on normal tissues and thus can produce severe side effects (skin rashes and cardiotoxicity). To avoid these side effects, Donaldson and co-workers have fused the domain III of the EGFR receptor (antigen) to an Erbitux scFv (antibody). The masked antibody will not bind normal or diseased tissue. The peptide linking the antigen to the antibody, however, contains a tumor specific protease site (MMP-9). Cleavage by the tumor associated protease releases the mask, allowing the therapeutic antibody to bind to the tumor associated antigen. The IgG coordinates are based on 1YY9.pdb. EGFR domain III is based on 1YY9.pdb.

Image courtesy of John Williams, Ph.D., and Joshua Donaldson, Department of Molecular Medicine, Beckman Research Institute, City of Hope.

Donaldson JM, Kari C, Fargoso R, Rodeck U, & Williams JC, Cancer Biology and Therapy, In press