

Division of Signal Transduction



Lewis C. Cantley, PhD,
Chief

● Overview

The Division of Signal Transduction is a non-clinical Division with a focus on determining the molecular mechanisms of cellular responses to growth factors, hormones and other regulators of cell function. The major goal of this Division is to elucidate biochemical mechanisms that control cell growth, cell survival, cell migration and cell cycle entry and to identify defects in these pathways that lead to human diseases such as cancer, insulin resistance, diabetes, obesity, immune defects and cardiac hypertrophy. Importantly, there is a major interest in validating targets, such as protein kinases and lipid kinases, for pharmaceutical intervention in these diseases. Lewis C. Cantley, PhD, Professor of Medicine and Professor of Systems Biology is Chief of the Division, Stephen P. Soltoff, PhD, is an Assistant Professor of Medicine in the Division. John Asara, PhD, is an Instructor in Pathology and Director of the Mass Spectrometry/Proteomics Core located in the Division.

● Educational Programs

The Division of Signal Transduction plays a major role in training graduate students, medical students and postdoctoral fellows in basic research related to human diseases. Currently, 18 fellows (including MD, PhD and MD/PhD fellows) and 4 graduate students are in training in the Division. These trainees are supported by NIH training grants as well as by private foundations, including the Burroughs Wellcome Trust, the Charles A. King Trust, the Leukemia and Lymphoma Society and Damon Runyon. In addition, members of the Division give lectures in first year medical school courses, and in graduate school courses.

● Research Activities

The major activity of the Division of Signal Transduction is to conduct basic and translational biomedical research. The research activities are supported by more than \$2.5 million annually from government and non-government grants.

The research in Dr. Lewis Cantley's laboratory focuses on identifying new targets for intervention in cancer. Dr. Cantley is the Principal Investigator on an NIH P01 grant to investigate the molecular basis for prostate cancer. This disease frequently results from dysregulation of

Research Funding • AY'07

Federal Direct	3,618,515
Federal Indirect	1,131,234
Other Direct	1,316,568
Other Indirect	249,551

the phosphoinositide 3-kinase (PI3K) pathway, a pathway discovered in Dr. Cantley's laboratory. By generating mice in which components of this pathway are disrupted, potential targets for pharmaceutical intervention in this disease are being evaluated. Recent studies indicate that the PI3K pathway also plays a critical role in breast cancers, in colorectal cancers, in glioblastomas and in lung cancers. Drugs that inhibit PI3K are now in phase 1 clinical trials. The research in Dr. Cantley's laboratory with mouse models and human tissues is exploring how best to use these new drugs. In addition, research in Dr. Cantley's laboratory has revealed how cancer cells alter their metabolism in order to grow and survive at inappropriate locations.

● Faculty

John Asara, PhD
Lewis C. Cantley, PhD
Stephen P. Soltoff, PhD

Dr. Stephen Soltoff's laboratory is studying cell signaling in various cell systems, including the interrelationship between signal transduction proteins and specific ion transport systems in salivary gland epithelial cells. Other studies done in collaboration with Dr. Cantley's group made the unexpected finding that the C2 domain of PKCdelta, once thought to bind lipids, contains a phosphotyrosine binding domain that enables PKCdelta to bind to proteins phosphorylated on tyrosine having a particular motif, which was identified using peptide library screens. PKCdelta plays a critical role in activation of lymphocytes by antigen-presenting cells. Current studies are exploring the biochemical mechanism by which the C2 domain of PKCdelta regulates its specific functions in immune cells.

Dr. John Asara directs the Mass Spectroscopy Core for BIDMC and also has an independent research program looking into the development of new Mass Spectroscopy applications for biology. He is developing new techniques for quantifying proteins from cells, tissues or serum. In addition, he is developing a new approach for *de novo* sequencing of proteins from sources where genomic information is not available. This research has led to the first successful sequencing of proteins from extremely ancient extinct species, including dinosaurs (published in *Science*).

● Selected Publications

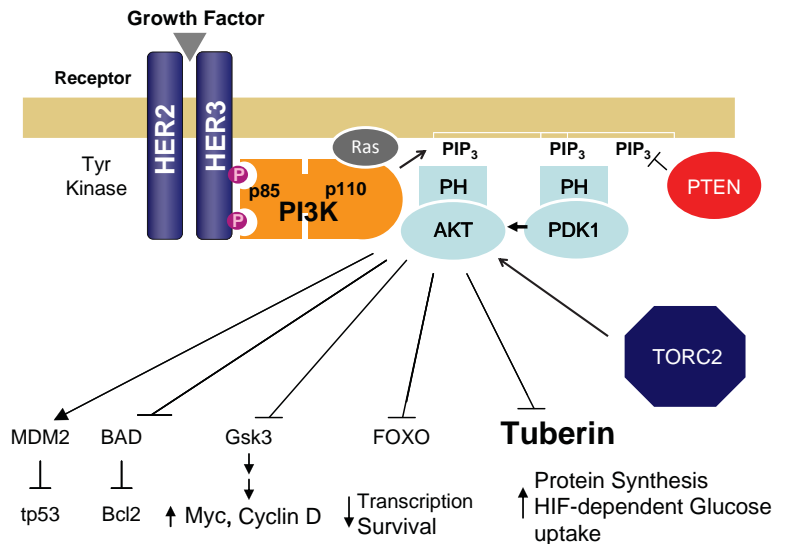
Manning BD, Cantley LC. AKT/PKB signaling: navigating downstream. *Cell* 2007; 12:1261-74.

Abbott DW, Yang Y, Hutti JE, Madhavarapu S, Kelliher MA, Cantley LC. Coordinated regulation of Toll-like receptor and NOD2 signaling by K63-linked polyubiquitin chains. *Mol Cell Biol* 2007; 27:6012-25.

Lee JY, Engelman JA, Cantley LC. PI3K charges ahead. *Science* 2007; 317:206-7.

Christofk HR, Vander Heiden MG, Wu N, Asara JM, Cantley LC. Pyruvate kinase M2 is a phosphotyrosine-binding protein. *Nature* 2008; 452:181-6.

Christofk HR, Vander Heiden MG, Harris MH, Ramanathan A, Gerszten RE, Wei R, Fleming MD, Schreiber SL, Cantley LC. The M2 splice isoform of pyruvate kinase is important for cancer metabolism and tumour growth. *Nature* 2008; 452:230-3.



- Mutations in components of the PI3K pathway are the most common event in solid tumors. Activation of PI3K results in cell growth, cell survival and cell cycle entry and these responses are in part mediated by activation of the Ser/Thr Kinase, AKT. Both PI3K inhibitors and AKT inhibitors are now in clinical trials for treating a variety of cancers.

Organ CL, Schweitzer MH, Zheng W, Freemark LM, Cantley LC, Asara JM. Molecular phylogenetics of mastodon and *Tyrannosaurus rex*. *Science* 2008; 320:499.

Soltoff SP, Hedden L. Regulation of ERK1/2 by Ouabain and Na,K-ATPase-dependent Energy Utilization / AMPK Activation in Parotid Acinar Cells. *Am J Physiol Cell Physiol* 2008; 295:C588-9.

Yuan TL, Choi HS, Matsui A, Benes C, Lifshits E, Luo J, Frangioni JV, Cantley LC. Class 1A PI3K regulates vessel integrity during development and tumorigenesis. *Proc Natl Acad Sci U S A* 2008; 105:9739-44.