Signal Transduction

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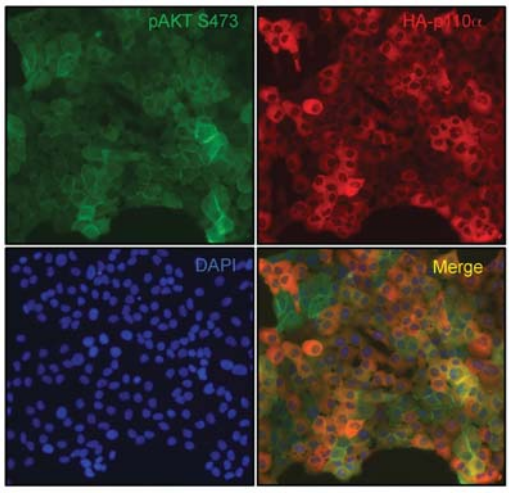
The Division of Signal Transduction is a non-clinical Division with a focus on determining the molecular mechanisms of cellular responses to growth factors, hormones and other regulators of cell function. The major goal of this Division is to elucidate biochemical mechanisms that control cell growth, cell survival, cell migration and



Single cell analysis reveals high variability in the level of expression of the PIK3CA oncogene in breast epithelial cells that correlates with activation of downstream signaling to the AKT oncogene. Red = p110alpha, green = activated AKT protein kinase, yellow = merge, blue = nuclei. (Curr Biol 2011; 21:173-83.)

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.

2009–2010 HIGHLIGHTS

Dr. Lewis Cantley and his "Dream Team" of scientists and clinicians from BIDMC, Dana-Farber Cancer Institute, Memorial Sloan Kettering, MD Anderson, Vanderbilt, Columbia and Val D'Hebron, Barcelona have been awarded a 15 million dollar grant from the Stand Up to Cancer/AACR organization. The goal of the research funded by this grant is to develop clinical trials that will identify the biomarkers that predict which breast, ovarian and endometrial cancer patients are most likely to respond to drugs that target the phosphoinositide 3-kinase (PI3K) pathway. This past year, the Cantley laboratory identified a novel tumor suppressor gene (INPP4B) that is frequently deleted in triple-negative breast cancer, as well as ovarian cancers, and showed that this gene acts as a tumor suppressor by blocking the PI3K signaling pathway (Gewinner et al., 2009). These results suggest that loss of INPP4B could be a biomarker for predicting which patients might respond to drugs that target PI3K.

The Division of Signal Transduction has focused on determining how metabolism is regulated in cancer cells. Previous studies from this Division showed that tumors revert to an embryonic form of the glycolytic enzyme, pyruvate kinase (PKM2). Further studies over the past year have elucidated how alternative splicing of the PKM gene results in cancer-specific expression of PKM2 (Clower et al., 2010). Both activators and inhibitors of PKM2 have been identified from high-through-put screens of chemical compound libraries, indicating that this enzyme could be targeted for treating cancers (Vander Heiden et al., 2010; Boxer et al., 2010). Dr. John Asara has developed a mass spectrometry metabolomics core to facilitate research in this field.

On May 27, 2009, Lew Cantley, PhD, appeared on CBS's The Early Show to promote his research through the Stand Up To Cancer Foundation. (L to R) **Harry Smith, Katie Couric, Dr. Ray DuBois, Dr. Craig Thompson, Dr. Lewis Cantley**.
(Photo Courtesy of Jason Kempin)

STAND UP TO CANCER
standup2cancer.org

The Stand Up to Cancer grant provides funds to conduct clinical trials in women's cancers using drugs that target PI3K, as well as to conduct co-clinical trials using the same drugs in mice that have been genetically engineered to develop cancers with the same mutations found in women's cancers.

SELECTED PUBLICATIONS

Gewinner C, Wang ZC, Richardson A, Teruya-Feldstein J, Etemadmoghadam D, Bowtell D, Barretina J, Lin WM, Rameh L, Salmena L, Pandolfi PP, Cantley LC. Evidence that inositol polyphosphate 4-phosphatase type II is a tumor suppressor that inhibits PI3K signaling. *Cancer Cell* 2009; 16:115-25.

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Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, Marks KM, Prins RM, Ward PS, Yen KE, Liau LM, Rabinowitz JD, Cantley LC, Thompson CB, Vander Heiden MG, Su SM. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 2009; 462:739-44.

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Clower CV, Chatterjee D, Wang Z, Cantley LC, Vander Heiden MG, Krainer AR. The alternative splicing repressors hnRNP A1/A2 and PTB influence pyruvate kinase isoform expression and cell metabolism. *Proc Natl Acad Sci USA* 2010; 107:1894-9.

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Lee SH, Poulogiannis G, Pyne S, Jia S, Zou L, Signoretti S, Loda M, Cantley LC, Roberts TM. A constitutively activated form of the p110beta isoform of PI3-kinase induces prostatic intraepithelial neoplasia in mice. *Proc Natl Acad Sci USA* 2010; 107:11002-7.

FACULTY

John Asara, PhD

Lewis Cantley, PhD

Akash Patnaik, MD, PhD

Atsuo Sasaki, PhD

Stephen Soltoff, PhD

HONORS AND AWARDS

Lewis Cantley, PhD, received the 2009 Rolf Luft Award from the Karolinska Institute, Stockholm for his research in the field of endocrinology and metabolism. He was the 2009 Sokolow Memorial Cancer Endowment Lecturer at UCSF and the 2010 Umesono Lecturer at The Salk Institute.

RESEARCH FUNDING

	Direct	Indirect
Federal	**4,555,344**	**1,633,780**
Non Federal	**2,845,686**	**183,772**