

Lewis Cantley discusses cancer metabolism in Rodbell Lecture

By Sheila Yong

The prestigious Dr. Martin Rodbell Lecture Series Seminar on Dec. 10 featured Lewis Cantley, Ph.D., discussing his research into phosphoinositide 3-kinase (PI3K) signaling and its role in cancer progression. In his talk, "PI3K and cancer metabolism," Cantley presented exciting discoveries he and his colleagues have made over the past several decades in PI3K signaling, and how they have translated their findings into new treatment strategies for various cancers and diseases.

Cantley

(http://weill.cornell.edu/news/releases/wcmc/wcmc_2012/09_12_12.shtml) is director of the Cancer Center at Weill Cornell Medical College and New York-Presbyterian Hospital, and the Margaret and Herman Sokol Professor in Oncology Research at Weill Cornell.

James Putney, Ph.D., head of the NIEHS Calcium Regulation Group in the Laboratory of Signal Transduction, and a longtime friend, compared Cantley's scientific career to Rodbell's. "Lew is an especially appropriate speaker for the Rodbell lecture, because both he and Marty initially conducted experiments that yielded unexpected results. While most people would have moved on to something else, they realized that these results were actually telling them something important."

Cantley's scientific instinct and dedication led him to the discovery of PI3K signaling in 1988, and subsequent advances in cancer research.

Crossing the line between normal cell growth and cancer

Cantley began his lecture with a description of the insulin signaling pathway, which controls glucose metabolism. Upon insulin stimulation, insulin receptors undergo phosphorylation and become active. This phenomenon triggers a signaling cascade mediated by class IA PI3Ks, which generate phosphatidylinositol (3,4,5)-triphosphate (PIP₃) from phosphatidylinositol (4,5)-bisphosphate (PIP₂), a phospholipid found in the cell membrane. PIP₃ serves as a docking site for several downstream proteins, including protein kinases AKT and PDK1.

These proteins, in turn, become activated and translocate to other locations in the cell to facilitate various downstream processes, thus promoting survival and growth. Produced by oncogenes, these proteins cause cancer when their functions are misregulated.

On the other hand, several proteins along the pathway, such as PTEN and tuberlin, serve as brakes to halt cell growth when nutrients and growth factors are low. This regulatory mechanism ensures that the pathway is active only when conditions are favorable. These tumor suppressors protect the cells from cancer.

Cancer forms when cells grow, even when nutrients or growth factors are absent, due to continuous activation of the growth pathway. "Mutations or amplification of these oncogenes, and the loss of function of these tumor suppressor genes, account for an incredible fraction of human cancers," Cantley emphasized, citing the Cancer Genome Database.

According to Cantley, 70-95 percent of common human cancers present with at least one mutation in the PI3K signaling network, especially women's cancers. Cantley now leads a team of prominent researchers funded by a \$15 million grant from [Stand Up To Cancer](#)

(<http://www.standup2cancer.org/>)

to design clinical trials that will determine which patients are likely to benefit from PI3K inhibitors.



Cantley's research has spurred drug development efforts for treating various cancers and hereditary familial syndromes. One significant success is everolimus, a drug used to treat lymphangioleiomyomatosis (LAM), a rare lung disease that affects mostly women. "In the past, LAM patients would have to undergo lung transplant. Unfortunately, the transplanted lung would eventually fail and the patients would die anyway," Cantley explained. With everolimus, LAM patients can now lead normal lives, without relying on supplemental oxygen or undergoing lung transplant. (Photo courtesy of Steve McCaw)



Researchers from across many disciplines attended Cantley's lecture, many of whom were seated in the front row. Shown, left to right, are senior scientists Jerrel Yakel, Ph.D., and Serena Dudek, Ph.D., from the NIEHS Laboratory of Neurobiology; Division of Intramural Research and Division of NTP senior scientist Richard Paules, Ph.D.; NTP Associate Director John Bucher, Ph.D.; biologist Wendy Jefferson, Ph.D., from the NIEHS Reproductive Medicine Group; and NIEHS Scientific Director Darryl Zeldin, M.D. (Photo courtesy of Steve McCaw)

A new player in cancer metabolism

Ten years after discovering PI3K, Cantley's group identified phosphatidylinositol 5-phosphate 4-kinase (PI5P4K), which converts phosphatidylinositol 5-phosphate to PIP2. "It has been very frustrating to figure out what this enzyme does," Cantley said. Mice that lack either the alpha or beta isoform of PI5P4K exhibit little to no phenotype, while mice lacking both isoforms are not viable. Interestingly, mice that lack both copies of p53, while retaining one copy of PI5P4K-beta, are protected from cancer.

p53 is among the most heavily studied tumor suppressors, and is frequently lost in many types of cancers. Not surprisingly, many of these tumors also exhibit high levels of PI5P4K expression. Through detailed experimentation, using mouse models and human cancer cell lines, Cantley's group determined that both p53 and PI5P4K provide alternative pathways for regulating glucose metabolism and suppressing oxidative stress.

When cells lose p53, the PI5P4K pathway becomes essential in combating oxidative stress. Therefore, cancer cells lacking p53 upregulate the PI5P4K pathway to promote cell survival. "We believe that PI5P4K is a good target for treating tumors that lack p53 while sparing normal tissues," he concluded.

(Sheila Yong, Ph.D., is a visiting fellow in the NIEHS Inositol Signaling Group.)



Cantley's lecture appealed to people across the Institute, such as Sean Chiou, Ph.D., contractor for the NIEHS Computer Technology Branch. A former bench scientist, Chiou performed research on insulin signaling during his graduate school days. (Photo courtesy of Steve McCaw)



Speakers in the Rodbell Lecture Series receive a statue depicting the hand of Nobel laureate and former NIEHS Scientific Director, [Martin Rodbell, Ph.D.](#), holding the three key elements involved in cell signaling. Sculptor Carl Regutti, who created the statue and attended the Rodbell lecture in 2012 as a family guest, died in April 2013. (Photo courtesy of Steve McCaw)



With his Rodbell statue in hand, Cantley joined, left to right, NIEHS and NTP Director Linda Birnbaum, Ph.D., Barbara Rodbell, and Putney for a group photo. Barbara, Rodbell's widow and honored guest, has attended every Rodbell lecture, since Rodbell gave the first talk in the series in 1998. (Photo courtesy of Steve McCaw)

The Environmental Factor is produced monthly by the [National Institute of Environmental Health Sciences \(NIEHS\)](#)

(<http://www.niehs.nih.gov/>)

, Office of Communications and Public Liaison. The content is not copyrighted, and it can be reprinted without permission. If you use parts of Environmental Factor in your publication, we ask that you provide us with a copy for our records. We welcome your [comments and suggestions](#). (bruskec@niehs.nih.gov)

This page URL: NIEHS website: <http://www.niehs.nih.gov/>
Email the Web Manager at webmanager@niehs.nih.gov