



For 20 years, this physician-scientist has navigated his bicycle through the streets of New York City to his lab, where he focuses on a different kind of traffic—the activity of cellular-signaling molecules called GTPases. These molecules are central to virtually all cellular processes, including those underlying disorders as diverse as autoimmune diseases and cancer. His team wants to interfere with the traffic pattern to find new routes to cancer drugs.

Traffic Patterns

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The Philips lab made an important discovery about the regulation of K-Ras (the Ras gene associated with pancreatic, lung and colon cancers). “We discovered that the position of K-Ras in membranes is not permanent, and that its positioning can be regulated by a signaling enzyme called protein kinase C, which causes a phosphate molecule to be added to K-Ras and thereby dislodges it from the membrane,” says Dr. Philips. “Most surprising of all, the dislodged K-Ras goes to the mitochondria, which regulates apoptosis. Once there, the K-Ras promoted cell death. We’re seeing a gene that we usually associate with out-of-control cell growth—aka tumors—actually causing those cells to commit suicide.” This suggests a novel method of treating human tumors with PKC agonists, one of several paths Dr. Philips is now pursuing.

“The road from rheumatology to cancer biology was via inflammation and some of the signaling molecules that control it—namely, small GTPases, including protooncogen Ras,” explained Dr. Mark Philips, describing his post-residency path from a senior fellowship in the Division of Rheumatology, to the NYU Cancer Institute, and his present lab in the Smilow Research Center.

The Philips lab is investigating small GTPases along a number of tracks, and has made several important discoveries connected to Ras along the way—including work that illuminated the dramatic differences between the three types of Ras genes. Ras proteins have captured the interest of cancer researchers since the late 1970s, when they were discovered to be oncogenes. Acting like molecular switches, the Ras proteins can be turned on and off to control pathways that regulate cell growth and survival. The mutated form gets locked into the “on” position and can’t be turned off, causing cells to grow uncontrollably—resulting in cancer.

When attempts to find a way to un-stick the “on” switch didn’t succeed, researchers turned their attention to Ras trafficking and the three enzymes that direct its journey from the cytosol to the cell’s membrane. Dr. Philips, who was the 2000 recipient of the Burroughs Wellcome Fund Translational Research Award, has continued to pursue this line of thinking. “We cloned the third enzyme, called Icmt, in my lab in 1998 and it is now a drug target for anti-cancer drugs,” said Dr. Philips. “We’re currently analyzing the structure and function of Icmt to assess its role in oncogenesis and tumor progression.”