



On December 1, World AIDS Day, Dartmouth received \$2 million to combat pediatric AIDS. The funds are going to a collaborative project run by DMS and Muhimbili University in Tanzania.

Hedgehog pathway presents many puzzles

To me, signal transduction is like a puzzle, except there is no picture that comes with it,” says David Robbins, Ph.D., an associate professor of pharmacology and toxicology. Robbins studies how proteins transmit signals from the outside to the inside of a cell in order to turn a target gene on or off. His lab is interested in a specific signaling pathway called Hedgehog, which plays a role in both early development and cancer.

The Hedgehog gene (or Hh, as it’s abbreviated) was first studied in fruit flies. It acquired its name because during embryonic development, its mutant in flies is covered with pointy denticles, so resembles a hedgehog. Three mammalian versions of Hh were subsequently discovered—Desert, Indian, and Sonic; the latter is named after a video game character with a row of blue spikes down its back.

Agent: A key reason for studying these pathways, explains Robbins, is their implications for drug development. In the past, drugs were discovered empirically. “If someone ate something and survived,” Robbins says, the substance became a new therapeutic agent. “Now drugs are developed more mechanistically,” he says, to target specific steps in signaling pathways. This method has yielded many effective medications, and understanding the Hh pathway could lead to the identification of more drug targets to treat cancer and developmental disorders.

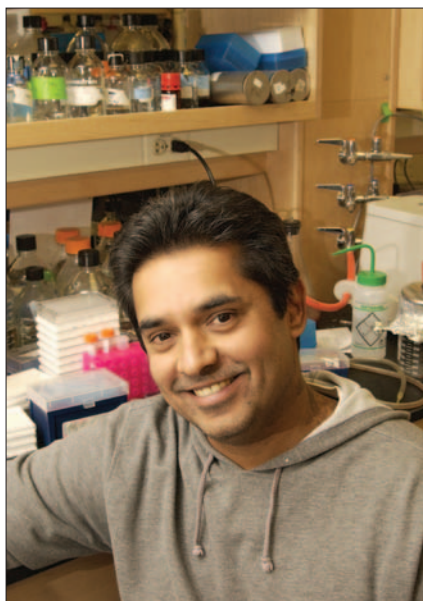
The mechanism of Hh signaling is largely unknown, however, so Robbins and his colleagues have been trying to learn more about it. They are interested in what happens both inside and outside the cell. Evidence has suggested the existence during development of a diffusible form of Hh—one capable of sending, over long as well as short distances, signals that cause cells to become specialized tissues. Robbins’s lab has succeeded in identifying

a native, diffusible form of Hedgehog thought to play this role.

Target: Meanwhile, inside the cell, the Hedgehog Signaling Complex (HSC) has been shown to play an important role in this pathway. One of Robbins’s key contributions to the field was the discovery of HSC. It consists of several proteins, including the transcription factor responsible for activating the target genes of the Hh pathway. The HSC acts as a “middleman” between the binding of Hh to its receptor and the activation of target genes inside the cell. Understanding the exact mechanism by which this occurs is Robbins’s next goal; his lab’s preliminary discoveries show the process to be very complicated. For example, there may be two forms of the HSC and three forms of the transcription factor.

So there are still many missing pieces to this intricate puzzle. But the fact that Robbins has “always liked puzzles” augurs well for his ability to eventually put them all together. KRISTEN GARNER

JON GILBERT FOX



David Robbins studies cell-signaling mechanisms.

Stentorian note

Building muscle is usually good—but not in your arteries. In fact, according to Michael Simons, M.D., chief of cardiology at DHMC, the growth of smooth muscle along the lining of arteries is the most common cause for the failure of stents—mesh tubes that reopen blocked blood vessels. A team led by Simons reported in *Circulation* that smooth muscle can proliferate in arteries after mechanical injury, such as from angioplasty or stenting. So stents coated with smooth muscle inhibitors are the treatment of choice, the authors concluded.



Pancreatic promise

Two recent studies show promise for combating pancreatic cancer, one of the most aggressive and deadly cancers. In a trial led by Murray Korc, M.D., chair of medicine, researchers injected a protein “sponge” into mice with human-derived pancreatic tumors. “The protein sponge completely suppressed pancreatic tumor growth,” Korc reported. “In all the tumors tested, there was a marked decrease in blood vessel formation, which is very exciting.” The other study—led by a postdoctoral fellow in Korc’s lab, Nicole Boyer Arnold, Ph.D.—described a pathway that is responsible for pancreatic cancer’s ability to become resistant to traditional chemotherapy.

