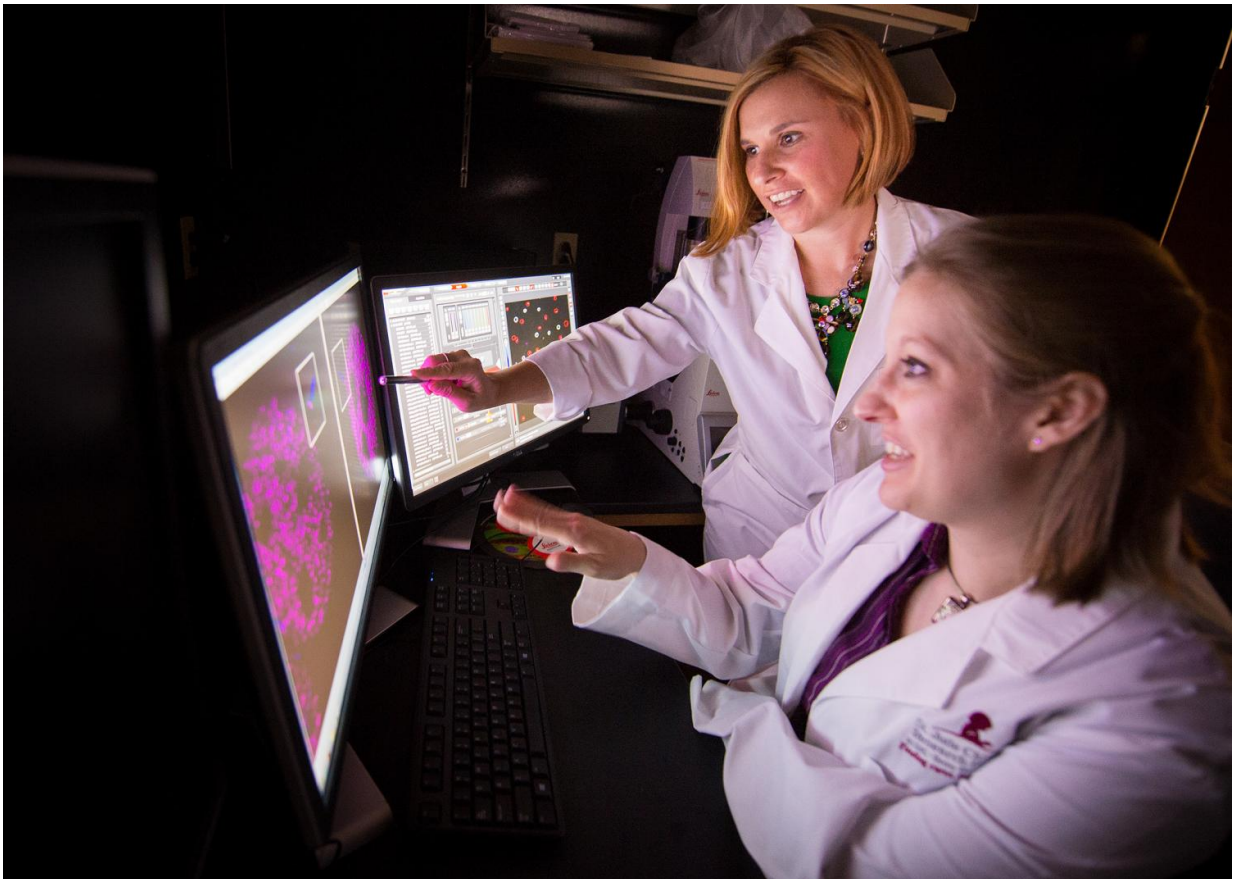


# Researchers identify a key controller of biological machinery in cell's 'antenna'

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First author Angela Arensdorf, Ph.D., and corresponding author Stacey Ogden, Ph.D., an associate member of the St. Jude Department of Cell and Molecular Biology. Credit: Peter Barta / St. Jude Children's Research Hospital

St. Jude Children's Research Hospital molecular biologists have identified an enzyme that activates and "supercharges" cellular machinery that controls how cells become specialized cells in the body.

Malfunction of that machinery, dubbed the Sonic Hedgehog pathway, causes a variety of developmental disorders and cancers, including childhood medulloblastoma and basal cell carcinoma. Researchers believe their basic discovery opens a new research pathway that could lead to drugs to treat such disorders.

Led by Stacey Ogden, Ph.D., an associate member of the St. Jude Department of Cell and Molecular Biology, the research was published June 6 in the journal *Cell Reports*.

The scientific puzzle the researchers sought to understand was how a major activator of the Sonic Hedgehog pathway, called Smoothened, manages to make its way into an antenna-like cell structure called a "primary cilium," where it communicates with its downstream signaling partners.

Every cell in the body sprouts a primary cilium, which harbors a whole factory of cellular machinery that the cell uses to translate external stimuli into cell responses. Such stimuli include mechanical movement and chemical signals such as hormones. Normally, Smoothened is barred from the [primary cilium](#), keeping the Sonic Hedgehog pathway safely controlled.

In their experiments with cell cultures, the researchers discovered that an enzyme called Phospholipase A2 triggers a mechanism that opens the way for Smoothened movement into the cilium. What's more, the phospholipase triggers an amplification that "supercharges" Smoothened signaling.

"We've basically revealed a new layer of regulation of Smoothed trafficking," Ogden said. "This is a very hot area of research now, because Smoothed trafficking appears to be a very crucial control point for signaling activity. So, if you can change Smoothed trafficking, you can very easily adjust the amplitude of Sonic Hedgehog signaling."

The basic finding has potential clinical importance, Ogden said, because reduced activity in the Sonic Hedgehog pathway is commonly found in genetic disorders of primary cilia function. These disorders include Joubert syndrome, Bardet-Biedl syndrome, Ellis van Creveld syndrome and polycystic kidney disease—one of the most common genetic diseases in the U.S., affecting more than 600,000 people. Better understanding of the control machinery for the Sonic Hedgehog pathway could lead to more effective therapies for the disorders, Ogden said.

Conversely, hyperactivity of the Sonic Hedgehog pathway is the cause of about 30 percent of childhood medulloblastomas. Medulloblastoma is the most common malignant brain tumor of childhood, accounting for about 20 percent of all childhood brain tumors. Current treatments using surgery, radiation and chemotherapy cause severe side effects, so more precise drug treatments are urgently needed.

"One of the drugs now being used to treat medulloblastoma is a Smoothed inhibitor," Ogden said. "But tumor [cells](#) frequently become resistant to this drug and begin to grow again because of mutations in Smoothed that enable it to overcome the drug's inhibition. We want to determine whether drugs to inhibit Phospholipase A2 could reduce Sonic Hedgehog activity in cases where Smoothed becomes insensitive to targeted inhibition."

In adults, Hedgehog pathway hyperactivation also causes [basal cell carcinoma](#), the most common skin cancer and one of the most common

cancers. Hedgehog pathway activation also may accelerate other types of tumors by affecting the tissue surrounding the tumor, called the stroma, to create an environment more conducive to growth, Ogden said.

"So Hedgehog pathway inhibitors may be useful in combination therapies with other traditional chemotherapies for other types of solid tumors," she said.

In further research, Ogden and her colleagues are continuing to examine Smoothed regulation and exploring drugs that affect its activity.

Provided by St. Jude Children's Research Hospital

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