# Scientists find a new way to boost common cancer drugs

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Shutting down a specific pathway in cancer cells appears to improve the ability of common drugs to wipe those cells out, according to new research from scientists at Fox Chase Cancer Center, published in the January issue of *Cancer Discovery*.

"Ideally, this research will eventually enable scientists to find drugs that disrupt this pathway and boost the impact of current therapies," says Igor Astsaturov, MD, PhD, Attending Physician in the Department of Medical Oncology at Fox Chase. "That's the long-term plan."

The new approach appears to enhance the tumor-killing ability of a commonly prescribed class of drugs that includes cetuximab (Erbitux), used to treat colorectal and head and neck cancers. These drugs work by blocking the activity of the epidermal growth factor receptor (EGFR), which sits on the cell surface and senses cues from the environment, telling cancer cells to grow and divide, says Astsaturov. "The whole mantra of modern day oncology is to suppress these inputs."

Although EGFR inhibitors succeed in killing cancer cells, some malignant cells still find ways to evade the drug, and become resistant to treatment. Consequently, many researchers are actively looking for ways to kill these surviving cancer cells, annihilating tumors completely.

In 2010, Astsaturov and his colleagues identified a pathway in the cell that, when blocked, completely suppressed EGFR activity. Interestingly, the pathway consists of a series of enzymes that, when working in

concert, synthesize new molecules of cholesterol, an essential component of the cell wall. This pathway is particularly important to cancer cells, which are constantly dividing and therefore need to produce more cholesterol for the new cells.

Working with cancer cells in the lab, the researchers inactivated a key gene in the cholesterol synthesis pathway, and found the cells became more vulnerable to treatment with cetuximab. The same was true in mice that lacked this particular pathway, says Astsaturov. "Most tumors are only moderately sensitive to inhibitors of EGFR, but when these tumors lack an essential gene in the cholesterol pathway, they become exquisitely sensitive to the anti-EGFR drugs," he says. "The cancers literally melt away in mice."

The researchers then removed one of the cholesterol genes from the mouse genome, and saw that mice developed patchy, scaly skin. When they biopsied this affected skin, they saw no activity of the EGFR protein, reaffirming that shutting down cholesterol synthesis interrupts EGFR. They also observed the same pattern in normal cell lines.

When the cholesterol biosynthesis pathway is blocked, explains Astsaturov, the normal chain of events that creates a cholesterol molecule is interrupted, and cells accumulate intermediate products of cholesterol that block the normal movement of substances around the cell. This cellular traffic jam makes it difficult for the cell to transport important components, such as EGFR, which has to move between the inside of the cell and its surface to function properly. "If you disrupt this traffic, the cancer cells don't survive."

Eventually, says Astsaturov, researchers can design drugs or look for existing ones that block this cholesterol synthesis pathway. For now, his lab is trying to uncover more details of how the pathway works, the role of each protein that is involved—and whether if, by blocking a protein,

they can wipe out tumors in humans that evade current therapies. "These proteins represent targets for additional drugs, which could be combined with EGFR inhibitors," he says.

Provided by Fox Chase Cancer Center