Novel anticancer strategy moves from laboratory to clinic

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Researchers at Emory University have developed a novel anti-tumor compound that represents a distinct strategy: targeting one of the most important "intercept points" for cancer cells.

The results of research on the compound in mice appear in the Jan. 1 issue of *Cancer Research*. The article is highlighted on the cover.

The compound was used for the first time in human patients with solid tumors in 2007.

The idea behind the intercept point strategy is to shut down the transmission of a large number of growth signals in cancer cells at once, says senior author Donald L. Durden, MD, PhD, professor of pediatrics at Emory University School of Medicine and the Emory Winship Cancer Institute.

Dr. Durden, scientific director of the Aflac Cancer Center and Blood Disorders Service at Children's Healthcare of Atlanta, compares a cancer cell to a building with too many of the lights left on.

"Doctors have been trying to treat cancer by turning out the lights in one room at a time, instead of going after the transformer box," he says.

Dr. Durden and his colleagues targeted a class of enzymes called PI-3 kinases, which represent an intercept point and occupy valuable real estate in almost every cell in the body.

"Nature made these enzymes central in controlling growth, differentiation and survival," he says. ÒBut you can't hit only one of them; they're redundant."

The intercept point concept of drug development was featured in a December 2007 review in Nature Clinical Practice Neurology by the Durden laboratory.

Scientists have found genes that encode the PI-3 kinases to be mutated in a large number of tumor types, putting them in overdrive. In addition, a single enzyme that opposes PI-3 kinases, called the PTEN phosphatase, is inactivated in a large fraction of human prostate, brain, endometrial and breast cancers--between 20 and 50 percent depending on the cell type.

In the Cancer Research article, Dr. Durden and his colleagues show that a chemical inhibitor of all PI-3 kinases, modified with a tag that directs the compound to the blood vessels needed by growing tumors, stops the growth of seven types of tumors in mice.

The compound, called SF1126, is active against prostate, breast, renal, multiple myeloma, neuroblastoma, glioblastoma and rhabdomyosarcoma, the authors show.

The first author of the Cancer Research article is Joseph Garlich, PhD, chief scientific officer of Semafore Pharmaceuticals. The firm and Dr. Durden collaborated on identifying the SF1126 compound, based on his work while on the faculty at Indiana University School of Medicine.

At the end of 2007, doctors in Arizona and Indiana began to test SF1126 in a phase I clinical trial in people with solid tumors. Another phase I trial for multiple myeloma patients will begin at Emory's Winship Cancer Institute and elsewhere in 2008. It is anticipated that SF1126 will

enter pediatric cancer trials within one year.

Scientists use PI-3 kinase inhibitors in test-tube experiments every day; however, the enzyme-inhibiting part of SF1126 was never used clinically despite its identification more than a decade ago.

"It was a total non-drug: toxic, insoluble and broke down too fast," Dr. Durden says.

Attaching the tag, called a RGD peptide, makes the inhibitor dissolve easier and last longer in the body. It also lets molecules on blood vessel walls grab the compound and send it into tumors, the authors show.

Tumors send out chemical signals for new blood vessels when they don't have enough oxygen. The authors found that in mice, the compound prevents tumors from growing new blood vessels by inhibiting part of their response to the lack of oxygen. SF1126 also sensitizes human tumors in mice to a chemotherapy agent called taxotere.

The authors found that tumor cell lines artificially engineered to be more "addicted" to PI-3 kinase growth signals are more sensitive to the drug. That predicts that some patients' tumors could be more sensitive than others, Dr. Durden says.

Source: Emory University