Drug discovery short-circuits cancer growth

February 10 2009

A new drug that blocks cancer's main source of growth has been created in the lab and proven effective in mice, scientists are reporting. It is now being readied for clinical trials in patients.

Far more potent than similar compounds already in clinical trial, the drug short-circuits the normal ability of cells to sense the need to grow and divide -- a signal that cancer cells exploit to spread in the body.

The scientists are working with clinicians to test the drug's effectiveness against a range of cancers that have proven difficult to treat.

The discovery is reported in the Feb. 10, 2009 edition of *PLoS Biology*, a journal published by the Public Library of Science.

The research was led by scientists at the University of California, San Francisco (UCSF) and the UCSF Helen Diller Family Comprehensive Cancer Center. Senior author of the paper is Kevan Shokat, PhD, Howard Hughes Medical Investigator and professor of cellular and molecular pharmacology at UCSF.

Normally, in response to growth signals, a multi-protein unit in cells called mTOR integrates information about the cell's nutritional and energy needs, and prompts the cell to manufacture key proteins for cell growth. But cancer exploits this signal for its own growth.

Clinical trials are underway to stymie cancer proliferation by using a drug called rapamycin—marketed as Rapamune--or related compounds

to block the growth signal cycle. The new drug greatly improves on rapamycin's effectiveness, the scientists reported. The name mTOR stands for "mammalian target of rapamycin."

Of serious concern to clinicians, rapamycin and related drugs can actually promote cancer at the same time they thwart it. This happens, the scientists found, because the drugs only partially block the cells response to a growth signal. When this happens, the drugs end up augmenting the growth signal itself because a feedback process in the cell kicks in to assure adequate nutrition. With the feedback system in play, cancer cells can regain needed nutrients and continue to proliferate.

The new drug totally blocks this feedback loop, said Shokat, who also is a faculty affiliate at the California Institute for Quantitative Biosciences, known as QB3, which is headquartered at UCSF.

"We were trying to synthesize compounds that could help us learn more about how cancer exploits normal growth controls," he explained. "Once we made it, though, we found it was even better than we thought it would be at blocking mTor signaling. It does everything that rapamycin does and more."

The new drug succeeds because there are two mTOR signal pathways, and it blocks both, the scientists found. Rapamycin only blocks one, and so allows the growth-signaling system to still function.

The scientists think that the drug's total blockage of the nutrient-sensitive mTOR and its feedback loop offer a major advance over rapamycin based drugs, which have been approved to treat only renal call carcinoma effectively.

"I hope the new drug can be used to treat a range of cancers," Shokat said. "We will work with clinicians to test it against a number of types of

cancer - colorectal, lung, breast, multiple myeloma and others. We want to first find the cancer that is most sensitive to it."

The new compound has been dubbed a TORKinib because it inhibits the mTOR signal. UCSF has applied for a patent and licensed the patent to a startup biotech company, co-founded by Shokat and colleagues, to advance its use in clinical trials to treat cancer.

mTOR is known as a kinase, a ubiquitous type of signaling molecule - there are more than 500 different kinases in the body - that essentially switches proteins on or off. The switch is one of the most common interactions in the body. The kinase adds a small molecule known as a phosphate group to the protein, and that single action either turns on the protein or dampens its activity.

Like all signaling systems in the body, the one involving mTOR goes through many steps to accomplish its duties. The different steps form a cascade that can ramp the signal up or down, depending on the conditions of the cells or tissues. These kinase cascades are embedded within complicated feedback loops, such as the one activated by rapamycin.

Research on the mTOR pathway is of increasing interest to drug companies, Shokat said.

Since mTOR acts "upstream" and "downstream" of other key kinases that are found to cause cancer-- such as the much-studied kinases PI3K and Akt-- he thinks blocking it will short-circuit the many feedback loops cancer cells use to generate and maintain a growth signal.

"We are extremely excited about the potential of targeting mTOR in this way to treat a number of cancers, although we are aware that there are many hurdles to reaching the finish line," Shokat said.

Source: University of California - San Francisco