Scientist develops enzyme inhibitor that may slow cancer growth

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University of Illinois scientist Tim Garrow, in collaboration with Jiri Jiracek of the Czech Academy of Sciences, has applied for a provisional patent on a class of chemicals that has future therapeutic uses in medicine, specifically cancer treatment.

"These chemicals are potent inhibitors of an enzyme called betaine-homocysteine-S-methyltransferase (BHMT)," said Garrow.

"BHMT catalyzes a reaction that converts homocysteine to methionine. Because cancer cells require high levels of methionine, the ability to slow methionine's production could result in a treatment that will selectively inhibit cancer growth," the U of I professor of nutrition said.

Methionine, an essential amino acid, is required for several important biological processes, including synthesis of a compound that cancer cells require more than other cells. "When scientists restrict dietary methionine in animals with cancer, cancer cells are more acutely affected than others," Garrow said.

Many drugs work by inhibiting the action of an enzyme, including the statin drugs used to lower cholesterol, he added.

Garrow became interested in BHMT, which is abundant in the liver and present in lesser amounts in the kidneys, because elevated levels of blood homocysteine have been linked with a number of diseases, including vascular disease and thrombosis.

"Our lab has always been interested in BHMT's role in modulating plasma homocysteine, and we've engaged in some productive research collaborations. Martha Ludwig's lab at the University of Michigan solved BMHT's crystal structure.

"That breakthrough enabled us to look at the enzyme in three dimensions, which helped us design inhibitors for it. Several of those compounds were very effective in blocking binding of the enzyme's normal substrates," he said.

Injecting one of these BHMT inhibitors into the abdomens of mice resulted in changes in metabolite concentrations and elevated levels of homocysteine in the animals, showing that "our chemical inhibitor made its way from the abdominal cavity into the mouse's liver, where the inhibitor blocked the BHMT-catalyzed reaction as we thought it would."

Garrow believes BHMT inhibitors may work best in concert with other drugs. "In today's medicine, there's rarely one magic-bullet drug. We know that when you decrease the availability of methionine to cancer cells, another cancer drug called cisplatin works better. So a drug that inhibits BHMT, which decreases methionine availability, may well enhance the efficacy of another cancer treatment drug," he said.

Elevated levels of homocysteine could be a negative side effect of such therapy, but Garrow said the benefits of the drug would likely outweigh the risk. "A cancer patient would probably take the BMHT inhibitor for a limited time, while vascular disease--associated with high homocysteine levels--progresses over the course of a lifetime."

Garrow believes another therapeutic application for BHMT inhibitors could involve betaine, one of the enzyme's substrates.

"When you inhibit BHMT, you also block the utilization of betaine.

Betaine not only donates a methyl group to homocysteine to form methionine, it also functions as an osmolyte, helping to regulate water content in the cells. We think the BHMT inhibitor could also be medically useful when there is unwanted diuresis or unwanted loss of water," he said.

Garrow's work with BHMT in mice was published in the June issue of the *Journal of Nutrition*. Co-authors include Michaela Collinsova, Jana Strakova, and Jiri Jiracek of the Academy of Sciences of the Czech Republic.

Source: University of Illinois at Urbana-Champaign