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Small molecule dervived from Rb2/p130 could act as cancer therapeutic

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A small molecule derived from the spacer domain of the tumor-suppressor gene Rb2/p130 has demonstrated the ability to inhibit tumor growth in vivo and could be developed into an anti-cancer therapeutic, according to researchers at Temple University's Sbarro Institute for Cancer Research and Molecular Medicine.

The researchers reported their findings, "A small molecule based on the pRb2/p130 spacer domain leads to inhibition of cdk2 activity, cell cycle arrest and tumor growth reduction in vivo," in the March 22 issue of the journal *Oncogene* (www.nature.com/onc). Rb2/p130 was discovered in the early 1990s by Antonio Giordano, director of the Sbarro Institute and the Center for Biotechnology in Temple's College of Science and Technology, who headed the study.

The researchers discovered that within Rb2/p130's spacer domain--a sequence of 212 amino acids located in the pocket or middle section of the gene--was a small portion that resembled an amino-acidic sequence contained in the protein p21, which acts as a cdk (cyclin dependent kinase) inhibitor. Cdks play a critical role in cell cycle regulation.

"What we tested was the ability of the Rb2/p130 spacer region to inhibit the kinase activity of cdk2, which is the same kinase p21 inhibits," said Giordano, one of the study's lead authors. "And to our surprise, it happened." The researchers then set about trying to reduce the spacer domain's 212 amino acids down to the smallest sequence that would still produce the same functionality as p21, explained Giordano.

"We thought we could narrow down the spacer region that contains the protein-like motif to a small portion that could be delivered as a small molecule or peptide," Giordano said.

They discovered a 39 amino-acid-long sequence, which they named Spa310. The molecule that was synthetically produced in the laboratory was introduced into mice that had been injected with tumor cells.

"Tumor growth was inhibited and the tumors began to reduce in size until they disappeared," Giordano said.

Giordano said because of the intrinsic nature of the compound, it can be easily reproduced as a biological drug in large quantities and does not require potentially dangerous means of delivery like viruses, as do most gene therapies; therefore Spa310 has a good chance to succeed as an anti-cancer therapy. For these reasons, he believes it may be easier to get approval for clinical trials.

"Fifteen years after discovering Rb2/p130, our research and hard work has led us to the discovery of this small molecule, which is a step forward in cancer research and a big step toward a cancer treatment," he said.

Source: Temple University