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Moffitt Cancer Center researchers find MK1775 active against sarcomas

10 percent of children with cancer are diagnosed with sarcomas

TAMPA, Fla. (Dec. 2, 2011) – MK 1775, a small, selective inhibitor molecule, has been found to be active against many sarcomas when tested by researchers at Moffitt Cancer Center in Tampa, Fla. Their findings, recently appearing in *Molecular Cancer Therapeutics*, published by the American Association for Cancer Research, suggest that a badly needed new agent against sarcomas – especially sarcomas affecting children – may be at hand.

According to corresponding author Soner Altıok, M.D., Ph.D., sarcomas are rare forms of cancers and are comprised of more than 70 types. Approximately 10 percent of children with cancer are diagnosed with sarcomas, compared to eight percent of young adults and one percent of adults. While chemotherapy and radiation play a role in treating some sarcoma patients, escalations of treatment are unlikely to be tolerable, nor will they prolong survival, said the researchers.

"There is a great need for new agents to treat sarcomas and improve patient outcomes," said Altıok. "Toxicity from radiation and chemotherapy is high and response rates for patients with sarcomas are modest, with improvement and survival negligible."

Sarcomas are cancers that result from transformed cells in one of a number of tissues that develop from embryonic mesoderm. Sarcomas include tumors of bone, cartilage, fat, muscle, vascular and hematopoietic tissues. Sarcomas are different from carcinomas that originate in epithelial cells and result in more common cancers, such as breast, colon and lung cancers.

Researchers from Moffitt's Experimental Therapeutics Program and the Sarcoma Program collaborated in testing MK1775's ability to inhibit Wee1, a nuclear kinase known to be a regulator of cell size and an initiator of cell division, or mitosis. Wee1 is known to play a role in determining the timepoint at which mitosis begins. Loss of Wee1 can produce smaller than normal daughter cells. The researchers hypothesized that inhibition of Wee1 could also induce apoptosis, or programmed cell death in sarcoma tumors.

"Inhibition of the pathways critical to tumor cell survival by molecularly targeted therapy represents an opportunity to reverse the biological basis of tumor formation," explained Altıok. "We found that MK1775 treatment induces apoptotic cell death in four sarcoma cell lines at clinically relevant doses."

To further prove that inhibition of Wee1 by MK1775 leads to mitotic cell death in sarcomas cells, the researchers performed additional studies, including studies on sarcomas related to mutations, such as with the p53 gene. They also showed that MK1775 was an active inhibitor of Wee1 regardless of the p53 mutation status of the tumors in the cell lines tested.

"The cytotoxic effect of Wee1 inhibition on sarcoma cells appears to be independent of p53 mutation status following our testing sarcoma cell lines with different p53 mutations," he said. "All of them were highly sensitive to MK1775, suggesting that Wee1 inhibition may represent a novel approach in the treatment of sarcomas."

The researchers concluded that their laboratory tests on sarcoma cell lines suggest that MK1775 is effective as a monotherapy even in the cell lines that include p53 wild, p53 null and p53 mutant statuses.

Other studies have shown that MK1775 is a well-tolerated drug. No toxicity dose limit has been established, making MK 1775 a potential therapeutic agent for treating both adult and pediatric sarcoma patients.

"Our data has shown that MK1775 treatment causes cell death suggesting 'mitotic catastrophe,' a type of cell death that occurs during cell mitosis," concluded Altıok.

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Located in Tampa, Florida, Moffitt Cancer Center is an NCI Comprehensive Cancer Center – a designation that recognizes Moffitt's excellence in research and contributions to clinical trials, prevention and cancer control. Moffitt currently has 14 affiliates in Florida, one in Georgia, one in Pennsylvania and two in Puerto Rico. Additionally, Moffitt is a member of the National Comprehensive Cancer Network, a prestigious alliance of the country's leading cancer centers, and is listed in U.S. News & World Report as one of "America's Best Hospitals" for cancer. Moffitt marks a very important anniversary in 2011 – 25 years committed to one mission: to contribute to the prevention and cure of cancer .

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