Scientists identify potential new drug for inherited cancer

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have identified a new drug candidate for an inherited form of cancer with no known cure.

The new study showed the drug candidate—known as FRAX97—slowed the proliferation and progression of tumor cells in animal models of Neurofibromatosis type 2. This inherited type of cancer, caused by mutations in the anti-tumor gene *NF2,* leads to tumors of the auditory nerve that connects the inner ear to the brain.

The new compound, originally developed to treat neurodegenerative disease, targets a protein family known as p21-activated kinases or PAKs. These kinases (enzymes that add a phosphate group to other proteins and change their function) play a critical role in the development of Neurofibromatosis type 2. PAK1 has also been implicated in the growth of breast and lung cancers.

"Our study shows that if we inhibit these kinases we can counter the formation of tumors in this brain disease," said Joseph Kissil, a TSRI associate professor who led the study.

In the new study, published in the October 4, 2013 issue of *The Journal of Biological Chemistry,* Kissil and his colleagues showed that the inhibitor slows down progression of Neurofibromatosis type 2 in animal models and reduces more than 80 percent of PAK1 activity.

Kissil notes a key challenge in developing drug candidates is finding potential agents that are both potent and highly selective for their targets—limiting its action to the desired arena and reducing unwanted side effects.

"This inhibitor turned out to be both potent and highly selective," he said. "The real question is why. We were able to show that it works through a unique mechanism."

While the binding site on PAK1 is quite large, it also contains a smaller pocket, a kind of backroom that juts off the larger site. The inhibitor not only takes up space in the larger site, but enters the back pocket as well. That extra binding gives the inhibitor its strong selectivity.

More information: Silvia Licciuli; Scott Troutman; Jasna Maksimoska; et al: "FRAX597, a Small Molecule Inhibitor of The P21-Activated Kinases, Inhibits Tumorigenesis of NF2-Associated Schwannomas," The *Journal of Biological Chemistry*, Vol. 288, Issue 40, 29105-29114, For more information on the paper, see: www.jbc.org/content/early/2013 … M113.510933.abstract

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