

Researchers report way to target hard-to-hit site in disease pathway

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Researchers have successfully targeted an important molecular pathway that fuels a variety of cancers and related developmental syndromes called "Rasopathies."

Reporting their results Nov. 20 in *Chemistry & Biology*, scientists at Cincinnati Children's Hospital Medical Center say they identified a class of lead compounds that successfully recognize a key target in the Ras signaling [pathway](#) - opening the door to future development of therapies that could make treatments more effective with fewer side effects.

Although still in the early stages of the development process for a new drug, the [researchers](#) were encouraged by how effectively their lead compound (NSC-658497) targeted the key catalytic activation of Ras by an enzyme called SOS1. They also reported the lead compound was effective at blocking SOS1-mediated molecular signaling in the Ras pathway that causes rapid cell proliferation, tumor development and [cancer](#).

"While Ras pathway activation is a dominant event happening in many diseases, so far, the immediate signaling module of the Ras pathway has been difficult to target. Most strategies for treatment have been geared toward hitting molecular effectors that are farther downstream," said Yi Zheng, PhD, principal author and director of Experimental Hematology and Cancer Biology at Cincinnati Children's.

"In this study, we have identified synthetic compounds that specifically

recognize the catalytic pocket of SOS-1 and demonstrated that they are effective inhibitors of Ras signaling in cells," Zheng explained. "This establishes a novel targeting approach for cancers and Rasopathies that is useful in developing therapeutics."

The Ras pathway is essential in the regulation of cells in the body - including differentiation, growth and cell senescence (when cells stop dividing). When dysregulation in the pathway occurs, as in the instance of genetic mutation, it prompts Ras signaling and cell growth to ramp up to harmful, disease-causing levels.

Rasopathies include a group of nine developmental syndromes that are caused by mutations in the Ras pathway (Noonan, LEOPARD, hereditary Gingival fibromatosis type 1, Capillary malformation-AV malformation, Neurofibromatosis type 1, Legius, Costello, Cardio-facio-cutaneous and autoimmune lymphoproliferative), according to the Rasopathies Network. The syndromes produce a variety of unique symptoms but share common characteristics including facial features, cardiac defects, cutaneous abnormalities, neurocognitive delay and a predisposition to cancer.

Dysregulation of the Ras pathway (including its SOS1 catalytic activator) is also linked to a number of cancers such as breast, non-small-cell lung, pancreatic, prostate, cervical and leukemia.

Using virtual screening via computer and experimental laboratory screening, the scientists - including first author Chris Evelyn, PhD, a research fellow in the Zheng laboratory - initially tested 30,000 synthetic molecular compounds in a database maintained by the National Cancer Institute. They looked for the compounds' ability to dock with the catalytic site of SOS1. This led the researchers to initial identification of NSC-658497 and derivatives as lead candidates for development of a prospective therapeutic.

The researchers also tested NSC-658497 in cell lines of mouse fibroblasts and prostate cancer. These experiments showed the compound successfully blocked SOS1 to Ras signaling and the proliferation of cancer cells.

Zheng said among the next steps needed to develop NSC-658497 into a plausible therapeutic for clinical use is conducting further medicinal [chemistry](#) to transform the compound into a drug that can be administered to a living organism. This would allow the researchers to begin testing the inhibitor in mouse models of different Rasopathies and cancers.

One of the targeted approaches the scientists will explore is whether NSC-658497 might be most promising in individuals who have a subset of disease in which SOS1 is significantly overexpressed or mutated.

Provided by Cincinnati Children's Hospital Medical Center

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