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Of 50,000 small molecules tested to fight cancer, two show promise

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A class of compounds that interferes with cell signaling pathways may provide a new approach to cancer treatment, according to a study published online this week in the *Proceedings of the National Academy of Sciences* (*PNAS*) Early Edition. The compounds, called PITs (non-phosphoinositide PIP3 inhibitors), limited tumor growth in mice by inducing cell death.

"PITs cause cells to self-destruct by interfering with the signaling pathways that regulate cell survival. As compounds that promote cell death, PITs show promise in halting the harmful, unwanted growth characteristic of cancer," said senior author Alexei Degterev, PhD, assistant professor in the biochemistry department at Tufts University School of Medicine (TUSM) and member of the biochemistry program faculty at the Sackler School of Graduate Biomedical Sciences at Tufts.

Degterev teamed up with colleagues at TUSM, Northeastern University, Massachusetts General Hospital, Harvard Medical School, and the National Chemical Laboratory in Pune, India, to identify compounds that could disrupt a cell signaling molecule called PIP3. Out of 50,000 small molecules screened, the team identified two that inhibited PIP3.

"We tested the more stable of these two molecules in mice and found that it inhibited tumor growth and induced cancer cell death," said co-first author Benchun Miao, PhD, formerly a postdoctoral associate in the biochemistry department at TUSM and fellow in Degterev's lab and now a postdoctoral associate in the Nutrition and Cancer Laboratory at the

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University.

"We also found that PITs showed an even stronger anti-tumor effect in cells with high PIP3 levels. In humans, these high-PIP3 cells are responsible for aggressive forms of cancer such as glioblastoma," said co-first author Igor Skidan, PhD, formerly a postdoctoral fellow in the department of pharmaceutical sciences at Northeastern University and now a senior scientist at Morphotek, Inc.

According to Degterev, PITs are a promising and relatively unexplored approach to cancer treatment. He says that PITs are a new class of compounds that inhibit PIP3, positioned at an early point in a cell signaling pathway over-activated in many human tumors. The study also presents a methodology for identifying other molecules similar to PITs. Degterev hopes that this approach will help researchers isolate other new compounds that halt cancer growth.

"We are not yet at the stage of considering PITS as leads for therapeutics. Our next focus, with our collaborators at National Chemical Laboratory, will be to develop PITS to be more effective," says Degterev.

Provided by Tufts University

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