Scientists discover class of potent anti-cancer compounds

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Working as part of a public program to screen compounds to find potential medicines and other biologically useful molecules, scientists from The Scripps Research Institute and Massachusetts Institute of Technology (MIT) have discovered an extremely potent class of potential anti-cancer and anti-neurodegenerative disorder compounds. The scientists hope their findings will one day lead to new therapies for cancer and Alzheimer's disease patients.

The research—scheduled for publication in the journal Proceedings of the National Academy of Sciences (*PNAS*) the week of March 7, 2011—was led by Benjamin F. Cravatt III, professor and chair of the Department of Chemical Physiology at Scripps Research and a member of its Skaggs Institute for Chemical Biology, and MIT chemistry professor Gregory Fu.

"It was immediately clear that a single class of compounds stood out," said Daniel Bachovchin, a graduate student in the Cravatt lab and the study's first author. "The fact that these compounds work so potently and selectively in cancer cells and mice, right off the screening deck and before we'd done any medicinal chemistry, is very encouraging and also very unusual."

Browsing in the Public Library

The National Institutes of Health (NIH) Common Fund Molecular

Libraries Program currently funds nine screening and medicinal chemistry-related centers at academic institutions around the United States to enable scientists to find biologically interesting molecules, independently of commercial labs (mli.nih.gov/mli/mlpcn/mlpcn-pr …-production-centers/). In these centers, academic scientists can test thousands of compounds at once through high-throughput screens against various biological targets to uncover "proof-of-concept" molecules useful in studying human health and in developing new treatments for human diseases.

"Initially the compounds in the NIH Molecular Libraries repository were purchased from commercial sources and augmented through chemical diversity initiatives," explained Ingrid Y. Li, director of the Molecular Libraries Program at the NIH National Institute of Mental Health (NIMH). "In recent years we've also encouraged academics to donate structurally unusual compounds, to add novelty to the library." (See mli.nih.gov/mli/compound-repository/)

In 2008, Fu's lab donated a set of molecules known as aza-beta-lactams (ABLs)— molecular cousins of penicillin and other beta-lactam antibiotics. "These were molecules that probably didn't exist in commercial compound libraries, and their bioactivity had been virtually unexplored," said Fu.

Meanwhile, across the country, in the Cravatt lab at Scripps Research campus in La Jolla, California, Bachovchin was developing an unusually fast and flexible test for enzyme activity, using fluorescent molecular probes that bind to an enzyme's active site. Researchers can use such tests to measure whether an enzyme of interest loses its activity in the presence of another chemical compound. Bachovchin, Cravatt, and their colleagues decided to apply the new technique to the NIH compound library, to find an inhibitor for an enzyme known as PME-1 (phosphatase methylesterase 1).

Long seen as a potential high-value drug target, PME-1 chemically modifies a growth-slowing enzyme, known as PP2A, in a way that negates PP2A's ability to serve as a tumor suppressor. Studies have shown that when PME-1 production is reduced in some kinds of brain cancer cells, the tumor-suppressing activity of PP2A increases, and cancerous growth is slowed or stopped. Researchers also have found hints that PME-1 might play a role in promoting Alzheimer's disease, by regulating PP2A's ability to dephosphoryate the Alzheimer's-associated tau protein.

"Despite its importance, no one had been able to develop a PME-1 inhibitor, mainly because standard substrate assays for the enzyme were difficult to adapt for high-throughput screening," said Cravatt. "But we believed that we could use our new 'substrate-free' screening technology for PME-1; and we knew that we needed to try a large, high-throughput screen, because our small-scale efforts to find PME-1 inhibitors had come up empty."

Scripps Research runs an NIH Molecular Libraries Program screening center at its Jupiter, Florida campus. There, the institute's researchers set up an automated version of Bachovchin's new screening technique and used it to search for strong PME-1 inhibitors among the 300,000-plus small-molecule compounds in the NIH library.

Super Potent, Super Selective

Like many molecules, ABLs can exist in two mirror-image versions, known as enantiomers, and they usually are synthesized as an equal mixture of both compounds. But Fu and his group had used new chemistry techniques to produce the ABLs in an "enantiomerically selective" way, in case one enantiomer of a compound had more activity than its mirror-image twin. And, in fact, one of these enantiomeric molecules, ABL127, turned out to fit so precisely into a nook on PME-1

that it completely blocked PME-1 activity in cell cultures and in the brains of mice. Aside from being extremely potent, it also was highly selective for PME-1, so that even at higher doses, it had negligible effects on other enzymes in the PME-1 family, known as serine hydrolases. In mice, ABL127's inhibition of PME-1 activity caused a more than one-third drop in the measured level of demethylated ("inactive") PP2A.

The Cravatt and Fu labs are now working together to synthesize more ABLs and explore their chemistry, looking for the best possible PME-1 inhibitor. The near-term goal is to use ABL127 as a scientific probe to study PME-1 functions in animals. A longer-term goal is to develop ABL127, or related compounds, as potential oncology or Alzheimer's disease drugs.

"Already several labs from both academia and industry have contacted us about collaborating on PME-1 research," said Cravatt. "So our findings here are scientifically interesting, and I think could, one day, be valuable clinically. But it's important to emphasize that we wouldn't have these findings at all, were it not for the NIH Molecular Libraries Program and its compound library. Both on the screening side and the chemistry side, the NIH enabled us academics to bring technologies to the table unlikely to be found in a traditional 'pharma' setting. Our discoveries thus stand as a fine example of the value of public screening for creating novel, in vivo-active pharmacological probes for challenging protein targets."

The paper's other co-authors were Justin T. Mohr and Jacob M. Berlin of the Fu laboratory at MIT; Timothy P. Spicer, Virneliz Fernandez-Vega, Peter Chase, Peter S. Hodder, and Stephan C. Schürer of the Scripps Molecular Screening Center in Jupiter, Florida; and Anna E. Speers, Chu Wang, Daniel K. Nomura and Hugh Rosen of the Scripps Research campus in La Jolla, California.

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