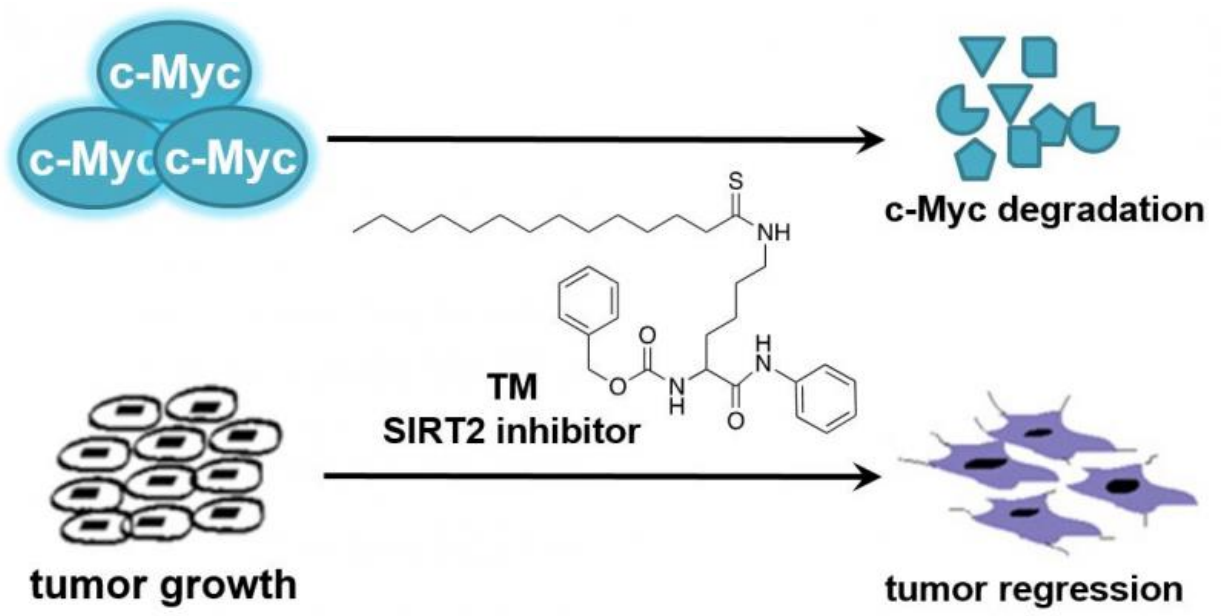
Enzyme inhibitor looks promising against many forms of cancer

March 22 2016, by Tom Fleischman



The oncoprotein inhibitor TM has been proven effective in suppressing the oncogene c-Myc, which is amplified in around half of all human tumors, and thus killing cancer cells.

Cornell researchers from the Ithaca and Weill Cornell Medicine campuses have collaborated to develop an enzyme inhibitor that shows effectiveness against several types of cancer, most notably leukemia, breast cancer and colorectal cancer.

Their work focuses on the oncoprotein c-Myc, which is amplified in nearly half of all human tumors, and on the enzyme SIRT2, which plays an important role in the viability of several cancer lines.

With a compound known as TM (a thiomyristoyl lysine compound), the group was able to inhibit SIRT2, decrease c-Myc protein level, and inhibit tumor growth in laboratory breast cancer mouse models. In the long race to find a cure for a disease that kills more than 8 million people worldwide each year, this work could represent yet another important step forward.

Their work is detailed in a paper published online March 14 in the journal *Cancer Cell*.

"This started from basic science, and the basic study led us to this path, which looks very promising. We have high hope that in a few years, we can develop an effective anti-cancer drug," said co-lead author Hening Lin, professor of chemistry and chemical biology in the College of Arts and Sciences and a Howard Hughes Medical Institute investigator.

The team includes senior co-author Paraskevi Giannakakou, professor of pharmacology in medicine at Weill Cornell Medicine. An intercampus seed grant from Cornell University helped support the work.

"This was part of an ongoing collaboration – for the last three years, at least," Giannakakou said. "This is an example of the power of having cross-campus collaborations, especially between scientists and clinical investigators at Weill Cornell, brainstorming, and having frequent communication."

Previous efforts at developing inhibitors to target the sirtuin class of enzymes, which include SIRT2, have been limited by insufficient potency and/or selectivity. By developing and testing TM alongside three

other similar compounds, Lin's group found TM showed excellent ability and selectivity to inhibit the SIRT2 protein.

The group sent TM to the Developmental Therapeutics Program of the National Cancer Institute for screening against approximately 60 cancer cell lines. Results showed that 10 microns of TM inhibited 36 of 56 cell lines by greater than 50 percent, including all leukemia and all but one colorectal cancer cell line.

Lin said the finding was a bit of a surprise, given the original goal.

"When we made TM, we were thinking of targeting SIRT6," he said, referring to a different enzyme within the sirtuin family of proteins. "We didn't know at that time that SIRT2 has this activity."

In fact, there was a belief, based on two previous studies, that the SIRT2 enzyme might actually be a tumor suppressor, and that targeting it might promote tumor formation. That turned out not to be the case; they carried out multiple lines of experiments to demonstrate that the anti-cancer effect of TM is achieved through inhibiting SIRT2.

Giannakakou said the collaboration – which involved conference calls and exchanging ideas – led to the discovery of the c-Myc connection.

"To date, we really don't have anything that is potent against c-Myc," she said. "Most of the inhibitors work indirectly- they target something else and then downstream they target c-Myc. TM is kind of the same, but it shows very promising activity, in vivo and in vitro. It has the potential to be developed into a clinical compound."

Collaborator and senior co-author Robert Weiss, professor of molecular genetics in the Department of Biomedical Sciences in the College of Veterinary Medicine, directed the mouse studies in this work.

"I think it's a really exciting development," he said. "The observation that this small molecule impacts the c-Myc oncoprotein potentially has great relevance, because Myc has been implicated in so many cancers."

One of the drawbacks the group must deal with is TM's limited solubility and bioavailability. Lin believes that by improving the solubility and bioavailability in the future, they can improve the TM's anti-cancer effect even further.

This latest work builds on previously published research from the Lin group, including papers in 2011 and 2013, and is evidence, Lin says, of the importance of the basic research he and his colleagues do.

"To me, it says basic science is important," he said. "If you really understand something, it helps you to make useful translational discoveries. It's very satisfying to utilize the basic discovery to improve human life."

More information: Hui Jing et al. A SIRT2-Selective Inhibitor Promotes c-Myc Oncoprotein Degradation and Exhibits Broad Anticancer Activity, *Cancer Cell* (2016). DOI: 10.1016/j.ccell.2016.02.007

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