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Researchers 'notch' a victory toward new kind of cancer drug

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(PhysOrg.com) -- Scientists have devised an innovative way to disarm a key protein considered to be "undruggable," meaning that all previous efforts to develop a drug against it have failed. Their discovery, published in the November 12 issue of *Nature*, lays the foundation for a new kind of therapy aimed directly at a critical human protein -- one of a few thousand so-called transcription factors -- that could someday be used to treat a variety of diseases, especially multiple types of cancer.

"There is a pressing need for drugs that target transcription factors, both for use as scientific tools in the laboratory and as therapies in the clinic," said senior author James Bradner, a Harvard chemical biologist and oncologist at the Dana-Farber Cancer Institute and an associate member of the Broad Institute of MIT and Harvard. "Our work brings us a step closer toward that goal for a protein with major roles in cancer, cardiovascular disease and stem cell biology."

If human physiology is like a puppet show, then transcription factors pull the puppet strings. They bind to DNA and turn genes on or off, setting in motion genetic cascades that control how normal cells grow and develop. They also help maintain tumor growth, underscoring their importance as cancer drug targets. Yet transcription factors are counted among the most difficult molecules to neutralize with a drug — in fact, no such drugs are currently available.

Based on his work as an oncologist, Bradner became deeply interested in a human protein called NOTCH. The gene encoding this protein is often

damaged, or mutated, in patients with a form of blood cancer, known as T-ALL or T-cell acute lymphoblastic leukemia.

Abnormal NOTCH genes found in cancer patients remain in a state of constant activity, switched on all the time, which helps to drive the uncontrolled cell growth that fuels tumors. Similar abnormalities in NOTCH also underlie a variety of other cancers, including lung, ovarian, pancreatic and gastrointestinal cancers.

Even with this deep scientific knowledge, drugs against NOTCH — or any other transcription factor — have traditionally been extremely difficult, if not impossible, to develop. Most current drugs take the form of small chemicals (known as "small molecules") or larger-sized proteins, both of which have proven impractical to date for disabling transcription factors.

A few years ago, Bradner and his colleagues hatched a different idea about how to tame the runaway NOTCH protein. Looking closely at its structure as well as the structures of its partner proteins, they noticed a key protein-to-protein junction that featured a helical shape.

"We figured if we could generate a set of tiny little helices we might be able to find one that would hit the sweet spot and shut down NOTCH function," said Bradner.

Creating and testing these helices involved a team of interdisciplinary researchers, including Greg Verdine, Erving Professor of Chemistry at Harvard University and director of the Chemical Biology Initiative at Dana-Farber Cancer Institute, as well as scientists at Brigham and Women's Hospital and the Broad Institute's Chemical Biology Program, which is directed by Stuart Schreiber.

Verdine invented a drug discovery technology that uses chemical braces

or "staples" to hold the shapes of different protein snippets. Without these braces, the snippets (called "peptides") would flop around, losing their three-dimensional structure and thus their biological activity. Importantly, cells can readily absorb stapled peptides, which are significantly smaller than proteins. That means the peptides can get to the right locations inside cells to alter gene regulation.

"Stapled peptides promise to significantly expand the range of what's considered 'druggable,'" said Verdine, who is a co-senior author of the study and an associate member of the Broad Institute. "With our discovery, we've declared open season on transcription factors and other intractable drug targets."

After designing and testing several synthetic stapled peptides, the research team identified one with remarkable activity. Not only could it bind to the right proteins and reach the right places inside cells, it also showed the desired biological effect: the ability to disrupt NOTCH function.

Moreover, experiments in cultured cells as well as in mice proved the peptide's ability to limit the growth of cancer cells fueled exclusively by NOTCH. Interestingly, these effects are also seen at the level of gene activity or "expression." The researchers looked at the expression levels of genes across the genome, in both cells and mice treated with the peptide, and observed markedly reduced expression of genes that are controlled directly and indirectly by NOTCH. These results offer some early insights into how the peptide works at a molecular level.

In addition to the potential therapeutic applications to NOTCH-dependent cancers, the *Nature* study also forms the basis of a general strategy for taking aim at other transcription factors. "A variety of key transcription factors assemble in a manner similar to NOTCH," said first author Raymond Moellering, a graduate student in Harvard University's

Department of Chemistry and Chemical Biology who works with both Verdine and Bradner. "Our approach could offer a template for targeting many other master regulators in cancer."

More information: Moellering et al. Direct inhibition of the NOTCH transcription factor complex. *Nature*; DOI: 10.1038/nature08543

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