

Tricking Cells Into Trashing Cancer

Fred Hutch chemical biologist rapidly reduces lung tumors in mice with a tagging system that grabs cancer-causing proteins and hauls them out with the molecular trash

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Many cancer drugs work by inhibiting the activity of proteins — the molecules that do most of the work in the cell.

But some misbehaving proteins that turn normal cells cancerous are difficult to inhibit, and even effective inhibitors lose their potency when cancer finds a workaround and becomes resistant to those drugs.

[A new approach now in clinical trials](#) called targeted protein degradation works a different way.

Instead of inhibiting the troublemakers, these new therapies trick the cell's natural garbage collectors into grabbing cancer-causing proteins and hauling them out with the rest of the molecular trash.

In a study published late last month in the [Journal of Clinical Investigation](#), Fred Hutch Cancer Center cancer chemical biologist [Behnam Nabet, PhD](#), and his collaborators describe how they used this approach in mice to rapidly destroy lung and pancreas tumors caused by a variant of a commonly mutated, cancer-driving gene.

"We nicely show that there is a really substantial reduction in tumor growth," Nabet said. "There is a remarkable improvement of survival of these mice."

A new way to dispose of "undruggable" proteins

The study focuses on a gene called [KRAS](#), which codes for a protein that acts like a signaling switchboard in normal cells, relaying external signals to the cell nucleus. KRAS regulates several fundamental biological processes including cell growth and division.

KRAS is an oncogene, a kind of gene that, when mutated, can potentially make normal cells cancerous. It's the most frequently mutated oncogene in cancer.

About 30% of patients with lung adenocarcinoma harbor KRAS mutations, which also drive pancreatic, colorectal and other cancers.

Nabet's team focused on a particular mutation called KRAS G12V, which has no specific inhibitor.

KRAS is notoriously "undruggable" because it doesn't have a well-defined pocket where an inhibitor drug can nestle and interrupt its function. The few recently discovered KRAS inhibitors that do work lose their effectiveness after long-term use.

Targeted protein degradation uses engineered degrader molecules to harness the cell's natural garbage collection and disposal system.

Unlike inhibitors, degrader molecules don't need a tidy pocket to nestle in. They can just grab on anywhere and trick the cell into hauling the targeted protein out with the trash. Rather than inhibit a particular function, they destroy the whole troublesome protein.

Some degraders currently in development in clinical trials have shown promise, making the approach a tempting option.

But because there is no specific inhibitor for KRAS G12V, researchers can't turn it on and off experimentally in a mouse to better understand the role it plays in cellular signaling to drive tumor growth.

That's the kind of information pharmaceutical companies would like to know before investing millions of dollars in a therapeutic degrader molecule for humans.

Nabet and his colleagues tackled that problem by making a genetically engineered mouse with several features that not only allow them to study how the KRAS G12V mutation works in a living organism, but also to test whether degrading KRAS G12V proteins gets rid of tumors.

Making a mouse

Nabet and co-senior authors [Hua Zhang, MD, PhD](#), and [Kwok-Kin Wong, MD, PhD](#), at the University of Pittsburgh and New York University respectively, designed a first-of-its-kind mouse that expresses the KRAS G12V mutation with some extra features.

They inserted a bit of code that acts like a brake that keeps the KRAS G12V mutation turned off until they are ready to activate it.

They can remove the brake with a virus and activate the mutation whenever and wherever in the body they choose, which allows them to precisely track changes in cellular signaling.

To activate KRAS G12V in the lungs, they gave mice a nasal mist with the virus to remove the brake.

They turned on KRAS G12V and sure enough, tumors began growing in the lungs.

That allowed them to find out what would happen if they grabbed the KRAS G12V proteins and

degraded them in the cell's garbage disposals, which are called proteasomes.

They grabbed the troublemakers with a targeted protein degradation system [Nabet's lab](#) has developed called [dTAG](#), which has successfully degraded a variety of proteins and enzymes, both in cellular lines and in mouse models of human disease.

The system uses a degrader molecule that acts like a pair of handcuffs. One cuff links to the enzyme that normally marks defective and damaged proteins for destruction. The other cuff links to a problem protein bearing a genetic tag that the degrader molecule recognizes.

For this study, the team engineered the KRAS G12V mouse to include the genetic tag that makes the protein recognizable to the dTAG system and amenable to degradation.

That's what made the mouse the first of its kind.

"The twist from the beginning is that we've added our tag to it," Nabet said.

Testing dTAG on tumors

Once they had a mouse that would express KRAS G12V at a time and place of their choosing, they put dTAG to the test and observed what happens when the degrader molecule is administered by injection in different dosages.

They confirmed that the dTAG molecules found the KRAS G12V proteins, handcuffed them and hauled them out with the trash, which disrupted their cancer-driving signals.

Then they measured what effect that disruption had on the growth of tumors.

They discovered that the dTAG system quickly stopped and reversed tumor growth.

"We have tumor reductions — very rapidly, within five days we start to see changes and then within three to four weeks, we see really robust, remarkable responses," Nabet said. "To our knowledge, this is the first report that demonstrates that degrading KRAS G12V oncoprotein abolishes lung tumors in mice."

They also used the dTAG system to destroy pancreas tumors in mice. Using pancreatic cancer cells that were grown in the mouse's flank, they administered the dTAG molecules to degrade KRAS G12V, and then watched the tumors shrink.

"The power here is being able to activate and then see if we can reverse it and what happens when we reverse it," Nabet said. "What we can do is completely get rid of a protein very, very quickly and uncover really new and exciting biology."

Because their model mice have intact immune systems, Nabet and his colleagues also were able to confirm that rapidly degrading the problem proteins also rewired the [surrounding normal cells](#).

[molecules, and blood vessels feeding tumor cells](#). That rewiring triggered a strong antitumor immune response, providing even more therapeutic benefit.

“This highlights the exciting potential of what a degrader targeting KRAS G12V could achieve,” Nabet said.

It remains an open question what precise benefit degraders will provide over an inhibitor drug that targets KRAS G12V.

But if a specific inhibitor for KRAS G12V is discovered, researchers can use the engineered mouse and dTAG system Nabet and his colleagues created as a platform to compare the performance of inhibitors and degraders directly.

“Our technology has been paradigm-shifting in the field, and so we are excited for the scientific community to continue to leverage our approach,” Nabet said.

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