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Flipping a Switch and Making Cancers Self-Destruct

Researchers at Stanford devised a strange new molecule that could lead to drugs that arm genes and make cancers work against themselves.

By Gina Kolata

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Within every cancer are molecules that spur deadly, uncontrollable growth. What if scientists could hook those molecules to others that make cells self-destruct? Could the very drivers of a cancer's survival instead activate the program for its destruction?

That idea came as an epiphany to Dr. Gerald Crabtree, a developmental biologist at Stanford, some years ago during a walk through the redwoods near his home in the Santa Cruz mountains.

"I ran home," he said, excited by the idea and planning ways to make it work.

Now, in a paper published Wednesday in the journal Nature, Dr. Crabtree, a founder of Foghorn Therapeutics, which is developing cancer drugs, along with Nathanael S. Gray, a professor of chemical and system biology at Stanford, and their colleagues report that they have done what he imagined on that walk. While the concept is a long way from a drug that could be given to cancer patients, it could be a target for drug developers in the future.

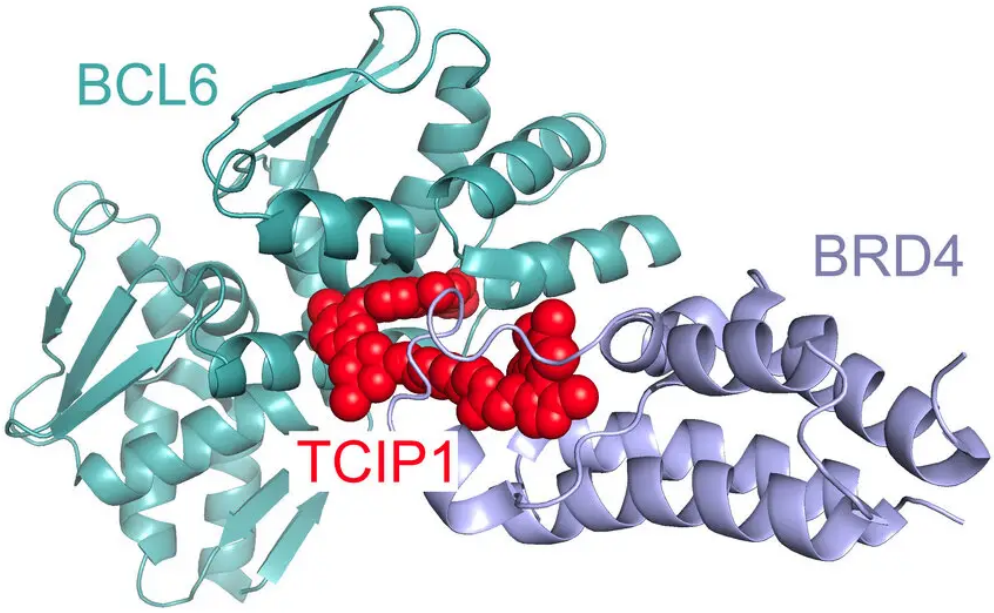
"It's very cool," said Jason Gestwicki, professor of pharmaceutical chemistry at the University of California, San Francisco. "It turns something the cancer cell needs to stay alive into something that kills it, like changing your vitamin into a poison."

"This is a potentially new way to turn cancer against itself," said Dr. Louis Staudt, director of the Center for Cancer Genomics at the National Cancer Institute. Dr. Staudt wrote an editorial to accompany Dr. Crabtree's paper.

Once the treatment is further developed, he added, "I would love to try it in a clinical trial with our patients who have exhausted all other options."

In laboratory experiments with cells from a blood cancer, diffuse large B-cell lymphoma, the researchers designed and built molecules that hooked together two proteins: BCL6, a mutated protein that the cancer relies on to aggressively grow and survive, and a normal cell protein that switches on any genes it gets near.

The new construction, a dumbbell shaped molecule, is unlike anything seen in nature. BCL6, at one end of the dumbbell, guides the molecule toward cell-death genes that are part of every cell's DNA and are used to get rid of cells that are no longer needed. But when a person has diffuse large B cell lymphoma, BCL6 has turned off those cell-death genes, making the cells essentially immortal.



A computational model of the molecule TCIP1 that hooked together the BRD4 and BCL6 proteins together. Andrey Krokhotin

When the dumbbell, guided by BCL6, gets near the cell-death genes, the normal protein on the end of the dumbbell arms those death genes. Unlike other processes in the cell that can be reversed, turning on cell-death genes is irreversible.

The new approach could be an improvement over the difficult task of using drugs to block all BCL6 molecules. With the dumbbell-shaped molecules, it is sufficient to rewire just a portion of BCL6 molecules in order to kill cells.

The concept could potentially work for half of all cancers, which have known mutations that result in proteins that drive growth, Dr. Crabtree said. And because the treatment relies on the mutated proteins produced by the cancer cells, it could be extremely specific, sparing healthy cells.

Dr. Crabtree explained the two areas of discovery that made the work possible. One is the discovery of "driver genes" — several hundred genes that, when mutated, drive the spread of cancer.

The second is the discovery of death pathways in cells. Those pathways, Dr. Crabtree said, "are used to eliminate cells that have gone rogue for one reason or other" — 60 billion cells in each individual every day.

The quest was to make the pathways driving cancer cell growth communicate with silenced pathways that drive cell death, something they would not normally do.

When the hybrid molecule drifted to the cells' DNA, it not only turned on cell-death genes but also did more. BCL6 guided the hybrid to other genes that the cancer had silenced. The hybrid turned those genes on again, creating internal chaos in the cell.

"The cell has never experienced this," Dr. Staudt said.

"BCL6 is the organizing principle of these cancer cells," he explained. When its function is totally disrupted, "the cell has lost its identity and says, 'something very wrong is happening here. I'd better die.'"

But the main effect of the experimental treatment was to activate the cell-death genes, Dr. Crabtree said. "That is the therapeutic effect," he said.

The group tested its hybrid molecule in mice, where it seemed safe. But, Dr. Staudt noted, "humans are a lot different than mice."

The work is "exciting," said Stuart L. Schreiber, professor of chemistry and chemical biology at Harvard and a previous collaborator with Dr. Crabtree. But he offered words of caution.

What Dr. Crabtree created "is not a drug — it still has a long way to go," he said.

Gina Kolata writes about science and medicine. She has twice been a Pulitzer Prize finalist and is the author of six books, including "Mercies in Disguise: A Story of Hope, a Family's Genetic Destiny, and The Science That Saved Them." More about Gina Kolata