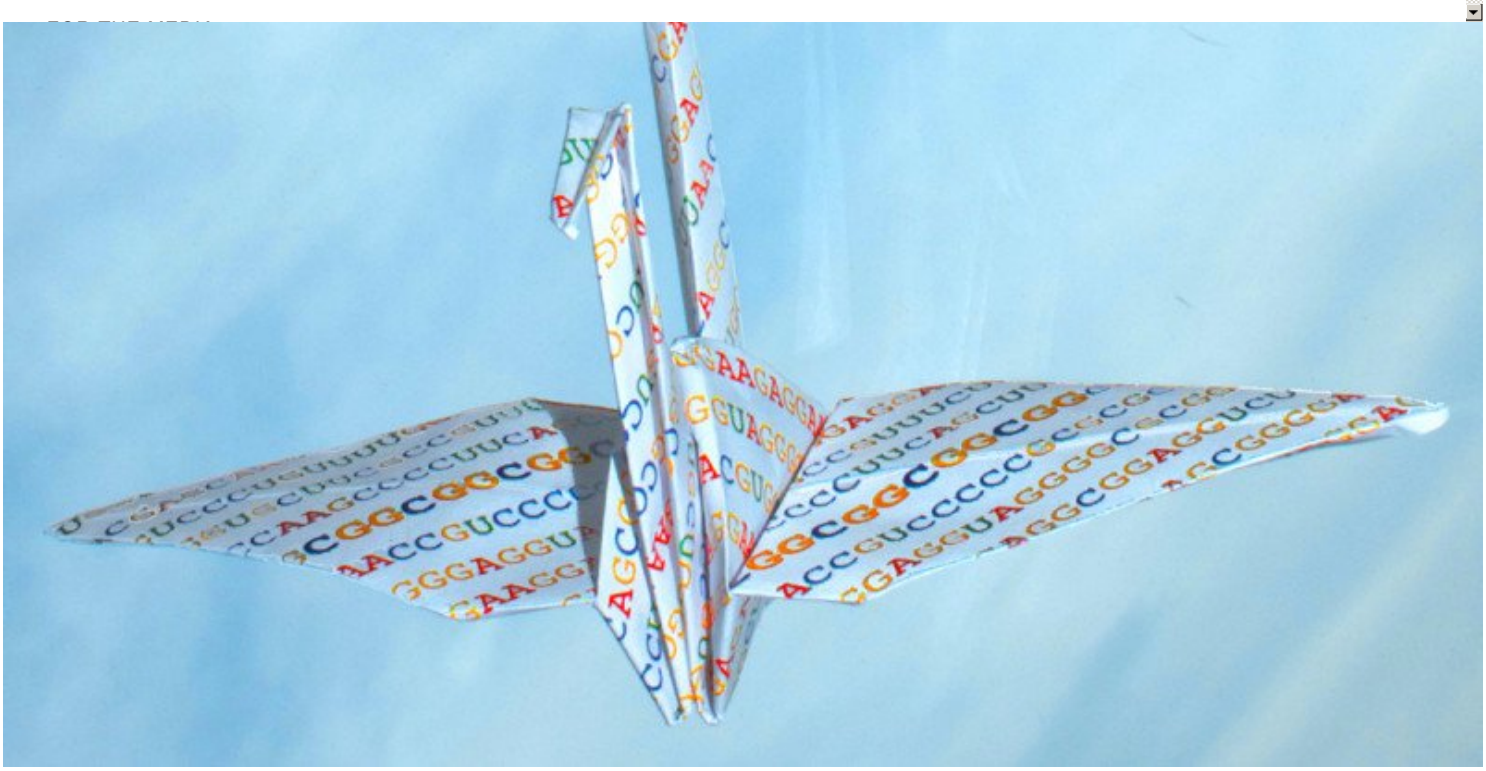

An origami crane illustrates the importance of RNA folding for regulating gene translation. The bolded sequences on the crane's wings indicate the portion that is critical for the manufacture of many cancer-causing proteins.

Summary

Memorial Sloan Kettering researchers have found a naturally occurring compound that can destroy cancer cells in mice by targeting *MYC*, a cancer-causing gene that has remained elusive until now.

Many of the most effective cancer therapies available today have been developed by determining which genes lead cells to become cancerous and figuring out how to block the activity of those genes with drugs. But scientists have not yet been able to find a drug to inhibit MYC, one of the first cancer-causing genes discovered and one of the most well studied.

Now Memorial Sloan Kettering investigators Andrew Wolfe and Kamini Singh and their colleagues have looked to nature and found a compound that blocks a cell's ability to produce the "undruggable" MYC protein. In the laboratory, the compound is proving capable of destroying leukemia and lymphoma cells and even some solid tumors. Treatment with an effective dose of the drug was well tolerated in animal models.

"For as long as we've known about MYC — about 40 years — we've looked for a way to block it," says Memorial Sloan Kettering cancer biologist Hans-Guido Wendel, the senior author of the study, which was published online yesterday in *Nature*. "MYC is clearly important for many different cancers, however, efforts in academia and in industry to target MYC have not been successful. Instead of targeting the MYC protein, we now have a drug that completely prevents its production — and this proves to be a highly effective alternative."

A New Method

The compound, called Silvestrol, does not work through the mechanisms used by most targeted therapies. "Many other drugs work by targeting kinases, proteins that are important in cell signaling and the regulation of other proteins," Dr. Wendel says.

Silvestrol works by targeting an RNA helicase, a type of protein that regulates genes by changing the structure of their RNA. Without this RNA helicase, cells are unable to translate the MYC gene into the MYC protein, preventing the cancer-inducing activity of the gene.

"With help from the team of Gunnar Rätsch, who developed new computational tools, we dug a little deeper into how Silvestrol works and found that it is effective against a group of proteins made by messenger RNAs that often share a structure, or molecular shape, called a G-quadruplex," says Dr. Singh, a postdoctoral fellow in Dr. Wendel's lab and one of the paper's two first authors. "This structure is found in many other cancer-causing genes, or oncogenes, which means that Silvestrol is able to inhibit other important oncogenes in addition to *MYC*."

"Cancer cells are dependent on the proteins encoded by these oncogenes," adds Dr. Wolfe, a former fellow in Dr. Wendel's lab and the other first author, who is now a postdoctoral fellow at Mount Sinai. "Removing them causes the cells to undergo apoptosis and die."

Back to top ^

Seeking Cancer Drugs in Nature

Silvestrol is a natural product found in a plant called *Aglaia foveolata*, which is native to Indonesia, Brunei, and Malaysia. Although, "nobody knows — it might also grow in Central Park or many other places," Dr. Wendel says.

The effort to develop drugs from natural products is based on the idea that these molecules have an inherent biological function that can be enhanced and exploited. Many of the most successful cancer drugs to date have been based on natural products, including paclitaxel (Taxol®), which was isolated from the Pacific yew tree, and vincristine, which comes from the Madagascar periwinkle.

Earlier research by McGill University biochemist Jerry Pelletier, a collaborator on the study, had indicated that Silvestrol can block protein translation in cancer cells. But because the compound could be extracted from the plant only in very small quantities, the research team also looked at analogs of Silvestrol that could be manufactured in a laboratory. Analogs are chemical compounds with a structure that is slightly altered from another compound but often have the same or a very similar chemical function.

"We've already found a highly effective analog of Silvestrol that works very well," Dr. Wendel says. "However, to take this drug to the clinic will require significant funding and additional chemistry work." He is hoping to find both at Memorial Sloan Kettering.

The next step is to continue testing Silvestrol and its analogs against leukemia as well as other types of tumors. The researchers emphasize that more study is needed to determine the most effective dose as well as any side effects that may occur before clinical trials can begin in patients.

"Blocking the production of key cancer genes is a completely new way of treating cancer," Dr. Wendel concludes. "That is exciting, and it also means we have a lot to learn about it."

Back to top ^

Funding information: This research was supported by the National Cancer Institute under grant number R01-CA142798-01, the Leukemia Research Foundation, the Experimental Therapeutics Center at MSK, and the American Cancer Society. Dr. Wendel is also a Scholar of the Leukemia & Lymphoma Society.

Connect

Contact us

Locations

APPOINTMENTS
800-525-2225

About MSK

About us

Careers

Giving

Cancer Care

Adult cancer types

Child & teen cancer types

Integrative medicine

Nutrition & cancer

Find a doctor

Research & Education

Sloan Kettering Institute

Gerstner Sloan Kettering Graduate School

Graduate medical education

MSK Library
