Rediscovered Drugs Hit Leukemia from Two Different Angles

To find a better FTO-targeting drug, researchers searched a collection of 260,000 chemicals housed by NCI.

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Scientists have found two old, abandoned drugs may have potential as treatments for a type of blood cancer called acute myeloid leukemia (AML). The rediscovered drugs, bisantrene and brequinar, substantially slowed the growth of AML in mice.

The study, partly funded by NCI, showed that both drugs hit leukemia from two important angles. One is by squashing cancer stem cells, a type of cell that may help cancer come back after treatment. The other is by helping the immune system better attack cancer.

Both drugs block the activity of a protein known as FTO. AML and some other types of cancer cells have more FTO than healthy cells, and earlier studies have shown that blocking FTO may slow the growth of these cancers.

But existing drugs that target FTO don't block the protein very well or need to be given in large doses. That led Jianjun Chen, Ph.D., of City of Hope cancer center in Duarte, California, and his colleagues to search for a better FTO-targeting drug. The researchers published their findings June 11 in Cancer Cell.

Bisantrene and brequinar are "significantly more effective" at blocking FTO than other drugs, Sarah Naomi Olsen, Ph.D., of Dana-Farber Cancer Institute, and Scott Armstrong, M.D., Ph.D., of Boston Children's Hospital, wrote in a commentary on the new study.

Several decades ago, scientists tested both drugs in studies of people with cancer, including AML. But for various reasons neither made it into larger studies. Now, interest is rising again. An ongoing trial is testing brequinar in people with AML, and studies of bisantrene for people with leukemia are in the works.

Searching for a Better FTO-Targeting Drug

To find a better FTO-targeting drug, the researchers turned to a collection of 260,000 chemicals housed by NCI's Developmental Therapeutics Program (DTP).

NCI makes this massive chemical “library” available to researchers at and outside of NCI, said Joel Morris, Ph.D., chief of DTP’s Drug Synthesis and Chemistry Branch. The library is a key resource for scientists looking for new cancer drugs or for new uses for existing cancer drugs.

“Last year, we sent out around 10,000 samples” of chemicals from the library, Dr. Morris noted. DTP also provides smaller sets of drugs, such as a set of cancer drugs approved by the Food and Drug Administration, he added.

Using the DTP library, Dr. Chen’s team virtually searched for chemicals that a computer program predicted would interact with FTO. That search resulted in 370 candidates. Among the 213 chemicals that they were able to test, bisantrene and brequinar were the best at blocking FTO in lab experiments.

Stopping Cancer and Cancer Stem Cells

With the top two drugs in hand, the researchers next looked at their effects on cancer cells with high levels of FTO.

Both drugs killed AML cells in lab experiments, even at relatively low doses. In mice implanted with AML cells, treatment with either drug shrank tumors and didn’t appear to cause any major side effects. Mice treated with either drug lived significantly longer than mice given a placebo.

The drugs also slowed the growth of breast, brain, and pancreatic cancer cells with higher-than-normal levels of FTO. This suggests that “inhibition of FTO may have broad potential in treating various types of cancer,” Dr. Chen noted.

What’s more, the drugs appeared to work against AML stem cells, which many scientists think is key for eliminating cancer. Both healthy cells and cancer cells can only divide a limited number of times. Cancer stem cells, on the other hand, can divide endlessly. Researchers think cancer stem cells may help explain why cancer sometimes comes back after what seems like successful treatment.

AML stem cells have more FTO than AML cells, the researchers found. Plus, bisantrene and brequinar killed AML stem cells in lab studies and in mice implanted with AML cells.

FTO Modifies RNA in Cancer

So why is FTO so important to cancer cells? FTO’s job is to remove chemical tags (called methylation) on RNA. After cells copy DNA into RNA, they use RNA to make proteins. Chemical tags affect how much protein is made from an RNA molecule. Because proteins control how cells function, RNA tags can have big effects on cells.

Scientists discovered that RNA had chemical tags in the 1970s. But “people didn’t realize that they are functionally important” until more recently, Dr. Chen said.

The development of new tools has helped scientists study RNA tags in more detail, said Margaret Klauzinska, Ph.D., of NCI's Division of Cancer Biology, leading to an entirely new field called epitranscriptomics. "It's an emerging, fast-growing, and very exciting field," she added.

Researchers have long known that chemical tags on both DNA and proteins control gene activity. "The discovery of the epitranscriptome revealed another layer and a new dimension of gene expression regulation," she explained. Recent studies have also shown that the pattern of chemical tags on RNA is changed in some cancers, she added.

Both bisantrene and brequinar upped the amount of chemical tags on certain RNAs in AML cells, the team found. Consequently, the expression of thousands of genes was shifted up or down.

Among them was a handful of genes that help cancer cells hide from the immune system. Treating AML cells with either drug lowered protein levels from these "immune checkpoint" genes. As a result, immune cells were better able to attack AML cells. In addition, treating mice with one of the drugs plus activated immune cells stopped AML growth better than either drug by itself.

Further Developing Bisantrene and Brequinar

Dr. Chen and his team are continuing to study bisantrene and brequinar as potential cancer treatments. They are currently tweaking the structure of the drugs to boost their cancer-killing effects and improve certain chemical properties—specifically the drugs' pharmacokinetics.

They are also thinking ahead to treating patients. "A single [drug] may not be sufficient to kill many types of cancer," Dr. Chen said. "We are also testing the combination of FTO inhibitors with other therapeutic agents, including chemotherapy, targeted therapy, and immunotherapy" in lab studies, he said.

The team is hopeful that they may be able to launch a clinical trial soon. The study would focus on patients with high levels of FTO in their cancer, Dr. Chen said.

Drugs like bisantrene and brequinar, which target proteins that add or remove RNA chemical tags "could lead to new, promising, and unexpected therapeutic strategies for [cancer] in the near future," Dr. Klauzinska said. Many such drugs are currently being studied, she added.

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