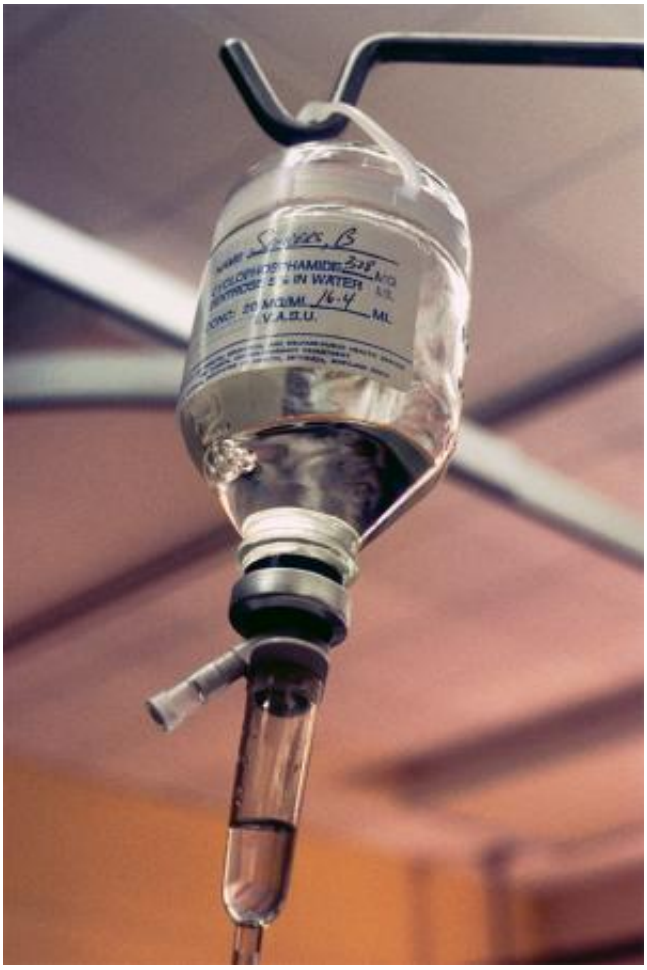
New weapon fights drug-resistant tumors

January 30 2014



A close-up of an intravenous (IV) bottle with Cyclophosphamide. Credit: LINDA BARTLETT

Cancer drugs that recruit antibodies from the body's own immune system to help kill tumors have shown much promise in treating several

types of cancer. However, after initial success, the tumors often return.

A new study from MIT reveals a way to combat these recurrent tumors with a drug that makes them more vulnerable to the antibody treatment. This drug, known as cyclophosphamide, is already approved by the Food and Drug Administration (FDA) to treat some cancers.

Antibody drugs work by marking tumor cells for destruction by the body's immune system, but they have little effect on tumor cells that hide out in the bone marrow. Cyclophosphamide stimulates the immune response in bone marrow, eliminating the reservoir of cancer cells that can produce new tumors after treatment.

"We're not talking about the development of a new drug, we're talking about the altered use of an existing therapy," says Michael Hemann, the Eisen and Chang Career Development Associate Professor of Biology, a member of MIT's Koch Institute for Integrative Cancer Research, and one of the senior authors of the study. "We can operate within the context of existing treatment regimens but hopefully achieve drastic improvement in the efficacy of those regimens."

Jianzhu Chen, the Ivan R. Cottrell Professor of Immunology and a member of the Koch Institute, is also a senior author of the paper, which appears in the Jan. 30 issue of the journal *Cell*. The lead author is former Koch Institute postdoc Christian Pallasch, now at the University of Cologne in Germany.

Finding cancer's hiding spots

Antibody-based cancer drugs are designed to bind to proteins found on the surfaces of tumor cells. Once the antibodies flag the tumor cells, immune cells called macrophages destroy them. While many antibody drugs have already been approved to treat human cancers, little is known

about the best ways to deploy them, and what drugs might boost their effects, Hemann says.

Antibodies are very species-specific, so for this study, the researchers developed a strain of mice that can develop human lymphomas (cancers of white blood cells) by implanting them with human blood stem cells that are genetically programmed to become cancerous. Because these mice have a human version of cancer, they can be used to test drugs that target human tumor cells.

The researchers first studied an antibody drug called alemtuzumab, which is FDA-approved and in clinical trials for some forms of lymphoma. The drug successfully cleared most cancer cells, but some remained hidden in the bone marrow, which has previously been identified as a site of drug resistance in many types of cancer.

The study revealed that within the bone marrow, alemtuzumab successfully binds to tumor cells, but macrophages do not attack the cells due to the presence of lipid compounds called prostaglandins, which repress macrophage activity. Scientists believe the bone marrow naturally produces prostaglandins to help protect the immune cells that are maturing there. Tumor cells that reach the bone marrow can exploit this protective environment to aid their own survival.

The finding is an important contribution to scientists' understanding of how antibody drugs act against these types of lymphomas, says Ravi Majeti, an assistant professor of medicine at Stanford University who was not part of the research team.

"There clearly has been a lack of understanding about why antibody therapies have been relatively unsuccessful as monotherapies," Majeti says, adding that it would be valuable to see if the findings extend to other types of cancer, such as solid tumors.

'Tricking the immune system'

The MIT team then tested a variety of cancer drugs in combination with alemtuzumab and discovered that cyclophosphamide can rewire the bone marrow microenvironment to make it much more receptive to macrophages, allowing them to destroy the tumor cells hiding there.

"After you treat with cyclophosphamide you get this flux of macrophages into the bone marrow, and these macrophages are now active and very capable of consuming the targeted tumor cells," Hemann says. "Essentially we are tricking the immune system to suddenly recognize an entity that it wouldn't typically recognize and aggressively go after antibody-bound tumor cells."

Following treatment with this combination of drugs, the mice survived, tumor-free, for the duration of the study—about 18 months.

Cyclophosphamide is often given to cancer patients as part of frontline chemotherapy. However, the MIT team found that when given in combination with alemtuzumab, it was effective at much lower doses than are typically given, which could help reduce side effects.

They also found that the timing of the drug delivery was critical: The antibody drug and cyclophosphamide have to be given at the same time, so that cyclophosphamide can create the right type of environment for macrophages to become activated in the bone marrow.

The researchers also got good results by combining cyclophosphamide with another antibody drug, rituximab, which is used to treat lymphoma and leukemia. They now plan to test cyclophosphamide with other types of antibody drugs, including those that target breast and prostate tumors. Both of those cancers often metastasize to the bone marrow and are very difficult to treat once they spread.

Pallasch is also planning to begin testing the alemtuzumab-cyclophosphamide combination in lymphoma patients.

"Altering the regimens and the timing of these regimens is quite feasible," Hemann says. "We're talking about more minor modifications in a trial that may have dramatic improvements in overall response."

This story is republished courtesy of MIT News (web.mit.edu/newsoffice/), a popular site that covers news about MIT research, innovation and teaching.

Provided by Massachusetts Institute of Technology