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Scientists find new way to attack cancerous cells

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Scripps Research Institute scientists have discovered a new way to target and destroy a type of cancerous cell. The findings may lead to the development of new therapies to treat lymphomas, leukemias, and related cancers.

The study, which appears in the June 10, 2010 edition of the journal *Blood,* showed in animal models the new technique was successful in drastically reducing B cell lymphoma, a cancer of immune molecules called B cells.

"[The method] worked immediately," said Scripps Research Professor James Paulson, who led the research. "We are very interested in moving this technology forward to see if it would be applicable to treatment of humans and to investigate other applications for this kind of targeting."

A Sweet Spot

In his research program at Scripps Research, Paulson has studied glycoproteins, which are proteins decorated with sugars, for many years. While these molecules have traditionally proven challenging to understand, limiting their pharmaceutical applications, Paulson has pioneered new techniques to study and manipulate these enigmatic molecules.

In the new research, Paulson and his colleagues applied some of the lab's

insights to a problem with great medical relevance—finding a new way to target and destroy cancer cells.

Specifically, in the new study the team set out to attack B cell lymphoma (which includes Hodgkin lymphoma and non-Hodgkin lymphoma), a type of cancer diagnosed most frequently in older individuals and those with compromised immune systems. Each year approximately 70,000 people are diagnosed with B cell lymphomas in the United States alone, according to the American Cancer Society. While the drug rituximab is often effective at treating the disease, each year 22,000 patients still die from B cell malignancies.

Normally, B cells provide an important immune function circulating throughout the bloodstream to help in the attack of infectious agents. But when B cells become cancerous, the question becomes how to pick them out of the crowd of other molecules in the body to target them for destruction, ideally without affecting surrounding tissues.

Because of his previous research, Paulson knew that B cells had a unique receptor protein on their surfaces that recognized certain sugars found on glycoproteins. Could the team create a viable potential therapeutic that carried these same sugars to identify and target these cells?

Toward a "Magic Bullet"

Paulson and colleagues decided to try a unique approach to this problem.

The scientists combined two different types of molecules into one, using both new and tried-and-true technology. One part of the potential therapeutic was composed of a specialized sugar (ligand) recognized by the B cell receptor, called CD22, expressed on the surface of B cells. This was attached to the surface of the other portion of the potential therapeutic, a nanoparticle called a "liposome," loaded with a potent

dose of a proven chemotherapy drug.

"The advantage is that we already know a lot about how liposomes act in the body because they are approved drugs," said Paulson. "They have a long circulatory half-life. They are formulated so they are not taken up by the macrophages in the liver. So we just used the same formulation, attached these ligands, and went right into in vivo studies."

The chemotherapy drug chosen was doxorubicin, which is used in the treatment of a wide range of cancers. First identified in the 1950s, doxorubicin was originally isolated from bacteria found in soil samples taken from a 13th-century Italian castle. The team used a nanoparticle formulation of doxorubicin called Doxil, in which the drug is encapsulated inside the liposomal nanoparticle, which Paulson explains protects normal cells from the drug until it reaches the cancer.

Normally Doxil is passively delivered to tumors by exiting leaky tumor vasculature, and the drug slowly leaks out to kill the tumor. But by decorating the nanoparticles with the CD22 ligand, the team made the nanoparticles into a type of Trojan horse that is actively targeted to and taken up by human lymphoma B cells, carrying the drug inside the cell.

In the current research, the team administered their new compound to immune-compromised mice that had been infected with B cell lymphoma cells (Daudi Burkitt type). The team used two different formulations of the molecule, one decorated with two percent ligands, the other with five percent. The mice received only one dose.

The results were remarkable. No mouse in the control group lived to the end of the 100-day trial, but five of the eight mice receiving the higher ligand dose of the compound survived.

The scientists then looked to see if they could detect any residual tumor

cells in the survivors, knowing that in a mouse that is paralyzed by the disease 95 percent of the cells in the bone marrow are tumor cells.

"When we looked at the bone marrow of those that had survived to 100 days, we couldn't detect any [tumor cells]," said Paulson. "Our detection limit was down to 0.3 percent. It was pretty impressive."

To extend the results, the scientists examined their compound's activity in blood samples from human patients with three types of B cell lymphomas—hairy cell leukemia, marginal zone lymphoma, and chronic lymphocytic leukemia. The scientists found that the compound also effectively bound to and destroyed these diseased B cells.

Encouraged by the results, the team is now working to further improve the drug platform, looking for ways to increase the specificity of B cell targeting as well as exploring the technology's use with other chemotherapy agents.

More information: bloodjournal.hematologylibrary … ood-2009-12-257386v1

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