Unexpected Twist: Using an Autoimmune Disease to Fight Cancer

Investigator Rapidly Developing Lupus Discovery into Breast and Ovarian Cancer Treatments

It seems fitting that the autoimmune disease lupus is named for wolves because the ferociousness with which lupus antibodies, proteins designed to protect us, can turn against and attack a patient's own immune system can be frightening.

Yet as harmful as these antibodies can be in lupus, their damaging traits found in one disease are actually being harnessed in the laboratory - in an ongoing Women's Health Research at Yale-funded pilot study - to develop new treatments for breast and ovarian cancer.

Dr. Peter M. Glazer, Professor and Chairman of Therapeutic Radiology, Professor of Genetics and a member of Yale Cancer Center, recently made the astonishing discovery that one type of these lupus antibodies, called 3E10, can kill cancer cells.

It does so by blocking the cancer cell's DNA-repair mechanism (a mechanism found in every cell to maintain its integrity) and thus shuts the cell down. Lupus patients, unlike those without this disease, create antibodies that penetrate and harm their own cells and DNA (deoxyribonucleic acid), the inherited blueprints for building and operating cells throughout the body. These very cell-penetrating, DNA-targeting capacities are what make 3E10 valuable for cancer treatment.

The tumor-killing power of 3E10, according to Glazer, is even greater when this antibody is combined with cancer chemotherapy drugs such as cisplatin or doxorubicin, or radiation therapy.

Why focus on cancers associated with the BRCA1/2 mutations?

These laboratory findings offer what Glazer considers a direct path to clinical use because many breast and ovarian cancer cells already have a defect in DNA repair, including cancer cells with inherited mutations in BRCA1 and BRCA2 genes. His laboratory work shows that 3E10 antibody used alone or when combined with traditional cancer treatments can have tremendous “killing power” against these cancer cells with BRCA mutations, he said.

These findings gained attention when the discovery by Glazer and his colleagues was announced in October in Science Translational Medicine, an interdisciplinary journal published jointly by the American Association for the Advancement of Science and Science magazine. This publication is at the forefront of reinventing translational medicine to speed the translation of new scientific knowledge into effective health measures.
Glazer received his WHRY Pilot Project Program grant in 2012. It was funded through our collaboration with the Yale Comprehensive Cancer Center to determine, in mice and in cancer cells in the laboratory, which combinations of 3E10 and chemotherapy drugs would be most effective at destroying breast cancer and ovarian cancer cells involving the BRCA gene mutations; thus beginning the development of the antibody into cancer therapy.

In the general population, about 12 percent of women (120 out of 1,000) can expect to be diagnosed with breast cancer in their lifetime, compared with about 60 percent of women (600 out of 1,000) who have inherited a BRCA1 or BRCA2 mutation, according to National Cancer Institute estimates. The NCI lifetime estimates for ovarian cancer among women in the general population indicate that 1.4 percent (14 out of 1,000) can expect to be diagnosed with ovarian cancer, compared with 15 to 40 percent (between 150 and 400 out of 1,000) who have inherited BRCA1 or BRCA2 mutations.

Given these increased risks and the fact that breast and ovarian cancers involving BRCA mutations account for sizable populations of women who undergo cancer treatment, Glazer’s discovery and his ongoing pilot research represent fundamentally important developments in dealing with these diseases.

Phase I clinical trials to test the antibody and combinations of the antibody with drugs in volunteer patients are planned within about two years, a fairly expeditious schedule for such human drug trials.

The Science of Discovery

The way Glazer’s serendipitous discovery came about proves the old adage that one person’s poison can be another’s treasure, and demonstrates the value of following research data wherever it leads.

Before the unexpected finding that 3E10 can destroy cancer cells, Glazer and his colleagues had been trying to develop 3E10 as a vehicle for delivering drugs that can protect healthy cells from radiation treatment for cancer or to enhance the effect of radiation against cancer cells. They chose 3E10 as the potential drug-delivery vehicle because it has the capacity to penetrate cells and had been effectively proven safe in humans when tested as a possible lupus vaccine.

Richard H. Weisbart, M.D., a scientist at the University of California at Los Angeles, had isolated the 3E10 antibody from a mouse model of lupus in 1990. The idea then was to create a vaccine that could be given to patients with lupus. UCLA scientists also found that the 3E10 antibody could penetrate cells, making it a good candidate for delivering medication into cells to treat various diseases.

Building on the UCLA findings, scientists at the University Hospital of Lausanne, Switzerland, in 1999 tested the 3E10 antibody as a vaccine in patients with systemic lupus erythematosus, development of a vaccine, citing competing priorities.
With the 3E10 antibody cast aside as a possible lupus vaccine, Glazer and his laboratory colleagues set out to use this antibody as their delivery vehicle for enhancing cancer therapy, starting with breast cancer. One of Glazer’s laboratory scientists, James E. Hansen, M.D., Assistant Professor of Therapeutic Radiology, had worked with the UCLA scientists and came to Yale’s residency program after earning his medical degree. He was doing clinical training in radiation oncology, and as part of his residency he chose to conduct research in Glazer’s laboratory. He was working with Glazer on developing 3E10 as the delivery vehicle for certain proteins, or cell building blocks, that can protect cells from radiation damage during cancer treatment.

“The serendipity came when we tested the effect of the antibody alone on how cells reacted to the radiation,” Glazer said. “Surprisingly, we found that cancer cells treated with the antibody – alone – were more vulnerable to the effects of radiation.”

They stared at the data for quite awhile and thought something in the laboratory had to have been done incorrectly, or the data itself had to be wrong. “It certainly wasn’t what we were looking for,” Glazer said, recalling that he finally realized the data were correct and told Hansen, “I think you have a new project now.”

As a medical researcher, Glazer said, “you live for these moments.”

And that is where Women’s Health Research at Yale’s support enters the picture, enabling the important laboratory work to move this antibody from discovery toward treatment.

Glazer said it is unlikely that the antibody will cause unexpected toxicity in patients, given the testing in Switzerland. But he will still need to follow a painstaking process to create a therapy that will pass muster in U.S. Food and Drug Administration toxicology testing. And he still needs to find a biotechnology or pharmaceutical firm as a drug-development partner.

Since graduating from Harvard College in 1979, and coming to Yale for a combined M.D./Ph.D. program, Glazer has always kept one foot in medical research and the other in clinical practice. The excitement of discovery and the satisfaction of developing a discovery to improve the lives of his patients make laboratory work meaningful, he said.

“It gives you an extra sense that what you are doing is worthwhile,” Glazer said. “This (3E10 antibody) could be the first thing to come out of my lab that could be given to a patient for treatment.”

Terminology and Definitions
**Antibody:** Specialized protein (immunoglobulin) produced by the immune system because of the introduction of an invading substance. The antibody combines with the invader to destroy it.

**Systemic lupus erythematosus:** Autoimmune disease commonly known as lupus, or SLE. Women account for 90 percent of cases. Instead of producing antibodies to attack invading substances (viruses, bacteria), the immune system creates autoantibodies that attack the immune system itself.

**3E10 Antibody:** Autoantibody created by the immune system in lupus. Dr. Glazer discovered that 3E10 can destroy cancer cells, a capacity enhanced when 3E10 is combined with cancer therapies.

**DNA:** Deoxyribonucleic acid - the carrier of our inherited genetic material, determining the makeup of all cells. DNA molecule includes two strands of nucleotides linked together in a structure resembling a ladder twisted in a spiral – the double helix.

**BRCA1 and BRCA2:** Human genes belonging to a class known as tumor suppressors. A woman’s risk of developing breast and/or ovarian cancer is greatly increased if she inherits particular BRCA1 or BRCA2 mutations. These inherited mutations also increase risk of breast cancer recurrence. Genetic tests are available to check for these mutations, and genetic counseling is recommended before and after testing.