New Anticancer Strategy Targets Gene

Scientists report encouraging results in the first attempt to stop tumor growth in humans by blocking the activity of a cancer-promoting gene. The new research holds out hope that clinicians may one day use this technique to halt the progression of breast and ovarian cancers.

"This is a very exciting time for us," says study leader Dennis J. Slamon of the University of California, Los Angeles, School of Medicine. "We finally have a good chance of developing an entirely new treatment against malignant forms of these cancers." Slamon's team described the work May 22 at the annual meeting of the American Association for Cancer Research (AACR), held in San Diego.

The researchers focused on the HER-2/neu gene, believed to play a role in turning slow-growing breast and ovarian tumors into fast-growing, aggressive malignancies. HER-2/neu is a normal gene that codes for the production of a protein receptor on the surface of breast and ovarian cells. When a substance called growth factor binds to that receptor, the cells start to divide.

By itself, HER-2/neu does not appear to cause cancer. Scientists believe cancer arises when damage to the cell somehow produces multiple copies of the gene, which then direct the cell to churn out lots of these receptors. The already abnormal breast and ovarian cells are thus blanketed with receptors for growth factor and start to proliferate rapidly.

In one study, Slamon's team inserted multiple copies of HER-2/neu into abnormal — but not yet cancerous — human breast and ovarian cells. The researchers discovered that this caused the cells to divide furiously, forming malignant tumors when injected into mice. In contrast, normal human breast and ovarian cells seemed unaffected by the inserted gene.

Next, the investigators wanted to see if they could block the receptor for the growth factor and thus prevent cancer's out-of-control proliferation in humans. They turned to a mouse-derived monoclonal antibody that binds with the receptor.

Slamon's group gave a single monoclonal antibody treatment to 10 women with breast cancer and 10 with ovarian cancer. Upon entering the study, these women had more than the usual number of HER-2/neu genes in their breast or ovarian cells and had not benefited from therapy with standard anticancer drugs, Slamon says. Approximately one-third of all women with ovarian or breast cancer have multiple copies of HER-2/neu, he says.

Although not designed to test the efficacy of the experimental treatment, the study revealed that the antibody found its receptor target. This hints that the treatment will block cell division, staving off cancer's advance, Slamon says. Its usefulness is limited, however, because more than one treatment with the mouse-derived antibody could trigger an immune response, he says. The researchers found no side effects associated with the treatment.

This week, they plan to start a trial using a human-derived monoclonal antibody, which Slamon believes is unlikely to provoke an immune reaction. Twenty women with breast cancer and another 20 with ovarian cancer will receive repeated injections of the antibody, he says. Both the mouse and human antibodies are manufactured by Genentech, Inc., of South San Francisco.

"The new approach shows great promise," says AACR President Harold L. Moses, a cancer researcher at Vanderbilt University in Nashville, Tenn. Slamon, however, cautions that he and his coworkers have a long way to go before they prove the treatment's ability to halt breast or ovarian cancer.

— K.A. Fackelmann

Gene therapy: Brain cancer yes, AIDS no

Brain cancer patients will soon join the small but growing number of people with dire diseases who may receive experimental treatment with gene therapy, according to a decision made this week by a panel of experts advising the National Institutes of Health. But the panel declined to approve a proposed gene therapy experiment involving AIDS patients until researchers can demonstrate the safety of the approach in animal tests.

The NIH Recombinant DNA Advisory Committee voted to allow a group led by Edward H. Oldfield of the National Institute of Neurological Disorders and Stroke to insert a "suicide" gene into the tumors of three patients with brain cancer. The researchers, who must also win approval from the Food and Drug Administration, expect the genes to render the tumors more vulnerable to chemotherapy.

Oldfield and his colleagues plan to use needles to inject mouse cells infected with genetically engineered viruses directly into the patients' brain tumors. The viruses will contain a gene from a herpes simplex virus that makes them susceptible to the antiviral drug ganciclovir. The researchers anticipate that the infected mouse cells will spread the engineered virus to the growing tumors, allowing subsequent ganciclovir treatment to kill the cancerous cells. On the basis of results from animal studies, they predict that the treatment will not affect healthy brain tissue, because the viruses can only infect dividing cells. Normal brain cells do not usually divide after birth.

Earlier this year, the NIH committee approved a more limited use of the suicide gene to treat ovarian cancer. This experiment, first proposed last summer (SN: 8/3/91, p.69), does not employ cells infected with live viruses. Instead, it relies on genetically engineered cells to transfer the gene to cancerous cells in a process that is not well understood.

During this week's meeting, the committee voted to defer consideration of a proposal to inject AIDS patients with genetically engineered white blood cells that might help combat HIV, the AIDS-causing virus. In the proposal, a team led by Clay Smith of the Memorial Sloan-Kettering Cancer Center in New York City sought approval to restore AIDS patients' depleted white blood cells with similar cells resistant to HIV infection.

Smith's group proposed to insert extra copies of a single HIV gene into white blood cells taken from the healthy twins of 15 AIDS patients and then to infuse these cells into the patients. During HIV infection, this gene, called TAR, must bind to a specific protein in order for HIV to reproduce all of its genes and multiply. The researchers hoped to flood the newly transplanted cells with superfluous TAR genes as a means to sop up all of these proteins and prevent HIV from infecting the new cells.

Smith and his colleagues have shown that this strategy slows the infection of white blood cells in culture dishes. But because the treatment could theoretically induce cancers or cause HIV to spread more rapidly, the committee refused to approve the proposal until the group confirms the safety and efficacy of the approach in animals.

In February, the committee approved the first gene therapy experiment for AIDS patients. It involves infusing patients with white blood cells containing a marker gene to determine whether the cells survive long enough to fight HIV.

— C. Ezzell