Promising Immunotherapy Technique

By Mike Fillon

In a study in the March 2012 *Nature Medicine*, researchers described a new immunotherapeutic technique that can “teach” immune system killer cells, known as CD8 T cells, and their antigen-presenting instructor cells, to destroy cancer cells. Just as important, the newly trained cells remain vigilant in case the cancer returns.

According to José A. Guevara-Patino, M.D., Ph.D., associate professor in the Oncology Institute of Loyola University Chicago Stritch School of Medicine, and coauthor of the study, “These findings may be useful in T cell–based vaccine design and adoptive T-cell therapy, where potent effector and memory formation are vital for successful eradication of acute and recurrent disease.”

Although the immune system can eliminate some cancerous cells, it does not always recognize them as “foreign.” Also, cancer may develop when the immune system breaks down or does not function adequately. Researchers are developing immunotherapeutic techniques to repair, stimulate, or enhance the immune system’s responses to cancer and other debilitating diseases.

Guevara-Patino said that in addition to getting instructions from the antigen-presenting cells, CD8 T cells need assistance from helper T cells to become effective killers. Under “normal” conditions, DNA directs helper T cells to overproduce a specific protein that unleashes the killer T cells’ lethal properties. However, these cells are typically repressed in patients with cancer or HIV.

Especially in cancer patients, one of a tumor’s menacing properties is its ability to prevent killer T cells from eliminating tumors by putting helper T cells into a suppressed stage, limiting their ability to assist CD8 T cells. According to the researchers, this new technique jump-started defective immune systems in immunocompromised mice and in human killer T cells taken from HIV patients. Guevara-Patino said a clinical trial in cancer patients could begin in about 3 years.

Boosting the Immune System

In the study, a device called a gene gun delivered snippets of DNA into skin instructor cells. The DNA directed the instructor cells to produce specific proteins, which act like molecular keys. When CD8 T cells interact with the instructor cells, the keys unlock the CD8 T cells’ killer properties, jump-starting them to seek out and kill pathogens and cancer cells.

With this technique, the killer T cells would not need helper T cells, said Guevara-Patino. So even if a tumor were to suppress the helper T cells, the killer T cells could still kill cancer cells.

Jeffrey S. Miller, M.D., deputy director of the Masonic Cancer Center and associate director of experimental therapeutics at the University of Minnesota, Minneapolis, said the study explains a small piece of subspecialized information about how the immune system works and adds it to the bigger picture. “Understanding all of these little things is very important, because we’re never going to completely figure out how to manipulate cell therapy for cancer and infectious-disease control until we can fill in the entire puzzle.”

Solving the Puzzle

Unlike the external forces commonly used to treat cancer—surgery, radiation, and chemotherapy—immunotherapy takes advantage of the body’s own immune recognition of cancer cells as foreign. Immunotherapies being researched include interferons, interleukins, colony-stimulating factors, monoclonal antibodies, vaccines, gene therapy, and nonspecific immunomodulating agents.

Steven A. Rosenberg, M.D., head of the Tumor Immunology Section and chief of surgery at the National Cancer Institute, has been studying immunotherapy for 35 years. He pioneered the development of gene therapy and was the first to insert foreign genes into humans and to conduct clinical studies of the gene therapy of cancer. He said immunotherapy can be divided into three main branches:

1. Nonspecific stimulation of the immune system. “The hope here is if you ‘rev up’ the immune system, it will attack the cancer,” said Rosenberg. To date, interleukin 2 (IL-2) has effectively treated patients with melanoma and kidney cancer but not other kinds of cancers. Also, ipilimumab (Yervoy) is used to treat melanoma.
2. Active immunotherapy (vaccines). Cancer vaccines are attractive because they are less toxic than chemotherapy and small-molecule targeted therapies, and they may have a lasting effect. Early results for vaccine effectiveness have been mixed, for several reasons. The U.S. Food and Drug Administration approved the Sipuleucel-T vaccine to treat metastatic prostate cancer. Also, a gp100 vaccine for melanoma and an anti-Id vaccine for follicular lymphoma succeeded in phase III trials, and phase III trials are evaluating others, including the Prostvac vaccine for prostate cancer and Stimuvax and Lucinix for non–small-cell lung cancer. Rosenberg and colleagues have cloned the genes encoding cancer-regression antigens and have used these to develop cancer vaccines to treat patients with metastatic melanoma.

3. Adoptive, or cell transfer, immunotherapy. With this technique, immune cells that can react against cancer are isolated, “grown and educated” to recognize and destroy cancer, and then “adopted” by patients. The aforementioned study using CD8 T cells uses this method. “Even though it is more labor intensive, adoptive therapy provides a little more control and could prove to be the most effective technique,” said Cassian Yee, M.D., from the Clinical Research Division at the Fred Hutchinson Cancer Research Center in Seattle. In the Aug. 2, 2011, issue of Nature Reviews Clinical Oncology, Rosenberg reported on a pilot trial that found that cancer immunotherapy using the adoptive transfer of autologous tumor-infiltrating lymphocytes resulted in objective cancer regression in 49%–72% of patients with metastatic melanoma.

Rosenberg said one of the greatest appeals of adoptive immunotherapy is that it should lead to truly personalized medicine. “By growing a patient’s own cells for therapy, we end up with a new individualized drug for each patient,” he said. “People like the idea that they can use the body’s own defenses to fight a disease rather than the more debilitating toxic approaches.”

Miller’s laboratory is focused on preclinical and clinical studies to develop effective antitumor immunotherapies. His early studies focused on nonspecific immune stimulation using subcutaneous IL-2. “Strong evidence suggests that this nonspecific therapy alone will be ineffective, and current efforts aim to target effectors specifically to tumor cells.” For natural killer (NK) cells, approaches include combined therapy with monoclonal antibodies and IL-2 to target therapy through antibody-dependent cytotoxicity.

Another major research focus by Miller is NK cell development. Receptors on NK cells have been identified that recognize class I MHC (major histocompatibility complex) molecules. Miller said the hypothesis underlying current research efforts is that “self” MHC molecules influence the NK cell receptor repertoire during development. These NK cell receptors may also play a physiologic role in cancer. “Laboratory evaluation and human clinical trials will test the hypothesis that a mismatch between NK receptor and class I alleles on recipient tumor will result in greater tumor kill,” said Miller. Clinical trials using allogeneic NK cells in acute leukemia and breast cancer are under way.

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Empowering the Body After Breast Surgery

By Kristine Crane

Alice no longer has to wear a sports bra. “My breasts don’t move,” said the breast cancer survivor, who had a double mastectomy and reconstructive surgery 2 years ago. Laughing, she explained, “My belly moves, but my breasts are like steel.”

Breasts of steel may be “one of the humorous parts” of an otherwise very emotional process, said Alice. But recreating the depleted muscles around the chest—from the abs to the shoulders—is an often-overlooked challenge for breast cancer patients who undergo surgery. Studies show that surgery patients often experience shoulder morbidity and pain associated with muscle loss.

Alice had been working out regularly with a trainer for a few years before her diagnosis, so she was fit when she had surgery. But afterward, she couldn’t pull weeds from the garden or pick up groceries. Many breast cancer survivors experience similar frustrations. Although surgery—whether it’s a lumpectomy, mastectomy, or reconstructive surgery—is usually the hardest part, the aftermath often leaves patients with bodies in need of rebuilding. And though a lumpectomy does conserve the breast tissue and surrounding muscle, it may involve removing the axillary nodes in the upper breast and armpit regions, which may affect range of motion and mobility.