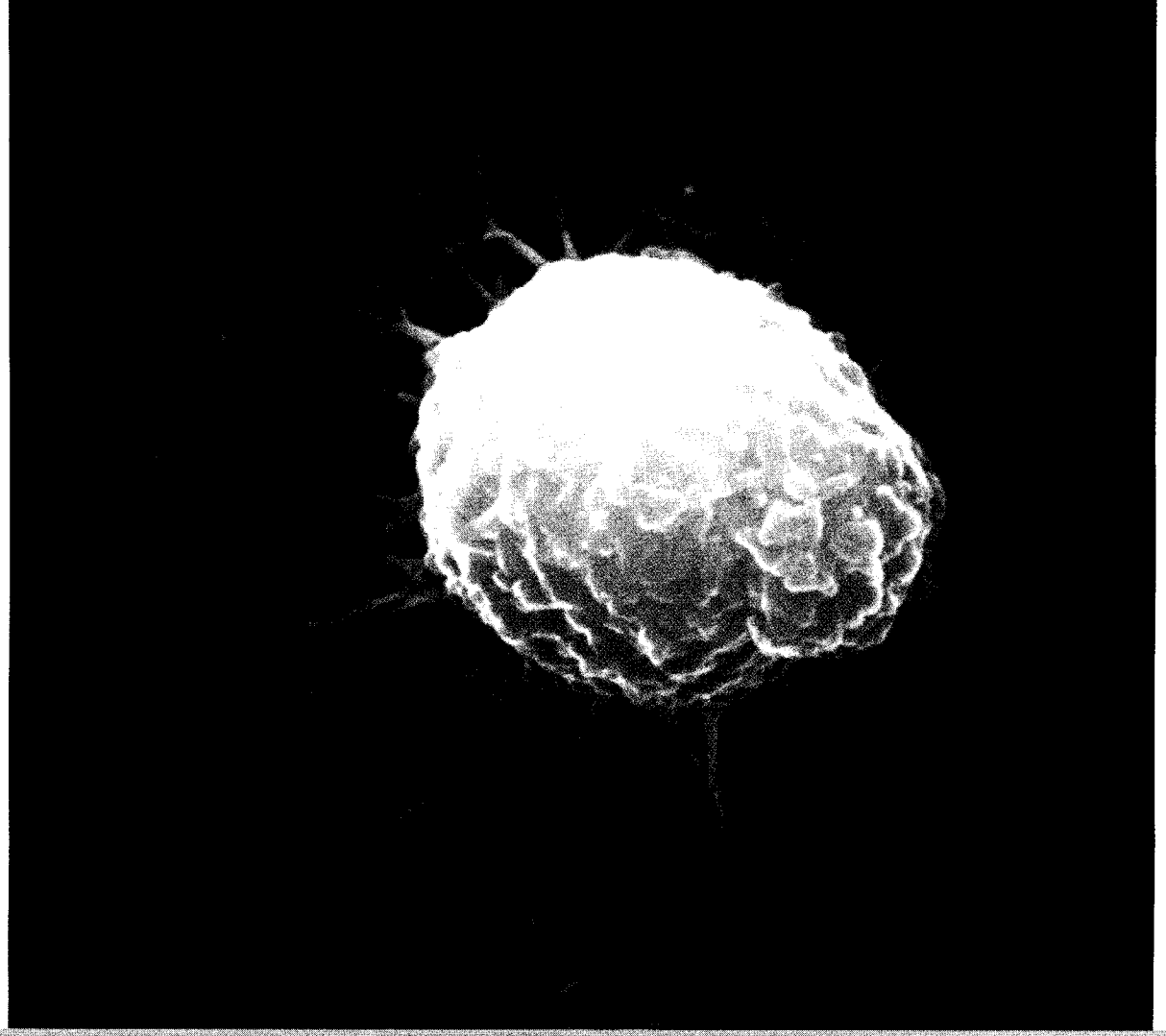

THE HEALER WITHIN

How scientists are training the body's immune system to treat (and prevent) breast cancer

by Pamela Weintraub

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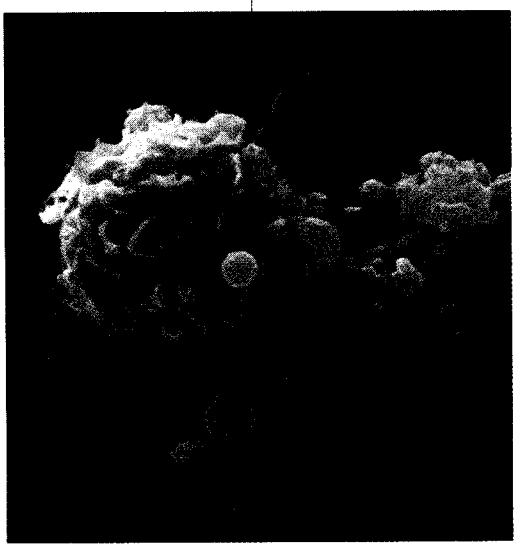
Scientists have long dreamed of preventing or curing cancer by tapping the same power of immunity used to vaccinate against viral and bacterial infections such as polio and smallpox. Today a series of sophisticated, customized vaccines in various stages of development stand poised to activate the healer within. Several of these experimental vaccines are being developed for breast cancer and although it may take several years for them to be studied in the group they can help most—those in the earlier stages of the disease—immune therapy could ultimately make a big difference to the millions of women who do not respond sufficiently to the chemo and radiation therapies currently available.



T cells (opposite and above) fight off intruders, known as antigens.

Once developed, the vaccines could be used in a variety of ways. According to University of Pittsburgh Cancer Institute (UPCI) oncologist Joseph Baar, M.D., who is creating a breast cancer vaccine, they could serve three separate purposes: (1) as a preventive measure for those at high risk of cancer; (2) as a barrier to relapse or recurrence in those with treated cancer; and (3) as a tool used in combination with radiation and chemotherapy to eradicate cancers still actively growing and metastasizing.

"We finally have the tools to create and manage these vaccines," says oncologist Leisha A. Emens, M.D., of The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, who is currently researching ways to combine breast cancer vaccination with other treatments. "We are learning how traditional therapies affect immunity and can now design clinical trials that combine vaccines with standard cancer drugs in effective ways."

The Initial Steps

One of the first hints that the immune system could be used to attack cancer just as it attacks infections came more than a century ago, when New York surgeon William B. Coley realized cancer patients with acute bacterial infections sometimes experienced regression of tumors. Convinced that the remissions were related to the infections, Coley took an intuitive leap, injecting live bacteria into patients with inoperable cancer. Some of the patients recovered. While tumors often disappeared, bacterial therapy had problems, not least of which were severe infections, since this was before the age of antibiotics. Radiation and chemotherapy became the treatments of choice.

The resarchers in the fight against cancer never forgot Coley's prescient findings, which were eventually explained in the context of the immune response. Bacterial infection stimulated the immune system, which made antibodies and a host of other toxins against the infection. In the course of its effort to cure the infection, the immune system eradicated the tumors, too.

The Challenge of Cancer and Immunity

Yet turning the immune system against cancers, while tantalizing, remained elusive. One reason is a remarkable molecular identity system that evolution designed to help us destroy microbial invaders without also destroying ourselves. The protective mechanism confers each individual with a unique designer brand label of sorts worn on the surface of cells. Called human

leukocyte antigens (HLA), these special proteins mark our own cells in a pattern clearly distinct from those of anyone else's. When our immune system dispatches its troops to repel invaders, HLA proteins signal them away from our body's own cells. Cancer cells, though mutants, are still self-cells and each one is labeled with HLA, just like any healthy cell from the liver to the eye.

Because of cancer's ability to masquerade as ordinary "self" cells, scientists realized the best approach to stimulating an immune response would be with a vaccine. Typically, a vaccine is made of disabled components of an infection, sometimes just a single molecule that identifies the microbe. Because the vaccines don't contain living infection, they don't give recipients the disease, but they still provoke the immune system to make antibodies against the injected foreign proteins. When a person is then exposed to real infection, the antibodies, already standing guard, mount a swift attack, preventing the infection from taking root.

What if, instead of injecting patients with a disabled virus as, say, Jonas Salk had done with polio, researchers could inject them with targeted parts of tumor cells? What if the HLA radar could somehow detect these tumor vaccines, so that the immune system would notice them and respond as if they were germs? With the right priming, the body's frontline troops of immunity—"B cells," which produce antibodies that target specific antigens, and "T cells," some of which destroy invaders with toxins—might be formidable weapons not just against microbes, but cancers, too.

The Language of Immunity

Antibody: Produced by the immune system in response to the presence of a virus, bacterium or other foreign substance. Antibodies bind to the substance, signaling other immune cells to attack and destroy it.

Antigen: A foreign substance (virus, bacterium, fungus) that enters the body and initiates an immune response.

B cell: White blood cells that produce antibodies.

Dendritic cell: A white blood cell that patrols the body and helps B and T cells recognize antigens.

HLA (human leukocyte antigens): Molecules located on the surface of each individual's cells that mark them as belonging to that person. They're called antigens because if your cells wind up in someone else (as in a kidney transplant), they will trigger an immune response in that person.

Monoclonal antibody: An antibody produced in a laboratory from a single clone of cells. Monoclonal antibodies can be used to deliver drugs, toxins or radioactive material directly to cancer cells.

T cell: White blood cells that attack and kill antigens.

The Antibody Approach

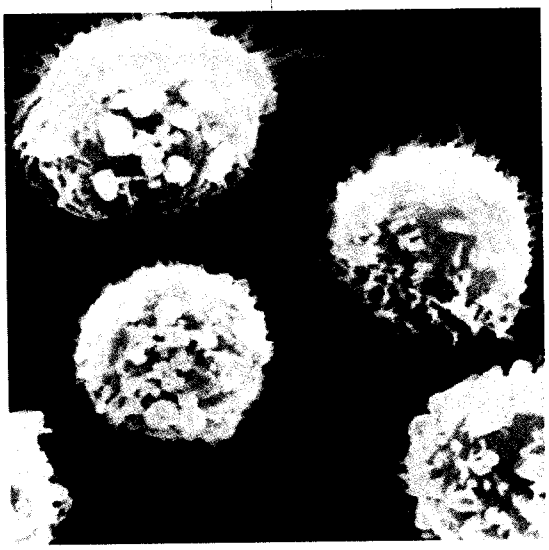
In breast cancer treatment, the first successful effort to emulate even part of what the immune system does was made when researchers discovered that about a quarter of patients with breast cancer had extra copies of the HER2 gene, which makes protein receptors that control the growth and division of cells. Women who produce too much (overexpress) HER2 can develop breast cancers that grow especially fast. The immune-based treatment of choice for these aggressive breast cancers is Herceptin (trastuzumab), a "monoclonal antibody" designed to target HER2 receptors just like natural antibodies produced by the immune system target parts of a microbe. Attaching to the HER2 receptors, Herceptin not only inhibits cell growth, but also signals the body's immune system, through "natural killer" (NK) cells, to get into the act. The NK cells bind to Herceptin and then kill the tumor cells.

Herceptin, of course, is not a vaccine, but an antibody. True vaccines would go a step further by injecting tumor cells into the body, stimulating the immune system to respond against them by making anti-

bodies. The tumor antibodies thus induced would attack the tumor just like polio antibodies attack polio. In the best-case scenario, the vaccine would "train" the immune system itself to create the perfect defense—T and B cells that target any given cancer cell and deliver natural killer molecules exactly when needed and in the right dose.

Finding the Markers

To develop vaccines that are effective against cancer, researchers need to identify appropriate markers: proteins or other molecules that are common enough in breast tumors (but not other tissue) to provoke the immune system to mobilize against the cancer. One such marker, the carbohydrate "Sialyl Tn (STn)," which is found on the surface of breast and other cancer cells, is now being tested in a new vaccine called Theratope. Under development by the Canadian company Biomira Inc., Theratope is composed of a synthetic mimic of the STn marker that is known to stimulate the immune system. In a series of clinical trials, researchers measured how successfully Theratope provoked an immune response against STn and whether this response had therapeutic value. So far the results have shown some promise. Results from the most recent phase III trials for women with metastatic breast cancer, announced in 2003, indicated a survival advantage in the subset of patients who received not just vaccination following chemotherapy, but hormonal treatment, too; vaccinated patients survived 36.5 months compared to 30.7 months for controls.



B cells secrete antibodies to disarm invaders and alert T cells.

Another vaccine entering clinical trials is based on the protein mammaglobin-A, found in high levels in 80 percent of breast cancers. Tim Fleming, Ph.D., research associate professor at Washington University School of Medicine and the Siteman Cancer Center in St. Louis, who helped discover the protein, says it is more common in breast tumors than the markers HER2 or STn are, suggesting the potential for broader use. The scientists hypothesize that the vaccine will stimulate T cells to recognize mammaglobin-A as a foreign antigen, ultimately destroying any cell where it is found, including breast cancers. At press time, the vaccine has been scheduled to be tested in a phase I clinical trial.

Tricking Cells

But just finding an appropriate target is not enough. Scientists also need to teach the immune system to recognize and destroy cancer cells as if they were living pathogens and not the body's own healthy cells. Joseph Baar of UPCI, for example, is producing a custom-designed vaccine for each breast cancer patient using cells from her own tumor in combination with bacterial components to "trick" the white blood cells, known as dendritic cells, into thinking they are being invaded by foreign elements. This trickery is intended to make dendritic cells more efficient at activating the immune system against the tumor.

According to Baar, dendritic cells are the patrol officers of the immune system, constantly roaming the byways of the body looking for invaders to "bust." When dendritic cells discover a rogue virus or bacterium, they literally engulf it and break it into pieces, presenting it to the T and B cells, which learn its molecular contours and then go back out to

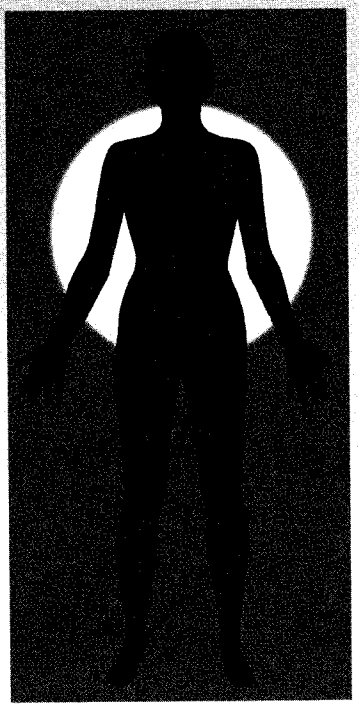
Decoding Immunity

Why do mutated (cancer) cells that develop in our bodies grow and even travel to other parts of the body without causing our immune system to respond?

Think about it: If you are infected with a bacterial or viral infection, your immune system charges into action, sending T cells—i.e., killer cells—to track down and destroy the invaders (antigens). The presence of an invader also activates the immune system's B cells, which don't attack the cells directly, but transform themselves into plasma cells and secrete millions of antibodies per second. The sheer number of antibodies often overwhelms the antigen.

But if the invader comes from within our own bodies, like cancer cells, it's very different.The mutated cells may grow into cancerous tumors unencumbered by an immune response. It's as if cancer cells have a protective coating on them that renders them invisible to T cells and B cells and the rest of the immune system. This phenomenon has spurred a wealth of scientific research and a specialized area of study called immunotherapy. Eventually, scientists hope that they will learn how to train the immune system to recognize cancer cells as invading cells.

The immune system resembles the circulatory system with an elaborate system of bean-shaped nodes, organs (like the spleen) and vessels running throughout the body. Instead of blood, the lymphatic system carries a clear liquid called lymph, which is composed of white blood cells and plasma, the straw-colored liquid in which blood cells are suspended and which coats body tissues.



For the immune system to protect the body from viruses, bacteria, fungus and other outside threats, it must be able to distinguish foreign cells from the body's own cells. It does this by checking out the cell's ID, a molecular chemical marker known as human leukocyte antigens (HLA), also called "major histocompatibility complex." Almost all the cells in your body, including mutated cancer cells, are labeled with this molecule and it serves as a protective passport that identifies a cell as being a part of the "self." In other words, it belongs to your body and the immune system will recognize it as such and not attack it. But if a cell's ID does not match that of your own cells, an alarm goes off, signaling the immune system to send out its cavalry of T cells, B cells and its "big killers," the macrophages, to defend the body. Only when an infection defeats this defense do we become sick. This can happen when our defense has been compromised, as it is by chemotherapy, or when our resistance (response) is inadequate, as it may be if we are stressed out.

The stronger our immune system response, the more likely we will be able to ward off invasions. When a bacteria or virus or other antigen has been defeated once, it becomes even more difficult for it to survive in our systems a second time. That's because our immune systems are sophisticated enough to remember previous invaders. Special cells called "memory" T cells and B cells store the signature of each antigen, and if one should invade the body again, the T and B memory cells recognize it immediately and launch an accelerated attack.

ILLUSTRATION: STEPHANIE PHELAN

seek and destroy matching cells. Since cancer cells are self-cells, marked with HLA, T cells on the prowl simply bypass them.

But Baar has been able to alter the equation in experiments with mice by culturing dendritic cells in the lab with tumor cells and bacterial particles. Once the dendritic cells have ingested the tumor cells, they process the tumor cell's molecular identity system in a much more efficient manner. In fact, the dendritic cells act as though an infectious agent has invaded them. When these tumor-fed dendritic cells are then injected back into the mouse, they signal the killer T cells to recognize the tumor cell contents as foreign. When the killer T cells are thus primed, they seek and kill tumor cells. Using his unique vaccine system, Baar has been able to destroy the tumors in virtually all of his mice. Human trials are scheduled to start soon.

The dance of immunity: A slender dendritic cell attaches to a T cell.

Unless intended purely for prevention, cancer vaccines will generally be used in combination with other treatments. At Johns Hopkins, researchers are studying the use of "educated" T cells to treat the blood cancer multiple myeloma, in which plasma cells—a type of white blood cell—grow out of control and produce tumors in the bone marrow. Comparing the cancer-fighting abilities of T cells taken from a patient's bone marrow versus those taken from the blood, the researchers have found that—after activating the T cells by exposing them to pieces of tumor in the lab—the T cells taken from bone marrow are able to stop the growth of myeloma almost 10 times as effectively as those taken from the blood. The next step is to determine if what works in the test tube will also work in patients. Ivan Borrello, M.D., who is leading the research, says the addition of a vaccine may increase the ability of these T cells to fight cancer.

Evidence from other research groups indicates that breast cancer patients also have T cells in their bone marrow specific to their tumors. The hope is that breast cancer patients may benefit from this type of immune therapy as well.

Outwitting Tumors

Before any vaccines make it to the therapeutic setting, a number of hurdles will have to be overcome. Even after scientists circumvent the HLA identity system, they will still have to address the immune system's tendency to ignore the presence of cancer. Indeed, part of a tumor's survival strategy is to create a host of molecules that slow the immune response. The larger the tumor, the more suppressors it spews. One way around the problem, says Johns Hopkins' Leisha Emens, may be to shrink the tumor as much as possible with standard therapies, then treat it with a cancer vaccine. However, the best solution could be vaccine helpers that actively boost the immune system and turn off immune suppressors while the vaccine does its job. Emens has helped find that the two chemotherapy treatments—cyclophosphamide and doxorubicin—when used in low doses, can enhance immunity and activate the vaccine.

"As a result of advances in cancer immunobiology, we now find ourselves at the threshold of a novel, exciting and, we hope, rewarding approach to the treatment of cancer," says Baar. But tweaking the details, from deciding on the ideal patient to finding the best partner therapies, will take some time.