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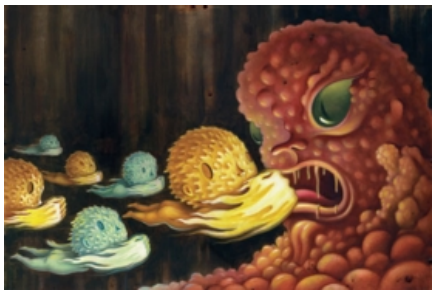
Health » Scientific American Volume 310, Issue 5 » Features

New Drugs Free the Immune System to Fight Cancer

By releasing the brakes that tumor cells place on the immune system, researchers are developing a new generation of more powerful treatments against malignancy

May 1, 2014 | By Jedd D. Wolchok |

In June 2004 I was asked to examine a 22-year-old woman who had just graduated from college and was engaged to be married. During the months leading up to her graduation, Shirley (not her real name) had been plagued by a nagging cough. Eventually a computed tomographic (CT) scan revealed multiple masses in and around her lungs. A biopsy indicated metastatic melanoma that had spread from a skin cancer Shirley did not know she had. She immediately began chemotherapy treatments timed around a hastily rescheduled wedding.



Christopher Buzelli

Unfortunately, two rounds of chemotherapy and radiation treatments to her brain over the next two years slowed but could not stop the tumors' spread. Shirley was running out of options. I told her about a new study in which an innovative medicine designed to supercharge a patient's own immune system against cancer was being tested.

It was a randomized trial, meaning not every participant would get the new medicine, at the time known as MDX-010, but Shirley agreed to participate. After four treatments, a new set of CT scans showed that every trace of melanoma had disappeared. To this day, Shirley remains in complete remission; she has two beautiful, healthy children and, in her own words, has “gotten her life back.”

For me, as a cancer specialist and a researcher, seeing Shirley's transformation validated many years of hope that scientists could develop powerful cancer therapies that would work by setting the body's own immune system against malignancies. Optimism grew throughout the medical community last year as we learned about similar successes with this and other immunotherapy treatments in patients with advanced leukemia and kidney and lung cancers. Although immunotherapy is by no means a panacea, the recent advances may allow us to make significantly more progress against the later stages of cancer than we have been able to achieve in recent decades.

Multilayered Defenses

The notion that the immune system could control cancer is not new. Attempts to harness host defenses against malignancy date back over 100 years to when William Coley, a surgeon at New York Cancer Hospital (now Memorial Sloan Kettering Cancer Center), tried using heat-killed bacteria for this purpose. After noticing that some patients seemed to live longer if they developed an infection after their cancer surgery, Coley hypothesized that the intrinsic defense system that had been mobilized against the pathogen could also affect the tumor.

During the ensuing decades, basic scientists have revealed much about the cells that make up this protective system, as well as the chemical mediators and molecular switches that precisely control it. In that time, they have learned how the immune system rapidly mobilizes to detect potentially dangerous infectious pathogens such as bacteria or viruses. Just as important, researchers have detailed the many checks and balances that usually signal the immune system to limit its response so that it does not wind up destroying too much normal tissue in the process. All told, they have gained detailed insights into how the immune system reacts to, and is affected by, cancer.

The first layer of defense against pathogens consists of a general response against bacteria and viruses that is coordinated by white blood cells known as neutrophils and monocytes. These cells belong to what is called the innate immune system, and their function is to recognize certain aspects of molecular anatomy common to all bacteria or viruses—such as parts of their outer coating or quirks in the structure of their DNA and RNA molecules that differ from what is found in higher organisms. Although these white blood cells do not target specific species or proteins for attack, they nonetheless manage to destroy many of the microbiological invaders and, as a result, generate molecular fragments, referred to as antigens, that other players of the immune system perceive as foreign.

Cells responsible for the second layer of defenses, called the adaptive immune system, take these antigens as the starting point for a much more precisely targeted response that, if successful, will create a living memory of the microbial invaders so that they can be more easily defeated in the future. Two different types of cells—T cells and B cells—lie at the heart of this adaptive response. There are various types of T cells, but all descend from precursors that emerge from the thymus gland, a small organ that sits just on top of the heart in the center of the chest. B cells, for their part, are originally derived from the bone marrow and give rise to antibody molecules. Antibodies and certain molecules on T cells home in on specific antigens, thereby allowing the immune system to target and destroy bacteria and infected cells that display these antigens on their surface.

When the immune system is working optimally, both its general and adaptive branches cooperate to identify and rid the body of dangerous pathogens. In addition, a subset of T cells retains a long-term molecular memory of the original threat so that it can be neutralized more quickly at a future date if it is encountered once again.

Cancers are not infections, of course. They arise when the body's own cells undergo certain genetic and other changes. Even so, the immune system ought to be able to recognize malignant cells because they display abnormal molecular fragments, which should look foreign to T and B cells. For various reasons, however, the immune system often fails to fight cancers effectively. Through the years, efforts to pump up the response have met with mixed results. The recent, more consistently successful

approaches take a different tack. It turns out that cancers sometimes co-opt the usual shutoff switches of the immune system and actively dampen immune responses to malignancies. The new approaches attempt to disable those brakes.

Checks and Balances

The experimental medication that saved Shirley's life fits into the new paradigm. It grew out of research into a protein called CTLA-4, which is present in many kinds of T cells but jumps into action only after certain T cells recognize their target and receive a “go” signal from other molecules. When activated, CTLA-4 and a number of other proteins work like a series of molecular brakes or checkpoints that prevent the immune system from becoming overly destructive.

The necessity of these checkpoints can be seen in animals deficient in them. Mice that have been genetically engineered so that they lack the CTLA-4 protein die within three to four weeks of age. With nothing to stop the escalation of the immune response, activated T cells infiltrate all the normal organs in the body, causing their complete destruction. This finding, published in 1995, showed that the permanent lack of this single molecule could cause a devastating autoimmune reaction.

That same year, James Allison, then working at the University of California, Berkeley, hypothesized that if the CTLA-4 molecular brake could be temporarily disabled, the immune system would be able to launch a more vigorous attack on cancer cells, resulting in the shrinkage of tumors. Allison and his colleagues set out to test that hypothesis in mice by delivering a synthetically developed antibody that obstructs CTLA-4 activity.

Sure enough, blocking CTLA-4 resulted in the regression of several types of tumors—including colon cancer and sarcoma—that had been transplanted into the laboratory animals. In other experiments, melanoma tumors shrank considerably when mice were treated with the CTLA-4-blocking antibody and an experimental vaccine, made from altered melanoma cells, that was designed to incite an immune attack specifically against that cancer.

The next step was to try this approach, technically referred to as immunologic checkpoint blockade, in people. Allison turned to the biotechnology company Medarex, which developed a fully human version of a CTLA-4-blocking antibody (originally called MDX-010 and now known as ipilimumab), and began clinical trials in patients who had very advanced cancers that had not responded to other therapies. Medarex was later bought by Bristol-Myers Squibb, which further developed the drug and won regulatory approval for it in 2011.

Starting with the first experiment and continuing with subsequent ones, some patients experienced profound tumor regressions. But before they did, early tests of whether the treatment was working gave curious results. Investigators soon learned that when it comes to immunotherapy, the usual ways of assessing whether a cancer treatment is working could be misleading.

Success Rates

Oncologists can usually tell fairly quickly how well a patient is responding to standard anticancer treatments. We use various imaging techniques—CT, positron-emission tomography or magnetic resonance imaging to measure the size of a tumor immediately before starting treatment and then again about six weeks later. If the malignant growth is appreciably smaller, we can decide to continue treatment

because we know it is having an effect, consider a different approach or stop treatment altogether.

Making such decisions about immunotherapy is not quite as straightforward. For starters, we have to allow more time for the immune system to become activated, so we generally do not take a second measurement of the tumor's size until 12 weeks after treatment has begun. Even considering the additional six weeks of observation and treatment, however, the results of the CTLA-4-blocking experiments were perplexing. Some patients had scans that were clearly better, whereas others showed enlargement of preexisting tumors and even the appearance of new growths. Yet some of the patients with bigger tumors actually felt better.

We now see two plausible explanations for why tumors grow after immunotherapy: the treatment is not working, or a large number of T cells and other immune cells have begun flooding the malignant growth. In other words, bigger tumors might, paradoxically, mean that the treatment is actually working; we just have to wait a little longer for the growths to shrink. Given how difficult it can be to measure progress during immunotherapy, researchers testing ipilimumab now use the simple and important assessment of overall survival (how long patients live) as the most appropriate end point for their analyses.

Results of the latest clinical studies show that just over 20 percent of patients with metastatic melanoma who are treated with ipilimumab demonstrate long-term control of their disease, remaining alive for more than three years since beginning treatment. This is an important fact to note because before the development of modern medicines such as ipilimumab, median life expectancy for metastatic melanoma was seven to eight months. Indeed, some of the earliest recipients, like Shirley, are alive more than five years after treatment.

Meanwhile research has progressed on a second immune system–braking molecule called PD-1, which dots the surface of many T cells. When bound by certain other molecules, PD-1 compels the cells on which it is found to destroy themselves—a normal process that, as with the closely related CTLA-4 protein, helps to bring an ongoing immune reaction to a safe stop. Some tumor cells, however, have evolved to defend themselves by covering their surface with molecules that trick the PD-1 proteins on T cells into starting the self-destruct sequence too soon. As a result, any T cell that attacks a cancer cell receives a signal to destroy itself instead. This striking example is one of the many ways that tumors can render the immune system ineffective.

Half a dozen companies—Bristol-Myers Squibb, CureTech, EMD Serono, Genentech, Merck and MedImmune—have now developed antibodies that block various tumors from inducing PD-1-mediated suicide in T cells. In recent trials, these experimental compounds have shown long periods of remissions, some lasting years, in more than 30 percent of patients with advanced melanoma. Several of my colleagues at Memorial Sloan Kettering and collaborators at many other centers have tried these PD-1-blocking agents in patients with a type of lung cancer. More than 20 percent of participants had durable regressions.

The lung cancer results, which were reported in June 2012, proved to be a turning point for the field of immunotherapy. No longer can skeptical clinicians dismiss the approach as likely to be viable for only a few specific kinds of tumors, such as melanoma and kidney cancer, that have previously been shown to be particularly sensitive to immune treatments. Immunotherapy now appears to work for a broader range of cancers as well. Odds are that this approach will soon join chemotherapy and radiation as a standard treatment for many kinds of tumors.

As with most cancer treatments, these immunotherapies trigger some side effects. Patients receiving anti-CTLA-4 medication, for example, may suffer inflammatory reactions in the skin and large intestine that are caused when immune cells release an overabundance of excitatory chemicals. The resulting rashes and painful bouts of cramps and diarrhea are typically controlled with immunosuppressing steroids such as prednisone. Patients who are given PD-1-blocking therapy may also experience these flare-ups—particularly in the kidneys, lungs and liver—but they are generally less frequent and usually of lower severity compared with those of a CTLA-4 blockade. Fortunately, the use of anti-inflammatory drugs does not seem to dampen the therapeutic effect of either drug on tumors.

Inflammation can lead to greater problems. For a long time, researchers worried that the excitatory cascade could lead to full-blown autoimmune reactions, in which the immune system cannot be stopped from targeting ever larger amounts of normal tissue for destruction. Unlike a true autoimmune disease, however, these inflammatory side effects appear to be transient and do not recur after they are initially treated.

Because antibodies against PD-1 and CTLA-4 seem to boost the immune response to tumors in different ways, it makes sense to

investigate whether concurrent treatment with the drugs can be safe and effective. In 2007 experiments on lab animals with colon cancer and melanoma showed that the combination of CTLA-4 and PD-1 blockade was more effective than using either agent alone. Therefore, in 2010 my group, working together with Mario Sznol of Yale University, decided to undertake a small safety study of ipilimumab and the PD-1-blocking drug nivolumab in 53 patients with metastatic melanoma.

The results, which we reported at a medical conference last year, were impressive. More than 50 percent of patients treated with what we considered to be optimal doses of the antibodies showed tumors shrinking by more than half their original size. These responses appear to be dramatically different from those seen with either agent by itself. Side effects were more common than with each medicine alone but were controllable, as before, with corticosteroids. It is important to note that these are early results in a modestly sized study and may not appear as favorable in a larger or longer trial. We are currently conducting a more extensive study of a combined blockade with ipilimumab and nivolumab in more than 900 melanoma patients.

Other researchers are investigating this combined immunotherapy for treating lung cancer, kidney cancer, gastric cancer, breast cancer, head and neck cancer, and pancreatic cancer. It is also possible that the addition of direct attacks on the tumor—with chemotherapy or radiation—may render immunotherapy even more effective if the cancer cells die in a way that triggers the innate branch of the immune system. The result could be a perfect therapeutic "storm" of killing tumor cells and allowing the debris to be recognized more avidly by the immune system. Such a combination should also allow the formation of memory T cells that will maintain an enhanced vigilance against further cancer growth long after treatment has stopped. Whether this kind of immunotherapy could or should be combined for potentially greater effect with some of the other types of immunotherapy now being developed—such as cancer vaccines—remains to be seen.

All in all, I believe it is finally time to start thinking realistically about long-term remissions, even cures, because we can now combine standard therapies that target the tumor with immunotherapies that boost a patient's own defenses.

This article was originally published with the title "Cancer's Off Switch."

ABOUT THE AUTHOR(S)

Jedd D. Wolchok is chief of the Melanoma and Immunotherapeutics Service at Memorial Sloan Kettering Cancer Center in New York City. He consults for the pharmaceutical companies Bristol-Myers Squibb, Merck, MedImmune and EMD Serono but has no financial interest in the success of the medications mentioned in this article.

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