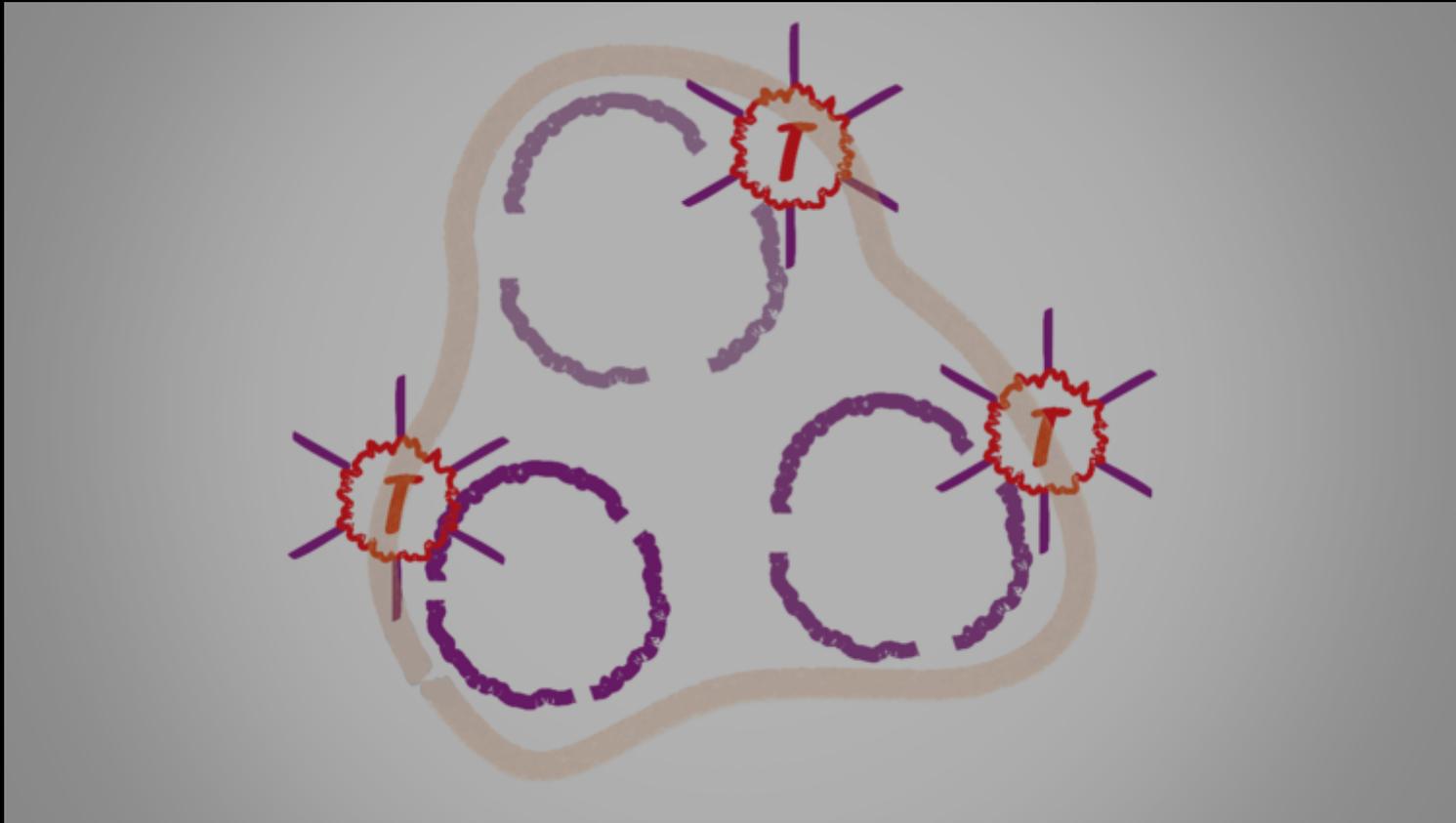


# Our perpetually vigilant internal guardian



Immunotherapy uses the body itself to kill cancer.

By **Bradley J. Fikes**

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**E**very second of our lives, we encounter threats to our health and very existence. Nearly all the time, we defeat these threats without even being aware of them.

We are surrounded by dangerous bacteria, viruses and parasites. They swarm in the air. They lurk on the things we touch. They reside on our skin and in what we eat and drink.

Standing between us and destruction is our immune system. And as modern science finds out more about this sophisticated network of defenses, the system is increasingly seen as an ally that can vanquish diseases far afield from its best-known role of fighting infections.

Otherwise fatal cancers are now being defeated by therapies that tap into the immune system's powers. These include [checkpoint inhibitors](#), drugs that unmask the disguise cancerous cells use to evade immune surveillance.

Checkpoint inhibitors can rescue people from cancer when other treatments have run out of effectiveness. One of those so rescued was Rikki Rockett, the drummer from Poison, [who was treated this year at UC San Diego](#).

In another advance that has received much publicity in recent years, genetically engineered immune cells called T cells home in on molecular signals emitted by cancerous cells and destroy them. While these are currently custom-made for each patient, newer research aims to produce off-the-shelf engineered T cells to lower cost and deliver therapy faster.

Promising drugs to treat autoimmune diseases such as multiple sclerosis are advancing through clinical trials, including one from Receptos, a San Diego company purchased last year for more than \$7 billion.

And future applications of immune system treatments hold even more dazzling promise.

Inflammation of the heart's blood vessels causes arteries to narrow and predisposing them to blockage, said Mitchell Kronenberg, president and chief scientific officer at the La Jolla Institute for Allergy and Immunology.

“That is a reaction by immune cells, [white blood cells called macrophages](#),” Kronenberg said. “So heart disease is in part at least, a problem of chronic inflammation, and chronic inflammation is caused by the immune system.”

Klaus Ley, one of the institute’s scientists, is researching [whether the inflammatory response can be averted by a vaccine](#). Testing in mice indicates that the vaccine works, and Ley’s team is working on translating this finding into a human vaccine.

“Chronic inflammation also contributes to neurodegenerative diseases, like Alzheimer’s,” Kronenberg said. “So the functioning of the immune system is pervasive. It’s really quite amazing.”

## Keeping germs out

And as with most features of your body, you probably don't think about your immune system much unless it fails to do its job.

A breach of these defenses results in infections in the skin, in internal organs and circulating throughout your blood. Usually, the damage is minor and is easily repaired.

Most of the harmful microbes in our environment are excluded by physical barriers, said Dr. Victor Nizet, a UC San Diego expert on infectious diseases.

The first line of defense is skin, which covers nearly all the body’s external surface area.

“Your skin is watertight,” Nizet said. “You can go swimming in a pool without exploding, so you can imagine that a microbe, which is much larger than a water molecule, is going to have a challenge to find its way deeper in the body.”

The rest of the body is protected by mucosal surfaces that cover the inside of the nose, the lungs, the beginning and end of the digestive tract, and other portals into the body. Mucus traps microbes so they can be removed from the body, Nizet said.

“In your respiratory tract, your mucus is being moved by little hairs called cilia,” he said. “That moves the entrapped microbes upwards imperceptibly, and we swallow them and get rid of them all the time.”

During pregnancy, a mucus plug forms around the cervix, blocking microbes from entering the uterus.

Mucus also contains antimicrobial peptides, which are small protein fragments, in addition to large proteins called antibodies. The main antibody in mucus is called immunoglobulin A, which broadly attacks bacteria. It also contains lysozyme, an enzyme which destroys the cells walls of some bacteria.

Finally, certain specialized cells of the immune system lurk in mucus that detect and destroy germs. These general-purpose warriors include white blood cells known as mast cells and macrophages, which actually digest bacteria and other cells, including our own damaged or dead cells.

Collectively, these all form part of what is called the innate immune system, a generalized defense against a broad spectrum of infectious threats, Nizet said. It is complemented by a second part — the adaptive immune system, which produces specific defenses against particular threats, such as strains of bacteria or viruses.

## Flexible defense

Antibodies provide the adaptive immune system's signature defense. They are Y-shaped molecules equipped with ends that fit onto particular molecular targets like a lock and key. These ends can be configured in innumerable ways, each one formed to bind to just one target. They can directly destroy or neutralize microbes. They can also indirectly destroy the target by marking it for attack.

Some antibodies, such as immunoglobulin A, provide a more generalized defense, and can be considered [a bridge between the adaptive and innate immune systems](#). But the kind of antibodies generated against such infections as the flu, are far more attuned to each individual pathogen. When you recover from these infections, it's because your immune system has "taught" special white blood cells called B cells how to make antibodies against that infection.

Vaccines increase the immune system's ability to ward off infections, by giving them a taste of the infectious agent. It's weak enough that it doesn't cause disease, but strong enough to cause an antibody response that can stop an infection before it takes hold.

Smallpox, for thousands of years one of the most deadly disease facing mankind, was eradicated through vaccination. [Polio](#) has also been rendered nearly nonexistent through a global vaccination program.

But flu viruses aren't so easily stopped through vaccination. Immunity from seasonal vaccines doesn't last, because flu viruses mutate rapidly, said Dr. David Spiro of the National Institute of Allergy and Infectious Diseases.

Viruses also make "decoy" sites that attract the attention of antibodies, Spiro said. These decoy sites aren't necessary to the virus' ability to infect, but they draw attention away from the virus' unchanging "conserved" regions that are essential to its infectious abilities.

The annual flu vaccine can prevent infection if it's well-matched to the circulating strain, said Spiro, chief of the Influenza, SARS and Related Viral Respiratory Diseases Section, part of the agency's Division of Microbiology and Infectious Diseases. But because it takes months to prepare the vaccine, a strain that's not included in the vaccine can unexpectedly arise and become widespread.

The 2009 flu pandemic was caused by a flu strain that was markedly different than those seen in recent years, Spiro said. However, there was far less illness among the elderly than expected. It turned out that the strain's conserved regions were like those of a strain that had appeared many decades ago. This provided a natural experiment indicating that vaccination targeting conserved regions should be able to protect against superficially different strains.

That knowledge has encouraged efforts to develop a broadly protective flu vaccine that could protect over multiple years, Spiro said. It may not meet expectations of a universal flu vaccine, that could wipe out virtually all strains. But it would be better than what we have now.

And in the case of HIV, most of those infected never make antibodies that can keep the virus in check. But antiviral medications can do that, converting HIV and AIDS from a fatal disease into one that can be managed.

A small percentage of those infected with HIV do make effective antibodies and control the virus on their own. Their immune systems have lucked into the right antibodies that neutralize HIV. Today, much of HIV research is devoted to understanding how this neutralizing response might be prompted by vaccination.

## **Wrong target**

Autoimmune diseases have both genetic and environmental components, said Thomas Esch, an autoimmune specialist at the same agency. People who have relatives with these diseases are at greater risk of developing them as well, said Esch, chief of the Autoimmune and Primary Immunodeficiency Diseases Section within the agency's Autoimmunity and Mucosal Immunity Branch.

A number of medications now on the market provide relief by depleting aberrant immune cells involved in autoimmune diseases, Esch said. This exposes patients to the chance of getting infections. So doctors must watch the drug dosage and the patient's health to avoid this.

Such drugs don't cure the diseases; when patients stop taking them, the symptoms tend to recur. One potential cure is to reset the patient's immune system by extracting immune cells, wiping out much of the patient's immune system with chemotherapy and then reinfusing the cells. The goal is to give the reconstituted immune system another chance to recognize the body as self, producing tolerance.

“In many reports, a number of people have had long-term remissions,” Esch said. “Whether they’re truly tolerant takes longer to assess.”

La Jolla-based [DiaVacs](#) is developing a therapy for the autoimmune disease type 1 diabetes. It uses technology licensed from the [University of Pittsburgh](#) and Baxter that targets dendritic cells. These are “the orchestra leaders of the immune system,” said Alan Lewis, president and CEO of DiaVacs.

“They can activate immune cells which attack the beta cells, but what we’re trying to do is the opposite, to suppress these dendritic cells from doing that,” Lewis said. “[We’ve been able to do that using antisense molecules.](#)”

The antisense compounds block proteins involved in activating T effector cells, [which attack the beta cells](#). This converts the dendritic cells into immunosuppressive dendritic cells, Lewis said.

“Our approach is take cells from the patient, manipulate them with antisense, then inject them back into the patient,” Lewis said.

The cells are injected through the skin near the pancreas. They enter the lymphatic system and end up in the pancreas. This localizes the effect, avoiding systemic immunosuppression, Lewis said.

“We have some clinical data on that program, which shows a positive start,” Lewis said.

Another program, which uses the Baxter technology, adds the antisense compounds to microspheres to be injected into the same region. “These microspheres get phagocytosed by the dendritic cells in the skin, and they migrate through the lymphatic drain system,” Lewis said. “We haven’t got clinical data for that one, but we’ve got very good animal data.

## **Pump it up**

While autoimmune diseases are caused by an immune system attacking cells it shouldn’t; in cancer the problem is just the opposite. The immune system is tolerating aberrant cells it should be attacking.

Cancer cells use many methods to evade immune attack. Solid tumors may be too shielded for immune cells to reach. Cancers may also secrete molecules that inhibit immune attack, or they may even actively recruit immune cells to their own defense.

An early success of immune therapy for cancer came from using monoclonal antibodies engineered to target molecules present on cancer cells. This is an example of “passive immunotherapy,” said [Ivor Royston, M.D](#), a founding father of San Diego’s biotechnology industry.

Active immunotherapy describes treatments such as engineered T cells that attack cancer on their own, said Royston, a biotech investor and oncologist who co-founded Hybritech, San Diego's first biotech.

Hybritech used monoclonals for diagnostics, including the first test for PSA. Hybritech was sold to Eli Lilly in 1986, and Royston along with other Hybritech executives went on to found more biotechs.

After cancer diagnostics with monoclonals, the next logical step was to develop passive immunotherapies, he said.

The first monoclonal cancer drug to be approved was [Rituxan in 1997](#). It was developed by Idec Pharmaceuticals, which Royston also co-founded.

Rituxan was first approved for non-Hodgkin's lymphoma, and then for other blood cancers and the autoimmune disease rheumatoid arthritis. All of these diseases have in common dysfunctions of B cells, the cells that make antibodies. Rituxan attacks a target found only on B cells, causing their destruction.

Although both normal and cancerous B cells are destroyed, patients can survive without them. There is some concern that Rituxan may increase the risk of infection, but its effects are reversible. When Rituxan is discontinued, blood-forming stem cells replenish the B cell population.

[Idec came close to collapsing](#) after its first cancer therapy, a customized immune treatment proved to be too expensive. But Rituxan's promise led to a partnership with Genentech that saved the company.

Rituxan became a blockbuster, and other monoclonal cancer therapies followed suit. Idec merged in 2003 with Cambridge, Mass.-based Biogen.

## **Future of cancer therapy**

The idea of using the immune system to fight cancer originated more than 100 years ago, with Dr. William Coley. He noticed that some cancer patients experienced dramatic remissions after recovering from infections. He reasoned that the immune system, roused by the infection, had also detected the cancer.

Coley devised a [cocktail of bacterial toxins](#) called "Coley's toxins." The method worked inconsistently, and it was abandoned with the advent of radiation therapy.

But the concept enjoyed a renaissance in recent decades, as it became clear that cancer was far from being eradicated. Since the immune system normally destroys the body's aberrant cells, it seemed reasonable that charging up the immune system might work.

Coley's toxins was a form of therapeutic vaccination, and biotech researchers sought to improve upon the concept by using substances from actual tumors.

Royston ventured into active immunotherapy with [CancerVax](#), a Carlsbad company that developed a vaccine against melanoma. The goal was to wake up the immune system to recognize the cancer. The vaccine, Canvaxin, used [allogeneic](#) irradiated cancer cells.

[Clinical testing of the vaccine failed](#), creating a personal and financial disappointment for Royston. But research continued. Today, there is one therapeutic cancer vaccine on the market, Provenge, an autologous treatment for metastatic prostate cancer.

Other cancer immune therapies now on the market include checkpoint inhibitors, drugs that unmask cancer cells, along with genetically engineered immune cells that kill cancer.

The latter, CAR T cell therapy, is an autologous treatment, made from T cells taken out of the body, genetically engineered, then reinfused into the patient. Biotech companies are researching allogeneic CAR T cell treatments that can be produced in mass quantities and therefore cheaper, and also immediately available.

Peter G. Schultz, president of The Scripps Research Institute, leads a team that is researching a refinement of CAR T cell therapy. This approach uses peptides that serve as a bridge between the CAR T cell and the target cell, [allowing control of the response](#). Existing CAR T cell treatments run the danger of creating an uncontrolled immune response that can kill the patient.

Royston said he's optimistic for more great progress against cancer.

"It makes a lot of sense to me that you would start clinical trials of cancer vaccines to give along with checkpoint inhibitors, and that I think is going to be the next big breakthrough immunotherapy," Royston said.

A cancer patient could be treated in several steps, he said. First, surgery to "debulk" the tumor to a small amount.

"Maybe at that point you can give a vaccine along with a checkpoint inhibitor to eradicate any tumor we can't see," Royston said. That may have a big impact on survival in the future."

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