



Photo illustration: Sharpe Davidson Dendritic cell slide: Ryan C. Fields

HARNESSING THE POWER OF THE HUMAN IMMUNE SYSTEM

Cancer vaccines in trials at U-M use the body's own defenses to outmaneuver the disease

by Sally Pobojewski
photos by Martin Vloet

Paul McClellan knows he should be dead by now. Diagnosed with melanoma at age 32, he has been fighting this aggressive and deadly form of cancer for 13 years.

“My back looks like railroad tracks from all the tumors I’ve had removed,” says McClellan, a 45-year-old production manager from Canton with four children. “They told me my life expectancy was five years. The doctors look at me as if they are amazed I’m still around.”

In March of 2001, after repeated surgeries, treatment with interleukin-2 (a drug that stimulates the immune system) and chemotherapy failed to stop his melanoma from coming back, McClellan volunteered for a clinical trial of an experimental cancer vaccine developed at the University of Michigan Comprehensive Cancer Center.

“There was nothing else I could do, and I didn’t feel like just sitting around waiting to die,” says McClellan. “At least if I tried everything, it would give me some peace of mind.”

So McClellan enrolled in the study, which was directed by Bruce G. Redman, D.O., a U-M clinical associate professor of internal medicine. For the next seven months, McClellan received injections of an experimental cancer vaccine. After each injection, he checked into U-M Hospital for supplemental infusions of interleukin-2, which made him violently ill. “It felt like the worst flu I’ve ever had,” he says. Just when he’d start to feel better, it was time to begin the cycle all over again.

When the trial was over in October of that year, McClellan felt better and tests indicated he was cancer-free. Four months later, when he returned for a routine check-up with what he thought was a bad head cold, McClellan learned he had a new tumor in his nasal cavity, which was surgically removed. Since then, he’s developed two additional growths in his sinuses, but no recurrences of melanoma on his back.

“The hardest thing is trying to stay positive and keep playing it for as long as you can,” says McClellan. “When I was going in for chemotherapy, I’d see these four- and five-year-olds with no hair, and I’d say, ‘If I leave today, I’ve still lived a full life.’ I try to set little goals for myself. I wanted to see my oldest son graduate from high school and I did that. Now I want to see all my kids graduate, and if I can dance with my daughter at her wedding, I’ll be a happy guy.”

Development of Paul McClellan’s cancer vaccine really started 10 years ago when the Tumor Immunology/Immunotherapy Program was established in the U-M’s Comprehensive Cancer Center. James J. Mulé, Ph.D., the Maude T. Lane Professor of Surgical Immunology and the program’s director, is responsible for the program’s overall activities and laboratory animal research on the immune system and cancer. Bruce Redman is the program’s associate director responsible for clinical research. In all, about 30 Medical School scientists and clinicians are involved in the program.

From the beginning, the Tumor Immunology/Immunotherapy Program was designed to take scientific advances

from the laboratory and transfer them to the clinic. Basic research on the immune system and how it responds to cancer is used to develop experimental vaccines and therapies, which are evaluated first in laboratory animals for safety and effectiveness, and then phased into human clinical trials.

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Professor of Oncology. “One of the approaches we are most excited about is immunotherapy, because it is based on a fundamental knowledge of how the human immune system works and recognizes cancers to destroy them. It also fits in with other therapies of the future, which use genetics and molecular biology to target cancers in a much more specific way. We are investing the majority of our research dollars in these new approaches to cancer treatment.”

THE IMMUNE SYSTEM AND CANCER

The human immune system is a complex network of cells, organs and lymph nodes connected by the lymphatic system. Its job is to protect the body by detecting and killing invading pathogens or cancer cells.

The immune system’s motto is *balance in all things*. If it overreacts, the system can target the body’s own cells, leading to rheumatoid arthritis and other autoimmune diseases. If it’s not sensitive enough, it won’t detect incoming pathogens until it’s too late to mount an effective defense. The key to its success is an amazing ability to tell the difference between cells that belong in the body and cells that don’t.

Specialized white blood cells called dendritic cells are the immune system’s first

line of defense. They patrol the body and alert the immune system to any “foreign invaders.” After surrounding and digesting the intruder, dendritic cells sound the alert by displaying bits of digested foreign protein called antigens on their long projecting arms.

The dendritic cell presents these antigens to white blood cells called T lymphocytes, or T cells, until it finds one with a receptor, or docking site, that fits the antigen. Once a match is made, the T cell sends out messenger molecules that stimulate the immune system to create an

army of T cell clones, all equipped with the exact receptor needed to immobilize and destroy one specific type of pathogen or cancer.

“I tell my patients that the immune system is like a TV western from the 1950s,” says Redman. “The dendritic cell is the scout and the lymphocytes are the guys in the blue uniforms, the cavalry. The dendritic cell goes out into the body and finds the enemy. It comes back to the cavalry and says, ‘OK, guys, this is where they are and this is how you identify them. They will be carrying this protein on their surface.’”

If the system always worked, there’d be no such thing as cancer, because dendritic cells would detect tumor antigens and alert T cells to destroy malignant cells before they had time to grow and spread. Unfortunately, cancer is a sneaky adversary. It has several very effective ways of staying one step ahead of the immune system.

“Whenever you have an immune response to a foreign antigen, either a tumor or a pathogen, it’s a race,” says Mulé. “It takes time to produce a targeted immune response. Sometimes tumors grow so fast, they outpace the ability of the immune system to deal with them.”

Tumors also secrete molecules that suppress the immune system, says Mulé, the best examples being brain tumors ➤

called gliomas. “The glioma tumor secretes a powerful immunosuppressive molecule called TGF-beta. Glioma patients have such high levels of TGF-beta circulating in their blood that their immune systems cannot respond to even the strongest antigen.”

Since cancer begins in a normal cell, many of its antigens are seen as harmless “self” proteins by lymphocytes, which allows the cancer to grow undetected. If the immune system recognizes the cancer as foreign, tumors can change their appearance. “If they have a strong antigen on their surface, they somehow get rid of it,” says Mulé. “So even if you make an army of T cells primed to attack that specific antigen, the tumor escapes, because it no longer expresses the antigen. It’s a moving target. The more immune pressure you put on it, the more the tumor will change.”

The immune system has a trick of its own, however, that makes it a formidable adversary for cancer. Once its T cells have been sensitized to specific tumor antigens, the immune system never forgets. Traditional therapies like surgery or radiation can remove or shrink the tumor, but if even a few cells remain, the tumor will grow back. Immunotherapy’s big advantage is its potential for a long-term response with T cells primed to destroy new cancer cells before they have a chance to grow. The immune system’s ability to recognize tumor antigens with pinpoint accuracy means that immunotherapies should be highly specific cancer-killing agents, with few, if any, adverse side effects.

BASIC SCIENCE LEADS THE WAY

Using the immune system to fight cancer is nothing new. In 1893, William B. Coley, M.D., a New York City surgeon, published results of what may be the first human clinical trial of an immunotherapy for cancer. Coley found that injecting his cancer patients with live streptococcal bacteria sometimes caused their tumors to shrink or disappear — assuming the patient lived through the therapy.

More than 100 years after Coley’s experiment, scientists are still searching for answers to fundamental questions about the immune system. Some of the most exciting new studies have taken place in Jim Mulé’s lab in the U-M Medical



James Mulé and Bruce Redman

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School, and many of these discoveries have already been incorporated into clinical trials in the U-M Cancer Center.

In 1988, Mulé was the first to show that it was possible to trigger an immune response and shrink tumors in animals using a vaccine made from dendritic cells mixed with whole tumor lysates — tumor cells which are frozen and thawed several times to kill them. “Our thought was to let the dendritic cells process the tumor and tell us which antigens were important,” says Mulé. “That’s what

Mother Nature created them to do and they are very good at it.”

Mulé’s lab also was the first to show that animals given interleukin-2 with the dendritic cell vaccine showed substantial tumor regression and lived longer than those treated with either the vaccine or IL-2 alone.

In recent studies of laboratory animals with cancer, Mulé’s research team found that the most effective time to give dendritic cell vaccines is following a bone

marrow transplant — after radiation has destroyed all the lymphocytes in the original immune system, but before the transplanted marrow has time to make new cells. Mulé's lab also is using genetic engineering to insert genes into dendritic cell DNA to increase the vaccine's effectiveness.

Alfred E. Chang, M.D., the Hugh Cabot Professor of Surgery and chief of Surgical Oncology in the U-M Health System, is developing a different type of cancer vaccine. Instead of using dendritic cells to activate an immune response, Chang uses cells from the patient's tumor, which he kills by exposing them to radiation.

"Irradiated tumor cells still express tumor antigens," explains Chang. "By injecting the tumor cells back into the patient as a vaccine, we can stimulate an immune response in the patient's T cells. Then we harvest the T cells, expand them in the laboratory and re-infuse them into the patient's bloodstream. Our hope is that these T cells will circulate and attack the tumor, causing it to shrink."

Scientists have learned a great deal about cancer vaccines in the last 15 years, according to Mulé. They've learned how to immunize safely, how to grow T cells which react to tumor antigens and how to generate an immune response. But answers to the big questions remain elusive: Why do some patients respond to the vaccine, while others don't? What is the tumor doing to prevent the therapy from working?

"You can equip the immune system with an army of highly functional cloned T cells that recognize the patient's tumor and destroy it in a test tube, but when you give those same cells to the patient, you get no response," says Mulé. "To a different patient in the room next door, you give the same number of highly reactive cells and that patient has a dramatic anti-tumor response. And we still have no clue why."

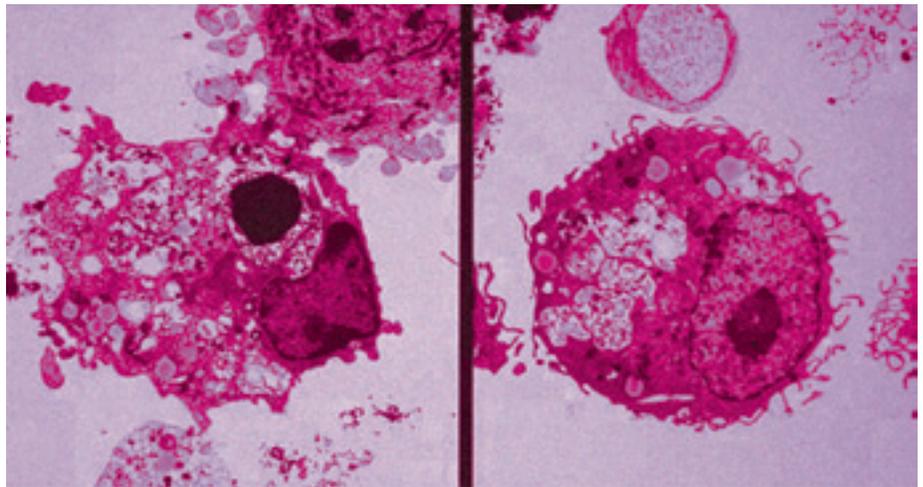
FROM MOUSE TO HUMAN

Clinical research has come a long way since William Coley's day when physicians were free to try all sorts of experimental treatments on patients with few controls and little oversight. Today, every step in a human clinical trial is strictly regulated by the U.S. Food and Drug Administration and the National

Institutes of Health. Before a clinical trial can begin, the researcher must submit to the FDA a three-inch binder filled with results from pre-clinical animal studies, a detailed description of the proposed research protocol, the type of patient to be enrolled, and possible side-effects of the experimental treatment.

The FDA approves three types of human clinical trials. Phase I trials of cell-based therapies like cancer vaccines are designed to answer basic questions like: Is it safe? Can you produce the vaccine with consistent quality using approved manufacturing standards?

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These electron micrograph images show dendritic cells that have taken up or "eaten" dead tumor cells (the black circle in the left photo). Ingestion of tumor cells by dendritic cells is the first step in activating the immune response against tumor antigens.

If the results of a phase I study are positive, researchers can apply for FDA approval to continue to phase II. Phase II clinical trials must prove that the therapy is effective and biologically active.

The final stage of human clinical trials is a phase III study in which researchers compare results in patients who received the experimental therapy with matched groups of patients who received conventional therapy or no treatment. Because phase III studies are very expensive, involve hundreds or thousands of patients in multiple hospitals and require lots of administrative support, they are rarely conducted at academic medical

centers. Usually, a pharmaceutical company, which has licensed the marketing rights for a new drug or therapy, administers and funds phase III trials.

So far, U-M cancer vaccines have been evaluated in three phase I trials — one in children and two in adults. The first study to test the safety of a dendritic cell vaccine in children was conducted three years ago by James D. Geiger, M.D., a U-M pediatric surgeon. In September 2000, Geiger published preliminary results from this trial in the British medical journal, *Lancet*. Even though it was only a small phase I study, the results

were surprising enough to be reported on ABC's "World News Tonight."

"Three patients showed a significant immune response and three of the children are still alive and doing well today," says Geiger, a member of the Tumor Immunology/Immunotherapy Program and an assistant professor of surgery in the U-M Medical School. "Because it was a phase I study, we can't take credit for their survival, but given their large tumor burden, we wouldn't have predicted they would survive. For a phase I study in advanced disease, it was really encouraging." ▶



THE MAKING OF A CANCER VACCINE



At left: Technician Guihua Jiang, Ph.D., mixes cells in a culture flask, one step in the vaccine production process.

Dendritic cell vaccines have two main ingredients — frozen cells from the patient’s tumor, removed during surgery, and frozen white blood cells from the patient, removed in a process called leukapheresis.

Seven to eight days before the first vaccination, the patient’s white blood cells and tumor cells are delivered to the controlled environment of the Human Applications Laboratory, called the HAL, in the U-M’s General Clinical Research Center. According to Jim Mulé, director of the U-M Tumor Immunology/Immunotherapy Program, the center is a major reason for the program’s success.

“We have the advantage of getting our trials up and running with the full support of a clinical infrastructure and a clean room production facility, which allows us to make vaccines right in the hospital,” says Mulé.

To produce the vaccine, technicians like Guihua Jiang, Ph.D., a senior research

associate, first use a centrifuge to separate the different types of cells in the patient’s blood sample. Monocytes, the precursors to dendritic cells, are washed, fed a special blend of growth factors and placed in culture flasks. Then the

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cells grow in an incubator for six to seven days. During the incubation period, the number of cells will expand up to 30 times.

Two to three hours before the patient’s first scheduled vaccination, Jiang washes the dendritic cells and mixes them with cells from the patient’s tumor. Samples of the vaccine are

removed for FDA-mandated tests for contaminants and toxins, which are performed in a separate U-M laboratory by quality control analysts. If the vaccine passes all quality control tests, Jiang fills an ordinary syringe with about one-half milliliter of the milky-white vaccine and carries it to the U-M Cancer Center where it must be injected into the patient’s thigh within 30 minutes.

Without a facility like the HAL, with technology that meets the U.S. Food and Drug Administration’s stringent standards for gene, cell and tissue-based therapies, clinical research on cancer vaccines would not be possible. Expanded and upgraded in 1995 with funding from the National Center for Research Resources and the U-M Health System, the HAL is a self-contained, HEPA-filtered clean room facility with four production modules.

The level of cleanliness in the HAL is meticulously maintained. Research associates wearing sterile white coveralls, boots and masks enter through an air lock. Staff technicians adhere to a strict cleaning protocol — regularly taking apart and sterilizing all the equipment and washing the floors, walls and ceilings. Everything inside is tested routinely to be sure that all surfaces, equipment and even the air itself are sterile.

“It’s our job to prove to the FDA that we are processing the right cells, giving them back to the right individual, and that the cells are alive and germ-free,” says Blake J. Roessler, M.D., an associate professor of internal medicine-rheumatology and director of the HAL. “We try to be as close as possible to pharmaceutical industry manufacturing production standards.”

—SFP

A phase II trial of Chang's T cell vaccine in adult patients with the most advanced form of renal cell cancer was completed recently, and results will be published soon in the *Journal of Clinical Oncology*. Twenty-seven percent of patients enrolled in this trial had complete or partial shrinkage of their tumors. Some patients have remained free of cancer for several years after the study. "These are patients for whom there were no other appropriate treatment options," says Chang. "Seeing those responses is what makes this type of work gratifying."

Three phase II trials of the dendritic cell vaccine are now under way in the U-M Cancer Center, according to Bruce Redman. Redman is directing two of these trials — one in adult patients with melanoma and the second in adults with advanced colorectal cancer. Cheryl T. Lee, M.D., an assistant professor of surgery in the Medical School, is directing the third study in adults with muscle-invasive bladder cancer. In this study, Lee is injecting dendritic cell vaccine directly into the patients' bladder tumors.

"All clinical trials so far have been conducted in stage IV patients with advanced disease," says Mulé. "We hope to test the vaccine in patients with a smaller tumor burden, which is why we want to test it immediately after a blood stem cell or bone marrow transplant. That's when you have minimal residual disease and the vaccine will be most effective."

"If the FDA approves our proposal, we will begin testing the vaccine late in 2003 in children with neuroblastomas and sarcomas who have received peripheral blood stem cell transplants," says Geiger, who will direct the phase I study. To complement Geiger's study in children, Mulé and Redman, with colleagues at the University of Southern California-Norris Cancer Center, are planning a phase I study of the vaccine in adult melanoma patients receiving a type of chemotherapy that reduces the number of lymphocytes produced by the patient's immune system.

U-M researchers also plan a future phase I trial with a new version of the dendritic cell vaccine, which has been genetically engineered to add the gene for a protein called SLC. In animal studies, Mulé found that SLC attracts "naive" T cells to the injection site where they are more likely to come in contact with dendritic cells in the vaccine and be primed to

attack antigens in the patient's tumor. "Jim has shown it works in mice. Now we need to try it in people," says Redman.

WHY DOES IT TAKE SO LONG?

U-M scientists realize that dramatic breakthroughs in cancer research are rare. It's much more likely, they say, that five to 10 more years of laboratory work and clinical trials will be needed before a U-M vaccine will be ready for patient use. In clinical research, even small steps forward can take years of work.

"We've learned how to stimulate the immune system," says Redman. "In some patients, we see signs of immune response, meaning the immune system is attacking antigens in



In spite of the challenges involved, Jim Mulé expects to see a U-M cancer vaccine, probably for melanoma, approved by the FDA and available to patients within 10 years. "We are committed to it and whatever it takes, we will do it."

the patient's tumor. Unfortunately, that's different than a clinical response where the tumor shrinks or disappears. It's just the first step."

Of great concern to scientists today is that increased government regulation of clinical trials will delay the process of getting new therapies to patients even more. Since the 1999 death of Jesse Gelsinger — a volunteer in a gene therapy trial at the University of Pennsylvania Medical Center — the amount of time, paperwork and FDA oversight required to conduct a human clinical trial has increased exponentially. Threats of lawsuits and federal investigations of scientists who direct clinical trials are not uncommon.

"Today, the clinical investigator is under siege. It's unfortunate, because it's such an important time in cancer research," says Max Wicha. "We need clinical investigators now more than ever."

"My biggest worry about the future of cancer research is that we're going to lose an entire generation of young clinical investigators," says Mulé. "The regulatory hurdles are becoming overwhelming. We need administrative infrastructures to deal with FDA requirements and liability issues, so researchers can focus on the clinical science."

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probably for melanoma, approved by the FDA and available to patients within 10 years. "We are committed to it and whatever it takes, we will do it," he says.

When he gets discouraged, Redman likes to remember Brian Piccolo, the 26-year-old running back for the Chicago Bears who died of testicular cancer in 1970. "After Brian Piccolo died, scientists announced the results of a clinical trial showing that one drug, cisplatin, was an important part of the cure for testicular cancer," says Redman. "Young men went into that trial dying of cancer and came out feeling great. For a medical oncologist, that's the home run — the big hit we're always looking for. That's what keeps us going — the chance to save the next Brian Piccolo."