meet

James

James Creaby was diagnosed with melanoma ten years ago.

In 1999, James Creaby — then 51 and a foreign exchange currency trader with Morgan Guaranty — was diagnosed with melanoma, the most serious form of skin cancer. Thus began a journey studded with numerous recurrences and remissions that continues to the present day. He is currently being treated at Memorial Sloan-Kettering with an innovative immunotherapy discovered and developed by James Allison, Chair of Sloan-Kettering Institute's Immunology Program. Mr. Creaby recently sat down with his physician Jedd Wolchok, Dr. Allison, and Jianda Yuan, head of MSKCC's Immune Monitoring Core Facility, to talk about the arduous and complex path of his therapy.

JAMES ALLISON
Chair, Immunology Program

JAMES CREABY
Patient

JEDD WOLCHOK
Medical Oncologist

JAMES CREABY

I first knew something wasn't right when a mole about the size of a pencil eraser appeared on my right side around the area of my ribs. My wife, Jane, said "Let's get that checked, Jim." But they run in my family, and I was sure it was nothing. So it wasn't until about eight months later that I finally went to a dermatologist. He removed the mole, and two days after that we got a call asking us to come to his office — where he told us it was melanoma.

Mr. Creaby underwent surgery to remove skin surrounding the melanoma in order to reduce the risk of recurrence. At the time of surgery, a biopsy showed that the sentinel lymph node under his right arm contained a few melanoma cells. The sentinel node is the first lymph node to which cancer cells are likely to spread from a primary tumor. Subsequent surgery to remove all the remaining underarm nodes showed no further spread of the disease.

I was fine — for about three years. Then I was sitting at work one day and stretched, just raised my arm, and felt this lump. I went for a needle biopsy and was told that it was melanoma that had metastasized to the base of my pectoral muscle.

MR. CREABY

In most patients with Stage 3 melanoma there is about a 50-50 chance of melanoma coming back. Some people are at higher risk and some at lower, but generally that's the reality.

DR. WOLCHOK

[Antigen-presenting cells] are what get the body's immune response going. The notion was to take advantage of these antigen-bearing dendritic cells to initiate an immune response against the melanoma.

DR. ALLISON

MR. CREABY The protocol at the time was high-dose interferon. [A type of protein produced by white blood cells, interferons have been shown to help stop the growth and spread of cancer cells.] It required infusions five days a week for a month, during which I'd have to stay home, unable to work — and then I'd have to inject myself three times a week for the next 11 months. When I learned that there was already a 50-50 chance that the melanoma would come back anyway — and that interferon would only increase the odds of it not returning by an additional 10 percent — I decided to forgo the injections and have the disease monitored with periodic CT and PET scans.

JEDD WOLCHOK **In most patients with Stage 3 melanoma there is about a 50-50 chance of melanoma coming back. Some people are at higher risk and some at lower, but generally that's the reality. And it's correct that interferon doesn't have a dramatic effect on recurrence.**

MR. CREABY I was fine — for about three years. Then I was sitting at work one day and stretched, just raised my arm, and felt this lump — again, on the right side. I went for a needle biopsy and was told that it was melanoma that had metastasized to the base of my pectoral muscle. It was surgically removed, and that's when I was referred to you, Dr. Wolchok. You referred me to James Young for the vaccine.

James Young, currently Interim Chief of MSKCC's Adult Bone Marrow Transplant Service, was then leading a clinical trial at the Center of a dendritic cell vaccine he had developed for the treatment of metastatic melanoma.

JAMES ALLISON **Dendritic cells are antigen-presenting cells [APCs]. APCs are what get the body's immune response going. They take inside themselves infections, viruses — even dying tumor cells — and break down the antigens on the cell surfaces into smaller pieces called peptides. They then display these peptides to the body's T cells. Receptors on the surface of the T cells recognize the peptides, bind to them, and become activated. Thousands of T cells are generated that can now go out and do their work — which is to kill target cells that express the antigen presented by the APCs. So the notion was to take advantage of these antigen-bearing dendritic cells to initiate an immune response against the melanoma.**

[Ralph Steinman of The Rockefeller University was a co-discoverer — with the late Zanvil Cohn — of dendritic cells, work for which he was awarded the 2007 Albert Lasker Award for Basic Medical Research.]

JAMES ALLISON
Chair, Immunology Program

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Patient

JEDD WOLCHOK
Medical Oncologist

JIANDA YUAN
Immunologist, Head, Immune Monitoring Core Facility

From your blood, we generated lots of dendritic cells. Then we loaded these cells with peptides — antigens derived from melanoma — and injected them back into you.

DR. YUAN

MR. CREABY I thought one of the most fascinating things was the theory behind it. That you took my blood and —

JIANDA YUAN **I was a member of Dr. Young's lab then — you gave us quite a lot of your blood! [Laughter] From it, we generated lots of dendritic cells. Then we loaded these cells with peptides of gp100 and tyrosinase — two differentiation antigens derived from melanoma — and injected them back into you.**

MR. CREABY I remember you also gave me antigens from a deep-sea organism.

DR. WOLCHOK **There's a pigment called keyhole limpet hemocyanin, made from a sea creature called a keyhole limpet, that's been shown to enhance the immune response against tumor antigens by interacting with T cells. In other words, this pigment is very interesting to T cells that have never seen it before.**

MR. CREABY And it did seem to work. My melanoma didn't come back for another three years. But then I went in for a PET scan and, lo and behold, it showed I had a growth on my right adrenal gland.

Mr. Creaby's adrenal gland was surgically removed, and Dr. Wolchok put him on temozolomide (Temodar®). It was now November 2005.

DR. WOLCHOK **Temozolomide is licensed for the treatment of certain types of brain tumors, but we use it "off-label" for melanoma. At the time there was no clinical trial that accommodated your situation, and it seemed reasonable to try to treat any micrometastatic disease with temozolomide. It's an oral medication without many side effects, so the risk-benefit profile was favorable.**

MR. CREABY And from November 2005 until June 2006 I was okay. Then I woke up one morning and felt a lump on the right side of my neck. It turned out to be melanoma, and the tumor was removed. You put me on GM-CSF [granulocyte macrophage colony-stimulating factor].

DR. WOLCHOK **GM-CSF is a protein of the immune system that helps regulate immune response. There's evidence showing that it may help rev up the immune system to fight melanoma. Again, we didn't have a trial that would've accommodated your circumstances, so I was drawing from the literature for any therapies I could offer.**

MR. CREABY Unfortunately, a few months later I found another tumor on my neck.

This tumor was removed in September 2006, and Mr. Creaby underwent radiation therapy to his neck. However, in December, while showering, he discovered a lump on his left oblique muscle.

MR. CREABY

The tumor was where your "love handles" are — it felt as if I'd inserted a pickle under my skin. A CT scan showed that there was also a lesion on my left pectoral muscle as well as multiple metastases in my liver and lungs. It was all over the place. There wasn't any possibility of surgery. But I have to be immensely thankful for the fact that this recurrence made me eligible for a clinical trial of anti-CTLA-4 [now known as ipilimumab] that was closing in two weeks. I'm blessed that I made it into the trial, and I'm blessed that it's worked.

To learn more about Dr. Allison's development of anti-CTLA-4, see the next page.

DR. WOLCHOK

What anti-CTLA-4 [ipilimumab] is saying to your T cells is, "Go, be free. See what you want to see."

Patients who are treated with ipilimumab usually exhibit a unique pattern of response. We're building an army of T cells — and it may take one person six weeks to muster that army while another person's immune response may not be seen for six or seven months.

DR. WOLCHOK

DR. ALLISON

Whatever's going on —

DR. WOLCHOK

— look at it —

DR. ALLISON

— and go crazy! To coin a phrase . . .

[Laughter]

DR. WOLCHOK

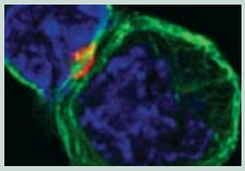
There's another aspect to this that's important to mention. Patients who are treated with ipilimumab usually exhibit a unique pattern of response. Unlike with traditional chemotherapy — where you give someone a treatment and within a fairly predictable time period you see tumors start to get smaller and hopefully go away — ipilimumab works very differently.

DR. ALLISON

Because we're not treating the tumor, we're treating the patient.

DR. WOLCHOK

We're building an army of T cells — and it may take one person six weeks to muster that army while another person's immune response may not be seen for as long as six or seven months. During that time, some patients' tumors may grow larger, or they may even develop new tumors as older tumors regress. There are also patients who have long periods of stable disease, meaning the tumors don't go away, yet they don't progress.

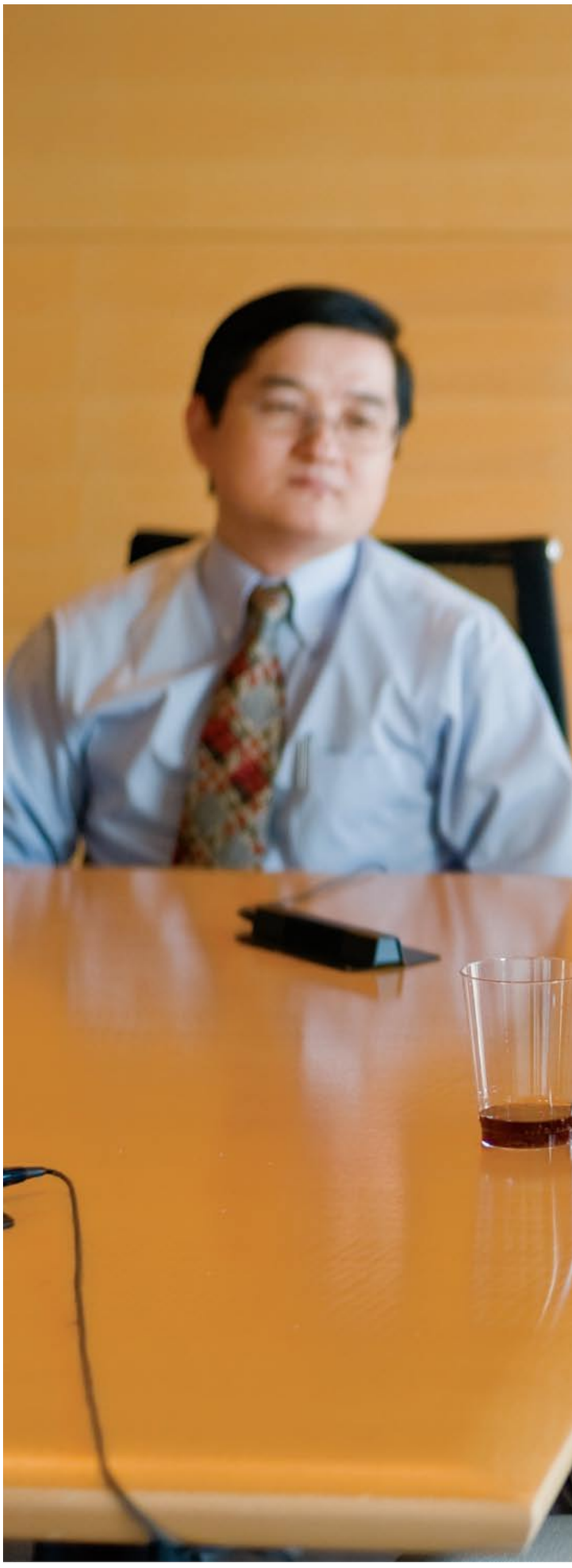


A T cell is shown interacting with an antigen-presenting cell. The red indicates the presence of CTLA-4 in the region of interaction between the two cells. (Image by Jackson Egen and James Allison.)

The Development of Anti-CTLA-4 (Ipilimumab)

For more than 20 years, James Allison's work has focused on understanding how T cells are activated and the mechanisms that regulate their response. He was chair of the immunology program at the University of California, Berkeley, when, in 1982, he and members of his laboratory discovered the receptor that T cells use to recognize antigens on the surface of antigen-presenting cells. However, recognition alone is not enough to stimulate T cell proliferation. In the late 1980s, Dr. Allison demonstrated that a protein called CD28 found on the surface of T cells was the co-stimulatory signal needed to activate a T cell response. He uses the analogy of an automobile.

"Just turning on the ignition won't get the car to go. There needs to be a second signal, a foot on the gas pedal so to speak. No one knew what that signal was until we showed the function of CD28." The final part of Dr. Allison's car analogy is the immune system's "brake," an immune-regulating molecule known as cytotoxic T lymphocyte-associated antigen-4, or CTLA-4. "Once your T cells have successfully killed all the invaders, CTLA-4 sends an inhibitory signal that decreases T cell production. It's what keeps the immune system from becoming hyperactivated and attacking the body's own tissues," he explains. "Members of my lab and I hypothesized that if we could find a way to block CTLA-4 this might enhance antitumor T cell responses. Eventually we were able to make antibodies to temporarily block CTLA-4's signal so that T cells could do their work unrestrained. In the simplest terms, anti-CTLA-4 takes the brakes off the immune system."




As we get more tumor specimens from patients whose tumors are regressing we'll be able to look at the specificity of the T cells *within* the tumors.
DR. WOLCHOK
Because any self-respecting, tumor-attacking T cell is going to be in the tumor — that's where the action is, presumably.
DR. ALLISON

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Patient

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Medical Oncologist

JIANDA YUAN
Immunologist,
Head, Immune Monitoring
Core Facility

I've been fortunate. Ipilimumab doesn't work for everybody . . .

MR. CREABY

. . . that's what we're trying to figure out in the Immune Monitoring Core Facility — why some people have very good, durable responses and others don't.

DR. YUAN

MR. CREABY

All my tumors have now disappeared. But during those three months after I got the first dose of ipilimumab the tumor in my pectoral muscle blossomed, the tumors in my liver grew, and the tumors in my lungs didn't go away — although they remained stable.

DR. WOLCHOK

You were on a randomized double-blind study evaluating the efficacy of several different dose levels of ipilimumab. Then the blind was broken, and we discovered that your first dose was a low one. Right after you had your 12-week scans we re-induced you with the high dose.

MR. CREABY

It's working for me. I can pretty much carry on with my normal life. My biggest side effect is itching.

DR. WOLCHOK

Patients may experience a rash and gastrointestinal problems. But they're almost always manageable.

MR. CREABY

I've been fortunate. Ipilimumab doesn't work for everybody.

DR. YUAN

Right. And that's what we're trying to figure out in the Immune Monitoring Core Facility — why some people have very good, durable responses and others don't. I want to say that we deeply appreciate all our patients who are so willing to contribute blood and tissue samples, because without them we couldn't learn.

DR. WOLCHOK

Your blood, Jim, has been very important to our efforts. One of the first things we did was to look in your blood for antibodies that may have been produced by your immune system to targets that we know are sometimes found on melanoma. The particular target we were interested in is a protein called New York ESO-1 [NY-ESO-1]. It was discovered here at the Ludwig Institute [by Lloyd Old, a Member of SKI's Immunology Program and Director of the New York Branch of the Ludwig Institute for Cancer Research]. We asked Jianda to look at the amount of NY-ESO-1 antibody in your blood — and this is where it got very interesting.

To read more about the Ludwig Center for Cancer Immunotherapy at MSKCC, please see page 39.

NY-ESO-1 is a member of a special class of proteins called cancer-testis, or CT antigens. CT antigens are expressed in almost half of all melanomas and in a variety of other cancers, but not in normal adult tissues, except for the germ cells of the testes and the placenta.

DR. WOLCHOK

You see, melanoma patients can spontaneously make immune responses to NY-ESO-1. And so you might ask, "If they can make these immune responses, then why doesn't the tumor get controlled?" Well, maybe there isn't enough of it, or maybe all the cells don't have it. We don't know the answer yet.

DR. YUAN

When you got your low dose of ipilimumab, we saw a low level of NY-ESO-1. But right after Jedd gave you the high dose, your NY-ESO-1 antibodies increased tremendously. And we also saw a beautiful T cell response. Your T cells, doing their work unrestrained, recognized NY-ESO-1. So we surmise that the T cells are indeed eliminating the tumor.

JAMES ALLISON
Chair, Immunology Program

JAMES CREABY
Patient

JEDD WOLCHOK
Medical Oncologist

DR. WOLCHOK It was at this same point that all your tumors regressed and you had a complete remission.

DR. ALLISON The difficult thing is that we still don't know for certain that the specific T cells we're measuring are the cause of the tumor going away. The tests we have for blood are useful, but may not be the most informative.

DR. WOLCHOK True. As we get more tumor specimens from patients whose tumors are regressing we'll be able to look at the specificity of the T cells *within* the tumors.

DR. ALLISON Because any self-respecting, tumor-attacking T cell is going to be in the tumor — that's where the action is, presumably.

DR. WOLCHOK So having tumor specimens is vital. One of the great advantages of working at Memorial Sloan-Kettering is that we're at the interface of science and medicine. There are very few institutions that could carry out the kinds of studies we've done — very few places that can run clinical trials and then try to understand the science of the drug they're investigating.

DR. ALLISON Also, we're taking what we've learned from analyzing patient specimens in the lab back to the animal model. We're now starting to manipulate some of the new molecules that we see are increased in patients on ipilimumab. As we identify these molecules that seem relevant in humans, we can go back and design carefully controlled mouse experiments where we'll learn if they're good therapeutic targets and build layer upon layer like this, over time.

DR. WOLCHOK It's really a gift to be able to bring things from the lab to the clinic and back to the lab — as Jim's just said, to complete the circle.

MR. CREABY It's been wonderful to be in the same room with all of you.

DR. ALLISON Well, it's always a thrill to meet people who have benefited from our work. [Pause] I've met a lot of the mice. They don't seem to care as much.

[Laughter]



(Above) James Allison (left) and Jedd Wolchok (middle) serve as Director and Associate Director for Clinical Research, respectively, at the Ludwig Center for Cancer Immunotherapy at MSKCC. Jianda Yuan (right) heads the Immune Monitoring Core Facility.

The Ludwig Center at MSKCC

Memorial Sloan-Kettering is one of six distinguished United States institutions to have been named a Ludwig Center. In 2006, the institutions shared in a $120 million gift from the Virginia and D. K. Ludwig Fund for Cancer Research, plus stock in a real-estate holding company, to create the Ludwig Centers. The Ludwig Center for Cancer Immunotherapy at MSKCC focuses on harnessing the power of the immune system to monitor and treat cancer. The support of the Ludwig Fund is accelerating the pace at which researchers can move the findings of basic scientific studies into translational work, so that promising innovative therapies and diagnostic approaches can be evaluated in people with cancer. James Allison and Jedd Wolchok serve as Director and Associate Director for Clinical Research, respectively. Jianda Yuan heads the Immune Monitoring Core Facility that is part of the Ludwig Center. That facility works to develop immune monitoring tests able to determine immune responses in patients receiving novel immunotherapies.

JAMES CREABY
Patient

JEDD WOLCHOK
Medical Oncologist

James Creaby is a member of the Pipes and Drums of the Jersey Shore Shillelaghs, a parade band located in Belmar, New Jersey. The nonprofit group plays approximately a quarter of its performances for charitable events, including fundraisers, and in support of other volunteer organizations.

MR. CREABY

One of the things I try to do now is to speak to other people with cancer. What I want is to give them hope. In other words, to tell them that there is the potential for a positive outcome.

DR. WOLCHOK

You're actually responsible, Jim, for at least one other person joining the ipilimumab trial even though that person was quite fearful and uncertain at first. And he's having a very good response — in fact, such a good response that he's missing office visits left and right because he can't take time off from work!

James Creaby receives a maintenance dose of ipilimumab every three months to periodically reinhibit CTLA-4. He continues to show no evidence of disease. To date, approximately 3,700 patients have been treated with ipilimumab, mostly for melanoma, although it is also being evaluated for the treatment of prostate, ovarian, and kidney cancers. Collaborative investigations continue at MSKCC to refine, discover, and develop new and more-effective immunotherapies against cancer.