Cell

Cell

Checkpoints

James P. Allison

I cup the harmonica and start playing with the rest of the band—The Checkpoints. The crowd gets on their feet, cheering and dancing to "King Bee." It was the 2015 annual American Society of Clinical Oncology (ASCO) meeting. The Society for Immunotherapy of Cancer had organized for us to play one night at the House of Blues in Chicago. The place was packed. Immunologists, oncologists, radiologists, pathologists, journalists, and patients attended our gig. They were celebrating. Not just the skills of the band members—all cancer researchers—but the field of cancer immunotherapy and the amazing clinical successes that were just announced at that ASCO meeting.

The field of cancer immunotherapy certainly has had its ups and downs. The promise of being able to use the immune system to treat cancer has been around for many decades. Before being able to fulfill the promise, though, we had to understand the immune system.

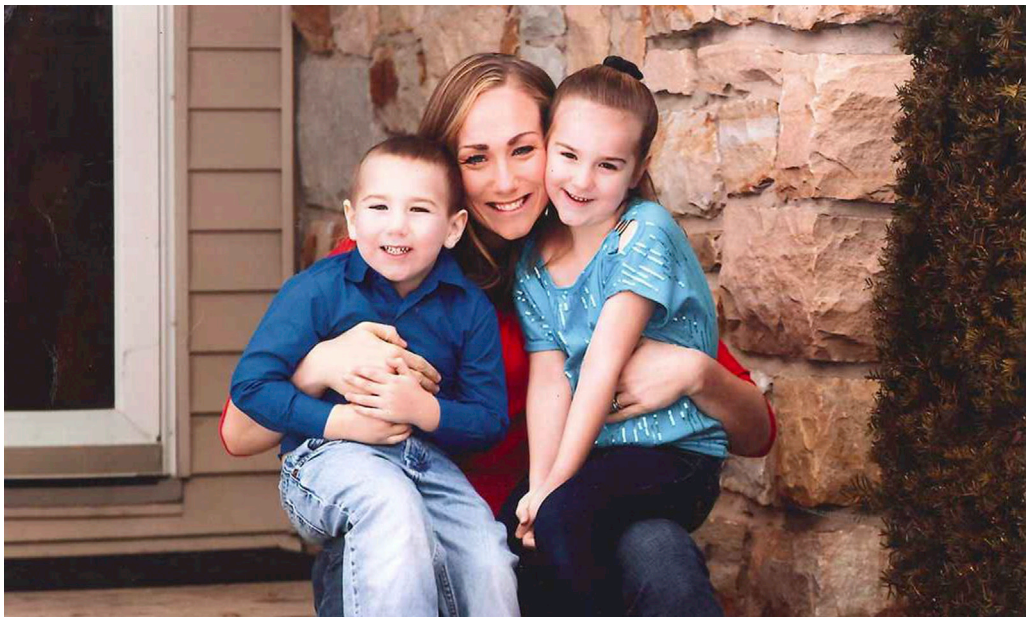
"All of a sudden, I was totally hooked on understanding T cell activation."

I was not trained as an immunologist. I was actually a biochemist. In my early years, while still a young assistant professor at the Smithville branch of MD Anderson Cancer Center, my friend and colleague, Ellen Ritchie, convinced me that I should pursue the holy grail of immunology, which, at the time, was identification of the T cell receptor. T cells are the soldiers of the immune system, but no one knew how they were turned on. Shortly after that, I attended a seminar by Irv Weissman, and it gave me an idea about how I may conduct an experiment to look for the T cell receptor. In 1982, I published a paper reporting what seemed to be the T cell antigen receptor protein. All of a sudden, I was totally hooked on understanding T cell activation.

By the mid-80s, I had moved to the University of California at Berkeley. Due to the work of Ron Schwartz, Marc Jenkins, and their colleagues at the NIAID, it was becoming clear that engagement of the T cell antigen receptor was by itself insufficient to generate T cell responses, and additional costimulatory signals were also required. Fiona Harding, in my lab, tackled this issue in collaboration with David Raulet and showed in 1992 that costimulatory signals mediated by the CD28 molecule were necessary and sufficient to allow full activation of virgin T cells.

However, there was yet another piece of the puzzle. CTLA-4, a gene induced in all T cells upon full activation, had been previously identified by Pierre Golstein and was highly homologous to CD28. Peter Linsley and his colleagues had found that the ligand for CD28 on antigen-presenting cells was the B7 molecule and went on to show that B7 was also a ligand for CTLA-4. The mystery now was what role this additional B7 counter-receptor was playing in T cell activation. Linsley's data suggested that CTLA-4 was another costimulatory molecule, and its role was to sustain T cell activation and prolong T cell responses. On the flip side, Jeff Bluestone with his colleagues and my lab argued the opposite—that CTLA-4 was an inhibitory molecule that served to limit T cell responses. Max Krummel, at that time a grad student in my lab, published the critical in vitro studies showing that CTLA-4 opposed CD28 costimulation. The inhibitory nature of CTLA-4 was confirmed later when Tak Mak's group, Arlene Sharpe's lab, and the late Cynthia Chambers,

James P. Allison at his laboratory in Berkeley, circa 1995.



Sharon Belvin, now almost 10 years after receiving anti-CTLA-4 therapy, with her two children.

in our lab, showed that the genetic ablation of CTLA-4 in mice resulted in unrestrained proliferation of T cells and death.

It was about 10 years between our publications on the T cell receptor and CTLA-4. During that time, I thought of myself as a basic scientist trying to uncover the secrets of T cell regulation. I did not think of myself as a cancer researcher or translational scientist. However, I had always been interested in cancer, in part because I had lost my mother and two uncles, and later my brother, to cancer and had seen firsthand the ravages of radiation and chemotherapy. So I did what I think any basic scientist should do: occasionally stop and think about the implications of your fundamental findings for application to human disease. Meanwhile, I also started putting the pieces of the "T cell activation" puzzle together.

"So I did what I think any basic scientist should do: occasionally stop and think about the implications of your fundamental findings for application to human disease."

It occurred to me that if T cells express CTLA-4 as an "off" signal every time they receive the "on" signals generated by T cell receptor and CD28, then the T cells would be limited in their ability to mediate anti-tumor responses. If only we could block the negative regulation by CTLA-4, then maybe T cell responses would be sustained long enough to eliminate cancer. Some of the implications of this strategy were very compelling. The first was that the therapy did not target the tumor cell but rather the patient's immune system. Thus, CTLA-4 could be effective against any tumor that bore antigenic targets for T cells and might be a universal treatment of cancer. The second was a practical point: we would not need to know the exact antigenic targets for each individual tumor in order to try to obtain therapeutic vaccination. We would be unleashing, not harnessing, the immune system to attack cancer.

As an initial test of the hypothesis, we designed an experiment to treat tumor-bearing mice with an antibody that blocked CTLA-4. When Dana Leach, a postdoc in the lab who carried out the first experiments, showed me the initial data, I was shocked and surprised. The mice that were treated with anti-CTLA-4 rejected the tumors and lived normally while the untreated mice died. It was too

Cell

good to be true. I didn't believe the initial results. We repeated the experiment blinded during the Christmas holidays in 1994. Dana injected the mice with tumors and treated with antibodies and I did the tumor measurements not knowing which mice had received control or anti-CTLA-4 antibodies. For about 2 weeks, all of the tumors grew in all of the mice. I was disappointed but continued to record the results. Then, as if by magic, one group of mice started to shown signs of tumor regression and then complete tumor rejection. We then treated many different tumor types. Anti-CTLA-4, as either monotherapy or in combination with agents such as vaccines or chemotherapy, led to improved anti-tumor responses and durable regression of a broad array of experimental tumors. While my group continued mouse studies and began to dissect the mechanisms of tumor rejection, my mind was elsewhere: I wanted desperately for CTLA-4 to be tested in clinical trials.

The road to convincing a company to develop a humanized anti-CTLA-4 antibody and test it in the clinic was filled with many bumps and colorful language along the way. Eventually, my friend Alan Korman at Medarex worked with me to develop a human version of anti-CTLA-4. Medarex made a fully human antibody and conducted the first clinical trial, and the rest, as they say, is history. Anti-CTLA-4 therapy led to durable tumor regression and improved overall survival in a subgroup of patients with late-stage melanoma. I still remember when it all dawned on me. I was at Memorial-Sloan Kettering Cancer Center in 2007 and Jedd Wolchok asked me to meet him in his clinic. He introduced me to Sharon Belvin, a lovely woman who had, in her mid-twenties, been diagnosed with metastatic, stage 4, melanoma. She failed other therapies and was given a few months to live before being enrolled in a clinical trial with anti-CTLA-4. I met her, her husband, and her parents on her one-year anniversary of having completed the treatment. Her disease had responded to the treatment and although she had not received any further treatment other than the 12-week course of anti-CTLA-4, she was considered in remission and possibly cured. She cried and I cried that day. Over the years, we have kept in touch, and she sent me photos of both of her two children.

I have had the pleasure of meeting many patients like Sharon over the years. As I am not a physician, these encounters have provided a real-life reminder of the potential impact of basic science in saving lives.

The antibody to CTLA-4, ipilimumab, has been approved by the Food and Drug Administration for the treatment of metastatic melanoma and is now a standard care for treatment of that disease. A recent retrospective study of about 5,000 patients treated with ipilimumab reported that about 22% of patients survived 10 years after a single round of treatment. While CTLA-4 was the first immune checkpoint to be identified, several others, each with their own mechanisms of action, are now known and at various stages of clinical development. The furthest along is PD-1, and antibodies targeting PD-1 have been approved by the FDA for the treatment of melanoma and lung cancer. The combination of antibodies to CTLA-4 and PD-1 elicits responses in about 50% of melanoma patients and has impact on several other types of cancer.

The new field of "Immune Checkpoint Therapy" has proudly taken its place as a pillar of cancer therapy. My goal now is to understand why some patients respond to treatment while others do not. To this end, I have partnered with a physician scientist, Padmanee Sharma, who conducts mechanism-based clinical trials to study immune responses in patients who receive the immune checkpoint agents. These studies have yielded promising new data, and I am truly optimistic that we can indeed apply immune checkpoint therapy, as monotherapy or in combination with other cancer treatments, to provide cures for patients with any type of cancer. The field of cancer immunotherapy looks brighter than ever, and I am honored to have played a part in it.