Established in 1990 as a triennial award, the Novartis Prizes for Immunology are considered by many as the most prestigious prizes specifically for immunology. The awards recognize breakthrough contributions to basic and clinical immunology as judged by an independent panel of experts. The 2013 Novartis Prizes for Immunology was presented on August 23, 2013, at the 15th International Congress of Immunology in Milan, Italy. This year’s prize in clinical immunology highlights achievement in cancer immunology research leading to the development and application of immunotherapy for cancer. The modern era of cancer immunology research was initiated by Dr. Lloyd J. Old nearly six decades ago. It is fitting that the 2013 Novartis Prize for Clinical Immunology was presented to Dr. James P. Allison, recipient of the first AACR-CRI Lloyd Old Award and a Deputy Editor of this journal, for his work “in understanding how cancers evade the immune system and developing therapies to help enhance the body’s immune response to cancers” (Novartis press release; June 17, 2013).

Dr. Allison is the department chair and professor of immunology at The University of Texas MD Anderson Cancer Center in Houston. He developed an antibody against a negative regulator of T-cell immune response, and demonstrated in mouse tumor models that anti-cytotoxic T lymphocyte antigen-4 (anti-CTLA-4) antibody safely enhanced the function of T cells and promoted immune-mediated tumor destruction. He continued this immunomodulatory approach against human cancers. In collaboration with industry, a fully humanized version of this anti-CTLA-4 antibody, known as ipilimumab, was developed and tested in two large randomized clinical trials resulting in increased survival of patients with advanced malignant melanoma, the most common lethal skin cancer.

Here is a transcript of Dr. Allison’s acceptance speech describing the basic science research leading to the development of effective immunotherapeutic strategies targeting checkpoint blockade against cancer:

Thank you for your kind words, Diane [Mathis], and also thanks to Novartis and the jury for selecting me for this prestigious prize. I am truly honored and also humbled by being a successor in a long line of outstanding immunologists who have preceded me. I am also very honored to receive the clinical immunology award. I have always considered myself a basic scientist, and still do, although now I am probably considered to be a translational tumor immunologist. My major interest has always been in understanding the mechanisms of regulation of T-cell responses. Since this prize is given to me largely for the development of the strategy of targeting immune checkpoints in the treatment of cancer, I believe it is worth describing the basic science that laid the foundation for what has proved to be a very effective cancer therapy.

In the early stages of my career at The University of Texas System Cancer Center, I studied T-cell lymphomas to test the hypothesis that different T lymphomas might express clonotypic antigens related to the T-cell antigen receptor. The work confirmed the hypothesis and resulted in the generation of antibodies that we used in biochemical studies to elucidate the structure of the antigen receptor.

Recognition of CD28 as a major costimulatory molecule led to considerable interest in identifying homologous molecules that might serve a similar function. CTLA-4, a gene originally cloned by Pierre Golstein [at INSERM-CNRS (Marseille,
France), was such a molecule. Peter Linsley showed that CTLA-4 bound the same ligands as CD28 and proposed that it provided additional costimulatory signals.

We were not so sure. Experiments carried out by Max Krummell in my laboratory were more consistent with CTLA-4 providing signals that inhibited T-cell proliferation and that were blocked by anti-CTLA-4 antibodies. Jeff Bluestone had come to the same conclusion, but the issue remained quite controversial for a few years, making for often lively discussion at conferences. The controversy largely came to an end with the observation by Tak Mak, Arlene Sharpe, and by the late Cynthia Chambers in my laboratory that CTLA-4–deficient mice died from an early and massive lymphoproliferative disorder initiated by T cells.

While the controversy was ongoing I had the idea that CTLA-4 might prematurely terminate T-cell responses to tumors and frustrate attempts to use therapeutic vaccines to treat cancer. The approach of blocking CTLA-4 as a strategy for cancer therapy was compelling for two reasons. The first is that, unlike conventional therapies that target the tumor, we would be targeting the patient’s immune system and not the tumor. Thus, the approach could potentially work against any kind of cancer. Second, since CTLA-4 blockade works at the level of T-cell cross-priming by tumor antigen-loaded dendritic cells, the method could possibly be used in combination with virtually any kind of therapy that killed tumors and not the tumor. Thus, the approach could potentially work to treat cancer. The initial results are promising, and we may be on the verge of delivering on the notion that the immune system can be harnessed to effectively treat cancer, regardless of type.

Over the next 15 years a series of outstanding students and postdocs, including Andy Hurwitz, Andrea van Elsas, Eugene Kwon, Marcella Fasso, Becky Waitz, and Michael Curran, showed that anti-CTLA-4, alone or in combination with conventional therapies, could lead to rejection of many different types of experimental tumors. Karl Peggs, Sergio Quezada, Tyler Simpson, and others worked out many of the cellular and molecular mechanisms involved in rejection.

In the late 1990s, Alan Korman and I initiated a collaboration to make reagents that targeted human CTLA-4 to bring this to the clinic. Ultimately Alan, together with Nils Lonberg of Medarex, made MDX-010, a fully human antibody that became ipilimumab. In early clinical trials, ipilimumab showed objective responses in several types of cancer, including melanoma, renal, and prostate. In 2011, Medarex and Bristol Meyers-Squibb reported the results of a very large phase III randomized, placebo-controlled trial in metastatic melanoma that showed about 4 months in mean survival. No other drug of any type had shown any survival benefit in a controlled, randomized trial. However, the most exciting thing was that 23% of the patients were alive 4.5 years after treatment. As a result, ipilimumab was approved by the U.S. Food and Drug Administration for both first- and second-line therapy of metastatic melanoma, and it is now a standard of care for that disease.

We now know that there are several molecules that mediate intrinsic inhibitory signals in T cells. Antibodies to PD-1, the best known of these, in early clinical trials have shown activity against several tumor types, including melanoma, renal, and non–small cell lung cancer, with response rates of about 25% to 30%.

It is known that CTLA-4 and PD-1 work by different mechanisms, and Mike Curran, while a postdoc in my laboratory, showed that combined antibody treatment was additive in a preclinical mouse study. This June, a clinical trial of combination therapy with ipilimumab and the anti-PD-1 antibody nivolumab in metastatic melanoma was reported, with 65% of patients showing some tumor shrinkage and close to 50% having objective responses.

So, while 5 years ago there was no effective treatment for late-stage melanoma, we may be on the verge of being able to obtain durable benefit. I hesitate to say cure, in close to half of patients with the disease.

There are currently ongoing trials in prostate, lung, kidney, gastric, pancreatic, and breast cancer. The initial results are promising, and we may be on the verge of delivering on the notion that the immune system can be harnessed to effectively treat cancer, regardless of type.

However, to some extent these are just numbers, and as someone whose experience has largely been as a mouse doctor, I did not have any real-world experience with ipilimumab until I met two patients. I would like to speak of my meeting with these two patients both named Sharon, which was kindly arranged by their physicians and my colleagues Antoni Ribas and Jedd Wolchok. Sharon of California was among the first patients to receive ipilimumab in a phase I trial in metastatic melanoma 12 years ago. When I met her over 2 years ago, she told me that she had only hoped that ipilimumab would keep her around long enough to see her sons graduate from high school, but has now seen them finish graduate school and begin their careers. Sharon of North Carolina was 28 years old when, 7 years ago, she was told that she only had a few months to live. After treatment with ipilimumab, she has had two children. To date, approximately 30,000 patients have been treated with immune checkpoint blockade.

The future of targeting immune checkpoints is still in its early stages. Other inhibitory molecules, such as B7-H3, and -H4, Tim-3, Lag-3, Vista, and others, offer compelling targets, and preclinical work suggests that positive checkpoints, such as OX-40, 4-1BB, and ICOS, are promising. Our job now is to understand the mechanisms so that we can make rational decisions as to effective combinations of immunologic as well as conventional and targeted therapies to obtain durable responses in a higher fraction of patients in a variety of tumor types.

While I was at Memorial Sloan-Kettering, my friend and mentor Lloyd Old and his fellow Padmanee (Pam) Sharma taught me that we can do detailed experiments to learn from every patient. Small mechanism-based trials can provide important information. With this in mind I made the
decision to move to The University of Texas MD Anderson Cancer Center, where my partner Pam Sharma and I are involved in building an immunotherapy platform, an institution-wide program across all tumor types with the goal of accelerating progress in the new field of immune checkpoint targeting as a strategy for treating cancer.

I have tried to individually thank those in my laboratory who directly contributed to this story and apologize to anyone who may have been omitted. I would also like to thank all the other fellows in the laboratory over the years, as well as colleagues at The University of California at Berkeley and the Memorial Sloan-Kettering Institute, who helped create an atmosphere of collaborative exploration. I would also like to thank those involved in the trials, including the pharma partners and clinicians who made an idea a reality. Finally, I would like to thank the many patients who had the courage and generosity to risk exposure to a new drug with uncertain benefit and possibilities of undesired side effects.

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