Dankesrede

von

Prof. Dr. James P. Allison

anlässlich der Verleihung

des Paul Ehrlich- und Ludwig Darmstaedter- Preises

2015

in der Paulskirche Frankfurt am Main

14. März 2015

Es gilt das gesprochene Wort

I am humbled to receive this prize from the Paul-Ehrlich Foundation, humbled to be selected to join the illustrious scientists who have received this award in the past. I thank the Committee for selecting me for this prize, and pledge that I will continue my efforts to make contributions that will justify this honor. I think that the award of the 2015 Ehrlich Prize to myself and Dr. June recognizes not just our own work, but also recognition that due to the efforts of many investigators and clinicians to establish immunology as a pillar of cancer treatment. This is particularly appropriate since in the early 20th century Dr. Ehrlich was the first to propose the concept of immunosurveillance, the idea that tumors arise all the time in our bodies, but are usually eliminated by the immune system before they become a clinical problem. By the 1960s the idea that it might be able to use the immune system to treat cancer in a very specific way that would spare normal cells and result in long lasting protection against recurrence was under active investigation. Although there were many ups and downs in the field, in the last few years with advances in our knowledge of fundamental mechanisms of the cellular immunity this has become a reality.

Active mobilization of the immune system, especially T cells, the warriors of the immune system, to attack cancer offers three unique features compared to other treatment modalities. The first is the specificity of T cells for unique antigens, many generated by the process of carcinogenesis itself, that are not found in normal cells. The second is adaptability – the immune system can respond to changes in the tumor by activating T cells with new specificities that can recognize new mutations that might make tumors resistant to targeted therapies, for example. And perhaps the most important feature of the T cell response is memory. After a T cell response there are a small number of self-renewing cells that can persist for a lifetime, and provide a rapid response if a tumor recurs.

In the 1980s the demonstration of tumor antigens in human melanoma led to strategies employing therapeutic vaccination to mobilize the immune system to attack cancer. Unfortunately there were few successes. The failure to induce effective immune responses by attempting to turn T cell response “on” with vaccines led many to become skeptical of the potential of immunotherapy.

Consideration of the complexity of fundamental mechanisms that regulate early aspects of T cell activation may provide one of many possible explanations for the limited effectiveness of these early vaccine trials. By the late 80s it was known that engagement of the antigen receptor (TCR) by antigen was not sufficient for T cell activation - additional signals provided by B7 molecules on antigen presenting cells were also required, and these costimulatory signals can only be provided by cells called antigen presenting cells (APC). When the B7 molecules on the APC engage the costimulatory receptor CD28 on the T cells simultaneously with TCR engagement, an event that can be likened to pressing the gas pedal on a car, the T cells become activated, start dividing at a very high rate, and differentiate into an army of warriors that move through the body to eliminate the invader, be it a virus infection, or, indeed, a mass of tumor cells. However, in the early 1990s Jeff Bluestone’s lab and mine showed that T cell activation resulted in the production of a molecule called CTLA-4, which like CD28 binds the B7 molecules but eventually turns the T cells off. Based on our knowledge of the function of CTLA-4, I proposed that blocking its interaction with the B7 molecules might allow T cell responses to persist sufficiently to achieve tumor eradication.

Our proposal of CTLA-4 as a strategy for cancer therapy was radical in two ways. First, it ignored the tumor cell and focused instead on treating the immune system. It was not necessary to know what the T cells would be directed against, or even the kind of tumor. If it worked, it should work against any kind of tumor, because tumors all express antigens that are not found in normal cells. The second departure from the paradigm was that it was not aimed at turning the immune response on, that is *harnessing* the immune system to attack cancer, but rather at *unleashing* the immune system to do so. A corollary of this is that CTLA-4 blockade could unleash T cells primed by tumor cell death that accompanies treatment with cytotoxic therapies, including radiation, chemotherapies, and targeted therapies, or those elicited by vaccination with tumor antigens. Our hypotheses were confirmed in a large series of pre-clinical studies in many different mouse tumor models showing that injection of antibodies into tumor-bearing mice, either alone or in combination with vaccines, radiation, or chemotherapy, could lead to tumor eradication and long lived immunity.

In the late 1990s we teamed up with Medarex to make antibodies to human CTLA-4 for human clinical studies. In early trials the antibody, called ipilimumab, showed objective clinical responses in many cancer types, including melanoma, kidney cancer, prostate cancer and others. In 2010 a large, randomized, placebo controlled trial of ipilimumab showed an increase of 4 months in median survival in metastatic melanoma patients, something that had never before been observed with any treatment of any type. But the most important outcome was that about 22% of the patients were alive 4.5 years after treatment. In 2011 it was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma and it is now a standard of care for that disease. A recent follow up study of almost 5,000 metastatic melanoma patients showed that a little over 20% were alive 10 years after treatment with ipilimumab.

While CTLA-4 was the first identified, we now know that there are more immunological checkpoints. In 2001 it was shown that a molecule called PD-1 also inhibits T cell function, but in contrast to CD28, PD-1 interferes with antigen receptor signaling. Like anti-CTLA-4, anti-PD1 antibodies have shown effectiveness against a variety of tumor types in early clinical trials. Two different antibodies to PD-1 have now been approved by the FDA for treatment of metastatic melanoma.

Since CTLA-4 and PD-1 have different mechanisms of action, we reasoned that blockade of both pathways together would be more effective with either alone. A recent trial of a combination of anti-CTLA-4 and PD-1 showed responses in over 50% of patients.

In the last few years, at least 5 additional checkpoints have emerged and are in either in preclinical or early clinical development, so there is still a lot to do.

Clearly, immune checkpoint blockade is now a pillar of cancer therapy. Among the most exciting developments in the field now is the beginning of development of rational combinations of checkpoint blockade with conventional therapies, and with adoptive T cell therapies. Success to date brings optimism that there will soon be cures for at least some types of cancer.