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Editorial

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Immunotherapy Against Cancer is Currently Fashionable

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In one of the most exciting historical moments for biomedical research, the Karolinska Institute of Sweden has just announced that the 2018 Nobel Prize for Medicine and Physiology goes to James P. Allison and Tasuku Honjo for “their discovery of cancer therapy by inhibition of negative immune regulation”. The recognition is due to his research on immunotherapy against cancer. In this manner the fight against cancer takes one of the most prestigious awards in the world.

The discoveries of both scientists have been key to varying the conditions of the immune system that are able to deal with tumors, what has meant a revolution in cancer therapies and has completely changed the way to face the disease. In particular, Allison (American immunologist born in 1948) and Honjo (Japanese immunologist born in 1942) discovered how to “liberate” two brakes on the immune system that, in practice, helped to spread cancer. Controlling its action, it is achieved that the body’s defenses generate a response against tumors, which has led to great results in the treatment of some types of cancer, such as melanoma or lung cancer, among others.

At the beginning of the 20th century, several researchers postulated that the activation of the immune system could be a strategy to attack tumor cells. But it has been in recent years when immunotherapy has revolutionized the methods to treat cancer. Thus the works of Allison and Honjo have been essential from the point of view of basic immunology. Their discoveries have allowed the design of drugs that actually are used in clinical practice for melanoma and some kidney and lung tumors, such as ipilimumab, nivolumab or atezolizumab. For all this, the discovery of the CTLA-4 and PD-1 proteins has been fundamental to the beginning of a new way of approaching the new cancer treatments.

The fundamental property of the immune system is the ability to discriminate between “own” and “strange”, so that invading bacteria, viruses and other hazards can be attacked and eliminated. T cells, a type of lymphocyte, are key players in this defense. It was shown that T cells have receptors that bind to structures recognized as not own and such interactions cause the immune system to compromise in the defense. But additional proteins are also required that act as T cell accelerators to trigger a full-blown immune response.

During the 1990s, in his laboratory at the University of California, James P. Allison studied the CTLA-4 protein present on T cells. He developed an antibody that could bind to it and block its function, so that the brake of the T cells would be disconnected and the immune system could be released to attack the cancer cells. Allison and his team performed a first experiment at the end of 1994 and the results were spectacular, in mice and in humans.

A few years before Allison’s discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T cells. Meticulously explored its function in a series of experiments conducted for many years in his laboratory at Kyoto University. The results showed that

PD-1, similar to CTLA-4, functions as a T-cell brake, but operates by a different mechanism. In animal experiments, PD-1 blockade also proved to be a promising strategy in the fight against cancer, as demonstrated by Honjo and other groups. With these results it was possible to use PD-1 in the treatment of patients. Clinical development occurred and in 2012 a key study demonstrated clear efficacy in the treatment of patients with different types of cancer.

With such findings, in recent years, immunotherapy has been postulated as one of the most effective weapons when it comes to dealing with cancer. In fact, *Science* journal has deemed *Cancer Immunotherapy* the 2013 “Breakthrough of the Year”. At present, the therapeutic pathway using immunotherapy benefits around 15%-20% of cancer patients, so we are still at the beginning of a progressive evolution in the new approaches of cancer. The current need is to study how it works so that it can be applied to other tumors and also understand why all patients do not respond equally. Although as with other cancer therapies, there are adverse side effects caused by an overactive immune response that leads to autoimmune reactions.

For this reason, current research also focuses on elucidating the mechanisms of action, with the aim of improving therapies and reducing side effects.

Meanwhile, the truth is that the list of tumors in which they are demonstrating the results of immunotherapy is increasing. In fact, favorable responses are being observed in several types of cancer, such as bladder or lymphoma. Recent data published in the *The New England Journal of Medicine* show its effectiveness in patients with non-metastatic lung cancer.

In addition, new clinical studies indicate that a combination therapy (targeting both CTLA-4 and PD-1) may be even more effective, as demonstrated in patients with melanoma. None of these findings and clinical advances would have been possible without the work of Allison and Honjo.