

# Nobel to immunotherapy in cancer

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The stimulation of the own immune system is the base of a treatment to attack tumor cells that has revolutionized the approach of this disease in the last years. The academics have recognized the researchers who allowed these clinical findings.

The immunologist Tasuku Honjo [1] (Born in Kyoto in 1942) from the University of Kyoto, Japan, identified PD-1, one of the molecules of the immune system, known as checkpoint, among whose functions is to act as a brake on the own defences. The treatments based on this discovery, checkpoint inhibitors, are now successfully used in various types of tumours.

James P Allison [2] (Born in Alice, Texas, in 1948) of the MD Anderson Cancer Centre in Texas, revealed how releasing these "brakes" could cause the immune system to attack cancer cells. He developed this concept until achieving a new oncological treatment, immunotherapy. This immunologist received the Lasker Medicine Award in 2015 for these works.

Allison and Honjo showed how different strategies to inhibit the brakes in the immune system can be used in the treatment of cancer. The fundamental discoveries of the two laureates are a milestone in the fight against cancer.

## A different idea

During the 1990s, in his laboratory at the University of California, Berkeley, James P. Allison studied the CTLA-4 T lymphocyte protein. He was one of the scientists who observed that CTLA-4 works as a brake on T cells. Other research teams exploited the mechanism as a target in the treatment of autoimmune disease. Allison, however, had a completely different idea. He had already developed an antibody that could bind to CTLA-4 and block its function. So he set out to investigate whether the blockade of CTLA-4 could disconnect the T-cell brake and release the immune system to attack the cancer cells.

Allison and her group conducted a first experiment in late 1994. The results were spectacular. The mice with cancer had been cured by treatment with the antibodies that inhibit the brake (anti-CTLA-4) and unblock the activity of the antitumor T cells. Despite the little interest of the pharmaceutical industry, Allison continued her intense efforts to develop the strategy in a therapy for humans. Promising results from several groups soon emerged, and in 2010 an important clinical study showed surprising effects in patients with advanced melanoma. In several patients the signs of remaining cancer disappeared. Such results have never been seen before in this group of patients.

## The PD-1 function

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T cells. Determined to unravel its role, he explored its function in a series of experiments conducted over many years in his laboratory from the University of Kyoto. 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, the blockade of PD-1 also proved to be a promising strategy in the fight against cancer, as shown by Honjo and other groups. This paved the way for using the molecule as an objective 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. The results were spectacular, which led to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

## Promising clinical development

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been spectacular. It is now known that the treatment, called immunotherapy, has fundamentally changed the outcome for certain groups of patients with advanced cancer. Like other cancer therapies, there are adverse side effects, which can be serious and even life-threatening. These effects are caused by an overactive immune response that leads to autoimmune reactions, but they are usually manageable. The intense research focuses on elucidating the mechanisms of action, with the aim of improving therapies and reducing such side effects.

Of the two treatment strategies, therapy against PD-1 has been shown to be more effective and positive results are being observed in several types of cancer, including lung cancer, kidney cancer, lymphoma and melanoma. New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, may be even more effective, as has been demonstrated in patients with melanoma. Numerous trials of checkpoint inhibitor treatments against most types of cancer are currently underway, and new checkpoint proteins are being tested as targets.

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**Received:** December 08, 2018; **Accepted:** December 26, 2018; **Published:** January 04, 2019

Let's not forget that none of these findings and clinical advances would have been possible without the magnificent work of the groups of Allison and Honjo.

### Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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