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Immune Checkpoint Inhibitors Discovery Bag the Nobel

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The Nobel Prize in Physiology and Medicine 2018 was awarded jointly to James P. Allison and Tasuku Honjo for their discovery of cancer therapy by inhibition of negative immune regulation. Cancer still continues to be the greatest health challenge as it kills millions globally. By stimulating the inherent ability of our immune system to attack tumor cells, this year's Nobel Laureates have established an entirely new principle for cancer therapy. James P. Allison studied cytotoxic T lymphocyte antigen 4 (CTLA 4) that functions as a brake on the immune system.¹ The potential of releasing this brake can unleash our immune cells to attack tumors. This concept has been utilised to create an anti-cancer drugs which have revolutionised the treatment of metastatic cancers. Simultaneously, Tasuku Honjo discovered a protein on immune cells responsible for programmed cell death (PD-1) which also operates as a brake. The seminal discoveries by these two Laureates constitute a landmark in the fight against cancer. Cancer therapeutics have earlier also received Nobel prizes. For e.g. Hormone treatment for prostate cancer (Huggins, 1966), chemotherapy (Elion and Hitchins, 1988), and bone marrow transplantation for leukemia (Thomas 1990).

The fundamental property of our immune system is the ability to discriminate "self" from "non-self" antigens. T cells that bind to non-self antigens trigger the immune system to engage in self-defense. T cell accelerators or T cell brakes can augment or ameliorate the T cell immune responses respectively. This intricate balance between accelerators and brakes is essential for tight control of the functioning of the T cell mediated immune response. Way back in 1990 James P. Allison at University of California, Berkeley studied the T-cell protein CTLA-4 and developed an antibody that could bind to CTLA-4 and block its function. He investigated if CTLA-4 blockade could disengage the

T-cell brake and unleash the immune system to attack cancer cells. He was successful in treating the cancer in the experimental mice in 1994. Finally in 2010 his experiment got translated into an important clinical study which cured patients suffering from advanced melanoma and thus; the anti CTLA 4 drug Ipilimumab was born which received approval from FDA for the treatment of Refractory Melanoma.

In 1992, a few years before Allison's discovery, Tasuku Honjo discovered PD-1, another protein expressed on the surface of T-cells. In animal experiments, PD-1 blockade was also shown to be a promising strategy in the fight against cancer, as demonstrated by Honjo. In 2012, a key clinical trial demonstrated the efficacy of anti PD-1 drugs in the treatment of patients with different types of cancer. Results were dramatic, leading to long-term remission and possible cure in several patients with metastatic cancer, a condition that had previously been considered essentially untreatable.

Immune checkpoint therapy for cancer today and in the future

After the initial studies showing the effects of CTLA-4 and PD-1 blockade, the clinical development has been dramatic. We now know that the treatment, often referred to as "immune checkpoint therapy", has fundamentally changed the outcome for patients with advanced cancer. But similar to other cancer therapies, adverse side effects are seen, which can be serious and sometimes even life-threatening. They are caused by an overactive immune response leading to autoimmune reactions, but are usually manageable. Intense continuing research is focused on elucidating mechanisms of action, with an aim of improving therapies and reducing side effects. Of the two treatment strategies, checkpoint

therapy against PD-1 has proven more effective and positive results are being observed in several types of cancer, including lung cancer,² renal cancer,³ hepatocellular carcinoma,⁴ and melanoma.⁵ New clinical studies indicate that combination therapy, targeting both CTLA-4 and PD-1, can be even more effective, as demonstrated in patients with melanoma by combination of Ipilimumab (anti CTLA 4 antibody) and Nivolumab (anti PD1) or Pembrolizumab (anti PD-1 inhibitors). Thus, Allison and Honjo have inspired efforts to combine different strategies to release the brakes on the immune system with the aim of eliminating tumor cells even more efficiently. A large number of immune checkpoint therapy trials are currently underway against different types of cancer, and new immune checkpoint proteins are being tested as targets.

For more than 100 years scientists attempted to engage the immune system in the fight against cancer. "Immune Checkpoint" therapy has now revolutionized cancer treatment and has fundamentally changed the way we view how metastatic cancer can be managed.

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