The Nobel Prize in Medicine and Physiology for 2018 was awarded to Dr. James P. Allison and Dr. Tasuku Honjo for making breakthrough discoveries on strategies for treating cancer by preventing the “ignorance” of tumors by the immune system. Developing cancer cells are normally detected by surveying white blood cells, or T-lymphocytes, that recognize the tumor progenitors as abnormal and target the abnormal cells for destruction. However, as a tumor develops, the cancer cells of the tumor begin to send inhibitory signals to immune cells, causing them to “ignore” the growing tumor until it is virtually invisible to the immune system. The ignorance, or immunotolerance, of these tumors is caused by cellular “brakes” placed on the immune cells. Dr. Allison’s and Dr. Honjo’s research focuses on two of these cellular brakes and how their influence can be lifted to induce the body to attack cancer.

In the 1990s, Dr. James P. Allison studied the function of a T-cell receptor called CTLA-4, a down-regulator of immune activity. The CTLA-4 receptor inhibits T-cell activity by blocking activating signals that come from other cells. Its function is like telling the T-cell to ignore a blaring cellular alarm that says “attack”. While other researchers sought to use CTLA-4 as a target for treating autoimmune disorders, Dr. Allison explored the possibility of targeting this protein to treat cancer. He developed an antibody that could bind to CTLA-4, called anti-CTLA-4, and block its function, thus preventing the inhibition of T-cell activity. Testing his hypothesis on mice yielded promising results; mice treated with the antibodies unlocked the devastating cancer-killing abilities of T-cells, effectively decreasing the size of their tumors. These results pushed the study forward to clinical trials, in which patients with skin cancer, called melanoma, showed drastic reduction in tumor advancement. Advanced-melanoma patients treated with the anti-CTLA-4 therapy showed persistent responses, some lasting 10 years. In a subset of other patients treated with the therapy, all signs of any remaining cancer had disappeared. Seeing the success of anti-CTLA-4 is baffling for researchers in the field; its success is shared with another therapy targeting a similar cellular brake known as PD-1.

PD-1 was discovered by Dr. Tasuku Honjo in 1992. Like CTLA-4, PD-1 is a surface protein found on T-cells that acts as a cellular brake. PD-1 and its associated proteins are generally involved in protecting the body’s own cells from immune attack, but they are also responsible for helping tumors and other infectious agents gain immunity against the body’s defenses. Dr. Honjo’s team characterized PD-1 in a series of elegant experiments and showed that blocking PD-1 by using an antibody called anti-PD-1 can be effective in treating cancer in mice. Following this success, clinical trials proceeded. The anti-PD-1 therapy clearly showed efficacy in treating a variety of cancers—patients showed dramatic improvement and long-term remission. The therapy was even effective in patients with severe metastatic cancers that had spread to multiple parts of the body, a feat that was previously unthinkable. Current research is moving forward with further characterization of how exactly these cellular mechanisms allow for T-cells to infiltrate the cancer and destroy tumors, as well as methods for increasing the likelihood of therapy success.

The discovery and targeting of both CTLA-4 and PD-1 led to the development of what is now called immune checkpoint inhibition therapy. Cancer is one of the top causes of death worldwide and conventional pillars of treatment include radiotherapy, surgery, and chemotherapy, each with its own drawbacks. Dr. Honjo’s and Dr. Allison’s research, along with many other researchers’ discoveries, have led to the substantial emergence of a new pillar,
termed immunotherapy. Earlier in 2017, two different treatments of this category, called Chimeric Antigen Receptor T-cell therapies (CAR-T) were approved by the Food and Drug Administration for the treatment of acute lymphoblastic leukemia. Similar to anti-CTLA-4 and anti-PD-1 antibodies, CAR-T therapy involves the manipulating the body’s own T-cells for attacking and destroying cancerous cells. Immunology is now a growing field of interest in targeting a variety of diseases aside from cancer, despite having only been heavily studied in recent years. The clinical proficiency of CAR-T and anti-CTLA-4/anti-PD-1 therapies in treating a multitude of cancers in a variety of patients is groundbreaking and extremely promising for doctors, researchers, and patients alike. These bright spots of hope for those receiving the devastating diagnosis of cancer would not be possible without the hard work, dedication, and scientific intuition of scientists and doctors like Dr. Allison and Dr. Honjo.

REFERENCES


