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COMMENTARY

2018 Nobel Prize in medicine awarded to cancer immunotherapy: Immune checkpoint blockade — A personal account

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James P Allison and Tasuku Honjo were awarded the 2018 Nobel Prize in Physiology or Medicine for the development of a revolution in cancer therapy[1]: immune checkpoint blockade. This is a truly well-deserved honor for both Allison and Honjo. The immune system has multiple levels of brakes, known as immune checkpoints, to negatively downregulate activation and function of T cells and other immune cells. Immune checkpoints are important mechanisms for preventing the immune system from attacking the host's own cells.

Jim's original idea that the temporary relief of immune checkpoints could mobilize the immune system to attack tumors was not popular. When I joined Jim's lab as a postdoctoral fellow in 2000 (Fig. 1), most people in the field did not believe cancer immunotherapy would work in the clinic. The landmark paper published in 1996 experimentally demonstrated Jim's idea for the first time that a monoclonal antibody against CTLA-4, one of the major immune checkpoints, blocked CTLA-4 function and enhanced the anti-tumor immunity, which led to a cure of cancer in mouse models.[2] A monoclonal antibody therapy against human CTLA-4 was approved by the Food and Drug Administration (FDA) in 2011 to treat malignant melanoma,[3] which was the first immune checkpoint inhibitor in cancer therapy. Honjo originally cloned PD-1 in 1992[4] and later showed PD-1 as another important immune checkpoint of T cells.[5] Subsequently Lieping Chen in 1999 and Gordon J Freeman in 2000 identified and characterized the

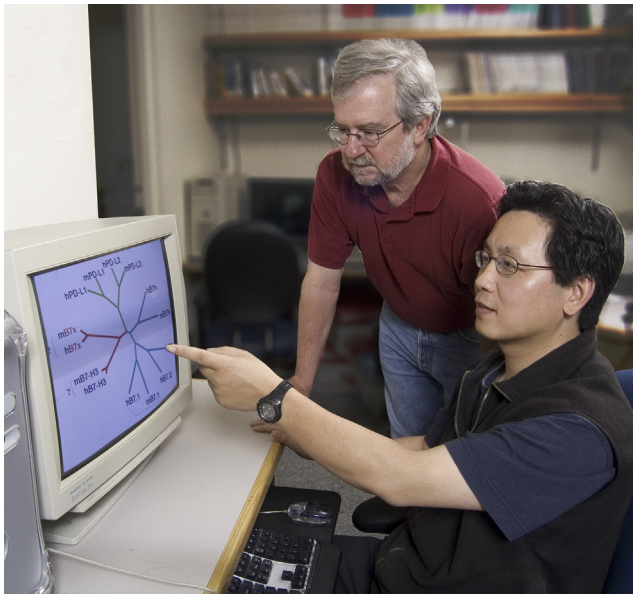

Figure 1 James Allison and Xingxing Zang in the University of California at Berkeley.

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first ligand for PD-1, B7-H1[6] or PD-L1.[7] Extensive studies on the PD-1/PD-L1 pathway led to several FDA approved blocking antibodies against PD-1 or PD-L1 for the treatment of a broad spectrum of human cancers. Cancer immunotherapy and traditional cancer treatments have completely different mechanisms. Traditional cancer treatments mainly target cancer cells, whereas cancer immunotherapy, particularly immune checkpoint blockade, utilizes the immune system to kill cancer cells. The 2018 Nobel Prize is a testament that the fundamental research can be translated into clinical therapy and that immunotherapy, along with surgery, chemotherapy, and radiation, is a reliable and objective approach to treat cancer.

The 2018 Nobel Prize awarded to cancer immunotherapy is only the beginning. One of the biggest challenges in the field is that the majority of cancer patients do not response to current immune checkpoint inhibitor antibodies against CTLA-4, PD-1 or PD-L1. My lab discovered several new immune checkpoints[8] such as B7x, HHLA2, TMIGD2, etc. In addition, we have also studied other immune checkpoints including Tim-3, B7-H3, BTNL2, ICOS, etc. Our recent work reveals that the majority of PD-L1 negative human cancers express B7x and HHLA2,[9] suggesting these new immune checkpoints have very different mechanisms and provide excellent targets to develop new immune checkpoint therapies. The future direction of immune checkpoint blockade should focus on new immune checkpoints and combination therapies.

References

1. *The Nobel Prize in Physiology or Medicine*; 2018. https://www.nobelprize.org/prizes/medicine/2018/press-release/.
2. Leach DR, Krummel MF, Allison JP. Enhancement of antitumor immunity by CTLA-4 blockade. *Science*. 1996;271:1734—1736.
3. FDA approves YERVOY™ (ipilimumab) for the treatment of patients with newly diagnosed or previously-treated unresectable or metastatic melanoma. https://news.bms.com/press-release/rd-news/fda-approves-yervoy-ipilimumab-treatment-patients-newly-diagnosed-or-previousl.
4. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *EMBO J*. 1992;11:3887—3895.
5. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*. 1999;11:141—151.
6. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med*. 1999;5:1365—1369.
7. Freeman GJ, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192:1027—1034.
8. Janakiram M, et al. The third group of the B7-CD28 immune checkpoint family: HHLA2, TMIGD2, B7x, and B7-H3. *Immunol Rev*. 2017;276:26—39.
9. Cheng H, et al. Wide expression and significance of alternative immune checkpoint molecules, B7x and HHLA2, in PD-L1-negative human lung cancers. *Clin Cancer Res*. 2018;24:1954—1964.