James P. Allison Receives the 2015 Lasker-Debakey Award in Clinical Medical Research

The 2015 winner of the Lasker-Debakey Clinical Medical Research Award is James P. Allison, PhD, Chairman, Department of Immunology, and Executive Director, Immunotherapy Platform, at the University of Texas MD Anderson Cancer Center in Houston, Texas. As noted on their website, Lasker-Debakey Award "honors investigators whose contributions have improved the clinical treatment of patients." Dr. Allison received this award "for the discovery and development of a monoclonal antibody therapy that unleashes the immune system to combat cancer."

Dr. Allison's fascinating career is a study in building on one's findings, rather than resting on one's laurels. He was a graduate student at the University of Texas, did a postdoc at the Scripps Clinic, and then started his professional career at the University of Texas System Cancer Center. It was this phase of Dr. Allison's nascent career in which he and his colleagues made their first oversized contribution—the isolation and characterization of the T-cell receptor (TCR), a molecule that had eluded immunologists for years. This is his remarkable contribution number one.

Dr. Allison then joined the faculty at the University of California, Berkeley, where he continued to pursue the question of how the TCR activated specific T-cell immune responses. It became clear that the TCR was required but not sufficient. His group identified the role that another T-cell membrane protein, CD28, played in this activation—it was the costimulatory, "second" signal that was necessary for full activation of the T cell. This is his remarkable contribution number two.

Recognition of the importance of CD28 led to a flurry of activity to uncover alternative molecules that might provide similar costimulatory signals. One candidate molecule, CTLA-4, which had been previously discovered by others, was found also to bind the ligand for CD28, B7, but with even greater affinity. While most investigators presumed this was another costimulator for TCR activation, Dr. Allison and Jeff Bluestone (then at the Ben May Institute for Cancer Research at the University of Chicago, and currently at the University of California, San Francisco) independently demonstrated that it could mediate an inhibitory signal. Dr. Allison's group then did some of the definitive experiments showing that CTLA-4 actually interfered with the activation of T cells. With remarkable insight, they reasoned that perhaps the immune system fought tumors ineffectually not because it did not recognize them, but because T cells in tumor-bearing individuals were inhibited by mechanisms that normally serve as checkpoints to wind down T-cell activation and prevent autoimmunity. While other researchers were attempting to boost the immune system with more stimulation or better vaccines, Dr. Allison's group showed that, by blocking negative signals with antibodies to CTLA-4, antitumor activity could be increased. This is his remarkable contribution number three.

Researchers who have made three significant intellectual advances in their career would certainly be excused if they retired to the islands. But driven by the prospect of developing a monkey wrench to throw into the wheel of inhibitions that were holding back effective antitumor immunity, Dr. Allison not only pursued the practical implementation of "checkpoint blockade" but also drove the process. He was determined to test this approach as a generalizable solution to the problem of incurable cancers.

Biotech start-ups and big pharmaceutical companies had grown somewhat leery of immunotherapies. One problem was that many of the strategies depended upon the development of individualized reagents that capitalized on unique mutations found in each tumor, but these were difficult to produce, laborious, and expensive. Other approaches tried to circumvent the need to know what the tumor epitopes were, by seeking "shared" tumor antigens, but often these epitopes were shared by normal cells as well, with toxic off-tumor effects. Alternatively, global boosting of the immune response, for example, by administering various cytokines, was pursued with the idea that tumor immunity would be enhanced, but perhaps not surprisingly this often resulted in rampant autoimmunity or a "cytokine storm," in which inflammatory reactions produced serious and potentially lethal immune-mediated injury.

Dr. Allison waded into this maelstrom with the conviction from his preclinical studies that he now had a better approach, but he needed to find a partner to produce a clinical grade humanized antibody for use in trials. After some false starts, he found a collaborator in a then early stage biotech company, Medarex, that shared his enthusiasm for this "checkpoint inhibition" approach and agreed to generate and clinically test a human antibody, now known as ipilimumab. Initial small trials in patients with melanoma and renal cancers showed astonishing promise. Dr. Allison moved from Berkeley to Memorial Sloan-Kettering Cancer Center in New York, where he could work with clinical researchers capable of organizing and executing clinical trials, initially in conjunction with Medarex, and subsequently with Bristol-Myers Squibb, which acquired Medarex. These efforts ultimately led to FDA approval of ipilimumab for the treatment of melanoma and other cancers. The results of these registration trials represent a true milestone for the field of immunotherapy. Not only were many of the treated patients living longer—most of whom had failed all other conventional therapies and had a life expectancy of less than 1 year—but a fraction of these patients appeared to be...
rendered free of disease. This is Dr. Allison’s remarkable contribution number four.

Although ipilimumab treatment now provides incurable cancer patients with renewed hope, their odds are improved even more by combining this antibody with other checkpoint blockers, such as antibodies that block the PD-1/PD-L1 inhibition system. Up to 50% of melanoma patients experience significant therapeutic responses to the combination. Dr. Allison’s perseverance and determination not only to understand the mechanisms of T-cell activation and regulation, but to translate that knowledge into clinical treatments for cancer, are both humbling and inspiring. We congratulate him, a deputy editor of this journal, and thank him for breaking open a dam and releasing the possibilities for harnessing the immune system to treat cancer.

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