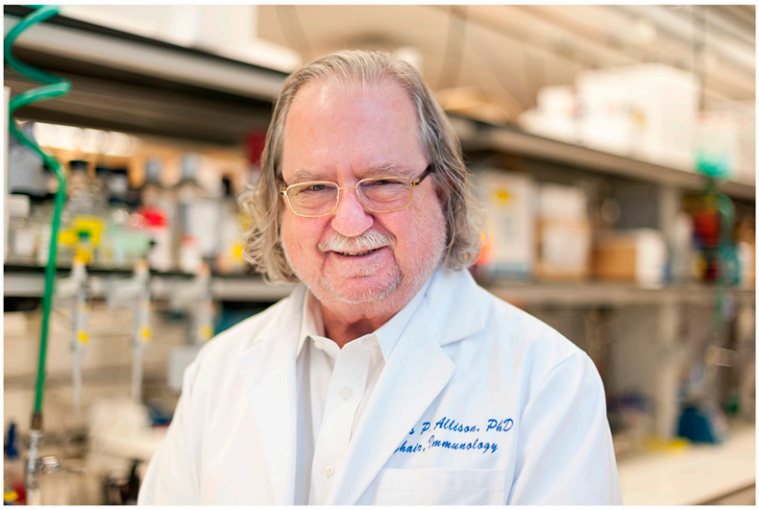
QnAs with James Allison

Prashant Nair, *Science Writer*

In May 2016, the United States Food and Drug Administration (FDA) approved atezolizumab for treating advanced bladder cancer. The drug, which marshals the immune system against cancer, is only the fourth in a class of drugs called checkpoint blockers to be approved by the FDA. By now a familiar term in cancer immunotherapy, checkpoint blockade is a strategy in which an engineered antibody is used to hobble otherwise crucial brakes on the immune system, thus loosing immune sentinels upon tumors. Now used to treat a range of cancers, such as metastatic melanoma, lung cancer, kidney cancer, and Hodgkin's lymphoma, the approach was first demonstrated in the mid-1990s, when MD Anderson Cancer Center immunologist James Allison, a member of the National Academy of Sciences, used antibodies against one such checkpoint brake called CTLA-4 to unfetter T cells and attack tumors in mice. (Previously, Allison and molecular biologists Jeff Bluestone at the University of California, San Francisco and Craig Thompson at Memorial Sloan-Kettering Cancer Center had simultaneously found that CTLA-4 hobbles T-cell activation.) Before long, Allison's approach was firmly validated in clinical trials of patients with metastatic melanoma. Those early gains revived long-dormant interest in cancer immunotherapy, and a diverse array of experimental approaches—bispecific T-cell antibodies, engineered cell therapies, neoantigen vaccines—crowd the current therapeutic landscape. For his pioneering contributions to a burgeoning field that has by turns inspired hope and hype, Allison has garnered an impressive host of scientific honors, notably the 2015 Lasker–DeBakey Clinical Medical Research Award. Allison spoke to PNAS about the field's growing pains and prospects.



James Allison. Image courtesy of Adolfo Chavez III (University of Texas MD Anderson Cancer Center, Houston).

PNAS: Five years ago, ipilimumab, the checkpoint-blocking monoclonal antibody that you conceptualized, was approved by the FDA for treating late-stage melanoma. Immunotherapy has since loped to the forefront of experimental cancer treatment, spawning large research consortia along the way. However, the optimism is cautious, largely because of the small number of patients predicted to benefit from the drugs and the modest response rates seen in clinical trials. What are some of the biggest scientific hurdles facing cancer immunotherapy?

Allison: Five years ago, the median survival of patients with metastatic melanoma was around 11 months. Now, with CTLA-4 inhibitors, ∼22% of patients are alive more than 10 years after a single round of treatment, as seen in recent trials. Combining CTLA-4 and PD-1 [another checkpoint brake on T cells] inhibitors has further increased the therapeutic benefit: the fraction of metastatic melanoma patients who survived three years after treatment has risen to greater than 50%. While these numbers might be modest, they must be considered in context. Several molecularly targeted drugs are approved on the basis of a 90-day increase in survival, so the therapeutic pay-off with checkpoint blockade is comparatively quite significant.

That said, there are several challenges ahead, and many of these have to do with gaining a better understanding of the mechanisms behind the benefits of immunotherapy. The patients who benefit the most from checkpoint inhibition seem to be those whose tumors have high mutational loads. (In melanoma, for example, these mutations are often the result of UV exposure, and in lung cancer, they result from carcinogens in cigarette smoke.) There is also a loose association between mutation loads in tumors and the extent to which the tumors are infiltrated by tumor-fighting T cells. We still don't know the optimal sequence in which combination therapies must be administered. Nor do we understand how localized treatments are able to trigger the innate immune system against distant tumors. These are active areas of research and just a handful of the outstanding challenges.

PNAS: The notion of enlisting the immune system to fight cancer is more than a century old. Tecentriq (atezolizumab), the latest checkpoint-blocking drug to gain FDA approval, may have been approved mere months ago, but the disease it targets has been treated with a form of immunotherapy for decades. (The standard treatment for moderate to high-grade bladder cancer is to administer

a formulation of tuberculosis bacteria to unmoor the immune system against the cancer.) How did you come upon the idea for checkpoint inhibition as a therapeutic strategy?

Allison: The idea for checkpoint inhibition came about after we realized that T-cell activation was a complex process. It came from the realization that T-cell activation wasn't simply a matter of self/nonself recognition, but that a number of costimulatory signals were involved. Around the time the role of the CD28 receptor in activating naive T cells came to light, the prevailing wisdom was that the CTLA-4 molecule, which bound to the same ligands as CD28 receptor, was a costimulatory molecule, whose job was to keep T cells going. It wasn't until Jeff Bluestone's group and mine showed independently that CTLA-4 was in fact an inhibitory molecule on T cells that its true function was revealed. Further work on costimulatory molecules on T cells supported the notion that CTLA-4 was indeed acting as a brake on the innate immune response to tumors. So the solution was to suspend the brakes.

PNAS: Your preclinical findings on CTLA-4 and checkpoint inhibition were not readily embraced by the scientific community when you first announced them. It was not until Jedd Wolchok's trials of your antibody showed its striking therapeutic effect that checkpoint blockade gained steam. How do you explain the initial skepticism?

Allison: At the time, there was a general feeling in the cancer community that immunotherapy was a pipe dream, given the number of failures. Moreover, the compelling notion that cancer can be treated by targeting the underlying mutations was gaining ground, so in some ways molecularly targeted cancer treatment eclipsed immunotherapy. So when the phase I trial results with ipilimumab came out, it surprised a lot of people. That trial was a paradigm for a couple of reasons: We were not trying to activate or induce a therapeutic response but merely to release the brakes on a natural immune response. Second, immunotherapy is focused on the immune system, not the cancer, so in a manner of speaking, it's a way to treat cancer by ignoring it.

PNAS: For cancer treatment, a growing list of trials suggests that combining immunotherapy with chemotherapy and/or radiation is likely to improve clinical outcomes. And one emerging line of research indicates that molecularly targeted drugs, which exploit genetic defects in tumors, might interact in intriguing ways with immunotherapy drugs. Are combinations of precision drugs and immunotherapy on the cancer-treatment horizon?

Allison: There are currently no such combination therapies approved, but the impact of molecularly targeted drugs on immunotherapy is another active area of research. In melanoma, for example, tumors in patients treated with a BRAF inhibitor experience increases in the levels of neoantigens [immunogenic peptides expressed on tumor cells but not on normal cells] and MHC [major histocompatibility complex molecules, which are crucial for immune recognition and response] levels. The drug-treated tumors become much more accessible targets for immunotherapy. I expect such combination therapies will be approved in the future.

PNAS: Does that mean immunotherapy is unlikely to be a stand-alone therapy at least for some cancers?

Allison: There is a lot of work on combining not only molecular targeted drugs but also radiation with immunotherapy. One goal of these studies is to try not to kill every last tumor cell with radiation or the drugs, but just enough to prime an effective T-cell response and allow the immune response to kick into gear. Once the mechanisms behind immunotherapies like checkpoint inhibition are clearly worked out, I think immunotherapy will eventually become a stand-alone therapy for some cancers. The immune system's specificity to the carcinogenic process, the persistence and memory of the immune response, and the adaptability of the immune system to the cancer's evolution argue in favor of this thinking.

PNAS: Neoantigen vaccines are fashioned using patients' individual mix of tumor-specific mutations. These experimental vaccines, which are designed to jolt the immune system into action against tumors while sparing normal cells, have basked in the spotlight in the past year. A handful of biotech companies are performing preclinical studies, and at least two have launched clinical trials in melanoma and breast cancer. What is your opinion on the promise of these hyperpersonalized therapeutic vaccines?

Allison: The success of neoantigen vaccines depends on the tumor having the correct mutations; it's a bit of a lottery in that respect. Having a higher mutational load in tumors does not guarantee a better vaccine response, though some trials have shown a positive association. It's true that the predictive algorithms used to design neoantigen vaccines are getting better and better. That said, although the algorithms are good at predicting which peptides are likely to trigger a CD8 T-cell response, their predictive ability for a CD4 T-cell response is still not as good as we would like it to be. And both responses are crucial for the vaccine's success.

PNAS: Engineered T-cell therapy, using chimeric antigen receptor (CAR) T cells, for example, has shown promise in trials for blood cancer. However, in some trials CAR-T cells have been associated with toxic side effects, such as dangerous cytokine surges that can rip through patients' bodies. Earlier this month, for example, the FDA briefly halted a prominent CAR-T clinical trial, which included a chemotherapy agent for preconditioning the immune system, after patients with advanced adult lymphoblastic leukemia died due to cerebral edema. What are the biggest challenges confronting the use of engineered T cells to fight cancer?

Allison: There has been a lot of understanding in the last few years on the mechanisms behind some of these unintended side effects, as well as ways to modify the dosage of the therapy to avoid cytokine storms, for example. The bigger challenge with engineered T-cell therapies is to find suitable target antigens on tumor cells. Aside from the well-defined target antigens for leukemias, there aren't that many known tumor-specific antigens, and proteomics studies are ongoing to look for such antigens.