PROFILES IN RESEARCH

A Conversation With James P. Allison, PhD

Independence and Tenacity Anchor Immunology Pioneer

By Beth Fand Incollingo

Photo by Matthew Septimus, courtesy of Memorial Sloan-Kettering Cancer Center

James P. Allison has never hesitated to buck the system.

As a teenager, the pioneering oncology researcher refused to take biology at his small-town Texas high school because the theory of evolution had been omitted from lessons for religious reasons. Instead, Allison took a university correspondence course, working alone in an empty classroom.

"I'd already decided that I wanted to be either a doctor or a scientist, and I knew that evolution is to biology as Newton is to physics, so I refused to take the course. It got me into trouble with some of the teachers," said Allison, 62, who went on to earn a doctorate in biological science and now serves as chairman of the Immunology Program at the Memorial Sloan-Kettering Cancer Center (MSKCC), New York, New York.

That readiness to challenge the status quo has stayed with Allison during a 30-year-plus career dedicated to stimulating the human immune system to fight cancer, particularly through discoveries about the workings of T cells, which help protect the body from pathogens. Spurred also by personal and familial experience with cancer, Allison has been willing to probe his theories even amid skepticism in the scientific community.

A case in point emerged when Allison began to suspect that the molecule CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) inhibited antibody response. He weighed that idea in the face of theories to the contrary: In textbooks, CTLA-4 had been categorized as a molecule that stimulated immune response.

Allison pursued his idea anyway. The result was ipilimumab, the promising melanoma treatment that the FDA is considering for approval, with a decision expected in March.

Allison's years of work on that project reaffirmed his guiding philosophy.

"Let your mind lead," advised Allison, a member of the National Academy of Sciences and the Institute of Medicine. "Don't pay attention to conventional wisdom if you've got data that show otherwise. Sometimes it's hard to go against the system, but you have to do it if something needs to be accepted."

A Move to a New Lab

Living by that credo led Allison not only to success in the lab, but also to MSKCC. He joined the staff there 7 years ago, excited that he would be working at a world-class cancer center with a strong interest in immunological approaches. It is among the 150 sites where clinical trials of ipilimumab were being conducted.

"As I saw my drug developing, I wanted to be a part of it," Allison said. "I wanted to learn more about what went on in the clinic and to offer advice, because this was a totally new concept. You can't approach it the same way you would if you were giving a drug that will go into a tumor cell and kill it."

The move to New York meant the end of a 20-year relationship with the University of California, Berkeley, where Allison had been a professor in the Division of Immunology and director of the Cancer Research Laboratory. In exchange, Allison took on roles as MSKCC's David H. Koch Chair in Immunologic Studies, director of the Ludwig Center for Cancer Immunotherapy, and attending immunologist in the Department of Medicine.

Now, amid administrative duties, including hiring colleagues, Allison spends his time examining data and overseeing his lab, where researchers carry out his ideas and some of their own.

Specifically, his work at MSKCC has included analyzing patients' immune responses to help predict which categories of patients will most likely benefit from ipilimumab and under what circumstances.

"Also, I've got some ideas for additional targets, and some came from learning what happened in the patients, things we hadn't noticed in mice," Allison said. "Now we can go back into mice and observe some of the same things to get new ideas about second-generation drugs."

High Expectations for Ipilimumab

The drug that started it all, ipilimumab, is an antibody that targets CTLA-4, a molecule on the immune system's T cells that impedes their ability to fight cancer. Once stimulated, T cells can protect the body from disease by attacking alien proteins, or antigens, such as tumor cells.

Normally, after a time, that attack is halted by CTLA-4, even though dangerous cells may remain. Ipilimumab is designed to eliminate CTLA's "stop" message, so that T cells can continue to fight indefinitely.

Administered intravenously, ipilimumab, also known as CTLA-4 blockade, works best if an anticancer therapy—such as radiation, chemotherapy, freezing, or targeted therapy—is used first to stimulate T cells to go on the attack, Allison said. Once that has been accomplished, the scientist said, the drug can be widely useful.

"You're treating the immune system, not the cancer, so it can be used, potentially, against every kind of cancer," he explained, adding that patients do not develop a resistance to the drug.

A phase III clinical trial of ipilimumab demonstrated improved overall survival of previously treated patients with metastatic melanoma, its sponsor, Bristol-Myers Squibb, announced in June 2010. Specifically, 44% to 46% of patients treated with ipilimumab were alive at 1 year as compared with 25% of patients treated in the control arm. At 2 years, 22% to 24% of patients treated with ipilimumab were alive as compared with 14% of patients treated in the control arm.

"Metastatic melanoma is one of the deadliest forms of cancer with no approved options for pretreated patients," said Steven J. O'Day, MD, chief of Clinical Research and director of the Melanoma Program at The Angeles Clinic and Research Institute, California, and presenter of the study results. "For the first time, a significant improvement in overall survival has been demonstrated in previously treated advanced melanoma patients in a large, randomized phase III study.

The FDA was expected to announce by March 26 whether it will approve the drug for use in advanced melanoma. Ipilimumab is also under review by the European Medicines Agency and other health authorities worldwide for pretreated advanced melanoma.

Meanwhile, Bristol-Myers Squibb is conducting a phase III trial of the drug in patients with prostate cancer.

Cancer Has Taken a Personal Toll

For Allison, that progress is meaningful on more than a professional level. Like the patients he's dedicated to helping, the researcher has lost much to cancer.

When Allison was 10, his mother died of lymphoma. Two of her brothers also succumbed to cancers, one to melanoma and the other to lung cancer. Then, 6 years ago, Allison's brother died of prostate cancer, around the same time that Allison underwent a prostatectomy as he fought the disease himself.

The scientist was in graduate school at the University of Texas at Austin when he vowed to investigate treatments for the disease.

"I just thought, 'This is a terrible thing, and there's got to be a better way than chemotherapy and radiation,' which my mother and one of my uncles had," Allison said. "I saw all the negative effects."

In 1982, Allison was working at the University of Texas System Cancer Center when his research sparked a discovery that has been at the heart of his work ever since: He became the first scientist to figure out how T cells recognize alien proteins within the body.

"We (identified) the antigen receptor on T cells," Allison said. "That was important because it's like the ignition switch on T cells, the thing that recognizes peptide or bacterial protein or tumor antigens."

Six years later, at Berkeley, Allison was among researchers who realized that T cells needed to do more than recognize invading pathogens to start their attack. They needed a costimulatory signal, another molecule, to act as a gas pedal and make them go. Allison's group determined that the costimulatory molecule was CD28.

The final piece of the puzzle fell into place in 1996, when Allison and his fellow researchers noticed a gene that was structurally similar to CD28—*CTLA4*—and started experimenting to see what it did.

"We found that if you delete CTLA-4, the T cells keep dividing. It's like you take the brakes off going downhill and can't stop," Allison said. "So I thought, 'Maybe this molecule shuts down T cells and keeps you from getting a strong enough immune response to deal with a tumor, and maybe if we block that molecule we can get the immune system to kill cancer cells and not cause side effects in mice.' And that's exactly what we found. With many tumors, injecting this 1 molecule was enough to get a tumor rejected."

New Research Targets in Sight

Allison's discoveries led not just to ipilimumab, but to a growing interest within the scientific community in using immune checkpoint blockade in tumor therapy. Another research group has developed a potential treatment, also part of Bristol-Myers Squibb's pipeline, that works by blocking an inhibitory molecule known as programmed death-1 (PD-1).

Meanwhile, Allison is continuing his research in the area. "A new molecule we found can be used to stimulate, rather than take the brakes off, of immune response," he said. "I'm looking forward to getting that into the clinic, too."

Ultimately, Allison hopes that kind of research will change the treatment paradigm for many cancers.

"There's a large faction of the cancer community that does not necessarily see that immunological approaches can work against cancer because they haven't in the past, but now we know they do," he said. "I'm looking forward to a time when we can combine targeted therapies with immunological approaches and take advantage of the special properties of each. There are already some combined trials underway, and in the next several years we'll see a lot of promise, data, and results."

It will likely be a road paved with the frustrations that research science, with its plodding pace, can bring, Allison said. Still, in his view, getting results is always worth the trip.

There's a rush that comes with a new discovery, he said—the thrill that drew him to science in the first place.

"I enjoy the feeling," he said, "of being the first one on the planet to figure something out."

Beth Fand Incollingo is a NJ-based writer and editor, and owner of the communications firm Texterity, LLC.

James P. Allison At a Glance

- Is married and has a son who is studying architecture
- Enjoys sailing
- Is a Willie Nelson fan
- Plays blues and country/western harmonica in a band called The Checkpoints, made up of cancer clinicians and researchers
- Recalls his experience working in a grain elevator as the worst job he's ever had. He kept the summer job during his undergrad days because "I just wanted to prove to myself that I could take it for a while."
- Likes the book *The Right Stuff*, by Tom Wolfe, because its main characters "stuck together, dedicated themselves to something, wouldn't let anybody stand in their way, and had a pretty good time"
- Says his interest in biology—and in giving something back to people in need—was spawned by his father, a country doctor who treated patients regardless of whether they could afford it. "Some people paid in tamales," Allison recalls.
- Believes it's his commitment to understanding the basics of the immune system—not his determination to cure cancer—that has led to his research breakthroughs
- Is concerned that the US government is vastly underfunding basic science research. "I'm afraid we're going to lose a generation of promising scientists because they'll have to raise the funding for the bulk of their research," he said. "That's a disgrace for a country like this."