CANCER RESEARCH INSTITUTE

Our Strategy & Impact

James Allison: The Texas T Cell Mechanic

Name: James P. Allison, Ph.D.

Location: Houston, TX

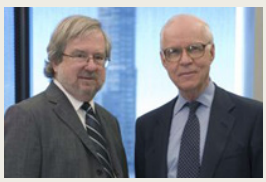
"Once you've generated T cells that can recognize cancer, you've got them basically for the rest of your life."

James Allison, Ph.D., knows his T cells. For the past 30 years, he's studied them inside and out, learning what makes them tick. From his laboratory have emerged some of the most important discoveries in immunology.

In the early 1980s, Allison was one of the first to identify the T cell receptor—the part of a T cell that binds to antigen and functions as the T cell's ignition switch. A few years later, in 1992, he showed that a molecule called CD28 functions as the T cell's gas pedal. Then, in 1995, when no one else was even thinking there would be such a thing, he identified the T cell's brakes, in the process opening up a whole new vista in cancer treatment.

Known as checkpoint blockade, the treatment approach uses antibodies to block the action of this braking molecule, called CTLA-4. By "taking the brakes off" the immune response, the treatment enables a more powerful anti-cancer response.

Some of the most dramatic clinical responses seen in recent years have occurred with checkpoint blockade antibodies, including ipilimumab (anti-CTLA-4) and nivolumab (anti-PD-1). Fittingly, in 2013, Science magazine named cancer immunotherapy the "breakthrough of the year," citing Allison's work in particular.



Allison is currently chairman of immunology at The University of Texas MD Anderson Cancer Center in Houston, Texas. He serves as director of CRI's Scientific Advisory Council, a position he assumed in 2011, when Lloyd J. Old, M.D., retired (pictured together on right).

For such a high-powered scientist, Allison is surprisingly down-to-earth. He speaks in the drawl of his native Texas, enjoys a good BBQ, and plays harmonica in a garage band called "The Checkpoints," composed of other immunologists.

We spoke to Dr. Allison about his research, his love of science, and his hopes for the future of cancer treatment.

CRI: What's the advantage of immunotherapy over other cancer therapies?
Dr. Allison: It's compelling to think of the immune system in cancer for three reasons. One is the incredible specificity of the immune system. Because cancer cells have distinct targets, the immune system can target those cancer cells specifically, and with very few of the side effects normally associated with conventional drugs.

The second one is that the immune system can adapt as the tumor changes. The immune system, if you keep stimulating it in the proper way, can change as the tumor changes.

The third one is that you can get memory and that's the hallmark of the immune system that doesn't exist for any other type of cancer therapy. Once you've generated T cells that can recognize cancer, you've got them basically for the rest of your life. Whereas with every other drug, they kill a bunch of tumor cells and then the drugs go away.

Also, you won't find the phenomenon of resistance with immune-based therapies. If the tumor comes back, you can treat it anti-CTLA-4 again, and again, and again. It never quits working.

CRI: How did you get into science?
Dr. Allison: My father was a doctor. I grew up in a very small town in south Texas and I guess from him I got an interest in medicine and then that led me to have an interest in science. And I was lucky enough in the eighth grade to go to Austin, Texas and participate in a science course there for high-level students. After that, I just knew I wanted to do science. And then later that grew into immunology. I became interested in cancer because I've lost a number of family members to cancer. My mother and two of her brothers, and my own brother died of cancer.

CRI: You're known for your work on ipilimumab, the anti-CTLA-4 checkpoint blockade therapy. Tell us how you got into that.
Dr. Allison: I began studying the basic science at the University of California at Berkley. We were interested in understanding regulation of T cell responses and I began to suspect that, in addition to positive signals that need to be given to initiate immune responses, there are also negative signals that no one had really thought of before that might limit responses. And it occurred to me that might be one reason why it was very difficult to actively mobilize the immune system to attack cancer cells. That it isn't enough to just try to push them into going, but you have to learn how to suspend the brakes, if you will, at least temporarily, to really realize the full potential of the immune response.

And so we found this molecule called CTLA-4 that fit those criteria and showed in mouse models that simply covering up that molecule with a monoclonal antibody could lead to rejection of many types of tumors in mice.

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CRI: So those were the laboratory results. Tell us about the clinical experience with ipilimumab.
Dr. Allison: It went into a very large trial in metastatic melanoma, where the survival rate is probably 12% for two years, and much, much less for three years and four years. It was very gratifying because when the results of the phase III clinical trial were unveiled, there was an eleven month increase in the overall survival, on average, in the popula[illegible]

That w[illegible] in history to show a survival advantage in metastatic melanoma—the first of any kind of drug. But the really exciting thing is that there were somew[illegible] 20%-25% of the patients who were alive at two years, three years, four years, and now even more. So there are a lot of people who are really getting cured b[illegible]t. That's a strong word to use, of course. I think we have to redefine the word 'cure' a little bit. I think, for practical purposes, if you're alive and are having no trouble a decade after your treatment, then I think that's as good as a cure.

I know a patient who was treated at UCLA in the phase I trial almost 12 years ago, who said that when she was first told about ipilimumab she had failed every other drug and was hoping to hang on long enough to see her two sons graduate from high school. Well, I saw her just last week and she told me that they've both now finished graduate school. She's almost 12 years out, no sign of disease, no re-treatment necessary. I think this is what we can begin to think is a reality now for immunotherapies.

CRI: How quickly will we start to see major changes in cancer treatment?
Dr. Allison: I see the field as a whole beginning to progress very rapidly from now. We know that the basic concept of checkpoint blockade works in a fraction of people. We've done a lot of preclinical work in mouse models showing that it works much better when you can combine it with other things, like vaccines. The nice thing about these approaches in general is that you can use the same drug for all kinds of cancer. CTLA-4 blockade has mostly been used in melanoma, but also has been shown to be effective in prostate cancer, ovarian cancer, renal cancer, and a few other types. It should be almost universally applicable to tumors, provided that we can get an immune response initiated to them. My colleague Jedd Wolchok says that's because you're treating the patient, not the cancer.

CRI: What do you see as the future of immunotherapy?
Dr. Allison: The way the field of immunotherapy is going now is toward combinatorial therapies, where we combine these different immune checkpoints blockers, and also combine these with drugs that actually kill tumor cells. We've seen long-term survivals in about a quarter of melanoma patients, but I think it's within our easy reach of doubling that or better just in the next few years with the tools that we now have. And since we're coming up with new tools all the time, I think it's just a really exciting period. The preclinical and clinical studies are just exploding with new ideas.

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CRI: How does CRI advance the science of cancer immunotherapy?
Dr. Allison: I think CRI plays a very important role in, among other things, funding the training of young scientists and trying to interest them in cancer, particularly cancer immunology. By focusing on that particular area of funding, CRI helps foster advances in the field that will lead to even more ways to treat cancer down the line.

There's also the CRI/Ludwig CVC Clinical Trials Network. The CVC is a network of people all over the world who share the same reagents and learn from each other and share data. I think that's really driven the field as a model for how to proceed. And that wouldn't have happened had there just been a lot of individual investigators going where their own nose was taking them. Now you can have these collaborations that together are much bigger than the sum of the parts.

CRI: What do you see as the major barriers to progress in the field?
Dr. Allison: One of the barriers that frustrates many of the people in the field is that the different drugs which could be used in combination are sometimes held by different companies. And it's very difficult for reasons that have nothing to do with science, but everything to do with business to get the proper pieces to come together in a way that makes the most sense for maximum benefit. But that's beginning to change.

CRI: What is CRI doing to try to overcome these barriers?
Dr. Allison: CRI's Clinical Accelerator program has started to actually engage pharmaceutical companies that have these drugs, with the goal of bridging the divide between academia and industry. CRI wants to see its scientists who have been involved in vaccine studies for many years actually have some say in how these company drugs are combined and how the trial is conducted—even perhaps suggesting a study that the company might not have thought of. I think that is going to help move the field forward much more rapidly.

It took from 1995 when we published the first paper on CTLA-4 to 2011 before it was approved, and that's way too long. Now that we know the lessons, we know how to handle these things. So CRI can really take advantage of that knowledge to shorten the time and bring new treatments to patients much, much faster.

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