The American Association of Immunologists
Oral History Project

Transcript

James P. Allison, Ph.D.
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Interview conducted by
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Williams: This is an interview with Dr. James Allison for the American Association of Immunologists Centennial Oral History Project. Dr. Allison is Chair of the Department of Immunology and Director of the Immunotherapy Platform at the University of Texas MD Anderson Cancer Center. He is also Deputy Director of the Koch Center for Applied Research of Genitourinary Cancers at MD Anderson.

Dr. Allison was president of the American Association of Immunologists from 2001 to 2002 and served as an AAI Council member from 1996 to 2001. He was awarded the AAI-Dana Foundation Award in Human Immunology Research in 2008 and the AAI Lifetime Achievement Award in 2011.

We are in Dr. Allison's office at the MD Anderson Cancer Center. Today is Tuesday, April 16, and I am Brien Williams.

Thank you, Dr. Allison, for doing this for the AAI. Le

was there for about twenty years altogether. I was lucky enough to be there when Willie Nelson moved from Nashville to Austin and began his big-time career. That was quite an exciting time around there, lots of music. Austin was a great place to be.

real focus of the counterculture or whatever you want to call it, as counterculture as you can be at a university in the center of the state of Texas. But it was a lot of fun, very educational.

Williams: Were you politically active at the time?

Allison: Yes, I was always pretty politically active. My wife worked at the Capitol in the reference library the legislature uses. A lot of my friends were involved with serving as aide

Allison: No, because I got a lawyer. [laughs] And I was borderline diabetic, had partial hearing loss, had flat feet, and generally a wreck, you know. [laughs]

Williams: I see.

Allison: I was in pretty good shape, but, you know, anyway. It was a fun time.

Williams: First of all, you chose to get a Ph.D., not an M.D.

Allison: Right.

Williams: Or both. I guess that's because you clearly were moving in the direction of research.

Allison: Right.

Williams: So once you got the Ph.D., then you chose not to stay at Austin to do postdoctoral work, but instead went to Scripps, is that right?

Allison: Right.

Williams: Why did you choose—how did you get there?

Allison: Bill Mandy, who was sort of my co-mentor for my Ph.D., knew a man named Ralph Reisfeld that was a real rising star in immunology. At the time, Scripps was one of the best places in the world for immunology, and it just seemed like the place to go. I was pretty naïve, but, anyway, I went there, and I continued doing biochemistry, really. I didn't really get to do real immunology, what I consider real immunology, for some time after that. But that's basically why I went there. It was a great place and looked like a good project to work on with Ralph.

Williams: Did anything major come of that work?

Allison: There were some interesting things came out of it. At the time there was a big debate in immunology. Of course, people knew what antibody molecules were and how they worked, knew about B cells, and T cells had just been identified, but nobody really knew how T cells worked, nobody knew what the receptor was, what they used to recognize their targets.

So I didn't work on that there, but I worked the other side of it, because it was known then that molecules called MHC molecules, major histocompatibility complex molecules, were involved in graft rejection and all this. So we began to realize they were involved in antigen presentation and the T cells in part saw them. So I was trying to purify the MHC molecules, human, to study the structure, but not really doing anything functional. But on the side, a postdoc and

university could be. As I said, it was fun at Smithville, a lot of really good people

But, anyway, the whole idea of immune surveillance fell out of favor for a while, and the whole notion of using the immune system to treat cancer, it doesn't matter whether immune surveillance is true or not, you could still think, even if it's wrong, you could use the immune system to attack similar cells. But, anyway, for a variety of reasons people just didn't take that very serious, other than a few people. Lloyd Old in New York at Memorial Sloan-Kettering, was one of those

ligands as CD28. So they concluded it was another co-stimulatory molecule, and that was pretty interesting.

So the idea then that sort of took hold in the field is you had antigen receptor signal, that's kind of like the ignition switch, you've got to turn that, and every one's different, and CD28 is more like the gas pedal, and so that gets things going. Then the idea was that the cells undergo activation and do cell death and just die when they're not needed anymore. You've got to stop that, right? Because if they start dividing really quick, you can't have that go on for very long.

But, anyway, my lab, we did some experiments. Max Krummel, who was a graduate student in my lab, did some experiments, and we concluded that it wasn't a co-stimulatory molecule, that it was actually an inhibitory molecule, so it acted sort of like the brakes.

At about the same time, Jeff Bluestone, who was at the University of Chicago at the time, came to the same conclusion. So we had lots of fun. We would go to conferences and AAI meetings and things like that arguing, because those were the two camps, the co-stimulatory guys and then Jeff and I who said, "No, no,

scientist and person—knocked out the gene for CTLA-4, and the mice developed this lymphoproliferative disorder and die. So it became clear that we were right.

But even before we knew that, we had the idea that if it really limits immune responses and works the way we think it does, accumulates as T cells get activated, and then stops them, I thought maybe this is why the immune system doesn't do very well at attacking cancer cells, because the cancer, if it's a big enough mass, the T cell just keeps hitting on it. And the antigen receptor signal itself turns on the gene that makes the CTLA-4, and so after a while the cell stops. So if we just block that with an antibody, maybe then the immune system can just keep going for an abnormally long time. So just temporarily it would disable the brakes.

So we did that in mice, and it worked. I mean, the tumors just melted and the mice were permanently immune. One of the reasons we were doing this is because it became clear that—well, it was inherent in the idea—two things, actually. One was that since you're treating the immune system and not the tumor, the kind of cancer is irrelevant. So you can have one drug that treats all cancer. Then the second thing was that if it works as a mono therapy by itself, the whole mechanism of action when you kill tumor cells, that results in activating the innate immune system and priming the adaptive, the T cells, to go out and kill the tumor cells.

So you can do that with radiation. You can do it with chemotherapy. You can do it by freezing. You can do it by all the things that are done in the clinic. They all kill tumor cells, not well, not well enough, because nothing really cures anybody, but enough to prime an immune response. So that was the idea.

But, anyway, we showed that all of that was true, that we treated colorectal cancer, renal cell cancer, prostate cancer, some breast cancer, some fibrosarcomas in many different kinds of mice, and we could always get them, not necessarily just by injecting the antibody but by combining the antibody with radiation or chemotherapy or whatev4(c)4pr œØ Í€ äA"# ä ¢Ö !B"ÎO2(B)4(c)4pr¤¤NB² Ñ"# À

Allison: Well, a little bit, but there's always a new batch of students coming in. So these were graduate students and postdocs that were in my lab.

Williams: So you were how many years in New York, was it?

Allison: Just under ten.

Williams: I notice that you not only had an assignment at the Sloan-Kettering, but you also were involved with Weill Cornell and with the Ludwig Center?

Allison: Yes.

Williams: How did you handle all those assignments? [laughs]

Allison: Well, the one with Weill Cornell Medical School, that's just where the graduate school was, so Sloan-Kettering couldn't have its own graduate school. So the faculty, a joint faculty had a department at Weill Cornell. Ultimately, Sloan-Kettering got its own graduate school, but it was strictly cancer biology with immunology departments. Sloan-Kettering immunology group and Cornell Weill sort of merged on this academic thing.

The Ludwig, my friend and mentor Lloyd Old, I mentioned several times, he was the head of the Ludwig Institute for Cancer Research for many, many years. One of the things that he set up was some funds basically to establish Ludwig centers. It's six places in the U.S. So one of them was there at Sloan-Kettering. What I did with the funding that came with that, I set up basically a human immunology lab with the help of Alan Houghton and Jedd Wolchok, who had engineered this to actually study what goes on in patients that are receiving immunotherapies.

By then the CTLA-4 antibody, there was a new one made that reacted with human CTLA-4; it's called ipilimumab. It was in clinical trials. So the idea was to have a laboratory that instead of having just clinical endpoints, you could go in and look at what's changing and try to figure out how it works. We already knew a lot about what it should look like with people from the mouse studies, but the idea was to try to see what happens in people.

Williams: How in the world did you come up with that name?

Allison: Ipilimumab? I didn't come up with that. The drug companies did. The FDA—it's funny, you can't anymore, maybe you used to be able to, but you can't have any kind of name for a drug that implies its function or that implies that it's good, so it ended up being nonsense. But MAB, the end of it, is monoclonal antibody, and MU is because the antibody is made in mice, so it's muMAb, and then the first part, IPILI, I don't know.

But there was another one that was called tremelimumab that was made by another company. Then, finally, when ipilimumab was approved by the FDA, which it was two years ago now, for the treatment of metastatic melanoma, the trade name is Yervoy. And I don't know where that came from either at all.

Williams: So summarize for us the accomplishments of your time at Sloan-Kettering.

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percent, something in there, it flattens out and stays there. So about a quarter to a fifth of the people are basically essentially cured long-term.

Allison: Bristol-Myers Squibb. A little company called Medarex that a friend of mine, Alan Korman, who had worked with me for a long time, was actually at Medarex. They were a small company. BMS decided to team up with them and help develop it, and then they just bought them when it looked like things were going well. So they're developing additional things.

Williams: You and your people were the ones behind both of these, is that—

Allison: Yes. Well, it was based on—we had the idea. They made the drug, but we had the idea.

Williams: So next step, back to Texas.

Allison: Back to Texas. Well, I realized after a while that I just really wasn't a New York guy. When we first moved there, my son was in high school. It was an interesting place to be. But with time, I don't know, I just—Memorial Sloan-Kettering was still a wonderful place to work with. It just kind of wore on me.

The other thing is I wanted to—I sound like I'm a zealot for tumor immunotherapy. I kind of have, because I think that we are within grasp. I mean, we are curing a large fraction of cancers. It's within our grasp now. But the old Phase One, safety; Phase Two, look for a clinical signal; Phase Three, compare it with whatever the new drug is to standard of care, we've got to start doing combinations, and that model, to my mind, doesn't work very well.

There's some people here I've been collaborating with for several years. In particular Pam Sharma, who's in the genitourinary group here, specializes in doing very small trials, where you get the tissue and you can analyze it and see what's going on. So you can really reduce the whole thing in humans to almost the level that you can with mice, where you understand combining the two is really a very powerful way of knowing. You can test the combination in ten or twenty patients instead of doing—you're not going to do anything dangerous. I mean, you've got to be careful about that. But you just do small trials and analyze them and decide this combination looks good, this one doesn't look so good, before you go to the 800-patient trial, where you look for a statistically significant difference from the standard of care.

So if they offered me the possibility of actually setting up—that's what the immunotherapy platform is that I'm setting up here. The underlying philosophy is to understand how these sorts of drugs work, understand and detail their impact on the immune system, and then help design clinical trials that'll accelerate combinations.

More of these negative molecules are coming along all the time. We found another one about ten years ago. We're still working on it. Other people have found four or five more. I mean, there are several of these, and they all work

differently, which is quite interesting, because that means you can put them together and they're additive. So it's an exciting time.

Williams: What's the significance or the meaning of the word "platform" in this case?

Allison: Well, there are a couple. One of them is that the usual thing that people call something like this would be a core facility, but this really isn't that because a core facility typically is like a sequencing facility, where you drop a piece of DNA in and they tell you what the sequence is or whatever, your protein, they'll tell you what the shape is or whatever. So this isn't that sort of thing. This is actually working with individual clinical investigators, help them understand how immunotherapy works, and then really do analysis of things that are really interesting scientifically and are going to have some clinical impact. So it's sort of moving that a step.

Allison: John Porter, a congressman from Illinois, I believe, was one of the main ones. Connie Mack, I think, from Florida, and there were a few others, but John Porter was one of the leaders in that. I had the pleasure, on behalf of the AAI, presenting him with the AAI Public Service Award when I was president. It's a lot harder now to do that.

Williams: Yes. I mean, you're talking about all of these things that are sort of just on the verge of discovery, but at the same time, the money's become so tight.

Allison: Yes. Yes, the money has become tight, and it's led many of us, myself included, to not rely so much on the National Institutes of Health and the federal government. I mean, most of the support that I have now, well, I got this Texas grant, the CPRIT gran

On the other hand, they also pay the place that you're at rent for your lab space and your office space, so you're a freebie. So I think their idea

Allison: Oh, that was a lot of fun. New Orleans is one of my favorite cities, so it was a great time. We had a celebration at the place where they store the floats for the Mardi Gras Parade, I remember, and also an evening in the aquarium there, which is a marvelous place. Other than the usual stuff at a meeting of having the scientific sessions and socializing and stuff, it was just a wonderful place to have a convention like that. It was very special. This year it's going to be in Honolulu, so that's going to be pretty special, too, I think.

Williams: In New Orleans you met with, I think, six other groups.

Allison: Yes. That was a meeting of the larger federation of the societies, FASEB.

Williams: And there were 14,000 registered.

Allison: Yes. That's a meeting that's—I preferred when we had what we called the standalone meetings with AAI, because that gets unwieldy having that many people. Having said that, this year I went to the American Association for Cancer Research meeting, and I think there were 18,000 people at that. Then I've been going the last few years to the American Society for Clinical Oncology, and there's typically 40,000 people at that. It's really hard to learn anything with that many people around, except in little small bites.

Williams: Have we covered pretty much the highlights of your scientific career?

Allison: Yes, I think so.

Williams: Okay. What advice are you giving trainees today about the future, their career future in immunology?

Allison: It's difficult these days. I mean, most of the people that I know, most of the people in my lab are doing science because they really are driven by it. They've just got something wrong with them, I guess. [laughs] They really want to just love it and crave it and work hard. It's certainly not for the money.

The scary thing, of course, is the funding situation now,

to be the first person on the planet who really knows something, you know. "I've figured this out. I understand this for the first time." For a little while—now I'm the tenth or something. Even if something's found in my own lab, they tell each other before. I think that's what drives it.

But also I think that people are beginning to see that you do have an obligation to do things that help society. I just try to give people a chance to realize both those things, try to give them a nice, comfortable place to work, where I take that worry about the money. I don't want them to have to worry about it. On the other hand, as they get further along, then they begin to realize that it is going to be difficult.

Williams: This is a theory of mine, and I shouldn't waste time on it, I suppose, but it seems to me that two areas today where discovery is just racing ahead are astronomy and immunology. Can you think of another field that is—

Allison: No, not right now, not that's really moving as fast.

Williams: The other interesting part of it to me, or intriguing part, is in both cases you're looking at such minute information. The fact that the reflection, the amount of light from a star varies. From that information, you can tell there's a planet going around it. It seems to me like discovering a protein on a cell. [laughs]

Allison: You've got to see some function, and then you see how it changes when you perturb it a little bit.

Williams: Interesting to draw that comparison. Had you to do your career over again, would you have taken different—

Allison: I don't think so. I don't know how I got here. It just seemed like I was just going along. But there were some decision points where I deci-1(i) tcnd thgeon(t)-2(know)2-2(o)10(h