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. Let's start with a little bit of your family background. Tell me where you and your people come from.

Allison: I'm a Texan. I'm from a long line of Texans. My mother's side of the family moved into South Texas in the 1860s, I believe, and began to raise cattle there. They were personally involved in the cattle-ranching business in the days of the old Chisholm Trail, you know, and farming. My father grew up in a town called Marlin, Texas, which is near Waco, in Central Texas, and went to medical school in Galveston. After he got his degree, he moved to Alice, and I think there was only one other doctor in the town at the time. He and my mother, I had two brothers, and I spent all my early years in Alice, a very small town about 120 miles, I think, south of San Antonio, Texas, way down in what's called the Rio Grande Valley.

Williams: What was life like in the Rio Grande Valley?

Allison: Hot. It was very hot in the summers, and there's not many trees other than mesquite trees, lots of cactus. It was fun, but it was a small town, a very small town.

Williams: Did you go to school there?

Allison: I went to school in Alice in the public schools. I was lucky enough to have a couple of really excellent teachers that got me into summer programs, most of them science, at the University of Texas at Austin. So beginning in eighth grade, I went to the University of Texas through the summer doing a variety of things, right up until I went to college.

Then I entered University of Texas, Austin, as a freshman and ended up getting my undergraduate degree there, my Ph.D. there, and then stayed on for another year before I went and did postdoctoral studies. So I was in Austin for about twenty years. Well, actually, I went away for three years and then came back. I

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.

Williams: I think I've heard that you had some interactions with Willie Nelson.

Allison: Yes. After I was doing a postdoc, actually, ended up through a very circuitous route, anyway, I played harmonica with a little band. I was doing my postdoc in La Jolla, California, north of San Diego, and I played in a band in a little town called Encinitas. Anyway, I met some music folk, and I ended up getting invited to a party that they were throwing for Willie Nelson when one of his albums went platinum, and so I talked with him.

It turned out it was interesting, because he was with his bass player and his drummer, and he said, "Is there any place I could play tomorrow night?" You'd think he'd want to take a day off, but he didn't. He wanted to go play. He said, "You live here. Maybe you can tell me a place I can play."

So I said, "Well, it's Talent Night at the Stingray."

So he said, "Well, why don't you take me up there."

So I ended up showing up for Talent Night with Willie Nelson. [laughs] It was quite an evening. As a result of that, I got invited by his people in his band to Hollywood when he played in L.A. at the first time at the Troubadour.

Williams: Invited to attend or invited to play with him?

Allison: Just to attend.

Williams: And that ended your association.

Allison: No, actually, it's interesting, for a while I was on an organization that's between the United States and Japan in immunology, but specializing in cancer immunology, and would meet alternate years, the U.S. or Japan, and then on the third year they'd meet in Hawaii. So it was at Maui. Willie lived in Maui for a number of years and had a ranch there. It just so happened he was playing a benefit for the Maui Montessori School, and I got wind of that and went and sort of crashed the party a little bit with a couple of friends. They thought we were the band. But, anyway, got to see him then.

Then saw him again, the last time was actually in New York at the Waldorf Astoria, where he was playing with Quincy Jones at a benefit that was put on for the Prostate Cancer Foundation, and saw him there. That was about three years ago now.

Williams: What about other adventures in harmonica land? Have you played a lot in different bands and whatnot?

Allison: Well, when I was a postdoc, I just played in this one little band for a few years, and then I quit and really didn't do anything. But the last five years, I guess, I've been playing with a group of scientists in a band that we call the Checkpoints, based on an aspect of our work. But it's a lot of fun. We play at professional meetings, society meetings. We never played at the AAI, but we played at the ASCO, the American Society for Clinical Oncology, and another group. So we play three or four times a year at different venues.

Williams: Did your parents stay in Alice?

Allison: Yes, my parents stayed in Alice their whole lives. My mother died of lymphoma when I was about ten or eleven, and my father stayed on there.

Williams: As a—

Allison: As a physician. So he was the one that sort of got me interested in science and medicine and whatever.

Williams: Did you go out on rounds with him and so forth?

Allison: He was a country doctor, and he had this feeling, which I guess was not all that uncommon in the fifties, that if you got infectious diseases when you were young and when your body could deal with it, then that's better than waiting until you're in your twenties or something. So if one of his patients had measles, I would go with him to see the kid, and then I would get measles then during the summer or whatever so it wouldn't interfere with stuff. Of course, there were no vaccines for those diseases back then, so now there are. So I remember that, but other than that, I don't think I went on rounds.

Williams: You said you had siblings?

Allison: Yes, I have two brothers.

Williams: Are they also scientists?

Allison: No. My eldest brother, who is actually here today, was a civil engineer, and then my middle brother was an attorney and a real estate person.

Williams: And they stayed in Texas?

Allison: Yes. My brother still lives near Alice, where we grew up, and my other brother lived in Dallas till he passed away about six years ago from prostate cancer.

Actually, all of us have prostate cancer, so. Well, I don't anymore. I'm a survivor.

Williams: Was your mother's death critical in terms of the direction that you've taken in your life?

Allison: Yes, my mother's death had quite an impact. It was not a pretty death. She had chemo and radiation. I mean, I won't say that that's the only thing that drove me into what I'm doing, but it certainly made me think that there must be a better way of dealing with cancer than radiation and poison.

Williams: You talked about a couple of teachers in Alice who were in the sciences?

Allison: One was a chemist, taught physics and chemistry, and then the other was math.

Williams: So they had an influence.

Allison: Yes.

Williams: Those three, your mother, and these two. So when you entered University of Texas at Austin, what was your goal? What would you see as the path ahead?

Allison: Well, when I first got there, I was just taking premed, you know. I was sixteen when I went to the university, so I just thought, well, I'll just do medicine. I liked biology and liked chemistry, so I thought I'd do that. But then I quickly realized that that wasn't what I really wanted to do. What I really wanted to do was—because I worked in labs that summer after my sophomore year and junior year in high school. I worked in labs, and then started volunteering working in a lab, I guess beginning my sophomore year in college, and I just really got the bug to do research.

Williams: Did you begin to specialize as an undergraduate? Did you see exactly where you wanted to be going?

Allison: Not really. My degree was in biochemistry. Well, it was in biological sciences, but I really did biochemistry, and I got interested in immunology because the project that I was doing ultimately involved mouse models of cancer. So the only guy that I knew that had mice was an immunology professor, Bill Mandy. I took immunology from him and just really decided it's a fascinating, fascinating topic, almost infinite things to learn about.

Williams: What was the University of Texas at Austin in the sixties, early seventies, what was it like?

Allison: In the sixties, early seventies, Austin was—I don't know, it tried to be like Berkeley, I think. With the Vietnam War and all the upheaval, it was certainly a

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 aides to various politicians. So it's when there was some movement to making the Democratic Party, which at the time, you know, it's hard to believe anymore, but at the time the state was completely Democratic, very conservative, though. So I got involved in local politics and went to the state convention a few times.

Williams: What about mentors, undergraduate and then into your graduate years, were particular influences on your thinking and your interests?

Allison: In my undergraduate days, I guess, well, and graduate days, the primary ones was Barrie Kitto, who was a biochemistry professor there. He was from New Zealand initially. He had a great love of science and also politics. He was pretty politically active. But he really gave me just the ability to do pretty much whatever I wanted, which is fun, you know. I wouldn't have it any other way. Then also Bill Mandy, who was the immunology teacher that I had. I did some work in his lab.

Williams: As a graduate student, were you working on particular projects of your own choosing that furthered your career?

Allison: I was always working on something of my choosing to a point, but just as I was starting graduate school, I got drafted and ordered to report for induction, and that didn't make me very happy. In fact, I finished college a semester early and started taking graduate classes, and just before finals, my first round of finals as a graduate student, I got this induction notice.

So we tried to get a student deferment, an extension of it, so I could go to graduate school. They said, "No, we won't extend you." Then we decided that if I worked on something medically related then maybe that would help a little bit. So that, believe it or not, factored into my choice of projects as a graduate student. So what I worked on was an enzyme that at the time was called asparaginase, had been proven to be useful to get short-term remissions at least in childhood leukemia. So I worked on that, trying to find better drugs. Anyway, that didn't work. Took the draft board about a year and then they drafted me again. At that point, I ended up with a medical deferment.

Williams: Because of the work you were doing.

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

I, just sort of on the sly, really, because my mentor considered it kind of a distraction from what I was supposed to be doing. But we got to study how virulent molecules interacted with MHC, and so we had papers out of that that were significant. Later it turned out that it's not that we were wrong, but there were some issues with the reagents that we used. That was before monoclonal antibodies.

Williams: So then the draw of Texas hits you again, and you came back here and worked, were assistant professor, and you had some involvement with the UT System's Cancer Center in Smithville?

Allison: Yes, yes. I really, really loved Austin. A friend of mine, actually an ex-roommate of mine from undergraduate days, had gotten his Ph.D. and had moved here and worked for the School of Public Health here in Houston. He knew that I was about to finish my postdoc and wanted to go somewhere, and so he told me that they were building a lab, "they" meaning MD Anderson, at the UT System Cancer Center, but that it was MD Anderson. They were building a laboratory near Smithville, Texas, which is in this really, really pretty part of the state called the Lost Pines area. The Colorado River winds through that area. There's a state park there called Buescher State Park, and the state park system donated about 800 acres, I think, of the park to the Cancer Center, to MD Anderson, and they built a lab building there. I was, I think, the sixth person hired there to work there.

It wasn't really in Smithville; it was seven miles from Smithville. Smithville was pretty famous in the county, because it actually had a three-color traffic light. It had red, yellow, and green. Bastrop, which is the other big town in the county, only had a flashing yellow. So Smithville was an interesting place. I bought some land in the woods adjoining the park, and I could just walk through the woods to my lab in the morning, and I had a house in Austin.

Williams: So you divided your time between the two.

Allison: Yes. It was complicated. First I commuted from Austin, but then when I bought the land near Smithville near the park, I did commute, but it was a reverse commute, because I spent the weeks at the lab and then the weekends in Austin so I could hear Willie Nelson and hear Jerry Jeff Walker and all the musicians that I liked to hear.

Williams: So you were doing that for six years.

Allison: Yes, a little bit longer, but, yes, something like that.

Williams: And how would you summarize the work?

Allison: It was a wonderful period. I was the only immunologist there. Luckily, after we got out there, they sort of forgot about us, and so for me at the time it was the perfect situation because I didn't have to teach, I didn't have to do any administrative stuff, there really weren't any committees to be on. There were just eight faculty at the time, and we were supported pretty well. So I just got to work on whatever I wanted to work on. I started working on carcinogenesis of the liver, making monoclonal antibodies to detect cell surface changes that happened with cancer, loss of things, gain of new things.

Anyway, then I heard the next guy who was really influential in my life, a guy named Irv Weissman, who was past president of AAI as well. Irv was and still is a professor at Stanford Medical School, and he came down to Houston, actually here at MD Anderson, and gave this talk about receptor-mediated leukemogenesis, which was this idea he and one of his fellows had about leukemia being basically an immunological disease where a virus, for example, would infect the T lymphocyte, and then the virus protein would then be made. Irv's idea was that the antigen receptor would then recognize something was made in the cell and then would tell it to divide, and since it was making its own thing and telling it to divide, if it was a cancer cell.

So I heard that and I thought this is really interesting. Again, at the time nobody knew what the antigen receptor was on T cells, and so I started thinking about it. The drive back to Smithville from here, it's about three hours, I think. Anyway, I started thinking about it, and I came up with a way that I thought we could find the structure, so ultimately we did. What we did was sort of assume that if you had a collection of T cell tumors, then they should have a different structure on them, just like the combining site of antibodies are called idiotypes, and every one of them is different depending on what it recognizes. I just assumed the T cells would have the same thing, so it should be a structure that's on all T cells but that has constant and variable regents.

So we made an antibody that reacted just with one T leukemia cell and not with any other ones and not with normal cells. Anyway, through a series of biochemical approaches showed that that was the antigen receptor, although it was controversial. A lot of people didn't believe us until other people came up with the same structure by different approaches.

Williams: That was a major step, wasn't it?

Allison: Yes, it was fun. I mean, again, the disadvantage of being at Smithville was that the race was on. Molecular biology was coming of age in immunology, I mean, and so the next thing to do was to try to clone a gene. That just really wasn't possible at Smithville, so I went on sabbatical. I went to Irv Weissman's lab at Stanford for almost a year and tried to clone the genes there, working with his team, but we got beat by Mark Davis, who's also at Stanford. But I spent a year at Stanford. That really sort of opened my eyes to what a large research

university could be. As I said, it was fun at Smithville, a lot of really good people to work with, but we rarely had seminars. We'd have to drive here, drive to Houston for seminars.

So while I was at Stanford in Irv's lab, I was asked by [Marian] "Bunny" Koshland, who was also an ex-president of AAI, to come to Berkeley and give a seminar. So I went and gave a seminar, and a couple weeks later she called me and said, "Do you want a job?"

So that scared me, because it was a pretty big city. It was more culture shock for me, those months in Stanford. But the whole Bay Area is—anyway, after several months of thinking about it, I decided that I should probably do it. Once again, I was talking to Irv Weissman about it. I said, "I don't know. I'm just really content here. I've got the lifestyle I want. I can hear music in Austin. I can work hard and all this."

He said, "What are you going to do, sit on your porch ten years from now and say, 'I could have been a contender'? You can't do that. You need to go. You need to go. Do it. You've made a discovery. You need to take advantage." So after I while, I decided he was right, and so I moved to Berkeley then.

Williams: When you got to Berkeley, what was the department? Which department were you in and what was it like?

Allison: It was initially the classic, old-school micro and immunology department. By that time, the two fields of microbiology and immunology were diversifying and were really two different departments where each side tolerated each other and everybody got to take turns hiring new faculty.

But at the time Dan Koshland was leading an effort to revitalize biology at Berkeley. There were forty-something biology departments then. There was anatomy and there was endocrinology, and basically he ended up with essentially two departments. There was integrated biology, which was studying ecology and animals and stuff. Then there was molecular and cell biology was the other department. So I became then the director of the Immunology Division. There were these six divisions, and I was the head of the immunology one. It was a fantastic time to be at Berkeley. Berkeley's just a wonderful place, students are amazing, and the whole intellectual community there is amazing.

Williams: How large a division was it?

Allison: Well, at first it was Bunny Koshland and I, and then there was a couple other people there. Anyway, we started hiring and got up to, I guess, seven, eight people by the time I left. It was small. It was one of the smaller groups there.

We constantly had to fight with some of the other divisions because there were a lot of people there who had the idea that if you're a real scientist, you should be studying fundamental mechanisms. How does DNA replicate? How does DNA make RNA? How does RNA make protein? How does a fruit fly's eye develop? The immune system? I mean, people said, "Oh, we can't have a discipline named for a tissue," or whatever.

But my feeling, we used to get in these debates and I'd say, "Well, maybe, but the immune system has this innate system." It's really more than one system, but there's the innate part of it where there are these cells that have hardwired receptors so they see things that are shared, all bacteria or kinds of DNA or RNA that are found only in viruses. They respond and they put up signals.

And then you have the other arm, which is the adaptive immune system where there are these randomly generated receptors, antibodies on B cells, and the T cell antigen receptors, and they're generated completely randomly. There are a huge number of possibilities, ten to the fifteenth power, it's been estimated by some people of different ones that could be made, and they're made randomly and then they're selected to work and not to attack you. So it's a positive and negative force. Then these things cruise around your body and communicate by touching other cells and each other and secreting little hormone-like things.

It's just wonderfully complex. I used to argue with my colleagues and say, "It's at least as interesting as a fruit fly's eye, because this protects you against disease and doesn't kill you." Unless something goes wrong, and then it can kill you. Anyway, I think we had a really wonderful group eventually of immunologists there at Berkeley.

Williams: Did your point of view prevail in the end?

Allison: Yes. I mean, my point of view prevailed with a lot of political help. Bunny Koshland, she was a marvelous woman. As I said, she was a leader in the AAI. She was president years ago. But she was powerful and her husband was also politically very powerful. So at first, you know, they sort of helped, and then later on with seniority and everything, I did well so nobody could mess with it.

Williams: Was it you who created the cancer research lab there?

Allison: No, the cancer research lab there had existed since the forties, I think. It was really centered around mouse genetics, or rat, actually, rat initially and then mice. The genetics of breast cancer basically was the specialty.

The cancer research center at the time, it was called—I don't even remember what they called it anymore, but it's a line item thing in the university budget. There are very few of these things, but it means it's independent of any departmental control and it has a line item budget. So what I did was I used that to build

common core shared facilities, first a cell sorter facility, and then some sequencing and peptides synthesis and stuff like that.

Williams: So did you remain the head of the division at the time that you became the director of the center? You had both posts then?

Allison: Yes. Then after a while I stopped being division head and then became co-chair of the Department of Molecular and Cell Biology.

Williams: Was there significance in the nomenclature, really, of going from immunology to cancer? I mean, was that a narrowing in the field at the time, would you say?

Allison: In a way, in a way, but I was always interested. I'd done one experiment when I was a graduate student that led me to be interested in cancer, immunology, using the immune system to attack cancer, and that wasn't anything new for the field. I mean, a number of people, including Lloyd Old, who later became my friend and mentor in New York, had since the sixties, early sixties been involved—well, before then, but had shown that you could immunity.

But I cured these mice. I had cured mice of leukemias by treating them with this enzyme asparaginase, and these leukemias can't make asparagines, this amino acid. They need it to grow, and so if you deplete it in the blood, they just starve to death, basically. But I cured some mice. And you inject it in their peritoneal cavity and they swell up. Inject this enzyme, and it just goes away in a few days. That's cool.

But then I injected them again with the tumor, just to see what would happen, and they rejected it. Inject them again with ten times as much, inject them with ten times as many cells, and they reject that. I thought, wow, this is something.

At the time there was a concept that was put forth by several people, actually, that called immune surveillance of cancer. The notion was that the reason you have an immune system is to protect you from cancer. Your body's so complex, and you have all these regulatory things and try to keep it all together. But, you know, people just couldn't imagine that that could work so perfectly all the time. So you're constantly getting cancers, little bitty ones, one cell or a few cells, but your immune system's wiping them out and you never know it.

So that was an interesting idea, very compelling, but people did some experiments in mice that were thought to nude mice that were thought to lack immune systems, and a variety of experiments, but the bottom line was it eventually became clear that these mice that didn't have immune system didn't get cancer at any higher frequency than mice that had an intact one. But actually there was a flaw in that work.

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 who constantly just kept that idea alive and just constantly worked at that.

Williams: Other things to say about your time in Berkeley?

Allison: Yes. One of the things, I began a series of experiments, actually, that is continuing. Well, not experiments, but a series of studies that's still continuing today. What we found was there were others—we didn't do it all, by any means. It was largely done by Ron Schwartz and Marc Jenkins when Marc was in Ron's lab at the NIH. But it became clear that the antigen receptor was not sufficient to get full activation of T cells, you needed a second signal. Pippa [Philippa] Marrack, who I think you interviewed, came up with a protein structure about the time that we did. Mark Davis found the genes and others made antibodies, too, but anyway, it began to be real evident that just getting that signal wasn't enough, that there was a co-stimulatory signal.

So we began to think about among other things, but everybody was trying to figure out what that second signal was, and so we succeeded. There were some hints that work by a guy named Jeff Ledbetter, who worked for Bristol-Myers Squibb at the time, on human cells, this molecule called CD28, if you add antibodies to it, T cells made more IL-2. But that's a slightly different thing than saying you need a second signal, and that's the second signal, that's the T cell start dividing.

There's also a phenomenon that Ron worked out called anergy. The other thing that happens, not only does a T cell not necessarily get activated, but it could be turned off if you get just the antigen receptor signal.

So, anyway, we did a series of experiments that showed the CD28 molecule was necessary and sufficient to provide that second signal. So that was a lot of fun. But when we cloned mouse CD28, there was another molecule called CTLA-4 that had already been identified by a group in France. It's called CTLA-4 because it's a cytotoxic T lymphocyte antigen number 4. But it turns out that was a misnomer because they showed that they just have the gene. They'd isolated the gene from a CTL, from a killer cell, but it turns out it's in all T cells, including helper cells, but only after they get activated. So there's not any in resting T cells.

So then the question was what does it do. A group in Seattle, a guy named Peter Linsley, actually showed that he had identified the other molecules that CD28 binds to the counter receptors B7-1 and B7-2, they were called, and he quickly made recombinant forms of CTLA-4 and showed that it bound exactly the same

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, that's backwards." And it made for a lot of fun. It's back in the days when people argued. I don't know what's happened, but everybody's much too civil these days.

Williams: I'm struck by how unsilo-like your work is. I mean, you're all sort of pursuing the same, on the same hunt, and where does competition come in, or are you all collaborators, all co-stimulators? [laughs]

Allison: I think the way it proceeds is when there's some big issue out there like what is the T cell receptor, what is the co-stimulator receptor, it's mostly, unfortunately, competition. Once you get past that, things settle down a little bit, then it becomes more collegially shared stuff. At least that's what I've observed.

Williams: For the nuances.

Allison: Yes, for the nuances. What about this, what about this? And then everybody gets together, you try to move on, until the next big thing comes up.

Williams: One question that occurred to me, and that is while you were at Berkeley, what relationship did you have with UCSF, if any?

Allison: So after we showed that the CTLA-4 was this negative, we postulated that it was a negative regulator, and we had a lot of data, but finally a Canadian immunologist named Tak Mak and a woman at Dana-Farber, Arlene Sharpe, and then a little bit later after that, Cynthia Chambers, who was a postdoc in my lab—she's since passed away from cancer, very young age, very tragic; she was a wonderful

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 whatever.

So then I started working with UCSF because it was impossible to do. I mean, there's no hospital at Berkeley, no medical activity. So I started working particularly with the prostate cancer group at UCSF, was going to have a lab there to do more, to try to move the stuff into humans a little bit to the extent that we could, and then keep a basic lab in Berkeley.

But then I got an offer from Harold Varmus to go to Memorial Sloan-Kettering and head the immunology program there, and then that offered me the chance to be involved. In the meantime, we had the patent that we'd filed issued and a company ended up licensing it, and ultimately Bristol-Myers Squibb developed the drug. But I went to New York so I could be there working alongside the clinicians that were actually going into people. They finally went into people.

Williams: And that was the prime reason that you chose to go to New York?

Allison: Yes. Berkeley was a wonderful place, but culture shock again. You know, a kid from a little tiny town in South Texas who thought Austin was a big, big city, and then Berkeley was culture shock, and then I moved to Manhattan. So it was the second big culture shock.

Williams: Were you bringing the family along in all these stages too?

Allison: Yes.

Williams: How did that work?

Allison: It worked well. They tolerated me.

Williams: Did you live in Manhattan?

Allison: Yes.

Williams: So talk about Sloan-Kettering as a cultural environment and whatnot, what was it like to be there, what was it like to work with Harold Varmus and so forth.

Allison: Sloan-Kettering and Memorial Hospital I mean are two branches the thing, but the intellectual environment there was tremendous. I mean, Harold hired—I mean, it was excellent anyway, but he hired some new people, and the level of activity was as high as Berkeley, I think, still a lot of basic research but leaning a little bit more towards cancer, of course. That's what it was, and with the clinical stuff going on and seeing the patients, it was quite an active, stimulating place to be. I could see the urgency. I mean, I'd lost several family members to cancer, so I had firsthand experience with it, but still this makes you take your work a little more seriously when you see the people that are there, that are sick.

Williams: Did you bring people with you from Berkeley?

Allison: Yes, I think eleven people moved with me.

Williams: I'm always amazed that that happens. What was Berkeley's reaction to that exodus?

Allison: Well, they wanted me to stay, I think. They said they wanted me to stay. I didn't leave there because I was unhappy about anything; it's just I had another opportunity.

Williams: But taking twelve people out of their program, did that really deplete it or not?

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.

Allison: I think I began to learn human immunology, learned how to at least appreciate the complexity of clinical trials and appreciate the importance of understanding, again beyond just the clinical signal that they might give, how important it is to really understand what's going on. The gratifying part of it, of course, was just seeing the people that were treated.

If I can just back up a little bit. There are three reasons why I and all of us try to mobilize the immune system to attack cancer and do so. One is the specificity, because the antigen receptor sees peptides, little bits of proteins, short bits of them that are made inside the cell, and recognizes it's foreign. So when a virus infects a cell, the cell starts making some virus stuff, and then the T cell goes by and says, "Oh, there's something weird. Something's going on in there. I'd better do something about it."

Well, cancer is caused by mutations. I mean, that's the fundamental process, mutations, translocations, changes in DNA. If those generate new peptides within the immune system, you see those. So what the immune systems sees, it's a little bit different wrinkle on the old idea of immune surveillance, but still the idea is that the mechanism that generates cancer, generates things that the immune system can see, are exactly what T cells see. So that's one thing.

The second thing is that you have memory. So once you've got T cells, you see a tumor cell that can recognize those antigens on tumor cells, they're there pretty much for the rest of your life. So if the tumor comes back, it just attacks it again unless it's lost those antigens, but then it can adapt. That's the third property, is that the immune system can adapt if a tumor changes, so it begins to escape, you can do some manipulation. So you can get the immune system to attack it again.

Anyway, anti-CTLA-4 worked, but in 2010 there was a big trial. It was reported a placebo-controlled randomized trial in metastatic melanoma, and the exciting thing about it was if you look at growth curves, percentage of people that are alive versus time, with a bad cancer like melanoma it goes down to essentially zero pretty fast. Then some drugs occasionally will move it over where the median survival, 50 percent survival, and it moves over four months or something like that. That's enough to get FDA approval.

Anyway, anti-CTLA-4 gave about a four-month improvement in immediate survival at trial. It was the first drug of any type to have ever done that in melanoma. The cool thing was that then the line comes down at about 23, 25

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.

I met a woman a couple years ago who was in the very first trial, which was almost, I think, twelve years ago now, who told me that she had had metastatic melanoma. I have CAT scans of her tumor I show in lectures sometimes, and she gave me permission, so I'm not violating any rules here. But, anyway, she had a grapefruit-size tumor in her lung, and she'd failed everything. Nothing had worked, and so her doctor, a guy named Toni Ribas, who I've come to know quite well at UCLA, said, "Well, we've got this new thing if you want to try it. It's never been used in people before, but it works well in mice." So, anyway, gave her an injection of it, a simple infusion into a vein, and five months later, her tumors were gone, and that was twelve years ago and she's not recurred, had no more treatments since then.

So, anyway, so there's no reason to think that these people that were four and a half years out in this clinical trial aren't going to make it for ten years or longer. There's no reason to think that they're ever—I mean, they're not going to get melanoma again. So the thing that we've got to do now, so we've got this tail on the curve. So now what we can think about doing is not worry about getting that tail—

The normal kind of drugs you were going to give to cure cancer cells, unless they cure every tumor cell, it's going to come back, and typically what happens is when it comes back, they're resistant to that drug. Even if it works, you have to keep giving the drug for a long time, because if you stop, if you didn't kill that last cell, if you stop, then it's just going to come back. Typically these things have half-lives that can be measured in hours to a few days, and so the tumor's going to win. Even the new targeted therapies that are based on determining the driving mutations that cause the cancer, same thing happens with them. Tumor cells keep having more mutations. That's one mechanism by which they can escape it. But every time they do that, it generates new things for the immune system to see, so they're playing into the immune system's hands, if you think about it that way.

Anyway, so now what we've got to do is figure out how to get that tail up from 25 percent to get it up to 50 percent, 75 percent, and more kinds of cancer. So that's what we're trying to do now. There's actually two big trials in prostate cancer that are finished. They're all randomized and nobody knows who was who, so as soon as they finish analyzing the data, probably this summer that'll be reported. I don't know how that's going to come out, but I hope it's going to be good. Then there's some other molecules that we've been working on since then along the same time.

Williams: Who's doing those two studies on prostate cancer?

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.

I'm sure you've heard that Ron DePinho, who's the new director here, has this idea about moon shots, he calls them, a metaphor from and of Texas, particularly because Houston's the space city, or was during the Apollo program. Remember the whole, "Houston, we have a problem." Anyway, it's that sort of can-do spirit, I think, that Ron has about [unclear], just like we have.

We know a lot about cancer now, a lot of different areas from cancer biology studies, from immunology, from genetics, and it's all coming together, if we could just get teams together and say where can you—if you just pushed really hard, you'd know what to do something. You can accomplish that in a couple years. One kind of cancer you could significantly reduce morbidity, we've already done it with melanoma, and we're going to do it some more. So, anyway, that's the moon shots. Anyway, the platform is the thing that the rockets are fired from, at least in my estimation. [laughs]

Williams: That's good. Let's turn now to the AAI for a moment. You were president in '01 and '02. What outstanding memories do you have of your association with the AAI?

Allison: Just the dedication of the staff, Michele Hogan and others that are committed to really having the society help further the field of immunology and beyond that. That was a time when the doubling of the NIH budget was beginning, and AAI was very—one of the things that I did a lot of, and they're still doing, was to meet with congressmen and convince them. Back then you didn't need to work very hard to convince them of the importance of basic biomedical research and immunology in particular. We didn't sweat the immunology so much at that level. It was just biomedical research is important and you need to support it. So the political arm of it was very important.

Williams: Who were the political forces behind the doubling, do you recall?

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 grant, to come here, but still, foundations are more and more important in supporting the kind of work that I do, which is basic. But on the other hand, as soon as we figure something out, we immediately try to move it into cancer therapy.

Williams: I think you ought to explain what CPRIT is.

Allison: CPRIT was something that was started in the state of Texas. I believe it was a constitutional amendment where they set aside $300 million a year for ten years just to further cancer research in the state of Texas. So part of it went to grants, the standard sort of competitive research grants, went to team projects, and then a lot of it went to recruit people to Texas to try to strengthen the biomedical research community in cancer in particular. So that was—

Williams: So that's also part of the reason why you're here.

Allison: Yes. Well, I was a Howard Hughes investigator at Berkeley and New York, but Howard Hughes has a rule that you can't move but once, and so I had to give up the Howard Hughes. If it hadn't been for the CPRIT money, there would have been no way I would have moved, because I'd have to basically start over.

Williams: Do you have any idea why there's that rule at the Hughes?

Allison: The Hughes is a pretty nice deal. They pay your salary. I mean, you work for the Hughes. I didn't work for University of California after I became Hughes, and I never worked for Memorial Sloan-Kettering. I was considered a non-stipend volunteer. Each year somebody in the bureaucracy would forget that, and they would cut off my email and stuff.

But, anyway, so they pay your salary. Hughes gives you a pretty hefty amount of money to do your research, and it's also just an outstanding intellectual environment because they have their own meetings, and their ideas just make it possible for people to do science and not worry about writing grants all the time.

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 was that they don't want people just jumping from institution to institution. "We'll pay your salary if you move here," etc., or people just frivolously moving around. They take the rule pretty seriously, I found out. [laughs]

Williams: How does the application for Howard Hughes—or do they find you?

Allison: Back in the day, they found you. There was no applying. The institutions could nominate people, individuals, but now they do let individuals apply for the first time.

Williams: Have you done the application? I guess not.

Allison: I'm not eligible.

Williams: Right, right.

Allison: Too old.

Williams: Also now, of course, during your tenure as president, 9/11 occurred. Did that have any kind of—

Allison: I'm trying to think. Yes, I guess that was. Did it have an effect on AAI? It didn't have any effect on them, I guess. It had quite an effect on New York, obviously. I forgot that that was while I was president.

Williams: You mentioned that in your presidential message, "This has been quite a year."

Allison: Okay. I forgot.

Williams: I'm just looking at my notes here for a moment. You made comments about your preference and AAI's preference for investigator-initiated research as opposed to specific set-asides, but then you also supported NIH dollars going to basic research on biodefense. That seemed to me a little contradictory. Is it, or you don't recall?

Allison: I don't recall doing that.

Williams: Okay. All right. Your annual meeting was in New Orleans, I believe.

Allison: Yes.

Williams: Talk about that.

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, where I'm afraid that we're going to end up losing a generation of young people that won't choose to put a grant in if you've got a one-in-ten chance of getting it, or less. And then they take 30 percent off administratively if you get that. So it's just becoming tough. So I try to not talk about that very much, first of all, with some of my students, because I don't want them to be thinking of the bummer all the time.

On the other hand, I try to give them a good place to work and have them realize just the joy of knowing something, of learning, learning how things work. I think that's why most people that are in science, particularly the successful ones, are in it. People can talk about a lot of ways or the high notions, idealism and everything, but I think deep down most people in science do it because they'd like

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 decided, and I don't think I would decide any differently now. I hope I wouldn't.

Williams: And what does a scientist do to have fun? I guess you pretty well explained yourself in a way with the music and so forth.

Allison: Yes. I used to ski and sail with Lewis Lanier, who you may have talked to. He was a real close friend of mine, and he and I used to sail a lot in San Francisco Bay. I can't do that anymore. My knees have gotten too bad to ski, but I still play harmonica. I guess I mentioned we have this band called the Checkpoints, for the immune checkpoints I work on. We play several times a year, and that's it. Listening to music, reading. I can't golf. A lot of people golf, but—. [laughs]

Williams: Anything else you'd like to say for the historical record at this point?

Allison: No, I think we covered it. I don't know if thanks is in order, but just one thing I've really enjoyed is having the series of just wonderful students and postdocs to

work with. They're the ones that keep things going. Also a lot of colleagues in the field, a lot of them in the AAI and leadership, they just made it worthwhile.

Williams: Thank you.

[End of interview]