



The American Association of Immunologists Oral History Project

Transcript

Jeffrey A. Frelinger, Ph.D.
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Williams: This is an interview for the American Association of Immunologists for their Centennial Oral History Project with Dr. Jeffrey A. Frelinger, professor of immunobiology at the University of Arizona and immediate past president of the AAI. We are at the 99th annual [ed. 96th annual] meeting of the AAI at the Sheraton Boston Hotel in Boston, Massachusetts. Today is Sunday, May 6, 2012, and I'm Brien Williams.

Dr. Frelinger, I'd like to start out by asking you a little bit about your family background.

Frelinger: So I was born in Brooklyn. My parents lived on Long Island, but when I was a little kid they lived in Brooklyn. We moved to California when I was in eighth grade, and I went to high school in California. My father was an engineer, worked in the aerospace industry, worked for many years with General Dynamics. My mother was a homemaker initially, and then the same year I graduated from college she got her nursing degree, and she worked as a nurse for about probably twenty-five years after that.

I have two siblings, one of whom is an immunologist, is a professor at the University of Rochester. He's actually here at this meeting. And the other one is a policy analyst for a RAND Corporation, who lives in Washington, D.C., actually lives in Gaithersburg [Maryland].

Williams: A male or female?

Frelinger: Male. Three boys in the family.

I married a woman called Acey Joy Frelinger, Acey Joy Vaughan when I married her, and she's an interesting person. We've been married forty-two years. We have two grown sons. One of them is a graduate student in computational biology at Duke [University], and the other one is a study coordinator doing genome-wide association studies for schizophrenia at the University of North Carolina, Chapel Hill.

Williams: You've got strong genes.

Frelinger: I don't know. My dad is ninety-one and he's still alive, so I guess I have genes for something.

Williams: Where did you go to school? You say in California in public schools?

Frelinger: I went to actually an Episcopal prep school called then San Miguel, which has now been absorbed by the Bishop School, which is an old Episcopal girl school that is now coed after it absorbed the boy school. That happened long after I left.

I went to the University of California, San Diego, where I was a biology major. In the first two years, I majored in beach and pool. [laughs] So at the end of two years as an undergraduate, my grade point average was 2.01, which was good enough to stay off probation but not good enough to do anything else.

At about that time, I started to work in a laboratory, a guy called Thomas Roth, who was a developmental biologist who studied mosquito oogenesis, and I worked in his lab for two and a half years as an undergraduate. I managed to actually improve my grades somewhat, so I think that my grades the last two years were, I don't know, 3.8 or something, and it was great. That was, for me, I discovered what I wanted to do and what I wanted to be.

Williams: I was going to ask you when did medicine, biology connect with you.

Frelinger: That was it. I mean, I started college with the kind of misguided idea that I wanted to be a physician, but, of course, I actually didn't know that it was possible to be a scientist without being a physician. So when I discovered you could do that and I discovered how much I loved working in the lab, it was all over. I mean, there was no question in my mind about doing anything else.

Williams: When you graduated from high school, did you have a sense of direction or not?

Frelinger: If you'd asked me then, I would have said I wanted to be a physician.

Williams: What was it about the lab that was such a turn-on?

Frelinger: Three things. So the first is you get to do stuff with your hands. My grandfather was a carpenter, my mother's father. My father, when his family owned the Frelinger Ironworks in Cincinnati when he was a kid, he worked in the ironworks. He was in the Navy in the Second World War. He was a machinist's mate, which meant he fixed things, but also means they made the things that needed to be fixed. I always liked working with my hands, and working in a lab is a way to work with your hands. It's really hard to explain how it's so satisfying to sit there and pipette small volumes of clear liquids from one tube to another. If you do that well or do any of the hand skills well, it feels good.

The second thing was you get to know something that no one else ever knew and you get to know that first. So for a time, you have a special piece of knowledge that's unique to you. Then the third thing is it's really hard, so it's not an easy thing to do, so it's always challenging because it's always hard.

So those are the three reasons that I kind of got psyched about it. You get a bonus if you work in an area like immunology, because it has the potential to be useful, and that's kind of a real bonus. I mean, it's not why you do it, but it's why it's good.

Williams: Talking about using your hands, I want to tell you that a few minutes ago we interviewed Dr. Cooper, Max [D.] Cooper.

Frelinger: Oh, Max. I love Max.

Williams: And he was talking about one of the procedures they did in many areas of research that he has done, was removing the thymus from newborn mice.

Frelinger: Yes, I've done that.

Williams: I can't imagine how small the elements are that you're working with.

Frelinger: Oh, they're big. So when I worked in Tom's lab, what I worked on was I injected mosquitoes and removed ovaries from mosquitoes.

Williams: It has to be with the help of a microscope.

Frelinger: With a microscope, but freehand.

Williams: You can't have the shakes.

Frelinger: No, and I couldn't do it now. I mean, I'm not steady enough now to do that, but when I was seventeen or eighteen, I could do that.

Williams: Criterion two, knowing something no one else does, did you have moments of that while you were at [University of California] San Diego?

Frelinger: Oh, yes. This sounds sort of bizarre, but we worked on a small problem. I worked on a small problem which is in developing embryos there's a whole lot of ribosomes because a zygote has to make a whole lot of protein starting from zero, and the question we wanted to know was where did the ribosomes come from. The ribosomes are the machinery for making new proteins.

When insects develop, and particularly when mosquitoes develop, there's a whole bunch of cells around them called nurse cells that people say feed, take care of the developing egg. The question we wanted to know is did the developing oocyte make its own ribosomes, that it was transcriptionally active and made and stored those products, or did they come from somewhere else. And what we showed was we showed that the ribosome RNA was made in the nurse cells and then transported into the developing oocyte. It was actually made in a very discrete time during oogenesis. So they made a whole lot of ribosomes, shoved them into the oocyte, and then everybody stopped. So that was really my first paper, which was published in the *Journal of Insect Physiology*. [laughs] Maybe not a real auspicious start for an immunologist, but that was it.

Williams: Then when you got your degree at 'SD, then where did you go?

Frelinger: I went to Caltech [California Institute of Technology] and I became interested in immunology. Just before I went to Caltech, there was a guy called [Richard W.] Dick Dutton, who is also one of the past presidents of AAI, who gave what now I realize is a job seminar at UCSD. I went to his talk. I'd always been interested in development. I thought, with incredible naiveté, that the immune system would be easier to understand and be the perfect model system for development. When he gave this talk, there were only two kinds of immune cells, the ones that stuck to plastic and the ones that didn't, and he showed they had to interact to make an immune response. I said, "This is way cool." So that's what I decided I wanted to do.

When I went to Caltech, I had originally thought I was going to do developmental biology and was going to work with a guy called Giuseppe Attardi, and after I got interested in immunology, I walked into Ray Owens' office and said, with amazing chutzpah, that I was going to work in his lab and I was going to be his graduate student. I guess he just was so taken aback, he said yes. [laughs]

So I started working for Ray and it was great. So he was the perfect mentor for me. He never ever told anybody what to do, and his guidance was modest in that I got my thesis project. He said, "Jeff, I think transferrins are interesting and pigeons are kind of interesting. Sandy Webb," who was a technician in the lab, "knows how to run starch gels. There are multiple alleles, and she'll show you how to do that. I think something interesting is there." So that was my thesis project, right? So that was kind of nonguidance, but in fact it was wonderful.

So I went and Sandy taught me how to run starch gels, and we started fussing. Turns out transferrin is found in egg whites. It's the second most abundant protein in egg whites after albumin, and in the body, most of the time transferrin functions as an iron-transport protein. It takes iron away from iron stores and delivers it to reticulocytes that get incorporated into hemoglobin. But in egg whites, there's no iron in the transferrin and it's bacteria static, so it's part of the innate immune system in a way because it keeps the eggs sterile.

Lots of bacteria have a trick. They know how to go through egg whites. I don't know how much you know about bird anatomy, but after you talked to Max, probably a lot, because birds have a cloaca, which is their all-purpose vent at the back end. So the genitals and the intestine all go through the same place, which you can imagine is dirty. So there's lot of bacteria, and so eggs have to have a way to stay sterile. If eggs don't stay sterile, then the embryos die. So transferrin keeps the egg sterile and allows the embryo to develop and also the transferrin gets absorbed by the developing embryo and gets used as its own transferrin.

So as a graduate student, my very first paper was a *Science* paper where we showed that the source of transferrin in a newborn chick comes from the egg whites, not made by the chick itself, and we did that by using genetically marked

transferrin. We also went on to show that females who are heterozygous for these two alleles at the transferrin locus are more fertile and that the fertility at least in part can be ascribed to the fact that the heterozygous that is having both kinds of transferrin present are better or more bacteria static than having only one kind.

Then I finally went on. This is one of the great things where I learned that sometimes it's really good to collaborate. We tried to make a mathematical model for how to do this, for how that kind of fertility, which is not the sort of standard over-dominance for fitness that you think about for resistant to malaria by sickle cell anemia, because it's kind of a twist on a fertility model.

I tried really hard for about three weeks to figure out how to make an algebraic model to do this, and Ray said, "You know, I know this guy [James F.] Jim Crow in Madison [Wisconsin]. You should just go over and see Jim, and he'll help you figure this out." So we bought a plane ticket. I flew to Madison. I stayed at Jim's house. Jim just died recently. In about three days, really one hour of his time, three days of my time, we figured this out. We published a paper full of equations in *The American Naturalist*.

It showed me that the right person can really fix a problem, and you don't have to know how to do everything that you need to do; you just have to know how to get help to do it. I don't know if you know about Jim Crow. He's a really famous population geneticist, but just the nicest man. I think he played the viola. Maybe it was the violin.

Williams: Now, this sounds like you were a postdoc, but you worked.

Frelinger: I was a graduate student.

Williams: You were a graduate student, so at the same time you were taking courses.

Frelinger: Sort of. So Caltech requires you to take a small number of courses outside of what your major is. So what I like to say is I took management accounting, I took a seminar in population problems, and I took another course. I can't remember what it was. It was another economics course. So I took no biology courses. I did T.A. [Teaching Assistant] in immunology every fall for the whole time I was in graduate school.

Williams: So your interaction with immunology was limited pretty much to what you were doing in the lab, is that right?

Frelinger: Yes.

Williams: And talking to people.

Frelinger: And talking to people. Ray was an interesting guy. He didn't require very much of you, but he required you to show up for coffee twice a day. So you had to be there at ten to have coffee in the morning, and you had to be there at three, and you had to arrange your day around that, and there we talked about everything. Ray was a real Angel's fan, so we sometimes talked about the Angels, so a really sad state of affairs in the early seventies particularly. But we also talked about immunology and we talked about people and we talked about how you do science. We talked about ethics. It was half an hour every day.

Williams: About how many people?

Frelinger: So there were six people in the group, and they worked on just this enormous range of problems, so there were people in the lab who worked on mice, there was a guy who worked on caenorhabditis, and there was another person who worked on pigeons with me, Sue Melvin. But it was really open-ended and it was made better because Ray, who was one of the people who discovered tolerance, had this kind of stream of visitors who would go through, and when the visitors came, he would sit everybody in the lab down and you had to do ten minutes about what your project was, why it was interesting, and where you were in it. Guys with Nobel Prizes would come and sit down, and you're supposed to talk to them and they asked you questions. It was made better or worse, depending on your view of the world, because of the environment at Caltech. It was the very end of the flowering of molecular biology where Caltech was the center of the world. Max Delbrück was there and Seymour Benzer was there. When I started as a graduate student, I think there were twenty-five faculty in the Biology Department and there were twenty-two members of the National Academy and three Nobel Prize winners.

Williams: Good company.

Frelinger: Yes. [laughs] That's how I thought the world was, right? One of the things that it did foster all the time was you had to think about what you were doing and why, and you had to be able to explain it to another scientist who didn't do what you do.

So a group of graduate students would go to lunch, and there would be neurobiologists and there would be immunologists and there would be biophysicists, and you had to be able to talk to them because that was the culture, right? You had to say what you were doing, why you were doing it, and you often got a lot of help because you were forced to think about what other people did and you were forced to think about things broadly and how other disciplines could help you. So it was a great place for me.

One of the things I'll tell you about is in immunology we had only a single oral exam the whole time you were a graduate student, plus your thesis defense. I sat in a room with three faculty. It was with Ray Owens, with Ed Lewis, who is a

Nobel Prize winner, and Lee Hood. I got asked one question, which was what do you think the five most important things in immunology in the last fifty years and why. We got partway through number three and they said, "You're done." [laughs] So you're asked to leave the room. So I was sure I'd failed.

I came back and they said, "Oh, you did great." [laughs] So that's the kind of place it was. It drove the big picture, not the details. You had to know the details of what you did, but that wasn't what they were about and that's not what science is about. It's about the big thing.

Williams: So your Ph.D. thesis was based on the work you were doing, which you just described?

Frelinger: Yes, pigeons.

Williams: What were the outcomes of that research?

Frelinger: So we published a *Science* paper, a *PNAS* paper, this evolution paper in *The American Naturalist*. We published a paper defining, which I did in Lee Hood's lab, where I defined the genetic difference between those alleles doing biochemistry, just, boy, bucket biochemistry the old-fashioned way, starting with dozens of pigeon eggs, purifying proteins.

I tell people now we do mass spec to do sequencing, and we made triptych peptides. We drew these peptide maps on these huge paper chromatograms and purified triptych peptides and then did amino acid analysis on those by hand and figured out the peptides that were different and what their amino acid compositions were. Then we got enough of it that we could sequence it, which was just a huge amount of work. So that was my thesis.

Williams: So then you went to Ann Arbor [Michigan].

Frelinger: I did go to Ann Arbor. It's true. How I went to Ann Arbor is actually kind of amusing. I had planned to go to [University of] Oxford to Walter Bodmer's lab, later Sir Walter Bodmer. Walter, I'd never met him, but we had corresponded. He had been at Stanford [University] before he went back to Oxford, and I flew up to Stanford to meet him. We were, in theory, working on a postdoctoral fellowship proposal, and we had written one which I think actually was funded by the American Cancer Society. But I met Walter and I decided I couldn't possibly work for Walter.

So I came back and told Ray that I couldn't go work for this guy. He said, "Okay. Well, what do you want to do?" Then Ray said this guy Don Shreffler, who had been Ray's graduate student, in fact had been Ray's graduate student about fifteen years before, said, "He's a pretty good guy. He's doing interesting stuff."

The problem I was interested in was in short-range recombination in the major histocompatibility complex. I was interested in it for two reasons. One is it was clear it caused tissue graft rejection, but it was also clear it was a place that you could look at very closely linked genes recombining because there were good markers.

So I said, “That sounds good,” and I met Don at a meeting, and he seemed like a good-enough guy, and so we went. So we wrote up a proposal which was effectively to discover what turned into MHC class II genes. In fact, that’s what we did. So I went to Don’s lab in Ann Arbor and we started working on this problem, which another postdoc in the lab at that time, Chella David, had already started on but had not gotten very far. We worked on this together, Chella and I worked on this together, for about a year and a half, and it all worked great. I mean, it worked just like it was written up in the proposal, which is horrifying because nothing ever works that way. But we described class II, and I got really hooked on trying to understand how these genes worked, what they did, because nobody understood graft rejection at all, and clearly these were really important in graft rejection.

After we published the original description, I published a *Science* paper, and we showed in the *Science* paper that these proteins were really important in the initiation of immune responses. It was after then I was kind of down the rabbit hole, because I just got into immunology deeper and deeper and deeper and I could never escape.

So that was it. So it was a really productive time. It was a great lab. The lab was incredibly productive while we were. Of the people in the lab, I guess there were two graduate students and Chella and I and Tommy Mayo [phonetic], three postdocs. So they wound up, Chella has just retired mostly as a professor at the Mayo Clinic. Ted Hanson is a professor at Wash U. Tommy Meo was a professor at the Pasteur Institute before he died. Don Murphy went to Yale [University]. So it’s not such a bad place to have kind of done stuff.

Williams: So why did you head west again then?

Frelinger: Because it doesn’t snow.

Williams: What attracted you, I should say, to USC?

Frelinger: I think, well, first of all it was the first job I was offered, but secondly, it’s one of the few places I went that they didn’t balk when I said, “I want to have 250 mouse strains,” and they said, “Sure.”

The snow seems flip. I mean, it’s really true. When we were still in Ann Arbor, the last year we were in Ann Arbor while I was still looking for a job, my wife and I went out to dinner. She grew up in El Centro [California]. I don’t know if

you know where that is, but it's kind of between Yuma and San Diego on the border. Her birthday is in May, May 25th. We were walking out of the Gandy Dancer, which was a restaurant that they'd turned a train station into, and there were snow flurries, and she cried because, she said, "When I was growing up, I had a pool party on my birthday." [laughs] So that was actually important to me, and so we went back to California.

Williams: What was the status of the department that you went into at USC at the time?

Frelinger: It was small. The chairman was a guy called Irv Gordon, who was a hepatitis virologist, was one of the World War II Rockefeller-trained cohort of ID docs, smart, nice man. I really liked him. He was a big draw for me, and he was a great mentor. He really wanted people to be successful.

Peggy Lieb was a woman who was a phage geneticist who had trained at Caltech, who was again kind of one of these old-school really smart genetics types, and she was just fun to talk to and fun to talk science about. There was some effort going on at USC, which I think has continued to go on. It's an odd place.

There were sort of five of us, four or five people who were hired within about two years, all of whom left, except one, left within ten. All were really successful and went to really good places. One person went to the Hutch [Fred Hutchinson Cancer Research Center]. One person went to UT [University of Texas] Southwest. One person went to UCSD. I went to [University of North Carolina] Chapel Hill. It's a place that couldn't seem to keep good people. They could identify good people and they could hire good people, and they didn't stay. I think part of it was life's hard in Los Angeles. East L.A., you can't live there, and so everybody commutes. It was hard to build community. So the closest place you could live was Pasadena, took twenty minutes. I lived in Santa Monica because it's really much nicer, and that took—my record was probably twenty-seven minutes getting to the lab, but mostly it was forty minutes. So people just didn't stay.

Williams: Would you have considered going back to Caltech?

Frelinger: I probably would have, because of the return-to-the-mothership feeling. It probably wouldn't have been a good place for me.

Williams: Why?

Frelinger: It's really a place where people build super groups, and people who are successful there have big labs and they function autonomously. I do better interacting with people and trying to build sort of collectives to do things. I think the big attraction for going back to a place like Caltech is the quality of the students, which this is immodest, but the average Caltech student is pretty good. So that's, I think, the big advantage of a place like that.

Williams: What were the students like at USC?

Frelinger: Awful. No. The very best students were okay, and the worst students were bad and there weren't very many. I had two students at USC, and they were okay, fine. They survived. They survived me. It was okay. The postdocs were better. I had great postdocs. My first postdoc was a guy, Peter Wettstein, who is now a professor at the Mayo Clinic. So they were good. I really was lucky in getting really good postdocs to come work for a new assistant professor, which was kind of fundamentally insane to do, but they did anyway.

Williams: So what reason did you have for moving on?

Frelinger: It was really clear by then that USC couldn't keep its act together. In retrospect, its problem is/was certainly that it had a huge clinical operation to provide indigent care to a huge number of people, so that means a very large number of service-oriented clinical faculty whose job it was to take care of sick people, and that makes it very hard to create an academic environment. Walt Kelly wrote, as Pogo, said, it's really hard to think about draining the swamp when you're up to your ass in alligators, right? Really, that's a big problem. So the academic atmosphere certainly never was able to be generated, while I was there anyway.

Williams: So what's the weather like on May 25th in Chapel Hill?

Frelinger: It's late spring. The azaleas, most of the azaleas, are still blooming. It's beautiful. The trees have just leafed out.

Williams: So you did not have a hard time convincing your wife?

Frelinger: So I did, actually. We had one of these momentous conversations sitting in our redwood hot tub behind our house in Santa Monica in the evening. She got used to the fact that I'd looked at a lot of jobs and I'd sort of gone and come back and would go away. But I said, "You know, I'm really getting serious about this."

And she said, "No." And her first words were, "It's not an ERA [Equal Rights Amendment] state. I can't go there."

So I think we probably made four or five trips to Chapel Hill before we signed on, and it's an idyllic place. It's Ann Arbor with better weather. We liked Ann Arbor. Ann Arbor's a very pleasant place to live. The weather in Ann Arbor is gruesomely bad. It's gray for nine months in the sort of lower Midwest, awful weather. But it's a college town. There's a lot of stuff to do. It's not big. It's accessible. It's cheap. You know, if you live in a college town as a faculty member, everybody's like you. We always used to say it was a blue dot in a red state. When Jesse Helms was a TV commentator, which was his previous occupation before he became a senator, the state of North Carolina was going to

build a state zoo, and he said, “We don’t need to build a state zoo. We can just put a fence around Chapel Hill.” And that was okay, because you lived in Chapel Hill, there were like-minded people. Occasionally the town had a foreign policy. [laughs] Never understood exactly why we needed a foreign policy, but we had one.

So it was fun and it was a nice place to live. We ultimately built a house on ten acres five miles from the lab. On a bad day it took eighteen minutes, and on a good day it took twelve minutes to get to work. I mostly biked, and it took twenty-five minutes on the bike. It was an easy place to live. For her, there’s a big vibrant writers’ community, and that was a big part of her life. So it was a really nice place to be.

Williams: For you in terms of medicine, what was the allure?

Frelinger: So there had been a big commitment by the state, driven by a couple of people, to create serious molecular biology, and they created a program in molecular biology and biotechnology in which they committed to hire fifty faculty over three years. That fundamentally changes an institution, and the cohort of people that came was just spectacular and included Oliver Smithies, who recently got a Nobel Prize, but a lot of research-oriented physicians.

As we first came, we met as a group. The faculty just met at somebody’s house once a month, had dinner, and somebody talked about what they were doing or what they were going to write a grant about, and it created this really good camaraderie of people, and we weren’t all in the same department. There were people in pathology and people in medicine and people in biochemistry and people in biology, a lot of people in biology. So we wound up with a web of people that you could interact with who knew, trusted, and liked each other.

One of the great things about Chapel Hill was—so first of all, there’s an overlay of required civility in the South. You could hate somebody and you were always polite. It was impossible. You could just not not be polite. So there’s that. But if you liked people, the gentility makes it easy to live with and even makes the conflicts easier to live with. I don’t know if you got this from Max, because Max is a southerner, but he is sort of the quintessential kind of gentle, calm southern gentleman. Even the people who were never in the South before they got the Chapel Hill, which was most of us, absorbed that culture, and it made it really nice. So that was an attraction.

So the attraction was it was going to grow and that that happened. The guy who recruited me, who was the chair of Microbiology and Immunology Department, was a guy called Fred Sparling. Fred is a Harvard-trained MGH ID physician, worked on *Neisseria gonorrhoeae*, and he’s one of the grandfathers of gonorrhea research, and really, really smart clinician, scientist, and he was remarkably effective at recruiting people. I can only think of the whole time that I knew Fred

that he failed to get—he probably hired twenty-five or thirty people between the time he was in ID and the time he was in Micro. I can only think of three people that he didn't actually manage to sign.

Williams: So with all this influx of new people, did you coalesce into various groups and study groups and so forth, or were you pretty independent?

Frelinger: Yes and no. I mean, so I had really serious interactions with a large variety of people over time. I had a very close collaboration for a long time with an x-ray crystallographer called Ed Collins, and as a result, if you screen the x-ray crystallography database, I have about eight structures that somehow I'm associated with, although I could never solve an x-ray structure if my life depended on it. So we had those.

I had a long collaboration with a guy called Roland Tisch on Type I Diabetes, and so both Ed and I and Roland and I had grants together for a long time. I had collaborations with clinicians, one which has lasted and still going on, with a burn surgeon, a guy called Bruce Cairns, who came to my lab as a fellow, spent two years in my lab, went away to be in the Navy, came back, finished his trauma fellowship and stayed on as a faculty, is now director of the Burn Center at UNC, on how big burns impact the immune response, which it turns out they do. I mean, there's huge impacts of the cytokine storms that go on after large burns.

Those kinds of things are stuff I would never ever think about if somebody wasn't pushing me to do that. We had collaborations with the renal guys and with the GI people and just had—all those things were fun, and they're bad because they sort of fed my ADHD [attention deficit hyperactivity disorder], but at the same time it was really neat to be able to do those things and to think about real clinical problems and to bring the basic science approach to them.

Williams: I haven't asked you about the work you were doing at USC or at Chapel Hill, and I don't want to get into a lot of detail because it's all been published, but what are the highlights of your work at both sites?

Frelinger: So there were two things. When I first went to USC, we spent a lot of time trying to understand how class II functioned in antigen presentation. There are still sessions going on at this meeting about how it works in antigen presenting, how you put peptides on, and trying to understand both the primary kinds of professional APCs and the ones that went on in other tissues.

What drove me is we started a collaboration with Lee Hood to clone these genes, and what we started to do at USC and I continued at the beginning when I moved to UNC was to go detailed structure function studies on MHC class I molecules by doing mutagenesis. We actually did those in mouse for a long time, and when I went on sabbatical to Oxford, I moved into doing those in humans. So we did

them in mouse and we did them in human in Oxford, and that really occupied the lab probably for fifteen years trying to drive that problem into the ground.

We wound up, because in humans a really good way to look at that was to study HIV, so we spent a lot of effort studying HIV in terms of how CTLs worked in HIV to control virus infection, how MHC polymorphisms dealt with that, and how to think about trying to make better potential vaccines.

I think one of the interesting things, and one of my favorite stories that I like to tell Congress critters, is as we were doing this, we were working with Ed Collins, crystallographer, aforementioned crystallographer. We were trying to figure out really the biophysics of how peptides stuck onto MHC. Ed came across this breast cancer epitope that's in HER2, and you may have heard of Herceptin. It's one of the targets of Herceptin, but it's also a target for cytotoxic T cells.

Ed and I were going to do a structure and it was just a terrible epitope. It didn't bind very well. You had to do it at low temperature. We said, "Well, this sucks. We've just got to fix this." So we realized that from the HIV stuff that we had done that we could make stuff that was better than natural. That is, we could make peptides that stuck better. That is, we changed—so peptides bind like a hotdog in a hotdog bun. So you can change the things that stick down and you can change the things that stick up. So for the T cells to work, you've got to leave the things that stick up the same, but you can make the stuff that sticks down gluier, so we did.

Together with John Serody, who was a hematologist oncologist who'd also been a fellow in my lab, we devised a clinical trial. So we published a bunch of papers where we showed that, yes, you can do this to HER2 and it's better and it's more immunogenic and all the things you want to be, and John organized a real dendritic cell therapy altered peptide ligand trial to do this.

It was sort of my first real human clinical trial thing, and, of course, the very first patient we treated had an objective response, which means her tumors got smaller, and the next thirteen did not. So in terms of changing clinical medicine, not so much, but in terms of taking a problem from biophysics to a patient, it was really good, and that was something which I could really only do in a place where I had lots of connections, where there was a lot of interest in collaborating across disciplines, and a lot of interest in being able to drive things from ideas to medicine.

Williams: That was at USC?

Frelinger: That was at UNC, UN-Chapel Hill. So that's kind of what we did. We did a lot of other stuff, too, as my, unfortunately, varied CV will show. But I think this is the kind of thing which I really liked about UNC.

Williams: You were there until just two years ago.

Frelinger: Two years ago. Almost exactly two years ago.

Williams: So there must have been other breakthroughs, no?

Frelinger: So one of the things that we did with Roland Tisch is one of the questions in autoimmune diabetes is where does the immunology happen. So the conventional idea is that all immunology happens in lymph nodes and effector cells leave lymph nodes and go to the target tissue. In the case of Type I Diabetes, that's the islets of Langerhans in the pancreas.

What we said was, okay, well, what we're going to do is we're going to look by sequencing the T cell receptors in the pancreatic lymph nodes and in the islets and ask whether they're the same. So if all the immunology goes on in the lymph nodes, those should be essentially the same distributions. You should have the same mix of kinds of cells. When we did that, what we found is while there were some that were the same, there were a whole bunch that were only found in the pancreas, were not found in the draining lymph node.

So if you're going to save conventional wisdom, you have to wave your hands really fast and you have to say, "Oh, they used to be there, but they left." So we're still doing experiments to drive that, but what we really did show is that almost certainly there are cells that are being developed in the pancreas, independent of the pancreatic lymph node, and the specificity of those is really important if what you want to do is block the progression of Type I Diabetes.

So during the disease course in walking-around human beings, people become glucose intolerant, and then if they control their diet, there's some rebound of their ability to control blood sugar. The clinicians call that the honeymoon period, and then eventually enough more beta cells in the pancreas get destroyed and you can't make enough insulin to regulate.

So the idea, if we could block progression at that point of disease, that would be really good because we could clearly regulate blood glucose better. We could clearly have people not take so much insulin. We could clearly fix a lot of the downstream sequelae of Type I Diabetes, which are really bad. So diabetes is the leading cause of amputation. You get retinopathy, so you go blind. People view these as bad side effects, and we call those poor prognostic indicators. So what we wanted to try and do is to be able to look at those, and we're still doing those kind of experiments in Arizona, both in mice and trying to be able to get samples to do it in people, to ask that same question about the diversity of the T cell repertoire.

We did lots of other amusing things. We had a really nice collaboration with Lishan Su, who is one of my colleagues in the Cancer Center, looking at what

people now call BLT mice, bone marrow, liver, thymus reconstituted, gamma C-null, SCID, NOD mice, reconstituted with human fetal liver and human thymus and human bone marrow. Those mice generate a pretty good human immune system, but they also have human liver.

What Lishan did, and we published a paper last year that came out in *Gastroenterology* showing we could infect those mice with Hepatitis B [ed. Hepatitis C] and we could get a human immune response in those mice. So that now gives you a way to study pathogenesis of Hepatitis C without poking needles into walking-around people, and it gives you ways to test therapies that you can't do otherwise. So we're pretty excited about those kinds of things, and we published a paper with Roland and some of the clinicians at UNC doing a similar thing in Type I Diabetes. So we're really interested in trying to develop these kinds of models where you can mimic a human disease with a human immune system in an animal model that you can get access to the important parts.

Williams: Is there a way, then, to work it back from the animal model into a therapy for the human or not?

Frelinger: We sure hope so. I mean, that's the plan, which is you can test those therapies in these animal models, and so you can do two things. One is you can get replicates of the same person, by making replicates of their immune system in multiple animals and you can have controls. You can have real isogenic controls, and then that allows you to ask a question about whether those controls are good enough, whether you can now translate this to a lot of people, or this is going to be idiosyncratic. If it's idiosyncratic, you can actually then go back, ask what's different about this patient than that patient. So I think it's potentially really powerful.

Williams: You describe your time at UNC as being pretty wonderful.

Frelinger: Yes, I had a good time.

Williams: So what prompted you to move to Arizona?

Frelinger: How politically correct do I need to be?

Williams: Not at all.

Frelinger: So I had been chair there for seventeen years, and I stepped down as chair and we hired a new chair who was uncomfortable having the old chair there. I figured I was still a real scientist, I could get another job, and, sure enough, I could.

I picked Arizona because Janko Nikolich-Zugich is a guy who is a Mike Bevan product, who was a postdoc with Mike, and I'd known for twenty years, had gone there a couple years earlier as a new chair to rebuild the department. I sent him an

email and said I knew he had gone there and said, “I’m sort of starting to look around.”

I think within three hours I had an email back saying, “When can you come?” [laughs] So I came. I went out and visited. I like the West. It doesn’t snow so much in Tucson. So, a brand-new building, money to hire people and to build a department, and that’s kind of fun to do.

Williams: So what are you looking forward to accomplishing there?

Frelinger: So I think the most important thing is I went there with the idea that we would create an interdepartmental, inter-programmatic first year for recruiting graduate students, and so that’s done. I mean, it’s not done, but I mean it exists. We just admitted our second class. The students are a lot better, so that’s a win. We revamped the departmental graduate program, which was pretty much a disaster. We got some kids finished. We had some kids who realized they’re better suited for other careers, so they’re mostly gone now.

We’re changing the culture so the work ethic is hugely different. When I first came, I like to say if you had a heart attack on Saturday morning when you were at work, you would lie there till Monday. Now that doesn’t happen. Right now there are people there every day. There are people there all the time. They work harder and we’re doing better. So that was part of what I wanted to do, to help Janko do that.

Janko’s a brave guy. He has two ex-chairs in his department, Maggie So, who was chair at Oregon, is there. I’d known Maggie for a long time. She’s a bacterial pathogenesis person. She actually had been one of Fred Sparling’s colleagues and worked on *Neisseria*, although she’s more interested in microbio and things now.

So there are three really good young faculty. Two of them got Pew Scholars Awards. So if we can keep them and make them happy and continue to do good science, I think that will be what I want to leave behind.

Williams: Are you able to spend most of your time doing science or what’s the balance?

Frelinger: You know, I think I’m spending 60 percent of my time doing science, 20 percent of my time doing this graduate program stuff to make that happen, and so that leaves 20 percent sort of random unpleasant stuff, writing IACUC [Institutional Animal Care and Use Committee] protocols, doing administrative things like that.

Williams: Do you have a teaching role?

Frelinger: I do. I teach a little bit. So Maggie So and Felicia Goodrum, who’s a CMB virologist, who’s one of these really good young faculty, and I put together a

course that's not a didactic course for all the graduate students in immunobiology. That's our only required course, and we spent a lot of time this year, because this is the first time we did it, but we put together a series of modules, which we did as two-week modules but we'll probably do as three-week modules next time, with a sort of six-week introduction, "Everything You Needed to Know About Immunology, Bacteriology, and Virology in Six Weeks," which is really fast and really shallow and really a 30,000-foot view.

Then everything else is focused on a question or disease or something. So we just did two weeks on neurotropic viruses and immunity to neurotropic viruses and things about how does that relate to MS, trying to focus on problems with one lecture and then five sessions of papers which are student-driven. So I think the next time we do it, it'll be a lot less work for us. The first time was hard. We did some stuff wrong, not a surprise. But my main teaching effort is there, on that course, to do that. So if you talk to somebody in the Biology Department, they would think I don't teach at all.

Williams: Growing a department like this, my guess is that you rely on certain amount of PR, publicity, outreach, and so forth that may not have been characteristic of other places that you have been or of the field in an earlier time. Would that be correct?

Frelinger: I think that's partly true. I think the issue now is with funding so bad that we're all going to be at least transiently much more dependent on private funding for things. Old farts like me like to say my startup package when I went to USC was \$6,000 and a microscope, which they already had. So I got this microscope. Now we figure it costs six or seven hundred thousand dollars to hire an assistant professor because you need to not only buy all the toys, but you need to be able to support the lab for three years.

So I was expected and did—I had two small grants before I got to USC, and I had a big American Cancer Society grant within the first year that I was an assistant professor. Now faculty don't even try to write a grant until halfway through their second year, and so it's really different. Part of it is the expectations for getting grants, for the funding agencies are so much higher than they were, and the success rates are so much lower, that when you really need to be able to have the resources to carry people till they prove that they can really set up a lab, they can have students, they can have postdocs, they can actually get stuff out the door. So it's quite different.

For us in Tucson, the state is not very warm and fuzzy about universities. I mean, it's qualitatively different than it was in North Carolina, which always had an educated, if not always sympathetic, legislature. So in Raleigh, all the black legislators went to one of the HBCUs [Historically Black Colleges and Universities] in North Carolina, North Carolina NT or North Carolina Central, though the white legislators went to NC State or UNC, and, of course, they're mostly lawyers and sort of a typical legislature.

In Arizona, the legislature is almost exclusively made up of high-school-graduate small businessmen, and so it's not the same, and they're much more actively antagonist towards the university than they were in North Carolina. North Carolina, they didn't like the university because they were full of them northern liberals, but, boy, they loved the basketball team, right? You could, and I did, I've been to pig pickings out in the country and you didn't talk about where you went to church, but you could be for any basketball team as long as it was UNC or State. [laughs] That was fine and you could talk about that, and that was sort of a unifying principle.

Williams: So where are you getting most of your funding for the department in Arizona?

Frelinger: So the university has been very generous to the department, and a lot of it's coming from the School of Medicine. We've been successful in getting NIH [National Institutes of Health] funds. Three of us, led by Janko, got a \$12 million contract last year from the NIAID [National Institute of Allergy and Infectious Diseases], and I came with grants, so that's what we're doing. I mean, the old people, that is, Maggie and me and Janko, are well funded. One of the young people, Felicia Goodrum, has two grants. She's done very well. She's kind of an old young person. So we're trying hard to do that and to bootstrap it.

I think for the foreseeable future, I think things are okay. What's going to happen in five years, I don't know. I sure don't know. I confess that I talk to my TIAA-CREF financial advisor, and if I retire tomorrow, my income will be \$70 a month less than it is now. [laughs] So I have an out anyway.

Williams: What's the \$12 million for?

Frelinger: It's for West Nile virus and looking at older populations to try and understand why West Nile is so much more serious in older people than in younger people. Our part of it is to look at the T cell receptor repertoire by doing deep sequencing of antigen-specific T cells from older and younger people. We have the samples collected now.

We're spending a lot of time learning to be better bioinformaticists, because it turns out that the ways that you can handle 500 or 1,000 sequences in Excel spreadsheets don't work when you're going to try and handle 100,000 or a million sequences. The scaling isn't so good. So we've spent a lot of time learning to do that better.

I have a great guy, Harsha Krovi, who was a UVA biomedical engineer who just spent two years in my lab, who's, unfortunately, going to go to graduate school in the fall, who's really been our interface between the biologists and the computational people, and a postdoc who's really driven hard—Adam Buntzman, who's trying to learn to be computational enough to do that. It's hard. I mean,

we're just not trained right. But we've had a good collaboration with people in electrical engineering at U of A who design gaming chips for games processors, and so they've designed and built a hardwired gaming GPU to analyze these kinds of sequences and to make models of them. So we're trying to write an NSF [National Science Foundation] grant with those guys to sort of forge ahead with that, kind of different from what we did before, but exciting and fun.

Williams: Let's turn to your experiences with AAI for a bit. You became a member in '76, I believe.

Frelinger: If that's what it says, that's probably true. [laughs]

Williams: What are some of your outstanding memories of the organization?

Frelinger: So I got involved really with AAI in the advanced immunology course. They got us to teach the course for a couple of years, and then I got asked—I guess they probably did it for five years, but I did it only for a few. They had a person come for half the course, and they called him the guru. What you did was you provided some continuity because the advanced-course people come in, they give their two-hour lecture, and they're around for a couple of hours and they bolt. So they wanted some senior people to be there to talk to the students, and when the students didn't understand something, they could ask questions of you and you weren't quite so forbidding because you didn't just pontificate for two hours about it, and they could ask.

So I did that. That was really fun. Bob Rich, one of the years I did that, was one of the other gurus. I'm trying to figure out exactly what Bob was doing then. I think he was probably an associate dean at Emory [University] then and was interested and realized that I was interested in kind of broader issues of policy. He was chair of the Public Affairs Committee. The sort of professional person on the Public Affairs Committee was a guy called Pat White, the Lauren Gross equivalent of the time.

So I was on the Public Affairs Committee for probably three or four years and made some [Capitol] Hill visits, and it was at a time when—so it must have been George [H. W. Bush] the first's time when the Republican legislature was very big on getting rid of all these onerous regulations. We were going to deregulate everything. So we tried to figure out ways to make life easier for people by pushing back against—there's always been this increasing regulatory burden that we have that's driven by someone's afraid for safety, someone's afraid that you're going to throw some deadly germ down the drain or that a terrorist is going to walk in and be able to find something in your lab. No one can find anything in the labs. But to try and figure out how to push back against increasing regulatory burden, and so he got me interested and I got interested in the larger policy questions.

So when Bob stepped down, I was asked to chair that committee, which I did, and I think I did it for three or four years, which now we don't do that anymore, but which was really good. I really got interested in trying to push AAI and push the government into thinking harder about support for biomedical research, how we do that, the things which are important to our members in terms of regulation and in terms of how we live our daily lives.

My personal feeling of the most useful thing I did on that committee is I had lunch with Pat White and the chief of staff from [Thomas R.] Harkin's office in the Senate cafeteria. It was at a time when one of the things I was and I'm still interested in, postdoctoral salaries, which I still think are too low, but at that time were really too low, so we were chatting about this, and this fellow says, "Well, how much do they get paid?"

I said, "Well, I had a fellow in my lab who was an M.D./Ph.D. board-certified pediatric rheumatologist, and he was making \$32,000 a year."

He said, "That's not possible."

I said, "Trust me. That's possible. That's what he gets paid on a T-32 with that much experience."

He said, "Well, we'll have to fix that."

So that year postdoctoral stipends went up about 25 percent. Now, I don't claim that I did that, and there are certainly lots and lots of people worried about postdoctoral stipends and not just me and people inside NIH, but it was clear that this was a really important guy who was the chief aide to a congressman who was really important on the right committee, and maybe it creates the receptive field for fertilization, but it happened. I think that's how you have to think about doing all the work on public affairs, is that you know you just can't point to something and say, yeah, that happened, but this is probably as close as you can get.

Williams: You say that the organization doesn't have committees anymore?

Frelinger: Oh, no, it does. It doesn't let people be chairs for three or four years at a time. They turn the committee chairs over much more frequently.

Williams: So talk about ascending to the presidency.

Frelinger: Oh, that's easy. You just, like, live. You live long enough, it happens, right? You get elected as a councilor and you hang out for five years, right? [laughs]

Williams: What about the role of councilor?

Frelinger: That was less work and more interesting than I thought it was. It's way less work than being public affairs chair. I mean, the real work of being a councilor is showing up twice a year and paying attention while you're there. So you've got to read the book on the plane on the way, right? But really its function is as part of the board and trying to be responsible and thinking about what's best for the organization, how can the organization help its members, and why we do particular things the way we do, and should we change them. That's really what we do. And keep Michele Hogan happy. That would be the other thing that the councilor is supposed to do.

Williams: Were there hot topics during your time on the council?

Frelinger: Oh, sure. I mean, the hottest topic was PubMed, PubMed Central, and *The JI* [*The Journal of Immunology*] having to deposit or the individual authors having to deposit manuscripts, which is, I'm sure you're aware, is a rule now that has to happen. Michele Hogan is correct in saying that's basically a violation of copyright and we shouldn't abet. As publishers of *The JI*, we should not abet giving away of material that we own. From the members' point of view, you've got to do it, and it's way easier if the journal does it and lots of other journals did it. All the ASM journals do that; that is, deposit the manuscripts for you.

That was the one thing which I would say I accomplished as president, is we now deposit the manuscripts for the authors into PubMed Central. It was a case for me of not that I was right and Michele was wrong, because she was absolutely right, but it was going to happen, and this was way better for the members and for the authors.

Williams: Why was it inevitable?

Frelinger: Because Congress wants it so, and the idea of the government paid for the research, it belongs to the people, and so it needs to be freely available to everybody. I mean, there's a lot of things that I feel uncomfortable about that particular viewpoint. You could always get it. You could always go to a library and it was always there. Right? I mean, you could get it and the libraries didn't charge you to read it, but somehow the idea that it needed to be accessible in your bedroom at three a.m. online to really be accessible, which I personally think is over the top, but it doesn't actually matter since the NIH and the government, the government and the NIH is really the more—required that all those manuscripts be accessible that way. So the choices were we do it as a society for our members or make them all do it themselves independently. I thought that was not much of a choice. It's officially a condition of funding that you do this. So it seemed to me to be a no-brainer and a service for our community to do it.

Williams: What about articles that derive from, say, Howard Hughes Institute funding? Are they required to do it?

Frelinger: So HHMI requires their investigators to do it as well, as does the MRC and does—what's Burroughs Wellcome turned into now? The Wellcome Foundation. Those two are the big funders in the U.K. I think now also all the eurozone countries have that as a condition of funding, that it be deposited in a database. I'm not sure about the Japanese and the Chinese, but I think that's the real—everybody needs it, and, in principle, if you do it on your own dime in your garage, you don't have to do it, and you can publish it and it's still yours, but that's such a small fraction of—

Williams: Did you ever enjoy proceeds from publication?

Frelinger: You mean like money for me?

Williams: Yes.

Frelinger: Let's see. I once edited a book and got \$200. [laughs]

Williams: But I mean your submissions to journals.

Frelinger: No, you pay. You pay. I pay.

Williams: I can see that being a major deal. Anything else during your presidency that was a hot topic?

Frelinger: No, that was it. I mean, there's always discussion about lots of things. What's our responsibility to IUIS, International Union of Immunological Societies, which I think is unclear. We're sort of always torn between being a rich country, and because we're a well-managed society, we're a rich society, and our need to participate in the global immunology community, and how should we do that, and what's the appropriate thing to do, and how do we make those kinds of things possible?

So we do some stuff. So we sponsor, I don't know, four or five or six students a year to come to the AAI's course from other countries. We send and we have scholarships for sending U.S. people to the international society meetings. Okay. So, you know, should we be doing more? What should we do? We can't really afford to give grants. We don't have that much money. We can't go to Zambia and say we're now going to sponsor AIDS clinical trials. So Bill Gates can do that, but Bill Gates's fortune is bigger than AAI's by a factor of ten-to-the-fifth. [laughs] So we can do things that cost \$1,000 or \$5,000, but we can't do things that cost \$500,000 or \$5 million.

Williams: The conference that occurred during your tenure was in San Francisco?

Frelinger: It was.

Williams: What was that like?

Frelinger: So this is difficult for me, because my father, who was then ninety, wanted to come to the conference, and so we brought him to the conference and he heard my presidential address. The next night we were getting ready to have this sort of fancy party like they did last night, and he fell and broke his femur. So he spent the next four weeks in San Francisco General [Hospital]. One of my former fellows, Bruce Cairns, the surgeon I told you about, actually had come to this meeting because I was president, and Bruce spent the night in the ED with my father. My brother was there, who spent a lot of time there, and I showed up here handing out pictures and signing things and presenting plaques. But it wasn't that much fun, and afterwards my brother and my wife and I sort of tag-teamed the time he was in San Francisco, going home, coming back, and staying with him. So it was less than wonderful personally. I heard the meeting was good.

Williams: A few last questions. I've been asking people what they think of the state of science today in the United States.

Frelinger: So that's a really complicated question. It seems simple, doesn't it? So science is great, right? And we have tools and ways to do stuff that we couldn't even imagine when I started doing science. In my lab, Adam Buntzman, this guy who's been doing the informatics stuff on T cell receptors, out of essentially our back pocket we have just completed the sequence of the hummingbird and the ostrich. The reason for the hummingbird is it's got a heart that beats 400 beats a minute, and they live twelve years. So how do they do it? I mean, there are enormous physiological adaptations you should be able to figure out, at least get clues from the sequences. So we can start to do those kind of things which are just insane, and it costs almost nothing now compared to what it used to. So the tools are awesome.

Our ability to understand things and drive things from ideas to the clinic, I mean, it's better now than it's ever been. The downside is the healthcare system is in total disarray. We're driving it in three directions at once, all of which are wrong, and so that makes things really hard to do. The societal appreciation of science, I feel like is at a new low. I think soon we'll pass a law saying that the world is flat and that you're going to fall off the edge if you go too far.

Our inability to communicate effectively with the public is amazingly bad. I mean, it's horrifying to me. And when people like our former president [George W. Bush] says, "Well, global warming is only a theory," well, gravitation is only a theory. Evolution is only a theory. Right? So I make some alternative explanation ad hoc and that is equal? So, I mean, we've done a really bad job of trying to teach people what science tells us and how it tells us those things, and I don't know how to fix that. I mean, I think all of us need to work harder at it, but if I had a way to work harder and smarter, I would be doing it right now.

We had a session here about scientific outreach, and we don't do that very well. So we've done that. We've degraded science as a perception, and people have this simultaneous awe and distrust of it. You can find people that believe we really have the cure for cancer and we're just holding out on them, and at the same time they don't believe in evolution. And those are so discordant. I can't resolve those in my own mind.

The rest of the world is doing better than us, and if we believe that the knowledge economy is important, we have to fix that. I think the best and brightest kids are going to be bankers because they can make more money. I think that's bad, and so I don't know how to fix that either, except say, you know, we have to fundamentally change the way we view science. So, as I said, I'm really conflicted about this. The science itself is so cool, and I just don't understand why other people can't understand that.

Williams: Do you encourage trainees to pursue a career in immunology today?

Frelinger: I think that unless you can't imagine not doing it, you shouldn't do it. When I made the decision to not go to medical school and to go to graduate school, I did it because I couldn't imagine what I would do if I couldn't work in the lab. I think that's got to be people's drive to do that. So the answer is no or yes, right? If you can't imagine getting up in the morning and not going to lab, then you should do some other thing, because it's too hard and you don't get paid that much and people beat you up all the time. It's kind of like what they do. "So I have this idea." "Well, your idea stinks." Do something else. So, yes and no.

Williams: Are we leaving anything unsaid that you wanted to contribute today?

Frelinger: I want to say how much I appreciated the AAI and how important it is to exist for the meetings and the courses. I'm enormously proud to be a member. I'm really proud that Gail Bishop, who's currently vice president, was a postdoc in my lab, and I'm proud of all the people who have been in my lab. I'm proud of the people who've gone off to work in companies. I have a graduate student who's a vice president at Merck. I have two other graduate students who are professors at small liberal arts colleges, and I'm just as proud of them because that's what they wanted to do and they're doing it really successfully. So I always felt like my goal as a professor and a mentor was not to clone, make little Jeffs, though I like that, so I have some of my people have done that, but also to really help them be able to do what they wanted to do while doing good science.

Williams: Good. Thank you.

[End of interview]