The American Association of Immunologists
Oral History Project

Transcript

Lewis L. Lanier, Ph.D.
January 23, 2013
San Francisco, CA

Interview conducted by
Brien Williams, Ph.D.

Transcription: TechniType Transcripts
Transcript copy editors: Bryan D. Peery and Elizabeth R. Walsh
Final edit by: John S. Emrich

To cite an interview, please use the following general format: [Name of interviewee], interview by [name of interviewer], [date], The American Association of Immunologists Oral History Project. http://www.aai.org/OHP (accessed [date]).

Williams: This is an interview with Dr. Lewis Lanier for The American Association of Immunologists and their Centennial Oral History Project. Dr. Lewis Lanier is professor and chair of the Department of Microbiology and Immunology at the University of California, San Francisco. Dr. Lanier was president of the American Association of Immunologists from 2006 to 2007 and served as an AAI Council member from 2001 to 2006. He was awarded the AAI Distinguished Service Award in 2001. We are in Dr. Lewis' office at the University of California. Today is Wednesday, January 23, 2013, and I'm Brien Williams.

Thank you for doing this, Dr. Lanier.

Lanier: Sure.

Williams: Let's start out with your family background, where you came from, and maybe a little about your own family.

Lanier: Okay. I have kind of an unusual background. I'm probably the most famous immunologist from the town of Joiner, Arkansas. It's a town about two hundred people on the Mississippi River, just outside of Memphis, Tennessee. So I was born there quite a while ago. My father was a farmer, cotton farmer, but died about a month before I was born. So subsequently, my mother, who was nineteen at the time, she then left me with my grandparents, took my father's V.A. benefits, and went back to college to become a schoolteacher. So I lived with my grandparents for a few years, until I was about six, in Memphis. Then after that, Mom got remarried to my stepdad, and we then moved to Texas and then onward to Virginia. So that's my early history.

Williams: So, talking about your own early history. Go ahead.

Lanier: Oh, okay. So what would you like me to give you facts about?

Williams: Well, where you went to school and your interests as a young person and so forth.

Lanier: Okay. I started being interested in science, I guess, when my stepdad was teaching high school biology. I'd go in with him after I'd get out of school, and he'd let me play with the microscopes and do some experiments. That was when I was in first and second grade, so that's my first introduction to science and my enthusiasm for it.

Williams: So your mother and your stepfather were both schoolteachers?

Lanier: Yes, they were both schoolteachers. We subsequently moved to Richmond, Virginia, when I was in elementary school. I guess I was in fifth or sixth grade at that time. My dad was a college teacher at that time at a little college called Virginia Polytechnical Institute, RPI, that's now Virginia Commonwealth University or VCU. My mom was in elementary school for her whole career.

I went to high school in Richmond, Virginia, and there it was one teacher, Bonnie Stepka [phonetic], who turned me on and made me what I am today in science. Her husband was a microbiologist at the medical school at Richmond. So she was an extraordinary tenth-grade high school biology teacher. Rather than just have us learn the parts of plants and things like that, she actually taught us experimental science. So that was where I really had a love of microbiology.

I started college, though, in engineering, because my mom thought—I had good math scores and stuff like that—it might be a good profession. My first quarter of college in engineering at Virginia Tech, and I really hated it. I couldn't decide what I was going to do. I couldn't decide whether maybe I wanted to be a writer, but then I remembered, well, I really liked this microbiology that I'd learned in tenth-grade high school biology class. So I said, "I'll try that."

So that was what really turned me on. The writing part of it, I had a teacher named Thelma Phillips [phonetic] in eighth grade in Richmond, Virginia, Tucker High School in Richmond, Virginia, and everybody hated Miss Phillips because she was tough. She would make you write an essay. She'd say, "Write a three-page essay." She'd correct it, hand it back, and she says, "Rewrite it now in a page and a half, but don't lose any of the context."

So you'd grumble and gripe, and you'd do it. Then she'd hand it back, graded, and say, "Write it as a one paragraph, keeping all the context." So that's what I do today when I'm writing scientific papers. So I've had two women teachers, when I was in eighth grade and tenth grade, really gave me the foundations that I have for why I'm successful today.

Williams: Probably that skill is good for grant writing too.

Lanier: Absolutely. That's what I was doing this morning. I have nine pages of grant, and I need six pages of grant, so Thelma Phillips is helping me condense that down. [laughs]

Williams: To this day.

Lanier: To this day.

Williams: Now, do you have siblings?

Lanier: I have one brother ten years younger than I am. He works for Immigration Department in Washington, D.C., so he's not a scientist.

Williams: So talk about your academic career, then.

Lanier: Okay. After I got out of high school, I left engineering and started in microbiology at Virginia Tech. There what really turned me on was—I think when I was a senior of college or a junior in college, I was in a virology class, and there was a guy named—I think Dr. [Robert C.] Bates was the virologist. He told us about this experiment that's now a classic and really is what made me an immunologist today. I can still remember the sunshine coming in the room and him lecturing that day.

There is a virus called LCMV that's used by many immunologists today and many virologists. And what he told us in that lecture was if you take an adult mouse and infect it with this LCMV virus, the mouse becomes sick and paralyzed, but if you inject that same virus into a newborn baby mouse, everything's fine. The mouse grows up, the virus infects the mouse for life, but it never causes any damage, and it can be transmitted to the babies of that mouse and not cause damage. So this really intrigued me.

Before that, I thought I was probably going to work on microbes. I was a microbiologist. But from that lecture, I said, "Hmm. This immunology stuff, how does that work?" How can you reject a virus when you're an adult or get sick from a virus, yet as a baby be infected and it caused no problem or you'd be tolerant of it?

About that time at Virginia Tech they had their first immunologist who started the first course in immunology. This was back in 1975, spring of '75. Klaus [D.] Elgert is the fellow's name. So Klaus, I was in his very first class of immunology at Tech, and so that's where I got my passion for immunology.

I subsequently applied to grad school and went to UNC, Chapel Hill to do a Ph.D. in the Department of Microbiology and Immunology, because I still wasn't sure whether I was going to train in the microbe side or in the immune side. When I first came to Chapel Hill, I met a professor named Geoffrey Haughton, who invited me to do a project in his lab, and that then set me on the course I'm on today. So I learned how to do science from Geoff.

Williams: And he steered you towards immunology as opposed to anything else, is that correct?

Lanier: Right. So Geoff had been a transplantation immunologist, so he tried to understand why when you graft skin from one mice onto another mouse, why it's rejected. What are the principles? What are the genetics involved in that process? So you can also tolerize mice. Peter Medawar had actually shown this back in the year, I think, I was born, that if you inject cells into a baby mouse, again, when that mouse grows up it can accept grafts, skin grafts from that same allogeneic mouse.

So my first project was to work on the skin-graft transplantation. But as it turned out, the first year I was in Geoff's lab, these mice that we had made genetically to study the skin-graft rejection were spontaneously developing lymphomas. At that time, there weren't any good models for human B cell lymphomas, and these mice started spontaneously acquiring these tumors. So my project ended up understanding and studying these mouse B cell lymphomas and making therapeutics to help cure them.

Williams: At what point did you first publish results of your work?

Lanier: I think that was about 1978, so I was a second- or third-year Ph.D. student. So it was on this novel mouse model that we had generated. There's a tumor called CH-1, or Chapel Hill-1, we named it. It's a B cell lymphoma and serves as a good model for human B cell lymphomas.

Williams: So why did you choose the Ph.D. versus the M.D.? You just never thought of going the clinical route, is that correct?

Lanier: When I was living with my grandfather as a little boy, he had a really bad heart and was in the hospital several times for months on end, and I just got a bad feeling about being in hospitals, so I didn't like being around sick people. I really liked the science of medicine, but I think that experience I had with my grandfather kind of gave me a phobia of hospitals.

Williams: Widely shared. So talk about your postdoc work then at UNC, I guess.

Lanier: Yes. So I stayed on and finished my Ph.D. with Geoff in about three years and wanted to finish up some projects. We had made antibodies against the surface immunoglobulin on these B cell tumors to serve therapeutically. So we treated these mice, which we'd given this lymphoma, with these antibodies against the surface Ig. They're called anti-idiotype antibodies that cured the mice. I wanted to finish up a few of those experiments and also then look around and decide where I wanted to go for a postdoc.

There were three places that I really seriously wanted to go to, was, one, in Sweden, to a guy named Hans Wigzell who was doing some exciting work at the time. The second one was Len Herzenberg at Stanford [University]. And the third was a fellow named Noel Warner, who was in New Mexico at the University of New Mexico but also working at the Los Alamos labs.

Well, Len sent me a rejection letter that my wife subsequently found in his filing cabinet when my wife was working for him many years later. [laughs] And I didn't hear back from Hans in Sweden, so I thought, well, he just ignored my letter.

But then Noel Warner flew me out to New Mexico. I went up to Los Alamos labs. They'd just invented flow cytometry in Los Alamos a few years before that, so I saw this fantastic new technology, appreciated what it could do for me as a cellular immunologist. Noel offered me a position, which I accepted. The day I accepted, I got a call from Sweden from Hans, telling me that he'd like me to come to Sweden. [laughs] But I'd already given my word to Noel by then that I would join him in New Mexico. So off I went to New Mexico for the next couple of years.

Williams: Looking back, if you'd gone to Sweden, might you have had a different kind of career path or not?

Lanier: Yes, I'm sure I would have had a very different career path because at the time, flow cytometry cell sorters really only existed in about three places in the world: Len Herzenberg's lab at Stanford, Los Alamos, and I think they had one of the prototypes at the NIH [National Institutes of Health] in Washington, D.C. But it was having access to one of the first flow cytometers in the world that really set the direction of my research. And it also led to, when I was in New Mexico, Becton, Dickinson [and Company], who had commercialized the cell sorters, wanting to set up a research lab in California to further develop the instrumentation but also make monochromal antibodies, which would be used in those machines. When I was a postdoc there, Becton Dickinson recruited my postdoctoral mentor, Noel Warner, to head the new small research lab in Palo Alto [California], and he offered me a position there as a staff scientist in biotech. So I'm sure if I went to Sweden, I would have never ended up in biotech or California.

Williams: And were you going to Becton Dickinson mainly to work on equipment or application of the equipment?

Lanier: Well, I mainly went to Becton Dickinson to develop antibodies that would be used then on the cell sorter to identify the different types of white blood cells, because at that time hybridoma technology had just been invented like two or three years before that, and today we have three or four hundred known CD antigens on the surface of white blood cells to say that all these cell types and subtypes and subsets. Well, none of that existed when I was a postdoc in the mid to late seventies. So when I went to Becton Dickinson, my initial charge there was to make antibodies against the human immune system and figure out what they did and if they were going to be useful for diagnostics or potentially therapeutics.

Williams: And how far along that road did you get?

Lanier: Well, I worked at Becton Dickinson for ten years, and we made a number of the antibodies. It was really a remarkable time in understanding the composition of the immune system. When I went to BD, we kind of knew there were B and T

cells, but we didn't have any really definitive markers. The T cell receptor had not been identified. We knew about surface immunoglobulin on B cells. That was about it. By the time I left BD, there were a couple of hundred known surface antigens. We'd developed antibodies against many cell subtypes and differentiation stages, and that was where I first also started working on natural killer [NK] cells, and that, then, has been my career for the last three decades.

Williams: Was it a difficult decision to move out of academia into the business world, or did that come very easily for you?

Lanier: Well, everybody wrote my scientific obituary when I told them I was going into industry, because at the time all the best and brightest postdocs went into academic careers and became assistant professors and associate professors and professors.

When I was a postdoc in New Mexico, I had never been to the West Coast before, and another postdoc and I, Dorothy [E.] Lewis, she and I drove out to a meeting in Asilomar in Monterey, California, driving up Highway 1, camping along the way, came to San Francisco, and I said, "I really like this place."

So when I was getting near the end of my postdoc, I applied for some academic positions, was offered an assistant professorship in Texas, and Noel Warner, my advisor who started this new lab in Palo Alto, California, said, "Would you like to be a staff scientist?"

So I said I'd give it a shot. I really liked San Francisco. I thought also that I want to try this new biotech stuff. It seemed exciting, different, and I said, "If it doesn't work out, I'll work here a couple of years at BD. Worst case, I go do another postdoc and then go back and be a professor." Well, there was a twenty-year lag between me making that decision and actually coming back to be a professor at UCSF.

Williams: How large a team was there at BD when you arrived in your area?

Lanier: BD is obviously a huge corporation stationed out of New Jersey, mostly known for making syringes at the time or thermometers, but they had set up a small research lab in Palo Alto in collaboration with Len Herzenberg's lab to take advantage of flow cytometry, which Len had helped invent, and also to make antibodies to make diagnostic and therapeutic agents. So I think there was probably less than forty of us the first year I was at BD, and by the time I left ten years later, I think it was over a thousand.

Williams: And they'd already moved over to San Jose by that point?

Lanier: Yes. We started on the edge of Palo Alto in Mountain View in a lab on Garcia Avenue. The last year I was at BD, we moved to San Jose, but I was there about six months and then started phase two of my career.

Williams: So BD not only was making products; they were making products based upon the science?

Lanier: Right. So what they wanted to do was make products to initially allow researchers to understand how the immune system works. I think the main breakthrough that happened for them commercially was it was during the early eighties that the AIDS epidemic hit, and it hit San Francisco extremely hard. Before they even knew what caused HIV or had isolated the virus, they knew that in those people who were becoming sick their white blood cell counts were going down. It was CD4 T cells that were disappearing because of being infected and destroyed by the HIV virus.

So BD, having a nice instrument that would fit on the desktop here, called a FACS analyzer, and having antibodies that would measure CD4 cells, even before it was possible to do a test to detect the virus, the blood banks started looking and buying BD antibodies to count CD4 cells, and if a person's CD4 cell count went below a certain number, then they would not transfuse that blood. Later that was replaced, obviously, just by the serological test. But that created a huge market, clinical market for flow cytometry.

Williams: So you say you were there for ten years, or twelve, right?

Lanier: I started, I think, in July of '81 and left in about '90, yes.

Williams: And what prompted your move?

Lanier: A couple of things happened. One is BD originally was putting a lot of resources and a lot of emphasis on the basic research, which I was doing. We were making a lot of the monochromal antibodies. We had discovered that natural killer cells were a real distinct population in the immune system, and we were defining the receptors and their service and how they worked.

BD was really putting pressure on me to make more clinical kits than continuing to do research. So at that time I had friends who were working at a research institute in Palo Alto called DNAX Research Institute. Originally DNAX was founded by Paul Berg, Charlie Yanofsky, and Arthur Kornberg. They had founded this small biotech in Palo Alto on California Street. I had friends there, and they said, "Well, we're expanding our staff, we have an opportunity, and we think you would be a great addition."

What DNAX was really known for in those days was their ability to use molecular biology to study the immune system, cloning all of the genes and

cytokines and things that make the immune system work. So at that time I realized that learning molecular biology was really the way forward in understanding how natural killer cells and T cells worked. So when they offered me the opportunity to take my group from BD and move from San Jose to Palo Alto, I said yes, and within a month had the whole gang working full-time in Palo Alto.

Williams: How large a gang was it?

Lanier: It wasn't big by most lab standards. I think there were seven or eight of us. But we had a lot of fun. The really unique thing about DNAX is I think there was only about twenty P.I.'s there. All of us worked at the bench. Even when I was director there, I worked at the bench, because I didn't have to write grants. [laughs]

Williams: Who first identified the NK cells?

Lanier: So the NK cells were identified as an activity by several labs, kind of mid-seventies. So when people were trying to study whether the immune system could recognize and attack cancer cells, several groups noticed that if they bled me or bled you or took a mouse that didn't have cancer and took the lymphocytes from those individuals and put them with cancer cells in a dish, some cells in that dish were killing the cancer cells.

I think it was Rolf Kiessling and Eva Klein in Stockholm at the Karolinska [Institutet], they coined the name "natural killer" because they naturally existed. You didn't have to do anything. Everybody had them. So the activity was identified mid-seventies. I kind of came on the stage about 1980 and said, "You know, we need markers to identify these and see if it's lots of cells doing this activity or whether it's a special cell doing this activity."

Williams: So talk about that exploration and how you came to conclusions.

Lanier: Well, I think one of the first ways people were kind of separating NK cells from the rest of the cells in the blood was based just on the density, the size of the cell. So if you used a Percoll gradient, which will separate cells based on the buoyant density or size, it was noted that if you spun the cells down, most of the cells went to the bottom. They were small, tiny lymphocytes. They would pellet in the bottom of the tube. At the interface of the Percoll gradient there was a fraction of the cells, maybe 10 percent of the total cells, and that had the killing activity.

So they were first called large granular lymphocytes, or LGLs, but you didn't know whether that was a mixture of a bunch of different big cells which were killing or whether it was a unique cell. The good luck was that a fellow who was my first postdoc, a fellow named Joe Phillips, who had trained for his Ph.D. with a friend of mine in Texas, came to BD as my first postdoc. He'd made an

antibody that we now call CD16, which is expressed as a marker on human NK cells.

So I remember it's one of these eureka moments when we took Joe's antibody, labeled it with the fluorochrome, used Len Herzenberg's cell-sorting technology, and we sorted the cells that had the CD16 marker and the ones that didn't. CD16 marks only about 10 percent of your blood, but all the killing activity was in the fraction that has the CD16. Those cells did not have markers of B and T cells. It was at that moment I said, "These cells are unique population distinct from B and T cells." Took about another decade to convince the rest of the world, but when we did that experiment, that's what convinced me that this was a unique population of cells, whose purpose was this killing activity.

Williams: There were other large cells that were not going through the filter, right?

Lanier: Yes.

Williams: And what were they like? What were they?

Lanier: Well, monocytes, a type of myeloid cell, those are larger. Those will also contaminate that big cell fraction. Some activated T cells will also—they're larger than resting T cells. So we could find those. Once we had Joe's CD16 marker, we could say, well, some of these big cells are big and are in this interface, but if we separate them out, they don't do anything. Only the ones that had this CD16 marker were the ones which worked.

Williams: So having made that discovery, then what's the path of application?

Lanier: Path of application. So we got involved early on with some doctors here at UCSF who were treating patients with a cytokine called Interleukin-2, because that can activate NK cells and make them much better killers. So today it's an approved drug. IL-2 is approved for melanoma treatment. It doesn't work terribly well and has side effects. But we were involved in plastic dish experiments showing that the natural killer cells were the ones actually responding to the IL-2, and we work with the clinicians here at UCSF to show that when the person was injected with IL-2, again, the tumor-killing activity of this person's NK cells against their own tumor was mediated by this population. We're still trying to figure out ways to tweak your NK cells for therapeutic purposes.

Williams: And they also have the property of memory, is that correct?

Lanier: Yes. That was a good surprise. It had previously been thought that NK cells were nonspecific and pretty stupid and short-lived. So about four years ago, I guess, now, we kind of had the other aha moment, that NK cells aren't stupid and they aren't short-lived.

Williams: Have you developed ways to increase the population of NK cells in an organism?

Lanier: Yes. You can increase NK cells, again, with cytokines. Again, when people have been treated with IL-2 therapeutically, the number of NK cells increases. Jerry Ritz and his colleagues at Dana Farber [Cancer Institute] have shown this quite convincingly. Also, many of the antibody drugs now that are used, like Herceptin for breast cancer and Retoxan for B cell involvement, it's actually the CD16 receptor on NK cells which is involved in killing the antibody-coded tumors. CD16 is the receptor for the FC portion of those antibodies.

Williams: So you're several years at DNAX, and then what?

Lanier: So I was at DNAX from '90 to '99, and at that time I had known many of the guys at UCSF and collaborated with them over the course of twenty years by then. Harold Varmus was a professor at UCSF, got the Nobel Prize for discovering oncogenes with Mike Bishop. Harold had gone to the NIH to become director of the NIH in the nineties. It's a presidential appointment. So they had held Harold's lab open and his position open while he was at the NIH, hoping that after he had retired from the NIH directorship that he'd come back to the Department of Microbiology at UCSF. But as it turns out, after he did his tenure as NIH director, [Memorial] Sloan-Kettering [Cancer Center] convinced him to come and be president.

I got a call from another AAI president, a good friend, Art Weiss, who said, "Harold says he's not coming back. We've got a professorship and a lab open here at UCSF. Why don't you think about coming and joining us."

Art then talked to Frank McCormick, who's head of the Cancer Center here, Liz Blackburn, and Tony DeFranco, chairman of Microbiology, and Bill Seaman, who's at the V.A., and they kind of put a consortium together and a movement to get me recruited to come and join them at UCSF, which I did in the fall of '99.

Williams: We didn't do short shrift with your career at DNAX, then? We've pretty much covered the work that you did there, or was there something—

Lanier: DNAX was a remarkable place. It was really fabulous. We had all the best technology, we had twenty bright, young P.I.'s, and were kind of unencumbered by any of the bureaucracy that usually takes you away from doing the best at the bench. So there was where I learned molecular biology, and we cloned many of the genes and coding a lot of these receptors on NK cells that allow them to recognize virally infected cells and cancer cells and attack them.

Williams: So that was a very positive experience for you being there.

Lanier: It was amazing. I call it the Bell Labs of immunology. It truly was.

Williams: Where did they get their funding?

Lanier: So early on, DNAX was acquired by Schering-Plough drug company in New Jersey, but they kept it as a discovery research unit, and that was really fabulous. The administration in New Jersey was very supportive of allowing us to kind of go and play in the sandbox and figure out how the immune system works. Many of the discoveries that are in the textbooks of immunology now came out of that tiny little place. There was twenty P.I.'s, about seventy or eighty postdocs, and the rest technicians. And Th1 and Th2 were discovered and invented at DNAX. Cytokines IL-4 and IL-10 were cloned there. We did all of our seminal early natural killer cell work there, so it was a lot of fun. It was the Bell Labs of immunology.

Williams: Schering-Plough really kept hands off?

Lanier: They kept hands off until I left. [laughs] That was one of the reasons that I left was, again, as I mentioned at BD, my heart is really in fundamental basic discovery and understanding the immune system. So in the 1990s, Schering-Plough sold an antihistamine called Claritin, and it sold billions of dollars a year. Its patent went off, I think, in about 2000, so the economic pressures were increasing to put more into the pipeline in a much shorter term, so kind of the focus was changing from discovery into more developmental aspects, which has got to be done, but I decided somebody else should do it, not me.

Williams: What happened to DNAX after you left, or are they still in existence?

Lanier: They're still in existence. I think they're not called DNAX anymore because it then became Schering-Plough Research Labs when they had a change of focus to a more applied developmental focus, and more recently, Merck bought Schering-Plough, so that now it's called the Merck Research Labs of Palo Alto. I still have friends there and they're still doing some great work there. It's a different emphasis now than when I was there.

Williams: How closely tied was it and is it to Stanford?

Lanier: So DNAX was started as a biotech by three Stanford professors, Berg, Kornberg, Yanofsky, and it physically is about two blocks away from Stanford, so, again, we had a lot of interactions there. I mentored some students who got their Ph.D. at Stanford through collaboration with others.

Williams: Did those three professors remain on the faculty at Stanford, or did they pull away to work full-time at DNAX?

Lanier: I think Paul Berg and Charlie Yanofsky are still at Stanford, and Arthur Kornberg was there until he died about two years ago. Berg and Kornberg both have Nobel laureates and been at Stanford since, I think, the fifties.

Williams: So what were the expectations of UCSF when you arrived? To be the second Harold Varmus?

Lanier: [laughs] I would hope so. In fact, when I showed up at UCSF, Harold's lab had been vacant for six years, so it had accumulated all of the junk. People had used it as a dumping ground. Anything that was operational and useful had been stolen by another lab, so I was left with everything, all the dead refrigerators and dead power packs. So took me and two postdocs about a week to clean out the lab before we could actually set up my lab. The one thing I didn't throw out was there was ice buckets with the name "Varmus" on them. And I've told Harold the story. I told my postdocs, I said, "We're keeping these ice buckets. They're really lucky." [laughter]

Williams: They may fetch a high price someday.

Lanier: [laughs] Yes.

Williams: So did you bring any people with you, or did you come on your own?

Lanier: When I came to UCSF from DNAX, it was, I think, October of '99, there were three postdocs who came with me, and then we started the lab with the four of us.

Williams: When you arrived with these others and cleared out the facilities, where were you headed?

Lanier: We had just identified a number of new receptors on NK cells at that time, as I was finishing up at DNAX. So I wanted to know what do these receptors do. I'd work for twenty years at the bench on human cells, human immunology, because I became dreadfully allergic to mice when I was a graduate student. So when I was working in the lab, if I got near a mouse, I'd anaphylax. So that's why I spent twenty years figuring out how human NK cells worked.

But after we had identified a lot of these receptors on human NK cells and cloned the genes, when I came here I appreciated we really have to go back in to animal models so that we can manipulate, take the gene away, infect mice or give mice tumors, and see how they behave when we manipulate these molecules that we discovered at DNAX.

So the first thing I did was start writing grants so I could get some money, because when I came from industry, I had no grant money. They had set me up with a nice package to kick-start me here at UCSF, but that was going to run out not too far away. So I started writing some grants and also recruiting a new group of students and postdocs to join me, writing the mouse protocols so we could do all these experiments, knocking the genes out in the mice, and infecting them and giving them tumors and seeing how they behaved.

Williams: And you did none of that work yourself?

Lanier: [laughs] Not the mouse work. Not the mouse work.

Williams: So this was sort of a continuation, then, of your DNAX interests.

Lanier: Absolutely. Like I said, one of the reasons I had left DNAX was I really wanted to understand what the biological function was of a lot of these molecules we had discovered at DNAX, without worrying about putting them to therapeutic use in a five-year timeframe, because I knew that that was probably not going to happen.

Williams: Was there any expectation that some of this work would flow back into DNAX, or were you completely severed? That relationship had been severed?

Lanier: No, I stayed on as a consultant for them, an advisor for a few years, and, in fact, I'm going back and advising the Merck group. Last month I was meeting with some of my old colleagues from DNAX who were still there, discussing the science. So it was a pleasant separation.

Williams: But it was understood that the work you were doing here that may have been built on the work you had done there, they would have no proprietary—

Lanier: Well, you know, when I was working at BD and at DNAX, the understanding was if we discovered something potentially useful, you would file the patent before you submitted the paper. So many of the molecules that we discovered in my lab at BD or then at DNAX, the patents were filed. So, in essence, by continuing to work on some of those molecules at UCSF, I was doing their work for free now, because if we found something interesting, we'd file the patent through them and they could potentially benefit from that.

Williams: And that did happen?

Lanier: They still are pursuing some of the things that I had started there a decade ago.

Williams: So talk about the high points of your career to date here. What have you been doing?

Lanier: At UCSF?

Williams: Yes.

Lanier: Okay. So, again, like I said, I did turn from the human to the mouse for practical reasons, and I think a couple of the voilà, eureka moments that happened here, the first one, I think, was when we had discovered this system that I'd started working on at DNAX, this receptor called NKG2D. It's a receptor that activates T cells

and NK cells. My postdoc, who was working at DNAX and then joined me here at UCSF, named Heidi Cerwenka, she cloned the ligands for this receptor, and they're really interesting because in mice and humans we have about ten genes that encode these ligands for this receptor, but those genes are silent in healthy tissue. But they become turned on in cancer cells, virally infected cells, and they become up-regulated in some autoimmune diseases.

So that really set the stage for much of what I've done since being at UCSF. We had a receptor that's on all NK cells, it's on all gamma-delta cells, and on human CD8 T cells. So when those cells, those immune cells are circulating through the body, typically there's no ligand for that receptor in healthy tissue, but either cancer or viral infection or autoimmunity can cause the expression of those ligands on the surface. It's good if you have cancer or have a viral infection. It's bad if you have autoimmunity. So we've set up several models, autoimmune models, viral infection models, and cancer models to show the importance of that receptor system.

Williams: In layman terms, describe the ligand.

Lanier: The ligand, they're a protein that is not expressed in healthy cells. When cells become unhappy and they're disturbed by infection or by cancer, they then will put this protein on the surface of the cell like a flag, saying, "Something's wrong with me. I need to be gotten rid of." The receptor on the killer cells can now see that flag, know that that's the cell to take out. So there's a variety of ways that those—stress can do it. Many types of stress of the cell causes that process to turn those genes on.

Williams: Now, it would sound like—a simple-minded person would say, well, you've cured cancer.

Lanier: [laughs] We've cured cancer in a lot of mice. That's the interesting part. Both viruses as well as cancer cells find a way to escape this mechanism.

Another good surprise was when we started working with a postdoc here, Courtney Crane, who's working with a neurosurgeon here. We were looking at glioblastoma patients. Now, most cancers express these stressed ligands, and if I put these cancer cells in a dish, the killer cells will kill them. But, obviously, that does not happen in the people who have cancer.

So when we started looking at the blood of these people who had cancer, we saw the receptor was not on the cell surface of the killer cells. It was gone. Why is that happening? It turns out that when the ligand engages the receptor, it's down-regulated and it makes it internalize and disappear. The blood cells, how do they get into the brain to have access to the glioblastoma to then down-regulate the receptor? It turns out that the glioblastoma cells secrete a soluble molecule which then make the person's own healthy monocytes make the ligand. So now you've

got decoys. You've got normal healthy cells putting the ligands on, which are preventing the killer cells from attacking the tumor, because now a lot of healthy cells have the ligand and cause the down-modulation receptor. That was a big surprise. We're now working together with Courtney and Andy to try and understand whether this can be of diagnostic use, or if you could stop the tumor from putting the ligand on the healthy cells, maybe the killer cells would find the glioblastoma and get rid of it.

We also had worked on several viruses which have ways of stopping cells from putting those ligands on the cell surface. So half of us are infected by a virus called cytomegalovirus. Once you're infected, you have it for life. It's like herpes, you know, that causes cold sores, or like chicken pox. Once you get it, you have that virus forever. Well, CMV, if you infect cells with CMV, the infection causes the infected cell to start synthesizing the ligands for this killer receptor. What happens, though, is the virus, CMV, in both mice and humans, makes proteins that then grab and capture those ligands inside the cell so they never make it to the surface.

So my first Ph.D. student here at UCSF, Melissa Lodoen—she's now assistant professor down at UC Irvine—she identified some of the CMV genes that allow the virus to stop this process from working. It grabs the ligands and keeps them inside so the killer cell can't see that the cell's unhappy. So that's been keeping me busy at UCSF for a decade; part of what's keeping me busy.

Williams: Okay. Talk about the other parts, other than grant proposals.

Lanier: [laughs] I'm a professional writer.

The other thing that I've been interested in is why do you have natural killer cells. Now, they were originally discovered because of their ability to kill cancer cells, but cancer usually happens in old people because of accumulation of genetic mutations. I think natural killer cells really arose to deal with viral infection. There are a few humans which have no natural killer cells that otherwise have normal immune systems. Those people suffer certain viral infections. That's what they end up in the hospital with and what has typically killed them. It's a really rare disease, but it's instructive that that's why these cells are there, is to deal with certain viruses.

Herpes viruses are what NK cells like to recognize and attack. So we've spent a lot of time working in the last ten years on cytomegalovirus in humans and mice. In the mouse, we're taking away receptors experimentally and manipulating the virus to see how it works. But we've also had the opportunity to work with clinicians, and one of my fellows now, Gundula Min-Oo, has been working on two people who have no NK cells, to find out why they don't have NK cells. Those people have chronic problems with herpes virus infections, and one of the

women has become infected with papillomavirus and has acquired cervical cancer because she can't take care of viral infection.

So that's been a lot of fun. I think we've just figured out why these people have no NK cells. I think we've found the mutant gene. Today, for less than $1,000 you can sequence all the axons in your genome. So we got blood from family members and from these two patients, sequenced them, and I think we have a good clue now. We're trying to validate that and prove we have the right gene. But that's been fun.

Williams: Anything else?

Lanier: The other thing I think that we really found that was surprising was that natural killer cells have memory, also that they can be completely virus-specific in some cases. So before, it was thought that NK cells were nonspecific, they would just kind of kill any cell that didn't look right, largely through this NKG2D pathway being one of the major ways they would do that. However, one of my fellows, Hisashi Arase, about 2002, he identified a receptor on NK cells in mice that allows it to specifically attack cells infected with cytomegalovirus, and he cloned the viral gene they recognized. So this is absolutely specific, which is a complete surprise that NK cells could be specific for CMV, have a receptor that would not see any other virus.

The other thing we found that was surprising was that once these NK cells recognize and respond to CMV, CMV stays with you forever. If you're infected at five years old, if you live to be a hundred, you'll still be infected with CMV. So you've got to keep it in check for a hundred years, if you're lucky. NK cells are part of that process. In mice, Hisashi found this receptor which specifically sees CMV and controls it.

So Joe Sun was a fellow who started working with me about five years ago and says, "Well, what happens to those NK cells after they see the CMV?" We know they kill the infected cells, but the virus hangs around. They've got to keep it in check forever, for the life of the mouse, like they do for the human. So Joe did a really clever trick. He took NK cells that have this specific receptor called Ly49H and put them into a mouse that was in all other aspects completely normal but lacked that receptor. We knew they would die of CMV. He could then track the fate of those NK cells.

Previously it had been said NK cells only live for two weeks. Joe put the cells in, these mature NK cells with this CMV receptor, into the mouse infected with CMV. The cells go crazy, control the virus. But Joe came in one day into my office and says, "You know, it's three months later and I can still find those cells I put in three months ago. They didn't die in two weeks like the textbook said they were supposed to do." That was our, "Wow."

NK cells are long-lived. We studied them and showed that they would then respond better the second time they saw a virus, saying, like B and T cells, they remembered, and they were also long-lived. Now it suggests that maybe you can vaccinate NK cells like you vaccinate other components of the immune system.

So that was about five years ago, and that's what's been driving the lab since then. The most fun thing we're doing now, I think, is we've shown that that also occurs in humans. I think we've found the receptor for human CMV and are trying to prove that that's true and come up with strategies to see if we could vaccinate your NK cells to make them work better against CMV.

Williams: How would you imagine you'd do that?

Lanier: Well, I think we know the receptor that humans NK cells use to recognize CMV. We don't know the viral ligand yet, so that's the grant I'm writing this morning, is to try and identify that. If we could find that, like you do for your flu vaccine or your chicken pox vaccine, we could inject that ligand with tasty adjuvant, expand the population of NK cells that would see the CMV-infected cells, and protect.

That can be important in transplant patients. Also 1 percent of human babies are born with CMV infection, and some of those go on to have hearing loss and they have developmental abnormalities. If you could vaccinate the moms, then you could prevent the kid from—because they usually get it during birth from their mother. So I'm hoping—that's the significance of my grant section, is hopefully we could stop this from happening to kids.

Williams: We don't want to keep you too long from getting back to that. [laughs] So I guess you've also discovered that there are different classes of NK cells.

Lanier: Yes.

Williams: And not only are they long-lived but they learn.

Lanier: Yes. They can remember, yes.

Williams: But you say that they're more effective after having—on the second attack.

Lanier: Yes. Like your T cells will work better after you've been vaccinated, so they are more potent.

Williams: Let's turn to the AAI for a moment.

Lanier: Okay.

Williams: You were president in '06 and '07. What drew you to stand for the Council and to become involved in the organization from that standpoint?

Lanier: Well, I always thought the AAI was a good organization. I joined, I think, when I was a postdoc in about 1980, and initially it was one of the first few places that as a young scientist I was invited to talk about my own work. That's something unique about the meeting. At a lot of meetings, smaller meetings, they invite the famous people. When you're just starting out, you're never going to get on the podium. AAI allows the people who actually do the work to talk about their own work. So as I was starting my own lab, I was invited several times to come to the AAI meeting, present my own work.

The Journal of Immunology is a fantastic journal. People say, "Oh, it's just a *JI* paper." Well, the first paper on the T cell receptor is published in that journal. The first description of Th1, Th2 is in that journal. My first NK paper is in that journal. So before things are fashionable, the journal and the society have really contributed to everyone's career early on in that fashion.

Williams: You were an editor, associate editor for a while?

Lanier: Yes. So as I started my relationship with AAI, they started inviting me to chair sessions at the meeting. The first papers I probably reviewed for a journal were for *JI*. Then they asked me to help with the editorial process. Then at one point they asked me to join the Program Committee and then become head of the Program Committee, which organizes the annual meeting. So that was kind of my steppingstones up to the Council and the presidency.

Williams: You received a distinguished award from the AAI, and I'm trying to find it in my notes here. Was that for your service on the Program Committee or not?

Lanier: Yes, that was largely for my work as program chair for a number of years, yes.

Williams: What was outstanding about your programs?

Lanier: [laughs] I'll let other people judge that. They were well attended, and I think everybody congratulated us on putting together good meetings that were well run and were exciting.

Williams: Did you introduce any innovations in the format or anything of that sort?

Lanier: It's been quite a while, so I don't remember. I think the key, though, is persuading the best people to be involved and present their best science, because AAI, unlike some other organizations, is all pro bono. You don't pay anyone to speak there, so you have to convince them that it's such an honor, and to get the top people in the field to come to the meeting and present their latest work without getting paid for it or getting the travel expenses paid. So I think my distinguished service was convincing a lot of really good people to come for free. [laughs]

Williams: Have you been to many since your presidency, the annual meetings?

Lanier: I've been to probably about half of them since. I went to every meeting for probably about twelve years while I was program chair and then councilmember and then president, and then took a little bit of a breather, but I'm going back to Hawaii this May for the 100th meeting.

Williams: Any particular memories of your years' tenure as president? Any outstanding memories?

Lanier: Let me think about that. Again, the highlight of the year was the meeting. That year it was in Miami Beach, and it was a terrific program and a tremendous setting, plus just being able also as president to give awards to and congratulate people on their lifetime achievements and give out the student awards and introduce the distinguished speakers, that was a real pleasure.

Williams: In your presidential message, you talked about the educational role of AAI and, in particular, about the introductory and advanced courses. I was really surprised to learn that the advanced course in '02, which was the only information I saw, had eighteen faculty. So that's a big operation, isn't it, that advanced course?

Lanier: The advanced course I took when I was a student, and it was the way you really got to put a face to all the papers you were reading. I think I was a second-year Ph.D. student at Chapel Hill. By then I was reading everything that was coming out at the time, but you didn't have a person and a personality to link that to.

The advanced AAI course at that time was held at Fort Hood College in Maryland, while they were out on summer break. I do remember they had no air-conditioning, so you can imagine Maryland in July—it was July of '76—with no air-conditioning. But it was a fabulous opportunity to get all the top immunologists in the field, to be able to meet them, ask them questions, and they would lecture for an hour or two on their very latest stuff.

I ended up on the faculty later. I was an instructor when they held the AAI advanced course at Stanford, probably about five or six years ago, I lectured three or four years in a row. So it was a lot of fun to have gone from student to faculty of that course.

But that course, anytime someone asked me, "I need a crash course in immunology," I'd say, "Take this one-week immunology camp that the AAI puts on, and you'll come out having met the people who are really the stars in the field and a full appreciation of what's new and exciting."

Williams: What about the introductory course? How would you characterize it?

Lanier: I haven't been to that. It's been taught largely on the East Coast in Philadelphia, so that's a new innovation, probably within the last ten years, and I haven't been on faculty. They usually get local faculty.

Williams: You also talked about public affairs and the need to make people better aware of the science, and you said that at the time NIH was doubling its funding, but that inflation meant that it really wasn't that big a deal.

Lanier: That's true, absolutely. I think that having people in D.C. at the AAI office, having staff there who have face time with the people writing the legislation and making the budgets is huge. When I was president of AAI, I got to go to Capitol Hill, and I've met some of the people. The people actually writing the laws and the budgets are essentially postdocs. It's not the congressmen. They're out there raising money, like I'm raising grant money. The people making the bills and making the laws are usually young people, some of them Ph.D.'s in science and immunology, right out of grad school who are going into public policy. If you can convince *them* that what you're doing is important, it's going to end up being helpful for everybody, and AAI is really doing that well.

Williams: You did sign a letter to Toni Scarpa, the director at the time in the Center for Scientific Research at the NIH, calling for some renovations in their procedures and whatnot. Has there been a sort of tradition of clashes between AAI and the immunologists and the NIH?

Lanier: With Toni Scarpa, yes. [laughs]

Williams: That was a special case?

Lanier: That was a pretty special case. I think we have much more amicable relationships. Every year Tony Fauci, who heads AID, comes and addresses the AAI Council at a small dinner or breakfast meeting every year. So we had a great relationship with him. Toni Scarpa had some changes that he wanted to make that were "my way or the highway," which we took exception with.

Williams: Today how is AAI helping fund the field and support the field?

Lanier: AAI's missions, they're doing a great job. Education's number one, with their educational program, the annual meeting really allows young people their first opportunity to give their lectures. The journal is very democratic. They review everything, and they don't just arbitrarily triage half the papers, like most journals do. Also, their public interactions with Congress, it couldn't be any more important than now when payouts are 6 percent. Convincing them that what we're doing is important and that immunology interfaces with every aspect of medicine is absolutely critical.

Williams: Are you sanguine about Congress accepting that, learning that lesson?

Lanier: [laughs] I would hope so. We've got to keep trying.

Williams: So far, what would you describe as your happiest moments in the field?

Lanier: Happiest moments. It's when I've done an experiment and known that it was important. When I gave my AAI presidential address, I talked about my eureka moments and actually even showed some pictures of my lab book of those times where I said, "I've found something. I know this is going to make the textbooks." So most people only have a couple of times in their life when that happens, but I've been fortunate to have a couple of those events in my life.

Williams: Talk a little bit about disappointments and dead ends and things like that.

Lanier: Well, that is the hardest part of science, because if you're out to find out things that are never known before, most of the time you will fail. So I know there was a fellow I worked with at BD, he's a Ph.D. in virology, but he went into the marketing department because he said, "I couldn't stand the failure rate. I would do an experiment and I'd get a positive answer and I'd get really excited." But as a scientist, you know that you've got to do it again, because sometimes they're just flukes. So he said he couldn't stand the batting average of the average scientist being so low. But the fun part is, every morning, if you get to come in and try out a new idea and learn something hopefully that was never known before, you only have to get that reinforcement every few years to kind of keep you going for the next major homerun.

Williams: How do you keep science going in your own department here? Is it regular meetings? Do you spend time in the lab? How does that work?

Lanier: So, in my lab we have a group meeting every Monday morning where the students and postdocs present their work. We go over it all Monday morning. On Friday afternoons every other week, the postdocs in the department all present their work, the kind of work in progress. We have a journal club every Thursday morning, that gets over a hundred people here, which is really remarkable, and students presenting or faculty presenting. So those are the kind of interactions.

Also, when I came here, there were a few other labs who were also working on natural killer cells or related areas, and I said, "You know, we need to talk to each other so we don't inadvertently end up doing the same experiment or getting paranoid or hiding data, so we're going to have a joint group meeting once a month called the NK Club, where everybody who's doing related things will come and just put it on the table."

That really set the tone, and it's been a lot of fun. It's led to a lot of collaborations. You bounce around a lot of ideas that you may be thinking about your experiments or results in one fashion, but if you have two or three other

really good people here, you present and they go, "That's wrong. That's baloney." It's a lot of fun. You get an active debate. So we do that once a month with my colleagues who work on similar cell types, and it's led to a great interaction.

Williams: Talk about UCSF as a culture, as a community.

Lanier: When I left DNAX, the reason I came here as opposed to going elsewhere—I had a couple other opportunities—was because I liked the people. I think there's about forty immunologists here, which is a huge critical mass. I think other than Harvard [University], it's hard to think of a place that has that number of immunologists doing a diversity of things. And the philosophy is we have to compete with the rest of the world, we don't need to compete with each other, let's help each other, and there's that kind of spirit. As well as doing science together, we also have a lot of fun together with the other faculty members. A lot of them play golf together. I like sailing, so I invite them out on my boat.

Williams: I notice the hospital is right next door.

Lanier: Yes.

Williams: Is there clinical activities that you undertake or your department undertakes?

Lanier: Yes. So, I mean, that's one of the advantages to being at medical school. I'm a Ph.D. I never had any interest in being a doctor, but I am interested in understanding how the human immune system responds to infection or transplantation. So I'm mentoring a young guy, Jeff Venstrom, who's a bone marrow transplant surgeon who's interested in NK cells.

Last year when we wanted to find out if NK cells in humans responded to CMV, I hooked up with the transplant surgeons because when they overdose people with immunosuppressants like cyclosporine, CMV reactivates. Then you can see what happens to the NK cells, and we found the NK cells that took off and responded specifically, showing that we, like mice, have specific NK cells that respond. I wouldn't have been able to do that if I didn't have the transplant surgeons down the hall, who would call me and say, "Oops. I gave this guy too much cyclosporine. He's viremic. Here's some blood."

Williams: What advice do you give to trainees in terms of career paths?

Lanier: So, like I say, people wrote my obituary when I went into industry back in the day. I tell people you really have to follow your passion, and your passion can be in industry. Your passion can be in policy. It can be in journalistic aspirations in our field. So I don't look down on anybody, but I say what you have to do is follow what makes you excited, because the worst possible case is having a job where you get up in the morning and dread going to work. So I can give you the

training and help you get the training in immunology and microbiology, but you've got to figure out what makes you happy and channel your training into something that will fit you.

Williams: Knowing as you do the prospects in the field, you don't feel a responsibility to steer anyone in a more profitable or promising direction than another?

Lanier: No. I think if you are smart and lucky and work hard, you can succeed in any of those different directions. But I always say there's three things that make a success: smart, hard work, and a little bit of luck. You've got to know when you got lucky.

Williams: Plus passion.

Lanier: [laughs] Plus passion.

Williams: Great. So talk to me a little bit about your personal life, what you do for fun. It sounds like it's on the water, and other sort of pursuits.

Lanier: One of the best things in this field is having friends over the entire world. I've trained now probably around fifty postdocs who are scattered around the globe, and I think, fortunately, most of us are still friends. Almost all of us are still friends. So I have the opportunity to go and still interact with them. Science is an international community, and that's part of the fun is going to other places and seeing how they do science, enjoying their culture, and then hosting them when they come here. So that's one of the things which is fun when I'm not here at UCSF.

The other one is, I say if you don't find me in the lab or on an airplane, you'll find me on a sailboat racing it.

Williams: Here on the Bay?

Lanier: Yes. I started sailing here back in the late eighties. I grew up in Richmond, Virginia, and, before that, in Memphis, Tennessee, so there weren't many sailing opportunities there. I used to canoe a lot. But when I came here, I bought a canoe, but there was nowhere to canoe.

Art Weiss, one of the prior presidents of AAI also, he, Jim Allison, another president, and Dan Littman, who was going to be president, they were taking beginner sailing lessons in the late eighties here on the Bay. I went out with them and said, "What's this all about?" and got the bug, joined a racing team, bought a sailboat, racing sailboat, eighteen years ago, and that's what I do now. I have a racing team. Sometimes it has some of my postdocs on it, sometimes it has other faculty on it, or sometimes it will just have local biotech guys or guys in the

community who are carpenters. We have a racing team, and my boat has about eight people and crew, and we race almost every weekend that I'm in town.

Williams: Interesting. What about the brain drain? Do you see that happening? People going elsewhere because the money's drying up here, and so forth, is that an issue, as far as you're concerned?

Lanier: No. I mean, people still think the center of scientific excellence is still the U.S., and San Francisco is one of those places, and that's also one of the reasons that I came here originally, because of the critical mass of people doing really exciting and innovative work, and I don't see it leaving anytime soon.

Williams: So what has immunology meant to you as a person?

Lanier: Immunology, it's been my passion. Since that day back in undergrad school when I heard Bates tell me about that mouse which got the virus when it was a baby and was okay and got sick when it was getting—just the intellectual curiosity of figuring out how does this whole thing work is a lot of fun.

Williams: So you're not unhappy that you chose this field?

Lanier: No, not at all.

Williams: Anything that you'd like to say for the historical record that we haven't covered?

Lanier: No. I have to say I'm lucky to be paid to do my hobbies, and if you can say that, then I think you've had a good career.

Williams: Great. Thank you very much.

[End of interview]