The American Association of Immunologists
Oral History Project

Transcript

Ronald N. Germain, M.D., Ph.D.
January 21, 2016
Bethesda, MD

Interview conducted by
Brien R. Williams, Ph.D.

Transcription: TechniType Transcripts
Transcript copy editors: John S. Emrich, Ph.D., and Charles L. Richter, M.A.
Final edit by: John S. Emrich, Ph.D.

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. Ronald N. Germain for the American Association of Immunologists Oral History Project. Dr. Germain is the Chief of the Lymphocyte Biology Section and the Laboratory of Systems Biology at the National Institute of Allergy and Infectious Diseases, as well as the Associate Director of Systems Biology and Technology at the NIH [National Institutes of Health] Center for Human Immunology, Autoimmunity, and Inflammation. He was awarded the AAI Meritorious Career Award in 2015. We are in Dr. Germain's office on the National Institutes of Health campus in Bethesda, Maryland. Today is Thursday, January 21st, 2016, and I'm Brien Williams.

Thank you, Doctor, for doing this with us.

Germain: Thank you.

Williams: I'd like to start by asking you to fill in a little bit on your family background and your growing up.

Germain: Well, my parents and the family before them were not professionals. My father, after the Second World War, had a lamp factory, actually, in New York, but that business didn't thrive, and he went into business with my uncle, my wife's [Ed. mother's] brother, in a garage in Rye, New York. My mother worked part-time as a bookkeeper. Both had started in college, but because of the Depression, didn't finish college. So they had great grades. My mother graduated high school at sixteen, but neither of them ever completed advanced education, but they were quite dedicated to my education.

Williams: Were you an only child?

Germain: No, I have a brother. He's a lawyer. So we both wound up going to professional schools.

Williams: And where did you grow up then?

Germain: I was born in the Bronx, moved to Long Island, and then to White Plains, New York, which is where I went to middle school and high school.

Williams: When did you get turned on to science?

Germain: In ninth grade I had to do a science project, and I went up to the library in my junior high school or middle school, and I started reading the *Time-Life Book of Science*, and I came across a picture of a white mouse with a brown patch of fur, which is a classical in utero tolerance experiment from [Rupert E.] Billingham, [Leslie] Brent, and [Peter B.]Medawar, and I said, "That's what I'm going to do," and I've been an immunologist since that day. It was an interesting project because initially I only could get mice from pet shops, and pinto mice from pet

shops are not very good for immunological experiments, at least the type I was interested in doing.

So here my father's garage came into play. He had a customer who was a regular, who worked at a branch of [Memorial] Sloan Kettering [Cancer Center] in Rye, New York. And he said, "My son's trying to do this science project, but he can't get the right mice. Could you help him?" Because this person was the veterinarian at this branch of Sloan Kettering.

And he said, "Sure. Send him out." And I showed up. And this person has an interesting name; it was Halsey Bagg, Jr. And the reason most people don't understand why that's significant is they don't know what a BALB/c mouse is, which is one of the most commonly used inbred mouse strains, but it stands for Bagg albino mouse, and Halsey Bagg, Sr. created those inbred mice. This was his son. And he sort of slipped me out the back doors four breeding pairs of inbred mice, gave me a book that I still have on the anatomy of the animal, so I knew where the spleen was and the lymph node and the thymus.

I went home, I built my own cages out of chicken wire and aluminum, absconded with the Ping-Pong table in our basement, it now became a platform for all these cages of mice, and started breeding them so I could do an experiment I had designed to see if I could cure what's called graft-versus-host disease in F1 mice given parental cells by thymic grafts. The only restriction that was placed on this by my parents is that I had to clean the cages very thoroughly before my mother's Canasta card-playing friends came over to the house each week. So that was my start.

Williams: [laughs] Did you report this interest to your science teacher at middle school or not?

Germain: The ninth-grade science teacher was fine with the project and what I did. The real push came with my biology teacher in high school the next year, who spent every day after school, except bowling Fridays, making sure that I could be supervised to continue the work in the laboratory that they had, a small laboratory they had in high school at that point. So, yes, that teacher was very supportive; Mr. Heath.

Williams: And did your association with him free up the Ping-Pong table?

Germain: Eventually, but not for a while.

Williams: So what was the result of your experimentation?

Germain: At the end of the day, I don't think I figured out a way to cure graft-versus-host disease. I think, in retrospect, I can say that. But I had some other interesting early experiences that shaped my career. So I said I wanted to do thymic grafts, but I'm a high school student, I had a little help from Halsey Bagg, Jr., but that

was actually at a time—this is 1965, ’66—we’re within a few years of the actual discovery by Jacques Miller of the putative function of the thymus in immunity. So I figure, why not go to the source? So I wrote Jacques Miller, as a high school student.

My letter followed him around the world, actually to NIH, where he was doing a sabbatical, and he answered me and he said, “This is how you do aseptic thymic grafting.”

Thirty years later, I get an email from Jacques Miller. This is during the period where my lab was focused on understanding histocompatibility molecule structure function and antigen processing and presentation, and it says “Dear Ron, you’re one of the world’s experts in antigen processing and presentation. Could you help me understand cross-presentation?”

And I wrote back, I said “You don’t remember, Jacques, but thirty years ago, I wrote you as a high school student.” And I still had the letter, so I sent him a copy of it, of my letter to him and the reply, and said, “It’s just really terrific that I can be the expert helping you thirty years later.” This is a story that the Walter and Eliza Hall Institute [of Medical Research] knows so well, that when I gave a lecture there, I was introduced by the director, who’s not an immunologist, and she told that story.

Williams: It’s a great story. So what led you to Brown then?

Germain: I applied to a variety of schools. Brown had a real reputation for focusing on undergraduate education. There’s a longer story about why I might not have wound up at Harvard that maybe we shouldn’t put into this video. [laughs] But of the different schools I was accepted to, I thought Brown was the best fit; again, this focus on undergraduate education. They had a very good set of science departments. They’re very strong in engineering, but they had a good biology department as well. So in the end, it fit well. I think I pretty much wanted to stay on the East Coast in a place I was comfortable with. So that was my choice, and it was a terrific choice and I had lots of opportunities there.

Williams: Looking back on your years there, did it narrow your focus or did it expand your focus, do you think?

Germain: I think it maintained it. When I first arrived, I became very interested in the communication among cells of the immune system, and I had read an interesting paper in *Science* about the possible transfer of RNA particles directly through connections between the membranes of lymphocytes and macrophages. So I went over to the building that housed the electron microscopes at Brown, introduced myself as a freshman, and said, “I want to do these experiments,” and wound up getting help from people there in training in electron microscopy, and then started doing experiments with a woman named Elizabeth Leduc, who was really very,

very well known as an EM person at the time, trying to replicate these experiments, and I spent hours and hours as a freshman over there embedding and sectioning and imaging in old RCA electron microscopes, never confirming the structures that were reported, because in the end, nobody ever confirmed the structures. But that introduced me to sort of morphological examinations which came back very strongly in my most recent work.

I also was befriended at that time by an instructor/new assistant professor. He turned out to become the Dean of Students years later, and took my son and I on a personal tour when my son was looking for institutions. He didn't normally take cold calls, but I called him thirty years after I had met him that way, and he immediately picked up the phone.

Williams: So did your son end up going to Brown?

Germain: No, he went to Stanford.

Williams: So your next step then was Harvard Medical School.

Germain: That's a longer story. When I was growing up, I had no intention to go to medical school. I was going to get a Ph.D. And my mother had been driving me into New York City to attend Zan [Zanvil A.] Cohn's seminar series at Rockefeller University. As a high school student, I was not allowed to drive in New York City itself, so she had to drive me. So she would sit there and wait while I went to the seminars. And I still have notes about macrophages and lymphocytes that I drew when I was attending the seminars.

So I decided, "I'm going to go to Rockefeller." I was not going to apply anywhere else, and I was just going to get a Ph.D. at Rockefeller.

Then as a junior in college, I worked for one summer for what used to be Ciba-Geigy. I don't even remember whether now which of the mega pharmas it actually is, but it's one of them [Novartis International AG]. And the person I worked for, who was a Ph.D., liked what I was doing so much, he introduced me at lunch one day to the head of the department, who was an M.D. or an M.D.-Ph.D. And he said, "Young man, what are you going to do?"

And I said, "I'm going to get a Ph.D."

And he said, "You're an idiot. You can get an M.D., you can do the same research, and they'll pay you a heck of a lot more for doing it." I sort of looked at him. I had never heard anything like this before.

So I got in touch with a woman I'd worked for for several years at Syracuse University, Bertie Argyris, who was a Ph.D., and I said, "Is this true?"

And she said, “Actually, yes.” [laughs]

So I decided to apply only to M.D.-Ph.D. programs, to Rockefeller just as the Ph.D., and the one exception I made was Harvard Medical School. They didn’t have a formal M.D.-Ph.D. program. But I’ll come back to that in a minute.

So I went through this process, and it was interesting along the way. My very first interview was at Cornell. And I’ve had the beard that I’ve had since high school, and you have to understand this is in the end of the sixties, the Vietnam protest generation, and there are hippies versus “serious people,” if you will. So I only had a goatee at the time. I was neatly groomed, wearing a three-piece pinstripe suit, white shirt, red tie, Brogue shoes, interviewed with what I then thought was a somewhat older—he was actually only sixty-something—nephrologist, and he said, “I don’t know what to make of you. You look like a hippie and you talk like a scientist.” [laughs] But I was accepted there.

I then had my interview at Rockefeller, for which I showed up a day late, something that I cannot reconstruct to this day, but, surprisingly, the person who was programmed to interview me interviewed me anyway, and that person was Nobel Prize winner Gerry [Gerald M.] Edelman. He had selected me to interview, in part, I think, because of my background, but also I had done a master’s as an undergraduate at Brown with one of his former trainees, Jack [John J.] Marchalonis. So there was another connection.

So I went into the very famous office of Gerry Edelman and we had an interview, of which I remember nothing other than the parting remark. He looked at me, he said, “You will get in here, but you won’t come here.” And given that I had grown up assuming the only place I would go was Rockefeller, I found that rather strange. But he turned out to be a very smart guy.

So the last part of this story is Harvard. So I was interviewing at NYU and being taken around by Chandler Stetson, the head of the Department of Pathology, and he said, “Is there anybody else you’d like to meet?” There were two immunologists that had been at NYU, turns out not at that moment. But as an undergraduate, I was reading papers, I’m a little bit out of date about what’s happening in real time. I wanted to see Jonathan Uhr and Baruj Benacerraf. Uhr was in Texas, and what he told me was that Benacerraf was at NIH, but he was going to become the head of Pathology at Harvard the following year. Benacerraf was only here for two years.

So I wrote Benacerraf, like I had written Jacques Miller. I’m bashful about this. And I said since I knew there was no M.D.-Ph.D. program, “Would you take medical students in your lab for research?” And he wrote me back saying that if he’s convinced of their worth and dedication—those aren’t exactly the words, but paraphrasing what he said—that he would do that.

So I went through the interview process. That itself was quite interesting. If you don't mind my digressing, there's a very famous psychiatrist who was notorious for torturing interviewees at Harvard. He would do things like nail the window shut and then ask them to open the window, or say, "I'm expecting an important phone call," leave the room, call the phone number, and then see whether the person who was in the room picked up or not. He came back and he said—you know, if they answered, he'd say, "Why are you answering my phone?" If they didn't answer, he'd come back and say, "Did I get a call?"

And they'd say, "Yes, the phone rang."

He said, "I told you I had an important call. Why didn't you answer it?" And it turns out that the whole point was that he selected students to interview that the school or the institution had concerns would not handle the stress of medical education.

I was programmed to be interviewed by the dean, who then had some late emergency meeting, and so I got summarily moved to an interview with this psychiatrist, having dreaded this forever. [laughs] But I wasn't one of his selectees, but he still had to interview me. And so going back to that first Cornell interview about my looking like a hippie, I debated back and forth and back and forth and back and forth taking off my beard, and eventually I decided it was prudent to do that, given those comments and some other things that had gone on. But my graduation picture that was used for all my applications had the beard on it. So, of course, he asked me, "Why did you take off your beard?"

And I was prepared. I said, "Do you know about Pascal's wager as a proof of God's existence?" And he sort of looks at me like, you know, what kind of answer is that? [laughs] I said, "Well, let me summarize it for you. God either exists or he doesn't, and you either believe in him or you don't. If he doesn't exist and you believe in him, you lose some things because you can't mess around. And if he doesn't exist and you don't believe in him, then you can do some extra things. Let's say he does exist. Well, now the odds become very different. If he does exist and you believe in him and you do the right things, eternal grace. And if you don't, well, big problems. So the only good wager is he exists and you believe in him. So now you either care that I have a beard or you don't." And I went through the parallel argument and I said, "The only prudent wager is to assume that it does matter to you and I should take it off."

And he was just floored, you know, just stunned into silence. It was terrific. This is a family story that my son knows and other people recount, because I don't think he ever in his wildest dreams expected someone to come back with a comment like that. So I was accepted to Harvard.

You'd asked me about my parents earlier, so I should point out there was one school I did not get into, and that was Penn, and my interview at Penn was with

the dean of the school, and it consisted of my coming into his office, him looking at me. He's saying, "Your father runs a garage, and you're going to do research and not do medicine, so goodbye."

The interesting point is the Billingham, Brent, and Medawar trio that I mentioned to you, although they did their work in England originally, Billingham was at Penn at the time, and so Penn was of substantial interest to me. So that's always sort of stuck around to show you that not everything is so straightforward. So, in any case, I wound up at Harvard.

Williams: So you got your Ph.D.-M.D., and that was in pathology?

Germain: The Ph.D. was in immunology. I then had a very special arrangement to get credit for a year of pathology internship, which enabled me to take part three of the national boards and obtain a medical license, but I rotated back into the laboratory during the course of that year by prearrangement, because it was quite clear at that point I was not going to practice medicine.

Williams: So having received your degrees, what did you see as your life's path ahead? Did you have goals set or not?

Germain: I did. When I talk to my fellows or just students in general, I point out to them that I made a very explicit decision about going to Benacerraf's lab to do my Ph.D. This was someone who eventually won a Nobel Prize, he hadn't won it when I started, but was not only the chair of Pathology there, but a very, very famous individual, very well both feared and respected in interesting ways. And my view was I didn't want to go into a career where I couldn't be highly successful at it, and, yes, I had done all this work since I was fifteen and been in labs and gotten an early master's degree and done everything else, but none of that was at a serious professional level, if you will. So my view was if I could go into Benacerraf's lab and emerge as a top contributor to the output of that group, to be respected among the top people who had been there, that would be a pretty good sign I probably, if I didn't mess up in some other unknown way, had what it took to do this.

And I do tell people, I say, "You should choose to challenge yourself and you should really ask that question as early as you can in making this decision, because if you're really going to do it, you should want to do it very seriously and you should want to be successful at it." So that was part of the decision-making. So by the time I had my M.D.-Ph.D., I had already, in essence, gotten the answer to that question. Many people ask me about my career path, and I point out to them I didn't do a postdoc. I went directly on to the Harvard faculty after I graduated, in part because Benacerraf had that confidence in me, in essence, to basically take charge of his laboratory at that young age without additional training.

Williams: Did you have pedagogical responsibilities too?

Germain: I taught some of the classes in the immunology course that was taught at Harvard, but that was minimal. It was basically pure research.

Williams: So why did you leave that promised land? [laughs]

Germain: In the very early 1980s, there was something called recombinant DNA beginning to float around, raise its head as an approach in science, and I said, "I don't know anything about this, and I'm unlikely to be able to recruit people. Even Benacerraf is unlikely to be able to recruit people who really know this topic. But I think this is going to be important in the future, and so I need to learn it."

So with his permission, I applied for and received an American Cancer Society Award for what is essentially an illegal sabbatical, because as a nontenured faculty member, you can't really take a sabbatical at Harvard, but I had my chair's approval to do that. The preference for both of us was for me to do that in Boston, but the only lab in Boston who would provide the right training would have been David Baltimore's lab, and he didn't want me there. [laughs] He just said, "I know you have your money, but no."

And I had decided I really wanted to clone major histocompatibility molecules because I had begun forging my own direction, you know, post—not truly post-Benacerraf, but where I was gaining real freedom, not just running his lab, and I actually had received a grant about T-cell activation, antigen processing and presentation from NIH, which was put on hold, and I needed to figure out what to do with that year. I said I'd worked out a strategy for cloning MHC [major histocompatibility complex] genes, and I found out that a junior member of Phil [Philip] Leder's department here, Jon [Jonathan] Seidman, was attempting to do that, but he was focused on MHC Class I molecules, and I wanted to do MHC Class II molecules. So he agreed to take me in his lab, and I came to NIH on this sabbatical, on sabbatical, where, actually, with other members of his group, I actually did clone mouse Class II molecules.

While I was here, I participated in a lot of the immunological community's activities, and there was a coincidence of events. The Laboratory of Immunology, headed by Bill [William E.] Paul, who also trained with Benacerraf, so it was a bit of sort of incestuous relationships here, and his laboratory were thinking that they would need a molecular immunologist. It had become clear over these few years that that was a direction that things needed to go, and here I was a card-carrying immunologist now trained in molecular biology, and so they made me an offer that in the end I couldn't refuse. So I was offered a tenured position here when I had two years left on a tenure clock at Harvard, trying to completely change the focus of my work, and it seemed prudent to take the offer.

Now, it wasn't quite that simple. Benacerraf really wanted me to come back to Harvard, and so I had an interesting phone call with him, because I had another offer, which was to be the head of Immunology at Scripps [Research Institute]. And Frank Dixon, who was the head at that time, was going to put a very large sum of money in the bank as hard, hard support, which is pretty rare, actually, at Scripps, to get me out there. So I had this conversation with Dr. Benacerraf and I said, "Well, I have three choices. I could come back and you offered me my own lab in the Dana-Farber, I could take this offer for a tenured position with the Laboratory of Immunology, or I could take Frank Dixon's offer and go to Scripps."

And Baruj said, "I'd really like you to come back to Harvard, but given that the Laboratory of Immunology is my baby and Bill was my trainee and perhaps closest associate, and I feel like it's my place, I couldn't tell you not to go there, and I'll never speak to you again if you go to Scripps." [laughs] I had other reasons besides that comment not to go to Scripps, but it was an interesting comment. And for a variety of reasons, including really separating myself from Benacerraf, even having, quote, "independent lab" back at Harvard would still keep me tied very closely to him, this seemed like the best option.

Williams: I'd like you to sort of trace the development of the structure of NIH in areas that you have participated in. I mean, you went to the Lab of Immunology. Then we have the program in Systems Immunology. What does that mean? And the Systems Biology concept. Can you talk about sort of the structural matters there?

Germain: If I go back to what we just discussed about recombinant DNA, you'll see there's sort of a thread in my career. Some people pick a particular topic and spend their entire working professional life studying that topic and drilling down further and further and further into that one topic, and those people are terrific and they really are critical to getting all the details about a particular aspect of biology, but it was pretty clear to me early on that my interest lie in taking different pieces of information and trying to blend them together. You know, people have different skill sets. I can't sing. I never learned a foreign language well. I don't play an instrument. I'm not a spectacular athlete. But I'm actually very good at doing what I just said. I can take different pieces of information, I can weave them together, I can see patterns in things that are going on. So I've been always interested in doing that.

Some people accuse me—"accuse" isn't the right word—feel that my lab is very diverse in what it does, but if you looked at it until maybe very recently where we actually work with myeloid cells, everything we did was with T lymphocytes, but we were interested initially in what do they see, and that's when we worked on MHC molecules and antigen presentation. Then how do they see it? We worked on signaling through the T cell receptor. Then when, where, and how do they actually get that signal? We began to do the imaging. So there's actually a theme in that regard.

But early on, we were doing molecular dissection of structure function analysis, we then did cell biology, we then did biochemistry and signaling, and then we moved into imaging. So we've really changed the way we approach things. And just as I brought recombinant DNA and molecular work into what had been purely cellular work early on, because I said that's really where it's going to go, I've sort of done that in each of the steps. I sort of try to look and I say where is there an opportunity to really get an enormous amount of additional information that I can use for this integrative purpose.

But this integrative view also is where the systems part comes from. People call it the immune system. What does that really mean? It has a lot of working parts, and you can become an expert on all the details of one little part, or you can say, "I want to look a little bit more broadly and try to understand the principles that exist that allow the different parts to work together to give us either good host defense or that cause disease and to look at it that way." And that's really what I've been interested in doing. And part of thinking that way is a realization that I came to many, many years ago, that there's a certain level of quantification that you really need to have. You have to go beyond sort of qualitative observations to understand certain types of behavior. Especially in a system like the immune system, where lymphocytes, in particular, can exponentially expand, very small differences are going to turn into big differences at the end of the day, and those are hard to intuit. And if you also begin reading outside of your immediate field, you learn that you start putting negative and positive feedback pathways together in a signaling circuit, you get very nonlinear behavior, and those are not things that we can intuitively figure out how they're going to work when you perturb the system.

So I had an interest in this, but just as I said I don't sing, I don't dance—well, I dance; that's another story—but I don't play musical instruments and so on, I'm not personally a computationalist. I did well in high school math. I'm not gifted in mathematics. And so in this case, rather than saying I could learn it all like I did some of the molecular biology, it was I need colleagues who can do it, and I began accepting or even going out and recruiting people into my group who were interested in doing modeling. That's how Grégoire Altan-Bonnet wound up in the lab. We built models of T cell receptors. And Martin Meier-Schellersheim, who's still a colleague here as a tenured faculty member with his own independent work, got together and did work in model environments, you know, how do you actually do modeling, and then used it for various things. So that was how those two pieces came together.

After a while, having had that experience within the lab, I tried to convince NIH that this was an important part of where biology was going. This is more the bottom-up part of systems biology as opposed to what most people think about, which is the informatics, which is more of the top-down big-data, you know, sort

of analysis work, though I saw value in that as well, but it wasn't initially what I was doing in my group.

And so through a very long, convoluted process that we don't need to go through, I eventually got the Institute to agree to start what they call a program in systems immunology that involved initially the folks within my group, but then with enough resources to begin recruiting faculty, and there was a parallel path trying to create a trans-NIH-systems program. That never succeeded, and the NIAID decided that they would just go ahead and create their own systems program. So that's how the Laboratory of Systems Biology came about. It started as this program within the Laboratory of Immunology, but with junior faculty already being recruited for that, they felt it needed its own identity and location, and that was the split-off of my group, with the rest of the Laboratory of Systems Biology from the Laboratory of Immunology about three or four years ago.

Williams: Did that split occur amicably?

Germain: Both Dr. Paul, who is the laboratory chief, and I had hoped we could come up to a way of avoiding that, but the Institute felt that if they're really going to invest in Systems Biology, it should be identified as a real effort in Systems Biology. They wanted it sort of branded in that regard. So it was not not amicable. That wasn't even an issue. It was only administratively and in terms of resources in a space where things could be, how could it best be organized, and the judgment from the Institute was it should be separated out this way. They probably were right in the sense that the resources didn't exist within the Laboratory of Immunology to grow the program in the way it's been grown here. Having the coherent localization and space that we have in this building, with all the faculty together has really worked well for what we're doing.

Williams: But it still stays under the rubric of the Institute?

Germain: It's still within the Institute, within NIAID.

Williams: So, as a research scientist, to date, looking back, what do you think your most important accomplishment has been?

Germain: Well, the first answer you'll get to that question, from almost everybody, is training people, not the actual science you do, because that's how you contribute well past your own direct contributions. And I've been incredibly fortunate to have some terrific younger colleagues that have worked with me in the lab that now are very senior people in their own right, really quite accomplished, many of them with many awards, and that's extremely satisfying because that broadens any one individual's contributions tremendously compared to what you can do in your own specific laboratory.

I think my own personal research group has made interesting and important contributions along the way in those various areas I told you about, whether it's MHC molecules in processing and presentation or whether it's in T cell recognition. But most people have told me—I go back and forth myself about it—that the work we've done for the last fifteen years or so that's built around imaging is perhaps the most original and having the biggest impact. That's very hard to measure. It's surely very popular. My wife would sit there and say she wishes it were a little less popular so I don't travel as much. But this has clearly been recognized, and the work that I've done with my colleagues here as really being novel, new, and extremely well done and teaching things that really weren't known before. You, I assume, know Polly Matzinger or the name.

Williams: Mm-hmm.

Germain: Polly's a pretty no-nonsense person, and so she came up to me early in the days of the imaging and said, "The pictures are beautiful, but I'm not sure I'm learning anything I didn't already know."

Came back to me about two or three years later, which is very uncharacteristic for Polly. "Ron, I was wrong. You're teaching us a lot of things we didn't know." And, you know, those are the kinds of comments I get about the work. "This is rewriting the textbooks. This should be in the textbooks now." And that's very gratifying.

Williams: From the layman's standpoint, what are the translational aspects or hopes for imaging?

Germain: So most of our work to this point has been in the mouse and laying out general principles, one of the most important of which is that as you look more and more carefully, you see more and more layers of spatial organization to the immune system in an important way, that you have this diversity of cells that have to communicate with each other, but they're moving around all the time. Some of them are very rare. If you thought it was all happening just sort of by random mixing, it would be an incredibly inefficient system, even though that was one of the emerging views when people just started doing the imaging and saw cells sort of crawling all over the place.

Now what we can see is that, no, it's really quite organized. Cells have to live in particular places to be near other cells that are going to provide them information, and you can see how the evolution's driven the system to allow for optimization. So that's the more basic part. But now, in the course of doing that, we've developed a whole new approach to mostly static imaging. Everybody loves the movies, but, in fact, they're very limited in certain ways, and so we've developed ways of doing many, many colors of staining, and now not just in sections, but even in 3-D volumes, where we can get the equivalent of a thousand times the information that a pathologist would get in a standard section.

So I'm in the middle of working on—and it's a little tricky to put this all together—creating a Center for Advanced Tissue Imaging, specifically for human tissues, that could be used to help the groups that are working on immunotherapies of cancer, for example, to better understand what the tumor environment is, what happens when you do the treatment, what's different about the cases where it succeeds versus where it fails, and this tremendous interest from academics and from companies to do that.

It's not typically what NIH does. We usually do small things and are very focused. So it's not trivial to try to set this up in the NIH environment, so it's still a work in progress. But the hope is to be able to take that type of technology and create not a service core here, but an integrative facility that enables these types of high-throughput, high-content analyses to be done, and we also would have it serve as a training center to disseminate the technology more broadly to other centers so it can be done on a larger scale. That clearly has lots of implications. Our earlier work is relevant and has played a big role in people's thinking about vaccine designs and how different CD4 and CD8 T cells cooperate and do their work, but I say this is the most likely to have a clinical impact in the future.

Williams: Technology is a big, important part of this, isn't it?

Germain: Yes.

Williams: Are you driving the technological developments or are you taking advantage of what the manufacturers are coming up with?

Germain: I'm not an optical physicist. I don't build instruments. Our developments have been more on doing the same thing in technology that I told you I did in biology, is taking pieces and putting them together to create a system that has, in the systems biology term, "emergent properties." It can do something that the individual pieces couldn't do. We've been very good at doing that. And it's never me personally. Like I said, I've had these spectacular colleagues in the lab who've worked extremely hard, some of them more knowledgeable on different pieces of it than I am to put this together to get it to work. So we do that.

We also work with people who are real instrumentation people. We're trying to design an instrument that would collect the data I just told you about 10 to 100 times faster, so that we can actually process many more samples, and the backlog there would be strictly on the data analysis side, rather than also a delay in collecting the data. So we're working with other individuals for that.

Martin Meier-Schellersheim, who is one of the modeling people I mentioned to you previously, through a connection I made now has collaborations with Google to improve his ability to do the simulations using their cloud system. I don't want to advertise a particular company, but it was more taking advantage of those types

of resources to again advance the science part. So we do that when we can, and so it's opportunistic.

Williams: In your career, have you experienced some real disappointments or wrong turns or things of that sort, or has it all been straightforward?

Germain: Well, there's a historical—I don't call it a disappointment—anomaly. So when I was at Harvard and working with Benacerraf, one of the very, very hot things in immunology was suppressor T cells, something pushed initially by Dick [Richard K.] Gershon at Yale and then Harvey Cantor and others, and I did a great deal of work in that area. Then there was a period of time—and I'd already begun transitioning away to other types of studies when this all happened—where all credence among, if you will, sort of the top immunologists of the suppressorology that existed to that point disappeared, and it's a sort of very sad period of time, because this was a very big part of immunology and cellular immunology for quite a while, and then everybody thought it was illusionary.

Then there was a parallel track for so-called helper, cell helper factors, which turned out, actually, to be fraudulent. That was never claimed through any of the suppressors, but there were issues about how good the science was. And I had done a lot of that. So people fell into two categories: the people who dedicated their careers to that, who suffered almost career-ending branding at that point in time, and then some of us who managed to, if you will, resurrect ourselves in other ways and be quite reputable, despite having this past.

So now, as you know, there are these regulatory T cells that are all the rage. So partially as a joke, but partially seriously, I have been asked on several occasions to give keynote talks to meetings on regulatory T cells, with the notion that I could give the history of the suppressor phenomenon and somehow, you know, explain why that died and didn't have any relationship, which it actually does, to the current focus on regulatory T cells, and do it where I'm not the angry person who died from that past event, but, rather, someone who has a significantly positive reputation, who survived that and could somehow put that together.

My disappointment there isn't personal. It was more the way a field handled concerns about particular results. I think there are questions that could have been and should have been raised about much of the data, but it was very personalized in a way that I don't think did science an enormous good, and where some people who had published in the area became the most vigorous critics without any self-criticism. And that, I think, is something we have to be very careful about, and it relates in a sort of peripheral but not irrelevant way to reviewing manuscripts. You can look at something and have questions about it, but there are reviewers who let their annoyance with what they're reading when they don't think it's right come through in their reviews, which even can become very personal in a way. I teach the folks in my lab, when we're working together, for example, on reviews, that the first thing is to look at what is the positive or is the potential positive that

comes in the paper, and then to criticize if you don't think the data are good enough, in a serious way and in a scholarly way. If you say it's been shown before, cite the paper. If you think they didn't do the right experiment, say what that experiment is or what the control needs to be. You can't just blow off steam. You have to remember that people have spent many years of their lives generating what goes into the paper, and even if you don't think it meets the standards that it should meet for that journal, you need to look at it from this other perspective. And I don't think that happened, necessarily, and I think some people did suffer under those conditions.

Williams: You were an editor for a time with *The JI* [*The Journal of Immunology*]. Were you practicing these principles yourself at that point or—

Germain: I tried. I'm not going to say I am perfect at doing this, but I do take reviewing very seriously. No matter how time-pressured, I will not just dash off a review, because I do always remember how much effort it's taken somebody or some group of people to reach the point of putting this together, and even if I don't think it meets, as I say, certain standards, it has to be given a serious look. You have to try to be dispassionate. And I try to recuse myself from lots of reviews, not from the perspective of I'm too busy, but really worrying about conflicts of interest. If I think I'm going to learn something from a paper that I would really want to use in my work, that I don't think I should know, I won't review the paper. I don't want to read it. I don't want to be in that kind of conflicted position. And it's tricky because I may be the best person to evaluate whether that paper has merit or not, and it could get in the literature and cause a problem for lots of people, including myself, if it's wrong, where that has to be overcome. But once you've read the paper, it doesn't go away from your head; you have that information. And I worry about that, so I take it pretty seriously. I think that that's the right way to do it.

Williams: You joined the AAI in 1978, I believe. What's, in your judgment, the importance of the organization to the field?

Germain: It has two major roles. I think on the scientific side and the training side, the annual meeting, the opportunity for very large numbers of people to both get together, but also for students, as well as fellows and for PIs, all to have an opportunity to present, whether it's at a poster or a short talk or a longer talk, it really does keep together a sense of community, and I think that's important, and, of course, exchange of a lot of scientific information. And a lot of collaborations are built out of those scientific interactions and also the social interactions that occur during these annual meetings.

The other part has to do with both the lobbying and the education, the more—it's not administrative, but the other aspects of what the AAI does, and over the years, they've had a lot of impact. Their outreach programs have helped high school teachers do a better job and keep them interested in this topic. They've run the

lower-level and higher-level courses to help train lots of people who are not formal immunologists, who are moving into the field. And they've done a lot of legislative activity. I think those are all positives in the larger sense. So I think that's been very good for the field.

Williams: When you were told that you were going to receive the AAI Meritorious Award, which occurred in—

Germain: Last year.

Williams: Yeah, last year. What was your reaction?

Germain: A bit surprised. You know when you're nominated for things, so you know you're in the mix. These are not complete surprises in that regard. But the people that have been selected for that are really terrific folks. And it's also a little bit strange because it's called a mid-career award. When you look at who's receiving it, there's virtually no one who's in what you would really call mid-career, unless you do an extrapolation and decide that all of us are going to work for longer than Michael Heidelberger at 102. But for any of these things, there are lots of meritorious people. There are very few of these; it's one a year. And there are a lot of immunologists, and there are a lot of terrific immunologists and scientists. So I was grateful, surprised that it actually happened and I was eager, also, because I don't, for a variety of reasons, have the opportunity to go to the AAI meeting every year, and so it was a chance to go and interact with people in that venue again, which was really very good. So it was a treat.

Williams: And what is the merit of your career? What is it sort of focused on or is it just very general?

Germain: No, I think it's usually, if you want to use mathematics, an integrative or an integral of what you've done over an arc of a career, whether it's in your reviews or whether it's in your primary scientific work, or whether it's in your training, even though it's not the mentoring award, but in the people you train. They sort of look at the whole package and say, "Has this really made a big contribution to the field where our primary focus is on the science?" So you have to have done substantive things over a very long period of time. The imaging would have been nice, but I suspect that they couldn't look back and say I'd done anything for the previous twenty years—well, maybe that wouldn't quite qualify here, but I think I have and I think all the other people who receive this are in like modes. Some are more of the focus type that I told you, where they've sort of been somewhat focal in a good way, and others maybe a little broader in what they've done, but there have been these continuous contributions.

Williams: I'm curious what do you tell your trainees about a future career in immunology. Are you encouraging it or cautioning them at all?

Germain: If anything, there are more opportunities in immunology now than there were in the past. My son is an M.D.-Ph.D. at Wash U [Washington University in St. Louis], and he just defended his thesis in a lab where he studied acute myelocytic leukemia. And I said, "All oncologists in the future will be immuno-oncologists." Because if you look at the emerging data right now, it's very much like bacteria and antibiotics and neutrophils. If you don't have neutrophils, antibiotics can sort of hold bacteria at bay, but you don't really cure people. If your immune system is not paying attention to your tumor, you can give drugs and shrink them, and you pretty much don't cure them. But if you get your immune system to cooperate, you actually do get cures. So I think in the future that's going to be an enormous part of dealing with cancer. We see all the enthusiasm and the breakthroughs of the year awards and so forth that are going through these checkpoint blockades, but there are many more pieces to that puzzle that have to be worked out.

For me, especially because because it's working out all the different pieces of the puzzle, putting the system together, how do you turn down the negative parts from the macrophages and the regulatory cells and the other mediators on that side, how do you turn up the cells you really do want, how do you avoid autoimmunity while you're doing that, it really is systems immunology coming home to roost in an interesting way. But I think there's obviously tremendous opportunities in that regard. We still don't have vaccines to many diseases where we hope a vaccine could be developed, and we need to understand much more about how the immune system works and what the real nature of host defense is to do that. So there are plenty of opportunities.

Williams: You've had your own brush with cancer. Am I correct in that?

Germain: Yes.

Williams: What effect has that had on your career or your thinking?

Germain: A couple of things. First, as an academic, I used to think, like many of my colleagues, that anything that was sort of slightly toxic you probably wouldn't want to think about in taking forward in drug development. And then I got treated with lots of toxic stuff that worked, and I said, "Well, yeah, sometimes you need to use toxic things." Now, hopefully, with immunotherapy tuned the right way, we can reduce the level of the toxic compounds we give. They may still be useful, even if they only induce expression of things like MICA and MICB to get NK [natural killer] cells that kill your tumor, but that still could be useful.

For me, there was a lesson that I have used in talking to my fellows, though. So when I was ill, I had to stop going to meetings. People didn't know if I was going to be around, so I wasn't going to get any invitations to anyplace new, so everything was pretty much in this very gray to black zone, as far as career was concerned, aside from my personal—my health, obviously. Once I was given a

pretty good bill of health and the expectation that things looked pretty good, it took a while and many years to know for sure it was good, but once everything looked good at that point at the end of therapy, I had to say, "Okay, everything's pretty much shut down." Nobody new's going to come to the—I didn't bring anybody new in the lab, we hadn't written any papers, I wasn't going to any meetings. And I said, "Okay, I had a pretty good career going. This has flattened everything out, if not gone down. I have to go and do something explicit to say I am around and I'm going to keep doing good stuff. I'm not disappearing."

So I thought about it for a while. Alain Townsend had just published a very important piece of work that showed that peptide was a really important part of the structure of MHC Class I molecules. And I said, "Well, given what I know, Class I and Class II are pretty similar molecules." And there was this old observation from the Strominger lab about peculiar behavior of Class II molecules, where if you didn't boil them in SDS, they didn't come apart into the two chains. And I said, "That might be an assay for the stabilization by peptide."

There was a great technician in the lab who had been trained by one of my former fellows, Andrea Sant, to do metabolic pulse-chase labeling immunoprecipitation experiments. So I said, "I want you to do these experiments where you have cells and you put a lot of protein in. I know it can be turned into peptide that they can present. And do this boiled-unboiled experiment, and I'll know in a week, when you develop those films, whether we're back."

She developed the films a week later, and we showed that they went from unstable to stable, and that increased in proportion when you put more antigen in they could load them with peptide. There's a lot of other work to be done, but basically I knew when we had those films that there was an important story there, and that was the step back in the lab.

Is that particular observation the most important one? No. But the lesson I tell people is, "You are responsible for your career. When you go out to start your own lab, don't just fill it up with, quote, 'hands' that you hope are going to do all the work for you, that are going to create the wonderful career you hope to have. You're the best-trained person, it's your career, and you have to make it work. So that's your responsibility. That's what you have to do."

So just as I told you previously that I went into Benacerraf's lab to challenge myself to see whether I could make it, here there was another challenge where I had to be sure. Nobody was going to rescue my career for me. I had to do that. And that's a lesson that I learned and have known for a long time, and it's one that I keep trying to convey to my fellows, that it is really you. Yes, the best science is most often done by collaborating with colleagues. It could be junior colleagues, it could be senior colleagues, and you interact. But in the end, the responsibility for the level of science that you do is you, and you have to be really

dedicated to that and be thinking about it and taking responsibility for it all the time.

Williams: Besides science, what recreational pursuits do you have in your life?

Germain: They're extremely blended with the science. It turns out that not quite as long as I've been doing immunology, I've been a photographer. In fact, for many years back in the film era, I had my own darkroom, I've actually loaded my own black-and-white film into canisters, shot and developed it and printed it in a darkroom. Eventually transitioned to digital. But if I go somewhere and somebody in a meeting doesn't see me with a camera, they'll ask, "How come you don't have your camera?" Because they assume that it's basically welded to my hand. [Williams laughs.] And I have gotten into the mode that you can read about in many photography blogs, which is that you sort of see almost everything from the view of "Is there a photograph there?" You know, if I'm just driving along or I'm walking, I'm looking at it, "Is that an interesting corner to photograph? Is there a good cloud formation?" I'm seeing things that way.

But I say it's not divorced from my work because what we do is imaging, and so this notion of seeing things, seeing patterns, being able to see them, and also having an aesthetic appreciation for what they look like. There are some folks who can take pictures or movies of the type we do in tissues, and they don't look so terrific. I just had one of my fellows give a data presentation this morning, and he is also a photographer, and the images are stunning. I mean, they could have been the whole calendar for Zeiss or Nikon for next year. They're just gorgeous. So there is an aesthetic that goes with it, and it turns out that's also my hobby.

Williams: If I asked you to show me your very favorite picture you've taken, would you be able to do that and what would it be?

Germain: I don't think I could pick one. It's like which is your favorite child. [laughs] It doesn't really work. There are some that I really like, I go back and I look at what I've done again and again, and there's some where I say, "Ah, I didn't do a really good job of that."

But I also have a couple of different opuses, if you will, and so some are scenic, they have to do with either landscapes or cityscapes, because I'm often walking around when I'm waiting for my hotel to allow me in when I arrive in Europe in the morning, so I'll walk around the city for a bit.

But I did something recently that has turned out to be very, very good. My brother needed a small black-and-white photo for a website, and so I took a garment bag and made it a black background and put him right in the window with some nice light and took a picture of him, and gave it to him in black-and-white, and I looked at that. I said, "This is a terrific portrait. I mean really nice." So I said I wonder if I could figure out how to use Photoshop to take photographs

I'd collected from around the world, just shots at meetings or people on the street, so they are colors and they have backgrounds and everything else, and make them look like that.

And I actually learned how to do that, and I have sort of self-published my own book of portraits, which look like they're posed, but they're someone in Old Jerusalem or they're someone on the street in Paris, or there is somebody at a meeting inside here at NIH with fluorescent lights and everything else, or the owner of the best rib place in St. Louis, but they all have been reworked to have these nice black backgrounds, all turned into black-and-whites with all the right kinds of balances. And that's turned out to be—so I like looking at that book. I like going back and seeing what I've done with that, because I had to do extra work, not just capture the image. But there are others.

Williams: On that happy note, shall we say we're done today?

Germain: Sure. Thank you so much.

Williams: Good. Thank you.

[End of interview]