The American Association of Immunologists
Oral History Project

Transcript

Dan R. Littman, M.D., Ph.D.
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Williams: This is an interview with Dr. Dan R. Littman for the American Association of Immunologists (AAI) Oral History Project. Dr. Littman is the Helen L. and Martin S. Kimmel Professor of Molecular Immunology in the Department of Pathology and Microbiology at the Skirball Institute of Biomolecular Medicine of New York University (NYU) School of Medicine. He is also Coordinator of the Molecular Pathogenesis Program at

many origins, probably even Muslims like Syrian émigrés who need to escape the horror that goes on in their country. So it's a really wonderful organization, and they helped us initially to settle in Providence because we came here essentially with no assets whatsoever.

Williams: Tricky. Just while you mentioned your brother, tell me just a little bit about him. What was his career path?

Littman: My brother's five years younger than me. He became a physician here. He actually still, even though he's younger than me, felt a real affinity to the country where we came from, and when he was in college, he read that there were children of Romanian emigrants who were going to medical school in Romania, so he decided to drop out after two years in college and applied to go to medical school in Bucharest, and did six years of medical school in Bucharest in the late 1970s, early eighties. Came back to the U.S., did a typical residency, and became a general internist, and he's been working in the Philadelphia area since then.

Williams: Interesting. Bucharest really had a hold on him.

Littman: It did. I guess he was much more interested in pursuing a career path early on. I was not at all sure what I really wanted to do. I wanted to explore things, and, like I said, I started out thinking about designing rockets and then moved on from there until I finally found what I really liked doing.

Williams: So talk a little bit more about that process of focusing your interest into a certain area.

Littman: I think after I decided that engineering was too narrow for me, I wasn't quite sure what I really wanted to do. I did a lot of reading over the summer, I love chemistry, and I was very good at math and physics when I was young, or so I thought. When I went to Princeton, I realized that there was nothing exceptional about my abilities in math and physics. There were people there who were really absolutely brilliant doing that kind of work and working at conceptual levels that I could not even approach, and it wasn't something that really bothered me that much. I was just looking for what I would like doing.

I just happened upon reading some biochemistry books and biology books because I hadn't studied any biology when I was in K through twelve, for reasons I don't really understand, but I was never really exposed to that. And I used to work as a lifeguard in Philadelphia during the summers in high school and then after my first year in college, and during that time I picked up a couple of books, including Jim [James D.] Watson's *Molecular Biology of the Gene*, which was in its first edition, and I also read his book *The Double Helix*, and I really latched on to it. I remember to this day seeing for the first time in the book electron micrographs of DNA and DNA replicating, and the whole idea that you could see the entire—you know, the information of life visually at the molecular level

through a microscope, that really, in a way, just blew my mind. [laughs] So I became very interested in how the process works, and I began to take biology courses at Princeton, and biochemistry, and I realized that I really loved it. So I felt fairly well set in that direction after my sophomore year.

Then something really wonderful happened, which was that—well, two things happened. At Princeton during your junior year, you're encouraged to find an advisor to do a thesis, and at that time there was a young new faculty hire at Princeton whose name is Marc Kirschner, who's now a very well-known scientist up at Harvard University, at Harvard Medical School. Marc had just arrived there, just was opening his lab, and somebody recommended him to me that I should go and talk to him. So I did so, and he got me very excited about some biological problems he was working on, which were very much cell biological problems of how the long, polymerized molecules that are involved in cell division and in cell migration, the so-called microtubules, how they are assembled and disassembled, how they polymerize and how they depolymerize.

So I decided to start working in his laboratory and perform some biophysical studies to try to understand the nature of microtubule assembly, and that involved a combination of biochemistry and biophysics. It was really a lot of fun. There was some mathematics involved in studying the properties of polymerization of the microtubules.

But then around the same time in my junior year, Princeton put on a course in immunology, and there was very little immunology being taught at any universities at that time in the early 1970s, but it was a time when there was a lot of excitement occurring because some new tools had become available to begin opening up the field. The whole idea of how adaptive immunity works and how is it possible for our immune system to recognize so many different types of threats, so many different kinds of microbial antigens, that's something that had been a question for some time, but it became possible in the early 1970s to begin to dissect that at a molecular level.

Because Princeton didn't have any immunologists, one of the virologists there, Arnie [Arnold J.] Levine, organized a course with a friend of his who was at the University of Pennsylvania, Norman Klinman. Norman was an immunologist and he basically enlisted about twenty of the top immunologists working in the field in the world at that time. So they each came and gave one or two lectures, and I just sat through that course and I was just totally captivated. It was really an inspirational time for me, and after that, I thought, "Boy, this is an area I really could see myself wanting to work in."

Williams: That's so interesting that you really were in the first cusp of immunology. I mean, Watson's book had just come out and so on and so forth. How dependent in those early development days was the science on technology? What's—

Littman: Well, the science is always dependent on technology, and at the time, the technology was fairly primitive, but what happened just during the next one to two years was a time when molecular biology and cloning came to the fore. It was really the time when Paul Berg at Stanford and a few other people who had discovered so-called restriction endonucleases that allow cutting of DNA at very precise locations, allowed these to now be cloned into bacterial plasmids so that one could propagate DNA of one's choice.

The technology that was developing in the early 1970s allowed for characterization of sequences that were identical to each other or complementary to each other through so-called hybridization approaches so that one could now detect changes in the DNA of the cell by looking at hybridization after cutting with the appropriate types of restriction enzymes. So that was the key technology that developed at that time, and that's what allowed then Susumu Tonegawa, who was at the time in Basel in Switzerland, to for the first time show that when an antibody-producing cell acquires the ability to make one particular antibody, which it was known at that time that each cell, each B lymphocyte makes a particular antibody, what he found was that there's a rearrangement of the DNA that makes that particular antibody.

So this was really a huge advance at the time. When I was taking this course, we didn't really know this. It was one of the hypotheses, but within I think a year or year and a half after that, I think it was 1974, '75, he published a paper showing that there is the arrangement in the somatic B lymphocytes of the segments that eventually were shown to be variable regions, basically becoming approximated

Littman: I was a junior. It was my spring semester in junior year.

Williams:

there's much more of a utilitarian approach to studying medicine, in which there is an impetus to just shove a lot of information at students and basically have them complete medical school as quickly as possible, get exposure to the clinic as early as possible. And to some degree it's understandable, but I think it also makes it less likely that those people who have a real aptitude for doing experimental science are going to discover that aptitude during their first couple of years in medical school. So that is a trend that's really been throughout the U.S. medical school system.

Williams: So talk a little bit about your medical versus Ph.D. side and your clinical experiences.

Littman: Well, my clinical experience was very limited. When you do an M.D.-Ph.D., at least in those times, you do two years of classroom work, with very little exposure to the clinic. Maybe with the M.D.-Ph.D. students they'd occasionally have us don a white coat and go and follow a physician around for one afternoon to see some example of some disease, but there was really very little exposure. And that's one area where I think now there's much more attention to getting the M.D.-Ph.D. students to be more involved in the clinical side of things.

But after two years, I went straight into the laboratory for three full years of research, and then coming back into medical school, you feel scared and unprepared. I felt just the way I think everybody feels in that regard. What we don't realize often is that during those three years of working in the laboratory, we really learn how to think about problems, so when you go back to the wards and now are thrown in the midst of medical students who have been studying all along the medicine, and residents and attending physicians who are basically querying us all the time about pathophysiology of the patients that we see, you don't necessarily need to have all that information at your fingertips, which I maybe had forgotten, because it's enough to actually apply the thought process and the problem-solving process to participating in that educational environment. So the fear that I had and I think that all of us have when we do this was somewhat misplaced, because there were other skills and other tools that we learned along the way that made it not so difficult really to adapt to going back into the clinical rotations.

But after my clinical rotations, which I enjoyed, despite the terrible hours and all the work, I remember I had a neurology resident during my rotation who didn't like doing spinal taps, and she found that I was very good at doing lumbar punctures, you know, to be able to get to the cerebrospinal fluid in patients. So she would wake me up at 4:00 in the morning and say, "Dan, we need you to do a lumbar puncture." So I happened to be good at doing that, so I became the go-to person as a medical student for doing that. But it made for very little sleep during that time.

Littman: I was there for five years. I tell my students and postdocs that the time you're a postdoctoral fellow should be the most fun time in your life, and I keep on telling people that,

the Ph.D. was not terribly successful from that point of view, although I learned a

soon as Mark gave me his protocol, within two weeks I was able to clone the CD8 gene from the mouse cells.

So this was in the spring of 1984, and after that, it was very easy to do the same thing with the CD4 gene, so within just a few months after that, I was able to also clone the CD4 gene. So these genes were important because they defined the two

residency, and that's why we moved to Philadelphia, because at that time there was a city hospital there called Philadelphia General Hospital, PGH, and PGH offered him a residency in psychiatry. So then eventually he became a child psychiatrist, and he worked at a number of hospitals in the Philadelphia area and some institutions for juveniles with psychiatric problems.

Williams: So he retired from that career.

Littman: He retired fairly late. My dad is still with us; he's ninety-six years old. He's still sharp as a tack, and he doesn't see patients anymore, but he definitely advises my brother on everything that he thinks he should advise him on. [laughs]

Williams: How do you escape such scrutiny?

Littman: I escaped both by delving into the science and also by running off to San Francisco. [laughs]

Williams: What about your mother?

Littman: My mom, she went into library science, so she got a master's degree in library science when we moved to Philadelphia. She went to Drexel University to take courses in that, and then she worked at the Free Library in Philadelphia for a few years and eventually at the law library at Villanova University where she spent, I think, probably more than twenty years working at Villanova in the law library there.

Williams:

Littman: It wasn't that easy, and I used to do a lot of translation for them, and I would come home from school every day and watch game shows with my mother and explain to her what the English—what was being said, and eventually she began to pick that up, and, obviously, if she went into studying library science, she had to be fairly proficient in the English language. So it was a slower process than for me, but I was eleven years old, which is a time of great plasticity still in our brains. [laughs]

Williams: So I'm curious, what prompted you after a certain number of years in San Francisco to return to New York?

Littman: I think there are a number of factors. I loved UCSF, I had fantastic colleagues there, and I was able to attract really good people to work in my laboratory, but there were

had very similar philosophies about how to do this, and we bought in with

when we saw something unusual show up, something interesting, following that lead and then discovering something new. So I think that's a great way of being able to do science. That's kind of the way we do it. There are other people who do science very differently, who really have one problem that they focus on and then really dig deeper and deeper and deeper until they really understand it at its most fundamental level. It's very important to be able to do that kind of science as well.

So what we have done, for example, we started studying how is it that you make CD4 cells versus CD8 cells, and we've continued to do this, but in the process, we identified a molecule that is a transcription factor that regulates expression of genes in the thymus in those T cells prior to their making that decision to go to branch one way or the other. But it turned out when we started looking at that molecule that it did something very different than what we initially set out to look for. It wasn't involved in this decision-making process; it was involved in survival of cells during development in the thymus, but then we found that it's also involved in development of lymphoid organs like lymph nodes, patches along the length of the intestine, so-called Peyers patches.

So we began to look in more detail at this, and in the process, we discovered that it's expressed also on T lymphocytes that exist in the intestine that we now call T helper 17 (Th17) cells, and the timing of this really coincided beautifully with the realization of others in the field that these Th17 cells are critical in most autoimmune diseases. So it was just a very nice timing of our finding this transcription factor and the field discovering the importance of Th17 cells.

Then we brought these together and found that the Th17 cells require this transcription factor which is called RORgammat. We found that this is a factor that can be targeted therapeutically, so that every pharmaceutical company now is making small molecules to try to target this to treat autoimmunity. We also in the process discovered—and by "we" I mean the postdoctoral fellow working on this, his name is Ivaylo Ivanov, who is now at Columbia University, he noticed that there were some unusual features of the Th17 cells in the colony of mice that we were keeping, and he figured out it had to do with the microbiota differences in these animals, and that led us to discover that you need particular microbes in the intestine for the Th17 cells to develop. So all of these came together from just being open to—we weren't interested in going after studying microbiota or after studying Th17 cells, we just kept our eyes open to what was coming across our viewfinder, in a way, and just followed those leads.

So at this point I'd say the things that are most interesting and most important in our laboratory are trying to understand how different microbes shape the immune system. These are microbes we all live with, what we call commensal microbiota

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

Littman: Sure.

Williams: You have been a member since 1987, I believe. How important has the organization been to you?

Littman: It's been very important through its bringing me closer to many of the colleagues in this field, and that was its importance in the early days. The first talk I ever gave was as a graduate student when the AAI meeting was part of the larger Federation's [Federation of American Societies for Experimental Biology] meeting. So the first talk I ever gave was in a Federation meeting in—I'm trying to remember where it was. I think it may have been in Washington, so that was probably about 1978 or '79, something like that, when I was first talking about my project on the two receptors versus one receptor recognition. At that meeting, there was another postdoctoral fellow from Harvard from Jack Strominger's lab who, I realized, was working in a related area, and we became friends from that. We didn't know about each other's works, and that came through our involvement with the AAI at the AAI meeting. So that was a very early time, obviously, when I was a graduate student.

But I've participated in the society since then in many ways in terms of the many meetings, having people from my laboratory participate in the meetings, and then eventually, in the more recent years, it's been very important for me in terms of policy and in terms of having the AAI really have an important voice in science policy in this country. So for that reason, I was very happy when I was nominated to be on the council. It was a time when funding for the sciences was beginning to be a little tenuous after the increase in the NIH budget during the late 1990s and early 2000s. I thought that the AAI could have an important role in that, and indeed the organization has done a fantastic job in doing that. I mean, the public affairs group led by Lauren Gross has really been front and center in dealing with policy regarding NIH funding, regarding priorities, and it's very well organized as an advocacy organization, meeting with people on Capitol Hill to try to push forth the importance of basic research, of the kinds of funding that foster that.

Williams: You actually participated in—I think it was 2015—going to the Hill and talking to members of Congress—

Littman: Yes, I've done that on a few occasions, and I'd like to think that we can contribute in some way. I had a postdoctoral fellow in my laboratory who became an AAI public policy fellow [Gretchen Diehl]. She's gone to Capitol Hill multiple times. She's met with local representatives. She is now in Houston.

So I think that these are all important aspects of what the AAI does. In addition, in this very difficult time of funding during the last few years, AAI has really stepped up and helped people who have had difficulties by funding fellowships,

postdoctoral fellows in some laboratories that maybe had some gap in their funding, and that's really very important, and it's really gratifying that AAI could do that because the investment arm of AAI has been very successful. They've managed the growth of the society very well, so they have the resources to be able

think that that is a fantastically exciting area. I tell incoming graduate students that I think that's going to be *the* most exciting area in immunology in the next decade, and I tell our administrators that they should be thinking about that. If they could develop some vision, that that's actually a place where science and medical science is going to, and I'm hoping that they will listen. [laughs]

Williams: You encourage your trainees and whatnot to pursue a career in science?

Littman: I'd say I certainly do encourage them, and most of the people who have come out of our laboratory have gone on to academic careers. Some have gone into industry. Some have become entrepreneurs. I have a former postdoctoral fellow [Yuelei Shen] who decided he wanted to start a business [ed. now Biocytogen] on making genetically modified mice and now has maybe the largest such enterprise in the world, with multiple plants and laboratories in China. It's run out of Massachusetts, but with laboratories in China making every imaginable type of gene-modified mouse. So people who have come out of the lab have been tremendously successful, by and large, and I certainly encourage that. That's really gratifying.

Williams: That's kind of hilarious that these mice are manufactured in China, along with everything else. [laughs]

Littman: Well, it's like everything else. It's a lot less expensive to make a mouse in China than to make a mouse in New Jersey.

Williams: I've asked everyone this question. What does a scientist like yourself do for fun?

Littman: I don't have as much fun as I'd like to have. [laughs] I like to travel. I am fortunate we have a place out in the end of Long Island, and I like to go out there and ride my bicycle and do road biking. But I can't say that I have any particular hobbies. What I try to do is stay physically active and go and visit really interesting places. I live in New York in large part because of the culture as well, which I didn't mention, but I love music, opera in particular, I love having the museums there, and being able to just walk over now to the Whitney [Museum of American Art], which is only two blocks or three blocks from where we live. So I manage to—the little bit of time that I have as free time is always occupied. [laughs]

Williams: You looked pretty happy on those boats in San Francisco Bay that your wife showed me. [laughs]

Littman: Well, I do like to sail. I'm not a particularly good sailor, but I have friends with boats. [laughs] Art [Arthur] Weiss and I and Rudy Grosschedl took a course in sailing in Sausalito when we were all assistant professors. None of us became a very proficient sailor, but they were very lax with us and allowed us to have