



The American Association of Immunologists Oral History Project

Transcription

Gabriel Nuñez, M.D.
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Interview conducted by
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Williams: This is an interview with Dr. Gabriel Nuñez for the American Association of Immunologists (AAI) Oral History Project. Dr. Nuñez is Paul de Kruif Endowed Professor in the Department of Pathology at the University of Michigan Medical School. He is also the Co-Director of both the Cell Biology Program and the Tumor Immunology and Transplantation Biology Program at the University of Michigan Comprehensive Cancer Center. Dr. Nuñez was the AAI Vanguard Lecturer in 2015. We are at IMMUNOLOGY 2017™ in Washington, D.C. Today is Sunday, May 14th [2017], and I'm Brien Williams.

Dr. Nuñez, can we start with a little bit of your family background?

Nuñez: Yes. So I grew up in Seville, which is a city in Andalusia, in the southern part of Spain. So I have a large family; we were ten children. I am the oldest. My father was a pharmacist, and I remember helping him, growing up, in the pharmacy. We didn't have any other family member that was a scientist. We have some doctors in the family. So growing up in a very large family, we were very, very busy always. We have to have turns eating to the rounds, so shifts for food. So I have very good memories in my family, having so many sisters and brothers around. So it was very harmonious, even with the large number of individuals, and I was very protected from everything, so I have a very good memory as a child growing up.

I have to say that that was difficult times because at that time [Francisco] Franco was in power, so I have many of my friends, we have disagreements with the older generation about that, and that included myself with my father. So it was an interesting time growing up. By that time already I was interested early on in science, so as a medical student I was doing experiments. I wanted to go to medical school not because to take care of patients at that time; because I wanted to be a scientist. It isn't clear to me where this sort of interests came from because I mentioned before I didn't have any family members around me that was in science.

The other thing I remember very well, I was very interested in filmmaking and, in fact, I was debating if I want to go to moviemaking school or to medical school, and I made a number of Super 8 movies at the time, and I was very interested in experimental moviemaking. I think my mother was very relieved when I told her I was going to go to medical school. [laughs] But I was very passionate about filmmaking at the time, doing experimental moviemaking at the time, editing the movie myself, shooting the movie, and things like that. So I recorded a number of movies at the time.

Williams: Was it fiction you were shooting?

Nuñez: Yeah, it was mostly reflecting—there was no acting, so basically was just filming with images and try to portray things in the society. So I remember traveling around in the countryside, for example, doing movies like that of people. So it

was an interest of mine and I was very interested in moviemaking. At the times during the Franco times, many of the movies were actually prohibited, so we have to go overseas or we have to go to special places to watch these sort of movies that were going on in the rest of Europe. We couldn't see them in the public open theaters.

Williams: So were you showing your work in underground places?

Nuñez: No, no, this was basically about myself and showing with friends and things like that. I was talking about movies of the time that were being shown in many other places, and we couldn't really see them in Spain at the time because they were censored. So we had to basically either join groups of cinefiles that were interested and brought the movies either in a way that would not be seen or places that I guess the government was not really worried about because they were very limited to the number of people going. It was not announced in a way, so I remember. So I have a large interest both in science but also in the arts, in moviemaking in particular.

Williams: Have you done any moviemaking since or—

Nuñez: No, no. That's something I stopped doing, but I enjoy watching movies, and I'm very interested and I study a lot about the different movements and art of moviemaking, so I'm still very interested in that, yes.

Williams: So what was the tipping point to push you over to medical?

Nuñez: I don't know. I guess it was probably very difficult. I could see a more easy career in science or medicine than in moviemaking at the time. I think that would probably be very difficult at the time to go through that way. I don't think we had very good even movie schools that you could join, so you probably had to go overseas, and it was not easy when you're like a seventeen-year-old to live by yourself, since I would not be able to support my family. [laughs] So I thought probably I postpone that. I said, "Well, I'll probably do that later on, on the side." [laughs] But probably I realized it was probably very difficult to just to go in that direction, yeah, as a career.

Williams: So what was it like going to medical school in Seville?

Nuñez: So I was a very good student, actually. I was in my class number two, in the class when I finished. But I remember the turmoil of the last years of Franco, so we had all the strikes and things like that. So I remember one year we had a strike lasted for the whole year, and we didn't go to the classes. So I was working in a laboratory, so it really didn't interfere with me because there were no strikes in the lab. [laughs] Then also the classes were not given by the hospital. The [unclear] hospital was working, so I go and see patients, but I didn't go to regular

classes that year because there was protests. This is not just in the medical school; this is in the entire university system in Spain. That was in '74, '75, '73.

Williams: When did Franco finally—

Nuñez: Seventy-five, that's when he died.

Williams: So you got an M.D.

Nuñez: Yes.

Williams: Would you have had the opportunity to do a Ph.D. at Seville or not?

Nuñez: Yeah, I could have, but as I mentioned, one way to go into science was to study medicine, and then you could do research in the medical school, but then I realized actually when I was exposed to the clinical medicine, I realized I also liked contact with the patients, so in the last year in the medical school, I was doing research in transplantation, so I went to Rome for a meeting in transplantation.

While in a restaurant, I met a professor from UT [University of Texas] Southwestern [Medical Center], Peter Stastny, and we started talking, and he told me, "Would you come to join my laboratory in Texas?"

I said, "Well, I'm going to do a residence in Madrid in internal medicine." Well, four months later, I was in Dallas. So that really changed my life. Going to Rome and then meeting this professor in a restaurant really changed my—I think there was many other attendees that were in the restaurant, and I happened to be sitting close to Peter Stastny. He told me, "Well, we work in the same area. Would you like to join the laboratory?" So that really changed my life. So that was around '78.

So in '79, I arrive in Texas and I had to learn English all over again, because I didn't understand anything what the Texans were talking about. [laughs] I used to go to England in the summertime to learn English, so I learned English in England. When I was eighteen, nineteen, I used to go to work in England. It's very near Spain, so we just take the plane and land. I'd have different type of jobs there in the summertime, then go back to medical school. So when I arrive in Texas, I notice they have a different accent. [laughs]

Williams: Just before we get to Texas, what about—I'm curious about your siblings. Did some of them follow in your footsteps or—

Nuñez: Yeah, there were three that went to medical school and then became doctors. One of them died recently of cancer, but the others are still—they're all living in Spain. All my family living in Spain. They have not left the town, and that is not

uncommon often in Europe and certainly in Spain that you basically stay where you are, particularly being in a big city like Seville, which have about one million people. So there are many things to do there, many job possibilities, and it's a very beautiful, historical city, and it's very good weather. So I think I not blame them for not even try to move overseas. I think they are very happy there.

Williams: So how did you make the adjustment to life in [unclear] Texas?

Nuñez: So Texas was really a big shock in the beginning, because, as I told you, this is the opposite that you see from here. So you are going to arrive, let's say, in Montreal in Canada or New York City or Chicago, you probably see a city life that's more closer to European environment. But Dallas, Texas, was totally the opposite. I mean, you have to go in a car everywhere, the distances were enormous, the cars were huge, I never seen cars like that, and there were highways everywhere. So that was really very different. I never seen anything like it before. That was very, very unusual. But you adapt to the new situations. The medical school, UT Southwestern, is outstanding in quality, and there were already very strong leaders there, so for me, it was really a very strong learning experience. I stayed there for five years.

Williams: Were you doing clinical work or strictly research?

Nuñez: I was doing work in rheumatology because Professor Stastny was interested in rheumatoid arthritis and transplantation. He had run the laboratory for HLA typing, so these antigens are involving rejection of organs but also a link to certain diseases, and he was originally a rheumatologist. So I did some studies with arthritis families early on, and then I work on more basic work in monocytes and other immune cells when I was there.

Williams: Then what prompted your move to Washington University in St. Louis?

Nuñez: So after five years—this happened to immigrants. They come here for different reasons, particularly you come for a career, so you have to make up your mind. Do you want to go back to your own country or not? That happens to every mostly immigrants, that they have option to go back. There's immigrants that don't have the option. They cannot go back to their own country for religious reasons, economical reasons, whatever. But I was fortunate enough to—I could go back to Spain, have a good career, and I knew that.

So you have to make a decision, and after five years I thought, "Well, I have to make the decision, do I stay here or I go back." So I decided to stay because I was very interested in research and I thought I have better opportunities. And at that time, I have to decide, "Do I go to do more training?" Actually, I was an M.D., so I thought maybe one possibility to do a residency in a specialty which allow me to do research at the same time.

Pathology came as particular interest to me, so I look around and look programs in pathology that would allow me to do research at the same time, do the clinical requirements, but also do more work in the laboratory. So I interview in a number—there were like five or six programs, residency programs in pathology in the country, that would allow me to do research, and one of them was Washington University. Professor [Emil] Unanue was a very famous immunologist, just came from Harvard [University] to take the chairmanship of Pathology. When I talked to him, he offered me, after the interview, the position, so I said, “Well, I’m coming to St. Louis.” And I think that was a very good decision, really. I thought it was very important for me, for my career, in going to Washington University.

Williams: And how so important to your career?

Nuñez: Because there were outstanding immunologists there. The department was really a leader in immunology. I didn’t work in immunology; I work actually with Professor Stanley Korsmeyer. He just came from NIH [National Institutes of Health]. He was an oncologist, working in lymphoma, and also was very good. But I was exposed to a lot of immunology in the department because that was the main focus of research in the department for many, many years.

So I work with Professor Korsmeyer, Stanley Korsmeyer. He was interested in B cells, and then in translocations related to lymphoma. So one of the genes that we were very interested in is called BCL2, and at that time we didn’t know that it was involving the pathogenesis of lymphoma. My project was to understand how BCL2 promotes follicular lymphoma. It turned out to promote this particular gene was part of a new field, which is apoptosis, or cell death regulation. So this promoted survival. So I sort of learned a new field, and this was new for everybody, including Professor Korsmeyer, so I enter a new field which is known as T cell immunology, although it’s related to many fields, which is the role of regulation of cell death, so I was learning that, like many people at the center. It was a new field, so I was very, I think, fortunate to get into this field, because I learn all of the molecular biology, other tools, really help me in my career down the road.

Williams: Were you tempted to just go on and stay at St. Louis and—

Nuñez: Well, at that time, when you finish the residency, typically most people look for positions elsewhere, so I interview with a number of positions, including University of Michigan. That’s where I end up going. So I was fortunate to have several offers, so I decided to go to University of Michigan after that. I think there was an interest later on from Washington University to recruit me back, and I was really honored to have that, but I think already was building my career in Michigan, and I thought that was probably better just stay Michigan.

Williams: So talk about the scientific community in Michigan that appealed to you.

Nuñez: Well, at that time, because I was in a new field, apoptosis, so it was really limited. There was Craig Thompson was a very famous immunologist came, and he also was interested in apoptosis, so we collaborated work with him, with Craig, and so I work in this area for about ten years. Then my focus changed, and I can explain to you why that happens. I went back to immunology. But that was very interesting years working with cell death. There were many implications of the cell death pathway for many different diseases, from cancer to neurodegeneration to many processes. So I was more linked to the cancer field, so I joined the Cancer Center at the time. That's where I had my—carried my—laboratory. That's when I move. But later on in the mid-'90s and late '90s, my focus on research changed dramatically.

Williams: So explain that shift.

Nuñez: So this doesn't occur overnight, but we were working with an apoptosis regulator called Apaf-1, which activate a caspase, called caspase-9, and we were looking for homologs to understand more the pathways of Apaf-1. So at that time, the Human Genome Project was not yet active, so there were no sequences, but there were a number of companies that they were making lab—called cDNAs, all the genes expressed in a cell.

I was in a meeting and also in the lunchtime, so the career changes when I'm doing something with food. So basically this company asked if we could join, we can go to his company to look for genes for Apaf-1 homologs, and I brought one very talented postdoc—Naohiro Inohara from Japan. He was incredible. He was the best postdoc I ever had, an incredible individual. So he came with me, and within thirty minutes, he found a molecule called Nod1 that was homolog, structural homolog of Apaf-1.

Well, it turned out that Nod1 and related molecules, there were nothing to do with regulation of apoptosis. Turned out to be sensors of microbes. It took like a couple years to realize this. And then we found that one of them, the second member that we cloned, Nod2, that it was a mutation, so Nod2 were highly linked to the development of Crohn's Disease, which is an inflammatory disease of the intestine. So working with people in University of Chicago, Judy Cho, and coworkers in my laboratory, we had a very influential paper in *Nature* in 2001, linking the mutations of Nod2 to Crohn's Disease.

So when I saw that, I thought—and we already had identified many other family members, so I thought this was a new field that linked to human disease, we don't know anything about it. I thought just to move from apoptosis to the new field of innate immunity that was really flourishing at the time. We're talking about 1998, 1999. So the main sensors that were at the time discovered were toll-like receptors, so they were isolated early on. And we came with a new family member. We had difficulty in publishing the papers at the beginning because they thought all the sensing of microbes for inducing protective responses against

infection were toll-like receptors. These family members were in the cytosol, so there was some reluctance to believe this. But then when the paper on clones came, I think they really changed the fate of this, so people started believing that indeed maybe this is involving immunity sensing.

So that was very important, so I thought that moving into this new field, this family linked to human disease, that was very important. So I basically within two or three years change the field, and also working from mostly biochemical approaches and molecular biology approaches, we have to work now with animal models because when you study infection, you cannot do this in vitro. So we switched from methodology also, so it's a major change in the tools and also the research emphasis in the laboratory.

So I will say within three years we really switched, so it was painful but I think was very—we were 50 percent on the grants from the cell death. I was not submitting more revisions or any more applications, so I decided to move to the new field, and I was really a little bit nervous if I could get funding. But I think that was the beginning of the field, and I think I was able to get funding to continue the work. And I think, in retrospect, that was a very, very good decision.

Williams: And has that been sort of your through-line right through to the present?

Nuñez: Yeah. So we have continued this work, although in the last five years we also move into a new area, but I still continue the other work, which is basically the microbiota. Many of the things we're publishing now is on this organism that is part of our bodies that we carry with us, and many laboratories now are interested in this topic. So we still continue the work that we started in the early 2000s, but also now we have also interest in the microbiota and how they protect us from pathogens and things like that. So, yeah, this is sort of a new interest we have in the laboratory, and I will say at least half of the laboratory is working on the microbiota at the moment.

Williams: And that area of study has become quite ubiquitous in the field.

Nuñez: Yes, now because it can affect many different processes, not just in immunology. I think what makes an area to be very successful, I will say very popular, is when it can have implications for different fields, from neurobiology, from—almost any field in biology is affected by this, and the same happened to cell death. So I think being in these two fields where there's a lot of interest, I think that's very gratifying for the scientist because you think you're working something important, so I think you're lucky if you work in an area like this. It's very competitive, but at the same time, it's very exciting. So I think that is more important.

Williams: Can you say what the significance of your work is that would be of interest to laypeople?

Nuñez:

Yes. I think when it gets to the microbiota, I think it's very easy to make the connection. I will say that the work on NOD-like receptors—these are the centers that we identified in the late 1998 and 1999, and then people start working in 2000 and so forth—I think it has been a big question for many scientists, but also as for laypeople, how do we defense against—how sense these microbes, and then we defense against them. So I think this is something maybe a regular individual would not think about it, but have to think, well, how do we—they know about the immune system. How do we—the immune system try to fight. Well, before you have to fight, you have to recognize it, so this is sort of the machinery that we have to recognize it, and then we can do something about it, the body can do something to fight.

So these are type of sensors that are very important for the fight against infection. Then on top of that, mutations in these sensing mechanisms are linked to common diseases, because probably when these diseases are mutated or they are normal, we don't allow the normal sensing of the microbes. So the microbe may accumulate because we cannot see it, and it start growing and produce more inflammation, so it could be a number of explanation for common diseases that in relation to infectious diseases, which this is fundamental.

I think the defense against pathogens is essential for any living organism, any organism. So I think that this is something that drove evolution, what you can be successful and you have to think about in terms of human history, plus antibiotic time has been very recent. So most of the human evolution, animal evolution, before antibiotics, so infectious disease was a major factor. We had to think about the medieval ages when the plague kill sometime 30, 40, 50 percent of a human population, and there were infections like going on every two or three years. So they could basically wipe out 80 percent of the population. So then we saw lot of room for selection, and also we didn't have any good ways to basically clean the water. We didn't have a concept of microbes. This is happening in the sixteenth century and the seventeenth century where the microscopes were discovered. So people knew they were getting sick, but they didn't know why. They basically thought maybe the gods were punish them. The same happened when the Spaniards arrived in Americas and brought in with many viruses, and the native population were perishing, and they thought they were protected because they had been exposed before. So we didn't have a concept of microbes. So during the childhood was a major, major loss of life, so that's before you could pass your genes to the next generation.

So all of the selection, these were infections were a major way to cause of death at the time, so it have major implications for human evolution, I will say. So I think people will probably understand that. Being around for 100,000 years or more, antibiotics only being introduced in 1940s, late '30s, so really before—now we have changed the causes of death, but you cannot change genes or affect human

population in 100 years. There's not enough. You have to think of pre-antibiotic era.

There's where we are now. We still are where we were before. Right now, our genetic makeup is reflecting more of pre-antibiotic era and exposure to microbes. Our lives and our genetic makeup has been really largely affected by these continuous encounter with pathogens, which now we are diminishing, particularly in the developed world, because we know what is causing it, we can do something about it. We can clean the water, we can do sanitation, and that was not really known until literally recently in human history.

Williams: Let's turn to the AAI for a moment. You joined in 1985, I believe.

Nuñez: Yes.

Williams: And what was the attraction?

Nuñez: Well, because I was working in immunology, so I thought that is the major—still is the major society for immunologists in this country, so I wanted to be part of that, part of the society. So, yeah, I think when you are a student or postdoc, you have a limited participation. You can go to the meetings and things like that. I think later on, you can more involve your interests in this.

Williams: You got involved with the journal [*The Journal of Immunology*] quite a bit.

Nuñez: Yes, yes. So I was section editor for a number of years, and then I became deputy editor. So I mean, yeah, this is affecting my daily life because many manuscripts come my way every day, so every week. So really this is a lesson that lasts ten years. I've been really doing some work for the society. This done entirely on a volunteer basis, so I think that I enjoy doing it and I think it helps me as a scientist, and also I can help the society, so I don't have any problems with that.

Williams: So you actually enjoy it, it sounds like.

Nuñez: Yeah, I think I enjoy doing it, yes. I think at the beginning when you learn how you can become very effective way to do this, because it's very time-consuming, so maybe a few days I don't like to do this because I'm very busy with other things, but generally speaking, I think I don't mind to help and also I think that it also benefit people in the sense that you learn how to read many papers and you see the comments of the reviewers, so really you can see and keep you up to date, and I think it's very helpful.

Williams: What work have you done with the Minority Affairs Committee?

Nuñez: Sometimes I give talks and things like that, but I'm not being involved with Minority Affairs, but I've been invited to give talks and things like that. But I

think you have to choose your—you cannot be everywhere. I mean, you have to choose your area of interest, and I think the journal is something I decided to do. I could do something there, yeah.

Williams: Help me with my confusion here, because I would not have thought that a Spanish native would be considered a minority in this country.

Nuñez: Yeah, I think this is a very, very good point. I learned because I didn't know. When they asked me if I'm—I sometimes I put it—I don't reply or sometimes put Hispanic or sometimes I say European. I don't know what I am. [laughs] So I don't typically use this for anything, so I don't—so, yeah, it could be confusing. The definition of the State Department, at least for some time, I'm not sure currently, they said I was someone with a Spanish culture background or something like that, because you were qualified. But someone from Spain, you could make the argument they're Europeans and they came here. So I don't know exactly what they are particularly. [laughs] So I don't want to take any strong views on this because I don't think it's necessary, but, yeah, sometimes it create confusion, including for myself. What am I? [laughs]

Williams: Have you taken on a bit of a mission to work with Americans with Hispanic backgrounds?

Nuñez: Unfortunately, there are not many applicants, but I have taken a postdoc recently from Mexico and also I have some applicants from Hispanic background, and there's one now we see, I'm going to interview next week, hopefully can join as a student, maybe can join my laboratory. So, yeah, I think that is something I would be very interesting in to do this, but, unfortunately, we don't have many applicants. We don't have many applicants, and I think there's a problem that we have to solve, which is basically graduation in high schools. There's a lot of loss of potentially talented individuals, minority individuals at that stage. So they don't have a chance to even to make—so you have a lot of attrition at that level. So I think if we increase the pool there, I think the number of programs to bring some of these individuals to some universities so they can work there for two months or three months or a year, and then if they are talented, they will make it.

I think when the number of pool is so small, it's very difficult, because you don't want to push someone because they're a minority if he's not talented, because that's a failure. So I think what you need to do is that you need to increase the pool of minorities working early on, to increase. Now you can see these talented individuals. By then the numbers already to begin with is very small, so then you cannot push it because at the end, it's a failure. So I think we have to work early on to increase the pool, and then we can find those talented individuals. They can be very successful. Then they would be, not because they are minority, because they are talented, so I think we should focus on that, because, otherwise, they cannot survive. You cannot put someone artificially because they're a minority. So the problem is to increase the number of those individuals that they can have

now the chance to show that they are talented, and I think that's the way I think it should be done.

I mean, what I said, all the people felt the same way. This is not—but I think it's a problem with the number. We don't see many applicants. Graduate students, we don't see many postdoctoral fellows that come in. There are some, but it's not 10 percent or 15 percent, and I think we have to increase the pool so we'll see these very minority talented individuals. They can compete with anybody else. So I don't think they want to be seen because they are helped because they are minorities. I think they wanted to show they are talented like anybody else. So I think the help has to happen early, early on. That's basically what the main problem is, attrition is there, to give them the opportunity to compete now in the open field.

Williams: Are there programs that you're familiar with in the state of Michigan that promote this awareness of young people as they're getting their education?

Nuñez: I don't know in Michigan, but probably there are. But what I see, I have some minority students from college, so I have several of those. There are some universities have these programs. During the senior year, they come for the summertime or sometimes take an extra year, and then they can come in and they can learn and they can see how they are. So I think you work with those individuals, you can foster their development. I think some of those will be the ones you wanted to see. So I think this has been done, and in Michigan we have these programs and they have some of those students. Some of them are graduate students at the moment, and some of them have posters here at this meeting. So I think it will work.

Williams: I'm just curious, was the situation any different at the University of Texas?

Nuñez: Well, at that time because I have a different role. In Michigan, I am a professor, so I have a different view of things. When I was there, I was basically a fellow, a postdoc, so really I didn't have much to say about that.

Williams: No, I know, but were there more Hispanics involved in the program there than—

Nuñez: I don't remember. I don't think at that time—this is in the early '80s. I don't think there were many minorities. You could see minorities as technicians, but you didn't see faculties or very rare faculty. In Texas is a large proportion of Mexican Americans, so I'm not sure if things have changed. I just don't know about that.

Williams: What about the state of immunology in Latin America? Do you have any sense of that?

Nuñez: Yes. Actually, I connect to some individuals in Latin America, particularly in Argentina and Chile and in Brazil, and also I know people in Mexico which I

visited. I think it's very difficult to do research in Latin America because economical reasons. So we have to think about that. They are very talented, but they are really having difficulty with funding. We have problems with funding here, but there is much worse, because many of their reagents, because they're made in the U.S. and other places, there are middlemen in between, so that double or triple the expense. Sometimes it takes like a month to get the reagents. So they really are in a very difficult situation. Already the economy is depressed, on top of that for the scientist to live with the really small amount of dollars to do research, and then the prices of the reagents are higher, so it's very, very difficult for them to succeed in their own countries. So I think this is something you hear when you talk to them all the time, yes.

Williams: What about the status of immunology in Spain?

Nuñez: So my connection with Spain has been I go there two or three times and I see my family and things like that. I have some connections. In Spain, there was another researcher improving immunology, but also there was a major crisis in the last ten years. So this also is not unique to Spain, perhaps with the exception of Germany, they also having problems with the economies, so the number of grants have been reduced. Many of these individuals are very well trained. They are well trained in the United States, and when they go back, there's always problems in becoming independent. Often in these countries, I think the same in Italy, for example, and Portugal, they are controlled by an elite group of individuals who have been in power for a long time academically, so it's very difficult for them to emerge as independent scientists because there's no room for any new laboratories and the funding somehow. So often they see themselves basically working for somebody else and very difficult to get a name for themselves. So I think, I mean, on top of that, they have limited amounts of funding. So I think there's a problem, yes.

Williams: In 2015, you gave the Vanguard Lecture to the AAI.

Nuñez: Yes.

Williams: And I thought your title of your work was quite intriguing, very big-picture and cutting-edge is what I thought. Do you recall linking pathogen, virulence, immunity, and microbiota?

Nuñez: Yeah. So, right.

Williams: That covers it all, doesn't it? [laughs]

Nuñez: In fact, I'm giving the distinguished lecture on Monday and have a very similar title, so I am going to give an update two years later of this talk on Monday, six o'clock. So, yeah, this is an area that we will be very interested in understanding the sort of interactions between the microbiota, pathogens, and immunity, and there's a lot of things there. It's a very broad topic, so we try to do our best to

understanding in our system. They work to understand, this is for interactions, how this work. So, yeah, I think that is of great interest to me and my people in the laboratory to this particular topic of putting all together, trying to understand the interactions between microbiota, the pathogens have to—particularly bacterial pathogens, which are now all of a sudden arrive in the really hostile environment full of bacteria which are already there, and then they have ways to get around that, to replicate. They have tricks. They evolve. The immune system have to put some order into this and try to get rid of the pathogen. So I think this is a very interesting topic which I'm very passionate about, and I think we have learned a lot in the last five years about this, yes.

Williams: It does seem to me that it's like a door is opening or a window is rising or something, that this acknowledgement of the connection between our organisms and immunity and so forth, it's a whole new area. Do you agree?

Nuñez: Well, I think, I mean, immunologists have been interested from the beginning. The immunology field came from the microbiology field in the late 1800s, so that many departments in this country of immunology were first bacteriology departments and then became microbiology and then they added immunology. So I think that everything is started in the late 1800s, there was a connection between certain bacteria and disease. So then they found the bacteria from tuberculosis to other bacteria that caused major diseases at the time.

Then, of course, the question is could we do anything about it, could we now get vaccines against to protect you from the diseases, which at the time, at the beginning of the nineteenth century, that was the major cause of death certainly in Europe. So there was a lot of emphasis in vaccination and figuring out ways to fight infection, with really limited knowledge of the immune system at the time. So most of the cells, immune cells, with the exception of microphages, we didn't know. We know where they were. But they were the emphasis. So I think the emphasis of the fight of infection, so I think immunology's always been interested in the main purpose of the immune system, which basically defend us from infection, typically bacterial viruses, parasites, or whatever, that's the main role of the immune system, not to cause diseases. Often these pathways go awry, and they are involving diseases, but the immune system is not there to cause disease, to cause suffering. It's there to save us from pathogens. But sometimes we have mutations and other factors that the inflammatory diseases use the same pathways they use to fight infection, to cause disease. But that's not the main purpose. This is not a normal situation. The main purpose the immune system is to eradicate the pathogen when you encounter the pathogen.

Williams: But isn't it novel to recognize that the microbiome, for example, is kind of a partner in this effort?

Nuñez: Yes, I think these new concepts are emerging. It's been known for a long time that pathogens can be outcompeted by the microbiota with antibiotics introduced

particularly in the '50s. Already there were experiments that you treat the animals with antibiotics to make them more sensitive, for example, to *Salmonella* through the oral route. So there were the concept of the protection of the microbiota against *Salmonella* colonization. So those were already concepts that came from the '50s, but then the microbiota field sort of die out after the '60s and is coming back in the last ten years. Now we have better tools to understand, and we can understand why the microbiota help us from pathogens and things like that.

Now we have a good example. We use these now tools to treating diseases. *Clostridium difficile*, which is colitis, which is introduced in individuals in hospitals who are treated with antibiotics, develop colitis because these pathogen grow, bloom in intestine. So now we treat it with fecal transplants, so basically transfer microbiota from one individual to another. So we already have a precedent already, a therapeutic way to use these concepts that were first introduced in the '50s after antibiotics were used in animal models. So I think that is a lot of excitement about this. We already have an example that we can use these concepts to treat human disease, yes.

Williams: So do you recommend a career in science to the students and trainees that you come in contact with?

Nuñez: I think you have to be passionate about it, because this is a very hard life, okay? You see all the glamour of the papers and the lectures, but science is basically a day-to-day situation. You have mountains and valleys all the time. You're going to have good times, you find all the discoveries, sometimes experiments don't work, so it's a very hard life. But you have to be passionate about discovery and try to basically to discover the secrets of life. That's what we're working about. Life have evolved very wise. Mother Nature put ways—we trying to figure out what are the secrets of that, so we can understand disease, understand how the immune system works.

So certainly I encourage young people to get into a career in science, in immunology or other fields, but at the same time, it's not going to be easy. You have to have the passion, to be passionate about it, because it's going to be sometimes difficult times. But if you're really passionate about this, that would not matter because you always have [unclear]. But right now with the talk about funding and it being not very good in the last five, ten years, even they seem to be more threatened, perhaps, so probably I discourage. You can see many of the students or postdocs see their mentors suffering with funding. I will say that that shouldn't maybe be an excuse. I think at the end, if you're interested and you're passionate about science, you can do it. I encourage you to enter the career, because you can overcome these problems. You can overcome these problems. But we have to be realistic. This is a very hard life, full of difficult times, but also full of happiness at the same time when you discover something. But it's a life, at least for myself, that really it's almost like a twenty-four-hour situation. I think the scientist is like a painter or a musician. There's something you're always

thinking about it, at least many people I know, and you're passionate about it, and you're always thinking, but you enjoy doing that. So I think you feel that way, I think you should pursue your dreams and get into science.

You can do other things in addition to that. I do other things, hobbies that has nothing to do with science, and I think that there's something also very important. Good scientists typically have—they're involved in science but also have different perspective in life. They like history or they like other things, so they don't think in a monolithic way. They have a broader perspective of politics, of society, art. All the good scientists I know, they also transcend their own science. They are very passionate and very involved in the science. They think about science all the time. But also they have other interests in life, and I think that is, with no exceptions, that's what my observations are, that typically good scientists also have other interests in life, very passionate about things.

Williams: Tell me a little bit about your other interests.

Nuñez: Well, some of my fellow immunologists know I'm a cook, so I do cook Spanish cooking, I do paellas and I raise many funds a year, about \$10,000 a year, for different charities or causes. I've been invited also to cook at meetings, to cook there for the organizers, so I've done cooking in Australia and Brazil. I tried to set up one in Tokyo. So I do a lot of cooking, and I learn how to cook in top restaurants, and then I—paella is a Spanish national dish. I also raise a lot of funds. I set up as a class, a master class, so I teach how to do it, and these people donate money, and I support the Ann Arbor Symphony Orchestra, for example, for educational programs for children, to the musicians who go and teach the classical music to the middle-schoolers, and also different charities, homeless and schools. I enjoy doing that, and I donate everything. So I am very passionate about that as well. But I also like a lot of history, also. I like history, yes.

Williams: So you read history, is that it?

Nuñez: I read history and also I like to talk about history. When I travel, this is one thing I do. When I go to a meeting, I stay there and I try to understand the history of that country or that city, and I enjoy doing that. So I think this is one of the perks, if you can call it that way, to be a scientist, that you get invited to give talks. You can also spend time all over the world and talk about science, but also talk about other things, human activity in those countries. And I think that sort of perspective make you, I think, a better scientist and also a better human being. That's my view.

Williams: I was quite amazed, in reviewing your CV, the full list of all the speeches you've given through your career, and it went on for pages.

Nuñez: Yeah, I enjoy doing that. It's very enjoyable to travel and talk to people from different countries and then learn about history when you get there, after the

meeting is finished, you stay another day. I think that is very gratifying and I really enjoy it a lot.

Williams: Coming from a family of ten kids, what have you done in the way of a family?

Nuñez: So I have two children, Pablo and Fernando. So one of them is a sophomore at the University of Michigan. He's now in Guatemala, helping Mayan families—I think he's coming back today or tomorrow—with programs of the University of Michigan in the environmental sciences. So they go there—and it's the second time he goes there to Guatemala—and try to help the indigenous population to do something with the environment and help them. So that's the sophomore in Michigan.

Fernando, which is my older son, he just finish a master's degree in biochemistry and he wants to go to medical school. So he wants to apply to medical school sometime. So I didn't really talk to him about much about anything. They evolved that for themselves. I don't think that it's a good idea for parents to push the kids in a particular direction. They have that by themselves.

Williams: I've encountered so many couples that are both scientists. Is your wife—

Nuñez: My wife, yes, my wife is originally from Spain, and she came with me when I came to Texas, and then we sort of separated for a while, and then she went to University of Virginia to do a Ph.D. in biochemistry, and then she went to [Johns] Hopkins [University] for a postdoc, and then we married about twenty-three years ago, and she came back to Michigan. She came to join me in Michigan.

Williams: So is she on faculty at Michigan too?

Nuñez: No, no, she work there—she's not working right now at the medical school, but she have work in the medical school when she arrived, yes. She's very active in many things.

Williams: Does she love paella?

Nuñez: Oh, yes, of course. She want me to cook for the friends, and sometimes on a Sunday she say, "Well, could you cook paella for me?" We call the neighbors, because when you cook paella, you don't want to cook for two people, so we just call the neighbors, and all of a sudden we have five or ten people there just on the spur of the moment. [laughs]

Williams: Anything you want to add to this?

Nuñez: No, I really enjoy chatting with you about this, my life and from different aspects of my career, so it's been very—I have to say, the thing I would like to add is that—and this applies to every scientist, that really your success in science is so

depending on the people who work in the laboratory. So I've been very, very lucky to have outstanding individuals. More than fifty postdocs come to my laboratory over the years. Really, I learn from them as well. I mentor them, but I learn from them as well. I think the key in a scientist's career is also to be surrounded by talented individuals, and I think that's really the ones who do the work and the ones that bring new ideas and make you younger when you become older. So I'm really grateful, grateful, super grateful to the very talented individuals that over the years have come to my laboratory. I think they deserve all the credit for the work.

[End of interview]