The American Association of Immunologists
Oral History Project

Transcript

Laurie H. Glimcher, M.D.
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Interview conducted by
Brien Williams, Ph.D.

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year, we had our immunology block, was taught by Kurt Bloch, who was a rheumatologist and allergist at the Mass General, and I became completely riveted by the idea that the immune system can recognize self tissues as self and not as foreign, and that many diseases arise when that recognition becomes impaired.

So I really kind of fell in love with immunology at that point and signed up for a one-on-one tutorial with one of the immunologists at Harvard, Emil Unanue, one of the illustrious immunologists in the country, in the world. So I did a reading course with Emil over the summer and also continued working in my dad's laboratory on skeletal biology, but it was really clear after that semester that immunology was the field I wanted to spend time in.

Williams: I'm struck by—let me put it this way. There are so many diseases that are likely to be dealt with by a study here, the knowledge of immunology, but how many people are working in autoimmunology, which—just talk about the allure of that and why.

Glimcher: Well, I can tell you from my point of view it was very alluring, and I think that the concept that your immune system all of a sudden forgets that your joint tissue is self, and thinks of it now as foreign, or your kidney or your lungs or whatever, since the immune system is so pervasive, is in many ways a startling and disturbing concept. So a lot of us, I think, got drawn into the field because of that, and I certainly did. I found a disease like systemic lupus to be utterly fascinating, and I remember thinking about where and in whose lab I would do immunology, because I spent my fourth year of medical school basically in an immunology laboratory. I went to Harvey Cantor, and I asked him whether I could join his laboratory, and I said, "Well, I really want to work on lupus, models of lupus."

And Harvey said something then which I have never forgotten, which is, the best way to understand autoimmune disease is to understand the normal immune system, and I think that's absolutely true. For many, many years it was really difficult to investigate particular diseases, particularly in the setting of human disease. Now there's a total revolution. You can really look at human tissues, and we have the genomic capabilities to look for gene associations. We're at a point now where what we call translational medicine is actually a reality. It wasn't a reality thirty, twenty, even ten years ago, and at that time the quality of basic immunology research was far higher than the quality of what we call applied research in immunology. I think that's changing, that it has changed.

Williams:

Williams: What was the culture like there as opposed to the medical school?

Glimcher: It was the medical school.

Williams: Okay. I'm sorry.

Glimcher: Compared to MGH? So Harvard School of Public Health is part of the medical school.

Williams: Part of the medical school, I see. Yes.

Glimcher: Yes.

Williams: But does it have a sort of different culture? Because it must have a

and to get outstanding students and be able to collaborate with outstanding colleagues. I never thought about Harvard in a sense as something separate, because I grew up there, so I never really saw anything else.

Williams: And what kind of a balance were you able to achieve between remaining a scientist and a clinician and in the leadership roles that you assumed there? How did that work?

Glimcher: It was easy to do at Harvard, because the expectation was that Harvard Me[illegible]

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pretty clear. We get taxpayers' money to do our research, and the government was willing to give the IP back to the universities but on the condition that we do everything we can to translate our discoveries into new therapeutics for patients.

So we need to ensure that this happens in an equitable way and that, as scientists, we participate in this as full partners. The impetus for revising our policy on that was that it hadn't been revised for many, many years. I think 1998 was the last time it had been looked at, and we wanted to make sure that we were being fair to our faculty members, to the inventors, fair to the university, and that the policy was clear and simple.

Really, it was not just the medical college and the sciences at the university; it was also Harvard Business School, the Law School. So we have representatives from almost every school at Harvard and worked together in many sessions with some help to come up with a policy that was very straightforward, easy to understand, and fair. And I think we got there. We had lots of different viewpoints, but I think we came up with a policy that everybody was comfortable with. It was also a learning experience.

Williams: Is that a policy that is widely accepted elsewhere?

Glimcher: Well, we obviously did our homework and looked at policies at other places, Stanford [University] and Yale [University] and MIT and so on and so forth, to adopt what we thought was the right mixture of them.

Williams: In a phrase, can you sort of indicate where the money went, where the money goes?

Glimcher: It gets divided between the inventors, the department, the particular school, say the School of Public Health, and the university, so the university gets—I think it's 15 percent is the number we came down to, and most of that goes to the tech transfer offices to help support them. The inventors' share goes to the inventors, and then the share that goes to the department and the school is a little more fungible so the department might say that the share they get will go back to the laboratory of the inventor, or they might not. And the school might say, well, we'll take this piece or we won't take this piece, we'll give this piece to the department. That varies between schools, departments.

Williams: What about pharma's share?

Glimcher: Well, that's different than divvying it up in the university. So that depends on the negotiations that an individual laboratory carries out with an individual pharmaceutical company. Usually the pharmaceutical company will license the invention, and for that they pay a fee. But the IP is the property of the university, so each investigator has to sign off that this intellectual property belongs to Harvard University. So an outside company can come in and say, "We're going

to license that invention," for X amount of dollars, and then you work out a deal. What are the milestones? What is going to be the sponsored research support for the laboratory? What's the percent royalties? That's a negotiation that occurs one-by-one, case-by-case basis.

Williams: So tell me, briefly talk about your scientific breakthroughs and accomplishments.

Glimcher: They've been kind of eclectic. So I started out as an immunologist and spent most of my first twenty years doing immunology. When I set up my own laboratory, we continued the work that I started with Bill Paul, trying to understand the relationship between the structure of MHC class-II molecules and T cell receptors. So what do you need to activate a T cell? And we made a whole series of class-II mutant cell lines, and we sequenced the mutants and found out where the mutations were.

At about that time, actually, the crystal structure of MHC class-II was solved, and so knowing what the key functional residues were, I think, was very helpful to the structural biologists because they made a lot of sense when you looked at the structure of the molecule. Oh, yes, that's a very key place, and that mutation abolishes function, and that mutation doesn't abolish function, and so on.

And that was fun for a while, but I actually got very intrigued, three or four years after I started my laboratory, by the regulation of gene expression, and we continued our focus on MHC class-II genes, because they're regulated during the course of an immune response by cytokines, primarily by cytokines. So you can induce the expression of MHC class-II on B lymphocytes if you treat them with interleukin-4. You can induce the expression of MHC class-II on macrophages and dendritic cells and many other cells, if you treat with interferon-gamma, another cytokine.

So we spent a few years really trying to understand why that happens and how that happens and what the regulatory regions of the genes, of what the coding that surround the coding -1.1 0(-1.1 (ow)2( )]T-2(ha-2( )]TJ 0 -1.15 TD [(s)-1(ur)3(r)-6(r)3(0 -1

cell make interleukin-4 and what makes a T cell make interferon-gamma. So we set out to try to figure that out.

The first factor that we isolated was a proto-oncogene called c-maf and discovered that that controls the production of interleukin-4 in T helper 2 cells, and it's only expressed in T helper 2 cells, and so that was a big discovery, and we published that in *Cell* in 1996, maybe, something like that. But it didn't quite make complete sense because maf did not control other Th2 cytokines, and a master regulated transcription factor should control the whole program. So it didn't control IL-5 or IL-10.

Then Richard Flavell's group and, simultaneously and independently, Anuradha Ray's group identified another factor called GATA-3 that controls the whole kit and caboodle a year or so later. So a lot was being done on T helper 2 cells and figuring out more details about what other factors were involved in controlling interleukin-4, and we worked on the NFAT factors for several years and made a bunch of knockout mice that deleted these factors and so on.

We were interested in the other major subset, T helper 1 cells, and nobody knew what controlled the production of interferon-gamma, and so we tried. We wanted to crack that. I had a new postdoc in the lab who had come from Ken Murphy's lab where she had worked on T helper 1 cells, and we decided that she would go after this. She'd go after trying to figure out what this factor was. We took what I think many people thought was sort of a nutty approach. Well, she certainly thought it was a nutty approach for a while, and we decided to do it in yeast by taking a chunk of a Th1-specific promoter, which was interleukin-2, actually, and doing a reporter assay and screening through a whole library of cDNAs that we had obtained by subtracting the genes in Th2 cells from the genes in Th1 cells. So we had as a probe a Th1-like probe, and we put the library from a Th1 cell into the yeast.

I remember Susanne sitting there with hundreds of yeast plates and looking for blue colonies and white colonies. I have to say we really didn't think this was going to work. Most people had done this yeast-two-hybrid system by using very short sequences, multimerized very short little sequences, and we couldn't do that because we didn't know what the sequence was. So we had to take the whole big chunk of the reality promoter and do that. Anyway, it worked, and out came the gene that I'm probably most known for, and that is T-bet, T-box expressed in T cells, we called it, and that's the master regulator of the Th1 program.

I don't know how many hundreds of papers have been published on T-bet by our lab and other laboratories, but it turns out to be a master regulator not only for T helper cells, but actually for almost every immune cell, so it controls what we call Type-1 immunity in dendritic cells and natural killer cells and CD4 cells and CD8 cells. It's like the gift that kept on giving.

We went on to make T-bet-deficient mice and put them through a lot of different disease models, and a lot of serendipitous things happened. We discovered that if you got rid of the adaptive immune system and deleted T-bet just in the innate immune system, mice spontaneously developed aggressive ulcerative colitis that went on to colon cancer as the human disease does, and that was transmissible. And we isolated the species of bacteria that were responsible for transmission. That was at the time a very novel discovery that you could transmit a disease from mother to pup or from adult to adult just by cohabitation, so that they get infected with the microbiota. I mean, it's a whole field now of microbiota is enormous, and I don't want to say that we started that field by any means, but it was a fascinating discovery and is being carried out and work's being carried on by Wendy Garrett. She has her own lab now at Harvard. So that was, I think, probably the discovery for which we are best known.

At the same time, though, we had been looking years before that for the transcription factors that regulated MHC class-II gene expression, and we had isolated a couple factors that in cell culture experiments seemed to regulate the MHC class-II genes, but in vivo veritas, right? So at that point, the technology was such that we could make these knockout mice, so we knocked out these factors, in particular one of them which we had called X-box binding protein, because it bound to a sequence called the X-box in one of human MHC class-II genes, a really thrilling name. I wish we'd named it something different.

When we knocked it out in lymphocytes, we didn't see any effect on MHC class-II expression, so maybe in vitro it controlled those genes, but when you knocked it out in the mouse, no effect. Instead what it did was to result in an absence of antibody. There were no plasma cells, which was the terminal stage of B cell differentiation, no plasma cells. Well, I mean, that was a complete surprise. We had an animal who had normal numbers of B cells but didn't have any plasma cells, so it was the first factor shown to be required for the differentiation of the mature B cell to an antibody-producing cell, to the plasma cell. And we were sitting there scratching our heads trying to figure out how does it do it? What genes is it controlling?

Lo and behold, six months later, three laboratories independently published the discovery that XBP1 was the long-sought-after mammalian homolog of a gene in yeast called Hac1p, and Hac1p and its upstream sensor, Ire1, control what's called the unfolded protein or ER stress response in a very elegant signaling system largely discovered by Peter Walter at UCSF.

So it made sense, because this ER stress system is designed to allow a cell that's making a lot of protein to handle that load and not become overwhelmed by the fact that it's stuffed full of proteins, and if you impair that system by deleting this critical factor, the cell oftentimes cannot survive. And there is no cell in the body that makes more proteins than the plasma cell. It's just a little antibody factory churning out all these proteins. So now it made sense, and it got us very

interested in the ER stress response, which I had known absolutely nothing about. I mean, I was always flying by the seat of my pants. Nothing about the ER stress response.

Most of the work in the ER stress response had been done using pharmacological stressors and had been done in yeast, and here we had a mouse that lacked this gene, and it enabled us to ask what is the function of the ER stress response not only in B cells but in macrophages and dendritic cells and in other organ systems. So if you just make a germ-line knockout of this gene, these mice die in utero because they get apoptosis, they get death of liver cells at about mid gestation, and we circumvented that problem by making a conditional knockout because that technology had just come on line, and got interested in what other organ systems really rely on a vigorous ER stress unfolded protein response for their survival.

So what happens if we put XBP1 back in the liver, get those mice to birth? What's the next organ that fails? Well, the next organ that fails is the pancreas, because the pancreas is producing tons of digestive enzymes, and if they don't have this ER stress response, if it's impaired, then they can't handle all the load of these digestive enzyme proteins, and they die. So these little mice when they're born, they can't digest the milk in their stomachs, so they basically die of hypoglycemia. They die of starvation.

We looked at the brain and the impact on neurodegenerative diseases because those are protein-folding diseases, and, sure enough, it plays a role in amyotrophic lateral sclerosis in Huntington's disease, and we're looking at Alzheimer's disease now. And we asked what it did in macrophages and we asked what it did in other organ systems. So we were able to say in a mammalian system when is this important and why it's important in pancreatic islet cells. So these mice that have deletion of XPB1 solely in pancreatic cells, in islet cells, they get diabetes.

Then we made another very serendipitous discovery. I guess this is just an example of keeping your mind open when you get a result you don't expect. We figured that because it was so important in fetal liver, because liver again is a very highly synthetic organ that's making lots and lots of proteins, we figured it would be important in the adult liver. So we wanted to delete it selectively in adult liver, which we did, and liver looked fine. It was making synthetic proteins pretty well. There was really no significant deficiency in levels of proteins that the liver makes.

And I said to the postdoc, "Well, it's got to be doing something in liver, so let's just check every lab value in these mice," and to our astonishment, we discovered that levels of cholesterol and triglycerides were extremely low in these animals. And that resulted in a 2008 paper in *Science* showing that XBP1 controls hepatic
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This brought us into lipid biology, a field that I knew less than nothing about,

Glimcher: It's a group of very devoted people, and we've been really fortunate to have Michele Hogan be the executive director of the AAI for so many years. She's just done a really superb job at making that community run, making that organization vibrant and alive. The councillors, it's an honor to be elected as a councillor to AAI, and that group of people really work hard together and try to expand the community of immunologists, make *The Journal of Immunology* outstanding, and organize the yearly AAI-FASEB [Federation of American Societies for Experimental Biology] meeting.

Glimcher: Immunology has grown by leaps and bounds in the last couple of decades. It's almost inconceivable when one thinks that it wasn't all that long ago that we

continue with, but you make all your reagents available to other investigators so they can pursue it.

Williams: You've talked about balancing career and family and what a challenge that is. What kind of recreational activities do you indulge in? What's the fun side of your life?

Glimcher: Like what hobbies do I have other than—you know, I'll tell you, when the kids were young and at home, I had very few recreational hobbies, because every spare minute I had was spent with them. I used to do a lot of acting when I was in college and high school and even a little bit in medical school, but that's not something that you can really do once you start your career. [laughs] I'm a very vigorous believer in exercise, so I run and I do the elliptical and I really am pretty religious about exercising. Love the opera, the theater. I love to garden. I think probably the only thing I miss about Boston is that I don't have a garden anymore. We had a big house out in the suburbs. I like to travel.

Williams: Are we leaving any important thing unsaid here for the historical record?

Glimcher: I would only say that I hate to see women sacrifice the chance to have children if they want to have children because they think that it will negatively impact their careers, and I think a number of women do that. It's fine if you don't want to have kids, great, definitely going to make your life easier. But if you do want to have them, you should go ahead and have them. My three children are really the lights of my life, and my grandson now.

Williams: What are your three children doing?

Glimcher: My daughter is a lawyer at the FDA [Food and Drug Administration], and she is the mother of the most perfect little boy in the world. He's almost two years old. My older son, Hugh, is a fourth-year surgical resident at the Mass General, wants to be a cardiothoracic surgeon. And my younger son, Jake, who's twenty-five, graduated from Harvard and shocked us all by becoming a first lieutenant in the Marine Corps, and he is back from Afghanistan, thank god, where he commanded a fleet of light armored reconnaissance vehicles in southern Helmand Province, leading to many sleepless nights. But he's back safely, and he will probably go into business or law. I think he's not going to make the military a career, but I have to admit that it was unbelievable experience for him, and I can say that now that he's back from Afghanistan.

Williams: Thank you so much.

[End of interview]