NNU
Daniel Larson
National Cancer Institute, National Institutes of Health
Bethesda, Maryland

by David Zierler
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DAVID ZIERLER: I am here with Dr. Daniel Larson at his office at the National Cancer Institute, National Institutes of Health. It is March 6th, 2020. This is David Zierler, oral historian for the American Institute of Physics. Dr. Larson, thank you so much for being with me today.

DR. DANIEL LARSON: My pleasure.

ZIERLER: OK, can you state your title and affiliation here?

LARSON: I am a senior investigator at the National Cancer Institute, and my lab is located in the Laboratory of Receptor Biology and Gene Expression.

ZIERLER: OK, and what exactly is the relationship between NCI and NIH generally?

LARSON: So the NIH is composed of, I think, 27 institutes thereabout.

ZIERLER: Yeah.

LARSON: Each institute has its own organizational structure. NCI is unique. It's the largest institute, of course, which is a holdover from the war on cancer in the '60s and '70s. It's also unique because it's the only institute that it gets—funding comes directly from Congress. So all the other institutes are funded under one omnibus through the NIH. The NCI is funded individually, and its director is a presidential appointee, direct presidential appointee.

ZIERLER: Uh-huh. So your employer is NCI or NIH?

LARSON: NCI.

ZIERLER: Uh-huh. That's what the checks say, NCI. [laugh]

LARSON: That's right, yeah. Well, I think the—

ZIERLER: From whenever the last time we got checks. [laugh]

LARSON: Yeah, and the Health and Human Services is the agency, and then National Cancer Institute is what I list as my affiliation.

ZIERLER: OK, great. OK, so let's start at the beginning. Tell me a little bit about where you were born.

LARSON: Sure. I was born in Madison, Wisconsin. My parents were grad students at the University of Wisconsin both in microbiology. And I—

ZIERLER: So this is destiny, basically. [laugh]

LARSON: My—both my brothers are scientists.

ZIERLER: Really?

LARSON: My parents are scientists. Yeah, it's in the blood, I guess.

ZIERLER: So three boys?

LARSON: Three boys.

ZIERLER: OK, where are your brothers?

LARSON: One is in San Francisco, and he works for a biotech company. They also—they both also were trained in the physical sciences both as chemists. The youngest one is now—

works on—in biotech sequencing blood to try and diagnose cancer. It's a field called liquid biopsy. The middle brother went into oceanography and then left eventually to sort of rebrand himself as a big data person. So he now works in finance but using a lot of the same things that he learned in that field.

ZIERLER: So he makes the money out of all of you?

LARSON: Yeah. Yeah.

ZIERLER: [laugh] And you're the oldest?

LARSON: I'm the oldest.

ZIERLER: OK. OK, so your parents were grad students at the University of Wisconsin.

LARSON: Yeah.

ZIERLER: And then where did they go from there?

LARSON: So after that, they both went, well, to Cincinnati. Sorry, no, they went to—my dad did a postdoc at Cornell in Ithaca, New York. And then after that, he took a job as a lab head at Procter & Gamble, so—in their—doing basic science at—in microbial ecology and whatnot.

ZIERLER: Uh-huh. In Cincinnati?

LARSON: In Cincinnati.

ZIERLER: OK.

LARSON: And then my mom didn't work when we were young, so she stepped back from the workforce. And we basically grew up in Cincinnati, and my parents still live in the same house that we grew up in.

ZIERLER: OK. Your mom finished her degree?

LARSON: She finished with a master's.

ZIERLER: Uh-huh, in?

LARSON: In microbiology.

ZIERLER: OK, did she re-enter the field at some point?

LARSON: She did. She eventually went back to work as a lab technician at Procter & Gamble. She taught high school biology for a while as well. So always in the sciences but never an independent investigator.

ZIERLER: Uh-huh. So powerhouse science family? The Larsons of Cincinnati. [laugh]

LARSON: It was a lot of science. Yeah. [laugh]

ZIERLER: And so how long was your dad at Procter & Gamble? Most of his career?

LARSON: He spent his entire career there. Yeah, retired in his late 50s.

ZIERLER: Uh-huh. Did he move up into administration, or he stayed in the sciences the whole time?

LARSON: Always stayed on the science track. It's—at Procter & Gamble, there is a science track and an executive business track, and he sort of went as high as you could go on the science track.

ZIERLER: OK. OK. So growing up, was it just sort of like so obvious that you were gonna enter into the sciences, or do you feel like—

LARSON: Yeah.

ZIERLER: —you pursued that more on your own?

LARSON: Well, it was strongly emphasized. It was assumed at some level [laugh] that we would go to graduate school. They—I don't think there was rules about it. I think technically I could have done other things, but that was obviously what I was around. I started off college as an engineering major, which I didn't like very much, and switched to literature for a while, and then eventually ended up in physics, actually.

ZIERLER: OK. So in high school, you were, I assume, like AP sciences and all of that stuff, right?

LARSON: Yeah. Yeah.

ZIERLER: Right. OK, and so you went to Ohio State University.

LARSON: That's right.

ZIERLER: You said you started in engineering?

LARSON: Yes.

ZIERLER: So why not just start right with biophysics? How come you—

LARSON: Yeah, so that's—

ZIERLER: What was the idea there?

LARSON: Yeah, that's a—

ZIERLER: A little bit of rebellion, maybe on your part? [laugh]

LARSON: Well, no, it's funny, my—I—the school I went to, a lot of kids declared in engineering. It was just the thing to do for kids who were—who had sort of a scientific inclination. So that's sort of what I started for. And the class that really did me in was the technical drawing class in engineering. And I had this view maybe rightly or wrongly that engineering was this really circumscribed field, and they were really obsessed with details. And it wasn't what I had remembered liking about science in high school. And then—and this drawing class really distilled that for me because they would mark down on your papers if you went outside the lines and stuff. And it was really—it was kinda juvenile, but—

ZIERLER: So you figured out early on like gene expression was where you were at basically?

LARSON: [laugh] Yeah, so then I looked at biology then, thought maybe I would want to do a genetics major, molecular genetics major. And also I felt that the biology side was—a lot of the exams were very fact-based recalling minute details of enzymology. Again, not what I thought was a good fit for me or what I was good at. And so the reason I got into physics is I was just taking the standard physics for science majors class, and I was basically just acing it. I hadn't

missed a question all semester. And I had this TA, my teaching assistant, who I became friends with, and she was a spectroscopist in the physics department. She was a grad student.

ZIERLER: What was her name?

LARSON: Karen. Karen Kepler. And she was descended from—

ZIERLER: From Johannes?

LARSON: Way back when, from the original Kepler, yeah.

ZIERLER: Whoa.

LARSON: Yeah, so she—it's funny, I hadn't thought about her in a while.

ZIERLER: [laugh]

LARSON: And [laugh] I had a little bit of a crush on her too.

ZIERLER: [laugh]

LARSON: But anyway, we—so I had said, "Hey, do you want to get a coffee sometime?", and I—we were talking. I said, "I'm looking to maybe get a job on campus just to—just for something different," and she said, "You should work in the physics department."

ZIERLER: OK, so you're like a sophomore at this point?

LARSON: A sophomore, yeah.

ZIERLER: It's a bold move asking a TA for coffee as a sophomore. [laugh]

LARSON: Yeah, and I think she sort of deflected that very kindly by suggesting we play racquetball. [laugh]

ZIERLER: OK. [laugh]

LARSON: And so anyway, she said that I—she said, "You should get—you should work in the physics department instead of just working at some random coffee shop." And so she walked me around the basement of the Ohio State physics building, a building called Clark Hall and basically said, "Do you have room for an undergraduate?" And she was really complimentary and saying, "He's acing the class, and he's got a bright future," et cetera.

ZIERLER: And this was just like a physics 101? This is where you started essentially?

LARSON: Yeah, yeah. And she said—and so one of the labs that she knocked—whose door she knocked on was a guy named Linn Van Woerkom who is—was doing laser physics, ultrafast spectroscopy, kind of in the branch of physics atomic, molecular, and optical (AMO). And he was a young guy and really engaging. You could see why someone would want to work for him. And he said, "Yeah, you can work in my lab."

ZIERLER: Oh, wow, OK.

LARSON: So I just started working in his lab, and I had a pretty reasonable background in electronics and programming, so I could do stuff like that. And they kinda put me on various tasks, and there was four or five grad students in the lab, no postdocs. He was new. He was untenured at Ohio State. And he—so I worked there for the whole year. And then that summer I went home, and I think I took organic chemistry or something, some courses at the—at a local

place, and came back, continued to work in the lab, and he suggested that I do an undergraduate thesis in his lab. And so at this point, I just declared as a physics major.

ZIERLER: OK, so a thesis is like as an honor student or—

LARSON: Yeah.

ZIERLER: OK.

LARSON: That's right, yeah.

ZIERLER: OK. OK, so what was the lab work? What was your thesis on?

LARSON: The thesis was on building a femtosecond laser. So at the time, most of these short pulse lasers were on the order of 100 to 200 femtoseconds, and recently a new design had come out where you could use a shorter crystal and maybe build a 10 to 15 femtosecond-ish laser. And that was gonna be my undergraduate thesis project, was to build one of these lasers and use it to do some spectroscopy. So involved optics and some machine shop stuff. And I wrote a proposal, and I got a research award from the college. And so my junior summer was something like $1,500 that was able to fund me for the summer.

ZIERLER: Wow.

LARSON: [laugh]

ZIERLER: Now, are you tinkering with the equipment to do this, or are you working with engineers? How are you building this?

LARSON: Yeah, so you—some of the things are off-the-shelf components, optics, holders, and whatnot. But basically you're building a—some hardware, in this case, some cooling hardware for the crystal and basically trying to assemble these things and align them and then do diagnostics on the laser to see how well it works when you finished it.

ZIERLER: Uh-huh. And what was the basic research question you were trying to answer from this process?

LARSON: Yeah, it wasn't—I would say it was not as clear. The idea was that we were gonna build this, and this is gonna be useful. And then—

ZIERLER: Useful for what? What application?

LARSON: For doing the spectroscopy. So looking at atomic spectra in gases. So you would—once you had the short pulse laser built, you would shoot it into a chamber containing—I think we're doing a SFO. Maybe I'm misremembering that. But anyway—and you would see the sort of—and the interesting thing about—at that time was that these lasers produce such strong electric fields that the electric fields were comparable to the fields that would hold electrons to the nucleus, right. So you're—this is not the usual type of spectroscopy where you would look at fluorescents or absorbance. You were fundamentally driving these electrons with very strong fields, and so you would—you saw different things than people had seen in the past.

ZIERLER: Yeah. Was your sense at the time this is pretty advanced stuff for an undergraduate to be involved in, working mostly with other graduate students?

LARSON: Exclusive with other grad students, yeah. And there were a few—and there are other grads—undergrads in the department who did research projects and some even in AMO.

ZIERLER: What is AMO?

LARSON: Atomic, molecular, and optical physics, which Ohio State was strong in. And I had a buddy—he's still a friend to this day who—we went to grad school together too—who worked on cooling and trapping of atoms. And so he was also in the basement just down the hall, and there was another—a guy—an undergrad working in solid state physics on his thesis. And so there was maybe like a handful of us doing undergraduate research in the department.

ZIERLER: Uh-huh. OK, so at this point, you're not specifically on a health sciences track? This is more like—

LARSON: Not at all.

ZIERLER: —pure physics.

LARSON: Yeah.

ZIERLER: You're sorta wide open at this point in terms of your next move.

LARSON: That's right. That's right.

ZIERLER: So you graduate, and then you stay on as a teaching assistant at Ohio State, right?

LARSON: No, no, I was a teaching—I taught some lab classes while I was there. So that was—

ZIERLER: As an undergraduate?

LARSON: —as an undergraduate, yeah.

ZIERLER: Oh, wow.

LARSON: So doing some—

ZIERLER: Did you need to get—what business does an undergraduate have doing that?

LARSON: [laugh] Yeah.

ZIERLER: Did you get special dispensation?

LARSON: I think I was just helping with lab stuff, right? They would have these lab classes and—

ZIERLER: OK, were you leading discussion sections or anything like that?

LARSON: Yeah.

ZIERLER: Wow, really?

LARSON: Yeah.

ZIERLER: That's—[laugh]

LARSON: Yeah, uh-huh.

ZIERLER: Were they paying you for this? Did they give you a break on tuition?

LARSON: I don't remember if they paid me or not.

ZIERLER: So free labor [??]

LARSON: I think they did actually. I think—I think I did get paid.

ZIERLER: OK.

LARSON: I think I did get paid.

ZIERLER: This is unusual stuff to have—I mean, it's one thing, I guess, a whiz kid who's working in the lab, but to actually be teaching other undergraduates—

LARSON: [laugh] Yeah, well, the thing that—so I think—I don't think I was unique. I think basically the upper level physics majors would help teach lab classes for the section, the track, which was I think the physics for poets kinda track. So this would be a first-year physics for people who had no intention of being science majors, and that's what—I think what we were dealing with.

ZIERLER: Right. Did you teach Paul Hewitt's book, *Conceptual Physics*, by any chance?

LARSON: No.

ZIERLER: That's one of the standard textbooks. I interviewed Dr. Hewitt.

LARSON: Oh, yeah?

ZIERLER: Yeah, he's—it's 13th edition now. He used that phrase also, physics for poets, basically.

LARSON: I don't remember what we taught out of. There was a physics education group at Ohio State directed by a guy name Alan Van Heuvelen. And he had kind of lots of—and so they were fairly innovative in how they're teaching this stuff, and so maybe we were using in-house textbook. I can—yeah.

ZIERLER: OK. OK, all right, so you graduate, and then—

LARSON: Yeah, so the transition of biophysics, which I think—I do think there's some historical interest in this, which—and I very—remember very distinctly there was a few of us. And the general—

ZIERLER: Few of us at OSU?

LARSON: Yeah, undergrads, and we were—I—around the time I was a junior or senior, I was starting to think that I would go to graduate school. Really when I was a junior, I started to think I would go to graduate school, and trying to decide what that would be in, right? So I was just talking to other folks in the department, high energy people, solid state people.

ZIERLER: Is there any one particular mentor that you're working with, or you're really talking to a bunch of professors?

LARSON: I talked a lot with Linn, my research mentor. There was a guy, younger guy named Bob Perry who was very close to the undergrads, and he was very accessible, and he was a theorist. I remember talking to him. There was a professor we had, Dick Furnstahl, who was also a good mentor, and then one—a person I admire greatly who is a statistical physicist named—what was his first name? His last name is Jayaprakash, Ciriyam Jayaprakash. And so I had a sense that I wanted to do biophysics, and I wanted to go in that direction. I felt like it was more open. It was less hierarchical. I didn't want to be a high energy physicist. I didn't see a lot of AMO stuff that looked strongly interesting to me.

ZIERLER: When you say less hierarchical, is that because there's the interdisciplinary nature of it that naturally allows it to be less hierarchical? Is that the idea?

LARSON: Yeah, it's partly and partly because I got the sense that you can make significant advances with small teams working in modest lab environments as opposed to going to an accelerator or large projects. But it seemed more wide open to me. It seemed like I could conceptualize biological questions easier than I could conceptualize physics questions.

ZIERLER: I see. Interesting. But you're not yet specially motivated by advancing human health? You're not on that wavelength—

LARSON: No.

ZIERLER: —at this point?

LARSON: Not at all.

ZIERLER: Interesting. OK, so you settle in on biophysics.

LARSON: So Ohio—so there was normally a biophysics department at Ohio State, and—

ZIERLER: OK, as a subset of the physics department?

LARSON: No, not at all, and when we made this discovery, several of us, we were sorta floored that this existed, and so we—

ZIERLER: How could you not have known? [laugh]

LARSON: Right, and it was way across campus, and we went over to talk to the woman. Her name was either Carol Gross or Elizabeth Gross, I think Carol Gross, and we said, "Well, what's all this about? Tell us about biophysics." And it was really different than what I imagined. It was basically mostly structural biology. So X-ray, crystallography. That was what passed mostly for

biophysics. But Ohio State had at the time—there was no biophysics subdiscipline in Ohio State. That was not—but they did have a—an undergraduate option which was called a B.S. Track Two where you could substitute upper level physics courses, Lagrangian mechanics, that sorta thing, for other courses in science. So you could instead of taking advanced mechanics or particle physics, you could take physical chemistry or biochemistry, and so that's what I did. So I switched to this other option in physics where I could use my senior electives to take upper level courses in other departments.

ZIERLER: And the physicist department was happy about this?

LARSON: They—this is something that I think was pretty unique to that department, and they were totally fine with this. They encouraged it. So I took a year of physical chemistry from the chemistry department as an upper level advanced elective, and I took biochemistry in the biochemistry department.

ZIERLER: Uh-huh, now the professors in the biophysics department or proto department or whatever it was called, were their degrees in biophysics? Was that a thing at that point?

LARSON: I don't know.

ZIERLER: 'Cause your PhD is in biophysics, right?

LARSON: It is.

ZIERLER: As a proper discipline, right?

LARSON: It is, yeah. Yeah, there were programs. Hopkins is a longstanding program, but again, I think they mostly came from the biology side and did things like X-ray crystallography or maybe ion channel or—

ZIERLER: Right. When you say it's across campus from where you were, I assume it was probably closer to the biology department.

LARSON: It was. It was in the biology campus.

ZIERLER: OK, so you got deep into that. You loved it.

LARSON: So anyway—so I did that, and then I was, again, looking at things that I might do, people I might work for. And there was a whole side of—a burgeoning area of microscopy of what was called multiphoton microscopy, which was using the lasers and the techniques that I had used as an undergraduate. So I thought this might be a nice bridge, that I could—my background in optics might allow me to be competitive for getting into some of this other programs and be a good background for doing microscopy. So that was the sorta conceptual leap for me. And then in terms of the places that were doing this, kinds of microscopy and really using high-end optics for biology, there were relative few places. So that strongly colored where I applied for graduate school.

ZIERLER: OK, I see. I see.

LARSON: Right? And so the places that I looked at are places like Hopkins, UC San Diego, which had a guy using these multiphoton microscopies to do—multiphoton microscopy to do neuroscience, and then Cornell, and there was the inventor of this technology, a guy name Watt

Webb. And Watt was—I don't think I quite appreciated this at the time, but really, a pioneer in optics and biology, using optical approaches in biology.

ZIERLER: Right, right. OK, so Cornell, that was your spot?

LARSON: So that's where I—so I applied there.

ZIERLER: Straight through? You didn't take a break from undergraduate?

LARSON: Correct, yeah.

ZIERLER: What did you do the intervening summer? Did you get to Ithaca right away?

LARSON: Yeah, I remember—no, I didn't go to Ithaca right away. It was pretty laid back. I think I traveled around with some friends. I worked in the lab again that summer a little bit, but I think Linn knew that that was a lost cause.

ZIERLER: [laugh]

LARSON: [laugh] And he was—looking back on it, I probably wasn't the most diligent. So—

ZIERLER: So you get to Cornell—

LARSON: So the thing about that application was—so he was—so Watt was a National Academy member. He—I went to the visiting days of Cornell, and he basically put in a personal pitch. He's like, "I think you should come here, and I think you should work in my lab." And when I came back to Columbus after that visit, there was a handwritten—a typed letter but sent in snail mail—it was in my apartment mailbox—basically saying, "I really enjoyed talking to

you. I think you should come work in my lab." And it just had a huge impact. I still have the letter. It just had a huge impact on me that he would take the time to do this. And so basically, I accepted, agreed to go there with the intention—knowing that I would work for Watt. So that's—so then I went—I changed my application, which had at the time been to the physics department, which was his—one of his home departments. He was in engineering and physics, and he said, "You should change your application to the biophysics program at Ohio State because it will be easier for you to get a training grant."

ZIERLER: Uh-huh, it's good advice. Did it work?

LARSON: So that's—so I did get this training grant, but I was admitted and then did my PhD work in the biophysics program, which didn't have a department. It wasn't a building, so you always had to have a home department, but it was the biophysics program at Ohio State—or at Cornell.

ZIERLER: Cornell.

LARSON: Yeah.

ZIERLER: And so what was the home program for you at Cornell?

LARSON: So I was located in the—oh, sorry, I was located in Clark Hall. Cornell was Clark Hall. Ohio State was Smith Hall. So I was in the building which housed physics and applied and engineering physics. So those are the two separate departments, and they were in this building.

ZIERLER: OK, and then what's the breakdown at the beginning at least between lab work and course work? How much are you sitting in classrooms? How much are you in the labs?

LARSON: So the first year was pretty heavy in coursework, and I took a mix of things that statistical physics people took, physical chemistry from statistical physics from a guy named Ben Widom [??], quantum mechanics, which was—had a spectroscopy angle, that sorta thing. And so it's more molecular physics, I guess you could say, was my first year coursework. I did some rotations, but they were pretty minimal, and the first year was largely coursework. But Cornell actually had a pretty minimal coursework requirement. They were very—that was the other thing that was attractive about that, is they were pretty independent at—or forward-looking in the sense that, yeah, you can—the—what constituted physics work or—there was someone doing their PhD in physics who was working on psychology and neuroscience. They were more forward-looking. But going back—so the thing I wanted to say at—I forgot to mention, at Ohio State is that when we approached people about doing biophysics, they were a little bit reluctant, right? There was a sense at the time this was not—this was squishy, and—

ZIERLER: When you say we approached people—

LARSON: Undergraduates.

ZIERLER: —whose the we, the undergraduates?

LARSON: Undergraduates. There was a group of us. It was like three or four of us were interested in biophysics. And there was a sense that, well, this wouldn't fit in their—in the Ohio State physics department, and that's why they had suggested do this option two. And—but I think they realized that there was more and more interest in this. So when we were there, they actually established—the physics department established sort of an exploratory committee with some faculty and student representatives and grad students to assess the idea of having a biophysics discipline within the physics department.

ZIERLER: Mm-hmm.

LARSON: So that didn't—so that biophysics discipline in the physics department didn't exist when I was there, but this exploration, this committee must have decided this was worthwhile 'cause eventually they did start a biophysics subgroup in the physics department, which is now thriving at Ohio State. So that was—we were kinda right on—

ZIERLER: In addition to that other department?

LARSON: Yes, so now there is—there are five or six professors at—in the Ohio State physics department doing biophysics, all of whom were recruited after I graduated in '97. So it did grow there, but it was—they were a little bit more deliberate in that regard. I think, say, Cornell was, but it was already accepted as a bona fide subdiscipline of physics.

ZIERLER: So the program at Ohio State, were they—when this new department—sub-department developed, were they working across purposes? Were they collaborating?

LARSON: I don't—I think there was very like discussion between them.

ZIERLER: Interesting.

LARSON: I think they just sort of decided this was—the other department was too biology. It was not biophysics the way it should be done in a physics department, and there was very little discussion.

ZIERLER: Right. So once you're getting comfortable at Cornell, your initial thoughts about going into biophysics because it's not hierarchical, because it is more open, was that confirmed? Did you feel like your hunch was correct?

LARSON: It was great.

ZIERLER: Yeah?

LARSON: Really—I really loved the type of work that was going on in the lab. It was very stimulating environment. You could work largely by yourself or with a small—maybe a collaborator, and there was no shortage of questions. It was just way easier for a younger person to navigate ideas, I felt.

ZIERLER: Sure, sure, and in terms of professors, is it mostly you're working with Watt, or there are other professors you're working with a lot also?

LARSON: Yeah, so I worked—I—so Watt was the—I guess the motivation of a lot of the work of Watt's grad students would be to develop some new technique, some microscopy technique usually optically based and find a biological problem that you could apply it to. So I built this microscope when I was there.

ZIERLER: Oh, as opposed to the other way around?

LARSON: Yeah.

ZIERLER: There's a biological problem, and then you reverse engineer.

LARSON: Yes.

ZIERLER: Is that a unique—I mean, intellectually, is that a unique way of doing things, or that's pretty standard in lab work?

LARSON: I think it's pretty standard in biophysics, which can be very technique-driven. I don't—it's not what we do now. Now we're more question-driven, biology-driven. I thought it was a good training environment. So basically, I was just let loose. I had my own room. I'd built my own microscope, and I collaborated with two labs primarily. Excuse me. The first was a laboratory working on the plasma membrane. So trying to do very precise measurements on receptors in the cell membrane. The woman who ran that lab is Barbara Baird, and she worked very closely with her husband who was also a senior scientist in that lab, Dave Holowka. So I worked closely with them, and I worked closely with a—in a—with a retrovirus lab in Volker Vogt. This lab was run by Volker Vogt. And so I built this microscope. It was really good at measuring interactions between biomolecules, and both of these labs had questions that could be answered with this microscope.

ZIERLER: So you build a microscope. If you're doing—it's the technology, and then you see what the biological practical influence of it is.

LARSON: Yeah.

ZIERLER: How do you know what to look for in terms of what it's good for? How do you know what to put under the slide in the microscope that says, oh, this is really good for x, y, and z? How does that work?

LARSON: Yeah, so they had the biological questions already ready. So in retrovirus biology, the question was how does the viral capsid assemble in cells, in living cells. There were no good techniques for looking at that, right? And so that was—we approached that question with this new microscope, this multiphoton microscope that I had built. So—

ZIERLER: And is it still the same model going back to your undergraduate where it's like off-the-shelf components that you're assembling in novel ways? How were you—how does that work? As opposed to like you think a Fortune 500 company that has the capacity to do whatever it wants, a graduate student working at a lab, how are you building a microscope that's never been built before and it's so good that it's actually answering these biological questions? Just walk us through the mechanics of that. How does that work?

LARSON: Yeah, so you—some of the things are off-the-shelf. Some of the things you build in a machine shop. Some things you might collaborate with industry on, right? So for example—

ZIERLER: So were you doing that?

LARSON: Yeah.

ZIERLER: You were collaborating with industry?

LARSON: Yeah, so for example, one of the novel things in this microscope, which is now standard in all laser optical—well, almost any microscope which uses laser scanning, was a new type of photomultiplier tube called a gallium arsenide phosphide.

ZIERLER: Should be called the Larson microscope, right?

LARSON: [laugh] And these photomultiplier had some advantages over existing photomultiplier tubes. They're a little bit more sensitive. They were sen…higher signal to noise. They had slightly different spectral response, which was conducive to light microscopy. And so working with another senior scientist in my lab, in Watt's lab, the lab that I was in, we started using these to build a new type of laser scanning microscope. OK, so the genesis of the

microscope is then, well, we want to use this type of detector, and we want to use this type of laser, this multiphoton laser, this short pulse laser 'cause then it has advantages for sci…so how do we design something where these are the two main features? So then you start drawing optical pathways and thinking about the optics that are gonna be in between. You start thinking about what objectives you want to use that would be advantageous for this. And so some of these pieces are out there. Some—and you have to repurpose them. Some of this is electronics on the backend to analyze the signal that comes out of this photomultiplier tube. And then—and some of this is repurposing existing microscope equipment. So maybe a microscope stand from Zeiss or a scanner from Bio-Rad. And then you want all these things to be lined up properly, and you want the detector to be in a very specific place that can—and maybe it can move in small increments, maybe you want it to move in x and y and z. So then you say, oh, we have to go the machine shop to build something, which is gonna precisely position this camera. So that's the kind of—so least that's how it worked for me.

ZIERLER: Uh-huh, uh-huh. Now, are the retrovirus people—are they answering the biological questions? Are you sort of handing the microscope off to them and they're answering, or you're involved in that as well?

LARSON: No, it was the other way around. So basically, they say, "Well, we can make these proteins, or we can clone these genes, and we can make them fluorescent," and once they do that, then they would come to us, and we would grow the cells. And we would do all the—putting these genes into cells so we could see them, and then all the microscopy would be done in my room with the biology collaborator sitting next to me. So we're looking at the cells together. We're trying to decide what looks right, how do we do this measurement. Then we start doing the measurement, and then all the data analysis would have been done by me. And then now

you're going—now you're doing this back and forth between, in this case, me and my collaborator, who's also a grad student in this other lab, a woman named May Ma. And they're sort of saying, "Well, this looks interesting. We should pursue this further in this way. We should test this more." So maybe I can make a different version of the protein and see how that behaves in the microscope. So at that point, you're sort of running in the open field, right? You have some ideas. You have initial data. It looks like the approach is working, and you're just sorta iterating it to get to the biological answer.

ZIERLER: Uh-huh, uh-huh. And is this a natural progression into your dissertation, or this is its own separate project?

LARSON: This was part of my dissertation.

ZIERLER: OK, OK, and at this point, are you thinking about grant writing? Are you thinking about articles, or you're just deep in the lab, you're not involved in sort of external considerations at this point?

LARSON: So we were—we did write grants. We did aid mostly the senior people at the lab who were doing the writing. So grad students that participate in that. And Watt also ran a center sorta had some official status as a funded center where people who wanted to use these cutting edge microscopy techniques could come into the center and do that.

ZIERLER: Yeah, yeah, OK. All right, so at what point are you getting ready to defend your dissertation? What year are we in now?

LARSON: So I finished—so most of my work came out in my 5th year of my PhD, right?

ZIERLER: OK, so 2003? 2002, 2003?

LARSON: Yeah, exactly. Yep. And so there was a long lag time partly because I was building this instrument, partly because I was also learning biology. So I was now taking some courses in the biochemistry department, the molecular biology department.

ZIERLER: This is your own motivation?

LARSON: Yeah, yeah, and we're—

ZIERLER: What did you feel you needed—what did you want these courses to do for you?

LARSON: I wanted to learn—so I could tell that I was gravitating towards cell biology as a discipline, and I liked—

ZIERLER: Right, but still as a physicist?

LARSON: As a physicist, yeah, yeah. And the thing that I liked most about this work, which I still love is there's something about microscopy, seeing a cell live, which is—

ZIERLER: So what does that mean, seeing a cell live?

LARSON: It's crawling around. It's doing stuff. The cell, for all intents and purposes, is the smallest unit of life. It makes decisions. It divides. It grows. You can't—an enzyme is inert. It's a molecule. You can do interesting biophysics. You can do structural biology, but it's not alive, and cells are alive.

ZIERLER: Yeah, yeah. Is there such a thing as seeing a cell dead? What's the difference between a live cell and a dead cell?

LARSON: Oh, we see lots of dead cells. [laugh] They change shape. They stop moving. There are more quantitative metrics of dead and alive, but that's basically what you see.

ZIERLER: Is it simply the difference between taking a cell out of something that's living versus something that's dead? Is it this—

LARSON: No, you have cells—so you can—there are cells which will grow indefinitely never coming from an organism. So there are human cells called cell lines that we work with which can just be grown in a dish, and HeLa cells being the first example of that, right? They were—they came from a patient. They came from a woman who had cancer, but those cells could be grown in plastic, and you can freeze them down. You can thaw them, and people have been doing that for decades, the same cells from the same patient.

ZIERLER: So there's just something visually exciting to you—

LARSON: Yeah.

ZIERLER: —about being able to see what these cells are doing?

LARSON: Yeah.

ZIERLER: And specifically with these microscopes, you cannot see what's going on unless you're using these microscopes? What's unique about these microscopes?

LARSON: Yeah, there's all different types of microscopes out there. Lots of microscopes can see living cells. The mic…at the time, what was unique about these microscopes is we could really probe interactions which were occurring on very small length scales. So most people who were doing microscopy then, you'd look at your cell, you could see the big things. We could see

things—interactions were occurring on length scales which were shorter than the wavelength of light, and so that's classically been a resolution barrier. You can't resolve things less than the wavelength of the thing you're using to look at. That's why you use X-rays versus visible light for some—for crystallography. But we had developed approaches to beat that, right? And so my thesis work, the physics part of the thesis was how do we probe these length scales on the nanometer scale, and these are the biological questions we solved using these approaches.

ZIERLER: So when you're looking to beat the previous approach, in terms of what? In terms of efficiency? In terms of resolution?

LARSON: Terms of resolution.

ZIERLER: Uh-huh, and so just obvious question, what's the advantage of seeing something at a higher resolution?

LARSON: That's—if you're trying to understand the interactions between biological macromolecules, that's the length scale you have to look at, right?

ZIERLER: OK, and then to probe this further, why do you want to see those interactions?

LARSON: Right. So for example, a retrovirus particle—so retrovirus is like HIV, or they were looking at a chicken virus called RSV, Rous sarcoma virus. The whole virus, the whole thing when it's finished and made is only 100 nanometers, right? So—

ZIERLER: Tell us—tell the audience what 100 nanometers is. How big is that? [laugh]

LARSON: [laugh] 100 nanometers—so a nanometer is 10 to the minus 9^{th} meter, so this is 1 times 10 to the minus 7^{th}. So less than a millionth of a meter. Trying to think of some—

ZIERLER: [laugh]

LARSON: —a human hair is probably like couple microns, so this would be 10 to the minus—so this would be 1,000 times smaller than that roughly. So you're trying to see this thing which you can't see with light. You can't—the wavelength of visible light is not—which is on the order of 300 nanometers, is too long to be able to see all the bits and pieces of this retrovirus. So you can't just look at it and see the shape of a retrovirus. You had to develop tricks to do that, and that's—those are the tricks that we worked on. So we used things called fluorescence resonance energy transfer or Förster resonance energy transfer (FRET). We used diffusion measurements, all these ways to infer how this virus was assembling in the cell.

ZIERLER: Yeah, yeah, and to be able to see it, is that the first step toward what, to antibodies, to a cure? What's the endpoint?

LARSON: Yeah, so exactly. Understanding how a retrovirus assembles could lead to small molecules or drugs which would stop it assembling. So that would be—those would be antiviral therapies. So at the time, it was pretty clear that there were antiviral therapies being made, and most of those antiviral therapies, which resulted in the famous sorta triple drug cocktails, which we now use to—

ZIERLER: For HIV?

LARSON: —basically control HIV infections, targeted things like integration of the virus into the host genome. It's a human genome. So that would—that was an antiviral therapy. The most famous ones, the first line were the so-called protease inhibitors, and these were things that stop the virus from developing into a fully infectious particle. So if you could inhibit this

protease, which wasn't present in human cells, you could—this was an antiviral therapy. And at the time, and I think this still may be true—I don't know for sure—there were no drugs which targeted assembly of the virus, which is what we are working on.

ZIERLER: What does that mean, assembly of the virus?

LARSON: How all this virus came together to make the thing that would leave the cell and infect other cells. That's assembly, and that's what we were trying to understand.

ZIERLER: Assembly makes me think of a factory. Is that a fair metaphor, that there's a place where these viruses are being assembled and like off of the conveyor belt kinda thing?

LARSON: Yeah, that's a fair metaphor. So you have to take—there's a protein called the capsid protein, and the name of it is Gag, and this capsid protein is present at nearly 1,000 copies in the finished capsid. The capsid is the thing you—whenever you see a picture of a virus, that's the capsid. So 1,000 of these individual protein somehow have to come together to seal up the genomic material of the virus and then escape from the cell, and that is assembly. And where it happened and how these individual capsid proteins came together was not known then. I still don't think it's fully known. And there was some in vitro biochemistry, test tube biochemistry, but there was nothing which looked at this process in the cell. So we were kinda pioneers at looking at how this assembly of a retrovirus happened in the cell.

ZIERLER: OK, all right, and then—

LARSON: And that was done with a microscope which we built. Yeah.

ZIERLER: Right, right. And then just specifically, your dissertation, its title, the topic, what was the actual research question?

LARSON: Oh, do I have the title? [laugh]

ZIERLER: [laugh]

LARSON: It's here somewhere. I think it's—

ZIERLER: This is really funny. You don't have the title at your fingertips.

LARSON: Oh, here it is. [laugh]

ZIERLER: [laugh] Here we go. OK.

LARSON: OK, so the dissertation title was Optical Approaches to the Study of Nanoparticles in Biology, Quantum Dots, Silica Dots, and Retroviruses.

ZIERLER: What are these dots, quantum dots, silica dots?

LARSON: Yeah, so it turns out that the microscope that I had built to look at assembly of—to interrogate objects which were smaller than the wavelength of light, sub resolution objects, you could also use it to look at materials. And so by materials, we were trying to develop new types of probes to use in live cell microscopy, and those probes, the ones which are more famous are called quantum dots. And those are heavy metal chunks, little crystals which are on the order of 10 nanometers. And this was I think a pretty big advance. We were working with material scientists who made these, and we were trying to characterize how they worked in solution and in cells. And so that was done on the same microscope, and a lot of the same approaches could

be used for looking at retroviruses and quantum dots. And these quantum dots would be—go on to become a product, a commercial product which is still in widespread use today.

ZIERLER: What kinda products? What kinda commercial value—

LARSON: They use 'em for everything from imaging in molecules and cells to animal imaging. Quantum dots are also used in displays. There's other nonbiology applications too. Yeah.

ZIERLER: Uh-huh. So while it's on your lap, who's on your committee?

LARSON: So that you have a better memory of.

ZIERLER: [laugh] Watt was your—was he your director?

LARSON: Watt was—he was the director of the committee. Barbara Baird was on my committee. There was—I'm trying to remember who officially was—Lois Pollack, a woman who did—who was a younger PI.

ZIERLER: You had an outside reader?

LARSON: Cornell didn't do that.

ZIERLER: Oh, interesting.

LARSON: And we didn't do a public defense either.

ZIERLER: How'd you know you passed?

LARSON: They just kind of [laugh] shake your hands.

ZIERLER: [laugh] OK.

LARSON: Was Volker on my commit…so my—Manfred Lindau. He was biophysics member in the department. And I can't remember Volker—he was my—he was the retrovirus collaborator. I can't remember he was an official member or just sort of a consigliere—

ZIERLER: [laugh]

LARSON: [laugh]—it's funny that those—all those det…even the title of the thesis kind of escape me. Just [laugh]—and there's no—

ZIERLER: 2004. It's 16 years already.

LARSON: Yeah, so—let's say—let's go—for the sake of posterity—

ZIERLER: [laugh]

LARSON: —let's say Watt Webb, Barbara Baird, Manfred Lindau, and Lois Pollack.

ZIERLER: OK, so 2004, what's your next move? What are you thinking at this point?

LARSON: So—

ZIERLER: Is there an option to stay on as a post-doc if you wanted to, or you want to leave?

LARSON: Sure, that was not something I considered, and I don't think Watt would have—I think he wanted me to—

ZIERLER: There's a big world out there.

LARSON: Exactly. Yeah, it's not—it certainly happens in rare circumstances, but it's not always advisable. Also, I had—at this point, I had spent my 20s, I think, in New York.

ZIERLER: Yeah, yeah, that's right. That's right.

LARSON: [laugh] So—

ZIERLER: [laugh] I'm from Utica, so I know all about it.

LARSON: Oh, really?

ZIERLER: Yeah, yeah.

LARSON: Oh, OK. Well, one of the nice things about that is you make good friends.

ZIERLER: Sure. That's right. That's right. [laugh]

LARSON: [laugh] You—so we—was—Utica Club—is that the—

ZIERLER: That's it.

LARSON: That's the—

ZIERLER: Very good. Sure. [laugh]

LARSON: [laugh] So I had—I—around this time, the Human Genome Sequencing Project was—

ZIERLER: This is like cutting edge stuff at this point, right?

LARSON: Yeah, was—basically parts of it had been complete. It was—certainly if it wasn't entirely done by then, it was like the lion's share of the work was done, it was clear that this was gonna change how biology was done. And so I had a vague sense that I wanted to do something, choose a post-doc that was related to genetics, genomics, which wasn't a term that people used at the time very much, gene regulation, something that was sequence adjacent. But I knew that I didn't want to be doing sequencing or doing biochemistry, and I wanted to stay with cell biology and preferably with microscopy. So I set off to find labs which I felt would meet those criteria, and there were remarkably few. So I wanted to be in a lab which was driven by problems in biology, that was more where the question came first.

ZIERLER: The other way around from how you were working is what is sounds like?

LARSON: Yeah, yeah, yeah, I wanted to—I didn't want to be known as—exclusively as a technique guy, right? I wanted to have some biology that I was connected with.

ZIERLER: How well were biophysicists represented in the genome world at that point? Would you have been a newcomer to this?

LARSON: Yes and no. There's always—there's a long history of physicists doing biology. You probably know it better than me, but even in the early days of molecular biology—

ZIERLER: Of course.

LARSON: and these kinda people—the person who in large part led—or was one of the of the Human Genome pro…Eric Lander was a mathematician. David Botstein, who developed the map—the method for mapping contigs, was strongly grounded in math and statistics and physical sciences. [laugh] But I think—so—but the labs where I was looking to work, I would

have been sort of the only physicist or the only biophysicist. They were mostly cell biology labs, and I think—I had published when I was—as a PhD student, I was an attractive candidate. And I think there was a little bit of a mystique like, "Oh, we're gonna bring this guy into our lab, and he's gonna develop some new microscopy technique, and it's gonna—we're gonna get a lot of good papers out of it."

ZIERLER: Right. So he's gonna do the techniques, but he's also gonna be interested in the biological questions.

LARSON: Yeah, yeah, yeah.

ZIERLER: So where'd you end up?

LARSON: So the problem with that is that I think a lot of traditional molecular biology or cell biology labs didn't have a sense of the time and money and resources that it took to develop new microscopy techniques. So you go to a lot of places, and they'd say, oh—they'd show you a corner of the—of one of the bays, a bench, and say, "You can build the microscope here." And you'd say, "Well, you need to have room, and you need to have optics table. And it's expensive, and I—it takes a while to do this stuff." And so the place that I ended up was Albert Einstein College of Medicine in the Bronx, and I felt, of all the places I looked at, they were the ones who had the deepest appreciation for developing new microscopy techniques and what you could really do with them. And they were willing to put their money where their mouth was.

ZIERLER: Now, I have to ask, as you're getting more interested into biological questions, does going for the MD—does that ever cross your mind?

LARSON: It didn't.

ZIERLER: OK, because that would have been a distraction in terms of what you were—your trajectory?

LARSON: It didn't, yeah. Not at all, yeah. And I still was sort of ambiguous about whether I wanted to be an academic or PI lab leader or whether I would go a more industrial route.

ZIERLER: Right, but interacting with patients, that's was never—

LARSON: No.

ZIERLER: —an interest of yours?

LARSON: No. In fact, I didn't really even have an appreciation for what the medical school environment was, and it's different from the university environment.

ZIERLER: So Albert Einstein you looked at as a medical school that had a lab as opposed to a lab that had a medical school?

LARSON: I looked—no, I was interested in the lab. It just happened to be in a medical school.

ZIERLER: OK, but you really didn't have much interaction with the medical school—

LARSON: No.

ZIERLER: —in terms of answering the biological questions, anything like that?

LARSON: No, not at that time, yeah.

ZIERLER: Interesting.

LARSON: Yeah.

ZIERLER: So what was the lab environment like at Albert Einstein?

LARSON: It was basically a molecular biology lab, cell biology lab, but they had a biophotonics center. And the biophotonics center was a mix of high end commercial microscopes, but they also had space for building new types of microscopes and developing new techniques. So that was the attraction for me.

ZIERLER: Now, you said this was—you entered there as a post-doc.

LARSON: Yeah.

ZIERLER: You were there for quite a while.

LARSON: Yeah—

ZIERLER: Was it just a really long post-doc, or did it morph into something else?

LARSON: Yeah, this—no, no, it was [laugh] long post-doc. I was there—I was—I had a job offer—

ZIERLER: Until what? Till 2011?

LARSON: I had the job offer in my 6th year there, and then I started here. And I stay—and I started here after my 7th year, yep.

ZIERLER: You had a job offer at Einstein?

LARSON: I had a job offer—no, I had—I did have one there. I had job offers at many other places, but the offers came in 2006, and then I started—

ZIERLER: I see. I see.

LARSON: I left in 2000—sorry. No, 2010.

ZIERLER: 2011 is when you started at NIH.

LARSON: 10—yeah. 2010 is when I had offers, and 2011 is when I arrived here, right?

ZIERLER: OK.

LARSON: So basically, it was—I was there six years before I had a permanent position offer.

ZIERLER: OK. So at Einstein, are you working on one basic research question this whole time, or you're all over the place? What's your day-to-day like?

LARSON: Kinda more all over the place. Again, the attractive technology they had and their focus there was the ability to image RNA. And—

ZIERLER: Yeah, which you really were not involved with in graduate school, RNA?

LARSON: Not at all. Not at all. Yeah. Retroviruses use RNA for assembly and infectivity. But they had the ability to image RNA, single RNAs in living cells, and it fit technically with what I had done in the past, a lot of the same ideas, a lot of the same approaches, a lot of the same microscopy concepts. But the lure for me was that I felt like RNA was a direct connection

to genomics, which was this nebulous idea that I wanted—I had—that I want—that I feel like that was the next—that would be a—that was the best career move for me.

ZIERLER: What was exciting about genomics for you, like frontier kinda thing?

LARSON: Yeah, it was just one of these—it's like now you have the whole sequence of human genome, so you would be able to look at how genes were expressed. You would be able to—now, sequencing, as it exists now, next generation sequencing, didn't exist then. So—but this was the blueprint. This is what tell—told cells what to do, and it just seemed like the most exciting area to be in at the time.

ZIERLER: Yeah, I remember when genomics was like 2004, 2005. Do you feel like in retrospect the excitement was a bit overblown in terms of what genomics was capable of doing in terms of unlocking all of the mysteries of human health and things like that? Or are we still on that trajectory and it is going to get there at some point?

LARSON: I think it will get there at some point. I think it's inconceivable to think about the way we do biology now without the human genome. It's just inconceivable, right?

ZIERLER: Because it is fully mapped now, right?

LARSON: It underlies everything that we—yes. There's reasons which are refractory to that, but—

ZIERLER: So what is the frontier if it's fully mapped now in terms of realizing its full potential?

LARSON: Understanding the rules, understanding how it tells which tissues—why your kidney cell is different than your muscle cell, right? They're all the same genome, but they develop in very different ways. In terms of cancer biology, it completely revolutionized what we could do in terms of detecting mutations, knowing the underlying cause of cancer.

ZIERLER: Yeah, yeah, OK.

LARSON: Yeah, so I didn't quite have that appreciation then, but—

ZIERLER: That's more a view of 35,000 feet, and I understand you're in the lab every day.

LARSON: Yeah, well, let—sometimes when I do teach, which is not very often, you get an interesting question—'cause before you had the human genome, say you found a protein of interest, some band on a gel or even a—you found an RNA of interest and you cloned it to sequence it, you'd be sorta scratching your head, where is this thing in the genome, what's next to it, what regulates it. You would—this would have things like the classic beta globin, right? Things involved in sickle cell anemia. These sorts of things were originally discovered is you'd find that you'd work backwards to determine the sequence. And you—and so now—and it's strange to think about how you just assemble these ideas piecemeal, each researcher. And so you're talking to students, and they ask this question—they say, "Why didn't you just sequence the genome first? 'Cause that would have made all this stuff easier." [laugh]

ZIERLER: [laugh] I used to be a smart undergraduate [laugh] just like you, you could tell them. [laugh]

LARSON: Yeah, and you're like, "Yes, had we known how to do that, it would have made things a lot easier, made the sequence of genomes first."

ZIERLER: [laugh] OK, so what were the circumstances leading to your arrival at NIH? How did that happen?

LARSON: So I—so the—I guess the main thing I developed as a post-doc was sort of the biophysical wherewithal to look at single genes turning on and off in cells. So that had never been done before. So by imaging RNA, you can see when a gene at the DNA level starts to transcribe, when it starts to make RNA, when it becomes active. And the view that emerged from this is that it was—there were all these stochastic random effects which we didn't appreciate, that there was variability between cells and populations—Some made a lot of RNA. Some made little RNA—and also the realization that if you could look at this process happening, you could begin to understand how gene regulation worked, which is what my lab works on. So I started looking at leaving, applying for jobs. This point, I knew I wanted to be a PI. I wanted to be an independent investigator, and I applied to maybe a dozen or so places, mostly on the East Coast. And it was a mix of physics departments, bioengineering departments, molecular biology departments, medical schools. And I was giving a talk at a conference, and somebody came up to me afterwards and said, "You should apply to the NIH." And I—to the NCI, specifically, and they had [??]. And I had a very dim understanding of what went on at the NIH. I didn't quite—coming from a physics background, it wasn't something that I was that familiar with. I knew many scientists here, especially from work—whose work I followed as a post-doc.

ZIERLER: Who did you know from here?

LARSON: Tom Misteli, Gordon Hager, Jim McNally, Carl Wu.

ZIERLER: Are they still here, any of them?

LARSON: All of them except Carl. Carl's at Hopkins now. And I knew—but I didn't understand—which is I guess naïve in retrospect—I thought that it was—that being an NIH investigator was a designation that you had, maybe some sort of secure funding, but that you had a lab somewhere else at a university like you would be an NIH investigator at John Hopkins or NIH investigator NYU.

ZIERLER: Right. Uh-huh, where you were essentially embedded wherever you were?

LARSON: Yeah, that was my—so I didn't appreciate that 'cause most of my interaction with the NIH was on the grant side.

ZIERLER: Yeah, so coming from Einstein, did you feel like you derived any intrinsic value from being at a teaching hospital, or it was really you were in the lab and it was basically an island, and it could have been attached to any institution?

LARSON: Closer to the latter. I feel the medical—the teaching aspect was almost completely separate from what we did.

ZIERLER: Right, and you weren't doing any teaching?

LARSON: I wasn't—and we—I was actually in the anatomy department. I was a post-doc in the anatomy instruction…we—they taught gross anatomy. All the med students came through this department, and there was a completely different faculty which taught them. You saw them in the hallways. There was no interaction. It was really more of an academic lab embedded in this medical school. But the—it's mostly—the medical school isn't—I could go at—on length about this, but the funding model is very different, right? So the reason why medical schools are attractive to some people is because you don't have to teach if you're a professor there. And you

can pay yourself a lot of money, and you can run a big lab, but you have to be very good at getting grants. And whereas if you're at a—what's called a—like a nine-month place like Cornell or Ohio State, you're paid to teach. That's what your job is. That's where most of your salary comes from, and if you want, you can supplement that money with grants. Whereas the medical school, the grants mostly pay your salary. So they're great places to do your research, but they can be sort of stressful for faculty.

ZIERLER: Yeah, right, if you don't have that entrepreneurial streak is what it sounds like.

LARSON: Exactly. Exactly. So I didn't—so I decided when I was there that that might not be the best fit for me. And so anyway, I interviewed at all these places, and I had a lot of offers. And some of 'em were—I had an offer at Cornell. I had an offer in physics departments. And—

ZIERLER: Was that attractive to you to go back to university environment or not so much?

LARSON: I thought a lot about it. I had always visualized myself as a professor with all that entailed, interacting with people from other disciplines, walking across the quad on a fall day, having—mentoring students, playing squash at the faculty club, like the whole thing.

ZIERLER: Sure, I get it. I got it.

LARSON: [laugh] And so—and that's not what the NCI is, right?

ZIERLER: Definitely not.

LARSON: And—but once I started to make that adjustment mentally, I felt like this was the best place for me to be a scientist.

ZIERLER: Because of the what? What does it allow you to do here?

LARSON: They're a couple things. The funding is more stable, and you have—

ZIERLER: Stable does not mean unlimited, though, right? 'Cause that's a misconception.

LARSON: Not—certainly not unlimited. It is—you have more freedom. You have more resources.

ZIERLER: Freedom in terms of what, collaboration? Like you could talk to whoever you want?

LARSON: What you work on. What—

ZIERLER: What you work on?

LARSON: Yep. And I felt—and you can start from day one. You arrive. You have a lab. You have people. You have money. So all those things are very attractive to a young, independent investigator starting out, but also, thematically, it was the best fit for me. I mean, there's just a long history here of gene expression work on the nucleus, work on chromosomes, the people I met. And that was probably overall the stronger inducement. So my colleagues, Tom—some of the same people I told you I admired, Tom Misteli and Gordon Hager—

ZIERLER: None of whom have a physics background or—

LARSON: —no—were here. They're in this building, right? So I could—I had a chance to be next to these people whose work was very inspirational for my own work.

ZIERLER: Right, right. So at this point, you were fully in with gene expression and genomics?

LARSON: Yeah.

ZIERLER: So you saw your—you wanted to continue your work at Einstein, and the question was what's the best institute to host this research?

LARSON: Yes.

ZIERLER: That's basically it.

LARSON: Yes.

ZIERLER: OK, so you came here as a Stadtman investigator?

LARSON: Yeah.

ZIERLER: Who was Stadtman? Do you know?

LARSON: Yeah, I do. [laugh] So Earl Stadtman—it's actually a husband and wife team, Earl and Thressa Stadtman.

ZIERLER: Are there many Stadtman, or you were the Stadtman—

LARSON: This was the first year that this existed, and the idea was that it was gonna be a named recruitment process with a little more in terms of resources and prestige. And it was a change in how NIH was doing hiring, so historically, NIH did hiring through the lab chiefs, which are department chairs, and these were these—some of the best jobs in American science, right? If you were a lab chief in the NCI, you had a lot of power and a lot of resources and a lot of sway over who got hired and who got tenure and—and when it worked, it worked really well. But when it didn't work, you would get nepotism, empires, and sort of genetic drift into

mediocrity. And so the idea was they're gonna divorce—they're gonna take the hiring and make it a little more centralized and just put out open calls for the best and brightest across all disciplines and then decide where they might fit [??]. So that's what the Stadtman process is.

ZIERLER: Uh-huh, and so one of the things I'm curious about—so you got tenure in 2019?

LARSON: Yeah.

ZIERLER: Congratulations.

LARSON: Thank you.

ZIERLER: So I'm curious how that works in terms of the academic model versus the NCI model. When you're applying as a post-doc with four years in as a post-doc or whatever that number was, right? Are you applying to these academic positions at the assistant line, or are you already applying for jobs that offering—are offering you tenure—

LARSON: No.

ZIERLER: —out of the box?

LARSON: No, all—

ZIERLER: So it's—basically, NCI is situating itself to be competitive with other opportunities that somebody at your level would have been considering at that time?

LARSON: Absolutely. You're hired at the assistant professor level. The tenure process here is very similar to other universities. You have to publish. You have to train other scientists, in this case post-docs as opposed to grad students. And you have—

ZIERLER: Which is more advanced to begin with, I suppose?

LARSON: Yeah, yeah, so the model here is mostly based on post-doc for the post-grad students, which honestly was another attraction to me. I felt like I would work better with post-docs than grad students. And you get letters from faculty and experts in the field who have to support your case for tenure.

ZIERLER: Beyond NCI?

LARSON: Yes. So about 16 people write letters, weigh in on my contributions to the field and whatnot, which is the same at a university.

ZIERLER: And is this—heaven forbid you don't get tenure, what's the situation there?

LARSON: Yeah, so—

ZIERLER: Like your—you have to find your—you have to find another job is the message?

LARSON: Yeah.

ZIERLER: Or you can stay on in an untenured—

LARSON: You got to find another job.

ZIERLER: You do. OK. OK, well, that's great news.

LARSON: Yeah, yeah, and it's—yeah, I—the—I'm fuzzy on what the actual statistics are. They give you numbers, but I don't—

ZIERLER: You don't want to think about that stuff, probably.

LARSON: [laugh] Still—but you definitely—there are a number of people from my cohort who didn't get tenure and left. So it happens.

ZIERLER: Yeah, so what—the trajectory of your research from when you started to where you are now, just give us a sense of that.

LARSON: Sure. So I came here still very much in the biophysics mold.

ZIERLER: But not really cancer? You're not really working on cancer at this point?

LARSON: No, no, not at all. At NCI, I had a long history of supporting basic research, but I have to say that not a lot of biophysics in the NCI, right? So there was—that was somewhat exotic for them.

ZIERLER: Yeah, and I have to ask, at the beginning, just before the other question, are you accepting this job knowing that you are sorta jumping in with two feet into cancer research—

LARSON: I had no—

ZIERLER: —or is that really adjacent to what you're doing?

LARSON: It's an adjacent. I had no plan to do cancer research.

ZIERLER: Yeah, so dumb question, why NCI then? Why is this not somewhere else?

LARSON: Yeah, yeah, because again, it was—I was attracted to the—my future colleagues. There was synergy with what we're do—and even though maybe they weren't trained as physicists, they were asking questions and doing research which I felt was very biophysical in its motivation and whatnot. And also, I at this point was confident in my abilities as a biophysicist

[laugh] and quantitative biology and felt like I would prosper more being around cell biologists and that going, for example, back to a biophysics department or a physics department or a bioengineering department, I would be doing the—I would be thinking the same ways and interacting with people who thought in the same ways. And I had seen—I had been exposed to the power of really having biologically motivated questions and a good biological intuition and thinking about things in a biological way at Einstein in terms of the other post-docs I worked with, and I could see that it was different. And there's this cliché that it's easier to go from physics to biology than biology to physics or biology to biophysics, and that's true at a superficial level. Obviously—

ZIERLER: Well, physics is more foundational.

LARSON: It's more foundational, and a biologist in their 20s or 30s is not gonna go back and learn multivariable calculus. And it's just not—so it's true at a trivial level. On the other hand, I do think that biologists learn to ask questions which are in some ways better suited to their field. They ask questions in different way. They're better at experimental design in many cases than physicists coming into biology. The concept of the control experiment doesn't exist in physics. It really doesn't. So when I get physicists in the lab, which I still hire people from physics backgrounds and biophysics backgrounds, they do an experiment, and then when I correct for this and they do this baseline and subtract this and normalize it, and you just say to them, "Well, why don't you just do a control where you remove this one piece of the puzzle?", and they're like—

ZIERLER: [laugh]

LARSON: —you can see the lightbulbs turn on ‘cause that's—‘cause the model in physics is you know everything except for the variable you’re changing, and the model in biology is you know nothing except for the variable you’re changing. And so how do you account for that? So anyway, I felt like this would be a good place for a lot of reasons. I had no intention doing cancer biology and neither was there an expectation that I would do cancer biology.

ZIERLER: And that remains true today?

LARSON: Yes.

ZIERLER: You’re not involved in any of that?

LARSON: No, now we are. Now we’re heavily involved.

ZIERLER: Now you are?

LARSON: Yeah, so it comes out in a second, yeah. So what I was told was—now, of course, when you have your quadrennial funding review—so we get reviewed by an external panel every four years. That's the funding model. If someone asked you how this is relevant to cancer biology, you better have an answer, but if you’re working on gene expression, it’s pretty easy. It’s not a hard leap. So we were asking fundamental questions about gene regulation, and that's relevant to cancer biology. So I felt like we would very much continue in that same mold, doing very high resolution measurements on transcription, which is the process of DNA making RNA and then RNA processing, in our case, splicing, which is how RNAs get cut up and reassembled to then code for proteins. So those are the two things we were gonna focus on.

And—but I have to say—so—and then around the time when I started in 2011, there was this outpouring of data, cancer genomic data, cancer data, which discovered a new class of mutations in some of the factors we were studying, these splicing factors. And these had never been seen before, and they were predominant in blood malignancies. So myelodysplasia, acute myeloid leukemia, chronic myeloid leukemia. And at the time, we thought, well, maybe we can use these mutations to tell us something about the processes we're interested in, whether or not we'll use the experiment, which has essentially been done by nature and humans, that says these mutations are important, and we're gonna use them to learn something about the basic biophysical process we're interested in. And that basic start morphed into this interest in the physiology of how these things actually cause cancer.

And this was—I have to say this was—I would say this was on par with the feeling I had as an undergraduate deciding that I really want to work on biology, deciding that I want to work on how these things cause cancer for a lot of—basically for simple reasons, which one is it was a very well-defined scientific problem, which is here's mutation, it kills people, figure it out, fix it. And the thing that I felt—and one of the things that has happened to me since I've been at NCI is you're exposed to these people who have actually done that in their career, people who have developed cellular therapy for cancer biology like Steven Rosenberg, people who developed HPV vaccine like Doug Lowy, essentially making cervical cancer a cured disease in some ways, preventable disease. And the thought, which I had never had before, is why not me, why not my lab. We're here. I have good people. I have good resources. I have freedom to do what I want. I want to work on something that's impactful, and so we have decided to—

ZIERLER: This is a departure from gene expression research?

LARSON: It's related to that, but it's definitely different. So now we're trying to understand how these splicing factor mutations cause disease, and this has taken us directly into clinical collaborations. So now we do work with MDS and patients and whatnot.

ZIERLER: OK. We, us—who's we? What's—who's the we in your—

LARSON: My lab.

ZIERLER: So tell me about your lab. Who's in your lab? Who's your A-team?

LARSON: OK. [laugh] So I have seven post-docs and one staff scientist. Staff scientist is a permanent position.

ZIERLER: Not on a tenure clock?

LARSON: No, he just is a GS employee, civil servant, but he has a PhD and has done advanced training. The lab is a mix of biophysicists. In the past, we've had straight mathematicians, straight computational people. I have two people coming soon, one who is actually a biophysics grad student from the physics department at Ohio State.

ZIERLER: [laugh]

LARSON: Kinda coming full circle. So this guy did his PhD—

ZIERLER: This is from the new program or the old program?

LARSON: The new program. The biophysics group which started after I left.

ZIERLER: OK, there you go.

LARSON: So this guy is coming from that background. And in addition to those, more physical science backgrounds. I have microbiologists and biochemists, and we're even at this point hiring a hematologist. So someone who has no physical sciences background.

ZIERLER: And what's the big research question you're after right now?

LARSON: I would say there's two of them. The big research question is understanding how genome architecture, how the folding of a genome—which is a question involving polymer physics and diffusion and self-organization, how that impacts which genes are turned on and off, how that impacts gene regulation. That's one side of the lab. The other side of the lab is focused on trying to understand how splicing factor mutations cause leukemia and what you can do to stop that.

ZIERLER: Mm-hmm. And are you—how much do you take advantage of the general research protocols that are happening at NIH across the board? Is this a dataset that is uniquely available to you?

LARSON: Oh, yeah, it's—you can do things here that I think it would be difficult if not impossible to do easily other places.

ZIERLER: Why?

LARSON: There are very few barriers between labs. There's a little bit more of a shared resource mentality, right?

ZIERLER: So ironically, it's almost like it's more academic here than in—

LARSON: In some ways.

ZIERLER: —traditional universities?

LARSON: In some ways, yeah. We—anyone who comes into the hospital here, the clinical center—

ZIERLER: Yeah, patient, any patient?

LARSON: —any patient is already on a research protocol. So—which means it's fairly straightforward to get samples to analyze them, and in fact, one of the things that happened early on is we were working on these splicing mutations. We had published a small paper on them, and I got a call from a physician, guy named Chris Horrigan, and he says, "I have patients with these mutations that you're working on. How do we treat them?" And I said, "I have no idea." [laugh] You're ask—I'm biophysicist. I—[laugh] you're barking up the wrong tree.

ZIERLER: But is there any tree to—other tree to bark up, is the question?

LARSON: No, so that was—so—and that got me thinking, well, why don't we work on this, why don't we do this. So now that it's very—so we routinely get samples from the clinical center, and we have—some of our research is evolving into a protocol to treat some of these patients based on work we've done. I don't think it's gonna be a sea change in outcome for these patients, but it's a start, right? And so now the line between the basic research in a lab and applied clinical research, the translational research is very diffuse. And I never would have anticipated this when I started here, coming again from this more biophysical mindset thinking I knew what we were gonna work on and where our contributions would be. And it's been wonderful for me, and also because it's just—I find people very optimistic here or maybe in the

medical profession in general. I don't know, but I go in and out of cynicism about my own research. And I had—

ZIERLER: You mean about how ultimately useful it is?

LARSON: How ultimately useful it is or wondering—I've been pretty successful as a grad student and pretty successful as a post-doc, and I had lots of faculty offers. And I had become pretty good at a certain type of science, right? Could identify a problem, do a—kinda come up with this biophysical solution to it or visualize it in a way that no one had visualized it before. And that work got a lot of notice, but a lot of times, that's where it ended. I wouldn't follow the stuff up, and I felt like I had—I was gaming the system a little bit, right? I knew what to do to publish high impact papers, but—

ZIERLER: But whether those papers actually had a high impact, that's the thing to be—to question?

LARSON: Yeah.

ZIERLER: So what's the feedback on something like that? How do you know when you hit and when you don't?

LARSON: Well, the most visible thing and thing that gets you notoriety and jobs is publishing papers in places like *Science*, and they get lots of press. They get lots of citations. People write about them. You get invited to give talks, whether these things were gonna be impactful three decades from now is harder to say. Time will tell. I know—I'm not saying these weren't important contributions, but I was looking for something which is—which was more long term that I thought would—and being here, you really see people who do things that move

the needle on human health. And that's a seductive path. You see people like—I'd mentioned his name already—Doug Lowy who was doing basic virology on the human papillomavirus 30 years ago, and now there's a vaccine for this which prevents cervical cancer that's used all over the world. That's a career, right? That's a—

ZIERLER: So let me—we'll transition into the big questions portion of the oral history interview, right? So I'd like to ask about open loops and closed loops in a career so far, right? So on that question, on all of these—as we've been doing this narrative of your career, I've heard a lot of loops that you've closed in terms—projects that you've been involved with, answering a research question, going onto the next one. What about the open loops in your careers? Are there things that if you had a time machine and you can go back to, are there things that you would want to reinvestigate? Are there questions that you have left unanswered that in a perfect world you would go back and look at for a second time?

LARSON: Yeah. That is—it's interesting when you think about it. Straight answer is not much. And I—and in a sense these things weren't fanning out into bigger projects, or maybe it was just the way I designed it and conceptualized it was guaranteed to make it a closed loop project. And that kinda goes back to what I was saying. It's like I—

ZIERLER: Like gaming the system?

LARSON: I was good at figuring out what would be the paper before I started it, whereas—as opposed to just asking open-ended biological questions. I think I'm better at that now.

ZIERLER: Is that just a matter of intellectual maturity, do you think?

LARSON: I think partly, yeah. Partly confidence, taking yourself more seriously as a scientist.

ZIERLER: Is the fact that you have tenure now—does that sort of open up—

LARSON: Doesn't hurt.

ZIERLER: Doesn't hurt, right.

LARSON: [laugh] I never felt confined here, but you do—I do think that thinking about more of the tenure questions, 20-year questions is easier now.

ZIERLER: Right.

LARSON: Right? And I think one of the things so ingrained in scientists during their training is thinking in terms of these three to four-year time scale about what's gonna be a paper, what's gonna get published, what's gonna get you to the next stage of your career. And I'm not saying it kills curiosity. I think I've always been curiosity-driven, but also been strategic in thinking about what I could do well. Whereas this cancer stuff, it's like we had no credibility as cancer biologists to speak of. But it's like, "We're gonna do this, and it's gonna be slow, and we're gonna make mistakes. But eventually, I feel like that coming into this with a fresh mindset is gonna be productive, and eventually we're gonna be contributors to this." But it was an admission to myself that it was not gonna be fast, and we were gonna be inefficient to start with.

ZIERLER: So when you talk about your colleagues, right, and their moments moving the needle, so what would be your Jonah Salk moment in terms of where your current research is? Where would that be heading, and what would be the thing that you did that actually moved the

needle? How would you define that? And you don't have to be so theoretical. You can just sort of advance, extrapolate your current research in terms of where that might be headed that would do that, that would give you that satisfaction.

LARSON: I think curing myelodysplasia would be the ultimate goal.

ZIERLER: Now, when you say cure, is that because you're also involved in the therapy aspect of it, or you're working with the people who do the therapy?

LARSON: We're working with the people who do the therapy.

ZIERLER: And who—

LARSON: So I'll never see a patient. It's too late for me to get MD.

ZIERLER: [laugh]

LARSON: But yeah, so the science—if the science that we have done and the pathways we have discovered and our idea for approaching them is the thing that results in the treatment, I will consider that my contribution.

ZIERLER: How do you get there from here? What's that path?

LARSON: Yeah, so we still—we're not only—there's more grinding through molecular pathways in cell biology. There are some technique advances, development technological advances which I think we can make. So I certainly—I remain convinced that biological advances come from technological advances.

ZIERLER: Mm-hmm, more so than intellectual ah-ha moments? That's a philosophical question—

LARSON: I think so. I think so. And the thing that—the impression that Watt really left with me was his desire to do the impossible experiment. He would say that all the time. It's—"You think this experiment is impossible now, but it's not always gonna impossible, and maybe we can make it more possible." So we still push ahead in that ethos, trying to develop new ways of looking at gene expression in single cells. But I think a lot of it will be just grinding out different ideas in this—in these systems. We've made some discoveries which I think is pointing us in a new direction, but there'll be more of the latter, this kinda day-to-day work than flashes of technological innovation.

ZIERLER: Sure. And how does that mindset or how do those goals affect your style as a mentor in terms of what you're encouraging your people to do, where you're telling them to go?

LARSON: Yeah, that's a good question. I still take a lot of ownership and responsibility for the fate of [laugh] people in my lab, and I want to see them be successful. And I was trained in environment where I had lots of freedom and lots of time—

ZIERLER: And lots of support it sounds like too.

LARSON: —and lots of support, amazing support. And you intimated as much yourself, right? It was a long PhD. It was a long post-doc. It wasn't like I had a supervisor breathing down my neck saying, "You got to write a paper tomorrow." So that's important to me, to have that kinda training environment and to still be able to have post-docs who have ownership of a project and have made a fundamental advance that they can take with them into their own jobs.

So I don't think it'll ever be my style to grind out pathways by grinding out post-docs to, say, have them just work on some minute aspect of a problem and all contribute and have projects that span 5, 10 years over these individual post-doc life skills, and they can't get a reward out of that. So that's part off the challenge, right? How do you advance the incremental science and still give people a chance to make their big discoveries? So I think about that a lot, and varies based on the person and the project.

ZIERLER: Do you think there is a unified theory of cancer research on the horizon or not? Is there something that unlocks—physicists talk about the unified theory of physics, right?

LARSON: Yeah, yeah.

ZIERLER: Is there a unified theory in cancer that puts it all together?

LARSON: I think we understand the rules, the—I think the standard models [laugh] as—of cancer biology is pretty well known. We know a lot about the mutations that cause cancer. We know a lot about the progression of cancer, the spread of cancer. I think one of the things that is lacking is the quantitative aspect, and I think that is what masquerades as this crisis in reproducibility sometimes, right?

ZIERLER: What do you mean crisis in reproducibility?

LARSON: There's a lot of talk, and especially in the life sciences, about how reproducible certain studies are, right? And there were some high profile studies from pharmaceutical companies, Amgen, the Amgen study saying that trying to reproduce the data and following exactly their protocols and their cell lines and that sorta thing, and only maybe some fraction—I

forget what the actual number was—maybe 60%—could they reproduce the fundamental findings? And that's a problem—

ZIERLER: Which throws into question the basic value of the study in the first place?

LARSON: That's a problem, right? But part of the problem is just—I don't think it's maliciousness or laziness or malfeasance. I just think it is biology is complicated and not always very quantitative. It has a sheen of quantitative behavior, right? You have error bars and statistics, whatnot but not a lot of mathematical models that say when you do this, this happens, right? And I think that—and so when you don't have those basic predictions, it just means you're missing some of the variables, right? So I think a lot—so when these things fail, it's because I feel like there were hidden variables, obviously, that we weren't appreciating, right? So I feel l've been—but in terms of actual—a unified model of how you treat cancer, I think there's a good understanding of where cancer comes from in unified model, as it were. How you treat it has been lacking in the [laugh] unified model, right? Maybe you can develop drugs for certain mutations and certain disease contexts, and some of those are wonder drugs, Gleevec being the classic example, right? If you have CML and you have chronic myelogenous leukemia and you have a BCR-ABL translocation, that used to be a death sentence. And you give these patients Gleevec, and they'll—this is a chronic disease now. They'll live their entire lives. They won't die from it. HPV vaccine, another example. The recent thing, which seems like it has a very bright future, is this—is immunotherapy, which is that if—that ultimately your immune system should be able to recognize malignant cells. So if it's not, are there ways to juice it up so it does recognize malignant cell? These are these checkpoint inhibitors. Or can you design new immune cells? These are engineer T cells, which would specifically attack these things, right? So that—I see these talks on a weekly basis at NCI, and this stuff is like science fiction. Patients who've

failed multiple clinical trials in melanoma were given three months to live and have survived five years. They're disease-free. This stuff is amazing but again only works in a fraction of the patients. So there are hidden variab…there's obviously something—so the success is there. You know that it can work, so why does it fail? What are the pieces that we're missing, right?

ZIERLER: What are some of the fundamental principles of physics that you have carried with you throughout your career, things that you keep coming back to that inform the way you see the world and inform the way you go about your research? 'Cause the general trajectory of our conversation, it seems to me, is that you are fundamentally a physicist, and you're bringing that mindset, that way of seeing the world into your lab in a biological setting. Is that a fair way of looking at it?

LARSON: I would—yeah, I may—I think in my—the first part of your question is correct. I feel like the training exerts a strong force on me to this day. I'll come back to that. I tend not to self-identify so much as a physicist anymore. I really—

ZIERLER: When did that transition happen? Like Einstein days?

LARSON: I'd say late in my post-doc, yeah. I—if I had to self-identify, I would say cellular biophysicist, cell biologist, cellular biophysicist. I don't often give talks in physics departments anymore partly because it's just too excruciating for me to have to go through so much of the biology background to get to the point where I'm interested in discussing research. And that's some laziness on my part, and I'm—I admit to that. I think this belief that if you do good measurements, the hypothesis will follow is—guides almost everything we do to this day.

ZIERLER: And that's you talking as a physicist?

LARSON: That's me talking as a physicist, right? And I still recoil a little bit sometimes when I'm sitting in job—in faculty interviews or recruitment committee meetings and people say, "Well, it's not hypothesis-driven." That's a knock against some research proposals. And the idea being that they want a candidate who's gonna say, "Well, I think that leukemia is caused by a failure in this pathway, and I'm gonna send—my whole lab is gonna work on this." And I think that's not my mentality, and it's not the physics mentality, and it's not the bio—where is to say, "We are gonna do the best measurement we possibly can, and that the answer or the question is gonna emerge from that."

ZIERLER: Which gets back to, I think, your original assertion that there needs to be more quantitative cancer research.

LARSON: Yeah, yeah.

ZIERLER: So that really sounds like what you're saying is you need more physicists in this field.

LARSON: I do, and I think—and I do, and I think the things that—the most productive lines of research in the lab are things where we did a really good new measurement. And we didn't know where it was gonna go, and I knew that we didn't know where it was gonna—that was not the point. But I was confident that something would emerge from that, and I think that works—can work well in biology. And so that's—I feel like that's the physics training that comes back a lot, OK?

ZIERLER: Right, all the way back from your undergraduate days?

LARSON: Yes, yeah. I think the tools, the physical tools that I use most readily on a day-to-day basis are actually the data analysis tools, statistics, a sense of how to properly analyze data, normalize data, these sorts of things more than any physical concept. So the physical concepts, unfortunately, of quantum mechanics, statistical mechanics don't manifest that much anymore in the work we do.

ZIERLER: Have there been advances in computational capacities that have helped—been helpful to you?

LARSON: Yeah, in fact—

ZIERLER: Big computers.

LARSON: Absolutely. In fact, that stuff has sorta passed me by. I wish I had been better at riding that wave and keeping up [laugh] with things a little bit better. I still program like a physicist.

ZIERLER: What does that mean, program like a physicist? Old-fashioned?

LARSON: Well, it—I can—I'm pretty good with algorithms and I—and that sorta thing, and I can—but it's not terribly efficient. I still use old languages like IDL, which is an astronomy language. I don't use sorta the newer ones, which are better for biocomputation like python or Perl or these kinda things. And I never really learned to fully do highly efficient parallel programming, that sorta thing. And so a lot of people who do that, strangely enough, come from the computer science side or maybe the computational biology side and not so much from the physics side.

ZIERLER: Uh-huh. All right, well, last question, I think. You've been pretty good at being hard on yourself, I think, during our discussion.

LARSON: Oh, yeah?

ZIERLER: You've been pretty good at identifying places where you could have done more, and here, if you must, you can hide behind some of the awards that you've won, many awards you've won and all of the wonderful things that many of your colleagues have said about you. But I think that you really—you should wrap it up in your own words. What have you contributed to the field both in terms of defining what the field is and what your contributions are? And not even looking forward, just like here we are, you retire today, right? You have moved the needle. If you hadn't—

LARSON: Yeah.

ZIERLER: —you wouldn't have gotten tenure, you wouldn't have gotten these awards, you wouldn't have gotten where you are. So you have moved the needle. How have you moved the needle?

LARSON: I think the motivation and the ability to do quantitative microscopy in living cells, saying that could be done, what you could do with it was at the forefront at the time. I think we—I think I was—

ZIERLER: And to situate that in history, at what time, what forefront?

LARSON: So sorta that turn of the century kinda, that--

ZIERLER: OK, so really your transition from grad school to post-doc?

LARSON: Yeah, so this is a time when I would still give talks, and people would say things like, "This live cell—looking at—live cell microscopy really seems to have a future." And I would just think to myself, of course it has a future. [laugh]

ZIERLER: [laugh]

LARSON: So the work we did on the possibilities, both theoretical and experimental on the possibilities of what you could do with a microscope in living systems, I think, was forward-looking. In terms of biology, I think this idea that you can look at single molecules in cells and understand the basic aspects of gene expression, look at gene transcribing, look at RNA being made, look at RNA being processed, has really changed how people think about gene regulation in single cells. And up until then, everything was done on thousands or millions of cells. So a single cell gene—and I guess that's somewhat a validation of my intuition when I was finishing my PhD, was that there was gonna be something good about doing gene regulation and combining microscopy, and I think that's where I'm most recognized in biology communities. And it is true now that there is a whole field of single cell gene expression which now uses more biochemical techniques, single cell sequencing, that sort of thing, and they ask different questions. They have a different focus, but I think the microscopy people, myself included, the work we did really paved the way for that field. That's my view.

ZIERLER: Well, great. I think we'll leave it there. This has been terrific. Thank you so much.

LARSON: OK.

[End]