SMB
Dr. Richard Pastor
NIH
Bethesda, Maryland

by David Zierler
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DAVID ZIERLER: All right. Here we are. This is David Zierler, March 10th, 2020. It's my great pleasure to be with Dr. Richard Pastor of the NIH. Dr. Pastor, would you please tell us your affiliation here at NIH?

DR. PASTOR: I'm in the National Heart, Lung, Blood Institute, and my laboratory is the Laboratory of Membrane Biophysics.

ZIERLER: And you are the Chief of Laboratory Membrane Biophysics?

PASTOR: Yes.

ZIERLER: OK. Good. OK. Perfect. So let's start right at the beginning. Tell us a little bit about where you were born, your family.

PASTOR: I was born in Long Island in 1951. My father wanted to be a concert pianist but, after World War II, he came back and started a family and then he just went into business. My mother was from Chile. Her father was a mining engineer and had been all over the world. She told me he spoke many languages. Ended up in Patagonia, loved Chile, met my grandmother. He was a German American. And then my mother moved here after World War II.

ZIERLER: And that's when your parents met?

PASTOR: Yes.

ZIERLER: Uh-huh.

PASTOR: And I guess my mother always just had very, very high standards for what she wanted her kids to be.

ZIERLER: Yeah.

PASTOR: So she always pressured us a lot. Maybe like an immigrant mother of a certain type.[laugh]—

ZIERLER: [laugh]

ZIERLER: And siblings? You have siblings?

PASTOR: Yes. I have a brother and a sister.

ZIERLER: OK. Where are you in the order?

PASTOR: I'm the first one.

ZIERLER: Oldest.

PASTOR: Yeah.

ZIERLER: OK. Now, usually at this point, I ask about early interests in science, but given that you were a philosophy major at Hamilton, I wonder if your interest in science came later on, or you were interested in science as a child also?

PASTOR: No. I was always interested in science. At first, I had hoped to become a doctor so I could take all the necessary science courses at Hamilton and be a philosophy major, which just seemed like an interesting thing to do.

ZIERLER: Uh-huh.

PASTOR: But then I just got more interested in the science and decided that was better for me.

ZIERLER: So your intention from the beginning was to pursue an MD.

PASTOR: Yes.

ZIERLER: And you took science classes but—

PASTOR: Yeah.

ZIERLER: —the philosophy was just an opportunity to become sort of—

PASTOR: Well read.

ZIERLER: —more well read and—

PASTOR: Yeah, yeah.

ZIERLER: —worldly and things like that.

PASTOR: It sounded like an interesting thing to do. It was sort of a dumb thing to do, but—

ZIERLER: [laugh]

PASTOR: —I was tantalized by the deep thinking of philosophers, then just frustrated by it.

ZIERLER: And so you would have been at Hamilton like 1968 to '72, like that?

PASTOR: '69 to '73.

ZIERLER: OK. Were there antiwar protests and things like—

PASTOR: Yeah.

ZIERLER: —that going on on campus?

PASTOR: Yeah, yeah, yeah. I had protested. I gave my draft card to someone who was going to collect them all and then send them to wherever.

ZIERLER: Right.

PASTOR: Yeah. Which was a big moment, because you could get in trouble for that.

ZIERLER: Sure.

PASTOR: It turned out that, years later, the guy still had all the draft cards in some carton under his bed and they never got sent, so my protest was never heard. [laugh]

ZIERLER: OK. [laugh]

PASTOR: It was a personal thing.

ZIERLER: But you were of draft age. Theoretically, you could have been drafted.

PASTOR: Yeah, yeah, yeah.

ZIERLER: Yeah.

PASTOR: And I guess I would have been gone to Canada or something.

ZIERLER: Right, right. OK.

PASTOR: I was against the war.

ZIERLER: Sure, sure. OK. So 1973, and do you go straight to Syracuse from there or do you take some time off?

PASTOR: No. I took one year off to catch up on more math and physics courses.

ZIERLER: Uh-huh.

PASTOR: Because at Hamilton, I hadn't taken enough of them.

ZIERLER: Right.

PASTOR: It was sort of more the pre-med, basically the single one physics course and math or calculus.

ZIERLER: Right.

PASTOR: But, at that point, I decided I needed to get more of that, so I ended up taking courses at Rochester for a year.

ZIERLER: University of Rochester?

PASTOR: Yeah.

ZIERLER: Uh-huh.

PASTOR: All the courses I would have needed for a physics major,

ZIERLER: Yeah.

PASTOR: and almost for a math major. And that gave me the feeling that I had the right background.

ZIERLER: Right.

PASTOR: I needed that extra year to catch up. Plus, I worked. A guy had a business in his home putting together circuit boards for operating big machinery. I was pretty good at that, and that's how I supported myself.

ZIERLER: Uh-huh.

PASTOR: And then I went to Syracuse, and I was originally going to get a PhD there with Willem Prinz and—

ZIERLER: Mm-hmm. A PhD in chemistry?

PASTOR: Yeah. Well, it was in biophysics.

ZIERLER: Biophysics.

PASTOR: Yeah. But it was in the chemistry department. He was a polymer guy. And then he died in a boating accident in the summer between when I accepted and when I was to go there. And so then I didn't have an adviser lined up.

ZIERLER: Yeah.

PASTOR: So I did experiments. I joined Bill Woodruff's lab doing resonance Raman spectroscopy and took physics courses and basic physical chemistry-like stuff, thermodynamics, statistical mechanics. And I remember doing a synthesis for my research with Woodruff. I was

sharing an apartment with a physics graduate student. And he came in just as I was finishing this synthesis of a very oxidant-sensitive compound. I had synthesized it over the course of two weeks and I was going to take an infrared spectrum. I remember putting the sample on the little plate and closing it, obviously not sealing it correctly. I didn't know that. My roommate had just come into the lab. I said, "Oh, you want to go see this—I'm just about to take a spectra of my compound." So we ran up to the third floor and I put the plate in the spectrometer and the spectrum was coming like a regular spectrum is supposed to look. And then, I could look at the little plate and there was this black ring just coming in, [laugh] enveloping the whole thing. And the needle of the chart recorder rose to 100% absorbance as the sample turned black.

ZIERLER: But what did that tell you?

PASTOR: Well, that it oxidized. But what my roommate told me, he said, "You know, in the two weeks you've spent doing this, you could've learned something about Bessel functions." So that told me that I didn't want to do experiments. [laugh]

ZIERLER: [laugh]

PASTOR: The very next day I spoke with the theoretician, Jerry Goodisman, who had been teaching one of my courses and just said, "Is it possible to work for you?"

ZIERLER: Yeah.

PASTOR: And I said, "But I've already agreed to work with Woodruff, and I feel I want to finish the project," because it would have been a lousy thing to do to jump.

ZIERLER: Yeah.

PASTOR: So he said, "Yes." And then I talked to Woodruff and I agreed to work the summer to finish the project, because he was a new assistant professor. I worked really hard that summer doing experiments, but then the following fall I started doing theoretical work with Jerry Goodisman. And he was the perfect adviser to really help me catch up.

ZIERLER: What was his background? What was he studying?

PASTOR: Well, he had been a student of Bill Klemperer at Harvard, and so his background was in quantum mechanics. However, he had, on a sabbatical, decided he was going to become more involved in statistical mechanics. He was interested in double-layer theory of electrodes, and that was sort of where he was going. He was leaving quantum mechanics and entering this. So we kind of were new to it, both of us. We learned it with each other. And there was this interesting equation relating the surface tension of a mercury drop with the voltage called the Lippmann equation. And so he thought, well, why don't we work together on that. At that point I wasn't sure if I was going to stay for a PhD or a masters, but I was sort of learning towards just getting a masters and then moving on.

ZIERLER: Syracuse had the PhD program if you wanted to stay on?

PASTOR: Yeah.

ZIERLER: Uh-huh.

PASTOR: I was accepted into the PhD program but when Prinz died, someone said, "Keep your bags packed." So it evolved to just get a masters and then to move on to maybe a place that's more biophysics oriented.

ZIERLER: Uh-huh. And this was the chemistry department you were in?

PASTOR: Yeah.

ZIERLER: OK. That had people that were doing biophysics, or you were really not involved with biophysics at this point?

PASTOR: The only one doing biophysics was Prinz doing polymers, which was sort of biophysics.

ZIERLER: Right.

PASTOR: So I wasn't really, aside from that, near biophysics. I realized it was the wrong department for biophysics after Prinz died.

ZIERLER: Yeah.

PASTOR: But, you know, I was there. The resonance Raman with Woodruff was on heme groups which was "biophysicsy", but then I didn't want to do it. Goodisman didn't do biophysics at all.

ZIERLER: Right.

PASTOR: So my project was to calculate the surface tension of a molten salt as an entry to the Lippmann equation. It turned out there was a statistical mechanical theory by Kirkwood, Buff, and-Fowler in the 1940s that had rigorously expressed the surface tension of a liquid vapor interface, in terms of the difference in the normal and tangential pressures Surface tension is going to come back throughout my entire career, so it's when I started getting involved in these pressure tensors.

ZIERLER: Uh-huh.

PASTOR: And so Kirkwood-Buff-Fowler simplified the rigorous equation by assuming that you could use the radial distribution function for just the liquid part, and the vapor would be zero. And the density was just a step function. So Goodisman said, "Well, why don't you see if you can do this for the molten salt." So that seemed like the next thing up from liquid argon. The Kirkwood-Buff-Fowler theory is in textbooks, and so it seemed like a good pre-project. I worked through the generalized mean spherical approximation in statistical mechanics to get the radial distribution functions. That took me a while. And then I plugged in those distribution functions into the Kirkwood-Buff formula and we got, like, negative surface tensions. [laugh] So that was my first scientific result. [laugh] I mean, that was my first theoretical result, getting negative surface tensions.

ZIERLER: Which tells you what, when you get a negative surface result?

PASTOR: It means something's dramatically wrong—

ZIERLER: With your experiment?

PASTOR: Well, theory, but—

ZIERLER: With the theory? I see.

PASTOR: Yeah. But the surface tension can't be negative, right?

ZIERLER: OK.

PASTOR: I mean, the surface tension of a droplet is positive. You have two phases, and as you raise the temperature and surface tension gets lower.

ZIERLER: OK.

PASTOR: Eventually, when the thing evaporates, the surface tension is zero, right?

ZIERLER: Uh-huh.

PASTOR: So negative—

ZIERLER: It can't go below zero.

PASTOR: It can't go below zero. [laugh]

ZIERLER: I see. And what is the practical value of being able to measure surface tensions, broadly speaking? What's the larger field that's of interest here?

PASTOR: Well, it's an important property of liquids. The surface tension of a water vapor interface is a measure of the cohesive force of a liquid.

ZIERLER: And you would need to know this for what?

PASTOR: Well, I guess, getting back to the original problem Goodisman was interested in, it was you measure the surface tension of this mercury droplet with voltage, which how these electrolytic cells work—I wasn't too involved in that. I was just focusing on the surface tension. Later on, it turns out the surface tension becomes extremely important in lipid bilayer simulations, which is what I do. In industry you also look at the surface tensions as a way to measure the effect of surfactants.

ZIERLER: Mm-hmm. Like in soap and things like that?

PASTOR: Yeah, yeah. Soaps lower the surface tension of water.

ZIERLER: Uh-huh.

PASTOR: That's very basic chemistry. And so that's one of the ways of looking at the effect of surfactants. You have a monolayer. You measure the surface tension of the monolayer, then you add surfactants, and that lowers the surface tension. And that gives you an idea of the interactions of this surfactant. And then that does come back to—and I'll explain that a little bit later, maybe with a piece of paper, I'm not sure—

ZIERLER: OK.

PASTOR: —there are a lot of surface-active membrane peptides, which is what I do now, that lower the surface tensions of these bilayers. This changes the mechanical properties and then allows the bilayer to fuse and to make holes in it. So it ultimately becomes a very rich aspect of cell function. But at this time, I was just trying to do a very simple thing using a formula to calculate the surface tension of this molten salt, which is, like, 500 degrees or something. Had nothing to do with biology.

ZIERLER: Right. Now, at this point, you said you were thinking as an undergraduate about going for your MD.

PASTOR: Yeah.

ZIERLER: But at this point, had you officially sort of changed course or you were—

PASTOR: Yes.

ZIERLER: —still thinking about pursuing that?

PASTOR: No, no. That was long gone.

ZIERLER: OK. And so at this point—

PASTOR: I was all in to trying to become a scientist.

ZIERLER: Become a scientist. And you weren't yet specifically interested in health science research? This was more theoretical?

PASTOR: Yeah. I was interested in biophysics longer term, but I wanted the physics part of the biophysics.

ZIERLER: Yeah.

PASTOR: And I felt that, in the long run, this would end up being something to do with health science. And I remember my mother asking me—this was the mother who hassled me, "What are you going do?"

ZIERLER: Yeah.

PASTOR: What does a theoretician even do?

ZIERLER: Yeah, yeah.

PASTOR: And then I think I said—I don't know if this was when I was starting with Karplus or still in Syracuse—that, "Well, one day we'll be able to make medicines with this stuff." But, you know, I was lying about "one day". I knew that "one day" would be a really long time in the future. [laugh]

ZIERLER: [laugh] Sure. Sure.

PASTOR: But it turns out—just to super fast-forward—I actually finally have a paper where we actually designed a new drug using computer simulations—it was just published in January.

ZIERLER: Uh-huh.

PASTOR: So it did happen.

ZIERLER: It did happen.

PASTOR: It just took 40 years, right? [laugh]

ZIERLER: You didn't know it, but it did happen in the end.

PASTOR: I mean, I had faith, right?

ZIERLER: Good.

PASTOR: But I guess underlying this thing is that you have faith in physics, that it's ultimately—I don't want to sound like I'm trying to proselytize, but I did have faith that the physics would lead to this.

ZIERLER: Yeah.

PASTOR: And this was like you're basing it on fundamental stuff. That was also the notion. And I'll get back into the molecular dynamics simulations in a little bit.

ZIERLER: Sure.

PASTOR: 'Cause that's why I went to Karplus, that if you do it really right, you're on firm footing. I used to be a rock climber and, you know, you always want to be on firm footing.

ZIERLER: Yeah.

PASTOR: Just like you don't take jumps.

ZIERLER: You mean like theoretical footing?

PASTOR: Yes. That's what I meant. I mean, this is based on Newton's equations and then quantum mechanics as necessary. You're not modeling it just with some made-up equation that looks linear or something that you just slapped together.

ZIERLER: Right.

PASTOR: You're always basing it on Newton's equations or a more rigorous equation. That's the whole notion of doing the physics as opposed to modeling in a looser manner.

ZIERLER: And then what was your thesis project at Syracuse?

PASTOR: Well, it ended up being the surface tensions of molten salts.

ZIERLER: OK.

PASTOR: Goodisman was the one who actually figured this part out, 'cause I was still pretty young. and he's smart, that the Kirkwood-Buff-Fowler equation, applied to a charged system, like a molten salt as opposed to liquid argon, if you add it up how you were doing the sums, it actually violated electroneutrality. Kirkwood, famous guy, right? And this textbook equation—

ZIERLER: What does it mean to violate electroneutrality?

PASTOR: When you integrate it over the liquid, it had a net charge.

ZIERLER: OK.

PASTOR: Because you cut the intervals off when they hit the surface, so at any one point you would integrate over it and the charge wouldn't be zero.

ZIERLER: Uh-huh.

PASTOR: And if you're doing it correctly, the charge is zero. Plus, it also violated some symmetry properties. So it was a very interesting experience. You go in, you look at something that should be right, it turns out to be way wrong and—

ZIERLER: Now, what's wrong, the experiment is wrong or the theory is wrong?

PASTOR: The theory was wrong.

ZIERLER: Uh-huh.

PASTOR: The experiment gave surface tensions that were positive, as is physically correct. The theory applied rigorously gave negative surface tensions.

ZIERLER: Right.

PASTOR: The reason for that was there was this explicit assumption in the theory with the cutoff, when it's applied to a molten salt with positive and negative charges, that they were not canceling out correctly. And the system ended up with a net charge.

ZIERLER: Which means this tells you that the theory needs to be corrected?

PASTOR: Yes.

ZIERLER: And this is the thesis, essentially.

PASTOR: Yeah, yeah.

ZIERLER: OK.

PASTOR: It was a Master's thesis. So we put on a fix for the theory to scale it. It was kind of a simple fix and ad hoc to enforce electroneutrality. And then we got correct surface tensions, positive surface tensions.

ZIERLER: Right.

PASTOR: But that was more Goodisman doing that. I mean, I wasn't ready for it yet.

ZIERLER: Yeah, yeah.

PASTOR: I was pretty happy about it. I wasn't aware that I shouldn't have been quite happy because, for your PhD, you're really supposed to do it, not have an advisor do it for you. [laugh]

ZIERLER: [laugh]

PASTOR: But I didn't know that part.

ZIERLER: Right, right. And are you talking with Goodisman about your next move? Was he advising you to move on from Syracuse?

PASTOR: Yeah.

ZIERLER: What's the advice you're getting?

PASTOR: He is a very warm person.

ZIERLER: Yeah.

PASTOR: Just a great advisor. I see him—still in contact with him. I'm going to see him this summer.

ZIERLER: Oh, yeah? Is he still active in the field?

PASTOR: No, no. He's just retired.

ZIERLER: OK. From Syracuse? Did he stay there?

PASTOR: Yeah. He stayed there. So the next trip to Montreal we'll go up through Syracuse and say hi to him and his wife.

ZIERLER: OK. Very nice.

PASTOR: Yeah. He's a lovely person. I was his only student and so we always played—

ZIERLER: And he was assistant at this point—assistant professor?

PASTOR: No, no. He was a full professor.

ZIERLER: He was a full professor?

PASTOR: Yeah.

ZIERLER: OK.

PASTOR: Although not much older than I've learned since.

ZIERLER: Right, right.

PASTOR: Ten years or something. But already more accomplished, very accomplished.

ZIERLER: Yeah.

PASTOR: He had written books. And so we played the tennis during lunch every day in the warm weather and squash almost every day in the cold weather. And we had a very warm relationship. And I remember him saying about leaving, he said, "Well, if you want to make something of yourself, you have to have a pedigree."

ZIERLER: Yeah.

PASTOR: And we talked about Harvard and he knew Martin Karplus. He said, "Yeah, he'd be good."

ZIERLER: Yeah.

PASTOR: So he strongly advised me to move on.

ZIERLER: So this is now—you defend the master's thesis in—

PASTOR: '77.

ZIERLER: —'77.

PASTOR: Yeah.

ZIERLER: OK. And from there, he connects you to Martin Karplus, that's the connection?

PASTOR: Yeah.

ZIERLER: OK. Did you apply anywhere else, or that was your spot?

PASTOR: No. Several places. I got in most. I didn't get in the University of Chicago, but I was really happy I got into Harvard, so—

ZIERLER: Sure.

PASTOR: But I don't remember all the places at the moment.

ZIERLER: OK. And so, the decision to focus on biophysics specifically—

PASTOR: Yeah.

ZIERLER: —for the PhD, was the idea there that this was your original intent at Syracuse and it didn't work out so now this was your second chance to get directed with biophysics?

PASTOR: Yeah. I mean, but second chance building on—

ZIERLER: What you were doing already?

PASTOR: —all the physics that I had learned in Syracuse.

ZIERLER: Right, right.

PASTOR: I wasn't ready to be a theoretician when I first started Syracuse.

ZIERLER: Sure.

PASTOR: But, by the time I got to Harvard I kind of was.

ZIERLER: Right, right. And what did you know of Karplus's work up until this point?

PASTOR: Not much.

ZIERLER: Uh-huh.

PASTOR: I mean, I knew he was famous, a bigshot professor at Harvard. I knew about some of the NMR stuff he had done with the Karplus equation. But, at that point, Karplus was just transitioning himself, interestingly. He had just started only a couple of years earlier—the previous group of graduate students, the postdocs had just started molecular dynamics simulations. So, in fact, in '77, which is right when I started, he and McCammon and Gelin had just published this 3 picosecond simulation of BPTI, which is bovine pancreatic trypsin inhibitor. Do you know what that is?

ZIERLER: No.

PASTOR: OK. It's a 58-residue protein. Now, it was sort of funny, when you learn about proteins and, of course, they'll say a peptide is amino acids—you know this stuff?

ZIERLER: Mm-hmm.

PASTOR: OK. An amino acid is this one unit. A peptide is a collection of them.

ZIERLER: Yeah.

PASTOR: And then, when you get to around over 100, it's called a protein. So at that point, the official thing was like something that's 20 to 30 is a peptide. You have to be over 100, but this is 58. It was like borderline protein—

ZIERLER: OK.

PASTOR: —right? [laugh] But actually now it's considered a protein.

ZIERLER: OK. The threshold has dropped.

PASTOR: Yeah. The threshold dropped because that's all you can simulate, right? [laugh]

ZIERLER: [laugh]

PASTOR: Plus there was a crystal structure. So there were some other ones that size. So everyone agreed to lower the bar on it—

ZIERLER: Yeah.

PASTOR: —so they could do protein simulations.

ZIERLER: OK.

PASTOR: So do you know about molecular dynamics?

ZIERLER: A little bit, yeah.

PASTOR: OK. So you solve Newton's equation, this is the big deal. It's better if you have it in a solvent, but at that point you really couldn't have it in a solvent. And so they just would simulate this 58-amino acids, which was about 500 atoms. And they could simulate it for just 3 picoseconds, because the time step had to be a femtosecond and that's all you could do. They published that in *Nature.* And the result of that simulation was one of the tyrosine rings flipped a little bit, right? That was it. So it just went like this. That was the first one, but that was— just as I was starting, they had done that. It was really ground floor, the whole thing, right?

ZIERLER: Uh-huh.

PASTOR: So now you know—

ZIERLER: So Martin was new to this, and you jumped in at that point there?

PASTOR: Well, semi-new. He had done—like, one round of graduate students had done that.

ZIERLER: Uh-huh.

PASTOR: They had put that together. They had to do a lot of stuff. But, remember, Martin had been around a little bit. The work he won the Nobel Prize for he'd done with Warshel, which was a little bit earlier. But that was just on retinal, right? The idea of doing molecular dynamics wasn't completely new —people had started molecular dynamic simulations in the '60s, right? The physicists had been doing it, but with simple liquids like the liquid argon.

ZIERLER: Uh-huh.

PASTOR: There's a very good history of simulations in Allen and Tildesley, do you know about that?

ZIERLER: Yeah.

PASTOR: OK. So, remember, the whole simulation business started in Los Alamos, right?

ZIERLER: Yeah, right.

PASTOR: After the war, they had all these computers that were now kind of empty. So all the physicists started doing these simulations, right?

ZIERLER: Uh-huh.

PASTOR: They started out with hard spheres and realized soft spheres were actually easier and more realistic. During the '60s, all the advances were just liquid argon. And then, in the '70s, people started doing more complex systems, and that's when Karplus jumped in and did these peptides and small proteins at first. But Karplus had previously done simple molecular dynamics. His $H+H_2$ was just classical mechanics on a quantum mechanical surface. So you say, why should molecular dynamic simulations work, right?

ZIERLER: Yeah.

PASTOR: I mean, it almost doesn't make sense because you say, gee, those are atoms. Aren't they quantum mechanical? Well, it turns out, the potential energy surfaces, you need quantum mechanics to extract them, but once you have the potential energy surfaces, you can run classical mechanics on those surfaces. Others realized that. Karplus capitalized on it. This is what I keep saying is it's built on fundamental things.

ZIERLER: Right.

PASTOR: I remember talking with Karplus about that. Why should this stuff even work, but he knew.

ZIERLER: Yeah.

PASTOR: So you can run classical mechanics on a quantum-mechanical-based surface and get physics. So then he took that understanding—I mean, Karplus got his PhD with Linus Pauling, right?

ZIERLER: Yeah.

PASTOR: That's where he learned quantum mechanics. Interestingly, he had wanted to work with Kirkwood—I think Kirkwood was there—but Kirkwood had retired —so he worked with Pauling as his fallback.

ZIERLER: Yeah. That's a good fallback to have. [laugh]

PASTOR: Yeah. Rough life, right? [laugh] And so he came in as a physicist.

ZIERLER: Yeah.

PASTOR: I think of all the simulation groups, the Karplus group was probably the most physics based. Because Karplus seeded that, and the standards, the worldview, the whole element of rigor. But it's tricky. You also have to make approximations

ZIERLER: Now, were you working with him on a one-on-one basis or were you one of the graduate students in the lab that he was overseeing? What was the dynamic there?

PASTOR: Well, utterly different from with Jerry Goodisman. Jerry Goodisman was tennis every day and then conversations.

ZIERLER: Yeah, sure.

PASTOR: And I'd go over to his house and knew his family.

ZIERLER: But, as you said, you were his only student.

PASTOR: I was his only student.

ZIERLER: And how many did Karplus have at this point?

PASTOR: At that point, he had just come back from France, so he was rebuilding his group, and it quickly became around 10.

ZIERLER: OK. Right.

PASTOR: By the time I left it was 22. I remember that because it was enough for a football team—a football game.

ZIERLER: [laugh] And were his students working together in the lab?

PASTOR: Yeah. But some worked more together than others. It wasn't like we all had little assignments and we just did them and worked like a big team.

ZIERLER: Yeah.

PASTOR: Karplus tended to give us our own projects. But we'd talk and help each other.. It was a very, very nice group. We're still all very close friends.

ZIERLER: Right, right.

PASTOR: Even now, we still have these meetings. We see each other every year.

ZIERLER: The Karplus group?

PASTOR: The Karplus—we still in some way think of ourselves as the Karplusians

ZIERLER: [laugh]

PASTOR: —which is a little weird 'cause we're all approaching 70 and we're still his children, but whatever. [laugh]

ZIERLER: [laugh] Right. Sure, sure. Now, was biophysics its own department at Harvard—

PASTOR: No.

ZIERLER: —or was it a subset of the physics department?

PASTOR: It was a program. So I was accepted in the biophysics program.

ZIERLER: OK. Located within the department of physics?

PASTOR: No. It was—

ZIERLER: It's its own program?

PASTOR: —separate at that point.

ZIERLER: OK.

PASTOR: It was actually originally—when I got in, it was in the medical school. Then it was moved onto the main campus, to the Cambridge Campus.

ZIERLER: Uh-huh.

PASTOR: And as a PhD student in biophysics, you could work with anybody in any of the departments. A lot of people ended up working in the chemistry, but some in the biology. I don't know if any worked in the physics department because of a different kind of physics

ZIERLER: Yeah. [laugh]

PASTOR: Field theory and cosmology stuff, right?

ZIERLER: Sure, sure.

PASTOR: But there was a bunch of us in biophysics who ended up working with Karplus.

ZIERLER: Yeah.

PASTOR: So that was that. But the way he ran his group, he tended to give us our own projects and we would just evolve with them.

ZIERLER: And the projects that he gave out to the students, were they related because there was one general field of interest that he was pursuing? Or how did he go about assigning these ideas and topics to his grad students?

PASTOR: He would, I think, try to impose some relation, but not a super lot.

ZIERLER: Yeah.

PASTOR: I mean, some people just gravitated towards revamping the program, which is now called CHARMM—

ZIERLER: Right.

PASTOR: —Chemistry at Harvard Macromolecular Mechanics.

ZIERLER: Yeah.

PASTOR: So at that point, there was a program, but it was sort of slapped together. I think some of it was from Berendsen's group in Netherlands. Others, like Bruce Gelin, wrote parts, but at that point it was very highly tailored just to run these single things.

ZIERLER: Right.

PASTOR: Just the protein. So there was a group, like Bernie Brooks—are you going to talk to him?

ZIERLER: I hope so, yeah.

PASTOR: Bernie's good. Bernie was in on the original development of the version of the program that's now CHARMM.

ZIERLER: Uh-huh.

PASTOR: Bernie just ended up rewriting everything because there were mistakes in the other one, just the stuff that happens. So he revamped that. There was a group of more of the coder types who worked with each other. But Karplus would be more involved in the more theoretical parts like in the potential energy function, which is a big deal in these simulations.

ZIERLER: Yeah.

PASTOR: That's really the sort of garbage in, garbage out problem.

ZIERLER: Sure.

PASTOR: And so he gave Wally Reiher the water and we tried to work on the water model. And we ended up just taking the Jorgensen one. When I started, at some point I guess I told him I was interested in membranes or—I don't know exactly when this was, but I do remember very exactly the moment that I agreed to my thesis. He said something like, "You're a pretty smart guy." So, yeah, it's a trick, right? [laugh] And so he said, "Well, I think a good thesis would be

something on the techniques, the methods."—and I'll tell you what that was—"And then, something on potential energy functions and then something on membranes. You figure it out."

ZIERLER: OK.

PASTOR: The group had already started doing some Brownian dynamics simulations. Do you know what those are?

ZIERLER: No.

PASTOR: OK. So molecular dynamics simulations, you have your basic molecule and then you're supposed to put it in solvent and then, if you just propagate those equations, you get what that molecule does. The problem is that the solvent—there's a lot more solvent than there is molecules. You end up quote "wasting time."

ZIERLER: Just because molecules are tiny?

PASTOR: Yeah. But to put anything into a solvent means you have to put a box. So your box has a lot more solvent molecules and it has one little protein or butane or something. So you're calculating all the forces between all the particles. So I'm talking about 90% of your calculation is doing solvent.

ZIERLER: Mm-hmm.

PASTOR: So who cares, right? That's the essence of diffusion equations. I Look at a ball falling in a solvent. You would like to calculate the trajectory of that ball without calculating all the solvent, but you have to put the dissipative force of solvent in somehow. Brownian motion

can describe motion of a pollen particle" as Einstein did, or diffusion of a protein. You just follow the solute particle.

ZIERLER: Mm-hmm.

PASTOR: And you say, well, there's partial differential equation or you can make a stochastic equation for the motion of that particle. You take away all the solvent, you replace it with the forces that the solvent adds. So, at that point, there was code for Brownian dynamics and Langevin dynamics in the group. Langevin had the inertial motions. Brownian dynamics is the equivalent of the Smoluchowski equation. Langevin dynamics is the equivalent of the Fokker-Planck equation which has the inertial terms. So he said, "Well, why don't you just run butane and figure out what the differences are?" I guess he had an idea that sounded like a reasonable project. I later on found out, when I understood more of the theory, I could have done that whole project in, like, 10 minutes. [laugh]

ZIERLER: [laugh] Yeah.

PASTOR: Because there were equations that I hadn't know about that could tell the difference between the Smoluchowski and Fokker-Planck equations.

ZIERLER: Now, did Karplus know that? Was this one of his methods to—his teaching style?

PASTOR: I don't think he knew.

ZIERLER: Uh-huh.

PASTOR: It was sort of new to this field.

ZIERLER: Yeah.

PASTOR: So it just seemed like a technical thing.

ZIERLER: Yeah.

PASTOR: It was a reasonable question: should you run Langevin dynamics or Brownian dynamics? I don't think he had thought about it super deeply. Maybe he thought about it and said, oh, that sounds like a good way to learn something. Which it was.

ZIERLER: Yeah.

PASTOR: I don't think he knew that there was an analytic answer for that question. I mean, it was complicated because the analytic results were for harmonic oscillators, and this was more complicated. So I spent some time, a year or so, just running butane simulations with Brownian dynamics and Langevin dynamics, and doing a lot of rock climbing at that point. Karplus had gone off to France. I got to be a good rock climber.

ZIERLER: Oh, yeah?

PASTOR: Yeah. Karplus was not happy about that.

ZIERLER: Uh-huh. He wanted you in the lab more?

PASTOR: Yeah. So at one point he said to me, "You could be a pretty good scientist if you focus a little bit less on rock climbing."

ZIERLER: Uh-huh.

PASTOR: And, like a typical graduate student, the only thing I heard him say, "You could be a pretty good scientist."

ZIERLER: [laugh]

PASTOR: [laugh] So his subtlety was lost on me, yeah.

ZIERLER: Ah.

PASTOR: [laugh]

ZIERLER: So he went back to France for what? What was he doing in France?

PASTOR: A sabbatical.

ZIERLER: OK.

PASTOR: He would like to do that. Which is a kind of cool thing to do.

ZIERLER: Right. This is where he would write, or he talked there?

PASTOR: I don't know. He'd think there. [laugh]

ZIERLER: [laugh] OK, OK.

PASTOR: Once a week, he worked in a restaurant.

ZIERLER: Really?

PASTOR: Yeah. He's a very good cook.

ZIERLER: Huh.

PASTOR: So that was his relaxation.

ZIERLER: OK.

PASTOR: That was a time that you could just volunteer and they would let you do it. Now they'd probably make you pay, right?

ZIERLER: Sure, right.

PASTOR: But anyway, he just liked to work in a restaurant—

ZIERLER: Fascinating.

PASTOR: —one day a week. Yeah. He didn't get very involved in the technical details of our research. We had to do that ourselves.

ZIERLER: Sure.

PASTOR: But I remember at one point I asked him how to cook a goose and he gave me detailed instructions on the correct way to cook a goose.

ZIERLER: [laugh] Uh-huh.

PASTOR: And he would always give us advice on wine, and really good advice. Not, like, oh, you have to buy this super-expensive wine.

ZIERLER: Right, right.

PASTOR: He'd ask you how much you wanted to spend, and he'd recommend a bottle of wine for you.

ZIERLER: Uh-huh. Wow.

PASTOR: He was great like that. So he didn't hand-hold us about science, but he would always help us with that.

ZIERLER: [laugh]

PASTOR: So it was a fun place. Anyway, so I did that, the butane, and then I worked—

ZIERLER: And this is solo work, or you have other graduate students who are partnering with you on this?

PASTOR: No. I did that—I had one postdoc who was supposed to help me, but he never helped me at all. And I had a program that I had inherited from Wilfred van Gunsteren, but he had already gone, so I just figured it out myself.

ZIERLER: Mm-hmm.

PASTOR: And then, there was a problem in hydrodynamics about the friction constant—because, remember, you have to replace the solvent with a friction constant.

ZIERLER: Right.

PASTOR: It wasn't clear what the friction constant was. It turns out there was an interesting answer for it, so I spent a year figuring all that stuff out, reading the literature and coming up with a solution. I don't want to get into that, but that was another part of it of my research. And then this potential energy function stuff, it turned out I had a pretty good—what I thought was a good idea and Karplus agreed So I did all these quantum mechanics, and it turns out it was kind of terrible idea. I'll just leave it that way, all right?

ZIERLER: No. Please tell me.

PASTOR: I realize we could—

ZIERLER: Tell me. That's what we're here for.

PASTOR: Well, OK. But we're only in 1980 right now or something. [laugh]

ZIERLER: [laugh] That's OK. That's fine. That's fine.

PASTOR: OK. Anyway, the problem was how do you rigorously do quantum mechanics on a united atom. At that point we were trying to save computer time. So, you know a hydrocarbon has carbons and hydrogens, right?

ZIERLER: Yeah.

PASTOR: So butane is C, C, C, C, but there's actually ten hydrogens. You want to reduce that to just four balls that model butane.

ZIERLER: Mm-hmm.

PASTOR: This is called a united atom because you combine each carbon and its hydrogens made them one particle.

ZIERLER: Mm-hmm.

PASTOR: The problem is how would you model such a potential—starting from first principles.

ZIERLER: When you say "first principles," what does that mean? First principles of what?

PASTOR: Quantum mechanics.

ZIERLER: Uh-huh.

PASTOR: Beause the actual quantum mechanical system for butane contains carbons with two or three hydrogens. And there's orbitals and, you know, the whole thing. So how do you rigorously go from fourteen particles to four?

ZIERLER: Yeah.

PASTOR: And I had an idea that you could just add them in a certain way, and it seemed right. And that's what people had been doing. I followed that through and did quantum mechanics using density functionals, and it turned out to be all wrong.

ZIERLER: How'd you find out it was wrong?

PASTOR: Oh, because when we—well, it was funny. It turned out—now you're asking me stuff I'm a little vague about. I mean, I put it on my thesis. As you added the hydrogens, the effective radii was going down because of the Van der Waal's forces, and it didn't make sense. But it took me a long time to figure that out. And that was part of one of these things you learn in graduate school. You stick with something in just this blind way. And then you go back and you—if you had actually done the proper estimate at the very start, you would've realized this would've been a natural consequence. Karplus didn't tell me about that. I suppose he didn't really think about. It would've been kind of malicious, I think, to let me spend six months—

ZIERLER: [laugh]

PASTOR: I was also doing a lot of rock climbing, so I wasn't focused well enough anyway.**ZIERLER:** [laugh] Maybe he was sending you a message.

PASTOR: Could have been. I don't know. But I don't think he—it was like, when you have enough kids, you don't really worry too much about any given one.

ZIERLER: Sure, sure.

PASTOR: So I don't think he was—that was just his style.

ZIERLER: OK.

PASTOR: It was, like, figure it out.

ZIERLER: Right.

PASTOR: This project was a failure, and it turns out other people had been making the same assumption.. Later on, some of it was incorporated into CHARMM. But it wasn't as good as it really should have been, because this shrinkage was wrong. When I finally realized that I told him. He said, "Yeah. It's garbage. Let's just throw it away." So there went all that time. But you learn that lesson.

ZIERLER: But was this useful for your dissertation? Did it inform your project at all?

PASTOR: No.

ZIERLER: You switched courses at that point?

PASTOR: Yeah.

ZIERLER: OK.

PASTOR: But it was just like—it was the learning process of—

ZIERLER: Intellectually, it was probably—

PASTOR: Yeah.

ZIERLER: —very useful for you.

PASTOR: Yeah, yeah, intellectually. There's this interesting grid that some people find a offensive, maybe. This was by a German general, and he divided his army up into these categories: smart and stupid and hardworking and lazy. Have you ever seen this before?

ZIERLER: I have not, no.

PASTOR: You think that stupid and lazy would be the worst possible thing, but it's actually not.

ZIERLER: And so, for our listeners, we're looking at a nine-box grid where lazy is—

PASTOR: Well, it's really a 2 by 2.

ZIERLER: The 2 by 2? Those are the blanks?

PASTOR: Yes. So lazy and stupid is OK as, like, foot soldiers because you just tell them what to do—

ZIERLER: Sure. And they'll do it.

PASTOR: —and they'll just do it.

ZIERLER: Right.

PASTOR: Smart and hardworking, those are the officers. And those are people who are on the ball and think up of new stuff.

ZIERLER: Yep.

PASTOR: Smart and lazy are the generals.

ZIERLER: [laugh]

PASTOR: They're not lazy, but they have to delegate, right?

ZIERLER: Sure. Right.

PASTOR: But the most dangerous people are the hardworking and stupid.

ZIERLER: Ahh. [laugh]

PASTOR: [laugh] And you get that, right?

ZIERLER: Yeah.

PASTOR: And so I think where this applies in academia, where stupid really means inexperienced. You can choose not use the word "stupid" if you're keen on not doing that. I don't mind using it. So when you're just starting as a graduate student, you're in this lazy, stupid category, because you're just supposed to learn the basics and not get cocky.

ZIERLER: Right.

PASTOR: And then, by the time you're getting your PhD, you're up to smart and hardworking, and then when you're a PI you're lazy and smart.

ZIERLER: Yeah.

PASTOR: —because you don't do those details.

ZIERLER: Right.

PASTOR: But where you really get in a lot of trouble is if you're hardworking and stupid.

ZIERLER: So what kind of trouble can you get into in that category?

PASTOR: Well, depending on when someone stops you, right?

ZIERLER: OK. You mean, you could just be spinning your wheels for a long time?

PASTOR: Yeah. That's sort of personal trouble—

ZIERLER: Yeah.

PASTOR: —you know, you lose a lot of time. You're going to learn a blistering lesson from that.

ZIERLER: Right.

PASTOR: If you're using up a lot of the computer time or experimental resources, you're pulling down the group.

ZIERLER: Yup.

PASTOR: If you're invading Iraq, you're—[laugh]

ZIERLER: Yup.

PASTOR: —I mean, this is exactly what happened, right? People didn't know what they were doing, they thought they did. They were worked really hard at it and caused no end of trouble. But getting back to science, if you're sure of something, then you publish something that's wrong and waste everybody's time.

ZIERLER: Yeah.

PASTOR: So wasting people's time is bad enough. Getting people killed is where it really matters. So this a general phenomenon. So I think, during my PhD years, the quantum mechanics I did for Karplus partially immunized me about being hardworking and stupid.

ZIERLER: Uh-huh, uh-huh.

PASTOR: Not to say I haven't done it again.

ZIERLER: [laugh] You knew what to look for, though?

PASTOR: Yeah. At least I can recognize it a little bit sooner.

ZIERLER: Sure, sure.

PASTOR: And I think, just between us as scientists, I think that job of a PI is to keep everyone out of that hardworking stupid quadrant as much as possible. The process of getting a PhD probably involves some time there.

ZIERLER: Yeah.

PASTOR: But even now, when the postdocs are kind of off into something, I say, you know, we might be in the northeast quadrant here.

ZIERLER: Yeah. Right.

PASTOR: And so that's a very important thing I took with me. That was project number two.

ZIERLER: Yeah.

PASTOR: Project number one was the butane.

ZIERLER: Right.

PASTOR: I published a decent paper on it in JCP. But, fundamentally, the paper was showing, here's all these simulations, and there's pretty good theory that explains it well.. My last seminar to the Karplus group was on how I could have done this project in 15 minutes.

ZIERLER: Yeah.

PASTOR: And, you know, Karplus thought that was funny enough. But the main project was to do membrane things, and that's really what started me on my whole life's work here.

ZIERLER: And this is the dissertation, you settled on membranes?

PASTOR: Yeah. Well, the butane stuff—I mean, all these things are in it, right? It's a big dissertation.

ZIERLER: Oh, yeah. Wow. That is big.

PASTOR: Yeah. But the point is that the Langevin dynamics, the hydrodynamics, not the quantum mechanics, all this led to a membrane thing. So at that point—remember I said that if you have all the atoms in a lipid—do you know what a lipid bilayer is?

ZIERLER: Mm-hmm.

PASTOR: OK. It turns out to do a simulation of a lipid bilayer, the smallest possible one, you need almost 20,000 atoms. This the early '80s. That would have been impossible to do well.

ZIERLER: What was the limitation at that point?

PASTOR: Just not enough computer power to run it long enough.

ZIERLER: I see.

PASTOR: And the potential energy functions were not that good. But fundamentally, the computer power available to us hadn't changed too much since Karplus's early simulation where you get, like, 3 picoseconds. So there was this time-scale issue that one had to get to—you know, you can't just simulate a little thing, have it go in, and then say you're doing science.

ZIERLER: Yeah.

PASTOR: Maybe you could do that once, right?

ZIERLER: Yeah.

PASTOR: But you can't keep doing it.

ZIERLER: Right.

PASTOR: So the idea that we had was motivated by a talk on lipid bilayers I heard at a Gordon Conference. And the idea is you could analyze NMR ^{13}C relaxation and by calculating the decay of correlation functions from simulations, which you can then relate to motions. So I had gone to a Gordon Conference and—

ZIERLER: And what are those conferences?

PASTOR: Those are, in various topics—I think they still are, and maybe they're in other places now. When I was a graduate student, they would be in high schools and boarding schools in New Hampshire in the summer when they were vacant. So they would have conferences there. You'd sleep in dorm rooms and it was nice atmosphere. There'd be around 50-something people there, some combination of professors and graduate students and—

ZIERLER: All biophysics?

PASTOR: They would vary. There were many different kinds. There was one for cell biology, but the one I went to was a membranes one.

ZIERLER: OK.

PASTOR: And Michael Brown had just done these experiments. And he asked, "How is a single chain of a bilayer relaxing?" And there's three modes of relaxation fundamentally. One is just the gauche-trans isomerizations of the chains. Some of this is outlined in that 2002 accounts paper that I sent to you.

ZIERLER: Yep.

PASTOR: So you could just look at the chain relaxation. And there was this notion that then the entire lipid could diffusively wobble as a rigid-body-like object. And lastly the entire membrane could have collective motions. It was known at that point that the isomerizations were quite fast, because there's a frequency dependence in the NMR relaxation that can spot slower motions on certain time scales. So you run the NMR experiment on different magnet sizes, each

with a different Larmor frequency. Each magnet has so many teslas and so on. For the fast motion, likea liquid alkane, you could change magnets and you always get the same result. That's the way of saying that there's no frequency dependence. That's because the isomerizations are faster than any of the magnet resonance frequencies. You just get that relaxation as background, it's a constant. And what Michael Brown found is that, as you vary the frequencies, you get very different results for the NMR relaxation. When he gave that talk at the Gordon Conference I was halfway-ish through my PhD. It was time to work on the main project.

ZIERLER: And where was he at this point?

PASTOR: At Virginia, UVA, which is a real membrane center.

ZIERLER: Uh-huh.

PASTOR: He then moved to Arizona, where he still is. When I talked with him about it at the meeting it seemed interesting because then you have a hypothesis to test: was his experimental result coming from single molecule motion or collective modes ? Actually, could I excuse myself for a minute? I have to—

ZIERLER: Yeah. Sure. That's fine. That's fine. We're good.

PASTOR: Yeah. Just a second.

ZIERLER: Take your time.

PASTOR: Well, it won't be too long. If you want to go too you can. [pause] OK. I'm back.

ZIERLER: OK.

PASTOR: I don't know if you have to turn it back on, but—

ZIERLER: No. We're good. I'd just like—

PASTOR: Anyway—yeah, sure. So I—

ZIERLER: Michael Brown, UVA, you're talking with him.

PASTOR: Yeah, yeah. And so it seemed like finally maybe I could have a project, you know, this one that Karplus said a couple years earlier, "Do something on membranes." So that waswhat I was going to do.

ZIERLER: Mm-hmm.

PASTOR: By that time, I had done Langevin and Brownian dynamics. I understood that method pretty well, and I knew about the appropriate friction constant from the hydrodynamics I had done. I had a decent potential, at least a plausible potential energy function from the quantum mechanics I had done. At least I knew some of the limitations. I just said to Karplus, "Well, why don't I just run a single chain?" So instead of doing the entire bilayer, I just do one single chain and run it, and then see if I can test Brown's hypothesis because I could simulate these motions. Not the collective, but maybe the wobble and certainly the isomerizations. And then I needed some extra potential to keep this from just curling into a ball, right? 'Cause you have to model the rest of the bilayer. So then I found a paper by Seelig, a Swiss guy who had done NMR. And his graduate student by the name of Schindler had developed an energy function that came out of mean field theory. So you could use mean field theory to model the NMR order parameter profiles that you get from experiment, which is a measure of how oriented each of these carbons is with respect to the bilayer normal.

ZIERLER: Mm-hmm.

PASTOR: If there's no order, the order parameter is 0, it turns out. If you look at the order parameter profiles in bilayer, they have this very characteristic shape where they're pretty ordered in the center of the chains, and then towards the end they're very close to 0.

ZIERLER: Mm-hmm.

PASTOR: Using mean field theory, you could get that profile. Karplus did help me in that one moment I said, "You know, I just read this paper by Schindler and Seelig and I think it's really important" I had tried simulating the chain in a conical potential but it didn't work.. I didn't say to him "I haven't asked you for much, but just look at this paper. I think this is the answer." but my request got through,

ZIERLER: [laugh] Uh-huh.

PASTOR: [laugh] And then he read it and said, the next morning, "That's a potential of mean force." And that's all he had to say to me, 'cause then I—

ZIERLER: So what did that mean to you? What did he see—what was the value that he saw in that that signed to you, this is a greenlight to move forward on this?

PASTOR: That if I differentiate that mean field equation, I can get the force that I should apply to that single chain. I hadn't quite put that together. I was just about there, and he just gave me this little nudge.

ZIERLER: Uh-huh.

PASTOR: So I'd be wrong to say I did it all by myself.

ZIERLER: Sure, sure.

PASTOR: But I value that little—it was, to me, the perfect advisor thing to do.

ZIERLER: Yeah.

PASTOR: Because he didn't say, oh, and then you do this and this and this. No. He just said, "It's a potential mean force." So I knew what to do, and then I—

ZIERLER: And you're confident at this point you're not working at the intersection of stupid and hardworking? [laugh]

PASTOR: No, no. I was smart and hardworking.

ZIERLER: OK.

PASTOR: There was no stupid hardworking thing at that point. [laugh]

ZIERLER: OK. OK. [laugh]

PASTOR: And then that became my—

ZIERLER: So that's full-steam ahead for your dissertation topic?

PASTOR: Yeah, yeah, yeah. And then I just—

ZIERLER: And what year is this when you settle on the dissertation topic, like '82?

PASTOR: Well, I mean, the final thing was around ‘82, I think.

ZIERLER: Right.

PASTOR: We agreed it was about membranes, but—

ZIERLER: Yeah.

PASTOR: Yeah. And then I just worked really hard and then—

ZIERLER: Right, right. Who'd you get on your committee? Who else was on your committee?

PASTOR: Bob Griffin, an NMR person.

ZIERLER: OK. At Harvard?

PASTOR: Yeah.

ZIERLER: Uh-huh.

PASTOR: And Don Wiley. But at that point, there weren't committees that mentored you through the whole process. There was just one at the reading of the thesis.

ZIERLER: OK.

PASTOR: It changed. But these were the old days.

ZIERLER: OK. Right. And what did you see as the—what was the motivation for how this would contribute to the field? What was your goal in this dissertation? What were you trying to achieve?

PASTOR: It was to essentially disprove Michael Brown's hypothesis.

ZIERLER: Right.

PASTOR: That is wasn't collective motions. And that was enough for me at that point.

ZIERLER: Sure. Which would mean what?

PASTOR: Well, it would mean that—

ZIERLER: I mean, more broadly conceived.

PASTOR: Well, it's a way to understand—it turns out this ended up being extremely important. And when I finally got the correct potential energy functions for bilayers, it was a way to understand what are the dynamic processes inside this bilayer to explain the NMR relaxation times—what are the kind of motions that lipids make? And they make a whole bunch. There's single-molecule, wobble, diffusion, and then undulations. As membranes become more rigid, the undulations get cut out, but they still might have the same local motions.

ZIERLER: Mm-hmm.

PASTOR: But putting it in the context that you're asking, this is still at the stage of really trying to understand membranes properly.

ZIERLER: Yeah.

PASTOR: I would like to say, oh, and then I realized I could design a drug for this. No. That was only like—

ZIERLER: You're an explorer, essentially.

PASTOR: Well, I suppose I was an explorer, but I was also a tool maker.

ZIERLER: Uh-huh.

PASTOR: I really just had this faith that if I really understand these things on a fundamental level—

ZIERLER: The practical value will come later on?

PASTOR: Yeah. Like, good things will happen.

ZIERLER: Sure, sure.

PASTOR: And I still have that faith.

ZIERLER: And was that your own personal intuition of having that faith, or were you trained to think like that in your education? Meaning, if you understand the thing that you're working on, the value will come later. Would you see that as a sort of personal worldview, or is that how you were trained intellectually as a scientist?

PASTOR: That's Western history. [laugh].

ZIERLER: [laugh]

PASTOR: It's, like, Western culture.

ZIERLER: Yeah, yeah. That's the philosophy major in you talking, probably.

PASTOR: Yeah, could be. But I just felt that the world needs people to understand the basics.

ZIERLER: Right.

PASTOR: And maybe that is partly the philosophy major, but philosophers stopped doing that a long time ago.

ZIERLER: Yeah, sure.

PASTOR: I mean, they still want to understand abstract concepts, but someone has to try to understand things in nature.

ZIERLER: Of course, of course. But a big way of thinking, a lot of people go in the other direction. They see what the issue is and they reverse engineer to try to understand.

PASTOR: That's true, but that wasn't me.

ZIERLER: That was not you?

PASTOR: Yeah. [laugh]

ZIERLER: Got it. OK.

PASTOR: But, truly, if you think—even those people who do the reverse engineering spent a good amount of time understanding how to do reverse engineering.

ZIERLER: Right.

PASTOR: So they did become experts in something.

ZIERLER: Of course.

PASTOR: And then they apply it. It just didn't come out of nothing.

ZIERLER: Right. Of course.

PASTOR: I mean, the people who want to—you know this protein folding problem?

ZIERLER: Yeah, yeah.

PASTOR: You know who is now doing the absolute best protein folding?

ZIERLER: Who's that?

PASTOR: They have these competitions— they're now won by these people at Google who don't know anything about biology, but they know how to do machine learning.

ZIERLER: Yeah. Yep, yep, yep.

PASTOR: Now, I don't know when they started doing machine learning, what their motivation was. Maybe they always wanted to do something practical. But they spent time deeply understanding machine learning. Then they applied machine learning to proteins, and they win all the competitions now. But they did know something deep. They just didn't say, oh, I want to fold proteins, and do any old crap. There are people who do that and they're always failures. They're typically in the hardworking stupid category, right?

ZIERLER: [laugh] Right.

PASTOR: I actually started writing a novel where I have a professor—someone trying to explain that grid to a first-year graduate student and she gets all crazy on him because it is a little insulting, right?

ZIERLER: Yeah.

PASTOR: Right. [laugh]. So I say that to young people because they get all angry at me.

ZIERLER: [laugh] Right, right.

PASTOR: So at that point—so that was my PhD thesis. And then I had—

ZIERLER: Now, at this point, are you sequential? In other words, are you just so focused on finishing the dissertation you'll figure out what you're doing next, or are you plotting your next career move over the course of writing the dissertation? Do you know where you're headed the day after you defend, I guess is my question.

PASTOR: Well, of course I did the day afterward, because I immediately started a postdoc with Attila Szabo.

ZIERLER: Right. Here at NIH?

PASTOR: Yeah. Literally, three days afterward, because I had a kid already and I needed to get to work. But your question is a great one. At that point, I already had a Master's. I spent that year in Rochester. I was 33 when I got my Ph.D. I was getting kind of older. About a year before I defended, I was wondering whether or not this was really right for me. So I actually applied to a drug company, to Abbott Pharmaceuticals. I applied to three places for postdoc, Gene Helfand at Bell Labs, Abbott Pharmaceuticals wanted people from Karplus's group to start molecular modeling labs. So I was—

ZIERLER: What was the Bell Labs postdoc? What would you have done there?

PASTOR: Polymer theory.

ZIERLER: OK.

PASTOR: Oh, wait. I guess, Clemente, as well.

ZIERLER: What's Clemente?

PASTOR: He was a quantum mechanics guy, a famous quantum mechanics guy.

ZIERLER: OK.

PASTOR: And then Attila Szabo just sort of sent up randomly—because I knew of some of Szabo's stuff. And so I went to Clemente and had a very nice time with him, but—

ZIERLER: And where was Clemente at that point?

PASTOR: I think he was—not in Bell Labs but around there.

ZIERLER: OK.

PASTOR: I just forgot. And I guess the main thing I remember is it being kind of chaotic, but having a great discussion with him and his wife over dinner about ripe figs. The perfect time to,eat a fig.

ZIERLER: Uh-huh.

PASTOR: Because most of the time around here, if you eat a fig it's kind of crummy, right?

ZIERLER: Yeah, sure.

PASTOR: I mean, dried figs are just awful. And when someone says a women's lips are like figs. I'm, like, ewww. [laugh]

ZIERLER: [laugh]

PASTOR: But he explained to me that in Italy you can find the perfect fig to eat.

ZIERLER: I see, right.

PASTOR: And that's where the metaphor really comes from.

ZIERLER: OK, OK.

PASTOR: But I didn't want to do science with that guy. Got the job offer.

ZIERLER: [laugh]

PASTOR: The interview with Helfand was a disaster so he didn't offer me the job, and I knew that wouldn't have been right for me. Abbott Pharmaceuticals, I actually was offered the job, a really good-paying job for that time. And then the last one was Attila Szabo, who I was just meeting for the first time.

ZIERLER: Yeah.

PASTOR: We had this great conversation—

ZIERLER: What was your connection to him? How did that happen?

PASTOR: Oh, he had been a student of Karplus.

ZIERLER: I see. OK.

PASTOR: So I asked Karplus what he thought of Szabo and he said, "Szabo is the smartest person I ever met."

ZIERLER: Yeah.

PASTOR: Pretty darn good.

ZIERLER: Yeah, pretty good coming from Karplus. Wow.

PASTOR: He sure doesn't say that about me, right? [laugh]

ZIERLER: Maybe he says that about you to Szabo.

PASTOR: I doubt it. [laugh] So that was Attila's calling card. And he's just this very personable, fun guy.

ZIERLER: And what was he doing circa 1984 at NIH? What was he up to at that point?

PASTOR: Well, he was here.

ZIERLER: Yeah.

PASTOR: He was looking at NMR relaxation. We talked about NMR relaxation of these T_1s from Michael Brown, and he had some ideas. At that point, he had just published these papers with Lipari on NMR motional modeling. So the PhD thesis was more just the ability to run the single-chain mean field simulations and analyze the fast motions.

ZIERLER: Yeah.

PASTOR: And that was enough for the PhD. And then, the idea was to continue them here on a more rigorous basis.

ZIERLER: So you had a clear idea of the unfinished work—

PASTOR: Yeah.

ZIERLER: —of your dissertation?

PASTOR: Yeah, at that point.

ZIERLER: Yeah.

PASTOR: So the reason why I came to NIH instead of taking the high-paying job at the drug company was that Attila said something like, "Well, you'll make more money there but you'll have more fun here."

ZIERLER: Yeah.

PASTOR: "Fun" meaning intellectual fun.

ZIERLER: Of course.

PASTOR: My wife was also fine with me taking the lower paying job so I could stay in academic science. And so then I came here. And then I was—

ZIERLER: And you have one child at this point?

PASTOR: Yeah, yeah. The professor.

ZIERLER: The professor, right.

PASTOR: But he was 18 months old. Still pretty smart.

ZIERLER: [laugh]

PASTOR: And then what happened, interesting that—so the first day I started there—

ZIERLER: The postdoc with Attila?

PASTOR: Yeah, the postdoc with Attila. Attila's good friend Bill Egan—not to be confused with Bill Eaton—

ZIERLER: Right.

PASTOR: —was a lab chief at the FDA branch that used to be here, CBER

ZIERLER: Right.

PASTOR: They had wanted to start a molecular modeling lab, but then they hired someone who had left to take a job at a drug company right when the equipment was finally here. So my main calling card was I had turned down a job at a drug company, so I was probably not going to just skip town.

ZIERLER: Yeah.

PASTOR: So I was offered a tenure-track job at the FDA the moment I started, the first day almost that I started my postdoc. Which was good, because I did need money. [laugh]

ZIERLER: Right, right.

PASTOR: They managed to pay me almost the same amount. I was offered $42,000 at Abbott and they gave me $36,000, so pretty cool, right?

ZIERLER: Yeah.

PASTOR: They argued that this was what I was worth.

ZIERLER: Yeah.

PASTOR: And it was agreed that I keep working with Attila for the first year or two.

ZIERLER: So it was essentially like a joint appointment?

PASTOR: No, no.

ZIERLER: It was less formal than that?

PASTOR: It was less formal. Formally, I sort of skipped the postdoc. I started May 31st and the fiscal year ended September 30th, so I stayed, and my postdoc was that time officially. And then I moved to FDA on October 1st.

ZIERLER: OK.

PASTOR: But I kept working with Attila, and we're actually pretty good friends now still. We haven't published with each other recently, but we eat a lot, drink wine with each other. And so it was with Attila that I really worked out that next level of the NMR relaxation. The first of the important papers were published in 1988 when we showed that that collective model doesn't work. We rigorously analyzed all the motions.

ZIERLER: So you kept up your work with Attila while you were at the FDA?

PASTOR: Yeah. Which was agreed upon.

ZIERLER: Right. And you kept that relation all the way through—what was it, '96 or beyond? How long did you have that informal dual appointment with the FDA and Attila? 'Cause I see you only—you come to NIH officially in 2006.

PASTOR: Oh, yeah, yeah, yeah. But that was, then, different part of the story, though. The thing with Attila is that we published joint papers through the mid-90s.

ZIERLER: Yeah.

PASTOR: I don't believe we've published anything since then.

ZIERLER: Right.

PASTOR: We remain good friends. It was mostly about a 10-year period where I was working with Attila on more statistical mechanics and finishing up that aspect of the membrane stuff.

ZIERLER: Now, at FDA, was there a mandate that you had to fulfill and you were able to do your own stuff on the side, or you were really free to pursue whatever it was that you wanted to pursue? How did that work?

PASTOR: For the first 10 years or so, or first 12 years, I had the complete freedom to do research. And I'll show you a plot that—what happened. So during that time, I was very productive. I published those papers with Brownian dynamics. And then, my next big step—I worked with Attila on some other technical things, which are still cited a lot. I'll show you. It's kind of exciting that—in fact, some of Attila's papers are getting cited more now.

ZIERLER: Yeah.

PASTOR: They're growing—kind of interesting. Most things aren't like that. So my first big membrane step was to publish those Brownian simulations and provide an alternative to Brown's model. Now, Michael Brown is also very nice, too. So, in fact—

ZIERLER: He wasn't upset with you that you were working to disprove his theories?

PASTOR: He's a really idealistic, high-minded person. I'll tell you one Michael Brown story.

ZIERLER: Sure.

PASTOR: This was in the early '90s when those papers had come out and people were inviting me to go to international conferences. I had made slides on an FDA slide-maker, and I was at this conference in Italy to show why Michael Brown's theory was wrong. His experiments were right. He'd given me all his data prior to publication. But I argued that his theory was wrong. So I filled my slide tray and the slides jammed because they were the wrong size for the Italian projectors.

ZIERLER: Yeah.

PASTOR: So Michael actually got up out of his seat, stood up, and hand-fed my slides.

ZIERLER: Wow.

PASTOR: Like, who does that?

ZIERLER: That's magnanimous.

PASTOR: It sure is. And that's, like, the very essence of being a scientist, I think that's one of them.

ZIERLER: That's a beautiful story.

PASTOR: That's really—I mean, I'm so appreciative of that.

ZIERLER: Yeah, sure.

PASTOR: Anyway, but my next scientific step—

[Someone knocks on door and enters]Oh, sorry.

PASTOR: Yeah. Could you come back later? OK. Thank you. So my next scientific step—I recognized that having this single chain was good for a foothold, but you really had to do a simulation of a full bilayer, right?

ZIERLER: Yeah.

PASTOR: So I worked towards that for the next several years. I used what I learned from the Brownian dynamic simulations to build the initial conditions. You know what that means?

ZIERLER: No.

PASTOR: Oh. So you saw the Newton's equations of motion?

ZIERLER: Uh-huh.

PASTOR: You have to specify the initial condition to generate the equations of motion, and you need to start with a bilayer that's in the correct phase. You could just put your lipids in a highly ordered densely-packed arrangement, but that would be a gel phase. A biological membrane is in a fluid phase and the chains are much more disordered than in the gel.

ZIERLER: OK.

PASTOR: So I developed a Monte Carlo method to generate the disordered chains, and then we packed them into a bilayer. At that point, we had computer time on what was then a

supercomputer here. And we ran it for six months. And by doing that, we could get 200 picoseconds, which is hardly anything, but it was just enough to sample all the isomerizations properly.

ZIERLER: Yeah.

PASTOR: And then we did a simulation of a neat hexadecane, and we saw that the isomerization rates were nearly identical to the chains of the lipid bilayer. So we learned something. We also compared fast relaxation times from the simulation and Michael Brown's experiments, and they were nearly identical, as well. You know what hexadecane is?

ZIERLER: Yeah.

PASTOR: So that was the first rigorous simulation of a lipid bilayer. I think it's fair to say that it jumpstarted the whole membrane-simulation field.

ZIERLER: I see.

PASTOR: So that's looked upon as "the simulation" that started the field.

ZIERLER: So when you say "simulation," what exactly is being simulated?

PASTOR: The positions of every atom in that system.

ZIERLER: OK.

PASTOR: And I don't have a movie handy. I used to have them, but they're out of date. You know, they're wrong players now, so—

ZIERLER: [laugh]

PASTOR: —I don't have one really handy. One of the postdocs could show you one.

ZIERLER: OK.

PASTOR: So, basically, you follow the motions of all the atoms for some amount of time. And, depending on how big your computer is and how fast, it can simulate more of them for longer periods of time. So this simulation was 17,000 atoms for 200 picoseconds.

ZIERLER: Yeah.

PASTOR: Now, we ran 300,000 atoms for 30 microseconds, but it's the same methodology.

ZIERLER: Right.

PASTOR: You just propagate Newton's equations of motion.

ZIERLER: Now, you're experiencing in real-time improvements in computational power.

PASTOR: I'll say.

ZIERLER: Yeah?

PASTOR: Yes.

ZIERLER: And this is really allowing you to do better experiments? What exactly is the value of having more computer power?

PASTOR: Well, you get two things. You're able to, one, compare your simulations with more and more experiments to make sure they're on track.

ZIERLER: Yeah.

PASTOR: And then, once you check that box, you don't want to be stupid and hardworking, right?

ZIERLER: Yeah.

PASTOR: Then you can sort of start to explore and see new things. So I'll really go fast-forward now. One of the things that I'm doing, like, right now—so it's just been published. So I spent a long time just trying to get membranes right. I think this was the first example of the membrane being right.

ZIERLER: Yeah.

PASTOR: That was '96. And then I kept working and making it better, improved stuff. But, to some extent, those were sort of quantitative improvements, right? The FDA —this will be a brief history—it went downhill for me after '96. They decided then I had to start reviewing investigate new drug applications and product license agreements.

ZIERLER: So for 10 years they basically allowed you to pursue your own research?

PASTOR: Yeah.

ZIERLER: And then, after that point, they said, now you're going to start doing stuff that we really need you to do?

PASTOR: Yeah. They just had a reorganization and decided, what are these scientists doing here anyway? And my little cozy thing was over.

ZIERLER: Did you have a retort to that? Did you say, well, hang on a second here. I mean, this research actually is useful for you for X, Y, and Z? Or was not the dynamic?

PASTOR: That was on deaf ears.

ZIERLER: OK.

PASTOR: They just said, you want to do that, well, do it at NIH.

ZIERLER: OK.

PASTOR: We're worried about drug safety.

ZIERLER: Yeah.

PASTOR: So for a while it worked. I mean, I think it was a good thing, but ultimately the culture—as they were getting more new drugs to approve and under more pressure to do it faster, they were just, why are we wasting our time with these scientists?

ZIERLER: Right. So at least for those 10 years, were you happy with the budgetary and equipment support at FDA? Did they provide you with what you needed to pursue what you wanted to pursue?

PASTOR: Yeah. Basically, as long as I kept my goals focused and small.

ZIERLER: Yeah.

PASTOR: At any one point, I had just one staff scientist and one postdoc. And so I was mostly just doing the research myself with this very small group of a total of three people. So it's not like I had this big Karplus-sized group or anything, right?

ZIERLER: Right.

PASTOR: I always had a small group. At one point, I had two postdocs and that was the best I ever had. But that was a short time. But it was good enough. But once I had to do more regulatory work, then the bottom just dropped out.

ZIERLER: Yeah.

PASTOR: And I could show you a slide of that, if you'd like.

ZIERLER: Yeah. I'd love to see it. Sure.

PASTOR: At some point, I just stood outside of myself and wondered what the heck was happening to me. So I started this plot a long time ago. So this plot is the number of—so the first part of the plot—so this has two parts. This is my FDA years, '85 to 2005, and then the NIH years. But what's interesting, you can see that during these FDA years, my publication output was fairly constant, between usually one and five papers, right? But now you look at—but this plot here is how many citations per paper, right?

ZIERLER: Yeah.

PASTOR: So you see, by the time I was really at my peak, most of my papers were getting on the average of over 100 citations. In '96, which just happens to be here, I believe, this is when I was hit with all this regulatory work. And even though I was still publishing, my number of citations per paper just sort of went down.

ZIERLER: Interesting. What do you attribute that to?

PASTOR: I couldn't do science.

ZIERLER: [laugh]

PASTOR: I was just doing the regulatory work. I'm not going to blame this on—

ZIERLER: Even though you were still publishing?

PASTOR: Yeah. But it was the stuff that you just get out there as that proof of life, rather than real creativity.

ZIERLER: Uh-huh.

PASTOR: And you can see that this is the average. I can show you the actual numbers on the next page. But you can just see it was dropping down to almost zero.

ZIERLER: Yeah. And you knew this in real-time? This was not just looking at a graph after the fact, you sensed this?

PASTOR: No, no. I actually started making this plot around here, just watching myself, self-diagnosing. So they gave me the job offer at NIH at 2005, and I started—did some joint work with Bernie Brooks. And my productivity just popped right back up.

ZIERLER: So you were really doing the regulatory thing at FDA for eight, nine years?

PASTOR: Yeah. That almost destroyed my research career. And then the move to NIH—so, obviously, the most recent stuff won't be cited much, right?

ZIERLER: Right.

PASTOR: But you could see that stuff now, after 2005, every year the average number for these papers is—

ZIERLER: Goes back up.

PASTOR: —over 100 citations.

ZIERLER: Right, right.

PASTOR: And then, here are two famous ones. This is the CHARMM paper and this is new force field. There are thousands of citations.

ZIERLER: Sure, sure.

PASTOR: But the point is—and then, these, you can see, are picking right up. It's just a very dramatic example of the same person, you sort of starve him—

ZIERLER: Right.

PASTOR: The analogy I was thinking about—you know what ringing a tree is?

ZIERLER: Yeah, sure.

PASTOR: That's how you kill a tree, right?

ZIERLER: Yeah.

PASTOR: I was being "ringed" or "rung".

ZIERLER: So what were the circumstances that finally got you over to NIH? How did that work?

PASTOR: Blind luck.

ZIERLER: Yeah.

PASTOR: So I always maintained a good relationship, so I still—

ZIERLER: Had you kept up with Attila over the years?

PASTOR: Yeah. But he wasn't able to help me in that move. But we were friends. But mostly I did work with Bernie Brooks. Now, I actually had helped Bernie to come here when he came here in '85, I think. But then what happened around 2004 or something like that, the FDA had made another big reorganization and they weren't even going to let me replace my single postdoc.

ZIERLER: Uh-huh.

PASTOR: She hadn't even been that good.[laugh]

ZIERLER: [laugh]

PASTOR: And they said, OK, we just can't support you at all. You can keep Rick Venable, the staff scientist, and you can be the director of a testing division. So it really looked like I had had it.

ZIERLER: Yeah, yeah.

PASTOR: And then, Bernie called me that same week and he said—we were at NIH, on this main campus at the time.

ZIERLER: The FDA was, you mean?

PASTOR: Well, CBER was in building 29 and now it's over in—

ZIERLER: White Oak.

PASTOR: —White Oak. Bernie was in building 50. And he said, the institute director, Bob Balaban called him and said he was occupying prime lab space.

ZIERLER: Yeah.

PASTOR: He asked if Bernie would be willing to move to an off-campus site up near the Twinbrook Metro station, on Fishers Lane, so to free up that lab space. And then Bernie asked me, "So what do you think I should tell him?" I said, "Well, do you think you have any choice?" He said, no, he doesn't think he has any choice, really. I said, "OK. Well, if you have no choice, tell him that you'll do it, but to make this work you need a critical mass and you need to have Rich and Rick join his group."

ZIERLER: Yeah.

PASTOR: And he said, "Oh, what a great idea!" And I said, "Yeah. OK." And Balaban said, "Oh, yeah, sure." And at that point Balaban barely knew who I was. I don't think he knew—he was just thinking I was some joke. But, as long as it got Bernie off campus and freed up the lab space, he was willing to do it.

ZIERLER: [laugh]

PASTOR: So it's not like getting Rich was this super draft pick he just got. You know, a free-agent trade, right?

ZIERLER: Uh-huh, uh-huh.

PASTOR: And it worked. So I was given a postdoc and I kept working with Bernie and we restarted our collaboration. So during the '90s, Bernie and I had done some really good things with my postdocs. And then we—

ZIERLER: And you're still on membranes at this point? You're still working on membranes?

PASTOR: Yeah.. Still on membranes. And then we made—the next big advance was to get the potential energy function revised, that solved all the problems that I had known about. And that's now the de facto potential energy function that everyone uses for membranes. I'll show you. So that was published in 2010. You can see it's cited 1700 times and all the programs use it. Google has it over 2000. This is the CHARMM paper.

ZIERLER: Right. So between the CHARMM paper and the lipid FF paper, what's the standout nature of those papers that explain those big numbers for citations? What do you think?

PASTOR: Well, many people use CHARMM—I'm, one of 25 authors of that one because I've contributed some constant-pressure methods with Bernie. That's just the program that people use.

ZIERLER: Yeah.

PASTOR: There's several programs that people use in the field, GROMACS and NAMD are the other two big ones. AMBER is less big. So that's just their tool, right? The lipid force field solved this problem of balancing all the forces. Previously, we ran lipid bilayers at constant volume, but it turns out when you ran them at constant pressure—this gets back to the surface tension stuff, actually. I didn't delve on it, but the last issue is with that.

ZIERLER: Right.

PASTOR: They would shrink. They would contract because the tangential pressure was slightly off. So we balanced the forces, and then I used all that information that I had gotten over the years to—including the NMR relaxation times, and matched those so I could get that right. And that was my clue that that everything was well balanced and right. So that's the force field that everyone uses, and not just CHARMM users but all the programs use it. So, in fact, not to be a little nutty here, but you can see that there were 434 citations for CHARMM, right?

ZIERLER: Yeah.

PASTOR: But 292 for my force field. Now, people use CHARMM for everything, right?

ZIERLER: Right.

PASTOR: Proteins, DNA, whatever.

ZIERLER: But this is much more specific within CHARMM.

PASTOR: So it's actually not that these were all using CHARMM, no. Every other program used them, too.

ZIERLER: Yeah.

PASTOR: So, in a Darwinian fashion, this is the force field that everybody uses.

ZIERLER: Right, right.

PASTOR: But within my story, the reason why it's such a good force field is because I had always worried about those details, the NMR relaxation time and diffusion and all these things.

So I'm really proud of that force field, and now we're improving it. There are some issues about long-range Lennard-Jones terms that we've just fixed. So there will be a new force field coming out this year sometime, but it'll be of the same sort. And it's really based in all the physics and thoroughly tested and validated. And then, that frees everyone, including me, to do these more applied things that I told my mother about 40 years ago.

ZIERLER: [laugh] Right, right. And when you say, "it frees up," how does it free up? What do you mean? That you've established this and now that gives you the reputation or the authority to pursue other things? What do you mean by being freed up?

PASTOR: Oh, pardon me. I meant that I and everyone else could look at these complicated systems with a confidence that you know the wheels aren't going to fall off of this car.

ZIERLER: Yeah, yeah.

PASTOR: I actually still do—I'd call them more fundamental things concerning curvature and spontaneous curvature and the "physicsy" stuff. But now I feel confident that I can do these big systems, and very complicated ones. So one of the things that I'm particularly interested in right this moment is these mimetic peptides, these peptides that can stabilize various structures associated with fat-synthesis and cholesterol regulation. Do you know about good cholesterol?

ZIERLER: Sure.

PASTOR: That's high-density lipoprotein, HDL. And the bad cholesterol is—

ZIERLER: LDL.

PASTOR: —the low-density lipoprotein, LDL. There are proteins that stabilize these structures. In terms of therapy, using the whole protein doesn't work because they get degraded. So they make peptides of parts of them, depending on the exact applications. And these peptides can be delivered more easily. They're stable. You can make modifications so they can't be metabolized by enzymes, which they'll do to proteins. And so they'll be stable drugs that are easily delivered. Lately we've been working on these much, much larger systems. For the paper just published in *Science Translational Medicine* we did a simulation on the Anton supercomputer of APOC2, apolipoprotein C-II, which is pretty long. We found out what part of the protein bound most stably to the lipid bilayer surface. One part of it just glommed on, was an alpha helix, and the other stuff which is sort of floating around. I can show you pictures of that, if you want.

ZIERLER: Mm-hmm.

PASTOR: I think I might've sent you that paper.

ZIERLER: Yeah.

PASTOR: And then the experimentalists took that part of the protein, they made a peptide of just that part, and they used that for experiments. It turns out that has all these properties that had helped—it acts just like APOC-II and does some other stuff. And then they tested it in mice and it lowered the triglycerides in mice. So they're actually making a drug based on that now. I'm not involved in that. I mean, my work is done for that project. But that's finally where we are.

ZIERLER: Finally in medicine after 40 years?

PASTOR: Yeah. I'm overjoyed with that.

ZIERLER: Sure.

PASTOR: But it's only now.

ZIERLER: Because why, because you see that obvious practical effect?

PASTOR: Yeah, yeah.

ZIERLER: Positive influence on society?

PASTOR: Yeah, yeah. I'd love to make people better, right?

ZIERLER: Right.

PASTOR: I'm also working with Josh Zimmerberg at Child Health on viral fusion. Now, I don't think—

ZIERLER: What is viral fusion?

PASTOR: Well, it's the way a virus gets into your cell. So, you have the influenza virus, lands on your cell surface, it's taken in by a separate organelle called an endosome. And once it's in, it's still isolated from the inside of the cell. It's like a little balloon in there. The virus has proteins on the surface with domains called fusion peptides. The fusion peptide glom onto the host cell surface and fuse the viral membrane to it. And then the virus dumps itsparticles in your cell. We're actually simulating to the peptides of influenza viral fusion proteins, which is a hemagglutinin, and we put them on the membrane surface. And we had to apply an electric field to push it along, but the fusion peptide basically forms pores.

ZIERLER: Mm-hmm.

PASTOR: So we've shown how that poration can form on a computer We're doing other simulations now more without the electric field. They did experiments—the experiments came first, I have to say, this time.

ZIERLER: OK.

PASTOR: And they actually found that, yeah, these things form pores. And then there's some mathematics that they're doing, as well, regarding spontaneous curvatures, which is something else I work on. So with viruses we're getting a better understanding of what fusion peptides are really doing to the membrane surface.

ZIERLER: So I have to ask, is this relevant for coronavirus?

PASTOR: Yes. But the main thing with coronavirus is, short term, wash your hands. Not shake hands, even though it's a nice thing to do, right?

ZIERLER: Yeah.

PASTOR: They'll be the antiviral treatments. Hopefully that will come soon, and the vaccine, of course, but that's, truthfully, maybe in a year and half. My time in the FDA gave me some insight to how long things take.

ZIERLER: Right.

PASTOR: You just can't shove a vaccine in someone. That's how you got thalidomide, right? I mean, it's serious.

ZIERLER: Right.

PASTOR: I mean, you can't just use it without testing it, right?

ZIERLER: Right.

PASTOR: But, in the long run, I think understanding deeply how this fusion process takes place—because people don't quite know what each part does. How can you block viral fusion? How can you trick the virus into not fusing—how can you do these things? Another one we're doing is antimicrobial peptides. You know, you have two immune systems. Are you aware of that?

ZIERLER: No.

PASTOR: Yeah. It's pretty cool. So the one you're aware of, I'm sure, is the adaptive immune system. Those are vaccines, right?

ZIERLER: Yeah.

PASTOR: So you take a part of the invading particle, usually a virus, in this case now we're back on the coronavirus or smallpox, anything, and you inactivate it in some way. You can't put the actual stuff in, but you can take a protein from a virus. There's no virus—you'll get a response to it, and then you'll get T cells. And then, when you see the real live virus that has that protein, then your machinery can kill it. The only organisms that have the adaptive immune system are vertebrates. None of the other ones have it, insects, whatever, snails, they don't have it. All organisms, including plants, have what's called the innate immune system, meaning you're just born with it. And one of the components of the innate immune system is antimicrobial peptides. So your skin will keep bacteria out, but you have lots of mucous membranes, your

eyes, the surface of your lungs, your nose. And if a bacteria gets in there, it can actually get in your body, right?

ZIERLER: Mm-hmm.

PASTOR: So you have these peptides called antimicrobial peptides that get released by the cells and then they'll glom on the bacteria and they'll kill the bacteria, or at least slow them down enough so that the rest of your immune system can catch up. It wasn't understood how they work. They assumed they were forming pores. So we did simulations of those and we showed that they don't form pores, which makes sense, because it's a peptide that's used in, like, close proximity of the cell itself. So if you had something that could just, blast holes in membranes, it would blast holes in your own membranes, right? You can't have that.

ZIERLER: Yeah.

PASTOR: It's like killing someone next to you by blowing up a hand grenade. Well, it's not good, right? So with the simulations we've done, we've shown how these form defects rather than pores. The defect is funnel-like, which causes the membrane to be leaky and then destabilizes the bacterium.

ZIERLER: Uh-huh.

PASTOR: This is an example where the insight came from simulation, not experiment. Getting back to the APOC-II mimetic here's a picture on the journal cover of the peptide that we found.

ZIERLER: Uh-huh.

PASTOR: And this was—I guess I'm getting a little braggy here, but that's OK, right?

ZIERLER: Absolutely.

PASTOR: But this was the first time in this journal that they had—

ZIERLER: This is *Science Translational Medicine*?

PASTOR: Yeah. That they've had a simulation picture as the cover. It's only been around since 2009, so it's not like this is 1870 or something.

ZIERLER: Right.

PASTOR: But the point is that this all happened by the combination of idealism and hard work and some luck, and getting this job at NIH and leaving FDA when I about had it.

ZIERLER: Are there things that you can do at NIH that you can't do anywhere else?

PASTOR: Yeah.

ZIERLER: Like what?

PASTOR: Well, one example is to work on the force field as much as I did. There's one other guy, Alex MacKerell, who works on other force fields. And he works with me on the lipid one sometimes. But he does the protein ones. It's really hard to get funded for anything in methodology. I mean, you can get funding inphysics for fundamental work. That's fine. You can get funding for biological work where there's a clear application. The National Science Foundation will fund the physicists. The NIH will fund the more biological research.. But to get

funding for simulation methodology is actually quite hard. And we're fortunate that here we can just do it.

ZIERLER: 'Cause you can just do it?

PASTOR: We can just do it.

ZIERLER: Because the funding is available? Because the equipment is available? All of the above?

PASTOR: Well, the equipment—yeah, but it's mostly just we're free to do it. We have postdocs—

ZIERLER: You mean, more like it's academic freedom to pursue—

PASTOR: Yeah.

ZIERLER: —kind of more like what it was during the first phase of your FDA career?

PASTOR: Yeah. But academic freedom is not what it once was, right?

ZIERLER: Yeah.

PASTOR: So, in fact, the academic people in the field typically don't have the ability to work on a lot of these methodological problems just because, if you try to write a grant for it, you won't get funding. So I think that's a big thing. We can just do—methodological sounds a little maybe boring or something or subpar, maybe even lazy and stupid kind of stuff. But it's not. It's essential, and we have the freedom to do that.

ZIERLER: Right.

PASTOR: I think what we also have, which is, I think, probably people would stress more, is we can be very innovative. I don't think I'm that innovative in the grand scheme of things. I mean, I'm a little innovative but not—

ZIERLER: It's hard to quantify such a thing, right?

PASTOR: Yeah. And maybe in retrospect your work can look innovative, right?

ZIERLER: Yeah, yeah.

PASTOR: I mean, this is innovative, right?

ZIERLER: The cover. The imaging for *Science Translational Medicine*, right?

PASTOR: Well, and the fact that it was done through a computer simulation.

ZIERLER: Right.

PASTOR: Someone might've said, "Oh, that's really an innovative thing." Well, I mean what we did is to simulate it, right?

ZIERLER: Mm-hmm.

PASTOR: I mean, using stuff I'd been working on forever, but that's not, I think, super—it just looks like it's innovative, I think.

ZIERLER: So I guess I'll close with a big question now, sort of a broad view of your work. So how do you see your fundamental contributions to the field, and where do you hope those contributions will head beyond your career? Because your contributions will continue on the next generation. So I wonder if you could talk broadly, looking toward the past, about the sum

total of your work and how it's contributed to your field, and where you would hope to see—for the remainder of your career and beyond, where you hope to see this headed?

PASTOR: Well, the analogy I use for my students is that when you go to Europe, you see these medieval cathedrals that have been around for a thousand years. If you go to Jerusalem, you see a wall that's been around for three, right? [laugh]

ZIERLER: Right, sure.

PASTOR: And I'd like to think that—how does that stay up so long. It's that each person did a really good job on his brick. [laugh]

ZIERLER: Yeah. That's a great metaphor.

PASTOR: I guess I—

ZIERLER: So you see your work as a brick in the wall?

PASTOR: Yeah.

ZIERLER: What's the wall in this metaphor? What's the wall, biophysics?

PASTOR: Science.

ZIERLER: Science.

PASTOR: I think that—I mean, membrane science. Yeah. I mean, I have work that's just not biophysics. I mean, the statistical mechanics was physics, right?

ZIERLER: Yeah.

PASTOR: Pressure profiles, all that stuff. I feel that I've done those things well. And, because I've done them well and I've built on them, I've used them to refine the potential energy function. People trust my stuff. And it's a good brick. Maybe it's a big brick, maybe it's a little brick, I don't know, but it's a good brick.

ZIERLER: It's a good brick.

PASTOR: It's a solid brick.

ZIERLER: Leading to what?

PASTOR: This. I think that the next vaccines will—the biomedical stuff, I think people will use simulations to design drugs. They'll just know what to do faster. I mean, ideally—a lot of bioinformatic techniques are being used now, which is good. I think there will be times when you can just design some new drug using the computer simulation. You'll still have to do testing, you'll still have to do all this stuff, but we'll be able to see why the drugs work, even. I mean, I'll keep big-picture, but some of the work we've done with the APOA1, the way the peptides line up are not what was thought they did.

ZIERLER: Yeah.

PASTOR: The way the antimicrobial peptides—what they do is not what people thought they did, right?

ZIERLER: Right.

PASTOR: Simulations will do that.

ZIERLER: Right.

PASTOR: So yeah, so my hope is that this really will be used for biomedical things. And I'll be happy if that's true.

ZIERLER: OK. Wonderful. Well, Rich, thank you so much.

PASTOR: Well, thank you.

ZIERLER: This has been a tremendously enjoyable and enlightening discussion, and there's going to be a lot of people that will benefit from this, so I really appreciate it.

PASTOR: OK. Yeah.

ZIERLER: And we'll cut it there.

PASTOR: Good.

[End]