TRANSCRIPT

Key Conversations with Phi Beta Kappa

How Biophysicist Karen Fleming Explores the Rules of Life, Evolution, and Disease

The biophysicist has been running a discovery research lab for two decades at Johns Hopkins. She speaks with Fred about the randomness underlying all molecular processes, computer models that enable the integration of multiple scientific disciplines, and what she sees as compelling strategies for a more inclusive STEM pipeline.

Fred Lawrence: This podcast episode was generously funded by two anonymous donors. If you would like to support the podcast in similar ways, please contact Hadley Kelly at hkelly@pbk.org. Thanks for listening.

Hello and welcome to Key Conversations with Phi Beta Kappa. I'm Fred Lawrence, Secretary and CEO of the Phi Beta Kappa Society. On this podcast, we welcome thinkers, visionaries, and artists who shape our collective understanding of some of today's most pressing and consequential matters. Many of them are Phi Beta Kappa Visiting Scholars, who travel the country for us visiting campuses and presenting free lectures that we invite you to attend. For the Visiting Scholars schedule, please visit pbk.org.

Today, it's my pleasure to welcome Dr. Karen Fleming, Professor of Biophysics at the Johns Hopkins University, where she directs a discovery-oriented research lab. Utilizing the unique powers of biophysics, her work gives insight into the rules of life, mechanisms of disease, evolution, and biological design. In addition, Professor Fleming is an outspoken advocate for nurturing a more diverse, representative, and inclusive science and math pipeline. She has won numerous awards for her scientific achievements, as well as for her diversity and equity accomplishments.

Welcome, Professor Fleming.

Karen Fleming: Thank you. I'm delighted to be here.

Lawrence: So good to have you with us. You have described science as more of a calling than a choice that you made. So, you know, when prophets describe having been called, they

usually have a calling story, so do you have a burning bush story? Was there a moment when you felt called to be a scientist?

Fleming: Well, that's a great question. Was there a moment? I don't know that there was necessarily a moment that I was called to be a scientist. I mean, I was always curious about how things worked. Even as a kid, I was very curious about how, you know, gears worked, and how systems worked, and my mom was a nurse, and so I was naturally exposed a little bit to the medical career, and I always thought that was very interesting, and I had not really been exposed to science until I was in college, and I took a really great capstone biochemistry course and that sort of turned me on to thinking about basic science and the discoveries that you can do when you're a basic scientist.

Lawrence: That was at Notre Dame?

Fleming: That was at Notre Dame. Yes.

Lawrence: Where, if I have it right, you double majored in premedical studies, which the daughter of a nurse would certainly make sense, but also French. Where did that come from?

Fleming: So, I really love language. I had a really fabulous French teacher when I was in high school and I thought it was really fun to speak a different language, and I think it makes you think about language in a different way when you can speak a different language, because the constructs of language are different. It's also, I think, why I like coding, because writing code is sort of another language, and you can, you know, express yourself in a different way. And late in the game I was like, "Hmm, I don't know if I really want to be a physician or if I wanted to pursue a career more in research science."

I think it really had to do with the fact that I'm essentially a first generation college student, and was not raised with excess means, and I was worried about paying for medical school, and one of the great things about earning a PhD is that you work as a sort of a research graduate student, and that's a paid position, and you don't have to take out loans to advance your degree, so that pushed me in a direction of doing research, and then once I started doing research at the bench, I just fell in love with the discovery process.

Lawrence: After Notre Dame, you got your PhD at Georgetown in biochemistry and molecular biology, and then seven years at the celebrated MB&B department at Yale, the Molecular Biophysics and Biochemistry Department, and you came up through the ranks from postdoc and ultimately research scientist there. What were those years like at Yale?

Fleming: It was a magical time to be at Yale in MB&B. They have this fabulous structural biology center, so there was a lot of activity going on around solving structures of proteins. It was a very collaborative group. Jennifer Doudna, who won the Nobel Prize in chemistry, she was an assistant professor at Yale at the time. There was enormous freedom to explore science and directions of science, so there were a lot of scientists there who were at the same sort of stage as I was. A lot of postdocs. So, it was a great community

of scientists there and we were all trying to figure out what we wanted to study now and what we wanted to study in the future.

And I guess the final thing is my lab was next door to Tom Steitz's lab, and Tom Steitz won the Nobel Prize in, I think chemistry. I don't remember which one, for solving the structure of the ribosome. So, that work was ongoing while I was there, and we heard one of their original ribosome talks, and so it was just a magical place during that time.

Lawrence: So, maybe it's you. People who work next door to you wind up with the Nobel Prize.

Fleming: Maybe.

Lawrence: This is the difference between correlation and causation, right?

Fleming: That's right. That's right.

Lawrence: I was thinking that grossly oversimplified, science seems to be split into those areas going bigger and bigger and those going smaller and smaller, so, you know, we've gone from the earth being the focus of our study, to the solar system, to looking at and observing black holes 13 billion light years away. I can't even conceive of what that number means. Or smaller and smaller, from the organism level to the cell biology, molecular biology level. How do you explain the focus on the molecular level to those of us who live our lives on the organism level?

Fleming: When we think about molecules on the molecular level, it's like we are having a microscope that lets us see objects that we cannot normally see with our regular vision. That's one way to think about it, right? We could sit in our room and we could see our desk, and our chair, and our computer monitor, and our mouse, but they're made of much smaller entities, and so when we're studying molecules, we're basically using sort of zoomed in glasses to understand what is the structure underlying the objects that we are able to see, the microscopic objects.

And I like your analogy of bigger and bigger and smaller and smaller, because I would say science is going in both directions at the same time.

Because when we study our molecules, we study them in isolation, and we also study their interactions with one another, one on one, and then we also study their interactions as a network, and it's the network properties that are the basis for the definition of the cellular properties. And so, by going smaller, we're also going bigger at the same time.

Lawrence: One of the public lectures you're going to do for us as a Phi Beta Kappa Visiting Scholar is called Microbial Hot Potato. If I have it right, bacteria play a kind of hot potato triage game as they capture and directionally sort their outer membrane proteins to their proper cellular locations. Have I got that roughly right?

Fleming: You do.

Lawrence: So, tell us a little bit about why this hot potato triage game is significant and what do we learn from this?

Fleming: Sure. So, this is such a fun research area that my lab's been working on, and gram negative bacteria, like E. coli, which are found in your human colon, it's a commensal bacteria. They have a compartment that has two sort of fences around it, two membranes around it. And within that compartment, the proteins have to move from one side to the other, so it's like going from one side of your yard to the other side of your yard, and they have to do this without any input of energy. So, normally the cell would have energy-driven systems that maintain directional sorting of proteins in a cell. But within this particular special place called the periplasm, there's no energy. And so, when there's an absence of external energy, the only energy that's available for motion is thermal motion, kinetic energy that you have, and so the proteins bounce around randomly. They're on a random trajectory.

The proteins that we're interested in, that have to move from one side to the other, are outer membrane proteins, and they're not very soluble, so they tend to sort of bind to a helper protein, called a chaperone, and then they'll unbind and diffuse around, wander around randomly, and then bind to another chaperone. So they're bouncing around between these so-called chaperones, and when they seek refuge by binding to a chaperone, they're not there very long. The chaperone is a person who catches a memory protein that's a hot potato, so you catch it, you shelter it, then boom, you let it go again. The protein is bouncing around through the periplasm and then there's some probability that it will reach the place it's supposed to go, and when it hits that place randomly, then boom, it goes. It gets into the outer membrane.

So, this is a random process that leads to a directional sorting because the final protein in the end catches it and does not let it go.

Lawrence: Just by the way, when you said that the chaperone's not holding that hot potato very long, so what units of time are we talking about? How fast is this game taking place?

Fleming: This game is taking place on the millisecond time scale, and a bacterium doubles every 20 minutes. So, this is taking place on a time scale that is orders of magnitude faster than the doubling time of the bacterium, so the doubling time means a bacterium divides into two daughter cells.

Lawrence: Now, a lot of what you're doing on this is not just experimental observation, but computer modeling, right?

Fleming: That's correct.

Lawrence: So how do computers play a role in this? I want to ask you, you know, how computer modeling has affected your research generally, but let's start with the smaller question first. How has it made this project work? How has it made things possible? And then more broadly, how has it affected your research agenda?

Fleming: So, for this particular project, the computing aspects of this was essential. The hot potato game is played by a lot of different chaperones. It's not just one chaperone. From the biophysics point of view, when I'm trying to understand a system I'm thinking about reactions one on one, right? A plus B goes to C. But there's 10 different kinds of A here, and one kind of B, and B can bounce around amongst all these 10 different kinds of A, and so if you want to understand the properties of the system as a whole, you have to have a way to construct a master equation to think about everything all at once, and so we use computing to do that.

And I'm particularly proud that the computing algorithm we worked out for this particular study was primarily the brainchild of an undergraduate student, an undergraduate Hopkins biophysics major, who didn't have any computing experience when he began, so he-

Lawrence: Really?

Fleming: Yes. He brought this onboard. So, anyone can do this if you're interested. You can learn.

Lawrence: That is extraordinary, because I think a lot of people would have thought that this is for the "people who can do this." This isn't for me. But, not true.

Fleming: Not true. And the reason why this project as a whole is powerful is because we were able to adopt this computing tool and apply it to our biological problem and we were the experts in the biology.

Lawrence: Are there in fact problems that you would just not be able to tackle without this kind of algorithmic capacity?

Fleming: I think science is moving more and more towards computational skills and computational tools sort of integrated into what we're doing. So, we could think about this as we think about going smaller and smaller. You suggested it, right? We look at molecules at higher and higher magnification. Well, computing is really important in that area. And if we want to think about going bigger and bigger, like modeling, thinking about how does a whole cell work, or how does a whole organism work, it's true that computing is going to be a different kind of computing, but computing skills and computing tools will be really important for integrating all the various pieces together.

And in terms of molecules, you know a big tool that's used in our field is called molecular dynamics, and one of the limitations is the time scales. So, the time scale, the computing power allows us to only access very short time scales, but as we know, life happens on much longer time scales, and so that… Just improving that will let us ask questions we couldn't even ask five years ago.

Lawrence: Let's turn to a different part of your work and your life, your career, which is your substantial advocacy work for overcoming gender bias and barriers in the sciences for women. So, tell us a little bit about your own experience as a woman who became a scientist.

Fleming: You know, I'm the first woman in my department to be hired as an assistant professor and be promoted through the ranks. My department's 75 years old or something like that, and so when I earned tenure, one of the senior professors pointed this out to me and I had actually never really thought about it before. But as you go through your career in STEM, if you stay in the academy, you know, you become wiser based on your experiences, one hopes, right? And I think it could have been better, and I… That's part of the reason why I do this diversity, inclusion, equity work is because I want the next generation of women and marginalized groups to feel more welcome in the STEM pipeline.

Lawrence: What do you see as the major barriers and which are the ones that are relatively speaking easiest to address?

Fleming: So, let me just define the pipeline. So, the STEM pipeline is a metaphor that's used to describe the career path through the areas in science, technology, engineering, mathematics, and medicine sometimes. STEMM with two Ms. And so, that is the career trajectory, right? You are a student of science as an undergraduate, you typically do some kind of graduate work in science, you do postdoctoral, you know, your internship years, and then you enter a career. And what is known is that women and minorities drop out of the pipeline at every stage. The data from the National Science Foundation shows that, I think it's only 15% of full professors at R1 institutes in the natural sciences are women, and this is well below the representation of the population, which is close to 50%.

And furthermore, this number probably only describes white women, because much of this data is not broken down by race and underrepresented minorities are represented at even lower numbers in the STEM fields. And so, the question is why do women drop out? And in 2018, the National Academies of Science, Engineering and Medicine published a report on the climate for women in those areas, and the climate is hostile is what the study shows. And as you become older and wiser, then you understand, yeah, the climate is hostile.

I think climate is a really big deterrent against women and minorities staying in this career track. So, you need role models, because they're images. When you see someone, who looks like you in a position, in a career that you think you want to do, it completely changes how you think about whether or not you might belong in that career. So, we do need role models. But it's also well documented that women carry the same kind of biases that men do. And in particular, there's a study from 2012 published in PNAS that shows that women faculty discriminate against young women just as much as men faculty do.

And so, when I give talks about this, I like to say, "Well, women…" and these are probably white women, "are not magical unicorns." They're not. We're all biased. We all need to understand we bring our life experience with us to the table whenever we're doing anything. And that's bad because we're biased, but it's also good if we understand that once we recognize our bias, we can learn how to be better.

Lawrence: So, you've done a fair amount of work in this area, but you've also done workshops and seminars on bias. Can you tell us a little bit about what you think has been most successful in that work?

Fleming: So, I think there's two factors that are especially successful about this. I approach this topic like a scientist, because I am a scientist, and I'm talking to scientists for the most part, and scientists like to think about data. And so the way I like to discuss issues of inclusion and bias and discrimination in the pipeline has to do with discussing the data that reports on why we behave the way we behave. Another reason why I think it's successful is that I am not out to get men. That's not what this is about. We need men on board. Men are the dominant demographic in our scientific community, and they need to be part of the solution, and we need to welcome them to be part of the solution, and here's the data. Here's the evidence that shows us what the problem is and here's some more evidence that shows us how we can move our climate to one that is more inclusive.

And I guess a third thing I would say is I am a full professor of biophysics now at the Johns Hopkins University and that comes with some agency.

Lawrence: So, what advice would you give a college student today who is making the same decision that you as a young woman made at Notre Dame a while back about whether to go into applied science, medicine, nursing, and the like? How do you enter into that conversation with them?

Fleming: One thing I will say is that I feel like our students today have more opportunities for real life exploration of careers than I had when I was an undergraduate. For example, all of our biophysics majors do research, so they get that experience, and they get to know us, and they get to know the graduate students who are working in the lab. So, even if they're premed, they have to do this research experience. They can also shadow physicians, and, you know, have experiences on the medical campus, so they have more… I think I have a greater ability to sort of do little internships than I had, and so I guess I would say to them if you're uncertain, keep doing little internships or make sure you take advantage of these opportunities as an undergraduate so that you can try something.

If you're at the bench, doing bench research, people who are at the bench think, like we fall in love with it. It's not really… I can't really explain it.

Lawrence: Right. You can't-

Fleming: I just have to say it's kind of a calling, right?

Lawrence: Yes.

Fleming: You like it. You think about it all the time. You dream about your experiments. You wake up thinking about your experiments. You go to the lab and you want to do your experiments. So, it's a little bit like an obsession, and if that's how you feel, then that's

going to feed your soul and that's going to give you happiness, and that's what you should do.

Lawrence: That's going to feed your soul. Yes. You can't fake what you're passionate about. I want to give you a chance to answer one of my favorite questions to my guests on Key Conversations, to ask you to help build our listeners' book list. I wonder what you'd put on that list for an undergraduate who's trying to study a lot of wide areas, or a not so undergraduate, somebody later on in life who's trying to keep the lens of studied areas as wide as possible, still exploring the liberal arts.

Fleming: So, if I had to give a book recommendation for a general audience that's also interested in science, I would say *Good Germs, Bad Germs*. It's from a few years ago. I haven't read it in a few years, but I remember it being really important and really interesting to think about bacteria and their interactions with humans.

Lawrence: Jessica Snyder Sachs' book *Good Germs, Bad Germs*. Terrific. We are so grateful that you will be a Visiting Scholar this year and I know that you will have students on campus, as well as members of Phi Beta Kappa nationwide who will be listening in on some of your lectures, talking about hot potatoes at subcellular level, as well as social issues in the way in which we conduct science, and equity and inclusion in the science profession. Thanks for joining us this year as a Visiting Scholar and thank you so much for sitting down with me today on Key Conversations.

Fleming: You're welcome. This was a lot of fun. A great pleasure for me. I'm super excited to be a Scholar this year. It's really going to be an amazing experience.

Lawrence: Well, welcome to the Phi Beta Kappa family.

Fleming: Thank you.

Lawrence: This podcast is produced by Lantigua Williams & Co. Cedric Wilson is lead producer. Virginia Lora is our managing producer. Hadley Kelly is the Phi Beta Kappa producer on the show. Our theme song is "Back to Back" by Yan Perchuk. To learn more about the work of the Phi Beta Kappa Society and our Visiting Scholar program, please visit pbk.org. Thanks for listening. I'm Fred Lawrence. Until next time.

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