Interviewee: Antonina Roll-Mecak By: David Zierler

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ZIERLER: Okay. This is David Zierler, oral historian for the American Institute of Physics. It's my great pleasure to be here on June 1st, 2020, with Doctor Antonina Roll-Mecak. Antonina, thank you so much for being with me today.

ROLL-MECAK: Thank you for taking the time to do this interview in very special times.

ZIERLER: In very special times, indeed. Okay, so to start, please tell me your title and institutional affiliation.

ROLL-MECAK: So I'm a senior investigator at the National Institute of Health. My main appointment is in the National Institute of Neurological Disorders and Stroke. I also have a joint appointment at the National Heart, Lung, and Blood Institute. I'm the head of a unit, which is entitled Cell Biology and Biophysics, where our focus is on understanding how cell shape and movement are regulated.

ZIERLER: Okay, alright, so good. So let's now go right back all the way to the beginning. Tell me about your family background, and your childhood in Romania.

ROLL-MECAK: One parent is an engineer and a scientist. The other one is a musician. So early on it was imprinted on me that both the humanities and science education are very important. And I never saw them as opposing each other. My parents, and that upbringing, I think, gave me a rich lens through which to look at the world.

ZIERLER: Tell me a little bit about the educational system in Romania. Are there-- When you were growing up, was it only public schools? Were there private schools also?

ROLL-MECAK: The Romanian school system is a public system. There were no private schools or private universities. Even before the communist regime actually, Romania had a very good system of public schools. Of course, the events in the late 1940s opened education to more people and this increased the literacy rates considerably. Even before, the historical changes introduced by the Communist regime Romania had a high literacy rate, and a very good system of public schools that was modeled on the French system. And it is still is today. There is a baccalaureate exam at the end of high school and a very similar outlook, in terms of how subjects are taught and where emphasis is placed. I benefitted from an extraordinarily good science education. The eastern block had very strong science education. I would say probably more, stronger than, I think, on the humanities side. Science is also politically neutral, unlike humanities, and it also could be used to build the country. As a result, great emphasis and investments were made in science.

So as a result, I really enjoyed science, I enjoyed math, I enjoyed physics. In fact, I didn't enjoy biology, which is ironically what I'm doing now. I never thought I would study biology because it was taught in a way that was very boring and almost exclusively memory-based. It was a lot of taxonomy and so on. It was not really focused on mechanism. And it wasn't taught in a way that was rooted in the physical sciences. Also biology was considered a bit of an inferior science in comparison to math, physics, and chemistry. And so I benefitted from a great education. I went what was considered, and still is, one of the top science, math, and physics high schools in Romania. I spent a good chunk of my free time going to math or physics Olympiads and training for them during the summers in summer camps in the beautiful Romanian mountains.

ZIERLER: And where was, Antonina, where was your high school? Where was it located?

ROLL-MECAK: My high school was in Sibiu, which is in Transylvania, the western part of Romania. It's an old high school, almost 300 years old. It was called the Gheorghe Lazăr High School and it was specialized in the sciences, in particular math and physics. In order to enter that high school, you had to go through a competition, which was at the county level. Romania was

divided in 40 counties. The kids from all the schools would be given an entrance examination, and the roughly top 100 would attend that high school. After two years of high school there would be another examination, that was focused again on math and physics. And then you graduated with a baccalaureate in math and physics after four years.

ZIERLER: Now, did you apply to this school because you already had a talent in math and science? Was that the idea?

ROLL-MECAK: Yeah, I was already doing a lot of math. Interestingly, I wasn't actually that interested in school as a kid. It kind of worried my parents when I was in grade school. When I entered first and second grade, my mother actually was quite concerned about me, and would always feel rather bad when she will get into conversations with other parents and all the parents would say how much homework and what their kids were doing. My mother would think "Oh, my kid is just outside all the time and I can't get her to really finish any of her homework." So I wasn't very interested in, I guess, formal education. But I learned math early on. My dad being an engineer would bring back Fortran cards. I don't know if you know this, but in the old days, if you did programming in Fortran, there would be these Fortran cards that had little punch holes that you would feed with the code in your computer. And so my dad would bring a pile of these cards home that were no longer useful and he got me interested in numbers quite early. So, I learned very quickly to add and do all kind of other simple arithmetic.

However, I was not a fast reader. I look at my son now, and he's a very fast reader. He learned to pretty much read on his own. But numbers don't come so easily to him. I was the opposite. I was not a fast reader, but I really liked to work with numbers fairly early on. And so I then became interested in math. My dad would tutor me in the evenings in Newtonian mechanics when I was still little and I really enjoyed that. It was a way to connect with my dad. It was also something that came natural to me and I really enjoyed it. I enjoyed math more than physics. At the same time, I also played the

piano because my mother taught me and she was the musician in the family. And so my time was divided between piano and math during my early years.

ZIERLER: Now, I'm curious, it's mostly a cultural question. Being good at math and science in Romania as a woman, as a young woman, were you ever discouraged that that's not an appropriate field, or that's not how it was at all in your experience?

ROLL-MECAK: No, actually, the opposite. So, it is interesting you asked this question. I had not heard during my schooling that a woman would be less likely to succeed in math. In fact, I think my high school class, which was the top performing class in math and physics, the top students were roughly half girls and half boys. The top four students were two boys and two girls. My best friend was the other girl. She actually stuck with math and is a professor of mathematics in Sweden. So no, I don't think so. I sadly found that out in the U.S. system.

ZIERLER: Yeah.

ROLL-MECAK: And I find that interesting. At a recent Gordon research meeting, small selective meetings of about150 people in various fields, we had a discussion about diversity in the sciences especially in the hard sciences. And it was interesting that many of the women on that panel that had initial formative years outside the U.S. found the prejudice against women in science to be more pronounced the moment they came to the U.S. They didn't feel it in India or in Russia as much. And they thought they see it play out in the education of their children here also. I thought that was interesting. I'm not sure what the cultural dynamics are, but it's interesting to think that in those countries women don't necessarily enjoy more freedoms, personal freedoms, than the U.S. In fact, quite the contrary. I think the U.S. is much more open-minded in terms of the role of the woman as the bread-winner in the family than any of the countries that I've mentioned. But somehow, women in science seemed to be almost in a category that was not touched by that, and it was never a question of ability. Whether here I think, we're still having this conversation, about a woman’s innate ability to do science or not, sadly, in the year 2020.

ZIERLER: Right. And of course, your parents were as encouraging as anybody else, I take it?

ROLL-MECAK: Yeah, (laughs), it never entered their minds, I think that as a girl I would not be able to do whatever I wanted. Yes.

ZIERLER: So when you were leaving high school, what, in terms of thinking about college, were you thinking ahead about what kind of career you wanted to pursue, and that informed what you might want to study in college, and where you might want to study?

ROLL-MECAK: Yeah, I knew I was going into sciences. I had part of my family in the US and that pretty much crystallized for me where I would like to go to college. I really wanted to go to New York. And I didn't have a lot of money to pay tuition, and for me, Cooper Union was a fantastic opportunity. It's a place where, as you might know, many immigrants have gone to school, and have achieved amazing things. I don't think I'm in the category of the many that have gone to Cooper, but I hope that I will make a positive difference. Cooper Union was endowed by Peter Cooper. His view was that education should be as free as air, to quote him directly. And so he left a large endowment for Cooper Union with the idea that if you're smart enough, you should be able to go to college regardless of your socioeconomic status. I went to college with kids that were first generation immigrants and their parents were working a cashier at a small grocery in the outer boroughs of New York, and I had a classmate who was from a very wealthy family. And we didn't know at all

ZIERLER: Who was who?

ROLL-MECAK: How much money any of us had, in fact, until graduation day, when in fact we went to people's houses and then you realized. So it was an environment where we never talked about where we came from, but more about what we know and what we want to do.

ZIERLER: Now, you said your father got to New York first? Was the plan, was he trying to move the whole family to the United States?

ROLL-MECAK: No. My family never immigrated to the US. I've had multiple family members that were dissidents during the Communist regime. My grandfather died, actually, as a result of being

in a labor camp that the Communists set up. He died shortly after he came out. But they never left Romania for good. And so Cooper was a great place. You know, they offered free tuition regardless of whether you had the money or not. It was a great collection of smart kids that all wanted to work had and make something of themselves. I had a great professors and the classes were small. I think the biggest class I attended had 100 students. But most of my classes were 20 students or less.

ZIERLER: And how was your English when you got to New York? Did you learn English in high school?

ROLL-MECAK: Yeah, I spoke perfect English, I would say, probably the same as I speak now. I don't think it's changed much except that I spoke it with a British accent because that was what I had learned at home. But and I tried really hard to get rid of it very quickly by watching a lot of bad talk shows when I arrived. Like Jerry Springer and things like that because I really felt very, very conscious of my British accent. I think people thought it was very cute, but I really didn't like to have it. I wanted to have an American accent. I haven't succeeded entirely, but I worked really hard at it for those first years.

ZIERLER: Antonina, what was the curriculum like at Cooper Union? Was the expectation that you would sort of broadly take courses, you know, across the college? Or was the expectation to sort of specialize and declare a major earlier on?

ROLL-MECAK: So Cooper is unusual because you declare a major the moment you are accepted. They have three schools. There's the School of Engineering, the School of Architecture, and the School of Art. The school of engineering has four majors: chemical, mechanical, electrical engineering. That's three majors. Am I missing one out? Civil engineering. And so you declare your major when you come in. You can change in your first two years, because the curriculum is very heavy on math, physics, and chemistry and that is shared by all the majors, but then it diverges in the third and fourth years. We required, a very high number of credits in order to graduate, with a very small portion of those being electives.

<p>So there was very rigorous instruction in math, physics, and chemistry, especially math and physics. And you had to maintain a GPA, because your free tuition and continuation in the school depended on that. So I think it was a great place to be. I have to say thought that I didn't learn much new in math and physics and for the first two years. I took advanced classes while I was there because most of the college math that is covered in the U.S. in the first two years of college was covered in high school in the eastern block at the time, vector calculus, statistical mechanics, algebra, real analysis. We covered much of it in high school. And so those came pretty easy, and then I took tutorials with my faculty, which was fantastic, because Cooper was offering these free of charge, so it was just amazing. I mean, you'd just walk into a professor's office, and if he thought that you have an interest in a topic, they would just make a class for five kids, and that would be our math class for that semester, and it was fantastic. I don't know where you can get that kind of education, even if you pay for it.

And so I'm very saddened by the financial difficulties that Cooper Union has had. Because they were affected by the Maddow case and they lost a lot of money. They also own the Chrysler Building and quite a few landmark buildings throughout Manhattan. From my understanding there were some unfortunate deals made for the leases, and they found themselves in the red. And the school has to now charge tuition. Not near to full tuition, but still, they had to change their tuition-free status, which was very disappointing. I always find it surprising that a college like that cannot find a fat donor to really give them an endowment to guarantee that they can continue operating tuition-free like for the long term. They're still have a good endowment, but not high enough to keep everything free for all the students that are accepted.

ZIERLER: Now, Antonina, what was your overall game plan when you went to Cooper, was the idea that you were looking to make a life for yourself in the States, or were you thinking this is a great place to get educated, but I'm going to go back to Romania for my life? How much did you think about that during those years?

ROLL-MECAK: I didn't have any particular grand plan of where I will end up. People in their 20s feel the world their oyster, so I really didn't think that I would end up in one place or the other. My view was that I wanted to be really good at what I planned to do, and then I'll just find a place that is the best place for me to be for what I wanted to do. And I guess I had that blind confidence that, yeah, I would be able to go wherever I wanted. And in hindsight, yeah, maybe that was a bit foolish, but it has worked out.

ZIERLER: Sure, sure. And in the summer, did you do any science-relevant internships?

ROLL-MECAK: Yeah, I think I did. Maybe I did one almost each summer, I did a summer internship at Cooper and later on I did one at Mount Sinai School of Medicine. I didn't plan to do an internship at Mount Sinai, actually. It was a bit of a dare. I'm kind of a little bit embarrassed to admit how I ended up doing it. So Cooper Union and Princeton both had an early admission process with Mount Sinai Medical School to try to get good students in their sophomore year into their medical school program. I wasn't that interested in being a doctor, but I always thought it was kind of funny that they all complained about how terrible it was to get in. So I kind of applied on a dare, and went through it, and I got in, and of course my parents got really excited because it's, "Oh, finally! There's going to be a real doctor in the family. She can write prescriptions for us." And so they're like, fantastic, you know? We couldn't have planned this any better.

But fortunately for me I met somebody during my interview process who was working on molecular dynamics in biological systems, Harel Weinstein, and I had such a great conversation with him that after my interview and after I got in, I contacted him. I don't even know whether I wrote an email, or I called him up. I think I wrote an email and I asked him, can I just come over and work in your lab for a little bit, just to see what this thing is all about? Because I didn't know anything about biochemistry or molecular dynamics. And he said sure, why don't you come? And I spent the summer in his lab, and I had a really great time with the people there. They were so generous with their time and in insights. They gave so much importance to what I was doing. In the scheme of

things it was a pretty minor problem that I was studying, but I really put all my effort in it, and I made a--

ZIERLER: What was the problem? What were you studying?

ROLL-MECAK: Well, I guess it is not a minor problem. It turns out it is a pretty important basic problem, the entropic effects of buried residues in protein structures on the pKa. And so they gave me so much attention. They made me feel that, oh, if you find something here, it will be so important and fantastic. And so that made me want more. I wanted to be around people that are smart and enthusiastic about what they do, and that don't mind staying at work late and who really enjoy what they were doing. And so after talking to Harel for a while, I decided to apply to graduate programs that year, and MD/PhDs, because I wasn't quite sure, you know. I had this pressure from my family to keep the MD part. Long story short is that I did get accepted into MD/PhD programs and pure PhD programs. And then decided that was quite sure I didn't want to see patients or practice medicine. I didn't tell my family and I just made my decision, and I accepted the offer from Rockefeller University. And I told them everything once I had made my decision that actually, I'm really going to do just my PhD in biophysics. And my dad said, "Well, it's too late to do anything about it." (both laugh) So that was that.

ZIERLER: So Antonina, settling on biophysics, were you thinking specifically about the kinds of topics and subjects that you were most talented in? Was that part of the thought process?

ROLL-MECAK: No, no, not at all. I had no idea that I would have any aptitude. I definitely had an interest in it, but I had no idea that I would be any good at it. I feel young people nowadays are expected to accomplish so much by the time they go into graduate school, in terms of prior experience, because everything has become so hyper-competitive. When I got into graduate school, I had never done any bench work in biophysics or biology. The work I had done during my summer with Harel Weinstein at Mount Sinai at the time, he's now at Cornell, was really on molecular dynamics simulations, and actually some quantum chemistry. But I had gone to lectures while I was

there, that I really enjoyed. I was really fascinated by protein structure, because I mean, how you could not be fascinated by protein structure. Protein structures are just so beautiful, beautiful organizations of atoms that nature has selected to do exactly what needs to be done. And so I went to a bunch of talks on structural biology.

The early 1990s were the golden age of structural biology. All this work on protein x-ray crystallography was coming out. There was just so much excitement in the field. You could finally see how all these molecules that were doing amazing reactions in cells looked. What appeared before as a little box in biochemical pathways that said, A converts to B to C. We now knew their three-dimensional structures. We knew where every atom was placed and how it contributed to the whole function of that molecule. And so I was very interested in protein structure, but I had no practical experience, you know, I'd never been in a lab, I'd never done molecular biology, I'd never done anything in experimental, biophysics. But during the recruitment process at Rockefeller I met several fantastic structural biologists. One of them ended up being my PhD mentor, Stephen Burley, who is now the head of the Protein Data Bank that curates all the protein structures that are produced globally. The other was Rod MacKinnon, who I had a fascinating discussion on ion channels. It was pretty much because of Rod that I went to Rockefeller because Rod said to me "What does your gut say?" I said, "My gut says that I should just come to Rockefeller." (laughs) And he said, "Just do what your gut says."

ZIERLER: The other thing with Rockefeller is, Rockefeller is a very unique institution when you're thinking about—

ROLL-MECAK: It is.

ZIERLER: —the kinds of graduate schools to apply to. Can you talk a little bit about what makes Rockefeller so unique?

ROLL-MECAK: So, actually one of the reasons I went there is because I thought that I was done taking classes. Rockefeller at the time (it has changed now) was a place where you got in and you

were expected to start on an original problem. You didn't have classes to take. You could take them, and you had some credit system, but it wasn't a structured curriculum. So you just came into the graduate program, and you did what you wanted to do. There was very good support. You're in the middle of Manhattan, which, for a 20 year old was fantastic. I had a subsidized apartment which cost like, really, it was a joke by Upper East Side standards. So I loved being there.

I would start my day at 10 o'clock in the morning. I would work all the way to the evening. Then in the evening, I would go to the opera or to a concert from 8 o'clock to midnight. Then I would come back to the lab at 11 or midnight, I would do some more experiments in the lab for a couple of hours. Many times I would run into people who would do the same thing as me, including Günter Blobel, in his tuxedo coming back from the opera back to the lab to see what's going on. Then I would go have drinks with my friends somewhere downtown and then probably I'd get to bed at 4, 5 am in the morning after having a bagel at the bagel shop that was one block away from Rockefeller, right as the bagels were coming out. And then you'd wake up again at 10. I would be dead if I did this today. But when you're in 20s, I couldn't imagine there'd be any other way of living your life.

ZIERLER: Now I'm curious, given the fact that there is very little opportunity to take classes, and you're not really classically trained in biology, are you just self-taught? Are you sort of hitting the textbooks? What are you doing to catch yourself up in biology?

ROLL-MECAK: Yeah, that was pretty much it. You basically read and you went and asked people if you had questions. We did have courses. There were some fantastic ones. They were mostly lectures in cell biology and molecular biology. And it's quite ironic, because I remember taking some of those and thinking, "Oh my god, I have no idea what these people are talking about. And ironically, I'm teaching in one of those courses at Rockefeller in two weeks. (laughs). I would have never predicted that when I started because I didn't even know the lingo. I would be looking up terms like “southern”, what is this? I had no idea, But I knew my math and I knew my physics and I knew my statistical mechanics, and that came in helpful for many things, especially since I went into

structural biology and crystallography, so that end of things was very easy. And the rest I learned at the bench.

Actually, Rod MacKinnon taught me many things at the bench. He got the Nobel prize for ion channel structure while I was still at Rockefeller. He had just moved to Rockefeller. We were three people in his lab, and he taught me a lot at the bench, including his wife, Alice Lee, from whom I learned how to do molecular biology. So it was great fun. And I would be there late with another postdoc and Rod would be there late also, and sometimes we'd be at 4, 5 in the morning doing something. And then we'd look at each other and say, "Oh, we have lab meeting at 9 am in the morning." And Rod would say, "Oh, let's just cancel it." Since it was the three of us, and all three would be there at five o'clock in the morning. So that was great fun, and I learned a lot.

ZIERLER: Did you ever try your hand at crystallography? Did you ever try to take that on?

ROLL-MECAK: Yeah, so I did that, and that was the focus of my PhD thesis. There were some really hard moments during my Ph.D. when things didn't work. But in the end they did. And then I graduated and moved to my post doc in San Francisco.

ZIERLER: Now, the idea that at Rockefeller, you're supposed to come in out of the box with the research project ready to go, right? How did you accomplish that, not really being so well-versed in biology? Were you able to go to professors and sort of ask for some help, so that you can get that going? Or were you able to do that on your own?

ROLL-MECAK: So I didn't, but I'm sure if I would have, I know I would have found open doors. I started to read, and actually in a way, my ignorance was actually a blessing. And I'll tell you why. I started to read and I became interested in the process of how genetic information is translated, how do you make it actionable in the cell? And the way you make it actionable, you have to find a way to transcribe the genetic code into a set of instructions that make the protein. And the protein is what carries out "business" of the cell. Proteins are the ones that perform the myriad of reactions that keep us alive.

The shape of a protein is very much related to its function. So by looking on how it's built, we can try to extract how it actually functions. X-ray crystallography allows you to do that. It gives you high resolution picture of the shape of a protein, and I was interested in how the cell converts or translates the genetic code to protein, which is the process of translation. And that is all done through a system which is a large machine called the ribosome that decodes a three-letter code, the genetic code into a string of amino acids. Amino acids are building blocks of proteins. We have 20 of those. And so we have 20 types of amino acids that are all in all kinds of combinations and they make the tens of thousands of proteins that we have in our body. And all living creatures on Earth have the same 20 amino acid code. Now, each of those 20 amino acids is specified by a three-letter nucleotide code. The nucleotides are the building blocks for DNA.

And so but there's this machine that's like an enigma machine, right? The ribosome is the machine inside cells that translates the message from one system, the nucleotides, to the other, the amino acids. This is like the enigma machine for cells. You have to translate the nucleotide or the DNA and RNA into protein. And I was interested to understand how this machine is put together. And I became interested in a set of protein factors that actually help this decoding machine, called the ribosome, to figure out where the start of a sentence and the collection of proteins that the cell makes is a novel. So you can think about a protein as a sentence, and you have to know where the beginning is in that sentence. And so I became interested in the set of factors that help the cellular enigma machine find where the beginning of the sentence is. It's called the process of translation initiation. And this process uses energy. It uses a small molecule called GTP as energy to shape the ribosome so it can be in the right conformation to find the beginning of the sentence.

So these were very important factors, and I was reading through all of this, and I said, "Well, how come nobody knows how they look like?" Of course, I was too naive to realize that there were many people before me who were much smarter than I was, who also thought it would be very important to know how they looked like, but they had failed. And so I checked literature going back maybe ten

years? I didn't go all the way back. And so I said, this is a great idea. I'm going to start working on this. And my PhD advisor said, great idea, just go for it. And of course, as I started to work on this, and I was going through more and more literature further back I realized, oh, actually there's all these papers that people wrote about how what I was trying to do had not worked for them. (both laugh) Which was like, hmm. So at the time, I thought, maybe I should have read the literature more thoroughly. But then I would have never started this project. It was good that I didn't, because in the end I succeeded. And so I always tell my students, "Read just enough to be get you interested and be able to design good experiments, but don't read so much that you discourage yourself from doing the experiment.

ZIERLER: So what was your secret? What were you able to accomplish that your predecessors could not?

ROLL-MECAK: I think a lot of dogged determination and also I realized that nature had done a great evolutionary experiment that would help. The factor that I was trying to determine the shape of is found in all organisms on Earth from a bug that lives in the thermal vents under the ocean all the way to us. And so I reasoned, and also other people at the time were exploiting the same kind of thinking, that the bug living in the thermal vents, will make a protein that's much more sturdy than ours. Genomes were coming out for these various bugs at the time and so I took a look at all the bugs I could found the ones that were living in extreme environments where nature would have selected them to be more stable and I and my collaborator Tom Dever cloned them. And indeed, they were sturdier than the human version or the mouse version of the protein. And that allowed me to manipulate them and get a crystal and solve the three dimensional structure. So basically, I exploited the genius of evolution, that made this protein sturdy enough to work well at high pressures and temperatures in some organisms while retaining its overall on how this protein looks like. And that allowed me to finally decipher its structure and understand how it works.

ZIERLER: Did you publish this finding?

ROLL-MECAK: I did, I did. It was a very nice publication. However, I think the best part was not really the publication. It was that actually when Venki Ramakrishan, who actually got the Nobel prize for solving the ribosome structure, came to campus and I hosted him, he told me "You know, I started working on that protein and I gave up." (both laugh). That made my day. He was very gracious to say that. It was one of the highlights of my PhD.

ZIERLER: Now, I'm curious. At this point, you know, it's obvious now, you're not going to be a medical doctor. That's clear, right?

ROLL-MECAK: Yes, yeah.

ZIERLER: But are you thinking of your research specifically now in terms of advancing human health from the research side? Are you thinking along those lines? Or is this still, you know, this is a scholarly scientific pursuit, and you're still not thinking about where you might apply it ultimately?

ROLL-MECAK: I always keep in the back of my mind where this is going to go. However the thing to keep in mind is that our organisms, and especially us, are so complex that there is such a huge gap in knowledge that we still need to fill in order to make rational decisions about health and disease. And so yes, for example, the molecule that I worked on in my PhD, is an antibiotic target. Structural biology has had tremendous impact in drug discovery and drug design. In fact 80% of all drugs that come to market have benefited from determining a protein structure during the process. That's a staggeringly high number. 80% of all drugs on the market have had structural biology influence their design and testing. And that is because it's really important to know the shape of protein your drug is binding to. And so I think this is always in the back of my mind, but I'm also very humble in knowing that our knowledge of biological systems is still very limited.

While on one hand it is remarkable what we have achieved in the last 50 years, we still do not understand so many process well enough. I don't know if you have any relatives that had heart surgery. I like to think about this because now you can go into the hospital, have heart surgery, and come back home the next day. 30 years ago, you came back with a giant, big scar in the middle of

your chest after two or three weeks. Why can we do this so much better now? That's because we understand how to make smaller incisions, but also how to give small molecules for immune system boosting, for wound healing and how to fight infections with antibiotics. Now we have a whole set molecules that are based on basic research into the shape and function of protein machines in our bodies. I think it important that we remain committed as a country to that kind of investigation.

ZIERLER: So you defend your dissertation and then off to San Francisco you go.

ROLL-MECAK: Yes.

ZIERLER: Tell me a little bit about your post doc and how that came together.

ROLL-MECAK: So I went to my post doc because I was interested in force generation. The molecule that I studied in my PhD turned out to use a similar type of mechanism to induce a conformational change used by molecular motors in muscle. And so I got interested in molecular motors, and there were just three labs that really piqued my interest. And I interviewed in all of them and chose to go to San Francisco to work with Ron Vale, who discovered kinesin, which is a molecular motor that works on microtubules and is responsible intracellular transport in cells. And I went there be--

ZIERLER: And what's the institution? What's the institution in San Francisco?

ROLL-MECAK: I went to UCSF, which is University of California San Francisco. And I went there wanting to understand the dynamics of molecules and not only their static structures by learning single molecule fluorescence microscopy. And so that's what I went there for, and plus I love San Francisco. I thought I had lived enough in New York, and it was time to explore the West Coast and I fell in love with San Francisco. I tell people when they interview in my lab - I know you like the lab, but you're going to spend as much time in the lab and outside the lab, so if you hate the place where you live, you're really not going to be doing good work. You should really enjoy where you live. Not everybody has that option. But if you do, then live in a place that you like. And I loved the city, and I had a great post doc there.

ZIERLER: It was a one-year, two-year program?

ROLL-MECAK: Oh no, post docs in biological sciences are quite long compared to physical sciences, so I stayed there actually for six years. I had my job already after five years, but then I delayed starting my job at the NIH for more than a year. I had my own funding, and I was having a good time. (laughs)

ZIERLER: And did you stay on that same project the whole time, or you worked on different things also?

ROLL-MECAK: So I started a new project in Ron's lab that he didn't happen to love at the time. I ended up discovering a protein that is able to remodel the microtubule cytoskeleton, a protein that is able to break microtubules in little bits. And I worked on that for most of the time, and then when I moved to start my own lab, I decided to work on something completely different.

ZIERLER: Which was what? What did you work on?

ROLL-MECAK: So I worked on

ZIERLER: You're talking about at the NIH now?

ROLL-MECAK: Yes, yes. So my lab is interested in understanding how cells organize their components. So you can think about a cell as a city. And the city is connected with many highways and roads, and you have at the center of the city the nucleus, where the genetic information resides. And outside the nucleus, you have all the ribosomes and everything that's translating genetic information into proteins. But a big question is, how does all this cargo know to get from point A to B at the right time Microtubules are the highways of the cell. They're hollow long cylinders and they are very stiff, so they provide structure to the cytoplasm, and they are the tracks on which goods are trafficked. And those goods are trafficked by molecular motors that actually walk very much similarly to you and like I. They have little feet, actually. I know it sounds kind of crazy, but they do. They put one foot in front of the other, and that's how they walk on these cylindrical rods in the cell. Of course, they're more than a billion times smaller than we are.

But walk, and they carry large packets of cargo, which is actually heavier than they are. And so I was interested whether there are traffic signs on these tracks. And this has been postulated many years ago, that in fact cells encode chemical signs in their building blocks that specialize them for particular functions. This is called a tubulin code. And the idea is that there are chemical marks put on these tracks that tell a motor, you go here, or you stop and you don't go there, or you cut this microtubule, you get rid of it, and you build another one over here. So it is a chemical code for spatial information for microtubule tracks in the cell, right? But that was just a hypothesis, and nobody had really tested any of this or had any understanding of how this could possibly work. And so when I started my lab, I was really interested in this. A lot of people told me not to do it because it's not going to work out, and when it's not going to work out, I'm going to not get tenure. And it was a really risky thing to do when you start out.

ZIERLER: Now, are you thinking about your dissertation topic and how you proved everyone wrong? Was that part of the thinking?

ROLL-MECAK: (laughs) Yeah maybe that's one thing, I guess such an experience gives you the confidence or the knowledge that you can actually surpass some obstacles. So that's one thing the PhD gives you, the knowledge that you encountered the unknown before and you can find a way out. I also was quite confident that by choosing to go to the NIH and not at a university, I had the ability to do risky research, because the funding structure is very different at the NIH. I can work on something that's high-impact and risky and not worry that my payoff is not right around the corner. And so I think the appetite for risk is much higher at the NIH than at universities. I had many offers in top academic research institutions, but I thought the way the NIH is structured makes it more conducive to doing something that's high risk, high payoff.

ZIERLER: Now that's a very, Antonina, that's a very sophisticated understanding of NIH for a post doc, right? In terms of how NIH works. So I'm curious. If you just sort of divined that knowledge of how NIH works yourself, or you had colleagues there? Or how did you come to appreciate that this

would be a place where you would be able to do risky work and not worry about the implications of it?

ROLL-MECAK: So part of it is, I think, is because before I came to the NIH, I had already won quite a few grants and awards. So I knew how the funding system works. I had gone through the process; I saw all its advantages and disadvantages. And then when I interviewed at the NIH, it was very easy for me to grasp what the difference is. Also it was made very clear to me by the scientific director at the time, that they have a stomach for high risk research. I'm not sure how long that will continue. I think there is huge pressure to become risk-averse and show that we immediately can apply things and have a result. I think it's a great danger that the NIH finds itself in and I hope that we will be able to resist that and continue curiosity driven research which in the end has the highest payoff in terms of practical application.

ZIERLER: Where is that pressure coming from, Antonina? Where is that pressure coming from?

ROLL-MECAK: I think it's from everywhere. I think people just want high returns in very short amounts of time in all walks of life. And I think it's permeating the scientific enterprise. And it's very dangerous, because there is no ground-breaking work that was done in two, three years. If you look at it, if you make substantial progress in a new area in ten years, you're lucky. And most of it was done over 20, 30 years. You just have to trust the people involved. You have to trust that you invested in the right type of people. You know, give them a check from time to time, like you do with your car. Make sure the tires are inflated and that they have enough gas in the tank. But you have to let them go. Being a scientist is a great privilege, but it's a profession that people enter not because this is an easy way to make a living. I don't know of a single colleague who would not make more money than they do if they were to leave the pure research business. You do this because you find sometimes 100 hour weeks okay. Because you're motivated by it. And so, I think, if a result doesn't come out, it's because what you are pursuing is so exciting at the time. Nature is not going to give its secrets easily. And you just have to keep trying and have a good stomach for failure.

ZIERLER: What about as part of the attraction coming to NIH, the quality of the labs and the instrumentation? Was that a draw also?

ROLL-MECAK: It was great, yeah. It's great. I think there's great instrumentation. I think there's really great talent on campus, fantastic talent on campus. And people that are very generous, with their knowledge, and their equipment. Usually, people are like, "Yeah, sure, what do you want to do it?" There's never been a barrier. There's never been a quid pro quo, that you know, I do this for you and you do that for me. It was like I need this. And people would be like, okay how can I help you? And so I think that's also what is unique about the place. But I think the appetite for risk has been historically high at this institution. And I have to say there is political pressure to go so much into translational science. And I think it's really unfortunate that this is happening. Because all great medical discoveries actually were sparked by curiosity. The vast majority of it was initiated at the NIH in the 50s, 60s, and 70s. You can name me 20 things that make modern medicine possible, and they happened at the NIH during those years, and because the DNA of the place was to "think big". They were not thinking about, well, are you going to get a result in a year or two or four. No, if you get one in ten, great. In 20. But you deciphered the genetic code or you figured out how to do a heart transplant. So I think this short range thinking in science is very, very dangerous, and there is a lot of pressure from funding agencies to think in little bits. And it's not just for biology or biomedical sciences. It's for all sciences.

ZIERLER: Everywhere. Right.

ROLL-MECAK: It's for physics also.

ZIERLER: Now, you talked about this a little in terms of the spirit of collaboration with instrumentation, you know, being able to use other people's labs. What about on a scholarly and an intellectual level? In terms of not only going to colleagues in your own institute, but sort of drawing on the vast amount of experience and wisdom throughout the NIH? Do you find that there's a spirit of

collaboration where you can really workshop a problem and tap into a network and people are going to be interested and helpful to you?

ROLL-MECAK: Yeah, absolutely. The scientific enterprises is so international and collaborative. We help each other out all the time. Everything that we find out, we publish, and it's available for everybody to look and build upon. And so I think collaboration is strong within the NIH as well as i with other institutions in the U.S., and also internationally. We basically share information globally through publications that are open. Scientists in general just want to get their problem solved, right? And so we share our knowledge all the time. The entire scientific enterprise is predicated on communication and building on each other's findings.

ZIERLER: Now, is the fact that NIH has such a strong clinical component, that there are patients at NIH, is that advantageous to your research? Are you ever interfacing with medical doctors or even the patients themselves in terms of helping you advance your research questions?

ROLL-MECAK: I didn't do that at the beginning, actually. When I started my lab, this question of the tubulin code that I wanted to study was in such infancy that I really needed to set up a system that would allow me to study it. And so my lab had set up the first, basic in vitro reconstitution system, which you can use to actually study this problem. And now this has been adopted by other people in the field. And so because I was so focused on that, I didn't really have time to interface with my clinical colleagues. But in the last few years, actually, it's been great, because one of my clinical colleagues has found a bunch of mutations in tubulin, which is the building block of microtubules, in patients that have neurological symptoms, and we are now looking at those to try to understand how the microtubule tracks are impaired in those particular patients.

It's fantastic, we get cells from the patient. We get some from the skin of the patient, we propagate them, then we basically isolate the microtubules and we look how are they different from a healthy person? And why is this person having these symptoms? So it is informing us about what goes wrong in the disease. By looking at dysfunction, you actually learn more about the normal function of the

protein. Where is it that it has a weak point? Where is its Achilles heel? A lot of mutations happen all the time in your cells and mine, and they don't make us sick. Sometimes they do, because that's how we get cancers and so on, but most of the time, we get mutations that are benign. They don't do anything deleterious to us, but the ones that do tell us where the weak spot is for that protein and so you can use that information, then, to try to understand its true function. And by doing that, you can also understand how that patient is affected, and help eventually them. So the clinical program is very nice resource now that our basic research investigations have matured.

ZIERLER: Are there more than two end goals in terms of the ultimate motivation behind your research? In other words if the research is geared towards helping people, right? The two categories as I can see them, there's therapy and there's prevention, right? Do you-- I mean, just so I understand. Is there a third category in the way that you look at these things? In terms of--

ROLL-MECAK: You mean for application?

ZIERLER: Yeah. In order-- Here's the body of research that you have done, and when we're exploring the ways that it can be applied to advancing human health in the broadest possible sense, right? Is there another category beyond therapy and prevention for your research to be applied, to be helpful to people?

ROLL-MECAK: Actually, I would say that the most important one, or I think maybe the most important one in a way, is the one of acquisition of knowledge. And I'll tell you why. Because people think that acquisition of knowledge is just an esoteric search, to just satisfy the scientist. But I would say, for example, the COVID-19 crisis that we're living through right now is the perfect example why acquisition of knowledge is absolutely essential. It is because we cannot anticipate what will happen. The speed with which we are finding things about this virus is possible because of the acquisition of knowledge into how other viruses work. Many of our knowledge that we are now applying now to COVID19 comes from viruses that have no deleterious effect on human health at all.

But out of curiosity, we have figured out how these viruses actually work. By having defined biochemical pathways in cells, now we can use the thousands of drugs that are already pre-approved for safety and impact these various pathways, and test whether they can be effective against this new virus. There are now already several reports of small molecules that affect the trafficking of this virus, So it's really the constant acquisition of knowledge and improvements in technology that that allowed the scientific community to respond quickly to this new virus that nobody has seen before. Yes, scientists predicted that there would be some kind of virus in the future that will cause a pandemic, but we could have not predicted what kind of virus. It could have been any other class of virus, and not from the coronavirus class. And if we would have focused only on one type, we would have been left blind to all the others. So we need to acquire knowledge as deep and as vast as possible about the human body, about the cell. So that when we actually have a disease, or an infectious disease appearing, we can tap into that knowledge so that we can move very quickly. And so I do think that this is still the most important mission of the NIH, and it's the one that actually has the most applicable value.

ZIERLER: So it sounds like you never look at a particular health problem and reverse-engineer it to try to find a solution to that particular problem. You have a much more--

ROLL-MECAK: Not me directly. There are some molecules that we work on, where I think that is possible. For example, one of the more popular drugs used to stop cancerous cells from dividing acts on the microtubule cytoskeleton. And we have known for many years that particular tumors just don't respond to these drugs at all, or very poorly. And recently we have found out that this is because they those tumors make a particular flavor of the tubulin building block that does those compounds are not able to bind to. As a result, those patients are given these drugs but they do not respond to them at all. But those compounds are toxic for the patient and have a lot of painful side effects. You don't want to give them to a patient unless they know they would work i.e. they would stop the tumor from growing. So now that we know which tubulin building block can cause the problem, we can actually

profile the tumor to find out whether that is a drug that would be useful for that patient. So this is one area that we are moving more towards.

You can profile the tumor and say, "Does it have this building block?" If it does, you should not be giving the patient with this group of drugs, and you should be looking for something else. So we here because we were just initially very interested to figure out how these different building blocks for the microtubules were behaving. And then we realized, wait a second, some of them bind to this drug and some don't. And then you look at tumors that are resistant and guess what? The tumors have the building block that's resistant to the drug. And so if you can profile the tumor for each patient, that's personalized medicine, you will spare that patient really painful chemotherapy that is not going to be effective.

ZIERLER: Can you talk a little bit about, you mentioned, you know, big ideas. Right? That NIH is a place that celebrates big ideas. So, you know, you're young, obviously. So the big ideas—

ROLL-MECAK: Thank you.

ZIERLER: —that you have-- (laughs) The big ideas that you have are things that can be relevant to your own career for decades to come. Right? So I'm curious, how do you want to build on your experience so far? And thinking about the possible advances that could be made and how that might shape the kinds of questions that you might not even know to ask five, ten years from now.

ROLL-MECAK: I think the great questions are the ones that you might not even know how to ask well initially. And I think the important thing is to keep an open mind and a keen eye. Nature leaves you a few breadcrumbs, you should not ignore them, because it might actually lead you in an interesting direction. For example, my lab has pursued in the last two years a completely new line of investigations that were completely unexpected that have made us and the field change how we think about microtubules. So think about our microtubule building blocks, our cellular roads. Cells build microtubules all the time. We will sit here discussing in the last hour they have assembled and disassembled billions of microtubule roads. For the last 30 years, the thought was that microtubules

are built by adding little subunits at their ends. So they grow, and they shrink when you don't need them. Unlike your skeleton or highways, they're actually dynamic, growing and shrinking. And so the thought was that every time you needed to make a new one or refresh it, you would basically, get rid of it completely and build it again.

But what my lab discovered is actually, no, they actually repair themselves all the time. Cellular factors take out old building blocks and put new blocks back in. So cell cytoskeleton heals itself all the time, a process that we had not envisioned. We found that two proteins that are nervous system function are doing this. They actually repair and heal microtubule tracks. I would have never thought that is possible. If you had talked to me five years ago, I would have said, well that's impossible. There's no active repair or healing process for microtubules in the cell.

But it turns out that two genes that actually give rise to human disease, do this. That is why it is important to make sure you follow all interesting leads wherever they take you. I also think you have to be very unforgiving with yourself to make sure that you don't continue doing things that you already know how to do. And that's the hardest thing, actually, because as you advance in your career, you become more successful it's very easy to kind of keep doing the same thing. And so you have to really just prune, prune, prune all the time. You have to be willing to say, let's not do this anymore, let's just jump forward. And I think that's the hardest thing because if you find a comfortable place, you the tendency is very strong to stay there. And so you have to just constantly evaluate what you are doing and be willing to cut. I do this every year, I look at my projects and say, okay, this is important, but I think somebody else could do it also now, because the tools are there, we published. What is the next hard question? And that's where I try to move. And I make a point of doing that every year to make sure that I don't become complacent.

ZIERLER: It seems that both intellectually, by your education, and also by your obviously-fearless research agenda, right? You're more than happy to sort of take on anything, right? And so, of all of the things that you could take on, you're always limited by time and money and other resource

constraints. And so I'm curious, how do you bound your own research agenda? How do you know when something is sort of too far out of your wheelhouse to say, this is something that I can't deal with? Because, I mean, if you look at the things that you've accomplished and the things that you're interested in, and the things that you've studied, right? What's to stop you from saying not to do anything that's related to the broadest possible field of biophysics?

ROLL-MECAK: The scientific community is so rich. So if there is a problem that's really interesting, but it's clear that somebody who's very good is addressing it, even if I can, there's no point for me to do it. So I look for things where I think that my unique set of talents and the talent of the people that work in my lab, can make a difference. And I ask myself, can I make a difference? Is this important enough? And if I fail, will I learn something useful, even if I fail?

ZIERLER: Productive failing.

ROLL-MECAK: And so those I think are probably the things that guide me. And also as my lab matures, I've had my own lab now for 10 years, the dynamics also change, and I also get people who have their own interests, right? They work in this general area of microtubule function and tubulin code, but some come and say, I'm kind of curious about this thing. Do you think I could work on it? And if the person is driven, then I say go for it. So people in my lab also start growing their own branches. When I started out, you could say, I was almost like an arrow. I had a very clear path, and now as my lab has grown and get I talented people, they have their own ideas and they pursue them. You let them try new things, things that you did not think about and that makes your program richer. So I would say that I do not have as sharp focus as I did at the beginning. And that's very satisfying, because we end up actually finding new things that way. And so we go forth and explore and grow new branches. And then postdocs take these areas of investigation with them when they start their own labs, so I cut off that branch, and they can start their own. And I kind of continue growing my tree and I keep pruning it according to the principles that I highlighted before. I am not always successful, but I try.

ZIERLER: Now, in this constant assessment of making sure that you're working on programs that are important and impactful, right? You talked a little bit about productive failure, that if you're going to fail at something, at least learn something useful about what failed. But can you talk a little bit more about success? In other words, what are the feedback mechanisms for you that demonstrate that a given project that you're working on, not only is ultimately successful in however you define that, but that it continues to deserve to be nurtured along the way?

ROLL-MECAK: Well, I think there are some projects where it was clear that we answered what we wanted and in doing that, the new questions that were opened are not that exciting where you could say, I think I can guess how this is going to go. And so those maybe will not be continued. For other ideas, you start the project, and you realize, oh, well, I did solve my original question, but boy that was like the least important question out of all the other 20 that this thing has opened up. So those projects are the ones that, give you the propulsion for the next big step. Having said that, sometimes you actually find interesting, unexpected things in projects or in directions that you thought were kind of safe and boring. And this illustrates that we still know so little about the system. The human cell is so complex, that our predictive power is still lacking.

ZIERLER: Yeah. Hari Shroff, I mean one comment that he made that really stays with me is, we're still trying to figure out how the cell in a worm works, you know? (laughs)

ROLL-MECAK: Well, we're trying to figure out how a single cell on its own works, right?

ZIERLER: Right.

ROLL-MECAK: And we have learned a lot in biology. We know enough to allow my parents to live with high blood pressure, all because we have learned how molecules and cells work, right? The progress in terms of the quality of life for humans on Earth is astonishing Let's start from the 1950s, say 70 years of dedicated funding to research at a very small level compared to the GDP of the U.S. And what did we get for that? We have people who live productive lives playing tennis in Florida into their eighties and nineties. All because we understand how calcium pumps work, how this little

protein that sits on the membrane can, pump ions from one part to the other. We understand how antibiotics work. We know how antibodies bind viruses. We know how heart muscle contracts. So we know so much. That's why I think it's very hard sometimes for people who are not scientist to imagine that we know so much, but that's still like 1% or a fraction of 1% of what we need to know so that we can predict what a cell in an organism would do.

ZIERLER: Yeah, yeah.

ROLL-MECAK: And yeah, it's infinite, almost, right? And that's what's really daunting. You think about how little we know but how much it has impacted how we live. And then you think, god, if we knew even 100 times more than we know now, how would we live? If we understand how tissues are put together and how to integrate them with man-made materials and circuits. And I have no doubt that we will be there. Maybe I won't be alive, but I think it will be definitely in my son's generation. And how do we repair tissues and organs? I hope it will be done in an ethical fashion, but I think it will happen.

ZIERLER: Is there a particular health malady that motivates your research more than any other? Is there a particular condition that you say, you know, if I can contribute to a breakthrough on this, that's more important to me than anything else. Do you think along those lines?

ROLL-MECAK: Not necessarily. I'm very interested in how neurons are kept alive and in good shape. And basically why they degenerate, and that's because a lot of the processes we look at have to do with intracellular transport. Neurons, more than any cell in the body, have to transport information and content over huge distances and in very complex architectures. And so it's a really daunting transport logistics problem. And almost all diseases that affect the nervous system (I guess maybe I do want to live a long time and do this job for-- (laughs) Maybe I want to be pretty sharp, as long as possible) end up actually affecting intracellular transport on microtubule highways. So I think by understanding this process, it will give us insight into aging and diseases associated with aging. How do you keep a nimble neuron as you age? Because, unlike many other tissues, where cells

divide all the time, and thus you renew them, in the nervous system, the neuron you've got as an adult as to survive and adapt as you age. Thus neurons actually have to be much more resilient in terms of long term maintenance. And so that's what interests me.

ZIERLER: And it's all towards, as you said, gaining knowledge, and then figuring out what to do with that knowledge.

ROLL-MECAK: Yeah.

ZIERLER: Yeah. Well, I want to ask. I mean, I'm coming from you from the perspective of physics, from the American Institute of Physics, with your physics background. I'm curious, and this could go back all the way to your days in high school, maybe, when you first got exposed to physics. Are there concepts in physics that remain close to you that continue to inform the way you see how biology works, the way that you run your lab, the way that you define your projects? Are there things that you might have learned a long time ago in physics specifically, that continue to shape your career and your worldview?

ROLL-MECAK: Oh I think everything. The way I design and interpret experiments is rooted in that. Because I view everything quantitatively and very analytical. Modern biology is quantitative biology. I also think I have a pretty good instinct because of my foundation in math and physics. I like to think about the underlying principles for everything in a biological system. Because biology is still the physics of atoms. There is nothing special about it. It is the collective behavior of trillions and trillions of atoms that give rise to the behavior of the cell and ultimately the organism. There's no magic force in a cell. Our cells are alive because of the balance of forces in the cell generate the energy that keeps us alive. We're in a constant struggle. If we are at steady state we would die. I think, it's a physics way of looking at things. It's basically the same way I think that a physicist who's interested in the universe wants to know what each type of particle is doing in the universe. A biologist wants to know what atoms are doing what, and what timescale. And how is this jumble of molecules in a cell gives rise to a clear, physiological response. How do you get this collective

behavior from what looks like random collisions of molecules? We don't yet understand how all these molecules are connected to give you an emergent property. So I think that's a very physics question.

ZIERLER: I'm curious, before you mentioned, I think in the beginning of our talk, that all life forms on the planet share the same amino acids? Is that right? The same 20 amino acids?

ROLL-MECAK: Right.

ZIERLER: So maybe this is sort of beyond your area of expertise, but what does that tell us about the way life evolved on the planet? What's the big takeaway there? The fact that the amazing diversity of life on the planet, how we all share the same fundamental characteristic? What's the bigger takeaway from that, do you think?

ROLL-MECAK: Well, this is something for people who work on origin of life questions. And it's obviously a very fascinating area of research. But to give a limited answer to your question is, the thought is that we don't have an example of an organism that has any other number, say 15, 20 is because we don't have any example of an organism on Earth that is a precursor, or a predecessor to the time where the genetic code had been set. So the idea is that we had more simple ones before, and people are trying to make artificial cells with simplified codes.

But the idea is that at some point, this became set and then the cost for not having it was too high, because it was far better than anything else out there, and those organisms which did not have this set were not viable long term and thus were selected out. Once you have a machinery dedicated to a certain type of code, it's very hard now to change, right? There are too many steps or rules in the decoding process that need to change in order to accommodate a different number of building blocks. This is an actively pursued question i.e. how the genetic code was established. And I don't want to say more, because there are people who know a lot more about this than I do. Scientists are trying to make artificial proto-cells to understand how all this came about.

ZIERLER: Do you work on coronavirus issues at all?

ROLL-MECAK: No, not yet. We just had a discussion a couple of weeks ago, because we are looking at all the things that the coronavirus interacts with, and it turns out that a large number of interactions are with the microtubule cytoskeleton. And so we might actually start looking into the role of the microtubules in the lifecycle of the virus.

ZIERLER: Now, you've spoken about this already, but I'm curious. You know, there's a public frustration, and obviously, it comes from ignorance, about, you know, "why don't we just come up with a vaccine already? Why does this have to take so long? When can we reopen and be safe and all of these things?" So even though you're not specifically working on coronavirus now, can you give a sense, just from your knowledge of how these things actually operate, you know, why not? We've seen other coronaviruses in the past. What is actually so difficult? Why should it be not surprising that there's still so much that we have to understand about this particular new novel coronavirus?

ROLL-MECAK: Well, first of all, the coronaviruses, we know something about them. But because none of them were dangerous viruses to us, there wasn't that much research and definitely not much interest in a vaccine. This family of viruses were actually not the focus of great funding because they were not big killers for humans. But there's still a lot of work that has been done, and that is obviously helping the efforts right now. The scientific community has sequenced this virus, I think faster than any new virus. People have identified with what it interacts in a matter of months. I mean, it's mind-boggling. I mean, we are in May, and this thing started in February, okay? So it's kind of amazing that we are at this speed.

ZIERLER: But the public, I'm saying the public does not appreciate that, right?

ROLL-MECAK: Yeah.

ZIERLER: You appreciate that when you're talking about things that take ten or 20 years. The public is accustomed to, there's a problem, give me a solution. What's taking so long?

ROLL-MECAK: Yes, but that's a problem. Even the car which is much simpler than the human body is the result of hundreds of years of research - how do you make a combustion engine etc. The

fact that people don’t think about what went into all of the things we use in our daily lives is basically a testament to how successful science has been in changing modern life. People take all of this for granted, but it is the accumulation of years and years of research by hundreds of thousands of people.

People use their cell phones daily. I can be in my pajamas upstairs and see who's ringing my front door, and then turn on the coffee maker in my kitchen. I get a fever, I just go in the doctor’s office and get a panel of tests. Three days later I know that I have strep and I know exactly what kind of antibiotics I should be taking. But what I think the public does not know is that in order to have that strep test done, somebody had to work for tens of years to figure out how to culture it, how to sequence its DNA and what DNA signatures distinguishes it from other bugs. And so it's a testament to how science is constantly changing our lives, but I think because of that we are taking it for granted, and we have forgotten the kind of investment and long-term thinking that is required to keep those kinds of things coming. And it's going back to this idea of short-sightedness and a decreasing appetite for curiosity driven research.

Had we not been curious about other coronaviruses, we would be in a much more precarious situation right now. Luckily, we know something about them and we also know a lot about how to make vaccines. But the next difficult part is to try to predict how the human body will react to the vaccine, how will seven billion different people going to now react to this vaccine, seven billion of us who are different genetically and with different underlying conditions. It is hard to predict how a person’s immune system is going to react to a vaccine. The immune system is a repository of memories i.e. it will respond differently for people who are genetically identical if they had different experiences and have encountered different pathogens during their lives. So it is hard to know how each individual will respond to the vaccine, which is why the safety trial is done in a large number of people and cannot be rushed. There is no shortcut around that. We're all different. And so we need to make large studies with people to make sure we cover as much of this diversity as possible.

ZIERLER: So Antonina, and yet, despite everything that you just said, you're so clearly an optimist and you're so full of energy. So give me something to be optimistic about with coronavirus?

ROLL-MECAK: Oh I think we will find a vaccine. I'm not sure if it's going to be a perfect vaccine. Many vaccines go through multiple stages. Initially, the vaccine is not so effective. It works for only a couple of years, and then you need to do boosters, but then vaccines are being refined, and then you can end up with something that you give a person once, and you're done. So we might not have a perfect one on the first round, but we probably will have one that at least people on the front lines and people who are older and are at higher risk can get. This virus is not mutating as fast as others, which is an advantage. And also we can change the outcome with our behavior. We understand a lot about how this virus is transmitted. And we just have to be kind to ourselves and to each other, be mindful of our communities. We also will have to change the way we work to make sure we keep people safe. And that doesn't mean that we're not productive. We just have to change the way we are going to go about our business for a little while.

ZIERLER: Well, Antonina, last question. We've covered so much, it's been just incredible talking with you. I want to turn around that piece of advice that you gave to your post doc, you know, thinking about when you're int he shower in the morning, if you're not excited about what you want to accomplish for that day, then you've got to think about something else to do. So my last question for you, forward-thinking for, you know, hopefully the decades that you'll continue to make such impacts in the field. How would you expand that one morning in the shower over decades, right? What's the thing that is going to continue to motivate you day in and day out to continue working those 100-hour work weeks to accomplish what you want to accomplish? What is that motivation for you?

ROLL-MECAK: Well, I think it changed with time. I think when I was a postdoc and when started my lab, it was all about me doing the experiment and asking my question. I think now I get as excited thinking about the result that my post doc emailed me the night before. So I get excited about what

they find interesting, and what they think is cool to follow. I find that to be very gratifying. Nothing makes me feel better than getting an email from the lab unexpectedly telling me that something didn't go the way they planned. That actually usually is more exciting than actually having it go the way they planned. That gets me excited because I've got something else to think about that I don't know the answer to.

ZIERLER: Yeah, yeah. So you're a mentor, fundamentally, is what it comes down to?

ROLL-MECAK: I hope so, I think it's something that you continuously try to improve. I think your focus as a scientist and a mentor constantly changes with your career. I also have a lot of questions that I really want to answer by being at the bench myself and I can't wait to get back to lab to do that sometime in the future. (laughs)

ZIERLER: Me too, me too. Antonina, it's been so fun talking with you. I learned so much. This is going to be so useful to so many people. I'm so glad we were finally able to connect on this, so thank you so much.

ROLL-MECAK: Sorry about that. (Both laugh) So it was nice to see you, and I hope you manage okay with all the kids.

ZIERLER: That's right.

ROLL-MECAK: I've got only one, so. I don't know how you do it.

ZIERLER: All right, I'll cut the recording.