Scientific Curiosity Is in the Blood Says Irina Artsimovich

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SPEAKERS

Irina Artsimovich, David Staley, Janet Box-Steffensmeier, Eva Dale

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E **Eva Dale** 00:00

From the heart of the Ohio State University on the Oval, this is Voices of Excellence from the College of Arts and Sciences with your host, David Staley. Voices focuses on the innovative work being done by faculty and staff in the College of Arts and Sciences at The Ohio State University. From departments as wide ranging as art, astronomy, chemistry and biochemistry, physics, emergent materials, mathematics and languages, among many others, the college always has something great happening. Join us to find out what's new now.

D **David Staley** 00:32

Irina Artsimovich is a Professor in the Department of Microbiology at The Ohio State University College of the Arts and Sciences. She is a fellow of the American Academy of Microbiology, and a fellow of the American Association for the Advancement of Science. She has been a grant recipient from the National Institutes of Health, the National Science Foundation, and the American Heart Association. She has been here at Ohio State since 2001. Welcome to Voices, Dr. Artsimovich.

I **Irina Artsimovich** 00:58

Thank you, glad to be here.

D **David Staley** 00:59

I'm interested in your most recent research, I know that you've been working with proteins that enable E. coli, for instance, allow them to survive when they're barely growing. Tell us a little bit more about the work that you're doing here.

I Irina Artsimovich 01:13

So, when most bacterias spend their life not in the test tube, where we grow them at optimal concentrations on everything, and at 37 degrees centigrade, that's what they like. Instead, they grow in very hostile environments where there is barely any food and they are growing very slowly. And in that state, you can call it dormant. And in that state, they are, for example, very resistant to various negative impacts, including antibiotics, yet they still have to survive, and they have to grow. And one of the major challenges for bacterial cell is how to make its living blocks, how to make RNA, and how to use this RNA to synthesize proteins.

D David Staley 02:03

Remind us what RNA is.

I Irina Artsimovich 02:05

RNA is ribonucleic acid, which is a template from which proteins are made. So the DNA, which is the basic information encoded in our chromosomes, is a template from which enzymes called RNA polymerases, make RNA. And then proteins are being translated using that RNA as a template. But the first step is how to make this RNA, and RNAs could be very long in bacteria that could be hundreds, thousands of nucleotides basic units in length, and in few months, it's one million nucleotides. And to make this long molecule, RNA polymerase has to stay bound to it throughout the entire cycle. And it can take more than 24 hours in us, for example. So it's a long process. And when enzyme does it, it cannot possibly let go, so it has to remain bound. And what we work on are the mechanisms which help RNA polymerases to stay in action and to continue making the RNA, and then of course, it will ultimately lead to proteins. And that has to happen under all conditions, because you have to replenish what is lost, the RNAs and proteins are not infinitely stable. So in order for bacteria to resume growth, when things are well again, they have to have these molecules around at low levels, but have them.

D David Staley 03:42

So as I said, you work with E. coli. What does that mean? Obviously, E. coli is something that we hear in the news, quite a lot. Describe your work with E. coli.

I Irina Artsimovich 03:51

So you hear about it in the news, but the one we work with is very different. It's completely harmless.

D David Staley 03:58

A harmless E. coli, interesting.

I Irina Artsimovich 04:00

It's a laboratory strain, and if we were to let it swim, let's say in our in the Olentangy River, it will immediately die because it is lacking a lot of useful...well, most of the strains will die. And the strains that are used in the lab are of course nonpathogenic, they cannot possibly cause us any harm. They grow very quickly, E. coli doubles every 20 minutes. And so when you grow a very small cube, let's say for 16 hours overnight while you're at home, you get many millions of cells in the cube, so it simply provides great statistics, so it's a great model organism. There are other bacteria, but E. coli is kind of garden variety, molecular beast that we all use.

D David Staley 04:53

And the problematic variety?

I Irina Artsimovich 04:55

The problematic variety is different because it has... well, there are many different virulence factors that make it different. Most importantly, these are toxins, and these are also antibiotic resistant genes and things like that. So the proteins we actually study most intensely are the proteins that help E. coli and other bacteria to express these determinants, particularly toxins.

D David Staley 05:25

And it's the proteins that you're particularly interested in, more than the E. coli, the E. coli is what gets you there.

I Irina Artsimovich 05:30

The E. coli is our kind of global test system. We do experiments in bacteria, and we also do a lot of experiments in the test tube, so we cover everything. We work, we use genetic methods, which is simply make mutants and see what they do. We work with purified proteins in the cube, we solve structures with different complexes, we use by physical methods, it covers everything, but it's just simpler. The basic difference between bacterial, let's say transcriptional machinery, and human transcription machinery, is size. And in bacteria, you just have RNA polymerase, which has five subunits, and on only one polymerase, and in humans, you have three different polymerases at least, and the smallest one is 12 subunits. So it just more work, I'm trying to make life simpler.

D David Staley 06:31

When you say transcription machinery, what does that mean?

I Irina Artsimovich 06:34

It's an RNA polymerase, which is an enzyme, but it is composed of multiple subunits. And in addition to that, it uses multiple factors that tell it where to start making the RNA, how fast and how far to go, and where to release. So all of these, and this could be tens of them in mammalian systems, and basically under ten essential proteins in E. coli.

D David Staley 07:03

So what sorts of conclusions, tentative or otherwise, are you reaching with this research?

I Irina Artsimovich 07:08

We actually reach very, kind of, broad conclusions, because the proteins that we are working on are universally conserved, so they have the same structure in E. coli and in us. And therefore, we can just take a very simple system, analyze it in infinite detail at a biochemical, biophysical genetic level, and then draw conclusions that can be tested in more complicated system. And when they were tested, the result is identical, but we can simply do more experiments per unit of time and per dollar of money.

J Janet Box-Steffensmeier 07:52

I'm Janet Box-Steffensmeier, Interim Executive Dean and Vice Provost for the Ohio State University College of Arts and Sciences. Did you know that 23 of our programs are nationally ranked as top 25 programs with more than ten of them in the top ten? That's why we say the College of Arts and Sciences is the intellectual and academic core of the Ohio State University. Learn more about the college at artsandsciences.osu.edu.

D David Staley 08:16

I know part of your research is about killing these bacteria, especially through things like antibiotics, and I know antibiotics and especially bacterial resistant antibiotics are so much in the news. Are you working at all with these sorts of concerns?

I Irina Artsimovich 08:32

We are definitely working on it. I have been on an NIH grant panel that is on the mechanisms of antibiotic resistance and drug discovery applications, and that made me acutely aware of how big the problem is. Because on that panel, you have physicians and people who work in pharmaceutical companies. So there are two major problems. The first problem is that we do not have new antibiotics and have not had them for several decades, and, in addition to that, the companies are rapidly exiting this field, they are no longer interested in making new antibiotics. And this is simply because antibiotic treatment, even the most expensive one, will probably cost $1,000 per treatment time. And the drugs that people have to take for years and years and years, and are being much more profitable. So I think within the last half a year, maybe, two major companies exited that and so they no longer have their antibiotic programs.

So what it means, is that it's now back to academia to look for antibiotics. And this is really bad because, for example in China, I just been to a conference on drug discovery in Hong Kong, and in China, they have not only a lot of resistance in the clinical populations, but they have different pathogens, such as E. coli and Klebsiella, which causes pneumonia, that exchange antibiotic resistant determinants while they are, let's say, in the same hospital. And this is really scary, because you will have not only one strain being antibiotic resistant, but multiple pathogens carrying the same antibiotic resistances. And there are some strains now that are resistant to all available antibiotics, resistant at some level, because you can make, you can kill them, but you have to increase the concentration of antibiotics so much typically that they start causing kidney damage and other things.

D David Staley 10:55

So you say it's a challenge, or it's a problem in that, that in a sense, the ball has been served back to academia. Why is that a problem for academia to be wrestling with this problem?

I Irina Artsimovich 11:08

Well, it's a problem for academia, because we're not the best position to do it. It's actually not a big problem, it's just it would have been better if it happened a long time ago.

D David Staley 11:19

Is it because of capitalization, it requires a lot of capital to do this, or...?

I Irina Artsimovich 11:23

It doesn't require a lot of capital, but our goals are typically different. So I actually worked on probably six, seven different antibiotics that inhibit RNA polymerase. But my goal was not to find a wonder drug, my goal was to study how the enzyme works. And so most antibiotic, most academic researchers consider antibiotics as tools, they are molecular tools, how to... so basically, you're breaking the system to know how it works. And designing a new antibiotic involves knowing something that we usually don't know. For example, you need to find collaborators who know how to modify antibiotics, that you identify to make them better, to make them get into bacteria faster, to stay in bacteria, to have properties that would allow them to, to stay in the bloodstream, for example, something like that. And we are not thinking about this. So basically, we are thinking in very fine detail, how antibiotic binds to the target, and how it kills the target. And essentially, it requires collaborations that have our colleagues to make serious progress on the antibiotic. There is nothing wrong with that, but you have to be aware of it from the beginning. And that's what I, actually when I went to this conference, I found potential collaborators that I will work with to share antibiotics.

D David Staley 13:02

Do you mean other microbiologists or do you mean collaborations with other disciplines, chemists?

chemists?

I Irina Artsimovich 13:06

Chemists. You have to have collaborations with other disciplines. So within the last year, we have been working on antibiotics against two different bacterial targets, and we started using in silico computational design.

D David Staley 13:23

In silico compu- so like, virtually, in a machine?

I Irina Artsimovich 13:27

You take a structure, you need to have a high resolution structure over target, and then you throw at it - I cannot do it, but my collaborator at UCSD can - you throw at it a library of small molecules, millions of them, and you determine which ones will bind. And then you can purchase this compounds because there are companies that sell it to you, so you can purchase, we purchased ten, for example. And we tested them and among these, two were actually quite active in the cube. But they are not killing bacteria, because they cannot get into bacteria. That's the problem, why many of them are resistant. So what do you have to do? You have to have a chemist to modify these compounds so that they can enter the bacterial cell because that's where they have to act to kill it.

D David Staley 14:25

Are such collaborations unusual for this kind of problem or is that is that part of the challenges you face, or?

I Irina Artsimovich 14:31

They are just new, I never collaborated with a chemist, I collaborated with people who solve structures. I collaborated with people who work on, kind of, very high end by physical analysis of protein, but I never needed in my life to collaborate with a chemist. And also what I need if I work on antibiotics, I need to collaborate with people in medical school, because they have actually access to pathogenic strains, and they have models of pathogenesis. Because it doesn't matter that much if you kill bacteria in a tube, what matters if you kill kill them first step in mice, because that's what you need to know before you go to humans.

D David Staley 15:19

And you mentioned a potential growing problem about antibiotic resistant strains in China or Hong Kong.

I Irina Artsimovich 15:28

It's in the U.S. as well, we have very, a lot of Klebsiella pneumoniae strains that are resistant to multiple antibiotics. They are a lot of them in Midwest, I think there were a couple of bad cases in Pittsburgh. So we're not talking...while China is pretty developed country, particularly Hong Kong, but it is a problem everywhere. Because that's what bacteria are good at, you know, they have cell wall structure that enables them to survive in harsh environments. Antibiotic is just one of these.

D David Staley 16:00

And so, and I'll ask you to speculate, I suppose, what are the potential public health issues?

I Irina Artsimovich 16:06

Well, public health issues are huge, because the problem the bacteria, of course, it's similar to flu. When we had flu pandemic, it's now 200th anniversary of it, many millions of people died. And this is because it takes very little time to die, so you can die from bacterial infection within several days. But that's the commercial problem, that's why companies do not want to develop antibiotic, it's very expensive to develop a drug to the point where it can be applied to clinics.

D David Staley 16:41

Do you see that changing anytime soon, or do you see the academics like yourself collaborating, pushing companies to work in this area?

I Irina Artsimovich 16:50

Well, I'm afraid that from a practical point of view, the way it will change is if we will have a serious outbreak of antibiotic resistant something, let's say pneumonia, with many people dying, because that's what happened with HIV, for example.

D David Staley 17:07

I was afraid you were gonna say something like that.

I Irina Artsimovich 17:09

I hope it doesn't happen, but I do not see... it is already happening, at least in China, it's pretty serious.

D David Staley 17:17

David Staley 17:17

So I frequently have a scientist on this program, and I always ask scientists about their lab. And my understanding is you have a sort of an unusual lab structure?

I Irina Artsimovich 17:27

I have a very unusual lab structure, I always had. I never had more than five researchers in my lab.

D David Staley 17:34

Which is small, as labs go.

I Irina Artsimovich 17:36

It is very small, and I count myself as one of them. So I work in the lab as much as I can, and I find different times to do it. So for example, right now, I have one PhD student and two undergrads working in my lab, and a postdoctoral scientist will join us shortly. But that's the limit. And the reason I like doing it, because we actually are working on a lot of interesting but sort of risky projects. So if I give a risky project, which has, let's say, 20% probability of success to a graduate student, it actually doesn't serve a graduate student well, because should they fail, I kind of jeopardize their... the training is good, but I jeopardize their ability to publish papers. For me, it doesn't matter, if experiment doesn't work, I have nothing to lose. Except I will become upset.

D David Staley 18:33

What, and let's be clear, what do we mean by failure and success here? What does it mean for a project to fail?

I Irina Artsimovich 18:38

Some of what we do is sort of hypothesis driven. And if we build a model on the available data, and then do experiments to usually try to prove it wrong, or try to at least prove some aspects of it wrong, it could be that our hypothesis is so wrong, that basically, the results we will get are not particularly interesting. And people prefer to publish only interesting results. It actually, in practice, it was never a problem for us. If anything, we find more interesting things than we can handle. But it is always a consideration. Plus, also some times, I need to develop new methods because the field is moving very quickly, and since I have more experience, it just takes me less time to do it. So it's more efficient way to use me to do some of that. And, and most importantly, I actually like it. I got into science because I like working at the bench and I don't want to stop.

D David Staley 19:44

So what did get you into microbiology, since you raised this?

I Irina Artsimovich 19:47

Well, it was complicated. So when I was growing up, my family was all in physics. My grandparents and my parents were all physicists. But I'm an experimentalist, and experimental physics for a woman is terrible, absolutely terrible in Soviet Union where I grew up. I know because my mother was one. And it's pretty tough even in other countries. And so because of that, I initially said, okay, I'm not even going to do any science and let's just forget about it. But then, I worked in the lab at the Cardiology Center, and I really liked the lab work. And then I went to the College of Biological Sciences, and microbiology, it doesn't actually matter what we do - microbiology, biochemistry, biophysics - this is all now one big experimental field. I cannot tell you, I am doing microbiology, I'm doing everything that I need to do to make the project work.

D David Staley 20:49

What's next for your research?

I Irina Artsimovich 20:52

Oh, I can never predict that, because...

D David Staley 20:56

Really? Interesting.

I Irina Artsimovich 20:57

So all, all the projects that people do, if they are really good projects, they kind of take life of their own and they develop. For example, when I started the project that is our major project, we worked on a protein that we expected to behave exactly like all its relatives in from E. coli to cows, for example. However, this protein turned out to be something that we could not possibly predict. It's a metamorphic protein that exists in alternative structural states. And you would never expect the protein that is universally conserved and all other of its relatives don't do this, to behave like this. When I was telling my colleagues that it could have possibly these properties, they were telling me that I'm mad and this is absolutely impossible. Yes, it is possible, and it is now the best kind of model system for studying protein structural transformations. But what it means is just that if you really work hard on a topic, you will find things that you don't expect to find, and then you decide which way to go, what is the most interesting. That's why you can never predict what you will do. It's a nonlinear path. It's our job to find the most interesting direction and the most, I guess, fundamentally and practically important.

D David Staley 22:22

Well, and this is perhaps a vast oversimplification, but it sounds like you're driven as much by curiosity as by applied outcomes. Is that a fair statement?

I Irina Artsimovich 22:31

It is a fair statement. And it could be genetically encoded in me, because my grandfather is credited for saying that scientific process is what, is basically you're satisfying your curiosity at government's expense. However, it always leads to more than that, because in his case, for example, he was driving force in Soviet Union thermonuclear fusion program. So this is the way how you generate energy through that few atom fusion. And so it's the same thing, we all are driven by curiosity, but you can channel it. So right now I'm trying to channel it to find new antibiotics because we desperately need them.

D David Staley 23:20

Irina Artsimovich. Thank you.

I Irina Artsimovich 23:23

You're very welcome. It was fun.

E Eva Dale 23:26

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