Igor Shats

Behind the Mask

September 23, 2022

Barr: Good afternoon. Today is September 23, 2022. My name is Gabrielle Barr, and I'm the Archivist at the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Dr. Igor Shats. Dr. Shats is a Staff Scientist with the National Institute of Environmental Health Sciences (NIEHS). Today he is going to be speaking about some of his COVID-19 research and experiences. Thank you very much for being with me.

Shats: Thank you very much, Gabrielle, for inviting me to this interview.

Barr: Absolutely. To begin, will you speak about how you combine your training in pharmacy and your degree in biology in your work at NIH?

Shats: My background in pharmacy puts me a little bit apart from most biologists. I have more background in chemistry than most biologists, specifically pharmaceutical scientists. When you think about small molecules and stuff like that, I think this background helps. This is especially relevant for this coronavirus project that we will be talking about.

Barr: What encouraged you to make that career shift, because for a while you actually worked as a pharmacist?

Shats: Yeah. My studies of pharmacy were very interesting and very diverse, because you learn biology, chemistry, pharmaceutical sciences, and medicine. In contrast to that, I felt that the work of a community pharmacist is, I would say, not intellectually challenging. And I need the intellectual challenge. I didn't want to do that all my life. I wanted to go back to studies and learn more. I was really interested, beginning from the high school years, in more of a translational approach—so how we can really develop drugs. That's one of the reasons that I went to study pharmacy. For that I decided to do a Ph.D. in biology. Many people, after doing a Ph.D., think almost automatically about a career as a PI [principal investigators]. My next step was a postdoc. Then I would be a PI and continue to do science. To do my postdoc, I moved from Israel to the U.S. to Duke University and did my postdoc in their cancer genomics lab. After my experimental Ph.D., I was really impressed by the genomics developments in those years. I wanted to learn more of the computational science to combine it with the experimental, so that's the reason that I did my postdoc in cancer genomics, which combined computational and experimental approaches. At some stage, after several years as a postdoc, my career plans evolved a little bit and I started to feel that I wasn't sure I wanted the role of a PI. I was more interested in something like a Staff Scientist position—to focus on science and not necessarily on writing grants and teaching. That's the position that I ultimately got. Because I'm located in North Carolina, I found this position at NIEHS as a Staff Scientist in the lab of Dr. Xiaoling Li. Her focus is on studying metabolism. Actually, I found it very

interesting. It wasn't my background, but we kind of combined—she's not a cancer person and all of my training was in cancer—experimental and computational. It was a good complement. I use my skills, both computational and experimental, in cancer. Currently the lab has actually more or less switched to studying cancer. Many people study cancer and I learned a lot in terms of studies of metabolism.

Barr: You've done a lot with cell signaling.

Shats: In my Ph.D. work, I started doing cell signaling. My current lab also studies cell signaling, especially in the context of the influence of the environment on the cell. Not just what happens inside the cells, but how factors outside of the cells impinge on the cellular signal transduction mechanism and how it affects cell metabolism, and how the cell metabolism is then translated into signaling networks that ultimately lead to change in gene expression, and finally, the phenotype of the cells. For example, small molecules, or even such environmental things as bacteria. That was actually my project before COVID hit. I kind of accidentally discovered an important interaction between bacteria and mammalian NAD [nicotinamide adenine dinucleotide] metabolism. NAD is one of the key energy molecules. What we found is bacteria actually plays a role and helps build NAD inside the host cells. We mostly focus on gut microbiota. That was my project, and we published a paper, and then COVID hit.

We were all sent home to do remote work. After a couple of months of remote work, I kind of felt bored. I felt that as part of NIH, we need to contribute to the fight against COVID, not just sit at home. The only way to do that was to start some COVID project. I decided to see if NAD could also potentially be important for viral host interaction. The initial idea was to test whether manipulating NAD might help against COVID infection. Obviously, we cannot work with COVID [virus] because it requires BSL [biosafety level] 3, and we don't have those facilities here at the NIEHS, so I needed to work with other viruses such as the conventional coronaviruses. We tested our hypothesis about manipulating NAD, and we didn't find anything. We didn't find that it helps against COVID infection, at least in the in the experimental in vitro systems that we use. But I already established these systems. We have a collaborator, Stephen Shears. Actually, he wasn't a collaborator, but he became a collaborator because he is studying inositol pyrophosphate (IP). We have these departmental seminars to listen to each other's science. I heard the talk from his lab, and he was describing one of the projects in his lab that found that inositol pyrophosphate plays a role in RNA [ribonucleic acid] stability. Reading many papers about SARS-CoV-2 and coronaviruses in general, I knew that the RNA genome of coronavirus is also capped. I thought maybe trying their way of manipulating inositol pyrophosphate could help against coronavirus. I suggested to them that we collaborate.

Barr: Can you introduce inositol pyrophosphates, and why their properties hold promise to boosting immune responses to viruses like SARS-CoV-2?

Shats: Inositol pyrophosphates are very simple molecules with a six-carbon ring. What's unique about these molecules is that they are stuffed with phosphates. These are the most electro-negatively dense molecules in the cell. In this small thing, there are up to eight phosphates. They are hugely negatively charged molecules, and they have their different biological properties. I'm not an expert. They do a lot of interesting things in the cell. Actually, I wouldn’t say that inositol pyrophosphates by themselves hold promise to boost immunity. That’s not

my hypothesis—that's not what I'm going for. What I was going for was that it specifically somehow inhibits viral replication, even before we talk about antiviral immunity on the cellular level. Virus needs cellular machinery to replicate itself. IP6K is a kinase that adds another phosphate to the molecule with six phosphates, making it IP-7, and another phosphate can also be added to make it IP-8. What they showed in the project that I just mentioned was that this IP-7 may be important for RNA stabilization. My hypothesis was that if we inhibit this kinase IP6K, then maybe we will destabilize the viral RNA. That's how it started. I'm not focusing on the role of inositol pyrophosphates themselves—actually, I want to inhibit them. I want to inhibit the production. What I'm focusing on is on the inhibitors of IP6K kinase. Specifically, I want to mention Steve's biologist Huanchen Wang, who is spearheading this project [in Steve's lab] of developing specific IP6K inhibitors. They are developing this project in collaboration with UNC's Drug Development Center, with a goal of inhibiting this kinase for diseases such as diabetes or metabolic diseases. Basically, they don't think about the virus. I just said, "Okay, let's try your drugs and see if it does something for the virus." And I found that yes, actually, they are inhibiting the virus.

Barr: How did you go about testing that?

Shats: As I said, we can't work with SARS-CoV-2, so what I use is an in vitro system, in which I take human macrophages—basically, a monocytic that I differentiate into macrophages. Then I infect it with a so-called conventional coronavirus—those that give you a cold. Then I treat with this drug, and I measure the RNA of the virus. What I found is that these drugs inhibit replication of the virus in the cells. Later, because I wanted to do some in vivo assays when I saw that the drugs definitely work in vitro, I switched to a mouse model. But with mice, I needed to use mouse viruses. I used the MHV—mouse hepatitis virus—which is a well-established model of coronavirus. People who want to study SARS in mice frequently use MHV as a surrogate because it belongs to the same coronavirus family as SARS. It is a kind of similar virus. The receptors are different, obviously, but I believe that what happens inside the cells should be pretty conserved. First, I tested the effects of these drugs in cell culture. Again, I found that some of these inhibitors are very effective in vitro. Then I went to in vivo studies and also showed that they are very effective against the MHV infection, preventing the replication of this virus in the mouse liver. We also had a contract with an external company to test in vivo efficiency against SARS-CoV-2. This molecule also showed some promising data. It didn't get to statistical significance, because the study was a little bit too small—the number of animals was too small—but we could already see a trend for efficacy against SARS-CoV-2, and the mice actually survived better than mice that were infected but not treated. Currently, I'm trying to understand the molecular mechanism and how the drugs work. We know that they work, but we don't know how. This is taking a long time and will take some time to figure out, but that's where I'm at currently.

Barr: Are you interested in seeing how this works against different types of coronaviruses—if it works better with some than others—and also against the different variants, because the variants of COVID are so widely different?

Shats: I must say I don't understand why Omicron is still BSL 3. We all see that it's going everywhere—everyone is infected, and it's not that bad. In my opinion, it shouldn't be BSL 3, and we should be allowed to work with it in the lab. But it is still BSL 3 and so I cannot answer your question because I cannot work with it in the lab. As I said, MHV is another coronavirus, and the drugs do work very efficiently against this coronavirus.

Barr: Can you speak a little bit about what your role has been in this initiative as well as expand upon the roles and contributions of others in this project?

Shats: I basically initiated the project. I do all the experiments in this project. Basically, I'm responsible for this project. But again, the crucial thing is collaboration with Shears group and UNC. For the drug development, they have developed a whole series of tens, if not hundreds, of these IP6K [inositol hexakisphosphate kinase] inhibitors. We are going back and forth. I'm screening different inhibitors for antiviral activity and looking for correlations between the inhibition of different enzymes and antiviral activity. Three labs are really crucial for this—our lab and Steve's lab and the UNC lab, who actually make the drugs. The names again are Steve Shears—and especially Huanchen Wang in his lab—and the UNC's Drug Development Center is led by Xiaodong Wang. Obviously, my PI is Xiaoling Li. We have other collaborations trying to understand the molecular mechanism. Obviously, any work at NIEHS cannot be done without the excellent cores that we have. I'm extensively using all the cores that we have at NIEHS. The downside of being in North Carolina is that I'm not at the big NIH in Bethesda, so I didn't get to utilize the opportunities that are there. For example, it would be nice to collaborate with or use the cores at NIAID [National Institute of Allergy and Infectious Diseases] that can do experiments with the real SARS-CoV-2 so I could answer the questions you asked about different variants. That is in future plans.

Barr: In addition to being a scientist, you're also a person who's been living through the pandemic this past two and a half years. What have been some opportunities and challenges for you as an individual?

Shats: Starting with opportunities, I actually think that learning how to do remote work is great and it will stay with us for the future. Sometimes you need to work on data analysis, and you don't really need to be in the lab to do that. If you can save the traffic and do the work at home, it's great. It's good for everyone—for my time, for saving the environment, and for saving gas. Those are opportunities. I take the opportunity to listen to talks. Instead of going to a conference, now a lot of conferences are remote. It's also great that all this infrastructure was developed in terms of challenges of doing work. The beginning stages of the pandemic were severely interrupted by this. Only one person could work at a time, so the productivity was obviously lower at that time, but then pretty quickly it went to almost normal, I would say. Currently, I don't think we have many problems from COVID. We know about relatives and people we know that are getting sick and some even die, unfortunately, so that's obviously a big challenge.

Barr: You probably weren't able to see your friends and family abroad for a long time.

Shats: I didn't visit my parents in Israel for three years. I want to do it now.

Barr: Well, thank you so much for agreeing to speak. This was really interesting, and I look forward to seeing where the research heads.

Shats: Thank you very much.