Dr. Irini Sereti
Behind the Mask
April 19, 2022

Barr: Good afternoon. Today is April 19, 2022. My name is Gabrielle Barr. I am the archivist at the Office of NIH History and Stetten Museum, and today I have the pleasure of speaking with Dr. Irini Sereti. Dr. Sereti is the Chief of the HIV Pathogenesis section at the National Institute of Allergy and Infectious Diseases [NIAID], and today she is going to be speaking about several of her COVID-19 related studies as well as some of her other COVID related experiences and activities. Thank you very much for being with me.

Sereti: Thank you so much for having me.

Barr: To begin with one of your first studies, can you please explain the premise of your COVID-19 associated lymphopenia pathogenesis study?

Sereti: Sure. This was a study that we put together early after lockdown in order to give us the opportunity to study patients who had COVID disease or had recovered from COVID disease so that we could conduct some laboratory experiments related to some of the first observations we had, which were the fact that people developed low lymphocyte counts during COVID infection, people developed some coagulation disorders, and also some inflammatory disorders, as everybody knows now about the inflammation that we see in the most serious cases of COVID. We wanted to really have the means to get some samples from people who had COVID, so we put together this protocol in collaboration with Georgetown University Hospital and also Washington Hospital Center so we could actually access some of the patients from those sites.

Barr: What was your role?

Sereti: My role was to put the protocol together and take it through the regulatory process, but also, as a clinician and scientist running a lab, I was able to see patients here at the Clinical Center, and also find collaborators to help us recruit study participants. At the same time, I also had to try set up the laboratory during lockdown times and find staff who were willing to help and work during those really difficult times at NIH, and also to decide what kind of experiments to do and how to work with the patient samples. We also had to get approval to bring COVID samples in the laboratory. There were a lot of logistical issues and obviously a lot of clinical issues. And certainly, taking care of the safety of the personnel was a big thing.

Barr: Can you talk more about some of those challenges and some of the other challenges that you faced especially in the beginning.

Sereti: Yes, absolutely. Everybody knows it was a challenging time. There were times when the Clinical Center felt like a ghost town. I think the number one priority was to make sure everybody was safe. As a clinician, I felt the need to participate in the clinical care of patients, so I actually volunteered, and I was part of the COVID Response Clinical Team at the Clinical Center. Then also, as a physician scientist, you feel the urge and the need to do something about it research-wise and so that led to the generation of a couple of different protocols that we worked with. It was challenging. While at the same time, everything outside of work was changing, schools closing, supermarkets being empty. I think everybody went through a lot of difficulties outside of work. To some extent, I feel that although it was challenging to try to juggle both work and then whatever was happening outside of work, at the same time, I feel that some of us were lucky because we had the opportunity to be very actively participating in doing something about it. This made it obviously, to some extent, more tiring but also psychologically, I think, it was helpful to feel like we were acting against this virus, and we were trying to help people who had the infection.

Barr: Can you talk about some of your initial findings from this study and some of the longer-term objectives of the study as well?

Sereti: Absolutely. Yes. Some of the initial findings of the study were very consistent with some of what other investigators have found, or what other papers have reported. We found that there was a profound inflammatory response in the patients who had COVID. I wanted to highlight that our study included only people who were willing to participate and were able to sign consent. People who were critically ill and were on a ventilator, for example, and could not consent for themselves were not participating. Our range was a few outpatients, but for the most part, it was people who ended up in the hospital but not requiring to be ventilated or be immediately transferred to the Intensive Care Unit.

Some of our first findings had to do with this inflammatory response that is seen in patients, especially when they end up being hospitalized. We also found, again, inspired by some of our previous studies in HIV [the virus that causes AIDS], for example, that there was activation of what is called the inflammasome, which is a mechanism that leads to inflammation in our immune system, and we found that key players for this inflammatory response were the monocytes, something that we have also found sometimes in some of our HIV patients. We found that there was inflammasome activation in the monocytes of the patients, and these seem to relate very closely with what is called oxidative stress, which is basically when cells can be deprived of enough oxygen, and they have these reactive oxygen species that can be very toxic. We found that there was what it is called lipid peroxidation, and a lot of these stress oxygen remnants were basically associated with the inflammatory response.

Similar studies are coming out now that actually corroborate these findings, and I think that it is an important observation because these reactive oxygen species can be higher in people with obesity or in

older adults, who we know, have more severe COVID. I think one other important observation that we found is that some of these observations kept true and held up even a couple of months after recovery from COVID. In the long term, we are very interested in seeing whether there is any association between this oxidative stress and inflammasome activation in cases of long COVID. That is one of our long-term goals – to try seeing whether there is any association of these observations with long COVID.

Barr: Can you talk a little bit about how some of this research – it has a lot of different implications, not just explaining the pathogenesis of COVID-19. Can you expound upon that?

Sereti: Yes. Ideally, when you do a study and you look at these observations, you want to see how it may translate into either prevention or therapies. We do think that although some of the initial studies looking at antioxidants or blocking the inflammasome have not been tremendously successful, I think COVID is a disease that is testing our patience because timing is so critical. Therefore, it is very important to design interventions that are coming at the right time. It is a very Goldilocks effect. You cannot be too early, you cannot be too late, and I think that was highlighted so nicely with the corticosteroids: that if you give them too early you may actually harm the patient, but if you give them at the right time, when there is higher oxygen requirement, you actually improve mortality. We do think that some interventions of anti-inflammatory drugs that target specifically inflammasome, or some interventions that are repleting glutathione or work as antioxidants, especially if they are given early in the disease, they may have a good effect as far as disease progression. It will be interesting to see now how some of these additional interventions may help in combination with the existing therapies that have been found to be already successful in COVID- 19.

Barr: Do you have any studies in the works that look at any of these things or any that go further from the initial studies that you and your team have conducted?

Sereti: Yes, we have a study trying to see if Interleukin-7 (IL-7) may help at the very early stages of COVID-19 by supporting the T-lymphocytes, the adaptive immune system, that I think has been a little less studied or less understood from both the vaccine protection and also during COVID disease. Some studies have suggested that having very strong T-cell responses, T-lymphocyte responses, early in the disease may actually prevent progression. We think that by using a cytokine that supports certain lymphocytes, we may prevent progression of the disease. That is one of the studies that we have available now. In collaboration with other groups, we will also try to look at the impact of oxidative stress and inflammasomes in long COVID which is the other thing we are planning on doing.

Barr: Oh, that will be very interesting. Another study that you have been a part of was looking at the hyper-inflammatory syndromes that have emerged after SARS-CoV-2 mRNA vaccination in some

individuals with underlying immune dysregulation. Can you speak a little bit about this protocol, and what types of symptoms some of these individuals develop, and how quickly after being vaccinated do these conditions set in a very small subset of people?

Sereti: This was actually not a specific protocol. This was patients who happened to be enrolled in other protocols at NIH, and there were also patients from outside the NIH, in different institutions. This was a case series, a series of clinical observations. We think that the mRNA vaccines are fantastic. They are very efficacious, and they are very, very safe, as multiple studies have shown. We just wanted to highlight that people who have some underlying immune conditions that may affect inflammation need to be more closely followed up, because with the vaccination, you do stimulate the immune system, and so, sometimes, it may have some unwanted effects just by increasing inflammation in general. We just wanted to highlight that people who have persistent side effects after vaccination, should be evaluated, particularly when they have an underlying immune condition. We just wanted to alert people to be aware of the situation. The problem, of course, is that with billions of people being vaccinated, it is very hard to have a denominator and know how much of that is true or unrelated. We try to focus on people who had these side effects happening within the first couple of months of vaccination, but again, chance is a big component, and it is impossible to decipher whether this would have happened regardless of vaccine or with another stimulus. The important thing to also keep in mind is that this kind of hyper-inflammatory syndrome can actually happen with COVID itself, and it is much more frequent compared to the very rare possibility, that it may happen after vaccination in these patients.

Barr: Very interesting. Have you been involved in any other COVID-19 related initiatives? You said that you helped out at the Clinical Center as a clinician caring for patients. I have seen that you have spoken about that in some of your research.

Sereti: Yes, actually, at NIAID, we are also doing another study, trying to look at responses to vaccines or immunogenicity, as we say in a more obscure term. We are doing a study through the Division of Clinical Research [DCR]. The study is in seven countries, not the United States. It is done in Mongolia, Indonesia, Mali, DRC [Democratic Republic of Congo], Guinea, and Liberia, and in Mexico. We are looking at the immune responses to locally available vaccines. People get vaccinated through the national vaccine rollout programs, and we are just getting a baseline sample and another one two months after the completion of vaccination, and then we follow them longitudinally to try to do comparisons across different vaccine platforms and see what are the predictors of immunogenicity, whether we can find any immune correlates of breakthrough infection that may happen during the study, and also to check durability of the immune response in a real-life scenario in many different countries. I am very much involved in that initiative.

Barr: That is really great. How do you feel that your educational and professional background prepared you for tackling COVID-19? You have worked many years on HIV and AIDS.

Sereti: Yes, it is interesting that you ask that. I felt to some extent that this was a little bit like HIV in the early 1980s, which I did not experience as much because I was too young. But I think as a physician scientist it was a tremendous experience because we were faced with an unknown – both from the clinical perspective and also from the research perspective. It definitely was an admirable example of how science has advanced, especially with the quick sequencing of the virus and the vaccine development. On the other hand, it was a humbling experience of how little we have progressed, where the only thing we could do to fight the virus initially was stay in our homes and also how long it took us to actually have effective therapeutics, although we were far more successful with vaccines. Again, as a physician scientist for me it was very important to see patients and get to know the disease from the clinical perspective because my whole career has been very much bedside to [lab] bench and back. That prepared me very well: from seeing the patients, trying to come up with similarities with other diseases we understood better and we studied better in the lab, and then trying to advance the science by understanding better from the research and the bench perspective of what is really transpiring. Some things like the lymphopenia, and the inflammation, the coagulation issues, were all very similar themes that we have seen and studied in the HIV, but I also think the initial fear, the stigma, the unknown, were very reminiscent of the very early stages of the HIV epidemic.

Barr: In addition to being a physician and a scientist you are also a person who has been living through this pandemic. Can you talk a little bit about some of the opportunities and challenges that have arisen for you due to COVID?

Sereti: Right. I did become very popular with some people. I have been giving a lot of advice to friends and family and school. It has been good to be able to support other people. Definitely it had been challenging to try to balance keeping family safe, preserve routines as much as possible, and at the same time being able to work and offer support, and do as much as I could to help with the COVID effort. I think it was challenging as for every other person. Trying to find toilet paper in the supermarket, or trying to deal with a teen at home, but she was wonderful actually and very supportive. At the same time, it was very fulfilling. As I said from the beginning, it actually helps to have a more active role as opposed to being in the dark and not being able to help.

Barr: Have you been able to continue your HIV research?

Sereti: Yes, perhaps not as much as we would have liked to, but our protocol for HIV patients is actually people with advanced disease who are pretty sick. I would say that the majority of them kept coming into the Clinical Center, and although we were not enrolling as many new patients, we were able to both keep supporting our HIV patients in the area but also continue, obviously at a much slower pace, some of our HIV research. It was a great time to study more, to write some papers, and do more analyses. We made a very good plan with my team; I have an amazing team both in the clinic and in the lab. We did not miss a beat. We were able to continue our meetings online, we set up Doodle schedules for people

rotating in the lab so that there was no overlap. I think that we made the best out of a very, very difficult and unpleasant situation. We handled it as best as we could.

Barr: That is great. Well, is there anything else that you would like to add about your research, your care with COVID, or your experiences in general?

Sereti: Overall we did a great job. I think that to some extend it brought us all together. I hope that some of the things that came through COVID may stay: some of the flexibility of the work schedule, some of the access online to meetings that are not always easy to get to in person. I definitely do miss, though, having happy hour with my team or getting all together for lunches and such. I feel that when a crisis like this resolves, or starts to resolve, what is very important is to have some reflection and see what was done well, what could be done better, what things that are new could stay, and what things can go away and return back to our normal. I think that there is always room for improvement, and there are definitely things that could be done better the next time around at all the levels, so I hope now we will regroup and reflect and try to make plans for the future.

Barr: Sounds wonderful. Well, thank you very much for all you do, and I wish you and your team continued success.

Sereti: Thank you so much.

Barr: Continued health, as well, with these new waves that keep coming.

Sereti: Of course. Same to you! Thank you so much.