Elizabeth Fischer
Behind the Mask
June 15, 2021

Barr: Good afternoon. Today is June 15, 2021. My name is Gabrielle Barr, and I'm the archivist with the Office of NIH History and Stetten Museum. Today I have the pleasure of speaking with Ms. Elizabeth Fischer. Ms. Fischer is the Chief of the Rocky Mountain Laboratories Microscopy Unit which is part of the National Institute of Allergy and Infectious Diseases (NIAID), and today she is going to speak about some of her COVID work – some of it is displayed behind her right now. We really are looking forward to hearing about your work and experiences. Thank you for being with me.

Fischer: Thank you.

Barr: To get started, will you please describe the core functions of your unit and the group that you serve with at NIH?

Fischer: Sure. I'm part of what's called the Research Technologies Branch. In the last year and a half, I've been actually the Interim Chief for all of our Technologies. The Technologies are support groups of various expertise that supports all the DIR [Division of Intramural Research] investigators, all intramural research program investigators, and it ranges from things like genomics to flow cytometry to light microscopy imaging to protein chemistry where we understand different interactions of things, and we have Visual Medical Arts, structural biology, and then my group, that I am the chief of directly, is the section on electron microscopy and light microscopy out here at Rocky Mountain Labs. We provide support looking at structures and trying to relate that to functional studies for different scientists across the institute, including our investigators back in the Bethesda area campuses as well as here in Montana.

Barr: Interesting. You mentioned a little bit, but can you talk more in detail about some of the technologies you use to capture information about deadly viruses?

Fischer: Sure. For the microscopy group itself, we really try to understand how a bacterial virus would attach to say a host cell or where it would reside in a vector such as a tick or a mosquito. How does it gain entry? What does it do once it's inside? How is it successfully replicating – how it's making more of itself in ways that take over the host cell or the cell machinery? Some things are very devastating to the cells. They kind of are self-annihilating. Other things want to grow and just stay quietly under the radar, so they don't necessarily make the host quite as ill but find a way to reside persistently as an infection. Our goal is to really study that mechanism of how things get in and what they do inside, because different organisms can do things in different ways. Then, it also extends into things called like cryo-electron microscopy (cryo-EM) where you can look at interactions very specifically of say a virus or a bacteria and things that might attach to it, like a good vaccine target. So what antibodies and where they attach so you understand what becomes a good target for vaccine development.

Barr: Do you find that certain technologies and approaches work better for some types of viruses in comparison to others?

Fischer: It all really comes down to what question you're trying to ask. Sometimes investigators say, “Oh you have this new microscope, and it's really the latest thing. We want my sample on there.” It's sort of not always answering the questions that are being asked. That really comes down to us having a variety

of tools that can actually be used to look at things in many different ways and that gives us insight and a more holistic approach – both for electron microscopy but also for light microscopy, because there you can look at living cells and what's happening in real time.

Barr: How do you go about capturing certain parts of the life cycle of a virus or a bacteria? Say you wanted to document it in its different forms – whether it's emerging, once it gets in the cell, or once it annihilates the cell.

Fischer: We work closely with our investigators to set up a time series, so they usually have a good idea. This is often set up as a controlled laboratory cultured cell line so we can infect and then look at different time points. Again, different viruses or bacteria can have different time points. Some will take maybe 24 hours before they reproduce themselves; others are very quick. We can look over a course of the initial entry and then stop that. We use fixatives to render things dead. Once they're fixed, we don't have to worry about them infecting us, and so we will stop those time points early on at zero minute when you first add it to a cell culture. Then maybe 5 minutes, 10 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 8, 12, 18 hours, 24, 48 – really to try to capture that full life cycle and see what's happening within the cell and what cellular changes happen during that time.

Barr: Do you get a lot of the basic information about the viruses' life cycle from the investigators, or are you all part of this experimental process of learning when the virus does certain things and at what point?

Fischer: Yes, to both. Sometimes things are new and different; we're not sure how things work. That's just more exploratory. Other times, it's a virus that maybe is similar to another virus that we've seen so we maybe have an idea of what host cell machinery could be involved and that's what we'll look for. We can also do refined techniques of things called immune labeling where we can go in and target the cells this virus is going in. It's moving through the cell making these changes. Let's identify what proteins are acting in a particular region and be able to identify more specific targets. Those are important for things when you start thinking about chemotherapeutics, ways to intervene and stop an infection from progressing too far just by stopping that host cell response.

Barr: Very interesting. Can you talk a little bit about the process of how you all go about doing this from speaking to the investigators to actually performing the imaging?

Fischer: Yes. We will discuss with an investigator what they're hoping for, what they want to see, what they're trying to discover, and then come up with which tools will be best utilized in our area for that and our expertise in the technology. We may again suggest different kinds of experiments and sometimes go back and say, "Well, it would be helpful to know something maybe more about proteins that are expressed in different parts," or things like that. It's coordinating that back and forth information then again trying to relate, "Here's the structures I'm seeing. How does that relate to some of your other studies and your other assays that may give you insight into, say, metabolism or regulation of certain genes." Things like that. It's a kind of an iterative process with our investigators.

Barr: That's very interesting. Do you all do the infecting yourself of the cell line, or is that done by others?

Fischer: Generally, that's done by the investigators. Especially when you're talking about biosafety level three or four agents that require a lot of extra personal protective equipment. People are trained to

wear the suits and wear all that gear. As I mentioned, they'll do the experiments; they'll fix the samples with chemicals that will deactivate them so they will no longer be infectious, but also ones that preserve the structure the best that we can. Once they're deactivated, they bring the samples to us, and then we finish the processing. Our art is really the chemistry of trying to preserve samples in a way so we haven't totally destroyed their structure. It'll be a variety of fixatives. Some will fix the protein; some will pick the lipids in the cell. We have to get the water out of the cell because electron microscopes don't usually find compatibility with electron beams, so we have to find a way to replace that water. If you think about a grape and if you suck out all the water, you're left with a raisin. We don't want our cells to look like raisins, and so our art is trying to figure out ways to preserve that structure again as best we can.

Barr: How long after a fixative is put into a cell that's been infected do you all need to go in and image it?

Fischer: The first fixative is just the first step. We go through many steps to preserve the different parts of the cell. The length of time it sits in that primary fixative depends really on if it's in a tissue or a cell, and it really depends on the organism, what virus or bacteria it could be, because some will be fixed and deactivated really quickly. Other ones can survive in fixative for a while. For instance, like the mycobacterium tuberculosis, the bacteria that causes TB (tuberculosis), that one is very impermeable to the fixative. If we want to kill that and make sure it's dead, it's got to sit for at least 24 hours in fixative and in a small pellet with a lot of fixative volume. It's very sample dependent how long it takes in that first step, but usually if it's just a virus on surface, a lot of them are deactivated in 15 minutes. Some of them require 24 hours if we want to make sure, especially if it's something that there's no treatment for. We want to make sure it's dead dead. That may sit for 24 hours or 48 hours before it's brought over to us, and then we'll process it and put it through more chemicals. On average, for the scanning electron microscope pictures, which are the ones that you see in the background of my virtual background, those usually will take one day to process to completion and then we can start imaging. Other samples can take two or three days, and for cryo-EM studies – that data collection can go on for a week.

Barr: Were you really worried – were you very safe in the beginning with COVID? Making it like a 48-hour period before you started imaging?

Fischer: Yeah. That was really determined by the investigators and the protocols. They treated it actually in the BSL-4 (biosafety level 4) lab, so everything was done very carefully. We have extra layers of containment and try and take care of ourselves, but I think the difference between doing things in a laboratory environment where you're used to working with dangerous pathogens, bacteria, and viruses – it's a very, again, controlled environment. You kind of know how to handle things, to protect yourself as well.

Barr: Yes. I think we're going to move on to COVID, which is the crux of this interview. When did you and your team first start producing images of SARS-CoV-2?

Fischer: We got our first samples from one of the first U.S. patients. It was provided by the CDC, and the laboratory here received it and started growing the virus up in the laboratory cells back in February of 2020. Our first images were produced about the middle of February last year.

Barr: Interesting. Around how many images have you taken of the virus so far, and are there aspects of the pathogen that you would still like to capture?

Fischer: That number is hard to know. There [are] thousands of images with lots of different samples for many different studies. We are still capturing things to, again, sort of tease out that life cycle inside and trying to understand. We can transfect cells, that is what we call it, but we can take proteins that are produced by the virus and start one protein at a time, inserting that into the cell without the rest of the virus and see what action that has on the cell. Really we're trying to tease out those changes in the cellular structure and what host cell machinery is involved with making these replication factories, or basically viral factories, inside the cell.

Barr: How detailed can your technology go? Can it go into looking at particular elements?

Fischer: Using cryo-EM, we're at the atomic level of what's called resolutions, our ability to see detail. That's where you're looking at specific amino acids – so that very basic component of a protein and how it may interact with another protein.

Barr: Wow. That's very impressive. Since you work with many, many investigators across NIAID, do you ever give them suggestions of angles that they could look at with SARS-CoV-2 or how they could image things?

Fischer: Yeah; we've gotten into some projects for 3D whole cell reconstruction. Kind of getting the more global landscape view of the cell, and what's happening inside. That's been exciting. We've looked at some vaccine candidates by cryo-EM and trying to understand why some may work better than others. Those are sort of ongoing studies at this point. So yeah, it's just breaking it down into those smaller interactions to tease apart the pieces of the puzzle.

Barr: What have been some of the challenges that you and your team have faced in trying to image SARS-CoV-2?

Fischer: I don't know that we have challenges on the imaging side. We get samples fairly regularly so that part is not a problem. I think at the beginning, like many places, learning how to step down your operations to try to be safe in the work environment was a bigger part of our operation that was more limiting with reduced staffing and having to work around each other. And of course, we were also learning how transmission worked with the virus. You know – can you get it from a doorknob? We can't have anybody here. And it was more that barrier of just trying to continue working but trying to do it in a safe manner as things were being sorted out.

Barr: Can you speak a little bit about your role in some of NIAID's COVID research studies? Some of them that I saw that your group was a part of was this hospitalization landscape of SARS-CoV-2, and you all looked at the respiratory disease in rhesus macaques inoculated with SARS-CoV-2. Another one you all did was looking at an asymptomatic cancer patient with SARS-CoV-2. Those are among the ones I know about. Can you speak little bit about what your roles were in those as well as some of the others that you've been a part of?

Fischer: Yeah. The phosphorylation paper was really a worldwide effort, and we were approached by Nevan Krogan from UCSF [University of California, San Francisco], and I think this is where one of those silver linings of a pandemic created this atmosphere that was very collaborative among many people and that includes scientists. Obviously, people wanted information as quickly as could become available. They saw some of our images, and they had some ideas about how the virus was spreading between cells from a lot of their other data, again, this is looking at proteins in particular as well as some light

microscopy, but they needed the EM level of detail to start understanding a little bit how that transmission worked. It was really a wonderful collaboration. Just really put people together and connected us from all over the world. It was a massive, massive project. Then the other ones you know, things like the macaque one, that's sort of the first basic model when you are studying a new virus: finding an animal model that will work. That study was – you find an animal model that will work in terms of it being somewhat relevant to the human condition because to study how an animal behaves may not mean the same thing for a human. To have a valid animal model was really important. That study was here with Emmie de Wit and Vincent Munster's group, and then that that rolled into a lot of vaccine studies for them, so that was very validating. Looking at that structure in the macaque lungs, seeing what impact that the virus was having, and showing that the virus was actually reproducing there was what that study was involved with. And then the other virus [study] – you have this patient with long-term inability to clear the virus that was a cancer patient, and ultimately, she did but much, much longer and later than most people. Of course, that inhibited her ability, I think, to have treatment which was not a good thing. I think in that particular case, they were just looking at, “Does it look the same? Does it look like it's doing the same thing in the cells? Is there something different about it?” It pretty much seemed the same, so it was more on the host side that the problem occurred as far as her inability to clear the virus versus the virus doing something different.

Barr: That's really interesting. What projects are you working on currently?

Fischer: Again, I can't speak to too many of them right now, but we're really diving into that host cell interaction – what's happening in the host cell – and really teasing apart step by step as things are happening in the cells.

Barr: I had a technical-ish question. Once you create these images, how do you go about storing them? I see they are colored, and obviously they probably are not colored when you all take them, so how do you all go about doing things like that? And disseminating them?

Fischer: Obviously something like this captured global media attention. Pictures were in high demand, and you know our group has imaged pictures of all the world's deadliest pathogens. We have Ebola and Lassa and HIV and MRSA and group A strep. Our pictures have been used worldwide; they're on the NIAID Flickr site. These in particular, we've never really seen such impact as far as numbers of people looking at them. Yes, you're right – we take pictures in black and white. We send them off to one of our other branch sections, which is our Visual Medical Arts, and really their big role is helping communicate science to the public as well as supporting scientific endeavors here and people understanding things. We started realizing how important this was to communicate on a global level things about the virus, and I think it makes things more tangible for people. I think people have this idea, “There's a pandemic, there's a virus, and what does that mean?” Just that fear of this unknown thing coming over the borders and infiltrating us, and I think this gives you that, and maybe provides some sense of, maybe not security, but being able to look and say, “Okay, this is a thing. It exists. We're breaking it down. We're figuring out how it operates. We're figuring out how we can prevent it or treat it.” It happened incredibly fast, so I think in this case it was a way to communicate with the public in ways that were really felt widespread, at least for us. I've had inquiries, I still get inquiries, from all over the world asking about our images and just a fascination with that world of microscopy. But again, I think it just gave people that tangible feeling of what this virus is.

Barr: How do they decide on the colors?

Fischer: You know it's really funny. Some people get upset about colors, and why is it red? Why is it green? It's funny. Our Visual Medical Arts department has four very talented Visual Medical Arts specialists, and they all have kind of different styles. That comes out in the colorizations as well. A lot of it is just sort of personal taste in how they colorize them. We like to make sure that the eye is drawn to the feature of interest. The one right behind me that has the turquoise – the turquoise is the virus itself, but you can see it's a little bit brighter. It's what your eye goes to naturally. In the background of that is the cell that it's exiting from.

Barr: I had another question. When imaging an interaction, can you speak a little bit about how you go about thinking of it in terms of how many pictures would you take of that interaction? Some of the pictures, they seem like you all zoom in; some are from further back, or they're from different angles. Can you talk a little bit about that thought process?

Fischer: You know, a lot of it depends on again what the purpose is. If it's for a media event, it's often nice to be zoomed in a little bit so people know what they're looking at – they're looking at the virus. If you want to have that global look of what's happening to that whole cell, then you zoom out and get kind of that image of a whole cell being destroyed maybe. I think for studies, again it really depends on what we're looking for. If it's a hard to find event, we may not get as many pictures as we'd like. We have to be careful about how we're thinking about that. If it's something that we see in every single cell, the same kind of thing, we know it's very representative so that interpretation is something we have to think very carefully about and be very objective about.

Barr: Do you have an art background in addition to a science background?

Fischer: I have a science background, but I've always liked art. I love the merge of art and science. There's a lot of symmetry and beauty between the two, and I love the artistic side of what we do – the photography of it. I love to scuba dive and take pictures underwater too, and it's sort of an extension of that, I think. I love being able to share this very small micro-world that I'm privileged to get to experience. It's really nice to be able to share that with people.

Barr: That is very interesting. How has COVID impacted you personally?

Fischer: Fortunately, my family took it very seriously. My extended family and friends, too. We're all not too many people removed from knowing people that were affected very poorly as far as bad outcomes for family members. I think for us, it was a lot of work at the beginning where people couldn't go to work. A lot of us had to work maybe overtime, and so some of the lab groups here worked seven days a week, long hours, every day for months. I think about the doctors and nurses and how much they have to put in and in not as a controlled an environment. I think, as everyone you know, you get tired of it, but it seems like it's an easy ask to wear a mask, right? It's really not that hard. I think the hard thing for me in the town we live in, sometimes it became very political, and that part was hard for me to want to accept. Because I think by nature you think, "Let's do what we can to protect each other," and it doesn't seem like that big of an ask.

Barr: Definitely. Is there something that you enjoy that has made the pandemic easier?

Fischer: You know, it brought some opportunities. As I mentioned, some of our branch is out in Bethesda, some of our branch is out here in Montana, and so it sometimes brought us together a little bit more closely. We had more regular meetings, we became creative in some of the smaller things we

can do. Some of us started a cooking class, so we still meet now once a month for the summer, just to get together, share a recipe, have a little girl time, and I think just having that opportunity to embrace the things that you can have control of and just become better at communicating with different people in different ways. That's been actually really fun.

Barr: That is very nice. Do they ship you the samples from Bethesda that they work on?

Fischer: Yep. We get samples shipped from Bethesda. Of course, a lot of the SARS-CoV-2 research at the beginning was done here at our level four lab facilities. A lot of them are just down the alley from where we are, but yes, we've received samples from Bethesda as well.

Barr: What is your favorite thing that you've made from your cooking class?

Fischer: We've had some good ones. It's kind of fun, because we consolidate and compress everything into one hour, so it's been pretty creative. We've had “bang bang” shrimp; that was pretty darn good as a pasta dish. We've had some good Indian food. We've done some Mexican food, carne asada, last week.

Barr: That sounds very, very fun! This is one of my last questions. You spoke about it a little bit, but how do you believe that these images of SARS-CoV-2 that you have taken and continued to take can have an impact on scientific research and the public's understanding of the virus?

Fischer: I think as things are more closely teased out, and we start understanding really those steps, hopefully there'll be new ways to interfere with the virus. Hopefully it leads to better vaccine design, although the vaccines that are out are really good, but it may set up for future viruses that emerge. Just trying to have that general understanding of what goes on. There's also the immune response side of things. When we provide pictures to look at to see how that parallels to different models that may be happening, and hopefully again people understanding that science is a process but there's a lot of tools that help us with that discovery and to be able to treat things. I mean, from a scientific perspective, it's just been incredibly fast to see how the response evolved, and how we're starting to feel like things are starting to get back where there's a light at the end of the tunnel and people are able to engage again. It's absolutely staggering to see how quickly all of that occurred in this country and worldwide.

Barr: Out of curiosity, what do the different variants look like in comparison to the wild virus?

Fischer: We have not done the cryo-EM studies on those yet. I think there's been some small mutations. You know, the coronavirus gets its name because it looks like a corona where you have the ball of virus, and you have all these little proteins that stick out all over the place [Fischer makes a fist with her left hand and uses her index finger on her right hand to demonstrate spikes]. Some of those mutations have occurred in some of those spike proteins that are part of that corona. If you're just looking at the pictures you see in the background, it would look exactly the same to you. You don't see that level of resolution. Where you might see some small changes is under the cryo-EM. We've not been given samples to do that study yet.

Barr: Is there anything else that you would like to add as a person who works at NIH but also as someone who's living through the pandemic?

Fischer: It's been a very interesting time in history to live through a pandemic. We all think about the 1918 flu and how that must have been, and here in real life we've learned it. I hope that this has taught us their resilience skills. I think a lot of people have shown a remarkable resilience and looking forward to getting past that. As far as the NIH goes, I am incredibly proud to work for an organization that had such major contributions to ending this pandemic.

Barr: Well, thank you very much for all that you do. I wish you and your team continued success as they tackle COVID and a lot of other diseases.

Fischer: Thank you so much Gabrielle.