Dr. Mitchell Ho and Jessica Hong

Behind the Mask

November 23, 2020

Barr: Good afternoon. Today is November 23rd, 2020, and I have the opportunity to speak to Dr. Mitchell Ho, who is the Senior Investigator and Deputy Chief in the Laboratory of Molecular Biology at the National Cancer Institute (NCI), and Jessica Hong, who is a Biologist in the Laboratory of Molecular Biology as well at the National Cancer Institute. Thank you very much for being with me today and talking a little bit about your COVID research.

Ho: Thank you for having us, Gabrielle. Thank you.

Barr: Absolutely. I'm very excited to hear more about it. In lay terms, can you describe the premise of your study that is looking at the development of neutralizing antibodies against SARS-CoV-2?

Ho: Thank you. First of all, I would like to thank you for this opportunity to share what we have been doing since March, and this is apparently a big pandemic, and we want to use the unique technology we have developed in the lab – that is nano(body) technology. Nanobody technology has been developed in the lab in the last several years, and we luckily get funding from both NIH [National Institutes of Health] and the NCI—innovation grants to develop these nanobody technologies. Those are the smallest antibodies in the animal kingdom. They keep the antigen-binding site, and they are very small so therefore they could actually bind to very unique antigens. Whether it's a cancer antigen or virus antigen, they just tend to bind to the proteins in a very unique way. In a way, they could penetrate into the so-called cavity on the proteins, and that cavity could be cell surface receptors, could be the viral envelope. Because of that kind of unique feature, we think the nanobody technology we developed in the lab might be very useful for this purpose.

We asked the NCI and NIH for approval to get our research started for this pandemic research, and luckily back in March, thanks to the NIH (COVID-19) Central (Task) Committee and NCI senior leadership, they allowed us to be able to work in the lab continuously since March to work on this important project. I'm going to talk a little bit later about how we come up with this technology and what this resource is about, but I want to just point out that nanobody technology is very unique. It has very different advantages that maybe other neutralizing antibodies may not have, and we think we want to contribute to this global research using our unique technologies and expertise. So hopefully we can work together with other groups to actually be able to overcome this big challenge.

Barr: You may speak about it later, but why is your technology so unique? Can you talk a little bit about what nanotechnology is like? It sounds like it's very specialized.

Ho: Okay. Yes, so in the animal kingdoms, there are the shark and the camels. They have evolved the same kind of so-called “heavy-chain antibodies”. So those naturally occurring antibodies [we are] talking about (such as) a shark, started on back to 400 to 300 million years ago, so that on the Earth is the age of the fish. And a shark is one of the fish, and we still have more than 400 species of shark on the Earth. Later on, scientists find that the camels also developed heavy-chain antibodies. At least as far as we know, a shark and a camel could develop unique heavy-chain antibodies—maybe other species as well, we probably just don't know.

Barr: Why those two animals and not other animals? What was it about them? I know this is maybe a little bit of a side question, but I thought that it was interesting like the shark and the camel – they didn't seem to go together.

Ho: Right yeah. I totally understand your question. I think from just the curiosity point of view those two species are quite extreme. One is actually living in the very dry desert area and the other, the shark, is in the deep oceans, and they travel a lot. The shark’s environment has a high salt concentration while camels are in a very dry environment, so they both live relatively in what we consider as harsh conditions, at least for humans. For some reason, they develop a heavy-chain antibody, and those antibodies develop quite a powerful immune system for them to protect them from any virus or pathogen disease, even for these precious species on the earth. They develop a unique immune system.

Most humans have a heavy and light chain antibody. Like we always talk about its IgG Y-shaped antibody, but some humans also develop a heavy-chain antibody disease, so it’s considered not normal. It's like a disease, and those humans also could have a heavy-chain antibody without the light chain. So I guess [if] the antibody (that) has a heavy and a light chain probably has some advantages whereas the heavy-chain antibody without the light chain can also have a different kind of advantages in the immune system. For us as immunologists and interested in protein engineering or antibody engineering, we are more interested in using the single domain, which is in the heavy-chain antibody, because they are very small. They don't need a light chain. So just to give you a concept: normal IgG [immunoglobulin G]s like 150 kilodalton in molecular weight and the single-domain antibody is only 11 or 13 kilodaltons. It's much, much smaller—like 10% of the normal IgG—and they are also stable. It's not just small. They have different conformations, and of course they are highly conserved between the single domain heavy chain to the IgG, but they do have a unique conformation. So we could see by the sequence of those nanobodies that they have a different location and the number of cysteines because the cysteines usually contribute to the conformation of a protein. And they have different numbers of cysteines and different locations of cysteines as compared to human and mouse antibodies. So they really have very unique conformations.

My laboratory got funding from NIH and NCI, the two innovation grants back several years ago, and tried to develop the nanobodies from sharks and camels. So by being supported by this kind of grants and the talented postdocs in the lab, we have actually built a larger shark and a camel nanobody library in phage. So it's a bacterial virus, so it's phage displayed nanobody libraries for sharks and camels. And those libraries are the unique resource and probably the largest nanobody libraries in the world. Nobody else has such a large camel or shark library like (the ones) we have.

Barr: That's incredible.

Ho: Yeah. So that's, you know, we developed this nanobody technology, the nanobody libraries originally for cancer therapy since we are in the cancer institute. But because of this pandemic, we thought maybe this could be very useful to treat viral infection. Because either viral protein or cancer protein, they all share similar kinds of conformations. They all have some kind of cavities and some grooves that may be accessible by nanobodies, but not by conventional antibodies. We think that might be a unique technology we can contribute to the field. Of course, there are many outstanding labs working on neutralizing antibodies using different technologies, but the technology we bring in is quite unique.

Barr: That's really interesting. What challenges have you all experienced to – oh, I'm going to go back, and I feel like I should ask this question. You did a pilot study before you were doing your current research. Can you speak a little bit about the findings of your pilot study and how that's informed your current study?

Ho: Right. Back to March, Jessica Hong was in the lab, so we were actually working together on a daily basis, we designed and planned this experiment using the nanobody libraries we have in the lab. Even before the pandemic, we made all of these libraries in the lab. And so we started to use these libraries to screen on the so-called spike protein of this virus, this SARS-CoV-2 virus, and that spike protein is considered to be the entry for the virus into the host human cells, and that would be the first door, or maybe you can say the gate, for the virus to get into the human cells. We ultimately think this might be the first candidate. Of course, there might be some other candidates that might be useful to target, but we started with that one using the nanobody libraries.

Jessica has screened six different camel libraries, some of the camels are very young, like several months, and some of the camels are pretty old, like 20 years old. There are three female and three male, and in the past, in our lab, we actually made six big libraries from these six camels. Jessica used those six libraries to screen on the spike protein from the SARS-CoV-2 in the lab. By doing the so-called (phage) screening, which is very tedious work, and to do the screening by many rounds and to be able to produce and express in E. coli and back to the screening again, this is called phage panning. We could do many rounds of panning on the host receptor binding domain, which is the exact binding site for the virus getting into the human cells, or we screen on the spike as a whole viral protein to do the panning. We do these different strategies to try to get the nanobodies.

In the end, what we find is some of the nanobodies could actually block the viral protein binding to their host human receptor called ACE2 so the nanobody we find from camels could block the interaction between the viral protein and the host protein, the host receptor. On top of that, we collaborated with other groups to try to set up so-called pseudovirus infections assay. Using that assay, we can show how our nanobody could block the viral infection into the human cells, in this case the human embryonic kidney cells overexpressing the human receptor that is ACE2. We can block the virus infection into the host cells by using nanobodies. This is what we found so far, and this is a pilot study.

We, at the moment, are looking for collaborators to do several things. Number one is to use the nanobody to treat different strains of live virus because the virus keeps mutating. We have to test the different live viruses, or maybe they are mutant viruses, to make sure which nanobody works best across different strains of a virus in the pandemic. We also want to look these nanobodies whether they can treat the viral disease in a mouse model, like an animal model. And we do have some collaborators actually in discussion with us and are trying to move this forward.

On the other hand, I believe to treat SARS-CoV-2 infection, we probably need to combine different mechanisms. To block the spike protein binding, it might be one of the major mechanisms. We might want to combine with the other small molecule or other drugs that target a different step of the viral infection. Then if we combine them, we probably have a better neutralization or an actually treatment to deliver to the patients.

Barr: What have been some of the challenges that you all have faced so far, and what has been something that maybe surprised you that you did not think about?

Ho: Well, I think that research is full of good surprises and bad surprises. A good surprise is when we screen the nanobody libraries on those SARS-CoV-2 viral protein at that time we did not have viral protein from SARS-CoV-1. So that is the virus that caused the disease in 2003, 17 years ago. We did not have that virus's protein. We only screened on SARS-CoV-2 viral protein, the spike protein, but surprisingly, Jessica found one of the many binders we have actually crossed with SARS-CoV-1 viral protein, which caused [SARS in] 2003. It's not even in our screening, but we find that that nanobody can cross that. So that is a very pleasant surprise. That means that such a nanobody could potentially be useful not only for the current COVID-19; it could potentially target the future SARS-like disease because they might share the similar kind of conformation recognized by this nanobody, or the epitope, the binding site of this nanobody. It might be useful maybe next time when we have SARS or different mutants of SARS virus we might potentially also use this nanobody because this nanobody can cross [these] different SARS-CoV viruses. That means it is more likely to cross other SARS-CoV viruses. That's actually something unexpected because we did not screen particularly for that purpose, but we found the scenario where it can cross both, and that is something that might be interesting.

The other thing is I think we learned when we're doing the research, as you've already known from last week to this week, Eli Lilly has gained approval from the FDA [for the] emergency use of their neutralizing antibody (that's a human antibody isolated from an infected patient) and that is a collaboration with the NIAID and NIH. The other company, Regeneron, they got another approval yesterday for their cocktail that is also neutralizing antibodies – isolated either from mice or from humans. Their mice are humanized mice, so they all make human antibodies. But in both approvals, if you look carefully, they are eligible for people with mild symptoms and not actually recommended for use for hospitalized patients, especially for those who need oxygen support which is the most severe symptom. That means that there is more we need to do if we want to use those antibodies for more severe diseases, more severe symptoms, and those patients who are hospitalized maybe in ICU or with oxygen support. We need a better treatment.

What we are learning, and it's a challenge not only for us but for everybody working on a neutralizing

antibody, I think we're facing the same challenge. The two approved ones aren't good enough for severe symptoms, not for ICU, not for hospitalized patients. Apparently, we need to probably find a good combination of multiple drugs or multiple mechanisms to be able to help those patients with more severe symptoms, and that is apparently something we need to think about and try to do. In fact, we already started the collaboration with other groups to try to screen whether our nanobody can combine with other small molecules with totally different mechanisms – some of them target the host cells, the host receptor for the virus; some of them target different viral proteins, not a spike – so we want to combine them [to see] whether we can overcome this barrier. Eventually, we could benefit the patient with the most severe symptoms rather than just mild symptoms, and I think that's something we are facing now.

Barr: And you were speaking a lot about your collaborations. Are they with academia? Are they with other government agencies, at NIH, or a combination?

Ho: At the moment we are collaborating with many labs, but they are all working at the NIH and some of them are working for the FDA [Food and Drug Administration]. They're all government (labs). In our cancer projects in my lab, we have years of experience collaborating with many companies to develop something for clinical trials. At this point, I think we only have contacted a few companies, very few companies, to discuss whether we can move them [the drugs] for commercialization and to further production. Actually, we started this kind of collaboration with the company already, but most of the collaboration I would say we have been doing so far is with NCI labs, NIH labs, and some of the FDA labs.

Barr: Okay. You spoke about your libraries, what are some of the other technologies and programs that you all are using in your research, and what metrics are you using to evaluate your research?

Ho: Yeah, that's really good. Thank you for asking that. When we are developing a novel cancer therapy in the lab, we not only just made those nanobody libraries, we also engineered a lot of different molecules to try to improve cancer therapy. We have experience and expertise is in protein engineering to design the different kinds of antibody therapeutics. And particularly, [we] have expertise in the design, for example, for the linker, the antibody format; what kind of structure might have a longer half-life or have a less immunogenicity. We could do protein engineering to deimmunize the camel nanobody to make it more like a human antibody. We could make it have a longer half-life, and we could make it maybe more stable. We know what the linker and what kind of a spacer we might need to make them fold better or express better in different organisms from E. coli to insect cells or mammalian cells. Over the years, we have accumulated a lot of expertise and the knowledge of protein engineering and antibody engineering. I think those protein and antibody engineering techniques could be very useful for this particular project.

Barr: That's really interesting. Can you all talk a little bit about your individual roles in this research. I know, Dr. Ho, you are the PI [Principal Investigator], but Jessica can you talk a little bit about what you've been doing in the project?

Hong: Sure. I just have been conducting the experiments under the guidance of Dr. Ho as well as maintaining the daily lab operations.

Barr: Can you talk a little bit about what that is like or some of the things that you do as part of that?

Hong: For experiments, we do phage panning, as Dr. Ho mentioned. We screened for nanobodies, and then I tested to validate those nanobodies to bind to the SARS-CoV-2 and from there, we set up different assays to further analyzed those nanobodies.

Barr: Okay. That's very good. That's quite a lot. Dr. Ho, what has been your role in this?

Ho: Yeah. Let me add a couple of sentences for Jessica's role because she is always very modest, so I want to just very enthusiastically put a couple of things on her role. I learned phage display back in 1997. That is like 23 years ago, and I also went to the University of Cambridge to learn phage display when I was a postdoc. I did phage display for many years, and I command myself to do the phage panning, the phage display in my own lab, even back to when I was a postdoc and a student. I could tell you many people learn how to do phage display or phage panning, but only very few people will actually be able to do it with a good success rate. Very, very few people. It's like you learn piano; some of them learn, but they will never be a good pianist. You just need the talent to do phage display and be good at it. So it's not easy; it's not the same thing as a routine assay – not anybody could do it. I could tell you for sure not everybody could do phage display. It's just like not everybody can play violin, or piano. It's just the way it is. We are very lucky to have Jessica, because she actually learned this from me, and she really had a good success rate and probably beat almost everybody as far as I know. That's why we want her to work in the lab during the shutdown – to do the screening. It's not about how many people work on the project; it's about needing the right person to do that.

Barr: Yeah, that's great. Did you do mostly that technique, Jessica, mostly in this project or have you been working on that technique for many years?

Hong: I've been working on that technique ever since I joined the lab. It's been something that I really enjoy doing and have lots of experience in.

Barr: That's great. Are there others?

Ho: Jessica also got some successful nanobodies to other cancer targets in the lab before this project.

Barr: I guess going back to another question, Dr. Ho, what has been your role in this project?

Ho: Right. For me, it was a very productive and rewarding role. I know during the pandemic, we were very stressed when we had to go home on March 17th. I remember NIH just said, "Shut down the lab," and we all go home. Then I came back from home, and my background is an antibody engineering background, a cancer biology background, and I'm typically a biochemist and molecular biologist. I started reading the papers from March to April. I read more than 100 papers in the field. So I told my postdocs and Jessica also, said, "I feel like I'm going back to school to study for a PhD thesis and prepare for a thesis proposal to a committee." That's exactly what happened. I studied all the virus papers, SARS-CoV-2 and SARS-CoV-1 back in 2003. I studied all of these and started to think about what we can do. I discussed with Jessica on a daily basis, and we discussed with each other on how we can handle and how we can conduct this experiment. We always have the problem whether this antigen or this panning does not work, or maybe this protein does not work, or this assay does not work, because we are not a virus lab – we are a cancer lab. We started to have a lot of trouble, but we actually worked together to solve this. I read a lot; we read every day, and in that time probably better than now. There're no meetings; there is nothing, you know. In the first two-three months, basically everybody was shocked. There are no meetings. There are no seminars. There is nothing. I actually focused only on the reading and planning and discussing with Jessica to try to do this project.

Then, back in May, I wrote a proposal and sent it to NIH. Eventually, we get an actually so-called ITAC [Intramural Targeted Anti-COVID-19 program] award funds. That is how you found us probably. We got the grant award from Michael Gottesman's office and that is the ITAC program. It's a very highly competitive program. I heard they had almost 300 applications and the only six in NCI got funded. I think we were very glad and pleased and grateful to the NIH to be able to fund us to do this work, but I spent a lot of time reading, planning, and discussing with Jessica to have the right proposal and submit in May.

Barr: That's great. What was some of the other research that you all are looking at that's informing and inspiring how you're doing your current study?

Ho: I think there are a lot of aspects, even though we are working on cancer, they are all biology essentially. We are always interested in molecular biology, biochemistry, cell biology, or cell surface receptors. In my own lab, we always study the ligand-receptor interaction like Wnt and glypicans. That's what we've studied for many years – how the ligand and the receptor interact. We're also interested in whether the antibody can block those signaling complex and disrupt the cancer signal. Those things are actually helpful for this project, because in the end, the virus getting to the host human cells is still similar like a ligand-receptor interaction. What we learned from our cancer biochemistry or biology about the ligand-receptor interaction and the signaling modulation actually can be useful here to understand how virus get into the human cells and be trafficking into the human cells, because we frequently look at the trafficking of the receptor in the tumor cells as well. Those things actually help us.

We are also interested in structural biology and bioinformatics and those things. It comes out to be very useful for this also, because we need to understand the structure of nanobodies and how they bind to the receptor. There are many things we learned from our cancer biology projects that are actually quite useful. Some of the even more directly useful, for example, in cancer we find the heparan sulfate

proteoglycan, we even make an antibody targeting heparan sulfate. Originally, we thought that it would be useful to treat liver cancer. We published several papers on that. Later on, even before everybody showed the data, I wrote the review paper saying, “Hey, maybe someone should look at the heparan sulfate, because in the previous virus paper I read for SARS-CoV-1 in 2003, people already show heparan sulfate may be another attachment on host cells for the virus.” Indeed, now there are several papers coming out showing heparan sulfate is an attachment site on the host cells for SARS-CoV-2. We do have an antibody for this heparan sulfate glycan, and we accumulate a lot of knowledge and tools in the lab about heparan sulfate, because that's also a cancer antigen. In that case, there are some common molecules between the cancer and the virus used to get into the cells. There may be some underlying biology there we just could not quite understand yet, because the cancer development is originally by the viral infection, like hepatitis vs. liver cancer and some others. It could be like HPV [Human papillomavirus in cervical cancer]. There is viral correlation relationship between viral infection and the cancer development.

Barr: That's very interesting. We don’t really think about that.

Ho: Yeah. So there's something there we haven't understood very well so far, but I think a lot of microbial infections cause chronic inflammation. That actually could potentially induce cancer development, and so the liver cancer, some of the liver cancer at least, may be initiated by hepatitis infection. Other hepatitis viruses also use the heparan sulfate as a co-receptor to get into the human cells. I guess some of the tumor antigens we studied on the cancer cell surface might be relevant to the viral infections and, of course, those kind of cause and consequence relationships need to study.

Barr: Well that's really fascinating. Is it just the two of you working on this project or are there others in your lab who are also working on it?

Ho: It's initiated by basically me and Jessica in the lab. Really only Jessica worked in the lab in the first three or four months, and after July, the people started to come back to the lab. At least the two other postdocs are also involved, and there are also some biostatistics, bioinformatics, and other collaborative groups gradually joined in the force, of course. I think the team is getting bigger and bigger now. In the beginning, for the discovery part, we have this unique technology called nanobody library panning and screening, and really, we only need Jessica to do. It would not help much even if we had another two or three people, because, as I said, not everybody could do it anyway.

Barr: Right. Jessica, can you talk a little bit about what it was like to be on campus and in the lab at a time when a lot of us were not on campus? And we're still not.

Hong: Well, it was definitely quite frightening at first to be on campus where everybody was very uncertain about what was going on, and as positive cases increased, the more anxiety increased as well. But over time, I think by taking all the precautions and communicating any doubts or fears, it slowly got better.

Barr: That's nice. What was it like Dr. Ho to direct, not from the lab, but from your home?

Ho: Well, it's very strange at times. Nobody had this experience before, and when I first had to come home from the lab, I felt quite a loss to be honest. I always want to almost live in the lab, and not to be able to be in the lab, it's really very brutal to me. I can't see my students; I can't see my staff. I can't actually look at my research lab. I enjoy talking with them every day. But I quickly adjusted myself. As I said, I want to be almost like a PhD student who tried to write a thesis proposal. I started reading a lot and knowing the detail about this virus and following the papers every day, because the papers come every day in just great detail to be able to understand it. In the end I think the science is actually still very attractive to me as a scientist because I don't think that we, at least in my career I have seen something like this before, thousands of hundreds of labs are immediately working on this project in different angles. Many labs like our lab never worked on a SARS-CoV-2 or those viruses. They are a totally different labs. They are like us, cancer labs, or there are other labs - they're chemistry labs or they're neuroscience labs. They are totally different labs, but they are suddenly all working on this important topic, and they bring all different expertises. When you look at this paper, I can tell you I worked on the antibody therapeutics and antibody development in cancer field for many years, and we know all the tools, but suddenly we see all these tools are being applied to this particular topic. It is amazing. Suddenly almost every company or academia lab or government or university or company, bring their unique technology like we do to this topic immediately. You see the papers come out with humanized mice and phage display like we are using nanobodies, we have unique very big nanobody libraries and nobody else has, but somebody else has a unique technology for other regard. They all bring to the table quickly, and that is amazing. You learn so much. After several months, we started a journal club. We actually read all these papers in the lab, and everybody is involved and discusses. I think, in the end, when we discuss science even in virtual meetings, they feel like we're home again.

Barr: That's nice. What have been some personal challenges and opportunities for both of you at this time? You spoke a little bit about some of the challenges, but what have been some of the opportunities? And your challenges don't necessarily have to be work-related as well.

Ho: I think Jessica could start first, but I remember that, Jessica already pointed out that they were very isolated, but I actually stopped by the lab sometime also during the shutdown; it was almost empty on the campus and even the facility was closed. Even the core facility also closed. So really amazing, the environment. I think that right at the first shutdown or about to shutdown in Building 37 where we are located, we even had a positive case. Then they need to come and sanitize the floor. It's actually on our floor. They have to sanitize our floor, and Jessica has to just, you know, working at that similar time, but fortunately nothing else happened. At that time, we were probably more nervous because we knew less than what we know now. Whenever that happened, even back to March, people got even more nervous. We had one case in the building, even on the same floor. Fortunately, everything is getting under control after the shutdown, and Jessica still comes to the lab every day. We really made sure Jessica is safe because nobody else comes to the lab anyway.

Hong: Dr. Ho mentioned, but a personal opportunity is being able to contribute to the search of a solution to this pandemic and being able to utilize the skills that I had acquired here at NIH under Dr. Ho's mentorship. I feel extremely honored to be part of this mission.

Barr: That's really great. What do you all think are the implications of your research sort of in real time? Like do you think it'll lead to some kind of therapeutic or vaccine or something along those lines? Or are you not quite sure, just a basic understanding of the virus? Or any combination?

Ho: Well, I think you touch all of them, obviously.

Barr: If you want to elaborate, either of you, that would be great.

Ho: I'd be happy to. You touched everything. The nanobodies are unique tools, and those tools provide a very unique resource for people to study this virus's biology and virus infection and understand how this virus works. They bind unique sites on the virus, and we are actually very transparent. We are open for everybody to use our nanobodies for whatever purpose. Whoever asks us, I think Jessica knows, from any lab, we basically just say yes as long as we can provide it. I think at the moment, we provide to everybody, but if we, at a certain point, can't provide to everybody, we will find a way to provide everybody, whether it is to provide protein or DNA or just sequences, so they can use it by themselves. Those things are clear – we want to contribute to global efforts to do this, and this is really for everybody. We are working and, as Jessica said, we're honored to do this. In the beginning, when NCI leadership asked me, "What are you going to do if you have this nanobody? What are you going to do next?" At that time, I'm a cancer lab, I don't know what I can do. I basically told my senior leadership in NCI that once we have the nanobody, we will make it free to everybody. Just let everybody use it. That's probably the best way at this point I can tell.

In terms of translational point, we are thinking about the nanobodies. They are small; they are soluble; they are stable. We are looking for a company to contact NCI to get this nanobody to make an inhaled drug. There's some evidence showing nanobodies are a very good candidate for inhaled drugs, because they're small and soluble. And they're cheaper – they can easily make a lot. For respiratory diseases like Covid-19, that might be a good candidate or strategy, so we are looking for companies to do that. We are also looking for other companies that have other expertise. For example, cell-based therapy, or bi-specific antibody, or a cocktail combined with other drugs. We are open for almost any kind of possibility to use it to treat patients. For diagnostic, nanobodies, because they're small, they might be very good agent for imaging the viral infection and such. For environmental, they can be used as an environmental sensor to detect the virus. Maybe on the surface in certain areas you may want us to have nanobodies. You don't need the -80, and they are very stable even in the room temperature or at 4^{o}C. They can be useful to even detect the virus as a detector or sensor. There are many things you can potentially use the nanobody as very unique tools. We're open for any kind of those collaborations Certainly, we are not a drug company, so we can't develop any drugs. We always, even for cancer therapy, we rely on companies to develop drugs, so we partner with them. We are more focused on basic research and discovery, and we rely on the company to collaborate with us to develop a drug. That

is what we did for cancer therapy, but I'm pretty sure that's what we are going to do for the SARS-CoV-2 as well.

Barr: That makes sense. You were talking a little bit about in addition to discovering cross neutralizing nanobodies to Covid-19 you're also hoping to detect cross neutralizing nanobodies to SARS and to MERS. Are there significant differences amongst these different types of coronaviruses that make this objective that you all have difficult, and have you all made more inroads with one type of coronavirus than another?

Ho: We are still studying it like any other scientists. I think, just as a biochemist and a molecular biologist, that family of the coronavirus, or at least the SARS-like virus, might share a similar conformation. They might share the conserved mechanism to get into the human cells; they might bind to a similar or even the same receptor on the human cells. It's reasonable to believe we can have a kind of antagonist nanobody that can block all of them, if they bind to the same receptor on the cells or they use the same molecule or same mechanism to get into the cells. Hypothetically, it should be possible, but in reality, we know we still don't know much about the difference between this SARS-CoV-1, SARS-CoV-2, and MERS – particularly MERS. They are quite different in terms of the virus infection rate and how they spread and even the structure, the high resolution structure. Whether their subtle differences make them unique or it may be more challenging to find such a so-called universal inhibitor; whether it's very impossible or it's possible – just very rare. We don't know. I think my understanding, as far as we know, based on the data we have so far and the data from other labs, it's not going to be easy to find such a uniform or universal inhibitor. It's not going to be easy. If it were easy, you would already see it. It's not going to be easy. The reason it's not easy, the main reason, first of all: the basic research. We don't know enough about the mechanism of all these viruses: how they get into the cell, the structural biology, and so on. On the other hand: technology. As I said, we have the very big nanobody library, but on the other hand most of the research field is focused on human antibodies. Those are actually usually from infected individuals, but most infected individuals apparently only have a neutralized antibody focused on one virus, not the other viruses as far as we know so far. We really need to look at all different technologies, even including nanobody technology and other technologies. We really need to have a more different approach to attack this problem.

Barr: That's interesting. This is one of the last questions. It's a fun question. What is a new skill that you all feel that you have acquired or one that you've improved upon since the pandemic began?

Ho: Well, that's a really interesting question. I think number one: I read a lot. I learned a lot from the literature. Just very intense learning of this field, and even though some of them may be just used for this virus treatment, we learn a lot even as a biochemist or molecular biologist by how they address this problem with all different approaches. It's quite entertaining to see how people use different technologies to address this problem, and I think overall we learned a lot by just reading and from our own research. For example, we always work on cancer, so we have never set up a pseudovirus virus infection assay in the lab. Now we have it, and Jessica is doing this almost every day now. That really broadened our research spectrum, and so, in a way, we potentially can do a more potent assay, not only for SARS-CoV-2, maybe in the future for a different virus. Just because of this COVID-19 project and it is

funded by the ITAC program in the next two or three years, we are probably capable of doing (research on) other virus infections using our nanobody technology. I mean from now on. Before (the pandemic), we probably couldn't do it. We are a typical biology lab and trying to develop cancer therapies. Now I think because of this Covid project supported by NIH and ITAC program up to the end of the 2022 I think, 2023 – actually three years. I think for this period to fully funded by NIH is almost like a separate project in addition to our cancer project. We are basically running two labs now. We have a separate project for Covid-19 funded by NIH, and that has really helped us to build up a previously nonexistent program using nanobody technology to actually study and develop therapy for viral infections.

Barr: That's interesting. Jessica, do you feel like you've gained any new skills? It can be fun too. I would say, for me, I've gotten very good at videoing because of the pandemic, and probably the skill I've lost is casual conversation. Do you have anything that you feel like you've gained and anything that maybe you feel like you've lost as a result of the pandemic?

Hong: I feel like my adaptability and resilience were improved considerably due to COVID-19. The ability to respond to the changes and being more self-aware and prioritizing mental wellness, which is something that I did not consider too much in the past but can definitely see the impact and importance of taking those actions to maintain that wellness when necessary.

Barr: That's really great. Is there anything that either of you would like to share in terms of you know being NIH scientists but also people living through the pandemic? Any last things you would want to bring up?

Ho: I think NIH has been a great place to do research at all the time. During the pandemic, I think NIH scientists, as Jessica said, overall, we are very resilient, and we really want to focus on the research. Whether they are reading or planning at home or they are actually doing experiments like Jessica and a front-line worker or nurse or doctor in the clinical hospital. We are all try our best to actually contribute to this global pandemic research and try to find a cure or diagnostic or other tools. The NIH is the place to do science and the research. I think, on the other hand, NIH is a very caring environment, so everybody tried to take care of everybody. During the pandemic, I think we tried to help our fellows and some of our fellows actually stayed in the United States, but they are quite far away from their families. Some of them are from China, some of my Fellows are from China, and they have no parents or no husband or wife here. They are totally by themselves and here doing the postdoc in my lab, and then we shut down, so they are really away from their parents and families. Unlike some of us, we actually have family here so those of the fellows they don't have family, I think they have a big challenge during the shutdown. We tried to have regular lab meetings, journal club, and project meetings – we still have during the shutdown. We tried to support each other, and to make sure they feel like it's still a home. For those international postdocs, I particularly feel that the lab is usually their home, and so when the lab is closed, they really feel very isolated. We try our best to help them.

GB: Well that's great. Definitely a lot of challenges. Thank you very much, both of you, for being with me, and I wish you all the best in your research and that you continue to stay very safe.

Ho: Thank you Gabrielle.