Dr. Joshua Tan
Behind the Mask
June 3, 2021

Barr: Good afternoon. Today is June 3, 2021. 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. Joshua Tan. Dr. Tan is the chief of the Antibody Biology Unit and is an Earl Stadtman Tenure Track Investigator at the National Institute of Allergy and Infectious Diseases (NIAID), and today he will be speaking on monoclonal antibodies. Thank you for being with me today.

Tan: Thank you.

Barr: My first question is in the era of COVID -19 there's been a lot of discussion about monoclonal antibodies. What exactly is the monoclonal antibody, and what does it allow scientists to do in terms of creating therapeutics and vaccines?

Tan: An antibody is a protein that's made by a cell called a B cell, and antibodies are produced by the immune system in order to attack foreign pathogens such as SARS- CoV-2. They can prevent the virus from invading target cells. If we look at the word monoclonal, a monoclonal antibody is simply an antibody that comes from a single, or a mono, B-cell clone, and what many scientists have done in the context of COVID-19 is to try to isolate potent monoclonal antibodies against SARS- CoV-2. Since these antibodies can prevent the virus from invading the host cells or destroy the virus, they can be used directly to prevent or treat COVID-19. What we do is, we identify very important monoclonal antibodies, and then once we know the DNA sequence of these antibodies, we can make them in the lab at large scale, and then we can test them for their potency against the virus.

Barr: How do you make them into something that you can test? You were saying you get the DNA sequence. How do you exactly do that?

Tan: We get a DNA sequence, and then we make plasmids, which contain the DNA sequence of the antibodies, and then at the lab level, we transfect cells—we put the plasmids into cells—and then the cells will start producing the antibody of interest.

Barr: This sounds like a very novice question, but what is a plasmid?

Tan: A plasmid is a circular piece of DNA that originally was from bacteria, but it's a very common tool used in the lab to make protein.

Barr: Okay, how long does that process take for you from getting the DNA sequence to making the monoclonal antibody?

Tan: About two months I would say.

Barr: Can you speak more a little bit about how you select the DNA sequences that you choose to make the monoclonal antibodies?

Tan: Yes, first we get B cells from individuals who have recovered from COVID-19 as they are the ones who are likely to have antibodies against the virus, and then we sort the B cells. We use a device, an optofluidic

device that draws cages of light around the B cells and pushes them into tiny chambers. We then test them for production of antibodies that can bind to the SARS-CoV-2 spike protein, which is the main protein on the surface of the virus. Once we find the single B cells that can do that, we then lyse the B cells, and then we get the RNA sequence from inside the B cells and convert them to DNA. We really select the DNA sequences based on the original B cells that can produce the antibodies we're looking for.

Barr: Interesting. What obstacles do you and your team encounter when you go through a process like this?

Tan: I think one of the main obstacles is that we were just setting the system up when the COVID-19 pandemic happened, and we had to learn a lot during the process. We needed to learn how to use the machines, and some of the equipment was new, and that definitely was a steep learning curve in the process.

Barr: Have you and your team made any interesting findings so far?

Tan: So far, we have identified several potent monoclonal antibodies from the individuals who have had COVID-19, and we found that they target different parts of the spike protein on the virus. Some of them are effective against the variants of interest that have emerged in the last months, including the variant that was identified in the UK I think now they're calling it the Alpha variant and the Beta variant that was identified in South Africa.

Barr: What makes certain antibodies more potent than others?

Tan: That's something that we're still investigating. For some of them, there is an obvious answer. The virus uses the spike protein to engage with a receptor called ACE2 on human cells. So an antibody that can bind to the right part of the spike protein and block that interaction would normally be able to neutralize the virus to some degree, but not all antibodies that are potent against the virus act that way so we're still exploring some of these other antibodies.

Barr: What are some of the ways these other antibodies have interacted?

Tan: They just bind to different parts of the spike protein not the part that directly interacts with the receptor. You know some of it could just be steric hindrance, maybe they just physically block the virus as a whole. They may cause a change in the shape of the protein, but we're not sure at this point of how those other antibodies that we have, work.

Barr: Did you notice any trends among the people you say have produced all these different kinds of antibodies?

Tan: In our study, we obtained them from a blood center. Unfortunately, there was very little clinical data from these individuals, so we were not able to say that our most potent antibodies came from someone who recovered quickly. We unfortunately don't know.

Barr: How do monoclonal antibodies work with COVID-19 patients in comparison with monoclonal antibodies with those with other diseases? I know that you and your team have worked a lot with other diseases, namely malaria.

Tan: Yes, before this, my work has mainly been on malaria as you said, and up to this point, the clinical trials with monoclonal antibodies against malaria have just started and so there's very little information out there on that.

Barr: That is so interesting because malaria has been around for so long in human history.

Tan: It is, but I think up until recently monoclonal antibodies have not been used widely in infectious disease. There have been a few examples before this, but COVID-19 is an example where they are actually being used more widely.

Barr: I did not realize that; that's really interesting. Can you speak in particular about the study that you were involved in that looked at whether ultra-potent and bispecific antibodies neutralize merging SARS-CoV-2 variants and what your role was? You mentioned it a little bit earlier.

Tan: I was the PI [Principal Investigator] of the study along with a collaborator another PI, Peter Crompton. We both started the study together, and so as I mentioned, we screened individuals who had recovered from COVID for monoclonal antibodies against SARS-CoV-2, and we found several antibodies. They were potent that targeted different sides of the protein. We decided to try to combine some of these potent antibodies in a bispecific antibody format. A bispecific antibody is basically two monoclonal antibodies put in one, combined into one molecule, so that's where the name bi-specific comes from. We found that several of these antibodies were effective against the variants of concern that I mentioned earlier, and they do target the two different sides of the spike protein.

Barr: Did one of them do better with one variant versus another?

Tan: I would say that. We've tested two with, you know published in that bioRxiv paper, about two variants so far. Most of our antibodies neutralize the UK [Alpha variant]; they worked quite well, and then the one that was identified in South Africa, the Beta variant, fewer of the antibodies worked against that one, but we did find some bispecific antibodies that work equally well against that compared to the original string of the virus.

Barr: Are you and your team planning on looking at other variants?

Tan: We're definitely interested in looking at the variant that emerged, that was found in India, the Delta variant, and I would say whenever a variant becomes a variant of concern, we'll be interested in looking more into that as well.

Barr: What particularly enthuses you about the bispecific antibodies as a countermeasure that seems really interesting?

Tan: As SARS-CoV-2 infects more people, more variants are going to emerge, and one of the dangers of these variants is that the virus mutates in parts of the spike protein that are targeted by monoclonal antibodies that are out there, including those in the clinic now. And if that happens, the monoclonal antibodies may no longer be able to bind target the spike protein, and they may no longer work against

that variant. So bispecific antibodies target two different parts of the spike protein so even if the variant has a mutation in one part that prevents binding there, the other part of the bispecific antibody should still be able to bind and target that variant. We hope that this the bispecific antibodies would be able to maintain their potency against a larger spread of variants.

Barr: Do you think that that approach will be used for other types of diseases?

Tan: HIV [which causes AIDS], for example, you know different groups have made bispecific or even trispecific [antibodies] so there's three combined into one antibody against HIV. So I would say that's definitely an area of research that I think more groups will look into.

Barr: What are some of your next steps in terms of your research?

Tan: I am definitely going to continue with malaria research now, focus more on that as well. In terms of COVID, we're trying to find antibodies that target a broader range of coronaviruses. There's always a danger of the next one emerging. We're trying to find antibodies that will hopefully be able to target even newer coronaviruses that emerge.

Barr: That's really nice. How do you feel that your work with the SARS- CoV-2 virus has allowed you to grow as a scientist?

Tan: I think that for me it's easy sometimes to be a bit disconnected from the outside—to feel that my work is, it's not real, it's disconnected from real life, that what we do day-to-day in the lab, doesn't really affect things outside. And you know working on SARS-CoV-2 and seeing the COVID -19 pandemic has been a reminder that the research in general matters a lot, and that it has the potential to help people, to save a lot of lives, and that's been a very strong reminder especially with the vaccines that have been out. I think that it's very helpful to have that always in front of me when doing the day-to-day research to know that's the goal.

Barr: That's really nice. Have you participated in any other COVID related research or initiatives both at NIH or outside of NIH?

Tan: We have sent our antibodies to a consortium called COVIC and this is a consortium that's run by La Jolla Institute in California and has several partners including the Gates Foundation and Welcome in the UK. The goal is to develop therapeutic agents against COVID-19 especially for use in low resource settings, and we've sent them our antibodies to be tested in this series of assays to see if they are suitable for use.

Barr: Interesting. We're going to switch from you as a clinician to you as a person who's also been living through the pandemic. What have been some personal challenges and opportunities that COVID has presented for you?

Tan: I think a major challenge has been the sense of separation from others during the pandemic. It's definitely been a challenge not being able to meet with friends in person or family in person for an extended period of time. In terms of opportunities it's been interesting actually working on COVID-19 because of the kind of relationship to everyday life that we can see and so I've probably talked more about my research to friends and families than I have for the rest of my life before this. So it's been nice to at least see that intersection with real life.

Barr: That is really nice. What was it like to manage a lab during the pandemic, and what did you do to ensure the safety of those who work with you while also seeing that they're getting the educational and professional experience that they need?

Tan: There were not many of us in the lab at that time so it was not too difficult to maintain distancing, and we were working on samples from COVID-19 patients, of course, but these samples should not have had the virus, and we confirmed this by doing a test of all the samples to be sure that by PCR there was no virus present. This was just an extra big step of precaution to make sure that we know we will not be exposed to the virus through these samples. I think it's been a learning experience for everyone in the lab including myself. Working on a new pathogen, a new disease, there was a lot to learn—how to use the tools that we had to switch to for COVID-19—and that's been definitely a rewarding experience for all of us.

Barr: That's great. How many people work in your lab with you?

Tan: At the moment there are three others in the lab.

Barr: Are they post-bacs or post-docs?

Tan: I have one post-doc at the moment, one lab manager and one biologist.

Barr: Okay that's really nice, so all different stages. What is one thing that you like doing that has made the pandemic more enjoyable?

Tan: I like to go for walks outside and that's helped a lot. I go to a nearby lake, just walking around, that helps to just get some fresh air and not be so cooped up inside all the time.

Barr: Yes, definitely. Well, is there anything else that you would like to add as an NIH scientist but also as somebody who's going through the pandemic?

Tan: I think that's it really from my end.

Barr: Thank you for all that you do, and I hope that your research continues to go well.

Tan: Thank you very much.