Dr. T. Jake Liang

Behind the Mask

December 3, 2020

Gabrielle Barr: Good afternoon, today is December 3rd, 2020, and I have the pleasure of speaking to Dr. Jake Liang. Dr. Liang is an NIH Distinguished Investigator and is the Chief of the Liver Diseases Branch at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Thank you very much for being with us today and talking about your COVID-19 research into developing new antiviral drugs for COVID-19, which is none too soon considering the escalating numbers of cases. Dr. Liang, can you speak a little bit about how you devised your study to find these new antiviral treatments? What are your steps in your methodology?

JL: Thank you for inviting me to speak on our research. I just want to echo your comment that it continues to amaze me how much this pandemic has caused global disruptions and impacted various aspects of our society. So certainly, whatever we can do to combat this virus has emerged as our research focus over the last year. Regarding our approach, I would say that my research program has been focusing quite a bit over the last 10-15 years on viral hepatitis which is a viral infection that causes chronic liver disease. One of the major themes of our program is to develop novel therapeutics against several forms of them [hepatitis]. That's really been our interests, expertise and research program for many years. When this pandemic hit we thought perhaps we can leverage our expertise to develop new treatments because we have the expertise and experience in these types of research, although we certainly don't know a lot about the coronaviruses. The hepatitis viruses are not coronaviruses, so certainly [it was] something we have to learn but that's not difficult. I think the concept of therapeutic development is the same whether you're studying hepatitis virus or coronavirus. So that's really sort of where we began: we are drawing from our expertise on viral hepatitis therapeutic development to anti-COVID-19 treatment, shortly after the beginning of the pandemic.

GB: There are different aspects of your study. Can you speak a little bit about the different phases of your study?

JL: Let me summarize what our approach has been. One is to develop an efficient platform so we can screen for antiviral therapy and that could take on several forms. Initially our idea was to develop what we call a non-infectious cell culture system to screen for compounds that we're interested in. It certainly has the advantage that we don't have to use a live infectious virus which requires certain high containment facilities which we did not have access to back then. The easiest thing would be to develop cell culture models that do not generate infectious virus, and we still can study specific stages of viral infections. That's been our approach.

There are various different assays that we have tried to develop to study different stages of the viral infections. So we had to develop tools initially, but it wasn't very difficult because the technology is available. We just had to generate the reagents. The viral sequence is known so we could easily produce that type of reagent. Once we developed the technology platform, we began to apply it to the compounds that we are interested in. The first thing we considered is that we have been developing drugs for viral hepatitis, particularly hepatitis C virus, and what we have found [is] that some of the drugs that we are developing are targeting a very conserved stage of the viral infection, which is how the virus gets into the cells. Knowing the mechanisms how virus gets in, the step involved in the fusion of the virus into the cells and release the virus genome is quite conserved. We figured out that our compounds against hepatitis C virus is targeting this conserved step of a viral infection.

Our hypothesis then was that maybe these compounds also act against other viruses. Once we developed these assays for SARS-2 virus, we began testing some of these compounds to see whether they are active against the SARS-2 virus in this non-infectious cell platform and, lo and behold, some of our compounds were indeed active against the SARS-2 virus.

Subsequently we tested these compounds in the live infectious virus in cell culture system and also showed efficacy. This is a very important transition step from a so-called non-infectious cell culture model to actually an infectious cell culture model because results from non-infectious cell models may not actually replicate what we see in live infectious cell systems. That is where we are at now.

We are also taking another approach for anti- SARS-2 drug development, that is to screen large diverse compound libraries, so we may identify other compounds against the SARS-2 virus, first by using some of these non-infectious cell culture models we have developed. We talked about the assay on the entry of the virus, but we also are developing other non-infectious culture models on the replication of the virus once it gets into the cells. These are additional tools we're developing but that will take time.

Once we have various screening tools, we'll have to screen hundreds, if not thousands, of compounds and then try to work through all the compounds to see whether they are real or not and whether they're good enough for further development. That's a much more long-term project and we are at the early phase. The compounds that we have right now in our hands, they're in late pre-clinical phase because we know a lot about these compounds targeting the fusion of the SARS virus. We think we are in a unique position to develop this further, perhaps into a late pre-clinical and hopefully clinical stage.

GB: How many compounds have you tested so far and how many do you hope to ultimately test?

JL: We first tested a limited set of compounds because those are the ones that we know are active against the hepatitis C virus, and so I would say maybe in the hundreds. We were able to quickly narrow down to three main classes of compounds. They are structurally different, but they all seem to be targeting the same mechanism of how viruses get into the cells. Within three major classes, we have many compounds that are related. Thus we have three classes that we are most interested in, and they are furthest along. One class of compounds actually came about from our effort in repurposing existing

drugs for COVID-19. From this effort, we discovered that an approved antihistamine drug for seasonal rhinitis is active against SARS-2.

Repurposing existing compounds for anti-SARS has been a major effort. Actually, as a matter of fact, most of the drugs being right now are drugs that have been developed for other reasons. The major advantage of repurposing is that we can easily test these drugs in human trials.

GB: Can you break it down a little bit for people, what the attributes and properties of the drugs are that you are testing in these three different classes? What you're looking for?

JL: Obviously, identifying the compounds being active against the virus is the first step. There are many other steps after the initial identification to turn them into drugs, which typically takes a long time and intense effort. Many people may not realize how much time drug development often takes and also what the potential stumbling blocks are once you're trying to move these so-called probes into a preclinical leads.

The important step is to test whether these compounds are active in an animal model in vivo. All our work so far are done in vitro, so the next step is trying to move into animal models, not only to determine whether these compounds are effective in a SARS-CoV-2 animal model but also to assess whether it has certain a pharmacological features that make them attractive as a drug. We need to figure out whether it can be given orally, for instance, whether it will stay around for a while, and how much and how often do we have to give the drug. All these things are very important in terms of developing a potential clinical drug. That's the stage we are in now with many of these compounds. All these steps will be necessary before we proceed onto the actual human studies.

GB: How extensive are your pre-clinical trials and what happens after you decide that certain candidates can be moved on for further screening?

JL: There are many different steps that typically are necessary along the therapeutic developmental process. We need to test whether the drug is potentially be toxic. This is a very important point. We have to test these compounds exhaustively and to make sure that we don't see any potential signal of toxicity that may be problematic in humans.

We also have to make sure that we understand how the compound is metabolized by the human cells, by the human body, and to determine how long it will stay in the human body. We need to know whether it is stable for an extended period of time in humans, which is a desirable property, or it gets degraded and metabolized quickly so the effect is short-lasting and would have to be given at a much higher dose or greater frequency. These questions are the things that we are working on. Much of the work has already been done previously when we were developing them into drugs against hepatitis C virus. right now, we are working on whether these compounds can indeed be a worthwhile lead to develop into a clinical trial against COVID-19.

GB: Can you talk a little bit about what metrics you use to assess your work? What percent of targeting SARS-Cov-2 with these drugs do you consider to be promising?

JL: I would say the metrics for our cell culture studies and in vitro model have been pretty well defined in the literature. We need to know that the compound is potent—capable of suppressing more than 90 percent of the infections—and it doesn't cause cell death. And the compound should have certain attractive properties for further drug development. Now obviously for us, we want to see whether the compounds that we're testing in the animal models have any effect on suppressing the SARS-CoV-2 infections in these animal models by measuring the viral levels, by reviewing the pathologies, and by assessing the severity of the disease in the infected animals. We would want to see whether there's a reduction in the death of these animals when they are challenged with the COVID-19 virus. These are the metrics to determine whether a drug is active against COVID-19 virus.

GB: Have you experienced any challenges to date and also have you had any surprises?

JL: I guess the challenge is always finding collaborations —I mean, none of these can move forward without them. My lab doesn't really have all the expertise to conduct the type of studies we want to do, so we have to find collaborators either within or without NIH to help us with reagents and technology. I would say that this has been a challenge but not insurmountable. We were able to identify appropriate collaborators and people who can provide us with reagents and help us on various experiments. Establishing a mutually beneficial and collaborative relation is always a challenge but in a special environment like NIH, such a challenge is not difficult to overcome.

Any surprise findings? I would say that's part of the science. I don't know whether you can call anything surprising because science is always surprising. You can come up with some kind of a hypothesis, but more often than not, they [results] are not what you expect. So, I would say, “Yes, they are many surprises”. We sometimes thought the experiments would go certain way but got the opposite results—and then we had to figure out why— that's always just part of the doing science. It's not unusual for people to be surprised by the results when they are doing science. I would think that's good. I mean, that's how we learn and move science.

GB: You readjusted since March based on, being a little bit based on, what you've been finding and your experience.

JL: Right, doing science is always evidence-based, so you have to adjust your experimental approaches based on evidence and then move forward. Science never works in a straight path – that is what keeps it interesting, I guess. Absolutely, we all have to adjust to the COVID-19.

GB: What types of tools, programs, and technologies are you using to conduct your research?

JL: We use a lot of standard molecular, virologic and cell biology techniques as well as animal models. Many of these things have been developed previously, so we just really have to learn and apply appropriate tools and technology for our research. It often takes time to read and gather what's in the literature, what reagents and tools are in the public domain. Sometimes these reagents are available in the public domain and sometimes they are not as easy to acquire them for whatever reason. You just have to work on and take advantage of your connections and network of colleagues. I would say it's kind of like a jigsaw puzzle. You really have to get the right pieces together to make your experiment work and but it doesn't really take a genius to put a jigsaw puzzle together. Sometimes you just have to take your time for trial and error, so I would say that there has not been any major stumbling block in terms of gathering appropriate tools, technologies, and support for our project.

GB: Can you talk a little bit about your collaborations with those at NIH and outside of NIH with this research?

JL: This project, as I mentioned, started from our work on hepatitis C virus in close collaboration with NCATS, the National Center for Advancing Translational Sciences. They've been our main collaborators for many years for our research on viral hepatitis. We continue to work with them closely on developing antivirals against SARS-CoV-2.

Outside NIH, I've worked with certain people I've known for many years. Mu colleagues at Washington University in Saint Louis have various different expertise [and] technologies that complement what we do. Specifically, in the beginning we didn't have access to live viral assay. Our collaborators at Washington University have access to live viral assay, which was absolutely essential in moving the project forward.

We also have been collaborating with some folks in Rockefeller University and UNC [University of North Carolina] as they have developed critical reagents for the SARS-2 virus research. Our project certainly would not have been successful without close collaborations.

Are you still there Gabrielle? Okay, all right. Just kind of disconnected a little bit. Okay can you hear me?

GB: Yes, I can hear you okay. What are the positions of those in the team that you are leading?

JL: You mean all collaborators or people?

GB: No, intramurally the team you're leading.

JL: In my group. I would say it's a mix of staff scientists, research fellows, and post-bac students. It's a team of people with different levels of expertise, different experience, and it's not a huge team. I would say about five or six people. The great thing about NIH is that you can really change your research direction very quickly. I pulled these people who were working on other research projects into this COVID-19 research as soon as we decided, I guess, I decided, that this project is something that we should pursue because of our previous experience and expertise. We would able to do this pretty quickly, to assemble a team of people with appropriate expertise to support this research program.

GB: What's it been like to lead people during the pandemic when you know the circumstances are a little bit different than normal?

JL: It relies a lot on getting people together virtually, via either Zoom meetings or whatever platform people use to communicate with each other, which is quite different from what we always used to do. You don't just go over and talk to people. In the beginning people were not used to communicate this way but once people got used to it, it works out okay. But It does require a lot more conscious effort to keep it together. For now I would say is working fine.

GB: That's really good. Have you mostly been on campus, at home, or a combination?

JL: Initially I've been mostly home. When the stay-home order started in March of this year, people are allowed to come on campus for COVID-19 related research. The people on my team have been going into work, but I have not. I can direct them remotely so I don't need to go in. Now I've been going a little more often because NIH opened up more returning to workspaces. I would say I work about three days or so at home, two days or so at work. Even on those two days I don't really put in the full eight hours in the office. If I don't need to stay there, I just come home and work there.

GB: Is your lab continuing to do your hepatitis research and, if so, how are you managing doing both?

JL: We do, although we did have to take a pause during the initial phase of stay-at-home. But I would say over the last several months or so that people who work on the hepatitis virus projects have returned to work and resumed some of the projects, although it's not ideal because most of them are only able to work part-time. I would say things are picking up but it's not as much I'd like. We are working on some potentially exciting findings in the our hepatitis research.

GB: I guess now we're gonna shift more into your personal experience. So, what have been some personal challenges you've faced due to the pandemic and also what have been some highlights that have happened during the pandemic for you?

JL: I would say the pandemic really changed this whole staying home situation. Your sense of time is altered. When we go to work, we work, and when we come home, we try not to bring much work home, although occasionally you have to. Now everything seems to blend together. When you're home, you're supposed to be working. That's sort of the challenge that we have to face, but you get used to it. The silver lining is that you can take a break by not having to leave your office. It's quite a different style. I'm really not used to teleworking. I understand some people have been doing it full-time in other capacities even before the pandemic, so this took me a while to get used to.

Also, because of this stay-at-home situation, I'm able to spend time on what I'm really interested in doing, especially learning about SARS-CoV-2 which I did not know much about before the pandemic. This situation really gave me time to learn about it, to read about it, to really try to understand what we know about the virus. I think if I didn't have the time from this situation, it would have been hard to move the project forward as much as I would like. Having more time to really learn about something is very important, so the stay at home situation was a silver lining.

GB: Where do you go to learn about it? Obviously, you probably are on multiple listservs, but what are some other ways?

JL: The internet. You go on journal sites, set up alerts, and be ready to leverage the new info when the alert pops up. A lot of scientific journals now do a pretty good job in trying to put COVID-19 related papers and new info [out there]. Sometimes you get a one sentence blurb about some of the new findings. I get that all the time. Also, I would try to sign up for some of these virtual meetings, conferences on COVID-19. NIH has some of these programs as well asd other sites. Also, because I'm home, I often have the news channel on. Actually, CNN does a pretty good job on updating a lot of science and medicine of COVID-19. Sometimes you hear about it through them first. You also read about it in a newspaper as well. So, it's really multimedia. You learn about various media platforms and realize which one is actually better. When you stay home, you are there, so you pick up a lot of info that would have been difficult to do if we have to go to work. I would say that's how I have really been learning and picking up a lot of valuable information over the last year.

GB: Do you dedicate a certain amount of time of your day to learning about SARS-CoV-2?

JL: I would say there's no specific designated time to do that. What I would often try to do is when I have time, when I have a break, or when I don't have other things to do, I would review these info. But if I don't have time, I would flag it so I would come back and look at them later. For meetings I would sign

up and set aside that block of time wherever the meetings or symposia are. If there are preset programs, I would set aside time. If notI would try to fit in whenever I can. I would take the time to search the literature for any specific info.

GB: When you have stumbling blocks, are there other places where you've turned for inspiration for your research?

JL: I would say a combination of things I would do. I would reach out to people I know, who may be able to help me and give the answer. Networking is also a useful resource. I've been taking advantage of all these venues.

GB: That's really great. It's very interesting. What are just some ways that you have dealt with the pandemic? The pandemic has brought about a lot of different emotions and have you any new hobbies? Anything like that? Any traditions that have come up? Any hobbies that you already have?

JL: I would say what I kind of miss, I think I might have alluded to, those in-person contacts with my colleagues, and other people. The virtual platform is okay but it's not as good as I like. I think that's something I miss. You do what you can obviously, but I think that's something I really miss. Sometimes the whole virtual platform does miss something. I certainly would say that's something I have to grapple with. It's not just people I work with at NIH but also my friends, my family, and other people I socialize with.

Regarding hobbies, I would say all sorts of outdoor activities, which are obviously much safer than doing indoor activities. Especially over the summer, I have been picking up various different hobbies, such as riding bikes and kayaking. I personally do play a lot of tennis so I would take advantage of it in outdoor courts. Unfortunately, now the cold weather is making it harder to do outdoor activities, but you do what you can.

GB: This is a fun question. You've already somewhat answered it. What is something you have found that you can live without during the pandemic and something you've discovered you really need more than you thought? I would say for me I can live without furniture. I have learned that.

JL: You still have furniture on your background.

GB: I found out I really need to be with other people far more than I ever thought that I needed to be with people.

JL: I do agree with you on this. I really miss personal interaction. I mean it's fortunate for me that my wife and I are close. We kind of have each other. I think that makes it much easier than if you're by yourself. I certainly empathize with all the people who live by themselves in the pandemic that makes it very hard. Some of my children are working now, and they are single so they're kind of on their own, so I feel for them.

I would say something that I can live without, probably traveling. I love traveling. My wife and I would travel quite a bit before this. It's always been a part of our life. So now we really haven't been traveling for almost a year, so we seem to be okay with it. We do miss it but instead we realize that better be safe than sorry. I know a lot of people still travel quite a bit, but we really have not, which is fine. We can do it later once things settle down.

GB: Is there anything else you would want to share as an NIH scientist but also as a person living through the pandemic?

JL: I would say that the important thing during any trying times, not just the pandemic, is to find a purpose to keep you going. I think for me what really sustained me was that I felt that my purpose is to make a difference in the pandemic by working on the type of research I do. So just to find a purpose and then pursue it in whatever way works for you. Having a purpose is what make our time easier to pass as well as to enjoy. Obviously trying to remain in contact with friends and colleagues, loved ones, as much as you can. That's very important to do, to maintain that semblance of human contact.

GB: Well, thank you so much for your help and for your words and I wish you the best in your research and hope that you continue to stay safe.

JL: Yes, thank you very much for interviewing me.