Dr. John Schneekloth Oral History

Behind the Mask

December 9, 2020

GB: Good morning. Today is December 9, 2020, and I [Gabrielle Barr] have the pleasure of speaking to Dr. John Schneekloth. Dr. Schneekloth is the senior investigator at the Chemical Biology Laboratory and the head of the Chemical Genetics Section at the National Cancer Institute (NCI) and today he will be talking about his research at targeting functional RNA elements in the Sars-CoV, genome which should be very interesting. So, thank you very much for being with us and talking to me about your research.

JS: Thank you for inviting me.

GB: To get started, what do you think the flaws are in inhibiting viral products and the inhibiting viral proteins approach for COVID-19? Is there something inherent about the virus that makes this traditional approach more difficult?

JS: Well, I think other people are trying to inhibit proteins that the virus produces, and I think that's a great approach. Our approach is just as you mentioned, a little different which is to target the RNA of the virus which is how the virus stores its genetic material. This is a virus that exists that has its genome in RNA, unlike humans in whom we store our genomes as DNA, and so we're going directly after sort of the source which is how that virus exists in isolation.

GB: So, what is unique about your method of developing small molecule inhibitors that target viral RNAs?

JS: Most approaches to make drugs go after proteins and this is true not just for viruses but for all sorts of cancers as well. I work at the National Cancer Institute and that's our primary background. My lab's interest in general has been to think about RNA as a drug target, which is fundamentally different than most approaches and what it does is, it allows us sort of a new tool in the toolbox and to think about how to develop medicines. As you know and as we've all seen, it's been really hard to identify medicines that are effective against the corona, the Sars-CoV-2 coronavirus, but also against cancers, too. Our approach is a basic science one which is to strike out in new directions and to try to identify new approaches for developing potential medicines.

GB: Yeah, that's really great. Can you talk a little bit about how you're going about conducting your research?

JS: We look in the lab. We use a high-throughput screening approach which means we take an RNA that we're interested in, and in this case, we're talking about coronavirus RNA but we do it with cancer associated RNAs as well. We look at tens of thousands of different molecules that might bind to that RNA and try to perturb it and try to try to alter its function. We use what's called a small molecule microarray approach where we print molecules on glass surfaces and then try to see which RNAs will stick to the location on the surface where the different molecules are printed. What this does is it allows us to really quickly look at many thousands and tens of thousands of molecules to try to identify candidates to study further.

GB: So why are small molecules particularly good for targeting functional elements of Sars-CoV-2? You had said that you're particularly looking at the frame shifting element and the stem loop two motif. If you could describe maybe more what those elements are and then also why the small molecules are so good about that.

JS: I'll tell you first about small molecules in general. Small molecules make great drugs. A small molecule means a compound that's relatively little in comparison to say a protein. It's very small so these are molecules that have just a relatively low number of atoms.

GB: Right, they're not that big.

JS: You know examples of small molecules that most people might be familiar with would be, you know, aspirin or Tylenol. The advantage that small molecules have are they're often orally available: you can actually eat them although you can also inject them as well. It turns out that about 80 percent of all drugs are small molecules and so they have properties that make them good for being drugs in general. But historically it's been very hard to identify small molecules that bind to things like RNA and DNA in a selective way. Our approach has been to try and find small molecules that target RNA and ask why we chose these specific elements, these specific RNAs in the coronavirus. It turns out that because the coronavirus has a pretty small genome, it's not that many nucleotides long. What it does is it includes functional elements in the genome although most people think of RNA as a message for protein. But in the coronavirus, and in human RNAs as well, there are RNAs that do different sorts of things that have functions and so our goal here has been to target those functions, like the frame shifting element which is a piece of RNA that tells the virus which of two different proteins to make. By targeting that and controlling it, we can alter the function of the virus and hopefully develop molecules that have antiviral activity.

GB: Are there other elements that you will be looking at in the coming months?

JS: In fact there are lots of different elements and one of the exciting things about working on something that's new is that you get to explore all sorts of different new things and so as new elements appear, we're going to try to target them as well, and I think one of the challenges here is that people don't know which element is most important to target with the molecule. What makes a good target we don't know the answer to that yet, and so one of the advantages of our approach is that it lets us look at lots of different things quickly to hopefully try and answer that question. We're continuing to work on that and trying to identify with collaborators all over the world what to do next and what's the most important thing.

GB: Have you experienced any challenges to date and also anything that has surprised you yet with your research?

JS: It's still pretty early. We have actually identified some molecules that seem to have some activity. That's really exciting and encouraging, but I would say there are always challenges. Right, it's really hard to discover new things and to learn about complicated systems like viruses, especially since I'm not a virologist. So, we rely heavily on collaborating with people who are, and so that's both exciting and challenging.

GB: But we know it's been a challenge with the pandemic to just get into the lab in general.

JS: Because we're working on the coronavirus, we can get in. That's been viewed as important by everyone, but I think it's difficult on the scientists who are doing the research because we're all very stressed about the situation. So that's been a challenge and so you know this is not business as usual. Everything is different now except for what it's been saying and so that's been a challenge, too, on top of how difficult it normally is to develop new molecules that do different things.

GB: Can you speak a little bit about where you have drawn inspiration from, as well as who you are collaborating with, both within NIH and outside of NIH?

JS: We draw inspiration from a lot of different people. I was trained by a really creative chemical biologist and so I draw a lot of my inspiration from him, and I'm also really inspired by the people who work in the lab, who have been really amazingly resilient during this whole pandemic which has been, of course, challenging for everyone. We collaborate with, as I mentioned, a lot of different people. Our collaborators on this project include Stuart Le Grice who's here at the NCI. We also work with Adrian R. Ferré-D'Amaré who is at NHLBI. We work with Jon Dinman, who's at the University of Maryland in College Park, and we also work with Danny Incarnato who's a professor at the University of Groningen in the Netherlands. It's been really—and a lot of this has evolved pretty quickly as the projects have

evolved—it's been really exciting to just interact with people of different backgrounds to try to kind of come together to solve a complicated problem or at least make progress towards solving it.

GB: So, what has been your role in this project?

JS: It's a collaborative project so there are a lot of different investigators and groups who are working on it. As I mentioned, our group is chemists by training. Most of the people in the lab identify and make new molecules that have these interesting properties and we have interacted with people like structural biologists and virologists who can help us understand really what the molecules are doing. It really requires this sort of interdisciplinary approach of people with really different backgrounds who can bring different perspectives to make progress.

GB: So, what was it like? You do have a background working with small molecules; from that to COVID-19 what have been the differences? Has there been a learning curve in switching diseases?

JS: There's definitely a learning curve and I think everyone will tell you that. This is a virus that was only discovered last year and so there's absolutely a learning curve. We're fortunate in that the primary interest of my lab is to study molecules that influence cancer, but we have worked on other viruses in the past and so that was a benefit. We've published on molecules that interact with part of the HIV genome and we've also worked on Zika before, too, and so we were fortunate to have thought about viral RNAs before. Although I'm not a virologist, that was a real benefit. There are lots of reasons why we've also worked on cancer viruses as well as on KSHV, Kaposi's sarcoma herpesvirus, so you know we have thought about viruses in the past and so that was a real benefit. Still anytime you work on a new system there's always a big learning curve and the trick has been how is this virus different from other ones and what can we do here that we couldn't do before or vice versa?

GB: So, can you talk a little bit about what you hope that your study will accomplish?

JS: The real hope here is that this is a basic science approach and so we're hoping that we can make discoveries that enable drug companies to make new drugs that would eventually help not only understand how the virus works or how to think about targeting it but also more broadly again, from a science perspective, how to think about targeting RNA because it's really a fundamentally new approach. We're really hoping that we can make some advances in that way that would really pave the road towards making new drugs down the road.

GB: That would be very welcome considering the infectivity rate right now. Another question: What do you envision your subsequent research looking like? I know that's probably a hard question considering you're in the thick of things.

JS: At some level you have to go where the science tells you is the right way to go. But you know we're hoping to continue to work on coronaviruses. Our main interest, as I mentioned, is really cancer-associated RNAs, but anything we can learn about this we think will probably have an impact in how we think about cancer as well.

You know we continue to work on molecules that influence RNAs in general as that's our main interest.

If we or somebody else could make a drug that targets RNA, any of these would have a really big impact on human health. So, this is an area that's being studied intensely by a lot of other people besides me right now. It's a very exciting time to be involved.

GB: So now we're gonna switch from you as a scientist to you as a person living through the pandemic. Have you been working mostly at home, on campus or a combination and what has the experience been like?

JS: I have been working a combination of at home and in the office and that's been for several reasons. As a scientist, you want to be in the lab; you want to be there and you want to be talking to people about what they're doing; and that's really what motivates me is the ability to work with other great scientists. These great post-docs are willing to come from all over the world and work together and that's really a motivating thing. But at a sort of personal level, you know we're under restrictions. We don't want to have too many people in the lab at once because of potential infection and so I try to work at home some of the time as well in order to accommodate that and let people get into the lab. The other personal challenge is that we have two young sons and, of course, daycare and school have been a pretty major challenge. In Maryland all the schools are virtual right now which means that our third grader has been at home on a Chromebook and has been learning how to do multiplication virtually, which is a challenge. And then we have a two-year-old as well who's in daycare full-time. Now he's back in full daycare but the daycare was closed for a long while in the spring. So it's really been a challenge and a balancing act to try and find out how to make sure that my kids are getting what they need while also my being able to manage the lab and help people in the lab do what they need to do.

GB: Have there been any personal challenges for you during this time?

JS: The silver lining is that I have had more time to spend with my sons. I think I travel a lot during non-pandemic times and so we've been at home spending a lot more time with the kids and that's been great. I think on a professional level another thing that's been really sort of unexpected is that you know you spend a lot more time meeting people from all over the world that you might not interact with so

conferences are virtual. There might be a conference in another part of the world that you would be challenged to get to, but you can go to virtually. We've had a number of really interesting opportunities to meet people, who I would have met otherwise, sort of virtually. That's been really fun, actually, although disappointing to not be able to travel because, you know again, one of the great things about being a scientist is you get to meet people from all over with really different backgrounds.

GB: How has COVID-19, do you think, made you a better scientist?

JS: The one thing that I've learned is that you have to be flexible. I think that the pandemic, everyone will tell you, has required us all to be a lot more flexible than we would have otherwise and that's been both the challenge and the opportunity. You have to be very nimble on your feet and willing to look at new opportunities or deal with problems not just in the lab but in your personal life in a very different way. So that's been a big sort of area of growth for me personally, which has been taking a break from the Zoom meeting to help my son reconnect or solve a times table problem he's having, and then get right back to it. These are all opportunities for growth. I think everyone has faced sort of different challenges. That's the other thing, challenges, challenges—and they all seem to be a little different. It's been a challenge, but you know we press on.

GB: This is a fun question. What has been your favorite social media platform to use during the pandemic?

JS: I definitely like Twitter the best. I use Twitter. I tweeted a lot less during the pandemic but I'm still really actively following all sorts of scientists. This is another opportunity: that you hear about things on Twitter that you might not hear otherwise. You know it's even been an opportunity and we have collaborations that have started because of interactions on Twitter, including one of the coronavirus collaborations that we have actually and so that's been a real opportunity. You hear about somebody publishing an interesting paper that you might not have come across otherwise or a friend who's gotten an award who you can sort of publicly congratulate or you know a student who's passed a candidacy exam or something like that or, you know, I got my degree even though I was attending classes virtually. You hear a lot of positivity there and I think that there's a great community of scientists on Twitter who have been really trying to not only interact but to be positive and communicate what the truth is out there and how to understand what it means for the vaccines being developed and also just for whatever field of science that we're in under normal times, too. So, I've really enjoyed Twitter and following all sorts of different scientists on Twitter for sure.

GB: Have you continued with your cancer research at this time at all?

JS: Absolutely and in fact that remains the main focus of our lab, so the coronavirus project was really more of an opportunity for growth in the lab than a shift in priorities. Absolutely we remain 100 percent committed to trying to go after the cancers we've been studying and so that continues though, because we're at reduced capacity, obviously it's a challenge, but that will remain our main focus: targeting cancers with shortages and things of that nature.

GB: Was it easy to get the materials you needed to conduct your experiments so far?

JS: We have been able to get what we need, and it's been more challenges which have been just getting in. Everything's just slowed down a little bit because people are in the lab less and so if you're trying to use an instrument that's in a common area, it's a little harder to get into that room. Everyone wants to stay safe and healthy and that's our first priority, but we have to find different ways to go about doing things. But we haven't had trouble getting materials that we've needed so far, but it's more been trying just to get everybody into the lab, and everyone really wants to be in the lab. They want to be there but we all, of course, understand.

GB: Is there anything else that you would like to share as a researcher and as a person dealing with the pandemic?

JS: I guess you know I've been really proud of my group for really continuing to work hard and really trying to get things done throughout what's turned out to be a really difficult time for everyone. I'm just really proud to be a part of all this and hope to continue doing the important research.

GB: That's great. Well, thank you very much for speaking with me today. I wish you the best on your research and I hope that you and your family and everyone in your lab continues to stay safe.

JS: Thank you so much for inviting me and I hope you stay safe as well.