Dr. Matthew Hall
Behind the Mask

May 20, 2021

Barr: Good afternoon. Today is May 20, 2021. My name is Gabrielle Barr, and I am the archivist with the Office of NIH History and Stetten Museum, and today I have the pleasure of speaking with Dr. Matthew Hall. Dr. Hall is the Biology Group Leader and Director in the Division of Pre-Clinical Innovation in the Early Translation Branch of NCATS, and today he will be speaking about some of his COVID work and experiences. Thank you very much for being with me.

Hall: Thank you, I am really happy to meet you. It is nice to be here.

Barr: It is nice to finally speak to you as well. I have seen your name in different publications as well as on different emails. It is nice to, finally, put a face to the name. To begin, will you please speak about some of your findings from a really early study that you are a part of: "Serologic Cross-Reactivity of SARS-CoV-2 with Endemic and Seasonal Beta-Corona Viruses"?

Hall: There were a couple of things I was involved with early on in the pandemic, trying to think about what we could do. I am in the intramural program at NIH, which is traditionally very investigator driven. That is not really how NCATS operates, so thinking about team science and what we could do quickly to respond to what was happening, back—it feels like a million years ago—but back in early March of 2020, one of the questions that we had been discussing, and that we will probably end up talking about today, was: "How do we know how many people have been infected with the virus?" At that point, there was not really a test assay available for people who were infected in the United States. There probably was one, but there was limited access to it, and so we were thinking and recognizing that there are a lot of people who could potentially be infected, and never really get that positive test. We knew we could sample blood and look for antibodies in their blood that would say, "Yes, this person has been infected with SARS-CoV-2".

We were all getting involved in science that was not necessarily our core daily expertise but, recognizing that we had the skills to join up with other people as a team and build some things that just did not exist, we decided to try and see what we could do to build a study at NIH tracking this. We were actually only thinking about employees at NIH. At the time, we did not know how long this was going to last, but we imagined there could be a scenario where we would need to know people who were immune to COVID because they had been infected.

I had a good friend, Dom Esposito, a scientist at Frederick National Laboratory for Cancer Research, who makes proteins, and we needed a lot of proteins to create these assays, and found, funnily enough through social media, another investigator at NIH named Kaitlyn Sadtler at NIBIB. So, three people,

three institutes. We reached out to the Scientific Director Steven Holland at NIAID to say, “Is there anything happening within NIH starting up these kinds of serosurveys, where you take sample blood from people?” And he said, “No there is not,” but he introduced us to another really great investigator, Matt Memoli, who is an expert in respiratory viruses, which is what SARS-CoV-2 is. Together, we put together a team really quickly to build a study.

We imagined that we would maybe recruit a couple of hundred people at NIH who would be willing to donate a little spot of blood. After the study was advertised, we ended up having hundreds of thousands of expressions of interest, and from there, we quickly pivoted to a study working with a couple of clinical centers in the United States that literally have call centers. They would call people who volunteered to participate, and we recruited just around 10,000 people right across the United States to participate in this study. We had to send out kits; we had to receive back samples in the mail; all of the assays had to be built and the samples run. This great team of scientists and their labs worked together to accomplish this. The study is still going. The first round of testing those 10,000 people was finished around summer, and that article has been out for a while, and it was very clear that, probably, around up to the middle of summer, five times more people have been infected with SARS-CoV-2 than we knew about from the testing that was available. That was were pretty exciting and important finding.

Barr: Really interesting finding. Did that have any implications in terms of like public health policy or any other studies?

Hall: Yes. One of the things that we decided to do while we were doing that, and because the data is blinded, we could not match individuals with names with results, but given what we were seeing in terms of what is called the sero-prevalence, or the sero-positivity, we decided to turn it into a longitudinal study—which just means over time. We were actually going back to those same volunteers a couple more times. One of those [studies] is underway right now and [we’re] sampling them to see how the total positivity in the population is increased, but also to find out maybe some of those people who were positive last summer but do not test positive anymore: What is their immunity like? Does it wane?

Of course, a lot of people are being vaccinated and we added a question to the survey we have in this study to say: “Have you been vaccinated?” We are also going to get some insight into how people from within our study group are participating in vaccination as well. I think that since then NIH launched a couple of different programs: NCI runs a program called “SeroNet”, coordinating a national network of these and we work with them as well, and have been interacting with them a lot, and one of the things that we wanted to try and do, and we ended up being able to do, is just find out how quickly we could set up a survey across a population like this because—you are probably going to hear me say again and again—there may not be a next time in our lifetime, but there may be. And knowing that, we have got this. We have everything we need within the intramural program at NIH to do anything and so, being able to identify needs and move quickly, to stop what we were doing and do something completely different but very important, was an experiment of its own. I think it worked well. All four

groups within that particular study were from four completely different institutes, on three different campuses, but also all working at home. We managed to get a lot done.

Barr: Yes, definitely. Part of this study was also looking at cross-reactivity with other kinds of coronaviruses. Can you speak a little bit more about that and also why understanding cross-reactivity is so important?

Hall: Sure. I guess there are two sides to that. [You] create an assay, which is just a biological experiment that you can run to say, "Are there antibodies against SARS-CoV-2 in this person's blood?" "Have they had SARS-CoV-2?" There are other coronaviruses that humans get. There were really the famous bad ones like SARS from around 2002, and MERS, which every now and then appears in the Middle East. Those are coronaviruses but you really would not expect many people to be walking around in the United States who have had those. The other types of coronaviruses are common cold coronaviruses that you and I get maybe every year so. We made assays actually to look for the antibodies for each of those other coronaviruses, specifically, as well, but we wanted to make sure that we were not accidentally using an assay that was actually detecting all of those other coronaviruses, otherwise everyone would seem like there were positives to suspect through SARS-CoV-2 when we were just measuring cold coronavirus.

We built those other assays and we pulled or obtained access to blood samples from as early as 2019, that were archival, before SARS-CoV-2 existed, and they were all negative despite people being positive for cold coronaviruses. So we knew that we had an assay that was very specific, and that was going to be important because the last thing we wanted to do was over-measure and/or have what we call false positive detection. It is really important when you are building any of these detection kits to make sure that you understand or have tested the limitations of your assay.

Barr: How long did it take you to develop these different assays?

Hall: There are a couple of different steps to it, but the initial assay was stood up pretty quickly. I remember that we all got together for the first time around St. Patrick's Day. I happened to remember, March 17, last year [2020] no one went out because we were basically in lockdown, but it was while we were building the clinical study and getting the approval. Matt Memoli was the lead clinical investigator. Katelyn Sadler said, "My scientists in my lab can set up these assays." Scientists from NCATS went down there to help with setting that up and automating it, and Dom Esposito's group was making the proteins we needed for these. It all happened within about six weeks. It moved very quickly. The good news is that the basic scientific approach for making these is very established. It does not mean that they will work well, and you have got to do a lot of work to make sure you understand the strengths and weaknesses of the assay.

Barr: That is really interesting. Another initiative that you have been really involved with is the NCATS COVID-19 OpenData portal. Can you please talk about when you started creating this resource and what considerations you and others put into producing it?

Hall: Sure. The OpenData portal is a website and, as the name suggests, what we really were thinking about when we started this—and I will say a little about how it all came about—was how do we know how to talk about NCATS? At NCATS, a lot of what we do is what we call "translational science"; so perhaps drug discovery is one way of thinking about that. We have experts that know how to create biological experiments to study different diseases. We have robots and people and drug libraries, and we can literally screen up to 10,000 different approved and experimental drugs looking for drug repurposing opportunities, and to test hundreds of thousands of new compounds to see whether we can discover things that are active.

When SARS- CoV-2 came around, it was a brand-new disease. There were no therapeutics for it and a lot of people put a lot of effort into asking, and this is what we basically asked ourselves, "How many different ways can we study this virus and run experiments against this virus, testing all of the drugs that are already out there and that we can test in humans to find out what works, that might be useful for treating patients?" Because there was nothing. We knew vaccines were going to come, and they came even quicker and better than we imagined. We knew things like that would come, and we knew that new drugs could be created. We also knew there is a timeline associated with those, so this was kind of the initial rapid response. At NCATS, we basically stopped doing all other research, and in February 2020, pretty quickly we were already thinking about assays to set up that needed to be created by our biologists to start screening, and as we generated all of this data, we have generated well over a million data points of data now.

Barr: Oh, my goodness.

Hall: Yes, a lot of work but, we needed to work out how to share it. As scientists, we think a lot about the publication, which is really important for sharing information with the scientific community. And that is always done very carefully and cautiously but it takes a lot of time, and this was not an environment where we were going to try and publish papers in great journals and feel good and stroke our egos. This was about generating data for an important public health crisis. We were wondering what is the quickest way to share this data with everyone, not just for ourselves, not just for NIH, but globally, and so, we realized that the best way to do that would be to build a website.

The initial piece of this OpenData portal, as the name suggests, was to take all drug screening data that we generated against all of the assays that we were generating and make it all available immediately to the scientific community. Obviously, as we were looking at the data, we were analyzing it. We were looking for things that were worth following up on; we were also trying to invent new assays, and we were following the science that was just exploding everywhere in the world and adopting those. If someone found a new experiment or a new approach, we would replicate it, show that it worked,

screen it, share the data. The goal was not to worry about publications, not to worry about slow timelines, but generate data and share the data as quickly as possible.

It evolved into quite a few different things, so it has become a little bit of a Swiss army knife of dissemination for science. We have been working to try and take one or two antiviral drug candidates forward into human clinical trials with partners, and we have even been sharing those experiments that needed to go to the FDA eventually, and say we would like to conduct a clinical trial, and we have been sharing that data as well.

More recently, we have been working through this great program that Dr. Collins set up called ACTIV which is a public-private partnership, and we have been working with them and other partners like NCBI, another [NIH division], which is part of National Library of Medicine at NIH, to study all of the variants that are emerging and that we worry about, and to test therapeutics. And also collect all the data that exists globally and is released, compile it, and put it into our OpenData portal. As new problems emerged, we tended to find ourselves in the position that people would say, "Oh good, we have a tool for sharing COVID-19 science. It is the open data portal." And so, it has grown and expanded in ways we did not anticipate, but then again SARS-CoV-2 has spread and expanded in ways we did not anticipate as well. It has really tracked with the science.

Barr: Going back, how do you all screen over 10, 000 existing compounds that could possibly help patients with COVID-19? That seems like quite a big endeavor.

Hall: It does. The important thing to say is that to think about this kind of approach, generally, before SARS-CoV-2, up to SARS-CoV-2 and during as well, we're disease agnostic at NCATS. We think about drug discovery and translational science, but we do not have a specific disease or problem in the title of our institute other than the challenge of therapeutic development, and improving human health, which is the whole NIH mission. We could do this because we have always been doing this. Scientists at NCATS for the last 10 years have created and collected every approved drug, and it was already there in a library and ready to go and test for this, the way it is for lots of different rare diseases that we care a lot about and do a lot of work on. The goal was to leverage our collections of pre-existing libraries. It is a lot of work to track all of those approved drugs in the United States, in Europe, Japan, and even Australia. We get them all; we collect them all; we put them into libraries. We also collect lots of drugs that have also been in trials but maybe did not work and never got approved. They failed in that clinical trial, but we still know they are a safe compound that has been in humans, and if we find another use for it, we could run another clinical trial and take that back into patients to test against a new indication or disease, whether it is an infectious disease like SARS-CoV-2 or a rare disease. Those pieces were already there.

Additionally, we have robots, as I mentioned, that can help our biologists invent an assay. We work with our automation engineers. It takes a team of people with different skills to take that biology, experiment, teach the robots how to do it, take our drug libraries, bring them together, and test and just

keep testing and testing against as many different biological assays or experiments and approaches as we possibly can.

Barr: That is very interesting. When I was looking on the site, it seemed like there were many compounds and not all of the compounds have been tested for every single scenario that you have as possibilities. Is that by design, or are some of these compounds still being looked at for these different situations?

Hall: The science is still underway, and even though the scientific community has probably exhausted a lot of those drug repurposing opportunities, asking those questions about which drugs might possibly be useful for treating SARS-CoV-2 [is still important]. There is work yet to be done so, if you are seeing gaps, we are still filling in some of those gaps. There are also some complicated technical reasons why you might see some of those gaps. Some of our drug libraries have the same drugs, and so we do not test a drug multiple times; therefore, you will see drugs left out sometimes.

Barr: Oh, okay, that makes sense. How are you all constantly staying up to date with all the different variants?

Hall: Good question. NIH has a couple of different programs that we are engaged with, working with partners like the CDC, who are obviously really important from a public health point of view, the FDA, and institutes at NIH, like NIAID, which we have worked very closely with, and others. The NIH ACTIV program, I mentioned before, has a program called TRACE. CDC is constantly tracking and sequencing viruses that they take from people who are infected, and that is happening globally as well. Sometimes we are aware of a variant that might be appearing in other countries first, and it is being monitored and tracked here; others appeared within the United States first, or first came to attention here so, as we become aware of them, we and lots of other scientists at NIH and across the U.S. government are obtaining the virus, and also creating models of those viruses, those mutated viruses, so that we can screen and test drugs to make sure that drugs are still working, that vaccines are still working, and to ask whether the immunity that people acquired to maybe the original form of the virus that was first spreading in the United States are going to be have cross-immunity to these new variants as they come along. Thankfully, what we are seeing is that while some of them [the variants] are worrying, some of them are more infectious, when we do the science, we are finding, generally, that people are protected.

Barr: Do you have to completely redo the entire process in terms of testing when it is against the variants?

Hall: Pretty much. We have a group of scientists now who are dedicated to working on the variants, and whenever a new variant becomes available, which means isolating the virus, this is done by scientists.

They isolate the virus, and they can distribute it to their special labs called “biosafety level three”, which are not normal labs. [While working in these labs], they have to wear protective equipment including a respirator. We already know how to do the biology experiments, but we have to set them up and make sure they work all over again with each new viral variant. One of the things we are doing with some of those variants is going back and re-screening all of the approved drugs as well just to make sure that we are not missing anything. Maybe there is a drug that works now against a variant that did not work before and to make sure the drugs that already work keep working.

Barr: How would you like to enhance this resource?

Hall: One of the challenges is that, sometimes, the science comes at us, and we were not even anticipating it. We are constantly thinking about new things. There are two things we are doing at the moment. We are actually reaching out to lots of other labs globally that did drug screening as well, to ask if they will give us all of their data so we can add it, compile it, and make that all available. That will be useful for now, but our goal is to make it a forever resource. That is one of the great things about NIH. When we think about future pandemics, future outbreaks, having this resource [of] testing drugs against other viruses, in the future we will be able to compile all of this data and maybe predict what drugs will be useful against other pandemic threats before they come along or once they have come along so that we could respond more rapidly.

We are also thinking about animal data. There is a lot of published animal data, and we are thinking about ways to gather all of that and curate it, which means to make sense of the data, and communicate it back out to the public in a way that is a useful resource mainly for the scientific community, but we have had people from all over the globe accessing the OpenData portal.

Barr: Obviously, scientists are looking at it, but how are clinicians and other kinds of people looking at it or using it?

Hall: That is a good question. Based on the queries we get we know that, for example, if people have been thinking about anecdotal evidence, whether a particular drug may have worked in some people, according to a doctor, when they are thinking about clinical trials. We get queries and people will use the data portal to say, “Looking at all of the assay data we have, does it work there? Do they see any antiviral effects?” and sometimes the answer has been “Yes”, and sometimes the answer has been “No, I am sorry. It does not seem to be the case”. Other scientists have been using it along with just sharing the data, every single protocol (which is kind of like if cooking has recipes for making a cake, scientific assays have protocols for how you repeat that experiment), every single assay we have done has a detailed, step-by-step protocol available and so other scientists who have wanted to replicate those or use those have been able to download our protocols, and they can repeat those experiments anywhere in the world as well.

Barr: Interesting. What have been some of the challenges that you and your team have faced in creating and maintaining the OpenData portal?

Hall: Obviously, creating a web page is challenging; creating one that you update or want to update every day or two can be quite challenging. From a philosophical scientific point of view, traditionally, scientists are trained and rewarded for publishing. The way you publish what we would call a "high impact" paper is by basically working in secret. You don't really share a lot of information about your science until you write that paper, and it makes a big splash when it is released. We were breaking all of those rules by doing our science this way. We could have saved up all of this data for six months, and wrote some ridiculously high impact paper, and made a big splash, but asking scientists to set aside that instinct to keep their science secret until they could tell one big story, that took some work as well. Everybody jumped on board once they recognized what the public health need was and what the opportunity was, but being a very non-traditional approach to doing science (which I think is what we should be doing at NIH), it took some talking to get people to come around. There was a universal buy-in on this, as we went along.

The other challenge is a long-term one. This is a boring answer, but you know everything including websites costs money to maintain and to keep up so, thinking strategically, we have just been working through making sure that we can resource this and support it so that it is there forever. You would hate for this kind of information to go away.

Barr: Definitely, so it seems, and I understand why so much attention was put on re-purposing existing medications because we had very sick patients that needed care then, plus the weight in terms of testing and approval, but are there efforts to create brand new medications just for COVID?

Hall: Absolutely. Last November, I worked with some colleagues at NIAID, and a really great scientist named Jim Anderson who works under Dr. Collins in the Office of the Director (he is a Deputy Director in his own right), to create a summit at NIH: "SARS-CoV-2 Antiviral Summit." We brought together people from Pharma, from government, from academia experts, and had a four-hour discussion around antiviral drugs: what have we got, what do we know, and what we do not have, and what do we need? Dr. Collins opened and closed the meeting, which was really exciting, and Dr. Fauci spoke about Dr. Austin, who at the time was the director of NCATS, and that really helped focus attention on, "Okay, we have done a lot of drug re-purposing. We are going to need new medications."

Drug development takes a long time. It can take 10 to 15 years from the beginning of a program in Pharma to create a new drug that gets approved, and it can cost billions of dollars. It takes a long time. It is expensive, and one of the reasons it is expensive on average is that a lot of drug development fails. Do you know the reason that the vaccines and the drug re-purposing type approaches were so important? It is because there are timelines associated with drug development that are challenging. There have been multiple drugs that Pharma have developed, and the NIH ACTIV program has coordinated a really amazing set of clinical trials to work with Pharma, to help and to support the development of those.

I suspect or years to come there will be new drugs being developed, what we call candidates, so that even if we manage to eradicate SARS-CoV-2 or if we do not, we have good therapeutic antiviral treatments available, and if there is ever another coronavirus-like outbreak, we would like to think that along with a drug like remdesivir, which we might chat about a bit later, we have got a set of these antivirals that we can go to, ready to test and say, "Look that one and that one works. Let us try them in humans." And not be quite in the position we were in with SARS-CoV-2, where no one had ever developed a coronavirus antiviral before, despite the fact humans catch a couple of different cold coronaviruses. We have had epidemic-type outbreaks of coronaviruses.

We also have to think about non-coronaviruses. There are other viruses that we know which can be a threat to society such as Zika, a few years ago. There are no Zika antivirals despite the fact that it happened. Ebola—there has been some really great work at NIAID and other places creating treatments for Ebola. We need to think about all of the things that we know could cross from animals to humans and make sure we have got the treatments ready to at least test and take into humans when that time comes. I think you will see a lot of antiviral work take place over the next five years and beyond, and NIH is going to play a really important role in driving that antiviral drug development.

Barr: Another thing that you are involved with is a study that looked at whether a neutralizing antibody pipeline could defeat SARS-CoV-2. So what is the value of neutralizing antibodies in comparison to other kind of therapeutics?

Hall: We have an antibody development program, generally at NCATS, which could be used for any disease. A lot of really amazing work has been done in the scientific community on neutralizing antibodies. We wrote a review, or an overview, that kind of described what existed and what was going to be needed for creating neutralizing antibodies. When you become immune, you have an immune response to an infectious disease [and] you generate antibodies, and so one of the approaches that can be taken, and there are a few different ways to do this, is to create antibodies against a virus, and when someone else becomes infected, you infuse them or inject them with that antibody so, before that person's own immune response can kick in, you give them neutralizing antibodies which bind to the virus and inactivates them. So that is why they are called neutralizing, because they truly neutralize the virus.

One of the drawbacks, of course, is that they need to be injected. You cannot take an antibody as a pill. It does not work that way. People tend to either find it at what we call an infusion center when they become infected. But there have been a number of neutralizing antibodies that have been developed by Pharma and that have authorizations by the FDA. Eli Lilly has one; Regeneron has one. Those are the two sets of cocktails of antibodies that we mainly hear about, and they have been valuable and effective in helping treat patients who are infected and trying to prevent them from getting sick or getting sicker.

Barr: What are some of the other challenges with antibodies?

Hall: Going back to variants, one of the things that we worry about, and we have seen it a little bit, is that antibodies that bind to the original virus, do not bind as strongly to some of these variants so the viruses escape. The antibodies do not work as well, and so you can imagine, people have needed to create updated antibodies, and make sure that they neutralize the new variants as well. We need to make sure that we continue to have therapeutics that work against all of these variants and making them can be quite challenging; manufacturing enough and making sure they are distributed right across, for example, the United States, that is really essential.

A big and important part of drug discovery and drug development is a drug manufacturer and drug supply, and we have seen that again and again in the last 14 months—that making sure we have enough of the therapeutics that work and that making sure that they're distributed is very important, and we see that with vaccines as well. There are lots of challenges all the way along what we call the translational science pipeline, from working out how you are going to try and discover a drug, all the way through to we have one and the FDA has approved it or authorized it and making sure that you have got a supply chain that can actually meet the demand. Especially for something like this where at one point hundreds of thousands of people a day were being diagnosed as positive.

Barr: Can you comment on the creation of therapeutics or administration of therapeutics for people who have SARS-CoV-2, but they are not hospitalized, or it is not critical? It seems like a lot of the drugs are for people who are on their death beds with this disease.

Hall: Certainly, in a bed, you are right. Remdesivir is an antiviral drug. The neutralizing antibodies require infusion. In the case of Remdesivir; that tends to mean people who have been hospitalized, so they are ill enough to be admitted to hospital. The neutralizing antibodies, you do not have to be in hospital, you can go to an infusion center, and you do literally get an IV line, and they will infuse you with the antibody, and you go home. That is why we need to develop a set of antiviral drugs that you can take as a pill so that when you are either exposed to someone, or you test positive for SARS-CoV-2, but you have minimal or no symptoms, you can take an antiviral. It should be like Tamiflu for the flu. This is the analogy people use. It should shorten the window of time when you feel unwell and reduce your symptoms as well, and then, by doing that, it will also minimize the amount of time when you could potentially infect others as well. So it is improving the outcomes for that individual patient, and making sure you are preventing them from ever getting sick enough to be hospitalized. Those are the kind of challenges that are being tackled at the moment. There are a few antivirals that are in clinical trials being tested in people. There appears to be some positive news around some of those, and a lot more work to be done.

Barr: Another study that you participated in and looked at was “Whether the SARS-CoV-2 Cytopathic Effect is Blocked with Autophagy Modulators” First, can you define what cytopathic effects and what autophagy modulators are? And what are the cytopathic effects of SARS-CoV-2?

Hall: This is just one example of a study of many studies and many assays that we ran for the OperData portal program. This particular scientific study was led by a scientist at NCATS named Kirill Gorshkov. As with every assay in every project, lots and lots of scientists from the team across NCATS are contributing to this.

First of all, what is the cytopathic effect? I will take it back a step, how do we discover drugs? How are we finding antivirals that work? One thing we knew about SARS-CoV-2 and other viruses is that a lot of viruses when you put them in human cells in a dish, the virus kills the cells eventually, and that is called a cytopathic effect: killing the cells. If you have an antiviral and you add it in with the virus and the cells, if it works, the cells do not die because [the antivirals] stop the virus from getting into the cells and replicating and killing the cell. So one of the very first ways we tackled trying to screen for antivirals was by doing exactly this: putting virus on cells, testing 10 000 drugs, and asking which ones protect those human cells from dying. So, that is the cytopathic effect.

Once we had the results from those studies, we noticed that there are a whole bunch of compounds or drugs that modulated something called autophagy. Autophagy is an interesting effect in cells. It is like many important things associated with how a cell works, there was a Nobel Prize given for understanding this process. It is actually an efficiency process within cells, where it is one way that they break down material in the cell, recycle it, and reuse it. It was found that a lot of drugs that affect this recycling mechanism within cells, when we blocked that, it protected the cells from the virus. This is really interesting because there is not really a drug that does this, but by finding all of these compounds that worked in this way we learned something about how the virus infects cells and that was another learning point in terms of our understanding about what the virus does inside the cells and what we might be able to do to try and prevent it. Some aspects of this science are still underway. We are still trying to use those molecules to see whether they can be improved, if they work to help in animal models, and that would give us the confidence to maybe move forward with something like this as a drug development opportunity.

Barr: I was reading about the study that there is a lot of toxicity with some of these kinds of drugs, these autophagy modulators. How have NCATS [scientists] been dealing with that and what are some alternatives?

Hall: For any drug for any disease, there are lots of challenges with developing {the drug}, but the two big ones are to make a molecule that works well in dishes in the lab, but also in animal models of that disease. You need to show that it works well before you can take it to humans, and it needs to be safe, it cannot be toxic. You can have molecules that work really well in terms of the biology you are trying to trat, but they are also toxic to cells, and they are not really something you would want to give to people or even to animals because they are going to make them feel unwell and so that is not a good drug development opportunity. As with all medicines that you take, you know the dose to take, and it should help you feel better, and hopefully, it does not make you feel any side effects. Sometimes, people feel

one or two side effects for a drug but nothing worse than that. With these compounds, one of their limits was that they also at [a dose] just a little bit more than what you needed to [kill] the virus, kill the cells and that is obviously far from an ideal scenario. Therefore, one of the things that we are trying to work through is: "How do you make a less toxic version of these compounds, so they still work on the autophagy pathway, they still stop viral infection, but they are safe?" That is one of the things we are thinking about and working through, and that is a classic challenge for every drug development program.

Barr: What other COVID research and initiatives have you been involved with at NIH? You can speak just briefly about that. I know it has been a lot.

Hall: Sure. Let me see. I have been involved quite a bit in working across the Institutes at the NIH and trying to work with people to coordinate the COVID-19 research that has been taking place. There are some very exciting committees that are involved in that, and every committee is exciting, so, [I have been trying to] help people communicate and be aware of the science that is taking place.

The other thing I will just mention briefly is way back at the beginning when Remdesivir was first noticed, we wrote a review article about Remdesivir and what it is and how it works and where it came from. It was developed and discovered at a drug company called Gilead but collaborating with a couple of different U.S. government labs at NIH, that included most recently NIAID for Ebola. As I have mentioned, we wrote the article because we wanted to know, "Where does this drug come from?" Every drug has a biography, but not many of them have those biographies written. This was such an important molecule that we felt it was important to write this article, and it ended up getting quite a bit of attention because no one else had written a biography about Remdesivir.

I think that there are a lot of science communication challenges that we have seen with SARS-CoV-2 and COVID-19. Understanding therapeutic development is hard and complicated even for therapeutic development experts, and vital in the case of SARS-CoV-2 virologists, so thinking about how to communicate the science that we all do here at NIH, not just to the scientific community globally, but also to the average U.S. citizen, has been something we think about a lot. Some of those articles we have written are pitched at scientists, but we always try to take the opportunity to find ways to tell the same story at other levels to the community, so that people understand what this means. I don't think anyone two years ago had an opinion about the brand of a vaccine they were about to be given, and I do not think they knew much about futility and clinical trials. Also, I do not think they necessarily knew what drug re-purposing was. There has been a really amazing opportunity for NIH to not just be really important in terms of responding to this particular pandemic, but also demonstrating to people how diverse the science that takes place at NIH is, and how it was able to respond in so many different ways, all in parallel, all at once, trying to tackle the challenges as they came along.

Barr: That is definitely very important. We are going to transition from you as a scientist to you as a person, quickly. What are some personal challenges and opportunities that arose for you due to the pandemic?

Hall: Wow! Personal challenges and opportunities. I think that the opportunities and the challenges were two sides of the same coin. I am married, and I have two children. They were all at home as was I (not in the lab) so, that was really great to spend time in everyone else's pocket for so long at home together, but I am not sure they all agreed with me that it was so great to be always together all the time, especially with me.

When people have asked how I am for the last 14 months, the answer has always been, "I am really tired." It has been quite tiring but also really exciting to apply all of NIH's capabilities and abilities, and NCATS' capabilities and abilities to such an important problem. I have met an incredible number of people that I did not know before who work in other institutes. Institutes can tend to be a little bit siloed; they have their own problems, and they are trying to solve those problems, and they are really focused on them. This was a really wonderful opportunity to show how we can all work together when there is a specific opportunity and a specific need to do so, and we do it really well. There are a lot of really amazing people here at NIH. I have a great group of scientists in my own research group and coordinating them when they were in the lab and I was not allowed to be, presented some really new challenges. Working remotely with people all over the country, we have always done that, but working remotely with people who I would normally be able to walk up to and have a quick chat with to solve a problem, was a really big challenge. Would I want the pandemic to happen all over again? Absolutely not, but if I did not already have maximum admiration for our mission at NIH, it grew even more just by seeing what all of my colleagues around me were doing, not just at NCATS but right across NIH over the last 14 months. It has been incredibly satisfying and exhilarating in some ways to see all of this science play out.

Barr: That is really wonderful. How did NCATS broadcast some of its resources? They are not always as well-known as other things that other institutes produce but you all have done a lot with the pandemic so how did you broadcast your resources so widely?

Hall: There are a lot of what we would call "little institutes" at NIH. There are a couple of really big ones and lots of little institutes that develop this science, and we generated it, there are a few scientific ways to do it. I tried to speak at as many conferences and seminars [as I could]. All of them are online. I also use social media a lot so sharing everything that NCATS was doing, with other partners, and making sure you are attributing your colleagues from other institutes and making sure it does not sound like it is you and only you. Everything we have done took a lot of different people working together to do this. Social media has been really valuable, of course. Every institute has a communications office. We have a really great communications office, and they are really good at identifying stories that can be told again. There is usually a scientific accomplishment, but then there is a sort of a general narrative that can be told to help people understand what the mission of NCATS is.

Ultimately, creating drugs is a really challenging process. There are a lot of different ways to fail, and our job is to try and reduce that failure rate, make it easier to develop drugs more efficiently, and get more

treatments to more people. A good example of that is to say, “Well, this worked for SARS-CoV-2. How do we do this for other challenges?” We think a lot about rare diseases. There are over 8,000 rare diseases. Not many of them have treatments. When SARS-CoV-2 goes away, and we get to completely 100% return to our day job, we have got an important mission around tackling and treating rare diseases and the same communication challenges around people being aware and understanding all of the difficulties and challenges that go with treating and finding treatments for thousands and thousands of diseases that do not have one right now. SARS-CoV-2 is just one disease.

Barr: Well, we will get back to that point, but what is one way that you have, one thing that you have enjoyed that has helped you cope with the pandemic?

Hall: What have I enjoyed? Well, I love reading murder mystery novels like Agatha Christie, 1920s, 30s, murder mysteries. I tried to make sure I read something every day. I ended up reading a lot of short stories because I did not have a lot of spare time. It only takes 20 minutes to read a short story. Something totally random I ended up doing was genealogy. I love genealogy research, and I try to do something to distract myself every now and then, and that kept me busy as well.

Barr: Did you find anything interesting about your family?

Hall: I think I found out everything I possibly can about my family. The most clichéd thing about me, like many Australians, is that I am descended from convicts so I particularly enjoy studying my criminal ancestors and trying to find out as much about their lives as possible.

Barr: Why were they in prison? Have you found that out yet?

Hall: Oh, yes. I think I had five or six so, all sorts of things. You did not have to do much back then to be transported to the other side of the world for seven years or forever. Someone stole a piece of meat; someone pickpocketed someone; one of them stole a watch from a store; one of them stole a horse, which I guess is like being a car thief now. It is pretty remarkable the range of crimes that people could commit and get sent away from their family forever.

Barr: This is one of my last questions and it is a thought-provoking question. How do you hope that drug research with COVID-19 will positively contribute to the elimination or killing of other common conditions or even possibly the next epidemic disease?

Hall: Great! I love that question! We have been thinking about this a lot. I really think that before this we did not necessarily have what we might call the "playbook" for how to think about tackling an epidemic when it occurs if it becomes a pandemic. I think we know how to do that now. It is important that we capture how quickly we responded and how we work together so we do not have to re-learn that next time. I think it is also important, as I said a little earlier, that we make sure we develop the antiviral drugs against lots of different virus classes so, when they come along, we are more ready than we were this time. That is one answer. I am sorry, I think I forgot part of your question.

Barr: How do you hope that SARS-CoV-2 drug research will positively contribute to research towards other conditions or even the next episode?

Hall: I am probably editorializing a bit when I say this, but possibly one of the frustrating aspects of SARS-CoV-2 is imagining if we could put this much effort into every disease. Obviously, we cannot, but if we can identify the things that really worked and again take that playbook, especially for things like rare diseases that we care a lot about at NCATS, to ask, "What will it take on a disease-by-disease basis to try and make a big difference to as many diseases as quickly as possible?" That is the other lesson we really need to take away from this: What worked and how can we apply this model to rare diseases. There are some really common diseases that need a lot of attention as well, for example, Alzheimer disease does not have any effective treatment. Scientists have also learned how to work together well and how to identify opportunities to work together quickly. We need to take all of these lessons and not forget them and to carry them forward and treat every single disease with the urgency that we treated SARS-CoV-2.

Barr: Yes, definitely. Is there anything else that you would like to add either as a scientist at NIH but also as a person who is living through the pandemic like everyone else in the world right now?

Hall: I think the one thing I did not say when you asked me about my challenges as a person is that it was really scary a lot of the time. I had a lot of anxiety, and I think I was lucky that I was so busy doing science that sometimes I could distract myself from what was happening, but there were lots of times, especially news cycles were awful. You would see a headline, and of course the important thing about headlines is to find out what the science is behind the headline because it is usually not nearly as bad as they say it was. So, lots of anxiety and scary times just like anyone else, but also a lot of optimism for not just all of NIH but the Intramural Program. We really showed that in some ways the Intramural Program is a little bit like a national facility, a national resource that can meet a health crisis, and I think we all did that really well, in a really coordinated way, together, and that gives me a lot of optimism for how NIH can continue to work together, right across the board, to tackle lots of other big problems.

Barr: How did your family and friends fare in Australia in comparison to the U.S.?

Hall: No one in my family in Australia had SARS-CoV-2 because Australia is an island, and it basically closed down so very few people have been into Australia in the last 14 months. If you do enter Australia, you have to spend 14 days in quarantine, so I think in Australia, only a few thousand people ever had it. There were a few little outbreaks, and they had lock down, using public health measures to see it out. Thankfully, all of my family in Australia have been safe, as have my family through my wife in the United States as well.

Barr: That is great.

Hall: It has been interesting to see how different countries have been able to or not able to deal with the public health crisis as it emerged.

Barr: Yes. Well, thank you very much for your service and for all your contributions, and I wish you all the best as you continue, and that you and your family continue to stay safe.

Hall: Thank you, Gabrielle. It was really nice to talk to you and meet you today.