Vanderbilt Health DNA: Discoveries in Action
Season 2, Episode 8
Mutant Ninjas: How Researchers Are Conquering Viruses

Dr. Natasha Halasa: It's like my whole life has been prepared to continue to study not only this virus, but all other viruses, and really trying to understand how can we get the best vaccines for these individuals. It's so important to continue to do surveillance because, who knows? I mean, every couple of years, there's new things, new viruses that are emerging, and continuing in this platform is important. It's important. There's so many questions that are out there that need to be answered.

Dr. Seth Zost: Already with the wild success of MRNA platforms for vaccination, there's renewed interest. There was interest before, but it's been turbocharged now. And can we apply this to flu? Can we apply this to RSV or all these other human pathogens? And how far can we push this technology?

Dr. Andrea Pruijssers: What we want to develop is silver bullets, basically, that will knock the virus out once and for all.

Clark Buckner: Back when I first talked to today's guests, COVID's Delta variant was not sweeping like wildfire across the country. ICUs were not bursting at the seams. Yet, here we are living in the latest chapter of the COVID story. This episode is called Mutant Ninjas because while we were stumbling through our lives, calculating our risk tolerance, or eyeballing whether that random person is really six feet away, the guests you're about to hear from put their daily science or clinical practice on pause and unleashed their specialized knowledge on the ever evolving SARS-CoV-2. They're trying to get out ahead of the virus that causes COVID-19 and find ways to neutralize it. Let's meet them.

Dr. Natasha Halasa: My name is Natasha Halasa. I'm a professor in pediatrics in the Division of Pediatric Infectious Diseases.

Dr. Seth Zost: Hi, my name is Seth Zost and I'm a post-doctoral fellow in the Crowe Lab at the Vanderbilt Vaccine Center.

Dr. Andrea Pruijssers: Hello, my name is Andrea Pruijssers. I am the director of the Coronavirus Antivirals Program here at Vanderbilt.

Clark Buckner: You're listening to season two of Vanderbilt Health DNA: Discoveries in Action. I'm your host, Clark Buckner. The reasoning behind the show is quite simple, the path to better health lives in our DNA. Discoveries in action is about the big ideas and breakthroughs happening right here in Nashville, Tennessee from Vanderbilt Health. Our drive to discover, care, learn, and share is in our DNA. It defines who we are just as your DNA defined you.

Today's guests specialize in separate but crucial areas in the pandemic response. They are each part of the leading edge teams tracking viruses, watching for variants, and developing treatments and vaccines to fight them. Let's start with Dr. Zost, an influenza expert in the lab of Dr. James Crowe, who we met on the first episode this season, Blueprint for a Pandemic-Ready Society. His specialty was influenza A, which is endemic, meaning it keeps circulating. As we all know, there is no one shot for the different flu strains. That's why we have to get a vaccine every year. Dr. Zost was already interested in how viruses escape our antibody responses, and that was before COVID. Even though he's intimately familiar with infectious diseases and their lethal pandemic potential, working through one was an entirely different experience.

Dr. Seth Zost: It's almost if you're involved in infectious disease research, you have the intellectual appreciation of when there is a pandemic, it can be a very big deal. There's also nothing really prepares you for the emotional shock of when natural was safer at home. And actually you could argue that that threat will continue to increase, and that there's potential for novel coronaviruses, there's potential for new flu strains to make the jump from animals to humans, and there's also potential for other what we call zoonotic threats, so animal to human transmission, that we don't actually even appreciate yet.

So I'm trying to bridge SARS-CoV-2 research, as well as restart some influenza work that we sort of mothballed when things started to spiral last year. I have interest in how virus has evolved to escape your antibody responses.

You may have heard in the news about SARS-CoV-2 variants. What those are, are viruses that we see that have acquired certain constellations of mutations, and the ones we're most worried about from the standpoint of vaccines are the ones that are in the spike protein. Those mutations can, in some cases, prevent the binding of antibodies that are elicited by either natural infection or vaccination. And if the virus evades enough antibodies, then, in principle, you could be reinfected, and that's what people are concerned about now and it's a... That's why I did my PhD for influenza. We know an influenza that has a name, it's called antigenic drift. We know that your natural infections or vaccinations give you a much more limited window of protection, and the virus is constantly evolving to escape population immunity. In the field, we think that while it's still early days, we're starting to see the beginning of that for SARS-CoV-2.

So that's one of the areas in the lab that we're interested in now is for the antibodies that we found, how has the virus changing and is it changing in ways that impact the binding and ability of those antibodies to neutralize and protect?

Clark Buckner: We get vaccinations at different intervals or even different stages of life. Think about tetanus, flu, chickenpox, shingles, measles, whooping cough. Why is that?

Dr. Seth Zost: So when you think about some of the vaccines that we've had that are extremely successful, I think probably the gold standard vaccine is smallpox because there's now smallpox in two

labs, there's absolutely no smallpox that circulates. And that vaccine is so good, we can push very virulent pathogen to the point of eradication. Another example would be measles vaccine, where the reason why we have measles outbreaks is not because the vaccine is ineffective or the vaccine is leaky. It's able to take a pathogen that is highly transmissible and it's able to give you life-long protection if you have the vaccine course.

And it's interesting to compare and contrast measles and influenza and SARS-CoV-2, where for influenza, we know that you don't have that long-lasting protection from natural infection. You do in the case of natural infection or vaccination for measles, and those are both RNA viruses. They both have a high mutation rate, but there's something about the interaction of your immune system with the proteins on measles that backs measles into a corner where there's just not available options for the virus to acquire mutations that prevent the binding of your antibodies and escape.

And for flu, one of the things that we're interested in is we know that while there's a lot of different sites in the virus that target, your immune system double or triples down on the same sites. Sometimes for some individuals, it's almost their entire antibody response is focused on a single site, and then with one change, the virus can escape that.

And recent work from others for measles has shown that actually your response is very balanced against measles proteins and you target multiple redundant epitopes. And so, the virus can't escape by changing one site. It would have to somehow simultaneously change four or five, six, or seven sites in order to escape your response.

The type of response you make to measles is very different than the type of response you make to flu. There's a lot more redundancy. That's what we would like to try to do for influenza and what we'd like to try to do for SARS-CoV-2, is target enough sites where you have enough antibodies that even if there is a variation in one site, your response against the other sites is protective. And then, in an ideal world, you could then back the virus enough into a corner that you would drive down circulation. If everyone's response is completely protective and there's no path forward for the virus to escape, then the virus wouldn't be circulating in people.

It's something that I think we're... So I was brought in, I guess this is a little bit of background. The plan for us was the simulated pandemic, and that was what we thought 2020 was going to have in store for us as we were going to, with our DARPA contract, simulate a flu pandemic and how we would rapidly isolate antibodies of this "pandemic strain of flu." So it was essentially a drill. And as the flu expert in the lab, I was working with other members of the lab to provide some of the flu know-how and design that strategy. And then, it became very clear early in January that we were actually not going to be simulating a pandemic. We were going to be working on a real pandemic. And one thing I was sort of... That can be pretty stressful, especially when there's not a margin for error.

One thing I was thinking of to describe what it felt like was I remember when after college with my wife, I went on a trip to Italy and we were on this bus in Southern Italy that was driving along the coastline, and there was 600-foot cliffs and just the ocean crashing against the base of the cliff on the other side. I was just looking over the buses. We went around all these winding roads and it was sort of... I have been feeling like, "Well, if something were to happen, there's no sense worrying about it because it is what it is," and that was a little bit what it felt like, the mentality that you had to get yourself into when we were getting samples from donors, where we had basically one shot to try to isolate antibodies. There wasn't a margin for error. And so, because there wasn't a margin for error, you just needed to go and do it.

There was a lot of... While that's extremely stressful, it was also extremely gratifying because, for me, having worked in a lab in undergrad, worked in a lab in my PhD, there were skills that I had acquired along the way. And then, this was one of those times where I thought that I felt like every skill that I had acquired played some sort of role in helping get us across the finish line. It was also really gratifying as well to work with a group of people where everyone on our team was locked in, and day in, day out, we were relying on everyone's skillset and people bringing diverse skills to the table and being experts in their areas in order to actually successfully get us to the finish line.

Clark Buckner: Our next guest worked in a VUMC lab that's been searching for treatments to back coronaviruses into the corner for two decades. Dr. Pruijssers was a coronavirus and antiviral expert in the world-renowned lab of Dr. Mark Denison. And she now works with the pharmaceutical company, Merck, developing the next generation of virus treatments. I spoke with her about her work at VUMC.

Dr. Andrea Pruijssers: Originally, I'm from the Netherlands originally, born and raised. It's where my accent is from. I studied that Wageningen University, which was a small life sciences university. The virology that was ongoing there, it was not a mammalian focus. I studied insect viruses before I came to Nashville. I've only been in the lab for three and a half years now, so I can only talk about "the lab" as in this operation that has been going on for 30 years. So Dr. Dennison, who I work for, who's also been a guest on this podcast, has been working on these coronaviruses fastidiously for 30 years, even before they were a big deal, even before they caused a pandemic. And so, really, all the credit goes to him.

But when I joined, we were working on these two drugs and we really want to apply them to treat MERS-CoV which was, at that point, the ongoing outbreak in the Middle East. It's a very lethal coronavirus and we also don't have antiviral treatments for it, so there was a great need already. So I thought I was doing something really important at the time that I joined, but it wasn't until a little bit over a year ago that I realized that what I was doing was even more important than that and urgent. And so, for me, to be able to be in this place doing this type of work at this time, for a researcher like me who's been studying basic processes and basic research for also almost two decades, I mean, it was a dream come true.

So our team has been studying some of these basic fundamental processes that don't really seem to have an application at first for a long time. And because so many detailed studies were done, we were actually able to understand the virus better and understand how to target it, and we've been applying that knowledge even before I joined the lab since seven years ago in a form of testing anti-viral compounds, so that could be turned into drugs, that target the coronavirus replication machinery. And really, we needed that knowledge of how this works to understand why do some drugs inhibit and other drugs don't inhibit. With that knowledge, the lab was able to move forward two antivirals, one is called Remdesivir, that's the only small molecule antiviral that's right now approved by the FDA for use in COVID-19 patients, and the other one is called Molnupiravir, and that one is still in late stage clinical trials. It's very promising as well. Now, these drugs, like I said, we've been studying now for way longer.

Clark Buckner: What's it like to be on the hunt for an antiviral for SARS-CoV-2?

Dr. Andrea Pruijssers: The difference between antibiotics and antivirals, it's fairly simple. Antibiotics, they target bacteria, and antivirals, they target viruses. We have lots of antivirals that work really well for other viruses. We can treat influenza with Tamiflu. We have HIV drugs, antivirals that target HIV and will inhibit the virus. And so, it will actually protect somebody from developing AIDS or delay that process. For coronaviruses, it's been a little bit more elusive. The field has been working on antivirals against coronaviruses since the SARS-CoV outbreak in early 2000, so it's less old to field because we didn't know we needed drugs against coronaviruses because before that time, they were mainly innocuous viruses that may cause a common cold. Who needs to be treated for the common cold? So there wasn't really a whole lot of money available either for that kind of research.

But then when SARS-CoV broke out in China in 2002, that's when the whole world started looking for antivirals to treat this particular virus. And back then for MERS-CoV, but also for the current virus that we're dealing with right now, SARS-CoV-2, it's a very attractive idea to repurpose antivirals that have been shown to be effective against other viruses, against other viral diseases. So right now, we see the coronavirus, the current pandemic is evolving all the time, and that's just something that viruses and, in particular, RNA viruses, so viruses that their genome is made up of RNA, that's what they do. They mutate constantly. They exist in what we call viral clouds. Different varieties of the same thing co-exist together, and then whatever selective pressure they're put on there, whether it's a host or drug treatments or monoclonal antibody treatments, they find ways around that because certain sub-lineages or subsets of the viral population will be better able to cope with those pressures and they will adapt and they will then become the dominant strain.

And so, we're constantly chasing this virus, especially with things like monoclonal antibodies, which they're very effective. And the treatments we have right now are very effective at keeping people out of the hospital and making them survive COVID-19, which is really great, but the virus constantly mutates in that area that the monoclonal antibodies binds in order to neutralize the virus is particularly under heavy selection pressure, so the virus is constantly evolving to try to get out of that pressure. And once it's out of that pressure, then those monoclonal antibodies, they become obsolete. You can't treat the

virus anymore. So you have to come up with new monoclonal antibodies and make new therapies and combinations that actually work.

Clark Buckner: Dr. Natasha Halasa, a pediatric infectious diseases and vaccine expert who has traveled around the globe doing disease surveillance, leapt into action when COVID hit. She knew her team would have a limited amount of time to collect precious, precious samples that will be the foundation for research for years and maybe even decades to come. They switched into gear and got after it.
Dr. Natasha Halasa: I did my pediatric residency at Ohio State and really wanted to get an MPH, learn clinical research, and be mentored under Kathy Edwards. I was going to be here for three years and then go back to Ohio, but once I got here and got exposed to research and epidemiology of acute respiratory illness surveillance and vaccine studies and seeing how we could prevent severe illness through vaccines, that led me to stay here. So over pre-COVID, our group does acute respiratory illness surveillance. We do it both locally and internationally and had surveillance in Jordan. Actually even the pre-COVID era, we had done it first in 2007 for three months, and then went back again and did a three-year surveillance because we saw that RSV was very prominent during those three months, but we did it through the peak seasons. And then, went back and did it over a three-year surveillance period and found that RSV was still very prominent there in kids less than two that were hospitalized.

And then, Dr. Edwards had been doing acute respiratory surveillance here that I had modeled our surveillance in Jordan called the New Vaccine Surveillance Network, and it's CDC run. It started here in Nashville and in Rochester and Cincinnati, where they would bring in people with fever and/or respiratory symptoms, get nose and throat swabs, and then do PCR to figure out what the burden of illness. It was like we were born to do the surveillance. And so, we already had protocols in place. So we had a protocol in place that was actually looking at surveillance of respiratory illness in kids, but then we knew this started affecting adults and families. So we literally, in a weekend, switched the protocol to include adults, made it more broad, and then we're able to then enroll within a week because our team knew how to build REDCap databases. Our team knew how to do surveillance. So we were able to deploy quickly because we had built 18-plus years of experience to be able to handle this kind of surveillance.

So when the vaccine came out, same thing happened again. We had a protocol that we've been studying flu vaccine and healthy controls to compare them to our immunocompromised hosts. One weekend, we're like, "Oh my gosh, they're going to start giving the vaccine to people and we really need healthy controls," so switched it. And then all of a sudden, they're giving it to immunocompromised hosts and they never studied immunocompromised hosts. So now here we had healthy controls that got the vaccine, and now we have a set of immunocompromised hosts that they hadn't been tested. And so now, we have this program already in place to be able to deploy quickly to collect samples. Because you can't go backwards and collect samples, right, so having the system to be able to quickly do surveillance. We don't have the funding to test everything and do everything that we need right away because the most important thing is you can't go backwards in time to get a sample. So we knew how important it was to quickly deploy out and do that.

Clark Buckner: With the surveillance infrastructure in place, Dr. Halasa and her team have been watching the data closely, looking for trends and new insights into the behavior of the virus and its lasting impact on our health.

Dr. Natasha Halasa: So those long COVID, the only way... Because we have a cohort that we enrolled in March, we can say now it's a year out plus plus because we enrolled people very early in the pandemic. So that's where the advantage of what's happening immunologically to these people because we've gotten samples right around the time they got the disease, a month later, three months, six months, and then a year later. And then, if they've gotten the vaccine or if they've gotten re-infection, we've had a couple people who got reinfected, we're like, "What? You got reinfected. We want to know more about you," but we have their blood before their second infection because we followed these people over time. And so, with the vaccine to know, is that effective, is it working, or what about someone who had SARS-CoV first and then now are getting the vaccine?

So there's some data out there like, "Well, after one dose, they have a pretty good immune response compared to someone who never saw SARS-CoV, they really need two doses."

And then, there's this new thing that came out that looked at 30 people that had solid organ, some of them had gotten three doses. Do they need three doses? We don't know. The fact that the vaccine came out as fast as... I mean, it literally is a miracle. I mean, if you think about vaccine history and the fact that this vaccine... I mean, from discovery of, "Here's a new virus that's causing a pandemic" to when the vaccine came out is a miracle. Majority and millions and millions of people are going to do great. They're going to get antibodies and they're going to do well.

Well, there's a subset that have a side effect from a vaccine, just like a subset of people are having side effects from the virus. More people are actually having side effects from the virus itself, right? This virus, itself, is devastating. It's killing people, giving them sequelae, making them more tired than they normally were. They lost their sense of smell. They lost their sense of taste. They're tired. They're having chest pain. They're brain fog. They talk about this brain fog, right? Why? Why does someone get more severe disease, someone got mild disease, someone was asymptomatic, yet some of those mild diseases turned into something that was more severe.

So those are the things of like, "This virus is like no other respiratory virus because it's affecting all organ systems," versus flu, right? Flu is still severe. Flu is still severe in kids. We have a vaccine that's not 100% effective, but if you get it, you're less likely to get severe disease. But flu is still severe. We have a thing where we're comparing kids in the ICU with flu compared to COVID, they're still presenting the same way. They're still sick. They're still requiring oxygen. The COVID kids are staying maybe one or two days later in the ICU, but the kids are still sick with flu, and 25% of them don't have an underlying medical condition. Why? Those are the things that... Like for RSV, majority of the kids that get hospitalized with

RSV don't have an underlying medical condition. Why? Those are the things that I continue to think about.

Clark Buckner: Did you know there are 24 letters in the Greek alphabet? Yeah, I looked that up. And I hope by the time you're listening to this, we are not getting acquainted with yet another letter. One thing is for sure though, COVID and SARS-CoV-2 are going to be around for a very long time. So what does that mean for research on coronaviruses and other diseases? There are other diseases, as we've been so clearly reminded this summer. The unusual summer spike in RSV in children took a lot of parents by surprise. Where's this research going to go? And what do our guests hope we, as a global society, learn about not only SARS-CoV-2, but research in general, and about how to blunt the blow of pandemics, which will assuredly happen again?

Dr. Seth Zost: It's interesting because there were very few corona virologists or coronavirus experts prior to the SARS-CoV-2 pandemic. It was a field where there were very talented people working in it, but there were not a lot of people working in it. It was a small tight-knit group. And then there's been this massive influx, and I'm an example of this where I'm classically trained in influenza, people who surged in as part of pandemic response. And then, I think eventually some of those people are going to go back to their own fields. They brought things to the table that they applied to the pandemic, and they're going to take things back and then think about applying them to their own areas of interest and new areas in the future. I think that will be something that's very fruitful.

One thing that's really interesting is, and people are already talking about, there was a momentum towards this universal influenza vaccine that would target flu viruses broadly and would also provide longer-lasting protection. And people are already in coronaviruses thinking about, "What about a parent coronavirus vaccine, where if SARS-CoV-3 is hiding out in bats somewhere, would we already have a vaccine that would be highly effective against it," because it induces such a broad response that it covers that.

And for some of the stuff that we in the Crowe Lab do, it's also with antibody discovery, one thing we'd like to do is see, can we isolate antibodies against some of these potential pandemics before they happen, so then we would have an idea of what would be the most potent antibodies? You could even imagine stockpiling some of those in the case of an outbreak where you would try to squelch it before it ended up spreading too widely, or at least blunt its effects. And then also, scale up the production of those where, while a vaccine was still being worked on, you would have a stopgap that you could use to treat people.

I think everyone in the field is actually really tired right now, but I'm sure that when people finally have a chance to catch their breath, the people in the field will be reinvigorated. But I also hope that there's a younger generation of people that sees the importance of this and there's a renewed interest in infectious diseases. It's interesting to think about the historical examples where I think there were multiple cases in the 1970s where we thought that we would... People were talking about, "Why are we

even training Infectious Disease doctors anymore? We have all these successful vaccines. It's not even going to be a field anymore." And obviously, that was a bit of a rosy view and we do need those. We did need those people, and we still will. The potential for zoonotic threats is always going to be there. Hopefully, one silver lining of the pandemic is that it inspires another generation of people who will push us even further in the field.

Clark Buckner: Staying ahead of the next COVID variant or viral pandemic and finding treatment is what motivates Dr. Pruijssers to continue her research.
Dr. Andrea Pruijssers: Right now, we played an active role in the Moderna vaccine and the testing of the samples, and it was really fulfilling. I'm stoked to know that it's already saved so many lives and are protecting people and helping the society reopen. Vaccines are great, they're very effective and we're seeing really good results, but there are still people that are in hospital. We still need better drugs. Monoclonal antibody therapies are great and effective, but they will probably be not useful for the next pandemic, the current virus that's going around, but also for the next coronavirus that's going to emerge. Because we've had SARS-CoV, we've had MERS-CoV, we still have MERS-CoV, and then we have SARS-CoV-2, and it seems to be a new pandemic or a new outbreak every decade. So when is the next one going to come and are we going to be ready? That's what keeps me up at night.

Clark Buckner: One of the unforeseen plot twists in this pandemic is how measures we all took to protect ourselves from COVID also led to the mildest flu and RSV season in decades. But the return of RSV in a different season, our warm months, raises questions. Dr. Halasa's team is watching to see if there are long-term positive outcomes from a reduced winter exposure and studying why RSV came roaring back out of season. We live among many infectious diseases, and the events of the last two years are creating new opportunities to understand the human pathogen relationship.

Dr. Natasha Halasa: You don't know what happens five years later after exposure until it's five years, right? So I can't tell you what's going to happen five years from now. What happened to all these kids that didn't see RSV because it went away the first year? Are we going to see less asthma? We won't know that, because Tina Hartert at Vanderbilt shows that if you are a young child and you get hospitalized with RSV during January and February, your risks of getting asthma is greater than someone who never got RSV during that same time period for younger than six months, younger than a year age group. Getting that childhood exposure for...You can't diagnose asthma until four or five years, right, because you can get reactive airway disease, but does it last? And so, you won't know that until they're older. And so, we don't know.

Five years from now, we'll have a cohort of kids that didn't see RSV for an entire winter. Will we see less asthma? We don't know. We don't know until we know. Where is flu? When is flu coming? When does RSV started coming? If you ask me would RSV be coming in May? No way. If you asked me that years ago, the mask community mitigation, I mean, that's the most effective. You couldn't ask for a better vaccine, right, when you said masks preventing RSV and young kids from being hospitalized. Isn't that amazing? Maybe. That'd be pretty cool because it's a chronic illness. How cool would that be that we

have less asthma because these kids did not see RSV because we... But we need the kids in school, right? We need kids to socialize. We can't shut down a whole community, but maybe we just do some things like when you're sick, stay home. If you're sick, make the whole family wear some masks. Those kinds of things. Maybe we can adapt, like wash your hands, use hand sanitizer. All these little simple things that our grandmothers told us to do.

It's like my whole life has been prepared to continue to study not only this virus, but all other viruses in young kids and specialized populations, and really trying to understand how can we get the best vaccines for these individuals. This is a lifetime career of another 20 years. After being at Vanderbilt for 20, I can see myself being here for another 20, and just watching the young people help answer these questions is really exciting. But knowing what I know now, I'd still do exactly what I'm doing. I wouldn't change it. I just love it because I've never had the same day ever.

Dr. Andrea Pruijssers: I've always taken my job very seriously because, I don't know, that's just kind of... I've always loved science and research and doing laboratory work. And I feel like in the last three years ever since I started working coronaviruses, it's taken on this extra level of importance that, "Okay, I'm actually trying to fight the disease here. Can we do it?" And we made a really important contributions. And so, for me, it's gone from playing in a sandbox to, "Okay, it's showtime now. We have to perform," and we were ready.

Clark Buckner: Get vaccinated and stay safe out there, DNA listeners. Thanks for joining us today. To learn more about the show, check out episode extras, and find more information about Vanderbilt Health and today's experts, visit listendna.com. You can also find us on Twitter @VUMC_Insights, and all of your favorite platforms, @VanderbiltHealth. And of course, don't forget to follow, rate, and review this show anywhere and everywhere you get your podcasts like Apple Podcasts, Google, and Spotify. We're there.

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